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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Small Bowel Adenocarcinoma

Version 1.2025 — December 4, 2024

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NCCN Small Bowel Adenocarcinoma Panel Members
Summary of the Guidelines Updates

Duodenum
- Workup and Primary Treatment (SBA-1)
- Adjuvant Therapy (SBA-2)

Jejunum/Ileum
- Workup and Primary Treatment (SBA-3)
- Adjuvant Therapy (SBA-4)

Metastatic Adenocarcinoma (SBA-5)
Recurrence (SBA-5)

Principles of Imaging and Endoscopy (SBA-A)
Principles of Pathologic Review (SBA-B)
Principles of Surgery (SBA-C)
Principles of Systemic Therapy (SBA-D)
Principles of Radiation Therapy (SBA-E)
Principles of Survivorship (SBA-F)

Staging (ST-1)
Abbreviations (ABBR-1)

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

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Updates in Version 1.2025 of the NCCN Guidelines for Small Bowel Adenocarcinoma from Version 5.2024 include:

SBA-1
- Primary Treatment
  - Locally Unresectable or Medically Inoperable
    - ◊ Treatment option added: Checkpoint inhibitor immunotherapy for dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb] (Also for SBA-3)
    - ◊ Footnote h added: Checkpoint inhibitor therapy options include: nivolumab ± ipilimumab, pembrolizumab, cemiplimab-rwlc, dostarlimab-gxly, retifanlimab-dlwr, toripalimab-tpzi, or tislelizumab-jsgr. (Also for SBA-3)

SBA-2
- Adjuvant Treatment
  - Footnote removed: Survival benefit in adding oxaliplatin to fluoropyrimidine has not been demonstrated in patients >70 years for colon cancer adjuvant management. (Also for SBA-4)

SBA-5
- Workup
  - Metastatic Adenocarcinoma
    - ◊ Molecular testing language modified: ~~MMR/MSI testing, Testing for BRAF V600E and HER2 amplifications, and consider tumor mutational burden (TMB), POLE/POLD1 testing~~
      - – *Molecular testing, including:*
        - ▪ *KRAS mutations and BRAF V600E mutations; HER2 amplifications; MMR or MSI status (if not previously done)*
        - ▪ *Testing should be conducted as part of broad molecular profiling, which would identify rare and actionable mutations and fusions such as POLE/POLD1, RET, NTRK, and tumor mutational burden (TMB).*

SBA-A 1 of 2
- Principles of Imaging and Endoscopy
  - Initial Workup/Staging
    - ◊ Chest, abdomen, pelvis CT
      - – Sub-bullet 5 revised: Consider CT enterography ~~or enteroclysis~~ for specific cases...
    - ◊ MRI
      - – Sub-bullet 1 revised: MR of the abdomen/pelvis *or MR enterography* may be considered where there is contraindication to CT. ~~MR enterography or enteroclysis may similarly be considered when conventional CT or MR with contrast have failed to discern a tumor.~~
      - – Reference removed: Boudiaf M, Jaff A, Soyer P, et al. Small-bowel diseases: prospective evaluation of multi-detector row helical CT enteroclysis in 107 consecutive patients. Radiology 2004;233:338-344.

SBA-B
- Principles of Pathologic Review
  - Text modified: For more information on molecular testing for NTRK, BRAF, *KRAS,* POLE/POLD1, RET, HER2, etc.,...

Continued

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Updates in Version 1.2025 of the NCCN Guidelines for Small Bowel Adenocarcinoma from Version 5.2024 include:

SBA-D 1 of 9
- Principles of Systemic Therapy for Advanced or Metastatic Disease
  - Tables have been revised and reformatted
    - ◊ Initial Therapy header modified: Initial Therapy *(pMMR/MSS)*
    - ◊ Second-Line and Subsequent Therapy (if not previously given)
      - – Regimens added: If KRAS G12C mutation positive: sotorasib or adagrasib
    - ◊ For Any Line of Therapy
      - – Qualifier revised: (if dMMR/MSI-H or POLE/POLD1 mutation *with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb]*) (Also for SBA-D 6 of 9)
      - – The following immunotherapy agents have been added:
        - Cemiplimab-rwlc
        - Retifanlimab-dlwr
        - Tislelizumab-jsgr
        - Toripalimab-tpzi

SBA-D 2 of 9
- Footnote e revised: Bevacizumab has been shown to be safe in advanced SBA, although efficacy has not been proven. ~~An FDA-approved biosimilar is an appropriate substitute for bevacizumab.~~
- Footnote removed: Functional POLE/POLD1 mutations. See Principles of Pathologic Review (SBA-B). Ma X, et al. Nat Genet 2022;54:996-1012.
- Footnotes added:
  - Footnote c: An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
  - Footnote l: Sotorasib and adagrasib have showed activity as monotherapy, but have not been tested in combination with EGFR inhibitors in SBA.
  - Footnote m: Nivolumab + ipilimumab may be considered as subsequent therapy if checkpoint inhibitor monotherapy was previously received.

SBA-D 3 of 9
- Header modified: *NEOADJUVANT OR* ADJUVANT THERAPY REGIMENS
  - Duration removed for capecitabine and CAPEOX regimens: ....every 3 weeks ~~x 24 weeks~~

SBA-D 6 of 9 and **SBA-D 7 of 9**
- Regimens and dosing updated.

SBA-D 8 of 9 and **SBA-D 9 of 9**
- References updated.

SBA-E
- Principles of Radiation Therapy
  - Duodenum
    - ◊ Bullet 4, Treatment Information
      - – Sub-bullet 5, RT dosing revised: Adjacent small bowel dose should be limited to ~~50~~ *Dmax 55* Gy, V45 Gy should be ~~<195~~ *≤150* cc for a bowel bag avoidance, or V~~15~~ *50* should be ~~<120~~ *≤30* cc for individual small bowel loops, if possible.
        - Reference added: Alvarez JA, Shi Q, Dasari A, et al. Alliance A022104/NRG-GI010: The Janus Rectal Cancer Trial: a randomized phase II/III trial testing the efficacy of triplet versus doublet chemotherapy regarding clinical complete response and disease-free survival in patients with locally advanced rectal cancer. Supplement 2. Protocol update to Alliance A022104. BMC Cancer 2024;24:901.

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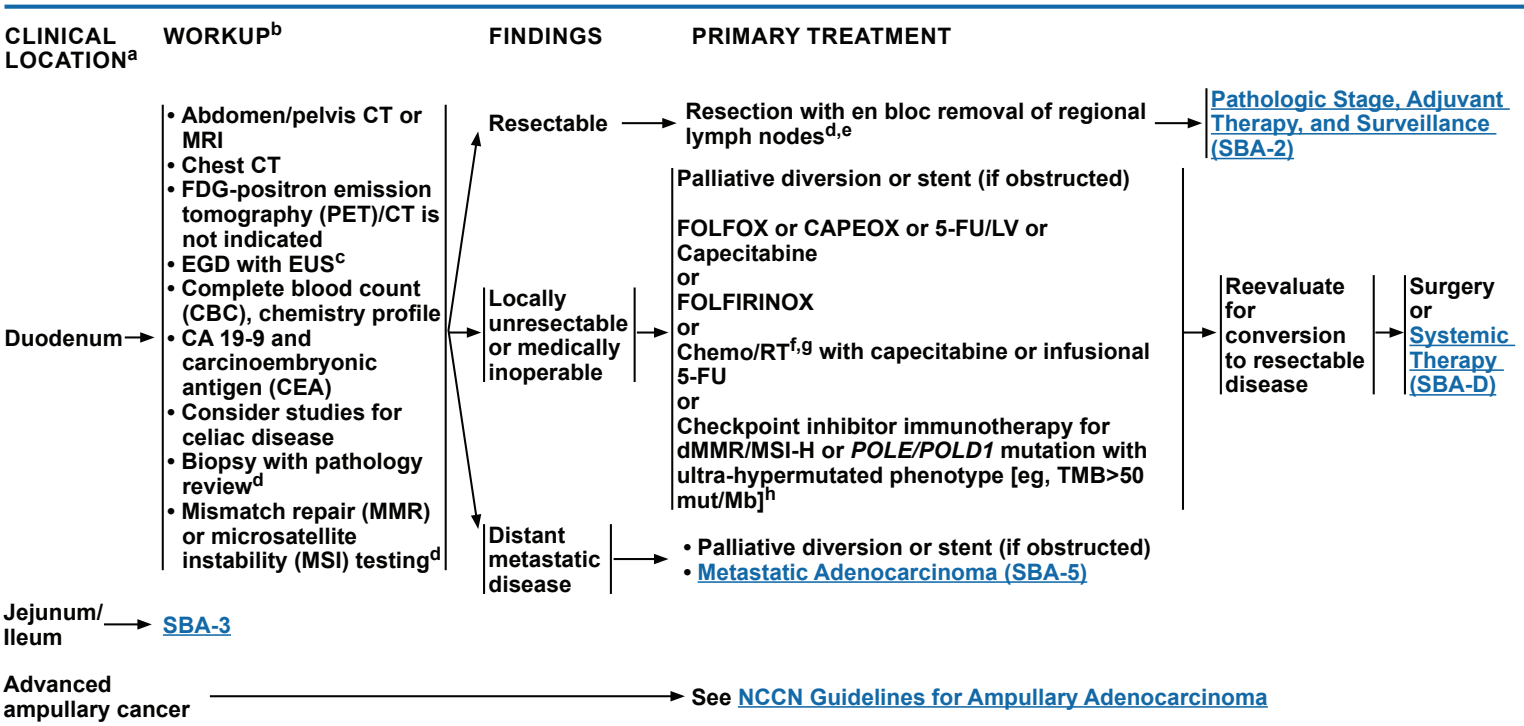

[a] All patients with small bowel adenocarcinoma (SBA) should be counseled for familial malignancies and considered for risk assessment, including Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]), familial adenomatous polyposis (FAP), and other polypoid mutations. Refer to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.

[b] Principles of Imaging and Endoscopy (SBA-A).

[c] EUS should be considered when needed to discern duodenal malignancy from ampullary, distal common bile duct, or pancreatic head malignancy. Also consider if other radiologic imaging is insufficient for clinical staging.

[d] Principles of Pathologic Review (SBA-B). Depending on tumor location and patient history, celiac disease or Crohn's disease may need to be assessed.

[e] Principles of Surgery (SBA-C).

[f] Principles of Radiation Therapy (SBA-E).

[g] Preoperative chemo/RT should be considered in patients who remain unresectable following a course of induction chemotherapy.

[h] Checkpoint inhibitor therapy options include: nivolumab ± ipilimumab, pembrolizumab, cemiplimab-rwlc, dostarlimab-gxly, retifanlimab-dlwr, toripalimab-tpzi, or tislelizumab-jsgr.

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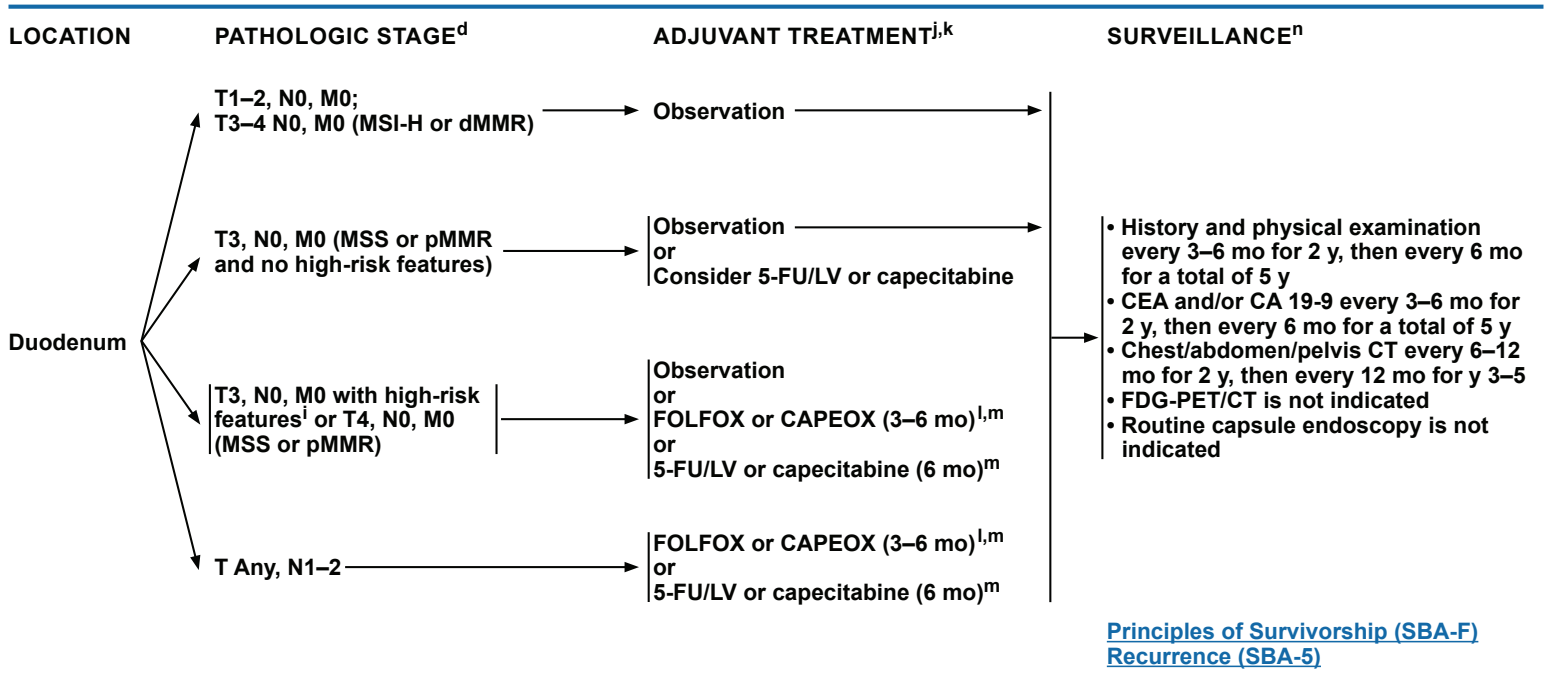

[d] Principles of Pathologic Review (SBA-B). Depending on tumor location and patient history, celiac disease or Crohn's disease may need to be assessed.
[i] High-risk features in stage II SBA include close or positive resection margins, <5 lymph nodes examined if duodenal location or <8 lymph nodes examined if jejunal/ileal primary tumor location, and tumor perforation. Further consideration may be made for administering chemotherapy in patients with stage II disease who have lymphovascular or perineural invasion, or poorly differentiated histology due to data extrapolated from colorectal cancer studies.
[j] Enrollment in a clinical trial is encouraged (eg, Phase III Trial Investigating the Potential Benefit of Adjuvant Chemotherapy for Small Bowel Adenocarcinoma [BALLAD]: https://clinicaltrials.gov/ct2/show/NCT02502370).
[k] Principles of Systemic Therapy (SBA-D 3 of 9).
[l] No patients with SBA were included in the IDEA pooled analysis of adjuvant colon cancer trials. However, in the absence of any direct data regarding SBA, the finding of noninferior 3-year disease-free survival with 3 months of CAPEOX compared to 6 months of CAPEOX in colon cancer may be extrapolated.
[m] If positive margin, consider sequential chemo/RT with capecitabine or infusional 5-FU. See Principles of Radiation Therapy (SBA-E).
[n] No studies have been performed to assess ideal surveillance intervals for SBA. The data in colorectal cancer surveillance is generally accepted as appropriate for SBA.

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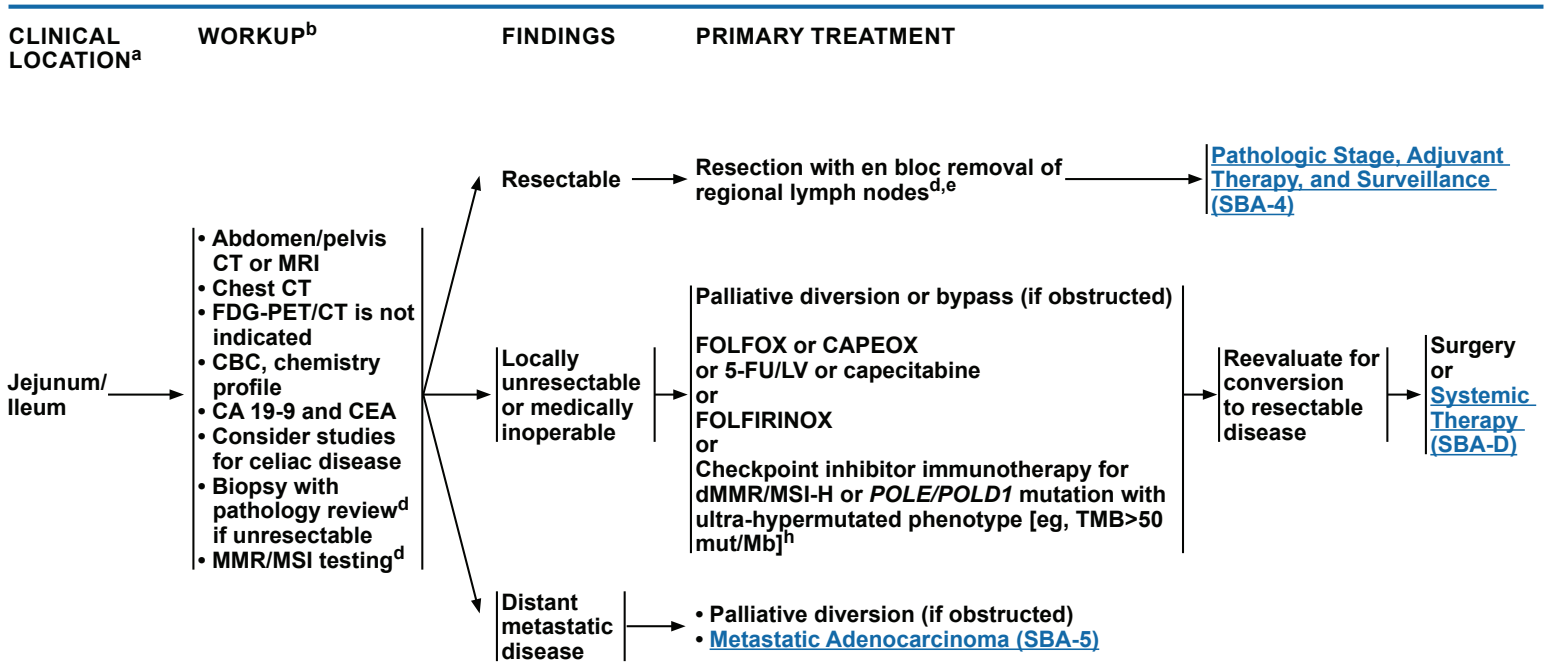

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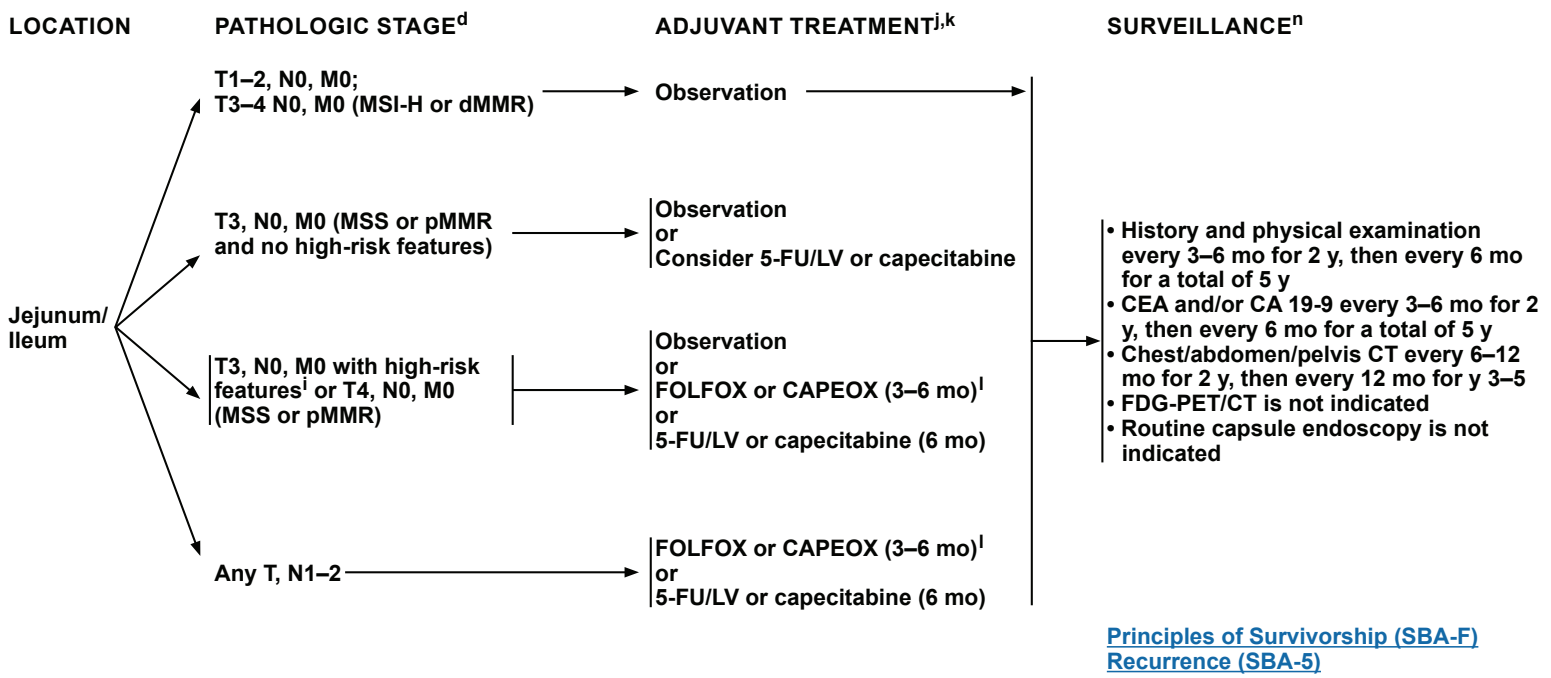

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METASTATIC AND/OR RECURRENCE | **WORKUP**

Metastatic adenocarcinoma[o] →

- **Chest/abdomen/pelvis CT[b]**
- **CBC, chemistry profile**
- **CA 19-9, CEA**
- **Molecular testing, including[d]:**
  - ***KRAS* mutations and *BRAF* V600E mutations; HER2 amplifications; MMR or MSI status (if not previously done)**
  - **Testing should be conducted as part of broad molecular profiling, which would identify rare and actionable mutations and fusions such as *POLE/POLD1*, *RET*, *NTRK,* and tumor mutational burden (TMB).**

→ **Principles of Systemic Therapy (SBA-D)**

Serial biomarker elevation →

- **Physical examination**
- **Endoscopic evaluation(s)**
- **Chest/abdomen/pelvis CT with contrast**

→ **Negative evaluation** →
- **Consider FDG-PET/CT**
- **Reevaluate biomarker and CT with contrast in 3 months**

→ **Positive evaluation** → **See "Metastatic adenocarcinoma" above**

[b] Principles of Imaging and Endoscopy (SBA-A).
[d] Principles of Pathologic Review (SBA-B). Depending on tumor location and patient history, celiac disease or Crohn's disease may need to be assessed.
[o] Potentially resectable visceral or peritoneal metastases are extremely rare for SBA. See Discussion for information on metastasectomy and cytoreductive surgery/intraperitoneal chemotherapy, which may be considered for select patients.

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PRINCIPLES OF IMAGING AND ENDOSCOPY

Initial Workup/Staging

- **Chest, abdomen, pelvis CT**
  - **Evaluate local extent of tumor infiltration into surrounding structures.**
  - **Assess for distant metastatic disease to lungs, lymph node, liver, peritoneal cavity, and other organs.**
  - **Abdomen/pelvis CT should be performed with intravenous (IV) iodinated contrast and oral contrast agents unless contraindicated.**
  - **Chest CT does not require contrast (although it may be given if performed with abdominal CT).**
  - **Consider CT enterography for specific cases where primary tumor is poorly visualized by standard methods.**
  - **If IV iodinated contrast is contraindicated, then MR examination of the abdomen/pelvis with IV gadolinium-based contrast may be obtained instead. In patients with chronic kidney failure (including patients on dialysis), IV gadolinium-based contrast may be administered in select cases using gadobutrol, gadopentetate dimeglumine, gadobenate dimeglumine, or gadoteridol.[1]**
- **MRI**
  - **MR of the abdomen/pelvis or MR enterography may be considered where there is contraindication to CT.[2,3,4]**
  - **Consider MR of the abdomen with and without contrast for further evaluation of indeterminate liver lesions on CT.**
  - **Magnetic resonance cholangiopancreatography (MRCP) may need to be obtained in the initial workup of suspected duodenal malignancies to further ascertain tumor site of origin, particularly in cases of biliary obstruction.**
- **FDG-PET/CT is not indicated as efficacy and clinical benefit have not been examined compared to CT or MR.[5]**
  - **Consider obtaining FDG-PET/CT in instances of equivocal CT or MR results, including the evaluation of potential peritoneal disease, particularly where potential lesions are sized greater than the lower limits of FDG-PET detection.**

[1] Weinreb JC, Rodby RA, Yee J, et al. Use of intravenous gadolinium-based contrast media in patients with kidney disease: consensus statements from the American College of Radiology and the National Kidney Foundation. Radiology 2021;298:28-35.
[2] Masselli G, Casciani E, Polettini E, et al. Magnetic resonance imaging of small bowel neoplasms. Cancer Imaging 2013;13:92-99.
[3] Cronin CG, Lohan DG, Browne AM, et al. Magnetic resonance enterography in the evaluation of the small bowel. Semin Roentgenol 2009;44:237-243.
[4] Masselli G, Di Tola M, Casciani E, et al. Diagnosis of small-bowel diseases: Prospective comparison of multi-detector row CT enterography with MR enterography. Radiology 2016;279:420-431.
[5] Cronin CG, Scott J, Kambadakone A, et al. Utility of positron emission tomography/CT in the evaluation of small bowel pathology. Br J Radiol 2012;85:1211-1221.

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PRINCIPLES OF IMAGING AND ENDOSCOPY

Initial Workup/Staging

- **Endoscopy**
  - **Esophagogastroduodenoscopy (EGD)**
    - ◊ **May be used for detection and pathologic sampling where duodenal malignancy is suspected. If simultaneous intestinal obstruction is detected, palliative stenting may be considered.[6]**
  - **Endoscopic ultrasound (EUS)**
    - ◊ **Useful for enhanced pre-therapeutic clinical staging of proximal small intestinal malignancies and to discern duodenal from ampullary, biliary, or pancreatic primaries.[7]**
  - **Push- or device-assisted enteroscopy (double- or single-balloon enteroscopy)**
    - ◊ **Not required for routine staging workup, although may be considered in patients with small intestinal strictures for diagnostic and/or palliative benefit. Biopsy may be performed during these procedures.[8-10]**
  - **Capsule endoscopy**
    - ◊ **Consider when radiographic imaging and other forms of endoscopy fail to reveal a suspected primary lesion.[11,12] This is not the preferred primary method for diagnostic workup due to inability to obtain tissue for diagnosis.**
    - ◊ **Contraindicated where small bowel obstruction or strictures exist.**

Monitoring

- **Chest, abdomen, pelvis CT with contrast**
  - **Prior to adjuvant therapy to assess response to resection or primary therapy.**
  - **During re-evaluation of conversion to resectable disease (neoadjuvant therapy).**
  - **CT enterography is not routinely indicated for monitoring and should be reserved for instances of clinical necessity.**

Surveillance

- **Surveillance for recurrence should be judiciously applied. Recommend similar approach to colorectal surveillance due to lack of small bowel adenocarcinoma (SBA)-specific data.**
- **Patients with confirmed Lynch syndrome should have appropriate screenings commensurate with their genotype and family cancer history. This may include small intestinal screening moving forward.[13]**

[6] Hara AK, Leighton JA, Sharma VK, et al. Imaging of small bowel disease: comparison of capsule endoscopy, standard endoscopy, barium examination, and CT. Radiographics 2005;25:697-711; discussion 711-718.
[7] Nylund K, Odegaard S, Hausken T, et al. Sonography of the small intestine. World J Gastroenterol 2009;15:1319-1330.
[8] Cazzato IA, Cammarota G, Nista EC, et al. Diagnostic and therapeutic impact of double-balloon enteroscopy (DBE) in a series of 100 patients with suspected small bowel diseases. Dig Liver Dis 2007;39:483-487.
[9] Sunada K, Yamamoto H, Kita H, et al. Clinical outcomes of enteroscopy using the double-balloon method for strictures of the small intestine. World J Gastroenterol 2005;11:1087-1089.
[10] Chen WG, Shan GD, Zhang H, et al. Double-balloon enteroscopy in small bowel diseases: Eight years single-center experience in China. Medicine (Baltimore) 2016;95:e5104.
[11] Bailey AA, Debinski HS, Appleyard MN, et al. Diagnosis and outcome of small bowel tumors found by capsule endoscopy: a three-center Australian experience. Am J Gastroenterol 2006;101:2237-2243.
[12] Cobrin GM, Pittman RH, Lewis BS. Increased diagnostic yield of small bowel tumors with capsule endoscopy. Cancer 2006;107:22-27.
[13] Koornstra JJ. Small bowel endoscopy in familial adenomatous polyposis and Lynch syndrome. Best Pract Res Clin Gastroenterol 2012;26:359-368.

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PRINCIPLES OF PATHOLOGIC REVIEW

Small Bowel Adenocarcinoma Appropriate for Resection
- Prefer pathologic confirmation of disease prior to resection, where possible

Discrimination of Duodenal Malignancy from Other Primary Sites
- To differentiate SBA from ampullary malignancies in duodenal cancers of the second portion, the epicenter of the tumor or precursor lesion should not be at the ampulla, and >75% of the mass should not be within the ampulla

Pathologic Stage
- The following parameters should be reported:
  - Primary tumor site (ie, duodenum, jejunum, ileum, overlapping, not otherwise specified [NOS])
  - Grade of cancer
  - Tumor depth of invasion (T stage)
  - Number of lymph nodes evaluated and number of lymph nodes positive (N)
  - Status of proximal, distal, radial or mesenteric, uncinate, bile duct, pancreas, and other margins, as appropriate
  - Specimen orientation and inking involves both the pathologist and surgeon as this will help to ensure accurate assessment of the size and extent of the tumor. There should be either direct communication between the surgeon and pathologist for proper orientation and margin identification, or the surgeon should identify the important margins with a clearly understood and documented method (eg, written on the pathology requisition); see above – Status of margins.
  - Lymphovascular invasion
  - MSI/MMR status
  - Evidence of celiac disease
  - Presence of Crohn's disease
  - Presence of polyps

Lymph Node Evaluation
- The AJCC recommends a minimum evaluation of eight lymph nodes, although the College of American Pathologists notes no clear number of minimum lymph nodes to predict complete lymph node negativity has been established
- Regional lymph nodes differ by site of primary tumor:
  - Duodenum: retropancreatic, hepatic artery, inferior pancreaticoduodenal, and superior mesenteric
  - Jejunum/ileum: cecal (terminal ileum only), ileocolic (terminal ileum only), superior mesenteric, mesenteric, and NOS

Microsatellite Instability/Mismatch Repair Testing
- Universal MMR or MSI testing is recommended in all newly diagnosed patients with SBA
- Incidence of deficient MMR (dMMR)/MSI-high (MSI-H) and the possibility of germline mutation is enriched in patients with SBA compared to those with colon and rectal cancer, making this an important prognostic and/or predictive biomarker[1,2]
- Patients with stage II dMMR/MSI-H may have improved survival compared to patients with proficient MMR (pMMR)/microsatellite stable (MSS); however, this has not been confirmed in the SBA population and is extrapolated from colorectal cancer data
- MMR or MSI testing should be performed only in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories
- Testing for MSI may be performed by validated next-generation sequencing (NGS) panels

For more information on molecular testing for *NTRK*, *BRAF*, *KRAS*, *POLE/POLD1*, *RET*, HER2, etc., see the Principles of Pathologic and Molecular Review in the NCCN Guidelines for Colon Cancer.

[1] Aparicio T, Svrcek M, Zaanan A, et al. Small bowel adenocarcinoma phenotyping, a clinicobiological prognostic study. Br J Cancer 2013;109:3057-3066.
[2] Schrock AB, Devoe CE, McWilliams R, et al. Genomic profiling of small-bowel adenocarcinoma. JAMA Oncol 2017;3:1546-1553.

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PRINCIPLES OF SURGERY

Principles for All Primary Sites:

- **Intraoperative staging of the abdomen, particularly including the mesentery, omentum, and peritoneum, should be completed in all cases.**
- **Adequate lymph node dissection, consisting of the resection and evaluation of at least eight lymph nodes, should be the goal for all resections.[1,2]**

Duodenum

- **Pancreaticoduodenectomy (Whipple)**
  - **Should be considered for all duodenal malignancies, particularly if arising in the second portion of the duodenum or invading any portion of the ampulla or pancreas.**
  - **Pylorus preservation is acceptable in the absence of a hereditary condition.**
  - **Minimally invasive procedures should be used only by experienced surgeons.**
  - **Margins should be considered for frozen section at the time of resection if there are concerns about the margins. If margins <5 mm, the surgeon should consider re-excision of involved margin.**
- **Limited segmentectomy**
  - **Although controversial, may be considered for select cases in the absence of a hereditary condition, particularly in lesions on the anti-mesenteric side of the intestine that involve the third and fourth segments of the duodenum.**
  - **Due to reported lower yield of lymph nodes sampled during segmental resection, particular attention will need to be made for complete lymph node dissection and evaluation.[3]**
  - **Case reports suggest segmentectomy and other limited resection methods may be considered for lesions of the first portion of the duodenum,[4] particularly for lesions located on the mesenteric side of the intestine and for those <2 cm in size.**

Jejunum/Ileum

- **Segmentectomy**
  - **Lymph nodes should be identified and resected down to the origin of feeder vessels. Clinically suspicious nodes outside of the field of resection should be biopsied or resected whenever possible.**
  - **Margins of at least 5–10 cm on either side of the tumor should be obtained.**
  - **Terminal ileal resection with right hemicolectomy should be used for distal ileal tumors.**

[1] Overman MJ, Hu CY, Kopetz S, et al. A population-based comparison of adenocarcinoma of the large and small intestine: insights into a rare disease. Ann Surg Oncol 2012;19:1439-1445.

[2] Overman MJ, Hu CY, Wolff RA, Chang GJ. Prognostic value of lymph node evaluation in small bowel adenocarcinoma: analysis of the surveillance, epidemiology, and end results database. Cancer 2010;116:5374-5382.

[3] Onkendi EO, Boostrom SY, Sarr MG, et al. 15-year experience with surgical treatment of duodenal carcinoma: a comparison of periampullary and extra-ampullary duodenal carcinomas. J Gastrointest Surg 2012;16:682-691.

[4] Hashimoto D, Arima K, Chikamoto A, et al. Limited resection of the duodenum for nonampullary duodenal tumors, with review of the literature. Am Surg 2016;82:1126-1132.

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PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c]

INITIAL THERAPY (pMMR/MSS)

Intensive Therapy Recommended

- FOLFOX[d] ± bevacizumab[e]
- CAPEOX[d] ± bevacizumab[e]
- FOLFIRI ± bevacizumab[e,f]
- FOLFIRINOX[d] ± bevacizumab[e]

Intensive Therapy NOT Recommended[g]

- 5-FU/LV ± bevacizumab[e]
- Capecitabine ± bevacizumab[e]

Initial Therapy if previous FOLFOX/CAPEOX in the adjuvant setting within past 12 months or contraindication

- FOLFIRI ± bevacizumab[e]
- Taxane-based chemotherapy
- If *BRAF* V600E mutation-positive:
  - Dabrafenib + trametinib
- If TMB-high (≥10 mut/Mb)[h,i]:
  - Pembrolizumab (category 2B)

SECOND-LINE AND SUBSEQUENT THERAPY (if not previously given)

- FOLFOX[d] ± bevacizumab[e]
- CAPEOX[d] ± bevacizumab[e]
- FOLFIRI ± bevacizumab[e]
- Irinotecan
- Taxane-based chemotherapy
- If *BRAF* V600E mutation-positive:
  - Dabrafenib + trametinib
- If TMB-high (≥10 mut/Mb)[h,i]:
  - Pembrolizumab (category 2B)
- If *NTRK* gene fusion-positive:
  - Entrectinib
  - Larotrectinib
  - Repotrectinib[j]
- If *RET* gene fusion-positive:
  - Selpercatinib
- If HER2-amplified (IHC 3+)[k]:
  - Fam-trastuzumab deruxtecan-nxki
- If *KRAS* G12C mutation positive:
  - (Sotorasib or adagrasib)[l]
- Best supportive care

FOR ANY LINE OF THERAPY (if dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])[h,i,m]

- Cemiplimab-rwlc
- Dostarlimab-gxly
- Nivolumab
- Nivolumab + ipilimumab
- Pembrolizumab
- Retifanlimab-dlwr
- Tislelizumab-jsgr
- Toripalimab-tpzi

Footnotes on SBA-D 2 of 9

Regimen Dosing
(SBA-D 4 of 9)

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PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – FOOTNOTES

[a] Many of the regimens recommended in these guidelines are extrapolated from data for colorectal cancer.
[b] For infection risk, monitoring, and prophylaxis recommendations for targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[d] Discontinuation of oxaliplatin should be strongly considered after 3 to 4 months of therapy (or sooner for unacceptable neurotoxicity) while maintaining other agents until time of progression. Oxaliplatin may be reintroduced if it was discontinued for neurotoxicity rather than for disease progression.
[e] Bevacizumab has been shown to be safe in advanced SBA, although efficacy has not been proven.
[f] The majority of data on first-line treatment of metastatic SBA are for oxaliplatin-based regimens.
[g] For patients who are older, please complete geriatric assessment to aid appropriate prediction of treatment risks. See NCCN Guidelines for Older Adult Oncology, OAO-2.
[h] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[i] If no previous treatment with a checkpoint inhibitor.
[j] On the TRIDENT-1 trial, repotrectinib showed activity both in NTRK TKI naïve and NTRK TKI-pretreated patients.
[k] May not be indicated in patients with underlying lung issues due to lung toxicity (3.5% report of drug-related deaths from interstitial lung disease on the DESTINY-CRC01 trial).
[l] Sotorasib and adagrasib have showed activity as monotherapy, but have not been tested in combination with EGFR inhibitors in SBA.
[m] Nivolumab + ipilimumab may be considered as subsequent therapy if checkpoint inhibitor monotherapy was previously received.

Regimen Dosing
(SBA-D 4 of 9)

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NEOADJUVANT OR ADJUVANT THERAPY REGIMENS[a,c,n]

- **mFOLFOX6[1-3]**
  - **Oxaliplatin 85 mg/m² IV day 1[o]**
  - **Leucovorin 400 mg/m² IV day 1[p]**
  - **5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion**
  - **Repeat every 2 weeks**

- **5-FU/leucovorin[1-3]**
  - **Leucovorin 500 mg/m² given as a 2-hour infusion and repeated weekly x 6**
  - **5-FU 500 mg/m² given bolus 1 hour after the start of leucovorin and repeated weekly x 6**
  - **Every 8 weeks for 4 cycles**

- **Simplified biweekly infusional 5-FU/LV (sLV5FU2)[1-3]**
  - **Leucovorin 400 mg/m² IV day 1,[p]**
  - **followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion**
  - **Repeat every 2 weeks**

- **Capecitabine[1-3]**
  - **Capecitabine 1000–1250 mg/m² PO twice daily for 14 days every 3 weeks**

- **Capecitabine + RT[4]**
  - **Capecitabine 825 mg/m² PO twice daily Monday–Friday, on days of radiation treatment only, throughout the duration of RT (typically 28–30 treatment days)**

- **5-FU + RT[4]**
  - **5-FU 225 mg/m² IV over 24 hours (continuous infusion) daily on days 1–5 or 1–7 for 5 weeks with RT**

- **CAPEOX[1-3]**
  - **Oxaliplatin 130 mg/m² IV day 1[o]**
  - **Capecitabine 1000 mg/m² twice daily for 14 days every 3 weeks[q]**

References on SBA-D 8 of 9

[a] Many of the regimens recommended in these guidelines are extrapolated from data for colorectal cancer.
[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[n] The role for adjuvant chemotherapy remains controversial due to conflicting results across a number of retrospective analyses. Participation in clinical trials is strongly recommended.
[o] 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. Cerek A, Park V, Yaeger 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.
[p] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
[q] The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine 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 capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.

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ADVANCED OR METASTATIC THERAPY REGIMENS[a,c]

- **FOLFOX**
  - **mFOLFOX6[5-7]**
    - ◊ **Oxaliplatin 85 mg/m² IV day 1[o]**
    - ◊ **Leucovorin 400 mg/m² IV day 1[p]**
    - ◊ **5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion**
    - ◊ **Repeat every 2 weeks**
  - **mFOLFOX7[6-8]**
    - ◊ **Oxaliplatin 85 mg/m² IV day 1[o]**
    - ◊ **Leucovorin 400 mg/m² IV day 1[p]**
    - ◊ **5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion**
    - ◊ **Repeat every 2 weeks**

- **FOLFOX + bevacizumab[9,10]**
  - **Bevacizumab 5 mg/kg IV day 1[r]**
  - **Repeat every 2 weeks**

- **CAPEOX[11]**
  - **Oxaliplatin 130 mg/m² IV day 1[o]**
  - **Capecitabine 1000 mg/m² twice daily PO for 14 days[q]**
  - **Repeat every 3 weeks**

- **CAPEOX + bevacizumab[9,10,12]**
  - **Oxaliplatin 130 mg/m² IV day 1[o]**
  - **Capecitabine 1000 mg/m² PO twice daily for 14 days[q]**
  - **Bevacizumab 7.5 mg/kg IV day 1[r]**
  - **Repeat every 3 weeks**

- **FOLFIRI[13]**
  - **Irinotecan 180 mg/m² IV over 30–90 minutes, day 1**
  - **Leucovorin 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1[p]**
  - **5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion**
  - **Repeat every 2 weeks**

- **FOLFIRI + bevacizumab[9,10]**
  - **Bevacizumab 5 mg/kg IV, day 1[r]**
  - **Repeat every 2 weeks**

- **FOLFIRINOX[14,15,s]**
  - **Oxaliplatin 85 mg/m² IV day 1[o]**
  - **Leucovorin 400 mg/m² IV over 2 hours on day 1**
  - **Irinotecan 180 mg/m² IV over 30–90 minutes on day 1**
  - **Fluorouracil 400 mg/m² IV push day 1, fluorouracil 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion**
  - **Repeat every 2 weeks**

Additional Regimens (SBA-D 5 of 9)
References on SBA-D 8 of 9

[a] Many of the regimens recommended in these guidelines are extrapolated from data for colorectal cancer.
[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[o] 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. Cerek A, Park V, Yaeger 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.
[p] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
[q] The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine 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 capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.
[r] Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).
[s] FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of fluorouracil (3200 mg/m² over 48 hours). Patients in the United States have been shown to have greater toxicity with fluorouracil. The dose of fluorouracil (2400 mg/m² over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for U.S. patients.

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ADVANCED OR METASTATIC THERAPY REGIMENS[a,c]

- **Modified FOLFIRINOX[15,16,s]**
  - **Oxaliplatin 85 mg/m² IV day 1[o]**
  - **Leucovorin 400 mg/m² IV over 2 hours on day 1**
  - **Irinotecan 150 mg/m² IV over 30–90 minutes on day 1**
  - **Fluorouracil 1200 mg/m² IV continuous infusion daily on days 1–2 (2400 mg/m² IV over 46 hours)**
  - **Repeat every 2 weeks**

- **FOLFIRINOX or mFOLFIRINOX + bevacizumab[9,10,15,s]**
  - **Bevacizumab 5 mg/kg IV, day 1[r]**
  - **Repeat every 2 weeks**

- **Capecitabine + RT[4]**
  - **Capecitabine 825 mg/m² PO twice daily Monday–Friday, on days of radiation treatment only, throughout the duration of RT (typically 28–30 treatment days)**

- **5-FU + RT[4]**
  - **5-FU 225 mg/m² IV over 24 hours (continuous infusion) daily on days 1–5 or 1–7 for 5 weeks with RT**

- **5-FU/leucovorin**
  - **Roswell Park regimen[17]**
    - ◊ **Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36**
    - ◊ **5-FU 500 mg/m² IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, and 36**
    - ◊ **Repeat every 8 weeks**
  - **Simplified biweekly infusional 5-FU/LV (sLV5FU2)[18]**
    - ◊ **Leucovorin 400 mg/m² IV over 2 hours on day 1,[p]**
    - ◊ **followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion**
    - ◊ **Repeat every 2 weeks**
  - **Weekly[19]**
    - ◊ **Leucovorin 20 mg/m² IV over 2 hours on day 1**
    - ◊ **5-FU 500 mg/m² IV bolus injection 1 hour after the start of leucovorin**
    - ◊ **Repeat every week**

      or
    - ◊ **5-FU 2600 mg/m² by 24-hour infusion on day 1**
    - ◊ **Leucovorin 500 mg/m² over 2 hours on day 1**
    - ◊ **Repeat every week**
  - **Bolus or infusional 5-FU + bevacizumab**
    - ◊ **Bevacizumab 5 mg/kg IV day 1[r]**
    - ◊ **Repeat every 2 weeks**

- **Capecitabine[20]**
  - **Capecitabine 850–1250 mg/m² PO twice daily, for 14 days**
  - **Repeat every 3 weeks**

- **Capecitabine + bevacizumab[20]**
  - **Bevacizumab 7.5 mg/kg IV day 1[r]**
  - **Repeat every 3 weeks**

- **Irinotecan[21,22]**
  - **Irinotecan 125 mg/m² IV over 30–90 minutes, days 1 and 8**
  - **Repeat every 3 weeks**

    or
  - **Irinotecan 180 mg/m² IV over 30–90 minutes, day 1**
  - **Repeat every 2 weeks**

    or
  - **Irinotecan 300–350 mg/m² IV over 30–90 minutes, day 1**
  - **Repeat every 3 weeks**

Additional Regimens (SBA-D 6 of 9)
References on SBA-D 8 of 9

[a] Many of the regimens recommended in these guidelines are extrapolated from data for colorectal cancer.
[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[o] 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. Cerek A, Park V, Yaeger 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.
[p] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
[r] Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).
[s] FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of fluorouracil (3200 mg/m² over 48 hours). Patients in the United States have been shown to have greater toxicity with fluorouracil. The dose of fluorouracil (2400 mg/m² over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for U.S. patients.

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ADVANCED OR METASTATIC THERAPY REGIMENS[a,c]

- **Pembrolizumab[23,24] (dMMR/MSI-H or TMB-high [≥10 mut/Mb] or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])**
  - **Pembrolizumab 2 mg/kg IV every 3 weeks**
    or
  - **Pembrolizumab 200 mg IV every 3 weeks**
    or
  - **Pembrolizumab 400 mg IV every 6 weeks**

- **Nivolumab[25] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])**
  - **Nivolumab 3 mg/kg every 2 weeks**
    or
  - **Nivolumab 240 mg IV every 2 weeks**
    or
  - **Nivolumab 480 mg IV every 4 weeks**

- **Ipilimumab + nivolumab[26] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])**
  - **Nivolumab 3 mg/kg (30-minute IV infusion)**
  - **Ipilimumab 1 mg/kg (30-minute IV infusion)**
  - **Once every 3 weeks for four doses, then**
  - **Nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks**

- **Dostarlimab-gxly[27] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])**
  - **Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1000 mg IV every 6 weeks**

- **Cemiplimab-rwlc[28,29] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])**
  - **350 mg IV day 1**
  - **Repeat every 3 weeks**

- **Retifanlimab-dlwr[30,31] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])**
  - **500 mg IV day 1**
  - **Repeat every 4 weeks**

- **Tislelizumab-jsgr[32-35] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])**
  - **200 mg IV day 1**
  - **Repeat every 3 weeks**

- **Toripalimab-tpzi[36,37] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])**
  - **3 mg/kg IV day 1**
  - **Repeat every 2 weeks**

- **Albumin-bound paclitaxel[38]**
  - **Albumin-bound paclitaxel 220–260 mg/m^2 IV every 21 days**

- **Docetaxel[39]**
  - **Docetaxel 75–100 mg/m^2 IV on day 1 every 21 days**

- **Paclitaxel[39]**
  - **Paclitaxel 135–250 mg/m^2 IV on day 1 every 21 days**
    or
  - **Paclitaxel 80 mg/m^2 IV weekly**
    or
  - **Paclitaxel 80 mg/m^2 IV on days 1, 8, and 15 every 28 days**

- **Gemcitabine + albumin-bound paclitaxel[39]**
  - **Albumin-bound paclitaxel 125 mg/m^2 IV on days 1, 8, and 15**
  - **Gemcitabine 1000 mg/m^2 IV on days 1, 8, and 15**
  - **Every 28 days**

- **Gemcitabine + docetaxel[39]**
  - **Gemcitabine 1000 mg/m^2 IV days 1 and 8**
  - **Docetaxel 75 mg/m^2 IV day 8**
  - **Every 21 days**

- **Gemcitabine + paclitaxel[39]**
  - **Gemcitabine 1000 mg/m^2 IV days 1, 8, and 15**
  - **Paclitaxel 110 mg/m^2 days 1, 8, and 15**
  - **Every 28 days**

Additional Regimens (SBA-D 7 of 9)
References on SBA-D 8 of 9

[a] Many of the regimens recommended in these guidelines are extrapolated from data for colorectal cancer.
[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

Note: All recommendations are category 2A unless otherwise indicated.

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ADVANCED OR METASTATIC THERAPY REGIMENS[a,c]

- **Carboplatin + paclitaxel[39]**
  - **Paclitaxel 175 mg/m² IV day 1**
  - **Carboplatin AUC 5 IV day 1**
  - **Every 21 days**

- **Gemcitabine, docetaxel, and capecitabine (GTX)[39]**
  - **Gemcitabine 750 mg/m² IV at a rate of 10 mg/m²/min on days 4 and 11**
  - **Docetaxel 30 mg/m² IV days 4 and 11**
  - **Capecitabine 750 mg/m² PO twice daily for 14 days**
  - **Every 21 days for 2–6 cycles**

- **Larotrectinib[40] (*NTRK* gene fusion-positive)**
  - **100 mg PO twice daily**

- **Entrectinib[41] (*NTRK* gene fusion-positive)**
  - **600 mg PO once daily**

- **Repotrectinib[42] (*NTRK* gene fusion-positive)**
  - **160 mg PO daily for first 14 days,**
  - **Then increase to 160 mg PO twice daily**

- **Selpercatinib[43] (*RET* gene fusion-positive)**
  - **Patients ≥50 kg: 160 mg PO twice daily**
  - **Patients <50 kg: 120 mg PO twice daily**

- **Dabrafenib + trametinib[44] (*BRAF* V600E mutation-positive)**
  - **Dabrafenib 150 mg PO twice daily**
  - **Trametinib 2 mg PO daily**
  - **Every 28 days**

- **Fam-trastuzumab deruxtecan nxki[45] (HER2-amplified, IHC 3+)**
  - **5.4 mg/kg IV on day 1**
  - **Every 21 days**

- **Adagrasib[46] (*KRAS* G12C mutation positive)**
  - **600 mg PO BID**

- **Sotorasib[47] (*KRAS* G12C mutation positive)**
  - **960 mg PO daily**

References on SBA-D 8 of 9

[a] Many of the regimens recommended in these guidelines are extrapolated from data for colorectal cancer.
[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

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PRINCIPLES OF RADIATION THERAPY

Duodenum:

- **Database analysis suggests no survival benefit from the addition of adjuvant chemo/RT versus chemotherapy alone in patients with surgically resected duodenal adenocarcinoma.[1] A separate retrospective study showed mixed results regarding the efficacy of either preoperative or postoperative chemo/RT for the management of locally advanced or margin-positive duodenal adenocarcinomas.[2] Therefore, chemo/RT following chemotherapy should be considered only in patients with positive margins.**
- **Preoperative chemo/RT 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 RT is being considered.**
- **Treatment Information:**
  - **Fluoropyrimidine-based chemotherapy should be delivered concurrently with RT.**
  - **Treatment can be delivered using 3D conformal RT (3D-CRT). When appropriate, advanced treatment planning, such as intensity-modulated RT (IMRT), should be considered to limit toxicity to adjacent normal organs.**
  - **Image-guided RT (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 RT 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 Dmax 55 Gy, V45 Gy should be ≤150 cc for a bowel bag avoidance, or V50 should be ≤30 cc for individual small bowel loops, if possible.[3]**

Jejunum/Ileum:

- **RT 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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PRINCIPLES OF SURVIVORSHIP

- **Surveillance recommendations on SBA-2**
- **Survivorship Care Planning**
  - **Should have defined roles for the oncologist and the primary care provider following curative-intent therapy**
  - **Overall summary, including dates, of all diagnostic and surgical procedures, chemotherapy received (including drug and number of cycles), and RT (including dose) should be provided to the patient at end of treatment**
  - **Description of long-term toxicities and when they may resolve, as well as potential delayed toxicity**
  - **Surveillance recommendations and schedule**
  - **Health behavior recommendations**
  - **Fertility counseling**
- **Management of Late/Long-term Sequelae of Treatment**
  - **For issues related to distress, pain, neuropathy, fatigue, or sexual dysfunction, see NCCN Guidelines for Survivorship**
- **Oxaliplatin-Related Neuropathy**
  - **Only consider duloxetine, pregabalin, or gabapentin in cases where pain is present, as these are ineffective in treating numbness or tingling associated with the long-term use of oxaliplatin**
  - **Consider non-pharmacologic interventions, including balanced physical activity, acupuncture, heat or ice, or other methods**
- **Lifestyle Modifications**
  - **Avoid gluten in patients with confirmed celiac disease**
  - **Eat a plant-based diet**
  - **Maintain healthy body weight throughout life**
  - **Engage in regular physical activity**
  - **Undergo all age- and gender-appropriate preventive health and cancer screenings at recommended intervals with primary care provider**
  - **Avoid the use of alcohol or tobacco**
- **Crohn's Disease**
  - **Patients with Crohn's disease and history of SBA remain at elevated risk for developing further SBAs. Surveillance screening should be considered for these individuals.[1,2]**

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American Joint Committee on Cancer (AJCC) TNM Staging Classification for Small Intestine Adenocarcinoma 8th ed., 2017

Table 1. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia/carcinoma *in situ*
T1	Tumor invades the lamina propria or submucosa
T1a	Tumor invades the lamina propria
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa, or extends into nonperitonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures (e.g., other loops of small intestine, mesentery of adjacent loops of bowel, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas or bile duct)

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one or two regional lymph nodes
N2	Metastasis in three or more regional lymph nodes

M	**Distance Metastasis**
M0	No distant metastasis
M1	Distant metastasis present

Table 2. **AJCC Prognostic Stage Groups**

	T	**N**	**M**
Stage 0	Tis	N0	M0
Stage I	T1-2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4	N0	M0
Stage IIIA	Any T	N1	M0
Stage IIIB	Any T	N2	M0
Stage IV	Any T	Any N	M1

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ABBREVIATIONS

AUC	area under the curve
CBC	complete blood count
CEA	carcinoembryonic antigen
CLIA	Clinical Laboratory Improvement Amendments
dMMR	mismatch repair deficient
EGD	esophagogastroduodenoscopy
EUS	endoscopic ultrasound
FAP	familial adenomatous polyposis
HNPCC	hereditary nonpolyposis colorectal cancer
IGRT	image-guided radiation therapy
IMRT	intensity-modulated radiation therapy
MMR	mismatch repair
MRCP	magnetic resonance cholangiopancreatography
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
NGS	next-generation sequencing
NOS	not otherwise specified
pMMR	proficient mismatch repair
SBA	small bowel adenocarcinoma
TKI	tyrosine kinase inhibitor
TMB	tumor mutational burden
3D-CRT	three-dimensional conformal radiation therapy

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

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Discussion

This discussion corresponds to the NCCN Guidelines for Small Bowel Adenocarcinoma. Last updated September 13, 2024

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Discussion update in progress

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Overview

In 2024, an estimated 12,440 new cases of small bowel cancer will occur, and 2090 patients will die of this disease.[1] Compared to 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. Small bowel cancers affect males and females relatively equally, with an incidence of 2.6 per 100,000 for males and 2.0 per 100,000 for females.[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 rectal, which decreased in incidence across the same timeframe.[2] The four most common cancer histologies originating in the small bowel are adenocarcinomas, neuroendocrine tumors, gastrointestinal stromal tumors (GISTs), 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, there are very few established guidelines for SBA management. 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 Small Bowel Adenocarcinoma. These guidelines begin with the clinical presentation of the patient 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 (Table 1 in the algorithm).[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

Prior to the development of the NCCN Guidelines for Small Bowel Adenocarcinoma, an electronic search of the PubMed database was 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 peer-reviewed biomedical literature.[7] 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 (eg, 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. NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. When citing published studies and recommendations from other organizations, the terms used (eg, *male*, *female)* reflect the cited sources.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website at www.NCCN.org.

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Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[8] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms *men*, *women*, *female*, and *male* when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Risk Factors for Small Bowel Adenocarcinoma

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 [HNPCC]), 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.

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.[9] Additionally, the results of a pooled analysis of more than 500,000 individuals in the Asia Cohort Consortium reported that elevated body mass index (BMI) and high alcohol consumption were associated with a non-significant trend towards an increased risk of SBA, although this analysis did not identify smoking as a risk factor.[10]

Inflammatory Bowel Disease 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.[11-16] The results of a retrospective, multicenter observational cohort study of 9100 patients with IBD found that the relative risk of small bowel cancer was 3.70 (95% CI, 1.23–11.13).The rate of death and cancer remission did not differ between patients who maintained treatment for IBD compared to those who stopped IBD treatment.[11] Additionally, in a cohort study of 48,119 individuals with celiacs disease (CD), 0.06% (n = 29) patients were diagnosed with SBA within 1 year of a CD diagnoses, suggesting a possible link between these conditions.[17] 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

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with SBA should be counseled for familial malignancies and considered for risk assessment of various genetic syndromes, including Lynch syndrome, PJS, FAP, and other polypoid mutations. A brief description of some of these syndromes is included below. See the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric for more information.

Familial Adenomatous Polyposis

FAP is an autosomal dominant condition characterized by a germline mutation in the *APC* gene, located on chromosome 5q21.[18,19] 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, generally at a later age than those with classic FAP.[18,19] While the incidence of SBA in patients with FAP has not been well established, the lifetime risk has been estimated as 3% to 5%.[20] The duodenum and periampullary region are the most common locations for SBA in patients with FAP.[20]

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.[20,21] A majority of PJS cases occur due to mutations in the *STK11 (LKB1)* gene.[22,23] However, other genetic mutations may be involved, as an estimated half of patients with PJS do not have detectable *STK11/LKB1* mutations.[24] 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 to the general population,[25] and the lifetime risk of SBA has been estimated between 1.7% to 13% for individuals with PJS.[20,25,26]

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 >100 compared to the general population.[27,28] 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 (PCR) 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.[29]

Many NCCN Member Institutions and other comprehensive cancer centers 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.[7,30-33] This approach may also be applied to patients with SBA, particularly since it has been reported that SBA has a higher percentage of MSI-high (MSI-H)/MMR-deficient (dMMR) tumors compared to CRC.[34,35] The NCCN Colon/Rectal/Anal Cancers Panel endorses universal MMR or MSI testing of all newly diagnosed patients with SBA to identify individuals with Lynch syndrome. This testing is also relevant for treatment selection in stage IV disease (see *Pembrolizumab, Nivolumab ± Ipilimumab, or Dostarlimab-gxly [for dMMR/MSI-H tumors]*, below). A more detailed discussion is available in the NCCN Guidelines for Colorectal Cancer Screening.

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Clinical Presentation and Workup

The treatment recommendations in this guideline only refer to SBA. For GISTs, 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.

Most cases of SBA arise in the duodenum, accounting for approximately 52% to 58% of cases. The remainder arise in the jejunum (15%–29%), ileum (10%–13%), or in an unspecified location of the small bowel (4%–16%).[36-39] Patients with SBA tend to be younger at diagnosis and often present with a higher stage and grade compared to those with CRC.[40] 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.[36,41,42] 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 (CBC), chemistry profile, carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), and MMR or MSI testing. In addition, patients with metastatic and/or recurrent disease should also be tested for *BRAF* V600E mutation and HER2 amplification. Testing for tumor mutational burden (TMB) and *POLE/POLD1* mutation should be considered for these patients. Depending on the tumor's location and the patient's history, studies for celiac disease or IBD may be indicated. As discussed above, MMR or MSI testing is recommended for all patients with SBA as 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 Small Bowel Adenocarcinoma*, above).

For more information on molecular testing for *NTRK*, *BRAF*, *POLE/POLD1*, *RET*, HER2 amplifications, and TMB, see the Principles of Pathologic and Molecular Review in the NCCN Guidelines for Colon Cancer.

Imaging and Endoscopy

Esophagogastroduodenoscopy (EGD) with endoscopic ultrasound (EUS) 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.[43] EUS is useful for pre-therapeutic staging of proximal small bowel malignancies and may be used to discern duodenal lesions from ampullary, biliary, or pancreatic primaries.[44]

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.[45-47] Specifically, the use of this method may be of particular benefit for patients with small bowel strictures.[48] While 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.[49-51] 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.[43]

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CT or magnetic resonance (MR) imaging 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, 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 discern a tumor.[52-55] 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 ($P = .0412$).[56]

While FDG-PET/CT has not been formally evaluated for ability to detect metastatic SBA, or compared to MR or CT, there have been reports describing its usefulness for this disease.[57] Therefore, while FDG-PET/CT is not routinely indicated, it may be considered when CT or MR results are equivocal.

See *Posttreatment Surveillance*, below, for the use of these imaging methods for posttreatment surveillance and for use in individuals with inflammatory bowel disease, celiac disease, or familial syndromes.

Pathology and Staging

SBA staging is based on the TNM staging system.[6] 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 nonperitonealized 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.[6]

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).[6] A number of sources have reported stage III or IV SBA as having significantly worse outcomes compared to earlier stage disease.[6,58,59]

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.[6] 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 following 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.[40,60-62] 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.[61,62] Analyses that pooled duodenal and jejunoileal tumors found that 8 regional lymph nodes should be assessed

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for adequate staging,[40,60] although some data have suggested that harvesting even higher numbers of lymph nodes may better predict SBA survival outcomes.[63] 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. While there have been no prospective randomized trials to inform surgical technique, retrospective reviews on the subject have been published.[64-67] 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 anti-mesenteric side of the intestine, although this approach is controversial based on reports of lower lymph node yields.[66] However, a retrospective study of 1611 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 to a simple removal of the primary site, after controlling for confounding factors.[68] This finding was despite greater lymph node retrieval with radical resection. Another systematic review and meta-analysis of observational studies including 6438 patients with duodenal cancer also reported that both segmental resection and pancreaticoduodenectomy allowed adequate assessment of lymph nodes and no difference in OS was observed between the two techniques with distal duodenal primary tumors.[67] Limited resection may also produce more favorable rates of overall morbidity and postoperative pancreatic fistula.[69] 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.[65]

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.[60-62] See *Lymph Node Evaluation*, above, 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.[70] 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*, below.

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 to observation alone for

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patients with stage I–III SBA.[71,72] 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,[39,73-75] some showing no benefit,[37,76,77] and some showing an equivocal or non-significant benefit.[78,79]

The IDEA collaboration was a large trial of patients with colon cancer that investigated whether limiting adjuvant treatment to 3 months of FOLFOX or CAPEOX—which would markedly decrease the incidence of neuropathy—would compromise oncologic outcomes.[80,81] While the non-inferiority of 3 months versus 6 months of CAPEOX was not proven, 3 months of CAPEOX numerically appeared similar to 6 months of CAPEOX for 5-year OS (82.1% vs. 81.2%; HR, 0.96), with considerably less toxicity. These results support the use of 3 months of adjuvant CAPEOX over 6 months for patients with stage III colon cancer. For stage II disease, the duration of therapy was associated with a small (and not statistically significant) difference in disease-free survival (DFS) between 3 and 6 months of CAPEOX.[82] There were significantly less grade 3–5 toxicities with 3 months versus 6 months. While the IDEA trial enrolled no patients with SBA, extrapolation from these colon cancer data are reasonable in the absence of any direct data regarding adjuvant treatment of SBA with the caveat that, stage-for-stage, survival is worse for SBA than for colon cancer.[58,59]

Data supporting the use of adjuvant chemoradiation are especially limited, with a 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 to those who received chemotherapy alone (n = 694), even in high-risk cases.[83] 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.[84] Tumors showing the presence of MSI are classified as either MSI-H or MSI-low (MSI-L), depending on the extent of instability in the markers tested, whereas tumors without this characteristic are classified as microsatellite-stable (MSS).[85] 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.[86-88] 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.[87-89] However, a study of 1913 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.[90] A study of patients in the CALGB 9581 and 89803 trials came to a similar conclusion, though notably this used older, non-standard chemotherapy regimens.[91] 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 Panel recommends:

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- Three to 6 months of adjuvant treatment with capecitabine plus oxaliplatin (CAPEOX) or 6 months of adjuvant treatment with FOLFOX, 5-FU/LV, or capecitabine for any locally advanced SBA with positive lymph nodes (stage III). Following adjuvant systemic therapy, sequential chemoradiation with capecitabine or infusional 5-FU may be considered for stage III duodenal cancer that is margin-positive following resection.

- Observation or adjuvant treatment with 3 to 6 months of CAPEOX or 6 months of FOLFOX, 5-FU/LV, or capecitabine for stage II tumors that are MSS or MMR proficient (pMMR) and have high-risk features. High-risk features include T4 stage, close or positive surgical margins, few lymph nodes examined (<5 for duodenal or <8 for jejunal/ileal primary tumor location), or tumor perforation.[40,60,76] Studies in CRC, and a retrospective report in SBA, have identified lymphovascular or perineural invasion and poorly differentiated histology as poor prognostic factors.[76,92-94] Therefore, adjuvant therapy may be considered for patients with these factors as well. Following adjuvant systemic therapy, sequential chemoradiation with capecitabine or infusional 5-FU may be considered for high-risk stage II duodenal cancer that is margin-positive following 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 following surgical treatment for all stage I tumors and for stage II tumors that are MSI-H or dMMR.

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 demonstrated 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 out of 10 patients showed conversion to resectable disease following neoadjuvant therapy. At the time of data collection, 5 patients were still alive (ranging from 18–83 months postoperatively), suggesting prolonged survival following conversion to resectable disease.[95] In addition, neoadjuvant chemoradiation was studied in two 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 following neoadjuvant chemoradiation.[96] Another small prospective study of patients with duodenal or pancreatic adenocarcinomas reported that all 4 patients with duodenal cancer underwent curative resection following neoadjuvant chemoradiation and experienced a complete pathologic response.[97]

Since 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,[41] with obstruction being a common complication for SBA, accounting for 22% to 57.9% of these cases.[41,98-100] Malignant small bowel obstruction may be treated palliatively with either surgical diversion or stenting. While 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.[41,101-104] One retrospective study concluded that there was no difference in post-stent survival between patients with pancreatic and nonpancreatic cancers, and that patients with nonpancreatic cancers (including SBA) showed a longer OS.[101]

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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 following a course of induction chemotherapy, but degree of benefit 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) Small Bowel Adenocarcinoma

Approximately 32% of patients diagnosed with SBA have stage IV (distant metastatic) disease.[40] The most common sites for metastatic spread include the peritoneal cavity and liver, consistent with other gastrointestinal malignancies.[6] While 5-year survival is relatively high (85%) for localized disease, patients with stage IV SBA have a 5-year relative survival of only 42%.[105] In addition, recurrence rates of localized SBA treated with surgery are high, with many of these patients developing distant metastases.[36] The NCCN recommendations for treatment of stage IV SBA are discussed below.

Metastasectomy

While resectable metastases are rare for SBA and the data supporting metastasectomy for SBA are limited, a retrospective analysis of patients with non-CRC, nonendocrine liver metastases (including 28 patients with small bowel cancers and 12 patients with duodenal cancers) showed promising survival rates following resection of liver metastases.[106] 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. In addition, 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.[107] In total, 44.1% of patients in this study survived >3 years and 88.2% of patients in this study received perioperative chemotherapy. 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.[108] Peritoneal carcinomatosis generally carries a poor prognosis with a reported median OS of 5.9 months.[109] The goal of treatment for unresectable peritoneal metastases is palliative and primarily consists of systemic therapy (see *Systemic Therapy for Metastatic Disease*).

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 carried out 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.[109-114] In addition, a phase III PRODIGE 7 study showed no benefit of oxaliplatin-based HIPEC in patients with CRC compared to cytoreduction alone.[115] Significant morbidity and mortality are

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associated with this procedure. Various studies have reported morbidity rates ranging from 19% to 31% for serious adverse events (AEs) and mortality rates ranging from 0% to 4%.[110-114] Furthermore, recurrences after the procedure are common.[113,114] 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 adenocarcinoma of the small bowel were also almost entirely limited to retrospective reports,[116-119] although recently several small phase II trials for SBA have been reported. Based on the results from these studies, several systemic 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 where intensive therapy is recommended (ie, a patient with a good tolerance for this therapy and for whom a high tumor response rate would be potentially beneficial), the Panel recommends a choice of combination chemotherapy regimens: FOLFOX, CAPEOX, FOLFIRI (infusional 5-FU plus irinotecan), or FOLFIRINOX (infusional 5-FU, LV, oxaliplatin, irinotecan); any of which may be combined with bevacizumab. For patients for whom intensive therapy is not recommended, 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. For both intensive and non-intensive therapy, the checkpoint inhibitors pembrolizumab or nivolumab, with or without ipilimumab, are recommended as initial therapy options for tumors that are dMMR/MSI-H.

For subsequent lines of therapy, many of the chemotherapy regimens recommended as first-line options may be given as subsequent line, if not given previously. In addition, taxane-based chemotherapies are also options for non-first line therapy. Checkpoint inhibitors are an option for dMMR/MSI-H disease or *POLE/POLD1* mutation with ultra-hypermutated phenotype if a checkpoint inhibitor was not previously given. Larotrectinib, entrectinib, or repotrectinib are options in subsequent lines of therapy for metastatic SBA with neurotrophic tyrosine receptor kinase (*NTRK)* gene fusion and no satisfactory alternative treatments. Finally, selpercatinib is an option in subsequent lines of therapy for rearranged during transfection (*RET*) gene fusion-positive metastatic SBA 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 two cancer types SBA is most often likened to. While *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; $P < .001$).[35] 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 to CRC.[34,35]

SMAD4 and *CDKN2A* mutations are more commonly seen compared to 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.[35] Importantly, human epidermal growth factor receptor 2 (HER2) alterations, MSI-H/dMMR, programmed death-ligand 1 (PD-L1) expression, and tumor mutational burden-high (TMB-H) are enhanced in SBA compared to

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CRC,[35,120-122] and may reveal greater importance of targeted or immunotherapeutic treatments compared to current CRC treatment algorithms. One study showed higher rates of PD-L1 positivity in SBA associated with Crohn's or celiac disease, compared with sporadic SBA.[123]

Regimens Not Recommended for SBA

While many of the systemic therapy regimens recommended for treatment of metastatic SBA are extrapolated from data for CRC, there are several regimens 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.[124] Subsequently, a phase II trial published in 2018 showed that panitumumab has no clinically meaningful activity in *RAS* wild-type SBA[125]; 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, there are no data to support their use for SBA and are, therefore, not recommended.

FOLFOX or CAPEOX

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 a complete response.[126] 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.[127] 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.[128] 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.[129] AEs reported across these three trials were similar, with neutropenia, thrombocytopenia, nausea, vomiting, diarrhea, peripheral neuropathy, and fatigue reported most frequently.[126-128] 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.[118,130,131] 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. FOLFOX or CAPEOX may also be appropriate as subsequent therapy if not given as first-line therapy, although there is a lack of data for their use in this setting.

Results of the OPTIMOX1 study showed that a "stop-and-go" approach using oxaliplatin-free intervals resulted in decreased neurotoxicity but did not affect OS in patients with CRC receiving FOLFOX as initial therapy for metastatic disease.[132] Other trials have also addressed the question of treatment breaks, with or without maintenance therapy, and found that toxicity can be minimized with minimal or no effect on survival.[133,134] Therefore, the Panel recommends adjusting the schedule/timing of oxaliplatin as a means of limiting AEs. Discontinuation of oxaliplatin from FOLFOX or CAPEOX should be strongly considered after 3 months of therapy, or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained for the entire 6 months or until time of tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity.

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FOLFIRINOX

While the role of FOLFIRINOX 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.[135] 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 FOLFIRINOX is extrapolated from the results of this study.

FOLFOX, CAPEOX, or FOLFIRINOX Plus Bevacizumab

While data supporting the addition of biologics to FOLFOX, CAPEOX, or FOLFIRINOX 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.[136] Retrospective analyses have supported these results, reporting favorable outcomes in patients treated with bevacizumab-containing chemotherapy regimens without adding significant toxicity.[124,137] Based on these data, FOLFOX, CAPEOX, or FOLFIRINOX may be given with or without bevacizumab for treatment of advanced SBA.

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing biologic therapy. Several biosimilars are now available in the U.S. market, including biosimilars to bevacizumab.[138,139] The NCCN Panel has agreed that an U.S. Food and Drug Administration (FDA)-approved biosimilar may be substituted for bevacizumab wherever it is recommended within the NCCN Guidelines for Small Bowel Adenocarcinoma.

Pembrolizumab, Nivolumab ± Ipilimumab, or Dostarlimab-gxly (for dMMR/MSI-H tumors or POLE/POLD1 mutation with ultra-hypermutated phenotype)

Pembrolizumab is a PD-1 inhibitor that was evaluated as a subsequent-line therapy for treatment-refractory metastatic cancers in a phase 2 study that included 3 cohorts: 1) dMMR colorectal adenocarcinomas; 2) MMR-proficient colorectal adenocarcinomas; and 3) dMMR cancers of types other than CRC.[140] This third cohort included 2 patients with small bowel cancers. The immune-related objective response rate and immune-related PFS rate were 40% and 78%, respectively, for patients with dMMR CRC and 71% and 67% for patients with dMMR non-CRC. Common AEs of clinical interest included rash or pruritus; thyroiditis, hypothyroidism, or hypophysitis; and asymptomatic pancreatitis.[140] Based on the results of this study, the FDA granted accelerated approval to pembrolizumab in May 2017 for patients with unresectable or metastatic dMMR or MSI-H solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options.[141]

More recently, other phase II studies of pembrolizumab have included patients with previously treated SBA. The KEYNOTE-158 study enrolled 233 patients with dMMR/MSI-H advanced non-CRC, including 19 patients with SBA.[142] For the whole study population, ORR was 34.3%, with a median PFS of 4.1 months and median OS of 23.5 months. For SBA specifically, ORR was 42.1%, including three complete responses, median PFS was 9.2 months, and the median duration of response and OS had not been reached at the time of publication. The ZEBRA study evaluated the efficacy of pembrolizumab in 40 patients with previously treated, advanced SBA, regardless of MMR/MSI status.[143] While pembrolizumab did not achieve the goal ORR for this study, 50% of patients with MSI-H tumors (n=4) had a partial response to therapy and remained alive without progression at the time of data collection. One patient with MSS disease showed a partial response while a second patient achieved an unconfirmed partial response, both of whom were TMB-H. The disease

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control rate was 38%. On this study, 63% of patients had grade ≥3 AEs and 28% had AEs of grade 4 or 5.

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, multi-cohort CheckMate-142 trial.[144,145] 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 AEs occurred in 20% of patients, with increased amylase and increased lipase being the most common.[144] Another cohort of the CheckMate-142 trial included 119 patients with dMMR CRC who were treated with nivolumab in combination with 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 AEs occurred in 32% of patients, but were manageable.[145] The phase II DART SWOG S1609 trial, which tested nivolumab plus ipilimumab in rare tumors, has published an abstract reporting results for a cohort of patients with small bowel cancer (n = 25).[146] For the 23 patients who received treatment on this cohort, ORR was 8% (with 1 complete and 1 partial response). Median PFS and OS was 2 and 6 months, respectively. Furthermore, the safety and efficacy of nivolumab monotherapy in previously treated solid tumors was evaluated in the KM-06 open-label, multicenter, single-arm, phase II trial for tumors harboring genetic alterations in DNA damage response and repair (DDR) genes leading to MSI and TMB-H. The trial consisted of 48 patients mostly with colorectal cancer (41.7%) and with an MSI score of >2.5 in addition to a TMB of >12 mutations/Mb.[147] Partial response was achieved by 8 patients resulting in a 17.8% ORR, median progression-free survival was 2.9 months, and a disease control rate of 60%; however, most patients (91.7%) experienced a treatment related adverse event of ≥3.[147] It is important to note that nivolumab monotherapy is not currently recommended in MSS/TMB-H setting.

A third humanized IgG4 PD-1 blocking antibody, dostarlimab-gxly, has been FDA-approved for the treatment of adult patients with dMMR recurrent or advanced solid tumors that have progressed on or following treatment and who have no satisfactory alternative treatment options.[148] The safety and efficacy of dostarlimab-gxly was evaluated in the ongoing phase I GARNET study of patients with advanced solid tumors who had previously received systemic therapy for advanced disease.[149,150] In the entire efficacy population for patients with dMMR and MSI-H or *POLE* mutated tumors (n = 327). Of 327 patients, 23 had small-intestinal solid tumors, of which 21.7% (n = 5) achieved a complete response; 17.4% (n = 4) achieved a partial response; the ORR for these patients was 39.1% (95% CI, 19.7–61.5); mDOR was not reached; mPFS was 8.1 months (95% CI, 2.5–16.5); and mOS was 31.6 months (95% CI, 8.2–not reached).[149,150] The most common immune-related adverse events were hypothyroidism (6.9%), increase in alanine aminotransferase (5.8%), and arthralgia (4.7%). Additionally, the GARNET trial contained 11 patients with *POLE* mutated advanced tumors and dostarlimab monotherapy showed promising anti-tumor activity within this small population; ORR of 54.5% and a PFS of ≥ 1 year.[149,150]

Extrapolating from positive data on first-line use of checkpoint inhibitors in CRC, pembrolizumab monotherapy and nivolumab combination therapy, with or without ipilimumab, are also initial therapy options for dMMR/MSI-H disease or *POLE/POLD1* mutation with ultra-hypermutated phenotype.[151,152] Data suggests that *POLE/POLD1* short variant mutations are associated with an ultra-hypermutated phenotype, and this patient

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population has a significant benefit with checkpoint inhibitors. [152-154] Moreover, certain SBA patients could also benefit from ICI treatment as emerging data has resulted in a higher incidence of dMMR/MSI-H and higher rates of PD-L1 IHC positivity compared to CRC.[34,35,120] Additionally, in 2017 a prospective analysis was performed to compare genomic profiles of SBA (n = 317) to CRC (n = 6353) and gastric carcinomas (GC) (n = 889), data from this analysis resulted in a *POLE* mutation incidence rate of 0.3% in both SBA and CRC. [35] The same incidence rates of *POLE* mutation for both SBA and CRC further support the use of similar treatment options for both patient populations in this setting. Based on these positive results for CRC, and the data showing benefit of pembrolizumab in SBA, the NCCN Panel recommends pembrolizumab; nivolumab, with or without ipilimumab; or dostarlimab-gxly as subsequent-line treatment options for dMMR/MSI-H or *POLE/POLD1* mutation positive advanced SBA.

Pembrolizumab for Tumor Mutational Burden (TMB)-High (>10 mut/Mb)

Pembrolizumab has also been FDA-approved as a treatment for unresectable or metastatic, TMB-H solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options.[141] TMB-H is defined in the label as ≥10 mutations/megabase by an FDA-approved test. Multiple studies have demonstrated TMB-H in approximately 9% to 11% of SBA solid tumors samples, which was significantly higher than CRC (4.3%) suggesting treatment implications with checkpoint inhibitors in the SBA population.[35,155] The approval of pembrolizumab was based off results of the phase 2, KEYNOTE-158 study that enrolled patients with advanced solid tumors.[156] Patients with TMB-H tumors who were treated with pembrolizumab had an ORR of 29% compared to 6% of those with non–TMB-H tumors. However, of the 796 patients who were evaluated for efficacy in this study, none had small bowel or colorectal cancers. Additionally, the ZEBRA study had one patient achieve a PR with low MSS and a high TMB.[143] The phase II TAPUR basket study reported results for 27 patients with TMB-H advanced CRC who were treated with pembrolizumab.[157] One partial response and seven cases with stable disease for at least 16 weeks were reported, for a disease control rate of 28% and an ORR of 4%. A retrospective, single-center study that included three patients with TMB-H small intestine or duodenal cancer reported that only one of these three cases demonstrated a partial response to pembrolizumab.[158]

Furthermore, in 2017 a prospective analysis performed by Schrock et al. compared genomic profiles of SBA (n = 317) to CRC (n = 6353) and gastric carcinomas (GC) (n = 889). Of the entire cohort, 9.5% (n = 30) of SBA samples had a TMB of >20 mutations/Mb compared to 4.3% (n = 276) of CRC samples (P = .001) and 5.6% (n = 50) of GC samples (P = .03). Although, MSS was not specified in the TMB-H population; of the entire cohort, 49% (n = 156) of SBA samples were MSS.[35] Based on emerging data for SBA, the NCCN Panel believes TMB biomarker testing should be considered for all patients with metastatic disease. Pembrolizumab monotherapy is an NCCN category 2B recommended treatment option for patients with TMB-H (>10 mut/Mb) advanced SBA solid tumors.

Dabrafenib plus Trametinib (for BRAF* V600E*-positive tumors)

Treatment combination of dabrafenib plus trametinib blocks MAPK pathway signaling while inhibiting growth and survival of *BRAF-V600*E mutated cells, in addition to enforcing anti-tumor activity.[159] Data suggests the prevalence of *BRAF* V600E mutated solid tumors in SBA is consistent with that of mCRC and is detected in 5% to 10% of patients.[160] A prospective analysis by Schrock et al. reported *BRAF* mutation in 9.1% (n = 29 of 317) and of those 29 patients 10.3% (n = 3 of 29) were *BRAF* V600E mutation positive. [35]

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Additionally, in the phase II basket trial, ROAR, safety and efficacy of dabrafenib in combination with trametinib was analyzed in 8 cohorts of patients with a *BRAF* V600E mutation and an advanced rare cancer.[159] Out of the 8 cohorts within the trial, 3 patients had adenocarcinoma of the small intestine.[159] The primary endpoint of the ROAR trial was investigator-assessed overall response rate (ORR) supported by independent radiology assessment that resulted in an ORR of 67% in the small intestine cohort.[159] The secondary endpoint assessed median duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. The median DoR in the small intestine cohort was 7.7 months while median PFS was not evaluable, and OS was 21.8 months.[159]

Additionally, adverse events (AEs) related to the study treatment of either dabrafenib or trametinib were reported in 87.9% (*n* = 181) across all 8 cohorts. Commonly reported AEs were pyrexia (*n* = 84; 40.8%), fatigue (*n* = 53; 25.7%), chills (*n* = 52; 25.7%), nausea (*n* = 49; 23.8%) and rash (*n* = 42; 20.4%). Serious AEs possibly linked to the study treatment were observed in 46 patients (22.3%) and fatal SAEs were reported in 9 patients (4.4%).[159]

The data represented in the ROAR trial supported the FDA approval of dabrafenib (BRAF kinase inhibitor) in combination with trametinib (MEK inhibitor) for unresectable or metastatic solid tumors with *BRAF* V600E mutations for patients whose disease has progressed following prior treatment and have no satisfactory alternative treatment options.[161] The NCCN Panel recommends these therapies as options for subsequent-line treatment of advanced or metastatic SBA that is *BRAF* V600E mutation positive.

Fam-trastuzumab Deruxtecan-nxki [HER2 amplified (IHC 3+)]

The safety and efficacy of fam-trastuzumab deruxtecan-nxki was evaluated in the multicenter studies, DESTINY-PanTumor02 and DESTINY-CRC02, for HER2 amplified solid tumors with confirmed immunohistochemistry (IHC) of (3+/2+).[162-164] Patient enrollment criteria included previously treated locally advanced or metastatic disease and/or no available alternative treatment options. In the DESTINY-PanTumor02 trial, 267 patients received treatment with trastuzumab deruxtecan (5.4 mg/kg once every 3 weeks) across 7 cohorts of solid tumors, including 1 patient in the rare solid tumor cohort with intestinal adenocarcinoma. The objective response rate (ORR) in all patients was 37.1% (n = 99; [95% CI, 31.3 to 43.2]); median DOR was 11.3 months (95% CI, 9.6–17.8); median PFS was 6.9 months (95% CI, 5.6–8.0); and the median OS was 13.4 months (95% CI, 11.9–15.5).[162] In comparison, patients with HER2 amplified IHC 3+ expressed tumors (n = 75) had an ORR of 61.3% (95% CI, 49.4–72.4); a median DOR of 22.1 months (95% CI, 9.6–not reached), a median PFS of 11.9 months (95% CI, 8.2–13.0), and a median OS of 21.1 months (95% CI, 15.3–29.6). The highest response rates and longest DOR, PFS, and OS; regardless of prior treatment, were observed in those with HER2 IHC 3+ expression profiles.[162]

Investigator-assessed drug-related adverse events were observed in 84.6% (n = 226) patients, most commonly, nausea (55.1%) anemia (27.7%), diarrhea (25.8%), vomiting (24.7%), and fatigue (24.7%). Drug-related AEs grade ≥3 were observed in 40.8% (n = 109) with the most common being neutropenia and anemia. AEs leading to discontinuation of treatment occurred in 8.6% (n = 23) and dose reduction in 20.2% (n = 54). There were four deaths and ILD/pneumonitis was observed in 20.5% (n = 28) of patients.[162]

In the DESTINY-CRC02 trial, the safety and efficacy of trastuzumab deruxtecan was evaluated at (5.4 and 6.4 mg/kg every 3 weeks) in patients with HER2+ mCRC IHC 3+ or IHC 2+/in situ hybridization (ISH+). Most patients had an IHC 3+ in the 5.4 mg/kg and the 6.4 mg/kg arms (78.0% and 85.0%), *RAS* wt tumors (82.9% and 85.0%), and an average

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of 3-4 prior lines of therapy, respectively.[164] Confirmed objective response rate (cORR) was 37.8% (95% CI, 27.3–49.2%) in the 5.4 mg/kg arm and 27.5% (95% CI, 14.6-43.9%) in the 6.4 mg/kg arm.[164]

Based on these data the NCCN Panel recommends fam-trastuzumab deruxtecan-nxki as a treatment option for locally advanced or metastatic small bowel adenocarcinoma for HER2 IHC (3+) solid tumors in previously treated patients and/or those with no available alternative treatment options.

Taxane-Based Chemotherapy

While almost all of the phase II trials of systemic therapy for SBA have focused on first-line therapy, a phase II trial including 13 patients with SBA studied the efficacy of nab-paclitaxel in the refractory disease setting.[165] Patients with SBA in this trial had received a median of 2 prior lines of therapy including a fluoropyrimidine and oxaliplatin. Of the 10 patients with SBA who were evaluable for efficacy, 2 showed a partial response to nab-paclitaxel and an additional 3 had stable disease per RECIST criteria, yielding a disease control rate of 50%. Common grade 3 or 4 toxicities across the entire study population included fatigue (12%), neutropenia (9%), febrile neutropenia (9%), dehydration (6%), and thrombocytopenia (6%).[165]

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).[166] 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

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.[167] 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. While FOLFIRI has not been studied as first-line treatment for advanced SBA, it may be a reasonable first-line option for some patients based on extrapolation of studies in CRC and the regimen's differing toxicity profile compared to oxaliplatin-containing regimens.

Larotrectinib, Entrectinib, or Repotrectinib (for NTRK gene fusion-positive tumors)

A pooled analysis of 3 studies (a phase 1 including adults, a phase 1/2 involving children, and a phase 2 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.[168] 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 AEs were grades 1 or 2 and no treatment-related AEs of grades 3 or 4 occurred in >5% of patients.[168]

An integrated analysis of three global phase I/II studies (ALKA-372-001, STARTRK-1, and STARTRK-2) tested the efficacy and safety of entrectinib in 54 adult patients with advanced or metastatic *NTRK* gene fusion-positive solid tumors.[169] For the whole population, ORR was 57% (95% CI, 43.2%–70.8%), median PFS was 11 months (95% CI, 8.0–14.9), and median OS was 21 months (95% CI, 14.9–not estimable) by independent review. Median duration of response was 10 months (95%

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CI, 7.1–not estimable). Of the four patients with CRC on this study, one was recorded as having a response. Notably, a similar ORR (50% vs. 60%) was observed among those with central nervous system metastasis, indicating that entrectinib has activity in this population. Entrectinib was found to be well-tolerated as most treatment-related AEs were grade 1 or 2 and managed with dose reduction, leading few (4%) patients to discontinue therapy due to treatment-related AEs.

The phase I/II TRIDENT-1 trial tested repotrectinib in two cohorts of patients with *NTRK* gene fusion-positive advanced solid tumors; 40 patients in the NTRK TKI-naïve cohort, who received repotrectinib as their first NTRK TKI treatment, and 48 patients in the NTRK TKI-pretreated cohort, who had already received larotrectinib or entrectinib.[170] One patient on the NTRK TKI-naïve cohort had CRC and two had CRC in the NTRK TKI-pretreated cohort. An abstract presented at ESMO Congress 2023 reported a confirmed ORR of 58%, 12-month DOR of 86%, and 12-month PFS of 56% for the TKI-naïve group and a confirmed ORR of 50%, 12-month DOR of 39%, and 12-month PFS of 22% for the TKI-pretreated population. Grade ≥3 treatment-emergent AEs occurred in 51% of patients (29% were treatment-related), with dizziness being most common. Treatment discontinuation due to AEs occurred in 7% of patients. Although there were no SBA patients in the TRIDENT trial, treatment implications are based on the data extrapolated from the patients with CRC. Based on these data, the FDA has approved larotrectinib, entrectinib, and repotrectinib for metastatic solid tumors with *NTRK* gene fusion and no satisfactory alternative treatment,[105] and the NCCN Panel recommends these therapies as options for subsequent-line treatment of metastatic SBA that is *NTRK* gene fusion positive.

Selpercatinib (for RET gene fusion-positive tumors)

In the ongoing phase 1/2 LIBRETTO-001 trial, the efficacy and safety of the highly selective RET kinase inhibitor selpercatinib is being investigated in a diverse group of patients with *RET* gene fusion-positive tumors, including 10 patients with colon cancer and 1 patient with small bowel cancer.[171] Patients in this trial had received a median of 2 prior lines of systemic therapy and 31% of patients received 3 or more prior lines of treatment. Of a total of 41 efficacy-evaluable patients, the ORR by independent review was 43.9% (95% CI, 28.5%–60.3%). There were 2 complete responses (5%), including the one patient with small bowel cancer involved in the study. By independent review, the median duration of response for the patient with small bowel cancer was 24.5 months. For the entire cohort, median PFS was 13.2 months (95% CI, 7.4–26.2) by independent review, median OS was 18 months (95% CI, 10.7–not evaluable), and median duration of response was 24.5 months (95% CI, 9.2–not evaluable). The most common grade 3 or higher treatment emergent AEs were hypertension and transaminitis. The most common treatment-related serious AEs were drug-induced livery injury, fatigue, and hypersensitivity. One patient had to permanently discontinue selpercatinib due to drug-induced liver injury.

Based on these data, the FDA has approved selpercatinib for locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.[172]

Posttreatment Surveillance

After curative-intent surgery and adjuvant chemotherapy, if administered, post-treatment 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%

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developed carcinomatosis, 7% recurred in the abdominal wall, and 17% developed local recurrences.[36] 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; CEA and/or CA 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.

Patients with SBA who were determined to have Crohn's disease or familial syndromes (ie, Lynch syndrome, FAP, PJS) may require more intensive surveillance due to their elevated risk of developing further SBAs.[12,13] Endoscopy may be a feasible method for SBA surveillance in patients with Crohn's disease,[13,173] although one prospective study found a low (33%) sensitivity rate for SBA endoscopic screening.[174] A number of studies have supported the use of endoscopy/enteroscopy for small bowel surveillance in patients with Lynch syndrome, FAP, or PJS.[175-182] For further details on endoscopic small bowel evaluation, see the section on *Imaging and Endoscopy* under *Clinical Presentation and Workup*, above.

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.[12,13,183] This section will provide an overview of the Panel recommendations for survivorship; for more detailed information, see the *Survivorship* section in the NCCN Guidelines for Colon Cancer.

The Panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written.[184] 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.[185-189] Specific management interventions to address these and other side effects are described in a review.[190] 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 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 post-treatment 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 to 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

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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.

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