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ORIGINAL ARTICLE

A phase II study of S-1 therapy for patients with advanced and recurrent esophageal cancer resistant or intolerable to fluorouracil, platinum, and taxane therapy (OGSG 1404)

Motoo Nomura[1] · Takayuki Kii[2] · Junji Kawada[3] · Masashi Hirota[4] · Takashi Ohta[5] · Jin Matsuyama[6] · Daisuke Sakai[7] · Toshio Shimokawa[8] · Yukinori Kurokawa[9] · Hisato Kawakami[10] · Toshimasa Tsujinaka[11] · Taroh Satoh[7]

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Abstract

Background Fluorouracil (FU), platinum (PT), and taxane (TAX) therapy was the standard chemotherapy for esophageal squamous cell carcinoma (ESCC) before the era of anti-programmed death-1 antibodies. The aim of this phase II trial was to evaluate the efficacy and safety of S-1 monotherapy for patients with recurrent or metastatic (R/M) ESCC resistant or intolerable to FU, PT, and TAX therapy.

Methods Eligible patients had R/M ESCC; no prior S-1 use; were intolerant or refractory to prior FU, PT, and TAX therapy; aged ≧ 20 years; and Eastern Cooperative Oncology Group performance status 0 or 1. S-1 was administered orally from days 1 to 28, every 6 weeks until disease progression. The primary endpoint was the disease control rate (DCR) for each patient, assessed by Response Evaluation Criteria in Solid Tumors, version 1.1. Secondary endpoints were overall survival, progression-free survival, time to treatment failure, response rate, and toxicity.

Results Between October 2015 and December 2017, 17 patients were recruited, and the trial was terminated because of slow accrual. The DCR was 46.7%. The response rate was 13.3%. The median progression-free survival was 2.0 months. The median time to treatment failure was 1.9 months. The median overall survival was 8.4 months, and the 1 year overall survival rate was 30.5%.

Conclusions Although this trial closed early because of slow accrual, we observed modest clinical activity with S-1 in patients with R/M ESCC who could not tolerate or whose tumors were refractory to FU, PT, and TAX therapy.

Keywords Esophageal cancer · Metastasis · Chemotherapy

✉ Motoo Nomura
excell@hkg.odn.ne.jp

[1] Department of Clinical Oncology, Kyoto University Hospital, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

[2] Department of Cancer Chemotherapy Center, Osaka Medical and Pharmaceutical University, 2-7 Daigakumachi, Takatsuki, Osaka 569-8686, Japan

[3] Department of Surgery, Kaizuka City Hospital, 3-10-20 Hori, Kaizuka, Osaka 597-0015, Japan

[4] Department of Surgery, Toyonaka Municipal Hospital, 4-14-1, Shibahara, Toyonaka, Osaka 560-8565, Japan

[5] Department of Clinical Oncology, Kansai Rosai Hospital, 3-1-69, Inabasou, Amagasaki, Hyogo 660-8511, Japan

[6] Department of Surgery, Yao Municipal Hospital, 1-3-1, Ryuge-cho, Yao, Osaka 581-0069, Japan

[7] Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, E21-19, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan

[8] Clinical Study Support Center, Wakayama Medical University Hospital, 811-1 Kimiidera, Wakayama, Wakayama 641-8509, Japan

[9] Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, E2, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan

[10] Department of Medical Oncology, Kindai University Hospital, 377-2, Onohigashi, Osakasayama, Osaka 589-8511, Japan

[11] Department of Surgery, Izumi City General Hospital, 4-5-1, Wake-cho, Izumi, Osaka 594-0073, Japan

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Introduction

Esophageal cancer is the seventh most common cancer worldwide [1]. The incidence of esophageal adenocarcinoma has been increasing dramatically in developed countries in recent decades. However, most esophageal cancers in Japan are squamous cell carcinomas, with adenocarcinomas accounting for only 2.7% of all esophageal cancers [2].

Anti-programmed cell death protein-1 antibody therapy in combination with chemotherapy has become the standard regimen for recurrent or metastatic (R/M) disease [3, 4]. Among cytotoxic agents, combination chemotherapy with fluorouracil and cisplatin and single-agent chemotherapy with a taxane have been most commonly prescribed as standard chemotherapy for R/M esophageal squamous cell carcinoma (ESCC).

A previous report showed that chemotherapy might provide a survival benefit over best supportive care (BSC) for patients who could not tolerate or whose tumors were refractory to fluorouracil, platinum, and taxane therapy, and patients treated with fluorouracil alone, mostly S-1, had the longest overall survival compared with those who received the other regimens [5].

The aim of this phase II trial was to evaluate the efficacy and safety of S-1 monotherapy for patients with R/M ESCC who were intolerant to or whose tumors were resistant to fluorouracil, platinum, and taxane therapy (OGSG1404).

Patients and methods

Patient population

This was a multicenter, open-label, phase II study, that recruited patients from 6 medical centers in Japan. Patients met the following inclusion criteria: (1) R/M esophageal cancer; (2) histological diagnosis of squamous cell carcinoma or adenosquamous cell carcinoma; (3) no prior use of S-1; (4) intolerant or refractory to prior fluorouracil, platinum, and taxane therapy; (5) aged ≧ 20 years; (6) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; (7) presence of measurable lesion was not required; (8) longer than 14 days from the end of prior therapy; and (9) adequate bone marrow, hepatic, and renal function (neutrophils $\geq 1500/mm^3$, hemoglobin ≥ 8.0 g/dL, platelet count $\geq 10 \times 10^4/mm^3$, total bilirubin ≤ 1.5 mg/dL, aspartate aminotransferase ≤ 100 IU/L, alanine transaminase ≤ 100 IU/L, creatinine clearance ≥ 50 mL/min). The Written informed consent was obtained from all patients. The study was approved by the institutional review board of each institution and was conducted in accordance with the Declaration of Helsinki and was registered in the University Hospital Medical Network Clinical Trials Registry in Japan (UMIN000016830; http://www.umin.ac.jp/ctr/).

Procedures

S-1 was administered orally from day 1 to day 28, every 6 weeks until disease progression, unacceptable toxicity, or withdrawal of consent. The initial dose of S-1 for each patient was determined according to body surface area (BSA) and creatinine clearance, as shown in Supplementary Table 1 A first dose reduction was recommended if grade 4 hematologic or grade 3 or more non-hematologic toxicity occurred in the previous cycle. A second dose reduction was allowed if needed. However, a third dose reduction was not allowed (Supplementary Table 2).

The tumor response was assessed by RECIST v1.1 every 6 weeks, and adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

The primary endpoint was the disease control rate (DCR), defined as the percentage of patients who achieved complete response, partial response and stable disease, as assessed by RECIST v1.1. Secondary endpoints were overall survival (OS), progression-free survival (PFS), time to treatment failure, response rate, and adverse events. OS was defined from the date of registration until the date of death from any cause. PFS was defined from the date of registration until disease progression or death from other causes. Time to treatment failure was defined from the date of registration until the date of treatment discontinuation, disease progression, or death from other causes. Time-to-event distributions were estimated with the Kaplan–Meier method, and confidence intervals (CI) were calculated using Greenwood's formula. Statistical analysis was performed using SAS, version 9.4 software (SAS Institute, Cary, North Carolina, USA) at the OGSG data center.

A minimum sample size of 38 was required to provide a power of 0.90 with a one-sided significance level of 0.10 and to detect an alternative DCR of 50% compared with a null hypothesis of 30% on the population proportion. A total accrual of 40 patients was planned, with allowance for a few dropouts. All patients had at least 1 year of follow-up as of the data cutoff of January 2018.

Results

Patient characteristics

Between October 2015 and December 2017, 17 patients were recruited, and the trial was terminated because of slow accrual. The trial scheme and flow diagram are shown in Supplementary Fig. 1. One of the 17 patients was ineligible due to having prior cancer cured within less than 5 years. Thus, 16 eligible and treated patients were evaluable and included in the main efficacy analysis, where 15 patients had measurable lesions and one patient had no measurable lesion who was excluded from analysis of response rate and disease control rate. For the toxicity analysis, all 17 treated patients were included. Patient characteristics are summarized in Table 1.

Response and survival

The DCR was 46.7% (7/15 patients; 95% CI 21.3–73.4), and the primary endpoint was not met. The response rate was 13.3% (2/15 patients; 95% CI 1.7–40.5) (Table 2). No patient achieved a complete response; 2 patients achieved a partial response; and 5 patients had stable disease. The response of one patient without measurable lesion was non-complete response/non-progressive disease. The median PFS was 2.0 months (95% CI 1.4–4.6) (Fig. 1A). The median time to treatment failure was 1.9 months (95% CI 1.4–4.6) (Fig. 1B). The median OS was 8.4 months (95% CI 3.3–13.7), and the 1 year OS rate was 30.5% (95% CI 9.8–54.5) (Fig. 1C).

Safety

The incidences of toxicities greater than grade 2 according to CTCAE v4.0 are shown in Table 3. The most common grade 3 adverse events were white blood cell count decreased (18%) and neutrophil count decreased (18%), followed by diarrhea (12%). No grade 4 or 5 adverse events were observed.

Treatment delivery

Only one patient was still receiving S-1 without disease progression at the time of the analysis. Progressive disease was the main reason for discontinuation of S-1 in 12 patients (70.6%). Three patients (17.6%) refused to continue S-1. Other reasons for discontinuation were as follows: 1 patient (5.9%) did not meet the starting criteria of the course, and 1 patient (5.9%) could not continue based on the physician's discretion, due to a femoral neck fracture.

Table 1 Patient characteristics

Characteristic	$n = 17$
Age, years	
Median	67
Range	54–77
Gender, *n*	
Male	13
Female	4
PS, *n*	
0	8
1	9
Lung metastasis, *n*	
No	10
Yes	7
Liver metastasis, *n*	
No	13
Yes	4
Lymph node metastasis, *n*	
No	5
Yes	12
Pleural dissemination, *n*	
No	15
Yes	2
Peritoneal dissemination, *n*	
No	15
Yes	2
Primary tumor location, *n*	
Ce/Ut	3
Mt	7
Lt/Ae	7
Previous surgery, *n*	
No	8
Yes	9
Definitive surgery	5
Palliative surgery	4
Previous radiotherapy, *n*	
No	9
Yes	8
Creatinine clearance, mL/min	
Median	61.7
Range	43.2–107
Carcinoembryonic antigen, ng/mL	
Median	4.9
Range	2.0–18.5
Squamous cell carcinoma antigen, ng/mL	
Median	2.5
Range	0.7–67.5
Alkaline phosphatase, IU/mL	
Median	269
Range	123–402
Lactate dehydrogenase, U/L	
Median	205

Table 1 (continued)

Characteristic	$n = 17$
Range	146–431
Hemoglobin, g/dL	
Median	10.5
Range	8.4–13.2
C-reactive protein, mg/dL	
Median	0.89
Range	0.1–14.5

Ae abdominal esophagus, *Ce* cervical esophagus, *Lt* lower thoracic esophagus, *Mt* middle thoracic esophagus, *Ut* upper thoracic esophagus

Table 2 Tumor response

	$n = 15$
Complete response, *n*	0
Partial response, *n*	2
Stable disease, *n*	5
Progressive disease, *n*	8
Response rate, %	13.3
Disease control rate, %	46.7

Discussion

Insufficient evidence exists regarding the efficacy of S-1 for patients with R/M ESCC after standard chemotherapy. To the best of our knowledge, this is the first prospective trial to evaluate the efficacy and safety of S-1 for patients with R/M ESCC who previously received fluorouracil, platinum, and taxane therapy. Although OGSG1404 was discontinued because of slow accrual, we observed moderate clinical activity of S-1 in patients with R/M ESCC who could not tolerate or whose tumors were refractory to fluorouracil, platinum, and taxane therapy. Nevertheless, we failed to reject the null hypothesis, probably due to the smaller than expected number of enrolled cases.

The results of previous retrospective studies of salvage chemotherapy with S-1 are summarized in Table 4. First, Nomura et al. reported the efficacy of salvage chemotherapy in comparison with BSC after the failure of fluorouracil, platinum, and taxane therapy in patients with R/M ESCC [5]. In that study, 16 patients were treated with fluorouracil (14 of 16 patients received S-1 monotherapy), and the response rate, DCR, and median OS with fluorouracil were 13.3%, 66.7%, and 12.9 months, respectively. In contrast, the median OS with BSC was 4.3 months. Other studies evaluated the efficacy of S-1 monotherapy as a second- or third-line regimen after failure of fluorouracil plus cisplatin [6–8], showing modest disease control rates.

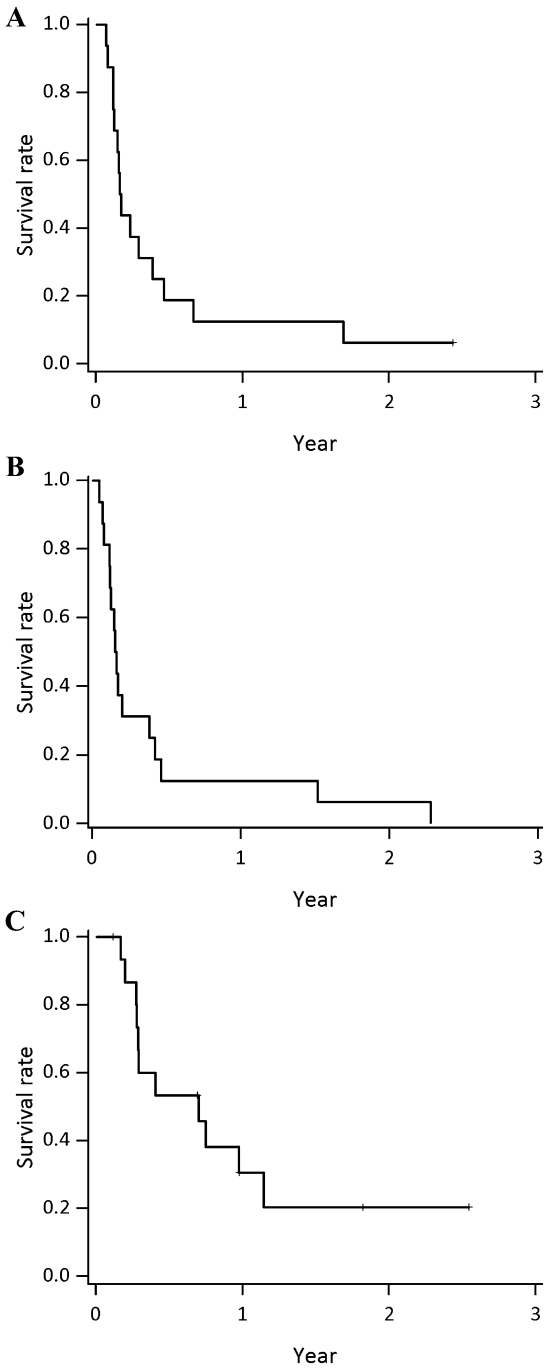

Fig. 1 Kaplan–Meier curves for progression-free survival (**A**), time to treatment failure (**B**), and overall survival (**C**) of patients with recurrent or metastatic esophageal squamous cell carcinoma undergoing S-1 therapy. Supplementary Fig. 1 Patient disposition during the study

Similar to the previous studies, our trial showed that S-1 has potential as a salvage therapy in patients with ESCC heavily pretreated with chemotherapeutic agents including fluorouracil. One possible reason is that S-1 monotherapy could have modest activity in patients with R/M ESCC who

Table 3 Adverse events

	All grades, *n*	Grade 1, *n*	Grade 2, *n*	Grade 3, *n*	Grade 3, %
Hematologic adverse events					
White blood cell count decreased	7	3	1	3	18
Neutrophil count decreased	6	0	3	3	18
Anemia	14	3	9	2	12
Platelet count decreased	3	1	1	1	6
Hypoalbuminemia	11	8	3	0	0
Aspartate aminotransferase increased	4	3	1	0	0
Alanine aminotransferase increased	5	4	1	0	0
Hyponatremia	9	8	0	1	6
Hyperkalemia	3	2	1	0	0
Hypokalemia	5	4	0	1	6
Hypocalcemia	4	3	1	0	0
Non-hematologic adverse events					
Anorexia	8	3	4	1	6
Nausea	6	3	2	1	6
Vomiting	2	1	1	0	0
Diarrhea	6	1	3	2	12
Hypertension	1	0	1	0	0
Esophageal stenosis	1	0	0	1	6
Enterocolitis	2	1	1	0	0
Lung infection	3	0	3	0	0
Rash, maculopapular	1	0	1	0	0
Abdominal pain	2	1	1	0	0
Peripheral sensory neuropathy	1	0	1	0	0
Pain	2	0	1	1	6

Table 4 Summary of studies evaluating the efficacy of S-1 salvage chemotherapy for patients with esophageal squamous cell carcinoma

Author	Study design	*n*	Previous treatment			Treatment	Response rate	Disease control rate	Median overall survival
			Fluorouracil	Platinum	Taxane				
Nomura et al	Retrospective	16	All	All	All	Fluorouracil or S-1	13.3%	66.7%	12.9 months
		147	All	All	All	BSC	No data	No data	4.3 months
Akutsu et al	Retrospective	20	All	All	Part of all	S-1	25%	60%	330 days
Tamaoki et al	Retrospective	15	All	All	Part of all	S-1	6.6%	66.7%	10 months
Ito et al	Retrospective	11	All	All	Part of all	S-1	22.2%	36.4%	11.7 months
Our study	Phase II	16	All	All	All	S-1	13.3%	46.7%	8.4 months

BSC best supportive care

were previously receiving an insufficient relative dose intensity of fluorouracil. It is likely that not a small number of patients are treated in the salvage line without being resistant to fluorouracil. Although a previous study could not show a clear relationship between the efficacy of S-1 monotherapy and the relative dose intensity of prior fluorouracil [8], further investigation is warranted in this regard. Another possible reason is that dihydropyrimidine dehydrogenase (DPD) overexpression is the potential resistance mechanism against 5-fluorouracil in ESCC cells [9], and DPD-related 5-FU resistance can be overcome by S-1, given that the gimeracil component of S-1 is a potent inhibitor of DPD, though we did not measure the level of DPD expression in the tumors of our patients. Another potential explanation is that the longer interval between the last administration of prior fluorouracil and S-1 monotherapy might have allowed for the sensitivity to S-1 to be restored, which warrants further study.

Our trial found that in this setting, the antitumor efficacy of S-1 as measured by the response rate, disease control rate, and 1 year OS was inferior to that of patients treated with nivolumab monotherapy in the ATTRACTION-1 trial [10]. Currently, based on the results of the ATTRACTION-3 trial

and the KEYNOTE-181 trial, the standard second-line treatment is nivolumab [3, 4]. Recently, the results of the KEYNOTE-590 trial and the CheckMate-648 trial were reported one after another [11, 12]. Both the KEYNOTE-590 trial and the CheckMate-648 trial showed that patients treated with combination chemotherapy with an immune-checkpoint inhibitor (ICI) had significantly longer OS compared with those who received cytotoxic chemotherapy alone. From these results of those trials, combination chemotherapy with an ICI was established as a standard first line treatment for patients with R/M ESCC. Although ICIs are also key agents for ESCC, the results of this trial may be useful in the ICI era, because ICIs have a different mechanism from the remaining key agents for ESCC, consisting of fluorouracil, platinum, and taxanes.

This study has several limitations. First, it was terminated early due to slow accrual. Second, detailed information on the relative dose intensity and treatment course of previous treatments was not collected. Third, information on subsequent treatments was not collected. Thus, the possibility of including cases that subsequently received ICIs could not be ruled out, although ICIs were not approved during the study period.

In summary, although this trial closed early because of slow accrual, we observed modest clinical activity with S-1 in patients with R/M ESCC who could not tolerate or whose tumors were refractory to fluorouracil, platinum, and taxane therapy. The value of S-1 in this setting should be examined in the era of first-line ICI + 5-FU + CDDP for ESCC.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10388-022-00931-8.

Declarations

Ethical Statement Written informed consent was obtained from all patients. The study was approved by the institutional review board of each institution and was conducted in accordance with the Declaration of Helsinki and was registered in the University Hospital Medical Network Clinical Trials Registry in Japan (UMIN000016830; http://www.umin.ac.jp/ctr/).

Conflict of interest Motoo Nomura, Takayuki Kii, Junji Kawada, Masashi Hirota, Jin Matsuyama, Toshio Shimokawa, and Toshimasa Tsujinaka do not have conflicts of interest to declare and do not have financial or funding support to disclose. Takashi Ohta has received honoraria from Bristol-Myers Squibb, Chugai Pharmaceutical, Teijin Pharma, and Takeda Pharmaceutical, and research funding from Takeda Pharmaceutical. Daisuke Sakai has received honoraria from Chugai Pharmaceutical, and Daiichi Sankyo, research funding from Eli Lilly, scholarship donations from Chugai Pharmaceutical, Ono Pharmaceutical, and Yakult Honsha. Yukinori Kurokawa has received lecture fees from Taiho Pharmaceutical. Hisato Kawakami has received grants from Chugai Pharmaceutical, Eisai, Kobayashi Pharmaceutical, and Taiho Pharmaceutical, consulting fees form Daiichi-Sankyo, honoraria from Bayer Yakuhin, Bristol-Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly Japan, Glaxo Smith Kline, Merck Biopharma, MSD, Ono Pharmaceutical, Otsuka Pharmaceutical, Taiho Pharmaceutical, Takeda Pharmaceutical, Teijin Pharma, and Yakult Pharmaceutical Industry. Taroh Satoh has received honoraria from Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, and Ono Pharmaceutical, research funding from Bei Gene, Chugai Pharmaceutical, MSD, Ono Pharmaceutical, and Yakult Honsha, scholarship donations from Taiho Pharmaceutical, endowed chairs from Chugai Pharmaceutical, Ono Pharmaceutical, and Yakult Honsha.

Human rights statement and informed consent All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients before inclusion in the study.

References

1. Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. Watanabe M, Tachimori Y, Oyama T, et al. Comprehensive registry of esophageal cancer in Japan, 2013. Esophagus. 2021;18:1–24.
3. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:1506–17.
4. Kojima T, Shah MA, Muro K, et al. Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. J Clin Oncol. 2020;38:4138–48.
5. Nomura M, Iwasa S, Tsushima T, et al. Active salvage chemotherapy versus best supportive care for patients with recurrent or metastatic squamous cell carcinoma of the esophagus refractory or intolerable to fluorouracil, platinum, and taxane. Cancer Chemother Pharmacol. 2016;78:1209–16.
6. Akutsu Y, Kono T, Uesato M, et al. S-1 monotherapy as second- or third-line chemotherapy for unresectable and recurrent esophageal squamous cell carcinoma. Oncology. 2013;84:305–10.
7. Tamaoki M, Ezoe Y, Aoyama I, et al. S-1 salvage chemotherapy for esophageal squamous cell carcinoma refractory to the standard chemotherapy. J Cancer Sci Ther. 2017;9:353–7.
8. Ito T, Honma Y, Hirano H, et al. S-1 Monotherapy after failure of platinum plus 5-fluorouracil chemotherapy in recurrent or metastatic esophageal carcinoma. Anticancer Res. 2019;39:3931–6.
9. Kikuchi O, Ohashi S, Nakai Y, et al. Novel 5-fluorouracil-resistant human esophageal squamous cell carcinoma cells with dihydropyrimidine dehydrogenase overexpression. Am J Cancer Res. 2015;5:2431–40.
10. Kudo T, Hamamoto Y, Kato K, et al. Nivolumab treatment for oesophageal squamous-cell carcinoma: an open-label, multicentre, phase 2 trial. Lancet Oncol. 2017;18:631–9.
11. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet. 2021;398:759–71.
12. Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. N Engl J Med. 2022;386:449–62.