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Adjuvant chemotherapy in resected colon cancer: When, how and how long?

Alain J. Gelibter*, Salvatore Caponnetto, Federica Urbano, Alessandra Emiliani, Simone Scagnoli, Grazia Sirgiovanni, Valerio M. Napoli, Enrico Cortesi

Department of Radiology, Oncology and Pathology, Policlinico Umberto, I Sapienza University of Rome, Italy

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ABSTRACT

The benefit of adjuvant chemotherapy has been clearly established in the adjuvant setting for node-positive colon cancer. A number of trials in the adjuvant setting have analyzed the efficacy of multiple-agent combinations, including irinotecan, oxaliplatin, bevacizumab and cetuximab. Only oxaliplatin added to fluorouracil/capecitabine has been shown to be superior beyond a fluropyrimidine alone in the adjuvant setting. As such, standard treatment options include fluorouracil (FU) or capecitabine with or without oxaliplatin. However, oxaliplatin is associated with cumulative dose-dependent neurotoxicity, characterized by distal or perioral paresthesias or dysesthesias; for this reason, in this review we discuss the results of the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) trial. The IDEA trail is the largest prospective clinical trial ever conducted in colorectal cancer, wherein patients were treated with either 3 months or 6 months of adjuvant chemotherapy. In the era of cancer gene expression–based subtyping, the Colorectal Cancer Subtyping Consortium has proposed a four-subgroup molecular classification system for colorectal cancer, consisting of CMS1 (immune), CMS2 (canonical), CMS3 (metabolic) and CMS4 (mesenchymal). In this review, we present and analyze the available data on efficacy and toxicity of the combination regimen approved for treatment of resected colon cancer, and discuss the questions of when, how and how long we need to treat such patients.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death worldwide [1]; thus, after surgery, more effective and less toxic treatments are required to prevent recurrence and prolong survival of the resected CRC patients. The benefit of adjuvant chemotherapy has been clearly established in the adjuvant setting for node-positive colon cancer. Standard treatment options include fluorouracil (FU) or capecitabine with or without oxaliplatin.

Adjuvant chemotherapy (intravenous fluoropyrimidine (FP) monotherapy) for 6 months was associated with improved survival in patients with stage III and possibly high-risk stage II CRC. Subsequent studies have tested the noninferiority of oral FP alternatives and the benefit of FP-based polychemotherapy, confirming that capecitabine is equivalent to infusional 5-(FU) and that the addition of oxaliplatin to either infusional or oral FP therapy provides superior results to monotherapy with FP alone.

In this review, we present and analyze the available data on efficacy and toxicity of the combination regimen approved for treatment of resected colon cancer, and discuss the questions of when, how and how long we need to treat such patients.

2. Trials of 5-FU plus leucovorin as adjuvant therapy

Historically, two trials have established the disease-free survival (DFS) and overall survival (OS) benefit of postoperative FU-based chemotherapy compared with surgery alone in locally advanced colon cancer. Namely, these are the NCCTG trial and the INT-0035 trial. These trials defined 5-FU plus levamisole, given for 1 year, as standard adjuvant treatment in stage III colon cancer; however, they did not show similar conclusions for patients with stage II disease [2]. Although garnering great interest initially, the combination of 5-FU plus levamisole resulted in inferior survival benefit compared to 5-FU plus leucovorin (LV) in subsequent comparative trials. Table 1 summarizes the main phase III trials of 5-FU plus LV.

The INT-0089 study [3] was a four-arm study that randomized high-risk stage II (obstructing and/or perforating lesions) and all stage III resected colon cancer patients to receive adjuvant 5-FU plus levamisole for 1 year or one experimental treatment chosen between: low-dose LV

* Corresponding author. Department of Radiology, Oncology and Pathology, Policlinico Umberto I, Sapienza University of Rome, Via del Policlinico, 155 00100, Rome, Italy.
E-mail address: agelibter@yahoo.it (A.J. Gelibter).

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Table 1
Phase III trials comparing different postoperative 5-FU/LV strategies in locally advanced colon cancer.

Trial	First author	Year	Phase	Inclusion criteria	Patients, n	Treatment	Primary endpoints	DFS	OS
INT-0089	Haller	2005	III	High risk stage II and all stage III	3794	Arm 1: Mayo Clinic regimen Arm 2: Roswell Park regimen Arm 3: Mayo Clinic/LEV Arm 4: FU/LEV	OS	Difference not statistically significant	Difference not statistically significant
NSABP C-04	Wolmark	1999	III	Stage II-III	2151	Arm 1: FU + LV Arm 2: FU + LEV Arm 3: FU + LV + LEV	OS	FU + LV vs FU + LEV: 64% *vs* 60%; $P < 0.05$	FU + LV vs FU + LEV: 74% *vs* 69%; $P < 0.05$
GERCOR C96.1	André	2007	III	Stage II-III	905	Arm 1: semimonthly LV5FU2 Arm 2: monthly mFU/LV	DFS	Difference not statistically significant	Difference not statistically significant
X-ACT	Twelves	2011	III	Stage III	1987	Arm 1: capecitabine Arm 2: Mayo Clinic	DFS	Difference not statistically significant	Difference not statistically significant

DFS: Disease-free survival; FU: Fluorouracil; LEV: Levamisole; LV: Leucovorin; OS: Overall survival.

plus FU (the Mayo Clinic regimen consisting of LV 20 mg/m^2 and FU 425 mg/m^2 on days 1 through 5 by intravenous (i.v.) push, repeated at 4 wk, 8 wk, and then every 5 wk, for a total of six courses), high-dose LV plus FU (Roswell Park regimen; consisting of LV 500 mg/m^2 by a 2-h infusion and FU 500 mg/m^2 by i.v. push at 1 h after the start of the LV infusion, repeated six times weekly, followed by a 2-wk rest period, for a total of four 8-wk courses), low-dose LV plus levamisole plus FU (consisting of levamisole 50 mg orally every 8 h for 3 d, repeated every 14 d for 6 mo, administered with the same chemotherapy as the Mayo Clinic regimen). A total of 80.5% of patients had stage III disease, and the remainder had high-risk stage II disease. After a median follow-up of 10 years, none among the four treatment arms was statistically superior in DFS or OS for patients with resected stage II and III colon cancer [3].

The NSABP C-04 protocol [4] was a three-arm trial comparing six cycles of FU plus high-dose LV, FU plus levamisole and a combination of FU plus high-dose LV plus levamisole in patients with stage II and III colon cancer. The trial demonstrated that FU plus LV had better DFS (64% *vs* 60%; $P < 0.05$) and 5-year OS (74% *vs* 69%; $P < 0.05$) than 5-FU plus levamisole both in stage II and stage III disease, while there were no significant differences in DFS and OS between the combination of FU with LV or with LV and levamisole.

In 2007, Andrè et al. [5] published the final results of the GERCOR C96.1 trial, a randomized phase III study comparing a semimonthly (LV5FU2) with a monthly (mFU/LV) regimen of FU plus LV as adjuvant treatment for stage II and III colon cancer patients. LV5FU2 was administered semimonthly for 2 days as a LV 2-h infusion, followed by 400 mg/m^2 FU bolus and a 600-mg/m^2 FU 22-h continuous infusion; while in the mFU/LV regimen, FU and LV were administered monthly for 5 days as LV 15-min infusion, followed by a 400 mg/m^2 FU 15-min infusion. A total of 905 patients with stage II (43%) and III (57%) colon cancer was enrolled. The median follow-up was 6 years. There was no statistically significant difference between mFU/LV and LV5FU2 in terms of DFS and OS, despite the favorable toxic profile of the infusional FU schedule [6]. These results were comparable both in stage II and III colon cancer.

Finally, the X-ACT trial was a randomized phase III trial of oral capecitabine (a prodrug of 5-FU) *versus* 5-FU/folinic acid in resected stage III colon cancer. Patients were randomized to receive 24 weeks of capecitabine 1250 mg/m^2 twice daily on days 1–14 every 3 weeks or the Mayo Clinic regimen [7]. With a median follow-up of 6.9 years, capecitabine was found to be equivalent to 5-FU/folinic acid in terms of DFS and OS.

A FU-based postoperative chemotherapy is the standard treatment for stage III resected colon cancer patients, while its role is still debated for stage II disease. Historical data suggest no survival benefit from adjuvant treatment in stage II colon cancer patients [8,9], but confirmatory data are lacking. The main reason is that the above-mentioned large randomized trials were not powered to look at stage II or stage III patients separately and did not have a sugery control arm.

3. Trials of combination therapy in the adjuvant setting

Oxaliplatin is a third-generation platinum derivative. When combined with FU and LV (FL), it is among the most effective chemotherapies for metastatic colorectal cancer [10,11]. A number of trials in the adjuvant setting have analyzed the efficacy of multiple-agent combinations, including irinotecan, oxaliplatin, bevacizumab and cetuximab [12–15]. Only oxaliplatin has demonstrated a significant benefit in the adjuvant setting [16].

We analyzed three randomized controlled trials that had evaluated the impact of oxaliplatin, in the adjuvant setting, in association to fluoropyrimidines in resected stage II and III colon cancer [18,20,22]. Table 2 summarizes the main data for the combination of 5-FU/LV/oxaliplatin reported in the above mentioned phase III trials, including patient characteristics, arms of treatment, endpoints and toxicities.

Table 2
Phase III trials of adjuvant chemotherapy with combination treatment in localized colon cancer.

Trial	Authors	Year	Phase	Inclusion criteria	Patients, *n*	Treatment	Primary endpoints	DFS	OS	Toxicity
MOSAIC	Andrè et al.	2004	III	Stage II-III	2246	FOLFOX *vs* 5-FU/LV	DFS	73.3% *vs* 67.4%	78.5% *vs* 76%	G3 neuropathy 12.4% *vs* 0.2% G3/4 diarrhea 10.8% *vs* 6.6% G3/4 neutropenia 41.1% *vs* 4.7%
NSABP C07	Kuebler et al.	2007	III	Stage II-III	2407	FLOX *vs* bolus 5-FU/LV	DFS	73.2% *vs* 67%	80.2% *vs* 78.4%	G3 neuropathy 8.4% *vs* 0.7% G3/4 diarrhea 38% *vs* 32.2%
XELOXA	Schmoll et al.	2007	III	Stage III	1864	XELOX *vs* bolus 5-FU/LV	DFS	70.9% *vs* 66.5%	77.6% *vs* 74.2%	G3/4 neuropathy 11% *vs* < 1% G3/4 diarrhea 19% *vs* 20% G3/4 neutropenia 9% *vs* 16%

DFS: Disease-free survival; FOLFOX: 5-Fluorouracil, leucovorin plus oxaliplatin; FU: Fluorouracil; G: Grade; LV: Leucovorin.

The benefit of oxaliplatin was assessed for the first time in the European MOSAIC trial [17,18], which compared 6-mo treatment with infusional 5-FU, LV and oxaliplatin (FOLFOX) and 5-FU/LV in 2246 patients with completely resected stage II and III colon cancer. In the fluorouracil-leucovorin (FL) group, each cycle comprised a 2-h infusion of 200 mg/m^2 of LV followed by a bolus of 400 mg/m^2 of FU and then a 22-h infusion of 600 mg/m^2 of FU given on 2 consecutive days every 14 d, for 12 cycles. In the group given FL plus oxaliplatin (FOLFOX6)), the same FL regimen was used, plus a 2-h infusion of 85 mg/m^2 of oxaliplatin on day 1. The overall rate of DFS at 3 years was 78.2% in the group given FOLFOX6) and 72.9% in the FL group. The 10-year OS rates in the bolus/infusional FU plus LV (LV5FU2) arm and the LV5FU2 plus oxaliplatin (FOLFOX6) arm were 67.1% and 71.7% (hazard ratio (HR): 0.85; $P = 0.043$) in the whole population.

Similar results were seen in the randomized phase III trial NSABBP C-07 [19,20], that compared the efficacy of FLOX with FL (FU 500 mg/m^2 by i.v. bolus weekly for 6 wk; LV 500 mg/m^2 by i.v. weekly for 6 wk of each 8-wk cycle for three cycles) for prolonging DFS in 2407 patients with stage II or III colon cancer. The rates of 4-year DFS were 73.2% for FLOX and 67.0% for bolus 5-FU/LV, with an HR of 0.81 ($P = 0.005$). With 8 years median follow-up, the OS was similar between the treatment groups (HR: 0.88; $P = 0.08$). FLOX remained superior for DFS (HR: 0.82; $P = 0.002$).

In the XELOXA trial [21,22], capecitabine was assessed only for stage III colon cancer in combination with oxaliplatin (XELOX). Patients were assigned to adjuvant treatment with either XELOX or intravenous bolus FU/LV. The XELOX regimen consisted of a 2-h i.v. infusion of oxaliplatin 130 mg/m^2 on day 1 and oral capecitabine 1000 mg/m^2 twice daily given for 14 d of a 3-week cycle, for a total of eight cycles (24 wk). The Mayo Clinic regimen consisted of a rapid i.v. infusion of LV 20 mg/m^2 followed by an intravenous bolus of FU 425 mg/m^2 on days 1–5 of a 4-wk cycle, for a total of six cycles (24 wk). The Roswell Park (Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States) regimen consisted of a 2-h i.v. infusion of LV 500 mg/m^2 plus an i.v. bolus injection of FU 500 mg/m^2 on day 1 of weeks 1–6 of an 8-wk cycle, for a total of four cycles (32 wk). The final results of this trial showed an improved 7-year DFS rate in the XELOX arm compared with the bolus 5-FU/LV arm (66% *vs* 58%; HR: 0.78; $P = 0.002$) and a 7-year OS improvement in the XELOX arm compared with the 5-FU/LV arm (73% *vs* 67%; HR 0.83; $P = 0.04$).

Another phase III trial compared XELOX to modified (m)FOLFOX6 in 408 patients with stage III or high-risk stage II colon cancer. No significant differences were seen in either the 3-year DFS or 3-year OS [23].

3.1. Outcome stratification by stage

The MOSAIC [17,18] and NSABP C-07 [19,20] studies included patients with stage II and III disease. Although these two studies were under-powered for the analysis, both carried out posthoc exploratory analysis of stage. In the MOSAIC trial, stage III DFS at 5 years was 58.9% in the 5-FU/LV arm and 66.4% in the FOLFOX arm ($P = 0.005$), and stage III 10-year OS in FOLFOX group was statistically significantly increased compared with 5-FU/LV group (67.1% *vs* 59.0%; HR: 0,80; $P = 0.016$).

A subgroup analysis of low risk and high risk stage II patients was reported in a separate publication. It did not show a significant DFS benefit of FOLFOX over 5-FU/LV for patients with high-risk stage II disease at a follow-up of 6 years (HR: 0.84; $P = 0.258$). After longer follow-up, no difference in the 10-year OS was observed in the stage II subpopulation (79.5% *vs* 78.4%; HR: 1.00; $P = 0.98$). In addition, patients with high-risk stage II disease (disease characterized by at least one of the following: T4 tumor; tumor perforation; bowel obstruction; poorly differentiated tumor; venous invasion; < 10 lymph nodes examined) receiving FOLFOX did not show significantly improved DFS compared with those receiving infusional 5-FU/LV (82.3% *vs* 74.6%; HR: 0.72; $P = 0.063$). Furthermore, no OS benefit was seen in the stage II population overall or in the stage II population with high-risk features.

The exploratory subset analysis by stage of the NSABP C-07 trial showed significant differences for DFS in stage III (increase of 6.6% for 5-year DFS in the FLOX arm; 64.4% *vs* 57.8%) and a hint of benefit in stage II (2% increased 5-year OS with FLOX; 82.1% *vs* 80.1%). The 5-year OS improvement estimated in stage III patients was 2.7% favoring FLOX treatment (73.8% *vs* 76.5%). OS did not vary significantly by treatment in stage II patients ($P = 0.84$), differing by only 0.1%.

Those data support the lack of benefit to the addition of oxaliplatin to adjuvant regimens in stage II disease.

3.2. Toxicity

In all combination therapy trials, the addition of oxaliplatin has been found to be correlated with higher rate of toxicity. In the MOSAIC trial, although 92.1% of the patients treated with FOLFOX6 had peripheral neuropathy during treatment, half of these episodes were of grade 1. The incidence of grade 3 peripheral sensory neuropathy was 12.4% for patients receiving FOLFOX and only 0.2 for patients receiving 5-FU/LV. Long-term safety results showed a gradual recovery for most of these patients [25]. Neutropenia, diarrhea and vomiting were the most frequent grade 3 or 4 adverse effects in the group given

FOLFOX (41.1% *vs* 4.7.%, 10.8% *vs* 6.6% and 5.8% *vs* 1.4%, respectively). In only 1.8% of cases neutropenia was complicated with fever or infection.

In the NSABP C-07 trial, rates of grade 3/4 neurotoxicity, diarrhea and dehydration were higher with FOLFOX than with 5-FU/LV (8.4% *vs* 0.7%, 38% *vs* 32.2% and 17.2% *vs* 11.8%, respectively) [24]. It is interesting to note that neither neutropenia nor thrombocytopenia have been reported as grade 3/4 adverse events in this trial.

In a cross-study comparison between the MOSAIC and NSABP C-07 trials, the incidence of grade 3/4 diarrhea seems to be considerably higher with bolus 5-FU/LV compared to infusional 5-FU/LV, both when given as monotherapy and in combination with oxaliplatin (32.2% and 38% in the NSABP C-07 trial *vs* 6.6% and 10.8% in the MOSAIC trial). In the XELOXA trial, rates of grade 3/4 diarrhea were similar in both treatment arms (19% in the XELOX arm and 20% in the FU/LV arm). However, compared with patients receiving bolus FU/LV, the patients receiving XELOX experienced less all-grade neutropenia, febrile neutropenia and stomatitis (9% *vs* 16%, < 1% *vs* 4% and < 1% *vs* 9%, respectively) but more thrombocytopenia, neurosensory toxicity and hand-foot syndrome (5% *vs* < 1%, 11% *vs* < 1% and 5% *vs* < 1%, respectively). In particular, grade 3 (G3) peripheral sensory neuropathy (PSN), witch is one of the most impairing and long term toxicity, was higher in all cited studies in arms containing oxaliplatin. In MOSAIC study was reported in 138 patients (12.5%) in the FOLFOX4 group and 0.2% of the patients in the LV5FU2 group. 18 months after the end of treatment 24% of these patients still report PSN of various grade. In NSABP-C07 PSN G2-G3 was reported in 30.4% of patients in oxaliplatin containing regimen vs 3.6% of patients in 5FU alone regimen.

In conclusion, the MOSAIC trial, the NSABP C-07 trial and the XELOXA trial demonstrated the superiority (i.e. DFS and OS) of infusional or oral fluoropyrimidine plus oxaliplatin over 5-FU/LV alone for patients with stage III colon cancer. This superiority translates into the recommendation of administer 6-months adjuvant FOLFOX or XELOX in patients with resected stage III colon cancer.

However, the addition of oxaliplatin carries along some additional and dose-limiting toxicities, so combination therapy may be considered in patients for whom these side effects could be tolerated.

3.3. IDEA trial

The standard treatment for patients with stage III colon cancer is surgery followed by 6 mo of oxaliplatin-based adjuvant therapy with either FOLFOX or oral capecitabine plus oxaliplatin (CAPOX) [23]. However, oxaliplatin is associated with cumulative dose-dependent neurotoxicity, characterized by distal or perioral paresthesias or dysesthesias, which often occurs during or immediately after the oxaliplatin infusion. In addition, many patients develop a chronic peripheral neurotoxicity that can substantially affect their quality of life [24,25]. The IDEA trial [26] is a prospective, preplanned pooled analysis of six randomized phase 3 trials that were conducted concurrently to evaluate the noninferiority of adjuvant therapy with either FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPOX (capecitabine and oxaliplatin) administered for 3 months, as compared with 6 months. The primary end point was the rate of disease-free survival at 3 years. Noninferiority of 3 months *versus* 6 months of therapy could be claimed if the upper limit of the two-sided 95% confidence interval of the hazard ratio did not exceed 1.12. The IDEA trial [26] enrolled 12,834 patients across 12 countries (SCOT [United Kingdom, Denmark, Spain, Sweden, Australia, New Zealand], TOSCA [Italy], Alliance/SWOG 80702 [United States, Canada], IDEA France [France], ACHIEVE [Japan], HORG [Greece]. However, the Alliance/SWOG 80702 and HORG trials do not have mature data at present.

The international SCOT trial (NCT00749450) is a noninferiority randomized study designed to determine whether 3 months of adjuvant chemotherapy with FOLFOX or CAPOX in stage III/high-risk stage II CRC is as effective as 6 months of treatment. DFS was analyzed, showing 76.9% (95%CI: 75.0%–78.7%) for the 3-mo treatment arm and 76.1% (95%CI: 74.2%–78.0%) for the 6-mo treatment arm for the CAPOX regimen (HR: 0.94; 95%CI: 0.84–1.07; $P = 0.002$) and the 3-year DFS to be 76.3% (95%CI: 73.5%–79.0%) for the 3-mo treatment arm and 79.2% (95%CI: 76.6%–81.8%) for the 6-mo treatment arm for the FOLFOX regimen (HR: 1.16; 95%CI: 0.96–1.39; $P = 0.592$). The SCOT trial showed that 3 mo of adjuvant treatment is not inferior to 6 mo of treatment, regardless of the chemotherapy regimen used. The frequency of grade 3–5 diarrhea (p = 0·033), neutropenia (p = 0·031), pain (p = 0·014), hand-foot syndrome (p = 0·031), and sensory neuropathy (p < 0·0001) was significantly higher in the 6 month group than in the 3 month group. Diarrhea and hand-foot syndrome were more frequent in patients receiving CAPOX and neutropenia was more frequent in patients receiving FOLFOX [27].

The TOSCA study is a phase III, randomized, open-label, noninferiority, multicenter trial conducted in 130 Italian centers and involving patients with resected colon cancer. Sixty-four percent of the patients received FOLFOX4 and thirty-six percent received XELOX in either arm. Sixty-five percent of patients in both arms had stage III disease, with eighteen percent in the arm of 3-months treatment and seventeen percent in the arm of 6-mo treatment presenting with more than 3 positive lymph nodes. The primary endpoint was relapse-free survival, with the rate at 8 years being 75%. This trial has demonstrated no difference for the 3 months of oxaliplatin-based adjuvant treatment compared to the 6 months of treatment; the HR of the 3-mo *versus* the 6-mo treatment for relapse/death was 1.14 (95%CI: 0.99–1.31; P for noninferiority = 0.253). The 3-months treatment benefit *versus* the 6-months benefit was shown in terms of neurological toxicity [28].

ACHIEVE is an open-label, multicenter trial that randomized patients with stage III colon cancer to receive 3 months or 6 months of mFOLFOX6 or CAPOX after surgery, and the primary endpoint is DFS. Seventy-five percent of patients received CAPOX, the highest proportion of patients included among the six trials of IDEA. This Asian trial showed that short duration of adjuvant chemotherapy significantly decreased grade 2 neurotoxicity in 14% and 36% of the 3-months arm and the 6-mo arm, respectively [29].

The IDEA-France trial randomized 2022 patients with stage III colon cancer, with 90% of the patients being treated with the mFOLFOX6 regimen and 10% of the patients with XELOX. The 3-year DFS rates were 72% and 78% ($P = 0.0112$) for patients receiving the 3 months and 6 months of adjuvant therapy, respectively. The overall maximal neuropathy grade 0–1, 2 or 3–4 was 63.6%, 28.5% or 7.9% in the 3-mo treatment group and 33.4%, 41.3% and 25.3% in the 6-mo treatment group ($P < 0.0001$). The IDEA France study, having 90% of patients treated with the mFOLFOX6 regimen, has shown that 6 months of adjuvant treatment is superior to 3 months of treatment. IDEA France, in which 90% of patients received mFOLFOX6, shows superiority of 6 months of adjuvant chemotherapy compared with 3 months, especially in the T4 and/or N2 subgroups [30].

In the IDEA trial tumor (T) and nodal (N) stages were grouped together to make a pragmatic choice between low-risk (T1–3 N1) and high-risk (T4 and/or N2) patients. High risk patients gave different features, regardless, because T4 disease fared different than N2 disease [26]. A large difference, about 20% at 3 years, was observed between these cancers. Although T4 and N2 patients were grouped together in the IDEA analysis, these subsets may represent different tiers of risk, as the investigators proposed. Grouping T4 and N2 patients together “confounded” the analysis, as there was no difference between the N1 and N2 patients in the effect of duration of therapy.

For N1–2 groups combined, if separated by T stage, the HR was 1.04 for T1–3 disease (95% confidence interval (CI): 0.96–1.13), meaning noninferiority remained unproven. The difference came with the T4 patients, where the HR increased to 1.16 (95%CI: 1.03–1.31), clearly showing inferiority for 3 months of treatment and setting T4 patients apart (even if they are grouped together with N2). This means that the real factor that separates low and high risk is the T4, while N1 and N 2

Table 3
Pooled Analysis of IDEA trial (12834 pts).

3 VS 6 MONTHS HR (95% CI)	CAPOX	FOLFOX	All patients
LOW RISK T1-3 N1	0.85(0.71–1.01)	1.10(0.96–1.26)	1.01(0.90–1.12)
HIGH RISK T4 or N2	1.02 (0.89–1.17)	1.20(1.07–1.35)	1.12(1.03–1.23)
All patients	0.95(0.85–1.06)	1.16(1.06–1.26)	1.07(1.00–1.15)

are similar, even if T4 and N2 are grouped together. It is in the T4 that the 3-mo regimen shows inferiority. (Tables 3 and 4).

The goal of the IDEA trial was to demonstrate if 3 months of chemotherapy was as effective as 6 months, but the primary endpoint was not proven statistically; in fact, the 3-mo course of chemotherapy was associated with a less than 1% lower chance of being free of colon cancer at 3 years compared to the standard 6-mo course (74.6% *vs* 75.5%). In the subgroup of patients with lower risk colon cancer, accounting for about 60% of all patients in the study, the DFS rate at 3 years was almost identical for those who received 3 months (83.1%) and 6 months of chemotherapy (83.3%), but with a reduction in neurotoxicity in the 3-months schedule. For high-risk stage III patients (N2 or T4), 6 mo of treatment represented a gold standard, and CAPOX should be preferred over FOLFOX (Fig. 1).

The results of the IDEA trial—the largest prospective clinical trial ever conducted in CRC—show that patients with stage III colon cancer should be considered at low risk for recurrence and may be treated effectively, and incur less neurotoxicity, with a 3-months oxaliplatin-based regimen as compared with the standard 6-months regimen [26]. In this prospective study, the shorter course was associated with a dramatic reduction in neurotoxicity, with little to no compromise in DFS at 3 years.

3.4. Mismatch repair (MMR)

Although most CRCs develop a chromosomal instability alteration pathway, only about 15% of CRCs have a defective DNA MMR system that results in the cells' inability to repair single nucleotide DNA mismatches. This alteration in the germ line is also the principal pathogenetic mechanism involved in CRCs associated to Lynch syndrome (or hereditary nonpolyposis CRC). Defective (d)MMR can be measured by the presence of high microsatellite instability (MSI-H) or by (testing) the loss of the proteins involved in DNA MRR, such as MLH1, MSH2, MSH6 and PMS2.

Sporadic CRC MSI-H is often associated with specific pathological and clinical features, including proximal colon predominance, poor differentiation, mucinous histology, tumor-lymphocytic infiltration, older age at diagnosis, female sex, cigarette smoking [31,32]. and the presence of BRAF V600E mutations [33].

3.5. Prognostic value of MSI

The prognostic role of MSI has been demonstrated in several retrospective and prospective clinical trials. We reviewed the data from the main important studies that analyzed the prognostic MSI value in patients treated with adjuvant chemotherapy.

Sargent et al. [34] has reported a significant prognostic role of MSI status in untreated stage II and stage III CRCs, with a better prognosis for patients with MSI-H (DFS HR: 0.51; 95%CI: 0.29–0.89; $P = 0.009$ and OS HR: 0.47; 95%Cl: 0.26–0.83, $P = 0.004$); no DFS and OS differences were observed in treated patients, mostly due to the effect of adjuvant therapy in the microsatellite stable tumor (MSS) subgroup. The joined analysis of NSABP C07 and NSABP C08 performed by Gavin et al. [35,36] on 1796 patients of both II and III stage has demonstrated good prognosis with a lower frequency of recurrence (HR: 0.48; 95%CI: 0.33–0.7; $P < 0.0001$) and a positive trend on OS for dMMR tumors (HR: 0.63; 95%CI: 0.46–0.89; $P = 0.0084$). Conversely, the survival after recurrence has been worse in the MSI-H subgroup (HR: 1.60; 95%CI: 1.07–2.41; $P = 0.02$).

In disagreement with these results, Sinicrope et al. [31] showed that, for 2580 stage III patients, MMR status was not significantly associated with DFS (HR: 1.04; 95%CI: 0.83–1.29; $P = 0.07$). The prognostic role of MMR status in stage III CRC patients is still controversial [36]. Similarly, a meta-analysis [38] that included randomized phase III clinical trials involving 7642 patients with stage II and III CRCs, has shown that MSI is associated with an improved prognosis, regardless of stage influence (HR: 0.67; 95%CI: 0.58–0.78; $P = 0.31$), and suggest that these tumors may be resistant to 5-FU.

3.6. Predictive value of MSI

Preclinical studies have demonstrated that CRC cell lines with dMMR are resistant to drugs that induce a specific type of DNA damage, such as 5-FU [39,40]. This data has been confirmed in different clinical studies. The phase III trial by Sargent et al. [34] randomized 457 patients with stage II and III CRCs to receive adjuvant 5-FU-based chemotherapy *versus* observation. The subgroup analysis showed that patients with MSI-H tumors receiving 5-FU had no improvement in DFS (HR: 1.10; 95%CI: 0.42–2.91; $P = 0.85$) compared to patients with MSS status. Moreover, in stage II CRCs with MSI-H (dMMR), adjuvant 5-FU treatment has been associated with reduced DFS and OS (HR: 2.3; 95%CI: 0.84–6.24; $P = 0.09$ and HR: 2.95; 95%CI: 1.02–8.54; $P = 0.04$). The detrimental effect of 5-FU adjuvant therapy on MSI-H patients has not been confirmed in subsequent studies.

A systematic review with meta-analysis [41] conducted on seven studies representing 3690 patients has confirmed these results. Among the stage II (25%) and stage III (75%) patients, MSI-H was found in 454 (14%). No statistical differences were found in relapse-free survival nor OS between the treated (with adjuvant 5-FU-based chemotherapy) and untreated patients with MSI-H status. The significant interaction between MSI status and adjuvant treatment suggested a larger benefit for MSS patients.

Oxaliplatin is an alkylant agent that generates platinum-adducts with DNA. This DNA-binding process leads to DNA-cross linking and inhibits DNA synthesis and transcription. This damage is not recognized by the MMR system. For this reason, dMMR tumors should not be resistant to this damage. However, in clinical trials with oxaliplatin–based chemotherapy, no predictive value of MSI status has been demonstrated [42]. The MOSAIC trial [43] demonstrated a benefit in 10-year DFS and 10-year OS for stage III CRCs with addition of oxaliplatin, regardless of MMR status. Similarly, the NSABP C07 and C08 trials showed no interactions between MMR status and platinum chemotherapy [35,36].

In a retrospective analysis [44] conducted on 233 unselected stage III CRC patients, oxaliplatin treatment was associated to statistically significant better DFS (HR: 0.17; 95%CI: 0.04–0.68; $P = 0.001$) in MSI-

Table 4
3 VS 6 MONTHS 3yrs *DFS rate.*

3 VS 6 MONTHS 3yrs DFS rate	FOLFOX 3 mts	FOLFOX 6 mts	CAPOX 3 mts	CAPOX 6 mts	CAPOX + FOLFOX 3 mts	CAPOX + FOLFOX 6 mts
LOW RISK T1-3 N1	81,90%	83,50%	85%	83.1%	83.1%	83.3%
HIGH RISK T4 or N2	61.50%	64,70%	64.1%	64%	62.7%	64.4%
All patients	73.6%	76%	75.9%	74.8%	74.6%	75.5%

RISK GROUP	POSSIBLE DURATION OF ADJUVANT THERAPY
T1-3 N1	3 Months
T4	6 Months
N2	6 Months

Fig. 1. Recommended duration of adjuvant therapy from the IDEA trial. IDEA: International Duration Evaluation of Adjuvant Chemotherapy.

H subgroup (32 patients). Another trial [37] suggested possible DFS benefit with irinotecan based-chemotherapy in MSI CRCs, but this data has not been confirmed in a subsequent analysis [45].

3.7. MMR and RAS/BRAF mutations

BRAF and RAS mutations are not usually investigated in nonmetastatic CRCs. A meta-analysis performed by Taieb et al. [46] on 4689 stage III FOLFOX-treated patients showed a significant shorter time-to-treatment relapse (TTR), survival-after-recurrence (SAR) and OS in MSS patients harboring the BRAF V600E mutation (TTR HR: 1.54; 95%CI: 1.25–1.92; $P = 0.001$, SAR HR: 3.02; 95%CI: 2.32–3.93; $P = 0.001$ and OS HR: 2.01; 95%CI: 1.56–2.57; $P = 0.001$) and KRAS codon 12 and 13 alterations (TTR HR: 1.6; 95%CI: 1.4–1.83; $P = 0.001$, SAR HR: 1.2; 95%CI: 1.01–1.44; $P = 0.04$ and OS HR: 1.62; 95%CI: 1.38–1.91; $P = 0.001$). In MSI-H patients, these mutations seem to have no prognostic role. This recent systematic review had confirmed the results from previous studies [31,35,47].

BRAF mutations are frequently associated with MSI-H status but do not seem to have negative prognostic value in this particular population.

3.8. MSI and CRC molecular classification

In the era of cancer gene expression–based subtyping, the CRC Subtyping Consortium has proposed a four-subgroup molecular classification system, namely being CMS1 (immune; 14%), CMS2 (canonical; 37%), CMS3 (metabolic; 13%) and CMS4 (mesenchymal; 23%) [48]. The CMS1 group represents the majority of MSI-H tumors, and is characterized by hypermutations, CIMP phenotype, intra- and peritumoral immune-infiltration, BRAF mutation and worse survival after relapse.

Llosa et al. [49] showed that MSI-H tumors are frequently associated with diffuse immune $Th1^+$ and cytotoxic lymphocyte-positive infiltrate, not found in the majority of MSS tumors. This microenvironment is counter-balanced by high up-regulated expression of immuno-checkpoint genes, such as PD-1, PD-L1, CTLA4, LAG3 and IDO. AntiPD1/PD-L1 antibodies have been shown to have important efficacy in metastatic CRC with dMMR status [50]. Consequently, in our opinion, these immuno-target therapies could be evaluated in the adjuvant setting for selected MSI-H patients, considering their intrinsic resistance to some drugs.

Finally, one additional element has been introduced recently to help physicians and patients to make a correct and shared decision about the need for an adjuvant treatment in borderline cases: Oncotype DX® Colon Cancer Assay. This 12-gene assay measures gene expressions in colon cancer tissue using a transcription polymerase chain reaction (RT-PCR). Utilizing the expressions of these 12 genes in a quantitative algorithm, it generates a Recurrence Score® (RS) result that provides an estimated risk of recurrence [51]. The prognostic value of the 12 gene assay has been validated in 3 different clinical trials for stage II [51,52] and stage III [53,54] disease. In a large study with stage II patients treated with surgery alone [52] the 3-year risks of recurrence were 12%, 18%, and 22% for predefined low, intermediate, and high Recurrence Score groups, respectively. The RS result has been confirmed as an independent prognostic factor even if it is strongly correlated with T4 stage and MMR status in stage II disease. In fact, T4 tumors had a higher risk of recurrence and had a strong benefit from adjuvant treatment while dMMR stage II tumors had the lowest risk of recurrence and lower benefit from adjuvant 5FU chemotherapy (less than 2%). The authors conclude that the 12 gene RS assay could provide prognostic information that could help physicians especially in stage II disease with T3 and proficient MMR status. Following this suggestion Srivastava G et al. [54] have shown that in 141 stage II pMMR/T3 patients the use of the Oncotype DX assay led to a change in treatment recommendation in 45% of cases, with a treatment decrease for 33% and increase for 11% of patients.

The Japanese SUNRISE study[53] performed on 597 patients with stage II (270) and stage III (350) colon cancer treated with surgery alone, confirmed the prognostic value of the RS result in both stages of disease. It also showed that high risk (RS $>$ 41) stage II patients and low risk (RS $<$ 30) stage IIIA/B patients had similar 5-y rates of recurrence (19 vs 20% respectively) and could therefore be treated in the same way.

Standing to these results, the 12-gene assay could be useful in some stage II and stage III colon cancer patients to provide an additional objective evaluation element to improve clinical decision-making for adjuvant chemotherapy.

4. Conclusions

In this review, we evaluated the benefit of adjuvant chemotherapy in resected colon cancer. We presented and analyzed the available data on efficacy and toxicity of the combination regimen approved for treatment of resected colon cancer.

In particularly we showed and commented the results of the IDEA trial—the largest prospective clinical trial ever conducted in CRC. Data emerging from this trial demonstrated that patients with stage III colon cancer should be considered at low risk for recurrence and may be treated with a 3-mo oxaliplatin-based regimen as compared with the standard 6-mo regimen. In fact the shorter course was associated with a dramatic reduction in neurotoxicity, without compromising DFS at 3 years. However, precise criteria for initial selection of patients candidate for reduced course of adjuvant chemotherapy still need to be defined and caution should be used in interpreting the presented data. We believe that today this data should be discussed with each patient evaluating benefits and risks for a shortened treatment.

We also described, in the era of cancer gene expression, the clinical impact of expression of MSI-H (dMMR) and the four-subgroup molecular classification of CRC that in the near future could led to a more individualized treatment.

Author contributions

All authors contributed equally to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the submitted version.

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