Statistical Analysis Plan for clinical research study RA-2011-025 "Genomic and Imaging Study for Patients Undergoing Surgery for Liver Cancer"

Primary Site Study identifier: RA-2011-025

NCI CTRP identifier: NCI-2012-02095

ClinicalTrials.gov identifier: NCT01395030

Excerpted without modification from page 87 of the grant application of NIH/NCI grant award R01CA161209, approved July 1, 2011 (NIH Project Start Date)

Statistical Approach and ROC Analysis: Excel (Microsoft) and SAS ver9+ (SAS Institute) will be used for statistical analysis. Kinetic analysis will be applied to all PET studies to obtain the relevant parameters (e.g., K1 and Vd) of the model selected. The following static and kinetic PET parameters will be considered: SUVmax, SUVmax normalized to lean body mass, visual score (1-5 intensity), TBR, and tentatively K1 and Vd. Logistic models will be used to regress tumor presence, based on histopathologic or follow-up diagnosis, for each tu- mor sample on each PET parameter, expressed on a continuous or ordinal scale. Similarly, logistic regression will assess the association between PET parameters and tumor features such as histologic grade and vascular invasion. Data may be grouped and considered by underlying liver disease (eg. HBV, HCV, NASH, etc.).

The diagnostic performance of kinetic and static (i.e., SUV) PET parameters as predictors of histopathologic diagnosis will be assessed by using ROC analysis as in previous studies (*42, 45*). The primary unit of analysis will be individual tumor specimens, although subsequent analyses may be performed at the patient level. For each parameter, the ROC curve will plot sensitivity versus 1 minus specificity for a range of parameter thresh- old values. Areas under the ROC curve (AUC) will computed along with 95% confidence intervals as an indi- cator of overall diagnostic performance. The relative diagnostic performance of the PET parameters will be assessed by comparing their AUCs using non- parametric methods for comparing two or more ROC curves es- timated from the same set of patients (*52*). A global test of all curves will be made and then if warranted, pair- wise comparisons will be made, controlling for multiple comparisons. The potential confounding effect of vari- ous patient or tumor characteristics on the ROC curve will be explored by regressing the curve on the confounders (*53, 54*). These adjustment variables will be limited in number given the sample size. Tests will be 2-sided, and p-values < 0.05 will be considered significant. Individual patients may have more than one tis- sue sample in this analysis. However, controlling for the correlation structure, such as by overdispersion con- trol, will not affect the ROC analysis. Therefore, sensitivity analysis, as a search for possible influential pa- tients, will be made by jackknife analysis. Classification thresholds will be defined for each PET parameter, corresponding to the point on the ROC curve that is maximally distant from the “chance” line in ROC-space.