A three-arm Phase III trial was started in November 2012. Preoperative chemotherapy with cisplatin plus 5-fluorouracil is the current standard treatment for locally advanced esophageal cancer in Japan, while preoperative chemoradiotherapy with cisplatin plus 5-fluorouracil is the standard in Western countries. Preoperative chemotherapy with docetaxel, cisplatin plus 5-fluorouracil is another promising regimen. The purpose of this study is to confirm the superiority of docetaxel, cisplatin plus 5-fluorouracil over cisplatin plus 5-fluorouracil and the superiority of cisplatin plus 5-fluorouracil with chemoradiotherapy over cisplatin plus 5-fluorouracil as preoperative therapy for squamous cell carcinoma of esophagus. A total of 501 patients will be accrued from 41 Japanese institutions within 6.25 years. The primary endpoint is overall survival and the secondary endpoints include progression-free survival, %R0 resection, response rate, pathologic complete response rate and adverse events.

**Key words:** esophageal cancer -- preoperative chemotherapy -- preoperative chemoradiotherapy -- clinical trial -- Phase III
studies. In a randomized Phase III trial to compare post-operative chemotherapy with cisplatin plus 5-fluorouracil (5-FU) (CF) to surgery alone (JCOG9204), the superiority of post-operative chemotherapy in disease-free survival was demonstrated (3). In the following randomized Phase III trial (JCOG9907), the survival benefit of preoperative chemotherapy with CF over post-operative chemotherapy with the same regimen was confirmed (4). Therefore, preoperative chemotherapy has become the current Japanese standard treatment for locally advanced esophageal cancer.

In Western countries, on the other hand, survival benefits from preoperative chemoradiotherapy over surgery alone have been demonstrated in several clinical trials (5), and now it is accepted as the standard treatment for locally advanced esophageal cancer. However, many Asian physicians are reluctant to introduce these Western evidences directly to their clinical practice because the Western evidences came from trials where the majority of the enrolled patients had adenocarcinoma and the protocol-defined surgery was mostly transhiatal esophagectomy at least in part. The prognosis observed in the Western trials were usually poorer than that in Asia, and Asian physicians believe that their transthoracic esophagectomy with regional lymphadenectomy can achieve better local control (6). In addition, adenocarcinoma occupies only 1.5% of all esophageal cancers in Japan and a series of JCOG trials have included only squamous cell carcinoma. Nevertheless, the fact that local recurrences were observed among not a few patients in JCOG9907 indicates the possible need for more intensive local control. Thus, the first purpose of this trial is to investigate whether preoperative chemoradiotherapy with radical surgery is effective even for ‘Eastern’ esophageal cancer.

Reinforcement of systemic control with more intensive preoperative chemotherapy is another strategy to improve survival for locally advanced esophageal cancer. Docetaxel is one of the most promising drugs for esophageal cancer and recently preoperative chemotherapy with docetaxel plus CF (DCF) has been investigated in some exploratory trials. Hara et al. (7) conducted a feasibility study of this regimen for 44 patients with locally advanced esophageal cancer and showed a good response rate (60.0%) with no treatment-related death. Thus, the second purpose of this trial is to investigate whether DCF has better survival benefits over CF as a preoperative chemoradiotherapy for locally advanced esophageal cancer.

Based on these backgrounds, we have launched a three-arm randomized controlled trial to confirm the superiority of DCF and the superiority of chemoradiotherapy with CF (CF-RT) in overall survival over CF as preoperative therapy for locally advanced esophageal cancer.

The JCOG Protocol Review Committee approved this study protocol in November 2012 and patient enrollment was started in December 2012. In each institution, approval by the institutional review board is obtained before starting patient accrual. This trial was registered at the UMIN Clinical Trials Registry as UMIN000009482 (http://www.umin.ac.jp/ctr/index.htm).

### OBJECTIVES

The purpose of this study is to confirm the superiority of DCF and the superiority of CF-RT in overall survival over CF as preoperative therapy for locally advanced esophageal cancer.

### STUDY SETTING

A multi-institutional three-arm open label randomized Phase III study.

### ENDPOINTS

The primary endpoint is overall survival in all randomized patients. Overall survival is defined as the number of days from randomization to death from any cause, and it is censored at the last day the patient is alive. The secondary endpoints are progression-free survival (PFS), %R0 resection, response rate, pathologic complete response rate and adverse events.

PFS is defined as the number of days from randomization to progression or death from any cause, and it is censored at the latest day the patient is alive without any evidence of progression. Disease progression during preoperative therapy is not regarded as an event of PFS if R0/R1 resection is conducted. In cases of R2 resection, radiologically confirmed progression after surgery is regarded as a PFS event (8).

Adverse events include those during preoperative therapy, surgical morbidity, late radiation toxicity and serious adverse events.

### ELIGIBILITY CRITERIA

**Inclusion criteria**

(i) Histologically proven squamous cell carcinoma, adenocarcinoma or basaloid cell carcinoma.

(ii) All lesions are located in the thoracic esophagus.

(iii) Clinical stages IB, II and III (excluding T4) based on the 7th UICC-TNM classification.

(iv) 20–75 years of age.

(v) ECOG performance status of 0 or 1.

(vi) Measurable lesions not required.

(vii) No prior therapy against esophageal cancer except for complete resection by endoscopic mucosal resection/endooscopic submucosal dissection with either pM1/M2 disease or pM3 disease without vascular infiltration.

(viii) No prior chemotherapy, radiotherapy or hormonal therapy against any cancers except for hormonal therapy for prostate cancer with more than 5 years of disease-free interval.

### FUNDING

This study was supported by the National Cancer Center Research and Development Fund (23-A-16, 23-A-19).

### PROTOCOL DIGEST OF THE JCOG1109

(i) Histologically proven squamous cell carcinoma, adenocarcinoma or basaloid cell carcinoma.

(ii) All lesions are located in the thoracic esophagus.

(iii) Clinical stages IB, II and III (excluding T4) based on the 7th UICC-TNM classification.

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(viii) No prior chemotherapy, radiotherapy or hormonal therapy against any cancers except for hormonal therapy for prostate cancer with more than 5 years of disease-free interval.
RANDOMIZATION

Courses of CF (cisplatin, 75 mg/m²/day, day 1; 5-FU, operative chemoradiotherapy (41.4 Gy/23 fractions) with two 1–5) repeated every 3 weeks. Patients in arm C receive preoperative CF (cisplatin, 70 mg/m²/day, day 1; 5-FU, 750 mg/m²/day, days 1–5) repeated every 3 weeks. Patients in arm B receive three courses of preoperative DCF (docetaxel, 70 mg/m²/day, day 1; cisplatin, 80 mg/m²/day, day 1; 5-FU, 800 mg/m²/day, days 1–5) repeated every 3 weeks. According to the Schoenfeld and Richter’s method (9), the sample size was calculated as 161 patients per arm with a study-wise one-sided alpha level of 5%, a power of 70% for each pair-comparison, an expected accrual period of 6.25 years and a follow-up period of 3 years. One-hundred and seventy events were expected for each pair-comparison. We adjusted for multiplicity due to two pair-comparisons with the Bonferroni method to maintain the study-wise one-sided alpha level of 5%. The total sample size was set at 501 patients considering some patients lost to follow-up. Only when the superiorities of both preoperative DCF and CF-RT over preoperative CF are demonstrated, the direct comparison between preoperative DCF and CF-RT is to be conducted with a one-sided alpha of 5% in a closed testing procedure.

TREATMENT METHODS

Patients in arm A receive two courses of preoperative CF (cisplatin, 80 mg/m²/day, day 1; 5-FU, 800 mg/m²/day, days 1–5) repeated every 3 weeks. Patients in arm B receive three courses of preoperative DCF (docetaxel, 70 mg/m²/day, day 1; cisplatin, 70 mg/m²/day, day 1; 5-FU, 750 mg/m²/day, days 1–5) repeated every 3 weeks. Patients in arm C receive preoperative chemoradiotherapy (41.4 Gy/23 fractions) with two courses of CF (cisplatin, 75 mg/m²/day, day 1; 5-FU, 1000 mg/m²/day, days 1–4) repeated every 4 weeks.

Radiotherapy in arm C is delivered with 6–10 MV photons to a total dose of 41.4 Gy in 23 fractions over 5 weeks. Three-dimensional treatment planning is required. The gross tumor volume is defined as the volume of the primary tumor and the metastatic lymph nodes measuring ≥5 mm along the short axis. The clinical target volume (CTV) includes the primary tumor with a 2-cm cranio-caudal margin, metastatic lymph nodes and regional lymph nodes. The regional lymph nodes include bilaterally supraclavicular fossae and superior mediastinal lymph nodes for carcinoma of the upper thoracic esophagus and mediastinal lymph nodes for carcinoma of the middle or lower thoracic esophagus. Perigastric and celiac axis lymph nodes are not included as elective regional lymph nodes with consideration for anastomotic leak. The planning target volume is defined as CTV plus a 0.5–1 cm margin in the lateral direction and a 1–2 cm margin in the cranio-caudal direction to account for respiratory organ motion and daily set-up error.

Follow-up

All randomized patients are followed up for at least 5 years after patient accrual is completed while the analysis of primary endpoint is performed at 3 years after accrual completion. Tumor markers (carcinoembryonic antigen and squamous cell carcinoma) are evaluated at least every 3 months for the first year, every 6 months from the second to the fifth year and every year afterwards. Enhanced computed tomography for the cervix, chest and abdomen is evaluated at least 6 months for the first 5 years.

STUDY DESIGN AND STATISTICAL ANALYSIS

This three-arm randomized trial is designed to confirm the superiority of preoperative DCF and the superiority of preoperative CF-RT over preoperative CF in terms of overall survival. We assumed 3-year survival with preoperative CF to be 63% and expected a 10% increase in 3-year survival for preoperative DCF and preoperative CF-RT. According to the Schoenfeld and Richter’s method (9), the sample size was calculated as 161 patients per arm with a study-wise one-sided alpha level of 5%, a power of 70% for each pair-comparison, an expected accrual period of 6.25 years and a follow-up period of 3 years. One-hundred and seventy events were expected for each pair-comparison. We adjusted for multiplicity due to two pair-comparisons with the Bonferroni method to maintain the study-wise one-sided alpha level of 5%. The total sample size was set at 501 patients considering some patients lost to follow-up. Only when the superiorities of both preoperative DCF and CF-RT over preoperative CF are demonstrated, the direct comparison between preoperative DCF and CF-RT is to be conducted with a one-sided alpha of 5% in a closed testing procedure.
All statistical analyses will be conducted at the JCOG Data Center.

INTERIM ANALYSIS AND MONITORING
We plan to conduct two interim analyses, taking multiplicity into account using the Lan-DeMets method with O’Brien and Fleming type alpha spending function. The first interim analysis will be conducted after half of the planned number of patients are enrolled and the second interim just before the planned patient accrual is completed. The Data and Safety Monitoring Committee of the JCOG will review the interim analysis reports independently from the group investigators and group statistician. If the superiority of only one of the test arms is demonstrated with an adjusted alpha level, the study will be terminated. If the superiorities of both test arms are demonstrated over the preoperative CF arm, the study will be continued only with the two test arms. If either of the test arms is terminated because of futility, the study will be continued with the other two arms.

In-house monitoring will be performed every 6 months by JCOG Data Center to evaluate and improve study progress, data integrity and patient safety.

PARTICIPATING INSTITUTIONS
(FROM NORTH TO SOUTH)
Hokkaido University, Iwate Medical University, Tohoku University, Ibaragi Prefectural Central Hospital, Tochigi Cancer Center, Saitama Cancer Center, National Cancer Center Hospital East, Chiba Cancer Center, Chiba University, Tokyo Dental College Ichikawa General Hospital, National Cancer Center Hospital Tokyo Women’s Medical University, National Hospital Organization Tokyo Medical Center, Keio University, Showa University, Tokyo Medical and Dental University, Cancer Institute Hospital, Toranomon Hospital, Tokai University, Yokohama Municipal Citizen’s Hospital, Niigata Cancer Center, Niigata University, Toyama University, Shizuoka Prefectural General Hospital, Shizuoka Cancer Center, Aichi Cancer Center, Kyoto University, Osaka University, Osaka Medical Center for Cancer and Cardiovascular Disease, National Hospital Organization Osaka Medical Center, Osaka City General Hospital, Osaka Medical College, Kobe University, Hyogo Cancer Center, Hiroshima University, Hiroshima City Asa Hospital, National Hospital Organization Shikoku Cancer Center, Kochi Medical Center, National Hospital Organization Kyushu Cancer Center, Kurume University, Kyushu University.

Conflict of interest statement
Yuko Kitagawa received non-specific support in research from SANOFI in 2012.

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