Independent Investigative Inquiry (III)
Scholarship of Discovery
Project Proposal Coversheet

UW Medicine
UW SCHOOL OF MEDICINE

Please submit completed Project Proposals in **PDF format** by **February 1, 2019** through the III Canvas site. Students can expect to receive notification of the committee's decision by February 22, 2019.

Questions? Please contact SOM Curriculum Office at [redacted]

Project Information

Title	Platinum chemotherapy rechallenge in patients with recurrent urothelial carcinoma
Location	Seattle Cancer Care
Category (Laboratory-based, Clinical research, Health Services, QI, etc)	Clinical research

Student Information

Name	[redacted]
UW Email Address	
Phone	
First-year Site	

Faculty Mentor Information

Name & Degrees (e.g. M.D.)	[redacted]
Faculty Title	
Do you hold a UWSOM Faculty appointment (yes, no)	
Department & Institution	
UW Box Number (if applicable)	N/A
Street Address, City, State, Zip	[redacted]
Email Address and Phone	

Faculty Co-Mentor Information
(Complete this section only if your Faculty Mentor does **not** hold a UWSOM Faculty Appointment)

Name & Degrees (e.g., M.D.)	
Faculty Title	
Department & Institution	
UW Box Number (if applicable)	
Street Address, City, State, Zip	
Email Address and Phone	

Project Description

Background

Urothelial carcinoma is the sixth most common cancer in the United States.[1] Although most cases are non-muscle invasive at diagnosis, approximately 70 percent of patients will have a recurrence or new occurrence within five years, with 25 percent of patients developing more advanced muscle-invasive or metastatic disease.[1] Platinum-based chemotherapy is the preferred treatment for patients with high-risk localized or metastatic urothelial malignancies.[2-4] First-line treatments include gemcitabine with cisplatin or adriamycin with cisplatin, methotrexate, and vinblastine.[2-4] In patients who relapse after initial combination platinum-based chemotherapy, second-line chemotherapy has a limited role, with only immune-oncology antibodies that target PD-1 or PD-L1 being the only other standard.[5] Given the limited options for treatment, physicians will often either repeat a platinum-base chemotherapy regimen or offer an alternative chemotherapy regimen with a different mechanism of action.

For patients who relapse after first-line chemotherapy for muscle-invasive urothelial carcinoma, the prognosis is generally poor. To date, there is no consensus on how to best treat these patients. Our project is to determine if rechallenge with platinum-based combination regimens in the metastatic disease setting offers siginficant clinical efficacy over utilization of other systemic chemotherapy treatment regimens for patients who previously received initial cisplatin-combination chemotherapy for high-risk localized urothelial carcinoma patients and relapse.

Study Design Methods

This study will be a retrospective cohort study in nature. Patients with urothelial tract carcinoma with T2-4 disease amenable to definitive local therapy will be included in the study. The patients will be gathered from the Retrospective International Study of Cancers of the Urothelium (RISC) and University of Southern California (USC) database. There are over 3,000 patients in these databases with clinopathologic, treatment, and outcomes data that will be analyzed. The data for this project has already been abstracted from the appropriate databases and an institutional IRB approval is in place.

The primary variables will be overall survival, progresion-free survival, response to platinum-based combination rechallenge, and length of rechallenge therapy. We will stratify the population for type of platinum chemotherapy received and whether the rechallenge treatment is the same platinum chemotherapy or if there is a switch to a different platinum chemotherapy regimen. Care will be taken in the interpretation of these associations given the potential for selection bias inherent in retrospective analyses. As a result, we will control for well known prognostic factors, including the Charlson comborbidity index, time from prior chemotherapy, number of prior treatment reigmens, albumin, and type of response to prior platinum-baed chemotherapy treatment (complete response vs partial response vs stable diseease). Multivariable analyses of the above prognostic factors will be performed to determine whether certain patient characteristics are associated with better outcomes with platinum-based chemotherapy rechallenge. Results will be considered statistically significant for $p \leq 0.05$.

Expected Signifiance of Results

The results of these analyses will generate important hypotheses for future prospective trial testing. Specifically, this may help determine if patients are better rechallenged with platinum-combination chemotherapy in the relapsed, metastatic disease setting or if a treating physician should switch to a different chemotherapy regimen. This analysis also has potential to identify patient characteristics that associate with benefit from platinum-based chemotherapy rechallenge or alteration of chemotherapy regimen.

Student Role

My role in this project will be to organize the clinical data in the database and work closely with the biostatistician to analyze the data and answer the clinical questions. By the end of the summer, the goal is to begin work on an abstract, poster presentation and manuscript for formal publication.

Preliminary Literature Search (5-10 references that address your research question)

1. Bellmunt A, Orsola A, Leow JJ et al., Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up, *Ann Oncol*, 2014;25 Suppl 3:iii40-8.

2. Plimack ER, Hoffman-Censits JH, Viterbo R, et al., Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter Phase II study with molecular correlates of response and toxicity, *J Clin Oncol*, 2014;32:1895–901.

3. Galsky MD, Pal SK, Chowdhury S, et al., Comparative effectiveness of gemcitabine plus cisplatin versus methotrexate, vinblastine, doxorubicin, plus cisplatin as neoadjuvant therapy for muscle-invasive bladder cancer, *Cancer*, 2015;121:2586–93.

4. Zargar H, Espiritu PN, Fairey AS, et al., Multicenter assessment of neoadjuvant chemotherapy for muscle-invasive bladder cancer, Eur Urol, 2015;67:241–9.

5. Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin- ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *Lancet Oncol.* 2017;18(11):1483-1492. doi: 10.1016/S1470-2045(17)30616-2.

Project Timeline

Your project timeline should allow you to complete the project before the second year begins in September.

	Tasks to be completed
Week 1	Read journal articles on urothelial carcinoma, determine what data elements to collect
Week 2	Gather data elements relevant to study
Week 3	Work with biostatistician to analyze data
Week 4	Work with biostatistician to analyze data
Week 5	Work with biostatistician to analyze data
Week 6	Work with biostatistician to analyze data
Week 7	Work with biostatistician to analyze data
Week 8	Begin work on abstract/poster
Week 9	Begin work on abstract/poster

Human and Animal Subjects

If your project involves human subjects, your Project Proposal must address how you will obtain any required Institutional Review Board (IRB) approvals in advance of the project start date. Similarly, if the project involves animal use, this will require approval from the Animal Care and Use Committee (ACUC). **You are required to provide a copy of the IRB or ACUC approval to Curriculum (somcurr@uw.edu) prior to starting your project.**

Students, with the assistance of their Faculty Mentors, are responsible for determining IRB requirements. Your Faculty Mentor should be well versed in what approval has already been granted and what approval is required for you to engage in the project. If you are unsure what approval is required, you can contact the UW Human Subjects Division (HSD) at hsdinfo@uw.edu.

It is the responsibility of the Faculty Mentor to assist students with submission of UW and other pertinent IRB or ACUC applications as early as possible and no later than March 1, 2019, regardless of where research is taking place, however some complex projects may require more advance planning.

	Yes	No
Does the project require IRB review or a determination of exemption?	x	

If yes, has the project been approved by an Institutional Review Board or has a Determination of Exemption by HSD?

x **Yes**, this project has been granted IRB approval or received a determination of exemption under study # 7723.

___ **No**, this project has not yet been approved. The following plan for obtaining required IRB approvals is in place:

Are experiments with vertebrate animals involved?		

If yes, has the animal protocol been approved by the appropriate Animal Use and Care Committee?

___ **Yes**, this project has been granted IACUC approval under study # _____.

___ **No**, this project has not yet been approved. The following plan for approval is in place:

Faculty Mentor Statement

Students are asked to work with a faculty member who may be any UWSOM faculty member with an Affiliate, Clinical, or Regular faculty appointment, including those at the Instructor level. Fellows and residents do **not** hold Faculty appointments, and are **not** eligible to be a research mentor or co-mentor. If the Faculty Mentor **does not** have a UWSOM faculty appointment, the student will need a **Faculty Co-mentor** who **does** have a UWSOM faculty appointment. The Faculty Mentor must be experienced and familiar with the project topic and methods used in the study. The Faculty Mentor's role is to help the student plan the study, regularly meet with the student (weekly at minimum) during the execution of the project, review and sign-off on the final poster, and submit an evaluation of the student's work.

In the space below, please provide a brief paragraph on: 1) your willingness to mentor the student, 2) the role the student will play in the project and how you will ensure this is an independent project 3) your evaluation of the student's ability to carry out the work, and 4) your agreement with the project proposal and timeline above. The application will be considered incomplete if this information is not included.

I look forward to inviting [redacted] as a new member of my research group in the summer of 2019. I have a history of mentoring many junior faculty, fellows, residents, medical students and undergraduates, with many of these individuals eventually achieving independent academic careers. As a result of this track record, I hope that you will view this application in a favorable light.

I interviewed a total of 5 applicants who showed interest in this proposal, and after much deliberation, I decided that [redacted] was the most motivated and passionate student for this specific research project. Although I have chatted with [redacted] a couple of times already about this project, [redacted] wrote 90% of this proposal herself. I find [redacted] to be bright, motivated and eager to learn more about the research method. She is dedicated to the research project, and most importantly, finds excitement and curiosity in the field of medical oncology.

[redacted] will take on the primary role of selection of appropriate patients for analysis, data organization and help lead the data analysis with the aid of some of my biostatistician collaborator (Sarah K. Holt, Ph.D.). I will oversee this work and meet with [redacted] on a weekly basis during her proposed III timeline, but she will independently lead the project. She will be working both remotely and at the Seattle Cancer Care Alliance. I believe her proposed timeline is feasible and that [redacted] will be successful in completing this project.

I fully anticipate that this project will eventually lead to a manuscript that will be published in a middle impact factor peer-reviewed journal. Furthermore, I am hopeful we will be able to present this project as an abstract at either the Genitourinary Cancers Symposium or American Society of Clinical Oncology in the coming year (2020). I expect that [redacted] will lead us successfully to this result. Therefore, I am able to commit resources to help supplement the summer III stipend.

Signatures

Signature of Student	[redacted]
Signature of Faculty Mentor	[redacted]
Signature of Faculty Co-Mentor (if applicable)	
Date	1/5/2019

[redacted]