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Nutritional status and quality of life with or without Ninjin'yoeito during first-line chemotherapy for metastatic colorectal cancer: an exploratory, open-label randomized phase II trial

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Research Article

Keywords: Ninjin'yoeito, Kampo medicine, colorectal cancer, chemotherapy, body mass index, quality of life

Posted Date: September 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10847475/v1

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Abstract

Purpose

Cancer-associated malnutrition during chemotherapy may impair treatment tolerance and quality of life (QoL). Ninjin'yoeito (NYT), a Japanese Kampo medicine, is used to treat anorexia, fatigue, and general malaise. We evaluated NYT during first-line chemotherapy for metastatic colorectal cancer (mCRC).

Methods

This exploratory, open-label, multicenter, randomized phase II trial compared NYT plus CAPOX and bevacizumab with CAPOX and bevacizumab alone in patients with unresectable mCRC. Co-primary endpoints were longitudinal changes in Controlling Nutritional Status (CONUT) scores and grade ≥ 3 nonhematological adverse events. Secondary endpoints included body mass index (BMI), QoL, and progression-free survival (PFS).

Results

Enrollment was terminated early because of slow accrual. Of 78 randomized patients, 74 were included in the full analysis set (NYT, n = 39; non-NYT, n = 35). Neither co-primary endpoint differed significantly between groups: CONUT score changes (least-squares mean difference [LSMD], − 0.05; 95% confidence interval [CI], − 0.53 to 0.42; P = 0.822) and grade ≥ 3 nonhematological adverse events (25.6% vs 20.0%; P = 0.593). Exploratory analysis showed better BMI maintenance with NYT (LSMD, 0.66 kg/m²; 95% CI, 0.19–1.13; P = 0.007). Appetite loss was lower with NYT and remained significant in sensitivity analysis, whereas insomnia scores were higher. PFS did not differ significantly between groups (HR, 1.21; 95% CI, 0.44–3.33; log-rank P = 0.713).

Conclusions

NYT did not significantly affect either co-primary endpoint. Exploratory findings suggested better BMI maintenance and reduced appetite loss, whereas insomnia scores were higher. These findings are hypothesis-generating and require confirmation in adequately powered trials.

Clinical trial registration

This trial was registered in the Japan Registry of Clinical Trials (ID jRCTs041190071) on October 2, 2019.

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide, and systemic chemotherapy remains the mainstay of treatment for unresectable metastatic CRC (mCRC) [1–3]. Oxaliplatin-based regimens, including capecitabine plus oxaliplatin (CAPOX) with bevacizumab, are established first-line treatments [4]. However, treatment-related adverse events, including anorexia, fatigue, and peripheral neuropathy, can impair treatment tolerance and quality of life (QoL) [5].

Malnutrition is common in patients with gastrointestinal malignancies and is associated with impaired treatment tolerance and poorer clinical outcomes [6–8]. The Controlling Nutritional Status (CONUT) score is an objective nutritional screening tool calculated from serum albumin, total cholesterol, and total lymphocyte count, reflecting protein reserves, lipid metabolism, and immune status, respectively [9]. It categorizes nutritional status as normal, mild, moderate, or severe malnutrition and has demonstrated prognostic relevance in several malignancies, including CRC [10–13]. Because it is based on routinely collected laboratory parameters, the CONUT score can be assessed repeatedly during chemotherapy. However, evidence supporting its use as a longitudinal endpoint for evaluating changes in nutritional status during active chemotherapy remains limited.

Ninjin'yoeito (NYT) is a standardized Japanese Kampo formulation comprising 12 herbal components and has traditionally been used to treat fatigue, anorexia, and general malaise [14, 15]. Clinical studies have suggested potential benefits of NYT for frailty, malnutrition, and chemotherapy-related symptoms, including peripheral neuropathy, although robust evidence in patients with cancer remains limited [16–19]. Preclinical studies have also suggested effects on appetite regulation, inflammation, and energy metabolism [20–23], providing a rationale for evaluating NYT as supportive care during chemotherapy.

We therefore conducted the NYX study, a multicenter, open-label, randomized phase II trial, to evaluate NYT in patients with unresectable mCRC receiving first-line CAPOX plus bevacizumab. The study assessed nutritional status, treatment-related toxicity, QoL, and treatment outcomes, with longitudinal changes in CONUT score and grade ≥ 3 nonhematological adverse events as the co-primary endpoints.

Materials and Methods

Study Design and Participants

This multicenter, open-label, randomized phase II trial was conducted at 15 hospitals in Japan. Eligible patients were aged ≥ 20 years and had histologically confirmed unresectable mCRC, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, and adequate organ function. Patients with severe malnutrition (CONUT score ≥ 9) were excluded. Detailed eligibility criteria and the study protocol have been reported previously [24].

Patients were centrally randomized 1:1 to CAPOX plus bevacizumab with NYT (NYT group) or CAPOX plus bevacizumab alone (non-NYT group) using a permuted-block method, stratified by ECOG PS (0–1 vs. 2), baseline CONUT category (normal, mild, or moderate), and participating institution. The allocation sequence was generated and implemented through a centralized electronic system managed by an

independent data center (Mebix Co., Ltd., Tokyo, Japan). Patients were enrolled through December 2022 and followed for efficacy and safety outcomes until June 30, 2023.

Treatment

All patients received CAPOX plus bevacizumab every 3 weeks, consisting of oxaliplatin 130 mg/m² intravenously on day 1, capecitabine 1,000 mg/m² orally twice daily on days 1–14, and bevacizumab 7.5 mg/kg intravenously on day 1. Patients in the NYT group additionally received NYT (TJ-108; Tsumura & Co., Tokyo, Japan) 3.0 g orally three times daily from cycle 1 day 1 through week 24. Treatment was continued for up to eight cycles or until disease progression, unacceptable toxicity, or conversion surgery. Dose modifications and treatment interruptions were permitted according to the protocol [24]. Adherence to NYT and capecitabine was assessed through patient interviews. Concomitant medications and supportive care, including nutritional support, were provided according to standard practice at each institution and were not protocolized.

Outcomes

The co-primary endpoints were (1) longitudinal changes in nutritional status assessed by the CONUT score and (2) the incidence of grade ≥ 3 nonhematological adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [25]. The CONUT score was calculated from serum albumin, total cholesterol, and lymphocyte count and categorized as normal (0–1), mild (2–4), moderate (5–8), or severe (9–12) [9].

Secondary endpoints included body mass index (BMI), progression-free survival (PFS), and QoL assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), version 3.0 [26]. CONUT score and BMI were assessed at baseline and each treatment cycle, and QoL at baseline, cycle 5, and cycle 9. PFS was defined as the time from randomization to disease progression or death from any cause.

Plasma concentrations of capecitabine and its metabolites (5'-deoxy-5-fluorocytidine and 5'-deoxy-5-fluorouridine) were measured at 0, 1, and 2 h after capecitabine administration during cycles 1 and 2 to assess potential pharmacokinetic interactions with NYT. Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 [27].

Statistical Analyses

The target enrollment was 150 patients based on feasibility considerations; no formal power calculation was performed. No interim analysis or formal stopping rule was specified. The full analysis set (FAS) comprised randomized patients who received at least one dose of study treatment and had at least one postbaseline assessment; patients were analyzed according to their assigned group. The safety analysis

set (SAS), used for additional all-grade safety summaries, comprised all randomized patients who received at least one dose of study treatment.

Longitudinal changes in CONUT score, BMI, and QoL were analyzed using mixed models for repeated measures (MMRM). Model 1 included treatment group, assessment time, and treatment-by-time interaction as fixed effects. Model 2 additionally adjusted for the corresponding baseline value and was used as the primary MMRM model. A compound symmetry covariance structure and Kenward–Roger method for denominator degrees of freedom were used. Least-squares means (LSMs), between-group least-squares mean differences (LSMDs), and 95% confidence intervals (CIs) were estimated. A change of ≥ 10 points from baseline in EORTC QLQ-C30 scores was considered clinically relevant [28].

Grade ≥ 3 nonhematological adverse events were compared using Fisher's exact test. PFS was estimated using the Kaplan–Meier method and compared using the log-rank test; hazard ratios (HRs) and 95% CIs were estimated using a Cox proportional hazards model. Primary MMRM analyses used observed data under the missing-at-random assumption. As a sensitivity analysis, missing values were imputed using the last observation carried forward (LOCF) method, and the MMRM analysis was repeated using the same model. All tests were two-sided, with $P < 0.05$ considered statistically significant. Analyses were performed using SAS version 9.4 or later (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics

Between October 2019 and December 2022, 78 patients were randomized to the NYT (n = 40) or non-NYT (n = 38) group. Enrollment was terminated early because of slow accrual. After excluding four patients, 74 were included in the FAS (NYT, n = 39; non-NYT, n = 35) (Fig. 1). Twenty-eight and 22 patients completed eight treatment cycles, and eight and seven underwent conversion surgery, respectively. Among patients in the NYT group, 33 (84.6%) received at least two-thirds of the planned NYT dose. Baseline characteristics are shown in Table 1.

Table 1
Baseline characteristics of the study population.

Characteristic	Total (N = 74)	NYT group (N = 39)	Non-NYT group (N = 35)	P value
Age, years				
Mean ± SD	66.2 ± 10.1	64.3 ± 9.7	68.4 ± 10.1	0.083*
< 65 years n (%)	26 (35.1)	17 (43.6)	9 (25.7)	0.289†
65–74 years n (%)	35 (47.3)	16 (41.0)	19 (54.3)	
≥ 75 years n (%)	13 (17.6)	6 (15.4)	7 (20.0)	
Sex n (%)				
Male	44 (59.5)	26 (66.7)	18 (51.4)	0.237†
Female	30 (40.5)	13 (33.3)	17 (48.6)	
Disease status n (%)				
Unresectable/metastatic	61 (82.4)	32 (82.1)	29 (82.9)	1.000†
Recurrent	13 (17.6)	7 (17.9)	6 (17.1)	
Recent surgical intervention n (%)				
Yes	65 (87.8)	33 (84.6)	32 (91.4)	0.486†
No	9 (12.2)	6 (15.4)	3 (8.6)	
Prior adjuvant chemotherapy n (%)				
Yes	1 (1.4)	1 (2.6)	0 (0.0)	1.000†
Primary tumour site, n (%)				
Cecum–ascending colon	15 (20.3)	11 (28.2)	4 (11.4)	0.258‡

Values are presented as means ± standard deviations (SDs) or numbers (%). *P values were calculated using Student's t-test for continuous variables. †P values were calculated using Fisher's exact test for categorical variables. ‡P values were calculated using the chi-square test for categorical variables.

Recent surgical intervention was defined as any surgical procedure performed within 4 weeks before the initiation of chemotherapy. Patients with severe malnutrition (CONUT score ≥ 9) were excluded from the study.

Abbreviations: BMI, body mass index; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; NYT, Ninjin'yoeito; SD, standard deviation.

Characteristic	Total (N = 74)	NYT group (N = 39)	Non-NYT group (N = 35)	P value
Transverse colon	10 (13.5)	3 (7.7)	7 (20.0)	
Descending–sigmoid colon	23 (31.1)	11 (28.2)	12 (34.3)	
Rectum	25 (33.8)	13 (33.3)	12 (34.3)	
Anal canal	1 (1.4)	1 (2.6)	0 (0.0)	
RAS/BRAF mutation status, n (%)				
RAS/BRAF wild-type	35 (47.3)	20 (51.3)	15 (42.9)	0.205†
RAS-mutated	36 (48.6)	19 (48.7)	17 (48.6)	
BRAF-mutated	3 (4.1)	0 (0.0)	3 (8.6)	
ECOG performance status n (%)				
0–1	71 (95.9)	37 (94.9)	34 (97.1)	1.000†
2	3 (4.1)	2 (5.1)	1 (2.9)	
CONUT score				
Mean ± SD	2.2 ± 2.2	2.2 ± 1.9	2.2 ± 2.5	0.924*
Normal (0–1) n (%)	37 (50.0)	18 (46.2)	19 (54.3)	0.593†
Mild (2–4) n (%)	26 (35.1)	16 (41.0)	10 (28.6)	
Moderate (5–8) n (%)	11 (14.9)	5 (12.8)	6 (17.1)	
BMI, kg/m^2, mean ± SD	22.6 ± 4.2	22.8 ± 4.1	22.5 ± 4.4	0.724*
Total cholesterol, mg/dL, mean ± SD	195.4 ± 48.8	199.8 ± 52.7	190.5 ± 44.4	0.417*
Albumin, g/dL, mean ± SD	3.7 ± 0.6	3.6 ± 0.6	3.7 ± 0.6	0.534*

Values are presented as means ± standard deviations (SDs) or numbers (%). *P values were calculated using Student's t-test for continuous variables. †P values were calculated using Fisher's exact test for categorical variables. ‡P values were calculated using the chi-square test for categorical variables.

Recent surgical intervention was defined as any surgical procedure performed within 4 weeks before the initiation of chemotherapy. Patients with severe malnutrition (CONUT score ≥ 9) were excluded from the study.

Abbreviations: BMI, body mass index; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; NYT, Ninjin'yoeito; SD, standard deviation.

Characteristic	Total (N = 74)	NYT group (N = 39)	Non-NYT group (N = 35)	P value
Total lymphocyte count, cells/μL, mean ± SD	1501.2 ± 535.5	1534.5 ± 507.1	1464.1 ± 570.6	0.576*
C-reactive protein, mg/dL, mean ± SD	1.7 ± 2.9	1.6 ± 2.1	1.9 ± 3.7	0.678*
Values are presented as means ± standard deviations (SDs) or numbers (%). *P values were calculated using Student's t-test for continuous variables. †P values were calculated using Fisher's exact test for categorical variables. ‡P values were calculated using the chi-square test for categorical variables.				
Recent surgical intervention was defined as any surgical procedure performed within 4 weeks before the initiation of chemotherapy. Patients with severe malnutrition (CONUT score ≥ 9) were excluded from the study.				
Abbreviations: BMI, body mass index; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; NYT, Ninjin'yoeito; SD, standard deviation.				

Nutritional Status (Co-primary Endpoint)

Longitudinal changes in CONUT scores are shown in Fig. 2. In the primary MMRM analysis (Model 2), the LSM CONUT scores were 1.89 (95% CI, 1.57–2.21) in the NYT group and 1.94 (95% CI, 1.59–2.29) in the non-NYT group (LSMD, − 0.05; 95% CI, − 0.53 to 0.42; P = 0.822). The treatment-by-cycle interaction was not significant (P = 0.694). Although CONUT scores appeared relatively stable during later cycles in the NYT group, no statistically significant between-group difference was observed. The sensitivity analysis using LOCF imputation yielded similar results (Supplementary Table 2).

Nonhematological Adverse Events (Co-primary Endpoint)

The incidence of grade ≥ 3 nonhematological adverse events did not differ significantly between the NYT and non-NYT groups (25.6% vs. 20.0%; P = 0.593) (Table 2). Among individual adverse events, the incidence of grade ≥ 3 peripheral neuropathy was numerically lower in the NYT group than in the non-NYT group (5.1% vs. 20.0%), although this difference did not reach statistical significance (P = 0.075). One case each of gastrointestinal perforation and sudden cardiac death occurred in the NYT group; both events were considered unrelated to study treatment. Among all-grade nonhematological adverse events, peripheral neuropathy was common in both groups (92.3% vs. 94.4%). Palmar-plantar erythrodysesthesia syndrome and diarrhea were numerically less frequent in the NYT group, whereas fatigue was numerically more frequent (Supplementary Table 6).

Table 2
Incidence of grade ≥ 3 nonhematological adverse events in the full analysis set.

Adverse event	NYT (N = 39), n (%)	Non-NYT (N = 35), n (%)	P value
Grade ≥ 3 events	10 (25.6)	7 (20.0)	0.593
Peripheral neuropathy	2 (5.1)	7 (20.0)	0.075
Liver dysfunction	1 (2.6)	0 (0.0)	1.000
Anorexia	1 (2.6)	0 (0.0)	1.000
Edema	1 (2.6)	0 (0.0)	1.000
Hypoalbuminemia	1 (2.6)	0 (0.0)	1.000
Dehydration	1 (2.6)	0 (0.0)	1.000
Fatigue	3 (7.7)	0 (0.0)	0.242
Stomatitis	1 (2.6)	0 (0.0)	1.000
Hypertension	1 (2.6)	0 (0.0)	1.000
Gastrointestinal perforation	1 (2.6)	0 (0.0)	1.000
Sudden cardiac death	1 (2.6)	0 (0.0)	1.000
Values are presented as n (%). Patients may have experienced more than one adverse event. P values were calculated using Fisher's exact test.			
Abbreviations: NYT, Ninjin'yoeito.			

Changes in Body Mass Index (Secondary Endpoint)

Longitudinal changes in BMI during chemotherapy are shown in Fig. 3. BMI increased during later treatment cycles in the NYT group but remained relatively stable or slightly decreased in the non-NYT group. In the primary MMRM analysis, the LSMs were 22.79 kg/m² (95% CI, 22.47–23.10) in the NYT group and 22.13 kg/m² (95% CI, 21.78–22.48) in the non-NYT group (LSMD, 0.66 kg/m²; 95% CI, 0.19–1.13; P = 0.007). The treatment-by-cycle interaction was significant (P = 0.005). The sensitivity analysis using LOCF imputation yielded similar results.

Quality of Life (QoL) (Secondary Endpoints)

In exploratory analyses using the primary MMRM model (Model 2), significant between-group differences were observed in social functioning (LSMD, 4.21; 95% CI, 0.08–8.34; P = 0.046) among the functional scales and in appetite loss (LSMD, − 6.97; 95% CI, − 13.65 to − 0.29; P = 0.041), financial difficulties (LSMD, − 8.93; 95% CI, − 15.29 to − 2.57; P = 0.007), and insomnia (LSMD, 8.45; 95% CI, 2.12–14.78; P = 0.010) among the symptom scales. Other QoL domains showed no significant between-group differences, and results for all QoL domains are provided in Supplementary Table 3. Longitudinal

changes from baseline in the four domains with significant between-group differences are shown in Fig. 4. At cycle 9, mean changes from baseline in the NYT group exceeded 10 points in the direction of improvement for social functioning and financial difficulties. In the sensitivity analysis using LOCF imputation, between-group differences remained significant for appetite loss and insomnia but not for social functioning or financial difficulties (Supplementary Table 4).

Progression-Free Survival

Seventeen PFS events occurred (NYT, n = 11; non-NYT, n = 6). PFS did not differ significantly between groups (HR, 1.21; 95% CI, 0.44–3.33; log-rank P = 0.713). Median PFS was not reached in either group.

Pharmacokinetic Profiles

No significant differences in the pharmacokinetic ratios of capecitabine and its metabolites (5'-DFCR and 5'-DFUR) were observed in either the between-group comparisons on day 22 or the within-patient comparisons between day 1 and day 22 (Supplementary Table 5).

Discussion

This exploratory phase II trial did not demonstrate statistically significant effects of Ninjin'yoeito (NYT) on either predefined co-primary endpoint, namely longitudinal changes in CONUT scores or the incidence of grade ≥ 3 nonhematological adverse events. Exploratory secondary analyses suggested better preservation of BMI and differences in selected patient-reported outcomes, whereas no significant difference in PFS was observed. However, the trial was terminated early with fewer than half of the planned patients included in the analysis, and these secondary findings should be regarded as hypothesis-generating.

The absence of a significant effect on CONUT scores warrants consideration. Although CONUT is a validated prognostic index based on serum albumin, total cholesterol, and lymphocyte count and has demonstrated prognostic relevance in CRC [9, 10, 12], its utility as a longitudinal measure during active chemotherapy is less established. In addition, half of the study population had normal CONUT scores at baseline, while patients with severe malnutrition (CONUT ≥ 9) were excluded, potentially limiting the ability to detect improvement because of a floor effect. Furthermore, CONUT components, particularly serum albumin, are influenced by systemic inflammation and disease burden as well as nutritional status [29, 30]. These factors, together with the limited sample size, may have reduced the sensitivity of CONUT to detect modest changes during treatment.

In contrast, BMI was better preserved in the NYT group, with an adjusted between-group difference of 0.66 kg/m². This finding may suggest an effect on overall nutritional or energy balance during chemotherapy but requires cautious interpretation. BMI does not distinguish skeletal muscle, adipose tissue, and fluid retention, and body composition was not assessed. Longitudinal serum albumin concentrations remained stable, CRP showed no evidence of progressive inflammatory deterioration,

and no clinically relevant hypokalemia was observed; however, one grade ≥ 3 edema event occurred in the NYT group. Thus, a contribution of fluid retention to the observed BMI difference cannot be excluded. Future studies incorporating CT-based body composition and skeletal muscle measurements are needed to clarify the nutritional significance of this finding.

Exploratory QoL analyses identified between-group differences in social functioning, appetite loss, financial difficulties, and insomnia. Appetite loss was the most consistent favorable finding, remaining statistically significant in the LOCF sensitivity analysis. This finding is of potential clinical interest because appetite loss contributes to reduced oral intake, weight loss, and functional decline during chemotherapy [31]. Previous studies have suggested that NYT may influence appetite through orexigenic pathways, including ghrelin signaling and hypothalamic neuropeptide Y activation [14, 20, 32], providing biological plausibility for this observation.

Mean changes from baseline in social functioning and financial difficulties in the NYT group exceeded 10 points in the direction of improvement at cycle 9, suggesting potentially clinically relevant changes. However, the between-group differences in these domains were not statistically significant in the sensitivity analysis using LOCF imputation, indicating sensitivity to missing-data assumptions. Moreover, multiple QLQ-C30 domains were evaluated without adjustment for multiplicity. These findings should therefore be interpreted as exploratory rather than confirmatory. Insomnia scores were higher in the NYT group, and this difference remained significant in the sensitivity analysis using LOCF imputation. Although the mechanism is unclear, this finding warrants attention in future studies.

The incidence of grade ≥ 3 nonhematological adverse events, a co-primary endpoint, did not differ significantly between groups. Grade ≥ 3 peripheral neuropathy was numerically less frequent in the NYT group (5.1% vs. 20.0%), although the difference was not statistically significant. OIPN is a cumulative and clinically important toxicity of oxaliplatin-based chemotherapy [5], and the observed numerical difference is consistent with a previous preliminary report suggesting a potential neuroprotective effect of NYT [17]. However, the present study was not powered to evaluate individual adverse events, and this finding requires prospective confirmation.

No statistically significant difference in PFS was observed between groups; however, only 17 PFS events occurred, resulting in a wide confidence interval around the hazard ratio. Therefore, no firm conclusions can be drawn regarding the effect of NYT on treatment efficacy.

Several limitations should be acknowledged. First, enrollment was slower than anticipated, partly related to the COVID-19 pandemic, and the trial was terminated early after 78 of the planned 150 patients had been randomized, with 74 included in the FAS. The resulting limited statistical power increases uncertainty surrounding both negative and positive findings. Second, the QoL analyses were exploratory and were performed without adjustment for multiplicity. QoL data also became increasingly incomplete over time, particularly in the non-NYT group, and several findings were sensitive to the missing-data approach. Third, body composition was not assessed, precluding determination of whether the BMI difference reflected changes in skeletal muscle, adipose tissue, or fluid. Fourth, detailed information on

dietary intake, oral nutritional supplements, dietitian interventions, and other supportive-care measures was not prospectively collected, and their potential influence could not be evaluated. Finally, the open-label design may have influenced patient-reported outcomes and physician-assessed adverse events through expectation or reporting bias.

In conclusion, this exploratory randomized phase II trial did not demonstrate significant effects of NYT on either predefined co-primary endpoint. Exploratory findings suggest that NYT may help preserve BMI and influence selected patient-reported outcomes, particularly appetite loss, during first-line CAPOX plus bevacizumab for mCRC. These findings are hypothesis-generating and require confirmation in adequately powered randomized studies incorporating comprehensive nutritional and body-composition assessments.

Abbreviations

FAS
full analysis set
NYT
Ninjin'yoeito
CAPOX
capecitabine plus oxaliplatin.

Declarations

Author contributions

YM was the principal investigator. All authors contributed to the study design, protocol development, data collection, and data analysis. SM, YM, and KS were responsible for the statistical analysis plan and data interpretation, and the analyses were performed by an external company (Mebix Co., Ltd.). KS drafted the manuscript. All the authors critically revised and approved the final version of the manuscript.

Funding source

This study was an investigator-initiated trial supported by a research grant from Tsumura & Co. (Tokyo, Japan). Statistical analyses were performed by Mebix Co., Ltd., which was contracted by Fukui-ken Saiseikai Hospital. Tsumura & Co. provided financial support for the statistical analyses, but had no role in the study design, conduct, data collection, analysis, interpretation, or manuscript preparation.

Availability of data and materials

The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Ethical approval and consent to participate

This prospective, multicenter, randomized, open-label phase II trial was approved by the Clinical Research Review Board of Kanazawa Medical University and registered in the Japan Registry of Clinical Trials (jRCTs041190071) on October 2, 2019. This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Conflict of interest

YM has received lecture fees from Tsumura & Co. NY has received research grants and lecture fees from Tsumura & Co. SI has received lecture fees from Tsumura & Co. EB has received scholarship donations from Chugai Pharmaceutical Co., Ltd. AT has received lecture fees from Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Merck Biopharma Co., Ltd., Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb K.K., Daiichi Sankyo Co., Ltd., Bayer Yakuhin, Ltd., MSD K.K., and AstraZeneca K.K. All other authors declare no conflicts of interest.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT (OpenAI) to improve the language and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Figures

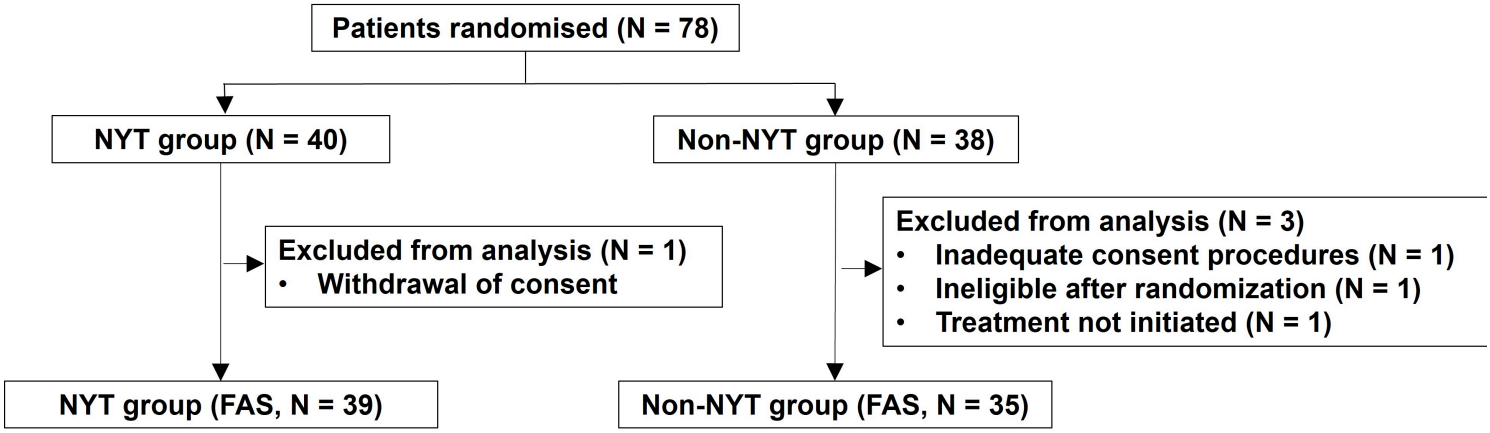


Figure 1

CONSORT flow diagram.

Seventy-eight patients with unresectable mCRC were randomized to receive CAPOX plus bevacizumab with Ninjin'yoeito (NYT group, N = 40) or without NYT (non-NYT group, N = 38). One patient in the NYT group withdrew consent and was excluded from the analysis. In the non-NYT group, three patients were excluded from the analysis because of inadequate consent procedures (N = 1), ineligibility after randomization (N = 1), and treatment not initiated (N = 1).

Abbreviations: FAS, full analysis set; NYT, Ninjin'yoeito; CAPOX, capecitabine plus oxaliplatin.

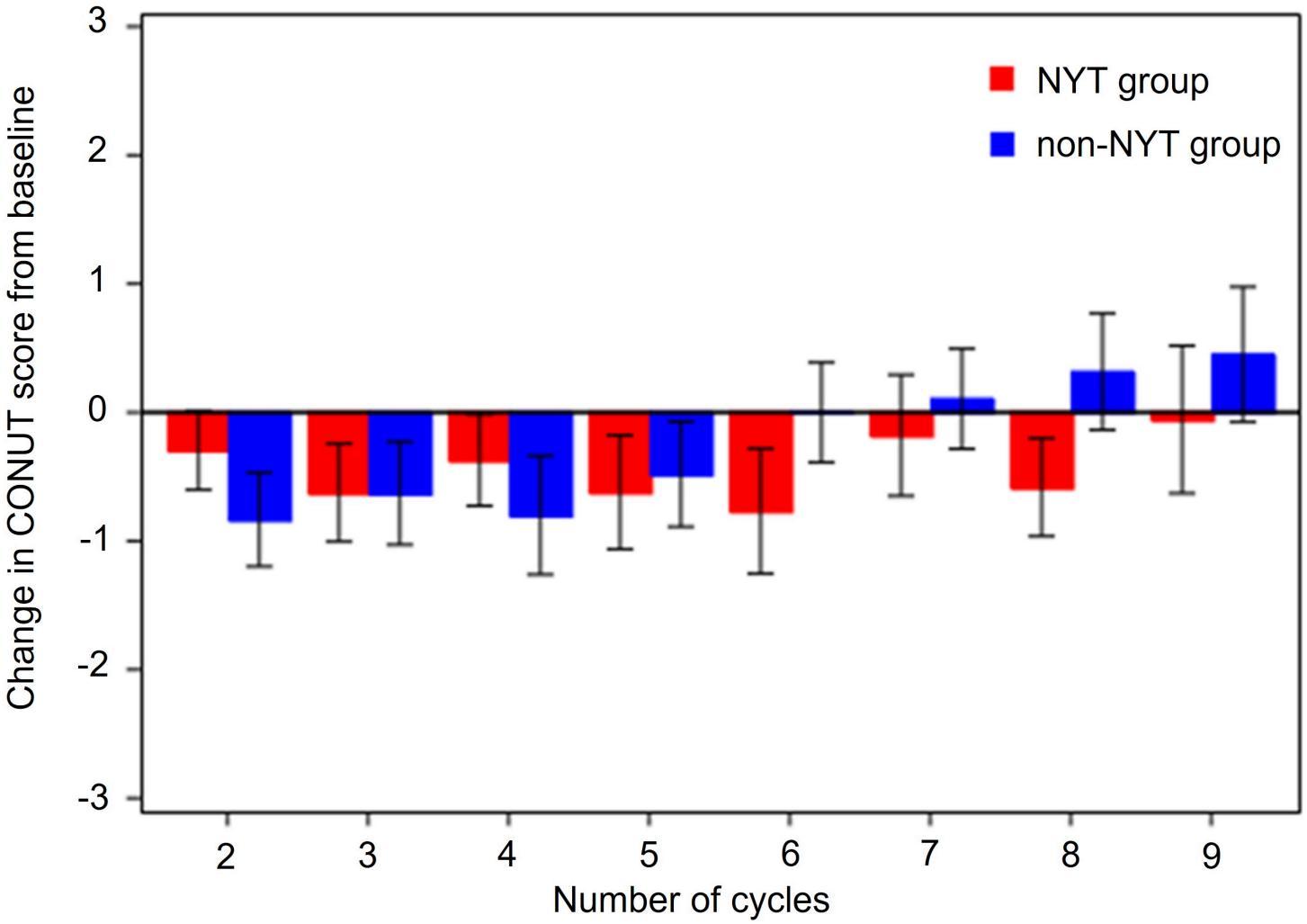


Figure 2

. Longitudinal changes in CONUT scores from baseline.

Changes in CONUT scores from baseline in the NYT and non-NYT groups (full analysis set). Data are presented as the mean changes from baseline. Error bars indicate standard errors.

Abbreviations: CONUT, Controlling Nutritional Status; NYT, Ninjin'yoeito.

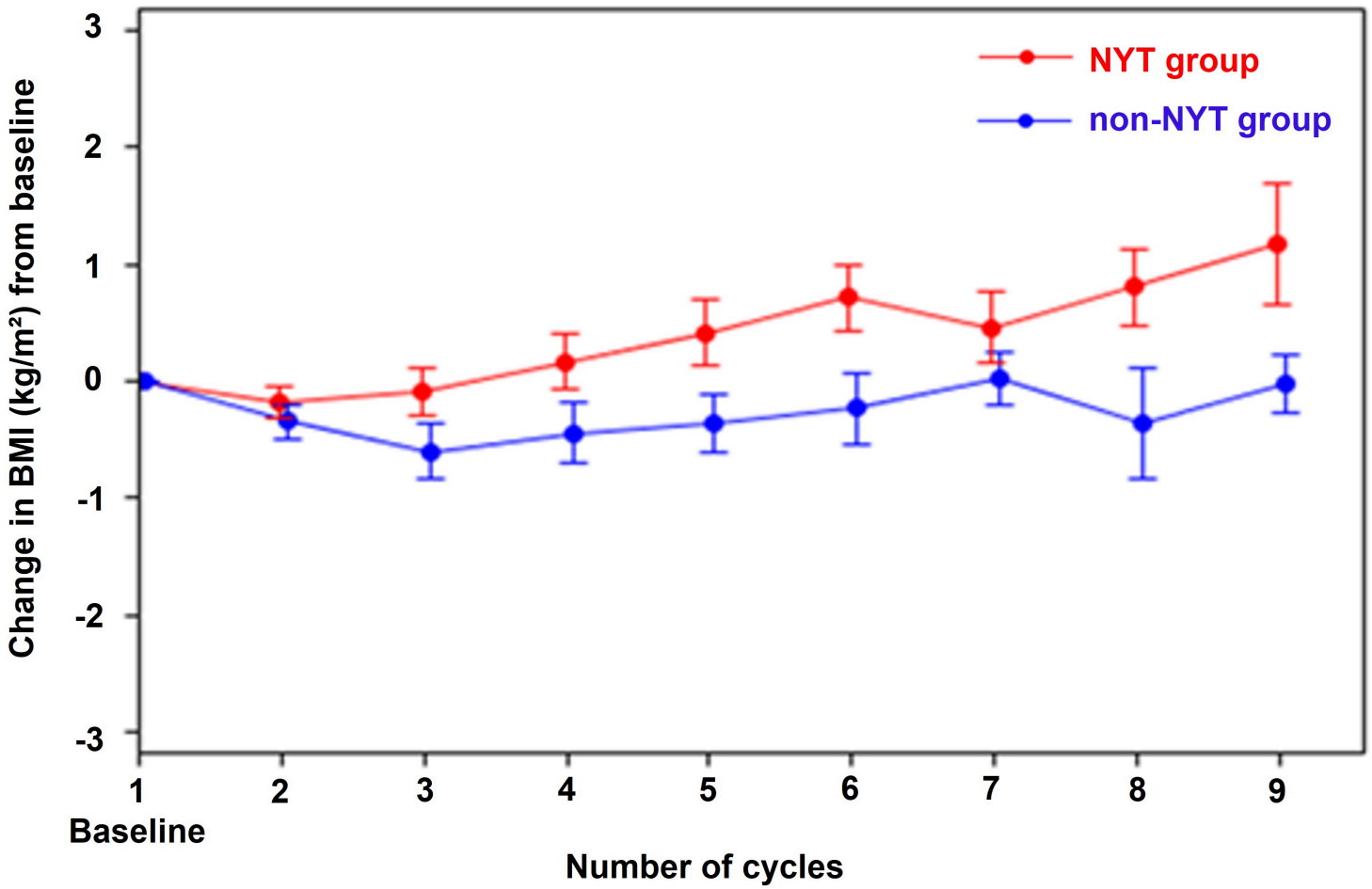


Figure 3

Longitudinal changes in body mass index from baseline.

Changes in BMI from baseline in the NYT and non-NYT groups (full analysis set). Data are presented as the mean changes from baseline. Error bars indicate standard errors.

Abbreviations: BMI, body mass index; NYT, Ninjin'yoeito.

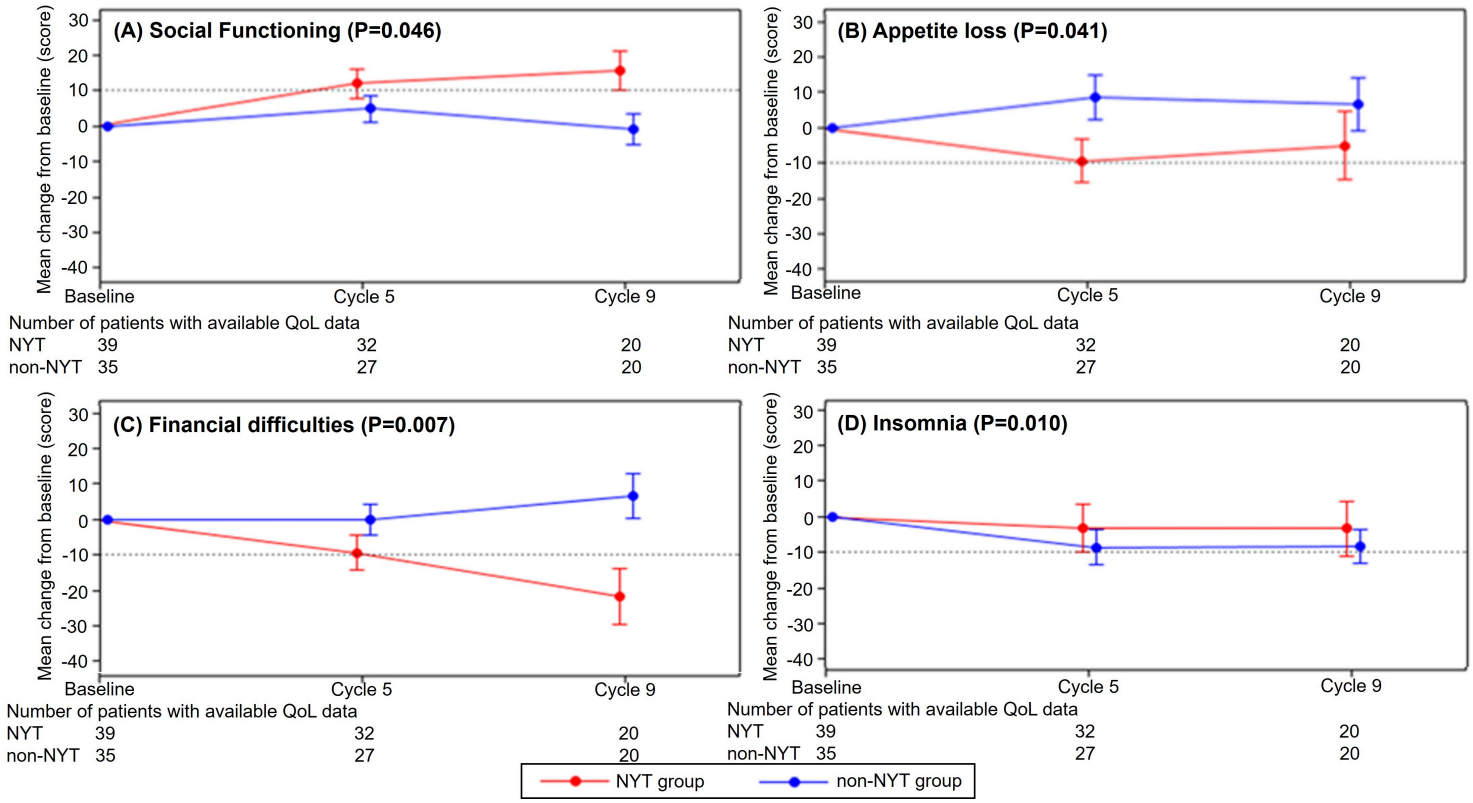
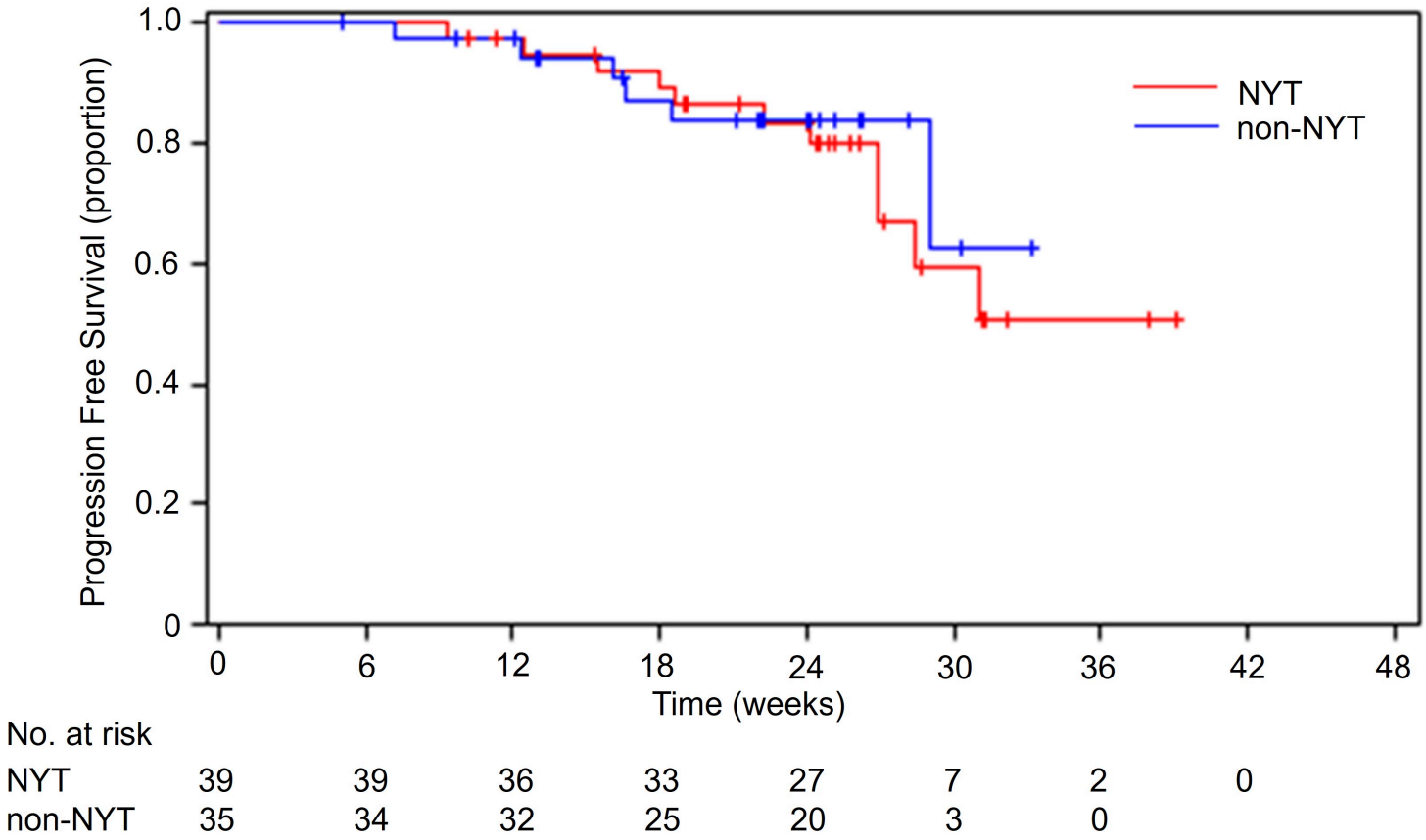


Figure 4

Longitudinal changes from baseline in EORTC QLQ-C30 domains with statistically significant between-group differences.

Longitudinal changes from baseline in EORTC QLQ-C30 domains with statistically significant between-group differences in the MMRM analysis (Model 2). (A) Social functioning, (B) appetite loss, (C) financial difficulties, and (D) insomnia. Data are presented as mean changes from baseline with standard errors. Dotted horizontal lines indicate a 10-point change from baseline in the direction of improvement for each domain. The numbers below each panel indicate the numbers of patients with available QoL data at each assessment. P values represent the between-group treatment effect estimated using the primary MMRM model (Model 2). MMRM, mixed-effects model for repeated measures.

Abbreviations: NYT, Ninjin'yoeito; QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; QoL, quality of life.



No. at risk								
NYT	39	39	36	33	27	7	2	0
non-NYT	35	34	32	25	20	3	0	

Figure 5

Progression-free survival.

Kaplan–Meier curves for progression-free survival (PFS) in the NYT and non-NYT groups (full analysis set). The median PFS was not achieved in either group. There was no significant difference between groups (hazard ratio [HR], 1.21; 95% confidence interval [CI], 0.44–3.33; log-rank p = 0.713).

Abbreviations: CI, confidence interval; HR, hazard ratio; NYT, Ninjin'yoeito; PFS, progression-free survival.