Esophagogastric Cancers
Overview

- Her2/EGFR targeted therapy
- Antiangiogenic therapy
- Three studies
  - AMG337
  - FOLFOX +/- onartuzumab
### Approved HER2 targeting agents

<table>
<thead>
<tr>
<th>Anti-HER2 Agent</th>
<th>First approved by FDA</th>
<th>Compound</th>
<th>Target</th>
<th>Major mechanism</th>
<th>Approved indications</th>
<th>Typical regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>2007</td>
<td>Small molecule tyrosine kinase inhibitor</td>
<td>EGFR HER2</td>
<td>Reversibly blocking ATP-binding site on kinase domain of EGFR and HER2 [28]</td>
<td>HER2-positive metastatic breast cancer with prior exposure to trastuzumab</td>
<td>Lapatinib + capecitabine [12]</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>2012</td>
<td>Humanized murine monoclonal antibody</td>
<td>HER2</td>
<td>Binding to domain II of HER2, blocking ligand-dependent dimerization of HER2 with other HER members [29]</td>
<td>HER2-positive breast cancer in metastatic or neoadjuvant setting</td>
<td>Pertuzumab + trastuzumab + docetaxel [13, 30, 113]</td>
</tr>
<tr>
<td>Ado-trastuzumab emtansine (T-DM1)</td>
<td>2013</td>
<td>Trastuzumab linked with a non-reducible linker to DM1</td>
<td>HER2</td>
<td>Anti-tumor properties of trastuzumab combined with cytotoxic microtubule-depolymerizing DM1 [31]</td>
<td>HER2-positive metastatic breast cancer with prior exposure to trastuzumab</td>
<td>Single agent [14]</td>
</tr>
<tr>
<td>Afatanib</td>
<td>2013</td>
<td>Small molecule tyrosine kinase inhibitor</td>
<td>EGFR HER2 HER4</td>
<td>Irreversibly blocking kinase domain of EGFR/HER2, including erlotinib-resistant EGFR T790 M variant [32]</td>
<td>Advanced NSCLC with EGFR mutation</td>
<td>Single agent [24]</td>
</tr>
</tbody>
</table>

**Abbreviations:** EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer.
Suggested HER2 testing algorithm in GC/GEJ cancer

Patient tumour sample

IHC

0
+1
+2 (retest)

FISH/SISH*

- +

Eligible for trastuzumab

*cut off for FISH, SISH = HER2:CEP17 ratio ≥2

Van Cutsem E et al; ECCO/ESMO 2009
Bang Y, Van Cutsem E et al Lancet 2010

Presented By Eric Van Cutsem at 2015 Gastrointestinal Cancers Symposium
ToGA trial design
Phase III, randomized, open-label, international, multicenter study

3807 patients screened
810 HER2-positive (22.1%)

HER2-positive tumour (centrally assessed)
- IHC 3+ and/or FISH+
- Stratification factors
  - advanced vs metastatic
  - GC vs GEJ adenocarcinoma
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU*
  - *Chosen at investigator’s discretion
  - GEJ, gastroesophageal junction

5-FU or capecitabine^a + cisplatin
(n=290)

5-FU or capecitabine^a + cisplatin + trastuzumab
(n=294)

ToGA study: Primary end point: OS

Presented By Eric Van Cutsem at 2015 Gastrointestinal Cancers Symposium
Median OS increased to >1 year with Trastuzumab-based treatment

Presented By Eric Van Cutsem at 2015 Gastrointestinal Cancers Symposium

- BSC (1)
- FAMTX (2)
- C+S1 (3)
- CF (4)
- IF (5)
- EOF (6)
- DCF (4)
- ECF (6)
- ECX (6)
- XP (7)
- EOX (6)
- Trastuzumab + XP/FP (8)

Trastuzumab + XP/FP (8) for HER2 IHC 2+/FISH+ and IHC 3+

Logic study

HER2 Amplified AGC (N=545)

R

CapOX + Lapatinib

CapOX

CapOX + Lapl
CapOX + Placebo

Median survival
12.2 months
10.5 months

HR 0.91 [95% CI, 0.73-1.12]
P=0.3492

Hecht JR, Bang YJ, Qin S, et al ASCO 2013

Presented By Eric Van Cutsem at 2015 Gastrointestinal Cancers Symposium
## Ongoing phase III studies of HER2-targeting therapy for advanced gastric cancer

Presented By Eric Van Cutsem at 2015 Gastrointestinal Cancers Symposium

<table>
<thead>
<tr>
<th>Agents</th>
<th>Line</th>
<th>Treatment</th>
<th>N</th>
<th>Endpoint</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab (JACOB)</td>
<td>1</td>
<td>CX + Trastuzumab ± Pertuzumab</td>
<td>780</td>
<td>OS</td>
<td>Ongoing</td>
</tr>
<tr>
<td>TDM-1 (GATSBY)</td>
<td>2</td>
<td>TDM-1 vs taxane</td>
<td>412</td>
<td>OS</td>
<td>On-going</td>
</tr>
</tbody>
</table>
Targeting EGFR

Presented By Eric Van Cutsem at 2015 Gastrointestinal Cancers Symposium

EGFR

Overexpression: > 50%
KRAS/BRAF mutations: rare

Cetuximab: EXPAND
✓ XP vs. XP + cetuximab

Panitumumab: REAL3
✓ EOX vs. mEOX + panitumumab
### Phase III Studies of anti-EGFR antibodies for advanced gastric cancer

**Presented By Eric Van Cutsem at 2015 Gastrointestinal Cancers Symposium**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>N</th>
<th>Endpoint</th>
<th>Results in months</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real 3</td>
<td>EOX</td>
<td>553</td>
<td>OS</td>
<td>11.3</td>
<td>HR: 1.37 (1.07-1.76) p=0.013</td>
</tr>
<tr>
<td>UK</td>
<td>EOX + Panitumumab</td>
<td></td>
<td></td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>EXPAND</td>
<td>Capecitabine/cisplatin</td>
<td>904</td>
<td>PFS</td>
<td>5.6</td>
<td>HR: 1.091 (0.920-1.292) p=0.316</td>
</tr>
<tr>
<td>Germany</td>
<td>Capecitabine/cisplatin + cetuximab</td>
<td></td>
<td></td>
<td>4.4</td>
<td></td>
</tr>
</tbody>
</table>

Waddel T et al, Lancet Oncology 2013
Lordick F et al. Lancet Oncology 2013
AVAGAST: A Randomized Double-Blind Placebo-Controlled Phase III Study

Locally advanced or metastatic gastric cancer

Capecitabine*/Cisplatin (XP) + Placebo q3w
Capecitabine*/Cisplatin (XP) + Bevacizumab q3w

Stratification factors:
1. Geographic region
2. Fluoropirimidine backbone
3. Disease status

*5-FU also allowed if cape contraindicated
Cape 1000 mg/m² oral bid, d1–14, 1-week rest
Cisplatin 80 mg/m² d1
Bevacizumab 7.5 mg/kg d1
Maximum of 6 cycles of cisplatin
Cape and bevacizumab/placebo until PD

Kang ASCO 2010
Overall Survival

HR = 0.87
95% CI 0.73–1.03
p = 0.1002

Study month

Number at risk

XP + Placebo
XP + Bev

Kang ASCO 2010
Ramicurimab

- Fully human IgG1 antibody
- Binds to extracellular domain of VEGF receptor 2
- Blocks binding of VEGF-A, VEGF-C and VEGF-D
REGARD

Randomized Phase III 2\textsuperscript{nd} Line Ramucirumab vs. Placebo

Second line metastatic gastric and GEJ adenocarcinoma

Ramucirumab IV q 2 weeks

Placebo q 2 weeks

Primary EP: OS
N = 355

Fuchs GI ASCO 2013
### REGARD

<table>
<thead>
<tr>
<th></th>
<th><strong>Ramicirumab</strong></th>
<th><strong>BSC</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS</strong></td>
<td>5.2 mo HR 0.776 [0.63, 0.998]</td>
<td>2.6 mo</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>2.1 mo HR 0.483 [0.376, 0.620]</td>
<td>1.3 mo</td>
</tr>
<tr>
<td><strong>RR</strong></td>
<td>3.3%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

Fuchs GI ASCO 2013
Randomized Phase III 2\textsuperscript{nd} Line Paclitaxel +/- Ramucirumab

Primary EP: OS
N = 665

\textbf{Second line metastatic gastric and GEJ adenocarcinoma}

Stratified by..
Region*
Measurable vs. non-measurable disease
Time to progression on 1\textsuperscript{st} line therapy (< 6m vs. > 6m)

Paclitaxel 80 mg/m\textsuperscript{2} d1, 8, 15 + Ramucirumab IV q 2 weeks
N=33

Paclitaxel 80 mg/m\textsuperscript{2} d1, 8, 15 + Placebo q 2 weeks

*Region 1 = Australia/Western countries; Region 2 = S. America; Region 3 = Asia
RAINBOW: Overall Survival

HR (95% CI) = 0.807 (0.678, 0.962)
Stratified log rank p-value = 0.0169

<table>
<thead>
<tr>
<th>Patients / Events</th>
<th>RAM + PTX</th>
<th>PBO + PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median(mos) (95% CI)</td>
<td>330 / 256</td>
<td>335 / 260</td>
</tr>
<tr>
<td>9.63 (8.48, 10.81)</td>
<td>7.36 (6.31, 8.38)</td>
<td></td>
</tr>
</tbody>
</table>

6-month OS
RAM + PTX: 72%
PBO + PTX: 57%

12-month OS
RAM + PTX: 40%
PBO + PTX: 30%

Δ mOS = 2.3 months

Adapted from Wilke GI ASCO 2014
**Efficacy Summary**

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>RAM + PTX</th>
<th>PBO + PTX</th>
<th>HR p-value</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td>28%</td>
<td>16%</td>
<td>p = 0.0001</td>
<td>+ 12%</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>80%</td>
<td>64%</td>
<td>p &lt; 0.0001</td>
<td>+ 16%</td>
</tr>
<tr>
<td>PFS (med, mos)</td>
<td>4.40</td>
<td>2.86</td>
<td>HR 0.635</td>
<td>+ 1.5</td>
</tr>
<tr>
<td>- at 6-months</td>
<td>36%</td>
<td>17%</td>
<td>p &lt; 0.0001</td>
<td>+ 19%</td>
</tr>
<tr>
<td>- at 9-months</td>
<td>22%</td>
<td>10%</td>
<td></td>
<td>+ 12%</td>
</tr>
<tr>
<td>OS (med, mos)</td>
<td>9.63</td>
<td>7.36</td>
<td>HR 0.807</td>
<td>+ 2.3</td>
</tr>
<tr>
<td>- at 6-months</td>
<td>72%</td>
<td>57%</td>
<td>p = 0.0169</td>
<td>+ 15%</td>
</tr>
<tr>
<td>- at 12-months</td>
<td>40%</td>
<td>30%</td>
<td></td>
<td>+ 10%</td>
</tr>
</tbody>
</table>

A consistent additive effect of RAM in combination with paclitaxel was observed across all efficacy endpoints.
Targeting MET

Multiple Mechanisms of MET Activation

- HGF
- Ligand binding
- Overexpression Amplification
- Activating mutation
- Cross-talk

- EGFR
- EGFRvIII
- erbB3
- RON
- Integrin
- CD44...

Proliferation
Motility
Survival
Migration/Invasion
AMG 337 is a Potent and Highly Selective Small-Molecule Inhibitor of MET

<table>
<thead>
<tr>
<th>MET Isoform (Enzymatic Activity)</th>
<th>IC$_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>V1092I</td>
<td>21.5</td>
</tr>
<tr>
<td>H1112R</td>
<td>1</td>
</tr>
<tr>
<td>D1228H</td>
<td>&gt; 4000</td>
</tr>
<tr>
<td>Y1248H</td>
<td>1077</td>
</tr>
<tr>
<td>M1250T</td>
<td>4.7</td>
</tr>
<tr>
<td>HGF-stimulated pMET (PC3 cells)</td>
<td>&lt; 10</td>
</tr>
</tbody>
</table>

- Competitive binding assay conducted with 402 human kinases
  - AMG 337 bound only to MET
- Secondary pharmacology assays with enzymes, transporters, ion channels, and receptors
  - Binding to the adenosine transporter was the only activity inhibited

Hughes PE, et al. Presented at: AACR Annual Meeting; April 2014; San Diego, CA. Abstract 728
Figure adapted from Manning G, et al. Science. 2002;298:1912-1934.
Phase 1, Multicenter, Open-Label Study of AMG 337 Monotherapy

**Key Eligibility**
- Advanced solid tumors
- Age ≥ 18 years
- ECOG PS ≤ 2
- Adequate organ function
- Informed consent

**Treatment Cohorts**

<table>
<thead>
<tr>
<th>PO QD Escalation (3–9 Patients/ Cohort)</th>
<th>PO BID Escalation (3–9 Patients/ Cohort)</th>
<th>PO QD Expansion (~50 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QD MTD: 300 mg</td>
<td>BID MTD: not reached</td>
<td>300 mg in MET-amplified cancer</td>
</tr>
<tr>
<td><strong>25 mg</strong></td>
<td><strong>100 mg</strong></td>
<td></td>
</tr>
<tr>
<td><strong>50 mg</strong></td>
<td><strong>150 mg</strong></td>
<td></td>
</tr>
<tr>
<td><strong>100 mg</strong></td>
<td><strong>150 mg</strong></td>
<td></td>
</tr>
<tr>
<td><strong>150 mg</strong></td>
<td><strong>200 mg</strong></td>
<td></td>
</tr>
<tr>
<td><strong>200 mg</strong></td>
<td><strong>250 mg</strong></td>
<td></td>
</tr>
<tr>
<td><strong>300 mg</strong></td>
<td><strong>400 mg</strong></td>
<td></td>
</tr>
</tbody>
</table>

Patients received AMG 337 until progression or unacceptable toxicity.

**Endpoints**

**Primary**
- Safety/tolerability
- PK
- MTD

**Secondary**
- Response by RECIST 1.1

**Exploratory**
- Correlation of MET amplification with response

Presented By Eunice Kwak at 2015 Gastrointestinal Cancers Symposium
### Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>59 (19–85)</td>
</tr>
<tr>
<td>Men</td>
<td>55 (61.1%)</td>
</tr>
<tr>
<td>White</td>
<td>76 (84.4%)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>35 (38.9%)</td>
</tr>
<tr>
<td>1</td>
<td>51 (56.7%)</td>
</tr>
<tr>
<td>2</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td>Prior therapy, median (range)</td>
<td>2 (0–9)</td>
</tr>
<tr>
<td>MET amplification(^a)</td>
<td>19 (21.1%)</td>
</tr>
<tr>
<td>Escalation</td>
<td>9</td>
</tr>
<tr>
<td>Expansion</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>N = 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEJ/gastric/esophageal</td>
<td>21 (23.3%)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>18 (20.0%)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>10 (11.1%)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>5 (5.6%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td>Carcinoma of unknown origin</td>
<td>3 (3.3%)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>3 (3.3%)</td>
</tr>
<tr>
<td>Bladder</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Breast</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Other(^b)</td>
<td>18 (20.0%)</td>
</tr>
</tbody>
</table>

\(^a\)MET amplification was determined by a local CLIA-certified laboratory. \(^b\)Other included anal, gall bladder, head and neck, pancreatic, prostate, small cell lung, thyroid, testicular, and uterine cancer, and GBM and peritoneal mesothelioma. Data cutoff: July 23, 2014.
RECIST Responses in Patients With MET-Amplified GEJ/Gastric/Eosophageal Cancer

- 13 patients with MET-amplified GEJ/gastric/esophageal cancer treated to date; ORR = 8/13 (62%)

Presented By Eunice Kwak at 2015 Gastrointestinal Cancers Symposium
Response in 63-Year-Old Male With GEJ Cancer and MET Amplification

FDG-PET
Max Intensity Projections

Baseline
Week 5

Green: MET
Red: EGFR
Cyan: Chromosome 7

CT %Δ
Sum of Diameters From Baseline

%Δ SOD From Baseline

0% 5% 9% 17% 25% 33% 41% 49% 57% 65% 73% 81% 89% 97% 105%

PR
CR

Weeks on Treatment

Dose
Recist Response
Prior Therapy
TTP on Prior Therapy

200 mg
CR
FOLFOX
9 weeks

*Patient is still on treatment at 155 weeks, but more recent central read CT scans are not available.

Presented By Eunice Kwak at 2015 Gastrointestinal Cancers Symposium
FOLFOX +/- onartuzumab

Methods

Eligibility criteria
- Age >18
- Metastatic GEC
- HER2 negative
- ECOG PS 0/1
- No prior therapy for metastatic disease
- Tissue available
  N=123

R 1:1

mFOLFOX6+ onartuzumab (10 mg/kg) q2w
N=62

Onartuzumab
PD

12 cycles

mFOLFOX6+ placebo
q2w
N=61

Placebo
PD

• Stratified by Lauren histologic subtype and prior gastrectomy
• Primary objectives: PFS in the ITT population and the MET-positive subgroup (≥50% high staining by IHC)
• Secondary objectives: OS (ITT and MET-positive population), ORR, safety
• With 120 patients enrolled and 84 PFS events observed, target HRs were 0.70 in the ITT population and 0.60 in the MET-positive subgroup
• Conducted over 30 sites across Australia, Korea, Singapore, Taiwan, Thailand and USA

*Oxaliplatin 85 mg/m² + leucovorin 200 mg/m² + 5-fluorouracil 400 mg/m² bolus and 2400 mg/m² iv

Presented at the Gastrointestinal Cancers Symposium
Presented by: Manish Shah
## MET expression

<table>
<thead>
<tr>
<th>MET Expression</th>
<th>Onartuzumab + mFOLFOX6 (N=58)</th>
<th>Placebo+ mFOLFOX6 (N=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>50% cut-off:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET 2+/3+</td>
<td>16 (28)</td>
<td>19 (33)</td>
</tr>
<tr>
<td>MET 0/1+</td>
<td>42 (72)</td>
<td>38 (67)</td>
</tr>
<tr>
<td>MET 1+/2+/3+</td>
<td>57 (98)</td>
<td>55 (96)</td>
</tr>
<tr>
<td>MET 0</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td><strong>90% cut-off:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET 2+/3+</td>
<td>6 (10)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>MET 0/1+</td>
<td>52 (90)</td>
<td>49 (86)</td>
</tr>
<tr>
<td>MET 1+/2+/3+</td>
<td>53 (91)</td>
<td>49 (86)</td>
</tr>
<tr>
<td>MET 0</td>
<td>5 (9)</td>
<td>8 (14)</td>
</tr>
</tbody>
</table>

*Assessed by Ventana® CONFIRM Anti-total c-MET (SP44) IHC assay

Presented at the Gastrointestinal Cancers Symposium

Presented by: Manish Shah
Secondary endpoints

- At the time of the OS final analysis data cut-off (29 January 2014), 34 patients (54.8%) from the onartuzumab arm and 30 patients (49.2%) from the placebo arm had died.

**ITT**

- Median OS: 10.61 vs 11.27
- Stratified HR: 1.06
- (95% CI 0.64–1.75)
- p=0.8341

**MET-positive**

- Median OS: 8.51 vs 8.48
- Stratified HR: 1.12
- (95% CI 0.45–2.78)
- p=0.8021

- The stratified HR for OS in the MET-negative population was 1.09 (95% CI: 0.56–2.12)
- ITT ORR: 60.5% (26/43, n=4 complete response) for onartuzumab + mFOLFOX6 and 57.1% (24/42, n=1 complete response) for placebo + mFOLFOX6

*50% staining cut-off

Presented by: Manish Shah
Conclusions

• The addition of onartuzumab to mFOLFOX6 in metastatic GEC did not improve PFS in either an unselected population or in patients with MET-positive tumors.

• The safety profile of onartuzumab was similar to previous studies: edema, venous thromboembolism, and AEs leading to treatment discontinuation were more frequent in the onartuzumab arm than the placebo arm.
Hepatobiliary Cancers
Overview

• Profiling biliary tract cancers

• Prophylaxis of Hepatitis B

• Three studies
  – MM398
  – Ramicurimab for 2nd line HCC
  – 1st line HCC: Dovitinib vs. sorafenib

• Neuroendocrine update
Cancer of the Biliary Tract

- Three tumors:
  - Intrahepatic Cholangiocarcinoma (IHCCA)
  - Extrahepatic Cholangiocarcinoma (EHCCA)
  - Gallbladder Carcinoma (GBCA)

- Can be difficult to pinpoint the site of origin intra-operatively
- Extrahepatic tumors may be difficult to distinguish from pancreatic ductal carcinomas
- Intrahepatic tumors may be difficult to distinguish from non-biliary tract metastatic carcinomas
- Typically present at an advanced clinical and pathologic stage
- Typically are refractory to conventional therapies including cytotoxic chemotherapy and radiation

Presented at the Gastrointestinal Cancers Symposium

Presented by: Jeffrey S. Ross, M.D.
# Clinicopathologic Features of 554 Biliary Tract Cancers

<table>
<thead>
<tr>
<th>Feature at Time of Gene Profiling</th>
<th>Intrahepatic Cholangio-carcinoma (412 cases)</th>
<th>Extrahepatic Cholangio-carcinoma (57 Cases)</th>
<th>Gallbladder Carcinoma (85 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Patient Age</td>
<td>55.9 years</td>
<td>58.9 years</td>
<td>62.4 years</td>
</tr>
<tr>
<td>Gender</td>
<td>64% Female, 36% Male</td>
<td>37% Female, 63% Male</td>
<td>76% Female, 24% Male</td>
</tr>
<tr>
<td>Tumor Grade</td>
<td>0% Grade 1, 64% Grade 2, 36% Grade 3</td>
<td>4% Grade 1, 74% Grade 2, 23% Grade 3</td>
<td>6% Grade 1, 65% Grade 2, 29% Grade 3</td>
</tr>
<tr>
<td>Tumor Stage</td>
<td>46% Stage I, 18% Stage II, 18% Stage III, 18% Stage IV</td>
<td>0% Stage I, 2% Stage II, 25% Stage III, 74% Stage IV</td>
<td>1% Stage I, 5% Stage II, 39% Stage III, 55% Stage IV</td>
</tr>
<tr>
<td>Sample Used for Sequencing</td>
<td>82% Primary Tumor, 18% Metastasis Biopsy</td>
<td>28% Primary Tumor, 72% Metastasis Biopsy</td>
<td>41% Primary Tumor, 59% Metastasis Biopsy</td>
</tr>
</tbody>
</table>
### Summary of Genomic Alterations in Biliary Tract Cancers

<table>
<thead>
<tr>
<th>CGP Findings</th>
<th>IHCCA</th>
<th>EHCCA</th>
<th>GBCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GA/patient</td>
<td>3.6</td>
<td>4.4</td>
<td>4.0</td>
</tr>
<tr>
<td>CRGA/patient</td>
<td>2.0</td>
<td>2.1</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>ERBB2 Amplification</strong></td>
<td>4%</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>BRAF Substitutions</strong></td>
<td>5%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>KRAS Substitutions</strong></td>
<td>22%</td>
<td>42%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>PI3KCA Substitution</strong></td>
<td>5%</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>FGFR1-3 Fusions and Amplifications</strong></td>
<td>11%</td>
<td>0</td>
<td>3%</td>
</tr>
<tr>
<td><strong>CDKN2A/B Loss</strong></td>
<td>27%</td>
<td>17%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>IDH1/2 Substitutions</strong></td>
<td>20%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>ARID1A Alterations</strong></td>
<td>18%</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>MET Amplification</strong></td>
<td>2%</td>
<td>0</td>
<td>1%</td>
</tr>
</tbody>
</table>
ERBB2 Amplified GBCA Responds to Trastuzumab + Chemotherapy

A 64 year old female with recurrent gallbladder carcinoma. Axial contrast-enhanced CT images demonstrate (A) a 1.2 cm nodule in the gallbladder fossa adjacent to the hepatic flexure, and (B) a 1.6 cm nodule in the portocaval region. Both nodules were new from the postoperative scan (following resection of recurrent tumor in the gallbladder fossa), in keeping with recurrence. (C, D) Eight months later, both nodules are stable. (Case provided by Milind Javle, MDACC)
Expanded Analyses of NAPOLI-1: Phase 3 Study of MM-398 (nal-IRI), with or without 5-Fluorouracil and Leucovorin, versus 5-Fluorouracil and Leucovorin, in Metastatic Pancreatic Cancer (mPAC) Previously Treated with Gemcitabine-based Therapy

Presented By Li-Tzong Chen at 2015 Gastrointestinal Cancers Symposium
MM-398, Nanoliposomal Irinotecan (nal-IRI)*

- MM-398, liposome irinotecan injection, (120 mg/m²) has extended circulation
  - AUC of total irinotecan in blood is 1652 vs. 24 hr·μg/ml of conventional irinotecan (300 mg/m²)¹

- 72 hours after MM-398 dosing, SN-38 (active metabolite) level was 9.6 ng/g in tumor tissue and 1.7 ng/ml in blood²

Median OS of 5.2 months for MM-398 in single arm Phase 2 study of gemcitabine-refractory metastatic pancreatic cancer³

---

*Also known as PEP02, PharmaEngine, Inc., Taiwan.

Stratification factors: Albumin, KPS and ethnicity
Primary endpoint: Overall survival
Key secondary endpoints: PFS, ORR, CA19-9 response and safety

* Study was amended to add the MM-398 + 5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5FU/LV arm after the amendment (N=119), were used as the control for the combination arm.
Overall Survival: Intent to Treat Population (ITT)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, Months (95% CI)</th>
<th>Stratified HR**</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM-398+5-FU/LV</td>
<td>6.1 (4.8-8.9)</td>
<td>0.57 (0.41-0.80), p = 0.0009</td>
<td></td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>4.2 (3.3-5.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, Months (95% CI)</th>
<th>Stratified HR***</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM-398</td>
<td>4.9 (4.2-5.6)</td>
<td>0.93 (0.71-1.21), p = 0.5545</td>
<td></td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>4.2 (3.6-4.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Protocol-defined primary analysis data cut (14Feb2014, after 305 events). Survival follow-up is ongoing and the final results will be reported once all patients are off treatment and at least 90% events have taken place. Primary analysis for the study was by un-stratified log-rank test.

** Un-stratified HR: 0.67 (0.49-0.92), p = 0.0122

*** Un-stratified HR: 0.99 (0.77-1.28), p = 0.9416

Presented By Li-Tzong Chen at 2015 Gastrointestinal Cancers Symposium
Summary

• ITT analysis demonstrated statistically significant increase in overall survival (OS) of MM-398 + 5-FU/LV (MM-398 80 mg/m² q2w regimen) over 5-FU/LV
  • Significant increase also observed in PFS, ORR and CA19-9 response
  • MM-398 single agent, 120 mg/m² q3w regimen, did not show a significant difference in OS

• Forest plot sensitivity analyses favored MM-398 + 5-FU/LV over 5-FU/LV across prognostic subgroups, tumor characteristics and previous treatment

• In the PP population, the MM-398 + 5-FU/LV combination regimen achieved a median OS of 8.9 months (stratified HR: 0.47, p = 0.0018)

• Safety profile was manageable, with most frequent Grade ≥ 3 AEs including neutropenia, fatigue and GI effects (diarrhea and vomiting)
Phase 2 Open-Label Study in Frontline HCC

**N = 165**
- Advanced HCC (stage B or C)
- No prior systemic therapy for HCC
- ECOG performance status ≤ 1
- ≥ 1 measurable lesion per RECIST v1.1
- Child-Pugh Class A (5-6 points) with no encephalopathy

**Randomization 1:1**

- **Dovitinib (n = 82)**
  - 500 mg, once daily
  - 5 days on/2 days off

  **Stratification**
  - ECOG performance status (0 vs 1)

- **Sorafenib (n = 83)**
  - 400 mg, twice daily

**Endpoints**
- Primary: OS
- Secondary: time to tumor progression (per investigator assessment), disease control rate (per investigator assessment), time to definitive deterioration in ECOG performance status, safety, and pharmacokinetics

ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria In Solid Tumors.
Key Patient Eligibility

- Advanced HCC,\(^1\) stage B or C\(^2\)
- ECOG performance status of 0 or 1
- Not eligible for or have disease progression after surgical and/or locoregional therapies (which must not have contained sorafenib)
- ≥ 1 measurable lesion per RECIST v1.1
- Current cirrhotic status of Child-Pugh Class A (5-6 points) with no encephalopathy
- Adequate bone marrow, liver, and renal function
- No prior systemic therapy

OS Was Similar Between the Arms

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n/N</th>
<th>Median (95% CI), Weeks</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dovitinib</td>
<td>69/82</td>
<td>34.6 (28.6-39.4)</td>
<td>1.27 (0.90-1.79)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>67/83</td>
<td>36.7 (23.3-49.3)</td>
<td></td>
</tr>
</tbody>
</table>

- The observed OS drop in the KM plot in the dovitinib arm between weeks 24 and 42 was not due to toxicity.
  - Patients whose OS was within 24 to 42 weeks and who had already discontinued dovitinib due to AEs lived between 6.9 and 37.1 weeks after they discontinued dovitinib.

KM, Kaplan-Meier; n, number of events included in the analysis; N, number of patients included in the analysis.
# Neuroendocrine Tumors

## Tools: Tumor growth

<table>
<thead>
<tr>
<th></th>
<th>SSAs</th>
<th>Biologics</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td></td>
<td>Everolimus updated OS (Yao, ESMO 2014)</td>
<td>TemCape* (Fine, GI ASCO 2014)</td>
</tr>
</tbody>
</table>

* = not FDA-approved as antiproliferative

---

Presented By Pamela Kunz at 2015 Gastrointestinal Cancers Symposium
Diagnosed with NET

Locoregional / Resectable

- Surgery

Metastatic / Unresectable

- Cisplatin/Etoposide

- Observe SSA

Poorly-differentiated

Well-differentiated

Asymptomatic or stable disease

Progressive and / or symptomatic

Systemic treatment if widespread

Hepatic artery embolization if liver dominant disease

Pancreatic NET

- SSA
- Everolimus
- Sunitinib
- Cytotoxic chemotherapy

Non-Pancreatic NET

- IFN
- SSA

A multidisciplinary approach is critical

Presented By Pamela Kunz at 2015 Gastrointestinal Cancers Symposium
## Treatment characteristics

<table>
<thead>
<tr>
<th>Favor SSA (Octreotide/Lanreotide)</th>
<th>Favor Everolimus</th>
<th>Favor Sunitinib</th>
<th>Favor Chemo (STZ, Temozolomide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease factors:</td>
<td>Disease factors:</td>
<td>Disease factors:</td>
<td>Disease factors:</td>
</tr>
<tr>
<td>- Slow pace</td>
<td>- Functional tumors</td>
<td>- Fast pace</td>
<td>- High volume</td>
</tr>
<tr>
<td>- Low volume</td>
<td></td>
<td>- High volume</td>
<td></td>
</tr>
<tr>
<td>Patient Comorbidities:</td>
<td>Patient Comorbidities:</td>
<td>Patient Comorbidities:</td>
<td>Patient Comorbidities:</td>
</tr>
<tr>
<td>- Older patients</td>
<td>- Heart disease</td>
<td>- Severe lung disease</td>
<td>- Younger patients</td>
</tr>
<tr>
<td></td>
<td>- HTN</td>
<td>- Uncontrolled DM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Bleeding risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Key NET Protocols: GI and Lung

<table>
<thead>
<tr>
<th>Phase</th>
<th>Regimen</th>
<th>Tumor type</th>
<th>n</th>
<th>NCT</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>Octreotide LAR + IFNα vs. Octreotide LAR + Bevacizumab (SWOG 0518)</td>
<td>GI and lung NET</td>
<td>400</td>
<td>NCT00569127</td>
<td>Accrual complete</td>
</tr>
<tr>
<td>III</td>
<td>Everolimus vs. placebo (RADIANT-4)</td>
<td>GI and lung NET</td>
<td>302</td>
<td>NCT01524783</td>
<td>Accrual complete</td>
</tr>
<tr>
<td>II</td>
<td>Pazopanib vs. placebo (A021202)</td>
<td>GI and lung NET</td>
<td>165</td>
<td>NCT01841736</td>
<td>Ongoing</td>
</tr>
<tr>
<td>III</td>
<td>High-dose Octreotide LAR vs. PRRT (NETTER-1)</td>
<td>Midgut</td>
<td>280</td>
<td>NCT01578239</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
# Key NET Protocols: Pancreatic NETs

<table>
<thead>
<tr>
<th>Phase</th>
<th>Regimen</th>
<th>Tumor type</th>
<th>n</th>
<th>NCT</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Everolimus + Octreotide LAR +/- Bevacizumab (CALGB 80701)</td>
<td>pNET</td>
<td>138</td>
<td>NCT01229943</td>
<td>Accrual complete</td>
</tr>
<tr>
<td>II</td>
<td>Temozolomide vs. Temozolomide + Capecitabine (ECOG 2211)</td>
<td>pNET</td>
<td>145</td>
<td>NCT01824875</td>
<td>Ongoing</td>
</tr>
<tr>
<td>III</td>
<td>Everolimus followed by STZ-5FU vs. STZ-5FU followed by Everolimus (SEQTOR)</td>
<td>pNET</td>
<td>180</td>
<td>NCT02246127</td>
<td>Ongoing</td>
</tr>
<tr>
<td>II</td>
<td>Everolimus vs. placebo (ECOG 2212)</td>
<td>pNET after R0/R1 resection of hepatic metastasis</td>
<td>150</td>
<td>NCT02031536</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
Colorectal Cancer
Overview

• Two studies
  – Vitamin D status and survival in metastatic colorectal cancer
  – RAISE: FOLFIRI-RAM vs. FOLFIRI alone in 2nd line metastatic colorectal cancer

• Molecular profiling
Vitamin D Status and Survival of Metastatic Colorectal Cancer Patients:
Results from CALGB/SWOG 80405 (Alliance)

Kimmie Ng¹, Alan P. Venook², Kaori Sato¹, Bruce W. Hollis³, Donna Niedzwiecki⁴, Cynthia Ye⁴, I-Wen Chang⁵, Bert H. O’Neil⁶, Federico Innocenti⁷, Heinz-Josef Lenz⁸, Charles D. Blanke⁹, Robert J. Mayer¹, Charles S. Fuchs¹, Jeffrey A. Meyerhardt¹

¹Dana-Farber Cancer Institute, ²University of California San Francisco, ³Medical University of South Carolina, ⁴Alliance Statistics and Data Center, ⁵Wayne Memorial Hospital, ⁶Indiana University Hospital, ⁷University of North Carolina at Chapel Hill, ⁸University of Southern California, ⁹Oregon Health and Science University

Presented By Kimmie Ng at 2015 Gastrointestinal Cancers Symposium
Background: Vitamin D and Colorectal Cancer

- Vitamin D inhibits cell proliferation and angiogenesis, induces cell differentiation and apoptosis, and has anti-inflammatory effects

- Vitamin D receptor (VDR) and 1-α-hydroxylase are expressed in colorectal cancer (CRC) cells
  - Anti-proliferative effects greatest in cell lines with high VDR\(^1\)

- Treatment of \(APC^{min}\) mice with vitamin D decreases tumor burden,\(^2\) whereas adenoma numbers and size are increased in VDR-null \(APC^{min}\) mice\(^3\)

- Low plasma 25(OH)D levels associated with risk of CRC

---

CALGB/SWOG 80405: Final Design

Original

mCRC 1st-line

KPS ≥ 80 (codes 11 to 213)

Strata:
- FOLFOX/FOLFIRI
- Prior adjuvant chemo
- Prior XRT

FOLFIRI or FOLFOX

MD choice

Chemo + Cetuximab

Chemo + Bevacizumab

Chemo + Bevacizumab and Cetuximab

n = 1140 – 2334

1° Endpoint: Overall Survival

Presented at the Gastrointestinal Cancers Symposium

Presented by: Kimmie Ng, MD, MPH
## Baseline Characteristics (1)

*Median 25(OH)D = 17.2 ng/mL*

<table>
<thead>
<tr>
<th></th>
<th>Q1 (n=208)</th>
<th>Q2 (n=209)</th>
<th>Q3 (n=208)</th>
<th>Q4 (n=210)</th>
<th>Q5 (n=208)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median 25(OH)D, ng/mL (range)</td>
<td>8.0 (2.2-10.8)</td>
<td>13.6 (10.9-15.4)</td>
<td>17.2 (15.4-19.2)</td>
<td>21.4 (19.3-24.0)</td>
<td>27.5 (24.1-72.7)</td>
<td>--</td>
</tr>
<tr>
<td>Median age, years</td>
<td>59</td>
<td>60</td>
<td>60</td>
<td>61</td>
<td>61</td>
<td>0.07</td>
</tr>
<tr>
<td>Male, %</td>
<td>48</td>
<td>64</td>
<td>58</td>
<td>64</td>
<td>55</td>
<td>0.004</td>
</tr>
<tr>
<td>Black, %</td>
<td>25</td>
<td>12</td>
<td>6</td>
<td>7</td>
<td>2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ECOG 0 / 1, %</td>
<td>49 / 50</td>
<td>64 / 36</td>
<td>58 / 42</td>
<td>63 / 37</td>
<td>70 / 30</td>
<td>0.002</td>
</tr>
<tr>
<td>RAS WT / mut / unknown, %</td>
<td>33 / 30 / 37</td>
<td>31 / 30 / 39</td>
<td>26 / 39 / 35</td>
<td>38 / 29 / 33</td>
<td>37 / 21 / 42</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Baseline Characteristics (2)

- No significant difference in chemotherapy backbone, history of prior adjuvant therapy, or assigned biologic between quintiles of 25(OH)D

- Significantly lower 25(OH)D seen in:
  - Patients living in the north and northeast ($P < 0.0001$)
  - Patients with blood drawn in winter and spring ($P = 0.03$)
  - Obese patients ($P = 0.0006$)
  - Less physically-active patients ($P = 0.004$)
  - Patients not reporting vitamin D supplement use ($P < 0.0001$)
Higher Vitamin D Levels Associated with Better Survival

<table>
<thead>
<tr>
<th>Quintile</th>
<th>mOS (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24.5</td>
<td>21.7-28.6</td>
</tr>
<tr>
<td>2</td>
<td>30.0</td>
<td>25.8-32.2</td>
</tr>
<tr>
<td>3</td>
<td>28.4</td>
<td>24.2-31.0</td>
</tr>
<tr>
<td>4</td>
<td>27.2</td>
<td>25.0-31.5</td>
</tr>
<tr>
<td>5</td>
<td>32.6</td>
<td>27.7-36.9</td>
</tr>
</tbody>
</table>

Log-rank P = 0.01

Presented at the Gastrointestinal Cancers Symposium

Presented by: Kimmie Ng, MD, MPH
Multivariate Analysis

• Final model adjusted for:
  – Age
  – Sex
  – Race
  – ECOG performance status
  – Chemotherapy backbone
  – Previous adjuvant therapy
  – Assigned biologic
  – RAS mutation status
  – Season of blood draw
  – Geographic region of residence
  – Body-mass index
  – Physical activity
Multivariate Hazard Ratios: Overall Survival

Patients with the highest levels of vitamin D have a 35% improvement in overall survival.

P trend = 0.001
Randomized Double-Blind Phase II Trial of Vitamin D in Metastatic CRC

**FOLFOX-bevacizumab + Vitamin D3 8,000 IU/day x 2 weeks (loading dose), followed by Vitamin D3 4,000 IU/day (maintenance dose)**

- Bank blood at serial intervals for 25(OH)D assays
- Restaging scans and CEA every 4 cycles
- Treat until disease progression
- Primary end point = PFS

**Participating Sites:**
- DFCI
- MGH
- BIDMC
- DF/HCC satellites
- DF/HCC affiliates
- Northwestern
- Vanderbilt
- MSTI (Boise, ID)

Randomization 1:1

n=120

Presented at the **Gastrointestinal Cancers Symposium**

Presented by: Kimmie Ng, MD, MPH
Conclusions

• Metastatic CRC patients are frequently vitamin D deficient

• Higher vitamin D levels are associated with significantly improved overall survival and PFS

• This association persists across all patient subgroups and after adjusting for multiple prognostic factors

• A phase II randomized trial to evaluate the impact of vitamin D supplementation as an adjunct to chemotherapy is currently ongoing
RAISE: Study Design

Randomize (1:1)

Progression during or after bevacizumab, oxaliplatin, and a fluoropyrimidine

Ramucirumab (8 mg/kg) and FOLFIRI* every 2 weeks per cycle N=525

Placebo and FOLFIRI* every 2 weeks per cycle N=525

Treatment until disease progression or unacceptable toxicity

Primary endpoint: Overall survival

Secondary endpoints: PFS, ORR, PRO, Safety, PK, IG

Stratification factors:
- Geographic regions
- KRAS mutation status
- Time to disease progression after beginning first-line therapy

Sample size assumptions
- Hazard ratio of 0.8
- Median overall survival of 10 months in the control arm vs 12.5 months with ramucirumab with a 2-sided α level of 0.05
- Enrollment of 1050 patients with 756 events for 85% power
- Gatekeeping from OS to PFS to ORR

Abbreviations: IG=immunogenicity; PFS=progression-free survival; PK=pharmacokinetics; OS=overall survival; ORR=objective response rate.
*Inotecan: 160 mg/m²; Folinic acid: 400 mg/m²; 5-Fluorouracil: 400 mg/m² bolus, followed by 2400 mg/m² administered intravenously over 46 to 48 hours (continuously).

Presented By Josep Tabernero at 2015 Gastrointestinal Cancers Symposium
Key Inclusion Criteria

- Diagnosis of metastatic CRC (histological or cytological confirmation)
- Known KRAS mutation status
- ECOG PS score of 0 or 1
- Documented progressive disease during or after a first-line combination therapy of bevacizumab, oxaliplatin, and a fluoropyrimidine
- At least two doses of bevacizumab in first-line therapy
- Disease progression ≤6 months after the last dose of first-line therapy
- Adequate hematologic and biochemical parameters

Key Exclusion Criteria

- Previous first-line systemic therapy, other than a combination of bevacizumab, oxaliplatin, and a fluoropyrimidine
- Uncontrolled hypertension
- Arterial thrombotic event within 12 months
- Received bevacizumab ≤28 days or chemotherapy ≤21 days prior to randomization
- Known brain metastasis
- Grade 3 or higher bleeding event ≤3 months prior to randomization

Abbreviations: CRC=colorectal carcinoma; ECOG PS=Eastern Cooperative Oncology Group performance status.
## RAISE: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab + FOLFIRI (N=536)</th>
<th>Placebo + FOLFIRI (N=536)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>62 (21-83)</td>
<td>62 (33-87)</td>
</tr>
<tr>
<td><strong>Age group, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>212 (39.6)</td>
<td>215 (40.1)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>289 (53.9)</td>
<td>326 (60.8)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>405 (75.6)</td>
<td>410 (76.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>111 (20.7)</td>
<td>103 (19.2)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>263 (49.1)</td>
<td>259 (48.3)</td>
</tr>
<tr>
<td>1</td>
<td>268 (50.0)</td>
<td>273 (50.9)</td>
</tr>
<tr>
<td><strong>Number of metastatic sites, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>171 (31.9)</td>
<td>157 (29.3)</td>
</tr>
<tr>
<td>2</td>
<td>205 (38.2)</td>
<td>194 (36.2)</td>
</tr>
<tr>
<td>≥3</td>
<td>157 (29.3)</td>
<td>182 (34.0)</td>
</tr>
<tr>
<td><strong>Liver only metastasis, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>92 (17.2)</td>
<td>95 (17.7)</td>
</tr>
<tr>
<td><strong>Carcinoembryonic antigen, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200 µg/L</td>
<td>389 (72.6)</td>
<td>393 (73.3)</td>
</tr>
<tr>
<td>≥200 µg/L</td>
<td>108 (20.1)</td>
<td>107 (20.0)</td>
</tr>
</tbody>
</table>

Some patients may be missing from some categories.
RAISE: Overall Survival

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab + FOLFIRI</th>
<th>Placebo + FOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>536</td>
<td>536</td>
</tr>
<tr>
<td>Median, months</td>
<td>13.3</td>
<td>11.7</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(12.4, 14.5)</td>
<td>(10.8, 12.7)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.84 (0.73, 0.98)</td>
<td></td>
</tr>
<tr>
<td>P-value (log-rank)</td>
<td>0.0219 (stratified)</td>
<td></td>
</tr>
</tbody>
</table>

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Ram + FOLFIRI</th>
<th>Placebo + FOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>536</td>
<td>536</td>
</tr>
<tr>
<td>3</td>
<td>497</td>
<td>486</td>
</tr>
<tr>
<td>6</td>
<td>421</td>
<td>400</td>
</tr>
<tr>
<td>9</td>
<td>345</td>
<td>329</td>
</tr>
<tr>
<td>12</td>
<td>269</td>
<td>228</td>
</tr>
<tr>
<td>15</td>
<td>195</td>
<td>166</td>
</tr>
<tr>
<td>18</td>
<td>114</td>
<td>108</td>
</tr>
<tr>
<td>21</td>
<td>78</td>
<td>66</td>
</tr>
<tr>
<td>24</td>
<td>53</td>
<td>44</td>
</tr>
<tr>
<td>27</td>
<td>34</td>
<td>22</td>
</tr>
<tr>
<td>30</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>33</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>39</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>42</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; HR=hazard ratio; Ram=ramucirumab.
RAISE: Progression-free Survival

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab + FOLFIRI</th>
<th>Placebo + FOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>536</td>
<td>536</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>5.7 (5.5, 6.2)</td>
<td>4.5 (4.2, 5.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.79 (0.70, 0.90) (stratified)</td>
<td></td>
</tr>
<tr>
<td>P-value (log-rank)</td>
<td>0.0005 (stratified)</td>
<td></td>
</tr>
</tbody>
</table>

Patients at Risk

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ram + FOLFIRI</td>
<td>536 381 234 142 77 38 20 11 6 5 2 1 1 0 0 0</td>
</tr>
<tr>
<td>Placebo + FOLFIRI</td>
<td>536 345 182 92 52 31 17 10 3 1 0 0 0 0 0</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; HR=hazard ratio; Ram=ramucirumab.
Conclusions

- RAISE met its primary endpoint.
  - Demonstrated a statistically significant improvement in overall survival for ramucirumab and FOLFIRI vs placebo and FOLFIRI
  - In second-line metastatic CRC patients who progressed after first-line treatment with bevacizumab, oxaliplatin, and a fluoropyrimidine
- Consistent survival benefits were observed across subgroups.
- Ramucirumab in combination with FOLFIRI was well tolerated in patients with mCRC. Overall, the adverse events were considered manageable.
Molecular profiling

Cost of Sequencing

Baseline information:
Cost of genome sequencing compared with Moore’s law for computers

- Public Effort first human genome draft 2004
  13 years, $3,000,000,000

- Celera Effort first Human genome draft 2004
  $300,000,000

- Jim Watson Genome 2007
  $2,000,000

- Today
  $5,000-$10,000

- Goal
  $1,000

Source: Broad Institute

http://www.economist.com/node/16349358

Presented by Peter O’Dwyer – GI ASCO 2015
Who should not get tested?

- There can be no recommendation for who should get tested – this is an option, not currently SOC
- Patients who do not need a treatment option should not be tested outside of a clinical trial
- Patients who are too sick to avail of a treatment
- Recognize that positive findings are not equally likely across GI cancers
Benefit to Patient – Response?

• Currently anecdotal – responses reported to multiple targeted interventions
  – Colorectal
  – Esophageal/Gastric
  – Pancreatic
  – Hepatoma
• Examples such as the case discussed are widely-published but benefit not quantifiable
• Off-label drugs can be hard to negotiate
Molecularly-guided Trials

- Trials in Progress
  - Lung MAP – lung squamous cell carcinoma
  - FOCUS4 – First-line metastatic colorectal
  - MODUL - First-line metastatic colorectal
  - SIGNATURE – not disease-specific

- Evolving Trials
  - MATCH – Any line –not selected by primary site
  - ASSIGN – 2nd line colorectal – Phase II/III
Questions