CHAPTER 16
Systemic treatment according to the tumor stage

Stage II

Better progression -free survival and OS have been demonstrated in patients in stage II and stage III treated with fluoropyrimidine-based adjuvant chemotherapy compared to those treated with surgery only.[1–4]

The Quasar study randomized 3238 patients in stage III treated with chemotherapy based on 5FU vs. observation, finding only one tendency towards a better 5 -year OS (83.9 vs. 81.5%, respectively).[5] The Impact B2 study found a small but not statistically significant improvement in DFS and OS at 5 years with the adjuvant treatment.[6]

On the other hand, Cancer Care Ontario found a small but significant improvement (5-10%) in DFS.[7]

In 2004, an expert panel of the American Society of Cancer Oncology (ASCO) concluded that the evidence does not support the routine use of adjuvant chemotherapy for colon cancer in stage II.

The Intergroup included data from 3302 patients with stage II and stage III colon cancer from 7 randomized trials comparing surgery and 5FU vs. surgery alone. For stage IIdisease, there was a statistically significant improvement in 5-year DFS in favor of chemotherapy (76% vs. 72%), but there was no statistically significant improvement for OS (81% vs. 75%).[8]

The Accent group analyzed a group of patients with stage II over the long term, finding that adjuvant chemotherapy was associated with a 5% absolute improvement in OS at 8 years (72 vs. 66.8%).[1–3]

According to ASCRS, there is controversy regarding the treatment of all patients with stage II, so they have been classified as low and high risk based on 5-year DFS, which reaches 90% in patients with well-differentiated T3 tumors and 74% in those with poorly differentiated T4b tumors.[9] Most evidence suggests that there is minimal benefit from adjuvant chemotherapy in patients with low-risk stage II colon cancer

The MOSAIC trial initially demonstrated that the addition of OXA to patients with high-risk stage II was beneficial. However, a recent analysis of this same trial did not demonstrate any benefit with OXA, regardless of whether the patient was in high- or low-risk stage II.[10]

In general, the prognosis of patients with stage II is better than that of patients with stage III. However, subgroups of stage II with MSI, deletion of chromosome 18q or elevation of CEA have been identified, with an aggressive biological behavior similar to or even worse than that of some stage III subgroups. In this subgroup of high-risk or poor-prognosis patients, the relative benefit of adjuvant treatment would be clearly superior.[11–14]

Patients with high-risk stage II colon cancer are defined as those with perforation, obstruction, lymph node count less than 12, positive resection margin, T4b, poor cell differentiation, lymphovascular or perineural invasion, high-grade tumor budding, with or without MSI.[13,14] These patients, with one or more of these factors present, have a similar risk of recurrence to patients with stage III and are currently considered for routine adjuvant chemotherapy, as it may offer a survival benefit. Evidence IIB.[1–3]

Stage II risk groups

There are major and minor clinical and pathologic factors that affect the time to recurrence of stage II colon cancer. The presence of major factors such as T4 (including perforation) and lymph node count less than 12 nodes increases the risk of recurrence, while other additional factors are less significantly associated. Surveillance is an option for low-risk stage II patients, but chemotherapy is recommended for those at intermediate and high risk. Level of evidence IB.[1–3,15]

Although the Gramont regimen with fluoropyrimidine and LV is the only one that has demonstrated efficacy in this scenario, Cape is also an option, especially when the use of central lines is contraindicated. Evidence IB.[1–3,15]

In the Japanese phase III SACURA study, tumor budding and histologic grade were independent prognostic factors in stage II. The budding score was significantly correlated with recurrence in the liver, lungs, lymph nodes, and peritoneum, so they recommend its evaluation in all cases. They also found that in patients with high tumor budding, the fluoropyrimidine monotherapy regimen was associated with improved relapse-free survival.[16,17]

In a retrospective study, Shin et al.[18] evaluated 1390 patients operated on between 2007 and 2013 for stage II colon cancer, defining high-grade tumor budding as the presence of $\geq$ 10 cellular nests. They found that 10.5% of those with high-grade tumor budding also had advanced T stage, poor cell differentiation, lymphatic invasion, and perineural invasion. There were no differences in 5-year OS, but DFS was lower in this group (81.3 vs. 93.5%; $p < 0.03$) and there was no benefit from adjuvant therapy. They concluded that high-grade tumor budding associated with vascular and perineural invasion, and adjuvant treatment were independent factors for worse prognosis.

In intermediate- and high-risk patients, there is a trend towards improved chemotherapy benefit with the addition of OXA. Evidence IB.[1–3]

The IDEA trial demonstrated that in the high-risk group the optimal duration of treatment with CAPOX regimen is 3 months and with FOLFOX 6 months.[19]

The presence of MSI/MMR indicates a better prognosis and less benefit from adjuvant therapy, so chemotherapy with OXA should be indicated with caution in this group.[11,20]

For ASCO, NCCN and ESMO, in high-risk stage II patients, poorly differentiated histology represents an adverse feature only if they do not have MSI and lack a BRAF mutation.[21]

The addition of aspirin reduces the risk of polyp formation and may improve survival in approximately 20% of patients with colon cancer. However, this claim remains under study in ongoing trials.

OXA in stage II

No study has achieved statistical power to consider the addition of OXA as standard in stage II, although this could be argued for high-risk groups. There is little evidence to support that patients considered high risk are more likely to benefit from chemotherapy than from surgery alone plus observation. The long-term results of the MOSAIC and NSABP studies did not demonstrate any clinical benefit of the addition of OXA to a 5FU regimen for the treatment of patients with colon cancer in stage II.[21,22]

MOSAIC compared adjuvant 5FU/LV for 6 months vs. FOLFOX in patients with stage II (40%) and stage III colon cancer (60%) and in an initial analysis the addition of OXA demonstrated a small but significant increase in 6-year OS (79 vs. 76%) limited to stage III patients. In stage II patients, 5-year DFS was not significantly longer with FOLFOX (84 vs. 80%) and 6-year OS was identical (87%).[10] In 2015, an updated analysis demonstrated a greater absolute OS benefit for OXA in stage III (57% vs. 59%) while FOLFOX demonstrated absolutely no survival benefit over 5 FU/LV for stage II (78% vs. 79%). This study suggests that patients

with high-risk stage II (e.g. T4b) might benefit from the addition of OXA with regard to DFS, although it is underpowered.[21]

NSABP C-07 compared the Roswell Park regimen (5FU/LV) vs. the FLOX regimen (5FU ± weekly infusional LV + biweekly OXA) for stage II and stage III. With 8-year follow-up, in stage III, the 5-year DFS significantly favored FLOX (69 vs. 64%), but the OS was not significantly different (80 vs. 78%). However, there was no benefit in stage II.[22]

Improvement in OS has been shown in high-risk stage II, but this benefit is limited to those patients with intestinal perforation, obstruction, T4 tumors or less than 12 nodes evaluated.[23]

Despite the lack of studies with sufficient evidence, major guidelines suggest considering the high-risk subgroup when deciding on adjuvant chemotherapy. FOLFOX and CAPOX remain the current standard of care for this group of patients. The FLOX regimen has a higher incidence of diarrhea and is therefore not currently considered. Irinotecan (Iri), cetuximab (Cetu) and bevacizumab (Bev) have not demonstrated clinical activity in localized disease and should therefore not be included in adjuvant treatment in this setting.[24–27]

In a 2010-2016 study of high-risk stage II patients (T4, perineural invasion, poor cell differentiation, and less than 12 nodes on histological analysis), 3 groups were evaluated: 1) without high-risk factors (18,056 patients), 2) with 1 factor (9,426 patients), and 3) with ≥2 factors (3,503 patients) and compared with 34,842 stage III patients. The 3- and 5-year survival rates were 59.1 and 68.1%, respectively, in stage III. In stage II without risk factors, it was 74.9 and 90.7%; with 1 risk factor, 67.1 and 82.4%; and with ≥ 2 factors, 49.2 and 59.5%, showing that this subgroup of stage II patients with multiple high-risk factors have a worse survival rate than those with stage III..[28]

Lymphatic, vascular, and perineural invasion are known to be prognostic factors for colon cancer. However, their prognostic significance based on the location of vascular invasion (intra- or extramural) in stage II remains unclear. This finding was evaluated in a cohort of 1130 patients who underwent radical surgery at Seoul National University Hospital between 2003 and 2015. The DFS and OS of patients with extramural invasion were significantly worse than those of patients without invasion or with intramural invasion. Multivariate survival analysis confirmed that extramural (as opposed to intramural) invasion is a highly significant independent prognostic factor associated with a worse prognosis in stage II colon cancer.[29]

Mucinous adenocarcinoma is a rare histological feature of CRC, with different oncological properties from adenocarcinoma. In a retrospective cohort study, 2532 patients in stage II and stage III were studied between 2010 and 2015. At 86 months, DFS and OS were significantly lower in the mucinous adenocarcinoma group. When evaluating subgroups, multivariate analysis demonstrated that mucinous adenocarcinoma was a poor prognostic factor for DFS and OS only in stage III patients. Therefore, in stage II patients, mucinous adenocarcinoma could not be considered an independent risk factor requiring chemotherapy for favorable oncological outcomes. However, for stage III colon cancer, patients with mucinous adenocarcinoma require close observation.[30]

Choice of chemotherapy régimen

The 5FU/LV regimen is the most commonly used. Cape is an option, although there are no data on the benefit of this drug in patients with stage II since the X-ACT study was conducted in patients with stage III.[31]

Some guidelines such as the NCCN, in patients with MSI or MSS (proficient DNA repair system, pMMR) tumors, recommend Cape alone as an alternative to FOLFOX or the 5FU/LV regimen. The FOLFOX regimen is an alternative to fluoropyrimidines for patients with high-risk stage II tumors with MSI (dMMR), since it can overcome the chemoresistance of these tumors.[32]

ESMO Recommendations:[1]

- In patients with low-risk stage II colon cancer, follow-up is recommended.
- In patients with intermediate-risk stage II colon cancer (MMR/MSS and any risk factor except pT4 or less than 12 nodes evaluated), a regimen with flouropyrimidine is recommended.
- Patients with high-risk stage II colon cancer (pT4 or less than 12 nodes, or with multiple intermediate risk factors, regardless of MSI), are candidates for treatment with OXA.
- In patients with high-risk stage II colon cancer, treatment with 3 months of CAPOX or 6 months of FOLFOX is recommended, according to the results of the IDEA study.

Fig. 16.1 outlines ESMO recommendations for adjuvant treatment of stage II colon cancer.

NCCN Recommendations:[32]

- Patients with T3-4N0M0, dMMR/MSI tumors should only be given observation.
- Patients with T3N0M0, MSS and no high-risk factors, should be given observation or consider fluopyrimidines for 6 months.
- Patients with T3N0M0, high-risk factors or T4N0M0 with stable MSS/pMMR tumors should be given a regimen with fluorpyrimidine, or OXA-based chemotherapy (CAPOX, FOLFOX) or observation without clarifying the duration of treatment.

Recommendations from Pan-Asian guidelines:[2,3]

- In patients with stage II colon cancer, clinical follow-up is recommended. Evidence IA.
- For stage II patients with intermediate risk and no MSI/MMR mutation associated with any of the risk factors except pT4 or evaluation of less than 12 lymph nodes, the recommended treatment is 6 months of fluoropyrimidines. Evidence IB.
- An acceptable alternative in patients in good general condition is treatment with 3 months of CAPOX.
- In patients with high-risk stage II, pT4, perforation, less than 12 evaluated lymph nodes, or multiple intermediate risk factors regardless of MMR status, given the high risk of relapse, the addition of OXA to the base regimen should be considered. Evidence IC.
- Patients with high-risk stage II can follow a 3-month CAPOX regimen according to the non-inferiority analysis of the IDEA study, or a 6-month FOLFOX regimen. Evidence IIB.

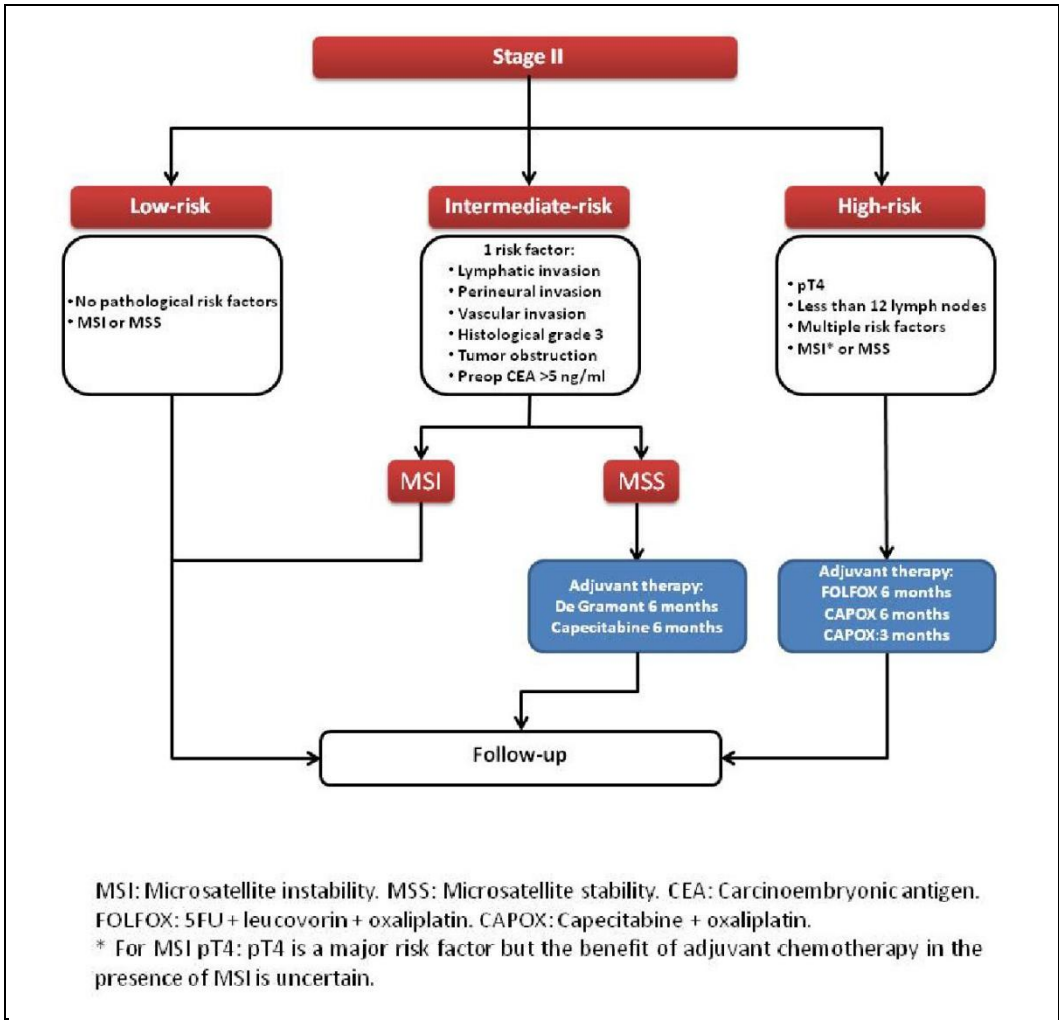


Figure 16.1. *Adjuvant treatment of stage II colon cancer recommended by ESMO.*

Stage III

In 1990, the NIH developed a consensus establishing adjuvant chemotherapy as the new standard of care for patients with resected stage III colon adenocarcinoma. This was based on a study showing that 5-year DFS in patients with positive lymph nodes was 44% with surgery alone vs. 61% when 5FU and levamisole were added, representing a 39% reduction in mortality ($p < 0.0001$).[1]

Levamisole was progressively replaced by LV (folic acid analog), a 5FU biomodulator with demonstrated clinical benefit in advanced disease. The NSABP conducted its C-03 study comparing 5FU + LV vs. MOF (semustine, vincristine, 5FU). The results showed superiority of the weekly 5FU/LV regimen with regard to DFS.[33]

Subsequently, the NSABP C-04 included 2151 patients with stage II and stage III, randomized into 3 groups: 5FU/LV, 5FU/LV/levamisole, and 5FU/levamisole. The 5-year DFS was 65% vs. 60% ($p = 0.04$), concluding that the addition of levamisole did not add benefit.[34] A similar finding was obtained by the INT-0089 Intergroup, concluding that the addition of levamisole does not add anything to the treatment. Therefore, 5FU/LV-based regimens are considered standard for adjuvant treatment in colon cancer.[35]

In patients with stage III colon cancer, adjuvant therapy is generally recommended. Evidence IA.[4]

In patients stage III, large multi-institutional studies have shown a survival benefit with OXA-based adjuvant chemotherapy. Cape is a safe and efficient alternative and can be used in combination with OXA (CAPOX).[1,4,27] In 2018, the International Duration Evaluation of Adjuvant Therapy collaboration (IDEA) published similar findings regarding outcome in patients with T1-T3 and N1 who received 3 or 6 months of OXA, with a 3-year DFS of 83%. However, in patients with T4 or N2, DFS was superior with 6 months of treatment.[19]

The current era of adjuvant therapy is based on studies that demonstrated benefit in OS by adding 5FU/LV to surgical treatment compared to surgery alone, with a 30% decrease in recurrence and 25-32% in mortality.

The current standard of care for adjuvant therapy in stage III is the combination of a fluoropyrimidine and OXA. This regimen is independent of MSI status. The significant DFS benefit of this combination over fluoropyrimidine monotherapy was demonstrated in three pivotal trials: MOSAIC, NSABP C-07 and NO16968.

In the MOSAIC study, the survival benefit (67 vs. 59%) was maintained at 10 years. The FOLFOX regimen was approved for adjuvant therapy of stage III colon cancer based on this study.[21]

The NSABP C-07 study randomized 2407 patients with stage II and stage III colon cancer, comparing a 5 FU/LV + OXA (FLOX) regimen vs. 5FU/LV for 6 months. With an 8-year follow-up, 5-year DFS favored the FLOX regimen

(69 vs. 64%), although the difference in OS was not statistically significant (80 vs. 78%).[36]

Study NO16968 compared 5 months of treatment with 5FU/LV (Roswell Park regimen) with CAPOX in 1886 stage III patients. At 74 months follow-up, both 7-year DFS (63 vs. 56%) and OS (73 vs. 67%) were significantly superior with CAPOX.[37]

NSABP C-07 used a bolus of fluoropyrimidine in both arms (5 FU/LV/Iri/OXA), whereas the XELOXA study used a bolus of fluoropyrimidine vs. a CAPOX regimen. The MOSAIC and NSABP C-07 studies included patients with colon cancer in stage II and stage III, whereas NO16968 included only stage III.

Although the chemotherapy regimens were different in the three studies, the addition of OXA resulted in a similar risk reduction (23% in MOSAIC and 20% in the other two studies). With long-term follow-up, all three trials demonstrated an improvement in OS with a reduction in the risk of death of 16% in MOSAIC, 12% in NSABP C-07, and 17% in NO16968. However, the improvement in OS was significant only in stage III.

In stage III colon cancer, CAPOX and FOLFOX regimens remain the current standard of care. The addition of Iri, Cetu, and Bev has not demonstrated relevant clinical significance in patients with localized cancer, so they should not be included in adjuvant treatment regimens in these cases. Evidence IE.[4]

Choice of chemotherapy regimen and treatment duration (IDEA Collaboration)

Cumulative sensory peripheral neuropathy toxicity is greater with 5FU + OXA. A 6-region, international, prospective, collaborative noninferiority study (IDEA) evaluated 12,834 patients with inflammatory bowel disease-associated colon cancer randomly assigned to receive 3 or 6 months of treatment with FOLFOX or CAPOX.[38]
According to the results of this study, the duration of treatment depends on the choice of regimen. In patients receiving the CAPOX regimen, 3-month treatment was non-inferior to 6-month treatment (3-year DFS 75.9 vs. 74.8%, respectively). In contrast, the 3-month FOLFOX regimen was definitely inferior (3-year DFS 73.6 vs. 76%). Therefore, non-inferiority was only demonstrated for a 3-month CAPOX regimen.

A subgroup analysis was also performed: lower risk (T1-T3 + N1) and higher risk (T4, N2, or both). For the higher risk subgroup, 3-month treatment was inferior.

After a follow-up of 72 months, 5-year OS was similar (82.4 vs. 82.8%). For low-risk patients, the difference in 5-year OS with 3 vs. 6 months of treatment was 89.6 vs. 88.9%, while for high-risk patients it was 72 vs. 74%. In patients treated with CAPOX, there was no significant difference in the 3- vs. 6-month regimen, but the results were inferior with 3 months of FOLFOX (5-year OS 68.4 vs. 71.7%).[19]

In the Asian ACHIEVE study, the HR for 3 months of treatment vs. 6 months of treatment was 1.07 for FOLFOX and 0.9 for CAPOX, similar to the findings of the IDEA study. This study recommends 3 months of CAPOX as the most appropriate therapy in low-risk stage III patients (T1-3 + N1).[39]

In conclusion, both the 3-month CAPOX regimen and the 6-month FOLFOX regimen can be recommended as adjuvant chemotherapy for patients with stage III colon cancer. Evidence IA.[1]

Fig. 16.2 outlines ESMO recommendations for adjuvant treatment of stage III colon cancer.

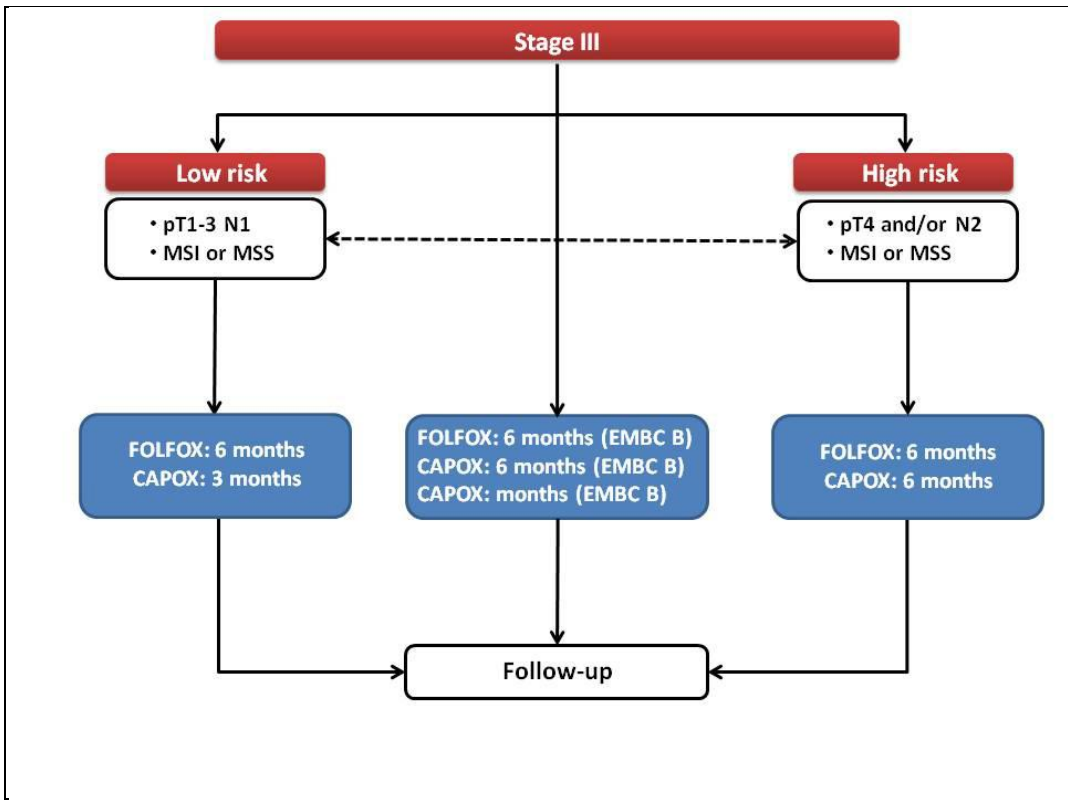


Figure 16.2. *Adjuvant treatment of stage III colon cancer recommended by ESMO.*

High and low risk groups in stage III

Although based on low-quality evidence, the IDEA study established high- and low-risk subgroups in EII. Evidence IVB.

In the low-risk subgroup (T1-T3 with N1), 3 months of adjuvant treatment would seem to be sufficient, when the CAPOX regimen is implemented. Evidence IIB.[4]

In the high-risk subgroup (T4, N2, or both), 6 months of treatment is necessary, especially when the regimen is FOLFOX, although the same is true for the CAPOX regimen. Evidence IIB.[1]

Final recommendations

- The combination of fluoropyrimidine, either 5FU or Cape, associated with OXA constitutes the basis for adjuvant treatment of EIII colon cancer. Evidence IA.
- The duration of OXA-based treatment can be 3 to 6 months for the CAPOX regimen and 6 months for the FOLFOX regimen, according to the evidence from the IDEA study. Evidence IA.
- Adjuvant treatment can be individualized by subgroups, with caution and strict analysis of each case: 3 months of CAPOX for T1-3 + N1, 6 months of CAPOX for any T4 or any N2, or 6 months of FOLFOX for any of these scenarios, according to the IDEA study.
- For patients unsuitable or intolerant to OXA, either Cape or 5FU/LV constitute acceptable regimens with a duration of 6 months. Evidence IA.
- It is important to start chemotherapy as soon as possible after surgery, ideally not later than 8 weeks. Evidence IA.

Stage IV

Adjuvant therapy in stage IV will be discussed in detail because it has multiple aspects related to resectability, the possibility of cure, conversion to resectable disease, and treatment aimed at controlling progression and symptoms.

Stage IV in colon tumors is associated with synchronous distant metastases in organs such as the liver, lung, peritoneum, brain, and lymph nodes not related to the primary tumor and in other less frequent organs (bone, spleen, adrenal glands). The incidence of synchronous metastases according to the Japanese Society registry[27] is shown in Table 16.1.

Table 16.1. Incidence of colon cancer metastasis by site. Registry of the Japanese Society for Cancer of the Colon and Rectum.[27]

Site of metastasis	Liver	Lung	Peritoneum	Bone	Brain	Virchow's lymph node	Other
%	11.8	2.2	5.7	0.3	0.01	0.1	1.3
N = 15391	1815	338	875	47	6	23	205

According to the ESMO 2023 guidelines, in general terms the strategy and planning of treatment for metastatic colon cancer can be summarized as follows (Fig. 16.3):[40]
- If both the primary tumor and distant metastases are resectable, curative resection of the primary tumor is indicated and resection of the metastases is considered.
- If the primary tumor is resectable but the metastases are unresectable, resection of the primary tumor is indicated based on the clinical picture and its impact on prognosis.
- If the primary tumor is unresectable and the metastases are resectable, another therapeutic option is considered instead of initial surgical resection.

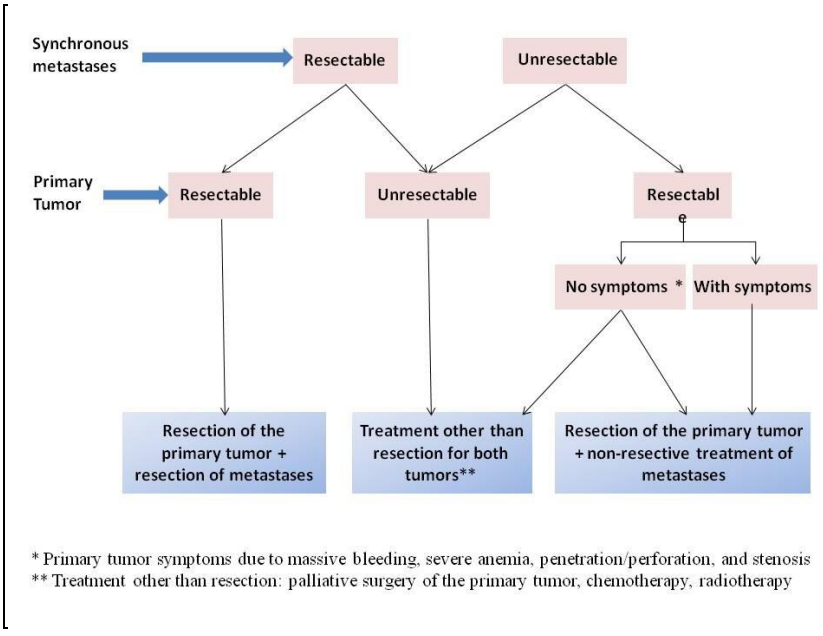


Figure 16.3. *Treatment strategies for metastatic colon cancer according to ESMO 2023 guidelines.*[40]

Stage IV resectable or potentially resectable

Before planning treatment, it is important to clearly distinguish resectable metastatic disease from that which can potentially be converted to resectable disease after preoperative chemotherapy. Conversion to resectable disease is based on the standard chemotherapy regimen with the combination of Bev or Cetu.

In patients with resectable lung or liver disease with curative intent, resection of the primary tumor should be considered, particularly in patients with good performance status,[4,41] This algorithm is summarized in Fig. 16.4.

The treatment of patients with stage IV colon cancer should be approached in a multidisciplinary context, as with most complex cases. Evidence IB.4 The multidisciplinary approach has been shown to increase the rate of metastasectomy and improve survival in patients with stage IV colon cancer.[40]

Patients with resectable liver metastases can be treated with neoadjuvant chemotherapy followed by surgical resection or initial surgery, depending on the type of metastasis and the experience of the team. Evidence IIB.[4] According to ESMO, if the liver metastasis is resectable, it should be resected after confirming radical excision of the primary tumor. Resection of the primary tumor and the metastases can be performed simultaneously or synchronously depending on the difficulty and complexity of the liver resection. If the complexity is greater, the recommendation is metachronous resection. There is still controversy about whether resection has an impact on the prognosis of the disease depending on whether it is simultaneous or deferred. [4,40]

In patients with resectable metastases, favorable prognostic criteria, and good surgical approach, systemic perioperative treatment may not be necessary. Evidence IIB.[4]

In left colon tumors with wild type (KRAS-wt) or non-mutated KRAS, conversion chemotherapy should be indicated when the goal is R0 resection. A perioperative regimen based on OXA, associated with anti-EGFR monoclonal antibodies, is recommended. Evidence IIA.[4]

In patients with right colon cancer and/or mutated KRAS, the FOLFIRINOX regimen, also called FOLFOXIRI (5FU/LV + OXA + Iri), associated with Bev should be considered as the best treatment option. Evidence IA.[4]

The role of systemic chemotherapy in the setting of resectable liver metastases was evaluated in the EORTC 40983 trial in patients with up to 4 resectable liver metastases. They randomized treatment with surgery alone vs. 6 cycles of neoadjuvant FOLFOX, followed by metastasectomy and then 6 cycles of adjuvant therapy with the same regimen. Complications of liver resection were higher (25 vs. 16%) in the chemotherapy arm. At 3 years, there was a 7% higher progression-free survival (35 vs. 28%) in the perioperative chemotherapy arm. With a follow-up of 8.5 years, 5-year OS did not differ significantly between the two groups (51 vs. 48%). Based on evidence of improved disease-free progression with perioperative chemotherapy, the investigators recommend this approach.[41]

Current NCCN guidelines recommend two approaches for patients with resectable synchronous or metachronous liver metastases from colon cancer: initial surgery, or neoadjuvant therapy followed by surgery and then adjuvant therapy.[32]

According to ESMO, the initial recommendation for patients with oligometastatic disease is to perform systemic treatment and then assess response. If the disease is progressive, assess whether to continue with systemic treatment or perform local treatment of the metastases. If there is response to systemic treatment, continue with local treatment of the metastasis.[40]

The decision to perform a single or combined procedure should be individualized. In patients with resectable liver metastases, combined single-stage surgery is recommended if possible for relatively low-complexity cases and sequential or staged surgery for more complex cases. Evidence 2B.[4]

A multicenter study that included 475 staged procedures and 135 combined surgeries demonstrated that the addition of minor liver resection to colon resection surgery did not result in increased severe morbidity (12.5 vs. 14.5%). However, the addition of major liver resection resulted in increased severe morbidity compared with major liver resection surgery alone (36 vs. 15%), with major hepatectomy being an independent predictor of severe morbidity.[42]

In 2015, a US National Surgical Quality Improvement Program (NSQIP) study provided evidence in favor of combined surgery for relatively low-complexity cases and staged surgery for more complex cases. In this study, cumulative postoperative morbidity was 25% for low-risk colectomy (right colectomy) combined with low-risk hepatectomy (left hepatectomy) and 39% for high-risk colectomy (total colectomy) combined with high-risk liver resection (right hepatectomy).[43]

In a recent retrospective study of 145 simultaneous vs. 53 staged surgeries, morbidity was comparable in both groups, even in the group undergoing major liver resection. Total hospital stay was significantly shorter for simultaneously resected patients, suggesting that simultaneous resections may be safe even in complex cases and should be performed at referral centers with extensive experience in colon cancer surgery and major liver surgery.[44]

Schubert et al.,[43] found that the mortality of synchronous resection increases as the risk of a complex colectomy and a major hepatectomy increases by up to 5%. Clearly, the lowest mortality rate is given by a minor hepatectomy associated with a low-risk colectomy. Reverse surgery (initial approach to the metastases and later to the primary tumor) is indicated in patients with significant liver disease and asymptomatic primary tumors (without intestinal obstruction).

Barros Scheloto,[45] in his conference on hepatic metastases of colonic origin offered at the Asociación Argentina de Cirugía, recommended to discriminate each case according to the form of presentation of the colon tumor (with or without symptoms) and the resectability of the metastases, in order to decide on the course of action. Considering these elements, 4 scenarios may arise to decide on the treatment of synchronous liver metastasis:

1) Symptomatic colon cancer with resectable metastasis: it is surgical at the start.
2) Symptomatic colon cancer with unresectable metastasis: it is not surgical.
3) Asymptomatic colon cancer with unresectable metastasis: it is not surgical.
4) Asymptomatic colon cancer with resectable metastasis: it could be surgical at the start.

Seen from another perspective, according to the same author, both liver and colon surgery can be high or low risk and there are also 4 scenarios:

1) Low-risk colon surgery with low-risk liver surgery: synchronous resection is possible
2) High-risk colon surgery but with low-risk liver surgery: attempt resection
3) Low-risk colon surgery but high-risk liver surgery: synchronous surgery is not possible.
4) High-risk colon surgery and high-risk liver surgery: synchronous surgery is contraindicated.

The NSQIP review reported mortality from synchronous colorectal liver resections according to the extent of colonic and liver resection:[43]

- Low-risk colectomy and minor hepatectomy: 1.4%
- High-risk colectomy and minor hepatectomy: 0.9%
- Low-risk colectomy and major hepatectomy: 3.4%
- High-risk colectomy and major hepatectomy: 5%

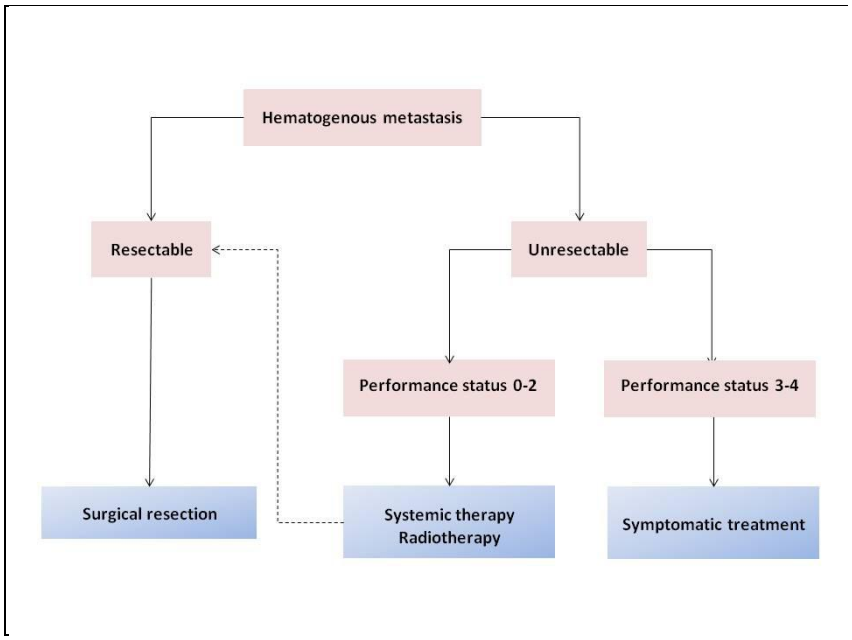


Figure 16.4. *Therapeutic approach to hematogenous metastases*

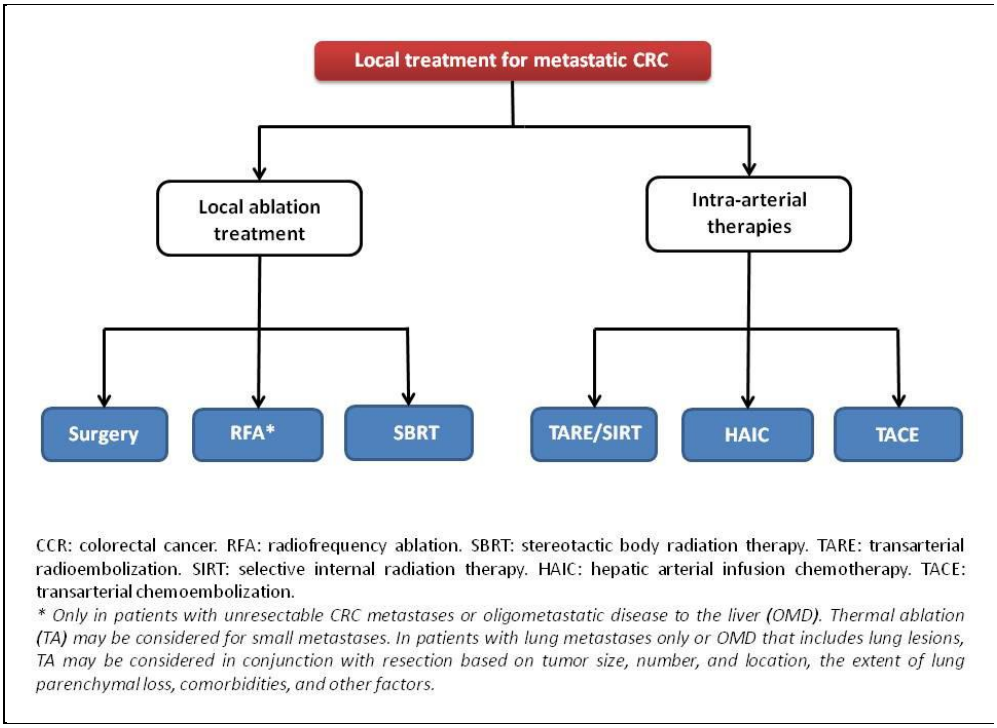
Initial unresectable liver metastases

Patients with colon cancer and initially unresectable liver metastases should be considered for neoadjuvant chemotherapy to attempt to convert them to a resectable state. Evidence IB 3.[40]

A 2017 systematic review and meta-analysis of 11 studies demonstrated that neoadjuvant therapy with 5FU combined with OXA (FOLFOX) or Iri (FOLFIRI) combined with Bev achieved conversion in 39% (27-53%) of patients with colon cancer with initially unresectable liver metastases and in these converted patients R0 could be achieved in 28% (18-41%) of cases.[24]

Neoadjuvant treatment with FOLFOX, FOLFIRI, or FOLFIRINOX plus Bev or Cetu for KRAS-wt tumors resulted in a 55-85% response, a 10-61% conversion to resectable tumors, and an R0 of up to 54%.[3,40]

In addition to systemic chemotherapy and immunotherapy, other approaches exist to increase the resectability of liver metastases, such as systemic chemotherapy combined with hepatic artery infusion chemotherapy. Level of evidence IB (Fig. 16.5).[40]



CCR: colorectal cancer. RFA: radiofrequency ablation. SBRT: stereotactic body radiation therapy. TARE: transarterial radioembolization. SIRT: selective internal radiation therapy. HAIC: hepatic arterial infusion chemotherapy. TACE: transarterial chemoembolization.

** Only in patients with unresectable CRC metastases or oligometastatic disease to the liver (OMD). Thermal ablation (TA) may be considered for small metastases. In patients with lung metastases only or OMD that includes lung lesions, TA may be considered in conjunction with resection based on tumor size, number, and location, the extent of lung parenchymal loss, comorbidities, and other factors.*

Figure 16.5*. Therapeutic strategies in metastatic colon cancer recommended by ESMO.*[40]

Lung metastases

In patients with resectable colon cancer and lung metastases, resection of lung metastases should be considered because it may prolong survival. Evidence IIB.[4]

A Japanese national study of 553 patients reported a 5-year recurrence-free survival of 80% and 68% for patients undergoing segmentectomy or wedge resection.[46]

In the Spanish national registry of 522 patients, DFS and specific survival were 28 and 55 months, with better outcomes in those treated with major lung resections and lymphadenectomy.[47]

The Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) cohort study randomized patients with resectable lung metastases comparing surgical vs. nonsurgical treatment and reported an OS of 3.5 vs. 3.8 years, so nonsurgical treatment should also be considered in these patients.[48]

Stereotactic radiation therapy (SBRT) could also be considered in these cases, but is less effective than resection in terms of disease-free progression and OS.[3,40]

According to ESMO, if the lung metastasis is resectable, its resection should be considered after resection of the primary tumor. Delayed resection is generally the usual approach.[40]

Peritoneal metastases

The risk of peritoneal metastasis after an advanced tumor is approximately 30%. Patient survival without treatment is 5 months and with systemic treatment between 5 to 12 months.49 Twenty-five percent of patients with metastatic disease will have disease limited to the peritoneum.[50]

According to the ASCRS, in patients with resectable colon cancer and peritoneal metastases, cytoreductive surgery with or without intraperitoneal chemotherapy should be considered after a complete multidisciplinary decision. Evidence IB.[4]

In this group of patients, initial treatment includes systemic chemotherapy, with or without resection of peritoneal involvement, with or without intraperitoneal chemotherapy.

Systemic therapy based on modern chemotherapy agents and targeted biological therapy has improved the course of carcinomatosis associated with CRC, with an average survival of 16 to 24 months. Five-year survival with OXA-based therapy is less than 5% and there is minimal benefit with the addition of Bev.[51,52]

The surgical approach includes the combination of cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin C or OXA, with or without hyperthermia. The first randomized trial of cytoreduction plus HIPEC vs. standard systemic OXA demonstrated an improvement in OS for the first group. After a median follow-up of 21.6 months, the median survival was 22.3 months in the experimental group vs. 12.6 months in the control group (log rank test, $p = 0.032$).[53]

The COLOPEC study evaluated cytoreduction plus HIPEC as adjuvant therapy in patients with high-risk primary tumors. Patients with clinical or pathological T4N0-2M0 tumors or perforated colon cancer were randomly assigned to an experimental cytoreduction plus HIPEC arm vs. a standard systemic chemotherapy control arm. After 5 years of follow-up, there were no differences in OS (69.6 vs. 70.9%, log-rank; $p = 0.692$), or in DFS (55.7 vs. 52.3%, log-rank; $p = 0.875$).[54] Current guidelines state that there is insufficient evidence to recommend HIPEC in these situations.

In 2021, the multicenter randomized controlled trial PRODIGE-7 analyzed 132 patients with cytoreductive surgery vs. 133 patients with cytoreduction plus HIPEC and reported more adverse events after HIPEC, with no benefit in OS, with 41 to 42 months in both arms.[55] However, there was a favorable difference in OS in the subgroup of patients with PCI (peritoneal carcinomatosis index) of 11 to 15.

The 2020 Chicago consensus, based on this study, recommended preoperative systemic therapy, with or without the addition of immunotherapy for MSI-H tumors, in high-risk patients and initial cytoreductive surgery, with or without the use of intraperitoneal chemotherapy, in low-risk patients.[56]

Complete resection is recommended when the tumor is easily resectable. ESMO recommends complete cytoreductive surgery. The addition of HIPEC should only be considered in experimental studies. There is no current recommendation in this regard.[40]

Distant lymphatic metastases

The treatment of distant lymphatic metastases remains controversial, as there are no comparative trials demonstrating therapeutic benefit. However, in recent years, resection of metastatic para-aortic lymph nodes has been linked to a potential improvement in long-term survival and radical treatment of the disease.

Metastasis in other sites

Although reports have been published on the resection of multiple metastases in other sites, such as bone, brain, spleen, etc., there are no clear benefits in survival.

In the case of multiple metastases that usually involve the liver and lung, resection should be considered if it is possible to remove the primary tumor.

Given the high rate of recurrence after radical surgical treatment, adjuvant chemotherapy is recommended.

Author's comment

Strategies and techniques for the treatment of distant metastases (liver, lung, etc.) constitute a chapter in themselves, so this report will not address these aspects. In fact, the treatment of metastatic involvement of each organ separately could be considered as a topic for a future report.

Biomarkers

The molecular classification of patients with colon tumors has therapeutic implications. The genes involved include: KRAS, BRAF V600 E, MMR, Her2.

KRAS/NRAS gene

KRAS/NRAS gene mutations are detected in approximately 40-50% of patients with unresectable or metastatic colon tumors. There is a high concordance between the characteristics of the primary tumor and synchronous metastases, while in metachronous metastases the discordance can reach 20%. The most common mutation is that of exon 2 (in codons 12 and 13) of the KRAS gene.

Anti-EGFR antibody therapy such as Cetu and panitumumab (Pani) has been reported to be ineffective in tumors with these mutations. For this reason, it is recommended that this mutation be determined prior to first-line therapy for patients who are to receive systemic treatment.[32]

There is specific therapy aimed at this mutation, such as the use of sotorasib, with a progression-free survival of 4 months and follow-up at 12 months.57 Another option is the combination of Cetu with adgrasib, which improves the response rate and disease control, all in phase II studies.[58]

BRAF V600E gene

The BRAF gene mutation is detected in approximately 5-10% of patients with unresectable colon tumors. The most frequent mutation is in codon 600 (V600E, valine for

glutamic acid). This mutation is more frequent in right colon tumors and has a tendency to peritoneal dissemination. It is associated with smoking and is a poor prognostic factor. Mutations in other codons may have a better prognosis. The use of anti-EGFR (Pani, Cetu) alone does not confer an adequate response.

According to the Tribe study, in a subgroup of patients, first-line therapy with FOLFOXIRI plus Beva was superior for mutations in this gene. The use of 2 or 3 lines of treatment for mutated BRAF V6000E results in longer OS, higher progression-free survival and pathological response rate, all at the expense of higher toxicity, which for triple therapies is around 60%.[59]

In patients with BRAF-mutated metastatic colon cancer, NCCN currently recommends the combination of encorafenib plus Cetu. It is also recommended to test for this mutation in patients with dMMR and in those with suspected Lynch syndrome.[32]

MMR genes

MMR (dMMR) deficiency, or deficiency of DNA repair proteins, is seen in Lynch syndrome patients carrying a germline mutation of genes associated with MMR proteins and also in sporadic colon cancer caused by acquired methylation of the MLH1 gene.

Testing for dMMR includes analysis of microsatellite instability (MSI) and immunohistochemistry for MMR proteins. There is a high rate of concordance between positive MSI and MMR protein testing by immunohistochemistry.

MSI is recognized in approximately 5% of patients with unresectable colon cancer. There is no established specific systemic therapy for these patients with dMMR. Under these circumstances, treatment regimens are similar to those indicated for patients with sporadic colon tumors. Recently, the efficacy of anti-PD-1 antibody therapy such as pembrolizumab (Pembro) and nivolumab (Nivo) was reported in this subgroup of patients.[3,4,40]

HER-2 gene

HER-2 overexpression or amplification occurs in 5% of patients with CRC and is determined by immunohistochemistry. It is associated with non-mutated RAS/BRAF-wt, with expression being less than 1% in mutated patients. It is more frequent in tumors of the left colon.

In this group of patients, there are multiple phase II studies evaluating the response rate (30 to 40%) with drugs such as trastuzumab, lapatinib, pertuzumab and tucatinibe.[3,4,40]

Stage IV unresectable

In patients with incurable colon cancer, the goals of planning should be symptom control and quality of life. Palliative therapy consists of initial systemic chemotherapy, or palliative surgery for intractable bleeding or obstruction, including colectomy, ablative procedures, and definitive ostomy.

In these cases, the goal of adjuvant systemic therapy is to prolong life and control symptoms associated with the tumor, delaying disease progression. Individualized treatment of these patients should be considered based on life expectancy.

In patients without any type of systemic therapy, the median survival is approximately 8 months. Recently, systemic therapy has increased survival to 30 months..[60,61]

In patients with incurable stage IV colon cancer and asymptomatic primary tumor, initial systemic chemotherapy is recommended. Evidence IB.4

The choice of strategy depends on the primary objective, i.e. tumor shrinkage or control of progression, clinical presentation of the tumor and its characteristics, presence or absence of metastases and their location, progressive or non-progressive nature of the disease, RAS gene status, patient-related factors (very symptomatic or asymptomatic disease, presence of comorbidities) and possibility of conversion with successful systemic therapy.

Randomized controlled trials in patients with good performance status demonstrate that systemic therapy is associated with significantly longer survival times.[62,63]

For patients without severe comorbidities and with good performance status, considered tolerant to first-line therapy, the first choice is a regimen containing OXA or Iri (FOLFOX, FOLFIRI or CapeOx) associated with monoclonal antibodies based on genetic determination. Patients with severe comorbidities or inadequate performance status are vulnerable or inappropriate for intensive systemic therapy and are considered intolerant to first-line therapy.

In patients considered appropriate for systemic therapy, determination of RAS (KRAS/NRAS) and BRAF (V600) mutations should be performed before the start of first-line therapy.

Cetu and Pani are monoclonal antibodies that act by binding to the epidermal growth factor receptor tyrosine kinase (EGFR). They are only indicated for patients with non-mutated KRAS/NRAS-wt.

Bev is a monoclonal antibody that binds to a protein called vascular endothelial growth factor (VEGF) and is indicated for patients with mutated KRAS/NRAS. Pani is indicated for patients with high-frequency microsatellite instability (MSI H).

The Tribe study demonstrated the superiority of the FOLFOXIRI + Bev regimen over the FOLFIRI + Bev regimen, with respect to progression-free survival and response rate.[59]

The OLIVIA trial demonstrated that FOLFOXIRI + Bev improved R0 resection compared with FOLFOX + Bev in patients with unresectable colon cancer and liver metastases.[59,62]

For patients not amenable to intensive systemic therapy, NCCN guidelines added the anti-PD-1 (anti-programmed death) checkpoint inhibitor antibodies Nivo and Pembro, especially for dMMR or MSI-H disease.[32]

In patients with incurable stage IV colon cancer and asymptomatic primary tumor, controversy exists regarding management. An argument in favor of initial nonsurgical treatment was prospectively evaluated using initial therapy with FOLFOX and Bev. At 21 months of follow-up, 14% of patients experienced primary tumor-related morbidity and only 12% required surgery, with obstruction being the most common cause. The probability of requiring unplanned surgery at 6 to 12, 12 to 24, and > 24 months was 8.1, 6.7, and 5.3%, respectively.[64] Risk factors for unplanned surgery were female sex, left-sided tumors, and young patients.[63]

In 2021, a study of 165 patients demonstrated no survival benefit when comparing resection of the symptomatic primary tumor with chemotherapy. OS was 26 months in the group with initial surgery vs. 26.7 months in the group with chemotherapy.[65]

In contrast, there is insufficient evidence to indicate early surgery. This comes from a single-center retrospective study published in 2016 and a 2019 meta-analysis. Both concluded that resection of the primary tumor is associated with better survival compared to chemotherapy, although it has higher morbidity.[3,40]

Thus, based on the existing evidence, the most important argument is to indicate initial chemotherapy, evaluate response, estimate prognosis and re-evaluate in a multidisciplinary context. Two ongoing prospective studies (CAIRO 4 and GRECAR 8) may clarify the management to follow in these patients.

In patients with obstructive colon cancer and incurable metastases, when life expectancy is less than one year, endoscopic decompression or diverting colostomy is preferred over colectomy. Evidence IB.[4] In this group of patients, endoscopic decompression has been shown to have

lower mortality, fewer permanent ostomies and a shorter interval to start chemotherapy, with no difference in survival. Likewise, the stent was associated with a shorter hospital stay when compared to surgery, although reinterventions at one year were more frequent in the stent group and readmissions were similar in both groups.

In case of tumor growth through the stent, the replacement of a new one has been shown to be safe and effective in most patients.

There is evidence of a higher perforation rate in patients with stents treated with Bev compared with those treated with standard chemotherapy (12% vs. 7%).[3,40]

Table 16.2 shows the chemotherapy regimens for unresectable colon cancer recommended by different international guidelines.

Table 16.2. Comparison of chemotherapy regimens for unresectable colon cancer recommended by different major guidelines.

Japonese Guidelines[27]	NCCN[32]	ESMO[40]
Intensive chemotherapy		
FOLFOX+Beva	FOLFOX+Beva	FOLFOX+Beva
CapeOX+Beva	CapeOX+Beva	CapeOX+Beva
FOLFIRI+Beva	FOLFIRI+Beva	FOLFIRI+Beva
SOX+Beva	-	-
FOLFOX+Cetu/Pembro	FOLFOX+Cetu/Pembro	FOLFOX+Cetu/Pembro
FOLFIRI+ Cetu/Pembro	FOLFIRI+ Cetu/Pembro	FOLFIRI+ Cetu
FOLFIRI+Beva	FOLFIRI+Beva	FOLFOXIRI
FL/cape/5FU+LV/S1/Beva	FL/cape+Beva	IRIS
Cetu/Beva		
Non-intensive chemotherapy		
FL/cape/5FU+LV+beva	FL/cape+beva	5FU+LV/cape+beva
Cetu/Pembro	Cetu/Pembro	FOLFOX
	Nivolumab/Pembro	capeOx
		FOLFIRI
		IRIS

FOLFOX: 5-Fluorouracil + Oxaliplatin; Beva: Bevacizumab; CapeOX: Capecitabine + Oxaliplatin; FOLFIRI: 5-Fluorouracil + Irinotecan; SOX: S1 + Oxaliplatin; Cetu: Cetuximab; Pembro: Pembrolizumab; FOLFOXIRI: 5-Fluorouracil + Oxaliplatin + Irinotecan; Cape: Capecitabine; FL: 5-Fluorouracil infusional; IRIS: S1 + Irinotecan; 5FU+LV: 5-Fluorouracil + folinic acid/leucovorin.

Immunotherapy

The frequent diagnosis of advanced stages and the high risk of systemic toxicity, poor response and low efficacy have led to the development of new therapies and better therapeutic options, with specific selectivity directed to the tumor.

Targeted therapies provide an alternative for patients with metastatic colon cancer. These therapies work by blocking specific molecules involved in the growth and spread of cancer.

Over the past 20 years, many potential therapies with different mechanisms of action have been studied:

- Inhibition of the epidermal growth factor receptor (EGFR).
- Suppression of the RAS-Raf-MEK-ERK gene pathway, responsible for tumor growth and proliferation.
- Inhibition of tumor angiogenesis (neoangiogenesis) promoted by epithelial endothelial growth factor A (VEGF-A).
- Inhibition of immune controls or checkpoints (PD-1, PD-L1, CTLA-4), the most recent therapy.

Bev, the first anti-VEGF-A monoclonal antibody, was approved in 2004. The FDA has also approved aflibercept (a VEGF-A inhibitor), ramucirumab (a fully humanized monoclonal antibody against VEGFR-2), and regorafenib (a VEGF-2 inhibitor) for the treatment of metastatic colon cancer.

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies directed against activating T-cell receptors, particularly the programmed cell death receptor 1 (PD-1), including programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) expressed on T cells and antigen-presenting cells. In patients with MSI-H and dMMR cancers, these antibodies have shown encouraging responses. However, in cancers with microsatellite stability (MSS) or low microsatellite instability (MSI-L), which represent 95% of colon tumors, the role of these antibodies is not defined.

These therapies have started a new and promising chapter in the treatment of colon cancer. Currently, PD-1 and PD-L1 inhibitors could have significant potential in patients with metastatic colon cancer with MSI-H/dMMR. The role of drugs such as Pembro (anti PD-1) and atezolizumab (anti PD-L1) has been studied in trials such as KEYNOTE-177, KEYNOTE-164 and ATOMIC, in comparison with standard chemotherapy in patients with MSI-H/dMMR, demonstrating an improvement of 32-41% in progression-free survival up to 12 months, constituting an alternative for this subgroup of patients with lack of response to standard chemotherapy with FOLFOX or FOLFIRI.[66–68]

Regorafenib is likely involved in the induction of the pathway responsible for macrophage activation and the production of inflammatory cytokines responsible for the activation of cytotoxic T cells. The combination of regorafenib with Nivo also appears promising in non-randomised small cohort studies.[69]

According to ASCRS, immunotherapy with PD-1 and PD-L1 inhibitors should be considered in patients with MSI-H/dMMR colon cancer. Evidence IA.[4,69] However, these therapies are ineffective in patients with non-microsatellite instability/MMR-proficient colon cancer.

Immunoprevention

Immunoprevention of CRC consists of administering vaccines based on DNA repair protein deficiency (dMMR) that generate neoantigens consisting of peptides or fragments of the DNA chain. Different types of vaccines are proposed: those based on peptides, those guided by a viral vector, those based on dendritic cells and those based on RNA.

The obstacles to the application of these vaccines are related to effectiveness, tolerance and the possibility of early identification of the chains and achieving sufficiently broad coverage to include the entire chain.

REFERENCES

1. Argilés G, Tabernero J, Labianca R, et al. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31:1291–305.
2. Yoshino T, Argilés G, Oki E, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis treatment and follow-up of patients with localised colon cancer. *Ann Oncol*. 2021;32:1496–510.
3. Yoshino T, Cervantes A, Bando H, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with metastatic colorectal cancer. *ESMO Open*. 2023;8:101558.
4. Vogel JD, Felder SI, Bhama AR, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the management of colon cancer. *Dis Colon Rectum*. 2022;65:148–77.
5. Quasar Collaborative Group, Gray R, Barnwell J, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet*. 2007;370:2020–29.
6. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. *Lancet*. 1995;345:939–44.
7. Figueredo A, Charette ML, Maroun J, et al. Adjuvant therapy for stage II colon cancer: a systematic review from the Cancer Care Ontario Program in evidence-based care's gastrointestinal cancer disease site group. *J Clin Oncol*. 2004;22:3395–407.
8. Costas-Chavarri A, Nandakumar G, Temin S, et al. Treatment of patients with early-Stage colorectal cancer: ASCO Resource-Stratified Guideline. *J Glob Oncol*. 2019;5:1–19.
9. Vogel JD, Eskicioglu C, Weiser MR, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the treatment of colon cancer. *Dis Colon Rectum*. 2017;60:999–1017.
10. André T, Boni C, Navarro M, et al. Improved overall survival with

oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*. 2009;27:3109–16.
11. Quah H-M, Chou JF, Gonen M, et al. Identification of patients with high-risk stage II colon cancer for adjuvant therapy. *Dis Colon Rectum*. 2008;51:503–7.
12. Zhang C, Yin S, Tan Y, et al. Patient selection for adjuvant chemotherapy in high-risk stage II colon cancer: A systematic review and meta-analysis. *Am J Clin Oncol*. 2020;43:279–87.
13. Teufel A, Gerken M, Fürst A, et al. Benefit of adjuvant chemotherapy in high-risk colon cancer: A 17-year population-based analysis of 6131 patients with Union for International Cancer Control stage II T4N0M0 colon cancer. *Eur J Cancer*. 2020;137:148–60.
14. Cienfuegos JA, Martínez P, Baixauli J, et al. Perineural invasion is a major prognostic and predictive factor of response to adjuvant chemotherapy in stage I-II colon cancer. *Ann Surg Oncol*. 2017;24:1077–84.
15. Castillo J. Cáncer del colon. Tratamiento oncológico. En: Lumi CM. Bianchi R, Canelas A, Collia Ávila K, Farina PA, Laporte M, Mattacheo AE, Pastore RLO, eds. *Enfermedades del colon, recto y ano*. Buenos Aires: Sociedad Argentina de Coloproctología; 2023:697-725.
16. Ueno H, Ishiguro M, Nakatani E, et al. Prospective multicenter study on the prognostic and predictive impact of tumor budding in stage II colon cancer: Results from the SACURA trial. *J Clin Oncol*. 2019;37:1886–94.
17. Ueno H, Ishiguro M, Nakatani E, et al. Optimal criteria for G3 (poorly differentiated) stage II colon cancer: Prospective validation in a randomized controlled study (SACURA trial). *Am J Surg Pathol*. 2020;44:1685–98.
18. Kyong Shin J, Ah Park Y, Wook Huh J, et al. Is high-grade tumor budding an independent prognostic factor in stage II colon cancer? *Dis Colon Rectum*. 2023;66:e801-8.
19. André T, Meyerhardt J, Iveson T, et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials. *Lancet Oncol*. 2020;21:1620–29.
20. Roth AD, Delorenzi M, Tejpar S, et al. Integrated analysis of molecular and clinical prognostic factors in stage II/III colon cancer. *J Natl Cancer Inst*. 2012;104:1635–46.
21. André T, de Gramont A, Vernerey D, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III Colon Cancer: Updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. *J Clin Oncol*. 2015;33:4176–87.
22. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol*. 2011;29:3768–74.
23. Baxter NN, Kennedy EB, Bergsland E, et al. Adjuvant therapy for stage II colon cancer: ASCO Guideline update. *J Clin Oncol*. 2022;40:892–910.
24. Tomasello G, Petrelli F, Ghidini M, et al. FOLFOXIRI plus bevacizumab as conversion therapy for patients with initially unresectable metastatic colorectal cancer: a systematic review and pooled analysis. *JAMA Oncol*. 2017;3:e170278.
25. Sargent D, Sobrero A, Grothey A, et al. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. *J Clin Oncol*. 2009;27:872–77.
26. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? *J Clin Oncol*. 2004;22:1797–806.
27. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. *Int J Clin Oncol*. 2020;25:1–42.
28. Hajirawala LN, Yi Y, Herritt BC, et al. Multiple high-risk features for stage II colon carcinoma portends worse survival than stage III disease. *Dis Colon Rectum*. 2023;66:1076–84.
29. Cho SS, Park JW, Kang GH, et al. Prognostic impact of extramural lymphatic, vascular, and perineural invasion in stage II colon cancer: a comparison with intramural invasion. *Dis Colon Rectum*. 2023;66:366–73.
30. Kim S, Huh JW, Lee WY, et al. Prognostic Impact of mucinous adenocarcinoma in sage II and III colon cancer. *Dis Colon Rectum*. 2023;66:1473–80.
31. Twelves C, Scheithauer W, McKendrick J, et al. Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. *Ann Oncol*. 2012;23:1190–97.
32. Benson AB, Venook AP, Adam M, et al. Colon Cancer, Version 3.2024, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*.;22 . Epub ahead of print June 2024. DOI: 10.6004/jnccn.2024.0029.
33. Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. *J Clin Oncol*. 1993;11:1879–87.
34. Wolmark N, Colangelo L, Wieand S. National Surgical Adjuvant Breast and Bowel Project trials in colon cancer. *Semin Oncol*. 2001;28:9–13.
35. Haller DG, Catalano PJ, Macdonald JS, et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. *J Clin Oncol*. 2005;23:8671–78.
36. Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol*. 2007;25:2198–204.
37. Schmoll H-J, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results of the NO16968 randomized controlled phase III trial. *J Clin Oncol*. 2015;33:3733–40.
38. André T, Vernerey D, Mineur L, et al. Three versus 6 months of oxaliplatin-based adjuvant chemotherapy for patients with stage III colon cancer: disease-free survival results from a randomized, open-label, international duration evaluation of adjuvant (IDEA) France, phase III trial. *J Clin Oncol*. 2018;36:1469–77.
39. Yoshino T, Yamanaka T, Oki E, et al. Efficacy and long-term peripheral sensory neuropathy of 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy for colon cancer: the ACHIEVE phase 3 randomized clinical trial. *JAMA Oncol*. 2019;5:1574–81.
40. Cervantes A, Adam R, Roselló S, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34:10–32.
41. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2013;14:1208–15.
42. Reddy SK, Pawlik TM, Zorzi D, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. *Ann Surg Oncol*. 2007;14:3481–91.
43. Shubert CR, Habermann EB, Bergquist JR, et al. A NSQIP review of major morbidity and mortality of synchronous liver resection for colorectal metastasis stratified by extent of liver resection and type of colorectal resection. *J Gastrointest Surg*. 2015;19:1982–94.
44. Silberhumer GR, Paty PB, Temple LK, et al. Simultaneous resection for rectal cancer with synchronous liver metastasis is a safe procedure. *Am J Surg*. 2015;209:935–42.
45. Barros Scheloto E. Sesión Científica de la Academia Argentina de Cirugía. Tratamiento de las metástasis hepáticas de origen colorrectal. *Academia Argentina de Cirugía*. Available from: https://academiadecirugia.org.ar/sesiones-2023/. Accessed October 23, 2024.
46. Kanzaki R, Suzuki O, Kanou T, et al. The short-term outcomes of pulmonary metastasectomy or stereotactic body radiation therapy for pulmonary metastasis from epithelial tumors. *J Cardiothorac Surg*. 2020;15:43.
47. Hernández J, Molins L, Fibla JJ, et al. Role of major resection in pulmonary metastasectomy for colorectal cancer in the Spanish prospective multicenter study (GECMP-CCR). *Ann Oncol*. 2016;27:850–55.
48. Milosevic M, Edwards J, Tsang D, et al. Pulmonary metastasectomy in colorectal cancer: updated analysis of 93 randomized patients - control survival is much better than previously assumed. *Colorectal Dis*. 2020;22:1314–24.
49. Zani S, Papalezova K, Stinnett S, et al. Modest advances in survival for patients with colorectal-associated peritoneal carcinomatosis in the era of modern chemotherapy. *J Surg Oncol*. 2013;107:307–11.
50. Cashin PH, Mahteme H, Spång N, et al. Cytoreductive surgery and intraperitoneal chemotherapy versus systemic chemotherapy for colorectal peritoneal metastases: A randomised trial. *Eur J Cancer*. 2016;53:155–62.
51. Franko J, Shi Q, Goldman CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. *J Clin Oncol*. 2012;30:263–67.
52. Razenberg LGEM, van Gestel YRBM, Lemmens VEPP, et al. Bevacizumab in addition to palliative chemotherapy for patients with peritoneal carcinomatosis of colorectal origin: a nationwide population-based study. *Clin Colorectal Cancer*. 2016;15:e41–6.
53. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003 Oct 15;21(20):3737-43.
54. Zwanenburg ES, El Klaver C, Wisselink DD, et al. Adjuvant hyperthermic intraperitoneal chemotherapy in patients with locally advanced colon cancer (COLOPEC): 5-year results of a randomized multicenter trial. *J Clin Oncol*. 2024;42:140–45.
55. Quénet F, Elias D, Roca L, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:256–66.
56. Chicago Consensus Working Group. The Chicago Consensus on peritoneal surface malignancies: management of colorectal metastases. *Ann Surg Oncol*. 2020;27:1761–67.

57. Hong DS, Fakih MG, Strickler JH, et al. KRAS inhibition with sotorasib in advanced solid tumors. *N Engl J Med*. 2020;383:1207–17.
58. Yaeger R, Weiss J, Pelster MS, et al. Adagrasib with or without cetuximab in colorectal cancer with mutated G12C. *N Engl J Med*. 2023;388:44–54.
59. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol*. 2015;16:1306–15.
60. Folprecht G, Gruenberger T, Bechstein W, et al. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). *Ann Oncol*. 2014;25:1018–25.
61. Kemeny NE, Chou JF, Boucher TM, et al. Updated long-term survival for patients with metastatic colorectal cancer treated with liver resection followed by hepatic arterial infusion and systemic chemotherapy. *J Surg Oncol*. 2016;113:477–84.
62. Gruenberger T, Bridgewater J, Chau I, et al. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. *Ann Oncol*. 2015;26:702–8.
63. McCahill LE, Yothers G, Sharif S, et al. Primary mFOLFOX6 plus bevacizumab without resection of the primary tumor for patients presenting with surgically unresectable metastatic colon cancer and an intact asymptomatic colon cancer: definitive analysis of NSABP trial C-10. *J Clin Oncol*. 2012;30:3223–28.
64. Bond MJG, Bolhuis K, Loosveld OJL, et al. First-line systemic treatment strategies in patients with initially unresectable colorectal cancer liver metastases (CAIRO5): an open-label, multicentre, randomised, controlled, phase 3 study from the Dutch Colorectal Cancer Group. *Lancet Oncol*. 2023;24:757–71.
65. Kanemitsu Y, Shitara K, Mizusawa J, et al. Primary tumor resection plus chemotherapy versus chemotherapy alone for colorectal cancer patients with asymptomatic, synchronous unresectable metastases (JCOG1007; iPACS): a randomized clinical trial. *J Clin Oncol*. 2021;39:1098–107.
66. André T, Shiu K-K, Kim TW, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383:2207–18.
67. Le DT, Kim TW, Van Cutsem E, et al. Phase II open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: KEYNOTE-164. *J Clin Oncol*. 2020;38:11–9.
68. Sinicrope FA, Ou F-S, Zemla T, et al. Randomized trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III colon cancer and deficient mismatch repair (ATOMIC, Alliance A021502). *J Clin Oncol*. 2019;37:e15169.
69. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:303–12.