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Original Research

Prognostic factors of overall survival in children and adolescents enrolled in dose-finding trials in Europe: An Innovative Therapies for Children with Cancer study

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Abstract ***Objectives:*** Dose-finding trials are fundamental to develop novel drugs for children and adolescents with advanced cancer. It is crucial to maximise individual benefit, whilst ensuring adequate assessment of key study end-points. We assessed prognostic factors of survival in paediatric phase I trials, including two predictive scores validated in adult oncology: the Royal Marsden Hospital (RMH) and the MD Anderson Cancer Center (MDACC) scores.
Methods: Data of patients with solid tumours aged <18 years at enrolment in their first dose-finding trial between 2000 and 2014 at eight centres of the Innovative Therapies for Children with Cancer European consortium were collected. Survival distributions were compared using log-rank test and Cox regression analyses.
Results: Overall, 248 patients were evaluated: median age, 11.2 years (range 1.0–17.9); 46% had central nervous system (CNS) tumours and 54% extra-CNS tumours. Complete responses were observed in 2.1%, partial responses in 7.2% and stable disease in 25.9%. Median overall survival (OS) was 6.3 months (95% confidence interval, 5.2–7.4). Lansky/Karnofsky ≤80%, no school/work attendance, elevated creatinine and RMH score ≥1 correlated with worse OS in the multivariate analysis. The RMH and MDACC scores correlated with OS in adolescents (12–17 years), p = 0.002, but not in children (2–11 years).
Conclusions: Performance status of 90–100% and school/work attendance at enrolment are strong indicators of longer OS in paediatric phase I trials. Adult predictive scores correlate with survival in adolescents. These findings provide a useful orientation about potential prognosis and could lead in the future to more paediatric-adapted eligibility criteria in early-phase trials.

1. Introduction

Phase I, also called dose-finding, trials play a key role in drug development for patients with advanced cancer. These studies identify the optimal dose of novel agents for subsequent evaluation of efficacy in phase II and III trials. Phase I trials in children have been proven to be safe, with dose-limiting toxicities occurring in 12–13% of patients and toxic deaths reported in 0–0.5% [1–3]. Thus, they are increasingly being integrated into therapeutic strategies for patients with relapsed/refractory tumours at earlier time points of treatment failure.

In order to avoid unnecessary exposure to potential toxicities and additional interventions with no real chance of gain, as well as to ensure fulfilment of trial objectives, adequate selection of patients remains crucial. Widely accepted eligibility criteria include adequate organ function, reasonable performance status and life expectancy greater than 8–12 weeks. However, accurate prediction of survival is notoriously difficult. Two clinical scores have been validated in adult cancer patients to predict survival: The Royal Marsden Hospital (RMH) score, including albumin <35 g/L, lactate dehydrogenase (LDH) above the upper limit of normal (ULN) and the presence of ≥3 metastatic sites [4–7]; and the MD Anderson Cancer Center (MDACC) score, including the RMH score items plus gastrointestinal tumour type and Eastern Cooperative Oncology Group (ECOG) performance status ≥1 [8]. These scores have not been validated in children. We assessed prognostic factors of overall survival (OS) specific for children and adolescents enrolled in phase I trials and evaluated the RMH and MDACC scores in this cohort.

2. Patients and methods

2.1. Study design

Patients enrolled on dose-finding trials between 1st January 2000 and 31st December 2014 at the eight highest recruiting centres of the Innovative Therapies for Children with Cancer European consortium were reviewed [9]. Patients aged <18 years at the time of enrolment in a trial with a dose-finding component (phases I or IB) and histological diagnosis of a solid tumour (except low-grade gliomas) or clinicoradiological diagnosis of diffuse intrinsic pontine glioma (DIPG) with progression postradiotherapy were eligible. Screening failures were excluded. All phase I trials had been approved by local institutional review boards. Informed consent by parents/legal guardians and patients had been obtained for participation to the corresponding trial.

Clinical parameters collected at study entry included: age, gender, diagnosis, number and location of metastatic sites, previous treatments, type of study drug (targeted or cytotoxic), laboratory values (haemoglobin, neutrophils, platelets, creatinine, total bilirubin,

albumin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], LDH), time elapsed from initial diagnosis to enrolment, school/work attendance for patients aged ≥5 years (including part time), requirement of opioids (defined as the use of strong opioids, such as morphine, oxycodone, fentanyl, either regularly or for breakthrough pain more than once weekly) and performance status.

Performance status assessed according to Lansky or Karnofsky scales were deemed interchangeable, since both apply comparable items. Lansky/Karnofsky scales were converted to ECOG scale for MDACC score calculations or vice versa, for survival analyses, as follows: Lansky/Karnofsky of 90–100%, 70–80%, 50–60% or 30–40%, were equivalent to an ECOG of 0, 1, 2 or 3, respectively. Tumour responses were classified according to protocol-specific criteria. The dates of progression, end of study and death or last follow-up, as well as the reason for study discontinuation, if different from disease progression, were also collected. The RMH and MDACC scores were determined in those patients with complete data in all the score items [4,7,8].

2.2. Statistical considerations

Data from patients for efficacy and survival analyses were included only at enrolment in their first phase I trial. Time to progression (TTP) was measured from day 1 of cycle 1 (C1D1) until disease progression. OS was measured from C1D1 until death or last follow-up. Early mortality rates were determined at 30 and 90 days from C1D1. Descriptive statistics were used to summarise the baseline patients' characteristics. Categorical data were described with contingency tables including counts and percentages and compared using chi-squared test, whenever appropriate. Continuously scaled measures were described with median, range and 95% confidence interval (95% CI). Survival curves were estimated by the Kaplan–Meier method. Univariate log-rank test and multivariate Cox regression analyses were used to compare survival distributions between groups. Cox regression analysis was conducted for those variables identifiable at enrolment that were significant in the univariate analysis. Statistical analyses were performed using the SPSS® statistical package version 16.0.

3. Results

3.1. Baseline patient characteristics

Data from 248 patients treated across 21 trials (Suppl. Table 1) were evaluated. Patients' demographics (Table 1) showed: median age, 11.2 years (range, 1.0–17.9); male-to-female ratio, 1.2:1; predominant diagnoses included medulloblastoma/primitive

Table 1
Demographics of the study population (N = 248).

Items	Number (%)
Baseline patient characteristics	
Age at inclusion (years):	
Median (range)	11.2 (1.0–17.9)
<2	3 (1.2)
2–11	134 (54.0)
12–17	111 (44.8)
Gender:	
Female	114 (46.0)
Male	134 (54.0)
Diagnosis:	
CNS tumours:	114 (46.0)
Medulloblastoma/PNET	37 (14.9)
High-grade glioma	27 (10.9)
DIPG[a]	20 (8.1)
Ependymoma	16 (6.5)
Other CNS tumours[b]	14 (5.6)
Extra-CNS tumours:	134 (54.0)
Neuroblastoma	33 (13.3)
Ewing's sarcoma	24 (9.7)
Osteosarcoma	17 (6.9)
Rhabdomyosarcoma	17 (6.9)
Non-rhabdo STS[c]	14 (5.6)
Other extra-CNS tumours[d]	29 (11.6)
Performance status (Lansky–Karnofsky/ECOG):	
90–100%/0	170 (71.1)
70–80%/1	55 (23.1)
40–60%/2–3	14 (5.8)
Not available	9 (N/A)
School/work attendance (for ≥5-year-olds):	
No	42 (25.1)
Yes	125 (74.9)
Not available	40 (N/A)
Not applicable (age <5 years)	41 (N/A)
Previous treatments	
Previous chemotherapy:	
Median (range)	2 (0–8)
0 lines	19 (7.7)
1–2 lines	130 (52.4)
≥3 lines	99 (39.9)
Previous surgery:	
No/biopsy only	53 (22.3)
Non-GTR	57 (23.9)
GTR	128 (53.8)
Not available	10 (N/A)
Previous radiotherapy:	
No	53 (21.4)
Yes	195 (78.6)
Previous ASCT:	
No	63 (51.2)
Yes	60 (48.8)
Not applicable[e]	125 (N/A)
Experimental treatment	
Trial category:	
Single-targeted agent	142 (57.3)
Single cytotoxic agent	65 (26.2)
>1 targeted agent	2 (0.8)
>1 cytotoxic agent	22 (8.9)
Targeted + cytotoxic agent	17 (6.9)
Response criteria:	
RECIST 1.0	64 (28.2)
RECIST 1.1	69 (30.4)
Other[f]	94 (41.4)
Not available	21 (N/A)
Best response:	

Table 1 (*continued*)

Items	Number (%)
Complete response	5 (2.1)
Partial response	17 (7.2)
Stable disease[g]	61 (25.9)
Progressive disease	153 (64.8)
Not available/evaluable	12 (N/A)
Reason for study discontinuation:	
Progressive disease	198 (84.2)
Toxicity	14 (6.0)
Withdrawal of consent	4 (1.7)
Other[h]	19 (8.1)
Not available	13 (N/A)
Clinical scores	
RMH score:	
0	61 (42.1)
1	60 (41.4)
2	23 (15.8)
3	1 (0.7)
Not available	103 (N/A)
MDACC score:	
0	49 (34.5)
1	54 (38.0)
2	32 (22.5)
3	6 (4.2)
4	1 (0.7)
5	0 (0.0)
Not available	106 (N/A)

ASCT: autologous stem cell transplant; ATRT: atypical teratoid rhabdoid tumour; CNS: central nervous system; CR: complete response; DIPG: diffuse intrinsic pontine glioma; ECOG: Eastern Cooperative Oncology Group; GTR: gross total resection; INRC: International Neuroblastoma Response Criteria; MDACC: MD Anderson Cancer Center; N/A: not available/applicable; Non-rhabdo STS: non-rhabdo soft tissue sarcomas; PD: progressive disease; PNET: primitive neuroectodermal tumour; RANO criteria: Response Assessment in Neuro-Oncology criteria; RECIST: Response Evaluation Criteria In Solid Tumours; RMH: Royal Marsden Hospital; WHO criteria: World Health Organization criteria.

[a] DIPG patients were only eligible if they had experienced progression after radiotherapy prior to enrolment.

[b] Other CNS tumours: atypical teratoid rhabdoid tumour (n = 8), pineoblastoma and neurosarcoma (n = 2 each), posterior fossa tumour NOS and glioblastoma/undifferentiated sarcoma (n = 1 each).

[c] Non-Rhabdo STS: inflammatory myofibroblastic tumour (3), synovial sarcoma (3), extrarenal rhabdoid (2), undifferentiated sarcoma (2), desmoplastic small round cell tumour (2), fusiform cell sarcoma (1), and myxofibrosarcoma (1).

[d] Other extra-CNS tumours: Wilms tumour (9), hepatoblastoma (5), germ cell tumour (4), melanoma (4), carcinoma (3), lymphoma (3), and peripheral PNET (1).

[e] Only tumour types for which ASCT is generally accepted as part of their treatment, either at diagnosis or at relapse, were included (i.e. medulloblastoma/sPNET, pineoblastoma, neuroblastoma, Wilms tumour, Ewing's sarcoma, peripheral PNET, lymphomas, and ATRT/extracranial rhabdoid tumours).

[f] Other response criteria included: RANO, McDonald, INRC, WHO, or protocol specific.

[g] Including patients with non-measurable disease who achieved non-CR/non-PD.

[h] Other reasons for study discontinuation included: completion of trial protocol, complete response, consolidation with further treatment (e.g. surgery, radiotherapy, stem cell transplant), error of posology, adverse events not related to study drug and investigator's decision.

neuroectodermal tumour (14.9%), neuroblastoma (13.3%) and high-grade glioma (HGG) (10.9%). Lansky/Karnofsky of 90–100% correlated with school/work attendance ($p < 0.0001$; data not shown). However, among cases with both performance status and school/work data available, 13.5% (15/111) of patients with Lansky/Karnofsky of 90–100% did not attend school/work; and 50% (27/54) of patients with Lansky/Karnofsky ≤80% were going to school/work at least part time.

The patients had received a median of two prior lines of chemotherapy (range, 0–8). Nineteen patients (7.7%) had not received any first-line chemotherapy at enrolment, including the following diagnoses: DIPG (n = 9), ependymoma (n = 4), inflammatory myofibroblastic tumour and melanoma (n = 2 each), HGG and neurosarcoma (n = 1 each). The median follow-up for the entire cohort was 5.6 months (range, 0.23–148.8).

3.2. Response rate and time to progression

Response assessments were available in 236 patients (95.2%). Complete response (CR) was seen in 2.1% of patients, partial response (PR) in 7.2%, stable disease (SD) in 25.9% and progressive disease (PD) at first evaluation in 64.8% (Table 1). Overall, the clinical benefit ratio (CR + PR + SD) was 35.2%. Overall, 81.8% of patients with CR/PR (n = 18/22) and 42.6% with SD (n = 26/61) stayed on trial for >4 months. There were no significant differences in the rate of CR/PR between targeted or cytotoxic agents: 10.4% versus 6.9%, respectively ($p = 0.367$; data not shown). The median TTP of the entire cohort was 1.7 months (95% CI, 1.62–1.84) (Fig. 1A).

3.3. Overall survival and early mortality rates

The median OS of the entire cohort was 6.3 months (95% CI, 5.2–7.4) (Fig. 1B). The 30-d mortality was 7.3% (n = 18/248; 95% CI, 4.1–10.5). The 90-d mortality was 29.0% (n = 72/248; 95% CI, 23.4–34.7). No toxic deaths were reported.

3.4. Prognostic factors of overall survival

The impact on OS of 28 clinical variables was evaluated. In the univariate analysis (log-rank), factors associated with poorer OS included: <2 years from diagnosis to C1D1, performance status ≤80%, no school/work attendance, requirement of strong opioids, creatinine > ULN, LDH > ULN and PD at first evaluation (Tables 2 and 3; Fig. 1C).

Subsequently, response to treatment was excluded from the multivariate analysis (Cox regression) because this variable is not predictable at enrolment. In the multivariate analysis, factors associated with worse OS included: performance status ≤80%, no school/work

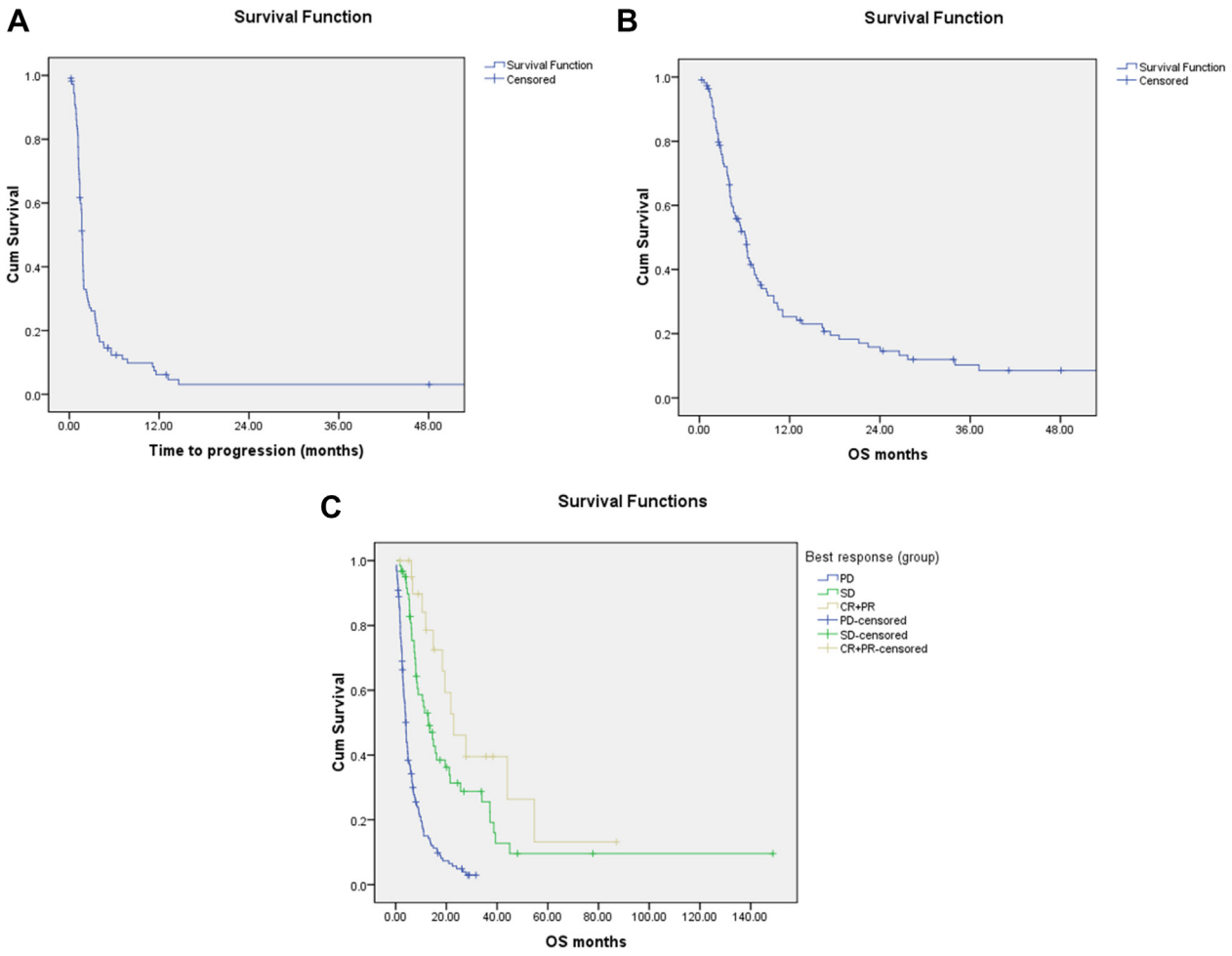

Fig. 1. Kaplan–Meier curves of the entire cohort for time to progression (A), overall survival (B) and survival according to response categories (C). OS, overall survival; PD, progressive disease; SD, stable disease; CR, complete response; PR, partial response.

attendance and creatinine > ULN (Table 4). When 69 patients with performance status ≤80% were excluded, the median OS of the cohort was 7.4 months (95% CI, 5.6–9.2) and the 30- and 90-d mortality were 3.5% (n = 6/170; 95% CI, 0.7–6.3) and 20.6% (n = 35/170; 95% CI, 14.5–26.7), respectively.

3.5. Validation of predictive scores for overall survival

Overall, 145 and 142 patients had complete data for calculation of the RMH and MDACC scores, respectively. In the univariate analysis, both the RMH and MDACC scores correlated with survival when the prognostic categories were assessed both separately or grouped as 0 versus ≥1 (Table 3, Fig. 2). In the multivariate analysis (Table 4), RMH score ≥1 was significantly associated with shorter median OS: hazard ratio, 4.16 (95% CI, 1.26–13.71; p = 0.019). When 84 patients with RMH score ≥1 were excluded, the median OS of the cohort was 12.9 months (95% CI, 6.3–19.6) and the 30-d and 90-d mortality were 1.6% (n = 1/61; 95% CI, 0.0–4.8) and 18.0% (n = 11/61; 95% CI, 8.4–27.6), respectively.

Since the scores were designed for adults, its performance was subsequently assessed in children (2–11 years) and adolescents (12–17 years) separately (Table 5). Both the RMH and MDACC scores correlated with the median OS in adolescents (log-rank test, p = 0.002 each), but not in children (log-rank test, p = 0.257 and p = 0.495, respectively).

4. Discussion

This series is the largest to date assessing prognostic factors of survival in paediatric phase I trials. Demographic data of our sample were comparable to those reported in former reviews [1,2,10,11] and constitute an appropriate representation of the population entered into paediatric phase I trials: recruitment of infants aged <2 years is rare, around half of the patients are diagnosed with central nervous system tumours and approximately 70% of patients have metastatic disease at enrolment.

Table 2
Median overall survival and log-rank test for univariate analysis according to patient characteristics and laboratory values at baseline.

N[a]	Characteristics	Number (%)	Median OS (months)	95% CI (months)	Log-rank test (p value)
Baseline patient characteristics					
Age at C1D1 (years):					
248	<2	3 (1.2)	4.13	1.25–7.01	0.764
	2–11	134 (54.0)	6.90	4.73–9.07	
	12–17	111 (44.8)	6.13	4.90–7.36	
Gender:					
248	Female	114 (46.0)	6.77	4.73–8.81	0.746
	Male	134 (54.0)	6.23	5.20–7.27	
Tumour location:					
248	CNS	114 (46.0)	5.43	3.84–7.02	0.334
	Extra-CNS	134 (54.0)	7.13	5.60–8.66	
≥2 years from diagnosis to C1D1:					
248	No	139 (56.0)	4.83	3.42–6.24	**0.014**
	Yes	109 (44.0)	7.93	5.63–10.23	
Performance status (Lansky or Karnofsky scales):[b]					
239	90–100%	170 (71.1)	7.40	5.64–9.16	**<0.001**
	≤80%	69 (28.9)	3.17	2.02–4.32	
School/work attendance:					
167	No	42 (25.1)	2.50	1.29–3.71	**<0.001**
	Yes	125 (74.9)	7.57	6.06–9.08	
Requirement of opioids:					
248	No	207 (83.5)	6.67	5.32–8.03	**0.001**
	Yes	41 (16.5)	3.17	1.43–4.91	
Number of metastatic sites:					
248	0 sites	70 (28.2)	5.43	3.41–7.45	0.748
	1–2 sites	158 (63.7)	6.47	5.01–7.93	
	≥3 sites	20 (8.1)	6.13	1.31–10.95	
Metastatic sites involved:					
248	Lung	No: 182 (73.4)	6.63	5.16–8.10	0.365
		Yes: 66 (26.6)	6.03	4.31–7.75	
248	Bone	No: 189 (76.2)	5.87	4.78–6.96	0.576
		Yes: 59 (23.8)	8.27	5.42–11.12	
248	Bone marrow	No: 217 (87.5)	5.87	4.94–6.80	0.114
		Yes: 31 (12.5)	11.43	5.59–17.27	
248	Liver	No: 239 (96.4)	6.30	5.02–7.58	0.767
		Yes: 9 (3.6)	6.27	5.97–6.57	
248	CNS	No: 188 (75.8)	6.30	5.04–7.56	0.692
		Yes: 60 (24.2)	6.23	3.43–9.03	
248	Other sites[c]	No: 199 (80.2)	6.63	5.05–8.21	0.189
		Yes: 49 (19.8)	5.73	4.51–6.95	
Laboratory values at baseline					
Anaemia:[d]					
248	Grade ≤1	214 (86.3)	6.33	5.10–7.56	0.304
	Grade ≥2	34 (13.7)	4.20	<0.1–8.89	
Neutropenia:[d]					
239	Grade ≤1	220 (92.1)	6.40	5.14–7.66	0.571
	Grade ≥2	19 (7.9)	9.53	0.61–18.45	
Platelets:					
241	$\geq 150 \times 10^9$/L	233 (96.7)	6.40	5.14–7.66	0.520
	$<150 \times 10^9$/L	8 (3.3)	3.10	<0.1–13.08	
Creatinine:					
243	≤ULN	238 (97.9)	6.40	5.10–7.71	**0.035**
	>ULN[e]	5 (2.1)	3.83	<0.1–8.98	
Total bilirubin:					
236	≤ULN	228 (96.6)	6.63	5.38–7.89	0.264
	>ULN[e]	8 (3.4)	2.57	1.70–3.44	
Albumin:					
214	≥35 g/L	179 (83.6)	6.30	4.92–7.68	0.080
	<35 g/L	35 (16.4)	5.50	2.37–8.63	
ALT:					
241	≤ULN	214 (88.8)	6.40	4.93–7.87	0.743

(continued on next page)

Table 2 (*continued*)

N[a]	Characteristics	Number (%)	Median OS (months)	95% CI (months)	Log-rank test (p value)
	>ULN[e]	27 (11.2)	6.40	3.24–9.56	
AST:					
235	≤ULN	198 (84.3)	6.90	5.33–8.47	0.573
	>ULN[e]	37 (15.7)	5.50	2.32–8.68	
LDH:					
161	≤ULN	80 (49.7)	9.20	6.75–11.75	**0.004**
	>ULN	81 (50.3)	5.43	3.87–6.99	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C1D1, cycle 1–day 1; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; LDH, lactate dehydrogenase; N, sample size for each variable; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; ULN, upper limit of normal; 95% CI, 95% confidence interval.
Significant p values <0.05 are represented in bold.

[a] Patients for whom the item was not applicable/available were excluded from the univariate analysis—recalculated sample sizes have been added as applicable.

[b] Lansky and Karnofsky scales were used interchangeably, performance status reported as per ECOG scale were converted to Lansky/Karnofsky as described in the Methods section.

[c] Other metastatic sites included: non-locoregional lymph nodes, pleura, mediastinum, breast, peritoneum, pancreas, adrenal glands, testes and soft tissues.

[d] Grading as per CTCAE v4.03.

[e] Creatinine, bilirubin, ALT and AST parameters above the upper limit of normal were all within the limits permitted as per protocol-specific eligibility criteria.

In terms of activity, we observed similar response rates to those reported in the literature, with objective responses and disease stabilisation ranging between 3.8–9.6% and 17–37.7%, respectively [1,2,10,12]. The 30-d and 90-d mortality rates observed in our sample were slightly higher than those reported in a large study of adult cancer patients (3 and 16.5%, respectively) [5]. This finding might be related to the different underlying biology of childhood cancers; a lower proportion of patients treated in drug combination trials in our sample compared to the adult cohort (16.6% versus 37.2%, respectively); and the nature of the targeted agents explored in paediatric trials, with very few of them addressing clear oncogenic drivers in selected patient populations (e.g. BRAF V600 mutations), in part because paediatric cancers as a whole have fewer known targetable driver mutations [13]. The median TTP and OS in our population were also comparable to those previously reported: 1.3–2.8 months for TTP and 3.6–8.5 months for OS [1,2,10,11].

Regarding prognostic factors of survival, a more aggressive course of the underlying disease (i.e. <2 years from diagnosis to C1D1, elevated LDH and PD at first evaluation) was associated with poorer outcomes in the univariate analysis, whereas good performance status (Lansky/Karnofsky 90–100%) and school/work attendance, which is a surrogate for good performance status, were associated with improved outcome in the multivariate analysis.

Lansky, Karnofsky and ECOG performance scales constitute semiquantitative methods that are easily applicable, comparable and widely used in clinical trials. Their shortcomings include variability subject to physician's judgement and the lack of a universal agreement as regards the most appropriate age cutoff to apply each scale.

School/work attendance, being independent from the observer's criteria, constitutes a more robust variable and also provides a better perception of the well-being of the patient as a continuum, as opposed to the performance status which is assessed at specific time points and can be biased by intercurrent conditions. Interestingly, we observed that half of the patients with performance status ≤80% were able to attend school/work at least part time. However, school/work attendance cannot be easily quantified; it might be influenced by factors not necessarily related to the performance status, as illustrated by the 13% of patients of our sample with performance status 90–100% who were not attending school/work (e.g. patient/parents' decision, school/work centre regulations, physician's preference); and this variable is not routinely assessed in clinical trials. Overall, school/work attendance could be taken into consideration to improve our estimation of the performance status.

The requirement of opioids was also assessed as a surrogate for performance status, but its prognostic value was only determined in the univariate analysis. Additionally, in our series, only five patients had creatinine levels above the ULN, but below the standard cutoff of 1.5 times the ULN required for enrolment in clinical trials. Thus, the prognostic implications of elevated creatinine levels should be interpreted cautiously. Conversely, haematological (haemoglobin, neutrophils, platelets) and liver function tests (total bilirubin, albumin, ALT, AST) that were outside the normal ranges, but still within the corresponding cutoffs permitted for trial eligibility, were not associated with poorer survival. Hence, this finding suggests that minor variations in the haematological and liver parameters do not impact upon survival and therefore provides evidence to support the current cutoff values used in paediatric phase I trials.

Additionally, despite children with brain tumours generally tend to experience shorter survival than those with extracranial tumours [14], in our cohort, both groups showed comparable survival outcomes, thereby

Table 3
Median overall survival and log-rank test for univariate analysis according to previous treatments, experimental treatment and clinical scores.

N[a]	Characteristics	Number (%)	Median OS (months)	95% CI (months)	Log-rank test (p value)
Previous treatments					
Previous chemotherapy:					
248	0–2 lines	149 (60.1)	6.27	5.30–7.24	0.605
	≥3 lines	99 (39.9)	6.33	3.63–9.03	
Previous surgery:					
238	No/biopsy only	53 (22.3)	5.77	2.79–8.76	0.195
	Non-GTR	57 (23.9)	6.40	4.81–7.99	
	GTR	128 (53.8)	6.27	4.64–7.90	
Previous radiotherapy:					
248	No	53 (21.4)	8.13	5.34–10.92	0.065
	Yes	195 (78.6)	5.57	4.36–6.78	
Previous ASCT:[b]					
123	No	63 (51.2)	7.77	5.17–10.37	0.447
	Yes	60 (48.8)	7.77	4.36–11.18	
Experimental treatment					
Trial category:					
248	Targeted agent(s)	144 (58.0)	5.20	3.68–6.72	0.782
	Cytotoxic agent(s)	87 (35.1)	6.47	4.92–8.02	
	Combined	17 (6.9)	10.37	6.57–14.18	
Best response:					
236	CR/PR	22 (9.3)	22.87	12.64–33.10	**<0.001**
	SD	61 (25.9)	12.93	8.49–17.37	
	PD	153 (64.8)	4.03	3.57–4.49	
Clinical scores					
RMH score (continuous)					
145	0	61 (42.1)	12.93	6.27–19.59	**0.001**
	1	60 (41.4)	4.13	2.38–5.88	
	2	23 (15.8)	5.50	1.65–9.35	
	3	1 (0.7)	2.80	.	
RMH score (categorical)					
145	0	61 (42.1)	12.93	6.27–19.59	**<0.001**
	1–3	84 (57.9)	4.73	3.07–6.39	
MDACC score (continuous)					
142	0	49 (34.5)	13.67	7.35–20.00	**0.005**
	1	54 (38.0)	6.13	4.23–8.03	
	2	32 (22.5)	4.07	3.49–4.65	
	3	6 (4.2)	2.27	0.66–3.88	
	4	1 (0.7)	2.80	.	
	5	0 (0.0)	.	.	
MDACC score (categorical)					
142	0	49 (34.5)	13.67	7.35–20.00	**0.005**
	1–5	93 (65.5)	5.50	3.97–7.03	

ASCT, autologous stem cell transplant; ATRT, atypical teratoid rhabdoid tumour; CR, complete response; GTR, gross total resection; MDACC, MD Anderson Cancer Center; N, sample size for each variable; OS, overall survival; PD, progressive disease; PNET, primitive neuroectodermal tumour; PR, partial response; RMH, Royal Marsden Hospital; SD, stable disease; 95% CI, 95% confidence interval.
Significant p values <0.05 are represented in bold.

[a] Patients for whom the item was not applicable/available were excluded from the univariate analysis—recalculated sample sizes have been added as applicable.

[b] Only tumour types for which ASCT is generally accepted as part of their treatment, either at diagnosis or at relapse, were included (i.e. medulloblastoma/PNET, pineoblastoma, neuroblastoma, Wilms tumour, Ewing's sarcoma, peripheral PNET, lymphomas, and ATRT/extra-cranial rhaboid tumours).

supporting the enrolment of children with brain tumours in phase I trials.

This is also thus far the largest paediatric study assessing the role of the RMH and MDACC scores, which were initially devised to predict OS and early mortality in adults enrolled in phase I trials [5,7,8,15–18]. Wheler et al. [8] included some paediatric patients when developing the MDACC score, but this subset was not analysed separately. Subsequently, the same institution evaluated 40 patients aged 2–17 years enrolled in phase I trials. The only prognostic factor associated with improved OS in the multivariate analysis was age ≥15 years [11]. However, the generalisation of these results is limited by the small sample size and the fact that 33% of the cases had been enrolled in two or more trials, since a potential carry-over effect might influence the evaluation of prognostic factors of survival.

As regards the validation of the RMH and MDACC scores in our sample, we assessed survival in each of the prognostic categories separately and in two groups:

Table 4
Cox regression for multivariate analysis of survival according to clinical and analytical factors.

Items	N	Hazard ratio	95% CI	p value
≥2 years from diagnosis to C1D1	248	0.91	0.55–1.51	0.721
Performance status[a] ≤80%	239	1.98	1.07–3.64	**0.029**
School/work attendance	167	0.42	0.24–0.74	**0.002**
Requirement of opioids	248	1.28	0.63–2.58	0.494
Creatinine > ULN	243	7.52	2.11–26.81	**0.002**
LDH > ULN	161	0.90	0.43–1.87	0.777
RMH score ≥1	145	4.16	1.26–13.71	**0.019**
MDACC score ≥1	142	0.54	0.20–1.46	0.225

Significant p values <0.05 are represented in bold.
[a] According to Lansky or Karnofsky scales: C1D1, cycle 1–Day 1; LDH, lactate dehydrogenase; MDACC, MD Anderson Cancer Center; RMH, Royal Marsden Hospital; ULN, upper limit of normal; 95% CI, 95% confidence interval.

those scoring 0 compared to ≥1, instead of between 1 and 2 as in adult studies [4,7]. The cutoff was set between 0 and 1 because this showed minimal overlap between prognostic categories in the Kaplan–Meier curves and their median OS ± 95% CI for both scores. In the multivariate analysis, only RMH ≥1 was associated with worse OS.

Interestingly, the hypothetical exclusion of patients with RMH score ≥1 would increase the median OS by 6.6 months and reduce the 30-d and 90-d mortality by 5.7% and 11.0%, respectively, but would reduce recruitment by at least 33.9%. Similarly, excluding patients with performance status ≤80% would increase the median OS by 1.1 months and reduce the 30-d and 90-d mortality by 3.8% and 8.4%, respectively; however, this would reduce recruitment by at least 27.8%. Therefore, while we have observed specific factors that significantly correlate with OS, caution should be exercised at the time of using these to determine the eligibility criteria in forthcoming trials. These findings support the current standard cutoffs for performance status at 50–70% and highlight the need for a better understanding of patient selection for paediatric phase I trials.

In this respect, when the sample was subdivided into age groups, we observed that distribution of survival

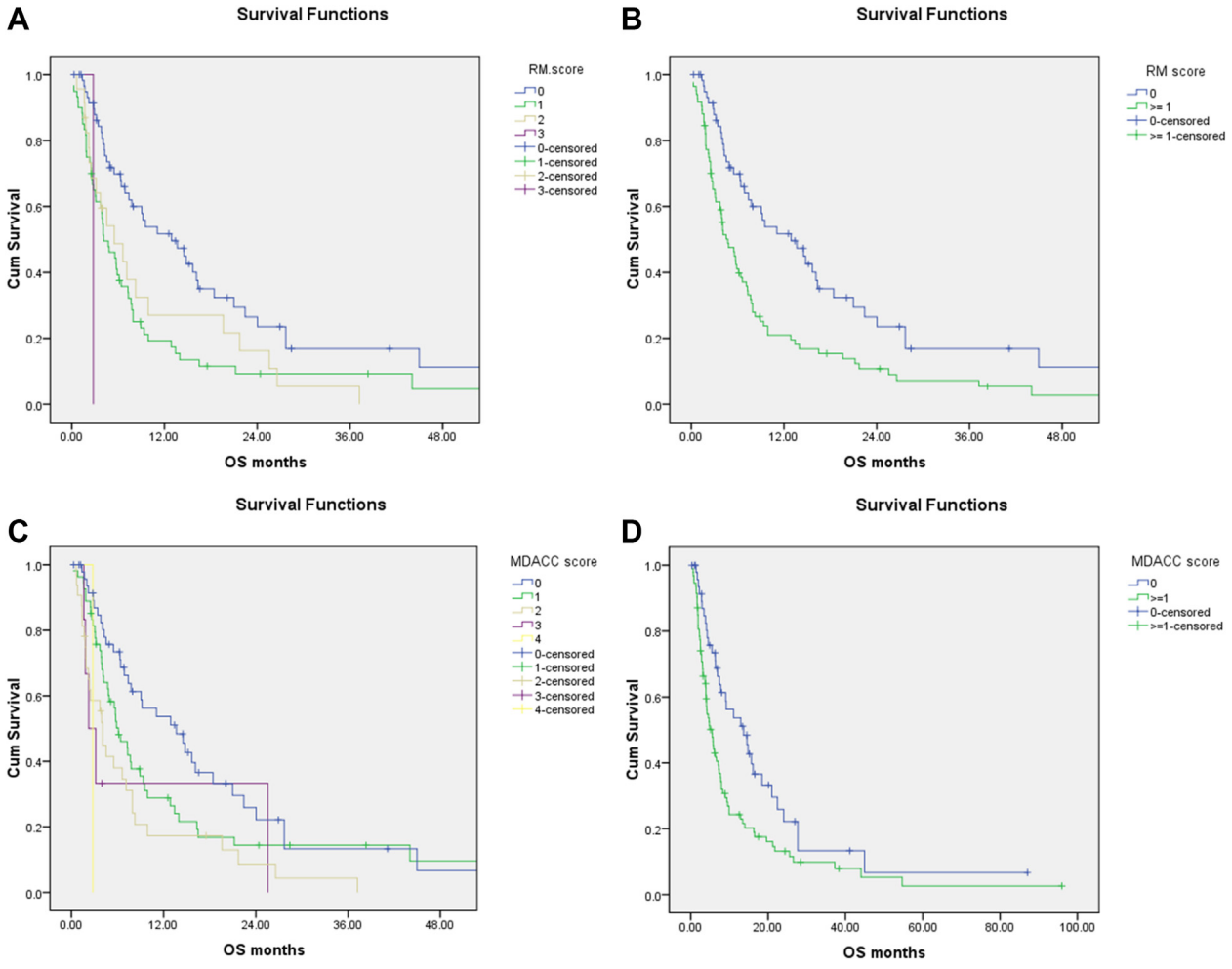

Fig. 2. Kaplan–Meier curves of overall survival according to Royal Marsden Hospital and MD Anderson Cancer Center scores assessed either as continuous variables or grouping patients according to scores of 0 versus ≥1: RMH continuous (A), RMH groups 0 versus ≥1 (B), MDACC continuous (C), and MDACC groups 0 versus ≥1 (D). MDACC, MD Anderson Cancer Center; RMH, Royal Marsden Hospital; OS, overall survival.

Table 5
Median overall survival and log-rank test of clinical scores in children and adolescents.

Groups	Children (2–11 years)			Adolescents (12–17 years)		
	Number (%)	Median OS (95% CI) in months	Log-rank (p value)	Number (%)	Median OS (95% CI) in months	Log-rank (p value)
RMH score (n = 143)[a]						
0	29 (39.7)	9.53 (<0.1–19.54)	0.257	31 (44.3)	12.93 (6.36–19.50)	**0.002**
1	34 (46.6)	4.83 (2.16–7.50)		25 (35.7)	4.07 (2.93–5.21)	
2	10 (13.7)	19.60 (<0.1–40.44)		13 (18.6)	4.53 (1.16–7.91)	
3	—	—		1 (1.4)	2.80 (N/A)	
Overall	73 (100)	7.67 (5.52–9.82)		70 (100)	6.33 (4.36–8.30)	
MDACC score (n = 140)[a]						
0	23 (32.4)	14.53 (5.02–24.04)	0.495	25 (36.2)	12.93 (7.15–18.72)	**0.002**
1	30 (42.3)	5.77 (2.25–9.29)		23 (33.3)	6.40 (3.95–8.85)	
2	15 (21.1)	5.50 (1.15–9.85)		17 (24.6)	3.73 (2.02–5.44)	
3	3 (4.2)	3.17 (1.03–5.31)		3 (4.3)	2.27 (1.25–3.29)	
4	—	—		1 (1.5)	2.80 (N/A)	
5	—	—		—	—	
Overall	71 (100)	7.77 (4.76–10.78)		69 (100)	6.40 (5.00–7.80)	

MDACC, MD Anderson Cancer Center; N/A, not applicable; OS, overall survival; RMH, Royal Marsden Hospital; 95% CI, 95% confidence interval.
Significant p values <0.05 are represented in bold.
[a] Note that two patients aged <2 years were excluded from this analysis.

showed a significant correlation between higher scores and poorer OS in adolescents (12–17 years), whereas this could not be demonstrated in children (2–11 years).

The limitations of our study include its retrospective nature, the use of different response assessment criteria depending on the trial and the lack of a validation cohort.

In summary, this study provides valuable insight into the prognostic factors of OS of children and adolescents enrolled in phase I trials. Our findings suggest that performance status of 90–100% and school/work attendance at enrolment in a paediatric phase I trial are strong indicators of longer OS. We also showed that the RMH and MDACC scores correlated with survival in adolescents. This may add further weight to the international multi-stakeholder arguments that adolescents can be safely enrolled into adult phase I trials to allow them earlier access to promising therapeutic options [19].

Overall, these findings are useful to orientate patients, parents and clinicians about potential prognosis and could lead in the future to more adapted eligibility criteria in early-phase trials. Better tools, including paediatric-specific scores, are still needed to more finely hone enrolment in paediatric dose-finding trials. This will not only improve the efficiency of dose-finding studies, but will also enhance the ethical aspects of recruitment [20]. Collaboration between cooperative networks and the prospective evaluation of prognostic factors will be crucial in helping achieve these goals.

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Conflict of interest statement

I.J. acknowledges travel/accommodation expenses from MSD. F.D. has had a consulting role for Novartis and travel/accommodation expenses from Novartis. M.C. has had a consulting role for Novartis, Boehringer and Roche. D.R.H. has had a consulting role for Roche, Astra Zeneca, Boehringer, GSK and Thrombogenics, received honoraria from Roche, Astra Zeneca and Boehringer, and travel/accommodation expenses from Roche, Astra Zeneca, Boehringer, GSK, Thrombogenics and Merck. L.V.M. has had a consulting role for Astra Zeneca. A.D.J.P. has received honoraria from Astra Zeneca, Boehringer and Novartis. L.M. has had a consulting role for Novartis, Astra Zeneca and Roche. All other authors declare no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.08.008.

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