Targeted and Chemotherapeutic Approaches to mCRC Management

This activity is provided by:

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Date
September 9, 2017

Faculty
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Advanced Practice Clinician
Advanced Oncology Certified Nurse Practitioner, Department of Hematology/Oncology
Fox Chase Cancer Center
Department of Medicine, Section of Gastroenterology
Philadelphia, PA

Time
Lecture @ 3:10-PM

Location
JW Marriott Los Angeles L.A.
Los Angeles, CA

Target Audience
This educational activity is designed to meet the needs of oncology nursing professionals involved in the care of patients with mCRC.

Statement of Need
Oncology nursing professionals play an extremely vital role on the interprofessional team managing patients with mCRC. They frequently assume front-line functions in preparing patients for therapy, recognizing treatment-related toxicities and symptoms, and managing these complications while educating patients about their treatments and related side effects. As the treatment landscape for mCRC continues to evolve with new therapies, treatment regimens, and guideline recommendations, it is imperative that oncology nurses and advanced practice nurses be up-to-date on the latest developments in the field and be able to apply this knowledge to their roles in managing patients with mCRC and assist their fellow clinicians in improving patient outcomes and quality of life.

Learning Objectives/Learning Outcomes

Upon completion of this educational activity, learners should be better able to:

1. **Critically evaluate** current clinical trial evidence supporting the use of targeted and chemotherapeutic approaches, and their combinations, in the management of mCRC across multiple lines of treatment
2. **Explain** which factors driving patients segmentation (prognostic and predictive biomarkers, comorbidities, patients' preference) impact the treatment decision-making process in different clinical scenarios across disease progression
3. **Review** current best practices for the management of adverse events associated with targeted therapies in mCRC and how to maximize tolerability and adherence to different therapeutic regimens

Activity Agenda

- Welcome and Introduction (including pre activity survey)
- Brief Review of CRC
    - Epidemiology and Prognosis
    - Case-based challenge question
- Initial Treatment of Metastatic CRC
    - Biomarkers and their implications for treatment
    - Treatment Options – what oncology nurses need to know about our current armamentarium
    - What the latest guidelines say about management
    - Adverse events to be watchful for, and strategies for management when they occur
    - Case: Initial treatment of a newly-diagnosed patient with mCRC
    - Challenge questions
- Treatment of Metastatic CRC at Progression
    - Biomarkers and their implications for treatment
    - Treatment Options – what oncology nurses need to know about our current armamentarium
    - What the latest guidelines say about management
    - Adverse events to be watchful for, and strategies for management when they occur
    - Case: Our newly patient's disease has progressed—where do we go from here?
    - Challenge questions
- Question & Answer Session and Closing Remarks (including post-activity survey)
- Acknowledge of patient resource materials from Fight Colorectal Cancer

To promote active learning and engage learners, audience polling questions and discussion cases have been incorporated in the activity design.

Accreditation and Credit Statements

American Academy of CME, Inc. is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

American Academy of CME, Inc. designates this educational activity for 1.0 contact hour (.8 pharmacotherapeutic contact hour).

Method of Participation

There are no fees for participating and receiving CE credit for this activity. In order to receive a CE certificate, learners must:

1) Review the CE information including the learning objectives and disclosure statements;
2) Attend the activity and document attendance;
3) Successfully complete and return the activity evaluation, your certificate will be made available

Please contact Paul Miniter, pminiter@academycme.org if you experience issues.

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Faculty

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Ms. Ross discloses the following:
Other Relationship: Presenter on Medscape Activity "The Nurse View: Updates in Management of Metastatic Colorectal Cancer"

Planning Committee

John JD Juchniewicz, MCIS, CHCP, Paul J. Miniter, MS, Natalie Kirkwood, RN, BSN, JD, Lead Nurse Planner, and Wendy Gloffke, PhD, American Academy of CME : No relevant financial relationships with any commercial interests.

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Faculty Biography

Ms. Ross has over eleven years of total nursing experience in Oncology, including practice as Registered Nurse and Nurse Practitioner. She has been a Nurse Practitioner for six years and has practiced at the University of Pennsylvania in Radiation Oncology, and more recently at Fox Chase Cancer Center in GI Medical Oncology. She has been Adjunct Clinical Nursing Faculty for La Salle University since 2010. Her interests include symptom management and patient education.

Supplemental Patient Resource

The American Academy of CME, Inc (Academy) and Fight Colorectal Cancer jointly provide the following patient resource for oncology nurses and their patients.

About Fight Colorectal Cancer (Fight CRC)

Fight CRC is a national patient empowerment nonprofit founded in 2005, focusing on four 'pillars':

- advocacy/policy
- research
- awareness
- patient education

Fight CRC is a leader in providing a robust channel of free online and printed resources addressing the unique needs of the CRC community to ensure access to medically reviewed, innovative, contemporary resources. According to a 2016 survey, those who use Fight CRC resources report satisfaction and trustworthiness of the resources, and that the resources increase their knowledge on a variety of topics. In addition to presenting our resource library at national cancer conferences, Fight CRC is happy to partner with the National Comprehensive Cancer Network's Rectal and Colon Patient's Guides.

Fight CRC's resources include the following range of educational modalities: webinars, podcasts, blogs, topic specific mini- magazines, and videos. To learn more and to access the resources, visit: https://fightcolorectalcancer.org/fight/library/

Your Guide in the Fight

Your Guide in the Fight **(GITF) is Fight CRC's flagship resource: a 3-part book designed to empower patients and point them toward trusted, credible information.** Version 3 was released in January 2017 after in depth focus groups with patients and medical professionals. The resource is a recipient of the Hermes Creative Award. All content was written and edited by Fight CRC and underwent medical review prior to publication. GITF undergoes yearly updates for relevance.

GITF is an easy-to-read resource for stage III, stage IV, and recurrent CRC patients. Some topics covered include:

- understanding your diagnosis & approved treatment options for late-stage patients
- genetic syndromes
- biomarkers & tumor testing
- palliative care & side effects management
- survivorship, psychosocial health, practical support & caregiver support
- tumor banking & end-of-life care

GITF is divided into 3 distinct parts:

- Part 1: Diagnosis through Treatment
- Part 2: Treatment Side Effects & Survivorship
- Part 3: Supportive Care, Practical Issues & Resources

GITF is available by free digital copy or printed copy. Those who sign up to receive GITF receive monthly email updates with links to the latest patient education resources.

To download or order a free copy, visit:
https://fightcolorectalcancer.org/fight/library/your-guide-in-the-fight/
To order bulk copies, email: Sharyn@fightcolorectalcancer.org

Targeted and Chemotherapeutic Approaches to Management of Metastatic Colorectal Cancer

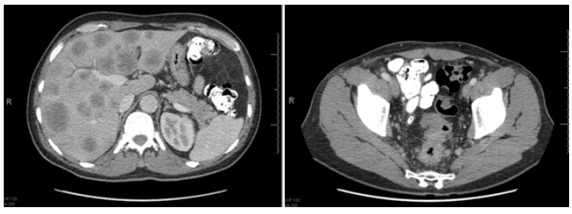
Nicole M. Ross, MSN, CRNP, AOCNP
Fox Chase Cancer Center

Learning Objectives

- **Critically evaluate** current clinical trial evidence supporting the use of targeted and chemotherapeutic approaches, and their combinations, in the management of metastatic colorectal cancer (mCRC0 across multiple lines of treatment.
- **Explain** which factors driving patients' segmentation (prognostic and predictive biomarkers, comorbidities, patients' preference) impact the treatment decision-making process in different clinical scenarios across disease progression
- **Review** current best practices for the management of adverse effects associated with targeted therapies in mCRC and how to maximize tolerability and adherence to different therapeutic regimens

Case: F.F.

- 49 year old otherwise healthy man presented with constipation for 3 months and abdominal pain.
- 30 lb weight loss over the last 3 months.
- Low grade fever, increasing right upper quadrant pain

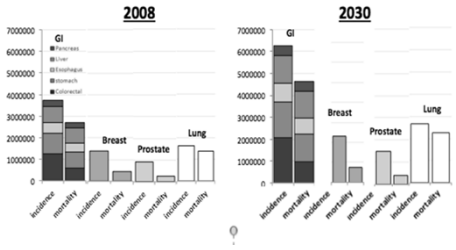


Case: F.F.

- CEA- 702
- LFT mildly elevated, bilirubin normal

- Colonoscopy nearly obstructive mass in the recto-sigmoid junction
- Biopsy – moderately differentiated adenocarcinoma

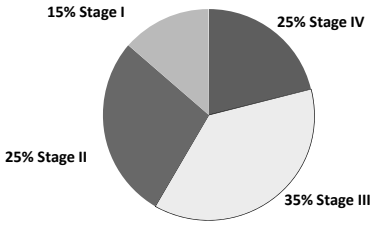
Worldwide Cancer Statistics



Bray F et al. *Lancet Oncol*. 2012;13:790-801; http://www.cancer.org/aboutus/globalhealth

Epidemiology

- Estimated US incidence (new cases): 142,820
- Estimated US mortality: 50,830
- Third most common malignancy in man and woman.

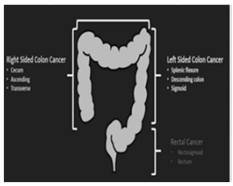


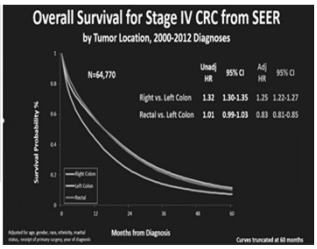
Siegel R et al. *CA: Cancer J Clin*. 2013;63:11-30.

Colon Cancer: More Than One Disease

- Molecular
  - MSI vs MSS
  - RAS WT vs MUT
- Anatomic
  - Right versus left
  - Rectal versus colon

Right vs. Left: Sidedness Matters





Median age at diagnosis:

- Right sided: 70.2 years
- Left sided: 65 years

Schrag D et al. *J Clin Oncol.* 2016;34(suppl; abstr 3505). Abstract 3505.

Pre-Treatment Evaluation in mCRC

Imaging:

- CT chest/abdomen/pelvis
- PET-CT and MRI useful for specific questions i.e. resection.

Lab/Pathology/Molecular testing

- Confirm path/ biopsy of metastases
- Baseline CEA
- KRAS mutation status (all patients) prior to anti-EGFR therapy
- BRAF mutation (?)
- MSI status
- UGT1A1*28 (not recommended routinely, consider before irinotecan)

Resection of Primary Tumor in mCRC

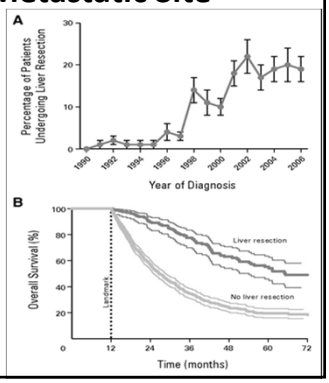
- C-10 phase II multicenter study.
- 86 patients, front line FOLFOX+Bev with intact primary tumor.
- Primary end point surgical resection required due to symptoms related to primary tumor.

	N	%
Surgery due to symptoms from primary tumor	10	11.6
Death with symptoms from primary tumor	2	2.3
Primary tumor resected with curative intent	8	9.3
Patient died with intact tumor	28	32.6
Patient was alive at last follow up with intact tumor	35	40.7

McCahill LE et al. *JCO.* 2012;30:3223-3228.

Resection of Metastatic Site

- Data from MD Anderson + Mayo 2,470 patients. 231 underwent hepatic resection.
- Rates of resection increased.
- Survival improved with resection.



Kopetz S et al. *J Clin Oncol.* 2009;27:3677-3683.

Treatment – Conversion to Surgery

Original article

Annals of Oncology 16: 425–429, 2005
doi:10.1093/annonc/mdi092
Published online 27 January 2005

Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741

T. Delaunoit[1], S. R. Alberts[1], D. J. Sargent[2]*, E. Green[2], R. M. Goldberg[3], J. Krook[4], C. Fuchs[5], R. K. Ramanathan[6], S. K. Williamson[7], R. F. Morton[8] & B. P. Findlay[9]

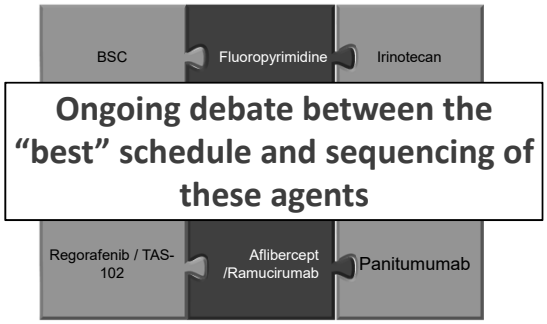
Original article

Annals of Oncology 15: 933–939, 2004
DOI: 10.1093/annonc/mdh217

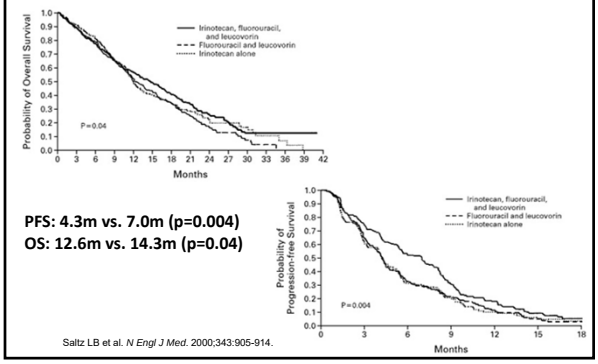
Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients

C. Pozzo[1], M. Basso[1], A. Cassano[1], M. Quirino[1], G. Schinzari[1], N. Trigila[1], M. Vellone[2], F. Giuliante[2], G. Nuzzo[2] & C. Barone[1]*

More Agents Available Now…



Addition of Irinotecan

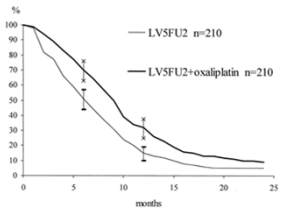


PFS: 4.3m vs. 7.0m (p=0.004)
OS: 12.6m vs. 14.3m (p=0.04)

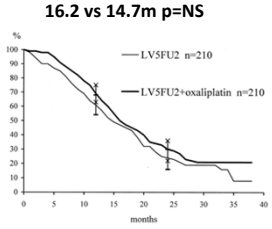
Saltz LB et al. *N Engl J Med.* 2000;343:905-914.

Addition of Oxaliplatin

Progression free survival
9.0 vs 6.2m p=0.0003



Overall survival
16.2 vs 14.7m p=NS

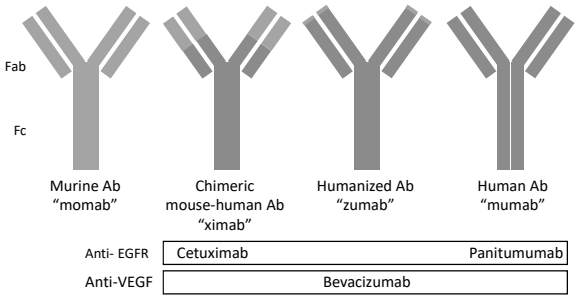


de Gramont A et al. *J Clin Oncol.* 2000;18:2938-2947

F.F. Treatment Plan

- Metastatic adenocarcinoma, multiple liver metastasis (10+)
- MSS
- KRAS wild type
- Discussion with oncologist.
  - Goal: best shot to live as long as possible; needs to keep working; insurance carrier for family
  - Has teenage children in high school
  - Decision to avoid surgery and initiate FOLFIRI/Cetuximab

Biologic Agents- Monoclonal Antibodies



Troiana T et al. *Expert Opin Investig Drugs*. 2012;21:949-959.

FOLFIRI Cetuximab

- Port placement
- Given every 14 days
- Infusion room time and 46 hour infusion at home
- Pre-meds
- Anti-emetics for home

Diarrhea

- Brat diet
- Imodium
- Lomotril
- Hydration
- Check electrolytes
- Review other medications (antihypertensives, diuretics)
- Consider admission when needed

Grade I	Increase of <4 stools per day over baseline
Grade II	Increase of 4-6 stools per day over baseline
Grade III	Increase of >7 stools per day over baseline; hospitalization indicated; limits self care ADL's
Grade IV	Life-threatening consequences; urgent intervention
Grade V	Death

Adverse Effects of EGFR Inhibition

- Cutaneous adverse effects
  - Papulopustular reaction involving skin
  - Can affect compliance and QOL
  - Leaves skin vulnerable to bacterial overgrowth and infection
  - Skin rash can lead to dose modification or treatment discontinuation
  - Sun protection
  - Topical clindamycin 2% / 1% hydrocortisone cream
  - Oral doxycycline if moderate to severe
  - Consider dermatology if needed
- Dry eyes

Case: F.F.

- First CT at 3 months with great response to treatment
- Stable disease after 9 months
- Increasing diarrhea and neutropenia requiring Neulasta
- Restaging CT 2 months later for new cough. New pleural effusion + malignancy

But What Impacts the Patient's Decision Making?

- Patient goals
- Quality of life
- Side effect profile of drugs
- Comorbid conditions
- Logistics

Next Steps in Treatment

- FOLFOX/bevacizumab
- PleurX catheter placement
- Palliative care consult
- Patient education

Bevacizumab Risks

- Hypertension (~20%)
- Arterial thrombosis (2-5%)
  - SCD, MI, CVA, TIA
  - Increased with poor PS or age > 65
- GI perforation (1-2%)
- Grade 3-4 bleeding (2-5%)
- Post-operative bleeding/wound healing (1-2%)
  - Perforation, fistula, abscess, surgery within 60 days

Kozloff M et al. *The Oncologist.* 2009;14:862-870.

Nursing Implications for the Patient Receiving FOLFOX

- Patient education
  - Nausea
  - Diarrhea
  - Cold sensitivity
- Ask about peripheral neuropathy
  - Assessment CTCAE grading
  - Management
- Infusion pump safety

Peripheral Neuropathy

- Numbness
- Tingling
- Pain
- Like walking on broken glass
- Off balance
- Stiffness

CTCAE v4.0 Peripheral Neuropathy

Grade I	Asymptomatic, lost of DTRs or paresthesia
Grade II	Moderate symptoms; limiting instrumental ADL's
Grade III	Severe symptoms limiting self care ADLs
Grade IV	Life – threatening consequences
Grade V	Death

Management Strategies

- Assessment via CTCAE
- Considering of modification of dose/holding drug
- Gabapentin, Cymbalta, Lyrica
- PT/OT
- B-complex

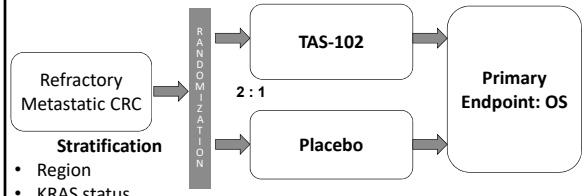
Case: F.F.

- Disease progression after 9 months of FOLFOX/bevacizumab
- HTN managed with ACE inhibitor
- Grade II peripheral neuropathy - stable
- Middle child graduated from high school
- New lung metastasis and increasing liver metastasis

F.F. Treatment Decision

- Consideration of clinical trial
- TAS 102
- Regorafenib

RECOURSE: TAS-102 in Refractory mCRC



Stratification

- Region
- KRAS status
- Time form diagnosis of mets to randomization

TAS-102 Treatment Schedule
35mg/m2 BID 5 days per week with 2 days rest, 2 weeks on 2 weeks off.

Mayer R et al. *NEJM*. 2015;3872:1909-1919.

RECOURSE: TAS-102 in Refractory mCRC – PFS

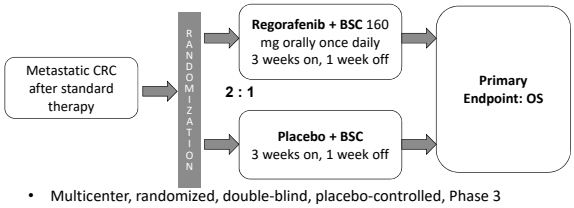
Adverse Event	Grade 3-4 (%)
Neutropenia	38%
Febrile Neutropenia	4%
Anemia	18%
Thrombocytopenia	5%
Stomatitis	<1%
Hand foot syndrome	0
Cardiac ischemia	<1%
Diarrhea	3%
Fatigue	4%.

Mayer R et al. *NEJM*. 2015;3872:1909-1919.

Nursing Considerations with TAS-102

- Patient education for schedule
  - Calendars
  - Prefer a Monday start date (M-F, M-F, off 2 weeks)
- Watch for s/s of bleeding
- Diarrhea management
- Labs
  - Labs at Day 14 and prior to start of next cycle

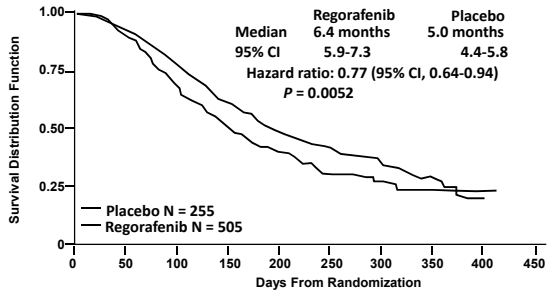
*CORRECT Study Design



- Multicenter, randomized, double-blind, placebo-controlled, Phase 3
  - 2:1 randomization
  - Stratification factors: prior anti-VEGF therapy, time from diagnosis of metastatic CRC, geographical region
- Global trial: 16 countries, 114 active centers;1052 screened, 760 enrolled
- Secondary endpoints: PFS, ORR, DCR

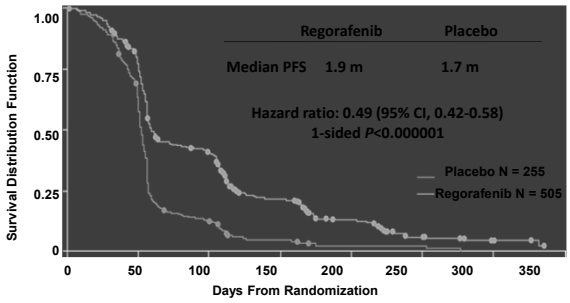
Grothey A et al. *Lancet.* 2013;381:303-312.

CORRECT: Overall Survival



Grothey A et al. *Lancet.* 2013;381:303-312.

CORRECT: PFS



Grothey A et al. *Lancet.* 2013;381:303-312.

CORRECT: Adverse Events

Adverse event, %	Regorafenib N = 500			Placebo N = 253		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hand–foot skin reaction	46.6	16.6	0	7.5	0.4	0
Fatigue	47.4	9.2	0.4	28.1	4.7	0.4
Hypertension	27.8	7.2	0	5.9	0.8	0
Diarrhea	33.8	7.0	0.2	8.3	0.8	0
Rash/desquamation	26.0	5.8	0	4.0	0	0
Anorexia	30.4	3.2	0	15.4	2.8	0
Mucositis, oral	27.2	3.0	0	3.6	0	0
Thrombocytopenia	12.6	2.6	0.2	2.0	0.4	0
Fever	10.4	0.8	0	2.8	0	0
Nausea	14.4	0.4	0	11.1	0	0
Bleeding	11.4	0.4	0	2.8	0	0
Voice changes	29.4	0.2	0	5.5	0	0
Weight loss	13.8	0	0	2.4	0	0

Grothey A et al. *Lancet.* 2013;381:303-312.

Management of Patients on Regorafenib

- Home BP log; weekly BP checks in office.
- Skin care
- Weekly LFT's for first 2 cycles
- Safe administration (calendars)
- Hand-foot skin reaction
- Treatment of diarrhea

Hand-Foot Syndrome

AE Term	Definition	Management
Grade I	Changes or dermatitis without pain	• Udder cream, Eucerin • Monitor
Grade II	Skin changes with pain limiting function	• Hold drug • Resume when grade I • Moisturize
Grade III	Severe skin changes with pain limiting ADLs	• Hold drug • Moisturize • Treat pain, topical lidocaine

Microsatellite Instability

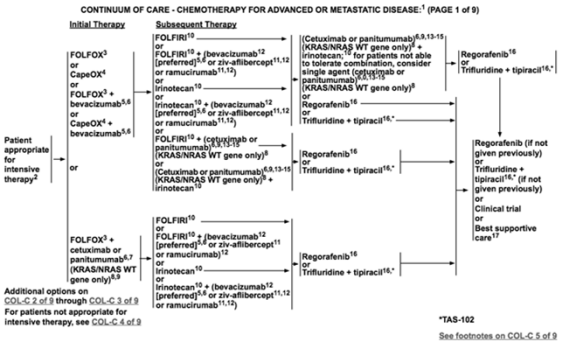
- Hypermutatable phenotype
  - 10-100X somatic mutation rate
- Characterized by loss of DNA mismatch repair activity and simple repetitive sequences of DNA
- More likely to be:
  - Right-sided/proximal colon
  - Poorly differentiated
  - Younger, female patients
  - Contain lymphocyte infiltrates
- Less likely to be KRAS or p53 mutated
- Associated with hereditary colon cancer syndromes (Lynch Syndrome)
- Overall better prognosis

Boland CR, Goel A. *Gastroenterology.* 2010;138:2073-2087.
Le DT et al. *NEJM.* 2015;372:2509-2520.

Immunotherapy

- 10-15% of sporadic colon cancers will have microsatellite instability
- Pembrolizumab IV infusion given every 3 weeks

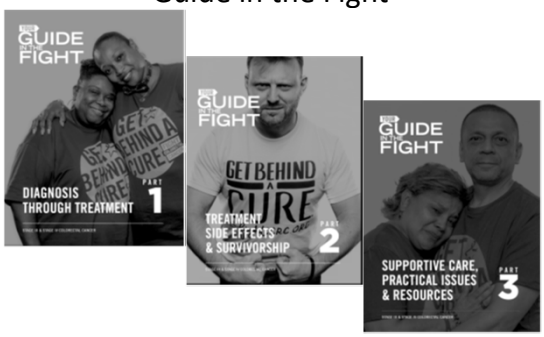
NCCN Guidelines 2.2016: Treatment of Advanced or Metastatic CRC



Summary

- The prognosis of patients with mCRC has improved over the last decade.
- Standard of care in the 1st and 2nd line setting: combination chemotherapy and biologic agent
- Additional studies are needed for identification of novel targets and better biomarkers

Fight Colorectal Cancer:
Guide in the Fight



https://fightcolorectalcancer.org/fight/library/your-guide-in-the-fight/

Thank You!