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Bladder preservation therapy in combination with atezolizumab and radiation therapy for invasive bladder cancer (BPT-ART) – A study protocol for an open-label, phase II, multicenter study

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ABSTRACT

Radical cystectomy (RC) is recommended for muscle-invasive bladder cancer (MIBC) or highest-risk non-muscle-invasive bladder cancer (NMIBC). Trimodal therapy (TMT) is the most favorable strategy among bladder preservation therapies (BPT) for patients who are ineligible for or refuse RC. However, referrals for TMT, especially following chemotherapy, are limited by the patient's condition. Therefore, new BPT approaches are needed. Atezolizumab inhibits programmed death-ligand 1, is well-tolerated in patient populations heavily dominated by renal insufficiency, and is expected to have synergistic anti-tumor effects in combination with radiation therapy (RT). Therefore, we have conducted this open-label phase II multicenter study to evaluate the efficacy and safety of RT in combination with atezolizumab for T2-3 MIBC and highest-risk T1 NMIBC patients. This study was initiated in January 2019, and we aimed to enroll a total of 45 patients. The study is registered in the Japan Registry of Clinical Trials (Identifier: RCT2031180060).

1. Background

Bladder cancer is the 14th most common cancer in Asia and is considered to be a disease of the elderly, with a high incidence in individuals aged over 60 years [1,2]. Non-metastatic bladder cancer is classified into non-muscle invasive cancer and muscle invasive cancer, which accounts for about 20–25% of cases [3,4]. Radical cystectomy (RC) is the primary treatment modality for muscle-invasive bladder cancer (MIBC). While highest-risk non-muscle-invasive bladder cancer (NMIBC) is defined as T1 Grade 3 (G3)/high grade (HG) and is associated with concurrent bladder carcinoma in situ (CIS), multiple, large, and/or recurrent T1G3/HG according to European Association of Urology guidelines, RC is only indicated for those patients with the highest-risk NMIBC before they progress to muscle-invasive tumor [5,6].

In patients with high-risk NMIBC, intravesical bacillus Calmette-Guérin (BCG) after transurethral resection of the bladder tumor (TURBT) reduces the risk of tumor recurrence [7]. In contrast, RC is also recommended for patients who had been unsuccessfully treated with BCG either due to tumor failure or due to severe side effects, preventing the completion of BCG treatment. Some studies on this have reported positive results [8–12].

However, RC with urinary diversion is very likely to decrease patients' post-treatment comfort and quality of life (QOL). In addition, due to advanced age and comorbidities, some patients are considered unsuitable for cystectomy [13]. Thus, several bladder preservation

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therapies (BPT) have evolved over the past 20 years, utilizing chemotherapy and radiation therapy (RT).

Currently, the most favorable strategy among BPTs is the trimodal therapy (TMT), which consists of transurethral resection of the bladder tumor and concurrent chemoradiation (CCRT). TMT has shown results similar to that of RC, with the advantage of preserving organ function and QOL in selected patients. Table 1 summarizes the clinical results of TMT for MIBC showing that the 5-year overall survival (OS) rates range between 48 and 57% [14–21] (Table 1).

However, proper patient selection is considered essential for the application of TMT. Some conditions such as tumor invading outside the bladder (cT4), TURBT incompletion, presence of hydronephrosis, presence of CIS, and presence of diffuse multifocal disease are considered to be associated with worse prognosis in patients treated with TMT. Hence, these patients would be better suited for treatment with RC [22–24]. RT is an essential treatment modality for BPT, but historically, RT has mainly been used in patients with frailty or multiple comorbidities that interfere with the use of chemotherapy. Thus, the results of RT alone as BPT are known to be inferior to that of CCRT [25,26]. The 5-year overall survival (OS) rates reported by some studies on RT alone range between 24% and 45% [27–30].

Chemotherapy used concurrently with RT is aimed as a radiosensitizer in TMT. According to the National Comprehensive Cancer Network (NCCN) guidelines, preferred chemotherapy regimens for organ-preserving CCRT are cisplatin alone, 5-FU with or without mitomycin, or paclitaxel when feasible [31].

In contrast, the population of patients with an ideal indication for TMT is limited due to the oncological conditions mentioned above, as well as patient conditions, including advanced age and comorbidities ineligible for chemotherapy. Therefore, new BPT approaches for patients who are unsuitable for CCRT are needed.

The abscopal effect, which induces tumor regression at non-irradiated distant tumor sites, is increasingly recognized in preclinical and clinical studies for the immune-mediated anti-tumor impact of RT [32,33]. With the development of immuno-oncology, the synergistic anti-tumor effect of cancer immunotherapy, and especially of immune checkpoint inhibitors, is expected when these agents are combined with RT [34]. Although there is strong evidence from preclinical works that RT and immunotherapy fit together, clinical reports detailing the interaction of RT with immunotherapies are limited [35–37].

Atezolizumab is a monoclonal antibody that suppresses programmed death-ligand 1 (PD-L1). Studies have shown its efficacy and acceptable safety profile in various cancers, including metastatic urothelial carcinoma. Even in patients with renal insufficiency, atezolizumab appears to be safe and well-tolerated [38–40].

To our knowledge, several small single-arm phase I/II trials and one phase III trial have been conducted, where PD-1 or PD-L1 inhibitors were used as neoadjuvant or adjuvant therapy in combination with RT or CCRT (Table 2). Therefore, we have planned this open-label phase II multicenter study (BPT-ART) to evaluate the efficacy and safety of RT combined with atezolizumab for clinical T2-3 MIBC and highest-risk T1 NMIBC patients who were considered unsuitable for RC or refused RC. We will also assess the efficacy and safety of long-term administration of atezolizumab in this setting.

Table 1
Outcome of trimodal bladder preservation therapy for MIBC.

Author	Year	Number	Clinical stage	3-y OS (%)	5-y OS (%)	3-y PFS/DFS (%)	5-y PFS/DFS (%)
Housset et al. [14]	1993	54	T2-4 N+	59		62	
Hussain et al. [15]	2004	41	T2-4 N+		36	65	59–67
Eapen et al. [16]	2004	185	T2-4 N+	60	48		
Krause et al. [17]	2011	331	T2-4 N+		54		
James et al. [18]	2012	182	T2-4 N-		48		
Tunio et al. [19]	2012	230	T2-4 N-	80	53	80	47
Efstathiou et al. [20]	2012	343	T2-4 N-	65	52		
Mak et al. [21]	2014	468	T2-4 N-		57		

Abbreviations; MIBC: muscle-invasive bladder cancer, Y: year, OS: overall survival, PFS: rogression free survival, DFS: disease free survival.

2. Materials and methods

2.1. Study design

Participating sites are the following: University of Tsukuba, Osaka Medical College, and Saitama Cancer Center in Japan. This trial is registered in the Japan Registry of Clinical Trials (Identifier: RC-T2031180060), and the study protocol was approved by the independent ethics committee of each study site. The inclusion and exclusion criteria are listed in Table 3. The patients who were suitable for concurrent chemoradiotherapy were not excluded.

Table 2
Ongoing trials of immune checkpoint inhibitors for non-metastatic bladder cancer.

Drug	Trial	Population	Radiation therapy	Combined drugs	Number	Primary endpoint
Pembrolizumab	NCT02662062	T2-4aNxM0	64 Gy/32 Fr	Cisplatin	30	MTD
Pembrolizumab	NCT02621151	T2-4aN0M0 unsuitable or refused RC	52 Gy/26 Fr	Gemcitabine	54	2y-BIDFS
Pembrolizumab > Withdraw	NCT02560636	T2-4NxMx	36 Gy/6 Fr/6 weeks	–	34	MTD
Durvalumab	NCT03150836	T3-4NxMx	33 Gy/5 Fr	–	6	Toxicity
Durvalumab + Tremelimumab	NCT03702179	T2-4aN0M0	46 Gy (small pelvis) 18–20 Gy (bladder)	–	32	Pathological response
Avelumab	NCT03747419	T2-4aN0M0	Undescribed (2 way)	–	24	3y-Complete CCR
Avelumab	NCT03950362	T1N0M0 BCG unresponsive	60–66 Gy (bladder)	–	67	1y-High risk RFS (HG,T1,CIS)
Ipilimumab + Nivolumab	NCT03844256	T2-4aN0-1M0	40 Gy/20 Fr	MMC, capecitabine	50	Toxicity, DLT, 5y-DFS, 5y-DFS rate
Atezolizumab	NCT03620435	T2-4aN0M0	50 Gy/25 Fr	Gemcitabine	25	Toxicity
Atezolizumab	NCT03697850	T2-3N0M0	>60 Gy	Any	77	DFS
Atezolizumab	NCT03775265	T2-4aN0M0	Undescribed	GEM, CDDP, 5-FU, MMC	475	5y-BI-EFS

Abbreviations; y: year, BIDFS: bladder-intact disease-free survival rate, MTD: maximum tolerated dose, CCR: clinical response rate, RFS: relapse free survival, BI-EFS: bladder intact event-free survival, DLT: incidence of dose limiting toxicity, DFS: disease free survival.

Table 3
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Written informed consent	Patients with extension to the prostate (cT4), upper urinary tract tumor, and urethral tumor.
• Age >20 years	Patients with hydronephrosis
• Patients who underwent transurethral bladder tumor resection (TURBT) within 90 days prior to enrollment and have been histologically diagnosed with urothelial cancer	Patients with previous autoimmune disease or those who had received therapies targeting CD137, CTLA4, or PD-L1–PD-1,
• cT1-3N0M0 invasive bladder cancer (UICC/AJCC 8th edition) Patients who are unsuitable for radical cystectomy or refused radical cystectomy	Other malignancy within the past 5 year
• For patients with cT1N0M0, at least one of the following (highest risk group T1)	Complete inclusion and exclusion criteria are listed in the protocol
a) Multiple T1 tumors (more than 2)	
b) Remaining T1 lesion on the tissue of 2nd-TUR	
c) T1 tumor with associated CIS	
d) BCG resistant T1 tumor	
e) Recurrent T1 tumor with BCG intolerance	
• For patients with cT2-3N0M0, maximum tumor diameter is 5 cm or less	
• Patients with 0 or 1 Performance Status (PS) (Eastern Cooperative Oncology Group: ECOG)	

2.2. Endpoints

The primary endpoint is progression-free survival (PFS). The primary evaluation analysis is planned to be performed after a 3-year follow-up for all patients. The major secondary endpoint is pathological complete remission (pCR) rates 24 weeks after atezolizumab administration. The pCR rate will be analyzed during the pCR assessment for all patients by the central pathology review. The presence or absence of a complete pathological response is known to affect recurrence and prognosis after chemoradiation for bladder cancer [21]. Other secondary endpoints are recurrence-free-survival (RFS), overall survival (OS), bladder-preservation rate (BPR), and duration of complete remission (CR). Safety is also assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [41].

2.3. Statistical analyses

Primary analysis is using the Kaplan-Meier method to estimate PFS at three years and its 95% confidence interval based on the double log-transformation. We will judge the efficacy when the lower confidence limit exceeds 45%. Secondary analyses are using the Kaplan-Meier method to estimate PFS at one and two years and calculating pCR rate at 24 weeks.

2.4. Sample-size calculation

Based on previously published data, the 3-year OS rate after RC was 64%–70% for stage II, 44%–54% for stage III, and the 3-year PFS rate was 52%–78% [42–44]. In cases of TMT for MIBC, the 3-year OS and PFS rates were 60%–80% and 62%–80%, respectively [14–21]. We therefore hypothesized that, in this study, we expect a 3-year PFS of 70%, and the threshold is set at 45%. Threshold was determined based on the previous results of radiotherapy alone. We determined that the 3-year PFS could be approximated by a 5-year OS because there were no reports of a 3-year PFS with radiotherapy alone, and the median survival of recurrent metastatic urothelial carcinoma is approximately 2 years [45]. With a 5-year OS of 24–40% for radiotherapy alone [27–30], we set the threshold at 45%. A total of 34 patients will yield an 80% success probability for the primary analysis (95% lower confidence limit exceeds 45%). To compensate for ineligible patients and lost follow-up mainly due to an elderly population, the target number of patients is set at 45.

2.5. Protocol treatment

Patients will first receive RT combined with intravenous atezolizumab (1200 mg/body) administered every 21 days and repeated at 8 cycles. In terms of RT, a total irradiation dose of 41.4 Gy in 23 daily fractions will be given to the small pelvis and 16.2 Gy in 9 daily fractions to the whole bladder. We selected the small pelvic irradiation because the probability of lymph node metastasis is 10–40% in stages II–III [46,47] and to be comparable with the past clinical trials to evaluate safety and efficacy [21]. Patients will undergo response assessments using CT imaging and cystoscopy at baseline and every 12 weeks for 12 months thereafter until disease progression, withdrawal of consent, or death, and pathological evaluation by a central independent facility is planned using TUR biopsy as an interim evaluation at 24 weeks for tumor control. Patients without recurrence or progression at interim evaluation will continue to receive an additional 7 cycles of atezolizumab every 21 days until unacceptable toxicity or progression of the disease.

3. Discussion

RC is the golden standard for highest-risk NMIBC and MIBC, but TMT is considered to be as attractive a method as BPT. Although there is no randomized controlled trial comparing the results of RC with TMT, the evidence suggest that TMT has successfully provided comparable outcomes to RC over the past decades in some populations [48]. In contrast, a large number of patients who are either elderly or have impaired renal function are unable to receive cisplatin-based systemic chemotherapy in actual clinical practice. Hence, the present study is designed to investigate the safety and efficacy of RT combined with atezolizumab, an immune checkpoint inhibitor, for highest-risk clinical T1 NMIBC and T2-3 MIBC patients who are unfit for or refuse RC. The study is not considered to be a randomized trial comparing conventional TMT with utilizing cisplatin due to the nature of the target patients. For these reasons, this study was conducted as an open-label phase II study.

The primary rationale for combining atezolizumab and RT in this patient group is twofold. First, atezolizumab generally seems to be safe and well-tolerated even in patients who are ineligible for systemic chemotherapy such as cisplatin because of their comorbidities [40].

Second, combining RT and immune checkpoint inhibitors is expected to induce a synergistic abscopal effect, which can cause tumor regression at not only the irradiated field but also out of the irradiated field.

For these reasons, the results of this study will provide a new treatment option of BPT for bladder cancer patients who are ineligible for the standard TMT by CCRT using cisplatin-based chemotherapy.

Ethics approval

The institutional review board of the University of Tsukuba Hospital (Approval #I-29).

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Declaration of competing interest

Dr. Nishiyama reports personal fees and other support from Chugai Pharmaceutical Co Ltd, during the conduct of the study. Dr. Kimura reports other support from Chugai Pharmaceutical Co Ltd, during the conduct of the study. Dr. Tsuzuki reports honoraria and non-financial support from Chugai, honoraria from AstraZeneca, Nippon Kayaku, Takeda, Janssen, Astellas, Pfizer, Novartis, Bayer, Ono, and Bristol Myers Squibb. The other authors declare that they have no competing interests.

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