**S1314 Frequently Asked Questions**

1. **What is COXEN?** COXEN stands for CO-eXpression ExtrapolatioN, a process of using a large database at the NCI to model chemotherapy responses. *In vitro* data from the NCI-60 is “humanized” with relevant gene expression from a specific clinical setting (e.g. bladder cancer patients) to derive the COXEN formula for that setting. Every patient in the S1314 study will have their tumor analyzed to determine if the gene expression signature predicts for response to pre-operative chemotherapy.
2. **What is the rationale for S1314?** COXEN has been applied to several published data sets of chemotherapy-treated patients with associated gene expression data. It has successfully shown a correlation with the COXEN score and clinical outcomes in several tumor types including bladder, breast, ovarian, and lung cancers. In this study, the feasibility of assessing COXEN in bladder cancer biopsies in a multi-institutional setting will be studied, with the COXEN scoring and statistical data analysis plans set prospectively.
3. **Is the chemotherapy assigned by COXEN on the trial?** No. There are two standard chemotherapy regimens commonly used for neoadjuvant bladder cancer: MVAC (Methotrexate, Vinblastine, Doxorubicin/Adriamycin and Cisplatin and also the combination of Gemcitabine and Cisplatin (GC). In this phase II study, patients will be randomized between GC and dose-dense MVAC, but COXEN won’t be used to direct therapy. Prospective rules using established COXEN scoring have been put in place to determine if the COXEN score is associated with a pathologic complete response at the time of surgery. If this study is positive, future studies of COXEN-directed therapy may be pursued.
4. **Is the submission of tissue blocks required on the study?** Initially, the trial was designed to calculate the COXEN score from a core sample taken from a tumor block. However, due to feedback from participating centers on the practical issues of submitting tumor blocks, a protocol revision has been made to allow for the submission of slides for evaluation. (See S1314 Protocol Section 15.1) Tumor blocks no longer need to be sent for analysis.
5. **Is filgrastim or pegfilgrastim required on S1314?** In patients treated with dose-dense MVAC, the rate of Neutropenic fever is sufficient to require the use of filgrastim or pegfilgrastim in all patients. In the GC arm, the use of these agents is at the discretion of the treating provider, based on their assessment of risk on a patient-by-patient basis.
6. **Are there requirements of the urologist performing the cystectomy on S1314?**  This has changed. Initially, all urologists were required to have performed at least 50 cystectomies over the preceding 3 years. Based on feedback from centers unable to participate due to this requirement, this was removed in the latest trial revision.
7. **Are other correlative studies planned?** Yes. In addition to RNA expression assessment as a part of the COXEN scoring, other correlative assessments will be performed. DNA is being collected for genetic analysis (tumor and germ line) of chemotherapy prediction. Additionally, proposals for SNP and microRNA assessments have been submitted. For this work to be done, TURBT/bladder biopsy tissue submission is required as a part of the study. In addition, urine and whole blood samples will be collected at the time of enrollment, as well as any residual tumor at the time of cystectomy. If you have correlative testing proposals, please contact the Study PI – Thomas Flaig: [Thomas.Flaig@ucdenver.edu](mailto:Thomas.Flaig@ucdenver.edu).