Prognostic effect of single versus multiple somatic mutations in non-small cell lung cancer (NSCLC)

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Background and Methods

• Prognostic role of single or multiple molecular mutations in early stage NSCLC still unclear
  – *P53*, *KRAS* (Tsao et al. 2007)
  – *KRAS* (Shepherd et al. 2013)
  – *KRAS, P53, EGFR* (Kosaka et al. 2009)

• Retrospective/Biomarker correlation study
  – Patients diagnosed with NSCLC from 1998-2014
  – Available tissue was analyzed with next-generation sequencing with either MiSeq/Proton or Sequenom
  – Mutation status was correlated with clinical and demographic data retrieved from electronic patient records
Mutations

Mutations Detected (Whole Cohort)

- P53 (152) 35%
- KRAS (92) 21%
- EGFR exon 19 or 21 (50) 12%
- EGFR other (24) 6%
- PIK3CA (16) 4%
- BRAF (12) 3%
- STK11 (11) 3%
- ERBB (11) 3%
- CTNNB1 (10) 2%

Common Co-Mutations

- p53 + non EGFR/KRAS mutation (34) 27%
- KRAS + p53 (33) 26%
- EGFR (ex 19/21)+ P53 (26) 12%
- KRAS + other mutations (15) 7%
- Two EGFR mutations (9) 5%
- EGFR (ex 19/21)+ other mutations (7) 3%
- Other concurrent mutations (4) 1%
Prognostic effect of Multiple Mutations in Stage I-III Resected NSCLC

P = 0.0008
HR 2.13, 95% CI 1.12-4.04, p = 0.021 (1 vs 0)
HR 3.07, 95% CI 1.62-5.81, p = 0.0006 (≥2 vs 0)

Adjusted HR:
(1 vs 0) 1.83, 95% CI: 0.96-3.51, p= 0.068
(≥2 vs 0) 2.26, 95% CI: 1.17-4.36, p = 0.015

P = 0.15
HR 2.22, 95% CI 0.87-5.65, p = 0.10 (1 vs 0)
HR 2.46, 95% CI 0.78-5.14, p = 0.06 (≥2 vs 0)
## Stage I-III resected subgroups

<table>
<thead>
<tr>
<th>Mutation</th>
<th>No. of patients</th>
<th>95% CI</th>
<th>Hazard Ratio</th>
<th>P-Value</th>
<th>95% CI</th>
<th>Hazard Ratio</th>
<th>P-value</th>
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<tbody>
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<tr>
<td>KRAS</td>
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<tr>
<td>Negative</td>
<td>157</td>
<td>1.05-2.13</td>
<td>1.49</td>
<td>0.025</td>
<td>1.11</td>
<td>0.68-1.82</td>
<td>0.67</td>
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<tr>
<td>Positive</td>
<td>56</td>
<td>1.05-2.13</td>
<td>1.49</td>
<td>0.025</td>
<td>1.11</td>
<td>0.68-1.82</td>
<td>0.67</td>
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<tr>
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<td>1.4-3.06</td>
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<td>0.0002</td>
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<tr>
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<td>107</td>
<td>0.97-1.85</td>
<td>1.34</td>
<td>0.08</td>
<td>1.3</td>
<td>3.34</td>
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<tr>
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<td>KRAS alone</td>
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<td>1.25-5.55</td>
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<td>KRAS + P53</td>
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<td>1.98-10.94</td>
<td>2.93</td>
<td>0.0004</td>
<td>0.94</td>
<td>8.47</td>
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<td>KRAS + other</td>
<td>11</td>
<td>1.3-6.58</td>
<td>4.65</td>
<td>0.009</td>
<td>0.19</td>
<td>5.31</td>
<td>0.99</td>
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</table>
Prognostic summary

• Mutational status is significantly prognostic in resected NSCLC
  – Multiple mutations are associated with worse outcomes compared to 0 vs 1 mutations on univariate and multivariate analysis
  – KRAS and EGFR status are associated with poorer DFS
  – P53 status is associated with poorer OS
    – *Additional data to be shown tomorrow morning*

• Larger datasets will be required for validation
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• Marguerite Ennis

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