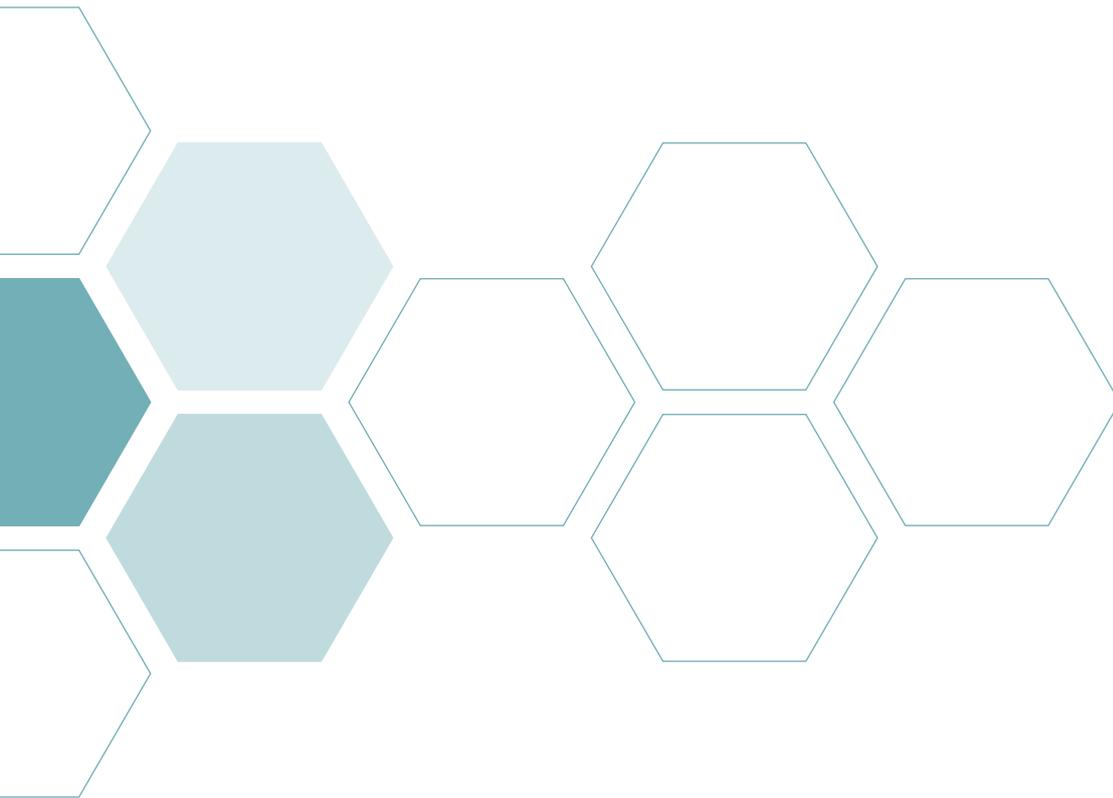




New Horizons in the Treatment and Management of Metastatic Colorectal Cancer (mCRC): Best Practices for Improved Patient Outcomes

A CME/CNE Approved Activity



JOURNAL of MANAGED CARE MEDICINE 

This activity is supported by educational grants from Bayer Healthcare and Merck & Co.

New Horizons in the Treatment and Management of Metastatic Colorectal Cancer (mCRC): Best Practices for Improved Patient Outcomes

Instructions for CME/CNE: Activity is valid from October 20, 2017 to October 31, 2019.

A score of 70% must be achieved on the post-test to receive continuing education credits.

Read the monograph, answer the post-test, complete the evaluation form, and send completed post test and evaluation to:

By E-mail: Jeremy Williams at jwilliams@namcp.org By Fax: Jeremy Williams at 804-747-5316

By Mail: Jeremy Williams
NAMCP CME Dept.
4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060

Authors:

Dr. Globe, MD, PhD, is a Professor of Medicine and Professor of Pharmacology and Cancer Biology at Duke University.

Dr. Minsig Choi, MD, is Director of GI Oncology and an Associate Professor at Stony Brook University Hospital.

Dr. Edward Chu, MD, is a Professor of Pharmacology & Chemical Biology and Chief, Division of Hematology-Oncology at the University of Pittsburgh School of Medicine and Interim Director of the University of Pittsburgh Cancer Institute

Dr. Cathy Eng, MD, FACP, holds the Sophie Caroline Steves Distinguished Professorship in Cancer Research in the Department of GI Medical Oncology and is Associate Medical Director, Colorectal Center at The University of Texas MD Anderson Cancer Center.

Dr. John L. Marshall, MD, is Chief of Hematology and Oncology at the Georgetown University Hospital.

Learning Objectives:

1. Analyze the rationale and role of VEGF- and EGFR-targeted agents in the treatment of metastatic colorectal cancer (mCRC)
2. Explore the role of novel immunotherapies in the treatment of MSI-positive mCRC
3. Assess the relative benefits and limitations of current therapy for mCRC beyond second-line therapy
4. Examine the role and use of biomarkers and molecular testing to guide treatment selection for patients with mCRC
5. Discuss challenges associated with disease progression in mCRC and strategies for managing later lines of therapy
6. Integrate clinical data and guideline recommendations into decisions about the optimal use of VEGF- and EGFR-directed therapy and immunotherapy in treatment protocols for patients with mCRC
7. Individualize management based on factors that affect outcomes including tumor characteristics, treatment history, common adverse effects, and age for optimal care
8. Discuss strategies to mitigate side effects related to treatment with VEGF- and EGFR-targeted agents and immunotherapies in patients with mCRC.

Faculty Disclosure:

Dr. Globe reports a financial interest/relationship or affiliation in the form of a consultant for Genentech/Roche, speaker's bureau for Genentech/Roche, and received income from Genentech/Roche.

Dr. Choi serves on the speaker's bureau for Bayer, Celgene and Novartis and has received research funding from Merck. Dr. Chu has no relevant affiliations or financial relationships to disclose.

Dr. Eng reports a financial interest/relationship or affiliation in the form of research grants from Advaxis, Forty-Seven, Inc, Genentech/Roche, speaker's bureau for Genentech/Roche and Lilly, and consultant for Bayer, Eli Lilly, Forty-Seven, Inc, Merck, Roche, and Sirtex.

Dr. Marshall has no relevant affiliations or financial relationships to disclose.

All material has been peer reviewed for bias.

Planning Committee Disclosure

Bill Williams, MD; Jacquelyn Smith, RN, BSN, MA, CMCN; Jeremy Williams and Will Williams have no real or perceived financial relationships to disclose.

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New Horizons in the Treatment and Management of Metastatic Colorectal Cancer (mCRC): Best Practices for Improved Patient Outcomes

Post-Test Questions

- Genetic mutation of which of the following genes is associated with hereditary non-polyposis colorectal cancer (CRC, Lynch syndrome)?
 - BRAF.
 - Mismatch repair (MMR)
 - p53 tumor suppressor gene
 - VEGF
- Which of the following is a true statement about metastatic colorectal cancer (mCRC)?
 - Overall, 5 year OS for mCRC is 5 percent.
 - 40 percent of patients with CRC have metastatic disease at presentation.
 - Median survival for the untreated patient with metastatic CRC (mCRC) is six months.
 - Median survival with chemotherapy is six years.
- When just comparing left versus right origin of CRC, those with ____ side origin have worse overall median survival.
 - Right
 - Left
- Which of the following regimens is the first line recommended regimen in mCRC with KRAS/NRAS wild type and MSI-H for patients able to receive intensive therapy?
 - Combination chemotherapy (FOLFOX, FOLFIRI, etc.)
 - Cetuximab
 - Nivolumab
 - Combination chemotherapy plus bevacizumab
- Which of the following regimens is the first line recommended regimen in mCRC with KRAS/NRAS wild type and MSI-H for patients unable to receive intensive therapy?
 - EGFR inhibitor
 - Capecitabine or 5-FU and bevacizumab
 - Panitumumab
 - Any of the above are acceptable
- Which of the following is the appropriate biomarker test for immunotherapy in mCRC?
 - BRAF
 - MSI
 - VEGF
 - HER2 expression
- Which of the following agents causes hand foot syndrome, rash, and desquamation?
 - Regorafenib
 - Bevacizumab
 - Vemurafenib
 - Panitumumab
- Which of the following is an adverse event seen with bevacizumab?
 - hypotension
 - neutropenia
 - hemorrhage
 - neuropathy
- Which of the following is an accurate statement about mismatch repair (MMR)?
 - MMR-proficient cells have microsatellite instability (MSI).
 - MSI-H is seen in 15 percent of sporadic CRC cases.
 - MMR-deficient cells have other mechanisms for repairing DNA mismatches.
 - CRC is the only cancer where MMR has been identified.
- Which of the following is the most appropriate use of TAS-102 in mCRC?
 - First-line
 - Second-line
 - Third-line

Activity Evaluation and Improvement Process

*(Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor)*

- Based on the content presented I am better able to:

Analyze the rationale and role of VEGF- and EGFR-targeted agents in the treatment of metastatic colorectal cancer (mCRC).

4 3 2 1

Explore the role of novel immunotherapies in the treatment of MSI-positive mCRC.

4 3 2 1

Assess the relative benefits and limitations of current therapy for mCRC beyond second-line therapy.

4 3 2 1

Examine the role and use of biomarkers and molecular testing to guide treatment selection for patients with mCRC.

4 3 2 1

Discuss challenges associated with disease progression in mCRC and strategies for managing later lines of therapy.

4 3 2 1

Integrate clinical data and guideline recommendations into decisions about the optimal use of VEGF- and EGFR-directed therapy and immunotherapy in treatment protocols for patients with mCRC.

4 3 2 1

Individualize management based on factors that affect outcomes including tumor characteristics, treatment history, common adverse effects, and age for optimal care.

4 3 2 1

Discuss strategies to mitigate side effects related to treatment with VEGF- and EGFR-targeted agents and immunotherapies in patients with mCRC

4 3 2 1
- The activity met my expectations. 4 3 2 1
- The activity and presenters were free of bias. 4 3 2 1
- The activity was applicable to my position. 4 3 2 1
- Do you expect that the information you learned during this activity will help you improve your skills or judgement within the next six months? (4 definitely will change - 1 definitely will not change)
- How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)
- What other topics interest you? _____
- My goal of participating in this activity was: _____
- Did the content of the activity help in meeting your above goal?

Yes No
- Due to the content of this activity, I will change my practice patterns by:

Identifying opportunities to improve treatment options for patients.

Providing guidelines and resources on new therapies to providers.

My practice patterns will not change.

Other (specify): _____
- Will the content presented increase your abilities in any of the following areas? Please check all that apply.

Management and leadership skills

Business and/or financial expertise to manage the medical loss ratio.

Exchange ideas and network with colleagues to improve patient outcomes.

Be aware of updates of Congress, pharmaceutical, Health and Human Services and other regulatory services.

Clear knowledge of practice of medicine, especially common disease.

Stay updated on clinical conditions.

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4435 Waterfront Drive, Suite 101
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(804) 527-1905
fax (804) 747-5316

EDITOR-IN-CHIEF

J. Ronald Hunt, MD

PUBLISHER

Jeremy Williams

JOURNAL MANAGEMENT

Douglas Murphy
Communications Inc.
P.O. Box 71895
Richmond, VA 23255-1895
(804) 387-7580
fax (703) 997-5842

MANAGING EDITOR

Barry Barnum
barry.barnum@douglasmurphy.com

GRAPHIC DESIGN

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jwilliams@namcp.org,
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New Horizons in the Treatment and Management of Metastatic Colorectal Cancer (mCRC): Best Practices for Improved Patient Outcomes

Gerard C. Globe, MD, PhD; Minsig Choi, MD; Edward Chu, MD; Cathy Eng, MD, FACP; John L. Marshall, MD

INTRODUCTION

COLORECTAL CANCER (CRC) IS THE THIRD most common cancer in men and second most common in women. In 2017, it is expected that there will be more than 135,000 new cases of CRC and over 50,000 deaths from this disease.¹

The median age at diagnosis of CRC is 68, but clinicians have been noting an increase in CRC in young patients.² The increase in disease in young patients is thought to be partially related to alterations in the gastrointestinal (GI) biome. The current younger generation has received more antibiotics, washed with antibacterial soaps, and eaten generally cleaner food with lower levels of bacterial contamination than generations past. The human GI biome changes over time as we age and is affected by disease and environment; the connection between biome changes and disease development such as cancer is an area of intense study.³ Screening for CRC is recommended for the average risk patient, starting at the age of 50.

Genetic mutations are important in the development of CRC and include inherited mutations of adenomatous polyposis coli (APC, Familial Adenomatous Polyposis and Gardner syndrome), mismatch repair (MMR, Hereditary non-polyposis CRC (HNPCC)/Lynch syndrome), and acquired mutations in V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), v-Raf murine sarcoma viral oncogene homolog B (BRAF), p53 tumor suppressor gene, and many others.⁴⁻⁷ As shown in Exhibit 1, different genetic mutations play a role at different stages of the cancer development process. Although familial inheritance does play a role in CRC development, the majority of the cases (~75%) are still considered sporadic.⁴ Sporadic CRC

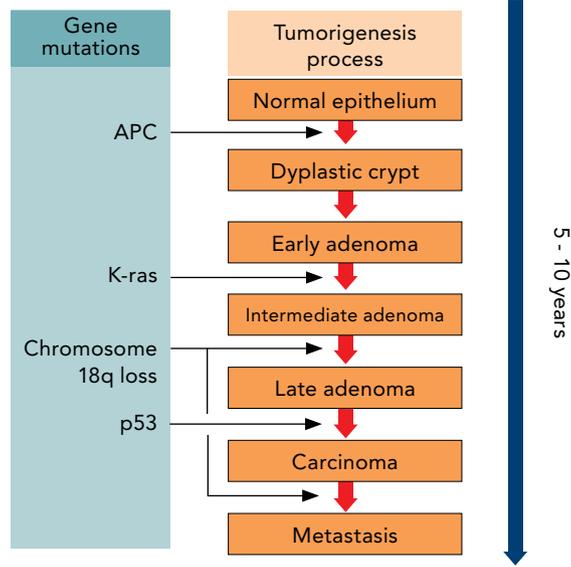
frequently arises from preneoplastic lesions through the activation of oncogenes (KRAS and BRAF) as well as the inactivation of tumor suppressor genes (APC, p16, p53) and mutations in MMR genes. CRC is now thought of as many different diseases rather than one single disease (Exhibit 2). Tumors are identified based on both molecular and anatomic markers.

The five-year overall survival (OS) rate with CRC depends on the stage of disease (degree of tumor penetration through the bowel wall, presence or absence of nodal involvement, presence or absence of distant metastases) at diagnosis. Overall, the five-year OS is 64.9 percent. Those with local disease (Stage I) at diagnosis have a much higher five-year OS (89.9%) than those with more advanced disease. The five-year OS for Stage IV (metastatic) disease is 13.9 percent.²

Unfortunately, 20 percent of patients have metastatic disease at presentation.² Median survival for the untreated patient with metastatic CRC (mCRC) is six months. Median survival with chemotherapy is two years and can be up to 30 months with treatment with targeted biologic agents. Although not considered curable, mCRC survival continues to improve with treatment advances.

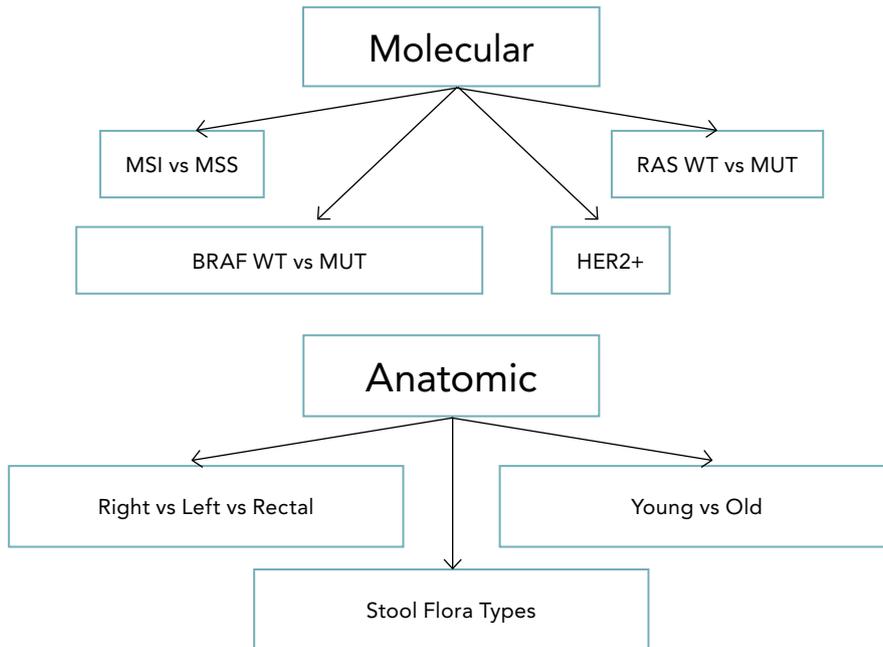
In addition to the stage of disease, other prognostic factors in CRC include bowel obstruction or perforation, elevated pretreatment levels of carcinoembryonic antigen (CEA), microsatellite instability (MSI), and the area of the colon that the disease originates from (left versus right disease). Bowel obstruction or perforation, elevated CEA, and right sided disease are all predictors of poor prognosis. Embryologically, the right and left colon develop from different tissues. When just comparing

Exhibit 1: Genetic Model of Colorectal Cancer



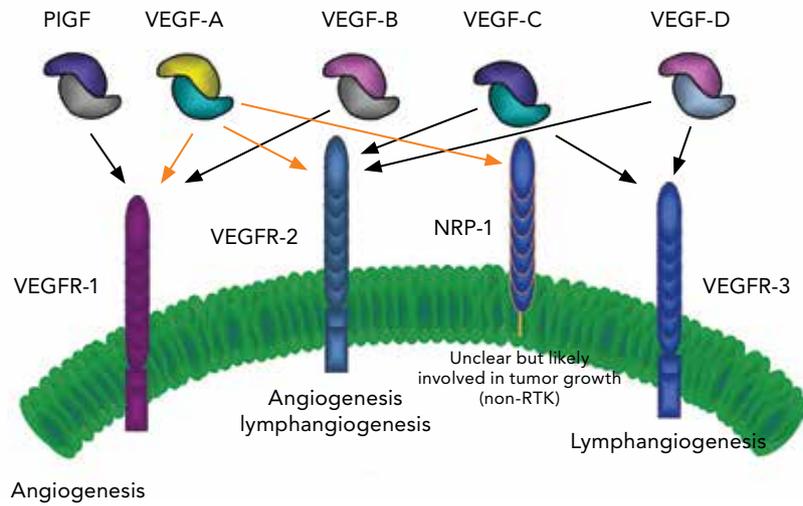
APC = adenomatous polyposis coli
 KRAS = V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
 p53 = tumor protein p53

Exhibit 2: Colon Cancer is More than One Disease



MSI = microsatellite instability
 MSS = microsatellite stable
 WT = wild type
 MUT = mutation
 KRAS = V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
 BRAF = v-Raf murine sarcoma viral oncogene homolog B
 HER+ = human epidermal growth factor receptor positive

Exhibit 3: The Angiogenesis Family



SI = microsatellite instability
 MSS - microsatellite stable
 WT = wild type
 MUT = mutation
 KRAS = V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
 BRAF = v-Raf murine sarcoma viral oncogene homolog B
 HER+ = human epidermal growth factor receptor positive

left versus right origin, those with right side origin have worse overall median survival (19.4 vs 33.3 months).⁸ Young patients with CRC tend to have right side disease and thus a worse prognosis. MSI, which is discussed in more detail later, is associated with improved survival independent of the tumor stage. Other prognostic markers that need validation include allelic loss of chromosome 18q and thymidylate synthase expression.

Treatment of Newly Diagnosed CRC

CRC treatment is based partially on the stage of disease at diagnosis. Stage I and II are primarily treated with surgical resection. Stage III is treated with surgery and adjuvant chemotherapy to prevent recurrence. Systemic therapy is needed for Stage IV, but resection of metastatic disease when possible is considered. Locoregional therapy with radiotherapy or radiofrequency ablation to reduce metastases may also be indicated. For rectal cancer only, chemotherapy and radiation therapy are recommended for Stage II to prevent recurrence. Palliative and supportive care are also treatment options for each stage of disease.

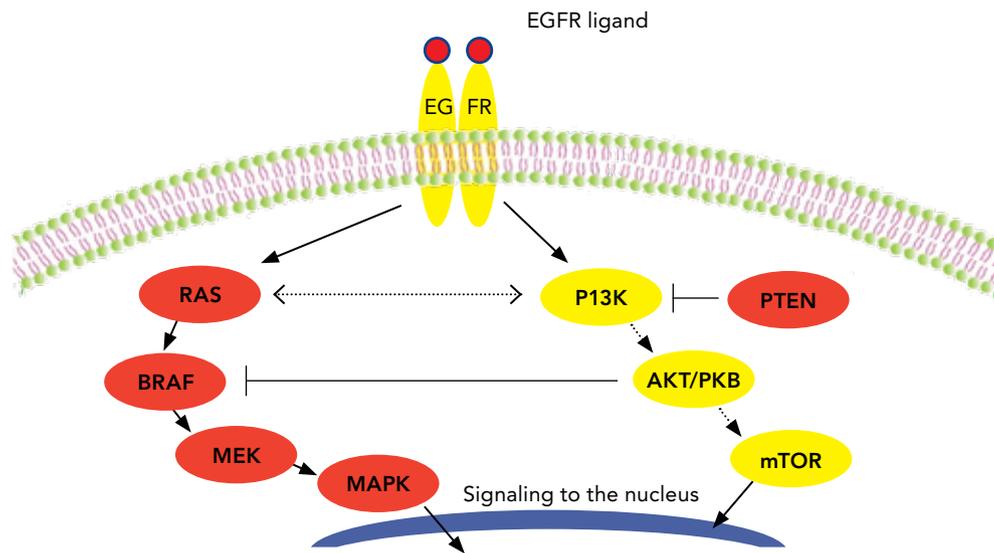
There have been tremendous advancements in treatment options for mCRC in the last 25 years. Treatment for metastatic disease will depend on whether the disease is resectable or not. The majority of treatment in the first-line setting for meta-

static, nonresectable disease involves chemotherapy. Established chemotherapy agents in mCRC include 5-fluorouracil (5-FU), capecitabine, irinotecan, and oxaliplatin. First-line chemotherapy for mCRC improves median OS over best supportive care (12-21 vs 6 months). The choice of the chemotherapy regimen used will depend on patient factors, prior chemotherapy exposure, and risk for adverse effects. For example, oxaliplatin is more likely to cause irreversible neuropathy and irinotecan causes more hair loss. FOLFOX [leucovorin, 5FU, oxaliplatin] and FOLFIRI [leucovorin, 5-FU, irinotecan] are two commonly used chemotherapy regimens.

The development of targeted biologic therapies has been one major advance in mCRC therapy. Combination chemotherapy (FOLFOX or FOLFIRI) with biologic therapy results in better OS (24 - 29.8 months) than chemotherapy alone (12-21 months).^{9,10} Targeted biologic therapies approved for mCRC include anti-vascular endothelial growth factor (VEGF) monoclonal antibodies [bevacizumab (Avastin[®]), ziv-aflibercept (Zaltrap[®]), ramucirumab (Cyramza[®])]; anti-epidermal growth factor receptor (EGFR) monoclonal antibodies [cetuximab (Erbix[®]) and panitumumab (Vectibix[®])]; and a multi-kinase inhibitor [regorafenib (Stivarga[®])].

Angiogenesis is required for solid tumor growth and VEGF is a key angiogenic factor (Exhibit 3).

Exhibit 4: EGFR Signal Transduction Pathway



EGFR = epidermal growth factor receptor
 RAS = rat sarcoma
 BRAF = v-Raf murine sarcoma viral oncogene homolog B
 MEK = mitogen-activated protein kinase
 MAPK = mitogen-activated protein kinases
 P13K = phosphatidylinositol 3-kinase
 PTEN = phosphatase and tensin homolog
 AKT/PKB = Protein Kinase B
 mTOR = mammalian target of rapamycin

VEGF promotes endothelial cell proliferation and survival and increases permeability of tumor vasculature. VEGF is upregulated in many tumors; inhibition of VEGF signaling is an effective anticancer approach in a range of tumors. The anti-VEGF agents bind to and inhibit the function of VEGF in various ways. For example, bevacizumab binds to VEGF-A.

Another pathway targeted in mCRC is EGFR. Epidermal growth factor increases tumor proliferation and invasion, inhibits apoptosis, and promotes metastasis. It has proangiogenic activity via stimulation of VEGF synthesis. Inhibition of EGFR signaling is an effective anticancer approach in a range of tumors, including mCRC. Both cetuximab and panitumumab bind to the EGFR ligand on normal and tumor cells, which has many downstream anticancer effects (Exhibit 4). They competitively inhibit binding of EGF, transforming growth factor- α (TGF- α), and other ligands; inhibit tumor cell growth and induce apoptosis; and cause receptor internalization and downregulation.

Cetuximab is a chimeric monoclonal antibody, whereas panitumumab is a fully human monoclonal antibody. The nonhuman portion of cetuximab results in allergic hypersensitivity reactions in 20 to 25

percent of those who receive this agent who reside primarily in the Southern United States (U.S.). For an unknown reason, a significant portion of people in this geographic region have pre-existing IgE antibodies to a specific sugar molecule on cetuximab.¹¹

In the setting of anti-EGFR therapy, patients with tumors with KRAS mutations do not benefit from this therapy.¹² In the presence of a KRAS mutation, despite the anti-EGFR therapy, there is still downstream activation of the MAP kinase pathway (Exhibit 4). KRAS mutations are found in 30 to 50 percent of all patients with mCRC. Other RAS mutations, including NRAS or BRAF mutations, also impact whether someone will respond to anti-EGFR therapy.¹³ BRAF mutations occur in less than 10 percent of all CRC patients. The V600E mutation accounts for 90 percent of BRAF mutations and its presence is a predictor of poor prognosis. NRAS mutations have been found in 10 to 15 percent of CRC. Thus, anti-EGFR therapy should only be used in those who are wild-type (WT) for all currently known RAS mutations.

Clinicians have wondered whether to choose anti-EGFR or anti-VEGF therapy in treatment naïve RAS WT patients in combination with chemotherapy. Anti-VEGF therapy in combination with

Exhibit 5: Efficacy of Treatment and Line of Therapy

Parameter	1st-Line	2nd-Line	≥3rd-Line
ORR (%)	38 - 65	5 - 35	1 - 17
PFS (month)	9 - 12	4 - 7	2 - 4

ORR = overall response rate
PFS = progression free survival

chemotherapy has been the standard of care in first-line. One trial found the use of anti-EGFR therapy in those with RAS WT resulted in a greater OS compared with anti-VEGF treatment (33.1 vs 25.6 months), but this was a controversial trial and this finding was a secondary endpoint of the trial.¹⁴ In another U.S. designed trail with OS as the primary endpoint, it did not matter which agent the patient received in terms of progression-free survival (PFS) and OS.⁸ Thus, clinicians can choose either for first-line therapy in those who are RAS WT. Those with RAS mutations should receive an anti-VEGF agent.

As mentioned previously, BRAF mutation also impacts response to therapy. Those whose tumors have this mutation respond poorly to either anti-EGFR or anti-VEGF therapy in the front-line setting (OS, 12.3 vs 13.7 months).¹⁴

In addition to impacting OS, the location of the primary tumor in CRC may impact the treatment selection. There is worse survival with right sided disease when patients receive cetuximab.⁸ The National Comprehensive Cancer Network (NCCN) Guidelines now recommend that for newly diagnosed surgically nonresectable patients only bevacizumab be used for right sided tumors.¹⁵

Treatment Lines and Sequencing in mCRC: Best Practices Beyond First-Line Therapy

First-line therapy is most important for survival; the response to subsequent lines of therapy diminishes (Exhibit 5). Additionally, the number of patients who can tolerate another line of therapy based on performance status also diminishes after the first treatment.

Beyond first-line therapy, there are various options, including clinical trials, alternative chemotherapy regimens, alternative targeted biologics, rechallenge with a previously used agent, and palliative/supportive care. Patients should have access to all the FDA approved therapies to best prolong

survival in the second line and beyond.

Chemotherapy alone has modest second-line response rates of 4 to 28 percent (depending on the regimen), with median progression-free survival (PFS) in terms of a few months.^{16,17} Biologics plus chemotherapy add modestly to clinical efficacy. If the patient has been receiving bevacizumab, there are data to show that continuing the anti-VEGF therapy at progression is still beneficial in terms of OS (11.2 vs 9.8 months).¹⁸⁻²⁰

Another option is to change anti-VEGF therapy to ziv-aflibercept, which is also known as VEGF-trap. It is a fully human fusion protein and soluble recombinant decoy VEGF receptor consisting of VEGFR-1 Ig domain 2, VEGFR-2 Ig domain 3, and human IgG1 Fc with stronger binding to VEGF-A than bevacizumab. It also binds to VEGF-B and blocks PlGF (Exhibit 2). This agent has a broader spectrum of VEGF inhibition compared to bevacizumab, but this broader action leads to higher rates of adverse effects. Adding ziv-aflibercept to FOLFIRI in mCRC patients previously treated with an oxaliplatin-based regimen resulted in significant benefits in OS (13.5 vs 12.06 months) and PFS (6.9 vs 4.67 months).²¹ The benefits of ziv-aflibercept were seen regardless of prior treatment with bevacizumab, and prior treatment with bevacizumab did not appear to have an impact on the safety profile of ziv-aflibercept.

Another option in the second-line setting is ramucirumab, a fully human IgG1 antibody directed against VEGFR-2, which is thought to be the main receptor mediating tumor angiogenesis. It prevents binding of VEGF-A, VEGF-C, and VEGF-D to VEGFR-2, resulting in inhibition of VEGF signaling. Ramucirumab, like ziv-aflibercept, has a broader spectrum of activity than bevacizumab but also a higher rate of adverse effects. In a trial in those with mCRC and progression during or after bevacizumab, oxaliplatin, and a fluoropyrimidine, ramuci-

Exhibit 6: Cross-Trial Comparison of Second-Line VEGF Agents¹⁸⁻²²

End Point	FOLFIRI + Ziv-aflibercept	FOLFOX + Bev	FOLFIRI + Ramucirumab	Chemo + Continuation Bev
RR (%)	19.8%	19.8%	13.4%	22.0%
PFS (month)	6.9	7.4	5.7	5.7
OS (month)	13.5	12.5	13.3	11.2

VEGF = vascular endothelial growth factor
 Bev = bevacizumab
 RR = response rate
 PFS = progression free survival
 OS = overall survival

rumab treatment results in improvement in median OS (13.3 vs 11.7 months).²²

Exhibit 6 compares outcomes across trials for second-line therapy with anti-VEGF agents.^{18,22} Treatment with these agents results in very similar response rates, PFS, and OS. It is important to note that there are no direct comparison trials of these regimens and conclusions of superiority of one regimen over another cannot be made from this cross-trial comparison.

Although the clinical activity of bevacizumab, ziv-aflibercept, and ramucirumab appear similar in the second-line setting, there may be differences in toxicity. There are higher rates of GI adverse effects and infection with aflibercept. There are definitely differences in economic costs, with increased economic costs with ramucirumab (\$15,000/month vs \$6,000 for the other two agents).²³ The differences in cost, clinician experience with bevacizumab, and the generally good tolerability of bevacizumab has led to bevacizumab being favored for second-line therapy in the U.S.

Anti-EGFR therapy is also an option in the second-line setting. Panitumumab in combination with FOLFIRI is more effective than FOLFIRI alone. In a KRAS WT mCRC population that had recurred on bevacizumab and oxaliplatin, panitumumab was not as effective as bevacizumab when both were combined with FOLFIRI (OS 18 vs 21.4 months; PFS 7.7 vs 9.2 months).²⁴ Cetuximab in combination with FOLFOX is more efficacious than FOLFOX alone in the second-line setting.²⁵ These two anti-EGFR agents have been compared in one trial in the third-line setting and found to have very

similar efficacy (OS 10.4 vs 10.0, PFS 4.1 vs 4.4).²⁶

In addition to using genetic mutation biomarkers, the choice of whether to use anti-VEGF or anti-EGFR-targeted agents to meet the needs of patients depends on many factors. These include patient/disease characteristics, previous treatments, patient preferences of oral versus intravenous therapy and risk for adverse effects, financial costs/insurance coverage, performance status/co-morbid illnesses, and baseline liver and/or renal function. Patient quality of life is a major consideration given that patients are living three or more years with mCRC. Additionally, in the presence of tumor-related symptoms, an anti-EGFR agent is preferred if a patient has a bulky tumor that is causing symptoms.

Those with BRAF-mutated tumors have limited treatment options since anti-VEGF and anti-EGFR agents are not effective. Irinotecan, cetuximab, and vemurafenib (VIC) have been evaluated in the BRAF-mutated mCRC.²⁷ Vemurafenib (Zelboraf[®]) is a BRAF inhibitor FDA approved for BRAF-mutated melanoma. PFS (2.3 months better) and the disease control rate were better with the VIC regimen compared to irinotecan/cetuximab (IC). The VIC regimen can be considered a potential treatment option in mCRC patients with KRAS WT and BRAF V600E mutation. It should be considered in patients who have previously been treated with irinotecan-based chemotherapy. The addition of vemurafenib to IC showed activity even after progression on IC. It is active in both right and left sided tumors although it appears to be more active in left sided tumors.

In 2017, bevacizumab beyond progression, other

anti-VEGF molecules, and anti-EGFR antibody therapy are available treatment options for patients with mCRC. Anti-EGFR antibody therapy (cetuximab or panitumumab) is an appropriate option for patients with RAS WT and BRAF WT disease and in those with tumor-related symptoms and/or in those who may be considered for surgical resection if tumor shrinkage is sufficient.

Chemorefractory Disease

Chemorefractory disease is when the patient has progressed after two lines of therapy. Two options are FDA approved for chemorefractory disease – regorafenib and TAS-102. Regorafenib, an oral multi-kinase inhibitor, and its major active metabolites, M-2 and M-5, inhibit the activity of VEGFR1, VEGFR2, VEGFR3, RAF-1, BRAF, BRAF V600E, and numerous other kinases in normal cells and cancer cells.²⁸ It is FDA approved for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS WT, an anti-EGFR therapy. Treatment with this agent results in a small improvement in median OS (1.4 months) and PFS (0.2 months) in heavily pretreated patients.²⁹ The response rate in this trial was only 1 percent.²⁹ Thus, this agent has limited clinical efficacy in the chemorefractory setting and causes significant toxicity, which is discussed later.

TAS-102 (Lonsurf[®]) is an oral chemotherapy which contains trifluridine, a nucleoside analog, and tipiracil, a thymidine phosphorylase inhibitor. The trifluridine component of TAS-102 has tumor activity, whereas the tipiracil hydrochloride component suppresses trifluridine breakdown. As a nucleoside analog, trifluridine is incorporated into replicating DNA strands, where it inhibits DNA synthesis and further cellular proliferation. TAS-102 has the same FDA approved mCRC indication as regorafenib. Like regorafenib, TAS-102 treatment results in a small improvement in median OS (1.8 months) and PFS (0.3 months) in heavily pretreated patients with a 1.4 percent response rate and a 44 percent disease control rate.³⁰ This trial showed improvements in OS and PFS in patients with KRAS WT and mutant tumors who received TAS-102 versus placebo, with a favorable safety profile. While the effect on PFS was the same for KRAS WT and mutant groups, OS showed a more pronounced effect with KRAS WT with a HR of 0.6 and 0.8, respectively. Although similar improvements with TAS-102 were seen for OS and PFS with respect to BRAF status, the small patient sample size limited definitive conclusions.

Overall, there are now two active agents with

comparable clinical benefit in the chemorefractory disease setting. Safety and frequent dose modifications with regorafenib require care in patient and dose selection. TAS-102 is a much more tolerable agent than regorafenib. Both drugs result in greater benefit in RAS WT than RAS mutant disease.

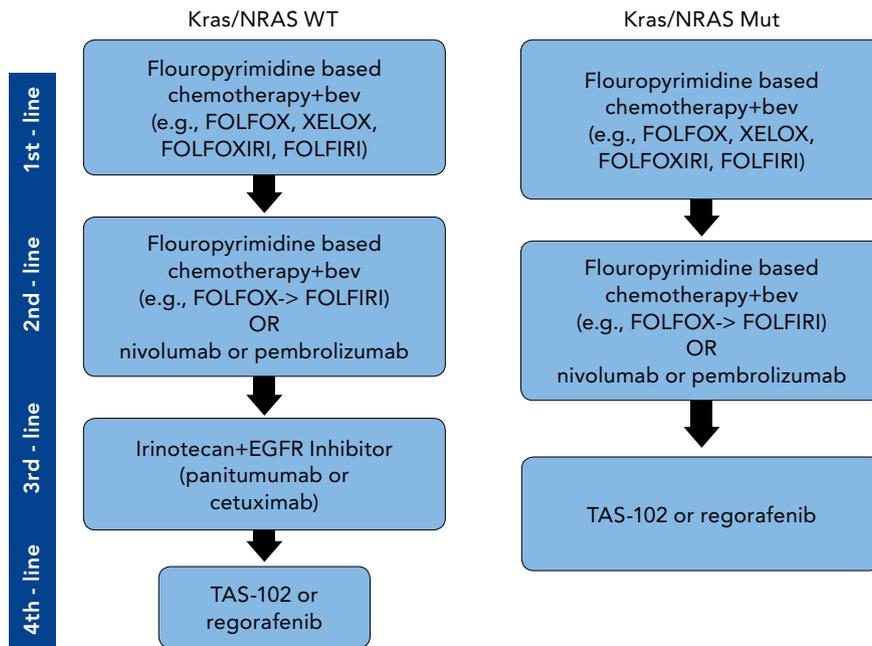
Integration of Novel Immunotherapies in the Treatment Paradigm of MSI-Positive mCRC

Another exciting development in mCRC treatment and many other cancers is the use of the immunotherapy to allow the innate immune system to better recognize cancer cells and destroy them. Tumor cells have numerous different ways of either hiding from the immune system or actually downregulating the body's immune response. The current two targets of immunotherapy are programmed cell death-1 (PD-1), programmed cell death ligand-1 (PD-L1), and T-lymphocyte-associated antigen-4 (CTLA-4), which are all important in the body recognizing self from non-self cells. Although CTLA-4 inhibitors are FDA approved for other cancers, so far none has shown significant benefit in mCRC.

In mCRC, it has been discovered that mutational burden in the tumor correlates with response to immunotherapy. CRC tumors can have significant numbers of mutations because of impaired mismatch repair (MMR) pathway functions. This pathway is supposed to fix nucleotide mistakes in DNA replication. MMR deficiency (dMMR) is caused by inherited germline mutation in MMR genes, acquired MMR gene mutations, or epigenetic silencing of MMR gene and results in microsatellite instability (MSI). MSI is increased duplication of tandem dinucleotide repeats (microsatellites), which results in an increased mutation rate and a higher risk of colon cancer. MMR-deficient cells have many mutations – 1,700 on average compared with just 70 in a typical cancer cell.³¹ Cases can be labeled dMMR or MSI high (MSI-H). MSI-H is found in greater than 90 percent of patients with (HNPCC) and in 15 percent of sporadic CRC.^{32,33} It is commonly found in right sided CRC. In addition to mCRC, MSI-H is observed in uterus, stomach, biliary tract, pancreas, ovary, prostate, and small intestine cancers.

The genomes of MSI-H tumors harbor thousands of mutations, which if expressed as proteins, can potentially be recognized by the immune system as foreign antigens. This abundance of mutant associated neo-antigens (MANA) results in the tumor appearing foreign to the host immune system. This MANA foreignness results in an inflamed microenvironment with very high expression of immune checkpoint signaling, which can be harnessed with

Exhibit 7: Sequencing MSI-H mCRC Intensive Treatment



immunotherapy.³⁴ Infiltration of immune cells into the tumor can be seen on immunohistochemistry testing. MMR status is a clear prognostic factor, with the five-year disease-free survival increasing from 56 percent in patients with proficient MMR tumors to 80 percent in patients with dMMR tumors.³²⁻³⁵

The programmed death 1 (PD-1)-mediated signaling pathway represents an important immune escape mechanism for many tumors. Blockade of the PD-1 pathway enhances tumor antigen-specific CD8+ T cell responses, which leads to T cell activation and proliferation. PD-1 and PD-L1 agents act more in the tumor micro environment than checkpoint inhibitors that target CTLA-4, which may explain anti-PD-1 efficacy in mCRC. Significant advances have been made by targeting this pathway with highly durable tumor response and minimal toxicity in the treatment of several tumor types, including melanoma, non-small cell lung cancer, renal cell cancer, bladder cancer, and Hodgkin's lymphoma.

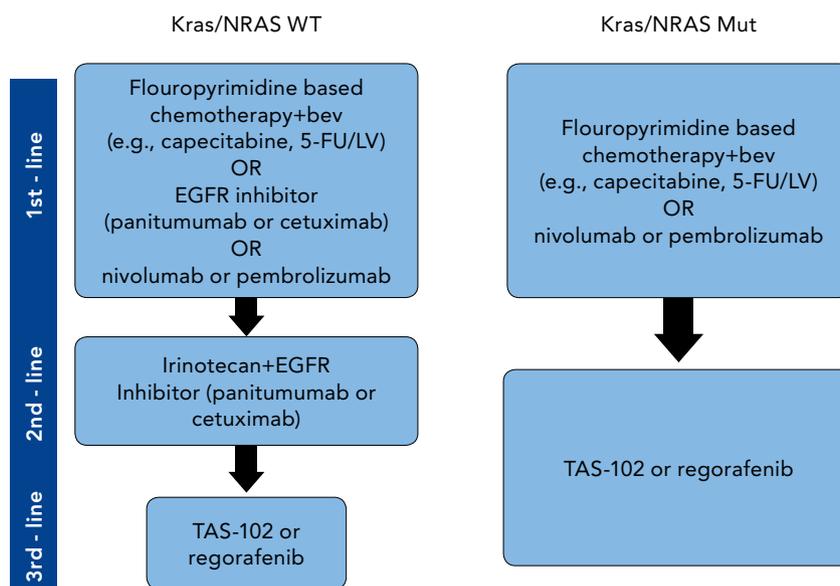
Two anti-PD-1 agents have been FDA approved - pembrolizumab (Keytruda®) and nivolumab (Opdivo®) - for mCRC. Both are FDA approved for adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or with MSI-H or dMMR CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.³⁶ These are the first FDA's first tis-

sue/site agnostic approvals.

The early Phase I and II studies of anti-PD-1 immunotherapy in mCRC found good responses in a small percentage of patients, and it was found that those who responded were MSI-H. In patients who had tumors that expressed PD-L1, the only patient in a small trial that responded to pembrolizumab was MSI-H.³⁷ In another trial, pembrolizumab treatment resulted in better response rates and PFS in those with MSI-H CRC than those without.³⁸ CEA response was also more in those with MSI-H disease. Median OS had not been reached before publication of this trial (OS in those with proficient MMR was 5.98 months). In an ongoing multicenter, open-label, Phase II trial, nivolumab provided durable responses and disease control in pretreated patients with MSI-H mCRC.³⁹ Although small, the trials of anti-PD-1 immunotherapy led to the FDA approval of these agents for mCRC.

When immunotherapy works, there is a durable response. Complete and durable responses are seen in more than 50 percent of patients. Currently, approximately 20 percent of patients in an ongoing pembrolizumab trial have reached the two-year mark and anti-PD-1 has been held. Nivolumab or pembrolizumab are considered first-line option for MSI-H patients not appropriate for intensive therapy and are an option for MSI-H patients in second-line therapy and beyond.¹⁵ Exhibits 7 and 8 illustrate the various options for the MSI-H patient depending on

Exhibit 8: Sequencing MSI-H mCRC Non-Intensive Treatment



KRAS/NRAS status.

Across tumor types tested, pembrolizumab responders tend to have baseline T cell inflammation, but there is a group of nonresponders who have also had this inflammation. Researchers are still trying to determine what is different about these tumors. A correlation between neoantigen load and immune infiltrates has been investigated as one possibility.⁴⁰ There appears to be higher percentage of HLA mutations, which may be a mechanism of nonresponse in face of T cell inflammation.

Intense efforts are focused on developing immunotherapy strategies for microsatellite stable (MSS) mCRC in the chemorefractory setting, which is a large portion of patients. A combination of cobimetinib, a MEK inhibitor plus atezolizumab (Tecentriq[®], anti-PD-L1) appears promising and is being investigated in a Phase III trial.

There is a question of how best to combine immunotherapy, chemotherapy, and targeted biologics. Studies are ongoing looking at various combinations. Questions also exist on how long to continue immunotherapy and how best to evaluate response. With immunotherapy, there can be the appearance of worsening disease (i.e., tumor growth), but this is likely pseudo-progression from immune response around the tumor and may actually be a marker of efficacy.

Strategies for Managing Adverse Events Associated with Therapy

Each treatment for mCRC is associated with a

unique set of adverse effects that must be carefully monitored and managed to ensure the best outcomes. Individualizing risk, minimizing and managing adverse effects, and counseling patients and their families/caregivers regarding their treatment plan may improve the quality of life of the patient and improve adherence.

Toxicities associated with chemotherapy include acute and long-term adverse effects. Acute nausea, vomiting, allergic reactions, and phlebitis occur frequently, depending on the specific chemotherapy. Other common adverse effects are bone marrow suppression, mucositis/stomatitis, diarrhea, and alopecia. There are also irreversible adverse effects which can limit the use of chemotherapy, including cardiotoxicity, hepatotoxicity, nephrotoxicity, neurotoxicity, ototoxicity, and secondary carcinogenesis.

Anti-VEGF therapy is typically well tolerated, but there are some adverse effects of concern. The major toxicities of anti-VEGF therapy are hypertension, hemorrhage and thrombus, proteinuria, impaired wound healing, and GI perforation.³¹ Each of these occur because of the effects of VEGF inhibition in normal tissues. Hypertension, which occurs in about 30 percent of patients, is managed with antihypertensive medications. Proteinuria is usually asymptomatic and resolves after treatment ends. Serious impairment of renal function is rare. Serious bleeding events occur in less than 10 percent of patients treated with anti-VEGF therapy.

Dermatologic toxicity is the limiting factor in using anti-EGFR therapy. This includes diffuse acneiform rashes of the torso and face, very dry skin, and paronychia inflammation. EGFR inhibition causes skin reactions through altered growth and migration of keratinocytes and inflammatory chemokine expression.⁴² Proactive therapy with topical corticosteroids and oral antibiotics are given to prevent the rash from becoming serious. Hydrocortisone 1% cream combined with a skin moisturizer, sunscreen (SPF \geq 15) daily, and oral minocycline or doxycycline for the first six weeks of therapy are generally recommended. Good skin care and avoidance of sun exposure are also used to minimize skin toxicity. Patient education on skin toxicities of anti-EGFR therapy is very important before and during therapy. Additionally, clinicians need to monitor electrolytes closely and replace magnesium, potassium, and phosphates as needed.

Regorafenib, because of its multikinase actions, causes significant skin reactions, including hand-foot syndrome, rash, and desquamation. Fatigue and GI toxicities (diarrhea, colitis) are also major adverse effects. Regorafenib is less well tolerated than anti-EGFR or anti-VEGF therapies.

Immunotherapy is generally well tolerated, but 20 to 40 percent of patients can develop an immune-mediated toxicity which can be very serious. By taking the brakes off the immune system, the body begins attacking itself. Immune toxicities occur most commonly in the lungs, skin, liver, kidneys, GI tract, pancreas, and thyroid. Patients need education to recognize an immune reaction and how to quickly seek treatment. These reactions are treated with systemic corticosteroids, if moderate or severe. Immunotherapy may be temporarily held or discontinued depending on the grade of toxicities.

Biomarkers

Because the biologic agents and immunotherapy are expensive agents, clinicians and managed care would like for the right patient to get the right medication. Biomarkers can be used to personalize therapy by selecting the most appropriate therapy.

The state-of-the-art in mCRC is measurement of selected biomarkers. At this time, MSI is the best biomarker available for predicting response to immunotherapy in CRC. Testing for MSI should be universal in those with HNPCC and patients with a personal history of colon or rectal cancer. It is also useful for prognostic relevance in Stage II CRC, for use of immuno-oncology agents in first or second line, and for clinical trial options in met-

astatic CRC. Additional predictive biomarkers to determine which patients will best respond to immunotherapy are under study, including markers of tumor immune infiltration (CD3, CD8 cells), ligand expression on tumor (PD-L1, PD-L2), mutational load/neoepitopes (POLE mutations), and the immunogenic microenvironment of tumors. Gene sequencing is done to identify the length of microsatellites compared to normal and can be done by next-generation sequencing. Normal tissue also has to be tested to clarify whether the patient has an inherited syndrome or whether only the tumor has the MSI.

At this time, RAS mutation testing is generally reserved for mCRC cases. BRAF testing is sometimes done if the tumor is RAS WT.

Gene profiling is also being done. In the adjuvant setting, Oncotype and Coloprint testing can be done to predict who needs adjuvant chemotherapy after surgical removal of the cancer. These gene profiles unfortunately do not give a black and white answer and thus are not ideal. In the metastatic setting, Caris and Foundation are the leading companies in gene profile testing in the U.S. Most patients with mCRC will benefit from gene profiling to direct therapy.

Tumors are now being tested for HER2 expression, but no therapies are FDA approved for HER2-positive mCRC. HER2 positivity occurs in 5 to 10 percent of mCRC. Trastuzumab and lapatinib, both already approved for treating HER2 positive breast cancer, have been studied in HER-2 positive mCRC.⁴³

Prospective incorporation of molecular profiling will transform global cancer care. Although currently expensive, every cancer patient should be profiled. Rapidly evolving technology should lead to cost reductions. Continued research is needed to prove better outcomes and improved value by cutting waste of ineffective empiric therapy with molecular profiling.

Conclusion

When discovered early, CRC is highly treatable. However, when the disease has metastasized, treatment and management becomes much more difficult. Fortunately, targeted and immunotherapy options have become available for patients with mCRC, giving clinicians more options in managing this patient population.

CRC is now being considered based on molecular subsets and sidedness. Treatment pathways will vary according to molecular biology, anatomy, and the performance status of the patient. Clinical trial enrollment is always encouraged when possible.

Gerard C. Blobe, MD, PhD, is a Professor of Medicine and Professor of Pharmacology and Cancer Biology at Duke University.

Minsig Choi, MD, is Director of GI Oncology and an Associate Professor at Stony Brook University Hospital.

Edward Chu, MD, is a Professor of Pharmacology & Chemical Biology and Chief, Division of Hematology-Oncology at the University of Pittsburgh School of Medicine and Interim Director of the University of Pittsburgh Cancer Institute

Cathy Eng, MD, FACP, holds the Sophie Caroline Steves Distinguished Professorship in Cancer Research in the Department of GI Medical Oncology and is Associate Medical Director, Colorectal Center at The University of Texas MD Anderson Cancer Center.

John L. Marshall, MD, is Chief of Hematology and Oncology at the Georgetown University Hospital.

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