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Efficacy of neoadjuvant atezolizumab treatment in patients with advanced urothelial bladder cancer according to the BASQ classification: a study protocol for an open-label, two-cohort, phase II trial

Hyeong Dong Yuk,[1,2] Chang Wook Jeong,[1,2] Cheol Kwak,[1,2] Hyeon Kim,[1,2] Kyung Chul Moon,[2,3] Ja Hyeon Ku [1,2]

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[1]Urology, Seoul National University Hospital, Seoul, The Republic of Korea
[2]College of Medicine, Seoul National University, Seoul, The Republic of Korea
[3]Pathology, Seoul National University Hospital, Seoul, The Republic of Korea

Correspondence to
Dr Ja Hyeon Ku;
kuuro70@snu.ac.kr

ABSTRACT

Introduction Atezolizumab is a programmed death ligand-1 inhibitor for urothelial bladder cancer treatment. Atezolizumab has become the standard therapy for patients with urothelial bladder cancer who are not responding to cisplatin-based chemotherapy and is also used as a first-line treatment in cisplatin-ineligible patients. However, the efficacy of atezolizumab as a neoadjuvant chemotherapy for radical cystectomy has not yet been published and is still under study. This trial investigates the effectiveness of basal/squamous-like (BASQ) classification in the selection of an effective target group of patients with muscle-invasive bladder cancer (MIBC) for neoadjuvant atezolizumab treatment.

Methods and analysis This study is an open-label, two-cohort, phase II trial. It was designed to evaluate the efficacy of neoadjuvant atezolizumab treatment in patients with MIBC (T2–4N0M0) pathological responses after neoadjuvant chemotherapy and radical cystectomy. According to the molecular subtype characteristics of previous transurethral resection of the bladder specimens, patients are divided into two groups: luminal type (KRT5/6−KRT14−FOXA1+GATA3+) and basal type (KRT5/6+KRT14+FOXA1−GATA3−). Every 3 weeks, atezolizumab is administered at a dose of 1200 mg for three cycles prior to radical cystectomy in patients with MIBC. The primary end point is objective pathological responses in the intention-to-treat patients. The secondary end point is a 1-year progression-free survival difference according to the BASQ classification in patients who underwent neoadjuvant atezolizumab treatment.

Ethics and dissemination The study protocol was approved by the Institutional Review Board of Seoul National University Hospital, Seoul, Republic of Korea (H 1806-051-950). The trial is registered at ClinicalTrials.gov. The trial results will be published in peer-reviewed journals and at conferences.

Trial registration number NCT03577132.

Strengths and limitations of this study

- This is the first open-label, two-cohort, phase II trial to explore the effect of neoadjuvant immune checkpoint inhibitors on molecular subtypes in urothelial bladder cancer.
- The trial is designed to evaluate the efficacy of neoadjuvant atezolizumab treatment in patients with muscle-invasive bladder cancer (T2–4N0M0).
- It is also designed to evaluate the pathological responses to neoadjuvant atezolizumab treatment and radical cystectomy according to the basal/squamous-like classification.
- The purpose of this study is to select a target group for which neoadjuvant immune checkpoint inhibitors may be more effective.
- The limitation of this study is the shorter follow-up period.

INTRODUCTION

Blocking programmed cell death protein-1 (PD-1) and programmed death ligand-1 (PD-L1) is an effective way to treat advanced-stage urothelial bladder cancer (UBC).[1–3] Atezolizumab was first approved by the US Food and Drug Administration in May 2016 as a PD-L1 inhibitor for UBC.[4] This new drug has become the standard therapy for patients with UBC who are not responding to cisplatin-based chemotherapy and is also used as a first-line treatment in cisplatin-ineligible patients.[5] Several treatments are currently being studied, and in addition to cisplatin-based chemotherapy as the first-line neoadjuvant treatment for advanced UBC, it is reported that the benefits of immune checkpoint inhibitors are positive.[6] In the PURE-01 (Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle-Invasive Urothelial Bladder Carcinoma) study to determine the activity of neoadjuvant pembrolizumab in 50 patients

with T2–T3bN0 UBC, 21 patients showed a pathological complete remission (pCR) rate of 42% (95% CI: 28.2% to 56.8%).[7] In the ABACUS[8] study of neoadjuvant atezolizumab in patients with T2–T4aN0M0 cisplatin chemotherapy inability, the pCR rate was 29% (95% CI: 19% to 42%).[8 9]

Recently, several research groups have conducted a detailed analysis of the molecular genetic characteristics of bladder cancer through The Cancer Genome Atlas (TCGA) study and are working to apply it to UBC treatment.[10–13] A consensus was reached regarding the existence of a group of basal squamous-like tumours designated basal/squamous-like (BASQ) characterised by the high expression of KRT5/6 and KRT14 genes and the low/undetectable expression of FOXA1 and GATA3 genes.[14] This novel molecular classification can improve the identification of optimal patient populations for different treatment modalities. Specifically, luminal type and basal type may have different treatment responses and prognosis after initial definitive treatment, such as neoadjuvant treatment.[14] However, there is not much evidence for this topic, particularly the clinical efficacy of neoadjuvant PD-L1 inhibitors according to the BASQ classification in patients with advanced UBC. This study assesses the efficacy of the neoadjuvant atezolizumab treatment in patients with muscle-invasive bladder cancer (MIBC) and the difference in the efficacy of neoadjuvant atezolizumab treatment according to the BASQ classification.

METHODS AND ANALYSIS

Research design

This study is an open-label, two-cohort, phase II trial for patients with histologically confirmed muscle-invasive UBC. It was designed to evaluate the efficacy of neoadjuvant atezolizumab treatment in patients with locally advanced or metastatic UBC pathological responses (pT0 change) after neoadjuvant chemotherapy and radical cystectomy.

Study hypothesis and objectives

The main hypothesis of this study is that patients with locally advanced or metastatic UBC can tolerate a neoadjuvant atezolizumab dosing regimen and that there will be differences in the effect of neoadjuvant immunotherapy between basal and luminal subtypes on immunohistochemistry (IHC), according to their BASQ classification.

The main objective of this study is to investigate and compare the efficacy and clinical responses (pT0 change) to neoadjuvant atezolizumab treatment in patients with MIBC according to their BASQ classification.

In patients with MIBC, the basal type is expected to have better efficacy and clinical responses to neoadjuvant atezolizumab treatment than the luminal type.

Study end point

The primary end point is objective pathological responses (pT0 change) in the intention-to-treat patients. After neoadjuvant treatment with atezolizumab in patients with advanced MIBC, objective pathological responses are compared according to the BASQ classification. The second end point is 1-year progression-free survival (PFS) difference according to the BASQ classification of patients who underwent neoadjuvant atezolizumab treatment (box 1). PFS is defined as the time between the date of first documented disease progression or death, whichever occurs first. Disease progression is determined on the basis of investigator assessment with the use of Response Evaluation Criteria In Solid Tumours version 1.1 (RECIST v1.1). Patients who would not have experienced disease progression or death at the time of analysis will be censored at 1 year after treatment.

Safety assessments are performed for 90 days after the last atezolizumab administration in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

Box 1 Key end points and inclusion criteria of study

Primary end point

- Objective pathological responses (pT0 change) after neoadjuvant atezolizumab treatment.

Secondary end point

- One-year progression-free survival difference according to the basal/squamous-like (BASQ) classification of patients who underwent neoadjuvant atezolizumab treatment.

Inclusion criteria

- ≥18 years of age.
- Histologically confirmed muscle-invasive urothelial carcinoma.
- Patients undergoing radical cystectomy.
- Advanced status requiring neoadjuvant systemic therapy.
- Eastern Cooperative Oncology Group performance status score of 0 or 1.
- Adequate organ and haematological functions.
- Available immunohistochemistry data for the BASQ classification.

Safety item and measurement

Adverse reactions due to the injection of anticancer drugs are as follows: adverse events reported in clinical trials, immune-mediated adverse events, infection, infusion-related reactions and immunogenicity. The safety assessment is performed from the beginning of the study up to 90 days after the last injection of atezolizumab, in accordance with NCI CTCAE, version 4.03. The incidence, characteristics and severity of side effects are graded in accordance with NCI CTCAE, version 4.0, and changes in biometric signals, physical examination results and clinical examination results are identified.

Safety monitoring was conducted at the time of registration of five research subjects. All subjects were followed up on a regular basis. When an adverse reaction occurred, the adverse reaction content, seriousness, predictability and causal relationship were evaluated and reported. In the case of serious adverse events, they were immediately reported to the Subject Protection Centre.

Study population

A total of 40 patients with MIBC undergoing radical cystectomy following neoadjuvant treatment with atezolizumab are to be included. All patients must have undergone transurethral resection of the bladder (TURB) before radical cystectomy. According to the molecular subtype characteristics of previous TURB specimens, we divided the patients according to the BASQ classification (KRT5/6, KRT14, FOXA1 and GATA3) into two groups: luminal type (KRT5/6−KRT14−FOXA1+GATA3+) and basal type (KRT5/6+KRT14+FOXA1−GATA3−). A total of 40 patients, 20 for each group, were included in the study.

BASQ classification

The BASQ classification is a consensus conclusion agreed by multicentre researchers who conducted TCGA studies.[10–13 15] According to these classification criteria, invasive bladder cancer subtypes are divided into basal type and luminal type. The basal type is characterised by extensive expression of KRT5/6 and KRT14 and low expression levels of FOXA1 and GATA3 at the RNA and protein levels. KRT5/6 and KRT14 are extensively expressed in cancer cells without epithelial compartmentalisation.[10–13 15] The basal type is associated with a high resistance to chemotherapy and poor prognosis.[14]

Inclusion criteria

Inclusion criteria for the study are the following: (1) ≥18 years of age; (2) histologically confirmed muscle-invasive urothelial carcinoma; (3) patients undergoing radical cystectomy; (4) advanced status requiring neoadjuvant systemic therapy; (5) Eastern Cooperative Oncology Group performance status score of 0 or 1; (6) adequate organ and haematological functions; and (6) available IHC data for the BASQ classification (box 1).

Exclusion criteria

Exclusion criteria for the study are the following: (1) non-urothelial carcinoma histology; (2) active autoimmune disease or inflammatory bowel disease; (3) prior severe or persistent immune-related adverse events; (4) previous exposure to anti-PD-1 or anti-PD-L1 therapy; (5) requirement for 10 mg/day of prednisone or equivalent; (6) inadequate liver, kidney function, and hematological dysfunction; (7) inoperable case, such as untreated central nervous system metastases; and (8) no available archival tumour tissue for evaluating the BASQ classification.

Sample size consideration

The efficacy of atezolizumab as a neoadjuvant chemotherapy for radical cystectomy has not yet been published and is still under study. This study is a pilot study concept. To maximise its excellence in research progress and feasibility, we set the number of patients prospectively to 40, divided into two groups of 20. To detect a difference with 80% power and 5% significance level, we needed at least about 15 patients per cohort. About 80–100 patients had undergone radical cystectomy in our institution. We considered the number of patients diagnosed with MIBC who had undergone TURB in our institution and who could have a BASQ classification. Considering patients' refusal to take part in the study and drop out of the study, about 40 patients are considered to be able to participate in the study for about 3–4 years.

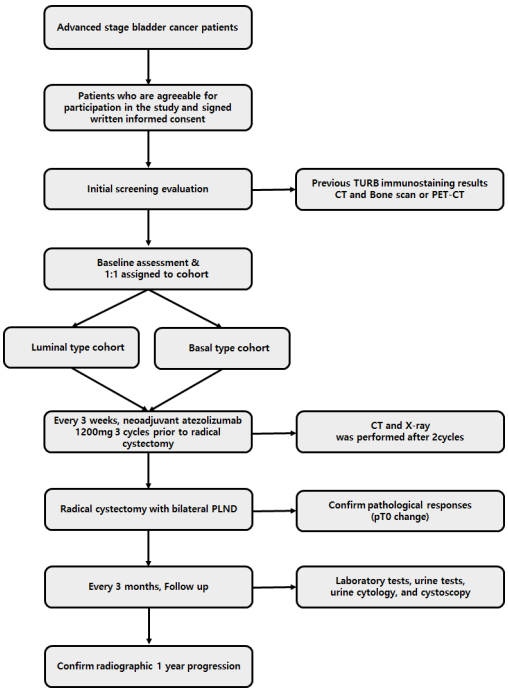

Figure 1 Study flow diagram. PET, positron emission tomography; PLND, pelvic lymphadenectomy; TURB, transurethral resection of the bladder.

Drug regimens

The dose level of atezolizumab in this study is 1200 mg (equivalent to an average body-weight-based dose of 15 mg/kg) administered by intravenous infusion every 3 weeks (21 days). The initial dose of atezolizumab is delivered over 60 min. If the first infusion is tolerated without infusion-associated adverse events, the second and third infusion will be delivered over 30 min every 3 weeks, for a total of three cycles prior to radical cystectomy.

Data collection

The studies were planned following the flow shown in figure 1. Screening tests included CT of the chest, abdomen, and pelvis. Bone scans or positron emission tomography/CT was performed at the time of screening, when necessary. Previous TURB specimens of all patients underwent immunostaining with KRT5/6, KRT14, FOXA1 and GATA3 antibodies using tissue microarray (TMA), and the BASQ classification results were obtained according to the immunostaining expression pattern.

At the time of screening, we collected information on clinical tumour, node, metastases (TNM) stage, tumour grade, BASQ classification information, American Society of Anesthesiologist physical status, previous medical history, haematology, serum chemistries, coagulation and serology.

After two cycles of neoadjuvant atezolizumab, CT scan and X-ray analyses were performed. After radical cystectomy, pathological TNM stage, tumour grade, positive surgical margin and lymphovascular invasion were determined. The follow-up was performed every 3 months after radical cystectomy, and progression was confirmed by CT scan 1 year later. Laboratory tests, urine tests, urine cytology and bladder cystoscopy were performed at each follow-up. Radiological tests such as chest, abdomen and pelvis CT were performed 1 year after operation. We also collected various types of oncological data, including recurrence, progression, mortality and cancer-related mortality rates.

TMA construction and IHC

We constructed TMA blocks from formalin-fixed paraffin-embedded tissue blocks (Superbiochips Laboratories, Seoul, Korea). In brief, two representative tumour cores (2 mm in diameter) were selected from the viable tumour area. The cancer tissues of patients were examined microscopically by a skilled pathologist, and the TMA was prepared after selecting the most representative cancer tissues. Immunostaining was performed for KRT5/6, KRT14, FOXA1 and GATA3 antibodies on TMA slides, and the expression patterns were quantitatively analysed using a scanning programme. Based on the expression patterns, the patients were divided according to the BASQ classification (KRT5/6, KRT14, FOXA1 and GATA3).

IHC staining was performed on 4 µm thick sections of TMA blocks using the Benchmark XT autostainer (Ventana Medical Systems, Tucson, Arizona, USA). The sections were incubated with the following primary antibodies: mouse monoclonal antibodies against KRT5/6 (64 min; 1:50; Dako, Glostrup, Denmark), KRT14 (32 min; 1:50; Cell Marque, Rocklin, California, USA) and GATA3 (32 min; 1:500; clone 156-3C11; Cell Marque), and rabbit polyclonal antibody against FOXA1 (16 min; 1:700; ThermoFisher Scientific, Rockford, Illinois, USA).

Statistical analysis

Objective pathological responses were assessed by well-experienced genitourinary pathologists. Comparisons between BASQ groups were made via t-tests and Fisher's exact tests. Continuous variables are presented as median value and IQRs or average value and SDs. Nominal variables are presented as the frequency of events (%). The Kaplan-Meier method was used to predict PFS, and significance among groups was determined using the log-rank tests. Safety analyses were performed on the as-treated population, defined as all enrolled patients who received atezolizumab. We used the logistic model to analyse the association between BASQ and pT0 response.

All statistical tests were performed using IBM SPSS Statistics V.25.0 (IBM) and STATA V.14 (StataCorp LP, College Station, Texas, USA). A p value <0.05 was considered statistically significant.

Patient and public involvement

Patients and/or the public were not involved in the design, recruitment and conduction of this study.

DISCUSSION

Unlike studies of other neoadjuvant settings of immune checkpoint inhibitors, this study combines a neoadjuvant immunotherapy with a molecular subtype, which is clinically and theoretically innovative. First, unlike the ABACUS and PURE-01 studies, the purpose of our study was to select a target group for which neoadjuvant chemotherapy may be more effective. Second, this is a two-cohort study with prospective molecular subtypes. The ABACUS and PURE-01 studies are single-arm studies. Third, in the ABACUS study, cancers are retrospectively classified as TCGA subtypes to suggest an effective molecular subtype. Finally, there is a difference between the drug and the regimen used. Pembrolizumab is used in the PURE-01 study, and two cycles of neoadjuvant atezolizumab are used in the ABACUS study. According to our knowledge, this study is the first open-label, parallel-group, controlled clinical trial to explore the effect of neoadjuvant immune checkpoint inhibitors on molecular subtypes in bladder cancer. This will contribute to the development of an effective neoadjuvant immunotherapy for patients with MIBC . This study will provide us unique opportunities to identify patients and to predict better outcomes before neoadjuvant immunotherapy.

In addition, this study also provides an opportunity to further study neoadjuvant immunotherapy and personalised care in patients with MIBC. It can be an opportunity to provide better explanatory data on the neoadjuvant immunotherapy theory. The effects of immunotherapy on individual molecular characteristics can be used as a basis for changing the current consensus guideline recommendations.

Atezolizumab is a humanised monoclonal anti-PD-L1 antibody and has demonstrated efficacy and safety as a first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic bladder cancer in the phase II IMvigor210 trial.[16] The primary outcome was an objective response rate of 23.5% (95% CI: 16.2% to 32.2%) in the group receiving atezolizumab.[16] Researchers also performed a subgroup analysis of the effect of atezolizumab on the molecular UBC subtype.[14] Nivolumab showed the most effective drug response in the basal I subtype in the CheckMate 275 trial.[17] The luminal I subtype was low in PD-L1 and low in response to atezolizumab and nivolumab in tumour cells.[16 17]

Genetic analysis of urothelial carcinoma found TCGA subtypes such as luminal and basal subtypes and TCGA clusters I–IV.[10 11] However, the classification of molecular subtyping presents various criteria for each study, making it difficult to standardise the classification of TCGA subtypes.[10–13 15] In the discussion of this classification, several researchers have defined BASQ as a molecular subtype classification of bladder cancer.

The basal type is associated with a high resistance to chemotherapy and poor prognosis.[14] This molecular subtype of urothelial carcinoma is related to cell differentiation and is distinguished as basal and luminal type by a keratin marker.[11 18] The basal type is characterised by a high-molecular-weight keratin, which represents the basal and stem cell compartment, and the luminal-type keratin represents the umbrella cell compartment.[11 18]

The recently presented neoadjuvant atezolizumab ABACUS[8] trial at American Society of Clinical Oncology 2018 was similar to ours, but the difference was that two cycles of neoadjuvant atezolizumab were performed.[8 9] In our study, three cycles of neoadjuvant atezolizumab are performed. According to a report of ABACUS[8] trial in 2018, the PURE-01 study used three cycles of pembrolizumab and showed a pCR rate of 42%. And the ABACUS study used two cycles of atezolizumab and showed a pCR rate of 31%. We believe from the above two results and the characteristics of immunotherapy that there is an increase in effect as the cycle increases, and we expect three cycles to be more effective than two cycles. Seventy-five patients with T2–T4aN0M0 urothelial carcinoma were enrolled, of which 29% of the patients had pCR and 39% of them were downstaged with non-MIBC.[8 9] In PD-L1-positive patient group, pCR was as high as 40%.[8 9]

There are a number of potential problems with this work: there is a lack of mature follow-up period that indicates survival outcome, and there is insufficient evidence for pT0 responses after immunotherapy to predict survival rates as in previous chemotherapy studies.

In conclusion, this study was designed to evaluate the effectiveness of the BASQ classification to select an effective target group for neoadjuvant atezolizumab treatment in patients with MIBC . This study will provide data that support a rational basis for selective neoadjuvant immunotherapy depending on the molecular characteristics of the individual tumour in the patient with bladder cancer, and it will be helpful in treating patients with MIBC by encouraging new neoadjuvant immunotherapy-related studies. We hope to reflect the results of personalised treatment according to the characteristics of individual tumours in patients with bladder cancer.

TRIAL STATUS

The protocol version number was ver.1.1. The first patient was enrolled on 13 August 2018, and a total of 18 patients have registered and are currently undergoing treatment (11 cases of basal type and 7 cases of luminal type). By August 2021, we expect that recruitment will be approximately completed.

ETHICS AND DISSEMINATION

The study protocol, information on Informed Consent Forms (online supplemental file 1) to be provided to the patient and relevant support information were reviewed and approved by the Institutional Review Board (IRB) of Seoul National University Hospital, Seoul, Republic of Korea (H 1806-051-950). Before the study began, patient recruitment data were approved by the IRB. Written consent to participate in the study was obtained prior to conducting the study-specific screening or evaluation. All screenings were completed and reviewed to ensure that patients met all eligibility criteria before treatment with neoadjuvant medication. Anonymous research results will be disseminated as a summary of research results between researchers, published manuscripts in peer-reviewed academic journals, presented abstracts, or presentations at conferences and academic meetings.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Ja Hyeon Ku http://orcid.org/0000-0002-0391-2342

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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. Athezolizumab 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	Potoperative 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