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TITLE: University of Michigan Phase 1/2 Assessment in Kidney Cancer Therapeutics (UMPAKT)

PRINCIPAL INVESTIGATOR: Dr. Ulka N. Vaishampayan

CONTRACTING ORGANIZATION: University of Michigan

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14. ABSTRACT The commitment of U-M as a clinical site within the consortium is to prioritize kidney cancer trial accrual and develop phase I/II studies of agents with a focus on kidney cancer to expedite novel drug and biomarker development. Per our aims we have established a multidisciplinary team of investigators and trainees who are working on kidney cancer therapeutics. Regular meetings of this team are being conducted with discussion of kidney cancer related preclinical and clinical projects and collaborations. The deliverables are consortium trial activation in May 2022, and 13 patients enrolled between May 2022 to Sept 1 2022. We anticipate exceeding the DOD target of 15 patient enrollments annually. A protocol concept entitled "Phase II trial of tivozanib and nivolumab in advanced non clear cell Renal Cancer" was written by UM investigators, received funding support and approved by the consortium.					
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1. Introduction –

The grant application has an overarching goal of creating a Kidney Cancer Team focused on Early Therapeutics at the University of Michigan (U-M). The commitment of U-M as a clinical site within the consortium is to prioritize kidney cancer trial accrual and develop phase I/II studies of agents with a focus on kidney cancer to expedite novel drug and biomarker development.

Specific Aim 1: To meet the metrics required as a clinical trial site within the Kidney Cancer Research Consortium (KCRC): This objective will be achieved by development of an outstanding team focused on kidney cancer therapeutics within the University of Michigan. The mission is to advance high impact, innovative therapeutics to improve clinical outcomes in kidney cancer and reduce the impact of the disease. The award to U-M will help establish the infrastructure to design, develop and conduct high quality Phase I or Phase I/II clinical trials in kidney cancer. It will enable rapid execution of investigator-initiated trials in renal cell cancer (RCC). It will also facilitate collaboration with the coordinating center and networking with other sites for exchange of ideas and novel target and drug development. Aim 1 will consist of 3 sub aims.

Specific Aim 1A: To create a kidney cancer focused early therapeutics team within the multi-tumor experimental therapeutics (MET) program at the University of Michigan. [University of Michigan Phase I/II Assessment in Kidney Cancer Therapeutics/ U-MPAKT]

Specific Aim 1B: Active participation in the KCRC as a Clinical Trial Site and meeting the required metrics.

Specific Aim 1C: To increase clinical trial enrollment for populations within RCC that are currently underrepresented on clinical trials.

Specific Aim 2: To enable discovery of novel targets and translational biomarkers that will enable selection of individualized therapies towards developing a personalized approach to kidney cancer management.

Specific Aim 2A: To enable discovery of novel targets and prognostic and predictive biomarker development in RCC

Specific Aim 2B: To develop “personalized medicine” pathways for guiding the treatment of refractory kidney cancer

2. Keywords – Acronyms

EAB	External Advisory Board
KCRC	Kidney Cancer Research Consortium
MET	Multi-tumor Experimental Therapeutics
RCC	Renal Cell Cancer
SoC	Standard-of-Care
U-M	University of Michigan

3. Accomplishments- Grant period between Oct 2021- Sept 30 2022

A) Personnel:

Grant coordinator Nabeela Iqbal was on medical leave for 6 months and then left the institution in June 2022. A new grant coordinator Neha Shah was hired and started in July 2022. A study coordinator Joe Dib, BS worked on the grant between Oct 2021- June 2022

The following is a summary of UM activity and progress report on the grant to date:

- a. December 2021-present: Start of The Kidney Cancer focused team building and monthly meetings have been conducted regularly. The steering committee and co-investigators are actively engaged. First kick off meeting was held in Sept 2021
- b. February 2022: Activated a biomarker development study “Pilot Study to Evaluate the clinical utility of Circulating Ensembles of Tumor-Associated Cells profiling to predict selection of preferred standard-of-care (SoC) treatment regimens in newly diagnosed or recurrent advanced refractory Renal Cell Carcinomas.” The accrual will be complete in December 2022 (40 evaluable patients enrolled) and we anticipate reporting of preliminary results at ASCO-GU symposium in Feb 2023. If feasibility is proven this will be developed into a concept for the consortium.
- c. February 2022: Approval of the concept by KCRC. May 2022: Protocol entitled “ PHASE 2 STUDY OF COMBINATION TIVOZANIB AND NIVOLUMAB IN ADVANCED NON-CLEAR CELL RENAL CELL CARCINOMA (FORTUNE)” was proposed and approved by the consortium for development. The protocol has been developed and written, funding has been procured and regulatory processing will start within the next few months.
- d. April 2022: activated the trial PI- Dr Ajjai Alva “Outcomes Database to prospectively aSSEs the changing TherapY landscape in Renal Cell Carcinoma (ODYSSEY RCC)” [lead site: Duke University, PI- Dr Dan George]. This will likely be approved as a consortium trial. U-M has enrolled 5 patients as of 9/1/22.
- e. May 2022: Activation of the first consortium study entitled “Monitoring Disease Burden and Biology Using Tumor Cell Free DNA in Metastatic Kidney Cancer” (Lead institution: Vanderbilt) and enrollment of 13 patients at U-M as of 9/1/22.
- f. Active Participation of the PI at KCRC monthly meetings, EAB meetings and KidneyCan Advocacy. Feedback into protocol concepts ad active collaboration in development of the study at U-M.
- g. Publications in Renal Cancer by the UMPAKT team: Trainees shown with *
 - 1) Bell HN*, Kumar-Sinha C, Mannan R, Zakalik D, Zhang Y, Mehra R, Jagtap D, Dhanasekaran SM, Vaishampayan U. Pathogenic ATM and BAP1 germline mutations in a case of early-onset, familial sarcomatoid renal cancer. Cold Spring Harb Mol Case Stud. 2022 Apr 28;8(3):a006203. doi: 10.1101/mcs.a006203. Print 2022 Apr.PMID: 35483881
 - 2) Hannah Bell* , Brittney H Cotta* , Simpa S Salami, Hyung Kim, Ulka Vaishampayan.. "PROBE"ing the Role of Cyto-reductive Nephrectomy in Advanced Renal Cancer. Kidney Cancer J 2022 Mar 15;6(1):3-9. doi: 10.3233/kca-210010.

4 Impact-

A) Infrastructure of personnel and team established.

B) One consortium study was activated at U-M and 2 are under consideration for regulatory approval.

C) Accrual deliverables: 13 patients enrolled at cutoff of Sept 1 2022.

D) Novel biomarker being developed and if feasible will be brought for validation to the consortium

E) Collaborative projects and grants and publications within kidney cancer focus team

F) Grant funding and extension application for 12 months was approved.

5. Changes/Problems

A) Only one study was active for participation in KCRC.

B) COVID related staffing turnover and hiring, orientation and training of new staff

C) Delays in protocol activations and approvals

6. Products – Not Applicable

7. Participants & Other Collaborating Organizations-

Name:	Ulka Vaishampayan
Project Role:	PD/PI
Researcher Identifier (e.g. ORCID ID):	0000-0001-5800-4571
Nearest person month worked:	2.4 calendar months
Contribution to Project:	Dr. Vaishampayan is responsible for introducing studies to the consortium and contributing accrual of patients annually. She will be responsible for interactions of the U-M clinical site with the coordinating center and ensuring compliance with the policies of quality control, monitoring, biomarker acquisition and publication. She will organize meetings for the UMPAKT team and attending the external advisory board meetings. She will be responsible for submission of the progress reports.
Funding Support:	N/A

Name:	Ajjai Shivaram Alva
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-1898-3522
Nearest person month worked:	0.6 calendar months
Contribution to Project:	Dr. Alva is an active participant in kidney cancer clinical trials patient accrual as well as in clinical trial development and design for this study.
Funding Support:	N/A

Name:	Rohit Mehra
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-6955-8884
Nearest person month worked:	0.6 calendar months
Contribution to Project:	Dr. Mehra is lead pathologist who is responsible for clinical pathology review of kidney cancer cases and helps coordinate the biomarker correlatives conducted on the consortium clinical trials at the U-M site.
Funding Support:	N/A

Name:	Jeremy Michael George Taylor
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0003-2791-1229
Nearest person month worked:	0.66 calendar months
Contribution to Project:	Dr. Taylor is responsible for working with the team to develop statistical study design for the investigator initiated study proposals that are developed under the grant.
Funding Support:	N/A

Name:	Yi-Mi Wu
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-3789-4445
Nearest person month worked:	0.6 calendar months
Contribution to Project:	Dr. Wu is responsible for conducting comprehensive genomic profiling for refractory RCC patients and for participating in developing and conducting rational biomarker correlatives for consortium clinical trials.
Funding Support:	N/A

Name:	Nabeela Iqbal
Project Role:	Clinical Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	5 calendar months Oct 2021- Feb 2022
Contribution to Project:	Ms. Iqbal was responsible for coordinating grant activities on behalf of the U-M Oncology Clinical Trials Unit, including feasibility studies, attending consortium meetings, and tracking grant activities.
Funding Support:	University of Michigan, Michigan Medicine Oncology-Clinical Trial Support Unit Administration

Name:	Neha Shah
Project Role:	Clinical Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	3 calendar months Jul - Sep 2022, ongoing

Contribution to Project:	Ms. Shah is responsible for with coordinating grant and regulatory activities on behalf of the U-M Oncology Clinical Trials Unit, including feasibility studies, attending consortium meetings, and tracking grant activities. She will be working on database, patient enrollment activities as well.
Funding Support:	Prostate Cancer Foundation (PCF)

Name:	Joe Elie Dib
Project Role:	Clinical Research Assistant
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	5.26 calendar months
Contribution to Project:	Mr. Dib assisted with with submission and approvals of the consortium protocols, and database entry and maintenance.
Funding Support:	N/A

Active participation within KCRC from PI, co-investigators and lead coordinator.

The specific aims and statement of work with the progress and activity at year 1 is shown below.

Specific Aim 1: To meet the metrics required as a clinical trial site within the Kidney Cancer Research Consortium (KCRC):

Specific Aim 1A: To create a kidney cancer focused early therapeutics team within the multi-tumor experimental therapeutics (MET) program at the University of Michigan. [University of Michigan Phase I/II Assessment in Kidney Cancer Therapeutics/ U-MPAKT]

Specific Aim 1B: Active participation in the KCRC as a Clinical Trial Site and meeting the required metrics.

Specific Aim 1C: To increase clinical trial enrollment for populations within RCC that are currently underrepresented on clinical trials.

Specific Aim 2: Discovery of novel targets and translational biomarkers that will enable selection of individualized therapies towards developing a personalized approach to kidney cancer management.

Specific Aim 2A: To enable discovery of novel targets and prognostic and predictive biomarker development in RCC

Specific Aim 2B: To develop “personalized medicine” pathways for guiding the treatment of refractory kidney cancer

Tasks	Timeline	Work conducted Year 1
Specific Aim 1: to meet metrics of KCRC		
Specific Aim 1A: To create a kidney cancer focused team: Organize Monthly meetings	Start Month 1 Continue monthly	Started Sept 6 2021 kickoff meeting

Regulatory approval of consortium protocols	Month 1- month 4	1 consortium protocol regulatory approval
Attend consortium teleconferences	Start Month 1 Continue for grant duration	Attended by PI and coordinator monthly. Attended and presented at 2 EAB and 1 Program review
Patient accrual to consortium trials	Month 4- month 24 1-2 patients per month accrual	13 patients accrued to date
Veteran Patient evaluation and screening for consortium trials	Months 4- month 24 Upto 10 patients	2 veteran patients prescreened for trials Were not eligible
Clinical Trial development Clinical trial introduced to consortium Clinical trial introduced to consortium Clinical trial introduced to consortium Clinical trial introduced to consortium	month 1-month 6 month 7- month 12 month 13- month 16 month 17- month 20	Months 1-6 Clinical trial "FORTUNE" introduced to consortium and approved. Funding obtained from Aveo Inc. Months 7-12 Protocol design development and protocol writing. IND submission to FDA,
Specific Aim 2: Discover targets and enable personalized medicine		
Molecular profiling of upto 20 advanced RCC patients	months 1-month 20	1 case of BAP-1 mutation and germline ATM mutation profiled. Publication with trainee (medical student): Bell H et al. PMID: 35483881
Compiling and reporting results, manuscript preparation	months 20-month 24	N/A
Correlative studies development for clinical trials	Month 1- month 24	Correlative work is developed for FORTUNE trial
Pilot trial for liquid biopsy : Protocol development	Month 1- month 6	Feasibility trial activated
Regulatory approval	Month 7-month 10	Regulator approval obtained.
Protocol accrual	Month 11- month 20	47 patients enrolled.
Compiling results and reporting	Month 21-month 24	Abstract submission planned year 1.

8. Special Reporting Requirements- Not applicable

10. Appendices -

Updated Other Support for Dr. Vaishampayan

Updated Other Support for Dr. Alva

Updated Other Support for Dr. Mehra

Updated Other Support for Dr. Taylor

Updated Other Support for Dr. Wu