International Rare Cancers Initiative (IRCI)
Gynaecological Sarcoma Group ASCO 2016 Minutes

Saturday 4th June, 10.00-12.00 (CDT)
Salon A4, Hilton Chicago Hotel, 720 South Michigan Avenue Chicago, Illinois 60605

Chair – Dr Martee Hensley

Attendees: Martee Hensley (MH), Ajlan Atasoy (AA), Danielle Battle (DB), Antonio Casado (AC), Paolo Casali (PC), Isabelle Ray-Coquard (IRC), Paolo Deitos (PD), Palma Dileo (PD), Helena Earl (HE), Suzanne George (SG), Bob Golson (BG), Saskia Litiere (SL), Sandrine Marreaud (SM), David Miller (DM), Anastassia Negrouk (AN), Nelleke Ottevanger (HO), Clare Scott (CS), Ted Trimble (TT), Jack Welch (JW)

Approval of IRCI Gynecological Sarcoma Group Minutes from ASCO 2015 and meeting outcomes (Appendix 1)

MH welcomed the group and the minutes of the previous meeting held on 30.05.2015 were approved. Helena Earl advised that Charlotte Benson (who was not present at the meeting) had taken over from Helen Hatcher as the new UK lead.

MH updated the group regarding actions from the previous meeting and advised that screening logs were being collected at every opportunity for the uLMS study. MH advised that a Letter of Intent (LOI) for the HGUS study had been submitted to NCI CTEP for review. At the previous meeting, members had discussed potential new study concepts for endometrial stromal sarcoma (ESS), and it was agreed that new ESS trial ideas should be submitted to the office in advance the next meeting (which was further discussed under agenda item New Study Concepts).

Uterine leiomyosarcoma (uLMS) study update

MH provided an update on the status of the uLMS study. The study was activated in the US in 2012, and opened to recruitment in the EU in 2015. MH informed the group 33/210 patients had been recruited to date (27 patients from the US, 5 patients from the UK and 1 patient from Spain). The trial is currently open to recruitment at 388 US sites and 6 UK sites. Sites in Norway, France, Spain, Belgium and the Netherlands are also open to recruitment. Members were encouraged that further sites had opened over the last 12 month, and that the rate of patient accrual had increased over 2016 Q1/Q2. However, the group expressed continued concerns regarding recruitment to the study. MH advised that the trial continues to be closely monitored by NCI CTEP and Cancer Research UK. At the last group meeting, MH advised that following review of the uLMS study by NCI CTEP, a letter had been sent to GOG advising that the trial can continue to remain open on an annual basis contingent of following conditions:

1. The study must accrue 35 patients per year for the next 5 years starting with the 12-month period from 7/1/2015 to 7/30/2016.
2. If the study does not achieve this accrual goal of 35 patients over each 12-month period starting with the 7/1/2015 to 7/30/2016 period, the trial will be administratively closed by CTEP.

MH informed members that conversations were ongoing with CTEP, and had stressed the importance of keeping the trial open. IRC re-iterated that is was important to send a strong message to the US. Members of the group acknowledged that a lot of time and energy had been invested into this study. The ethical considerations of closing the trial early were also highlighted. MH expressed confidence that the study would continue and was pushing hard to keep the trial open.

[Post-meeting note – Following review of the uLMS study by NCI CTEP, the investigators received a letter on September 6th 2016, requesting that the trial close early due to poor patient recruitment. The uLMS trial is now closed in the US, Europe and the UK].

High Grade Uterine Sarcoma (HGUS) study update

IRC informed the group that to date, 16/54 patients have been recruited to the HGUS trial (15 patients registered, 5 patients randomised). The study is currently open to recruitment at 8 sites across Europe (Belgium, Netherlands, France, Spain and Italy). The first UK site was activated to recruitment in February. Two UK sites are currently open with further sites in set up. To date, one UK patients has been registered (from Addenbrookes Hospital).

MH updated that in the US, the study concept/LOI has been submitted to CTEP NCI in the summer of 2015. Together with EORTC, MH had prepared and submitted a reply to CTEP's comments in February 2016. In April 2016, MH informed the EORTC that CTEP has provided conditional approval to enroll a maximum of 20 patients from NRG Oncology. The deadline to open the first US site is 8 October 2016.

MH acknowledged that US involvement has required extensive operational accommodations, and was somewhat complicated due to blinding and drug supply. AN acknowledged that this represented a challenge. MH updated that a conference call had taken place to explore potential solutions. Patient enrollment in the US will be via OPEN. The tissue will be sent to a central pathologist and the result will be fed into the EORTC's automatic registration system. Confirmation will then be sent from EORTC to US counterparts and randomisation will be facilitated via ORTA. This will then be fed back to US drug supply.

New study concepts

Uterine Carcinosarcomas

Members of the group discussed new study concepts. MH highlighted that the group had thus far prioritised gynaecological rare cancers, and asked the group to explore whether uterine carcinosarcomas (not originally part of the groups work plan) would be of viable interest. It was highlighted that investigators consider DNA repair inhibitors in combination with DNA-damaging agents. It was noted that most carcinosarcomas exhibit p53 mutations and epithelium-to-mesenchymal transition (EMT). It was proposed that one could look at various combinations with or without inhibitors. However, members acknowledged that this would constitute a very big trial, and careful consideration should be given to the commitment required to undertake such a study. The group also agreed that at present, there are very little data driven ideas. Moreover, the data emerging from of phase II studies trials was considered to be not that helpful. Members suggested that a smaller randomised phase II study (e.g. weekly paclitaxel with or without ATR inhibitor) might be of interest.

HE queried whether this type of cancer would be considered rare enough for the remit of IRCI (noting that there are around 300 cases per year in the UK). MH confirmed that carcinosarcoma is indeed classified as a rare cancer and members agreed that this was an area of significant unmet need. It was also noted that there are ongoing efforts to sequence carcinosarcomas in order to establish the genomic differences. CS added that there is likely to be a genetic/cell model and likely to be a single consistent driver, and would welcome a discussion about what the choice of agent(s) would be. HE added that there is currently no pre-clinical model, and this particular rare cancer is difficult to study.

Members confirmed their enthusiasm for working on uterine carcinosarcomas and the MH emphasised that there is a lot to learn about his particular type of cancer, both in terms of the underlying biological mutations and the different ways carcinosarcomas are treated. MH asked members whether they were motivated to tackle the 1st line question or whether the recruitment question would be more feasible. HE highlighted that it would be worth looking at first line treatment, adding that patients may lose out as they are unlikely to be offered alternative treatment options. It was mentioned that there are few large front line studies expected to report in appropriately 6-12 months.

The group also discussed the possibility of including both uterine and ovarian cancers and were keen to explore precision medicine approaches. Members acknowledged that patient accrual is currently the biggest hurdle. Furthermore, the feasibility of recruiting to rare cancer studies is often flagged as a concern when grant applications are sent for peer review. As such, employing strategies to may make trials more open (e.g. expanding to include ovarian cancers) should be considered going forwards.

ACTION: All to consider potential carcinosarcoma trial designs (and agents) and send ideas to MH via email.

Observational study for ESS

It was noted that the Italian sarcoma group have developed an observational study for ESS. MH suggested pooling all ESS patients to generate an international database. The group also discussed potential studies (including low-grade leiomyosarcomas), and members highlighted that there was an interest within the pathology community to sub-classify these further. Other ideas included STUMP (soft tissue timing of uncertain malignant potential). However, it was noted that STUMP is particularly hard to study.

ACTION: Members to consider potential ideas to investigate STUMP and low grade LMS (leiomyosarcomas) and send to MH.

Pecomas

The group also briefly discussed pecomas (perivascular epithelioid cell tumours) of the gynecological tract as a potential rare cancer target. MH asked whether there was sufficient interest within the group. JYB expressed enthusiasm this rare cancer type, adding that these tumours can occur anywhere. SG informed members that there may be an industry-led study close to reporting. It was suggested that collaborations and leveraging relationships with industry and other partners could be a way forward in terms of improving accrual rates in rare cancer trials.

ACTION: SG to establish whether there are currently any industry-led studies and feedback to the group.
ACTION: SG and MH to explore opportunities for collaboration with industry and other partners in rare cancer studies.

AOB

MH summarised the discussions from the session and thanked everyone for their contribution. MH reiterated that whilst the HGUS study is progressing well in Europe, there are lessons to be learned from the uLMS study. MS added that recruiting to a 'treatment versus observation' study had been particularly difficult. MH suggested that circulating a group newsletter to the research community (quarterly or bi-annually) with updates on both uLMS and HGUS trials could be useful and may help raise the visibility of the group's activities. It was also suggested that references to both Gynaecological Sarcoma studies could be added onto the IRCI website.

ACTION: MH/IRCI office to draft IRCI Gynaecological Sarcoma group newsletter and circulate to the IRCI community.
ACTION: IRCI office to reference both the uLMS and HGUS trials on the IRCI Gynaecological Sarcoma webpage.

The Chair highlighted that several questions and challenges remain for both the group and IRCI in terms of running prospective trials in rare cancers. MH also acknowledged that the group did not yet have a new randomised controlled trial on the table, but added that the suggestions presented at the meeting provided a good platform for further discussion going forwards.

The group discussed the possibility of collaborating with other IRCI groups and setting up a study that could span several histologies. Members agreed that they needed to identify 'value added' of IRCI. JW advised that potentially, there are many work packages could be badged as IRCI, whether it be a bio-repository or observational study. JW added that he would raise the registry concept with the IRCI Board and feedback to the group. It was further noted that the group would benefit from a translational focus. However, many of the new ideas require some pre-packaging and work prior to approaching partners. Members added that lack of funding continues to be stumbling block and pathways to funding mechanisms remained unclear.

Summary of actions:

ACTION: All to consider potential carcinosarcoma trial designs (and agents) and send ideas to MH via email.
ACTION: Members to consider potential ideas to investigate STUMP and low grade LMS (leiomyosarcomas) and send to MH.
ACTION: SG to establish whether there are currently any industry-led studies and feedback to the group.
ACTION: SG and MH to explore opportunities for collaboration with industry and other partners in rare cancer studies.
ACTION: MH/IRCI office to draft IRCI Gynaecological Sarcoma group newsletter and circulate to the IRCI community.
ACTION: IRCI office to reference both the uLMS and HGUS trials on the IRCI Gynaecological Sarcoma webpage.