Targeting new (and old) driver oncogenes in lung adenocarcinoma

Naiyer Rizvi, MD
Lung Adenocarcinomas

- KRAS mutation
- EGFR mutation
- 35% Unknown
- BRAF mutation
- ALK rearrangement
- MEK mutation
- PIK3CA mutation
- HER2 mutation
- ROS1 fusion
- RET fusion
- MET amplification
Timeline for the discovery of significant molecular alterations in lung cancer.

1. Farnesylcysteine mimetic: prevents RAS attachment to the membrane
2. HSP90 inhibitors
3. Target downstream effectors of RAS (PI3K, MEK, MTOR)
Ridaforolimus in KRAS Mutant Lung Cancers

Patients with:
Stage IIIB/IV NSCLC
KRAS mutation
2 prior regimens
ECOG PS 0-2

- PR: Continue ridaforolimus
- SD: ridaforolimus
- PD: placebo

Primary Objective:
PFS of randomized patients

Secondary Objectives:
OS in the randomized population
Overall RR, PFS, survival
Safety profile

Riely et al ASCO 2012
Ridaforolimus in *KRAS* Mutant Lung Cancers

Overall survival 18 months versus 5 months (n=28)

- Complete Response: 0/79 (0%)
- Partial Response: 1/79 (1%)
- Stable Disease: 36/79 (46%)
- Progressive Disease*: 42/79 (53%)

*Riely et al ASCO 2012*
Selumetinib

- Selumetinib (AZD6244, ARRY-142886) is a potent and selective allosteric inhibitor of MEK 1/2\(^1\)
- Tendency for greater sensitivity to selumetinib in BRAF/RAS-mutant cell lines\(^2\)

Docetaxel +/- Selumetinib in KRAS Mutant Lung Cancers

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

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

- 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

Janne et al ASCO 2012
Response Rate
docetaxel +/- selumetinib

<table>
<thead>
<tr>
<th></th>
<th>Selumetinib + docetaxel (n=43)</th>
<th>Placebo + docetaxel (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best objective response (RECIST 1.0), number (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>16 (37.2)*</td>
<td>0§</td>
</tr>
<tr>
<td>SD ≥6 weeks</td>
<td>19 (44.2)</td>
<td>20 (50.0)</td>
</tr>
<tr>
<td>PD</td>
<td>8 (18.6)</td>
<td>18 (45.0)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>0</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Median DoR, days</td>
<td>182</td>
<td>-</td>
</tr>
</tbody>
</table>

*11 confirmed, 5 unconfirmed
§One patient was classed as non-evaluable due to non-evaluable non-target lesions and would have had a partial response according to RECIST 1.1 criteria

†Fisher's exact 2-sided mid p value

Janne et al ASCO 2012
Overall survival
docetaxel +/- selumetinib

There was a 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

Janne et al ASCO 2012
There was a statistically and clinically significant improvement in PFS:
- 71/83 events (85.5%): selumetinib + docetaxel 35/43, placebo + docetaxel 36/40

Janne et al ASCO 2012
Summary

- First prospective study to demonstrate clinical benefit for patients with \textit{KRAS}-mutant NSCLC
- Selumetinib 75 mg BID combined with docetaxel 75 mg/m\textsuperscript{2} provided significant improvements in all secondary endpoints (PFS, RR, change in tumor size and APF6); numerical, but not significant, increase in OS (hazards were non-proportional)
- Tolerability findings were as expected based on monotherapy tolerability profiles of selumetinib and docetaxel
  - Toxicity was typically increased with the addition of selumetinib, but some disease-related AEs were improved
- Further investigation of selumetinib combined with docetaxel and other chemotherapies in \textit{KRAS}-mutant NSCLC is required
  - Clinical activity of the combination could also be affected by dosing order\textsuperscript{1} and concurrent tumor suppressor loss\textsuperscript{2} (eg LKB1 and p53)

Combined PI3K and MEK inhibition shrinks KRAS G12D induced lung tumors

An Open-Label, Phase Ib Dose Escalation Trial of Oral Combination Therapy with MSC1936369B and SAR245409 in Subjects with Locally Advanced or Metastatic Solid Tumors
MEK inhibitor GDC-0973 and the PI3K inhibitor GDC-0941

LoRusso et al
ASCO 2012
ROS1

• ROS1 is a receptor tyrosine kinase of the insulin receptor family.

• Chromosomal rearrangements involving the ROS1 gene were originally described in glioblastomas, where ROS1 (chromosome 6q22) is fused to the FIG gene and have been shown to be transforming in transgenic mice.

• More recently, ROS1 fusions were identified as potential driver mutations in an NSCLC cell line (HCC78; SLC34A2-ROS1) and an NSCLC patient sample (CD74-ROS1) (Rikova et al: Cell 131:1190-1203, 2007).
Crizotinib also inhibits ROS1

Adapted from Bergethon, Shaw, Ou et al., JCO 30(8): 863-70, 2012
ROS1

- Using a ROS1 FISH assay, 1,073 patients with NSCLC were screened for ROS1 and ALK.
- Of 1,073 tumors screened, 18 (1.7%) were ROS1 rearranged by FISH, and 31 (2.9%) were ALK rearranged.
- Compared with the ROS1-negative group, patients with ROS1 rearrangements were significantly younger and more likely to be never-smokers (each P < .001).
- 14/18 (78%) ROS1-positive cases were never smokers.
- All of the ROS1-positive tumors were adenocarcinomas, with a tendency toward higher grade.
- ROS1-positive and -negative groups showed no difference in overall survival.

Bergethon JCO 2012
A ROS1-positive patient treated with crizotinib showed tumor shrinkage, with a near complete response.
**Summary of Tumor Responses in Patients with Advanced ROS1+ NSCLC (N=14*)**

<table>
<thead>
<tr>
<th>Decrease or Increase From Baseline (%)</th>
<th>PD</th>
<th>SD</th>
<th>PR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>-100</td>
<td>15+</td>
<td>16+</td>
<td>18+</td>
<td>8+</td>
</tr>
<tr>
<td>-80</td>
<td>4+</td>
<td>12+</td>
<td>22+</td>
<td>44+</td>
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<tr>
<td>-60</td>
<td>18+</td>
<td>18+</td>
<td>18+</td>
<td>44+</td>
</tr>
<tr>
<td>-40</td>
<td>20+</td>
<td>35+</td>
<td>48+</td>
<td></td>
</tr>
<tr>
<td>-20</td>
<td>20+</td>
<td>35+</td>
<td>48+</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>57%</td>
<td></td>
<td></td>
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</table>

Response Rate: 57%

Shaw et al ASCO 2012
Crizotinib in ROS1 Lung Cancers

• Crizotinib demonstrates preliminary efficacy in this subtype of lung cancer
• Routine identification of these patients will be necessary for completion of the clinical evaluation
Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies


KIF5B-RET fusions in lung adenocarcinoma

Takashi Kohno, Hitoshi Ichikawa, Yasushi Totoki, Kazuki Yasuda, Masaki Hiramoto, Takao Nammo, Hiromi Sakamoto, Koji Tsuta, Koh Furuta, Yoko Shimada, Reika Iwakawa, Hideaki Ogiwara, Takahiro Oike, Masato Enari, Aaron J Schetter, Hirokazu Okayama, Aage Haugen, Vidar Skaug, Suenori Chiku, Itaru Yamanaka, Yasuhito Arai, Shun-ichi Watanabe, Ikuo Sekine, Seishi Ogawa, Curtis C Harris, Hitoshi Tsuda, Teruhiko Yoshida, Jun Yokota & Tatsuhiro Shibata

RET, ROS1 and ALK fusions in lung cancer

Kengo Takeuchi, Manabu Soda, Yuki Togashi, Ritsuro Suzuki, Seiji Sakata, Satoko Hatano, Reimi Asaka, Wakako Hamanaka, Hironori Ninomiya, Hirofumi Uehara, Young Lim Choi, Yukitoshi Satoh, Sakae Okumura, Ken Nakagawa, Hiroyuki Mano & Yuichi Ishikawa
<table>
<thead>
<tr>
<th>RET fusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/561 (2%)</td>
<td>Lipson et al</td>
</tr>
<tr>
<td>10/159 (6%) in driver negative patients</td>
<td>Lipson et al</td>
</tr>
<tr>
<td>14/1116 (1.3%)</td>
<td>Takeuchi et al</td>
</tr>
<tr>
<td>6/319 Japanese (1.9%)</td>
<td>Kohno et al</td>
</tr>
<tr>
<td>1/80 U.S (1.3%)</td>
<td>Kohno et al</td>
</tr>
<tr>
<td>4/28 (U.S.) (14%) in driver negative never smokers</td>
<td>Drilon, Rizvi et al (unpublished)</td>
</tr>
</tbody>
</table>
(f) Ba/F3 cells with the KIF5B-REF fusion were treated with different drugs at the indicated concentrations, and viable cells were measured after 72 h of treatment and plotted relative to untreated controls. (g) Cells treated with increasing concentrations of sunitinib or gefitinib for 6 h, and immunoblotting was used to detect the indicated proteins.
RET

- Mutually exclusive driver oncogenes
- Frequency of 1-2% of population
- RET noted in 6% of “known negative” ADC in one trial
- More frequent in never smoker population
- Druggable target
- XL184 phase 2 trial
Accelerating Drug Development

- EGFR TKIs approved
- EGFR mutation discovery
- EGFR-Mt enriched phase II studies reported

2003 2004 2006

- first Crizotinib trial
- EML4/ALK discovered
- expansion cohort for EML4/ALK

2005 2007

- Crizotinib approved

2011

- RET fusions Reported (Ju et al)
- MSK IRB approved RET-enriched protocol
- first RET fusion patient treated at MSK

11-2011 7-2012
MSKCC lung adenocarcinoma targeted trials (excluding EGFR/ALK)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Status</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>KRAS</td>
<td>30%</td>
<td>IPI-504 + everolimus</td>
</tr>
<tr>
<td>AKT</td>
<td>&lt;1%</td>
<td>BKM120/MEK</td>
</tr>
<tr>
<td>MEK1</td>
<td>1%</td>
<td>MSC1936369B + SAR245409</td>
</tr>
<tr>
<td>PI3K</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>NRAS</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>BRAF</td>
<td>1-3%</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>HER2</td>
<td>2-5%</td>
<td>Dacomitinib</td>
</tr>
<tr>
<td>RET</td>
<td>1%</td>
<td>Cabozantinib</td>
</tr>
<tr>
<td>ROS1</td>
<td>1%</td>
<td>Crizotinib</td>
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