Herbert Irving Comprehensive Cancer Center

Columbia University Irving Medical Center
NewYork-Presbyterian

COLUMBIA

TITLE: A phase 2, randomized, open-label study of gemcitabine/cisplatin plus cemiplimab (REGN2810, anti-PD-1) with or without fianlimab (REGN3767, anti-LAG-3) for organ preservation in patients with localized muscle-invasive bladder cancer (NeoSTOP-IT)

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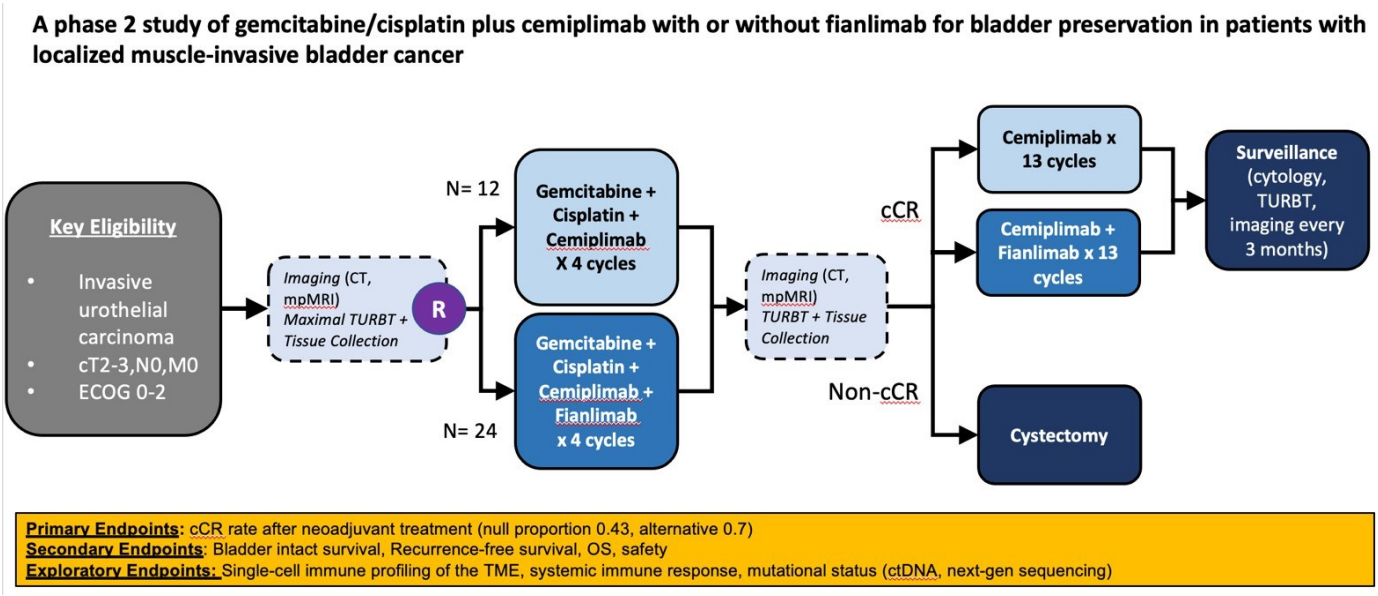
Protocol Synopsis

Title	A phase 2, randomized, open-label study of gemcitabine/cisplatin plus cemiplimab (REGN2810, anti-PD-1) with or without fianlimab (REGN3767, anti-LAG-3) for organ preservation in patients with localized muscle-invasive bladder cancer (NeoSTOP-IT)
Short Title	Platinum doublet chemotherapy plus anti-PD1/-LAG3 for bladder preservation in MIBC
Protocol Number	AAAV3927
Phase	Phase 2
Methodology	This is a phase 2, open-label, randomized trial with continuous toxicity monitoring to ensure safety using Bayesian toxicity monitoring. Patients will undergo maximal transurethral resection of bladder tumor (TURBT) followed by the start of treatment on Week 1 with gemcitabine and cisplatin (per standard of care routine dosing/administration). At 1:2 ratio, patients will be randomized to receive concomitant cemiplimab (350 mg IV q3week) or cemiplimab and fianlimab (1600 mg IV q3weeks). After 4 cycles of treatment, patients will undergo repeat maximal TURBT with cross sectional imaging. Patients with clinical complete response will continue maintenance cemiplimab or cemiplimab/fianlimab for 13 more cycles on a q3week basis while undergoing surveillance with cytology, cystoscopy, and cross-sectional imaging every 3 months. Patients without a complete clinical response will undergo cystectomy. The primary endpoint is complete clinical response after neoadjuvant treatment.
Study Duration	We estimate that the trial will require approximately 48 months to capture the primary endpoint, with 36 months for accrual (1 patient per month) and an additional 12 months to reach the primary endpoint timepoint. After completion of single or dual immune checkpoint blockade, patients will be actively followed for approximately 12 months. Therefore, the total duration of the study will be approximately 60 months (5 years).
Study Center(s)	Columbia University Irving Medical Center
Objectives	Primary Objective: To evaluate the clinical complete response following neoadjuvant gemcitabine, cisplatin, cemiplimab with or without fianlimab in patients with pT2-pT3 bladder cancer with urothelial-predominant histology. Secondary Objectives: To assess the toxicity and evaluate the effects of platinum-doublet chemotherapy plus cemiplimab and fianlimab on bladder intact survival, recurrence free survival, and overall survival. Exploratory Objectives: • To compare the pre- and post-treatment immune microenvironment using single-cell RNA sequencing from patients treated with gemcitabine, cisplatin, and cemiplimab with or without fianlimab. • To evaluate the systemic immune response over time by

	quantifying circulating cytokines and immune cell populations. • To correlate clinical responses and disease recurrence with circulating tumor DNA. • To identify specific mutations using whole exome sequencing in pre-treatment tumor biopsies that may predict treatment responses. Additional studies may be performed at later date.
Number of Subjects	40 patients will enroll (sign consent) and for a total of 36 treated.
Study Product, Dose, Route, Regimen	• Gemcitabine 1000 mg/m^2 IV (days 1 and 8 of 21 day for 4 cycles) • Cisplatin 70 mg/m^2 IV (day 1 of 21 day cycle for 4 cycles) or renally-dosed split-dose cisplatin 35 m/m^2 IV (day 1 and 8 of 21 day cycle for 4 cycles) • Cemiplimab (REGN 2810) 350 mg IV every 3 weeks (17 cycles) Fianlimab (REGN3767) 1600 mg IV every 3 weeks (17 cycles)
Duration of administration	Patients will continue investigational treatment with cemiplimab and fianlimab for 12 months, or less if there is progression of disease, unacceptable toxicity, or death. Patients may not continue gemcitabine and cisplatin past the neoadjuvant phase.
Reference therapy	Investigational treatment (cemiplimab and fianlimab) will be administered for 12 months (4 neoadjuvant doses and 13 maintenance doses).
Statistical Methodology	The primary endpoint is clinical complete response after 4 cycles of neoadjuvant gemcitabine, cisplatin, cemiplimab with or without fianlimab. We hypothesize that gemcitabine, cisplatin, and cemiplimab with or without fianlimab will result in higher clinical complete response compared to historical controls. This study is designed to evaluate 36 pts with 24 of those patients randomized to the dual cemiplimab/fianlimab arm. With a potential dropout rate of 10%, we will accrue 21 patients in this arm. We expect a proportion of 0.70 patients in the dual cemiplimab/fianlimab arm will have a clinical complete response compared to 0.43 from historical controls. 21 patients will therefore give us at least 80% power for a one- sided Z-test at a significance of 0.05.

Protocol Schema:

Figure 1. Phase 2 Trial Design



1. INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312/812 and International Conference on Harmonization guidelines), applicable government regulations and Columbia University Irving Medical Center institutional research policies and procedures.

2. STUDY OBJECTIVES

We hypothesize that 4 cycles of neoadjuvant gemcitabine, cisplatin, and cemiplimab (REGN2810, anti-PD-1) with fianlimab (REGN3767, anti-LAG-3) in patients with localized muscle-invasive bladder cancer will result in a superior rate of clinical complete responses compared to historical controls treated with chemotherapy alone.

2.1 Primary Objective

- To measure the rate of clinical complete response in patients with localized muscle-invasive bladder cancer following treatment with gemcitabine, cisplatin, and cemiplimab with or without fianlimab. Complete clinical response will be defined as:
    - No high-grade malignancy on repeat TURBT
    - No malignant cells on urine cytology
    - No definitive evidence of invasive local or metastatic disease on cross-sectional imaging (CT chest, abdomen, and pelvis with contrast or, if renal dysfunction, MRI with contrast)

2.2 Secondary Objectives

- To estimate bladder-intact survival in patients with localized muscle-invasive bladder cancer following treatment with gemcitabine, cisplatin, and cemiplimab with or without fianlimab. Bladder-intact survival is defined as the time from start of treatment until cystectomy or death.
- To estimate recurrence-free survival in patients with localized muscle-invasive bladder cancer following treatment with gemcitabine, cisplatin, and cemiplimab with or without fianlimab. Recurrence-free survival is defined as the time from start of treatment until disease recurrence or death.
- To estimate overall survival in patients with localized muscle-invasive bladder cancer following treatment with gemcitabine, cisplatin, and cemiplimab with or without fianlimab. Overall survival is defined as the time from start of treatment until death.
- To estimate safety and tolerability in patients with localized muscle-invasive bladder cancer following treatment with gemcitabine, cisplatin, and cemiplimab with or without fianlimab.

2.3 Exploratory Objectives

- To compare the pre- and post-treatment immune microenvironment using single-cell RNA sequencing from patients treated with gemcitabine, cisplatin, and cemiplimab with or without fianlimab.
- To evaluate the systemic immune response over time by quantifying circulating cytokines and immune cell populations.
- To correlate clinical responses and disease recurrence with circulating tumor DNA.
- To identify specific mutations using whole exome sequencing in pre-treatment tumor biopsies that may predict treatment responses.

Additional studies may be performed at later dates.

3. STUDY DESIGN

3.1 General Design

This is a phase 2, open-label, randomized trial with continuous toxicity monitoring to ensure safety using Bayesian toxicity monitoring, which will evaluate treatment with doublet platinum-based chemotherapy (gemcitabine and cisplatin) plus cemiplimab (REGN2810) with or without fianlimab (REGN3767) for localized MIBC. The primary endpoint is clinical complete response following 4 cycles of treatment as defined by no evidence of malignancy on cystoscopy; no malignant cells in urine cytology; and no evidence of local or distant recurrence as seen on cross-sectional imaging.

Additional secondary endpoints include bladder-intact survival, recurrence-free survival, overall survival, and safety and tolerability. Correlative studies will also be performed to understand the treatment effects on the tumor microenvironment.

Study Intervention

Patients will undergo maximal TURBT with tissue collection for molecular correlates. At a ratio of 1:2, patients will be randomized to the gemcitabine/cisplatin/cemiplimab arm or the gemcitabine/cisplatin/cemiplimab/fianlimab arm. Patients will be treated for 4 cycles on the following schedule:

- Gemcitabine 1000 mg/m^2 IV (days 1 and 8 of 21 day cycle for 4 cycles)
- Cisplatin 70 mg/m^2 IV (day 1 of 21 day cycle for 4 cycles) or renally-dosed split-dose cisplatin 35 m/m^2 IV (day 1 and 8 of 21 day cycle for 4 cycles)
- Cemiplimab (REGN 2810) 350mg IV every 3 weeks (4 cycles)
- For patients randomized to the dual immunotherapy arm, Fianlimab (REGN3767) 1600mg IV every 3 weeks (4 cycles)
- The use of filgrastim, pegfilgrastim, or any biosimilars on day 9 of each cycle for prevention of chemotherapy-induced febrile neutropenia will be at the discretion of the treating investigator

Following these 4 cycles, patients will undergo cystoscopy and cross-sectional imaging. For patients with a clinical complete response and no evidence of metastatic disease, no tumor tissue will be obtained. Patients with clinical complete response will continue with 13 further cycles of maintenance immunotherapy – either single-agent cemiplimab (350 mg IV every 3 weeks) or dual-agent cemiplimab (350 mg IV every 3 weeks) and fianlimab (1600mg IV every 3 weeks) depending on their initial randomization. Patients with residual clinical disease in the bladder will undergo radical cystectomy. Any patient with metastatic disease regardless of response at primary site will be removed off trial and treated under standard of care per the treating physician.

Duration of Treatment

Patients will be randomized to 4 cycles of 3 weeks each (12 weeks total) with gemcitabine, cisplatin, and cemiplimab with or without fianlimab. Patients achieving a clinical complete response will continue 13 more cycles of immunotherapy (39 weeks total). The total duration of systemic treatment, including neoadjuvant therapy, will be 52 weeks.

In addition to the actual time on treatment, there will be time off treatment for recovery after neoadjuvant treatment and before adjuvant treatment. First, between the neoadjuvant phase and cystoscopy (with TURBT for residual disease), there will be up to 4 weeks off treatment. In between the cystoscopy/TURBT and start of adjuvant immunotherapy, there will be an additional up to 4 week interval for recovery.

Adverse events will be monitored throughout the trial and graded in severity according to the guidelines in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

4. SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

To be eligible for participation in this trial, subjects must:

1. Be willing and able to provide written informed consent for the trial.
2. Be age ≥18 years of age on day of signing informed consent.
3. Have life expectancy > 12 months.
4. Have a performance status of 0-2 using the ECOG Performance Scale.
5. Have histologically confirmed muscle-invasive urothelial carcinoma of the bladder defined as T2-T3, N0, M0 stage. Mixed histology is permitted if there is a urothelial component. Upper tract disease in not permitted.
6. Prior BCG or other intravesical treatment of non-muscle invasive bladder cancer is permitted if completed at least 6 weeks prior to initiating study treatment. Only one course (includes induction + maintenance) of BCG or intravesical therapy is permitted.
7. Have no metastatic disease based on cross-sectional imaging.
7. Be considered cisplatin eligible based on:
    - Creatinine clearance ≥ 50 ml/min
    - ECOG performance status 0-1
    - Grade < 2 hearing loss
    - Grade < 2 neuropathy
10. Have not received any adjuvant or neoadjuvant chemotherapy or immunotherapy.
13. Have adequate organ and marrow function as defined below:
    - Leukocytes ≥3,000/mcL
    - Absolute Neutrophil Count ≥1,500/mcL
    - Platelets ≥100,000
    - Hemoglobin ≥ 9.0g/dL (without transfusion in past 2 weeks)
    - PT/INR, PTT ≤ 1.5 ULN (except if on therapeutic anti-coagulation in which case the patient can be enrolled if stable and anti-coagulation levels are appropriate for their condition per good clinical practice).
    - AST(SGOT)/ALT(SGPT) ≤3.0 × institutional upper limit of normal
    - Total bilirubin ≤1.5 x normal institutional limits. Note: Patients with hyperbilirubinemia clinically consistent with an inherited disorder of bilirubin metabolism (e.g. Gilbert's syndrome) will be eligible at the discretion of the treating physician and/or the principal investigator.
    - Creatinine clearance of ≥ 50 mL/min. Creatinine clearance (CrCl) should be

calculated at screening using the Cockcroft-Gault formula.

14. Agree to pre- and post-treatment TURBT as well as surveillance with cystoscopies, cross-sectional imaging, and urine cytology unless medically contraindicated in the opinion of the treating physician, and discussed with the principal investigator
15. The effects of cemiplimab (REGN2810) and fianlimab (REGN3767) on the developing human fetus are unknown. For this reason and because the investigational agents [as well as other therapeutic agents used in this trial] are known to be teratogenic, men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of cemiplimab (REGN2810) and fianlimab (REGN3767) administration. Should a woman become pregnant or suspect she is pregnant while her partner is participating in this study, she should inform her treating physician immediately.

4.2 Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has concurrent upper urinary tract (i.e., ureter, renal pelvis) invasive urothelial carcinoma. (NOTE: Patients with history of non-invasive (Ta, Tis) upper tract urothelial carcinoma that has been definitively treated with at least one post-treatment disease assessment (i.e. cytology, biopsy, imaging) that demonstrates no evidence of residual disease are eligible).
2. Received prior immune checkpoint inhibitors (including anti–PD-1, anti–PD-L1, anti-CTLA4, anti-LAG-3 or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways), as well as cellular vaccines, cellular therapies, or systemic oncolytic virus therapy.
3. Received bladder-directed radiation therapy previously for bladder cancer.
4. Has received prior systemic chemotherapy for muscle-invasive bladder cancer.
5. Is receiving any other investigational agents concurrently or within 4 weeks of start of treatment.
6. Had a solid organ or hematologic transplant.
7. Ongoing or recent (within 2 years) evidence of an autoimmune disease that required systemic treatment with immunosuppressive agents. The following are non-exclusionary: vitiligo, childhood asthma that has resolved, residual hypothyroidism that requires only hormone replacement, psoriasis not requiring systemic treatment
8. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (at a dose greater than 10mg/day of prednisone equivalent) or any other form of immunosuppressive therapy within 14 days prior to the first dose of trial treatment. Inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
9. Has a history of myocarditis.
10. Has Troponin T (TnT) or Troponin I (TnI) > 2x institutional upper limit of normal at baseline. Patients with TnT or TnI levels between > 1 to 2x ULN are permitted if repeat levels within 24 hours are ≤ 1xULN. If TnT or TnI levels are > 1 to 2x ULN within 24 hours, the subject may undergo a cardiac evaluation and be considered for treatment by the investigator based on medical judgement in the patient's best interest.
11. Patients with another active second malignancy other than non-melanoma skin cancers.
12. Has a known history of, or any evidence of, interstitial lung disease or active noninfectious pneumonitis.

13. Has peripheral neuropathy > grade 1.
14. Has an active infection requiring systemic therapy.
15. History or current evidence of significant (CTCAE grade ≥2) local or systemic infection (eg, cellulitis, pneumonia, septicemia) requiring systemic antibiotic treatment within 2 weeks prior to the first dose of trial medication.
16. Has a history of current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator, including dialysis.
17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
18. Uncontrolled infection with HIV, HBV, or HCV infection; or diagnosis of immunodeficiency that is related to, or results in chronic infection.
    Notes:
    a. Patients with known HIV who have controlled infection (undetectable viral load and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are permitted. For patients with controlled HIV infection, monitoring will be performed per local standards.
    b. Patients with known hepatitis B (HepBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of HBV DNA per local standards and must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug.
    c. Patients who are known hepatitis C virus antibody positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.
    d. Patients with HIV or hepatitis must be reviewed by a qualified specialist (eg, infectious disease or hepatologist) managing this disease prior to commencing and regularly throughout the duration of their participation in the trial
19. Has received a live vaccine within 30 days of planned start of study therapy (Cycle 1, Day 1). Note: The killed virus vaccines used for seasonal influenza vaccines for injection are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
    a. Live or live attenuated vaccination with replicating potential. If a patient intends to receive a COVID-19 vaccine before the start of study drug, participation in the study should be delayed at least 1 week after any COVID-19 vaccination. During the treatment period, it is recommended to delay COVID-19 vaccination until patients are receiving and tolerating a steady dose of study drug. A vaccine dose should not be less than 48 hours before or after study drug dosing.
20. Has a history of severe hypersensitivity reaction to gemcitabine or cisplatin.
21. Has a prior history of hypersensitivity to monoclonal antibody.
22. Has a history of hypersensitivity to any of the excipients.
23. Is pregnant or is a breastfeeding woman.
24. Women of childbearing potential (WOCBP) who are unwilling to practice highly effective contraception prior to initial dose/start of treatment, during study, and for at least 6 months after the last dose. (WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and

bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. Pregnancy testing and contraception are not required for women who are post-menopausal or permanently sterile.) Highly-effective contraceptive measures include:

a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening;
b. intrauterine device; intrauterine hormone-releasing system;
c. bilateral tubal occlusion/ligation;
d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure); and/or
e. sexual abstinence. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle f the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception. Female condom and male condom should not be used together.

25. Men who do not agree to not to donate sperm during the trial and for 6 months after receiving the last therapy dose.
26. WOCBP who do not agree to not donate eggs (ova, oocytes) for the purposes of assisted reproduction during the entire trial and until 6 months after last treatment

STATISTICAL CONSIDERATIONS

Study Design/Endpoints

Prior randomized clinicals of radical cystectomy with or without neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer demonstrated that up to 38% of patients had no residual disease (pT0) at the time of radical cystectomy.[3] Most patients who were pT0 were cured of their disease, with a 5-year overall survival rate of 85%.[8] Such a finding raised the possibility that radical cystectomy may be avoidable in some patients with clinical complete response.

The primary endpoint is clinical complete response defined as (a) the absence of any residual tumor on cystoscopy after 4 cycles of neoadjuvant chemoimmunotherapy, (b) the absence of any metastatic disease on cross-sectional imaging after 4 cycles of neoadjuvant chemoimmunotherapy, and (c) negative urine cytology after 4 cycles of neoadjuvant chemoimmunotherapy. Cystoscopy and cross-sectional imaging should happen within 4 weeks of the end of neoadjuvant chemoimmunotherapy. We hypothesize that administration of 4 cycles of gemcitabine, cisplatin, and cemiplimab will increase the rate of clinical complete response compared to historical controls.

We additionally hypothesize that adding fianlimab to gemcitabine, cisplatin, and cemiplimab will further increase clinical complete response.

This study is designed to evaluate 36 pts with 24 of those patients randomized to the dual cemiplimab/fianlimab arm. We expect a proportion of 0.70 patients in the dual cemiplimab/fianlimab arm will have a clinical complete response compared to 0.43 from historical controls. 21 patients will therefore give us at least 80% power for a one-sided Z-test at a significance of 0.05. With a potential dropout rate of 10%, we will plan to accrue up to 24 patients in the cemiplimab/fianlimab arm and 12 patients in the cemiplimab arm.