Individualized Therapy for Non-Small Cell Lung Cancer

Lung Cancer Mutation Consortium: Adenocarcinomas

- EGFR
- KRAS
- EML4-ALK
- MET Amplification
- BRAF or PIK3CA
- HER2, MEK1, NRAS, AKT1

Mutations found in 60% of tumors completely tested

Kris MG. The Lung Cancer Mutation Consortium. Presented at: 12th Annual Targeted Therapies in Lung Cancer; February 2012; Santa Monica, CA.

Testing for Rearrangements: ALK

Pros and Cons of Direct Sequencing

- **Pros**
  - Broad: detects known, rare, and new mutations across multiple exons
  - Widely available

- **Cons**
  - Labor intensive (cost, turnaround time)
  - Requires relatively tumor-rich sample (and/or requires microdissection)
  - Sensitivity

Alternatives to Direct Sequencing

- **More focused tests**
  - eg, real-time quantitative PCR
    - Improved depth (can find mutations in a sample with a lower percentage of tumor)
    - Less labor intensive (turnaround time)
    - Sacrifices breadth – doesn’t include rarer mutations or novel mutation

Not All Mutations Are Equal

Not All Mutations Are Even Tested

**Sensitizing Mutations in EGFR**
- Exon 19 deletions
- L858R
- L861Q
- G719X
- S768I

**Resistance Mutations in EGFR**
- T790M
- Exon 20 insertions
- E746Y
- L747S
- T854A

Breadth of coverage varies by lab; 2 major commercial labs performing RT-PCR reported covering these.
Interpreting Results:
Things to Consider

• “Negative” report may not be truly so
  – Was the tumor sample adequate for testing?
  – Which exons/mutations were screened?
  – Is it worth re-biopsying to get a better sample?

Molecular Markers:
Why/When to Test

Prognostic vs Predictive

• Prognostic Marker
  – Indicates survival benefit/detriment regardless of therapy
  – Stage, tumor size, sex

• Predictive Marker
  – Predicts for differential benefit from a particular therapy

Predictive Markers in NSCLC

- Predictive markers in advanced NSCLC
  - EGFR mutation: EGFR-TKIs
  - EML4-ALK translocations: crizotinib
- Potentially Predictive; low levels = sensitivity
  - Thymidylate Synthase (TS): pemetrexed
  - ERCC1: platinum
  - RRM1: gemcitabine
  - BRCA 1: low platinum, but HIGH for taxanes

Prospective Biomarker Adjuvant Trials

<table>
<thead>
<tr>
<th>Stage</th>
<th>Therapy</th>
<th>Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG 0720</td>
<td>I (&gt;2cm) +/- Chemotherapy (Cisplatin/Gemcitabine)</td>
<td>ERCC1/RRM1</td>
</tr>
<tr>
<td>ITACA</td>
<td>I-IIIA</td>
<td>Cisplatin/Pemetrexed</td>
</tr>
<tr>
<td>TASTE</td>
<td>I-IIIA</td>
<td>Cisplatin / Erlotinib</td>
</tr>
<tr>
<td>SCAT</td>
<td>I-IIIA</td>
<td>Platinum / Docetaxel</td>
</tr>
</tbody>
</table>

Adjuvant Trial of Bevacizumab (E1505) (extensive biomarker analysis planned. Adjuvant Trial of Erlotinib includes EGFRmut and other biomarkers.

Randomized International Phase 3 Trial of ERCC1/RRM1

- Randomized trial of standard platinum doublet versus customized therapy
- PFS 6.1 vs 6.9 mo, P = .18
- OS 11.0 vs 11.3 mo, P = .66
- Both favored CONTROL arm

ERCC1 Isoform Expression and DNA Repair in NSCLC - Old/New

- 761 tumors (589) of 1867 total pts on trial
- Old 44%: New 77% ERCC1 positive
  2008: HR 1.20 [0.91-1.59]
  New: HR 0.96 [0.74-1.25; \( P = .78 \)]
- Old 56%: New 23% ERCC1 negative
  2008: HR 0.76 [0.59-0.98]
  New: HR 0.81 [0.50-1.31; \( P = .39 \)]


ERCC1 Analysis Conclusions

- Technical biases interfered with prior use of ERCC1 IHC as a predictive marker for platinum chemotherapy
- Current antibodies cannot adequately discriminate the ERCC1-202 isoform, which is the only active isoform
- Highlights importance of assessing multiple isoforms and function in biomarker studies
- Functional assays required for better predictive capacity


Spanish Lung Cancer Group (SLCG) BRCA1-RAP80

- Randomized trial of standard platinum doublet versus customized therapy
  – PFS 5.5 vs 4.4 mo, \( P = .07 \)
  – OS 12.7 vs 11.3 mo, NS
- Both favored CONTROL arm
- Customized arm included single agent docetaxel, which performed poorly

Biomarkers for Chemotherapy

- TS levels MAY correlate with pemetrexed activity, or may be prognostic
- ERCC1 MAY predict for platinum efficacy
- RRM1 MAY predict for gemcitabine efficacy
- BRCA MAY predict for taxane efficacy
- Definitive trials still pending
- Chemo-sensitivity assays not validated


NSCLC: EGFR Mutations

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>EGFR Mutations</th>
<th>Frequency of mutations(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2105</td>
<td>350</td>
<td>All</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>612</td>
<td>231</td>
<td>38</td>
</tr>
<tr>
<td>Smokers</td>
<td>1382</td>
<td>116</td>
<td>8.4</td>
</tr>
<tr>
<td>Female</td>
<td>814</td>
<td>244</td>
<td>30</td>
</tr>
<tr>
<td>Male</td>
<td>1287</td>
<td>106</td>
<td>8.2</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1634</td>
<td>263</td>
<td>17.3</td>
</tr>
<tr>
<td>BAC</td>
<td>147</td>
<td>34</td>
<td>23</td>
</tr>
<tr>
<td>Large Cell</td>
<td>287</td>
<td>33</td>
<td>11.5</td>
</tr>
</tbody>
</table>


Iressa Pan-Asia Study (IPASS)

Patients
- Chemonaïve
- Age ≥ 18 years
- Adenocarcinoma
- Histology
- Never or light ex-smokers*  
  
  • Life expectancy ≥ 5 years  
  • PS 0-3  
  • Measurable stage III / IV disease

Endpoints
Primary
- Progression-free survival (non-inferiority)

Secondary
- Objective response rate  
  • Clinical outcome  
  • Quality of life  
  • Disease-related symptoms  
  • Safety and tolerability

Exploratory
- Biomarkers
  • EGFR mutation
  • EGFR gene-copy number
  • EGFR protein expression

Gefitinib
250 mg / day

Carboplatin (AUC 5 or 6) / paclitaxel (200 mg / m2) / 3 weekly*


*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥ 15 years ago and smoked ≤ 10 pack years; limited to a maximum of 6 cycles carboplatin/paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor.
IPASS: PFS in EGFR Mutation Positive and Negative Patients

<table>
<thead>
<tr>
<th>EGFR mutation positive</th>
<th>EGFR mutation negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib (n=122)</td>
<td>Gefitinib (n=55)</td>
</tr>
<tr>
<td>Carboplatin / paclitaxel (n=120)</td>
<td>Carboplatin / paclitaxel (n=45)</td>
</tr>
<tr>
<td>HR (95% CI) = 0.48 (0.36, 0.64)</td>
<td>HR (95% CI) = 2.85 (2.05, 3.98)</td>
</tr>
<tr>
<td>P &lt; .0001</td>
<td>P &lt; .0001</td>
</tr>
<tr>
<td>No. events gefitinib, 97 (73.5%)</td>
<td>No. events gefitinib, 88 (96.7%)</td>
</tr>
<tr>
<td>No. events C / P, 111 (86.0%)</td>
<td>No. events C / P, 70 (82.4%)</td>
</tr>
<tr>
<td>RR - 71%; 47%</td>
<td>RR - 1.1%; 23%</td>
</tr>
</tbody>
</table>

EurTAC Study

Patients
- Chemonaive
- Exon19 deletion or L858R Exon 21
- PS 0-2
- Measurable stage IIIb / IV disease

Endpoints
- Primary
  - Progression-free survival (non-inferiority)
- Secondary
  - Objective response rate
  - Overall survival

Data cut-off: 26 Jan 2011

EurTAC: PFS in ITT Population

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Erlotinib (n=86)</th>
<th>Chemotherapy (n=87)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>9</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>12</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>15</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

HR=0.37 (0.25-0.54)
Log-rank P < .0001
First-Line EGFR-TKI in EGFR Mutation+

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arm</th>
<th>N</th>
<th>RR</th>
<th>PFS (mo.)</th>
<th>OS (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEJ002</td>
<td>Gefitinib</td>
<td>114</td>
<td>74%*</td>
<td>10.8*</td>
<td>30.5</td>
</tr>
<tr>
<td>NEJ002</td>
<td>CT</td>
<td>114</td>
<td>31%</td>
<td>5.4</td>
<td>23.6</td>
</tr>
<tr>
<td>WJTOG</td>
<td>Gefitinib</td>
<td>86</td>
<td>62%*</td>
<td>9.2*</td>
<td>35.5</td>
</tr>
<tr>
<td>WJTOG</td>
<td>PD</td>
<td>86</td>
<td>32%</td>
<td>6.3</td>
<td>38.8</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib</td>
<td>82</td>
<td>83%*</td>
<td>13.7*</td>
<td>22.7</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>CG</td>
<td>72</td>
<td>36%</td>
<td>4.6</td>
<td>28.8</td>
</tr>
<tr>
<td>EURTAC</td>
<td>Erlotinib</td>
<td>77</td>
<td>55%*</td>
<td>9.4*</td>
<td>22.9</td>
</tr>
<tr>
<td>EURTAC</td>
<td>P/CG, P/CD</td>
<td>76</td>
<td>11%</td>
<td>5.2</td>
<td>18.8</td>
</tr>
</tbody>
</table>

*P < .001


LUX-LUNG 3 Study Design

- Stage IIIB/IV lung adenocarcinoma (AJCC version 6)
- EGFR mutation in tumor (central lab testing; Therascreen EGFRTM RRQ PCR)
- Randomization 2:1
- Stratified by:
  - EGFR mutation (Del19/L858R/other)
  - Stage IIIB (wet)/IV lung adenocarcinoma (AJCC version 6)
  - EGFR mutation in tumor (central lab testing; Therascreen EGFRTM RRQ PCR)
- Race (Asian/non-Asian)
- Afatinib 40 mg/day†
- Cisplatin/Pemetrexed
  - 75 mg/m2 + 500 mg/m2
  - i.v. q21 days, up to 6 cycles
- Primary endpoint: PFS (RECIST 1.1, independent review)
- Secondary endpoints: ORR, DCR, DoR, tumor shrinkage, OS, PRO, safety, PK

*EGFR29:19 deletions in exon 19, 3 insertions in exon 20, L858R, T790M, G719S, G719A and G719C (or G719X), S768I.
†Dose escalated to 50 mg if limited AE observed in cycle 1. Dose reduced by 10 mg decrements in case of related G3 or prolonged G2 AE.
‡Tumor assessments: q6 wks until wk 48 and q12 wks thereafter until progression/start of new therapy.
§Patient-reported outcomes: Q-5D, EORTC QLQ-C30 and QLQ-LC13 at randomization and q3 wk until progression or new anti-cancer therapy.

Primary Endpoint: PFS

- Independent review – all randomized patients

**Objective Response**

- All patients
- Common mutations (Del19/L858R)

**Most Frequent Related Adverse Events**

- >20% difference between treatment arms

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EGFR Mutation Testing in Lung Cancer Tumors

- Test all patients whose tumors are found to be nonsquamous carcinoma
- Consider testing in never or light smokers who have squamous cell carcinoma
- Testing in earlier stages of lung cancer may be beneficial for when disease progresses
- Tumor tissue:
  - Assure adequate sample
  - Preserve for later testing


EGFR-TKIs: Secondary Resistance

- 37 patients re-biopsied at the time of progression
- 6/18 patients with T790M had other molecular abnormalities
- 5 patients had SCLC phenotype


T790M in Acquired Resistance

- Acquired exon 20 mutation found in >50% of patients with acquired resistance to TKI
- Increases relative affinity of mutant EGFR for ATP, may also cause steric hindrance to erlotinib
- More likely to show progression in lungs/pleura
- Less commonly detected in CNS
- May have better prognosis than non-T790M

LUX-Lung 1: Trial Design

Patients with:
- Adenocarcinoma of the lung
- Stage IIIB/IV
- Progressed after one or two lines of chemotherapy (incl 1 platinum-based regimen) and ≥ 12 wks of treatment with erlotinib or gefitinib
- ECOG 0–2

N=585

Randomization 2:1
(Double blind)

Oral afatinib 50 mg once daily
plus BSC

Oral placebo once daily
plus BSC

Primary endpoint: Overall survival (OS)
Secondary: PFS, RECIST response, QoL (LC13 & C30), safety

- Radiographic assessments at 4, 8, 12 weeks and every 8 weeks thereafter
- Exploratory biomarkers
- Archival tissue testing for EGFR mutations (optional; central lab)
- Serum EGFR mutational analysis (all patients)


LUX-Lung 1: PFS by Independent Review

Placibo, PFS events = 133, median = 11.1 months (95% CI: 9.95-16.68)
Afatinib, PFS events = 275, median = 3.3 months (95% CI: 2.79-4.40)
Hazard ratio (95% CI) = 0.38 (0.306, 0.475)
P < .0001

LUX-Lung 1: OS

Placibo, deaths = 114 (58.5%), median = 11.96 months (95% CI: 10.15-14.26)
Afatinib, deaths = 244 (62.6%), median = 10.78 months (95% CI: 9.95-11.99)
Hazard ratio (afatinib vs placibo) = 1.077 (0.862, 1.346)
P = .7428

**Afatinib + Cetuximab Study Schema**

- NSCLC with EGFR mutation AND
- Stable disease (SD) ≥ 6 months on erlotinib/gefitinib OR Partial or complete response to erlotinib/gefitinib
- Disease progression
- Stop erlotinib/gefitinib for ≥ 72 hours
- Dose escalation schema: 3-6 patients per cohort
  - Afatinib PO daily + escalating doses of IV cetuximab q 2 weeks
  - Dose levels starting at: afatinib 40 mg + cetuximab 250 mg/m²
  - Predefined maximum dose: afatinib 40 mg + cetuximab 500 mg/m²

**Afatinib + Cetuximab at MTD: Responses by T790M Mutation**

- Maximum percent decrease from baseline

**CO-1686 Summary**

- 42 pts (74% T790M+) treated w/ CO-1686 up to 1800 mg/day
- Encouraging activity has been observed in heavily pretreated T790M+ EGFR mutant patients resistant to erlotinib, especially at higher doses
- Metastasis shrinkage has been observed at multiple organ sites, including in the CNS
- 3 of 4 T790M+ evaluable patients on 900 mg bid achieved PRs to date
- A hydrobromide form of CO-1686 w/ improved exposure and reduced PK variability will be used in phase 1/2 study later in 2013
- The recommended phase 2 dose of CO-1686 is not yet defined

Janjigian YY, et al. ESMO 2012. Abstract 1227O.

Rapid Progression With Discontinuation of EGFR TKI After Prolonged PFS
Rapid acceleration of disease progression resulting in hospitalization and/or death after D/C of gefitinib or erlotinib and before initiation of study drug.

There is probably a sensitive clone that remains. Continuing EGFR-TKI or re-introduction of EGFR-TKI is reasonable, but not THE standard of care.


Current Treatment Options
- Continue TKI
- Continue TKI and add chemotherapy
- MET Inhibitors (trials)
- Stop TKI and use chemotherapy
- Irreversible TKI (trial)
- Clinical trials

Identification of the Transforming EML4-ALK Fusion Gene in NSCLC
- Screened cDNA library derived from tumor
- Fusion results from a small inversion within chromosome 2p
- N-terminal half of EML4 is fused to intracellular kinase domain of ALK

Clinical and Demographic Features of Patients With ALK-positive NSCLC

<table>
<thead>
<tr>
<th></th>
<th>N=149</th>
<th>N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>52 (21–86)</td>
<td>52 (29-82)</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>49/51</td>
<td>47/53</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White 95 (64)</td>
<td>87 (64)</td>
</tr>
<tr>
<td></td>
<td>Asian 41 (28)</td>
<td>43 (32)</td>
</tr>
<tr>
<td></td>
<td>Others 13 (9)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>Former smoker 42 (29)</td>
<td>39 (29)</td>
</tr>
<tr>
<td></td>
<td>Current smoker 5 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td>Adenocarcinoma 144 (97)</td>
<td>136 (99)</td>
</tr>
<tr>
<td></td>
<td>Squamous 2 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Other 3 (2)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Prior treatment regimens, n (%)</td>
<td>0 24 (16)</td>
<td>24 (18)</td>
</tr>
<tr>
<td></td>
<td>1 47 (33)</td>
<td>47 (33)</td>
</tr>
<tr>
<td></td>
<td>2 31 (21)</td>
<td>21 (15)</td>
</tr>
<tr>
<td></td>
<td>≥3 47 (41)</td>
<td>47 (41)</td>
</tr>
</tbody>
</table>


Tumor Responses to Crizotinib in 82 Patients With ALK-positive NSCLC

- Progressive disease
- Stable disease
- Confirmed partial response
- Confirmed complete response

Confirmed ORR: 57% (63% if 5 as yet unconfirmed PRs included)
8-week DCR: 87%

*Partial-response patients with 100% change have non-target disease present.

PFS by Independent Radiologic Review (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (n=173)</th>
<th>PEM/DOC (n=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>100 (58)</td>
<td>127 (73)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>7.7</td>
<td>3.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.49 (0.37 to 0.64)</td>
<td></td>
</tr>
</tbody>
</table>

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (n=173)</th>
<th>PEM/DOC (n=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>49 (28)</td>
<td>47 (27)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>23.3</td>
<td>22.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.02 (0.68 to 1.54)</td>
<td></td>
</tr>
</tbody>
</table>

Common AEs of Any Cause in ≥25% of Patients

<table>
<thead>
<tr>
<th>AE</th>
<th>Crizotinib (n=172)</th>
<th>Chemotherapy (n=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual disturbance</td>
<td>103 (60)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>103 (60)</td>
<td>33 (19)</td>
</tr>
<tr>
<td>Nausea</td>
<td>94 (55)</td>
<td>64 (37)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>80 (47)</td>
<td>30 (18)</td>
</tr>
<tr>
<td>Constipation</td>
<td>73 (42)</td>
<td>39 (23)</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>66 (38)</td>
<td>25 (15)</td>
</tr>
<tr>
<td>Edema</td>
<td>54 (31)</td>
<td>27 (16)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>44 (26)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>46 (27)</td>
<td>57 (33)</td>
</tr>
</tbody>
</table>

*Clustered term; bantiemetic use significantly higher in chemotherapy arm compared with crizotinib arm (67% vs 20%); patients in chemotherapy arm also received more dexamethasone (94% vs 25%); cincludes febrile neutropenia, reported in 1 patient treated with crizotinib and 16 patients treated with chemotherapy.

Grade 3/4 AEs of Any Cause in >5% of Patients

<table>
<thead>
<tr>
<th>AE</th>
<th>Crizotinib (n=172)</th>
<th>Chemotherapy (n=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated transaminases</td>
<td>27 (16)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>23 (13)</td>
<td>33 (19)</td>
</tr>
</tbody>
</table>

*Defined as treatment duration significantly higher in chemotherapy arm compared with crizotinib arm (67% vs 20%); patients in chemotherapy arm also received more dexamethasone (94% vs 25%)

Resistance to Crizotinib

- Resistance can occur through
  - Secondary ALK Mutations
  - ALK gene copy number gain
  - Activation of alternative pathways including EGFR, c-Kit, KRAS
  - Multiple mechanisms may be present in the same patient's cancer

- Possible options
  - Isolated progression: RT and continue crizotinib
  - Novel ALK inhibitors (LDK378, AP26113, CH5424802)

Marked Activity of LDK378 in Patients With Advanced ALK+ NSCLC

- Best % change from baseline in target lesions
  - LDK378 400–750 mg/day
  - Prior crizotinib
  - Crizotinib-naive

- Patients with at least 1 post-baseline assessment of target lesions (investigator assessment)

Conclusions

• LDK378 exhibits potent antitumor activity in ALK+ NSCLC at doses of 400-750 mg/day
  – ORR 57% in crizotinib-treated patients
  – ORR 60% in crizotinib-naïve patients
  – Median PFS 8.6 months
• LDK378 has activity in the CNS
• The most common adverse events were nausea, diarrhea, vomiting, and fatigue; and most were Grade 1 or 2
• LDK378 induces responses in a majority of crizotinib-treated patients, including patients who have not acquired a new ALK mutation or amplification
• Several other ALK inhibitors also had promising data at ASCO 2013 including: AP26113, CH5424802

Clinical Results: HSP90 Inhibition in ALK+ NSCLC

Simulated waterfall plot based on reported results


Immunotherapy Review

Ipilimumab: Background

- Anti-CTLA4
- Evidence of activity in a broad range of tumors, including:
  - Melanoma: first-line, second-line, and adjuvant therapy
  - Treated melanoma 3.6 mo med OS benefit (P < .001)²³
  - Prostate, lung, renal pancreatic, NHL, and others⁴⁻⁶
- Safety profile in melanoma is well-characterized and mechanism-based.
  - The key drug-related side effects are immune-related
    - Skin rash, diarrhea, endocrine dysfunction, transaminitis


Ipilimumab in NSCLC: Randomized Phase 2 Study Design

Chemo: Paclitaxel (175 mg/m²)/Carboplatin (AUC=6) IV
C: chemotherapy doublet
IPI: Ipilimumab (10 mg IV)
p: Placebo

Note: Steroids were given as premedication with paclitaxel.

Ipilimumab and Chemotherapy in NSCLC: Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Control</th>
<th>Concurrent</th>
<th>Phased</th>
</tr>
</thead>
<tbody>
<tr>
<td>mWHO-BORR</td>
<td>14%</td>
<td>21%</td>
<td>32%</td>
</tr>
<tr>
<td>mWHO-DCR</td>
<td>73%</td>
<td>57%</td>
<td>78%</td>
</tr>
<tr>
<td>ir – BORR</td>
<td>18%</td>
<td>21%</td>
<td>32%</td>
</tr>
<tr>
<td>ir – DCR</td>
<td>82%</td>
<td>70%</td>
<td>87%</td>
</tr>
</tbody>
</table>

PFS

<table>
<thead>
<tr>
<th></th>
<th>Concurrent</th>
<th>Phased</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>P &lt; .03</td>
<td>HR = 0.61, P = .05</td>
</tr>
</tbody>
</table>

mWHO – increase in index lesion by ≥25% or any new lesion, or a progression of non-index lesions were considered mWHO progression
ir-RC – new lesions added to index lesions (not counted as PD), changes in non-index lesions not counted, >25% growth for PD


BORR = best overall response rate
DCR = disease control rate
PD-1 and CTLA-4 Play Distinct Roles in Regulating T-Cell Immunity

• CTLA-4 modulates the early phases of activation of naïve or memory T cells in response to TCR stimulation by MHC-peptide complexes displayed by antigen presenting cells.

• In contrast, PD-1 is expressed on antigen-experienced T cells in the periphery and serves to limit the activity of T cells at the time of an inflammatory response, thereby protecting normal tissues from collateral destruction.


Nivolumab (MDX-1106/ONO-4538)

• Fully human IgG4 anti-human PD-1 blocking Ab

• PD-1 expression on tumor infiltrating lymphocytes (TILs) in NSCLC has shown:
  – Decreased cytokine production and decreased effector function

• PD-L1 expression noted in NSCLC


Study Design: Phase 1 Multi-dose Regimen

Day 1 15 29 43 57
8-week treatment cycle

Rapid PD or clin. deterioration

Unacceptable toxicity

CR/PR/SD or PD but clinically stable

Follow-up every 8 wks x 6 (48 wks)

SCANS CR/PR/SD or PD but clinically stable

Treat to confirmed CR, worsening PD, unacceptable toxicity, or 12 cycles (96 wks)

Day 1       15         29        43       57
8-week treatment cycle

Rapid PD or clin. deterioration

Unacceptable toxicity

CR/PR/SD or PD but clinically stable

Follow-up every 8 wks x 6 (48 wks)

SCANS CR/PR/SD or PD but clinically stable

Treat to confirmed CR, worsening PD, unacceptable toxicity, or 12 cycles (96 wks)

Eligibility: Advanced MEL, RCC, NSCLC, CRC, or CRPC with PD after 1-5 systemic therapies

* Dose administered IV q 2weeks

Doses tested for NSCLC: 1, 3, 10 mg/kg

Summary of Key Safety Results

- In NSCLC patients (122 evaluable for safety):
  - All grade AE: 64% vs 70% in total population
  - Grade 3-4 related AEs occurred in 8% of patients
  - Fatigue, pneumonitis, AST (2 patients each)
  - Grade 1-2 pneumonitis was noted in 4 (3%) patients
  - Drug-related deaths (2) occurred in NSCLC patients with pneumonitis

Clinical Activity by Histology, Efficacy Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nivolumab Dose, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>ORR, No. patients* (%)</td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>0</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>0 (n=5)</td>
</tr>
<tr>
<td>SD ≥24 weeks, No. patients (%)</td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>0</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>1 (8)</td>
</tr>
<tr>
<td>PFSR at 24 weeks, (%)</td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>0 (n=5)</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>14 (n=6)</td>
</tr>
</tbody>
</table>

*1 patient of unknown histology who received 1 mg/kg had an OR.
3 Patients with fatal pneumonitis; diarrhea, rash, pruritis, also immune AEs.

Response of Metastatic NSCLC
(Nivolumab, 10 mg/kg)

- Initial progression in pulmonary lesions of a NSCLC patient with non-squamous histology was followed by regression
- Dx '04, EGFR mutation +; Rx Gem/carbo, erlotinib, erlotinib + LBH589 (trial for T790 mutation), and lastly pemetrexed

OS for Patients With NSCLC Treated With Nivolumab Monotherapy

Correlation of PD-L1 Expression in Pretreatment Tumor Biopsies With Clinical Outcomes

Summary: Anti-PD1 mAb (Nivolumab)

- Side effects similar to other immunotherapies and include severe pneumonitis
- Durable responses seen in NSCLC that compare favorably to chemotherapy 2nd line and beyond
- PD-L1 IHC may be a useful biomarker of response
- Favorable results in squamous histology tumors
- 2nd line trials vs docetaxel in development for squamous and non-squamous NSCLC
MPDL3280A Anti-PD-L1 Antibody Phase Ia: Efficacy Summary  
Investigator Assessed

<table>
<thead>
<tr>
<th></th>
<th>RECIST 1.1 Response Rate (ORR*)</th>
<th>SD of 24 Weeks or Longer</th>
<th>24-Week PFS Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>21%</td>
<td>16%</td>
<td>45%</td>
</tr>
<tr>
<td>NSCLC (n = 41)</td>
<td>22%</td>
<td>12%</td>
<td>46%</td>
</tr>
<tr>
<td>Non-squamous (n = 31)</td>
<td>19%</td>
<td>13%</td>
<td>44%</td>
</tr>
<tr>
<td>Squamous (n = 9)</td>
<td>23%</td>
<td>11%</td>
<td>44%</td>
</tr>
</tbody>
</table>

1 patient had an undetermined histology status.

All responders continued to respond at last assessment.

* ORR includes investigator-assessed unconfirmed and confirmed PR.

4 patients that did not have a post-baseline scan were included as non-responders.

Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013.


Emerging Novel Agents

Ganetespib

- Ganetespib is a novel, second-generation Hsp90 inhibitor
- Active as monotherapy in ALK+, mut BRAF NSCLC
- Tolerated well both as monotherapy and in combination with docetaxel
- Associated with substantially less visual impairment (<3%) as compared to other 2nd-gen Hsp90 inhibitors (>50%)
Docetaxel + Ganetespib

Stage 1: Phase 2b

Choice of patient population

Docetaxel: 75 mg/m² (d1 Q3W); Ganetespib: 150 mg/m² (d1,15 Q3W)

Stage 2: Phase 3

N=500

Eligibility criteria

- Stage IIIB/IV NSCLC
- ECOG 0, 1
- 1 prior Rx advanced setting
- Measurable disease
- Documented PD
- Clinically stable CNS metastases
- Available tumor tissues
- Adequate organ function

Statistical assumptions

- Co-primary: 90% power PFS 6→12 wks (median LDH pts); 5→10 wks (KRAS pts)
- Key secondary: all adenocarcinoma pts; 85% power PFS 3→4.5 mo; 75% power OS 6→8.5 mo
- 1-sided alpha of 0.05

Galaxy1: RPhII of Docetaxel +/- Ganetespib: OS Diagnosis of Advanced Disease >6 m Population

- HR=0.61 (95% CI: 0.43, 0.87), p=0.0093
- Cox regression: HR=0.55 (90% CI: 0.38, 0.79), p=0.0036

Selumetinib: A MEK Inhibitor

- Selumetinib (AZD6244, ARRY-142886) is a potent and selective allosteric inhibitor of MEK 1/2
- Tendency for greater sensitivity to selumetinib in BRAF/RAS mutant cell lines
Selumetinib: Phase 2, Double-blind, Randomized, Placebo-controlled, Multi-center Trial; NCT00890825

**Patients**
- Locally advanced or metastatic NSCLC (stage IIIB-IV)
- Failed first line therapy
- Confirmed KRAS mutant tumor
- WHO PS 0-1
- Excluding asymptomatic brain metastases

**Endpoints**
- **Primary**
  - OS
- **Secondary**
  - PFS
  - ORR
  - Duration of response
  - Change in tumor size
  - Alive and progression-free at 6 months
  - Safety and tolerability

Selumetinib 75 mg BID + docetaxel 75 mg/m^2

**Randomization (1:1 ratio)**

- Placebo BID + docetaxel 75 mg/m^2

**Randomization**

- Patients
  - Locally advanced or metastatic NSCLC (stage IIIB-IV)
  - Failed first-line therapy
  - Confirmed KRAS mutant tumor
  - WHO PS 0-1
  - Excluding asymptomatic brain metastases

- Docetaxel was administered every 21 days; selumetinib/placebo administered daily.
- Following completion of patient enrollment, the primary endpoint was changed from PFS to OS, without changing the sample size.
- OS analysis was planned for after approximately 58 events; HR 0.57, 80% power assuming a 1-sided 10% significance level.

**Selumetinib: OS**

<table>
<thead>
<tr>
<th>Median OS</th>
<th>Selumetinib/docetaxel (n=43)</th>
<th>Placebo/docetaxel (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.4 mo</td>
<td>5.2 mo</td>
<td></td>
</tr>
<tr>
<td>HR 0.80</td>
<td>80% CI 0.56, 1.14</td>
<td></td>
</tr>
<tr>
<td>P = .2069*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Numerical increase in OS (median follow-up 7.2 mo); hazards non-proportional.
  - 56/83 deaths (67% maturity): selumetinib/docetaxel 29/43, placebo/docetaxel 27/40.

**Selumetinib: PFS**

<table>
<thead>
<tr>
<th>Median PFS</th>
<th>Selumetinib/docetaxel (n=43)</th>
<th>Placebo/docetaxel (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3 mo</td>
<td>2.1 mo</td>
<td></td>
</tr>
<tr>
<td>HR 0.58</td>
<td>80% CI 0.42, 0.79</td>
<td></td>
</tr>
<tr>
<td>P = .0138*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Statistically and clinically significant improvement in PFS.
  - 71/83 events (85.5%): selumetinib/docetaxel 35/43, placebo/docetaxel 36/40.

Selumetinib: Safety Profile

<table>
<thead>
<tr>
<th></th>
<th>Selumetinib + docetaxel</th>
<th>Placebo + docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE*</td>
<td>26 (56.1)</td>
<td>13 (31.6)</td>
</tr>
<tr>
<td>AE leading to death**</td>
<td>4 (9.1)</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>AE leading to...</td>
<td>21 (47.7)</td>
<td>8 (18.1)</td>
</tr>
<tr>
<td>AE leading to...</td>
<td>6 (13.6)</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>AE leading to...</td>
<td>15 (34.1)</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to...</td>
<td>20 (46.5)</td>
<td>4 (9.5)</td>
</tr>
</tbody>
</table>


ROS1 Rearrangements in NSCLC

- Present in ~1% of NSCLC cases (also found in some GBMs and cholangiocarcinomas)
- Enriched in younger never or light smokers with adenocarcinoma histology
- No overlap with other oncogenic drivers


Summary of Tumor Responses in Patients With Advanced ROS1+ NSCLC (N=14)

Lung Adenocarcinoma: Molecular Drivers

Conclusions

• New testing guidelines
• New therapy targets
• Emerging treatments

Click on the Question Bank tab to hear responses to questions asked during live sessions.
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