Background

We have previously, in collaboration with AbbVie, demonstrated that aetiology has a significant impact on response of HCC to sorafenib using the M10-963 study [1]. We have also developed a new, and extensively validated, model to assess liver function in patients with HCC - the 'ALBI score' [2,3]. We are now interested to examine how liver function (as assessed by the ALBI score) deteriorates during the course of targeted therapies in patients with advanced HCC. This only requires serial values for serum albumin and bilirubin but we are also requesting access to other parameters for comparison with the more conventional ways of assessing liver function

Aim

To document the changes in liver function (in aggregate) according to aetiology; and document the changes in fibrosis as assessed by the derived function FIB-4 index, and the platelet count.

Statistical Analysis Plan (SAP)

- Description of the population under analysis
  - Median and interquartile range for continuous variables, number and percentages for categorical variables.
  - Examine distributional histogram of the continuous variables
  - Median overall survival from date of randomisation until date of death of last follow-up.
- Endpoints
  - Change in liver function (as assessed by ALBI score) as the primary endpoint; and changes in the degree of hepatic fibrosis as the secondary endpoint.
- Examination of the changes in ALBI and FIB4 through time post sorafenib treatment.
  - Statistical modelling of covariates
    - Fractional polynomial regression: A curve will be fitted to each patient so that values at fixed time points can be interpolated and an aggregate curve thereby generated. This will be achieved by fitting a fractional polynomial (FP) of each variable[4] with ALBI or FIB4 as the dependent variable and "time from date of randomisation" as the explanatory variable. Specifically, in fitting these functions, both first- and second-degree functions (FP1 and FP2, respectively) curve shapes will be considered. A selection procedure will then be utilised to select the "best" FP function model (i.e. the one with the lowest deviance) as described by Royston and Sauerbrei[4]. Using the selected FP function for each patient, predicted values will be generated for each patient at various time points post-treatment. From these predictions, median at regular six-monthly time points will be calculated for up to 2 years after treatment. 95% confidence intervals will be generated by the bootstrap method.
  - Overall median, interquartile range, mean and standard deviation of ALBI and FIB4 for all patients at each visit.
- Analysis of subgroups; different types of intervention
  - Changes in ALBI and FIB4 across time will be investigated according to aetiology, within the sorafenib and linifanib-treated patients.
- Statistical tests and methods
  - Kaplan-Meier curves examining survival according to aetiology and/or treatment. Log-rank tests to compare between survival groups. T-tests and Wilcoxon rank-sum tests to compare ALBI and FIB4 between different aetiology and treatment groups at baseline.

- ❖ Missing data
  - Patients with missing data will be excluded.

References

1. R. Jackson R Psarelli E, Berhane S, Khan H, Johnson P. Impact of viral status on survival in patients receiving sorafenib for advanced hepatocellular cancer: A meta-analysis of randomised phase III trials. Journal of Clinical Oncology (In press)

2. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015;33:550-8.

3. Pinato DJ, Sharma R, Allara E, Yen C, Arizumi T, Kubota K, Bettinger D, Jang JW, Smirne C, Kim YW, Kudo M, Howell J, Ramaswami R, Burlone ME, Guerra V, Thimme R, Ishizuka M, Stebbing J, Pirisi M, Carr BI. The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol. 2016 Sep 24.

4. Royston P, Sauerbrei W. Multivariable model-building: a pragmatic approach to regression anaylsis based on fractional polynomials for modelling continuous variables: John Wiley & Sons, 2008.