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A double-blind phase III trial of immunomodulating nutritional formula during adjuvant chemoradiotherapy in head and neck cancer patients: IMPATOX

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ABSTRACT

Background: In a previous phase II study an immunonutrient supplement was found to reduce severe acute toxicities for head and neck squamous cell cancer (HNSCC) patients treated with concomitant cisplatin and radiotherapy.

Objectives: The primary objective of the present study was to evaluate efficacy of the same immunonutrient supplement on severe mucositis. Secondary objectives included tolerance, compliance to oral supplementation, chemotherapy interruptions and delays, quality of life, and progression-free survival (PFS) and overall survival (OS) at 1, 2, and 3 y.

Methods: Between November 2009 and June 2013, 180 HNSCC patients eligible for adjuvant chemotherapy after surgery with curative intent were included in our double-blind phase III multicenter trial. They were assigned to receive oral supplementation (3 sachets/d) of either a formula enriched with L-arginine and omega-3 (n–3) fatty and ribonucleic acids (experimental arm), or an isocaloric isonitrogenous control (control arm), for 5 d before each of 3 cycles of cisplatin. Intention-to-treat (ITT) and per-protocol (PP) analyses were undertaken, along with subgroup analyses of ≥75% compliant patients, to compare the incidence of acute mucositis (Radiation Therapy Oncology Group and WHO scales) and 36-mo survival.

Results: At 1 mo after terminating chemoradiotherapy (CRT), no differences were observed in the incidence of grade 3–4 mucositis between treatment groups, in the ITT, PP (172 patients), and subgroup (≥75% compliance, $n = 112$) analyses. The immunomodulating supplement did not significantly improve survival in the ITT and PP analyses at 3 y after CRT. Among ≥75% compliant patients, however, OS at 3 y was significantly improved in the immunomodulating formula group (81%; 95% CI: 67%, 89%) compared with controls (61%; 95% CI: 46%, 73%; $P = 0.034$), as well as PFS (73%; 95% CI: 58%, 83% compared with 50%; 95% CI: 36%, 63%; $P = 0.012$).

Conclusions: Although this immunomodulating formula failed to reduce severe mucositis during CRT, the findings suggest that the long-term survival of compliant HNSCC patients was improved. This trial was registered at clinicaltrials.gov as NCT01149642. *Am J Clin Nutr* 2020;112:1523–1531.

Keywords: head and neck cancer, chemoradiotherapy, immunonutrition, survival, side effects, supportive care

Collaborators: all individual names of the Head and Neck Oncology and Radiotherapy Group (GORTEC) working group collaborators are listed in the "Collaborators" section at the end of the article.

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Supplemental Tables 1–3 and Supplemental Figures 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Data described in the article, code book, and analytic code will be made available upon request pending application and approval.

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Abbreviations used: CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; GORTEC, Head and Neck Oncology and Radiotherapy Group; Gy, Grey; HNSCC, head and neck squamous cell cancer; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; PP, per protocol; RTOG, Radiation Therapy Oncology Group.

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Introduction

Among oncology patients, involuntary weight loss caused by a combination of reduced food intake and metabolic alterations acts as an independent predictor of decreased survival (1). Immunonutrition has been reported to improve the immune status of perioperative cancer patients, reducing infectious complications for patients undergoing surgery with a high risk of morbidity for digestive malignancies (2). For patients undergoing chemoradiotherapy (CRT) in particular, we lack large and powerful studies that would enable recommendations to be issued regarding immunonutrition supplementation (3). Such patients undergoing radiation therapy after head and neck surgery are prone to salivary gland dysfunction, neuropathic pain, and dysphagia, and thus require nutritional care (4). These effects are increased when chemotherapy is combined with radiation therapy (5, 6).

In the case of high-risk locally advanced head and neck squamous cell cancer (HNSCC), postoperative concomitant adjuvant CRT has been established as the standard treatment since the publication of 2 major studies (5, 6). They demonstrated a significant improvement of progression-free survival (PFS) and overall survival (OS) compared with radiotherapy alone, despite a significantly greater frequency of grade 3 or higher acute oral mucositis that ranged from 41% to 77% in the CRT group compared with 21%–34% in the radiotherapy-alone group. Oral mucositis, painful inflammation and ulceration of the mucous membranes, induces deterioration of the patients' quality of life with difficulty eating and speaking, limited mouth opening, dysgeusia, and pain. It was shown to decrease treatment efficacy by causing unplanned treatment interruptions or modifications owing to pain or toxicities (7–10). Although at present the management of oral mucositis is largely limited to symptomatic treatment (11), a growing understanding of its pathobiology implicates inflammatory pathways and reactive oxygen species (12).

In our previous prospective nonrandomized phase II study, oral immunonutrient supplementation with arginine, omega-3 fatty acids, and ribonucleic acids was found to reduce severe acute oral mucositis in 40 patients treated for HNSCC when compared with historical data (13). Forty patients were treated with radiotherapy combined with cisplatin and received the immunomodulating supplements for 5 d, 3 times/d, before each cycle of chemotherapy. Whereas 52.5% of patients showed ≥1 grade 3–4 toxicity, only 12.5% reported grade 3 or 4 oral mucositis. For compliant patients (≥75% of product intake, i.e., ≥20.3 g ribonucleic acid, 128.3 g arginine, and 43.9 g ω-3-like fatty acids), the rate of severe mucositis was 6.8%, compared with 27.3% in low-compliant patients. Moreover, the 1-y PFS estimates were 92% (95% CI: 45%, 95%) in compliant patients and 82% (95% CI: 73%, 98%) in the noncompliant subgroup.

Herein we present a double-blind, randomized, multicenter phase III study conducted in patients with HNSCC treated with concomitant CRT after surgery using the same protocol to further evaluate the effects of the oral immunomodulating formula used in the phase II study on the prevention of severe mucositis and on PFS and OS.

Methods

Study design and objectives

In our phase III double-blind multicenter study (NCT01149642), patients were randomly assigned to receive an oral immunonutrient supplement or an isocaloric isonitrogenous control. Neither the patient nor the investigator knew whether the immunonutrient or control was received. Stratification was performed according to the center and nutritional status (14). Randomization was performed using a random block method, on TenAlea (www.aleaclinical.eu). All patients gave their informed consent before the study. The study was conducted in accordance with the Declaration of Helsinki principles of good clinical practice and the protocol was approved by the local ethics committee. The primary objective was to evaluate the immunonutrients' efficacy on severe mucositis. Secondary objectives included tolerance, compliance, chemotherapy interruptions and delays, and PFS and OS at 1, 2, and 3 y.

Patients and CRT

HNSCC patients treated surgically with curative intent and eligible for adjuvant CRT based on unfavorable clinical or pathological factors, from 16 centers which are members of the Head and Neck Oncology and Radiotherapy Group (GORTEC), were included in the study (**Figure 1**A). Inclusion criteria were starting CRT no later than 8 wk after surgery, age 18–75 y, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, a Nutritional Risk Index ≥ 83.5 (no severely malnourished patients), and no mucositis (14). Main exclusion criteria were a nasopharyngeal or paranasal sinus tumor, septicemia, immunonutrients in the month before inclusion, previous parenteral nutrition, or allergies to any component of the immunonutrients. CRT combined a radiation dose ≤54 Grey (Gy) in a volume encompassing the primary site and all draining lymph nodes at risk and a 12-Gy boost in high-risk regions in 5 fractions of 2 Gy/wk; concomitant cisplatin-based chemotherapy (100 mg/m^2) was administered on days 1, 21, and 42 (Figure 1B).

Study products and compliance

The oral immunomodulating formula (Oral Impact®, Nestle) was enriched with L-arginine, ω-3 fatty acids, and ribonucleic acids (**Supplemental Table 1**) (13). The control was an isocaloric isonitrogenous product of the same composition except for the immunonutrients. Both products were conditioned as sachets of 74 g powder, to be diluted by the patient at home in 250 mL water. During 5 d before each chemotherapy cycle, patients were asked to take 3 sachets/d in water at 10:00, 15:00, and 17:00, of either the immunonutrients or the control (Figure 1B). Both products were prepared and blinded by the manufacturer.

Patients were reminded by phone to take the product 6 d before starting the chemotherapy, i.e., the day before taking the first sachet, and on days 14 and 35. Compliance to the study products was assessed before each chemotherapy course (numbers of sachets distributed, tastes, and dates) and at chemotherapy administration [date of product ingestion, number of sachets taken, administration mode (oral/probe)].

Assessments

The primary endpoint, acute mucosal toxicity, was assessed the day before treatment, then weekly until 1 mo after the

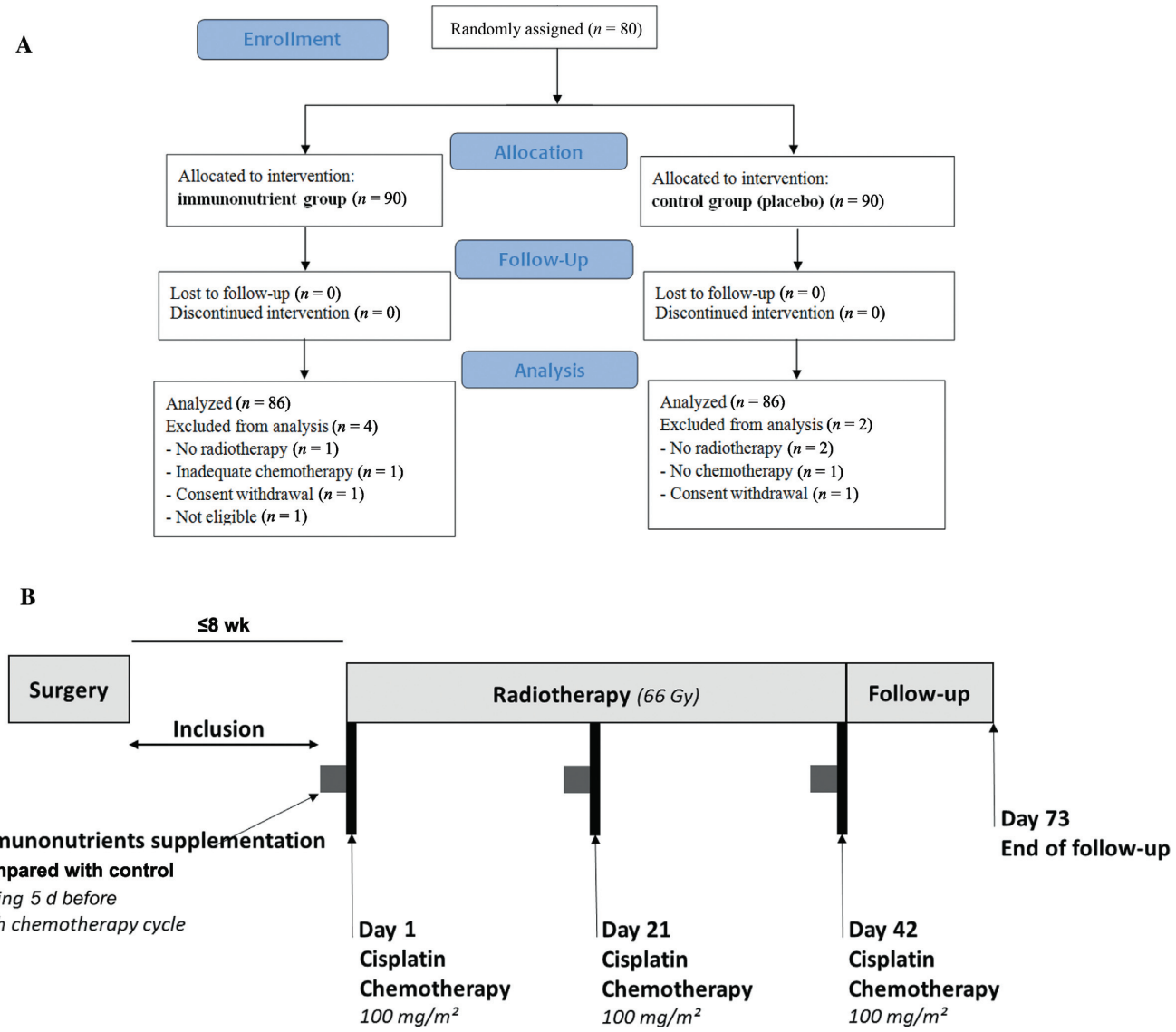

FIGURE 1 CONSORT diagram (A) of the study and study flowchart (B). Gy, Grey.

end of radiotherapy. It was graded according to the Radiation Therapy Oncology Group (RTOG) (15) and the WHO (16) scales. Other toxicities were assessed according to the National Cancer Institute—common terminology criteria for adverse events version 3.0 criteria. Chemotherapy delays (days) and interruptions (*n*, percentage of patients with interruptions) were reported during the whole duration of treatment.

Statistical analysis

Statistical analyses were performed in intention-to-treat (ITT) (all randomly assigned patients) and per-protocol (PP) (including all patients who received ≥1 radiotherapy session, 1 course of chemotherapy, and 4 d of immunonutrients or control) analyses. Analyses were also performed for both ITT and PP protocols in subgroups with ≥75% or <75% compliance (≥75% of product intake, i.e., ≥75% of the number of sachets prescribed). It was assumed (13) that 45% of control patients would present with grade 3–4 mucositis, with an expected reduction to 20% incidence among the experimental group. With a 2-sided $\alpha = 0.05$ and a $1 - \beta = 0.90$, 140 patients were required; taking into account patients lost to follow-up, 160 inclusions were planned, 80 patients in each group. Categorical data were expressed as frequencies and percentages, compared using the χ^2 or Fisher tests. Quantitative data were expressed as medians and ranges or means ± SDs, compared using the Wilcoxon Rank Sum test.

OS and PFS were evaluated every year for 3 y. For the ITT and PP global analyses, OS and PFS were defined as the time between the randomization date and the date of death or last follow-up, or disease progression, respectively. For compliance subgroup analyses, OS and PFS were estimated from the date of the end of radiotherapy. Survival estimates were calculated using the Kaplan–Meier method and presented with 95% CIs; comparisons of the distribution of survival between the groups were conducted using the log-rank test. All tests were 2-sided;

TABLE 1 Baseline patient and tumor characteristics in the intention-to-treat population[1]

	Immunonutrients ($n = 90$)	Control ($n = 90$)	Total ($n = 180$)
Age, y	59.0 [20–75]	56.5 [34–72]	58.0 [20–75]
Male	75 (83.3)	74 (82.2)	149 (82.8)
ECOG			
0	45 (50.0)	60 (66.7)	105 (58.3)
1	42 (46.7)	29 (32.2)	71 (39.4)
2	3 (3.3)	1 (1.1)	4 (2.2)
NRI	101.5 [84.7–142.2]	103.0 [85.1–119.2]	102.1 [84.7–142.2]
Nutritional status			
Moderate malnutrition (83.5 < NRI < 97.5)	25 (27.8)	25 (27.8)	50 (27.8)
Normal nutrition (NRI > 97.5)	65 (72.2)	65 (72.2)	130 (72.2)
Current weight, kg	70.0 [38–113]	71.5 [41–117]	74.5 [43–135]
BMI, kg/m^2	23.7 [15.8–35.7]	24.0 [16.0–37.8]	23.8 [15.8–37.8]
Underweight	12 (13.3)	6 (6.7)	18 (10.0)
Normal	39 (43.3)	47 (52.2)	86 (47.8)
Overweight	32 (35.6)	29 (32.2)	61 (33.9)
Obese	7 (7.8)	8 (8.9)	15 (8.3)
Enteral artificial nutrition	21 (23.3)	25 (27.8)	46 (25.6)
Primary tumor site			
Oral cavity	39 (43.8)	29 (32.2)	68 (38.0)
Oropharynx	30 (33.7)	37 (41.1)	67 (37.4)
Hypopharynx	4 (4.5)	5 (5.5)	9 (5.0)
Larynx	7 (7.9)	8 (8.9)	15 (8.4)
Others	9 (10.1)	9 (10.0)	18 (10.1)
Missing	*1*	*0*	*1*
Pathological stage (UICC)			
I	0 (0.0)	0 (0.0)	0 (0.0)
II	3 (3.3)	6 (6.7)	9 (5.0)
III	18 (20.0)	11 (12.2)	29 (16.1)
IV	69 (76.7)	73 (81.1)	142 (78.9)
Median time from diagnosis to surgery, wk	3.5 [−1.3* to 46.1]	3.3 [−0.4* to 177.4]	3.5 [−1.3* to 177.4]
Median time from surgery to postoperative CRT, wk	7.5 [3.9–34.9]	7.5 [3.7–34.6]	7.5 [3.7–34.9]
High-risk characteristics			
Extracapsular spread	52 (69.3)	57 (75.0)	109 (72.2)
Vascular embolisms	31 (44.3)	31 (47.7)	62 (45.9)
Perineural involvement	28 (45.2)	25 (39.1)	53 (42.1)
Smoking status			
Smoker	22 (25.0)	17 (19.1)	39 (22.0)
Nonsmoker	14 (15.9)	15 (16.9)	29 (16.4)
Previous smoker	52 (59.1)	57 (64.0)	109 (61.6)
Missing	*2*	*1*	*3*

[1]Values are *n* (%) or median [range] unless otherwise indicated. *Time between diagnosis and surgery was negative for patients who underwent surgery at a time at which no biopsy for diagnosis had yet been performed. Diagnosis was then confirmed with anatomopathological results on a surgical sample. CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; NRI, Nutritional Risk Index; UICC, Union for International Cancer Control.

P values < 0.05 were considered significant. Analyses were performed using Stata software version 13.1 (StataCorp LLC).

Results

Patients

Between November 2009 and June 2013, 180 patients with HNSCC were enrolled in the study and randomly assigned to receive the immunonutrients ($n = 90$) or the control ($n = 90$). Four patients were excluded from each arm for the PP analysis, 1 was discovered to be ineligible after initial enrolment, 2 withdrew consent, and 4 were not treated with an appropriate CRT regimen for subsequent comparisons (Figure 1A). Patients' characteristics at baseline were well balanced between the 2 groups (**Table 1**). Median age was 58.0 y (range: 20–75 y) and 82.8% were male. Tumor localization was mainly oral cavity (38.0%) and oropharynx (37.4%). The median time from diagnosis to surgery was 0.8 mo (range: −0.3 to 40.8 mo). Almost all patients had a good baseline clinical status (performance status ECOG 0–1).

CRT

A total of 174 patients (96.7%) underwent radiotherapy (**Table 2**). Intensity-modulated radiation therapy was administered in the majority of cases (58.3%). The median delivery dose was 66 Gy (range: 12–74 Gy) in 33 fractions (range: 33–37 fractions),

TABLE 2 Description of chemoradiotherapy received during the study in the intention-to-treat population[1]

	Immunonutrients ($n = 90$)	Control ($n = 90$)	Total ($n = 180$)	P value
RT				
Type of planned RT				0.8798
Classic	38 (42.2)	37 (41.1)	75 (41.7)	
IMRT	52 (57.8)	53 (58.9)	105 (58.3)	
Patients treated by RT	86 (95.6)	88 (97.8)	174 (96.7)	0.422
Total days of RT	48.0 [36–72]	49.5 [12–69]	49 [12–72]	0.585
Total delivered dose, Gy	66 [60–70]	66 [12–74]	66 [12–74]	0.864
Any interruption of RT	64 (74.4)	70 (79.5)	134 (77.0)	0.422
Total days of interruption	2.0 [1–18]	3.0 [0–13]	3.0 [0–18]	
Chemotherapy				
Median per patient	3 [1–3]	2 [1–3]	3 [1–3]	0.805
Courses received				0.952
1	5 (5.7)	5 (5.7)	10 (5.7)	
2	37 (42.5)	39 (44.8)	76 (43.7)	
3	45 (51.7)	43 (49.4)	88 (50.6)	
Total dose received, mg	440 [150–600]	400 [71–600]	400 [71–600]	0.823
Compliance to immunonutrition < 75%	392 [260–600]	394 [150–600]	392 [150–600]	
Compliance to immunonutrition ≥ 75%	451 [150–600]	400 [71–600]	442 [71–600]	
Any interruption or dose modification	6 (6.7)	13 (14.4)	19 (10.6)	0.069
Compliance to immunonutrition < 75%	2 (2.2)	8 (8.9)	10 (5.6)	
Compliance to immunonutrition ≥ 75%	4 (4.4)	5 (5.6)	9 (5.0)	

[1]Values are n (%) or median [range] unless otherwise indicated. Statistical analyses were performed using the χ^2 or Fisher tests for categorical variables and Wilcoxon test for continuous variables. Gy, Grey; IMRT, intensity-modulated radiation therapy; RT, radiotherapy.

during a median period of 49 d (range: 12–72 d). Radiotherapy was combined with concomitant cisplatin chemotherapy; patients received 1, 2, or 3 courses of chemotherapy in 5.7%, 43.7%, and 50.6% of cases, respectively. For 6 patients, the investigators replaced cisplatin with carboplatin. The median time to receive CRT treatment after surgery was 1.7 mo (range: 0.8–8.0 mo). No significant differences in CRT received were observed between the 2 groups. Among the 172 patients treated with CRT, 88 patients received both radiotherapy and 3 courses of chemotherapy (Table 2).

Oral supplementation

Study treatment was administered according to the protocol in both arms. Median duration of the oral supplementation intake was 5 d (range: 0–15 d) for a median number of 15 sachets (range: 0–51 sachets). No difference between the 2 arms was observed. It was taken orally by 75.0% of patients, by probe by 24.2% of patients, and by both modes by 0.8%.

Mucositis and other toxicities

No difference was observed in the acute oral mucositis rates reported during CRT between the 2 arms in the ITT analysis. Grade 3–4 mucositis was reported in 33.7% in the immunonutrients group and 34.9% in the control group, according to the RTOG scale, and in 34.9% and 33.7% of patients of the immunonutrients and control groups according to the WHO scale (**Table 3**). One month after the end of CRT, no difference was reported in grade 3–4 mucositis using either scale. Overall, no difference was observed for severe toxicities reported during CRT between the 2 arms.

Survival

After a median follow-up of 38.3 mo (95% CI: 37.9, 38.6 mo), both in the ITT and in the PP analyses, no significant differences were observed in OS or PFS between the 2 groups (**Figure 2**). The 3-y OS rate was 77% (95% CI: 66%, 85%) in the immunonutrients group and 68% (95% CI: 56%, 77%; $P = 0.261$) in the control group; the 3-y PFS rate was 70% (95% CI: 58%, 79%) and 59% (95% CI: 48%, 69%; $P = 0.138$) in the immunonutrients and control groups, respectively (Figure 2). The median OS and median PFS durations were not reached.

Oral supplementation compliance

Of the 172 patients treated with CRT, 112 patients (65.1%) were classified with ≥75% compliance and 60 patients with <75% compliance to the immunonutrients. Among the 112 compliant patients, 50.9% took the immunonutrients and 49.1% the control.

Subgroup analyses in the compliant population

Subgroup analyses according to compliance for the product were performed. Compliant and noncompliant patients were not different in terms of demographics, disease, or CRT characteristics, in both the immunonutrients and control groups (**Supplemental Tables 2**, **3**).

Mucositis.

The subgroup analysis of the ≥75% compliant population found no significant difference in grade 3–4 mucositis between

TABLE 3 Occurrence of acute and severe mucositis during the course of postoperative chemoradiotherapy in the per-protocol population[1]

	Immunonutrients ($n = 86$)	Control ($n = 86$)	Total ($n = 172$)	P value
All patients				
RTOG scale				0.872
Grade 3	28 (32.6)	27 (31.8)	55 (32.2)	
Grade 4	1 (1.2)	3 (3.5)	4 (2.3)	
Missing	*0*	*1*	*1*	
WHO scale				0.872
Grade 3	27 (31.4)	24 (28.2)	51 (29.8)	
Grade 4	3 (3.5)	5 (5.9)	8 (4.7)	
Missing	*0*	*1*	*1*	
Patients with compliance < 75%, *n*	29	31	60	
RTOG scale				0.326
Grade 3–4	17 (58.6)	14 (45.2)	31 (51.7)	
WHO scale				0.599
Grade 3–4	16 (55.2)	15 (48.4)	31 (51.7)	
Patients with compliance ≥ 75%	57	55	112	
RTOG scale				0.326
Grade 3–4	12 (21.1)	16 (29.1)	28 (25.0)	
WHO scale				0.913
Grade 3–4	14 (24.6)	14 (25.5)	28 (25.0)	

[1] Values are *n* or *n* (%) unless otherwise indicated. Statistical analyses were performed using the χ^2 or Fisher tests for categorical variables. RTOG, Radiation Therapy Oncology Group.

the 2 groups: 21.1% and 29.1% in the immunonutrients and control groups using the RTOG scale, respectively, and 24.6% and 25.5% with the WHO scale, respectively (Table 3).

Survival.

In the ≥75% compliance subgroup, OS at 3 y was significantly improved in the immunonutrients group (81%; 95% CI: 67%, 89%) compared with controls (61%; 95% CI: 46%, 73%; $P = 0.034$), as well as the PFS (73%; 95% CI: 58%, 83% compared with 50%; 95% CI: 36%, 63%; $P = 0.012$) (**Figure 3**). In contrast, among those patients in the <75% compliance subgroup, OS and PFS at 3 y were not improved in the immunonutrients group compared with controls. Results were the same whether the analysis was done from the randomization or from the end of the radiotherapy (**Supplemental Figures 1**, **2**).

Discussion

The present study is, to our knowledge, the first multicentric phase III randomized trial of oral immunonutrients administration during CRT in head and neck cancer patients. The study failed to achieve its primary endpoint of reducing the incidence of mucositis, but this oral immunonutrient product may improve survival. For patients strictly adhering to the supplementation protocol—the ≥75% compliance subgroups—the findings provide some evidence for an improvement of both 3-y OS and PFS in the immunonutrients group.

Our phase III trial did not confirm the positive results of the previous phase II study on severe mucositis reduction. During phase II, mucositis occurrence was assessed using the WHO grading only. Here, assessment was performed with both the WHO and RTOG scales, with the agreement of the GORTEC participating centers. This double gradation may have been quite burdensome in clinical practice, especially in a phase III study with less follow-up and a loss of power compared with the phase II study, all the more so for a study with solely academic funding.

This study suggests a consequent survival improvement, unexpected for such a supplementation product, and confirms the encouraging phase II survival results. The Bernier et al. (6) and Cooper et al. (5) pivotal clinical trials showed PFS of 45%–55% at 3 y and OS of 55%–65% at 3 y. In our study, survival results in the compliant patients of the immunonutrients group were very encouraging with a significant increase compared with the compliant control patients (PFS: 73% compared with 50%, $P = 0.012$; OS: 81% in the immunonutrients group compared with 61% in the control group, $P = 0.034$). These results of the subgroup analyses are to be interpreted with caution because the study was not designed to assess survival as a primary endpoint.

Is it plausible that a multi-immunonutrient supplementation could have an effect on survival? Beyond the need to provide sufficient caloric intake for HNSCC patients undergoing concurrent CRT (1, 2, 13), the addition of immunonutrients seems to improve the nutritional status of these patients, in phase II studies, while enhancing their immunological response (17–19). Arginine-enriched formulas have been found to significantly reduce fistulas and hospital stays among HNSCC patients (20, 21). It is likely that the antitumor effect of arginine acts via better oxygenation of tumor tissues and thus via the "oxygen effect," shown to have a key role in the occurrence of indirect antitumoral lesions, because of free radicals. ω-3 Fatty acid supplementation may attenuate postsurgical inflammatory responses and enhance immunity (22), whereas ribonucleic acid may facilitate cell growth and repair during recovery (23). Nutritional interventions probably have an effect at different levels. Our intervention is multimodal, with a multitype nutritional supplementation, when current international guidelines favor individualized single-nutrient nutritional intake. However, these multitype intakes

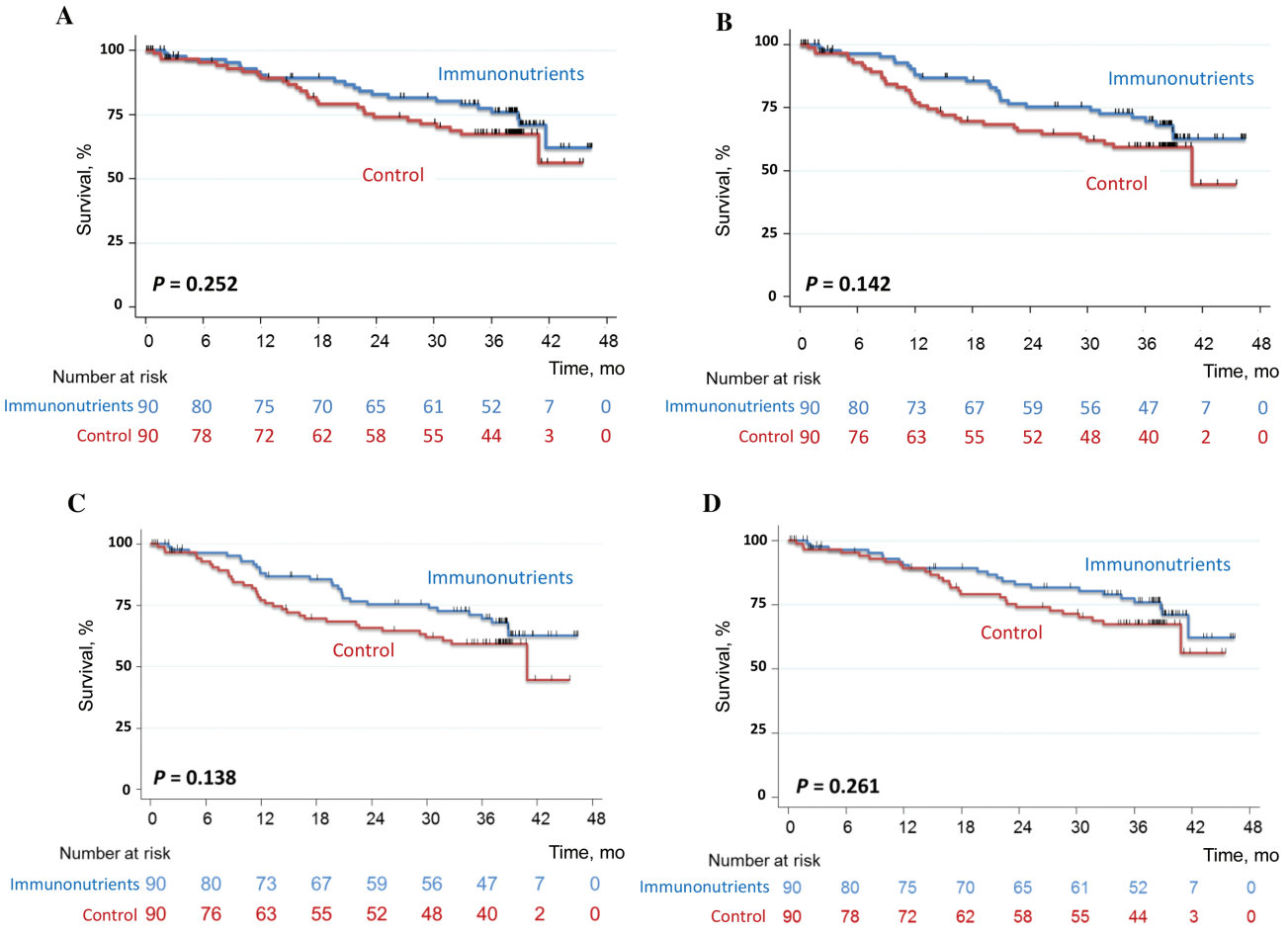

FIGURE 2 PFS (A, C) and OS (B, D) according to study treatment in the intention-to-treat analysis (A, B) and the per-protocol analysis (C, D). PFS: time from date of randomization to date of first evidence of progression or death; in compliant patients, PFS was calculated from the end of radiotherapy. OS: time from date of randomization to death, whatever the cause, or date of latest news for alive patients; in compliant patients, OS was calculated from the end of radiotherapy. OS, overall survival; PFS, progression-free survival.

are probably synergistic (23). Mechanistic studies are needed to better understand the effect of this multimodal nutritional intervention on tumor cells.

Strengths and limitations

Our study shows some strengths and limitations. Nutritional supplement prescriptions are heavily reliant upon patient cooperation; compliance has been shown to be an important component to monitor during nutrition outcome studies (24). Our previous phase II and present phase III studies have employed an innovative protocol: *1*) easy-to-take, 3 times daily during the 5 d before each chemotherapy course; *2*) for short periods, and before chemotherapy, so that patients are less likely to suffer from nausea and vomiting; *3*) with no serious adverse events; and *4*) inexpensive in addition to the oncologic therapy. Compliance in these settings is often quite low; 47% was observed in the longer-term supplement protocol of a previous study (24). In our study, 65% of patients achieved ≥75% compliance; although this figure is lower than the 72% compliance observed in our monocentric phase II study for which this protocol was initially developed (13), our results are far greater than seen elsewhere in the literature. This may be explained by the fact that our patients were not in a palliative situation, probably experiencing greater motivation for and implications of their treatment; also, gastrostomy was set up for some patients, as recommended in the current guidelines (3); lastly, patients were reminded by phone 1 d before each supplementation course to take the product. However, one could hope for a better compliance for a product aiming at decreasing severe toxicities with such impact on quality of life; it may even be higher if the given product is shown to increase survival. Among the limitations, as aforementioned, this study was not conceived with survival as a primary endpoint, and the results of the subgroup analyses must be interpreted with caution. Also, compliance was not assessed using confirmatory biomarkers; it was collected using patient-reported answers, the numbers of sachets distributed, and details on product administration.

Future directions

The exploration of the effects of this immunonutrients supplementation protocol on survival in HNSCC patients undergoing postsurgical CRT (25) is planned. Funding has been secured

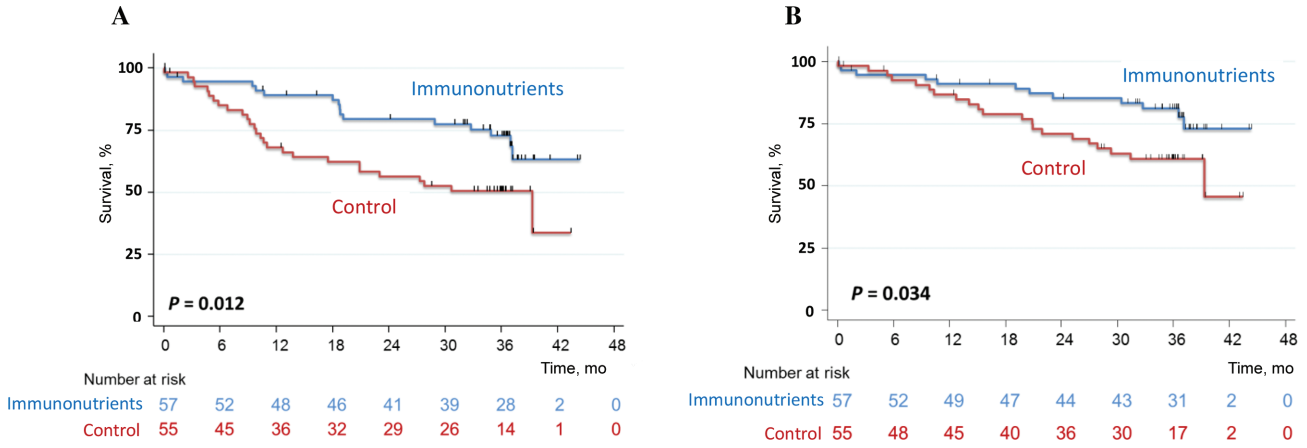

FIGURE 3 PFS (A) and OS (B) according to study treatment in compliant patients (compliance ≥ 75%). PFS: time from date of randomization to date of first evidence of progression or death; in compliant patients, PFS was calculated from the end of radiotherapy. OS: time from date of randomization to death, whatever the cause, or date of latest news for alive patients; in compliant patients, OS was calculated from the end of radiotherapy. OS, overall survival; PFS, progression-free survival.

and recruitment is now under way for a new phase III double-blind randomized multicenter study. An ancillary study will further explore compliance and adherence, seeking to better understand those patients that choose not to participate in the trial, as well as any factors affecting unintentional nonadherence, acceptability of these oral supplements, and any possible alternative administration routes.

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