TITLE PAGE

Title:

Outcome of children and adolescents with central nervous system tumors in phase I trials.

Authors:

Fernando Carceller[1,2], Francisco J. Bautista[3,4], Irene Jiménez[5], Raquel Hladun-Álvaro[3,6], Cécile Giraud[7], Luca Bergamaschi[8], Madhumita Dandapani[9,10], Isabelle Aerts[5], François Doz[5,11], Didier Frappaz[7], Michela Casanova[8], Bruce Morland[9], Darren R. Hargrave[12], Gilles Vassal[13], Andrew D.J. Pearson[1,2,*], Birgit Geoerger[3], Lucas Moreno[4], Lynley V. Marshall[1,2].

Affiliations:

[1] Pediatric and Adolescent Drug Development, Children and Young People's Unit, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, SM2 5PT, United Kingdom.

[2] Division of Clinical Studies and Cancer Therapeutics, The Institute of Cancer Research, 15 Cotswold Road, Sutton, SM2 5NG, United Kingdom.

[3] Department of Pediatric and Adolescent Oncology, Gustave Roussy, UMR 8203, CNRS, Univ. Paris-Sud, 114 Rue Edouard Vaillant, 94800, Villejuif, France.

[4] Clinical Trials Unit, Pediatric Oncology Department, Hospital Infantil Universitario Niño Jesús, Av. de Menéndez Pelayo, 65, 28009, Madrid, Spain (current address for FB).

[5] Department of Pediatric, Adolescents and Young Adults Oncology, Institut Curie, 26 Rue d'Ulm, 75005, Paris, France.

[6] Department of Pediatric Oncology, Vall d´Hebron Hospital, Passeig de la Vall d'Hebron, 119-129, 08035, Barcelona, Spain (current address for RHA).

[7] Department of Pediatric Clinical Trials and Department of Pediatric Neuro-Oncology, Institut Hématologique et d'Oncologie Pédiatrique, 1 Place Professeur Joseph Renaut, 69008, Lyon, France.

[8] Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Giuseppe Ponzio, 44, Milan, Italy.

[9] Department of Pediatric Oncology, Birmingham Children's Hospital, Steelhouse Ln, Birmingham B4 6NH, Birmingham, United Kingdom.

[10] Department of Pediatric Oncology, Notthingham Children's Hospital, Derby Road, Nottingham, NG7 2UH, United Kingdom (current address for MD).

[11] Université Paris Descartes, 12 Rue de l'École de Médecine, 75006, Sorbonne Paris Cité, France.

[12] Pediatric Oncology Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond St, London, WC1N 3JH, United Kingdom.

[13] Department of Clinical Research, Gustave Roussy, Université Paris-Sud, 114 Rue Edouard Vaillant, 94800, Villejuif, France.

* Retired.

Authors e-mails:

Fernando Carceller: fernando.carceller@icr.ac.uk

Francisco Bautista: franciscojose.bautista@salud.madrid.org

Irene Jiménez: irene.jimenez@curie.fr

Raquel Hladun-Álvaro: rhladun@vhebron.net

Cécile Giraud: cecile.giraud@lyon.unicancer.fr

Luca Bergamaschi: Luca.Bergamaschi@istitutotumori.mi.it

Madhumita Dandapani: Madhumita.Dandapani@nottingham.ac.uk

Isabelle Aerts: isabelle.aerts@curie.fr

François Doz: francois.doz@curie.fr

Didier Frappaz: didier.frappaz@ihope.fr

Michela Casanova: Michela.Casanova@istitutotumori.mi.it

Bruce Morland: Bruce.Morland@bch.nhs.uk

Darren Hargrave: Darren.Hargrave@gosh.nhs.uk

Gilles Vassal: Gilles.Vassal@gustaveroussy.fr

Andrew D.J. Pearson: andy1pearson@btinternet.com

Birgit Geoerger: Birgit.Geoerger@gustaveroussy.fr

Lucas Moreno: lucas.moreno@salud.madrid.org

Lynley V. Marshall: LynleyVanessa.Marshall@icr.ac.uk

Corresponding author:

Dr. Fernando Carceller

- Pediatric & Adolescent Drug Development Unit, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, SM2 5PT, United Kingdom
- Phone: +44 – 208 642 6011 (ext 4099);
- Fax: +44 – 208 661 3617;
- Email: Fernando.Carceller@icr.ac.uk

Type of manuscript: Clinical study

Abstract: max 250 words → 250

Main text: max 3,000 words → 2,358

Tables & Figures: max 5 → 3 Tables, 2 Figures.

Supplementary material → 1.

References (max 50) → 17

ABSTRACT. ***Max 250 words* (currently 250)**

Introduction. Central nervous system (CNS) tumors are a leading cause of death in children and adolescents. We evaluated the outcome of patients with CNS tumors enrolled in pediatric phase I trials within the Innovative Therapies for Children with Cancer (ITCC) consortium.

Methods. Data of patients with solid tumors aged <18 years at enrolment in their first dose-finding trial between 2000-2014 at eight ITCC centers were collected retrospectively, including two predictive scores validated in adults: the Royal Marsden Hospital and MD Anderson Cancer Center scores. Survival analyses were conducted using long-rank test, Cox regression and Kaplan-Meier methods.

Results. Overall, 114 patients with CNS tumors were assessed. Median age: 10.2 years (range, 1.0-17.9). Main diagnoses included medulloblastoma/PNET (32.5%) and high-grade gliomas (23.7%). Complete/partial responses were reported in 7.4% patients and stable disease in 23.8%. In the univariate analysis, performance status ≤80%, no school/work attendance and ALT/AST above the upper limit of normal correlated with worse OS. In the multivariate analysis, no factors were significantly associated with OS. Adult scores were not prognostic of OS. Median Overall Survival (OS) was 11.9 months with complete/partial response, 11.0 months with stable disease and 3.1 months with progressive disease ($p<0.001$) according to RECIST (n=43).

Conclusions. One third of the patients with CNS tumors derived clinical benefit. Sustained disease stabilization as per RECIST in children with CNS tumors should also be regarded as a signal of activity in phase I trials. These outcomes will serve as a reference for future phase I trials for pediatric CNS tumors.

Keywords (4 to 6):

Survival; children; adolescents; central nervous system tumor; brain tumor; phase I trial.

Acknowledgements

Ms Carole Lecinse, Innovative Therapies for Children with Cancer (ITCC) and Ms Gynette Cook, The Royal Marsden NHS Foundation Trust.

This work was supported by the ITCC infrastructure. Additionally, F.C. holds a senior fellowship funded by the National Institute for Health Research Biomedical Research Centre (BRC) at the Royal Marsden and by the Sohn Foundation. I.J. holds a fellowship funded by the Nelia et Amadeo Barletta Foundation. D.R.H. is supported by the BRC at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London. A.D.J.P. is supported by Cancer Research UK (CRUK): programme grant C1178/A10294 - Chair in Pediatric Oncology. L.Mo. is funded by the Juan Rodés senior fellowship from Instituto de Salud Carlos III. L.V.M. is funded by the Oak Foundation (Grant OCay-04-169).

TEXT

INTRODUCTION

Approximately 16-20% of the cancers diagnosed in children aged 0-14 years in Europe are central nervous system (CNS) tumors [1]. CNS tumors constitute a leading cause of cancer-related death in children in Europe, United States and Canada [1–3]. Hence, there is an unmet need of novel drugs to improve survival outcomes. Dose-finding trials (phase I and seamless phase I/II trials) are crucial in the evaluation of novel anti-cancer agents for children, since these studies determine the Recommended Phase II Dose for a given drug. However, patients with CNS tumors are sometimes excluded from these trials due to doubts about drug penetration across the blood-brain barrier and/or concerns raised by previous seizures, steroid requirements and risk of certain neurologic complications, such as raised intracranial pressure, CNS bleeding or spinal cord compression. Nonetheless, dose-finding trials are increasingly being incorporated at earlier time points of treatment-failure for children with advanced solid tumors and a better understanding of the current landscape of pediatric CNS tumors treated in phase I trials across Europe will contribute to optimize recruitment and maximize the efficiency of future phase I trials.

Our main objective was to evaluate the survival outcomes of children and adolescents with CNS tumors enrolled in phase I trials within the Innovative Therapies for Children with Cancer (ITCC) European consortium. In addition, we assessed potential prognostic factors of overall survival (OS) and tested two predictive scores previously validated in adult cancer patients: the Royal Marsden Hospital (RMH) score and the MD Anderson Cancer Center (MDACC) score [4–6].

PATIENTS AND METHODS

The present study is a post-hoc analysis of the patients with CNS tumors included in the ITCC study evaluating prognostic factors of OS in children and adolescents aged <18

153 years at enrolment in their first dose-finding trial [7]. Patients were enrolled between 1st
154 January 2000 and 31st December 2014 across eight European centers. All phase I trials
155 had been approved by local institutional review boards. Informed consent by
156 parents/legal guardians and patients had been obtained for participation to the
157 corresponding trial.
158 Only patients who had completed trial screening and had been dosed successfully were
159 included in this analysis. All diagnoses of refractory or recurrent CNS tumors were
160 eligible, except for low grade gliomas. Relevant clinical data at baseline and efficacy
161 outcomes were collected accordingly. Lansky and Karnofsky performance status scales
162 were converted to Eastern Cooperative Oncology Group (ECOG) scale for calculation of
163 the MDACC score as follows: Lansky/Karnofsky of 90-100%, 70-80%, 50-60% or 30-
164 40% were equivalent to an ECOG of 0, 1, 2 or 3, respectively.
165 Outcome data were collected as follows: best response was defined according to
166 protocol-specific response assessment criteria from day 1 of cycle 1 (C1D1) until best
167 radiological response at any timepoint (including disease stabilization) or disease
168 progression, whichever occurred earlier; time-to-progression (TTP) was defined from
169 C1D1 until disease progression on trial, death or study discontinuation, whichever
170 occurred earlier; OS was measured from C1D1 until death or last follow-up. Early
171 mortality rates were also calculated at 30 and 90 days from C1D1. If patients had been
172 taken off study for reasons other than disease progression, these were collected where
173 available, as well as the end of study date. In addition, the RMH and MDACC scores
174 were calculated for patients with data available in all score items (score calculation was
175 made accounting for 1 point per item). These included albumin <35 g/L, lactate
176 dehydrogenase (LDH) above the upper limit of normal (ULN) and the presence of ≥3
177 metastatic sites, for the RMH score [4, 5]; and the aforementioned RMH score items plus
178 gastrointestinal tumor type and Eastern Cooperative Oncology Group (ECOG)
179 performance status ≥1, for the MDACC score [6].

Descriptive statistics were used to present patients' characteristics. Categorical data were compared using Chi-squared test. Survival curves were estimated by the Kaplan-Meier method. Univariate log-rank test was used to compare survival distributions according to twenty four clinical parameters. Multivariate Cox regression analysis was performed with those variables identifiable at study entry that correlated with survival in the univariate analysis. Statistical analyses were conducted with SPSS® version 16.0.

RESULTS

Baseline patient characteristics.

Out of 248 patients with solid tumors treated across 18 dose-finding trials, 114 (46%) were diagnosed with CNS tumors (Table 1). For patients with CNS tumors, median age was 10.2 years (range, 1-17.9) and male to female ratio was 1.15:1. The most frequent diagnoses were medulloblastoma/primitive neuroectodermal tumor (PNET), high grade glioma and diffuse intrinsic pontine glioma (DIPG) in 32.5%, 23.7% and 17.5% of cases, respectively. Approximately half of the patients (48.2%) had metastatic disease at study entry. The patients had received a median of one line of chemotherapy (range, 0-7) prior to enrolment. Fifteen patients (13.1%) had not received any chemotherapy at study entry, including the following diagnoses: DIPG (n=9), ependymoma (n=4), high grade glioma and neurosarcoma (n=1 each). In 80% cases patients had undergone some debulking surgery and 93% of patients had received prior radiotherapy. The majority of patients (67.5%) were treated in trials with single targeted agents (Table 1). Only 5 cases (4.5%) were discontinued from the trial due to toxicity.

Response rate and time to progression.

Overall, 109 patients (95.6%) were evaluable for response. Best response included complete response (CR) in 2.8% of patients, partial response (PR) in 4.6%, stable disease (SD) in 23.8% and progressive disease (PD) in 68.8% (Table 1). The patients with CR were diagnosed with medulloblastoma/PNET (n=2) and high grade glioma (n=1).

208 The patients with PR were diagnosed with high grade glioma (n=3),
209 medulloblastoma/PNET (n=1) and atypical teratoid rhabdoid tumor (n=1). The clinical
210 benefit ratio (CR+PR+SD) was 31.2%. Overall, 88% of patients with CR/PR (n=7/8) and
211 50% of those with SD (n=13/26) stayed on trial for ≥4 months. Additionally, 63% of
212 patients with CR/PR (n=5/8) and 23% of those with SD (n=6/26) stayed on trial for ≥6
213 months. The median TTP for the whole cohort was 1.8 months (95%CI, 1.6-2.0).
214
215 *Prognostic factors of overall survival and adult predictive scores.*
216 The median follow-up from C1D1 for the entire cohort was 4.9 months (range, 0.2-96).
217 The median OS of the whole cohort was 5.4 months (95%CI, 3.8-7.0). Eleven patients
218 died within 30 days of C1D1: 9.6% (95%CI, 4.2-15.0); and 37 patients died within 90
219 days of C1D1: 32.5% (95%CI, 23.9-41.1). No drug-related deaths were reported.
220 In the univariate analysis (log-rank test), factors associated with poorer OS included:
221 performance status ≤80%, no school/work attendance, alanine aminotransferase (ALT)
222 or aspartate aminotransferase (AST) above the upper limit of normal (ULN), but within
223 the maximum limits permitted according to protocol eligibility criteria, and lack of
224 response or disease stabilization (Table 2).
225 Objective response and disease stabilization in patients with CNS tumors were
226 associated with improved survival either when evaluated without distinguishing between
227 specific response criteria (Table 2), or when evaluated according to RECIST guidelines
228 (Table 3, Fig. 1).
229 The multivariate analysis (Cox regression) excluded the response to treatment, because
230 this cannot be determined at enrolment and therefore does not constitute a baseline
231 prognostic factor. No clinical variables were significantly associated with OS in the
232 multivariate analysis, although performance status and school/work attendance were
233 close to the 95% significance level: p=0.059 and p=0.063, respectively (Table 2).
234 The RMH and MDACC scores were calculated in 59 (51.8%) and 57 (50%), respectively.
235 None of them correlated with OS in the univariate analysis (Table 2, Fig. 2).

DISCUSSION

Despite numerous clinical trials, treatment options for relapsed CNS tumors are generally limited and survival outcomes across tumor types are still modest, with 5-year survival rates of children with CNS tumors in Europe of 57.5% [1]. Hence, novel therapies are still needed for recurrent/refractory pediatric CNS tumors and the fact that nearly half of all patients included in the pediatric ITCC phase I trials were children with CNS tumors reflects this medical need [7], as well as the feasibility of enrolling these patients in paediatric phase I trials.

Adults with CNS tumors have historically been excluded from phase I trials due to their poor prognosis, concomitant drug interactions, concerns about excessive toxicities and limited efficacy. For instance, in a multicentric review of 2,182 adult cancer patients participating in phase I trials, the rate of patients with CNS tumors was <7% and in a large institutional cohort of 1,181 adult cancer patients in phase I trials only 12 (0.01%) had CNS tumors [6, 8]. Notwithstanding, adults with CNS tumors enrolled in phase I trials seem to have a survival advantage compared to those not enrolled [9]. Since there is a paucity of data in children and adolescents with CNS tumors for reference, we assessed the outcomes of 114 children and adolescents with CNS tumors who participated in a dose-finding trial. This is to date the largest series of its kind.

Patients with CNS tumors represented 46% of the population enrolled in dose-finding trials across 8 large pediatric oncology units in 4 European countries over a period of 15 years [7]. This is relatively similar to that reported in a former review of pediatric phase I trials in the United States conducted between 1992 and 2005, where 35% of the patients had brain tumors [10].

The age and gender distributions in our sample are similar to those previously reported in two European centers reviewing the participation in pediatric phase I and phase II trials, with a median age of 10-12 years and a mild predominance of male patients [11,

12]. Trial participation was deemed safe, with only 4.5% of cases being discontinued because of toxicity and no reported deaths attributed to the study drug.

As regards efficacy, approximately one third of the patients with CNS tumors enrolled in a phase I trial derived some clinical benefit (CR+PR+SD). Patients assessed according to RECIST v1.0 or v1.1 were analyzed jointly for study purposes, based on the fact that the main differences between RECIST v1.0 and v1.1 relate to the maximum number of target lesions and evidence from a cohort of more than 6,500 adults with metastatic cancer who were evaluated according to both versions showed that the reduction in the number target lesions, as per v1.1, did not affect the overall response rate and only affected minimally the PFS [13]; therefore simplifying the measurements, but without reducing the prognostic value of the response criteria. The response rates observed in our pediatric and adolescent cohort are comparable to those reported in previous reviews of pediatric phase I trials, showing objective responses in 3.8-9.6% of cases and disease stabilization in 17-37.7% [10–12, 14]. Likewise, the median TTP and OS in our cohort are similar to those previously reported: 1.3-2.8 months for TTP and 3.6-8.5 months for OS [10–12, 15]. However, these studies did not analyze efficacy in the subset of patients with CNS tumors separately. Hence, our findings could serve as a suitable reference for evaluation of early signs of activity in children and adolescents with CNS tumors in future phase I trials.

In terms of survival outcomes, as it is to be expected, we observed that response correlates with survival. In adults enrolled in phase I trials, it has been shown a near-linear relationship between tumor shrinkage assessed by RECIST and OS [16]. In pediatric phase I trials, we have previously shown that the grade of tumor shrinkage, by RECIST, also correlates with the duration of response and the OS [17]. But importantly, in agreement with previous reports [7, 17], in our cohort patients with CNS tumors who achieved disease stabilization had survival rates comparable to those with objective responses. These findings suggest that novel targeted therapies, even if they cannot induce significant tumor shrinkage, may halt tumor growth sufficiently as to confer a

291 survival advantage for some patients. Therefore sustained disease stabilization in
292 pediatric CNS tumors should also be regarded as a “signal of activity” in early phase
293 trials of novel agents.
294 As regards other prognostic factors, we have previously shown that some indicators of
295 the patient´s well-being, such as performance status and school/work attendance at
296 enrolment, were associated with OS in pediatric phase I trials [7]. In the subset of patients
297 with CNS tumors, performance status ≤80% and no school/work attendance at enrolment
298 were associated with worse OS in the univariate analysis and there was a trend towards
299 poorer OS in the multivariate analysis. Conversely, the association of elevated ALT and
300 AST with worse OS in the univariate analysis might be anecdotal and should be regarded
301 with caution. In addition, two clinical scores previously validated in adult cancer patients
302 as good predictors of survival were assessed in this patient population: the RMH score
303 and the MDACC score [4–6]. Both scores were suboptimal in our cohort of patients with
304 CNS tumors. Likewise, the RMH score did not correlate with survival in 55 adults with
305 CNS tumors enrolled in phase I trials [9]. These findings illustrate the lack of reliable
306 indicators of OS and highlight the need to identify prognostic factors specific for children
307 and adolescents with CNS tumors to optimize patient selection for phase I trials.
308 Limitations of this study to be acknowledged include its retrospective nature, the use of
309 different response assessment criteria depending on the trial and the lack of a validation
310 cohort.
311 In summary, this study is the largest review of children and adolescents with CNS tumors
312 participating in a dose-finding trial and is representative of the European drug
313 development landscape over the past 15 years. Overall, CNS tumors represented half
314 of the diagnoses of children enrolled in phase I trials across Europe. Up to one third of
315 the patients with CNS tumors derived clinical benefit from the phase I trial. Response
316 was associated with improved OS. Interestingly, survival rates in patients with disease
317 stabilization as best response were comparable to those with objective responses. These
318 response rates and survival outcomes will serve as a reference for future phase I trials

for children and adolescents with CNS tumors. Performance status ≥90% and school/work attendance at study entry were associated with improved OS in the univariate analysis, but more specific prognostic factors are still needed to optimize the selection of patients with CNS tumors in pediatric phase I trials. Overall this study shows that entering children/adolescents with CNS tumors in phase I trials is feasible, safe and offers potential benefit for the patients.

Conflicts of interest

This work was supported by the ITCC infrastructure. Additionally, F.C. holds a senior fellowship funded by the National Institute for Health Research Biomedical Research Centre (BRC) at the Royal Marsden and by the Sohn Foundation. I.J. holds a fellowship funded by the Nelia et Amadeo Barletta Foundation. D.R.H. is supported by the BRC at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London. A.D.J.P. is supported by Cancer Research UK (CRUK): programme grant C1178/A10294 - Chair in Pediatric Oncology. L.Mo. is funded by the Juan Rodés senior fellowship from Instituto de Salud Carlos III. L.V.M. is funded by the Oak Foundation (Grant OCay-04-169).

These results were presented in part at the International Symposium of Pediatric Neuro-Oncology (ISPNO) held in June 2016.

REFERENCES.

1. Gatta G, Botta L, Rossi S, et al (2014) Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. Lancet Oncol 15:35–47. doi: 10.1016/S1470-2045(13)70548-5
2. Johnson KJ, Cullen J, Barnholtz-Sloan JS, et al (2014) Childhood brain tumor epidemiology: a brain tumor epidemiology consortium review. Cancer Epidemiol Biomarkers Prev 23:2716–36. doi: 10.1158/1055-9965.EPI-14-0207
3. Hargrave D, Bartels U, Bouffet E (2006) Diffuse brainstem glioma in children: critical review of clinical trials. Lancet Oncol 7:241–8. doi: 10.1016/S1470-2045(06)70615-5
4. Arkenau H-T, Olmos D, Ang JE, et al (2008) Clinical outcome and prognostic factors for patients treated within the context of a phase I study: the Royal Marsden Hospital experience. Br J Cancer 98:1029–1033. doi: 10.1038/sj.bjc.6604218
5. Arkenau H-T, Barriuso J, Olmos D, et al (2009) Prospective validation of a prognostic score to improve patient selection for oncology phase I trials. J Clin Oncol 27:2692–6. doi: 10.1200/JCO.2008.19.5081
6. Wheler J, Tsimberidou AM, Hong D, et al (2012) Survival of 1,181 patients in a phase I clinic: the MD Anderson Clinical Center for targeted therapy experience. Clin Cancer Res 18:2922–9. doi: 10.1158/1078-0432.CCR-11-2217
7. Carceller F, Bautista FJ, Jiménez I, et al (2016) 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 67:130–140. doi: 10.1016/j.ejca.2016.08.008
8. Olmos D, A'Hern RP, Marsoni S, et al (2012) Patient Selection for Oncology Phase I Trials: A Multi-Institutional Study of Prognostic Factors. J Clin Oncol 30:996–1004. doi: 10.1200/JCO.2010.34.5074
9. Coleman N, Michalarea V, Alken S, et al (2016) Safety, efficacy and survival of

patients (pts) with primary CNS tumors in phase 1 (Ph1) trials: A 12-year single institution experience. J Clin Oncol 34, 2016 (suppl; abstr 2043)

10. Kim A, Fox E, Warren K, et al (2008) Characteristics and Outcome of Pediatric Patients Enrolled in Phase I Oncology Trials. Oncologist 13:679–689. doi: 10.1634/theoncologist.2008-0046

11. Bautista F, Di Giannatale A, Dias-Gastellier N, et al (2015) Patients in pediatric phase I and early phase II clinical oncology trials at Gustave Roussy: a 13-year center experience. J Pediatr Hematol Oncol 37:e102-10. doi: 10.1097/MPH.0000000000000237

12. Morgenstern DA, Hargrave D, Marshall L V, et al (2014) Toxicity and outcome of children and adolescents participating in phase I/II trials of novel anticancer drugs: the Royal Marsden experience. J Pediatr Hematol Oncol 36:218–23. doi: 10.1097/MPH.0000000000000003

13. Bogaerts J, Ford R, Sargent D, et al (2009) Individual patient data analysis to assess modifications to the RECIST criteria. Eur J Cancer 45:248–260. doi: 10.1016/j.ejca.2008.10.027

14. Lee DP, Skolnik JM, Adamson PC (2005) Pediatric phase I trials in oncology: an analysis of study conduct efficiency. J Clin Oncol 23:8431–41. doi: 10.1200/JCO.2005.02.1568

15. Corrales-Medina FF, Herzog C, Hess K, et al (2014) 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 1:522–30.

16. Jain RK, Lee JJ, Ng C, et al (2012) Change in tumor size by RECIST correlates linearly with overall survival in phase I oncology studies. J Clin Oncol 30:2684–90. doi: 10.1200/JCO.2011.36.4752

17. Carceller F, Bautista FJ, Fowkes LA, et al (2016) Response Assessment in Paediatric Phase I Trials According to RECIST Guidelines: Survival Outcomes,

394 Patterns of Progression and Relevance of Changes in Tumour Measurements.
395 Pediatr Blood Cancer. doi: 10.1002/pbc.26039
396

FIGURE CAPTIONS

Fig. 1 Kaplan-Meier curves of overall survival according to radiological response as per Response Evaluation Criteria In Solid Tumors (RECIST); n=43

Fig. 2 Kaplan-Meier curves of Overall Survival for Royal Marsden Hospital score (A) and MD Anderson Cancer Center score (B)

Fig. 1 Kaplan-Meier curves of Overall Survival according to radiological response as per Response Evaluation Criteria In Solid Tumors (RECIST); n=43

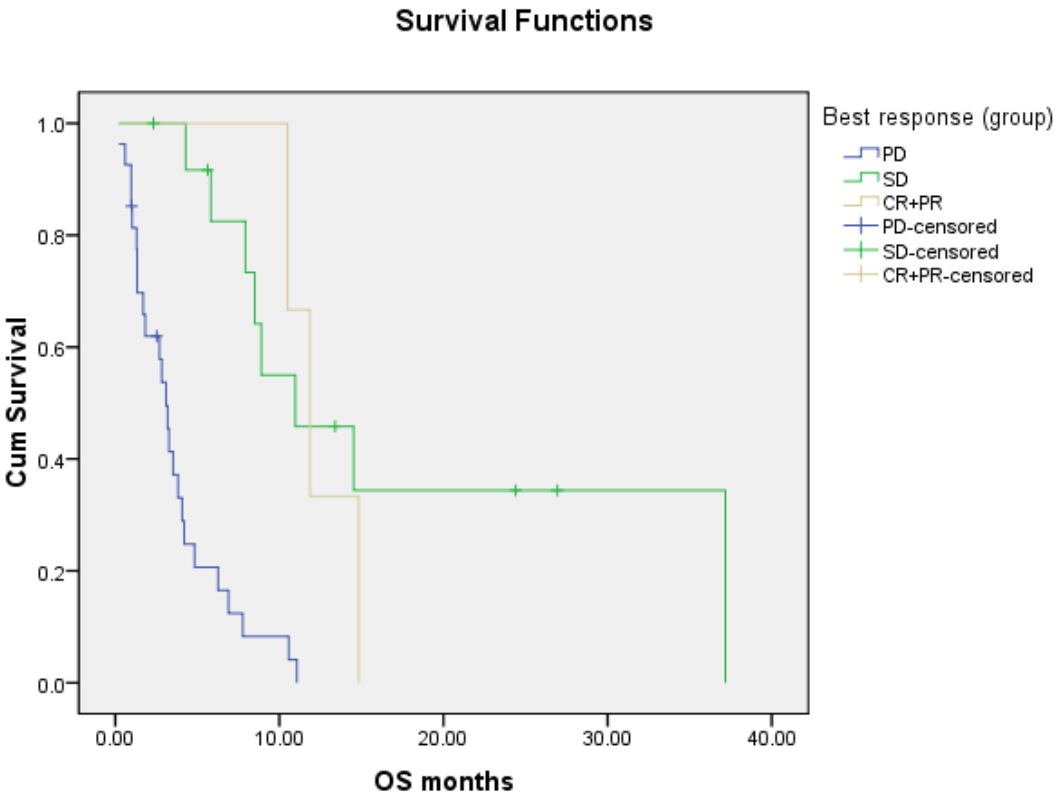
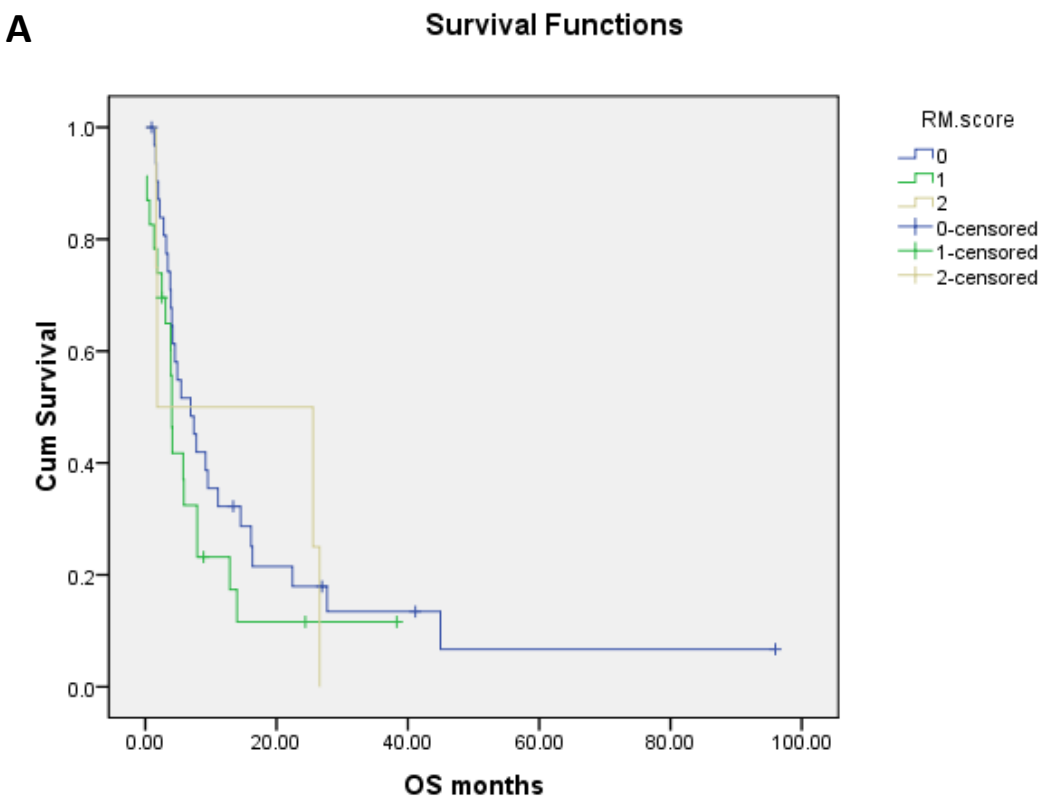


Fig. 2 Kaplan-Meier curves of Overall Survival for Royal Marsden Hospital score (A) and MD Anderson Cancer Center score (B)



B

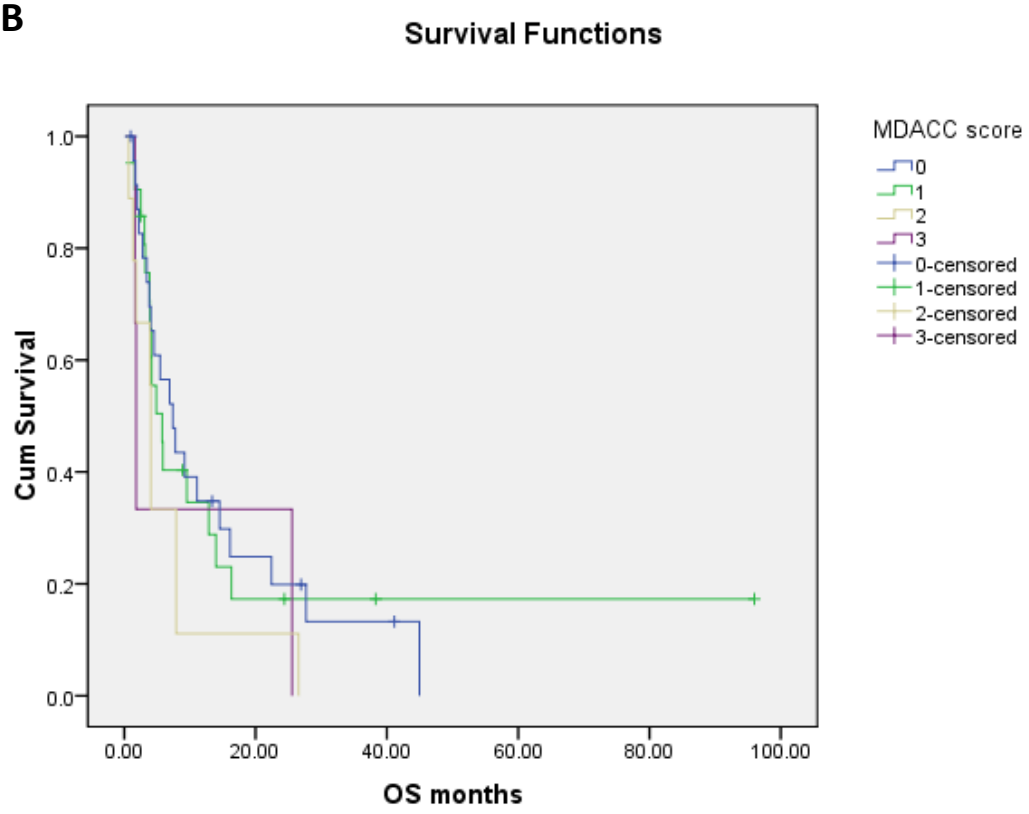

Survival Functions
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0.00
20.00
40.00
60.00
80.00
100.00
OS months
MDACC score
0
1
2
3
0-censored
1-censored
2-censored
3-censored

Table 1: Demographics of the study population (N=114).

Items	Number (%)
BASELINE PATIENT CHARACTERISTICS	
Age at inclusion (years):	
Median (range)	10.2 (1.0 – 17.9)
<2	3 (2.6)
2-11	69 (60.5)
12-17	42 (36.8)
Gender:	
Female	53 (46.5)
Male	61 (53.5)
Diagnosis:	
Medulloblastoma/PNET	37 (32.5)
High Grade Glioma	27 (23.7)
DIPG[1]	20 (17.5)
Ependymoma	16 (14.0)
Other CNS tumors[2]	14 (12.3)
Performance status (Lansky/Karnofsky):	
90-100%	70 (63.1)
60-80%	41 (36.9)
Not available	3 (-)
School/Work (for ≥5 year-olds):	
No	27 (32.5)
Yes	56 (67.5)
Not available	13 (-)
Not applicable (age <5 years)	18 (-)
Metastatic disease:	
No	59 (51.8)
Yes	55 (48.2)
PREVIOUS TREATMENTS	
Previous chemotherapy:	
Median (range)	1 (0 – 7)
0 lines	15 (13.1)
1-2 lines	72 (63.2)
≥ 3 lines	27 (23.7)
Previous surgery:	
No/Biopsy only	22 (20.2)
Non-GTR	32 (29.4)
GTR	55 (50.4)
Not available	5 (-)
Previous radiotherapy:	
No	8 (7.0)
Yes	106 (93.0)
Previous ASCT:	
No	26 (55.3)
Yes	21 (44.7)
Not applicable[3]	67 (-)
EXPERIMENTAL TREATMENT	
Trial category:	
Single targeted agent	77 (67.5)
Single cytotoxic agent	21 (18.4)
>1 targeted agent	0
>1 cytotoxic agent	11 (9.6)
Targeted + cytotoxic agent	5 (4.4)
Response criteria:	
WHO	32 (34.4)
RECIST 1.0	27 (29.0)
RECIST 1.1	18 (19.4)
Other[4]	16 (17.2)
Not available	21 (-)
Best response:	
Complete response	3 (2.8)
Partial response	5 (4.6)
Stable disease[5]	26 (23.8)
Progressive disease	75 (68.8)

Not available/evaluable	5 (-)
Reason for study discontinuation:	
Progressive disease	100 (90.1)
Toxicity	5 (4.5)
Other[6]	6 (5.4)
Not available	3 (-)
CLINICAL SCORES	
RMH score:	
0	32 (54.2)
1	23 (39.0)
2	4 (6.8)
3	0
Not available	55 (-)
MDACC score:	
0	24 (42.1)
1	21 (36.8)
2	9 (15.8)
3	3 (5.3)
4	0
5	0
Not available	57 (-)

[1] DIPG patients were only eligible if they had experienced progression after radiotherapy prior to enrolment; [2] Other CNS tumors include: ATRT (n=8), pineoblastoma and neurosarcoma (n=2 each), posterior fossa tumor NOS and glioblastoma/undifferentiated sarcoma (n=1 each); [3] Only tumor 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, ATRT); [4] Other response criteria included: McDonald (n=8), RANO (n=6) or protocol-specific (n=2); [5] Including patients with non-measurable disease who achieved non-CR/non-PD; [6] Other reasons for study discontinuation included: completion of trial protocol (n=3), complete response (n=2), error in administration (n=1).

ASCT: autologous stem cell transplant; ATRT: atypical teratoid rhabdoid tumor; CNS: central nervous system; DIPG: diffuse intrinsic pontine glioma; GTR: gross total resection; MDACC: MD Anderson Cancer Center; PNET: primitive neuroectodermal tumor; RANO criteria: Response Assessment in Neuro-Oncology criteria; RECIST: Response Evaluation Criteria In Solid Tumors; RMH: Royal Marsden Hospital; WHO criteria: World Health Organization criteria.

Table 2: Median overall survival, log-rank test for univariate analysis and Cox regression for multivariate analysis according to clinical and analytical factors.

N[1]	Characteristics	Number (%)	Median OS (months)	95%CI (months)	Log-rank test (p value)[2]	Cox regression (p value)[2]
BASELINE PATIENT CHARACTERISTICS						
Age at Cycle 1 Day 1 (years):						
114	<2 2-11 12-17	3 (2.6) 69 (60.5) 42 (36.8)	4.1 5.8 4.8	1.3 – 7.0 3.3 – 8.2 2.6 – 7.0	0.710	-
Gender:						
114	Female Male	53 (46.5) 61 (53.5)	6.0 5.2	3.2 – 8.8 3.2 – 7.3	0.841	-
Time from diagnosis to Cycle 1 Day 1:						
114	<2 years ≥2 years	68 (59.6) 46 (40.4)	4.3 7.6	3.5 – 5.1 5.0 – 10.1	0.094	-
Performance status (Lansky or Karnofsky scales):[3]						
111	90-100% ≤80%	70 (63.0) 41 (37.0)	6.7 3.9	4.9 – 8.5 3.3 – 4.6	**0.010**	0.059
School/Work attendance:						
83	No Yes	27 (32.5) 56 (67.5)	2.7 6.9	0.6 – 4.8 4.5 – 9.3	**0.011**	0.063
Requirement of opioids:						
114	No Yes	107 (93.9) 7 (6.1)	5.5 1.8	3.9 – 7.0 1.2 – 2.4	0.208	-
Metastatic disease:						
114	No Yes	59 (51.8) 55 (48.2)	4.9 6.0	3.1 – 6.7 4.1 – 8.0	0.780	-
LAB VALUES AT BASELINE						
Anemia:[4]						
114	Grade ≤1 Grade ≥2[4]	107 (93.9) 7 (6.1)	5.4 6.3	3.9 – 6.9 <0.1 – 14.4	0.723	-
Neutropenia:[4]						
109	Grade ≤1 Grade ≥2[5]	102 (93.6) 7 (6.4)	5.8 4.1	4.0 – 7.7 <0.1 – 8.8	0.120	-
Platelets (x10^9/L):						
110	≥ 150 < 150[5]	107 (97.3) 3 (2.7)	5.8 3.1	3.9 – 7.7 <0.1 – 7.5	0.168	-
Creatinine:						
111	≤ ULN > ULN[5]	110 (99.1) 1 (0.9)	5.5 3.8	3.7 – 7.2 N/A	0.394	-
Total Bilirubin:						
105	≤ ULN > ULN[5]	102 (97.1) 3 (2.9)	5.8 1.6	3.7 – 7.8 1.2 – 2.1	0.840	-
Albumin (g/L):						
100	≥ 35 < 35[5]	92 (92.0) 8 (8.0)	5.5 1.8	3.5 – 7.5 0.4 – 3.2	0.266	-
Alanine aminotransferase (ALT):						
109	≤ ULN > ULN[5]	98 (89.9) 11 (10.1)	5.8 3.1	3.8 – 7.8 0.1 – 6.1	**0.029**	0.553
Aspartate aminotransferase (AST):						
107	≤ ULN > ULN[5]	98 (91.6) 9 (8.4)	5.9 3.1	3.7 – 8.0 1.1 – 5.2	**0.039**	0.229
Lactate dehydrogenase (LDH):						
63	≤ ULN > ULN[5]	34 (54.0) 29 (46.0)	5.5 5.4	1.9 – 9.1 3.6 – 7.3	0.446	-
PREVIOUS TREATMENTS						
Previous chemotherapy:						
114	0-2 lines ≥ 3 lines	87 (76.3) 27 (23.7)	5.2 5.5	3.7 – 6.8 1.0 – 10.0	0.860	-
Previous surgery:						
109	No/Biopsy only Non-GTR GTR	22 (20.2) 32 (29.4) 55 (50.4)	4.3 5.5 6.3	2.5 – 6.1 2.1 – 8.8 2.5 – 10.1	0.278	-
Previous radiotherapy:						
114	No Yes	8 (7.0) 106 (93.0)	6.3 4.9	3.6 – 8.9 3.5 – 6.3	0.137	-
Previous autologous stem cell transplant :[6]						

47	No Yes	26 (55.3) 21 (44.7)	6.7 7.6	0.6 – 12.8 2.3 – 12.9	0.889	-
EXPERIMENTAL TREATMENT						
Trial category:						
114	Targeted agent(s) Cytotoxic agent(s) Combined	77 (67.5) 32 (28.1) 5 (4.4)	4.3 5.4 10.5	2.7 – 5.9 4.1 – 6.7 8.4 – 12.6	0.696	-
Best response (all response criteria combined):						
109	CR/PR SD[7] PD	8 (7.3) 26 (23.9) 75 (68.8)	11.9 14.5 3.7	8.5 – 15.2 7.3 – 21.8 2.9 – 4.4	**<0.001**	N/A[8]
CLINICAL SCORES						
Royal Marsden Hospital (RMH) score:						
59	0 1 2 3	32 (54.2) 23 (39.0) 4 (6.8) 0 (0.0)	6.9 4.1 1.8 -	3.4 – 10.4 3.8 – 4.4 <0.1– 25.3 -	0.433	-
MD Anderson Cancer Center (MDACC) score:						
57	0 1 2 3 4 5	24 (42.1) 21 (36.8) 9 (15.8) 3 (5.3) 0 (0.0) 0 (0.0)	7.4 5.8 4.1 1.8 - -	3.8 – 11.0 3.4 – 8.2 3.9 – 4.3 1.5 – 2.2 - -	0.391	-

[1] Patients for whom the item was not applicable/available were excluded from the univariate analysis and re-calculated sample sizes were added as applicable; [2] Significant p values (<0.05) are represented in bold; [3] Lansky and Karnofsky scales were used interchangeably, performance statuses reported as per ECOG scale were converted to Lansky/Karnofsky as described in the Methods section; [4] Grading as per CTCAE v4.03; [5] Abnormal lab parameters at baseline were within the limits permitted per protocol and all patients were successfully enrolled in their respective trials; [6] Only tumor 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 and ATRT); [7] Including patients with non-CR/non-PD; [8] Not included in the multivariate analysis of prognostic factors, because tumour response cannot be known at baseline.

ATRT: atypical teratoid rhabdoid tumor; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; GTR: gross total resection; N: sample size for each variable; N/A: not applicable; OS: overall survival; PD: progressive disease; PR: partial response; PNET: primitive neuroectodermal tumor; SD: stable disease; ULN: upper limit of normal; 95%CI: 95% confidence interval.

Table 3: Median overall survival and log-rank test for univariate analysis according to best response assessed by RECIST guidelines (v1.0 or v1.1).

N[1]	Best response	Number (%)	Median OS (months)	95%CI (months)	Log-rank test (p value)[2]
43	Complete/Partial response Stable disease[3] Progressive disease	3 (7.0) 13 (30.2) 27 (62.8)	11.9 11.0 3.1	9.7 – 14.1 2.9 – 19.0 2.4 – 3.8	**<0.001**

[1] Two patients who were not evaluable were excluded from the univariate analysis; [2] Significant p values (<0.05) are represented in bold; [3] Including patients with non-Complete Response/non-Progressive Disease.

OS: overall survival; RECIST: Response Evaluation Criteria In Solid Tumors; 95%CI: 95% confidence interval.

SUPPLEMENTAL MATERIAL

Suppl Table 1: List of phase I trials included in the study.

#	Study drug	Category	Mechanism
1	AT9283	Targeted	Aurora kinase inhibitor
2	Dabrafenib	Targeted	B-RAF inhibitor
3	Dalotuzumab +/- Ridaforolimus	Targeted	Antibody anti-IGFR1 +/- mTOR inhibitor
4	Erlotinib	Targeted	EGFR inhibitor
5	Figitumumab	Targeted	Antibody anti-IGFR1
6	LDE225 (sonidegib)	Targeted	SHH inhibitor
7	LEE011 (ribociclib)	Targeted	CDK4/6 inhibitor
8	LDK378 (ceritinib)	Targeted	ALK inhibitor
9	Regorafenib	Targeted	Multi-kinase inhibitor
10	Ridaforolimus	Targeted	mTOR inhibitor
11	Vemurafenib	Targeted	B-RAF inhibitor
12	Rapamycin/Irinotecan	Targeted/Cytotoxic	mTOR inhibitor / Topoisomerase inhibitor
13	Cisplatin/Temozolomide	Cytotoxic	DNA cross-link / DNA alkylation
14	Liposomal daunorubicin	Cytotoxic	Inhibition of DNA synthesis
15	Liposomal doxorubicin	Cytotoxic	Inhibition of DNA synthesis
16	Oxaliplatin	Cytotoxic	Inhibition of DNA synthesis
17	Plitidepsin	Cytotoxic	JNK and p38 MAPK activation
18	Topotecan/temozolomide	Cytotoxic	Topoisomerase inhibitor / DNA alkylation