National Research Ethics Committee

NREC-CT A Meeting

17th November 2021

Attendance

Name	Role
Prof. Alistair Nichol	Chairperson, NREC CT-A
Dr Heike Felzmann	Deputy Chairperson, NREC-CT A
Prof. Mary Donnelly	Deputy Chairperson, NREC-CT A
Dr John O'Loughlin	Committee Member, NREC-CT A
Prof. Tina Hickey	Committee Member, NREC-CT A
Dr Dervla Kelly	Committee Member, NREC-CT A
Dr Jimmy Devins	Committee Member, NREC-CT A
Mr Gerard Daly	Committee Member, NREC-CT A
Prof. Patrick Dillon	Committee Member, NREC-CT A
Ms Ann Twomey	Committee Member, NREC-CT A
Prof. Catherine Hayes	Committee Member, NREC-CT A
Ms Muireann O'Briain	Committee Member, NREC-CT A
Prof. David Brayden	Committee Member, NREC-CT A
Prof. John Wells	Committee Member, NREC-CT A
Dr Geraldine Foley	Committee Member, NREC-CT A
Prof. Gene Dempsey	Committee Member, NREC-CT A
Ms Aileen Sheehy*	Programme Manager, National Office for RECs
Dr Laura Mackey*	Project Officer, National Office for RECs
Dr Lucia Prihodova	Programme Manager, National Office for RECs
Dr Emily Vereker	Programme Manager, HRCDC

Ms Brigid McManus	Chairperson, HRCDC
Mr Jonathan Barrett	Project Officer, HRCDC

*Drafted minutes

Apologies: Dr Darren Dahly

Quorum for decisions: Yes

Agenda

- Welcome & Apologies
- 21-NREC-CT-131
- 21-NREC-CT-132
- 21-NREC-CT-134
- 21-NREC-CT-120
- 21-NREC-CT-133
- AOB

- The Chair welcomed the NREC-CT A.
  - The minutes from the previous NREC-CT A meeting on 20th October 2021 were approved.
  - The NREC Business Report was discussed and noted.
  - The Chair welcomed members of the HRCDC who attended for observation.

Applications

21-NREC-CT-131

Principal Investigator: Professor Gerard Clarke

Study title: A Multicenter, Randomized, Double-Blind, Parallel-Group Study to Assess the Efficacy and Safety of Oral Etrasimod as Induction and Maintenance Therapy for Moderately to Severely Active Crohn's Disease

Lead institution: University Hospital Limerick

- NREC-CT comments:

- The NREC-CT A noted that this application represents a Multicenter, Randomized, Double-Blind, Parallel-Group Study to Assess the Efficacy and Safety of Oral Etrasimod as Induction and Maintenance Therapy for Moderately to Severely Active Crohn's Disease
- The NREC-CT A spoke positively about the participant materials and commended the approach taken to explain a complex trial in an understandable manner.
- While the NREC-CT A noted that while the application was clearly presented, additional information was required to inform its deliberations before a final ethics position could be returned.

  - NREC-CT Decision:

- Request for Further Information

  - Further Information Requested:

- The NREC-CT A requested further information on additional supports in place to support participants, such as those from an older demographic, given the broad age range described in the inclusion criteria. The NREC-CT A requested that these additional supports, if any, are included in the PIL.
- The NREC-CT A requested clarity on how frequently each participant will undergo colonoscopy and biopsy procedures. The Committee requested that this is further elucidated in the PIL, in addition to a fuller explanation of the risks of a large number of biopsies per procedure.
- The NREC-CT A noted the large number of medications from which the participant must refrain from taking when participating in the trial and requested that the information in the PIL specifies that the participant should speak with their GP or specialist about any potential impact this may have on the participant's ongoing treatment and health status.
- The NREC-CT A also requested clarification on whether the restriction of antibiotics while in the trial is only in relation to the treatment of CD, or for all illnesses when participating in the trial.
- The NREC-CT A noted that numerous questionnaires must be completed and requested the following information:
  - Why are there no questionnaires to monitor psychological distress?
  - What supports in place for Irish participants who experience psychological distress?
  - How many QoL measures are administered and how frequently?
  - What is the estimated time participants will need require to complete all of these measures/surveys?
- The NREC-CT A requested that the PIL makes reference to the Health Research Regulations.

- The NREC-CT A requested that the PIL is amended to further elucidate that transfer of care for participants referred by a physician outside of the trial centres will necessitate the participant's agreement to move their treatment to a trial site.
- The NREC-CT A requested clarification whether VZV vaccination is a condition to participation. If so, this should be explicit in the PIL.
- The NREC-CT A requested that if the applicant deems it necessary to use advertising materials in Ireland at a later date, that these materials are submitted to the Committee for review as a substantial amendment.
- The NREC-CT A noted that samples will be deposited with 'Precision Care Medicine'. The Committee requested further information about this organisation and their relationship with the Sponsor.
- The NREC-CT A requested confirmation that any future research projects using samples or data from participants involved in this study will undergo full ethics review.
- The NREC-CT A requested that the results and SDMB letter are shared with the Committee for notification after each phase of the study.
- The NREC-CT A requested confirmation that adequate insurance cover is in place, as the current certificate does not cover the full duration of the trial.

21-NREC-CT-132

Principal Investigator: Dr Anne Fortune

Study title: A Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) versus Bendamustine plus Rituximab in Untreated Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN-CLL-313)

Lead institution: Mater Misericordiae University Hospital

- NREC-CT comments:

- The NREC-CT A noted that this application represents a Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) versus Bendamustine plus Rituximab in Untreated Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN-CLL-313).
- The NREC-CT A acknowledged that this trial was well-designed overall.
- The NREC-CT A agreed that additional clarification was required in a number of areas to inform its deliberations and was not in a position to return a final ethics opinion.

- NREC-CT Decision:

- Request for Further Information

- Further Information Requested:

- The NREC-CT A requested clarification around the standard of care participants will receive on both arms of the study and confirmation that participants will not be denied treatments with known efficacy in place of an experimental trial treatment.
- The NREC-CT A recommended setting a minimum of 24 hours between the participant receiving information about the trial and the formal consent process.
- The NREC-CT A considered the PIL to be comprehensive but lengthy and requested that a brief plain English executive summary of the salient points of the study is included at the beginning of the PIL.
- The NREC-CT A requested the complex side-effects related to the treatment is further elucidated in the participant materials in a lay and understandable way to ensure participants are fully aware of the potential harms.
- The NREC-CT A noted the risk of infection, but queried whether COVID vaccine dosing guidelines should be included in the PIL.
- The NREC-CT A requested that the recruitment materials refrain from using abbreviations such as CLL and SLL.
- The NREC-CT A requested that the risks related to pregnancy are clearly included in the GP letter.
- The NREC-CT A requested a that more comprehensive version of the Site Suitability Form is completed, as the information in the current documents submitted were too vague.
- The NREC-CT A noted there is reference to patient advocacy groups within the documentation which has not been described in the application form and requests further information on the involvement of patient advocacy groups in the study.
- The NREC-CT A requested that the reference to insurance cover is adapted to an Irish setting.
- The NREC-CT A noted that the application states the use of GP records as part of recruitment procedures, which contravenes national legislation pertaining to data protection. The Committee requested further information around how the recruitment process will be adapted for an Irish setting in line with national legislation.
- The NREC-CT A requested clarity on plans for data retention given discrepancies noted in the documentation and requested that the relevant documents are amended.
- The NREC-CT A noted that the DPIA did not reflect the information included in the PIL such as including information on exploratory and future research. The Committee requested that the DPIA is tailored specifically to the trial at hand.
- The NREC-CT A requested that the text on travel and expenses is adapted to provide clarity on what will be covered in Ireland, and what is the maximum amount of compensation provided to participants for travel and refreshments.
- The NREC-CT A requested a statement around the source and allocation of funding related to this study.

21-NREC-CT-134

Principal Investigator: Dr Dearbhaile Collins

Study title: A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Paclitaxel With or Without Bevacizumab for the Treatment of Platinum-resistant Recurrent Ovarian Cancer (KEYNOTE-B96 / ENGOT-ov65)

Lead institution: Cork University Hospital

- NREC-CT comments:

- The NREC-CT A noted that this application represents a Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Paclitaxel With or Without Bevacizumab for the Treatment of Platinum-resistant Recurrent Ovarian Cancer (KEYNOTE-B96 / ENGOT-ov65).
- The NREC-CT A spoke positively about the quality of the participant materials, noting the inclusion of a well-written summary PIL.
- The NREC-CT A agreed that additional information was required to inform its deliberations, before a final ethics decision could be returned.

- NREC-CT Decision:

- Request for Further Information

- Further Information Requested:

- The NREC-CT A requested further information on how the complex stratification will be implemented across the two Irish sites and proposed eight participants to protect against investigator bias.
- The NREC-CT A noted that participants who withdraw, or are discontinued, will not be replaced as part of the trial and queried whether this should be considered for Irish participants due to the relatively few participants.
- The NREC-CT A requested further information on the statistical feasibility of the study with 616 participants across 26 countries.
- The NREC-CT A requested further information on the number of trial sites internationally.
- In Page 2 of the PIL Summary, the NREC-CT A suggested rephrasing some of the language to ‘on average…’ or ‘up to…’ rather than using ‘about’ when referencing participant time commitments.
- The NREC-CT A requested that reference to partners is included in the Pregnancy PIL to ensure they are adequately informed of any potential risks.
- The NREC-CT A requested the rationale for including information in the PIL that planned genetic and biomarker research would not be provided to the participant’s GP or trial doctor.

- The NREC-CT A requested an update on the agreed compensation process for participants once an agreement has been made with individual sites.
- The NREC-CT A requested a copy of the CV of Dr Cadoo.
- The NREC-CT A requested confirmation that any personal data from Irish participants transferred outside of the EU will be handled in line with national and EU legislation.
- The NREC-CT A noted discrepancies in the documentation in relation to the length of time in which data will be stored. The Committee requested clarity on plans for data retention and requested that the relevant documents are amended accordingly.
- The NREC-CT A noted that the FBR ICF states that results of the FBRs will be available on clinical trial websites, however elsewhere in the document it states that FBR would not be for future clinical trials, but separate pieces of research. The Committee requested further information on this discrepancy.
- The NREC-CT A requested confirmation that any future research project using samples or data from participants involved in this study will undergo full ethics review.
- The NREC-CT A noted that the Sponsor may 'license, transfer or sell' the trial or the trial drug. In that event, the Committee requested that it would be notified of this**.**

21-NREC-CT-120

Principal Investigator: Professor Alan Irvine

Study title: EPIK-P3: A phase II study to evaluate the long-term safety and efficacy of alpelisib in patients with PIK3CA-Related Overgrowth Spectrum (PROS) who previously participated in Study CBYL719F12002 (EPIK-P1)

Lead institution: Our Lady's Children's Hospital

- NREC-CT comments:

- The NREC-CT A noted that this application represents a phase II study to evaluate the long-term safety and efficacy of alpelisib in patients with PIK3CA-Related Overgrowth Spectrum (PROS) who previously participated in Study CBYL719F12002 (EPIK-P1).
- The NREC-CT A commented that this study was well-prepared overall.
- The NREC-CT A agreed that additional information was required to inform its deliberations, before a final ethics decision could be returned.

- NREC-CT Decision:

- Request for Further Information

- Further Information Requested:

- The NREC-CT A noted that there is a flat dose as part of the trial despite the wide age range (ages 2-18) and requested further information on the pk/pd data available to support this dosing schedule.
- The NREC-CT A noted that the study steering group only involves company staff and researchers and recommended that an independent third party is included in this group to ensure the participant interests are assessed and protected.
- The NREC-CT A requested a brief plain English executive summary of the salient points of the study is included at the beginning of the PIL.
- The NREC-CT A suggested that the GP letter includes further information on the concomitant drugs.
- The NREC-CT A requested further information on the general recruitment process. Specifically, which member of the trial team with undertake the interview with the participant, how this will take place, who on the trial team will lead on the consenting process, and the time allowed for the parent and child to discuss.
- The NREC-CT A noted that the study investigator's GCP training is out of date and requested confirmation on whether the investigator has since undergone a GCP course to update their qualifications.
- The NREC-CT A noted the consent process for the future use of biological samples and data is not in line with national regulations on 'explicit consent', which should be limited to specified health research, either in relation to a particular area or more generally in that area or a related area of health research**.**
    - The NREC-CT A requested that the applicant provides the participant with specific choices as to how their samples and underlying data will be used for future purposes, such as limiting future use to a specific disease area.
    - The NREC-CT A requested confirmation that any future research project using samples or data from participants involved in this study will undergo full ethics review.

21-NREC-CT-133

Principal Investigator: Professor Sean Raymond McDermott

Study title: An Open-label, Randomized Phase 3 Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Belzutifan (MK-6482) and Lenvatinib (MK-7902), or MK-1308A in Combination with Lenvatinib, versus Pembrolizumab and Lenvatinib, as First-line Treatment in Participants with Advanced Clear Cell Renal Cell Carcinoma (ccRCC)

Lead Institution: Tallaght University Hospital,

- NREC-CT comments:

- The NREC-CT A noted that this application represents an Open-label, Randomized Phase 3 Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Belzutifan (MK-6482) and Lenvatinib (MK-7902), or MK-1308A in

Combination with Lenvatinib, versus Pembrolizumab and Lenvatinib, as First-line Treatment in Participants with Advanced Clear Cell Renal Cell Carcinoma (ccRCC).

- The NREC-CT A spoke positively about the participant materials and commended the summary PIL.
- The NREC-CT A agreed that it was not in a position to return a final ethics opinion and that further information was required to inform its deliberations.

  - NREC-CT Decision:

- Request for Further Information

  - Further Information Requested:

- The NREC-CT A requested further information on how potential participants will be approached about the study at the recruitment site, including:
  - What is the process for identifying these potential participants?
  - Who will undertake this role?
  - Will it be those healthcare professionals already providing direct care to the potential participants play a role?

- AOB:
  - Ms Aileen Sheehy gave short presentation on the Clinical Trials Regulation and review processes to be implemented in January 2022.

- The Chair closed the meeting.