Updates in the Treatment of Metastatic Colorectal Cancer
Updates in the Treatment of Metastatic Colorectal Cancer

John L. Marshall, MD
Georgetown Lombardi Cancer Center

Robin Sommers, DNP, ANP-BC, AOCNP®
Dana-Farber Cancer Institute
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
Colorectal Cancer: 20 Years Later
meta-analysis 1992  80405 results

Fig 2. Overall survival.

Survival

Overall

CALGB/SWOG 80405

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>5-FU</th>
<th>5-FU + LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 578</td>
<td>436</td>
<td>253</td>
</tr>
<tr>
<td>6 436</td>
<td>588</td>
<td>62</td>
</tr>
<tr>
<td>12 369</td>
<td>187</td>
<td>32</td>
</tr>
<tr>
<td>18 130</td>
<td>64</td>
<td>16</td>
</tr>
<tr>
<td>24 62</td>
<td>38</td>
<td>8</td>
</tr>
<tr>
<td>30 32</td>
<td>19</td>
<td>5-FU</td>
</tr>
<tr>
<td>36 16</td>
<td>8</td>
<td>5-FU + LV</td>
</tr>
<tr>
<td>42 19</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>48 8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
FOLFOXIRI + Bev
(up to 12 cycles)
FOLFIRI + Bev
(up to 12 cycles)

Maintenance
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>KRAS status</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>BRAF status</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>

WT = wild type

CAIRO 3: Maintenance With Capecitabine + Bevacizumab vs. Observation

Study Design

SD or better after 6 cycles CAPOX- B

Observation

Capecitabine + bevacizumab

R

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><strong>PFS1 probability</strong></td>
<td>4.1 m [95%CI: 3.9-4.4]</td>
<td>8.5 m [95%CI: 6.9-10.2]</td>
</tr>
<tr>
<td><strong>Stratified HR</strong></td>
<td>0.44 [95%CI: 0.36-0.53]</td>
<td></td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>&lt;.00001</td>
<td></td>
</tr>
</tbody>
</table>

**No. at risk**

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0</strong></td>
<td>279</td>
<td>279</td>
</tr>
<tr>
<td><strong>6</strong></td>
<td>85</td>
<td>172</td>
</tr>
<tr>
<td><strong>12</strong></td>
<td>18</td>
<td>89</td>
</tr>
<tr>
<td><strong>18</strong></td>
<td>9</td>
<td>44</td>
</tr>
<tr>
<td><strong>24</strong></td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td><strong>30</strong></td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td><strong>36</strong></td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

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

Cell Membrane

Signaling Proteins

Cell Response to Signaling

EGFR

PI3-K

AKT

mTOR

Shc

Grb2

Sos-1

Ras

Raf

MEKK-1

MEK

MKK-7

ERK

JNK

Apoptosis Resistance

Proliferation

Angiogenesis

Metastasis
Pathway vs Network Signaling

Pathway
“Newtonian”

Network
“Chaotic”

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

- PI3-K
- Grb2
- Sos-1
- Ras
- MEK
- MEKK-1
- MKK-7
- JNK
- ERK
- mTOR
- AKT
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%**
- **RAS WT ~ 50%**
- **New RAS mt ~ 10%**
- **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%

## FIRE-3 ORR
### Primary Endpoint

<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><strong>ORR</strong></td>
<td>%</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>ITT population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(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>Assessable for</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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>
</tbody>
</table>

P = Fisher's exact test (one-sided).
Number at risk:
FOLFIRI + cetuximab 297 100 19 10 5 3 0 0
FOLFIRI + bevacizumab 295 99 15 6 4 0 0 0

<table>
<thead>
<tr>
<th>Treatment</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

FIRE-3 Overall Survival


<table>
<thead>
<tr>
<th>arm</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**

**KRAS**
- EXON 1
- EXON 2
- EXON 3
- EXON 4

**NRAS**
- EXON 1
- EXON 2
- EXON 3
- EXON 4

**BRAF**
- EXON 11
- EXON 15

15% additional RAS mutations!

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

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>FOLFIRI + bevacizumab</td>
<td>110/171 (64.3%)</td>
<td>25.6</td>
</tr>
</tbody>
</table>

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

Median \( \Delta = 7.5 \) months

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)**

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

**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 +1.3%
  - 12 13

- EXON 3
  - 59 61
  - 1.8%

- EXON 4
  - 117 146
  - 5.9%

**NRAS**

- EXON 2
  - 12 13
  - 2.3%

- EXON 3
  - 59 61
  - 4.2%

- EXON 4
  - 117 146
  - 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 (10.3-12.6)</td>
<td>1.1 (0.9-1.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>CT + Cetux</td>
<td>270 (241)</td>
<td>11.4 (9.6-12.9)</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 (26.9-34.3)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.40</td>
</tr>
<tr>
<td>CT + Cetux</td>
<td>270 (177)</td>
<td>32.0 (27.6-38.5)</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><strong>Primary endpoint</strong></td>
<td>Response rate</td>
<td>Overall survival</td>
</tr>
<tr>
<td><strong>CT backbone</strong></td>
<td>All FOLFIRI</td>
<td>FOLFOX 74%/FOLFIRI 26%</td>
</tr>
<tr>
<td><strong>ITT (KRAS WT Exon 2)</strong></td>
<td>(n = 295 vs 297)</td>
<td>(n = 559 vs 578)</td>
</tr>
<tr>
<td><strong>RR, %</strong></td>
<td>58 vs 62; ( P = 0.183 )</td>
<td>57.2 vs 65.6; ( P = 0.02 )</td>
</tr>
<tr>
<td><strong>PFS, months</strong></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><strong>Median OS, months</strong></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><strong>RAS WT</strong></td>
<td>(n = 201 vs 199)</td>
<td>(n = 256 vs 270)</td>
</tr>
<tr>
<td><strong>RR, %</strong></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><strong>PFS, months</strong></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><strong>OS, months</strong></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, \( P = 0.34 \)

Nordlinger 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

HR 1.49 95% CI (1.04, 2.12)  P = 0.030

HR 1.48 95% CI (0.85, 2.58)  P = 0.163


*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

Hope  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

- GI Cancer Patients
- Central Consent
- BioBank Team
- Regulatory Review

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

Central Imaging
Unified CRF/EMR
Treatment Outcomes

Cancer Centers
Profilers
Pharma + Guidelines

Revised "Comprehensive" Cancer Centers
System Hubs

Master Protocol
Molecular Profiling
Central IRB
Treatment A
Treatment B
Treatment C
Treatment D
Data Collection
Simplified and Unified Data Management

Targeting "Substantial Therapeutic Improvement" - Priority Status

Standard of Care Pathway
Healthcare System
Central Pharmacy
Central Education of Staff
Control Arm
Medically/Physically Supported

Those Patients serve as the CONTROL ARM

Pharma + Guidelines

GI Cancer Profilers

Unified CRF/EMR
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
- Patient
- Pathologist
- Radiation Oncologist
- Nursing
- Gastroenterologist
- Nutritionist
- Social Worker
- Palliative Care
- 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  
B. Send one of the liver lesions for biopsy  
C. Order PET CT  
D. Recommend surgery consult  
E. Both B & D  

Audience Response Question
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

Reproduced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V.3.2015. © 2015 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. National Comprehensive Cancer Network®, NCCN Guidelines®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.
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  
B. FOLFOX or FOLFIRI +/- panitumumab or cetuximab  
C. CAPOX plus bevacizumab  
D. Liver resection  
E. Either A or C
What would be the next reasonable treatment option for this patient?

A. FOLFOX or FOLFORI +/- bevacizumab
B. FOLFOX or FOLFORI +/- panitumumab or cetuximab
C. CAPOX plus bevacizumab
D. Liver resection
E. Either A or C
**NCCN Guidelines 3.2015 Colon Cancer**

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>ADJUVANT THERAPY</th>
<th>SURVEILLANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable synchronous liver and/or lung metastases only</td>
<td>FOLFOX/CapeOx preferred</td>
<td>If patient stage IV, NED:</td>
</tr>
<tr>
<td>Synchronous or staged colectomy with liver or lung resection or Neoadjuvant therapy (for 2–3 months)</td>
<td>Consider observation or shortened course of chemotherapy</td>
<td>• History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y</td>
</tr>
<tr>
<td>FOLFIRI or FOLFOX or CapeOx ± bevacizumab or FOLFIRI or FOLFOX ± panitumumab or cetuximab (KRAS/NRAS wild-type [WT] gene only) followed by synchronous or staged colectomy and resection of metastatic disease</td>
<td></td>
<td>• CEA every 3–6 mo x 2 y, then every 6 mo x 3–5 y</td>
</tr>
<tr>
<td>Colectomy followed by chemotherapy (for 2–3 months)</td>
<td>Consider observation or shortened course of chemotherapy</td>
<td>• Chest/abdominal/pelvic CT scan every 3–6 mo x 2 y, then every 6–12 mo up to a total of 5 y</td>
</tr>
<tr>
<td>FOLFIRI or FOLFOX or CapeOx ± bevacizumab or FOLFIRI or FOLFOX ± panitumumab or cetuximab (KRAS/NRAS WT gene only) and staged resection of metastatic disease</td>
<td></td>
<td>• Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If advanced adenoma, repeat in 1 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If no advanced adenoma, repeat in 3 y, then every 5 y</td>
</tr>
</tbody>
</table>

Reproduced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V.3.2015. © 2015 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. National Comprehensive Cancer Network®, NCCN Guidelines®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.
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&lt;sup&gt;1&lt;/sup&gt;</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&lt;sup&gt;2&lt;/sup&gt;</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&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>2008</td>
<td>Neuroxa trial, reduced grade 3 neuropathy Ca/Mg&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>2010</td>
<td>Retrospective review from CAIRO2 trial of Ca/Mg infusions showed no benefit&lt;sup&gt;5&lt;/sup&gt;</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&lt;sup&gt;6&lt;/sup&gt;</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&lt;sup&gt;7&lt;/sup&gt;</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 hepatectomy
- Pathology shows a 2-mm focus of metastatic disease in addition to necrotizing granulomas
- Resumes postoperative adjuvant chemotherapy to complete total of 12 cycles
Resection Margin

Image from Dr. Sommers' personal archive.
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
Updates in the Treatment of Metastatic Colorectal Cancer

JOHN MARSHALL, MD: Thank you very much for that kind invitation. Thank you guys for sticking it out and hanging in there. It’s not sunny at all outside, it’s terrible and so you might just as well be here talking about something cheerful like colon cancer, so thanks very much for sticking it out. Robin and I are going to spend the next hour or so kind of going through and I’m going to start by going through some data and Robin’s got some cases that she is going to walk us through. We are going to do our post questions again and I think we have plenty of time for Q&A to really talk about colorectal cancer and all that's happening in that disease. So with that let’s dive in. These are my disclosures. These are the learning objectives and I believe they’re printed elsewhere for you in other places. Let’s set the stage for this disease because when you ask anybody in the clinic, a fellow resident, nurse, anybody what the most common cancer is, what does everybody always answer?

Lung cancer, right? You know the Chinese are doing everything in their power to make them number one in that too, they’re smoking their way to that. Then we talk about breast cancer and prostate cancer, but the reality is those of us who do GI oncology for a living know that we in fact sadly are the most common, most fatal collection of cancers on the planet. And when you look at what's going to happen over the next couple of decades, you recognize that this is a major public health problem. Right now today around the world, only about one in seven people on our planet has access to any form of cancer care. So as the emerging middle class around the world who happen to have cell phones and
Wi-Fi, but not access to cancer care, they know they don’t have access to cancer care. One of our biggest struggles out there is how are we going to deliver that to those people because cancer care in the United States and really in most of western society today is a luxury item. It is like shopping at Nordstrom’s with somebody else’s credit card. All right? Which is a lot of fun to do if you’ve ever done that.

So how are we going to get to a place where the whole world can afford complex cancer care? It’s not just the drugs, everything we do is expensive. Have you thought about what you need to do to deliver cancer care? You need a CT scanner, you need interventional radiology, you need surgeons, you need an infusion unit, you need a hospital, right? You need all sorts of equipment to deliver even basic cancer care and we haven’t really figured out how we are going to deal with this really important problem, but beyond this and forget about common, which of the cancers is by far the most important? Which one? There’s a correct answer to this. It’s not colorectal, it’s absolutely not. Come on, what color did every NFL team wear? It’s by far the most important cancer on our planet; ten times more funding for breast cancer than all the other cancers combined. All right? And that’s within our federal budget by the way, so that’s policy, I come from Washington and that’s our policy, is that breast cancer is by far – It’s the one we’re racing to cure. I hate October. And the first Sunday in October the football game comes on or you get on an airplane and the pink tie or the pink towels or whatever, and the initial reaction is warmth, right? That’s a good thing, there’s somebody paying attention to cancer, but what do you think
that people who don’t have breast cancer think when they turn on that first Sunday in October?

You know it’s like we’re racing to cure this one, but screw the rest, they’re left behind. And they really feel that way, but they cannot say that out loud. It is sacred. Breast cancer is sacred and they can’t say that to anybody because who knows, their friend might have had it, right? And so we have to change this, we have to balance this out because which one kills more people, colon cancer or breast cancer? We somehow need to balance this out in our society and so part of our job today is to get this in the loop and be aware of this. What we really need is a new way to say what we have to say, so we’re coming up with this T shirt, hang on. So if you walk down the street with a T shirt that said, “FU, FU, FU”, right? Would you wear this T shirt? I mean, you and I, you wear the pink ribbon all the time, would you wear this? So we all know that that is indeed 5-FU. I have shirts for sale, they are $1,000.00 each, they are right outside there. And we will sell these shirts and balance out that funding for colon cancer. You like that? I like that. All right.

So everybody in the room learned that colon cancer happens like this, that we start with this benign polyp-y thing and over time mutations occur and then you get invasive cancer, then it spreads to the lymph nodes and ultimately spreads to other areas, metastasizes to the liver, lungs, and places like that. And we’ve believed this, we’ve justified and based all of our drug development on this theory that metastatic diseases where we test our drugs and then we bring it to stage 2 and stage 3 disease, where it turned out the drugs that worked in
metastatic disease don’t work in the adjuvant setting. Only two do, 5-FU and oxaliplatin are the only two drugs that work in stage 2 and stage 3 disease, so there’s a disconnect, we maybe learned wrong about the whole biology of colorectal cancer. And so we are now beginning to sort the disease into its various molecular subtypes. Everybody knows HER2, ER, PR, right? Triple negative for breast cancer. In colon cancer we have microsatellite unstable or not, and KRAS mutations or not and we’ll discuss both of these in turn. But it turns out that though we thought all colon cancer was the same, it may be not all the same. Young is different than old and right-sided is different than left-sided colon cancer. And maybe, just maybe we’ve been looking at the wrong side of the equation because everybody just took a break and fed their little calling that lives inside them. I like to think of it as a coral reef, it’s much more pleasing to think about it as a coral reef, it’s in lovely balance, everybody’s got a different coral reef out there.

Somebody who put chocolate in their coral reef just now who’s put that evil carcinogen bacon in their coral reef – Yeah, it was great wasn’t it? So it turns out that your coral reef matters. Everybody knows that alcohol causes colon cancer, right? Not for everybody. You have to have the right kind of bacteria. If you have the right kind of bacteria and you drink alcohol you turn the alcohol into an aldehyde, which is a carcinogen, but if you don’t have that bacteria, the bar’s open now, so it’s all right. So it turns out that we are interacting with our environment incredibly intimately with our coral reef and how we understand that and how it influences different kinds of colon cancers is just beginning to be
understood. So now we look at a very complex map like this and it’s evolving to where side matters, the different gene profiles matter, and we are beginning finally to sort colon cancer into the different molecular diseases that it is and with this we will see even further improvement in outcomes. Now I want to really focus mostly on metastatic colon cancer today because that’s where most of the action has been happening. And the first thing any of us should do when we see a brand new patient with metastatic colon cancer, I don’t care if we are the first doc that has seen then or nurse or we are the third, we want to stop and think, is this patient potentially resectable.

Now that was blasphemy 20,000 years ago and I learned in the world of oncology you didn’t operate on metastatic disease. There were going to be more weeds in the garden, there was never just one or two weeds in the garden, but it turned out in colorectal cancer that’s not so. There sometimes are just a few metastases and we don’t really have a marker for that, but when we find it, if you notice we are going after these metastases. Pictures have gotten better, surgeons have gotten better, the recovery from this is very quick, and so we are now going whittling on all sorts of patients so you can see on one side of the graph is the patient potentially resectable because some of those patients will be cured of their metastatic colon cancer. Not by chemo, but by surgeons or radiofrequency ablation, this kind of thing. But unfortunately most folks are stuck on the other side of this graph where they have too many weeds in the garden and the weeds are in such bad places that surgery is not really going to be possible. And these are the people where we have to play an elegant chess
game that’s all of a sudden become longer and longer and longer as we have new medications going forward. Now I’m not going to pretend to cover all of the chess game, we are really going to focus mostly on frontline therapy today because that’s where some of the hot stuff is, but we can talk about that during the Q&A if you like. So here are all the chess pieces; for 40 years we had one drug and what was the one drug? You bought the T shirt, 5-FU. And with 5-FU the median survival of patients with metastatic colon cancer was somewhere around 10 months. Don't get attached, go back and take care of your breast cancer patients. All right?

Now with all of these new medications we are actually seeing patients with 3+ years on the backs of this chess game, trying the different medications and you see we have 5-FU, irinotecan, capecitabine which is oral 5-FU, oxaliplatin, the biologics come in, we have two EGFR inhibitors, cetuximab and panitumumab, we have three VEGF inhibitors, bevacizumab, aflibercept, and ramucirumab, all of which are pretty much the same. You have now TAS-102 that got approved two weeks ago and about a year or so ago we got regorafenib or Stivarga approved, so with these chess pieces and playing them wisely patients are living longer and longer with their metastatic disease. Here are the curves; when I started as an oncologist I promised I am not claiming the success, but it’s been fun to watch so that was the average survival and now in the most recent clinical trial – Isn’t the format quite right – we now have a near 30 month improvement in survival – 30 months of median survival. This graph depicts how it’s not just the first treatment that we give, that's the blue line there. That’s been
about the same whether it's FOLFOX or FOLFIRI or biologics or other things, it's been about the same over many, many kinds of trials. It is the orange line which has gone up and these are subsequent lines of therapy, second, third, fourth moves on the chessboard with patients. So the concept of making sure you expose all the patients to all the drugs is born on the backs of these kinds of analyses and you can see the survival really comes from these subsequent lines of therapy.

I'm just going to do a few clinical trials which make some main points and then we're going to get in and do some cases which is a lot more fun. So this is the TRIBE clinical trial. I like to think of this as the kitchen sink versus the bathroom sink, all right? So FOLFOXIRI bev, has anybody prescribed that one yet? Given that out? So that's the key. Everybody knows what FOLFOX looks like, does everybody know that, so Mediports, two day infusion pump, has anybody in this room actually ever worn an infusion pump for two days? How many have you hooked up? It's mean what we do to people. It is, they go home and the pump upsets the cat and the batteries go crazy, it gets caught when they get up to go pee and gets stuck under the bed and pulls, you know, right? You should try that. We should actually all take one home, don't tell, tie it around your neck and carry it--take a shower with one, right? See how that goes. You have to put batteries in it, it has to wrrrr, okay, so that's part of the deal. But this is oxaliplatin, irinotecan, and 5-FU and bevacizumab versus FOLFIRI bev and it turns out that this clinical trial is positive, it actually worked well, but one of the things that emerged was this BRAF mutated patients, only about 9 or 10% of all
colon cancer and we think of it as a bad cancer. It's a mean fast growing cancer, but the kitchen sink, if you give that to the patient you actually show an improvement in outcome.

And so instead of just picking whichever treatment I feel like giving today, we are beginning to say, okay, if you have this molecular subtype or this kind of tumor, we are going to give you this recipe and be smarter about this. Does that make sense? And this is coming on the backs of this. We mentioned in the pre case this concept of maintenance therapy and this is very common in a lot of cancers now and it was first really worked out by some French scientists or physicians who randomized patients between what I like to call a European vacation and a U.S. vacation. So they got their frontlines, say FOLFOX plus bevacizumab and you can’t keep giving FOLFOX, right, because you get neuropathy. You get this cumulative neuropathy from it, so half the patients on the study kept getting oxaliplatin until they couldn’t tie their shoes, the other got just 5-FU and it turned out that less was just as good, it worked fine, but they went one step further and did a study where half the patients got the 5-FU and the other half got nothing. No treatment whatsoever, what I call, what do Europeans do when they go on vacation? They shut the shop, right? They go to the beach, they turn off their phone, they take off their clothes and they sit down, right? That’s what they do.

What do we do? We go to the beach, right, you have this, I’ll be right there, I’ll be right there, you go play this hole, I got this call. Let me do my e-mails, then we’ll go, right? Whose vacation is that? And if you don’t you really get
in trouble, right? If you take a week off and don’t do your e-mails you’re smeared, right? So you have to, right? So it turns out doing a U.S. vacation was a little better than doing a European vacation. It was a European study and it’s called the CAIRO 3 study and half the patients after they were on initial combination chemotherapy got just capecitabine (Xeloda) and bevacizumab (Avastin), not the traditional two week on, one week off dosing, but low continuous dosing of capecitabine which is very well tolerated by the way, versus observation, which is a European vacation. And it turns out that it doubles their progression free survival. So eight months compared to four if we keep a little something going and this is a nice break. They come in every three weeks for a hit of bev, they’re oral chemotherapy, and you tell them on average eight months before your cancer is going to grow again, that’s a nice break in the chess game for patients with metastatic colon cancer. So it is quickly becoming a standard.

Now I’m going to shift gears and make sure everybody in the room understands this concept of RAS testing and what we are talking about and why. So using breast cancer science was the concept of trickle down research. If you funded breast cancer science it would help all the other cancers, right? So using that, when we developed HER1 drugs, you all know about HER2 drugs, EGFR is HER1, a cousin, so we said if it’s going to work you need a receptor, right? Because you need HER2 receptors, well you’ve got to have a receptor and the original clinical trials were driven around receptor positive colon cancer. And it turned out that didn’t seem to make any difference, but we were still seeing some patients benefit and some patients not. And it turned out that it was something
downstream, that little pink guy is Benjamin Moore 1412 I think, that RAS thing right there. It was broken in about 40% of patients we now know it’s about 60% of patients, but at the time about 40 and broke and stuck in the on position. The engine’s revving, so if you think of a receptor as a gas pedal this is something under the hood that’s busted.

And so we were measuring gas pedals when we were really not measuring that little fancy sensor that Volkswagen inserted to keep the cars running, you know? That’s what it was. And so if you have a broken, mutated RAS gene, if your tumor does, then these drugs don’t work. You can do anything you want to the gas pedal, it’s going to rev, the engine is still going to rev under the hood, but we didn’t understand that. Now let’s go one deeper. Because we draw these kinds of diagrams, you’ve seen hundreds of them, as this very structured sort of—I like to think of it as a pool game. You hit the ball just the right way and all the other balls go in their right direction. But is targeting—is molecular signaling really like that or is it much more like the diagram on the other side which is actually a diagram of my daughter Emma’s room. Now a couple of you in the audience actually know Emma and Emma’s incredibly smart, she does perfectly in school, but her room actually mostly when she was a teenager looked like that and she said that if we moved one of her socks she would not be able to find her math book, that somehow those two things were connected.

Now are there any other endless – I mean I just figured I was a bad parent, but no, there – Okay, it could be both, right? It could be both. So what we are looking at here is which one of these is really right? Okay? And so we did an
experiment and we took the same pathway that we are all used to seeing and we ping the EGFR receptor, we turn it on, and we don’t just measure the stuff that we know about. We measure every single protein and gene in that cell and when you do this not only do the stars sort of realign, but I bet it will be this way tonight if you go outside, the stars really come out. And when you ping the EGFR receptor 638 genes move. What do parents do with a kid like Emma and that room? You shut the door. What to molecular biologists do when it turns out it’s Emma’s room? You shut the door. And we draw it back the other way. We can’t measure this, we don’t know how to understand it. That’s a wonderful finding that at least 60% of this haystack comes out with just one gene, RAS, but there’s more to come, right? That’s personalized medicine and that’s what we need to figure out how to go forward. So just a rough depiction, if you just give receptors only about one in ten patients responds, if you start to enrich around the patients with the right molecular profile you see the response rate go up and up and so on that backdrop the belief was is that we had a good target that we could really drive against and if that’s true, then using the EGFR therapies in frontline therapy should win, right?

If you find the right patient and give them the right drug they should win. And this is the first of the two clinical trials I’m going to show you, it’s called FIRE-3. It’s a European study and it has caused a rift between what used to be a very collegial relationship between U.S. GI oncologists and the European group. So FIRE-3 is a smaller 600 patient study, half got FOLFIRI cetuximab and the other half got FOLFIRI bevacizumab frontline chemotherapy and the curves which
were actually powered for response rate which is sort of unusual and you can see that yeah, maybe the cetuximab side of things was a little higher response rate, but not statistically so. What shook everything is these are the progression free survival curves. Now these are the chosen people, right? The EGFR arm should be coming out of this, but it’s not, they are sitting right on top of each other, but then when we look at overall survival this really funny thing happens. If you could draw a line up from 12 months, that’s about how long the patients were on their initial chemotherapy, the clinical trial. And the curves are right on top of each other. It’s not until maybe six months or a year later that the curves actually separate and the Europeans take this to say that EGFR therapy frontline in the RAS wild type patient is the right thing to do and we’re like, wait a minute. Because we’ve got a U.S. study that tells us something different. This is the all RAS data on that same clinical trial. But in the United States, made in the good old, US of A, right?

This is an 1,100 patient study chaired by a guy named Alan Venook who’s great and this was the same idea. You could pick your poison, FOLFOX or FOLFIRI, but then in the RAS wild type patients you randomize to either get cetuximab or bevacizumab in the frontline, right? Same basic trial. And in this clinical trial we learned about new exons, I’m not going to drill down on that too much, but here you see that there really isn’t any difference in the curves in that tail and what we believe in the United States is that if you play all of the chess pieces properly the curves stay together. The Europeans tend to be a little less heavy handed with subsequent lines of therapy and some of that is a value
decision they are making, a money decision, because the medications are expensive in keeping them going, but if you use all of the chess pieces you actually see no difference one for the other, so in the United States there still is a bias to use VEGF drugs like bevacizumab frontline and even in the RAS wild type patient whereas in Europe there tends to be more use of the EGFR drugs. You know why the EGFR drugs are a little hard to give? Rash. You get an acne like rash, a pimply – Somebody pull up on your phone and put in cetuximab grade 3 rash images. Dare ya. It’s not pretty. It’s not a pretty rash and so while the drugs do work very nicely, there’s a very public side effect that we have to work about and deal with. And I won’t go through this too much, but the one outlier arm on the very bottom there is the 25 month of the FOLFIRI bev and we believe in the U.S. that’s because they didn’t use much in the way of biologics in through the second and third line.

The second real controversial area is that we have created this new kind of patient. They are stage 4 no evidence of disease. We have taken out their liver met, we have taken out their lung met and now what do we do? We tend to like to give preop chemo, no data to support that, we often will give adjuvant, a magic six months of chemotherapy, does anybody know where that number six comes from? We just pulled it out of our tail folks, so we feel compelled to give 12 cycles, right, like that’s some magic number, but that’s not really true. Are we treating metastatic disease or are we treating adjuvantly? Adjuvant therapy is a little like you know killing seeds that can live in your garage over the winter, little crunchy things, whereas treating metastatic disease is small plants, right, and our
drugs don’t cure small plants, they help, but they don’t cure. Our drugs kill the little crunchy seeds that are out there and so if you’ve already got small plants growing, then probably the other things are small plants too, so we don’t really have evidence that there is an adjuvant effect in this patient population. The rationale around giving chemotherapy is we want to see the biology, we think we are getting micro metastatic disease, the small seeds, some treatment, we can maybe help with surgery, but the downside is that we make people sick, there’s toxicity from all of this and so we have to weigh it against those two things. We only have one study and we conclude different things from this study, that’s why I’m bringing it to you. It again was done in Europe, that’s where all really good research is done, half the patients got surgery alone, the other half got FOLFOX for three months, then surgery, then some more FOLFOX just like you see here and it turned out that there was a difference in about three years of 8%, but then as you kept going out there really wasn’t. The curves came together. If you had adjuvant effect, the curves would have stayed apart, you would have cured some people of their metastatic cancer whereas others you wouldn’t, right? And we never see that, so I take this as it doesn’t really have the adjuvant effect. Others say yes it does, but the study wasn’t powered to find that small difference. So we can still quibble about it, but it’s quite controversial out there.

And here’s a study that says well just throw stuff at ‘em, this is very much what we do in cancer medicine. Got a new drug, try it. Well this was a study used in cetuximab, one of the EGFR drugs, in this same metastatic window and even when you enriched for RAS, this is kind of scary because if you look there the
experimental arm is below, it was worse, it was tumor food, right? And so this idea that drugs that work in the metastatic setting will also work in the adjuvant setting, again, not borne out and in fact harmful in this subset in this clinical trial done. Again, this was done in Great Britain.

The biggest news in colorectal cancer was presented at ASCO by Dong Lee. She’s fabulous, this group did a great clinical trial. Do you all know what mismatch repair is? Colon cancer comes in two basic flavors, okay? You think about the big pie and 80% of the pie is that classic polyp cancer, right? You have the polyp, the polyp evolves into more stuff, right? But 20% of the pie has completely different biology. And the different biology is mismatch repair. Some of the 20%, actually 5 of the 20 inherit it and that’s called the Lynch syndrome or HNPCC. But some people just picked it up along the way, they didn’t actually –

You can’t blame your parents, they just got it because they ate too much bacon, that’s what. They just picked it up along the way. And so if it turns out if you have MSI high and you can do this test on all our patients, we used to only do it in young people and we would do it in patients where we suspected the syndrome, but that’s about it, but now with this data if you use PD-1 blockers, you all know about these? Immune therapy. This is hot stuff. But in the roughly 4 to 5% of metastatic colon cancer patients who have MSI high tumors, almost all of them respond. So the red bars here are the patient’s red vanilla polyp colon cancer and the green bars are those patients who had MSI high either colon cancer or in black there I think is the color other mismatch repair tumors. And when you give PD-1 inhibitors to this subgroup of patients it works in everybody. So we’re all of
a sudden on the backs of this small study, *New England Journal*, big presentation at ASCO. Not a big randomized study, small, right drug, right patient, right time, transformed. This drug will be approved very quickly for these patients and you can get it now if you have one, so we are looking at everybody. This thing on the – looks like a spider, it’s called a spider plot and you can see these are durable responses, the swimmers plot are the ones that are in the lanes there, these responses last for a long period of time and so this is dramatic impact in the right patients, so all patients with colon cancer are now tested for micro satellite instability in the hopes of this. I’m going to close my comments a little bit to kind of talk about the future of oncology and developing drugs and how are we going to go forward because everybody in this room is an employee of an incredible industry of oncology.

We work privately, we work in the healthcare industry, we do all sorts of bits of it, but it’s a big business. It used to be a kind of small business where everybody knew everybody and now it’s a huge, multibazillion dollar business, right? Who’s got a brand new squeaky clean cancer center? I don’t. But we love it, it’s home, right? We love it. So how are we going to go forward? Everybody knows we’re in a little bit of hot water. We’re expensive, can we justify what we do? And so when one looks at risk/benefit ratio what’s on the scale right now is what we normally measure, overall survival, does it have a palliative effect. I think of hope as really what patients report, you know their quality of life I would say is hope. On the other side we have of course toxicity and despair, but we don’t put cost on here and we don’t actually put harm. It turns out that some of our drugs
push the curve down, not push it up, it’s not a no harm, no foul setting, so when we empirically give people treatment and hope it works eight weeks later, some of those patients we’re hurting, we’re shortening their time and we don’t really know to measure that or incorporate it into our decision making.

So price is what you pay, value is what you get, but this is how we’re going to be judged going forward, there’s a new metric in the world of cancer. But how are we going to measure this? So like in Washington we are going to follow this recipe, right? This is exactly what they do over on Capitol Hill. They come together, they listen to each other, they respect what they hear. This is it, right? We’re going to give them all guns and see how it goes. We are going to find the common thread, right, and we do weave a new fabric, but this is a very important way we have to go forward in our complex big world that we live in. I believe precision medicine will be one of the ways that we come together, that by doing prospective profiling on patients we will learn more. Everyone in this room, if you had metastatic whatever, you’d want your tumor profiled because there are rare targets where we have great drugs, we learn a lot in the process of doing broad molecular profiling, but right now it’s not clear that this is going to be covered through health insurance. But one of the things we have to do is begin to do drug development on the backs of this, and we need to do it on a big scale. So no cooperative group, no healthcare service can actually do this, we have to have a big fat pipe of patients flowing through. Just as an example…What if I wanted to do a 50 patient study of a new drug for colon cancer, a common illness, but the target is only expressed in 10% of patients and arguably that’s a common
expression? And if I want to do that study in a year I have to screen 43 patients a month to find my 50 patients. No center can do that and no company wants to profile a hundred people to find 10 and throw the 90 away and no patient wants to wait around to see if they're one of 10, right? So what we need is a portfolio and you know about these bucket studies, you've heard of them, or basket trials where molecular testing is done and there's a portfolio of different options depending on what genes are mutated in what patients and this is the way forward, the phase three randomized study is dying in exchange for this and it's how I would want to be treated.

I would want you to biopsy my tumor and do state of the art profiling and have at my ready the right drugs that you think are the smartest thing for me to have based on my gene profiling. That's how I would want to be treated, but we have to do this in a shared, cooperative manner. We have to share our data. Our cancer patients – HIPAA is a terrible law. Cancer patients are more than ready to give you whatever you want, take some, please and study it. Right? This whole concept that they are unwilling to have that shared is just not true and we need to figure out how to do that. And our EMRs, we are all highly paid data entry specialists. Do you feel that way some days? Yeah, maybe not so highly paid, some highly paid? That's what we do and we don't do it all very well, some of us are really good documenters, use all the pull-downs, and some of us just type it all in which is useless. So we need to be better data collectors for our patients as well.
So yesterday and tomorrow, we are in the middle somewhere here. We were in a world of consumption. The more I ordered, the more tests I did, the more money we made and we are now in a world of outcomes, we are going from individual practices to systems, rich countries do all as you can see here. So lots of big change over time and we are going to go to our case studies, so I am afraid I have taken way too much of our time, so Robin’s turn. There you go.

**ROBIN SOMMERS, DNP, ANP-BC, AOCNP:** Thank you very much, Dr. Marshall. So I’m going to share with you a case. It’s actually a case that, I took care of this patient probably a couple of years ago. Things have changed, you know it’s not very specific. I changed around some of the details, but I think it really ties in very nicely. You'll see some controversial points. I think all of us may have a different way on how we’re going to manage this case after listening to Dr. Marshall’s very enlightening presentation. So this is a 49-year-old perimenopausal Caucasian female. Had a 2-month history of abdominal cramping and intermittent vomiting. Had a colonoscopy, which showed an obstructing lesion and biopsies were taken. The pathology revealed a moderately differentiated invasive adenocarcinoma. Her CEA was elevated. Her CT scan showed multiple small lesions in both lobes of the liver, the largest one measuring about 1 cm. There was irregular concentric thickening consistent with her primary and there was no lymphadenopathy.

So just listening to that patient we all know multidisciplinary care really is the standard of care nowadays. After listening especially to Dr. Marshall’s talk, determining the best treatment option in treating colon cancer patients is very,
very difficult. And so a multidisciplinary team of all these different professionals - and I neglected to even put in genetic counselor here because they should be at least in the outlier because our patients are sometimes referred to them—come together to try to determine what the best treatment plan is. They develop the plan keeping in mind the patient’s medical, physical and other supportive care needs that may affect their care. So with that being said, now treatment is no longer just the responsibility of the sole oncologist or the surgeon, it’s now a team of multiple professionals. I’m lucky I work in a cancer center and so we have all these different disciplines, all our patients are referred to a multidisciplinary clinic, not all these people will be together at the same time, but certainly if it’s a rectal patient we may have a radiation oncologist, we certainly will have our social workers available in case there’s issues, we’ll have a surgeon, we’ll have a radiologist, the oncologist, etc. So collaborative practice, we’ve heard all about that and I’m hoping that all of you had the chance to read the publication that’s hot off the press that was put in all our bags upon arrival on collaborative practice and the role of the advanced practice nurse in oncology. With that being said, there’s been a lot said about our roles moving forward. ASCO’s predicted a significant shortage of oncologists over the next decade, the number of people visiting oncologists is expected to increase by about 48% and the supply is not going to meet that demand. ASCO actually published in 2011 a study that really looked at the use of advanced practice clinicians in oncology care and they actually found – the results of that study actually found that – they really referred to them as non-physician providers, I’ll refer to them as advanced practice
clinicians, but in that study they actually found that NPs or PAs can help improve productivity within a clinical practice, that MD and advanced practice clinicians were satisfied with the collaborative practice model and more importantly their patients understood what collaborative care was, they understood who they were being taken care of. So these are just some of the roles an advanced practice clinician will provide in this type of model.

And I think if I query everybody in this room there are probably a number of us that practice in different ways. There’s the independent model where the nurse practitioner is in rural practice and she is seeing all these patients by themselves. We are restricted by our state governments that tell us how we can practice. Most of us are in a collaborative model, but even in that and even within the institute that I work with, we have varying different models. So we have the primarily independent model, but could be blended if you’re having a CT scan the patient has progression of disease, your physician’s in clinic with you and he has to come in the room. You have the model that the NP goes into the room, she comes back out of the room, she gives a report to the physician and then the physician and the nurse practitioner or the PA go back in the room and see the patient together. And so a lot of it is looking at how we can best meet the needs of the practice and improve access to care, which is a big crunch right now. Cancer instances are increasing and so we are trying to figure out how we can get new patients in, so adding an advanced practice clinician into the practice may help because they can see the follow-up patients that allows the physician to therefore see the new patients. And with that said Dr. Schulman in 2013
actually also conducted a similar study and the four or five major things that he found was adding advanced practice clinicians, yes, it can improve productivity, yes, it improved patient care because it was actually patient satisfaction surveys that were sent out, yes there was satisfaction between the MD and the advanced practice clinician, yes, the advanced practice clinician can help see urgent patients, and yes, we can also help provide coverage for our physicians, especially those physicians that are in academic practices that travel, that had academic responsibilities, have teaching responsibilities, have research responsibilities that we can actually help make a difference in a good model.

So with that being said, the patient that we just talked about and I pointed it out, you can see this is the patient’s primary cancer that’s here, an obstructing lesion. A little bit more about her history, had a history of GERD, past surgical history was D&C, there was no family history of cancer in the family, she’s married, she has three children and she’s a non-smoker and she does not drink alcohol. So what would you recommend for this patient at that time based on the information that’s been given to you so far? Initiate chemotherapy for metastatic disease, biopsy the liver lesion, order a PET/CT, recommend a surgery consult, or both B and D? And we can see the results here. We have a great audience. Both B and D 74% and looking at these options again and listening to Dr. Marshall’s presentation, we could. You would have queried probably another provider and there may have been a different answer there.

To carry on with the case study, the patient underwent a partial colectomy with laparoscopic liver biopsy and insertion of a PowerPort. Three spots were
found in the liver, one of them was accessible. The pathology revealed an adenocarcinoma, mucinous type, invasion into the serosa, adhesions to the transverse colon wall. Liver biopsy was positive for metastatic disease consistent with the primary and the pathology was read as KRAS mutant. So the patient was a stage 4, N1C, no lymph nodes and N1A tumor. And here you can see the liver lesion on this film and again, this is a CT scan and sometimes on CT imaging studies it’s very difficult depending on the phase of contrast to see these so at times sometimes an MRI is ordered. So when treating or making treatment recommendations, certainly the oncologist in collaboration with his colleagues, we all look at what are some of the co-morbid conditions and so you want to know when you just saw all those drugs that are now available for colon cancer patients, certainly you know if you are considering FOLFOX with the oxaliplatin neuropathy, do you want to give it to a patient that’s a diabetic and already has baseline neuropathy. You are considering adding bevacizumab to frontline regimen and you have a patient that’s a poorly controlled hypertensive so all those things really need to be taken into consideration. Performance status: how well is the patient functioning and are they going to be able to tolerate aggressive therapy. Financial concerns: as we just heard, the cost of these therapeutic treatment regimens is really very, very high and a lot of our patients have co-pays that they have to meet in order to have the treatment. Social support getting back and forth to the clinics, their occupation and what do they do for work, are they going to be able to continue working, and certainly the patient’s preference,
how many of us have had a patient that said, “I don’t want a port put in. I don’t want to be hooked up to that pump,” that Dr. Marshall explained.

So what do you think the next reasonable treatment option for this patient would be? A.) FOLFOX or FOLFIRI plus bevacizumab; FOLFOX or FOLFIRI plus panitumumab or cetuximab; CAPOX plus bev; undergoing a liver resection or either A and C? And about a third of the audience chose one and the last answer, A or C, 50%. So we have a little bit of variation between the first answer and the last answer. Looking at the NCCN Guidelines and I apologize because I actually went on-line this morning and version 2016 is now posted. So this just following the NCCN Guidelines for the rationale behind that last answer, the patient had a colectomy and this is that kind of area is it neoadjuvant, it is adjuvant therapy. The patient had a colectomy followed by chemotherapy and if this is a patient that you’re really deeming may be potentially resectable, then you’d want to restage this patient certainly after a couple of months of therapy to see if they would be a candidate. In our practice in particular, the physician determines the treatment recommendations and usually that’s discussed in clinic. Patients don’t usually start clinic the same day that the doctor has gone over the results of all their tests and then they’ve decided on a treatment option. So the patient generally will come back to clinic and then they’ll meet with the advanced practice clinician and we’ll go over and review the side effects that the physician had gone over and again, reinforcing the information that was given, going over the potential management of some of those, discussing birth control if its applicable, reviewing insurance coverage because how many times do we write
prescriptions for all those other medications that they’re going to go on for the management of those side effects to find out that there’s coverage issues and certainly if the patient needs any referrals for any nutrition or social support.

So the patient comes in for the fourth cycle of FOLFOX, there’s tingling - She has tingling in her fingers and her toes, again, no gross motor or fine motor dysfunction and again, thinking about this case which was a few years ago, goes on calcium and magnesium infusions pre and post oxaliplatin. So how many of us way back when calcium and magnesium was in vogue and we’re like, yep, going to put everyone on calcium and magnesium because we want to try to prevent that neurotoxicity from occurring very early. Well, lo and behold we gave calcium and magnesium and then other studies came out as you can see on the screen negating what the first studies said and so, okay, now we’re not going to give calcium and magnesium and another study came out and said, no really, I think it’s okay to give calcium and magnesium, it might offer the patient some benefit. We finally have the answers in 2014 in the results of the most recent trial. It was a randomized three-arm trial that actually concluded no benefit to using calcium and magnesium to protect against the oxaliplatin neurotoxicity. So restaging scans following four cycles show that the liver lesions appear to be consistent with benign lesions. So this was a very, very challenging case. The CEA level has normalized. The MRI shows liver lesions, two of them are cystic, but it actually wrote in the report that the change may be consistent with treated liver lesions. So it was unclear whether they were benign or malignant. And the
PET scan did not light up. So what would you do next, continue chemotherapy, evaluate eligibility for a clinical trial, a surgery consult, or repeat biopsy?

And we have about half the audience saying a surgery consult and that is the correct answer in this particular case. The other answer, thinking about another biopsy, was reasonable. So this patient in particular actually went back to the surgeon for the surgery consult and he actually presented three different options to her. One was he would go in and she would be deemed inoperable; two, that these lesions were in fact benign; and three, that there may be complications, etc., so there really was a three arm tree, but the patient had opted with the physician’s recommendation to go on to surgery. And the NCCN guidelines here again, we had talked about really reevaluating this patient for conversion after a couple of months. So the patient went on and had a right hepatectomy, it showed a 2 mm focus of metastatic disease in addition to granulomas and resumed postoperative adjuvant therapy for a total of six months. So this was one of those cases that we had a little bit of controversy and you know who’s neoadjuvant, who’s adjuvant and how many cycles and how did we come up with that number? So this just shows you a picture on why I love to have visual ideas, so this just shows her resection margin and just in surveillance because this patient is high risk for recurrence so according to the NCCN Guidelines and I won’t read all this, I’ll refer you to the guidelines, certainly that surveillance monitoring for this patient with stage 4 disease is pretty close. In addition and a colonoscopy because she had an obstructing lesion, you wouldn’t want to wait a whole year to get another colonoscopy, they are recommending it
sooner. So in summary, multidisciplinary team collaboration is essential and most of us have tumor boards that are available to us and multidisciplinary treatment clinics, an effective team with trust, respect, communication, and certainly establishing a practice that best meets the needs of your division and more importantly the best needs of our patients. Thank you. Any questions from the audience?

**ATTENDEE:** You talked a little bit about how you deal with the toxicity of regorafenib.

**DR. MARSHALL:** How one deals with the toxicity of regorafenib. Carefully. It's a difficult drug to give. The standard dose is 160 mg four pills daily. Very few people can tolerate that. The two strategies are start them high and watch very carefully reducing quickly. The other strategy is start them low and dose escalate up, but it's not a drug you give them a month’s worth and say, see you in a month. You see them in one week.

**DR. SOMMERS:** Yeah, I agree with Doc.

**DR. MARSHALL:** How do you deal with Stivarga/regorafenib dosing and toxicity?

**DR. SOMMERS:** And I agree with Dr. Marshall. We have found in our practice that the 160 mg we have significant toxicity and it's interesting because our sarcoma colleagues, all their patients can go start at 160 and they don't see the severe toxicity that our patients do, so I'm not quite sure why, but generally we start at about 80 mg and then see how they do. If they tolerate it we may consider titrating the dose up.
DR. MARSHALL: All right, thank you guys very much.

DR. SOMMERS: Thank you.