DANA-FARBER CANCER INSTITUTE | BWH BRIGHAM AND WOMEN'S HOSPITAL

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October 28, 2014

Alice Chen, M.D.
Senior Clinical Investigator
Investigational Drug Branch
CTEP, DCTD, NCI

Re: Career Development PTMA of Panagiotis Konstantinopoulos, M.D.
Mentor Support Letter

Dear Dr. Chen:

I am pleased to support the Career Development PTMA of Dr. Panagiotis (Panos) Konstantinopoulos. Panos recently joined the faculty in the Department of Medical Oncology at the Dana-Farber, where he is a member of the Gynecologic Oncology Program, the Center for DNA Damage and Repair and the Early Drug Development Center, where he works under my direction.

Panos has embarked on a translational career in academic oncology, focusing on identification of novel therapeutic agents for patients with gynecologic malignancies. His primary interest is in epithelial ovarian cancer (EOC). Specifically, he is focusing his career on DNA repair in this disease. He is most interested in conducting a study of gemcitabine/cisplatin ± VX-970 in platinum-resistant disease, but has also indicated on his PTMA that he is interested in trials of VX-970 in platinum-sensitive disease as well as in combination with topotecan.

Panos has great potential to emerge as a leader in the field of DNA repair in ovarian cancer. His previous work led to the development of a gene expression profile of BRCAness that correlates with responsiveness to platinum and PARP inhibition in EOC. The work resulted in a first author publication in the *Journal of Clinical Oncology* and was selected for oral presentation at ASCO. In addition to his work on BRCAness, he has shown that the Keap1-Nrf2 pathway mediates platinum resistance in ovarian cancer and is activated at baseline in the relatively chemoresistant clear cell subtype of this disease. Panos is the first author of a publication in *Cancer Research* detailing these results.

Since his arrival to Dana-Farber, Panos has been working on identification and preclinical evaluation of novel agents that exhibit synthetic lethality in tumors that are deficient in homologous recombination (HR) DNA repair, as well as of agents that inhibit the HR pathway. He has been extremely productive and has accomplished a large body of work over the past 1-2

years. He has recognized that combinations involving PARP inhibitors with agents that inhibit HR may represent an effective strategy to enhance the activity of PARP inhibitors, especially in HR-proficient tumors. In one example of this approach, he has shown that the HDAC inhibitor SAHA inhibits HR and enhances the activity of olaparib in HR-proficient ovarian cancer cells *in vitro* and in HR-proficient EOC xenografts. This work has been published in *Gynecologic Oncology*. More recently, Panos developed preclinical data combining HSP90 inhibition and PARP inhibition. He has shown that sublethal concentrations of 17-AAG inhibit HR and sensitize HR-proficient EOC cell lines to olaparib and carboplatin *in vitro*. This work has been published in *Oncotarget*. Furthermore, as part of an Ovarian Cancer Research Fund Program Project Development grant, Panos will evaluate the HSP90 inhibitor/PARP inhibitor combination in luciferized patient derived xenograft models.

Panos also has a strong interest in the recently recognized group of ovarian cancers harboring *CCNE1* amplification that comprise a subset of the platinum-resistant group. These tumors are under replication stress and dependent on homologous recombination repair. They may have particular sensitivity to HR inhibitors, such as an ATR inhibitor, and will certainly be enriched in the ovarian cancer population enrolled to a trial for platinum-resistant patients.

Currently, Panos also has clinical effort and has participated in a variety of clinical trials related to EOC. He is an extremely conscientious investigator with excellent clinical judgment. Involvement in the VX-970 Project Team as a Clinician Scientist will offer him the opportunity for clinical trial leadership within the Phase 1 and Women's Cancers programs at the DFCI, and nationally if the trial is open throughout the ETCTN. In this regard, he is a superb candidate to lead a trial of VX-970 in gynecologic cancers. His outstanding knowledge base in the field will allow him to easily interface with other clinicians, as well as with translational and basic investigators.

For this project, I will serve as the primary mentor based on my experience with VX-970 and conduct of early phase studies. We will also have the support of Dr. Ursula Matulonis, who will be available for guidance from DFCI's Gyn Program. I will work very closely with him on all aspects of the project, including writing of the study, enrollment of patients, management of adverse events and data reporting, execution of correlative studies, as well as interaction with other ETCTN investigators, and will insure that the proposed work is accomplished in a timely fashion.

In summary, leadership of a VX-970 study in gynecologic malignancies represents a natural extension of the research program Panos is pursuing. He brings an extensive background to the clinical development of the proposed combination. He has my highest recommendation and I expect that he will be a tremendously effective and motivated Principal Investigator, who will contribute substantively to the VX-970 Drug Development Plan and who will be an asset to the CTEP program. Thank you for your consideration of his Career Development PTMA.

Sincerely,

Geoffrey Shapiro

Geoffrey Shapiro, M.D., Ph.D.