

Meeting Special Session Report

The hard road to data interpretation: three or six months of adjuvant chemotherapy for patients with stage III colon cancer?

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Abstract

Background: Six months of adjuvant oxaliplatin-based chemotherapy is standard for patients with stage III colon cancer following surgery. However, oxaliplatin is associated with peripheral neurotoxicity which worsens over the treatment duration. Consequently, a shorter treatment duration, if equally effective would be extremely beneficial. A pooled analysis of data for 12,834 stage III colon cancer patients, from six randomised phase III trials of adjuvant therapy, the IDEA study, was performed and the results presented at the ASCO Annual Meeting 2017. The results left the audience and investigators so uncertain about the impact of the new data on clinical practice that ESMO decided to sponsor a special session at their 2017 Annual Meeting dedicated to achieving a more meaningful interpretation of the results.

Methods: Medical oncologists from Europe, the US and Asia selected for their involvement in the trials, together with an independent statistician and an independent clinician, were invited to provide their independent interpretations of the results, and contribute to a moderated panel discussion. The pooled analysis evaluated the non-inferiority of 3- versus 6-months of adjuvant FOLFOX/CAPOX therapy.

Results: There was strong evidence of an interaction between the choice of regimen (CAPOX or FOLFOX) and duration of treatment. Patients were classified as either 'fighters' or 'fatalists', and 3 months CAPOX was considered standard for patients classified as fatalists, even if they had high-risk disease. However, patients classified as 'fighters' would only receive 3 months of CAPOX if they had low-risk disease but would always receive 6 months of CAPOX/FOLFOX if they had T4 disease. The panel was split on whether they would advocate 3 or 6 months CAPOX therapy based on high-risk N2 disease.

Conclusions: The main drivers of the duration of treatment were choice of regimen and patient attitude, with risk, based mainly on T4 stage, having less influence.

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Introduction

Currently, the standard treatment for patients with stage III colon cancer is surgery followed by 6 months of oxaliplatin-based adjuvant therapy with either infusional 5-fluorouracil (5-FU), leucovorin and oxaliplatin (FOLFOX) or oral capecitabine plus oxaliplatin (CAPOX [(XELOX)]) [1, 2]. Unfortunately, however, oxaliplatin is associated with cumulative dose-dependent neurotoxicity which can be debilitating for a significant number of patients in both the short- and long-term. Symptoms of neuropathy, characterised by distal or perioral paresthesias or dysesthesias, often occur during or immediately after oxaliplatin infusion and have been reported to be reversible within a few days. In addition, many patients develop a chronic peripheral neurotoxicity that can substantially affect their quality of life [3-7]. Consequently, dose reductions and early discontinuations of oxaliplatin-based therapy are common. Thus, the question becomes ‘can a shorter duration of adjuvant treatment benefit patients with stage III colon cancer without a loss of efficacy?’

To this end, six randomised phase III trials were conducted concurrently across 12 countries (**SCOT** [UK, Denmark, Spain, Sweden, Australia, New Zealand], **TOSCA** [Italy], **Alliance/SWOG 80702** [US, Canada], **IDEA France** [France], **ACHIEVE** [Japan], **HORG** [Greece]), to investigate 3 months versus 6 months of adjuvant chemotherapy with FOLFOX or CAPOX. This culminated in the prospective, pre-planned, International Duration Evaluation of Adjuvant chemotherapy (IDEA) study, a pooled analysis of 12,834 patients with stage III colon cancer enrolled across the six trials, the results of which were reported at the ASCO Annual Meeting 2017 [8] and showed that 6 months of adjuvant chemotherapy conferred a <1% benefit over 3 months of adjuvant therapy. However, because the upper limit of the 95% confidence interval (CI) for the hazard ratio (HR) for 3-year disease-free survival (DFS) at 1.15 was greater than the predefined upper limit for non-inferiority of 1.12, the non-inferiority of 3 months of oxaliplatin-based adjuvant therapy versus 6 months of oxaliplatin-based adjuvant therapy was considered not proven. Furthermore, the outcomes for comparison of the results for 3 months versus 6 months of adjuvant therapy were dependent on risk group and treatment regimen. This lack of a clear outcome resulted in a lack of certainty not only about the impact of the results on clinical decision making, but if and how the new data might be implemented in clinical practice.

Against this backdrop an ESMO special symposium was convened at the ESMO 2017 Annual Meeting in Madrid, Spain, to discuss whether shortening the duration of adjuvant therapy from 6 months to 3 months, based on both the latest data from the individual trials and the data from the IDEA pooled analysis [8, 9], was a realistic proposition, and discuss how the information provided by these studies might impact on the standard of care, and the ESMO Clinical Practice Guidelines, for early stage colon cancer [1].

Methods

Nine of the authors were selected as a panel of expert medical oncologists from the colorectal cancer (CRC) research groups and centres of excellence across Europe, the US and Asia involved in the trials together with a statistician (Professor Marc Buyse) and a clinician (Professor Tim Maughan) to provide independent interpretations of the results, and Professor Andres Cervantes, Chair of the ESMO Educational Committee, and member of the ESMO Guidelines Committee, to discuss how the latest data might impact on the management and treatment of patients with stage III colon cancer. The panel members convened for the special symposium in Madrid to present and evaluate the latest data from the four most mature (SCOT, TOSCA, ACHIEVE, IDEA-France) of the six randomised phase III trials of adjuvant therapy included in the IDEA pooled analysis [10-13] together with the latest results from the pivotal IDEA pooled analysis [8, 9] of data from all six trials.

Following the presentations and independent interpretations, the data were discussed in a moderated panel discussion lead by Professor Alberto Sobrero with the aim of identifying the current clinical opinions, among the experts present, on the duration of adjuvant therapy in the treatment of patients with early-stage colon cancer.

The data

SCOT trial

The international SCOT trial (NCT00749450), conducted at 224 centres across six countries worldwide, compared 3 versus 6 months of oxaliplatin-based adjuvant chemotherapy in patients with stage III or high-risk stage II tumours of both the colon and rectum. Approximately 67% of patients received CAPOX.

The 3-year DFS rate for the overall patient population was 76.7% for the 3-month treatment arm and 77.1% for the 6-month treatment arm. The HR for non-inferiority was 1.01 (95% CI 0.91 - 1.11) ($P = 0.012$) [10], which did not cross the 1.13 non-inferiority boundary, indicating that 3 months of adjuvant treatment was non-inferior to 6 months of adjuvant treatment. Analysis of DFS according to regimen, CAPOX or FOLFOX, showed the 3-year DFS to be 76.9% (95% CI 75.0% - 78.7%) for the 3-month treatment arm and 76.1% (95% CI 74.2% - 78.0%) for the 6-month 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-month treatment arm and 79.2% (95% CI 76.6% - 81.8%) for the 6-month treatment arm for the FOLFOX regimen (HR 1.16 [95% CI 0.96 - 1.39], $P = 0.592$) (Table 1). Thus, 3 months treatment with CAPOX was non-inferior to 6 months treatment, whilst 3 months treatment with FOLFOX was not non-inferior to 6 months treatment. Analysis of DFS by stage III disease risk group (T1-3/N1 vs. T4 or N2), showed minimal differences between the two treatment durations. Neuropathy measured by patient questionnaire over time according to treatment duration (GOG NTX4 neuropathy score) [14] was considerably higher for patients receiving a 6-month regimen, with curves diverging at 4 months and remaining significantly different for at least 5 years.

Overall the SCOT trial met its non-inferiority target for 3 months of adjuvant treatment. However, the duration of adjuvant therapy was regimen-dependent with 3 months treatment sufficient for patients receiving CAPOX, whereas 6 months may be needed with FOLFOX.

TOSCA trial

TOSCA (NCT00646607) is a phase III, randomised, trial conducted in patients with stage II and III colon cancer from 130 Italian sites, and is the most mature of the six randomised trials included in the IDEA analysis [15]. Patients were randomised to receive either 3 months or 6 months of FOLFOX4 or XELOX (CAPOX) at the choice of the physician. Approximately a third of the patients received CAPOX. The HR for relapse or death for the 3614 patients was 1.14 (95% CI 0.99 - 1.32, P value for non-inferiority = 0.506) (Table 1), with the upper limit of the 95% CI crossing the non-inferiority boundary of 1.2. Counterintuitively the 3-year DFS rate for patients with stage II disease treated with 6 months of adjuvant therapy was markedly superior to the DFS rate for those who received 3 months therapy (HR 1.41 (95% CI (1.05 - 1.89), with a 3-year difference in DFS of 5.7% in favour of 6-months treatment (Table 1). Thus, the TOSCA trial was unable to demonstrate that 3 months of adjuvant oxaliplatin-based therapy was as effective as 6 months of adjuvant therapy. As expected, toxicity was significantly worse for patients receiving 6 months of adjuvant therapy compared with 3 months of therapy.

ACHIEVE trial

ACHIEVE (UMIN000008543) is a phase III, randomised, open-label, non-inferiority, multicentre trial conducted in Japan in patients with resected stage III colon cancer. Seventy-five percent of patients received CAPOX. Of the 1313 patients randomised, data from 1291, were analysed for the latest analysis [13]. The overall 3-year DFS rates for patients receiving 3 months versus 6 months of adjuvant therapy were 79.5% and 77.9% respectively, and the DFS HR was 0.95 (95% CI 0.76 - 1.20). Analysis of 3-year DFS rates by risk group and regimen showed 3 months of CAPOX therapy to be superior to 6 months of CAPOX therapy in low-risk patients (HR = 0.64, 95% CI 0.38 - 1.08). For patients with high-risk disease 6 months of adjuvant therapy may be required, with HRs of 1.09 (95% CI 0.67 - 1.78) and 1.06 (95% CI 0.76 - 1.48) for FOLFOX and CAPOX, respectively. Three months of adjuvant treatment

was associated with significantly decreased neurotoxicity with the proportion of patients with \geq grade 2 toxicity 14% vs. 37% for 3 vs. 6 months of adjuvant chemotherapy, respectively ($P < 0.001$). Overall, the data suggest that 3 months of adjuvant therapy maybe adequate, but that for patients with high-risk disease 6 months treatment may be required. Three months of adjuvant therapy significantly reduced the incidence of neurotoxicity, but it should be noted that 75% of patients in the ACHIEVE study received CAPOX which weighted the overall result.

IDEA - France trial

The phase III, IDEA-France trial (NCT00958737) randomised 2022 patients with stage III colon cancer from 129 centres in France and 2010 (99%) and 1757 (87%) were included in the mITT patient population. Ninety percent of patients included in the trial received FOLFOX6, thus the CAPOX data are very limited and the results based on small patient numbers. The 3-year DFS rates were 72.1% and 75.7% (HR = 1.24, 95% CI 1.05 - 1.46, $P = 0.01$) for patients receiving 3 months and 6 months of adjuvant therapy respectively in the mITT population (Table 1), and 72% and 78% (HR = 1.36, 95% CI 1.14 - 1.63, $P = 0.0007$) for patients receiving 3 months and 6 months of adjuvant therapy respectively in the modified per protocol patient population. For patients in the mITT population the 3-year DFS rates were 80% and 83% for the 1245 T1-3/N1 patients receiving 3 and 6 months of treatment respectively (HR = 1.15, 95% CI 0.91 - 1.47), and 59% and 65% for the 764 T4/N2 patients receiving 3 months and 6 months of treatment respectively, (HR = 1.38, 95% CI 1.10-1.73) Table 1. Neuropathy $>$ grade 1 was observed in 36% and 67% of patients ($P < 0.0001$) during treatment, and with a median follow up of 43 months residual $>$ grade1 neuropathy was observed in 2.5% and 6.7% of patients ($p < 0.001$), in the 3- and 6-month treatment arms, respectively. Thus, the IDEA-France trial shows that 6 months of adjuvant chemotherapy is superior to 3 months, based on data from patients treated with FOLFOX6 in 90% of cases.

Alliance/SWOG 80702 and HORG

The individual data from the Alliance/SWOG 80702 (NCT01150045) and HORG (NCT01308086) trials were not presented due to the absence of mature data.

IDEA pooled analysis

IDEA is a prospective, preplanned, pooled analysis of six concurrently conducted randomised phase III trials of 3 months versus 6 months of oxaliplatin-based adjuvant therapy in patients with stage III colon cancer and represents an independent, academic collaboration of clinicians and statisticians from the six trials. The primary endpoint was 3-year DFS. Non-inferiority was considered to have been demonstrated if the two-sided 95% CI for the HR for DFS (3 months vs. 6 months) estimated by a stratified Cox model was below 1.12. The present analysis included 12834 patients from 12 countries accrued between June 2007 and December 2015. The characteristics of the patients used in this pooled analysis are summarised in supplementary Table S1. As expected, the adverse event rates were lower for patients receiving 3 months of adjuvant therapy than for those receiving 6 months (Table 2). The 3-year DFS rates were 74.6% and 75.5% (HR = 1.07, 95% CI 1.00 - 1.15) for patients receiving 3 months and 6 months of adjuvant therapy, respectively (Figure 1). However, as the upper boundary of the 95% CI was 1.15, and greater than the pre-specified boundary for non-inferiority of 1.12, the non-inferiority of 3 months of adjuvant treatment compared with 6 months of adjuvant treatment was not established for patients with stage III colon cancer. Subgroup analyses showed 3 months of CAPOX to be non-inferior to 6 months of CAPOX (HR = 0.95, 95% CI 0.85 - 1.06), but 3 months of FOLFOX to be inferior to 6 months of FOLFOX (HR = 1.16, 95% CI 1.06 - 1.26) (Table 3). Three months of CAPOX was non-inferior to 6 months of CAPOX for the treatment of patients with low-risk (T1-3, N1) disease (Table 3), which accounted for approximately 60% of the patients in the analysis. The non-inferiority of 3 months of FOLFOX for the treatment of patients with low-risk (T1-3, N1) disease (Table 3), was not proven. Treatment duration was shown to matter for treatment with FOLFOX, but not for treatment with CAPOX, with a P -value for interaction of 0.0061 (Table 3). For the patients with high-risk T stage 4 (T4) and/or

N2 disease, approximately 40% of patients in the analysis, 3 months of FOLFOX was inferior to 6 months of FOLFOX, whilst the non-inferiority of 3 months versus 6 months of CAPOX treatment in the same patient group was not proven. The *P*-value for interaction between low-and high-risk patients irrespective of adjuvant treatment regimen was 0.11 (Table 3). Overall, across the two risk groups, 3 months of CAPOX was non-inferior to 6 months of CAPOX whilst 3 months of FOLFOX was inferior to 6 months of FOLFOX (Table 3).

Interpretation of the data

The independent clinician's view

Professor Tim Maughan confirmed that toxicity is always one of the major concerns for patients receiving adjuvant therapy because as was reported in the SCOT trial the neuropathy associated with oxaliplatin-based therapy can persist for as long as 3 - 5 years [10]. These data are also potentially important in terms of healthcare budgets. A rough calculation based on NICE cost data and Globocan statistics suggests that there could be a saving of more than half a billion Euros if every stage III colon cancer patient in Europe received 3 months of CAPOX rather than 6 months of FOLFOX. Professor Maughan presented the data for the CAPOX and FOLFOX regimens in the IDEA pooled analysis, separately. The CAPOX data for 5071 patients show 3 months of adjuvant therapy to achieve a 75.9% DFS rate with a HR of 0.95 and a CI the upper limit of which, at 1.06, is well inside the non-inferiority boundary of 1.12 (Table 3). The FOLFOX data on the other hand not only failed to demonstrate the non-inferiority of 3 months FOLFOX versus 6 months of FOLFOX adjuvant treatment, but clearly demonstrated the inferiority of 3 months treatment with an HR of 1.16 (95% CI 1.06 - 1.26) and a 3-year DFS rate for 6 months of treatment of 76.0% (95%CI 74.6 - 77.5) almost identical to that of 3 months CAPOX therapy. The test for interaction between treatment regimen and duration of treatment was highly significant (*P* = 0.0061) (Table 3). So, the question is, 'what is driving the difference in outcome between the two regimens?' Does continuous exposure to 5-FU improve efficacy over the 3 months? No difference was observed when bolus 5-FU/leucovorin was compared with the bolus-infusional regimen as adjuvant therapy [16] suggesting that the 48 hour infusion may be of insufficient duration to prove its efficacy as an adjuvant therapy. In contrast, Chau et al., [17] showed 12 weeks of infusional 5-FU alone to be superior to bolus 5-FU/leucovorin and Twelves et al., [18] showed capecitabine to be superior to bolus 5-FU/leucovorin suggesting that more continuous exposure to fluoropyrimidines may be important in this setting. However, this is not supported by the data from studies in patients with metastatic CRC.

Analysis of the data by stage (N stage and T stage) showed none of the tests for interaction to approach significance, N stage (*P* = 0.44) and T stage (*P* = 0.36). However, on the Forest plots the comparison for patients with T4 disease although not significantly different appeared as an outlier. For the N1 and N2 stage patients combined, receiving either CAPOX or FOLFOX, those with T stage 1-3 disease (79% of the patients analysed) the DFS HR was 1.04 (95% CI 0.96 - 1.13) not quite confirming non-inferiority (non-inferiority unproven) for 3 months of treatment (Table 4). In contrast for patients with T4 disease (21% of patients) the DFS HR was 1.16 (95% CI 1.03 - 1.31) confirming the inferiority of 3 months of adjuvant treatment. The questions then become how does this split by regimen and how should we treat high-risk N2 patients? The evidence (Table 4) suggests that when using CAPOX, we don't need to worry about N2 patients because 3 months treatment with CAPOX is clearly non-inferior to 6 months treatment in patients with T1-3/N1 or N2 disease. It is the treatment of the patients with T4 disease that is less clear, as 3 months treatment with CAPOX does not achieve non-inferiority in this patient group. Professor Maughan described how he will offer all his patients 3 months of CAPOX adjuvant treatment going forward. For high-risk patients who are not fit enough for treatment with CAPOX or who can't tolerate CAPOX he would recommend 6 months of FOLFOX therapy. For patients with T4 disease he would discuss the possibility of an extra 3 months of chemotherapy. However, Professor Maughan's view was that the higher toxicity and cost implications make this option unattractive.

For those oncologists who routinely use FOLFOX, are the data strong enough to make them switch to CAPOX? Certainly the 3-year DFS rate was 76% for 6 months FOLFOX versus 75.9% for 3 months of CAPOX (Table 3), which is as strong evidence as we will obtain given this question is very unlikely to

be assessed in a randomised study. Clearly there are strong toxicity and health economic drivers to making the switch, but when using FOLFOX there are no data to support shortening the duration of treatment to 3 months.

The independent statistician's view

The aim of the IDEA efficacy analysis was to estimate the HR for DFS comparing 3 versus 6 months of adjuvant therapy across the six trials using a Cox proportional hazards regression model. However, the results were not as clear cut as expected. The analysis of all patients, irrespective of treatment regimen (Table 3) showed a HR for 3-year DFS of 1.07 (95% CI 1.00 - 1.15), suggesting that 3 months of adjuvant treatment is inferior to 6 months of adjuvant treatment. However, analysis of the interaction between treatment duration and patient risk group showed 3 months treatment to be non-inferior in low-risk patients but not in high-risk patients. The *P*-value for interaction between low- and high-risk patients irrespective of adjuvant treatment regimen was 0.11 (Table 3), confirming a moderate interaction. More surprising was that treatment duration mattered for FOLFOX but not for CAPOX, with a *P*-value for interaction of 0.0061, confirming a strong interaction. Thus, if FOLFOX is the chosen regimen the patient should be given 6 months treatment. Unfortunately, the data do not allow us to answer the question of how 3 months of adjuvant treatment with CAPOX compares with 6 months of adjuvant treatment with FOLFOX, because patients were not randomised between CAPOX and FOLFOX. This is a missed opportunity and a factorial design of the IDEA trials would have been far more informative, had it been feasible to randomize patients to CAPOX vs. FOLFOX and to 3 months vs. 6 months of therapy. Furthermore, the IDEA primary analysis was carried out in patients who received at least 3 months of therapy. This analysis may be biased because patients with early failures are excluded. On the other hand, inclusion of these patients favours the hypothesis of non-inferiority and is therefore undesirable. On reflection, patients should have been randomised at 3 months to stopping therapy or to continuing for another 3 months. The SCOT trial had, in fact, used such a delayed randomisation strategy initially, but feasibility considerations led to a change in design and patients were subsequently randomised prior to starting chemotherapy, as in the other trials [19].

Moderated panel discussion

The IDEA study yielded two very clear results. Firstly, the decreased toxicity associated with the 3-month regimens which showed grade 2-4 neurotoxicity to range from 2 to 6 times lower, and the incidence of diarrhoea to be >20% lower, with an overall reduction in the incidence of adverse events. Secondly, the difference in 3-year DFS for the different treatment durations (3 vs. 6 months) is very small (<1.0%) with a HR of 1.07 (95% CI 1.00 - 1.15). So why are we still debating the treatment options?

Firstly, because differences in treatment outcome of between 1% and 4% still matter to patients. The importance of small differences in outcome was demonstrated by a poll conducted by Professor Sobrero at the ESMO WGICC in Barcelona 2017 in which 45 CRC patients were asked the question 'Considering the toxicities and inconveniences suffered, what percentage cure rate would you be willing to sacrifice for a shorter adjuvant treatment duration (3 months vs. 6 months)?' The result showed that 30% of those polled were prepared to accept a 1-2% reduction in cure rate, 30% a 2-4% reduction and 30% a 4-10% reduction, and for the purposes of this discussion were classified according to their responses as either 'fighters', the first group, 30% of patients or 'fatalists', the second and third groups, 60% of patients. The importance attributed to small sacrifices in efficacy was entirely consistent with an earlier report by Love et al. [20] in patients with CRC.

Secondly, we are still debating because the IDEA analysis shows that both the chemotherapy regimen and patient risk group matter when making treatment choices.

Thirdly, and finally, because we will never have better data than these, because this study will never be repeated.

In an attempt to establish some clarity of opinion, the 11 clinicians present, comprising nine involved in the IDEA trials, the independent discussant and the ESMO Educational Committee Chairman, were

then asked to provide their responses to the eight questions listed below depending on whether their patients were ‘fighters’ or ‘fatalists’.

1. If you only had the choice of FOLFOX for 3 vs. 6 months in low-risk T1-3 N1 patients?
2. If you only had the choice of FOLFOX for 3 vs. 6 months in high-risk T4 N2 patients?
3. If you only had the choice of CAPOX for 3 vs. 6 months in low-risk T1-3 N1 patients?
4. If you only had the choice of CAPOX for 3 vs. 6 months in high-risk T4 N2?
5. Now you are free to decide FOLFOX or CAPOX, what do you advise to low-risk patients?
6. Now you are free to decide FOLFOX or CAPOX, what do you advise to high-risk patients?
7. Now you are free to decide FOLFOX or CAPOX, what do you advise to high-risk N2 patients?
8. Now you are free to decide FOLFOX or CAPOX: what do you advise to high-risk T4 patients?

The results of the voting are summarised in Table 5 and were as follows:

- i) a patient who is classified as a ‘fatalist’ will always receive 3 months CAPOX even if he/she has high-risk disease,
- ii) a patient who is classified as a ‘fighter’ will only receive 3 months of CAPOX if they have low-risk disease,
- iii) a patient who is classified as a ‘fighter’ with high-risk N2 disease will usually receive 3 months CAPOX (8/11 clinicians) but sometimes 6 months (3/11 clinicians) (Table 5, ignoring extra votes), and
- iv) a patient who is classified as a ‘fighter’ with high-risk T4 disease will always receive 6 months adjuvant therapy CAPOX/FOLFOX (11/11 clinicians).

In summary

The IDEA pooled analysis data, together with the individual trial data, provided an excellent framework for the discussion of the benefits and risks of reducing the duration of adjuvant therapy in certain stage III colon cancer patients, and it is remarkable to note the complexity of the data interpretation. The same data presented at the ASCO Annual meeting 2017 concluded that the main driver of the decision about the duration of adjuvant treatment was risk, whereas three months later at the special ESMO symposium reported here, the same group of investigators concluded that the main drivers for the duration of adjuvant treatment were treatment choice and the patient's attitude to his/her disease.

Key message

Oxaliplatin-based adjuvant therapy for patients with stage III colon cancer (CC) is associated with cumulative, debilitating peripheral neurotoxicity, impacting on treatment delivery and patient quality of life. The results of a pre-planned pooled analysis of the data from six adjuvant trials suggests that 3 months adjuvant therapy is indeed appropriate for the majority of stage III CC patients.

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Table 1. Results by individual study for SCOT, TOSCA, ACHIEVE and IDEA France

	SCOT		TOSCA (PPP)		ACHIEVE (mITT)		IDEA France (mITT)	
Endpoint	N=6088		N=3614		N=1291		N=2010	
	3m	6m	3m	6m	3m	6m	3m	6m
Primary outcome analysis (overall population)								
3-yr DFS, % (95% CI)	76.7(75.1-78.2)	77.1(75.6-87.7)	81.1	83.0	79.5(76.2-82.4)	77.9(74.4-80.9)	72.0(69.0-75.0)	76.0(73.0-78.0)
Δ 3-yr DFS, %	-0.4% (-2.6-1.8)		-1.9 (-4.8-1.0)		1.6		-4.0	
HR (95% CI)	1.06 (0.91-1.11)		1.14 (0.99-1.32)		0.95 (0.76-1.20)		1.24 (1.05-1.46)	
Non-inferiority <i>P</i> -value	0.012		0.506-		-		0.01	
DFS by regimen								
CAPOX								
3-yr DFS, % (95% CI)	76.9(75.0-78.7)	76.1(74.2-78.0)	82.5	82.5	81.4(77.6-84.6)	79.7(75.8-83.1)	72.0(63.0-80.0)	71.0 (60.0-79.0)
Δ 3-yr DFS, %	0.8 (-1.9-3.5)		0.0 (-4.5-4.5)		1.7		1.0	
HR (95% CI)	0.94 (0.84-1.07)		0.98 (0.77-1.26)		0.90 (0.68-1.20)		0.97 (0.59-1.59)	
Non-inferiority <i>P</i> -value	0.002		-		-		-	
FOLFOX								
3-yr DFS, % (95% CI)	76.3(73.5-79.0)	79.2(76.6-81.8)	80.4	83.3	73.9(66.4-80.0)	72.3(64.5-78.7)	72.0(69.0-75.0)	76.0(73.0-78.0)
Δ 3-yr DFS, %	-2.9 (-6.7-0.8)		-2.9 (-6.2-0.4)		1.6		-4.0	
HR (95% CI)	1.16 (0.96-1.39)		1.23 (1.03-1.46)		1.07 (0.71-1.60)		1.27 (1.07-1.51)	
Non-inferiority <i>P</i> -value	0.592		-				0.01	
DFS by stage III risk group								
T1-3/N1								
3-yr DFS, % (95% CI)	85.3(82.5-88.2)	84.0(80.6-87.5)	85.5	91.2	90.5(87.0-93.1)	87.3(83.3-90.5)	80.0(76.0-83.0)	83.0(79.0-85.0)
Δ 3-yr DFS, %	1.3 (-1.5-4.1)		-5.7 (-9.7-1.7)		3.2		-3.0	
HR (95% CI)	0.91 (0.75-1.10)		1.41 (1.05-1.89)		0.81 (0.53-1.24)		1.15 (0.91-1.47)	
Non-inferiority <i>P</i> -value	0.011		-		-		-	

T4 or N2							
3-yr DFS, % (95% CI)	63.0(60.2-65.9)	64.8(62.0-67.7)	78.8	78.7	65.4 (59.6-70.7)	66.5(60.6-71.7)	59.0(54.0-64.0) 65.0(60.0-70.0)
Δ 3-yr DFS, %	-1.8 (-5.8-2.3)		0.1 (-3.4-3.6)		-1.1		-6.0
HR (95% CI)	1.07 (0.93-1.22)		1.07 (0.91-1.26)		1.07 (0.81-1.40)		1.38 (1.10-1.73)
Non-inferiority p-value	0.191		-				

Abbreviations: CAPOX, capecitabine plus oxaliplatin; CI, confidence interval; DFS, disease-free survival; FOLFOX, infusional 5-fluorouracil, leucovorin and oxaliplatin; mITT, modified intention to treat population; HR, hazard ratio; N, node; PPP, per-protocol population; T, tumour, yr, year.

Table 2. Summary of key adverse events for 3 versus 6 months treatment by regimen in the IDEA pooled analysis

	FOLFOX			CAPOX		
Adverse Events*	3 months	6 months	p-value ¹	3 months	6 months	P-value ¹
All						
G2	32%	32%	<.0001	41%	48%	<.0001
G3-4	38%	57%		24%	37%	
Neurotoxicity						
G2	14%	32%	<.0001	12%	36%	<.0001
G3-4	3%	16%		3%	9%	
Diarrhea						
G2	11%	13%	<.0001	10%	13%	0.0117
G3-4	5%	7%		7%	9%	

¹Chi-squared test for trend. *There were a total of 19 grade 5 events, also adverse events were only collected for the first 617 patients enrolled in to the SCOT trial.

Abbreviations: CAPOX, capecitabine plus oxaliplatin; FOLFOX, infusional 5-fluorouracil, leucovorin and oxaliplatin; G, grade.

Table 3. Summary results by risk group and regimen from the IDEA6 pooled analysis

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 months	6 months		3 months	6 months		3 months	6 months	
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 and / 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		1.07 (1.00-1.15)

Abbreviations: CAPOX, capecitabine plus oxaliplatin; CI, confidence interval; DFS, disease-free survival; FOLFOX, infusional 5-fluorouracil, leucovorin and oxaliplatin; HR, hazard ratio; N, node, T, tumour, yr, year.

Key for 'non-inferiority' of 3months versus 6 months of adjuvant therapy:

Non-inferior

Not proven

Inferior

Table 4. 3-year disease-free survival by T stage and chemotherapy regimen

Stage	T1-3/(N1/N2) HR (95% CI) for 3 vs. 6 months	T4/(N1/N2) HR (95% CI) for 3 vs. 6 months
Regimen		
Overall, either regimen CAPOX or FOLFOX	1.01 (0.90 – 1.12)	1.12 (1.03 – 1.23)
FOLFOX	1.10 (0.96 – 1.26)	1.20 (1.07 – 1.35)
CAPOX	0.85 (0.71 – 1.01)	1.02 (0.89 – 1.17)

Abbreviations: CAPOX, capecitabine plus oxaliplatin; CI, confidence interval; FOLFOX, infusional 5-fluorouracil, leucovorin and oxaliplatin; HR, hazard ratio; N, node, T, tumour.

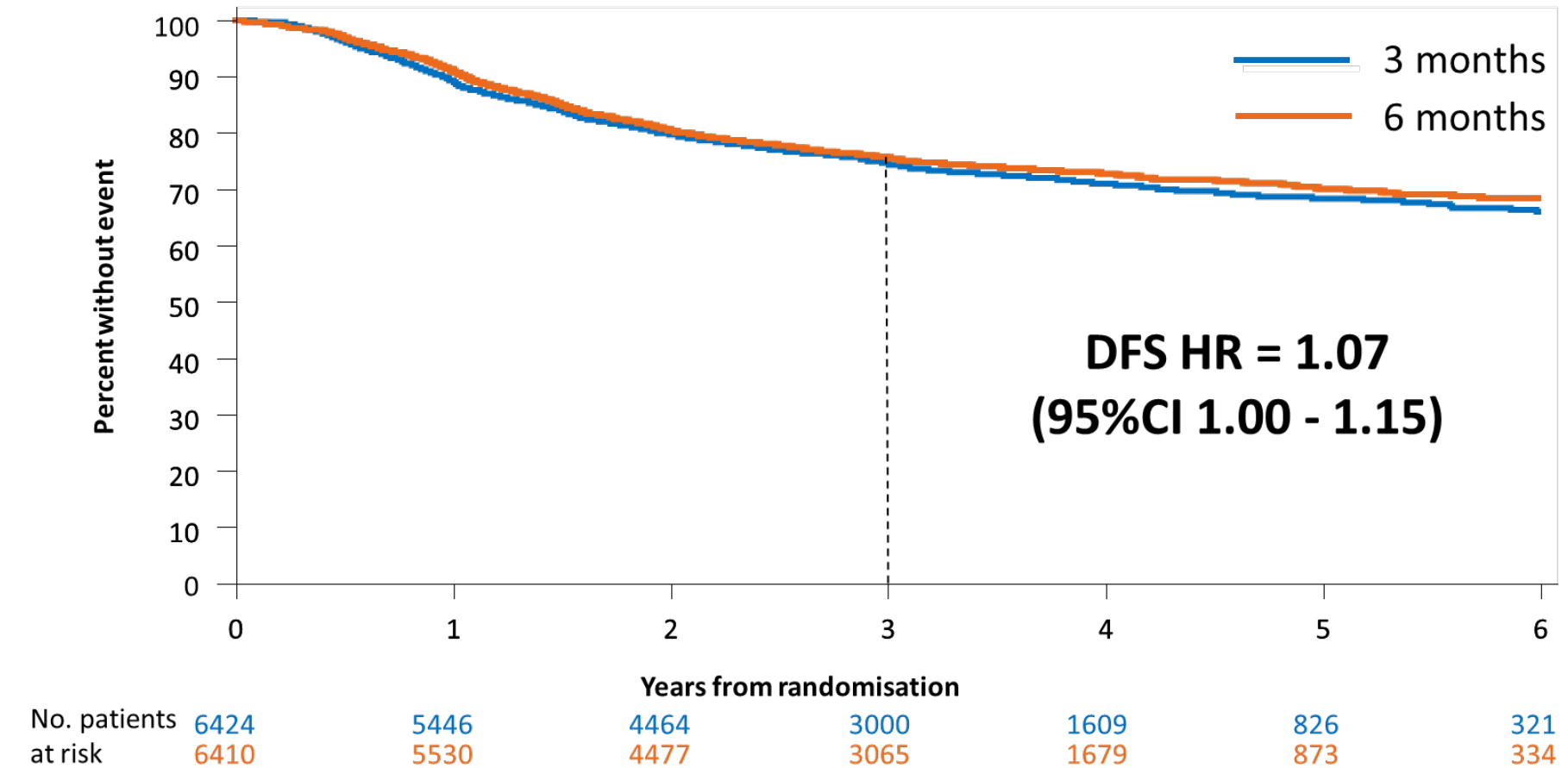
Table 5. Voting by the expert panel of 11 clinicians in response to questions in the moderated discussion

Treatment	CAPOX 3 months	FOLFOX 3 months	CAPOX 6 months	FOLFOX 6 months
Question	Votes, n	Votes, n	Votes, n	Votes, n
1. If you only had the choice of FOLFOX for 3 vs. 6 months in low-risk T1-3 N1 patients?				11 for fighters
2. If you only had the choice of FOLFOX for 3 vs. 6 months in high-risk T4 N2 patients?				11 for both fatalists and fighters
3. If you only had the choice of CAPOX for 3 vs. 6 months in low-risk T1-3 N1 patients?	11 for both fatalists and fighters			
4. If you only had the choice of CAPOX for 3 vs. 6 months in high-risk T4 N2 patients?	11 for fatalists and 4 for fighters		7 for fighters	
5. Now you are free to decide FOLFOX or CAPOX, what do you advise to low-risk patients?	11 for both fatalists and fighters	1 extra vote for fatalists*		1 extra vote for fighters*
6. Now you are free to decide FOLFOX or CAPOX, what do you advise to high-risk patients?	11 for fatalists and 4 for fighters		5 for fighters*	3 for fighters*
7. Now you are free to decide FOLFOX or CAPOX, what do you advise to high-risk N2 patients?	11 for fatalists and 8 for fighters		2 for fighters*	3 for fighters*
8. Now you are free to decide FOLFOX or CAPOX, what do you advise to high-risk T4 patients?	11 for fatalists		9* for fighters	3 for fighters

*Extra votes from one participant.

Abbreviations: CAPOX, capecitabine plus oxaliplatin; FOLFOX, infusional 5-fluorouracil, leucovorin and oxaliplatin; N, node; T, tumour.

Figure 1. Primary outcome analysis from IDEA pooled analysis



Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio, No, number.

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