Impact of Lean Body Mass–Based Oxaliplatin Dose Calculation on Neurotoxicity in Adjuvant Treatment of Stage III Colon Cancer: Results of the Phase II Randomized LEANOX Trial

Eric Assenat, MD, PhD[1,2]; Meher Ben Abdelghani, MD[3]; Sophie Gourgou, MSc[4]; Hervé Perrier, MD[5]; Faiza Khemissa Akouz, MD[6]; Romain Desgrippes, MD[7]; Marie-Pierre Galais, MD[8]; Chloé Janiszewski, BSc[9]; Thibault Mazard, MD, PhD[1]; Yves Rinaldi, MD[10]; Côme Lepage, MD, PhD[11]; Raphael Tetreau, MD[12]; and Pierre Senesse, MD[13]

DOI https://doi.org/10.1200/JCO-24-02754

ABSTRACT

PURPOSE Oxaliplatin-based adjuvant chemotherapy is used for stage III colon cancer, but may induce disabling neurotoxicity. We previously showed that the incidence of oxaliplatin-induced peripheral neurotoxicity (OIPN) is higher for oxaliplatin doses >3.09 mg per kg of lean body mass (LBM). This proof-of-concept, multicenter, randomized trial assessed whether LBM-based oxaliplatin dose adjustment reduces OIPN (ClinicalTrials.gov identifier: NCT03255434).

METHODS Among the patients with resected stage III colon cancer eligible for adjuvant leucovorin, fluorouracil, and oxaliplatin chemotherapy, those without LBM reduction received body surface area (BSA)–based oxaliplatin doses (85 mg/m², arm 1). Patients with reduced LBM were randomly assigned (1:1) to receive BSA-based (arm 2) or LBM-based oxaliplatin doses (3.09 mg/kg LBM, arm 3). The primary end point was the percentage of patients without grade ≥2 OIPN in the first six cycles.

RESULTS In all, 33, 64, and 63 patients were enrolled in arms 1, 2, and 3, respectively (median age, 63 years; 52.5% of men; 89.3% Eastern Cooperative Oncology Group 0; 57.5% pT3; 60.6% pN1). The primary end point was achieved by 67.2% of patients in arm 3 versus 42.1% in arm 2 (P = .01). Longer grade ≥2 OIPN-free survival (hazard ratio [HR], 0.53 [95% CI, 0.34 to 0.84]; P = .01), longer time to grade ≥2 OIPN onset (P = .006), higher cumulative oxaliplatin doses without grade ≥2 OIPN (P = .044), and fewer oxaliplatin dose reductions (P < .001) were reported in arm 3. Relapse-free survival (HR, 1.05 [95% CI, 0.54 to 2.06]) and overall survival (OS; HR, 1.20 [95% CI, 0.36 to 3.92]) were similar in arms 2 and 3 (median follow-up of 38.6 months). Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy 20 scores were better in arm 3.

CONCLUSION In adjuvant settings for stage III colon cancer, using an LBM-based oxaliplatin dose significantly reduces OIPN and improves quality of life without affecting relapse-free survival and OS.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

Accepted May 13, 2025
Published June 20, 2025

J Clin Oncol 43:2616-2627
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INTRODUCTION

Oxaliplatin is a platinum-based antitumor agent and the mainstay treatment for GI cancers. However, 40-50% of patients develop oxaliplatin-induced peripheral neuropathy (OIPN).[1-3] Acute OIPN generally resolves within 1 week; however, 20%-50% of patients will develop severe, dose-dependent, chronic, and potentially debilitating OIPN.[4-6] For instance, 43.9% and 47.7% of patients with stage III colorectal cancer treated with adjuvant leucovorin, fluorouracil, and oxaliplatin (FOLFOX) therapy for 6 months experienced grade ≥2 chronic cumulative neurotoxicity.[1,7] Thus, OIPN significantly affects treatment continuity and quality of life (QoL) in patients with cancer and survivors.[8,9]

According to international guidelines, no intervention has been found to prevent chemotherapy-induced peripheral neuropathy, despite numerous trials.[8,9] The most common and pragmatic method remains reducing oxaliplatin dose (with a random threshold) or its withdrawal (often too

CONTEXT

Key Objective

Oxaliplatin-based chemotherapy often induces chronic peripheral neurotoxicity, significantly affecting clinical outcomes and quality of life (QoL). Oxaliplatin dose is usually based on the patient's body surface area (BSA); however, it is not clear whether dose adjustments based on lean body mass (LBM) could reduce oxaliplatin-induced peripheral neurotoxicity (OIPN) in patients with colon cancer.

Knowledge Generated

The LEANOX trial provides evidence that in adjuvant settings, individualized LBM-based oxaliplatin doses significantly reduce grade ≥2 OIPN, delay its onset, and improve grade ≥2 OIPN-free survival and QoL, without compromising relapse-free survival and overall survival in patients with stage III colon cancer.

Relevance *(A.H. Ko)*

Personalized dosing of oxaliplatin based on LBM, rather than strictly by BSA, is appropriate to consider in patients receiving adjuvant therapy for colon cancer, particularly those with sarcopenia. The practicality of this approach will depend on widespread adoption of radiology software tools that can provide reliable body composition measurements.*

*Relevance section written by *JCO* Associate Editor Andrew H. Ko, MD, FASCO.

late).[2,10] Standard chemotherapy dose calculation is traditionally based on the patient body surface area (BSA).[11] However, chemotherapy agents have narrow therapeutic indexes, and BSA is a poor indicator of the optimal dose.[12] Indeed, BSA-based doses do not take into account variations in the patients' body composition parameters, such as lean body mass (LBM) and fat distribution. Yet, patients with similar BSA can have different body compositions.[13] Ultimately, suboptimal chemotherapy doses can increase adverse events and potentially lead to dose reductions or treatment discontinuation that may compromise clinical outcomes.

Accumulating evidence shows that body composition may be a better criterion than BSA.[14] Indeed, chemotherapy doses based on body composition may more accurately reflect the drug distribution across the body compartments and potentially reduce toxicity. Moreover, patients with reduced muscle density (sarcopenia) have the highest risk of developing dose-limiting toxicities (DLTs).[15,16] We previously showed that OIPN incidence was higher in patients receiving oxaliplatin at doses >3.09 mg per kg of LBM.[13] In the present proof-of-concept, multicenter, randomized trial, we evaluated whether LBM-based dose adaptation could reduce OIPN in patients with stage III colon cancer receiving adjuvant oxaliplatin-based chemotherapy.

METHODS

Study Design and Eligibility

The French multicenter, phase II, randomized LEANOX study was approved by the local ethics committee (Comité de Protection des Personnes Sud Méditerranée III, 2016.11.03 bis) and the French National Agency Authority for the Safety of Health Products (March 1, 2017, 160943A-12). This trial was carried out following the French Public Health Code, the Good Clinical Practice, and the Declaration of Helsinki and was registered on ClinicalTrials.gov (identifier: NCT03255434) and eudract.ema.europa.eu (2016-002576-27). All patients provided the appropriate written informed consent.

The main inclusion criteria were age ≥18 years, colon adenocarcinoma, curative-intent resection, and planned adjuvant simplified leucovorin, fluorouracil, and oxaliplatin (85 mg/m^2; FOLFOX4) regimen. Eligibility criteria included Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 for <70-year-old patients and ECOG PS of 0 for 70- to 75-year-old patients. Chemotherapy started 1 month after surgical resection and required stable hematological, liver, and renal functions. Before treatment initiation, insertion of a central venous access device with an implantable port and screening for dihydropyrimidine dehydrogenase deficiency were mandatory.

Patients with any pre-existing peripheral neuropathy, previous exposure to neurotoxic therapies (eg, taxanes, vinca alkaloids, cisplatin), treated with neuropathy-specific agents, or unable to comply with the protocol were excluded.

LBM Surface Assessment

LBM was assessed using computed tomography (CT) images with or without contrast recorded within 30 days before treatment initiation to accurately represent the baseline body

composition. Patient height and weight, recorded closest to the CT date, were used to calculate the BMI (kg/m²). CT images were securely transmitted to the Montpellier Cancer Institute radiology team via an online platform (Keosys Imaging, Saint Herblain, France) that also managed data anonymization and quality insurance. LBM assessment was completed within 72 hours using the Myrian software (Intrasense SA, Montpellier, France) that was previously customized and validated[17] to facilitate skeletal muscle area quantification based on L3 cross-sectional CT slices according to previous works.[18-21] Whole-body LBM (kg) was calculated using the following formula: (L3 muscle area measured by CT [cm²] × 0.3) + 6.06, with a correlation coefficient of 0.94[19] (see an example of LBM calculation in Appendix Fig A1, online only). Results were uploaded on the platform and a notification was sent to the recruitment center. Then, patients were enrolled via electronic case report forms and received an inclusion or randomization number.

Treatment and Random Assignment

On day 1, patients started a simplified FOLFOX4 regimen: oxaliplatin infusion over 2 hours followed by fluorouracil (FU) bolus (400 mg/m²) and 46-hour FU infusion (2,400 mg/m²). This treatment was administrated every 2 weeks for up to 12 cycles.

Patients without sarcopenia (LBM index <3.09 mg/kg, arm 1) received BSA-based oxaliplatin doses (85 mg/m²). Patients with sarcopenia (LBM index ≥3.09 mg/kg) were randomly assigned to receive BSA-based (arm 2) or LBM-based oxaliplatin doses (3.09 mg/kg LBM; arm 3). Random assignment (1:1) was stratified by center, age (≤65 *v* >65), and weight loss (≤5% *v* >5% from usual weight).

Outcome Measures

The primary end point was the percentage of patients without grade ≥2 OIPN during the first six cycles of adjuvant oxaliplatin-based chemotherapy, assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Secondary end points included time to onset (ie, time from oxaliplatin treatment start to first grade ≥2 neurotoxicity onset) and duration of grade ≥2 chronic neurotoxicity, cumulative dose of oxaliplatin tolerated without dose-limiting chronic neurotoxicity, tolerance, recurrence-free survival (RFS; ie, time from random assignment to first cancer-related event onset or death from any cause), overall survival (OS), and QoL. Event-free patients were censored at the date of last follow-up. No specific methodological approach to intercurrent events was applied. QoL was evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), European Quality of Life 5 Dimensions (EQ5D), and EORTC QLQ Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20) questionnaires.[22] Neurotoxicity was evaluated after each chemotherapy cycle and then at 1, 3, 6, 12, 18, 24, and 36 months following treatment. The QLQ-CIPN20 questionnaire was completed at baseline, before each chemotherapy cycle, and at 3, 6, and 12 months after treatment. Other QoL evaluations were performed at baseline and at months 3 and 6 after treatment.

Sample Size

Sample size calculation for the randomized arms was based on a binomial comparison of the primary end point, using a two-sided α of 5%, beta of 20%, with P1 = 55% for arm 2 and P2 = 80% for arm 3. To achieve 80% of power in detecting a 25% difference in grade ≥2 OIPN incidence, a sample size of 108 patients was required (54 evaluable patients per arm).

Statistical Considerations

Continuous variables are presented as number of observations, median, minimum, and maximum and were compared using the Kruskal-Wallis or Wilcoxon test. Categorical variables are reported as number of observations (N) and frequencies (%), and compared using the chi-square or Fisher's exact test. The exact binomial method was used to determine the 95% CIs. The primary end point was reported as a percentage with its 95% CI. Comparison of percentages between arms 2 and 3 was performed using the chi-square or Fisher's exact test. Follow-up duration was defined as the interval between enrollment and the last update, with deaths censored. The median follow-up duration was determined using the Kaplan-Meier inverse method with 95% CI. Survival rates and the median survival times were estimated using Kaplan-Meier survival analyses. No multiplicity control was applied, and all *P* values were exploratory except for primary end point. All statistical tests were two-tailed and the significance level was set at 5%. Statistical analyses were performed with STATA v13.0.

RESULTS

Study Population

Between December 2017 and December 2021, 160 patients were enrolled across 18 centers (Fig 1). Four patients did not receive treatment and were excluded from the primary end point and tolerance analyses.

The baseline characteristics were well balanced in the three arms (Table 1). The median age was 63 years (range, 29-77), 52.5% of patients were men, and 89.3% had an ECOG PS of 0. Fifty percent of tumors were located in the left colon, 43.1% in the right colon, and 5% in the transverse colon. Tumors were mainly pT3 (57.5%) and pN1 (60.6%), and were moderately differentiated in 55.6% of patients. At enrollment, 48.8% of patients had normal BMI and 48.5%, 46.9%, and 39.7% had overweight or obesity in arm 1, 2, and 3, respectively. Moreover, 52.7% of patients experienced a >5% weight loss compared with usual weight (stratification

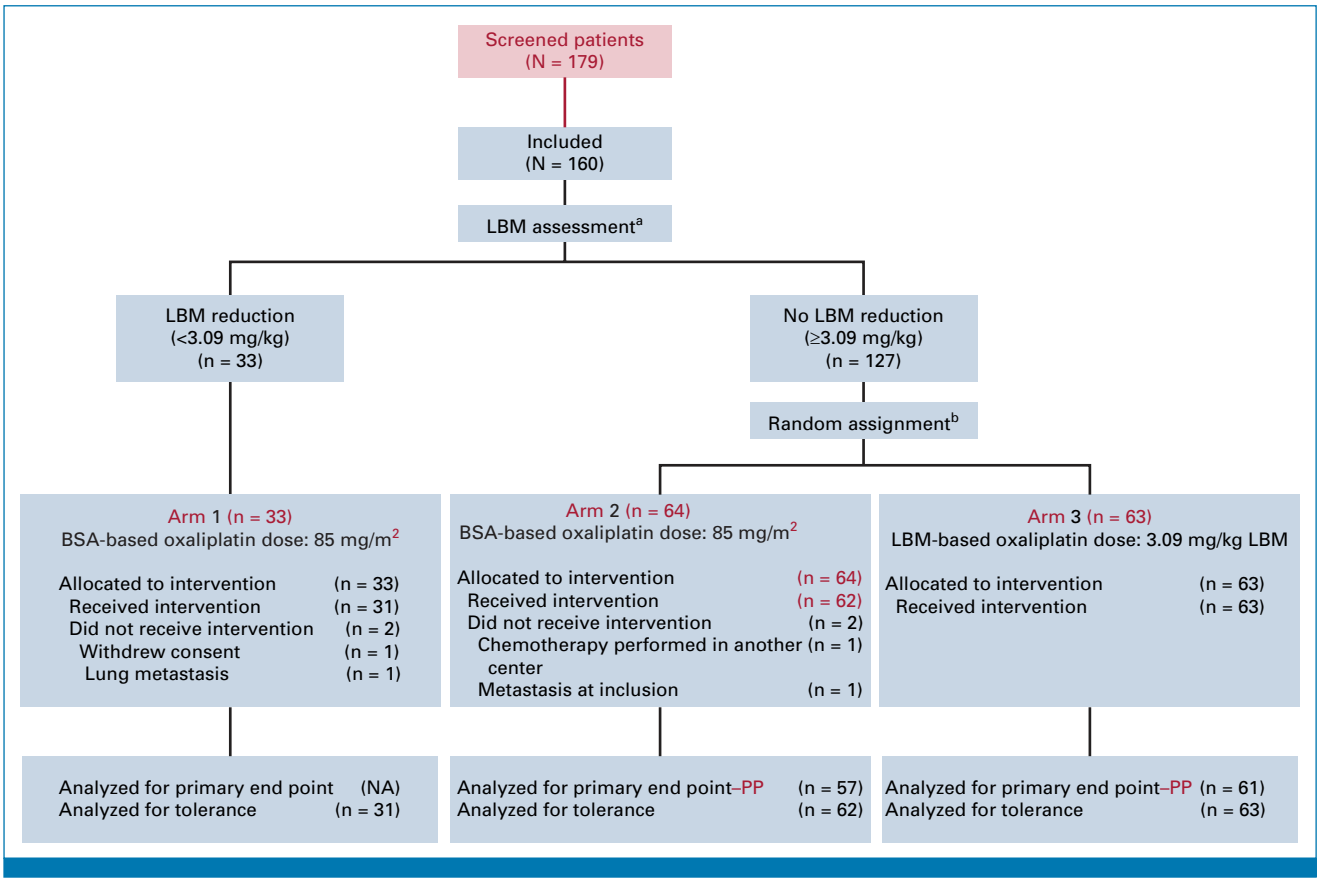


FIG 1. Study flow chart. [a]To quantify the skeletal muscle area, the total muscle cross-sectional area was measured using CT images taken at the third lumbar vertebra level (L3) and the Slice-O-Matic software. The muscle area was then normalized to the square of the height (m^2) and reported as the lumbar skeletal muscle index. LBM in kg was calculated using the following formula: (L3 muscle area measured by CT [cm^2] × 0.3) + 6.06. [b]According to center, age (≤65 years *v* >65 years), and weight loss (≤5% *v* >5%). BSA, body surface area; CT, computed tomography; LBM, lean body mass; NA, not appropriate; PP, per protocol.

criterion). The median muscle tissue surface area at L3 was 130 cm^2 (range, 77-271). The median LBM was 57 kg (range, 27-87), 41 kg (range, 30-65), and 42 kg (range, 29-58) in arm 1, 2, and 3, respectively, with a cohort-wide median LBM of 45 (range, 29-87) kg.

Treatment Administration

Overall, 93.9%, 96.9%, and 100% of patients received chemotherapy in arm 1, 2, and 3, respectively. Table 1 and Appendix Figure A2 summarize the number of cycles and relative dose intensity. Of note, the relative dose intensity remained stable throughout the treatment for patients in arm 3 (P = .298, Kruskal-Wallis test). At least one dose delay was reported for 73.7% of patients in the whole cohort: 80.7% in arm 1, 75.8% in arm 2, and 68.3% in arm 3. Moreover, 84% of patients had at least one dose modification, 68% of patients experienced a dose reduction, 26.3% had a treatment interruption, and 48.1% had both a dose reduction and a delay in treatment administration. Hematological toxicity delayed treatment in 34.6% of patients. Oxaliplatin dose modifications were required for 74.4% of patients; 50% had at least one FU bolus dose modification and 30.1% one FU infusion dose modification. Treatment was prematurely discontinued in 23.7% of patients (n = 37) due to patient's decision (n = 12, 32.4%), adverse event (n = 11, 29.7%), or investigator's decision (n = 10, 27%).

Efficacy

The percentage of patients without grade ≥2 OIPN during the first six cycles (approximately 3 months) was 67.2% in arm 3 versus 42.1% in arm 2 (P = .01). Grade ≥2 OIPN-free survival was significantly higher in arm 3 than in arm 2 (hazard ratio [HR], 0.53 [95% CI, 0.34 to 0.84]; P = .01; Fig 2; Appendix Fig A3A). This represented a 25.1% reduction in grade ≥2 OIPN in the first 3 months of treatment. The difference between arms 2 and 3 remained over time, with a 47% reduction for the whole treatment period.

Time to grade ≥2 OIPN onset was significantly longer in arm 3 (5.7 months; 95% CI, 4.4 to NA) than arm 2 (2.3 months; 95% CI, 1.8 to 4.6; P = .01; Table 2). During treatment, fewer patients experienced at least one grade ≥2 OIPN event in arm 3 than arm 2 (46% *v* 67.7%; P = .01), but post-treatment rates were similar (19.1% *v* 29%; P = .19).

TABLE 1. Baseline Characteristics and Adjuvant Treatment Features

Characteristic	Arm 1 (n = 33)	Arm 2 (n = 64)	Arm 3 (n = 63)	Total (N = 160)
Baseline characteristics				
Sex, No. (%)				
Male	29 (87.9)	27 (42.2)	28 (44.4)	84 (52.5)
Female	4 (12.1)	37 (57.8)	35 (55.6)	76 (47.5)
Age, years, median (range)[a]	64 (29-75)	63 (40-77)	63 (33-75)	63 (29-77)
≤65, No. (%)	NA	36 (56.3)	35 (55.5)	71 (55.9)
>65, No. (%)	NA	28 (43.8)	28 (44.4)	56 (44.1)
ECOG-PS, No. (%)				
0	29 (87.9)	55 (85.9)	58 (93.6)	142 (89.3)
1	4 (12.1)	9 (14.1)	4 (6.5)	17 (10.7)
Height, cm^2, median (range)	171 (150-191)	168 (150-192)	169 (144-190)	169 (144-192)
Usual weight, kg^2, median (range)	84 (49-112)	78 (45-129)	72 (50-110)	76 (45-129)
Weight at inclusion, kg^2, median (range)	76 (35-105)	73 (42-118)	67 (48-110)	72 (35-118)
Weight loss, No. (%)[a]				
≤5%	NA	31 (48.4)	29 (46)	60 (47.2)
>5	NA	33 (51.6)	34 (54)	67 (52.8)
BMI, No. (%)				
<18.5	2 (6.1)	5 (7.8)	4 (6.4)	11 (6.9)
18.5-25	15 (45.5)	29 (45.3)	34 (54.0)	78 (48.8)
25-30	9 (27.3)	18 (28.1)	15 (23.8)	42 (26.3)
≥30	7 (21.2)	12 (18.8)	10 (15.9)	29 (18.1)
SMA, cm^2, median (range)	170 (102-271)	116 (81-197)	119 (77-174)	130 (77-271)
LBM, kg^2, median (range)	57 (37-87)	41 (30-65)	42 (29-58)	45 (29-87)
Tumor characteristics				
Classification T, No. (%)				
1	0	1 (1.6)	1 (1.6)	2 (1.3)
2	3 (9.1)	5 (7.8)	4 (6.4)	12 (7.5)
3	22 (66.7)	29 (45.3)	41 (65.1)	92 (57.5)
4	8 (24.2)	29 (45.3)	17 (27.0)	54 (33.8)
Classification N, No. (%)				
0	0 (0.0)	2 (3.1)	0	2 (1.3)
1	17 (51.3)	37 (57.8)	43 (68.3)	97 (60.6)
2	16 (48.5)	25 (39.1)	20 (31.8)	61 (38.1)
Treatment administration				
Number of patients treated, No. (%)	31 (93.9)	62 (96.9)	63 (100)	156 (97.5)
Missing, n	2	2	0	4
Number of cycles, median (range)				
Oxaliplatin	10 (5-12)	9 (1-12)	10 (2-12)	9.5 (1-12)
FU bolus	12 (1-12)	11.5 (1-12)	12 (2-12)	12 (1-12)
FU infusion	12 (6-12)	12 (1-12)	12 (2-12)	12 (1-12)
RDI, median (range)				
Oxaliplatin	72.6 (40.6-99.6)	72.7 (24.0-100.1)	81.3 (28.5-104.7)	76.4 (24-104.7)
FU bolus	87.1 (5.8-100.2)	81.4 (6.4-101.7)	82.1 (12.9-100.5)	85.2 (5.8-101.7)
FU infusion	88.6 (42.2-100.4)	89.4 (36-105.9)	94 (54.86-105.1)	90.5 (36-105.9)
RDI ≥80%, No. (%)				
Oxaliplatin	11 (35.5)	26 (41.9)	32 (50.8)	69 (44.2)

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; FU, fluorouracil; LBM, lean body mass; NA, not appropriate; RDI, relative dose intensity; SMA, skeletal muscle area.
[a]Stratification factor.

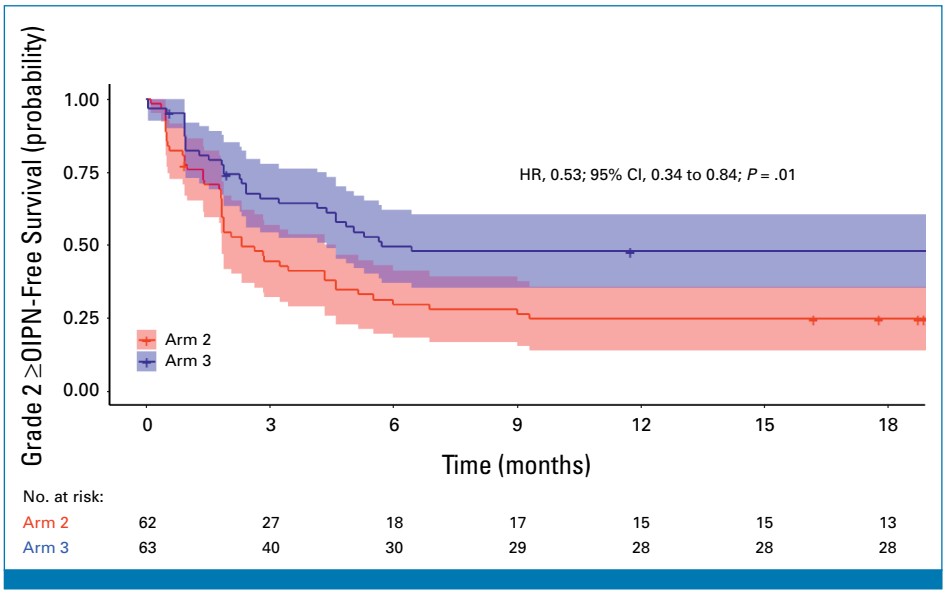


FIG 2. Kaplan-Meir estimates of grade ≥2 OIPN-free survival. Kaplan-Meier estimates of grade ≥2 OIPN-free survival in arm 2 (BSA-based dose) and arm 3 (LBM-based dose). The shaded regions represent the 95% CIs. HRs were calculated using the Cox proportional hazards model, with 95% CI based on log transformation and exponentiation for CI estimation, and *P* values determined with the log-rank test. BSA, body surface area; HR, hazard ratios; LBM, lean body mass; OIPN, oxaliplatin-induced peripheral neuropathy.

The median cumulative oxaliplatin dose delivered without reaching grade ≥2 OIPN was 465.9 mg/m² of BSA and 18.54 mg/kg of LBM, with higher rates in arm 3 than arm 2 (P = .04; Table 2). Arm 3 had fewer oxaliplatin dose reductions (P < .001). The total grade ≥2 OIPN duration was not different between arms 2 and 3 (P = .65). Oxaliplatin was interrupted due to OIPN in 28.9% of patients in the whole cohort, without differences among arms (P = .91).

Tolerance

The main toxicities are reported in Appendix Table A1; 99.4% of patients experienced at least one treatment-related adverse event. Hematological and nonhematological toxicity rates were comparable among arms. No grade 5 toxicity was reported. Grade 4 toxicities were observed in all groups: neutropenia (n = 1 in arm 1; n = 1 in arm 2; n = 4 in arm 3), OIPN (n = 2 in arm 2), and cardiogenic shock, diabetic ketoacidosis, and stroke (n = 1/each in arm 3). The rate of grade ≥3 neutropenia was higher in arm 3 (11.1%) than in arms 1 and 2 (<6.5%).

Survival

The median follow-up was 38.6 months (95% CI, 31.3 to 40.5) for the whole cohort (N = 160) and 33.4 months (95% CI, 29.8 to 39.6) for the intention-to-treat population (ie, arms 2 and 3; n = 127; Fig 3; Appendix Figs A3B and A3C). The 36-month RFS was 71% (95% CI, 64 to 79) in the whole cohort, 73% (95% CI, 58 to 91) in arm 1, 70% (95% CI, 58 to 84) in arm 2, and 71% (95% CI, 59 to 84) in arm 3. The 36-month OS was 91% (95% CI, 86 to 96) for the whole cohort, 93% (95% CI, 83 to 100) in arm 1, 94% (95% CI, 87 to 100) in arm 2, and 88% (95% CI, 79 to 98) in arm 3. RFS (HR, 1.05 [95% CI, 0.54 to 2.06]; P = .88) and OS (HR, 1.20 [95% CI, 0.36 to 3.92]; P = .77) were not different between arms 2 and 3 (five deaths per arm; Appendix Table A2).

QoL

No difference was observed in the EQ5D (Appendix Fig A4) and QLQ-C30 scores (data not shown). The QLQ-CIPN20 scores were better in arm 3 (Fig 4). The QLQ-CIPN20 questionnaire response rates were 38.8% at baseline, 30.1% at the end-of-treatment visit, 34.4% at month 3 after treatment, and 27.7% at month 6 after treatment. The sensory and autonomy dimension scores were not different among arms. However, a significant difference in motor function was observed at cycle 11 (P = .03), with median scores of 4 (range, 0-8) in arm 1, 8 (range, 0-25) in arm 2, and 0 (range, 0-33) in arm 3.

DISCUSSION

The LEANOX study is the first randomized clinical trial showing that LBM-based oxaliplatin dose calculation significantly reduces OIPN by 25% after 3 months of treatment and by 47% over the entire treatment duration. It also improved grade ≥2 OIPN-free survival and delayed grade ≥2 OIPN onset. Conversely, grade ≥2 OIPN duration was similar

TABLE 2. Oxaliplatin-Induced Peripheral Neurotoxicity

OIPN Characteristic	Arm 1 (n = 33)	Arm 2 (n = 62)	Arm 3 (n = 63)	Total (N = 156)	*P*
Primary end point (per-protocol population)					
No.	NA	57	61	118	
Patients without grade ≥2 OIPN during the first six cycles, No. (%)	NA	24 (42.1)	41 (67.2)	NA	.01[a]
Secondary end points (safety population)					
Time to onset of the first grade ≥2 OIPN, months					
Median (95% CI)	4.1 (3.1 to NA)	2.3 (1.8 to 4.6)	5.7 (4.4 to NA)	4.3 (3.1 to 5.7)	.01[b]
Patients with at least one grade ≥2 OIPN during treatment, No. (%)					.01[a]
No	13 (41.9)	20 (32.3)	34 (54)	67 (43)	
Yes	18 (58.1)	42 (67.7)	29 (46)	89 (57.1)	
Patients with at least one grade ≥2 OIPN after treatment, No. (%)					.19[a]
No	22 (71)	44 (71)	51 (81)	117 (75)	
Yes	9 (29)	18 (29)	12 (19.1)	39 (25)	
In patients treated with oxaliplatin with at least one neurotoxicity of grade ≥2					
Duration of first grade ≥2 OIPN, months[c]					.83[b]
No.	15	32	29	76	
Median (range)	6 (0.1-15.8)	6.3 (2.27-22.51)	5.9 (3-18)	6 (0.1-22.5)	
Missing, No.	5	14	3	22	
Total duration of grade ≥2 OIPN[d]					.65[b]
No.	14	32	29	75	
Median (range)	4.5 (0.1-15.8)	6.3 (2.3-22.5)	5.9 (3-18)	6 (0.1-22.5)	
Missing, No.	6	14	3	23	
Cumulative oxaliplatin dose without OIPN grade ≥2, mg/m^2					
No.	30	62	63	155	
mg/m^2, median (range)	509.4 (248.6-1,021.3)	340.9 (68.6-1,025.1)	465.9 (72.3-964.3)	465.9 (68.6-1,025.1)	.04[b]
mg/kg of LBM, median (range)	18.2 (8-37.3)	15.5 (2.6-48.5)	18.9 (3.1-37.4)	18.5 (2.6-48.5)	.31[b]
Missing, No.	1	0	0	1	

Abbreviations: LBM, lean body mass; NA, not appropriate; OIPN, oxaliplatin-induced peripheral neurotoxicity.
[a]Comparisons between arms 2 and 3 were performed using the chi-square test.
[b]Comparisons between arms 2 and 3 were performed using the Fisher's exact test.
[c]Time from the onset of the first grade ≥2 OIPN to its resolution.
[d]Time from the onset of the first grade >2 OIPN to the resolution of the last grade ≥2 OIPN.

between arms. Most DLTs occurred during chemotherapy, leading to dose reduction (25%-50%) and treatment interruption. The LBM-based dose calculation (never implemented in routine practice) resulted in a reduction by 12% of the oxaliplatin dose in patients with sarcopenia compared with the BSA-based dose calculation. Nonetheless, patients in arm 3 maintained high and stable oxaliplatin relative dose intensity throughout the treatment (12 cycles), with higher cumulative dose delivered without reaching grade ≥2 OIPN (+36%; $P = .044$). Moreover, the OS and RFS rates were similar between arms 2 and 3. Finally, the EQ5D and QLQ-C30 scores (QoL assessment) were similar in arms 2 and 3. However, the QLQ-CIPN20 scores suggest a potential trend toward better outcomes in arm 3, particularly in the functional dimension, without affecting RFS and OS.

Our results are in line with the literature on body composition and DLT in patients with colon cancer. We previously found a higher OIPN prevalence with oxaliplatin doses >3.09 mg per kg of LBM.[13] Previous studies suggested this hypothesis, but they mainly enrolled patients with metastatic disease and were limited by small sample sizes.[23-26] Furthermore, none compared early treatment discontinuation, dose delay, and dose reduction, which are critical outcomes for patient safety and survival. Retrospective studies in patients with nonmetastatic colon cancer undergoing surgery were also performed.[27-29] The C-SCANS study in an American cohort showed that low LBM is associated with increased toxicity and poor adherence to adjuvant FOLFOX therapy.[27] Yokoi et al[28] found in a Japanese cohort that sarcopenia independently predicts adjuvant capecitabine and oxaliplatin (CAPOX) chemotherapy discontinuation: patients with low LBM receive lower doses and complete fewer cycles. Cao et al[29] demonstrated BSA limited capacity to predict chemotherapy-induced DLT compared with L3 body composition measurements to identify at-risk patients.

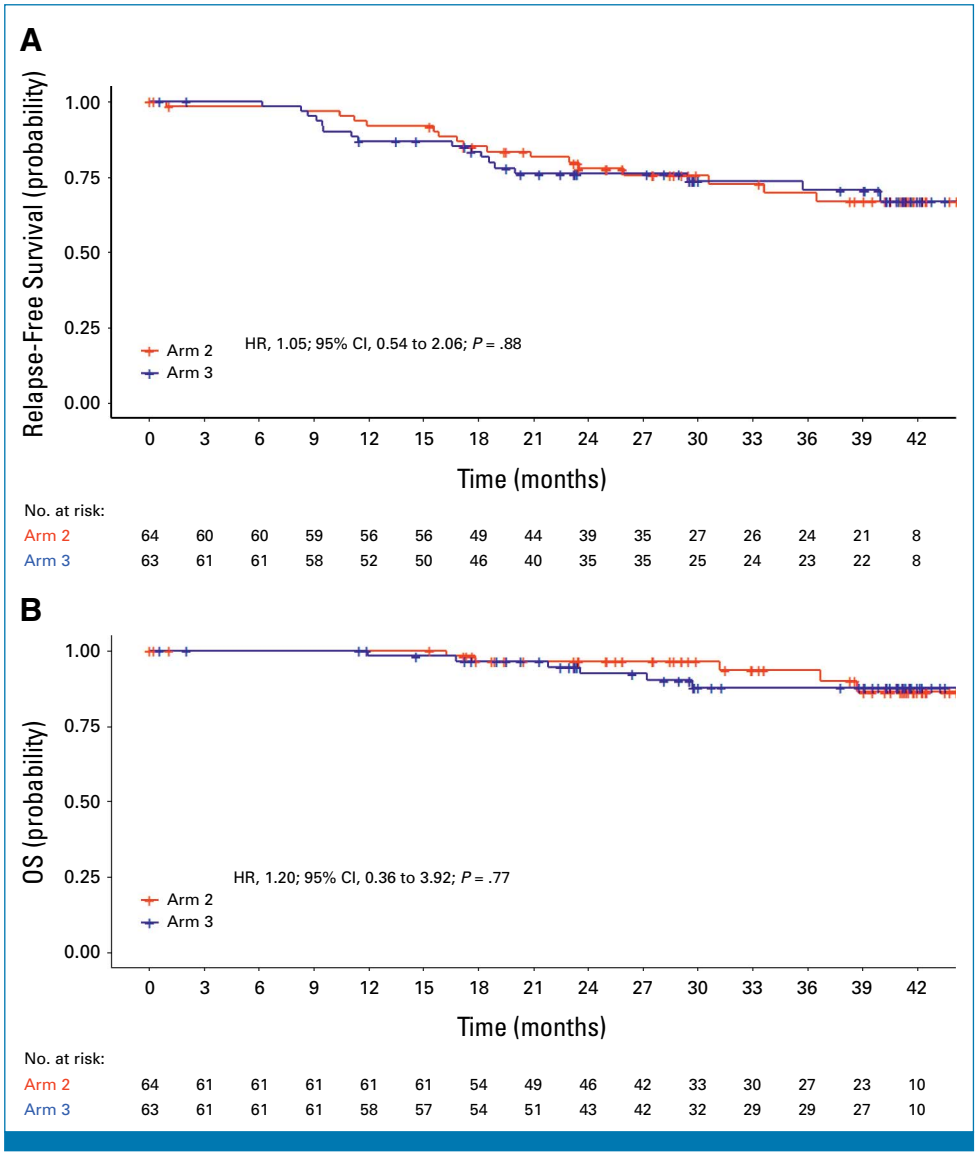


FIG 3. Kaplan-Meir estimates of relapse-free survival and OS. Kaplan-Meier estimates of (A) relapse-free survival and (B) OS in arm 2 (BSA-based oxaliplatin dose) and arm 3 (LBM-based oxaliplatin dose). HRs were calculated using the Cox proportional hazards model, with 95% CI based on log transformation and exponentiation for CI estimation, and *P* values determined with the log-rank test. BSA, body surface area; HR, hazard ratios; LBM, lean body mass; OS, overall survival.

We found that LBM-based dose calculation reduces toxicities. Moreover, this approach does not seem to affect treatment outcomes. This is highly relevant for patient management in adjuvant and probably metastatic settings, and paves the way for personalized LBM-based dose administration. Moreover, new semi-automatic software, like Myrian, facilitates routine body composition assessment, enabling the centralization of image analysis, improving reproducibility, and minimizing evaluation biases.[19,30-32]

Despite efforts to prevent OIPN, oxaliplatin dose reduction or discontinuation remains the most effective strategy. Several trials (N04C7, CONcePT, and N08CB/Alliance) investigated high doses of calcium and magnesium or GM1 as potential neuroprotectants, but found no significant benefit in preventing OIPN.[2,10,33,34] This trial was conducted in the adjuvant setting to minimize biases related to the chemotherapy regimen, its duration, and tumor progression. The goal was to minimize the risks of chronic neuropathic sequelae because most patients were expected to achieve complete remission. As a result, LBM-based oxaliplatin dose calculation has recently been recommended by the French Scientific Society for Diseases and Cancers of the Digestive Tract.[35] Nevertheless, optimizing oxaliplatin treatment acceptability and durability is critical in all settings.[36-38]

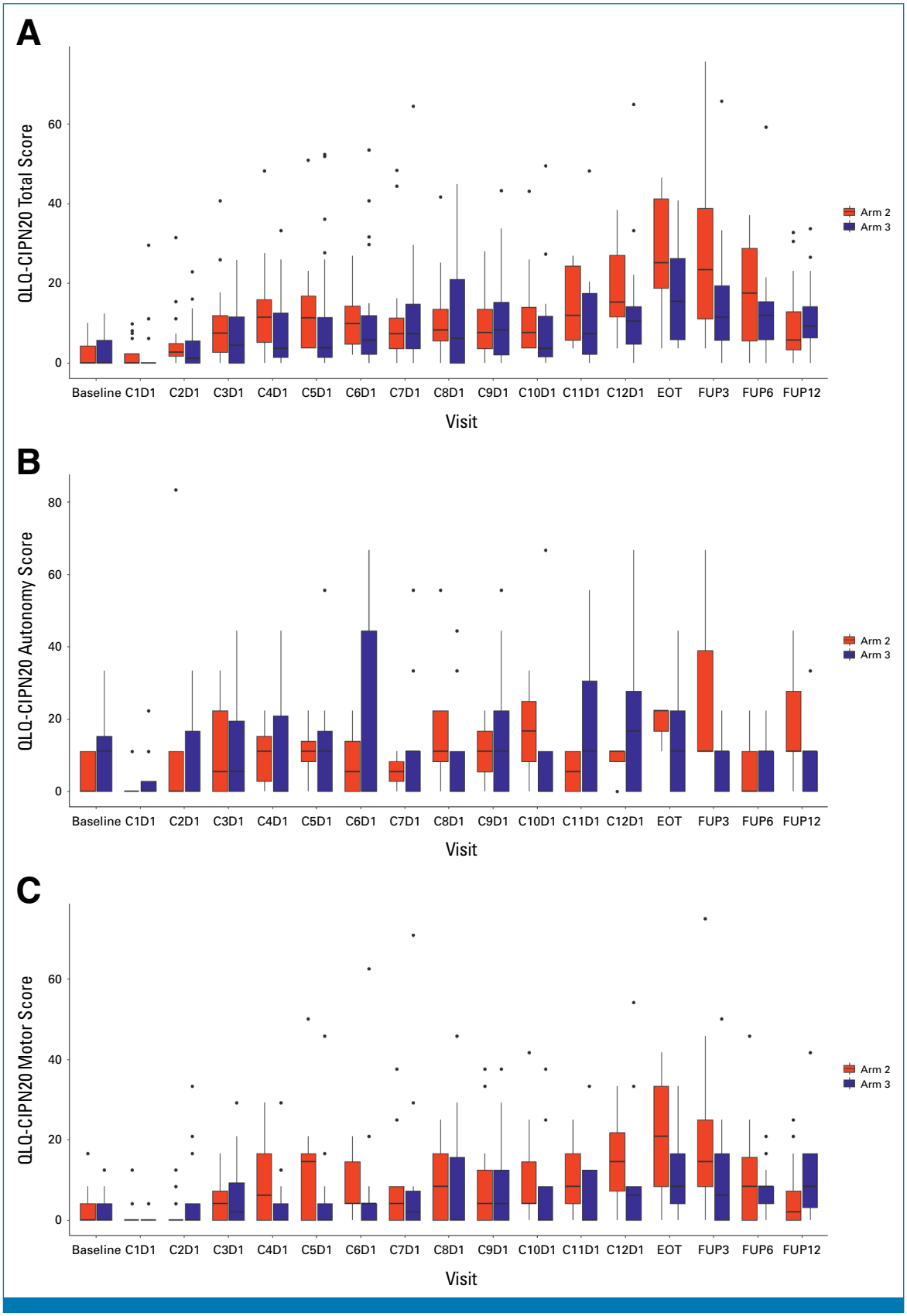


FIG 4. EORTC QLQ-CIPN20 scores. Longitudinal analysis of the (A) total, (B) autonomy, (C) motor, and (D) sensory subscale scores of the EORTC QLQ-CIPN20 questionnaire in arm 2 (BSA-based dose) and arm 3 (LBM-based dose) at baseline, from C1D1 to C12D1, at the EOT, and during the follow-up visits (FUP3, FUP6, and FUP12, corresponding to 3, 6, and 12 months after treatment). Box plots display the median, and 25th and 75th percentiles; (continued on following page)

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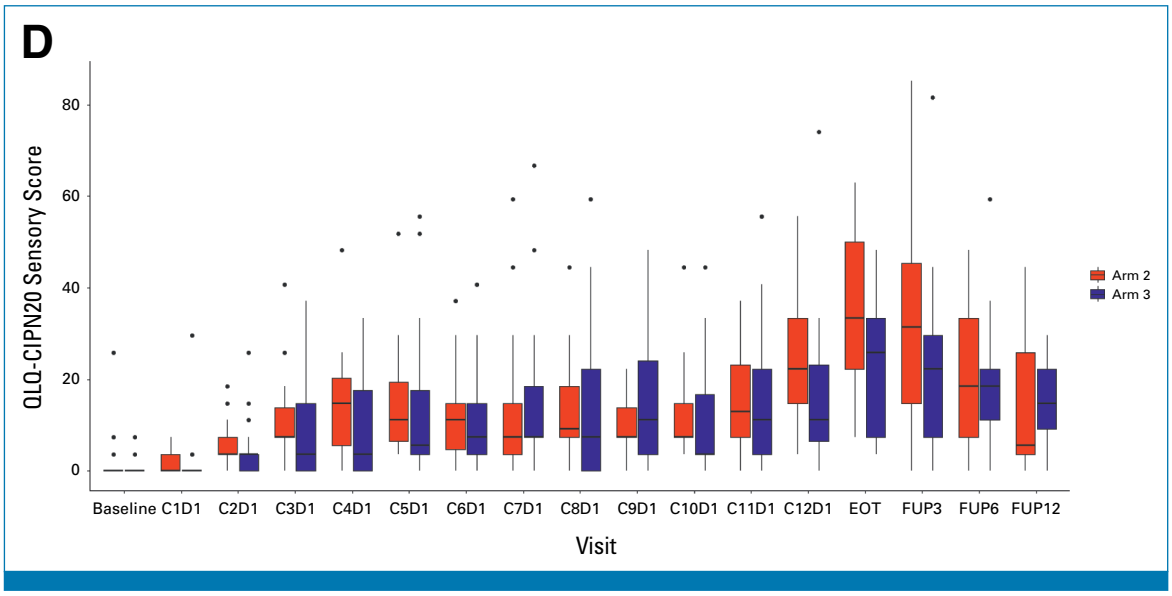


FIG 4. (Continued). whiskers denote extreme values; and outliers are shown as circles. BSA, body surface area; C12D1, cycle 12 day 1; C1D1, cycle 1 day 1; EORTC QLQ-CIPN20, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy 20; EOT, end of treatment; FUP, follow-up; LBM, lean body mass.

Our study has some limitations and potential biases. All patients were enrolled in France, a country with a predominant Caucasian population. This may limit the generalizability of these results to other ethnicities. Nonetheless, in our initial work we enrolled French and North American patients,[13] and other studies support our findings in American, European, and Asian populations. Notably, although the objective CT-based analysis revealed the presence of sarcopenia in 79% of patients, our cohort included >40% of individuals with overweight or obesity, like North American cohorts.[15,16] The study protocol, initiated in 2015, used simplified FOLFOX4 (up to 12 cycles) as standard adjuvant treatment. Despite the 2018 recommendations for treatment de-escalation based on risk stratification,[39,40] we chose to maintain our protocol to focus on grade ≥2 OIPN incidence in the first six cycles (approximately 3 months) of FOLFOX and minimize bias. Recent data confirmed the negative effect of OIPN and sarcopenia on adjuvant CAPOX completion rate in patients with colon cancer.[28] In our trial, we measured LBM only at enrollment. Our findings, especially the relative dose intensity rates of oxaliplatin in arm 3 throughout the treatment, support our decision, at least in the adjuvant setting. In the metastatic setting, repeated LBM measurements could be beneficial (optimization of oxaliplatin dosing). The trial was not blinded. However, the risk of bias was mitigated because it was carried out at 18 centers with standardized evaluation of severe neurotoxicity. Moreover, self-assessment using the EORTC QLQ-CIPN20 questionnaire corroborated the data on grade ≥2 OIPN. This was not a noninferiority trial, but survival rates were comparable between treatment arms and were in line with the clinical characteristics of the studied population.

In conclusion, this randomized clinical trial demonstrated that individualized LBM-based chemotherapy dose calculation significantly reduces OIPN. Personalized LBM-adapted treatment should become standard practice to mitigate OIPN in patients with nonmetastatic colon cancer treated with oxaliplatin. These findings may influence clinical practice by optimizing chemotherapy dosing and by suggesting the implementation of therapeutic interventions to increase muscle mass in metastatic settings.

AFFILIATIONS

[1]Department of Medical Oncology, Montpellier Cancer Institute (ICM), Montpellier University, Montpellier, France
[2]Digestive Oncology Department, CHU Montpellier, Montpellier University, Montpellier, France
[3]Medical Oncology Department, ICANS, Strasbourg, France
[4]Biometric Unit, Montpellier Cancer Institute (ICM), Montpellier University, Montpellier, France
[5]Oncology Department, Saint Joseph Hospital, Marseille, France
[6]Department of Gastroenterology and GI Oncology, CH Saint-Jean, Perpignan, France
[7]Department of Hepatogastroenterology and Digestive Oncology, CH Saint-Malo, Saint-Malo, France
[8]Department of Digestive Oncology, Baclesse Center, Caen, France
[9]Clinical Research and Innovation Department, Montpellier Cancer Institute (ICM), Montpellier University, Montpellier, France
[10]Hepatogastroenterology Department, European Hospital of Marseille, Marseille, France

[11]Department of Hepato-Gastroenterology & Digestive Oncology, INSERM EPICAD CTM 1231, University Hospital of Dijon Bourgogne, Dijon, France
[12]Department of Radiology, Montpellier Cancer Institute (ICM), Montpellier University, Montpellier, France
[13]Department of Clinical Nutrition and Gastroenterology, Montpellier Cancer Institute (ICM), Montpellier University, Montpellier, France

CORRESPONDING AUTHOR

Eric Assenat, MD, PhD; e-mail: e-assenat@chu-montpellier.fr.

PRIOR PRESENTATION

Presented at the European Society for Medical Oncology (ESMO) Congress, Barcelona, Spain, September 15, 2024.

SUPPORT

Supported by the French Ministry of Health (PHRC-K 15-209) and the French National Institute of Cancer (INCA DOM number 2019-207).

CLINICAL TRIAL INFORMATION

NCT03255434

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-24-02754.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-24-02754.

AUTHOR CONTRIBUTIONS

Conception and design: Eric Assenat, Sophie Gourgou, Chloé Janiszewski, Côme Lepage, Raphael Tetreau, Pierre Senesse
Financial support: Eric Assenat
Administrative support: Hervé Perrier, Côme Lepage, Raphael Tetreau
Provision of study materials or patients: Eric Assenat, Marie-Pierre Galais, Thibault Mazard, Yves Rinaldi
Collection and assembly of data: Eric Assenat, Meher Ben Abdelghani, Sophie Gourgou, Faiza Khemissa Akouz, Thibault Mazard, Yves Rinaldi
Data analysis and interpretation: Eric Assenat, Sophie Gourgou, Hervé Perrier, Romain Desgrippes, Marie-Pierre Galais, Thibault Mazard, Côme Lepage, Pierre Senesse
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors warmly thank all patients, their family, and all medical teams who helped to achieve this trial. They also thank the "Fédération Française de Cancérologie Digestive (FFCD)-PRODIGE Group for their support. The authors also thank Nadia Bensmail for monitoring pharmacovigilance data throughout the study. The authors also thank Dr Fanny Salasc of the Montpellier Cancer Institute for providing medical writing and editorial support, and Dr Elisabetta Andermarcher for editing the manuscript.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Impact of Lean Body Mass–Based Oxaliplatin Dose Calculation on Neurotoxicity in Adjuvant Treatment of Stage III Colon Cancer: Results of the Phase II Randomized LEANOX Trial

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Honoraria: Bayer, Ipsen, Novartis, Amgen, Sanofi/Aventis, Servier, AstraZeneca, Roche, Incyte, Deciphera
Consulting or Advisory Role: Bayer, Ipsen, BTG, AstraZeneca, BMS GmbH & Co KG, Servier, Roche
Travel, Accommodations, Expenses: Bayer, Pfizer, Ipsen, Roche, Servier, Deciphera

Meher Ben Abdelghani
Consulting or Advisory Role: Incyte, Pierre Fabre, BMS, Deciphera, Merck Serono, Servier, Bayer, Viatris, Mundipharma
Travel, Accommodations, Expenses: Amgen, Servier, Viatris, Merck Serono, Roche

Faiza Khemissa Akouz
Honoraria: Servier, Roche, AstraZeneca
Travel, Accommodations, Expenses: Servier, AstraZeneca, MSD Oncology, Nestlé Homecare

Romain Desgrippes
Honoraria: Takeda, MSD, Pierre Fabre
Travel, Accommodations, Expenses: Takeda, Sandoz, Pierre Fabre

Marie-Pierre Galais
Honoraria: Servier, BMS, Pierre Fabre
Travel, Accommodations, Expenses: Roche, Pierre Fabre, Servier, Bayer, Merck, MSD Oncology

Thibault Mazard
Honoraria: Takeda, AstraZeneca (Inst)
Consulting or Advisory Role: Pierre Fabre, Merck Serono, Servier, Galapagos NV
Research Funding: Amgen (Inst)
Travel, Accommodations, Expenses: Pierre Fabre, Merck Serono, MSD Oncology, Takeda

Yves Rinaldi
Honoraria: Viatris, Amgen Astellas BioPharma

Côme Lepage
Honoraria: Amgen, Pierre Fabre, Takeda, Servier, Deciphera, Novartis
Consulting or Advisory Role: Ipsen, AbbVie, Pierre Fabre
Travel, Accommodations, Expenses: Pierre Fabre, Merck Serono, Astellas Pharma

Pierre Senesse
Honoraria: NHC (Inst), Elivie (Inst), Nestle Health Science (Inst)
Consulting or Advisory Role: Pfizer (Inst), Danone (Inst)
Travel, Accommodations, Expenses: Pfizer, Danone/Nutricia, NHC

No other potential conflicts of interest were reported.

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APPENDIX

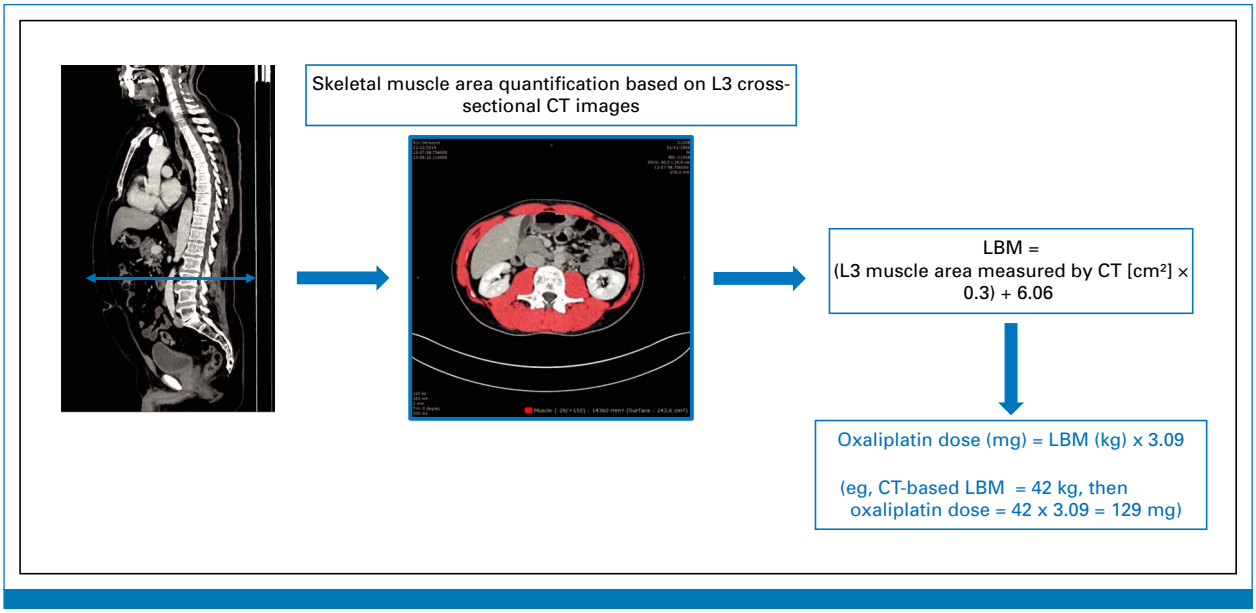


FIG A1. Example of LBM determination and oxaliplatin dose adaptation in function of the LBM using the Myrian software (Intrasense SA, Montpellier, France). CT, computed tomography; LBM, lean body mass.

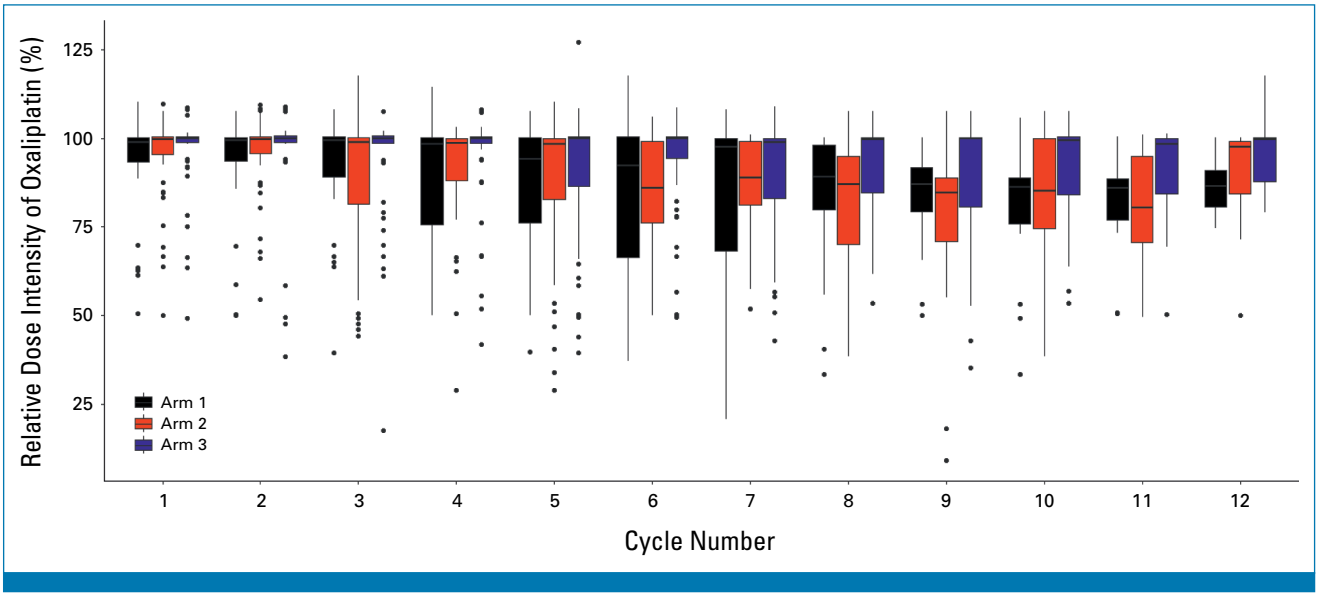


FIG A2. Changes in the relative dose intensity of oxaliplatin according to the treatment arm. Patients in arm 1, without significant LBM reduction, received a BSA-based oxaliplatin dose. Patients with reduced LBM were randomly assigned (1:1) to receive a BSA-based dose (arm 2) or LBM-based dose (arm 3) of oxaliplatin. Box plots show the median, and 25th and 75th percentiles; whiskers indicate extreme values; and outliers are represented as circles. BSA, body surface area; LBM, lean body mass.

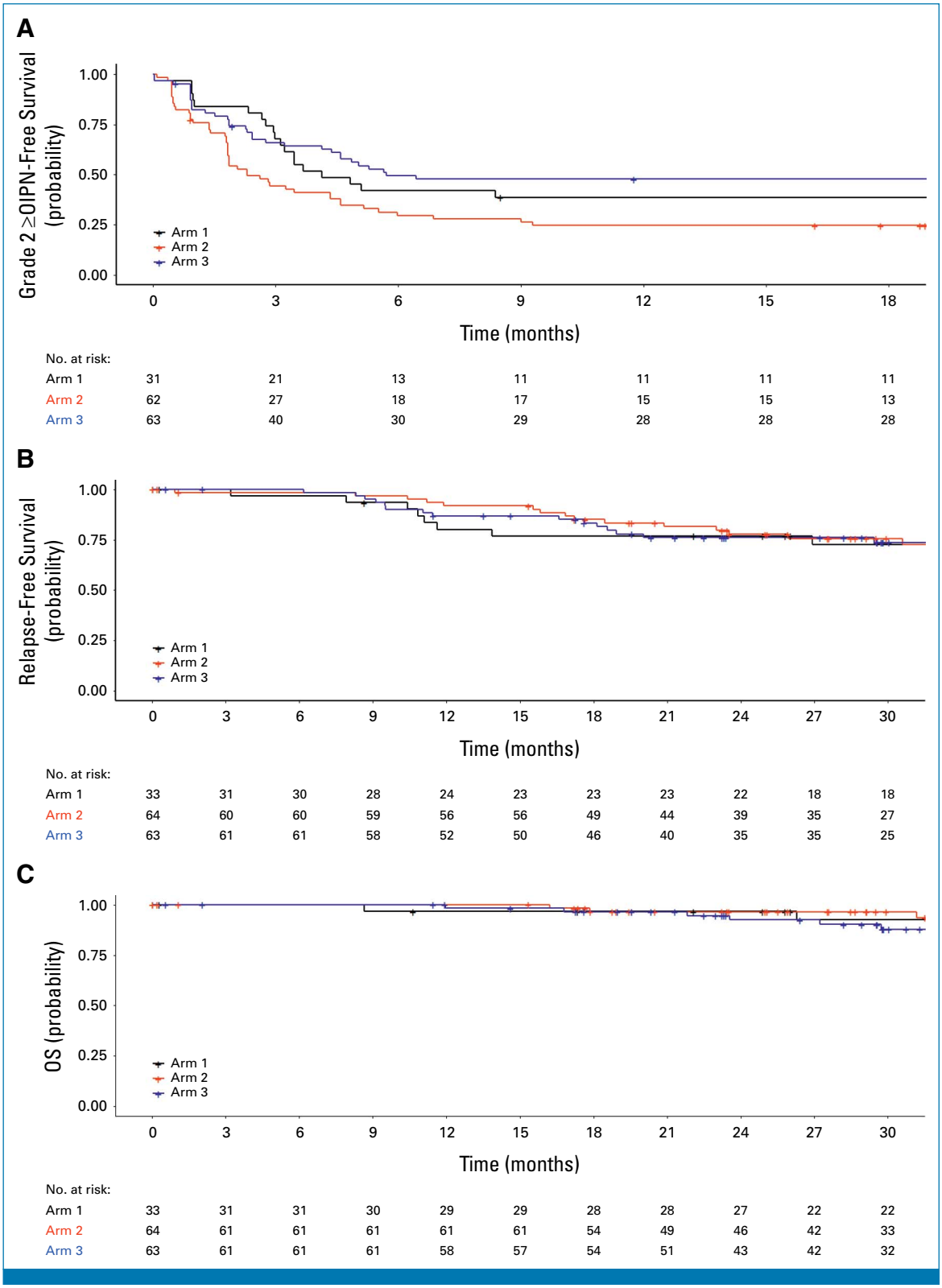


FIG A3. Kaplan-Meir survival curves. (A) Grade ≥2 OIPN-free survival, (B) relapse-free survival, and (C) OS stratified by treatment arm. Arm 1 includes patients without LBM reduction receiving a BSA-based oxaliplatin dose, whereas arms 2 and 3 include patients with LBM reduction, randomly assigned to BSA-based or LBM-based oxaliplatin dose, respectively. BSA, body surface area; LBM, lean body mass; OIPN, oxaliplatin-induced peripheral neuropathy; OS, overall survival.

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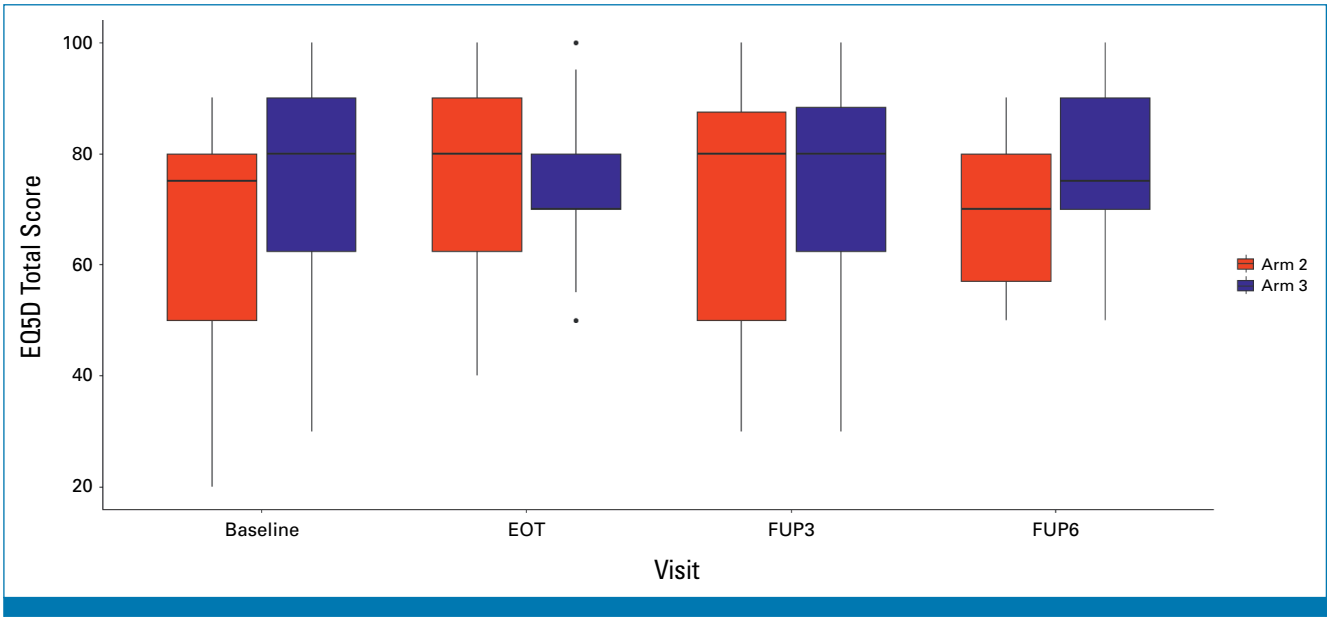


FIG A4. EORTC EQ5D scores. Longitudinal analysis of the total scores of the EORTC EQ5D questionnaire in arm 2 (BSA-based dose) and arm 3 (LBM-based dose) at baseline, at the EOT, and during the follow-up visits (FUP3, FUP6, corresponding to 3 and 6 months after treatment). Box plots display the median, and 25th and 75th percentiles; whiskers indicate extreme values; and outliers are shown as circles. BSA, body surface area; EORTC EQ5D, European Organization for Research and Treatment of Cancer European Quality of Life 5 Dimensions; EOT, end of treatment; FUP, follow-up; LBM, lean body mass.

TABLE A1. Treatment-Related Toxicities

Toxicity	Arm 1 (n = 33), No. (%)	Arm 2 (n = 64), No. (%)	Arm 3 (n = 63), No. (%)	Total (N = 160), No. (%)
Hematological toxicities				
Neutropenia				
All	4 (12.9)	5 (8)	8 (12.7)	17 (10.9)
Grade ≥3	1 (3.2)	3 (4.8)	7 (11.1)	11 (7)
Febrile neutropenia				
All	0	1 (1.6)	0	1 (0.6)
Grade ≥3	0	1 (1.6)	0	1 (0.6)
Thrombopenia				
Grade 1-2	0	3 (4.8)	5 (7.9)	8 (5.1)
Anemia				
Grade 1-2	2 (6.4)	3 (4.8)	4 (6.3)	9 (5.7)
Nonhematological toxicities				
Nausea				
All	18(58)	39 (62.9)	45 (71.4)	102 (65.4)
Grade ≥3	1 (3.2)	1 (1.6)	0	2 (1.3)
Vomiting				
All	7 (22.6)	10 (16.1)	11 (17.5)	28 (18)
Grade ≥3	2 (6.4)	0	0	2 (1.3)
Mucositis				
All	6 (19.3)	11 (17.7)	10 (15.9)	27 (17.3)
Grade ≥3	1 (3.2)	2 (3.2)	0	3 (1.9)
Diarrhea				
All	15(48.4)	29 (46.8)	30 (47.6)	74 (47.4)
Grade ≥3	1 (3.2)	1 (1.6)	1 (1.6)	3 (1.9)
Hypokalemia				
Grade ≥3	0	1 (1.6)	0	1 (0.6)
Hand-foot syndrome				
Grade 1-2	4 (12.9)	3 (4.8)	2 (3.2)	9 (5.8)
OIPN				
All	31 (100)	61 (98.4)	61 (96.8)	153 (98)
Grade ≥3	9 (29)	28 (45.2)	18 (28.6)	55 (35.3)
Fatigue				
All	22 (70.1)	43 (69.3)	42 (66.7)	107 (68.6)
Grade ≥3	0	4 (6.4)	0	4 (2.6)
Infection				
All	1 (3.2)	2 (3.2)	1 (1.6)	7 (4.5)
Grade ≥3	1 (3.2)	0	1 (1.6)	2 (1.3)
Allergy/hypersensitivity				
Grade ≥3	1 (3.2)	5 (8)	1 (1.6)	7 (4.5)
Thromboembolism				
Grade ≥3	1 (3.2)	0	0	1 (0.6)

NOTE. One grade 4 toxicity was reported in arm 1 (neutropenia), two grade 4 toxicities in arm 2 (n = 1 neutropenia and n = 2 OIPN), and six grade 4 toxicities in arm 3 (n = 3 neutropenia, n = 1 cardiogenic shock, n = 1 diabetic ketoacidosis, and n = 1 stroke). No grade 5 toxicity (death) was reported.

Abbreviation: OIPN, oxaliplatin-induced peripheral neuropathy.

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TABLE A2. Number of Events for Time-to-Event End Points

Parameter	Arm 1 (n = 33)	Arm 2 (n = 64)	Arm 3 (n = 63)	Total (N = 160)
Overall survival				
Events, No.	6	5	5	17
Recurrence-free survival				
Events, No.	9	17	17	43
Grade ≥2 OIPN-free survival				
Events, No.	20	46	32	98
Months, median (95% CI)	4.14 (3.12 to NR)	2.30 (1.84 to 4.60)	5.72 (4.37 to NR)	4.34 (3.12 to 5.65)

Abbreviations: NR, not reached; OIPN, oxaliplatin-induced peripheral neuropathy.