2015-05 Johnson (R2) – Statistical Analysis Plan (SAP) _23Apr2015

It is proposed to carry out a network meta-analysis using individual patient data (IPD) of patients randomized to receive chemotherapy with the aim of investigating the effect of comparing the effect of Sorafenib against Linifinab (Cainap C. et al Linifinab vs Sorafenib…. J Clin Oncol 2015; 33(2): 172-9) and other agents in various population subgroups. Data to be analyzed will be taken from Johnson PJ et al Brivanib vs Sorafenib…. JClinOncol 31; 3517-24, 2103 and Cheng A-L et al, Sunitinib vs Sorafenib… JClinOncol 31; 4067-75, 2013 studies from which data is already obtained.

Overall Survival (OS) and response rate will be the primary endpoints of interest. The efficacy parameter of interest for OS will be the hazard ratios comparing the effect of chemotherapy as well as other key prognostic covariates. A Bayesian hierarchical approach which will include IPD data shall be used to estimate a parametric form for the OS of patients. Both piecewise exponential and flexible parametric approaches shall be explored. The parametric model will facilitate the prediction of patient survival and adjust for key prognostic variables of interest. The hierarchical nature of the data will allow for the fact that variability occurs both within and between studies that are included within the analysis. Study will be included as a frailty term in the model which will enable us to investigate heterogeneity across studies. Due to the large number of covariates under consideration, statistical significance of terms into the multivariable model will be defined using the Bonferonni-Holm correction for multiple comparisons.

Aside from estimating parametric forms for OS, valuable subgroup analyses will also be performed to investigate the varying effect of chemotherapy agents with the aim of identifying population subgroups who gain the most benefit from the drugs administration. Subgroups of specific interest are: aetiology, country of origin, performance status, Child-Pugh score, ALBI score, disease stage, extra-hepatic metastasis and macro-vascular invasion. All two-way interaction terms between key covariates of interest will also be examined to investigate which particular subgroups are driving the difference in drug performance. Individual models shall be produced for each agent in the analysis including Linifinab. Patient performance across population subgroups shall be assessed using hazard ratio as well as key assessment criteria such as survival rates at 1,3 and 5 years.

A direct comparison of Linifinab against other agents is also planned. Through this pair-wise comparison, a direct estimate of parametric OS (hazard ratios) along with its associated 95% credibility interval will be provided. Here overall comparisons of Linifinab to other chemotherapy agents will be provided along with comparisons within key subgroups.

Response rate shall be summarized as a two-level categorical variable again being compared using a Bayesian hierarchical approach.