Welcome and introductions

Colin Watts (CW) welcomed attendees to the meeting. All meeting attendees introduced themselves.

Anaplastic meningioma

Pricilla Brastianos (PB) presented her proposed study for patients with anaplastic meningioma. PB explained that meningioma is the most common type of brain tumour in the US, primarily managed surgically. PB summarized the meningioma studies that have been carried out, highlighting that skull base meningiomas are particularly challenging to treat. She explained that, prior to last year, the spectrum of genetic changes for meningiomas remained undefined. However, recently sequencing has been carried out and in addition to NF2 mutations, AKT1 mutations (E17K) have been identified, (a member of the PI3K pathway). There are inhibitors that target this pathway. Recurrent mutations in SMO, a member of the Hedgehog (Hh) signaling pathway, were also identified. Again, there are inhibitors that target this pathway. Based on this knowledge, PB has designed a phase II trial of SMO/AKT1 inhibitors in progressive meningiomas with SMO/AKT1 mutations:

Given that the mutation rate is low (approx. 10% of patients have an AKT1 mutation and approx. 5% of patients have a SMO mutation), international collaboration would be of benefit for this study. It is planned for the central pathology review to be carried out at Brigham’s Women’s Hospital. It will be necessary to decide where the genotyping will be carried out and was suggested that a single site in the UK, Europe and the US could be identified. A high resolution platform will be required.
The key inclusion criteria were discussed. Progressive disease was defined by an increase in size of the measurable primary lesion on imaging by 25% or more (bidirectional area). The inclusion criteria stipulated that the change must occur between scans separated by no more than 18 months. Following discussion it was agreed that this would be amended to say ‘no more than 12 months’. Vasillis Golfinopoulos (VG) highlighted that this would be consistent with the trabectedin study. The co-primary endpoints of the study will be response rate and 6 month progression free survival. Exploratory objectives are also planned to evaluate genetic biomarkers in meningioma, to evaluate QoL during treatment with AKT1 and SMO inhibitors using the MDASI-BT questionnaire, and to evaluate dynamic contrast enhanced MRI during treatment with AKT1 and SMO inhibitors.

Eva Galanis (EG) highlighted that if this trial proves to be positive then it could be a quick path to registration. EG explained that Genentech had not insisted on their diagnostic being used for this study. A suitable diagnostic would need to be developed. JW informed the group that the NCI has a CRADA with Genentech for Vismodegib, but that a trial specific agreement may need to be put in place for the GDC0068. Anastassia Negrouk (AN) highlighted that as standard the NCI CRADAs allow the company access to the trial data, which would be problematic for Europe. It was agreed that it is important to discuss these issues as soon as possible.

EG explained that an application to CTEP will be submitted very shortly and the outcome will be shared with the group. CW agreed to discuss this study with the NCRI Brain CSG in the UK and with the UCL Clinical Trials Unit (CTU). Matt Seymour (MS) explained that in the UK it will be important for the patients screened (approx. 600) to be participating in an observational study and for tissue to be collected, even though only 60 patients will be randomised. Jack Welch (JW) suggested that a BISQUICK application in the US would be worth considering.

MS informed the Group that the IRCI Board had been approached by the Wellcome Trust Sanger Institute to offer WGS for tumour samples collected as part of rare cancer trials developed via IRCI. The group was interested to explore the potential of this collaboration further.

Martin McCabe (MM) questioned whether Genentech may be interested in testing their smoothened inhibitors for medulloblastoma. PB was unsure, but agreed to speak with Genentech about their level of interest.
**Adult medulloblastoma**

MM presented a trial concept for a randomised study for patients with adult medulloblastoma (see appendix 1 for slides). MM reported that the vast majority of medulloblastoma cases (>50%) are in young patients (under 30). He described the possible risk factors for the disease to be: age, completeness of resection, tumour site, large cell histology and M-stage.

With regards to radiotherapy, the available data on dose-response is weak and there is a suggestion that CSI >30Gy and PFB >50-55Gy is desirable. 35.36Gy is the most commonly reported dose and there is little evidence for the use of low dose radiotherapy. A number of different chemotherapy regimens have been used to treat the disease, with ‘Packer’ being the most commonly used regimen. The majority of randomised evidence for chemotherapy in this disease setting is from paediatric studies, including SIOP1, CSG-942 and POG. However, chemotherapy is used in approx. 50% of adult patients without any robust evidence, which is of concern. It was mentioned that Dr Brandes has recently updated her series and, as low risk patients do not do very well (60% 1-year survival), a recommendation to treat low risk patients with chemotherapy has been made. The true proportion of adult patients driven by the sonic hedgehog mutation is unknown, and there is no good target for patients without this mutation. However, for adult patients with the sonic hedgehog mutation smoothened inhibitors would be a logical therapy. There is some evidence that smoothened inhibitors may interact with chemotherapy and radiotherapy. MM therefore proposed the trial below:

A small phase Ib study would be required initially, starting at a standard dose of radiotherapy and smoothened inhibitor, with the option to decrease the dose if necessary. It was agreed that it would be best to randomise patients from the start, even whilst piloting the dose, perhaps using a multi-arm, multi-stage (MAMS) design. MM explained that Wendi Qian, the statistician, had estimated that a sample size of approx. 200 patients would be required with a 10% significance level using a frequentist design, but that the use of Bayesian statistics had yet to be considered. MM estimated that in the UK about 20 medulloblastoma patients over 16 are diagnosed each year and that this can be extrapolated to about 170 patients in total in Europe and the US. As the majority of patients are young the expectation would be that a large proportion of patients would be recruited to a trial of this nature. Wendi Qian should be put in contact with Bayesian statisticians (e.g. Cindy Billingham) to further consider the most appropriate statistical approach for the study.

There was general support for the study from the group. The inclusion/exclusion criteria were discussed and it was agreed that high risk patients should also be included in this study, as the
evidence is not strong enough to suggest that high risk patients must receive chemotherapy. It was suggested that if the US clinicians would not feel comfortable recruiting high risk patients to this trial then it would be acceptable for the US to recruit only low and intermediate risk patients, as it will be essential to take a pragmatic approach. MS suggested that it may be possible to separate the 2 studies in a 2x2 factorial design, allowing the US to participate in selected randomisations. EG highlighted that this approach would need to be clearly described in the protocol and that the statistical plan would need to allow for it.

The chemotherapy regimen to be used in the US for the high risk patients was discussed. A number of regimens are used and there is no evidence to identify the best. It was suggested that it would be best to select a small number of regimens (2-3) for use within this study, rather than to have open clinicians’ choice.

MM mentioned that the PNET 5 study in the UK currently recruits patients up to the age of 21, which would pose a potential conflict with this study as it will be necessary for the lower age limit for this study to be 16, because otherwise the pool of available patients would shrink.

It was agreed that MM and Gillian Whitfield (GW) will work with EG to further develop this trial concept and to identify appropriate agents to study. CW agreed to take this concept to the NCRI Brain CSG. It was mentioned that Dr Brandes is open to the idea of collaboration.

Next meeting
It was agreed that the next face-to-face meeting would be scheduled to take place alongside ESMO 2014 (in September). It was agreed that Piotr Rutkowski (Poland) should be invited to the meeting.

ACTIONS:
• PB agreed to speak with Genentech about their level of interest in testing their smoothened inhibitors for medulloblastoma.
• The NCI CRADA with Genentech to be discussed, specifically the release of data to the company.
• CW to discuss the anaplastic meningioma study with the NCRI Brain CSG and the UCL CTU.
• MM and GW to work with EG to further develop the adult medulloblastoma trial concept.
• Wendi Qian should be put in contact with Bayesian statisticians (e.g. Cindy Billingham) to further consider the most appropriate statistical approach for the adult medulloblastoma study.
• CW to discuss the adult medulloblastoma study with the NCRI Brain CSG and the UCL CTU.