Official Title: An Open-Label, Multi-Center Trial of INO-5401 + INO-9012 in Combination with Atezolizumab in Subjects with Locally Advanced Unresectable or Metastatic/Recurrent Urothelial Carcinoma.

NCT ID: NCT03502785

Document Date: 01 July 2023

UCa-001

An Open-Label, Multi-Center Trial of INO-5401 + INO-9012 in Combination with Atezolizumab in Subjects with Locally Advanced Unresectable or Metastatic/Recurrent Urothelial Carcinoma

Sponsored by:
Inovio Pharmaceuticals, Inc.

IND #: 17712
EudraCT #: 2018-000309-21

Protocol Version: 3.0

Protocol Version Date: 30 June 2023

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Medical Monitor Approval Page

Drug: INO-5401 + INO-9012
Atezolizumab

Sponsor: Inovio Pharmaceuticals, Inc.
660 W. Germantown Pike, Suite 110
Plymouth Meeting, PA 19462

Medical Monitor: [redacted], MD
[redacted]
Inovio Pharmaceuticals, Inc.

Approval Signature:

(Signed and dated electronically)

[redacted], **MD**
[redacted]
Inovio Pharmaceuticals, Inc.

Date

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PRINCIPAL INVESTIGATOR ACKNOWLEDGEMENT

I have read and understood this Protocol and agree that it contains all details necessary to conduct the clinical trial. I understand that it must be reviewed by the Institutional Review Board (IRB)/Research Ethics Board (REB)/ Ethics Committee (EC) overseeing the conduct of the clinical trial and approved or given favorable opinion before implementation.

The Principal Investigator's (PI's) signature constitutes the PI's approval of this Protocol and provides the necessary assurances that this clinical trial will be conducted in accordance with International Council for Harmonization (ICH)/Good Clinical Practice (GCP), International Organization for Standardization (ISO) guidelines, local legal and regulatory requirements, and all stipulations of the Protocol.

Principal Investigator Signature:

Principal Investigator Printed Name	
Principal Investigator Signature	Date (ddMmmyyyy)

Clinical Trial Site Number: _____

Clinical Trial Site Name: _____

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SUMMARY OF CHANGES

The following are significant protocol changes from version 2.0 dated 23 Jul 2019 to version v3.0 dated 30 Jun 2023. All other changes are administrative and do not significantly affect the safety of subjects, trial scope, or scientific quality of the protocol.

1. Section 7.11 Management of Specific Adverse Events has been updated based on atezolizumab version 19, dated August 2022.

The following is the list of protocol changes from version 1.2 dated 23 January 2018 to version 2 dated 23 July 2019.

1. The sample size of the study has been truncated from 85 subjects to 35 subjects. This is not a result of safety or efficacy data from this study.
2. Enrollment of the study was stopped at 35 subjects (28 subjects enrolled in Cohort A and 7 subjects enrolled in Cohort B). Subsequent study procedures will be limited to administration of study drugs INO-5401 + INO-9012 and Atezolizumab as per prior schedule. Assessments will be limited to standard-of-care assessments (i.e. vital signs, physical exam, safety labs, and urinalysis) only. No further evaluation of efficacy or immunogenicity will be performed. Subjects enrolled in the study will no longer require long-term follow-up for efficacy. The relevant sections of the protocol have been updated to reflect this change.
3. Section 9, Statistical Analysis has been updated based on the enrollment of 35 subjects.
4. Protocol sections related to treatment after initial progression have been removed as a confirmatory scan will not be required, and the decision to continue study treatment will be at the investigator's discretion.
5. Section 5 has been updated to provide clarification with regards to returning of investigational device.
6. Safety follow-up for Serious Adverse Events (SAE) and Adverse Event of Special Interest (AESI) has been reduced from 90 days to 30 days post-last dose of study drug, consistent with other clinical programs.
7. Several administrative changes have been made throughout (e.g, Medical Monitor information updated).
8. Grammatical errors have been corrected throughout.

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CLINICAL PROTOCOL SYNOPSIS

Protocol Title: An Open-Label, Multi-Center Trial of INO-5401 + INO-9012 in Combination with Atezolizumab in Subjects with Locally Advanced Unresectable or Metastatic/Recurrent Urothelial Carcinoma (UCa)

Protocol Number: UCa-001

Trial Phase: I/IIA

Estimated Number of Trial Centers and Countries/Regions: Approximately 25-30 sites in the U.S & EU

Formulation:

1. INO-5401 (9 mg dose IM): A mixture of 3 separate synthetic plasmids that target WT-1, PSMA and hTERT proteins, respectively; and
2. INO-9012 (1 mg dose IM): A synthetic plasmid that expresses human IL-12;
3. Atezolizumab (1200 mg dose IV infusion): A fully humanized, engineered monoclonal antibody of IgG1 isotype against the programmed cell death-ligand 1 (PD-L1)

Criteria for Evaluation:

Research Hypothesis: INO-5401 and INO-9012 delivered by intramuscular injection (IM) followed by electroporation (EP) with CELLECTRA™ 2000 device in combination with atezolizumab, will be generally safe, well tolerated, immunogenic and lead to anti-tumor responses in adult subjects with locally advanced unresectable or metastatic/recurrent UCa.

Objectives and Endpoints:

Primary Objectives:	Associated Primary Endpoints:
1. To determine the safety and tolerability of INO-5401 + INO-9012 delivered by IM injection followed by EP with CELLECTRA™ 2000 device in combination with atezolizumab among subjects with locally advanced unresectable or metastatic/recurrent UCa	• All adverse events (AEs) including adverse events of special interest (AESI) classified by system organ class (SOC), preferred term (PT), severity and relationship to drug • Clinically significant changes in safety laboratory parameters from baseline: CBC with Differential; Chemistry Panel; Urinalysis; T3, Free T4 and TSH; creatine phosphokinase (CPK)
2. To evaluate preliminary immune response to INO-5401 + INO-9012 in combination with atezolizumab in subjects with locally advanced unresectable or metastatic/recurrent UCa	• Antigen-specific cellular immune responses that may be assessed by but not limited to: ○ Interferon-γ secreting T lymphocytes in peripheral blood mononuclear cells (PBMCs) by ELI Spot • T-cell activation and cytolytic cell phenotype in PBMCs by Flow Cytometry or secretion of immune molecules • B cell activation/antibody secretion • Assessment of Myeloid Derived Suppressor Cells (MDSC)

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	• TCR sequencing of PBMCs for diversity and putative antigen specificity • Immune gene transcript profiling of PBMCs • Assessment of proinflammatory and immunosuppressive elements in neoplastic and adjacent normal tissue, where feasible
3. To evaluate objective response rate of INO-5401 + INO-9012 in combination with atezolizumab in subjects who have received and/or progressed on anti-PD-1/PD-L1 based therapy previously (cohort A)	• Objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by investigator review in subjects who have received and/or progressed on anti-PD-1/PD-L1 based therapy previously (cohort A)
Secondary Objective	**Associated Secondary Endpoints**
To evaluate the anti-tumor activity of INO-5401 + INO-9012 in combination with atezolizumab in subjects with locally advanced unresectable or metastatic/recurrent UCa	• Objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by investigator review for treatment naïve, cisplatin-ineligible subjects (cohort B) • ORR by immune RECIST (iRECIST) for both cohorts • Duration of Response (DoR) for both cohorts • Progression Free Survival (PFS) as assessed by RECIST version 1.1 and iRECIST for both cohorts • Overall Survival (OS) for both cohorts
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Trial Population:
The trial population is divided into two cohorts:

1. Cohort A: Subjects with locally advanced unresectable or metastatic/recurrent UCa who have confirmed disease progression during or following treatment with an anti-PD-1/PD-L1 therapy.
2. Cohort B: Subjects with locally advanced unresectable or metastatic/recurrent UCa who are treatment naïve and ineligible for cisplatin-based chemotherapy.

Enrollment of the study was stopped at 35 subjects (28 subjects enrolled in Cohort A and 7 subjects enrolled in Cohort B). Subsequent study procedures will be limited to administration of study drugs INO-5401 + INO-9012 and atezolizumab as per prior schedule. Assessments will be limited to standard-of-care assessments (i.e. physical exam, vital signs, hematology, serum chemistry, urinalysis, and thyroid functions test) only. No further evaluation of efficacy or immunogenicity will be performed. Subjects enrolled in the study will no longer require long-term follow-up for efficacy.

All statistical analyses will be descriptive and exploratory only.

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Trial Design:

This is a Phase I/IIA, open-label, multi-center trial to evaluate the safety, immunogenicity and preliminary clinical efficacy of INO-5401 + INO-9012 delivered by IM/EP, in combination with atezolizumab in subjects with locally advanced unresectable or metastatic/recurrent UCa. Subjects will be enrolled into two cohorts as described in the trial population section above. A safety run-in will be performed using a modified Rolling Six design which will enroll up to 6 subjects from cohort A.

The following procedures were performed for both cohorts prior to enrollment of 35 subjects:

1. For eligible subjects, the trial treatment of INO-5401+ INO-9012 in combination with atezolizumab will be initiated on Day 0 (First dose).
2. Tumor biopsies will be collected at the time of screening, at Week 9 (± 3 days) and at first evidence of radiographic or clinical disease progression. Subjects who are unable to undergo biopsy sample collection but otherwise meet criteria listed in the protocol may continue to receive trial treatment.
3. INO-5401+ INO-9012 will be administered IM followed by EP with CELLECTRA™ 2000 device every 3 weeks (± 3 days) for 4 doses then every 6 weeks (±3 days) for 6 additional doses, thereafter every 12 weeks (±3 days) until confirmed disease progression, unacceptable toxicity, or deemed intolerable by the investigator.
4. Atezolizumab will be administered every 3 weeks until confirmed disease progression, unacceptable toxicity or deemed intolerable by the investigator.
5. Either treatment may be stopped by the investigator while the other treatment continues.
6. INO-5401 + INO-9012 will be dosed approximately 1 hour after IV infusion of atezolizumab for the first dose. Subsequent doses of INO-5401 + INO-9012 and atezolizumab can be dosed in any order.
7. Imaging will be performed at 9 weeks (± 7 days) calculated from the first dose and will continue to be performed every 9 weeks (± 7 days), for the first 54 weeks, or earlier if clinically indicated. Thereafter, imaging will be performed approximately every 12 weeks (± 7 days). Imaging timing should follow calendar days and should not be adjusted for delays or changes in treatment administration dates.
8. In subjects who discontinue trial therapy for any reason other than radiologically defined confirmed progression, tumor imaging should be performed at the time of treatment discontinuation (± 4 weeks). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.
9. Subjects will be followed for all adverse events (AEs) for 30 days and for adverse events of special interest (AESI) and serious adverse events (SAEs) occurring up until 90 days after the last dose of trial treatment or until the start of a new anti-cancer treatment, whichever comes first. If the investigator becomes aware of an AESI or SAE that is considered related to trial treatment after discontinuation from the trial, those events should be reported to Inovio within 24 hours.
10. All subjects who experience disease progression, have unacceptable toxicity or start a new anti-cancer therapy and are discontinued from the trial will be followed for survival and subsequent anti-cancer therapy. Subjects should be contacted (i.e. by telephone) every 3 months to assess for survival status until death or subject withdraws consent.
11. Subjects who discontinue from trial treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessment until disease progression,

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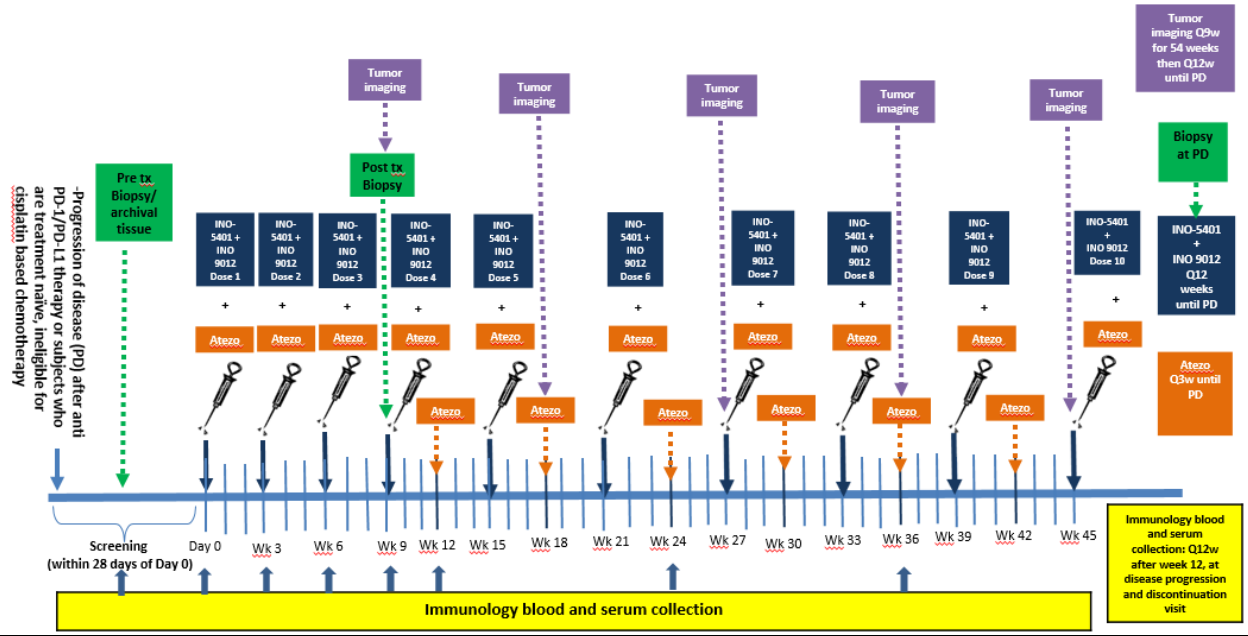
withdrawal of consent, or start of new anti-cancer therapy, death, or trial termination by Sponsor, whichever occurs first.

Trial schema of Cohort A and Cohort B prior to enrollment of 35 subjects:



PD: Progressive disease	Tx: Treatment
Q3w: Every 3 weeks	Q12w: Every 12 weeks
Atezo: Atezolizumab	PD-1/PD-L1: Programmed Death-1/Programmed Death Ligand-1
Q9w: Every 9 weeks	Wk: Week

The following procedures will be performed for both cohorts following enrollment of 35 subjects:

1. INO-5401+ INO-9012 will be administered IM followed by EP with CELLECTRA™ 2000 device every 3 weeks (± 3 days) for 4 doses then every 6 weeks (±3 days) for 6 additional doses, thereafter every 12 weeks (±3 days) until disease progression, unacceptable toxicity, or the investigator determines it is in the best interest of the subject to terminate study drug. Confirmation of disease progression is not required.
2. Atezolizumab will be administered every 3 weeks (±3 days) until disease progression, unacceptable toxicity or the investigator determines it is in the best interest of the subject to terminate study drug. Confirmation of disease progression is not required.
3. Either treatment may be stopped by the investigator while the other treatment continues.
4. INO-5401 + INO-9012 will be dosed approximately 1 hour after IV infusion of atezolizumab for the first dose. Subsequent doses of INO-5401 + INO-9012 and atezolizumab can be dosed in any order.
5. Imaging should be performed per standard of care, in order to determine whether study therapy should continue to provide clinical benefit.
6. Subjects will be followed for all AEs, AESI and SAE for 30 days after the last dose of trial treatment or until the start of a new anti-cancer treatment, whichever comes first. If the investigator becomes aware of an AESI or SAE that is considered related to trial treatment after discontinuation from the trial, those events should be reported to Inovio within 24 hours.

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7. All subjects, regardless of the reason for study discontinuation, should return for Study discontinuation visit 30 day after the last dose of trial treatment. This will be the last visit for the study.

Safety Run-In: A safety run-in will be performed using a modified Rolling Six design which will enroll up to six subjects (safety analysis subjects) from cohort A.

Once the first three subjects of these six subjects have completed Week 6 assessments, in the absence of any dose-limiting toxicity (DLT), enrollment may proceed to completion. However, if prior to the first three subjects completing Week 6, a single subject from the first six experiences a DLT, then enrollment will be limited to six subjects until all six subjects have reached Week 6, and are assessed for DLT. If no additional subjects, of these six, experience a DLT within the 6 week safety run in period, then enrollment may proceed to completion.

If a second of these first six subjects experiences a DLT within the first six weeks, enrollment will stop, and the Sponsor's medical monitor, in addition to the PI and investigator(s) at the subjects' site(s) will discuss the case, and a decision will be made whether to modify the trial, or to cease further enrollment. Enrollment will only be reinitiated after amendment of the protocol and approval of the amended protocol by the IRB.

Safety run-in subjects that withdraw from the study for reasons other than a DLT, prior to the end of the safety run-in period, will be replaced. The end of the safety run-in period is defined as the earliest of the following:

- The first three subjects in cohort A have all completed Week 6 with no DLTs experienced by any of the safety run-in subjects in that cohort (up to six); enrollment may then proceed to completion;
- All six subjects of the safety run-in phase, in cohort A, have completed week six with only one subject having experienced a DLT; enrollment may then proceed to completion;
- Two or more of the safety run-in subjects, have experienced DLTs prior to completing Week 6; enrollment will be suspended.

DLTs are defined in protocol Section 7.9.

Because this trial is combining INO-5401 + INO-9012 with atezolizumab for the first time, there will be a waiting period of one week between enrollment of the first subject and the second subject.

Trial Treatment:
Trial treatments include:
1. INO-5401 (3 mg of each WT-1, PSMA and hTERT SynCon® plasmids) combined with 1 mg INO-9012, (total 10 mg of DNA) IM injection followed by EP; INO-5401 + INO-9012 will be administered every 3 weeks (± 3 days) for 4 doses then every 6 weeks (±3 days) for 6 additional doses, and thereafter every 12 weeks (±3 days) until confirmed disease progression, unacceptable toxicity, or deemed intolerable by investigator.
2. Atezolizumab 1200 mg/20mL IV infusion will be administered every 3 weeks until confirmed disease progression, unacceptable toxicity, or deemed intolerable by investigator.

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For the purpose of this protocol, trial treatment is defined as combination of INO-5401 + INO-9012 and atezolizumab.

Following enrollment of 35 subjects (28 in Cohort A and 7 in Cohort B), the trial treatment will be modified as follows:

1. INO-5401+ INO-9012 will be administered IM followed by EP with CELLECTRA™ 2000 device every 3 weeks (± 3 days) for 4 doses then every 6 weeks (±3 days) for 6 additional doses, thereafter every 12 weeks (±3 days) until disease progression, unacceptable toxicity, or the investigator determines it is in the best interest of the subject to terminate study drug.
2. Atezolizumab will be administered every 3 (±3 days) weeks until disease progression, unacceptable toxicity or the investigator determines it is in the best interest of the subject to terminate study drug.

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Inclusion Criteria:

In order to be eligible for participation in this trial, the subject must:

1. Provide signed IRB approved informed consent in accordance with institutional guidelines;
2. Be 18 years of age or older on the day of signing the informed consent, and able and willing to comply with all trial procedures;
3. Have histologically or cytologically documented locally advanced unresectable or metastatic/recurrent urothelial carcinoma (including renal pelvis, ureters, urinary bladder, and urethra):
   a) **For Cohort A**: Subjects who have radiographically confirmed disease progression during or following treatment with an anti-PD-1/PD-L1 based therapy;
   b) **For Cohort B**:
      i. No prior chemotherapy for inoperable locally advanced or metastatic or recurrent UCa:
         - For subjects who received prior adjuvant/neoadjuvant chemotherapy or chemoradiation for UCa, a treatment-free interval greater than 12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment naive in the metastatic setting.
         - Prior local intervesical chemotherapy or intravesical immunotherapy is allowed if completed at least 4 weeks prior to the initiation of trial treatment.
      ii. Ineligible ("unfit") for cisplatin-based chemotherapy as defined by any one of the following criteria:
         - Impaired renal function (glomerular filtration rate [GFR] > 30 but < 60 mL/min); GFR should be assessed by direct measurement (i.e., creatinine clearance or ethyldediaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula)
         - A hearing loss (measured by audiometry) of 25 dB at two contiguous frequencies
         - Grade 2 or greater peripheral neuropathy (i.e., sensory alteration or parasthesias including tingling)
4. Have measurable disease, as defined by RECIST version 1.1 (investigator assessment). Target lesions must not have been previously treated with surgery, radiation therapy, or radiofrequency ablation unless there is documented progression in the lesion after such therapy and no other lesions are available for selection as target lesions;
5. Have a performance status of 0 or 1 on Eastern Cooperative Oncology Group (ECOG) Performance Scale;
6. Have a life expectancy of ≥ 3 months;
7. Be willing to provide a tissue sample for pre-treatment intra-tumoral assessment of proinflammatory and immunosuppressive factors. Preferably, tumor biopsies will be collected at the time of screening or newly obtained tissue can be used (no intervening treatment [local or systemic] involving the site of tissue biopsy once tissue biopsy is obtained up to the time of trial enrollment).
   Note: For cohort A, this refers to tissue obtained during fresh biopsy or archived post-anti-PD-1/PD-L1 based therapy progression. For cohort B, this refers to newly diagnosed, all treatment naïve archival or fresh tissue. Additionally for cohort A subjects, an archival sample (ideally treatment naïve) will be requested as well, however, enrollment is allowed for subjects unable to provide newly obtained or lacking tissue specimens after consultation with the Sponsor;
8. Have ECG with no clinically significant findings as assessed by the investigator performed within 28 days prior to first dose;

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9. Demonstrate adequate organ function: hematological, renal, hepatic, coagulation parameters as defined below and obtained within 28 days prior to the first trial treatment. Adequate hematologic and end-organ function:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/ µL
Platelets	≥100,000/ µL
Hemoglobin	≥9 g/dL, or ≥5.6 mmol/L without transfusion or EPO dependency within 7 days
Renal	
Creatinine OR Calculated creatinine clearance	≤ 1.5 x upper limit of normal (ULN) OR ≥ 30 mL/min for subject with creatinine level > 1.5 x institutional ULN Note: Creatinine clearance should be calculated per Cockcroft-Gault formula
Hepatic	
Total bilirubin	≤ 1.5 x ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN **OR** ≤ 5 x ULN for subjects with liver metastases
Albumin	≥ 2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

10. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of study treatment:
    - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
    - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic

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abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

For male subjects: Agree that during the period specified above, men will not father a child. Subjects must be surgically sterile (e.g, vasectomy) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of study treatment.

Exclusion Criteria:
Subjects who meet any of the following criteria will be excluded from trial entry:

Cancer-specific Exclusion Criteria:

1. Any approved anti-cancer therapy including chemotherapy, targeted small molecule therapy or radiation therapy within 2 weeks prior to trial Day 0; or if subject has not recovered (i.e., Less than or equal to grade 1 or returned to baseline level) from adverse events due to a previously administered agent; the following exceptions are allowed:
    - Palliative radiotherapy for bone metastases or soft tissue lesions should be completed > 7 days prior to baseline imaging;
    - Hormone-replacement therapy or oral contraceptives;
    - Subjects with grade 2 neuropathy or grade 2 alopecia;
2. Currently participating and receiving trial therapy or has participated in a trial of an investigational agent and/or has used an investigational device within 28 days prior to Day 0; Note: Subjects who have entered the follow-up phase of an investigational trial may participate as long as it has been 28 days since the last dose of the previous investigational agent or device;
3. Documented active or untreated central nervous system (CNS) metastases and/or carcinomatous meningitis. For suspected neurological involvement, CT or MRI evaluation is recommended during screening to rule out CNS metastases. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurological symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability;
4. Uncontrolled tumor-related pain:
    - Subjects requiring pain medication must be on a stable regimen at trial entry
    - Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should complete treatment at least 7 days prior to enrollment
    - Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment
5. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly and more frequently):
    - Subjects with indwelling catheters (e.g., PluerX) are allowed
6. Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab:

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- Subjects who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and do not have a history of clinically significant hypercalcemia are eligible
- Subjects who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while in the trial

7. Malignancies other than UCa within 3 years prior to Day 0, with the exception of those with negligible risk of metastasis or death treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent) or localized prostate cancer treated with curative intent and absence of prostate-specific antigen (PSA) relapse or incidental prostate cancer (T1/T2a, Gleason score ≤ 3 + 4, and PSA ≤ 0.5 ng/mL undergoing active surveillance and treatment naïve);

General Medical Exclusion Criteria

8. Pregnant or lactating, or intending to become pregnant or father children within the projected duration of the trial starting with the screening visit through 5 months after the last dose of anti-PD-1/PD-L1 based therapy and/or DNA vaccine;
9. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins;
10. Known hypersensitivity allergy or contraindication to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the PD-1/PD-L1 inhibitor formulation;
11. Active or history of autoimmune disease or immune deficiency, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener granulomatosis with polyangiitis, Sjögren's syndrome, Guillain-Barrè syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (See Appendix 3 for a more comprehensive list of autoimmune diseases and immune deficiencies).
    - Subjects with history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this trial
    - Subjects with controlled Type I diabetes mellitus on a stable dose of insulin regimen may be eligible for this trial
12. History or any evidence of interstitial lung disease such as idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug induced or active non-infectious pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan;
    - History of radiation pneumonitis in the radiation field (fibrosis) is permitted
13. History of HIV (If the investigator suspects clinical evidence of HIV, an HIV antibody test should be performed to exclude this possibility);
14. Active hepatitis B (hepatitis B surface antigen reactive) or active hepatitis C (HCV qualitative RNA detected); testing is recommended per investigator's clinical suspicion;
15. Severe infections within 4 weeks prior to enrollment, including, but not limited to, hospitalization for complications of infection, bacteremia, or the presence of any active infection requiring systemic therapy;
16. Received therapeutic oral or IV antibiotics within 2 weeks prior to Day 0
    - Subjects receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
17. History or current evidence of any condition, therapy or laboratory abnormality (e.g. chronic renal failure; angina, myocardial ischemia or infarction, class 3 or higher congestive heart

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failure, cardiomyopathy, or clinically significant arrhythmias) that in the opinion of the treating investigator might confound the results of the trial or interfere with the subject's participation for the full duration of the trial;

18. Prior allogeneic stem cell or solid organ transplant;
19. Received a live, attenuated vaccine within 28 days prior to randomization or anticipation that such a live attenuated vaccine will be required during the trial
    Note: Influenza vaccination should be given during influenza season only (approximately October to March). Subjects must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to Day 0, during treatment, or within 90 days following the last dose of trial treatment;
20. Fewer than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site
    - Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist);
    - Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
21. Presence of acute or chronic bleeding or clotting disorder that would contraindicate IM injections; or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks prior to Day 0;
22. Known previous or ongoing, active psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial;
23. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;

<u>Medication-Related Exclusion Criteria</u>

24. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies for cohort B:
    - Subjects who have received prior treatment with anti-CTLA-4 may be enrolled provided at least 5 half-lives (approximately 75 days) have elapsed from the last dose of anti-CTLA-4 to the first dose of trial treatment and there was no history of severe immune-mediated adverse effects from anti-CTLA-4 (Grade 3 or 4)
    - Prior cancer vaccines and cellular immunotherapy are permitted; subjects are encouraged to undergo a fresh pre-treatment sample collection for biopsy to evaluate immunological status
25. Treatment with systemic immunostimulatory agents (including but not limited to IFNs, IL-2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to first dose;
26. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosterioids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-α agents) within 2 weeks prior to initiation of trial treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:
    - Subjects who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study (after Sponsor approval has been obtained)
    - Subjects who received mineralcorticosteriods (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) for asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study

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Table 1: Trial Schedule of Events Prior to Enrollment of 35 Subjects

	Screening[a] Day -28 to Day -1	Day 0	Week 3	Week 6	Week 9	Every 3 weeks	Every 6 weeks	Every 9 weeks	Discontinuation Visit[b]	Follow-up
Signed Informed Consent Form(s)	X									
Medical, surgical, and cancer histories, including demographic information[c]	X									
Inclusion/Exclusion criteria	X	X								
Complete Physical exam[d]	X									
Targeted Physical exam[e]		X	X	X	X	X			X	
ECOG performance status[e]	X	X	X	X	X	X			X	
HIV, Hep B and Hep C serology[f]	X									
Concomitant Medications[g]	X	X	X	X	X	X			X	
Vital Signs and Weight[h]	X	X	X	X	X	X			X	
Height	X									
12-lead ECG[i]	X									
Tumor imaging[j]	X	Q9w from Day 0 for first 54 weeks (~12 months), there after Q12w								
RECIST/iRECIST	X	Q9w from Day 0 for first 54 weeks (~12 months), there after Q12w								
Hematology[k]	X	X[e]	X[e]	X[e]	X[e]	X[e]			X	
Serum Chemistry[l]	X	X[e]	X[e]	X[e]	X[e]	X[e]			X	
Coagulation Panel (aPTT, INR)	X									
Urinalysis[m]	X			X			X		X	
[redacted]										
Pregnancy[o]	X	X	X	X	X	X				
TSH, T3 and FT4[p]	X	X		X			X			
CPK	X								X	
Serum and Whole blood sample for immunology assessments[q]	X	X	X	X	X	At week 12 and Q12w thereafter until disease progression as well as at disease progression			X	
Tumor specimen[r]	X				X[s]	At first evidence of disease progression				
Adverse Events[t]	X	X	X	X	X	X			X	X
Atezolizumab[u]		X	X	X	X	X				
INO 5401 + INO-9012[v]		X	X	X	X	After week 9, Q6w for 6 more doses (week 45), thereafter Q12w until PD				
Download EP data[w]		X	X	X	X	After week 9, Q6w for 6 more doses (week 45), thereafter Q12w until PD				
Survival and new anti-cancer therapy follow-up[x]										X

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Note: Assessments scheduled on the days of trial treatment should be performed before the trial treatment unless otherwise noted.

[a] Written informed consent can be obtained up to 28 days prior to Day 0 and is required for performing any trial-specific tests or procedures. Tumor tissue may be submitted up to 28 days prior to Day 0. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 0 may be used for screening assessments rather than repeating such tests. Screening labs (CBC and chemistry) may be used for Day 0 if they are within 10 days of Day 0.
[b] Subjects who discontinue early from trial treatment for progression will be asked to return to the clinic within 30 days after the last dose for a treatment discontinuation visit.
[c] Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Previous progression data for cohort A should be collected as well. Demographic information includes sex, age, and self-reported race/ethnicity. Reproductive status and smoking history should also be captured.
[d] Complete and limited physical examinations are defined in Section 6.6.2.
[e] ECOG performance status, targeted physical exam, and local laboratory assessments may be obtained ≤ 72 hours before each dosing visit.
[f] Subjects should be tested for HIV locally prior to the inclusion into the trial only if investigator's clinical suspicion for HIV infection and HIV-positive subjects will be excluded from the clinical trial. Hepatitis B surface antigen, anti-HBc antibody, anti-HBs antibody, and Hepatitis C antibody immunoassays should be collected per investigator's clinical suspicion during screening and tested locally. In subjects who have positive serology for the anti-HBc antibody, HBV DNA should be collected prior to Day 0.
[g] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the subject has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.
[h] Vital signs include heart rate, respiratory rate, blood pressures, and temperature. For first infusion of atezolizumab, the subject's vital signs should be determined within 60 minutes before the infusion. If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (± 5 minutes for all timepoints) during the infusion, and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and at 30 (± 5) minutes after the infusion. Subjects will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their trial physician if they develop such symptoms.
[i] ECG recordings will be obtained during screening and as clinically indicated at other time points. Subjects should be resting and in a supine position for at least 10 minutes prior to ECG collection.
[j] Examinations performed as standard of care prior to obtaining informed consent and within 28 days of first dose of trial treatment may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. Tumor imaging should be performed by computed tomography (CT), but may be performed by magnetic resonance imaging (MRI) if CT is contraindicated, but the same imaging technique should be used in subject throughout the trial. CT scans (with oral/IV contrast unless contraindicated) must include chest, abdomen and pelvis. The investigator must review before dosing at the next visit. Subjects will undergo tumor assessments every 9 weeks (±7 days) for the first 54 weeks (approximately 12 months) following first dose of trial treatment, or earlier if clinically indicated. After 54 weeks, tumor assessments will be required every 12 weeks (±7 days). Subjects who discontinue from treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, start of new-anti cancer therapy, withdrawal of consent, or death. Investigators may perform additional scans or more frequent assessments if clinically indicated. Subjects who continue treatment beyond radiographic or clinical disease progression will be monitored with a follow-up scan at the next scheduled tumor assessment. Imaging timing should follow calendar days and should not be adjusted for delays or changes in treatment administration dates.
[k] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (absolute counts of neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells (if any)), and platelet count. A manual differential can be done if clinically indicated.
[l] Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or CO_2, calcium, phosphorus, glucose, total bilirubin (direct bilirubin only if total bilirubin is elevated), ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein, and albumin.

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[m] Urinalysis includes specific gravity, pH, glucose, protein, ketones, blood, and a microscopic exam if abnormal results are noted. Urinalysis to be performed every 6 weeks.

[redacted]

[o] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 72 hours prior to each dose.

[p] Thyroid function tests will be performed on first dose and every 6 weeks thereafter.

[q] Immunology samples are to be drawn at screening, Day 0, Week 3, Week 6, Week 9, Week 12 and thereafter every 12 weeks until disease progression, as well as at disease progression and discontinuation visit. [redacted] This is required at screening and on Day 0 to provide sufficient baseline sample for immunology testing.

[r] Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation. Ideally, a tumor specimen obtained after completion of the most recent systemic therapy should be submitted. In subjects undergoing a pre-treatment biopsy, an archival tumor specimen, if available, should also be submitted. After signing of the Informed Consent Form, tumor tissue should be submitted to the sponsor in a timely manner. An archival specimen, if available, may be submitted. See Section 6.11 for more details.

[s] All subjects will undergo a mandatory tumor biopsy sample collection, if clinically feasible as determined by the trial investigator, at the Week 9 (at the time of fourth dose) and at the first evidence of radiographic or clinical disease progression (i.e., not proceeded by meaningful tumor regression). Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. For core needle biopsy specimens, at least three cores should be submitted for evaluation. Subjects who are unable to undergo biopsy sample collection but otherwise meet criteria listed in Section 4.3.1 may continue to receive trial treatment.

[t] AEs will be collected from the time of informed consent until 30 days after the last dose of trial treatment or until initiation of another anti-cancer therapy, whichever occurs first. SAEs and AESIs will be collected from the time of informed consent until 90 days after the last dose of trial treatment of until initiation of anti-cancer therapy, whichever occurs first.

[u] Atezolizumab will be given every 3 weeks until confirmed disease progression, unacceptable toxicity, or deemed intolerable by investigator. The window for each visit is ± 3 days unless otherwise noted. A 30-40 minutes observation period is recommended after each trial treatment.

[v] INO-5401 + INO-9012 is administered every 3 weeks until week 9 (ie.,4 doses). Then every 6 weeks for 6 more doses (until week 45). Thereafter it will be administered every 12 weeks until confirmed disease progression, unacceptable toxicity, or deemed intolerable by investigator. The window for each visit is ± 3 days unless otherwise noted. A 30-40 minutes observation period is recommended after each trial treatment.

[w] The data from CELLECTRA™ 2000 device must be downloaded within 24-48 hours of INO-5401 + INO-9012 dosing and sent to Inovio.

[x] Survival follow-up information will be collected via telephone calls, subject medical records, and/or clinical visits approximately every 3 months until death, lost to follow-up, withdrawal of consent, or trial termination by Sponsor. All subjects will be followed for survival and new anticancer therapy information unless the subject requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the subject discontinue trial treatment without documented clinical disease progression, every efforts should be made to follow up regarding survival, progression (if not already progressed), and new anti-cancer therapy.

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Table 2: Trial Schedule of Events Following Enrollment of 35 Subjects

The table below (Table 2) highlights recommended assessments to be performed while a subject is on-study. These assessments are consistent with standard-of-care. The study will only collect information on trial treatment dosing, EP data, concomitant medications related to AEs, and study treatment discontinuation will be collected.

	Day 0	Week 3	Week 6	Week 9	Every 3 weeks	Every 6 weeks	Study Discontinuation Visit[a]
Physical Exam	X	X	X	X	X		X
Vital Signs	X	X	X	X	X		X
Hematology[b]	X	X	X	X	X		X
Serum Chemistry[c]	X	X	X	X	X		X
Pregnancy[d]	X	X	X	X	X		
Urinalysis	X		X			X	
TSH, T3 and T4	X		X			X	
Adverse Events	X	X	X	X	X		X
Atezolizumab[e]	X	X	X	X	X		
INO-5401 + INO-9012[f]	X	X	X	X	After week 9, Q6w for 6 more doses (Week 45), then Q12w until PD		
Download EP Data	X	X	X	X	After week 9, Q6w for 6 more doses (Week 45), then Q12w until PD		

TSH: thyroid stimulating hormone; T3: triiodothyronine; FT4: free thyroxine; EP: electroporation; Q6w/Q12w: every 6 weeks/every 12 weeks; PD: progressive disease

[a] Study Discontinuation Visit will be the last visit for the study, performed within 30 days of the last treatment; when the subject discontinues trial treatment, s/he will be asked to come for this Study Discontinuation Visit. The Study Discontinuation Visit is the same visit as the Treatment Discontinuation Visit.

[b] Hematology may include CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (absolute counts of neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells (if any)), and platelet count. A manual differential can be done if clinically indicated.

[c] Serum chemistry may include BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or CO_2, calcium, phosphorus, glucose, total bilirubin (direct bilirubin only if total bilirubin is elevated), ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein, and albumin.

[d] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) should be performed within 72 hours prior to each dose of study treatment.

[e] A 30-40 minutes observation period is recommended after each atezolizumab treatment.

[f] INO-5401 + INO-9012 to be administered every 3 weeks until week 9, then every 6 weeks for 6 more doses (until week 45). Thereafter it will be administered every 12 weeks until disease progression, unacceptable toxicity, or the investigator determines it is in the best interest of the subject to discontinue study drug. The window for each visit is ± 3 days unless otherwise noted. A 30-40 minutes observation period is recommended after each trial treatment.

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1. INTRODUCTION

This document is a protocol for a human research trial to be conducted according to US and international standards of Good Clinical Practice (GCP) (FDA Title 21 part 312, 812 and International Conference on Harmonization (ICH) guidelines), applicable government regulations and Institutional research policies and procedures.

1.1. BACKGROUND AND SCIENTIFIC RATIONALE

The trial is open to subjects with locally advanced unresectable or metastatic/recurrent Urothelial Cancer (UCa) who have disease progression during/following treatment with anti-PD-1/PD-L1 therapy or who are treatment naïve cisplatin ineligible.

1.1.1. BACKGROUND, EPIDEMIOLOGY AND CURRENT TREATMENT OF ADVANCED UNRESECTABLE OR METASTATIC UROTHELIAL CANCER

Urothelial (transitional cell) cancer (UC) describes a range of tumors that arise from the urothelial endothelium, which includes the bladder, renal pelvis, ureter, and urethra. The worldwide incidence of bladder cancer exceeds 400,000 cases annually, ranking it as the seventh most common cancer worldwide [1]. UC is the predominant histologic type of bladder cancer in the United States and Western Europe, where it accounts for approximately 90 percent of bladder cancers. In other areas of the world, non-urothelial histologies including squamous cell, adenocarcinoma, and small cell carcinoma are more frequent. UC also accounts for about 165,000 deaths worldwide annually. The overall 5-year survival rate for metastatic UC (mUC) is approximately 5.5% (http://seer.cancer.gov/statfacts/html/urinb.html). Poor prognostic factors for survival in subjects with mUC include advanced stage of disease at the time of initial diagnosis, Karnofsky performance status (KPS) < 80%, visceral metastasis (i.e., lung, liver, or bone) [2]. The presence of these unfavorable features was associated with a median survival of 4 months compared with 18 months in subjects without these features [3]. Subjects with previously untreated mUC typically receive platinum-based chemotherapy. The benefit conferred by cisplatin-based chemotherapy regimens in this population appears to provide a median OS of 13−15 months and therefore leaves a significant population in need of salvage therapy options [3, 4]. Poor performance status, impaired renal function, advanced age, and multiple comorbidities (e.g., neuropathy, congestive heart failure, and hearing loss) are fairly common in subjects with advanced mUC and can prohibit the use of cisplatin-based regimens. In this situation, carboplatin-based regimens were previously used in these subjects, but were less effective than cisplatin-based regimens [4] hence approval of checkpoint inhibitor (CPI) in cisplatin-ineligible subjects in first line setting was met with significant enthusiasm. Despite effectiveness of first line chemotherapy, nearly all subjects experience disease progression and will require second-line therapy. Prior to CPI, there were no approved second-line therapies for mUC in the United States and only one approved agent (vinflunine) in the European Union. Several chemotherapeutic agents have been previously studied and used in the second-line setting over the last two decades, the overall response rates were low (median survival in most series of 7 to 9 months, median PFS of 3 to 5 months) [5, 6] and associated with considerable toxicity. Additionally, no survival benefit was demonstrated with second-line chemotherapy.

In conclusion, advanced unresectable or metastatic UC remains a high unmet medical need as survival remains poor for most subjects who experience disease progression or intolerance to treatment during or after platinum-containing chemotherapy.

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1.1.1.1. CHECKPOINT INHIBITORS IN CANCER

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in advanced cancer subjects including mUC subjects. PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors PD-1 and B7.1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer [7, 8]. Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T-cell activation and cytokine production [9, 10]. Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion [11]. Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity. PD-L1 expression is prevalent in many human tumors, and elevated PD-L1 expression on tumor cells is associated with a poor prognosis in subjects with UCa [12, 13]. Targeting the PD-1/PD-L1 pathway with CPIs has demonstrated activity in subjects with many different tumor types who have failed standard-of-care therapies leading to recent approvals in many advanced cancer settings.

1.1.1.2. CURRENT STANDARD-OF-CARE IN ADVANCED OR METASTATIC UCA

Until the recent approval of checkpoint inhibitors, a variety of chemotherapeutic agents were used in this setting, and the prognosis of subjects with recurrent/progressive UCa was generally poor with median survival in most series of 7 to 9 months, median PFS of 3 to 5 months [5, 6]. The FDA approval of the PD-L1 monoclonal antibody Atezolizumab for the treatment of post-platinum metastatic UC (mUC) subjects in 2016 marked the first systemic therapy approval for UCa in three decades [14]. This sentinel event has established a new standard of care for post-platinum mUC subjects and sparked a renewed optimism for further improvements in clinical outcomes through the incorporation of immunotherapy into current and future treatment approaches. Atezolizumab is from a class of immunotherapy drugs called Checkpoint Inhibitors (CPIs) which have shown impressive efficacy in other difficult to treat tumor types such as metastatic Melanoma and Non-Small Cell Lung Cancer (NSCLC). Additional approvals for CPI followed including nivolumab, durvalumab, avelumab and pembrolizumab [15-18]. Furthermore, recently data shown with Pembrolizumab versus standard of care chemotherapy in post-platinum progressive mUC subjects demonstrated significant improvement in OS in both the all-comer (10 vs 7 months) and PD-L1 positive (combined positive score [CPS] 10%) subjects (8 vs 5 months) receiving pembrolizumab therapy and this led to full-approval of pembrolizumab in this subject population. However, this justified optimism from the approval of five CPI is tempered by the sobering reality that only 15-31% of mUC subjects treated with a CPI demonstrate tumor responses. Highest ORR was noted using durvalumab where 31% of subjects responded with a median follow-up time of 6.5 months however the response was limited only to PD-L1 positive subjects (46%) [17]. Similarly, using other CPIs, the biologically enriched subset of subjects with high immunohistochemistry (IHC) PD-L1 staining intensity (PD-L1 positive), responses are only seen in about one fourth of subjects. Furthermore, amongst PD-L1positive subjects treated with CPI, the median overall survival was not significantly improved compared to all-comer subjects a modest 11.4 months with a 12-month overall survival rate of 48% [14]. As many UCa subjects are not eligible for

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cisplatin chemotherapy in the first line metastatic setting, key trials were undertaken to demonstrate efficacy of CPI in this setting as well. Data from cohort 1 of IMvigor 210 demonstrated an ORR of 19% with a median follow-up of 14 months and OS of 16 months using atezolizumb in cisplatin ineligible subjects in the first line. Similarly, an initial analysis of 100 cisplatin ineligible subjects treated with pembrolizumab demonstrated an ORR of 24% in this population. These data led to the approval of both atezolizumab and pembrolizumab in the cisplatin-ineligible first line mUC population [19, 20]. However, for the majority of subjects, progression of disease either during or after treatment with a PD-L1 or PD-1 CPI therapy remains the norm and because these subjects do not experience meaningful clinical responses to checkpoint inhibitor monotherapy, rational immunotherapeutic combination approaches that improve subject outcome are highly needed.

1.1.2. RATIONALE FOR COMBINATION THERAPIES

Two critical needs have emerged as CPI have become widely used for treatment of post-platinum treated mUC subjects. First, there is a need for combination agents that can be safely added to PD-1/PD-L1 inhibitor naïve subjects to improve on the efficacy of CPI- monotherapy. Second, a significant need now exists to identify novel therapies with clinical benefit in the post-CPI mUC population as 70-80% of CPI-naïve subjects will progress on CPI therapy, and these subjects are relatively healthy due to the relatively clean safety profile of the CPIs. The need for innovative post-CPI options also extends to multiple non-UCa tumor types in which CPI therapies have been approved in recent years including: non-small cell lung cancer, melanoma, renal cell carcinoma, head and neck squamous cell carcinoma, and Hodgkin's lymphoma. The proposed trial is intended to focus on this CPI refractory population as there are over 1000 immuno-oncology combination trials ongoing, but there are few trials available for CPI refractory subjects representing a huge unmet medical need. These initial ongoing trials in CPI refractory subjects have focused on melanoma subjects. DNA vaccine trials have not yet been implemented in CPI refractory bladder subjects. Currently, there is one ongoing clinical trial in advanced bladder cancer subjects post-CPI progression where focused radiotherapy is administered in combination with pembrolizumab.

Combination treatment regimens (immunotherapy + immunotherapy; immunotherapy + chemotherapy; immunotherapy + radiation; immunotherapy + epigenetic therapy) represent logical approaches to increase tumor response rates and survival outcomes. In melanoma, the combination CPI regimen of Nivolumab (anti-PD-1) and Ipilimumab (anti-CTLA-4) demonstrated improved progression free survival (11.5 vs 6.9 months) compared to Nivolumab alone. However, this improvement came at the cost of a significantly higher rate of grade 3-4 toxicity in the combination arm (55.0%) compared to monotherapy (16.3%) [21]. A similar trend was seen with the Nivolumab plus Ipilimumab combination CPI regimen in metastatic renal cell cancer with improved response rates (45% vs 21%) but increased grade 3-4 toxicity (46% vs 11%) with combination therapy compared to monotherapy [22]. Collectively, these experiences in non-UC malignancies confirm that improvements in clinical outcomes can be achieved with immunotherapy combination approaches, however the high rates of grade 3-4 toxicity observed in these initial combination approaches pose significant challenges to utilizing such regimens in broader cancer populations not capable of withstanding such toxicity. In particular, cancer populations characterized by advanced age and frequent comorbidities such as mUC are in urgent need of alternative combination regimens capable of producing improvements in clinical outcomes while maintaining a more favorable safety profile.

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For successful immunotherapy combination therapies to realize improved outcomes, an enhanced tumor infiltration by activated CD8+ T-cells is critical. CPIs affect this end result by blocking key inhibitory signaling pathways which dampen T-cell activation. The net effect is increased T-cell activation. However, for CPIs to improve outcomes, CD8+ T-cells must be present within a tumor or the immediate surrounding microenvironment. Prior to CD8+ T-cells proliferating, trafficking to tumor, activating and resulting in a cytotoxic anti-tumor effect, a tumor antigen-specific recognition event in an antigen presenting cell (APC) in the context of MHC cell surface molecules and a co-stimulatory signal must occur. As such, approaches to increase the frequency of APC exposure to tumor-specific antigens represent an attractive strategy to increase the intensity of CD8+ T-cell tumor infiltration. Vaccine approaches, particularly DNA-based vaccines, have shown encouraging results with excellent safety profiles in multiple clinical trials conducted in the past decade.

The treatment for this clinical trial will be with INO-5401 + INO-9012, a DNA-based vaccine.

[redacted]

Using the identical platform, but targeting the E6/E7 antigens of human papilloma virus 16 and 18, treatment with the VGX-3100 vaccine demonstrated regression of cervical intraepithelial neoplasia grade 2 or 3 (CIN 2/3) to CIN 1 or normal at 6 months in 48.6% of subjects compared to only 30.6% of subjects treated with placebo control (p=0.043) [23]. Treatment was extremely well tolerated with a grade 3 or higher toxicity rate of 4.8%. Furthermore, positive clinical outcomes were associated with significant increases in antigen-specific CD8+ T-cells of a cytotoxic phenotype in the periphery and increases in CD8+ T-cells in the cervical tissue. The experience with VGX-3100 vaccine provides proof of concept in the ability of the platform to generate expansion of antigen-specific CD8+ T-cells with an outstanding safety profile and improvement in clinically relevant endpoints. Consequently, a strong rationale exists to test this platform using INO-5401 + INO-9012 in UCa subjects. Given the improvements in response rates seen with combination immunotherapy approaches in non-UCa malignancies, the recent approval of atezolizumab in post-platinum mUC, and the outstanding safety profile of the VGX-3100 DNA-based vaccine produced on an identical platform as INO-5401 + INO-9012, a strong rationale exists to trial the safety, immunologic and pharmacodynamic effects, and clinical efficacy of INO-5401 + INO-9012 given in combination with atezolizumab in metastatic/recurrent or locally advanced unresectable mUC subjects who are either PD-1/PD-L1 inhibitor naïve or who have progressed on or during PD-1/PD-L1 inhibitor therapy.

1.1.3. RATIONALE FOR IMMUNOTHERAPY DELIVERED WITH A DNA-BASED PLATFORM

DNA immunization has been recognized as a promising vaccine platform for almost 20 years [24]. Both DNA vaccines and various viral vector vaccines have been explored for diseases where a potent T-cell response may be required to achieve clinical improvement. Prophylactic and therapeutic DNA vaccines have generated immunogenicity that is similar

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to what has been achieved with viral vectors [25]. Potent T-cell immune responses can be generated to virtually any antigenic sequence. Although traditional live attenuated and viral vector vaccines may also elicit potent T-cell responses, these viral approaches bear safety concerns associated with their vector backbone, which DNA vaccines circumvent. In addition, as opposed to viral-based vaccines, which carry a risk of mutation back to a virulent state or spread to unintended individuals, DNA vaccines are not based on an intact natural pathogen and therefore cannot revert to a virulent form. Finally, repeated dosing of viral-based vaccines may be hindered by neutralization of targeted viral vector sequences. The plasmid backbones of DNA vaccines are associated with limited if any immune response, allowing repeated dosing to increase or maintain immune responses over long periods. Additionally, toxicology studies have found no evidence of genome integration as measured by PCR in two previous studies of several DNA vaccine products [26, 27] expressing a variety of inserts, such as HIV, Ebola, SARS, West Nile Virus and Malaria antigens (see Section 4 of Investigator's Brochure). In contrast, pre-existing anti-vector immunity can reduce immunogenicity and ability to utilize the viral vector for future immunizations. Finally, DNA vaccines can be readily produced in large quantities, and are generally stable for long periods of time. These advantages make DNA-based immunization a desirable immune-based modality for the prevention or treatment of disease.

In cancer therapeutics, immunotherapy through induction of anti-tumor cellular immunity has recently re-emerged as an important experimental therapy for the treatment of cancers, with promising results. Several immune modulators such as the inhibitors of Programmed Death Receptor – 1 (PD-1) or its ligand (PD-L1) are approved for use in cancers such as melanoma and non-small cell lung cancer. DNA immunization with plasmids directed towards cancer antigens are expected to also demonstrate clinical benefit, especially when administered in combination with immune modulators such as the checkpoint inhibitors.
INO-5401, a combination of multiple plasmids, is a recombinant plasmid-derived DNA-based vaccine targeting the PSMA, hTERT, and WT-1 antigens, which are known to be overexpressed in several human cancers (Table 3). PSMA, hTERT, and WT-1 antigens have been shown to be highly immunogenic in animal models and effective at driving tumor regression in preclinical tumor models. INO 9012, a DNA plasmid which encodes IL-12 is given as an immune adjuvant to enhance response to INO-5401.

Table 3: Percent Overexpression of Antigens in Multiple Tumor Types

	HCC	GBM	Pancreas	UCa	Ovarian
hTERT	88-93%	79% (IHC)	84-88%	58-93%	71%
WT-1	86-95%	86%	35-75%	33-65%	71-86%
PSMA	88%	89%	87%	17-100%	75-100%

Source: see text for references. HCC: hepatocellular carcinoma; GBM: glioblastoma multiforme; UC: urothelial cancer; IHC: immunohistochemistry; hTERT: human telomerase; WT-1: Wilms Tumor-associated antigen; PSMA: prostate-specific membrane antigen.

As described above, our experience with VGX-3100 vaccine provides confirmatory proof-of-concept in the ability to generate expansion of antigen-specific CD8+ T-cells with a tolerable safety profile and improvement in clinically relevant endpoints. Consequently,

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a strong rationale exists to trial the similarly manufactured, but differing targeted DNA vaccine INO-5401, in combination with INO-9012.

1.1.4. USE OF IL-12 PLASMID WITH DNA VACCINES

Preclinical studies showed that the immunogenicity of DNA vaccines can be substantially increased by the use of cytokine adjuvants [28-36]. Co-administration of cytokine plasmids with DNA vaccines has been studied in rodents [37] and provide the basis for evaluation of INO-5401 + INO-9012 in humans. IL-12 is a heterodimeric cytokine encoded by two separate genes, IL-12A (p35) and IL-12B (p40). Although p35 IL-12 gene transcripts are ubiquitous, p40 transcripts are unique to cells producing biologically active IL-12, which include monocytes, macrophages, dendritic cells (DCs), polymorphonuclear leukocytes (PMN), and B cells [38]. These studies demonstrated a dramatic increase in specific cytotoxic T-lymphocyte (CTL) activity when a DNA plasmid was co-administered with an IL-12 plasmid, as compared with results in animals receiving therapeutic plasmid alone. The molecular adjuvant activity of several Th1 cytokines (GM-CSF, IL-2, IL-12, IL-15, and IL-18) was evaluated in mice in a subsequent trial [34]. This trial revealed that the IL-12 plasmid was the best driver of major histocompatibility complex (MHC)-restricted CD8+ CTL activity. Co-delivery of IL-12 DNA with DNA vaccines was also evaluated in macaques and chimpanzees with enhanced responses to DNA immunogens with IL-12 plasmid injections [39-41]. A substantial enhancement of cellular immune responses with IL-12 DNA and DNA therapeutic plasmid administration compared with a DNA therapeutic plasmid alone in macaques has also been demonstrated [42, 43]. Of note, no significant additional toxicity has been observed when cytokine adjuvants were co-administered with DNA vaccines in preclinical studies.

In a clinical trial with a vaccine of HIV-1 DNA immunogen, co-administration of IL-12 DNA was associated with an enhanced CD8+ antigen-specific immune response [44, 45]. The use of IL-12 DNA has also been associated with expansion of antigen-specific interferon-gamma (IFN-γ) positive effector cells, as well as granzyme B production. The induced immunity included both a CD8+ as well a CD4+ component [41, 46]. The safety and tolerability of IL-12 in humans is discussed in Section 6 of Investigator Brochure.

1.1.5. USE OF ELECTROPORATION WITH DNA VACCINES

Several groups are developing methods to improve the immune responses of DNA vaccines, using genetic optimization, cytokine adjuvants, and alternative cellular delivery with devices such as electroporation (EP) [47]. Inovio employs all these methods with an emphasis on improving the transfection of DNA using *in vivo* EP. This physical process exposes the target tissue to a brief electric field pulse that induces temporary and reversible pores in the cell membrane to enhance the cellular uptake of large molecules such as DNA. By temporarily increasing the permeability of cell membranes, EP has been shown to be an efficient way to introduce DNA into cells [48, 49] and to increase the expression level of antigens encoded by DNA [50]. This technology has been used for more than three decades by molecular biologists for *in vitro* cell transfection.

The hypothesis is that EP will increase the uptake and expression of plasmid DNA (pDNA), generating significantly increased immunogenicity. Electroporation enhances both cellular and humoral immune responses, using less DNA than intramuscular immunizations alone [51]. Studies have demonstrated the ability of EP to augment specific cellular immune responses in mice [52] and in macaques [53]. It has been found that simian

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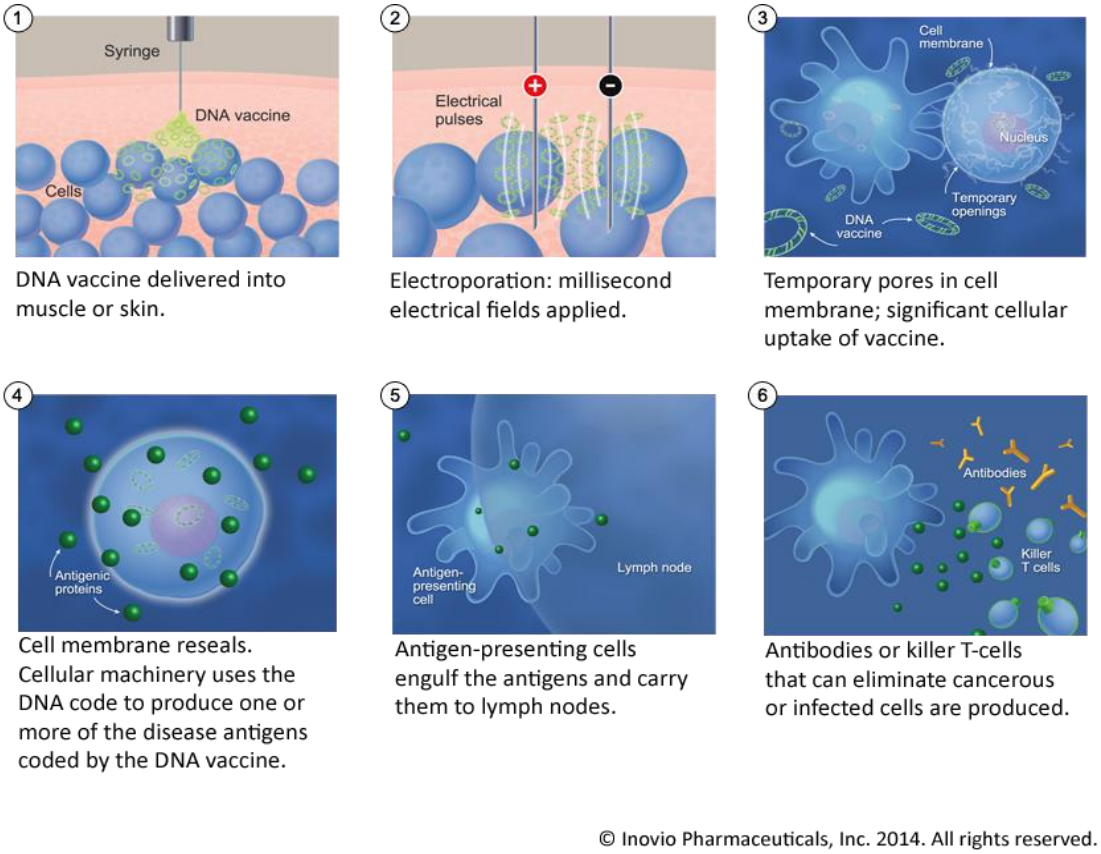
immunodeficiency virus (SIV) DNA vaccines potency can be increased 50-200 fold [33] when delivered intramuscularly (IM) followed by EP. There are various means of delivering EP (e.g. constant current vs. constant voltage) and testing these strategies in mice and pigs has shown a constant current device may be the most effective at generating immune responses [54]. Studies in macaques found that EP of SIV DNA + IL-12 plasmids yielded 10-fold higher responses than DNA without EP [50], and that this immune response was boosted with additional doses. These responses are also polyfunctional, as defined by the ability of immune cells from treated animals to generate Interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α) and IL-2. Furthermore, the functional consequence of EP delivery of DNA encoding an antigen in combination with IL-12 is an improved ability of specific $CD8^+$ T-cells to proliferate in culture in response to antigenic stimulation compared to delivery without EP [50]. Additionally, it has been shown that delivering DNA vaccines with electroporation has a significant dose-sparing effect, along with superior immunogenicity when compared to DNA vaccines delivered without the use of electroporation [45]. Figure 1 describes how EP works in the body.

Figure 1: How Electroporation Works in the Body



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Following successful proof-of-concept studies in animals, Inovio has optimized both pulse pattern and voltage to increase transfection efficiency. To date, however, EP remains experimental in humans; it has not been licensed by the FDA for clinical use. More recently, clinical applications of DNA or drug delivery via EP have been tested in the treatment of cancer and in gene therapy [55-58].

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1.2. TRIAL RATIONALE AND BENEFIT-RISK ASSESSMENT

As described above, encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in advanced cancer subjects including mUC subjects. On the basis of the above observations, the proposed trial will assess for safety, immunogenicity and efficacy of INO-5401 + INO-9012 in combination with atezolizumab.

This trial will enroll subjects in two cohorts: Cohort A will enroll subjects who are CPI refractory and may have received one or more lines of chemotherapy prior to CPI failure as well. There will be no restriction to the number of prior therapies as long as subjects have progressed on a CPI previously; to date no therapy has demonstrated any meaningful clinical response in this population.

Cohort B will enroll subjects who are treatment naïve cisplatin ineligible. There are two CPI inhibitors approved in this subject population however as described previously only less than a third of subjects respond to CPI monotherapy and rational combination approaches are highly desirable. In contrast to chemotherapeutic agents used for mUC, CPIs including atezolizumab, have been generally well tolerated with long-term durable responses and have not been associated with bone marrow suppression or other systemic toxicities (i.e., neuropathy, peripheral edema, nephrotoxicity, or febrile neutropenia) that may limit the ability to administer subsequent treatments.

Preliminary Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) response rates to atezolizumab in mUC have demonstrated clinical responses in a median of 8 weeks and as with other tumor types often responses seen are durable. However, to account for the possibility of pseudoprogression/tumor immune infiltration (i.e., radiographic increase in tumor volume due to the influx of immune cells; Hales et al. 2010) and the potential for delayed anti-tumor activity, this trial will use iRECIST (immune RECIST) criteria (in addition to RECIST v1.1) as a secondary endpoint. Subjects will be allowed to receive atezolizumab and INO-5401 + INO-9012 beyond initial radiographic progression until clinical deterioration or confirmation of radiographic progression occurs. Additionally, to understand the biology of pseudo progression/tumor immune infiltration as well as true disease progression (such as in subjects with true progression, a biopsy will help to elucidate mechanisms of primary/acquired resistance), a mandatory tumor biopsy sample (acceptable samples include core needle biopsies for deep tumor tissue [minimum three cores] or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions) will be collected if clinically feasible per the trial investigator in subjects who provide informed consent, at the first evidence of radiographic or clinical disease progression (i.e., not preceded by meaningful tumor regression). This evaluation will be used to trial the correlation between changes in tumor tissue and clinical outcome. These data, which will include assessing for the presence of tumor infiltrating lymphocytes [redacted], will inform the future use of a biopsy at first progression and may help to identify those subjects who are likely to benefit from further treatment with INO-5401 + INO-9012 and atezolizumab from those subjects who are unlikely to benefit from further treatment. In summary, treatment with INO-5401 + INO-9012 and atezolizumab offers the potential for clinical benefit in subjects with mUC.

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Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigator's Brochure (IB) and Informed Consent documents.

2. HYPOTHESIS

We hypothesize that INO-5401 + INO-9012 delivered by intramuscular injection (IM) followed by electroporation (EP) with CELLECTRA™ 2000 in combination with atezolizumab, will be generally safe, well tolerated, immunogenic and may lead to anti-tumor responses in adult subjects with locally advanced unresectable or metastatic/recurrent UCa.

3. TRIAL DESIGN, OBJECTIVES AND ENDPOINTS

This is a Phase I/IIA, open-label, multi-center trial to evaluate the safety, immunogenicity and preliminary clinical efficacy of INO-5401 + INO-9012 delivered by IM/EP, in combination with atezolizumab in subjects with locally advanced unresectable or metastatic/recurrent UCa. The trial population is divided into two cohorts:

Cohort A: Subjects with locally advanced unresectable or metastatic/recurrent UCa who have confirmed disease progression during or following treatment with an anti-PD-1/PD-L1 therapy.

Cohort B: Subjects with locally advanced unresectable or metastatic/recurrent UCa who are treatment naïve and ineligible for cisplatin based chemotherapy.

Safety Run-In: A safety run-in will be performed using a modified Rolling Six design [59] which will enroll up to six subjects (safety analysis subjects) from cohort A.

Once the first three subjects of these six subjects have completed Week 6 assessments, in the absence of any dose-limiting toxicity (DLT), enrollment may proceed to completion. However, if prior to the first three subjects completing Week 6, a single subject from the first six experiences a DLT, then enrollment will be limited to six subjects until all six subjects have reached Week 6, and are assessed for DLT. If no additional subjects, of these six, experience a DLT within the 6 week safety run in period, then enrollment may proceed to completion.

If a second of these first six subjects experiences a DLT within the first six weeks, enrollment will stop, and the Sponsor's medical monitor, in addition to the PI and investigator(s) at the subjects' site(s) will discuss the case, and a decision will be made whether to modify the trial, or to cease further enrollment. Enrollment will only be reinitiated after amendment of the protocol and approval of the amended protocol by the IRB.

Safety run-in subjects that withdraw from the study for reasons other than a DLT, prior to the end of the safety run-in period, will be replaced. The end of the safety run-in period is defined as the earliest of the following:

- The first three subjects in Cohort A have all completed Week 6 with no DLTs experienced by any of the safety run-in subjects in that cohort (up to six); enrollment will then proceed to completion;

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- All six subjects of the safety run-in phase, in Cohort A, have completed week six with only one subject having experienced a DLT; enrollment may then proceed to completion;
- Two or more of the safety run-in subjects, have experienced DLTs prior to completing Week 6; enrollment will be suspended.

DLTs are defined in protocol Section 7.9.

Because this trial is combining INO-5401 + INO-9012 with atezolizumab for the first time, there will be a waiting period of one week between enrollment of the first subject and the second subject.

Enrollment was stopped at 35 subjects (28 subjects in Cohort A and 7 subjects in Cohort B). Study procedures will be limited to administration of study drugs INO-5401 + INO-9012 and atezolizumab as per prior schedule. Assessments will be limited to standard-of-care assessments (i.e. physical exam, vital signs, hematology, serum chemistry, urinalysis, thyroid functions test) only. No further evaluation of efficacy or immunogenicity will be performed. Please see Table 2 for recommended assessments.

3.1. OBJECTIVES AND ENDPOINTS

Primary Objectives:	**Associated Primary Endpoints:**
1. To determine the safety and tolerability of INO-5401 + INO-9012 delivered by IM injection followed by EP with CELLECTRA™ 2000 device in combination with atezolizumab among subjects with locally advanced unresectable or metastatic/recurrent UCa	• All adverse events (AEs) including adverse events of special interest (AESI) classified by system organ class (SOC), preferred term (PT), severity and relationship to drug • Clinically significant changes in safety laboratory parameters from baseline: CBC with Differential; Chemistry Panel; Urinalysis; T3, Free T4 and TSH; creatine phosphokinase (CPK)
2. To evaluate preliminary immune response to INO-5401 + INO-9012 in combination with atezolizumab in subjects with locally advanced unresectable or metastatic/recurrent UCa	• Antigen-specific cellular immune responses that may be assessed by but not limited to: ○ Interferon-γ secreting T lymphocytes in peripheral blood mononuclear cells (PBMCs) by ELI Spot • T-cell activation and cytolytic cell phenotype in PBMCs by Flow Cytometry or secretion of immune molecules • B cell activation/antibody secretion; • Assessment of Myeloid Derived Suppressor Cells (MDSC) • TCR sequencing of PBMCs for diversity and putative antigen specificity

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	• Immune gene transcript profiling of PBMCs • Assessment of proinflammatory and immunosuppressive elements in neoplastic and adjacent normal tissue, where feasible
3. To evaluate objective response rate of INO-5401 + INO-9012 in combination with atezolizumab in subjects who have received and/or progressed on anti-PD-1/PD-L1 based therapy previously (cohort A)	Objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by investigator review in subjects who have received and/or progressed on anti-PD-1/PD-L1 based therapy previously (cohort A)
Secondary Objective	**Associated Secondary Endpoints**
To evaluate the anti-tumor activity of INO-5401 + INO-9012 in combination with atezolizumab in subjects with locally advanced unresectable or metastatic/recurrent UCa	• Objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by investigator review for treatment naïve, cisplatin-ineligible subjects (cohort B) • ORR by immune RECIST (iRECIST) for both cohorts • Duration of Response (DoR) for both cohorts • Progression Free Survival (PFS) as assessed by RECIST version 1.1 and iRECIST for both cohorts • Overall Survival (OS) for both cohorts
[redacted]	[redacted]

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4. TRIAL POPULATION

4.1. INCLUSION CRITERIA

In order to be eligible for participation in this trial, the subject must:

1. Provide signed IRB approved informed consent in accordance with institutional guidelines;
2. Be 18 years of age or older on the day of signing the informed consent, and able and willing to comply with all trial procedures;
3. Have histologically or cytologically documented locally advanced unresectable or metastatic/recurrent urothelial carcinoma (including renal pelvis, ureters, urinary bladder, and urethra):
   a) **For Cohort A**: Subjects who have radiographically confirmed disease progression during or following treatment with an anti-PD-1/PD-L1 based therapy
   b) **For Cohort B**:
      i. No prior chemotherapy for inoperable locally advanced or metastatic or recurrent UCa:
         - For subjects who received prior adjuvant/neoadjuvant chemotherapy or chemoradiation for UCa, a treatment-free interval greater than 12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment naive in the metastatic setting.
         - Prior local intervesical chemotherapy or intravesical immunotherapy is allowed if completed at least 4 weeks prior to the initiation of trial treatment.
      ii. Ineligible ("unfit") for cisplatin-based chemotherapy as defined by any one of the following criteria:
         - Impaired renal function (glomerular filtration rate [GFR] > 30 but < 60 mL/min); GFR should be assessed by direct measurement (i.e., creatinine clearance or ethyldediaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula)
         - A hearing loss (measured by audiometry) of 25 dB at two contiguous frequencies
         - Grade 2 or greater peripheral neuropathy (i.e., sensory alteration or parasthesias including tingling)
4. Have measurable disease, as defined by RECIST version 1.1 (investigator assessment). Target lesions must not have been previously treated with surgery, radiation therapy, or radiofrequency ablation unless there is documented progression in the lesion after such therapy and no other lesions are available for selection as target lesions;
5. Have a performance status of 0 or 1 on Eastern Cooperative Oncology Group (ECOG) Performance Scale;
6. Have a life expectancy of ≥ 3 months;
7. Be willing to provide a tissue sample for pre-treatment intra-tumoral assessment of proinflammatory and immunosuppressive factors. Preferably, tumor biopsies will be collected at the time of screening or newly obtained tissue can be used (no intervening treatment [local or systemic] involving the site of tissue biopsy once tissue biopsy is obtained up to the time of trial enrollment);
   Note: For cohort A, this refers to tissue obtained during fresh biopsy or archived post-anti-PD-1/PD-L1 based therapy progression. For cohort B, this refers to newly

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diagnosed, all treatment naïve archival or fresh tissue. Additionally, for cohort A subjects, an archival sample (ideally treatment naïve) will be requested as well, however, enrollment is allowed for subjects unable to provide newly obtained or lacking tissue specimens after consultation with the Sponsor (see Table 7);

8. Have ECG with no clinically significant findings as assessed by the investigator performed within 28 days prior to first dose;
9. Demonstrate adequate organ function: hematological, renal, hepatic, coagulation parameters as defined in Table 4 and obtained within 28 days prior to the first trial treatment;

Table 4: Adequate hematologic and end-organ function parameters

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/ µL
Platelets	≥100,000/ µL
Hemoglobin	≥9 g/dL, or ≥5.6 mmol/L without transfusion or EPO dependency within 7 days.
Renal	
Creatinine OR Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 x upper limit of normal (ULN) OR ≥30 mL/min for subject with creatinine level > 1.5 x institutional ULN Note: Creatinine clearance should be calculated per Cockcroft-Gault formula
Hepatic	
Total bilirubin	≤ 1.5 x ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN **OR** ≤ 5 x ULN for subjects with liver metastases
Albumin	≥ 2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

10. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of study treatment:
    - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of

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amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)
- Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

11. For male subjects: Agree that during the period specified above, men will not father a child. Subjects must be surgically sterile (e.g, vasectomy) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of study treatment.

4.2. EXCLUSION CRITERIA

Subjects who meet any of the following criteria will be excluded from trial entry:

Cancer-specific Exclusion Criteria:

1. Any approved anti-cancer therapy including chemotherapy, targeted small molecule therapy or radiation therapy within 2 weeks prior to trial Day 0; or if subject has not recovered (ie., Less than or equal to grade 1 or returned to baseline level) from adverse events due to a previously administered agent; the following exceptions are allowed:
   - Palliative radiotherapy for bone metastases or soft tissue lesions should be completed > 7 days prior to baseline imaging;
   - Hormone-replacement therapy or oral contraceptives;
   - Subjects with grade 2 neuropathy or grade 2 alopecia;
2. Currently participating and receiving trial therapy or has participated in a trial of an investigational agent and/or has used an investigational device within 28 days prior to Day 0;
   Note: Subjects who have entered the follow-up phase of an investigational trial may participate as long as it has been 28 days since the last dose of the previous investigational agent or device;
3. Documented active or untreated central nervous system (CNS) metastases and/or carcinomatous meningitis. For suspected neurological involvement, CT or MRI evaluation is recommended during screening to rule out CNS metastases. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurological symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability;
4. Uncontrolled tumor-related pain:
   - Subjects requiring pain medication must be on a stable regimen at trial entry
   - Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should complete treatment at least 7 days prior to enrollment

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- Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment

5. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly and more frequently):
   - Subjects with indwelling catheters (e.g., PluerX) are allowed
6. Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab:
   - Subjects who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and do not have a history or clinically significant hypercalcemia are eligible
   - Subjects who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while in the trial
7. Malignancies other than UCa within 3 years prior to Day 0, with the exception of those with negligible risk of metastasis or death treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent) or localized prostate cancer treated with curative intent and absence of prostate-specific antigen (PSA) relapse or incidental prostate cancer (T1/T2a, Gleason score ≤ 3 + 4, and PSA ≤ 0.5 ng/mL undergoing active surveillance and treatment naïve);

General Medical Exclusion Criteria

8. Pregnant or lactating, or intending to become pregnant or father children within the projected duration of the trial starting with the screening visit through 5 months after the last dose of checkpoint inhibitor and/or DNA vaccine;
9. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins;
10. Known hypersensitivity allergy or contraindication to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the PD-1/PD-L1 inhibitor formulation;
11. Active or history of autoimmune disease or immune deficiency, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener granulomatosis with polyangiitis, Sjögren's syndrome, Guillain-Barrè syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (See Appendix 3 for a more comprehensive list of autoimmune diseases and immune deficiencies):
    - Subjects with history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this trial
    - Subjects with controlled Type I diabetes mellitus on a stable dose of insulin regimen may be eligible for this trial
12. History or any evidence of interstitial lung disease such as idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug induced or active non-infectious pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan;
    - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
13. History of HIV (If the investigator suspects a clinical evidence of HIV, an HIV antibody test should be performed to exclude this possibility);

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14. Active hepatitis B (hepatitis B surface antigen reactive) or active hepatitis C (HCV qualitative RNA detected); testing is recommended per investigator's clinical suspicion;
15. Severe infections within 4 weeks prior to enrollment, including, but not limited to, hospitalization for complications of infection, bacteremia, or the presence of any active infection requiring systemic therapy;
16. Received therapeutic oral or IV antibiotics within 2 weeks prior to Day 0:
    - Subjects receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible
17. History or current evidence of any condition, therapy or laboratory abnormality (e.g. chronic renal failure; angina, myocardial ischemia or infarction, class 3 or higher congestive heart failure, cardiomyopathy, or clinically significant arrhythmias) that in the opinion of the treating investigator might confound the results of the trial or interfere with the subject's participation for the full duration of the trial;
18. Prior allogeneic stem cell or solid organ transplant;
19. Received a live, attenuated vaccine within 28 days prior to randomization or anticipation that such a live attenuated vaccine will be required during the trial;
    Note: Influenza vaccination should be given during influenza season only (approximately October to March). Subjects must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to Day 0, during treatment, or within 90 days following the last dose of trial treatment;
20. Fewer than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites;
    - Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site
    - Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)
    - Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area)
21. Presence of acute or chronic bleeding or clotting disorder that would contraindicate IM injections, or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks prior to Day 0;
22. Known previous or ongoing, active psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial;
23. Prisoner or subject who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;

<u>Medication-Related Exclusion Criteria</u>

24. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies for cohort B:
    - Subjects who have received prior treatment with anti-CTLA-4 may be enrolled provided at least 5 half-lives (approximately 75 days) have elapsed from the last dose of anti-CTLA-4 to the first dose of trial treatment and there was no history of severe immune-mediated adverse effects from anti-CTLA-4 (Grade 3 or 4)
    - Prior cancer vaccines and cellular immunotherapy are permitted; subjects are encouraged to undergo a fresh pre-treatment sample collection for biopsy to evaluate immunological status
25. Treatment with systemic immunostimulatory agents (including but not limited to IFNs, IL-2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to first dose;

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26. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF- α agents) within 2 weeks prior to initiation of trial treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:
    - Subjects who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study (after Sponsor approval has been obtained)
    - Subjects who received mineralcorticosteriods (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) for asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study

4.3. DISCONTINUATION/WITHDRAWAL OF TRIAL SUBJECTS

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, the investigator or the Sponsor has the right to withdraw a subject from the trial at any time.

Reasons for withdrawal from the trial may include but are not limited to the following:

- Subject withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the subject's safety if he or she continues in the trial
- Investigator or Sponsor determines it is in the best interest of the subject
- Subject non-compliance

Every effort should be made to obtain information on subjects who withdraw from the trial. Subjects will not be followed for any reason after consent has been withdrawn. Subjects who withdraw from the trial will not be replaced except for subjects that withdraw for reasons other than toxicity during the safety run-in phase of the study.

Subjects should discontinue trial treatment if they experience any of the following:

- Symptomatic deterioration (i.e., uncontrollable pain secondary to disease or unmanageable ascites, etc.) attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status
- Intolerable toxicity related to trial treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual subject's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the subject's safety if he or she continues on trial treatment
- Use of another non-protocol anti-cancer therapy (see Section 5.12.2)
- Pregnancy

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4.3.1. SUBJECT REPLACEMENT STRATEGY

A subject who receives at least one trial treatment and who discontinues from the trial for any reasons will not be replaced except for subjects that withdraw for reasons other than toxicity during the safety run-in phase of the study.

5. TRIAL TREATMENT

5.1. INVESTIGATIONAL DRUG PRODUCTS

The trial products to be used in this clinical trial are listed in and Section 5.1.1 and Section 5.1.2. All drug products must be stored in the appropriate temperature-controlled unit immediately upon arrival. The products require preparation prior to administration, which is outlined in the pharmacy manual.

5.1.1. INO-5401 AND INO-9012

Table 5: Investigational Drug Products

Product	Formulation	Unit (2-mL vial)
INO-5401	[redacted]	[redacted]
INO-9012	[redacted]	[redacted]

[redacted]

[redacted]. EP is a physical method of tissue transfection whereby the generation of short, controlled electrical pulses creates a localized electric field at the injection site of the DNA plasmid, which increases cell membrane permeability and improves uptake of the DNA. [49, 60] Details about the

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CELLECTRA™ 2000 device are found in the Investigator's Brochure and device User Manual.

5.1.2. ATEZOLIZUMAB

Atezolizumab is a monoclonal antibody that binds to PD-1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody-dependent cellular cytotoxicity. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

[redacted]

5.2. TREATMENT REGIMENS

Prior to enrollment of 35 subjects:

1. INO-5401+ INO-9012 will be administered followed by EP with CELLECTRA™ 2000 device every 3 weeks (± 3 days) for 4 doses then every 6 weeks (±3 days) for 6 additional doses, thereafter every 12 weeks (±3 days) until confirmed disease progression, unacceptable toxicity, or deemed intolerable by the investigator.
2. Atezolizumab will be administered every 3 weeks until confirmed disease progression, unacceptable toxicity, or deemed intolerable by the investigator.
3. Either treatment may be stopped by the investigator (e.g. due to toxicity) while the other treatment continues.
4. INO-5401 + INO-9012 will be dosed approximately 1 hour after IV infusion of atezolizumab for the first dose. Subsequent doses of INO-5401 + INO-9012 and atezolizumab can be dosed in any order.

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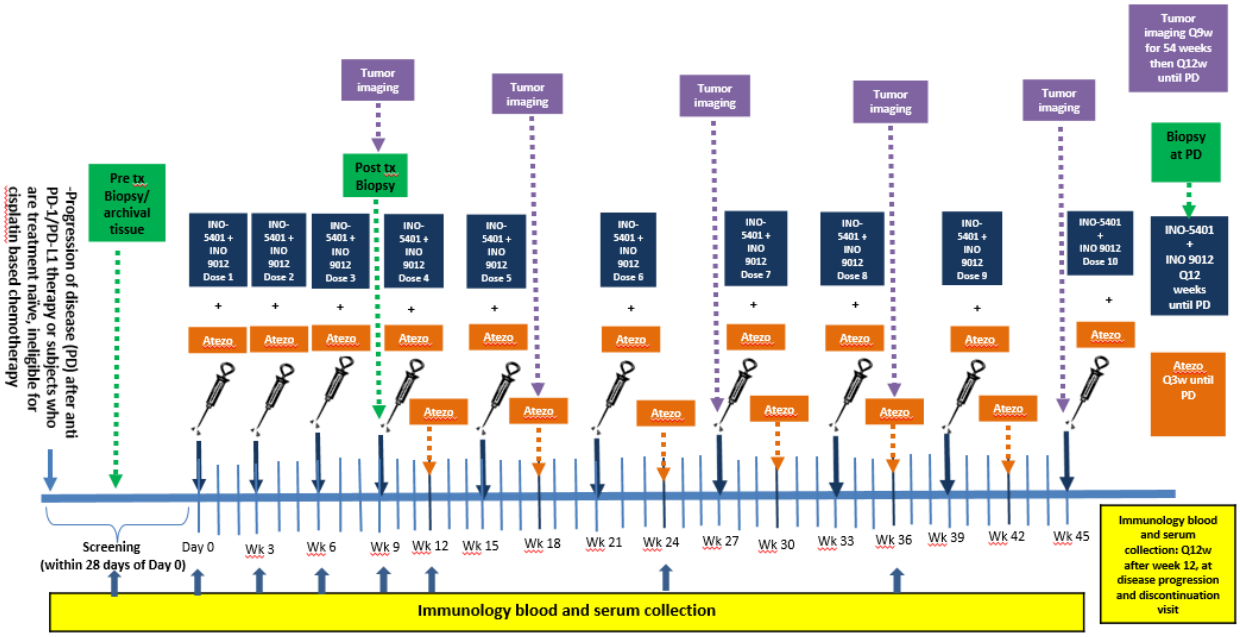
Figure 2: Trial Schema of Cohort A and Cohort B Prior to Enrollment of 35 Subjects:



PD: Progressive disease	Q3w: Every 3 weeks
Atezo: Atezolizumab	Q9w: Every 9 weeks
Tx: Treatment	Q12w: Every 12 weeks
PD-1/PD-L1: Programmed Death-1/Programmed Death Ligand-1	
Wk: Week	

The following procedures will be performed for both cohorts following enrollment of 35 subjects:

1. INO-5401+ INO-9012 will be administered IM followed by EP with CELLECTRA™ 2000 device every 3 weeks (± 3 days) for 4 doses then every 6 weeks (±3 days) for 6 additional doses, thereafter every 12 weeks (±3 days) until disease progression, unacceptable toxicity, or the investigator determines it is in the best interest of the subject to terminate study drug. Confirmation of disease progression is not required.

2. Atezolizumab will be administered every 3 weeks until disease progression, unacceptable toxicity or the investigator determines it is in the best interest of the subject to terminate study drug. Confirmation of disease progression is not required.

5.3. PACKAGING AND LABELING

This trial is open label. Therefore the subject, the investigator's site personnel and the Sponsor or its designee are not blinded to trial treatment. Each vial of investigational products will be labeled with a single panel label. Sample product labels for INO-5401, INO-9012 and atezolizumab are provided in the Investigator's Brochure for INO-5401 + INO-9012 and atezolizumab respectively.

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5.4. HANDLING AND STORAGE

5.4.1. INO-5401 + INO-9012

Inovio Pharmaceuticals, Inc. will be responsible for assuring the quality of the Investigational Product (IP) is adequate for the duration of the trial. Unless otherwise specified, [redacted]. If the temperature monitoring devices in the shipping containers denote temperatures outside the pre-specified ranges for any product, the Sponsor, or its designee should be contacted immediately.

[redacted] For further details see Pharmacy Manual and IB.

5.4.2. ATEZOLIZUMAB

[redacted]

5.5. PREPARATION AND DISPENSING

5.5.1. INO-5401 + INO-9012

[redacted]

5.5.2. ATEZOLIZUMAB

The dose level of atezolizumab in this trial is 1200 mg administered by IV infusion every 3 weeks.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. For more detailed information regarding administration, refer to the Investigator's Brochure and Pharmacy Manual. Table 6 provides instructions to follow during atezolizumab infusions.

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Table 6: Atezolizumab infusion instructions

First Infusion	Subsequent Infusions
• No premedication is permitted. • Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (±5 minutes for all timepoints) during the infusion and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±5) minutes after the infusion.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for dosing visit ≥ 2 at the discretion of the treating physician. The management of infusion-related reactions will be according to severity as follows:

- In the event that a subject experiences a mild [Common Terminology Criteria for Adverse Events (CTCAE) Grade 1] infusion-related event, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a subject experiences a moderate infusion-related event (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the subject should have his or her infusion immediately interrupted and should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the infusion-related event.
- For severe or life-threatening infusion-related events (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Subjects experiencing severe or life-threatening infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves.

For anaphylaxis precautions, see Appendix 2.

Guidelines for dosage modification, treatment interruption or discontinuation and for the management of specific adverse events are provided in Sections 7.10, 6.15.3 and 7.11.

Adverse events associated with an overdose or incorrect administration of trial drug should be recorded on the Adverse Event eCRF.

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Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

5.6. INVESTIGATIONAL PRODUCT ACCOUNTABILITY

It is the responsibility of the investigator to ensure that a current record of investigational product (IP) accountability is maintained at the study site. The accountability of INO-5401, INO-9012 and atezolizumab should be maintained individually. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area;
- Amount currently in storage area;
- Label ID number and use date or expiry date;
- Dates and initials of person responsible for each investigational product inventory entry/movement;
- Amount dispensed to each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount returned to Sponsor;
- Amount destroyed at study site, if applicable.

5.7. RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

Upon completion or termination of the study, all unused IP (INO-5401, INO-9012 and atezolizumab) must be destroyed at site per institution policy or returned to Inovio Pharmaceuticals, Inc. or its designee, if site cannot destroy IP.

The used IP vials will be discarded along with the disposable array within a sharps container at site. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused IP(s) should be arranged by the responsible Study Monitor. The unused IP can only be destroyed after being inspected and reconciled by the responsible Inovio Pharmaceuticals, Inc. or designated Study Monitor. If IP is returned to Inovio Pharmaceuticals, Inc., or its designee, must be accompanied by the appropriate documentation. The return of unused IP(s) should be arranged with the responsible Inovio personnel and/or Clinical Monitor.

5.8. USE OF INVESTIGATIONAL DEVICE

The instructions for use of the CELLECTRA™ 2000 device are provided in the User Manual. Each clinical site will receive training for use of the CELLECTRA™ 2000 device prior to first dose.

The CELLECTRA™ 2000 device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA™ 2000 User Manual describes all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. [redacted]

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[redacted]

5.9. PACKAGING AND LABELING OF INVESTIGATIONAL DEVICE

The CELLECTRA™ 2000 device, and its components, will be shipped directly from the manufacturer to the study site. The investigational labels of CELLECTRA™ 2000 device are provided in the Investigator's Brochure.

5.10. INVESTIGATIONAL DEVICE ACCOUNTABILITY

The investigative site is responsible for maintaining investigational device accountability logs. The device must have full traceability from the receipt of the products through subject use, disposal or return of the products. The Site must document acknowledgement of receipt and notify Inovio upon receipt of investigational devices. This includes the content shipped and condition upon receipt.

For each subject treatment, there must be a record of each product used for that subject, i.e. CELLECTRA™ 2000 serial number, applicator serial number, and array lot number. The CELLECTRA™ 2000 IM Applicator is intended to be used multiple times on the same subject and then disposed of after final use in accordance with accepted medical practice and any applicable local, state, and federal laws and regulations. Once the IM applicator is assigned to a subject, it may NOT be used on another subject. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

5.11. RETURN OF INVESTIGATIONAL DEVICES

Upon completion or termination of the study, an Inovio Representative will provide instructions regarding the component(s) to be returned to Inovio Pharmaceuticals, Inc., destroyed onsite or shipped to a destruction vendor.

All product returned to Inovio Pharmaceuticals, Inc. must be accompanied by the appropriate return documentation. Returned supplies should be in the original containers. The return of all product identified above should be arranged by the responsible Study Monitor. The arrays should be discarded in the sharps container immediately after use. The used applicators can either be destroyed at the site, shipped to a destruction vendor or returned to Inovio. If the used applicators are destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Inovio Pharmaceuticals, Inc., or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented.

5.12. CONCOMITANT MEDICATIONS/TREATMENTS

5.12.1. ACCEPTABLE CONCOMITANT MEDICATIONS

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a subject between the 7 days preceding the screening evaluation and the study treatment discontinuation visit.

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Subjects who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, diphenhydramine, and/or famotidine or another H2 receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists; see Appendix 2).

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of trial treatment but may be administered at the discretion of the treating physician in the event of an emergency or after consultation with the Sponsor. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for dosing visits ≥ 2 at the discretion of the treating physician after consultation with the medical monitor. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for subjects with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as an appetite stimulant is acceptable while the subject is enrolled in the trial.

Influenza vaccination should be given during influenza season only (approximately October to March). Subjects must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to randomization, during treatment, or within 90 days following the last dose of trial treatment but may receive inactivated vaccines.

Subjects who use hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer, oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low−molecular weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy (see Section 4.2) should continue their use.

Males and females of reproductive potential should use highly effective means of contraception and should continue for 5 months after last dose of trial treatment.

All concomitant medications related to adverse events should be reported to the investigator and recorded on the appropriate AE eCRF.

Subjects may be offered topical anesthetic [redacted]

Subjects may be offered a mild sedative [redacted]

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5.12.2. PROHIBITED CONCOMITANT MEDICATIONS

Any concomitant therapy intended for the treatment of cancer, whether health authority−approved or experimental, is prohibited. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (except for maintenance therapies outlined in Section 4.2)
    - After the completion of first trial treatment, certain forms of radiotherapy may be considered for palliation if subjects are deriving benefit (e.g., treatment of known bony metastases, symptomatic hematuria).
    - Subjects experiencing a mixed response requiring local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue trial treatment. Subjects who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases must be discussed with and approved by the Medical Monitor.
- Traditional herbal medicines should not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.

Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is strongly discouraged.

Subjects are not allowed to receive immunostimulatory agents, including but not limited to IFN-α, IFN-γ, or IL-2, during the entire trial. These agents, in combination with trial treatment, could potentially increase the risk for autoimmune conditions.

Subjects should also not receive immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of trial treatment. Systemic corticosteroids and anti−TNF-α agents may attenuate potential beneficial immunologic effects of trial treatment but may be administered at the discretion of the treating physician after consultation with the Medical Monitor. If feasible, alternatives to these agents should be considered.

In addition, all subjects (including those who discontinue the trial early) should not receive other immunostimulatory agents for 10 weeks after the last dose of trial treatment.

6. TRIAL PROCEDURES AND SCHEDULE

The Trial Schedule of Events (Table 1) summarizes the trial procedures to be performed at each visit, prior to enrollment of 35 subjects. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinical necessary by the investigator.

Enrollment was stopped at 35 subjects (28 subjects in Cohort A and 7 subjects in Cohort B). Following radiographic progression, trial treatment should be stopped, and confirmation of disease progression is not required. Study procedures will be limited to

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administration of study drugs INO-5401 + INO-9012 and atezolizumab as per prior schedule. Please see Table 2 for the Schedule of Events that summarizes the trial procedures that are suggested.

6.1. INFORMED CONSENT

All subjects must sign the informed consent prior to any trial related procedures being performed. The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified trial personnel will meet with prospective trial subjects, explain the trial, and provide them with an informed consent form (ICF) that describes the screening tests, eligibility criteria for entering the trial, trial treatments and follow-up procedures, in a language understandable to the subject. Explanation of the trial includes, but is not limited to, trial objectives, potential benefits and risks, discomforts/inconveniences, and the subject's rights and responsibilities. The subject or subject's legally acceptable representative is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the subject or subject's legally acceptable representative. The qualified trial personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the subject's source records and must be accessible for verification at any time.

6.2. INCLUSION/EXCLUSION CRITERIA

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee at screening and prior to first dose to ensure that the subject qualifies for the trial.

6.3. ASSIGNMENT OF SUBJECT IDENTIFICATION NUMBERS

Each subject who consents will be assigned a unique subject identification number (SID), which identifies the subject for all trial-related procedures. Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date will be documented on a screening and enrollment log/system and in the eCRF.

6.4. MEDICAL HISTORY

A medical history will be obtained by the investigator or qualified designee at the time of screening. Medical history will include all active conditions, and any other conditions that are considered to be clinically significant by the investigator. Details regarding the subject's urothelial cancer will be recorded separately and not listed as medical history. Illnesses first occurring or detected after initiation of screening procedures and/or worsening of an existing illness during the trial are to be documented as AEs on the CRF.

6.5. PRIOR AND CONCOMITANT MEDICATIONS REVIEW

6.5.1. PRIOR MEDICATIONS

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Prior treatment for urothelial cancer will be recorded separately and not listed as a prior medication.

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6.5.2. PRIOR TREATMENT DETAILS FOR UROTHELIAL CANCER

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries and record in the trial database.

6.5.3. CONCOMITANT MEDICATIONS

The investigator or qualified designee will record medications, if any, taken by the subject during the trial. All medications related to reportable SAEs and AESIs should be recorded as well.

6.5.4. SUBSEQUENT ANTI-CANCER THERAPY STATUS

The investigator or qualified designee will review all new anti-cancer therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the study treatment discontinuation visit should occur before the first dose of the new therapy.

6.6. SAFETY EVALUATIONS

Safety evaluations and management of toxicities are detailed in Section 7. Assessments for safety are described within this Section.

6.6.1. ADVERSE EVENTS MONITORING

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in Section 7.1 and more frequently if clinical indicated. Adverse events will be graded and recorded throughout the trial and during the follow-up period according to NCI CTCAE version 5.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving trial treatment all AEs of unknown etiology associated with either or both trial treatment exposure should be evaluated to determine if it is possibly an adverse event of special interest (AESI) of a potentially immunologic etiology.

Please refer to Section 7.7 for detailed information regarding the assessment and recording of AEs.

6.6.2. PHYSICAL ASSESSMENTS

6.6.2.1. FULL PHYSICAL EXAM

The investigator or clinical designee will perform a complete physician exam during the screening period (see Table 1: Trial Schedule of Events). A complete PE should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Clinically significant abnormal findings at baseline should be recorded as medical history.

6.6.2.2. TARGETED PHYSICAL EXAM

The investigator or qualified designee will perform a targeted, symptom-directed physical exam as clinically indicated at Day 0 and further visits as described in the Table 1 and Table 2. Targeted physical exam may be performed within 72 hours before each visit.

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New clinically significant abnormal findings should be recorded as AEs after the first dose of trial treatment.

6.6.3. 12-LEAD ECG

An ECG will be performed at screening within 28 days prior to Day 0 for all subjects to determine subject eligibility. Abnormal ECGs should be interpreted as clinically significant or not clinically significant by the investigator.

6.6.4. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCALE

The investigator or qualified designee will assess ECOG status at screening visit and prior to each dosing visit and at discontinuation visit as specified in Table 1: Trial Schedule of Events.

6.6.5. MEDICAL POST-TREATMENT REACTION ASSESSMENT

The investigator will assess local and systemic reactions post-treatment (within 30-60 minutes after each trial treatment). A 30-minute observation period is recommended after each infusion of atezolizumab, and each dose of INO-5401 + INO-9012. Any reported local post treatment reactions and systemic post treatment reactions will be graded per NCI CTCAE version 5.0 and all must be recorded.

6.6.6. VITAL SIGNS

Vital signs including body temperature, respiration rate, blood pressure, weight and heart rate will be measured at the trial visits as described in Table 1 and as suggested in Table 2. Height (cm) will be collected at the screening visit only.

For the first infusion of atezolizumab, the subject's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before the infusion. If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (± 5 minutes for all timepoints) during the infusion, and at 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and at the end of the infusion. Subjects will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their trial physician if they develop such symptoms. For all subsequent infusions of atezolizumab, vital signs should be recorded within 60 minutes prior to infusion and 30 (± 5) minutes after infusion.

6.6.7. TUMOR IMAGING AND ASSESSMENT OF DISEASE

Tumor imaging should be performed by computed tomography (CT), but may be performed by magnetic resonance imaging (MRI) if CT is contraindicated, but the same imaging technique should be used in a subject throughout the trial. CT scans (with oral/IV contrast unless contraindicated) must include chest, abdomen and pelvis.

6.6.7.1. INITIAL TUMOR IMAGING

Initial (screening) tumor imaging must be performed within 28 days prior to the first dose of trial treatment. The investigator/site radiologist must review pre-trial images to confirm the subject has measurable disease per RECIST 1.1.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality, captured on the same machine/modality

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as will be used on the study and performed within 28 days prior to the first dose of trial treatment.

6.6.7.2. TUMOR IMAGING DURING TRIAL

The first imaging assessment should be performed at 9 weeks (± 7days) from the first dose of trial treatment. Prior to the enrollment of 35 subjects, subsequent imaging should be performed every 9 weeks (± 7 days) or more frequently if clinically indicated. After the first 54 weeks (12 months) on trial therapy, the imaging interval should be decreased to every 12 weeks (± 7 days). Imaging should not be adjusted for delays or extension of trial treatment.

Following enrollment of 35 subjects, imaging should be performed per standard of care. The study does not mandate tumor imaging at 9 weeks from first dose or every 9 weeks thereafter. The study treatment should be stopped after initial radiographic progression, and confirmation of disease progression is not required.

6.6.7.3. ASSESSMENT OF DISEASE

Prior to the enrollment of 35 subjects, RECIST 1.1 will be applied by the investigator as the primary measure for assessment of tumor response and date of clinical disease progression. For those subjects that discontinue trial treatment for reasons other than disease progression, imaging will be repeated every 9 weeks (± 7 days), or every 12 weeks (± 7 days) after the first year following the initiation of trial therapy, until the subject experiences confirmed disease progression or starts a new anti-cancer therapy.

Following enrollment of 35 subjects, subjects will no longer require long-term follow-up for efficacy. Following radiographic progression, trial treatment should be stopped, and confirmation of disease progression is not required.

The investigator assessment with site radiology reading based on RECIST 1.1 will be used to determine subject eligibility.

6.6.8. TUMOR TISSUE COLLECTION, CORRELATIVE BLOOD SAMPLING [redacted]

Following enrollment of 35 subjects, subjects will no longer require long-term follow-up for efficacy. No further samples will be collected for tissue, whole blood [redacted] for immunology [redacted] assessment. Those samples collected prior to this may be used as described below.

Tumor Tissue Collection

Tumor tissue will be collected for immunology assessments including but not limited to markers related to inflammation, suppression, T cell infiltration, and associated tumor microenvironment characteristics.

Either an archival tumor tissue sample and/or a newly obtained core or excisional biopsy (fine needle biopsy not adequate) should be submitted to the sponsor in a timely manner.

If a tumor biopsy is to be obtained from an intended target lesion during eligibility assessment, the biopsy should be performed prior to obtaining the baseline scan. Otherwise, a new baseline scan should be obtained.

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Tumor biopsy should be obtained at Week 9 and at first evidence of radiographic or clinical disease progression as stated in Trial Schedule of Events Table 1, but are no longer required after enrollment of 35 subjects as noted above.

- Archival and fresh tumor tissue sample

  Representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, should be submitted for intra-tumoral immunology assessments

  [redacted]

  Tumor tissue should be of good quality based on total and viable tumor content Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation.

  Additional archival tumor specimens should be submitted if available.

  If a subject undergoes an optional fresh tumor specimen collection for biopsy (e.g., if an archival block is not readily available for testing), the sample, should be submitted to the sponsor in a timely manner.

  For fresh biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

  For archival samples, the remaining tumor tissue block for all subjects enrolled will be returned to the site upon request or 18 months after final closure of the trial database, whichever is sooner.

- Use and storage of remaining samples from trial-related procedures

  The remainder of samples obtained for trial-related procedures will be destroyed no later than 5 years after the end of the trial or earlier depending on local regulations. If the subject provides optional consent for storing samples at Inovio for future research, the samples will be destroyed no later than 15 years after the date of final closure of the clinical database.

Refer to the laboratory manual for additional details on laboratory assessments and sample handling.

Correlative blood collection

Blood for correlative biomarker studies should be collected at screening, Day 0, Week 3, Week 6, Week 9, Week 12 and thereafter every 12 weeks until disease progression as well as at disease progression and discontinuation visit (see Table 1 Trial Schedule of Events). [redacted]. This is required at screening and on Day 0 to provide sufficient baseline sample for immunology testing.

[redacted]

[redacted]

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[redacted]

6.6.9. PREGNANCY TEST

For women of reproductive potential, a negative result for serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit and prior to each administration of trial treatment. If at any point, the β-HCG (pregnancy) test is positive, indicating that the subject is pregnant, no additional trial treatment will be administered, but the subject will be followed for the duration of the trial and beyond to determine the outcome of the pregnancy (with the subject's consent).

6.7. LABORATORY EVALUATIONS

Blood samples will be collected as specified in Table 7. Screening labs (CBC and chemistry) may be used for Day 0 if they are within 10 days of Day 0. Otherwise, all labs associated with any treatment visit (CBC and chemistry) should be collected no more than 72 hours prior to treatment and reviewed/evaluated by the investigator prior to treatment.

Table 7: Laboratory Evaluations

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
White Blood Cell (WBC) count with automated differential (absolute counts of neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells (if any)	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3) (or Free T3)[b]
Red Blood Cell (RBC) Count	Bicarbonate or CO_2[b]	Microscopic exam, if abnormal results are noted	Free tyroxine (T4)
	Calcium	pH	Thyroid Stimulating Hormone (TSH)
	Chloride	Ketones	Creatine phosphokinase (CPK)
	Creatinine		

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	Glucose		
	Phosphorus		
	Potassium		Only if investigator suspects:
	Magnesium		
	Sodium		HIV screening test (antibody immunoassay test)
	Total Bilirubin		Hepatitis B Serology: HBsAg (hepatitis B surface antigen); anti-HBs IgG (antibodies to the HBV surface antigen); anti-HBc IgG (antibodies to the HBV core antigen)
			Hepatitis C antibody immunoassay
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen (BUN) or urea		
	Lactate Dehydrogenase (LDH)		

[a] Perform on women of childbearing potential only.
[b] If considered standard of care in your region

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. After Day 0, laboratory procedures can be conducted up to 72 hours prior to dosing and as per Table 1 and as suggested per Table 2. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

6.8. ASSESSMENT OF LABORATORY ABNORMALITIES

When evaluating laboratory abnormalities throughout the trial, the investigator will be instructed to use CTCAE version 5.0. Laboratory abnormalities are usually not recorded as AEs or SAEs unless deemed clinically significant by the investigator.

6.9. ASSESSMENT OF CLINICAL TRIAL ADVERSE EVENTS (AES)

The investigator is instructed to use CTCAE version 5.0 when evaluating adverse events including injection site reactions.

6.10. BLOOD COLLECTION FOR IMMUNOGENICITY ASSESSMENTS

Where available:

Details of the immunology sample collection and shipment information will be provided in the Laboratory Manual.

T cell responses may be assessed using antigen-specific IFN-γ ELISpot assay using overlapping peptide libraries covering the INO-5401 antigens. Additionally, PBMC responses against a pool of known antigenic epitopes combined from Cytomegalovirus,

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Epstein Barr Virus and Influenza (CEF) may be evaluated in order to track general cellular immune competence during the trial.

T cell responses may be additionally assessed via flow cytometry overlapping peptide libraries covering the INO-5401 antigens. Flow cytometric assays may include an examination of the influence of immunotherapy on the ability of subject T cells to exhibit phenotypic markers associated with cytolytic potential, activation or exhaustion after stimulation by peptides corresponding to INO-5401 antigens. Markers that may be used for this purpose include CD3, CD4, CD8, CD137, CD69, CD38, PD1, Granulysin, Granzyme A, Granzyme B and Perforin. These markers may change relative to new data becoming available that is informative for this assessment.

Assessment of the presence of cells that are known to play a role in immune suppression may occur via the application of flow cytometry. Flow cytometric assays may include an examination of the influence of these cells on the induction or expansion of an immune response after immunotherapy. Markers that may be used for this purpose include CD3, CD16, CD19, CD20, CD56, CD11b, CD14, CD15, CD33 and HLA-DR. These markers may change relative to new data becoming available that is informative for this assessment.

TCR sequencing from PBMCs to assess diversity and putative antigen specificity may be performed on PBMCs with or without prior in vitro stimulation.

Gene transcript signatures from PBMCs to assess the profile of immune-related gene transcripts may be performed on PBMCs with or without prior in vitro stimulation.

Humoral responses may be assessed via application of ELISAs or other methods for the detection of antigen specific antibody secretion and/or employment of flow cytometry for B cell phenotyping.

6.11. TISSUE COLLECTION FOR IMMUNOGENICITY ASSESSMENTS

[redacted].

Following enrollment of 35 subjects, subjects will no longer require long-term follow-up for efficacy. No further samples will be collected for tissue, whole blood [redacted] for immunology [redacted]. Those samples collected prior to this may be used as described below.

Please see Table 2 for the Schedule of Events that are suggested.

6.12. [redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

6.13. FUTURE BIOMEDICAL RESEARCH

The following specimens are to be obtained as part of this study protocol and should any samples remain following the completion of analysis in this protocol, the leftover samples may be used in future biomedical research:

- Leftover tumor tissue
- Leftover RNA or DNA isolated from biological samples (i.e. tumor, blood, urine)
- Leftover biomarker samples (serum, plasma, and PBMCs)

6.13.1. WITHDRAWAL FROM FUTURE BIOMEDICAL RESEARCH

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator in writing. If medical records for the main trial are still available, the investigator will contact the Sponsor. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. No future data will be collected, but any data already collected from analysis of specimens will remain with the Sponsor. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

6.14. OTHER PROCEDURES

6.14.1. CELLECTRA™ 2000 DEVICE DATA DOWNLOADING

After each electroporation of INO-5401 + INO-9102, the CELLECTRA™ 2000 device data must be downloaded and sent to Inovio. The instructions on how to download and send the device data will be provided separately.

6.15. PROCEDURES BY VISIT

Procedures by visit are outlined in Trial Schedule of Events (Table 1) and suggested procedures in Table 2.

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6.15.1. SCREENING

Approximately 28 days prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 4.0. Screening procedures may be repeated after consultation with the Sponsor.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose trial treatment except for the following:

- Laboratory tests and evaluation of ECOG status are to be performed within 10 days prior to the first dose of trial treatment
- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criterion is met.

6.15.2. TREATMENT PERIOD

Procedures by visit are outlined in Trial Schedule of Events (Table 1) .

Procedures by visit are outlined in Trial Schedule of Events (Table 2) following the enrollment completion of 35 subjects.

6.15.3. STUDY TREATMENT DISCONTINUATION VISIT

The Study Treatment Discontinuation Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Study treatment discontinuation visit should be recorded. Subjects with an AE of Grade >1 should be followed until the resolution of the AE to Grade 0-1 where possible or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 30 days of the end of treatment and before initiation of a new anti-cancer treatment should also be followed and recorded, where possible, until resolution or the beginning of a new anti-cancer therapy, whichever occurs first.

The study discontinuation visit will be the **last visit for the study**.

6.15.4. DURATION OF FOLLOW-UP

All subjects will be followed for AEs, SAEs and AESIs for at least 30 days after their last dose of trial treatment or until initiation of a new anti-cancer treatment, whichever occurs first. Subjects who are discontinued from the trial due to an unacceptable drug-related AE will be followed until the resolution of the AE or stabilization, disease progression, or initiation of a new therapy for their cancer, where possible, whichever occurs first.

Following enrollment of 35 subjects (28 in Cohort A and 7 in Cohort B), subjects will no longer require long-term follow-up for efficacy. Following initial radiographic progression, trial treatment should be stopped, and confirmation of disease progression is not required.

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6.15.5. SURVIVAL AND SUBSEQUENT ANTI-CANCER THERAPY FOLLOW-UP

Following enrollment of 35 subjects (a 28 in Cohort A and 7 in Cohort B), subjects will no longer require long-term follow-up for efficacy. Please see Table 2 for the Schedule of Events that are suggested.

7. EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1. ADVERSE EVENTS (AES)

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. In this trial, such changes will be monitored, classified, and summarized, as Clinical or Laboratory AEs. Medical condition/diseases present before starting the investigational drug will be considered AEs only if they worsen after starting trial treatment. Throughout the course of the trial, all solicited and unsolicited AEs will be monitored and reported on an AE CRF, including the event's seriousness, severity, action taken, and relationship to IP(s). AEs should be followed until resolution or stable and the outcome will be documented on the appropriate CRF. All AEs should be recorded in standard medical terminology rather than the subject's own words.

AEs include the following:

- Pre- or post-treatment complications that occur after signing of informed consent
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the trial drug phase of a human clinical trial, will also be considered an AE.
- Complications of pregnancy.
- All AEs that occur from the trial screening visit onwards and throughout the duration of the trial, including the follow-up off trial drug period will be recorded as an AE.

AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the Screening visit that do not worsen.
- Progression of the cancer under trial is not considered an adverse event unless it is considered to be drug related by the investigator.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae.
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed, is not an AE. It is considered to be pre-existing and will be documented on the medical history CRF.

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- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

To assure the safety of the subjects, information about all AEs, whether volunteered by the subject, discovered by investigator or trial staff questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded in the subject's source documents and followed as appropriate.

7.2. SERIOUS ADVERSE EVENTS

A SAE is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol.
- Is immediately life-threatening (e.g., subject was, in the view of the investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death.
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (including any overnight stay in the hospital, regardless of the length of stay, even if the hospitalization is only a precautionary measure to allow continued observation. However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in congenital anomaly or birth defect.
- An important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include:
    1. Allergic bronchospasm requiring intensive treatment in an emergency room or at home.
    2. Blood dyscrasias or convulsions that do not result in inpatient hospitalization
    3. The development of drug dependency or drug abuse

Clarification of Serious Adverse Events (SAEs)

- Death in itself is not an AE. Death is an outcome of an AE.
- The subject may not have been receiving an investigational medicinal product at the occurrence of the event.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- Inpatient hospitalization means that the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does

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not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

The following hospitalization scenarios are not considered to meet the criteria for a serious adverse events:

- Hospitalization for respite care
- Hospitalization to perform an efficacy measurement for the trial
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

The hospitalization for an elective surgery for a pre-existing condition.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

7.3. UNEXPECTED ADVERSE DRUG REACTIONS AND EXPEDITED REPORTING

An adverse drug reaction (ADR) is any noxious and unintended response to a medicinal product related to any dose for which a causal relationship between a medicinal product and an AE is at least a reasonable possibility (i.e., there is evidence to suggest a causal relationship between the product and the AE). An AE or ADR is considered unexpected if it is not listed in the applicable product information (Investigator's Brochure, protocol, or user manual) or is not listed at the specificity or severity which is consistent with the risk information provided in the Investigator's Brochure. The Sponsor will assess each serious adverse drug reaction report for expectedness, to determine if it is a suspected unexpected serious adverse reaction (SUSAR) which requires prompt reporting to regulatory authorities and participating investigators as an expedited report, in accordance with the applicable regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

In addition to single-case reports of SUSARs, the Sponsor will notify regulatory authorities and participating investigators of information that might materially influence the benefit-risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. Examples of such information include a clinically important increase in the rate of occurrence of a serious expected AE, the identification of a significant hazard to the subject population, or a major safety finding from a trial conducted in animals.

Reports will be made as soon as possible, and in no event later than seven (7) calendar days if the event is a death or is life threatening and 15 calendar days for all other reportable events after the Sponsor's initial receipt of the information. Each written notification may be submitted on a CIOMS-I form, a FDA Form 3500A, or in a tabular or narrative format in accordance with regulatory requirements. In each report, the Sponsor will identify all safety reports previously filed concerning a similar suspected adverse reaction, and will analyze the significance of the suspected adverse reaction in light of the previous, similar reports.

Follow-up information to a safety report will be submitted as soon as the relevant information is available. If the results of a Sponsor's investigation show that an AE not initially determined to be reportable is, in fact, reportable, the Sponsor will report the suspected AE in a written safety report as soon as possible, but in no event later than 15

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calendar days after the determination is made. Results of investigations of other safety information will be submitted, as appropriate, in an information amendment or annual report.

7.4. UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT (UADE)

A UADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Per the definition above, a UADE is a type of SAE that requires expedited reporting on the part of the Sponsor. As a reminder, all SAEs regardless of relationship to device, drug or procedure are to be reported to Sponsor by the trial investigator within 24 hours. Sponsor will assess each device related SAE to determine if anticipated based on prior identification within the investigational plan. The Sponsor may notify a regulatory authority within the time frame specified by local requirements but no later than 10 business days for UADE.

7.5. ADVERSE EVENTS OF SPECIAL INTEREST (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest (AESI) are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 7.8 for reporting instructions). AESI for atezolizumab are available in TECENTRIQ Investigator's Brochure.

7.6. METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events are recorded and reported to the sponsor in accordance with instructions provided in this Section.

For each adverse event recorded, the investigator will document an assessment of seriousness, severity, and causality.

7.6.1. Adverse event, Serious Adverse Event and Adverse Event of Special Interest Reporting Period

Investigators will seek information on adverse events at each subject contact. All AEs, SAEs and AESIs, whether reported by the subject or noted by trial personnel, should be recorded in the subject's medical record from the time of informed consent until 30 days following last administration of either or both trial treatment or until trial discontinuation/termination or until initiation of subsequent anti-cancer therapy, whichever occurs first. After this period, investigators should report only serious adverse events that are considered to be related to prior trial treatment.

7.6.2. Assessment of Severity of Adverse Events

The investigator will assess and grade clinical AEs or SAEs (based on discussions with trial subjects) in accordance with National Cancer Institute (NCI) CTCAE version 5.0.

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7.6.3. CAUSAL RELATIONSHIP OF CLINICAL MATERIAL TO ADVERSE EVENTS (AEs)

A causally related AE is one judged to have a reasonable causal relationship to the administration of the either or both investigational product (IP) and/or the investigational device. The investigator will assess causal relationship of the AE separately to each of the investigational drugs and also the investigational device. The reasonable causal relationship means that there are facts (evidence) or arguments to suggest a causal relationship. An AE may also be assessed as not related to either or both IP and/or the investigational device. Because the investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the IP, and monitors the subject's response to the IP, the investigator is responsible for reporting AEs and judging the relationship between the administration of the IP and EP and a subsequent AE. The investigator is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be product related and may have observed the event.

Investigators should use their knowledge of the trial subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the IP and/or the investigational device and the causal relationship reported "Yes" or "No" accordingly. Causality should be assessed by the investigator as related to drug or related to device or related to both drug and device (i.e., related to both or indiscernible) by the following criteria:

- Yes – there are facts, evidence or arguments that administration of the trial treatment (drug or device or both drug and device) contributed to the event.
- No – there are no facts, evidence or arguments that administration of the trial treatment contributed to the event and there are more likely causes.

The following guidance should also be taken into consideration:

- Temporal relationship of event to administration of IP and/or EP.
- Course of the event, considering especially the effects of dose reduction, discontinuation of IP, or reintroduction of IP (where applicable).
- Known association of the event with the IP, EP or with similar treatments.
- Known association of the event with the disease under trial.
- Presence of risk factors in the trial subject or use of concomitant medications known to increase the occurrence of the event.

7.7. RECORDING OF ADVERSE EVENTS

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Events eCRF; the use of colloquialisms and abbreviations should be avoided.

7.7.1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

For adverse events other than infusion-related reactions, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual

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event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF.

7.7.2. Abnormal Laboratory Values

Laboratory abnormalities are usually not recorded as AEs or SAEs unless deemed clinically significant by the investigator.

Any laboratory abnormality that is new in onset or worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded as an AE:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of trial treatment
- Has accompanying or inducing symptoms or signs
- Is judged by the investigator as clinically significant

Severity will be assessed as detailed in Section 7.6.2. Investigators are asked to take the CTCAE version 5.0 grading criteria into account when assessing if a laboratory abnormality qualifies as a laboratory AE. Their clinical judgment ultimately determines not only the severity of the event but also whether the abnormality in question is "clinically significant (CS)" or "not clinically significant (NCS)." CTCAE version 5.0 grading criteria can be used as a reference when making this determination. It is the responsibility of the Investigators to ensure all AEs are accurately reported and graded.

7.7.3. Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2× ULN (of which ≥ 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice

The most appropriate diagnosis or, if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest.

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7.7.4. Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in trial treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

7.7.5. Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 7.6.1) that are attributed by the investigator solely to progression of UCa should be recorded only on the Trial Completion/Early Discontinuation eCRF. All other on-trial deaths, regardless of relationship to trial drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 7.8).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

During post-trial survival follow-up, deaths attributed to progression of UCa should be recorded only on the Survival eCRF.

7.7.6. Disease Progression

Disease progression (i.e., worsening and/or progression of UCa) and symptoms related to disease progression should not be recorded as an adverse event.

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7.7.7. Adverse Events Associated with an Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of trial treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of trial drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

7.8. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious as defined in Section 7.2, the investigator should report this event to the Sponsor within 24 hours of becoming aware of the event. The investigator may also directly report this event to the Ethics Committee in accordance with its standard operating procedures. Expectedness of SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure and protocol.

The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to trial drug:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies
- Dose-limiting toxicities

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality on the basis of new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

At any time after completion of the SAE reporting period, if an investigator becomes aware of an SAE that is suspected by the investigator to be related to the trial drug, the event will be reported to the Sponsor or its designee.

7.8.1. Safety Contact Information

The events listed in Section 7.8 above should be reported to the sponsor within 24 hours as per the contact information provided below. Email/fax the report within 24 hours of the discovery of the events listed in Section 7.8.

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Table 8: Safety Contact Information (24 hour reporting)

United States sites:	
EMAIL:	[redacted]
SAFETY FAX:	[redacted]
SAFETY PHONE:	[redacted]
Spain sites:	
EMAIL:	[redacted]
SAFETY FAX:	[redacted]

The preferred method for providing safety reports or supporting documents to the Sponsor or designee is as an attachment to an e-mail message, to the email address as indicated above. Any supporting documents provided by facsimile (Fax) are to include a fax coversheet that identifies the contact information of the study site.

All supporting documents for safety reports, including medical records and diagnostic test results, will include reference to the study subject number. The study site will redact all other patient identifying information present on supporting documents prior to sending the report to the Sponsor.

In addition to providing the safety report to the sponsor within 24 hours of becoming aware of the event, the AE that is reported must be recorded in the Adverse Event eCRF. The entry into the eCRF should occur as soon as possible.

In the event of a pregnancy, the investigator will submit a Pregnancy Form to the Sponsor or designee to the safety email address or fax number within 24 hours of learning of the pregnancy.

If there is a need to speak to the medical monitor, please contact:

Medical Monitor	[redacted], MD or designee
Telephone	[redacted]
Email	[redacted]
Mailing address	Inovio Pharmaceuticals, Inc. 660 W. Germantown Pike, Suite 110 Plymouth Meeting, PA 19462

7.8.2. Reporting Requirements for Serious Adverse Events

The SAE report should contain all the clinical safety information that is available at the time of reporting. As new or additional information is received, an updated SAE report is to be submitted to the Sponsor within 24 hours. Each SAE must be followed up until resolution or stabilization and for a reported death, the investigator will supply the Sponsor and the IRB/EC with any additional requested information (e.g., autopsy reports and terminal medical reports). The original SAE form must be kept at the trial site. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities in accordance with the applicable regulatory requirements. SAEs

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must be followed by the investigator until resolution, even if this extends beyond the trial-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

7.9. DOSE-LIMITING TOXICITY MANAGEMENT AND SAFETY

During the safety run-in phase, up to six subjects (from cohort A) will be enrolled. During this phase, a dose-limiting toxicity, if related to atezolizumab or INO-5401 + INO-9012 will be defined as:

- Any Grade ≥4 hematologic toxicity
- Grade ≥3 thrombocytopenia >7 days or associated with bleeding
- Grade ≥3 non-hematologic toxicity, including adverse events of special interest (See Section 7.5).

The reporting requirements for dose-limiting toxicity is provided in Section 7.8.

7.10. DOSE MODIFICATION

There will be no dose reduction for trial treatment in this trial. Subjects may temporarily suspend trial treatment if they experience toxicity that is considered related to either or both trial drug(s) and requires a dose to be held of the drug(s) that caused toxicity. Either treatment may be stopped by the investigator while the other treatment continues. If either trial treatment is held because of related adverse events for > 42 days beyond when the next dose would have been given, then the subject may continue on the other trial treatment pending agreement between investigator and medical monitor. If both trial treatment are held because of related adverse events for > 42 days beyond when the next dose would have been given, then the subject will be discontinued from trial treatment pending agreement between investigator and medical monitor and will be followed for safety and efficacy as specified if agreed to discontinue. If, in the judgment of the investigator, the subject is likely to derive clinical benefit from resuming either or both trial treatment after a hold > 42 days, trial drug may be restarted with the approval of the medical monitor.

7.11. MANAGEMENT OF SPECIFIC ADVERSE EVENTS

Toxicities associated or possibly associated with atezolizumab or INO-5401 + INO-9012 treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of the trial treatment may not have an immediate therapeutic effect due to the long half-life of the drug or longer drug effect, and there is no available antidote for the trial treatment. In severe cases, immune-mediated toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNF-α inhibitors.

The primary approach to Grade 1−2 immune-mediated adverse events is supportive and symptomatic care; for higher grade immune-mediated adverse events, steroids by mouth or parenterally are given, and either skipping a dose or stopping therapy is appropriate. Recurrent Grade 2 immune-mediated adverse events may also mandate skipping a dose

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of either atezolizumab or INO-5401 + INO-9012 or the use of steroids. Consideration for benefit-risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given subject may be experiencing prior to further administration of atezolizumab or INO-5401 + INO-9012. Atezolizumab and/or INO-5401 + INO-9012 should be permanently discontinued in subjects with life-threatening immune-mediated adverse events.

The following are general recommendations for management of adverse events that may occur and are not otherwise specifically listed in the following subsections.

In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.

Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5-1 mg/kg/day of prednisone or equivalent) may be administered.

For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.

Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1-2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.

In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.

Immune-mediated pericardial disorders are considered to be a warning and precaution for atezolizumab. See the Investigator's Brochure for details on immune-mediated disorders related to atezolizumab.

Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.

Management of systemic immune activation (SIA) is presented below. See the atezolizumab Investigator's Brochure for details on management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity, and other immune-mediated adverse events. See Section 5.5.2 for guidelines for the management of infusion-related reactions (see Appendix 3 for precautions for anaphylaxis).

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7.11.1. SYSTEMIC IMMUNE ACTIVATION

Systemic immune activation (SIA) is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, SIA is considered a potential risk when given in combination with other immunomodulating agents. SIA should be included in the differential diagnosis for subjects who, in the absence of an alternate etiology, develop a sepsis-like syndrome after administration of atezolizumab.

Recommendations regarding early identification and management of SIA are provided below. In the event of suspected SIA, the medical monitor should be contacted immediately for additional guidance.

Early disease recognition is critical, and the clinician should consider SIA if, in the absence of alternate etiologies, the presence of ≥ 2 of the following are present:

- Hypotension refractory to aggressive IV fluid challenge
  - May/can require vasopressor support
- Respiratory distress requiring aggressive supportive care
  - Supplemental oxygen, possible intubation
- Fever greater than 38.5°C
- Acute renal or hepatic failure
- Bleeding from coagulopathy
- Unexplained laboratory abnormalities (change from baseline):
  - Cytopenias (≥ Grade 2 in two or more lineages), significant transaminitis, coagulopathy, elevated creatinine

Initial evaluation should include CBC with peripheral smear, PT, PTT, fibrinogen, D-dimer, ferritin, triglyceride, AST/ALT, total bilirubin, LDH, and a complete neurologic and abdominal examination (assess for hepatosplenomegaly).

If cytopenias (≥ 2 lineages and change from baseline) are present or ferritin is ≥ 3000 ng/mL, the following evaluations should also be performed:

- Bone marrow biopsy/aspirate (assess for evidence of hemophagocytosis)
- sCD25 (soluble IL-2 receptor)
- Natural killer cell activity
- Cytomegalovirus, Epstein-Barr virus and herpes-simplex virus evaluation (evaluate for reactivated or active disease)

SIA is a clinical syndrome characterized by the following:

- Onset greater than 24 hours after exposure to drug

AND

- Progressive clinical deterioration in an acutely ill subject (in the absence of an alternate etiology)

AND

- Involving multiple organs (≥ 2)

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AND

- Demonstrating specific laboratory abnormalities

Diagnosis of SIA should only be made in subjects who present with a constellation of clinical findings as outlined above and who fulfill the following established diagnostic criteria in the absence of an alternate etiology.

The diagnostic criteria and recommended management for systemic immune activation are provided in Table 9.

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Table 9: Diagnostic Criteria and Management for Systemic Immune Activation

Systemic Immune Activation		
SIA criteria apply only when alternate etiologies have been excluded.		
Major Criteria		Minor Criteria
• Fever ≥38.5°C (on more than one occasion) • Ferritin >3000 ng/mL • Cytopenias: ≥Grade 2 in two or more lineages • ≥2 age-adjusted SD elevation soluble IL-2 receptor • Severe multi-organ dysfunction • Decreased fibrinogen		• Splenomegaly • Hemophagocytosis BM, spleen or LN • Elevated GGT or LFTs (AST/ALT/tBili) • Elevated triglycerides • Elevated LDH • Decreased natural killer-cell activity
	Number of Criteria	Management
Consistent with SIA	4 major criteria	Consider tocilizumab (4 mg/kg IV) and Solumedrol® (1g IV QD). Contact the Medical Monitor for additional recommendations. Consider HLH-94 protocol if no clinical improvement.
Probable SIA	3 major criteria OR 2 major criteria AND 3 minor criteria	Depending on clinical severity, patient can be treated as per "Consistent with SIA" or "Possible SIA" case definition. Contact medical monitor for additional recommendations
Possible SIA	1 major criteria AND 4 minor criteria	Consider Solumedrol® (1g IV QD) Contact the Medical Monitor for additional recommendations. As per "Consistent with SIA" recommendations if no improvement or clinically worsening

7.12. POST-TRIAL REPORTING REQUIREMENTS

Investigators are not obligated to actively seek AEs or SAEs beyond the follow-up period for subjects. However, if the investigator learns of an AE or SAE that occurs after the completion or termination visit and the event is deemed by the investigator to be probably or possibly related to the trial treatment, he/she should promptly document and report the event to the Sponsor.

7.13. PROCEDURES FOR DOCUMENTING AND REPORTING PREGNANCY DURING THE TRIAL

Subjects who are pregnant or expect to become pregnant during the course of the trial will be excluded from participation in the trial. Should a subject become pregnant after enrolling in the trial, she will not be given any further treatments with the IP. A Pregnancy Form will be completed by the investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy (The pregnancy is reported to the Sponsor using the method described in Section 7.8.1). The investigator may also report this event to the IRB within 24 hours of becoming aware of the pregnancy per institution policy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to

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determine the [1]outcome of the pregnancy. When permission is received, subjects will continue to be followed for safety assessments to trial discharge per protocol. Results will be summarized in the clinical study report (CSR).

The investigators should report any pregnancy or lactation in a subject that occurs during the trial, or within 5 months of cessation of trial treatment or initiation of a new anti-cancer therapy, whichever is earlier. The investigator will monitor the subject and follow the outcome of the pregnancy. If the end of the pregnancy occurs after the trial has been completed, the outcome will be reported directly to the Sponsor.

Male subjects will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant until the end of follow-up period. A Pregnancy Form will be completed by the investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Attempts will be made to collect and report details of the course and outcome of any pregnancy in the partner of a male subject exposed to IP. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Form with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male subject or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

7.14. REPORTING OF DEVICE RELATED COMPLAINTS OR DEFICIENCIES

A product complaint/device deficiency is defined as any written, electronic, or oral communication that alleges deficiencies or inadequacies of the device or components related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the device or components after it is released for distribution within the clinical investigation. All product complaints that meet this definition (with the exception of SAEs requiring 24 hour reporting) must be reported to the Sponsor within 10 days of discovery.

Device Deficiencies include malfunctions, use errors and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Any problems experienced during the treatment procedure including potential malfunctions of the device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure must be reported to the Sponsor or designee immediately for evaluation. The error reporting or complaint form must be completed and emailed to the Sponsor at [redacted]

7.15. TRIAL DISCONTINUATION

INOVIO reserves the right to discontinue the trial at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Additionally, the trial may be discontinued at any time by an IRB, INOVIO, the FDA or other government agencies as part of their duties to ensure that research subjects are protected.

[1]

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Should the trial be terminated and/or the site closed for any reason, all investigational drugs and/or devices must be returned or destroyed based on Section 5.7 and 5.11. The Principal Investigator should ensure their site file documents are complete prior to archiving, and provide copies of any requested documents to INOVIO for its Trial Master File (TMF).

8. STATISTICAL CONSIDERATIONS

8.1. STATISTICAL AND ANALYTICAL PLAN

The formal Statistical Analysis Plan (SAP) is contained in the Sections that follow.

8.2. GENERAL CONSIDERATIONS

The statistical analysis of the data will be performed by Inovio Pharmaceuticals or its representative.

This is a single-arm (INO-5401 + INO-9012 in Combination with Atezolizumab), multi-center, open-label clinical trial in subjects who have received and/or progressed on anti-PD-1/PD-L1 based therapy previously (cohort A) and in subjects who are treatment naïve, cisplatin-ineligible (cohort B). The trial's primary analyses regard the safety, immunogenicity, and objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by investigator review (in cohort A) of INO-5401 + INO-9012 in Combination with Atezolizumab. The secondary analyses pertain to anti-tumor activity as assessed by objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by investigator review (in cohort B), ORR by immune RECIST (iRECIST), Duration of Response (DoR), Progression Free Survival (PFS) as assessed by RECIST version 1.1 and iRECIST, and Overall Survival (OS). [redacted]

Enrollment was stopped at 35 subjects (28 subjects in Cohort A and 7 subjects in Cohort B). Following initial radiographic progression, trial treatment should be stopped, and confirmation of disease progression is not required. Interventions will be limited to administration of study drugs INO-5401 + INO-9012 and atezolizumab as per prior schedule. Assessments will be limited to safety laboratory assessments only. No further evaluation of efficacy or immunogenicity will be collected. Please see Table 2 for the Schedule of Events that are suggested.

No formal statistical evaluation or hypothesis will be provided for data collected following this time, specifically related to efficacy or immunogenicity. All statistical analyses for this study will be deemed exploratory and descriptive.

8.3. STATISTICAL HYPOTHESES

Due to the limit of 35 subjects the study will not conduct any formal statistical analysis of the co-primary endpoints.

8.4. ANALYSIS POPULATIONS/DATASETS

The analysis of data will be based on different subsets according to the purpose of the analysis.

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8.4.1. Efficacy Analysis Sets

The Response-evaluable Population includes all subjects who receive at least three doses of the first four doses of both trial treatments (not necessarily at the same visits), have a baseline scan with measurable disease, have no important protocol deviations, and who have at least one on-treatment scan or experience rapid clinical progression, toxicity or death prior to their first on-treatment scan/response assessment. Subjects who experience toxicity without an on-treatment scan will be classified as non-responders for the ORR endpoints.
The As-treated Population will include all subjects who receive any one of the trial treatment (any of the investigative medications) and have a baseline scan with measurable disease.

All efficacy analyses will be based on both the Response-evaluable and the As-treated populations.

8.4.2. Safety Analysis Set

The safety analysis set includes all subjects who receive at least one dose of trial treatment. Subjects will be analyzed as to the treatment they received.

8.4.3. All Enrolled Analysis set

The all enrolled analysis set includes all subjects who are enrolled into the study.

8.5. DESCRIPTION OF STATISTICAL METHODS

Enrollment was stopped at 35 subjects. All statistical analyses will be purely descriptive and exploratory.

8.5.1. Analysis of the Primary Efficacy Endpoint

Where available, ORR will be presented as the proportion of overall best responses (CR or PR from at least one visit) for subjects using the RECIST version 1.1 criteria. The number of subjects with an overall best response of complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) will be also summarized.

All RECIST assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a subject discontinues trial treatment or receives another anticancer therapy. At each visit, subjects will be assigned a RECIST version 1.1 visit response of complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) depending on the status of their disease compared with baseline and previous assessments by the investigator. Baseline will be assessed within the 28 days prior to first dose of trial treatment. If a subject has had a tumor assessment that cannot be evaluated, then the subject will be assigned a visit response of not evaluable (unless there is evidence of progression in which case the response will be assigned as PD). See Appendix 1 for the RECIST version 1.1 definitions of CR, PR, SD and PD.

RECIST version 1.1 assessment/scans contributing towards a particular visit may be performed on different dates. When this happens the following rule will be applied;

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For investigator assessments, the date of progression will be determined based on the earliest of the RECIST version 1.1 assessment/scan dates of the component that indicates progression.

Note: For target lesions, only the latest scan date is recorded out of all scans performed at that assessment for the target lesions, and similarly for non-target lesions, only the latest scan date is recorded out of all scans performed at that assessment for the non-target lesions.

8.5.2. Analysis of the Primary Immunogenicity Endpoint

Where available, immune reactivity as assessed by ELISpot/Flow Cytometry/B cell activation/antibody secretion/Myeloid Derived Suppressor Cells/TCR sequencing/tumor infiltrating lymphocytes will be evaluated. Categorical responses will be descriptively summarized using counts and percentages, and continuous responses will be descriptively summarized using means, medians, standard deviations, minimums and maximums. The As-treated population will be used for these analyses.

8.5.3. Analysis of the Secondary Endpoints

Where available, ORR by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by investigator review (in cohort B) will be analyzed in the same manner as described for the primary endpoint in cohort A. ORR by iRECIST will be analyzed in the same manner, in each cohort.

The other secondary analyses may evaluate Progression-Free Survival (PFS) as assessed by RECIST version 1.1 and iRECIST, Overall Survival (OS), and Duration of Response (DoR), in each cohort, where available.

Where available, progression-free survival measures progression by growth of the primary tumor, nodal spread metastases, death from bladder cancer, or death from other causes. Progression free survival will be assessed by the periodic tumor assessment using imaging per the institutional guidelines at the schedules according to Table 1: Trial Schedule of Events.

Where available, progression-free survival (defined as the time from the date of the start of investigational product treatment until the date of death from any cause or date of objective progression (+1 day) whichever occurs first), overall survival (defined as the time from the date of the start of investigational product treatment until the date of death from any cause) and duration of response (defined as the time from the date of the first PR or CR to the date of death from any cause or objective progression whichever occurs first) will be summarized with Kaplan-Meier statistical methods within each cohort. Subjects without a CR or PR will have a duration of response of 0.

Subjects who have not progressed or died at the time of the analysis will be censored for PFS at the date of withdrawal of consent, date of anti-cancer medication, date of withdrawal from the study or the last progression RECIST version 1.1 or iRECIST assessment date (scan date). However, if a subject progresses or dies after two or more missed visits, the subject will be censored at the time of the latest evaluable RECIST version 1.1 or iRECIST assessment prior to two missed visits. PFS time will always be

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derived based on scan assessment or death dates and not visit dates. When censoring a subject for PFS, the subject will be censored at the latest of the dates contributing to a particular overall visit assessment. Censoring rules for duration of response (DoR) will be the same as for PFS.

Subjects who are not recorded has having died will be censored for overall survival at the last date the subject was known to be alive.

Table 10 provides a summary of the efficacy endpoints with their corresponding methods of assessment and populations.

Table 10: A Summary of Efficacy Endpoints with Corresponding Methods of Assessment and Populations

Type of efficacy endpoint	Cohort	Endpoint	Method
Co-primary	A	ORR	RECIST version 1.1
Secondary	B	ORR	RECIST version 1.1
	A and B	ORR	iRECIST
	A and B	PFS	RECIST version 1.1
	A and B	PFS	iRECIST
	A and B	OS	Death Records
	A and B	DoR	RECIST version 1.1
	A and B	DoR	iRECIST

Abbreviations: ORR=objective response rate, PFS=progression free survival, OS=overall survival, DoR=duration of response

8.5.4. Analysis of the Safety Endpoints

TEAEs are defined as any AEs that occur on or after day 0. All TEAEs that occur within 30 days after any treatment will be summarized by percentage of subjects and 95% Clopper-Pearson confidence intervals within each cohort and across both cohorts combined. These percentages will be presented overall and separately by dose, and will depict overall, by MedDRA system organ class and by preferred term, the percentage of subjects affected. Additional percentages will be presented with respect to maximum severity and to strongest relationship to trial treatment. Multiple occurrences of the same AE will be counted only once following a worst-case approach with respect to severity and relationship to trial treatment. All serious TEAEs will also be summarized as above.

AE duration will be calculated as AE Stop date – AE start date + 1 day.

All AEs and SAEs will be presented in listings.

Laboratory response variables will be descriptively summarized per time point and as changes/percent changes from baseline.

8.5.5. Disposition

Where possible, subject disposition will be summarized by cohort and overall for all enrolled subjects and will include the number and percentage enrolled, the number and percentage who received each planned dose and the number who completed the trial. The number and percentage of subjects who discontinued will be summarized overall and

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by reason. The number in each analysis population will also be presented in the All Enrolled population.

8.5.6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristic data will be descriptively summarized by cohort and overall for subjects in the As-treated population.

8.5.7. PLANNED INTERIM ANALYSES

No formal interim analyses will be performed for this trial.

8.5.8. MULTIPLICITY

Not applicable; no hypothesis will be tested.

8.5.9. MISSING VALUES

Missing data will not be imputed or replaced, and calculations will be performed on reported values.

[redacted]

8.6. SAMPLE SIZE/POWER

Since no formal hypothesis test will be conducted on this study and all statistical analyses will be purely descriptive and exploratory no formal power analysis is presented. A sample size of 35 subjects is expected to be adequate to assess the descriptive nature of the primary endpoints, specifically that of safety and tolerability in both cohorts A and B.

8.7. RANDOMIZATION AND BLINDING

Because this is an open-label trial site personnel, individual subjects and Inovio or its representative trial personnel will be aware of the treatment allocations for this trial. Also, because only one treatment group is used in this trial, randomization is not applicable.

9. ETHICS

Investigator and Sponsor Responsibilities

The investigator and Sponsor are responsible for ensuring that the clinical trial is performed in accordance with the protocol, the principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and applicable regulatory requirements.

Institutional Review Board or Ethics Committee or (IRB/EC)

The investigator will undertake the trial after full approval of the protocol and adjunctive materials (e.g., informed consent form, advertising) has been obtained from the applicable IRB/EC and a copy of this approval has been received by the Sponsor.

Investigator responsibilities relevant to the IRB/EC include the following:

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- Submit progress reports to the IRB/EC as required, and request re-review and approval of the trial at least once a year during the conduct of the trial.
- Notify the Sponsor immediately of any suspected unexpected adverse drug or device events/effects.
- Notify the IRB/EC immediately if the Sponsor notifies the investigator about any reportable safety events.
- Obtain approval from the IRB/EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements, as required.
- Submit reports on, and reviews of, the trial and its progress to the IRB/EC at intervals stipulated in their guidelines and in accordance with pertinent regulations and guidelines.
- Maintain a file of trial-related information (refer to trial files) that includes all correspondence with the IRB/EC.
- Notify the IRB/EC when the trial is completed (i.e., after the last trial visit of the final trial subject).
- After trial completion (within three (3) months is recommended) provide the IRB/EC with a final report on the trial.

Include a description of investigator responsibilities relevant to (Institutional Biosafety Committee (IBC) approval and reporting if applicable per local regulations.

Include a description of Sponsor responsibilities relevant to Office of Biotechnology Activities (OBA) approval and reporting, if applicable.

Protection of Human Subjects

Compliance with Informed Consent Regulations

Written informed consent is to be obtained from each subject prior to enrollment into the trial, and/or from the subject's legally authorized representative. The process for obtaining informed consent must also be documented in the subject's medical record. (Also refer to Section 6.1).

Compliance with IRB/EC Requirements

This trial is to be conducted in accordance with applicable IRB/EC regulations. The investigator must obtain approval from a properly constituted IRB/EC prior to initiating the trial and re-approval or review at least annually. Sponsor is to be notified immediately if the responsible IRB/EC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/EC correspondence with the investigator should be provided to Sponsor.

Compliance with Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

Compliance with Electronic Records/Signatures Regulations (21CFR Part 11)

When applicable, this trial is to be conducted in compliance with the regulations on electronic records and electronic signature.

Compliance with Protocol

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Subjects are not required to follow special instructions specific to the IP used in this trial. Subjects will be provided with investigator emergency contact information and advised to report all AEs. While every effort should be made to avoid protocol deviations, should a deviation be discovered, Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

Changes to the Protocol

The investigator should not implement any deviation from or changes to the protocol without approval by Sponsor and prior review and documented approval/favorable opinion from the IRB/EC of a protocol amendment, except where necessary to eliminate immediate hazards to trial subjects, or when the changes involve only logistical or administrative aspects of the trial (e.g., change in monitors, change of telephone numbers). While every effort should be made to avoid protocol deviations, should a deviation be discovered, Sponsor must be informed immediately. Any protocol deviation impacting Subject safety must be reported to the Medical Monitor immediately.

Vulnerable Subjects

Please provide details of any potential vulnerable subjects to be enrolled in the trial. Per ICH E6, vulnerable subjects are individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include subjects with incurable diseases, persons in nursing homes, unemployed or impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

10. DATA COLLECTION, MONITORING, AND REPORTING

10.1. CONFIDENTIALITY AND PRIVACY

A report of the results of this trial may be published or sent to the appropriate health authorities in any country in which the trial products are legally marketed or may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to the trial Sponsor, the governing health authorities or the Food and Drug Administration (FDA), if they inspect the trial records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the trial, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information (HIPAA).

Information about trial subjects will be kept confidential and managed in accordance with the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

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- What protected health information (PHI) will be collected from subjects in this trial
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of the research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the Sponsor retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect vital status, at a minimum, (i.e., that the subject is alive) at the end of their scheduled trial period.

11. SOURCE DOCUMENTS

Source data is all information, original records or clinical findings, laboratory results, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in original source documents.> Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medical records and within information technology systems that are involved in the clinical trial. The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data/documents related to this trial.

11.1. RECORDS RETENTION

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial related records.

CRFs will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by their subject identification number (SID).

It is the investigator's responsibility to retain trial essential documents for at least two (2) years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least two (2) years have elapsed since the formal discontinuation of clinical development of the IP. This retention period may be superseded by country requirements. The Sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained.

11.2. SAFETY AND QUALITY MONITORING

Clinical Monitoring

Clinical Monitoring of the clinical trial will be performed by experienced Clinical Monitors, who will report to the Sponsor or the Sponsor designee. Records for all clinical subjects in this trial will be monitored. The following clinical site monitoring tasks will be performed at all sites:

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- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the trial.
- The Clinical Monitor will address and document the following trial conduct activities and obligations:
  - Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies.
  - Discuss trial conduct issues and incidents of noncompliance with the investigator and/or trial personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the Sponsor.
  - Remind the investigator as necessary of the obligation to immediately report all SAE and provide subsequent follow-up report of the final outcome to the IRB.
  - Throughout the trial, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
  - Assure that the trial facilities continue to be acceptable.
  - Compare the trial CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed.
  - Assure that investigational drug and device accountability and reconciliation of records are complete and accurate.
  - Assure that all subject specimens are being stored and forwarded properly for testing per laboratory manual requirements.

12. FINANCING AND INSURANCE

Financing and insurance will be addressed outside of this protocol

13. PUBLICATION POLICY

All data or results arising out of the performance of this Trial shall be considered Confidential Information. The Clinical Site and Principal Investigator agree that the Sponsor shall have the right to the first publication of the results of the Trial which is intended to be a joint, multi-center publication of the Trial results made by Sponsor in conjunction with the principal investigators and Clinical Sites from all appropriate sites contributing data, analysis and comments. Notwithstanding the foregoing, following the first publication, the Clinical Site and/or Principal Investigator may publish data or results from the Trial; provided, however, that the Clinical Site and /or Principal Investigator submits the proposed publication to Inovio for review prior to the date of the proposed publication, as indicated in the Clinical Trial Agreement. Inovio may remove from the proposed publication any information that is considered confidential and/or proprietary other than Trial data and results. However, Inovio confirms there will be no multi-center Trial publication, the Clinical Site and/or Principal Investigator may publish the Trial results subject to Inovio's rights as set forth herein. The Clinical Site and the Principal Investigator agree not to publish any Trial related material other than in accordance with this Section.

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14. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
APC	Antigen presenting cell
APIs	Active pharmaceutical ingredients
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CIN	Cervical Intraepithelial Neoplasia
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPI	Checkpoint inhibitor
CPK	Creatine Phosphokinase
CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Lymphocytes
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
EP	Electroporation
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HBc	Hepatitis B Core Protein
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus

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HCV	Hepatitis C Virus
HER	Electronic Health Record
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA-DR	Human Leukocyte Antigen - antigen D Related
hTERT	human Telomerase Reverse Transcriptase
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	International Ethics Committee
IFN-γ	Interferon Gamma
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL-12	Interleukin 12
IL-2	Interleukin-2
IM	Intramuscular
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IRB/EC	Institutional Review Board or Ethics Committee or
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IUDs	Intrauterine devices
IV	Intravenous
MDSC	Myeloid Derived Suppressor Cells
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MRI	Magnetic Resonance Imaging
mUC	Metastatic Urothelial Carcinoma
NCI	National Cancer Institute
NCS	Not clinically significant
NIH	National Institutes of Health
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective response rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Protocol Deviation
PD-1	Programmed Death Receptor - 1
PD-L1	programmed cell death-ligand 1
PET	Positron Emission Tomography

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PFS	Progression Free Survival
PHI	Protected Health Information
PI	Principal Investigator
PR	partial response
PSA	prostate-specific antigen
PSMA	Prostate-Specific Membrane Antigen
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SIA	Systemic immune activation
SID	Subject identification number
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TILs	Tumor-infiltrating lymphocytes
TMF	Trial Master File
UADE	Unanticipated (Serious) Adverse Device Effect
UCa	Urothelial Carcinoma
ULN	Upper limit of normal
WT-1	Wilms Tumor-1

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16. APPENDICES

16.1. APPENDIX 1: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST V1.1)

Selected Sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228−47.) are presented below, with slight modifications and the addition of explanatory text as needed for clarity.

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows.

a. Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on “Baseline Documentation of Target and Non-Target Lesions” for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

c) Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone lesions:

- Technetium-99m bone scans (T-99m), sodium fluoride−positron emission tomography (NaF-PET) bone scans, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.

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- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

a. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

b. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during trial. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will be considered measurable only when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan on the basis of the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a subject is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the subject at baseline and during the trial should be guided by the tumor type under investigation and the anatomic location of the disease. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and

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should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the subject should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where subjects have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is > 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs but, additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Lesions irradiated within 3 weeks prior to Cycle 1, Day 1 may not be counted as target lesions.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to

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be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

a. Evaluation of Target Lesions

This Section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): disappearance of all target lesions
  - Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (nadir), including baseline.
  - In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
  - The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on trial.

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on trial. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While on trial, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the

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retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

However, to reiterate, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This Section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. Although some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level
  - All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits.
- PD: unequivocal progression of existing non-target lesions
  - The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Subject Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Subject Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of trial entry to have measurable disease.

The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease; that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the

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subject should be considered to have had overall PD at that point. Although it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

When the subject has bone lesions at baseline. When a bone scan is the sole indicator of progression, progression in bone will be defined as when at least two or more new lesions are seen on bone scan compared with screening. In situations where the scan findings are suggestive of a flare reaction or apparent new lesion(s) that may represent trauma, these results must be confirmed with other imaging modalities such as MRI or fine-cut CT to constitute progression. Only a single new bone lesion on bone scan is required for progression if the lesion can be correlated on CT or MRI.

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some “new” bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject’s baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a “new” cystic lesion, which it is not.

A lesion identified during the trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

New osteoblastic bone lesions identified on plain films, CT, or MRI will not be considered progression in an otherwise stable or responding subject if, in the opinion of the physician, the osteoblastic lesion appears to be healing or a response to therapy.

EVALUATION OF RESPONSE

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for subjects who have measurable disease at baseline.

When subjects have non-measurable (therefore non-target) disease only, Table 2 is to be used.

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Table 1: Timepoint Response: Subjects with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2: Timepoint Response: Subjects with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the subject is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with three measured lesions and, during the trial, only two lesions were assessed, but those gave a sum of 80 mm; the subject will have achieved PD status, regardless of the contribution of the missing lesion. If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the subject is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

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Table 3: Best Overall Response when Confirmation is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

c. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to “normal” size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of “zero” on the CRF.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping trial therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease as shown in Table 1−Table 3. For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

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If a subject undergoes an excisional biopsy or other appropriate approach (e.g., multiple passes with large core needle) of a new lesion or an existing solitary progressive lesion that following serial Sectioning and pathological examination reveals no evidence of malignancy (e.g., inflammatory cells, fibrosis, etc.), then the new lesion or solitary progressive lesion will not constitute disease progression.

In studies for which subjects with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

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16.2. APPENDIX 2: ANAPHYLAXIS PRECAUTIONS

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during trial drug infusion, the following procedures should be performed:

1. Stop the trial drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of trial drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by subject status and directed by the physician in charge.
5. Continue to observe the subject and document observations.

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16.3. APPENDIX 3: PREEXISTING AUTOIMMUNE DISEASE

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Subjects with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Please contact the Sponsor regarding any uncertainty over autoimmune exclusions.

Autoimmune Disease and Immune Deficiencies

Acute disseminated encephalomyelitis	Kawasaki's disease
Addison's disease	Lambert-Eaton myasthenia syndrome
Ankylosing spondylitis	Lupus erythematosus
Antiphospholipid antibody syndrome	Lyme disease – chronic
Aplastic anemia	Mooren's ulcer
Autoimmune hemolytic anemia	Morphea
Autoimmune hepatitis	Multiple sclerosis
Autoimmune hypoparathyroidism	Myasthenia gravis
Autoimmune myocarditis	Neuromyotonia
Autoimmune oophoritis	Opsoclonus myoclonus syndrome
Autoimmune orchitis	Optic neuritis
Autoimmune thrombocytopenic purpura	Ord's thyroiditis
Behcet's disease	Pemphigus
Bullous pemphigold	Pernicious anemia
Chronic inflammatory demyelinating polyneuropathy	Polyarteritis nodusa
Chung-Strauss syndrome	Polyarthritis
Crohn's disease	Polyglandular autoimmune syndrome
Dermatomyositis	Primary biliary cirrhosis
Diabetes mellitus Type I	Psoriasis
Dysautonomia	Reiter's syndrome
Epidermolysis bullosa acquista	Rheumatoid arthritis
Gestational pemphigold	Sarcoidosis
Giant cell arteritis	Scleroderma
Goodpasture's syndrome	Sjögren's syndrome
Grave's disease	Takayasu's arteritis
Guillain-Barré syndrome	Ulcerative colitis
Hashimoto's disease	Vogt-Kovanagi-Harada disease
IgA nephropathy	Granulomatosis with polyangiitis
Inflammatory bowel disease	
Interstitial cystitis	

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