Eligibility Criteria (see Section 3.0)

Pre-registration:

- See full pre-registration eligibility criteria in Section 3.2
- Histologically confirmed urothelial cancer of the bladder
- Radical cystectomy ≥ 3 weeks, but ≤ 12 weeks prior to pre-registration
- No evidence of residual cancer or metastases after surgery (imaging required prior to registration)
- Available tumor tissue for "central" Signatera testing to be submitted after pre-registration
- No active autoimmune disease or history of autoimmune disease that may recur
- No current or history of pneumonitis or myocarditis
- No known active Hepatitis B or C
- No postoperative/adjuvant systemic therapy or radiation
- No prior treatment with any PD-1 or PD-L1 axis inhibitors.
- Age ≥18 years; Non-pregnant and non-nursing
- ECOG PS 0-2

Registration:

- Radical cystectomy ≤ 18 weeks prior to registration.
- Must have evaluable ctDNA Signatera assay result [i.e., ctDNA(+) or ctDNA(-)] based on test performed as part of "central testing" after pre-registration to A032103.
- All patients must have confirmed disease-free status defined as no measurable disease by RECIST 1.1 within 60 days prior to registration

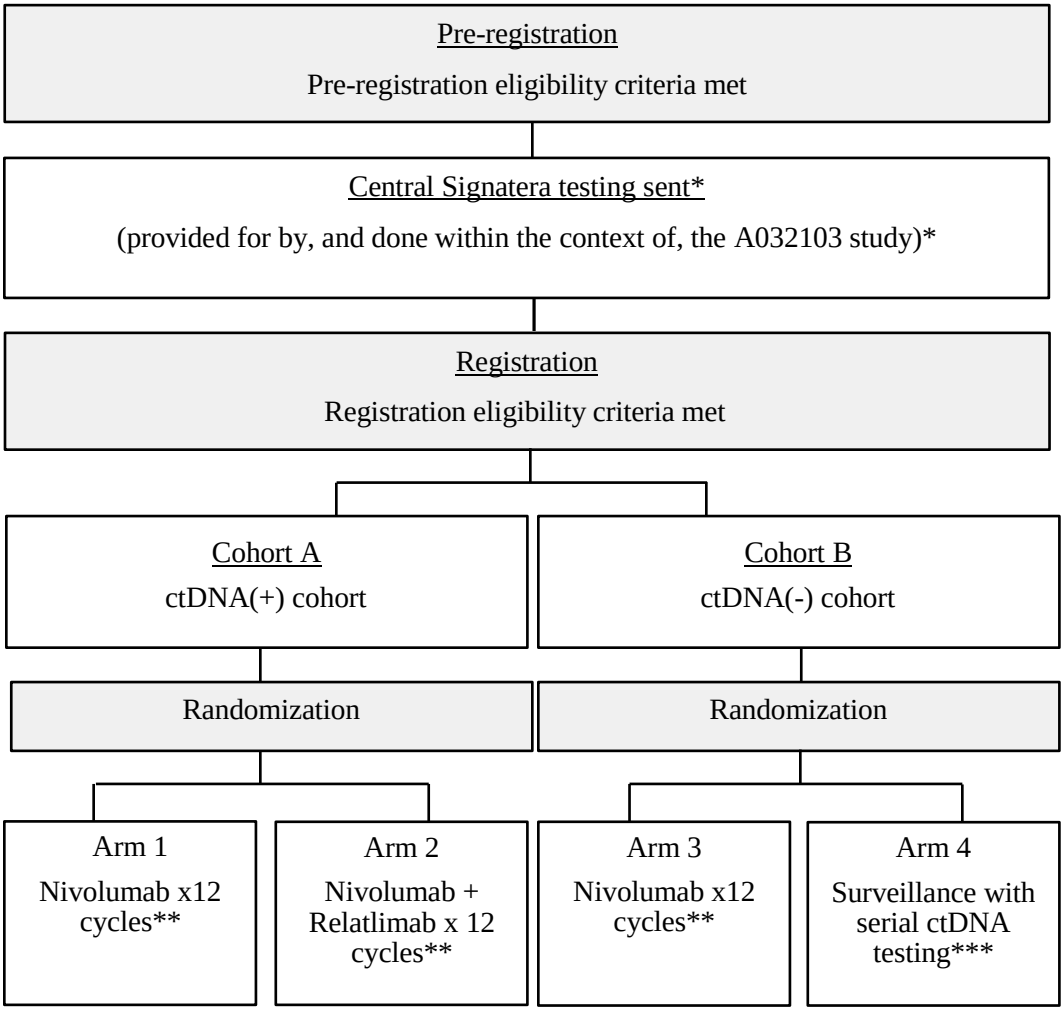
Eligibility Criteria for Cohort B Arm 4 patients initiating nivolumab after conversion of ctDNA assay from ctDNA(-) to ctDNA (+):

- Patient must have converted to ctDNA(+) during serial monitoring performed centrally in the setting of the A032103 study.
- No evidence of metastatic disease on the most recent scheduled imaging assessment as outlined in the study calendar [no repeat imaging is necessary specifically at the time of the conversion from ctDNA(-) to ctDNA(+)].
- No change in clinical condition and/or laboratory tests that would impact the safety of nivolumab in the opinion of the treating investigator.

Required Initial Laboratory Values

ANC	≥ 1200/mm^3
Platelet count:	≥ 100,000/mm^3
Hemoglobin:	≥ 8 g/dL
Creatinine:	≤ 1.5 upper limit of normal (ULN) or
Calc. creatinine Clearance:	≥ 30 mL/ min (using the Cockroft-Gault or either CKD-EPI formula)
Total bilirubin:	≤ 1.5 x ULN (except in patients with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL).
AST/ALT:	≤ 3 x ULN
For women of childbearing potential only:	A negative urine or serum pregnancy test done ≤ 14 days prior to pre-registration is required.

Schema



*Patients who pre-registered based on pT2N0 urothelial cancer with ctDNA(+) Signatera testing based on routine standard testing are only eligible if central testing confirms ctDNA(+) result. Note: This is distinct from patients with ypT2N0 urothelial cancer (i.e., after neoadjuvant chemotherapy) who are eligible with either ctDNA(+) or ctDNA(-) testing.

** 1 cycle = 28 days

***Patients in Cohort B (Arm 4) who develop a ctDNA(+) assay during serial monitoring may be eligible to be re-registered and receive or initiate nivolumab. **A re-registration step is required**.

Treatment is to continue until disease progression or unacceptable adverse event or completion of 12 cycles nivolumab +/- relatlimab. Patients will be followed for 5 years or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

3.1 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.2 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient: for example, medical conditions such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient. Clinicians should use their clinical judgement and have discussions with potential trial participants to assess their ability to follow protocol requirements safely.

Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.3 Pre-registration Eligibility Requirements

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

Please also review registration eligibility (3.3) at the time of reviewing pre-registration eligibility to mitigate any enrollment barriers.

___ 3.2.1 Diagnosis

- Histologically confirmed muscle-invasive urothelial carcinoma of the bladder. Variant histology, including neuroendocrine differentiation, is allowed if urothelial cancer is predominant histology (any amount of squamous differentiation is allowed provided the tumor is not a pure squamous cell cancer).
- Patient must have had radical cystectomy and lymph node dissection $\geq$ 3 weeks, but $\leq$ 12 weeks prior to pre-registration. Patients who have had a partial cystectomy as definitive therapy are not eligible.
- No gross cancer at the surgical margins. Microscopic invasive urothelial carcinoma at the surgical margins (i.e., "positive margins") are allowed. *Carcinoma in situ* (CIS) at margins is considered negative margins.
- No evidence of residual cancer or metastasis after cystectomy (imaging is not required prior to pre-registration but is required prior to registration).

___ **3.2.2 Documentation of Disease:**

- Have undergone a radical cystectomy with pathological evidence of urothelial carcinoma of the bladder at high risk of recurrence as described in one of the two scenarios below (i or ii). The 7th edition of AJCC staging will be utilized.:

  i) Patients who have not received neoadjuvant cisplatin-based chemotherapy: pT3-pT4* or pT0/x-pT4/N+ on cystectomy and are not eligible for adjuvant cisplatin chemotherapy

  Patients ineligible for cisplatin due to at least one of the following criteria and reason for ineligibility should be documented:

  - Creatinine Clearance (using Cockcroft-Gault): < 60 mL/min
  - CTCAE version 5, grade ≥ 2 audiometric hearing loss
  - CTCAE version 5, grade ≥ 2 or above peripheral neuropathy
  - New York Heart Association Class III heart failure
  - Eastern Cooperative Oncology Group (ECOG) performance status = 2

  Patients who are eligible for cisplatin may be candidates if they refuse available adjuvant chemotherapy, despite being informed by the investigator about the treatment options. The patient's refusal must be documented.

  *Patients with pT2N0 urothelial cancer on cystectomy (without prior neoadjuvant chemotherapy) with ctDNA(+) Signatera results based on an assay performed post-cystectomy as part of routine care outside of the study may proceed with pre-registration but require confirmation of ctDNA(+) Signatera testing on repeat "central testing" in the context of A032103 testing. Patients with pT2N0 with central testing not confirming ctDNA(+) will not be eligible for A032103 (Note: this is distinct from patients with ypT2N0 who are eligible based on ii).

  ii) Patients who received cisplatin-based neoadjuvant chemotherapy: ypT2-ypT4 or ypT0/x-pT4/N+ on cystectomy.

___ **3.2.3 Available tumor tissue for central Signatera testing to be submitted after pre-registration.** Central testing is defined as testing performed as part of the A032103 study prior to registration and is provided by the study and not routine standard commercial testing. Patients who have already had Signatera testing performed as part of routine care will require repeat central testing as part of the A032103 study to be eligible for registration/randomization. Tumor tissue from the cystectomy is preferred over tissue from prior transurethral resection.

___ **3.2.4 Age ≥ 18 years**

___ **3.2.5 ECOG Performance Status 0-2**

___ **3.2.6 Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects**

3.2.7 Prior Treatment

- No postoperative/adjuvant systemic therapy after cystectomy
- No adjuvant radiation after cystectomy
- No treatment with any other type of investigational agent ≤ 4 weeks before pre-registration
- Not have ever received prior treatment with PD-1/PD-L1 blockade.
- Not have ever received prior treatment with LAG-3 blockade.

3.2.8 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.2.9 Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC)	≥ 1,200/mm3
Platelet Count	≥ 100,000/mm3
Hemoglobin	≥ 8 g/dL
Creatinine	≤ 1.5 x upper limit of normal (ULN) or
Calc. Creatinine Clearance	> 30 mL/min (using either Cockroft-
AST/ALT	≤ 3 x ULN
Total Bilirubin	≤ 1.5 x upper limit of normal (ULN)
For women of childbearing	A negative urine or serum pregnancy

3.2.10 Comorbid conditions

- Not currently requiring **hemodialysis**.
- No current or prior history of **myocarditis**.
- **No active autoimmune disease** or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome because of the risk of recurrence or exacerbation of disease.
- **Patients with vitiligo, endocrine deficiencies including type I diabetes mellitus, thyroiditis** managed with replacement hormones including physiologic corticosteroids are eligible.
- **Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis** controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.
- No current **pneumonitis** or prior history of non-infectious pneumonitis that required steroids within the previous 5 years.
- **No known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).**
- For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
- **HIV-infected patients** on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible.

3.2.11 Concomitant medications

- No concurrent antineoplastic therapy.
- No current immunosuppressive agents (with the exception of corticosteroids as described below).
- No condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of pre-registration (with the exception of steroid pre-medications for contrast allergies). Inhaled or topical steroids and adrenal replacement doses < 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

3.4 Registration Eligibility Criteria

___ **3.3.1 Patient must have had radical cystectomy and lymph node dissection ≤ 18 weeks prior to registration.**

___ **3.3.2 Must have evaluable ctDNA Signatera assay result [i.e., ctDNA(+) or ctDNA(-)] based on test performed as part of central testing after pre-registration to A032103.** Central testing is defined as testing performed as part of the A032103. Local/commercial testing results may not be used for registration to A032103.

- **Cisplatin-ineligible (or cisplatin-declining) patients with a pT2N0 urothelial cancer on cystectomy who were pre-registered based on routine standard care ctDNA(+) Signatera testing must have confirmed ctDNA(+)** Signatera testing on central testing. If central Signatera testing yields a ctDNA(-) result, these patients are ineligible. NOTE: This is a distinct consideration from patients with ypT2-4 and/or ypN+ urothelial cancer (i.e., patients who had received neoadjuvant cisplatin-based chemotherapy) who are eligible with either ctDNA(+) or ctDNA(-) central Signatera testing.

___ **3.3.3 All patients must have confirmed disease-free status defined as no measurable disease by RECIST 1.1, or definitive non-measurable radiographic metastatic disease, within 60 days prior to registration.** Patients with equivocal nodes less than 15 mm in short axis, or < 10 mm in long axis for non-lymph node lesions, not considered by the investigator to represent malignant disease will be eligible. Attempts should be made to resolve the etiology of equivocal lesions with complementary imaging (e.g., PET scan) or biopsy.

___ **3.3.4 No major surgery ≤ 3 weeks before registration.**

___ **3.3.5 No live vaccine within 30 days prior to registration.** Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette– Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. COVID-19 vaccines are not live vaccines and are allowed.

3.5 Eligibility Criteria for Cohort B Arm 4 patients initiating nivolumab after conversion of ctDNA assay from ctDNA(-) to ctDNA (+)

- Patient must have converted to ctDNA(+) during serial monitoring performed centrally in the setting of the A032103 study.
- No evidence of metastatic disease on the most recent scheduled imaging assessment as outlined in the study calendar [no repeat imaging is necessary specifically at the time of the conversion from ctDNA(-) to ctDNA(+)].
- No change in clinical condition and/or laboratory tests that would impact the safety of nivolumab in the opinion of the treating investigator.
- ≤ 6 weeks from reporting of ctDNA(+) result by Natera.