LEARNING OBJECTIVES

• Classify high- and low-risk status based on pathology in patients with stage II CRC
• List criteria for resection of a primary tumor and metastases vs. systemic chemotherapy as first-line treatment of patients with stage IV CRC
• Discuss factors that would support and discourage maintenance therapy vs. a drug holiday in patients with CRC
• Determine the appropriate utilization situations for biomarker assays such as K-ras, B-raf, PTEN, and PI3-Kinase in patients with CRC
CASE STUDY 1

STAGE 2 ADJUVANT THERAPY

OUR PATIENT — MS

- 40-year-old female, presents with rectal bleeding for several weeks
- Married, 2 children
  - 3 siblings, all healthy
  - Parents alive, no family history of cancer
- No significant past medical history
- Patient is a scientist; husband is a physician
- Patient wants to be “aggressive” with her treatment
MS’S HISTORY

● Colonoscopy showed an ascending colon mass
  – Biopsy showed poorly differentiated adenocarcinoma
● Staging scans were all negative, CEA 6
● Right hemicolecotomy
  – T3N0 (0/22) M0, poorly differentiated adenocarcinoma, positive lymphocytic infiltrate, positive lymphovascular invasion
● Patient recovered well and is here for her 3-week post-op follow-up

YOUR CALL

● What would you recommend at this point (choose all that apply)?
  a. FOLFOX
  b. Capecitabine
  c. Genetic testing for MSI/MSS
  d. Genetic testing: LOH 18q
  e. Genetic testing: Oncotype Dx colon assay
  f. No treatment
YOUR CALL

- Would you test for MSI/MSS in this patient?
  a. Yes
  b. No

PANEL DISCUSSION

- Should we test for MSI/MSS in everyone?
  - Stage III patients? Stage IV?
  - Is the test being run quickly enough?
  - What is the role of germ-line mutation testing in MSI-H tumors?
- Has the Oncotype Dx colon assay been helpful for your patients?
PANEL DISCUSSION

● How do you determine high- and low-risk status based on pathology?
● How much of a benefit do you tell your stage II patients to expect from chemotherapy? 3%? 5%? Higher?
● Do you offer FOLFOX or 5-FU in stage II CRC?

CASE STUDY 2
SECOND-LINE THERAPY IN K-RAS WILD-TYPE PATIENT
OUR PATIENT — DF

- 71-year-old female
- Homemaker
- Well-controlled hypertension and hyperlipidemia
- BMI = 35

DF’S HISTORY

- Jan. 2010: Diagnosed with metastatic adenocarcinoma of the ascending colon with liver and bilateral lung metastases after workup for right upper quadrant pain
- K-ras from liver biopsy determined as wild-type
- Feb. 2010: Started on palliative chemotherapy with FOLFOX + bevacizumab
  - CT scans showed partial response in metastases after 4 and 8 cycles of therapy
  - Good tolerability
- Mild-to-moderate sensory neuropathy
DF’S HISTORY

- June 2010: Decision to hold oxaliplatin and continue therapy with capecitabine + bevacizumab as maintenance therapy
- Sep. 2010: Slowly rising CEA; no change in CT scans; good tolerability of therapy
- Nov. 2010: CT scan showed increase in combined size of metastases by 25% since June 2010
- Persistent mild-to-moderate sensory neuropathy

YOUR CALL

- Which of the following would you choose as the next step in the management of this patient?
  a. Continue therapy with capecitabine + bevacizumab
  b. Reintroduce FOLFOX and continue bevacizumab
  c. Switch to FOLFIRI and continue bevacizumab
  d. Reintroduce FOLFOX and add cetuximab or panitumumab
  e. Switch to FOLFIRI and add cetuximab or panitumumab
  f. Switch to cetuximab or panitumumab monotherapy
  g. Something else
PANEL DISCUSSION

● When has maintenance therapy failed? After what degree of progression would you switch therapy?
● In the second-line setting, should FOLFOX be reintroduced (OPTIMOX) or is an irinotecan-based regimen preferable, with oxaliplatin reserved for later?
● Are there situations in which bevacizumab should be continued beyond progression?
  – If yes, what criteria support continuation?

PANEL DISCUSSION

● Would we lose ground if EGFR antibodies were not introduced in second-line treatment but reserved for later treatment?
  – Do EGFR antibodies work better in later treatment?
● Do we need biologics at all in second-line treatment?
● Is there a rebound phenomenon after bevacizumab discontinuation?
  – How could this be evaluated?
CASE STUDY 3

MAINTENANCE THERAPY OR DRUG HOLIDAY?

OUR PATIENT — LG

- 52-year-old female photographer
- Presented with right upper quadrant pain
- Scans showed liver metastases and retroperitoneal lymph nodes
- Biopsy of the liver lesions showed a moderately differentiated adenocarcinoma, CK7-, CK20+, TTF1-
- Colonoscopy showed a mass in the ascending colon; biopsy was consistent with colon primary
LG’S TREATMENT

- LG underwent a laparoscopic colectomy, then started on FOLFOX + bevacizumab
- On first restaging, she had a partial response. Later scans showed no further shrinkage of tumor, but did show stable disease.
- She received six months of treatment and is tolerating her therapy well

YOUR CALL

What do you do at this point?

a. Continue FOLFOX + bevacizumab until progressive disease or toxicity
b. Stop the oxaliplatin and continue 5-FU-based therapy with bevacizumab until disease progression
c. Stop the FOLFOX and continue bevacizumab therapy until disease progression
d. Stop all therapy and give a treatment holiday
PANEL DISCUSSION

- Do you utilize treatment holidays? If so, what do you stop?
- What factors play a role in your decision to stop or continue therapy?
- What data do we have to guide us?
- If disease progresses on a treatment holiday, what therapy do you choose next?

YOUR CALL

Instead of FOLFOX + bevacizumab, you start this patient on FOLFIRI + bevacizumab and she has the same response. After six months, what do you do next?

a. Continue FOLFIRI + bevacizumab until progressive disease or toxicity
b. Stop the irinotecan and continue 5-FU-based therapy with bevacizumab until progression
c. Stop the FOLFIRI and continue bevacizumab therapy until progression
d. Stop all therapy and give a treatment holiday
PANEL DISCUSSION

- Does the chemotherapy backbone influence your decisions regarding chemotherapy holidays?

CASE STUDY 4

STAGE IV CRC
OUR PATIENT — AF

- 67-year-old male
- Retired dentist
- Excellent performance status
- No significant comorbidities

AF’S HISTORY

- Recent history of rectal bleeding & abdominal pain
- Colonoscopy reveals friable sigmoid mass at 20 cm; biopsy positive for adenocarcinoma
- CT scan of abdomen/pelvis shows 5 intrahepatic metastases (max 5 cm)
  - Two are close to hepatic veins
- CEA: 20 ng/mL
- K-ras testing of biopsy shows K-ras wild-type
YOUR CALL

- Which additional tests would you recommend for this patient (choose all that apply)?
  a. PET/CT scan
  b. Endoscopic ultrasound (EUS)
  c. CT chest
  d. PET/CT and CT chest
  e. PET/CT, CT chest, and EUS
  f. Other tests
  g. No additional tests are required for treatment decision

AF’S TEST RESULTS

- PET/CT scan did not show any additional signs of metastases
- Situation is considered borderline resectable for liver surgery
- Treatment goal: curative
YOUR CALL

● What would your next step be in the management of this patient?
  a. Surgery of the primary tumor and liver metastases followed by adjuvant chemotherapy
  b. Surgery of the primary tumor followed by chemotherapy and resection of liver metastases
  c. Preoperative chemotherapy followed by surgery of the primary tumor and metastases
  d. Something else

YOUR CALL

● Which of the following is the best regimen of preoperative chemotherapy for this patient?
  a. FOLFOX
  b. FOLFOX + bevacizumab
  c. FOLFOX + cetuximab or panitumumab
  d. FOLFIRI
  e. FOLFIRI + bevacizumab
  f. FOLFIRI + cetuximab or panitumumab
  g. FOLFOXIRI
  h. Something else
PANEL DISCUSSION

● When is the goal of therapy in stage IV CRC still curative?
  – With liver and lung metastases? If yes, how many are acceptable?
  – With retroperitoneal lymph node metastases?
  – With portal lymph nodes?
● Is resection of the primary tumor indicated here?
● Is resection of the primary tumor and metastases or systemic chemotherapy considered a first step?
  – What are the criteria?
    • Synchronous vs. metachronous metastases?
    • Volume of disease?

PANEL DISCUSSION

● With systemic chemotherapy as upfront conversion therapy, consider each of the following:
  – FOLFOX vs. FOLFIRI (or FOLFOXIRI)
  – Bevacizumab vs. cetuximab/panitumumab vs. no biologic
  – How long should chemotherapy be conducted?
● Post-operative adjuvant therapy
  – Should a biologic agent be used post-operatively in the adjuvant setting, even if the preoperative treatment with this biologic showed activity?
● Post-operative surveillance strategy
CASE STUDY 5

BIOMARKER TESTING

OUR PATIENT — SK

- 66-year-old male engineer
- Found on routine colonoscopy to have a splenic flexure mass
- Scans showed no metastatic disease
- Underwent resection and was found to have a stage IIIc cancer, with 10 lymph nodes positive for disease
  - Received 6 months of adjuvant FOLFOX therapy
- One year after completion of adjuvant therapy, new unresectable liver recurrence found
SK’S QUESTIONS

- SK has done a lot of Internet research on new cancer therapies. He also watched a recent television special that included vignettes on PI3-Kinase inhibitors and the new era of personalized therapy.
- After telling you about all of the research he has done, he asks, “When are you going to test my tumor for K-ras and B-raf?”

YOUR CALL

When do you test colorectal cancers for K-ras status?

- a. On initial pathology diagnosis, even for localized cancers
- b. At diagnosis of metastatic cancer
- c. In later-line therapy for metastatic disease before using an EGFR inhibitor
- d. I don’t test for K-ras status
YOUR CALL
Do you test for B-raf status?

a. Yes, whenever I test for K-ras status  
b. Yes, but only if the patient is found to be K-ras wild-type  
c. No, I do not test for B-raf status

PANEL DISCUSSION

● When should we test this patient for K-ras status?
● Should we test everyone or just before consideration of EGFR inhibitor?
● Should we be testing for B-raf status as well? If so, when?
YOUR CALL

SK mentions that he wants his tumor sent for testing of PI3-Kinase, PTEN, thymidylate synthase, and TOPO1 status. Would you agree with him?

a. Yes, the results of these tests will be helpful both in building a relationship with the patient and in determining treatment
b. Yes, the results will be helpful in building a relationship with the patient, but they will not influence treatment
c. Yes, although I would be more comfortable referring the patient to a more experienced colleague to discuss the results with this patient
d. No, these tests would have no value for me

PANEL DISCUSSION

● What do we do about newer tests that are now available for patients that may not have sufficient evidence backing their use?
● Where does personalized medicine stand for colorectal cancer?
● What is on the horizon with the targeted agents?