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TITLE: University of Pennsylvania Clinical Trial Site Application for Kidney Cancer Research Consortium Award

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CONTRACTING ORGANIZATION: TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA
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14. ABSTRACT

The purpose of the University of Pennsylvania Abramson Cancer Center Kidney Cancer Research Consortium (PENN/ACC KCRC) award is to support the development of a data sharing infrastructure using the Prometheus platform so that Penn can collaborate with other members of the KCRC in a seamless method and participate in consortium phase I and II clinical trials. Over this year one of funding, we have helped to form a governance structure for all of the members, which includes an external advisory board. We have formalized a contracting and review process between Penn and the lead coordinating site, MD Anderson Cancer Center. Following the completion of these tasks, we have both presented three clinical trials for consideration of KCRC participation and we have submitted the first KCRC translational protocol to the Penn and Central Institutional Review Boards for imminent activation at Penn. We anticipate a robust accrual to this protocol and future participation and accrual to future KCRC treatment protocols. Finally, the KCRC website has been activated.

15. SUBJECT TERMS
KCRC=Kidney Cancer Research Consortium; MDACC=MD Anderson Cancer Center; Penn/ACC = University of Pennsylvania Abramson Cancer Center

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1. INTRODUCTION:

The goal of the University of Pennsylvania Abramson Cancer Center Kidney Cancer Research Consortium (PENN/ACC) participation is to meaningfully contribute to phase I and II clinical research in the context of multi-institutional collaborations with the 3 other member sites. Over the past year, while meeting monthly with other member sites, we have helped to form a governance structure for all of the groups and implemented a data sharing infrastructure which is based on the Prometheus platform. We are in the process of activating our first consortium trial "Monitoring Disease Burden and Biology Using Tumor Cell Free DNA in Metastatic Kidney Cancer" (MDA IRB# 2021-0379) in collaboration with Vanderbilt (a new member of KCRC) through MDACC coordination which will collect biospecimens for DNA methylation. In addition, we have presented a neoadjuvant trial of pembrolizumab +/-lenvantinib in locally advanced renal cancer which we hope to open at several consortium sites. We anticipate that PENN/ACC participation in the Consortium will contribute patient numbers, intellectual input and translational research expertise to the KCRC and provide a critical platform for the co-development of renal cell carcinoma (RCC) clinical trials.

2. KEYWORDS:

ACC= Abramson Cancer Center
API= Application Programming Interface
BIDMC=Beth Israel New England Deaconess Medical Center
DAG= Database and Applications Group
EAB=External Advisory Board
EDC= Electronic Data Capture
EHR=Electronic Health Record
GU= Genitourinary
IIT=Investigator Initiated Trial
IRB=Institutional Review Board
KCRC= Kidney Cancer Research Consortium
MDACC= MD Anderson Cancer Center
PD1=Programmed death receptor 1
PENN= University of Pennsylvania
PSMA= Prostate Cancer Membrane Antigen
RCC=Renal Cell Carcinoma
TGFB=Transforming Growth Factor Beta
TKI=Tyrosine Kinase Inhibitor
UTSW= University of Texas Southwestern
VEGF=Vascular Endothelial Growth Factor

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aims
1. Design innovative clinical trials for the KCRC
2. Accrue at least 25 patients per year to KCRC trials
3. Perform translational research on samples obtained from KCRC trials

Major Task 1: Support an effective governance and management structure
Major Task 2: Endorse a harmonized protocol approval process
Major Task 3: Protocol participation, data automation, and monitoring platform
Major Task 4: Utilize Prometheus sample analysis infrastructure
Major Task 5: Create industry and philanthropic partnerships

Please refer to the next question for goals/tasks accomplished and timelines.

What was accomplished under these goals?

Specific Aims/Major Tasks	Timeline	Penn/ACC
Major Task 1: Design innovative clinical trials	**Months**	
Subtask 1: Submit for Human Research Protection Office (HRPO) review	1-3	This task was not relevant as it was not pertaining to the KCRC infrastructure.
Finalize cooperative agreements between institutions (contracting, IP agreements)	1-6	Cooperative contracting and intellectual property agreements between the PENN-ACC and MDACC were established months 1-6. KCRC Contractual Agreement was received from MDACC on 5/12/2020. PENN Lawyer, Kathleen Chen sent proposed changes 5/22/2020, MDACC routed to legal for signature 10/5/2020, The agreement was signed by ACC, MDACC, UTSW and BIDMC
Finalize data sharing infrastructure	1-6	The data sharing infrastructure was finalized in the past year: IRB Agreements were finalized between the MDACC coordinating center and the PENN/ACC. The biobanking protocol "Monitoring Disease Burden and Biology Using Tumor Cell Free DNA in Metastatic Kidney Cancer" (MDA IRB# 2021-0379) was the pilot protocol that identified and rectified details that impede activation. Major Task 3: Protocol participation, data automation, and monitoring platform: • By 10/20/20, the Application Programming Interface (API) was established. Under this Interface, the Penn electronic health record (EPIC) which contains data such as Demographics, Labs, Pathology, Vital Signs, Diagnosis, Staging, Performance Status as well as Tumor Measurements are linked to the Prometheus (with the same data det. Specifically, our ACC EHR and EDC set up "Hello World" and then an exchange test using anonymized patient data from a Penn Investigator initiated trial (IIT) was successfully implemented. Specific data are queried in EPIC Clarity and stored in a Penn Medicine database. • Additional tables are used to store protocol level data and the research labs that are collected for a given protocol. • API Request Client makes an API request with secure authentication for a subject(s) enrolled on a protocol(s) for a given date range. • API Endpoint API returns the data objects in JSON format to the client. *i.e. demographics, labs, vitals, etc.*
Subtask 3: Engage with Pharma and in-house team to develop clinical trial concepts	1-36	Proposed Penn Protocol Concepts: 1. Evaluating Lenvatinib and Pembrolizumab in sustaining progenitor exhausted CD8 T cells and durable T cell reinvigoration in renal cell carcinoma (Merck

		supported) 2. PSMA/TGFB CAR trial (Tmunity supported) Other CAR trials (Penn Philanthropy supported) Renal and other GU biobanking (Dibona, Mazzoleni Family Research Fund, and Penn Breakthrough Bike Challenge provide support)
Subtask 4: Develop and expand collaborations with translational researchers and industry partners for correlative endpoints	1-36	• A biomarker trial proposed by S. Haake: "Monitoring Disease Burden and Biology Using Tumor Cell Free DNA in Metastatic Kidney Cancer" (MDA IRB# 2021-0379) • The trial was initiated with MDACC IRB and submitted to WCG IRB April 2021. • WCG IRB meeting was on 5/25/2021 • Subsequent submission to WCG IRB for ICD configuration in accordance with state • Received acknowledgement from Penn IRB to cede IRB review on 9/27. IRB application submitted to WCG for central approval on 10/5/21.
Subtask 5: Submit clinical trial concepts for review to KCRC	3-36	3 proposals have been presented to the KCRC and reviewed: 1. Cryoablation of metastasis with ipilimumab and nivolumab 2. PSMA/TGFB CAR tumor agnostic trial 3. Evaluating Lenvatinib and Pembrolizumab in sustaining progenitor exhausted CD8 T cells and durable T cell reinvigoration in renal cell carcinoma
Subtask 6: Participate in monthly KCRC meetings to vet and approve trials	1-36	The meetings are held monthly on the 3rd Tuesday of the month at 5pm EST
Milestone(s) achieved:		
MDACC HRPO approval	3	
Contracting completed	6	**See Major Task 1:** Finalize cooperative agreements between institutions (contracting, IP agreements)
Data sharing infrastructure complete	6	See Finalize data sharing Infrastructure Major Task1
First clinical trial concept submitted	6	July 2020 - Cryoablation of metastasis with ipilimumab and nivolumab- KCRC committee voted no due to significant overlap with other trials open at the KCRC institutions PSMA/TGFB CAR trial to follow tumor agnostic trial- KCRC enthusiasm for this after preliminary data achieved in Penn tumor agnostic trial. June 2021, KCRC tentatively approved development of "Evaluating Lenvatinib and Pembrolizumab in sustaining progenitor exhausted CD8 T cells and durable T cell reinvigoration in renal cell carcinoma" as a multi-center KCRC trial.
Major Task 2: Accrue at least 25 patients per year to KCRC studies		
Subtask 1: Reciprocally open KCRC trials at	1-36	Evaluating Lenvatinib and Pembrolizumab in sustaining progenitor exhausted CD8 T cells and durable T cell

Clinical Trial Sites		reinvigoration in renal cell carcinoma has been proposed and multi-center trial partially funded by Merck has been submitted as a DOD clinical trial proposal by investigator Dr. Narayan. Initial planned accrual at MDACC and Penn/ACC.
Subtask 2: Optimize patient recruitment strategies	1-36	Ongoing. A patient kidney cancer conference (Judy Nicholson Kidney Cancer Foundation) convened at ACC/PENN on October 1. The biobanking trial and perioperative trial was highlighted in our clinical trials support module.
Milestone(s) achieved:		
Patient accrual rate achieved	1-36	We anticipate rapid accrual to the Haake "Monitoring Disease Burden and Biology Using Tumor Cell Free DNA in Metastatic Kidney Cancer" (MDA IRB# 2021-0379)" opening at Penn this month (10/21) (all KCRC sites are opening).
Aim 3: Perform translational research on samples obtained from KCRC studies		
Subtask 1: Finalize correlative sample tracking infrastructure	1-6	See Major Task1, Subtask 4. Haake "Monitoring Disease Burden and Biology Using Tumor Cell Free DNA in Metastatic Kidney Cancer" (MDA IRB# 2021-0379) biobanking trial is under review at Penn IRB. Once this is activated and accruing, we will test the institutional tracking infrastructure.
Subtask 2: Collect correlative samples	3-36	Nothing to report
Subtask 3: Transfer samples to site performing analyses	3-24	Nothing to report
Subtask 4: Perform analyses	12-36	Nothing to report
Subtask 5: Correlation to clinical data	12-36	Nothing to report
Milestone(s) achieved:		
Incorporation of translational research data into clinical trials	1-36	Nothing to Report

What opportunities for training and professional development has the project provided?

The Judy Nicholson Kidney Cancer Symposium for patients occurred October 1, 2021 and Project manager Janaiya Reason created website for kidney cancer clinical trial support. Research and Patient Symposiums planned for October 2022.

How were the results disseminated to communities of interest?

Nothing to Report. Judy Nicholson Kidney Cancer Symposium for patients took place October 1, 2021 and Kidney Cancer Research and Patient Symposiums planned again for October 2022.

What do you plan to do during the next reporting period to accomplish the goals?

Now that the Contracting, and Data Exchange Infrastructure is complete, the Penn/ACC major efforts will be directed to opening clinical and translational trials and accruing patients to these trials. We will continue to work with Philanthropy and Industry to support pilot projects and Dr. Narayan submitted a DOD application to support infrastructure for Phase II "Evaluating Lenvatinib and Pembrolizumab in sustaining progenitor exhausted CD8 T cells and durable T cell reinvigoration in renal cell carcinoma" as a multi-center KCRC trial.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The PI and other personnel involved in the Coordinating Center worked together to create an enabling infrastructure that will transform the way clinical trials are performed for patients with renal cell carcinoma. We anticipate that the Prometheus Infrastructure will accelerate trial design, budgeting and approval, efficient risk-based monitoring and third-party sample management will permit execution of novel trials.
Collaboration with now 6 institutions in the KCRC will permit more rapid initiation and accrual to clinical trials that would be difficult to complete at any single center. In addition, we have identified our catchment areas and underserved kidney cancer diseases and disease stages for clinical trials. Implementation of smaller trials in these populations will help provide valuable insights into these orphan diseases and will help provide objective information on the efficacy of therapies chosen to manage these diseases.

Renal Clear Cell Carcinoma Incidence Rates, Stratified by Race, Adults (18+), Both Sexes, University of Pennsylvania 2013-2017

Race/ Ethnicity	Stats	Year 2013	2014	2015	2016	2017	13'-17'
White	count	228	213	240	232	255	1168
	rate	75%	74%	85%	78%	79%	78%
Black/African American	count	64	58	37	54	54	267
	rate	21%	20%	13%	18%	17%	18%
Asian	count	6	7	3	5	7	28
	rate	2%	3%	1%	2%	2%	2%
Other/ Unknown	count	6	9	4	6	6	31
	rate	2%	3%	1%	2%	2%	2%

*Other/Unknown includes Unknown, American Indian, Native Hawaiian/Pacific Islander, & More than one race

KCRC

NAACCR AGE-ADJUSTED INCIDENCE RATES, 2000 US STANDARD POPULATION
BY RACE/ETHNICITY KIDNEY AND RENAL PELVIS, ALL AGES, BOTH SEXES, PENNSYLVANIA, 2013-2017

Race/Ethnicity	Stat	Year					
		2013	2014	2015	2016	2017	2013-2017*
White	Rate	17.11	17.05	17.65	17.80	17.84	17.49
	Count	2,394	2,410	2,504	2,544	2,591	2,489
Black	Rate	22.94	23.69	22.61	21.42	21.89	22.49
	Count	327	337	325	320	327	327
Asian/Pacific Islander	Rate	8.24	6.84	5.86	7.61	3.89	6.36
	Count	24	26	22	29	17	24
American Indian/ Alaska Native	Rate	~	~	~	~	~	~
	Count	~	~	~	~	~	~
Hispanic	Rate	13.24	14.33	17.27	16.27	15.13	15.31
	Count	64	74	93	97	88	83
Non-Hispanic White	Rate	17.27	17.13	17.71	17.83	18.06	17.60
	Count	2,347	2,355	2,428	2,466	2,533	2,426
Non-Hispanic Black	Rate	23.67	24.17	23.42	22.08	22.22	23.10
	Count	322	328	321	313	316	320

(Accessed on 5-19-2021)
Results based on data submitted in December 2019.
* Average annual cases.
Rates are per 100,000 population and are age-adjusted by five-year age groups to the 2000 U.S. standard population based on single years of age.
N.B. In areas with small Latino populations, methods to indirectly identify Latinos (like NHIAv2) can overestimate the ethnicity-specific counts of cancer cases. Also, even small errors in Latino population estimates can affect the magnitude of the cancer rates.
~ Counts and rates are suppressed when fewer than 6 cases were reported for the specific cancer. The suppressed cases, however, are included in the counts and rates for All Sites combined.

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report this cycle

5. **CHANGES/PROBLEMS:**
Changes in approach and reasons for change
Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

The Covid-19 pandemic resulted in a hiring freeze at Penn/ACC. As a consequence, we lost much of our research staff which resulted in delays of clinical trial implementation. The research staff have largely been replaced.

Changes that had a significant impact on expenditures

There was less expenditure than expected due to Covid-19 pandemic resulting in research staff needing to be replaced and delaying implementation of the KCRC award.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals

Not Applicable

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**
  Nothing to Report

  Journal publications.

  Nothing to Report

  Books or other non-periodical, one-time publications.

  Nothing to Report

  Other publications, conference papers and presentations.

  Nothing to report.

- **Website(s) or other Internet site(s)**

  The KCRC website went live on 10/15/2021. This website will support trial integration and collaborations.
  https://kcrc.io/

- **Technologies or techniques**

  Nothing to report

- **Inventions, patent applications, and/or licenses**

Nothing to report

- **Other Products**
  Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: **Naomi B. Haas, M.D.**
Project Role: Principal Investigator
Researcher Identifier: https://orcid.org/0000-0001-8907-7968
Nearest person month worked: 5

Contribution to Project: Dr. Haas is the PI and has participated in the monthly KCRC consortium calls. She has mentored Dr. Narayan and co-developed his proposed "phase II investigator-initiated trial with neoadjuvant pembrolizumab (PD-1) +/-lenvantinib (VEGFR-TKI) pre-nephrectomy followed by adjuvant pembrolizumab in locally advanced RCC." Additionally, she meets weekly with the kidney cancer research staff to review proposals received and submitted to the KCRC.

Name: **Vivek Narayan, M.D.**
Project Role: Co-Investigator
Nearest person month worked: 1

Contribution to Project: Dr. Narayan has developed a phase II investigator-initiated trial with neoadjuvant pembrolizumab +/-lenvantinib pre-nephrectomy followed by adjuvant pembrolizumab in locally advanced RCC. This is funded by Merck and Dr. Narayan is applying for a DOD Clinical trials award. This idea has been reviewed by the KCRC and is planned to be implemented at MDACC.

Name: **Janaiya Reason**
Project Role: PENN/ACC Institutional Clinical Trial Coordinator
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 2

Contribution to Project: Ms. Reason replaced Rebecca Cimildoro in this role and coordinates the efforts between PENN/ACC/KCRC and the lead site, MDACC and the other participating sites including the following:
1) Arrange the quarterly calls for the renal cancer clinical trials working group;
2) Continue to be on the monthly calls with the Kidney cancer clinical consortium and transmit information to the PENN/ACC investigators, with emphasis on new trial opportunities.
3) Keep an active list of renal cancer clinical trials ongoing in all sites in Kidney cancer clinical consortium

Name: ***A. Kathleen Harlacker***
Project Role: Research Nurse
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 1

Contribution to Project: Ms. Harlacker replaced Ms. Mindy Dahan and has reviewed the consent and protocol for the biobanking protocol "Monitoring Disease Burden and Biology Using Tumor Cell Free DNA in Metastatic Kidney Cancer" (MDA IRB# 2021-0379) and Dr. Narayans neoadjuvant kidney cancer proposal, "*Phase II investigator-initiated trial with neoadjuvant pembrolizumab (PD-1) +/-lenvantinib (VEGFR-TKI) pre-nephrectomy followed by adjuvant pembrolizumab in locally advanced RCC."*

Name: ***Sydnee O'Connor***
Project Role: Clinical Trial Coordinator (data manager)
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 0

Contribution to Project: "Monitoring Disease Burden and Biology Using Tumor Cell Free DNA in Metastatic Kidney Cancer" (MDA IRB# 2021-0379) Ms. O'Connor replaced Ms. Amera Galal. No work has been performed.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Janaiya Reason replaced Rebecca Cimildoro as the Research Coordinator. There was not change in effort or in assigned tasks.

What other organizations were involved as partners?
Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Nothing to report.

QUAD CHARTS:

9. APPENDICES: Nothing to report.