Evolving Considerations in the Individualization of Treatment in Metastatic Colorectal Cancer (mCRC)

Minsig Choi MD
Director of GI Oncology
Director of Outpatient Oncology
Associate Professor
Department of Internal Medicine
Stony Brook University

Disclosure
× Honorarium/Speaker Bureau for
Bayer, Celgene, Novartis
Objectives:

- Compare and contrast the safety and efficacy of VEGF- and EGFR-targeted agents in the treatment of mCRC
- Evaluate the relative benefits and limitations of current therapy for mCRC beyond second-line therapy
- Demonstrate the ability to manage potential challenges in later lines of therapy in mCRC
- Describe the role of molecular biomarkers in selecting appropriate targeted agents for patients with mCRC
- Integrate clinical data and guideline recommendations into decisions about the optimal use of VEGF and EGFR-directed therapy in treatment protocols for patients with mCRC
- Define the risks and adverse events associated with the VEGF- and EGFR-targeted agents for mCRC in order to maximize tolerability and adherence to therapeutic regimens

Lifetime risk of cancer

<table>
<thead>
<tr>
<th>Sex</th>
<th>BIRTH TO 39 Y</th>
<th>40 TO 59 Y</th>
<th>60 TO 69 Y</th>
<th>70 Y AND OLDER</th>
<th>BIRTH TO DEATH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.42 (1 in 70)</td>
<td>8.44 (1 in 12)</td>
<td>15.71 (1 in 6)</td>
<td>37.74 (1 in 3)</td>
<td>43.89 (1 in 2)</td>
</tr>
<tr>
<td>Female</td>
<td>2.07 (1 in 48)</td>
<td>8.97 (1 in 11)</td>
<td>10.23 (1 in 10)</td>
<td>26.17 (1 in 4)</td>
<td>37.35 (1 in 3)</td>
</tr>
</tbody>
</table>

Selected GI cancers: global statistics

<table>
<thead>
<tr>
<th>Cancer</th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>1,200,000</td>
<td>608,700</td>
</tr>
<tr>
<td>Gastric</td>
<td>989,600</td>
<td>738,000</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>748,300</td>
<td>695,900</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>280,000</td>
<td>266,000</td>
</tr>
</tbody>
</table>

American Cancer Society Estimates: 2017

New cases 135,430
Deaths 50,260
Opportunities for colon cancer prevention

Markowitz and Bertagnolli, NEJM 2009
Proportion of Colon Cancer Preventable in Middle-Aged Men: HPFS

- BMI $\delta$ 25 kg/m2
- Physical activity $\varepsilon$ 15 MET-hours/week
- Daily folate containing multivitamin
- Alcohol < 15 g/day
- Non-smoker
- Red meat $\delta$ 2 servings/week

- 3.1% of all men

- Eliminate 71% of all colorectal cancer
  (95% CI, 33-92%)

5-year Survival by Stage for Patients with Colon Cancer

× 79 yo WF presented with bowel habit changes for 2 months and has colonoscopy and Bx done in West Islip 12/2014 and dx. with sigmoid cancer and had ct that showed multiple liver mets.

× Patient initially had complaints of constipation that was worsening for 2 months. She had anoxemia, nausea, and abdominal fullness associated with bowel habit changes and pencil thin stools, and painful defecation.

× Mild microcytic anemia with hgb- 10

× CEA 813
Metastatic colorectal Cancer

- 20 percent at presentation
- 10 percent live 5 years
- Median survival untreated patient 6 months
- Median survival with chemotherapy is 2 years
- K-ras wild type = 30 months
Advances in the treatment of stage IV CRC

Treatment paradigms for mCRC

× Some patients with stage IV disease can be cured by an multidisciplinary approach

× FOLFOX = 5-FU, leucovorin and oxaliplatin

× CapOX = capecitabine and oxaliplatin

× FOLFIRI = 5-FU, leucovorin, irinotecan

× targeted biologics to chemotherapy has improved outcomes, but modestly!
FOLFOX vs. FOLFIRI in metastatic colorectal cancer

Landscape in mCRC

- VEGF and EGFR mAbs competing for first-line patients in KRAS wt CRC
- Bevacizumab, Ramucirumab and Aflibercept competing for second-line patients with each other, and with EGFR mAbs in KRAS wt CRC
- Best sequence of therapies (VEGF vs EGFR) still to be established
- Regorafenib and TAS 102 as salvage therapy option
Bevacizumab
(Recombinant humanized MAb to VEGF)

- 93% human, 7% murine
- Recognizes all isoforms of VEGF, $K_d = 8 \times 10^{-10}$ M
- Terminal half-life, 17-21 days
- No dose-limiting toxicity as single agent in initial phase I trials
  - No increase in chemotoxicity
- Dose-response relationship unclear from initial phase I/II studies

Bevacizumab

- Colorectal cancer
- Lung cancer
- Kidney cancer
- Glioblastoma multiforme

**Toxicity**
- Hypertension (12%-34%)
- Venous thrombus (8%)
- Arterial thrombosis (6%)
- Proteinuria (4% to 36%)
- Gastrointestinal perforation (≤4%)
- CNS hemorrhage

XELOX vs FOLFOX4 ± bevacizumab: NO16966 study design

<table>
<thead>
<tr>
<th>Recruitment</th>
<th>Recruitment</th>
<th>Protocol amended to 2x2 placebo-controlled design after bevacizumab phase III data became available (n=1,400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2003 – May 2004</td>
<td>Placebo + XELOX (n=350)</td>
<td>Placebo + XELOX (n=350)</td>
</tr>
<tr>
<td>XELOX (n=317)</td>
<td>Bevacizumab + XELOX (n=350)</td>
<td>Bevacizumab + XELOX (n=350)</td>
</tr>
<tr>
<td>FOLFOX4 (n=317)</td>
<td>Bevacizumab + FOLFOX4 (n=349)</td>
<td>Bevacizumab + FOLFOX4 (n=349)</td>
</tr>
<tr>
<td>Initial 2-arm, open-label study (n=634)</td>
<td>Protocol amended to 2x2 placebo-controlled design after bevacizumab phase III data became available (n=1,400)</td>
<td>Protocol amended to 2x2 placebo-controlled design after bevacizumab phase III data became available (n=1,400)</td>
</tr>
</tbody>
</table>

Cassidy & Saltz. JCO 2008
**PFS chemotherapy + bevacizumab superiority: primary endpoint**

HR = 0.83 (97.5% CI: 0.72–0.95) (ITT)  
*p* = 0.0023

FOLFOX4 + placebo/XELOX + placebo  
n=701; 547 events

FOLFOX4 + bevacizumab/XELOX + bevacizumab  
n=699; 513 events

Saltz, et al. JCO 2008

**PFS chemotherapy + bevacizumab superiority: XELOX and FOLFOX4 subgroups**

XELOX subgroup  
HR = 0.77 (97.5% CI: 0.63–0.94)  
*p* = 0.0026

FOLFOX4 subgroup  
HR = 0.89 (97.5% CI: 0.73–1.08)  
*p* = 0.1871

Saltz, et al. ASCO GI 2007
Bevacizumab added to chemotherapy in metastatic CRC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS months</th>
<th>OS months</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFL</td>
<td>6.8</td>
<td>8.8</td>
</tr>
<tr>
<td></td>
<td>15.1</td>
<td>20.3</td>
</tr>
<tr>
<td>FOLFOX&lt;sup&gt;2nd-line&lt;/sup&gt;</td>
<td>7.6</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td>23.1</td>
<td>NR</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>8.0</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td>19.9</td>
<td>&lt;sup&gt;21.3&lt;/sup&gt; NS</td>
</tr>
</tbody>
</table>

Hurwitz, NEJM, 2006; Giantonia, JCO, 2007; Fuchs, JCO, 2007; Saltz, JCO, 2008
Many Options Are Available for the First-Line Treatment of mCRC

Patients appropriate for intensive therapy

- FOLFOX/CAPOX ± bevacizumab
- FOLFOX ± panitumumab
- FOLFIRI ± bevacizumab
- FOLFIRI ± cetuximab* or panitumumab*
- 5-FU/LV or capecitabine ± bevacizumab
- FOLFOXIRI ± bevacizumab

Patients not appropriate for intensive therapy

- Infusional 5-FU/LV or capecitabine ± bevacizumab
- Cetuximab*‡
- Panitumumab*‡

*Cetuximab or panitumumab for RAS WT only

Provision of anti-EGFR therapy in the setting of any RAS mutant can be detrimental


VELOUR: Phase III study of FOLFIRI + aflibercept after failure of oxaliplatin-based treatment

Metastatic CRC

N = 1,200

Stratification:
- PS
- Prior bevacizumab

Overall Survival

Symbol=Censor
Placebo/FOLFIRI  Median = 12.06 months
Aflibercept/FOLFIRI  Median = 13.50 months

Stratified HR=0.817 [95.34%CI, 0.713-0.937]
Log-rank p = 0.0032

Number at Risk  Time (Months)
Placebo  614  573  485  401  286  193  131  87  51  31  14
AFLI  612  566  498  416  311  216  148  104  75  49  33

Angiogenesis signaling: redundancy of ligands and receptors
### Anti-EGFR in First line Treatment of CRC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Cetuximab</th>
<th>Panitumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRYS`1 AL1 (KRAS WT)</td>
<td>Cont. SFU/FAOx + Cetuximab</td>
</tr>
<tr>
<td></td>
<td>(N=350 vs 316)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COIN`2 (KRAS WT)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=367 vs 362)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NORDIC VII`3 (KRAS WT)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=185 vs 194)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRIME`2034 (KRAS WT)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=590 vs 593)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>FOLFIRI</th>
<th>FOLFIRI + Cetuximab</th>
<th>FOLF/XE L/OX</th>
<th>FOLF/XE/OX + Cetuximab</th>
<th>Cont. 5-FU/FAOx</th>
<th>Cont. SFU/FAOx + Cetuximab</th>
<th>FOLFOX</th>
<th>FOLFOX + Panitumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (mos)</td>
<td>20.0</td>
<td>23.5</td>
<td>17.9</td>
<td>17.0</td>
<td>22.0</td>
<td>20.1</td>
<td>19.7</td>
<td>23.9</td>
</tr>
<tr>
<td>P value</td>
<td>0.0093</td>
<td>0.80</td>
<td>0.003</td>
<td>1.038</td>
<td>0.006</td>
<td>1.14</td>
<td>0.17</td>
<td>0.89</td>
</tr>
<tr>
<td>PFS (mos)</td>
<td>8.4</td>
<td>9.0</td>
<td>8.6</td>
<td>8.6</td>
<td>8.7</td>
<td>7.9</td>
<td>8.6</td>
<td>10</td>
</tr>
<tr>
<td>P value</td>
<td>0.0012</td>
<td>0.70</td>
<td>0.002</td>
<td>0.959</td>
<td>0.006</td>
<td>1.07</td>
<td>0.01</td>
<td>0.80</td>
</tr>
<tr>
<td>ORR, %</td>
<td>39.7</td>
<td>57.3</td>
<td>57</td>
<td>64</td>
<td>47</td>
<td>46</td>
<td>48</td>
<td>57</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td></td>
<td>0.049</td>
<td>0.87</td>
<td>0.87</td>
<td></td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

### Cetuximab (Erbitux)

**Uses**
- Colorectal cancer, metastatic, KRAS wild-type
- Head and neck cancer (squamous cell)

**Toxicity**
- Dermatologic: Rash/desquamation (95%; grades 3/4: 16%) dry skin (57%), pruritus (47%), nail changes (31%)
- Endocrine & metabolic: Hypomagnesemia (55%; grades 3/4: 6% to 17%)
mAbs target tumor cell-bound EGFR

Extracellular

EGF-R

Ligand

Pi3K

Ras

PTEN

Raf

Akt

MEK

MAPK

Intracellular

DNA

Cell survival

Proliferation

Angiogenesis

Cell Motility

Metastasis

Moss and Burtzness, NEJM 2005; 353
mAbs target tumor cell-bound EGFR

Extracellular

Intracellular

Ligand

EGF-R

PI3K

PTEN

Akt

Raf

MEK

MAPK

Ras

Cell survival

Proliferation

DNA

Cell Motility

Angiogenesis

Metastasis

KRAS as biomarker for panitumumab response in mCRC

Patients with **KRAS WT**

<table>
<thead>
<tr>
<th></th>
<th>Panitumumab + BSC</th>
<th>Median (weeks)</th>
<th>Mean (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>115/124 (96)</td>
<td>12.3</td>
<td>19.0</td>
<td></td>
</tr>
<tr>
<td>114/119 (96)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients with **KRAS MT**

<table>
<thead>
<tr>
<th></th>
<th>Panitumumab + BSC</th>
<th>Median (weeks)</th>
<th>Mean (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>76/84 (95)</td>
<td>7.4</td>
<td>9.9</td>
<td></td>
</tr>
<tr>
<td>95/100 (95)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HR: 0.45** (95% CI: 0.34–0.59)

Stratified log-rank test: p<0.0001

Amado et al. JCO 2008
NCIC CTG CO.17: randomized phase III trial in mCRC cetuximab vs BSC (no cross-over)

<table>
<thead>
<tr>
<th>KRAS MT&lt;sup&gt;1&lt;/sup&gt;</th>
<th>KRAS WT&lt;sup&gt;1&lt;/sup&gt;</th>
<th>All patients&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSC (n=83)</td>
<td>Cetuximab (n=81)</td>
<td>BSC (n=113)</td>
</tr>
<tr>
<td>RR (%)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>OS (months)</td>
<td>4.6</td>
<td>4.5</td>
</tr>
</tbody>
</table>


CRYSTAL study: first line

- Primary endpoint: PFS (independent review)
- Secondary endpoints: RR, DCR, OS, Safety, QoL
- Sample size: 1,217 patients randomized; ITT: 1,198 pts
CRYSTAL: efficacy update after additional KRAS testing

<table>
<thead>
<tr>
<th>KRAS WT</th>
<th>FOLFIRI (n=350)</th>
<th>FOLFIRI + cetuximab (n=316)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (%)</td>
<td>39.7</td>
<td>57.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>8.4</td>
<td>HR=0.7</td>
<td>0.0012</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>20</td>
<td>HR=0.8</td>
<td>0.0093</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KRAS MT</th>
<th>FOLFIRI (n=183)</th>
<th>FOLFIRI + cetuximab (n=214)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (%)</td>
<td>36.1</td>
<td>31.3</td>
<td>0.34</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>7.7</td>
<td>7.4</td>
<td>0.26</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>16.7</td>
<td>16.2</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Van Cutsem, et al. JCO 2011

RAS, RAF and PIK3CA Mutations in Colorectal Cancer

- Mutation frequency
  - KRAS: 40%
  - NRAS: 5-10%
  - BRAF: 5%
  - PIK3CA: 15%

- BRAF and KRAS/NRAS mutations are mutually exclusive
- KRAS and NRAS mutations are mutually exclusive

De Roock, Lancet Oncol, 2010
PRIME Study: FOLFOX +/- Pmab
First-Line

A Progression-free Survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No.</th>
<th>Hazard Ratio for Progression or Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized KRAS exon 2</td>
<td>616</td>
<td>0.80 (0.66–0.97)</td>
</tr>
<tr>
<td>Altered KRAS exon 2</td>
<td>440</td>
<td>1.29 (1.04–1.62)</td>
</tr>
<tr>
<td>Prospective-retrospective analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized KRAS</td>
<td>512</td>
<td>0.72 (0.58–0.90)</td>
</tr>
<tr>
<td>Altered KRAS</td>
<td>548</td>
<td>1.31 (1.07–1.60)</td>
</tr>
<tr>
<td>Normalized KRAS exon 2, altered other RAS</td>
<td>188</td>
<td>1.29 (0.79–2.07)</td>
</tr>
</tbody>
</table>

PFS

Exon 2 WT/ Other Mut

OS

Exon 2 WT/ Other Mut

B Overall Survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No.</th>
<th>Hazard Ratio for Death from Any Cause (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized KRAS exon 2</td>
<td>616</td>
<td>0.83 (0.67–1.02)</td>
</tr>
<tr>
<td>Altered KRAS exon 2</td>
<td>440</td>
<td>1.24 (1.08–1.42)</td>
</tr>
<tr>
<td>Prospective-retrospective analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized KRAS</td>
<td>512</td>
<td>0.75 (0.62–0.90)</td>
</tr>
<tr>
<td>Altered KRAS</td>
<td>548</td>
<td>1.15 (1.00–1.35)</td>
</tr>
<tr>
<td>Normalized KRAS exon 2, altered other RAS</td>
<td>188</td>
<td>1.29 (0.79–2.07)</td>
</tr>
</tbody>
</table>

Panitumumab–FOLFOX Better

FOLFOX

Panitumumab–FOLFOX Better

FOLFOX

Adapted from: A Sobrero et al. GI Symposium 2012

* PFS “on treatment” HR = .73; p=.001

181: FOLFIRI +/- Panitumumab
PFS and OS

PFS

OS

Adapted from: A Sobrero et al. GI Symposium 2012

* PFS “on treatment” HR = .73; p=.001
**20050181: FOLFIRI +/- Pmab**

**Second-Line**

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>MT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS Exon 2</strong></td>
<td>0.73</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>WT</strong></td>
<td>0.59</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>KRAS Exon 2</strong></td>
<td>0.68</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>WT</strong></td>
<td>0.50</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>MT RAS</strong></td>
<td>0.55</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>WT RAS</strong></td>
<td>0.56</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>MT RAS</strong></td>
<td>0.56</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Un eval RAS</strong></td>
<td>0.57</td>
<td>0.71</td>
</tr>
</tbody>
</table>

**Efficacy Analysis Sets**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>HR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WT KRAS Exon 2</strong></td>
<td>597</td>
<td>0.65</td>
<td>0.50 - 0.75</td>
</tr>
<tr>
<td><strong>MT KRAS Exon 2</strong></td>
<td>486</td>
<td>0.65</td>
<td>0.50 - 0.75</td>
</tr>
<tr>
<td><strong>MT RAS</strong></td>
<td>415</td>
<td>0.63</td>
<td>0.50 - 0.75</td>
</tr>
<tr>
<td><strong>WT KRAS Exon 2 MT RAS</strong></td>
<td>593</td>
<td>0.70</td>
<td>0.56 - 0.90</td>
</tr>
<tr>
<td><strong>Un eval RAS</strong></td>
<td>178</td>
<td>0.80</td>
<td>0.57 - 1.25</td>
</tr>
</tbody>
</table>

**PFS**

**OS**

**Hazard Ratio (Pmab+FOLFIRI / FOLFIRI Alone)**

---

**VEGF vs EGFR antibodies in advanced CRC: simplified**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Strength</th>
<th>Weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VEGF antibodies</strong></td>
<td>Delay in tumor progression</td>
<td>Limited single agent activity</td>
</tr>
<tr>
<td></td>
<td>Gain in time</td>
<td>Weak effect on RR (per RECIST)</td>
</tr>
<tr>
<td></td>
<td>Toxicity profile</td>
<td></td>
</tr>
<tr>
<td><strong>EGFR antibodies</strong></td>
<td>Single agent activity</td>
<td>Gain in time-to-progression moderate</td>
</tr>
<tr>
<td></td>
<td>Consistent increase in RR</td>
<td>Toxicity profile</td>
</tr>
<tr>
<td></td>
<td>Activity independent of line of therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Predictive marker</td>
<td></td>
</tr>
</tbody>
</table>
Ras as a biomarker

× K-ras mutants do not benefit from EGFR Ab therapy
× testing for these additional codons could help screen 10-20% more patients with mCRC for treatment with EGFR inhibitors
× these data have not yet been prospectively validated
× This method could help to more accurately select patients who will benefit from EGFR inhibitors.
× NCCN now recommends testing for all RAS mutations

Phase III study design

- Patients ≥18 years with histologically confirmed diagnosis of mCRC
- ECOG PS 0-2
- prior adjuvant chemotherapy allowed if completed >6 month before inclusion

• Amendment in October 2008 to include only KRAS wildtype patients
• 150 active centers in Germany and Austria
**FIRE-3 Update ESMO 2013: Expanded Mutational testing**

**KRAS wt exon 2 subset**

<table>
<thead>
<tr>
<th></th>
<th>EXON 1</th>
<th>EXON 2</th>
<th>EXON 3</th>
<th>EXON 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>12, 13</td>
<td>wt</td>
<td>61</td>
<td>146</td>
</tr>
<tr>
<td>NRAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**KRAS wt exon 2 subset**

- **KRAS**
  - EXON 1: 12, 13
  - EXON 2: wt
  - EXON 3: 61
  - EXON 4: 146

- **NRAS**
  - EXON 1: 12, 13
  - EXON 2: 59
  - EXON 3: 61
  - EXON 4: 117

- **BRAF**
  - EXON 11: 0%
  - EXON 15: 10%

15% additional RAS mutations

Heinemann et al, ESMO 2013.

**FIRE-3 ESMO/ECCO Update Overall Survival**

**All-RAS* wild-type**

- **Events**
  - n/N (%)
  - Median (months)
  - 95% CI

<table>
<thead>
<tr>
<th>Events</th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>91/171</td>
<td>33.1</td>
<td>24.5 – 39.4</td>
</tr>
<tr>
<td>110/171</td>
<td>25.6</td>
<td>22.7 – 28.6</td>
</tr>
</tbody>
</table>

**HR 0.70 (95% CI: 0.53 – 0.92)**

*p (log-rank)= 0.011*

Frontline systemic therapy for colorectal cancer
CALGB 80405

Primary endpoint = overall survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>OS (m)* Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + Cetux</td>
<td>578 (375)</td>
<td>29.9</td>
<td>27.0-32.9</td>
</tr>
<tr>
<td>Chemo + Bev</td>
<td>559 (371)</td>
<td>29.0</td>
<td>25.7-31.2</td>
</tr>
</tbody>
</table>

P=0.34
HR 0.925 (0.78-1.09)

*Original FIRE-3: 28.7 vs. 25 mo
80405 Overall Survival By Arm: Updated ESMO 2014 (All RAS Wild Type Patients)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chem o + Bev</td>
<td>256 (178)</td>
<td>31.2 (26.9-34.3)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.40</td>
</tr>
<tr>
<td>Chem o + Cetux</td>
<td>270 (177)</td>
<td>32.0 (27.6-38.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NCCN Guidelines: Chemotherapy for Advanced or Metastatic Disease

1. **FOLFOX or CapeOX ± bevacizumab**

2. **FOLFOX + cetuximab or panitumumab**

3. **FOLFIRI or irinotecan ± bevacizumab or ziv-aflibercept**

4. **Cetuximab or panitumumab**

5. **FOLFIRI or irinotecan ± bevacizumab or ziv-aflibercept**

6. **Regorafenib/TAS 102**

7. **Regorafenib/TAS 102 clinical trial or BSC**

8. **Regorafenib/TAS 102 clinical trial or BSC**

*KRAS/NRAS wild-type only. **STIVARGA is a treatment option for patients who have progressed through all available regimens (e.g., KRAS/NRAS mutant or KRAS/NRAS wild-type with previous exposure to an anti-EGFR inhibitor).
NCCN Guidelines: Chemotherapy for Advanced or Metastatic Disease

1. NCCN Colon Cancer, v2. 2015.

FOLFIRI ± bevacizumab

1st Progression

FOLFIRI + cetuximab or panitumumab*

Cetuximab or panitumumab* ± irinotecan

FOLFOX or CapeOX ± bevacizumab

2nd Progression

Cetuximab or panitumumab* ± irinotecan

FOLFOX or CapeOX ± bevacizumab

3rd Progression

Regorafenib/TAS 102 clinical trial or BSC

Regorafenib/TAS 102 clinical trial or BSC

*KRAS/NRAS wild-type only. **STIVARGA is a treatment option for patients who have progressed through all available regimens (e.g., KRAS/NRAS mutant or KRAS/NRAS wild-type with previous exposure to an anti-EGFR inhibitor).

Phase III study of regorafenib versus placebo in refractory mCRC (CORRECT)

Regorafenib 160 mg PO
3 weeks on, 1 week off

N = 690

Met its primary endpoint!

To be presented 1/21/2012
Overall survival (primary endpoint)

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>6.4 mos</td>
<td>5.0 mos</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.9–7.3</td>
<td>4.4–5.8</td>
</tr>
</tbody>
</table>

Hazard ratio: 0.77 (95% CI: 0.64–0.94)
1-sided p-value: 0.0052
MSI-H and MSS as a biomarker

- Nivolumab and pembrolizumab monotherapy has activity in patients with MSI H status.

- Combination of nivolumab + ipilimumab also demonstrated promising preliminary activity.

- Cobimetinib + atezolizumab resulted in a higher clinical response rate in MSS patients than expected from either cobimetinib or atezolizumab alone.

- MEK inhibition + PDL1 in MSS colon cancer. A Phase 3 study to evaluate the combination in chemo-refractory mCRC is open and actively recruiting (NCT02788279)
Multidisciplinary Management of stage IV disease


The Arsenal for mCRC

In 2017, 11 agents are currently available for the treatment of mCRC
Summary

- Biomarkers tell us about the individual patient’s tumor
- K-ras and MSI-H tumors have specific therapies that can help individualized patients
- VEGF and EGFR therapies has modestly improved clinical outcome in CRC patients
- Integrating clinical data and guidelines can be improved with EMR and electronic chemo orders
- We are just at the beginning of this era of treatment options for patients using molecular markers
- Individualizing risk and adverse events to patients are potential challenges to our patients
- Large Data and clinical trials in elderly and patients with comorbidity is really needed

Total Number of Cancer Deaths Avoided from 1991-2005 in Men and from 1992-2005 in Women


Copyright ©2009 American Cancer Society
Thanks!

GI oncology questions
Minsig.choi@stonybrookmedicine.edu
cellphone 631-620-1381