## Appendix 1: Informed Consent Form

### Informed Consent Form

A Phase III, randomized, two armed, parallel, triple-blind, active controlled, equivalency clinical trial to determine the therapeutic efficacy and safety between Pertuzumab® (Manufactured by CinnaGen Co.) compared with active control group treated by Perjeta® (Pertuzumab, the reference drug, Manufactured by Genentech) in neoadjuvant treatment of HER 2 positive Breast Cancer patients

Mrs./Miss ……

We invite you to participate in the above-mentioned clinical study. Information about this research is provided in this sheet, and you are free to join this research or not.

You do not have to make an immediate decision and you are given a deadline to announce your opinion after consulting the research team and anyone you desire, about participation and your involvement in this research is entirely voluntarily. Before signing this consent, make sure that you understand all the information in this form and all of your questions are answered.
**Investigator:**

**1)** I know that purposes of this research are evaluation of the efficacy and safety of Pertuzumab (Manufactured by CinnaGen Co.) compared to Perjeta® (Manufactured by Genentech)

**2)** I know that my participation in this study is voluntary and I am not obligated to participate in this research. I was assured that if I were not willing to participate in this research, I would not be deprived of routine diagnostic and therapeutic care and my therapeutic relationship with the health center and my physician will not get affected.

**3)** I know that even after agreeing to participate in the research, I can resign freely at any time after informing the researcher, without giving any reason and my withdrawal from the research will not deprive me of the usual treatment services.

**4)** This is how my participation is in this study:
Whenever the physician diagnosed that I need to receive Pertuzumab to improve my clinical conditions, and I consented to receive it, treatment regimen according to the study protocol of will

be started and I will allocated in one of the treatment group (one of the treatment group receive Pertuzumab (Manufactured by CinnaGen Co.) and the next group will receive Perjeta® (Manufactured by Genentech)). During the study, I have to go to trial site in order to get my treatment drugs, laboratory test and other interventions of visits. The activity of visits of study include:

Duration of study is 18-20 weeks with pathological sampling test after surgery. With considering screening visit, I will have 8 visits (each visit is about 15 min without considering time of drug administration) in this study. The difference between screening and first visit (treatment visit) is maximum 2 weeks and the difference between other visits is 3 weeks. In screening visit, my health condition, medical history, height, weight and vital sign will be evaluated by physician. In addition, one blood sampling (3-5 mm) for general and specific laboratory test (CBC diff,. BUN, Cr, Bilirubin, ALP, AST, ALT, NA, K, Mg, Ca, P, Cl, Albumin, Glucose, LDH, INR, PTT/aPTT, HIV, HCV, HBs-Ag, assessment of antibody formation against drug, Unrine analysis, and pregnancy test if it is required) will be drawn. Other evaluation include Echocardiography, MRI, and ECG. If all of my lab results, imaging and clinical examination were confirmed by physician and I passed all eligibility criteria of the study, I can enrolled in the study after signing this consent form. During the study I will receive these drugs: in each treatment visits I will receive Carboplatin, Docetaxel, Trastuzumab and one of the Pertuzumab drugs. I know that my allocation to each treatment group will be randomly. My physician informed me that this blinding of the treatment is scientific and is to evaluate the efficacy of the drugs. My physician informed me that all of the treatments and interventions will be based on the routine treatment procedure and I do not need to have any extra visit of clinic. Regardless of treatment group, I will receive all of the required interventions and whenever participating in this study will considered not safe for me, I can discontinue the study and will receive appropriate treatment after my quit. I know that all of the drugs of this study between two treatment arms are similar and the only difference is related to Pertuzumab group.

In my next visits (visit 1-6), in each one of them, my health condition will be assessed by physician (investigator). In each visit and before drug administration (every 3 weeks), one blood sampling will be drawn in specified laboratory and these test include: CBC diff,. BUN, Cr, Bilirubin, ALP, AST, ALT, NA, K, Mg, Ca, P, Cl, Albumin, Glucose, LDH, assessment of antibody formation against drug (this test will be done with other lab test and there is no need to give extra blood sample).

In every 6 weeks interval (visit 3, 5, 7), echocardiography test is planned for me. In addition, in first visit and last visit (visit 7) or any other visit that physician consider necessary, MRI test is planned for me and there will be laboratory test in last visit which includes similar laboratory test with previous visits.

In addition, in each visit, questions related to my health condition, other used drugs will be asked. I know that laboratory and imaging test can be repeated based on the physician discretion.

I am assured that if in any time of the study, I had progress, I can discontinue the study and another treatment will start for me based on the physician discretion. In addition, if I received less than 3

doses of pertuzumab (less than 3 cycle of 6 cycle) due to my condition, I will be withdrawan form the study and new treatment based on the physician decision will be started for me.

By considering my health condition, I accept that during the study duration and 6 months after that, I will not try to be pregnant and if there is a chance that I became pregnant or had delay in my menstrual period, I will forthwith inform my physician (To be sure about pregnancy, there is pregnancy test in screening, visit 3 and 6)

**5)** The possible benefits of my participation in this study are as follows:

Pertuzumab is one of the novel drug which has FDA and EMA approval for breast cancer indication. The efficacy of Pertuzumab in breast cancer before and after surgery is confirmed and addition of this drug to chemotherapy regimen can increase significantly clinical response without increasing AE frequency. By participating in this study, I can receive pertuzumab while this drug is not easily accessable in my country and I do not need to pay any cost for this drug. In addition, I will be examined and evaluated by the physicians with greater precision and sensitivity regarding my condition and the side effects of drugs. Also, the effects of my treatment will be carefully evaluated

**6)** The possible harms and adverse events of my participation in this research are as follows:

It is possible to experience these adverse events after participation in this study, including diarrhea, cardia issue, hematologic issue, dermatologic issue, gastrointestinal issue, or reduce of white blood cells, alopecia, nausea, vomiting (most commonly related to chemotherapy regimen drugs and not necessarily related to Pertuzumab). The mentioned adverse events, can be occurred in both treatment groups and can be observed by other chemotherapy regimen too. I have to remember that these adverse events are temporary and after cessation of the tretamnet, all of these adverse events will be disappear after specific time. In addition, if any AEs were occurred, I or my family should inform the physician as soon as possible. This AE can be not related to the investigational drug of the study, but should be reported to the physician of the study.

**7)** In the case of unwillingness to participate in the research, the usual services (therapeutic, diagnostic, etc.) for me will be provided. My treatment will be based on the physician decision in case of unwillingness to participate in the research

**8)** I know that the researchers of this study will keep all of my information confidential and are only allowed to publish the overall and collective results of this research without mentioning my name and my profile.

**9)** I know that the Ethical Committee in my study is allowed to have access to my information to monitor my rights.

**10)** I know that I should not pay any costs of the trial drugs and tests including Chemotherapy regimen drugs, Trastuzumab drugs, Pertuzumab drugs, Pegagen drugs, laboratory test, MRI, Echocardiography, ECG, pathology test

**11)** Physician of the study and Mr. Siavash Bakhshian (sponsor representative) has been introduced to me for answering my questions, and I was told that during the study any time a health problem occurred to me or if I had a question regarding participation in this research, I can share with him and ask for guidance.

**12)** I know that if during and after the research any physical and mental problems arose because of my participation in this research, it will be the responsibility of the physician to treat the complications and the related damages.

**13)** I know that if I have a problem or objection to executors of the research or the research process, I can contact the ethic Committee of the Tehran University of Medical Sciences at the address of: Room 605, 6th Floor, Central headquarters of Tehran University of Medical Sciences, Qods Street, Keshavarz Blvd., Tehran, Iran. Telephone: 009821-81633626 or ethic committee of Guilan reseach center at the address of: Research and technology building, west beheshti blv, Rasht, Guilan and present my problem either verbally or in writing.

**14)** This form of information and informed consent is provided in two copies and will be signed by the physician and me. A signed copy will be given to me and a signed copy will be given to the physician.

**This section should be completed by patient**

I have read and understood the explanations mentioned above, and based on that, I declare my informed consent to participate in this research.

**Participant signature:**

**This section should be completed by investigator (physician) of the study**

I consider myself bound to comply with the obligations of the executor in the above provisions, and I undertake to work on the rights and safety of people participating in this research.

**Investigator signature:**