Targeting EGFR and ALK driven tumours

Invited Discussant for posters 59PD and 60PD
Rafael Rosell

Catalan Institute of Oncology, Badalona, Barcelona, Spain

Thursday, 04/14/2016, 02:45 - 04:00 PM, Room W
Association of *EGFR* mutation subtypes with clinical and demographic characteristics of patients with aNSCLC: IGNITE and ASSESS pooled analysis

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Previous meta-analyses show significant PFS prolongation in patients with exon 19 deletions, never smokers and women. *(Lee et al JCO 2015)*

Different pulmonary lobar locations depend on the type of *EGFR* mutations. L858R mutation are more common in women, never smokers and upper lobes. *(Tseng et al Carcinogenesis 2016)*
Lee et al JCO 2015
### Effect (EGFR mutation-positive patients / tumour-evaluable patients)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Description</th>
<th>OR</th>
<th>OR 95% CI</th>
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<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>ADC (1069/3156) vs non-ADC (101/1184)</td>
<td>3.919</td>
<td>3.082, 4.984</td>
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<tr>
<td><strong>Current disease stage</strong></td>
<td>IIIA (47/374) vs IV (1106/3456)</td>
<td>0.564</td>
<td>0.396, 0.805</td>
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<tr>
<td></td>
<td>IIIB (89/562) vs IV (1106/3456)</td>
<td>0.619</td>
<td>0.471, 0.813</td>
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<tr>
<td><strong>Ethnicity</strong></td>
<td>Asian (1015/2539) vs Caucasian (217/1823)</td>
<td>4.176</td>
<td>3.489, 4.998</td>
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<tr>
<td><strong>Gender</strong></td>
<td>Female (687/1484) vs male (555/2915)</td>
<td>1.603</td>
<td>1.311, 1.960</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td>Never-smoker (818/1597) vs ever-smoker (424/2802)</td>
<td>2.854</td>
<td>2.336, 3.485</td>
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</table>
ASSESS study
- Enrolled: n=1311 (Europe n=1011, Japan n=300)
- Tumour-evaluable: n=1184 (Europe n=903, Japan n=281)
  - EGFR mutation-positive\(^a\): n=191 (Europe n=105, Japan n=86)

IGNITE study
- Enrolled: n=3382 (Asia-Pacific n=2410, Russia n=972)
- Tumour-evaluable: n=3215 (Asia-Pacific n=2291, Russia n=924)
  - EGFR mutation-positive\(^a\): n=1051 (Asia-Pacific n=941, Russia n=110)

ASSESS and IGNITE pooled population
- Enrolled: n=4693
- Tumour-evaluable: n=4399
  - EGFR mutation-positive\(^a\): n=1242

EGFR mutation rate, 16% (191/1184)
Europe, 12% (105/903)
Japan, 31% (86/281)  
(Reck et al ELCC 2015)

42% (952/2249)
Asia-Pacific, 49% (862/1749)
Russia, 18% (90/500)  
(Han et al ELCC 2015)

Poster 59PD, Han et al (Nicola Normanno)
EGFR mutation testing was carried out in various sites with different methods.

ASSESS: EGFR mutational analysis was performed in 43 academic, hospital and commercial laboratories

IGNITE: EGFR mutational analysis was performed in 9 participating countries, also in academic, hospital and commercial laboratories

(Courtesy of Nicola Normanno)
• **EGFR mutations were more frequent in Stage IV.** The odds of having an *EGFR* positive tumour were reduced by 44% for Stage IIIA versus Stage IV (38% for Stage IIIB vs Stage IV)

• **Rare *EGFR* mutations (G719X, L861Q/P and exon 20 insertions) were more common in smokers** than never-smokers compared with L858R mutations / exon 19 deletions

• **Exon 20 insertions only detected in adenocarcinoma**

• **Caucasians, aged <65 years, or those with adenocarcinoma, more likely to harbor exon 19 deletions**

*Poster 59PD, Han et al (Nicola Normanno)*

ASSESS and IGNITE studies have paved the way for standard genotyping assessment in lung adenocarcinoma.
Inhibition of pEGFR in paired tumour biopsies from TKI treatment-naïve EGFR mutant NSCLC patients treated with gefitinib (EGFR inhibitor) or gefitinib in combination with durvalumab (anti-PD-L1)

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Only 1 other report was examined in PD-L1 expression in post-gefitinib EGFR mutant NSCLC, including 18 specimens. (Han et al Clinical Lung Cancer 2015)
1. How can we gauge early adaptive resistance to EGFR TKIs?
2. How often does early resistance occur?
3. Are early re-biopsies really necessary?
Impact of gefitinib on pEGFR expression at Day 10

The main goal was to demonstrate the inhibition of EGFR in clinical tumor samples.
Impact of gefitinib/durvalumab on pEGFR expression at Day 10

Can EGFR inhibition down-regulate PD-L1 expression, as has been shown in cell lines and animal models?

Poster  60PD, Yeh et al
Gefitinib treatment: all paired biopsies with baseline PD-L1 staining (5 in total) showed a decrease in PD-L1 staining (tumour membrane) after gefitinib treatment on Day 10 (left panel; patients 3 and 6 are superimposable); this is consistent with previously presented data\(^1\) for paired tumour biopsies (post-dose taken at Day 8 / Day 15) from patients treated with osimertinib (Tagrisso\(^{TM}\)), a third-generation EGFR inhibitor (middle panel).

Gefitinib / durvalumab treatment: only three paired biopsies were evaluable. No trend observed (right panel).

\(^1\)Poster 60PD, Yeh et al
11 sets of paired tumour biopsies (screen versus D10) were available for analysis: 3 from Arm 1 (gefitinib / durvalumab) and 8 from Arm 2 (gefitinib run-in). Seven pairs of biopsies were invaluable due to insufficient number of tumour cells in the on-treatment biopsies, consistent with the rapid decreases in tumour size observed.

Inhibition of pEGFR (Y1173) was observed in 9 of the 11 pairs, suggesting biological activity of gefitinib at the tumour site when dosed alone or in combination with durvalumab.

Inhibition of PD-L1 expression in tumour membrane cells by gefitinib was observed in all tumour pairs with adequate baseline expression.

Of 18 evaluable baseline tumour samples from both Arms, three were deemed PD-L1 ‘positive’ as defined by ≥25% tumour cells with membrane expression.

This study highlights the challenges in evaluating biological readouts when tumours rapidly respond in parallel. The third biopsy, when available, was not informative.
Why early re-biopsies in lung cancer?

An in depth look at re-wiring signaling pathways following single EGFR TKIs:

- Explanations and solutions can be found in EGFR mutant cell lines
- Biomarkers can accompany mutational analysis
Our working model (Rosell, Karachaliou, Chaib et al)
An in depth look at trends in lung cancer

- Benefit of monoclonal antibodies against PD-1 and PD-L1 is determined by baseline CD8+ T cell infiltration in the tumor microenvironment.
- The up-regulation of signal transduction and activation of transcription 3 (STAT3) occurs soon after EGFR TKI.
- STAT3 leads to the activation of DNMT1, dampening T cells in the tumor microenvironment.
- Liquid biopsy for cancer immunotherapy: PD-1 expression on circulating CD8+ T cells could serve as a biomarker.
- Circulating RTK levels (sheddase substrates), such as AXL, MET and others, predict resistance to MAPKi.