group.

It is expected that the rate of treatment completion prior to surgery, and the rate of treatment completion prior to postoperative adjuvant chemotherapy for the trial treatment group will not be greatly inferior to those of the standard treatment group. The analysis of progression-free survival shall be performed using the analysis method used for overall survival including all enrollments. Rate comparison between groups shall be conducted using the Fisher's exact test, and interval estimation shall be calculated using the exact confidence interval based on binomial distribution.

12.5. Final analysis

Following completion of the follow-up period, all endpoints will be analyzed after confirmation of the data obtained in the final survey.

For periods other than this, group comparison for primary endpoints and the efficacy of secondary endpoints will not be performed except when permission has been obtained from the Data and Safety Monitoring Committee and when noted in the protocol.

The Data Center will compile the results of final analysis into the 'final analysis report' and submit to the research secretariat, research chairperson, group representative, group secretariat, the Data and Safety Monitoring Committee and the JCOG representative.

The research chairperson/research secretariat will summarize the final analysis report and produce a general report from a clinical perspective focusing on conclusion of the overall trial, problems, discussion and interpretation of results and future course. After obtaining the approval of the group representative and JCOG Data Center, this will be submitted to the Data and Safety Monitoring committee and JCOG representative.

The trial shall be deemed concluded with the written approval of the general report by the Data and Safety Monitoring committee.

12.6. Exploratory analysis

To examine the interaction between treatment outcomes and some groups, exploratory subgroup analyses will be performed for the following factors. Adequate detectability cannot be ensures in these analyses, and no adjustment for redundancy will be performed, and therefore the results of each subgroup analysis shall be interpreted as exploratory results

Factors planned for subgroup analyses:

- Age (under 65 yo/65 yo or higher)
- Main lesion site : (U/M/L)
- Sex (male/female)
- Histological type : (differentiated/undifferentiated)
- cT : (T1-3/T4)
- No. 16a2/b1 and/or Bulky lymph node metastasis (present/abscent)
- HER2 status (IHC 3+/IHC 2+)

13.Ethical items

13.1. Patient protection

All participating researchers are required to conduct this trial in accordance with the Helsinki Declaration (appendix) and the "Ethical Guidelines on Clinical Research" (public notice 415 of the Ministry of Health Labour and Welfare, http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/index.html). In the protocol guidelines 'medical facility' corresponds to 'clinical research facility' in the guidelines above.

13.2. Informed consent

13.2.1. Explanation given to patients

Prior to enrollment, the attending physicians will provide patients with a written explanation of the trial (written explanation in the appendix and written explanation with modifications by the medical facilities) with the approval of the medical facility and a verbal explanation as outlined below:

Furthermore, in this protocol, "approval of the medical facility" refers to either of the following:

1. When the director of the medical facility provides written approval to the researcher on the basis of the results of an investigation by the ethical review board in consultation with the director of the medical facility (institutional review board: IRB).
2. When the committee provides written approval to the researcher on the basis of the results of an investigation by the ethical review board in consultation with the director of the medical facility.

1) Explanation of disease classification, staging, and anticipated prognosis.
2) Confirmation that the present trial is a clinical trial conducted by the JCOG.
3) Trial design and rationale (significance, enrollment number, prerequisites, purpose, allocation etc.)
4) Details of the protocol treatment

Drug name, administration method, dosage, treatment period, and total duration of protocol treatment, etc.

5) Anticipated response to treatment

Anticipated life prolongation, tumor shrinkage, symptom alleviation, etc.

6) Anticipated adverse events, complications, sequelae, and related treatment methods

Explanation of the incidence and extent of anticipated adverse events, including complications, sequelae, TRD rate, and related treatment methods.

7) Financial burden and compensation

Costs incurred because of treatment will be covered by the national health insurance scheme, and any compensation in the event of injury will be treated as part of general medical care.

8) Alternative treatment

Details of current common treatments (including palliative medicine), and standard treatments, effects, and toxicities, etc.

Advantages and disadvantages of choosing an alternative treatment

9) Anticipated advantages and potential disadvantages

Explanation of potential benefits and disadvantages incurred from trial participation.

10) Verification of medical history documents

Explanation of auditing methods, such as 'obtaining medical professionals from other facilities and obtaining permission from the director of the medical facility to verify source documents related to medical history for quality control'.

11) Consent withdrawal and refusal

Trial participants are free to refuse consent before the trial or withdraw consent once given, and if they do so, there will be no disadvantages in terms of unfair treatment.

* Consent withdrawal is divided into withdrawal of participation consent (in accordance with 2) and 3) below), and refusal to continue the protocol treatment (as in 1) below). If a participant declares that they wish to withdraw consent, either 2) or 3) below needs to be specified and the JCOG Data

Center needs to be contacted immediately.

① Patient refusal : refusal to continue protocol treatment (follow-up will be continued)

② Consent withdrawal : withdrawal of consent to participate in the trial. Thereafter , all treatment and follow-up in accordance with the protocol will not be permitted

③ Consent withdrawal (including all data used in the trial): withdrawal of consent to participate in the trial. All data from the start of participation will not be permitted for use in the present trial.

12) Protection of patient confidentiality

All efforts will be made to maintain the confidentiality of patient identity and personal information.

13) Secondary utilization of data

Only with the approval of the JCOG committee, may date be used for secondary purposes (meta-analysis, etc.) independent of information related to personal identity.

14) Open questioning

Contact details of the attending physician, the medical facility's principal investigator, and the research chairperson (or research secretariat) of the present trial will be provided in writing to enable open questioning pertaining to the trial or treatment

15)

13.2.2. Consent

Participation in the present trial will be requested after explaining the trial to potential participants, and allowing sufficient time for reflection, so that they fully understand the trial details. If the patient consents to participate in the present trial, the following should be verified in the consent forms in the appendix and those for the trial in a template determined by the medical facility: the name of the physician who gave the explanation, the name of the patient who received the explanation and gave consent, and the date that consent was given.

Two copies of the consent form are required; one is to be given to the patient, and the second copy is to be filed by the facility coordinator. The original document will be kept with the patient's medical records.

13.3. Patient identification and protection of personal information

Under the principle of respecting the personalities of individuals, the JCOG recognizes that the privacy of personal and medical information should be strictly protected and handled cautiously. The JCOG has established a 'privacy policy' to create an infallible management strategy to protect privacy. For details, refer to the JCOG home page (http://www.JCOG.jp/).

13.3.1. JCOG-compliant policies, regulations, and norms

In principal, the JCOG conducts trials in accordance with the 'JCOG privacy policy' in addition to the regulations and the norms below. In the event of regulations, norms, or policies other than those described below, they will also be followed

- Protection of personal information act (Act No. 57, May 30, 2003; final amendment: Act No. 119, July 16, 2003)
- Helsinki Declaration (Japanese translation by the Japanese Medical Association)
- Ethical guidelines on clinical research (public notice 415 of the Ministry of Health, Labour and Welfare, implemented on July 30, 2003, completed revision of December 28, 2004, complete revision on July 31, 2008)
-

13.3.2. Purpose, items, and method of personal information utilization

1) Purpose of utilization

The JCOG will use the patient's personal information to 'identify individual patients for investigations during the treatment period until after treatment completion to obtain correct results of the clinical trial, and to correctly handle the information acquired' in accordance with the

fundamental philosophy of 'providing the best medical treatment to the maximum patients'.

2) Items utilized

The JCOG will utilize the minimum number of items required for patient identification and inquiries as outlined below.

Patient ID (medical record number), date of birth, initials, and pathological specimen number (when necessary)

The patient's name and personal information other than that noted above will not be communicated by the participating medical facility to the Data Center. If patient information is released by mistake, the record will either be destroyed, regardless of the recording medium, or filed after taking appropriate measures to make the information undecipherable, such as masking the data.

3) Utilization method

The patient's personal and medical information will be recorded on various CRFs by researchers of the medical facility, and, as a general rule, it will be submitted to the Data Center by mail or in person for collection. However, submission of information be telephone and fax may only be used for patient enrollments that require rapid communication.

In addition, to ensure the accuracy of the collected data, when exchanging copies of various CRFs between the Data Center and researchers of medical facilities, data submission will be limited to mail or in person.

Furthermore, personal information will not be communicated by e-mail.

13.3.3. Secondary utilization of date

Only with the approval of relevant JCOG committees (Protocol Review Committee, etc.) may data obtained in this trial be used for secondary purposes (meta-analyses, etc.) independent of personal identity.

13.3.4. Safety management responsibility

A privacy protection supervisory manager and privacy protection officer will be appointed to take various safety control measures to minimize the risk of personal information being revealed.

13.3.5. Managing disclosure of patient information

As a general rule, a researcher of the facility of the patient concerned (facility principal investigator, institutional coordinator, or attending physician) will handle requests by the patient for the disclosure of privacy-related patient information collected by the JCOG.

13.3.6. General inquiries and complaints desk

General inquiries or complaints regarding the privacy policy may be submitted by mail, e-mail, or fax to the inquiry desk.

Inquiry desk : JCOG Data Center Privacy Protection Officer
Address: National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045 Japan
E-mail : JCOG_privacy@ml.JCOG.jp
FAX : 03-3542-3374

13.4. Protocol compliance

Researchers participating in this trial will abide by this protocol as long as it does not affect patient safety or patient rights.

13.5. Approval of the ethics review board at medical facilities

13.5.1. Approval at the start of trial participation

Approval of each medical facility will be required to participate in this trial, and a written explanation of the trial must be provided to each patient with a copy of the present protocol.

After obtaining approval, the coordinator of each medical facility must send a copy of the written approval to the Data Center. The original written approval form will be kept by the facility coordinator, while a copy will be kept by the Data Center.

Furthermore, all medical facilities may make additions to the written explanation for use with the approval of the medical facility concerned and given to the patient as long as the changes do not deviate from the scope of the clinical trial, however each medical facility are not permitted to make changes to the protocol. The same protocol will be used by all facilities. If content changes are required, amendments or revisions will be made to the protocol used by all medical facilities. Therefore, when there is a revision request made by a medical facility, the institutional coordinator must consult the research secretariat. If the written explanation is modified as instructed by the medical facility, the modified form must be submitted to the research secretariat. If the research chairperson or secretariat deems the modifications (deletions or content change) to be inappropriate, then the medical facility may request the primary investigator/institutional coordinator to reconsider the modifications.

13.5.2. Annual renewal of the approval of each medical facility

Each medical facility will determine whether annual renewal of the approval for the protocol and written explanation for the patient is necessary in accordance with the regulations of each medical facility. If the approval is renewed annually, the JCOG does not require each medical facility to submit written approval for annual renewal.

13.6. Change in details of protocol

13.6.1. Classification of protocol content changes

If changes are made to the protocol content, prior to implementation (activation) of the changes a 'protocol amendment application' must be submitted to the Data and Safety Monitoring Committee and approval obtained. However extension of the enrollment period of less than 6 months does not require protocol amendment.

While the JCOG will process changes to the protocol as either amendments or revisions after approval by the Protocol Review Committee, the director of the Data and Safety Monitoring Committee will differentiate amendments from revisions, and therefore all committee applications should be submitted by researchers as 'revision applications'. Furthermore, additional explanations that do not fall under the criteria of protocol content changes will be classified as a memorandum. Definitions and processing are as follows:

1) Amendment

Partial changes to the protocol may increase the risk to patients participating in the trial, or may substantially impact the primary endpoint of the trial; therefore, amendments require approval from the Data and Safety Monitoring Committee and each medical facility.

Furthermore, approval from the group representative concerned and the Data Center director is also required prior to submission of the application to the Data and Safety Monitoring Committee. The Data and Safety Monitoring Committee will add the dates of the approval and validation to the protocol cover page.

If patient enrollment continued at a point in time deemed to correspond to an 'amendment' by the Data and Safety Monitoring Committee, patient enrollment will be temporarily suspended until approval is obtained from each medical facility for the amendment content. In the event that approval is obtained, the institutional coordinator of each medical facility must send a copy of the written approval from each medical facility to the Data Center. Enrollments will be recommenced from facilities that confirmed the written approval.

2) Revision

A revision is considered a change to the protocol that will not increase patient risk, or substantially impact the primary endpoint of the trial. Revisions require approval from the Data and Safety Monitoring Committee director, and each medical facility. Each medical facility will determine at their

own discretion whether they will conduct a normal or rapid examination of the revision. As a general rule, patient enrollments will not be temporarily suspended for revisions.

Before the application is submitted to the Data and Safety Monitoring Committee chairperson, approval must be obtained from the representative of the group concerned, and the Data Center director.

The dates that the Data and Safety Monitoring Committee approved and validated the revision will be noted on the cover page of the protocol.

After validation of the revision, as a rule, the trial will be conducted in accordance with the approved revision content even before approval from medical institutions. If circumstances prevent the institution from implementing the revision content before approval from the medical facility, the research secretariat and Data Center should be consulted. When approval is obtained from each facility, a copy of the written approval from each medical facility does not need to be sent to the Data Canter, however the original document is to be kept by the institution coordinator for verification in the event of an audit.

3) Memorandum

A supplementary explanation of the protocol in any format must be distributed by the research chairperson/secretariat to all involved in the trial. This is not a change in protocol content but to decrease inconsistencies in interpretation of the text content, or to draw particular attention to the content.

Approval is required from the group representative and the Data Center director prior to distribution. Memorandums should be reported to the Data and Safety Monitoring Committee prior to, or immediately after distribution.

Memorandums do not need to be noted on the protocol's cover page.

13.6.2. Medical facility approval at the time of protocol amendment/revision

During the trial, if any revision is made to the protocol or written explanation given to the patient with the approval of the Data and Safety Monitoring Committee, the revised protocol or written explanation must be approved by each medical facility. If during patient enrollment, enrollments will be temporarily suspended until approval is obtained from each medical facility, and the institution will subsequently reopen enrollments after approval is obtained. Following approval for the revision, the institutional coordinator of each medical facility must send a copy of the written approval from each medical facility to the Data Canter. The original written approval will be kept by the institutional coordinator, while the copy will be kept by the Data Center.

Revisions (not amendments) made to the content also require approval from each medical facility. Each medical facility will determine whether to perform normal or rapid examination of the revision at their own discretion. When approval is obtained from each medical facility, a copy of the written approval from each medical facility does not need to be sent to the Data Center; however the original written approval must be kept by the institutional coordinator for verification in the event of an audit.

13.6.3. CRF correction (9.1.3. reprint)

Once the trial is initiated, if the CRF is incomplete (i.e., missing required data or incorrect category classification, it may be corrected with the approval of the Data Center Director and the research secretariat, so long as the correction does not exceed the range of collected data stipulated in section 8 above, 'Evaluation items, laboratory tests and evaluation schedule', and if the correction will cause no further medical or financial burden to the patient. For CRF corrections that do not require protocol revision, the JCOG will not revise the protocol. The regulations of the facility will be referenced to determine whether a report or revision application concerning CRF corrections should be sent to the director of the medical facility.

13.7. Management of conflicts of interest for members involved in JCOG research

Conflicts of interest (COI) of researchers involved in JCOG trials or individuals supporting the JCOG trial will be managed as described below:

1) COI of individuals involved in JCOG trials to investigate medical treatments in participating facilities, such as the facility's primary investigator or coordinator, will be managed in accordance with the regulations of the participating facility.
2) COI of individuals who play a key role in JCOG trials, such as the research chairperson, secretariat, or group representative/secretariat, will be managed by the JCOG COI committee. Furthermore, COI of members of the JCOG Data and Safety Monitoring Committee or staff at the JCOG Data Center/Operations Office who are involved in an individual JCOG trial, such as members of the JCOG Data and Safety Monitoring Committee, will be handled in a similar manner.

13.8. Compensation

Health injury incurred by participating in the present clinical trial will be treated appropriately according to the symptoms in the way as normal medical care and will be covered by the national health insurance scheme. Any medical expenses not covered by the national health insurance scheme will be incurred by the patient. Furthermore, patients will not receive any financial compensation such as consolations or various bonus medical treatment.

13.9. Intellectual property

The results, data, and intellectual property obtained in the present clinical trial belongs to 4 entities including the research chairperson, research secretariat, group representative, and National Cancer Research Center of Japan. The fundamental management and distribution of this property will be determined collaboratively by the 4 entities. Ownership of intellectual property involving the research chairperson, research secretariat, and group representative, whether it belongs to the individual or affiliated medical facility, will be determined with the agreement of the affiliated medical facility.

13.10. The provision of medications free of charge

The present trial will be performed under the advanced medical care (advanced medical care B) system, and under the instructions of the Research and Development Division of the Health Policy Bureau at the Ministry of Health, Labour and Welfare, and on the basis of a previously concluded agreement, trastuzumab (Herceptin ® infusion) shall be provided free of charge from the manufacturer and distributor, Chugai Pharmaceuticals; however, no funding associated with the present trial shall be provided. Furthermore, the intentions of Chugai Pharmaceuticals shall not influence the results of the present trial in any way.

14.Monitoring and auditing

14.1. Routine monitoring

As a general rule, biannual routine monitoring will be conducted to verify trial safety, protocol adherence, and accurate data collection.

Central monitoring will be performed based on data recorded on the CRFs collected from the Data Center, and there will be no site-visit monitoring including comparison with the original documents.

A routine monitoring report prepared by the Data Center will be submitted to the research secretariat, research chairman, group chairman, Data and Safety Monitoring Committee, and the JCOG representative, which will be examined in accordance with JCOG regulations.

Routine monitoring is designed to provide feedback on problem areas and improve science-related ethics, but not to expose problem areas of the trial or facility. The group representative will distribute the routine monitoring report at each group meeting for examination, so that the research secretariat, research chairman, and principal investigator can improve the problem areas indicated in the report.

14.1.1. Monitoring items

①Cumulative achievement status: enrollment number-accumulation/period, group/facility
②Eligibility: ineligible cases/patients who may be ineligible: group/facility
③Background factors prior to treatment: group
④During treatment/ following treatment, reason for termination/completion: group/facility
⑤Protocol deviation: group/facility
⑥Severe adverse events: group/facility
⑦Adverse reaction/adverse event: group
⑧Overall survival, progression0free survival: all enrolled cases
⑨Other problems related to trial progress and safety

14.1.2. Permissible range of adverse events

In the present trial, as in the JCOG 1002 trial conducted by a stomach cancer study group to examine preoperative chemotherapy for advanced gastric cancer with extensive lymph node metastasis, the point estimate for the rate of treatment-related deaths shall not exceed 5% in either group. When the number of treatment-related deaths reaches 4 cases in either group, it will be clear that the final point estimate will exceed 5%, and therefore enrollment shall be temporarily suspended. At this point the subsequent treatment of patients receiving treatment shall be examined. When there are 3 or fewer treatment-related deaths, each case shall be reported to the Data and Safety Monitoring Committee, and the judgement shall be sought pertaining to what needs to be done. However, as a general rule, enrollment shall continue until a conclusion is reached.

The definition of treatment-related deaths is described below.

Treatment-related death: Of all deaths, those that are assessed by the Data and Safety Monitoring Committee as having a causal relationship (definite, probable, or possible) with the protocol-based treatment.

14.1.3. Eligibility (eligible/ineligible)

The eligibility of all patients will be classified according to the following definitions. During monitoring, the Data Center will list cases that may be ineligible in the section of the monitoring report 'examination of eligibility', then after examination during a CRF review by the research secretariat, either 1), 2), 9), or 99) will be ultimately determined with the approval of the group representative prior to principal analyses.

Only '1) eligible' will be considered 'eligible cases', while cases falling under '2) ineligible after enrollment', '9) ineligible at the time of enrollment', and '99) enrollment violation' will be classified as 'ineligible cases'.

1) Eligible

Based on the stipulated methods and criteria in the protocol, all information provided prior to enrollment meets the patient selection criteria.

2) Ineligible after enrollment

If any of the patient selection criteria is not satisfied by information found after enrollment, or, when found prior to enrollment but not according to methods and criteria other than stipulated in the protocol.

E.g.)

① In a trial of stage II-III cancer, if bone metastasis is found by bone scintigraphy performed immediately after enrollment and the patient is diagnoses as stage IV, then the protocol treatment will be discontinued.

② In a trial of early stage gastric cancer, if blood in stool is observed after enrollment, and on performing colonoscopy, if advanced colorectal cancer is found, then the protocol treatment is discontinued, colectomy performed.

③ In a trial of gastric cancer (adenocarcinoma), if pathological diagnosis performed by the facility reveals malignant lymphoma.

9) Ineligible at the time of enrolment

When any of the patient selection criteria is not fulfilled by information emerging prior to enrollment according to the methods (implemented for all cases) and criteria stipulated in the protocol. This included cases in which information from before enrollment is found to be erroneous after enrollment.

E.g. When CT imaging conducted prior to enrollment according to regulations is reviewed by a specialist who finds clear liver metastasis (this is an oversight of the physician concerned and should not be included in future)

99) Enrollment violation

When a patient is intentionally (under false pretenses) enrolled while knowing that they do not meet the patient selection criteria. This is equivalent to false reporting and is treated as a very serious problem

14.1.4. Protocol violation and deviation

Violation of the protocol will be considered when any treatment such as drug administration, or surgical resection, laboratory testing and evaluations of toxicity or efficacy are not conducted as stipulated in the protocol.

With regard to monitoring, deviations exceeding the set permissible range determined for each trial by the Data Center and the research chairman/secretariat prior to or after the start of the trail will be ascribed in the monitoring report as a 'possible deviation' and are classified as any of the items below on examination by the research secretariat and research group.

1) Violation

A violation refers to protocol deviations that are clinically inappropriate and fall under the items below.

① Influence the evaluation of the trial endpoints.

② Caused by the attending physician or facility.

③ Intentional or systematic.

④ Considerable degree of dancer or deviation.

In publications, 'violation' should generally include details of individual violations.

2) Deviation

Deviations do not meet the criteria of: 1) violations, or fall within 3) the acceptable range.

If a specific deviation often occurs, it is recommended that the deviation be mentioned in all published articles.

In the monitoring report, a deviation is classified as any of the following:

① Deviation…an event that is undesirable and should be curtailed

② Deviation (unavoidable)…an event that does not need to be actively curtailed (e.g. delay due to the New Year, patient request, etc.)

③ Deviation (clinically valid)… a deviation that is positively affirmed by the attending physician/facility (if similar situations occurs again, it is recommended to deviate from protocol in a similar manner.

* A deviation does not necessarily indicate that the attending physician has experienced a problem. Because the safety of the patient is given first priority in research and clinical trials, if the protocol treatment is deemed dangerous, the medical decision of the attending physician should be to deviate. If the deviation is deemed clinically valid for the safety of the patient, it must be recorded as ③above, 'a deviation (clinically valid)'. Although a clinically valid deviation may not necessarily pose any specific problem, if it occurs frequently, it is highly likely that the protocol regulations re inappropriate and that protocol revision should be considered.

3) Acceptable range (of deviation)

An acceptable protocol deviation is defined as one that falls within the acceptable range established for each trial prior to or after the start of the trial by the JCOG, research group, research chairman, research secretariat, and the Data Center.

Deviations within the acceptable range established beforehand are not included in the monitoring report.

14.2. Site-visit audit

The JCOG conducts site-visit audits for educational purposes and to improve the scientific and ethical standards of the research.

A JCOG researcher (audit supervisor), appointed by the audit committee, will visit all facilities participating in the trial to verify the written approval of the medical facility and patient consent forms and compare the CRF data against medical records (direct inspection of source documents) in accordance with standard operating procedures (SOP) based on the audit manual established by the audit committee.

Furthermore, the audit results of each facility will be reported along with the JCOG audit committee examination results on the audit report form and submitted to the facility's principal investigator, director of the medical facility concerned, research secretariat, research chairman, group chairman, director of the JCOG Data Center, and JCOG chairman. If required, the audit results may also be reported to the group researcher and JCOG operations committee. In the event of sharing the report with other parties, the facility's name must not be disclosed.

15. Special notes

15.1. Advanced medical care (advanced medical care B) system-related items

15.1.1. Medical institution classification: reporting medical institution, coordinating medical institution, and cooperating medical institutions

1) Reporting medical institution (the medical institution responsible for the reporting of advanced medical care)

The reporting institution shall be Shizuoka Cancer Center, the affiliated medical institution of the research chairman.

2) Coordinating medical institution (the medical institution that compiles reports submitted by participating affiliated medical institutions and file those reports for them, when advanced medical care B is implemented as part of the multi-institutional collaborative study)

The coordinating institution shall be the National Cancer Center Central Hospital.

Furthermore, the Multi-institutional Clinical Trial Support Center shall serve as the secretariat of the coordinating medical institution and carry out the following duties.

- Support for the preparation of the advanced medical care implementation report and its application.
- Reporting to the director of the Regional Bureau (branch) of Health and Welfare, and to the director of the Health Bureau of the Ministry of Health, Labour and Welfare in the event of occurrence of "patients resulting in death, or patients at risk of death," and "cases set forth below" in the advanced medical care notification.
- Reporting to the Research and Development Division of the Health Policy Bureau at the Ministry of Health, Labour and Welfare upon amendments/revisions of the protocol in the advanced medical care notification.
- Support for "routine reports" in the advanced medical care notification.
- Communication with the manufacturers that provide medications.

3) Cooperating medical institutions (medical institutions that provide cooperation with the reporting medical institution regarding advanced medical care, when advanced medical care B is implemented as part of the multi-institutional collaborative study)

Cooperating institutions shall be medical institutions that participate in the present trial other than those listed in 1) and 2) (see section 16.8).

15.1.2. Procedures under the advanced medical care (advanced medical care B) system until the start of the present trial

1) The application procedures pertaining to advanced medical care B

The research chairman/research secretariat shall follow the application procedures pertaining to advanced medical care B after obtaining approval from the director of the medical institution on the basis of the IRB review by institutions participating at the start of the trial (of the "16.7. participating institutions," a total of 6 institutions participating at the start of the trial, consisting of the National Cancer Center Central Hospital, National Cancer Center East Hospital, Nagoya University School of Medicine, Osaka University School of Medicine, and Okayama University Hospital, shall be the "institutions participating at the start of the trial").

Patient enrollment in the preset trial shall start upon approval by the advanced medical care council, report to the Central Social Insurance Medical Council, and notice by the Minister of Health, Labour and Welfare.

Of participating institutions listed in section "16.7 participating institutions," for institutions other than the aforementioned "institutions participating at the start of the trial," the research chairman/research secretariat shall follow the application procedures pertaining to advanced medical care B for institutions

to become additional cooperating ones as they are approved by the IRB. Thereafter, patient enrollment through additional cooperating institutions shall be commenced upon announcement by the Minister of Health, Labour and Welfare.

2) Measures taken in the event of an amendment to the protocol or written explanation

After processing applications pertaining to advanced medical care B, in the event of an amendment made to the protocol or written explanation to the patient prior to the start of patient enrollment, as indicated by the advanced medical care council, the research chairman/research secretariat shall submit an application for protocol amendment summarizing the amendment content to the Data and Safety Monitoring Committee after obtaining approval for such an amendment from the advanced medical care council (with respect to approval by each participating institution, section "13.6.2." shall be followed).

15.2. Accompanying research

15.2.1. Accompanying research on biomarkers for the prognosis of HER2-positive gastric cancer and predicting the therapeutic effects of trastuzumab

Study purpose: Prognostic factors of HER2-positive gastric cancer and predictive factors of the therapeutic outcomes of trastuzumab for HER2-positive gastric cancer will be investigated through analysis of gene and protein expression using pathological specimens and blood samples obtained prior to preoperative chemotherapy.

Specimens: biopsy specimens and blood samples (whole blood) obtained prior to preoperative chemotherapy, etc.

Consent acquisition: Consent shall be obtained for accompanying research prior to enrollment in the present trial.

Study framework: The details shall be stipulated in the protocol for accompanying research.

Study cost: undetermined

15.2.2. Accompanying research on biomarkers for the resistance to trastuzumab therapy for HER2-positive gastric cancer

Study purpose: The underlying mechanism of chemotherapy resistance will be investigated by analyzing protein expression and gene expression using biopsy specimens obtained prior to preoperative chemotherapy and pathological specimens obtained after preoperative chemotherapy, then comparing the profiles of both. Furthermore, the mechanism of trastuzumab resistance will be examined by comparing the profiles of chemotherapy resistance between the non-trastuzumab group and trastuzumab group.

Specimens: Biopsy specimens obtained prior to preoperative chemotherapy, surgical specimens obtained after preoperative chemotherapy, and blood samples (whole blood) obtained before and after preoperative chemotherapy.

Consent acquisition: Consent shall be obtained for accompanying research prior to enrollment in the present trial.

Study framework: The details shall be stipulated in the protocol for accompanying research.

Study cost: undetermined

15.3. JCOG biobank

The present trial will participate in the JCOG biobank project.

Subjects: Of the patients who gave consent to the present trial, those who gave consent to providing samples to the biobank

Samples:

1) Whole blood

As a general rule, blood will be sampled prior to the start of the protocol-based treatment. However, blood samples obtained after the start of the protocol-based treatment will also be

permitted. A total of 14 mL of blood will be sampled, 7 mL x 2 EDTANa-coated collecting vellsels (for blood count) for exclusive use in the JCOG biobank project. The samples shall be stored at 4°C at each institution until handing over to the agent responsible for sample transfer and processing (for details, refer to the "JCOG biobank project protocol").

2) Histopathology

Pathological tissues preserved in routine medical practice, such as those obtained from surgery and biopsy/laboratory testing, are planned to be collected; however, at this point the specific operation method is undecided: decision as to whether or not the preserved tissue can be supplied without difficulty for the medical care of the patient concerned, the type of pathological tissue, sample preparation method and tissue amount, and the time and methods of collection.

Therefore, consent for utilization of the preserved pathological tissue following treatment shall be obtained at the time of consent for banking;however, actual collection shall begin upon establishment of the details after the revision of the "JCOG biobank project protocol" is made.

16. Research organizations

Changes to the content of this chapter shall be considered a revision; not an amendment.

Although revisions of the Data and Safety Monitoring Committee do not require inspection, they do require the approval from the research group chairman. If a change is made, the research chairman/secretariat must notify, in writing, each participating facility and the JCOG Data Center as soon as possible.

16.1. Main research group of this trial (sources of funds)

- Ministry of Health, Labour and Welfare scientific research fund, research project on the practical application of innovative cancer therapies H26-Innovative cancer- general-040
  Research chairman: Masanori Terashima (Shizuoka Cancer Center)
  "Clinical trial of the significance of preoperative trastuzumab combined with chemotherapy for HER2-positive gastric cancer with extensive lymph node metastasis"
- National Cancer Center Research Institute Research and Development Grant Designated Research, 26-A-4 , Principal investigator: Kensei Tobinai
  "Basic research for the establishment of the standard treatment of solid cancers in adults"

16.2. JCOG (Japan Clinical Oncology Group)

The JCOG is a multicenter collaborative clinical research group consisting of study groups that receive direct support for research by the National Cancer Center Multi-institutional Clinical Trial Support Center, and that are financed by public research funds primarily including the National Cancer Center Research Institute Research and Development grant, with the Health and Labour Sciences Research Grant.

This trial is conducted by the JCOG research organization in accordance with the regulations established by the JCOG Operations Committee (http://www.jcog.jp/).

- 26-A-4 , Principal investigator: Kensei Tobinai (National Cancer Center Central Hospital)
  "Basic research for the establishment of the standard treatment of solid cancers in adults"

16.3. JCOG representative

Kensei Tobinai　　National Cancer Center Central Hospital

16.4. Research group and group representative

JCOG Stomach cancer study group

Group representative: Mitsuru Sasako

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Group secretariat (surgery): Takeshi Sano

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Group secretariat (internal medicine): Norikazu Boku

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16.5. Principal investigator

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16.6. Study secretariat

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16.7. Reporting medical institution, coordinating medical institution, and cooperating institutions in the advanced medical care system

16.7.1. Reporting medical institution

Shizuoka Cancer Center

Principal investigator: Masanori Terashima

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16.7.2. Coordinating medical institution

National Cancer Center Central Hospital
Institution research investigator: Hitoshi Katai

The National Cancer Center, Multi-institutional Clinical Trial Support Center, Department of Research Promotion shall serve as the coordinating medical institution secretariat.

Inter-institutional coordinator: Haruhiko Fukuda (Director of the Trial Support Center, Department of Research Promotion)
Address: 5-1-1, Tsukiji, Chuo-ku, Tokyo, Japan, 104-0045
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16.7.3. Cooperating medical institutions

Cooperating medical institutions are participating medical institutions in the present trial other than the reporting and the coordinating medical institutions (see section 16.8)

16.8. Participating institutions

Changes in information with regard to participating institutions such as the addition of participating institutions, an erollable institution changing to a cooperating one in follow-up, and detailed changes in principal investigator or coordinator shall be made to coincide with protocol amendment/revision applications. These changes shall not be made at any other time. Furthermore, a summary of the latest participating institutions, which is renewed monthly, is available on the JCOG home page (http://www.jcog.jp/) for verification (as of December 2014).

Of the JCOG gastric cancer groups below, institutions participating at the start of the trial are indicated by "◎" in the first column, and additional institutions (institutions participating in the Gastric Cancer Study Group after the start of the trial) are indicated by "*" and "○." Furthermore, "△" indicates institutions that changed to cooperating ones.

Planned participation	Name of medical institution	Department (institutional name)	Principal investigator	Coordinator	Possible years of enrollment
○	Hakodate Koseiin Hakodate Goryokaku Hospital	Surgery	Akinori Takagane	Akinori Takagane	3
○	Keiyukai Sapporo Hospital	Gastrointestinal surgery	Yasuhiro Nishida	Hirosuke Okuda	1
○	Iwate Medical University	Surgery	Keisuke Koeda	Takehiro Chiba	2
○	NHO Sendai Medical Center	Surgery	Toshihiro Saito	Shin Teshima	1
○	Miyagi Cancer Center	Surgery	Tsuneaki Fujiya	Yasuhiro Hasegawa	1
	Yamagata Prefectural Central Hospital	Surgery	Norimasa Fukushima	Takashi Nomura	4
○	Tochigi Cancer Center	Surgery	Takao Inada	Takao Inada	1
○	National Defense Medical College	Surgery	Kazuo Hase	Hironori Tsujimoto	1
○	Saitama Prefectural Cancer Center	Gastrointestinal surgery	Youichi Tanaka	Yoshiyuki Kawashima	2
	Saitama International Medical Center	Upper gastrointestinal surgery	Shinichi Sakuramoto	Hiroshi Sato	*
◎	National Cancer Center East Hospital	Gastrointestinal oncology	Takahiro Kinoshita	Kohei Shitara	3
*	Chiba Cancer Center	Gastroenterology, surgery	Nobuhiro Takiguchi	Shuichi Hironaka	*
◎	National Cancer Center Central Hospital	Gastric surgery	Hitoshi Katai	Takeo Fukagawa	
	Cancer and Infectious Disease Center Komagome Hospital	Surgery	Yoshiaki Iwasaki	Kazuhito Yajima	
	Tokyo Medical and Dental University	Gastrointestinal surgery	Kenichi Sugihara	Kazuyuki Kojima	0
○	Cancer Institute Ariake Hospital	Gastrointestinal surgery	Takeshi Sano	Manabu Ohashi	6
	Toranomon Hospital	Gastroenterological medicine, surgery and clinical oncology	Harushi Udagawa	Mitsuru Kaise	
	Tokyo Metropolitan Bokuto Hospital	Surgery	Ikuo Wada	Ikuo Wada	
○	Kanagawa Cancer Center	Gastrointestinal surgery	Takaki Yoshikawa	Haruhiko Cho	2
	Kitasato University School of Medicine	Gastrointestinal medicine	Wasaburo Koizumi	Katsuhiko Higuchi	
○	Yokohama Municipal Citizen's Hospital	Gastrointestinal Disease Center	Chikara Kunisaki	Chikara Kunisaki	1
○	Niigata Cancer Center Hospital	Surgery	Atsushi Nashimoto	Hiroshi Yabusaki	3

Planned participation	Name of medical institution	Department (institutional name)	Principal investigator	Coordinator	Possible years of enrollment
○	Niigata Nagaoka Chuo General Hospital	Surgery	Yasuyuki Kawachi	Shigeto Makino	1
△	Tsubame Rosai Hospital	Surgery	Takao Shimizu	Takao Shimizu	
○	Toyama Prefecture Central Hospital	Surgery	Masahide Kaji	Masahide Kaji	1
○	Ishikawa Prefectural Central Hospital	Gastroenterology	Hisashi Doyama	Noriyuki Inaki	1
○	Gifu University School of Medicine	Surgical oncology	Kazuhiro Yoshida	Kazuya Yamaguchi	1
○	Gifu Municipal Hospital	Surgery	Makoto Yamada	Makoto Yamada	1
○	Shizuoka General Hospital	Gastroenterology	Masakazu Takagi	Masakazu Takagi	1
◎	Shizuoka Cancer Center	Gastric surgery	Masanori Terashima	Masanori Terashima	3
○	Aichi Cancer Center Central Hospital	Gastrointestinal surgery	Seiji Ito	Kazunari Misawa	2
◎	Nagoya University Graduate School of Medicine	Gastrointestinal surgery 1 and 2	Yasuhiro Kodera	Masahide Fukaya	
○	NHO Kyoto Medical Center	Surgery	Takashi Yamaguchi	Hiroaki Hata	1
◎	Osaka University Graduate School of Medicine	Gastroenterological surgery	Yuichiro Doki	Yukinori Kurokawa	
	Kinki University Faculty of Medicine	Surgery	Haruhiko Imamoto	Motohiro Imano	
	Osaka Medical center for Cancer and Cardiovascular Diseases	Gastrointestinal surgery	Yoshiyuki Fujiwara	Takeshi Omori	
	NHO Osaka Hospital	Surgery	Motohiro Hirao	Kazuhiro Nishikawa	
	Osaka General Medical Center	Gastrointestinal surgery	Kazumasa Fujitani	Junji Kawada	*
*	Osaka Rosai Hospital	Surgery	Masato Yoshikawa	Ryohei Kawabata	*
○	Osaka Medical College	Gastrointestinal surgery	Masahiro Goto	Sang-Woong Lee	1
△	Toyonaka Municipal Hospital	Surgery	Hiroshi Imamura	Hiroshi Imamura	1
○	Sakai City Hospital	Surgery	Yutaka Kimura	Yutaka Kimura	2
○	Kansai Medical University Hirakata Hospital	Surgery	Masanori Kon	Kentaro Inoue	1
	Kobe University School of Medicine	Gastroenterology / digestive surgery	Takeshi Azuma	Atsuki Ikeda	
	Kansai Rosai Hospital	Gastrointestinal surgery	Shigeyuki Tamura	Hirokazu Taniguchi	1
○	Hyogo College of Medicine	Upper gastrointestinal surgery	Sasako Mitsuru	Hiroki Niwa	4
○	Hyogo Cancer Center	Gastroenterology	Masahiro Tsuda	Takeshi Sakamoto	5
○	Itami City Hospital	Surgery	Masahiro Hiratsuka	Masahiro Hiratsuka	1
○	Tenri Yorozu Hospital	Surgery, abdominal	Tsunehiro Yoshimura	Yoshito Asao	1
○	Wakayama Medical University	Surgery 2	Hiroki Yamaue	Mikihito Nakamori	1
○	Shimane University Faculty of Medicine	Gastrointestinal/general surgery	Yoshitsugu Tajima	Noriyuki Hirahara	2
◎	Okayama University Hospital	Gastrointestinal surgery	Toshiyoshi Fujiwara	Masahiko Nishizaki	

Planned participation	Name of medical institution	Department (institutional name)	Principal investigator	Coordinator	Possible years of enrollment
*	Hiroshima University Hosital	Gastrointestinal surgery	Kazuaki Tanabe	Nobuaki Fujikuni	*
○	Hiroshima Citizen's Hospital	Surgery	Motoki Ninomiya	Yasuhiro Chouda	1
○	Hiroshima City Asa Hospital	Surgery	Naoki Hirabayashi	Mikihiro Kano	1
○	Fukushima City Hospital	Surgery	Hitoshi Idani	Shinya Asami	1
○	HNO Shikoku Cancer Center	Gastroenterological surgery	Akira Kurita	Shinji Hato	2
*	Tokushima Red Cross Hospital	Gastrointestinal surgery	Hiroshi Okitsu	Yasuhiro Yuasa	*
△	Kochi Health and Sciences Center	Gastrointestinal surgery	Kazuhide Ozaki	Yutaka Nishioka	
○	Oita University Hospital	Gastrointestinal surgery	Masafumi Inomata	Tsuyoshi Eto	1

Total: 69 individuals (at the start of the trial)

16.9. JCOG protocol review committee

This protocol was approved by the JCOG protocol review committee prior to submission to the IRB review of the participating facilities. Review of this protocol was supervised by the committee members and reviewers marked with a " ."

(The list of members and their affiliations constituting the committee is at the time of approval, and there has been no change)

For the latest information, refer to the website http://www.jcog.jp/basic/org/committee/protocol.html)

Chairman: Kensei Tobinai, National Cancer Center Central Hospital

Vice-chairman: Seiichiro Yamamoto, National Cancer Center, Center for Cancer Control and Information Services

Vice-chairman: Kaoru Kobuta, Nippon Medical School

Board members:
Yoshinori Ito, National Cancer Center Central Hospital
Hiroshi Nokihara, National Cancer Center Central Hospital
○ Shigehira Saji, Kyoto University Graduate School of Medicine
Takaki Yoshikawa, Kanagawa Cancer Center
Takayuki Yoshino, National Cancer Center East Hospital
Toyomi Sato, Tsukuba University Faculty of Medicine
○ Seiji Niho, National Cancer Center East Hospital
Ken Kato, National Cancer Center Central Hospital
Yukinori Kurokawa, Osaka University
Naoto Shikama, Saitama International Medical Center
Takashi Maruyama, Tokyo Women's Medical University
Kentaro Yamazaki, Shizuoka Cancer Center
Hideki Ueno, National Cancer Center East Hospital
Hirotsugu Kenmotsu, Shizuoka Cancer Center
Kohei Shitara, National Cancer Center East Hospital
Masanori Tokunaga, Shizuoka Cancer Center
Dai Maruyama, National Cancer Center Central Hospital
Makoto Ueno, Kanagawa Cancer Canter
Kohei Takizawa, Shizuoka Cancer Center
Tomoya Yokota, Shizuoka Cancer Center
Takuhiro Yamaguchi, Tohoku University Hospital
○Takeharu Yamanaka, National Cancer East Hospital
Shiro Tanaka, Kyoto University Graduate School of Medicine
Akihiro Hirakawa, Nagoya University Hospital
Izumi Kohara, Jichi Medical University
Izumi Wasada, Tokai University School of Medicine
○Yoko Sasayama,NHO Osaka Medical Center
Hiroi Kasai, Kyoto University Hospital

Inspector
○Hiroya Takeuchi, Keio University School of Medicine
○Noriko Fukuhara, Tohoku University Hospital
○ Masaaki Ito, National Cancer Center East Hospital
○ Makoto Ono, National Cancer Center Central Hospital
○ Akihiro Homma, Hokkaido Graduate School of Medicine
○ Haruhiko Fukuda, National Cancer Center/ JCOG Data Center

Secretary-general Hiroshi Katayama, National Cancer Center/ JCOG Operations Office