Current Status of Targeted Therapy for NSCLC

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Denver, Colorado
Potential Conflicts of Interest

- Served on advisory board for:
  - Genentech, Pfizer and BMS -- targeted therapy agents
  - Oncimmune--biomarkers lung cancer: Research grant pending approval; iSense: Research grant pending
IASLC/ATS/ERS International Classification of Lung Adenocarcinoma

www.JTO.Org

Travis et al J Thorac Oncology 2011; 6:244-283
Specimen Handling for Molecular Testing

- Molecular Testing of NSCLC is Hampered by Small Diagnostic Specimen
- Limited Tissue is Further Reduced by Diagnostic IHC Testing and Aggressive Tissue Block Facing
- “Molecular Only” Testing Offers a High Success Rate at University of Colorado

Aisner et al. *J Thorac Oncol* 2012; 7:S223 (Abstract #130)
Suitability of EBUS-TBNA Samples

- Final Diagnosis by EBUS in Whom Subtype Was Classified 77% (CI 73-80%)
  - Rate of NOS Was Significantly Reduced When IHC Performed (OR 0.50)

- EGFR Mutational Analysis Was Possible in 90% of the Patients (Adequate Samples)
  - These Were Experienced EBUS Centers

Navani et al. *AJRCCM* 2012; 186:255-260
Transthoracic Core Needle Biopsy
BATTLE Lung Trial

- 20G needle Bx in 151 NSCLC patients screened for trial
- 83% specimens were adequate for biomarker testing (11 markers)
- Metastatic lesions were 5X more likely to yield diagnostic tissue
- Pneumothorax in 15%; chest tube 9%
Use of Cytological Material for Molecular Diagnosis of Lung Cancer

Cell Block - Histology Sections

Fine Needle Aspiration  Pleural Fluid
EGFR Mutations in Tyrosine Kinase Domain

- 90% of lung cancer EGFR mutations
  - Exon 19 deletion LREA sequence (del E746-A750)
  - Exon 21 mutation; L858R (leucine to arginine substitution)
- Resistant mutation exon 20
  - T790M
  - Exon 20 insertion
EGFR mutation: Exon 19 deletion
At the development of acquired resistance:
- All Cells Remain Oncogene – Addicted
- T790M found in few cells, small fraction of total alleles
- Not all cells are resistant, in fact, most remain sensitive

EGFR TKI

EGFR TKI

Stop EGFR TKI?

EGFR TKI Resistance by RECIST
Continuation of TKI + Local Rx for TKI PD on Erlotinib or Crizotinib

<table>
<thead>
<tr>
<th>Study</th>
<th>N pts</th>
<th>PFS1</th>
<th>PFS2</th>
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<tbody>
<tr>
<td>Colorado</td>
<td>25</td>
<td>10</td>
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</tr>
<tr>
<td>MSKCC</td>
<td>18</td>
<td>19</td>
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</table>

Randomized trials of afatinib plus cetuximab versus afatinib alone in treatment-naïve and previously treated patients and with advanced, *EGFR* mut+ NSCLC

**Study 1 Eligibility:**
- Recurrent or advanced NSCLC
- Sensitizing *EGFR* mutation (i.e., exon 19 deletion, L858R)
- Chemotherapy and TKI-naïve
- PS 0-2

**Randomize**

- Afatinib PO 40mg daily + Cetuximab IV 500mg/m2 Q2 weeks
- Repeat Biopsy at Progression

**Primary Endpoint:** Progression-Free Survival

**Secondary Endpoints:** ORR, OS, Safety, Tolerability, QOL

**Exploratory Biomarkers:** Pre- and post-Rx T790M testing, whole exome sequencing, HER2 and MET FISH

**Study 2 Eligibility:**
- Recurrent or advanced NSCLC
- Sensitizing *EGFR* mutation (i.e., exon 19 deletion, L858R)
- Prior Chemotherapy
- TKI-naïve
- PS 0-2

**Initial Evaluation:**
- PET-CT
- Brain CT or MRI
- ECG, Echo/MUGA
- Tumor Molecular Analysis

**CT Scans q8 Wks**
Third Generation EGFR TKIs

• Irreversible Binding of Activating and T790M Mutations But Not Wildtype
  – WZ4002 (DFCI) - tool
  – CO-1686 (Clovis) OR=4/6 at highest dose (900mg BID-reformulation ongoing)
  – AP26113 (Ariad) – ALK, too OR 0/3 in T790M
  – TAS-2913 (Taiho)
  – AZD9291 (AZ) Phase 1 ongoing
  – Z650 (HEC Pharma)
EML4-ALK in NSCLC

• Screened 141 NSCLC based on ≥ 2 of following: female, Asian, NS/light smoker, and adenocarcinoma

• 19 of 141 (13%) were ALK mutations
  • 31 (22%) were EGFR mutations
  • 91 (65%) were wild type for both

Preselection Screening for ALK In German Lung Cancer Patients

- Patients were negative for EGFR mutations
- 61 patients; mean age 56; 90% ACA
  - 41% female
- 16% were positive for EML4-ALK
  - 60% female, smoked less and were younger

Tufman et al J Thorac Oncol 2014; 9:109
FDA Approves Crizotinib (Xalkori): August 26, 2011

- For advanced or metastatic NSCLC that is ALK transformation positive
- FDA approved Vysis ALK Break apart FISH probe kit (Abbott Molecular, Inc)
- 255 patients; 96% adenocarcinoma, 95% metastatic; 94% had prior treatment; median age 52 years
- ORR was 50% and 61% in 2 studies with MDR of 42 and 48 weeks; only 1% CR
- Mild visual disturbances; G3/4 SAE in 4%
  Fatal pneumonitis in 1.6% (1st 2 mos)
Parallel FISH and IHC Tests of ALK Reveal Major Discordances

• FISH by Abbott BA probe (Vysis) and Dako split probe is Rennes and Bordeaux cohorts respectively (2 probes equivalent in 100)

• IHC assayed in both centers using Abcam (clone 5A4)
  • In Rennes used Ventana automation immunostainer
  • In Bordeaux used Bond-maX automation immunostainer

Cabillic et al March 2014 J Thoracic Onc
Parallel FISH and IHC Tests of ALK Reveal Major Discordances

- 3244 consecutive NSCLC cases analyzed at two French Centers
- FISH and or IHC was + in 150 (4.6%)
  - Only 80 of 150 were + by both
  - FISH pos ; IHC neg in 36
  - FISH neg; IHC pos in 19
  - FISH noncontributory; IHC + in 15

Cabillic et al J Thorac Oncol 2014; 9:295
Ongoing Randomized Trials of Crizotinib in ALK + NSCLC

PROFILE 1007 (N=318)
- ALK-FISH positive
- 1 prior chemotherapy (platinum-based)

Crizotinib 250 mg BID (n=159) [continuous]
- pemetrexed 500 mg/m² or docetaxel 75 mg/m² (n=159) infused on day 1 of a 21-day cycle

PROFILE 1014 (N=334)
- ALK-FISH positive, non-squamous NSCLC
- No prior treatment for advanced disease

Crizotinib 250 mg BID (n=167) [continuous]
- pemetrexed/cisplatin or pemetrexed/carboplatin (n=167) infused on day 1 of a 21-day cycle
Crizotinib vs Chemotherapy

**PROFILE 1007 Primary Endpoint: PFS by Independent Radiologic Review**

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<tr>
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<th>Crizotinib (n=173)</th>
<th>PEM/DOC (n=174)</th>
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<tbody>
<tr>
<td>PFS events, n (%)</td>
<td>100 (58)</td>
<td>127 (73)</td>
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<td>Median, months</td>
<td>7.7</td>
<td>3.0</td>
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<td>HR (95% CI)</td>
<td>0.49 (0.37 to 0.64)</td>
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### No. of Patients at Risk

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### PFS, mo

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<td>2</td>
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<td>24</td>
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**Pem/Doc = pemtrexed/doceteaxel**

Shaw A, et al. [24]
### Phase 1/2 Trials of 2^{nd} Generation ALK Inhibitors

<table>
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<tr>
<th>Study</th>
<th>N pts</th>
<th>OR (N)</th>
<th>OR</th>
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<tr>
<td>LDK378 All*</td>
<td>114</td>
<td>66*</td>
<td>75%*</td>
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<tr>
<td>LDK CRZ pre*</td>
<td>79</td>
<td>45*</td>
<td>78%*</td>
</tr>
<tr>
<td>AP26113 pre**</td>
<td>24</td>
<td>15</td>
<td>73</td>
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<tr>
<td>CH5424802^</td>
<td>46</td>
<td>39</td>
<td>83</td>
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*ASCO 8010 OR=CR+PR+uPR; **ASCO 8031; ^ASCO 8033 all 2013

Is there space for second generation inhibitors of EGFR and ALK?
ROS1 Receptor Tyrosine Kinase Rearrangement & Crizotinib Rx

- FISH break apart assay: 250mg BID
- 25 treated and evaluable
  - Median age 51; 79% NS; 97% ACA
  - Prior Rx median 1 (range 0-7)
- ORR was 56%; 2CR; 12 PR; 8 stable
  - Median Rx duration 24 weeks
  - 6 months PFS probability 71%

Ou et al J Clin Oncol 2013; 31: abst 8032
RET Fusions

• About 1% of NSCLC

• KIF5B-RET or
  – CCDC6-RET

• Mutually Exclusive of EGFR, KRAS, and ALK Mutations
Strategies for Identifying ROS1 and RET mutations

• Occur in 2,000 to 3,000 ACA per year

• Screened 51 ACA that were negative for EGFR, ALK, KRAS, ROS1
  • 8 patients (15%) had RET fusions

• Screened 35 mutation neg (LCMC), never smokers with ACA
  • RET in 15% and ROS1 in 15%

J Clin Oncol 2013; 31 abstr 8024 (U of CO) and 8067 (MSKCC)
Vandetanib

- MultiKinase Inhibitor of RET
  - VEGFR-2
  - EGFR

- **Carbozantinib**: Blocks multiple RTK including RET

- Approved for medullary thyroid cancer, and some preliminary activity in Lung ACA with RET
Lung Cancer Mutation Consortium in Lung Adenocarcinoma

• 1007 patients tested for mutation
  • 733 tested for all 10 genes
  • 60% female; median age 63
  • 34% NS; 58% former smokers

• Driver mutation found in 62%
  • Two mutations in 4%

J Clin Oncol 2013; 31: abst 8019
Lung Cancer Mutation Consortium: Incidence of Drive Mutations

- MEK1: <1%
- NRAS: 1%
- MET: 1%
- PIK3CA: 1%
- BRAF: 2%
- HER2: 3%
- Mutation in >1 gene: 3%
- EGFR (other): 4%
- ALK: 8%
- EGFR (sensitizing): 17%
- KRAS: 25%
- No oncogenic driver detected: 36%
Lung Cancer Mutation Consortium in Lung Adenocarcinoma

- 938 had follow-up data
  - 264 with driver mutation and Rx with a targeted agent: MST 3.5 yrs
  - 313 driver mutation and no Rx with targeted agent: MST 2.4 yrs
  - 361 with no driver mutation had a MST of 2.1 years

J Clin Oncol 2013; 31: abst 8019
French Nationwide Screening for Six Driver Mutations

- EGFR, ALK, HER2, KRAS, BRAF, PI3KCA
- First 10,000 reported after one year
  - 63% males; 83% (ex)smokers
  - 76% adenocarcinoma
- 27% KRAS; 9% EGFR; 4% ALK
  - 1% HER2; 1.6% BRAF
- Feasibility of nationwide mutational testing

J Clin Oncol 2013; 31: abst 8000
Dabrafenib Receives Breakthrough Status by FDA for BRAF Mutated LC

- Has clinical activity in BRAF V600E melanoma patients
  - Nearly 3000 LC patients per year USA
- 17 patients with this mutation treated 150 mg PO BID
  - Median age 69; 12/17 males; all ACA and 13 were former smokers
- 7 PRs of 13 (54%) evaluable: DuR was 6+, 24+, 29 and 49 weeks

Planchard et al J Clin Oncol 2013; 31: abstr 8009
HER2 Mutations in Lung Cancer

- HER2 insertions in exon 20 identified in 65 (1.7%) of 3,800 tested
  - Median age 60; 69% women; 52% NS; all ACA
- 16 patients Rx; 11 PRs
  - DCR of 93% (n=15) with transtuzumab based Rx
  - DCR of 100% in 3 Rx with afatinib

Genomic Characterization of Squamous Cell Lung Cancer

• Comprehensive Genomic Characterization of Squamous Cell Lung Cancer: TCGA
  
  Nature 2012; 489:519-525

• Integrative and Comparative Genomic Analysis of Lung Squamous Carcinomas in East Asian Patients

Significantly Mutated Genes in Squamous Cell Lung Cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutated Percentage</th>
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<tbody>
<tr>
<td>TP53</td>
<td>81%</td>
</tr>
<tr>
<td>CCKN2A</td>
<td>15%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>16%</td>
</tr>
<tr>
<td>MLL2</td>
<td>20%</td>
</tr>
<tr>
<td>NFE2L2</td>
<td>15%</td>
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<tr>
<td>KEAP1</td>
<td>12%</td>
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<tr>
<td>PTEN</td>
<td>8%</td>
</tr>
<tr>
<td>NOTCH1</td>
<td>8%</td>
</tr>
<tr>
<td>RB1</td>
<td>7%</td>
</tr>
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</table>

TCGA Nature 2012;489:519
Genomic Characterization of Squamous Cell Lung Cancers: Potentially Targetable/Actionable Alterations

- FGFR1 amp
- FGFR2/FGF R3 mut
- DDR2 mut
- PIK3CA mut
- PDGFRA amp
- BRAF mut
- EGFR amp
- ERBB2 amp
- Unknown
TCGA: Squamous Cell

• Previously Unreported Mutation were Loss-of-Function in HLA-A Class I Major Histocompatibility Gene

• Significantly Altered Pathways* 
  - NFE2L2 and KEAP1 in 34% 
    (oxidative stress response) 
  - SOX2, TP63, NOTCH1 and 2 
    (squamous differentiation) 

(Somatic mutations, copy number alterations, or up or down regulation) 
Nature 2012;489:519
Squamous Cell Carcinoma: Korean Study

- Seven Most Common Genes Mutated
  - TP53, RB1, PTEN, NFE2L2, KEAP1, MLL2, and PIK3CA

- Mutations Were Similar to TCGA

- Identified Recurrent Occurrence of FGFR3-TACC3 Fusion
  - Potentially actionable

FGFR Gene Fusions in Diverse Cancers

- Whole exome sequencing (DNA) and transcriptome sequencing (RNA)
- Various cancers tested for FGFR fusions
  - Present in many cancers including Squamous cell LC and HNSCC
  - Six lung cancer with fusions of FGFR1 (1), FGFR2 (1), FGFR3 (4)
- FGFR fusions are active kinases

How Do PD-L1 Blockade and PD-1 Blockade Differ?

Freeman & Sharpe, Nat Immun 2012; 13 (113)

Presented by: Natasha Leighl at ASCO Annual 13 Meeting
MPDL3280A (Anti-PDL1) Inhibits the Binding of PD-L1 to PD-1 and B7.1

Blocking PD-L1 restores T-cell activity, resulting in tumor regression in preclinical model. Binding to PD-L1 leaves PD-1/PD-L2 interaction intact and may enhance efficacy and safety.
## Preliminary Efficacy Data in NSCLC

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>N</th>
<th>ORR%</th>
<th>SD&gt;24 wks</th>
<th>24 wk PFSR</th>
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<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab-BMS-936558 1-10 mg/kg</td>
<td>129</td>
<td>17.1%</td>
<td>10.1%</td>
<td>--</td>
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<tr>
<td></td>
<td>Nivolumab 5,10 mg/kg + Platinum Doublet</td>
<td>56</td>
<td>~45%</td>
<td>--</td>
<td>36-71%</td>
</tr>
<tr>
<td>PD-L1</td>
<td>BMS-936559 1-10 mg/kg</td>
<td>49</td>
<td>10%</td>
<td>12%</td>
<td>31%</td>
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<tr>
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<td>MPDL-3280A</td>
<td>41</td>
<td>22%</td>
<td>12%</td>
<td>46%</td>
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</table>

Brahmer et al. ASCO 2013 #8030; Rizvi et al. ASCO 2013, #8072; Brahmer et al NEJM 2012; Spigel et al. ASCO 2013 #8008
www.MYCANCERGENOME.ORG

- Select a disease
- Select a gene
- Select a mutation

Vanderbilt-Ingram Cancer Center
NCI Supported Genomic Clinical Trials

• SWOG 1400
  - Biomarker Driven master Protocol for Second Line Treatment of Lung cancer (4-6 arms)

• ALCHEMIST
  - Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial
ALCHEMIST TRIAL

- Resected non-squamous Stage IB, II, III

**EGFR and ALK in CLIA Lab**

- Rest of tissue sent for testing in The Cancer Genome Atlas study

- **EGFR mutations** enrolled in Alliance A081105 adjuvant erlotinib (n=410)

- **ALK fusions** enrolled in E4512 adjuvant crizotinib (n=360)
SWOG 1400

• Second line squamous cell mutational testing platform

• PI3K (PIK3CA mut): GDC0032 or chemo

• CDK4/6: PD0332991 or chemo
  • Mut CCND1, CDK4/6 amp, CDKN2 mut

• FGFR (amp, fus, mut): AZD4547 or chemo

• HGF (mut MET or amp): AMG102+erlotinib or chemo

• If no match then consider antiPDL1 vs CT
Suggested Mutations Approach in 2014

EGFR

ALK

KRAS
Additional FISH Testing 2014

ROS

RET

MET amp
WARNING:
SMOKING CAUSES
92% OF ORAL CANCERS
QUIT: 1800-438-2000