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REVIEW

Treatment options for advanced small bowel adenocarcinoma: a systematic review

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Small bowel adenocarcinoma (SBA) is a rare and increasingly recognised malignancy, accounting for only 3.4% of all gastrointestinal cancers. It often presents with non-specific or late-stage symptoms, resulting in delayed diagnosis and poor prognosis. For advanced disease, treatment recommendations rely primarily on small phase II trials and retrospective series with no established standard therapy. Moreover, although SBA commonly harbours *KRAS* mutations (43%), *CDKN2A* (p16) loss, and *HER2/ERBB2* mutations (12%), no targeted biological agents have demonstrated clinical efficacy against this disease. Our systematic review was conducted to comprehensively evaluate the available evidence on systemic therapies for patients with advanced or metastatic SBA, with particular focus on treatment efficacy, safety profiles, and the potential influence of molecular biomarkers.

Key words: small bowel adenocarcinoma, SBA, advanced disease, chemotherapy, systematic review

INTRODUCTION

Small bowel adenocarcinoma (SBA) is a rare yet increasingly recognised malignancy, accounting for only 3.4% of all gastrointestinal (GI) cancers despite the small intestine comprising 80% of the GI tract's length and 99% of its absorptive surface. In 2023, ∼12 070 new cases were diagnosed in the United States, with a median age of 62 years old and a slight male predominance (male-to-female ratio 1.19:1). SBA-related mortality has increased in recent years, with an estimated 2070 deaths in 2023, contrasting with declining mortality trends in colorectal cancer.[1-3] Among small bowel malignancies, neuroendocrine tumours are most prevalent (37.4%), followed by adenocarcinomas (36.9%), with sarcomas and lymphomas being less common. The duodenum is the most frequent site of SBA (49%-58%), followed by the jejunum (19%-29%) and ileum (10%-15%).[1-3]

Risk factors for SBA are not well defined; several environmental and lifestyle exposures have been implicated, including smoking, alcohol use, obesity, low dietary fibre, and high intake of red meat and saturated fats. Chronic inflammatory conditions, such as Crohn's disease and celiac disease, have been associated with increased SBA risk, particularly affecting the ileum and jejunum, respectively.[4-6]

SBA also occurs in the context of hereditary cancer syndromes. In familial adenomatous polyposis, germline *APC* mutations lead to a 3%-5% lifetime SBA risk. Peutz–Jeghers syndrome, involving *STK11* mutations and characterised by small intestinal hamartomatous polyps, carries a lifetime risk between 1.7% and 13%. Lynch syndrome, caused by mismatch repair (MMR) gene mutations (*MLH1, MSH2, MSH6, PMS2*), confers a 1%-4% lifetime SBA risk, with tumours frequently displaying microsatellite instability-high (MSI-H).

The molecular pathogenesis of SBA is thought to mirror the adenoma–carcinoma sequence described in colorectal cancer. Common genetic alterations include *KRAS* mutations (43%) and late p53 inactivation. *CDKN2A* (p16) loss is frequently seen, and *HER2/ERBB2* mutations are identified in up to 12% of tumours, usually mutually exclusive with *TP53* mutations. Other less common alterations involve *EGFR* (4%-8%), *IDH1*, *FGFR2*, *MET*, *PTEN*, and *NOTCH1*.[7-12]

SBA often presents with non-specific or late-stage symptoms, leading to a delayed diagnosis. Patients may report abdominal pain, nausea, vomiting, or weight loss, or present acutely with bowel obstruction, bleeding, or

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perforation. Duodenal tumours may cause biliary obstruction, jaundice, and cholangitis. In some cases, SBA is diagnosed incidentally during surveillance endoscopy for hereditary syndromes or inflammatory bowel disease.

Diagnosis relies on histological confirmation via endoscopic biopsy. The diagnostic modality—oesophagogastroduodenoscopy, capsule endoscopy, or enteroscopy—depends on tumour location. Capsule endoscopy is contraindicated in suspected obstruction. Imaging with computed tomography or magnetic resonance enterography improves lesion visualisation, and endoscopic ultrasound aids in assessing local invasion. Cross-sectional imaging of the chest, abdomen, and pelvis is essential for staging.[13-16]

Histologically, SBA may show mucinous features (up to 42%) or signet ring morphology (up to 37%). Immunophenotypes vary by site: lower GI-type tumours typically stain positive for CDX2, CK20, and villin, while duodenal tumours may exhibit pancreatobiliary features with CK7 positivity.

Surgical resection with regional lymphadenectomy is the standard treatment for localised SBA.[17] Duodenal tumours often require pancreaticoduodenectomy, while jejunal and ileal tumours are managed with segmentectomy or right hemicolectomy. However, recurrence rates remain high, and the role of adjuvant therapy is unclear. Data extrapolated from colorectal cancer support fluoropyrimidine—oxaliplatin-based chemotherapy in high-risk stage II and stage III disease, although evidence from randomised trials remains limited.[17-23]

Despite surgical advances, a substantial proportion of SBA cases present with or progress to advanced disease. Treatment recommendations are based largely on small phase II trials and retrospective series.

In this context, the present review aims to systematically evaluate and synthesise current evidence on systemic therapy for advanced SBA, including chemotherapy, targeted agents, and immunotherapy, with particular emphasis on efficacy, safety, and potential molecular biomarkers.

MATERIALS AND METHODS

Objective and design

This systematic review was conducted to comprehensively evaluate the available evidence on systemic therapies for patients with advanced or metastatic SBA, with particular focus on efficacy, safety, and the impact of molecular biomarkers. The review was designed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Data sources and search strategy

We conducted a comprehensive literature search of PubMed, EMBASE, and Cochrane Library databases up to March 2025 using combinations of the following key words: “small bowel adenocarcinoma”, “duodenal cancer”, “jejunal cancer”, “ileal cancer”, “chemotherapy”, “targeted therapy”, “immunotherapy”, “clinical trials”, and “advanced” or “metastatic”. Reference lists of included articles and relevant reviews were also screened for additional studies.

Two reviewers (FP and MG) independently screened all titles and abstracts for eligibility, with discrepancies resolved by consensus or by a third reviewer when needed (APe).

In addition, to identify ongoing clinical trials, we searched ClinicalTrials.gov on 30 March 2025, using the key words “small bowel adenocarcinoma”, “duodenal cancer”, “jejunal cancer”, and “ileal cancer”. Trials were included if they involved patients with advanced or metastatic SBA and investigated systemic therapy.

Eligibility criteria

Studies were included if they met the following criteria:

- Enrolled adult patients with histologically confirmed advanced or metastatic SBA or ampullary adenocarcinomas with intestinal subtype
- Reported outcomes on systemic therapies, including chemotherapy, targeted therapy, or immunotherapy
- Were phase II or III clinical trials, or retrospective observational studies
- Provided at least one of the following endpoints: objective response rate (ORR), progression-free survival (PFS), or overall survival (OS)

Exclusion criteria are as follows:

- Case reports, editorials, and non-English articles
- Studies on ampullary, neuroendocrine, or lymphoid malignancies without disaggregated SBA data

Data extraction and outcomes

Two independent reviewers extracted data on:

- Study characteristics (authors, year, design, population)
- Treatment regimens and lines of therapy
- Molecular biomarkers assessed (e.g. MSI/MMR status, *RAS*, *VEGF*, *EGFR*)
- Efficacy outcomes: ORR, PFS, OS (with 95% confidence interval where available)
- Safety outcomes: frequency and type of grade 3-4 treatment-related adverse events (AEs)

Discrepancies were resolved through consensus or third-party adjudication.

Study quality and risk of bias

Phase II and III studies were assessed for methodological quality using the Jadad score. Retrospective studies were evaluated using the Newcastle—Ottawa scale, focusing on cohort selection, comparability, and outcome assessment.

Data synthesis

Given the heterogeneity of designs and populations, a narrative synthesis was used to summarise the findings. Where appropriate, outcomes were stratified by treatment type (chemotherapy, targeted therapy, immunotherapy) and line of therapy (first versus subsequent lines). No

meta-analysis was carried out due to the limited availability of comparative randomised data.

RESULTS

This review includes 16 studies[24-39] evaluating systemic therapy for advanced or metastatic SBA or ampullary adenocarcinomas with intestinal subtype: 10 phase II clinical trials and 6 retrospective studies. Phase II trials explored chemotherapy, targeted therapy, and immunotherapy in both first-line and subsequent-line settings,[24-33] while retrospective studies provided real-world evidence, often including biomarker analyses or anti-angiogenic/anti-*EGFR* therapy cohorts (Table 1; Figure 1).[34-40]

Patient and tumour characteristics

Sample sizes ranged from as few as 8-25 patients in small single-centre trials to over 180 in large registry-based series. Median age, where reported, was generally in the late 50s to early 60s, with most patients having an Eastern Cooperative Oncology Group performance status of 0-1. Across studies, primary tumour location was duodenum in ∼50%-60% of cases, jejunum in 20%-30%, and ileum in 10%-15%. Several studies specifically evaluated molecularly defined subgroups:

- RAS wild-type tumours for anti-*EGFR* therapy[30]
- MSI-H/MMR-deficient (dMMR) tumours for immunotherapy[31-33]
- Vascular endothelial growth factor A (VEGF-A) expression for anti-angiogenic therapy[35]

First-line therapy outcomes

Oxaliplatin—fluoropyrimidine doublets (FOLFOX or CAPOX) were the most frequently investigated first-line regimens:

- Overman et al. (CAPOX) achieved an ORR of 50%, a median PFS (mPFS) of 11.3 months, and a median OS (mOS) of 20.4 months.[24]
- Xiang et al. [modified FOLFOX (mFOLFOX)] reported an ORR of 48.5%, an mPFS of 7.8 months, and an mOS of 15.2 months.[25]
- Horimatsu et al. (mFOLFOX6) achieved an ORR of 45%, an mPFS of 5.9 months, and an mOS of 17.3 months.[28]

The addition of bevacizumab to CAPOX yielded an ORR of 48.3%, an mPFS of 8.7 months, and an mOS of 12.9 months.[29] Retrospective series suggested OS improvements with bevacizumab, though statistical significance was not consistently reached.[34-38]

Triplet chemotherapy (CAPIRINOX) produced an ORR of 37.5%, an mPFS of 8.9 months, and an mOS of 13.4 months in McWilliams et al.,[27] but with increased grade 3-4 neutropenia (27%) and dehydration (15%).

Second-line and later-line therapy

For microsatellite stable (MSS)/MMR-proficient (pMMR) patients, second-line FOLFIRI achieved ORRs around 20% in retrospective series, with mPFS typically 3-5.5 months and mOS 12-16 months.[39]

Anti-*EGFR* therapy with panitumumab in heavily pretreated RAS wild-type patients yielded no responses, with an mPFS of 2.4 months and an mOS of 5.7 months.[30]

Immunotherapy in MSI-H/dMMR SBA demonstrated variable results:

- ZEBRA trial (pembrolizumab, later line)—ORR 8%, mPFS 2.8 months, mOS 7.1 months.[31]
- KEYNOTE-158 SBA cohort (pembrolizumab)—ORR 48%, mPFS 23.4 months, OS not reached at 3 years (OS rate 58.7%).[32]

Tumour site-specific observations

Where outcomes were stratified by primary site, duodenal tumours were more frequent and sometimes associated with slightly shorter PFS than jejunal/ileal primaries, though data were inconsistent and limited by small subgroup sizes. For example, Xiang et al. (2012) noted higher ORRs in duodenal primaries (50%) versus jejuno-ileal (42%), but without statistical testing.[25]

Safety profiles

Toxicities were consistent with known class effects:

- Oxaliplatin—peripheral neuropathy (9%-25%), neutropenia (10%-38%).
- Irinotecan—diarrhoea (21%), neutropenia (24%).
- Bevacizumab—hypertension (20%), proteinuria (rare).
- Immune checkpoint inhibitors (ICIs)—fatigue (4%-6%), rare immune-related events (thyroiditis, pneumonitis, Guillain–Barré).
- Triplet chemotherapy regimens produced higher haematologic toxicity rates (>25%).

Summary of efficacy range

Across all first-line trials, ORRs ranged 18%-50%, mPFS 5.0-11.3 months, and mOS 8.0-20.4 months.[24-29,33-38] In later-line settings, ORRs ranged 0%-48% depending on biomarker status, with an mPFS of 2.4-23.4 months.[30-32]

DISCUSSION

SBA remains a rare and biologically heterogeneous malignancy with poor prognosis and limited prospective data to guide systemic therapy. This systematic review consolidates the currently available evidence from phase II trials and retrospective studies to provide a comprehensive therapeutic landscape overview, highlighting key efficacy outcomes, molecular considerations, and persistent challenges in treatment optimisation.

The rarity of SBA has historically limited the development of randomised controlled trials, with most of the available data derived from single-arm phase II trials and observational studies. Nevertheless, some consensus has emerged regarding first-line treatment. Fluoropyrimidine—platinum doublets (FOLFOX/CAPOX) represent the

Table 1. Characteristics of the included studies

First authors (year)	Study type/ setting	Population (*n*)	Intervention regimen	Control regimen	Efficacy results (primary outcome, other outcome) (95%CI)	Safety results (more frequent G3-4 TRAEs)
Overman et al. (2009)[24]	Phase II First line	Ampulla of Vater ($n = 12$) Duodenum ($n = 7$) Jejunum ($n = 8$) Ileum ($n = 3$)	CAPOX	—	ORR: 50% (31% to 69%) mTTP: 11.3 months (4.4->35 months) mOS: 20.4 months (14->35 months)	Fatigue (30%) Peripheral neuropathy (10%) Vomiting (10%) Diarrhoea (10%) Neutropenia (10%)
Xiang et al. (2012)[25]	Phase II First line	Duodenum ($n = 26$) Jejunum + ileum ($n = 7$)	mFOLFOX	—	ORR: 48.5% (31% to 67%) mTTP: 7.8 months mOS: 15.2 months	Neutropenia (12.1%) Peripheral neuropathy (9.1%) Nausea (6%)
Kim et al. (2013)[26]	Phase II First line	Ampulla of Vater ($n = 21$, intestinal type $n = 7$)	CAPOX	—	mTTP: 7.6 months (6.7-8.5 months) mOS: 19.7 months ORR: 38%	Neutropenia (24%) Peripheral neuropathy (9%)
McWilliams et al. (2017)[27]	Phase II First line	Duodenum ($n = 19$) Jejunum ($n = 10$) Ileum ($n = 3$)	CAPIRINOX (dose on UGT1A1*28 genotype)	—	ORR: 37.5% (NR) mOS: 13.4 months mPFS: 8.9 months	Neutropenia (27%) Leukopenia (18%) Dehydration (15%) Diarrhoea (21%) Nausea (24%) Vomiting (18%)
Horimatsu et al. (2017)[28]	Phase II First line	Duodenum ($n = 14$) Jejunum ($n = 10$)	mFOLFOX6	—	1-year PFS: 23.3% (8.6% to 44.2%) ORR: 45% mPFS: 5.9 months (3.0-10.2 months) mOS: 17.3 months (11.7-19.0 months)	Neutropenia (38%) Anaemia (25%) Peripheral neuropathy (25%) Stenosis (17%)
Gulhati et al. (2017)[29]	Phase II First line	Duodenum ($n = 18$) Jejunum and ileum ($n = 5$) Ampulla of Vater ($n = 7$, intestinal type $n = 1$)	CAPOX + BEV	—	6-month PFS rate: 68% (52% to 88%) mPFS: 8.7 months (4.9-10.5 months) mOS: 12.9 months (9.2-19.7 months) ORR: 48.3% No ss in ORR ($P = 0.79$) or PFS ($P = 0.73$)	Fatigue (20%) Hypertension (20%) Diarrhoea (10%)
Gulhati et al. (2018)[30]	Phase II Later lines	Duodenum ($n = 3$) Jejunum and ileum ($n = 5$) Ampulla of Vater ($n = 1$). *RAS-WT,* 2 patients *BRAF*-mut, and 1 patient *PIK3CA*-mut	Panitumumab	—	Early stopped after 9 patients: ORR: 0% mPFS: 2.4 months mOS: 5.7 months	Anaemia (11%)
Pedersen et al. (2021) (ZEBRA)[31]	Phase II Later lines	MSI-H SBA: Duodenum ($n = 24$) Jejunum ($n = 10$) Ileum ($n = 6$)	Pembrolizumab	—	ORR: 8% (2% to 20%) mPFS: 2.8 months (2.7-4.2 months) mOS: 7.1 months (5.1-17.1 months)	Fatigue (4%) AST increase
Maio et al. (2022) (KEYNOTE-158)[32]	Phase II multicohort Later lines	MSI-H tumours: SBA (26/351)	Pembrolizumab	—	SBA cohort: ORR: 48% (27.8% to 68.7%) mDOR NR mPFS: 23.4 (4.3 months-NR) mOS: NR (16.2 months-NR) 3-year OS rate: 58.7%	Fatigue (0.6%) Diarrhoea (0.6%) Skin reactions (1.4%) Pneumonitis (0.9%) Guillain—Barré syndrome (0.6%)
Gibson et al. (2005)[33]	Phase II First line	Duodenum ($n = 17$) Jejunum ($n = 12$) Ileum ($n = 5$) Ampulla of Vater ($n = 4$)	FAM	—	ORR: 18% mPFS: 5.0 months mOS: 8.0 months	Vomiting (36%) Haematological (58%) Death (2.8%)
Amano et al. (2021)[34]	Retro First line	Duodenum and jejunum ($n = 65$) Ileum ($n = 9$)	CAPOX/mFOLFOX + BEV ($n = 16$)	CAPOX/mFOLFOX/ monotherapy ($n = 58$)	No ss. Longer PFS and OS in the interv. group ($P = 0.075$ and 0.077, respectively)	
Takayoshi et al. (2017)[35]	Retro First line	Duodenum ($n = 21$) Jejunum ($n = 7$) Ampulla of Vater ($n = 3$) Ileum ($n = 1$)	BEV-containing chemotherapy ($n = 9$) CET-containing chemotherapy ($n = 3$)	mFOLFOX/CAPOX/TS-1 plus CIS/FOLFIRI/GEM plus CIS/5-FU plus leucovorin/SOX/GEM ($n = 21$)	OS in BEV-containing group: 21.9 months OS in non-BEV-containing group: 11.4 months ($P = 0.179$)	

Continued

Table 1. Continued

First authors (year)	Study type/ setting	Population (*n*)	Intervention regimen	Control regimen	Efficacy results (primary outcome, other outcome) (95%CI)	Safety results (more frequent G3-4 TRAEs)
Aydin et al. (2017)[36]	Retro First line	Duodenum ($n = 16$) Jejunum ($n = 7$) Ileum ($n = 5$)	mFOLFOX/FOLFIRI + BEV ($n = 12$)	mFOLFOX/FOLFIRI ($n = 14$)	Longer PFS and OS and increase in ORR in the interv. group but not ss ($P = 0.48$, 0.73, and 0.44 respectively)	
Hirao et al. (2017)[37]	Retro First line	Duodenum ($n = 8$) Jejunum ($n = 11$) Ileum ($n = 8$)	CAPOX/mFOLFOX/ FOLFIRI + BEV mFOLFOX/FOLFIRI + CET mFOLFOX6/FOLFIRI/IRI + panitumumab Capecitabine + BEV ($n = 8$)	mFOLFOX/CAPOX/TS-1 ± CIS/5-FU plus leucovorin/ IRI plus CIS ($n = 19$)	Treatment with BEV was a significant positive prognostic factor ($P = 0.012$)	
Legué et al. (2019)[38]	Retro (cohort study) First line	Duodenum ($n = 112$) Jejunum ($n = 38$) Ileum ($n = 23$) Not specified ($n = 14$)	CAPOX/FOLFOX/CAP + BEV ($n = 25$)	CAPOX/FOLFOX/CAP ($n = 162$)	Longer OS in the interv. group but not ss ($P = 0.85$)	
Dell'Aquila et al. (2020)[39]	Retro	Duodenum ($n = 4$) Jejunum ($n = 4$) Ileum ($n = 5$)	FOLFIRI/FOLFOX/IRI + CET	—	mPFS: 5.5 months mOS: 15.9 months	

5-FU, 5-fluorouracil; AST, aspartate aminotransferase; BEV, bevacizumab; CAP, capecitabine; CAPIRINOX, capecitabine, irinotecan and oxaliplatin; CAPOX, capecitabine and oxaliplatin; CET, cetuximab; CI, confidence interval; CIS, cisplatin; FAM, 5-FU, mitomycin C, doxorubicin; FOLFIRI, 5-fluorouracil and irinotecan; FOLFOX, 5-fluorouracil and oxaliplatin; GBC, gall-bladder carcinoma; GEM, gemcitabine; interv., interventional; IRI, irinotecan; mDOR, median duration of response; mFOLFOX, modified FOLFOX; mTTP, median time to progression; mut, mutated; NR, not reported; ORR, overall response rate; SBA, small bowel adenocarcinoma; ss, statistically significant; TRAE, treatment-related adverse event; mOS, median overall survival; mPFS, median progression-free survival; WT, wild-type, retro, retrospective.

cornerstone of therapy. These regimens have shown mOS values ranging from 15 to 20 months and mPFS between 7.6 and 11.3 months, with ORR up to 50%. Such outcomes compare favourably to earlier regimens such as FAM (5-fluorouracil, mitomycin, doxorubicin), which reported OS of 8.0 months and ORR of 18% in a 2005 trial by Gibson et al.[33] However, when contextualised with data from metastatic colorectal cancer (mCRC), where similar regimens achieve an mOS of ∼30-36 months,[40] the survival benefit in SBA appears more modest, potentially reflecting distinct tumour biology, stage at diagnosis, or molecular profile. In mCRC, longer median survival times may partly reflect earlier diagnosis, larger trial cohorts, and more extensive treatment sequencing. Opportunities also exist to draw more explicit therapeutic parallels between SBA and upper GI malignancies, where oxaliplatin—fluoropyrimidine regimens have been tested, as well.[41,42]

Triplet chemotherapy regimens, such as CAPIRINOX, have also been explored, although data are limited to a single phase II trial.[27] This regimen, which combines capecitabine, irinotecan, and oxaliplatin with pharmacogenetic dosing adjustments, demonstrated an ORR of 37.5%, mPFS of 8.9 months, and mOS of 13.4 months. The clinical benefit, considering 10 partial responses (PRs), 2 complete responses (CRs), and 14 stable diseases (SDs), was 81%, but was associated with substantial GI and

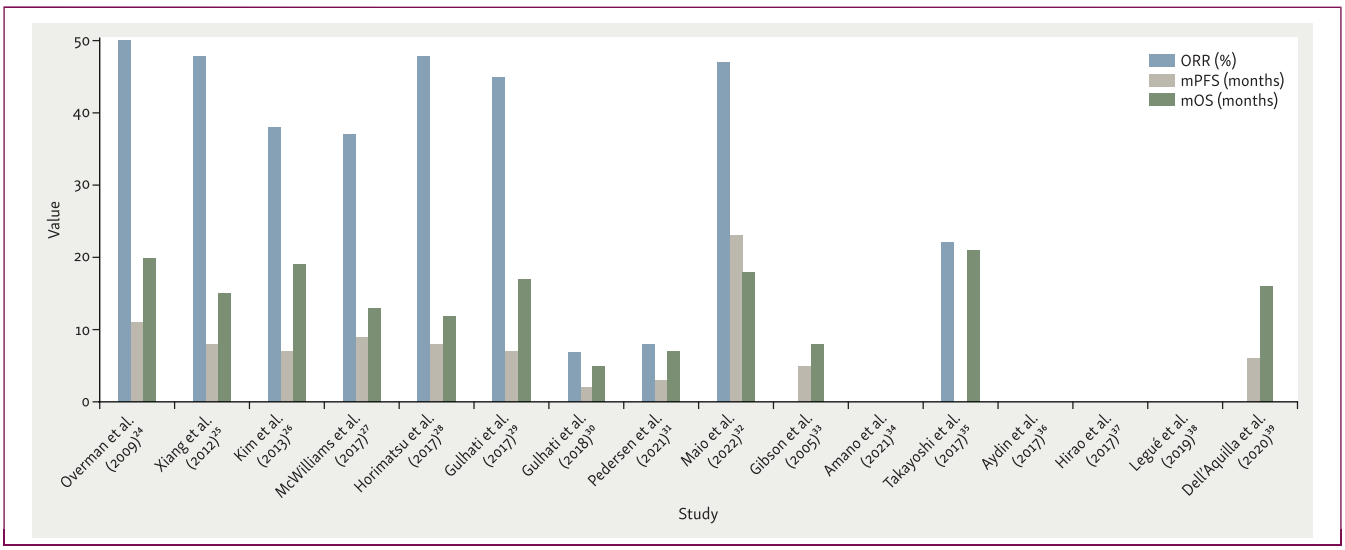

Figure 1. Overview of the outcomes (ORR, mPFS, mOS) for SBA across the trials included.
mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; SBA, small bowel adenocarcinoma.

haematologic toxicities. Capecitabine—irinotecan—oxaliplatin combinations are no longer widely recommended due to these toxicities. Historical regimens such as FAM achieved an ORR of 26% and an mOS of 11.0 months.[43] Data on other triplet regimens, such as FOLFOXIRI, are not currently available in advanced SBA, though they are under investigation in ongoing trials.

The incorporation of targeted therapies has also been evaluated, particularly anti-VEGF and anti-*EGFR* monoclonal antibodies. Bevacizumab, an anti-VEGF agent, has shown promising results when combined with FOLFOX or CAPOX, as observed in a phase II study by Gulhati et al.,[30] where the association of bevacizumab yielded an ORR of 48.3% and an mPFS of 8.7 months. One patient had a CR, 13 had a PR, and 10 patients had SD. As there was no comparison group in this single-arm trial, the contribution of bevacizumab to this outcome cannot be definitively determined. Similar trends were observed in retrospective studies, although none reached statistical significance due to small sample sizes. Importantly, high VEGF-A expression has been associated with improved outcomes, suggesting a potential biomarker-guided use of anti-angiogenic therapies.[34-36]

In contrast, anti-*EGFR* agents such as cetuximab and panitumumab have demonstrated limited activity in SBA, even in the setting of *RAS* wild-type tumours. The phase II study by Gulhati et al., which evaluated panitumumab in pretreated patients, was prematurely terminated due to lack of response.[30] In colorectal cancer, however, anti-EGFR efficacy is most pronounced in *RAS* wild-type disease when used in first-line settings, highlighting that timing of therapy and prior treatment exposure may critically influence outcomes.[44] Notably, one-third of the enrolled patients harboured *BRAF V600E* mutations, which may partly explain the absence of activity and limit the generalisability of these results.[30] This distinction suggests that the apparent lack of benefit in SBA may, at least in part, be related to suboptimal sequencing and warrants investigation in appropriately selected, treatment-naive populations.

This discrepancy underscores the molecular divergence between SBA and other GI malignancies and the need to validate biomarkers specific to this disease.

A significant breakthrough in SBA treatment has come from the recognition of MSI-H and dMMR as predictive markers for immunotherapy responsiveness. Pembrolizumab has demonstrated durable responses in MSI-H/dMMR SBA patients, as shown in the KEYNOTE-158 cohort, with an ORR of 48% and an mPFS of 23.4 months.[32] Similarly, the ZEBRA trial, though with lower response rates (ORR 8%), confirmed activity in this biomarker-selected population.[31]

Beyond standard MSI testing, comprehensive genomic profiling remains important to identify other rare but actionable alterations such as *BRAF V600E*, *NTRK* fusions, *RET* rearrangements, and *HER2* amplifications. Although infrequent, these aberrations have approved targeted therapies in a tissue-agnostic or tumour-specific setting—dabrafenib—trametinib for *BRAF*-mutated tumours, larotrectinib or entrectinib for NTRK fusions, and trastuzumab-based regimens for *HER2* amplification. Incorporating such targets into the treatment algorithm may offer additional therapeutic avenues, particularly for patients lacking standard systemic options. The rarity of these alterations highlights the importance of broad next-generation sequencing to ensure these opportunities are not missed.

For patients who progress on first-line oxaliplatin-based therapy and are MSS/pMMR, second-line options remain scarce. Retrospective data suggest moderate activity of FOLFIRI, with ORRs around 20% and mPFS near 3.2 months.[17] While these outcomes were described as modest, they may in fact be relatively encouraging when considered in the broader GI oncology context. In mCRC, for example, second-line regimens such as FOLFIRI or taxanes typically achieve ORRs in the range of 4%-13%.[45] This comparison suggests that a 20% response rate in SBA could be clinically meaningful, underscoring the need for careful contextualisation when interpreting efficacy in rare tumour types. These regimens offer reasonable alternatives for patients not eligible for immunotherapy, although the absence of prospective comparisons limits definitive recommendations.

Toxicity profiles across the studies were consistent with known class effects. Chemotherapy-induced GI and haematologic toxicities were frequent, with higher rates observed in triplet regimens. Peripheral neuropathy was a prominent issue with oxaliplatin-containing schedules, while hypertension and proteinuria were associated with bevacizumab. Immune-related AEs such as colitis, thyroiditis, and pneumonitis occurred in patients treated with ICIs but were generally manageable and less frequent than cytotoxic AEs.

Despite the therapeutic progress reflected in this review, numerous unmet needs remain. Notably, there is a lack of validated predictive biomarkers beyond MSI-H/dMMR. Additionally, the role of primary tumour location (duodenum versus jejunum versus ileum), histological subtype, and immune microenvironment in modulating response is still not fully elucidated. Recruitment to prospective trials remains a major challenge, particularly due to the low incidence of SBA and its geographic dispersal. This issue is further exacerbated by the frequent inclusion of ampullary tumours in trials, which may confound interpretation given their distinct biology and treatment responsiveness.

ONGOING STUDIES

Numerous clinical trials are exploring several treatment approaches for SBA, including novel combinations, biomarker-driven therapies, and innovative targets[46,47] (Table 2).

NCT02949219 and NCT06333314 investigate the connection between programmed death-ligand 1 (PD-L1) expression, MSI-H, and tumour mutational burden in relation to responses to ICIs, particularly pembrolizumab and

Table 2. Ongoing studies for SBA

	Phase	Status	Treatment regimen	Patient population
NCT02949219	II	Active, not recruiting	Pembrolizumab (single arm)	Advanced or metastatic disease, progression after prior first-line therapy (ICIs not included)
NCT05185947	II	Active, not recruiting	Paclitaxel i.p. + paclitaxel i.v. + nilotinib (single arm)	Peritoneal carcinomatosis, progression/no response after a prior line of therapy
NCT04729322	II	Active, not recruiting	FMT + pembrolizumab versus FMT + nivolumab	Metastatic disease, progression after a prior line with ICIs, dMMR/MSI
NCT04205968	II	Recruiting	Ramucirumab + paclitaxel versus FOLFIRI	Advanced or metastatic disease, progression after prior line with a fluoropyrimidine and/or oxaliplatin
NCT05472948	II	Recruiting	Surufatinib + sintilimab + capecitabine (single arm)	Metastatic disease, progression after prior line of therapy (bevacizumab included, ICIs/TKIs not included)
NCT06278545 (FOLFORINOX SBA)	II	Recruiting	mFOLFIRINOX versus mFOLFOX	Advanced or metastatic disease, no prior first-line therapy, pMMR/MSS
NCT06333314 (Pan-MSI-ACSE)	II	Recruiting	Dostarlimab versus SoC	Advanced or metastatic disease, no prior first-line therapy, dMMR/MSI-H
NCT06638931 (ANTARES)	II (basket)	Recruiting	Nivolumab (single arm)	Advanced or metastatic disease, progression after prior lines of therapy, PD-L1 CPS $\geq$ 10
NCT06835387	II	Not yet recruiting	NALIRIFOX (single arm)	Metastatic disease, no prior first-line therapy, pMMR/MSS

dMMR, mismatch repair-deficient; FMT, faecal microbiota transplantation; ICI, immune checkpoint inhibitor; i.p., intraperitoneal; i.v., intravenous; MSI-H, microsatellite instability; pMMR, mismatch repair-proficient; SoC, standard of care; TKI, tyrosine kinase inhibitor.

dostarlimab. These trials focus on stratifying patient responses based on molecular characteristics, enhancing precision oncology strategies.

NCT06638931 extends the tissue-agnostic approach by evaluating nivolumab in rare tumours (including SBA) with PD-L1 expression (combined positive score $\geq$ 10), further emphasising the role of immunotherapy across diverse malignancies.[48]

NCT04729322 uniquely combines faecal microbiota transplant (FMT) with ICI reintroduction (pembrolizumab/nivolumab) in non-responding dMMR colorectal and metastatic SBA patients. The inclusion of FMT is innovative, leveraging the role of the gut microbiome in immunotherapy response. If successful, it could lead to broader applications in treatment-resistant cases.[49]

NCT05472948 examines a combination of surufatinib (a VEGF receptor and fibroblast growth factor receptor inhibitor), sintilimab [an anti-programmed cell death protein 1 (PD-1) antibody], and capecitabine (a chemotherapy agent). By integrating targeted therapy with immunotherapy and cytotoxic chemotherapy, this trial seeks to maximise tumour suppression while maintaining manageable toxicity.

NCT04205968, NCT06278545, and NCT06835387 focus on refining chemotherapy regimens. NCT04205968 compares ramucirumab and paclitaxel with FOLFIRI in previously treated patients, NCT06835387 evaluates the NALIRIFOX regimen to determine optimal chemotherapy sequencing, and NCT06278545 evaluates the efficacy of mFOLFIRINOX and mFOLFOX to establish a more effective frontline treatment.

NCT05185947 evaluates the use of a combination of intraperitoneal and intravenous paclitaxel along with oral nilotinib to reduce the peritoneal disease burden to achieve resectability. Given the poor prognosis of peritoneal carcinomatosis in SBA patients, this novel integrated therapeutic strategy appears to be encouraging based on preclinical evidence that supports the synergy between paclitaxel and nilotinib. However, further validation in larger cohorts will be necessary.

Several challenges must be addressed in advanced SBA. Firstly, there is an absence of validated predictive biomarkers that could aid in identifying patient subgroups most likely to benefit from these treatment options.[50] Secondly, recruitment for rare malignancies like SBA has always been difficult due to small, geographically dispersed patient populations and disease heterogeneity.[51] Additionally, many studies include long-term extension phases that require participants to continue treatment, rendering them either disinterested in or ineligible for enrolment in other clinical trials.

CONCLUSIONS

Advanced SBA continues to present a significant therapeutic challenge with limited treatment options for physicians. Current evidence supports oxaliplatin—fluoropyrimidine doublets as the first-line standard, while bevacizumab may provide additional benefit in biomarker-selected populations. Subsequent-line options, including irinotecan-based or taxane-based regimens, demonstrate only modest efficacy. In this context, immunotherapy represents a paradigm shift for the subgroup of MSI-H/dMMR SBA and underscores the need for routine molecular profiling. Therefore, for fit patients experiencing rapid progression on first-line therapy, comprehensive molecular profiling should be pursued, with subsequent enrolment in clinical trials representing the optimal therapeutic approach when available. Due to the rarity of the disease, high-quality data from randomised clinical trials are difficult to collect, and the lack of validated biomarkers hampers treatment optimisation.

In conclusion, our review provides a comprehensive and up-to-date overview of the SBA's therapeutic scenario,

encompassing both established regimens and emerging investigational approaches. Future efforts should prioritise biomarker discovery, trial accessibility, and global collaboration, with the ultimate goal of enhancing clinical outcomes.

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