

# BMJ Open Combination of pembrolizumab and BCG treatment after endoscopic ablation of high-risk superficial upper urinary tract urothelial carcinoma in patients not candidates for radical nephroureterectomy: protocol for phase-II study

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## ABSTRACT

**Introduction** The treatment standard for high-risk upper urinary tract urothelial carcinoma (UUTUC) is radical nephroureterectomy. However, some patients may be unfit or unwilling, and in such patients the available alternatives are suboptimal. Therapies targeting the programmed death (PD) pathway have shown promise in urothelial carcinoma (UC). We designed the current study to determine the safety and efficacy of administering MK-3475 (a monoclonal antibody targeting interaction between PD-1 and its ligand) in combination with bacillus Calmette-Guerin (BCG) in high-risk non-muscle invasive UUTUC patients.

**Methods** This represents a single-centre phase-II efficacy study of MK-3475 therapy in combination with BCG for subjects, 18 years of age or older, with pathologically documented non-muscle invasive high-risk UUTUC unfit or unwilling to be treated with radical nephroureterectomy. Twenty subjects will be enrolled; patients will receive treatment with 200 mg of MK-3475 every 21 days, starting 2 weeks from the initial endoscopic resection and continuing for 6 weeks after the final dose of BCG. The primary objective is to determine the safety and efficacy of administering MK-3475 at a fixed dose of 200 mg every 3 weeks in conjunction with intrapelvic BCG. Secondary objectives include 19 week and the 3, 12 and 24-month post-treatment completion complete response and progression-free rate assessments.

**Ethics and dissemination** The study has been approved by the Institutional Review Board of the Henry Ford Hospital. The results of this study will be published in a peer-reviewed journal and presented at a scientific conference.

**Trial registration number** NCT03345134

## INTRODUCTION

Upper urinary tract urothelial carcinomas (UUTUCs) account for approximately 5% of urothelial malignancies and 5%–10% of renal cancers.<sup>1</sup> The treatment standard for high-risk UUTUC is radical nephroureterectomy.

## Strengths and limitations of this study

- One of the first clinical trials to assess the safety and efficacy of programmed death (PD)-1 inhibitors in combination with bacillus Calmette-Guerin (BCG) for subjects with non-muscle invasive high-risk upper urinary tract urothelial carcinoma (UUTUC) after endoscopic ablation.
- Study provides extensive follow-up and multiple objective measures assessing the safety and efficacy of PD-1 inhibitors.
- This study is non-randomised and unblinded with long-term enrolment and frequent clinical obligations may result in failure in the retention of subjects.
- Small sample size given rarity of disease and patient eligibility criteria.
- In the present study, accurate staging of non-muscle invasive UUTUC is solely dependent on endoscopic biopsy, which has been previously shown to result in understaging when compared with final pathology.

However, several patients with this disease have multiple comorbidities and are unfit for surgery, while others are unwilling to have such a radical surgery performed, especially when faced with a real risk of dialysis in the setting of bilateral tumours, tumour in a solitary kidney (congenital or after nephrectomy for a prior malignancy) or baseline renal insufficiency.

Endoscopic treatment is an alternative to radical nephroureterectomy. Patients that are candidates for endoscopic management of high-risk disease have been extensively studied, and the eligibility criteria include lesions that are papillary and superficial, completely visualised and <2 cm in diameter with no computed tomographic evidence of parenchymal

invasion.<sup>2</sup> Further, in efforts to decrease recurrence, adjuvant bacillus Calmette-Guerin (BCG) treatment has been used.<sup>3-5</sup> Unfortunately, more than 50% of patients recur by 5 years.<sup>2,3</sup> Hence, identification of new agents active in this disease is warranted.

The blockade of immune checkpoint pathway involving programmed death 1 (PD-1) receptor and its ligands, CD274 (PD-L1) and CD273 (PD-L2), has been recently shown to be effective in cancer therapy including for UC.<sup>6,7</sup> Furthermore, the treatment effect of PD-1 blockade may be exaggerated in UUTUC due the high prevalence of mismatch repair defects in these tumours.<sup>8,9</sup> We hypothesise that a combination of pembrolizumab and BCG following endoscopic treatment of high-risk UUTUC may be effective in improving outcomes of UUTUC after endoscopic treatment in patients unfit or unwilling to be treated with radical nephroureterectomy. The aim of this study is to determine the safety and response of administering MK-3475 (a monoclonal antibody designed to block the interaction between PD-1 and its ligand) in conjunction with BCG treatment in high-risk non-muscle invasive UUTUC patients. In this paper, we report the treatment protocol for the study.

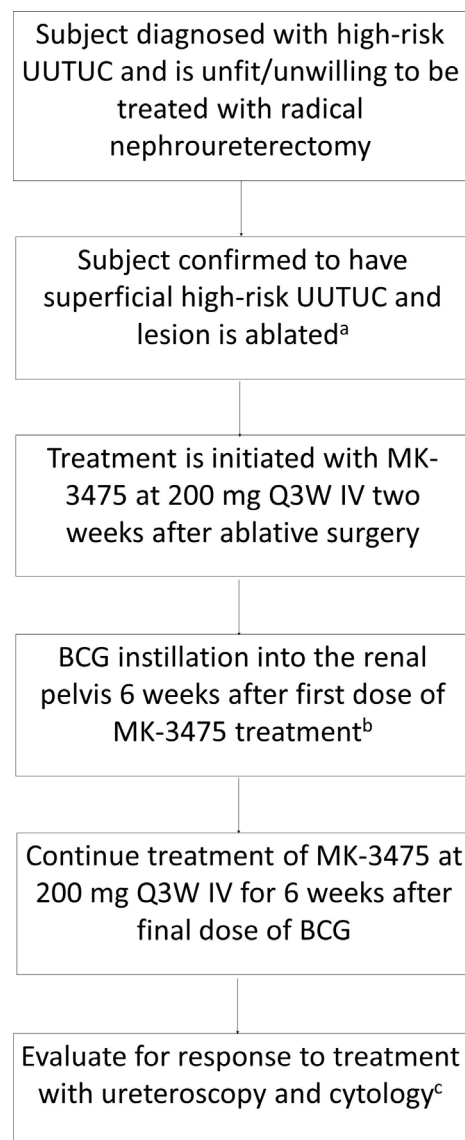
## METHODS AND ANALYSIS

### Rationale

PD-1 is an inhibitory cell-surface receptor that can be stimulated to be expressed on T cells, B cells, natural killer T cells, monocytes and dendritic cells (DCs).<sup>10</sup> PDL-1 is widely expressed by hematopoietic, non-hematopoietic and tumour cells, whereas PDL-2 is expressed mainly by DCs and macrophages.<sup>10,11</sup> Higher expression of PDL-1 in cancers is associated with poor survival as tumours can evade the immune system by stimulating PD-1.<sup>12-14</sup> Clinical trials with antibodies targeting PD-1 and PDL-1 have shown promising results in advanced cancers. In a study presented at the 2014 annual meeting of the American Society of Clinical Oncology, humanised monoclonal IgG4 anti-PD-1 antibody MK-3475 was administered to a non-randomised Cohort of 411 ipilimumab-naïve (IPI-N) and IPI-treated (IPI-T) melanoma patients. The authors observed that among the 365 patients with measurable disease at baseline, an overall response rate by response evaluation criteria in solid tumors (RECIST) criteria was 40% (95% CI 32% to 48%) in IPI-N and 28% (95% CI 22% to 35%) in IPI-T patients, and that the responses were durable. Median progression free survival by RECIST criteria was 24 weeks in IPI-N and 23 weeks in IPI-T patients and median overall survival (OS) was not reached, with 1 year OS of 71% in all patients. The authors then concluded that MK-3475 showed durable responses and a manageable safety profile across dose and schedules in IPI-N and IPI-T melanoma patients (<http://meetinglibrary.asco.org/content/133842-144>).

PDL-1 expression, a marker for response to anti-PD-1 agents, is observed in 7% of pTa, 16% of pT1 and 45% of carcinoma in situ (CIS) urothelial tumours.<sup>15</sup> PDL-1 expression in these tumours is also associated with high-grade disease. In addition, PDL-1 expression is found to

be extremely abundant in the BCG-induced transitional epithelium granulomata in patients failing BCG treatment.<sup>15</sup> Furthermore, as noted above, UUTUCs have aberrations in DNA mismatch repair genes that are detectable as microsatellite instability ((MSI); in about 45%).<sup>8</sup> This is important because pembrolizumab has been shown previously to have increased activity in tumours with mismatch repair deficiency. Le *et al* conducted a phase-II study to evaluate the clinical activity of pembrolizumab in 41 patients with progressive metastatic carcinoma with or without mismatch-repair deficiency. The authors then found that the immune-related objective response rate and immune-related progression-free survival rate were 40% (4 of 10 patients) and 78% (7 of 9 patients), respectively, for mismatch repair-deficient colorectal cancers and 0% (0



**Figure 1** <sup>a</sup>Ablation may be performed in an antegrade or retrograde fashion. <sup>b</sup>Six weekly doses of BCG in total. <sup>c</sup>Patients with suspicious lesions, or positive cytology, will be evaluated with renal pelvis biopsy under general anaesthesia. BCG, bacillus Calmette-Guerin; UUTUC, upperurinary tract urothelial carcinoma.

of 18 patients) and 11% (2 of 18 patients) for mismatch repair-proficient colorectal cancers.<sup>9</sup> Based on these data, a combination of pembrolizumab with BCG may be effective in preventing recurrence of UUTUC after endoscopic treatment.

### Trial blinding

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

### Study design

This is a single centre phase-II efficacy study of MK-3475 therapy used in combination with renal pelvis infused BCG treatment for subjects, 18 years or older, with pathologically documented high-risk superficial UUTUC unfit or unwilling to be treated with radical nephroureterectomy. Subjects will have confirmation of UUTUC non-invasive to the muscle. Approximately 30 subjects will be screened to treat 20 eligible subjects. Subjects will be enrolled to a single treatment group of a fixed dose of MK 3475 and BCG (figure 1). Patients to undergo regular follow-up including applicable labs, in addition to post-treatment ureteroscopy with clinically indicated biopsy to assess recurrence (figure 2).

### Trial schedule

Trial schedule (figure 2) summarises the trial procedures to be performed at each visit. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary by the sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C and so on), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

### Patient selection

Subjects, who meet required inclusion and exclusion criteria are eligible for enrolment into the study (figures 3 and 4).

### Patient and public involvement

Patient and public were not involved in the design, recruitment and conduction of the present study. Results of the study will be disseminated to the study participants on request. Patient advisors were not used in the conduction of this study.

### Trial treatment dosage, formulation, preparation and frequency

#### Bacillus Calmette-Guerin

The rationale for the use of the indicated dose of BC is based on Food and Drug Administration (FDA) approved and commercially provided product. Dosing for the intraluminal treatment of CIS and for the prophylaxis of recurrent papillary tumours consists of one vial of BCG suspended in

50 mL preservative-free saline. The preparation of the BCG suspension will be completed using aseptic technique and according to FDA approved labelling and use information. Patients may have treatment with more than one vial to ensure treatment of all tumour sites. BCG treatment will be administered beginning on day 1 of cycle 3 (week 7) of MK-3475 after all procedures/assessments have been completed as detailed on the trial flowchart. BCG treatment will be repeated every 7 days at weeks 8–12. BCG treatment may be administered up to 1 day before or after the scheduled date (at 7 days) due to administrative reasons. All trial treatments will be administered on an outpatient basis and according to institutional standards. BCG dose modification has been shown to reduce efficacy; therefore, no dose modifications will be attempted in this trial. The dose, frequency, route of administration and duration are summarised in figure 5.

BCG treatment will be withheld for grade two hematuria, grade one fever and drug-related grade four hematologic toxicities, and all other non-haematological toxicity grade  $\geq 3$  adverse effects including laboratory abnormalities and severe or life-threatening AEs. Treatment will be postponed until resolution of febrile illness, urinary tract infection or gross hematuria and adverse effect resolution to grade  $< 1$ . In the event of a grade 1 or 2 immune-related adverse event requiring corticosteroid treatment, BCG treatment may be delayed for up to 2 weeks with the expectation that steroid treatment will be discontinued prior to the next BCG treatment cycle. A delay of longer than 2 weeks will permanently discontinue the patient from BCG treatment within the study or permanent withdrawal of the patient from the study. The choice will be at the discretion of the treating investigator. Steroid treatment for grade three or higher immune mediated events will require discontinuation of BCG treatment and/or withdrawal from the study.

### MK-3475

The dose regimen of 200 mg Q3W (every 3 weeks) of MK-3475 is planned for all urothelial cancer trials. Trial treatment will be administered on day 1 of each cycle after all procedures/assessments have been completed as detailed on the trial flowchart. Trial treatment may be administered up to 3 days before or after the scheduled day 1 of each cycle reasons secondary to administration. Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic aetiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs. Known and theoretical risks of MK-3475 are documented within the original study protocol and management of said risks and AE's is also noted within the original study protocol.

### Objectives

#### Primary objective

To determine safety and efficacy of administering MK-3475 at a fixed dose of 200 mg every 3 weeks in

Clinical Procedures/ Assessments															
Treatment Week/ Title	Main Study screen <sup>a</sup>	1	4	7	8	9	10	11	12	13	16	19	Discontinuation <sup>b</sup>	Safety FU <sup>c</sup> 20	Follow-Up Visit <sup>d</sup>
Scheduling Window (Days)	-28 to -1	+/- 3	+/- 3	+/- 1	+/- 1	+/- 1	+/- 1	+/- 1	+/- 1	+/- 3	+/- 3	+/- 3	At time of Discontinuation	30 days Post discontinuation	3, 6, 9, 12, 18, 24 Post cyst
Complete endoscopic ablation of the UUT/TC lesion with repeat biopsy to confirm no muscle invasion <sup>e</sup>	X														
Review Adverse Events <sup>f</sup>	X	X													
Physical Exam <sup>g</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance Status <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG <sup>i</sup>	X														
Chest X-Ray <sup>j</sup>	X <sup>k</sup>														
Pulmonary Function Tests	X														
Laboratory Procedures/ Assessments: Analysis provided by Local Laboratory															
CBC w/ differential	X	X <sup>l</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
CMP	X	X <sup>l</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
T3, FT4, and TSH	X		X										X	X	
Pregnancy Test ( urine or sBhCG)	X														
PT/INR and aPTT <sup>m</sup> - As clinically indicated	X												X		
Hepatic Panel	X														

Trial Period	Screening Phase	Treatment Week/Cycle												End of Treatment	Post Treatment	
Treatment Week/ Title	Main Study screen <sup>a</sup>	1	4	7 <sup>n</sup>	8 <sup>n</sup>	9 <sup>n</sup>	10 <sup>n</sup>	11 <sup>n</sup>	12 <sup>n</sup>	13 <sup>n</sup>	16 <sup>n</sup>	19	Discontinuation <sup>b</sup>	Safety FU <sup>c</sup> 20	Follow-Up Visit <sup>d</sup>	
Scheduling Window (Days)	-28 to -1	+/- 3	+/- 3	+/- 1	+/- 1	+/- 1	+/- 1	+/- 1	+/- 1	+/- 3	+/- 3	+/- 3	At time of Discontinuation	30 days Post discontinuation	3, 6, 9, 12, 18, 24 Post cyst	
Administrative Procedures																
Informed Consent	X															
Inclusion/ Exclusion Criteria	X															
Subject Identification card <sup>e</sup>	X															
Demographics and Medical History prior and concomitant medication Review <sup>f</sup>	X	X														
Post-study anticancer therapy and recurrence status <sup>g</sup>													X		X	
Recurrence status <sup>g</sup>				X	X	X	X	X	X	X			X		X	
Phone Call <sup>h</sup>				X	X	X	X	X	X							

Trial Period	Screening Phase	Treatment Week/Cycle												End of Treatment	Post Treatment	
Treatment Week/ Title	Main Study screen <sup>a</sup>	1	4	7	8	9	10	11	12	13	16	19	Discontinuation <sup>b</sup>	Safety FU <sup>c</sup> 20	Follow-Up Visit <sup>d</sup>	
Scheduling Window (Days)	-28 to -1	+/- 3	+/- 3	+/- 1	+/- 1	+/- 1	+/- 1	+/- 1	+/- 1	+/- 3	+/- 3	+/- 3	At time of Discontinuation	30 days Post discontinuation	3, 6, 9, 12, 18, 24 Post cyst	
Study Treatment																
BCG		X	X	X	X	X	X	X	X	X	X	X				
MK 3475		X	X	X	X	X	X	X	X	X	X	X				
Efficacy Measurements																
Ureteroscopy <sup>i</sup>	X												X		X	
Biopsy if clinically indicated <sup>j</sup>	X												X		X	
Tumor Biopsies/ Archival Tissue Collection/ Correlative Studies Blood																
Specimen Collection <sup>k</sup>	X	X <sup>l</sup>	X	X	X	X	X	X	X	X	X	X	X		X <sup>o</sup>	

**Figure 2** <sup>a</sup>Main study screen visit: subjects who appear eligible will be consented with a main study consent allowing for all study screening and treatment procedures. Screening visit laboratory procedures may be used for day 1 cycle 1 if completed within 10 days of day 1 cycle 1. <sup>b</sup>Discontinuation visit: all subjects who discontinue treatment early for any reason should undergo all procedures listed in the flow chart for discontinuation visit. If a subject has completed all study treatment, the subject should complete the 30-day follow-up visit procedures listed in the flow chart. <sup>c</sup>Follow-up visits should occur at approximately 3, 6, 9, 12, 18 and 24 months from week 19 ureteroscopy. A 2-week window before and after the specified date is allowable to meet the timelines listed. Subject will complete final set of Questionnaires at the 3-month visit. Complete response follow-up information may be collected via medical record and document review only. However, patient contact via phone or in person may occur if information is not available via chart review. <sup>d</sup>Subject Identification card may be given at any time after main study informed consent has occurred and prior to treatment on day 1 cycle 1. <sup>e</sup>Prior and concomitant medications will include any medications taken within the 28 days prior to main study consent and through the safety visit and will include prescribed, over-the-counter and herbal/alternative remedies. <sup>f</sup>Post-study treatment anticancer therapy and recurrence status may be collected through follow-up chart review. <sup>g</sup>To monitor for systemic dissemination of BCG infection, daily phone calls of days 2–4 of each cycle of BCG treatment (weeks 7–12) will occur to monitor for fever and symptoms of systemic infection. Subjects will each be given an oral thermometer and a diary to record oral temperature twice daily (morning and evening) and to record any symptoms they may be having. The diary will be utilised days 1–7 for each of the six BCG cycles (weeks 7–12). <sup>h</sup>Transurethral resections: all TURBT will occur as part of SOC and as clinically indicated. For the purposes of entry into this study, the screening window for endoscopic ablation with repeat biopsy will be within 90 days of day 1. <sup>i</sup>Adverse events will be collected from the time of main study informed consent through 30 days post last study drug infusion/treatment. <sup>j</sup>Physical exam: full physical exams are required at screening and at the 30-day follow-up. All other exams may be symptom directed. <sup>k</sup>Performance status: ECOG performance status scale should be used. <sup>l</sup>ECG, chest X-ray and pulmonary function tests will be completed prior to day 1 cycle 1 and will only be repeated as clinically indicated. <sup>m</sup>PT/INR and aPTT will be completed prior to all resections/possibly biopsies as standard of care. All other monitoring of PT/INR and aPTT will be completed as clinically indicated (ie, if on Coumadin). <sup>n</sup>Ureteroscopy will be performed as standard of care but will be considered measures for efficacy. Biopsy will be performed as clinically indicated. <sup>o</sup>Specimen collection/correlative studies: whole blood, serum and urine will be collected at the time of screening consent/main study consent (only one collection at either time point) as well as each visit through week 19 repeat ureteroscopy (12 visits). Saliva will be collected only at baseline. Tumour tissue will only be collected at baseline and at week 19 biopsy if a biopsy is clinically indicated at the time of ureteroscopy. Specimen collection is requested at the 3, 6, 9, 12, 18, and 24-month follow-up visits if the subject is being treated locally at the site. Tissue will only be collected if a biopsy is clinically indicated at the time of ureteroscopy. <sup>p</sup>Chest X-rays performed in the 90 days' window prior to the screening visit are acceptable. <sup>q</sup>CBC, CMP and correlative labs do not need to be repeated on day 1 cycle 1 if they were completed within 10 days prior to day 1 cycle 1 during screening. aPTT, activated partial thrombin time; BCG, bacillus Calmette-Guerin; CB, complete blood count; CMP, comprehensive metabolic panel; ECOG, Eastern Cooperative oncology Group; HCG, Human chorionic gonadotrophin; INR, International Normalization Ratio; PT, Prothrombin time; SOC, standard of care; TURBT, Transurethral resection of bladder tumor; TSH, Thyroid stimulating hormone; UUTUC, upper urinary tract urothelial carcinoma.

1. Be willing and able to provide written informed consent
2. Be > 18 years of age on day of signing informed consent.
3. Have pathologically documented high grade UUTUC (CIS, Ta, T1) that could be completely ablated with ureteroscopy or through antegrade percutaneous access. <sup>a,b</sup>
4. Subject must be unwilling or unfit to undergo treatment with radical nephroureterectomy.
5. Have a performance status of 0-1 on the ECOG Performance Scale
6. Demonstrate adequate organ function. All screening labs are to be performed within 28 days of treatment initiation.
7. Female subjects of childbearing potential are to have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of the study medication. <sup>c</sup>
8. Female subjects of childbearing potential should be willing to use 2 methods of birth control or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medications. <sup>d</sup>
9. Male subjects should agree to use an adequate method of contraception starting the first dose of the study therapy through 120 days after the last dose of the study therapy.
10. Patients whom have received prior systemic chemotherapy, targeted small molecule therapy, or radiation therapy for UUTUC are allowed into the study under the condition that there is confirmed recurrence of the disease after previous treatment and the patient is unwilling or unfit to undergo radical surgery.

**Figure 3** <sup>a</sup>All pathology specimens used for enrolment are required to be read by the research site pathology laboratory.

<sup>b</sup>Patients are to have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumour lesion. Tissue must be obtained from the most recent upper urinary tract biopsy. However, in patients with small tumours or carcinoma in situ of the upper urinary tract, and considering the difficulty of obtaining sufficient tissue for testing beyond pathologic diagnosis, not providing this tissue is not going to exclude the patient from the study. <sup>c</sup>If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. <sup>d</sup>Subjects of childbearing potential are those who have not been surgically sterilised or have not been free from menses for >1 year. CIS, carcinoma in situ; ECOG, Eastern Cooperative Oncology Group; UUTUC, upper urinary tract urothelial carcinoma.

conjunction with intrapelvic BCG in high-risk superficial UUTUC patients, who are unfit or unwilling to be treated with radical nephroureterectomy.

### Secondary objective

To determine the 19-week and the 3-month, 12-month and 24-month post-treatment completion complete response rate and progression-free rate with combined

MK-3475 and intrapelvic BCG therapy for non-muscle invasive high-risk UUTUC for patients unfit or unwilling to be treated with radical nephroureterectomy.

### Exploratory objectives

Three objectives: to examine pre- and post-treatment (MK-3475/BCG) renal pelvis biopsy specimens for PD-1, PD-L1 and CD3; to examine whole exome sequencing

1. Active or progressive metastatic disease. <sup>a</sup>
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Has had a prior monoclonal antibody within 4 weeks before study day 1 or who has not recovered (i.e. Grade 1 or greater at baseline) from adverse events due to agents administered more than 4 weeks earlier.
4. Has had prior systemic chemotherapy, targeted small molecule therapy, or radiation therapy for UUTUC.
5. If subject has undergone major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
6. Has a known additional malignancy that is progressing or requires active treatment. <sup>b</sup>
7. Active autoimmune disease that had required systemic treatment in the past 2 years. <sup>c</sup>
8. Has history of (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease, or active, non-infectious pneumonitis.
9. Has an active infection, including a concurrent febrile illness, requiring systemic therapy.
10. Has a history or current evidence of any condition, therapy, or laboratory abnormality. <sup>d</sup>
11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 4 months after the last dose of trial treatment.
13. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) including anti-CD40 and anti-OX40 antibodies
14. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), Hepatitis B (e.g., AHBs Ag reactive) or Hepatitis C (e.g., HCV RNA)
15. Has known active tuberculosis. <sup>e</sup>
16. Has received a live vaccine in the last 30 days.
17. Has an active UTI, gross hematuria, or known broken mucosal barrier of the renal pelvis.
18. Less than 14 days post renal pelvis biopsy, TUR or traumatic catheterization
19. Evidence of muscle invasive renal pelvis cancer or TCC of the upper urinary tract.

**Figure 4** <sup>a</sup>Chest X-ray, CT urogram or MRI, and urogram are allowed to ascertain the superficial nature of the disease when indicated, but not required. If urogram protocol is not available or contrast allergy/poor renal function precludes such imaging, then non-contrast CT or MRI of the abdomen/pelvis within 90 days of study entry will suffice. <sup>b</sup>Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, localised prostate cancer with no recurrence after curative surgery or radiation, or in situ cervical cancer that has undergone potentially curative therapy. Lower urinary tract transitional cell carcinoma is also allowable on study as high-risk transitional cell carcinoma is commonly multifocal, and intraluminal BCG therapy is also used for treatment of lower urinary tract lesions in a manner similar to that of UUTUC. <sup>c</sup>Use of disease modifying agents, corticosteroids or immunosuppressive drugs. replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency and so on) is not considered a form of systemic treatment. <sup>d</sup>This includes anything that may confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator. <sup>e</sup>Subjects will not be specifically tested for the study; however, subjects that are tested within 28 days of beginning study or while on study and test positive with the PPD test before treatment should have active tuberculosis ruled out before therapy begins for their superficial renal pelvis cancer. BCG, bacillus Calmette-Guerin; PPD, purified protein derivative; TCC, transitional cell carcinoma; TUR, transurethral resection; UUTUC; upper urinary tract urothelial carcinoma.

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-3475 <sup>a</sup>	200 mg	Every 21 days	IV infusion	6 cycles	Experimental
TICE <sup>b</sup> BCG <sup>b</sup>	1 vial	Every 7 days	Renal Pelvis Instillation	6 cycles	Approved

**Figure 5** <sup>a</sup>MK-3475 dosing interval may be increased due to toxicity as is described in the dose modification and adverse effects section. BCG treatment may be interrupted or delayed as per the dose modification and adverse effects section. <sup>b</sup>BCG: one vial of TICE BCG suspended in 50 mL preservative-free saline. BCG is to be given through a urinary catheter into the renal pelvis either retrograde or antegrade through a nephrostomy tube. BCG treatment will occur once per week for 6 weeks. BCG treatment will commence on the third cycle of treatment with MK-3475, week 7. BCG is an FDA-approved treatment and will be supplied commercially through the study site pharmacy. The preparation of the BCG suspension will be completed using aseptic technique and according to FDA-approved labelling and use information. Patients may have treatment with more than one vial to ensure treatment of all tumour sites. additional lesions in patients with multi-focal disease will be treated per intuitional standard and directed by the treating urologist. BCG, bacillus Calmette-Guerin; FDA, Food and Drug Administration.

of subjects' germline DNA and formalin fixed, paraffin embedded tissue. With analysis of the correlation of mutations to treatment outcomes; analysis of blood and urine specimens from enrollees for potential development of blood and urine assays for determination of response to treatment.

### Adverse effects

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the detailed trial schedule and more frequently, if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE V.4.0. Toxicities will be characterised in terms regarding seriousness, causality, toxicity grading and action taken with regard to trial treatment. AEs will be recorded from the time the subject signs the consent through 30 days post the last study treatment. All AEs of unknown aetiology associated with MK-3475 exposure should be evaluated to determine if it is possibly an event of clinical interest of a potentially immunologic aetiology (irAE).

All known and theoretical risks and adverse effects of BCG and MK-3475 are documented within the original study protocol for reference. Potential adverse effects and risks are to be monitored for during each mandatory clinical visit. All of the known and theoretical risks and adverse effects of BCG and MK-3475 are to be managed by the investigational team and all other necessary support staff. Management of the aforementioned risks and AEs is documented within the original study protocol.

### Statistical measures and analysis

This protocol aims at assessing the activity of one treatment arm, BCG in combination with pembrolizumab after endoscopic ablation in patients with UUTUC. We

would like to detect an activity which is at least 25% greater than that of historical controls (50%) from case series of BCG only treatment.

Sample size calculation for this protocol is based on the work by Kahn *et al*<sup>16</sup> (2012). Using a one-stage design, 20 patients will be enrolled in this study. If 14 or more patients respond then the trial will stop. This design has 78.8% power to determine at the end whether the experimental arm is better than the historical control with a 1-sided type I error rate of 0.057. This design was selected because UUTUC is a rare disease, and we are willing to minimally sacrifice power to reach a sample size that could be achieved within the suggested study period and resources. Patient-related data will be collected and transferred to an excel spreadsheet for statistical analysis. SAS V.9.4 will be used for all data analysis. Descriptive statistics will be computed for all study variables. Continuous variables will be described with measures of central tendency (mean, median) and dispersion (range, SD). Categorical variables will be summarised as frequencies and percentages. Some examples include tumour stage (Ta, T1, CIS), age, Eastern Oncology Cooperative Group (ECOG) performance Scale (0, 1, 2), sex and the use of tobacco and alcohol.

For the primary objective, the proportion of patients with each AE will be reported along with the NCI CTCAE grade of the AE (V.4.0). The Quality of Life Questionnaire, which includes one question with seven categorical responses, will be described with frequencies and percentages. The American Urologic Association Symptoms Index Questionnaire, which includes seven questions each with a numerical score between 0 and 5 as well as a final numerical sum of all responses, will be described with measures of central tendency and dispersion. Due to the questionnaires being given at three time points (pretreatment, midtreatment and post-treatment), the responses may be analysed to look for longitudinal effects over time for specific variables of interest with repeated measures analysis of variance (ANOVA) to evaluate changes and control for individual differences (although this would be very low power due to n=15).

For the secondary objective, subjects will be assessed at 19 weeks, 3 months, 12 months and 24 months post-treatment completion for complete response. The outcome endpoint will be complete response status at 19 weeks, 3 months, 12 months and 24 months post-treatment to measure complete response, recorded as yes or no and summarised as proportions and a percent.

For the exploratory objectives, Pearson or Spearman's rank correlation coefficient will be used to estimate correlations between expression level change and treatment outcome, as well as the correlations between mutation presence and treatment outcome.

### ETHICS, CONFIDENTIALITY AND REGULATORY DETAILS

The investigator and sponsor of the study will adhere to all applicable data privacy and confidentiality laws and regulations (ie, health information portability and protection

act (HIPAA)). Those applicable include institutional, state and Federal Law. It is the responsibility of the investigator and sponsor to ensure the subject data as well as sensitive study information is handled according to applicable guidelines and laws. Appropriate authorisation and consent for use, disclosure or transfer of protected health information must be obtained.

Subject names will not be recorded on the case report form (CRF). Only the subject number and subject's initials will be recorded, where permitted. If the subject's name appears on any other document (eg, pathology report), it must be obliterated on the copy of the document as appropriate. Study data stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor or its designee, IRB and regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

Qualified staff of the Sponsor will monitor the study according to a pre-arranged monitoring plan. Monitoring of the study will include:

- ▶ Evaluation of study progress.
- ▶ Verification of CRF accuracy and completeness.
- ▶ Resolution of inconsistencies in study records.
- ▶ Assurance of protocol requirements and investigator's obligations are fulfilled.
- ▶ Assurance of compliance with applicable laws and regulations.

Study monitors will periodically review all CRFs and supporting source documentation of participating subjects. The CRFs and supporting documentation must remain up to date and available to the study monitor as arranged. CRF data entry will be verified to correspond with source documentation (laboratory, imaging, pathology reports and so on) and reviewed for completeness. Data discrepancies will be identified and reported to the investigator and site staff.

Protocol deviations will be identified and recorded on a deviation log.

## DISCUSSION

This open-label, single centre, phase-II, treatment trial intends to investigate the safety and efficacy of MK-3475 in combination with endoscopic ablative surgery and BCG. As previously mentioned, the optimal alternative to management of patients unfit or unwilling to undergo nephroureterectomy remains unknown. This prospective clinical trial attempts to provide a more definitive treatment option for UUTUC. This study uses traditional modalities in the form of endoscopic ablation in conjunction with newly available immunotherapeutic agents. Technical advancement in endoscopic ablative surgical treatment has allowed urological surgeons to provide a less invasive option in the treatment of UUTUC. With the development of progressively smaller and more durable

rigid and flexible ureteroscopes, retrograde endoscopic procedures have become more practical and effective, furthered by the use of different lasers (Ho:YAG and neodymium:YAG [Nd:YAG]). Ho:YAG laser can evaporate, coagulate and resect tumours. These can be used safely since its radiation affects only surface (<0.4mm).<sup>3</sup> The combination of BCG therapy has been shown to decrease recurrence, yet despite its efficacy, recurrence remains relatively high.

The design of the present study will allow the researchers to discern the safety and efficacy of MK-3475 and BCG as a viable option for high-risk superficial UUTUC. It has been well documented that although radical nephroureterectomy provides definitive cancer control in UUTUC, the associated morbidity and mortality continues to remain high. A non-surgical option following BCG-failure is desirable. Various other studies have demonstrated promising results in regards to efficacy of agents such as MK-3475 and its presumed that this trend will continue with increased investigation and utilisation. If the intravesicular combination of MK-3475 and BCG is to yield promising results, it would provide patients with an alternative to nephroureterectomy and potentially change the standard of care.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The study has been approved by the Institutional Review Board of the Henry Ford Hospital and registered at Clinicaltrials.gov (NCT03345134).

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