MULTICENTER PHASE II STUDY OF EFFICACY OF AN ORAL NUTRITIONAL SUPPLEMENT CONTAINING EPA IN ADVANCED GASTRIC CANCER PATIENTS WITH CACHEXIA

Kawabata R[1, 2], Nishikawa K[1, 3], Kawase T[1, 4], Kawada J[3], Kimura Y[1], Kashima Y[5], Ueda S[6], Takeno A[7], Shimomura K[8] , Imamura H[1, 4]

[1]Dept. of Surgery, Sakai City Medical Center, [2]Dept. of Surgery, Osaka Rosai Hospital, [3]Dept.of Surgery, Osaka General Medical Center, [4]Dept.of Surgery, Toyonaka Municipal Hospital, [5]Dept.of Surgery, Tochinoki Medical Center, [6]Dept.of Surgery, Kitano Hospital, [7]Dept .of Surgery, Kansai Rosai Hospital, [8]Dept.of Pharmacy, Aichi Cancer Center Hospital

Background

- Group D in the modified Glasgow Prognostic Score (mGPS), defined by serum albumin levels <3.5 g/dl and serum C-reactive protein levels ≥ 0.5 mg/dl, is considered to be a cachectic pattern and has a poor prognosis in various carcinomas.

  McMillan DC, et al. Cancer Treat Rev. 2013
  Toiyama Y, Miki C, et al. Exp Ther Med. 2011

- Eicosapentaenoic acid (EPA) is expected to improve the prognosis of cancer-bearing patients in combination with chemotherapy by suppressing inflammatory reactions mediated by IL-1 and IL-6.

  Read JA, et al. Support Care Cancer. 2007

Aim

To assess the potential benefit of an oral nutritional supplement containing EPA (ONS-EPA) for cachexia in patients with AGC..

Patients & Methods

➢ **Study Design: A multicenter open label single arm study**

Patient: AGC patient diagnosed as mGPS group D and receiving first-line chemotherapy

Intervention: EPA-enriched supplement (Prosure ®) 2 packs per day in addition to the standard diet during the first-line chemotherapy

Content per pack:
Calories 355 kcal
Protein   16 g
EPA   1.056 g
DHA   0.5 g

Abbott Japan, Tokyo, Japan

◆ **Primary endpoint:**
Time to treatment success (TTF) in patients who consumed ≥7 packs of ONS-EPA in 2 weeks; the minimum amount reported to be effective

Sample size n=75
Expected median TTF: 6.25 months, **threshold; 4 months,**
1-sided α=0.1, a power of 80%, Calculated accrual: 28

◆ **Secondary endpoint:**
Overall survival (OS), Progression free survival (PFS),
Nutritional assessment,
Quality of life,
Clinical outcome by adherence

Results

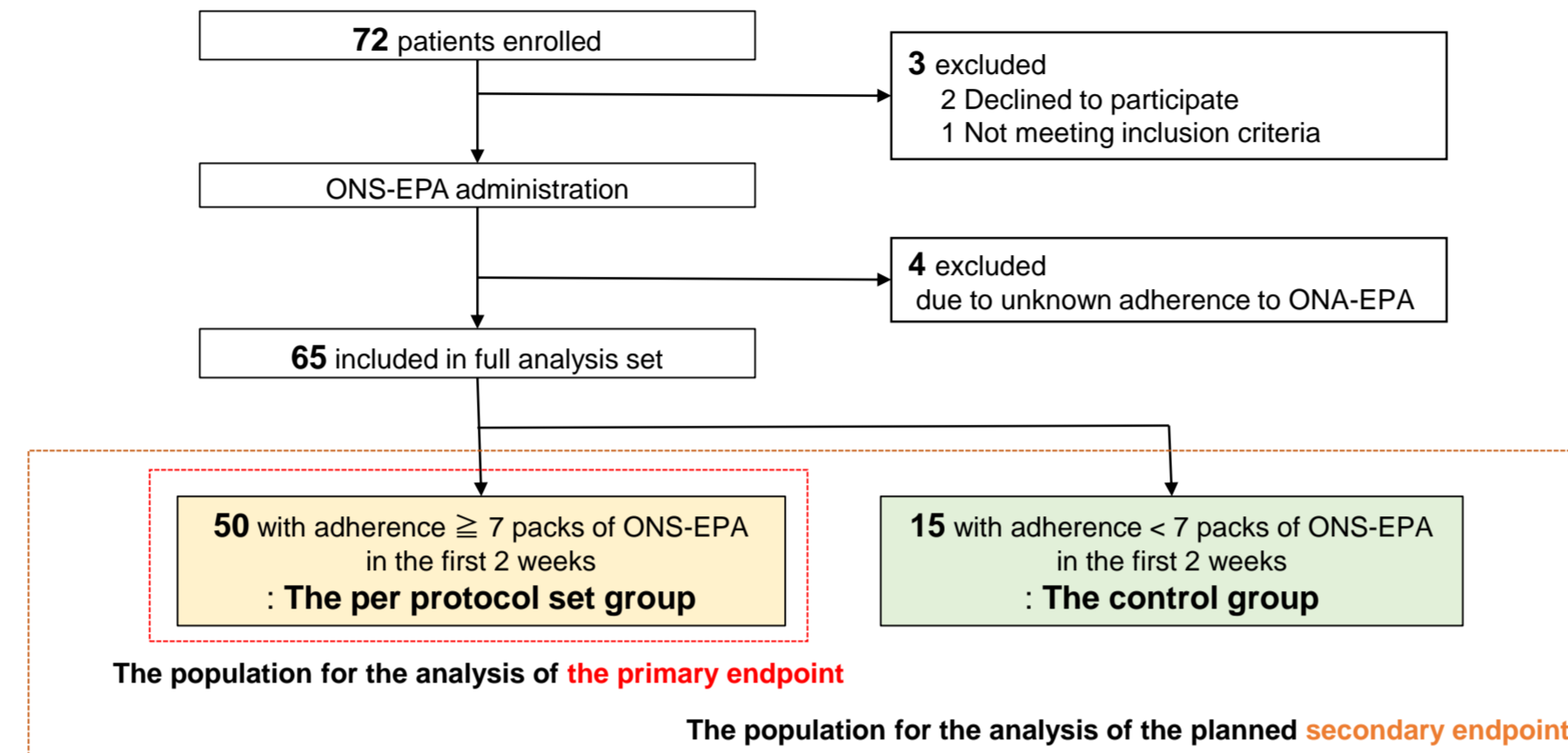**Fig. 1 CONSORT Diagram**

72 patients enrolled

3 excluded
2 Declined to participate
1 Not meeting inclusion criteria

ONS-EPA administration

4 excluded
due to unknown adherence to ONA-EPA

65 included in full analysis set

50 with adherence ≧ 7 packs of ONS-EPA in the first 2 weeks
: The per protocol set group

15 with adherence < 7 packs of ONS-EPA in the first 2 weeks
: The control group

The population for the analysis of the primary endpoint

The population for the analysis of the planned secondary endpoint

Fig. 2 Proportion of actual dose to planned dose of ONS-EPA in the first 2 weeks

Median ratio: 42.8%

7packs/2 week

n=65

The control group (n=15)

The per protocol set (PPS) group (n=50)
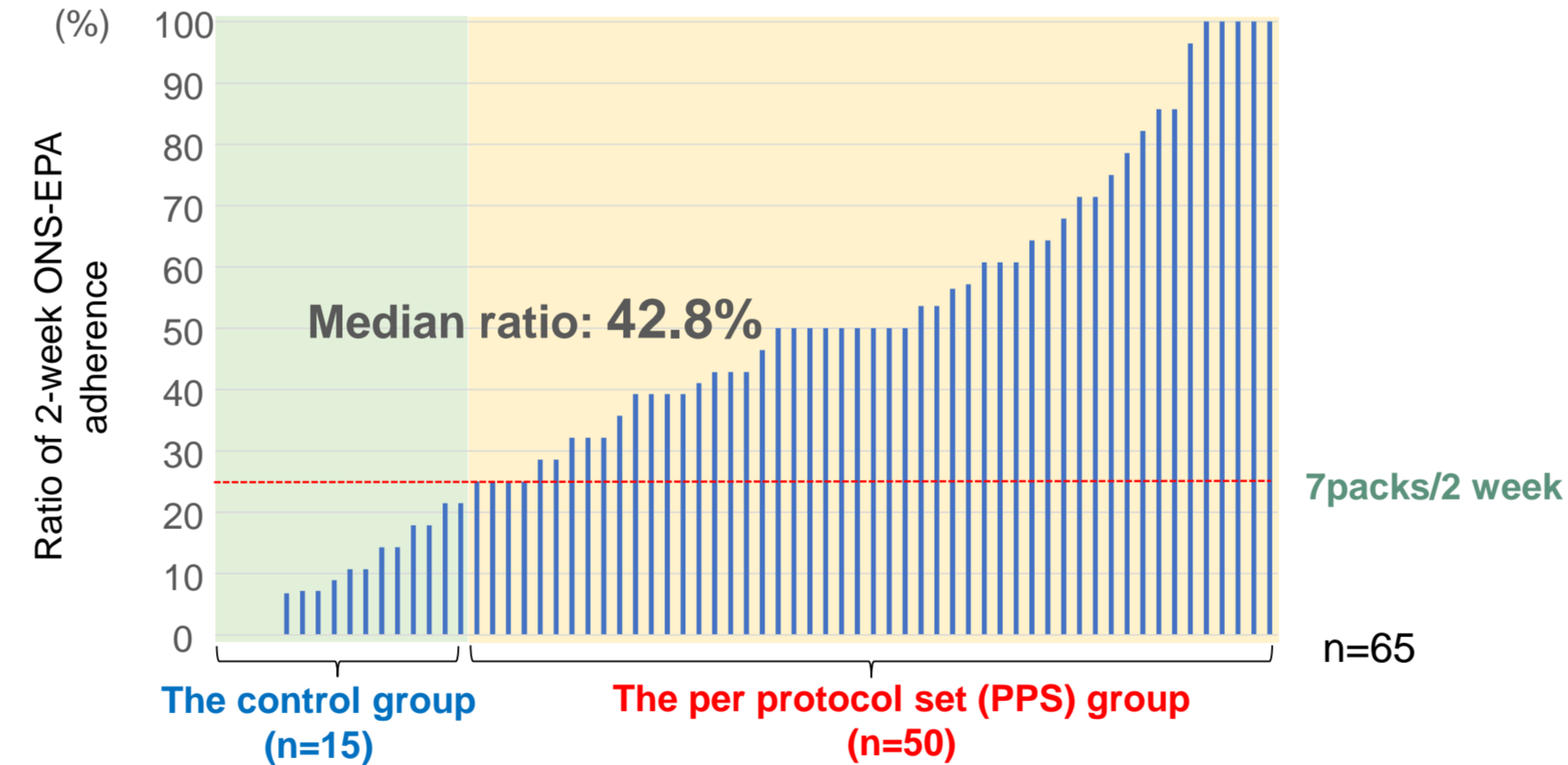
Fig. 3 Time to treatment failure in the per protocol set group: the primary endpoint

The median TTF: **4.8 months**
(95%CI: 3.6- 5.5 months)

No. at risk 50   5   3   1   1
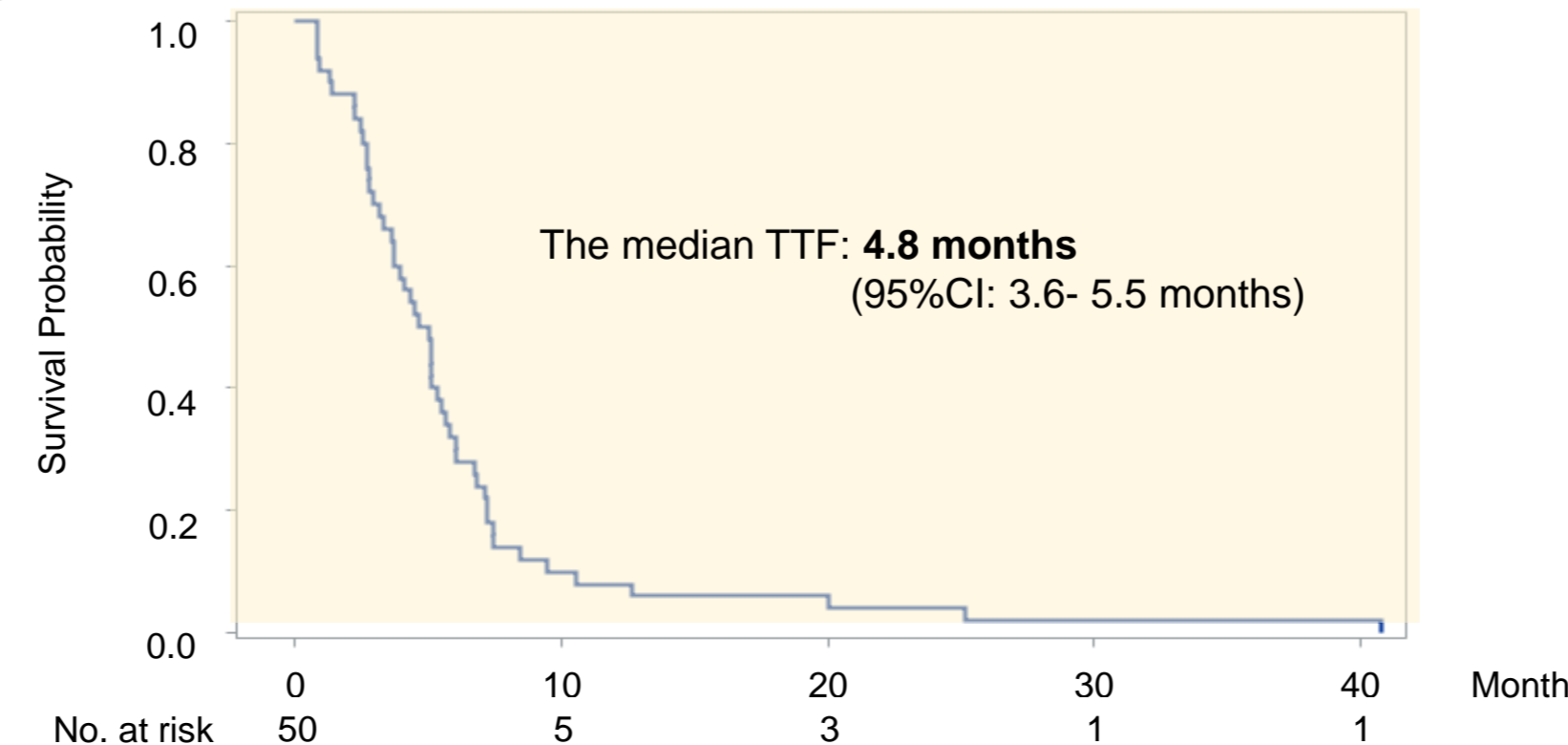
Table 1. Patient characteristics at baseline

	All patients (n=65)	The PPS group (n=50)	The control group (n=15)	p value
Age (years)				0.07
Median (range)	67 (33-80)	67 (33-80)	73 (59-79)	
Gender				1.00
Male	55 (84.6%)	42 (84.0%)	13 (86.7%)	
Female	10 (15.4%)	8 (16.0%)	2 (13.3%)	
ECOG performance status				0.04
0	32 (49.2%)	28 (56.0%)	4 (26.7%)	
1	21 (32.3%)	16 (32.0%)	5 (33.3%)	
2	12 (18.5%)	6 (12.0%)	6 (40.0%)	
HER2 status				0.34
Positive	19 (29.2%)	13 (26.0%)	6 (40.0%)	
Negative	46 (70.8%)	37 (74.0%)	9 (60.0%)	
Type of tumor				0.23
Advanced / recurrent	64 (98.5%)	50 (100%)	14 (93.3%)	
Post R1 or R2 resection	1 (1.5%)	0 (0.0%)	1 (6.7%)	
Body mass index (kg/m^2)				0.55
Median (range)	20.0 (14.3-26.5)	20.0 (14.3-26.5)	19.5 (14.8-24.6)	
Baseline lymphocyte count (/m^3)				0.15
Median (range)	1300 (87-4200)	1320 (520- 3809)	889 (87-4200)	
Baseline serum albumin level (g/dL)				0.07
Median (range)	2.9 (1.9-3.4)	2.9 (1.9-3.4)	2.8 (2.0-3.2)	
Baseline serum CRP level (mg/dL)				0.69
Median (range)	2.6 (0.5-16.3)	2.9 (0.5-16.3)	1.7 (0.7-11.7)	
Chemotherapy regimen				0.07
S-1+CDDP±Tmab	26 (40.0%)	23 (46.0%)	3 (20.0%)	
Capecitabine+CDDP±Tmab	10 (15.4%)	8 (16.0%)	2 (13.3%)	
S-1±Tmab	16 (24.6%)	8 (16.0%)	8 (53.3%)	
S-1+L-OHP	5 (7.7%)	4 (8.0%)	1 (6.7%)	
others	8 (12.3%)	7 (14.0%)	1 (6.7%)	

Fig. 4 Kaplan-Meier curves for TTF (A) and OS (B) between the per protocol set group and control group. Adjusted Kaplan-Meier curve for adjusted TTF (C) and adjusted OS (D) with inverse probability weight.
: the planned secondary endpoint

(A) HR 0.42, (95%CI: 0.23 – 0.78)
No. at risk 14 5 3 1 1 / 50

(B) HR 0.53, (95%CI: 0.29 – 0.96)
No. at risk 15 3 3 0 0 / 50 24 10 3 2 2 0

(C) HR 0.57, (95%CI: 0.29 – 1.13)

(D) HR 0.58, (95%CI: 0.29 – 1.14)
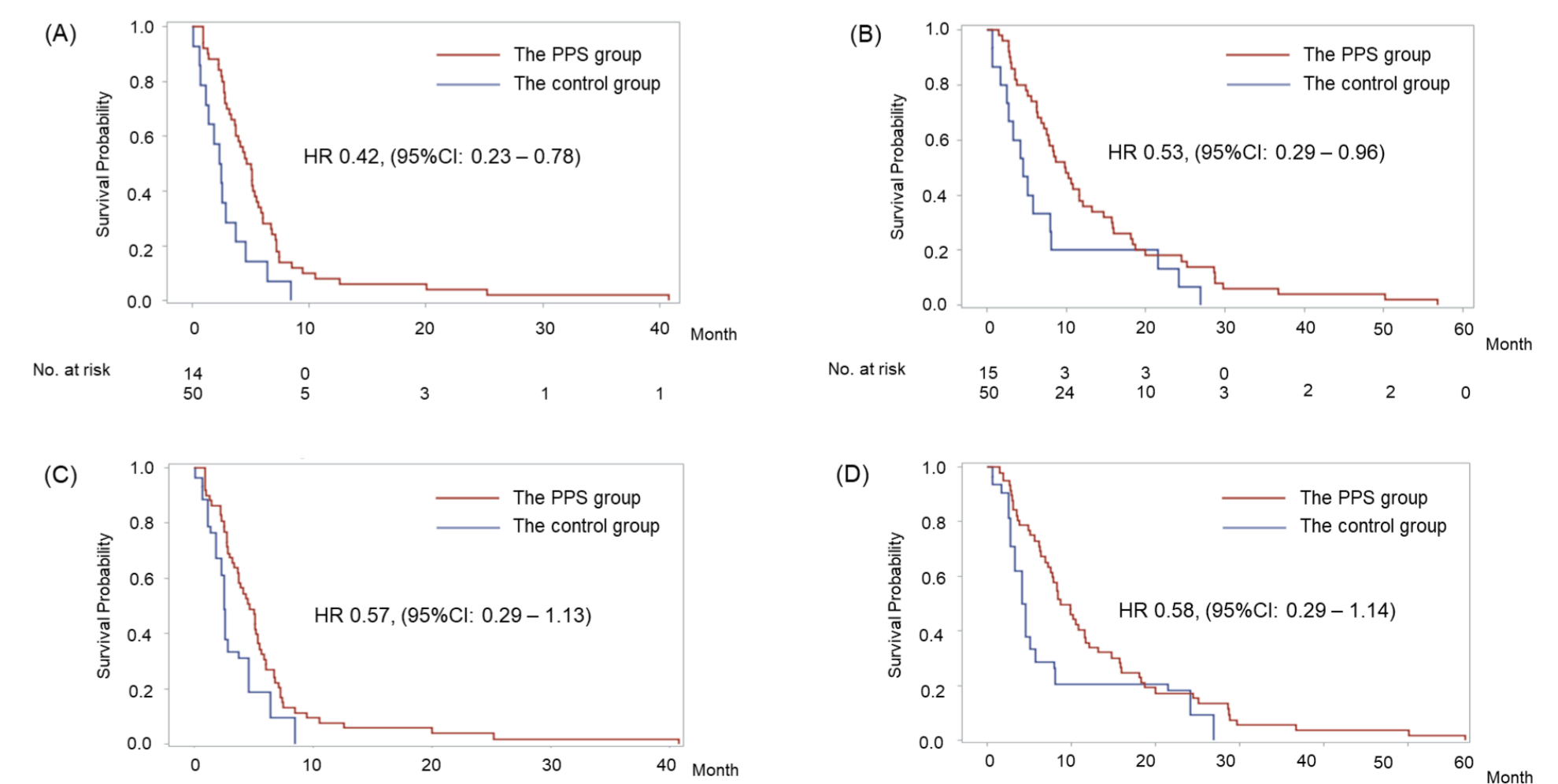
Conclusion

Although the primary endpoint was not achieved, the study suggests that ONS-EPA might have a potential role in benefiting AGC patients with cachexia.