Biomarker defined subgroups in gastric cancer, a case study

Nigel Baker
EFSPi, November 30, 2012
Overview

• Background
  • Gastric cancer
  • Biomarkers

• Phase 2 trial
  • Overall
  • Biomarker subgroup

• Conclusions

• Lessons
Gastric cancer

- Second leading cause of cancer-related death
- Poor 5-year survival (~25%) all stages combined
- ~10 month survival for metastatic stage
- Late diagnosis with no standard screening in North America: ~60% regional or metastatic disease at diagnosis
- No single global standard of care chemotherapy: epirubicin, cisplatin, fluoropyrimidine, based regimens most commonly used
Possible markers to define subgroups
Possible markers to define subgroups

- Pathway defined potential biomarkers
HGF/MET Pathway in Gastric Cancer

- The MET receptor and its ligand, hepatocyte growth factor (HGF), also known as scatter factor (SF), regulate multiple cellular functions, including proliferation, survival, motility, and morphogenesis\(^1\)

- MET and HGF are important in gastric and esophagogastric junction (G/EGJ) cancer
  - MET is expressed in 26% to 74% of gastric cancer (GC) cases, and MET is amplified in 2% to 23% of GC cases\(^1-8\)
  - MET expression is associated with tumor depth of invasion, metastasis, stage, and poor prognosis in patients with GC\(^2,3,6,7,9\)
  - MET expression occurs in 80% to 100% of EGJ cases and is associated with poor outcome\(^10,11\)

- Biomarkers can potentially be used to identify patients likely to benefit from agents targeting the HGF/MET pathway

- Rilotumumab is an investigational, fully human monoclonal antibody to HGF that blocks the binding of HGF to MET
Phase 2 Study of Rilotumumab + Epirubicin, Cisplatin, and Capecitabine (ECX) in G/EGJ cancer

Key Inclusion Criteria
- Pathologically confirmed unresectable locally advanced or metastatic G/EGJ cancer
- No prior systemic therapy for locally advanced or metastatic disease

Endpoints
- Primary: PFS
- Others: OS, ORR, PK, biomarkers

Patient Enrollment/Sites
- 121 patients were randomized from 42 sites (from 13 countries)

Data Analyses
- Estimation study to evaluate efficacy endpoints
  - Each dose of rilotumumab separately
  - Combined rilotumumab group
- Primary analysis: 79 PFS events, November 30, 2010
- Updated analysis: 102 PFS events and 74 OS events (~ 60%), April 1, 2011
Clinical Efficacy in the Intent-to-Treat Population*

**Progression-Free Survival**

- **Rilotumumab + ECX (n = 82)**: Median Months (80% CI) = 5.6 (4.9–6.9), HR† (80% CI) = 0.64 (0.48–0.85), P Value = 0.045
- **Placebo + ECX (n = 39)**: Median Months (80% CI) = 4.2 (3.7–4.6)

**Overall Survival**

- **Rilotumumab + ECX (n = 82)**: Median Months (80% CI) = 11.1 (9.5–12.1), HR† (80% CI) = 0.73 (0.53–1.01), P Value = 0.215
- **Placebo + ECX (n = 39)**: Median Months (80% CI) = 8.9 (5.7–10.6)

*Results based on the updated analysis with data cutoff of April 1, 2011.
†Adjusted for baseline randomization stratification variables (ECOG status [0 or 1] and disease extent [locally advanced or metastatic]).
Hypothesis testing requirements: Patient stratification biomarkers

- Effective drug or evidence of biologic activity
- Well-defined biologic hypothesis
  - Knowledge of pathway and target marker
  - Meaningful biomarker variation that is prevalent in indication of interest (e.g., KRAS in colorectal vs head and neck cancer)
- Appropriate setting to perform robust test
  - Adequate sample size with high rate of marker ascertainment
    - Depends on both biomarker prevalence and level of efficacy
    - Control arm to dissect prognostic vs. predictive value of marker
- Validated assay that addresses testable hypothesis
  - KRAS: limited known mutations, DNA assay
  - PTEN: huge gene, cytoplasmic and nuclear protein → challenges in assay interpretation and standardization
Biomarker Enrichment?

- Primary analysis – encouraging
- Strong historical evidence for a predictive and prognostic biomarker
- Pre-specified analysis plan to find biomarker that defines enriched population
- Aims:
  - Continue Amgen’s focus on personalised medicine
  - Strengthen chance of surviving portfolio planning
  - Strengthen chance of Regulatory success
## Sample Ascertainment

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>118</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MET immunohistochemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Acceptable tumor sample available, n (%)</td>
<td>90 (76%)</td>
</tr>
<tr>
<td>†MET(^{High}), n (%)</td>
<td>38 (42%)</td>
</tr>
<tr>
<td>†MET(^{Low}), n (%)</td>
<td>52 (58%)</td>
</tr>
<tr>
<td>Evaluable patients in each treatment arm</td>
<td></td>
</tr>
<tr>
<td>Rilotumumab + ECX</td>
<td>62 (78%)</td>
</tr>
<tr>
<td>Placebo + ECX</td>
<td>28 (74%)</td>
</tr>
</tbody>
</table>

*Per protocol analysis set.

†Criteria chosen for clinical trial assay:

MET\(^{High}\): > 50% of tumor cells with cytoplasmic staining
MET\(^{Low}\): ≤ 50% of tumor cells with cytoplasmic staining
Choosing Cut Point - OS by MET Expression With Increasing Threshold of Percent Positive

<table>
<thead>
<tr>
<th>Biomarker Subgroup (%) cell staining</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (≤ 10)</td>
<td>1.469 (0.406–5.313)</td>
<td>0.557</td>
<td>0.563</td>
</tr>
<tr>
<td>High (&gt; 10)</td>
<td>0.847 (0.429–1.672)</td>
<td>0.633</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 20)</td>
<td>1.027 (0.360–2.933)</td>
<td>0.960</td>
<td>0.769</td>
</tr>
<tr>
<td>High (&gt; 20)</td>
<td>0.855 (0.414–1.765)</td>
<td>0.672</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 30)</td>
<td>1.286 (0.498–3.323)</td>
<td>0.604</td>
<td>0.332</td>
</tr>
<tr>
<td>High (&gt; 30)</td>
<td>0.710 (0.327–1.541)</td>
<td>0.387</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 40)</td>
<td>1.699 (0.669–4.312)</td>
<td>0.265</td>
<td>0.051</td>
</tr>
<tr>
<td>High (&gt; 40)</td>
<td>0.501 (0.228–1.098)</td>
<td>0.084</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 50)</td>
<td>1.838 (0.778–4.343)</td>
<td>0.166</td>
<td>0.007</td>
</tr>
<tr>
<td>High (&gt; 50)</td>
<td>0.290 (0.111–0.760)</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 60)</td>
<td>1.879 (0.806–4.381)</td>
<td>0.144</td>
<td>0.104</td>
</tr>
<tr>
<td>High (&gt; 60)</td>
<td>0.262 (0.095–0.725)</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 70)</td>
<td>1.641 (0.743–3.628)</td>
<td>0.221</td>
<td>0.012</td>
</tr>
<tr>
<td>High (&gt; 70)</td>
<td>0.292 (0.099–0.858)</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 80)</td>
<td>1.473 (0.700–3.102)</td>
<td>0.308</td>
<td>0.010</td>
</tr>
<tr>
<td>High (&gt; 80)</td>
<td>0.166 (0.033–0.823)</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 90)</td>
<td>1.209 (0.625–2.337)</td>
<td>0.573</td>
<td>0.028</td>
</tr>
<tr>
<td>High (&gt; 90)</td>
<td>0.035 (0.002–0.678)</td>
<td>0.027</td>
<td></td>
</tr>
</tbody>
</table>
PFS and OS May be Improved in MET\textsuperscript{High} Patients

**Progression-Free Survival**

- **Rilotumumab + ECX (n = 27)**: Median = 6.9 months (5.1–7.5), HR = 0.51 (0.24–1.10), P = 0.085
- **Placebo + ECX (n = 11)**: Median = 4.6 months (3.7–5.2)

**Overall Survival**

- **Rilotumumab + ECX (n = 27)**: Median = 11.1 months (9.2–13.3), HR = 0.29 (0.11–0.76), P = 0.012
- **Placebo + ECX (n = 11)**: Median = 5.7 months (4.5–10.4)

*HR adjusted for baseline disease extent and ECOG*
Distribution of Bootstrap Hazard Ratios

<table>
<thead>
<tr>
<th>Percentile</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>2.43</td>
</tr>
<tr>
<td>95</td>
<td>0.64</td>
</tr>
<tr>
<td>50</td>
<td>0.26</td>
</tr>
<tr>
<td>5</td>
<td>0.07</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
High Levels of Tumor MET May Be Prognostic and Predictive

- Patients with gastric tumors with high MET expression may have a poorer prognosis but may receive more benefit from rilotumumab
## Rilotumumab Safety Profile in the MET\(^{\text{High}}\) Patient Subgroup

<table>
<thead>
<tr>
<th></th>
<th>MET(^{\text{High}})</th>
<th>MET(^{\text{Low}})</th>
<th>Unselected(^{\dagger})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rilotumumab (n = 27)</td>
<td>Placebo (n = 11)</td>
<td>Rilotumumab (n = 35)</td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>27 (100)</td>
<td>11 (100)</td>
<td>34 (97)</td>
</tr>
<tr>
<td>Grade ≥ 3 AE, n (%)</td>
<td>24 (89)</td>
<td>9 (82)</td>
<td>31 (89)</td>
</tr>
<tr>
<td>Serious AE, n (%)</td>
<td>16 (59)</td>
<td>7 (64)</td>
<td>22 (63)</td>
</tr>
<tr>
<td>Fatal AE, n (%)</td>
<td>0 (0)</td>
<td>2 (18)</td>
<td>8 (23)</td>
</tr>
</tbody>
</table>

\(^{\dagger}\)Safety analysis set.
Conclusions

• High tumor MET expression may predict clinical benefit for the addition of rilotumumab to ECX in patients with advanced G/EGJ cancer

• The outcome by MET expression in the placebo arm suggests that high tumor levels of MET is a marker of poor prognosis that may be reversed by rilotumumab

• Rilotumumab has a manageable safety profile among patients with high tumor MET expression

• Based on these results, a phase 3 trial is planned to confirm the efficacy of rilotumumab added to ECX in patients with MET-positive G/EGJ tumors as detected by a MET in vitro diagnostic assay
Lessons

• May increase probability of success
  • Internal decision making
  • Predicted Regulatory success

• May make Regulatory buy-in to a Phase 3 design easier
  • Exclude patients who are less likely to benefit

• Needs careful assessment
  • Biological justification
  • Pre-specified analysis plan
Acknowledgements

• Kelly Oliner, Amgen for her ASCO 2012 Slides
• Elwyn Loh, Rui (Sammi)Tang, Joe Jiang and Chrissie Fletcher for helpful review comments
References

• Slide 3:
  Jemal et al, CA Cancer J Clin 2011;61: 60-90
  Jemal et al, CA Cancer J Clin 2010;60;277-300
  Kang et al, Curr Treat Options Oncol 2011;12:96-106

• Slide 6:

• Slide 9:
  2008 ODAC briefing book