Beyond EGFR and ALK: Targeting ROS1, RET, and BRAF in Advanced Lung Cancers

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833 tumor samples from patients with lung adenocarcinoma sequenced on MSK-IMPACT™

**FDA-approved therapies**
- EGFR mutations: erlotinib, gefitinib, afatinib, osimertinib
- ALK fusions: crizotinib, alectinib, ceritinib
- ROS1 fusions: crizotinib

Refer to:
- NCCN Guidelines Version 2.2017 Non-Small Cell Lung Cancer
- Emerging targeted agents for patients with genetic alterations

• Recurrent gene rearrangements
  – $ROS_1$ rearrangements
  – $RET$ rearrangements

• Mutations
  – $BRAF^{V600E}$
ROS₁-Rearranged Lung Cancers
**ROS1-rearranged lung cancers**

- **ROS1 rearrangements**
  - Late 1980s: identified in GBM
  - 2007: identified in NSCLC
    - HCC78 cell line (SCL34A2-ROS1)
    - tumor biopsy (CD74-ROS1)
  - Multiple partners:
    - *TPM3*-ROS1 t(1;6)
    - *SDC4*-ROS1 t(6;20)
    - *SLC34A2*-ROS1 t(4;6)
    - *CD74*-ROS1 t(5;6)
    - *EZR*-ROS1 inv(6)
    - *LRIG3*-ROS1 t(6;12)

Rikova et al, Cell 2007; Bergethon et al JCO 2012
**ROS1-rearranged lung cancers**

- **ROS1-rearranged lung cancers**
  - 1-2% of NSCLCs
  - young never or former light smokers
  - Adenocarcinomas

- **Diagnosis**
  - IHC
  - FISH
  - DNA-based NGS
  - RNA sequencing
  - Plasma assays

Bergethon et al JCO 2012; Rimkunas et al CCR 2012; FISH image courtesy of Lu Wang, MSKCC
Crizotinib in ROS1-rearranged lung cancers

Shaw et al. NEJM 2014

Multicenter phase 1 expansion cohort
Crizotinib 250 mg twice daily
Primary endpoint: overall response

overall response 72% [95% CI 58-84]
33 responses in 50 ROS1-rearranged patients

Shaw et al. NEJM 2014
Crizotinib in \textit{ROS1}-rearranged lung cancers

\textbf{Median DoR 17.6 mos} [95\% CI 14.5-NR]

\textbf{Median PFS 19.2 mos} [95\% CI 14.4-NR]

\textbf{See First-line therapy options}
\textit{Adenocarcinoma (NSCL-24)}
\textit{Squamous cell carcinoma (NSCL-25)}
or
\textit{PD-L1 expression positive (\geq 25\%)}
\textbf{See First-Line Therapy (NSCL-23)}

\textbf{Shaw et al NEJM 2014 ; NCCN Guidelines NSCLC Version 2.2017, 10/26/16}
Ceritinib in *ROS1*-rearranged lung cancers

Korean phase 2 trial
Ceritinib 750 mg daily

Primary endpoint: overall response

<table>
<thead>
<tr>
<th></th>
<th>All (n=32)</th>
<th>Crizotinib-naïve (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>67%</td>
<td>62%</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Median PFS</td>
<td>10 months</td>
<td>20.7 months</td>
</tr>
<tr>
<td></td>
<td>(95% CI 2.5-17.4)</td>
<td>(95% CI 4.7-NR)</td>
</tr>
<tr>
<td>Median DoR</td>
<td>18.4 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI 8.0-18.4)</td>
<td></td>
</tr>
<tr>
<td>Intracranial response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CR/PR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 of 5 evaluable patients with brain metastases at baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cabozantinib in $ROS_1$-rearranged lung cancers

ALK inhibition does not always equate to $ROS_1$ inhibitor

Drilon et al, Clin Cancer Res 2015; Davare et al PNAS 2015
• \textit{ROS1} rearrangements
  – Actionable drivers that can be identified in the clinic
  – Crizotinib is FDA-approved
  – Acquired resistance to crizotinib can be mediated by the acquisition of \textit{ROS1} mutations
  – Other active drugs: ceritinib, cabozantinib, lorlatinib
    • not all ALK inhibitors are \textit{ROS1} inhibitors!!
RET-Rearranged Lung Cancers
**RET-rearranged lung cancers**

- **RET rearrangements**
  - Papillary thyroid CAs
  - 2011: identified in NSCLCs
  - Multiple partners:
    - KIF5B-RET
    - CCDC6-RET
    - NCOA4-RET
    - TRIM33-RET
    - KIAA1468-RET
    - CUX1-RET

- **Diagnosis**
  - FISH, DNA-based NGS, RNA sequencing, Plasma assays (IHC - not useful)

RET-rearranged lung cancers

- **Incidence**
  - 1-2% in unselected NSCLCs
  - mutually exclusive with other major lung cancer drivers

- **Clinical Features**
  - common in young (≤60 years), never/former light smokers with lung adenocarcinomas

- **Pathologic Features**
  - described largely in lung adenocarcinomas
    - solid subtype in ~2/3 of cases
    - >10% signet ring cells ~1/3 of cases

<table>
<thead>
<tr>
<th>RET Fusions</th>
<th>Never-Smokers Pan-Negative Lung AdenoCAs</th>
<th>Pan-Negative NSCLCs</th>
<th>Unselected NSCLCs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>95% CI [3-27%]</td>
<td>Lipson et al\textsuperscript{5} Nature 2012</td>
<td>Wang et al\textsuperscript{6} CCR 2012</td>
</tr>
<tr>
<td></td>
<td>n = 5/34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outcomes of RET-Rearranged Lung Cancers with Pemetrexed-Based Chemotherapy

<table>
<thead>
<tr>
<th>Patients</th>
<th>ORR (PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET-rearranged</td>
<td>45% (n = 5/11)</td>
</tr>
<tr>
<td>ROS1-rearranged</td>
<td>78% (n = 7/9)</td>
</tr>
<tr>
<td>ALK-rearranged</td>
<td>50% (n = 14/28)</td>
</tr>
<tr>
<td>KRAS-mutant</td>
<td>26% (n = 9/35)</td>
</tr>
</tbody>
</table>

**P value**: 0.02

- Durable clinical benefits were observed with pemetrexed-based chemotherapy in RET-rearranged lung cancers.

**RET-rearranged lung cancers**

- **RET Inhibitors**
  - all currently available drugs are multikinase inhibitors
  - cabozantinib
  - vandetanib
  - ponatinib
  - lenvatinib
  - sunitinib
  - sorafenib
  - alectinib

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET</td>
<td>1.8</td>
</tr>
<tr>
<td>VEGFR2</td>
<td>0.035</td>
</tr>
<tr>
<td>RET</td>
<td>5.2</td>
</tr>
<tr>
<td>KIT</td>
<td>4.6</td>
</tr>
<tr>
<td>AXL</td>
<td>7.0</td>
</tr>
<tr>
<td>TIE2</td>
<td>14</td>
</tr>
<tr>
<td>FLT3</td>
<td>14</td>
</tr>
</tbody>
</table>

Cabozantinib in \textit{RET}-rearranged lung cancers

\begin{tabular}{|c|c|}
\hline
\textbf{Best Response} & \textbf{\% (n)} \\
\hline
PR & 28\% (7/25) \\
SD & 72\% (18/25) \\
\textbf{ORR 28\%, 95\% CI 12–49} & \\
\hline
\end{tabular}

Median PFS 5.5 months
(95\% CI: 3.8 to 8.4)

Median DoR 4.7 months
(IQR 3.1–8.4)

Median OS 9.9 months
(95\% CI: 8.1 to NR)

Drilon et al. Lancet Oncology 2016

Memorial Sloan Kettering Cancer Center
**Global RET-Rearranged Lung Cancer Registry**

- **132 patients** with RET-rearranged lung cancer from Europe, the USA, and Asia were identified
  - **41 patients** were treated with single-agent RET TKI therapy outside the context of a clinical trial

### Best response* (n=35)

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
<th>Missing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Alectinib</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*unconfirmed and locally assessed by RECIST1.1

- **Rate of any response to therapy**
  - **Cabozantinib**: 31% (4/13)
  - **Vandetanib**: 18% (2/11)
  - **Sunitinib**: 22% (2/9)

Multikinase inhibitors in RET-rearranged lung cancers

Multicenter phase 2 trial
Primary endpoint: response
Lenvatinib ORR 16%

Korean phase 2 trial
Primary endpoint: response
Vandetanib ORR 18%

Japanese phase 2 trial
Primary endpoint: response
Vandetanib ORR 53%

## Multikinase inhibitors in RET-rearranged lung cancers

<table>
<thead>
<tr>
<th>Multikinase inhibitor with anti-RET activity</th>
<th>Dose Reduction Rate</th>
<th>HTN (any grade)</th>
<th>Rash (any grade)</th>
<th>Diarrhea (any grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>69%</td>
<td>16%</td>
<td>44% (PPE)</td>
<td>63%</td>
</tr>
<tr>
<td>Vandetanib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korean phase 2</td>
<td>22%</td>
<td>89%</td>
<td>72%</td>
<td>44%</td>
</tr>
<tr>
<td>Japanese phase 2</td>
<td>53%</td>
<td>84%</td>
<td>63%</td>
<td>79%</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>64%</td>
<td>68%</td>
<td>not reported</td>
<td>60%</td>
</tr>
</tbody>
</table>

• **RET rearrangements**
  - Actionable drivers that can be identified in the clinic
  - No FDA-approved therapies thus far
  - Active drugs: cabozantinib, vandetanib, lenvatinib, in addition to other multikinase inhibitors
    • Response rates comparable to other driver-positive lung cancers (i.e. *BRAF* V600E-mutant lung cancers)
    • Tolerability in the face of chronic dosing is an important concern
  - May require better drugs (i.e. RET-specific inhibitors) or combination therapy
BRAF V600E-Mutant Lung Cancers
**BRAF-Mutant Lung Cancers**

- **Incidence**
  - 1-4% of NSCLCs
  - 2% of lung adenocarcinomas

- **Features**
  - former/current smokers
    - *V600E*-mutant: more likely to be light/never smokers
  - mutually exclusive with other oncogenic drivers in most cases


**Lung Cancer Mutation Consortium**
(n = 733 lung adenocarcinomas)

**MSKCC**
(n=63 BRAF-mutant lung adenocarcinomas)
Prognosis

- V600E mutations confer improved survival (compared to non-V600E mutations)

Stage IIIB-IV (BRAF V600 vs. EGFR: p=0.25; BRAF V600 vs. KRAS: p=.12; EGFR vs. KRAS: p < 0.001)

Litvak and Riely, et al JTO 2014
Multicenter phase 2 basket study
Vemurafenib 960 mg twice daily
Primary endpoint: response at week 8

**overall response 42%** [95% CI 20-67]
8 PRs of 19 $BRAF_{V600E}$-mutant patients

Hyman, et al. NEJM 2016
Multicenter single-arm phase 2 study
Dabrafenib 150mg twice daily
Primary endpoint: overall response

**overall response 33% [95% CI 23–45]**
26 PRs of 78 BRAFV600E-mutant patients

Dabrafenib + Trametinib in *BRAF* V600E-Mutant Lung Cancers

Multicenter single-arm phase 2 study
Dabrafenib 150mg twice daily + Trametinib 2 mg daily
Primary endpoint: overall response

**overall response 63.2% [95% CI 49.3-75.6]**
36 PRs of 57 *BRAF* V600E-mutant patients

Dabrafenib+Trametinib in \textit{BRAFV600E}-Mutant Lung Cancers

Median PFS 9.7 months (95% CI 6.9–19.6)

Dabrafenib+Trametinib in *BRAF V600E*-Mutant Lung Cancers

Median duration of treatment 10.6 months (IQR 4.2–12.2 months)
# Targeted Therapy in *BRAF* V600E-Mutant Lung Cancers

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib</td>
<td>42% [95% CI 20-67]</td>
<td>7.3 months (95% CI 3.5-10.8)</td>
<td>Not reached</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>33% [95% CI 23-45]</td>
<td>5.5 months (95% CI 3.4-7.3)</td>
<td>12.7 months (95% CI 7.3-16.9)</td>
</tr>
<tr>
<td>Dabrafenib + Trametinib</td>
<td>63% [95% CI 49.3-75.6]</td>
<td>9.7 months (95% CI 6.9-19.6)</td>
<td>Not reached</td>
</tr>
</tbody>
</table>
Summary

• **BRAF mutations**
  – Actionable drivers that can be identified in the clinic
  
  – Active drugs for *BRAF V600E*: vemurafenib, dabrafenib, dabrafenib and trametinib
  
  – Dabrafenib + Trametinib with breakthrough designation by the FDA
• **Recurrent gene rearrangements**
  
  – *ROS1* rearrangements
    • Crizotinib, Ceritinib, Cabozantinib
  
  – *RET* rearrangements
    • Cabozantinib, Vandetanib, Lenvatinib

• **Mutations**
  
  – *BRAF V600E*
    • Vemurafenib, Dabrafenib, Dabrafenib + Trametinib