HR-NBL2 Newsletter

SIOPEN R NET

Solving Kids' Cancer

NEUROBLASTOMA UK
FIGHTING CHILDHOOD CANCER

December 2021

Issue 1

RANDOMIZED, INTERNATIONAL AND MULTICENTRIC PHASE 3 STUDY THAT EVALUATES AND COMPARES 2 TREATMENT STRATEGIES IN 3 THERAPEUTIC PHASES (INDUCTION, HIGH DOSE CHEMOTHERAPY AND RADIOTHERAPY) FOR PATIENTS WITH HIGH-RISK NEUROBLASTOMA.

Message from the National Coordinator

Martin Elliott

Dear research teams,

We are pleased to inform you that HR-NBL2 opened in the UK on 26th August this year with opening of Bristol Royal Hospital for Children, and the same day recruited and randomised its first patient. Four months on however, UK recruitment remains 1 patient, highlighting just how much we need all sites to open to help us recruit 205 patients by end 2025.

I'm extremely grateful to Solving Kid's Cancer and Neuroblastoma UK for the £609,762.40 they have given to fund the study in the UK. Building on from the successes of HR-NBL, I am hopeful this trial will establish which are the best care approaches for our patients and I am excited to be working with you to grant patients nationwide with access to this trial. Thank you for your collaboration and commitment. If you have any clinical concerns don't hesitate to get in touch. I can be contacted via the HR-NBL2 Trials office.

In the New Year we anticipate sharing with you details of a trial amendment to incorporate addition of an ALK inhibitor (Lorlatinib) for patients whose tumours harbour aberrations in the ALK gene...Exciting times!

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

International Sponsor
Gustave Roussy

International Coordinating Investigator
Dr Dominique Valteau-Couant

INSIDE THIS ISSUE

It's HR-NBL2's first Christmas!

We are marking this with the release of the first issue of the HR-NBL2 Newsletter. Your '*GO TO*' for updates on trial progress nationally and internationally, answers to common questions and announcements of changes to the trial protocol.

Recommendations for how to deliver the GPOH-N5 Regimen in the UK are now available. (see over page)

STOP PRESS

Message from the HR-NBL2 Trials Office

It might be cold outside but activity on HR-NBL2 is warming up. This is thanks to you!

Since opening Bristol in August and supporting them through treatment of their first patient we are now excited to be working with 19 recruitment sites and a further 4 radiotherapy sites across the UK including all four of the devolved nations to get this trial off the ground nationwide.

We expect to open ¾ of UK sites by end Q1 2022. Achieving this goal is essential if we are to recover the time lost on recruitment this year and meet our target of 205 patients by the planned recruitment end date of 31st December 2025. Whilst we recognise sites have struggled with set-up over the past year due to the impact of the pandemic, we are relying on you pulling out all stops for HR-NBL2 in the New Year and hope you will make it a priority to get HR-NBL2 open in Q1.

We believe you should all have received the version control checklist for this study and our local information pack. If there are any set-up documents you are missing please get in touch. We are here to help. Under the current guidance to "work from home where possible" we are working to a rota in the office and aim to provide you with your site files at the time of your initiation visit. We conduct our Initiation visits remotely.

We look forward to meeting you all (albeit virtually).

Seasons greetings and best wishes for 2022!

UK National Coordinator
Dr Martin Elliott

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CLINICAL QUERIES

Clinical queries during office hours should be directed to the UK Trials Office

SAE REPORTING

Report SAEs to Gustave Roussy online via My eClinical web portal
https://www.evereport.eu/myeclinical/form/IGR/login.php
If portal access is unavailable FAX forms to: +33 (0) 1 42 11 61 50

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International phase-3 study to improve treatment for patients with high-risk neuroblastoma

HR-NBL2 News

Key points for set-up and delivery of HR-NBL2

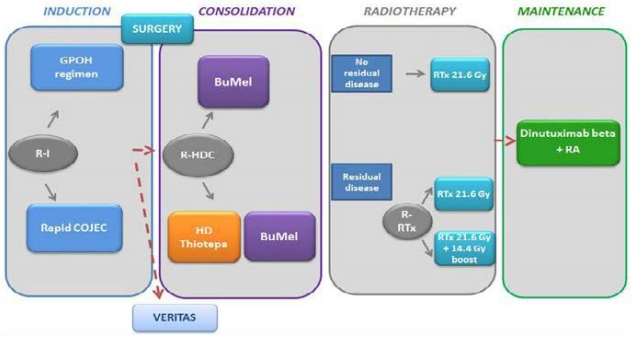
- The recruiting site registers patients onto the study via the TrialMaster Web interface which is used for randomisation and completing the case report form (CRF). Access to TrialMaster will be given at site activation.
- Where sites send patients to another hospital for a phase of treatment, the recruiting site completes the CRF and does any serious adverse event (SAE) reporting.
- SAEs are to be reported direct to the international sponsor via the My eClinical Web interface. Access to My eClinical will be given at site activation. Please don't report SAEs to us at the Trial office except in emergency.
- Patients are allocated a unique trial number (TNO) when they join the study which follows them throughout all three randomisations. The last two digits will always be XX because you must always put XX for the patient's initials at registration.
- Consent is collected for the main study and at each randomisation. There are PIS for each.
- Patients that are not eligible or do not consent for a randomisation can stay on the main study and participate at a later randomisation (if eligible). They will receive standard of care (SOC).
- To deliver radiotherapy on HR-NBL2 your site needs Radiotherapy Quality Assurance (RTQA) Approval from QUARTET. Follow the instructions in the QUARTET RTQA guidelines to get this. If your site is already approved you must still complete the HR-NBL2 sheet in the QUARTET facilities questionnaire to add HR-NBL2 to your list of studies.
- Before any radiotherapy is given, treatment plans for randomised patients need QUARTET approval. Upload plans for review via the EORTC RTQA uploader. You can register for login credentials at the EORTC uploader website.

HR-NBL2: The Background

High-risk neuroblastoma (HR-NBL) represents the largest neuroblastoma subgroup. Of the 100 patients diagnosed with Neuroblastoma in the UK each year, around 50 will have HR-NBL. The prognosis of these patients has been improved progressively over the years through an intensified induction regimen, surgery of the primary tumour, high-dose chemotherapy (HDC) followed by autologous stem cell rescue (ASCR), radiotherapy and immunotherapy such that 3-year event-free survival (EFS) is now around 40% from date of randomization and 55% for those patients who complete all parts of the treatment. However, further improvements in patient outcome are warranted. The standard-of-care protocols followed at each treatment phase vary internationally. It is desirable to understand which treatments offer the best outcome and in which patients so that doctors know they are giving their patients the best treatment available for them.

HR-NBL includes:

- Stage M disease > 12 months, any *MYCN* status
- Ms neuroblastoma 12-18 months, any *MYCN* status
- L2, M or Ms neuroblastoma with *MYCN* amplification



A patient's typical journey through treatment for HR-NBL includes 5 treatment interventions: (1) Induction chemotherapy, (2) Surgery, (3) Consolidation HDC & ASCR, (4) Radiotherapy, (5) Maintenance. The HR-NBL2 trial seeks to optimise SIOPEN treatment approaches at 3 of these 5 steps (treatments 1, 3 and 4). Local practice will be followed for the other steps (2 and 5).

HR-NBL2 Primary Objectives

1.

Induction: Compare the Event-Free Survival (EFS) rate from date of randomisation of GPOH and RAPID COJEC.

2.

HDC: Compare the EFS rate from date of randomisation of single HDC with Busulfan-Melphalan (Bu-Mel) versus tandem HDC with Thiotepa followed by Bu-Mel.

3.

Radiotherapy: Compare the EFS rate from date of randomisation of 21.6Gy radiotherapy to the preoperative tumor bed versus 21.6Gy radiotherapy and a sequential boost of an additional 14.4Gy to the residual tumor in patients with macroscopic residual disease.

International Update

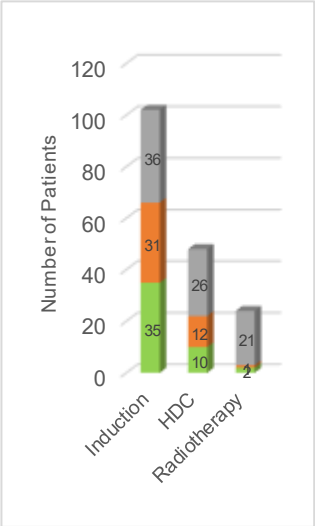
- France opened HR-NBL2 in Oct 2019 and consented the first patient in Nov 2019.
- 27 countries are co-sponsors.
- 5 co-sponsor countries have opened (The Netherlands (Jan 2021), Switzerland, Italy and Slovenia (Jul 2021), UK (Aug 2021)),
- Target international recruitment by end 2025 is 800

Induction: 686
Consolidation: 448
Radiotherapy: 226

Recruitment Figures Nov 2021:

Total international recruitment: 103 (13% of target)

UK recruitment: 1 (0.5% of target)



International recruitment and randomisation showing the numbers of patients registered on the study at each of the 3 treatment phases and the treatment received. Grey = Non-randomised standard of care (SOC), Green = Randomised SOC, [Rapid COJEC/Bu-Mel/21.6Gy], Orange = Randomised non-SOC [GPOH/Thiotepa + Bu-Mel/21.6Gy+boost].

GPOH-N5 Regimen.

Following a compatibility data review a number of options for how to administer the GPOH-N5 regimen in the UK have been determined by a team from the Paediatric Oncology Pharmacist Group.

These options were shared with you in a Mailshot on 22-Dec-2021.

Centres should consider what would be effective and safe under their ways of working. Please contact us if you have any queries.

Translational Research and HR-NBL2.

Section 8 of the HR-NBL2 protocol describes biological samples that may be collected alongside the trial for use in translational studies into the genetics of HR-NBL and prognostic and predictive biomarkers for the disease. In the UK we lack funding to collect and analyse these samples so are *not mandating* them. However, **through the CCLG Tissue Bank, HR-NBL2 patients can support translational research into HR-NBL.**

- Where appropriate invite all trial and non-trial HR-NBL patients to consent for their samples to be collected and stored in the CCLG Tissue Bank. For this the Tissue-Bank PIS and consent forms need to be used.
- You will allocate the patient a unique CCLG Tissue Bank number of the form XX-YYYYY. (XX = site no. YYYYY = unique patient no.). This is separate to their trial number.
- Refer to the Biobanking lab manual for guidance on the collection, storage and sending of samples to the Tissue Bank. For patients on the trial, this manual identifies a few additional blood, bone marrow and stem cell samples to be taken at timepoints through the patient's treatment. We will notify the CCLG Tissue Bank when your site is opened and PAXgene tubes required will be sent to you.