Targeted therapy in CRC

Cessal Thommachan Kainickal
Patient Characteristics Drive Decision Making in mCRC Treatment

- Performance status
- Age
- Comorbid illnesses
- Extent of disease
- Intent of treatment: palliative vs potentially curative
- Previous adjuvant therapy within 1 yr
- Organ function: hepatic and renal
- Underlying/uncontrolled hypertension
- Bleeding risks/concerns
mCRC goal: increasing OS

Classification

- Upfront resectable

Treatment strategy

- Resection

Treatment goal

- Curative surgery

Initially unresectable

- Potentially resectable: CT + biologic (20–30%)
- Permanently unresectable: CT + biologic (60–70%)

Relapse

Maximising OS, while maintaining QoL
Liver-Limited mCRC:

Scope of Problem

- 30% synchronous metastases
- Additional ~ 50% will develop metastases
- 30% to 35% “liver only” metastases

10% to 25% candidates for Surgery

75% to 90% not candidates for surgery
Palliative chemotherapy

Cure rate: 20% to 30%
5-yr survival: 40% to 60%

70% to 80% relapse within 2 yrs
Conversion Therapy: Practical Issues

• FOLFOX or FOLFIRI

• FOLFOXIRI attractive but at expense of increased toxicity

• Limit duration of preoperative therapy to 3-4 mos
  – Treat to resectability and not to best response
  – Minimizes hepatotoxicity

• Role of biologics is evolving
  – Data with cetuximab appears to be most mature in wild-type KRAS CRC
  – Bevacizumab is an appropriate option in setting of mutant KRAS
    – If bevacizumab is used, discontinue 6-8 wks before planned surgery
Treatment-Associated Liver Toxicity

- 5-FU: steatosis
- Irinotecan: steatohepatitis
- Oxaliplatin: sinusoidal/vascular injury
- Bevacizumab
  - Potential wound healing complications
  - Need to wait 6-8 wks before surgical resection
- Cetuximab: no acute or chronic effects to date
- Incidence of postoperative complications increases with prolonged use
First-line FOLFOX and FOLFIRI Are Equivalent

- Randomized phase III trial to determine which sequence is better (treatment switched at progression)

First-line FOLFOX and FOLFIRI Are Equivalent

- Median PFS after first-line therapy similar
  - 8.5 vs 8.0 mos for FOLFIRI vs FOLFOX6 ($P = .26$)

mCRC: Approved/Investigational Drugs

Emerging Therapeutics
- TAS102
- Erlotinib/Cetuximab
- Combinations

Anti-Angiogenesis
- Bevacizumab
- Ziv-Aflibercept
- Regorafenib

Anti-Growth
- Cetuximab
- Panitumumab

Classical Chemotherapeutics
- Oral/Intravenous Fluoropyrimidines
- Raltitrexed
- Irinotecan
- Oxaliplatin
- Mitomycin C
mCRC: Targeted Therapy – Anti-Angiogenic

Ziv-Aflibercept
Fusion protein/VEGF Trap

Bevacizumab
Anti-VEGFA antibody

PIGF
VEGF-B
VEGF-A

Lymphangiogenic Factors
VEGF-C
VEGF-D

No (Clinically) Predictive Biomarker

Regorafenib
Small molecule TKI targeting other TK receptors

PIGF = placental growth factor; TK = tyrosine kinase; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor

Figure adapted from: Fakih M. Expert Rev Anticancer Ther. 2013;13:427-438.[2]
Mechanism of action of bevacizumab

Regression of existing tumour vasculature\(^1\text{–}^3\)

Inhibition of new vessel growth\(^1\text{–}^3,^8\)

Anti-permeability of surviving vasculature\(^11\text{–}^13\)

Early and continued effects result in:
- Maintenance of more functional, normal vasculature
- Potentially improved drug delivery
- Inhibition of tumour growth and metastasis\(^1\text{–}^9\)

## Bevacizumab Associated Toxicity

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Incidence With Bev Across Indications,[¹] %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥ 3 ATE</td>
<td>2.6</td>
<td>- Risk of ATE increased in pts 65 yrs of age or older or with ATE history</td>
</tr>
<tr>
<td>Grade 3/4 HTN</td>
<td>5-18*</td>
<td>- Patients should receive otherwise standard CV prophylaxis and have BP monitored and managed</td>
</tr>
<tr>
<td>GI perforations</td>
<td>0.3-2.4</td>
<td></td>
</tr>
<tr>
<td>Grade ≥ 3 hemorrhagic event</td>
<td>1.2-4.6†</td>
<td>- Bevacizumab not recommended for pts with serious hemorrhage or recent hemoptysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Risk of major bleeding does not appear to be increased in pts receiving full-dose anticoagulation tx without other risk factors</td>
</tr>
<tr>
<td>Wound complications</td>
<td>15‡</td>
<td>- Discontinue 4-8 wks before surgery, resume 6-8 wks postsurgery</td>
</tr>
</tbody>
</table>

*Predominantly grade 3.
†May apply more to NSCLC.
‡When surgery conducted during bevacizumab therapy.

- Potential for increased VTE risk controversial, increased risk noted in 1 study, but not in others[²,³]

# First-line Chemotherapy + Bevacizumab in mCRC: Efficacy

<table>
<thead>
<tr>
<th>Comparative Regimens, Mos</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFL/Bev vs IFL(^1)</td>
<td>10.6 vs 6.2</td>
<td>20.3 vs 15.6</td>
</tr>
<tr>
<td>FOLFOX4/XELOX/Bev vs FOLFOX4/XELOX(^2)</td>
<td>9.4 vs 8.0</td>
<td>21.3 vs 19.9</td>
</tr>
</tbody>
</table>

N016966: Study Design

- Randomized phase III trial

Unresectable mCRC with no previous systemic therapy for mCRC and no previous oxaliplatin or bevacizumab

(N = 1401)

- XELOX + Placebo (n = 350)
- XELOX + Bevacizumab (n = 350)
- FOLFOX4 + Placebo (n = 351)
- FOLFOX4 + Bevacizumab (n = 350)

N016966: Efficacy Results

- PFS significantly increased with addition of bevacizumab to chemotherapy

mCRC: Approved/Investigational Drugs

Emerging Therapeutics
- TAS102
- Erlotinib/Cetuximab
- Combinations

Anti-Angiogenesis
- Bevacizumab
- Ziv-Aflibercept
- Regorafenib

Anti-Growth
- Cetuximab
- Panitumumab

Classical Chemotherapeutics
- Oral/Intravenous Fluoropyrimidines
- Raltitrexed
- Irinotecan
- Oxaliplatin
- Mitomycin C
Phase III VELOUR Study: FOLFIRI ± ziv-Aflibercept as Second-line Therapy in mCRC

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, safety, immunogenicity

Patients with mCRC progressing on first-line oxaliplatin-based chemotherapy (N = 1226)

- FOLFIRI + ziv-Aflibercept 4 mg/kg q2w (n = 612)
- FOLFIRI + Placebo q2w (n = 614)

*30% had previous bevacizumab

Stratified by previous bevacizumab (yes vs no), ECOG PS (0 vs 1 vs 2)

### VELOUR: OS and PFS Stratified by Previous Bevacizumab

#### OS

<table>
<thead>
<tr>
<th>Strata (as per IVRS)</th>
<th>N</th>
<th>HR (95.34% CI)</th>
<th>HR</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1226</td>
<td>0.82 (0.713-0.937)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous Bev</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>853</td>
<td>0.79 (0.669-0.927)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>373</td>
<td>0.86 (0.673-1.104)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### PFS

<table>
<thead>
<tr>
<th>Strata (as per IVRS)</th>
<th>N</th>
<th>HR (95% CI)</th>
<th>HR</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1226</td>
<td>0.76 (0.661-0.869)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous Bev</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>853</td>
<td>0.80 (0.679-0.936)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>373</td>
<td>0.66 (0.512-0.852)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mCRC: Approved/Investigational Drugs

Emerging Therapeutics
- TAS102
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- Cetuximab
- Combinations

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Fusion protein/VEGF Trap
- PIGF
- VEGF-B
- VEGF-A

Bevacizumab
Anti-VEGFA antibody
- Lymphangiogenic Factors
  - VEGF-C
  - VEGF-D

No (Clinically) Predictive Biomarker

Regorafinib
Small molecule TKI targeting other TK receptors
- VEGFR-1
- VEGFR-2
- VEGFR-3

PIGF = placental growth factor; TK = tyrosine kinase; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor

CORRECT: Regorafenib After Progression on All Available Std Therapies in mCRC

Patients with progression after all available standard therapies (N = 760)

2:1

Arm A: Regorafenib 160 mg PO QD + BSC
3 wks on, 1 wk off
(n = 505)

Arm B: Placebo + BSC
3 wks on, 1 wk off
(n = 255)

- Primary endpoint: OS
- ~50% of patients with ≥ 4 systemic therapies
  - All patients had received bevacizumab

CORRECT: Regorafenib After Progression on All Available Std Therapies in mCRC

Primary endpoint met prespecified stopping criteria at second interim analysis (1-sided $P \leq .009279$ at ~74% of events required for final analysis)

CORRECT: Adverse Events Occurring in ≥ 10% of Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Regorafenib (n = 500)</th>
<th>Placebo (n = 253)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Hand–foot skin reaction</td>
<td>47</td>
<td>17</td>
</tr>
<tr>
<td>Fatigue</td>
<td>47</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Anorexia</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

Dose modification due to adverse event in 67% of patients receiving regorafenib vs 23% of patients receiving placebo

EGFR in CRC

- KRAS mutant
- Resistant to EGFR Abs

EGFR

PTEN

PI3K

Akt

Raf

Ras

MEK

MAPK

DNA

Cell survival

Proliferation

Angiogenesis

Cell motility

Metastasis
# EGFR-Targeted Agents as First-line Therapy in KRAS WT mCRC: Efficacy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparative Regimens</th>
<th>Median PFS, Mos</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRYSTAL[1]</td>
<td>FOLFIRI/Cetux vs FOLFIRI</td>
<td>9.9 vs 8.4</td>
<td>23.5 vs 20.0</td>
</tr>
<tr>
<td>PRIME[2-4]</td>
<td>FOLFOX4/Pmab vs FOLFOX4</td>
<td>9.6 vs 8.0</td>
<td>23.8 vs 19.4</td>
</tr>
<tr>
<td>PRIME[2-4]</td>
<td>FOLFOX4/Pmab vs FOLFOX4 (KRAS/NRAS WT)</td>
<td>10.1 vs 7.9</td>
<td>26.0 vs 20.2</td>
</tr>
<tr>
<td>COIN[5]</td>
<td>FOLFOX/XELOX/Cetux vs FOLFOX/XELOX</td>
<td>8.6 vs 8.6</td>
<td>17.0 vs 17.9</td>
</tr>
</tbody>
</table>

- Worse PFS outcome with panitumumab + FOLFOX4 in mutant KRAS disease\[3\]

**KRAS Status in Response to Cetuximab**

- Retrospective analysis of CRYSTAL\(^\text{[1]}\)
  - PFS and ORR benefit of FOLFIRI + cetuximab only observed in mCRC patients with wild-type KRAS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Wild-Type KRAS (n = 348)</th>
<th>Mutated KRAS (n = 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFIRI + cetuximab</td>
<td>9.9</td>
<td>7.6</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>8.7</td>
<td>8.1</td>
</tr>
<tr>
<td>HR</td>
<td>0.68*</td>
<td>1.07(^\ddagger)</td>
</tr>
<tr>
<td>ORR, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFIRI + cetuximab</td>
<td>59.3(^\ddagger)</td>
<td>36.2</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>43.2</td>
<td>40.2</td>
</tr>
</tbody>
</table>

\(^*P = .017; ^\ddagger P = .75; ^\ddagger P = .0025\)

Phase III CRYSTAL Study of Cetuximab + FOLFIRI in mCRC: KRAS Update and OS

<table>
<thead>
<tr>
<th>Median Survival, Mos</th>
<th>KRAS WT (n = 172)</th>
<th>KRAS Mutant (n = 105)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>9.9</td>
<td>8.4</td>
<td>0.70</td>
<td>.0012</td>
</tr>
<tr>
<td>OS</td>
<td>23.5</td>
<td>20.0</td>
<td>0.80</td>
<td>.0093</td>
</tr>
</tbody>
</table>

OS: 20% reduction in risk of death with WT vs mutant KRAS

Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial

Timothy S Maughan, Richard A Adams, Christopher G Smith, Angela M Meade, Matthew T Seymour, Richard H Wilson, Shelay Idziaszczyk, Rebecca Harris, David Fisher, Sarah L Kenny, Edward Kay, Jenna K Mitchell, Ayman Madi, Bharat Jasani, Michelle D James, John Bridgewater, M John Kennedy, Bart Claes, Diether Lambrechts, Richard Kaplan, Jeremy P Cheadle, on behalf of the MRC COIN Trial Investigators

Lancet 2011; 377: 2103-14
PRIME Study: KRAS Status in Response to Panitumumab

• Randomized, global, open-label, phase III trial
  
  *Stratified by ECOG PS (0-1 vs 2) and geographic region (Western Europe, Canada, and Australia vs all other locations)*

  Patients with previously untreated mCRC
  
  (N = 1183)

  Panitumumab 6.0 mg/kg q2w + FOLFOX4 q2w
  
  (n = 593)

  FOLFOX4 q2w
  
  (n = 590)

PRIME Study: Efficacy Results

- PFS significantly improved with FOLFOX4 + panitumumab only in wild-type KRAS patients
- Worse PFS outcome with panitumumab addition in mutated KRAS patients

<table>
<thead>
<tr>
<th>PRIME</th>
<th>FOLFOX4/Pmab vs FOLFOX4</th>
<th>9.6 vs 8.0</th>
<th>23.8 vs 19.4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLFOX4/Pmab vs FOLFOX4 (KRAS/NRAS WT)</td>
<td>10.1 vs 7.9</td>
<td>26.0 vs 20.2</td>
</tr>
</tbody>
</table>

**KRAS Testing: What Are the Recommendations?**

- **NCCN guidelines**\(^1\)
  - Strongly recommends *KRAS* testing in all patients with mCRC at the time of diagnosis of metastatic disease
  - Testing should be performed in a CLIA-certified lab
  - Testing can be performed on either primary or metastatic tissue

- **ASCO Provisional Clinical Opinion**\(^2\)
  - All patients with mCRC who are candidates for anti-EGFR antibody therapy should have their tumor tested for *KRAS* mutations in a CLIA-accredited laboratory

- **In both cases, anti-EGFR agents (cetuximab and panitumumab) are recommended for wild-type KRAS patients only**\(^{1,2}\)

---

EGFR Blocker or VEGF blocker in KRAS wild type?
Phase III FIRE-3 Trial: First-line FOLFIRI + Either Cetux or Bev in KRAS WT mCRC

- Primary endpoint: ORR (mRECIST 1.0)
- Amendment in October 2008 to include only KRAS WT (ex 12/13) pts
- 150 active centers in Germany and Austria

FIRE-3 Trial of First-line FOLFIRI + Either Cetux or Bev in KRAS WT mCRC: OS

<table>
<thead>
<tr>
<th></th>
<th>Cetuximab + CT</th>
<th>Bevacizumab + CT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (primary endpoint not met)</td>
<td>62</td>
<td>58</td>
<td>.183</td>
</tr>
<tr>
<td>PFS, mos</td>
<td>10.0</td>
<td>10.3</td>
<td>.547</td>
</tr>
</tbody>
</table>

Phase III 80405 Trial: First-line CT + Either Cetux or Bev in KRAS-WT mCRC

Patients with mCRC and KRAS WT (codons 12, 13), ECOG PS 0/1 (N = 1137)

- FOLFOX or FOLFIRI + Bevacizumab q2w (n = 559)
- FOLFOX or FOLFIRI + Cetuximab q1w (N = 578)

A third arm with CT + bevacizumab + cetuximab was closed to accrual in September 2009

• Primary endpoint: OS
• Secondary endpoints: ORR, PFS, TTF, duration of response

CALGB/SWOG 80405: OS in the ITT Population

- **Population**: mOS (95% CI), mos
  - CT + Cetux: 29.9 (27.0-32.9)
  - CT + Bev: 29.0 (25.7-31.2)

- **HR**: 0.925 (0.78-1.09)
  - *P* = 0.34

Targeted agents

Any role in the Adjuvant treatment?
NSABP C08

1st endpoint: disease-free survival (DFS)

mFOLFOX6
12 cycles

mFOLFOX6 + Bev
12 cycles

Bev
6 months

Stage II-III (n=2700)

Closed October 2006
Bevacizumab in Stage II-III Colon Cancer: 5-Year Update of the National Surgical Adjuvant Breast and Bowel Project C-08 Trial

Carmen J. Allegra, Greg Yothers, Michael J. O’Connell, Saima Sharif, Nicholas J. Petrelli, Samia H. Lopa, and Norman Wolmark
Duration of treatment: 24 weeks

Primary endpoint: disease-free survival
Secondary endpoints: safety, overall survival, pharmacoeconomics, pharmacodynamics, convenience and satisfaction with chemotherapy

Stage II/III colon cancer (n=3450)

Closed June 2007
Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial

Aimery de Gramont, Eric Van Cutsem, Hans-Joachim Schmoll, Josep Tabernero, Stephen Clarke, Malcolm J Moore, David Cunningham, Thomas H Cartwright, J Randolph Hecht, Fernando Rivera, Seock-Ah Im, Gyorgy Bodoky, Ramon Salazar, Frederique Maindrault-Goebel, Einat Shacham-Shmueli, Emilio Bajetta, Martina Makrutchki, Alijing Shang, Thierry André, Paulo M Hoff

Lancet Oncol 2012; 13: 1225-33
N0147: Adjuvant mFOLFOX ± Cetuximab in Resected Stage III Colon Cancer

Patients with stage III colon cancer
(N = 2581)

mFOLFOX6
Oxaliplatin 85 mg/m² +
Leucovorin 400 mg/m² +
5-FU 2400 mg/m²
(infused over 46 hrs) q2w
(n = 1283)

12 cycles

mFOLFOX6 + Cetuximab
400 mg/m² loading dose then 250 mg/m² on Days 1, 8
(n = 1298)

Trend Toward Improved DFS, OS With mFOLFOX6 vs mFOLFOX6 + Cetuximab

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Wild-Type <em>KRAS</em></th>
<th>Mutant <em>KRAS</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mFOLFOX6 (n = 902)</td>
<td>mFOLFOX6 + Cetuximab (n = 945)</td>
</tr>
<tr>
<td>3-yr DFS, %</td>
<td>75.8</td>
<td>72.3</td>
</tr>
<tr>
<td>▪ HR (95% CI)</td>
<td>1.2 (0.96-1.5)</td>
<td>1.2 (0.9-1.6)</td>
</tr>
<tr>
<td>▪ <em>P</em> value</td>
<td>.22</td>
<td></td>
</tr>
<tr>
<td>3-yr OS, %</td>
<td>87.8</td>
<td>83.9</td>
</tr>
<tr>
<td>▪ HR (95% CI)</td>
<td>1.3 (0.96-1.8)</td>
<td></td>
</tr>
<tr>
<td>▪ <em>P</em> value</td>
<td>.13</td>
<td></td>
</tr>
</tbody>
</table>

*JAMA. 2012;307(13):1383-1393*
Conclusions

- Primary goal of CRC - increase OS
- Liver is the most common site of relapse
- Only surgery can cure stage IV disease
- Chemo therapy increased survival
- FOLFOX and FOLFIRI is equivalent
Conclusions- targeted therapy

- No role in the adjuvant setting
- No biomarker testing needed for bev
- EGFR should be given only in KRAS wild type
- Bev, cetuximab, panitumab- 1st line data
- Efficacy is minimal - weigh risk and benefit
- Afiblercept – only as second line
- Regorafenib- 3rd line or beyond
Thank you
Stage IV CRC: 2014

- Best supportive care
- 5-FU
- Irinotecan
- Capecitabine
- Oxaliplatin
- Cetuximab
- Bevacizumab
- Panitumumab
- Ziv-aflibercept
- Regorafenib

Median OS

OS (Mos)

0 10 20 30

Yr

Colorectal Cancer Clinical Management Decisions

• Goal: cure or palliation
• Address primary
  – Yes or no
  – Now or later
• Chemotherapy
  – FOLFOX/FOLFIRI/FOLFOXIRI/capecitabine
• Biologic upfront: bevacizumab or EGFR Ab
Continuum of Care - Chemotherapy for Advanced or Metastatic Disease

Initial Therapy

1. **FOLFIRI**
   - or CapeOX
   - or FOLFOX

2. **Patient appropriate for intensive therapy**
   - or FOLFIRI + bevacizumab
   - or FOLFOX + bevacizumab
   - or CapeOX + bevacizumab

3. **Cetuximab or panitumumab**
   - or KRAS/NRAS WT gene only
   - or irinotecan

4. **For patients not able to tolerate combination, consider single agent**
   - or Regorafenib

Therapy After First Progression

5. **FOLFOX**
   - or CapeOX

6. **Cetuximab or panitumumab**
   - or KRAS/NRAS WT gene only
   - or irinotecan

7. **For patients not able to tolerate combination, consider single agent**
   - or Regorafenib

Therapy After Second Progression

8. **FOLFOX**
   - or CapeOX

9. **Cetuximab or panitumumab**
   - or KRAS/NRAS WT gene only
   - or irinotecan

10. **For patients not able to tolerate combination, consider single agent**
    - or Regorafenib

Therapy After Third Progression

11. Regorafenib (if not given previously)
    - or Clinical trial
    - or Best supportive care

Additional options on COL-C 1 of 9 through COL-C 3 of 9

For patients not appropriate for intensive therapy, see COL-C 4 of 9

See footnotes on COL-C 5 of 9
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Chemotherapy Regimens</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI</td>
<td>Oxaliplatin 85 mg/m² IV over 2 hours, day 1 + 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours) IV continuous infusion</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>Oxaliplatin 130 mg/m² IV over 2 hours, day 1 + CapeOX 1</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>Oxaliplatin 150 mg/m² IV over 2 hours, day 1 + Bevacizumab 7.5 mg/kg IV / day 1</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td>FOLFIRI + Bevacizumab</td>
<td>Oxaliplatin 85 mg/m² IV over 2 hours, day 1 + 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours) IV continuous infusion + Bevacizumab 5 mg/kg IV, day 1</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>FOLFIRI + Bevacizumab</td>
<td>Oxaliplatin 150 mg/m² IV over 2 hours, day 1 + Capcitabine 850-1000 mg/m² PO twice daily for 14 days</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td>FOLFIRI + Bevacizumab</td>
<td>Oxaliplatin 150 mg/m² IV over 2 hours, day 1 + Bevacizumab 7.5 mg/kg IV / day 1</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td>mFOLFIRI+Bevacizumab</td>
<td>Oxaliplatin 85 mg/m² IV over 2 hours, day 1 + 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours) IV continuous infusion + Bevacizumab 5 mg/kg IV, day 1</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>mFOLFIRI+Bevacizumab</td>
<td>Oxaliplatin 150 mg/m² IV over 2 hours, day 1 + Capcitabine 850-1000 mg/m² PO twice daily for 14 days</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td>mFOLFIRI+Bevacizumab</td>
<td>Oxaliplatin 150 mg/m² IV over 2 hours, day 1 + Bevacizumab 7.5 mg/kg IV / day 1</td>
<td>Every 3 weeks</td>
</tr>
</tbody>
</table>
### CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 7 of 9)

<table>
<thead>
<tr>
<th>Regimen</th>
</tr>
</thead>
</table>
| **FOLFIRI**
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† continuous infusion
Repeat every 2 weeks |
| **FOLFIRI** + Bevacizumab
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks |
| **FOLFIRI** + Cetuximab
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Cetuximab 400 mg/m² IV over 2 hours first infusion, then 250 mg/m² IV over 60 minutes weekly
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks |
| **FOLFIRI** + Panitumumab
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks |
| **FOLFIRI** + ziv-afiblercept
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Ziv-afiblercept 4 mg/kg IV
Repeat every 2 weeks |
| **Capecitabine**
850–1250 mg/m² PO twice daily, days 1–14
Repeat every 3 weeks |
| **Capecitabine** + Bevacizumab
Capecitabine 850–1250 mg/m² PO twice daily, days 1–14
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks |
CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 8 of 9)

Bolus or infusional 5-FU/leucovorin
Roswell Park regimen\(^1\)
Leucovorin 500 mg/m\(^2\) IV over 2 hours, days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m\(^2\) IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, and 36
Repeat every 8 weeks

Simplified biweekly infusional 5-FU/LV (sLV5FU2)\(^8\)
Leucovorin\(^+\) 400 mg/m\(^2\) IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m\(^2\) and then 1200 mg/m\(^2\)/day x 2 days (total 2400 mg/m\(^2\) over 46-48 hours)\(^7\) continuous infusion
Repeat every 2 weeks

Weekly
Leucovorin 20 mg/m\(^2\) IV over 2 hours on day 1, 5-FU 500 mg/m\(^2\) IV bolus injection 1 hour after the start of leucovorin. Repeat weekly\(^1\)\(^7\)
5-FU 2600 mg/m\(^2\) by 24-hour infusion plus leucovorin 500 mg/m\(^2\)
Repeat every week\(^1\)\(^8\)
IROX\(^1\)\(^8\)
Oxaliplatin 85 mg/m\(^2\) IV over 2 hours, followed by irinotecan 200 mg/m\(^2\) over 30-90 minutes every 3 weeks

FOLFOXIRI\(^2\)\(^0\)
Irinotecan 165 mg/m\(^2\) IV day 1, oxaliplatin 85 mg/m\(^2\) day 1, leucovorin 400 mg/m\(^2\)/day 1, fluorouracil 1600 mg/m\(^2\)/day x 2 days (total 3200 mg/m\(^2\) over 48 hours)\(^7\) continuous infusion starting on day 1.
Repeat every 2 weeks

\pm Bevacizumab\(^2\)\(^1\)
5 mg/kg IV, day 1

Irinotecan
Irinotecan 125 mg/m\(^2\) IV over 30-90 minutes, days 1 and 8
Repeat every 3 weeks\(^2\)\(^2\)\(^3\)
or Irinotecan 180 mg/m\(^2\) IV over 30-90 minutes, day 1
Repeat every 2 weeks
or Irinotecan 300-350 mg/m\(^2\) IV over 30-90 minutes, day 1
Repeat every 3 weeks

Cetuximab (KRAS/NRAS WT gene only)
Cetuximab 400 mg/m\(^2\) first infusion, then 250 mg/m\(^2\) IV weekly\(^2\)\(^4\)
or Cetuximab 500 mg/m\(^2\) IV over 2 hours, day 1, every 2 weeks\(^1\)\(^2\)

Cetuximab (KRAS/NRAS WT gene only) + irinotecan
Cetuximab 400 mg/m\(^2\) first infusion, then 250 mg/m\(^2\) IV weekly\(^2\)\(^4\)
or Cetuximab 500 mg/m\(^2\) IV over 2 hours, day 1, every 2 weeks\(^1\)\(^2\)
Irinotecan 300-350 mg/m\(^2\) IV over 30-90 minutes, day 1
Repeat every 3 weeks
or Irinotecan 180 mg/m\(^2\) IV over 30-90 minutes, day 1
Repeat every 2 weeks
or Irinotecan 125 mg/m\(^2\) IV over 30-90 minutes, days 1 and 8
Repeat every 3 weeks

Panitumumab\(^2\)\(^5\) (KRAS/NRAS WT gene only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib\(^2\)\(^6\)
Regorafenib 160 mg PO daily days 1-21
Repeat every 28 days

See References on COL-C 9 of 9
Conversion Therapy: Practical Issues

• Role of FOLFOX or FOLFIRI

• FOLFOXIRI attractive but at expense of increased toxicity

• Limit duration of preoperative therapy to 3-4 mos
  – Treat to resectability and not to best response
  – Minimizes hepatotoxicity

• Role of biologics is evolving
  – Data with cetuximab appears to be most mature in wild-type KRAS CRC
  – Bevacizumab is an appropriate option in setting of mutant KRAS
    – If bevacizumab is used, discontinue 6-8 wks before planned surgery
Treatment-Associated Liver Toxicity

- 5-FU: steatosis
- Irinotecan: steatohepatitis
- Oxaliplatin: sinusoidal/vascular injury
- Bevacizumab
  - Potential wound healing complications
  - Need to wait 6-8 wks before surgical resection
- Cetuximab: no acute or chronic effects to date
- Incidence of postoperative complications increases with prolonged use
Phase III Study of Second-line FOLFIRI ± Panitumumab in mCRC

Patients with mCRC (55% KRAS WT), 1 prior regimen, ECOG PS ≤ 2 (N = 1186)

Primary endpoints
- PFS
- OS

Secondary endpoints
- ORR
- DOR
- Safety


<table>
<thead>
<tr>
<th>Outcome in KRAS WT Patients</th>
<th>FOLFIRI + Panitumumab (n = 325)</th>
<th>FOLFIRI (n = 221)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR, %</td>
<td>35</td>
<td>10</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>PFS, mos</td>
<td>5.9</td>
<td>3.9</td>
<td>.004 (HR: 0.73)</td>
</tr>
<tr>
<td>OS, mos</td>
<td>14.5</td>
<td>12.5</td>
<td>.12</td>
</tr>
</tbody>
</table>

Panitumumab 6.0 mg/kg + FOLFIRI* q2w (n = 591)

FOLFIRI* q2w (n = 595)

*180 mg/m² irinotecan, 400 mg/m² leucovorin, 500 mg/m² 5-FU
Molecular Biomarker Profiling for Colon Cancer

• Current NCCN guideline recommendations\textsuperscript{[1]}
  – KRAS mutation
  – BRAF mutation
    • Consider only if KRAS mutation is negative

• Further genetic characterization of CRC is continuing\textsuperscript{[2]}
  – CRC as many diseases?
  – Potential for more biomarkers for personalizing therapy

1. NCCN. Clinical Practice Guidelines In Oncology (NCCN Guidelines) for Colon Cancer. V.3.2014.
## Clinical Efficacy in *KRAS* Wild-Type Tumors by *BRAF* Mutation Status

<table>
<thead>
<tr>
<th>CRYSTAL Trial</th>
<th><em>KRAS WT/BRAF WT</em> (n = 566)</th>
<th><em>KRAS WT/BRAF MT</em> (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLFIRI (n = 289)</td>
<td>Cetuximab + FOLFIRI (n = 277)</td>
</tr>
<tr>
<td>Median OS, mos (95% CI)</td>
<td>21.6 (20.0-24.9)</td>
<td>25.1 (22.5-28.7)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.830 (0.687-1.004)</td>
<td>0.908 (0.507-1.624)</td>
</tr>
<tr>
<td><em>P</em> value*</td>
<td>.0547</td>
<td>.7440</td>
</tr>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>8.8 (7.6-9.4)</td>
<td>10.9 (9.4-11.8)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.673 (0.528-0.858)</td>
<td>0.934 (0.425-2.056)</td>
</tr>
<tr>
<td><em>P</em> value*</td>
<td>.0013</td>
<td>.0547</td>
</tr>
<tr>
<td>OR rate, % (95% CI)</td>
<td>42.6 (36.8-48.5)</td>
<td>61.0 (55.0-66.8)</td>
</tr>
<tr>
<td><em>P</em> value†</td>
<td>&lt; .0001</td>
<td>.9136</td>
</tr>
</tbody>
</table>

*Stratified log-rank test. †Cochran-Mantel-Haenszel test.

# mCRC: Current Options for Addition of Biological Agent

<table>
<thead>
<tr>
<th></th>
<th>First-line</th>
<th>Second-line</th>
<th>Third-line</th>
<th>Beyond Third-line</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>RAS</em> mutant</td>
<td>CT</td>
<td>CT</td>
<td>CT</td>
<td>Regor</td>
</tr>
<tr>
<td></td>
<td>Bev + CT</td>
<td>Bev + CT</td>
<td>Regor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Z-Afli + CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>RAS</em> wild (KRAS, in US)</td>
<td>CT</td>
<td>CT</td>
<td>CT</td>
<td>Regor</td>
</tr>
<tr>
<td></td>
<td>Bev + CT</td>
<td>Bev + CT</td>
<td>Cet + CT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pmab ± CT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-Afli + CT</td>
<td></td>
</tr>
</tbody>
</table>

CT = chemotherapy; Bev = bevacizumab; Cet = cetuximab; Pmab = panitumumab; Z-Afli = ziv-aflibercept; Regor = regorafenib
**BRAF Mutations in CRC**

- *BRAF* is primary effector of *KRAS* signaling\(^1\)

- *BRAF* mutations:
  - Occur most frequently in exon 15 (V600E)\(^1\)
  - Found in 4% to 14% of pts with CRC\(^1\)
  - Mutually exclusive with *KRAS* mutations\(^1,2\)

Management of Hand–Foot Skin Reactions With Regorafenib

• Occurs as early as 2-3 wks\[^1\]
• Painful blistersing plaques or rash\[^1,2\]
• Tender thickened plaques may develop on fingertips\[^1\]
• Management of the HFSR:
  – Minimize friction and trauma with comfortable well-fitting shoes and protective gloves\[^1\]
  – Topical corticosteroids to minimize inflammation on the hands and feet\[^1,2\]
  – Keratolytic creams such as urea or lactic acid to minimize inflammation and thickened hyperkeratotic plaques\[^1,2\]
  – Dose reduction, interruption, or discontinuation of regorafenib depending on the grade of toxicity\[^1,2\]

Cetuximab vs BSC in Chemo-Refractory mCRC: Median OS

Phase III CAIRO3 trial of continued bevacizumab + capecitabine versus observation demonstrated the importance of treatment duration

- Primary endpoint: PFS after re-introduction = PFS2
- Secondary endpoints: PFS1, OS, TT2P, ORR, safety
- PFS2 was considered to be equal to PFS1 in patients for whom bevacizumab + CAPOX was not reintroduced after PFS1 for any reason
- Upon PD1, 76% of patients received bevacizumab + CAPOX in arm A and 47% in arm B

Koopman, et al. ASCO 2013
Phase III study: patients with CRC and resectable liver metastases; WHO/ECOG performance status 0-2 (N = 364)

FOLFOX4 for 6 cycles (12 wks) (n = 182) → Surgery (n = 182) → FOLFOX4 for 6 cycles (12 wks)

Primary endpoint: PFS
Secondary endpoints: OS, complete resection

EORTC: Resectable Liver Metastases PFS

- 5-yr OS rate was not significantly different between FOLFOX or surgery alone (51.2% vs 47.8%; \( P = .34 \))