

# Bevacizumab, Irinotecan, or Topotecan Added to Temozolomide for Children With Relapsed and Refractory Neuroblastoma: Results of the ITCC-SIOPEN BEACON-Neuroblastoma Trial

Lucas Moreno, MD, PhD<sup>1</sup> ; Rebekah Weston, MSc<sup>2</sup> ; Cormac Owens, MD<sup>3</sup>; Dominique Valteau-Couanet, MD<sup>4</sup>; Marion Gambart, MD<sup>5</sup> ; Victoria Castel, MD, PhD<sup>6</sup> ; C. Michel Zwaan, MD, PhD<sup>7</sup> ; Karsten Nysom, MD, PhD<sup>8</sup> ; Nicolas Gerber, MD<sup>9</sup> ; Aurora Castellano, MD<sup>10</sup>; Genevieve Laureys, MD, PhD<sup>11</sup>; Ruth Ladenstein, MD, PhD<sup>12</sup> ; Jochen Rössler, MD<sup>13</sup>; Guy Makin, MD<sup>14</sup> ; Dermot Murphy, MD<sup>15</sup>; Bruce Morland, MD<sup>16</sup>; Sucheta Vaidya, MD<sup>17</sup> ; Estelle Thebaud, MD<sup>18</sup>; Natasha van Eijkelenburg, MD, PhD<sup>19</sup> ; Giuseppe Barone, MD, PhD<sup>20</sup> ; Julie Tandonnet, MD<sup>21</sup> ; Nadege Corradini, MD<sup>22</sup> ; Pascal Chastagner, MD, PhD<sup>23</sup> ; Catherine Paillard, MD<sup>24</sup> ; Francisco J. Bautista, MD, PhD<sup>7</sup> ; Soledad Gallego Melcon, MD, PhD<sup>1</sup> ; Bram De Wilde, MD, PhD<sup>11</sup> ; Lynley Marshall, PhD, MB, BCH<sup>17</sup>; Juliet Gray, MD, PhD<sup>25</sup>; Susan A. Burchill, PhD<sup>26</sup> ; Gudrun Schleiermacher, MD, PhD<sup>27</sup> ; Louis Chesler, MD, PhD<sup>17</sup>; Andrew Peet, MD, PhD<sup>16</sup> ; Martin O. Leach, PhD<sup>17</sup>; Kieran McHugh, MD<sup>20</sup>; Roisin Hayes, MD<sup>3</sup>; Neil Jerome, PhD<sup>17</sup> ; Hubert Caron, MD, PhD<sup>28</sup>; Jennifer Laidler, BSc<sup>2</sup>; Nicola Fenwick, BSc<sup>2</sup>; Grace Holt, MSc<sup>2</sup>; Veronica Moroz, MSc<sup>2</sup>; Pamela Kearns, MD, PhD<sup>2</sup> ; Simon Gates, PhD<sup>2</sup>; Andrew D.J. Pearson, MD<sup>17</sup> ; and Keith Wheatley, DPhil<sup>2</sup>; on behalf of Innovative Therapies for Children with Cancer (ITCC) and European Association for Neuroblastoma Research (SIOPEN)

DOI <https://doi.org/10.1200/JCO.23.00458>

## ABSTRACT

**PURPOSE** Outcomes for children with relapsed and refractory high-risk neuroblastoma (RR-HRNB) remain dismal. The BEACON Neuroblastoma trial (EudraCT 2012-000072-42) evaluated three backbone chemotherapy regimens and the addition of the antiangiogenic agent bevacizumab (B).

**MATERIALS AND METHODS** Patients age 1–21 years with RR-HRNB with adequate organ function and performance status were randomly assigned in a 3 × 2 factorial design to temozolomide (T), irinotecan-temozolomide (IT), or topotecan-temozolomide (TTo) with or without B. The primary end point was best overall response (complete or partial) rate (ORR) during the first six courses, by RECIST or International Neuroblastoma Response Criteria for patients with measurable or evaluable disease, respectively. Safety, progression-free survival (PFS), and overall survival (OS) time were secondary end points.

**RESULTS** One hundred sixty patients with RR-HRNB were included. For B random assignment (n = 160), the ORR was 26% (95% CI, 17 to 37) with B and 18% (95% CI, 10 to 28) without B (risk ratio [RR], 1.52 [95% CI, 0.83 to 2.77]; P = .17). Adjusted hazard ratio for PFS and OS were 0.89 (95% CI, 0.63 to 1.27) and 1.01 (95% CI, 0.70 to 1.45), respectively. For irinotecan (II; n = 121) and topotecan (n = 60) random assignments, RRs for ORR were 0.94 and 1.22, respectively. A potential interaction between I and B was identified. For patients in the bevacizumab-irinotecan-temozolomide (BIT) arm, the ORR was 23% (95% CI, 10 to 42), and the 1-year PFS estimate was 0.67 (95% CI, 0.47 to 0.80).

**CONCLUSION** The addition of B met protocol-defined success criteria for ORR and appeared to improve PFS. Within this phase II trial, BIT showed signals of antitumor activity with acceptable tolerability. Future trials will confirm these results in the chemoimmunotherapy era.

## ACCOMPANYING CONTENT

-  Appendix
-  Data Supplement
-  Protocol

Accepted October 5, 2023

Published January 8, 2024

J Clin Oncol 42:1135-1145

© 2024 by American Society of Clinical Oncology



View Online  
Article

Licensed under the Creative Commons Attribution 4.0 License

## INTRODUCTION

Neuroblastoma remains one of the main causes of death from childhood cancer. Despite many targeted and novel therapies being evaluated over the past decades and improvements in frontline therapy, long-term outcomes

remain poor, with 5-year survival below 20% for children with refractory/relapsed disease.<sup>1–5</sup>

Second-line chemotherapy regimens have been evaluated over the past 20 years reporting a wide range of response rates (0%–64%<sup>2,6,7</sup>), with little data about survival outcomes

## CONTEXT

### Key Objective

New therapeutic combinations are urgently needed for children with relapsed and refractory neuroblastoma.

### Knowledge Generated

The trial used a novel factorial multiarm multistage platform design to test multiple questions and has become the largest randomized trial in this setting. Three temozolomide (T)-based chemotherapy regimens and the addition of the anti-vascular endothelial growth factor bevacizumab (B) were tested.

### Relevance (S. Bhatia)

The addition of B to T-based chemotherapy improved best overall response rate in patients with high-risk relapsed/refractory neuroblastoma. An interaction between irinotecan and B is providing evidence for future studies that will compare irinotecan-T and B with a chemo-immunotherapy regimen in this population.\*

\*Relevance section written by JCO Associate Editor Smita Bhatia, MD, MPH, FASCO.

and, importantly, lack of clarity regarding comparative benefits, with only one trial being randomized.<sup>8</sup> Cooperative groups have developed several temozolomide (T)-based backbone regimens where novel drugs could be added.<sup>9-11</sup>

Antiangiogenic therapies are used in multiple adult cancer indications, although, to our knowledge, to date, none has demonstrated clear benefit in pediatric cancers.<sup>12-14</sup> Pre-clinical in vitro and in vivo data of bevacizumab (B; a monoclonal antibody against vascular endothelial growth factor [VEGF]) as single agent and in combination, including irinotecan-temozolomide (IT) as well as other anti-VEGF therapies, support the evaluation of antiangiogenic agents in neuroblastoma.<sup>15-22</sup> B is among the most established of antiangiogenic drugs and has gained approval in many adult indications.

The BEACON-Neuroblastoma trial opened in 2013 with two main aims: to identify the best backbone chemotherapy regimen on which to add new targeted therapies (T, IT, or topotecan-temozolomide [TTo]) and to establish the role of the addition of B in children with refractory/relapsed neuroblastoma within a randomized phase II trial.

## MATERIALS AND METHODS

### Patients

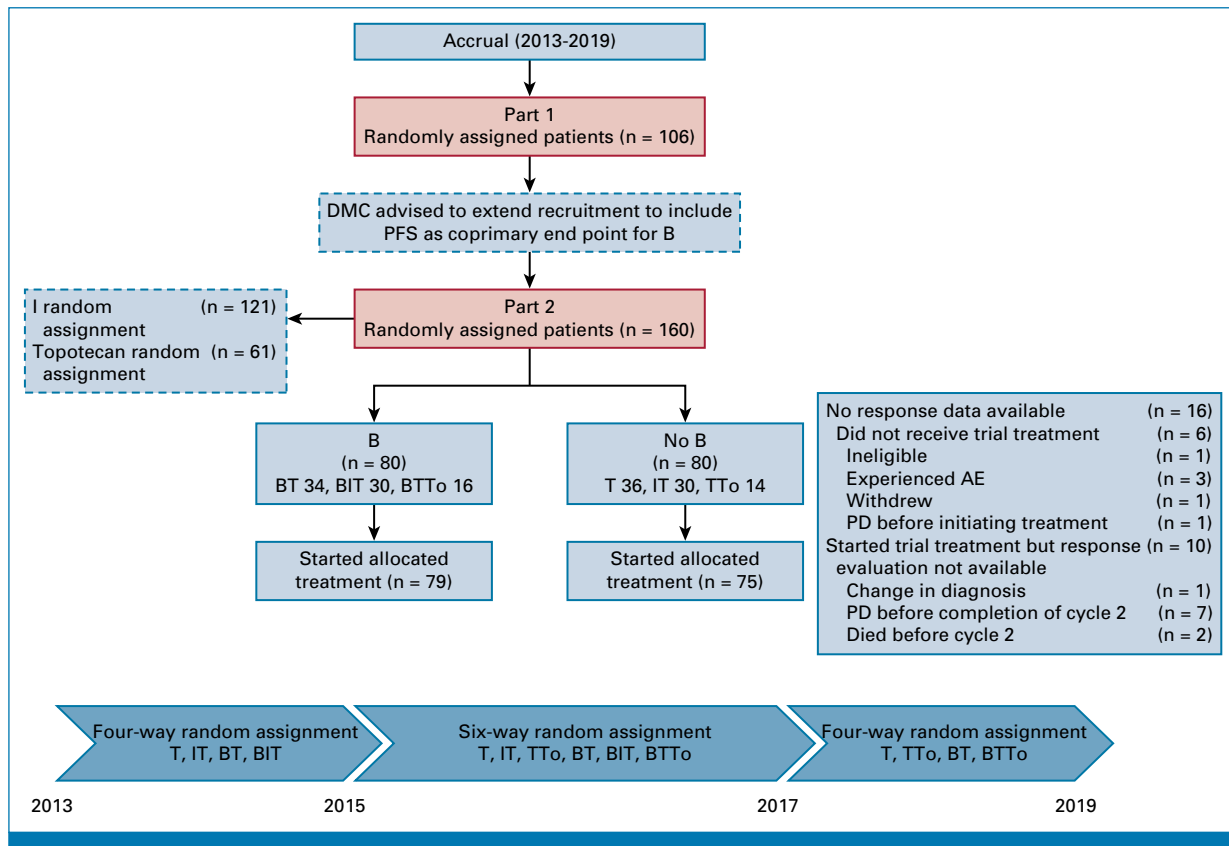
Eligible patients were age 1 to 21 years with confirmed diagnosis of high-risk neuroblastoma. Disease status was relapsed or refractory to frontline therapy. Refractory disease was defined as lack of adequate response to frontline therapy using European Neuroblastoma Research Network (SIOPEN) criteria used at the time of enrollment: persistence of three or more spots on metaiodobenzylguanidine (I<sup>123</sup> MIBG) scan (with or without persistence of bone marrow disease). Measurable (as per RECIST 1.1<sup>23</sup>) or evaluable

disease (uptake on I<sup>123</sup> MIBG scan) was required. Previous treatment with T, I, or B was not allowed. Patients with only bone marrow detectable disease were not eligible.

Eligible patients had adequate performance status, organ and bone marrow function, and appropriate wash out periods for previous therapies. Full eligibility criteria are provided in the trial protocol, available as Data Supplement (online only). All patients, parents, and/or legal guardians provided written informed consent. Assent was sought from minors where appropriate.

### Trial Design and Interventions

BEACON-Neuroblastoma (ITCC-032; ClinicalTrials.gov identifier: [NCT02308527](https://clinicaltrials.gov/ct2/show/study/NCT02308527); EudraCT 2012-000072-42) was an open-label, randomized phase II trial. The trial was started with a 2 × 2 factorial design, in which patients were randomly assigned to two chemotherapy regimens (T alone or IT), with or without B (bevacizumab-temozolomide [BT] and bevacizumab-irinotecan-temozolomide [BIT]). The allocation ratio was 1:1:1:1. In 2015, after release of results of the Innovative Therapies for Children with Cancer (ITCC) phase II trial of TTo,<sup>11</sup> the trial was amended to evaluate a third chemotherapy regimen (TTo), and the design was changed to a 3 × 2 factorial trial (allocation ratio 1:1:1:1:1). Subsequently, when the accrual target for the IT arm was reached, the trial reverted to a 2 × 2 factorial design. Trial arms and details of chemotherapy doses are depicted in [Figure 1](#) and Data Supplement (Table S1). The following minimization factors were used to balance all random assignments: (1) disease status (early relapse [defined as <18 months from the time of diagnosis] and late relapse [≥18 months] and refractory) and (2) measurable versus evaluable disease (as per RECIST v1.1). Interactions between treatment arms (ie, I and B) were not anticipated but were to be explored at trial completion using heterogeneity tests.



**FIG 1.** CONSORT diagram of the BEACON Neuroblastoma trial. AE, adverse event; B, bevacizumab; BT, bevacizumab-temozolomide; BIT, bevacizumab-irinotecan-temozolomide; BTT<sub>0</sub>, bevacizumab-topotecan-temozolomide; DMC, Data Monitoring Committee; I, irinotecan; IT, irinotecan-temozolomide; PD, progressive disease; PFS, progression-free survival; T, temozolomide; TT<sub>0</sub>, topotecan-temozolomide.

Trial treatment was given for six cycles. Patients with acceptable toxicities and response equal to or better than stable disease after six cycles were allowed to continue trial treatment for 12 cycles.

### Outcome Measures and Assessments

The primary outcome measure was initially overall response (complete or partial response) during the first six courses of trial therapy, evaluated locally at trial sites. Response was evaluated using RECIST 1.1 for patients with measurable disease.<sup>23</sup> For those with only evaluable disease, response was evaluated using the new draft International Neuroblastoma Response Criteria including data on MIBG scores and bone marrow disease, which were subsequently published.<sup>24</sup>

After completing planned recruitment for the first 106 patients and meeting the trial-defined success criteria, the Independent Data Monitoring Committee (IDMC) recommended expansion of the B random assignment to 160 patients to include progression-free survival (PFS) as a coprimary outcome measure.

Secondary outcome measures were toxicity of the regimens (per Common Terminology Criteria Adverse Events v4.0), PFS, and overall survival (OS).

Response was evaluated at baseline and every two cycles using cross-sectional imaging with computed tomography/magnetic resonance imaging and I<sup>123</sup> MIBG scans (or fluorodeoxyglucose-positron emission tomography scans if non-MIBG avid). Bilateral bone marrow aspirates and trephine biopsies were mandatory at baseline and repeated every two cycles in patients with bone marrow involvement at study entry or clinical suspicion of progression. All patients underwent mandatory imaging of the brain before study entry.

### Trial Design and Statistical Analysis

Efficacy data were analyzed on an intention-to-treat basis, and safety data were reported for all patients who received at least one dose of a trial drug. Trial sample size was calculated to detect a 15% increase in response rate with B. Assuming a baseline overall response rate (ORR) of 25% without B, using a two-stage Minimax Jung design with  $\alpha$  and  $\beta$  errors set to .2, 42 patients per arm were required for the first stage and 53 patients per arm were required in total. Predefined success criteria for the trial were  $\geq 4$  more responses in the B arm compared with the non-B arm. Allowing for patients with response not assessed, the planned sample size was  $n = 120$ . Following a recommendation of the study IDMC, the B random assignment was then expanded to include PFS as

coprimary end point: Assuming 40% PFS at 1 year in the control arm, with 160 patients and 80 events in total, there will be 80% power to detect a difference of 15% with a Cox proportional hazards model using a one-sided test with  $\alpha = .15$ . All statistical analyses performed were predefined in the BEACON Statistical Analysis Plan.

For the primary end point of PFS for the expanded B random assignment, an adjusted hazard ratio (HR) with 95% CI was produced using a Cox proportional hazards model stratified for the other treatment allocation (I or topotecan or neither). The posterior probability distribution was then plotted for PFS, using a noninformative prior, on the basis of the HR calculated from the Cox model and the number of events observed.

For all random assignments, response was a primary end-point. For response, risk ratios (RRs) with 95% CIs were calculated using logistic regression to compare responses (complete response/partial response) between arms for each random assignment. For the chemotherapy random assignments, Bayesian Beta-Binomial conjugate analyses were used to compare treatments by derived posterior distributions for the RR. Data in each arm are assumed to follow binomial distribution. A uniform prior  $\beta$  (1, 1) was used for the analysis. These plots are available to view in the Data Supplement (Figs S1-S3).

Toxicity, PFS, and OS were secondary end points. Toxicity was analyzed descriptively by presenting grade  $\geq 3$  adverse events (AEs) in each random assignment and those occurring in  $\geq 1\%$  of patients. Adjusted HRs with CI for the treatment effect for both PFS and OS outcomes were produced by implementing a Cox proportional hazards regression model for each treatment group (ie, for B and non-B, IT v T, and TTo v T), stratified for other treatment allocation. Kaplan-Meier survival curves were then produced for PFS and OS and survival estimates at 6, 12, and 24 months, and median survival time with 95% CIs was calculated. Heterogeneity tests in the form of forest plots were used for the PFS and OS outcomes to assess any potential interaction between arms (Data Supplement, Fig S1). Clinical trial protocol and statistical analysis plan are available as Data Supplement.

### Trial Oversight

This trial was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The trial obtained first competent authority and ethics committee approval in the United Kingdom (West Midlands—Coventry & Warwickshire Research Ethics Committee, reference 13/WM/0023) and then obtained competent authority and ethics committee approval in all the countries where it opened. The trial was designed by the Trial Management Group and the sponsor, the University of Birmingham, in collaboration with investigators from the ITCC and SIOPEN cooperative groups. Roche provided B supply and distribution. The authors attest to the accuracy

and completeness of the data and the fidelity of the trial to the protocol. The trial was registered before the first patient recruited on April 24, 2013 (ISRCTN40708286; Eudract2012-000072-42; ClinicalTrials.gov identifier: [NCT02308527](#)).

## RESULTS

### Screening and Random Assignment

Between July 8, 2013, and February 7, 2019, a total of 160 eligible patients were randomly assigned from 43 sites in 10 European countries (sites are detailed in Appendix [Table A1](#), online only): T (36), IT (30), TTo (14), BT (34), BIT (30), and BTTo (16). One hundred sixty patients were included in the B random assignment, 121 in the I random assignment, and 61 in the topotecan random assignment. [Figure 1](#) depicts the trial CONSORT diagram.

### Patient Characteristics and Treatments

Age at enrollment ranged from 1 to 21 years (median, 5; range, 1-21). Baseline characteristics and prior therapies are depicted in [Table 1](#) and the Data Supplement (Tables S2-S4): 93 patients (58%) had relapsed and 67 (42%) had refractory disease; 111 (69%) had measurable and 49 (31%) evaluable disease at study entry; 36 (23%) had tumors with MYCN amplification, and 64 (40%) had prior anti-GD2 immunotherapy.

The median follow-up for survivors was 1.5 years (IQR, 0.7-3.2 years; Data Supplement, Fig S2). Sixteen (10%) patients had response not evaluable and were considered nonresponders. Of them, six patients did not receive study treatment: one was ineligible post-random assignment, one experienced an AE, three withdrew from the study, and one patient progressed before treatment started. For the 10 patients who received study treatment, one patient had an unexpected change in diagnosis at cycle 2, six patients progressed before cycle 2 and one patient at cycle 2, and two patients died before cycle 2. For the present analysis, all 16 patients with response not assessed are considered nonresponders.

### B Random Assignment (T, IT, TTo v BT, BIT, BTTo)

Objective responses were seen in 21 of 80 patients (ORR, 26% [95% CI, 17 to 37]) in the B arms, and in 14 of 80 patients (ORR, 18% [95% CI, 10 to 28]) in the non-B arms ([Table 2](#)), the RR was 1.52 (95% CI, 0.83 to 2.77;  $P = .17$ ). The predefined success criterion for ORR of  $P < .2$  was met.

The HR for PFS was 0.89 (95% CI, 0.63 to 1.27). The 1-year PFS in the B arms was 0.46 (95% CI, 0.34 to 0.56) compared with 0.38 (95% CI, 0.27 to 0.49) in the non-B arms. PFS and OS for all random assignments and arms are shown in [Figure 2](#).

The HR for OS was 1.01 (95% CI, 0.70 to 1.45). The 1-year OS was 0.69 (95% CI, 0.57 to 0.77) for B arms compared with 0.58 (95% CI, 0.47 to 0.68) for non-B arms.

**TABLE 1. Patient Characteristics for the B Randomization**

| Characteristic                                                   | B (n = 80) | Non-B (n = 80) | Overall (N = 160) |
|------------------------------------------------------------------|------------|----------------|-------------------|
| Age, years, median (range)                                       | 5 (1-21)   | 5 (1-18)       | 5 (1-21)          |
| Age, No. (%)                                                     |            |                |                   |
| <2                                                               | 4 (5)      | 5 (6)          | 9 (5)             |
| 2 to <6                                                          | 38 (47)    | 43 (54)        | 81 (51)           |
| 6 to <12                                                         | 28 (35)    | 28 (35)        | 56 (35)           |
| 12 to <18                                                        | 7 (9)      | 3 (4)          | 10 (6)            |
| >18                                                              | 3 (4)      | 1 (1)          | 4 (3)             |
| Initial INSS stage, No. (%)                                      |            |                |                   |
| 1                                                                | 1 (1)      | 1 (1)          | 2 (1)             |
| 2                                                                | 3 (4)      | 0 (0)          | 3 (2)             |
| 3                                                                | 4 (5)      | 6 (7.5)        | 10 (6)            |
| 4                                                                | 68 (85)    | 69 (86)        | 137 (86)          |
| 4S                                                               | 2 (2.5)    | 2 (2.5)        | 4 (2.5)           |
| NA                                                               | 0 (0)      | 1 (1)          | 1 (0.5)           |
| Not known                                                        | 2 (2.5)    | 1 (1)          | 3 (2)             |
| MYCN amplification, No. (%)                                      |            |                |                   |
| Present                                                          | 20 (25)    | 16 (20)        | 36 (22)           |
| Absent                                                           | 58 (72)    | 62 (77)        | 120 (75)          |
| Unknown                                                          | 2 (3)      | 2 (3)          | 4 (3)             |
| Induction chemotherapy, No. (%)                                  |            |                |                   |
| COJEC                                                            | 25 (31)    | 21 (26)        | 46 (29)           |
| N7                                                               | 5 (6)      | 4 (5)          | 9 (5)             |
| TVD (after induction)                                            | 16 (20)    | 11 (14)        | 27 (17)           |
| Other                                                            | 14 (18)    | 12 (15)        | 26 (16)           |
| Missing                                                          | 20 (25)    | 32 (40)        | 52 (33)           |
| Prior major surgery, No. (%)                                     | 58 (73)    | 53 (66)        | 111 (69)          |
| High-dose chemotherapy with autologous stem-cell rescue, No. (%) | 47 (59)    | 46 (58)        | 93 (58)           |
| Prior radiotherapy, No. (%)                                      | 42 (53)    | 44 (55)        | 86 (54)           |
| Prior anti-GD2 therapy, No. (%)                                  | 32 (40)    | 32 (40)        | 64 (40)           |
| Performance status, No. (%)                                      |            |                |                   |
| Lansky                                                           |            |                |                   |
| 90-100                                                           | 58 (73)    | 63 (79)        | 121 (76)          |
| 70-80                                                            | 10 (12)    | 6 (8)          | 16 (10)           |
| 50-60                                                            | 5 (6)      | 2 (2)          | 7 (4)             |
| Missing                                                          | 7 (9)      | 9 (11)         | 16 (10)           |
| Karnofsky                                                        |            |                |                   |
| 90-100                                                           | 6 (7)      | 3 (4)          | 9 (6)             |
| 70-80                                                            | 2 (3)      | 2 (2)          | 4 (2)             |
| Missing                                                          | 72 (90)    | 75 (94)        | 147 (92)          |
| Disease status <sup>a</sup> , No. (%)                            |            |                |                   |
| Refractory                                                       | 34 (42)    | 33 (41)        | 67 (42)           |
| Early relapse                                                    | 31 (39)    | 32 (40)        | 63 (39)           |
| Late relapse                                                     | 15 (19)    | 15 (19)        | 30 (19)           |
| Disease evaluation at study entry, No. (%)                       |            |                |                   |
| Measurable disease                                               | 56 (70)    | 55 (69)        | 111 (69)          |
| Evaluable disease                                                | 24 (30)    | 25 (31)        | 49 (31)           |

Abbreviations: B, bevacizumab; COJEC, cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; INSS, International Neuroblastoma Staging System; I<sup>123</sup>-mIBG, metaiodobenzylguanidine; NA, not applicable; SIOPEN, European Neuroblastoma Research Network; TVD, topotecan, vincristine, doxorubicin.

<sup>a</sup>Refractory disease was defined using the SIOPEN definition at the time of trial conduct: persistence of three or more spots on I<sup>123</sup>. MIBG scan (with or without persistence of bone marrow disease). Early relapse was defined as those occurring <18 months from the time of diagnosis and late relapse those occurring ≥18 months from the time of diagnosis.

The posterior plot for PFS for the B random assignment derived from the HR, number of events, and a non-informative prior  $\beta$  (0.1, 0.1) is shown in the Data Supplement (Fig S3). The probability, given the data, of the true HR being  $<1$ , that is, in favor of B treatment, is 73%.

### I Random Assignment (T, BT v IT, BIT)

Objective responses were seen in 12 of 60 patients (ORR, 20% [95% CI, 11 to 32]) in the IT arms and 13 of 61 patients (ORR, 21% [95% CI, 12 to 34]) in the T arms (Table 2). The RR was 0.94 (95% CI, 0.47 to 1.89).

The HR for PFS was 0.59 (95% CI, 0.39 to 0.90) for patients in IT arms compared with those receiving T. The 1-year PFS was 0.53 (95% CI, 0.39 to 0.64) for IT arms compared with 0.30 (95% CI, 0.19 to 0.42) for patients receiving T only.

The HR for OS was 0.65 (95% CI, 0.43 to 0.99) for patients in IT arms compared with those receiving T. The 1-year OS was 0.70 (95% CI, 0.56 to 0.80) for IT arms compared with 0.58 (95% CI, 0.45 to 0.70) for patients receiving T only (Table 2).

A posterior distribution for the RR was derived by performing simulations on the number of responses and noninformative  $\beta$  (0.1, 0.1) prior for the I random assignment as shown in the Data Supplement (Fig S3). An RR of 0.939 (95% credible interval [CrI], 0.46 to 1.90) was obtained. A normal distribution curve is shown for comparison. The posterior probability of true RR  $>1.0$ , 1.2, 1.4, and 1.6 is presented.

### Topotecan Random Assignment (T, BT v TTo, BTTo)

Objective responses were seen in 8 of 30 patients (ORR, 27% [95% CI, 12 to 46]) in TTo arms and 7 of 31 patients (ORR, 23% [95% CI, 10 to 41]) in T arms. The RR was 1.22 (95% CI, 0.51 to 2.94).

The HR for PFS was 0.59 (95% CI, 0.33 to 1.08) for patients in TTo arms compared with those receiving T. The 1-year PFS was 0.47 (95% CI, 0.28 to 0.63) for patients receiving TTo compared with 0.23 (95% CI, 0.10 to 0.38) for patients in T arms.

The HR for OS was 0.80 (95% CI, 0.44 to 1.45) for patients in TTo arms compared with those receiving T. The 1-year OS was 0.60 (95% CI, 0.40 to 0.75) in TTo arms compared with 0.52 (95% CI, 0.33 to 0.67) in T arms.

A posterior distribution for the RR was derived by performing simulations on the number of responses and noninformative  $\beta$  (0.1, 0.1) prior for the topotecan random assignment as shown in the Data Supplement (Fig S3). An RR of 1.181 (95% CrI, 0.48 to 3.02) was obtained. A normal distribution curve is shown for comparison. The posterior probability of true RR  $>1.0$ , 1.2, 1.4, and 1.6 is presented.

### Potential Interactions

The trial design assumed no interaction between B and the different chemotherapy regimens. At trial completion, interactions were explored by heterogeneity tests. The unadjusted heterogeneity test for PFS showed some evidence of a potential interaction between irinotecan and B ( $P = .11$ ; Data Supplement, Fig S1A1), but not for OS nor for topotecan (Data Supplement, Figs S1A2 and S1B–S1K). PFS and OS for all treatment arms are shown in Figures 2G and 2H. One-year and 2-year PFS estimates for patients in the BIT arm were 0.67 (95% CI, 0.47 to 0.80) and 0.50 (95% CI, 0.31 to 0.66), respectively. One-year and 2-year OS estimates for patients in the BIT arm were 0.77 (95% CI, 0.57 to 0.88) and 0.73 (95% CI, 0.54 to 0.86), respectively. No formal statistical comparisons were planned between individual trial arms.

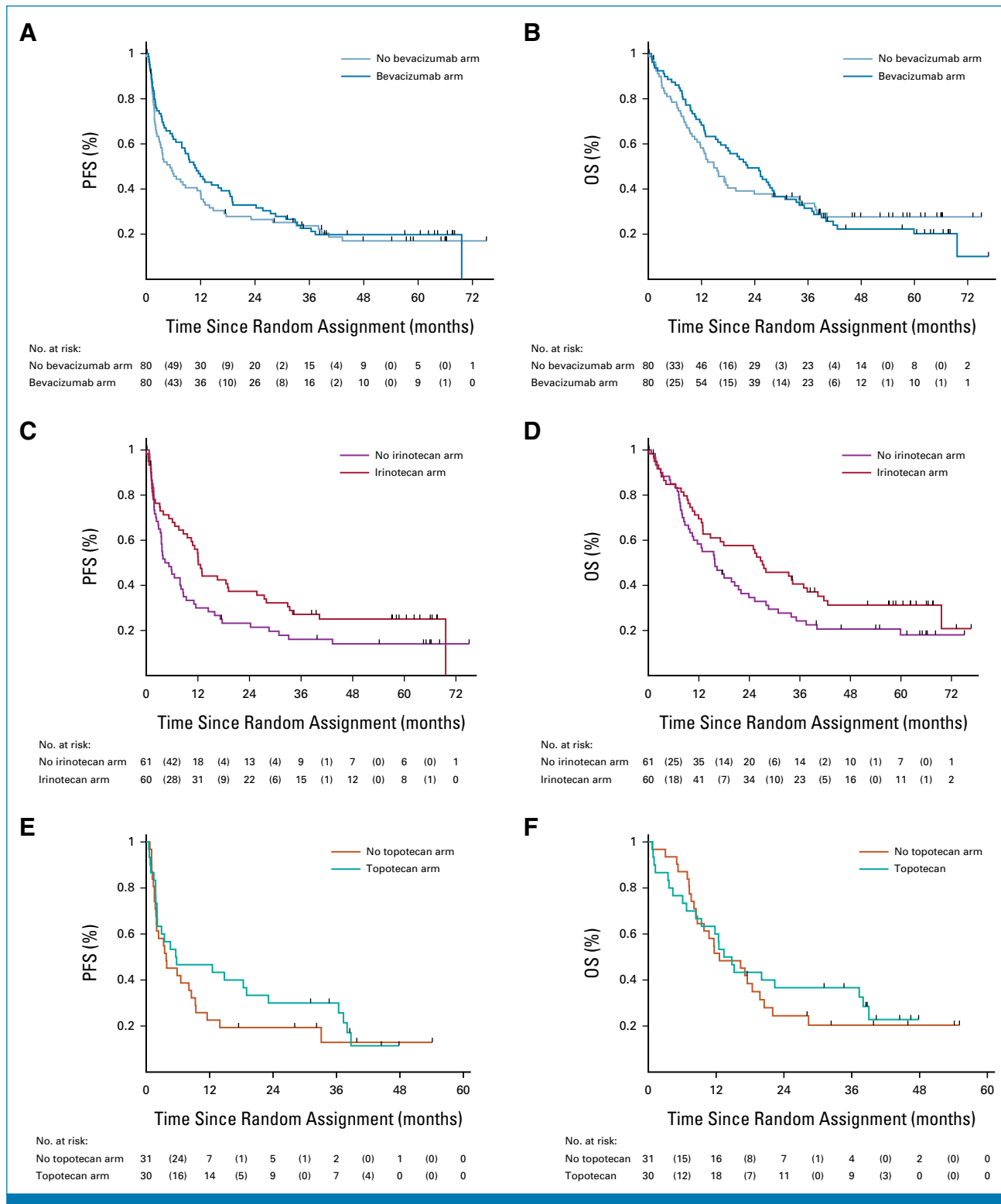
### Safety: B Random Assignment

Grade 3 or worse AEs are shown in Table 3 and the Data Supplement (Table S5). Patients receiving B experienced

**TABLE 2.** Evaluation of Best Response to Trial Treatment According to Each Random Assignment

| Response        | B Random Assignment, No. (%) |                            | I Random Assignment, No. (%) |                      | Topotecan Random assignment, No. (%) |                              |
|-----------------|------------------------------|----------------------------|------------------------------|----------------------|--------------------------------------|------------------------------|
|                 | B (BT, BIT, BTTo; n = 80)    | Non-B (T, IT, TTo; n = 80) | I (IT, BIT; n = 60)          | No I (T, BT; n = 61) | Topotecan (TTo, BTTo; n = 30)        | No Topotecan (T, BT; n = 31) |
| CR              | 6 (7)                        | 1 (1)                      | 4 (7)                        | 0 (0)                | 2 (7)                                | 1 (3)                        |
| PR              | 15 (19)                      | 13 (16)                    | 8 (13)                       | 13 (21)              | 6 (20)                               | 6 (19)                       |
| MR              | 2 (2)                        | 1 (1)                      | 3 (5)                        | 0 (0)                | 0 (0)                                | 0 (0)                        |
| SD              | 35 (44)                      | 32 (40)                    | 31 (51)                      | 25 (41)              | 9 (30)                               | 10 (33)                      |
| PD              | 15 (19)                      | 23 (29)                    | 10 (17)                      | 15 (25)              | 9 (30)                               | 11 (35)                      |
| Other/unknown   | 7 (9)                        | 10 (13)                    | 4 (7)                        | 8 (13)               | 4 (13)                               | 3 (10)                       |
| ORR, % (95% CI) | 26 (17 to 37)                | 18 (10 to 28)              | 20 (11 to 32)                | 21 (12 to 34)        | 27 (12 to 46)                        | 23 (10 to 41)                |

Abbreviations: B, bevacizumab; BIT, bevacizumab-irinotecan-temozolomide; BT, bevacizumab-temozolomide; BTTo, bevacizumab-topotecan-temozolomide; CR, complete response; I, irinotecan; IT, irinotecan-temozolomide; MR, minor response; ORR, overall response rate (complete + partial response); PR, partial response; PD, progressive disease; SD, stable disease; T, temozolomide; TTo, topotecan-temozolomide.



**FIG 2.** Survival analysis in the BEACON Neuroblastoma trial. Left panels show progression-free survival and right panels show overall survival. (A and B) Bevacizumab random assignment. (C and D) Irinotecan random assignment (T [no irinotecan] v IT [irinotecan]). (E and F) Topotecan random assignment (T [no topotecan] v TTo [topotecan]). (G and H) Survival for all trial arms. BT, bevacizumab-temozolomide; BIT, bevacizumab-irinotecan-temozolomide; BTTo, bevacizumab-topotecan-temozolomide; IT, irinotecan-temozolomide; OS, overall survival; PFS, progression-free survival; T, temozolomide; TTo, topotecan-temozolomide. (continued on following page)

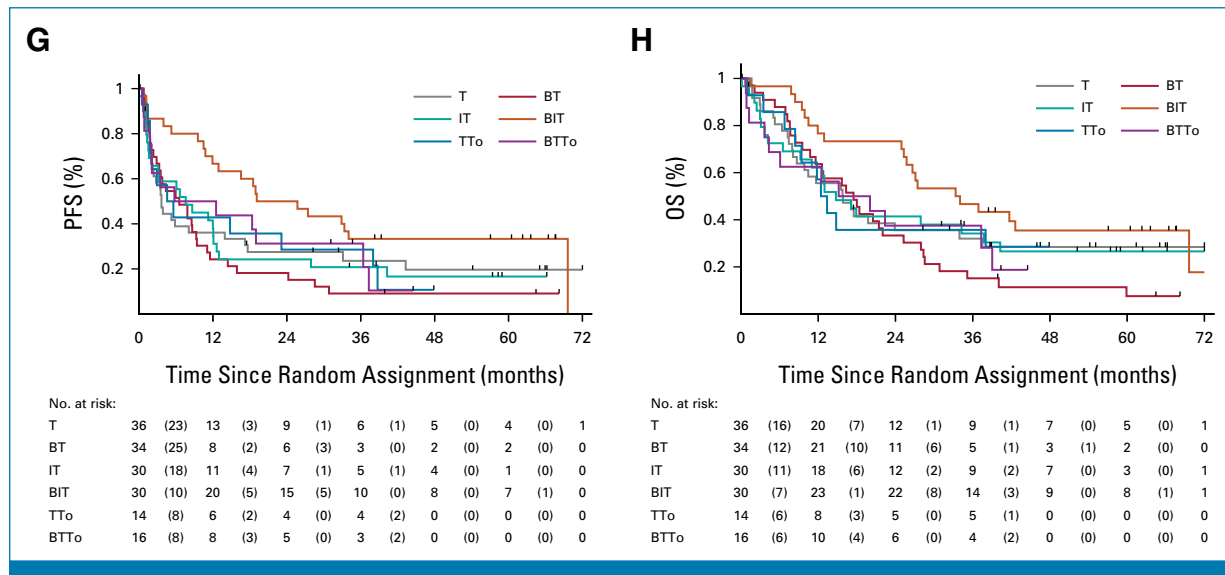


FIG 2. (Continued).

more AEs than those not receiving it. More patients in the B-receiving arms experienced neutropenia, anemia, and thrombocytopenia. Ten patients receiving B experienced proteinuria. Grade  $\geq 3$  proteinuria occurred in four patients (5%) receiving B and no patients receiving chemotherapy alone. No patients had episodes of grade  $\geq 3$  bleeding, wound healing complications, fistulae, posterior reversible encephalopathy syndrome, congestive heart failure, thromboembolic events, or GI perforation.

### Safety: Chemotherapy Random Assignments

Patients receiving irinotecan or topotecan experienced more AEs than those receiving T alone (Data Supplement, Table S6). Patients receiving irinotecan had an increased incidence of  $\geq$ grade 3 GI AEs, mainly diarrhea in eight patients (13%). Patients receiving topotecan had an increased incidence of grade  $\geq 3$  neutropenia, thrombocytopenia, and anemia.

## DISCUSSION

To our knowledge, we report the largest randomized trial in relapsed/refractory neuroblastoma conducted to date. Using a multiarm multistage factorial design, three chemotherapy regimens and a novel agent, B, added to conventional chemotherapy, were evaluated within one international cooperative group academic clinical trial.

At the time of designing the trial, there was considerable uncertainty as to which of the three chemotherapy regimens was superior for the treatment of relapsed/refractory neuroblastoma; all had shown promising activity in single-arm series with similar response rates and were commonly used internationally depending on physician preference.<sup>9–11</sup> Identifying the most appropriate backbone chemotherapy regimen is critical to evaluate novel combinations for future

therapy, and only a randomized controlled comparison can provide the necessary data.

The addition of irinotecan or topotecan to T did not achieve higher response rates but appeared to result in improved PFS. One-year PFS seemed higher in irinotecan- or topotecan-containing arms (23% and 24% higher, respectively) compared with T-only arms. Toxicity profiles confirmed that the addition of irinotecan is associated with more diarrhea and GI symptoms, whereas the addition of topotecan is associated with increased myelotoxicity. Whether one or the other toxicity profile is preferable remains a subject of debate and may vary from patient to patient. The trial did not include quality-of-life questionnaires or patient-reported outcome measures, which would have been extremely useful to base future choices incorporating the patients' and parents' voices. In the B random assignment of the BEACON trial, success criteria were met for response. PFS seemed to improve with the addition of B within the limitations of evidence generated within a randomized phase II trial. The addition of B also increased toxicity, mainly related to increased myelotoxicity. Consistent with other large trials in the pediatric population, B-specific toxicities seen in adults were rare, although grade 3–4 proteinuria occurred in 5% of patients.<sup>25,26</sup>

An unexpected potential interaction between irinotecan and B was seen, with possibly greater benefit of B in patients also receiving irinotecan. This interaction is biologically plausible: Although B is primarily an antiangiogenic agent, it has a number of effects on the tumor immune microenvironment, including promotion of tumor-infiltrating lymphocytes, with suppression in the number and function of inhibitory populations, including myeloid-derived suppressor cells, regulatory T cells, and M2 macrophages.<sup>27–29</sup> Irinotecan has also been reported to have immune and antiangiogenic

**TABLE 3.** Grade  $\geq 3$  AEs in the B Random Assignment Occurring in  $\geq 1\%$  of Patients

| CTCAE Category                                       | B Random Assignment (grade 3 and above AEs) |                                     |                            |
|------------------------------------------------------|---------------------------------------------|-------------------------------------|----------------------------|
|                                                      | B (BT, BIT, BTTTo; n = 80), No. (%)         | Non-B (T, IT, TTo; n = 80), No. (%) | Overall (N = 160), No. (%) |
| Investigations                                       | 218 (59)                                    | 190 (50)                            | 408 (54)                   |
| Neutrophil count decreased                           | 77 (30.5)                                   | 82 (23.5)                           | 159 (51.5)                 |
| Platelet count decreased                             | 86 (23)                                     | 68 (21)                             | 154 (21)                   |
| WBC decreased                                        | 23 (4)                                      | 14 (5)                              | 37 (9)                     |
| Lymphocyte count decreased                           | 18 (8)                                      | 13 (3)                              | 31 (10)                    |
| GGT increased                                        | 2 (1)                                       | 2 (2.5)                             | 4 (2)                      |
| ALT increased                                        | 5 (2.5)                                     | 9 (2.5)                             | 14 (2.5)                   |
| AST increased                                        | 1 (1)                                       | 4 (2.5)                             | 5 (2)                      |
| Blood and lymphatic system disorders                 | 32 (19)                                     | 23 (8)                              | 55 (13)                    |
| Anemia                                               | 25 (14)                                     | 17 (3)                              | 44 (16)                    |
| Febrile neutropenia                                  | 4 (5)                                       | 2 (3)                               | 6 (4)                      |
| Metabolism and nutrition disorders                   | 24 (14)                                     | 12 (6)                              | 36 (10)                    |
| Anorexia                                             | 5 (4)                                       | 8 (4)                               | 13 (4)                     |
| Dehydration                                          | 6 (6)                                       | 0 (0)                               | 6 (3)                      |
| GI disorders                                         | 21 (15)                                     | 13 (10)                             | 34 (13)                    |
| Diarrhea                                             | 12 (5)                                      | 2 (1)                               | 14 (3)                     |
| Vomiting                                             | 3 (4)                                       | 5 (2.5)                             | 8 (3)                      |
| Nausea                                               | 2 (2.5)                                     | 1 (1)                               | 3 (1)                      |
| Abdominal pain                                       | 0 (0)                                       | 2 (2.5)                             | 2 (1)                      |
| Infections and infestations                          | 20 (13)                                     | 9 (9)                               | 29 (11)                    |
| Catheter-related infection                           | 7 (6)                                       | 1 (1)                               | 8 (4)                      |
| Abdominal infection                                  | 3 (2.5)                                     | 0 (0)                               | 3 (1)                      |
| Lung infection                                       | 1 (1)                                       | 2 (2.5)                             | 3 (2)                      |
| Varicella                                            | 2 (2.5)                                     | 0 (0)                               | 2 (1)                      |
| Upper respiratory infection                          | 0 (0)                                       | 2 (2.5)                             | 2 (1)                      |
| General disorders and administration site conditions | 7 (5)                                       | 14 (5)                              | 21 (5)                     |
| Fever                                                | 2 (2.5)                                     | 5 (4)                               | 7 (3)                      |
| Pain                                                 | 3 (2.5)                                     | 4 (4)                               | 7 (3)                      |
| Renal and urinary disorders                          | 10 (4)                                      | 0 (0)                               | 10 (2)                     |
| Proteinuria                                          | 8 (4)                                       | 0 (0)                               | 8 (2)                      |
| Total No. of AEs                                     | 350                                         | 273                                 | 623                        |

NOTE. Only two patients experienced grade 5 toxicities during the trial: worsening general condition and pulmonary edema.

Abbreviations: AE, adverse event; B, bevacizumab; BIT, bevacizumab-irinotecan-temozolomide; BT, bevacizumab-temozolomide; BTTTo, bevacizumab-topotecan-temozolomide; CTCAE, Common Terminology Criteria Adverse Events; GGT, gamma-glutamyl transferase; IT, irinotecan-temozolomide; T, temozolomide; TTo, topotecan-temozolomide.

effects, including depletion of regulatory T cells, upregulation of major histocompatibility complex class I, and PD-L1 expression.<sup>30-32</sup> The benefits of randomized comparisons are highlighted as the results of the BEACON trial differ from a single-institution single-arm trial which showed no benefit of adding B to IT in patients with highly pretreated neuroblastoma.<sup>17</sup>

The unexpected potential interaction identified after completing the trial highlights one of the challenges of using factorial designs. The strength of this design was that it

allowed four different questions to be addressed within the same trial population and generated randomized phase II data.

The current results need to be analyzed in the context of recently reported trials in the relapsed/refractory neuroblastoma setting. The combination of anti-GD2 therapy with chemotherapy has shown very promising results in single-arm studies and smaller randomized trials.<sup>33-35</sup> In the Children's Oncology Group ANBL1221 trial, 53 children were treated with IT-dinutuximab-granulocyte-macrophage colony-stimulating factor, with an ORR of

41.5% and 1-year PFS of 67.9%. After completing the B random assignment, the BEACON trial was amended to evaluate the addition of anti-GD2 therapy with dinutuximab beta to chemotherapy.

Despite promising results, a significant proportion of patients still relapsed. Better understanding of the biology of refractory/relapsed and identifying biomarkers of response or resistance to therapy remain crucial. An ambitious ongoing translational research program (BEACON BIO) is currently analyzing more than 700

plasma, blood, and tumor samples collected during trial treatment.<sup>36</sup>

In conclusion, within the limits of a phase II trial, the BEACON trial provided some evidence that addition of B to T-based chemotherapy improved ORR. It also appeared to show some improvement PFS when adding irinotecan or topotecan to T. A potential interaction between irinotecan and B might explain better results for the BIT regimen. A future study in relapsed/refractory neuroblastoma will compare IT-B with a chemoimmunotherapy regimen.

## AFFILIATIONS

- <sup>1</sup>Vall d'Hebron University Hospital, Barcelona, Spain
- <sup>2</sup>University of Birmingham, Birmingham, United Kingdom
- <sup>3</sup>Children's Hospital Ireland, Dublin, Ireland
- <sup>4</sup>Institut Gustave Roussy, Paris, France
- <sup>5</sup>Hôpital des Enfants, Bordeaux, France
- <sup>6</sup>Hospital Universitario La Fe, Valencia, Spain
- <sup>7</sup>Princess Maxima Center, Utrecht, the Netherlands
- <sup>8</sup>Rigshospitalet, Copenhagen, Denmark
- <sup>9</sup>Universitäts-Kinderspital, Zurich, Switzerland
- <sup>10</sup>Bambino Gesù Children's Hospital, Rome, Italy
- <sup>11</sup>University Hospital Gent, Gent, Belgium
- <sup>12</sup>St Anna Kinderspital, Vienna, Austria
- <sup>13</sup>Inselspital, Universitätsspital Bern, Bern, Switzerland
- <sup>14</sup>Central Manchester and Manchester Children's University Hospitals NHS Trust, Manchester, United Kingdom
- <sup>15</sup>NHS Greater Glasgow and Clyde, Glasgow, United Kingdom
- <sup>16</sup>Birmingham Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom
- <sup>17</sup>The Royal Marsden NHS Foundation Trust & Institute for Cancer Research, London, United Kingdom
- <sup>18</sup>Hôpital Mère-Enfant, Nantes, France
- <sup>19</sup>The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, United Kingdom
- <sup>20</sup>Great Ormond Street Hospital, London, United Kingdom
- <sup>21</sup>Hôpital des Enfants, Hémato-Oncologie, Bordeaux, France
- <sup>22</sup>Centre Léon Bérard, Lyon, France
- <sup>23</sup>Hôpital d'Enfants, Nancy, France
- <sup>24</sup>Hôpital de Haute-pierre, Strasbourg, France
- <sup>25</sup>University Hospital Southampton, Southampton, United Kingdom
- <sup>26</sup>St James University Hospital, Leeds, United Kingdom
- <sup>27</sup>Institute Curie, Paris, France
- <sup>28</sup>Roche, Basel, Switzerland

## CORRESPONDING AUTHOR

Lucas Moreno, MD, PhD, Division of Pediatric Hematology & Oncology, Vall d'Hebron Barcelona Hospital Campus, Passeig Vall d'Hebron, 119, Barcelona 08035, Spain; e-mail: lucas.moreno@vallhebron.cat.

## PRIOR PRESENTATION

Presented in part at the ASCO Annual Meeting, Chicago, IL, May 31-Jun 4, 2019 and at the ASCO Annual Meeting, Chicago, IL, May 29-Jun 2, 2020.

## SUPPORT

Supported by Cancer Research UK (grant CRUK/11/056) and Imagine for Margo. Funding for national coordinating centers was also received

by K.N. from the Danish Childhood Cancer Foundation (grants no. 2015-13 and 2016-0318), the German Children's Cancer Foundation (DKS 2013.24), 111 des Arts, Enfance & cancer, Enfants Cancer Santé, Kom op tegen Kanker, Zoe for Life. L.M. was funded (2016-2018) through Juan Rodes Fellowship (JR15/00041) by Instituto de Salud Carlos III. M.O.L. and N.K. acknowledge support from the Cancer Research UK Cancer Imaging Center, the NIHR Clinical Research Facility and the NIHR Biomedical Research Center.

## CLINICAL TRIAL INFORMATION

EudraCT 2012-000072-42 (BEACON-Neuroblastoma) [NCT02308527](https://doi.org/10.1200/JCO.23.00458) (BEACON-Neuroblastoma)

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO.23.00458>.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Lucas Moreno, Cormac Owens, Dominique Valteau-Couanet, Juliet Gray, Hubert Caron, Nicola Fenwick, Veronica Moroz, Pamela Kearns, Andrew D.J. Pearson, Keith Wheatley

**Financial support:** Marion Gambart, Karsten Nysom, Jochen Rössler, Lucas Moreno, Pamela Kearns, Keith Wheatley, Andrew DJ Pearson, Nicholas Gerber

**Administrative support:** Jennifer Laidler, Nicola Fenwick

**Provision of study materials or patients:** Cormac Owens, Dominique Valteau-Couanet, Marion Gambart, Victoria Castel, C. Michel Zwaan, Karsten Nysom, Aurora Castellano, Genevieve Laureys, Guy Makin, Bruce Morland, Sucheta Vaidya, Natasha van Eijklenburg, Deborah A. Tweddle, Giuseppe Barone, Julie Tandonnet, Francisco J. Bautista, Bram De Wilde, Lynley Marshall, Gudrun Schleiermacher, Louis Chesler, Kieran McHugh, Nicola Fenwick

**Collection and assembly of data:** Lucas Moreno, Marion Gambart, Victoria Castel, Karsten Nysom, Nicolas Gerber, Aurora Castellano, Genevieve Laureys, Ruth Ladenstein, Guy Makin, Sucheta Vaidya, Estelle Thebaud, Natasha van Eijkelenburg, Deborah A. Tweddle, Giuseppe Barone, Julie Tandonnet, Bram De Wilde, Lynley Marshall, Juliet Gray, Gudrun Schleiermacher, Jennifer Laidler, Nicola Fenwick, Keith Wheatley, Cormac Owens, Dominique Valteau-Couanet, C. Michel Zwaan, Dermot Murphy, Bruce Morland, Nadege Corradini, Pascal Chastagner, Catherine Paillard, Francisco J. Bautista, Soledad Gallego Melcon

**Data analysis and interpretation:** Lucas Moreno, Rebekah Weston, Cormac Owens, Dominique Valteau-Couanet, Marion Gambart, C. Michel Zwaan, Karsten Nysom, Nicolas Gerber, Genevieve Laureys, Ruth Ladenstein, Jochen Rössler, Dermot Murphy, Bruce Morland, Sucheta

Vaidya, Deborah A. Tweddle, Giuseppe Barone, Nadege Corradini, Pascal Chastagner, Catherine Paillard, Francisco J. Bautista, Soledad Gallego Melcon, Juliet Gray, Susan A. Burchill, Gudrun Schleiermacher, Louis Chesler, Andrew Peet, Kieran McHugh, Roisin Hayes, Neil Jerome, Hubert Caron, Grace Holt, Veronica Moroz, Simon Gates, Andrew D.J. Pearson, Keith Wheatley, Martin O. Leach

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Accountable for all aspects of the work:** All authors

## ACKNOWLEDGMENT

We are enormously grateful to patients and families who participated in the trial. We would like to thank Roche for providing drug supply of bevacizumab and all study teams (investigators, study coordinators, and study nurses).

## REFERENCES

1. London WB, Castel V, Monclair T, et al: Clinical and biologic features predictive of survival after relapse of neuroblastoma: A report from the International Neuroblastoma Risk Group Project. *J Clin Oncol* 29:3286-3292, 2011
2. Moreno L, Rubie H, Varo A, et al: Outcome of children with relapsed or refractory neuroblastoma: A meta-analysis of ITCC/SIOPEN European phase II clinical trials. *Pediatr Blood Cancer* 64:25-31, 2017
3. Yanik GA, Parisi MT, Naranjo A, et al: Validation of postinduction curie scores in high-risk neuroblastoma: A Children's Oncology Group and SIOPEN group report on SIOPEN/HR-NBL1. *J Nucl Med* 59:502-508, 2018
4. Pinto N, Naranjo A, Hibbitts E, et al: Predictors of differential response to induction therapy in high-risk neuroblastoma: A report from the Children's Oncology Group (COG). *Eur J Cancer* 112:66-79, 2019
5. Basta NO, Halliday GC, Makin G, et al: Factors associated with recurrence and survival length following relapse in patients with neuroblastoma. *Br J Cancer* 115:1048-1057, 2016
6. Herd F, Basta NO, McNally RJ, et al: A systematic review of re-induction chemotherapy for children with relapsed high-risk neuroblastoma. *Eur J Cancer* 111:50-58, 2019
7. London WB, Bagatell R, Weigel BJ, et al: Historical time to disease progression and progression-free survival in patients with recurrent/refractory neuroblastoma treated in the modern era on Children's Oncology Group early-phase trials. *Cancer* 123:4914-4923, 2017
8. London WB, Frantz CN, Campbell LA, et al: Phase II randomized comparison of topotecan plus cyclophosphamide versus topotecan alone in children with recurrent or refractory neuroblastoma: A Children's Oncology Group study. *J Clin Oncol* 28:3808-3815, 2010
9. Rubie H, Chisholm J, Defachelles AS, et al: Phase II study of temozolomide in relapsed or refractory high-risk neuroblastoma: a joint Société Française des Cancers de l'Enfant and United Kingdom Children Cancer Study Group-New Agents Group Study. *J Clin Oncol* 24:5259-5264, 2006
10. Bagatell R, London WB, Wagner LM, et al: Phase II study of irinotecan and temozolomide in children with relapsed or refractory neuroblastoma: A Children's Oncology Group study. *J Clin Oncol* 29:208-213, 2011
11. di Giannatale A, Dias-Gastellier N, Devos A, et al: Phase II study of temozolomide in combination with topotecan (TOTEM) in relapsed or refractory neuroblastoma: A European Innovative Therapies for Children with Cancer-SIOP-European Neuroblastoma study. *Eur J Cancer* 50:170-177, 2014
12. Garcia J, Hurwitz HI, Sandler AB, et al: Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer Treat Rev* 86:102017, 2020
13. Maj E, Papiernik D, Wietrzyk J: Antiangiogenic cancer treatment: The great discovery and greater complexity (Review). *Int J Oncol* 49:1773-1784, 2016
14. Vafopoulou P, Kourtis M: Anti-angiogenic drugs in cancer therapeutics: A review of the latest preclinical and clinical studies of anti-angiogenic agents with anticancer potential. *J Cancer Metastasis Treat* 8:18, 2022
15. Rössler J, Monnet Y, Farace F, et al: The selective VEGFR1-3 inhibitor axitinib (AG-013736) shows antitumor activity in human neuroblastoma xenografts. *Int J Cancer* 128:2748-2758, 2011
16. Rössler J, Taylor M, Georger B, et al: Angiogenesis as a target in neuroblastoma. *Eur J Cancer* 44:1645-1656, 2008
17. Modak S, Kushner BH, Basu E, et al: Combination of bevacizumab, irinotecan, and temozolomide for refractory or relapsed neuroblastoma: Results of a phase II study. *Pediatr Blood Cancer* 10.1002/pbc.26448
18. Beaudry P, Nilsson M, Rieth M, et al: Potent antitumor effects of ZD6474 on neuroblastoma via dual targeting of tumor cells and tumor endothelium. *Mol Cancer Ther* 7:418-424, 2008
19. Cañete A, Navarro S, Bermúdez J, et al: Angiogenesis in neuroblastoma: Relationship to survival and other prognostic factors in a cohort of neuroblastoma patients. *J Clin Oncol* 18:27-34, 2000
20. Sims TL, Williams RF, Ng CY, et al: Bevacizumab suppresses neuroblastoma progression in the setting of minimal disease. *Surgery* 144:269-275, 2008
21. Segerström L, Fuchs D, Bäckman U, et al: The anti-VEGF antibody bevacizumab potentially reduces the growth rate of high-risk neuroblastoma xenografts. *Pediatr Res* 60:576-581, 2006
22. Dickson PV, Hamner JB, Sims TL, et al: Bevacizumab-induced transient remodeling of the vasculature in neuroblastoma xenografts results in improved delivery and efficacy of systemically administered chemotherapy. *Clin Cancer Res* 13:3942-3950, 2007
23. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 45:228-247, 2009
24. Park JR, Bagatell R, Cohn SL, et al: Revisions to the international neuroblastoma response criteria: A consensus statement from the National Cancer Institute clinical trials planning meeting. *J Clin Oncol* 35:2580-2587, 2017
25. Grill J, Massimino M, Bouffet E, et al: Phase II, open-label, randomized, multicenter trial (HERBY) of bevacizumab in pediatric patients with newly diagnosed high-grade glioma. *J Clin Oncol* 36:951-958, 2018
26. Chisholm JC, Merks JHM, Casanova M, et al: Open-label, multicentre, randomised, phase II study of the EpSSG and the ITCC evaluating the addition of bevacizumab to chemotherapy in childhood and adolescent patients with metastatic soft tissue sarcoma (the BERNIE study). *Eur J Cancer* 83:177-184, 2017
27. Rahma OE, Hodi FS: The intersection between tumor angiogenesis and immune suppression. *Clin Cancer Res* 25:5449-5457, 2019
28. Tamura R, Tanaka T, Ohara K, et al: Persistent restoration to the immunosuppressive tumor microenvironment in glioblastoma by bevacizumab. *Cancer Sci* 110:499-508, 2019
29. Tamura R, Tanaka T, Akasaki Y, et al: The role of vascular endothelial growth factor in the hypoxic and immunosuppressive tumor microenvironment: Perspectives for therapeutic implications. *Med Oncol* 37:2, 2019
30. Kaneko S, Ishibashi M, Kaneko M: Vascular endothelial growth factor expression is closely related to irinotecan-mediated inhibition of tumor growth and angiogenesis in neuroblastoma xenografts. *Cancer Sci* 99:1209-1217, 2008
31. Melichar B, Tousekova M, Vesely P: Effect of irinotecan on the phenotype of peripheral blood leukocyte populations in patients with metastatic colorectal cancer. *Hepatogastroenterology* 49:967-970, 2002
32. Iwai T, Sugimoto M, Wakita D, et al: Topoisomerase I inhibitor, irinotecan, depletes regulatory T cells and up-regulates MHC class I and PD-L1 expression, resulting in a supra-additive antitumor effect when combined with anti-PD-L1 antibodies. *Oncotarget* 9:31411-31421, 2018
33. Mody R, Naranjo A, van Ryn C, et al: Irinotecan-temozolomide with temsirolimus or dinutuximab in children with refractory or relapsed neuroblastoma (COG ANBL1221): An open-label, randomised, phase 2 trial. *Lancet Oncol* 18:946-957, 2017
34. Mody R, Yu AL, Naranjo A, et al: Irinotecan, temozolomide, and dinutuximab with GM-CSF in children with refractory or relapsed neuroblastoma: A report from the Children's Oncology Group. *J Clin Oncol* 38:2160-2169, 2020
35. Federico SM, McCarville MB, Shulkin BL, et al: A pilot trial of humanized anti-GD2 monoclonal antibody (hu14.18K322A) with chemotherapy and natural killer cells in children with recurrent/refractory neuroblastoma. *Clin Cancer Res* 23:6441-6449, 2017
36. Moreno L, Weston R, Viprey V, et al: Predicting outcomes with circulating adrenergic neuroblastoma mRNAs in children with relapsed and refractory neuroblastoma: A BEACON-neuroblastoma biomarker study. *J Clin Oncol* 40, 2022 (suppl 16; abstr 10039)

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Bevacizumab, Irinotecan, or Topotecan Added to Temozolomide for Children With Relapsed and Refractory Neuroblastoma: Results of the ITCC-SIOPEN BEACON-Neuroblastoma Trial**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to [www.asco.org/rwc](http://www.asco.org/rwc) or [ascopubs.org/jco/authors/author-center](http://ascopubs.org/jco/authors/author-center).

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

### Lucas Moreno

**Honoraria:** Bayer (Inst), EUSA Pharma (Inst)

**Consulting or Advisory Role:** Shionogi (Inst), Novartis (Inst), Boehringer Ingelheim (Inst), Norgine (Inst)

**Patents, Royalties, Other Intellectual Property:** Member of SIOPEN Executive Committee, SIOPEN receives royalties for the sales of dinutuximab beta (Inst)

**Uncompensated Relationships:** Ymabs Therapeutics Inc (Inst)

### Cormac Owens

**Employment:** Ymabs Therapeutics Inc

### Dominique Valteau-Couanet

**Honoraria:** Bellerophon Therapeutics

**Consulting or Advisory Role:** EUSA Pharma (Inst)

**Research Funding:** Orphelia Pharma (Inst)

### C. Michel Zwaan

**Consulting or Advisory Role:** Takeda (Inst), Pfizer (Inst), AbbVie (Inst), Jazz Pharmaceuticals (Inst), Incyte (Inst), Novartis (Inst), Kura Oncology (Inst), Gilead Sciences (Inst)

**Research Funding:** Takeda (Inst), AbbVie/Genentech (Inst), Pfizer (Inst), Jazz Pharmaceuticals (Inst), Kura Oncology (Inst), Daiichi Sankyo (Inst)

### Karsten Nysom

**Consulting or Advisory Role:** Bayer, Lilly

### Ruth Ladenstein

**Consulting or Advisory Role:** Apeiron Biologics, Boehringer Ingelheim, EUSA Pharma (Inst)

**Research Funding:** Apeiron Biologics (Inst), EUSA Pharma (Inst)

**Patents, Royalties, Other Intellectual Property:** Apeiron Biologics (Inst), EUSA Pharma (Inst)

**Expert Testimony:** Apeiron Biologics, EUSA Pharma

### Jochen Rössler

**Employment:** Novartis

**Stock and Other Ownership Interests:** Novartis

**Consulting or Advisory Role:** Roche

**Travel, Accommodations, Expenses:** SOBI

### Sucheta Vaidya

**Honoraria:** Zeiss Mediatec

**Travel, Accommodations, Expenses:** Zeiss Mediatec

### Natasha van Eijkelenburg

**Honoraria:** MSD Oncology

### Deborah A. Tweddle

**Honoraria:** EUSA Pharma

**Consulting or Advisory Role:** Norgine

**Travel, Accommodations, Expenses:** EUSA Pharma

### Giuseppe Barone

**Honoraria:** EUSA Pharma

**Consulting or Advisory Role:** EUSA Pharma

**Travel, Accommodations, Expenses:** EUSA Pharma

### Lynley Marshall

**Honoraria:** Bayer, Eisai, Merck

**Consulting or Advisory Role:** Illumina

### Juliet Gray

**Consulting or Advisory Role:** EUSA Pharma, Norgine, Ymabs Therapeutics Inc

**Speakers' Bureau:** BeiGene, Ology Medical Education

**Research Funding:** Celgene/Bristol Myers Squibb (Inst)

**Travel, Accommodations, Expenses:** EUSA Pharma

### Gudrun Schleiermacher

**Honoraria:** BMS

**Consulting or Advisory Role:** Servier

**Research Funding:** Bristol Myers Squibb (Inst), Pfizer (Inst), MSD Avenir (Inst), Roche (Inst)

**Travel, Accommodations, Expenses:** Roche, EUSA Pharma

### Neil Jerome

**Employment:** Siemens Healthineers

**Travel, Accommodations, Expenses:** Siemens Healthineers

### Hubert Caron

**Employment:** Roche

**Stock and Other Ownership Interests:** Roche

**Travel, Accommodations, Expenses:** Roche

### Veronica Moroz

**Employment:** GlaxoSmithKline UK Ltd

**Stock and Other Ownership Interests:** GlaxoSmithKline

### Pamela Kearns

**Consulting or Advisory Role:** Bristol Myers Squibb, Bayer, AstraZeneca

**Research Funding:** Pfizer (Inst), Bayer (Inst)

### Simon Gates

**Research Funding:** Bayer (Inst), Janssen (Inst)

**Andrew D.J. Pearson**

**Honoraria:** Lilly, Amgen, Developmental Therapeutics Consortium, Norgine

**Consulting or Advisory Role:** Lilly, Amgen, Developmental Therapeutics Consortium, Norgine

**Keith Wheatley**

**Research Funding:** Roche (Inst), Bio-Cancer Treatment International (Inst), EUSA Pharma (Inst), Bayer (Inst)

No other potential conflicts of interest were reported.

## APPENDIX

**TABLE A1.** List of Trial Sites and Innovative Therapies for Children with Cancer (ITCC) and European Association for Neuroblastoma Research (SIOPEN) Investigators

| Site Name                                         | Principal Investigator    | City        | Country            | No. of Patients |
|---------------------------------------------------|---------------------------|-------------|--------------------|-----------------|
| Institut Gustave Roussy                           | Dominique Valteau-Couanet | Villejuif   | France             | 13              |
| Hospital del Nino Jesus                           | Francisco J. Bautista     | Madrid      | Spain              | 9               |
| Royal Hospital for Sick Children (Yorkhill)       | Dermot Murphy             | Glasgow     | The United Kingdom | 9               |
| Royal Manchester Children's Hospital              | Guy Makin                 | Manchester  | The United Kingdom | 9               |
| Hôpital Mère-Enfant, Nantes                       | Estelle Thebaut           | Nantes      | France             | 8               |
| Princess Maxima Centrum                           | Natasha van Eijkelenburg  | Utrecht     | The Netherlands    | 8               |
| Birmingham Children's Hospital                    | Dave Hobin                | Birmingham  | The United Kingdom | 8               |
| The Royal Marsden Hospital                        | Sucheta Vaidya            | London      | The United Kingdom | 8               |
| Leeds General Infirmary                           | Martin Elliott            | Leeds       | The United Kingdom | 7               |
| Institut Curie                                    | Gudrun Schleiermacher     | Curie       | France             | 6               |
| Our Lady Children's Hospital                      | Cormac Owens              | Dublin      | Ireland            | 6               |
| Great Ormond Street Hospital                      | Giuseppe Barone           | London      | The United Kingdom | 6               |
| Royal Victoria Infirmary                          | Deborah Tweddle           | Newcastle   | The United Kingdom | 6               |
| Instituto de Investigación Sanitaria La Fe        | Victoria Castel           | Valencia    | Spain              | 5               |
| Rigshospitalet                                    | Karsten Nysom             | Copenhagen  | Denmark            | 4               |
| Hôpital des Enfants                               | Julie Tandonnet           | Bordeaux    | France             | 4               |
| Centre Leon Berard                                | Nadege Corradini          | Lyon        | France             | 4               |
| Hôpital d'Enfants                                 | Pascal Chastagner         | Nancy       | France             | 4               |
| Hôpital des Enfants                               | Marion Gambart            | Toulouse    | France             | 4               |
| Hôpital de Hautepierre                            | Sarah Jannier             | Strasbourg  | France             | 4               |
| Bambino Gesù Children's Hospital                  | Aurora Castellano         | Rome        | Italy              | 4               |
| Hospital Vall d'Hebron                            | Soledad Gallego           | Barcelona   | Spain              | 4               |
| Hôpital de la Timone                              | Carole Coze               | Marseille   | France             | 3               |
| Hôpital Armand Trousseau                          | Anne Auvrignon            | Trousseau   | France             | 3               |
| Center Oscar Lambret                              | Anne Sophie Defachelles   | Lille       | France             | 2               |
| Hospital de Cruces                                | Ricardo Lopez Almaraz     | Bilbao      | Spain              | 2               |
| University Children's Hospital                    | Nicolas Gerber            | Zurich      | Switzerland        | 2               |
| St Anna Kinderspital                              | Ruth Ladenstein           | Vienna      | Austria            | 1               |
| Universitair Hospital Gent                        | Bram De Wilde             | Gent        | Belgium            | 1               |
| Cliniques Universitaires Saint Luc (UCL)          | Benedicte Brichard        | UCL         | Belgium            | 1               |
| Istituto Nazionale Tumori                         | Roberto Luksch            | Milan       | Italy              | 1               |
| Erasmus Medical Centre/Sophia Children's Hospital | C. Michel Zwaan           | Rotterdam   | The Netherlands    | 1               |
| Centre Hospitalier Universitaire Vaudois          | Maja Beck-Popovic         | Lausanne    | Switzerland        | 1               |
| Royal Aberdeen Children's Hospital                | Courtney Willis           | Aberdeen    | The United Kingdom | 1               |
| University Hospital Southampton                   | Juliet Gray               | Southampton | The United Kingdom | 1               |
| University Children's Hospital Freiburg           | Simone Hettmer            | Freiburg    | Germany            | 0               |
| HELIOS Klinikum Berlin-Buch                       | Lothar Schweigerer        | Berlin      | Germany            | 0               |
| Universitätsklinikum Aachen                       | Udo Kontny                | Aachen      | Germany            | 0               |
| University Hospital Leipzig                       | Holger Christiansen       | Leipzig     | Germany            | 0               |
| Giannina Gaslini Children's Hospital              | Alberto Garaventa         | Genoa       | Italy              | 0               |
| Bristol Royal Hospital for Children               | Anthony Ng                | Bristol     | The United Kingdom | 0               |
| Alder Hey Children's Hospital                     | Lisa Howell               | Liverpool   | The United Kingdom | 0               |
| Sheffield Children's Hospital                     | Daniel Yeomanson          | Sheffield   | The United Kingdom | 0               |
| Total                                             |                           |             |                    | 160             |