LYMPARZA Tablets 100mg, 150mg

Protocol for Clinical Experience Investigation

in patients with relapsed ovarian cancer, who are sensitive to platinum-based chemotherapy (All case Investigation)

1. Objective

The objective of the Clinical Experience Investigation (CEI) is to collect following data to characterise safety and efficacy of LYMPARZA Tablets 100mg and 150mg (LYMPARZA) in usual post-marketing use.

1. Development of adverse drug reactions (ADRs)
2. Factors which may affect safety and efficacy of LYMPARZA
3. Development of adverse drug reactions (ADRs) unexpected from "Precautions for Use" of the LYMPARZA JPI

This investigation is an all case investigation that is required, as a condition for approval, to be continued until data from a predetermined number of patients is accumulated after launch.

2. Safety Specification Topics and Efficacy topics

Following events/topics will be investigated as safety specification topics:

Bone marrow depression, Interstitial lung disease, New primary malignancy, Embryofoetal toxicity and Exposure in patients with renal impairment

3. CEI PLAN

3.1 Target number of patients and its rationale

Target number of patients for analysis: 300 patients (as patients in the safety analysis set)

Rationale:

Number of patients for data analysis: The number of patients for data analysis was determined as 300 because, in 300 patients, at least one ADR with the frequency of 1% is to be detected within 95% confidence interval. The frequency of AEs related to "bone marrow depression" and "interstitial lung disease" (safety specifications of this investigation) in SOLO2 were as follows: anaemia 43.6%, neutropenia 19.5%, thrombocytopenia 13.8%, leukopenia 15.9%, lymphopenia 1.0% and ILD 1.5%. Thus, this investigation will allow us to collect and evaluate necessary information on these events.

Also, a sample size of 300 provides a 77.8% chance of observing an adverse reaction with a incidence of 0.5% in at least 1 patient.

3.2 Patients to be enrolled to the CEI

All the patients who are started on LYMPARZA during the registration period are the subjects of the CEI.

3.3 Number of investigation sites where the investigation is conducted

Up to 300 investigation sites mainly consisted of department of gynaecology

3.4 Methods

All Case Investigation is conducted with central registration method.

1. AZKK Medical Representatives (MRs) explain the objective, target patients and methods of this CEI to the physicians in charge of the CEI at the medical institutions where LYMPALSA is prescribed, and request conduct of the CEI to the head of the medical institutions. Written contract has to be concluded prior to the start of the CEI. In principle, the products are delivered after contract.
2. Method of the CEI is central registration. The MR in charge of the CEI site sends Case Registration Forms and CRFs to the physician in charge of the CEI. This investigation also enrols patients treated with LYMPARZA before the conclusion of the contract, including those treated with LYMPARZA under the compassionate use programme.
3. After a patient who fulfills the criteria of "3.2 Patients to be enrolled to the CEI" above starts treatment with LYMPARZA, the physician in charge of the CEI enters relevant information into the Patient Registration Form, and sends it to the registration centre by FAX.
4. After the registration is completed, written communication of the completion of the case registration is sent to the physician in charge of the CEI.
5. The physician in charge of the CEI follows up the patient according to the schedule of observation in “3.6 Data to be collected”. After the observation period is finished the physician enters data of the patient in CRF, enters his/her name with his/her seal, and hands the CRF to the MR.
6. After AstraZeneca K K PMS Control Unit collects the CRF, relevant information in the CRF is entered in the All Case Investigation Check List, and the MR hands the Checklist to the physician in charge of the CEI.
7. After the physician in charge of the CEI receives the All Case Investigation Check List, he/she will confirm whether all the patients prescribed LYMPARZA have been enrolled to the CEI or not. After the confirmation, the physician in charge of the CEI signs and hands it to the MR.

3.5 Investigation period

Planned enrolment period*: from the date of the product launch to the when approval conditions are lifted

CRFs will be collected from all patients who start receiving prescriptions for LYNPARZA by 31 July 2018.

(The patient enrolment that start receiving prescriptions for LYNPARZA on or after 1 August 2018 will be continued until the condition for approval of all case investigation is removed, in order to ensure that CRFs can be collected when necessary)

Planned investigation period*: 2 and a half years from the date of the product launch

* This includes the duration of the compassionate use programme for a part of patients with platinum chemotherapy sensitive relapsed ovarian cancer (from approval date to drug price listing)

3.6 Data to be collected

1. Information required for patient identification

   Patient ID Number

2. Patient demography (baseline data)

   Age, sex, indication of LYMPARZA (Maintenance therapy for platinum-sensitive relapsed ovarian cancer/others), use of LYNPARZA before the date of the first dose of LYNPARZA (yes/no), pregnancy (yes/no), histology of ovarian cancer, date of confirmed diagnosis, inpatient/outpatient classification, height, weight, smoking habit, ECOG Performance Status (PS), allergy (yes/no; if yes, specific allergenic substance [drug, food, others]), surgery for primary disease (yes/no and date of surgery if yes), distant metastasis (yes/no), radiotherapy (yes/no), history and concomitant anti-cancer drugs for primary disease, past medical history and concomitant disease (Renal impairment, Hepatic function disorder and Other disease [yes/no; if yes, seriousness)

3. Pregnancy during the observation period (yes/no)

4. Pregnancy-related information (The outcome of pregnancy and the newborn status)

5. LYMPARZA administration

   Start date, unit dose, and daily dose frequency

   When the treatment regimen was changed during the observation period of the CEI; changed unit dose/frequency of daily dose, date of the change, and reason of the change

   Whether LYMPARZA was continued/discontinued (the most recent administration date if LYMPARZA was continued, the last administration date, and reason of the discontinuation if LYMPARZA was discontinued)

6. Concomitant therapy (other than drugs)

   Concomitant therapy given during observation periods of this investigation (yes/no) (if yes, name of the therapy and purpose of the therapy; and the period of the therapy in patients who experience any adverse event)

7. Response evaluation

   Best overall response evaluation (according to the RECIST guideline) at the end of the one-year observation period, or at the time when LYMPARZA was discontinued.

   Clinical disease progression (yes/no)

8. Adverse event

Adverse events (AEs) (any unfavourable and unintended sign [including an abnormal laboratory finding], symptom or disease whether or not considered related to LYMPARZA) during the observation period (yes/no)

Progression of ovarian cancer lesion or death due to ovarian cancer is not regarded as an adverse event.

If yes, following data should be confirmed:

AE term, onset date, outcome, date of outcome, severity (CTCAE Grade), seriousness*, causality with LYMPARZA (yes/no), causality factors other than LYMPARZA (yes/no), discontinuation (yes/no), concomitant drugs that are possible etiologies other than LYNPARZA (name, dose level, indication for use, treatment period of the drugs) and laboratory test data relevant to AE(s) (test items, reference range at the investigation site, unit, test date, and data)

Date of death, cause of death and causality assessment between LYMPARZA and death (yes/no) are required for adverse event with fatal outcome

*: Definitions of "serious" follows the ICH definitions (PFSB Notification 0328007 of 28 March 2005:

Death, Life threatening, Results in persistent or significant disability/incapacity, Requires inpatient hospitalization or prolongation of existing hospitalization, Other medically important, and Congenital anomaly/birth defect

9. Others

Patients who discontinue treatment with LYNPARZA are to be followed up for adverse events for 30 days after treatment discontinuation as far as possible.

Schedule of the observation

	Baseline	Visit after Treatment Year 1 (completion of the 1-year observation period)[b]	LYMPARZA is discontinued[C]
Patient demography data	○		
LYMPARZA administration	←	→	○
Response to treatment[a]		○	○
Adverse event	←	→	○
Administration of concomitant drugs	←	→	○
Laboratory test[a]	←	→	○

a. Data are collected only from patients who are prescribed LYMPALSA in usual clinical settings.
b. The date of the end of the 1-year observation period is the nearest date to and within 4 weeks before/after the end of the 1-year observation period.
c. The date when LYMPARZA is discontinued is the date of the last visit during the treatment or the next day of the last administration of LYMPARZA. Patients who discontinue treatment with LYMPARZA are to be followed up for adverse events for 30 days after treatment discontinuation.

3.7 Data analysis: item and method

Summary statistics are to be calculated and presented for the analysis items listed below. Definitions and analysis method of the data of the target population are entered in Statistical Analysis Plan.

1. Data analysis sets
   1) Safety analysis set
   2) Efficacy analysis set
2. Analysis items
   1) Case constitution
      Number of patients enrolled in the investigation, number of CRFs collected, number of patients in the safety analysis set, number of patients in the efficacy analysis set, number of patients excluded from the CEI and reason of the exclusion, number of patients discontinued from the CEI and reason of the discontinuation.
   2) Patient demography
      age, in-patient/out-patient classification, weight, BMI, smoking habits, duration of the disease from the first onset, allergy (yes/no), past medical history, and concomitant disease (liver disorder, renal disorder or others) etc.
   3) Treatment
      unit dose, daily dose, concomitant therapy (yes/no, and the kind of the therapy)
   4) Safety
      Development of ADRs sorted by SOC and sorted by patient demography
      Development of serious adverse event sorted by SOC
      Development of the events of safety specification items
   5) Efficacy
      Number and percentage of patients sorted by best overall response category at the end of the 1-year observation period
      Presence or absence of disease progression (progression in lesion)

3.8 Organisation to conduct the CEI

The organisation to conduct the CEI is same as that in Attachment 2 to Japan Risk Management Plan.

3.9 Organisations to which the operations are to be outsourced, and scope of the contract

Outsourcing company;

Address: [redacted]
Name: [redacted]
Scope of the contract: [redacted]

4. MILESTONE AND MEASURES WHICH MAY BE ADOPTED ACCORDING TO THE RESULT OF THE ACTIVITY

The LYMPARZA Japan Risk Management Plan will be reviewed at each milestone. The review will include:

- Assessment of emergence of new safety specifications
- Necessity of pharmacovigilance activities and risk minimization activities for the new safety specifications
- Necessity of any changes to the pharmacovigilance activities and risk minimization activities for the current safety specifications

5. MILESTONES OF EVALUATIONS OF THE STATUS OF CEI PROGRESSION, AND RESULT OBTAINED FROM THE CEI, AND REPORTING TO PMDA

Milestones

At the time of J-PSUR submission, and at the time of the final report of CEI
(2 and a half years after the start of the CEI)

6. Other required items

1. Revision of the protocol

   Following information is always examined during the investigation; progress of CEI, number of patients withdrawn, onset of serious unexpected ADRs, large increase of the incidence of specific ADRs, and validness of the investigation items. The CEI protocol is to be reviewed and revised when it is necessary.

   When application for a partial revision of "Dosage and Administration" or "Indication" is approved during the CEI period (other than new establishment of the re-examination period), necessity of the revision of the CEI protocol is examined, and the protocol is revised as required.

2. Process when any issue or query is provided

   Necessity of additional S-CEI or a post-marketing clinical study is examined to detect or identify any factors of ADRs, or to verify the estimation obtained after data analysis of the CEI if there are any of the followings: an ADR which is not expected from "Precautions for Use" of the LYMPARZA JPI is suggested, frequency of an ADR has significantly increased, there is a safety or efficacy issue compared to the data before marketing, or development of an ADR which has a nature different to known ADRs is suggested.

3. Starting points of data collection

   Date collection in this investigation will begin at the following points:

For patients enrolled in the post-marketing clinical study, data collection will begin at the first dose of LYNPARZA after launch in the post-marketing setting.

For patients included in the compassionate use programme, data collection will begin at the first dose of LYNPARZA given as compassionate use.

For patients enrolled in other post-marketing surveillances, data collection will begin at the first dose of LYNPARZA.

End