

Attachment 1] Statement and consent form**Research Participation Statement and Consent Form****Efficacy of Neoadjuvant Atezolizumab Treatment in Patients with Advanced Urothelial Bladder Cancer According to the BASQ Classification: Study Protocol for an Open-label, Two cohorts, Phase II trial**

Subject Initials: _____ **Serial Number:** _____

This clinical trial has been approved by the Seoul National University Hospital Institutional Review Board (IRB), which is responsible for protecting the rights of subjects who participate in clinical trials. This document has been prepared to help you decide whether or not to participate in the study. You must read and understand this consent form before you agree to participate in the trial. This document explains why we do this research and what your rights and roles are. The purpose, process, benefits, side effects, and precautions of this trial are included. It also explains your options and your right to stop participating.

Purpose of the research:

Preoperative chemotherapy is also used to increase the survival rate for patients with advanced bladder cancer. A randomized study of preoperative chemotherapy based on cisplatin Cisplatin before radical cystectomy reported improved survival. Since then, methotrexate vinblastine + doxorubicin) + cisplatin (MVAC), gemcitabine + cisplatin (GC), and cisplatin + methotrexate + vinblastine (CMV) have been used as a combination of various anticancer drugs. No prospective randomized studies are showing the efficacy of such chemotherapy, but retrospective studies show that preoperative chemotherapy is a key factor in recurrence and overall survival after surgery, in reaching the complete remission rate. And reporting meaningful results. Atezolizumab is an antibody that affects the immune system by blocking the PD-L1 pathway. It is a type of protein produced by the body's immune system. The PD-L1 pathway is involved in regulating the body's natural immune response, but tumors can use it to partially resist or evade the immune system.

Atezolizumab can help the immune system stop or reverse tumor growth by blocking the PD L1 pathway. The doctor in charge of the test will give Atezolizumab at the hospital. Meanwhile, as a result of analyzing the genes of many bladder cancers, it has been reported that specific gene expression has a poor prognosis for bladder cancers, and accordingly, bladder cancers are classified according to a standard called BASQ. This is called a basal type of bladder cancer, and it is rich in biomarkers related to stem cell and epithelial-mesenchymal mutations. Basal type bladder cancer is known to have a lower disease-specific survival rate than other bladder cancers. In other words, it is known that the course of the disease varies depending on the immune staining reaction of the tissue. The effectiveness of anti-cancer treatment Atezolizumab has not been proven to improve the survival rate before surgery in patients with muscle-infiltrating bladder cancer, but it is believed to be effective based on existing studies. Please note that this clinical trial is conducted for research purposes and is an unverified clinical trial. Based on this, the institute intends to conduct a study to investigate the efficacy and safety of neoadjuvant atherolizumab before surgery for patients who are scheduled for radical cystectomy.

Participation Procedures, Research Progress, Duration of Participation:

If you decide to participate in this study, you will first fill out a consent form. One copy of the two signed consent forms will be given to you and one copy will be retained by the researcher.

The observation point and schedule for each observation item of the study are as follows.

Phase	Screening	Pre-neoadjuvant therapy	Neoadjuvant therapy			Radical cystectomy	Postoperative follow up									
			1 cycle	2 cycle	3 cycle		1 months	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months	
	1 week ago	Ward	Ward	Ward	Ward	Ward	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	
Subject consent	⊙															
Demographic information	⊙															
Accompanying Forces Survey	⊙															
Selection / exclusion criteria	⊙															
Group assignment		⊙														
Primary Endpoint evaluation						⊙										
Postoperative complications assessment						⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙
Evaluation of drug-related complications			⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙
Disease progress assessment			⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙

Follow-up tests are performed every 3 months following standard bladder cancer treatment principles. In addition, CT is performed for 2 years every 6 months after surgery. This follow-up test is based on general treatment guidelines, and participation in this study does not lead to further testing. In general, if you agree to participate in the study, please participate in the study until the second year after discharge. Additional visits may be made as needed. Study participation ends at the last visit. However, even after the end of the study, you will be followed up for outpatient follow-up according to standard treatment guidelines. Selecting a group for this clinical study First, an immunostaining chemistry test using bladder cancer tissue, which was performed to diagnose muscle-infiltrating bladder cancer, is performed. At this time, it is divided into the Luminal type group and Basal type group according to the results of this test. If you agree to this study, neoadjuvant Atezolizumab treatment will begin before surgery, and the composition of the anticancer drug will not be different for each group, or other drugs will not be administered. However, the reason for dividing the group is to limit the number of researchers to each group of 20 and to find out the difference in treatment response of this treatment according to the results of each immunostaining chemistry.

Methods of administration of this clinical agent:

1 vial of Tecentriq® (Atezolizumab 1200mg, 20ml) is administered 3 cycles every 3 weeks before surgery. Dosing is administered in a 60-minute until the disease progresses or unacceptable toxicity occurs. If unexpected complications occur, the administration is stopped and radical cystectomy is performed. If tolerated on the first infusion, all subsequent infusions may be administered for 30 minutes. This drug is not given by rapid intravenous infusion (IV push or IV bolus).

Foreseen risk or discomfort, and if the administration is stopped:

It is known that this drug has fewer side effects than conventional anticancer drugs. However, as side effects related to this drug, moderate pneumonia, elevated liver function levels, diarrhea or colitis, pituitary glanditis, muscle grade syndrome / muscular dystrophy of all grades, Guillain-Barre syndrome or meningococcal encephalitis, ocular inflammation, pancreatitis, moderate infusion Previous studies have reported that you may have reaction abnormalities, rashes, myocarditis and type 1 diabetes. Participants in this study stop administration when the above-mentioned side effects develop and perform planned radical bladder resection.

Expected Benefits and Examination Fees:

Patients participating in this study are routinely computed tomography, urine cells, urine tests, and blood tests. However, these tests are based on treatment guidelines that apply equally to patients who do not participate in the existing study. When participating in this study, the cost of anti-cancer drugs used before surgery will be borne by the researchers. In addition, 50,000 won per treatment visit is paid to patients who receive secondary chemotherapy as a case fee for study participation. However, a series of treatment, hospitalization and treatment costs and examination fees are not supported. Participation in this clinical trial cannot guarantee that your condition will improve. However, the information obtained in this exam will help others in the future.

Subjects must:

Patients participating in this study should be visited regularly according to the treatment schedule. In addition, if there is an adverse reaction, it is obliged to actively inform the medical staff.

Other treatments:

Standard bladder cancer treatment if you decide not to participate in this study You will be treated according to the schedule. Following the standard guidelines for bladder cancer treatment, existing anticancer drugs are administered or radical cystectomy is performed, and recurrence is observed. When recurrence or metastasis is observed, treatment is performed according to existing treatment guidelines.

The number of participants in this study:

40 patients were enrolled in the study and assigned to the Luminal group (20 patients) and the Basal group (20 patients) according to the results of pre-operative tissue immunity. As mentioned earlier, if you agree to this study, anti-cancer treatment will begin before surgery, and the composition of the anti-cancer drug in each group will not change, or other drugs will not be administered.

Eligible for study participation:

Patients who do not agree with this study, patients with active autoimmune disease or inflammatory bowel disease, diarrhea and colitis of grade 2 or higher, patients with previous severe or persistent immune-related side effects, previous anti-PD-1 or anti-PD-L1 Patients who have undergone therapy, patients with hypersensitivity to atezolizumab, patients who have undergone chemotherapy with other cancers within the past 6 months, and non-surgical conditions such as brain metastasis, storable tumor tissue for which BASQ classification cannot be evaluated Without this, patients with neutrophil counts less than 1,500 / mm³, pregnant or potentially pregnant women, nursing mothers, patients with severe liver dysfunction, patients with complications of infectious disease (infection may worsen and become fatal), infectious Patients with suspected fever (infection worsens and can become fatal), patients with severe bone marrow suppression (severe infections) A, and it can be fatal cause If you have symptomatic pituitary glanditis, adrenal insufficiency, hypothyroidism, hyperthyroidism, or grade 3 or 4 hyperglycemia, moderate or more ocular inflammatory disease, amylase or lipase levels in pancreatitis or blood

tests Participation in the study is excluded if the patient has an active rash that is not suitable for this study if the investigator judges that he or she currently has an active rash more than twice as normal.

Other treatments:

If you decide not to participate in this study, you will usually be treated according to your bladder cancer treatment schedule. Following the usual guidelines for bladder cancer treatment, existing anticancer drugs are administered or radical cystectomy is performed, and recurrence is observed. When recurrence or metastasis is observed, treatment is performed according to existing treatment guidelines.

The number of participants in this study:

40 patients were enrolled in the study and assigned to the Luminal group (20 patients) and the Basal group (20 patients) according to the results of pre-operative tissue immunity. As mentioned earlier, if you agree to this study, neoadjuvant Atezolizumab treatment will begin before surgery, and the composition of the anti-cancer drug in each group will not change, or other drugs will not be administered.

Eligible for study participation:

Patients who did not agree with the study, Patients with active autoimmune disease or inflammatory bowel disease, Diarrhea and colitis of grade 2 or higher, Patients with previous severe or persistent immune-related side effects, Patients with a history of previous anti PD-1 or anti-PD-L1 therapy treatment, Hypersensitivity patients to Atezolizumab, Patients who received chemotherapy for other cancers within the last 6 months, For diseases that are not suitable for surgery, such as brain metastases, If there is no storable tumor tissue that cannot be evaluated for BASQ classification, Patients with neutrophil counts less than 1,500 / mm³, pregnant women or women who may be pregnant, Lactating, Severe liver dysfunction, Patients with complications of the infectious disease (infection becomes worse and can be fatal), Patients with suspected infectious fever (the infection may worsen and become fatal), Patients with severe bone marrow suppression (can cause severe infections, etc., and can be fatal), Symptomatic pituitaryitis, Adrenal insufficiency, Hypothyroidism, Hyperthyroidism, Or grade 3 or 4 hyperglycemia, If you have moderate to moderate inflammatory disease, When amylase or lipase levels are more than 2 times higher than normal on pancreatitis or blood tests, If you currently have an active rash, Participation in the study is excluded if the investigator judges that he / she has an active disease not suitable for this study.

Identity protection:

Information that can verify your identity will be kept confidential. Your identity will remain confidential even if the results of this study are published.

Compensation for unexpected damage:

By participating in this study, we believe that you are unlikely to experience any unexpected damage. However, in the event of unexpected damage to you in connection with this study, the subject's physician will provide routine and customary treatment. In addition, if necessary, compensation is made by the rules for compensation for victims approved by the Institutional Review Board (IRB) of the Seoul National University Hospital.

Information protection and access to records:

All materials are strictly protected and protected by the confidentiality of the subject. If you agree to participate in

this trial, the data collected in this trial will be treated anonymously, and the researchers, health authorities, and hospital personnel of this study will be subject to the scope of the relevant regulations without prejudice to your confidentiality. You can view your medical records to verify the reliability of the research procedures and data within, this is deemed to have been agreed upon by your consent to participate in the study. In addition, if the results of the clinical trial are published, the identity of the subject will be kept confidential as well. You have the right to request access to your data.

Notice of new facts:

While participating in this study, if new information is gathered that may affect the continuity of study participation, the researcher will immediately notify you of the information.

Suspension of study:

Even while you are participating in this study, this study may be stopped without your consent if:

1. When the subject decides to withdraw from participation in clinical research
2. Unacceptable adverse reactions
3. Significant violations of the clinical trial plan
4. Intercurrent illness that cannot be administered with additional test drugs
5. Pregnancy
6. When other types of chemotherapy are required
7. The investigator determines that general or specific changes in the patient's condition will render additional treatment unacceptable.
8. Follow-up fails

If not participating in the study:

There must be a willingness to participate voluntarily in this study. If you decide not to participate in this study, there are no penalties for you, and you can discuss treatment with your doctor. Even if you decide to participate in the research, you can give up participation in the middle of the course and there will be no disadvantage.

Contact:

Please read the contents of this study and contact the Seoul National University Hospital Institutional Review Board (IRB) for additional information about your interests if you participated in this study. If a problem such as damage occurs in connection with this study, you can contact the responsible researcher and researcher at the contact information below.

Seoul National University Hospital Institutional Review Board (IRB) ☎ 02-2072-0694

Senior Researcher, Department of Urology, Seoul National University Hospital Ja Hyeon Ku ☎ 02-2072-0361

Researcher, Seoul National University Hospital Urology Hyeong Dong Yuk ☎ 02-2072-1968

Signature

I received an explanation of the above about 'the study of the effectiveness of atezolizumab before surgery in patients with advanced bladder cancer classified by BASQ classification', understood the contents, and decided to participate in the study according to my will I did it.

Clinical trial subjects

Test Subject Name (Static)

Subject Signature

Date (Year / Month / Day)

Observer (if applicable)

Visitor's Name (Static)

Observer's Signature

Date (year / month / day)

Research Director

Research Director's Name

Signature of Research Director

Date (year / month / day)

Subject's representative's signature, if applicable:

Name of the subject's representative (static)

Subject's Representative's Signature

Date (year / month / day)

Relationship between test subject and test subject representative