Promising Drugs in Clinical Development To Treat Advanced Colorectal Cancer

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Excluding skin cancers, colorectal cancer (CRC) is the third most common cancer diagnosed in men and women in the United States. Overall, the lifetime risk of developing the disease is approximately one in 21 (4.7%) for men and one in 23 (4.4%) for women. In the U.S., CRC is the second leading cause of cancer-related deaths in men and the third leading cause in women. According to the American Cancer Society, CRC is expected to cause more than 50,000 deaths in 2017.1

Patients with metastatic disease (mCRC) are usually treated with active chemotherapy as first- or second-line therapy. Current first-line active chemotherapy options include FOLFIRI (5-fluorouracil, leucovorin, and irinotecan) and FOLFOX (oxaliplatin, leucovorin, levoleucovorin, and 5-fluorouracil). More recently, targeted therapies have become available, including anti-epidermal growth factor receptor (EGFR) agents, such as cetuximab (Erbitux, Lilly), and anti-vascular endothelial growth factor (VEGF) receptor agents, such as bevacizumab (Avastin, Genentech).2 Patients with incurable disease receive palliative care.3

New drug development for CRC has focused on the EGFR signaling pathway because it is overexpressed in approximately 80% of colorectal carcinomas. Resistance to anti-EGFR agents depends on the patient’s Kirsten rat sarcoma (KRAS) mutation status (mutant or wild-type).2 Analysts have identified several unmet needs in the CRC marketplace. They include:4

- Overcoming mechanisms of resistance to EGFR inhibitors.
- Targeted treatments for BRAF mutation-positive patients.
- Effective neoadjuvant and adjuvant therapies for high-risk resectable disease.
- More effective later-line treatments for chemotherapy-resistant patients.

With these needs in mind, pharmaceutical companies are working to develop novel treatments for patients with advanced CRC (Table 1). Therapies in late-stage development are discussed below.

MOLECULAR-TARGETED AGENTS

Array Biopharma is developing a combination of oral encorafenib (a small-molecule BRAF inhibitor) and oral binimetinib (a MEK1/2 inhibitor) for the second-line treatment of patients with BRAF-mutant mCRC, coadministered with cetuximab.4 BRAF and MEK are key protein kinases in the MAPK signaling pathway (RAS-RAF-MEK-ERK). Research has shown that this pathway regulates several key cellular activities, including proliferation, differentiation, survival, and angiogenesis. Inappropriate activation of proteins in this pathway has been observed in several cancers, including CRC and melanoma. Encorafenib and binimetinib target key enzymes in this pathway.5

In a phase 1b/randomized phase 2 study, Tabernero and colleagues compared a triplet regimen of encorafenib, cetuximab, and alpelisib (a phosphoinositide 3-kinase–alpha inhibitor) with a doublet regimen of encorafenib plus cetuximab in 102 patients with advanced BRAF-mutant CRC. In phase 2, the primary endpoint was progression-free survival (PFS). The PFS analysis comparing the triplet regimen with the doublet regimen showed a hazard ratio of 0.69 (P = 0.064), with median PFS of 5.4 months versus 4.2 months, respectively. Grade 3–4 adverse events were reported in 79% of the triplet-treated patients compared with 58% of the doublet-treated patients. Although alpelisib provided a PFS benefit when added to encorafenib and cetuximab, it also caused additional toxicity.6

The phase 2 trial data led to a phase 3, open-label, randomized study (BEACON CRC) of encorafenib plus cetuximab with or without binimetinib compared with the investigator’s choice of either irinotecan/cetuximab or FOLFIRI/cetuximab as controls in an estimated 645 patients with BRAF V600E-mutant CRC whose disease had progressed after one or two prior regimens in the metastatic setting. The primary outcome measure in this ongoing study is overall survival (OS). The trial began in August 2016 and is expected to conclude in July 2019.5,7

If approved by the Food and Drug Administration (FDA), encorafenib plus cetuximab will be the first treatment indicated for patients with BRAF-mutant mCRC. The product’s anticipated U.S. launch date is 2020.4

Masitinib (AB Science) is an oral phenylaminothiazole-type tyrosine kinase inhibitor (TKI) that selectively targets the wild-type and mutated forms of c-Kit, platelet-derived growth factor receptor (PDGFR) alpha/beta, Lyn tyrosine kinase, and fibroblast growth factor receptor 3 (FGFR)3.8 Inhibition of the c-Kit pathway reduces histamine levels and mast cell infiltration. A high mast cell count is usually associated with a poor prognosis in patients with CRC.9

A small, open-label, phase 1b/2 trial investigated the efficacy of masitinib plus FOLFIRI in 36 patients with non-resectable mCRC after progression on first-line treatment. Half of the patients had KRAS mutation status. After a median follow-up period of 22.8 months, median OS was 17.6 months and median PFS was 6.2 months. The overall response rate was 28%.10

This study was followed by a phase 3, randomized, double-blind trial of masitinib plus FOLFIRI as second-line treatment in an estimated 550 patients (18 years of age and older) with non-resectable mCRC who had progressed after standard chemotherapy. Control patients in this ongoing trial are receiving FOLFIRI and placebo. The primary outcome measure is OS. The study began in January 2014, and the estimated completion date is June 2018.11

A major drawback to this investigation is that FOLFIRI is being used as...
Cancer stem cells possess the property of "stemness"—the ability to self-renew and differentiate into heterogeneous cell lineages. This allows the stem cells to act like seeds, causing a patient's cancer to relapse or metastasize. In cancer cells. This allows the stem cells to maintain cancer stemness. High STAT3 expression has been associated with a poor prognosis in CRC patients. The clinical efficacy of napabucasin plus panitumumab was evaluated in a small phase 1b/2 trial involving 24 patients with advanced KRAS wild-type mCRC. Disease control (stable disease [SD] plus partial response [PR]) was observed in four of nine (44.4%) anti-EGFR-naïve patients. Of those nine patients, two (22%) had PR (35.5% and 33.3% regressions), and two had SD. Disease control (SD only) was observed in eight (53.3%) of 15 patients who had failed anti-EGFR (cetuximab) therapy, two of whom had SD with regression (12.9% and 6.8%). Median FFS was 9.0 weeks and 16.4 weeks in anti-EGFR–naïve and previously exposed patients, respectively. An ongoing phase 3 trial, CanStem303C, is evaluating napabucasin in combination with the FOLFIRI regimen as second-line therapy in patients with mCRC. In this international, open-label, prospective, randomized study, an estimated 1,250 patients will be treated with napabucasin plus standard biweekly FOLFIRI or with standard biweekly FOLFIRI alone for three years. The primary outcome measure is OS. The study began in June 2016 and is expected to conclude in June 2019. The anticipated U.S. product launch date is 2020.

If napabucasin is approved, it is expected to be the first cancer stem cell inhibitor in the CRC marketplace.

**IMMUNOTHERAPIES**

Atezolizumab (Tecentriq, Genentech/Roche), a programmed death ligand-1 (PD-L1)–blocking antibody, is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) or metastatic non–small-cell lung cancer (NSCLC). It was the first approved PD-L1–targeted immunotherapy.

### Table 1 Promising Drugs in Phase 3 Development for Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Drug Developer</th>
<th>Therapeutic Class</th>
<th>Targeted Indication</th>
<th>Expected Pricing Strategy</th>
<th>Anticipated U.S. Launch Date</th>
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<tr>
<td><strong>Molecular-Targeted Agents</strong></td>
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<tr>
<td>Encorafenib (LGX-818) + Binimetinib (MEK-162) Array Biopharma</td>
<td>BRAF inhibitor/ MEK1/2 inhibitor</td>
<td>Second-line treatment in BRAF-mutant mCRC patients in combination with cetuximab (Erbilux, Lilly)</td>
<td>Likely to be priced at 5% discount to vemurafenib (Zelboraf, Genentech) + cobimetinib (Cotellic, Genentech) + dabrafenib (Tafinlar, Novartis) + trametinib (Mekinist, Novartis), whichever is lower</td>
<td>2020</td>
</tr>
<tr>
<td>Masitinib (AB-1010) AB Science</td>
<td>Tyrosine kinase inhibitor</td>
<td>Second-line treatment in mCRC patients who have progressed after standard chemotherapy</td>
<td>Likely to be priced similarly to imatinib (Gleevec, Novartis) and sunitinib (Sutent, Pfizer)</td>
<td>2019</td>
</tr>
<tr>
<td>Napabucasin (BBI-608) Boston Biomedical/ Sumitomo Dainippon Pharma</td>
<td>Small-molecule cancer stem cell stemness inhibitor</td>
<td>Second-line treatment in mCRC patients in combination with FOLFIRI regimen (5-fluorouracil, leucovorin, and irinotecan), with or without bevacizumab (Avastin, Genentech)</td>
<td>Likely to be priced similarly to imatinib and sunitinib</td>
<td>2020</td>
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<tr>
<td><strong>Immunotherapies</strong></td>
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<tr>
<td>Atezolizumab (Tecentriq) Genentech/Roche</td>
<td>Anti–PD-L1 monoclonal antibody</td>
<td>Third-line treatment for mCRC as monotherapy or in combination with cobimetinib (Cotellic, Genentech)</td>
<td>Likely to be priced in line with its pricing for UC and NSCLC</td>
<td>2020</td>
</tr>
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</table>

dMMR = mismatch repair-deficient; mCRC = metastatic colorectal cancer; MSI–H = microsatellite instability–high; NSCLC = non–small-cell lung cancer; PD-1 = programmed death receptor 1; PD-L1 = programmed death ligand-1; UC = urothelial carcinoma.

The comparator treatment, whereas the second-line standard of care for mCRC in Western countries is either an anti-VEGF monoclonal antibody (mAb) or an anti-EGFR mAb, with or without chemotherapy. Therefore, efficacy data from this trial are likely to meet some resistance in the United States.

If approved by the FDA, the masitinib/FOLFIRI combination is expected to be launched in 2019. Masitinib is also being investigated as a third- and fourth-line treatment for CRC in phase 2 studies. Napabucasin (Boston Biomedical/ Sumitomo Dainippon Pharma) is an oral agent designed to inhibit cancer stemness pathways by targeting signal transducer and activator of transcription 3 (STAT3). Cancer stem cells possess the property of "stemness”—the ability to self-renew and differentiate into heterogeneous cancer cells. This allows the stem cells to act like seeds, causing a patient’s cancer to relapse or metastasize. In preclinical studies, the STAT3 pathway was identified as an important pathway for maintaining cancer stemness. High STAT3 expression has been associated with a poor prognosis in CRC patients. The clinical efficacy of napabucasin plus panitumumab was evaluated in a small phase 1b/2 trial involving 24 patients with advanced KRAS wild-type mCRC. Disease control (stable disease [SD] plus partial response [PR]) was observed in four of nine (44.4%) anti-EGFR-naïve patients. Of those nine patients, two (22%) had PR (35.5% and 33.3% regressions), and two had SD. Disease control (SD only) was observed in eight (53.3%) of 15 patients who had failed anti-EGFR (cetuximab) therapy, two of whom had SD with regression (12.9% and 6.8%). Median FFS was 9.0 weeks and 16.4 weeks in anti-EGFR-naïve and previously exposed patients, respectively.
Bendell and colleagues conducted a phase 1b study of atezolizumab combined with the MEK inhibitor cobimetinib (Cotellic, Genentech) in 23 patients with CRC (22 with KRAscopy-mutant disease and one with wild-type CRC). Three responses were ongoing at the time of data cutoff (range, 4.0–7.7 months). Results from a serial-biopsy cohort showed enhanced PD-L1 upregulation, CD8 T-cell infiltration, and major histocompatibility complex I expression during treatment, providing a mechanistic rationale for combining atezolizumab and cobimetinib.

The ongoing phase 3 COTEZO trial is investigating atezolizumab as third-line therapy—either as monotherapy or in combination with cobimetinib—in an estimated 360 patients with mCRC. The study’s active comparator is regorafenib (Stivarga, Bayer), a receptor TKI, and the primary endpoint is OS. The study was initiated in July 2016 and is scheduled to be completed in April 2019. If approved for mCRC, atezolizumab is expected to be launched in 2020.

Pembrolizumab (Keytruda, Merck) is a programmed death receptor-1 (PD-1)-blocking antibody indicated for patients with unresectable or metastatic melanoma; metastatic NSCLC; or recurrent or metastatic head-and-neck squamous cell carcinoma. A small phase 2 study in mCRC patients found that pembrolizumab was more effective in those with DNA mismatch repair (MMR)-deficient disease than in those with MMR-proficient disease. The objective response rate and the PFS rate were 40% (four of 10 patients) and 78% (seven of nine patients), respectively, for MMR-deficient colorectal cancers and 0% (none of 18 patients) and 11% (two of 18 patients) for MMR-proficient cancers. Similarly, median PFS and median OS were not reached in the cohort with MMR-deficient disease but were 2.2 months and 5.0 months, respectively, in the cohort with MMR-proficient disease (hazard ratio [HR] for disease progression or death, 0.10 [P < 0.001]; HR for death, 0.22 [P = 0.05]).

In November 2015, Merck initiated a phase 3, open-label, randomized study (KEYNOTE-177) comparing pembrolizumab with the standard of care (i.e., bevacizumab or cetuximab in combination with FOLFOX or FOLFIRI) as first-line treatment in an estimated 270 patients with microsatellite instability-high (MSI-H) or MMR-deficient mCRC. The study’s primary endpoint is PFS. The projected completion date is September 2019.

Pembrolizumab is the only phase 3 pipeline drug currently being investigated as first-line therapy for mCRC patients. Based on early-stage results, pembrolizumab is expected to be launched in 2020 as monotherapy for patients with MSI-H or MMR-deficient mCRC in second- and third-line settings. Analysts anticipate that the product’s label will be expanded to include first-line treatment in 2020.

### BIOSIMILARS

The U.S. patent for bevacizumab—one of the standard-of-care treatments for mCRC—will expire in 2019, opening the way for biosimilar competitors. In addition to mCRC, bevacizumab is indicated for NSCLC, glioblastoma, metastatic renal-cell carcinoma, carcinoma of the cervix, and epithelial ovarian, fallopian tube, or primary peritoneal cancer. Several bevacizumab biosimilar products are in phase 3 development as first-line therapies for patients with NSCLC. Clinical data from this setting, however, may be extrapolated to any of the other reference product’s indications. Potential bevacizumab biosimilars are listed in Table 2.

<table>
<thead>
<tr>
<th>Drug Developer</th>
<th>Primary Completion Date</th>
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<tbody>
<tr>
<td>ABP-215</td>
<td>July 2015</td>
</tr>
<tr>
<td>Agen/Allergan</td>
<td></td>
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<tr>
<td>BI-659902</td>
<td>August 2017</td>
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<tr>
<td>Boehringer Ingelheim</td>
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<tr>
<td>FKB-238</td>
<td>June 2019</td>
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<tr>
<td>Centus Biotherapeutics</td>
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<tr>
<td>PF-06439535</td>
<td>July 2017</td>
</tr>
<tr>
<td>Pfizer</td>
<td></td>
</tr>
<tr>
<td>SB-8 Samsung Bioepis</td>
<td>June 2018</td>
</tr>
</tbody>
</table>

### REFERENCES


