CHILDREN’S CANCER AND LEUKAEMIA GROUP (CCLG)
NEUROBLASTOMA SPECIAL INTEREST GROUP

Options for the Treatment of Patients with Relapsed/Progressive High-Risk Neuroblastoma

MARCH 2015


The CCLG does not sponsor or indemnify the treatment detailed herein. These treatment recommendations are provided by the Neuroblastoma Special Interest Group to inform and for use at the sole discretion of treating clinicians who retain professional responsibility for their actions and treatment decisions. Treatment recommendations are based on current best practice and not what is necessarily proposed for any forthcoming clinical trial.
CONTENTS

Summary .................................................................................................................. 2
Background and context ....................................................................................... 2
General principles ............................................................................................... 5
Scenarios
  Relapse after myeloablative therapy ............................................................... 6
  Relapse before myeloablative therapy ............................................................. 9
  CNS relapse ......................................................................................................... 10
  Primary refractory disease ............................................................................... 11
Further advice ....................................................................................................... 12
Appendices
  Appendix 1 – Clinical Trials ........................................................................... 13
  Appendix 2 – Chemotherapy Regimens ........................................................... 15
  Appendix 3 – 131I-mIBG Therapy ..................................................................... 19
  Appendix 4 – Additional Experimental Approaches in the UK ................. 20
  Appendix 5 – Additional Experiment Approaches (Non-UK) ..................... 22
References ........................................................................................................... 24

CHANGES FROM PREVIOUS VERSION(S)

- No major changes to substance of treatment recommendations
- Overall guideline has been rewritten and expanded to provide additional information
1. SUMMARY

The optimum therapy for relapsed high-risk neuroblastoma is not clearly defined, due in large part to the lack of randomised studies. Ensuring optimum therapy for patients with relapsed high-risk neuroblastoma is of critical importance to ensure:

i) the best treatment is given for the individual patient;

ii) the maximum number of options are provided and

iii) new therapy approaches for relapse can be developed and then brought into frontline treatment for high-risk neuroblastoma.

This document:

i) outlines the therapeutic options for relapsed high-risk neuroblastoma;

ii) summarises second line chemotherapy regimens tested in Phase II trials in neuroblastoma since 2000

iii) strongly recommends that children with relapsed high-risk neuroblastoma are enrolled in a clinical trial whenever possible and

iv) recommends that tumours are re-biopsied at the primary or an accessible metastatic site time of relapse before entering clinical trials.

2. BACKGROUND AND CONTEXT

Neuroblastoma is the most common childhood extracranial solid tumour. Half of the children who present are considered to have high-risk disease (metastatic and/or MYCN amplified) (1). With the use of intensive chemotherapy, surgery, myeloablative (MAT) chemotherapy with haematopoietic stem cell rescue, radiotherapy and differentiation therapy with 13-cis-retinoic acid long-term survival for children with high-risk neuroblastoma has moderately improved over the past 30 years, but in long-term reports, overall survival is still below 50% (1-3). The recent introduction of immunotherapy into the multimodal treatment of neuroblastoma has shown promising results with improvements in 2-year Event Free Survival (EFS) of up to 20% after the addition of the anti-GD2 monoclonal antibody ch14.18 with interleukin-2 and GM-CSF, although the long-term benefit of this approach remains to be established as late relapses have been described (4,5) and long-term survival outcomes have not been published yet. Updated data presented at ANR 2014 show that at 4-year follow-up EFS is no longer statistically significantly different between the two groups, although the improvement in OS remains.

Nevertheless, up to 60% of children with high-risk neuroblastoma will experience relapse with current therapies. From historic Italian Registry Data, 10-year Overall Survival (OS) was 2% after relapse and 1.5% after progression in children with metastatic neuroblastoma (6). Advances in the therapy of high-risk neuroblastoma at initial presentation have come from randomised studies (2-4,7-9). However, there has been a lack of randomised studies in the relapsed setting and current therapy is not evidence based. Ensuring optimum therapy for
patients with relapsed high-risk neuroblastoma is of critical importance to ensure: i) the best
treatment is given for the individual patient; ii) the maximum number of options are
provided and iii) new therapy approaches for relapse can be developed and then brought
into frontline treatment for high-risk neuroblastoma.

In a review of the International Neuroblastoma Risk Group (INRG) database collecting
outcomes from 8800 children with neuroblastoma treated worldwide, London et al. (10)
reported a 5-year OS following relapse of 20% (all stages). For children aged ≥18 months at
diagnosis with relapsed metastatic neuroblastoma 5-year OS after relapse was 8% and only
4% for those with MYCN amplification (10). Time to First Relapse (TTFR) was statistically
significantly associated with OS, with a nonlinear relationship identified. Patients with TTFR
of 36 months or longer had the lowest risk of death, followed by patients who relapsed in the
period of 0 to <6 months or 18 to 36 months. Patients who relapsed between 6 and 18
months after diagnosis had the highest risk of death. The association of TTFR and OS post
relapse was strongest in stage 3 and 4 patients with MYCN amplified tumours.

Table 1 summarizes the results of second line therapies that have been evaluated for patients
with relapsed / refractory neuroblastoma (see also (11) for summary of treatment options).
Overall, objective response rates (CR + VGPR + PR) range from 10 – 25%, with 25 – 50%
experiencing disease stabilisation (SD). Patients with refractory disease appear to benefit
more than those with relapsed disease. Some of these regimens have been taken forward to
front-line therapy; for example topotecan-cyclophosphamide is now used at induction by
Children’s Oncology Group (COG) following the results of a non-randomised pilot study (12).
However, none of these combinations have been evaluated in randomised Phase II studies
and the relative benefits in terms of activity and toxicity have not been determined and are
uncertain. Interpretation of the results of these studies is highly complex as both relapsed
and refractory patients are included and prior therapy varied significantly. Results for
reported response rates must be interpreted cautiously. Furthermore, the benefits of
different therapeutic approaches for different scenarios (inadequate response, early
progression, early or late relapse) have not been demonstrated.
Table 1. Second line chemotherapy regimens tested in neuroblastoma since 2000.

<table>
<thead>
<tr>
<th>Regimen (Reference)</th>
<th>Collaborative group</th>
<th>Responses (No. patients)</th>
<th>Response Rate (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temozolomide (13)</td>
<td>UKCCSG/ SFOP</td>
<td>5/25 CR, VGPR, PR 7/25 SD/NR 3/25 MR</td>
<td>20%</td>
<td>40% (SD/NR/MR)</td>
</tr>
<tr>
<td>Irinotecan (14)</td>
<td>SFOP/ UKCCSG</td>
<td>0/37 CR, PR 5/37 SD</td>
<td>0%</td>
<td>13%</td>
</tr>
<tr>
<td>Temozolomide/</td>
<td>MSKCC</td>
<td>3/39 CR, PR, 5/39 SD</td>
<td>7.7%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Irinotecan (15,16)</td>
<td>COG</td>
<td>8/55 CR, PR 29/55 SD</td>
<td>15%</td>
<td>53%</td>
</tr>
<tr>
<td>Temozolomide/ oral</td>
<td>NANT</td>
<td>1/14 CR 5/14 SD</td>
<td>7%</td>
<td>36%</td>
</tr>
<tr>
<td>Irinotecan (Phase I) (17)</td>
<td>ITCC</td>
<td>3/38 CR, 6/38 PR, 4/38 MR, 17/38 SD (best response)</td>
<td>18%</td>
<td>55%</td>
</tr>
<tr>
<td>Topotecan/ Temozolomide (18,19)</td>
<td>SIOPEN</td>
<td>16/25 CR, PR 4/25 SD</td>
<td>64%</td>
<td>16%</td>
</tr>
<tr>
<td>Topotecan/ Vincristine/ Doxorubicin (20)</td>
<td>COG/ TPT/CYCL</td>
<td>24/87 CR, PR 15/87 MR</td>
<td>27.5%</td>
<td>17% (MR)</td>
</tr>
<tr>
<td>Topotecan/ cyclophosphamide vs. topotecan alone (12)</td>
<td>COG/ TPT</td>
<td>24/87 CR, PR 15/87 MR</td>
<td>27.5%</td>
<td>17% (MR)</td>
</tr>
<tr>
<td>Topotecan/ etoposide (21)</td>
<td>GPOH</td>
<td>17/36 (CR, PR) SD n/a</td>
<td>47%</td>
<td>n/a</td>
</tr>
</tbody>
</table>

UKCCSG: United Kingdom Children’s Cancer Study Group, SFOP: French Society for Paediatric Oncology, MSKCC: Memorial Sloan Kettering Cancer Centre, COG: Children’s Oncology Group TMZ: Temozolomide, VP16: Etoposide, IRI: Irinotecan, CYC: Cyclophosphamide, TPT: Topotecan
3. GENERAL PRINCIPLES

- It is strongly recommended that children with relapsed high-risk neuroblastoma are enrolled in a clinical trial whenever possible since this the only way that experience can be gained, information collected in a standardized and regulated way and ethically-acceptable approaches ensured.

- While protecting patients’ wellbeing, re-biopsy of tumours at the time of relapse at the primary or accessible metastatic site before entering early clinical trials is increasingly important, as the genomic profile can substantially change between presentation and relapse (for example, neuroblastoma can acquire ALK or TP53 mutations at relapse (22,23)). Tumour molecular profiling should be carried out at the time of relapse to facilitate access to early trials of specific molecularly targeted therapies and to improve our understanding of the biology of relapse. In the case of trials with molecular pre-selection with predictive biomarkers, re-biopsy is of critical importance.

- It is recommended that tumour samples from patients with relapsed/refractory high-risk neuroblastoma be routinely tested for ALK mutation/amplification status if this has not already been done. Referral for ALK-directed early phase clinical trials should be considered for patients in whom ALK aberrations are identified (approximately 10% of neuroblastoma cases (24,25) and a higher proportion at relapse (22)).

- Long-term survival after relapse of high-risk neuroblastoma is uncommon (26) and although therapy may be able to prolong survival, careful consideration needs to be given to the individual needs of patients, balancing toxicity and burden of therapy with likelihood of benefit.

- Children with high-risk neuroblastoma at first relapse will typically be managed with a chemotherapy-based induction regimen, followed by consolidation with molecularly-targeted radiotherapy. Further treatment with cis-RA and/or immunotherapy may then be considered for patients who have not previously received anti-GD2.

- Patients who relapse having not initially received myeloablative therapy (MAT) should receive MAT after induction as consolidation prior to immunotherapy (provided an adequate response to re-induction therapy has been achieved).

- Children with high-risk neuroblastoma, who experience a second relapse, should be offered an early phase clinical trial, if available, in the first instance.

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1 Such testing is currently available via the Northern Genetics Service based in Newcastle (email: cancer.cytogenetics@nuth.nhs.uk)

2 Although for most patients, recruitment to the BEACON-Neuroblastoma would probably be appropriate first-line treatment rather than ALK-directed therapy

3 Re-induction chemotherapy is not a prerequisite for radionucleotide therapy and molecularly-targeted radiotherapy may be suitable initial treatment option for some patients
4. SCENARIOS

4.1 Relapse after Myeloablative Therapy (MAT)

4.1.1 Induction phase

- The Phase II randomized study BEACON-Neuroblastoma (see Appendix 1) is an option for patients who experience relapse after MAT and should be considered first.

- If BEACON-Neuroblastoma is not available or parents decline
  
  o Topotecan-cyclophosphamide or topotecan, vincristine and doxorubicin (TVD) can be given and do not exclude subsequent enrolment of the patient in the BEACON-Neuroblastoma study.
  
  o Generally temozolomide is the regimen that is associated with the lowest toxicity and can be given orally (potentially obviating the need for a central venous catheter). Temozolomide has been demonstrated to produce objective response rates (CR & PR) of 20% and stabilisation of disease in 40% of patients. None of the other regimens have been proven to be superior in terms of efficacy.
  
  o Patients could receive other chemotherapy-based regimen such as temozolomide, irinotecan-temozolomide, topotecan-temozolomide, topotecan-cyclophosphamide or TVD if there is no cardiac contraindication (e.g. total cumulative dose of anthracyclines and cardiac function). Decisions should be individualised based on the parents’ and patient’s wishes, patient’s prior toxicity, prior therapies, the need for hospitalisation and central venous access with the different regimens.
The patient should be evaluated after two courses. If there is any response (CR, PR or SD) continuing chemotherapy for up to four to six courses, provided toxicity is acceptable, should be considered. If the patient’s family wishes to reduce hospitalisation or intensity of treatment, or the patient has poor bone marrow reserve, chemotherapy regimens such as temozolomide alone could be considered. There is no evidence to indicate that the addition of irinotecan improves the efficacy of temozolomide.

Consolidation therapy such as molecular targeted radiotherapy or immunotherapy is very strongly recommended after six courses. Treatment beyond 12 courses is currently not recommended because of the risk of second malignancy and consolidation therapy is recommended. The use of up to 32 cycles of cyclophosphamide/topotecan has been reported (27).

After two courses of chemotherapy-based regime, the possibility of participating in an early phase clinical trial could be explored, especially if there is a actionable mutation e.g. ALK, should the family wish. However, not all early phase clinical trials allow patients with stable disease or responding disease, so potential eligibility should always be checked with the early phase clinical trial sites before a formal referral.

4.1.2 Consolidation phase

After completing the induction phase, (i.e. after completion of BEACON-Neuroblastoma or 4-6 courses of TVD or 6-12 courses of irinotecan and temozolomide or temozolomide alone, or other alternative chemotherapy regime), if there is a response or stabilization of disease consideration should be given to consolidation with molecular targeted radiotherapy.

Molecular targeted radiotherapy appears to have most benefit in controlling soft tissue and focal bone disease, rather than diffuse and widespread bone marrow involvement (28). Molecular targeted radiotherapy should not be considered in the setting of uncontrolled CNS disease.

\[^{131}\text{I-mIBG}\] therapy could be administered, provided that the tumour is mIBG-avid (positive on mIBG scan) and adequate stem cells are available (mIBG therapy is typically delivered at a whole body dose that is myeloablative). This is currently available (in a non-trial setting) at UCLH (London) and the Royal Marsden Hospital (Sutton, Surrey).

In a meta-analysis of more than 1100 patients with neuroblastoma receiving \[^{131}\text{I-mIBG}\] therapy (29), \[^{131}\text{I-mIBG}\] therapy was demonstrated to be an active treatment (response rate between 0 and 75%, mean 32%). However, there were many permutations of dose and fraction. The place of \[^{131}\text{I-mIBG}\] therapy in the treatment of neuroblastoma remains unclear and further trials are warranted.
A novel alternative approach is $^{177}$Lu-DOTATATE treatment in the LuDO trial currently open at UCLH (see Appendix 2). $^{68}$Gallium octreotide avidity will need to be assessed for eligibility (PET scan to be undertaken at UCLH). Pre-screening with an octreoscan in the local centre may be helpful in identifying patients for whom LuDO will not be a suitable option. Unlike therapeutic mIBG, treatment with LuDO does not require stem cells.

Other than the use of autologous stem cell rescue to facilitate $^{131}$I-mIBG therapy, a second myeloablative procedure (with chemotherapy) cannot currently be recommended for patients with relapsed disease (unless there is a late relapse (>5 years) and the patient initially only received high dose melphalan). There is no evidence to show any benefit of a second HDT with autologous hematopoietic stem cell rescue. Studies performed to date on haploidentical transplants have not demonstrated a favourable risk/benefit ratio or improvement in survival; hence, haploidentical transplants is discouraged outside the confines of participation in an approved clinical trial.

4.1.3 Maintenance phase
Children who obtain a response or have stable disease after induction and consolidation therapy should be considered for immunotherapy. If the child has not previously received an anti-GD2 antibody, then Infusional anti-GD2 antibody study with IL-2 randomisation (continuous infusion of ch14.18/CHO ± subcutaneous Aldesleukin (IL-2)) should be offered.

Note that at present there are no European studies in which patients who have already received ch14.18 anti-GD2 are eligible to receive further immunotherapy with anti-GD2 after relapse.4

4.1.4 Further relapse/progression
In case of further relapse/progression, an Early Phase clinical trial (see Appendix 2) could be offered or alternatively oral etoposide or symptom care only may be the most appropriate options.

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4 One potential option would be murine anti-GD2, 3F8, although this is only available at Memorial Sloan Kettering Cancer Center in New York and costs would be very significant. A UK immunotherapy study protocol that would include patients who have previously received Ch14.18 anti-GD2 is currently in early development.
4.2 Relapse before Myeloablative Therapy (MAT)

**4.2.1 Induction phase**
Children with neuroblastoma who experience relapse/progression before MAT, or patients who experience relapse after high-risk neuroblastoma treatment that has not included MAT for any reason, should receive induction chemotherapy as described above. Participation in BEACON-Neuroblastoma trial should be considered first. Other treatment such as TVD, other topotecan-based regime, temozolomide alone or irinotecan-temozolomide can be considered if BEACON-Neuroblastoma trial is not available or patient is not eligible or declines.

**4.2.2 Consolidation phase**
Consolidation of any response should be pursued by using molecularly-targeted radiotherapy (Lu-DOTATATE or mIBG). Decisions will need to be individualized based on the patient’s prior toxicities and therapies.

**4.2.3 MAT**
Molecularly-targeted radiotherapy could be followed by MAT, i.e. high dose chemotherapy (busulfan-melphalan) with peripheral blood stem cell rescue (PBSCR) provided stem cells are available. Other options involving MAT should be discussed on a single case basis.

**4.2.4 Maintenance phase**
Children who obtain a response after MAT should be offered an immunotherapy clinical trial; currently in the UK the Infusional anti-GD2 antibody study with IL-2 randomisation.
4.2.5 Further relapse/progression

In case of further relapse/progression an Early Phase clinical trial (see Appendix 2) could be offered or alternatively oral etoposide or symptom care only may be the most appropriate options.

4.3 Patients with Central Nervous System (CNS) relapse

The estimated risk for CNS relapse following treatment for stage 4 neuroblastoma (all ages) is approximately 8% at 3 years (30). Half of these patients have isolated CNS relapse. For those with CNS relapse, the pattern of disease is evenly divided between parenchymal only, meningeal only and both parenchymal and meningeal involvement (30).

Historically, the outcome for these patients has been extremely poor with no curative options available and no consistent treatment strategy. Despite the poor prognosis, it has been shown that intensive directed therapy including surgical excision of isolated relapses (wherever feasible), craniospinal radiotherapy and consolidation with chemotherapy can achieve some control of CNS relapses. Memorial Sloan Kettering Cancer Center has reported preliminary results (albeit in the setting of a non-randomised trial and single institution experience) using intrathecal radio-immunotherapy after CNS relapse (31). The relative importance of the individual components of this treatment schedule is not yet established and at present intrathecal radio-immunotherapy in this context is only available at MSKCC as part of a clinical trial. Other molecular-targeted radiotherapy approaches ($^{177}$Lu-DOTATATE or $^{131}$I-mIBG) should not be considered in the setting of uncontrolled CNS disease.

A proposed treatment pathway for the UK is outlined below:

- Neurosurgical resection of CNS disease
- Craniospinal radiotherapy (21Gy in 1.5Gy fractions)
- Temozolomide ± irinotecan ⁵
- Patients with CR/VGPR who have not previously received myeloablative chemotherapy could then proceed to MAT (busulfan/melphalan), followed by systemic immunotherapy with anti-GD2 for patients who have not already received this, plus oral cis-retinoic acid

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⁵ Recruitment to BEACON-Neuroblastoma is also a possible option although patients with actively bleeding CNS metastases are not eligible due to the risk of bleeding associated with bevacizumab. Patients with stable disease (e.g. after irradiation of all target lesions) would need to show progressive disease before being enrolled on BEACON-Neuroblastoma.
4.4 Patients with primary refractory disease

Approximately 10-20% of patients with high-risk neuroblastoma have primary refractory disease and fail to achieve an adequate response that allows consolidation with MAT and minimal disease therapy. Patients on the SIOPEN high-risk neuroblastoma study with an inadequate response to induction chemotherapy (rapid COJEC or modified N7) may receive up to 2 cycles of TVD chemotherapy and remain on study.

Patients coming off study because of insufficient response, but who nevertheless have some response after 2 cycles of TVD may receive an additional 2–4 cycles of TVD provided that they have not previously received anthracyclines (e.g. as part of modified N7) with the aim of then proceeding to MAT.

Early consideration should be given to recruitment to the BEACON-Neuroblastoma trial that is open for patients with refractory as well as relapsed high-risk neuroblastoma.

Patients who achieve a response to re-induction chemotherapy may then benefit from consolidation with molecularly-targeted radiotherapy and/or myeloablative chemotherapy. Such approaches may be of benefit in patients with only a partial response (i.e. who don’t meet standard criteria for myeloablative chemotherapy) (32). Following myeloablative chemotherapy, such patients should be considered for a systemic immunotherapy clinical trial; currently in the UK the Infusional anti-GD2 Study with IL2.
### 5. FURTHER ADVICE

A National Neuroblastoma Advisory Panel under the auspices of the CCLG is in development. In the meantime, the following UK clinicians with a special interest in neuroblastoma may be contacted for advice on specific patients:

<table>
<thead>
<tr>
<th>Specialization</th>
<th>Clinician</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>Dr Mark Gaze</td>
<td><a href="mailto:mark.gaze@uclh.org.uk">mark.gaze@uclh.org.uk</a></td>
</tr>
<tr>
<td>Early phase trials</td>
<td>Dr Lynley Marshall</td>
<td><a href="mailto:lynley.marshall@rmh.nhs.uk">lynley.marshall@rmh.nhs.uk</a></td>
</tr>
<tr>
<td>BEACON trial</td>
<td>Dr Lucas Moreno</td>
<td><a href="mailto:lmorenom@cnio.es">lmorenom@cnio.es</a></td>
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<tr>
<td>Chemotherapy</td>
<td>Dr Kate Wheeler</td>
<td><a href="mailto:kate.wheeler@paediatrics.ox.ac.uk">kate.wheeler@paediatrics.ox.ac.uk</a></td>
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<tr>
<td></td>
<td>Prof Deb Tweddle</td>
<td><a href="mailto:deborah.tweddle@newcastle.ac.uk">deborah.tweddle@newcastle.ac.uk</a></td>
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<tr>
<td></td>
<td>Dr Martin Elliott</td>
<td><a href="mailto:martin.elliott@leedsth.nhs.uk">martin.elliott@leedsth.nhs.uk</a></td>
</tr>
<tr>
<td></td>
<td>Dr Guy Makin</td>
<td><a href="mailto:guy.makin@manchester.ac.uk">guy.makin@manchester.ac.uk</a></td>
</tr>
<tr>
<td></td>
<td>Dr Daniel Morgenstern</td>
<td><a href="mailto:daniel.morgenstern@gosh.nhs.uk">daniel.morgenstern@gosh.nhs.uk</a></td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Dr Juliet Gray</td>
<td><a href="mailto:juliet.gray@uhs.nhs.uk">juliet.gray@uhs.nhs.uk</a></td>
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<tr>
<td></td>
<td>Prof John Anderson</td>
<td><a href="mailto:j.anderson@ucl.ac.uk">j.anderson@ucl.ac.uk</a></td>
</tr>
</tbody>
</table>
BEACON – Neuroblastoma study

The BEACON-Neuroblastoma trial is designed to identify a backbone chemotherapy regimen that may be combined with molecularly targeted agents and to determine if targeting angiogenesis with bevacizumab (B), a monoclonal antibody against the Vascular Endothelial Growth Factor, adds to the activity of chemotherapy. It is the first randomized European study for refractory/relapsed neuroblastoma and is a critical element of the SIOPEN/ITCC collaborative strategy for the development of new agents for neuroblastoma. The Beacon-Neuroblastoma study (Sponsor: CRUK CTU Birmingham, CI: Prof Andrew Pearson, RMH) is currently open at several UK centres. The study’s primary objectives are: to test whether bevacizumab added to a backbone chemotherapy regimen (temozolomide or irinotecan-temozolomide) demonstrates activity in children with relapsed or refractory neuroblastoma; and to test whether the addition of irinotecan to temozolomide increases the activity of chemotherapy in children with relapsed or refractory neuroblastoma.

Children and adolescents aged 1-21 with relapsed neuroblastoma can be referred to a participating centre for enrolment in BEACON-Neuroblastoma trial.

These children will be randomized to receive one of the 4 combinations of drugs:

<table>
<thead>
<tr>
<th>Arm</th>
<th>Days 1 - 5</th>
<th>Days 1 - 5</th>
<th>Day 1 / Day 15</th>
<th>Every 3 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>Temozolomide 200 mg/m²/d PO</td>
<td>Temozolomide 200 mg/m²/d PO</td>
<td>Bevacizumab 10mg/kg IV</td>
<td>Every 4 weeks</td>
</tr>
<tr>
<td>BT</td>
<td>Temozolomide 200 mg/m²/d PO</td>
<td>Temozolomide 200 mg/m²/d PO</td>
<td>Bevacizumab 10mg/kg IV</td>
<td>Every 4 weeks</td>
</tr>
<tr>
<td>IT</td>
<td>Temozolomide 100 mg/m²/d PO</td>
<td>Temozolomide 100 mg/m²/d PO</td>
<td>Bevacizumab 10mg/kg IV</td>
<td>Every 3 weeks</td>
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<tr>
<td>BIT</td>
<td>Temozolomide 100 mg/m²/d PO</td>
<td>Temozolomide 100 mg/m²/d PO</td>
<td>Bevacizumab 10mg/kg IV</td>
<td>Every 3 weeks</td>
</tr>
</tbody>
</table>

Evaluation will be carried out every two courses. If there is response or stable disease a total of 6 courses should be administered. Additional 6 courses could be negotiable with the Sponsor provided that some response is demonstrated.

During 2015 it is planned to add two further arms (topotecan/temozolomide and topotecan/temozolomide/bevacizumab).

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LuDO Study
This is a Phase I/II study of Lutetium-177 DOTATATE (Sponsor: CRUK CTU Birmingham, CI: Dr Mark Gaze, UCLH) aiming to determine the toxicity profile and activity (as measured by objective tumour response by semi-quantitative $^{123}$I-mIBG scoring or PET-CT if mIBG negative) of $^{177}$Lu-DOTATATE in children with high-risk relapsed or primary resistant neuroblastoma. Note that unlike therapeutic mIBG treatment, patients receiving Lu-DO do not need to have stored stem cells.

Phase I/II infusional anti-GD2 Study
This is an early-phase study of ch14.18/CHO continuous infusion combined with subcutaneous Aldesleukin (IL-2) (UK Sponsor: CRUK CTU Birmingham, UK CI: Dr Juliet Gray, Southampton). The study protocol has recently been amended to introduce an IL-2 randomisation such that patients will receive either a standard arm of ch14.18/CHO with SC IL-2 or ch14.18/CHO alone. This study provides access to immunotherapy for children who have relapsed after or progressed during the HR-NBL (version 1.5) protocol and therefore will not be eligible for immunotherapy on the HR-NBL study, or who had an inadequate response to induction chemotherapy and had to come off study. Note that patients who have previously received anti-GD2 immunotherapy are not eligible.

Phase I studies in the UK
A number of Phase I and II clinical trials are open and available for children and adolescents with relapsed neuroblastoma. Many of these studies are biologically driven with a scientific rationale for using specific targeted therapies (e.g. ALK inhibitors) in neuroblastoma harbouring specific genetic alterations or activation of specific pathways; whereas other studies have broader inclusion criteria allowing all neuroblastomas.

Please check the most recent monthly update Phase I/II clinical trials list sent by the Novel Agent Group and available via the CCLG Website.

See Appendix 4 for more information.
APPENDIX 2 – CHEMOTHERAPY REGIMENS

Irinotecan and temozolomide

It is still unclear whether adding irinotecan to temozolomide improves the efficacy of the latter. This question is being addressed in the Phase II study BEACON-Neuroblastoma that is currently open.

<table>
<thead>
<tr>
<th>Days</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<td>●</td>
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<td>●</td>
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<tr>
<td>Temozolomide</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

**Irinotecan 50mg/m² daily IV infusion over 60 mins for 5 days**

Dose reduce irinotecan to 1.67mg/kg if body weight ≤12kg

**Temozolomide 100 mg/m² daily orally for 5 days (round dose to nearest 5mg)**

Dose reduce temozolomide to 3.3mg/kg if body weight ≤12kg

Note that:

- Each course to be given at 21 day intervals
- Irinotecan and temozolomide to be given when absolute neutrophil count >0.75x10⁹/L and platelets >75x10⁹/L, or ANC ≥ 0.5x10⁹/L and platelets ≥ 50x10⁹/L if bone marrow involved
- Prophylactic G-CSF not to be routinely administered. It can be used in case of delayed count recovery
- Prophylactic co-trimoxazole to be administered
- If the patient develops irinotecan induced diarrhoea, in the absence of any contraindications such as allergies, treatment with cefixime 8 mg/kg once a day (max daily dose 400 mg) could be considered and started 2 days before chemotherapy and continued daily until day 7, following local policies for the management of irinotecan-related diarrhoea.
- For delayed onset diarrhoea occurring >8 hours after irinotecan administration, children should receive loperamide. Loperamide should continue until a normal pattern of bowel movements returns. Oral hydration with large volumes of water and electrolytes should be prescribed during whole diarrhoea episode. If the delayed diarrhoea recurs, then cefixime should be given with the following courses.
- Evaluation should be carried out every 2 courses.
### Temozolomide (single agent)

<table>
<thead>
<tr>
<th>Days</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Temozolomide</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
</tbody>
</table>

**Temozolomide 200 mg/m² daily orally for 5 days (round dose to nearest 5mg)**

- Dose reduce temozolomide to 6.7mg/kg if body weight ≤12kg
- Each course to be given at 21 or 28 day intervals upon count recovery

### Topotecan, Vincristine and Doxorubicin

(As per the instructions in the current SIOPEN HR NBL study)

<table>
<thead>
<tr>
<th>Days</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>Topotecan</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td></td>
<td></td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>finish</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
<td></td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>finish</td>
<td></td>
</tr>
</tbody>
</table>

**Topotecan 1.5mg/m²/day short infusion days 1-5**

- Dose reduce topotecan to 0.05mg/kg if body weight ≤12kg

**Vincristine 1mg/m²/day (maximum dose 1 mg/day) 48 hour-continuous infusion Days 5-6 (starting 1 hour after the last topotecan infusion)**

- Dose reduce vincristine to 0.033mg/kg if body weight ≤12kg

**Doxorubicin 22.5mg/m²/day 48 hour-continuous infusion Days 5-6 (starting 1 hour after the last topotecan infusion)**

- Dose reduce doxorubicin to 0.75mg/kg if body weight ≤12kg
- Each course to be given at 21 day intervals
- Topotecan, vincristine and doxorubicin to be given when absolute neutrophil count >1.0x10⁹/L and platelets >100x10⁹/L or 50 if bone marrow involvement.
- Prophylactic G-CSF to be administered (starting 48 hours after the end of vincristine/doxorubicin infusion)
- Anti-emetics to be prescribed regularly for the duration of chemotherapy
- Prophylactic co-trimoxazole to be administered
- Evaluation should be carried out after 2 and 4 courses.
- If there is response or stable disease after 2 courses then a further 4 courses should be administered, dependent on cardiac function assessed after every 2 courses.

---

7 A further one third dose reduction is advised for infants ≤5kg. The dose can then be increased gradually following assessment of toxicity.
Oral etoposide (single agent)

**Etoposide 50mg/m² daily orally for 21 days**

Dose reduce etoposide to 1.67mg/kg if body weight ≤12kg

- Each course to be given at 28 day intervals subject to counts
- Dose adjustment may be required depending on bone marrow involvement and toxicity

Topotecan and cyclophosphamide

As per COG P9642 study (27). Note that these are lower doses than those currently used for induction chemotherapy for high-risk patients in the current COG protocols.

<table>
<thead>
<tr>
<th>Days</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topotecan</td>
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<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>●</td>
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<td>●</td>
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</table>

**Topotecan 0.75mg/m²/day short infusion days 1-5**

Dose reduce topotecan to 0.025mg/kg if body weight ≤12kg

**Cyclophosphamide 250mg/m²/day short infusion days 1-5**

Dose reduce cyclophosphamide to 8.3mg/kg if body weight ≤12kg

- Each course to be given on a 21-day cycle
- Topotecan and cyclophosphamide to be given when absolute neutrophil count >0.75x10⁹/L and platelets >75x10⁹/L (may be adjusted for patients with bone marrow involvement)
- 2hr pre/post hydration (125ml/m²/hr) for cyclophosphamide is recommended; mesna is not normally required
- Prophylactic G-CSF to be administered (starting on day 6)
Topotecan and temozolomide (TOTEM)

As per SIOPEN/ITCC Phase II study (19).

<table>
<thead>
<tr>
<th>Days</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temozolomide</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Topotecan</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

**Temozolomide 150mg/m²/day orally days 1-5**, followed by

Dose reduce temozolomide to 5mg/kg if body weight ≤12kg

**Topotecan 0.75mg/m²/day 30 minute IV infusion days 1-5**

Dose reduce topotecan to 0.025mg/kg if body weight ≤12kg

- Each course to be given on a 28-day cycle, when absolute neutrophil count >0.75x10⁹/L and platelets >75x10⁹/L (may be adjusted for patients with bone marrow involvement)
APPENDIX 3 – $^{131}$I-MIBG THERAPY

$^{131}$I-mIBG therapy is currently available in a non-trial setting at UCLH and the Royal Marsden Hospitals in the UK.

Administration of $^{131}$I-mIBG requires a patient to be isolated in a special lead-lined treatment room (which appears as a normal hospital side-room) until such time as the radioactive iodine has been excreted from the body, and their radiation level is low enough for them to be around other people. Typically, two $^{131}$I-mIBG administrations are given two weeks apart, so the inpatient stay may be up to four weeks, although patients may be allowed out (with restrictions on using public transport and being around other children and/or pregnant women) or to go home in weeks 2 and 4 depending on individual circumstances. Whilst in isolation, contact with ‘comforters and carers’ is kept to a reasonable minimum, and those needing to enter the room must carry a measuring device so their own cumulative levels of radiation exposure can be monitored.

Treatment is usually well-tolerated with minimal acute side-effects. The primary toxicity is myelosuppression. In the UK, $^{131}$I-mIBG therapy is typically administered according to the ‘MATIN’ schedule (33,34) in which administration of $^{131}$I-mIBG is combined with topotecan as a radiosensitizer. The cumulative myelosuppression of this combination requires autologous stem cell rescue and this is an important consideration in determining patient suitability for $^{131}$I-mIBG therapy.

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APPENDIX 4 – ADDITIONAL EXPERIMENTAL APPROACHES IN THE UK

There is a wide range of early phase clinical trials open for children and young people with neuroblastoma in the UK. Slots within these trials open and close rapidly as patients are recruited competitively at international level and a limited number of patients are enrolled in each dose cohort. Also they are open at a variable number of centres in the UK, however open centres are very willing and enthusiastic about accepting patients from anywhere in the UK and there are clear referral networks.

As of February 2015 the following early phase clinical trials are open:

For Anaplastic lymphoma kinase (ALK) mutated or amplified neuroblastoma

- **LDK378**
  A phase I, open-label, dose escalation study of LDK378 in paediatric patients with malignancies that have a genetic alteration in anaplastic lymphoma kinase (ALK). LDK378 (Ceritinib) is a novel ALK-inhibitor, more potent and specific than first generation ALK-inhibitors, such as crizotinib. ALK mutations occur in 8.5% and ALK amplification (more than 10 copies) occurs in 1.5% of neuroblastomas at presentation. LDK378 is given orally once daily. Capsules can be open for patients not able to swallow them or for administration via nasogastric/gastric tube.

For all neuroblastomas

- **Regorafenib**
  A phase 1, multi-centre, open-label, non-randomized, dose escalation design study of regorafenib (BAY 73-4506) in paediatric patients from 6 months to less than 18 years with a solid malignant tumour refractory to standard therapy. Regorafenib is a multi-tyrosine kinase inhibitor with anti-angiogenic activity due to its dual targeted VEGFR2-TIE2 inhibition. Neuroblastoma is a highly vascular tumour. Furthermore, high expression of VEGF A and B has been associated with poor prognosis. Strong preclinical evidence suggests that angiogenesis inhibition with different tyrosine kinase inhibitors or monoclonal antibodies produces anti-tumour responses in vitro and in vivo. Regorafenib is administered orally once daily and is available in tablets and granulate formulation.

- **Volasertib**
  An open, dose finding Phase I trial to investigate the paediatric dose, tolerability and pharmacokinetics of single and multiple doses of volasertib in children with relapsed or refractory acute leukaemia or advanced solid tumours. Volasertib is a polo-like kinase 1 inhibitor. Mitotic kinases of the Polo family have been identified as important regulators of cell division and its checkpoints. Preclinical data in paediatric tumour models indicate a potential inhibitory effect of volasertib on tumour growth in several solid tumours in childhood, including neuroblastoma. Volasertib is administered intravenously over 1 hour every 2 weeks.

- **Lenvatinib**
  Phase 1/2 Study of Lenvatinib in Children and Adolescents with Refractory or Relapsed Solid Malignancies in paediatric patients from 12 years to less than 18 years. Lenvatinib is a multi-tyrosine kinase inhibitor targeting the VEGFR-pathway.
Neuroblastoma is a highly vascular tumour. Furthermore, high expression of VEGF A and B has been associated with poor prognosis. Strong preclinical evidence suggests that angiogenesis inhibition with different tyrosine kinase inhibitors or monoclonal antibodies produces anti-tumour responses in vitro and in vivo. Lenvatinib is administered orally once daily and is available in capsules.

- **Abraxane (nab-paclitaxel)**
  A phase I/II, multicenter, open-label, dose-finding study to assess the safety, tolerability, and preliminary efficacy of weekly nab-paclitaxel (Abraxane) in paediatric patients with recurrent or refractory solid tumours, excluding primary or metastatic brain tumours. Abraxane is a human albumin bound nanoparticle formulation of paclitaxel. Taxanes are microtubule-stabilizing agents with demonstrated efficacy in a wide range of adult tumours. Preclinical studies have demonstrated activity of nab-paclitaxel in neuroblastoma models in vitro and in vivo. Abraxane is administered intravenously over 30 minutes weekly in a 3 week-on 1 week-off schedule.

The following early phase clinical trials are expected to open in the next 3-4 months:

- **Pembrolizumab**
  A Phase I/II Study of MK-3475 (Pembrolizumab) in children with advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumour (including primary CNS tumours) or lymphoma. Pembrolizumab is a potent and highly selective humanized monoclonal antibody directed to block the interaction between programmed cell death-1 (PD-1) and programmed cell death ligands 1 and 2 (PD-L1 and PD-L2).
  In tumour cells, the PD-1 pathway may be engaged by tumour cells to overcome active T-cell immune surveillance. Surface expression of PD-L1 has been speculated to impair host immune responses and instead facilitate tumour progression by diminishing the efficacy of an immunologic anti-tumour attack. Pembrolizumab will be administered intravenously over 30 minutes every 3 weeks.

- **Trametinib**
  An open-label, dose-escalation, phase I/II study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of the MEK Inhibitor Trametinib in children and adolescents with cancer or plexiform neurofibromas and Trametinib in combination with Dabrafenib in children and adolescents with cancers harbouring V600 mutations. Trametinib is a MEK-1 and 2 inhibitor. Trametinib inhibit the MAPK/ERK pathway implicated in cell growth and proliferation.
  A subgroup of neuroblastomas in vitro respond to MEK inhibition Trametinib and dabrafenib are orally available.

- **Afatinib**
  Phase I open label, dose escalation trial to determine the MTD, safety, PK and efficacy of afatinib monotherapy in children aged 2 years to <18 years with recurrent/refractory neuroectodermal tumours, rhabdomyosarcoma and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology. Afatinib is a tyrosine-kinase inhibitor targeting the epidermal growth factor receptor (EGFR) pathway. EGFR signalling cascades involve the PI3K/AKT/mTOR and the MAPK/ERK pathways. Afatinib is orally available.
APPENDIX 5 - ADDITIONAL EXPERIMENTAL APPROACHES (NON-UK)

The following list provides brief information about neuroblastoma-specific studies currently available overseas. All such therapies are experimental and participation can not therefore be recommended as a matter of routine. Information is provided to aid with answering family enquiries.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Collaborative group</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab, cyclophosphamide and zoledronic acid</td>
<td>NANT</td>
<td>Phase I study for recurrent/refractory high-risk neuroblastoma, combining cytotoxic chemotherapy with anti-angiogenic agent (Avastin®) and the bisphosphonate zoledronic acid (a potential immunomodulator)</td>
</tr>
<tr>
<td>Zoledronic acid and IL2</td>
<td>University of Alabama</td>
<td>Phase I study in refractory neuroblastoma</td>
</tr>
<tr>
<td>Fenretinide, ketoconazole and vincristine</td>
<td>South Plains Oncology Consortium</td>
<td>Phase I study for recurrent/refractory high-risk neuroblastoma using ketoconazole to increase the exposure to retinoids (fenretinide)</td>
</tr>
<tr>
<td>Dasatinib, rapamycin, irinotecan and temozolomide (RIST)</td>
<td>University of Regensburg, Germany</td>
<td>Phase II for relapsed/refractory high-risk neuroblastoma. Combination of mTOR inhibitor, multi-kinase inhibitor and conventional chemotherapy. The benefits of the addition of these agents to cytotoxic chemotherapy has not yet been demonstrated.</td>
</tr>
<tr>
<td>Lenalidomide and anti-GD2 antibody</td>
<td>National Cancer Institute</td>
<td>Phase I study in patients with relapsed/refractory high-risk neuroblastoma. Lenalidomide is being tested as a potential immunomodulatory agent.</td>
</tr>
<tr>
<td>Hu3F8</td>
<td>MSKCC</td>
<td>Phase I for patients with high-risk neuroblastoma of humanised version of murine anti-GD2 antibody, 3F8.</td>
</tr>
<tr>
<td>Difluoromethylornithine (DFMO) and celecoxib with cyclophosphamide/ topotecan</td>
<td>NANT</td>
<td>Phase I study for recurrent/refractory high-risk neuroblastoma. DFMO is an inhibitor of ODC1 (a MYCN target gene), the rate-limiting enzyme in the synthesis of polyamines. Preclinical evidence suggests possible synergy with celecoxib (COX2 inhibitor). NB: this study is distinct from the NMTRC single agent Phase II study of DFMO which is for patients in remission only.</td>
</tr>
<tr>
<td>Difluoromethylornithine (DFMO) and bortezomib</td>
<td>NMTRC</td>
<td>Phase I study of DFMO (see above) in combination with bortezomib (proteasome inhibitor)</td>
</tr>
<tr>
<td>Vaccine study (bivalent vaccine with OPT-821 adjuvant and oral β glucan)</td>
<td>MSKCC</td>
<td>Phase I/II study for patients with relapsed high-risk neuroblastoma who have achieved second (or subsequent) remission (CR or VGPR)</td>
</tr>
<tr>
<td>Molecularly engineered cytotoxic T-cells</td>
<td>Various</td>
<td>Several different early phase studies are underway or in preparation using molecularly engineered cytotoxic T-cells (typically directed against GD2) to treat relapse neuroblastoma. For example at National Cancer Institute, Seattle Children’s Hospital and Texas Children’s Hospital. A trial for anti-GD2 CAR T-cells is currently under development at Great Ormond Street Hospital, UK.</td>
</tr>
</tbody>
</table>

MSKCC: Memorial Sloan Kettering Cancer Center, New York
Haploidentical bone marrow transplantation

A synergistic effect of H-BMT and immunotherapy has been hypothesised, but no clinical results in neuroblastoma have yet been published. A clinical trial in Tübingen, Germany includes KIR-mismatched haplo-BMT as a conditioning regime (after initial re-induction chemotherapy and therapeutic mIBG), plus Ch14.18 anti-GD2 mAb and IL-2 following haplo-BMT. Preliminary data reported at ANR 2014 by Prof Peter Lang have shown that the approach is feasible and can be delivered to children with relapsed neuroblastoma with manageable toxicity (GvHD in only 1 of 34 patients). Evidence of added efficacy compared to other strategies still needs to be demonstrated.
REFERENCES


