Pediatric Blood & Cancer

Research Article

The efficacy and safety of bevacizumab/irinotecan/temozolomide (BIT) for relapsed/refractory neuroblastoma: the UK Children's Cancer and Leukaemia Group experience

Submission ID	ab90804b-2cf4-41e5-a918-3d0061d6840a
Submission Version	Initial Submission
PDF Generation	22 Dec 2025 17:21:33 EST by Atypon ReX

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Files for peer review

All files submitted by the author for peer review are listed below. Files that could not be converted to PDF are indicated; reviewers are able to access them online.

Name	Type of File	Size	Page
BIT paper with figures imbedded final 22.12.docx	Main Document - MS Word	598.6 KB	Page 5
Supplementary file 1.xlsm	Supplementary Material for Review	21.3 KB	*Not converted to PDF*
Supplementary files 2-4 22.12.25.docx	Supplementary Material for Review	27.7 KB	Page 21
Pediatric-Blood-Cancer-Author-checklist BIT NBL 22.12.25.docx	Pediatric Blood & Cancer Author Checklist	21.0 KB	Page 27

The efficacy and safety of bevacizumab/irinotecan/temozolomide (BIT) for relapsed/refractory neuroblastoma: the UK Children's Cancer and Leukaemia Group experience.

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Abstract 244 words
Manuscript: 1595 words

Abstract

Background

Patients with high-risk neuroblastoma who either are refractory to induction chemotherapy or relapse following multi-modal treatment have a dismal prognosis. Based on data from the BEACON trial, since 2021 the UK national guidelines recommend BIT (bevacizumab, irinotecan, temozolomide) for patients with relapsed/refractory disease.

Methods

A retrospective UK national study of patients under 25 years with relapsed/refractory neuroblastoma treated with BIT 1/3/2021-29/2/2024.

Results

66 patients were included from 15 UK centres; 40 (61%) had relapsed disease, 23 at 1st relapse. Overall objective response rate was 40.6% [95% CI 28.5-53.6%] and was higher in patients with refractory vs relapsed disease (56% vs 28%, p=0.0365). Objective responses were achieved within 6 cycles for over 90%. 17/26 (65%) patients with primary refractory disease received high dose chemotherapy with busulfan/melphalan and autologous stem cell rescue. 9 required additional therapies after BIT before they could proceed to high-dose treatment and 8 required BIT alone. Progression free- and overall survival was significantly longer in refractory patients (median PFS 13.2 vs 5.1 months p = 0.012, median OS not reached by 3 years vs 12.5 months, p=0.0003).

The most common CTCAE5.0 grade 3-4 toxicities were anaemia (32%), neutropenic fever (23%) and diarrhoea (13.6%). 1 patient discontinued treatment due to toxicity (diarrhoea).

Conclusions

The promising efficacy and tolerability of BIT reported by the BEACON trial is reproduced in real world data with a larger cohort size. Further randomised studies are needed to separately identify optimal treatment strategies for relapsed and refractory disease.

Introduction

Neuroblastoma is the most common extracranial solid tumour in children[1]. While the overall survival for patients with high-risk disease has significantly improved over the last decades with the introduction of high dose chemotherapy[2,3] and anti-GD2 immunotherapy[4,5], patients with refractory disease and poor response to induction chemotherapy or who relapse still face a dismal long-term prognosis[6–8].

Numerous different chemotherapy regimens have been described for treatment of relapsed neuroblastoma, mostly in single arm cohorts (reviewed in Herd et al.,[9]), but very few randomised studies have been performed in patients with relapsed and/or refractory disease. The Children's Oncology group (COG) demonstrated improved progression free survival (PFS) when cyclophosphamide was added to topotecan[10]. The BEACON study showed improved objective response rate (ORR) and PFS with addition of either topotecan or irinotecan to temozolomide, and with addition of the anti-VEGF agent bevacizumab to each of these 3 chemotherapy backbones[11].

Following the publication of the results of the BEACON study, UK CCLG guidelines for treatment of refractory/relapsed neuroblastoma were revised in 2021 and BIT (bevacizumab, irinotecan, temozolomide) was introduced as second-line treatment [12]. Here we describe the real-world outcomes and toxicities of BIT in this patient population.

Methods

This was a retrospective study of patients aged 0-24 years at time of diagnosis, with relapsed/refractory neuroblastoma, treated with BIT chemotherapy between March 1, 2021, and February 29, 2024 in a UK Children Cancer and Leukaemia Group primary treatment centre (PTC). The study was approved by the Royal Marsden Hospital R&D. Data on clinical and demographic data, first line treatment, molecular profile, radiological response, second line treatment, toxicities and survival were collected retrospectively from hospital medical records using a standardised tool (Supplementary file 1).

Staging was defined as per International Neuroblastoma Risk Group definitions[13]. Patients received bevacizumab 15mg/kg on day 1, irinotecan 50 mg/m2 iv over 30 minutes, daily on days 1-5 and temozolomide 100 mg/m2 PO, 1 hour prior to irinotecan, daily on days 1-5[11].

ORR was defined as any of complete response, complete metastatic response or partial response, with 95% confidence intervals (CI) calculated by binomial estimation. Toxicity was reported as per Common Terminology Criteria for Adverse Events version 5.0 (CTCAE5.0[14].

Descriptive statistics, including median and inter-quartile range (IQR), were calculated for continuous variables, while frequencies and percentages were reported for categorical variables. ORR were compared between patients with relapsed vs refractory disease using Fisher's exact test. Survival analyses were performed using Kaplan-Meier estimates to assess PFS and overall survival (OS) across the patient cohort. Time-to-event analyses for PFS and OS were conducted, with PFS being defined as the time from initiation of BIT to progression or relapse, and OS defined as the time from initiation of BIT to death. Statistical comparisons of survival between groups were made using log-rank tests, with p-values reported for each comparison. All statistical analyses were conducted in the R statistical environment using the packages 'readxl', 'gtsummary', 'tidyverse', 'survival', 'survminer', 'grid', 'gridExtra', 'flextable' and 'officer'. R code is available upon reasonable request.

Results

Sixty-six patients met inclusion criteria from 15 of the 20 UK PTCs. Demographic and clinical features are summarised in Table 1 and did not differ significantly between relapsed and refractory cases (supplementary figure 2). Twenty-six patients (39%) received BIT as treatment for induction-refractory disease, with the remaining 40 patients treated in the relapsed setting (23 at 1st relapse, 8 at 2nd relapse, 4 at 3rd relapse and 4 at 4th or later relapse). All patients had received induction chemotherapy prior to BIT, with 88% receiving rapid COJEC as per SIOPEN HR-NBL1 protocol . Additional therapies prior to BIT included surgery (52%), high-dose chemotherapy (45%), radiotherapy (44%), and dinutuximab beta (42%) (supplementary figure 3). Forty (61%) patients received BIT as first line of treatment of refractory/relapsed disease, 17 (26%) as second, 9 (13%) as third or later.

Patients received 1 to 12 cycles of BIT (median 4). Only one patient discontinued treatment because of diarrhoea.

Sixty-four of 66 patients were evaluable for response. Two patients were not evaluable for response because they either did not have further imaging after starting BIT or imaging studies were not available. The ORR was 40.6% (5 CR/mCR and 21 PR, 95% CI 28.5-53.6%) (Table 2). Although the distribution of responses between patients with refractory vs relapsed disease did not meet statistical significance (p = 0.058), there was a significantly better ORR in patients with refractory disease (ORR 56% (14/25) vs 28% (11/39) p = 0.0365). ORR was 30% for patients treated at 1st relapse.

Among the 26 patients with refractory disease, 17(65%) were eventually able to receive busulfan/melphan and autologous stem cell therapy (ASCT) with 8/17 requiring BIT only. Of the remaining 9 patients that required further treatment following BIT to achieve sufficient response to proceed to ASCT, the responses to BIT were 2 PD, 5 SD and 2 PR with sufficient residual disease requiring further treatment.

The median number of cycles to best response was 2 (range 1-9) and was longer in patients with responding disease (Figure 1). Only 2/26 (8%) patients with an objective response achieved this after more than 6 cycles.

Eighty one percent of patients had further treatment following BIT (supplementary figure 4). Most patients with refractory disease with inadequate responses to BIT received cyclophosphamide-topotecan and/or treatment on the MiNivAn study (miBG, nivolumab and dinutuximab beta). Patients with relapsed disease received various chemotherapy regimens and early phase clinical trials. Use of anti-GD2 based chemo-immunotherapy was rare (3 patients), reflecting the fact that dinutuximab is only

available in the UK for maintenance treatment following myeloablative chemotherapy and ASCT or as part of a clinical trial.

At a median follow-up time of 12.1 months (IQR 5.7-22.2 months), the median PFS and OS for the whole cohort was 7.6 [95%CI 4.3-13.4] and 25.3 [95% CI 17.3-not reached] months respectively. Patients with relapsed disease had shorter PFS and OS than those with refractory disease (median PFS 5.1 vs 13.3 months p = 0.012, Median OS 12.5 months vs not reached by 3 years, p =0.0003) (Figures 2 and 3).

Common grade 3-4 toxicities included anaemia (32%), neutropenic fever (23%), diarrhoea (13.6%), hypertension (6.1%), non-neutropenic fever (4.5%), thrombocytopenia (4.5%) and proteinuria (1.5%). One patient discontinued treatment after one cycle due to diarrhoea which was perceived as unacceptable due to the overall condition of the child. No grade 5 toxicity was reported.

Discussion

We have described the UK real-world experience with the BIT regimen in 66 patients with relapsed/refractory neuroblastoma, more than twice the number of patients than were treated with this regimen within the BEACON trial which established the benefit of the addition of bevacizumab to a chemotherapy backbone. We report an ORR of 41% (95% CI: 29-54%) for BIT, which compares favourably to the pooled ORR of 26% (95% CI 17-37%) for all bevacizumab containing arms (BT, BIT and BTTo) in the BEACON trial, despite a similar proportion of relapsed cases. This response rate is also higher than the 18% ORR observed in the first non-randomised trial of BIT for neuroblastoma[15], though differences in administration schedule, response definition and cohort mix may partially explain the difference response rate in our study.

BIT was well tolerated, and no unexpected toxicity was observed. Though our results suggest that continuing beyond 6 cycles is unlikely to result in an improved response, the good tolerability makes it an attractive treatment for patients who achieve stable disease and have no other treatment options (though we note in our study BIT was more likely to be used as first or second line for relapsed disease and most had subsequent therapies).

Both the ANBL1221 and BEACON-immuno trials, support the addition of anti-GD2 therapy (dinutuximab or dinutuximab-beta) to a chemotherapy backbone for treatment of relapsed/refractory disease with ORRs of 53%[16] and 30%[17] respectively. However direct comparison of ORR between these two trials is potentially confounded by differences in proportion of relapsed cases, which may have poorer response rates, as we have found for BIT, and other baseline patient characteristics. For example, children with isolated bone/bone marrow relapse have better response rates[16], and patients with progressive disease after induction show a different response profile to chemo-immunotherapy[18]. BEACON-2 is a currently open multi-arm randomised adaptive phase I/II trial designed to assess the efficacy and safety of regimens for relapsed neuroblastoma. This will be the first opportunity to directly compare the efficacy of BIT with anti-GD2 based chemo-immunotherapy (temozolomide, irinotecan and dinutuximab-beta).

The main limitations of our study are its retrospective nature and lack of central radiology review. As a retrospective study, it is subject to incomplete data capture, likely to result in underrepresentation of the toxicity profile. However, we note that except for thrombocytopenia and transaminitis, we have a similar incidence of side

effects to the bevacizumab arms in the BEACON trial. In addition, the lack of central radiology review may have affected the reliability of our response rate data.

While there are no known biomarkers to identify patients who are most likely to benefit from BIT, this remains a suitable treatment option for patients who do not have targetable genomic variants and therefore are not candidates for molecularly targeted treatments. Also, whilst our study was not designed to formally assess the health economics, given that bevacizumab biosimilar drugs are now available, BIT may also represent a more economically viable regimen than dinutuximab-based chemo-immunotherapy in more resource constrained settings.

In conclusion, the BIT regimen demonstrated an encouraging efficacy and manageable toxicity profile in patients with relapsed/refractory neuroblastoma. These findings continue to support the use of BIT as a second-line treatment.

Further randomised studies are needed to separately identify optimal treatment strategies for relapsed and refractory neuroblastoma.

CreDiT authorship statement

TJJ: Investigation, methodology, data curation, visualisation, Writing – Original Draft Preparation

MS: Project administration, Investigation, Methodology, Writing – Original Draft Preparation

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Funding
TJJ is funded by a NIHR Clinical Lectureship. No specific funding was received for this service evaluation

Conflict of Interest statement
The authors report no relevant conflicts of interest

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298 Table 1 Baseline clinicopathological characteristics of patients included in this study
299

Characteristic	N = 66[1]
Age at diagnosis (years)	4.1 (2.8, 5.6)
Gender	
Female	32 (48%)
Male	34 (52%)
Primary site	
Abdominal-pelvic	6 (9.2%)
Abdominal	45 (69%)
Multifocal	2 (3.1%)
Thoraco-abdominal	5 (7.7%)
Thoracic	7 (11%)
Unknown	1
Stage	
L2	5 (7.7%)
M	60 (92%)
Unknown	1
mIBG Avid	
Heterogeneous	3 (4.7%)
Yes	57 (89%)
No	2 (3.1%)
Not performed	2 (3.1%)
Unknown	2
MycN Amplification	
Yes	16 (26%)
Gain	6 (9.7%)
No	40 (65%)
Unknown	4
ALK status	
ALK 1174 mutation	1 (1.5%)

Characteristic	N = 66[1]
ALK amplification	3 (4.5%)
Not mutated/unknown	62 (94%)
11q loss/LOH	28 (48%)
Unknown	8
Disease state prior to BIT	
Refractory	26 (39%)
Relapsed	40 (61%)

[1]Median (IQR); n (%)

Table 2 Best objective responses to BIT

Characteristic	**Refractory**, N = 26[1]	**Relapsed**, N = 40[1]	**p-value**[2]
Cycles received	4.0 (3.0, 6.0)	4.0 (2.0, 6.0)	0.6
Best response			0.058
CR/mCR	2 (8.0%)	3 (7.7%)	
PR	12 (48%)	9 (23%)	
SD	7 (28%)	9 (23%)	
PD	4 (16%)	18 (46%)	
Unknown	1	1	

[1]n (%); Median (IQR)

[2]Fisher's exact test; Wilcoxon rank sum test

Figures

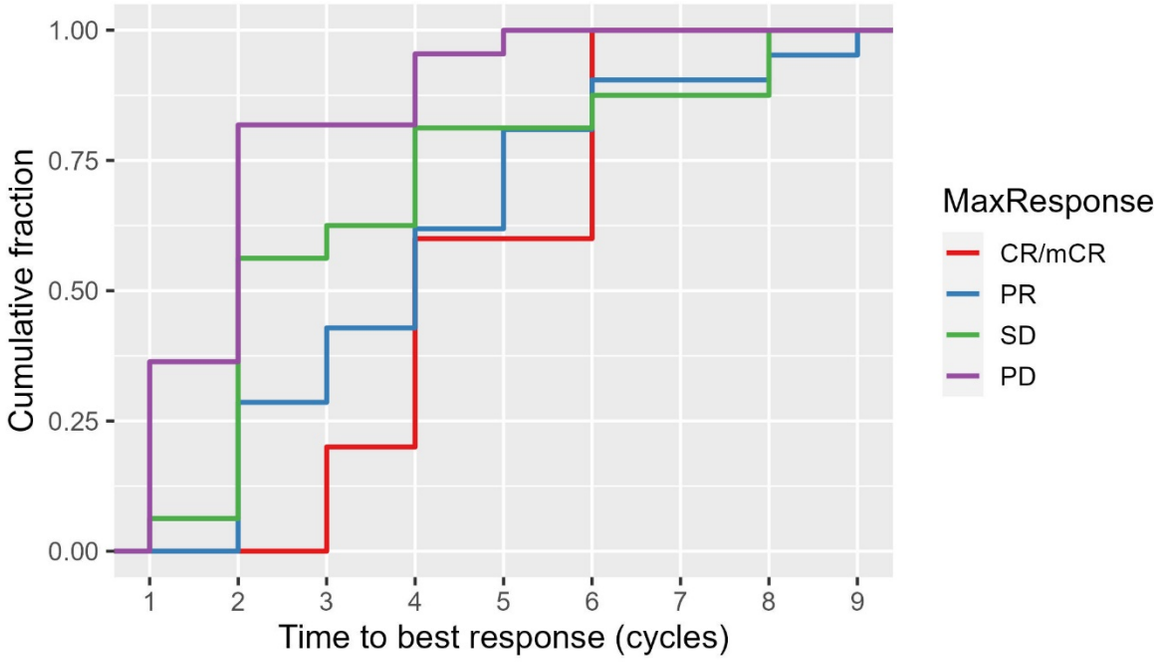

Figure 1 Cumulative frequency distribution of time to best objective response, stratified by the best response achieved. CR/mCR = Complete response or complete metastatic response, PR = partial response, SD = stable disease, PD = progressive disease n=64

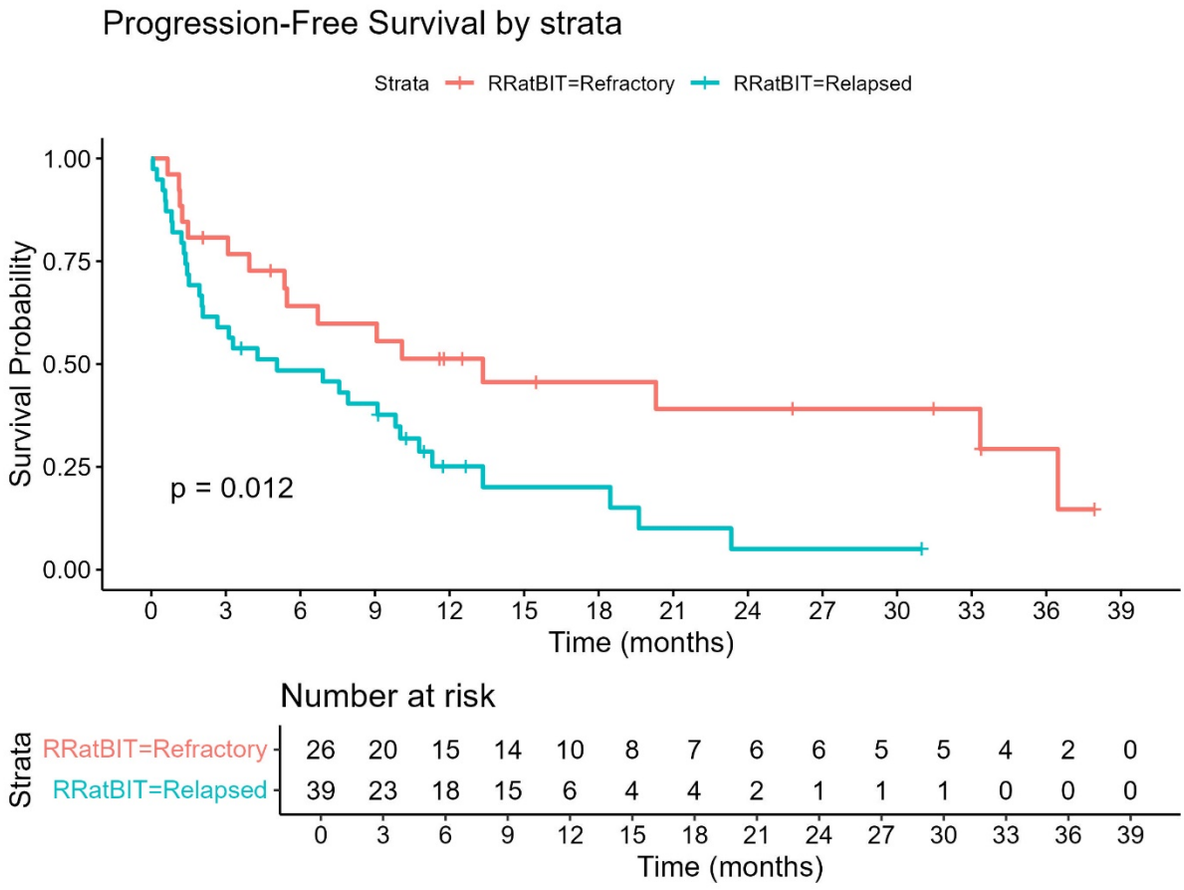

Figure 2 Kaplan-Meier survival curves for progression free survival, stratified by disease status prior to BIT (relapsed vs refractory). 80% patients had at least one additional therapy following BIT.

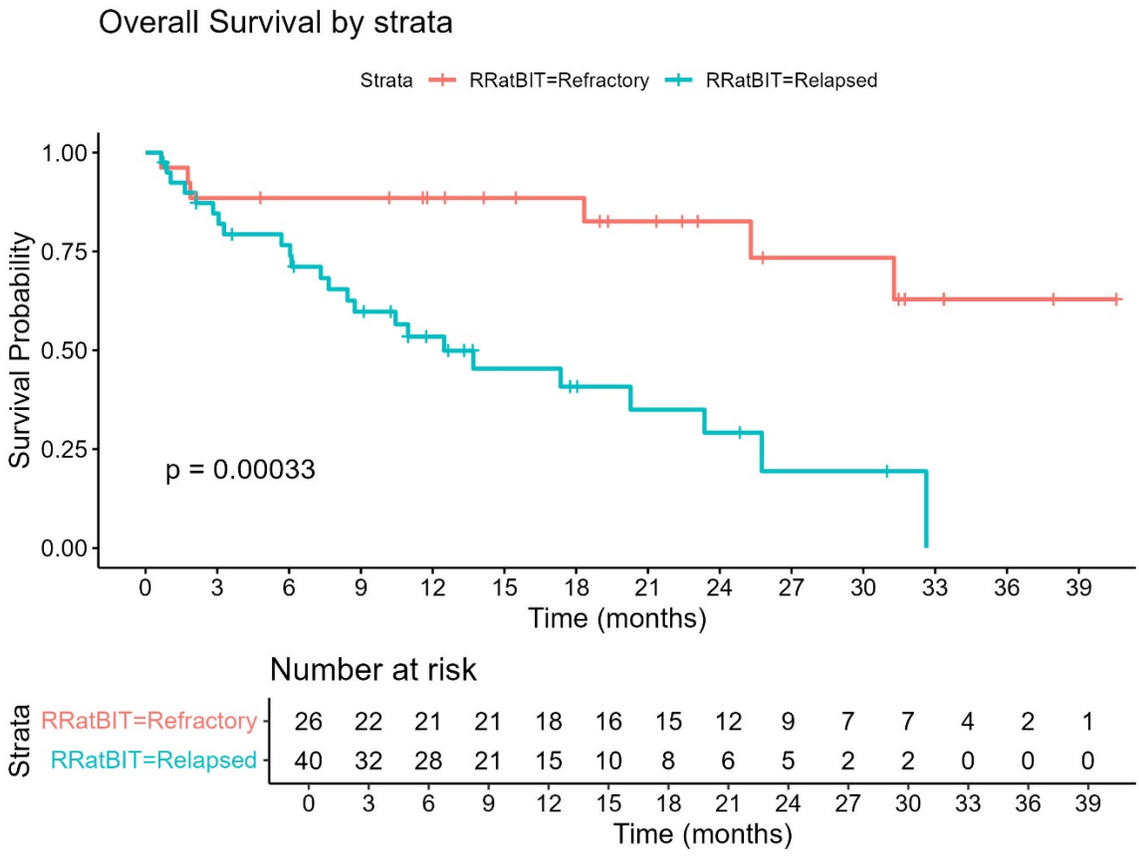

Figure 3 Overall survival curves stratified by disease status prior to BIT (relapsed vs refractory)

Supplementary Figures

1) Data collection tool
2) Comparison of baseline characteristics between relapsed and refractory cases
3) Summary of therapies received prior to BIT
4) Summary of therapies received following BIT

Supplementary Figure 2: Comparison of baseline characteristics between patients with relapsed and refractory disease at time of BIT

Characteristic	**Refractory**, N = 26[1]	**Relapsed**, N = 40[1]	**p-value**[2]
Age at diagnosis (years)	4.3 (2.2, 5.5)	4.0 (2.9, 5.5)	>0.9
Gender			0.8
Male	13 (50%)	21 (53%)	
Female	13 (50%)	19 (48%)	
Primary site			0.6
abdomen	20 (77%)	25 (64%)	
Thorax	3 (12%)	4 (10%)	
abd-pelvis	1 (3.8%)	5 (13%)	
Thoraco-abd	2 (7.7%)	3 (7.7%)	
multifocal	0 (0%)	2 (5.1%)	
Unknown	0	1	
Stage			0.6
M	25 (96%)	35 (90%)	
L2	1 (3.8%)	4 (10%)	
Unknown	0	1	
mIBG Avid			>0.9
Yes	22 (88%)	35 (90%)	
Heterogeneous	1 (4.0%)	2 (5.1%)	
No	1 (4.0%)	1 (2.6%)	
not done	1 (4.0%)	1 (2.6%)	
Unknown	1	1	
MycN Amplification			0.11
No	18 (75%)	22 (58%)	
Yes	6 (25%)	10 (26%)	
Gain	0 (0%)	6 (16%)	
Unknown	2	2	

Characteristic	**Refractory**, N = 26[1]	**Relapsed**, N = 40[1]	**p-value**[2]
ALK status			>0.9
Not mutated/unknown	25 (96%)	37 (93%)	
ALK amplification	1 (3.8%)	2 (5.0%)	
ALK 1174 mutation	0 (0%)	1 (2.5%)	
11q loss/LOH	8 (35%)	20 (57%)	0.10
Unknown	3	5	

[1]Median (IQR); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Supplementary Figure 3: Summary of therapies received prior to BIT

Characteristic	**N = 66**[1]
Induction regimen	
Rapid COJEC	57 (88%)
GPOH	2 (3.1%)
Modified N7	2 (3.1%)
others	4 (6.2%)
Unknown	1
Induction response	
Complete metastatic response	2 (3.3%)
PR	46 (75%)
PR SIOPEN Score<3- BM<5%	4 (6.6%)
SD	2 (3.3%)
PD	7 (11%)
Unknown	5
Surgery	
Complete resection	16 (28%)
Incomplete resection	15 (26%)
Not performed	26 (46%)
Unknown	11
High dose chemotherapy	
No	35 (55%)
Yes BuMel	28 (44%)
Yes CEM	1 (1.6%)
Unknown	2
Radiotherapy	
No	35 (56%)
Yes 21 Gy	24 (39%)
Yes 36 Gy	3 (4.8%)
Unknown	4
Immunotherapy received	
Dinutuximab	24 (39%)

Characteristic	N = 66[1]
Dinutuximab+IL2	1 (1.6%)
None	36 (59.4%)
Unknown	5

[1]n (%)

Supplementary Figure 4: Summary of therapies received following BIT

	Overall		Refractory		Relapsed	
Treatment	N	%	N	%	N	%
Radiotherapy	20	30.3%	11	42.3%	9	22.5%
BuMel and ASCT	18	27.3%	17	65.4%	1	2.5%
MiNivAn	18	27.3%	10	38.5%	8	20%
Cyclophosphamide +Topotecan	16	24.2%	8	30.8%	8	20%
Dinutuximab+cisRA	13	19.7%	11	42.3%	2	5%
None	12	18.2%	3	11.5%	9	22.5%
Surgery	9	13.6%	8	30.8%	1	2.5%
Oral etoposide	7	10.6%	1	3.8%	6	15%
Topotecan+MIBG	4	6.1%	2	7.7%	2	5.0%
Venetoclax	4	6.1%	0	0%	4	10.0%
DFMO	3	4.5%	1	3.8%	2	5.0%
Idasanutlin	3	4.5%	0	0%	3	7.5%
Naxitamab	3	4.5%	1	3.8%	2	5.0%
CAR-T	2	3.0%	0	0%	2	5.0%
Temozolomide + irinotecan+Dinutuximab	2	3.0%	2	7.7%	0	0%
Arginase	1	1.5%	0	0%	1	2.5%
Cryoablation	1	1.5%	0	0%	1	2.5%
GD2/GD3 vaccine	1	1.5%	1	3.8%	0	0%
ICE (Ifosfamide, cisplatin, etoposide)	1	1.5%	0	0%	1	2.5%
Lorlatinib	1	1.5%	0	0%	1	2.5%
SCOOP (Niraparib + Dostarlimab)	1	1.5%	0	0%	1	2.5%
Temozolomide	1	1.5%	0	0%	1	2.5%
Topotecan +temozolomide+Dinutuximab	1	1.5%	1	3.8%	0	0%
Vincristine+cisplatin	1	1.5%	1	3.8%	0	0%

Pediatric Blood & Cancer Author Checklist

Sub-specialty Classification ***(****Research Articles and Brief Reports* ***ONLY.*** *If your manuscript is not a Research Article or Brief Report, please select* ***N/A)***

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Transplantation	☐ Yes
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Histiocyte Society	☐ Yes
International Society of Paediatric Oncology (SIOP)	☒ Yes
International Society of Pediatric Surgical Oncology	☐ Yes
None of the Above	☐ Yes