What lessons can we learn from targeting cMET and IGFR in gastrointestinal cancers?

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Disclosure

• Advisory Board: Sanofi Oncology, Eli-Lilly, Bristol Meyers Squibb, Merck Serono, Gilead Science

• Research funding: Sanofi Oncology, Roche, Merck-Serono, Novartis

• Honorarium: Taiho, Pfizer, Amgen, Eli-Lilly, Bayer
IGF-1R and MET signalling pathways

IGF-1R

- Insulin
- Hetero- or homodimerization
- IGFR/INSR TKIs: Linletinib, others
- MTOR inhibitors: Ridaforolimus, Temsirolimus
- AKTI
- BAD
- MTOR
- Protein synthesis
- Blocked apoptosis
- Cellular proliferation
- Increased cell motility

MET

- Heparin Proteoglycans
- pro-HGF
- AMG102 Ficlatuzumab
- HGFA
- HGF (activated)
- Stromal/mesenchymal cell
- Epithelial/cancer cell
- Cabozantinib
- Crizotinib
- Foretinib
- MGCD265
- Tivantinib
- GRB2
- GAB1
- PI3K
- Raf
- Ras
- MEK
- ERK
- Akt
- FAK
- ROCK
- RHQ-bound
- SHC
- GRB2
- p110
- SOS
- RAS
- RAF
- MEK
- ERK
- Altered integrin expression
- Invasive/metastasis
- Survival
- Proliferation

Iams and Lovly Clin Cancer Res 2015;
Appleman et al J Clin Oncol 2011
## Similarities and differences of IGFR and MET targeted therapy

### Similarities
- Upstream of MAPK and PI3K-AKT-mTOR pathways
- Abundant preclinical data to support targeting these pathways
- Resistance mechanisms of existing therapy for GI cancers
- Multiple phase II and III trials conducted in many solid tumour types
- Testing in combination with cytotoxic chemotherapy or other seemingly rational targeted therapy (with almost universal failures)

### Differences
- IGFR phase III trials
  - no patient or biomarker pre-selection
  - Biomarker retrospectively explored
- cMET phase III trials
  - Biomarker pre-specified
  - Validity of biomarker cutoff retrospectively explored
Randomised phase II study of gemcitabine ± ganitumab or conatumumab in metastatic pancreatic cancer

ARM A
Ganitumab (12 mg/kg) + gemcitabine (n = 42)

ARM B
Conatumumab (10 mg/kg) + gemcitabine (n = 41)

ARM C
Placebo + gemcitabine (n = 42)

Stratification factor: ECOG PS 0 vs 1

Gemcitabine: 1000 mg/m² IV, Day 1, 8 and 15 Q4 weeks

Kindler et al Ann Oncol 2012
Randomised phase II study of gemcitabine ± ganitumumab or conatumumab in metastatic pancreatic cancer

Progression free survival

<table>
<thead>
<tr>
<th></th>
<th>Gem + ganitumumab</th>
<th>Gem + placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS</td>
<td>5.1 months</td>
<td>2.1 months</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.65 (95% CI: 0.41, 1.04)</td>
<td>p=0.072</td>
</tr>
</tbody>
</table>

Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Gem + ganitumumab</th>
<th>Gem + placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS</td>
<td>8.7 months</td>
<td>5.9 months</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.67 (95% CI: 0.41, 1.12)</td>
<td>p=0.12</td>
</tr>
</tbody>
</table>

Kindler et al Ann Oncol 2012
Randomised phase II study of gemcitabine ± ganitumumab or conatumumab in metastatic pancreatic cancer

<table>
<thead>
<tr>
<th>Baseline biomarker</th>
<th>Biomarker subgroup</th>
<th>Number of Patients (Number of events)</th>
<th>Number of events</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>PInteraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IGF-1</td>
<td>Low (≤105)</td>
<td>17 (13)</td>
<td>13 (11)</td>
<td>0.59 (0.24–1.43)</td>
<td>0.24</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>High (&gt;105)</td>
<td>14 (7)</td>
<td>16 (14)</td>
<td>0.25 (0.09–0.67)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>IGF-2</td>
<td>Low (≤1800)</td>
<td>13 (11)</td>
<td>20 (17)</td>
<td>0.95 (0.44–2.08)</td>
<td>0.91</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>High (&gt;1800)</td>
<td>20 (11)</td>
<td>13 (11)</td>
<td>0.24 (0.09–0.68)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>IGFBP-1</td>
<td>Low (≤28)</td>
<td>15 (7)</td>
<td>13 (11)</td>
<td>0.41 (0.16–1.09)</td>
<td>0.07</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>High (&gt;28)</td>
<td>16 (7)</td>
<td>13 (11)</td>
<td>0.50 (0.19–1.29)</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>IGFBP-2</td>
<td>Low (≤158)</td>
<td>16 (8)</td>
<td>13 (11)</td>
<td>0.19 (0.07–0.55)</td>
<td>0.002</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>High (&gt;158)</td>
<td>14 (11)</td>
<td>15 (13)</td>
<td>0.69 (0.30–1.59)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>Low (≤2)</td>
<td>15 (12)</td>
<td>14 (12)</td>
<td>0.94 (0.37–2.38)</td>
<td>0.90</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>High (&gt;2)</td>
<td>16 (8)</td>
<td>15 (13)</td>
<td>0.28 (0.11–0.73)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>IGFBP-4</td>
<td>Low (≤43)</td>
<td>14 (8)</td>
<td>19 (15)</td>
<td>0.63 (0.23–1.70)</td>
<td>0.36</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>High (&gt;43)</td>
<td>19 (14)</td>
<td>14 (13)</td>
<td>0.39 (0.17–0.88)</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Patients with data for ≥1 biomarker: 34 (22) vs 33 (28)
Randomised phase II study of gemcitabine ± ganitumab or conatumumab in metastatic pancreatic cancer

McCaffery et al Clin Cancer Res 2013
Randomised phase III study of gemcitabine ± ganitumab at 2 different doses in metastatic pancreatic cancer (GAMMA)

**ARM A**
Placebo + gemcitabine (n = 322)

**ARM B**
Ganitumab (12 mg/kg) + gemcitabine (n = 318)

**ARM C**
Ganitumab (20 mg/kg) + gemcitabine (n = 160)

Gemcitabine: 1000 mg/m² IV, Day 1, 8 and 15 Q4 weeks

Stratification factors:
- ECOG PS 0 vs 1
- Liver mets yes vs. no
- Geographical regions

Fuchs et al Ann Oncol 2015
Randomised phase III study of gemcitabine ± ganitumab at 2 different doses in metastatic pancreatic cancer (GAMMA)

Progression free survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS (95%CI)</th>
<th>HR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3.7 months</td>
<td>1.00</td>
<td>0.520</td>
</tr>
<tr>
<td>(12mg/kg)</td>
<td>(0.84,1.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganitumab 12 mg/kg</td>
<td>3.6 months</td>
<td>0.97</td>
<td>0.403</td>
</tr>
<tr>
<td>(0.77-1.22)</td>
<td>(0.27-2.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganitumab 20 mg/kg</td>
<td>3.7 months</td>
<td>1.00</td>
<td>0.520</td>
</tr>
<tr>
<td>(0.84,1.20)</td>
<td>(0.27-2.96)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>7.2 months</td>
<td>1.00</td>
<td>0.494</td>
</tr>
<tr>
<td>(12mg/kg)</td>
<td>(0.82,1.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganitumab 12 mg/kg</td>
<td>7.0 months</td>
<td>0.97</td>
<td>0.397</td>
</tr>
<tr>
<td>(0.76-1.23)</td>
<td>(0.55,1.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganitumab 20 mg/kg</td>
<td>7.1 months</td>
<td>0.97</td>
<td>0.397</td>
</tr>
<tr>
<td>(0.76-1.23)</td>
<td>(0.55,1.61)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fuchs et al Ann Oncol 2015
Randomised phase III study of gemcitabine ± ganitumab in metastatic pancreatic cancer (GAMMA)

### Overall survival

<table>
<thead>
<tr>
<th>Baseline Biomarker</th>
<th>Biomarker Subgroup</th>
<th>Ganitumab Dose</th>
<th>Patients Receiving Ganitumab, n (Events, n)</th>
<th>Patients Receiving Placebo, n (Events, n)</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1</td>
<td>Low (&lt;74 ng/mL)</td>
<td>12 mg/kg</td>
<td>111 (81)</td>
<td>121 (93)</td>
<td>0.82</td>
<td>0.61–1.10</td>
<td>.189</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High (&gt;74 ng/mL)</td>
<td>20 mg/kg</td>
<td>61 (40)</td>
<td>122 (67)</td>
<td>1.02</td>
<td>0.71–1.45</td>
<td>.931</td>
<td></td>
</tr>
<tr>
<td>IGFBP-2</td>
<td>Low (&lt;1706 ng/mL)</td>
<td>12 mg/kg</td>
<td>124 (80)</td>
<td>114 (64)</td>
<td>1.17</td>
<td>0.78–1.77</td>
<td>.448</td>
<td>.067</td>
</tr>
<tr>
<td></td>
<td>High (&gt;1706 ng/mL)</td>
<td>20 mg/kg</td>
<td>53 (36)</td>
<td>129 (96)</td>
<td>1.14</td>
<td>0.75–1.72</td>
<td>.537</td>
<td></td>
</tr>
<tr>
<td>ESCIPA Analysis Set</td>
<td></td>
<td>12 mg/kg</td>
<td>226 (158)</td>
<td>243 (160)</td>
<td>0.88</td>
<td>0.66–1.19</td>
<td>.423</td>
<td>.021</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg/kg</td>
<td>113 (81)</td>
<td></td>
<td>1.09</td>
<td>0.77–1.56</td>
<td>.622</td>
<td>.899</td>
</tr>
</tbody>
</table>

### Progression free survival

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<thead>
<tr>
<th>Baseline Biomarker</th>
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<th>Patients Receiving Ganitumab, n (Events, n)</th>
<th>Patients Receiving Placebo, n (Events, n)</th>
<th>HR</th>
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<td>111 (88)</td>
<td>121 (97)</td>
<td>0.91</td>
<td>0.68–1.21</td>
<td>.503</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High (&gt;74 ng/mL)</td>
<td>20 mg/kg</td>
<td>61 (45)</td>
<td>122 (93)</td>
<td>0.94</td>
<td>0.66–1.34</td>
<td>.719</td>
<td></td>
</tr>
<tr>
<td>IGFBP-2</td>
<td>Low (&lt;1706 ng/mL)</td>
<td>12 mg/kg</td>
<td>124 (91)</td>
<td>114 (87)</td>
<td>1.03</td>
<td>0.69–1.52</td>
<td>.496</td>
<td>.914</td>
</tr>
<tr>
<td></td>
<td>High (&gt;1706 ng/mL)</td>
<td>20 mg/kg</td>
<td>53 (35)</td>
<td>129 (103)</td>
<td>1.12</td>
<td>0.79–1.50</td>
<td>.899</td>
<td>.882</td>
</tr>
<tr>
<td>ESCIPA Analysis Set</td>
<td></td>
<td>12 mg/kg</td>
<td>226 (175)</td>
<td>243 (160)</td>
<td>0.99</td>
<td>0.76–1.29</td>
<td>.843</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg/kg</td>
<td>113 (80)</td>
<td></td>
<td>1.00</td>
<td>0.78–1.32</td>
<td>.926</td>
<td></td>
</tr>
</tbody>
</table>

Fuchs et al Ann Oncol 2015
Randomised phase II study of cixutumumab (IMC A-12) in patients with colorectal cancer failed on 1 prior EGFR antibody

IMC A-12: cixutumumab

IMC A-12 10mg/kg every 2 weeks

IMC A-12 10mg/kg every 2 weeks + Cetuximab 500mg/m² every 2 weeks

IMC A-12 10mg/kg every 2 weeks + Cetuximab 500mg/m² every 2 weeks (K-ras wild type only)

Reidy et al J Clin Oncol 2010
## Objective response rate

<table>
<thead>
<tr>
<th>Arms</th>
<th>A-12 alone</th>
<th>A-12 + cetux</th>
<th>A-12 + cetux (K-ras wild type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>23</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Response</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Response rate</td>
<td>0%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>95% CI</td>
<td>0-15%</td>
<td>0-24%</td>
<td>0-17%</td>
</tr>
</tbody>
</table>

Reidy et al J Clin Oncol 2010
Survival outcome

Progression free survival

Overall survival

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**Survival outcome**

**Progression free survival**

**Overall survival**
Double blind randomised phase II/III study of irinotecan/cetuximab ± dalotuzumab in patients with chemorefractory colorectal cancer

- All patients received:
  - Irinotecan  - as per prior dose/schedule
  - Cetuximab  - 400mg/m² loading, then 250mg/m² weekly

Arm A: Dalotuzumab 10mg/kg once weekly (n=119)

Arm B: Dalotuzumab 15mg/kg loading, then 7.5mg/kg every alternate week (n=119)

Arm C: Placebo control (n=116)

Sclafani et al J Natl Cancer Inst 2015
**Double blind randomised phase II/III study of irinotecan/cetuximab ± dalotuzumab in patients with chemorefractory colorectal cancer**

### Progression free survival

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
<th>HR</th>
<th>p</th>
<th>(95%CI)</th>
<th>Median OS</th>
<th>HR</th>
<th>p</th>
<th>(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalotuzumab</td>
<td>3.9 months</td>
<td>1.33</td>
<td>0.07</td>
<td>(0.98, 1.83)</td>
<td>Dalotuzumab</td>
<td>10.8 months</td>
<td>1.41</td>
<td>0.06</td>
</tr>
<tr>
<td>Weekly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weekly</td>
<td></td>
<td></td>
<td>(0.99, 2.00)</td>
</tr>
<tr>
<td>Dalotuzumab</td>
<td>5.4 months</td>
<td>1.13</td>
<td>0.44</td>
<td>(0.83, 1.55)</td>
<td>Dalotuzumab</td>
<td>11.6 months</td>
<td>1.26</td>
<td>0.18</td>
</tr>
<tr>
<td>2-weekly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-weekly</td>
<td></td>
<td></td>
<td>(0.89, 1.79)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.6 months</td>
<td>-</td>
<td></td>
<td></td>
<td>Placebo</td>
<td>14.0 months</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

---

**Overall survival**

<table>
<thead>
<tr>
<th></th>
<th>Median OS</th>
<th>HR</th>
<th>p</th>
<th>(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalotuzumab</td>
<td>10.8 months</td>
<td>1.41</td>
<td>0.06</td>
<td>(0.99, 2.00)</td>
</tr>
<tr>
<td>Weekly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalotuzumab</td>
<td>11.6 months</td>
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<td>0.18</td>
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</tr>
<tr>
<td>2-weekly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>14.0 months</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sclafani et al J Natl Cancer Inst 2015
Pre-specified biomarker analysis

**IGF-1R Immunohistochemistry***

**Epiregulin (EREG)**
q-rtPCR

Combined dalotuzumab arms Vs Placebo control

- Cut points for each biomarker were predefined
- PFS endpoint

*rabbit monoclonal antibody CONFIRM® anti-IGF-1R (G11)
(Ventana, Arizona, US)

Sclafani et al J Natl Cancer Inst 2015
Pre-specified biomarker analysis

<table>
<thead>
<tr>
<th></th>
<th>Dalotuzumab (n)</th>
<th>Control (n)</th>
<th>PFS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>n=345</td>
<td>233</td>
<td>112</td>
</tr>
<tr>
<td>IGF-1R‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=187</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>54</td>
<td>34</td>
<td>1.78 (1.01-3.13)</td>
</tr>
<tr>
<td>Low</td>
<td>67</td>
<td>32</td>
<td>1.02 (0.60-1.73)</td>
</tr>
<tr>
<td>EREG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=288</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>97</td>
<td>47</td>
<td>1.26 (0.80-1.96)</td>
</tr>
<tr>
<td>Low</td>
<td>96</td>
<td>48</td>
<td>1.41 (0.92-2.16)</td>
</tr>
</tbody>
</table>

‡ Model includes EREG as a covariate

Sclafani et al J Natl Cancer Inst 2015
Important considerations in phase III trials

• biomarker assay correct
• Assay cut-point correct
  • % of cell staining and intensity of cell staining
  • median level of circulating biomarkers (different median levels between phase II and III trials)
• Circulating vs. tissue based biomarkers
Evaluating targets and predictive biomarkers

Novel target

Drug X

All comers

Assess biomarker prospectively

Stratify patient by biomarker

Control

Drug X or Control + drug X
## Biomarker validation - IHC

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CANCER</th>
<th>IHC Antibody</th>
<th>Biomarker +ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilotumumab¹</td>
<td>OG cancer</td>
<td>MET4 mAb (Dako, CA)</td>
<td>≥25% membrane</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>staining of tumour cells at any intensity</td>
</tr>
<tr>
<td>Onartuzumab²</td>
<td>Non small cell lung cancer</td>
<td>CONFIRM SP44 anti-MET monoclonal antibody (Ventana AZ)</td>
<td>≥50% tumour cells with strong intensity OR ≥50% tumours cells with moderate or higher staining but &lt;50% with strong intensity</td>
</tr>
<tr>
<td>Tivantinib³</td>
<td>Hepatocellular carcinoma</td>
<td>CONFIRM SP44 anti-MET monoclonal antibody (Ventana AZ)</td>
<td>≥50% tumour cells with at least moderate intensity</td>
</tr>
</tbody>
</table>

Randomised phase II study of ECX ± rilotumumab (AMG102) in advanced OG cancer

**ARM A**
Rilotumumab (15 mg/kg) + ECX Q3W (n = 40)

**ARM B**
Rilotumumab (7.5 mg/kg) + ECX Q3W (n = 40)

**ARM C**
Placebo + ECX Q3W (n = 40)

Stratification factors:
ECOG PS 0 vs 1
LA vs Metastatic

- Epirubicin: 50 mg/m² IV, Day 1
- Cisplatin: 60 mg/m² IV, Day 1
- Capecitabine: 625 mg/m² BID orally, Days 1-21

- Rilotumumab: IV over 60 ± 10 minutes prior to chemotherapy

Iverson et al Lancet Oncol 2014
Survival outcome on all patients

Progression free survival

Overall survival

Iverson et al Lancet Oncol 2014
Survival outcome according to MET status

MET +ve defined as:
≥25% tumour membrane staining
64% pts were MET +ve

Progression free survival

Overall survival

Median survival (months)
ECX+ Rilotumumab placebo
MET+ve 10.6 5.7
MET-ve 11.1 11.5

Iverson et al Lancet Oncol 2014
Randomised phase III rilotumumab in advanced OG cancer trial design (RiloMET)

Advanced lower oesophageal, OGJ or gastric adenocarcinoma ≥ 25% tumour membrane staining for MET staining

n=609

ECX + placebo
Treatment given every 21 days

ECX + rilotumumab 15mg/kg
Treatment given 21 days

Primary endpoint: Overall survival (ITT population)
Overall Survival

• More deaths in the rilotumumab arm, primarily due to disease progression

Cunningham et al ASCO 2015
## OS and MET Expression

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>MET Expression Tertile</th>
<th>Subjects, n</th>
<th>Events, n</th>
<th>Median OS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilotumumab (n=304)</td>
<td>25%–&lt;45%</td>
<td>95</td>
<td>43</td>
<td>10.2</td>
<td>7.2–12.4</td>
</tr>
<tr>
<td></td>
<td>45%–&lt;80%</td>
<td>98</td>
<td>41</td>
<td>8.1</td>
<td>6.4–11.9</td>
</tr>
<tr>
<td></td>
<td>≥80%</td>
<td>110</td>
<td>44</td>
<td>10.7</td>
<td>7.2–15.9</td>
</tr>
<tr>
<td>Placebo (n=305)</td>
<td>25%–&lt;45%</td>
<td>100</td>
<td>37</td>
<td>12.4</td>
<td>8.9–NE</td>
</tr>
<tr>
<td></td>
<td>45%–&lt;80%</td>
<td>103</td>
<td>39</td>
<td>10.4</td>
<td>8.6–15.4</td>
</tr>
<tr>
<td></td>
<td>≥80%</td>
<td>102</td>
<td>31</td>
<td>11.1</td>
<td>9.5–NE</td>
</tr>
</tbody>
</table>

### OS by MET Level

**Event (R/P) Hazard Ratio P-Value**

- Lower MET Tertile (25% – <45%): 43/37, 1.53, 0.84
- Mid MET Tertile (45% – <80%): 41/39, 1.28
- Upper MET Tertile (≥80%): 44/31, 1.32

**Notes:** Within the selected MET-positive population, higher MET expression did not correlate with poorer prognosis or better outcome with rilotumumab.

Cunningham et al ASCO 2015
Tumour MET FISH analyses

- MET gene amplification was analyzed by FISH using the Research Use Only (RUO) MET/CEN-7 IQFISH Probe Mix assay (Dako)

Cunningham et al ASCO 2015
Randomized phase II trial of onartuzumab in combination with erlotinib in patients with advanced non–small-cell lung cancer

Progression free survival

Overall survival

MET positivity was defined as a score of 2+ (≥ 50% of tumour cells with moderate or higher staining but < 50% with strong intensity); or 3+ (≥ 50% of tumour cells staining with strong intensity)

Spigel et al J Clin Oncol 2013
Phase III study of erlotinib ± onartuzumab

Median 9.1 months (95% CI 7.7–10.2)

HR 1.27 (95% CI: 0.98–1.65)
p=0.07

Median 6.8 months (95% CI 6.1 – 7.5)

Number of patients at risk:
Placebo + erlotinib 249 183 110
Onartuzumab + erlotinib 250 177 100

Time (months)

Placebo + erlotinib (n=249)
Onartuzumab + erlotinib (n=250)
Censored

Spigel et al ASCO 2014
Randomised phase III onartuzumab (MetMAb) in advanced gastric cancer trial design (METGastric)

Advanced OGJ or gastric adeno-carcinoma ≥50% of tumour cells showing weak, moderate and/or strong staining intensity

Co-primary endpoint: Overall survival (ITT population)

Overall survival (Met-IHC 2+ or 3+ subgroup)

FOLFOX + placebo
Treatment given every 14 days
n=283

FOLFOX + onartuzumab
Treatment given 14 days
n=279

Shah et al ASCO 2015
Overall survival

**Intention-to-treat**

- P+mFOLFOX6 (n=283)
- O+mFOLFOX6 (n=279)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>P+mFOLFOX6</th>
<th>O+mFOLFOX6</th>
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</thead>
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<tr>
<td>0</td>
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<td>3</td>
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<td>3</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Censored: 11.0

OS (%)

HR: 0.82
95% CI: 0.59, 1.15
p=0.24

**MET 2+/3+**

- P+mFOLFOX6 (n=109)
- O+mFOLFOX6 (n=105)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>P+mFOLFOX6</th>
<th>O+mFOLFOX6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>109</td>
<td>105</td>
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<tr>
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<td>6</td>
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<tr>
<td>9</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

Censored: 9.7

OS (%)

HR: 0.64
95% CI: 0.40, 1.03
p=0.062

Shah et al ASCO 2015
Randomised phase II tivantinib in advanced hepatocellular cancer trial design

Advanced HCC patients with 1 prior systemic therapy and radiological progression or intolerance to therapy

n=71

Tivantinib 240mg bd

n=33

Placebo

Santoro et al Lancet Oncol 2013
Randomised phase II tivantinib in advanced hepatocellular cancer (ITT population)

Time to progression

Overall survival

Santoro et al Lancet Oncol 2013
Randomised phase II tivantinib in advanced hepatocellular cancer (MET high subgroup)

Time to progression

Overall survival

HR: 0.43; 95% CI:0.19-0.97; p=0.03)  
HR: 0.38; 95% CI:0.18-0.81; p=0.01)

Samples that scored at least 2+ in at least 50% of tumour cells were regarded as having high MET expression (MET-high)
Phase III randomized double-blind study of tivantinib monotherapy as second-line treatment in patients with advanced, pretreated, MET-high HCC (METIV-HCC)

- Approximately 303 adult pts, from ~120 sites in ~28 months
- Stratification factors:
  - Vascular invasion
  - Extrahepatic spread
  - AFP (< or ≥200 ng/ml)
- 2:1 randomization
- Tivantinib 120 mg p.o. b.i.d.
  - 202 pts
- Placebo p.o. b.i.d.
  - 101 pts
- End points:
  1° OS
  2° PFS, safety
  3° TTP, ORR, DCR, type of PD, PK, biomarkers, quality of life

Rimassa et al Hepatic Oncol 2014
Conclusions

• Suppressing one growth factor receptor pathway might lead to activation of other compensatory resistant pathways

• Drugs evaluated with the putative mechanism of actions might be inadequate

• Definition of tissue-based biomarker positivity could be subjective and varied (expression vs. median level)

• Parallel effort in optimising biomarker might be necessary during phase III studies
Acknowledgement

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