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FOLFOX and FLOX Regimens for the Adjuvant Treatment of Resected Stage II and III Colon Cancer

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Abstract

The MOSAIC trial showed that the use of adjuvant oxaliplatin and an infusional regimen of 5-FU/LV in the treatment of stage II/III colon cancer improved disease-free survival (DFS). The NSABP's C-07 trial evaluated the addition of oxaliplatin to a weekly Roswell Park regimen of bolus 5-FU/LV and found a similar improvement in DFS. The benefit of oxaliplatin appears to be independent of the 5-FU/LV regimen used. This paper reviews the efficacy and toxicities of these two regimens and is meant to serve as a guide for clinical practice.

Keywords

Colon cancer; adjuvant chemotherapy; oxaliplatin; adjuvant therapy

INTRODUCTION

In the past decade significant progress has been made in the treatment of colon cancer. Oxaliplatin and irinotecan given with 5-fluorouracil (FU) and leucovorin (LV) or capecitabine are now standard chemotherapeutic agents for the treatment of advanced colorectal cancer (CRC).^(1–4) When targeted agents such as bevacizumab or cetuximab are added to these chemotherapy agents, further benefits are achieved. (5, 6) Panitumumab is the most recent targeted agent to join this arsenal.⁽⁷⁾

There has also been progress in the treatment of resected CRC. In 2004, André et al. established the benefit of adding oxaliplatin to infusional 5-FU and LV (FOLFOX versus FL) for the treatment of resected CRC in the MOSAIC (Multi-center International Study of Oxaliplatin/ 5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial.⁽⁸⁾ This study proved that adding oxaliplatin, a third-generation platinum, to FL can improve disease-free survival (DFS) in stage II and III resected CRC compared to FL alone, which led to the approval

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ClinicalTrials.gov ID for NSABP C-07: NCT00004931

of FOLFOX by the US Food and Drug Administration (FDA) as standard adjuvant treatment for stage III colon cancer after a curative resection.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) launched Protocol C-07 in 2000. This trial was designed to compare oxaliplatin and bolus 5-FU/LV to bolus 5-FU/LV alone (FLOX versus FULV, Roswell Park regimen (9)) for resected stage II and III CRC. The definitive analysis of the primary endpoint for this trial, disease free survival (DFS), has been published.⁽¹⁰⁾ The results from this study confirm the superiority of an oxaliplatin-based regimen in the adjuvant treatment of CRC, with benefit similar to that reported by André et al. from the MOSAIC study.⁽⁸⁾ The purpose of this review article is to compare these two adjuvant studies. Although longer follow-up data are available from the MOSAIC trial⁽¹¹⁻¹²⁾ than from NSABP C-07, we have elected to compare the data from both these trials based on the original publications with median follow-up times of 38 months for MOSAIC and 42 months for NSABP C-07. Updated information on MOSAIC at 5- and 6- year median follow-up time-points will also be reviewed. Study organization, patient demographics, efficacy data, and safety and toxicity results from the two regimens used in these studies are discussed, and practical considerations are provided to assist clinicians in the use of these regimens.

Statistical Methodology Employed In This Manuscript

Patient characteristics and toxicities were compared across trials using chi-square tests or Fisher's exact tests. Caution should be exercised in interpreting these cross-study toxicity comparisons since the comparisons are not randomized. Apparent differences in toxicity may be due to differences in patient characteristics or differences in methods for collecting toxicity information and may not be solely due to differences in treatment.

THE MOSAIC AND NSABP C-07 TRIALS

The MOSAIC study, a Sanofi-Synthelabo-sponsored international trial that was conducted primarily in Europe between October 1998 and January 2001, enrolled 2246 patients in 20 countries. NSABP C-07, conducted primarily in North America, by the NSABP enrolled 2492 patients from the US, Canada, Australia, and New Zealand between February 2000 and November 2002.

Study Design

Planned as parallel studies, the study design, stratification, and primary endpoint were very similar, as shown in Table 1.

Statistical Design—Both the MOSAIC and NSABP C-07 trials were randomized multicenter clinical trials with randomization performed centrally. Both used stratified randomization: the stratification on MOSAIC was based on T stage (T2, 3 versus 4), N stage (0, 1, 2), perforation, obstruction or venous invasion and NSABP C-07 stratification was based only on N stage (0, 1, 2). Both trials used minimization methods to balance the treatment allocation within strata.

The MOSAIC trial recruited 2246 patients, 2200 of whom received treatment. The study was designed to detect a 6 percent improvement in 3-year DFS rate in the FOLFOX group from the 73 percent in the FL-only arm with 90 percent power using a two-sided log-rank test with $\alpha = 0.05$.

NSABP C-07 recruited 2492 patients, 2407 of whom were eligible with follow-up in the definitive analysis. The study was powered at 89 percent to detect a 5.4 percent improvement in 3-year DFS rate in the FLOX arm from the 73.2 percent DFS rate in the FULV arm using a two-sided log-rank test stratified for N stage with $\alpha = 0.05$.

The primary endpoint of DFS in the MOSAIC trial was defined as the time from randomization to relapse or death, whichever occurred first. Second CRCs were considered relapses; non-CRCs were disregarded in the analysis. The primary endpoint for NSABP C-07 was also DFS, which was defined as time to first recurrence, death, or second primary cancer. (See Table 1).

Patient Population

In both these trials, eligible patients were to have undergone complete resection of their adenocarcinoma of the colon. Patients with either stage II (T3 or 4, N0, M0) or stage III (any T, N1 or N2, M0) disease were allowed on both these trials. Similar baseline Karnofsky performance-status score of at least 60 and adequate liver, bone marrow, and kidney function were required. Selected patient demographics are compared and summarized in Table 2. The median age of patients enrolled in both trials was 60 years; ~56 percent were males in both studies. Patients in the MOSAIC study had significantly fewer positive nodes than those on NSABP C-07 (40 versus 29 percent negative nodes, 45 versus 52 percent 1–4 positive nodes, 15 versus 19 percent 5 or more positive nodes, $p<0.0001$). There was also a difference in the distribution of T stage between the two trials ($p<0.0001$), the most notable being the predominance of T4 stage patients on the MOSAIC trial. On the MOSAIC trial, 19.0 percent patients receiving FOLFOX versus 18.5 percent patients receiving FL had T4 disease. Whereas on NSABP C-07, 6.8 percent patients receiving FLOX versus 6.0 percent patients receiving FL had T4 disease. Treatment was started within seven weeks following surgery on both studies. Both trials were approved by local institutional review boards and required written informed consent from study participants.

Treatment Regimens

MOSAIC Study: Infusional 5-FU and LV (FL) with oxaliplatin, FOLFOX (Figure 1)

—In this study, LV was given as a 2-hour IV infusion in a dose of $200\text{mg}/\text{m}^2$ followed by a 5-FU bolus of $400\text{mg}/\text{m}^2$. An infusion of 5-FU followed at a dose of $600\text{mg}/\text{m}^2$ over 22 hours on 2 consecutive days given every 14 days for 12 cycles (6 months). Oxaliplatin was given in the experimental arm at $85\text{mg}/\text{m}^2$ on day 1 simultaneously with LV over 2 hours.

NSABP C-07: Bolus 5-FU and LV (FULV) with oxaliplatin, FLOX (Figure 1)

—LV was given as a 2-hour IV infusion in a dose of $500\text{mg}/\text{m}^2$ weekly with 5-FU administered as an IV bolus 1 hour after the LV infusion was begun at a dose of $500\text{mg}/\text{m}^2$, for 6 consecutive weeks (on days 1, 8, 15, 22, 29, 36 of the treatment cycle), followed by a 2-week rest period. Oxaliplatin was administered in the experimental regimen as a 2-hour infusion in a dose of $85\text{mg}/\text{m}^2$ prior to LV and 5-FU on days 1, 15, and 29 of the treatment cycle. Patients received three 8-week cycles of therapy for a total treatment duration of 24 weeks (6 months).

RESULTS

The results of the MOSAIC trial have been presented previously,^(8,11) and an update of overall survival (OS) on MOSAIC was presented at ASCO in 2007.⁽¹²⁾ NSABP C-07 results have also been previously reported.^(10,13) The results of these two clinical trials, summarized in Table 3, focus on the definitive analyses of DFS,^(8,10) with 38 months median follow-up for MOSAIC and 42 months median follow-up for NSABP C-07.

Efficacy

The MOSAIC trial and NSABP C-07 both demonstrate the superiority of oxaliplatin-containing regimens FOLFOX and FLOX compared to FL and FULV, respectively, in improving DFS in patients with resected colon cancer. The DFS at 3 years in the MOSAIC trial was 78.2 percent for FOLFOX versus 72.9 percent for FL. FOLFOX increased the probability a patient would be alive and disease-free at 3 years by 5.3 percent. Treatment with

FOLFOX resulted in a 23% reduction in the relative hazard of a DFS event with hazard ratio (HR) 0.77 (95% CI 0.65 – 0.91) compared to FL. FOLFOX was found superior to FL with a two-sided p-value of 0.002.

Similar results were seen in NSABP C-07. Three-year DFS was 76.1 percent on the FLOX arm compared to 71.8 percent in the FULV arm. FLOX increased the probability that a patient would be alive and disease free at 3 years by 4.3 percent compared to FULV. The relative hazard of a DFS event was reduced by 20% with FLOX treatment as compared to FULV with a HR of 0.80 (95% CI 0.69 – 0.93). FLOX was found superior to FULV with a two-sided p-value of 0.0034.

These data document a significant DFS benefit when oxaliplatin is added to FL or FULV. The point estimates for HRs for treatment effect in these trials are nearly identical, and the 95% confidence intervals for HR estimates for the two trials have significant overlap. It is also important to note that DFS in the control arms of FL and FULV in these studies were also comparable. The Kaplan-Meier estimates from the definitive analyses for both these trials are presented in Figure 2.

The results of the MOSAIC trial, updated at ASCO 2007 with a median follow-up of 6 years, (12) showed a trend toward improvement in survival for patients treated with FOLFOX (p=0.057) using an intent-to-treat analysis. The survival rates at 6 years were 78.6 percent for FOLFOX and 76.0 percent for FL. OS data for NSABP C-07 have not yet been reported.

Toxicities

Although both FOLFOX and FLOX were reasonably well tolerated by study participants, a clinically important difference in the pattern of toxicities emerged that is described below, for the benefit of clinicians using these regimens.

Neutropenia with and without fever—More Grade 3+ neutropenia was reported with FOLFOX than with FLOX, 41.1 percent (Grade 4+, 12.3 percent) versus 8.1 percent (Grade 4+, 2.4 percent). However, this difference may be due to the fact that neutrophil nadir counts were reported for MOSAIC, whereas neutrophil counts on the day of therapy were reported for NSABP C-07. This difference in reporting precludes any meaningful comparison of neutropenia between published results of these studies. However, clinically significant neutropenia with fever or infection was reported in only 1.8 percent of patients treated with FOLFOX versus 4.8 percent of those treated with FLOX (p<0.0001).

Neuropathy—In comparing sensory neuropathy from oxaliplatin on both these trials, it is important to consider that the NCI Common Toxicity Criteria for Adverse Events (CTCAE) scoring system used in the MOSAIC trial was version 1.0, and the one used in NSABP C-07 was version 2.0. In addition to better definition for the grades, version 2.0 also has a Grade 4, not present in version 1.0, defined as “permanent sensory loss that interferes with function.” Therefore Grade 3 in version 1.0 is considered similar to Grades 3 and 4 combined, in version 2.0 (v2.0). NSABP C-07 also used the NCI-Sanofi Neurosensory Toxicity Scale that captures paresthesias that may be cold-induced in addition to grading persistent sensory neuropathy seen with oxaliplatin administration.(14) However, only neurotoxicity on NSABP C-07 according to NCI CTCAE 2.0 is summarized in this paper to better facilitate comparison with the MOSAIC trial. A higher incidence of Grade 3/4 neurotoxicity occurred in FOLFOX-treated patients (12.4 percent) than FLOX-treated patients (6.9 percent; p<0.0001) (Data provided by Greg Yothers, PhD., NSABP Biostatistical Center). This decreased to 1.3 percent at six months after FOLFOX and to 0.5 percent on FLOX. The grades of neuropathy on both the trials at different time points are summarized in Table 4. These differences in neurotoxicity are likely related to the 25 percent lower planned cumulative dose of oxaliplatin used in NSABP C-07.

On both protocols, most patients received at least 80 percent of the planned dose of oxaliplatin (Table 3). The planned cumulative dose of oxaliplatin on MOSAIC was 1020mg/m² versus 765mg/m² on NSABP C-07. Therefore, it can be concluded that giving a reduced cumulative dose of oxaliplatin on the FLOX regimen in NSABP C-07 did not appear to compromise efficacy and also decreased the incidence of sensory neuropathy.

Four-year follow-up data on sensory neuropathy on FOLFOX is available and is summarized in Table 4. This information is not available for NSABP C-07.

GI toxicity—The incidence of Grade 3 and 4 diarrhea was 10.8 percent for FOLFOX and 38.0 percent for FLOX. In addition, the spectrum of GI toxicity was different between the two trials. On NSABP C-07, a pattern of severe diarrhea associated with bowel wall injury (BWI, small or large bowel) characterized by hospitalization for the management of diarrhea or dehydration, with radiographic or endoscopic evidence of bowel wall thickening or ulceration, developed in 79 of 1857 (4.3 percent) patients. (15) Fifty-one (64.6 percent) of these events were in patients treated with FLOX and 28 (35.4 percent) in those treated with FULV ($p<0.01$). Enteric sepsis (ES), defined as Grade 3 or greater diarrhea, and Grade 4 neutropenia with or without proven bacteremia was another syndrome that occurred in 22 patients in the FLOX treatment group, versus 8 patients in the FULV treatment group ($p=0.01$).⁽¹⁵⁾ Patients older than 60 years (FLOX 6.7 percent versus FULV 2.9 percent, $p<0.01$) and female patients (FLOX 9.1 percent versus FULV 3.9 percent, $p<0.01$) were at a higher risk for BWI.⁽¹³⁾ There were 5 deaths related to enteropathy; 2 from ES alone in the FLOX-treated patients and 3 attributable to BWI and ES both (2 in the FLOX and 1 in the FULV arm). The majority of these GI syndromes occurred during the third or fourth week on the first cycle of therapy, suggesting that the development of these toxicities was not related to the cumulative doses of chemotherapy received. BWI was seen more frequently and somewhat earlier in the FLOX arm, indicating that oxaliplatin independently contributed to this gastrointestinal toxicity.

No definite enteropathy syndromes were reported following treatment with FOLFOX in the MOSAIC trial. Perhaps the delineation of these enteropathy syndromes in the NSABP C-07 trial and the special effort by the NSABP to collect this information prospectively using special data forms can account for some of the difference in reporting. However, it is clear that the incidence of Grade 3 and 4 diarrhea reported was substantially higher with FLOX compared to FOLFOX. (Table 5).

Treatment mortality—All cause mortality was reported in 0.5 percent of patients treated with FOLFOX within one month after the end of therapy versus 1.2 percent of those treated with FLOX within 60 days after the end of therapy in the primary publications of the MOSAIC and NSABP C-07 studies, respectively.^(8,10) However, the all-cause mortality for FLOX within one month after the end of therapy was 0.92% in NSABP C-07 (unpublished data). The difference in mortality between FOLFOX and FLOX within one month after completing therapy is not statistically significant ($p=0.33$).

DISCUSSION

Based on the work of Sargent et al.⁽¹⁶⁾ the FDA has accepted 3-year DFS as an appropriate regulatory endpoint for approval of adjuvant chemotherapy in colon cancer. We now have 6 and 4 years of median follow-up from MOSAIC and NSABP C-07, respectively, and there is a continuing DFS advantage with the addition of oxaliplatin in both studies. The MOSAIC trial, with 6 years of median follow-up, was updated at ASCO 2007, and indicated a strong trend toward a survival advantage for the FOLFOX regimen.⁽¹²⁾ Longer follow-up will be required to evaluate the impact of the FLOX regimen on survival in NSABP C-07.

It appears that FOLFOX and FLOX are similar in terms of efficacy. However, their toxicity profiles are different. These differences reflect both the different methods of administration of 5FU and leucovorin as well as the addition of oxaliplatin. With respect to severe diarrhea, the infusional schedule of FL used in the MOSAIC trial has a major advantage over the bolus schedule of FULV used in NSABP C-07. The rate of Grade 3 or 4 diarrhea was 6.7% with FL versus 32.2% with FULV. This observation is consistent with previous reports of these regimens^(17,18) for the treatment of colorectal cancer.

Although the addition of oxaliplatin clearly improves DFS, it also increases the rates of Grade 3 or 4 diarrhea to 10.8% with FOLFOX and 38% with FLOX. Even though treatment-related mortality was not increased, clinicians using the FLOX regimen should be aware of the potential for severe diarrhea, select patients accordingly, carefully monitor patients particularly during the first cycle of therapy, and provide vigorous supportive therapy if diarrhea occurs. Oxaliplatin also adds the potential for severe peripheral neuropathy, which was more common with FOLFOX (12.4%) than with FLOX (6.9%). These data need to be considered as part of a comprehensive clinical assessment of individual patients when choosing an adjuvant regimen.

The incidence of enteropathy syndrome (BWI or ES) from FLOX was 6.9 percent.⁽¹⁵⁾ It was significantly higher in those >60 years than in those <60 and in women more than in men (both $p < 0.001$). It is not entirely clear if this was due to a delay in the treatment of symptoms, to associated medical conditions, to a difference in metabolism of the drug, or to a greater intrinsic susceptibility to bowel wall toxicity from oxaliplatin with FULV. Early recognition and fluid replacement appear to be the key in preventing dehydration. Although toxicity can be severe and sometimes prolonged, upon recovery, many patients can continue therapy safely with a reduced dose of the FULV regimen and the discontinuation of oxaliplatin. It is possible, however, that treatment benefit may be reduced in patients required to receive adjuvant therapy attenuated because of toxicity. Therefore, FLOX may not be a good choice for elderly patients, for those who have underlying bowel conditions causing diarrhea, or for those who are susceptible to complications from dehydration, such as patients with cardiovascular or cerebrovascular disease.

The significantly lower incidence of neuropathy seen in C-07 was a likely result of the lower cumulative dose of oxaliplatin given. Over the course of 6 months of therapy, patients on NSABP C-07 received a median of 676mg/m² of oxaliplatin versus the median dose of 894mg/m² received on the MOSAIC study. Despite the lower cumulative oxaliplatin dose given to patients on NSABP C-07, at 4 years of median follow-up, the benefit in DFS is similar. Therefore, because of the lower incidence of severe neuropathy FLOX may offer an advantage to be considered for patients who are at risk for neuropathy or those with a pre-existing Grade 1 sensory neuropathy.

There are also several practical considerations in deciding to use one of these regimens over the other. FOLFOX therapy requires the placement of a central venous catheter, which places the patient at risk from complications of the procedure, subsequent infections, port malfunction, and clot formation in the subclavian vein. In addition, carrying a pump for the 22-hour FU infusion can be quite cumbersome for some.

FLOX therapy does not require a central venous catheter and can be administered through a peripheral vein. There is no added issue of discontinuation of the FU infusion with FLOX. FLOX therapy does, however, require more time in the clinic and more frequent visits to the office (18 visits rather than 12 visits for FOLFOX during the course of the therapy). From the perspective of the patient, FOLFOX requires fewer office visits; on the other hand, infusion pumps may be regarded as more cumbersome. Also, reimbursements and incentives vary in

different practice facilities, which may or may not factor into the preference of one regimen over the other.

FOLFOX is currently the FDA approved adjuvant therapy for resected stage III colon cancer in the United States. FLOX is also an effective surgical adjuvant regimen for colon cancer that represents an alternative, and may be preferable for some patients, particularly those in whom a central venous catheter cannot be placed.

CONCLUSION

The MOSAIC and NSABP C-07 trials have established that the addition of oxaliplatin to 5-FU/LV significantly improves DFS in stage II/III colon cancer patients whose tumors have been resected. The results of both these trials clearly define the superiority of an oxaliplatin-based regimen for adjuvant colon cancer therapy and indicate that the benefit of oxaliplatin appears to be independent of the schedule of 5-FU/LV administered. Therefore, it can be concluded that both FLOX and FOLFOX are appropriate regimens for colon cancer adjuvant therapy. The risk and benefit ratios of these regimens need to be kept in mind before deciding upon therapy. A longer duration of follow-up will be necessary to determine if a statistically significant survival advantage emerges from either the MOSAIC trial or the NSABP C-07 trial.

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EXPERIMENTAL ARM	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8
<u>MOSAIC (FOLFOX)</u>								
5-FU 400 mg/m ² bolus, d1, d2 600 mg/m ² over 22 hrs, d1, d2	X	Rest	X	Rest	X	Rest	X	Rest
LV 200 mg/m ² bolus, d1, d2	X	Rest	X	Rest	X	Rest	X	Rest
Oxaliplatin 85 mg/m ² over 2 hrs, d1	X	Rest	X	Rest	X	Rest	X	Rest
<u>NSABP C-07 (FLOX)</u>								
5-FU 500 mg/m ² bolus, d1	X	X	X	X	X	X	Rest	Rest
LV 500 mg/m ² bolus, d1	X	X	X	X	X	X	Rest	Rest
Oxaliplatin 85 mg/m ² over 2 hrs, d1	X		X		X		Rest	Rest

Figure 1.

Comparison of treatment doses and schedules on MOSAIC and NSABP C-07 (Treatment on both trials was repeated for a maximum duration of 24 weeks)

No. at Risk							
FL+oxaliplatin	1123	1086	1023	959	888	663	395
FL	1123	1066	981	903	817	619	356

No. at Risk					
FLOX	1200	1082	966	675	340
FULV	1207	1079	921	638	291

Figure 2a and Figure 2b.

Figure 2a. Kaplan-Meier estimate of disease-free survival in the MOSAIC trial.

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Figure 2b: Kaplan-Meier estimate of disease-free survival in the NSABP C-07 trial.

Adapted from Figure 2, Kuebler JP 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* 25 (16), 2007: 2198–2204. Reprinted with permission.

Table 1
Comparison of study design, MOSAIC and NSABP C-07

	MOSAIC^a	NSABP C-07^b
Sample size	2246	2407
Study design	Randomized, phase III	Randomized, phase III
Tumor stage	Resected stage II, III	Resected stage II, III
Stratification	<ul style="list-style-type: none"> • T stage: 2, 3 vs. T4 • N stage: 0, 1, 2 • Perforation or obstruction or venous invasion 	N stage: 0, 1, 2
Planned cumulative doses:		
Oxaliplatin	1020 mg/m ²	765 mg/m ²
5-FU	24,000 mg/m ²	9,000 mg/m ²
Primary endpoint	DFS	DFS
DFS defined ^c	Time to relapse or death whichever comes first (non-colorectal cancers were disregarded in the analysis)	Time to first recurrence, death or second primary cancer
Primary analysis cut-off	3 years from enrollment of last patient or 303 events (relapse or death) in test arm whichever comes later	675 events on the combined arms (estimated to be at approximately 3 years from enrollment of last patient)
Secondary endpoints	Safety, overall survival, long-term adverse events	Safety, overall survival, and recurrence-free interval
Statistical power	90% to detect a 6% increase in DFS at 3 years	89% to detect a 5.4% increase in DFS at 3 years

^a André, T et al. N Eng J Med. 2004, 350:2343–2351.

^b Kuebler, JP et al. J Clin Oncol. 2007, 25:2198–2204.

^c Primary efficacy variable definition was different between the two trials.

Table 2
Patient characteristics

	MOSAIC ^a		NSABP C-07 ^b	
Characteristics All patients	FOLFOX (N=1123)	FL (N=1123)	FLOX (N=1200)	FULV (N=1207)
Age				
Median, years	61	60	59.0	59.0
< 65 years, %	64.4	66.2	68.9	67.0
Sex, %				
Male	56.1	52.4	55.3	57.8
Female	43.9	47.6	44.7	42.2
T stage, % ^c				
T1	0.0	0.0	2.8	2.5
T2	4.5	4.8	8.6	10.0
T3	76.0	75.9	81.8	79.6
T4	19.0	18.5	6.8	6.9
Unknown	0.5	0.8	0.3	0.7
Nodal status, % ^c				
0 (stage II)	40.2	39.9	28.8	28.8
1-4	44.4	45.7	52.6	51.5
5+	15.1	14.2	18.0	19.5
Unknown	0.2	0.2	0.2	0.3

^a André, T et al. N Eng J Med. 2004, 350:2343–2351.

^b Kuebler, JP et al. J Clin Oncol. 2007, 25:2198–2204.

^c The distribution of positive nodes and T stage are the only patient characteristics significantly different between the two trials (p<0.0001 for each).

Table 3
Comparison of results of MOSAIC and NSABP C-07^b

	MOSAIC		NSABP C-07 ^b	
	FOLFOX	FL	FLOX	FULV
DFS at 3 years, % (95% CI)	78.2 ^a (75.6, 80.7)	72.9 ^a (70.2, 75.7)	76.1 (73.6, 78.5)	71.8 (69.2, 74.4)
Absolute improvement in DFS at 3 yrs (95% CI)	5.3% ^c (0.0, 10.6)		4.3% (-0.8, 9.3)	
Hazard Ratio (95% CI) (reduction in hazard, %)	0.77 (0.65, 0.92) ^d (23%) ^a		0.80 (0.69, 0.93) (20%)	
p-value	0.002 ^a		0.0034	
Median cumulative dose received				
5-FU	21759mg/m ²	24000mg/m ²	7003mg/m ²	7800mg/m ²
Oxaliplatin	894 mg/m ²	NA	676 mg/m ²	NA

^a André, T et al. N Eng J Med. 2004, 350:2343–2351.

^b Kuebler, JP et al. J Clin Oncol. 2007, 25:2198–2204.

^c de Gramont A, et al. ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement), 2005, (Abstr 3501).

^d de Gramont A, et al. Proc Am Soc Clin Oncol 22:2003, (Abstr 1015).

Table 4

Comparison of peripheral sensory neuropathy

NCI CTC AE ^a Grades	During treatment (%)		Six months after treatment (%)		4-year follow-up (%)	
	FOLFOX ^b N=1106	FLOX ^c N=1189	FOLFOX ^b N=1058	FLOX ^c N= 1030	FOLFOX ^d N=811	FLOX ^e
Grade 0	7.9	21.3	59.0	71.4	84.3	NA ^e
Grade 1	48.2	52.1	31.9	23.4	12.0	NA
Grade 2	31.6	19.8	7.8	4.8	2.8	NA
Grade 3	12.4	6.7	1.3	0.5	0.7	NA
Grade 4		0.2 ^d		0 ^d		

^aNSABP C-07 used CTCAE version 2.0, that grades neurosensory from 0–4. MOSAIC used CTCAE version 1.0, which grades neurosensory from 0–3.

^b André, T et al. N Eng J Med. 2004, 350:2343–2351.

^c Unpublished data, Greg Yothers, PhD. (NSABP Biostatistical Center)

^d de Gramont, A et al. J Clin Oncol, 2007 ASCO Annual Meeting Proceedings Part 1. Vol 25, No. 18S (June 20 Supplement), 2007, (Abstr 4007).

^eNA = Not available.

Table 5

GI toxicities

	MOSAIC ^a	NSABP C-07 ^b	Comparison between experimental arms of MOSAIC and NSABP C-07
NCI-CTC ≥ Grade 3	FOLFOX vs. FL (N=1108 N=1111) % patients	FLOX vs. FULV (N=1234 N=1230) % patients	FOLFOX vs. FLOX (N= 1108 N=1234) % patients
Diarrhea	10.8 vs. 6.7 ^c	38.0 vs. 32.2 ^c	10.8 vs. 38.0 ^{c d}
Nausea	5.1 vs. 1.8 ^c	15.6 vs. 11.0 ^c	5.1 vs. 15.6 ^{c d}
Vomiting	5.8 vs. 1.4 ^c	12.7 vs. 8.4 ^c	5.8 vs. 12.7 ^{c d}

^a André, T et al. N Eng J Med. 2004, 350:2343–2351.

^b Kuebler, JP et al. J Clin Oncol. 2007, 25:2198–2204.

^c p-value <0.01

^d p-values generated by Greg Yothers, PhD. (NSABP Biostatistical Center)