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Phase III trial comparing 3–6 months of adjuvant FOLFOX4/XELOX in stage II–III colon cancer: safety and compliance in the TOSCA trial†

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Background: Six months of oxaliplatin-based adjuvant chemotherapy is standard of care for radically resected stage III colon cancer and an accepted option for high-risk stage II. A shorter duration of therapy, if equally efficacious, would be advantageous for patients and Health-Care Systems.

Patients and methods: TOSCA ['Randomized trial investigating the role of FOLFOX-4 or XELOX (3 versus 6 months) regimen duration and bevacizumab as adjuvant therapy for patients with stage II/III colon cancer] is an open-label, phase III, multicenter, noninferiority trial randomizing patients with high-risk stage II or stage III radically resected colon cancer to receive 3 months (arm 3 m) versus 6 months (arm 6 m) of FOLFOX4/XELOX. Primary end-point was relapse-free survival. We present here safety and compliance data.

Results: From June 2007 to March 2013, 3759 patients were accrued from 130 Italian sites, 64% receiving FOLFOX4 and 36% XELOX in either arm. Treatment completion rate without any modification was 35% versus 12% and with delays or dose reduction 52% versus 44% in arm 3 and 6 m. Treatment was permanently discontinued in 8% (arm 3 m) and 33% (arm 6 m). In arm 6 m, 50% of patients discontinuing treatment did so after completing 80% of planned program. Grade 3+ toxicities were higher in arm 6 m than that in 3 m. Grade 2+ neuropathy was 31.2% versus 8.8% ($P < 0.0001$) while grade 3+ was 8.4 versus 1.3 ($P < 0.0001$), in arm 3 and 6 m. Seven deaths within 30 days from last treatment administration in arm 6 m and three deaths in arm 3 m were observed (0.3% versus 0.1%, $P = 0.34$).

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Conclusions: TOSCA is the first trial comparing 3 versus 6 months of adjuvant chemotherapy completing accrual within the international initiative of treatment duration evaluation (International Duration Evaluation of Adjuvant, IDEA). High compliance to treatment in control arm will allow a correct assessment of potential differences between the two treatment durations.

ClinicalTrials.gov Registration Number: NCT00646607.

Key words: colon cancer, adjuvant chemotherapy, duration

introduction

Six months of adjuvant chemotherapy treatment with oxaliplatin (OXA) and a fluoropyrimidine, either 5-fluorouracil + leucovorin (FOLFOX) or capecitabine (XELOX), following complete surgical resection is the current worldwide standard of care for stage III colon cancer patients, and an accepted option for selected high-risk stage II patients [1, 2].

Incidence of neurotoxicity is a limiting factor for OXA-based combination therapies. The MOSAIC trial showed 12% grade III neurotoxicity persisting for 1 year since the end of therapy, and around 50% grade I–II at 2 years [3].

Few studies have addressed the optimal duration of adjuvant chemotherapy. The initial demonstration of the efficacy of adjuvant 5-fluorouracil (5FU) was based upon 12 months of therapy [4]. Thereafter, 6 months of treatment proved to be as effective as 12 months in a large randomized study [5]. A more recent trial compared 6 months of bolus 5FU/leucovorin (LV) with 12 weeks of protracted venous infusion 5FU on 801 stage II and III colon cancer patients, showing that the 3 months regimen was as effective as the 6 months with a significantly lower toxicity [6]. Additionally there are evidences from the literature on advanced colon cancer trials that response to treatment is generally achieved in a very short time and that efficacy is not significantly enhanced by prolonged treatment programs [7, 8].

We conducted the Three or Six Colon Adjuvant (TOSCA) trial of FOLFOX4/XELOX adjuvant therapy for 3 versus 6 months with the purpose of evaluating the efficacy and safety of a shorter course of treatment in radically resected stage II/III colon cancer patients.

methods

study design

TOSCA study is a phase III, randomized, open-label, noninferiority, multicenter trial conducted in 130 Italian centers and involving patients with resected colon cancer located >12 cm from the anal verge by endoscopy and/or above the peritoneal reflection at surgery. No gross or microscopic evidence of residual disease after surgery was allowed.

The study was conducted in accordance with the Declaration of Helsinki and adhered to Good Clinical Practice guidelines. Approval was obtained from local Ethics Committee for each participating site, and all patients provided written informed consent to the study.

After stratification by center and stage (high-risk stage II versus stage III), patients between 3 and 10 weeks from surgery were randomly assigned in a 1:1 ratio to receive 3 months of FOLFOX-4/XELOX (experimental group, Arm 3 m) or 6 months of FOLFOX-4/XELOX (control group, Arm 6 m). Randomization was centrally carried out at Mario Negri Institute with the use of permuted blocks of variable size.

Primary end-point was relapse-free survival (RFS), defined as time from date of randomization up to date of first relapse or death from any cause. Second primary colorectal cancer and other primary cancer were ignored, and patients were lost to follow-up, not recurring or died while on study have been censored at last disease assessment date. Secondary end-points were OS and safety. For the evaluation of the safety profiles of the treatment groups, multiple parameters were collected: toxicity, graded according to the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI-CTC v3.0); frequency and nature of adverse events (AEs) as well as serious adverse events (SAEs); total cumulative dose of drugs, frequency and timing of dose reductions, delays and permanent discontinuations of either the doublets or one of the drugs (OXA or fluoropyrimidine alone, few cases).

The study was designed by two senior academic investigators (AS and RL) and sponsored by GISCAD Foundation. Data were electronically collected by Mario Negri Institute who was also responsible for data monitoring and analysis. The two principle investigators had access to all the blinded data. All authors revised subsequent drafts and made the decision to submit manuscript for publication.

patients

Histologically confirmed stage III or high-risk stage II (fulfilling at least 1 of the following criteria: T4 tumor, grade >3, onset with bowel obstruction/perforation, vascular or lymphatic/perineural invasion, <12 nodes examined) colon cancer was included. Additional inclusion criteria were age >18 years, curative surgery carried out no less than 3 and no more than 10 weeks before randomization, ECOG Performance Status (ECOG-PS) ≤1, and signed written informed consent obtained before any study specific procedures.

Main exclusion criteria were macroscopic or microscopic evidence of residual tumor, prior cytotoxic chemotherapy/radiotherapy/immunotherapy for colon cancer, other malignancies within the last 5 years, lactating women, history/presence of other dysfunction or clinical laboratory findings suggesting a disease or condition that contraindicates experimental therapy or high risk of treatment complications and chronic daily treatment with high-dose aspirin (>325 mg/day).

treatment

FOLFOX-4 treatment was administered as intravenous infusion of OXA 85 mg/m^2 over 2 h, concurrently with LV 100 mg/m^2, followed by 5-FU 400 mg/m^2 as bolus injection and 5-FU 600 mg/m^2 as intravenous infusion over 22 h on day 1. On day 2, LV 100 mg/m^2, 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 intravenous infusion over 22 h were administered as previous day. Cycles were repeated every 14 days for a total of 6 cycles in arm 3 m or 12 cycles in arm 6 m.

XELOX treatment consisted of an intravenous infusion of OXA 130 mg/m^2 administered over 2 h on day 1, followed by capecitabine (CAPE) 1000 mg/m^2 per os twice daily on day 1–14. Cycles were repeated every 21 days for a total of four cycles in arm 3 m or eight cycles in arm 6 m.

Dose modification as a result of AEs and toxicity graded according to the NCI-CTC v3.0 was made on the basis of standard clinical practice except for OXA-induced neurotoxicity that had specific dose modification guidelines detailed in the protocol.

assessment

Medical history, physical examination, ECOG-PS, vital signs, existing signs and symptoms, concomitant medications and laboratory assessments were recorded at baseline and at each chemotherapy cycle. Toxicities were evaluated according to NCI-CTC v3.0 and any treatment modification was recorded.

A safety assessment was carried out after end of treatment, documenting reason and date of chemotherapy discontinuation or dose reductions.

In follow-up phase, patients were evaluated with visits every 4 months during the first 3 years after completion of study treatment phase. Laboratory assessment and abdominal ultrasound (US) were carried out, and a yearly abdominal CTscan and chest-XR were required as a minimum. After the first 3 years, the visits, serological and imaging tests were scheduled on a yearly basis. Colonoscopies were carried out within 1 year from surgery, then (if negative) every 3–5 years.

A complete patient work-up including abdominal/abdomino-pelvic CTscan or US, chest-XR or thoracic CTscan, and biochemical assessment was requested at relapse and registered together with date and sites of recurrence.

data management and statistical analysis

Trial was planned as a phase III, randomized, noninferiority trial. We planned to randomize 2860–4100 patients (depending on case mix of high-risk stage II and stage III) to observe ~944 events among patients enrolled in the study; with that number of events, it was estimated that study would have 80% power to exclude an HR ≥1.2 between the two arms at a one-sided significance level of 2.5%.

Intention-to-treat (ITT) population was defined as all randomized patients, who had not major violations of eligibility criteria.

All efficacy analyses will be carried out on per-protocol (PP) population, defined as all randomized patients, who had not major violations of eligibility criteria as well as of study conduct, and who received at least one dose of treatment (FOLFOX-4 or XELOX).

Safety analyses were conducted on safety population, including patients of ITT population who received at least one dose of 5-FU/CAPE and OXA. Patients randomized in arm 3 m, who continued beyond 3 months, were censored at 3 months both for compliance and for safety analyses.

All safety parameters have been analyzed and presented in terms of analytical and summary tables. Proportions were compared with standard χ^2 test for heterogeneity. All reported *P*-values are two-sided. Neurotoxicity incidence was also described as function of cumulative OXA dose. Kaplan–Meier curves were used to describe neurotoxicity incidence and incidence of discontinuation to treatment.

results

From June 2007 to March 2013, 3759 patients were accrued from 130 Italian sites.

As a result of exclusion of 44 patients due to major violations (22 in arm 3 m and 22 in arm 6 m), the ITT population resulted in 3715 patients, 1848 in arm 3 m and 1867 in arm 6 m. Proportion of FOLFOX4 and XELOX was 64% and 36% in both arms.

Eighteen patients with incomplete data were excluded from compliance population ($n = 3697$, arm 3 m: 1839, arm 6 m: 1858), and 3654 patients receiving at least one treatment administration were included in safety analyses, while 19 patients in arm 3 m and 24 in arm 6 m never started treatment were excluded. In addition,

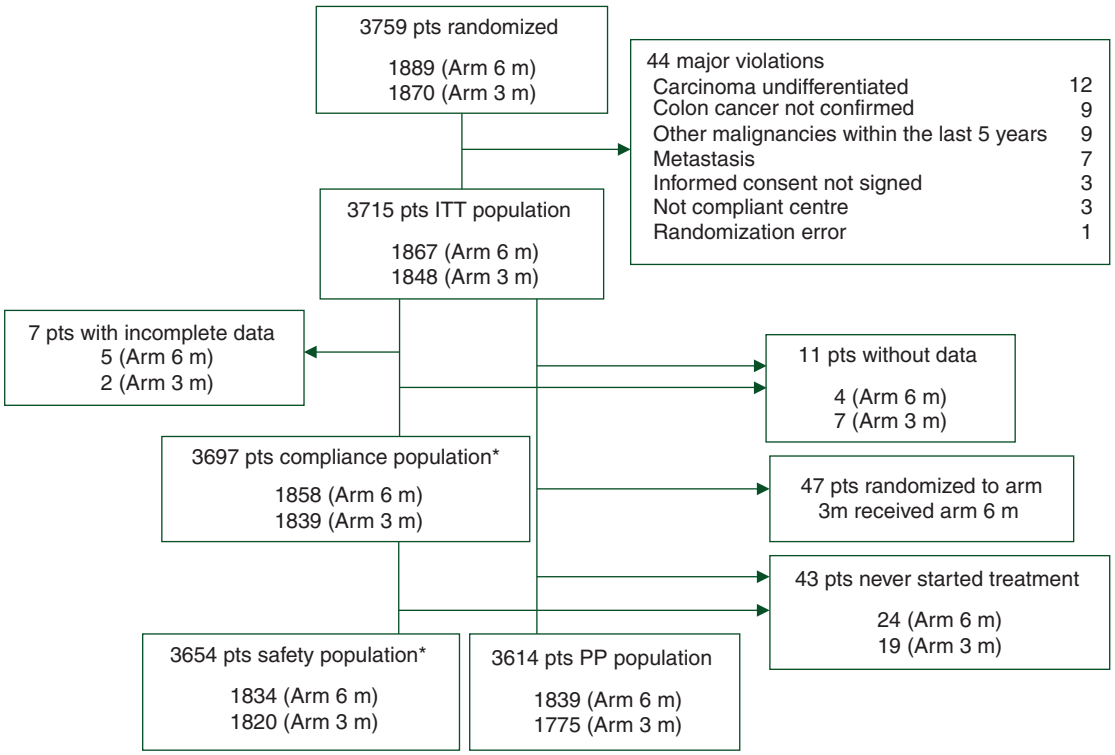


Figure 1. CONSORT flow diagram representing study populations.

Table 1. Patients' and tumors' characteristics (intention-to-treat population)

	Arm 6 m	Arm 3 m	Total
Number of patients	1687 (50.2)	1848 (49.8)	3715 (100)
Age in years			
Mean (SD)	63.1 (9.8)	63.4 (9.5)	63.3 (9.7)
Range	21.0–83.8	21.0–83.0	21.0–83.8
Sex, *n* (%)			
Female	837 (44.9)	807 (43.8)	1644 (44.4)
Male	1027 (55.1)	1035 (56.2)	2062 (55.6)
Missing data	3	6	9
ECOG Performance status, *n* (%)			
0	1760 (94.5)	1749 (95.0)	3509 (94.8)
1	103 (5.5)	90 (4.9)	193 (5.2)
2	0	1 (0.1)	1 (0.1)
Missing data	4	8	12
Tumor site, *n* (%)			
Ascending colon	537 (31.5)	570 (33.9)	1107 (32.6)
Sigmoid colon	429 (25.2)	444 (26.2)	873 (25.7)
Descending colon	247 (14.5)	230 (13.6)	477 (14.0)
Sigmoid rectum colon	235 (13.8)	220 (13.0)	455 (13.4)
Transverse colon	130 (7.6)	110 (6.5)	240 (7.1)
Splenic flexure	69 (4.0)	60 (3.6)	129 (3.8)
Hepatic flexure	57 (3.4)	58 (3.4)	115 (3.4)
Unknown	5	1	6
Histology, *n* (%)			
Adenocarcinoma	1633 (87.9)	1624 (88.3)	3257 (88.1)
Mucoid adenocarcinoma	210 (11.3)	198 (10.8)	408 (11.0)
Ring cell carcinoma	8 (0.4)	8 (0.4)	16 (0.4)
Adenosquamous carcinoma	1 (0)	3 (0.1)	4 (0.1)
Medullary carcinoma	1 (0)	2 (0)	3 (0.1)
Small-cell carcinoma	1 (0)	0 (0)	1 (0)
Squamous carcinoma	1 (0)	0 (0)	1 (0)
Other	2 (0)	5 (0.3)	7 (0.2)
Unknown	10	8	18
Stage, *n* (%)			
II	648 (34.7)	641 (34.7)	1289 (34.7)
III	1219 (65.3)	1207 (65.3)	2426 (65.3)
Grade, *n* (%)			
Gx	8 (0.4)	11 (0.6)	19 (0.5)
G1	107 (5.8)	107 (5.9)	214 (5.9)
G2	1174 (63.9)	1152 (63.6)	2326 (63.8)
G3	549 (29.9)	540 (29.8)	1089 (29.8)
Unknown	29	38	67
T stage, *n* (%)			
Tx	5 (0.3)	7 (0.4)	12 (0.3)
T0	2 (0.1)	0 (0)	2 (0)
T1	44 (2.4)	33 (1.8)	77 (2.1)
T2a	98 (5.3)	74 (4.0)	172 (4.7)
T2b	35 (1.9)	43 (2.4)	78 (2.1)
T3	1358 (73.2)	1391 (75.9)	2749 (74.5)
T4	313 (16.9)	285 (15.6)	598 (16.5)
Unknown	12	15	27
N stage, *n* (%)			
Nx	9 (0.5)	4 (0.2)	13 (0.4)
N0	632 (34.1)	623 (34.1)	1255 (34.1)
N1	895 (48.3)	869 (47.6)	1764 (48.0)
N2	313 (16.9)	327 (17.9)	640 (17.4)
N3	3 (0.2)	4 (0.2)	7 (0.2)
Unknown	15	21	36

47 patients randomized to 3 months of therapy decided to continue for 6 months (Figure 1, CONSORT diagram).

Among ITT population, all patient and tumor characteristics were balanced in the two arms (Table 1). In particular, 65% of patients in both arms had stage III disease (stratification factor), with 18% in arm 3 m and 17% in arm 6 m presenting with more than three positive lymph nodes.

Median time between surgery and treatment initiation was 7 weeks (inter-quartile range 6–8), with 97% of patients starting adjuvant therapy within 10 weeks, as recommended.

Table 2. Compliance to treatment (compliance population, $n = 3697$), n (%)

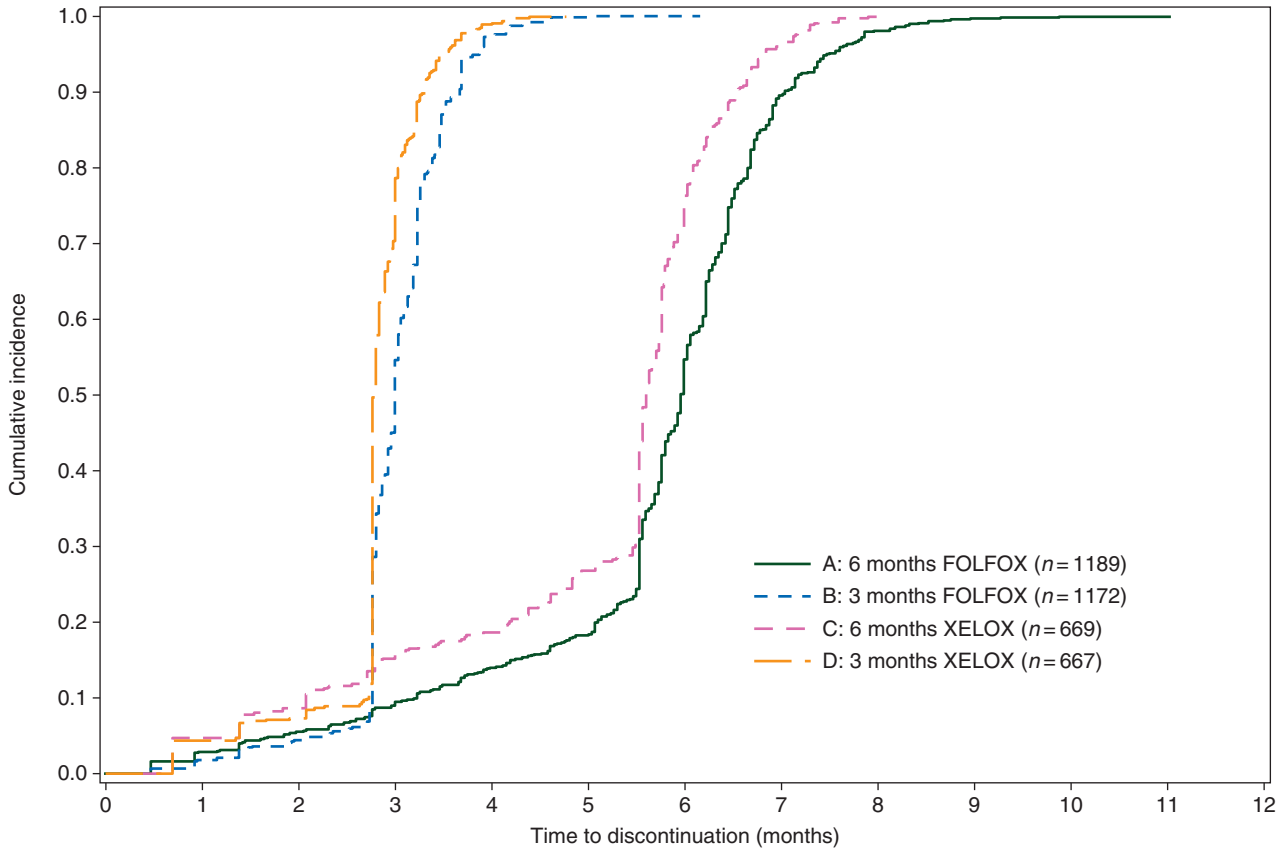
	Arm 6 m	Arm 3 m	Total
Number of patients	1858	1839	3697
Never started	24 (1.3)	19 (1.0)	43
Started treatment	1834 (98.7)	1820 (98.9)	3654
Treatment continued beyond the established number of cycles	–	47 (2.6)	47
Completed treatment	1231 (66.3)	1622 (88.2)	2853
Completed both FP and OXA without time or dose changes	224 (12.1)	642 (34.9)	866
Completed both FP and OXA with time or dose changes	824 (44.4)	960 (52.2)	1784
Completed FP without completing OXA	183 (9.9)	20 (1.1)	203
Interrupted	603 (32.5)	151 (8.2)	754

compliance and toxicity

Forty-three patients out of 3697 included in compliance population (1.2%) never started treatment (Table 2), 19 in arm 3 m and 24 in arm 6 m, mainly due to refusal after randomization (12 patients in both arms).

Because completion rates among patients receiving FOLFOX4 or XELOX were almost identical, the percentages that follow are an average between the two schedules. For precise values, refer to Figure 2.

Eight-five percent of patients in arm 3 m completed the planned chemotherapy cycles, 35% without any time or dose modification while 52% with delays and/or dose reduction. In arm 6 m, 66% of patients received all planned treatment cycles,



Patients discontinued treatment

Time	0	1	2	3	4	5	6	7	8	9	10	11	12
A	0	36	66	113	166	216	664	1053	1152	1172	1173	1174	1174
B	0	24	52	673	1129	1157	1158	1158	1158	1158	1158	1158	1158
C	0	51	70	106	124	177	511	636	660	660	660	660	660
D	0	29	53	528	654	660	660	660	660	660	660	660	660

Figure 2. Treatment compliance, % of patients discontinuing therapy along months of treatment in the two arms according to regimen received (FOLFOX-4 or XELOX) ($n = 3654$, safety population).

Table 3. Total dose received by patients who started treatment ($n = 3654$) (Q1: first quartile; Q3: third quartile)

	FOLFOX		XELOX	
	Arm 6 m	Arm 3 m	Arm 6 m	Arm 3 m
Total dose (mg/m^2)				
Oxaliplatin				
Expected	1020	510	1040	520
Median	930	510	880	520
Q1–Q3	736–1020	485–510	620–1040	490–520
Range	85–1200	85–555	100–1040	85–520
5 FU bolus				
Expected	4800	2400		
Median	4400	2400		
Q1–Q3	3600–4800	2200–2400		
Range	400–5600	400–2550		
5 FU ic				
Expected	7200	3600		
Median	6600	3600		
Q1–Q3	5700–7200	3400–3600		
Range	600–14 580	600–14 400		
Capecitabine				
Expected			8000	4000
Median			7000	4000
Q1–Q3			5540–8000	3600–4000
Range			750–12 000	974–4250

For 47 patients randomized to arm 3 m who continued the treatment beyond the fixed number of cycles, data were censored at 3 months.

Table 4. Treatment duration in patients who started treatment ($n = 3654$) (Q1: first quartile; Q3: third quartile)

	FOLFOX		XELOX	
	Arm 6 m	Arm 3 m	Arm 6 m	Arm 3 m
Treatment duration (months)				
Median	6.0	3	5.6	2.8
Q1–Q3	5.5–6.5	2.8–3.2	4.8–6.0	2.8–3.0
Range	0.5–16.5	0.5–7.7	0.7–8.0	0.7–4.8

12% without time or dose modifications and 44% with delays or dose reductions (Table 2).

Treatment was permanently discontinued in 8% of patients in arm 3 m versus 33% in arm 6 m. Reasons for treatment permanent discontinuation were toxicity or AE in 6% of patients in arm 3 m versus 20% of those in arm 6 m ($P < 0.001$). Eighty-nine percent of patients in arm 6 m received a minimum of 3 months of treatment (proportion almost identical to that of patients in arm 3 m). Eighty-one percent of patients in arm 6 m received at least 10 cycles of FOLFOX4 or 6 cycles of XELOX (supplementary Figure S1, available at *Annals of Oncology* online). This is in keeping with the total dose received, indicating that the observed values were very close to the expected values (Tables 3 and 4). It is also remarkable that only 10% of patients in arm 6 m and 1% in arm 3 m patient discontinued OXA continuing on the fluoropyrimidine according to the protocol.

Table 5. Details on toxicities reaching grade 3–4 in >2% of patients (safety population, $n = 3654$) (G = grade)

	G0		G1–2		G3–4		χ^2 for trend
	n	%	*n*	%	*n*	%	
Leukopenia							
Arm 3 m	1281	70.4	501	27.5	38	2.1	<0.0001
Arm 6 m	1130	61.6	653	35.6	51	2.8	
Febrile neutropenia							
Arm 3 m	1764	96.9	31	1.7	25	1.4	<0.0001
Arm 6 m	1719	93.7	65	3.5	50	2.7	
Nonfebrile neutropenia							
Arm 3 m	1036	56.9	433	23.8	351	19.3	<0.0001
Arm 6 m	833	45.4	545	29.7	456	24.9	
Thrombocytopenia							
Arm 3 m	1193	65.5	598	32.9	29	1.6	<0.0001
Arm 6 m	934	50.9	861	46.9	39	2.1	
Diarrhea							
Arm 3 m	1196	65.7	532	29.2	92	5.1	<0.0001
Arm 6 m	1083	59.1	634	34.6	117	6.4	
Nausea							
Arm 3 m	1076	59.1	704	38.7	40	2.2	<0.0001
Arm 6 m	930	50.7	853	46.5	51	2.8	
Asthenia							
Arm 3 m	1303	71.6	495	27.2	22	1.2	<0.0001
Arm 6 m	1119	61.0	639	34.8	76	4.1	
Neurological toxicity							
Arm 3 m	908	49.9	751	41.3	161	8.8	<0.0001
Arm 6 m	579	31.6	683	37.2	572	31.2	
Allergic reaction							
Arm 3 m	1750	96.2	61	3.4	9	0.5	<0.0001
Arm 6 m	1681	91.7	117	6.4	36	2.0	

Safety population included 3654 patients receiving at least one treatment administration, (arm 6 m: $n = 1834$, arm 3 m: $n = 1820$). Overall, grade 3 or higher AEs incidence was more common in arm 6 m compared with arm 3 m: 46% versus 31% ($P < 0.001$).

Toxicities reaching grade 3–4 in >2% of patients are detailed in Table 5. As expected, toxicity profile was slightly different in FOLFOX4- versus XELOX-treated patients, having more neutropenia in 5-FU backbone and more diarrhea in capecitabine backbone (data not shown). Grade 3+ toxicities were higher in arm 6 m versus arm 3 m: neutropenia (27.6% versus 20.7%, $P < 0.0001$), diarrhea (6.4% versus 5.0%, $P < 0.0001$) and allergic reactions (2.0% versus 0.5% $P < 0.0001$). As expected, Grade 2+ neuropathy was higher in arm 6 m compared with arm 3 m (grade 2, 22.8% versus 7.5%, respectively; grade 3, 8.2% versus 1.1%, respectively; and grade 4, <1% each, $P < 0.0001$) The relationship between the incidence of neurotoxicity and cumulative oxaplatin dose is described in supplementary Figure S2A and B, available at *Annals of Oncology* online.

One hundred and eighty patients experienced at least one SAE, 75 in arm 3 m and 105 in arm 6 m (4.2% versus 5.6%, $P = 0.066$). Thirty-day mortality rates were 0.2% (3 patients) and 0.4% (7 patients) for arm 3 m and 6 m, respectively.

At the present analysis, all patients are off-treatment and median follow-up is 35 months.

discussion

Ability to maintain efficacy of treatment with a reduced duration of therapy would clearly be advantageous to patients, health-care providers and health-care systems. Therefore, the design of TOSCA is such that no matter the outcome, these results will profoundly impact clinical practice. In fact, if the trial will show that 3 months is noninferior to 6 months, a new standard of shorter duration of therapy will be recommended. This will be particularly relevant if the reduced OXA administration will translate in a lower incidence of protracted neurotoxicity, quite unique long-term toxic effect in a percentage of these patients. On the other hand, if this trial will show that shortening the duration of therapy will impair the efficacy of the adjuvant treatment, this information will be very relevant anyway. In fact, today, a significant proportion of patients discontinues the adjuvant programs for toxicity or simply for unjustified decisions that should no longer be acceptable in case of negative results of this trial, i.e. 6 months 'better' than 3 months.

There were four major challenges when TOSCA was designed and started the accrual: the first was feasibility (evidently overcome); the second was the worry that 3 months could have been too short (nothing doing until we know the efficacy data) and the third was the concern that patients randomized to the control arm, planned to receive 6 months of therapy, would have indeed received a much shorter duration, resulting in a potential comparison of 3 versus 4/4.5 months of treatment. The relevance of this publication addresses this specific point and reassures us that the efficacy data will indeed reflect the best standard arm (with >5 months of treatment on average versus the planned 3 months of the experimental arm). Figure 2 is the heart of this publication and it emphasizes the compliance to the experimental plan. Of note was the fact that this high proportion of patients receiving chemotherapy in the control arm actually got both OXA and the fluoropyrimidine; we could have expected that a high proportion of patients completing all the scheduled 6-month cycles would have done so just for 5-FU, because OXA was discontinued earlier. This may raise the suspicion that Italian oncologists are particularly 'determined' with their patients, which could have a negative connotation. The low incidence of neurotoxicity though excludes this interpretation.

The fourth concern was that TOSCA would have been underpowered for showing an acceptable level of noninferiority, say around 2%–3%. Indeed that is the case. And this is the reason why we have worked together with other investigators to set up the IDEA enterprise: a consortium of trials all having the same three versus six core question, so that a combined analysis is done and sufficient patients are accrued to show adequately powered minimal differences, if any [9, 10].

The major reason for treatment discontinuation was toxicity or AE. This finding is comparable to the data from MOSAIC trial, where 75% of patients in experimental arm did not receive the last month of treatment [3]. However, although all compliance outcomes were reduced in the groups randomized to 6 months of chemotherapy, >80% of patients had at least 10 cycles of FOLFOX4 or 6 of XELOX, corresponding to a total dose higher than those planned in NSABP-C07 (765 mg/mq) [11]. We believe therefore that the efficacy analysis should be reliable for the primary end-point.

Toxicities were predictable. They reproduced those reported in the adjuvant OXA-based chemotherapy trials (grade 3–4 toxicity: 59% in TOSCA arm B versus 52%–70% in other trials, [3, 11]). In addition, toxicity frequencies were comparable in the two arms except for neurotoxicity. In fact, grade 3–4 diarrhea and neutropenia are acute effects expected to occur predominantly in the first 3 months of treatment (thus with similar incidence in the two arms). In contrast, both acute and long-term, OXA-driven peripheral neuropathies depend on number of cycles and cumulative dose received: that is why its manifestation markedly differs in the two arms: 9% versus 31% in arm 3 and 6 m, respectively. These data are similar to those of recently presented SCOT trial [12], with a rate of grade 2–3 neurotoxicity reported in 24% versus 56% of cases by 3- and 6-month therapy, respectively.

In summary, the safety analysis of TOSCA confirms better compliance and tolerance of 3 months of treatment compared with 6 months. In addition, as in other OXA-adjuvant studies, rate of treatment completion in arm 6 m in this pragmatic trial reflects what commonly happens in clinical practice and justifies efforts for investigating the efficacy of a shorter administration.

Follow-up is ongoing to assess the impact on efficacy end-points. Mature data, combined with those emerging from all the trials participating to IDEA project, will enable to establish if a reduced adjuvant treatment remains effective and its balance between gain or loss in survival and toxicity.

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disclosure

The authors have declared no conflicts of interest.

appendix

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