3-year progress report for the International Rare Cancers Initiative (IRCI)

Background and aims

Together, rare cancers account for more than 20% of all cancer diagnoses - this is more than any single common cancer. Unfortunately, the average outcome for patients with a rare cancer is inferior to those with more common cancers. In an attempt to address this issue, the International Rare Cancers Initiative (IRCI) was established in 2011. IRCI is a partnership between the National Institute for Health Research Clinical Research Network: Cancer (NIHR CRN: Cancer), Cancer Research UK (CRUK), the European Organisation for Research and Treatment of Cancer (EORTC), the USA National Cancer Institute (NCI), the French National Institute of Cancer (INCa) who joined in 2013, and the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) who joined in 2014. A memorandum of understanding exists between these partner organisations. Discussions are currently also underway with the Poland regarding joining the partnership.

The objective of this initiative is to facilitate the development of international clinical trials for patients with rare[1] cancers in order to boost the progress of new treatments for these patients. The initiative encourages the use of innovative methodologies to maximise the potential for answering research questions and to identify and overcome barriers to international trials. The selection of rare cancers included in IRCI is based, not only on the rarity of the disease, but also ensuring that there are no existing randomised controlled trials and existing international trial group for the diseases. IRCI organises face-to-face meetings and teleconferences to allow potential clinical trial designs to be discussed and developed. Wherever possible these face-to-face meetings are run alongside international conferences that the leads and other experts are already likely to be attending.

Group activity and key updates

Of the initial nine groups taken on by IRCI, seven are actively developing trials (see Figure 2 for further details on the status and key challenges faced by each IRCI trial). Two groups, anaplastic thyroid cancer and fibrollamellar hepatocellular carcinoma, after discussion, decided that there is no immediate role for an interventional trial and are therefore no longer active. In 2013 the initiative established two new groups for Desmoplastic Small Round Cell Tumour (DSRCT) and Rare brain cancer (see Figure 1 for further details). A number of other key landmarks/significant updates for the initiative are as follows:

- Four trials are actively recruiting (uveal melanoma, uLMS, HGUS and metastatic anal cancer) and another study has recently been successfully activated in continental Europe and is now awaiting its first patient (Salivary gland).
- The Uveal Melanoma group has expanded to cover all rare melanomas (including Merkel cell carcinoma).
- An NCRI Working party for Non Gynaecological Peritoneal malignancy has been established in the UK, with a view to this potentially expanding to an IRCI group in the future. This is following receipt of three UK expressions of interest in this area.
- An IRCI project manager has been put in post at the EORTC Headquarters to oversee the operational/regulatory aspects of the IRCI trials approval/set up. A project managing system called Timestones is in the process of being adapted by the EORTC to be appropriate for IRCI - it is anticipated that this system will help streamline the international trial approval/set-up process.
- An IRCI Methodological meeting was held alongside ESMO 2013 from which a paper has been developed and published in the European Journal of Cancer (see Box 1).

Figure 1. New IRCI groups adopted in 2013. Includes the IRCI group leads, trial status and key challenges to date.

New group, and group leads	Status	Key challenges
Desmoplastic Small Round Cell Tumour Jeremy Whelan (UK) Paul Meyers/ Richard Gorlick (US) Wynette Van der Graaf (EORTC)	This group met for the first time alongside ASCO 2013 and then alongside CTOS 2014. The group are presently discussing a randomised study considering the role of maintenance treatment.	The key challenge for this group to date has been reaching a consensus that a trial for these patients is feasible. A trial concept has now been developed for discussion at the next group meeting.
Rare brain cancer Colin Watts (UK) Eva Galanis (US) Wolfgang Wick (EORTC)	This group met for the first time alongside ASCO 2013, then at SNO 2013, ASCO 2014 and SNO 2014. The group is discussing opening an Alliance/CTEP approved study in Anaplastic meningioma internationally, and is also in the process of developing a trial in Adult medulloblastoma, led by the UK.	Establishing this new group has highlighted that in order to ensure success, it is necessary to balance the membership of the group with representatives from each partner organisation, and to ensure that meetings are held alongside appropriate international conferences to facilitate a balanced attendance.

[1] for the purpose of this Initiative 'rare' has been broadly defined as an incidence of <2 per 100,000. The initiative has not been focussed on looking at rare sub-sets of more common cancers.

Figure 2. *IRCI trial status and key challenges. Includes details of the IRCI groups leads, the trial leads and the lead co-ordinating centre/co-sponsors.*

Group, and group leads	Group trials, co-ordinating centre and trial leads	Trial status	Key challenges
Rare Melanoma Rich Carvajal (US) Paul Nathan (UK) Poulam Patel (EORTC)	**A randomised two-arm phase II study of Trametinib alone and in combination with GSK214795 in patients with advanced uveal melanoma (IRCI 005)** Lead co-ordinating centre: MSKCC EU co-sponsor: EORTC Chief Investigator: Rich Carvajal - Columbia UK Lead: Ernie Marshall- Clatterbridge EU mainland lead: Serge Leyvraz - CHUV	Approved by CTEP, PRC and CTAAC. Open to recruitment in the US (to interim stage only). Following a thorough review of the phase I safety data of the trametinib and GSK795 combination, the GSK leadership team is discontinuing further investigation of the combination. The trial will continue to the interim analysis stage in the US centres, however will not be activated in sites within continental Europe and the UK. GSK remain supportive of the translational research plan.	This study is not run through a co-operative group system. Instead MSKCC is leading on the trial. However CTEP is still required to review the protocol, group's specific appendix and all the intergroup and GSK contracts. The trial documentation review between MSKCC, CTEP, GSK and the EORTC added considerably to the timeline/resource required which could be made more efficient in the future.
	This group expanded its remit to include all Rare Melanoma. Drawing on the strength of the international collaboration developed, the group is in discussions regarding their next IRCI trial/s in patients with Merkel cell carcinoma and Uveal melanoma.		
Small bowel adenocarcinoma Richard Wilson (UK) Rob McWilliams (UK) Arnaud Roth (EORTC)	**The BALLAD study: A global study to evaluate the potential benefit of adjuvant chemotherapy for small bowel adenocarcinoma (IRCI 002)** Lead co-ordinating centre: Glasgow CTU International Chief Investigator: Richard Wilson UK Regulatory Chief Investigator: Jeff Evans US Lead: Rob McWilliams - Mayo Clinic French lead: Thomas Aparico - Hôpital Avicenne Japanese Lead: Kenichi Nakamura - National Cancer Centre	Approved by CTAAC, the French Ministry of Health/FFCD Faculte de Medecine and JCOG. The EORTC will not participate, however there is continued interest from individual European and Scandinavian sites to join the trial. Potential involvement of selected centres in the USA, Canada and Australia is being further discussed towards the end of 2016. The protocol has been approved in the UK by the MHRA and Research Ethic Committee and is anticipated to open to recruitment in May 2015 in the UK.	There is a lack of interest from co-operative groups to take on this study in the US. There has been discussion regarding whether a large US cancer centre can be sponsor (similar to the model used by the above Ocular melanoma study) or whether a coalition study/intergroup model could be used. The EORTC decided not to take on the study as the EU GI Steering Committee did not consider the question posed to be of significant interest, however the EU GI steering committee does not represent the whole European opinion, as individual European centres will be joining the study. Australian wide sponsorship was also not approved, and therefore an autonomous model with Australian centres has also been recommended.
Relapsed Anal cancer Rob Glynn-Jones (UK) Al Benson (US) Dirk Arnold (EORTC)	**InterAAct: A phase II International multicentre randomised advanced anal cancer trial comparing cisplatin plus 5FU vs. carboplatin plus weekly paclitaxel in patients with relapsed or metastatic disease (IRCI 003)** Lead co-ordinating centre: Royal Marsden CTU US co-sponsor: ECOG Chief Investigator: Sheela Rao - Royal Marsden US Lead: Cathy Eng - MD Anderson EU Lead: Dirk Arnold – Arcor	Approved by CTAAC, PRC, and the AGITG. The concept has been approved by CTEP. Pending outcome of CTEP review. Open to recruitment in UK and Norway, and a number of other continental European sites in Germany, France and Portugal are in set up. 13 patients have been recruited. It is anticipated that recruitment in Australia will begin in May 2015.	This trial is progressing well and the IRCI group has initiated discussion of the follow on phase III trial design. A new model of collaborative pharmacovigilance reporting has been put in place between EORTC and Royal Marsden to cope with the European obligations related to safety reporting to Eudravigilance.
Thymoma Frank Detterbeck (US) Mike Lind (UK) Sanjay Popat (EORTC)	**PORT: Randomised phase 3 study of resected stage III Invasive thymoma with or without postoperative radiation therapy** Lead co-ordinating centre: ECOG Chief Investigator: Heather Wakelee - Stanford University UK lead: Mike Lind - Hull EU Lead: Sanjay Popat – Imperial	The NCI has rejected the study which has now been withdrawn by CTEP. The trial has been approved for participation by the French Rhythmic Intergroup and has also been endorsed in Australia. There is also interest to participate in Asia.	CTEP requested a resubmitted application addressing a number of design issues along with reassurance of the international recruitment feasibility. A resubmission was made to CTEP, however this was rejected. The EORTC decided not to participate in the study due to the results of their feasibility survey.

Gynaecological sarcoma Martee Hensley (US) Helen Hatcher (UK) Jean Yves-Blay (EORTC)	**HGUS: A randomised phase II study evaluating the role of maintenance therapy with Cabozantinib in High Grade Uterine Sarcoma (HGUS) after stabilisation or response to chemotherapy following surgery or in metastatic first line treatment (IRCI 006)** Lead co-ordinating centre: EORTC US co-sponsor: GOG Chief Investigator: Isabelle Ray-Coquard - Léon Bérard Cancer Center UK Lead: Helena Earl - Cambridge US Lead: Martee Hensley - MSKCC	Approved by PRC and CTAAC. Pending submission to CTEP. In set up in UK and recently activated in several countries continental Europe (France, Italy and Spain); Continental Europe already enrolled 4 patients so far.	During development there needed to be a lot of flexibility in the design to account for the varying standards of care/regimens and drug availability between countries. The GOG initially did not engage in any operational discussions as the concept had not been formally reviewed, which was very limiting to the EORTC as the lead sponsor who needed information from the GOG in order to proceed in Europe. It highlighted that in order for the IRCI trials to succeed, an operational counterpart is required in each country. The GOG has now engaged in operational discussions ahead of CTEP review. However resource is now beings spent addressing operational matters (the main issue is who will hold the IND) ahead of knowing if CTEP will be supportive.
	uLMS: A phase III randomised trial of gemcitabine plus docetaxel followed by doxorubicin versus observation for uterus-limited, high grade uterine leiomyosarcoma (IRCI 001) Lead co-ordinating centre: GOG, EU co-sponsor: EORTC Chief Investigator: Martee Hensley - MSKCC UK Lead: Helen Hatcher - Cambridge EU Lead: Jean Yves Blay - Léon Bérard Cancer Center/Petronella Ottevanger (EU, Radbound University Medical Center Nijmegen)	Approved by CTEP, PRC and CTAAC. Open to recruitment in the US (17 patients enrolled so far). Open to recruitment in the UK (2 patients enrolled so far) and recently in several continental Europe (Norway, Spain, France) as well with a first patient entered in Spain.	Set up of this study in Europe was initially delayed due to challenges faced around US state department clearance. Now that the study is recruiting, it has been highlighted that the NCI accrual targets are too challenging for an international rare cancer trial and therefore the NCI need to consider the possibility of making their rules more fit-for-purpose for a rare cancer study.
	A trial for patients with endometrial stromal sarcorma (ESS) – Drug supply and a trial design consensus has not been agreed internationally to date for a study in patients with ESS. New trial ideas for patients with ESS are therefore currently being considered.		
Salivary gland Lisa Licitra (EORTC) Kevin Harrington (UK) Alan Ho (US)	**A randomised phase II study to evaluate the efficacy and safety of chemotherapy vs. androgen deprivation therapy in patients with recurrent and/or metastatic, androgen receptor expressing, salivary gland cancer (IRCI 007)** Lead co-ordinating centre: EORTC US co-sponsor: Alliance Chief Investigator: Lisa Licitra - Istituto Nazionale dei Tumori Milan UK Lead: Kevin Harrington - ICR US Lead: Alan Ho – MSKCC	Approved by PRC and CTAAC. Not approved by CTEP. Open to recruitment in Belgium, and in set up in the UK and several continental countries in Europe.	The Alliance and the EORTC have spent considerable time discussing operational aspects of this study. For example mainland EU and US sites would not be able to participate unless drugs were provided and securing drug supply required huge efforts and time. The concept has subsequently ended up being declined by CTEP who require major scientific amendments to the protocol and are facing resource issues following the CTEP re-organisation. Going forward, CTEP has developed a process to require a discussion of the international structure of the trial early in the development to determine if it can be supported through the NCTN.
Penile cancer Steve Nicholson (UK) Curtis Pettaway (US) Christine Theodore (EORTC)	**InPACT – International Penile Advanced Cancer Trial (IRCI 004)** Lead co-ordinating centre: ICR CTSU US co-sponsor- ECOG International Study Chair: Steve Nicholson (locum) UK Regulatory Chief Investigator: Nick Watkins (St George) US Lead: Curtis Pettaway - MD Anderson	Approved by CTAAC. Pending submission to CTEP. The EORTC will not participate. Protocol in development.	This is a complex protocol being developed collaboratively with a number of international experts overseen by a writing group. An application to CTEP is planned once the protocol is further advanced (although early input is being requested ahead of the protocol becoming fixed). The EORTC Disease Orientated Group did not support the study, however the EORTC HQ has agreed to assist the ICR CTSU administratively with the set-up of sites in continental Europe although is not able to assist with site selection.
PRC: review board at the EORTC, CTAAC: review board at CRUK, CTEP: review board in the US			

IRCI evaluation and areas for improvement

A meeting was held alongside the ASCO 2014 conference bringing together each of the IRCI group leads with the IRCI Board to facilitate a discussion on the progress of the initiative to date and to share successes and common challenges. It was agreed that to date, despite challenges, the initiative had successfully initiated a platform for future collaboration. It was also highlighted that the groups were developing an international community for work beyond the design of trials, with subgroups forming to develop consensus statements, position papers, registries, virtual biobanks and databases.

The challenges outlined by the IRCI clinicians (see Figure 2 for a number for specific examples), can be summarised into the following themes that need to be considered moving forward;

- Challenges reaching design consensus and finding common standards of care in differing clinical infrastructures, where there is variation in how treatment is approached.
- The lack of knowledge on the biology of rare cancers. Further consideration is required as to how sample collection and translational research is approached and funded.
- Not obtaining approval from partner organisations committees who have differing scientific priorities (e.g. challenges obtaining initial buy in from the co-ordinating groups CTU, EORTC HQ and co-operative groups prior to application, and then the potential for partner's respective funding body not to support study).
- The need for NCI/co-operative group recognition of IRCI and a simplified approval procedure for the IRCI trials; work needs to be done to improve the understanding and awareness of IRCI within the co-operative groups and CTEP.
- The IRCI platform for international collaboration needs to be further promoted to industry. There has been difficulty accessing drugs (including generics) due to lack of involvement from industry, and also due to the inability of some countries to access registered, but off-label drugs under their existing healthcare coverage - a challenge which is emphasised by a lack of funding (as with more funding, drugs could be purchased and supplied via a CRO).
- Ways of working need to be such that up-front operational expertise from participating countries is available ahead of submission for approval/funding (e.g. to clarify upfront issues such as drug supply, sponsorship arrangements and finance and insurance).
- An operational working group is required to discuss solutions to common operational challenges faced across the IRCI studies and to find ways to improve/streamline the trial approval/set-up process.
- Stronger project management is required with an upfront project plan detailing a timeline of approval and trial set-up activities (e.g. particularly to overcome contract complexity, GSA and protocol approval).
- Setting up the IRCI trials to date has proved to be a time consuming effort, and high energy Chief Investigators/trial leads are required to drive forward progress. Where there is over-commitment with other responsibilities, delegation to a Regulator Chief Investigator or trial lead should be considered.

The future of the initiative

- Continue to support the existing IRCI groups in their trial development by facilitating group meetings/telephone conferences as required.
- The Timestones tool should be initiated to improve project management during the international trial approval and set-up process.
- The IRCI Board is currently consulting regarding how to integrate upfront translational research into the initiative that may inform future clinical trial development through learning more about the biology of a rare cancer. However, care is being taken around the assumption that knowing patients biology will improve treatment, and therefore it is currently favourable to move forward with a complimentary approach of pragmatic randomised control trial (that address required basic chemotherapy and radiotherapy questions) alongside an approach using targeted agents that are anticipated to have an effect based on a patients biology. Conversations are underway with the Sanger Institute regarding a proposal put forward to carry out whole genome sequencing on samples collected prospectively from patients entering IRCI trials, and also potentially more broadly from rare cancer patient not entering an IRCI trial through alignment with the SPECTArare initiative currently in development by the EORTC.
- The IRCI Board will be considering criteria for the adoption of existing/pre-developed trials into the IRCI portfolio.
- Moving forward further consideration needs to be given to the resource available to support developing IRCI trials and new groups in the initiative. The EORTC has for the time being reached capacity in the trials it is able to support administratively at its Head-quarters. The NCI limitation on review of trials outside of the National Clinical Trial Network whilst the restructure takes effect is improving and there is currently some flexibility for considering rare trial concepts on a case-by-case basis whilst the situation is being resolved - the NCI has advised to contact the appropriate CTEP disease specific leads regarding this. Discussions are currently underway with senior member of the NCI regarding a potential simplified process/structure for review of the IRCI trials, for example with potential pathways through the Centre for Global Health.
- Moving forward the CTEP disease specific leads will be engaged in the trial development process before the concept is reviewed by CTEP. The aim of this is to allow the CTEP disease site lead to provide feedback that can be considered earlier in the trial development process so as to avoid barriers/delays before a trial is reviewed. Additionally should a rare cancer trial pass the time required for CTEP activation due to administrative reasons only, the concept may re-circulate to the original steering committee, and if the concept is still scientifically valid the activation clock can be re-stared.

Box 1: The IRCI Methodological meeting and paper

An IRCI Methodological meeting was held alongside the ECCO 2013 Annual meeting, bringing together over 30 of the IRCI statisticians and clinicians to provide the invaluable opportunity to exemplify the approaches used to design credible trials in rare cancers. The meeting was jointly chaired by Jan Bogaerts (EORTC) and Matt Sydes (MRC) who subsequently led on writing a collaborative co-authored paper capturing and assessing each of the IRCI trial design methodologies. The paper has been published by the European Journal of Cancer with open access: http://www.ejcancer.com/article/S0959-8049(14)01063-6/abstract?cc=y

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