I have been extremely grateful for this award and am pleased to provide this final progress report. The support of the CRF provided invaluable capabilities for me to make significant research discoveries and, importantly, to successfully obtain follow-on funding to advance our work in urothelial cancer. I summarize the specific achievements below:

Our original research hypothesis was that validated genetic “platinum susceptibility” biomarkers will allow identification of urothelial cancer patients most likely to benefit from platinum-based chemotherapy.

**Aim 1** proposed to prospectively enroll and study a cohort of urothelial cancer patients receiving neoadjuvant cisplatin-based chemotherapy in order to analyze germline genetic variants that may predict achievement of complete pathologic response (target 60 patients).

It was soon realized that prospective recruitment of an adequate number of patients from our single institution would not occur quickly enough to reach the target accrual in a timely fashion, so we formed a very active research collaboration with investigators at Memorial Sloan Kettering Cancer Center (MSKCC; D. Bajorin, PI) and Fox Chase Cancer Center (E. Plimack, PI) in order to assemble a larger sample set. This collaboration was extremely fruitful, in that we were able to accrue 59 patients and performed the primary genomic analysis by October 2012. This analysis showed that two germline single nucleotide polymorphisms (SNPs) of interest (rs244898 and rs7937567) – both selected based on prior evidence (generated via our own cell-based work) of governing platinum sensitivity in pre-clinical and clinical models - were demonstrated to confer  strong  associations with complete response to cisplatin-based neoadjuvant chemotherapy in this cohort. Patients lacking these two SNPs were highly unlikely to achieve complete pathologic response to chemotherapy (negative predictive value = 88%). A separate germline SNP (rs10964552) was significantly associated with pathologic down-staging after cisplatin-based neoadjuvant chemotherapy. These findings were presented at the 2013 ASCO – Genitourinary annual meeting (*J Clin Oncol* 31, 2013 (suppl 6; abstr 290)).

In order to increase the confidence in these findings, and because the collaboration with MSKCC and FCCC permitted our three institutions to combine samples that we could assemble into a validation set, we next sought replication testing in this independent, multi-institutional validation cohort of patients. We assembled 146 patients in this validation cohort. This cohort size provided >80% power to detect independent effects of the identified SNPs on complete response using a multivariate logistic model, assuming odds ratios of effect and minor allele frequencies equivalent to those in the discovery cohort. Unfortunately, none of the three germline SNPs were associated with response to cisplatin-based neoadjuvant chemotherapy in the large replication cohort. Reasons for failure may include unmeasured clinical differences in patient cohorts, a difference in rate of use of an alternative chemotherapy combination in the validation set compared to the discovery set, or simply a spurious association in the discovery cohort. On a positive side, the study marked the successful performance of a germline pharmacogenomic study with replication in urothelial cancer – a first of its kind. The results demonstrated that multi-institutional
collaborations are feasible and will likely be necessary to achieve advances in urothelial cancer pharmacogenomics. These findings were presented at the 2014 ASCO – Genitourinary annual meeting (J Clin Oncol 32, 2014 (suppl 4; abstr 342)). The full manuscript describing these findings was submitted to Cancer and was rejected after full review. We are now submitting a revised manuscript to BJU Int.

In addition, this award also supported publication of the following article describing the above as well as other prior and ongoing investigations in urothelial cancer pharmacogenomics (O'Donnell PH. Bladder Cancer Pharmacogenomics: Recent Insights and Future Perspectives. Pharmacogenomics, 13(14):1553-6, 2012.).

**Aim 2** proposed to examine a large population of urothelial cancer patients who received cisplatin-based chemotherapy for metastatic disease, with time to progression and overall survival from the time of chemotherapy initiation as the primary and secondary endpoints (proposed approximately 300 patients).

**Aim 3** is related, in that it proposed to examine a population of urothelial cancer patients who were unfit for standard cisplatin therapy due to poor renal function but who received alternative carboplatin-based chemotherapy for metastatic disease (propose approximately 150 patients).

Progress on Aims 2 and 3 has proceeded well and is ongoing. Importantly, in order to achieve Aims 2 and 3 - specifically in order to accrue the sample size necessary for these Aims - we realized that multi-institutional collaboration would be essential. We therefore capitalized on the already-formed relationship with investigators at MSKCC and decided to pursue follow-on funding with those investigators to fully support these Aims.

Toward that end, I am a named collaborator on two grant applications that have now been awarded to study the germline pharmacogenomics of platinum-based chemotherapy in advanced urothelial cancer patients.

1. The V Foundation for Cancer Research (H. Furberg and V. Joseph, PIs, MSKCC) 8/1/14 – 7/31/16
   Role: Named collaborator
   “The role of germline genetic variation in host response and vascular toxicity from systemic chemotherapy for advanced urothelial cancer”

2. Cycle for Survival (H. Furberg, PI, MSKCC) 9/1/14 – 8/31/15
   Role: Named collaborator
   “Pharmacogenetics of advanced bladder cancer treatment response and vascular toxicity”

Both of these grants – in addition to the CRF award – support ongoing research on the above Aims. We also recently submitted an application to the RIKEN Institute of Japan through the Pharmacogenomics Research Network (PGRN) – RIKEN Collaboration to seek funding of additional genotyping for 850 patients treated with platinum-based therapy in both the neoadjuvant (Aim 1) and metastatic settings (Aims 2 and 3). We are awaiting word on this funding decision. These 850 patients have been assembled through the active accrual of patients at The University of Chicago (supported by the CRF award) and MSKCC, in addition to gaining approval to use of samples from the Alliance for Clinical Trials in
Oncology trial #NCT00942331 (clinicaltrials.gov – “Gemcitabine Hydrochloride and Cisplatin With or Without Bevacizumab in Treating Patients With Advanced Urinary Tract Cancer”, J. Rosenberg PI). In my role as Pharmacogenomics and Population Pharmacology committee representative to the Genitourinary committee of Alliance, I facilitated this collaboration within Alliance and have been actively involved in the study design and analysis plan. I met with MSKCC investigators in person in April 2015 in New York, NY, and conduct monthly teleconference calls to maintain progress on the Aims.

In summary, I hope that you find this progress report to be reflective of the measurable difference your funding has made to me and to the proposed science. It has not only permitted me to generate publishable new knowledge about therapies for urothelial cancer, but has led to follow-on external grant funding and a very rewarding ongoing collaboration with peers at outside institutions in order to do team science to discover additional findings. We are very hopeful that this research will directly improve the lives of patients with urothelial bladder cancer.

Thank you kindly for your support.

Peter H. O'Donnell