Small Bowel Adenocarcinoma, Version 1.2020

ABSTRACT

Small bowel adenocarcinoma (SBA) is a rare malignancy of the gastrointestinal tract that has increased in incidence across recent years. Often diagnosed at an advanced stage, outcomes for SBA are worse on average than for other related malignancies, including colorectal cancer. Due to the rarity of this disease, few studies have been done to direct optimal treatment, although recent data have shown that SBA responds to treatment differently than colorectal cancer, necessitating a separate approach to treatment. The NCCN Guidelines for Small Bowel Adenocarcinoma were created to establish an evidence-based standard of care for patients with SBA. These guidelines provide recommendations on the workup of suspected SBA, primary treatment options, adjuvant treatment, surveillance, and systemic therapy for metastatic disease. Additionally, principles of imaging and endoscopy, pathologic review, surgery, radiation therapy, and survivorship are described.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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The complete and most recent version of these guidelines is available free of charge at NCCN.org.
Overview

In 2019, an estimated 10,590 new cases of small bowel cancer will occur and 1,590 patients will die of this disease.1 Compared with cancers of other organs in the gastrointestinal tract, small bowel cancers are relatively rare, accounting for only about 3% of cancers occurring in this organ system.1 Small bowel cancers affect men and women relatively equally, with an incidence of 2.6 per 100,000 for men and 2.0 per 100,000 for women.2 The median age at diagnosis is 66 years. The incidence of small bowel cancers is increasing, with an annual percent increase of 1.8 between 2006 and 2015. This trend is in contrast to other gastrointestinal malignancies, including esophageal, gastric, colon, and rectum, which decreased in incidence across the same timeframe.2 The 4 most common histologies of cancers originating in the small bowel are adenocarcinomas, neuroendocrine tumors, gastrointestinal stromal tumors, and lymphomas.3,4 The treatment recommendations in this guideline only refer to small bowel adenocarcinoma (SBA), which comprise an estimated 30% to 40% incidence of small intestinal cancer diagnoses.4 Due to the rarity of this disease, very few established guidelines for management of SBA exist. In 2018, a French intergroup published the first clinical practice guidelines for SBA.5 These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Small Bowel Adenocarcinoma are the second.

This discussion summarizes the NCCN Guidelines for SBA. These guidelines begin with the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, surgical management, perioperative treatment, patient surveillance, management of recurrent and metastatic disease, and survivorship. When reviewing these guidelines, clinicians should be aware of several things. First, these guidelines adhere to the TNM (tumor, node, metastases) staging system (see definitions of TNM in Table 1, available online, in these guidelines, at NCCN.org).6 Furthermore, all recommendations are classified as category 2A except where noted in the text or algorithm. Although the guidelines are believed to represent the optimal treatment strategy, participation in a clinical trial is especially encouraged for patients with SBA based on the dearth of clinical trial data on which to base treatment decisions for this disease.

Literature Search Criteria and Guidelines Update Methodology

Before the development of the NCCN Guidelines for SBA, an electronic search of the PubMed database was translated into a reference list, which was then reviewed and used to develop the guidelines. The search included articles published from January 2008 to August 2018. The search was updated to include articles published from January 2019 to August 2019. The search was performed using the following terms: small bowel cancer, small intestinal cancer, adenocarcinoma, neuroendocrine tumor, gastrointestinal stromal tumor, and lymphoma. The search was limited to articles published in English. Additionally, the search was limited to articles published in PubMed. The search was performed using the following terms: small bowel cancer, small intestinal cancer, adenocarcinoma, neuroendocrine tumor, gastrointestinal stromal tumor, and lymphoma. The search was limited to articles published in English. Additionally, the search was limited to articles published in PubMed.
performed to obtain key literature in the field of small bowel cancer, using the following search terms: (small bowel cancer) OR (small intestine cancer) OR (jejunum cancer) OR (duodenum cancer) OR (ileum cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial; Multicenter Study; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles and articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the discussion section (e.g., e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel’s review of lower-level evidence and expert opinion.

The complete details of the “Development and Update of the NCCN Guidelines” are available at NCCN.org.

**Risk Factors for SBA**

Risk factors for SBA are similar to those for colorectal cancer (CRC), including lifestyle factors, inflammatory bowel disease (IBD), and certain familial syndromes such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer), Peutz-Jeghers syndrome (PJS), and familial adenomatous polyposis (FAP). Therefore, it is recommended that all patients with small bowel cancer be queried regarding their family history and considered for risk assessment, as detailed in the NCCN Guidelines for Colorectal Cancer Screening (available at NCCN.org).

**Lifestyle Factors**

Although data on the role of lifestyle factors in relation to the risk of developing SBA are very limited due to low incidence of disease, lifestyle factors that have been reported as raising the risk of SBA generally agree with known risk factors for CRC. A systematic review of the literature has reported that high levels of alcohol consumption, smoking, and dietary factors, including low intake of fiber and high intake of red/processed meat and sugary drinks, may increase the risk of SBA. Additionally, the results of a pooled analysis of more than 500,000 subjects in the Asia Cohort Consortium reported that elevated body mass index and high alcohol consumption were associated with a nonsignificant trend toward an increased risk of SBA,
although this analysis did not identify smoking as a risk factor.9

**IBD and Celiac Disease**

It is well recognized that individuals with IBD (ulcerative colitis or Crohn’s disease) are at increased risk for CRC. Several studies have also reported an increased risk of distal SBA in patients with IBD.10–13 The results of a retrospective, multicenter observational cohort study of 9,100 patients with IBD found that the relative risk of small bowel cancer was 3.70 (95% CI, 1.23–11.13) for patients with IBD. The rate of death and cancer remission did not differ between patients who maintained IBD treatment compared with those who stopped IBD treatment.10 Additionally, although the data are mostly limited to case studies and literature reviews, cases of SBA have been reported in patients with celiac disease, suggesting a possible link between these conditions.14–16 The association with celiac disease is poorly understood and a distinct difference from CRC, for which celiac disease is not a risk factor.

**Familial Syndromes**

Due to the relative rarity of SBA and the disease’s association with several genetic syndromes, the NCCN panel recommends that all patients with a personal history of SBA should be counseled for familial malignancies and considered for risk assessment, including Lynch syndrome (HNPCC), FAP, and other inherited polyposis mutations. Refer to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal17.

**Familial Adenomatous Polyposis**

FAP is an autosomal dominant condition characterized by a germline mutation in the APC gene, located on chromosome 5q21.17,18 Patients with FAP develop large numbers of adenomatous polyps in the large bowel, beginning as early as adolescence, and most patients with classic FAP will develop polyps by the age of 25. Patients with attenuated FAP due to a germline MUTYH mutation develop fewer numbers of polyps and generally at a later age than those with classic FAP.17,18 Although the incidence of SBA in patients with FAP has not been well established, the lifetime risk has been estimated as 3% to 5%.19 The duodenum and periampullary region are the most common locations for SBA in patients with FAP.19
Peutz-Jeghers Syndrome

PJS is an autosomal dominant condition mainly characterized by multiple hamartomatous and adenomatous gastrointestinal polyps, predominantly located in the jejunum and ileum. A majority of PJS cases occur due to mutations in the STK11 (LKB1) gene. However, other genetic mutations may be involved, because an estimated half of patients with PJS do not have detectable STK11/LKB1 mutations. SBA can arise from either hamartomatous or adenomatous polyps, predisposing patients with PJS to SBA. The relative risk of developing SBA has been estimated as 520 compared with the general population, and the lifetime risk of SBA has been estimated between 1.7% and 13% for individuals with PJS.

Lynch Syndrome

Lynch syndrome is a hereditary syndrome resulting from germline mutations in DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2). Individuals with Lynch syndrome are estimated to have a lifetime risk of 4% of developing SBA, representing a relative risk of more than 100 compared with the general population. Although identifying a mutation in an MMR gene through germline sequencing is definitive for Lynch syndrome, patients usually undergo selection for screening by considering family history and performing an initial test on tumor tissue before sequencing. One of two (or both) different initial tests can be performed on SBA specimens to identify individuals who might have Lynch syndrome: (1) immunohistochemical analysis for MMR protein expression, which is often diminished because of mutation; or (2) polymerase chain reaction analysis for microsatellite instability (MSI), which results from MMR deficiency and is detected as changes in the length of repetitive DNA elements in tumor tissue caused by the insertion or deletion of repeated units.

Many NCCN Member Institutions and other comprehensive cancer centers now perform immunohistochemistry (IHC) and sometimes MSI testing on all newly diagnosed CRC and endometrial cancers regardless of family history to determine which patients should have genetic testing for Lynch syndrome. This approach may also be applied to patients with a personal history of SBA, particularly since it has been reported that SBA has a higher percentage of MSI-high (MSI-H)/MMR-deficient (dMMR) tumors compared with CRC.

The NCCN Colon/Rectal/Anal Cancers Panel endorses universal MMR or MSI testing of all patients with a
personal history of SBA to identify individuals with Lynch syndrome. This testing is also relevant for treatment selection in stage IV disease [see "Pembrolizumab or Nivolumab With or Without Ipilimumab (for dMMR/MSI-H tumors) as Subsequent-line Therapy," page 1125]. A more detailed discussion is available in the NCCN Guidelines for Colorectal Cancer Screening (available at NCCN.org).

Clinical Presentation and Workup
The treatment recommendations in this guideline only refer to SBA. For gastrointestinal stromal tumors, see the NCCN Guidelines for Soft Tissue Sarcoma; for neuroendocrine tumors, see the NCCN Guidelines for Neuroendocrine and Adrenal Tumors; and for small bowel lymphomas see the NCCN Guidelines for B-Cell Lymphomas (all available at NCCN.org).

Most cases of SBA arise in the duodenum, accounting for approximately 52% to 57% of cases. The remainder arise in the jejunum (18%–29%), ileum (10%–13%), or in an unspecified location of the small bowel (4%–14%).\textsuperscript{35–37} Patients with SBA tend to be younger at diagnosis and often present with a higher stage and grade compared with those with CRC.\textsuperscript{38} SBA often presents with a local complication of the tumor, most often gastric outlet obstruction in the case of a duodenal SBA or cramping abdominal pain in the case of a jejunal or ileal SBA.\textsuperscript{35,39,40} Occult gastrointestinal bleeding is another common presentation for SBA, occurring in approximately one-quarter to one-third of cases.

Patients who present with small bowel cancer require a complete staging workup, including biopsy (if appropriate), pathologic tissue review, imaging studies (see “Imaging and Endoscopy,” below), complete blood count, chemistry profile, carbohydrate antigen 19-9, and carcinoembryonic antigen. Depending on the tumor’s location and the patient’s history, studies for celiac disease or IBD may be indicated. As discussed previously, MMR or MSI testing is recommended for all patients with SBA because MMR/MSI status can function as a prognostic and/or predictive marker and can help identify patients who should be tested for Lynch syndrome (see “Risk Factors for SBA,” page 1111).

Imaging and Endoscopy
Esophagogastroduodenoscopy with endoscopic ultrasound is recommended during initial workup and staging for detection and pathologic sampling when a duodenal malignancy is suspected. If obstruction is
detected during imaging, palliative diversion or stenting may be considered. Endoscopic ultrasound is useful for pretherapeutic staging of proximal small bowel malignancies and may be used to discern duodenal lesions from ampullary, biliary, or pancreatic primaries. Other endoscopic techniques that are not required for routine staging, but may be useful in certain circumstances, include double balloon endoscopy and capsule endoscopy. A number of studies, both prospective and retrospective, have reported on the effectiveness and safety of double balloon endoscopy for workup of patients with small bowel cancer. Specifically, the use of this method may be of particular benefit for patients with small bowel strictures. Although capsule endoscopy allows for a more detailed examination of the entire small bowel mucosa, possibly resulting in the diagnosis of SBA when other imaging methods have failed to reveal a primary lesion, it is not the preferred method for initial workup due to its inability to biopsy tissue for diagnosis. In the case of a small bowel obstruction or stricture, the capsule may not be excreted naturally, requiring surgical removal. Therefore, capsule endoscopy is contraindicated for these conditions.

CT or MRI may be used during initial workup of SBA to evaluate the extent of local tumor invasion and to assess for distant metastases. CT or MR enterography or enteroclysis, techniques involving administration of enteric contrast agent to the gastrointestinal system via oral intake or nasogastric tube, respectively, may improve imaging of the small bowel and, therefore, may be considered when conventional CT or MR with contrast have failed to show a tumor. A prospective study comparing CT enterography to MR enterography in 150 patients with suspected small bowel disease, but negative findings on endoscopy, reported that MR enterography was more accurate than CT enterography, particularly for neoplastic diseases (P = .0412). Although PET/CT has not been formally evaluated for ability to detect metastatic SBA, or compared with MRI or CT, reports describing its usefulness for this disease have been published. Therefore, although PET/CT is not routinely indicated, it may be considered when CT or MR results are equivocal.

See “Posttreatment Surveillance” (page 1128) for the use of these imaging methods for posttreatment surveillance and for use in individuals with IBD, celiac disease, or familial syndromes.
Pathology and Staging

SBA staging is based on the TNM staging system. In the 8th edition of the AJCC Staging Manual, T1 tumors involve the lamina propria or submucosa; T2 tumors penetrate through the submucosa into the muscularis propria; T3 tumors penetrate through the muscularis propria into the subserosa or extend into non-peritonealized perimuscular tissue; and T4 tumors perforate the visceral peritoneum or directly invade other organs or structures. Regional lymph node classification includes N0 (no regional lymph node metastasis), N1 (1–2 positive lymph nodes), and N2 (3 or more positive nodes). SBA is classified as M1 when distant metastasis is present.

SBA is staged as I or II when a tumor is present without regional lymph node or distant metastases (any T, N0, M0). Stage III disease includes disease with regional lymph node, but not distant metastasis (any T, N1-2, M0). Stage IV is distant metastatic disease (any T, any N, M1). A number of sources have reported stage III or IV SBA as having significantly worse outcomes compared with earlier stage disease.

Other factors that may be useful for prognostication, but not used for staging, include the primary tumor site (ie, duodenum, jejunum, ileum); histologic grade; number of lymph nodes evaluated; margin status; lymphovascular invasion; MSI/MMR status; evidence/presence of celiac or IBD; and presence of polyps. The NCCN panel recommends reporting of these parameters during pathologic review.

Lymph Node Evaluation

Regional lymph nodes differ based on the site of the primary tumors: retropancreatic, hepatic artery, inferior pancreaticoduodenal, and superior mesenteric nodes are regional to the duodenum; cecal or ileocolic (terminal ileum only, superior mesenteric, or mesenteric [not otherwise specified]) nodes are regional to the jejunum and ileum.

Multiple analyses of patients with SBA in the SEER database have found that longer survival after resection is strongly associated with a lower ratio of positive-to-negative lymph nodes as well as with a higher number of regional lymph nodes assessed during surgery. Two of these analyses, which considered duodenal and jejunoileal adenocarcinomas separately, concluded that, for adequate staging, a minimum of 5 lymph nodes should be retrieved for duodenal tumors and a minimum of 9 lymph nodes for jejunal or ileal tumors. Analyses that pooled duodenal and jejunoileal tumors found that...
8 regional lymph nodes should be assessed for adequate staging, although some data have suggested that harvesting even higher numbers of lymph nodes may better predict SBA survival outcomes. Based on these studies, NCCN recommends that a goal for all SBA resections should be the retrieval of at least 8 regional lymph nodes for evaluation.

**Treatment of Stage I–III Small Bowel Adenocarcinoma**

**Surgical Management of Localized Resectable Disease**

For local (stage I–III) SBA, primary treatment consists of surgical resection with en bloc removal of the regional lymph nodes. Although no prospective, randomized trials have been published to inform surgical technique, retrospective reviews on the subject have been published. Intraoperative staging of the abdomen—particularly including the mesentery, omentum, and peritoneum—should be completed in all cases.

The type of resection used to treat localized SBA depends on the location of the primary tumor. Segmental resection of the small bowel is often the mainstay of treatment, although duodenal tumors may require either pancreaticoduodenectomy or segmental duodenal resection. For tumors of the jejunum or ileum, segmentectomy is the preferred method of resection.

Pancreaticoduodenectomy, also known as the Whipple procedure, should be considered for all duodenal cancers and is particularly appropriate for those arising in the second portion of the duodenum or invading into any portion of the ampulla or pancreas. Minimally invasive procedures, such as laparoscopic surgery, may be considered for pancreaticoduodenectomy but should only be used by experienced surgeons. Limited segmentectomy may be considered in SBA involving the third and fourth segments of the duodenum and on the antimesenteric side of the intestine, although this approach is controversial based on reports of lower lymph node yields. However, a retrospective study of 1,611 patients with duodenal adenocarcinoma found that patients who were treated with radical resection did not show an improvement in overall survival (OS) or disease-specific survival compared with a simple removal of the primary site, after controlling for confounding factors. This finding was despite greater lymph node retrieval with radical resection. Case reports have suggested that segmentectomy and other limited resection methods
may be considered for lesions in the first portion of the duodenum, particularly for those 2 cm in size and located on the mesenteric side of the intestine.63

NCCN recommends that a goal for all SBA resections should be the retrieval of at least 8 regional lymph nodes for evaluation based on the strong prognostic impact of lymph node metastases and studies showing improved outcomes with higher numbers of lymph nodes assessed during surgery.58–60 See “Lymph Node Evaluation” (page 1116) for more information on pathologic review of dissected lymph nodes.

Adjuvant Therapy
Localized SBAs are treated with surgical resection, but local and distant recurrences are common, and optimal perioperative therapy is unknown.66 Therefore, participation in a clinical trial is preferred for all patients with SBA who are considering adjuvant therapy. For discussion of neoadjuvant therapy, see “Primary Treatment of Unresectable Disease” (page 1120).

The ongoing, international phase III BALLAD trial is the first prospective trial investigating the role of adjuvant 5-FU/leucovorin (5-FU/LV) or 5-FU/LV plus oxaliplatin (FOLFOX) compared with observation alone for patients with stage I-II SBA.67,68 Until the results of BALLAD have been reported, the potential benefits of adjuvant therapy for SBA can be estimated only through retrospective reports. The data from retrospective studies or meta-analyses that have sought to assess the efficacy of adjuvant therapy (either chemotherapy or chemoradiotherapy) for SBA have been mixed, with some showing a benefit to adjuvant therapy,69–71 some showing no benefit,76,72,73 and some showing an equivocal or nonsignificant benefit.74,75 Data supporting the use of adjuvant chemoradiation are especially limited, with a recent retrospective review of patients with resected, nonmetastatic duodenal adenocarcinoma showing that patients who received adjuvant chemoradiotherapy (n=550) had no significant improvement in survival compared with those who received chemotherapy alone (n=694), even in high-risk cases.76 Therefore, chemoradiation should be considered only in highly selected patients.

MSI/MMR Status for Adjuvant Therapy
MSI/MMR is an important piece of information to consider when deciding whether to use adjuvant chemotherapy in patients with stage II SBA. Mutation of MMR genes or modifications of these genes (eg, methylation) can result in MMR protein deficiency and MSI.77 Tumors showing
the presence of MSI are classified as either MSI-H or MSI-low, depending on the extent of instability in the markers tested, whereas tumors without this characteristic are classified as microsatellite-stable (MSS). Patients determined to have dMMR status are biologically the same population as those with MSI-H status.

Data from several large studies in colon cancer have shown that MSI-H (ie, dMMR) tumors have a decreased likelihood to metastasize and that MSI-H/dMMR may function as a prognostic marker for favorable outcomes in stage II disease. Some of these same studies also show that a dMMR/MSI-H tumor status may be a predictive marker of decreased benefit and possibly a detrimental impact from adjuvant therapy in patients with stage II colon cancer. However, a recent study of 1,913 patients with stage II CRC from the QUASAR study, half of whom received adjuvant chemotherapy, showed that although dMMR was prognostic, it did not predict benefit or detrimental impact of chemotherapy. A study of patients in the CALGB 9581 and 89803 trials came to a similar conclusion, though notably this used older, nonstandard chemotherapy regimens. Extrapolating from these colon cancer data, patients with stage II MSI-H/dMMR SBA may have a good prognosis and the benefit from adjuvant therapy is unclear.

NCCN Recommendations for Adjuvant Therapy

Based on the limited data available from retrospective studies of SBA, and extrapolation from studies of colon cancer, the NCCN Small Bowel Adenocarcinoma Panel recommends:

- Six months of adjuvant treatment with FOLFOX, capcitabine plus oxaliplatin (CAPEOX), 5-FU/LV, or capcitabine for any locally advanced SBA, though efficacy has not been proven.
- Nivolumab is a treatment option for patients with metastatic SBA that is NTRK gene fusion positive.

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Small Bowel Adenocarcinoma, Version 1.2020

PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

<table>
<thead>
<tr>
<th>PATIENT STATUS</th>
<th>INITIAL THERAPY</th>
<th>MISMATCH REPAIR STATUS</th>
<th>SUBSEQUENT THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient appropriate for intensive therapy</td>
<td>Clinical trial (preferred) or FOLFOX ± bevacizumab(b) or CAPEOX ± bevacizumab(b) or FOLFOXIRI ± bevacizumab(b)</td>
<td>dMMR/MSI-H</td>
<td>Clinical trial (preferred) or Pembrolizumab or Nivolumab ± ipilimumab</td>
</tr>
<tr>
<td>Patient not appropriate for intensive therapy(b)</td>
<td>Clinical trial (preferred) or 5-FU/LV ± bevacizumab(c) or Capecitabine ± bevacizumab(c)</td>
<td>pMMR/MSS</td>
<td>Clinical trial (preferred) or Pembrolizumab or Nivolumab ± ipilimumab</td>
</tr>
<tr>
<td>Patient with prior oxaliplatin exposure or contraindication (SBA-D 2 of 7)</td>
<td></td>
<td></td>
<td>Clinical trial (preferred) or FOLFOX or Irinotecan</td>
</tr>
</tbody>
</table>

\(a\)Many of the regimens recommended in these guidelines are extrapolated from data for colorectal cancer.

\(b\)For elderly patients, please complete geriatric assessment to aid appropriate prediction of treatment risks. See NCCN Guidelines for Older Adult Oncology, OAD-2, 2019 edition.

\(c\)Bevacizumab has been shown to be safe in advanced SBA, though efficacy has not been proven.

\(d\)Larotrectinib is a treatment option for patients with metastatic SBA that is NTRK gene fusion positive.

\(T\) To view the most recent version of these guidelines, visit NCCN.org.
capecitabine or infusional 5-FU is another option for duodenal cancer that meets these criteria and is margin-positive after resection.

- Observation or 6 months of adjuvant treatment with 5-FU/LV or capecitabine for T3, N0, M0 (stage IIA) tumors that are MSS or pMMR and have no high-risk features.

- Observation after surgical treatment of all stage I tumors and for stage II tumors that are MSI-H or dMMR.

Due to poorer survival in stage III SBA compared with CRC and the fact that the trial enrolled no patients with SBA, extrapolation from the IDEA collaboration (wherein 3 months of fluoropyrimidine/oxaliplatin was shown to be noninferior to 6 months of therapy for CRC) is not currently recommended for SBA.

**Primary Treatment of Unresectable Disease**

For some patients with locally unresectable or medically inoperable SBA, conversion to resectable disease may be a goal. A limited amount of data has shown that neoadjuvant therapy may be beneficial in converting unresectable SBA to resectable disease. A retrospective study of patients with unresectable or recurrent duodenal adenocarcinoma who were treated with neoadjuvant chemotherapy or chemoradiation found that 9 of 10 patients showed conversion to resectable disease after neoadjuvant therapy. At data collection, 5 patients were still alive (ranging from 18–83 months postoperatively), suggesting prolonged survival after conversion to resectable disease. In addition, neoadjuvant chemoradiation was studied in 2 small prospective trials. A phase II trial including patients with duodenal or pancreatic adenocarcinomas reported that 4 of 5 patients with tumors in the duodenum were able to undergo resection after neoadjuvant chemoradiation. Another small prospective study of patients with duodenal or pancreatic adenocarcinomas reported that all 4 patients with duodenal cancer underwent curative resection after neoadjuvant chemoradiation and experienced a complete pathologic response.

Because many small bowel cancers present at an advanced stage, malignant small bowel obstruction is a common complication. One retrospective Eastern European study reported that most patients with small bowel cancer presented due to an emergency situation. Malignant small bowel obstruction may be treated palliatively with either surgical diversion or stenting. Although most of the...
literature on palliative treatment of malignant small bowel obstruction comes from pancreatic cancer, there are a few studies that include SBA cases.39,95 –97 One retrospective study concluded that there was no difference in poststent survival between patients with pancreatic and nonpancreatic cancers, and that patients with nonpancreatic cancers (including SBA) showed a longer OS.95

Based on these data, the panel recommends that patients with locally unresectable or medically inoperable SBA may undergo neoadjuvant therapy, during which they should be routinely monitored for conversion to resectable disease. Neoadjuvant chemoradiation may be indicated for duodenal disease that remains unresectable after a course of induction chemotherapy, but this is controversial and should be considered on an individual case basis. Alternatively, in cases where conversion to resectable disease is not feasible, palliative chemotherapy may be considered. Palliative diversion or stenting is recommended if a small bowel obstruction is present.

**Treatment of Distant Metastatic (Stage IV) SBA**

Approximately 32% of patients diagnosed with SBA have stage IV (distant metastatic) disease.38 - The most common sites for metastatic spread include the peritoneal cavity and liver, consistent with other gastrointestinal malignancies.6 Although 5-year survival is relatively high (85%) for localized disease, patients with stage IV SBA have a 5-year relative survival of only 42%.38 In addition, recurrence rates of localized SBA treated with surgery are high, with many of these patients developing distant metastases.35 The NCCN recommendations for treatment of stage IV SBA are discussed subsequently.

**Metastasectomy**

Although resectable metastases are rare for SBA and the data supporting metastasectomy for SBA are limited, a retrospective analysis of patients with non-CRC, non-endocrine liver metastases (including 28 patients with small bowel cancers and 12 patients with duodenal cancers) showed promising survival rates after resection of liver metastases.99 The 5-year survival rate for small bowel cancers was 49% with a median survival of 58 months. For duodenal cancers, the 5-year survival rate was 21% with a median survival of 34 months. Recently, another retrospective study of 34 patients undergoing resection of SBA metastases reported a median OS of 28.2 months and a relapse-free survival of 18.7 months.100 In this study, 41.2% of patients survived more than
Many of the regimens recommended in these guidelines are extrapolated from data for colorectal cancer.

1 OXaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Corek A, Park V, Yaeurer R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract. 2016;12:e548-553.

2 Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².

3 The majority of safety and efficacy data for this regimen have been developed in Europe, where a capcitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capcitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capcitabine.

4 Bevacizumab may be safely given at a rate of 5.0 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes.

5 Bevacizumab may be safely given at a rate of 3.5 mg/kg/day (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

6 Many of the regimens recommended in these guidelines are extrapolated from data for colorectal cancer.

7 Poor differentiation, invaded margins, and lymphatic invasion of the primary tumor were identified as poor prognostic factors. Therefore, certain patients with SBA and limited metastasis to visceral organs may be candidates for metastasectomy. If metastasectomy is being considered, a multidisciplinary team, including a surgeon experienced in the resection of metastases, should be consulted.

**Peritoneal Carcinomatosis**

Peritoneal carcinomatosis (peritoneal metastases) has been shown to affect 25% to 50% of patients with stage IV SBA. Peritoneal carcinomatosis occurs more frequently in tumors arising from the jejunum or ileum and less commonly in duodenal tumors. Poor differentiation, invaded margins, and lymphatic invasion of the primary tumor were identified as poor prognostic factors. Therefore, certain patients with SBA and limited metastasis to visceral organs may be candidates for metastasectomy. If metastasectomy is being considered, a multidisciplinary team, including a surgeon experienced in the resection of metastases, should be consulted.

Peritoneal carcinomatosis generally carries a poor prognosis with a reported median OS of 5.9 months. The goal of treatment of unresectable peritoneal metastases is palliative and primarily consists of systemic therapy (see “Systemic Therapy for Metastatic Disease,” next section).

For resectable peritoneal carcinomatosis, surgical cytoreduction may be considered. For peritoneal metastases that present synchronously with the primary tumor, resection of the primary and cytoreduction of peritoneal metastases may be performed concurrently. A multidisciplinary team evaluation at an experienced center is important if considering this treatment approach. Data supporting the use of hyperthermic intraperitoneal chemotherapy (HIPEC) for SBA with peritoneal carcinomatosis are extremely limited, consisting entirely of small, retrospective studies. In addition, the recent phase III PRODIGE 7 study showed no benefit of oxaliplatin-based HIPEC in patients with CRC compared with cytoreduction alone. Significant morbidity and mortality are associated with this procedure. Various studies have reported morbidity rates ranging from 19% to 31% for serious adverse events and mortality rates ranging from 0% to 4%. Furthermore, recurrences after the procedure are common. Based on this lack of evidence, HIPEC cannot be recommended for this population unless more robust data become available.

**Systemic Therapy for Metastatic Disease**

Data supporting systemic therapy for advanced adeno-carcinoma of the small bowel were also almost entirely limited to retrospective reports, although recently several small phase II trials for SBA have been reported. Based on the results from these studies, several systemic therapy regimens (SBA-D 5 of 7) See References (SBA-D 7 of 7)
therapy regimens are recommended for treatment of metastatic SBA. However, participation in clinical trials is especially encouraged for patients with SBA, based on the lack of data.

The choice of therapy is based on consideration of the goals of therapy, the type and timing of prior therapy, and the differing toxicity profiles of the constituent drugs. Furthermore, an evaluation of the efficacy and safety of these regimens for an individual patient must take into account the performance status of the patient. As initial therapy for advanced disease in a patient appropriate for intensive therapy (ie, one with a good tolerance for this therapy for whom a high tumor response rate would be potentially beneficial) without prior platinum resistance, the panel recommends a choice of 3 chemotherapy regimens: FOLFOX, CAPEOX, or FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan); any of which may be combined with bevacizumab. For patients who are not appropriate for intensive therapy, treatment options would exclude the more toxic components of these regimens, with 5-FU/LV or capecitabine with or without bevacizumab recommended as first-line therapy for these patients.

The choice of second-line therapy depends on the MMR/MSI status of the tumor. For tumors that are dMMR or MSI-H, checkpoint inhibitor therapy with anti-CTLA4 inhibitors, alone or in combination with an anti-CTLA4 inhibitor, is recommended in the second-line setting. FOLFIRI or taxane-based chemotherapies are options in the second line for pMMR/MSS tumors, or those that are refractory to checkpoint inhibitor therapies. Larotrectinib is an option in subsequent lines of therapy for metastatic SBA with neurotrophic tyrosine receptor kinase (NTRK) gene fusion and no satisfactory alternative treatments.

Genetic Alterations in SBA
Emerging research has shown that SBA has a distinct genetic profile, which sets it apart from CRC or gastroesophageal cancers, the 2 cancer types SBA is most often likened to. Although KRAS and TP53 alterations are frequently identified in both SBA and CRC, APC mutations are significantly less common in SBA (27% in SBA vs 76% in CRC; $P<0.001$). Considering the near ubiquity of APC mutation and its well-established role in CRC carcinogenesis, this suggests that neoplastic transformation in SBA is unique compared with CRC.

SMAD4 and CDKN2A mutations are more commonly seen compared with gastroesophageal cancers and CRC. Though BRAF mutations occur at a similar rate as seen...
in CRC, only 10% of BRAF-mutant SBAs have a V600E alteration, compared with >70% in BRAF-mutant CRC. Importantly, human epidermal growth factor receptor 2 (HER2) alterations, MSI-H/dMMR, programmed death-ligand 1 (PD-L1) expression, and high tumor mutational burden are enhanced in SBA compared with CRC, and may reveal greater importance of targeted or immunotherapeutic treatments compared with current CRC treatment algorithms.

**Regimens Not Recommended for SBA**

Although many of the systemic therapy regimens recommended for treatment of metastatic SBA are extrapolated from data for CRC, several regimens are commonly used for metastatic CRC that are not recommended for SBA based either on a lack of data supporting their use or data suggesting that these regimens do not work for metastatic SBA.

A 2017 retrospective analysis reported that the efficacy of cetuximab-containing chemotherapy for RAS wild-type SBA was inconclusive. Subsequently, a phase II trial published in 2018 showed that panitumumab has no clinically meaningful activity in RAS wild-type SBA; therefore, cetuximab or panitumumab should not be used for treatment of SBA.

While trifluridine-tipiracil or regorafenib are recommended as subsequent therapy options for metastatic CRC, no data are available to support their use for SBA. They are, therefore, not recommended.

**FOLFOX or CAPEOX as First-line Therapy**

Both FOLFOX and CAPEOX have been evaluated prospectively for first-line treatment of advanced SBA in phase II clinical trials. One of these trials evaluated CAPEOX in 30 patients with advanced adenocarcinomas of the small bowel and ampulla of Vater. The overall response rate (ORR) (the primary endpoint) was 50%, with 10% achieving complete response. A similar response rate of 48.5% (95% CI, 31%–67%) was seen in another small phase II study of 33 patients that assessed the efficacy of FOLFOX in first-line treatment of advanced SBA. Likewise, another phase II study reported an ORR of 45% for 24 patients with metastatic or unresectable SBA who were treated with FOLFOX, with a median progression-free survival (PFS) and OS of 5.9 and 17.3 months, respectively. These response rates to CAPEOX and FOLFOX were much higher than the 18% response rate seen in another small phase II study that evaluated 5-FU/doxorubicin/mitomycin C in patients with metastatic SBA. Adverse events reported

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**ADVANCED OR METASTATIC THERAPY REGIMENS**

- **Nab-paclitaxel**
  - Albumin-bound paclitaxel 260 mg/m² IV every 21 days

- **Docetaxel**
  - Docetaxel 75–100 mg/m² IV on day 1 every 21 days

- **Paclitaxel**
  - Paclitaxel 135–250 mg/m² IV on day 1 every 21 days or
  - Paclitaxel 80 mg/m² IV weekly or
  - Paclitaxel 80 mg/m² IV on days 1, 8, 15 every 28 days

- **Gemcitabine + albumin-bound paclitaxel**
  - Albumin-bound paclitaxel 125 mg/m² IV on Days 1, 8, 15
  - Gemcitabine 1000 mg/m² IV on Days 1, 8, 15
  - Every 28 days

- **Gemcitabine + docetaxel**
  - Gemcitabine 1000 mg/m² IV on days 1 and 8
  - Docetaxel 75 mg/m² IV on Day 8
  - Every 21 days

- **Gemcitabine + paclitaxel**
  - Gemcitabine 1000 mg/m² IV on days 1, 8, 15
  - Paclitaxel 110 mg/m² IV on days 1, 8, 15
  - Every 28 days

- **Carboplatin + paclitaxel**
  - Paclitaxel 175 mg/m² IV on Day 1
  - Carboplatin AUC 5 IV on Day 1
  - Every 21 days

- **Gemcitabine, docetaxel, and capecitabine (GTX)**
  - Gemcitabine 750 mg/m² IV at a rate of 10 mg/m²/min on days 4 and 11
  - Docetaxel 30 mg/m² IV on days 4 and 11
  - Capecitabine 750 mg/m² PO twice daily on days 1–14
  - Every 21 days for 2–6 cycles

- **Larotrectinib**
  - NTRK gene fusion positive
  - 100 mg PO twice daily

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across these 3 trials were similar, with neutropenia, thrombocytopenia, nausea, vomiting, diarrhea, peripheral neuropathy, and fatigue reported most frequently.118–120 Retrospective studies have supported the results of these trials, reporting that the combination of a fluoropyrimidine with oxaliplatin was the most effective first-line therapy for advanced SBA.111,122,123 Based on these data, FOLFOX or CAPEOX are recommended as first-line therapy options for treatment of patients with advanced SBA who are appropriate for intensive therapy.

**FOLFOXIRI as First-line Therapy**

Although the role of FOLFOXIRI for treatment of SBA has not been formally evaluated, CAPIRINOX (capecitabine, irinotecan, oxaliplatin) has been tested as first-line treatment in a phase II trial of 33 patients with advanced SBA.124 In this trial, CAPIRINOX—dose-adjusted according to UGT1A1 genotype—showed a response rate of 37.5% (95% CI, 21%–56%), with a median PFS and OS of 8.9 and 13.4 months, respectively. Neither hematologic toxicity nor tumor response rate differed significantly by UGT1A1 genotype, supporting the feasibility of genotype-directed dosing for CAPIRINOX. The NCCN panel does not recommend use of CAPIRINOX for SBA due to concerns about toxicity, but the recommendation for FOLFOXIRI is extrapolated from the results of this study.

**FOLFOX, CAPEOX, or FOLFOXIRI Plus Bevacizumab as First-line Therapy**

Although data supporting the addition of biologics to FOLFOX, CAPEOX, or FOLFOXIRI are currently extremely limited, a single-phase II trial has reported that CAPEOX in combination with bevacizumab is safe and efficacious in patients with SBA.125 Retrospective analyses have supported these results, reporting favorable outcomes in patients treated with bevacizumab-containing chemotherapy regimens without adding significant toxicity.116,126 Based on these data, FOLFOX, CAPEOX, or FOLFOXIRI may be given with or without bevacizumab as first-line therapy for advanced SBA.

**Pembrolizumab or Nivolumab With or Without Ipilimumab (for dMMR/MSI-H tumors) as Subsequent-line Therapy**

Pembrolizumab is a PD-1 inhibitor that was evaluated as a subsequent-line therapy for treatment-refractory metastatic cancers in a phase II study that included 3 cohorts: (1) dMMR colorectal adenocarcinomas,
PRINCIPLES OF RADIATION THERAPY

Duodenum:
- Database analysis suggests no survival benefit from the addition of adjuvant chemoradiation versus chemotherapy alone in patients with surgically resected duodenal adenocarcinoma. A separate retrospective study showed mixed results regarding the efficacy of either preoperative or postoperative chemoradiation for the management of locally advanced or margin-positive duodenal adenocarcinomas. Therefore, chemoradiation should be considered only in highly select patients.
- Preoperative chemoradiation should be considered in patients who remain unresectable following a course of induction chemotherapy.
- Patients should be evaluated by multidisciplinary teams at high-volume centers in cases where either preoperative or postoperative radiation therapy is being considered.
- Treatment Information:
  - Fluoropyrimidine-based chemotherapy should be delivered concurrently with radiation therapy.
  - Treatment can be delivered using 3-D conformal radiation therapy. When appropriate, advanced treatment planning, such as intensity-modulated radiation therapy (IMRT), should be considered to limit toxicity to adjacent normal organs.
  - Image-guided radiation therapy (IGRT) with kilovoltage (kV) imaging, MR guided imaging, and cone-beam CT imaging should be routinely used during the course of treatment with IMRT.
- Target Volumes:
  - The primary site and regional lymph node basins should be included in the radiation therapy fields.
- RT Dosing:
  - Doses of 45–54 Gy in 1.8–2 Gy daily fractions should be used based on tolerance limits of adjacent normal tissues.
  - Adjacent small bowel dose should be limited to 45 Gy, if possible.

Jejunum/Ileum:
- Radiation therapy is not generally indicated for lesions arising in these sites. Any consideration for such therapy must be made on a highly selected basis by a multidisciplinary team.

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Another PD-1 inhibitor, nivolumab—alone or in combination with the CTLA-4 inhibitor, ipilimumab—has been studied in patients with dMMR metastatic CRC in the phase II, multicohort CheckMate-142 trial. One cohort of this trial included 74 patients with dMMR CRC who were treated with nivolumab. ORR for these patients was 31.1% (95% CI, 20.8–42.9), with 69% of patients having disease control for at least 12 weeks. Median duration of response had not yet been reached at the time of data collection. PFS and OS were 50% and 73%, respectively, at 1 year. Grade 3 or 4 drug-related adverse events occurred in 20% of patients, with increased amylase and increased lipase being the most common. Another cohort of the CheckMate-142 trial included 119 patients with dMMR CRC who were treated with nivolumab and ipilimumab. For this cohort, ORR was 55% (95% CI, 45.2–63.8) and the disease control rate for at least 12 weeks was 80%. PFS and OS were 71% and 85%, respectively, at 1 year. In addition, significant, clinically meaningful improvements were observed in patient-reported outcomes of functioning, symptoms, and quality of life. Grade 3 to 4 treatment-related adverse events occurred in 20% of patients, but were manageable.

Based on these positive results for CRC and the data showing benefit of pembrolizumab in SBA, the NCCN
A single-center, retrospective review reported on 20 patients with advanced SBA who were treated with taxane-based therapy (either as single therapy or in combination).\textsuperscript{133} Of these cases, 30\% showed disease response, 35\% showed stable disease, and 35\% showed progression. Median time to progression was 3.8 months (95\% CI, 2.9–4.6) and median OS was 10.7 months (95\% CI, 3.1–18.3). Based on these data, taxane-based chemotherapy is a recommended option for second- or subsequent-line therapy, although only nab-paclitaxel has prospective, published data to support its use for treatment of SBA.

**FOLFIRI as Subsequent-Line Therapy**

A retrospective, multicenter study evaluated the efficacy of FOLFIRI as second-line therapy for patients with advanced SBA who had received platinum-based chemotherapy in the first-line setting.\textsuperscript{134} Of the 28 patients who fit this treatment paradigm, the ORR was 20\% and disease control rate was 52\%. The median PFS and OS were 3.2 and 10.5 months. Grade 3–4 toxicity was reported in 48\% of patients. Based on these data, FOLFIRI is recommended as a treatment option for second- or subsequent-line treatment of advanced SBA.
Larotrectinib as Subsequent-Line Therapy
A pooled analysis of 3 studies (a phase I including adults, a phase I-II involving children, and a phase II involving adolescents and adults) studied the safety and efficacy of larotrectinib in patients with NTRK gene fusion-positive tumors, including 4 patients with colon cancer and 1 with cancer of the appendix.\textsuperscript{135} For the whole population, the ORR was 75\% (95\% CI, 61\%–85\%) by independent review and 80\% (95\% CI, 67\%–90\%) by investigator assessment. Larotrectinib was found to be well-tolerated as the majority (93\%) of adverse events were grades 1 or 2 and no treatment-related adverse events of grades 3 or 4 occurred in more than 5\% of patients.\textsuperscript{135} Based on these data, the FDA approved larotrectinib for metastatic solid tumors with \textit{NTRK} gene fusion and no satisfactory alternative treatments on November 26, 2018.\textsuperscript{136}

Posttreatment Surveillance
After curative-intent surgery and adjuvant chemotherapy, if administered, posttreatment surveillance of patients with SBA is performed to evaluate for possible therapeutic complications, identify disease recurrence, and discover new metachronous neoplasms at a preinvasive stage. A retrospective study of 146 patients with SBA who underwent cancer-directed surgery found that 39\% subsequently developed disease recurrence, with a median time to recurrence of 25 months. Of the patients with disease recurrence, 57\% developed distant metastases, 19\% developed carcinomatosis, 7\% recurred in the abdominal wall, and 17\% developed local recurrences.\textsuperscript{35} Due to the lack of data regarding optimal surveillance following curative-intent treatment of SBA, a similar approach to CRC surveillance is recommended—including history and physical examination; carcinoembryonic antigen and/or carbohydrate antigen 19-9 measurement; and CT of the chest, abdomen, and pelvis. For data supporting the recommended surveillance approach for CRC, see the “Posttreatment Surveillance” section in the NCCN Guidelines for Colon Cancer, available at NCCN.org.

Patients with SBA who were determined to have Crohn’s disease or familial syndromes (ie, Lynch, FAP, PJS) may require more intensive surveillance due to their elevated risk of developing further SBAs.\textsuperscript{11,12} Endoscopy may be a feasible method for SBA surveillance in patients with Crohn’s disease,\textsuperscript{12,137} although one prospective study found a low (33\%) sensitivity rate for SBA endoscopic screening.\textsuperscript{138} A number of studies have supported the use of endoscopy/enteroscopy for small bowel surveillance in patients with Lynch syndrome, FAP, or PJS.\textsuperscript{139–146} For further details on endoscopic small bowel evaluation, see “Imaging and Endoscopy” (page 1114).

Survivorship
Based on the rarity and poor prognosis of SBA, there is a dearth of data regarding survivorship for this disease. The panel recommendations for survivorship are largely extrapolated from the NCCN Guidelines for Colon Cancer, with some specific recommendations included for patients with celiac or Crohn’s disease who are at elevated risk of developing additional SBAs.\textsuperscript{11,12,14} This section provides an overview of the panel recommendations for survivorship; for more detailed information, see the “Survivorship” section in the NCCN Guidelines for Colon Cancer (available at NCCN.org).

The panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written.\textsuperscript{147} The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to the patient. Other recommendations include monitoring for late or long-term sequelae of treatment, such as oxaliplatin-induced peripheral neuropathy, fatigue, pain, sexual dysfunction, and emotional or social distress.\textsuperscript{148–152} Specific management interventions to address these and other side effects are described in a review.\textsuperscript{153} Disease preventive measures, such as immunizations; early disease detection through periodic screening for second primary cancers (eg, breast, cervical, or prostate cancers); and routine good medical care and monitoring are recommended. The NCCN Guidelines for Survivorship (at NCCN.org) provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment to aid health care professionals who work with survivors of adult-onset cancer in the posttreatment period, including those in specialty cancer survivor clinics and primary care practices.

Summary
SBA is a rare malignancy, with a rising incidence in recent decades. Compared with CRC, SBA is more often diagnosed at advanced stages, suggesting the difficulty of detecting these cancers and highlighting the lack of screening programs, even for high-risk individuals. The majority of SBAs arise in the duodenum and are associated with poorer prognosis, with up to a third of resectable patients experiencing early relapse. To date, the only curative therapy for SBA is surgery.

For local disease, segmental resection of the small bowel is the mainstay of treatment, though duodenal tumors may require either pancreaticoduodenectomy or segmental duodenal resection. Database analyses have reported significantly improved outcomes when 8 or more lymph nodes are resected. In addition, the use of radiation therapy for retroperitoneal-based duodenal adenocarcinomas is a complex decision-making process. Fluoropyrimidine-based adjuvant therapy may be considered for some patients with SBA, though no studies...
have yet shown a definitive benefit of this approach. Results from the international, phase III adjuvant clinical study (BALLAD) investigating observation versus 5-FU versus FOLFOX for patients with resected stage I–III SBA should shed light on this approach in the coming years. Metastatic SBA may rarely be treated with curative intent via primary tumor resection and metastasectomy; however, most patients with metastatic SBA are treated with systemic therapy. Systemic therapy options include fluoropyrimidine-based chemotherapy, taxane-based chemotherapy, or checkpoint inhibitors. Recently, SBA’s unique genetic profile has been a topic of research, which may lead to new targeted or immunotherapeutic treatment options for SBA.

References


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<th>Clinical Research Support/Data Safety Monitoring Board</th>
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<th>Promotional Advisory Boards, Consultant, or Speakers Bureau</th>
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<tr>
<td>Mahmoud M. Al-Hamary, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Diagnostic/Interventional Radiology</td>
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<tr>
<td>Mustafa A. Arain, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Boston Scientific Corporation</td>
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<tr>
<td>Al B. Barenk, MD</td>
<td>AstraZeneca, Amgen Inc.; AstraZeneca Pharmaceuticals Inc.; Bristol-Myers Squibb Company; Celgene Corporation; Infinity Pharmaceuticals, Inc.; Medimmune, Inc.; Merck &amp; Co., Inc.; Novartis Pharmaceuticals Corporation; and Taiho Pharmaceuticals Co., Ltd.</td>
<td>AstraZeneca US Inc.; Bayer HealthCare; Bristol-Myers Squibb Company; Eli Lilly and Company; Exelixis Inc.; Genentech, Inc.; Merck &amp; Co., Inc.; Purdue Pharma LP; and Taiho Pharmaceuticals Co., Ltd.</td>
<td>None</td>
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<tr>
<td>Yi-Jen Chen, MD, PhD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Radiation/Radiation Oncology</td>
</tr>
<tr>
<td>Kristen K. Clombr, MD</td>
<td>Abbott Inc.; Amgen Inc.; Array Biopharma Inc.; Bayer HealthCare; Bristol-Myers Squibb Company; Daichi Sankyo Co.; Incepta Corporation; Merck &amp; Co., Inc.; National Cancer Institute; NuCana PH; Pfizer Inc.; and sanofi-aventis U.S. LLC</td>
<td>Bayer HealthCare, and Taiho Pharmaceuticals Co., Ltd.</td>
<td>Foundation Medicine</td>
<td>Medical Oncology</td>
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<tr>
<td>Stacey A. Cohen, MD</td>
<td>Taiho Pharmaceuticals Co., Ltd.</td>
<td>None</td>
<td>Medical Oncology</td>
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<td>Harry L. Cooper, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Pathology</td>
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<td>Dustin A. Deeming, MD</td>
<td>Bristol-Myers Squibb Company; Genentech, Inc.; and Merck &amp; Co., Inc.</td>
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<td>Ignacio Garrido-Laguna, MD, PhD</td>
<td>Agios, Inc.; Bayer HealthCare; Bristol-Myers Squibb Company; Eli Lilly and Company; Flatiron Health, Inc.; Halozyme, Inc.; Incepta Corporation; Medimmune, Inc.; Novartis Pharmaceuticals Corporation; OncMed Pharmaceuticals, Inc.; Pfizer Inc.; and Taiho Pharmaceuticals Co., Ltd.</td>
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<td>Jean L. Gren, MD</td>
<td>Elion Oncology, and ICON plc</td>
<td>None</td>
<td>Medical Oncology</td>
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<td>Sarah E. Heffe, MD</td>
<td>Varian Medical Systems, Inc.</td>
<td>None</td>
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<tr>
<td>Joleen Hubbard, MD</td>
<td>Bayer HealthCare; Boston Biomedical, Inc.; Incepta Corporation; Medpace; Merck &amp; Co., Inc.; Sarepta Pharmaceuticals; Taiho Pharmaceuticals Co., Ltd.; and Tress Bio</td>
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<td>Surgery/Surgical Oncology</td>
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<td>Ahmed Kamel, MD</td>
<td>Boston Scientific Corporation</td>
<td>Boston Scientific Corporation and Sirtex Medical</td>
<td>Bard Peripheral Vascular, Inc. and Boston Scientific Corporation</td>
<td>Diagnostic/Interventional Radiology</td>
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<td>Natalie Keverit, MD</td>
<td>None</td>
<td>None</td>
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<td>Smitha Krishnamurthy, MD</td>
<td>Abbott Inc.</td>
<td>None</td>
<td>Medical Oncology, and Internal Medicine</td>
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<tr>
<td>Wells A. Mearesworth, MD</td>
<td>Aduro Biotech, Inc.; ALX Oncology; D3 Pharma; Genentech, Inc.; Immunomedics, Inc.; Incepta Corporation; Pfizer Inc.; Roche Laboratories, Inc.; and Tanabe Research Labs USA Inc.</td>
<td>Five Prime Therapeutics, Inc.; and Gilead Sciences, Inc.</td>
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<td>Jeffrey Meyerhardt, MPH, MD</td>
<td>Costa Healthcare</td>
<td>Taiho Pharmaceuticals Co., Ltd.</td>
<td>Medical Oncology</td>
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<td>Eric D. Miller, MD, PhD</td>
<td>None</td>
<td>None</td>
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<td>Mary F. Mulcahy, MD</td>
<td>None</td>
<td>None</td>
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<td></td>
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<tr>
<td>Steven Nien, MD, MS</td>
<td>None</td>
<td>None</td>
<td>Surgery/Surgical Oncology</td>
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<tr>
<td>Michael J. Overman, MD</td>
<td>Bristol-Myers Squibb Company; Medimmune, Inc.; Merck &amp; Co., Inc.; Nektar Therapeutics; and Roche Laboratories, Inc.</td>
<td>Bristol-Myers Squibb Company; Medimmune, Inc.; Novartis Pharmaceuticals Corporation; and Roche Laboratories, Inc.</td>
<td>None</td>
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</tr>
<tr>
<td>Aparna Parikh, MD</td>
<td>Array Biopharma Inc.; Bristol-Myers Squibb Company; Guardant Health Inc.; Novartis Pharmaceuticals Corporation; Plexikon Inc.; and TESARO, Inc.</td>
<td>Foundation Medicine, and Puretech Health</td>
<td>None</td>
<td>Medical Oncology</td>
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<tr>
<td>Hitendra Patel, MD</td>
<td>Bristol-Myers Squibb Company, and Medimmune, Inc.</td>
<td>None</td>
<td>Medical Oncology</td>
<td></td>
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<tr>
<td>Katrina S. Pedersen, MD, MS</td>
<td>Merck &amp; Co., Inc.</td>
<td>None</td>
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<td></td>
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<tr>
<td>Leonor B. Salt, MD</td>
<td>Taiho Pharmaceuticals Co., Ltd.</td>
<td>None</td>
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<td>Charles Schneider, MD</td>
<td>None</td>
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<td>David Shihab, MD</td>
<td>None</td>
<td>None</td>
<td>Surgery/Surgical Oncology</td>
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<td>John M. Skliver, MD</td>
<td>None</td>
<td>None</td>
<td>Surgery/Surgical Oncology</td>
<td></td>
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<tr>
<td>Constantinos T. Soutsousqos, MD, PhD</td>
<td>Ethicon, Inc.</td>
<td>Ethicon, Inc.; and Terumo Corporation</td>
<td>Ethicon, Inc.</td>
<td>Diagnostic/Interventional Radiology</td>
</tr>
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<td>Elana M. Stoffel, MD, MPH</td>
<td>None</td>
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<td>Gastroenterology</td>
<td></td>
</tr>
<tr>
<td>Eden Stotyky-Himelfelt, BSN, RN</td>
<td>None</td>
<td>None</td>
<td>Patient Advocate</td>
<td></td>
</tr>
<tr>
<td>Alain P. Vercel, MD</td>
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<td>Medical Oncology, and Hematology/Hematology Oncology</td>
<td></td>
</tr>
<tr>
<td>Christopher G. Willett, MD</td>
<td>None</td>
<td>None</td>
<td>Radiation/Radiation Oncology</td>
<td></td>
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</table>

The NCCN Guidelines Staff have no conflicts to disclose.