New experimental targets for gastric cancer

Andrés Cervantes
Professor of Medicine
Outline

• Acquired capabilities of Cancer
• IGFR pathway
• PI3K-AKT-m-TOR pathway
• MET pathway
• FGFR pathway
• Check point inhibitors
1. Self-Sufficiency in Growth Signals
   a. Receptors: EGFR-family, IGF1R, MET, FGFR
   b. Downstream effectors: PI3K, mTOR, AKT
2. Insensitivity to Antigrowth Signals
3. Evading Apoptosis
4. Limitless Replicative Potential
5. Sustained Angiogenesis
6. Tissue Invasion and Metastasis
Emerging Hallmarks

- Deregulating cellular energetics
- Avoiding immune destruction
- Genome instability and mutation
- Tumor-promoting Inflammation

Enabling Characteristics

Hanahan and Weinberg, 2011
ADQUIRED CAPABILITIES OF CANCER: SELF SUFFICIENCY IN GROWTH SIGNALS

• RECEPTORS:
  – EGFR FAMILY
  – IGFR1
  – MET
  – FGFR

• DOWNSTREAM EFFECTORS:
  – PI3K
  – AKT
  – m-TOR
Multivariate Cox regression analyses of overall survival since the start of first-line chemotherapy: correlation with protein expression and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>HR  (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1R neg vs positive</td>
<td>2.14 1.20-3.82</td>
<td>0.01</td>
</tr>
<tr>
<td>PS 0 vs 1-2</td>
<td>1.83 1.15-2.91</td>
<td>0.01</td>
</tr>
<tr>
<td>Intestinal vs Diffusse</td>
<td>1.71 1.08-2.70</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**CO EXPRESSION WITH EGFR + (55%) AND HER2 +++ (15%)**

Rationale for Targeting Other Receptors & Downstream Signaling Proteins

**Met receptor**

- Hepatocyte growth factor (HGF) & c-Met highly expressed in GC specimens: 73% and 77% (Chen, 2007)
- *MET* gene amplification in 10-15% GC (Bechletner, 2008)
- Estimulation of c-Met with HGF induces signal transduction, that is abrogated with c-Met TKIs (Catenacci, 2008)
- Met inhibitors in the clinic in GC: Foretinib - GSK089 (Jhawer, 2009) and XL880 (Jhawer, 2008)
TREATMENT STRATEGIES

**Specific MET antibodies**
- MetMab
- DN-30
- AMG 102
- CE-355621
- Fliclutzumab
* Decoy MET

**Tyrosine kinase inhibitors:**
- Non-competitive:
  - ARQ-197* (Tivantinib)
- Competitive
  - XL880 (Foretinib)
  - XL184 (Cabozantinib)
  - PF-2341066 (Crizotinib)
  - SGX523
  - XcoveryMET-1
  - SGX126
  - MGCD265
  - PF-04217903

**Receptor/effecter antagonists**
- HSP-90, mTOR, MEK, STAT inhibitors

---

Figure 1. The MET/HGF signaling pathway and its therapeutic inhibition.
Molecular Heterogeneity and Receptor Coamplification Drive Resistance to Targeted Therapy in MET-Amplified Esophagogastric Cancer

Molecular Heterogeneity and Receptor Coamplification Drive Resistance to Targeted Therapy in MET-Amplified Esophagogastric Cancer

# Targeted therapies in First-line treatment for Advanced Gastric Cancer: Summary of Phase III Trials

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>CHEMOTHERAPY</th>
<th>BIOLOGICAL</th>
<th>HR</th>
<th>P value</th>
<th>Increase in median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA¹</td>
<td>Cisplatin+5FU/capecitabine</td>
<td>Trastuzumab</td>
<td>0.74</td>
<td>.04</td>
<td>+2.8 months</td>
</tr>
<tr>
<td>AVAGAST²</td>
<td>Cisplatin+capecitabine</td>
<td>Bevacizumab</td>
<td>0.87</td>
<td>.10</td>
<td>+2.0 months</td>
</tr>
<tr>
<td>EXPAND³</td>
<td>Cisplatin+capecitabine</td>
<td>Cetuximab</td>
<td>1.00</td>
<td>.95</td>
<td>-1.3 months</td>
</tr>
<tr>
<td>REAL-3⁴</td>
<td>Oxaliplatin+epirubicin+capecitabine</td>
<td>Panitumumab</td>
<td>1.37</td>
<td>.013</td>
<td>-2.5 months</td>
</tr>
<tr>
<td>RILOMET-1⁵</td>
<td>Cisplatin+epirubicin+capecitabine</td>
<td>Rilotumumab</td>
<td>--</td>
<td>--</td>
<td>Stopped in futility analysis</td>
</tr>
<tr>
<td>METGASTRIC⁶</td>
<td>FOLFOX6</td>
<td>Onartuzumab</td>
<td>1.06</td>
<td>.83</td>
<td>-0.6 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Cancer type (incidence, if known; reference)</th>
</tr>
</thead>
</table>
| FGFR1 | Amplification| Squamous NSCLC (20%; ref. 9)  
Breast cancer (10%; ref. 10)  
Ovarian cancer (~5%; ref. 11)  
Bladder cancer (3%; ref. 12)  
Others: oral squamous cell carcinoma, esophageal squamous carcinoma, prostate cancer (13–15) |
|       | Mutation     | Melanoma (rare), glioblastoma (16, 17)                                                                                                                                                 |
|       | Translocation| 8p11 myeloproliferative syndrome, chronic myeloid leukemia (rare; refs. 18, 19)                                                                                                       |
| FGFR2 | Amplification| Gastric cancer (10%; ref. 20)  
Breast cancer (4% of triple-negative cases; ref. 21)                                                                                                                              |
|       | Mutation     | Endometrial cancer (12%; ref. 22)  
Squamous NSCLC (5%; ref. 8)  
Gastric cancer (rare; ref. 23)                                                                                                                                                    |
|       | Germline SNP | Second intron SNP: breast cancer susceptibility (24)                                                                                                                                     |
| FGFR3 | Amplification| Bladder cancer (25)  
Salivary adenoid cystic cancer (26)                                                                                                                                                    |
|       | Mutation     | Bladder cancer (50–60% non-muscle invasive; 10–15% muscle invasive; ref. 27)  
Cervical cancer (5%; ref. 28)  
Myeloma (5% of the translocated cases; ref. 29)  
Prostate cancer (3%; ref. 30)  
Spermatocytic seminoma (7%; ref. 31)  
Colorectal cancer (23)  
Oral squamous cancer (32)                                                                                                           |
|       | Translocation| Myeloma (15%–20%; ref. 33)  
Peripheral T-cell lymphoma (rare; ref. 34)                                                                                                                                              |
<p>| FGFR4 | Mutation     | Rhabdomyosarcoma (7%–8%; ref. 35)                                                                                                                                                       |
|       | Germline SNP | Coding SNP: poor prognosis in many cancer types (36)                                                                                                                                    |</p>
<table>
<thead>
<tr>
<th>Aberration</th>
<th>Tumor</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR1</td>
<td>Amplification Breast (hormone receptor</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>positive)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung (squamous cell carcinoma)</td>
<td>10–20</td>
</tr>
<tr>
<td></td>
<td>Lung (small cell)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Head and neck (squamous cell carcinoma)</td>
<td>10–17</td>
</tr>
<tr>
<td></td>
<td>Esophageal (squamous cell carcinoma)</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Ovarian</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma</td>
<td>5</td>
</tr>
<tr>
<td>FGFR2</td>
<td>Amplification Breast (triple-negative)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Gastric</td>
<td>5–10</td>
</tr>
<tr>
<td></td>
<td>Endometrial</td>
<td>12</td>
</tr>
<tr>
<td>FGFR3</td>
<td>Mutation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bladder (nonmuscle invasive)</td>
<td>50–60</td>
</tr>
<tr>
<td></td>
<td>Bladder (muscle-invasive)</td>
<td>10–15</td>
</tr>
<tr>
<td></td>
<td>Glioblastoma</td>
<td>3–7</td>
</tr>
<tr>
<td>FGFR4</td>
<td>Amplification Colorectal</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Rhabdomyosarcoma</td>
<td>8</td>
</tr>
</tbody>
</table>
Purpose

Target FGFR pathway as oncogenic driver

Reverse resistance to targeted agents

Target angiogenesis

Which is the optimal setting?

Enrich for patients harboring the specific oncogenic alteration

After PD to another targeted agent?

After PD to another antiangiogenic agent?

Challenges

Molecular screening
Avoid resistance to anti-FGFR agents

How to combine anti-FGFR and other targeted agents?

FGF activation as selection criteria?

Unsolved questions

• Selective vs. nonselective anti-FGFR
• Feasibility of combinations
• Long-term safety of FGFR inhibition
<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Clinical trials.gov</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multikinase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dovitinib</td>
<td>Phase II</td>
<td>NCT01379534</td>
<td><em>FGFR2</em>-mutant or wild-type endometrial cancer</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>NCT01732107</td>
<td><em>FGFR3</em>-mutant or overexpressed BCG refractory urothelial carcinoma</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>NCT01719549</td>
<td><em>FGFR2</em>-amplified gastric cancer</td>
</tr>
<tr>
<td>Lucitanib</td>
<td>Phase I/II</td>
<td>NCT01283945</td>
<td>Expansion cohort in <em>FGFR1</em>-amplified tumors</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Phase II/III</td>
<td>NCT01761747</td>
<td>Advanced squamous cell lung cancers with FGFR kinase alterations</td>
</tr>
<tr>
<td><strong>Selective FGFR inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZD4547</td>
<td>Phase I</td>
<td>NCT00979134</td>
<td>Expansion cohort in <em>FGFR1</em>- or <em>FGFR2</em> amplified tumors</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>NCT01457846</td>
<td>Gastric or lower-esophageal cancer, <em>FGFR2</em>-amplified or not, randomized to AZD4547 or paclitaxel</td>
</tr>
<tr>
<td></td>
<td>Phase I/II</td>
<td>NCT01202591</td>
<td>Estrogen receptor + and <em>FGFR1</em>-amplified breast cancer, randomized to AZD4547 plus fulvestrant or fulvestrant alone</td>
</tr>
<tr>
<td>BGJ398</td>
<td>Phase I</td>
<td>NCT01004224</td>
<td><em>FGFR1</em>- or <em>FGFR2</em>-amplified, <em>FGFR3</em>-mutant advanced cancer</td>
</tr>
<tr>
<td>LY2874455</td>
<td>Phase I</td>
<td>NCT01212107</td>
<td>Advanced cancer with FGFR aberrations during dose expansion</td>
</tr>
<tr>
<td>JNJ-42756493</td>
<td>Phase I</td>
<td>NCT01703481</td>
<td>Expansion cohort in <em>FGFR1</em>-, <em>FGFR2</em>-, or <em>FGFR4</em>-amplified tumors</td>
</tr>
</tbody>
</table>
High-level clonal FGFR amplification and response to FGFR Inhibition in a translational clinical trial

Pearson A, et al. Cancer Discovery 2016,

Published OnlineFirst on May 13, 2016; DOI: 10.1158/2159-8290.CD-15-1246
ADQUIRED CAPABILITIES OF CANCER: SELF SUFFICIENCY IN GROWTH SIGNALS

• RECEPTORS:
  – EGFR FAMILY
  – IGFR1
  – c-MET

• DOWNSTREAM EFFECTORS:
  – PI3K
  – AKT
  – m-TOR
Rationale for Targeting Other Receptors & Downstream Signaling Proteins

- PI3K-mTOR inhibitors
  - RAD001 (everolimus) is a derivative of rapamycin which act as a signal transduction inhibitor of mTOR
  - RAD001 attenuates production of HIF-1α and VEGF in GC \textit{in vitro} and markedly inhibits NCI-N87 GC xenografts growth (Cejka, 2008)
  - Preliminary results showed that RAD001 monotherapy is generally well tolerated with promising activity in pts with previously treated advanced GC\textsuperscript{1}

\textsuperscript{1}Muro et al. J Clin Oncol 2008 (ASCO)
THE PHOSPHATIDYLINOSONITOL 3 KINASE (PI3K) SIGNALING PATHWAY
GENETIC VARIATIONS IN THE PI3K/PTEN/AKT/MTOR PATHWAY IN ESOPHAGEAL CANCER

GENETIC VARIATIONS IN THE PI3K/PTEN/AKT/m-TOR PATHWAY IN ESOPHAGEAL CANCER

A

Comprehensive Molecular Characterization of Gastric Adenocarcinoma: Molecular platforms
Comprehensive Molecular Characterization of Gastric Adenocarcinoma: Molecular platforms

- Array-based somatic copy number analysis
- Whole exome sequencing
- Array-based DNA methylation profiling
- Messenger RNA sequencing
- microRNA sequencing
- Reverse Phase Protein Array (RPPA)

Comprehensive Molecular Characterization of Gastric Adenocarcinoma: PI3KCA mutations by subtype
1072 samples from gastric cancer patients after surgery
Immunohistochemical assessment of mTOR and pmTOR

Phase I: 2 PRs out of 4 patients with metastatic, heavily pretreated cancer of the stomach or gastroesophageal junction
Phase II: No OR, DCR was 55% (29/53 pts), mPFS was 83 days (95% CI: 50-91 days)
# Gastric Cancer: Second Line Chemotherapy Trials Comparing BSC versus Active Treatment

<table>
<thead>
<tr>
<th>Trial Author</th>
<th>Year</th>
<th>Patients Random (n)</th>
<th>Treatment</th>
<th>HR OS</th>
<th>P value</th>
<th>Gain in Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thuss-Patience et al.¹</td>
<td>2011</td>
<td>40 1:1</td>
<td>Irinotecan</td>
<td>0.48</td>
<td>.0023</td>
<td>2.4 months</td>
</tr>
<tr>
<td>Park et al.²</td>
<td>2012</td>
<td>193 2:1</td>
<td>Irinotecan, Docetaxel</td>
<td>0.65</td>
<td>.004</td>
<td>1.3 months</td>
</tr>
<tr>
<td>Ford et al.³</td>
<td>2014</td>
<td>168 1:1</td>
<td>Docetaxel</td>
<td>0.67</td>
<td>.01</td>
<td>1.6 months</td>
</tr>
<tr>
<td>Otshu et al⁴</td>
<td>2013</td>
<td>656 2:1</td>
<td>Everolimus</td>
<td>0.90</td>
<td>.124</td>
<td>0.9 months</td>
</tr>
<tr>
<td>Fuchs et al⁵</td>
<td>2014</td>
<td>355 2:1</td>
<td>Ramucirumab</td>
<td>0.77</td>
<td>.047</td>
<td>1.4 months</td>
</tr>
</tbody>
</table>

Phase II Study of weekly Paclitaxel +/- Olaparib for second line in advanced gastric cancer

Stratification:
- ATM Low

A: weekly Paclitaxel
B: weekly Paclitaxel plus Olaparib 100 mg bid

- Primary end point: PFS
- Co-Primary end point: PFS in ATM Low
- Secondary end points: OS, OS in ATM Low, Toxicity

Phase II Study of weekly Paclitaxel +/- Olaparib for second line in advanced gastric cancer

Phase II Study of weekly Paclitaxel +/- Olaparib for second line in advanced gastric cancer

Challenges

• Target discovery has resulted in numerous novel drugs in clinical development

• Signal transduction inhibition does not guarantee tumor response:
  – Target presence and dependence
  – Redundancy
  – Cross-talk

• Molecular-based population enrichment needed

• Combinations: mechanistic interactions

• Phase III trials are warranted
PD-1 Pathway and Immune Surveillance

- PD-1 is a negative co-stimulatory receptor expressed primarily on activated T cells\(^1\)
- Binding of PD-1 to its ligands PD-L1 and PD-L2 inhibits effector T-cell function\(^1\)
- Expression of PD-L1 on tumor cells and macrophages can suppress immune surveillance and permit neoplastic growth\(^2\)

Pembrolizumab (MK-3475) Is a Humanized IgG4, High-Affinity, Anti-PD-1

- Dual blockade of PD-L1 and PD-L2
- No cytotoxic (ADCC/CDC) activity
- Pharmacokinetics support dosing every 2 weeks (Q2W) or every 3 weeks (Q3W)
- Low occurrence of anti-drug antibodies, which have no impact on pharmacokinetics
- Demonstrated clinical activity in multiple tumor types\(^1\)\(^-\)\(^7\)
- Recently approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

Screening: 65 of 162 (40%) patients assessed for PD-L1 expression had PD-L1-positive tumors

Patients: 19 patients from Asia and 20 patients from the rest of the world

Treatment: 10 mg/kg IV Q2W

Response assessment: Performed every 8 weeks per RECIST v1.1

Muro K, et al. ASCO GI 2015; Abstract nr.03
• PD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody
• Positivity was defined as staining in the stroma or in ≥1% of tumor cells

Muro K, et al. ASCO GI 2015; Abstract nr.03
PD-L1 Expression in Gastric Cancer Samples

Gastric carcinoma

### Pembrolizumab induces Responses in Chemorefractory Gastric Cancer

<table>
<thead>
<tr>
<th></th>
<th>Central review*</th>
<th>Investigator review</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asia (n=17)</td>
<td>Rest of the world (n=19)</td>
</tr>
<tr>
<td><strong>Objective response (%), 95% CI†</strong></td>
<td>4 (24%, 7-50)</td>
<td>4 (21%, 6-46)</td>
</tr>
<tr>
<td><strong>Best overall response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response‡</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response‡</td>
<td>4 (24%)</td>
<td>4 (21%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3 (18%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7 (41%)</td>
<td>12 (63%)</td>
</tr>
<tr>
<td>No assessment§</td>
<td>0</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Not determined¶</td>
<td>3 (18%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Time to response (weeks)</strong></td>
<td>8 (7-8)</td>
<td>8 (8-12)</td>
</tr>
<tr>
<td><strong>Duration of response (weeks)</strong></td>
<td>40 (32-NR)</td>
<td>NR (22-NR)</td>
</tr>
<tr>
<td><strong>Median progression-free survival (95% CI; months)</strong></td>
<td>1.9 (1.8-5.7)</td>
<td>1.8 (1.6-5.8)</td>
</tr>
<tr>
<td><strong>Median overall survival (95% CI; months)</strong></td>
<td>11.4 (3.1-NR)</td>
<td>NR (3.5-NR)</td>
</tr>
</tbody>
</table>

---

Maximum Percentage Change From Baseline in Tumor Size \(^a\) Keynote-012 (RECIST v1.1, Central Review)

64-Year-Old Male With Recurrent Gastric Cancer Treated with Pembrolizumab

March 22, 2014

May 8, 2014

July 3, 2014

August 28, 2014

September 26, 2014

November 6, 2014
Multifactorial Biomarkers of Clinical Response to PDL-1 Blockade