Protocol for an investigator-initiated, multicenter phase II clinical study examining the safety and efficacy of atezolizumab monotherapy as sequential therapy following chemoradiotherapy for unresectable, locally advanced esophageal squamous cell carcinoma

Abbreviation: TENERGY study

TEce**N**triq monoth**ER**apy followin**G** definitive chemoradiotherap**Y**
for esophageal cancer

Coordinating investigator (representative): Takashi Kojima
Medical Director, Department of Gastrointestinal Oncology, National Cancer Center Hospital East
6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577
Tel: 04-7133-1111 (extension: 91266)
E-mail: takojima@east.ncc.go.jp

Coordinating investigator: Hideaki Bando
Medical Director, Department of Clinical Oncology, Aichi Cancer Center
1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681
Tel: 052-762-6111 (main)
E-mail: hbando@aichi-cc.jp

Coordinating investigators: Daisuke Kotani, Nozomu Fuse
Department of Gastrointestinal Oncology/Clinical Research Support Unit,
National Cancer Center Hospital East
6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577
Tel: 04-7133-1111 (extension: Kotani, 91377; Fuse, 91029)
E-mail Kotani: dkotani@east.ncc.go.jp
Fuse: nofuse@east.ncc.go.jp

EPOC Protocol No.: EPOC1802
Version No.: 6.0; Date Prepared: January 14, 2020

Revision history:

August 29, 2018: Investigator-initiated clinical study protocol version 1.0 prepared
October 10, 2018: Investigator-initiated clinical study protocol version 1.1 prepared
December 10, 2018: Investigator-initiated clinical study protocol version 2.0 prepared
January 15, 2019: Investigator-initiated clinical study protocol version 3.0 prepared
March 18, 2019: Investigator-initiated clinical study protocol version 4.0 prepared
May 20, 2019: Investigator-initiated clinical study protocol version 5.0 prepared
January 14, 2020: Investigator-initiated clinical study protocol version 6.0 prepared

Abbreviations

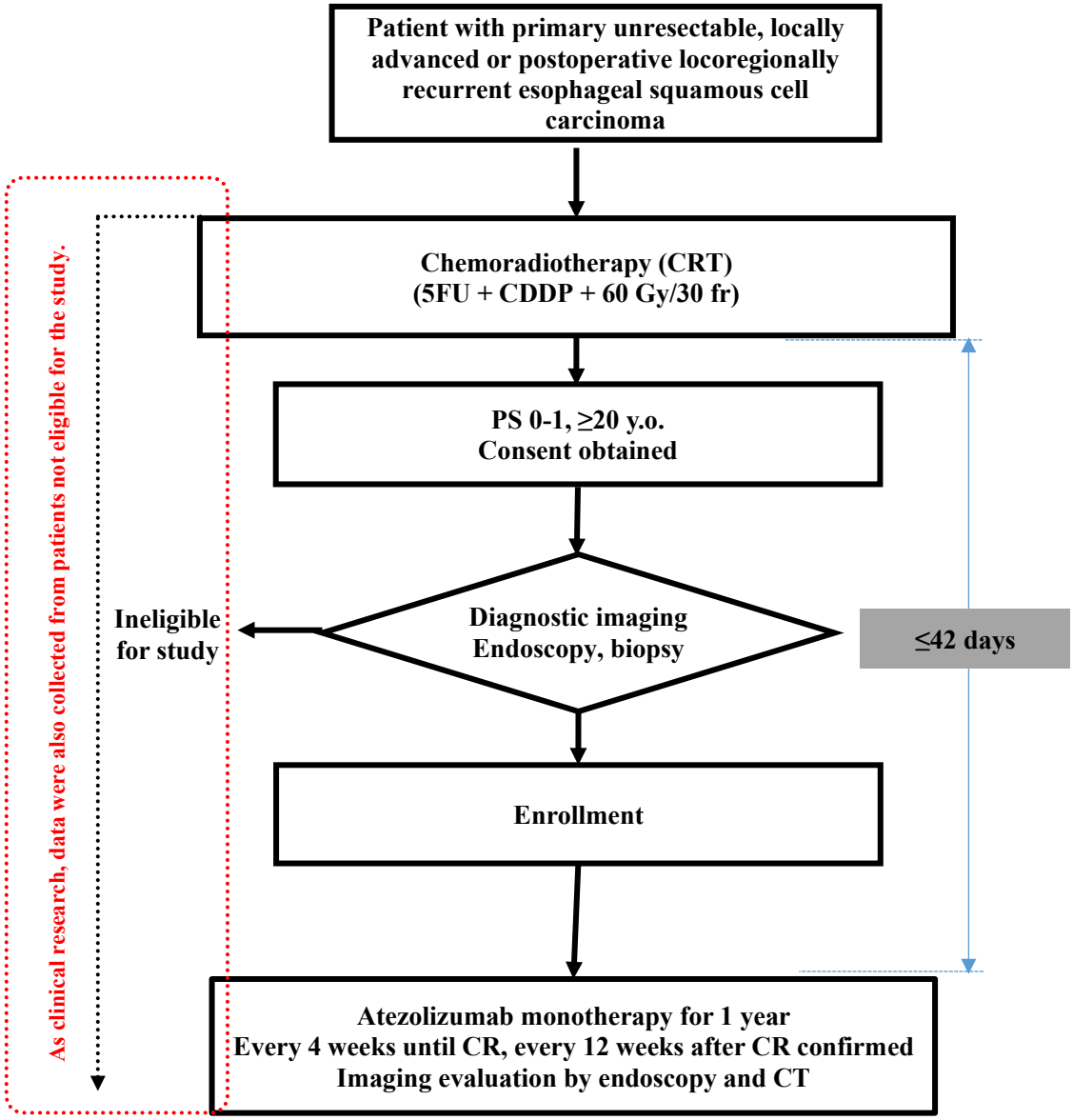
Abbreviation	Definition
5-FU	5-Fluorouracil
ACTH	Adrenocorticotropic hormone
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMED	Japan Agency for Medical Research and Development
AST	Aspartate aminotransferase
ATM	Ataxia telangiectasia mutated
AUC	Area under the concentration-time curve
BAL	Bronchoalveolar lavage
BUN	Blood urea nitrogen
CCr	Creatinine clearance
CD137	Cluster of differentiation 137
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CDDP	Cisplatin
CEA	Carcinoembryonic antigen
CHO	Chinese hamster ovary
CI	Confidence interval
CK	Creatine kinase
CL	Clearance
Cmax	Peak (maximal) concentration of drug in plasma
Cmin	Trough concentration
COI	Conflict of interest
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CRT	Chemoradiotherapy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CTV	Clinical target volume
DC	Dendritic cell
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DS	Dysphagia score
DVH	Dose volume histogram
ECMO	Extracorporeal membrane oxygenation
ECOG	Eastern Cooperative Oncology Group
EDC	Electric data capture
EGFR	Epidermal growth factor receptor
EMR	Endoscopic mucosal resection
EPID	Electronic portal imaging device
FAS	Full analysis set
FDG	Fluorodeoxyglucose
fT3	Free triiodothyronine
fT4	Free thyroxine

GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GIST	Gastrointestinal stromal tumor
GLP	Good Laboratory Practice
GTV	Gross tumor volume
Hb	Hemoglobin
HBs	Hepatitis B virus surface proteins
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HTLV	Human T-lymphotropic virus
IC	Tumor-infiltrating immune cells
IgG	Immunoglobulin G
ILD	Interstitial lung disease
IP	Inorganic phosphorus
IRB	Institutional review board
ITT	Intent-to-treat
IUD	Intrauterine device
JCOG	Japan Clinical Oncology Group
LD	Low dose
LDH	Lactic dehydrogenase
LFT	Liver function test
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
mUC	Metastatic urothelial cancer
NCI	National Cancer Institute
NEC	Neuroendocrine carcinoma
NET	Neuroendocrine tumor
NSCLC	Non-small-cell lung carcinoma
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PET	Positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
POC	Proof-of-concept
PR	Partial response
PS	Performance status
PT-INR	International normalized ratio of prothrombin time
PTV	Planning target volume
QA	Quality assurance
QC	Quality control
RANKL	Receptor activator of nuclear factor kappa-B ligand
RECIST	Response Evaluation Criteria in Solid Tumors

RNA	Ribonucleic acid
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
SAD	Source axis distance
SCC	Squamous cell carcinoma associated antigen
SD	Stable disease
SD	Standard dose
SP	Safety population
SpO_2	Peripheral oxygen saturation
T-Bil	Total-bilirubin
TC	Tumor cells
TCR	T-cell receptor
TSH	Thyroid stimulating hormone
UA	Uric acid
UC	Urothelial cancer
UICC	Unio Internationalis Contra Cancrum
ULN	Upper limit of normal
VAD	Ventricular assist device
Vss	Steady-state volume of distribution

1 Synopsis

Schema



Phase	Phase II
Subjects	Patients with primary unresectable, locally advanced esophageal squamous cell carcinoma (ESCC) and patients with unresectable postoperative locoregionally recurrent ESCC who have undergone curative chemoradiotherapy (CRT) with fluorouracil (5-FU) and cisplatin (CDDP)
Objective	To examine the clinical efficacy and safety of monotherapy with atezolizumab, an anti-PD-L1 antibody drug, as sequential therapy in patients with unresectable, locally advanced ESCC who had undergone curative CRT with 5-FU and CDDP. **[Primary locally advanced ESCC part]** Clinical efficacy and safety will be evaluated when atezolizumab is administered sequentially to patients with primary unresectable, locally advanced ESCC ("primary locally advanced patients " below) who have undergone curative CRT. **[Postoperative locoregionally recurrent ESCC part]** Clinical efficacy and safety will be evaluated on an exploratory basis when atezolizumab is administered sequentially to patients with unresectable postoperative locoregionally recurrent ESCC ("postoperative locoregionally recurrent patients" below) who have undergone curative CRT. **Primary endpoint:** ● The complete response (CR) rate confirmed by the investigator's assessment **Secondary endpoints:** ● The CR rate confirmed by central assessment[1)] ● Progression-free survival (PFS)[2)] ● The objective response rate (ORR) based on the RECIST guideline version 1.1 (partially modified for this study) ● Overall survival (OS)[2)] ● Failure pattern[2)] ● Incidence of adverse events determined using CTCAE version 4.0 1) Central assessments will be performed for primary locally advanced patients if promising results are obtained for the CR rate confirmed by the investigator's assessment in this study. 2) PFS, OS, and failure pattern will be followed for 5 years after the completion of this study through additional clinical studies associated with this study, and the data for these endpoints will be determined. **Additional studies:** ● Observational study of the status of chemoradiotherapy administration and long-term prognosis in unresectable, locally advanced ESCC (TENERGY study–observational research) ● Biomarker exploratory study associated with the investigator-initiated, multicenter phase II clinical study examining the safety and efficacy of atezolizumab

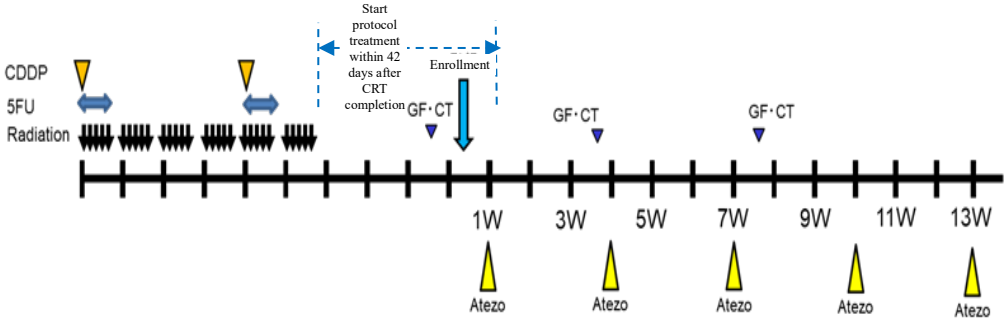
	monotherapy as sequential therapy following chemoradiotherapy for unresectable, locally advanced ESCC (TENERGY study–TR research) ● Investigation of quality control (QC) and quality assurance (QA) in radiation therapy
Study design	This is an open-label, single-arm, multicenter phase II clinical study to examine the clinical efficacy and safety of monotherapy with atezolizumab, an anti-PD-L1 antibody drug, as sequential therapy following curative CRT with 5-FU and CDDP in primary locally advanced and postoperative locoregionally recurrent patients.
Study population	**Inclusion criteria** **[Primary locally advanced ESCC part]** 1. Primary esophageal squamous cell carcinoma, adenosquamous carcinoma, or basaloid cell carcinoma diagnosed histologically (Accessory lesion biopsy is not required, but if performed, squamous cell carcinoma, basaloid cell carcinoma, adenosquamous carcinoma, or basaloid cell carcinoma is identified.) 2. Primary esophageal lesion present in the thoracic esophagus (UICC-TNM 7th edition). However, the patient with invasion of the cervical and abdominal esophagus will be eligible if curative CRT is judged to be feasible and already administered. In addition, accessory lesions for which endoscopic resection is absolutely indicated may be present at other locations. 3. Macroscopic radical resection is judged unfeasible based on cervicothoracic/abdominopelvic contrast-enhanced CT performed before CRT. That is, either (1) or (2) below is applicable. However, the patient will be ineligible if esophageal perforation, esophageal-respiratory tract fistula, esophageal-mediastinal fistula, bleeding associated with arterial invasion, or airway stenosis symptoms are seen clinically or on diagnostic imaging before CRT. (1) The depth of the primary tumor invasion (UICC-TNM 7th edition and Japanese Classification of Esophageal Cancer 11th edition) is classified as cT4b [invasion of the aorta (great vessel), trachea, bronchus, pulmonary artery, pulmonary vein, or a vertebral body]. (2) Regional lymph node metastases or supraclavicular lymph node (#104) metastases have invaded an organ other than the esophagus. NB: Even if the short axis of the lymph node is ≥5 mm and <10 mm, it will be considered lymph node metastasis if the lesion can clearly be judged to be malignant by means such as FDG-PET, ultrasound, or the patient's clinical course. NB: Whether a measurable lesion is present in cervicothoracic/abdominopelvic CT performed before CRT administration is not taken into account. 4. No metastasis to distant organs other than the supraclavicular lymph nodes seen on cervicothoracic/abdominopelvic CT performed before CRT administration 5. No history of treatment other than endoscopic resection for esophageal cancer before CRT administration 6. CRT fulfilling the conditions indicated below was administered,* and the protocol treatment can be started within 42 days after the final session of radiation therapy. • Cycle 1 of chemotherapy started at doses of 70 mg/m^2 of CDDP on Day 1 and 700 mg/m^2 of 5-FU on Days 1 to 4, with 4 weeks considered 1 cycle and a total of 2 cycles administered. A dose reduction will be allowed in the 2nd cycle of chemotherapy depending on the toxicity of Cycle 1.

	• Irradiation was performed at a dose of 60 Gy/30 fr without exceeding the dose limit for at-risk organs. *: CRT will be performed as indicated in Sections 3.3 "Standard chemoradiotherapy" and 3.4 "Standard radiation therapy plan." 7. No distant metastasis seen in imaging procedures performed at the completion of CRT, and no esophageal perforation, esophageal-respiratory tract fistula, esophageal-mediastinal fistula, bleeding associated with arterial invasion, or airway stenosis seen clinically or on diagnostic imaging **[Postoperative locoregionally recurrent ESCC part]** 1. Primary esophageal squamous cell carcinoma, adenosquamous carcinoma, or basaloid cell carcinoma diagnosed histologically using surgical specimens NB: Squamous cell carcinoma, adenosquamous carcinoma, or basaloid cell carcinoma if an histological diagnosis is performed for accessory lesions NB: Subclassification will be performed according to the quantitatively predominant histological type, in accordance with the Japanese Classification of Esophageal Cancer 11th edition. Patients will be considered eligible if they have a diagnosis of squamous cell carcinoma, adenosquamous carcinoma, or basaloid cell carcinoma in the pathological diagnosis of surgical specimens based on this classification. 2. The patient who underwent surgical resection with a curability classification of A or B for esophageal cancer. However, recurrent foci are seen in the mediastinum, anastomotic region, or regional lymph nodes (in the 3 areas for surgical resection), which are unresectable, but it is concluded that curative CRT is possible for all of the recurrent foci. 3. No metastasis to distant organs other than the supraclavicular lymph nodes are seen on cervicothoracic/abdominopelvic CT performed before CRT administration. 4. If the patient has a history of neoadjuvant chemotherapy, at least 24 weeks has passed from the last day of administration to the start of CRT. 5. CRT fulfilling the conditions indicated below was administered,* and the protocol treatment can be started within 42 days after the final cycle of radiation therapy. • Cycle 1 of chemotherapy started at doses of 70 mg/m^2 of CDDP on Day 1 and 700 mg/m^2 of 5-FU on Days 1 to 4, with 4 weeks considered 1 cycle and a total of 2 cycles administered. A dose reduction will be allowed in the 2nd cycle of chemotherapy depending on the toxicity of Cycle 1. • Irradiation will be performed at a dose of 60 Gy/30 fr without exceeding the dose limit for at-risk organs. *: CRT will be performed as indicated in Sections 3.3 "Standard chemoradiotherapy" and 3.4 "Standard radiation therapy plan." 6. No distant metastasis seen in imaging procedures performed at the completion of CRT, and no esophageal perforation, esophageal-respiratory tract fistula, esophageal-mediastinal fistula, bleeding associated with arterial invasion, or airway stenosis symptoms seen clinically or on diagnostic imaging **[Both primary locally advanced ESCC and postoperative locoregionally recurrent ESCC parts]**

	1. Aged ≥20 years at time of informed consent 2. PS of 0 or 1 according to ECOG criteria (PS must be recorded in the medical records without fail.) 3. All of the following criteria met in the most recent tests performed within 14 days before enrollment (The results from the same day of week 2 weeks before the day of enrollment may be used). (1) Neutrophil count: ≥1200/mm^3 (2) Platelet count: ≥7.5 × 10^4/mm^3 (3) Hemoglobin: ≥8.0 g/dL (no blood transfusion to be received within 14 days before the date of blood drawing for test used for enrollment) (4) Albumin: ≥2.5 g/dL (5) T-bil: ≤ 1.5 × ULN (≤2.5 × ULN allowed if patient has Gilbert's syndrome) (6) AST/ALT: ≤100 U/L (7) Serum creatinine: ≤1.5 mg/dL or creatinine clearance* ≥45 mL/min *: For creatine clearance, can use both value calculated using Cockcroft-Gault equation and value from 24-hour pooled urine. (8) SpO_2: ≥95% (room air) 4. If the patient is a woman of childbearing potential, the result of a pregnancy test performed within 14 days before enrollment is negative. (See Section 6.2 "Pregnancy and contraception," for the definition of a woman of childbearing potential.) 5. The patient who is willing to use appropriate contraception from the time of informed consent to 5 months after the end of investigational product administration (See Section 6.2 "Pregnancy and contraception," regarding appropriate contraception.) 6. Expected to survive for at least 3 months 7. The patient who has provided written informed consent to participate in the study **Exclusion criteria** 1. Diagnosed with multiple active cancers (simultaneous multiple cancers or multiple cancers with a disease-free interval of ≤3 years before enrollment). However, multiple active cancers does not include intraepithelial carcinoma or lesions corresponding to intramucosal carcinoma, which are judged to have been cured with localized treatment. 2. An active infection requiring systemic treatment (Fever of ≥38.0°C and demonstrated to be a bacterial infection by diagnostic imaging or bacteriological testing; does not include localized infections that do not affect the patient's general condition.) 3. Concomitant inflammatory bowel disease or a past history of such disease 4. Concomitant pneumonia or interstitial lung disease (ILD) or a past history of either 5. A concomitant autoimmune disease or a past history of a chronic or recurrent autoimmune disease 6. The patient who requires administration of a systemic corticosteroid (excluding prophylactic administration for an allergic reaction or administration on an as-needed basis for purposes such as alleviating edema associated with radiation therapy) or immunosuppressant or was administered such a treatment within 14 days before enrollment 7. Concomitant thyroid dysfunction (hyperthyroidism or hypothyroidism) or a past history thereof

	NB: Patients with hypothyroidism who are stable with hormone replacement therapy may be enrolled at the discretion of the principal investigator 8. A past history of or finding indicating cardiovascular risk to which any of the following are applicable: • Left ventricular ejection fraction <50% • A past history of or finding indicating poorly controlled arrhythmia that is clinically problematic. Exception: Patients with atrial fibrillation that has been controlled for more than 30 days before enrollment may be included. • A past history of an acute coronary syndrome (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months before enrollment • Past history of or findings indicating congestive heart failure of Grade II or higher based on the New York Heart Association (NYHA) functional classification • Refractory hypertension (defined as high blood pressure of systolic BP >140 mmHg and diastolic BP >90 mmHg that cannot be controlled with treatment) • Fitted with an implantable defibrillator or permanent pacemaker 9. Poorly controlled diabetes mellitus 10. Positive HIV antibody test, HBs antigen test, or HCV antibody test* *: Also excluded are patients with a positive HBs or HBc antibody test and an HBV-DNA assay that equals or exceeds detection sensitivity. 11. Pregnant or lactating patient 12. A serious, unstable psychiatric disorder or other medical condition that could undermine safety, prevent informed consent, or impede compliance with study procedures 13. Previous use of atezolizumab or an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody or other drug therapy for T-cell regulation 14. The patient unwilling or unable to comply with the procedures described in the protocol 15. The principal investigator determines that the patient is unsuitable as a study subject because the patient has a condition that could prevent toxicity assessment.
Sample size Statistical analysis	Unresectable, locally advanced ESCC is a refractory disease, with a CR rate of 0% to 25% and median overall survival time of 9 to 14 months in the primary locally advanced patients. In this study, the CR rate for primary locally advanced patients was specified as the primary endpoint. The target sample size determined using the exact method based on a binomial distribution was 38 patients. This was calculated using a threshold CR rate of 20% for the protocol treatment, an expected CR rate of 40%, a one-tailed significance level of 5%, and statistical power of 80%. Assuming that enrollment will be carried until it is determined that the full analysis set (FAS) will comprise 38 subjects, a maximum of 40 primary locally advanced patients are to be enrolled. However, in order to enroll patients until the FAS of 38 subjects is confirmed, more than 40 patients may be enrolled if the FAS for primary locally advanced patients does not reach 38 subjects. If a CR is obtained in at least 13 of the 38 patients in the FAS, it will be concluded that there is value in examining the protocol treatment for further therapeutic development. Forty primary locally advanced patients, including some ineligible patients, will be enrolled in this study. In addition, up to 10 postoperative locoregionally recurrent patients will be enrolled on an exploratory basis.

<table>
<tr><td></td><td>Primary locally advanced ESCC part: 40 patients
Postoperative locoregionally recurrent ESCC part: 10 patients

Thus, the maximum total sample size for this study was specified at 50 patients.</td></tr>
<tr><td>Administration method</td><td>Atezolizumab monotherapy
Atezolizumab 1200 mg intravenous infusion will be started <u>within 42 days after the completion of CRT</u>. Atezolizumab 1200 mg will be administered on Day 1 in each cycle consisting of 21 days. Atezolizumab administration will be continued for a maximum of 12 months (maximum of 17 cycles, with final administration in Week 49), unless the disease progresses as judged by endoscopy or CT, intolerable toxicity occurs, or the patient's consent to participate in the study is withdrawn.
 

<table>
<tr><th>Type of Drug</th><th>Drug Name</th><th>Dose (single dose)</th><th>Administration Frequency</th><th>Administration Route</th></tr>
<tr><td>Test product</td><td>Atezolizumab</td><td>1200 mg</td><td>Every 3 weeks</td><td>Intravenous infusion</td></tr>
</table></td></tr>
<tr><td>Safety evaluation</td><td>● Safety will be evaluated using CTCAE version 4.0.
● <u>When the first 10 patients in the primary locally advanced ESCC part of the study complete 2 cycles (6 weeks) of treatment, the data and safety monitoring committee will be asked to evaluate the safety of atezolizumab in the patients with primary unresectable, locally advanced ESCC who underwent curative CRT.</u> Patients may be enrolled during the evaluation period at the discretion of the coordinating committee.</td></tr>
<tr><td>Efficacy evaluation</td><td>CR is defined as fulfilling both of the following conditions in the assessment of primary lesions and lymph node metastases (must be confirmed after an interval of at least 4 weeks from the first CR assessment):
(1) In evaluating the primary lesion by upper gastrointestinal endoscopy, it was concluded that all endoscopic findings suggestive of malignant lesions have been disappeared (primary lesion CR), based on the criteria for evaluating primary lesions specified in the Japanese Classification of Esophageal Cancer, 11th edition.
(2) In tumor assessments using cervicothoracic/abdominopelvic contrast CT that were performed according to the new response evaluation criteria in solid tumors (RECIST guideline version 1.1) that were modified for this study, the response was assessed as CR for the target and non-target lesions.

Regarding pathological lymph nodes, the RECIST guideline version 1.1 were modified in this study in terms of the following:</td></tr>
</table>

	● Lymph nodes with short axis ≥ 10 mm will be considered pathological lymph nodes and evaluated as target lesions. ● Lymph nodes with short axis < 10 mm and ≥ 5 mm will be considered non-target lesions if they are clinically diagnosed as metastatic nodes, and will not be considered pathological nodes if they are clinically diagnosed as non-metastatic nodes. ● Lymph nodes with short axis < 5 mm will not be considered pathological nodes. An evaluation performed within 28 days before the start of CRT will be considered the baseline evaluation. After CRT is completed and before the protocol treatment is started, upper gastrointestinal endoscopy and CT will be performed. After the start of the protocol treatment, an evaluation will be performed every 4 weeks (±2 weeks) until an assessment of CR is obtained. After the assessment of CR is obtained, an evaluation will be performed at least 4 weeks after the previous examination to confirm CR. After CR confirmation, an evaluation will be performed every 12 weeks (±4 weeks).
Biomarker analysis (additional study)	An analysis of genetic and immunological biomarkers related to the protocol treatment is planned using biopsy specimens and peripheral blood specimens collected before curative CRT [if the patient consents to participate in the TENERGY study–TR research; if consents to participate in the "Research on the Elucidation of the Immune Status of Patients with Gastrointestinal and Other Solid Cancers and Its Clinical Significance (Research No. 2015-048)" and agrees to the secondary use of specimens; or if stored tumor tissue specimens and blood specimens collected in routine clinical practice are available], before the start of atezolizumab administration, at the time of the CR assessment after the start of atezolizumab administration, and during endoscopic examinations performed when progression occurs. The biomarker analysis will be performed as separate research from this study, and an informed consent document will be used to separately obtain consent for the use of lesion tissue and patient peripheral blood collected before the start of neoadjuvant CRT and during the protocol treatment period. At present, the following analyses are planned. 1. Comprehensive genetic analysis (genomic DNA and RNA) 2. Search for neoantigens and analyses of tumor mutational burden (TMB) and microsatellite instability (MSI) 3. Human leukocyte antigen (HLA) haplotyping 4. Phenotype analysis of immunocompetent cells 5. Histopathology analysis
Planned study period	Study start (first patient's first visit): November 2018 Completion of patient enrollment (last patient's first visit): May 2020 Study completion (last patient's last visit): May 2021
Number of institutions	6
Representative coordinating investigator	Takashi Kojima, National Cancer Center Hospital East

Planned study centers	● National Cancer Center Hospital East ● National Cancer Center Hospital ● Saitama Cancer Center ● Cancer Institute Hospital of JFCR ● Shizuoka Cancer Center ● Aichi Cancer Center
Study administrative structure	● This study will be conducted with financial support from the Practical Research for Innovative Cancer Control project (FY 2018) of the Japan Agency for Medical Research and Development (AMED), and with the investigational product and safety information provided at no charge by Chugai Pharmaceutical Co., Ltd. ● For information on data centers, monitoring, and auditing, see the appendix.

Contacts for inquiries: tenergy_core@east.ncc.go.jp
Matters requiring clinical decisions, such as inclusion criteria and criteria for dose modification in the protocol treatment: coordinating investigators (cover sheet)
Enrollment process, EDC input: EP-CRSU Co., Ltd. (Appendix 1)
Adverse event information, etc.: EP-CRSU Co., Ltd. (Appendix 1)

Table of Contents

2 Objective

To examine the clinical efficacy and safety of monotherapy with atezolizumab, an anti-PD-LI antibody drug, as sequential therapy in patients with unresectable, locally advanced ESCC who have undergone curative chemoradiotherapy (CRT) with fluorouracil (5-FU) and cisplatin (CDDP).

[Primary locally advanced ESCC part]

Clinical efficacy and safety will be evaluated when atezolizumab is administered sequentially to patients with primary unresectable, locally advanced ESCC ("primary locally advanced patients" below) who have undergone curative CRT.

[Postoperative locoregionally recurrent ESCC part]

Clinical efficacy and safety will be evaluated on an exploratory basis when atezolizumab is administered sequentially to patients with unresectable postoperative locoregionally recurrent ESCC ("postoperative locoregionally recurrent patients" below) who have undergone curative CRT.

Primary endpoint:

- The complete response (CR) rate confirmed by the investigator's assessment

Secondary endpoints:

- The CR rate confirmed by central assessment[1)]
- Progression-free survival (PFS)[2)]
- The objective response rate (ORR) based on the RECIST guideline version 1.1 (partially modified for this study)
- Overall survival (OS)[2)]
- Failure pattern[2)]
- Incidence of adverse events determined using CTCAE version 4.0

1) Central assessments will be performed for primary locally advanced patients if promising results are obtained for the CR rate confirmed by the investigator's assessment in this study.
2) PFS, OS, and failure pattern will be followed for 5 years after the completion of this study through additional clinical studies associated with this study, and the data for these endpoints will be determined.

Additional studies:

- Observational study of the status of chemoradiotherapy administration and long-term prognosis in unresectable, locally advanced ESCC (TENERGY study–observational research)
- Biomarker exploratory study associated with the investigator-initiated, multicenter phase II clinical study examining the safety and efficacy of atezolizumab monotherapy as sequential therapy following chemoradiotherapy for unresectable, locally advanced ESCC (TENERGY study–TR research)
- Investigation of quality control (QC) and quality assurance (QA) in radiation therapy

3 Background

3.1 Epidemiology related to study subjects

In 2016, the number of deaths in Japan from esophageal cancer was 11,483, accounting for 3.1% of all deaths from malignant neoplasms (Cancer Registry and Statistics, Cancer Information Center). Esophageal cancer is the 7th most common type of cancer in Japanese males. The peak age of esophageal cancer morbidity is the 70s. Thus, it is a disease that affects a relatively large number of elderly individuals. In 2009, the main histological type in patients who underwent resection for esophageal cancer was squamous cell carcinoma (86.7%), and the frequency with which esophageal cancer occurred at the various sites was 3.6% for the cervical esophagus; 11.4% for the upper thoracic esophagus; 46.3% for the middle thoracic esophagus; 29.8% for the lower thoracic esophagus, 8.4% for the abdominal esophagus, including the esophagogastric junction; and 0.7% for other sites. Thus, thoracic esophageal cancer was the most common.

The criteria for staging currently used in clinical studies of esophageal cancer are in accordance with the UICC-TNM classification (UICC-2009 7th edition) and the Japanese Classification of Esophageal Cancer 11th edition. The T category describes tumor depth, the N category the number of regional lymph nodes involved, and the M category the presence or absence of distant metastasis. T4 is subclassified into T4a and T4b. T4a is defined as a tumor that has invaded the pleura, pericardium, diaphragm, lung, thoracic duct, azygos vein, or a nerve. T4b is defined as a tumor that has invaded the aorta, vertebral bodies, trachea, bronchus, pulmonary artery, or pulmonary vein. Cancer Statistics in Japan 2015 showed the 5-year relative survival rate by stage to be 85.5% for Stage I, 51.5% for Stage II, 26.6% for Stage III, and 11.7% for Stage IV.

Unresectable, locally advanced squamous cell carcinoma, the target disease of the present study, is limited to approximately 7.0% (percentage of Stage III patients receiving radiation therapy + drug therapy, Cancer Registry Report of the Nationwide Designated Cancer Care Hospitals 2015)[1] or 13.1% (Comprehensive Registry of Esophageal Cancer in Japan 2011, cT4 NanyMany) of patients with esophageal cancer as a whole. Based on the esophageal cancer morbidity data for 2013 (Cancer Registry and Statistics, Cancer Information Center, 22,812 individuals: 19,171 male patients, 3,641 female patients)[2], it is a rare type of esophageal cancer that affects an estimated 1,600 to 3,000 patients a year.

3.2 Current standard treatment for the target disease

Beginning in around 1980, treatments were developed in Europe and the U.S. to improve treatment response through the use of radiation therapy (RT) alone or in combination with chemotherapy. In the early 1990s, the Radiation Therapy Oncology Group (RTOG) conducted a randomized comparative study (RTOG 85-01) [3,4] of chemoradiotherapy (CRT) and RT alone as non-surgical treatments for resectable locally advanced esophageal cancer. The 3- and 5-year survival rates were 30% and 27%, respectively, in the CRT group and 0% for both in the RT monotherapy group. Thus, the study found CRT to be superior to RT alone and indicated that simultaneously combined CRT was the standard non-surgical treatment for resectable locally advanced esophageal cancer.

In Japan, a phase II study[5] of sequentially combined CRT consisting of 2 cycles of radiation therapy (30 Gy) followed by 1 cycle each of CDDP + 5-FU for unresectable, locally advanced ESCC [T4 and/or M1 lymph node metastasis (M1LYM)] was conducted between 1992 and 1994 as the collaborative research of the Japanese Foundation for Multidisciplinary Treatment of Cancer. Participating in the study were 8 institutions of the Japan Esophageal Oncology Group of the Japan Clinical Oncology Group (JCOG). The results were favorable, with the CR and response rates in the 45 patients enrolled being 11% and 64.4%, respectively. Subsequently, the JCOG9516[6] study and a phase II study of simultaneously combined CRT [CDDP + 5-FU, 60 Gy, irradiation stopped midway (split)] (National Cancer Center Hospital East[7]) were conducted for the same disease. The CR rate was 15% and 33%, respectively, and the median overall survival

time (MST) was 10 and 9 months, respectively, which were the favorable results. The results established CRT as the standard treatment for unresectable, locally advanced ESCC. The regimen used as the standard simultaneously combined chemotherapy overseas was chemotherapy (CDDP 70 to 75 mg/m^2 on Day 1 and 5-FU 700 to 1000 mg/m^2/day for 4 consecutive days every 4 weeks for a total of 2 cycles), along with simultaneously combined radiation therapy. Thus, the overseas standard therapy is not substantially different from that used in Japan.

In Japan, divided administration of low-dose 5-FU and CDDP was frequently used in simultaneous combination with radiation therapy, referred to as low-dose CF + RT (LD-CF + RT), beginning from the 1990s because of the expectation of a radiosensitization effect and the preconception that toxicity would be lower. The JCOG0303 study[8] compared standard-dose CDDP + 5-FU + simultaneously combined radiation therapy (SD-CF + RT therapy: CDDP 70 mg/m^2 on Day 1 and 5-FU 700 mg/m^2/day for 4 consecutive days every 4 weeks for a total of 2 cycles; radiation therapy: 2 Gy/30 fr, total of 60 Gy, not split) with LD-CF + RT, and showed that MST was 13.1 and 14.4 months, respectively, the 3-year survival rate was 25.9% and 25.7%, respectively, and no difference was seen between the 2 regimens in the incidence of adverse events (AEs) of Grade 3 or higher. However, the results did not show LD-CF + RT therapy to be non-inferior to SD-CF + RT therapy. Consequently, the significance of LD-CF + RT therapy was negated, and chemoradiotherapy with SD-CF + RT is recognized as the standard therapy for unresectable, locally advanced esophageal cancer in Japan.

As a result of the therapeutic development described above, simultaneously combined chemoradiotherapy with SD-CF + RT is the standard treatment for unresectable, locally advanced esophageal cancer. However, the CR rate is 0% to 25%, and median OS is 9 to 14 months (Table 3.2.1). Thus, the cancer remains intractable with poor therapeutic outcomes, and the standard treatment has not changed for more than 20 years. Therefore, further therapeutic development is awaited.

Table 3.2-1 Therapeutic outcomes for chemoradiotherapy in unresectable, locally advanced ESCC

	N	CR Rate	PFS (m)	MST (m)	Reference
Ishida et al	**45**	**11%**	**NR**	**215 days**	**(3)**
JCOG9516	**60**	**15%**	**NR**	**10**	**(4)**
Ohtsu et al	**44**	**33.3% [25% (T4)]**	**6**	**9**	**(5)**
JCOG0303 SD-CF+RT*	**68**	**0%****	**NR**	**13.1**	**(6)**
JCOG0303 LD-CF+RT*	**71**	**1.4%****	**NR**	**14.4**	**(6)**

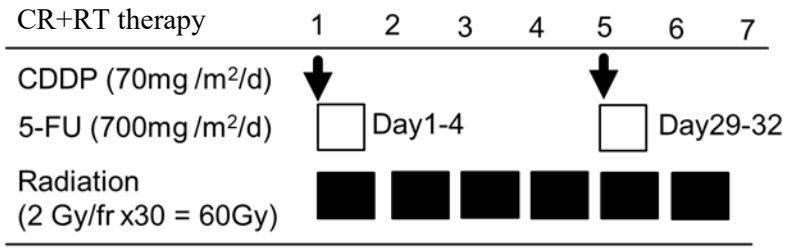
*SD: standard dose, **LD: low dose

**: The CR rate in study JCOG0303 was 0% in the SD-CF + RT group and 1.4% in the LD-CF + RT group, which were lower than in other studies. Possible reasons for this include the possibility that the timing of the CR evaluation was inappropriate for some patients because of the procedure for the CR evaluation ("response of the primary lesion will be assessed endoscopically 4 to 5 weeks after treatment completion, which is the overall response assessment covering target, non-target, and new lesions") and that follow-up was inadequate because the study was terminated early due to the ineffectiveness of the treatment.

3.3 Standard chemoradiotherapy

The CRT typically administered for unresectable, locally advanced esophageal cancer is as follows.

1) CRT



- The following chemotherapy regimen is the standard regimen used in Japan. One cycle is administered every 4 weeks and repeated for 2 cycles.

Drug	Dose	Dosing Method	Duration	Administration Day
CDDP	70 mg/m^2	div	2 h	Day 1
5-FU	700 mg/m^2	civ	96 h	Days 1-4

- Radiation (60 Gy/30 fr/6 weeks) administered simultaneously in combination
- Radiation is administered at a dose of 2 Gy once a day, 5 times a week (changes due to national holidays permitted). Treatment will be discontinued or resumed as indicated below under the criteria for suspending radiation therapy and criteria for resuming radiation therapy.
- Radiation therapy and 5-FU/CDDP will both be started on Day 1 of Cycle 1.
- On the day the 2nd cycle of chemoradiotherapy is scheduled to start or the day before, administration of 5-FU and CDDP will begin after it is confirmed that all of the criteria for starting chemotherapy indicated below are met. However, if the criterion for creatinine clearance (CCr) is the only criterion that is not met (CCr is <40 mL/min), only CDDP will be discontinued, and 5-FU will continue to be administered at the same dose level as in the previous cycle.
- Administration in the 2nd cycle will start within 14 days after the date the 2nd cycle is scheduled to start (Day 29 after the start of Cycle 1) if all of the following criteria for starting chemotherapy are met.
- If the postponed 2nd cycle cannot be started even beyond 14 days after the date the 2nd cycle is scheduled to start, all of the remaining chemotherapy sessions will be skipped, and only radiation therapy will be continued.
- Even if the criteria for starting chemotherapy are not met and it is not started, radiation therapy will be continued as long as none of the criteria for suspending radiation therapy below are applicable.

Criteria for starting, discontinuing, and resuming a cycle (for both chemoradiotherapy and adjuvant chemotherapy)

Adverse Event	Criteria for Starting Chemotherapy (all must be met)	Criteria for Suspending Chemotherapy (one or more applicable)	Criteria for Suspending Radiation Therapy (one or more applicable)	Criteria for Resuming Radiation Therapy (all must be met)
Neutrophil count	≥ 1000/mm^3 (≤ Grade 2)	< 500/mm^3 (Grade 4)	< 500/mm^3 (Grade 4)	≥ 500/mm^3 (≤ Grade 3)
Platelet count	≥ 7.5 × 10^4/mm^3	< 2.5 × 10^4/mm^3 (Grade 4)	< 2.5 × 10^4/mm^3 (Grade 4)	≥ 2.5 × 10^4/mm^3 (≤ Grade 3)
AST	≤ 100 U/L	> 100 U/L	-	-
ALT	≤ 100 U/L	> 100 U/L	-	-
total bilirubin	≤ 1.5 mg/dL	> 2.5 mg/dL	-	-
Creatinine	≤ 1.5 mg/dL	-	-	-

Adverse Event	Criteria for Starting Chemotherapy (all must be met)	Criteria for Suspending Chemotherapy (one or more applicable)	Criteria for Suspending Radiation Therapy (one or more applicable)	Criteria for Resuming Radiation Therapy (all must be met)
Creatinine clearance (estimate)	≥ 40 mL/min	-	-	-
Pneumonitis	≤ Grade 1	Grade 2	Grade 2	≤ Grade 1
Oral mucositis	≤ Grade 1	Grade 3	-	-
Esophagitis	≤ Grade 2	Grade 3	Grade 3	≤ Grade 2
Diarrhea	Grade 0	Grade 3	-	-
Skin rash	≤ Grade 1	Grade 3	-	-
Radiation dermatitis	≤ Grade 2	Grade 3	Grade 3	≤ Grade 2
Febrile neutropenia	Grade 0	Grade 3	Grade 3	Grade 0
Infection	Grade 0	Grade 3	Grade 3	Grade 0
G-CSF use on day irradiation scheduled	No	Yes	Yes	No

- The 5-FU and CDDP doses in the 2nd cycle will be reduced depending on toxicity according to the following dose-reduction criteria for dose reduction and dose levels.

Criteria for dose reduction for the 2nd cycle

Adverse event/drug		CDDP	5-FU
Worst value in Cycle 1			
Neutrophil count	< 500/mm^3 (Grade 4)	Dose reduction by 1 level	Dose reduction by 1 level
Platelet count	< 2.5 × 10^4/mm^3 (Grade 4)	Dose reduction by 1 level	Dose reduction by 1 level
AST	> 200 U/L	No dose reduction	Dose reduction by 1 level
ALT	> 200 U/L	No dose reduction	Dose reduction by 1 level
Total bilirubin	> 3.0 mg/dL	No dose reduction	Dose reduction by 1 level
Oral mucositis	Grade 3	No dose reduction	Dose reduction by 1 level
Esophagitis	Grade 3	No dose reduction	Dose reduction by 1 level
Fatigue	Grade 3	Dose reduction by 1 level	No dose reduction
Diarrhea	Grade 3	No dose reduction	Dose reduction by 1 level
Skin rash*	Grade 3	No dose reduction	Dose reduction by 1 level
Febrile neutropenia	Grade 3	Dose reduction by 1 level	Dose reduction by 1 level
Infection**	Grade 3	Dose reduction by 1 level	Dose reduction by 1 level
Peripheral sensory neuropathy	Grade 2	Dose reduction by 1 level	No dose reduction
Peripheral sensory neuropathy	Grade 3	Treatment discontinuation	No dose reduction
Auditory disorder	Grade 2	Dose reduction by 1 level	No dose reduction
Auditory disorder	Grade 3	Treatment discontinuation	No dose reduction
Day cycle is planned to start or the day before			
CCr ≥ 60 mL/min		Level 0	No dose reduction
CCr ≥ 50, < 60 mL/min		Level −1	No dose reduction
CCr ≥ 40, < 50 mL/min		Level −2	No dose reduction
CCr < 40 mL/min		Discontinuation	No dose reduction

NB: Grade 4 non-hematotoxicity falls under treatment discontinuation.

NB: If a further dose reduction is required when CCr reaches Level −2, administration of the drug will be discontinued.

Skin rash*: maculopapular rash, palmar-plantar erythrodysesthesia syndrome, urticaria

Infection**: infections of the lung, mediastinum, pleura, biliary tract, urinary tract, and peritoneum; catheter-related infection; and sepsis

Chemoradiotherapy dose levels

Drug	Dose Level	Dose	Dosing Method
5-FU	Level 0 (full dose)	700 mg/m^2	civ*
	Level −1	600 mg/m^2	civ
	Level −2	400 mg/m^2	civ
CDDP	Level 0 (full dose)	70 mg/m^2	div**
	Level −1	60 mg/m^2	div
	Level −2	40 mg/m^2	div

*civ: continuous intravenous infusion, **div: intravenous drip infusion

2) CRT total dose

The standard radiation dose in radiation therapy for Stages cIB, cII, and cIII (CT1b - T3) is 50.4 Gy. For cT4b, the standard dose is 50 to 50.4 Gy, according to the 2018 NCCN guidelines version 1. The rationale for this is that the INT0123 multi-group study conducted in the United States (RTOG 94-05), which compared the standard dose (50.4 Gy) with a high dose (64.8 Gy), found no advantage for the high dose.[9] However, based on the curative standard dose used in a randomized phase III study (JCOG1510) comparing curative chemoradiotherapy with conversion surgery following induction docetaxel + CDDP + 5-FU in unresectable, locally advanced thoracic ESCC, a curative standard dose of 60 Gy was determined to the adequate standard in the present study. The rationale for this was as follows.

(1) In the INT0123 study, only 17 patients (8%) with T4 disease were enrolled. This is thought to be an inadequate basis for concluding that 50 to 50.4 Gy is the optimal dose for T4 tumors.

(2) In cT4b disease, the tumor load is large, which makes a higher dose of 60 Gy the curative radiation dose needed to obtain a certain CR rate.

(3) In the Guideline for Diagnosis and Treatment of Carcinoma of the Esophagus 2017, nearly all of the reports from Japan used a radiation regimen of 60 Gy/30 fr/6 to 8 weeks, which was described as safe, although it was not described according to T category. Conversely, there is a lack of clinical data on the use of the 50.4 Gy dose in Japan.

(4) The feasibility of the 60 Gy dose was previously confirmed in the JCOG0303 study, and the Japan Esophageal Oncology Group of the JCOG considered CF (70/700) + RT (60 Gy) to be the standard treatment for patients in the JCOG1510 study.

3) Prophylactic irradiation in CRT

The usefulness of prophylactic irradiation has not yet been determined. Although the results of several retrospective analyses regarding prophylactic irradiation have previously been reported, no conclusion has been reached about its usefulness, and views on this subject are divided. Moreover, prophylactic irradiation was not performed in study JCOG0303, and a potential disadvantage of prophylactic irradiation is an increase in late complications, such as radiation pneumonitis and cardiotoxicity. This could result in an increase in adverse events when atezolizumab is administered as sequential therapy following CRT.

Based on these considerations, it was determined that prophylactic irradiation will not be performed in this study.

4) Adjuvant chemotherapy after CRT

Although the significance of adjuvant chemotherapy after CRT has not been established, 2 cycles of adjuvant chemotherapy with 5-FU and CDDP have been administered in nearly all clinical studies conducted in Japan and other countries.[5,7-9] Evaluations of treatment efficacy were performed before adjuvant chemotherapy in 2 studies conducted in Japan, and the adjuvant chemotherapy was administered only if a partial response (PR) or CR was seen. Adjuvant chemotherapy is expected to result in an increase in adverse

events, although there is no evidence indicating a clear difference. The Guideline for Diagnosis and Treatment of Carcinoma of the Esophagus 2017 does not strongly recommend that adjuvant chemotherapy be administered (Evidence Strength C). As will be discussed later, adjuvant chemotherapy will not be administered and atezolizumab administration will begin within 42 days after CRT in the present study in order to maximize the synergistic effect of radiation therapy and the immune checkpoint inhibitor.

3.4 Standard radiation therapy plan

The plan for the radiation therapy to be administered to study subjects as the standard regimen is described below.

1) Timing of treatment start, discontinuation, etc.

- Radiation therapy will start on the same day as chemotherapy (Day 1). No scheduled treatment suspension period has been established.
- If irradiation cannot be performed for a reason such as a national holiday, it will be postponed until the next working day with no change in dose.

2) Dose and fractionation

- A single dose of 2 Gy will be administered once daily 5 days a week. No other doses for a single administration will be permitted.
- A total of 30 fractions and a total dose of 60 Gy will be administered. The total treatment duration will be 40 days within an allowable total treatment period of 63 days.

3) Radiation therapy system

- The system to be used is one that generates x-ray photons with 6 to 10 MV of energy and that has a source axis distance (SAD) of ≥100 cm.
- However, when treating supraclavicular lymph node metastases, 4 MV x-ray may be used.

4) Target volume

- Treatment will be administered based on a three-dimensional radiation treatment plan that uses CT. Target volume will be defined as described below. Treatment planning using an x-ray simulator that references CT images will not be permitted.

(1) Gross tumor volume (GTV)

Esophageal lesions (GTV primary)

This will be the tumor extent observed by upper gastrointestinal endoscopy and visualized by thoracic CT at the time of CRT planning. If an upper GI series is performed, these findings also will be used for reference. If it is difficult to determine the extent of the primary lesion, clipping of the tumor on the oral and anal ends by upper gastrointestinal endoscopy will be recommended.

Metastatic lymph nodes (GTV node)

Metastatic lymph nodes will be considered to be those visualized with a short axis ≥10 mm on thoracic CT performed at the time of CRT planning or those with a short axis ≥5 mm and <10 mm and judged clinically to have metastases.

Recurrent lesions (GTV recurrence)

In recurrent patients, GTV recurrence will be the extent of recurrent tumors determined by a diagnostic imaging method such as CT or MRI, by endoscopy, or by macroscopic examination.

(2) Clinical target volume (CTV)

Esophageal lesion (GTV primary)

Taking into account subclinical extension, this will be the GTV primary plus 2 cm on both the cranial

and caudal ends.

Metastatic lymph nodes (CTV node)

Basically identical to GTV node.

Recurrent lesions (CTV recurrence)

Basically identical to GTV recurrence.

(3) Esophageal intramural metastasis, intraepithelial extension, and multiple lesions

i) Accessory lesions meeting the absolute indication for endoscopic resection will not be specified as GTV primary lesions.

ii) Depending on their location, intramural lesions and accessory lesions do not need to be treated in the same radiation field as a major lesion [see (4) below].

(4) Planning target volume (PTV)

This adds an appropriate margin (approximately 0.5 to 1 cm laterally, 0.5 to 2 cm cranially and caudally) to the CTV described above that takes into account errors in factors such as respiratory movement and the reproducibility of patient immobilization (PTV primary, PTV node, PTV recurrence).

The radiation field will take into account an approximately 5 to 8 mm margin appropriate for the beam penumbra and will generally be specified to include the PTV for them.

- A multileaf collimator will be used to form the radiation field.
- The isocenter will be specified at an appropriate location in the target volume. For treatment of the primary lesion in the middle and lower thoracic esophagus (UICC-TNM), multiportal irradiation with ≥3 portals will be recommended to reduce cardiotoxicity. The number of portals used in treating the primary lesion of the upper thoracic esophagus and supraclavicular lymph node metastases will be left to the discretion of each institution.
- If PTV primary and PTV node are separately located, it will not be necessary to treat them in the same radiation field. If they are adjacent to each other, expanding the radiation field to make it continuous will be permitted if there is no marked increase in the dose received by normal tissue.
- To observe the stipulations of Sections 3.4, 5), (2) "Target dose homogeneity" and 3.4, 7) "Dose limits for at-risk organs," excluding part of the PTV from the irradiation portal or adding part of the PTV to it will be permitted (field-in-field technique).
- Abutted field radiation using the half-field technique will be permitted if it is preferable due to the GTV location or irradiation area. However, care should be taken to ensure that the abutted site (cross-section that includes the isocenter plane) does not encroach on PTV primary or PTV node. To compensate for uncertainty regarding the dose at the abutted site, it will be necessary to change the site at appropriate times.
- All portals will be irradiated in a single treatment. Irradiating only 1 portal a day in irradiation to 2 or more portals will not be permitted.
- Intensity-modulated radiation therapy (IMRT) will not be permitted.

5) Dose distribution calculation

(1) Target reference point

The target reference point will be placed at an appropriate location in the PTV. To the extent possible, a location outside of low electron density regions such as the lung fields and airway spaces will be specified. Treatment will involve 60 Gy irradiation in PTV primary and PTV node.

(2) Target dose homogeneity

It is desirable that the dose delivered to 95% of the PTV (D95) be at least 93% of the target reference point dose. In many cases, however, it is difficult to achieve the desirable dose in the thoracic region where the electron density is inhomogeneous. Therefore, it will not be considered mandatory in the present study, and the decisions made in this regard by the radiation oncologist at the study sites will be respected.

(3) Dose distribution curve and dose calculation

In dose calculations, heterogeneity correction will be implemented using a three-dimensional radiation treatment planning device and computational algorithms equivalent or superior to the superposition or AAA algorithms. IMRT will not be permitted in this study. A dose volume histogram (DVH) will be created for the PTV, spinal cord, lungs, and heart.

6) Positioning

Based on the specified target volume, positioning will be performed using treatment planning CT, and verification films will be prepared at the same time. Positioning films will always be taken with the treatment system when treatment is started and at other times as needed. Position verification using an electronic portal imaging device (EPID) may be substituted for this.

7) Dose limits for at-risk organs–maximum dose (the dose determined by dose distribution calculation, not the prescribed dose when total dose of 60 Gy is used)

- Spinal cord: generally not to exceed 46 Gy (non-binding target).
- Spinal cord volume irradiated with ≥48 Gy is not to exceed 1 cc (mandatory target).
- Heart (overall): mean dose <40 Gy. The volume irradiated will be limited to the smallest possible.
- Lung: V5 <65% (non-binding target), V20 <35% (mandatory target). The volume irradiated will be limited to the smallest possible.
- Small intestine and duodenum: 50 Gy
- Colon: 50 Gy

8) Combined use of G-CSF and radiation

If G-CSF is administered for reasons such as leukopenia, radiation therapy will be suspended until G-CSF administration is completed and will not be administered during G-CSF administration.

3.5 Radiation and immunotherapy

Radiation therapy and immunity

A theory regarding the effectiveness of irradiation against cancer cells is that radiation damages various genes, particularly the ATM and p53 genes, thereby halting the cell cycle and causing apoptosis. Furthermore, radiation stimulates signaling involved in immune responses, such as the protein kinase C, MAPK, and NF-κB signaling pathways. This alters the nature of the cancer cells prior to apoptosis and stimulate interaction with the immune system.[10] Thus, the immune system plays important roles in the antitumor effect of radiation, the most important of these being the role of CD8 T cells stimulated by dendritic cells (DCs).[11]

Immune checkpoint inhibitors and radiation therapy

Recently, the increased therapeutic benefit resulting from the combined use of radiation and immunotherapy has drawn attention. A synergistic effect between anti-CTLA-4 antibody and radiation was previously shown in investigations in a variety of *in vivo* models. Moreover, sequential combination therapy with anti-PD-1 antibody drug and radiation in an investigation in *in vivo* models using malignant melanoma and breast cancer cell lines was reported to increase the proportion of complexes of tumor antigen and major

histocompatibility complex (MHC), increase cross-presentation* in lymph nodes, and increase T-lymphocyte infiltration into tumors.[12] Although there are no data verifying that these effects are related to direct therapeutic benefit, it is anticipated that $CD4^+$ and $CD8^+$ T cells that infiltrate into tumors support this activity by means of the MHC complex and CD 80/86 proteins and differentiate into effector $CD4^+$ and $CD8^+$ T cells, inducing more potent and sustained cancer cell elimination. In addition, radiation has been reported to augment PD-L1 expression in tumor cells.

*cross-presentation: A mechanism in which antigen-presenting cells incorporate tumor antigens and, after processing them, present them to cytotoxic T-cells together with the MHC class-I molecules.

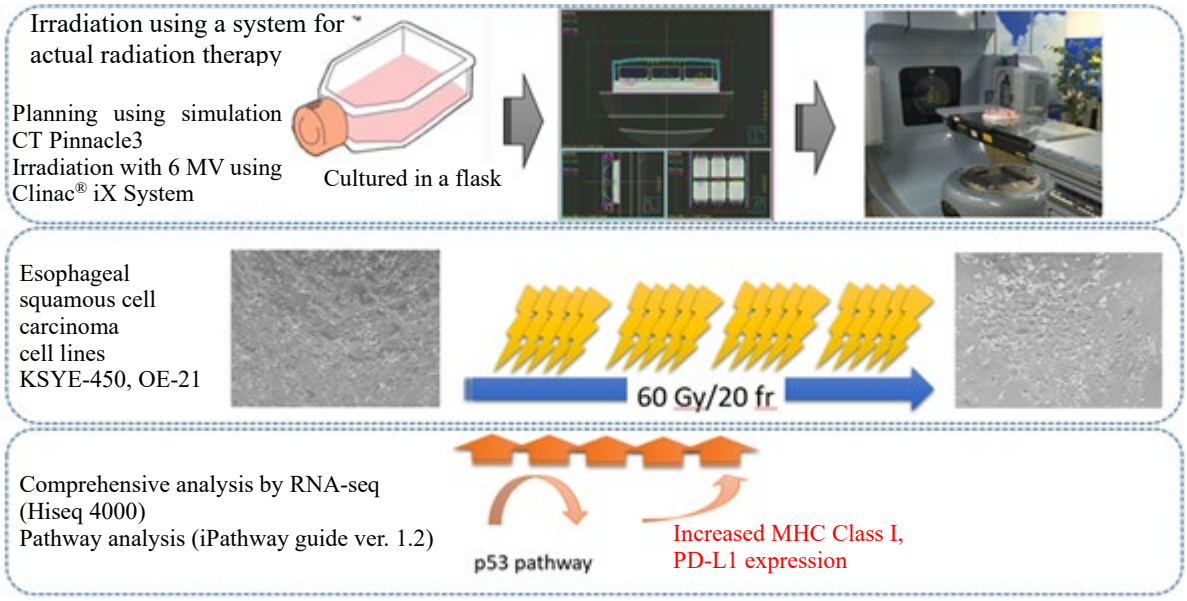
When local radiation therapy is administered to malignancies with distant metastases, not only do the tumors in the radiation field decrease in size, but an antitumor effect is seen in the tumors outside the radiation field. This phenomenon is called the abscopal effect.[15] In recent years, combination therapy with immunotherapy and radiation has been reported to increase the abscopal effect.[16] An investigation using breast and colon cancer cell lines found that simultaneous combination therapy with anti-CTLA-4 antibody and radiation reproduced this phenomenon and that IFN-γ^+ CD8 T cell frequency was involved in the abscopal effect.[17] In an *in vivo* model using malignant melanoma and renal cell carcinoma cell lines, sequential combination therapy with radiation and an anti-PD-1 antibody drug showed marked response not only of the primary lesion in the irradiation area but also of secondary tumors outside the irradiation area. Thus, the abscopal effect can also be expected with an anti-PD-1 antibody drug.[18]

The abscopal effect has also been reported to occur in actual clinical practice with simultaneously combined radiation therapy and immunotherapy for diseases such as malignant melanoma and non-small cell lung carcinoma.[19] The results of a phase I study of simultaneous combination therapy with ipilimumab or pembrolizumab and radiation designed to produce the abscopal effect were previously reported, with response rates of 10% to 13.5% seen in a variety of cancers at non-irradiated sites in organs such as the liver and lungs.[20,21] In ESMO2018, results were reported from a randomized phase II study in patients with cancer of the head and neck who had metastases. The study compared treatment efficacy in a group that received nivolumab in combination with stereotactic radiation with a group that received nivolumab alone. Although no significant difference in response rate (the primary endpoint) was seen between the combination therapy group (25.9%) and the monotherapy group (30.8%, P=0.93), further examination is needed.

Thus, a strong synergistic effect between radiation and immune checkpoint inhibitors is anticipated. At present, however, there is insufficient data that would allow examination of which target checkpoint, CTLA-4, PD-1 or PD-L1, provides the greatest efficacy and which treatment timing, simultaneous combination or sequential combination, is appropriate. To select the optimal treatment, it was considered most important to identify (1) the appropriate target molecule and (2) the appropriate timing of administration. However, in the studies involving animal experiments that have been reported, a radiation dose of approximately 10 Gy has generally been used. This is significantly different from the dose used clinically, which makes direct clinical application and determining the timing of administration difficult. To answer these questions, we analyzed gene expression in ESCCs at our institution by administering radiation at 60 Gy/30 fr to esophageal cancer cell lines using a system for actual radiation therapy (Fig. 3.5.1). Although the results showed an increase in the expression of immunity-related genes such as those for PD-L1 and MHC class I following administration of approximately 30 Gy/10 fr, no increase was seen in expression of the PD-L2 gene (unpublished data). Formulated based on these results was a clinical hypothesis that targeting mainly the PD-L1 checkpoint would result in a greater combined effect with combined administration of a immune checkpoint inhibitor for esophageal epithelial carcinoma. With regard to the

appropriate timing of administration, although the increase in PD-L1 expression occurred after irradiation with 30 Gy/10 fr, lymphocytes, which are important sites of action for immune checkpoint inhibitors, are extremely vulnerable to radiation, with a tolerance dose of approximately 2 Gy. It was therefore thought that lymphocytes and immunocompetent cells in tumor tissue and lymph node regions would incur severe damage during irradiation with approximately 30 Gy/10 fr. Consequently, it was concluded that the greatest response would be obtained by administering the drug approximately 1 week after irradiation is completed and the lymphocytes have recovered. Thus, based on the basic research conducted at our institution, the previously published reports and clinical hypothesis, it was surmised that sequential combination therapy targeting PD-L1 with the combination of radiation and an immune checkpoint inhibitor for ESCC (following radiation therapy) would likely provide the greatest response.

Figure 3.5.1 Clinical irradiation of cell lines



Efficacy and safety of sequential administration of an anti-PD-L1 antibody drug for unresectable, locally advanced non-small-cell lung cancer

Efficacy after administration of an immune checkpoint inhibitor following CRT in unresectable, locally advanced non-small-cell lung cancer (NSCLC) was previously verified in a phase III study (PACIFIC trial). In this study, patients with unresectable, locally advanced NSCLC who exhibited no progressive disease (PD) after receiving CRT with a platinum anticancer agent were randomly assigned at a ratio of 2:1 to a group that received durvalumab, an anti-PD-L1 antibody, from Day 1 to Day 42 after CRT (12 months) and a placebo group (12 months). Median PFS, the primary endpoint, was 16.8 months in the durvalumab group and 5.6 months in the placebo group. The stratified hazard ratio was 0.52 [95% confidence interval (CI): 0.42-0.65, P<0.0001]. Thus, PFS was significantly longer in the durvalumab group. In addition, the time to distant metastasis, rate of distant metastasis, and rate of brain metastasis were lower in the durvalumab group, indicating that the anti-PD-L1 antibody drug contributed not only to local control but also to distant metastasis control. The response rate was 28.4% in the durvalumab group and 16.0% in the placebo group, the rate in the durvalumab group being significantly higher (P<0.001).[20] In addition, in May 2018, OS was reported to be significantly longer in the durvalumab group.

The reported incidence of all adverse events was 96.8% in the durvalumab group and 94.9% in the placebo

group. The incidence of Grade 3/4 adverse events was 29.9% in the durvalumab group and 26.1% in the placebo group. Among these events, the incidence of Grade 3/4 pneumonitis was 4.4% in the durvalumab group and 3.8% in the placebo group. The proportion of patients for whom the treatment was discontinued due to adverse events was 15.4% in the durvalumab group and 9.8% in the placebo group. The incidence of serious adverse events was 28.6% in the durvalumab group and 22.6% in the placebo group. There was no clear trend toward an increase in adverse events, including lung-related adverse events, in the durvalumab group, indicating that sequential administration of an anti-PD-L1 antibody drug following thoracic CRT is safe and effective.

3.6 Rationale for concluding that an anti-PD-L1 antibody is likely to be efficacious in ESCC

Development status of immune checkpoint inhibitors for ESCC

As immune checkpoint inhibitors for ESCC, both pembrolizumab and nivolumab are currently undergoing therapeutic development for unresectable and/or recurrent esophageal cancer.

The results of the KEYNOTE-028 study were previously reported in the therapeutic development of pembrolizumab for esophageal cancer. The study enrolled 23 patients with PD-L1-positive esophageal cancer (17 patients with squamous cell carcinoma, 5 with adenocarcinoma, 1 with mucoepidermoid carcinoma). The results were promising: the overall response rate was 30% (29.4% in squamous cell carcinoma, 40.0% in adenocarcinoma), and the median response duration was 15 months.[23] In light of these results, two studies are currently being conducted: a single-arm, phase II study of the efficacy of pembrolizumab monotherapy as third-line therapy (KEYNOTE-180 study) and an open-label, randomized, phase III comparative study in which patients are assigned at a ratio of 1:1 to receive pembrolizumab monotherapy or a standard therapy selected by the investigator (a taxane or irinotecan, etc.) as second-line therapy (KEYNOTE-181 study). Enrollment in these studies has been completed, and follow-up and an analysis of the results are underway.

In Japan, a phase II study of nivolumab in ESCC and adenocarcinoma for which standard treatment had been completed (ONO-4538-07 study) was conducted. Sixty-five patients with squamous cell carcinoma were enrolled. The response rate was 17%, median PFS was 1.5 months, and median OS was 10.8 months.[24] In an open-label, randomized phase III comparative study (ONO-4538-24) in mainly Japanese patients, the patients are assigned at a 1:1 ratio to receive nivolumab alone and a taxane drug (docetaxel, paclitaxel) as second-line therapy. Enrollment has been completed, and follow-up and an analysis of the results are underway.

As is described above, therapeutic development targeting immune checkpoints consists entirely of studies in unresectable and/or recurrent esophageal cancer. There has been no therapeutic development like the present study of an immune checkpoint inhibitor as sequential therapy in unresectable, locally advanced esophageal cancer following curative CRT.

PD-L1 expression in esophageal cancer

In an immunostaining investigation of 286 surgical specimens of ESCCs at National Cancer Center Hospital East, 67 specimens (23.4%) were positive for PD-L1 expression ≥1%; using E1L3N antibody, Cell Signaling Technology).[23] In the esophageal cancer part of a phase I study in various unresectable and/or recurrent cancers for which there are no effective treatment options (KEYNOTE-028), 37 of the 83 patients (44.6%) tested positive for PD-L1 expression (≥1%; using 22C3 antibody, DAKO).[25] In a Kumamoto University investigation of PD-L1 expression (using E1L3N antibody, Cell Signaling Technology) in esophageal cancer (279 patients with squamous cell carcinoma, 15 with adenocarcinoma, 11 with other types), a trend toward an increase in the proportion of PD-L1-positive patients with progression of the pathological stage was seen, with positivity for PD-L1 seen in 11 of 123 Stage I patients (8.9%), 16 of 80

Stage II patients (20.0%), and 26 of 102 Stage III patients (25.5%). This suggests that the proportion of PD-L1 expression may increase with progression of the stage of esophageal cancer.[26]

Relationship between immune checkpoint inhibitor efficacy and PD-L1 expression

A phase II study (ONO-4538-07) examined the efficacy of the PD-1 antibody drug nivolumab in unresectable, recurrent esophageal cancer. Sixty-five patients with squamous cell carcinoma were enrolled, regardless of PD-L1 expression status. The overall CR rate was only 17.2%. However, an analysis according to the percentage of PD-L1-positive cells (≥1%/<1%, ≥5%/<5%, ≥10%/<10%; using 28-8 antibody, DAKO) showed a trend toward an increase in the CR rate for nivolumab in PD-L1-positive patients, with the CR rate of 23.8% (5 of 21 patients) for the percentage of PD-L1-positive cells of ≥1%, 38.5% (5 of 13 patients) for ≥5%, and 33.3% (3 of 9 patients) for ≥10%.[27]

In the previously mentioned PACIFIC study, an analysis of PD-L1 expression (using SP263 antibody, Ventana) and treatment efficacy was performed using specimens collected before CRT. The percentage of tumor-cell (TC) PD-L1 expression of <25% (TC <25%), ≥25% (TC ≥25%), and no specimen/not analyzable (unknown) specimen were 39.3%, 24.2%, and 36.6%, respectively, in the durvalumab group. The hazard ratio for PFS was 0.59 with TC <25% and 0.41 with TC ≥25%. Thus, although the results were more favorable with TC ≥25% than in the placebo group, strong treatment efficacy was seen regardless of PD-L1 expression.[28]

There are no efficacy data for the PD-L1 antibody drug atezolizumab in esophageal cancer. However, the open-label phase III OAK study examined the efficacy of atezolizumab versus docetaxel monotherapy in the second-line and subsequent treatment of NSCLC. The results showed that in the high PD-L1 expression groups with TC3 [expression in ≥50% of tumor cells (TCs)] or IC3 [expression in ≥10% of tumor-infiltrating immune cells (ICs)], the median survival time was 20.5 months in the atezolizumab group and 8.9 months in the docetaxel group (hazard ratio: 0.41; 95% CI: 0.27-0.64). Thus, the greatest treatment benefit tended to be seen in the atezolizumab group.[29]

Change in PD-L1 expression following CRT

Analyses of rectal cancer biopsy and surgical specimens showed an increase in the percentage of PD-L1-positive cells after CRT.[30,31] Moreover, as was mentioned previously, a basic investigation in which an ESCC cell line was irradiated with 60 Gy/30 fr using a system for actual radiation therapy was conducted at National Cancer Center Hospital East. Increased expression of immunity-related genes such as PD-L1 and MHC class I was seen with approximately 30 Gy/10 fr, but no increase in PD-L2 expression was seen. These findings suggested that increased PD-L1 expression would also be seen with radiation therapy in ESCC and that with combined administration of an immune checkpoint inhibitor for ESCC, a high level of combined efficacy may be possible with a drug that targets mainly PD-L1.

Summary

Although there are no data on PD-L1-positive rates in unresectable, locally advanced ESCC, the following can be concluded based on discussion thus far: The percentage of the PD-L1 expression increases with progression of the stage of or disease in esophageal cancer; the antitumor effect of atezolizumab also increases in parallel with the PD-L1-positive rate in patients with esophageal cancer; and the PD-L1 positivity rate increases after CRT in these patients, and, as in patients with non-small-cell lung cancer, a higher antitumor effect can be expected in patients with esophageal cancer when atezolizumab is administered sequentially after CRT.

In many clinical studies, including the present one, the evaluation of PD-L1 expression is often performed using specimens collected before CRT, when sufficient specimens can be collected. However, because

changes in PD-L1 expression can be expected after CRT, it is difficult to predict treatment efficacy based on PD-L1 expression in biopsy specimens collected before CRT. Moreover, in the PACIFIC study, improvement in PFS was seen regardless of PD-L1 expression. Therefore, the plan for the present study calls for patients to be enrolled regardless of pre-CRT PD-L1 expression. However, as additional research in the present study, the relationship between PD-L1 expression and the antitumor effect of atezolizumab will be analyzed using pre-CRT biopsy specimens.

4 Rationale for Study Plan

4.1 Atezolizumab

4.1.1 Atezolizumab overview

Tecentriq® (atezolizumab) is a humanized immunoglobulin (IgG1) monoclonal antibody produced using Chinese hamster ovary (CHO) cells. Atezolizumab targets PD-L1 expressed on ICs or TCs and inhibits its interaction with the PD-1 receptor and B7.1 (CD80), which are expressed on T-cells and other immune cells and function as inhibitory receptors. Inhibiting interaction between PD-L1 and PD-1 and PD-L1 and B7.1 in this way may improve the strength and nature of the tumor-specific T-cell response by enhancing the initial sensitization, proliferation, and effector function of T cells.

Atezolizumab is an antibody that has been modified to inhibit Fc-region effector function by means of a single amino acid residue substitution at position 298 on the heavy chain. This amino acid residue substitution results in no glycosylation of the heavy chain and minimal binding to Fc receptors. Consequently, Fc-region effector function is reduced to undetectable levels. As a result of the reduction in Fc effector function and avoidance of antibody-dependent cellular cytotoxicity, activated effector T cells are not depleted in an antibody-dependent fashion.

PD-L1 is expressed at a high frequency in many human tumor cells,[32] and a relationship has been seen between PD-L1 overexpression and poor prognosis in certain cancers.[31-34] Inhibition of the PD-L1/PD-1 pathway is therefore an appealing method of reactivating tumor-specific T-cell immunity.

4.1.2 Non-clinical safety pharmacology and toxicity

Non-clinical pharmacology

Atezolizumab exhibits strong subnanomolar binding affinity for recombinant human and mouse PD-L1, and it exhibits similar binding affinity for PD-L1 on cynomolgus monkey (Macaca fascicularis) T cells.

In animal models, PD-L1 inhibition induced complete regression in a colorectal cancer MC38 cell line whose immunogenicity had been increased and resulted in an overall response rate of up to 60% in mice transplanted with an MC38 cell line without increased immunogenicity. Tumor growth inhibition was in the range of 76% to 19%. In a study that evaluated the effects of concomitant PD-L1 inhibitor and MEK inhibitor use, no antitumor effect was seen with each drug alone, while an antitumor effect was seen in 30% of animals administered atezolizumab and the MEK inhibitor cobimetinib. Therefore, PD-L1 inhibition, whether through administration of a PD-L1 inhibitor alone or in combination with another agent, appears to be a highly appropriate strategy for strengthening the antitumor T-cell response in the treatment of solid tumors.

Toxicity and safety pharmacology

The following toxicity studies were conducted: an exploratory 2-week repeated-dose study (including a 4-week washout period) in mice that was not Good Laboratory Practice (GLP)-compliant; a GLP-compliant 8- and 26-week repeated-dose study (including 12- and 13-week washout periods; safety pharmacology evaluated) in cynomolgus monkeys; an *in vitro* cytokine release study (non-GLP-compliant); an *in vitro* hemolysis and hemocompatibility study (GLP-compliant); and a tissue crossreactivity study using human and cynomolgus monkey tissues (GLP-compliant).

When atezolizumab in solid or liquid form was cultured *in vitro* with peripheral blood mononuclear cells (PBMCs), the atezolizumab did not induce cytokine release from the PBMCs. Favorable tolerability was seen when atezolizumab was administered once weekly for 2 weeks (total of 3 administrations) to C57BL/6 and CD-1 mice at doses of up to 50 mg/kg. In C57BL/6 mice administered doses of ≥10 mg/kg, histopathological findings for the sciatic nerve showed the presence of minor nerve lesions. The finding of minor nerve lesions

was consistent with the observation that while autoimmune inflammation occurred spontaneously in multiple tissues including the peripheral nerves in 20- to 25-week-old female NOD-H2b/bPdcd1-/-mice (PD-1 deleted), no such lesions were seen in mice of the same age that expressed PD-1.[35] Therefore, the lesions were attributed to PD-L1 inhibition by atezolizumab. No changes in general signs were seen in association with this finding. In CD-1 mice, no atezolizumab-related histopathological findings were observed.

Favorable tolerability also was seen in cynomolgus monkeys when atezolizumab was administered at doses of up to 50 mg/kg for 26 weeks. No atezolizumab-related changes have been seen in safety pharmacology parameters for the central nervous system (standard neurobehavioral assessment panel), cardiovascular system [electrocardiogram (ECG), blood pressure, heart rate], or respiratory system (respiratory rate, pulse oximetry). Although arteritis or periarteritis assumed to be related to atezolizumab was seen in a variety of tissues, this is consistent with PD-L1 inhibition, the pharmacological action of atezolizumab, and breaking of peripheral immune tolerance. A reversible effect on the menstrual cycle (irregular menstrual cycle pattern) related to atezolizumab occurred during the treatment period of the 26-week dosing study in all females in the 50 mg/kg group. The estimated area under the concentration-time curve (AUC) in this case corresponded to approximately 6-fold greater than that seen with administration of the dose recommended for patients. As a whole, the risks identified in nonclinical studies of atezolizumab were consistent with the pharmacological action of inhibiting the PD-L1/PD-1 pathway.

Clinical pharmacokinetics

With a dose range of 1 to 20 mg/kg (including a fixed dose of 1200 mg) administered once every 3 weeks, the atezolizumab exposure level increased in proportion to dose. The results of a population pharmacokinetics (popPK) analysis of 472 patients administered doses of 1 to 20 mg/kg (PCD4989g, JO28944 studies) showed clearance (CL) of 0.20 L/day, steady-state volume of distribution (Vss) of 6.9 L, and a terminal-phase half-life ($t_{1/2}$) of 27 days for the population. The popPK analysis suggested that steady state was reached after repeated administration for 6 to 9 weeks (2 to 3 cycles). In an examination of systemic accumulation, AUC, the maximum serum concentration (Cmax), and the trough concentration (Cmin) were 1.91-fold, 1.46-fold, and 2.75-fold, respectively. An analysis of data concerning the relationships between exposure and safety and between exposure and efficacy showed no clinically significant effects of the following factors: age (21 to 89 years), body weight, sex, positive ADA, albumin level, tumor load, region/ethnicity, renal impairment, mild hepatic disorder, PD-L1 expression level, and ECOG performance status (PS).

The effects of moderate to severe hepatic disorder [bilirubin > upper limit of normal (ULN) and AST > ULN; or bilirubin ≥ (1.0 to 1.5) × ULN and AST increased regardless of level] on atezolizumab pharmacokinetics are unknown.

No formal pharmacokinetic or drug interaction studies of atezolizumab have been conducted. The likelihood of drug interactions with atezolizumab is unknown.

4.1.3 Clinical efficacy and safety

Clinical efficacy

Both preliminary and more long-term efficacy and safety data available as of October 2017 suggest that atezolizumab administered alone or in combination with other therapies provides antitumor activity in patients with hematopoietic neoplasms and various other carcinomas (including infantile tumors), patients who have received a variety of prior therapies, and the different PD-L1 expression subgroups.

Clinical efficacy studies of monotherapy and combination therapy are currently being conducted in multiple cancers, and the latest investigator's brochure for atezolizumab is also available as a reference.

Monotherapy

- In patients receiving second- and third-line therapy for NSCLC, atezolizumab provided a clinically significant increase in OS as compared with docetaxel in an intention-to-treat (ITT) cohort and all PD-L1 expression subgroups.
- In patients with metastatic urothelial cancer in whom first-line CDDP therapy was unsuitable and responsive patients with metastatic urothelial cancer receiving second-line and subsequent therapy, the CR rate was high, and efficacy persisted longer than with conventional chemotherapy.
- In patients with metastatic triple-negative breast cancer, promising clinical outcomes were seen following atezolizumab administration, particularly in a group with PD-L1 IC2/3 expression and patients receiving first-line therapy.

Combination therapy

- Combination therapy with atezolizumab + bevacizumab showed clinical benefit (as compared with sunitinib monotherapy) with respect to ORR and PFS in IC1/2/3 patients with renal cell carcinoma receiving first-line therapy. The combination also showed clinical benefit with respect to ORR in patients with colon cancer receiving second-line and subsequent therapy.
- Combination therapy with atezolizumab + cobimetinib + vemurafenib resulted in an ORR of 45% to 65.8% in patients with metastatic melanoma receiving first-line or subsequent therapy.
- Data obtained at the end of an atezolizumab + obinutuzumab run-in period in patients with recurrent/refractory follicular lymphoma showed a response rate of 56.5% based on the Lugano criteria.

Non-small cell lung carcinoma: atezolizumab as monotherapy

Through October 2017, 1651 patients with locally advanced or metastatic NSCLC comprising all PD-L1 expression subgroups had received atezolizumab alone in 5 studies [OAK, POPLAR, BIRCH, FIR, PCD4989g (NSCLC cohort)]. Most of these patients had previously undergone chemotherapy (second-line and subsequent therapy), but patients undergoing first-line therapy also were enrolled in all of the single-group studies. Overall, the therapeutic benefit of atezolizumab was consistent across the 5 studies, and the results were as follows:

- In comparison with docetaxel, atezolizumab alone resulted in a clinically significant increase in OS in the ITT cohort (OAK, POPLAR only), regardless of histological type (non-squamous, squamous), in all PD-L1 expression subgroups of an NSCLC ITT cohort receiving second- or third-line therapy.
- In patients with a high level of PD-L1 expression in TCs or ICs, the ORR was high, and median PFS was long.
- In all of the PD-L1 expression groups, efficacy was sustained over a long period.

The open-label, randomized phase III OAK study, which enrolled 1,225 patients, was a confirmatory study of maintenance and subsequent therapy with atezolizumab in NSCLC. The study subjects were patients with locally advanced or metastatic NSCLC in whom chemotherapy with a platinum-containing drug was ineffective. The study compared the efficacy and safety of atezolizumab (1200 mg i.v. once every 3 weeks) with those of docetaxel (75 mg/m^2 once every 3 weeks). The primary analysis was performed when 569 deaths had occurred (clinical cutoff date: July 7, 2016), based on data for the first 850 subjects randomized (425 subjects in each group).

As compared with docetaxel, atezolizumab showed statistically and clinically significant increases in OS in the ITT cohort and TC 1/2/3 and IC 1/2/3 PD-L1 expression subgroups, which was the primary endpoint in this study. The stratified hazard ratio for the ITT cohort (N=850) was 0.73 (95% CI: 0.62-0.87, *P*=0.0003).

Median OS was 13.8 months (95% CI: 11.8-15.7) in the atezolizumab group, and 9.6 months (95% CI: 8.6-11.2) in the docetaxel group. An important point in the OAK study was that a clear benefit was obtained even in subjects with the lowest levels of tumor PD-L1 expression (TC0 and IC0).

Clinically significant treatment efficacy was seen in all PD-L1 expression subgroups, with more striking improvement seen in subjects with the highest levels of expression (TC3 or IC3). An increase in survival time as a result of atezolizumab administration was seen in subjects with non-squamous and squamous histological types, subjects with brain metastases at baseline, and most of the clinically significant subgroups, including subjects with a history of smoking. Patients positive for epidermal growth factor receptor (EGFR) mutation did not show increased OS with atezolizumab administration as compared with docetaxel. In the ITT cohort of the OAK study, no significant difference in PFS or ORR was seen between the treatment groups. However, in the the TC3 and IC3 subgroups, the atezolizumab group showed obviously greater improvements in PFS and ORR. In the ITT cohort, a sustained response was seen in the atezolizumab group: the median duration of response (DOR) in this group was markedly greater than that seen with docetaxel.

The OAK study results related to survival were consistent with those of the POPLAR study, a phase II study of the same design as the OAK study in patients with NSCLC receiving second/third-line therapy. In the POPLAR study, atezolizumab showed an OS-prolonging effect in the ITT cohort that surpassed that of docetaxel. The stratified hazard ratio was 0.69 (95% CI: 0.52-0.92), and median OS was 12.6 months (docetaxel group, 9.7 months). On the other hand, because the improvements in PFS and ORR were seen mainly in subjects with high levels of PD-L1 expression, the PFS and ORR results may have reflected the treatment effect of atezolizumab.

Taken together, the results of the OAK and POPLAR studies showed a significant increase in OS even in subjects with low or no PD-L1 expression, suggesting potent treatment efficacy in the total population without limitation by the PD-L1 expression status.

The BIRCH study was a single-group phase II study that evaluated administration of atezolizumab alone (1200 mg i.v. once every 3 weeks) in patients with NSCLC who were selected based on PD-L1 expression (TC2/3 or IC2/3). The subjects were enrolled according to treatment line: Cohort 1 for first-line therapy, Cohort 2 for second-line therapy, and Cohort 3 for third-line and subsequent therapy (3L+). Only Cohort 1 is discussed here.

With the clinical cutoff date updated to August 1, 2016, the median survival follow-up period for subjects undergoing first-line therapy (Cohort 1) was 22.5 months (range: 0.1 to 28.7 months). The ORR assessed by the investigator according to the RECIST guideline version 1.1 improved from 22.3% at the time of the primary analysis to 25.4%. There were 4 newly added responsive patients (CR: 3 patients; PR: 1 patient). With this update, median OS increased from 14.0 months at the time of the primary analysis to 23.5 months, and the proportion of subjects with events was 47.1%.

Metastatic urothelial carcinoma: atezolizumab as monotherapy

The efficacy data available as of October 2017 were data for 524 patients with metastatic urothelial cancer who received atezolizumab monotherapy as first-line or subsequent therapy in 2 single-group studies, the phase Ia PCD4989g study and the phase II IMvigor210 study. Overall, clinical benefit was obtained with respect to the ORR, sustained response, and OS in patients with metastatic urothelial cancer in all of the treatment lines in which atezolizumab was administered.

The IMvigor210 study is a single-group phase II study to evaluate the administration of atezolizumab alone (1200 mg i.v. once every 3 weeks) in the treatment of patients with metastatic urothelial cancer. Subjects were enrolled in 2 cohorts.

Enrolled in Cohort 1 were patients with no history of treatment for metastasis (first-line therapy) in whom CDDP was unsuitable [defined as patients with renal dysfunction (GFR >30 mL/min, <60 mL/min), hearing loss of 25 dB, peripheral neuropathy ≥Grade 2, or ECOG PS of 2]. Patients with a treatment interval of more than 12 months since receiving neoadjuvant or adjuvant chemotherapy or CRT also were eligible for Cohort 1. Atezolizumab administration to patients in Cohort 1 was stopped when obvious PD was first seen in imaging findings based on RECIST version 1.1.

Enrolled in Cohort 2 were patients in whom PD was seen after they underwent at least 1 regimen of chemotherapy with a platinum-containing drug (second-line and subsequent therapy). Patients in whom PD was seen within 12 months after starting neoadjuvant or adjuvant chemotherapy with a platinum-containing drug also were considered patients receiving second-line and subsequent therapy. For patients in Cohort 2, continuation of atezolizumab was also permitted after PD was seen in imaging findings, until the investigator assessed that there was no longer any clinical benefit.

Cohort 1

The clinical cutoff date for the primary analysis of Cohort 1 was September 14, 2015. An update of the clinical cutoff date to July 4, 2016 resulted in an increase in the follow-up period of approximately 10 months from the time of the primary analysis. The shortest follow-up period at the time of the update was 15 months (for the final patient), and the median survival follow-up period was 17.2 months. The ORR for the total population (no limitations on subjects) determined by an independent review facility (IRF) in accordance with RECIST guideline version 1.1 was 22.7%, which was comparable to the 19.3% seen in the primary analysis. Another 4 patients were added to the responsive patients at the time of the update, resulting in a total of 11 CR patients and 16 PR patients.

Even with addition of 10 months to the follow-up period, the response was sustained as previously. At the time of the update, events had occurred in 29.6% of responsive patients (4.3% in primary analysis) in the total population (no limitations on subjects). However, the median DOR assessed by the IRF in accordance with RECIST guideline version 1.1 was not evaluable (NE).

Median OS in the total population (no limitations on subjects) increased from 10.6 to 15.9 months (95% CI: 10.4-NE), and the proportion of subjects with events was 49.6%. The 12-months OS rate was 57.2% (95% CI: 48.2-66.3).

Cohort 2

The clinical cutoff date for the primary analysis of Cohort 2 was May 5, 2105. The update of the clinical cutoff date to July 4, 2016 (N=310) resulted in an increase in the follow-up period of 14 months from the time of the primary analysis. The shortest follow-up period at the time of the update was 20.0 months (for the final patient), and the median survival follow-up period was 21.1 months.

The ORR for the total population (no limitations on subjects) determined by the IRF in accordance with RECIST guideline version 1.1 was 15.8%, which was consistent with the 15.1% seen in the primary analysis. The total number of responsive patients in the total population with no limitations on subjects was 49 (47 in the primary analysis), in whom CR was seen in 19 patients and PR in 30 patients. The ORR at the time of the update was 28.0% in the IC2/3 subgroup and 10.0% in the IC0/1 subgroup, again suggesting a high ORR in patients with high levels of PD-L1 expression.

In subjects who showed PD within 12 months after the start of neoadjuvant or adjuvant chemotherapy with a platinum-containing drug, which was a subset of the total population (no limitations on subjects), the ORR improved from 20.0% to 25.9% (95% CI: 15.0-39.7, 14 of 54 subjects) in the analysis performed at the time of the update.

The proportion of subjects who had events at the time of the update was 72.9%, and median OS for the total population (no limitations on subjects) was 7.9 months, the same as at the time of the primary analysis. The 12-month OS rate for the total population (no limitations on subjects) was 36.9% (95% CI: 31.42-42.33). OS was 11.9 months (95% CI: 9.0-NE) in the IC2/3 subgroup and 6.7 months (95% CI: 5.4-8.0) in the IC0/1 subgroup. These results also suggested that the level of PD-L1 expression in ICs is correlated with the median OS.

The follow-up period increased by 14 months from the time of the primary analysis. As a result, the number of responsive patients in the total population (no limitations on subjects) with PFS events increased from 8.5% to 34.7%. However, the median DOR was not evaluable (NE) (95% CI: 16.0-NE) as before.

Clinical safety

A total of more than 16,000 patients with solid cancers or hematopoietic neoplasms participated in clinical studies and were administered atezolizumab alone or in combination with cytotoxic chemotherapy and/or a molecular targeted therapy.

Safety findings obtained with administration of atezolizumab alone in patients with various neoplasms in the clinical development program were consistent with the atezolizumab mechanism of action and underlying disease symptoms that have been identified. Atezolizumab tolerability was generally favorable, and the adverse events profile was manageable. The maximum tolerated dose has not yet been determined, and no dose-limiting toxicity (DLT) or clear tendency for the incidence of adverse events to be dose-dependent has been seen. The following were particularly common adverse events (occurred in ≥10% of patients) in the 3,075 subjects who were administered atezolizumab alone and for whom integrated safety data are available: fatigue, decreased appetite, cough, nausea, dyspnea, constipation, diarrhea, fever, vomiting, arthralgia, back pain, asthenia, anemia, pruritus, rash, headache, and peripheral edema.

The adverse events observed with atezolizumab in combination with chemotherapy and/or molecular targeted therapy were consistent with the expected risks of the treatment in each study. A potential risk associated with atezolizumab in combination with other immunomodulatory agents is a systemic overreaction of the immune system characterized by an excessive immune response.

The atezolizumab-related adverse events that occurred were similar in patients administered atezolizumab alone or in combination with a molecular targeted therapy and/or chemotherapy. No atezolizumab-related adverse events were seen that worsened when atezolizumab was administered in combination with those other drugs.

The immune-related adverse events were consistent with the role that the PD-L1/PD-1 pathway plays in the regulation of peripheral immune tolerance. In the clinical development program for atezolizumab, inflammation-related and immune-mediated adverse events were carefully monitored in view of atezolizumab's mechanism of action. The following immune-related adverse events were reported as being related to atezolizumab when the investigator's brochure was updated (version 15): pneumonitis, hepatitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barre syndrome, myasthenic syndrome/myasthenia gravis, meningoencephalitis, myocarditis, nephritis, and myositis.

Clinical safety studies of monotherapy and combination therapy are currently being conducted in multiple cancers, and the latest investigator's brochure for atezolizumab is also available as a reference.

4.2 Study design

This is an open-label, single-arm, multicenter phase II clinical study to examine the clinical efficacy and safety of monotherapy with atezolizumab, an anti-PD-LI antibody drug, as sequential therapy following curative CRT with 5-FU and CDDP in patients with primary unresectable, locally advanced ESCC and

patients with postoperative locoregionally recurrent.

If promising therapeutic outcomes are seen in unresectable, locally advanced ESCC in this study, an application for partial change of approval items to add this indication will be considered.

4.3 Establishment of endpoints

The endpoints in this study will be as follows.

Primary endpoint:

- The complete response (CR) rate confirmed by the investigator's assessment.

Secondary endpoints:

- The CR rate confirmed by central assessment[1)]
- PFS[2)]
- ORR based on the RECIST guideline version 1.1
- OS[2)]
- Failure pattern[2)]
- Incidence of adverse events determined using CTCAE version 4.0.

1) Central assessments will be performed for primary locally advanced patients if promising results are obtained for the CR rate confirmed by the investigator's assessment in this study.
2) PFS, OS, and failure pattern will be followed for 5 years after the completion of this study through additional clinical studies associated with this study, and the data for these endpoints will be determined.

Additional studies:

- Observational study of the status of chemoradiotherapy administration and long-term prognosis in unresectable, locally advanced ESCC (TENERGY study–observational research)
- Biomarker exploratory study associated with the investigator-initiated, multicenter phase II clinical study examining the safety and efficacy of atezolizumab monotherapy as sequential therapy following chemoradiotherapy for unresectable, locally advanced ESCC (TENERGY study–TR research)
- Investigation of QC and QA in radiation therapy

<u>Rationale for primary endpoint</u>

In view of the points listed below, the CR rate determined from the assessment of the principal investigator or subinvestigator for primary locally advanced patients who started protocol therapy was established as the primary endpoint for this study. In addition, as a secondary endpoint, the CR rate will be evaluated centrally to confirm the robustness of the assessment of the principal investigator or subinvestigator.

1) In a retrospective investigation in 139 patients with esophageal cancer who underwent curative CRT (5-FU + CDDP + RT combination therapy) at National Cancer Center East Hospital, the primary lesions were evaluated endoscopically as in the present study. The results showed that the 3- and 5-year survival rates over a median observation period of 53 months were 55% and 46%, respectively, with primary lesion CR and 11% and 6%, respectively, with primary lesion non-CR.[36] These findings indicate that achieving CR after CRT is clearly associated with long-term prognosis and that the CR rate is therefore a surrogate endpoint for long-term prognosis.
2) To obtain an indication for atezolizumab monotherapy following curative CRT in patients with unresectable, locally advanced ESCC, a phase III comparative study with overall survival as the primary endpoint was concluded to be necessary. As was indicated in point 1) above, it was concluded that the

CR rate would be the most useful endpoint for assessing OS at an earlier stage when atezolizumab monotherapy is administered to the population of this study.

3) Many previous single-arm phase II studies that examined the efficacy of chemoradiotherapy in esophageal cancer used a CR rate based on the physician's assessments as the primary endpoint rather than a CR rate based on central assessments.[9,37,38] Moreover, the actual protocol treatment and examinations will be carried out based on the CR assessments of the investigator (assessments based on CT or endoscopic assessments by the investigator). In the central assessments, therefore, cases in which a response is not evaluable (NE) due to the inappropriate timing of a CT or endoscopic evaluation may occur.

4.4 Clinical hypothesis and rationale for planned sample size

1) Clinical hypothesis

The clinical hypothesis is that monotherapy with the anti-PD-L1 antibody drug atezolizumab will result in a superior response rate when administered as sequential therapy in patients with unresectable, locally advanced ESCC who have undergone curative CRT with 5-FU and CDDP. If a CR is obtained in at least 13 of the 38 patients in the FAS, it will be concluded that the clinical usefulness of the therapy is confirmed.

2) Rationale for response rate threshold and expected value

Table 4.4-1 Therapeutic outcomes for chemoradiotherapy in unresectable, locally advanced ESCC (reproduction of Table 3.2.1)

	N	CR Rate	PFS (m)	MST (m)	Reference
Ishida et al	45	11%	NR	215 days	(3)
JCOG9516	60	15%	NR	10	(4)
Ohtsu et al	44	33.3% [25% (T4)]	6	9	(5)
JCOG0303 SD-CF+RT*	68	0%**	NR	13.1	(6)
JCOG0303 LD-CF+RT*	71	1.4%**	NR	14.4	(6)

*SD: standard dose, **LD: low dose

**: The CR rate in study JCOG0303 was 0% in the SD-CF + RT group and 1.4% in the LD-CF + RT group, which were lower than in other studies. Possible reasons for this include the possibility that the timing of the CR evaluation was inappropriate for some patients because of the procedure for the CR evaluation ("response of the primary lesion will be assessed endoscopically 4 to 5 weeks after treatment completion, which is the overall response assessment covering target, non-target, and new lesions") and that follow-up was inadequate because the study was terminated early due to the ineffectiveness of the treatment.

Unresectable, locally advanced ESCC is a refractory disease, with a CR rate of 0% to 25% and median overall survival time of 9 to 14 months in the primary locally advanced patients administered with conventional CRT using 5-FU and CDDP (Table 4.4.1).[4,5]

In the study by Ishida et al., 5-FU and CDDP were used in sequential combination with radiation therapy, which differs from the simultaneous combination to be used in the present study. In the JCOG0303 study, CR assessment was performed only once, which differs from the CR assessment method in the present study. Because of these differences, these studies were excluded from the threshold CR rate calculation.

The patients described in the article by Ohtsu et al., except for the T4 patients, had distant lymph node metastases in cervical or abdominal lymph nodes. In these patients, surgical resection is often performed as long as there is no invasion of other organs, which partially distinguishes these patients from those included in the current clinical studies in unresectable, locally advanced ESCC. Therefore, the threshold was specified

based not on the overall CR rate reported by Ohtsu et al. but rather on the CR rate for just the T4 patients in that study. On the other hand, some of the patients enrolled in the JCOG9516 study, in which efficacy was seen with chemoradiotherapy using 5-FU and CDDP in locally advanced ESCC, also may have had distant lymph node metastases in cervical or abdominal lymph nodes, but the CR rate for the T4 patients alone could not be determined from the article. However, in the article by Ohtsu et al., the CR rate in patients with ≤T3 and distant lymph node metastases in the cervical or abdominal lymph nodes was 50% (9 of 18 patients), which was better than the CR rate in T4 patients. In light of this, the threshold CR rate will not be underestimated in the present study, which will include patients with T4b or invasion of organs other than the esophagus by regional lymph node or supraclavicular lymph node (#104) metastases, even if it is determined based on the CR rate for all patients in the JCOG9516 study, which did not exclude the patients with ≤T3 and distant lymph node metastases, together with the results of Ohtsu et al.

Consequently, based on the CR rate of 25% for the 36 T4 patients described in the article by Ohtsu et al. and the CR rate of 15% for the 60 patients in the JCOG9516 study, a threshold CR rate of 20% was selected for the present study. Moreover, as an expected CR rate, it was concluded that if the CR rate were greater than 40%, the treatment would be considered clinically promising and further development could be expected.

With regard to the therapeutic outcome of CRT in patients with primary unresectable, locally advanced ESCC, while enrollment was performed before CRT was started, it will be performed at the completion of CRT in the present study. Patients who intend to participate in this study will enroll in the associated observational research (TENERGY study–observational research) before the start of CRT. Patients enrolled in the observational research will generally be enrolled in the present study to eliminate patient bias to the extent possible. As a reference analysis, calculating the CR rate for all patients enrolled in the observational research also will be considered.

3) Rationale for sample size

The target sample size determined using the exact method based on a binomial distribution was 38 patients. This was calculated using a threshold CR rate of 20% for the protocol treatment, an expected CR rate of 40%, a one-tailed significance level of 5%, and statistical power of 80%. Enrollment in this study will be carried until it is determined that the full analysis set (FAS) will comprise 38 subjects, and up to 40 primary locally advanced patients are planned to be enrolled. However, in order to enroll patients until an FAS of 38 subjects is confirmed, more than 40 patients may be enrolled if the FAS for primary locally advanced patients does not reach 38 subjects. If a CR is obtained in at least 13 of the 38 patients in the FAS, it will be concluded that there is value in examining the protocol treatment for further therapeutic development.

In addition, up to 10 postoperative locoregionally recurrent patients will enrolled on an exploratory basis. Therefore, the total number of patients to be enrolled in the study was specified as up to 50.

4.5 Anticipated cumulative enrollment, enrollment period, and follow-up period

All of the medical institutions participating in this study are hospitals that specialize in cancer and have treated many patients with unresectable, locally advanced ESCC. They are expected to be able to enroll approximately 50 patients in a year. Therefore, an enrollment period of 1 year was selected as the period needed to accumulate a total of up to 50 patients with primary unresectable, locally advanced ESCC or postoperative locoregionally recurrent ESCC. The follow-up period after completion of the enrollment period will be 1 year from the date the final patient is enrolled.

The follow-up period for each patient in this study will be until the patient dies, is lost to follow-up or withdraws consent, or the follow-up period or study is completed, whichever comes first.

The follow-up period to be used for the primary analysis in the study will be 1 year from the date the final

patient is enrolled, because the longest treatment duration for atezolizumab monotherapy is 1 year. However, to obtain survival outcome data for an adequate follow-up period, a 5-year follow-up investigation of outcome is planned as subsequent clinical research.

4.6 Summary of anticipated benefits and disadvantages associated with participation in the study

4.6.1 Anticipated benefits

Curative CRT with 5-FU and CDDP has been established as the standard treatment for patients with primary, unresectable, locally advanced ESCC or postoperative locoregionally recurrent ESCC.

Although the efficacy of atezolizumab monotherapy as sequential therapy following CRT has not been verified, basic experiments have suggested that sequential combination therapy with atezolizumab may increase local and distant control by increasing post-CRT PD-L1 expression. In addition, a phase III study (PACIFIC trial) compared a group that received the anti-PD-L1 antibody durvalumab (12 months) with a placebo group (12 months) in patients with unresectable, locally advanced NSCLC who had received CRT based on a platinum anticancer agent and had not exhibited PD. The patients were randomly allocated to treatment at a proportion of 2:1. For the durvalumab group, a significant increase in PFS was verified, and a significant increase in OS was reported in May 2018.

Based on these findings, further improvement in therapeutic outcome is also expected in patients with primary, unresectable, locally advanced ESCC.

4.6.2 Foreseeable risks and disadvantages

The incidence of adverse events with atezolizumab monotherapy is low as compared with the incidence with typical cytotoxic anticancer agents, and measures to address treatment-related adverse events have been established. However, there is no information on treatment-related adverse events during atezolizumab monotherapy following curative CRT, and unexpected adverse events may occur during atezolizumab monotherapy or the subsequent follow-up, posing risks and disadvantages for study participants.

When the first 10 patients in the primary locally advanced ESCC part of the study complete 2 cycles of treatment (6 weeks), the data and safety monitoring committee will be asked to evaluate the safety of atezolizumab in the patients with primary unresectable, locally advanced ESCC who underwent curative CRT, and care will be taken to minimize the risks and disadvantages for the study participants. Patients may be enrolled during the evaluation period at the discretion of the coordinating committee.

The data and safety monitoring committee will determine whether the adverse events fall within the scope of those expected. Moreover, a system has been established to ensure that the necessary measures, such as reporting the events to the committee and notifying the participating institutions, are taken when serious or unexpected adverse events occur.

4.7 Reason why the study will include only patients for whom macroscopic radical resection is judged unfeasible based on pre-CRT cervicothoracic/abdominopelvic CT

The definition of "unresectable, locally advanced" in the primary locally advanced ESCC part of this study is ESCC without distant metastasis that meets either or both of the following conditions: (1) the primary esophageal tumor has invaded an organ near the mediastinum, such as the trachea or aorta; and (2) regional lymph node or supraclavicular lymph node (#104) metastases have invaded other organs.

The JCOG is currently conducting a phase III study (JCOG1510) to verify the efficacy of conversion surgery following induction therapy with docetaxel + CDDP + 5-FU in patients ranging from those to whom (1) and/or (2) clearly apply to those for whom (1) and/or (2) cannot be ruled out. The objective of the JGOG1510 study is to improve therapeutic outcome by performing conversion surgery following induction chemotherapy in many patients.

However, in previous clinical studies in unresectable, locally advanced esophageal cancer, the subjects have been those to whom (1) and/or (2) clearly apply, for which conversion surgery is unlikely even if induction chemotherapy results in a reduction in tumor size. Similar patients have been the subjects in studies such as the JCOG0303 study, which compared low-dose CDDP + 5-FU + radiation therapy (LD-CF + RT) and standard-dose CDDP + 5-FU + radiation therapy (SD-CF + RT).

The objective of the present study is to examine the efficacy and safety of curative CRT and subsequent atezolizumab. To allow the comparability with previous clinical studies in unresectable, locally advanced esophageal cancer, the study subjects will be limited to patients to whom (1) and/or (2) clearly apply.

4.8 Rationale for atezolizumab dose regimen and treatment period

A phase I study of atezolizumab monotherapy (PCD4989 study) examined PK in patients administered atezolizumab at a dose of 0.01 to 20 mg/kg once every 3 weeks. Blood atezolizumab concentration increased in proportion to dose, and in patients administered 10 to 20 mg/kg, the Cmin geometric mean remained above the lower limit of quantification and the target serum level (6 μg/mL). Therefore, 1200 mg, which corresponds to 15 mg/kg, was selected as the dose in subsequent studies. Moreover, a dose regimen of 1200 mg i.v. once every 3 weeks was used in studies such as a phase III study in unresectable NSCLC (OAK study), a phase II study in metastatic urothelial carcinoma (IMvegor 210 study), and a phase II study in unresectable renal cell carcinoma (IMmotion 150 study), and its safety and efficacy have been established in various cancers. Based on these considerations, the atezolizumab dose regimen in this study was specified at 1200 mg i.v. once every 3 weeks.

For the reasons indicated below, an atezolizumab treatment period of up to 12 months was selected (up to 17 cycles, with the day on which investigational product administration begins considered Day 1, administration every 3 weeks, and final administration at Week 49).

In a phase III study comparing the anti-PD-1 antibody drug nivolumab with the anti-CTLA-4 antibody drug ipilimumab in patients with Stage III or IV malignant melanoma who underwent complete resection, a significant increase in relapse-free survival (RFS) with few Grade 3/4 adverse events was reported.[39] Similarly, in a phase III study in patients with Stage III malignant melanoma who underwent complete resection, a significant increase in RFS was reported with the anti-PD-1 antibody drug pembrolizumab as compared with placebo. In these 2 studies, a treatment period of 1 year was specified for nivolumab and pembrolizumab.[40] As was previously mentioned, in the PACIFIC trial, which examined the efficacy of the anti-PD-L1 antibody drug durvalumab following CRT in patients with NSCLC, the durvalumab treatment period was 12 months.

In the present study, an atezolizumab treatment period of 12 months was selected in view of the safety and efficacy seen in the 3 phase III studies described above.

4.9 Reason for conducting the study as an investigator-initiated study

ESCC is relatively common in Asia, and it is the 7th most common disease among Japanese males. However, it occurs less frequently in Europe and the United States. Unresectable, locally advanced squamous cell carcinoma, the disease that will be examined in this study, accounts for a small fraction, roughly just 7.0% to 13.1% of esophageal cancer as a whole, and it affects an estimated 1,600 to 3,000 patients annually. Consequently, it is unlikely that a pharmaceutical company would independently undertake the development of a novel therapy for unresectable, locally advanced squamous cell carcinoma.

However, with regard to atezolizumab monotherapy as sequential therapy following curative CRT, basic experiments have suggested that sequential combination therapy with atezolizumab may increase local and distant control by increasing post-CRT PD-L1 expression. For unresectable, locally advanced NSCLC, a phase III study (PACIFIC trial) was conducted. In the study, patients with unresectable, locally advanced

NSCLC who exhibited no PD after receiving CRT were randomly assigned at a ratio of 2:1 to a group that received the anti-PD-LI antibody durvalumab (12 months) and a placebo group (12 months) to compare the treatment efficacy, and a significant increase in PFS was verified in the durvalumab group. If a promising response rate is seen in the present study, an application for partial change of approval items to add this indication will be considered.

Thus, an investigator-initiated study planned by physicians well versed in neoadjuvant CRT and atezolizumab administration was concluded to be most suitable for examining the efficacy and safety of a treatment that offers the promise of efficacy for the subjects and is a complex combination of CRT and chemotherapy.

5 Criteria and Definitions to Be Used in the Study

5.1 Staging criteria

In this study, anatomical subsites and clinical classifications will be specified according to the UICC TNM Classification of Malignant Tumors, 7th edition (2009) (UICC-TNM 7th edition), and the depth of T1 lesions, definitions of T4a and T4b, and histological classifications will be specified according to the Japanese Classification of Esophageal Cancer 11th edition.

Because a comparison with other studies and an integrated analysis are envisaged after the study is completed, data for UICC TNM Classification of Malignant Tumors, 8th edition (2017) (UICC-TNM 8th edition) will also be collected at the same time. The main differences between the 7th and 8th editions for this study are staging criteria, as indicated below.

5.1.1 Location of tumor (both UICC-TNM 7th and 8th editions)

The anatomical subsites of tumors will be specified according to the UICC-TNM classifications. (Note that although these are virtually identical to those of the Japanese Classification of Esophageal Cancer, the lower thoracic esophagus in the UICC-TNM classifications corresponds to a combination of the lower thoracic esophagus and abdominal esophagus in the Japanese classification.)

Cervical esophagus (Ce): This commences at the lower border of the cricoid cartilage and ends at the thoracic inlet (suprasternal notch), approximately 18 cm from the upper incisor teeth.

Thoracic esophagus (Te):

Upper thoracic esophagus (Ut): Extending from the thoracic inlet to the level of the tracheal bifurcation, approximately 24 cm from the upper incisor teeth.

Middle thoracic esophagus (Mt): The proximal half of the esophagus between the tracheal bifurcation and the esophagogastric junction. The lower level is approximately 32 cm from the upper incisor teeth.

Lower thoracic esophagus (Lt): Approximately 8 cm in length (includes abdominal oesophagus), is the distal half of the oesophagus between the tracheal bifurcation and the esophagogastric junction. The lower level is approximately 40 cm from the upper incisor teeth.

5.1.2 TNM classification (both UICC-TNM 7th and 8th editions)

The Japanese translation used will be the Japanese version of the UICC TNM Classification of Malignant Tumors, 7th edition, published by the Japanese Joint Committee on TNM Classification.

T–Primary tumor

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ/high-grade dysplasia

T1: Tumor invades lamina propria, muscularis mucosae, or submucosa

T1a: Tumor invades lamina propria or muscularis mucosae

T1b: Tumor invades submucosa

T2: Tumor invades muscularis propria

T3: Tumor invades adventitia

T4: Tumor invades adjacent structures

T4a*: Tumor invades pleura, pericardium, diaphragm, lung, thoracic duct, azygos vein, or nerve

T4b*: Tumor invades aorta (great artery), trachea, bronchus, pulmonary artery, pulmonary vein, or vertebral body

*: T4a and T4b defined according to the Japanese Classification of Esophageal Cancer 11th edition.

N–Regional lymph nodes

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in 1 to 2 regional lymph nodes
N2: Metastasis in 3 to 6 regional lymph nodes
N3: Metastasis in 7 or more regional lymph nodes

M–Distant metastasis

M0: No distant metastasis
M1: Distant metastasis
The category M1 may be further specified according to the following notation:
pulmonary, PUL; bone marrow, MAR; osseous, OSS; pleura, PLE; hepatic, HEP; peritoneum, PER; brain, BRA; adrenals, ADR; lymph nodes, LYM; skin, SKI; others, OTH

Residual tumor (R) classification

RX: Presence of residual tumor cannot be assessed
R0: No residual tumor
R1: Microscopic residual tumor
R2: Macroscopic residual tumor

Definition of regional lymph nodes (both UICC-TNM 7th and 8th editions)

The regional lymph nodes, irrespective of the site of the primary lesion, are those in the esophageal drainage area including celiac axis nodes and paraesophageal nodes in the neck but not the supraclavicular nodes.
In this study, the regional lymph nodes in the UICC-TNM 7th and 8th editions will be defined as follows using the lymph node terms in the Japanese Classification of Esophageal Cancer. The definitions and lymph node terms below will be used in determining the stage.

Table of correspondence between regional lymph nodes of the thoracic esophagus (both UICC-TNM 7th and 8th editions) and the Japanese Classification of Esophageal Cancer (covers lymph node station numbers 101 to 114, 1 to 11, 16, 19, and 20)

Lymph node term (Japanese Classification of Esophageal Cancer 11th edition) Lymph node stations number in parentheses	Thoracic esophagus (upper, middle, lower) regional lymph nodes (both UICC-TNM 7th and 8th editions)
Cervical	
• Cervical paraesophageal lymph nodes (101)	Paraesophageal lymph nodes in the neck
• Deep cervical lymph nodes (102up, 102mid)	
• Peripharyngeal lymph nodes (103)	
• Supraclavicular lymph nodes (104)	
Thoracic	
• Upper thoracic paraesophageal lymph nodes (105)	Upper thoracic paraesophageal lymph nodes (superior to azygos vein)
• Thoracic paratracheal lymph nodes (106rec, 106pre, 106tb)	Mediastinal lymph nodes
• Subcarinal lymph nodes (107)	Subcarinal lymph nodes

• Middle thoracic paraesophageal lymph nodes (108)	Lower thoracic paraesophageal lymph nodes (inferior to azygos vein)
• Main bronchus lymph nodes (109)	Subcarinal lymph nodes
• Lower thoracic paraesophageal lymph nodes (110)	Lower thoracic paraesophageal lymph nodes (inferior to azygos vein)
• Supradiaphragmatic lymph nodes (111)	Mediastinal lymph nodes
• Posterior mediastinal lymph nodes (112aoA, 112aoP, 112pul)	
• Ligamentum arteriosum lymph nodes (113)	
• Anterior mediastinal lymph nodes (114)	
Abdominal	
• Right paracardial lymph nodes (1)	Perigastric lymph nodes excluding celiac axis lymph nodes
• Left paracardial lymph nodes (2)	
• Lesser curvature lymph nodes (3)	
• Lymph nodes along the greater curvature (4sa, 4sb, 4d)	
• Suprapyloric lymph nodes (5)	
• Infrapyloric lymph nodes (6)	
• Lymph nodes along the left gastric artery (7)	Perigastric lymph nodes excluding celiac axis lymph nodes
• Lymph nodes along the common hepatic artery (8a, 8p)	
• Lymph nodes along the celiac artery (9)	Celiac axis lymph nodes
• Lymph nodes at the splenic hilum (10)	
• Lymph nodes along the splenic artery (11p, 11d)	
• Lymph nodes around the abdominal aorta (16a1, 16a2, 16b1, 16b2)	
• Infradiaphragmatic lymph nodes (19)	Perigastric lymph nodes excluding celiac axis lymph nodes
• Lymph nodes in the esophageal hiatus of the diaphragm (20)	Mediastinal lymph nodes

Stage classification (UICC-TNM 7th edition)

Used to determine the clinical stage, surgical stage, and pathological stage.

Items pertinent to the present study are shaded.

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1, T2	N1▲	M0
IIIA	T4a*	N0	M0
	T3	N1▲	M0
	T1, T2	N2▲	M0
IIIB	T3	N2▲	M0

IIIC	T4a*	N1, N2▲	M0
	T4b*	Regardless of N▲	M0
	Regardless of T	N3▲	M0
IV	Regardless of T	Regardless of T	M1◎

T4a*: Tumor invades pleura, pericardium, diaphragm, lung, thoracic duct, azygos vein, or nerve.
T4b*: Tumor invades aorta (great artery), trachea, bronchus, pulmonary artery, pulmonary vein, or vertebral body.
*: T4a and T4b defined according to the Japanese Classification of Esophageal Cancer 11th edition.
▲: Only unresectable regional lymph node metastasis eligible
◎: Only unresectable supraclavicular lymph node (#104) metastasis eligible

Stage classification (UICC-TNM 8th edition)
Clinical stage: Used to determine the clinical stage.

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0, N1	M0
II	T2	N0, N1	M0
	T3	N0	M0
III	T1, T2	N2	M0
	T3	N1, N2	M0
IVA	T4a, T4b*	N0, N1, N2	M0
	Regardless of T	N3	M0
IVB	Regardless of T	Regardless of N	M0

T4a*: Tumor invades pleura, pericardium, diaphragm, lung, thoracic duct, azygos vein, or nerve
T4b*: Tumor invades aorta (great artery), trachea, bronchus, pulmonary artery, pulmonary vein, or vertebral body
*: T4a and T4b defined according to the Japanese Classification of Esophageal Cancer 11th edition.

5.1.3 Clinical findings (Japanese Classification of Esophageal Cancer 11th edition)

Depth of tumor invasion (T)

TX: Depth of tumor invasion cannot be assessed
T0: No evidence of primary tumor
T1a: Tumor invades mucosa
  T1a-EP: Carcinoma in situ (Tis)
  T1a-LPM: Tumor invades lamina propria mucosae
  T1a-MM: Tumor invades muscularis mucosae
T1b: Tumor invades submucosa (SM)
  T1b to SM1: Tumor invades the upper third of the submucosal layer
  T1b to SM2: Tumor invades the middle third of the submucosal layer
  T1b to SM3: Tumor invades the lower third of the submucosal layer
T2: Tumor invades muscularis propria (MP)
T3: Tumor invades adventitia (AD)
T4: Tumor invades adjacent structures (AI)
  T4a: Pleura, pericardium, diaphragm, lung, thoracic duct, azygos vein, or nerve
  T4b: Aorta (great artery), trachea, bronchus, pulmonary artery, pulmonary vein, or vertebral body

Grading of lymph node metastasis (N)

NX: Lymph node metastasis cannot be assessed
N0: No lymph node metastasis
N1: Metastasis involving only Group 1 lymph nodes
N2: Metastasis to Group 2 lymph nodes
N3: Metastasis to Group 3 lymph nodes
N4: Metastasis to distant (Group 4) lymph nodes

If the lymph node metastatic lesions invade an organ other than the esophagus, it will be treated as T4 and indicated as follows: T4 ("metastatic lymph node station number" – "organ invaded").
Example: T4b (No. 112aoA – aorta)

Distant organ metastasis (M)

MX: Distant organ metastasis cannot be assessed
M0: No distant organ metastasis
M1: Distant organ metastasis

Lymph node groups according to the location of the tumor (Japanese Classification of Esophageal Cancer 11th edition)

Thoracic esophagus	Group 1 (N1)	Group 2 (N2)	Group 3 (N3)
Upper	101, 105, 106rec	104, 106tbL, 107, 108, 109	102mid, 106pre, 106tbR, 110, 112aoA, 112pul, 1, 2, 3a, 7, 20
Middle	106rec, 108, 1, 2, 3a	101, 104, 105, 107, 109, 110, 112aoA, 112pul, 7, 9, 20	106tbL
Lower	110, 1, 2, 3a, 7, 20	101, 106rec, 107, 108, 109, 112aoA, 112pul, 9	104, 105, 106tbL, 111, 8a, 11p

5.1.4 Histological classification (Japanese Classification of Esophageal Cancer 11th edition)

Items pertinent to the present study are shaded.

I. Malignant epithelial neoplasms
1. Squamous cell carcinoma
   a. Well differentiated
   b. Moderately differentiated
   c. Poorly differentiated
2. Basaloid (-squamous) carcinoma
3. Carcinosarcoma
4. Adenocarcinoma
5. Adenosquamous carcinoma
6. Mucoepidermoid carcinoma
7. Adenoid cystic carcinoma
8. Neuroendocrine cell tumor
   a. Neuroendocrine tumor (NET) G1 or G2
   b. Neuroendocrine carcinoma (NEC)

9. Undifferentiated carcinoma
10. Others

II. Non-epithelial tumors
1. Smooth muscle tumor
2. Gastrointestinal stromal tumor (GIST)
3. Neurogenic tumor
4. Others

III. Lymphoid tumors
The definition is according to the WHO classification.

IV Other malignant tumors
1. Malignant melanoma
2. Others

5.1.5 Definition of complete response (CR) in this study

CR assessment by upper gastrointestinal endoscopy and cervicothoracic/abdominopelvic contrast CT will be used in this study to evaluate curative CRT and protocol therapy, with the results of tests performed within 28 days before the start of curative CRT used as the baseline.

CR will be assessed as having occurred when both of the following conditions have been met (must be determined after an interval of at least 4 weeks from the first CR assessment):

(1) In assessing the primary lesion by upper gastrointestinal endoscopy, it is concluded that all endoscopic findings suggestive of malignant lesions have been disappeared (primary lesion CR), based on the "response evaluation criteria for primary lesion using endoscopy" specified in Japanese Classification of Esophageal Cancer 11th edition.

(2) In tumor assessments using cervicothoracic/abdominopelvic contrast CT that were performed according to the RECIST guideline version 1.1, the response was assessed as CR for the target and non-target lesions.

In this study, the RECIST guideline version 1.1 was modified in terms of the following:

Pathological lymph nodes: Lymph nodes with short axis ≥ 10 mm will be considered pathological lymph nodes and evaluated as target lesions.

- Lymph nodes with short axis < 10 mm and ≥ 5 mm will be considered non-target lesions if they are clinically diagnosed as metastatic nodes, and will not be considered pathological nodes if they are clinically diagnosed as non-metastatic nodes.
- Lymph nodes with short axis < 5 mm will not be considered pathological nodes.

For primary lesions, the assessment will be CR if all of the following criteria 1) to 4) are satisfied on endoscopy.

1) All endoscopic findings suggestive of malignant lesions have been disappeared.[*1*2]

*1: The following types of lesions will be considered "endoscopic findings suggestive of malignant lesions." In other words, the assessment will not be CR if the following types of lesions are seen.

- Erosive changes with irregularities
- Ulcerative lesion
- Obvious elevation (including submucosal mass elevation)

*2: The following types of lesions will not be considered "endoscopic findings suggestive of malignant lesions." In other words, the assessment may be CR even if the following types of lesions are seen.

- Scar
- Stenosis

- Iodine unstained area
- Small, granulomatous elevation assessed as negative for carcinoma on biopsy

2) No carcinoma is seen histopathologically by endoscopic biopsy*3 of the site where the primary lesion was present before treatment.

*3: Endoscopic biopsy will be performed from the area where the primary lesion had been present.

3) The entire esophagus can be observed by endoscopy.

4) There are no endoscopic findings suggestive of active esophagitis (flat, erosive changes, white moss).

5.1.6 Definitions of lesions in this study

Primary lesion

A primary lesion is defined as follows.

1) In the case of a solitary lesion, the main lesion

2) In the case of multiple lesions, the main lesion and all accessory lesions

Esophageal intramural metastasis

Esophageal intramural metastases are defined as being intramural metastases that are clearly detached from the primary lesion.

Intraepithelial extension

The intraepithelial extension is defined as consisting of mucosal intraepithelial lesions that extend continuously from the primary lesion.

Main and accessory lesions

In the case of multiple lesions, the main lesion will be defined as being the lesion considered the most deeply invasive on clinical diagnosis, and the accessory lesions will be defined as being the other lesions. Each will include the intraepithelial extension.

Diagnosis of the depth of invasion of accessory lesion from endoscopic findings

Endoscopic ultrasound will not be required to diagnose the depth of invasion of an accessory lesion. If it is difficult to clinically differentiate T1a-LPM (M2) and T1a-MM (M3), the latter will be considered the depth.

Accessory lesions for which endoscopic mucosal resection is absolutely indicated

Accessory lesions for which endoscopic mucosal resection (EMR) is absolutely indicated will be lesions endoscopically diagnosed as being in T1a-EP (M1) to T1a-LPM (M2), which are subcategories of the depth of invasion.

Dysphagia score

Dysphagia score (DS): Modified from "Management of malignant dysphagia by intubation at endoscopy."[41]

0: Able to eat normal diet
1: Unable to swallow certain solids
2: Able to swallow semisolid foods
3: Able to swallow liquids only
4: Unable to swallow liquids

Definition of unresectable, locally advanced esophageal cancer

In this study, unresectable, locally advanced esophageal cancer will be cases in which (1) or (2) below

applies.
(1) The invasion depth (UICC-TNM 7th edition, Japanese Classification of Esophageal Cancer 11th edition) of the primary tumor is assessed as follows:
i) cT4b
(2) Regional lymph node or supraclavicular lymph node (#104) metastasis is assessed as follows:
i) Invasion of an organ other than the esophagus

Post-treatment findings
Post-treatment findings will be indicated with the prefix 'y.' Post-treatment clinical findings will be indicated with 'yc' and post-treatment pathological findings with 'yp.'

5.2 Performance Status (ECOG classification)

See Appendix 1.

5.3 Adverse event evaluation criteria

Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, Japanese edition, translated by the Japan Clinical Oncology Group (JCOG) (corresponds to CTCAE version 4.03/MedDRA version 12.0), and the results will be recorded. In the present study, this procedure will conform to JCOG operations.

5.4 Response rate evaluation criteria

In evaluating tumor images in this study, the criteria modified from the RECIST guideline version 1.1 will be used.
See Appendix 2 for details.

6 Inclusion and Exclusion Criteria

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled as subjects to receive the protocol therapy.

6.1 Inclusion criteria

[Primary locally advanced ESCC part]

1. Primary ESCC, adenosquamous carcinoma, or basaloid cell carcinoma diagnosed histologically (Accessory lesion biopsy is not required, but if performed, squamous cell carcinoma, basaloid cell carcinoma, adenosquamous carcinoma, or basaloid cell carcinoma is identified.)
2. Primary esophageal lesion present in the thoracic esophagus (UICC-TNM 7th edition). However, the patient with invasion of the cervical and abdominal esophagus will be eligible if curative CRT is judged to be feasible and already administered. In addition, accessory lesions for which endoscopic resection is absolutely indicated may be present at other locations.
3. Macroscopic radical resection is judged unfeasible based on cervicothoracic/abdominopelvic contrast-enhanced CT performed before CRT. That is, either (1) or (2) below is applicable. However, the patient will be ineligible if esophageal perforation, esophageal-respiratory tract fistula, esophageal-mediastinal fistula, bleeding associated with arterial invasion, or airway stenosis symptoms are seen clinically or on diagnostic imaging before CRT.
   (1) The depth of the primary tumor invasion (UICC-TNM 7th edition and Japanese Classification of Esophageal Cancer 11th edition) is classified as cT4b [invasion of the aorta (great vessel), trachea, bronchus, pulmonary artery, pulmonary vein, or a vertebral body].
   (2) Regional lymph node metastases or supraclavicular lymph node (#104) metastases have invaded an organ other than the esophagus.

   NB: Even if the short axis of the lymph node is ≥5 mm and <10 mm, it will be considered lymph node metastasis if the lesion can clearly be judged to be malignant by means such as FDG-PET, ultrasound, or the patient's clinical course.

   NB: Whether a measurable lesion is present in cervicothoracic/abdominopelvic CT performed before CRT administration is not taken into account.
4. No metastasis to distant organs other than the supraclavicular lymph nodes seen on cervicothoracic/abdominopelvic CT performed before CRT administration.
5. No history of treatment other than endoscopic resection for esophageal cancer before CRT administration
6. CRT fulfilling the conditions indicated below was administered,* and the protocol treatment can be started within 42 days after the final session of radiation therapy.
   • Cycle 1 of chemotherapy started at doses of 70 mg/m^2 of CDDP on Day 1 and 700 mg/m^2 of 5-FU on Days 1 to 4, with 4 weeks considered 1 cycle and a total of 2 cycles administered. A dose reduction will be allowed in the 2nd cycle of chemotherapy depending on the toxicity of Cycle 1.
   • Irradiation was performed at a dose of 60 Gy/30 fr without exceeding the dose limit for at-risk organs.
   *: CRT will be performed as indicated in Sections 3.3 "Standard chemoradiotherapy" and 3.4 "Standard radiation therapy plan."
7. No distant metastasis seen in imaging procedures performed at the completion of CRT, and no esophageal perforation, esophageal-respiratory tract fistula, esophageal-mediastinal fistula, bleeding associated with arterial invasion, or airway stenosis seen clinically or on diagnostic imaging

[Postoperative locoregionally recurrentESCC part]

1. Primary ESCC, adenosquamous carcinoma, or basaloid cell carcinoma diagnosed histologically using surgical specimens

   NB: Squamous cell carcinoma, adenosquamous carcinoma, or basaloid cell carcinoma if an histological diagnosis is performed for accessory lesions

   NB: Subclassification will be performed according to the quantitatively predominant histological type, in accordance with the Japanese Classification of Esophageal Cancer 11th edition. Patients will be considered eligible if they have a diagnosis of squamous cell carcinoma, adenosquamous carcinoma, or basaloid cell carcinoma in the pathological diagnosis of surgical specimens based on this classification.
2. The patient who underwent surgical resection with a curability classification of A or B for esophageal cancer. However, recurrent foci are seen in the mediastinum, anastomotic region, or regional lymph nodes (in the 3 areas for surgical resection), which are unresectable, but it is concluded that curative CRT is possible for all of the recurrent foci.
3. No metastasis to distant organs other than the supraclavicular lymph nodes are seen on cervicothoracic/abdominopelvic CT performed before CRT administration.
4. If the patient has a history of neoadjuvant chemotherapy, at least 24 weeks has passed from the last day of administration to the start of CRT.
5. CRT fulfilling the conditions indicated below was administered,* and the protocol treatment can be started within 42 days after the final cycle of radiation therapy.
   - Cycle 1 of chemotherapy started at doses of 70 mg/m^2 of CDDP on Day 1 and 700 mg/m^2 of 5-FU on Days 1 to 4, with 4 weeks considered 1 cycle and a total of 2 cycles administered. A dose reduction will be allowed in the 2nd cycle of chemotherapy depending on the toxicity of Cycle 1.
   - Irradiation will be performed at a dose of 60 Gy/30 fr without exceeding the dose limit for at-risk organs.

   *: CRT will be performed as indicated in Sections 3.3 "Standard chemoradiotherapy" and 3.4 "Standard radiation therapy plan."
6. No distant metastasis seen in imaging procedures performed at the completion of CRT, and no esophageal perforation, esophageal-respiratory tract fistula, esophageal-mediastinal fistula, bleeding associated with arterial invasion, or airway stenosis symptoms seen clinically or on diagnostic imaging

[Both primary locally advanced ESCC and postoperative locoregionally recurrent ESCC parts]

1. Aged ≥20 years at time of informed consent
2. PS of 0 or 1 according to ECOG criteria (PS must be recorded in the medical records without fail.)
3. All of the following criteria met in the most recent tests performed within 14 days before enrollment (The results from the same day of week 2 weeks before the day of enrollment may be used).
   (1) Neutrophil count: ≥1200/mm^3
   (2) Platelet count: ≥ 7.5 × 10^4/mm^3
   (3) Hemoglobin: ≥8.0 g/dL (no blood transfusion to be received within 14 days before the day of blood drawing for test used for enrollment)
   (4) Albumin: ≥2.5 g/dL
   (5) T-bil: ≤ 1.5 × ULN (≤ 2.5 × ULN allowed if patient has Gilbert's syndrome)
   (6) AST/ALT: ≤100 U/L
   (7) Serum creatinine: ≤1.5 mg/dL or creatinine clearance*: ≥45 mL/min

   *: For creatine clearance, can use both value calculated using Cockcroft-Gault equation and value from 24-hour pooled urine.

   (8) SpO_2: ≥95% (room air)

4. If the patient is a woman of childbearing potential, the result of a pregnancy test performed within 14 days before enrollment is negative. (See Section 6.2 "Pregnancy and contraception," for the definition of a woman of childbearing potential.)
5. The patient who is willing to use appropriate contraception from the time of informed consent to 5 months after the end of investigational product administration (See Section 6.2 "Pregnancy and contraception," regarding appropriate contraception.)
6. Expected to survive for at least 3 months
7. The patient who has provided written informed consent to participate in the study

Exclusion criteria

1. Diagnosed with multiple active cancers (simultaneous multiple cancers or multiple cancers with a disease-free interval of ≤3 years before enrollment). However, multiple active cancers does not include intraepithelial carcinoma or lesions corresponding to intramucosal carcinoma, which are judged to have been cured with localized treatment.
2. An active infection requiring systemic treatment (Fever of ≥38.0℃ and demonstrated to be a bacterial infection by diagnostic imaging or bacteriological testing; does not include localized infections that do not affect the patient's general condition.)
3. Concomitant inflammatory bowel disease or a past history of such disease
4. Concomitant pneumonia or interstitial lung disease (ILD) or a past history of either
5. A concomitant autoimmune disease or a past history of a chronic or recurrent autoimmune disease
6. The patient who requires administration of a systemic corticosteroid (excluding prophylactic administration for an allergic reaction or administration on an as-needed basis for purposes such as alleviating edema associated with radiation therapy) or immunosuppressant or was administered such a treatment within 14 days before enrollment
7. Concomitant thyroid dysfunction (hyperthyroidism or hypothyroidism) or a past history thereof
   NB: Patients with hypothyroidism who are stable with hormone replacement therapy may be enrolled at the discretion of the principal investigator.
8. A past history of or finding indicating cardiovascular risk to which any of the following are applicable.
   • Left ventricular ejection fraction <50%
   • A past history of or finding indicating poorly controlled arrhythmia that is clinically problematic. Exception: Patients with atrial fibrillation that has been controlled for more than 30 days before enrollment may be included.
   • A past history of an acute coronary syndrome (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months before enrollment
   • Past history of or findings indicating congestive heart failure of Grade II or higher based on the New York Heart Association (NYHA) functional classification
   • Refractory hypertension (defined as high blood pressure of systolic BP >140 mmHg and diastolic BP >90 mmHg that cannot be controlled with treatment)
   • Fitted with an implantable defibrillator or permanent pacemaker
9. Poorly controlled diabetes mellitus
10. Positive HIV antibody test, HBs antigen test, or HCV antibody test*
    *: Also excluded are patients with a positive HBs or HBc antibody test and an HBV-DNA assay that equals or exceeds detection sensitivity.
11. Pregnant or lactating patient
12. A serious, unstable psychiatric disorder or other medical condition that could undermine safety, prevent informed consent, or impede compliance with study procedures

13. Previous use of atezolizumab or an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody or other drug therapy for T-cell regulation
14. The patient unwilling or unable to comply with the procedures described in the protocol
15. The principal investigator determines that the patient is unsuitable as a study subject because the patient has a condition that could prevent toxicity assessment.

6.2 Pregnancy and contraception

Women of childbearing potential (including patients who are amenorrheic for a medical reason such as chemical menopause) include all women who have experienced menarche, have not undergone sterilization surgery (e.g., hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), and have not undergone menopause. Postmenopausal will be defined as having been amenorrheic continuously for ≥48 weeks in the absence of a noteworthy reason for the amenorrhea. Women who are using an oral contraceptive or mechanical method of contraception, such as an intrauterine device or barrier method, will be regarded as being of childbearing potential.

To avoid pregnancy, female subjects of childbearing potential will be required to use appropriate, reliable means of contraception such as those indicated below from the time of informed consent to 5 months after the final administration of the investigational product. If a subject is determined not to be of childbearing potential because the subject is menopausal (amenorrheic for ≥1 year) or has undergone hysterectomy, this will be clearly indicated in the subject's source documents.

Male subjects will be required to use appropriate contraception to prevent pregnancy from the time of informed consent to 5 months after the final administration of the investigational product.

Reliable methods of contraception are indicated below in (1) and (2).

(1) For the following methods of contraception, 2 or more are used in combination.

- Latex condom (used by males)
- Diaphragm
- Various hormonal contraceptives (e.g., oral contraceptives)
- Intrauterine device (IUD, T-shaped without progesterone)

(2) Either of the following procedures have been performed.

- Tubal ligation
- Vasectomy

7 Enrollment

7.1 Enrollment procedure

The study subjects will be confirmed to meet all of the inclusion criteria and none of the exclusion criteria, and enrolled using a web-based enrollment system.

Contact information and reception hours for patient enrollment

Information such as the URL for web-based enrollment will be provided separately in the "EDC Input Manual."

(Enrollment will be possible 24 hours a day. If the system will be inaccessible for reasons such as maintenance, advance notice will be given.)

■Inquiries on enrollment

EP-CRSU Co., Ltd.
Tel: 03-5946-8270
Weekdays 10 a.m. to 5 p.m. (closed on holidays and weekends)

■Inquiries on the inclusion/exclusion criteria for patients

Coordinating investigator (representative): Takashi Kojima
Department of Gastrointestinal Oncology, National Cancer Center Hospital East
6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577
Tel: 04-7133-1111 (extension: 91114); E-mail: takojima@east.ncc.go.jp

Coordinating investigator: Hideaki Bando
Medical Director, Department of Clinical Oncology, Aichi Cancer Center
1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681
Tel: 052-762-6111 (main); E-mail: hbando@aichi-cc.jp

7.2 Points to note for enrollment

1) Enrolling a patient after he or she has started the protocol treatment will be prohibited without exception.
2) If there is insufficient information to determine a patient's eligibility, enrollment will not be accepted until all the criteria have been satisfied.
3) After a patient's eligibility is confirmed, an enrollment number will be issued. With issuance of an enrollment number, enrollment is completed.
4) Except in the case where the subject withdraws consent, which includes declining to allow their data to be used for research, once a subject is enrolled, their enrollment will not be canceled (deleted from the database). In the case of duplicate enrollment, the initial enrollment information (enrollment number) will always be used.
5) When mistaken or duplicate enrollment occurs, it will be promptly reported.
6) If a subject is being treated at another hospital or department when they are enrolled, the attending physician will be notified of the subject's participation in the study.

8 Treatment Plan and Criteria for Treatment Changes

As long as the subject's safety is not threatened, the treatment and any treatment changes will be implemented as described in this section. If treating a subject according to this protocol is judged to be medically risky, the principal investigator or subinvestigator (hereinafter referred to as the "investigator") may change the treatment according to their medical judgment.

8.1 Protocol treatment

The protocol treatment in this study is sequential administration of atezolizumab monotherapy for up to 12 months following curative CRT.

Patients will be enrolled in the study and begin atezolizumab monotherapy within 42 days of the day following the day curative CRT is completed (defined as the last day of the final cycle of radiation therapy; monotherapy may be started on the day of enrollment). Investigational product administration will start on Day 1 and continue once every 3 weeks for up to 12 months (administered up to 17 times, final administration in Week 49). After atezolizumab administration begins, imaging evaluations by upper gastrointestinal endoscopy and CT will be performed every 4 weeks (±2 weeks) until a CR, as defined in Section 5.1.5, is judged to have occurred. Subsequently, evaluations by upper gastrointestinal endoscopy and CT will be performed every 12 weeks (±4 weeks).

Administration will be discontinued after less than 12 months in the following cases: PD is determined by upper gastrointestinal endoscopy or CT (except when the investigator determine that continued administration would benefit the patient*); an alternative cancer therapy is started; intolerable toxicity is seen; consent is withdrawn; or administration is discontinued for other reasons.

*: The investigator will report evidence strongly suggesting clinical usefulness and the reasons justifying continued administration of the protocol treatment individually to the coordinating committee, and review the determination individually with the coordinating committee according to the circumstances.

The following terminology is used on this protocol.

- Discontinuation: Administration of the investigational product will not be resumed.
- Interruption: The investigational product is not administered while waiting for resolution, after which it is administered.
- Interruption period: The period during which the investigational product is not administered.

8.1.1 Treatment regimen

1) The day on which atezolizumab is first administered will be considered Day 1, and 1 cycle will be 21 days (±3 days).

A single dose of atezolizumab will be 1200 mg (20 mL/vial). There will be no atezolizumab dose reductions in this study. The contents of a 20 mL vial of atezolizumab will be extracted with a syringe and added to about 250 mL of isotonic sodium chloride solution (JP). This solution will then be administered by intravenous infusion over 60 minutes (±15 minutes) using a 0.2 or 0.22 μm inline filter. If the first administration is well tolerated, the administration time of the second and subsequent administrations can be reduced to 30 minutes (±10 minutes). The investigational product will be prepared at the time of use and used promptly after preparation.

Table 8.1-1 Dosing regimen

Type of Drug	Drug Name	Dose (single dose)	Administration Frequency	Administration Route

Investigational product	Atezolizumab*	1200 mg	Once every 3 weeks	Intravenous Infusion

2) Whether to administer or withdraw the treatment will be determined when atezolizumab is administered every 21 days (±3 days), based on the criteria specified in Section 8.2 "Atezolizumab interruption and discontinuation criteria."
3) Administration will continue until the criteria specified in Section 8.4.1 "Protocol treatment discontinuation/completion criteria" are applicable.

8.2 Atezolizumab interruption and discontinuation criteria

If an adverse drug reaction (ADR) related to atezolizumab administration occurs, atezolizumab will be withdrawn or discontinued based on the following criteria. (Measures considered most appropriate will be taken, also with reference to the latest investigator's brochure.) If the treatment is withdrawn and the adverse drug reaction improves after the end of the specified period, a decision will be made to resume atezolizumab in consultation with the coordinating committee.

Even if none of the criteria below are applicable, atezolizumab will be withdrawn if the investigator determines that withdrawal is necessary.

Table 8.2-1 Atezolizumab interruption and discontinuation criteria

Adverse Drug Reaction	Grade*	Measures Taken
Respiratory disorder such as interstitial lung disease	Grade 2	Atezolizumab will be withdrawn until resolution to ≤ Grade 1. If the ADR does not resolve to ≤ Grade 1 even with withdrawal for more than 12 weeks, atezolizumab will be discontinued.
	≥ Grade 3 or recurrent	Atezolizumab will be discontinued.
Hepatic function disorder	Continues at Grade 2 (AST or ALT 3 to 5 times the upper limit of normal, or total bilirubin 1.5 to 3 times the upper limit of normal) for more than 5 days	Atezolizumab will be withdrawn until resolution to ≤ Grade 1. If the ADR does not resolve to ≤ Grade 1 even with withdrawal for more than 12 weeks, atezolizumab will be discontinued.
	≥ Grade 3 (AST or ALT >5 times the upper limit of normal, or total bilirubin >3 times the upper limit of normal)	Atezolizumab will be discontinued.
Immune-mediated colitis/diarrhea	Grade 2 or 3	Atezolizumab will be withdrawn until resolution to ≤ Grade 1. If the ADR does not resolve to ≤ Grade 1 even with withdrawal for more than 12 weeks, atezolizumab will be discontinued.
	Grade 4	Atezolizumab will be discontinued.
Elevated amylase or lipase	≥ Grade 3 elevation of amylase or lipase	Atezolizumab will be withdrawn until resolution to ≤ Grade 1. If the ADR does not resolve to ≤ Grade 1 even with withdrawal for more than 12 weeks, atezolizumab will be discontinued.

	Recurrence of ≥ Grade 3 elevation of amylase or lipase	Atezolizumab will be discontinued.
Immune-mediated pancreatitis	Grade 2 or 3 pancreatitis	Atezolizumab will be withdrawn until resolution to ≤ Grade 1. If the ADR does not resolve to ≤ Grade 1 even with withdrawal for more than 12 weeks, atezolizumab will be discontinued.
	Grade 4 pancreatitis, Recurrence of Grade 2 or 3 pancreatitis	Atezolizumab will be discontinued.
Hyperglycemia	≥ Grade 3 hyperglycemia	Atezolizumab will be withdrawn until blood glucose level becomes stable. Starting insulin therapy will be considered. If the symptoms improve/resolve and the blood glucose level becomes stable, atezolizumab resumption will be considered.
Hypophysitis (panhypopituitarism)	Grade 2 or 3	Atezolizumab will be withdrawn until resolution to ≤ Grade 1. If the ADR does not resolve to ≤ Grade 1 even with withdrawal for more than 12 weeks, atezolizumab will be discontinued.
	Recurrence of Grade 2 or 3 hypophysitis (panhypopituitarism), Grade 4	Atezolizumab will be discontinued.
Hypothyroidism (symptomatic)	All grades	Atezolizumab will be withdrawn. Starting thyroid hormone replacement therapy will be considered. If symptoms are controlled and thyroid function improves/recovers, atezolizumab resumption will be considered.
Hyperthyroidism (asymptomatic)	• Thyroid stimulating hormone level < 0.1 mU/L	In the case of life-threatening, immune-mediated hyperthyroidism: • Atezolizumab will be discontinued. In other cases: • Atezolizumab will be withdrawn. • If symptoms are controlled and thyroid function improves/recovers, atezolizumab resumption will be considered.
Hyperthyroidism (symptomatic)	All grades	
Adrenal insufficiency (symptomatic)	≥ Grade 2 adrenal insufficiency	Atezolizumab will be withdrawn until resolution to ≤ Grade 1. Intravenous or oral corticosteroid administration will be considered. If the ADR does not resolve to ≤ Grade 1 even with withdrawal for more than 12 weeks, atezolizumab will be discontinued.
Immune-mediated	All grades	Atezolizumab will be discontinued.

encephalitis, meningitis		
Immune-mediated nerve disorder	Grade 2	Atezolizumab will be withdrawn until resolution to ≤ Grade 1. If the ADR does not resolve to ≤ Grade 1 even with withdrawal for more than 12 weeks, atezolizumab will be discontinued.
	≥ Grade 3	Atezolizumab will be discontinued.
Immune-mediated myocarditis	Grade 2	Atezolizumab will be withdrawn until resolution to ≤ Grade 1. If the ADR does not resolve to ≤ Grade 1 even with withdrawal for more than 12 weeks, atezolizumab will be discontinued.
	≥ Grade 3	Atezolizumab will be discontinued.
Myasthenia gravis, Guillain-Barre syndrome	All grades	Atezolizumab will be discontinued.
Immune-mediated skin disorder	Grade 3	Atezolizumab will be withdrawn until resolution to ≤ Grade 1. If the ADR does not resolve to ≤ Grade 1 even with withdrawal for more than 12 weeks, atezolizumab will be discontinued.
	Grade 4	Atezolizumab will be discontinued.
Immune-related nephritis	Grade 2	Atezolizumab will be withdrawn until resolution to ≤ Grade 1. If the ADR does not resolve to ≤ Grade 1 even with withdrawal for more than 12 weeks, atezolizumab will be discontinued.
	≥ Grade 3	Atezolizumab will be discontinued.
Immune-mediated eye disorder	Grade 2	Atezolizumab will be withdrawn until resolution to ≤ Grade 1. If the ADR does not resolve to ≤ Grade 1 even with withdrawal for more than 12 weeks, atezolizumab will be discontinued.
	≥ Grade 3	Atezolizumab will be discontinued.
Infusion reaction	Grade 1	Infusion rate will be reduced to 50%. The patient will be observed for 30 minutes after the reaction improves, and if there is no recurrence, the original infusion rate can be restored.
	Grade 2	Atezolizumab will immediately be suspended and aggressive symptomatic treatment administered. Administration will not be resumed until the symptoms return to their baseline status. When atezolizumab is resumed, the infusion rate will be reduced to 50%.

	≥ Grade 3	Atezolizumab will immediately be discontinued. Aggressive resuscitation and supportive therapy will be started. In subjects with a severe or life-threatening event related to an infusion reaction, atezolizumab administration will not be resumed, and the condition will be managed according to clinical needs until the event resolves.
Immune-related myositis	Grade 2 or 3	Atezolizumab will be withdrawn until resolution to ≤ Grade 1. If the ADR does not resolve to ≤ Grade 1 even with withdrawal for more than 12 weeks, atezolizumab will be discontinued.
	Grade 4, Recurrence of Grade 3 myositis	Atezolizumab will be discontinued.

*: Grades are specified in accordance with NCI-CTCAE version 4.

8.3 Atezolizumab resumption criteria

Atezolizumab administration will be resumed if all of the following resumption criteria are met.

- The adverse drug reaction caused by atezolizumab administration resolve to ≤ Grade 1.
- If prednisolone administration is started due to the adverse event, the dose can be reduced to <10 mg/day (or equivalent).

8.4 Protocol treatment discontinuation/completion criteria

If any of the following are applicable to the subject, the protocol treatment will be discontinued or completed. In addition, the reason for the discontinuation/completion will be recorded in the subject's source documents.

8.4.1 Protocol treatment discontinuation/completion criteria

1) Atezolizumab administration for up to 12 months and up to 17 cycles was completed.
2) Progression of the primary disease is seen, and the investigator determines that administration will not benefit the patient. (The case includes obvious progression as determined by diagnostic imaging and clinically obvious progression.)
3) The subject requests discontinuation of the protocol treatment.
4) An adverse event is seen that is related to the protocol treatment and to which discontinuation specified in Table 8.2.1 is applicable. However, if it is determined that administration would significantly benefit the patient, the advisability of continued administration will be reexamined in consultation with the coordinating committee.
5) If the duration of protocol treatment withdrawal (counted from the first day atezolizumab is not administered) exceeds 12 consecutive weeks (84 days). If is determined that administration would significantly benefit the patient, the advisability of continued administration will be reexamined in consultation with the coordinating committee.
6) Based on the efficacy of the protocol treatment, it is concluded that conversion surgery can be performed.

7) The study period (1 year from the date final patient is enrolled) is completed.
8) The subject becomes pregnant.
9) The subject is lost to follow-up.
10) The patient dies during the protocol treatment.
11) The investigator otherwise concludes that discontinuation is necessary (including cases in which another chemotherapy, surgery or radiation therapy not specified in the protocol is required).

Even if a criterion for discontinuation/completion of the protocol treatment is applicable, the decision will reexamined on an individual basis in consultation with the coordinating committee, depending on the circumstances, if there is evidence that strongly suggests that the protocol treatment is clinically useful and there is justification for continued administration of the treatment.

8.4.2 Data collection and follow-up of subjects after discontinuation/completion of the protocol treatment

If a criterion for discontinuation/completion of the protocol treatment is applicable, the treatment will be discontinued/completed, the timing and reason for the discontinuation/completion and patient's clinical course will be entered on the case report form (CRF), and the examinations specified for the time of discontinuation/completion will be carried out. However, this will not apply if the investigator determines that the examinations are unnecessary or cannot be performed for ethical reasons or in consideration of the safety and interests of the subject.

8.5 Concomitant and supportive therapies

8.5.1 Permitted concomitant drugs and therapies

In general, the concomitant use of drugs and therapies determined to be necessary to treat a subject will be permitted in the absence of separate stipulations. Other information on concomitant drugs and therapies is provided in the atezolizumab investigator's brochure.

All concomitant drugs and therapies used during atezolizumab monotherapy or within 28 days from the date the protocol treatment is discontinued or completed (if subsequent treatment is started, until the day before it is started) will be entered on the CRF. These drugs include not only those prescribed by a physician but also OTC drugs, crude drug products, and blood transfusions.

Drugs other than anticancer drugs that are used to treat progression of the primary disease and drugs used for examinations and diagnosis will not need to be entered on the CRF. However, drugs that may have been involved in adverse events will be entered on the CRF.

8.5.2 Recommended concomitant and supportive therapies

The following concomitant and supportive therapies are recommended. Not administering them will not be considered a protocol deviation.

1) For subjects who previously exhibited an infusion-related reaction before a reaction to atezolizumab infusion becomes a concern, prophylactic administration of acetaminophen or diphenhydramine prior to atezolizumab administration will be considered.

8.5.3 Permitted concomitant and supportive therapies

The following concomitant and supportive therapies may be administered as necessary.

1) Antiemetics, fluid replacement
2) Antidiarrheals

3) Antipyretics, prophylactic antimicrobials
4) Inactivated influenza vaccination
5) Endoscopic resection of accessory lesions and new lesions limited to the mucosa

8.5.4 Prohibited concomitant therapies

Concomitant use of the following drugs will be prohibited except when judged necessary for safety and ethical reasons, such as to treat an adverse event.

(1) Immunosuppressants and immunopotentiators (e.g., IFN-α, IFN-γ, and IL-2)
(2) Live attenuated vaccines
(3) Corticosteroids

Corticosteroids may be administered locally, as in the case of topical, intraarticular or intranasal administration, ocular instillation, or inhalation. They also may be temporarily used to treat or prevent conditions such as a contrast media allergy or an adverse event.

If an immune-related adverse event (irAE) occurs during the course of therapy, supportive therapy with a corticosteroid preparation and infliximab will be administered as described in Appendix 3) "Management of Atezolizumab-Specific Adverse Events."

(4) All anticancer drugs, including antibody preparations (e.g., chemotherapy, hormone therapy, molecular targeted therapy, and immunotherapy)

The use of any anticancer drug, including local administration of Picibanil, will not be permitted.

(5) Radiopharmaceuticals

Radiopharmaceutical may be used for examination or diagnosis.

(6) Bisphosphonates and anti-RANKL antibodies

The use of bisphosphonates and anti-RANK antibodies will be permitted only if they continue to be administered using the same dose and dosing regimen as before enrollment in the study.

(7) Transplantation therapy
(8) Other unapproved drugs (including drugs administered in clinical studies, unapproved combination drugs, and drugs in new dosage forms)

8.6 Handling of tumor specimens and analysis of biomarkers

Genetic and immunological biomarker analyses will be performed in this study using tissue specimens collected during endoscopy performed in all enrolled subjects during the period from the day after the informed consent is obtained to the day before atezolizumab administration every 4 weeks (±2 weeks) until a CR defined in Section 5.1.5 is seen, and every 12 weeks (±4 weeks) after the CR. The analyses will also use blood specimens drawn at the same time points (blood specimens will be collected until tests at 4 weeks after start of study participation).

The biomarker analyses will be performed as a study separate from the present study (TENERGY study–TR research), and informed consent for that study will be obtained using a separate informed consent document. If tumor or blood specimens are collected before the start of CRT in the routine clinical practice and stored, or if the patient consents to participate in the study conducted at the National Cancer Center Hospital East titled "Research on the Elucidation of the Immune Status of Patients with Gastrointestinal and Other Solid Cancers and its Clinical Significance (Research No.: 2015-048) and agrees to the secondary use of the specimens, they will also be used in the biomarker analysis after the analysis is explained to the patient and his or her consent is obtained.

8.7 Subsequent treatment

No subsequent treatment will be specified for subjects for whom the protocol treatment is discontinued.

9 Information on the Investigational Product

9.1 Atezolizumab drug information

Investigational product	Atezolizumab (RO5541267)
Dosage form	Injectable (vial)
Manufacturer	Chugai Pharmaceutical Co., Ltd./Hoffmann-La Roche Ltd.
Content	Formulation F03 (for commercial use and use in late phase I/II and phase III clinical studies) of the atezolizumab preparation is provided as a sterile, clear, colorless to pale yellow liquid for intravenous infusion not containing preservatives in a 20 mL single-dose glass vial (USP, EP). The vial is designed so that 20 mL of atezolizumab solution (1200 mg) can be administered. However, it may be filled with an excess amount so that the entire 20 mL can be administered. The atezolizumab preparation is 60 mg/mL of atezolizumab in a pH-5.8 solution containing histidine-acetate, sucrose, and polysorbate 20 (formulation for use in phase III clinical study).
Storage conditions and stability after dissolution	Both atezolizumab preparations (F01 and F03) and their diluents will be stored refrigerated at 2°C to 8°C (36°F to 46°F) from receipt until use. Atezolizumab diluted with isotonic sodium chloride solution can be stored at 2°C to 8°C for 24 hours and at ≤25°C for 8 hours. This includes the storage time and the time required for intravenous infusion.
Dosing regimen	Formulation F03 atezolizumab (1200 mg/vial) will be administered using an infusion line equipped with a 0.9% NaCl infusion bag and a 0.2 or 0.22 μm inline filter.
Administration route	Intravenous administration
Shelf life	See investigational product label
Labeling	Information such as the content, storage method, and the name, title, address of the coordinating investigator is indicated on the outer box, along with the fact that the product is for investigational use.

Atezolizumab will be provided at no cost by Chugai Pharmaceutical Co., Ltd., the investigational product provider. The investigational product provider will also provide investigational product manufacturing records and quality testing records.

9.2 Investigational product management

The investigational product, atezolizumab, will be provided by Chugai Pharmaceutical Co., Ltd. The investigational product manager at each study site will appropriately manage the investigational product in accordance with the procedure manual for investigational product management provided by the coordinating committee.

The investigator will prescribe the investigational product in the quantities specified in the protocol. The investigational product is not to be administered in a manner other than that specified in the protocol.

9.3 Expected adverse events

Expected adverse events related to atezolizumab are classified as unknown and known events based on the information provided in the most recent investigator's brochure and package insert. An event whose

occurrence or pattern of occurrence, such as the number of occurrences, incidence, and conditions for occurrence, cannot be predicted based on the investigator's brochure for the investigational product is defined as an "unknown" event, and an event whose occurrence or pattern of occurrence can be predicted is defined as a "known" event. However, a new event that has already been reported to the study sites may be treated as a "known" event even if it is not indicated in the investigator's brochure.

10 Endpoints, Laboratory Tests, and Evaluation Schedule

10.1 Observations and endpoints

The endpoints of the study are indicated below. All of the information required by this protocol will be recorded.

Table 10.1-1 Observations and tests

Administration status	Atezolizumab dose, administration start date, administration completion or discontinuation date, whether treatment was withdrawn, and reason for withdrawal
Subject demographic characteristics	Sex, age (at time of informed consent), past history, concomitant illnesses, clinical diagnosis, clinical stage, histological diagnosis, previous treatment history
Physical measurements	Height, body weight
Vital signs	Temperature, pulse rate, systolic/diastolic blood pressure, peripheral oxygen saturation (SpO_2)
Performance status	PS (ECOG)
Adverse events	The presence or absence of adverse events and their severity will be evaluated using CTCAE version 4.0.
Concomitant drugs and therapies	Name of drug or concomitant therapy, route of administration, start day of concomitant use, end day of concomitant use, reason for concomitant use
Hematology tests	Red blood cell count, Hb, white blood cell count, neutrophil count, lymphocyte count, platelet count
Blood chemistry tests	AST (GOT), ALT (GPT), ALP, LDH, albumin, total bilirubin, direct bilirubin, BUN, creatinine, CK, electrolytes (Na, K, Cl, Ca), UA, blood glucose (as needed), C-reactive protein (CRP)
Blood coagulation tests	PT, PT-INR
Endocrine function tests	Thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), ACTH
Immunology tests	KL-6
Infection	HIV antibody, HBs antigen, HBs antibody, HBc antibody, HCV antibody
Urine test	Urine protein (qualitative)
Pregnancy test	Serological test when pregnancy suspected based on a urine test Performed for women who are premenopausal or women for whom final menstruation was less than 1 year ago
Tumor markers	CEA, SCC
Electrocardiogram	Resting 12-lead ECG

Tumor assessment	Upper gastrointestinal endoscopy*, cervicothoracic/abdominopelvic contrast CT (chest x-ray, brain CT, and brain MRI**, *** as needed) *: Endoscopy performed according to schedule in the case of postoperative relapse patients for whom the recurrent tumor can be observed and biopsied by endoscopy. Endoscopy will be considered unnecessary in patients for whom the recurrent tumor cannot be endoscopically observed and biopsied. **: In patients with allergies/sensitivity to the contrast media used in CT and MRI, these procedures will be performed without using contrast media. If atezolizumab administration is discontinued for a reason other than a worsening of the underlying disease seen on imaging, evaluations will be performed until worsening is confirmed. ***: Information from upper gastrointestinal endoscopy and cervicothoracic/abdominopelvic contrast CT performed before the start of CRT (within 28 days before the start of CRT) also will be collected.
Biomarker analysis (optional)	Tumor biopsy, blood drawing
Subsequent treatment	Description of the subsequent treatment (treatment regimen, date treatment started)
Outcome investigation	The date of death or date survival last confirmed, and the cause of death if the patient died.

10.2 Evaluation schedule

The evaluations will be performed according to the schedule shown in Table 10.2.1. However, variances of ±3 days for clinic visits and laboratory tests will be permitted as long as the appropriate sequence is maintained (variances during the new year holiday and long consecutive holidays will not be treated as deviations if the schedule is adjusted with the investigator beforehand).

Table 10.2-1 Schedule

	Screening[$] (enrollment within 42 days after CRT completion)	During Protocol Treatment						Examination at Discontinuation/ Completion[†]	30 Days After Final Administration[‡]	Observational Study[#]
		Cycle 1 (21 days per cycle)			Cycle 2 and later cycles					
Day	−42 to enrollment day	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	0 to +14	−3 to +7	Every 3 months from enrollment to 2 years; every 6 months from 2 to 5 years
Informed consent obtained	●[*1]									
Subject demographic characteristics	●									
Investigational product administration										
Atezolizumab administration		1200 mg intravenous infusion every 3 weeks								
Observation findings										
Height, body weight[*2]	●									
Vital signs	●	●	●		●			●	●	
ECOG PS	●	●	●		●			●	●	
Clinical findings (including adverse events) Concomitant drugs/therapies	●	●	●	●[*9]	●	●[*9]	●*[9]	●	●	○
Laboratory tests, diagnostic imaging										
Hematology/blood chemistry tests	●[*14]	●[*3]	●	○	●	○	○	●	●	
Blood coagulation function tests	●[*14]	●[*3]	○	○	●	○	○	●	●	
Endocrine function tests	●[*14]	●[*3]	○	○	●	○	○	●	●	
Immunology tests	●[*14]	○			● Every 12 weeks			●		
Infection tests[*4]	●									
Urinalysis	●[*14]	●[*3]			●			●	●	
Urine pregnancy test[*5]	○[*14]				○ Every 12 weeks			○	○	
Tumor markers	●[*14]				●[*6]			●		
12-lead ECG	●[*7]							●		
Upper gastrointestinal endoscopy[*13] (with biopsy)	●[*7]	Every 4 weeks (± 2 weeks) until CR determination by upper gastrointestinal endoscopy and CT; every 12 weeks (± 4 weeks) after CR determination[*10]						○[*11]		○[*11,]
Cervicothoracic/ abdominopelvic CT[*13]	●[*7]	Every 4 weeks (± 2 weeks) until CR determination by upper gastrointestinal endoscopy and CT; every 12 weeks (± 4 weeks) after CR determination[*10]						○[*11]		○[*11,]
Biomarker exploratory study Tumor and blood specimens	○[*8]	Only for patients who provided informed consent. Tumor specimens collected every 4 weeks (± 2 weeks) until CR determination by upper gastrointestinal endoscopy and CT and every 12 weeks (± 4 weeks) after CR determination[*8] Blood specimens collected only for tests at 4 weeks after start of study participation								
Subsequent treatment, outcome investigation										
Subsequent treatment										●
Outcome investigation										●[*12]

●: Required, ○: As needed

†: The protocol treatment discontinuation date is defined as the date on which the investigator decides to discontinue the protocol treatment for the subject. It will be permissible to perform the examinations at discontinuation/completion within 14 days after discontinuation/completion or before the start of subsequent treatment. However, if the tests and observations

cannot be carried out within the allowable time frame due to condition of the subject, they will be performed within the earliest possible time frame.

‡: The specified examinations will be performed at the earliest date either within 30 days after the final administration or before the start of subsequent treatment. If the subject cannot visit the clinic before subsequent treatment is started, the investigation will be conducted by telephone (PS, clinical findings, etc.). If the examinations to be performed 30 days after the final administration are performed within 2 weeks after the examinations at discontinuation/completion, they can be performed at the same time.

#: After protocol treatment discontinuation, a survival/recurrence investigation will be carried during the observational study associated with the present study through 5 years from the date of enrollment in the present study.

$: Starting the protocol treatment on the same day as enrollment will be permitted.

*1: Informed consent will be obtained before enrollment.

*2: Measurement during the protocol treatment will not be required. Even if these are measured, entry on the CRF will not be required. However, if the investigator judges the course of weight loss to be clinically problematic, it may be considered an adverse event.

*3: Examinations performed within 14 days before Day 1 of Cycle 1 (permitted through the same day of week 2 weeks before) may be used.

*4: A test performed within 6 months before enrollment may be substituted.

*5: In female subjects of childbearing potential, performed within 14 days before enrollment and every 12 weeks starting from Day 1 of Cycle 2.

*6: Measured on Day 1 of Cycles 2 to 4 and of the subsequent even-numbered cycles (Cycles 6, 8, 10, 12, 14, and 16).

*7: Performed between the time of informed consent and the start of the protocol treatment. Results obtained in examinations performed before informed consent also may be used if they are performed after CRT completion.

*8: In subjects who have received an explanation of the exploratory study from the investigator and provided separate informed consent, tumor and blood specimens will be collected before the start of protocol treatment and every 4 weeks (± 2 weeks) beginning from the administration start date (Day 1 of Cycle 1) until CR determination by upper gastrointestinal endoscopy and CT and every 12 weeks (± 4 weeks) after CR determination [blood specimens will be collected until tests at 4 weeks (± 2 weeks) after the administration start date].

*9: If the investigator determines that there are no problems with adverse events, etc., the clinic visits on Day 15 of Cycle 1 and Days 8 and 15 of Cycle 2 and later cycles will not be required.

*10: Until a CR determination is made, the dates on which upper gastrointestinal endoscopy and CT are performed will be determined starting from the administration start date (Day 1 of Cycle 1). After CR determination, they will be determined starting from the date of CR determination.

*11: If PD is seen by upper gastrointestinal endoscopy or CT and atezolizumab is discontinued, these examinations will not be required. If atezolizumab is discontinued for a reason other than progression of the primary disease seen on imaging, the examinations will be performed within 2 weeks after the completion of administration. In addition, the examinations will be carried out until progression of the primary disease is seen in the tumor assessments (assessment by upper gastrointestinal endoscopy or CT) or until subsequent treatment begins. They will be performed every 4 weeks (± 2 weeks) until a CR determination is made and every 12 weeks (± 4 weeks) after the CR determination.

*12: As part of the observational research associated with this study, survival/recurrence investigations will be conducted based on upper gastrointestinal endoscopy and CT examinations performed in the actual clinical setting after discontinuation/completion of the present study. The investigations will be carried out every 3 months (12 ± 4 weeks) from the date of enrollment in the study to 2 years. From 2 years onward, they will be conducted every 6 months (24 ± 8 weeks) to completion of the observational research (up to 5 years).

*13: The evaluations will be carried out using the results of an examination performed within 28 days before the start of CRT as the baseline.

*14: It will be confirmed that the most recent examination and test results obtained within 14 days before enrollment meet all of the inclusion criteria.

Table 10.2-2 Allowable time frames for protocol treatment and examinations/tests

Examination/Test	Protocol Specification	Allowable Time Frame
Laboratory tests (Day 1 of Cycle 1)	Before administration	−14 days
Laboratory tests (From Day 8 of Cycle 1 onward)	Before administration	±3 days
Protocol treatment (atezolizumab administration)	Day 1 of each cycle	±3 days
Immunology tests	Every 12 weeks (starting from Day 1 of Cycle 2)	±2 weeks (14 days)
Pregnancy test	Every 12 weeks (starting from Day 1 of Cycle 2)	±2 weeks (14 days)
Tumor markers	Day 1 of Cycles 2 to 4	±1 week (7 days)
	Subsequent to above: Day 1 of even-numbered cycles (Cycles 6, 8, 10, 12, 14, 16)	
Upper gastrointestinal endoscopy, cervicothoracic/ abdominopelvic contrast CT	Every 4 weeks [starting from start day of investigational product administration (Day 1 of Cycle 1)], examination for CR determination performed at least 4 weeks (28 days) after previous examination	±2 weeks (14 days) Examination for CR determination ≤ 27 days after previous examination is not permitted
	Every 12 weeks after CR determination (starting from date of CR determination)	±4 weeks (28 days)

10.3 Examination findings

10.3.1 Subject demographic characteristics

- Sex, age (at the time of consent)
- Past history (conditions judged clinically significant within the previous 10 years), concomitant illnesses
- Clinical diagnosis (at diagnosis, before CRT)
  - Primary tumor location, length, and macroscopic type; presence or absence of accessory lesions; presence or absence and extent of intraepithelial extension; presence or absence of intramural metastasis
  - Presence or absence of lymph node metastasis, number and location of metastases (location indicated based on Japanese Classification of Esophageal Cancer 11th edition)
- Clinical stage (at diagnosis, before CRT)

  UICC-TNM 7th edition will be used for staging, but an evaluation using UICC-TNM 8th edition will also be indicated.
- Histological diagnosis
  - The pathology report will be used to confirm histologically that the disease is ESCC.
  - For patients with unresectable postoperative locoregionally recurrent ESCC, the pathological stage obtained from the pathological diagnosis will also be indicated.
- Previous treatment history

- Status of CRT administration
  Chemotherapy: Doses and dosing frequency of 5-FU and CDDP
  Radiation therapy: Irradiated sites, radiation dose, radiation frequency
- Whether endoscopic resection performed, surgery performed, surgical procedure, date of operation
- Whether surgical resection performed, surgery performed, surgical procedure, date of operation
- Whether other therapy administered, description of the therapy, and period administered

10.3.2 Height/body weight measurements and vital signs

The subject's height, body weight, and vital signs [temperature, pulse rate, systolic/diastolic blood pressure, peripheral oxygen saturation (SpO_2)] will be determined at the times indicated in the schedule shown in Table 10.2.1. Vital signs will be measured with the subject in the same posture at all time points.

10.3.3 ECOG Performance Status

ECOG PS (see Appendix 1) will be measured at the time points indicated in the schedule shown in Table 10.2.1.

10.3.4 Adverse events/concomitant drugs and therapies

From the start of protocol treatment to 28 days after discontinuation/completion of the protocol treatment or the start of subsequent treatment, whichever comes first, the subject will be observed for adverse events (signs and symptoms) and information will be collected on concomitant drugs and therapies (name of drug or therapy, route of administration, concomitant use start date, concomitant use completion date, reason for concomitant use) and recorded on the CRF. For the handling of adverse events, see Section 12 "Adverse Events Reporting."

10.4 Laboratory tests

10.4.1 Resting 12-lead ECG

Recording of the resting 12-lead ECG will be started after the subject is confirmed to be resting in the supine position, and qualitative abnormalities will be evaluated.

10.4.2 Hematology/blood chemistry/blood coagulation tests and urinalysis

Tests indicated in Table 10.1 will be performed at the time points indicated in Table 10.2.1 or when judged clinically necessary. As necessary, clinically significant laboratory parameters will be evaluated repeatedly until the test value returns to the baseline level, becomes clinically stable, or another treatment is started.

10.4.3 Endocrine function/immunology tests

Thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), ACTH, and KL-6 will be measured at the time points indicated in the schedule shown in Table 10.2.1.

10.4.4 Infection tests

HIV antibody, HBs antigen, HBs antibody, HBc antibody, and HCV antibody will be measured before enrollment. If the tests were performed within 6 months before enrollment, those results may be used instead.

10.4.5 Pregnancy test

If the subject is a woman of childbearing potential, a urine test performed within 14 days before enrollment will be confirmed to be negative. Urine tests will subsequently be performed every 12 weeks starting from

Day 1 of Cycle 2. If pregnancy is suspected based on a urine test, it will be determined using a serological test. If a subject is determined not to be of childbearing potential because the subject is menopausal (amenorrheic for ≥1 year) or has previously undergone tubal ligation or hysterectomy, this will be clearly indicated in the subject's source documents.

10.4.6 Tumor markers

Two parameters, CEA and SCC, will be measured at the time points indicated in the schedule shown in Table 10.2.1.

10.5 Tumor assessment

The investigator or radiologist will perform tumor assessments according to RECIST guideline version 1.1 that was modified for this study (see Appendix 2). The assessment results, including the responses in target and non-target lesions and the appearance of new lesions, will be used as criteria for assessing the advisability of continuing the protocol treatment.

10.5.1 Cervicothoracic/abdominopelvic contrast CT

For all subjects, a cervicothoracic/abdominopelvic contrast CT scan (simple CT scan permitted if patient has a contrast allergy) will be performed at the time points indicated below until progression is seen in tumor assessments performed according to the criteria specified in RECIST guideline version 1.1 that was modified for this study. A cervicothoracic/abdominopelvic contrast CT scan performed within 28 days before the start of CRT will be used as the baseline. CR determination will be required (see Table 10.2.2).

- Slice thickness will be ≤5 mm.
- Although a CT scan before CRT is outside the protocol of this study, it will be performed within 28 days before the start of CRT to the extent possible. Pre-CRT CT scans also will be evaluated according to the RECIST guideline version 1.1 modified for this study.
- CT scans after CRT completion and before the start of the protocol treatment. Generally performed after informed consent and before the start of administration, but results obtained before consent may be used if scan performed after CRT completion.
- Until CR determination, CT scans will be performed every 4 weeks (± 2 weeks) starting from the administration start date. CT scans for CR determination will be performed at least 4 weeks (28 days) after the previous examination.
- After CR determination, CT scans will be performed every 12 weeks (± 4 weeks) starting from the date of CR determination.
- If atezolizumab is discontinued for a reason other than a progression of the primary disease seen on imaging, a CT scan will be performed within 2 weeks of discontinuation. In addition, CT scans will be performed every 12 weeks (± 4 weeks) until progression of the primary disease is seen in a tumor assessment (by CT or upper gastrointestinal endoscopy) or subsequent treatment is started.

10.5.2 Upper gastrointestinal endoscopy

For all subjects, upper gastrointestinal endoscopy will be performed at the time points indicated below until progression is seen in the following evaluation of the primary lesion based on the Japanese Classification of Esophageal Cancer 11th edition. Upper gastrointestinal endoscopy performed within 28 days before the start of CRT will be used as the baseline. CR determination will be required (see Section 5.1.5 for CR determination criteria).

- Although upper gastrointestinal endoscopy before CRT is outside the protocol of this study, it will be

performed within 28 days before the start of CRT to the extent possible. In pre-CRT upper gastrointestinal endoscopy examinations as well, thorough observations will be carried out for the primary lesion evaluation based on Japanese Classification of Esophageal Cancer 11th edition, and sufficient specimens will be collected for the exploratory biomarker research associated with the present study.

- Upper gastrointestinal endoscopy after CRT completion and before the start of the protocol treatment. Performed after informed consent and before the start of administration, but results obtained before consent may be used if endoscopy performed after CRT completion.
- Until CR determination, upper gastrointestinal endoscopy will be performed every 4 weeks (± 2 weeks) starting from the start day of administration. Endoscopy for CR determination will be performed at least 4 weeks (28 days) after previous examination.
- After CR determination, upper gastrointestinal endoscopy will be performed every 12 weeks (± 4 weeks) starting from the date of CR determination.
- If atezolizumab is discontinued for a reason other than a progression of the primary disease seen on imaging, endoscopy will be performed within 2 weeks of discontinuation. In addition, endoscopy will be performed every 12 weeks (± 4 weeks) until progression of the primary disease is seen in a tumor assessment (by CT or upper gastrointestinal endoscopy) or subsequent treatment is started.

10.5.3 Central assessments

In this study, central assessments will be performed for primary locally advanced patients if promising results are obtained for the CR rate based on the investigator's assessments. In this case, the principal investigator will provide the subject's images (CT and endoscopy images) for use in the central assessment.

A procedure manual for the independent review committee that provides details regarding the central assessments and the organization performing them will be prepared separately.

10.6 Collection of tumor specimens and patient peripheral blood for exploratory biomarker research (optional)

For the subjects enrolled in the study, a variety of immunocompetent cells and immunity factors will be analyzed *ex vivo* to profile the subject's immune status, and its relationship to the clinical efficacy of sequential combination therapy with curative CRT and atezolizumab will be examined. The analysis will use lesion tissue specimens collected during endoscopy performed after CRT completion and before the start of the protocol treatment, as specified in the study, every 4 weeks (± 2 weeks) starting from the start day of administration until CR determination, and every 12 weeks (± 4 weeks) after CR determination. It will also use patient peripheral blood specimens collected at the same time points as the tumor specimens (during the treatment period, collected only at 4 weeks after the start of study participation). Any stored pathology specimens and peripheral blood for which secondary use has been approved that were collected before CRT in clinical studies or the routine clinical setting also will be used in the investigation. For a detailed description of the research, see the protocol for the additional research (TENERGY–TR research).

If a promising biomarker is found, a subgroup analysis related to the efficacy analysis will be considered.

10.7 Subsequent treatment

If subsequent treatment is started after the protocol treatment is discontinued, a description of every subsequent treatment (treatment regimen, start date) will be recorded on the subject's CRF.

10.8 Outcome investigation

After discontinuation of the protocol treatment, outcome will be investigated basically every 3 months

until death or through 1 year after the final patient is enrolled in the study. If direct follow-up is not feasible for a reason such as transfer to another hospital, necessary means, such as making an inquiry to that hospital, will be taken to confirm the subject's outcome to the extent possible. The findings will be indicated in the subject's source documents.

11 Data Collection

11.1 Handling and retention of CRF data

EP-CRSU Co., Ltd. will manage the data, including CRF data management and retention. It will prepare a data management protocol that will specify access restrictions, such as restrictions on viewing and entering data in the database, and appropriately manage and store records.

11.2 Specification of source documents

The source documents for this study are as follows.

Medical records
Consent form
Investigational product management table
Laboratory test data
Diagnostic imaging film, etc.

12 Reporting of Adverse Events

12.1 Evaluation of adverse events

12.1.1 Definition of an adverse event

An adverse event is any unfavorable or unintended sign (including abnormal changes in laboratory values), symptom, or disease in a subject who received the protocol treatment, whether or not considered related to the treatment.

If a symptom or sign of ≥Grade 1 (based on CTCAE version 4.0) is observed before the start of atezolizumab administration (during baseline evaluation), it will be treated as an adverse event only if the grade worsens as compared with the grade before administration.

12.1.2 Method of recording adverse events

Adverse events will be graded by selecting the closest definition from among Grades 0 to 5. If a sign (including abnormal laboratory values) or symptom is included in a diagnosis, the diagnosis based on CTCAE version 4.0, rather than the individual sign or symptom, will be recorded on the CRF.

An abnormal laboratory value will be reported as an adverse event only if the investigator judges any of the following to be applicable.

(1) It led to clinical signs or symptoms
(2) It is judged to be clinically significant
(3) It requires treatment
(4) It requires additional tests (excluding retesting only)
(5) It requires a measure such as investigational product discontinuation or dose reduction

12.1.3 Items recorded for adverse events

The following information will be recorded on the CRF for adverse events that occur.

(1) Name of adverse event
(2) Severity (CTCAE version 4.0 Grades 0 to 5, serious/non-serious)
(3) Causal relationship to protocol treatment
(4) Date occurred, date outcome determined, outcome
(5) Whether treated

12.1.4 Causality assessment

The causal relationship to the protocol treatment will be assessed as being in either of the following 2 categories.

Related
Unrelated

The causal relationship to the investigational product will be assessed as "related" if there is concluded to be a logical relationship to the investigational product and "unrelated" if it is concluded there is no such relationship.

12.1.5 Follow-up of the clinical course when an adverse event occurs

If an adverse event occurs, the investigator will promptly take the appropriate measures.

The subject's clinical course will be followed up until resolution or improvement of the symptoms (laboratory values) is confirmed, even after the end of the adverse events evaluation period (see Section 12.1.6 "Adverse events evaluation period"). However, follow-up of the clinical course of an adverse event can be terminated if at least 1 of the following are applicable.

Follow-up of the adverse event will be terminated if:

- The adverse event is not serious, it is concluded that a causal relationship to the investigational product can be ruled out, and at least 28 days have passed since discontinuation/completion of the protocol treatment.
- The principal investigator concludes that the symptoms are stable and there are no medically significant problems.
- Subsequent treatment has been administered and the causal relationship to the investigational product cannot be evaluated.
- Follow-up of the clinical course is difficult for reasons such as a transfer to another hospital.
- The subject refuses to be followed up.
- The subject died.

12.1.6 Adverse events evaluation period

Information on adverse events in this study will be collected during the adverse events evaluation period. The period will start from the start day of the protocol treatment and end either 28 days after its discontinuation/completion or, if subsequent treatment is started before then, before subsequent treatment begins, whichever time point comes first.

For the period from 29 days after the protocol treatment completion date onward, information will be collected on adverse events judged to be causally related to the protocol treatment.

After progression of the primary disease is seen, information will not be collected on adverse events that occur as a result of the new progression.

12.2 Reporting of serious adverse events

12.2.1 Definition of a serious adverse event

Adverse events, as defined in Section 12.1.1 "Definition of an adverse event," to which any of the following apply will be considered serious adverse events that:

(1) results in death or is life-threatening,

(2) results in persistent or significant disability/incapacity,

(3) results in a congenital anomaly/birth defect,

(4) requires inpatient hospitalization or results in prolongation of an existing hospitalization

Except for the following:

– Inpatient hospitalization or death as a result of the primary disease after progression of the primary disease is seen

– Hospitalization or prolongation of an existing hospitalization to alleviate the burden on a subject visiting from a distant location

– A previously planned hospitalization or prolongation of an existing hospitalization

– Hospitalization or prolongation of an existing hospitalization not related to an adverse event

– Hospitalization or prolongation of an existing hospitalization for ≤24 hours only to follow up the subject's clinical course,

(5) is a medically important event, defined as one that might jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed above.

12.2.2 Reporting obligations of the investigator and reporting procedures

1) Reporting to the head of the study site and coordinating committee

(1) Initial reporting

If a serious adverse event (see Section 12.2.1 "Definition of a serious adverse event") occurs, the investigator will immediately take the appropriate measures. The subinvestigator will promptly report the event to the principal investigator.

The investigator will report serious adverse events to the head of the study site and coordinating committee in writing [e-mail*, fax, or voice (telephone)] within 24 hours of learning of the occurrence of the event. If an initial report is made without using the "Serious Adverse Event Report Form," the event will promptly be reported using that form (by e-mail or fax).

In addition, investigator will report the details of the serious adverse event to the head of the study site and coordinating committee in writing within 5 working days of learning of the occurrence of the event.

*: Reporting by e-mail is recommended.

(2) Additional reporting

The investigator will implement follow-up of serious adverse events (see Section 12.1.5 "Follow-up of the clinical course when an adverse event occurs"). Additional information will be indicated on the "Serious Adverse Event Report Form (Additional Report)," which will promptly be sent to the head of the study site and coordinating committee.

Coordinating committee contact information: Coordinating committee secretariat

E-mail: tenergy_core@east.ncc.go.jp

Tel: 03-6759-9904; Fax: 03-5842-6432

The investigator will respond to any requests for further information from the coordinating committee, head of the study site, IRB, or investigational product provider.

12.2.3 Reporting obligations of the coordinating committee and reporting procedures

For a serious adverse event reported in the initial or additional reporting, the coordinating committee will determine its seriousness, causality, and predictability, and the need to report it to the regulatory authority [Pharmaceuticals and Medical Devices Agency (PMDA); based on Article 80-2, Paragraph 6 of the Pharmaceuticals and Medical Devices Act and Article 273 of the Enforcement Regulations of the Pharmaceuticals and Medical Devices Act].

The reporting procedure is described in detail in the "Procedures for Handling Safety Information."

1) Reporting to each principal investigator
   The coordinating committee will promptly report any reported serious adverse events and the decisions above to each principal investigator. The principal investigator will report these matters to the head of the study site as promptly as possible, in accordance with the rules of each study site.
2) Reporting to PMDA
   If the coordinating committee determines that reporting an event to the PMDA is necessary, it will respond based on Article 273 of the Enforcement Regulations of the Pharmaceuticals and Medical Devices Act and related notifications.
3) Reporting to data and safety monitoring committee
   If the coordinating committee determines that a deliberation by the data and safety monitoring committee is required for a serious adverse event, it will report the event in writing and seek opinions regarding the views of the principal investigator and coordinating committee regarding the adverse event and the appropriateness of the response to the adverse event (assessment of seriousness, causality, predictability of the event).
4) Reporting to the investigational product provider

After receiving the report from the investigator, the coordinating committee will promptly report the serious adverse event reported by the investigator to Chugai Pharmaceutical, the investigational product provider. In addition, the coordinating committee will respond as needed to requests for information other than that provided on the "Serous Adverse Event Report Form."

12.2.4 Duties of the data and safety monitoring committee

The data and safety monitoring committee will examine the adverse event reports and provide written advice to the coordinating committee on how to respond, including whether the study should be continued and the protocol revised. The procedure for this will be carried out according to the separately established "Procedures for the Data and Safety Monitoring Committee."

12.3 Collection of safety information

If it receives information concerning the safety of the investigational product from the investigational product provider, the coordinating committee will respond in accordance with Article 273 of the Enforcement Regulations of the Pharmaceuticals and Medical Devices Act and relevant notifications. The coordinating committee will report the safety information to each principal investigator, who will report the safety information to the head of the study site as promptly as possible, in accordance with the rules of each study site.

The reporting procedure is described in detail in the "Procedures for Handling Safety Information."

In addition, the coordinating committee will determine the need to revise the protocol and informed consent documents and provide an explanation to the subjects and will respond accordingly when such measures are necessary.

12.4 In the case of pregnancy or breast-feeding

If a female subject of childbearing potential is reported to be pregnant during the study or within 5 months after the final administration of the investigational product, the protocol treatment will be discontinued, and the pregnancy will be reported in writing to the investigational product provider via the coordinating committee. The subject will receive an explanation of the risks associated with pregnancy and the potential effects on the fetus and will continue to be monitored through the end of gestation. If a serious adverse event involving pregnancy is confirmed (e.g., a fetal event, a maternal event during/after pregnancy, and a congenital anomaly/birth defect in the newborn), it will promptly be reported to the coordinating committee and investigational product provider.

If a partner of a male subject becomes pregnant during the study or within 5 months after discontinuation or the final investigational product administration, this will be promptly reported to the investigational product provider via the coordinating committee. Efforts will be made to collect and report information on the details regarding the course and outcome of pregnancy in the partner of a male subject exposed to the investigational product. The partner of a male subject will continued to be monitored through the end of gestation. If a serious adverse event involving pregnancy is confirmed (e.g., a fetal event, a maternal event during/after pregnancy, and a congenital anomaly/birth defect in the newborn), it will promptly be reported to the coordinating committee and investigational product provider.

The reporting procedure will be carried out according to the separately established "Procedures for Handling Safety Information."

12.5 Overdosage and other cases

In cases such as overdosage of the investigational product, the investigator will take the appropriate

measures and promptly report the event in writing to the investigational product provider via the coordinating committee, in accordance with the "Procedures for Handling Safety Information." Overdosage is defined as any accidentally or intentionally administered dose that is considered excessive.

13 Assessment of Response and Definitions of the Endpoints

13.1 Assessment of response

Tumor response will be assessed according to the RECIST guideline version 1.1 modified for this study (Appendix 2).

It will be assessed by performing cervicothoracic/abdominopelvic contrast CT (simple CT permitted in the case of contrast allergy) and upper gastrointestinal endoscopy according to the schedule shown in Table 10.2.1 and measuring the tumor size on the images. Examinations for CR determination will be performed after at least 4 weeks (28 days). In the case of PD, see Section 10.5 "Tumor assessment."

13.2 Definition of endpoints

13.2.1 Complete response (CR) rate

A CR is defined as meeting both of the following conditions in the evaluations of the primary lesion and lymph node metastases (must be determined): (1) in the primary lesion evaluation by upper gastrointestinal endoscopy, it is concluded that all endoscopic findings suggestive of malignant lesions have been disappeared (primary lesion CR), and (2) in the tumor assessment performed using cervicothoracic/abdominopelvic contrast CT according to the RECIST guideline version 1.1 modified for this study, the response assessment for the target and non-target lesions is CR.

The proportion of subjects with a CR will be considered the CR rate.

13.2.2 Objective response rate (ORR)

A PR is defined as meeting both of the following conditions (must be determined), using upper gastrointestinal endoscopy and cervicothoracic/abdominopelvic contrast CT evaluations performed within 28 days before the start of CRT as the baseline: (1) in the primary tumor evaluation by upper gastrointestinal endoscopy, it is concluded the endoscopic findings suggestive of a neoplastic lesion indicate no obvious progression (primary tumor CR or non-CR/non-PD), and (2) in the tumor evaluation performed using cervicothoracic/abdominopelvic contrast CT according to the RECIST guideline version 1.1 modified for this study, the efficacy assessment for the target and non-target lesions is PR.

The proportion of subjects with either a CR, as indicated in Section 13.2.1, or PR will be considered the ORR.

13.2.3 Progression-free survival (PFS)*

This will be the period from the date of enrollment to either the date that progression is determined or the date of death from any cause, whichever comes first.

- Progression is PD based on either (1) obvious progression in endoscopic findings suggestive of malignant lesions in the primary lesion evaluation by upper gastrointestinal endoscopy (primary lesion PD) or (2) diagnostic imaging using cervicothoracic/abdominopelvic contrast CT (performed according to the RECIST guideline version 1.1 modified for this study). The date of progression will be the date of endoscopy in the case of progression based on (1) and the date of the imaging procedure in the case of progression based on (2). If the protocol treatment is discontinued due to clinical PD, the date that clinical PD was determined to have occurred will be used as the date of progression if a PD assessment based on diagnostic imaging cannot be performed due to worsening of the subject's condition.
- Surviving patients who are not assessed as having progression will be censored on the last date on which an absence of progression is confirmed on imaging (hereinafter referred to as the "last date of

PFS confirmed"). (If information on progression or progression-free is obtained from a medical institution to which the patient was transferred or referred, a patient referral document indicating the basis for the diagnosis will be received and retained. Obtaining the information by telephone only will not be permitted.)

- For patients who died without being assessed as progression, whether to treat them as having an "event occurring on the date of death" or as being "censored on the last date of PFS confirmed" will be determined in the case review meeting to be held before the data are finalized. In principle, if the period from the last date of PFS confirmed to the date of death is ≤24 weeks, the patients will be treated as having an "event occurring on the date of death," while if the period from the last date of PFS confirmed to the date of death is >24 weeks, the patient will be treated as being "censored on the last date of PFS confirmed."
- If the study treatment is discontinued for a reason such as an adverse event or the subject's refusal to continue and another treatment is given as subsequent treatment, censoring will be performed on the start day of the subsequent treatment.
- The occurrence of a second malignancy (multiple metachronous cancers) will be considered neither an event nor a censoring event, and the progression-free survival will be the period until another event is observed.

13.2.4 Failure pattern*

The distribution of the number of patients according to site of progression will be considered the failure pattern, and this will be summarized by category. The categories to be used are indicated below. Multiple categories will be selected if progression is seen at multiple sites simultaneously when the initial progression occurs.

Local progression, distant metastasis, other, unknown

13.2.5 Overall survival (OS)*

This will be the period from the date of enrollment to the date of death from any cause.

For all surviving subjects, censoring will be performed on the final date on which survival is confirmed (confirmation of survival by telephone permitted; the fact that survival was confirmed will be documented in the medical record, etc.).

For subjects lost to follow-up, censoring will be performed using the final date on which survival was confirmed before the subject was lost to follow-up.

*For PFS, failure pattern, and OS, the 5-year outcome will be followed in a clinical study separate from the present study ("Observational study of the status of chemoradiotherapy administration and long-term prognosis in unresectable, locally advanced ESCC").

13.2.6 Incidence of adverse events

For each type of adverse event resulting from the protocol treatment, the incidence of the worst grade across all of the cycles will be determined using CTCAE version 4.0.

13.2.7 Analysis of biomarkers related to the therapeutic benefit of CRT and atezolizumab monotherapy

An analysis of genetic and immunological biomarkers related to the protocol treatment will be performed using biopsy specimens and peripheral blood specimens collected before curative CRT, before the start of atezolizumab administration, at the time of the CR assessment, and during upper gastrointestinal endoscopy

performed when progression occurs. Details will be provided in the separately established "Exploratory Biomarker Research Protocol."

If a promising biomarker is found, a subgroup analysis related to the efficacy analysis will be considered.

14 Statistical Matters

An overview of the statistical analysis plan is provided below. Details will be provided in the separately established statistical analysis plan. "An analysis of biomarkers related to investigational product sensitivity and resistance mechanisms" will be conducted according to a separately established plan.

14.1 Handling of subjects

Details of handling of subjects will be determined by the case review meeting.

14.2 Definition of analysis populations

The analysis populations are defined below.

Abbreviation	Analysis Population	Definition
All enrolled patients (ITT)	Intention to treat (ITT)	Analysis set based on the ITT principle. The set of subjects enrolled in the study excluding those who were enrolled multiple times or mistakenly enrolled.
FAS	Full analysis set	The analysis set that is the closest possible to the ITT principle. It is the analysis set that excludes subjects in the ITT set to whom either of the follow apply. • Never administered atezolizumab monotherapy • Later found to be ineligible based on information obtained according to the protocol (does not meet 1 or more of the inclusion criteria or does meet 1 or more of the exclusion criteria)
SP	Safety population	The set of enrolled patients who were never administered the protocol treatment.

Depending on the findings from the case review meeting, the above classifications may not be necessary (e.g., in the case where the ITT and FAS are the same group). In this case, only 1 analysis set will be indicated when the analysis results are reported in the analysis report and clinical study report (e.g., if the ITT set and FAS are the same and the FAS is used as the analysis set for the primary analysis, it will be indicated as ITT in reporting the results due to the importance placed on the uniformity of the analysis results.)

14.3 Data handling

The handling of the data (conditions for analysis set inclusion/exclusion, etc.) will be determined by the coordinating committee in consultation with the principal investigators. Details regarding data handling will be provided in the statistical analysis plan.

14.3.1 Handling of missing values and outliers

Analyses that impute missing values or include outliers will generally not be performed. However, if there are found to be missing values or outliers that could have a significant effect on the analysis results before the data are finalized, the means of addressing this will be indicated in the statistical analysis plan.

14.3.2 Actions for additional analyses

An analysis performed after the statistical analysis plan is finalized will be considered an additional analysis. The results of any additional analysis will be reported either in a manner that makes it clear that the analysis was not planned in advance or in a separately prepared additional analysis report.

14.4 Positioning of analyses and analysis methods

The decision-making criteria and development policy for the period following the study will not be clearly established. However, the protocol treatment will be concluded to be a promising treatment if the CR rate is statistically shown to exceed the 20% threshold in primary locally advanced patients based on the Japanese Classification of Esophageal Cancer 11th edition for upper gastrointestinal endoscopy, the primary endpoint, and the RECIST guideline version 1.1 modified for this study for cervicothoracic/abdominopelvic contrast CT, and if improvements in efficacy and safety are confirmed for the secondary endpoints.

If promising results are obtained in this study, the POC is established, and safety is confirmed, it is likely that the phase III study to be planned by Chugai Pharmaceutical, the provider of atezolizumab, will be conducted. In addition, if the 40% CR rate that was established as the expected rate is substantially exceeded, use of the Conditional Early Approval System for Pharmaceuticals will also be considered.

The analyses described below are planned for this study.

(1) Primary analysis: An analysis of the CR rate after the CR rate confirmed by the assessment of the principal investigator or subinvestigator in 38 patients in the FAS for primary locally advanced patients, which is required for the primary analysis, has reached the evaluable level (analysis of all endpoints other than those of the "exploratory study of biomarkers related to the therapeutic benefit of CRT and atezolizumab monotherapy" and the "investigation of QC and QA in radiation therapy").

(2) Final analysis: After the primary analysis, data on a 5-year follow-up of data for outcome, etc. until fully developed data can be obtained will be collected and analyzed in the separately planned observational research.

The primary analysis will **examine whether the lower limit of the binomial distribution-based exact 90% confidence interval for the CR rate exceeds the 20% specified as the threshold** for the **38 patients in the FAS** for primary locally advanced patients. **For reference, a similar examination will be performed by constructing the binomial distribution-based exact 95% confidence interval**.

14.5 Efficacy analyses

The efficacy analysis set will be the FAS for primary locally advanced patients. As a sensitivity analysis, an analysis will also be performed for the ITT analysis set. In addition, for the postoperative recurrent patients, the following efficacy analyses will be performed for the FAS at the time of the final analysis only.

14.5.1 Analyses of the primary endpoint

The CR rate confirmed by the assessment of the principal investigator or subinvestigator will be calculated based on the definitions in Section 13.2 "Definition of endpoints." Based on the binomial distribution-based 90% CI will be constructed according the exact method. As a reference, the 95% confidence interval also will be constructed. If 13 or more of the 38 patients in the FAS for primary locally advanced patients have a CR (ORR ≥34.2%), it will be regarded as statistically significant.

If a subgroup analysis is performed, the therapeutic benefit across subgroups will be summarized using appropriated analysis methods such as Fisher's exact test and a logistic regression model.

14.5.2 Analyses of the secondary endpoints

Analyses of the secondary efficacy endpoints are specified as follows.

(1) PFS

The Kaplan-Meier method will be used to estimate PFS, progression-free survival (PFS) rate at a

specific time point, and median PFS. The 95% CI for PFS rate at a specific time point will be estimated using Greenwood's formula, and the 95% CI for the median PFS will be estimated using the method of Brookmeyer and Crowley.

If a subgroup analysis is performed, the therapeutic benefit across subgroups will be summarized using appropriate survival analysis methods, such as the log-rank test and Cox's proportional hazards model.

Survival will be calculated with 1 year equaling 365.25 days and 1 month equaling 365.25/12 days, with the calculation defined by an equation: (Event date or censoring date) − (Date of study enrollment) + 1 day.

(2) OS

The analysis will be the same as that performed for PFS.

(3) CR rate confirmed by central assessment

The CR rate confirmed by central assessment will be calculated based on the definition in Section 13.2 "Definition of endpoints." The binomial distribution-based 95% CI will be constructed according the exact method. If a subgroup analysis is performed, the therapeutic benefit across subgroups will be summarized using appropriated analysis methods such as Fisher's exact test and a logistic regression model.

(4) ORR

The ORR determined by the assessments of the principal investigator or subinvestigator will be calculated based on the definition in Section 13.2 "Definition of endpoints." The binomial distribution-based 95% CI will be constructed according the exact method. If a subgroup analysis is performed, the therapeutic benefit across subgroups will be summarized using appropriated analysis methods such as Fisher's exact test and a logistic regression model.

(5) Failure pattern

The distribution of the number of patients according to site of initial progression will be considered the failure pattern, and this will be summarized by category. As necessary, the local progression rate and distant metastasis rate will be determined, and their binomial distribution-based exact 95% CIs will be constructed.

14.6 Safety analyses

The safety population will be the SP for primary locally advanced patients. A summary of the incidences of respective adverse events will be reported as the incidence of adverse events. As needed, the binomial distribution-based 95% CIs constructed according to the exact method or spaghetti plots summarizing the changes in variables such as laboratory values over time will be reported. In addition, for the postoperative recurrent patients, the safety analysis described above will be performed for the SP, only at the time of the final analysis.

14.7 Target sample size

[Primary locally advanced patients]: 38

(However, if there are less than 38 patients in the FAS at the point where 38 primary locally advanced patients have been enrolled, enrollment will be carried out until it is confirmed that the FAS for the primary locally advanced ESCC part of the study comprises 38 patients. Basically, up to 40 primary locally advanced patients will be enrolled.)

[Postoperative recurrent patients]: 10

Total number of patients: Maximum of 50

14.7.1 Rationale

See Section 4.4 "Clinical hypothesis and rationale for planned sample size."

14.8 Interim analysis

No interim analysis will be performed in this study.

14.9 Final analysis

In the final analysis, which will be performed after the primary analysis, all endpoints will be analyzed. After the final analysis, a statistical analysis report will be prepared according to the statistical analysis plan.

14.10 Special notes

14.10.1 Other exploratory analyses

1) Demographic and other
   These will be summarized using appropriate descriptive statistics.
2) Tabulation of treatment compliance data
   Details of summaries of the course of treatment and tabulations of information such as the reasons for discontinuation will be specified in the statistical analysis plan.
3) Subgroup analyses
   Exploratory subgroup analyses related to the efficacy analysis will be performed for the factors indicated below. These analyses will not necessarily have adequate statistical power, and no adjustments will be made for multiplicity. Therefore, the results of the subgroup analyses will strictly be interpreted as being exploratory results.
   • Sex (male/female)
   • Age (<70 years / ≥70 years)
   • Primary tumor location (upper thoracic esophagus, middle thoracic esophagus, lower thoracic esophagus)
   • In addition, if a promising biomarker is found in the biomarker research associated with the present study, a subgroup analysis related to the efficacy analysis will be considered.

4) Items to be tabulated in the clinical study report
   The items to be tabulated in the clinical study report will basically correspond to the sections indicated below. Summary indices will be calculated as needed.
   <Efficacy evaluation (analysis set: FAS and SP)>
   • 11.2 Demographic data
   • 11.4.1.1 Complete response rate (CR rate)
   • 11.4.1.2 Objective response rate (ORR)
   • 11.4.1.3 Progression-free survival (PFS)
   • 11.4.1.4 Overall survival (OS)
   • 11.4.1.5 Failure pattern
   <Safety evaluation (analysis set: SP)>
   • 12.2.1 Incidence of adverse events (number of patients with events and incidence by worst grade)
   • 12.4.2 Summary statistics of and changes over time in laboratory values
   <Indices referred to but not included in the text of the clinical study report>
   • 14.3.2 Listings of deaths, other serious adverse events and other significant adverse events
   • 14.3.4 Listings of laboratory values by patient

<Appendices>
• 16.2.1 Listing of patients for which the protocol treatment was discontinued
• 16.2.2 Listing of patients with major protocol deviations
• 16.2.3 Listing patients excluded from the FAS
• 16.2.4a Listing of demographic data
• 16.2.4b Previous treatment
• 16.2.4c Listing of concomitant drugs and therapies
• 16.2.5 Compliance
• 16.2.6 Listing of efficacy response data (tumor assessments, OS, PFS, subsequent treatment, tumor markers) by patient
• 16.2.7 Listings of adverse events by patient

15 Ethical Matters

15.1 Policies, laws and regulations, and standards with which the study complies

The study will be conducted in compliance with the protocol, Declaration of Helsinki (http://www.med.or.jp/wma/), Article 80-2 of the Pharmaceuticals and Medical Devices Act, Ministerial Ordinance on Good Clinical Practice (Ordinance No. 28 the Ministry of Health and Welfare, dated March 27, 1997) and its amendments, and related notifications.

15.2 Informed consent

15.2.1 Explanation to subjects

The investigator directly give the subject an informed consent document approved by the IRB and orally explain the following in detail.

1) That the study involves research
2) The purpose of the study
3) The name, title, and contact information of the investigators
4) The method of the study (including the experimental aspects of the study and inclusion/exclusion criteria for patients)
5) Expected clinical benefits and foreseeable risks or inconveniences
6) The availability of alternative treatments and their important potential risks and benefits of those treatments
7) The expected duration of the patient's participation in the study
8) That the patient's participation in the study is voluntary and that the patient may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the patient is otherwise entitled
9) That the monitor(s), the auditor(s), the IRB(s), and the regulatory authority(ies) will be granted direct access to the patient’s source documents without violating the confidentiality of the patient, and that, by signing the informed consent form, the patient is authorizing such access
10) That if the results of the study are published, the patient’s identity will remain confidential
11) The person(s) at the study site to contact for further information regarding the study and the rights of patients, and whom to contact in the event of study-related injury
12) The compensation and/or treatment available to the patient in the event of study-related injury
13) The approximate number of patients involved in the study
14) That the patient will be informed in a timely manner if information becomes available that may be relevant to the patient’s willingness to continue participation in the study
15) The foreseeable circumstances and/or reasons under which the patient’s participation in the study may be terminated
16) The anticipated expenses, if any, to the patient for participating in the study
17) The anticipated payment, if any, to the patient for participating in the study
18) The patient's responsibilities
19) Type of the IRB investigating and reviewing the appropriateness of the study, matters to be investigated and reviewed by each IRB, and other study-related matters concerning the IRB
20) That the patient may check the written procedures for the IRB set forth in the preceding item and should request if he or she wants to do so. In addition, if the written procedures for the IRB, etc. are disclosed on a website, the fact that the address of the website is provided. If not disclosed, the fact that they are publicly available for review
21) That data may be secondarily used

15.2.2 Informed consent

The investigator will request the patients to participate in the study after giving an explanation on the study and sufficient amount of time to think to the patients, and confirming that they have understood well about the contents of the study. If the patients personally consent to take part in the study, each of the investigator who gave the explanation, the study collaborator who provided a supplementary explanation, and the patient who received the explanations and consented will record the dates of the explanations or consent and sign the informed consent form approved by the IRB. The investigator will retain the signed informed consent form in the medical records and hand a copy of the signed informed consent form to the patient.

In the case where information that may affect the patients' willingness to continue participating in the study is obtained, the investigator will promptly notify it to the patients who are in the study, verify his or her willingness to continue his or her participation in the study, and record such a fact in a document. In addition, when the principal investigator judges that a revision of the informed consent document is necessary based on the information or because of other reasons, it will be promptly revised, and approval of the IRB will be obtained. After approval of the IRB, an explanation will be provided again using the revised informed consent document, and written informed consent should be obtained again.

15.3 Protection of personal information and subject identification

Personal information and information concerning privacy such as medical data will be recognized as those requiring strict protection and careful handling under the spirit of respecting individuals' personality, and full management measures will be taken to protect privacy. The Act on the Protection of Personal Information and the Act Partially Amending the Act on the Use of Numbers to Identify a Specific Individual in Administrative Procedures (Act No. 65 of September 9, 2015) will be followed.

15.3.1 Handling of personal information

1) Information that can identify an individual
   Subject identification (ID) codes, enrollment numbers
2) Anonymization and correspondence table management
   If personal information is provided to an entity outside of the study site, it will first be anonymized. As the minimum information for identifying a subject, the subject ID number and enrollment number will be used as "information that allows the identification of an individual." A correspondence table matching information such as patient's name and the enrollment number will appropriately be managed under the supervision of the principal investigator at each study site in accordance with the policies of that site.
   That is, information that can be used to identify an individual without a correspondence table, such as a subject's name, will not be disclosed to entities outside the study site.
3) Methods of handling personal information
   The personal information of the subject will be entered on the eCRF by the investigator or study collaborator and collected by reporting it to the data center.

15.3.2 Secondary use of data

Data obtained from this study may be secondarily used (e.g., metaanalysis) in a manner that they are not link to information identifying individuals only if approved by the coordinating committee and investigational product provider.

15.3.3 Safety management responsibility system

When using personal information, safety management measures will be taken in accordance with rules at each study site to minimize the risk of information leakage. The data center will properly manage personal information in accordance with the guidelines for personal information.

15.3.4 Handling of disclosure of the subjects' information

As a rule, the person who will respond to a request from a subject for the disclosure of private information held by the study will be an investigator at the study site where the subject is participating in the study.

15.4 Approval of the institutional review board (IRB)

15.4.1 Approval at the start of the study

When implementing this study, the principal investigator will submit the documents specified by the GCP ministerial ordinance such as the protocol and informed consent document to the head of the study site and receive approval of the IRB. As soon as approval of the IRB is granted, the principal investigator will send a copy of the written approval of the IRB and the informed consent document (study site version) to the coordinating committee secretariat, and retain the original of the written approval of the IRB.

The contents of the protocol will not be modified by the individual study sites. The protocol in common among all the study sites will be used. When the IRB requested to modify the main text of the protocol, the principal investigator will consult with the coordinating committee to consider its handling.

15.4.2 Approval of the IRB for the appropriateness of continuing the study

The appropriateness of continuing the study will be reviewed by the IRB once a year. If the IRB approved the continuation of the study, the principal investigator will send a copy of the written approval of the IRB to the coordinating committee secretariat, and retain the original of the written approval of the IRB.

15.4.3 Changes in the contents of the protocol

Revisions of the protocol, informed consent document and other relevant documents will be made in accordance with the procedure manual for preparing each document.

15.4.4 Categories of changes in the content of the protocol

In this study, changes in the content of the protocol will be handled as follows.

1) Revision
   A revision refers to a change in the content of the protocol. Approval of the IRB is required. In addition, when the coordinating committee determines that the change needs to be reviewed by the data and safety monitoring committee, the change will be reviewed and approved by the data and safety monitoring committee.
2) Notification letter
   When any insufficiency is found in the protocol and it is judged necessary to disseminate the details to persons involved in the study, a notification letter will be issued. The coordinating committee will determine whether the approval by the IRB at each study site is needed.
3) Questions and answers (Q & A)
   Regarding the interpretation of the description of the protocol, a Q & A document will be issued and disseminated to persons involved in the study.

15.4.5 Approval of the IRB at the time of protocol revision

When the protocol is revised during the study, the revised documents must be approved by the IRB.

15.5 Management of conflicts of interest (COIs)

The conflict of interest (COI) for persons involved in this study such as the investigators and coordinating investigators will be properly managed in accordance with the rules at the study sites. In addition, the COIs for the companies are managed in accordance with the companies' office regulations and compliance programs.

The investigational product provider (Chugai Pharmaceutical Co., Ltd.) will not be involved in any essential part of the study such as the operation of the study and the interpretation of results.

15.6 Compensation

In the event of health injuries attributable to the study in the patients, the study site should provide compensation in accordance with the "Procedures for Compensation for Health Injuries" even if the study site is not legally liable.

The compensation provided in this study will be the provision of medical expenses and medical benefits, in addition to medical care; no compensation payments will be made. The principle of compensation does not prevent the subjects from exercising their right to seek damages.

16 Monitoring and Audits

16.1 Monitoring

Monitoring will be performed by visiting the sites in accordance with the procedure manual for monitoring.

The monitoring will employ means such as direct access to source documents to verify that the study is being conducted appropriately and that the reliability of the data is being adequately maintained. After monitoring is carried out, a monitoring report will be prepared and submitted to the coordinating committee, the sponsor-investigator, and the head of the study site.

16.2 Protocol deviations and violations

The investigator will record all actions that deviate from the protocol, regardless of the reason. In the case of a protocol deviation that was medically unavoidable in order to avoid an emergent risk to the subject, the principal investigator will report the deviation to the heads of the study sites in writing in accordance with the procedure manual specified at each study site, and submit a copy of the same report to the coordinating committee.

After being reviewed by the coordinating committee, deviations will be classified into the following categories:

1) Major deviation
   A major deviation is defined as a deviation from the provisions of the protocol that is clinically inappropriate and to which more than one of the following conditions are applicable.
   (1) Affecting the evaluation of endpoints in the study
   (2) Intentional or systematic
   (3) Hazardous, or marked in degree
2) Deviation
   A deviation other than major deviations defined in 1) above.

16.3 Audits

The auditors will conduct audits in accordance with the "Procedures for Auditing" and the "Audit Plan" to confirm that the study is being appropriately conducted and the reliability of the data adequately maintained, by means such as direct access to source documents.

16.4 Direct access

The study site will cooperate with monitoring, audits, and inspections by the IRB and the regulatory authority, and will provide all source documents and other study-related records for direct access as necessary.

17 Special Notes

17.1 Retention of records

17.1.1 Sponsor-investigator

Records will be retained from the date of marketing approval to the date 5 years after the date of approval (if learning that records will not be attached to the application form, the date 3 years after the date of notification of such or the date 3 years after the date of study discontinuation or completion, whichever is later). For details, see the "Procedures for Retention of Records."

17.1.2 Study sites

The heads of the study sites and the founder of the IRBs will retain the essential documents, records and other relevant materials to be retained in accordance with the GCP ministerial ordinance, until either of the following dates whichever comes later. However, if longer retention is required, the coordinating committee will be consulted with regarding the length and means of retention. For the retention of records, the head of the study site will designate a record retention manager.

(1) Date of marketing approval for the investigational product (if notification is received that development has been discontinued or the study results will not be attached to the approval application, the date 3 years after the date of being notified either of the decision to discontinue development or of the fact that the study results will not be attached to the application)
(2) Date 3 years after study discontinuation or completion

17.2 Completion of the study

When the study is completed, the principal investigator will notify the head of the study site of the completion in writing and report a summary of study results in writing.

17.3 Discontinuation at a study site

If the sponsor-investigator finds that a study site has impeded proper study conduct through significant or persistent noncompliance with the GCP ministerial ordinance or the protocol, the sponsor-investigator may discontinue the study at that site. In this case, the sponsor-investigator will report to the head of the study site in writing that the study will be discontinued at that site. The sponsor-investigator will also report to the regulatory authority in writing that the study has been discontinued.

The investigator will promptly communicate this to the subjects, provide them with appropriate medical care, and take any other necessary measures.

17.4 Suspension of the study and discontinuation of the entire study

17.4.1 Suspension of the study

If it is concluded that the incidence of adverse events during the study exceeds the acceptable range, or if the principal investigator and coordinating committee decide that it is necessary to suspend the study because subject safety is markedly jeopardized by a serious adverse drug reaction or new information about the investigational product, the principal investigator will promptly notify the heads of the study sites of this and the reason for the suspension in writing. In addition, the coordinating committee will notify the regulatory authority in writing that the study is suspended.

17.4.2 Discontinuation of the entire study

If the principal investigator and coordinating committee decide that it is necessary to discontinue the

entire study because subject safety is markedly jeopardized during the study by a serious adverse drug reaction or new information about the investigational product, the principal investigator will promptly notify the heads of the study sites of this and the reason for the discontinuation in writing. In addition, the principal investigator will notify the regulatory authority in writing that the study has been discontinued.

The investigator will promptly communicate this to the subjects, provide them with appropriate medical care, and take any other necessary measures.

18 Study Organization

Because this is a multicenter, investigator-initiated clinical study, a coordinating committee will be established.

18.1 Study implementation structure

See Appendix 1

18.2 Funding source of the study

This study will be conducted with financial support from the Practical Research for Innovative Cancer Control program (FY 2018) of the Japan Agency for Medical Research and Development (AMED), and with the investigational product provided at no charge by Chugai Pharmaceutical Co., Ltd.

19 Attribution of Study Findings and Publication of Study Results

The study findings will be attributed to the National Cancer Center Japan. The coordinating committee will confer with the principal investigators and other related persons to make decisions regarding the presentation of the study results at academic conferences or their publication in papers, before such presentation or publication.

20 References

1. Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med. 1992;326(24):1593-8.
2. al-Sarraf M, Martz K, Herskovic A, Leichman L, Brindle JS, Vaitkevicius VK, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol. 1997;15(1):277-84.
3. Ishida K, Iizuka T, Ando N, Ide H. Phase II study of chemoradiotherapy for advanced squamous cell carcinoma of the thoracic esophagus: nine Japanese institutions trial. Jpn J Clin Oncol. 1996;26(5):310-5.
4. Ishida K, Ando N, Yamamoto S, Ide H, Shinoda M. Phase II study of cisplatin and 5-fluorouracil with concurrent radiotherapy in advanced squamous cell carcinoma of the esophagus: a Japan Esophageal Oncology Group (JEOG)/Japan Clinical Oncology Group trial (JCOG9516). Jpn J Clin Oncol. 2004;34(10):615-9.
5. Ohtsu A, Boku N, Muro K, Chin K, Muto M, Yoshida S, et al. Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol. 1999;17(9):2915-21.
6. Shinoda M, Ando N, Kato K, Ishikura S, Kato H, Tsubosa Y, et al. Randomized study of low-dose versus standard-dose chemoradiotherapy for unresectable esophageal squamous cell carcinoma (JCOG0303). Cancer science. 2015;106(4):407-12.
7. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol. 2002;20(5):1167-74.
8. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA, Jr., Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. Jama. 1999;281(17):1623-7.
9. Kato K, Muro K, Minashi K, Ohtsu A, Ishikura S, Boku N, et al. Phase II study of chemoradiotherapy with 5-fluorouracil and cisplatin for Stage II-III esophageal squamous cell carcinoma: JCOG trial (JCOG 9906). Int J Radiat Oncol Biol Phys. 2011;81(3):684-90.
10. Garnett CT, Palena C, Chakraborty M, Tsang KY, Schlom J, Hodge JW. Sublethal irradiation of human tumor cells modulates phenotype resulting in enhanced killing by cytotoxic T lymphocytes. Cancer research. 2004;64(21):7985-94.
11. Gupta A, Probst HC, Vuong V, Landshammer A, Muth S, Yagita H, et al. Radiotherapy promotes tumor-specific effector CD8+ T cells via dendritic cell activation. Journal of immunology (Baltimore, Md : 1950). 2012;189(2):558-66.
12. Sharabi AB, Nirschl CJ, Kochel CM, Nirschl TR, Francica BJ, Velarde E, et al. Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses via Cross-Presentation of Tumor Antigen. Cancer immunology research. 2015;3(4):345-55.
13. Mole RH. Whole body irradiation; radiobiology or medicine? The British journal of radiology. 1953;26(305):234-41.
14. Demaria S, Golden EB, Formenti SC. Role of Local Radiation Therapy in Cancer Immunotherapy. JAMA oncology. 2015.
15. Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009;15(17):5379-88.
16. Park SS, Dong H, Liu X, Harrington SM, Krco CJ, Grams MP, et al. PD-1 Restrains Radiotherapy-Induced Abscopal Effect. Cancer immunology research. 2015;3(6):610-9.
17. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. The New England journal of medicine. 2012;366(10):925-31.
18. Tang C, Welsh JW, de Groot P, Massarelli E, Chang JY, Hess KR, et al. Ipilimumab with Stereotactic Ablative Radiation Therapy: Phase I Results and Immunologic Correlates from Peripheral T Cells. Clinical cancer research : an official journal of the American Association for Cancer Research. 2017;23(6):1388-96.
19. Luke JJ, Lemons JM, Karrison TG, Pitroda SP, Melotek JM, Zha Y, et al. Safety and Clinical Activity of Pembrolizumab and Multisite Stereotactic Body Radiotherapy in Patients With Advanced Solid Tumors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(16):1611-8.
20. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017.
21. Doi T, Piha-Paul SA, Jalal SI, Saraf S, Lunceford J, Koshiji M, et al. Safety and Antitumor Activity of the Anti-Programmed Death-1 Antibody Pembrolizumab in Patients With Advanced Esophageal Carcinoma. J Clin Oncol. 2017:Jco2017749846.
22. Kudo T, Hamamoto Y, Kato K, Ura T, Kojima T, Tsushima T, et al. Nivolumab treatment for

oesophageal squamous-cell carcinoma: an open-label, multicentre, phase 2 trial. The lancet oncology. 2017;18(5):631-9.
23. Hatogai K, Fujii S, Kojima T, Daiko H, Nomura S, Doi T, et al. Large-scale comprehensive immunohistochemical biomarker analyses in esophageal squamous cell carcinoma. Journal of cancer research and clinical oncology. 2017;143(11):2351-61.
24. Yagi T, Baba Y, Ishimoto T, Iwatsuki M, Miyamoto Y, Yoshida N, et al. PD-L1 Expression, Tumor-infiltrating Lymphocytes, and Clinical Outcome in Patients With Surgically Resected Esophageal Cancer. Annals of surgery. 2017.
25. Hara H, Kojima T, Hironaka S, Kato K, Tsushima T, Ura T, et al. Phase II Study of Nivolumab (ONO-4538/BMS-936558) for Esophageal Cancer Clinical Activity by PD-L1 Expression Analysis. Japanese Society of Medical Oncology Annual Meeting. 2016.
26. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(20):1919-29.
27. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255-65.
28. Hecht M, Buttner-Herold M, Erlenbach-Wunsch K, Haderlein M, Croner R, Grutzmann R, et al. PD-L1 is upregulated by radiochemotherapy in rectal adenocarcinoma patients and associated with a favourable prognosis. European journal of cancer (Oxford, England : 1990). 2016;65:52-60.
29. Lim YJ, Koh J, Kim S, Jeon SR, Chie EK, Kim K, et al. Chemoradiation-Induced Alteration of Programmed Death-Ligand 1 and CD8(+) Tumor-Infiltrating Lymphocytes Identified Patients With Poor Prognosis in Rectal Cancer: A Matched Comparison Analysis. Int J Radiat Oncol Biol Phys. 2017;99(5):1216-24.
30. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nature medicine. 2002;8(8):793-800.
31. Thompson RH, Kuntz SM, Leibovich BC, Dong H, Lohse CM, Webster WS, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer research. 2006;66(7):3381-5.
32. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(9):3360-5.
33. Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. International immunology. 2007;19(7):813-24.
34. Hino R, Kabashima K, Kato Y, Yagi H, Nakamura M, Honjo T, et al. Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. Cancer. 2010;116(7):1757-66.
35. Yoshida T, Jiang F, Honjo T, Okazaki T. PD-1 deficiency reveals various tissue-specific autoimmunity by H-2b and dose-dependent requirement of H-2g7 for diabetes in NOD mice. Proceedings of the National Academy of Sciences of the United States of America. 2008;105(9):3533-8.
36. Tahara M, Ohtsu A, Hironaka S, Boku N, Ishikura S, Miyata Y, et al. Clinical impact of criteria for complete response (CR) of primary site to treatment of esophageal cancer. Jpn J Clin Oncol. 2005;35(6):316-23.
37. Satake H, Tahara M, Mochizuki S, Kato K, Hara H, Yokota T, et al. A prospective, multicenter phase I/II study of induction chemotherapy with docetaxel, cisplatin and fluorouracil (DCF) followed by chemoradiotherapy in patients with unresectable locally advanced esophageal carcinoma. Cancer Chemother Pharmacol. 2016;78(1):91-9.
38. Yokota T, Kato K, Hamamoto Y, Tsubosa Y, Ogawa H, Ito Y, et al. Phase II study of chemoselection with docetaxel plus cisplatin and 5-fluorouracil induction chemotherapy and subsequent conversion surgery for locally advanced unresectable oesophageal cancer. British journal of cancer. 2016;115(11):1328-34.
39. Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. The New England journal of medicine. 2017;377(19):1824-35.
40. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. The New England journal of medicine. 2018.
41. Atkinson M, Ferguson R, Ogilvie AL. Management of malignant dysphagia by intubation at endoscopy. Journal of the Royal Society of Medicine. 1979;72(12):894-7.

Appendix 1) Performance Status (ECOG classification)

PS	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.

Appendix 2) New response evaluation criteria in solid tumors (revised RECIST guideline) version 1.1 (modified for this study)

This study will use the new response evaluation criteria in solid tumors (revised RECIST guideline) version 1.1, Japanese edition, translated by the Japan Clinical Oncology Group (JCOG). However, because the measurable lesions will be limited to lymph nodes, and criteria for evaluating primary lesions endoscopically will be included, responses will be evaluated using the criteria modified from the RECIST guideline with a focus on the shaded parts below.

Malignant lymph nodes: Lymph nodes with short axis ≥ 10 mm will be considered malignant lymph nodes and evaluated as target lesions.

- Lymph nodes with short axis < 10 mm and ≥ 5 mm will be considered non-target lesions if they are clinically diagnosed as metastatic nodes, and will not be considered malignant nodes if they are clinically diagnosed as non-metastatic nodes.
- Lymph nodes with short axis < 5 mm will not be considered malignant nodes.

Primary esophageal lesion: The primary lesion will be evaluated as a non-target lesion using endoscopy as an additional evaluation based on the "response evaluation criteria for primary lesion using endoscopy" specified in Japanese Classification of Esophageal Cancer 11th edition.

Tumor markers: Tumor markers will not be used to evaluate responses in this study.

New lesions: The following will not be assessed as new lesions:

1) Esophageal ulcers or scars judged to have resulted from irradiation; flat, erosive changes; white moss; iodine unstained areas, and small elevations assessed as negative for cancer cells on biopsy.
2) If a CR is assessed in the response evaluation of the primary lesion, newly discovered esophageal lesions that are judged to have resolved with endoscopic or other localized treatment.

Overall response: As is indicated in Table 2-9-1, an overall evaluation will be performed that takes into account the combined responses in the target and non-target lesions and the primary lesion and whether new lesions have appeared.

2-1. Baseline evaluation

- In accordance with the examination schedule, tumor lesions will be identified by upper gastrointestinal endoscopy and cervicothoracic/abdominopelvic contrast CT before enrollment, and each lesion will be categorized as measurable or non-measurable.
- Tumor diameter will be measured on CT cross-sectional images; measurements in the sagittal and coronal planes obtained with three-dimensional reconstructed images will not be used.
- Even if the short axis of the lymph node is ≥5 mm and <10 mm, it will be considered lymph node metastasis if the node can clearly judged to be malignant by means such as FDG-PET and ultrasound, or from the patient's clinical course.
- The baseline evaluation will be performed using the results of the most recent imaging procedure performed within 28 days before the start of CRT.

2-2. Definition of a measurable lesion

A lesion will be considered measurable if any of the following are applicable (In the present study, distant metastasis to areas other than the #104 lymph nodes are not included in the evaluations. Therefore, measurable lesions do not include non-nodal lesions.)

- Malignant lymph nodes with short axis ≥ 10 mm on CT with a slice thickness of ≤5 mm

(Malignant lymph nodes with short axis ≥ 5 mm and < 10 mm that are clinically judged to be metastases will be considered unmeasurable lesions. Lymph nodes with short axis ≥ 5 mm and < 10 mm that are clinically judged not to be metastases and lymph nodes with short axis < 5 mm will not be considered malignant lymph nodes.)

2-3. Selection of target lesions and baseline documentation

Of measurable lesions (lymph node metastases) identified at enrollment, up to 2 lesions will be selected as target lesions in descending order of the length of short axis. Whether lesions allow reproducible repeated measurements will be taken into account in selecting target lesions (lesions that are large in diameter but difficult to measure will be avoided).

For the selected target lesions, the site, test method, test date examined, short axis, and the sum of diameters of all of the target lesions (hereinafter referred to as the "sum of diameters") will be recorded as the baseline tumor evaluation.

2-4. Baseline documentation of non-target lesions

All lesions not selected as target lesions will be considered non-target lesions regardless of whether they are measurable, and their site, test method, and test date will be recorded as the baseline tumor evaluation.

2-5. Assessment of tumor response

The target and non-target lesions will be evaluated using the same method of examination as at enrollment, and the diameters of the target lesions and whether the non-target lesions resolved or progressed will be recorded.

2-6. Response criteria for target lesions

• Complete response (CR)

Any nodal target lesions must have reduction in short axis to <5 mm. Even if the sum of the diameters is not 0 mm, the target lesions may be assessed as CR.

• Partial response (PR)

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

• Progressive disease (PD)

At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

• Stable disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

• Not all evaluated (NE)

No test can be performed for some reason, or lesions cannot be assessed as any of CR, PR, PD, or SD.

Percentage reduction in the sum of diameters = (Pre-treatment sum of diameters) − (Sum of diameters at assessment) / (Pre-treatment sum of diameters) × 100%

Percentage increase in the sum of diameters = (Sum of diameters at assessment) − (Smallest sum of diameters) / (Smallest sum of diameters) × 100%

NB: All target lesions should have their actual measurements recorded whenever they are measurable (e.g., even when <5 mm). However, if target lesions are reported as "too small to measure," irrespective of CT slice thickness, the diameter will be recorded as 0 mm if the lesion has likely disappeared, or as 5 mm if the lesion is faintly seen but too small to measure.
NB: When the percentage reduction meets the criteria for PR, and the percentage increase meets the criteria for PD at the same time, PD should be determined.
NB: For lesions that split during treatment, the fragmented portions should be added together to calculate the sum of diameters.
NB: If multiple lesions have coalesced during treatment and they are no longer separable, the diameter of the coalesced lesion should be added to calculate the sum of diameters. If lesions coalesce, and a plane between them may be maintained, the diameter of each individual lesion should be added to calculate the sum of diameters.

2-7. Response criteria for non-target lesions

1) Response criteria for non-target lesions other than the primary lesion

• Complete response (CR)
All non-target nodal lesions must be non-pathological in size (<5 mm short axis).

• non-CR/non-PD
Persistence of one or more non-target lesion(s) (including persistence of non-target nodal lesions measuring ≥5 mm in short axis).

• Progressive disease (PD)
"Unequivocal progression" of existing non-target lesions (including recurrence).
When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. When the response of target lesions is SD or PR, an increase in the tumor burden of a non-target lesion much higher than a decrease in the tumor burden is considered to be "unequivocal progression." If not, it is assessed as non-CR/non-PD.
When the patient has only non-measurable disease: As an idea, "unequivocal progression" is an increase in a non-target lesion that is determined to clearly exceed the tumor burden representing a 20% increase in the diameter and an additional 73% increase in volume.
• Not all evaluated (NE)
No test can be performed for some reason or when lesions cannot be assessed as any of CR, non-CR/non-PD or PD.

2) Response criteria for the primary lesion
• Primary lesion complete response (CR)
The assessment will be primary lesion CR if all of the following findings are obtained.
1) All endoscopic findings suggestive of malignant lesions have been disappeared.*1*2
*1: The following types of lesions will be considered "endoscopic findings suggestive of malignant lesions." In other words, the assessment will not be CR if the following types of lesions are seen.
• Erosive changes with irregularities
• Ulcerative lesion
• Obvious elevation (including submucosal mass elevations)
*2: The following types of lesions will not be considered "endoscopic findings suggestive of malignant lesions." In other words, the assessment may be CR even if the following types of lesion are seen.
• Scar

• Stenosis
• Iodine unstained area
• Small, granulomatous elevation assessed as negative for carcinoma on biopsy

2) No carcinoma is seen histopathologically by endoscopic biopsy*3 of the site where the primary lesion was present at baseline.

*3: Endoscopic biopsy will be performed from the area where the primary lesion had been present.

3) The entire esophagus can be observed by endoscopy.

4) There are no endoscopic findings suggestive of active esophagitis (flat, erosive changes; white moss)

• Primary lesion non-CR/non-PD

If neither a CR nor PD can be determined for the primary lesion, the assessment will be primary lesion non-CR/non-PD. This includes cases in which it is difficult to differentiate cicatricial stenosis associated with the treatment from esophageal stenosis associated with an increase in tumor volume.

• Primary lesion progressive disease (PD)

The assessment will be primary lesion PD when tumor volume has clearly increased as compared with the best findings obtained before or after the start of treatment, esophageal stenosis associated with an increase in tumor volume has worsened, or a new lesion* has appeared.

*: The assessment will not be PD if the assessment for the primary lesion is a CR or non-CR/non-PD, or if a new superficial lesion (e.g., an endoscopically resectable intramucosal carcinoma) has appeared in the esophageal mucosa at a location different from that of the primary lesion.

• Primary lesion not all evaluated (NE)

The assessment will be NE for the primary tumor in either of the following cases.

(1) No endoscopy can be performed for some reason.

• Except when the assessment is PD, the assessment will be non-CR/non-PD rather than NE in cases where biopsy cannot be performed in the area where the primary lesion was present.

(2) When the primary lesion cannot be assessed as any of CR, non-CR/non-PD, or PD.

2-8. Presence or absence of new lesions

When a lesion, which was not present at baseline, is identified after the start of treatment, it should be considered to be the appearance of a "new lesion."

The finding of a "new lesion" should be unequivocal: Not attributable to any difference from baseline in scanning technique, change in imaging modality or findings thought to represent something other than tumor. For example, necrosis of a liver metastatic lesion appeared as a new cystic lesion should not be handled as a new lesion. A lesion identified on a follow-up examination in an anatomical location that was not required to be scanned at baseline (pre-enrollment evaluation) is handled as a new lesion.

If a lesion disappears and reappears at a subsequent time point, it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumor had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumor status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently "disappeared" single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorization is based upon the realization that most lesions do not actually "disappear" but are not visualized because they are beyond the resolving power of the imaging modality employed.

If a lesion may be new but equivocal, the lesion should not be recorded as a new lesion, but imaging examination should be repeated after a clinically appropriate interval. If a repeat imaging test confirms that it is a new lesion, then a new lesion should be declared using the date of the imaging test when it is confirmed to

be a new lesion.

However, the following will not be assessed as a "new lesion."

1) An esophageal ulcer or scar judged to have resulted from irradiation; a flat, erosive change; white moss; an iodine unstained area, and a small elevation assessed as negative for carcinoma on biopsy.

2) A newly discovered esophageal lesion that is judged to have been cured with localized treatment including endoscopic treatment, in cases where the primary lesion is assessed as CR.

2-9. Overall response

Overall response will be assessed based on a combination of the response of target lesions, response of non-target lesions and the appearance of a new lesion in accordance with Table 2-9-1 below. If no non-target lesion is present at baseline, overall response will be assessed based on the response of target lesions and the appearance of a new lesion. If no target lesion is present at baseline, overall response will be assessed based on a combination of the response of non-target lesions and the appearance of a new lesion in accordance with Table 2-9-2.

Table 2-9-1 Overall response at each time point: patients with target lesions

Target Lesions	Non-Target Lesions		New Lesions	Overall Response
	Primary Lesion	Non-Primary Lesions		
CR	CR	CR	No	CR
CR	CR	Non-CR/non-PD	No	PR
CR	Non-CR/non-PD	CR	No	PR
CR	Non-CR/non-PD	Non-CR/non-PD	No	PR
CR	CR	Not all evaluated	No	PR
CR	Non-CR/non-PD	Not all evaluated	No	PR
CR	Not all evaluated	CR	No	PR
CR	Not all evaluated	Non-CR/non-PD	No	PR
CR	Not all evaluated	Not all evaluated	No	PR
PR	Non-PD or NE	Non-PD or NE	No	PR
SD	Non-PD or NE	Non-PD or NE	No	SD
Not all evaluated	Non-PD or NE	Non-PD or NE	No	NE
PD	Any	Any	Yes or No	PD
Any	PD	Any	Yes or No	PD
Any	Any	PD	Yes or No	PD
Any	Any	Any	Yes	PD

Table 2-9-2 Overall response at each time point: patients with non-target lesions only

Non-Target Lesions		New Lesions	Overall Response
Primary Lesion	Non-Primary Lesions		
CR	CR	No	CR
CR	Non-CR/non-PD	No	Non-CR/non-PD
Non-CR/non-PD	CR	No	Non-CR/non-PD
CR	Not all evaluated	No	NE
Not all evaluated	CR	No	Non-CR/non-PD
Non-CR/non-PD	Non-CR/non-PD	No	Non-CR/non-PD
Non-CR/non-PD	Not all evaluated	No	NE
Not all evaluated	Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	Not all evaluated	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

2-10. Best overall response

The best overall response will be considered "better" in the order of CR > PR > SD > PD > NE. The best overall response will be assessed based on the overall responses during the entire study period in accordance with the criteria specified below. When a response falls under multiple categories based on their definitions, the response should be classified into the best one of the applicable categories (any of CR, PR, SD, PD, and NE).

If no target lesions are present, the best overall response will be considered "better" in the order of CR > non-CR/non-PD > PD > NE. The best overall response will be assessed based on the overall responses during the entire study period in accordance with the criteria specified below.

• Complete response (CR)

An overall response of CR is obtained at least 2 consecutive times at intervals of at least 4 weeks (28 days).

The date on which a best overall response of CR is determined after an overall response of CR has been confirmed for the second time will be considered the "date of CR determination."

• Partial response (PR)

An overall response of PR or better (CR or PR) is obtained at least 2 consecutive times at intervals of at least 4 weeks (28 days). The date on which a best overall response of PR is determined after an overall response of PR or better has been confirmed for the second time will be considered the "date of PR determination."

• Stable disease (SD)

A best overall response of CR or PR is not obtained, but the overall response through the assessment at 6 weeks after the start of the treatment is not PD, and an overall response of SD is obtained at least once.

• Progressive disease (PD)

The criterion for a best overall response of CR is not satisfied, and the overall response of PD is determined.

• Not evaluable (NE)

Inevaluable

• Non-CR/non-PD

A best overall response of CR or PR is not obtained, but the overall response through the assessment at 6 weeks after the start of the treatment is not PD, and an overall response of non-CR/non-PD is

determined at least once.

Appendix 3) Management of atezolizumab-specific adverse events

Toxicity related or suspected of being related to atezolizumab should be managed according to standard medical procedures. In addition, follow-up examinations such as autoimmune antibody tests and biopsies will be performed to examine whether an immunogenic etiology may be involved.

Nearly all immune-related adverse events observed in patients administered an immunomodulatory agent are mild and resolve spontaneously. However, to avoid the possibility of a serious complication, events such as these should be detected early and treated promptly. A therapeutic benefit may not immediately be seen by discontinuing atezolizumab administration. With severe immune-related toxicity, acute-phase management by topical or systemic administration of a corticosteroid preparation or administration of another immunosuppressant may also be necessary.

If atezolizumab administration is to be continued, the investigator should first examine the benefits versus risks for the patient. Even in a patient who meets the criteria for permanent discontinuation, resuming atezolizumab administration may be considered after complete recovery from an immune-related event if a benefit has been obtained. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.

In managing an adverse event, the most suitable measures to take will be determined by also referring to the most recent atezolizumab investigator's brochure.

Pulmonary events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and lung infiltration have been seen in association with atezolizumab administration. Patients will be evaluated for lung-related signs and symptoms throughout the study period. In addition, a thoracic CT scan will be performed during each tumor evaluation.

For all pulmonary events, a thorough evaluation of other commonly reported causes (e.g., pneumonia/pulmonary infection, lymphangiosis carcinomatosa, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, pulmonary hypertension) also should be carried out. Guidelines for managing pulmonary events are shown in Table 3-1.

Table 3-1 Guidelines for managing pulmonary events including pneumonitis

Event	Management
Grade 1 pulmonary event	• Continue atezolizumab administration and implement careful monitoring. • Perform the imaging procedure again. • Consider referral to a pulmonologist.
Grade 2 pulmonary event	• Interrupt atezolizumab for up to 12 weeks after the occurrence of event.[a] • Refer to a pulmonologist and infectious disease specialist and consider bronchoscopy or BAL. • Start corticosteroid administration at a dose equivalent to oral prednisone at 1 to 2 mg/kg/day. • If event improves to ≤ Grade 1, resume atezolizumab.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify coordinating committee.[c] • If the event is a recurrence, handle it as a Grade 3 or 4 adverse event.

Grade 3 or 4 pulmonary event	• Permanently discontinue atezolizumab administration and notify the coordinating committee. • Bronchoscopy or BAL is recommended. • Start oral prednisone administration at 1 to 2 mg/kg/day or an equivalent dose. • If the event does not improve within 48 hours after the start of corticosteroid therapy, consider adding an immunosuppressant. • If the event improves to ≤ Grade 1, taper the corticosteroid dose over a period of at least 1 month.

BAL = bronchoalveolar lavage

a. If it is necessary to reduce the corticosteroid dose (if started) to the equivalent of an oral prednisone dose of 10 mg/day or lower, the duration of atezolizumab interruption can be extended (can exceed 12 weeks after event onset). The length of extension allowed must be determined by agreement of the principal investigator at each site and the coordinating committee.
b. If corticosteroid therapy is started, the dose must be tapered to the equivalent of an oral prednisone dose of 10 mg/day or lower over a period of at least 1 month before atezolizumab is resumed.
c. Resumption of atezolizumab administration may be considered after complete recovery from an immune-related event if the patient has benefited from atezolizumab. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.

Hepatic events

Immune-related hepatitis is seen in association with atezolizumab administration. Patients who are eligible for the study must have adequate liver function based on their measured values for total bilirubin and liver transaminases. Liver function monitoring will be carried out throughout the investigational product administration period. Guidelines for managing hepatic events are shown in Table 3-2.

Patients who experience right upper quadrant pain or cryptogenic nausea or vomiting will immediately undergo liver function tests (LFT: total bilirubin, AST, ALT), and the results of those tests will be determined before the next administration of the investigational product. For patients with elevated LFT values, possible causes such as concomitant drugs, viral hepatitis, and toxicity or neoplasms will be examined and treatment provided as necessary.

Table 3-2 Guidelines for managing hepatic events

Event	Management
Grade 1 hepatic event	• Continue atezolizumab administration. • Monitor LFTs until values return to normal range.
Grade 2 hepatic event	**All events:** • Monitor LFTs more frequently until values return to baseline levels. **Events that persist for more than 5 days:** • Interrupt atezolizumab for up to 12 weeks after the occurrence of the event.[a] • Start corticosteroid administration at a dose equivalent to oral prednisone at 1 to 2 mg/kg/day. • If event improves to ≤ Grade 1, resume atezolizumab.[b]

	• If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify coordinating committee.[c]
Grade 3 or 4 pulmonary event	• Permanently discontinue atezolizumab administration and notify the coordinating committee. • For a liver biopsy to identify the cause of the liver disorder and evaluating the results, consider referral to a gastroenterologist. • Start corticosteroid administration at a dose equivalent to oral prednisone at 1 to 2 mg/kg/day. • If the event does not improve within 48 hours after the start of corticosteroid therapy, consider adding an immunosuppressant. • If the event improves to ≤ Grade 1, taper the corticosteroid dose over a period of at least 1 month.

LFT = liver function tests

a. If it is necessary to reduce the corticosteroid dose (if started) to the equivalent of an oral prednisone dose of 10 mg/day or lower, the duration of atezolizumab interruption can be extended (can exceed 12 weeks after event onset). The length of extension allowed must be determined by agreement of the principal investigator at each site and the coordinating committee.

b. If corticosteroid therapy is started, the dose must be tapered to the equivalent of an oral prednisone dose of 10 mg/day or lower over a period of at least 1 month before atezolizumab is resumed.

c. Resumption of atezolizumab administration may be considered after complete recovery from an immune-related event if the patient has benefited from atezolizumab. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.

Gastrointestinal events

Immune-related colitis is seen in association with atezolizumab administration. Guidelines for managing diarrhea and colitis are shown in Table 3-3. For all cases of diarrhea or colitis, a thorough evaluation of other more common causes should be performed. If the event is protracted or severe, or associated with signs of systemic inflammation or an acute-phase reaction (e.g., increased CRP/platelet count, increased band cells), sigmoidoscopy (or colonoscopy when appropriate) and a colon biopsy (3 to 5 specimens for a standard paraffin block) will performed to identify inflammation and lymphocytic infiltration for making a definitive diagnosis of colitis.

Table 3-3 Guidelines for managing gastrointestinal events (diarrhea or colitis)

Event	Management
Grade 1 diarrhea or colitis	• Continue atezolizumab administration. • Start symptomatic treatment. • Endoscopy is recommended if symptoms persist for more than 7 days. • Monitor carefully.
Grade 2 diarrhea or colitis	• Interrupt atezolizumab for up to 12 weeks after the occurrence of the event.[a] • Start symptomatic treatment. • Referral to a gastroenterologist is recommended.

	• If event is a recurrence or persists for more than 5 days, start corticosteroid administration at a dose equivalent to oral prednisone at 1 to 2 mg/kg/day. • If event improves to ≤ Grade 1, resume atezolizumab.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify the coordinating committee.[c]
Grade 3 diarrhea or colitis	• Interrupt atezolizumab for up to 12 weeks after the occurrence of the event.[a] • Refer to gastroenterologist for evaluation and confirmatory biopsy. • Start corticosteroid administration at a dose equivalent to intravenous methylprednisolone at 1 to 2 mg/kg/day. If improvement is seen, switch to oral prednisone at 1 to 2 mg/kg/day or an equivalent dose. • If event improves to ≤ Grade 1, resume atezolizumab.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify the coordinating committee.[c]
Grade 4 diarrhea or colitis	• Permanently discontinue atezolizumab administration and notify the coordinating committee. • Refer to gastroenterologist for evaluation and confirmatory biopsy. • Start corticosteroid administration at a dose equivalent to intravenous methylprednisolone at 1 to 2 mg/kg/day. If improvement is seen, switch to oral prednisone at 1 to 2 mg/kg/day or an equivalent dose. • If the event does not improve within 48 hours after the start of corticosteroid therapy, consider adding an immunosuppressant. • If the event improves to ≤ Grade 1, taper the corticosteroid dose over a period of at least 1 month.

a. If it is necessary to reduce the corticosteroid dose (if started) to the equivalent of an oral prednisone dose of 10 mg/day or lower, the duration of atezolizumab interruption can be extended (can exceed 12 weeks after event onset). The length of extension allowed must be determined by agreement of the principal investigator at each site and the coordinating committee.

b. If corticosteroid therapy is started, the dose must be tapered to the equivalent of an oral prednisone dose of 10 mg/day or lower over a period of at least 1 month before atezolizumab is resumed.

c. Resumption of atezolizumab administration may be considered after complete recovery from an immune-related event if the patient has benefited from atezolizumab. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.

Endocrine events

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have occurred in association with atezolizumab administration. Guidelines for managing endocrine events are shown in Table 3-4. Patients who exhibit cryptogenic symptoms such as headache, fatigue, myalgia, impotence, constipation, or mental status changes will be tested for endocrine disorders of the thyroid, pituitary, and adrenals. If an endocrine disorder is suspected, the patient should be referred to an endocrinologist. To determine whether a thyroid abnormality is present, thyroid stimulating hormone (TSH), free T3 (fT3), and free T4 (fT4) levels

will be measured. Testing pituitary hormone levels and pituitary function (e.g., TSH, growth hormone, luteinizing hormone, follicle stimulating hormone, testosterone, prolactin, and adrenocorticotropic hormone (ACTH) levels and the ACTH stimulation test) and brain magnetic resonance imaging (MRI; detailed cross-sectional scanning of pituitary) may be useful for differentiating primary hypopituitarism from primary adrenal insufficiency.

Table 3-4 Guidelines for managing endocrine events

Event	Management
Subclinical hypothyroidism	• Continue atezolizumab administration. • Start thyroid hormone replacement therapy. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Interrupt atezolizumab. • Start thyroid hormone replacement therapy. • Monitor TSH weekly. • Consider referral to an endocrinologist. • If symptoms are manageable and thyroid function improves, resume atezolizumab.
Subclinical hyperthyroidism	**If TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab administration. • Monitor TSH every 4 weeks. **If TSH < 0.1 mU/L:** • Follow the guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Interrupt atezolizumab. • Start antithyroid drug therapy (e.g., methimazole, carbimazole) as needed. • Consider referral to an endocrinologist. • If symptoms are manageable and thyroid function improves, resume atezolizumab. • In the case of life-threatening immune-related hyperthyroidism, permanently discontinue atezolizumab administration and notify the coordinating committee.[c]
Grade 2 to 4 symptomatic adrenal insufficiency	• Interrupt atezolizumab for up to 12 weeks after the occurrence of the event.[a] • Refer to an endocrinologist. • Perform appropriate Imaging procedures. • Start corticosteroid administration at a dose equivalent to intravenous methylprednisolone at 1 to 2 mg/kg/day. If improvement is seen, switch to oral prednisone at 1 to 2 mg/kg/day or an equivalent dose. • Resume atezolizumab if event improves to ≤ Grade 1 and condition stabilizes with replacement therapy.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption or if the condition does not stabilize with replacement therapy, permanently discontinue atezolizumab administration and notify the coordinating committee.[c]

Grade 1 or 2 hyperglycemia	• Continue atezolizumab administration. • Test for diabetes mellitus. If type 1 diabetes mellitus is present, handle the event as a Grade 3 event. If type 1 diabetes mellitus is not present, treat it according to the guidelines of the study site. • Monitor glucose control.
Grade 3 or 4 hyperglycemia	• Interrupt atezolizumab. • Start insulin therapy. • Monitor glucose control. • Resume atezolizumab if symptoms improve and blood glucose levels stabilize.
Grade 2 or 3 hypophysitis (panhypopituitarism)	• Interrupt atezolizumab for up to 12 weeks after the occurrence of the event.[a] • Refer to an endocrinologist. • Perform brain MRI (pituitary protocol). • Start corticosteroid administration at a dose equivalent to intravenous methylprednisolone at 1 to 2 mg/kg/day. If improvement is seen, switch to oral prednisone at 1 to 2 mg/kg/day or an equivalent dose.[a] • Start hormone replacement therapy as clinically necessary. • If event improves to ≤ Grade 1, resume atezolizumab.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify the coordinating committee.[c] • If the hypophysitis is a recurrence, handle it as a Grade 4 adverse event.
Grade 4 hypophysitis (panhypopituitarism)	• Permanently discontinue atezolizumab administration and notify the coordinating committee.[c] • Refer to an endocrinologist. • Perform brain MRI (pituitary protocol). • Start corticosteroid administration at a dose equivalent to intravenous methylprednisolone at 1 to 2 mg/kg/day. If improvement is seen, switch to oral prednisone at 1 to 2 mg/kg/day or an equivalent dose.[a] • Start hormone replacement therapy as clinically necessary.

MRI: nuclear magnetic resonance image; TSH: thyroid stimulating hormone

a. If it is necessary to reduce the corticosteroid dose (if started) to the equivalent of an oral prednisone dose of 10 mg/day or lower, the duration of atezolizumab interruption can be extended (can exceed 12 weeks after event onset). The length of extension allowed must be determined by agreement of the principal investigator at each site and the coordinating committee.

b. If corticosteroid therapy is started, the dose must be tapered to the equivalent of an oral prednisone dose of 10 mg/day or lower over a period of at least 1 month before atezolizumab is resumed.

c. Resumption of atezolizumab administration may be considered after complete recovery from an immune-related event if the patient has benefited from atezolizumab. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.

Ocular events

Visual complaints (e.g., uveitis, retinal events) should be evaluated by an ophthalmologist. Guidelines for managing ocular events are shown in Table 3-5.

Table 3-5 Guidelines for managing ocular events

Event	Management
Grade 1 ocular event	• Continue atezolizumab administration. • Referral to an ophthalmologist is strongly recommended. • Start treatment with steroidal and immunosuppressant ophthalmic solutions. • If symptoms persist, treat as a Grade 2 adverse event.
Grade 2 ocular event	• Interrupt atezolizumab for up to 12 weeks after the occurrence of the event.[a] • Referral to an ophthalmologist is strongly recommended. • Start treatment with steroidal and immunosuppressant ophthalmic solutions. • If event improves to ≤ Grade 1, resume atezolizumab.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify the coordinating committee.[c]
Grade 3 or 4 ocular event	• Permanently discontinue atezolizumab administration and notify the coordinating committee. • Refer to an ophthalmologist. • Start corticosteroid administration at a dose equivalent to oral prednisone at 1 to 2 mg/kg/day. • If the event improves to ≤ Grade 1, taper the corticosteroid dose over a period of at least 1 month.

a. If it is necessary to reduce the corticosteroid dose (if started) to the equivalent of an oral prednisone dose of 10 mg/day or lower, the duration of atezolizumab interruption can be extended (can exceed 12 weeks after event onset). The length of extension allowed must be determined by agreement of the principal investigator at each site and the coordinating committee.

b. If corticosteroid therapy is started, the dose must be tapered to the equivalent of an oral prednisone dose of 10 mg/day or lower over a period of at least 1 month before atezolizumab is resumed.

c. Resumption of atezolizumab administration may be considered after complete recovery from an immune-related event if the patient has benefited from atezolizumab. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.

Immune-related myocarditis

Immune-related myocarditis has been seen in association with atezolizumab administration. If a sign or symptom suggestive of myocarditis [including, but not limited to, an abnormal laboratory value (e.g., brain natriuretic peptide [BNP]) or abnormal cardiac imaging test, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, syncope] is seen, immune-related myocarditis should be suspected. Immune-mediated myocarditis must be differentiated from myocarditis occurring secondary to a condition such as an infection (e.g., a patient with a recent history of a gastrointestinal disorder that is primarily viral),

an ischemic event, underlying arrhythmia, worsening of pre-existing heart disease, or progression of a malignancy.

In all patients with suspected myocarditis, examinations such as appropriate cardiac enzyme tests, electrocardiography, chest X-ray, echocardiography, and cardiac MRI are to be performed emergently according the guidelines of the study site. A cardiovascular specialist should be consulted. If clinically necessary, consider performing an endomyocardial biopsy for definitive diagnosis and appropriate treatment.

Patients with a sign or symptom of myocarditis for which no other etiology has been identified will be managed according the guidelines shown in Table 3-6.

Table 3-6 Guidelines for managing immune-related myocarditis

Event	Management
Grade 2 immune-related myocarditis	• Interrupt atezolizumab for up to 12 weeks after the occurrence of the event[a] and notify the coordinating committee. • Refer to a cardiovascular specialist. • Start treatment according to the guidelines of the study site, and consider treatment with an antiarrhythmic drug, temporary pacemaker, ECMO, or a VAD as necessary. • Consider corticosteroid administration at a dose equivalent to intravenous methylprednisolone at 1 to 2 mg/kg/day. If improvement is seen, switch to oral prednisone at 1 to 2 mg/kg/day or an equivalent dose. [a] • If event improves to ≤ Grade 1, resume atezolizumab.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify the coordinating committee.[c]
Grade 3 or 4 immune-related myocarditis	• Permanently discontinue atezolizumab administration and notify the coordinating committee.[c] • Refer to a cardiovascular specialist. • Start treatment according to the guidelines of the study site, and consider treatment with an antiarrhythmic drug, temporary pacemaker, ECMO, or a VAD as necessary. • Start corticosteroid administration at a dose equivalent to intravenous methylprednisolone at 1 to 2 mg/kg/day. If improvement is seen, switch to oral prednisone at 1 to 2 mg/kg/day or an equivalent dose.[a,b] • If the event does not improve within 48 hours after the start of corticosteroid therapy, consider adding an immunosuppressant. • If the event improves to ≤ Grade 1, taper the corticosteroid dose over a period of at least 1 month.

ECMO: extracorporeal membrane oxygenation; VAD: ventricular assist device

a. If it is necessary to reduce the corticosteroid dose (if started) to the equivalent of an oral prednisone dose of 10 mg/day or lower, the duration of atezolizumab interruption can be extended (can exceed 12 weeks after event onset). The length of extension allowed must be determined by agreement of the principal investigator at each site and the coordinating committee.

b. If corticosteroid therapy is started, the dose must be tapered to the equivalent of an oral prednisone dose of 10 mg/day or lower over a period of at least 1 month before atezolizumab is resumed.
c. Resumption of atezolizumab administration may be considered after complete recovery from an immune-related event if the patient has benefited from atezolizumab. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.

Infusion reaction-related events

No premedication will be permitted before the initial administration of atezolizumab. However, in patients with an infusion reaction-related event (IRR) in atezolizumab Cycle 1, premedication with an antihistamine or antipyretic analgesic will be permitted from Cycle 2 onward. Due to concern that it could cause agranulocytosis, the use of metamizole (dipyrone) to treat IRRs when atezolizumab is administered will be prohibited.

Guidelines for administering medications for IRRs during Cycle 1 are shown in Table 3-7. IRR events that occur during or after Cycle 2 will be managed according to the guidelines of the study site.

Table 3-7 Guidelines for managing infusion reaction-related events

Event	Management
Grade 1 IRR	• Reduce the infusion rate to half the rate used when the event occurred. • After the event resolves, the investigator continues administration at the slower rate for 30 minutes and observes the patient's status. • If administration at the slower rate is tolerated for 30 minutes after the event resolves, the rate can be returned to the original rate.
Grade 2 IRR	• Suspend atezolizumab administration. • Implement aggressive symptomatic treatment (e.g., oral or intravenous administration of an antihistamine, antipyretic, glucocorticoid, epinephrine, bronchodilator or oxygen, or intravenous fluids). • If the symptoms return to baseline status, resume intravenous infusion at half the rate used when the event occurred. • When administering atezolizumab subsequently, orally administer an antihistamine, antipyretic and/or analgesic beforehand and carefully monitor IRRs.
Grade 3 or 4 IRR	• Suspend atezolizumab administration. • Implement aggressive symptomatic treatment (e.g., oral or intravenous administration of an antihistamine, antipyretic, glucocorticoid, epinephrine, bronchodilator or oxygen, or intravenous fluids). • Permanently discontinue atezolizumab administration and notify the coordinating committee.[a]

IRR = infusion reaction-related event

a. Resumption of atezolizumab administration may be considered after complete recovery from an immune-related event if the patient has benefited from atezolizumab. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.

Pancreatic events

Abdominal pain symptoms associated with increases in amylase and lipase that are suggestive of pancreatitis have occurred in association with atezolizumab. Evaluation for pancreatitis should be included in the differential diagnosis of acute abdominal pain. An appropriate complete work-up should include an evaluation for pancreatic duct occlusion and serum amylase and lipase tests. Guidelines for managing pancreatic events including pancreatitis are shown in Table 3-8.

Table 3-8 Guidelines for managing pancreatic events including pancreatitis

Event	Management
Grade 2 increase in amylase and/or lipase	**Amylase and/or lipase > 1.5 to 2.0 × ULN:** • Continue atezolizumab administration. • Monitor amylase and lipase weekly. • For persistently increased test values (e.g., for more than 3 weeks), consider corticosteroid administration at a dose equivalent to oral prednisone at 10 mg/day. **Asymptomatic and amylase and/or lipase > 2.0 to 5.0 × ULN:** • Handle it as a Grade 3 event.
Grade 3 or 4 increase in amylase and/or lipase	• Interrupt atezolizumab for up to 12 weeks after the occurrence of the event.[a] • Refer to a gastroenterologist. • Monitor amylase and lipase every other day. • If improvement is not seen, consider corticosteroid administration at a dose equivalent to oral prednisone at 1 to 2 mg/kg/day. • If event improves to ≤ Grade 1, resume atezolizumab.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify the coordinating committee.[c] • If the event recurs, permanently discontinue atezolizumab administration and notify the coordinating committee.
Grade 2 or 3 immune-related pancreatitis	• Interrupt atezolizumab for up to 12 weeks after the occurrence of the event.[a] • Refer to a gastroenterologist. • Start corticosteroid administration at a dose equivalent to intravenous methylprednisolone at 1 to 2 mg/kg/day. If improvement is seen, switch to oral prednisone at 1 to 2 mg/kg/day or an equivalent dose. • If event improves to ≤ Grade 1, resume atezolizumab.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify the coordinating committee.[c] • If the event recurs, permanently discontinue atezolizumab administration and notify the coordinating committee.
Grade 4 immune-related pancreatitis	• Permanently discontinue atezolizumab administration and notify the coordinating committee.[c] • Refer to a gastroenterologist.

	• Start corticosteroid administration at a dose equivalent to intravenous methylprednisolone at 1 to 2 mg/kg/day. If improvement is seen, switch to oral prednisone at 1 to 2 mg/kg/day or an equivalent dose. • If the event does not improve within 48 hours after the start of corticosteroid therapy, consider adding an immunosuppressant. • If the event improves to ≤ Grade 1, taper the corticosteroid dose over a period of at least 1 month.

a. If it is necessary to reduce the corticosteroid dose (if started) to the equivalent of an oral prednisone dose of 10 mg/day or lower, the duration of atezolizumab interruption can be extended (can exceed 12 weeks after event onset). The length of extension allowed must be determined by agreement of the principal investigator at each site and the coordinating committee.
b. If corticosteroid therapy is started, the dose must be tapered to the equivalent of an oral prednisone dose of 10 mg/day or lower over a period of at least 1 month before atezolizumab is resumed.
c. Resumption of atezolizumab administration may be considered after complete recovery from an immune-related event if the patient has benefited from atezolizumab. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.

Skin events

Rash has been seen in association with atezolizumab administration. Most cases of rash are mild and resolve spontaneously, and the rash may or may not be accompanied by pruritus. If persist and/or severe rash or pruritus is seen, refer to a dermatologist for examination. Biopsy should be considered if not contraindicated. Guidelines for managing skin events are shown in Table 3-9.

Table 3-9 Guidelines for managing skin events

Event	Management
Grade 1 skin event	• Continue atezolizumab administration. • Consider treatment with a topical corticosteroid and/or other symptomatic treatment (e.g., an antihistamine).
Grade 2 skin event	• Continue atezolizumab administration. • Consider referral to a dermatologist. • Start topical corticosteroid administration. • If the event does not improve, considered administering a stronger topical corticosteroid.
Grade 3 skin event	• Interrupt atezolizumab for up to 12 weeks after the occurrence of the event.[a] • Refer to a dermatologist. • Start corticosteroid administration at a dose equivalent to oral prednisone at 10 mg/day. If improvement is not seen within 48 to 72 hours, increase the dose to 1 to 2 mg/kg/day. • If event improves to ≤ Grade 1, resume atezolizumab.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify the coordinating committee.[c]

Grade 4 skin event	• Permanently discontinue atezolizumab administration and notify the coordinating committee.[c]

a. If it is necessary to reduce the corticosteroid dose (if started) to the equivalent of an oral prednisone dose of 10 mg/day or lower, the duration of atezolizumab interruption can be extended (can exceed 12 weeks after event onset). The length of extension allowed must be determined by agreement of the principal investigator at each site and the coordinating committee.
b. If corticosteroid therapy is started, the dose must be tapered to the equivalent of an oral prednisone dose of 10 mg/day or lower over a period of at least 1 month before atezolizumab is resumed.
c. Resumption of atezolizumab administration may be considered after complete recovery from an immune-related event if the patient has benefited from atezolizumab. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.

Nerve disorders

Myasthenia gravis and Guillain-Barre syndrome have been seen with administration of atezolizumab alone. The patient may exhibit signs and symptoms of a sensorimotor neuropathy. Detailed diagnostic examination is essential to accurately differentiate from other etiology. Guidelines for managing nerve disorders are shown in Table 3-10.

Table 3-10 Guidelines for managing nerve disorders

Event	Management
Grade 1 immune-related nerve disorder	• Continue atezolizumab administration. • Investigate etiology.
Grade 2 immune-related nerve disorder	• Interrupt atezolizumab for up to 12 weeks after the occurrence of the event.[a] • Investigate etiology. • Start treatment according to the guidelines of the study site. • If event improves to ≤ Grade 1, resume atezolizumab.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify the coordinating committee.[c]
Grade 3 or 4 immune-related nerve disorder	• Permanently discontinue atezolizumab administration and notify the coordinating committee.[c] • Start treatment according to the guidelines of the study site.
Myasthenia gravis and Guillain-Barre syndrome (all grades)	• Permanently discontinue atezolizumab administration and notify the coordinating committee.[c] • Refer to a neurologist. • Start treatment according to the guidelines of the study site. • Consider starting corticosteroid administration at a dose equivalent to oral or intravenous prednisone at 1 to 2 mg/kg/day.

a. If it is necessary to reduce the corticosteroid dose (if started) to the equivalent of an oral prednisone dose of 10 mg/day or lower, the duration of atezolizumab interruption can be extended (can exceed 12 weeks after event onset). The length of extension allowed must be determined by agreement of the principal investigator at each site and the coordinating committee.

b. If corticosteroid therapy is started, the dose must be tapered to the equivalent of an oral prednisone dose of 10 mg/day or lower over a period of at least 1 month before atezolizumab is resumed.
c. Resumption of atezolizumab administration may be considered after complete recovery from an immune-related event if the patient has benefited from atezolizumab. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.

Immune-related meningoencephalitis

Immune-related meningoencephalitis has been identified as a risk associated with atezolizumab administration. If signs or symptoms suggestive of meningitis or encephalitis (including, but not limited to, headache, cervical pain, confusion, convulsive seizure, sensorimotor dysfunction, and change/decrease in consciousness level) are seen, immune-related meningoencephalitis should be suspected. Encephalopathy resulting from a metabolic or electrolyte imbalance must be differentiated from meningoencephalitis caused by infection (bacterial, viral, fungal) or progression of a malignancy and meningoencephalitis secondary to a paraneoplastic process.

For patients in whom meningoencephalitis is suspected, a brain CT and/or MRI scan should be performed urgently to check for metastasis, inflammation, or edema. Lumbar puncture should be performed if the physician treating the patient determines that it is safe, and a neurologist should be consulted.

Patients with a sign or symptom of meningoencephalitis for which no other etiology has been identified will be managed according the guidelines shown in Table 3-11.

Table 3-11 Guidelines for managing immune-related meningoencephalitis

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab administration and notify the coordinating committee.[a] • Refer to a neurologist. • Start corticosteroid administration at a dose equivalent to intravenous methylprednisolone at 1 to 2 mg/kg/day. If improvement is seen, switch to oral prednisone at 1 to 2 mg/kg/day or an equivalent dose. • If the event does not improve within 48 hours after the start of corticosteroid therapy, consider adding an immunosuppressant. • If the event improves to ≤ Grade 1, taper the corticosteroid dose over a period of at least 1 month.

a. Resumption of atezolizumab administration may be considered after complete recovery from an immune-related event if the patient has benefited from atezolizumab. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.

Nephritis

Immune-related nephritis is associated with atezolizumab administration. Eligible subjects need adequate kidney function, and monitoring of serum creatinine and other measures of kidney function will therefore be required throughout the investigational product administration period. Subjects with abnormal kidney function must be evaluated and treated for more common causes (prerenal and postrenal causes, concomitant

drugs such as nonsteroidal anti-inflammatory drugs). If clinically necessary, subjects should be referred to a nephrologist. A kidney biopsy may be necessary for definitive diagnosis and appropriate treatment.

Subjects with signs and symptoms of nephritis for which no other etiology has been identified will be handled according to the guidelines shown in Table 3-12 if any other cause of acute kidney injury has not been identified.

Table 3-12 Guidelines for managing renal events

Event	Management
Grade 1 renal event	• Continue atezolizumab administration. • Monitor kidney function, including serum creatinine, until the test values return to the normal range or baseline levels.
Grade 2 renal event	• Interrupt atezolizumab for up to 12 weeks after the occurrence of the event.[a] • Refer to a nephrologist. • Start corticosteroid administration at a dose equivalent to oral prednisone at 1 to 2 mg/kg/day. • If event improves to ≤ Grade 1, resume atezolizumab.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify the coordinating committee.[c]
Grade 3 or 4 renal event	• Permanently discontinue atezolizumab administration and notify the coordinating committee.[c] • Refer to a nephrologist and consider kidney biopsy. • Start corticosteroid administration at a dose equivalent to oral prednisone at 1 to 2 mg/kg/day. • If the event does not improve within 48 hours after the start of corticosteroid therapy, consider adding an immunosuppressant. • If the event improves to ≤ Grade 1, taper the corticosteroid dose over a period of at least 1 month.

a. If it is necessary to reduce the corticosteroid dose (if started) to the equivalent of an oral prednisone dose of 10 mg/day or lower, the duration of atezolizumab interruption can be extended (can exceed 12 weeks after event onset). The length of extension allowed must be determined by agreement of the principal investigator at each site and the coordinating committee.

b. If corticosteroid therapy is started, the dose must be tapered to the equivalent of an oral prednisone dose of 10 mg/day or lower over a period of at least 1 month before atezolizumab is resumed.

c. Resumption of atezolizumab administration may be considered after complete recovery from an immune-related event if the patient has benefited from atezolizumab. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.

Immune-related myositis

Immune-related myositis is associated with atezolizumab administration. Myositis and inflammatory myopathy constitute a group of diseases that have characteristics common to inflammatory muscle injury. The most common of these diseases are dermatomyositis and polymyositis. The initial diagnosis involves an

examination based on clinical findings (muscular weakness, myalgia, rash associated with dermatomyositis), blood chemistry findings (increased serum creatinine kinase), and imaging findings (electromyography/MRI) and is confirmed by muscle biopsy. Subjects with signs and symptoms of myositis for which no other etiology has been identified will be managed according to the guidelines for managing immune-related myositis shown in Table 3-13.

Table 3-13 Guidelines for managing immune-related myositis

Event	Management
Grade 1 immune-mediated myositis	• Continue atezolizumab administration. • Refer to a rheumatologist or neurologist. • Start treatment according to the guidelines of the study site.
Grade 2 immune-related myositis	• Interrupt atezolizumab for up to 12 weeks after the the occurrence of the event[a] and notify the coordinating committee. • Refer to a rheumatologist or neurologist. • Start treatment according to the guidelines of the study site. • Start corticosteroid administration at a dose equivalent to intravenous methylprednisolone at 1 to 2 mg/kg/day. If improvement is seen, switch to oral prednisone at 1 to 2 mg/kg/day or an equivalent dose. • If the event does not improve within 48 hours after the start of corticosteroid therapy, consider adding an immunosuppressant. • If event improves to ≤ Grade 1, resume atezolizumab.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify the coordinating committee.[c]
Grade 3 immune-related myositis	• Interrupt atezolizumab for up to 12 weeks after the the occurrence of the event[a] and notify the coordinating committee. • Refer to a rheumatologist or neurologist. • Start treatment according to the guidelines of the study site. • Breathing assistance may be required in more severe cases. • Start corticosteroid administration at a dose equivalent to intravenous methylprednisolone at 1 to 2 mg/kg/day, or at a higher dose if severe symptoms (e.g., cardiac or respiratory symptoms, dysphagia, weakness that significantly limits movement) are seen. If improvement is seen, switch to oral prednisone at 1 to 2 mg/kg/day or an equivalent dose. • If the event does not improve within 48 hours after the start of corticosteroid therapy, consider adding an immunosuppressant. • If event improves to ≤ Grade 1, resume atezolizumab.[b] • If event does not improve to ≤ Grade 1 during atezolizumab interruption, permanently discontinue atezolizumab administration and notify the coordinating committee.[c] • If the event is a recurrence, handle it as a Grade 4 event.
Grade 4 immune-related myositis	• Permanently discontinue atezolizumab administration and notify the coordinating committee.[c]

	• Refer to a rheumatologist or neurologist. • Start treatment according to the guidelines of the study site. • Breathing assistance may be required in more severe cases. • Start corticosteroid administration at a dose equivalent to intravenous methylprednisolone at 1 to 2 mg/kg/day, or at a higher dose if severe symptoms (e.g., cardiac or respiratory symptoms, dysphagia, weakness that significantly limits movement) are seen. If improvement is seen, switch to oral prednisone at 1 to 2 mg/kg/day or an equivalent dose. • If the event does not improve within 48 hours after the start of corticosteroid therapy, consider adding an immunosuppressant. • If the event improves to ≤ Grade 1, taper the corticosteroid dose over a period of at least 1 month.

a. If it is necessary to reduce the corticosteroid dose (if started) to the equivalent of an oral prednisone dose of 10 mg/day or lower, the duration of atezolizumab interruption can be extended (can exceed 12 weeks after event onset). The length of extension allowed must be determined by agreement of the principal investigator at each site and the coordinating committee.

b. If corticosteroid therapy is started, the dose must be tapered to the equivalent of an oral prednisone dose of 10 mg/day or lower over a period of at least 1 month before atezolizumab is resumed.

c. Resumption of atezolizumab administration may be considered after complete recovery from an immune-related event if the patient has benefited from atezolizumab. Atezolizumab administration can be resumed only after the consent of the principal investigator (or an appropriate designated person) at each site and the coordinating committee is obtained.