European Journal of Cancer 227 (2025) 115627

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Original research

Prognostic factors of early mortality in children and adolescents with relapsed/refractory solid tumors participating in dose-finding trials in the targeted and immune therapies era: An ITCC study

Fernando Carceller [a,b,*], Francisco Bautista [c,d,e], Harm Van Tinteren [e], Alicia Castañeda [c,1], Aurore Surun [f], Ajla Wasti [a,2], Gabriel Revon-Rivière [g], Luca Bergamaschi [h], Marta Cortés [d,3], Raquel Hladun-Álvaro [c,4], Irene Jiménez [f,5], Cécile Giraud [i], Gerard Millen [j], Quentin Campbell-Hewson [k], Antonio Juan-Ribelles [l], Jasper Van der Lugt [e,m], Loredana Amoroso [n,6], Nicoletta Bertorello [o], Darren Hargrave [p], Lorena Vega-Piris [q], Franca Fagioli [o], Riccardo Haupt [n], C. Michel Zwaan [e,m], Adela Cañete [l], Bruce Morland [j,7], Antony Ceraulo [i], Michela Casanova [h], Arnauld Verschuur [g], Nicolas André [g,r], Isabelle Aerts [f], François Doz [f,s], Andrew D.J. Pearson [a,b,7], Lynley V. Marshall [a,b], Gilles Vassal [c,t], Pamela Kearns [j,u], Birgit Geoerger [c,v], Lucas Moreno [d,4]

[a] Children & Young People's Unit, The Royal Marsden NHS Foundation Trust, London, UK
[b] Division of Clinical Studies, The Institute of Cancer Research, London, UK
[c] Department of Pediatric and Adolescent Oncology, Gustave Roussy, Université Paris-Saclay, Villejuif, France
[d] Department of Pediatric Oncology, Hematology and Stem Cell Transplantation, Hospital Niño Jesús, Madrid, Spain
[e] Prinses Máxima Center for Pediatric Oncology, Utrecht, the Netherlands
[f] SIREDO, Institut Curie, Paris, France
[g] Department of Pediatric Oncology, La Timone Children's Hospital, APHM, Marseille, France
[h] Department of Pediatric Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[i] Department of Pediatric Clinical Trials, Institute of Hematology and Pediatric Oncology (IHOPe), Centre Léon Bérard, Lyon, France
[j] Department of Oncology, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK
[k] Department of Pediatric Oncology, The Great North Children's Hospital, Newcastle, UK
[l] Department of Pediatric Hemato-Oncology, La Fe University Hospital, Valencia, Spain
[m] Department of Pediatric Oncology/Hematology, Erasmus MC, Rotterdam, the Netherlands
[n] Department of Pediatric Hematology-Oncology, IRCCS Istituto Giannina Gaslini, Genova, Italy
[o] Department of Pediatric Onco-Hematology Division, Regina Margherita Children's Hospital, AOU Città della Salute e della Scienza, Turin, Italy
[p] Department of Pediatric Oncology, UCL Great Ormond Street Institute for Child Health, London, UK
[q] Department of Statistics, Health Research Institute, La Princesa University Hospital, Madrid, Spain
[r] Reverse Molecular Pharmacology in Pediatric Oncology, CRCM, Aix-Marseille Université, CNRS, INSERM, Marseille, France
[s] Université Paris Cité, Paris, France
[t] Department of Clinical Research, Gustave Roussy, Université Paris-Sud, Villejuif, France
[u] University of Birmingham, Birmingham, UK
[v] INSERM U1015, Université Paris-Saclay, Paris, France

* Correspondence to: Children & Young People's Unit, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton (Surrey) SM2 5PT, United Kingdom.
E-mail address: fernando.carceller@icr.ac.uk (F. Carceller).
[1] Current address: Pediatric Cancer Center Barcelona, Hospital Sant Joan de Déu, Barcelona, Spain.
[2] Current address: Department of Pediatric Oncology, University College London Hospital, London, UK
[3] Current address: Department of Pediatric Oncology, Regional University Hospital of Malaga, Malaga, Spain.
[4] Current address: Division of Pediatric Hematology and Oncology, Vall dHebron Comprehensive Cancer Center, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain.
[5] Current address: Department of Pediatric Oncology, Hospital Virgen de la Arrixaca, Murcia, Spain.
[6] Current address: Pediatric Onco-Hematology Unit, Policlinico Umberto I, Sapienza University of Rome, Italy.
[7] Retired.

https://doi.org/10.1016/j.ejca.2025.115627
Received 26 May 2025; Received in revised form 4 July 2025; Accepted 7 July 2025
Available online 15 July 2025
0959-8049/© 2025 Elsevier Ltd. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

ARTICLE INFO

Keywords:
Children
Pediatric
Cancer
Phase I
Clinical trial
Mortality

ABSTRACT

Introduction: Phase I/II trials are essential to introduce novel agents for children with cancer. Defining risk factors of early mortality could maximize the efficiency of such trials.
Methods: Patients < 18 years with relapsed/refractory solid tumors in their first phase I/II trial were eligible in retrospect. Mortality at 30 and 90 days on treatment (30-DM, 90-DM) were calculated. Clinical/laboratory parameters and adult prognostic scores (Royal Marsden Hospital -RMH-, MD Anderson Cancer Center -MDACC-) were assessed at baseline and correlated with 90-DM (univariate analysis, logistic regression) to devise a pediatric-specific prognostic score (ITCC).
Results: N = 507. Median age 11.6 years (range 0.5–17.9); 45 % females. 30-DM and 90-DM (95 %CI) were 4.7 % (3.1–7.0 %) and 22.9 % (19.3–26.8 %), respectively. RMH (n = 348) and MDACC (n = 345) scores correlated with 90-DM ($p < 0.001$). Performance status ≤ 80 %, no school attendance and lactate dehydrogenase (LDH) above normal levels strongly correlated with higher 90-DM, constituting the ITCC score (1 point each). The 90-DM with ITCC score (n = 306) of 0, 1, 2 and 3 was 2.7 %, 10.7 %, 36.4 % and 80.0 %, respectively. Odds ratios (95 %CI) for 90-DM with 1, 2 and 3 points were 4.23 (1.28–19.1); 20.0 (6.55–87.4); and 140 (37.4–720), respectively. Among patients with predicted risk of 90-DM ≥ 75 %, those who ultimately died within 90 days represented 1.4 % (RMH, MDACC) versus 7.8 % (ITCC) of the sample; $p < 0.001$.
Conclusions: The early mortality rates reported here will serve as a reference for future phase I/II trials. Risk scoring based on performance status, school attendance and LDH levels can estimate 90-DM in oncology phase I/II trials.

1. Introduction

The development of new therapeutics for children and adolescents with relapsed/refractory cancer relies on phase I/II trials. Life expectancy beyond 8–12 weeks is a common eligibility criterion across clinical trials, but it cannot be estimated objectively. Additionally, identification of antitumor activity is key to making go/no-go decisions early in the drug development process and inclusion of patients with a short life expectancy can dampen such signals. A better understanding of prognostic factors of early mortality in oncology phase I/II trials is essential to facilitate participants deriving greater benefit from such therapies, whilst contributing to trial objectives.

Innovative Therapies for Children and adolescents with Cancer (ITCC) is the largest European consortium focused on pediatric oncology drug development. A previous ITCC-led pilot international study evaluated prognostic factors of overall survival (OS) in pediatric cancer trials with a dose-finding component [1]. Two prognostic scores validated for adult phase I trials, the Royal Marsden Hospital (RMH) and the MD Anderson Cancer Center (MDACC) scores [2–6], underperformed in children < 12 years [1]. Additionally, factors such as performance status (PS) and being able to attend school were prognostic [1]. The current study aimed to determine prognostic factors of mortality within the first 90 days on treatment in phase I/II trials and to develop a pediatric prognostic score to assess this risk objectively.

2. Methods

2.1. Study objectives

The primary objectives were to determine: 1) the mortality rates at 30 and 90 days from first dose of the study drug in children and adolescents enrolled in their first clinical trial with a dose-finding component (phase I or I/II); and 2) a pediatric-specific score (ITCC score) to identify patients at higher risk of death within the first 90 days of trial treatment.

The secondary objectives were: 1) to evaluate the capacity of the RMH and MDACC scores to identify patients at higher risk of death within the first 90 days of trial treatment; and 2) to compare these scores against the ITCC score.

2.2. Definitions

The 30 and 90-day mortality (30-DM and 90-DM) were defined as the percentage of patients who died within 30 and 90 days, respectively, from the first dose of the study drug (i.e. cycle 1 day 1 -C1D1-). OS was measured from C1D1 until death or last follow-up, whichever occurred earlier. Objective response rate (ORR) included complete (CR) and partial responses (PR). Clinical benefit ratio (CBR) combined ORR and stable disease (SD) based on the radiological criteria applied in each trial.

The RMH score includes: ≥ 3 metastatic sites, albumin < 35 g/L and LDH above the upper limit of normal (ULN) [2]. The MDACC score includes all RMH score items plus Eastern Cooperative Oncology Group (ECOG) ≥ 1 and diagnosis of "gastrointestinal tumor" [6]. The same cut-offs were applied for these variables in our study population. ECOG ≥ 1 was converted to Lansky or Karnofsky PS ≤ 80 %. For other clinical and laboratory parameters, generic cut-offs based on widely used eligibility criteria or the ULN were applied, as clinically relevant. Laboratory parameters reported as '>ULN' would have still been within the ranges permitted for enrolment; 'number of metastatic sites' refers to each organ/tissue involved (e.g. multiple lung metastases count as one site); 'requirement of opioids' was defined as the use of potent opioids (e.g. morphine, etc) regularly or intermittently at least once weekly; 'school attendance' was evaluated in children ≥ 5 years, including full-time and part-time.

2.3. Study design

This is a multicentric, international, retrospective study evaluating early mortality rates and their prognostic factors in patients < 18 years at enrolment in their first phase I or I/II trial between January 2000 and March 2018. Enrolment in the dose escalation or the expansion part of the trial was permitted. Two independent datasets were used. Dataset #1 included patients treated between 2000 and 2014 and was used in the previous ITCC study [1]. Dataset #2 included patients treated between January 2015 and March 2018. All designated ITCC phase I centers were invited to contribute to dataset #2; centers which had not taken part in the previous study were allowed to include patients treated before 2015. Patients with low grade gliomas had been excluded from dataset #1 to avoid survivor bias [1], but they were allowed in dataset #2. Otherwise, both datasets had superimposable eligibility criteria (Suppl. Table 1) [1].

Informed consent by patients/parents/legal guardians had been obtained for participation in the corresponding trial. The clinical/laboratory parameters and outcome data collected in dataset #2 are listed in Suppl. Table 2. RMH and MDACC scores were calculated for patients in both datasets with available data for all items of each score.

2.4. Statistics

Patients' baseline characteristics were summarized with descriptive statistics. Categorical data were described with percentages (%) and absolute numbers (n). Continuously scaled measures were described with median or mean, range and 95 % confidence interval (95 %CI). For inclusion in the logistic model, continuous variables were transformed in categorical variables using cut-offs based on standard reference values or according to median values. Median survival was estimated using the Kaplan-Meier method.

A pediatric/adolescent-specific prognostic score was devised as follows. Firstly, an association analysis was performed using Fisher's exact test or Pearson's Chi-squared test to identify variables correlating with 90-DM. Factors with p-value ≤ 0.05 in the univariate analysis were considered in a multivariable analysis using logistic regression. The most parsimonious model was selected with the Likelihood-Ratio test (LR test). Missing values were imputed (if <15 %) with the most common value, except for LDH, RMH and MDACC. The multivariable model including LDH was based on a complete-case analysis. The factors and estimates of the model with and without were compared and happened to differ only slightly. Results are presented as odds ratios (ORs) with 95 %CI and p-values. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were used to assess model fit. The selected predictors were used to develop a predictive model represented as a nomogram; 1000 Bootstrap resampling was used for internal verification. The association of the RMH, MDACC and ITCC scores with 90-DM was calculated separately. The area under the receiver operating characteristic (ROC) curve (AUC), calibration chart and decision curve analysis were used to evaluate the accuracy, consistency and clinical utility of the prediction model. Statistical analyses were performed using R v4.3.1.

3. Results

3.1. Patient characteristics and early mortality rates

Fourteen centers participated in the study (Suppl. Tables 3–4). In total, 507 individuals were included. Baseline patient characteristics are presented in Table 1. For dataset #1 clinical trials are listed elsewhere [1]; and for dataset #2 in Suppl. Table 5. Overall, 74 % of patients received targeted therapies -including immunotherapies- (Table 2). The ORR was 13 % and 28 % cases had SD, accounting for a CBR of 41 % (Table 2).

The median and 1-year OS were 7.4 months (95 %CI 6.7–8.5) and 35 % (95 %CI 31–40 %), respectively. No toxic deaths attributable to the study drugs were reported (Table 2). The 30-DM and 90-DM (95 %CI) were 4.7 % (3.1–7.0 %) and 22.9 % (19.3–26.8 %), respectively (Table 2). There were no statistically significant differences in the early mortality rates of both datasets (Suppl. Table 4).

3.2. Adult prognostic scores

Overall, 348 (69 %) and 345 (68 %) patients had data on all items of the RMH and MDACC scores, respectively. Higher scores correlated with higher 90-DM (both $p < 0.001$; Suppl. Table 6). The sensitivity, specificity, positive and negative predictive values (PPV, NPV) are shown in Table 3. The ROC curves had AUC (95 %CI) of 75.6 % (70.0–81.1 %) RMH; and 78.5 % (72.8–84.2 %) MDACC (Table 3; Suppl. Fig. 1A-B); no statistical difference (DeLong's test).

3.3. Prognostic clinical/laboratory parameters

Twenty-eight clinical and laboratory parameters were evaluated in the univariate analysis (Suppl. Tables 7–10). Parameters associated with higher 90-DM included: PS ≤ 80 %, requirement of opioids, no school attendance, ≥ 3 metastatic sites, hemoglobin < 100 g/L, total bilirubin

Table 1
Demographics and tumor characteristics of 507 children and adolescents participating in pediatric phase I/II trials with a dose-finding component.

Variable	n[a]	Overall[b] (N = 507)
Datasets	507	
Dataset #1 (2000–2014)		239 (47 %)
Dataset #2 (2015–2018)		268 (53 %)[c]
Sex	507	
Female		230 (45 %)
Male		277 (55 %)
Age at Diagnosis (yrs)	507	
Median (IQR; range)		8.5 (4.1–12.4; 0.04 – 17)
Age at C1D1 (yrs)	507	
Median (IQR; range)		11.6 (7.2–14.9; 0.5 – 17.9)
Age group at C1D1 (yrs)	507	
< 2		8 (1.6 %)
2–11		261 (51 %)
12–17		238 (47 %)
Diagnosis	507	
Extra-CNS tumors		304 (60 %)
Neuroblastoma		55 (18 %)
Osteosarcoma		48 (16 %)
Non-Rhabdo STS		47 (15 %)
Rhabdomyosarcoma		44 (14 %)
Ewing's sarcoma		41 (13 %)
Other extra-CNS tumors[d]		69 (23 %)
CNS tumors		203 (40 %)
High Grade Glioma (excluding DIPG)		64 (32 %)
Medulloblastoma/CNS-PNET[e]		47 (23 %)
Low Grade Gliomas		23 (11 %)
DIPG		21 (10 %)
Ependymoma		20 (10 %)
Other CNS tumors[f]		28 (14 %)
Performance status (Lansky or Karnofsky scores / ECOG)	498	
90–100 / 0		355 (71 %)
70–80 / 1		121 (24 %)
40–60 / 2–3		22 (4 %)
Not available		9
Requirement of potent opioids	506	
No		407 (80 %)
Yes		99 (20 %)
Not Available		1
School Attendance	354	
No		94 (27 %)
Yes (incl. part-time)		260 (73 %)
Not applicable (<5 yrs old)		77
Not available		76
Number of metastatic sites	507	
No metastases		153 (30 %)
1–2 sites		302 (60 %)
≥ 3 sites		52 (10 %)
Previous Chemotherapy	507	
Median (range)		2 (0 – 8)
0 lines		34 (7 %)
1–2 lines		287 (57 %)
3 + lines		186 (37 %)
Previous Surgery	262	
No/Biopsy only		39 (15 %)
Non-GTR		98 (37 %)
GTR		125 (48 %)
Unknown		245
Previous Radiotherapy	440	
No		108 (25 %)
Yes		332 (75 %)
Not available/applicable		67
Previous Autologous Stem Cell Transplant[g]	209	
No		108 (52 %)
Yes		101 (48 %)
Not available/applicable		298
RMH Score	348	
0		176 (51 %)
1		117 (34 %)
2		50 (14 %)
3		5 (1 %)

(continued on next page)

Table 1 (*continued*)

Variable	n[a]	Overall[b] (N = 507)
Unknown[h]		159
MDACC Score	345	
0		139 (40 %)
1		119 (35 %)
2		59 (17 %)
3		22 (6 %)
4		6 (2 %)
Unknown[h]		162

CNS: central nervous system; C1D1: cycle 1 – day 1; DIPG: Diffuse intrinsic pontine glioma; ECOG: Eastern Cooperative Oncology Group; GTR: gross total resection; MDACC: MD Anderson Cancer Center; PNET: primitive neuroectodermal tumor; RMH: Royal Marsden Hospital; STS: Soft tissue sarcoma.

[a] Number of patients with available data.

[b] Median (IQR) or Frequency (%), unless stated otherwise.

[c] 32 cases in this group (12 %) participated in phase I/II trials over the period of 2000–2014; but they were included in dataset #2 because the corresponding treating centre had joined at this stage of the study.

[d] Other extra-CNS tumors: Wilms tumor (n = 19), lymphomas (n = 12), carcinomas (n = 8), plexiform neurofibroma (n = 7), hepatoblastoma (n = 6), melanoma (n = 5), extra-CNS germ cell tumors (n = 4); chordoma, clear cell sarcoma of the kidney, undifferentiated sarcoma of the kidney, high-grade renal tumor not-otherwise-specified, Langerhans cells histiocytosis, neuroendocrine tumor of the pancreas, paraganglioma, peritoneal carcinomatosis with unknown primary (n = 1 each).

[e] Medulloblastoma/CNS-PNET: this group includes 29 medulloblastomas and 5 CNS-PNET from dataset #2 plus 13 cases of medulloblastomas/CNS-PNET (grouped together) from dataset #1. Of note, the term 'CNS-PNET' does no longer exist in the current WHO classification of CNS tumors, but this was still a valid diagnosis at the time when these patients were enrolled in their respective trials.

[f] Other CNS tumors: atypical teratoid rhabdoid tumor (n = 15), multiple/complex diagnoses (n = 4, including a multiphenotypic cerebral tumor not classifiable, an ependymoma reclassified as CNS-PNET at relapse, a case of CNS-PNET Vs anaplastic oligodendroglioma, and an undifferentiated CNS sarcoma on a background of previous glioblastoma and choroid plexus carcinoma in a child with suspected Li-Fraumeni syndrome), pineoblastoma (n = 3), neurosarcoma (n = 2); germ cell tumor of the CNS, papillary high-grade glioneuronal tumor, posterior fossa tumor not-otherwise-specified, suprasellar/chiasmatic glioneuronal tumor (n = 1 each).

[g] Tumor types for which autologous stem cell transplant was considered applicable included: ATRT/extracranial rhabdoid tumors, Ewing's sarcoma, germ cell tumors (CNS and extra-CNS), lymphomas, medulloblastoma, neuroblastoma, pineoblastoma, PNET (CNS and extra-CNS), Wilms tumor.

[h] RMH and MDACC scores were calculated only for subjects with data available in all the score items.

Table 2
Safety and efficacy outcomes of 507 children and adolescents participating in pediatric phase I/II trials with a dose-finding component.

Variable	n[i]	Overall[j] (N = 507)
Trial Category	507	
Single-targeted agent[k]		307 (61 %)
Single cytotoxic agent		104 (21 %)
> 1 targeted agent[k]		12 (2 %)
> 1 cytotoxic agent		25 (5 %)
Targeted+cytotoxic agent(s)[k]		58 (11 %)
Oncolytic viruses		1 (0.2 %)
Biomarker-driven trials	268	
No		134 (50 %)
Yes (biomarker mandatory)		101 (38 %)
Enriched[l]		33 (12 %)
Unknown		239
DLT occurrence (evaluable cases only)	159	
No		137 (86 %)
Yes		22 (14 %)
Best response	485	
PD		284 (59 %)
SD		137 (28 %)
PR		48 (10 %)
CR		16 (3 %)
Not evaluable		4
Not available		18
Reason for discontinuation	470[m]	
PD		397 (84 %)
Toxicity		26 (6 %)
Withdrawal consent		10 (2 %)
Other		31 (7 %)
Not available		6 (1 %)
Cause of death	399[n]	
PD		393 (98 %)
Toxicity		0
Other		4 (1 %)
Not available		2 (0.5 %)
Early mortality rates	507	
30-DM		24 (4.7 %; 95 %CI 3.1–7.0)
90-DM		116 (22.9 %; 95 %CI 19.3–26.8)

CR: complete response. DLT: dose limiting toxicities. PD: progressive disease. PR: partial response. SD: stable disease. 30-DM: 30-day mortality. 90-DM: 90-day mortality. 95 %CI: 95 % confidence interval.

[i] Number of patients with available data.

[j] Median (IQR) or Frequency (%), unless stated otherwise.

[k] Including immune checkpoint inhibitors.

[l] The presence of a biomarker was required for inclusion in a pre-specified proportion of cases.

[m] 37 patients were still on study at last follow-up.

[n] 108 patients were alive at last follow-up.

>ULN, albumin < 35 g/L, LDH >ULN, and aspartate aminotransferase >ULN. 'Response to treatment' also correlated with 90-DM (Suppl. Table 10), but this was not taken forward to the multivariable analysis as this is not evaluable at enrollment. The following parameters remained associated with higher 90-DM in the multivariable analysis (Table 4): PS ≤ 80 %, no school attendance and LDH >ULN. These variables constituted the ITCC score.

3.4. Pediatric prognostic score (ITCC score)

The ITCC score estimates the probability of 90-DM assigning 1 point to each item of the score (Suppl. Table 11). Overall, 306 patients had data on all items. The 90-DM in this subset of patients was 20.3 %. The 90-DM with an ITCC score of 0, 1, 2 or 3 points was: 2.7 % (n = 108), 10.7 % (n = 102), 36.4 % (n = 66) and 80.0 % (n = 30), respectively (Table 5, Fig. 1A). The score nomogram is shown in Fig. 1B. LDH >ULN was the score item more strongly associated with 90-DM (Suppl. Table 11). The sensitivity, specificity, PPV and NPV are shown in Table 3. The AUC of the ROC curve was 84.6 % (95 %CI 79.3–89.9 %) (Table 3, Fig. 1C).

The ITCC score performed better than the RMH score (p = 0.02), but it was not different from the MDACC score (p = 0.12). Among patients with predicted 90-DM ≥ 75 %, the ITCC score identified more patients who ultimately died within that period: 1.4 % (5/348) RMH score; 1.4 % (5/345) MDACC score; and 7.8 % (24/306) ITCC score; p < 0.001 (Table 3). The risk of dying within the first 90 days of trial treatment with an ITCC score of 3 was 140 times greater than with 0 points (Table 5).

4. Discussion

This is the largest study to date evaluating prognostic factors of early mortality in pediatric oncology phase I/II trials. Most early phase trials exclude subjects whose life expectancy is < 8–12 weeks. We developed a prognostic score specific for children and adolescents to estimate short-term life expectancy more objectively and reduce uncertainty when assessing eligibility for early phase trials.

This study population is representative of the pediatric drug development landscape in Europe over a period of 18 years, encompassing a broad array of phase I/II trials (single agent vs combinations, cytotoxic vs targeted therapies, all-comers vs biomarker-driven); Table 2, Suppl.

Table 3
Comparison of metrics between the RMH, MDACC and ITCC scores.

Score Metrics	RMH	MDACC	ITCC
Sample size[o]	348	345	306
Maximum score	3	5	3
Sensitivity (%)	85.3	90.3	77.4[p]
Specificity (%)	60.4	48.4	80.3[p]
Positive Predictive Value (%)	37.2	31.6	50[p]
Negative Predictive Value (%)	93.8	95.0	93[p]
AUC (95 %CI)	75.6 % (70.0–81.1 %)	78.5 % (72.8–84.2 %)	84.6 % (79.3–89.9 %)
Number (%) of patients with predicted 90-DM ≥ 75 %	5 (1.4 %)	6 (1.7 %)	30 (9.8 %)
Number (%) of patients with predicted 90-DM ≥ 75 % who died during this period (p < 0.001)	5 (1.4 %)	5 (1.4 %)	24 (7.8 %)

AUC: area under the curve; ITCC: Innovative Therapies for Children and adolescents with Cancer; MDACC: MD Anderson Cancer Center; NPV: negative predictive value; PPV: positive predictive value; RMH: Royal Marsden Hospital; 95 %CI: 95 % confidence interval.

[o] Number of patients with data available for all items of the score.

[p] ITCC score characteristics for the optimal threshold in the AUC. If the threshold was set at 3 points, the parameters would be: sensitivity 38.7 %, specificity 97.5 %, PPV 80.0 %, NPV 86.2 %.

Tables 4–5. Notwithstanding, the study could be subject to potential selection biases related to the fact that nearly two thirds of the patients were recruited among three centers (Suppl. Table 3), which could have led to regional epidemiological variations; as well as a shift towards a higher number of biomarker-driven trials since 2011 [7], which could have increased the representation of tumor types with a higher frequency of actionable targets, such as gliomas, or neuroblastomas. Whilst standard treatments at frontline and relapse have evolved over the study period, the prognosis of patients with relapsed/refractory solid tumors remains disappointing for the most part. Overall, 75 % of the patients received targeted therapies, illustrating the paradigm shift observed in drug development over recent decades [7–10].

Regarding early mortality rates, the 30-DM (5 %) suggests that current eligibility criteria are fairly accurate at discriminating patients at higher risk of death during the standard dose-limiting toxicities (DLT) assessment period, similarly to other pediatric studies [11]. Conversely, the 90-DM (23 %) was higher than in adult phase I trials (14.8–16.5 %) [3,5]. In practice, this 90-DM indicates that nearly 1 in 4 children had a life expectancy which could have compromised their trial eligibility.

A study evaluating 40 patients ≤ 18 years treated in phase I trials reported that RMH score ≥ 2 and MDACC score ≥ 3 correlated with decreased median OS [12]. These adult prognostic scores also correlated with 90-DM in our population [2,4,6]. However, some limitations were encountered. Firstly, the RMH score does not include PS, which correlated with the 90-DM and OS in children/adolescents [1]. Secondly, the MDACC score includes 'gastrointestinal tumor' as a prognostic criterion [6]. But gastrointestinal tumors are extremely rare in children/adolescents and have different histologies from their adult counterparts. Lastly, adult prognostic scores had less capacity to identify patients who died within the first 90 days of trial treatment among those with a predicted 90-DM ≥ 75 % than the ITCC score: < 2 % with RMH and MDACC scores versus 8 % with ITCC score (Table 3).

The ITCC score comprises PS, school attendance and LDH levels. The 306 patients with whom the score was developed had a 90-DM similar to that of the overall sample (20.3 % Vs 22.9 %, respectively), illustrating

Table 5
The 90-day mortality rates and odds ratios of 306 children and adolescents with relapsed-refractory solid tumors participating in phase I/II trials based on performance status, school attendance and LDH levels (ITCC score).

ITCC score	n	Dead within 90 days	90-DM (%)	OR (95 %CI)
0	108	3	2.7	–
1	102	11	10.7	4.23 (1.28 – 19.1)
2	66	24	36.4	20.0 (6.55 – 87.4)
3	30	24	80.0	140 (37.4 – 720)
Overall	306	62	20.3	N/A

ITCC: Innovative Therapies for Children and adolescents with Cancer consortium; N/A: not applicable; OR: odds ratio; 90-DM: 90-day mortality; 95 %CI: 95 % confidence interval.

Table 4
Univariate and multivariable (logistic regression model) analyses of prognostic factors identifiable at baseline correlated with 90-day mortality (90-DM) in pediatric phase I/II trials with a dose-finding component.

Variables		N / Events	Univariate analysis		Multivariable (regression)	
			OR (95 %CI)	**p-value**	**OR (95 %CI)**	**p-value**
Performance Status[q]	90–100 % ≤ 80 %	498 / 111	– 3.89 (2.50 – 6.08)	**< 0.001**	– 2.46 (1.06 – 5.72)	**0.037**
Requirement of potent opioids	No Yes	506 / 116	– 2.95 (1.84–4.73)	**< 0.001**	– 2.16 (0.92–5.06)	0.076
School attendance	No Yes[r] N/A[s]	431 / 96	– 0.11 (0.06–0.19) 0.38 (0.20–0.72)	**< 0.001**	– 0.18 (0.07–0.43) 0.63 (0.21–1.82)	**< 0.001**
Number of metastatic sites	≤ 2 ≥ 3	507 / 116	– 2.34 (1.26–4.24)	**0.007**	– 2.25 (0.78–6.45)	0.13
Hemoglobin (g/L)	Hb ≥ 100 Hb < 100	500 / 114	– 2.14 (1.27–3,56)	**0.004**	– 1.15 (0.44–2.89)	0.8
Total Bilirubin	≤ULN >ULN	492 / 113	– 9.55 (2.71 – 44.2)	**< 0.001**	– 3.30 (0.36 – 72.8)	0.3
Albumin (g/L)	Alb ≥ 35 Alb < 35	466 / 108	– 1.87 (1.03 – 3.29)	**0.039**	– 0.53 (0.18–1.45)	0.2
LDH	≤ULN >ULN	367 / 78	– 8.30 (4.64 – 15.6)	**< 0.001**	– 9.15 (4.10 – 22.3)	**< 0.001**
AST	≤ULN >ULN	490 / 108	– 1.76 (1.00 – 3.01)	**0.049**	– 0.79 (0.29–2.04)	0.6

AST: aspartate aminotransferase; LDH: lactate dehydrogenase; OR: odds ratio; ULN: upper limit of normal; 95 %CI: 95 % confidence interval.

[q] Lansky or Karnofsky performance scales.

[r] Including part-time.

[s] Not applicable (<5 years old).

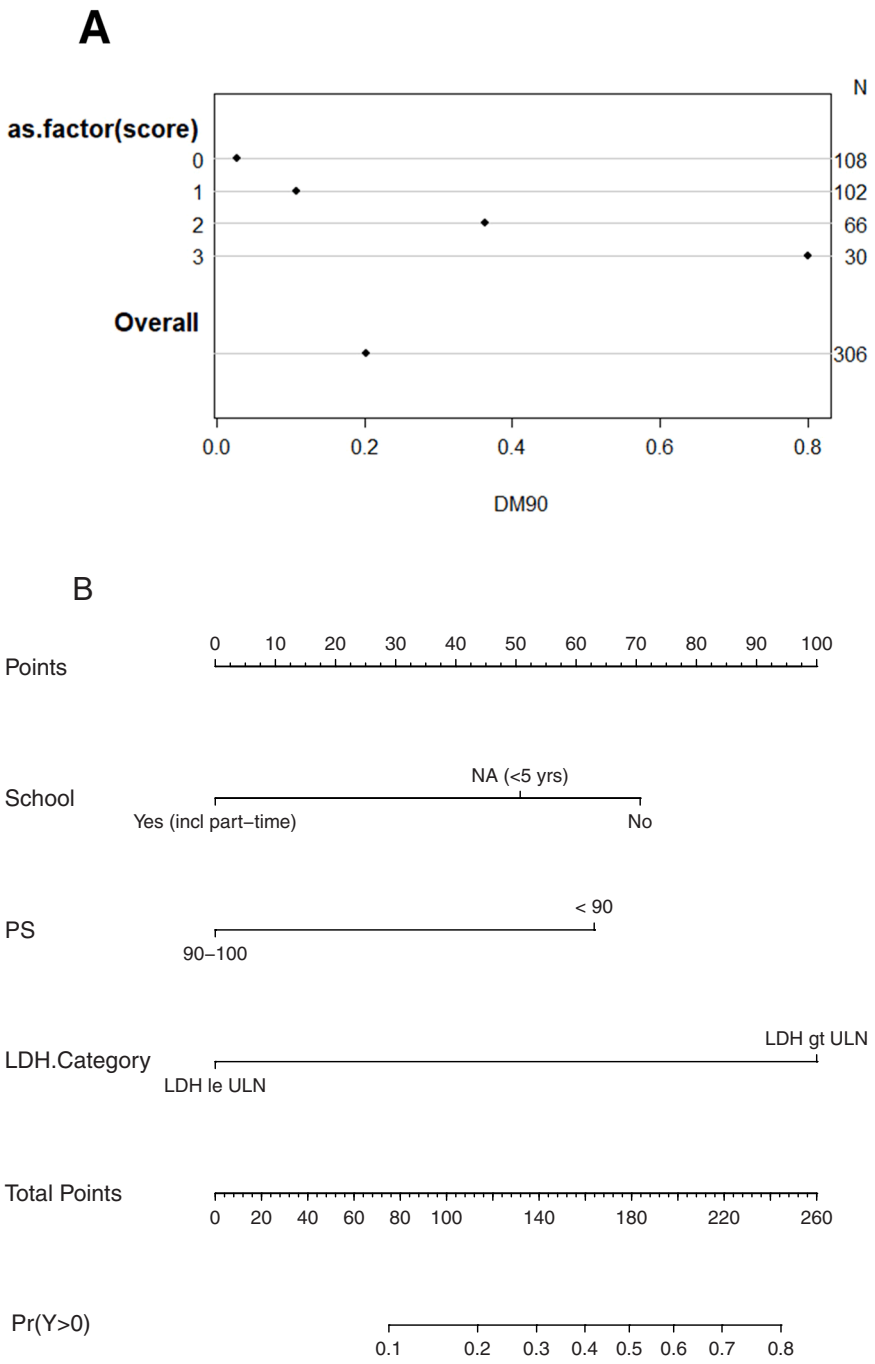

Fig. 1. Probability of 90-Day Mortality (90-DM) based on ITCC score. (A) 90-DM for each scoring category and overall sample: X axis displays the 90-DM rates for patients in each scoring category; Y axis (left) displays each scoring category (0–3 points and overall); Y axis (right) displays the number of patients in each scoring category. (B) Nomogram for the calculation of the probability of 90-DM (predicted value) based on school attendance, PS and LDH levels: gt, greater than; LDH, lactate dehydrogenase; le, less or equal than; NA, not available/applicable; PS, performance score; ULN: upper limit of normal. (C) Area under the curve (AUC) of the receiver operating characteristic (ROC) curve for the ITCC score.

that this subset of patients was representative of the whole cohort. All three parameters correlated with 90-DM in the univariate and multivariable analyses (Table 4). The 90-DM was 2.7 % with 0 points versus 80 % with 3 points; patients scoring 3 points were also 140 times more likely to die within the first 90 days than those scoring 0 points (Table 5).

Compared to adult prognostic scores, the ITCC score has lower sensitivity and higher specificity. This means that the score was not so good at identifying all the individuals who died within 90 days, which is illustrated by the fact that 61 % (38/62) of those who died within the first 90 days scored ≤ 2 points; but it was better at detecting the individuals who were alive at 90 days, as 98 % (238/244) of cases who were alive at 90 days scored ≤ 2 points. This is relevant for patient selection to early phase trials, as it is more important to avoid inappropriate exclusion of patients who could benefit from the study than to include some patients who ultimately don't meet the 90-day eligibility criterion.

On that note, if the 30 patients scoring 3 points were excluded, the

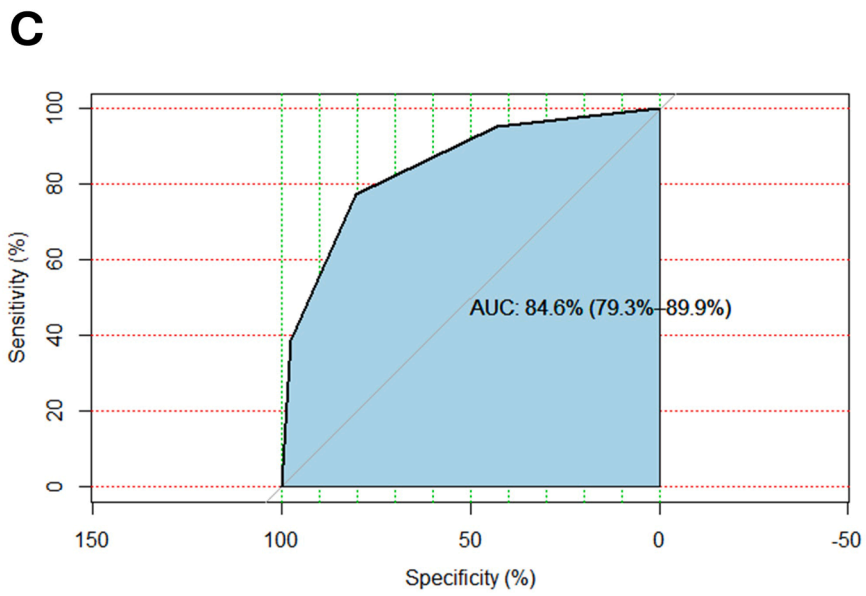

Fig. 1. (*continued*).

resulting 90-DM would be 13.7 %; similarly to adult phase I oncology trials [3,5]. Those 30 cases represented 10 % of the sample; among them, only 6 (2 %) did not die within the first 90 days, consistent with a higher PPV of the ITCC score compared to adult prognostic scores.

A trial population with lower 90-DM could mitigate the bias resulting from patients with rapidly progressive tumors. This is important for go/no-go decisions early in the drug development process, as potentially active drugs could be prevented from further development if tested in a suboptimal population.

Importantly, the following issues should be considered. Firstly, this score is based on a retrospective cohort. Prospective validation is necessary prior to any clinical implementation. Currently no decisions about eligibility for clinical trials should be made based on the ITCC score.

Secondly, 'school attendance' was assessed in children ≥ 5 years to avoid confounding factors, such as differences in access to childcare. Therefore, the current score cannot be applied to children < 5 years. Additionally, some individuals may not attend school for reasons unrelated to their clinical condition (e.g. comorbidities, cultural or socioeconomic factors); in which case failing to attend school should not carry prognostic implications.

Thirdly, LDH >ULN carried a higher association with 90-DM than each of the other two prognostic factors (Table 4, Suppl. Table 11, Fig. 1B). Hence, a scoring system where LDH >ULN had carried more points relative to the other two prognostic factors may have improved the performance of the score.

Next, the 'requirement of opioids' was associated with 90-DM in the univariate, but not in the multivariable analysis; although there was a trend towards statistical significance ($p = 0.076$, Table 4). Perhaps a definition encompassing only the daily use of opioids could have better reflected the clinical condition of the subject. Therefore, the 'requirement of opioids' should not be entirely ruled out as potentially prognostic.

Furthermore, the ITCC score was not evaluated in individual tumor types at this stage, as smaller patient populations would have limited the statistical power. Future refinements of the score could contemplate its performance for specific diagnoses.

Lastly, some targeted therapies, such as BRAF, ALK and NTRK inhibitors, have shown remarkable responses in pediatric cancers [13–21]. Therefore, patients with rapidly progressing tumors may still be suitable for biomarker-driven clinical trials with drugs expected to display a higher chance of success.

Based on lessons learned from this study, we are working to develop a more refined version of the ITCC score to seek formal prospective validation. Notwithstanding, the broad representation of children and adolescents and early phase trials over the last two decades make this cohort a suitable reference framework for comparison with future trials. Our study also shows that current eligibility criteria are fit-for-purpose to identify patients at higher risk of death within the first 30 days on treatment, which is the most common timeframe for DLT assessment. This study also constitutes the first structured approach to predicting short-term life expectancy in pediatric early phase trials and sets a precedent to continue honing patient selection for such studies.

In summary, we have determined the early mortality rates at 30 and 90 days in a large international cohort of children and adolescents with relapsed/refractory solid tumors treated in their first phase I/II trial. The RMH and MDACC scores correlated with the 90-DM in this population. The ITCC score (i.e. PS, school attendance and LDH) increased the prediction of 90-DM for this age group. Further refinement and prospective validation of the ITCC score could improve patient selection in early phase trials and optimize go/no-go decisions for novel agents.

Declaration

The author Birgit Geoerger is an Editor of the EJC and was not involved in the editorial review or the decision to publish this article

CRediT authorship contribution statement

Lucas Moreno: Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Antonio Juan-Ribelles:** Writing – review & editing, Resources, Investigation. **Jasper Van der Lugt:** Writing – review & editing, Resources, Investigation. **Pamela Kearns:** Writing – review & editing, Resources, Investigation, Conceptualization. **Gerard Millen:** Writing – review & editing, Resources, Investigation. **Birgit Geoerger:** Writing – review & editing, Resources, Investigation, Conceptualization. **Quentin Campbell-Hewson:** Writing – review & editing, Resources, Investigation. **Marshall Lynley V:** Writing – review & editing, Resources, Investigation, Conceptualization. **Gilles Vassal:** Resources, Investigation. **Cécile Giraud:** Resources, Investigation. **CARCELLER FERNANDO:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data

curation, Conceptualization. **Pearson Andrew DJ:** Writing – review & editing, Resources, Investigation, Conceptualization. **Raquel Hladun-Álvaro:** Writing – review & editing, Resources, Investigation. **Irene Jiménez:** Writing – review & editing, Resources, Investigation. **Isabelle Aerts:** Writing – review & editing, Resources, Investigation. **Luca Bergamaschi:** Writing – review & editing, Resources, Investigation. **François Doz:** Resources, Investigation. **Marta Cortés:** Writing – review & editing, Resources, Investigation. **Arnauld Verschuur:** Resources, Investigation. **Ajla Wasti:** Writing – review & editing, Resources, Investigation. **Nicolas André:** Resources, Investigation. **Gabriel Revon-Rivière:** Writing – review & editing, Resources, Investigation. **Antony Ceraulo:** Resources, Investigation. **Alicia Castañeda:** Writing – review & editing, Resources, Investigation. **Michela Casanova:** Writing – review & editing, Investigation. **Aurore Surun:** Resources, Investigation. **Adela Cañete:** Resources, Investigation. **Francisco Bautista:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Bruce Morland:** Resources, Investigation. **Harm Van Tinteren:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Data curation. **Riccardo Haupt:** Resources, Investigation. **Zwaan C. Michel:** Writing – review & editing, Resources, Investigation. **Franca Fagioli:** Resources, Investigation. **Darren Hargrave:** Writing – review & editing, Resources, Investigation. **Lorena Vega-Piris:** Methodology, Formal analysis, Data curation. **Loredana Amoroso:** Writing – review & editing, Resources, Investigation. **Nicoletta Bertorello:** Writing – review & editing, Resources, Investigation.

Funding

FC and LVM acknowledge support from the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at The Royal Marsden and The Institute of Cancer Research; and Experimental Cancer Medicines Centre (ECMC) funding via the Pediatric ECMC Network. Additionally, we acknowledge individual funding from the Oak Foundation grant OCay-04–169 (LVM); The Giant Pledge via the Royal Marsden Cancer Charity (FC); the Hall-Hunter Foundation and Courtney's Team Marsden Fund via the Royal Marsden Cancer Charity to the Paediatric Neuro-Oncology and Drug Development Units at Royal Marsden (FC, LVM).

IJ was funded by the "Alexandre Zaninger" clinical fellow in paediatric oncology drug development (2015–2016) and the Curie Institute scholarship for doctoral students (2016–2021).

LA and RH acknowledge funding from the Associazione Italiana per la Lotta al Neuroblastoma, RINB project and the OPEN OdV, SurPass-DOPO project.

NA acknowledges INCA funding for pediatric Centre Labelisé par Inca Phase Precoce of AP-HM and funding from INCA for South-Rock Pediacriex.

DH is supported by the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London.

BG is founded by the 'Parrainage médecin-chercheur' of Gustave Roussy.

Lu.Mo. was funded by a Juan Rodes Fellowship (2016–2018) by Instituto de Salud Carlos III (JR15/00041).

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: FC has a consulting role for Ipsen UK.

FB is a member of a data monitoring committee (DMC) for a clinical trial sponsored by Sanofi, had a consultant advisory role for Bayer, Amgen, Roche Genentech and EusaPharma and received honoraria for speaking at symposia from Roche Genentech and Servier.

AJR has had a consulting/advisory role for Alexion and Bayer; has participated in educational activities organized by Eusa Pharma, Abbott, and Alexion; and has received travel expenses by Nestle and Alexion.

DH received institutional funding for clinical trials from AstraZeneca/Alexion; has held consultant roles for AstraZeneca/Alexion, Biodexa, Day One Therapeutics, Ipsen, Novartis, Roche/ Genentech.

Mi.Ca. had consultant advisory roles for AstraZeneca/Alexion, Roche/Genentech, and Servier.

CMZ received institutional funding for clinical trials from Pfizer, Daiichi Sankyo, Jazz Pharma, Takeda, Abbvie and Kura Oncology; has a consultant role for Janssen, Novartis, Syndax, BMS, Incyte, Sutro, Kestrel, Beigene, and Sanofi; and has received travel expenses from Syndax.

NA has had an advisory role for Bristol Myers Squibb; institutional funding for clinical trials from Bristol Myers Squibb, Pierre Fabre, Pfizer, Astra Zeneca, Merck; travel support from Roche, Novartis, Alexion; and IDMC roles for Accord Healthcare.

ADJP has consulted for Lilly, Norgine and Developmental Therapeutics Consortium Limited and been an advisor for Amgen.

LVM has had an advisory role for Tesaro, Bayer, BMS and Illumina; has helped lead educational activities for Bayer, and has been an IDMC member for trials led by Eisai and Merck.

BG has had an advisory role for Astra Zeneca, and IDMC roles for Roche and Novartis.

LM is member of a Data Monitoring Committee (DMC) for clinical trials sponsored by Novartis, Actuate Therapeutics, Shionogi, Incyte, the University of Southampton and the Royal Marsden NHS Foundation Trust; had a consulting role for Novartis, Bayer, BMS, Merck, Gilead and Shionogi, has received travel expenses from Recordati Rare Diseases; and is President of SIOPEN (European neuroblastoma research cooperative group), organization which receives royalties for the sales of dinutuximab beta. His institution receives funding from sponsors for DMC participation, advisory role or conducting industry-sponsored clinical trials.

For the remaining authors, no potential conflicts of interest were declared.

Acknowledgements

We would like to thank all children, adolescents, and their families who participate in clinical trials. We thank Mrs Carole Lecinse and the entire administrative team at ITCC for their invaluable support. We thank our colleagues within the ITCC and their teams (physicians, nurses, study coordinators, data managers) for their interest in and commitment to clinical research to improve care for children and adolescents with cancer.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115627.

References

[1] Carceller F, Bautista FJ, Jiménez I, et al. Prognostic factors of overall survival in children and adolescents enrolled in dose-finding trials in Europe: an innovative therapies for children with cancer study. Eur J Cancer 2016;67:130–40. https://doi.org/10.1016/j.ejca.2016.08.008.

[2] Arkenau HT, Olmos D, Ang JE, de Bono J, Judson I, Kaye S. Clinical outcome and prognostic factors for patients treated within the context of a phase I study: the Royal Marsden Hospital experience. Br J Cancer 2008;98(6):1029–33. https://doi.org/10.1038/sj.bjc.6604218.

[3] Arkenau HT, Olmos D, Ang JE, et al. 90-Days mortality rate in patients treated within the context of a phase-I trial: how should we identify patients who should not go on trial? Eur J Cancer 2008;44(11):1536–40. https://doi.org/10.1016/j.ejca.2008.04.017.

[4] Arkenau HT, Barriuso J, Olmos D, et al. Prospective validation of a prognostic score to improve patient selection for oncology phase I trials. J Clin Oncol 2009;27(16):2692–6. https://doi.org/10.1200/JCO.2008.19.5081.

[5] Olmos D, A'Hern RP, Marsoni S, et al. Patient Selection for oncology phase I trials: a multi-institutional study of prognostic factors. J Clin Oncol 2012;30(9):996–1004. https://doi.org/10.1200/JCO.2010.34.5074.
[6] Wheler J, Tsimberidou AM, Hong D, et al. Survival of 1,181 patients in a phase I clinic: the MD anderson clinical center for targeted therapy experience. Clin Cancer Res 2012;18(10):2922–9. https://doi.org/10.1158/1078-0432.CCR-11-2217.
[7] Bautista F, Verdú-Amorós J, Geoerger B, et al. Evolution of the innovative therapies for children with cancer consortium trial portfolio for drug development for children with cancer. J Clin Oncol 2024;42(21):2516–26. https://doi.org/10.1200/JCO.23.01237.
[8] Pearson ADJ, Herold R, Rousseau R, et al. Implementation of mechanism of action biology-driven early drug development for children with cancer. Eur J Cancer 2016;62:124–31. https://doi.org/10.1016/j.ejca.2016.04.001.
[9] Pearson ADJ, Pfister SM, Baruchel A, et al. From class waivers to precision medicine in paediatric oncology. Lancet Oncol 2017;18(7):e394–404. https://doi.org/10.1016/S1470-2045(17)30442-4.
[10] DuBois SG, Corson LB, Stegmaier K, Janeway KA. Ushering in the next generation of precision trials for pediatric cancer. Science 2019;363(6432):1175–81. https://doi.org/10.1126/science.aaw4153.
[11] Rubio-San-Simón A, Hladun Alvaro R, Juan Ribelles A, et al. The paediatric cancer clinical research landscape in Spain: a 13-year multicentre experience of the new agents group of the Spanish Society of Paediatric Haematology and Oncology (SEHOP). Clin Transl Oncol 2021;23(12):2489–96. https://doi.org/10.1007/S12094-021-02649-Y.
[12] Corrales-Medina FF, Herzog C, Hess K, et al. Clinical characteristics and outcomes of pediatric oncology patients with aggressive biology enrolled in phase I clinical trials designed for adults: the university of Texas MD anderson cancer center experience. Oncoscience 2014;1(7):522–30. ⟨http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4278323&tool=pmcentrez&rendertype=abstract⟩. Accessed January 10, 2016.
[13] Banerjee A, Jakacki RI, Onar-Thomas A, et al. A phase I trial of the MEK inhibitor selumetinib (AZD6244) in pediatric patients with recurrent or refractory low-grade glioma: a Pediatric Brain Tumor Consortium (PBTC) study. Neuro Oncol 2017;19(8):1135–44. https://doi.org/10.1093/NEUONC/NOW282.
[14] Kieran MW, Geoerger B, Dunkel IJ, et al. A phase i and pharmacokinetic study of oral dabrafenib in children and adolescent patients with recurrent or refractory BRAF V600 mutation-positive solid tumors. Clin Cancer Res 2019;25(24):7294–302. https://doi.org/10.1158/1078-0432.CCR-17-3572.
[15] Hargrave DR, Bouffet E, Tabori U, et al. Efficacy and safety of dabrafenib in pediatric patients with BRAF V600 mutation-positive relapsed or refractory low-grade glioma: results from a phase I/IIa study. Clin Cancer Res 2019;25(24):7303–11. https://doi.org/10.1158/1078-0432.CCR-19-2177.
[16] Mossé YP, Voss SD, Lim MS, et al. Targeting ALK with crizotinib in pediatric anaplastic large cell lymphoma and inflammatory myofibroblastic tumor: a children's oncology group study. J Clin Oncol 2017;35(28):3215–21. https://doi.org/10.1200/JCO.2017.73.4830.
[17] Fischer M, Moreno L, Ziegler DS, et al. Ceritinib in paediatric patients with anaplastic lymphoma kinase-positive malignancies: an open-label, multicentre, phase 1, dose-escalation and dose-expansion study. Lancet Oncol 2021;22(12):1764–76. https://doi.org/10.1016/S1470-2045(21)00536-2.
[18] Goldsmith KC, Park JR, Kayser K, et al. Lorlatinib with or without chemotherapy in ALK-driven refractory/relapsed neuroblastoma: phase 1 trial results. Nat Med 2023;29(5):1092–102. https://doi.org/10.1038/S41591-023-02297-5.
[19] Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378(8):731–9. https://doi.org/10.1056/NEJMoa1714448.
[20] Laetsch TW, DuBois SG, Mascarenhas L, et al. Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. Lancet Oncol 2018;19(5):705–14. https://doi.org/10.1016/S1470-2045(18)30119-0.
[21] Desai AV, Robinson GW, Gauvain K, et al. Entrectinib in children and young adults with solid or primary CNS tumors harboring NTRK, ROS1, or ALK aberrations (STARTRK-NG). Neuro Oncol 2022;24(10):1776–89. https://doi.org/10.1093/NEUONC/NOAC087.