Award Number: W81XWH-21-2-0025

TITLE: Kidney Cancer Clinical Trials Consortium

PRINCIPAL INVESTIGATOR: Brian Rini, MD

CONTRACTING ORGANIZATION: Vanderbilt University Medical Center

REPORT DATE: OCTOBER 2022

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PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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1. REPORT DATE: **OCTOBER 2022**	**2. REPORT TYPE:** **Annual**	**3. DATES COVERED** **9/15/2021-9/14/2022**
4. TITLE AND SUBTITLE Kidney Cancer Clinical Trials Consortium		**5a. CONTRACT NUMBER** W81XWH-21-2-0025 **5b. GRANT NUMBER** **5c. PROGRAM ELEMENT NUMBER**
6. AUTHOR(S): **Brian I. Rini, MD** E-Mail: brian.rini@vumc.org		**5d. PROJECT NUMBER** **5e. TASK NUMBER** **5f. WORK UNIT NUMBER**
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Vanderbilt University Medical Center 1161 21st Ave S STE D3300 MCN Nashville, TN 37232-0011		**8. PERFORMING ORGANIZATION REPORT**
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012		**10. SPONSOR/MONITOR'S ACRONYM(S)** **11. SPONSOR/MONITOR'S NUMBER(S)**
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13. SUPPLEMENTARY NOTES		

14. ABSTRACT: Vanderbilt University Medical Center (VUMC) has been an active and engaged participant in the Kidney Cancer Clinical Trials Consortium over the course of the reporting period. VUMC has led the first protocol conducted through the Consortium (Haake, PI) looking at circulating tumor DNA (ctDNA) in advanced renal cell carcinoma (RCC) patients receiving immune-based systemic therapy. This trial has accrued X patients out of Y planned and will generate preliminary data for future studies and extramural funding. Further, the first therapeutic study from the Consortium was proposed and will be led by an VUMC investigator (Beckermann, PI) investigating the combination of ipilimumab/nivolumab plus a small molecule inhibitor of the adenosine signaling pathway. Drs. Beckermann and Rini are active participants at the monthly Consortium meetings providing critical feedback regarding new proposals and the general direction and governance of the Consortium.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION**	**18. NUMBER OF PAGES 8**	**19a. NAME OF RESPONSIBLE PERSON USAMRDC**
a. REPORT U	**b. ABSTRACT** U	**c. THIS PAGE** U	U U		**19b. TELEPHONE NUMBER** *(include area code)*

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1. **INTRODUCTION:** VUMC has long been home to a critical mass of RCC basic, translational, and clinical researchers. To amplify the impact of VUMC's efforts, RCC Consortium membership was sought and accomplished in the last funding cycle. Harnessing the expertise of VUMC members, two protocols have been accepted by the Consortium for execution as described below.

2. **KEYWORDS: RENAL CELL CARCINOMA, CTDNA, CIFORADENANT**

3. **ACCOMPLISHMENTS:** VUMC with Dr. Scott Haake has created the first translational study understanding novel techniques to measure ctDNA in patients with kidney cancer at time of diagnosis and while on therapy. On this protocol 69 patients were enrolled at Vanderbilt, 24 at MDACC, 13 at UPENN, 6 at UTSW, and 12 at UMich. This protocol will complete accrual Q1 2023.

Dr. Beckermann and Rini created the first therapeutic clinical trial conducted under Consortium auspices. Ciforadenant is an investigational immunotherapeutic small molecule that selectively and reversibly binds adenosine-2A receptors (A_{2A}Rs) on T lymphocytes and other cells of the immune system. Preclinical studies show that the addition of ciforadenant to CTLA4 and PD1 blockade shows enhanced efficacy and in some cases elimination of the established tumors (Willingham et al., 2018). Recently, in a first in human study, the A2AR antagonist ciforadenant was found to be safe and showed activity as monotherapy in RCC patients with refractory disease following multiple lines of therapy showing a median progression free survival (mPFS) of 4.1 months (Fong et al., 2019). INC is a Phase 1b/2 single-arm, multicenter study to assess safety and efficacy of the combination of ipilimumab, nivolumab, and ciforadenant in the

frontline treatment of patients with advance clear cell renal cell carcinoma. The primary objective is to determine the safety and tolerability and to assess the depth of response (>50% by RECIST 1.1 Eisenhaur, 2009) based on a Bayesian design in patients with advanced RCC treated with ipilimumab, nivolumab, and ciforadenant. Secondary objectives will estimate the objective response rate (ORR), duration of response (DOR) progression free survival (PFS), progressive disease (PD) rate, and irAE rate of ipilimumab, nivolumab, and ciforadenant combination in untreated advanced RCC. Exploratory objectives include assessing gene expression signatures and pharmacodynamic parameters with outcome.

4. **IMPACT:** The projects noted above have the potential to impact RCC therapeutics. ctDNA is emerging across cancers as a potentially effective way to monitor for disease recurrence and the effectiveness of systemic therapy. RCC has been considered a 'low shedding' tumor, and techniques developed through the Consortium ctDNA project will enable better ctDNA detection. This is a critical first step in applying the technology to the therapeutic setting. Further, the clinical trial of Ipi/Nivo + ciforadent will represent one of the first all-immune triplets to be tested in advanced RCC. Adenosine signaling contributes to immune suppression by downregulating T cell activity and increasing myeloid suppressive activity with preclinical and early phase clinical data to support the use of ciforadenant an adenosine 2A receptor antagonist to block the pathway. The propose Phase ½ trial will have a lead in of 8 patients assessing safety in the novel combination with ipilimumab and nivolumab and then an expansion for a total of 51 patients to enroll will assess efficacy by asking if this combination increases the percentage of patients achieving a >50% shrinkage in tumor volume. We believe the establishment of safety and a signal of clinical activity will lead to large-scale clinical trials that could impact the initial standard of care in advanced RCC.

5. **CHANGES/PROBLEMS: NONE**

6. **PRODUCTS: NONE**

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- What individuals have worked on the project?
  Please see below:

Name:	**Brian Rini, MD**
Project Role:	Principal investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-2212-080X
Nearest person month worked:	2.4
Contribution to Project:	Dr. Rini is the PI of the VUMC Consortium grant. He oversees all aspects of VUMC's participation including coordination of proposal submission, concept review and execution of Consortium projects and clinical trials.
Funding Support:	CDMRP, NCI

Name:	Kathryn E Beckermann, MD
Project Role:	Sub PI
Researcher Identifier:	0000-0002-4616-6140
Nearest person month worked:	5.6
Contribution to Project:	As sub-PI, Dr. Beckermann attends monthly consortium meetings, participates in critical discussion of proposed projects, has written and developed the first interventional clinical trial to be run through the consortium.
Funding support:	CDMRP/NCI
Name:	**Rebekah J. Caza**
Project Role:	**Clinical Trials Manager**
Researcher Identifier:	N/A
Nearest person month worked:	11.7
Contribution to Project:	Ms. Caza manages the portfolio of RCC clinical trials at VUMC including the Consortium projects noted here. She oversees all aspects of clinical protocol execution including scientific/IRB submissions, budget and contract negotiations, protocol-specific requirements, and protocol execution.
Funding support:	N/A
Name:	**Andrea M. Koontz**
Project Role:	**Data management**
Researcher Identifier:	N/A
Nearest person month worked:	0.5
Contribution to Project:	Ms. Koontz oversees all aspects of data management as it relates to VUMC's participation in Consortium-related projects.
Funding support:	N/A

- *Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?* - **Yes, please see below:**

Brian Rini, MD – Principal Investigator:

This Award
KC200245 (PI: B. Rini) **began** 09/15/2021
Title: Kidney Cancer Clinical Trials Consortium
Role: Co-Investigator
Effort: 2.40 calendar months
Performance Period: 09/15/2021 - 09/14/2024 (NCE)

New
KC210158 (Rini) **began** 09/01/2022
Title: RNAseq-Based Biomarkers Identify Targetable Biologic Drivers of Kidney Cancer
Supporting agency**:** CDMRP
Performance Period**:** 09/01/2022 – 08/31/2025
Effort**:** 1.2 calendar months
Role: PI

New
KC210255/W81XWH-21-KCRP-CTA(Rini**) began** 9/01/2022
Title: OPtimal Treatment by Invoking biologic Clusters in Renal Cell Carcinoma (OPTIC RCC)
Supporting agency: CDMRP
Performance Period**:** 09/01/2022 – 08/31/2026
Effort**:** 1.2 calendar months
Role: PI

Ended
3P30 CA068485-25S2 (Pietenpol) **ended** 8/31/2022
Title**:** The COVID-19 and Cancer Consortium: NCI Administrative Supplement to P30 (CCSG)
Supporting agency**:** NCI
Performance Period: 05/01/2021–08/31/2022
Effort: 1.8 calendar months
Role: Co-Project Lead

Kathryn E Beckermann, MD – Sub PI

This Award
KC200245 (PI: B. Rini) **began** 09/15/2021
Title: Kidney Cancer Clinical Trials Consortium
Role: Co-Investigator
Effort: 1.80 calendar months
Performance Period: 09/15/2021 - 09/14/2024 (NCE)

New, began 06/01/2022
Title: *Vanderbilt-Arsenal Bio Collaboration*
Role: PI
Effort: 0.24 calendar months
Performance Period: 06/01/2022 - 05/30/203

New, began 08/01/2022
Title: *Vanderbilt-Aravive Research Collaboration*
Role: PI
Effort: 0.24 calendar months

Performance Period: 08/01/2022 - 07/31/2023

New, began 09/01/2022
KC210158 (PI; B. Rini) **began** 09/01/2022
Title: *RNAseq-Based Biomarkers Identify Targetable Biologic Drivers of Kidney Cancer*
Role: Co- Investigator
Effort: 0.96 calendar months
Performance Period: 09/01/2022 - 08/31/2025

New began 09/01/2022
KC210255/W81XWH-21-KCRP-CTA(Rini**) began** 9/01/2022
Title: OPtimal Treatment by Invoking biologic Clusters in Renal Cell Carcinoma (OPTIC RCC)
Supporting agency: CDMRP
Performance Period**:** 09/01/2022 – 08/31/2026
Effort**:** 1.2 calendar months
Role: PI

Ended 9/29/2022
Title: Endogenous retrovirus expression, chromatin abnormalities and response to immune checkpoint blockade in clear cell renal cell cancer
Role: Co-Investigator
Principal Investigator: Shridar Ganesan
Effort 0.6 calendar months
Performance Period: 09/30/2019- 09/29/2022 (NCE)

8. SPECIAL REPORTING REQUIREMENTS

APPENDICES - NONE