West Japan Oncology Group

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Phase I study of nivolumab + abemaciclib + endocrine therapy in patients with HR-positive HER2-negative metastatic breast cancer

Nivolumab Evaluation With endocrine therapy (Pulvexrant or Letrozole) and AbeMaciclib (NEWFLAME) study

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2. **Objective.**

To evaluate the efficacy and safety of nivolumab plus abemaciclib plus endocrine therapy in hormone receptor (HR)-positive human epidermal growth factor receptor 2 (HER2) negative metastatic or recurrent breast cancer. Two cohorts (letrozole and fulvestrant cohort) with potential synergistic effects will be established with a view of validation in a phase III study.

**Letrozole cohort**

**Step 1 (Safety part)**

To evaluate the safety of nivolumab plus abemaciclib plus letrozole in HR-positive HER2-negative metastatic or recurrent breast cancer based on the incidence of dose limiting toxicity (DLT). The investigators will also determine whether to continue the study. The evaluation period will be from the start of study treatment until before the administration of Day 1 of the second course.

- **Primary endpoint:** DLT incidence
- **Secondary endpoint:** Incidence of adverse events

**Step 2**

Evaluate efficacy and safety in all eligible patients, including those enrolled in the safety part.

- **Primary endpoint:** Overall response rate
- **Secondary endpoint:** Safety, disease control rate, progression-free survival
  - 6-month progression-free survival rate,
  - 12-month progression-free survival rate
  - 12-month overall survival rate, overall survival

**Fulvestrant cohort**

**Step 1 (Safety part)**

To evaluate the safety of nivolumab + abemaciclib + fulvestrant combination therapy in HR-positive HER2-negative metastatic or recurrent breast cancer by the incidence of DLT. In addition, whether or not to continue the study will be determined. The evaluation period will be from the start of study treatment until before the administration of Day 1 of the second course.

- **Primary endpoint:** DLT incidence

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Secondary endpoint: Incidence of adverse events

Step 2
Evaluate efficacy and safety in all eligible patients, including those enrolled in the safety part.
Primary endpoint: Overall response rate
Secondary endpoint: safety, disease control rate, progression-free survival
- 6-month progression-free survival rate,
- 12-month progression-free survival rate
- 12-month overall survival rate, overall survival

3. Background and rationale for research Plan

3.1. Subject (of taxation, etc.)

3.1.1. Target disease

Epidemiology
In Japan, the number of patients with breast cancer has increased gradually since the 1960s, and in 1995 it surpassed gastric cancer to become the leading malignant tumor incidence among women. In 2016, the number of breast cancer deaths was about 14,015 women, accounting for about 9% of all cancer deaths among women. In 2013, the number of cases of female breast cancer was about 76,839 (excluding epithelial cancer), accounting for about 21% of all cancer cases in women. The number of cases and deaths are on the rise. Breast cancer is considered a cancer with a relatively good prognosis, but metastatic or recurrent breast cancer is difficult to cure, and the 10-year survival rate after recurrence is reported to be about 5%, which remains a poor prognosis. In some cases, inoperable locally advanced breast cancer is diagnosed at the time of diagnosis. For inoperable locally advanced or metastatic/recurrent breast cancer, the mainstay of treatment is pharmacotherapy to palliate symptoms and prolong life.

Pharmacotherapy
Pharmacotherapy is administered according to subtype, classified according to hormone receptor (HR) expression and human epidermal receptor type 2 (HER2) expression. HR-positive patients are often treated with endocrine therapy first, followed
by chemotherapy if the disease becomes resistant to endocrine therapy, etc. If the disease is HER2-positive, chemotherapy is standard. In the case of HER2-positive patients, the standard treatment is a combination of anti-HER2 drugs and chemotherapy; in the case of HR-negative and HER2-negative patients, chemotherapy is the standard treatment. Recently, immune checkpoint inhibitors, anti-(protein found on T-cells) PD-1 antibodies, have been developed for a variety of types of cancer. They provide antitumor effects by inhibiting the immune escape system in tumor cells, and are also being developed in the area of breast cancer.

3.1.2. Target group

The target populations for this study are the following two cohorts.

Letrozole cohort
- Patients with de novo locally advanced or metastatic breast cancer who have not previously been treated with endocrine therapy.
- Patients with disease progression after 12 months since the last dose of postoperative endocrine therapy (aromatase inhibitor (AI) or selective estrogen selective modulators (SERM), and no prior treatment with endocrine therapy for locally advanced or metastatic breast cancer.

Fulvestrant cohort
- Patients with disease progression during postoperative endocrine therapy (AI or SERM).
- Patients with disease progression within 12 months of the last dose of postoperative endocrine therapy (AI or SERM).
- Patients with disease progression after 12 months since the last dose of postoperative endocrine therapy (AI or SERM), with a history of one regimen of endocrine therapy (AI or SERM) for locally advanced or metastatic breast cancer, and with disease progression or intolerance to such therapy.
- Patients with a history of one regimen of endocrine therapy (AI or SERM) for de novo locally advanced or metastatic breast cancer with disease progression or intolerance to such therapy.
3.1.3. Rationale for selection of target population

HR-positive HER2-negative breast cancer is the most common subtype among all breast cancers. The majority of patients with HR-positive HER2-negative breast cancer are diagnosed as early-stage breast cancer, but recurrence is seen in about 1/3 of patients after surgery and postoperative endocrine therapy. Thus, the majority of breast cancer-related deaths occur in patients with HR-positive HER2-negative breast cancer.

In principle, patients with HR-positive HER2-negative metastatic or recurrent breast cancer are started on endocrine therapy in the absence of imminent life-threatening events (extensive liver metastases, lung metastases, lymphangitis carcinomatosa, etc.) and in cases with a long time to recurrence. The anti-tumor effect of endocrine therapy is not observed in all patients, and both de novo resistance and acquired resistance are observed. Recently, CDK4/6 inhibitors have been developed for the treatment of HR-positive, HER2-negative metastatic or recurrent breast cancer. The phase III PALOMA-2 and MONARCH-3 trials demonstrated the efficacy of CDK4/6 inhibitor plus aromatase inhibitor (letrozole) combination therapy as first-line treatment, and the PALOMA-3 and MONARCH-2 trials demonstrated the efficacy of CDK4/6 inhibitor plus fulvestrant combination therapy as second-line therapy, and as one of the standard treatments. There are no clinical trials that have demonstrated improvement in OS in patients with CDK4/6 inhibitors plus endocrine therapy. The need for effective treatment options for long-term survival in patients with HR-positive HER2-negative metastatic or recurrent breast cancer is high and remains unmet. Various preclinical data suggest that the combination of nivolumab plus abemaciclib plus endocrine therapy (fulvestrant or letrozole) may be synergistic.

Therefore, we decided to investigate the efficacy and safety of nivolumab + abemaciclib + endocrine therapy (fulvestrant or letrozole) combination in patients with HR-positive HER2-negative metastatic or recurrent breast cancer.

3.2. Standard treatment for the subject

Metastatic or recurrent breast cancer is treated with systemic therapy, i.e., pharmacotherapy. The selection of pharmacotherapy involves evaluation of predictors of response (estrogen receptor (ER), progesterone receptor (PgR), HER2), and the...
Hortobagyi algorithm for treatment of metastatic or recurrent breast cancer and the National Comprehensive Cancer Network (NCCN) guidelines are commonly used. In principle, drug therapy for HR-positive HER2-negative metastatic or recurrent breast cancer is initiated with endocrine therapy if the patient is sensitive to endocrine therapy, has no imminent life-threatening events (extensive liver metastases, lung metastases, lymphangitis carcinomatosa, etc.), and has a long time to recurrence. If primary endocrine therapy is successful, it is continued until the disease worsens. Similarly, second- and third-line endocrine therapy is administered. Chemotherapy is the treatment of choice if the patient is not sensitive to endocrine therapy, or even if sensitive, if the disease is imminently life-threatening, or if the time to recurrence is short. Combination therapy with an luteinizing hormone releasing hormone (LH-RH) agonist plus tamoxifen is widely used as primary endocrine therapy for premenopausal/perimenopausal HR-positive HER2-negative metastatic or recurrent breast cancer.

Although there is no established standard of care as a secondary endocrine therapy, there are several different combinations of LH-RH agonist + fulvestrant + CDK4/6 inhibitor, LH-RH agonist + aromatase inhibitor, LH-RH agonist + fulvestrant, and progestins (megestrol acetate or medroxyprogesterone) that are considered treatment options. The only high-quality randomized controlled trials for premenopausal metastatic or recurrent breast cancer are the PALOMA-3 trial and the MONARCH-2 trial, which tested the efficacy of fulvestrant plus a CDK4/6 inhibitor. Both trials showed significant improvement in the primary endpoint of PFS in the fulvestrant plus CDK4/6 inhibitor arm. Aromatase inhibitors alone, in combination with an aromatase inhibitor plus a CDK4/6 inhibitor, or fulvestrant alone, are recommended as the standard of care for primary endocrine therapy in postmenopausal HR-positive HER2-negative metastatic or recurrent breast cancer. Several randomized controlled trials have been conducted on the efficacy of single agent aromatase inhibitors versus tamoxifen, and a meta-analysis reported that single agent aromatase inhibitors significantly prolonged OS compared to tamoxifen. For the aromatase inhibitor + CDK4/6 inhibitor combination, the phase III trials PALOMA-2, MONALEESA-2, and Monarch3 significantly prolonged PFS compared to aromatase inhibitor alone. The results were also highly consistent in a meta-analysis of the four trials. For fulvestrant monotherapy, the FALCON study, a phase III trial, showed significantly prolonged PFS compared to anastrozole. The choice of single-agent aromatase inhibitor, aromatase inhibitor plus CDK4/6 inhibitor, or single-agent fulvestrant, is based on the
balance of harm and benefit as well as patient preference. For secondary endocrine therapy, fulvestrant alone, fulvestrant plus CDK4/6 inhibitor, exemestane plus everolimus, etc. are recommended for patients with aromatase inhibitor resistance, while aromatase inhibitor alone is recommended for patients with tamoxifen resistance as standard therapy.

3.3. Protocol treatment

3.3.1. Study treatment regimen for this clinical trial

Protocol therapy for HR-positive HER2-negative metastatic or recurrent breast cancer includes the following administration...
Letrozole cohort

Nivolumab 240mg/body on day 1 and 15, every 28 days is 1 cycle
Letrozole 2.5mg once a day orally, continuously administered during the protocol treatment period
Abemaciclib 150mg twice a day orally, continuously administered during the protocol treatment period

The administration will be continued until it meets the criteria for discontinuing treatment.

Fulvestrant cohort

Nivolumab 240mg/body on day 1 and 15, every 28 days is 1 cycle
Fulvestrant 2 vials (containing 500mg of fulvestrant) Inject 1 vial into each buttock on days 1, 15, and 29 From day 29 onwards, administer every 28 days
Abemaciclib 150mg twice a day orally, continuously administered during the protocol treatment period

The administration will be continued until it meets the criteria for discontinuing treatment.

In premenopausal/perimenopausal patients, a gonadotropin releasing hormone (Gn-RH) agonist is used in combination with leuprorelin 3.75 mg every 28 days, (or 11.25 mg every 12 weeks, or 22.5 mg every 24 weeks), or goserelin 3.6 mg every 28 days, (or 10.8 mg every 12 weeks).

3.3.2. Rationale for setting treatment regimens

Drug

Letrozole

Letrozole is an aromatase inhibitor that lowers estrogen production by inhibiting the aromatase enzyme that converts androgens produced by the adrenal glands into estrogen. Several randomized comparative studies of letrozole's efficacy with tamoxifen have been conducted, and a meta-analysis reported that aromatase inhibitors alone significantly prolonged OS compared to tamoxifen.\textsuperscript{14,15} For letrozole plus CDK4/6 inhibitor combination, the phase III trials PALOMA-2\textsuperscript{16}, MONALEESA-2\textsuperscript{17}, and MONARCH-3\textsuperscript{18} significantly prolonged PFS compared to letrozole alone. Based on the above, letrozole alone or letrozole alone plus CDK4/6 inhibitor combination is
recommended as one of the standard treatments as primary endocrine therapy for postmenopausal HR-positive HER2-negative metastatic or recurrent breast cancer. The major side effects include osteoporosis, dyslipidemia, and hepatic disorder.

**Fulvestrant**

Fulvestrant is an agonist-independent estrogen receptor downregulator that binds to, blocks, and degrades estrogen receptors, thereby completely inhibiting estrogen receptor signaling. Because it inhibits not only genomic action but also non-genomic action, it is expected to be effective in patients who have become resistant to other endocrine therapies.

Aromatase inhibitors have been the standard of care as primary treatment for postmenopausal hormone receptor-positive metastatic or recurrent breast cancer, but the FALCON study, a phase III trial, showed significantly prolonged PFS in the single-agent fulvestrant group compared with anastrozole. The CONFIRM study also validated the efficacy of 500 mg fulvestrant versus 250 mg fulvestrant, with the 500 mg group significantly superior in the primary endpoint of PFS. Based on the above, fulvestrant is one of the standard treatments for first-line treatment of postmenopausal hormone receptor-positive metastatic breast cancer. The major side effects include arthralgia, hot flashes, and liver damage.

**Abemaciclib**

Abemaciclib is a CDK4/6 inhibitor developed by Eli Lilly for the treatment of inoperable or recurrent breast cancer, targeting cyclin dependent kinase (CDK). CDK4/6 inhibitors inhibit the activation of the cyclin-CDK complex, thereby inhibiting Rb phosphorylation, which is an important checkpoint for the transition from G1 to S phase of the cell cycle and regulates cell proliferation. and thus inhibits tumor growth by blocking Rb phosphorylation, regulating the Rb-E2F pathway, and arresting cell cycle progression. While CDK4/6 inhibition has been shown to attenuate cell growth in experiments with luminal-type breast cancer cell lines, its growth inhibitory effect is limited in triple-negative breast cancer cells. CDK4/6 inhibitors have been shown to inhibit cyclin D1 overexpression and cyclin D1-encoding most effectively in tumors with amplification of the CCND1 gene. Multiple phase III trials have shown the efficacy of abemaciclib in metastatic and recurrent breast cancer. In the U.S., the drug is FDA-approved as a single agent and in combination with hormone therapy.
MONARCH-3 trial demonstrated the efficacy of abemaciclib plus a nonsteroidal aromatase inhibitor as first-line therapy in HR-positive, HER2-negative metastatic or recurrent breast cancer, and showed the efficacy of abemaciclib plus fulvestrant as second-line therapy. The phase II MONARCH-1 study also reported efficacy of abemaciclib as monotherapy. The most common adverse reactions include diarrhea, myelosuppression (neutropenia, leukopenia, anemia, thrombocytopenia), fatigue, nausea, stomatitis, and rash.

**Nivolumab**

Nivolumab is a human IgG4 monoclonal antibody against human programmed cell death-1 (PD-1), created by Ono Pharmaceutical Industries, Ltd. and Medarex (now Bristol-Myers Squibb Company). The PD-1 receptor has two types of ligands, PD-L1 and PD-L2. Tumor cells express PD-L1 and PD-L2, which bind to PD-1 expressed on activated T cells and transmit inhibitory signals to T cells. Nivolumab is thought to exert its antitumor effects by inhibiting the binding of PD-1 to its ligands, PD-L1 and PD-L2, and by enhancing the proliferation, activation, and cytotoxic activity of cancer antigen-specific T cells.

In November 2014, the results of the phase III Checkmate-066 trial were reported, demonstrating the efficacy of nivolumab for the first time in the world. The efficacy of nivolumab and dacarbazine was tested in 418 patients with untreated BRAF wild-type malignant melanoma and showed significantly improved overall survival in the nivolumab arm. Since then, clinical trials have been conducted in various cancer types and efficacy has been reported. In Japan, the drug was approved in September 2014 for malignant melanoma that cannot be radically resected, and has since been approved for expanded indications for non-small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, head and neck cancer, gastric cancer, and malignant pleural mesothelioma. For breast cancer, several clinical trials are ongoing, mainly for triple negative breast cancer.

Adverse events are characterized by immune-related adverse events such as thyroid dysfunction and type 1 diabetes, but generally tend to be less toxic than previous cell-killing agents. Adverse reactions observed in clinical trials (CheckMate-066, n=206) are listed below (Table 3.3-1).
Table 3.3-1 Adverse Events in the International Phase III Study (CheckMate-066) for Malignant Melanoma

<table>
<thead>
<tr>
<th>Adverse event name</th>
<th>Nivolumab</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>G3 or higher %</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19.9</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>17.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>16.5</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Rash</td>
<td>15.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>10.7</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.7</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Nivolumab dosage regimen

Nivolumab 240 mg/body, 2-week intervals, dosed over 30 minutes was approved in Japan in August 2018 as monotherapy for non-small cell lung cancer, renal cell carcinoma, classic Hodgkin lymphoma, malignant melanoma, head and neck cancer, gastric cancer, and malignant pleural mesothelioma, according to the attached document.

Rationale for nivolumab, abemaciclib and endocrine therapy (fulvestrant or letrozole) in combination

The combination of nivolumab with abemaciclib and endocrine therapy (fulvestrant or letrozole) is expected to have synergistic effects based on various preclinical data.

**CDK4/6 inhibitor + anti-PD-1/ programmed cell death ligand 1 (PD-L1) antibody combination**

In vivo studies in a mouse model of breast cancer have reported that CDK4/6 inhibitors act on tumor cells and regulatory T cells to increase tumor immunogenicity. CDK4/6 inhibitors activate expression of endogenous retroviral elements in tumor cells, thereby increasing double-stranded RNA intracellular levels, stimulating the production of type III interferons, and enhancing tumor antigen presentation. In
addition, CDK4/6 inhibitors markedly suppress proliferation of regulatory T cells and reduce DNMT-1 gene expression, while having little effect on cytotoxic T cells. These effects are associated with decreased activity of DNA methyltransferase, a target of E2F, which ultimately promotes tumor cell elimination via cytotoxic T cells. In addition, the anti-tumor immune response is further enhanced by the combination of immune checkpoint inhibitors, with decreased PD-1 and CTLA-4 expression in cytotoxic T cells and increased PD-L1 expression in tumor cells. The above mechanisms have also been confirmed in transcriptome analyses of pre- and post-dose biopsy specimens in patients treated with abemaciclib. These reports provide a biological rationale for combining CDK4/6 inhibitors with immunotherapy.

While it has been reported that the response to immune checkpoint inhibition in some cancer types may correlate with the level of PD-L1 expression in tumor cells and tumor-infiltrating immune cells, a novel molecular mechanism has been reported in which cell cycle kinases (CDK4/6) regulate PD-L1 protein stability, and CDK4/6 inhibitors may provide a biological rationale for combination therapy with immune checkpoint inhibitors. PD-L1 protein expression is regulated through proteasome-mediated degradation by cyclin D-CDK4 and cullin 3-SPOP E3 ligase. In vivo studies have shown that CDK4 and CDK6 inhibition increased PD-L1 protein expression by inhibiting cyclin D-CDK4-mediated phosphorylation of SPOP (speckle-type POZ protein), and enhancing its degradation by late mitotic step-promoting complex activator FZR1. Anti-PD-1 antibodies together promoted tumor shrinkage and improved overall survival in a mouse tumor model.

Other reports have shown that CDK4/6 inhibitors reduce T cell proliferation, but enhance tumor infiltration and activation of effector T cells by deregulating NFAT-related proteins and genes, which are important regulators of T cell function. In addition, CDK4/6 inhibition has been shown to potentiate the effects of PD-1 inhibition in novel ex vivo organotypic tumor spheroid cultures and in several in vivo murine synergistic models. These provide a biological rationale for combining CDK4/6 inhibition with immunotherapy.

These preclinical data have led to clinical trials on the combination of anti-PD-1/PD-L1 antibodies and CDK4/6 inhibitors. At the 2017 San Antonio Breast Cancer Symposium, an interim report of a phase Ib trial (JPCE), investigating the combination of pembrolizumab + abemaciclib combination in HR-positive HER2-negative metastatic or recurrent breast cancer (JPCE study) interim report...
was presented. This study included 28 patients with HR-positive, HER2-negative, metastatic breast cancer who had received different kinds of treatment. The response rate at 16 weeks was 14.3%. The most common adverse event was diarrhea (78.6%), with no unexpected adverse events or treatment-related deaths. The response rate at 16 weeks in the MONARCH-1 trial, which evaluated the efficacy of single-agent abemaciclib, was 6.8%. In addition, a phase II trial of the CDK4/6 inhibitor palbociclib + anti-PD-1 antibody + NSAI combination is ongoing. There are currently no clinical trials on the combination of abemaciclib + nivolumab + endocrine therapy.

**Endocrine therapy + anti-PD-1/PD-L1 antibody combination**

The E2 pathway has been reported to be associated with tumor growth in a variety of cancer types, but its other role as a modulator of tumor immune responses has been shown to involve the promotion of an immunosuppressive tumor microenvironment (TME). Therefore, inhibition of the E2 pathway using endocrine therapy is expected to augment the efficacy of immunotherapy as a novel strategy to reverse the immune imbalance within the tumor microenvironment.

The E2 pathway contributes to the regulation of antitumor immunity and enhances many tumor responses within the tumor microenvironment. Recent reports indicate that E2 can promote immunosuppressive TME within the tumor microenvironment, by shifting the balance in favor of the production of tumor-promoting cytokines (IL-6, IL-4, TNFa, and IL-17A) and Th2 responses associated with M2 TAM invasion, relative to Th1 cytokines (IL-12, IFN-γ), and Th1 responses associated with M1 TAM invasion. It has been reported that E2 can promote immunosuppressive TME by shifting TME toward a balance. E2 can also promote tumor immune evasion through proliferation of Treg and MDSC populations, increased tumor cell PD-L1 expression, and inhibition of CD8+ T cell and NK cell-induced apoptosis.

Post-hoc analysis of gene expression in ER-positive breast cancer patients has been shown to increase the infiltration of B-cell and T-helper lymphocyte subsets at early and late time points after treatment with endocrine therapy.

In a more recent meta-analysis, FoxP3+ Treg infiltration was significantly correlated with poor OS in patients with ER-positive breast cancer, but did not improve survival in ER-negative patients. Furthermore, ER-α positive breast cancer in patients after endocrine therapy showed a significant decrease in FoxP3+ Treg after treatment.

These reports provide a biological rationale for combining endocrine therapy with
immune checkpoint inhibitors.

Based on the above, the combination of nivolumab + abemaciclib + endocrine therapy used in this study is expected to have a synergistic effect and is a promising treatment option whose efficacy and safety should be evaluated. Letrozole and fulvestrant, which have been shown to be effective in combination with abemaciclib, are the endocrine therapies of choice. Two cohorts (letrozole cohort and fulvestrant cohort) will be established in this trial to evaluate the efficacy and safety of each, with a view to validation in a Phase III trial.

3.4. Test design

3.4.1. Clinical Hypothesis and Phase Setting for this Clinical Trial

This is a multi-arm phase II study to evaluate the efficacy and safety of nivolumab plus abemaciclib plus endocrine therapy (fulvestrant or letrozole) in the treatment of HR-positive HER2-negative metastatic or recurrent breast cancer. The safety of the combination of nivolumab + abemaciclib + endocrine therapy (fulvestrant or letrozole) has not been established. Therefore, a phase II study including a safety component was planned.

If the study shows efficacy and safety, we envision a phase III trial comparing nivolumab plus abemaciclib plus endocrine therapy (fulvestrant or letrozole) to the current standard of care, abemaciclib plus endocrine therapy (fulvestrant or letrozole).

3.4.2. Basis for setting endpoints

Letrozole cohort

Step 1 (Safety part)

1) Primary endpoint: DLT incidence

The purpose of the safety part is to evaluate the safety of the protocol treatment, and to determine whether the study can be continued. As a measure of safety, the primary endpoint will be the incidence of DLT in the 6 patients.

2) Secondary endpoint: Percentage of adverse events

Adverse events are used as a secondary endpoint as a measure of safety.
Step 2
Evaluate efficacy and safety in all eligible patients, including those enrolled in the safety part.
1) Primary endpoint: Overall response rate
2) Secondary endpoint: safety, disease control rate, progression-free survival
   6-month progression-free survival rate,
   12-month progression-free survival rate
   12-month overall survival rate, overall survival

Fulvestrant cohort

Step 1 (Safety part)
1) Primary endpoint: DLT incidence
   The purpose of the safety part is to evaluate the safety of the protocol treatment and to determine whether the study can be continued. As a measure of safety, the primary endpoint will be the incidence of DLT in the 6 patients.
2) Secondary endpoint: Percentage of adverse events
   Adverse events are used as a secondary endpoint as a measure of safety.

Step 2
Evaluate efficacy and safety in all eligible patients, including those enrolled in the safety part.
1) Primary endpoint: Overall response rate
2) Secondary endpoint: safety, disease control rate, progression-free survival
   6-month progression-free survival rate,
   12-month progression-free survival rate
   12-month overall survival rate, overall survival

Since this is a phase II trial designed to explore the effect of adding nivolumab to the standard treatment combination of abemaciclib and endocrine therapy (fulvestrant or letrozole), the response rate would be the primary endpoint.

The response rate is the percentage of tumor shrinkage. Tumor shrinkage cannot be considered a true benefit, but on the other hand, it can be evaluated in a relatively small number of patients and in a short period of time, and it is less susceptible to the natural history of the disease, making it easier to directly evaluate the effect of the drug itself.
is considered suitable and is widely used for endpoints in trials. Progression-free survival is the time until tumor progression or death. It is often used as an alternative endpoint to overall survival, but has the disadvantage of being susceptible to the testing interval for tumor shrinkage effect and to the natural history of the disease. If efficacy is demonstrated in this trial, a phase III trial with a primary endpoint of progression-free survival (or overall survival) may be warranted to test the efficacy of the combination of nivolumab + abemaciclib + endocrine therapy (fulvestrant or letrozole). Since this is a phase II study aimed at exploratory evaluation of these combination therapies, the response rate was used as the primary endpoint.

3.4.3. Basis for setting the number of registrations

Letrozole cohort
Step 1 (Safety part)

The purpose of the safety part was to evaluate the safety of the protocol treatment and to determine whether to continue the Phase II study. Therefore, the required number of patients was set at 6.
Step 2

In previous phase III trials comparing CDK4/6 inhibitor plus letrozole to letrozole alone in HR-positive HER2-negative metastatic or recurrent breast cancer, the response rate for CDK4/6 inhibitor plus letrozole combination therapy ranged from 40.7-48.2%, but in the subgroup with measurable disease was reported to be 52.7-59.2%. Based on the above, the threshold and expected response rate were set at 55% and 75%, respectively, in anticipation of a synergistic effect of the nivolumab combination in this trial.

Number of patients required for analysis of primary endpoint: 18 (including 6 for safety part)

Threshold objective response rate (ORR) 55
Expected ORR 75
Alpha error 0.2
Beta error 0.2
Number of cases required: 16 (18 considering deviations)

Fulvestrant cohort

Step 1 (Safety part)

The purpose of the safety part was to evaluate the safety of the protocol treatment and to determine whether to continue the Phase II study. Therefore, the required number of patients was set at 6.

Step 2

In the phase III MONARCH-2 trial comparing abemaciclib plus fulvestrant to fulvestrant alone in HR-positive HER2-negative metastatic or recurrent breast cancer, the response rate for abemaciclib plus fulvestrant was 35.2% (95%CI, 30.8%-39.6%) However, in the subgroup with measurable disease, the response rate was reported to be 48.1% (95%CI, 42.6%-53.6%). Based on the above, we set the threshold for the response rate at 45% and the expected response rate at 60% in this trial in anticipation of a synergistic effect of the nivolumab combination.

Number of patients required for analysis of primary endpoint: 35 (including 6 for safety part)

Threshold ORR 45
Expected ORR 60
Alpha error 0.2
Beta error 0.2
Required number of cases: 32 (35 considering deviations)
3.4.4. Safety Assessment

Since there are no safety reports on the combination of nivolumab + abemaciclib + endocrine therapy (fulvestrant or letrozole) to be conducted in this study, safety will be evaluated in the first 6 patients in each cohort as the safety part of the study. For the combination of anti-PD-1 antibody + abemaciclib, the safety of the combination of pembrolizumab + abemaciclib was reported in a phase Ib study conducted for breast cancer. 34)

3.5. Summary of anticipated benefits and disadvantages associated with study participation

The combination of nivolumab plus abemaciclib plus endocrine therapy (fulvestrant or letrozole) is expected to have a higher response rate and longer progression-free survival than the current standard of care, abemaciclib plus endocrine therapy (fulvestrant or letrozole). The disadvantage is that this is a novel combination therapy and there is a possibility of unknown adverse events.

3.6. Planned Enrollment and Clinical Trial Duration

Planned enrollment: Letrozole cohort: 18 patients (including 6 in safety part)  
Fulvestrant cohort: 35 patients (including 6 patients in safety part)  
Total 53 cases
Clinical trial period: June 17, 2019 to December 04, 2020  
Registration period: June 17, 2019 to December 04, 2019  
Follow-up period: 1 year from the last case enrollment date  
(If the follow-up of adverse events is completed in all cases, it must be before December 4, 2020. The clinical trial shall be terminated even if the patient is not in the study area).

4. Criteria and definitions used in this study

4.1. Definition of period

The duration of this study is defined below.

Clinical trial duration: from the starting date of enrollment to the end of the follow-up period

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Registration period: From the registration start date to the last registration date
Follow-up period: 1 year after the last enrollment date

4.2. Definition of pathological diagnosis
Follows WHO classification, 4th ed.

4.3. Definition of staging
Use the mammary staging system (UICC, 8th ed.).

4.4. Definition of menopausal status
Postmenopausal definition (meets at least one of the following criteria)

- Over 60 years old
- The patient is under 60 years of age, has stopped menstruating regularly for at least 12 months, and has no other pathological or physiological cause. Serum estradiol and FSH levels are within the reference laboratory values for postmenopausal women.
- Records show that she underwent bilateral oophorectomy.
- Ovarian dysfunction is medically confirmed.

4.5. Definition of Effectiveness Determination
Tumor shrinkage efficacy is determined in accordance with the "Revised RECIST guideline (version 1.1)Japanese translation of the JCOG version of the new guideline for determining treatment efficacy in solid tumors.

Lesions with a history of local therapy treatment
Tumor lesions that have undergone prior radiation therapy or other local therapy may be considered measurable lesions only if progression of the treated area is clearly documented after completion of such therapy.

Best Overall Response
Once all patient data are available, the best overall effect is determined: CR>PR>SD>PD>NE, with better being the best overall effect.
Complete Response (CR)
At least two consecutive overall effective CRs at intervals of at least 4 weeks (28 days).

Partial Response (PR)
When an overall response (CR or PR) of at least two consecutive PRs at an interval of at least 4 weeks (28 days) is obtained.

Stable Disease (SD)
If neither CR nor PR of best overall effect was obtained, but the overall effect is not PD until after the 6-week determination after study enrollment, and the overall effect is SD or better on at least one occasion.

Progressive Disease (PD)
If the best overall effect CR, PR, or SD is not applicable and the overall effect is PD.

Not Evaluable (NE)
If the overall effect is all NE.

4.6. Definition of Beyond PD
Beyond PD, is defined as when PD is determined by imaging evaluation, and all the following Beyond PD conditions are met, and protocol treatment is continued at the discretion of the attending physician.

Beyond PD Conditions
(i) Clinical benefit of continuing protocol therapy without rapid disease progression is expected to be
(ii) Tolerates the protocol treatment.
(iii) Eastern Co-operative Oncology Group (ECOG) Performance Status is stable.
(iv) Continuation of the protocol treatment will result in serious complications (e.g., brain metastases) associated with disease progression.

Do not delay prophylactic intervention against radiation therapy during administration of the protocol therapy.
Surgical treatment is prohibited.
4.7. **Definition of Adverse Events** (Error! Reference source not found. See Section 9.1)

An adverse event is an unfavorable medical event that occurs during or after the administration of a pharmaceutical product, or a worsening of symptoms or signs that existed prior to administration, and includes all events regardless of whether they are causally related to the administration of the pharmaceutical product. An unfavorable medical event is any symptom (e.g., nausea, chest pain), sign (e.g., tachycardia, hepatomegaly), or abnormal test result (e.g., laboratory test results, ECG). In this study, adverse events are reported from the start of the first dose of study drug until 30 days after the last dose or the date of decision to discontinue, whichever is later. If post-treatment is started during the period up to that time, discontinuation is permitted after the start of post-treatment.

The handling of adverse events shall be in accordance with the following

- If an adverse event of Grade 1 or higher was observed in NCI-CTCAE Version 5.0 before the start of the first course of administration (at the baseline evaluation), the event will be treated as an adverse event if the Grade of the adverse event worsens by one or more levels from the level before the start of administration and the investigator determines that the event is medically undesirable. The principal investigator or other relevant personnel will determine that the adverse event is not medically undesirable.

- For aggravation of the primary disease, concomitant symptoms of the primary disease, and complications, an adverse event shall be defined as one that is medically determined to be beyond the scope of its natural course. In the case of an aggravation of a complication, the date when the aggravation is confirmed shall be the date of onset of the adverse event.

- For an event with multiple symptoms (including signs and abnormal laboratory value fluctuations), a diagnosis/disease name should be listed in the case report as an adverse event with the diagnosis/disease name.

5. **Patient Selection**

5.1. **Eligibility Criteria**

All the following conditions shall be met.

Age, informed consent (IC), Sex
1) The 20 years old or older woman at the time consent.
2) Written consent has been obtained from the patient herself after a full explanation of the study was given prior to enrollment in the study.

Menopausal status
3) The following criteria must be met for menopausal status.
   Letrozole cohort: postmenopausal.
   Fulvestrant cohort: any menopausal status.

Tissue type, marker
4) Patients with histologically or cytologically confirmed invasive breast cancer.
5) Estrogen receptor (ER)-positive or progesterone receptor (PgR)-positive (>1% positive cells in immuohistochemistry (IHC) or >3 points in Allred score).
6) Confirmed HER2 negative immunohistochemistry (IHC1)+ or less or fluorescence in situ hybridization / double in situ hybridization (FISH/DISH) negative (IHC2+ has been confirmed to be negative by FISH/DISH method).

Provided by the organization
7) Tumor tissue specimens from biopsy tissue or surgical specimens (even metastases) can be provided.

Spread of lesions
8) Locally advanced or metastatic breast cancer, chemotherapy-naive patients for whom curative resection or radiation therapy is not indicated.
9) Have measurable lesions as defined by response evaluation criteria in solid tumors (RECIST) ver 1.1 on imaging within 28 days prior to enrollment. Tumor lesions treated with radiation therapy or other local therapy may be considered measurable lesions only if progression of the treated area is clearly documented after completion of such therapy.
10) Patients must not have bone metastases only. (Even bone metastases that are considered evaluable by RECIST ver 1.1 are not acceptable)
11) The patient does not have active central nervous system metastases or cancerous meningitis (patients treated for brain metastases must have stable brain metastases and not be using steroids for symptom management related to brain metastases). Patients are considered to have active brain metastases if any of the following apply.
   • Use of steroids for symptom management related to brain metastases or treatment for brain metastases within 7 days prior to enrollment.
• When there are obvious neurological symptoms due to brain metastases.
• Within 14 days of the last irradiation of radiotherapy for brain metastases.
• If your physician determines that the patient is active.

Previous treatment
12) Patients must meet one of the following criteria
   Letrozole cohort
   • Patients with de novo locally advanced or metastatic breast cancer who have not previously been treated with endocrine therapy.
   • Patients with disease progression after 12 months since the last dose of postoperative endocrine therapy (AI or SERM) and no prior treatment with endocrine therapy for locally advanced or metastatic breast cancer.

   Fulvestrant cohort
   • Patients with disease progression during postoperative endocrine therapy (AI or SERM).
   • Patients with disease progression within 12 months of the last dose of postoperative endocrine therapy (AI or SERM).
   • Patients with disease progression after 12 months since the last dose of postoperative endocrine therapy (AI or SERM), with a history of one regimen of endocrine therapy (AI or SERM) for locally advanced or metastatic breast cancer, and with disease progression or intolerance to such therapy.
   • Patients with a history of one regimen of endocrine therapy (AI or SERM) for de novo locally advanced or metastatic breast cancer with disease progression or intolerance to such therapy.

13) No prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-cytotoxic T lymphocyte-associated antigen (CTLA-4) or other T-cell co-stimulatory receptor-targeted drug therapy.
14) No prior treatment with cytotoxic agents (except perioperative treatment), molecular targeted agents (e.g. everolimus, CDK4/6 inhibitors, PI3K inhibitors), or fulvestrant.
15) Patients who have not received radiotherapy within 14 days prior to enrollment. (Irradiation on the same day of the week 14 days prior to enrollment qualifies.)
16) Patients who have not received any other investigational drug within 28 days prior to enrollment. (Dosing on the same day of the week 28 days prior to enrollment is considered eligible.) However, this does not apply to patients who have been confirmed to be in the placebo group in a double-blind, randomized study.

General condition, pregnancy
17) Patients with ECOG performance status of 0-1
18) Patients expected to survive for at least 3 months.
19) Patients without visceral crisis (Visceral crisis is not only the presence of visceral metastases, but also the presence of severe life-threatening organ failure and rapid disease progression).
20) Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.
21) Women of childbearing potential (including patients who are not menstruating for medical reasons such as chemical menopause* who have agreed to dual contraception† for at least 5 months after the last dose of study drug from the time consent is obtained. Also, patients who have agreed not to breastfeed for at least 5 months after the last dose of study drug from the time consent is obtained.
   * Women of childbearing potential include all women who have experienced menarche, have not undergone sterilization procedures (hysterectomy, bilateral tubal ligation or bilateral oophorectomy, etc.), and are not yet menopausal. Postmenopausal is defined as having been amenorrheic for at least 12 consecutive months, despite the absence of any reason of note. Women using oral contraceptives or mechanical contraceptive methods (e.g., intrauterine devices or barrier methods) shall be considered to be of childbearing potential.
   †For contraception, the patient must agree to dual contraception: vasectomy or condom for the male partner, tubal ligation for the female patient, contraceptive pessary, intrauterine device, or oral contraceptive pills.

Clinical Laboratory
22) Clinical laboratory tests performed within 14 days prior to enrollment meet the following criteria: (1) to (7). However, the patient must not have received granulocyte colony stimulating factor (G-CSF product) administration or blood
transfusion within 14 days prior to the date of blood collection.

1. Neutrophil count ≥ 1500 / mm³
2. Platelet count ≥ 10 x 10⁴ / mm³
3. Hemoglobin ≥ 8.0 g/dL
4. Aspartate aminotransferase (glutamic-oxaloacetic transaminase) (AST (GOT) ≤ 100 IU/L
5. Alanine aminotransferase (pyruvic transaminase) (ALT (GPT) ≤ 100 IU/L
6. Total bilirubin ≤ 1.5 mg/dL
   However, for Gilbert's syndrome, total bilirubin <3.0 mg/dL
7. Creatinine ≤ 1.5 mg/dL

23) Hepatitis B surface (HBs) antigen, total hepatitis core (HBc) antibody, and HBs antibody test results are all negative, or
   HBs antigen negative and positive for both or either HBs or HBc antibodies
   Hepatitis B virus (HBV)-DNA quantification must be below detection sensitivity; hepatitis C virus (HCV) antibody negative, or in the case where the HCV antibody is positive, HCV-RNA quantification must be below detection sensitivity.

5.2. Exclusion criteria

Cases with any of the following items should be excluded

Duplicate cancer
1) Patients with a history of invasive malignancy within the past 3 years from the time of enrollment. However, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (intraepithelial carcinoma), or intramucosal carcinoma equivalent that is considered curable with local treatment, will not be included as active multiple cancers.

Preceding treatment, etc.
2) Patients who received a live vaccine within 30 days of enrollment.
3) Patients who required systemic corticosteroids or immunosuppressant drugs of more than 10 mg/day of prednisolone equivalent within 28 days prior to enrollment. (Temporary administration for testing or prophylactic administration is excluded.)

Complications, etc.
4) Patients with active infections requiring systemic treatment by intravenous administration.

5) Patients with interstitial lung disease/pulmonary inflammation or a history of interstitial lung disease/pulmonary inflammation requiring systemic corticosteroid administration. (Interstitial lung disease/pulmonary inflammation includes radiation pneumonitis.)

6) Pregnant, possibly pregnant, or lactating patients.

7) Patients with significant cardiovascular disease. Patients who have undergone myocardial infarction, acute coronary artery disease, or coronary angioplasty/stent/bypass surgery within the past 6 months.

8) Patients with New York Heart Association Class III-IV congestive heart failure.

9) Patients with the following pre-existing diseases, comorbidities, or complications, 
   ① Poorly controlled diabetes  
   ② Symptomatic Peptic Ulcer Disease  
    ③ Treatment history of blood stem cell transplantation, bone marrow transplantation  
    ④ Other serious complications (kidney failure, liver failure, etc.)

10) Patients with confirmed HIV-1 or HIV-2 antibody positivity.

11) Patients with psychiatric disorders that may affect the conduct of the clinical trial.

12) Patients with a history of hypersensitivity to the investigational drug and concomitant therapy or its analogues.

6. Case registration

6.1. Registration Procedure

The investigator will explain the subject about the clinical trial and obtain written consent.

After the investigator and others confirm that the participant meets all the selection criteria and none of the exclusion criteria, the subject will be enrolled by electronic data capture (EDC). There will be no randomization in this study.

Registration by EDC:
The physician in charge or collaborator will access the web registration system for this clinical trial via the Internet.

Follow the instructions in the registration system to enter the required information and register.

Registration is available 24 hours a day, except during maintenance.

6.2. Precautions

1) Once a patient is registered, the registration is not cancelled (i.e., not deleted from the database).

2) In case of duplicate registration, the first registration information (registration number) shall be adopted in principle.

3) If misregistration or duplicate registration is identified, the Clinical Trials Coordinating Committee shall be notified immediately.

7. Protocol treatment plan

7.1. Investigational new drug

Nivolumab will be provided as an investigational drug by Ono Pharmaceutical Co.

7.1.1. Characteristics of the investigational drug

- Name: ONO-4538 Injection (generic name) nivolumab
- Storage: Store at 2–8 °C under light-shielded conditions.
- Dosage form / Content: Water soluble injection containing 100 mg of ONO-4538 in one vial (10 ml)
- Packaging: Large box with 6 small boxes containing 1 vial.

7.1.2. Packaging and labeling of investigational drugs

Labeling and packaging shall be described in the "Procedures for the Management of Investigational New Drugs," which is separately prescribed.

7.1.3. Storage of investigational drugs

The investigational drug should be stored in a safe place under appropriate storage conditions. Appropriate storage and transport conditions are described on the label attached to the box of the investigational drug, in the investigational drug summary and in the procedure manual for the management of investigational drugs.
7.1.4. Administration of investigational drugs

The investigational new drug will be provided by the investigational new drug provider to the investigator of each site through the Clinical Trial Coordinating Committee at a predetermined time after the submission of the clinical trial plan. Specific procedures for the provision of investigational new drugs are prescribed in the "Procedures for Management of Investigational New Drugs," which is separately stipulated. The investigator who conducts the clinical trial himself/herself explains the details of the clinical trial to the investigational drug manager at his/her site, submits the "Protocol for Management of Investigational Drugs," and then requests storage and management of the investigational drug. The investigational drug manager shall appropriately store and manage the investigational drug and its outer package regardless of whether the investigational drug is used or not during the clinical trial period, and shall prepare an investigational drug management chart to grasp the usage status of the investigational drug. The investigator who conducts the clinical trial shall check the consistency of the contents of the investigational drug control record, the remaining drug, and the case report form, and if any inconsistency is found, immediately investigate the cause, and make the necessary correction.

After completion of the clinical trial, the investigational drug manager returns the unused investigational drug and empty box to the person who conducts the clinical trial him/herself. When returning them, the subject's name (initials), medical record ID, and other information pertaining to the subject's privacy should not be legible. If an unused investigational new drug or empty box is lost, a record should be made of the contents and the reason for the loss. The investigator who conducts the clinical trial himself/herself shall return all unused investigational new drugs returned by the investigational new drug administrator to the investigational new drug donor via the investigational new drug coordinating committee.

7.2. Concomitant Therapies

The drugs used in this study, abemaciclib and fulvestrant and letrozole, are over-the-counter drugs used in medical institutions. The characteristics, storage and administration of the concomitant medications will be described in the attached document.
7.3. Clinical trial treatment (protocol treatment)

7.3.1. Dosage and administration

Protocol treatment for HR-positive HER2-negative metastatic or recurrent breast cancer includes the following administration.

The course is defined by the date of administration of the investigational drug. Concomitant therapy drugs are administered according to their own defined criteria, independent of the course concept.

**Letrozole cohort**

- Nivo: Nivolumab
- LET: Letrozole
- Abema: Abemaciclib

Nivolumab 240 mg/body day 1, 15, and 30, intravenous infusion over 30 minutes (acceptable range 20-40 minutes)

One course of 28 days.

Letrozole: 2.5 mg once a day orally, administered daily for the duration of protocol treatment

Abemaciclib: 150 mg twice a day orally, administered daily for the duration of protocol treatment

Continue administration until treatment discontinuation criteria are met.
Fulvestrant cohort

*Premenopausal/perimenopausal cases are treated with a gonadotropin releasing hormone (Gn-RH) agonist.

- **Nivo**: Nivolumab
- **FUL**: Fulvestrant
- **Abema**: Abemaciclib

**Figure title?**

Nivolumab: 240 mg/body

- Day 1, 15...30: Intravenous infusion over 30 minutes (acceptable range 20-40 minutes)
- One course of 28 days.

2 tubes of fulvestrant (containing 500 mg of fulvestrant)

- Day 1, 15, 29: Intramuscular injection in the right and left buttocks
- Dose every 28 days after day 29

Abemaciclib 150 mg twice a day orally, administered daily for the duration of the protocol treatment

Continue administration until treatment discontinuation criteria are met.

* In premenopausal/perimenopausal patients, a gonadotropin releasing hormone (Gn-RH) agonist is used in combination with leuprolelin 3.75 mg every 28 days, (or 11.25 mg every 12 weeks, or 22.5 mg every 24 weeks), or goserelin 3.6 mg every 28 days (or 10.8 mg every 12 weeks) or 6 mg every 28 days (or 10.8 mg every 12 weeks).

* The start date of each course can be +/- 3 days from the start date of the immediately preceding course.
- Day 15 dosing within a course is allowed up to +/- 3 days from the start of each course.
- The investigator may, at his/her own discretion, bring forward or postpone the administration of the drug due to national holidays, etc., up to a maximum of -3 to +7 days from the scheduled date of administration.
- However, under no circumstances is it permissible to advance the date of administration by more than -4 days or postpone it by more than +8 days from the scheduled date.
<Dosage and administration period of the investigational drug>

Nivolumab 240 mg is administered intravenously over 30 minutes at 2-week intervals. Nivolumab will be administered continuously until the investigator or subinvestigator determines that "6.5.3. Criteria for Discontinuation of Nivolumab" is met. No change in the nivolumab dose (240 mg) is allowed. Nivolumab should be administered at least 11 days after the previous dose, i.e., at least 10 days after the middle of the day. Refer to the most recent Investigational New Drug Summary and Procedures for the Administration of Investigational New Drugs for information on the proper storage, handling, preparation, and administration of nivolumab.

<Prophylactic Administration of Investigational Drugs>

For subjects who experience an infusion-related reaction after receiving nivolumab, we recommend prophylactic premedication with acetaminophen or diphenhydramine prior to nivolumab administration beginning with the next dose.

7.3.2. Criteria for DLT in Step 1 (safety part)

The DLT evaluation period is defined as the period from the start of study treatment until before the administration of Day 1 of the second course, and a DLT is defined as a DLT when the following criteria for the development of DLT are met. However, even if the following criteria are met, if a causal relationship between toxicity and treatment can be ruled out, the patient is not considered to have a DLT.

1. Grade 3 non-hematologic toxicity (excluding nausea, vomiting, diarrhea, electrolyte abnormalities)
2. Grade 3 or higher nausea, vomiting, or diarrhea that cannot be controlled despite appropriate supportive care
3. Grade 4 hematologic toxicity lasting more than 5 days
4. Grade 3 or higher “febrile neutropenia”
5. Abemaciclib or endocrine therapy withdrawal rate >50% during the DLT evaluation period

7.3.3. Step 1 (safety part) evaluation procedure

Since there are no safety reports on the combination of nivolumab + abemaciclib + endocrine therapy (fulvestrant or letrozole) in this study, safety will be evaluated in the first 6 patients in each cohort as the safety part of the study by the DLT incidence rate. The DLT evaluation period will be defined as the period from the start of study
treatment until before the administration of the second course of Day 1. Once the start of treatment is confirmed in the sixth case, new enrollment in the study will be suspended and the case report form (CRF) on safety will be collected for the first course in each case. The Clinical Trial Coordinating Committee will conduct a safety evaluation, determine whether to continue the trial, and obtain approval from the investigator. The decision on whether to continue the clinical trial is made comprehensively, including the incidence of serious adverse events and treatment-related deaths, as well as the DLT incidence rate. If the Clinical Trial Coordinating Committee determines that a review by the Efficacy and Safety Evaluation Committee is necessary, a discussion by the latter committee members will be held. If the Trial Coordinating Committee, investigator or Efficacy and Safety Evaluation Committee determines that the study cannot be continued, further enrollment will be terminated (in such cases, the Efficacy and Safety Evaluation Committee will discuss whether the investigational drug administration and data analysis for the cases enrolled up to that point can be continued. The study will be terminated if three or more cases of DLT occur that are judged to be causally related to the treatment.

When the sixth case of the safety part reaches 28 days after the start of treatment, information on safety up to that point will be collected and shared with Ono Pharmaceutical Co. and Bristol-Myers Squibb (BMS).

7.4. **Start of treatment**

In principle, protocol treatment should be initiated within 14 days of enrollment (the same day of the week as the enrollment date is acceptable), after the safety confirmation. If treatment cannot be started within 14 days of enrollment, the reason should be reported to the Clinical Trial Coordinating Committee.

7.4.1. **Pre-treatment discontinuation**

If it is determined that the protocol treatment cannot be initiated for any reason, the protocol treatment should be terminated prior to treatment, and the details should be included in the End of Treatment Report and submitted promptly.
7.5. **Dosing and treatment modification criteria for the investigational drug (nivolumab)**

Every consideration should be made to administer the therapeutic agent according to the planned dosing schedule. Generally, adverse events should be the criteria for dose discontinuation, withdrawal and skipping, and adverse effects should be the criterion for dose modification.

The terminology for dosing and treatment modification criteria shall be as follows.

- **Discontinuation**: termination of part or all of the treatment without resumption
- **Suspension/withdrawal**: may resume, temporary suspension
- **Skip**: To skip administering part or all of the treatment and proceed to the next schedule

### 7.5.1. **Criteria for course initiation and in-course dosing**

If the following dosing criteria are not met on the day of, or before nivolumab administration, nivolumab will not be administered. Nivolumab will be skipped, but the start of the course will generally not be postponed, and the course will be maintained every 4 weeks.

### 7.5.2. **Nivolumab dosing criteria**

Skip nivolumab dosing if the following nivolumab initiation criteria are not met

1) Total bilirubin $\leq 2.0$ mg/dL
   However, for Gilbert's syndrome, total bilirubin $<3.0$ mg/dL
2) AST $\leq 100$ IU/L
3) ALT $\leq 100$ IU/L
4) Adverse events undeniably related to nivolumab less than or equal to Grade 2 (lung inflammation less than or equal to Grade 1)
5) Injection-related reactions that cannot be ruled out as causally related to nivolumab are Grade 2 or less (if an injection-related reaction has occurred since the previous dose). However, if a second injection-related reaction of Grade 2 or higher occurs despite treatment for the injection-related reaction, subsequent doses of nivolumab should be discontinued.
6) No other adverse events for which the physician in charge determines that it is inappropriate to initiate administration.
7.5.3. Criteria for discontinuation of nivolumab

Nivolumab should be discontinued if any of the following are observed.
No dose adjustment of nivolumab will be made during each course.

1) Discontinue nivolumab if Grade 2 or higher pulmonary inflammation develops, regardless of causality.
2) Discontinue nivolumab if a Grade 3 or higher infusion-associated reaction occurs for which a causal relationship to nivolumab cannot be ruled out; if a Grade 2 or lower infusion-associated reaction occurs and a second Grade 2 or higher infusion-associated reaction occurs despite treatment for the infusion-associated reaction, discontinue further nivolumab.
3) If an adverse event other than those listed above occurs that is Grade 3 or higher and for which a causal relationship to nivolumab cannot be ruled out, administration should be discontinued.
4) Discontinue nivolumab if the patient fails to receive nivolumab for more than 56 days after the last nivolumab dose.
5) Nivolumab should be discontinued in the presence of any other adverse events for which the physician in charge determines that administration is inappropriate.

7.6. Criteria for the administration of concomitant medications and treatment modification

Concomitant medications will be administered during the protocol treatment period based on the criteria set forth below, independent of the course concept.

7.6.1. Letrozole withdrawal and resumption criteria

1) If a Grade 3 adverse event occurs for which a causal relationship to letrozole cannot be ruled out, the drug should be withdrawn. 2.

2) If the relevant adverse event recovers to Grade 2 or less by Day 42, starting on Day 1 of the Letrozole suspension, the patient should resume taking Letrozole.

3) If the subject himself/herself has discontinued the drug at his/her own discretion, he/she should be seen promptly (a telephone call by the physician is acceptable) to determine resumption of the drug.
4) No other adverse events for which the physician in charge determines that resumption of dosing is inappropriate.

7.6.2. Letrozole discontinuation criteria

Letrozole will be discontinued if any of the following are observed. In this case, treatment with nivolumab and abemaciclib should be continued unless the criteria for the 6.8 Discontinuation of Protocol Treatment are met.

Letrozole dosage adjustment is not performed.
1) Discontinue administration in the event of a Grade 4 or higher adverse event for which a causal relationship to letrozole cannot be ruled out.
2) Discontinue letrozole if it has not been administered for more than 42 days since the last dose of letrozole.
3) Letrozole should be discontinued in the event of any other adverse events for which the physician in charge determines that administration is inappropriate.

7.6.3. Criteria for withdrawal and resumption of fulvestrant

1) Grade 3 adverse events with undeniable causal relationship to fulvestrant
   If the patient is not on the medication, the drug should be withdrawn.
2) The corresponding adverse event by day 56, starting on day 1 of fulvestrant cessation.
   If the patient recovers to Grade 2 or below, resume administration of fulvestrant.
3) No other adverse events for which the physician in charge determines that resumption of dosing is inappropriate.

7.6.4. Criteria for discontinuation of fulvestrant

Fulvestrant will be discontinued if any of the following are observed. In this case, treatment with nivolumab and abemaciclib will be continued unless the criteria for the 6.8 Discontinuation of Protocol Treatment are met.

No dose adjustment of fulvestrant is made.
1) Adverse events of Grade 4 or higher that cannot be ruled out as causally related to fulvestrant
If the patient is not receiving the drug, discontinue administration.

2) Failure to administer fulvestrant for more than 56 days after the last dose of fulvestrant  
   Discontinue administration of fulvestrant.

3) If there are other adverse events that your physician determines are  
   inappropriate to administer the full  
   Discontinue administration of fulvestrant.

7.6.5. Abemaciclib Withdrawal and Resumption Criteria [Resumption of the Same  
   Dose, Resumption of a Reduced Dose].

1) “Table 7.6-1 Abemaciclib Withdrawal and Resumption Criteria [Same Dose Resumption, Reduced Dose Resumption], for abemaciclib.

2) If the applicable adverse event recovers by Day 43, starting on Day 1 of the  
   abemaciclib suspension, Tables 6.6-1, and Table 7.6-2 are used to restart  
   abemaciclib oral administration.

3) If the participant withdraws from the drug at his or her own discretion, he or  
   she should be seen promptly (a telephone call from the physician is acceptable)  
   and the investigator / physician should refer to Tables 6.6-1 and 6.6-2 to  
   determine if abemaciclib should be resumed.

4) Other dose reductions of abemaciclib by one or, if necessary, two steps are  
   acceptable at the discretion of the investigator or physician in charge,  
   depending on the type and severity of the adverse event. If a dose reduction is  
   implemented, the dose should not be increased even if adverse events improve.

5) No other adverse events for which the physician in charge determines that  
   resumption of dosing is inappropriate.

Table 7.6-1 Abemaciclib Withdrawal and Resumption Criteria [Same Dose Resumption,  
   Reduced Dose Resumption].

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Degree</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Grade 1*</td>
<td>Drug withdrawal or dose reduction is not required.</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>If the patient does not recover within 24 hours, the drug should be withdrawn until the patient recovers to Grade 1 or below.</td>
</tr>
</tbody>
</table>
When resuming, no weight reduction is required.

| Grade 2 with symptoms that persist despite treatment or relapse after resumption without dose reduction | Withdrawal of the drug until recovery to Grade 1 or below. When restarting, the dose should be reduced by one step. |
| Requires hospitalization or grade 3 or 4 |

<table>
<thead>
<tr>
<th>Hematologic toxicity (leukopenia, neutropenia, anemia, thrombocytopenia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
</tr>
<tr>
<td>Drug withdrawal or dose reduction is not required.</td>
</tr>
<tr>
<td>Grade 3 (First time expression)</td>
</tr>
<tr>
<td>Withdrawal of the drug until recovery to Grade 2 or below. When resuming, the dose should be reduced by one step if necessary.</td>
</tr>
<tr>
<td>Grade 3 (second or subsequent manifestation) or 4</td>
</tr>
<tr>
<td>Withdrawal of the drug until recovery to Grade 2 or below. When resuming, the dose should be reduced by one step.</td>
</tr>
<tr>
<td>When G-CSF preparations are administered</td>
</tr>
<tr>
<td>Withdraw until at least 48 hours after the last dose of G-CSF preparation and until the dose is less than grade 2. When resuming, the dose should be reduced by one step.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side effects other than those listed above</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
</tr>
<tr>
<td>Drug withdrawal or dose reduction is not required.</td>
</tr>
<tr>
<td>Grade 2 with persistent or recurrent symptoms despite treatment and failure to recover to baseline or Grade 1 within 7 days</td>
</tr>
<tr>
<td>Withdraw as needed until recovery to baseline or Grade 1. When resuming, the dose should be reduced by one step as needed.</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Withdraw until recovery to baseline or Grade 1. When resuming, the dose should be reduced by one step.</td>
</tr>
</tbody>
</table>

*Grade conforms to NCI-CTCAE ver. 5.0.

**Table 7.6-2 Abemaciclib Dose Reduction Criteria**

When reducing the dose of Abemaciclib due to the occurrence of side effects, consider reducing the dose by 50 mg each dose depending on the symptoms and severity of the side effects.

<table>
<thead>
<tr>
<th>Decrease level</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual dosage</td>
<td>150 mg twice daily</td>
</tr>
</tbody>
</table>
7.6.6. Criteria for Discontinuation of Abemaciclib

Abemaciclib will be discontinued if any of the following are observed. In this case, treatment with nivolumab and endocrine therapy (letrozole or fulvestrant) should be continued unless the criteria for 6.8 Discontinuation of Protocol Treatment are met.

1) Development of Grade 4 or higher hepatic dysfunction (increased AST, ALT) in which a causal relationship with abemaciclib cannot be ruled out
2) If further dose reduction of abemaciclib is required after two steps of abemaciclib reduction
3) Abemaciclib should be discontinued if dosing cannot be resumed by Day 43, with the first day of abemaciclib suspension.
4) Abemaciclib should be discontinued in the presence of any other adverse events for which the physician in charge determines that administration is inappropriate.

7.7. Adjunctive and Supportive Therapies

7.7.1. Adjunctive and Supportive Therapies as Prescribed

There are no specific concomitant or supportive therapies specified in this study. Adjunctive and supportive therapies for reactions to the injection are not specified.

All concomitant medications and concomitant therapies used from the date of administration of the investigational drug, to 14 days after the last dose shall be listed in the case report. However, drugs used for various tests and diagnostic procedures need not be listed in the CRF, except when necessary to determine causal relationship of adverse events, etc.

7.7.2. Recommended Adjunctive and Supportive Therapies

The following concomitant and supportive therapies are recommended. Failure to do so shall not constitute a deviation.

1) Supportive care for HBe antibody-positive and/or HBs antibody-positive cases
We recommend testing and supportive care in accordance with the "Guidelines for the Control of Hepatitis B Caused by Immunosuppression and Chemotherapy."

2) Response to immune-related adverse events associated with nivolumab administration

Refer to the "Guidelines for Cancer Immunotherapy (edited by the Japanese Society of Clinical Oncology)", and respond appropriately based on the latest evidence reported at that time, in consultation with experts in each field.

3) Nausea, vomiting

Depending on the patient's condition, dopamine receptor antagonists (e.g., metoclopramide), steroids, anti-anxiety medications, serotonin 5HT3 antagonists, etc.

4) Diarrhea

Depending on the patient's condition, oral diarrhea medication such as loperamide or supplemental fluids should be administered.

5) Anemia, thrombocytopenia

If anemia (hemoglobin <8.0 g/dL) or decreased platelet count (platelet count <2.0 x 10^4/mm^3) is observed, a blood transfusion should be administered as appropriate at the discretion of the physician in charge.

6) Other

Concomitant use of bone-modifying drugs (including denosumab), drugs for complications, and drugs for symptom relief such as morphine is allowed, if there is no interaction with the anticancer drug being used.

7.7.3. Unacceptable concomitant or supportive care

No other investigational drugs will be tolerated during this study.

In addition, other anticancer agents, corticosteroids, immunosuppressive agents, biologic response modifiers (BRM), agents other than G-CSF agents, hormonal agents, radiation therapy, hyperthermia and immunotherapy that affect protocol therapy are not acceptable.

As for corticosteroids, concomitant use of corticosteroids equivalent to prednisolone at a dose of 10 mg/day or less is acceptable. In addition, temporary use of corticosteroids
for the treatment or prevention of contrast media allergy or adverse events is allowed, and topical administration such as topical, intra-articular, intranasal, ophthalmic, and inhalation is allowed regardless of the duration of administration.

7.8. Discontinuation of the protocol treatment

The protocol treatment will be discontinued if any of the following apply:

1) When the protocol treatment is determined to be ineffective
   (i) When the overall effect is judged as PD by the investigator or others in accordance with RECIST Version 1.1
   (ii) Although the patient was determined to have PD on imaging, treatment was continued as Beyond PD, and then the patient was treated as an in-patient. When it is judged by the investigator that no bedside benefit can be obtained
   (iii) Inappropriate to continue treatment due to apparent worsening of clinical symptoms judged to be due to disease progression
       If it is determined that:
       Even if (i) applies, if the case falls under “Beyond PD” as defined in this trial the patient can continue the protocol treatment.

2) Reasons if the protocol treatment cannot be continued:
   (i) If the patient meets the criteria for discontinuation of nivolumab (6.5.3. Criteria for discontinuation of nivolumab).
   (ii) If the investigator or subinvestigator determines that the protocol treatment cannot be continued due to safety considerations.

3) If the patient requests discontinuation of protocol treatment.
   (i) If the patient wishes to discontinue for reasons that cannot be ruled out in relation to the adverse event.
   (ii) If the patient wishes to discontinue for reasons unrelated to the adverse event.
   (iii) If the patient withdraws her consent (7.8.4 See also 6.8.4)

4) Death during the protocol treatment.

5) If, after enrollment, the patient is found to be ineligible and it is determined that continuation of protocol treatment would be to the patient’s detriment.

6) Transfer of the patient from the hospital for any reason during the protocol
treatment period.

7.8.1. **Definition of protocol treatment completion**

Since the protocol treatment will continue until progression in this trial, there will be no definition of treatment completion.

7.8.2. **Protocol treatment invalidation**

Clinical judgment shall take precedence over "invalidity" as a reason for discontinuation of the protocol treatment.

7.8.3. **Definition of adverse events at the time of discontinuation of the protocol treatment**

Excluding the following adverse reactions (hematologic toxicity) in Common terminology criteria for adverse events (CTCAE) v5.0.

- "anemia,"
- "bone marrow hypocellular,"
- "lymphocyte count decreased,"
- "neutrophil count decreased,"
- "white blood cell count decreased,"
- "platelet count decreased,"
- "CD4 lymphocyte count decreased."

Grade 4 occurrences of biochemical tests that are not considered life-threatening are not a requirement for treatment discontinuation.

7.8.4. **Cautionary Note on Withdrawal of Consent**

Withdrawal of consent will result in no further data collection. The patient's willingness to either refuse protocol treatment/testing or to withdraw true consent should be fully ascertained.

7.9. **Deferred treatment**

If the protocol treatment is discontinued due to toxicity or other reasons, in principle, treatment for the current disease will not be administered until the deterioration of the primary disease is confirmed. However, this does not apply when the patient's wishes and interests are given priority. In the case of post-treatment, the details of such treatment are not stipulated. In addition, post-treatment with a protocol therapy other than the investigational drug after discontinuation of the protocol therapy does not fall under the category of post-treatment, and can be administered at the discretion of the
attending physician.

8. **Assessment Items and Laboratory Tests**

8.1. **Pre-registration Testing and Evaluation Items**

All tests 1) to 4) shall be performed and evaluated before registration. If the results of tests performed within the stipulated period are available, the test results performed prior to obtaining consent can be used after obtaining the patient's consent, and there is no need to repeat tests after obtaining consent.

1) Basic patient information
   a) Subject Identification Code
   b) Date of birth (may be substituted with "* (asterisk)*) / Age
   c) Date consent was obtained
   d) Sex
   e) ECOG Performance Status (PS)
   f) Stature
   g) Major medical history (if there is a history of malignancy, date of last treatment and treatment details)
   h) Medication at the time of registration
   i) Major complications
   j) Drug allergies
   k) Clinical stage (stage IIIb, IIIc, IV or recurrence)
   l) Presence or absence of primary nests
   m) Presence or absence of metastasis, location
   n) History of surgery for primary disease (treatment and date of last surgery)
   o) Pathological diagnosis, histology
   p) Estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2)
   q) Pre- and post-operative drug therapy, treatment details, and duration of treatment
   r) Radiotherapy history (treatment details, date of last irradiation)
   s) History of drug therapy treatment for metastatic recurrent disease (hormonal therapy and molecular targeted drugs)
   t) Menopausal status
u) Targeted and non-targeted lesions

2) Inspections to be performed within one year prior to registration
HBs antigen, HBs antibody, HBe antibody, HCV antibody

3) Inspection to be performed within 28 days prior to registration (the same day of the week as the registration date is acceptable)
   a) Chest radiograph
   b) Thoracoabdominal pelvic computed tomography (CT): contrast-enhanced CT is preferred, but simple CT is acceptable if the Principal Investigator or subinvestigator determines that non-contrast-enhanced CT can be used to determine efficacy. (In the case of simple CT, substituting positron emission tomography [PET]-CT images is not permitted.)
   c) Contrast-enhanced CT or contrast-enhanced magnetic resonance imaging (MRI) only if brain metastasis is suspected
   d) Bone scintigraphy or PET-CT
   e) Tumor markers: CEA, CA15-3

4) Observations and tests performed within 14 days prior to registration (same day of the week as registration is acceptable)
   a) ECOG PS
   b) Body weight
   c) Vital signs: temperature, systolic/diastolic blood pressure, transcutaneous oxygen saturation (SpO₂)
   d) Subjective symptoms
   e) Laboratory tests
      (i) Peripheral blood counts:
      White blood cell count, differential white blood count (neutrophils, lymphocytes, eosinophils, basophils, monocytes), hemoglobin, red blood cell count, platelet count
      (ii) Blood biochemistry:
      Total protein, albumin (Alb), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), blood urea nitrogen (BUN), creatinine (Cr), total bilirubin (T-Bil), sodium (Na), potassium (K), chloride (Cl), lactate dehydrogenase
(LDH), blood sugar as needed, uric acid, Creatine kinase (CK), calcium (Ca), C-reactive protein (CRP)

(iii) Urinalysis: urine protein, urine occult blood

(iv) Immunological tests: antinuclear antibodies (ANA), SP-D, KL-6

(v) Hormone test: thyroid-stimulating hormone (TSH), free-T3\textsuperscript{※}, free-T4

(vi) Diabetes test: hemoglobin A1c (HbA1c)

(viii) Pregnancy test: urine test (for premenopausal women or women less than one year since their last menstruation)

f) Resting 12-lead ECG: QTc (Bazett's correction formula: \( QTc = \frac{QT \text{ actual value}}{RR \text{ interval}^{1/2}} \))

*: If free-T3 is difficult to measure, non-measurement is not considered a deviation.

8.2. Tests and Endpoints During Protocol Treatment

Laboratory and clinical findings after initiating treatment should be reported up to one month after the last day of protocol treatment and before initiating post-treatment if post-treatment is initiated within one month.

8.2.1. Safety endpoints

The following items will be evaluated on day 1 and day 15 of each course or the day before each course.

a) ECOG PS

b) Vital signs: temperature, systolic/diastolic blood pressure

c) Physician recorded symptoms

d) Laboratory tests

(i) Peripheral blood counts:

White blood cell count, differential white blood count (neutrophils, lymphocytes, eosinophils, basophils, monocytes), hemoglobin, red blood cell count, platelets

(ii) Blood biochemistry:

Total protein, Alb, AST, ALT, γ-GTP, BUN, Cr, T-Bil, Na, K, Cl, LDH, blood sugar as needed, uric acid, CK, Ca, CRP
(iii) Urinalysis: urine protein, urine occult blood

*Hormone tests (TSH, free-T3, free-T4) and diabetes tests will be evaluated monthly as appropriate.
*Adrenocorticotropic hormone (ACTH) and blood cortisol should be measured as hormone tests when pituitary dysfunction is suspected.
*Weight measurements will be clinically determined by the Principal Investigator or subinvestigator, as appropriate.

8.2.2. Efficacy endpoints

Similar to baseline assessments, the following imaging studies will be performed at 8 (±1), 16 (±1), 24 (±1), and 12 (±1) weeks, starting from the date of enrollment. No change from the baseline evaluation method is permitted, although simple CT is acceptable if contrast administration is not feasible and the Principal Investigator or subinvestigator determines that the patient can be evaluated.

1) Thoracoabdominal pelvic contrast CT (slice thickness 5 mm or less)
2) Contrast-enhanced MRI or contrast-enhanced CT of the brain (only if lesions are detected on pre-registration testing)
3) Bone scintigraphy or PET (as appropriate and deemed important for disease assessment)
4) Tumor markers: CEA, CA15-3

If initiating the treatment course is postponed owing to toxicity, imaging evaluation of the tumor should not be postponed.

If protocol treatment is discontinued for reasons other than disease progression, only thoracoabdominopelvic contrast CT will be continued until disease progression is confirmed or until post-treatment initiation (the evaluation interval will be determined at the discretion of the Principal Investigator or subinvestigator based on the frequency during the study period).

Even if the overall efficacy is determined as progressive disease (PD), protocol treatment may be continued (rather than discontinued) if deemed clinically appropriate to continue protocol treatment. In such a case, even after the overall efficacy is determined as PD, the tumor shrinkage efficacy will be continuously determined during the study period while the protocol treatment is ongoing at established frequencies.
8.3. Tests and Evaluation Items at Study Discontinuation

The following items will be evaluated 28 days (within ±7 days) after the last dose of the study drug or before initiating post-treatment if post-treatment is initiated before 28 days (within ±7 days).

a) ECOG PS

b) Vital signs: temperature, systolic/diastolic blood pressure

c) Subjective symptoms

d) Clinical examination

(i) Peripheral blood counts:

- White blood cell count, differential white blood count (neutrophils, lymphocytes, eosinophils, basophils, monocytes), hemoglobin, red blood cell count, platelets

(ii) Blood biochemistry:

- Total protein, Alb, AST, ALT, γ-GTP, BUN, Cr, T-Bil, Na, K, Cl, LDH, blood sugar as needed, uric acid, CK, Ca, CRP

(iii) Urinalysis: urine protein, urine occult blood

8.4. Examinations During the Follow-up Period, Endpoints

Examinations and assessments are to be performed after completion or discontinuation of study treatment until the respective case expires, corresponding to the "follow-up period" of the protocol. The assessments to be performed every six months from the enrollment of each subject until one year after the last subject enrollment date of the trial are as follows

8.4.1. Safety evaluation after completion of treatment

1) Clinical examination

No special provisions are made, and the usual practice is followed.

2) Adverse events

Outcomes of adverse events requiring follow-up that occurred during the trial (see 9-5)
8.4.2. **Efficacy evaluation after completion of treatment**

1) **Information regarding disease worsening**

Note: If protocol treatment is discontinued for reasons other than disease progression, image evaluation should continue until disease progression is confirmed or until post-treatment is initiated (see 7.2.2 Efficacy endpoints).

- Date of exacerbation, site of exacerbation, and method of diagnosis

2) **Survival information**

- Date of last check, date of death (if death occurs), cause of death

3) **Post-treatment** (surgery, radiotherapy, drug name, date treatment initiation, PS treatment initiation)

8.5. **Exploratory Biomarker Studies**

This trial will investigate biomarkers associated with treatment response and adverse events for combined nivolumab + abemaciclib + endocrine therapy (fulvestrant or letrozole).

For exploratory biomarker research, the donation and storage of tumor tissue prior to initiating the clinical trial is mandatory. After initiating the clinical trial, tumor tissue will be provided and stored voluntarily when deemed necessary by the attending physician, followed by collection. Collection, provision, and storage of blood and stool specimens will be performed on a voluntary basis, conducted only for subjects who provide consent separately.

Refer to the "Handling Procedures for Samples for Biomarker Research" for details regarding the collection, processing, and storage of specimens. A separate accompanying research protocol should be prepared to measure and analyze these specimens.

8.5.1. **Specimen collection**

For details, refer to the "Procedure for Handling Samples for Biomarker Research.

<Time of specimen collection>.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Time harvested</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>53</td>
</tr>
</tbody>
</table>
### 8.5.2. Specimen processing and storage procedures

Processing and storage of blood, tumor tissue, and stool specimens

For details, refer to the "Procedure for Handling Samples for Biomarker Research.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Collection container</th>
<th>Processing method</th>
<th>Storage containers</th>
<th>Storage conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood</strong></td>
<td>CPT tube for peripheral blood mononuclear cells (PBMC) 8 ml × 2 bottles</td>
<td>Centrifuged, separated and cryopreserved</td>
<td>For PBMC cryopreservation 4 tubes</td>
<td>-70°C or less</td>
</tr>
<tr>
<td></td>
<td>Serum collection tubes 4 ml × 1 bottle</td>
<td>Centrifuged, separated and cryopreserved</td>
<td>Serum storage 4 tubes × 4 tubes</td>
<td>-70°C or less</td>
</tr>
<tr>
<td></td>
<td>Plasma collection tubes 10 ml x 2 bottles</td>
<td>Centrifuged, separated and</td>
<td>Plasma storage 5 tubes x 5 tubes</td>
<td>-70°C or less</td>
</tr>
</tbody>
</table>
8.5.3. Storage and disposal of specimens

For details, refer to the "Procedure for Handling Samples for Biomarker Research.

Sample storage location

The specimens will be stored at the Showa University Institute for Advanced Cancer Therapy and the Showa University Institute of Clinical Pharmacology. Junji Tsurutani (Director, Showa University Institute for Advanced Cancer Therapy) is the appointed Storage Manager. The storage period is 10 years from the final study analysis. The storage area will be secured by the entrance to the study site, a locked laboratory door, and a key to a deep freezer.

Specimen disposal

The stored samples will be discarded when the sample donor withdraws consent, when the registration number can no longer be recognized due to a label, computer malfunction, etc., when sample mix-up or contamination has occurred or is strongly suspected, or when the investigator recognizes the need to discard the sample. In such cases, the registration number and other information should be deleted before disposal. Specimens that have been stored for 10 years after the final analysis will be discarded unless a specific reason for non-disposal is stated.

7.5.4. Withdrawal of consent for sample use

If a subject withdraws consent for using a biological sample provided, the biological sample will be disposed of/disposed of and not used for analysis; however, this does not
apply if the study results have been published at the time of consent withdrawal. If the measurement/analysis has already been performed, the Clinical Research Coordinating Committee is not obligated to dispose of the results.

The Clinical Trial Coordinating Committee shall ensure that the following are in place:

- The subject’s withdrawal of consent for using the provided sample is immediately reported to the Clinical Trial Coordinating Committee. If biological samples collected from the subject are stored at the site, they must be immediately identified and disposed of/destroyed, which must be recorded.
- That the withdrawal of consent was immediately communicated to the laboratory holding the biological sample, that the biological sample was disposed of/destroyed, that this was documented, and that documentation of the disposition/disposal of the biological sample was provided to the study site.
- The disposal/destruction of the biological sample has been reported to the subject and the Clinical Trial Coordinating Committee.
- The Clinical Trial Coordinating Committee shall ensure that the laboratory where the biological sample is stored is immediately informed regarding the withdrawal of consent. It should also confirm that the biological sample has been disposed of/destroyed and that a record of this has been submitted to the site.

The Clinical Trial Coordinating Committee will ensure that biological samples are discarded at the end of the specified period, as described in the consent document.

7.5.5. Methods of protecting personal data

Careful consideration will be given to protecting the privacy of subjects. Subjects will be identified by a unique number to ensure their personal information is anonymized and strictly controlled.
8.6. Study Calendar

Table 8.6.1 Evaluation schedule during treatment, post-observation, and follow-up periods

<table>
<thead>
<tr>
<th></th>
<th>Before registration $^a$</th>
<th>Course 1$^b$</th>
<th>Course 2 onwards$^c$</th>
<th>At discontinuation $^d$</th>
<th>At the follow-up examination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Within 28 days</td>
<td>Within 14 days</td>
<td>Day 1 (±3)</td>
<td>Day 15 (±3)</td>
<td>Day 15 (±3)</td>
</tr>
</tbody>
</table>

- **Letrozole cohort**
  - Nivolumab: ●
  - Letrozole: ●
  - Abemaciclib: ●

- **Fulvestrant cohort**
  - Nivolumab: ●
  - Fulvestrant: ●
  - Abemaciclib: ●

**General condition**

<table>
<thead>
<tr>
<th>Basic Information</th>
<th>Patient Information</th>
<th>Before registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>●</td>
<td>As appropriate (as clinically determined by the attending physician)</td>
</tr>
<tr>
<td>Vital signs</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>PS</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

**Safety assessment**

| Subjective symptoms |● | ● | ● | ● | ● | ● |
|Peripheral blood count | ● | ● | ● | ● | ● | ● |
|Blood chemistry      | ● | ● | ● | ● | ● | ● |
|Urinalysis           | ● | ● | ● | ● | ● | ● |
|Immunology test      | ● | ● | ● | ● | ● | ● |
|Hormone test         | ● | Approximately once a month, as needed |
|Diabetes test        | ● | Approximately once a month, as needed |
|Pregnancy test (when possible) | ● |
|Resting 12-lead ECG  | ● |
|HBs antigen HBs antibody |● |Within 1 year prior to registration |
|HBc antibody HCV antibody |● |

**Validity assessment**

| CT of Thoracoabdominal pelvic region |● | Once every 8 weeks ($\leq$1 week), 16 weeks ($\leq$1 week), 24 weeks ($\leq$1 week), and 12 weeks ($\leq$1 week) thereafter; starting from the registration date $^e$ |

---

$^a$ Initial assessment 3 days before treatment initiation.
$^b$ Within 28 days.
$^c$ Within 14 days.
$^d$ Within 28 days; withdrawal from treatment is scheduled.
$^e$ Within 28 days; withdrawal from treatment is scheduled.

---

Bone scintigraphy or PET/CT

○: As needed (when deemed important for disease assessment)

Tumor marker

○: Once every 8 weeks (± 1 week), 16 weeks (± 1 week), 24 weeks (± 1 week), and 12 weeks (± 1 week) thereafter, starting from the registration date.

Biomarker testing (provision of tumor tissue prior to the start of the trial is mandatory, otherwise optional)

Tumor tissue

When deemed necessary by the Principal Investigator, such as before initiating the clinical trial (at diagnosis, during surgery, or after recurrence), on disease worsening, when immunological side effects occur, when the tumor has a specific response, or when nivolumab is discontinued.

Blood

Before nivolumab injection, before Course 1 day 15, Course 2 day 1, Course 3 day 1 injection, Course 8 day 1 injection, or on discontinuation of nivolumab, when disease worsening, when immunological side effects occur, when the tumor shows a special reaction, or when your doctor deems necessary.

Stool

Before nivolumab injection, Course 3 day 1 (7 days before up to the day of injection).

Follow-up (e.g., in computer graphics)

Post-treatment details

○: Required

Outcome study

○: Optional

CT, computed tomography; PET, positron emission tomography

Note: If results of tests performed within the stipulated period are available, the test results before obtaining consent can be used after obtaining patient consent, and there is no need to repeat the test after obtaining consent.

1: Day 1 and day 15 dosing for each course is allowed up to ±3 days. However, skipping, bringing forward or postponing administration (-3 to +7 days) due to national holidays or any such scenario is acceptable at the discretion of the Principal Investigator or subinvestigator.

*2: If protocol treatment is discontinued for reasons other than disease progression, only thoraco-abdominopelvic contrast CT will be continued until disease progression is confirmed or until initiating post treatment (the evaluation interval will be performed at the discretion of the Principal Investigator or subinvestigator based on the frequency during the study period).

*3: Evaluate 28 days (within ±7 days) after the last dose of the study drug if post-treatment is initiated before 28 days (within ±7 days).

9. Data Collection

9.1. Registration Number

The registration number assigned at the time of registration is used to identify the patient.

9.2. Case Reports

9.2.1. Types of case reports

1) Before registration
2) Each course
3) Concomitant therapies

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4) Image diagnosis  
5) Time of discontinuance  
6) Dose-limiting toxicity (DLT) evaluation  
7) Observational items at any time (adverse events, concomitant medications, concomitant therapy, treatment after discontinuing protocol treatment, and exacerbation information)  
8) Follow-up period  

9.2.2. Case report form

This clinical trial will use an electronic case report system (EDC) to record case reports electronically.

Preparation of case reports using the EDC  
1) The Sponsor Investigator (Principal Investigator) enters data into the case report form using the EDC.  
2) The Principal Investigator will ensure that the case report forms are accurate, complete, and properly submitted and that the registration number is used to identify the patient.  
3) Data in the case report form based on the source documents must be consistent with the source documents. If there is any discrepancy with source documents, the Principal Investigator shall prepare a record explaining the reason for the discrepancy, submit it to the Clinical Trial Coordinating Committee, and retain a copy. In this clinical trial, the following items shall be treated as source documents when entered directly into EDC as case report forms.  
   a) Reasons for withdrawal, dose reduction, or discontinuation of protocol treatment at the discretion of the Principal Investigator or subinvestigator, or reasons why the Principal Investigator or subinvestigator deemed the treatment can be resumed after withdrawal  
   b) Reason for concomitant use or implementation of concomitant medications or therapies  
   c) Determination of abnormal changes in laboratory values  
   d) Determination of serious and non-serious adverse events
e) Grade of the adverse event, the causal relationship to the investigational drug, and treatment related to the investigational drug

f) Reason for discontinuation of the subject

g) Comments

4) In the case of changes or corrections in the case report record, the Principal Investigator shall make the changes or corrections in accordance with the guidance. The change or amendment must not obscure the original information.

9.3. Method of Collecting the Case Report Form

Case report forms shall be collected by transmission via EDC. Timing of submission shall be based on the "EDC Entry Guideline" to be separately established.

10. Safety Handling

10.1. Definition of Adverse Events

An adverse event is an unfavorable medical event that occurs during or after the administration of a pharmaceutical product or the worsening of symptoms or signs that existed prior to the administration of the product, including all events, regardless of whether they are causally related to the administration of the pharmaceutical product. An unfavorable medical event is any symptom (e.g., nausea, chest pain), sign (e.g., tachycardia, hepatomegaly), or abnormal test result (e.g., laboratory test results, ECG). In the present study, adverse events will be reported from the start of the first dose of the study drug until 30 days after the last dose or the date of the decision to discontinue, whichever is later. If subsequent treatment is initiated during this period, the trial may be terminated on the date of initiation of the subsequent treatment. Additionally, deterioration of the underlying disease, accompanying symptoms, and complications beyond the scope of the natural course of the disease, as determined by medical judgment, will be considered adverse events.

10.2. Definition of Serious Adverse Events

A serious adverse event is an adverse event that occurs regardless of the dose of the test or control drug and meets one or more of the following criteria
• An event that leads to death
• Life-threatening
• An event requiring hospitalization or extended hospitalization for treatment*1
  • Permanent or substantial disability or dysfunction
  • Events resulting in congenital anomalies
  • Considerable medical events that would endanger the subject or require medical attention to avoid the consequences described above

*1: Among hospitalizations, hospitalizations needed to conduct the present study or the following hospitalizations are not considered serious adverse events.

  • Hospitalization or prolonged hospitalization for therapy that was planned prior to the study (e.g., surgery or tests that were planned prior to initiating the study)
  • Hospitalization for examination, education, or prolonged hospital stay (hospitalization for examinations or educational hospitalization)
  • Hospitalization for surgery or prolonged hospital stay owing to a change in the treatment plan due to complications or associated symptoms, although not attributed to the worsening of the complication or associated symptoms
  • Hospitalization for follow-up or prolonged hospital stay, although the patient is cured or has a mild illness
  • Hospitalization or admission to a hospice, nursing home, or rehabilitation facility
  • Hospitalization or prolonged hospitalization for new treatment of the underlying disease, such as a second treatment after completion of the investigational drug
  • Hospitalization or prolonged hospitalization for social reasons (e.g., nurse’s leave or absence of family members)

Adverse events judged to be other medically significant conditions:
Other important adverse events are classified as "other important adverse events" if they are of clinical importance other than serious adverse events and adverse events judged to be other medically significant conditions.
events that led to discontinuation of the investigational drug in the subject.

10.3. Adverse Event Assessment

Common Terminology Criteria for Adverse Events v5.0 (CTCAE v5.0), Japanese translation JCOG/JSCO version, is used for establishing adverse events.

For grading adverse events, grading should be assigned according to the closest match to the definition of grade. Considering treatment-related deaths, the causal relationship between an adverse event and death should be discussed in the case report after reporting the adverse event.

The expected adverse events of nivolumab are defined as "unknown" when the occurrence of the event, or the trend of occurrence such as the number of occurrences, frequency of occurrences, or conditions of occurrence, cannot be predicted from the investigational new drug summary of the investigational drug concerned, and "known" when they can be predicted. However, a new event reported to the site can be treated as "known" even if not described in the investigational new drug summary.

10.4. Determination of Causality

The Principal Investigator shall determine the causal relationship between the investigational product and the adverse event and shall specify either "Yes" or "No" to the question "Do you believe there is a reasonable possibility that the adverse event may have been caused by the investigational product?" (Yes or No).

In the case of serious adverse events, the causal relationship to other treatments and study procedures should also be determined. If the serious adverse event is considered to be related to the investigational procedure, the causal relationship is "Yes".

10.5. Handling and Follow-up of Adverse Events

The Principal Investigator or subinvestigator will observe subjects for adverse events from initiating the first dose of the investigational drug up to 30 days after the last dose or the date of discontinuation (whichever is later), taking appropriate action and conducting follow-up investigations in the case of adverse events. If post-treatment is started, discontinuation will be allowed after the start date of post-treatment.
All adverse events observed during the above period will be followed up until their disappearance unless, at the discretion of the Principal Investigator or subinvestigator, the events are considered to be irreversible owing to the subject’s underlying disease (existing disease such as complications) or a reasonable reason exists, such as post-treatment, non-attendance or death. If follow-up is not possible, this will be documented in the medical record.

10.6. Reportable Adverse Events (Report Serious Adverse Events)

If the Principal Investigator or subinvestigator (or other coordinating investigator) learns of the occurrence of a serious adverse event during the clinical trial, the Principal Investigator or subinvestigator (or other coordinating investigator) shall immediately (within 24 h) report the adverse event to the Trial Coordinating Committee using a detailed report form ((Medical Form 12, Form for Detailed Description) in accordance with the separately prescribed “Procedures for Handling Safety Information”. In addition, the adverse event shall be reported to the head of the study site in accordance with the regulations of the study site.

To report a serious adverse event for the first time, the Principal Investigator requires the registration number or subject identification code, the name of the adverse event, the severity, and the date of occurrence. In addition, the following detailed information must be reported as soon as possible.

- Severity (of an illness)
- Transition (date of disappearance, if possible)
- Causal relationship (causal relationship with the investigational drug, concomitant therapy, and concomitant medications, if applicable)
- Date of serious illness
- Discontinuation of the investigational drug or not
- Treatment of adverse events
- Adjunct therapy (excluding treatment for adverse events)
- Concomitant medications (include previous treatments if causal relationship to the adverse event cannot be assessed)
- Date of birth and sex
- Current medical history (complications)
- Relevant medical history
- Date of death and course of events leading up to death, if applicable

Multiple adverse events may be recorded as adverse events that caused discontinuation or resulted in death. If the cause of death is unknown, the event will be considered a "death of unknown cause". If an autopsy was performed, provide a copy of the report, if necessary.

(2) The Clinical Trial Coordination Committee shall report serious adverse events reported by the Principal Investigator, subinvestigator, or investigational drug supplier, to the Principal Investigators/sponsor investigators and investigational drug suppliers at other sites. Upon receiving the report, the Principal Investigators/sponsor investigators at other sites will inform the Clinical Trial Coordinating Committee.

The Principal Investigator must immediately report any additional information regarding a serious adverse event or a non-serious adverse event that subsequently becomes serious in accordance with the above procedure.

10.7. Report to the Minister of Health, Labor and Welfare

The Clinical Trial Coordinating Committee shall be responsible for the implementation of "Error! Reference source not found. Error! Reference source not found." if it is necessary to report an adverse event established in "9.6 Report of Serious Adverse Events" to the Minister of Health, Labour and Welfare. The Principal Investigator, in coordination with the subinvestigator, shall prepare a report in accordance with the separately prescribed "Procedures for Handling Safety Information" and submit it to the Pharmaceuticals and Medical Devices Agency (PMDA) within a prescribed period.

10.8. Reporting to the Investigational Drug Supplier

The Clinical Trials Coordinating Committee shall be responsible for implementing "Error! Reference source not found. Error! Reference source not found.". The Clinical Trial Coordinating Committee shall immediately report any serious adverse event reported in "9.6 Reportable Adverse Events (Report of Serious Adverse Events)" to the investigational drug supplier. In addition, the Principal Investigator shall immediately
report serious adverse events reported in "9.7 Error! Reference source not found. Error! Reference source not found." to the investigational drug supplier. If a report is submitted to the PMDA in "9.8 Report of Serious Adverse Events", a copy of the report shall be submitted to the investigational drug supplier.

In addition, for pregnancy, Error! Reference source not found. Error! Reference source not found., pregnancy should be reported to the investigational drug supplier in accordance with "9.9 Handling of Pregnancy Information" and the separately prescribed "Procedures for Handling Safety Information". Overdosage should also be reported to the investigational drug supplier in accordance with the separately prescribed "Procedures for Handling Safety Information".

10.9. Pregnancy

Exposure of female participants

If a subject becomes pregnant during the study, the protocol treatment should be discontinued immediately.

Pregnancy per se is not considered an adverse event, except in cases where the contraceptive is considered less effective due to the investigational drug. Congenital anomalies and spontaneous abortion are reported as serious adverse events. Uncomplicated abortion is not treated as an adverse event. However, the outcome (spontaneous abortion, induced abortion, ectopic pregnancy, normal birth, congenital abnormality) of all pregnancies, including those in which the subject discontinued the clinical trial, will be followed up and recorded. If the Principal Investigator becomes aware of a pregnancy during the clinical trial period or within 5 months after the last investigational drug administration, the Principal Investigator shall immediately (within 24 h of becoming aware of the pregnancy) report the event to the Clinical Research Coordinating Committee. The Clinical Trial Coordinating Committee, in cooperation with the Principal Investigator, will provide all relevant information to the investigational drug supplier. The same reporting deadlines apply to any information obtained regarding outcomes.
11. Efficacy Determination and Endpoints

11.1. Central Determination of Diagnostic Imaging

In the present clinical trial, diagnostic imaging will be performed by central determination. The procedure details will be specified in a separate standard operating procedure.

11.2. Endpoint Definition

11.2.1. Overall survival

Overall survival is defined as the period from the date of enrollment until death from any cause. For patients alive at the time of analysis or untraceable, censoring will be performed based on the date of last known survival.

11.2.2. Progression-free survival

Progression-free survival is the period from the date of registration to the date of death owing to any cause, the date of disease exacerbation confirmed by imaging studies, or the date of clinical diagnosis of disease exacerbation.

Disease exacerbation is defined as an apparent worsening by imaging studies or an apparent worsening based on the patient’s symptoms or physical findings (clinical exacerbation).

Patients who have no confirmed death or exacerbation at the time of analysis, or for whom the date of reaching these events is unknown, will be censored based on the most recent outpatient visit or inpatient clinic date before the loss to follow-up.

11.2.3. Response rate

The proportion of patients whose best overall response is either complete response (CR) or partial response (PR) is defined as the response rate.

Tumor shrinkage efficacy is determined according to the Revised RECIST guideline (version 1.1)-Japanese translation of the JCOG version, considering the new guideline for determining response to treatment of solid tumors (RECIST guideline)" (version 1.1).

Baseline evaluation will be performed using imaging studies prior to initiating treatment.
12. Statistical Methods

An outline of the statistical analysis is provided. A statistical analysis plan will be prepared separately and will specify details of the analysis methods.

12.1. Definition of the Population to be Analyzed

The definition of the population to be analyzed in this clinical trial will be as follows. The handling of each case will be determined based on a discussion between the Clinical Trial Coordinating Committee and the statistical analyst prior to data fixation.

Definition of "largest analysis set": Full Analysis Set (FAS)

All patient populations that meet enrollment criteria and have received at least one protocol treatment, as well as subsequent observation for efficacy. The primary analysis of this trial will be performed on the FAS.

Per Protocol Set (PPS): Definition of "target population conforming to the protocol.

A population of patients who meet enrollment criteria and have received at least one protocol treatment, available primary endpoint measurements, and no serious protocol violations.

Definition of "Safety Analysis Set:"

All patient populations who received at least one protocol treatment.

12.2. Data Management

12.2.1. Management of data deviating from the clinical trial protocol

The Clinical Trial Coordinating Committee will decide how to handle any deviations that require discussion.

12.2.2. Management of missing, rejected, and anomalous data

Items that have never been inspected or observed are treated as missing data. Data supplementation with estimated or calculated values will not be performed for missing data.

12.3. Statistical Analysis Methods

Efficacy endpoints will be analyzed in the FAS and PPS, with primary analysis performed using the FA and secondary analysis in the PPS to examine the consistency
of results.
   Safety endpoints will be analyzed for the Safety Analysis Set.
   The patient background will be analyzed for FAS and PPS.

12.3.1. Patient background
   The summary statistics for the patient background will be calculated.

12.3.2. Principal analysis and criteria
Main analysis: Response rate
   The proportion of patients whose best overall response is either CR or PR is defined as the response rate.
Secondary analysis:
   Safety, disease control rate, progression-free survival, 6-month progression-free survival rate, 12-month progression-free survival rate, 12-month overall survival rate, overall survival

Percentage of disease control
   The percentage of patients whose best overall response is CR, PR, or SD is the disease control ratio.
Progression-free survival, overall survival
   The Kaplan-Meier method will be used to estimate progression-free survival curves, survival curves, median survival time, and annual survival percentages.
Safety
   1) Clinical findings
      The frequency of adverse event occurrence and the worst grade will be calculated.
   2) Clinical laboratory test results
      The summary statistics of the worst abnormal low or worst abnormal high will be summarized for each hematologic and biochemical laboratory data item.

   In addition, the response rate will be analyzed based on patient background factors, such as hormone receptors and age.
12.4. Interim Analysis

No interim analysis will be conducted in the present study. However, an interim analysis of efficacy and safety data may be conducted when a certain number of cases are collected; this analysis can be used to reach an early decision on moving to the next phase of the study rather than to alter the study design or analysis plan of this study.

13. Ethical Issues

All participating investigators will conduct this study in accordance with the Declaration of Helsinki (Seoul Revision, October 2008), the standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the Pharmaceuticals and Medical Devices Act, and the “Ministerial Ordinance Concerning Good Clinical Practice (GCP)” (Ministry of Health and Welfare Ordinance No. 28, 1997).

In addition, the investigators will comply with this protocol to the extent that the safety and human rights of the subjects are not compromised.

13.1. Protecting Patient Privacy

Information that identifies the subject, such as the subject's name, will not be communicated to the Clinical Trial Coordination Committee from the study site.

Subjects are identified and discussed using the registration number issued at the time of registration, subject identification code®, gender, and date of birth or age, such that third parties cannot identify the subject, including the subject's name.

The case report forms and any relevant documentation will only be used for the purpose of this clinical trial.

®Subject identification code: A subject identification code is a number (code) used by the study site to provide subject information to external parties.

13.2. Obtaining Consent

Before subject enrollment, the Principal Investigator or sub investigator (or relevant personnel) shall provide a sufficient explanation regarding the following items using the consent explanation document, which has been approved by the investigational review committee (IRB) and decided by the head of the study site. In addition, subjects will be
allowed to ask any questions and have sufficient time to decide whether or not to participate in the present study.

After confirming that the subject fully understands the contents of the present clinical trial, the subject’s free and voluntary consent to participate in the clinical trial will be obtained in writing.

The Principal Investigator shall promptly hand a copy of the signed and dated consent form to the subject.

13.3. Items to be Explained to the Patient in the Written Explanation

1) That the clinical trial is a research undertaking
2) Purpose of the clinical trial
3) Name, title, and contact information of the Principal Investigator or subinvestigator
4) Methods of the trial, including the experimental aspects of the trial, the inclusion and selection criteria for subjects, and the probability of assignment to each treatment if random assignment is used
5) Anticipated clinical benefits and risks or inconveniences (if there is no anticipated benefit to the subject, the subject must be informed of the fact). Subjects must be informed of all current information relevant to the anticipated risks based on the clinical trial.
6) If the subject is a patient, the availability of other treatment options and the anticipated crucial benefits, as well as risks associated with such treatment options, must be clarified to the patients.
7) Expected duration of subject’s participation in the clinical trial
8) That participation in the clinical trial is of the subject’s own free will and that the subject or the subject’s surrogate may refuse or withdraw consent to participate in the clinical trial at any time. Furthermore, it should be clarified that refusal or withdrawal of consent will not result in unfavorable treatment or loss of any benefits that he/she would have received if he/she had not participated in the clinical trial.
9) The original medical record must be accessible to monitors, auditors, IRBs, and regulatory authorities. In such cases, the confidentiality of the subject shall be maintained. In addition, the subject or the subject’s surrogate must sign or affix
his/her name and seal to the consent document to authorize access to the records.

10) Subject confidentiality will be maintained even if the clinical trial results are publicized.

11) A consultation service at the site, which can be referred to or contacted if they wish to obtain further information regarding the clinical trial and their rights or if they experience any health concerns related to the clinical trial.

12) Compensation and treatment to which subjects are entitled in the event of adverse health effects related to the clinical trial.

13) (iii) Types of IRBs that investigate and deliberate on the appropriateness of the clinical trial, matters to be reviewed by each IRB, and other matters related to the IRB for the relevant clinical trial.

14) (2) That the procedure manual of the IRB can be checked, and that the Principal Investigator can be requested to make an offer if he/she wishes to check the procedure manual of the IRB. In addition, if the written procedures, of the IRB are published on a website, the address of the website shall be available for public inspection.

15) Number of subjects expected to participate in the clinical trial.

16) Any information that may influence the subject's or the subject's surrogate's decision to continue participation in the clinical trial will be promptly communicated to the subject or the surrogate.

17) Conditions or reasons for discontinuation of clinical trial participation.

18) If the subject is required to bear the cost, a description of the cost must be provided.

19) If money or other payments are to be made to the subject, the details of such payments (e.g., arrangements for calculating the amount to be paid) should be elaborated.

20) Items to be observed by the subject.

21) Intellectual property matters.

22) Matters concerning conflicts of interest.

23) Other necessary matters.
13.4. Preparation and Revision of the Written Explanation and Informed Consent
Forms/Provision of Information to Subjects

1) The Principal Investigator at each site shall prepare the site version of the written explanation and the informed consent form with reference to the written explanation to obtain the consent template and informed consent form template prepared by the Clinical Trial Coordinating Committee.

2) On obtaining information that may influence the subject's intention to continue participation in the clinical trial, the Principal Investigator or subinvestigator shall promptly convey such information to the subject and confirm the subject's intention to continue participation in the clinical trial. The date the information was provided to the subject, the content of the information provided, and the results of the confirmation shall be recorded in the original medical record.

3) When the Principal Investigator deems it necessary to revise the consent and explanation documents (when new important information that may be relevant to the subject's consent is obtained), the Principal Investigator shall promptly revise the consent and explanation documents based on available information and obtain the approval of the IRB in advance. Using the revised explanatory document, the Principal Investigator and subinvestigator will provide an additional explanation to the subject who has previously consented and is participating in the clinical trial participation, obtaining the subject's free and voluntary consent in writing for continued participation in the clinical trial.

13.5. IRB Approval

When participating in the clinical trial, a decision must be reached by the head of the study site based on the approval of the respective IRB regarding the propriety of conducting this clinical trial.

If approval is granted, the original approval document shall be properly stored at the site, and a copy shall be sent to the Trial Coordinating Committee, which shall properly store the copy.

13.6. Continued Review by the IRB

1) The Principal Investigator shall submit a written summary of the current status of the clinical trial to the head of the site annually or more frequently as requested by the IRB for continued review.
2) When the director of the site receives a report on the current status of the clinical trial, a report on adverse drug reactions during the clinical trial, a report from the Principal Investigator on the occurrence of death or other serious adverse events possibly caused by adverse drug reactions, or information that may influence the subject’s decision to continue participating in the clinical trial, the director of the site shall request the opinion of the IRB on the continuation of the clinical trial, as deemed necessary. If obtained, or if deemed necessary, the opinion of the IRB shall be sought regarding the continuation of the clinical trial.

3) When the head of the study site receives a monitoring report or an audit report on the present clinical trial, he/she shall request the IRB for its opinion on the propriety of the conduct of the clinical trial at that institution.

13.7. Liability and Compensation for Patient Health Hazards

The Principal Investigator/sponsor investigator will provide the best possible treatment to the subject if any adverse health effects occur to the patient due to the conduct of the present clinical trial. If the adverse event is determined to be an unknown serious adverse event resulting from this clinical trial, it will be handled in accordance with the outline of the compensation system stipulated separately. The subject’s health insurance will cover other necessary measures for health damage.

14. Monitoring and Auditing

14.1. Monitoring

(2) The person who conducts the clinical trial on his/her own shall prepare a procedure manual for monitoring to confirm that the human rights of subjects are protected, their safety is maintained, and their welfare is improved; that the clinical trial is conducted in compliance with the latest protocol and GCP ordinance; and that the clinical trial data reported by the Principal Investigator or subinvestigator are accurate, complete, and verifiable considering source documents and other clinical trial-related records. A procedure manual for monitoring should be prepared to confirm that the clinical trial is conducted in compliance with the latest protocol and GCP ordinances and that the clinical trial data reported by the Principal Investigator or subinvestigator are accurate, complete, and verifiable considering source documents.
and other trial-related records; the monitors should conduct monitoring in accordance with the procedure manual based on opinions from the IRB at the study site.

14.2. Monitoring Report

Based on the performed monitoring, if the monitor confirms that the clinical trial at the site fails to meet the GCP ordinance or the protocol, he/she will immediately inform the Principal Investigator at the site.

(1) Whenever monitoring is conducted, the monitor shall submit a monitoring report describing the following items to the sponsor investigator, the head of the study site related to the monitoring, and the Clinical Trial Coordinating Committee.

   (1) Date and time of monitoring
   (2) Monitor's name
   (3) Name of the investigator(s) interviewed during the monitoring
   (4) Summary of monitoring results
   (5) (2) Matters notified to the Principal Investigator pursuant to the provisions of the preceding paragraph
   (6) Measures to be considered with respect to matters specified in the preceding item and the findings of the monitor regarding such measures

The progress, enrollment eligibility, and safety of this clinical trial shall be reported to the sponsor investigator and the head of the study site involved in monitoring.

14.3. Audit

(2) To ensure the quality assurance of a clinical trial, the sponsor investigator shall prepare a plan and a procedure for auditing to evaluate whether the clinical trial is conducted in compliance with the GCP ordinance, protocol, and procedure, independently and separately from the usual monitoring and quality control operations of the clinical trial, and shall have the Audit Manager conduct the audit in accordance with the plan and procedure based on the opinions of the IRB of the study site.

14.4. Audit Report

When an audit is conducted, the Audit Manager shall prepare an audit report to record matters confirmed in the audit, along with an audit certificate certifying that the audit was conducted, submitting it to the person who conducts the clinical trial
him/herself, the head of the site, and the Trial Coordinating Committee.

15. Quality Control and Quality Assurance of Testing

15.1. Data Quality Control
To ensure the conduct of this clinical trial and the safety, accuracy, and reliability of the data, the sponsor investigator shall implement quality control of this clinical trial in accordance with the procedure manual and shall record and preserve the management records.

15.2. Data Quality Assurance
The Audit Manager will assure the quality of this clinical trial in accordance with "13-3. Audit" and "13-4. Audit Report".

15.3. Viewing Records
(2) The head of the study site shall cooperate with the monitoring and audits conducted by the site’s in-house investigators and IRB investigations. (2) When monitoring, audits, or investigations are conducted, the head of the study site shall make all clinical trial-related records, such as source documents, available for inspection at the request of the monitor, Audit Manager, IRB, or relevant personnel.

15.4. Data Management and Recording
15.4.1. Handling of case reports and data records
Considering the handling of case reports or laboratory reports, or copies thereof, the study site shall take all necessary precautions to protect personal information and ensure that information is not leaked, lost, transcribed, or copied in an unauthorized manner.

15.4.2. Data records
The case reports, laboratory report, or a copy thereof shall be retained until the date specified below.
1) Study site

(2) Essential documents to be retained by the head of the study site or the establisher of the IRB shall be appropriately kept by the person in charge of record keeping designated by the head of the study site. The retention period shall be until (1) or (2), whichever occurs later. If the site operator requires these documents to be stored for a longer period, the storage period and storage method shall be discussed with the site operator.

(1) Date of manufacturing and marketing approval for the test drug concerned (in the case of notification of discontinuation of development or that test results from clinical trials will not be included in the application for approval, the date on which three years have elapsed since the date of such notification)

(2) Three years after discontinuing or terminating the present clinical trial

2) Sponsor investigator

(1) The sponsor investigator shall appropriately preserve records related to this clinical trial until (1) or (2) below, whichever occurs later, in accordance with the “Procedures for Preservation of Records” stipulated separately. The Principal Investigator may request the head of the institution to which the Principal Investigator belongs to perform the preservation of such records. If the person conducting the clinical trial no longer belongs to the respective institution, the head of that institution may be responsible for preserving said records.

(2) When storage is no longer deemed necessary, the person conducting the clinical trial shall notify the head of the study site or the establisher of the IRB via the head of the study site.

(1) The date on which the investigational drug supplier obtains manufacturing and marketing approval for a pharmaceutical product pertaining to the study drug (three years after the date of notification of the decision to discontinue development or the decision not to attach the materials regarding the clinical trial study results to the application)

(2) Three years after discontinuing or terminating the present clinical trial

In addition, on approval of the investigational study drug, the person who obtains approval is required to maintain relevant records for a prescribed period in accordance with Article 101 of the Enforcement Regulations of the Pharmaceuticals and Medical Devices Law, and the sponsor investigator shall take necessary measures, such as
entering into an agreement with the investigational drug supplier, regarding the handling of such records.

3) Principal Investigator

The Principal Investigator shall preserve documents related to the clinical trial in accordance with the instructions of the head of the implementing medical institution.

16. Changes, Discontinuation, and Termination of Clinical Trials

16.1. Revision of Clinical Trial Protocol

1) If the sponsor investigator recognizes the need to revise the protocol other than administrative matters of the clinical trial (e.g., modification of wording such as change of telephone number), he/she shall discuss the appropriateness of the revision and its impact on the evaluation of the clinical trial with other sponsor investigators, the Trial Coordinating Committee and, if necessary, the Effectiveness and Safety Evaluation Committee, etc., subsequently making the necessary revisions. The revision shall be made after consultation with other sponsor investigators, the Clinical Trial Coordinating Committee, and the Effectiveness and Safety Evaluation Committee, etc., as necessary.

2) The sponsor investigator shall promptly inform the head of each study site and the Clinical Trial Coordinating Committee of the revised clinical trial protocol and follow the procedures stipulated by each study site.

16.2. Deviation from the Clinical Trial Protocol

1) The Principal Investigator or subinvestigator of each medical institution shall not deviate from or change the protocol without the written approval of the Principal Investigator based on a prior review by the IRB. However, this shall not apply when it is unavoidable from a medical standpoint, such as to avoid immediate danger to the subjects.

2) The Principal Investigator or subinvestigator shall record all deviations from the study protocol, regardless of the underlying reason.

3) The investigator or subinvestigator may deviate from or change the protocol for unavoidable medical reasons, such as to avoid immediate danger to the subject. In such cases, the investigator shall immediately submit a written statement regarding deviations/changes and the reasons thereof to the head of the study site and shall promptly report any deviations/changes and the reasons thereof to the
IRB via the head of the study site.

16.3. Discontinuation or Suspension of Clinical Trials

If the Principal Investigator decides to discontinue or suspend the clinical trial itself, the decision shall be reached in consultation with the Trial Coordinating Committee, which will be promptly reported, along with reasons thereof, in writing to the head of the site and the regulatory authority.

Discontinuation is defined as the discontinuation of the entire trial or part of it earlier than planned for any of the following reasons:

- When it is determined that there is a problem with the safety of the present clinical trial
- In the event that the significance of this clinical trial is not met
- When it is deemed difficult to complete the study owing to delays in case enrollment or other similar factors.

In case of discontinuation, the follow-up period will start from the last enrollment date and follow the description in this study protocol.

Even if the clinical trial is terminated, the Principal Investigator will discuss with the investigational drug supplier whether the patient can continue drug administration if he/she desires, provided that there are no therapeutic impediments.

16.4. Discontinuation and Interruption at Study Site

(2) If a study violates the GCP ordinance and the protocol, and the study site is deemed to be an obstacle to proper clinical trials (except for unavoidable medical reasons such as to avoid immediate danger to subjects), the study site operator shall notify the Trial Coordinating Committee in advance and discontinue the clinical trial at the site. (2) The sponsor investigator shall not conduct the clinical trial at the study site.

(3) When the Principal Investigator suspends or discontinues a clinical trial, the Principal Investigator shall promptly report the suspension/discontinuation and the reason in writing to the head of the study site and the TICC. The Trial Coordinating Committee shall promptly notify the suspension/discontinuation and the reasons through the Trial Coordinating Committee to the sponsor investigator at other medical institutions. On discontinuing a clinical trial due to non-compliance, the sponsor investigator shall promptly report to the regulatory authority.

When the head of the study site receives a report from the Principal Investigator that
the clinical trial is to be suspended or discontinued, the head of the site shall promptly notify the IRB in writing and explain the situation in detail.

16.5. Effectiveness and Safety Evaluation Committee

An Effectiveness and Safety Evaluation Committee will be established to objectively evaluate the efficacy and safety of the clinical trial from ethical and scientific perspectives and recommend the continuation, modification, or discontinuation of the clinical trial to the sponsor investigator. The operation of the Efficacy and Safety Evaluation Committee shall be in accordance with the "Procedures for Deliberations of the Efficacy and Safety Evaluation Committee" stipulated separately.

17. Study Completion and Reporting

After clinical trial completion, the Principal Investigator shall notify the head of the study site in writing that the clinical trial has been terminated and provide a written summary of trial results. When the head of the study site receives a report from the Principal Investigator stating that the clinical trial has been terminated, the head of the study site shall notify the Principal Investigator in writing to that effect and submit a summary of the results to the IRB.

18. Cost-sharing of Examinations

18.1. Examination Administration Fee

Ono Pharmaceutical Co., Ltd. will support the costs of operating this clinical trial.

18.2. Cost for Protocol Treatment

The subject's health insurance will cover the cost of laboratory and diagnostic imaging during the clinical trial period, as well as the cost of the concomitant medications (abemaciclib, letrozole, and fulvestrant) used in the present clinical trial. In addition, the subject's health insurance will cover other necessary measures for health hazards.
19. Conflict of Interest (COI)

Although this clinical trial will be supported by Ono Pharmaceutical Co., Ltd., it will be conducted as an investigator-initiated clinical trial. Conflicts of interest of researchers involved in this clinical trial and those who support this clinical trial in WJOG will be managed as follows.

1. The participating institution shall determine conflicts of interest of individuals involved in this clinical trial.
2. The WJOG Ethics Committee will manage conflicts of interest for the chairperson and members of the Clinical Trial Coordinating Committee, the President, the Executive Director, and others who have a central role in this clinical trial.

In addition, the WJOG secretariat staff involved in this clinical trial will manage conflicts of interest similarly.

20. Publication of Test Results and Attribution of Results

20.1. Publication of Results

After clinical trial completion, the results will be summarized, coordinated by the Clinical Trial Coordinating Committee and the sponsor investigator/Principal Investigator, and published in appropriate domestic and international academic societies and scientific journals.

20.2. Attribution of Results

The results of this clinical trial shall belong to the Clinical Trial Coordinating Committee and Ono Pharmaceutical Ltd.

20.3. Clinical Study Report

After clinical trial completion, the Trial Coordinating Committee and the person who conducts the clinical trial shall make adjustments and prepare a Clinical Study Report in accordance with the "Procedures for Preparation of Clinical Study Reports," which is specified separately.
20.4. Intellectual Property Rights

The study protocol, the design of the registration form and case report forms, the database files created as a result of the study execution, and the forms obtained from them belong to the Clinical Trials Coordinating Committee. Intellectual property rights related to the study drug invention* shall belong to Ono Pharmaceutical Co., Ltd.

If any intellectual property rights (excluding intellectual property rights related to the subject drug invention), including patent rights, arise in the execution of this clinical trial, they will be shared by WJOG and Ono Pharmaceutical Co., Ltd.

20.5. Secondary Use of Data

If the Clinical Trial Coordinating Committee, the sponsor investigator, or the WJOG (standing) Board of Directors determines that secondary use of data obtained in the present clinical trial for integrated analysis, meta-analysis, or additional analysis, would be beneficial, the secondary use of data, excluding personal information, may be permitted after obtaining consent from Ono Pharmaceutical Co., Ltd.

20.6. Provision of Data

After clinical trial completion, anonymized data and forms may be provided for a fee or free-of-charge as directed and guided by the regulatory authorities.

21. Pre-registration of the Clinical Trial Protocol

Prior to conducting the clinical trial, WJOG will register this clinical trial protocol in the Japic Clinical Trials Information (Japic CTI) database of the Japan Pharmaceutical Information Center.

22. Clinical Trial Conduction System

See separate volume.
23. Others

1) Training for clinical trial staff

The sponsor investigator/Principal Investigator shall train trial staff involved in the study at the respective site regarding procedures and systems to be employed before enrolling the first subject and record the training results.

2) The contract between WJOG and the study sites

To support the conduct of this clinical trial, WJOG will enter into a support agreement with each site to provide financial support, support for obtaining investigational new drugs, obtaining liability insurance for the clinical trial, and support for other tasks commissioned to the Clinical Trial Coordination Committee by the sponsor investigator/Principal Investigator.
24. Literature
14. Mauri et al. Survival with aromatase inhibitors and inactivators versus standard

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34. Rugo HS et al. A phase 1b study of abemaciclib plus pembrolizumab for patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC). Presented at: 2017 San Antonio Breast Cancer Symposium; San Antonio, Texas, December 5-9, 2017. presentation P1-09-01.

35. Pembrolizumab, letrozole, palbociclib in treating postmenopausal patients with newly diagnosed metastatic stage IV estrogen receptor positive ClinicalTrials.gov Identifier: NCT02778685.


25. Implementation Plan Revision History

March 22, 2019  Ver 1.0 (approved by the WJOG Executive Board)
June 28, 2019  Ver 2.0 (approved by the WJOG Executive Board)
September 23, 2019  Ver 3.0 (approved by the WJOG Executive Board)
June 10, 2020  Ver 4.0 (Approved by WJOG Executive Board)