Novel Agents and Emerging Strategies in the Management of Metastatic Colorectal Cancer

FACULTY INTERVIEWS

John L Marshall, MD
Eric Van Cutsem, MD, PhD

EDITOR

Neil Love, MD

Bonus Audio: Access approximately 30 minutes of additional content available only on the web at ResearchToPractice.com/MCRC115
OVERVIEW OF ACTIVITY
Metastatic colorectal cancer (mCRC) is a common and often lethal condition, and its clinical management is constantly evolving. As published results from ongoing trials lead to the emergence of novel biomarkers and new therapeutic targets and regimens, existing treatment algorithms may be altered. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances. To bridge the gap between research and patient care, this special edition interview program uses one-on-one discussion with 2 leading gastrointestinal oncology investigators. By providing access to the latest scientific developments and the perspectives of experts in the field, this CME activity assists medical oncologists with the formulation of up-to-date management strategies.

LEARNING OBJECTIVES
• Coordinate comprehensive biomarker analysis for patients diagnosed with mCRC, and use this information to guide evidence-based care for these patients.
• Communicate the benefits and risks of approved anti-VEGF, anti-EGFR and other targeted biologic therapies to patients with mCRC, and develop an evidence-based algorithm to sequence available options based on disease- and patient-specific characteristics.
• Understand practical considerations surrounding the use of regorafenib for patients with mCRC to ensure appropriate administration and patient safety.
• Assess the potential role of anti-PD-1 antibodies in the treatment of mCRC.
• Counsel appropriately selected patients with mCRC about participation in ongoing clinical trials.

ACCREDITATION STATEMENT
Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT
Research To Practice designates this enduring material for a maximum of 2 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CREDIT FOR INTERNATIONAL CLINICIANS
Based on an agreement between the European Union of Medical Specialists and the American Medical Association, physicians may convert AMA PRA Category 1 Credits™ to European CME credits (ECMECs) for this program. Learners should check with their individual boards to verify individual guidelines.

HOW TO USE THIS CME ACTIVITY
This CME activity contains an audio component. To receive credit, the participant should review the CME information, listen to the CD and bonus web-only audio, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located in the back of this booklet or on our website at ResearchToPractice.com/MCRC115/CME. A complete list of supporting references may also be accessed at ResearchToPractice.com/MCRC115.

This activity is supported by educational grants from Bayer HealthCare Pharmaceuticals and Lilly.

Release date: December 2015; Expiration date: December 2016
This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.
QUESTIONS (PLEASE CIRCLE ANSWER):

1. A study presented at ASCO 2015 investigating the association between plasma vitamin D levels and survival in patients with mCRC enrolled on the CALGB-80405 trial demonstrated that higher vitamin D levels do not correlate with improved overall survival.
   a. True
   b. False

2. Patients with BRAF-mutant mCRC ___________.
   a. Have a poor prognosis
   b. Do not benefit significantly with BRAF inhibitors alone in late-line therapy
   c. Both a and b

3. A study investigating the efficacy of immune checkpoint inhibition with pembrolizumab according to DNA mismatch repair status in patients with metastatic carcinoma demonstrated dramatic responses in patients with mismatch repair-deficient tumors.
   a. True
   b. False

4. Adverse events associated with the oral nucleoside TAS-102 include ___________.
   a. Neutropenia
   b. Fatigue
   c. Deep vein thrombosis
   d. Both a and b
   e. All of the above

5. ESMO clinical practice guidelines recommend genomic testing for ___________ in patients with mCRC.
   a. RAS mutations
   b. BRAF mutations
   c. Both a and b

6. The incidence of BRAF mutations in patients with CRC is ___________.
   a. Less than 15%
   b. Approximately 50%
   c. 60% to 80%

7. Which of the following statements is true regarding the toxicity associated with regorafenib?
   a. Dose reduction can be used to mitigate adverse events
   b. The most severe side effects are observed in later cycles
   c. Severe side effects include hand-foot reaction, fatigue and diarrhea
   d. Both a and c
   e. All of the above

8. Which of the following appears to be true from cross-trial comparison of anti-angiogenic agents in mCRC?
   a. Bevacizumab is more active than aflibercept and ramucirumab
   b. Aflibercept is more active than bevacizumab and ramucirumab
   c. Ramucirumab is more active than bevacizumab and aflibercept
   d. All have similar activity
SELECT PUBLICATIONS

Atreya CE et al. Updated efficacy of the MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E mutated (BRAFm) metastatic colorectal cancer (mCRC). Proc ASCO 2015;Abstract 103.

Cleary JM et al. Population pharmacokinetic (PK) analysis of TAS-102 in patients (pts) with metastatic colorectal cancer (mCRC): Results from 3 phase 1 trials and the phase 3 RECURSE trial. Proc ASCO 2015;Abstract 2579.


Ng K et al. Vitamin D status and survival of metastatic colorectal cancer patients: Results from CALGB/SWOG 80405 (Alliance). Proc ASCO 2015;Abstract 507.


Siena S et al. Trastuzumab and lapatinib in HER2-amplified metastatic colorectal cancer patients (mCRC): The HERACLES trial. Proc ASCO 2015;Abstract 3508.


Van Cutsem E et al. Results from the large, open-label phase 3b CONSIGN study of regorafenib in patients with previously treated metastatic colorectal cancer. ESMO World Congress on Gastrointestinal Cancer 2015;Abstract LBA–05.

Van Cutsem E et al. TAS-102 vs placebo (PBO) in patients (pts) ≥65 years (y) with metastatic colorectal cancer (mCRC): An age-based analysis. Proc ASCO 2015;Abstract 3595.

Van Cutsem E et al. Updated results of the MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in patients (pts) with BR. ESMO World Congress on Gastrointestinal Cancer 2015;Abstract LBA–07.

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Novel Agents and Emerging Strategies in the Management of Metastatic Colorectal Cancer

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART 1 — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

<table>
<thead>
<tr>
<th>Topic</th>
<th>BEFORE</th>
<th>AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation between DNA mismatch repair status and benefit from immune checkpoint blockade in mCRC</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Activity and tolerability of ramucirumab as second-line therapy for mCRC</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Results of the Phase III CONSIGN study of regorafenib for patients with previously treated mCRC</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Correlation between central tumor necrosis observed radiographically and benefit from regorafenib</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Available data with TAS-102 and current integration into the management of mCRC</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Efficacy of BRAF/MEK inhibitors in combination with anti-EGFR antibodies for BRAF mutation-positive mCRC</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>ESMO clinical practice guidelines for patients with mCRC</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
</tbody>
</table>

Practice Setting:
☐ Academic center/medical school ☐ Community cancer center/hospital ☐ Group practice
☐ Solo practice ☐ Government (eg, VA) ☐ Other (please specify) ..................

Approximately how many new patients with CRC do you see per year? ................ patients

Was the activity evidence based, fair, balanced and free from commercial bias?
☐ Yes ☐ No If no, please explain: ........................................................................

Please identify how you will change your practice as a result of completing this activity (select all that apply).
☐ This activity validated my current practice
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain): ..................................................................................

If you intend to implement any changes in your practice, please provide 1 or more examples:
..............................................................................................................................

The content of this activity matched my current (or potential) scope of practice.
☐ Yes ☐ No If no, please explain: ........................................................................

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

<table>
<thead>
<tr>
<th>LO</th>
<th>4 = Yes</th>
<th>3 = Will consider</th>
<th>2 = No</th>
<th>1 = Already doing</th>
<th>N/M = LO not met</th>
<th>N/A = Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>As a result of this activity, I will be able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Coordinate comprehensive biomarker analysis for patients diagnosed with mCRC, and use this information to guide evidence-based care for these patients...</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Communicate the benefits and risks of approved anti-VEGF, anti-EGFR and other targeted biologic therapies to patients with mCRC, and develop an evidence-based algorithm to sequence available options based on disease- and patient-specific characteristics</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

As a result of this activity, I will be able to:

- Understand practical considerations surrounding the use of regorafenib for patients with mCRC to ensure appropriate administration and patient safety.
- Assess the potential role of anti-PD-1 antibodies in the treatment of mCRC.
- Counsel appropriately selected patients with mCRC about participation in ongoing clinical trials.

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

Would you recommend this activity to a colleague?
- Yes
- No
- If no, please explain:

Additional comments about this activity:

PART 2 — Please tell us about the faculty and editor for this educational activity

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
</tr>
</thead>
<tbody>
<tr>
<td>John L Marshall, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Eric Van Cutsem, MD, PhD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
</tbody>
</table>

Editor

Knowledge of subject matter: 4 3 2 1
Effectiveness as an educator: 4 3 2 1

Please recommend additional faculty for future activities:

Other comments about the faculty and editor for this activity:

REQUEST FOR CREDIT — Please print clearly

Name: ________________________________ Specialty: ________________________________

Professional Designation:
- MD
- DO
- PharmD
- NP
- RN
- PA
- Other

Street Address: ________________________________ Box/Suite: ________________________________

City, State, Zip: ________________________________

Telephone: ________________________________ Fax: ________________________________

Email: ________________________________

Research To Practice designates this enduring material for a maximum of 2 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be ____ hour(s).

Signature: ________________________________ Date: ________________________________

The expiration date for this activity is December 2016. To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at www.ResearchToPractice.com/MCRC115/CME.
The compact disc, Internet content and accompanying printed material are protected by copyright. No part of this program may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or utilizing any information storage and retrieval system, without written permission from the copyright owner.

The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors. Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management.

Any procedures, medications or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients’ conditions and possible contraindications or dangers in use, review of any applicable manufacturer’s product information and comparison with recommendations of other authorities.