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Tumour Review

Refining adjuvant therapy for non-metastatic colon cancer, new standards and perspectives

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ABSTRACT

Colon cancer is the third most frequent cancer in males and the second in females. Approximately 75% are diagnosed at a localized stage. Recurrence occurs in 30% of patients when there is nodal involvement (stage III) due to micrometastatic spreading. To date only chemotherapeutic drugs such as fluoropyrimidines or oxaliplatin have proven effective to kill this residual disease and are currently recommended by scientific societies. To improve patient management in the near future, recent research has focused on new ways of using currently available agents, tools to better define each individual patient prognosis more clearly so as to tailor adjuvant treatment, and molecular profiling to identify specific subgroups of patients with tumors that may benefit from specific therapeutic approaches. In this review, we will focus on current scientific knowledge on adjuvant treatment in localized colon cancer, the duration and timing of adjuvant therapy and the perspectives for better selection of patients who will benefit from adjuvant treatments.

Introduction

With 1 360 802 new cases worldwide in 2012, colon cancer is the third most frequent cancer in males and the second in females [1]. More than 95% are adenocarcinoma, and 75% are diagnosed at a localized stage [2]. Even diagnosed at a localized stage, recurrence occurs in 30% of patients when there is nodal involvement (stage III) due to micrometastatic spreading. Hence, research has sought effective post-surgery treatments to kill this residual disease. To date only chemotherapeutic drugs such as fluoropyrimidines or oxaliplatin have proven effective and are currently recommended by scientific societies [2,3]. However, while these treatments are saving thousands of lives each year, they are also associated with short- and long-term toxicities and are only useful for 15–25% of treated patients, meaning than more than 70% of patients receive chemotherapy without benefit and with toxicity.

To improve patient management in the near future, recent research has focused on new ways of using currently available agents, tools to better define each individual patient prognosis more clearly so as to tailor adjuvant treatment, and molecular profiling to identify specific subgroups of patients with tumors that may benefit from specific therapeutic approaches.

In this review, we will focus on current scientific knowledge on adjuvant treatment in localized colon cancer, the duration and timing of adjuvant therapy and the perspectives for better selection of patients who will benefit from adjuvant treatments.

Stages I and II colon cancer

Stage I colon cancer is defined as a tumor invading at worst the muscularis propria of the colon (pT1-2N0M0). A consensus has been found for these tumors: no adjuvant chemotherapy is recommended as 5-year overall survival (OS) is an estimated 85–95% with surgery alone [2,3].

Stage II colon cancer is defined as a tumor invading at worst adjacent organs but without any nodal involvement (pT3-4N0M0). Stage II colon cancer covers a very heterogeneous group of patients. Indeed, 5-year survival varies between 58.4% for stage IIc (adjacent organ invasion) disease and 87.5% for stage IIa disease (T3-N0) [4]. When considering the whole stage II population, the benefit of adjuvant chemotherapy is debated. Data come mainly from the QUASAR study, the NSABP-C01-02 studies and the IMPACT-B2 meta-analysis [5,6].

In the IMPACT B2 meta-analysis, adjuvant chemotherapy did not

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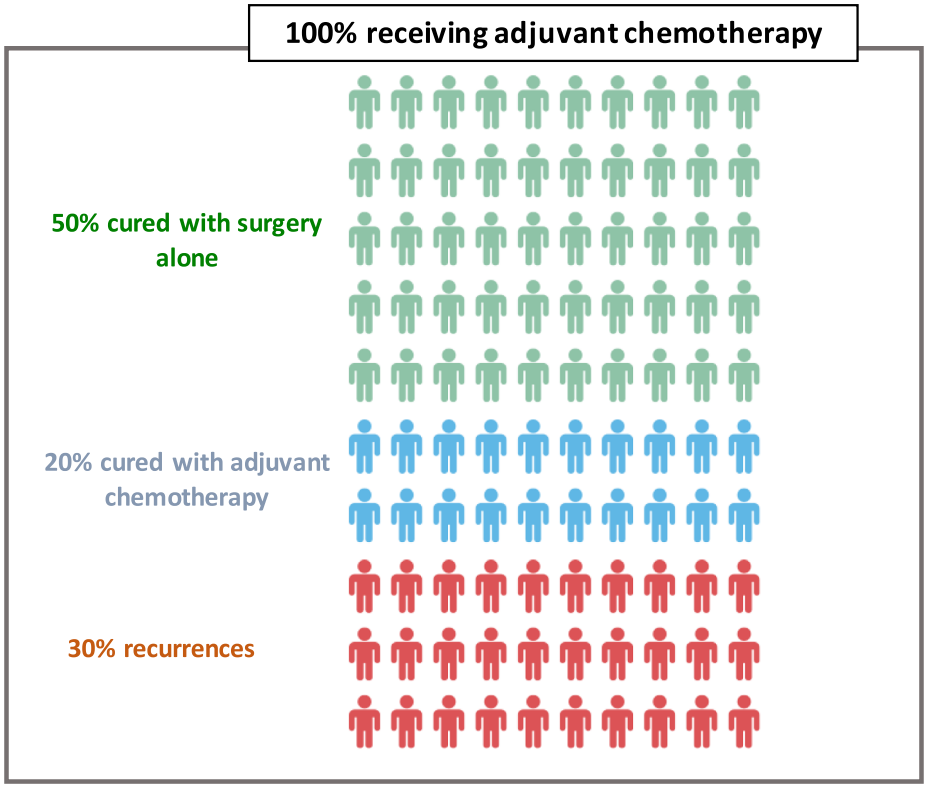

Fig. 1. Paradigm in stage III colon cancer.

benefit stage II colon cancer [6]. A total of 1016 patients from 5 randomized trials were included in this study. The 5-year OS rate was 82% in the 5FU/LV group and 80% in the control group (HR: 0.86, 90% CI: 0.68–1.07, p = 0.057) and the 5-year event-free survival was 76% in the chemotherapy group and 73% in the surveillance group (HR: 0.83, 90% CI: 0.72–1.07). However, the differences were not significant.

Contradictory results were obtained with the subgroup analysis of stage II patients enrolled in the NSABP C01 and 02 studies [7–9]. NSABP C01 and C02 compared adjuvant chemotherapy to surgery alone in 1409 patients with colon cancer, among whom 705 had stage II colon cancer. While NSABP C01 did not show any benefit of adjuvant chemotherapy in terms of OS (5-year OS rate 75% vs 72% for chemotherapy and surgery groups, respectively, p = 0.73), NSABP C02 showed the superiority of perioperative portal venous infusion compared with surgery alone in stage II colon cancer (5-year OS 88% vs 76% for chemotherapy and surgery groups, respectively, p = 0.005). The QUASAR study randomized 3239 patients with localized colon and rectal cancer between 5FU-based adjuvant chemotherapy and post-operative observation [5]. Stage II patients represented 91% of the whole population (n = 1483 in the chemotherapy arm and n = 1480 in the observation arm). In the subgroup analysis of the stage II population, the study showed a benefit for adjuvant chemotherapy in terms of relative risk of recurrence, which decreased by 29% (HR: 0.71, 95% CI: 0.54–0.92, p = 0.01), with a trend for better OS (HR: 0.83, 95% CI: 0.65–1.07). However, the absolute benefit of adjuvant fluoropyrimidine was only 2.9%, leading in many countries to an absence of consensus regarding whether or not to treat these patients. In the patients included in the QUASAR study, the median number of lymph nodes examined was only 6, indicating that the QUASAR population almost certainly had a large population of undiagnosed stage III patients [5]. Likely due to enhanced accuracy of staging, recurrence rates have fallen significantly over time in clinical trials that included patients with stage II disease with identical treatment, reflecting stage migration over time.

Finally, the 10-year update of the MOSAIC study showed no statistical benefit in adding oxaliplatin to LV5FU2 in stage II colon cancer in terms of disease-free survival (DFS) or OS, even in patients with poor prognostic factors such as tumor stage T4, bowel perforation and/or fewer than 10 nodes examined (HR for DFS: 0.79, 95% CI: 0.55–1.13, and HR for OS: 0.89, 95% CI: 0.60–1.32) [10,11].

We should highlight that all these results are from subgroup analyses of phase III trials, and no specific trial has been designed to answer the stage II colon cancer question directly. Moreover, the combination of 5FU plus oxaliplatin has never been compared with surgery alone.

In the light of these results and the 2–5% improvement of survival with adjuvant chemotherapy in stage II colon cancer, adjuvant treatment for stage II colon cancer is indicated according to tumor-related prognostic factors and should be balanced against patient comorbidities and life expectancy.

Recently, the major prognostic value of mismatch repair (MMR) status in resected stage II colon cancer led to the recommendation that MMR status should be determined in those patients and that no adjuvant chemotherapy should be administered to deficient MMR (dMMR) stage II patients, whatever the other risk factors [3,12]. In proficient MMR (pMMR) tumors, adjuvant chemotherapy is nowadays discussed individually for patients with risk factors for relapse, defined with a consensus for T4-stage, bowel perforation, number of nodes examined <12, and without a clear consensus for vascular, perineural or lymphatic invasion, undifferentiated tumor and obstruction [2,3].

Stage III colon cancer

Unlike in stage II colon cancer, the situation is clearer for stage III colon cancer. Indeed, adjuvant treatment is recommended for all patients [2,3]. Fluoropyrimidine-based chemotherapy is the standard adjuvant treatment. It decreases the risk of death by 10–15% when fluorouracil monotherapy follows surgical resection, and by 20–22% when it is used in combination with oxaliplatin (Fig. 1).

It has been known since the 1990s that fluorouracil monotherapy is beneficial versus observation after surgical treatment of stage III colon cancer [13]. In this study, Moertel et al. found that adjuvant

Table 1
Results of the main studies in adjuvant colon cancer.

Study	Year of publication	Phase	Stage	Control arm	Exp arm	DFS control/exp	OS control/exp
IMPACT B2	J Clin Oncol 1999	Meta-analysis	II	No chemotherapy (n = 509)	Adjuvant chemotherapy (n = 507)	5y event-free survival 73%/76% (HR: 0.83, 90% CI: 0.72–1.07).	5y 80%/82% (HR: 0.86, 90% CI: 0.68–1.07, p = 0.057)
10y results NSABP C01	Wolmark J Natl Cancer Inst 1988 Smith et al. J Natl Cancer Inst 2004	III	Duke B, C	No treatment (n = 394)	Postoperative chemotherapy (5-FU/ semustine/vincristine (n = 379); or postoperative BCG (n = 393)	7% difference in terms of DFS at 5y 10y DFS: MOF vs surgery HR:0.88 (0.72–1.07) P 0.19	10y OS:HR 0.89 (0.72–1.09) P = 0.24
NSABP C02	Wolmark J Clin Oncol 1990	III	Duke A, B, C	Surgery alone (n = 581)	Perioperative portal venous infusion 5FU (n = 577)	5y 60%/69% p = 0.02	5y 70%/78% p = 0.07
NSABP C03	Wolmark J Clin Oncol 1993		II and III	MOF (n = 542)	5FU/LV (n = 539)	5y 54%/66% p = 0.0004	5y 66%/76% p = 0.003
QUASAR	QUASAR collaborative group Lancet 2007		I–III	Surgery alone (n = 1617)	Chemotherapy (n = 1622)	RR for recurrence 0·78 (95% CI 0·67–0·91; p = 0·001	RR (chemotherapy vs surgery) 0·82 (95% CI 0·70–0·95; p = 0·008
MOSAIC	André et al. J Clin Oncol 2015	III	II and III	LV5FU2 (1123)	FOLFOX4 (n = 1123)	10y 61.7%/67.5% HR 0.82 (0.71–0.95) p = 0.007	10y 67.1%/71.7% HR 0.85 (0.73–0.99); *P* 0.043
NSABP C07	Kuebler J Clin Oncol 2007/Yothers J Clin Oncol 2011	III	II and III	5FU/LV (n = 1245)	5FU/LV-oxali (n = 1247)	5y 64.2%/69.4% FLOX vs FULV: HR DFS 0.82 (0.72–0.93) 0p = 0.02	5y 78.8%/81.8%
XELOXANO16968	Schmoll J Clin Oncol 2015	III	III	FU/FA, (n = 942)	CAPOX, (n 944)	7y 56%/63% HR (exp vs control) 0.80; 95% CI, 0.69–0.93; *P* 0.004	7y 67%/73% HR (exp vs control), 0.83; 95% CI, 0.70–0.99; *P* 0.04
NSABP C08	Allegra J Clin Oncol 2011	III	II and III	FOLFOX6 (n = 1356)	FOLFOX6 + bevacizumab (n = 1354)	3y 75.5%/77.4% HR (exp vs control), 0.89; 95% CI, 0.76–1.04; P 0.15	/
AVANT	De Gramont Lancet Oncol 2012	III	III	FOLFOX (n = 955)	FOLFOX or CAPOX + bevacizumab (n = 1912)	HR for bevacizumab–FOLFOX4 versus FOLFOX4 was 1·17 (95% CI 0·98–1·39; p = 0·07), and for bevacizumab–XELOX versus FOLFOX4 was 1·07 (0·90–1·28; p = 0·44).	HR for bevacizumab– FOLFOX4 versus FOLFOX4 was 1·27 (1·03–1·57; p = 0·02), and for bevacizumab–XELOX versus FOLFOX4 was 1·15 (0·93–1·42; p = 0·21).
PETACC-8	Taieb Lancet Oncol 2014	III	III	FOLFOX (n = 1279)	FOLFOX cetuximab (n = 1280)	*RAS* wt pop: 3y 78%/75.1% HR (exp vs control) 1·05 (95% CI 0·85 − 1·29	3y 91.2%/89.7% HR (exp vs control) 0·98 (95% CI 0·67 − 1·44)
NCCTG NO147	Alberts JAMA 2012	III	III	FOLFOX6 (n = 1337)	FOLFOX6 cetuximab (n = 1349)	*KRAS* wt: 3y 74.6%/71.5% HR (exp vs control), 1.21; 95% CI, 0.98–1.49; P = 0.08	3y 87.3%/85.6% HR (exp vs control) 1.25 (0.92–1.68) p = 0.15
PETACC-3	Van Cutsem J Clin Oncol 2009	III	III	LV5FU2 (1149)	FOLFIRI (n = 1149)	5y 54.3%/56.7% p = 0.106	5y 71.3%/73.6% p = 0.094

Abbreviations: DFS: disease-free survival, OS: overall survival; Exp arm: experimental arm; 3y, 5y, 7y, 10y: three years, five years, seven years, ten years; HR: hazard ratio, RR: relative risk; Treatments: MOF: semustine + vincristine + 5 fluorouracil 5FU/LV or LV5FU2 or FU/FA: 5 fluorouracil + leucovorin, FOLFOX: LV5FU2 + oxaliplatin, CAPOX: capecitabine + oxaliplatin, FOLFIRI: LV5FU2 + irinotecan.

fluorouracil and levamisole decreased the relative risk of recurrence by 41%, and at 3.5 years the DFS was 16% higher in the adjuvant chemotherapy group compared with the observation group. Similar results were observed with other fluoropyrimidine-based regimens, showing a benefit of 12–16% in terms of 5-year OS [5,6,11,14]. The LV5FU2 regimen was finally preferred to the FUFOL regimen because of its better tolerability profile and good efficacy [15,16]. Oral fluoropyrimidines have also been assessed in this setting. The X-ACT trial compared capecitabine with 5FU/LV (Mayo Clinic regimen) as adjuvant therapy for stage III colon cancer [17,18]. This trial randomized 1987 patients with stage III colon cancer (n = 1004 in the capecitabine group, n = 983 in the 5FU group). The analysis of the primary endpoint (DFS) showed that capecitabine was not inferior to 5FU (HR: 0.87, 95% CI: 0.75–1.00), with a trend toward superiority for capecitabine (p value for planned superiority analysis: 0.05). The same results were obtained for OS (HR: 0.86, 95% CI: 0.74–0.99, p value for superiority: 0.07). Safety analysis showed significantly fewer adverse events in the capecitabine arm than in the fluorouracil plus leucovorin arm ($p < 0.001$), except for hand-foot syndrome. Tegafur-uracil, an oral pro-drug of 5FU, also showed some efficacy in the adjuvant setting [19,20], but is no longer available in most countries. Recently, another oral fluoropyrimidine called tegafur-gimeracil-oteracil potassium (or S1) was compared with capecitabine [21]. In this Japanese non-inferiority phase III trial, 1564 patients were randomly assigned to capecitabine (n = 782) or S-1 (n = 782). S-1 failed to show its non-inferiority with a 3-year DFS of 82% for the capecitabine group and 78% for the S-1 group (HR 1.23, 95% CI 0.89–1.70; one-sided p non-inferiority = 0.46). Capecitabine thus remains the only oral alternative to intravenous 5FU as adjuvant treatment for stage III colon cancer, outside Asia, where S1 is available in this indication.

Addition of oxaliplatin to 5FU and folinic acid has been tested in 2 main randomized control trials: MOSAIC and NSABP C07 [10,22]. In the stage III population of the MOSAIC trial, addition of oxaliplatin to LV5FU2 increased 10-year OS by 8.1% (HR: 0.80, 95% CI: 0.66–0.96, p = 0.016). This OS improvement was greater in the N2 population (absolute 10-year OS increase of 12.9%, HR: 0.70, 85% CI: 0.53–0.93, p = 0.013). The same results were seen in the NSABP C07 trial, where oxaliplatin in addition to fluorouracil increased 3-year DFS by 6.6% [22]. The superiority of XELOX (capecitabine and oxaliplatin) over bolus 5FU/LV as adjuvant treatment for stage III colon cancer was shown in the 1886 patients of the NO16968 trial [23]. Haller et al. reported a 3-year DFS of 71.0% for capecitabine/oxaliplatin vs. 67.0% for 5FU bolus/LV (HR 0.80, p = 0.0045) [24].

Finally, a meta-analysis of 5 randomized trials confirmed in 12 233 patients that addition of oxaliplatin to fluoropyrimidines had a significant positive impact on outcomes in stage III patients [25]. However, this gain in survival is balanced by an increase in treatment-related toxicities and particularly 12% of grade 3 sensory neuropathy induced by oxaliplatin at the end of the 6 months of adjuvant therapy [11]. These results were replicated with the combination of capecitabine and oxaliplatin, and thus both FOLFOX and CAPOX regimens are nowadays considered as standard adjuvant treatments for stage III colon cancer [23].

The addition of irinotecan to fluorouracil has been tested in 3 trials, all negative [26–28].

Attempts to improve adjuvant treatment of stage III disease by adding targeted agents such as cetuximab and bevacizumab have also been unsuccessful [29–33]. The C-08 study found that a one-year bevacizumab adjuvant treatment in combination with FOLFOX did not significantly improve DFS (HR: 0.89, 95% CI: 0.76–1.04, p = 0.15) [29,30]. The authors also underlined the fact that there was a trend to a benefit of bevacizumab during the first 15 months, suggesting that it could help control residual disease but not eradicate it. In the AVANT study, there was a trend to a detrimental effect of the addition of bevacizumab to FOLFOX in terms of DFS (HR: 1.17; 95% CI: 0.98–1.39, p = 0.07), and to CAPOX (HR:1.07; 95% CI: 0.90–1.28, p = 0.44) [31].

Similar results were obtained with the addition of cetuximab [32,33]. The PETACC8 study found no difference between FOLFOX and FOLFOX + cetuximab, the 3-year DFS rates being 79.1% in the FOLFOX arm and 75.9% in the cetuximab-FOLFOX arm (HR:0.99, 95% CI: 0.76–1.28, p = 0.92) in the *KRAS* wild-type population [33]. However, when looking at patients wild-type for *KRAS/NRAS and BRAF* in a post-hoc analysis, there was a trend to cetuximab efficacy (adjusted HR: 0.70; 95% CI: 0.48–1.03, p = 0.07) [34].

In summary, in stage III colon cancers 50–60% of patients are cured by surgery alone, 20% with addition of adjuvant chemotherapy, and 20–30% will experience recurrence [2] (Fig. 1). To date the only chemotherapy regimens having shown improved survival are fluoropyrimidines alone or in combination with oxaliplatin, Table 1.

Timing and duration of adjuvant treatments

The interval between surgery and the beginning of adjuvant chemotherapy is codified. A meta-analysis of 14 studies showed that an interval above 8 weeks increased the relative risk of death (HR: 1.20, 95% CI: 1.15–1.26, p = 0.001) [35]. These results corroborate those of Hershman et al. in 2006 [36], who found in more than 4000 patients with stage III colon cancer from the SEER database that colon cancer-specific mortality was associated with a time until initiation of adjuvant chemotherapy of more than 3 months (HR 1.48, 95% CI: 1.15–1.92). Finally, many population-based studies have shown that even though starting adjuvant chemotherapy before 8 weeks is ideal, it might still be useful even with a longer interval, with a maximum of 5–6 months depending on the study [37–39]. For example, Gao et al. found, in a SEER database cohort of 18,491 patients with stage III colon cancer, that there was still a benefit of adjuvant chemotherapy 17 weeks after surgery when compared with patients who did not have adjuvant treatment [37]. This benefit in terms of OS became nonsignificant after 21 weeks between surgery and adjuvant treatment onset [37]. Possible bias in these results relates to post-operative complications, patient comorbidities, emergency surgery in patients whose adjuvant chemotherapy was initiated more than 8 weeks after surgery. These factors can *per se* explain the longer wait until adjuvant therapy together with the lower survival rates observed in these patients. Pending better studies, it is recommended to start adjuvant chemotherapy ideally within 8 weeks after surgery.

Except for fluoropyrimidines and oxaliplatin, no anticancer agents in the metastatic setting have proven effective in the adjuvant setting in the last 15 years, and so physicians and researchers have tried to modify the timing and duration of this doublet standard, to improve patient outcomes and decrease treatment-related toxicity. Two main strategies have been developed: use chemotherapy perioperatively instead of postoperatively only and shorten treatment duration to spare toxicity and health-related costs.

Important results from the IDEA project were presented in 2017 at the ASCO and ESMO meetings. The IDEA project pooled the analysis of 6 large randomized controlled trials (4 from Europe, one from Japan and one from the US) that compared 3 versus 6 months of adjuvant standard treatment with a doublet of fluoropyrimidines and oxaliplatin (FOLFOX or CAPOX) [40].

We should highlight that IDEA is not the first study to raise the question of optimal adjuvant treatment duration in colon cancer. Previous attempts to reduce adjuvant chemotherapy duration from 12 to 9 and then to 6 months have been successful [15,41–44]. Four studies showed that a 6-month fluoropyrimidine-based adjuvant treatment was not inferior to longer treatment duration. For example, André et al. found, in stage II and III colon cancer, no difference in terms of DFS and OS between 24 weeks (n = 454) and 36 weeks (n = 451) of treatment, with an HR of 0.942 (95% CI: 0.73–1.21p = 0.63) and 1.28 (95% CI: 0.90–1.80p = 0.17) for DFS and OS, respectively [15]. Similarly, Sadahiro et al. found no difference between 6 months (n = 534) and 18 months (n = 537) with oral uracil/tegafur + leucovorin in terms of

DFS and OS with HR:1.00 (95% CI: 0.80–1.24, p = 0.98) and HR 1.05 (95% CI: 0.78–1.42, p = 0.07) for DFS and OS, respectively [41].

Six-month adjuvant treatment being considered as the standard duration, Chau et al. compared a 3-month protracted venous infusion (PVI) of 5FU (n = 397) with 6-month 5FU/LV (n = 401) [44]. They reported that 3 months of PVI 5FU was associated with a trend to better survival (HR: 0.79 95% CI: 0.61–1.03p = 0.08). However, in the control arm, 5FU/LV was not optimally administered as it was 5FU 425 mg/m^2 on days 1–5 every 4 weeks.

The IDEA project randomized a total of 12 834 patients [40], 2402 of whom were included in the TOSCA study (Italy), 3983 in the SCOT study (UK, Denmark, Spain, Australia, Sweden, New Zealand), 2010 in the IDEA France study (France), 2440 in the CALGB/SWOG study (USA, Canada), 708 in the HORG study (Greece), and 1291 in the ACHIEVE study (Japan) [45–49]. CAPOX was administered to 39.5% of patients (from 0% in the US trial to 75.1% in the Japanese trial), and 41.3% of the patients had T4 and/or N2 disease (from 34.5% in the TOSCA study to 49% in the SCOT study). The primary endpoint of these 6 trials was non-inferiority in terms of DFS of 3 versus 6 months of adjuvant treatment.

With a median follow-up of 41.8 months, non-inferiority of 3 months of therapy versus 6 months was not confirmed in the modified intent-to-treat population (HR 1.07; 95% CI: 1.00–1.15p = 0.11). These results should be interpreted in the light of the preplanned subgroup analysis depending on the T and N stages and of adjuvant regimens (CAPOX vs FOLFOX), but not preplanned low- (T1-3N1 patients) and high-risk groups (T4 and/or N2). In the low-risk group (T1-3N1 patients), 3 months of CAPOX was not inferior to 6 months of CAPOX (3y DFS 85% and 83.1% for the 3 and 6 months groups, respectively, HR: 0.85 95% CI: 0.71–1.01), Table 2. However, the non-inferiority was not proven for 3 months of FOLFOX in these patients (81.9% and 83.5% for the 3- and 6-month groups, respectively, HR: 1.10 95% CI: 0.96–1.26) Table 2. Continuous exposure to 5FU is one of the hypothesis for this difference, as suggested in the study from Chau et al. with PVI FU [44]. If we consider the high-risk population (T4 and/or N2), 3 months of adjuvant treatment was inferior to 6 months (Table 2). In detail, the non-inferiority was not proven for CAPOX with 3y DFS of 64.1% and 64.0% for the 3- and 6-month groups, respectively (HR: 1.01 95% CI: 0.89–1.17), and 6-month FOLFOX was superior to 3 months, with 3y DFS of 61.5% and 64.7% for the 3- and 6-month groups, respectively (HR: 1.20 95% CI: 1.07–1.35). These subgroup analyses involve a large number of patients, and can therefore be interpreted reliably. There was no randomization between the FOLFOX and CAPOX regimens and thus patients selected for one or other regimen may have differed in terms of comorbidities, physical activity and other important prognostic factors. Moreover, dose intensity results concerning capecitabine in the 6-month CAPOX arm, are missing. Questions are raised by the higher DFS rates of patients receiving 3 months of CAPOX as compared to the patients receiving 6 months of CAPOX (85 vs 83.1%), with the same rate of treatment-related death in both groups.

Based on these results, clinical guidelines were changed and recommend 3 months of CAPOX adjuvant treatment for low-risk stage III colon cancer (3 months of FOLFOX being an option for patients not able to receive capecitabine), and 6 months of FOLFOX treatment for high-risk stage III colon cancer (6 months of CAPOX being an option) [2].

Beyond efficacy results, the IDEA project showed that a reduced duration of adjuvant chemotherapy was associated with a substantial reduction in long-term side effects and a significant reduction in health-related costs. The safety analysis of the IDEA France trial showed that reducing the adjuvant chemotherapy duration resulted in a decrease of 13% and 23% in Graded 2 and 3/4 maximal peripheral sensory neuropathy (PSN) in the overall population [46]. Moreover, patients receiving the 6 months of treatment experienced significantly more residual PSN 3.6 years after randomization, with 8% of Grade >1 residual PSN as compared to 2.5% in the 3 months arm (p < 0.001). The same kind of results were obtained in the SCOT, ACHIEVE and TOSCA trials [47–49]. More than PSN, all grade 3 adverse events were significantly reduced in the 3 months arm (29% versus 56% in the IDEA France study, 29% versus 43% in the ACHIEVE study) [46,47]. The safety analysis of the IDEA France and TOSCA trials found that grade 3+ neutropenia was also significantly more frequent (17% versus 12%, p = 0.005; and 27.6% vs 20.7%, p < 0.0001 for the IDEA France and

Table 2
Summary of 3-year DFS rates according to treatment arm and risk group from the IDEA study (Grothey et al., N Engl J Med, 2018).

3 yr DFS rate (%) and HR by regimen and risk group		Regimen								
		CAPOX			FOLFOX			CAPOX/FOLFOX combined		
		3 yr DFS, % (95% CI)		HR (95% CI)	3 yr DFS, % (95% CI)		HR (95% CI)	3 yr DFS, % (95% CI)		HR (95% CI)
		3 m	6 m		3 m	6 m		3 m	6 m	
Risk group	Low-risk (T1-3 N1) ~60%	85.0 (83.1-86.9)	83.1 (81.1-85.2)	*0.85* (0.71-1.01)	81.9 (80.2-83.6)	83.5 (81.9-85.1)	*1.10* (0.96-1.26)	83.1 (81.8-84.4)	83.3 (82.1-84.6)	*1.01* (0.90-1.12)
	High-risk (T4 or N2) ~40%	64.1 (61.3-67.1)	64.0 (61.2-67.0)	*1.02* (0.89-1.17)	61.5 (58.9-64.1)	64.7 (62.2-67.3)	*1.20* (1.07-1.35)	62.7 (60.8-64.4)	64.4 (62.6-66.4)	*1.12* (1.03-1.23)
	Risk groups combined	75.9 (74.2-77.6)	74.8 (73.1-76.6)	*0.95* (0.85-1.06)	73.6 (72.2-75.1)	76.0 (74.6-77.5)	*1.16* (1.06-1.26)	P-value interaction test: Regimen: 0.0061 Risk group: 0.11		

Non-inferior | Not proven | Inferior

Abbreviations: 3 yr: three years; DFS: disease-free survival; CAPOX: capecitabine + oxaliplatin; FOLFOX: 5 fluorouracil + oxaliplatin.

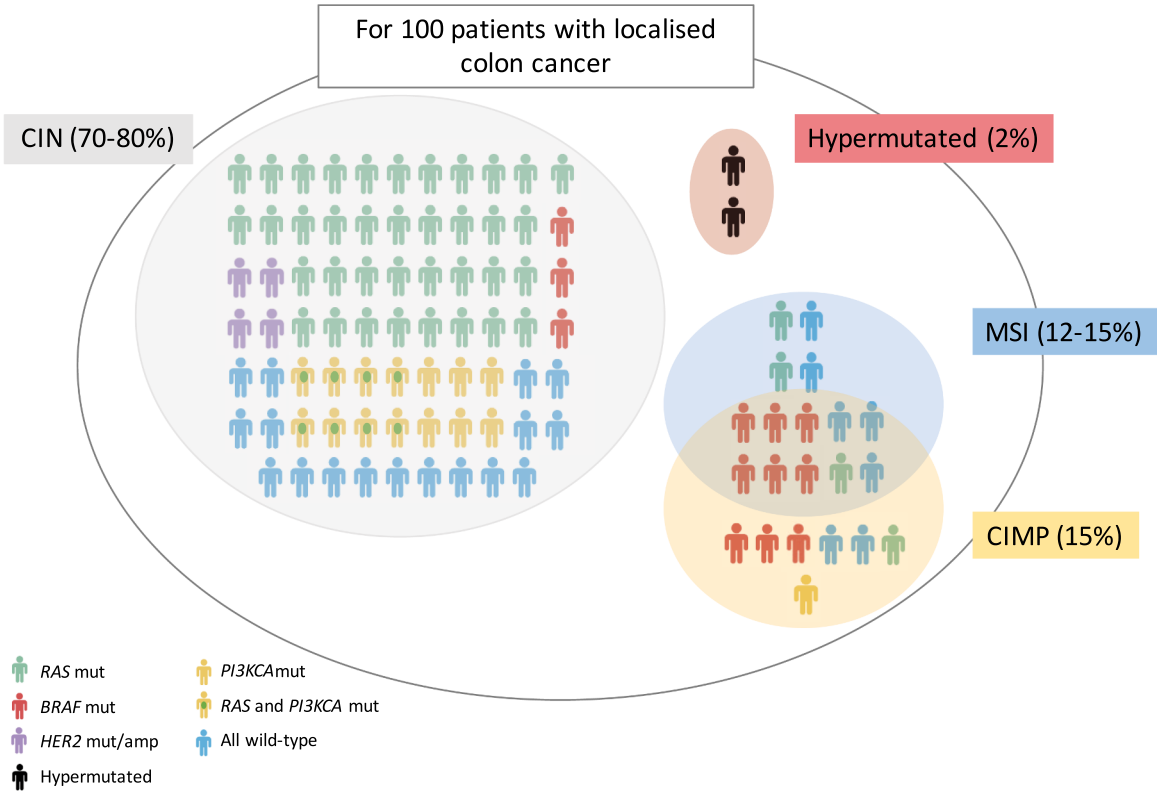

Fig. 2. Colon cancer diversity. Colon cancer is composed of multiple subtypes that may be differently treated in the future in the adjuvant setting.

TOSCA trials, respectively) in the 6 months arm, as were diarrhea and allergic reactions [46,49].

Considering the best schedule to administer chemotherapy in operable colon cancer and due to the success of pre- or perioperative treatment strategies in many GI cancers (esophageal, gastric, rectal, colorectal liver metastasis), three studies were designed to assess the efficacy of perioperative chemotherapy in this setting [50–52]. The ongoing phase III FOxTROT study (NCT00647530) has yielded preliminary feasibility results on 150 patients randomized between perioperative chemotherapy (n = 99) and upfront surgery (n = 51) [50]. In the perioperative chemotherapy group, there were more R0 resections (96% versus 80%, p = 0.002). The treatment was feasible with identical complication rates between the groups and 83% of the patients in the perioperative group started postoperative chemotherapy. The second trial, Prodige 22 (NCT01675999), is a randomized phase II trial assessing the efficacy and feasibility of FOLFOX in a perioperative strategy in patients with localized stage III disease or high-risk II (n = 52 in the perioperative FOLFOX arm, n = 52 in the adjuvant FOLFOX arm) [52]. The primary endpoint was the rate of high tumor regression grade (TRG). The Prodige 22 trial showed that perioperative FOLFOX in patients with locally advanced nonmetastatic colon cancer does not increase post-surgery morbidity and is associated with a significantly higher TRG compared with upfront surgery (TRG1-2 44% in the neoadjuvant chemotherapy group versus 8% in the upfront surgery group). Finally, Jakobsen et al. found similar results in another randomized phase II trial comparing neoadjuvant CAPOX + panitumumab to neoadjuvant CAPOX treatment alone [51]. The aim of this last study was to assess whether neoadjuvant chemotherapy was able to convert high-risk patients into low-risk and to explore the effect of the addition of anti-EGFR therapy. Among the 71 patients included in the study, 48% experienced downstaging, even if the addition of panitumumab did not result in a higher rate of downstaging. However, the neoadjuvant chemotherapy may also lead to the risk of progression before surgery (11% in the Jakobsen study, but only 2% in Prodige 22). Moreover, there is no clear consensual recommendation concerning baseline staging for these patients, especially the staging of nodal status, and the risk to over-stage patients is an issue here. We still have to explore the best way to stage these patients using only CT-scans or MRI and TEP-scans together with the best radiological criteria to avoid over-staging and exposure of some of them to a useless preoperative treatment.

Though these pilot trials showed the feasibility and good tolerability of pre-operative chemotherapy in locally advanced nonmetastatic colon cancers, we have to wait for the results of ongoing phase III trials before determining whether this approach can be used in our daily practice and for which patients.

Adjuvant treatment in elderly patients

Sargent et al. showed in 2001 the benefit of adjuvant chemotherapy (versus no chemotherapy) in elderly patients with localized colon cancer [53]. In this pooled analysis of 7 randomized trials, they included 1269 patients, aged 60–70 years, and 506 patients older than 70 years. Adjuvant chemotherapy seemed to benefit patients over 70 in terms of recurrence-free survival and OS, but no statistical comparison was available concerning this population. No significant interaction was observed between age and the efficacy of treatment. The incidence of toxic effects was not increased among the elderly (age >70), except for leukopenia in one study [53]. These results were corroborated by a smaller analysis of a German randomized trial [54].

Concerning the benefit of addition of oxaliplatin to fluoropyrimidines, a pooled analysis of the NSABP C-08, XELOXA, X-ACT, and AVANT studies led by Haller et al. suggested a benefit in terms of DFS and OS for addition of oxaliplatin to 5FU in elderly patients (aged >70)

Table 3
Ongoing studies in adjuvant colon cancer.

	Trial number	Type of study	Title	Acronym	Treatment	Population (number, characteristics)
Molecular-driven trials	NCT02912559	phase III	Combination Chemotherapy With or Without Atezolizumab in Treating Patients With Stage III Colon Cancer and Deficient DNA Mismatch Repair	ATOMIC Alliance A021502	mFOLFOX6 +/− atezolizumab	700 patients with dMMR colon cancer
	NCT02466906	phase II	RhGM-CSF as Adjuvant Immunotherapy in Treating Stage III Colon Cancer		RhGM-CSF vs placebo	60 stage III
	NCT02467582	phase III	Adjuvant Aspirin Treatment for Colon Cancer Patients	ASPIK PRODIGE 50	Aspirin versus placebo	185 patients with stage III or high-risk stage II colon cancer harboring PI3KCA mutation
Clinical and age-driven trials	NCT02967289	phase III	IRinotecan and Oxaliplatin for Colon Cancer in Adjuvant Setting	IROCAS	FOLFOX versus FOLFIRINOX	640 high-risk stage III colon cancer (pT4 and/or N2)
	NCT02978612	phase II	Adjuvant Chemotherapy In Elderly With Colon Cancer Stage III	ACE	Capecitabine	170 patients with stage III colon cancer and older than 75 years
	NCT02355379	phase III	Randomized Study Evaluating Adjuvant Chemotherapy After Resection of Stage III Colonic Adenocarcinoma in Patients of 70 and Over (ADAGE)	PRODIGE 34 ADAGE	Capecitabine or 5FU, CAPOX or FOLFOX, observation	774 patients with stage III colon cancer and older than 70 years
	UMIN000013036	Phase III	Adjuvant chemotherapy for colon cancer with high evidence in high risk stage	JFMC48-1301-C4 ACHIEVE-2	mFOLFOX6 or XELOX for 3 months as adjuvant chemotherapy compared to 6 months mFOLFOX6/ XELOX in terms of DFS for high –risk stage II colon cancer	High risk stage II colon cancer
ctDNA-driven trials	NCT02842203	observational	Use of ctDNA for Monitoring of Stage III Colorectal Cancer		Evaluate ctDNA as a prognostic marker and as a monitor of disease recurrence in stage III colorectal cancer	150 stage III colon cancer
	NCT03312374	observational	ctDNA as a Prognostic Marker for Postoperative Relapse in Early and Intermediate Stage Colorectal Cancer		Evaluate circulating tumor DNA (ctDNA) as a predictive marker for DFS in stage II and III colorectal cancer	350 patients with stage II and III colon cancer
	NCT03637686	observational	Circulating Tumor DNA Analysis to Optimize Treatment for Patients With Colorectal Cancer (IMPROVE)		To confirm that ctDNA detected in plasma after intended curative treatment for CRC can be applied in clinical practice as a marker of subclinical residual disease and risk of recurrence.	1800 stage I to III colon cancer
	ACTRN12615000381583		ctDNA analysis informing adjuvant chemotherapy in stage II colon cancer	DYNAMIC	To evaluate the use of ctDNA to guide adjuvant chemotherapy on RFS	Stage II colon or rectal cancer
	ACTRN12617001566325	Phase II/III	Tumour DNA analysis informing adjuvant chemotherapy in stage III colon cancer: a multicenter phase II/III randomized controlled study (DYNAMIC-III)	DYNAMIC III	To compare treatment informed by ctDNA results to standard care in patients with stage III colon cancer	Stage III colon cancer
	EudraCT 2019–000935-15 –	Phase III		CIRCULATE France CIRCULATE Germany	To compare FOLFOX versus observation in ctDNA positive stage II colon cancer patients after R0 resection	Stage II colon cancer

FOLFOX: 5 fluorouracil + oxaliplatin, RhGM-CSF: recombinant human granulocyte–macrophage colony-stimulating factor, FOLFIRINOX: 5 fluorouracil + oxaliplatin + irinotecan, CAPOX: capecitabine + oxaliplatin. dMMR: deficient mismatch repair, ctDNA: circulating tumor DNA.

(n = 1119, HR = 0.94 95% CI: 0.78–1.13 for DFS and HR = 1.04 95% CI: 0.85–1.27 for OS) [55]. However, this benefit was not found in other studies [22,56–58].

In the studies assessing the benefit of adjuvant chemotherapy, elderly patient numbers were low and selection bias may limit the interpretation of the study results in the elderly population. Consideration of patient comorbidities is a key point in decision-making regarding adjuvant treatment in elderly patients with colon cancer.

In summary, elderly patients do benefit from adjuvant chemotherapy, but may benefit less from addition of oxaliplatin than younger patients. The decision to administer adjuvant treatment should be made according to patient comorbidities, performance status and life expectancy. The PRODIGE 34-ADAGE trial (NCT02355379) is currently recruiting patients in order to assess the benefit of adjuvant chemotherapy +/− oxaliplatin in patients over 70 who have stage III colon cancer.

Prognostic and predictive markers

The best way to improve adjuvant treatment in colon cancer is to define prognostic groups better and to find predictive markers of the benefit of adjuvant treatment. In this perspective, many pathological, biological, and molecular factors have been studied during the last decade.

Carcinoembryonic antigen (CEA) has been largely studied in localized colon cancer. Konishi et al. showed that postoperative levels of CEA were more relevant than preoperative levels [59]. Moreover, the cut-off, usually set at 5 ng/mL, is debated [60–63]. A cut-off point between 1.30 and 3 was found to be more relevant in various studies in stage I-III colon cancer [62]. However, no predictive value of CEA was found for adjuvant chemotherapy benefit and this low-cost marker seems only useful for prognostication in localized disease.

Supervised prognostic genomic signatures have been developed to summarize the prognostic information provided by molecular factors. The main genomic signatures have been widely analyzed in both retrospective and prospective studies, including Oncotype Dx Colon Cancer®, ColoPrint®, Veridex® and GeneFx Colon® [64–66]. Most validation studies have focused on stage II disease, but several included stage III disease, especially using the Oncotype Dx Colon Cancer® signature [64]. The accuracy of these scores is controversial, as they currently do not allow us to guide our treatment decision because their prognostic discrimination capacity is insufficient.

Immunologic features have been studied in order to define prognosis better [67–71]. The Immunoscore® developed by Galon et al. is currently the most studied [70] and has recently been validated prospectively, using a predefined statistical hypothesis, in a large trial population of stage III patients with MSI assessment [72]. However, this validation did not include other important prognostic factors such as CEA level, *BRAF* and *RAS* mutational status, and adjuvant standard treatment for all patients. Moreover, the accuracy of the Immunoscore® was not perfect, as the c-index for DFS prediction was 0.58. Clinical trials are needed to assess the decision-making utility of Immunoscore® in guiding therapeutic decision-making. In this setting, first results were presented this year at the ASCO GI 2019 symposium. In a cohort of 1130 patients with untreated stage II colon cancer, Galon et al. showed that high risk patients with high Immunoscore® had similar time to recurrence compared with low risk stage II patients [73]. However, precisions concerning the patients included and the impact of Immunoscore® on treatment outcome are needed in order to validate its decision making utility. These immunological tools could also be of interest in future immunotherapy trials in the adjuvant setting.

The analysis of large phase III trials has increased our understanding of the prognosis of patients with stage III colon cancer. Recently, *KRAS* and *BRAF* mutations together with a methylator phenotype (CIMP) were found to be independently associated with shorter DFS, survival after recurrence, and OS [74–77].

Other molecular factors have been studied in order to refine prognosis. Colon cancers without Caudal-type homeobox transcription factor 2 (CDX2) over- expression are often associated with aggressive features such as advanced stage, poor differentiation, vascular invasion, BRAF mutation, and the CpG island methylator phenotype [78–81]. Recently, Dalerba et al. showed that a lack of CDX2 expression (4.1–6.9% of colon cancers) was associated with worse outcome in stage II and III colon cancer (HR for disease recurrence 3.44, 95% CI 1.60–7.38, P = 0.002) [82]. In stage III colon cancer, adjuvant treatment was beneficial in both CDX2-positive and negative tumors, but CDX2 seemed to be predictive of benefit in stage II patients [82]. Though very promising, these findings on the prognostic and predictive value of CDX2 need to be confirmed in external series based on patients enrolled in clinical trials, in order to increase the quality of clinical data and the robustness of this marker before using it in daily practice.

We can also highlight the PI3KCA mutations that are present in approximately 10–20% of colon cancers. They seem to be associated with the benefit of aspirin as adjuvant treatment [83,84]. Ng et al. showed that patients with stage III colon cancer treated with aspirin showed a trend to better DFS and OS (HR 0.61, 95% CI = 0.36–1.04; and 0.48, 95% CI = 0.23–0.99, respectively) [84]. However, prospective studies still need to be conducted to validate these results.

Finally, with the breakthrough of liquid biopsy, circulating tumor DNA (ctDNA) has been assessed in early stage colon cancer [85–87]. Its very high prognostic value for OS and RFS has been shown in very small cohorts [86,87]. To date, no study has assessed the prognostic value of ctDNA in stage III colon cancer, but 3 studies are ongoing (NCT03416478, NCT02842203, NCT03312374).

All these findings underline the need for an integrative approach, which would include clinical, pathological, biological and molecular features, in order to define prognosis better and to find predictive markers of the benefit of adjuvant chemotherapy in daily practice.

Perspective in the future management of nonmetastatic colon cancer

Colon cancer is heterogeneous and at least 4 entities are already characterized at the genomic level to define colon carcinogenesis: microsatellite instability, chromosomal instability, hypermethylated colon cancers and hypermutated colon cancers (Fig. 2). On the top of these 4 entities several mutational profiles may be of interest to better treat our patients including MMR, PI3K, BRAF, HER-2, mutation in DNA polymerase (PolD/PolE) and RAS.

MMR, BRAF and RAS status are nowadays usually determined in colon cancer patients in the metastatic setting. Moreover, targeting HER2 in HER2+ metastatic colon cancer patients recently gave promising results. Some of these advances may translate in new trials the adjuvant setting.

Recently, immunotherapy was shown to be effective in dMMR/MSI metastatic tumors [88]. In the adjuvant setting, immunotherapy has already proven effective, particularly in melanoma [89], and one study is currently ongoing in the adjuvant setting for dMMR/MSI colon cancer, Table 3 (NCT02912559).

Along the same lines, progress made in the metastatic setting for HER2 mutated or amplified colon cancer has been assessed in the localized setting [90]. For unresectable colon cancer, including non metastatic locally advanced patients, a trial is currently assessing dual HER2 inhibition (pertuzumab plus trastuzumab) compared with chemotherapy (NCT03365882). Adjuvant project for R0 resected non metastatic colon cancer are currently discussed.

PI3KCA mutated colon cancer patients are another molecular subgroup of patients currently under study. Mutations in the PI3KCA signaling pathways are present in approximately 15–20% of colon cancer. In the metastatic setting, PI3KCA mutations seem to confer resistance to anti-EGFR treatment (in *RAS* wild type patients). Recently, evidence of the potential benefit of aspirin on colon cancer specific mortality in

PI3KCA mutated colon cancer was observed [83]. Thus, the PRODIGE 50-ASPIK trial (NCT02467582) is testing aspirin adjuvant treatment in PI3KCA mutated stage III or high-risk stage II patients, and the JCOG1503C trial (UMIN000031532) regardless of the PI3KCA mutation.

Better use of the usual chemotherapy drugs may also improve management of nonmetastatic colon cancer, and trials are exploring the intensification of adjuvant treatment for high-risk stage III colon cancer (IROCAS, NCT02967289) and treatment de-escalation in elderly patients (ACE NCT02978612, and PRODIGE 34-ADAGE NCT02355379). As described above, the perioperative regimen is also a potential source of improvement for the management of non metastatic colon cancer. In the FOxTROT trial, perioperative chemotherapy was shown to be feasible, with an increase of 16% in R0 resections and no increase in post-surgery complications [50].

Finally, the very high prognostic value of ctDNA for OS and RFS was showed in very small cohorts. Indeed, Tie et al., showed in 230 patients with stage II colon cancer that ctDNA was detectable in 7.9% of patients without adjuvant chemotherapy and 11% of patients with adjuvant chemotherapy [87]. In this study, ctDNA postoperative detection was associated with worse RFS in treated and untreated patients (multivariate HR: 7.5 95%CI: 2.6–22 and HR: 3.3 95%CI:1.6–7.0, respectively) [87]. Moreover, patients who had postoperative positive ctDNA but post-adjuvant chemotherapy negative ctDNA seemed to have better outcome. Those impressive results have led to the development of studies assessing the prognostic value of ctDNA in stage II and III colon cancer (NCT02842203, NCT03312374, NCT03637686), and other studies are going to explore the value of ctDNA-driven adjuvant treatment in stage II and III colon cancer.

Table 3 summarizes the main studies designed to improve adjuvant treatment for specific subgroups of colon cancer.

Conclusion

The landscape of adjuvant treatment for colon cancer is still moving. It is clear that no treatment is needed for stage I and dMMR/MSI II colon cancer. For pMMR stage II colon cancer, with its consensual poor prognostic features (T4, perforation and less than 12 nodes examined), adjuvant treatment with fluoropyrimidines is recommended, the lack of a clear overall survival benefit when oxaliplatin is added makes FOLFOX an option in many guidelines. For stage III colon cancer, adjuvant treatment with fluoropyrimidines and oxaliplatin is recommended: 3 months of treatment for low-risk stage III (T3N1) and 6 months for high-risk stage III colon cancer (T4 and/or N2). No strong predictive factor has been identified to date. Patients with specific druggable molecular targets may benefit from targeted agents. Ongoing trials are mainly dedicated to rare subgroups that may benefit from a specific treatment (dMMR, HER2+, PI3KCA mutated, BRAF mutated), new treatment settings (peri-operative FOLFOX), treatment with chemotherapeutic agents of specific patient subgroups (elderly patients, high risk stage III) and treatment guidance by ctDNA.

Conflict of interest statement

J. Taieb declared providing advisory or speaker role for Roche Merck KGaA Amgen Lilly Servier and Sirtex Medical. T. André declared honoraria from Roche/Genentech Bristol Myers Squibb Servier xBiotech Bayer Sanofi Amgen PRMA Consulting, and declared providing advisory role for Roche/Genentech Amgen Bristol Myers Squibb Mundipharma International HalioDX JT Oncology Servier Guardant Health Bayer. E. Auclin declared no conflicts of interest.

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