**International Rare Cancer Initiative**

**Ocular melanoma meeting**

Sunday 25th September 2011, 11.00am - 1.00pm

Tegner room, Best Western Kom Hotel, Dobelnsgatan 17, SE -111 40, Stockholm

**Leads:** Dr Richard Carvajal (MSKCC, US), Professor Poulam Patel (University of Nottingham, EORTC) (joined by teleconference), Dr Ernie Marshall (Clatterbridge Centre for Oncology NHS Foundation Trust, UK) (unable to attend)

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**Meeting attendees:**

Dr Omid Hamid (The Angeles Clinic) (joined by teleconference)
Dr Martine Jager (Leiden University) (joined by teleconference)
Miss Nicola Keat (CR-UK)
Miss Kate Law (CR-UK)
Professor Serge Leyvraz (Centre du Cancer Lausanne)
Dr Paul Lorigan (Christie NHS Foundation Trust)
Professor Christian Ottensmeier (University of Southampton) (joined by teleconference)
Dr Sophie Piperno-Neumann (Institut Curie)
Dr Igor Puzanov (Vanderbilt-Ingram Cancer Center)
Dr Sara Selig (Ocular Melanoma Foundation) (joined by teleconference)
Dr Jack Welch (NCI)
Professor Matt Seymour (NCRN)
Mr Matt Sydes (MRC)
Dr Jedd Wolchok (MSKCC)

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**Background:**

Introductions were made. Dr Richard Carvajal (RC) explained the potential opportunities that he could see for ocular melanoma within the International Rare Cancers Initiative (IRCI). These included; (1) the chance to strengthen international collaboration in the field, (2) the possibility of rapidly assessing novel agents, (3) the development of a potentially practice changing clinical trial, (4) a mechanism to obtain biospecimens from a large number of patients. RC then highlighted the challenges, both scientific/clinical and practical, that he could foresee. He stated the aims of this meeting to be to assess the level of interest in pursuing an international study and, should there be enthusiasm, to agree a suitable study design and to identify targets of interest/potential investigational agents.

Professor Matt Seymour (MS) concurred with RC’s summary of the IRCI and encouraged the Group to be ambitious and to aim to fully develop at least one clinical trial, ideally with a randomised design. He presented the background to the initiative and highlighted the necessity of international collaboration for rare cancers such as ocular melanoma. MS explained that the rare cancers that had been selected by the IRCI were those for which there is no current activity. MS emphasised the catalytic nature of the IRCI and stressed the expectation that, with the support of the ‘funders’, those present at the meeting would be required to drive forward any meeting outcomes. He explained that the meetings organised by the IRCI to date have been alongside international conferences in order to improve availability of investigators and to keep costs to a minimum. MS informed the Group of the intention of the NCRN and CR-UK, the NCI and the EORTC to ensure a coordinated and expedited approach to the review process for any trial ideas developed as a result of the IRCI.

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**Patient numbers:**

The number of available patients was considered. Professor Serge Leyvraz (SL) informed the Group that a previous study co-ordinated by the EORTC had managed to recruit 25-30 patients per year,
but that this particular study had stringent eligibility criteria and that approximately 60 patients per year had been screened to determine eligibility. RC stated that the US had managed to recruit approximately 50 patients per year from just a few participating centres. As a result of these figures a conservative expected recruitment rate of 100 patients per year was considered to be appropriate.

Potential study design – Multi-Arm, Multi-Stage (MAMS):
RC introduced the Multi-Arm, Multi-Stage (MAMS) study design that had been discussed by the three leads via teleconference prior to this meeting. He explained that this approach would allow assessment of multiple agents (perhaps 2 or 3 experimental arms), and rapid rejection of less promising agents, within a single trial, with the additional flexibility to be able to add new arms over time as other potentially beneficial agents emerge. This seemed to be an appropriate approach given the lack of consistency in treating this disease and the high event rate associated with ocular melanoma. An early endpoint such Progression Free Survival (PFS) at 3 months or RECIST response is commonly used for the ‘sifting phase’ of a study with a MAMS design. PFS would also allow cross-over within the study design, however, cross-over would make analysis of Overall Survival (OS) challenging. OS would commonly be used at the phase III stage. Mr Matt Sydes (MSy) explained the statistical principles associated with MAMS study designs. Assuming a 4-arm study, with a 1:1:1:1 allocation ratio, MSy showed two possibilities, the first based on a recruitment rate of 100 patients/year and the second based on an initial recruitment rate of 50 patients per year, subsequently increasing to 100 patients per year. Assuming an accrual rate of 100 patients per year recruitment could complete within 3 years and it should be possible to complete the first analysis within 1½ years.

A concern emerged that a study design of this type would prevent the use of immunotherapy, in particular ipilimumab. An endpoint of 3 month PFS was not considered appropriate for ipilimumab. In order to incorporate ipilimumab a trial would require an endpoint of OS, or at an absolute minimum an endpoint of PFS at 6 months. It was agreed that patients could not all cross-over onto ipilimumab as this would not tell us anything about the activity of ipilimumab. It was suggested that perhaps it would be appropriate for a patient to drop-off of the trial in order to receive ipilimumab.

The Group discussed whether or not a control arm was essential. It was suggested that perhaps a control arm was not necessary; however, there was consensus that the inclusion of a control arm would be beneficial in order to anchor the activity of the trial and in order to monitor changes over time given that some variation in historic PFS has been seen in previous clinical trials. Also, the control arm data collected in the phase II setting could potentially be used in any future phase III comparison. The MAMS study proposals described by MSy involved a control arm. It was suggested that the most appropriate control arm may be ‘best supportive care’; however, it was felt that recruitment to a study with a control arm of ‘best supportive care’ may be difficult. Alternatively, dacarbazine (DTIC) was considered likely to be an acceptable option internationally. Ipilimumab was also mentioned as a possible control arm. It was suggested that perhaps the control arm could be ‘investigators choice’.

Potential study design – incorporating ipilimumab:
Professor Poulam Patel (PP) queried the feasibility of a MAMS study design but with an additional independent arm for ipilimumab. It was suggested that the independent ipilimumab arm could have an OS outcome measure. MSy considered this to be exceptionally complex and suggested that perhaps a standard MAMS study design could be used and that it could be stated in the protocol that after progression ipilimumab could be given. Some were concerned that with-holding ipilimumab may be problematic given that many patients already request ipilimumab. As an alternative it was suggested that perhaps patients could start with ipilimumab treatment and at the time of progression patients could be randomised to experimental agents in a MAMS-style study.
design. This was not thought to be feasible in the UK and it was not considered appropriate for all patients to be given ipilimumab upfront. MS suggested an upfront ipilimumab randomisation, ipilimumab priming (perhaps a duration of 3 months) versus no ipilimumab, followed by a MAMS-style study design.

It was suggested that perhaps ipilimumab versus ‘investigators choice’ would be an appropriate trial to consider, with 6-month PFS as the primary endpoint. Ipilimumab versus placebo was also suggested, with time to treatment failure as the primary endpoint. This is likely to be inappropriate as ipilimumab is not a ‘quiet’ drug, i.e. it has side-effects.

Given the preference of the group to conduct a relatively short-term initial study, rather than a longer-term study with an OS outcome measure, it was acknowledged that it may be necessary to exclude ipilimumab from initial trial designs, but that ipilimumab is an important agent to take into consideration.

**Target/candidate drugs:**

RC referred to slides that summarised all of the current international trials. See slides in *Appendix 1*. He stressed the importance of not duplicating efforts already underway and suggested possible target/candidate drugs to consider. RC felt it important to capitalize upon the CTEP portfolio and existing relationships with industry. RC explained that there was published data to show that MEK and AKT inhibition may be interesting pathways to study. He suggested perhaps AZD6244 + MK2206 (CTEP drugs) or GSK1120212 + GSK2141795 (GSK). It was stressed that from results obtained from combination treatments it is often difficult to attribute the activity and to demonstrate that the combination has greater activity than a single agent would have. RC also suggested c-MET (ARQ197 - CTEP or XL184 - Exelixis), angiogenesis inhibitors (VEGF-Trap - CTEP), CTLA4 (ipilimumab - CTEP) and ADI-SS PEG 20,000 mv (arginine deaminase). Agents suggested by others included sorafenib and sunitinib.

Dr Sophie Piperno-Neumann (SP-N) suggested that it may be beneficial to update the slides in *Appendix 1* with the outcomes of those studied that have completed in order to inform the choice of agents to study.

**Summary:**

The group were keen to progress with a study that was simple enough to begin to build an international collaborative platform, upon which future more complex studies could be built. By the end of the meeting a possible two-step study seemed to be emerging. This involved a phase II decision-making study aimed at identifying appropriate arms for a subsequent definitive phase III study.

**Step 1:**

Step 1 would involve a randomised phase II ‘pick the winner’ trial comparing any number (most likely 2-3) of novel treatments from among the single drugs or combinations discussed, excluding ipilimumab (and any other drugs for which PFS would be an invalid endpoint). The primary endpoint would be PFS. It may not be essential (but perhaps advisable) to have a control arm within step 1 as the aim of the interim analysis would be to reject any arm performing less well than the average of the other arms. With a ‘pick the winner’ study design it may not be essential for every arm to start simultaneously, however administratively and statistically it would be easier if every arm could start together. Step 1 would be open to both first-line and second-line patients. The second-line patients could be confined to those patients that have received ipilimumab or could allow any prior treatments (other that the study drugs). Patients would need to be stratified according to the prior treatment that they had received and also an appropriate washout period would need to be implemented. Accrual to step 1 would take approximately 2½ - 3 years based on earlier discussions.
The post-trial therapy would not need to be fixed but basic outcome data could be collected opportunistically; this could be used as a mechanism to obtain information regarding the efficacy of ipilimumab.

**Step 2:**
Step 2 would be a phase III, first-line therapy trial comparing the ‘winner’ from step 1 with ipilimumab (assuming that in three years time there is still enthusiasm to use this agent). It would be essential to have clear criteria to define the ‘winner’. It is likely that the most appropriate endpoint would be OS. However, given the number of patients available, a reduced power may be necessary. Second-line therapies including local ablative therapies and crossover would be inevitable, so it may be unrealistic to demonstrate OS benefit with the numbers available and perhaps a landmark failure-free survival (FFS) endpoint may be appropriate.

**Actions:**
- NK to circulate RC’s slide set, details of all those involved with the meeting and the meeting minutes.
- Meeting attendees to consider further the ideas proposed at today’s meetings and to exchange thoughts.
- NK to organise a teleconference for the three leads for approximately 2 weeks time in order to further develop the ideas from today’s meeting.
- Discuss with the FDA the possibility of using a MAMS design with a DTIC arm as a potential registration study.
- Dr Sara Selig (SS) offered to facilitate interactions.
- A priority list of agents to be agreed.
### Targets & Ongoing Trials for Uveal Melanoma

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<th>Target</th>
<th>Trial</th>
<th>Sponsor/Lead Center</th>
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<td>IGF1R</td>
<td>Phase II IMC-A12</td>
<td>MDACC</td>
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<td>VEGF</td>
<td>Phase II Temozolomide &amp; Bevacizumab</td>
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<td>VEGFR, PDGFR, KIT</td>
<td>Phase II Sunitinib (STREAM)</td>
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<td>VEGFR, PDGFR, KIT</td>
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<td>KIT, PDGFR, ABL Somatostatin Receptor/mTOR</td>
<td>Phase II SOM230 &amp; RAD001</td>
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<td>PKC</td>
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<td>Phase II AZD6244 versus Temozolomide</td>
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### On-going Metastatic Uveal Melanoma Trials

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<th>Agent</th>
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<tr>
<td>Liposomal vincristine (Marqibo)</td>
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<td>Hana Biosciences, Inc</td>
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<td>Paclitaxel Albumin-Stabilized Nanoparticle Formulation</td>
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<td>IV versus Hepatic Arterial Infusion of Fotemustine</td>
<td>III</td>
<td>EORTC</td>
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<td>Temozolomide &amp; Sunitinib</td>
<td>I/II</td>
<td>University of California, Los Angeles</td>
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<tr>
<td>Gemcitabine &amp; Treosulfan versus Treosulfan</td>
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<td>Charite University, Berlin, Germany</td>
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