Updates in the Treatment of Metastatic Colorectal Cancer
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Financial Disclosure

- Dr. Marshall has acted as a consultant and served on speakers bureaus for Amgen, Celgene, Genentech, and Roche.
- Dr. Sommers has nothing to disclose.
Learning Objectives

- Restate the current standard of care options for the first-line metastatic colorectal cancer (mCRC) therapy, using chemotherapy in combination with targeted agents
- Identify which patients should undergo mutation testing, and understand how these results impact selection of therapy
- Assess the potential utility of other predictive biomarkers
- Update the incorporation of biologics into the management of colorectal cancer
- Discuss indications for and potential benefits of radiation therapy in patients with unresectable disease
- Compare the potential benefits and limitations of oral cancer therapy for mCRC
2030 values are estimated using projected incidence and mortality rates from 2008 to 2030 and weighting for prevalence in developed compared to developing countries.

What Do You See?

5-FU!
Our Current Model of Colon Cancer

Image from National Cancer Institute
Colon Cancer: More Than One Disease

Molecular
- MSI vs MSS
- RAS WT vs MUT

Anatomic
- Right vs Left
- Rectal vs Colon

Stool Flora Types
- ?????
Management of mCRC: An Evolving Treatment Algorithm

Diagnosis of mCRC

- Resectable
  - Neoadjuvant/Preoperative Therapy
  - Surgery
  - Adjuvant Therapy

- Unresectable
  - First Line
  - Second Line
  - Third Line
  - Fourth Line

Borderline/Potentially Resectable

Treatment Continuum
Advances in the Treatment of Colorectal Cancer


5-FU
Irinotecan
Capecitabine
Oxaliplatin
Cetuximab
Bevacizumab
Panitumumab

Targeted therapies

KRAS
Aflibercept
Regorafenib
RAS
Ramucirumab
TAS 102
Colorectal Cancer: 20 Years Later
meta-analysis 1992  80405 results

Fig 2. Overall survival.

CALGB/SWOG  80405

Although OS Continues to Improve, PFS Has Been Mostly Stable With First-Line Therapy in the Chemobiologic Era

Although OS Continues to Improve, PFS Has Been Mostly Stable With First-Line Therapy in the Chemobiologic Era

TRIBE Study Design

508 mCRC pts
First-line unresectable stratified by
- Center
- PS 0/1-2
- Adjuvant CT

RANDOMIZATION

Induction
FOLFIRI + Bev
(up to 12 cycles)

Maintenance
FOLFOXIRI + Bev
(up to 12 cycles)

5-FU/LV + Bev
5-FU/LV + Bev

PD

CT = chemotherapy; FU = fluorouracil; LV = leucovorin; Bev = bevacizumab; PD = progressive disease; FOLFOXIRI = fluorouracil, leucovorin, oxaliplatin, and irinotecan; FOLFIRI = fluorouracil, leucovorin, and irinotecan.

TRIBE Study Subgroup Analyses of PFS: Molecular Characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>N</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mut</td>
<td>200</td>
<td>0.84</td>
<td>0.973</td>
</tr>
<tr>
<td>WT</td>
<td>193</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td><strong>BRAF status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mut</td>
<td>28</td>
<td>0.55</td>
<td>0.323</td>
</tr>
<tr>
<td>WT</td>
<td>365</td>
<td>0.83</td>
<td></td>
</tr>
</tbody>
</table>

**BRAF**
- Mutated
- WT

**KRAS**
- Mutated
- WT

WT = wild type

CAIRO 3: Maintenance With Capecitabine + Bevacizumab vs. Observation

Study Design

SD or better after 6 cycles of CAPOX-B

R

Observation

Capecitabine + bevacizumab

PD

Re-introduction CAPOX-B

PFS1

PFS2

PD

Adjusted HR = 0.41, \( P < .001 \)

Median PFS1

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS1</td>
<td>4.1 m</td>
<td>8.5 m</td>
</tr>
<tr>
<td>95% CI</td>
<td>[3.9-4.4]</td>
<td>[6.9-10.2]</td>
</tr>
<tr>
<td>Stratified HR</td>
<td>0.44</td>
<td>0.44</td>
</tr>
<tr>
<td>95% CI</td>
<td>[0.36-0.53]</td>
<td>[0.36-0.53]</td>
</tr>
<tr>
<td>( P ) value</td>
<td>&lt;.00001</td>
<td>&lt;.00001</td>
</tr>
</tbody>
</table>

What Is the Role of the Epidermal Growth Factor Receptor (EGFR) in Cancer?

EGFR

Cell Membrane

Signaling Proteins

Cell Response to Signaling

Ras

PI3-K → AKT → mTOR

Shc

Grb2

Sos-1

Raf

MEKK-1 → MEK → ERK

MKK-7 → JNK

Sos-1

What Is the Role of the Epidermal Growth Factor Receptor (EGFR) in Cancer?
Pathway vs Network Signaling

Pathway

“Newtonian”

Network

“Chaotic”

What Is the Role of the Epidermal Growth Factor Receptor (EGFR) in Cancer?

EGFR

Cell Membrane

Signaling Proteins

Cell Response to Signaling

Apoptosis Resistance
Proliferation
Angiogenesis
Metastasis

PI3-K → Shc → Ras

Ras → Sos-1 → MEK → ERK

Raf

MEKK-1

MKK-7

JNK

AKT

mTOR
Which Target?

- PI3-K
- Grb2
- Sos-1
- Ras
- MEKK-1
- Raf
- MEK
- MKK-7
- MEK
- JNK
- ERK
- AKT
- mTOR
Courtesy of I. Serebriiskii and E. Golemis, Fox Chase Cancer Center.
The EGF Receptor Interactome

Where's the target?

638 Genes

Courtesy of I. Serebriiskii and E. Golemis, Fox Chase Cancer Center.
EGFR Biomarkers

<table>
<thead>
<tr>
<th>Enrichment</th>
<th>% Patients</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR Receptors</td>
<td>100%</td>
<td>8-11%</td>
</tr>
<tr>
<td>KRAS</td>
<td>60%</td>
<td>15-20%</td>
</tr>
<tr>
<td>Extended RAS</td>
<td>40%</td>
<td>?</td>
</tr>
<tr>
<td>Future</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

**Distribution**

- KRAS mt ~ 40%
- New RAS mt ~ 10%
- RAS WT ~ 50%
- Rare KRAS Mutations
- NRAS Mutations

Reference?
FIRE-3 Phase III Study Design

- **Primary objective:** overall response rate (ORR) (investigator assessed)
- **Designed to detect a difference of 12% in ORR induced by FOLFIRI + cetuximab (62%) as compared to FOLFIRI + bevacizumab (50%)**
- **284 evaluable patients per arm needed to achieve 80% power for an one-sided Fisher's exact test at an alpha level of 2.5%**

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI + Cetuximab</th>
<th>FOLFIRI + Bevacizumab</th>
<th>Odds ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR</td>
<td>95% CI</td>
<td>ORR</td>
<td>95% CI</td>
</tr>
<tr>
<td>ITT population (N = 592)</td>
<td>62.0</td>
<td>56.2–67.5</td>
<td>58.0</td>
<td>52.1–63.7</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Assessable for response (N = 526)</td>
<td>72.0</td>
<td>66.2–77.6</td>
<td>63.0</td>
<td>57.1–68.9</td>
</tr>
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</tbody>
</table>

*P* = Fisher's exact test (one-sided).
FIRE-3 PFS

<table>
<thead>
<tr>
<th></th>
<th>Events n/N (%)</th>
<th>Median (mo)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI + cetuximab</td>
<td>250/297 (84.2%)</td>
<td>10.0</td>
<td>8.8-10.8</td>
</tr>
<tr>
<td>FOLFIRI + bevacizumab</td>
<td>242/295 (82.0%)</td>
<td>10.3</td>
<td>9.8-11.3</td>
</tr>
</tbody>
</table>

HR = 1.06 (95% CI: 0.88-1.26) (log-rank) P = 0.55

Number at risk:  
FOLFIRI + cetuximab 297 218 111 297 295 214 111  
FOLFIRI + bevacizumab 218 111 60 29 9 0  

FIRE-3 Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Events n/N (%)</th>
<th>Median (mo)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI + cetuximab</td>
<td>158/297 (53.2%)</td>
<td>28.7</td>
<td>24.0-36.6</td>
</tr>
<tr>
<td>FOLFIRI + bevacizumab</td>
<td>185/295 (62.7%)</td>
<td>25.0</td>
<td>22.7-27.6</td>
</tr>
</tbody>
</table>

HR = 0.77 (95% CI: 0.62-0.96)  
(log-rank) P = 0.017

FIRE-3 Update: Tested Mutations

**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><strong>KRAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 13</td>
<td>61</td>
<td>117 146</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WT</td>
<td>4.3%</td>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NRAS</strong></td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>12 13</td>
<td>59 61</td>
<td>117 146</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.8%</td>
<td>2%</td>
<td>0%</td>
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</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BRAF</strong></td>
<td></td>
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<tr>
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<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>600</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

15% additional RAS mutations!

**FIRE-3 ESMO/ECCO Overall Survival Update: All-RAS Wild-Type**

<table>
<thead>
<tr>
<th></th>
<th>Events n/N (%)</th>
<th>Median (mo)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI + cetuximab</td>
<td>91/171 (53.2%)</td>
<td>33.1</td>
<td>24.5-39.4</td>
</tr>
<tr>
<td>FOLFIRI + bevacizumab</td>
<td>110/171 (64.3%)</td>
<td>25.6</td>
<td>22.7-28.6</td>
</tr>
</tbody>
</table>

HR = 0.70 (95% CI: 0.53-0.92) (log-rank) \( P = 0.011 \)

Median \( \Delta = 7.5 \) months

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CALGB/SWOG 80405: Head-to-Head Bevacizumab vs Cetuximab in First-Line KRAS WT mCRC

Untreated advanced or metastatic CRC KRAS WT tumors (N = 1137) → Randomized

Bevacizumab + FOLFOX or FOLFIRI q2wk

Cetuximab + FOLFOX or FOLFIRI q2wk

Re-open: 6/09
Closed to accrual: 2/12
Patients enrolled:
N = 2334 (total)
N = 1177 (final endpoint)

- **Primary endpoint**: OS
  - Superiority trial with 90% power to detect an OS HR of 1.25 (2-sided α = 0.05)

- **Secondary endpoints**: ORR, PFS, TTF, DOR, and safety

OS, overall survival; ORR, objective response rate; PFS, progression-free survival; TTF, time to treatment failure; DOR, duration of response.

CALGB/SWOG 80405: RAS Mutations

- 670/1137 patients (59%) with KRAS codon 12/13 WT tumors evaluable
- 621/1137 (55%) analyzed
- 95/621 (15.3%) patients new RAS mutation identified
- 526 patients with RAS WT CRC available

**KRAS***
- EXON 2: WT (12 13)
- EXON 3: +1.3%
- EXON 4: 1.8%

**NRAS***
- EXON 2: 2.3%
- EXON 3: 4.2%
- EXON 4: 0%

*Percentages relate to fraction of RAS evaluable patients with mutations in particular exons.
†One patient had a mutation at both NRAS Exon1 codon 12 and NRAS Exon3 codon 61.

CALGB/SWOG 80405: PFS and OS in All RAS WT Patients

**PFS**

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>mPFS (months)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT + Bev</td>
<td>256 (221)</td>
<td>11.3</td>
<td>1.1</td>
<td>(0.9-1.3)</td>
</tr>
<tr>
<td>CT + Cetux</td>
<td>270 (241)</td>
<td>11.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**OS**

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>mOS (months)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT + Bev</td>
<td>256 (178)</td>
<td>31.2</td>
<td>0.9</td>
<td>(0.7-1.1)</td>
</tr>
<tr>
<td>CT + Cetux</td>
<td>270 (177)</td>
<td>32.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### FIRE-3 and CALGB/SWOG 80405: Efficacy by RAS Status

<table>
<thead>
<tr>
<th></th>
<th>FIRE 3 CT + Bev vs CT + Cetux</th>
<th>CALGB/SWOG 80405 CT + Bev vs CT + Cetux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>Response rate</td>
<td>Overall survival</td>
</tr>
<tr>
<td>CT backbone</td>
<td>All FOLFIRI</td>
<td>FOLFOX 74%/FOLFIRI 26%</td>
</tr>
<tr>
<td>ITT (KRAS WT Exon 2)</td>
<td>(n = 295 vs 297)</td>
<td>(n = 559 vs 578)</td>
</tr>
<tr>
<td>RR, %</td>
<td>58 vs 62; ( P = 0.183 )</td>
<td>57.2 vs 65.6; ( P = 0.02 )</td>
</tr>
<tr>
<td>PFS, months</td>
<td>10.3 vs 10.0; HR = 1.06 (( P = 0.547 ))</td>
<td>10.8 vs 10.4; HR = 1.04 (( P = 0.55 ))</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>25.0 vs 28.7; HR = 0.77 (( P = 0.017 ))</td>
<td>29.0 vs 29.9; HR = 0.92 (( P = 0.34 ))</td>
</tr>
<tr>
<td>RAS WT</td>
<td>(n = 201 vs 199)</td>
<td>(n = 256 vs 270)</td>
</tr>
<tr>
<td>RR, %</td>
<td>58.7 vs 65.3; OR = 1.33 (( P = 0.18 ))</td>
<td>53.8 vs 68.6; ( P &lt; 0.01 )</td>
</tr>
<tr>
<td>PFS, months</td>
<td>10.2 vs 10.3; HR = 0.97 (( P = 0.77 ))</td>
<td>11.3 vs 11.4; HR = 1.1 (( P = 0.31 ))</td>
</tr>
<tr>
<td>OS, months</td>
<td>25.0 vs 33.1; HR = 0.70 (( P = 0.006 ))</td>
<td>31.2 vs 32.0; HR = 0.9 (( P = 0.40 ))</td>
</tr>
</tbody>
</table>

Stage 4 NED: Role for Chemo?

- Pre-op
- Post-op
- Treating Mets? treat to progression
- Treating Adjuvant? fixed time, but only 5-FU and oxaliplatin

NED = no evidence of disease
Rationale for Neoadjuvant Therapy

- Assess biology / chemo-responsiveness of disease
- Treat micro-metastatic disease (which chemotherapy can cure) as soon as possible
- Potentially decrease surgical complications by making surgery more feasible
- Potential downsides: Hepatotoxicity; complications; complete response can hide metastatic sites; fear of “lost opportunity” if progression; etc
EORTC 40983, Peri-Operative FOLFOX for Hepatic Metastases
(For patients with initially resectable disease)

CRC w/ resectable liver metastases
n = 364

FOLFOX4
6 cycles (3 m), n = 182

Surgery

FOLFOX4
6 cycles (3 m)

Surgery
No chemotherapy
n = 182

Important toxicity data: only small increase in peri-operative complications with chemo, although only 63% in chemo group received it post-operatively

Nordlinger B. Lancet Oncol. 2013;14:1208-1215.
EORTC 40983: Peri-Op FOLFOX for Liver Mets

Progression-Free Survival

- mPFS, 20 m vs 12.5 mo
- Absolute difference: 8.2%
- HR = 0.81, $P = 0.068$

Overall Survival

- mOS, 61 m vs 54 mo
- Absolute difference: 3.4%
- HR = 0.88, $P = 0.34$

Nordling B. Lancet Oncol. 2013;14:1208-1215.
EPOC: Chemotherapy ± Cetuximab Before and After Liver Resection in KRAS WT CRC

Operable (including borderline operable) colorectal liver metastases

CT → Liver Resection → Chemotherapy

CT + Cetuximab → Liver Resection → CT + Cetuximab

Cetuximab + CT ↑ the pre-operative RR

Progression-Free Survival

Overall Survival

PD-1 Blockade in Tumors With Mismatch-Repair Deficiency


The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
Providence Cancer Center, Portland, OR
Stanford University School of Medicine, Stanford, CA
Bons Secours Cancer Institute, Richmond, VA
University of Pittsburgh, Pittsburgh, PA
Ohio State University Comprehensive Cancer Center, Columbus, OH
Merck & Co., Inc., Kenilworth, NJ

Target Lesions

Duration of Disease Control

Risk/Benefit

Cost | Harm?

Despair | Hope
Toxicity | Palliation

OS
Value as Our New Metric

“Price is what you pay. Value is what you get.”
—Warren Buffet
Fighting a Smarter War on Cancer
Provide **Global** Cancer Care With **Value**

- Come together
- Listen to each other
- Respect what we hear
- Find the common threads
- Weave a new fabric
  - Rapid discovery of more efficacious, more cost-effective cancer treatments
  - Increased access to underserved populations/expand markets
Precision Medicine

Prospective incorporation of molecular profiling will transform global cancer care
GI Cancer Alliance Network (GI CAN): Smart Centers

Cancer Centers

GI Cancer Patients

Profile All

Central Consent

BioBank Team

Data Cloud: Shared & IP Protected
Managed by DSM, STATS
HIPAA compliant

Regulatory Review

Central Imaging

Unified CRF/EMR

Treatment Outcomes

Pharma + Guidelines

Revised “Comprehensive” Cancer Centers

System-Hubs*

Master Protocol

Molecular Profiling

Central IRB

Data Collection

Simplified and Unified Data Management

Targeting “Substantial Therapeutic Improvement” - Priority Status

Treatment A

Treatment B

Treatment C

Treatment D

Standard of Care Pathway

Healthcare System

Central Pharmacy

Central Education of Staff

Control Arm

Those Patients serve as the CONTROL ARM

Pharma + Guidelines

Guidelines
Fundamental Shifts in Cancer Care: A Time of Opportunity

**Yesterday**
- Consumption
- Individual practices
- Rich countries
- Microscope
- Safety and efficacy
- Single large trials
- 1.4 months
- QOL
- Patient as a “subject”
- Chaotic data collection
- National approvals

**Tomorrow**
- Outcomes
- Healthcare systems
- All countries
- Gene profile
- Value
- Portfolio of small trials
- “Substantial improvement”
- Patient-reported outcomes
- Patient as a “partner”
- Standard data collection
- Global approvals
Case Study

- 49-year-old perimenopausal Caucasian female
- 2-mo history of abdominal cramping and intermittent vomiting
- Colonoscopy: Obstructing mass, biopsies taken
- Pathology: Moderately differentiated invasive adenocarcinoma
- CEA 70
- CT scan: Multiple small lesions in both lobes of liver, largest measuring 10 mm. Irregular concentric thickening of the wall of the upper sigmoid colon. No lymphadenopathy.
Multidisciplinary Team Approach

- Oncologist
- Surgeon
- Advance Practice Clinician
- Pathologist
- Radiation Oncologist
- Nursing
- Gastroenterologist
- Social Worker
- Palliative Care
- Nutritionist
- Psychiatry/Psychologist
Collaborative Practice Model: Role of the AP

- Develops individualized holistic and comprehensive plan of care with patient and other members of healthcare team
- Ongoing assessment and management of identified problems in collaboration with team
- Orders, conducts, and interprets diagnostic tests
- Prescribes and implements treatment interventions that are evidence based whenever possible
- Educated patient/family about expected and potential adverse effects and costs of prescribed pharmacologic and nonpharmacologic interventions.
- Evaluates need for additional resources, makes referrals as needed
Colon Primary

Image from Dr. Sommers' personal archive.
Additional History

- Past medical history: GERD
- Past surgical history: D & C
- Family history: no family history of cancer
- Social history: Married, 3 children, does not work
- Habits: Nonsmoker, no ETOH
What would you recommend at this time?

A. Initiate chemotherapy for metastatic disease JL716
B. Send one of the liver lesions for biopsy JL717
C. Order PET CT JL718
D. Recommend surgery consult JL719
E. Both B & D JL720
What would you recommend at this time?

A. Initiate chemotherapy for metastatic disease
B. Send one of the liver lesions for biopsy
C. Order PET CT
D. Recommend surgery consult
E. Both B & D
NCCN Guidelines 3.2015 Colon Cancer

CLINICAL PRESENTATION

Suspected or proven metastatic synchronous adenocarcinoma (Any T, any N, M1)

- Colonoscopy
- Chest/abdominal/pelvic CT
- CBC, chemistry profile
- CEA
- Determination of tumor gene status for RAS (KRAS exon 2 and non-exon 2, and NRAS) and BRAF
- Needle biopsy, if clinically indicated
- Consider PET-CT scan if potentially surgically curable M1 disease in selected cases
- Multidisciplinary team evaluation, including a surgeon experienced in the resection of hepatobiliary and lung metastases

WORKUP

- Computed Tomography (CT) scan

FINDINGS

- Resectable
- Unresectable (potentially convertible or unconvertible)

- Synchronous liver only and/or lung only metastases
- Synchronous abdominal/peritoneal metastases
- Synchronous unresectable metastases of other sites

See Treatment and Adjuvant Therapy (COL-6)
See Treatment and Adjuvant Therapy (COL-7)
See Primary Treatment (COL-6)
See Chemotherapy for Advanced or Metastatic Disease (COL-C 1 of 9)
Case Study (cont)

- Patient underwent laparoscopic partial colectomy with laparoscopic liver biopsy and insertion of power port
- Found 3 spots in liver, one of them accessible to laparoscopic liver biopsy
- Pathology: Adenocarcinoma, mucinous type, invasion through serosa and adhesion to transverse colonic wall; liver biopsy + focal metastatic adenocarcinoma, consisted with primary, KRAS mutant
- Stage pT4a, N1c (0/17 lymph nodes positive), M1a tumor
Liver Lesion

Image from Dr. Sommers' personal archive.
Treatment Recommendations

Considerations
- Comorbid conditions
- Performance status
- Financial concerns
- Social support
- Occupation
- Patient preference
What would be the next reasonable treatment option for this patient?

A. FOLFOX or FOLFIRI +/- bevacizumab  JL721
B. FOLFOX or FOLFIRI +/- panitumumab or cetuximab  JL722
C. CAPOX plus bevacizumab  JL723
D. Liver resection  JL724
E. Either A or C  JL725
Audience Response Question

What would be the next reasonable treatment option for this patient?

A. FOLFOX or FOLFIRI +/- bevacizumab
B. FOLFOX or FOLFIRI +/- panitumumab or cetuximab
C. CAPOX plus bevacizumab
D. Liver resection
E. Either A or C
### TREATMENT
Resectable\(^9\) synchronous liver and/or lung metastases only

- Synchronous or staged colectomy\(^{cc}\) with liver or lung resection
- Neoadjuvant therapy (for 2–3 months)
  - FOLFIRI or FOLFOX or CapeOx\(^{dd}\) ± bevacizumab\(^{ee}\) or FOLFIRI or FOLFOX ± panitumumab or cetuximab\(^{ff}\) (KRAS/NRAS wild-type [WT] gene only)\(^6,8,9\) followed by synchronous or staged colectomy\(^{cc}\) and resection of metastatic disease
- Colectomy\(^{cc}\) followed by chemotherapy (for 2–3 months)
  - FOLFIRI or FOLFOX or CapeOx\(^{dd}\) ± bevacizumab\(^{ee}\) or FOLFIRI or FOLFOX ± panitumumab or cetuximab\(^{ff}\) (KRAS/NRAS WT gene only)\(^6,8,9\) and staged resection of metastatic disease

### ADJUVANT THERAPY\(^y\)
(resected metastatic disease)

- FOLFOX/CapeOx preferred

### SURVEILLANCE
(6 MO PERIOPERATIVE TREATMENT PREFERRED)\(^h\)

- If patient stage IV, NED:
  - History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
  - CEA every 3–6 mo x 2 y, then every 6 mo x 3–5 y
  - Chest/abdominal/pelvic CT\(^i\) scan every 3–6 mo x 2 y, then every 6–12 mo up to a total of 5 y
  - Colonoscopy\(^b\) in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 mo
    - If advanced adenoma, repeat in 1 y
    - If no advanced adenoma,\(^u\) repeat in 3 y, then every 5 y\(^v\)

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Treatment Recommendations

- FOLFOX/bevacizumab: Treatment plan reviewed, consented by MD
- Advanced practitioner role
  - Reinforce adverse side effects of oxaliplatin, 5-FU, leucovorin, and bevacizumab
  - Discuss management of potential side effects
  - Discuss birth control
  - Reviews insurance coverage for medications including prescriptions
  - Referral to nutritionist
  - Referral to social worker
Case Study (cont)

- Returns for 4th cycle of FOLFOX/bevacizumab
- Notes tingling in fingers, more intense than last cycle, no evidence of gross motor or fine motor dysfunction
- Patient initiated calcium/magnesium infusions pre/post oxaliplatin
## Preventing Neurotoxicity

<table>
<thead>
<tr>
<th>Year</th>
<th>Calcium and Magnesium Infusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Retrospective, unrandomized study 161 patients treated with Ca/Mg infusions before and after oxalipatin indicated less frequent and severe acute neuropathies(^1)</td>
</tr>
<tr>
<td>2007</td>
<td>Concept (Combined Oxaliplatin Neurotoxicity Prevention Trial) Interim analysis suggested decrease response rate, leading to premature closure of the trial(^2)</td>
</tr>
<tr>
<td>2008</td>
<td>Independent review of all scans verifying RR demonstrated no significant difference in response rate or TTF between groups(^3)</td>
</tr>
<tr>
<td>2008</td>
<td>Neuroxa trial, reduced grade 3 neuropathy Ca/Mg(^4)</td>
</tr>
<tr>
<td>2010</td>
<td>Retrospective review from CAIRO2 trial of Ca/Mg infusions showed no benefit(^5)</td>
</tr>
<tr>
<td>2011</td>
<td>NO4C7 trial, double blinded placebo controlled showed significant lower grade 2 neurotoxicity in Ca/Mg arm, less muscle cramping, but no difference in cold sensitivity(^6)</td>
</tr>
<tr>
<td>2014</td>
<td>NO8CB, a randomized 3 arm trial that showed no benefit to using calcium/magnesium to protect against oxalipatin induced neurotoxicity(^7)</td>
</tr>
</tbody>
</table>

Case Study (cont)

- Restaging scans following 4 cycles: Show liver lesions appearance consistent with benign lesion
- CEA normal
- MRI ordered showed multiple lesions, two cystic lesions seg 6, change may represent treated metastases, unclear benign or malignant
- PET scan: Low attenuation lesions in liver, not PET avid
Audience Response Question

What would you do next?

A. Continue chemotherapy  JL726
B. Evaluate eligibility for clinical trial  JL727
C. Surgery consult  JL729
D. Repeat biopsy  JL730
What would you do next?

A. Continue chemotherapy
B. Evaluate eligibility for clinical trial
C. Surgery consult
D. Repeat biopsy
Case Study (cont)

- Patient undergoes right heptectomy
- Pathology shows a 2-mm focus of metastatic disease in addition to necrotizing granulomas
- Resumes postoperative adjuvant chemotherapy to complete total of 12 cycles
NCCN Guidelines: Surveillance

- **H & P**
  - Q 3–6 mo x 2 yr, then q6mo x total of 5 yr

- **CEA**
  - Q 3–6 mo x 2 yr, then q6mo x 3–5 yr

- **CAP**
  - Q 3–6 mo x 2 yr, then q6-12mo up to total of 5 yr

- **Colonoscopy**
  - 1 yr except if no pre-op colonoscopy due to obstructing lesion, then colonoscopy in 3–6 mo
    - Advanced adenoma, repeat 1 year
    - No adenoma, repeat in 3 yr, then every 5 yr

Summary

- Multidisciplinary team collaboration essential
  - Tumor board
  - Multidisciplinary clinics

- Effective team
  - Trust, respect, open communication

- Establish practice that will best meet the needs of your division and more importantly, the needs of your patients