Curr. Treat. Options in Oncol. (2019) 20: 8
DOI 10.1007/s11864-019-0600-2

The Optimal Duration of Adjuvant Therapy for Stage III Colon Cancer: the European Perspective

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Published online: 26 January 2019

This article is part of the Topical Collection on *Lower Gastrointestinal Cancers*

Keywords Colon cancer · Adjuvant chemotherapy · IDEA trial · Clinical trial interpretation

Opinion statement

The International Duration Evaluation of Adjuvant Therapy (IDEA) collaboration was created to pool data from different studies worldwide in order to assess whether a shorter duration of adjuvant treatment in colon cancer could maintain the expected benefit while reducing toxicity. The results of the IDEA trials were clinically relevant. They confirmed a two- to sixfold reduction in neurotoxicity for the shorter duration across trials. Overall, the 3-year disease-free survival was very similar: only 0.9% lower for the 3 months group. However, the results were partially unexpected, because they revealed a difference among chemotherapy regimens (CAPOX better than FOLFOX) and risk groups within stage III. The similar outcome between 3 and 6 months of CAPOX coupled with the substantial reduction in toxicity makes us use the CAPOX regimen for 3 months for most stage III patients. An exception to this general rule is the patient with very high risk, i.e., either T4N1b-T4anyN2 or anyTN2b where we use 6 months of CAPOX. Our take from the trial results is also that FOLFOX should never be given for 3 months and preferably not used at all in the adjuvant setting. The conduction of the IDEA enterprise was truly global. The European contribution was major with three fourths of patients enrolled in the four European trials. Herein, we review the results of the "3 versus 6" trials and the literature regarding the interpretation of the collected data in Europe and in the rest of the world.

Introduction

The undisputed standard adjuvant therapy for stage III colon cancer has been 6 months of chemotherapy with oxaliplatin and a fluoropyrimidine, either 5-fluorouracil and leucovorin (FOLFOX) [1–5] or capecitabine (CAPOX) [6, 7] since 2004.

Though efficacious, these treatment regimens are burdened with relevant toxicity, especially the oxaliplatin-induced cumulative peripheral sensory neuropathy which can be disabling, long-lasting, and irreversible. In consideration of the potential curability and long survival of patients undergoing adjuvant chemotherapy, oxaliplatin-induced neurotoxicity is a clinically relevant issue.

The question whether this toxicity can be reduced with a shorter adjuvant therapy, while maintaining the benefit granted by 6 months of chemotherapy, has recently been addressed by different trials, all gathered in one collaborative study. The International Duration Evaluation of Adjuvant Therapy (IDEA) collaboration was created to prospectively pool data from six independent phase III trials in order to evaluate the primary hypothesis that 3 months of adjuvant oxaliplatin-based therapy would be noninferior to standard 6 months, with disease-free survival at 3 years (3y-DFS) as primary endpoint. The trials involved were as follows: TOSCA (Italy), IDEA France (France), SCOT (UK, Denmark, Spain, Australia, Sweden, New Zealand), ACHIEVE (Japan), HORG (Greece), and CALGB/SWOG (USA and Canada) [8•]. Some of these trials had already been started as stand-alone trials, such as the TOSCA and the SCOT studies, while the others were subsequently initiated thereby generating the IDEA enterprise.

The data

IDEA trial

The IDEA trial [8•] was designed as a noninferiority trial of 3 months versus 6 months of therapy stratified according to tumor and nodal status and chemotherapy regimen. Patients could receive either FOLFOX or CAPOX (except in the CALGB/SWOG trial, which allowed the use of only FOLFOX). The choice of the treatment regimen was not randomized and depended on clinician's choice and the patient's characteristics.

After a median follow-up of 41.8 months, a population of 12,834 stage III colon cancer patients, mainly treated with FOLFOX (~ 60%), was analyzed. The trial showed a 1% difference in 3y-DFS (74.6% vs 75.5%) in the modified intention-to-treat population (mITT), but noninferiority of 3 versus 6 months of therapy could not be demonstrated since the hazard ratio (HR) was 1.07 with a confidence interval (CI) upper limit of 1.15. Noninferiority would have been confirmed if the upper limit of the 95% CI of the HR would not have crossed 1.12. The safety results confirmed a two- to sixfold reduction in neurotoxicity for the shorter duration across trials.

The subgroup analyses gave unexpected but clinically relevant results, mainly regarding risk groups and the choice of chemotherapy regimen. The authors reported that the patient population could be divided into two different prognostic groups. In the T1–3 N1 population (58.7% of patients), that the authors defined "low-risk stage III" patients, 3 months of therapy were noninferior to 6 months (HR 1.01; 95% CI 0.90–1.12) with a 3y-DFS of 83.1% and 83.3%, respectively. In the "high-risk stage III" patients (T4, N2, or both) (41.3% of patients), 6 months of therapy were superior to 3 months (HR of 1.12; 95% CI 1.03–1.23), even though the difference in 3y-DFS was just 1.7% (62.7% vs 64.4%).

These results emphasize the huge prognostic differences dividing stage III patients. While stage III risk of relapse without adjuvant chemotherapy is

usually estimated around 50% [1], the IDEA trial shows how wide the difference in 3-year DFS is between high-risk and low-risk patients receiving adjuvant chemotherapy, ranging between 46.5 and 86.9%.

Regarding the chemotherapeutic regimens, FOLFOX and CAPOX performances were very different. Three months of CAPOX therapy were noninferior to 6 months (HR 0.95; 95% CI 0.85–1.06), with a gain in 3y-DFS of 1.1% (75.9% vs 74.8%). Matching the risk group and the chemotherapy regimen, the main result was the noninferiority of 3 months of CAPOX to 6 months in low-risk patients (HR 0.85; 95% CI 0.71–1.01), with a gain in 3y-DFS of 1.9% (85.0% vs 83.1%). Among high-risk patients, 3 months of CAPOX were associated with a similar 3y-DFS (64.1% vs 64.0%) but crossed the noninferiority margin (HR 1.02; 95% CI 0.89–1.17). On the other hand, 6 months of FOLFOX were superior to 3 months (HR 1.16; 95% CI 1.06–1.26) with a 3y-DFS difference of 2.4% (73.6% vs 76.0%) independently of risk group. In high-risk patients (HR 1.20; 95% CI 1.07–1.3), the 3y-DFS loss was 3.2% (61.5% vs 64.7%).

The authors concluded that 3 months of therapy are probably appropriate for low-risk patients, while in high-risk patients, 3 months could be insufficient. They also underlined how the enormous amount of data now available should allow individualizing treatment duration for each patient.

The European studies

Four of the six trials that composed the IDEA collaboration were designed and conducted mainly in European countries.

TOSCA trial

TOSCA was the first trial of the IDEA collaboration to be conceived and to start accrual, enrolling 3759 patients, most of them (~ 60%) treated with FOLFOX [9]. Since doublet chemotherapy was the standard adjuvant treatment for high-risk stage II patients at the time of trial design, TOSCA accrued both stage III (two thirds of the study population) and high-risk stage II patients.

After a median follow-up of 62 months, the absolute difference in 3-year relapse-free survival (3y-RFS) was only 1.9% between 3 and 6 months of therapy (81.1% vs 83%). Despite the RFS curves of 3 and 6 months being almost identical, the upper limit of the HR CI crossed the noninferiority margin, set at 1.20 (HR 1.14, 95% CI 0.99–1.32). Therefore, noninferiority could not be demonstrated.

Although noninferiority of the 3-month therapy arm was not demonstrated in any subgroup, CAPOX performed better than FOLFOX, as seen in the whole IDEA analysis. In fact, the RFS curves of CAPOX were virtually identical, meaning that 3 months of CAPOX were as good as 6 months. On the other hand, the absolute 3y-RFS difference with FOLFOX was 3.2% in favor of 6 months.

Regarding risk groups, the TOSCA trial yielded counter-intuitive results, showing a growing difference in RFS benefit as risk goes down. These unexpected findings in TOSCA were strengthened by the results on stage II patients. In fact, the difference between 3 and 6 months of therapy peaked in the low-risk patients (stage II), where 3 months of chemotherapy were clearly inferior with an absolute 3y-RFS difference of 5.6% in favor of 6 months. In the high-risk

population (stage III), the two RFS curves appeared to be identical, with a negligible absolute 3y-RFS difference.

SCOT trial

The SCOT trial was the largest of the six trials, designed as a stand-alone trial, which included a population of 6088 patients with a median follow-up of 37 months [10]. It was one of the two trials that enrolled both stage III and high-risk stage II patients (18% of the entire population) and the only one that enrolled both colon and rectal cancer.

In the overall population, irrespective of stage and site, the difference in 3y-DFS was less than 1% (0.4%) between 3 and 6 months of therapy (76.7% vs 77.1%, respectively) with a HR of 1.006 (95% CI 0.909–1.114), significantly below the noninferiority margin of 1.13. The authors concluded that 3 months of chemotherapy were noninferior to 6 months for high-risk stage II and stage III colorectal cancer.

Post hoc analyses regarding chemotherapy regimen and risk groups gave the same results as the IDEA trial. For CAPOX and low-risk stage III patients (T1–3/N1), 3 months of therapy were noninferior to 6 months with a gain in 3y-DFS (0.8% and 1.3%, respectively). For FOLFOX and high-risk stage III patients (T4 or N2), noninferiority was indeed not proven with a loss of 2.9% and 1.8% in 3y-DFS with 3 months of therapy. Post hoc analyses regarding high-risk stage II or rectal cancer patients were not performed due to the low number of patients within these subgroups, even though the forest plot did not show any difference compared to stage III and colon cancer, respectively.

IDEA France trial

IDEA France was generously not designed as a separated trial, but rather as an add-on to the IDEA enterprise without its own power calculation (efficacy analyses were only descriptive) [11].

The mITT population (which includes all patients who received at least one cycle of chemotherapy) was composed of 2010 patients, 90% of which received FOLFOX. Three months of adjuvant chemotherapy were associated with a decreased 3y-DFS rate (72% vs 76%) compared to 6 months (HR 1.24; 95% CI 1.05–1.46). The FOLFOX subgroup confirmed these results, especially in the high-risk patients (8% loss), while in the low-risk patients, the difference in 3y-DFS was clinically less relevant (2% loss).

Patients receiving CAPOX had better results: 3 months of therapy resulted in a 72% 3y-DFS, 1% better than their 6 months counterparts. The strength of the findings regarding CAPOX is largely weakened by the small size of the sample, even though they are in line with IDEA results.

Subgroup analyses according to risk group showed that 6 months of chemotherapy gave a 3% 3-year DFS benefit in low-risk and a 6% benefit in high-risk stage III patients.

HORG trial

HORG trial was one of the earliest but smallest participating trials, and as the IDEA France trial, it was designed as a part of the IDEA collaborative study [12]. Among the 708 stage III patients enrolled, 3y-DFS was 73.2% in the 3-month

arm and 74.9% in the 6-month arm. For patients receiving FOLFOX, 3y-DFS rates were 71.8% versus 77.7% in the 3- and 6-month arms, respectively. In patients receiving CAPOX, once again, the 3y-DFS difference was really small (74.7% vs 74.8%), in line with the IDEA results as well. Given the small sample size, the authors concluded that the results should be interpreted in the context of the IDEA results.

Non-European trials

Two more studies were designed and carried out in the rest of the world: one in Japan and the other in the US and Canada.

The ACHIEVE trial was the only study of the IDEA collaboration performed in the Asian population [13]. The study enrolled 1291 Japanese stage III patients. Notably, it was the trial with the largest proportion of patients receiving CAPOX (75% vs 25% receiving FOLFOX). In the overall population, the DFS was higher in the 3-month arm compared to 6 months with a 3y-DFS of 79.5% versus 77.9%, respectively. Subgroup analyses by risk group and regimen were consistent with the IDEA global results: CAPOX performed better than FOLFOX especially in the low-risk patients.

The results of the CALGB/SWOG 80702 trial have not been either published or presented separately. It was the only trial giving FOLFOX to all of the 2440 stage III patients enrolled in the USA and Canada.

What differences are we talking about?

When we look at percentage differences in DFS, all trials point to the same direction. IDEA had a – 0.9% difference in DFS between 3 and 6 months of therapy; TOSCA – 1.9%, SCOT – 0.4%, and HORG – 1.7%. The only trial that had a DFS percentage greater than 2.7% in 3y-DFS (the loss in DFS considered clinically acceptable by the IDEA investigators) was IDEA France, with – 4% of DFS difference. The ACHIEVE trial was the only study to show a gain in 3y-DFS of + 1.6% with 3 months compared to 6 months in the overall population (Table 1).

Table 1. CAPOX and FOLFOX: results of stage III patients by risk group in the IDEA trials

Trial	Overall population		Low-risk patients		High-risk patients	
	N pts	Δ 3y-DFS	%	Δ 3y-DFS	%	Δ 3y-DFS
IDEA	12,834	– 0.9	59	– 0.2	41	– 1.7
TOSCA*	2402	0.1	66	–	34	–
SCOT	4946	– 0.4	54	1.3	46	– 1.9
IDEA France	2010	– 4	62	– 3	38	– 6
HORG	708	– 1.7	59	–	41	–
ACHIEVE	1291	1.6	56	3.2	44	– 1.1
CALGB/SWOG 80702	2440	–	64	–	36	–

N pts, number of patients; *Δ 3y-DFS*, disease-free survival at 3 years of 3 months versus 6 months of chemotherapy
*TOSCA: 3y-RFS relapse-free survival at 3 years (not DFS)

Table 2. CAPOX: results of stage III patients by risk group in the IDEA trials

Trial	Overall population		Low-risk patients		High-risk patients	
	%	Δ 3y-DFS	%	Δ 3y-DFS	%	Δ 3y-DFS
IDEA	40	1.1	56%	1.9	44%	0.1
TOSCA*	35	–	–	–	–	–
SCOT	66	0.8	54%	3.4	46%	– 1.4
IDEA France	10	1	69%	– 6	31%	15
HORG	58	– 0.1	–	–	–	–
ACHIEVE	75	1.7	57%	4.7	43%	– 2.4
CALGB/SWOG 80702	0	–	–	–	–	–

N pts, number of patients; *Δ 3y-DFS*, disease-free survival at 3 years of 3 months versus 6 months of chemotherapy
*TOSCA: 3y-RFS relapse-free survival at 3 years (not DFS)

Subgroup analysis results were consistent across trials, showing that FOLFOX is less efficacious than CAPOX and needs to be given for 6 months not to lose its efficacy.

On the other hand, 3 months of CAPOX had the same (or better) DFS as 6 months in all trials: + 1.1% in the IDEA trial, 0% difference in TOSCA trial, + 0.8% in SCOT trial, and – 0.1% in the HORG trial (Tables 2 and 3).

The main difference among the trials was the IDEA France results as compared to the results of the other studies. IDEA France showed a – 4% 3y-DFS difference of 3 months compared to 6 months, with a – 8% DFS difference in stage III high-risk patients. These large losses of benefit can be explained with the 90% of patients receiving FOLFOX in this study, since all the other studies suggest the same negative trend for FOLFOX. The IDEA France results support the evidence that FOLFOX is not as good as CAPOX in the adjuvant setting.

Table 3. FOLFOX: results of stage III patients by risk group in the IDEA trials

Trial	Overall population		Low-risk patients		High-risk patients	
	%	Δ 3y-DFS	%	Δ 3y-DFS	%	Δ 3y-DFS
IDEA	60	– 2.4	60%	– 1.6	40%	– 3.2
TOSCA	65	–	–	–	–	–
SCOT	34	– 2.9	54%	– 2.9	46%	– 2.7
IDEA France	90	– 4	61%	– 2	39%	– 8
HORG	42	– 5.9	–	–	–	–
ACHIEVE	25	1.6	51%	– 1.2	49%	2.3
CALGB/SWOG 80702	100	–	–	–	–	–

N pts, number of patients; *Δ 3y-DFS*, disease-free survival at 3 years of 3 months versus 6 months of chemotherapy
*TOSCA: 3y-RFS relapse-free survival at 3 years (not DFS)

The stage II enigma

Out of the results of the 3 versus 6 months trials, one finding stood out as totally unexpected. Stage II patients in the TOSCA trial had the largest difference in DFS between 3 and 6 months of chemotherapy [9]. While in the overall population the difference in DFS was under 2%, stage II patients receiving 3 months of chemotherapy had an absolute benefit loss of approximately 6% compared to those receiving 6 months.

Are these data reliable? Three aspects need to be considered for the sake of interpretation: whether these data are confirmed by other trials, whether they are statistically sound, and their biological plausibility. Regarding external validity, these findings were not confirmed by the other trials enrolling stage II patients. Although data about stage II patients were not conclusive due to the relatively small sample size, in the SCOT trial, the results in high-risk stage II patients did not differ from those seen in stage III [10].

The internal statistical strength of these results is questionable too, since the interaction test for stage resulted nonsignificant.

Plausibility is most troublesome: the idea that lower risk patients should be the ones to benefit the most from longer treatment is hard to accept. Yet, recent data show that stage II and stage III might be two biologically different entities regarding metastatic spread patterns and sensitivity to chemotherapy [14•]. The biology of stage II colon cancer might account for the need for prolonged exposure to fluoropyrimidine treatment as seen in the TOSCA trial.

The clinical relevance of these conflicting data is however limited. In fact, the standard adjuvant therapy in high-risk stage II microsatellite stable colon cancer remains the same: fluoropyrimidine monotherapy for 6 months.

Global perspective versus European perspective

In a search for a pragmatic message to whoever approaches the prohibitive statistical complexity of the duration of colon cancer adjuvant therapy, why do not we look at how these data have been interpreted by clinicians? Experts have expressed their interpretation of the IDEA results through editorials, commentaries, and a special session that took place at the ESMO Annual Meeting 2017.

Clinicians worldwide have given various interpretations of the IDEA data, so much so that it would be hard to talk about a "global perspective" or a "European perspective." Both at the global and at the European levels, there have been similarities and differences in the interpretation of the "3 versus 6" problem.

Although reactions to the IDEA results have varied largely among geographic regions, due to previous habits and to the results of the local part of the IDEA collaboration, a common theme has emerged worldwide: the importance of patients' attitude. Since the results in the high-risk group of patients leave room for discussion, the point of view of the patient on the expected benefit and on how much toxicity is considered acceptable should be taken in high regard. How to evaluate the patient's attitude in order to decide accordingly? One way is to categorize patients according to how much benefit they would trade off against reduced toxicity. One such attempt was done at the special session at ESMO 2017, where patients were described as "fighters" (i.e., willing to sacrifice

no more than 2% benefit in order to reduce toxicity) and "fatalists." Experts from Europe, America, and Japan were invited to declare what they would suggest to "fighter" or "fatalist" patients in various clinical conditions [15••].

The importance of the relationship between the treating oncologist and the patient has also been underlined in editorials and paper discussions.

Editorials by US clinicians Ilson and Schilsky have highlighted the importance of discussing the patient's attitude towards benefit loss and potential toxicities in order to decide the duration of treatment [16, 17].

The authors of the SCOT trial have dealt with this matter in their paper discussion. Although the trial had positive results in the overall population, high- and low-risk categories in the SCOT trial confirmed the results of the IDEA. Therefore, the authors concluded that CAPOX for 3 months can now be considered a standard for low-risk patients, while the choice between 3 and 6 months of therapy in high-risk patients demands to be discussed with the patient.

Most differences in interpretation have dealt with the use of CAPOX in populations that are traditionally more inclined to the use of FOLFOX.

No matter the results of CAPOX in the IDEA trial, in the USA, capecitabine use is still under discussion mainly due to two factors: (1) the CALGB/SWOG 80702 trial had no CAPOX patients; (2) published data show geographic area-specific fluoropyrimidine toxicities. CAPOX administration in the adjuvant setting has been shown to be responsible for higher incidence of grade 3 hand-foot syndrome in the USA than in the rest of the world [18]. Although it is unclear whether this difference depends on different ways of reporting toxicities or on population habits (like folate dietary intake), the reported toxicity has led to a reluctance in administering capecitabine. The IDEA results have generated a debate about this drug, since US opinion leaders are considering the shift to 3 months of CAPOX in stage III low-risk patients.

Oncologists unwilling to use capecitabine in spite of the IDEA data underline that the analysis of the treatment regimen was neither randomized nor pre-planned, and therefore not completely reliable [19].

Other than in the USA, FOLFOX is the doublet of preference in France too. This is mainly due to historical reasons, since French researchers investigated the use of FOLFOX in the adjuvant setting. The landmark MOSAIC trial was the first study to show the benefit granted by 6 months of adjuvant FOLFOX in stage III colon cancer patients [1]. French clinicians are now considering the use of CAPOX in low-risk patients, even though CAPOX advantage was not evident in their national study because of the paucity of patients receiving this regimen. In high-risk patients, since there was no apparent benefit of CAPOX over FOLFOX given for 6 months, they still consider FOLFOX standard of care.

Future perspectives: where do we go now?

The IDEA collaboration is the first example of globalization in Oncology.

In addition, the 3 versus 6 effort has already changed the way we look at adjuvant treatment, mainly due to two unexpected findings of the trials: (1) the better definition of the recurrence risk profile of stage II–III colon cancer based on the underlying biology; (2) the different benefits of capecitabine and 5-fluorouracil.

Since the IDEA population could be the field for further investigation of new ways to optimize the application of adjuvant chemotherapy, the next step would be the analysis of the tumor samples that have been banked from the different trials. Molecular analyses could yield a more in-depth knowledge of tumor biology leading to a better selection of patients according to prognostic and predictive factors [20, 21].

Planned exploratory analyses (e.g., the TransSCOT study and molecular analyses of the TOSCA trial) are already investigating known prognostic and predictive features such as the tumor sidedness, RAS and BRAF mutational status, and microsatellite instability status.

Looking beyond known predictive and prognostic factors, ongoing research is investigating other tumor biomarkers such as multigene-expression signatures (molecular subtyping systems), immune and inflammatory profiles (Immunoscore), and the implementation of liquid biopsies through the assessment of circulating tumor DNA.

Funding Information

Supported in part by grant AIRC 2018 (Associazione Italiana per la Ricerca sul Cancro)

Compliance with Ethical Standards

Conflict of Interest
The authors declare they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350:2343–51.

2. André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, 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.

3. 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.
4. André T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, 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.
5. 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.
6. Haller DG, Tabernero J, Maroun J, de Braud F, Price T, van Cutsem E, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011;29:1465–71.
7. Schmoll HJ, Tabernero J, Maroun J, de Braud F, Price T, van Cutsem E, 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.
8.• Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med. 2018;378:1177–8.

Prospective pooled analysis of six trials evaluating the noninferiority of 3 versus 6 months of adjuvant chemotherapy in colon cancer.

9. Sobrero A, Lonardi S, Rosati G, et al. FOLFOX or CAPOX in stage II to III colon cancer: efficacy results of the Italian Three or Six Colon Adjuvant Trial. J Clin Oncol. 36:1478–1485.
10. Iveson TJ, Kerr RS, Saunders MP, Cassidy J, Hollander NH, Tabernero J, et al. 3 versus 6 months of adjuvant oxaliplatin-fluoropyrimidine combination therapy for colorectal cancer (SCOT): an international, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2018;19:562–78.
11. André T, Vernerey D, Mineur L, Bennouna J, Desrame J, Faroux R, 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.
12. Souglakos J, Boukovinas I, Xynogalos S, et al. Three versus six months adjuvant oxaliplatin plus fluoropyrimidine chemotherapy for patients with stage III colon cancer: the Hellenic Oncology Research Group (HORG) participation to the International Duration Evaluation of Adjuvant (IDEA) chemotherapy project. J Clin Oncol. 2018;36:83–93.
13. Yoshino T, Yamanaka T, Kotaka M, et al. Efficacy of 3 versus 6 months of oxaliplatin-based adjuvant chemotherapy for stage III colon cancer (CC): results from phase III ACHIEVE trial as part of the International Duration Evaluation of Adjuvant therapy (IDEA) collaboration. Ann Oncol. 2017;28(Issue suppl_5,1).
14.• Naxerova K, Reiter JG, Brachtel E, et al. Origins of lymphatic and distant metastases in human colorectal cancer. Science. 2017;357:55–6.

Archival tissue study showing the biological difference between stage II and stage III colon cancers.

15.•• Sobrero A, Grothey A, Iveson T, et al. The hard road to data interpretation: 3 or 6 months of adjuvant chemotherapy for patients with stage III colon cancer? Ann Oncol. 2018;29:1099–10.

Report of a special session at the Annual ESMO Meeting discussing the results of the IDEA trials and patients' attitude.

16. Ilson DH. Adjuvant therapy in colon cancer: less is more. Lancet Oncol. 2018;19:442–3.
17. Schilsky RL. A new IDEA in adjuvant chemotherapy for colon cancer. N Engl J Med. 2018;378:1242–4.
18. Haller DG, Cassidy J, Clarke SJ, Cunningham D, van Cutsem E, Hoff PM, et al. Potential regional differences for the tolerability profiles of fluoropyrimidines. J Clin Oncol. 2008;26:2118–23.
19. Venook AP. Advances in adjuvant therapy for colon cancer: P value or practical value. J Clin Oncol. 2018;36:1461–2.
20. Formica V, Zaniboni A, Loupakis F, Roselli M. Noninferiority of three months versus six months of oxaliplatin-based adjuvant chemotherapy for resected colon cancer. How should IDEA findings affect clinical practice? Int J Cancer. 2018;143:2342–50.
21. Tang M, Price TJ, Shapiro J, Gibbs P, Haller DG, Arnold D, et al. Adjuvant therapy for resected colon cancer 2017, including the IDEA analysis. Expert Rev Anticancer Ther. 2018;18:339–49.