HER2 and lung cancer

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Molecular events in lung cancer
HER2 disregulation in lung cancer

**Overexpression**: <10%

**Amplification**: <10%

**Mutation**: <3%

**HER2 amplification is not prognostic in resected NSCLC**

Cappuzzo et al., JTO 2012
HER2 mutation seems not prognostic in NSCLC

The EGFR/HER Family

Arcila et al., Clin Cancer Res 2012
HER2 expression is not predictive for EGFR-TKI sensitivity

Fig 1. Time to progression and HER2 expression.

Cappuzzo et al., JCO 2003

HER2 increased gene copy number enhances sensitivity to EGFR-TKis

Cappuzzo et al., JCO 2005
HER2 amplification and resistance to EGFR-TKIs

High levels of HER2 amplification are responsible for acquired resistance to EGFR-TKIs in absence of T790M

Takezawa et al., Cancer Discovery 2012
HER2 increased gene copy number enhances sensitivity to cetuximab in colorectal cancer

High levels of HER2 amplification reduce sensitivity to cetuximab in colorectal cancer
High levels of HER2 amplification are responsible for acquired resistance to cetuximab in colorectal cancer

![Graph showing survival rates with and without HER2 amplification.](image)

**HER2 Mutations in NSCLC**

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Race</th>
<th>%</th>
<th>Never Smoker (%)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sasaki</td>
<td>95</td>
<td>Japan</td>
<td>1.0</td>
<td>2.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Marchetti</td>
<td>403</td>
<td>Caucasian</td>
<td>2.2</td>
<td>3.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Shigematsu</td>
<td>671</td>
<td>All</td>
<td>1.6</td>
<td>3.2</td>
<td>3.6</td>
</tr>
<tr>
<td>Stephens</td>
<td>120</td>
<td>Caucasian</td>
<td>4.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arcila</td>
<td>560</td>
<td>All</td>
<td>5.0*</td>
<td>5.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

* In EGFR and KRAS wild-type population
HER2 Mutant Cells are Resistant to Reversible EGFR-TKIs but still Sensitive to HER2 Inhibitors

Anti-HER2 Agents Active in HER2 Mutated

HER2 exon 20 mutation

Cappuzzo et al. NEJM 2006
Trastuzumab efficacy in pretreated NSCLC patients harboring HER2 mutation

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Therapy</th>
<th>Best Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vinorelbine-trastuzumab</td>
<td>Partial response</td>
</tr>
<tr>
<td>2</td>
<td>Carboplatin-paclitaxel-trastuzumab</td>
<td>Stable disease</td>
</tr>
<tr>
<td>3</td>
<td>Docetaxel-masitinib</td>
<td>Progression</td>
</tr>
<tr>
<td>4</td>
<td>Vinorelbine-trastuzumab</td>
<td>Partial response</td>
</tr>
<tr>
<td>5</td>
<td>Carboplatin-paclitaxel-trastuzumab</td>
<td>Partial response</td>
</tr>
<tr>
<td>6</td>
<td>Vinorelbine-trastuzumab</td>
<td>Partial response</td>
</tr>
<tr>
<td>7</td>
<td>Vinorelbine-trastuzumab</td>
<td>Stable disease</td>
</tr>
<tr>
<td>8</td>
<td>Lapatinib</td>
<td>Progression</td>
</tr>
<tr>
<td>9</td>
<td>Vinorelbine-trastuzumab</td>
<td>Partial response</td>
</tr>
<tr>
<td>10</td>
<td>Lapatinib</td>
<td>Progression</td>
</tr>
<tr>
<td>11</td>
<td>Vinorelbine-trastuzumab</td>
<td>Progression</td>
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<tr>
<td>12</td>
<td>Docetaxel-trastuzumab</td>
<td>Partial response</td>
</tr>
<tr>
<td>13</td>
<td>Vinorelbine-trastuzumab</td>
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<tr>
<td>14</td>
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<tr>
<td>15</td>
<td>Vinorelbine-trastuzumab</td>
<td>Stable disease</td>
</tr>
<tr>
<td>16</td>
<td>Trastuzumab</td>
<td>Partial response</td>
</tr>
</tbody>
</table>

Modified from Mazieres et al. ESMO 2012

Overall RR: 56.2%

Dacomitinib

- Pan – HER inhibition
  - No kinase activity
  - IC_{50} = 6.0 nmol/L
  - IC_{50} = 45.7 nmol/L
  - IC_{50} = 73.7 nmol/L

- Irreversible inhibition\(^1\)
  - Permanent blockade of catalytic activity
  - Non-competitive inhibition
  - Higher specificity and selectivity
  - Low intracellular levels capable of inhibiting TK activity

Inhibition of all kinase-active HER receptors offers potential for a more complete inhibition of HER signaling: receptor dimerization is key to HER-family signaling

\(^1\) In vitro kinase assay against WT receptor; ↑ [ATP] = high concentrations of ATP (e.g. intracellular concentrations)

\(^{1}\) Potential benefits – based on preclinical data

**Study 1017: Clinical Activity of Dacomitinib (PF-00299804) in First-Line Advanced NSCLC with an EGFR-activating Mutation**

**Cohort A:**
- Non- or former light-smoker  
- or  
- EGFR-mutation  
- (1st line)  
- n=89 (fully enrolled)

**Dacomitinib**  
45 mg QD  
(amended to 30 mg for selected patients)  
Until progression

**Optional biopsy on progression**

**Cohort B:**
- HER2 mutation or HER2 amplification  
- Target n=25 (still recruiting)

**Waterfall Plot for Patients with HER2-Mutant Lung Cancers (n=18)**

<table>
<thead>
<tr>
<th>Change from baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
</tr>
</tbody>
</table>

*Patient was treated for 55 days but was removed from treatment due to an edge recurrence of a previously treated brain metastasis
†Patient was treated for 28 days but discontinued due to an AE

Mok T, et al. LBA18 presentation at the 35th ESMO, 2010
Conclusions

- HER2 is overexpressed, amplified or mutated in a significant fraction of lung adenocarcinoma
- HER2 gene copy number affect sensitivity to anti-EGFR agents
- HER2 amplification is one of the mechanisms responsible for acquired resistance
- Combination of anti-EGFR and anti-HER2 agents should be considered
- Anti-HER2 agents and particularly monoclonal antibodies seems effective in thenHER2 mutant population