OPINION

Early phase clinical trials of anticancer agents in children and adolescents — an ITCC perspective

Lucas Moreno, Andrew D. J. Pearson*‡, Xavier Paoletti, Irene Jimenez, Birgit Geoerger, Pamela R. Kearns, C. Michel Zwaan, Francois Doz, Andre Baruchel, Josef Vormoor, Michela Casanova, Stefan M. Pfister, Bruce Morland and Gilles Vassal on behalf of the Innovative Therapies for Children with Cancer (ITCC) Consortium*

Abstract | In the past decade, the landscape of drug development in oncology has evolved dramatically; however, this paradigm shift remains to be adopted in early phase clinical trial designs for studies of molecularly targeted agents and immunotherapeutic agents in paediatric malignancies. In drug development, prioritization of drugs on the basis of knowledge of tumour biology, molecular 'drivers' of disease and a drug's mechanism of action, and therapeutic unmet needs are key elements; these aspects are relevant to early phase paediatric trials, in which molecular profiling is strongly encouraged. Herein, we describe the strategy of the Innovative Therapies for Children with Cancer (ITCC) Consortium, which advocates for the adoption of trial designs that enable uninterrupted patient recruitment, the extrapolation from studies in adults when possible, and the inclusion of expansion cohorts. If a drug has neither serious dose-related toxicities nor a narrow therapeutic index, then studies should generally be started at the adult recommended phase II dose corrected for body surface area, and act as dose-confirmation studies. The use of adaptive trial designs will enable drugs with promising activity to progress rapidly to randomized studies and, therefore, will substantially accelerate drug development for children and adolescents with cancer.

The introduction of novel therapeutic agents, including molecularly targeted agents (MTAs) and immunotherapeutic agents, into frontline treatments for paediatric malignancies is essential to improve the outcomes of children and adolescents with cancer. A major unmet need for new therapies exists, as evidenced by the high number of deaths from paediatric cancer[1], and by the substantial proportion of survivors who experience the long-term sequelae of currently available treatments[2]. New agents need to be efficiently and rapidly evaluated, and the appropriate drug dose, schedule, efficacy and toxicity profile, and pharmacological properties need to be determined. Progress will be fragmented and slow unless the mechanisms to conduct these assessments are agreed upon. Novel anticancer agents comprise different drug classes, including small-molecule tyrosine-kinase inhibitors (TKIs), drugs targeting epigenetic alterations, immune-checkpoint inhibitors or monoclonal antibodies, among others[3]. The goal of contemporary paediatric oncology is to achieve a comprehensive therapeutic approach that integrates drugs targeting cancer vulnerabilities with inhibitors of processes driven by genomic and/or epigenetic alterations, and also involves anticancer immune responses[4].

In 1998, a consensus article on the conduct of phase I studies in children with cancer was published by international investigators in paediatric oncology drug development[5]. The authors of this manuscript reported on the best methodology for the evaluation of the cytotoxic agents most commonly used at that time for children with cancer, establishing principles that are now used in early phase clinical trials for paediatric cancer (BOX 1). The members of the Innovative Therapies for Children with Cancer (ITCC) Consortium (comprising 51 paediatric oncology units across 12 European countries and Israel[6]), however, consider that the methodology described in 1998 should change and be adapted to the current era of targeted therapies and immunotherapies. The use of this methodology results in substantial delays in the evaluation of new anticancer drugs in children, and increases the risk of giving a non-active dose, without reducing the risks of toxicity associated with early phase clinical trials. A key challenge, therefore, is the development of a new consensus on the conduct of early phase clinical trials of targeted drugs for children with cancer.

The complexity of anticancer drug development has increased remarkably with the large number of molecular subtype classifications currently defined for most malignancies, and the advent of combination therapies, companion diagnostics, and immunotherapies. Nevertheless, the number of MTAs being evaluated each year has grown considerably[7]. As of July 2016, more than 70 MTAs had been approved by the FDA and European Medicines Agency (EMA) for the treatment of cancers that usually occur in adults, but only three agents had been approved for the treatment of childhood cancers[8,9]: imatinib for chronic myeloid leukaemia (CML), everolimus for subependymal giant-cell astrocytoma, and dinutuximab for neuroblastoma[8,9]. Furthermore, despite the changes in the landscape of oncology prompted by the adoption of precision-medicine approaches, new drugs are only slowly integrated into phase III trials in paediatric populations, and MTAs have not been introduced into frontline therapy for many paediatric

Box 1 | **Definition of early phase clinical trial**

The term 'early phase clinical trial' encompasses the first stages of the clinical development of a therapeutic agent, in which results about optimal dosing, toxicity profile, pharmacodynamic biomarkers, and early signals of antitumour activity are collected before transitioning to 'late-stage' phase II or III trials aimed at determining the antitumour efficacy of the therapeutic agent.

An early phase clinical trial has two principal components:

- A dose-confirmation or escalation-confirmation phase, in which the toxicity profile, the recommended phase II dose and preliminary pharmacokinetic (PK) parameters are determined
- Expansion cohorts, in which additional PK, pharmacodynamic, and safety data and, importantly, early signals of antitumour activity, are obtained

malignancies with a poor prognosis (BOX 2). Nevertheless, MTAs (for example, inhibitors of BCR–ABL1, ALK and BRAF, and bispecific T-cell engagers) are increasingly used to treat paediatric patients. The design of first-in-child trials needs to be adapted to enable efficient evaluation of such agents while maintaining safety. Trial designs that differ from those required with cytotoxic drugs must be adopted when using treatments matched to the molecular characteristics of a tumour. MTAs have different toxicity profiles to cytotoxic agents (predominantly non-haematological toxicities). Moreover, in general, the efficacy of MTAs does not increase with dose augmentation, and their therapeutic index is wider than that of cytotoxic agents[10–12]. An important consideration is that all patients who meet the enrolment criteria and wish to receive these new drugs should be offered the opportunity to participate in such clinical trials, in order to increase the therapeutic options available for children and adolescents with relapsed disease.

Major changes have occurred in relation to paediatric early phase clinical trials, resulting in a new landscape for anticancer drug development for children. Globally, all stakeholders (academia, the pharmaceutical industry, parents or carers, patient advocates, regulatory agencies, public-health agencies, research-funding agencies, and philanthropic organizations) are working closely together to accelerate drug development for children and adolescents[13,14]. In North America and Europe, new regulations aimed at encouraging the interest of the pharmaceutical industry in conducting studies with children have been implemented, including the European Paediatric Medicine Regulation EC No. 1901/2006 (REFS 15–18) and, in the USA, the Best Pharmaceuticals for Children Act (BPCA)[19], the Paediatric Research Equity Act (PREA)[20], and the Creating Hope Act.

Current process in paediatric trials

The development of drugs for paediatric patients remains largely centred on adult conditions (with the exception of anti-GD2 targeted therapies for neuroblastoma[21]) and, thus, most drugs that reach paediatric clinical development have already been extensively explored in adult trials. In spite of the motivation of regulatory bodies and clinicians to initiate first-in-child studies for any given drug upon completion of first-in-man trials, the reality is that phase I trials in children generally start after pivotal phase III studies in adult patients are near completion; this situation substantially delays the access of these new therapeutic agents to children and adolescents.

Phase I — dose-escalation. In paediatric oncology, drug-evaluation processes usually begin with a dose-escalation phase, using methods such as the 3 + 3 method[22] or the rolling six method[23], in which drugs are administered at multiple dose levels until a maximum tolerated dose (MTD) and recommended phase II dose (RP2D) are identified. The starting dose in dose-escalation studies with children has conventionally been 80% (and frequently below) of the adult RP2D[5]. Classic dose-escalation designs were developed for cytotoxic drugs, for which the main toxicities are often dose-related (for example, haematological toxicities); the main objective of these designs was to prevent and/or limit severe toxicities by ensuring that only small groups of patients receive increasing doses of the agent(s). This approach, although successful with some drugs, has sometimes resulted in long phase I trials with many dose levels tested, multiple episodes of suspended recruitment while patients waited for assessment of dose-limiting toxicities (DLTs), and the requirement of large numbers of patients (TABLE 1). Hence, for MTAs the use of this classic dose-escalation model based on the identification of DLTs and the definition of an MTD has slowed progress while not resulting in an enhanced protection against undesirable adverse events[24].

Upon completion of phase I studies, drug activity is traditionally evaluated in single-arm phase II studies. These single-arm phase II trials typically enrol 25–60 patients and lead to response rates, data of which are then compared with historical data. This comparison is frequently problematic owing to differences in patient populations and context, resulting in unclear conclusions and leading to testing of agents in multiple phase II studies in different relapsed disease settings before reaching frontline trials.

Disadvantages of the process for evaluating new drugs in children. Drug development in paediatric oncology is largely driven by the availability of drugs developed or marketed for adults, rather than on the basis of the drug mechanism of action (MoA)[25]. Moreover, the current process for evaluation of new anticancer drugs is not suitable for paediatric studies of MTAs and immunotherapeutic agents. Firstly, most toxic effects that arise from MTAs are not necessarily dose-related, but rather class-related[26]. Tolerable doses of MTAs for paediatric patients are often equivalent to those for adult patients corrected for body surface area (BSA), resulting in the same pharmacokinetic (PK) values (area under the concentration–time curve and trough levels) for both children and adults. In a published analysis[24] of the MTD for 25 MTAs approved by the FDA or EMA for adult cancers and evaluated in paediatric cancers up to 2012, we demonstrated that, for 75% of those MTAs, the established RP2D for paediatric patients was 90–130% of the BSA-adjusted approved dose for adults. Importantly, in this report we also showed that the toxicities associated with the administration of these MTAs to children were the same as those observed in adult patients, and the values of the main PK parameters were comparable for children and adults[24,27]. Of these 25 drugs, sunitinib was the only one for which DLTs were observed in children at lower dose levels than in adults. Despite similar PK parameters, the main toxicities associated with sunitinib treatment also differed: myelosuppression and elevated transaminase levels were the most commonly reported toxicities in children compared with fatigue and gastrointestinal symptoms in adults. The mechanisms underlying these differences are uncertain. Furthermore, the choice of patient population — heavily pretreated children with relapsed and/or refractory

solid tumours — might have contributed to this finding[28,29]. Thus, the methods to determine the dosing of MTAs for clinical trials involving children need to be revised for some targeted agents for which the RP2D for adults is not based on toxicity and is below the MTD. For such agents, the dosing for children can begin at the BSA-adjusted RP2D for adults. A further consideration is that MTAs are evaluated in paediatric patients at doses below those already established to be active in adults, an approach that raises ethical concerns because therapeutic intent should be central to studies in children[30] (BOX 3). Herein, we propose that the starting dose for most agents in paediatric oncology trials should be a dose equivalent to the minimally active target exposure determined for adults.

One of the most challenging areas in paediatric drug development is the evaluation of pharmacological differences and the risk of toxicities affecting development in children younger than 3 years of age[31]. The limited number of infants and young children who participate in early phase clinical trials poses practical difficulties in addressing PK differences at each dose level, or even during the whole dose-escalation trial. In a report from eight large ITCC centres[32], only nine of 270 (3.3%) patients participating in dose-determining trials were <3 years of age. In addition, the evaluation of developmental toxicities requires long survival and follow-up durations, and is therefore studied in late-phase or upfront trials. For some agents with response rates greater than 50%, however, data on developmental toxicities should also be collected in early phase trials[33].

In summary, trial designs that require systematic dose-escalations have proved not to be efficient for the development of MTAs or immunotherapeutic agents in paediatric clinical trials; such designs add unnecessary time to the duration of studies, and require some patients to be treated at doses lower than the adult MTD/RP2D, while at the same time not protecting paediatric patients from unacceptable, unexpected, or paediatric-specific toxicities.

Box 2 | **Precision medicine in children and adolescents**

Precision medicine can be defined as the therapeutic decisions guided by the molecular or genomic features — and not by the clinicopathological features — of a tumour. Central to precision medicine for paediatric malignancies is the understanding of the molecular pathways and key drivers of the disease, focusing on aberrations that demonstrate a proof of 'tumour dependence'. Key considerations include:

- The genetic and epigenetic repertoire of driver mutations specific to childhood malignancies differs from that underlying more-common malignancies in adults. As a result, many anticancer agents developed for adult patients are not effective in childhood cancers
- Childhood tumours harbour, on average, a 100-fold fewer mutations than adult malignancies[108]
- Information on the presence of actionable target mutations can be obtained; the challenging task is the determination of the functional relevance of those mutations (for example, in tumour-cell survival or tumour–host interactions)

Currently, precision medicine in paediatric oncology is focused on actionable target mutations, particularly those for which drugs developed for adult cancers are available (for example, *ALK* or *BRAF*); these actionable target mutations can be detected in ~10% of tumours[84–87]. The major current challenges in implementing precision medicine in paediatric oncology include the focus on only a few actionable mutations, the presence of multiple alterations in each patient, and the limited access to targeted agents. The number of targeted anticancer drugs available to target drivers of childhood cancers is limited — a hurdle that needs to be overcome to successfully apply precision medicine principles. To address this need, the multiple-agent ITCC European proof-of-concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumours (ESMART) study (NCT02813135)[58] is not restricted to patients with predefined molecular alterations. On the contrary, the secondary objective of this study is to compare outcomes of patients with molecular abnormalities, matching the treatment to those without druggable targets.

Despite important progress being made, drug development for children with cancer is still focused on clinical research on adult conditions. A recent analysis suggests that 54% of new anticancer agents, whose evaluation in children was waivered, had a target or mechanism of action that, on the basis of existing molecular data (A.D.J.P., S.M.P. and G.V., unpublished results), would warrant paediatric development. In a mechanism-of-action-based approach to drug development for children and adolescents with cancer, all hallmarks of cancer including epigenetics and immune evasion should be targeted.

We propose that prioritization of targeted agents should be facilitated by an international Paediatric Strategy Forum. The output of a Paediatric Strategy Forum would provide an overview of the landscape, which would facilitate sharing of information across all stakeholders, and would also advance learning, informing subsequent decisions.

Proposed new framework

Objectives of first-in-child studies. The main aim of first-in-child studies is to determine the toxicity profile, the RP2D, and optimal dose-scheduling of a new drug in children before other features are evaluated. For determination of the RP2D, available data related to the toxicity profile measured at all treatment cycles (and not only the first one), including PK, pharmacodynamic (PD; target inhibition), biomarkers and preliminary data about activity, can be taken into account. For a number of drugs in which biological activity has guided the determination of the RP2D for children, establishment of a MTD is not required because biological activity can be achieved at doses below the MTD. Thus, in paediatric trials of MTAs, a drug-escalation phase to determine the MTD can be avoided, and an RP2D based on the integration of available toxicity, activity and biomarker-related data extrapolated from studies in adults can be used instead[34]; much of this information can be confirmed in later phases of the drug-development process in children.

Initial dose for first-in-child early phase clinical trials. For paediatric patients, the RP2D of most MTAs ranges between 90–130% of the BSA-adjusted approved dose for adults and, in the absence of DLT, is often based on PK and PD end points[24]. This observation, together with the fact that the short-term safety profiles and DLT described in paediatric phase I trials are similar to those reported for adult patient populations, means that identifying toxicities in children not previously documented in adults is very rare. Furthermore, owing to an absence of DLT, a MTD is never identified in 25% of paediatric dose-finding trials of MTAs[24].

If the toxicity profile and the PK parameters observed in children treated at the RP2D established for adults are similar to those observed in adults, a dose-escalation to the MTD established for adults is not required, unless a dose–activity relationship has been documented in adults. We therefore recommend that, when possible, paediatric first-in-child studies of MTAs should start at 100% of the BSA-adjusted equivalent approved RP2D for adult patients (FIG. 1). In some specific situations, the benefit–risk ratio should be weighed against this recommendation. For

Table 1 | **Summary of dose-finding clinical trials in paediatric oncology and haematology (2009–2015)[54]***

Parameter	Median	Range
Age at enrolment (years)	10	1–30
Number of dose levels tested in escalation cohort	3	1–10
Number of patients enrolled in dose-escalation cohort	18	2–67
Number of patients enrolled in study	24	6–79
Median duration of trials, including dose-escalation phase and dose-expansion cohorts/phase II (months)	30	5–92
Median duration of the trials that only had dose-escalation cohorts ($n = 54$; months)	27.5	5–73

$n = 92$ trials, with 112 dose-escalation cohorts (some trials had several parallel dose-escalation cohorts). *I.J. and X.P., unpublished results.

example, therapeutic agents associated with specific, serious, dose-related toxicities, or a narrow therapeutic index should have dose-escalation initiated at 80% of the RP2D for adults and increased to 100% and 120%, if indicated (FIG. 1). Examples of such agents include blinatumomab[35], moxetumomab[36] or EGFR inhibitors[37]. In this context, the therapeutic index is defined as the ratio between the highest dose of the drug that results in no toxicity and the dose that produces the desired efficacy[38]. This recommendation is supported by the results of 25 dose-finding trials performed since 2003 by ITCC members, and by the conclusions of a systematic review of paediatric dose-finding studies (published in 2013)[24], which indicate that, for MTAs, starting at low doses does not result in the prevention of severe toxicities.

We propose an approach aimed at obtaining the maximal amount of information from adult studies, extrapolating from existing data when possible — an approach supported in 2016 by the EMA[34]. Such extrapolation is feasible for studies of MTAs for conditions that affect both adults and children (such as CML), or which share molecular aberrations (for example, cancers with *BRAF* mutations, such as melanoma and high-grade glioma[39]). Thus, for many drugs with a wide therapeutic index (approximately 25% of MTAs), only a dose-confirmation study with a limited sample size needs to be conducted. For example, in a study with ten patients, the risk of missing adverse events with a ≥33% prevalence and the probability of not identifying a drug with a ≥30% activity-rate would be as low as 5%. Furthermore, the sample size would enable the estimation of key PK parameters (provided that the PK parameters in adults are known[40]), and the determination of the RP2D for children (if the safety profile and PK parameters are equivalent to those in adults; FIG. 1). In these conditions, escalating up to the MTD in children is not necessary if this dose is higher than the RP2D. Studies with small cohorts can provide sufficient information to proceed to later-phase studies to define drug activity and efficacy, as exemplified by studies with nilotinib[41]. Most monoclonal antibodies do not generally require a dose-escalation phase; for example, the evaluation of brentuximab (for CD30-positive lymphomas)[42,43] and antibodies against IGF-1R[44–48] for paediatric patients required only small-dose confirmation studies. Regardless of agent class, if the RP2D for adults is not based on toxicity and is below the adult MTD, then the dosing for children can begin at the BSA-adjusted RP2D for adults.

In the absence of particular safety issues, trial designs that involve the study being closed for substantial periods of time should not be used, because waiting for trial allocation is an additional burden for patients and their parents or carers. Uninterrupted trial recruitment should be a priority as soon as a trial is deemed safe (for example, after the first dose-level or cohort of patients is analysed).

New dose-escalation designs, such as the Bayesian logistic regression model (BLRM)[49], or the continuous reassessment method (CRM)[50], can maximize the efficiency of the dose-escalation phase. CRM-based extensions have the advantage of incorporating events that occur after the first treatment cycle, if needed, and provide a useful tool to monitor the risk of toxicity during the expansion cohort. Several studies that use simulations have shown the superiority of the BLRM and CRM designs over the 3 + 3 or the rolling six methods in the context of paediatric trials[51–54]. A review of 84 first-in-man, phase I trials of MTAs with adult patients revealed that the number of trials using CRM to determine the median number of dose levels was double the number of trials using the 3 + 3 method; with a similar median number of patients enrolled for both trial designs, the number of patients treated at doses higher than the MTD was lower in CRM-based trials than in trials based on the 3 + 3 or the accelerated-titration design[22]. In the accelerated titration design, before the first DLT is observed, dose levels are escalated after each new patient tolerates the treatment (no grade >1 toxicities); after the first DLT, the design reverts to the classic 3 + 3 design[55]. To date, similar comparisons in paediatric oncology have not been established because of the difficulty associated with selecting a method that is not independent of the type of agent tested, and the difficulty in estimating the required number of doses to be tested. The rolling six design, however, would be acceptable if a limited number of dose levels were to be explored and patient accrual was not too fast; in this situation, more than six patients at the RP2D dose would be required for the PK parameters to be evaluated (TABLE 2; Supplementary information S1 (table)).

Inclusion of expansion cohorts. The addition of expansion cohorts of patients with homogeneous characteristics provides additional PK, PD, and safety data that are similar to those obtained in phase II settings, and enables the identification of early signals of antitumour activity[56]. The aim of incorporating these cohorts is to enrich the patient population that have tumours (or genomic aberrations) with a maximal probability of response on the basis of molecular characteristics[39], or to detect first signals of drug activity in diseases of interest. The size of the expansion cohorts can be defined according to statistical calculations in order to achieve enough statistical power to inform on 'go/no-go' decisions[57]. In the context of biomarker-enriched trials, the use of expansion cohorts provides evidence that, although not definitive, supports further development of a particular drug. When the characteristics of the paediatric population are similar to those of the adult cohort in which the PK parameters have been established, a smaller sample size can

Box 3 | **Ethical aspects related to early phase clinical trials in paediatric oncology**

Ethics should guide all aspects of early phase clinical trials within the legal framework[30]. The scientific information gained from an early phase clinical trial must be weighed against ethical aspects, which can be broadly grouped into four areas: research ethics, legal and ethical consistency, professionalism, and consent. The following aspects always need to be considered:

- The research objectives and underlying scientific rationale must be strong
- Therapeutic intent is central to early phase clinical trials in paediatric malignancies
- Enrolment in an early phase clinical trial is an option to be proposed to the patient and his/her parents or carers
- The availability of tumour material at the time of enrolment in an early phase trial will enable the maximal knowledge to be obtained from the study
- The inclusion of ancillary/biological studies (tumour analysis and pharmacodynamic (PD) studies) increases the scientific value of early phase clinical trials, and thus, the future use of the drug. For example, genetic variability of drug metabolism, or mechanisms of drug resistance are central questions that should be studied as early as possible during the development of a therapeutic agent
- Information on PD biomarkers can be obtained noninvasively or by blood sampling. Liquid biopsies have an important potential role as they might provide relevant molecular diagnostic, prognostic, and predictive information, and can be used during treatment to predict response and/or resistance to treatment with minimal distress to the patients

A way forward should be developed so that early drug development can be efficient and based on scientific information from PD and biological studies, while abiding by ethical constraints:

- The evaluation of drugs in paediatric patients at doses substantially below those established to be active in adults raises ethical concerns, as therapeutic intent is central to studies in children. A dose equivalent to the minimum active dose in adults should be the mandatory starting dose for children with most agents
- Protocols should be designed with the aim of minimizing aspects related to distress for patients and their environment (for example, number of hospital visits, uncomfortable tests, frequent sedations, painful procedures, or the number of diagnostic procedures)

be sufficient to validate the PK estimates. For drugs with a large therapeutic index, dose-confirmation in patient populations selected according to tumour histologies or molecular profiles will enable the assessment of therapeutic activity in these patient subgroups.

The go/no-go decision rules affecting the expansion cohorts need to be defined in the study protocols, particularly if this decision is also based on signs of antitumour activity. Once the RP2D has been determined, expansion cohorts are established for patients with disease or molecular subtypes that match the biological rationale for the drug's MoA, or for whom an indication of antitumour activity has been obtained in the dose-confirmation/escalation phase. A design with go/no-go decision rules dependent on drug activity can be applied to the expansion cohort. For example, we are implementing an Ensign three-stage design[57] in the multiple agent ITCC European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumours (ESMART) study (NCT02813135)[58]. In this study, cohorts of ten patients (including those from the dose-confirmation study) are being recruited and will receive the RP2D. If no responses are observed in these first ten patients, further evaluation of the drug will then be postponed or abandoned. If responses are observed, a further 16 patients will be enrolled, and an interim analysis and an early stopping rule have been incorporated. The first advantage of the three-stage design is that the ten patients treated at the RP2D in the dose-confirmation — or possibly dose-escalation — stage can be evaluated for response; therefore, this design is driven by a statistically and clinically sound rationale with the aim of facilitating the transition from the dose-confirmation/escalation phase to the expansion cohort. Given the low rates of patient accrual in paediatric clinical trials, the second advantage of a three-stage design is that it enables a frequent examination of the data, and offers the possibility of stopping the trial of an inefficient drug early in the evaluation process. Alternative designs, such as Bayesian approaches, can also be adopted, as long as data provided at the end of the trial are reliable and enable initiation of further comparative, practice-changing trials (FIG. 1).

In trials testing agents targeting specific oncogenic drivers present in tumours with a well-defined predictive biomarker (such as BRAF inhibitors for gliomas harbouring mutations in *BRAF*, or ALK inhibitors in anaplastic large-cell lymphoma (ALCL)), a small, enrichment expansion cohort will be sufficient to determine whether the drug is active (on the basis of response rate). Conversely, in trials testing inhibitors of cell signalling pathways, and in the absence of a predictive biomarker (for example, MEK or PI3K inhibitors in unselected populations), expansion cohorts might not be sufficient to determine single-agent activity. Single-agent studies with these drugs might only enable documenting inhibition of a PD target when performed in a cohort of patients with homogeneous characteristics who all receive the same dose. On the basis of these results, the study would then progress to an early phase combination study, which would be required for the detection of antitumour activity. In the absence of a highly predictive biomarker and/or when resistance to monotherapy is frequent, drug combinations have to be tested as early as possible to prevent recruiting patients to single-agent expansion cohorts with a low probability of therapeutic activity; this approach is being adopted in new trials[59,60]. The potential activity of a drug in a single-agent regimen depends on its MoA. For some drugs, antitumour activity can be expected from monotherapy (for example, agents targeting the product of a key oncogenic driver (such as *BRAF* or *ALK*) but, for others, a combination study is required. General assumptions cannot be made, but a drug should not be disregarded early if it is expected to be active only in combination regimens. Trials in which expansion-cohort studies are combined with dose-confirmation studies are similar to phase I/II trials; we propose to refer to these trials as 'early phase clinical trials' (BOXES 1,4; FIG. 1).

Later phases of drug development. In single-arm phase II trials, the success or failure criteria define a clinically acceptable response rate that would lead to further evaluation of the drug. Such criteria are always estimations based on historical data, which often underestimate the real effect of standard treatment[61] and thus, randomized phase II trials are preferred[62]. Given the low incidence of paediatric cancers, novel designs (such as Bayesian or two-stage minimax Jung designs)[63,64] can be used to minimize the sample size to 25–35 patients per cohort[65,66]. Randomized phase II trials are feasible approaches to evaluate new drugs in the first-relapse setting for most paediatric patients with a poor prognosis, in whom the outcome

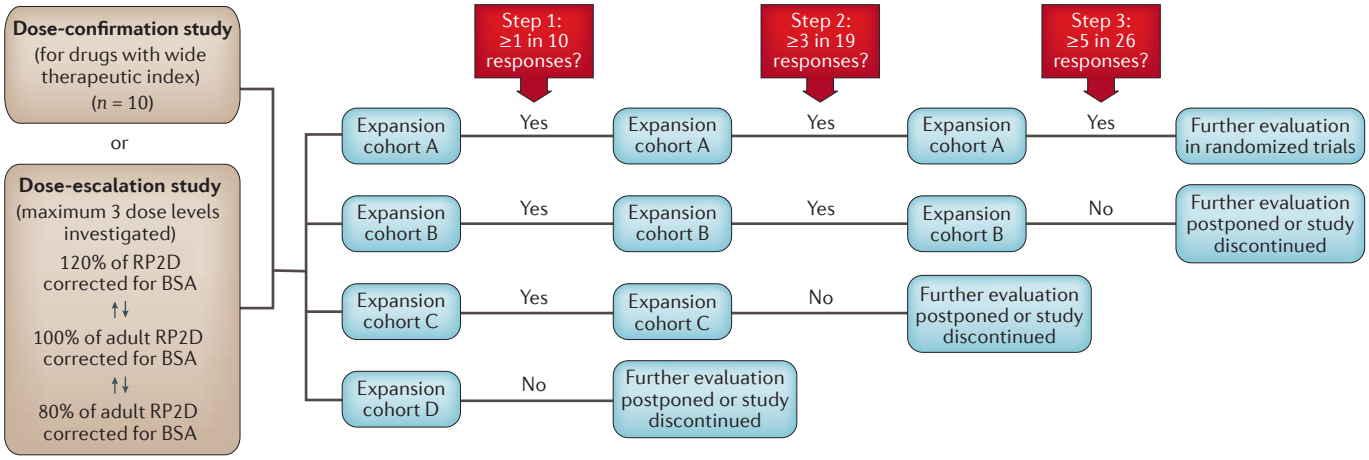

Figure 1 | **Proposed three-stage (Ensign) design of early phase clinical trials in children.** The aim of this design is to evaluate thFerapeutic agents by assessing toxicity and antitumour activity (>30% and never <10% at any stage). Expansion cohorts are defined by molecular characteristics or disease entities. Patients in the dose-confirmation study can be included in the expansion cohort if they received the recommended phase II dose (RP2D) for paediatric patients. A molecularly targeted agent (MTA) or immunotherapeutic agent without serious, dose-related toxicities and a wide therapeutic index has a starting dose of 100% of body surface area (BSA)-corrected RP2D for adults. By contrast, an MTA or immunotherapeutic agent with serious, dose-related toxicities and a narrow therapeutic index has a starting dose of 80% of BSA-corrected RP2D for adults. Dose-escalation is performed using a Bayesian logistic regression model (BLRM) or continuous reassessment method (CRM).

after first relapse is poor and new therapies are needed. For example, targeted agents for neuroblastoma are being studied in three ongoing randomized clinical trials worldwide, involving 74–160 patients[66–68]. Similar platforms are being developed in North America and Europe for other common tumour types, such as Ewing sarcoma[69] or rhabdomyosarcoma[70].

The recruitment of sufficient numbers of patients is a challenge in studies of tumour types with low incidence, or studies associated with better outcomes, such as acute lymphoblastic leukaemia or Wilms tumour — a situation that supports the need for global studies. Even small, randomized trials provide better evidence than single-arm trials[65,66]. The major advantage of a randomized phase II trial is that it provides more solid evidence of drug efficacy compared with single-arm trials, in which the estimations for considering an agent successful or unsuccessful are based on historical controls; hence, performing randomized phase II trials will eventually result in the requirement of smaller cohorts to make the decision of whether the drug should further be evaluated in a phase III trial. Herein we propose an approach whereby only single-agent regimens or combinations that show initial signals of activity in the expansion-cohort phase of an early phase clinical trial should be taken forward to randomized phase II trials. With this approach, therapeutic agents can move from first-in-child to frontline-therapy trials in only three steps.

The pharmacological audit trail

The pharmacological audit trail is a paradigm applied in drug development for adult patients that is being adopted in early phase studies in children, including the ITCC ESMART study[58]. This approach incorporates a biological rationale into early clinical trials by including a continuous bench-to-bedside and back-again strategy incorporating predictive and PD biomarkers, with the aim of accelerating and improving drug development[71]. PD biomarkers demonstrate target inhibition and feedback into dose-escalation through continuous measurement. Pharmacogenetic studies that explore the variability of individual responses to new drugs (at the level of drug metabolism) should be incorporated into paediatric trials. Biomarkers need to be incorporated in paediatric early phase clinical trials[72]; importantly, data derived from predictive and PD biomarkers obtained in clinical trials with adult patients must be applied in children, if relevant[72] (Supplementary information S2 (table)). Examples of the successful application of the pharmacological audit trail in early phase clinical trials in children include the Children's Oncology Group (COG) phase I trial of the AKT inhibitor MK2206 (REF. 73) and a phase I trial initiated by Cancer Research UK of the aurora kinase inhibitor AT9283 (REF. 74). In some instances, new biomarker assays relevant to the biology of paediatric tumours will have to be developed and validated in studies involving children (for example, drugs against targets specific to paediatric cancers, such as MYCN[75]). Liquid biopsies might provide opportunities to conduct sequential PD studies in children without performing repeat tumour biopsies[76]. Also, studies in children have included functional imaging as a non-invasive approach; for example, dynamic contrast-enhanced MRI in a study of pazopanib[77], or tumour-perfusion assessment by MRI in a study of vandetanib[78]. Extrapolation of post-treatment PD data from adult patients (with confirmation of comparable PK data in adults and children) should also be considered. When a predictive or PD biomarker for a targeted agent has not been found to correlate with therapeutic activity, exploration of this relationship could continue during later stages of development of the drug. Similarly, a biomarker that has been identified as an exploratory end point in an early phase trial should be validated in later stages of drug development.

Genomic studies in tumours

The availability of tumour material at the time of enrolment in an early phase trial increases the overall amount of information that can be obtained from a study. Samples of the tumour taken at clinical presentation can be relevant for some characterizations, but the use of such samples is usually deemed inappropriate, because evidence indicates that clonal evolution occurs in the vast majority of tumours in children[79–81]; tumour heterogeneity, which is very

Table 2 | **Drug-dosing recommendations for early phase studies in children based on findings from studies in adults**

Data from adult patients	Recommendation for early phase trials in children				Examples
	Objectives and end point(s)	Starting dose (% of RP2D used for adults)	Design	Dose-escalation criteria	
MTD not defined	• Dose confirmation • DLT rate • PK and PD parameters • Toxicity profile • Antitumour activity	100%	Validation and/or confirmation of findings from adults	Only increase if drug distribution (AUC or clearance) suggests underdosing or insufficient target inhibition	• Monoclonal antibodies*: cetuximab[109], bevacizumab[110] • BRAF inhibitors*: dabrafenib[39]
MTD defined, wide therapeutic index	• Dose confirmation • DLT rate • PK and PD parameters • Toxicity profile • Antitumour activity	100%	Validation of findings from adults	Decrease if high toxicity rate and increase if drug distribution (AUC or clearance) suggest under dosing	• EGFR inhibitors‡: gefitinib[111]
MTD defined, narrow therapeutic index	• Toxicity profile • DLT rate	≤80%	Identification of MTD for paediatric patients	Increase if acceptable rate of DLTs	• Sunitinib§[28] • Blinatumomab[35]

*The MTD of most monoclonal antibodies and BRAF inhibitors has not been defined. ‡The MTD of gefitinib has been defined; this agent has a wide therapeutic index and the effective dose is different to the MTD in adults. §The MTD of sunitinib has been defined; this agent has a narrow therapeutic index and the effective dose is very close to the MTD in adults. AUC, area under the curve; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; PD, pharmacodynamic; PK, pharmacokinetic; RP2D, recommended phase II dose.

frequently present, also needs to be taken into consideration[82]. The requirement of tumour samples taken immediately before study entry, however, needs to be placed within the context of the agent being studied, the objectives of the clinical trial, the ethical justifications for tumour sampling, and the clinical status of the patient population being studied. The use of liquid biopsies (analysing, for example, circulating cell-free DNA[83]), with samples collected sequentially during an early phase trial, is a promising approach that is currently applied in studies with paediatric patients. Initiatives from the ITCC and other groups are now in place to routinely molecularly profile tumours at relapse[84–89]. The use of these protocols will provide information regarding the evolution of the tumour and its heterogeneity and, in addition, will help to determine if actionable mutations are present after treatment, thereby identifying potential MTAs for future precision-medicine studies with stratified groups defined by molecular enrichment and/or predictive biomarkers.

Considerations on age groups

Infants and very young children <2 years. Compared with older children and adults, renal and hepatic functions are different in children younger than 3 years of age[90]; thus, drug metabolism and PK profiles can differ in cohorts incorporating patients in this age group. The collection of PK data from children younger than 3 years of age is required, in particular, for agents indicated for malignancies occurring at younger ages, such as rhabdoid tumours or infant leukaemias[91]. Owing to the low frequency of disease relapse in this population, the early phase trial protocol should not predefine the number of infants (children under 2 years of age) to be enrolled; this data should be collected in later phase studies. In trials involving infants, PK data should also be collected during the expansion cohort or subsequent studies. Hence, trials of anticancer agents in children should not be stratified in age cohorts.

Adolescents. The upper age limit for enrolment in paediatric early phase clinical trials, although not based on medical or biological grounds, is often below 18 years — also the lower age limit of many phase I studies with adults. A distinction between paediatric and adult populations is understandable, but studies should be adapted to the population of interest. A first-in-child early phase study with the objective of defining the dose and PK profile for paediatric patients should include only children and adolescents.

Conversely, the 18 years of age 'boundary' should not exclude the access of adolescents (12–17 years old, according to the International Conference on Harmonization E11)[92] from early trials of new anticancer agents of interest. The PK, PD, and toxicity profiles of drugs are very likely to be similar in adolescents and adult patients[93]. For studies with a strong biological rationale, or for malignancies that affect adolescents and young adults (12–24 years of age), such as Ewing sarcoma, Hodgkin lymphoma, high-grade glioma, soft-tissue sarcoma or osteosarcoma, adolescents have been allowed to participate in phase I studies predicated on adults. This strategy is a valid means to accelerate drug development for the adolescent patient population, while ensuring that the population of interest is well-represented. For example, adolescents older than 12 years with Ewing or other sarcomas were included in phase I trials of anti-IGF-1R monoclonal antibodies[44]. Also, trials of the mTOR inhibitor CC-115 included an expansion cohort for patients with Ewing sarcoma that included adolescents[94], as did studies of nivolumab in melanoma[95] and *ALK*-positive malignancies (ALCL and sarcomas; CREATE)[96]. Building on this approach, for agents with a relevant MoA, adolescent patients should be included in phase I trials for adults after the dose-escalation phase is completed; this approach should complement paediatric evaluation. We propose that additional therapeutic opportunities will be provided if adolescents are included in phase I, II, or III trials for children, and if young-adult patients participate in phase II or III trials for paediatric patients, especially if their diagnosis matches a predominantly paediatric cancer type (such as medulloblastoma).

Some malignancies common in adults are rare in the paediatric population and occur infrequently in adolescents (for example, metastatic melanoma or thyroid cancer). When a drug developed for such conditions is to be evaluated in children and adolescent patients with the same condition (and possibly at the same time

Box 4 | **Summary of recommendations**

Trial design

- Tailor to specific drug/target/condition; no longer 'one size fits all'

Selection of candidate drugs for first-in-child trials

- Prioritization driven by tumour biology
- Drug selection according to molecular pathways, tumour biology, and key drivers of paediatric malignancies
- The preclinical data required to initiate first-in-child trials with a therapeutic agent is variable and has to be adapted to each target/drug/malignancy

Early phase trials

- In paediatric oncology, early phase trials encompass first-in-child and phase II elements

Objectives and end points

- The main aim is to determine the RP2D and schedule for further evaluation, and the toxicity profile. The inclusion of expansion cohorts enables additional PK, PD, and preliminary drug-activity data to be obtained; this latter information will be completed in later phases of drug development

Tumour molecular profiling

- Essential at enrolment in early phase trials
- Tissue should be collected at the time of diagnosis and relapse and, when possible, at study entry and at disease progression

Extrapolation from adults

- Early phase trials can serve to validate dose and pharmacological findings from trials in adults

Dose-escalation

- Shortened using novel, adaptive designs
- Designs that involve frequent closure periods or waiting lists must be avoided
- In the absence of specific dose-related toxicities or a narrow therapeutic index, first-in-child trials should start at 100% of the BSA-adjusted equivalent RP2D approved in adults (short dose-confirmation studies)
- In the presence of dose-related toxicities or a narrow therapeutic index, dose-escalation should generally start at 80% of BSA-adjusted adult-approved RP2D, then increased to 100% and 120%
- Age-defined cohorts are not required

Expansion cohorts

- Safety, PK, PD, and preliminary drug-activity data need to be collected in homogeneous expansion cohorts
- Promising agents tested can then progress directly into randomized phase II studies

Definition of DLTs

- DLTs have to match the expected toxicity profile of the drug
- Toxicities occurring beyond first cycle, or relevant low-grade toxicities must be considered. DLT should be based on first cycle and serve to identify the MTD. Toxicities occurring beyond first cycle must be considered for the decision of the RP2D and incorporated to the definition of DLT on an individual drug-by-drug basis

Adolescents and young adults

- A key objective of studies with this age-group is to show whether the PK and toxicity profile is the same as for adults
- Dose-escalation studies are not required
- Adolescents >12 years of age should be eligible for phase I trials in adults after the dose-escalation phase is completed, if the mechanism of action of the drug or the tumour type of interest indicate patients might benefit

Infants

- Pharmacology must be carefully studied in this patient population; however, the participation of infants in early trials is infrequent. Hence, the collection of PK data should continue through late-phase trials

Biomarkers

- Predictive biomarkers should be used to select the patient population most likely to benefit from drugs targeting oncogenic drivers
- PD biomarkers are crucial to demonstrate target inhibition and inform on whether to pursue late-phase trials of a therapeutic agent
- PK analyses address drug metabolism in children, particularly in younger patients including infants
- Functional imaging can provide non-invasive biomarkers
- Biomarkers that guide treatment decisions need to be thoroughly validated

BSA: body surface area; DLT: dose-limiting toxicity; PD, pharmacodynamic; PK, pharmacokinetic; RP2D: recommended phase II dose

point as in adults), one of the objectives of the study is to demonstrate that the drug has similar toxicity, PK, and PD profiles in children, adolescents and adults and hence, a dose-confirmation — and not a dose-escalation — study is required. PK modelling is a useful tool to improve and reduce the required cohort size.

Finally, a malignancy common in adults might be rare in children and adolescents, but the drug developed to treat that condition might be relevant for other paediatric

cancers. An MoA-based drug-development approach focusing on targets present in different diseases frequent in children and not on single diseases in isolation — for example, dabrafenib in high-grade and low-grade gliomas harbouring *BRAF*^{V600E}, and Langerhans cell histiocytosis — would overcome these challenges[39].

Late toxicities

Concerns about late toxicities in children, affecting areas such as growth, development, or neurocognition, which cannot be appropriately addressed in first-in-child studies, might arise with new MTAs; however, toxicity data beyond the first cycle and in surviving patients should be collected. In situations with specific concerns, appropriate monitoring (for example, bone age, growth plate or dental studies) should be implemented. For instance, several antiangiogenic agents have been evaluated in children, but only two agents (sunitinib and pazopanib) have been associated with alterations of the growth plate that were observed during a phase I trial[97]. As a result, increased monitoring of bone and musculoskeletal growth has been incorporated into ongoing phase II trials for bevacizumab and pazopanib[98,99]. The real long-term effects of these changes, however, will only be evaluated when these agents have been investigated in frontline studies and in larger populations — including long-term survivors. Another example is that of the Sonic hedgehog inhibitors vismodegib and sonidegib, which were shown to cause irreversible closure of growth plates in animal models[100]. These results, however, were not confirmed in first-in-child trials[101,102], and data from phase II trials are awaited[103]. Finally, long-term growth delay has been reported after the chronic use of the TKI imatinib[104]. Such toxicities can only be identified after long-term surveillance (and possibly prolonged use) of the drugs and, therefore, will not be easily identified during early clinical trials but rather, in late-phase trials or during the post-marketing authorisation phase. Early phase clinical trial designs must take into account the anticipated life-expectancy of patients and consider the balance between incorporating rigorous assessments to detect emerging toxicities and being too burdensome for study participants.

The long-term tolerance of new drugs is of even greater importance for children in whom cancer becomes a chronic disease (CML is the prime example). Growth retardation has been reported with some BCR–ABL1 TKIs; this observation could influence the choice of a particular drug within the same class of inhibitors[105]. Similarly, long-term sequelae from the use of new drugs are of great relevance for malignancies with a good prognosis (for example, BRAF or MEK inhibitors for low-grade gliomas), for which efficient second-line chemotherapy regimens are available but are associated with known late effects; new drugs are needed for patients with these malignancies. Collaboration with survivorship programmes, such as Pan Care (Pan-European Network for the Care of Survivors after Childhood and Adolescent Cancer), is recommended[106]. The Paediatric Oncology Platform–ACCELERATE[13], is implementing long-term follow-up measures for children and adolescents receiving new anticancer drugs. In this platform, a system for the long-term monitoring of the low number of survivors of paediatric early phase clinical trials has been proposed. This initiative requires coordination between academia and the pharmaceutical industry, and compliance with drug regulations.

Conclusions

In the past 15 years, the landscape of drug development for children with cancer has changed remarkably. The methodology used in drug development must be adapted to this new landscape, providing more-efficient results and answers to ethical aspects[107]. MTAs and immunotherapeutic agents require a new paradigm of drug development based on MoA and tumour biology[25]. In parallel with adopting this approach for the selection of new agents, early phase clinical trials must include dose-confirmation studies at the BSA-adjusted RP2D for adults, and expansion cohorts that integrate evaluation of the response rate with biomarker-defined end points to address biological hypotheses. In many situations, the aim of a study is the validation of the dose determined for adults for use in a paediatric population and thus, extrapolation of data from adult studies should be undertaken when feasible. When a drug has specific, serious, dose-related toxicities or a narrow therapeutic index, dose-escalation studies should start at 80% of the RP2D for adults, and trial efficiency should be increased by using new dose-escalation models, such as CRM or BLRM. The addition of expansion cohorts can provide preliminary evaluation of therapeutic activity, enabling the selection of drugs for further randomized multi-arm or umbrella studies. These approaches would enable drugs to transition from first-in-child to frontline-therapy trials in only three steps. Importantly, therapeutic intent is central to the design of early phase studies in children; safety and therapeutic activity remain as key objectives, whereas the duration of the trial is minimized. The probability of overdosing or underdosing will be reduced when the probability of patients receiving optimum therapeutic doses is increased. This approach is ethically desirable for the evaluation in children of drugs for which an active dose has already been established in adults, and is being applied in ESMART.

Some anticancer agents developed to treat adults in the past few years cannot be used to treat cancers in children because the genetic and epigenetic repertoire of driver mutations of childhood malignancies differs from that of malignancies common in adults. Indeed, a limited number of available anticancer drugs target the oncogenic drivers of paediatric cancers; therefore, another key challenge of precision medicine in paediatric oncology is the development of drugs that target such driver mutations. An MoA model of drug development alongside innovative and rationally designed early phase studies will radically accelerate the development of anticancer drugs for children and adolescents.

Lucas Moreno is at the Paediatric Phase I-II Clinical Trials Unit, Paediatric Haematology & Oncology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain.

Andrew D. J. Pearson was at the Paediatric Drug Development, Children and Young People's Unit, The Royal Marsden NHS Foundation Trust, Sutton, UK; and at the Division of Clinical Studies and Cancer Therapeutics, The Institute of Cancer Research, Sutton, UK.

Xavier Paoletti is at the Biostatistics and Epidemiology, INSERM U1018, Gustave Roussy, Paris, France.

Irene Jimenez and Francois Doz are at the Department of Paediatric, Adolescents and Young Adults Oncology, Institut Curie; and at the University Paris Descartes, Paris, France.

Birgit Geoerger is at the Department of Paediatric and Adolescent Oncology, CNRS UMR 8203 Vectorology and Anticancer Treatments, Gustave Roussy, University Paris-Sud, Villejuif, France.

Pamela R. Kearns is at the Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK.

C. Michel Zwaan is at the Department of Paediatric Oncology/Haematology, Erasmus MC/Sophia Children's Hospital, Rotterdam, Netherlands.

Andre Baruchel is at the Department of Paediatric Haematology, Hôpital Robert Debré, AP-HP; and at the University Paris Diderot, Paris, France.

Josef Vormoor is at the Wolfson Childhood Cancer Research Centre, Northern Institute for Cancer Research, Newcastle University; and at the Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK.

Michela Casanova is at the Paediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

Stefan M. Pfister is at the German Cancer Research Center (DKFZ); German Cancer Consortium (DKTK); and at the Heidelberg University Hospital, Heidelberg, Germany.

Bruce Morland is at the Department of Paediatric Oncology, Birmingham Children's Hospital, Birmingham, UK.

Gilles Vassal is at the Department of Clinical Research, Gustave Roussy, Paris-Sud University, Paris, France.

**These authors contributed equally to this work.*

‡Retired.

Correspondence to A.D.J.P.
andy1pearson@btinternet.com

doi:10.1038/nrclinonc.2017.59
Published online 16 May 2017

1. Pritchard-Jones, K. & Sullivan, R. Children with cancer: driving the global agenda. *Lancet Oncol.* **14**, 189–191 (2013).
2. Skinner, R., Wallace, W. H. B., Levitt, G. A. & UK Children's Cancer Study Group (UKCCSG) Late Effects Group (LEG). Long-term follow-up of people who have survived cancer during childhood. *Lancet Oncol.* **7**, 489–498 (2006).
3. Di Martino, S. *et al.* Overview of FDA-approved anti cancer drugs used for targeted therapy. *World Cancer Res. J.* **2**, e553 (2015).
4. Hanahan, D. & Weinberg, R. A. Hallmarks of cancer: the next generation. *Cell* **144**, 646–674 (2011).
5. Smith, M. *et al.* Conduct of phase I trials in children with cancer. *J. Clin. Oncol.* **16**, 966–978 (1998).
6. Zwaan, C. M. *et al.* The role of the 'innovative therapies for children with cancer' (ITCC) European consortium. *Cancer Treat. Rev.* **36**, 328–334 (2010).
7. Pharmaceutical Research and Manufacturers of America. List of 2015 medicines in development for cancer 2015. *PhRMA* http://phrma-docs.phrma.org/sites/default/files/pdf/2014-cancer-report.pdf (2014).
8. Vassal, G., Geoerger, B. & Morland, B. Is the European pediatric medicine regulation working for children and adolescents with cancer? *Clin. Cancer Res.***19**, 1315–1325 (2013).
9. National Cancer Institute. Targeted cancer therapies. *Cancer* https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet (2017).
10. Postel-Vinay, S. *et al.* Clinical benefit in Phase-I trials of novel molecularly targeted agents: does dose matter? *Br. J. Cancer* **100,** 1373–1378 (2009).
11. Gupta, S. *et al.* Meta-analysis of the relationship between dose and benefit in phase I targeted agent trials. *J. Natl Cancer Inst.* **104,**1860–1866 (2012).
12. Moreno Garcîa, V. *et al.* Dose-response relationship in phase I clinical trials: a European Drug Development Network (EDDN) Collaboration Study. *Clin. Cancer Res.* **20,** 5663–5671 (2014).
13. Vassal, G. *et al.* Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer. *Eur. J. Cancer* **51**, 218–224 (2015).
14. Vassal, G. *et al.* New drugs for children and adolescents with cancer: the need for novel development pathways. *Lancet Oncol.* **14**, e117–e124 (2013).
15. Vassal, G. Will children with cancer benefit from the new European Paediatric Medicines Regulation? *Eur. J. Cancer* **45**, 1535–1546 (2009).
16. Rocchi, F. *et al.* The European paediatric legislation: benefits and perspectives. *Ital. J. Pediatr.* **36**, 56 (2010).
17. Vassal, G., Blanc, P. & Pearson, A. Need for change in implementation of paediatric regulation. *Lancet Oncol.* **14**, 1156–1157 (2013).
18. *Regulation (EC) No 1901/2006 of the European Parliament and of the council of 12 December 2006.* http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf (2006).
19. Committee on Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), Board on Health Sciences Policy & Institute of Medicine. *Safe and Effective Medicines for Children: Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act* (eds Field, M. J. & Boat, T. F.) (National Academies Press, 2012).
20. Food and Drug Administration. Pediatric Research Equity Act of 2003. *FDA* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077853.pdf (2003).
21. Yu, A. L. *et al.* Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N. Engl. J. Med.* **363**, 1324–1334 (2010).
22. Le Tourneau, C., Gan, H. K., Razak, A. R. & Paoletti, X. Efficiency of new dose escalation designs in dose-finding phase I trials of molecularly targeted agents. *PLoS ONE* **7**, e51039 (2012).
23. Skolnik, J. M., Barrett, J. S., Jayaraman, B., Patel, D. & Adamson, P. C. Shortening the timeline of pediatric phase I trials: the rolling six design. *J. Clin. Oncol.* **26**, 190–195 (2008).
24. Paoletti, X. *et al.* A comparative analysis of paediatric dose-finding trials of molecularly targeted agent with adults' trials. *Eur. J. Cancer* **49**, 2392–2402 (2013).
25. Pearson, A. D. *et al.* Implementation of mechanism of action biology-driven early drug development for children with cancer. *Eur. J. Cancer* **62**, 124–131 (2016).
26. Le Tourneau, C., Diera, V., Tresca, P., Cacheux, W. & Paoletti, X. Current challenges for the early clinical development of anticancer drugs in the era of molecularly targeted agents. *Target. Oncol.* **5**, 65–72 (2010).
27. Lee, D. P. *et al.* Pediatric phase I trials in oncology: an analysis of study conduct efficiency. *J. Clin. Oncol.* **23**, 8431–8441 (2005).
28. DuBois, S. G. *et al.* Phase I and pharmacokinetic study of sunitinib in pediatric patients with refractory solid tumors: a Children's Oncology Group study. *Clin. Cancer Res.* **17**, 5113–5122 (2011).
29. Chu, T. F. *et al.* Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet* **370**, 2011–2019 (2007).
30. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* **310**, 2191–2194 (2013).
31. Norris, R. E. & Adamson, P. C. Challenges and opportunities in childhood cancer drug development. *Nat. Rev. Cancer* **12**, 776–782 (2012).
32. Carceller, F. *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 (ITCC) study. *Eur. J. Cancer* **67**, 130–140 (2016).
33. Zwaan, C. M. *et al.* Dasatinib in children and adolescents with relapsed or refractory leukemia: results of the CA180-018 phase I dose-escalation study of the Innovative Therapies for Children with Cancer Consortium. *J. Clin. Oncol.* **31**, 2460–2468 (2013).
34. European Medicines Agency. Reflection paper on extrapolation of efficacy and safety in paediatric medicine development. *EMA* http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/04/WC500204187.pdf (2016).
35. Locatelli, F. *et al.* Phase 1/2 study in pediatric patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia receiving blinatumomab treatment. *Blood* **124**, 2292 (2014).
36. Wayne, A. S. *et al.* Pediatric phase 1 trial of moxetumomab pasudotox: activity in chemotherapy refractory acute lymphoblastic leukemia (ALL) [abstract]. *Cancer Res.* **74** (19 Suppl.), CT230 (2014).
37. Geoerger, B. *et al.* Innovative therapies for children with cancer pediatric phase I study of erlotinib in brainstem glioma and relapsing/refractory brain tumors. *Neuro Oncol.* **13**, 109–118 (2011).
38. Muller, P. Y. & Milton, M. N. The determination and interpretation of the therapeutic index in drug development. *Nat. Rev. Drug Discov.* **11**, 751–761 (2012).
39. Kieran, M. W. *et al.* Phase 1 study of dabrafenib in pediatric patients with relapsed or refractory BRAF V600E high- and low-grade gliomas, Langerhans cell histiocytosis, and other solid tumors [abstract]. *J. Clin. Oncol.* **33** (Suppl.), 10004 (2015).
40. Bland, M. Detecting a single event. *University of York* https://www-users.york.ac.uk/~mb55/bsi_study/single_event.pdf (2013).
41. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01077544 (2015).
42. Neville, K. *et al.* Phase I/II study of brentuximab vedotin in pediatric patients with relapsed or refractory Hodgkin lymphoma or systemic anaplastic large-cell lymphoma: interim phase I safety data [abstract]. *J. Clin. Oncol.* **31** (Suppl.), 10028 (2013).
43. Locatelli, F. *et al.* Phase 1/2 study of brentuximab vedotin in pediatric patients with relapsed or refractory Hodgkin lymphoma or systemic anaplastic large-cell lymphoma: preliminary phase 2 data for brentuximab vedotin 1.8 mg/kg in the Hodgkin lymphoma study arm. *Blood* **122**, 4378 (2013).
44. Olmos, D. *et al.* Safety, pharmacokinetics, and preliminary activity of the anti-IGF-1R antibody figitumumab (CP-751, 871) in patients with sarcoma and Ewing's sarcoma: a phase 1 expansion cohort study. *Lancet Oncol.* **11**, 129–135 (2010).
45. Juergens, H. *et al.* Preliminary efficacy of the anti-insulin-like growth factor type 1 receptor antibody figitumumab in patients with refractory Ewing sarcoma. *J. Clin. Oncol.* **29**, 4534–4540 (2011).
46. Malempati, S. *et al.* Phase I/II trial and pharmacokinetic study of cixutumumab in pediatric patients with refractory solid tumors and Ewing sarcoma: a report from the Children's Oncology Group. *J. Clin. Oncol.* **30**, 256–262 (2012).
47. Pappo, A. S. *et al.* R1507, a monoclonal antibody to the insulin-like growth factor 1 receptor, in patients with recurrent or refractory Ewing sarcoma family of tumors: results of a phase II Sarcoma Alliance for Research through Collaboration study. *J. Clin. Oncol.* **29**, 4541–4547 (2011).
48. Frappaz, D. *et al.* Phase I study of dalotuzumab monotherapy and combination therapy ridaforolimus-dalotuzumab in pediatric patients with advanced solid tumors. *Eur. J. Cancer* **62**, 9–17 (2016).
49. Neuenschwander, B., Branson, M. & Gsponer, T. Critical aspects of the Bayesian approach to phase I cancer trials. *Stat. Med.* **15**, 2420–2439 (2008).
50. O'Quigley, J., Pepe, M. & Fisher, L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics* **46**, 33–48 (1990).
51. Onar-Thomas, A. & Xiong, Z. A simulation-based comparison of the traditional method, rolling-6 design and a frequentist version of the continual reassessment method with special attention to trial duration in pediatric phase I oncology trials. *Contemp. Clin. Trials* **31**, 259–270 (2010).
52. Zhao, L., Lee, J., Mody, R. & Braun, T. M. The superiority of the time-to-event continual reassessment method to the rolling six design in pediatric oncology phase I trials. *Clin. Trials* **8**, 361–369 (2011).
53. Doussau, A. *et al.* Dose-finding designs in pediatric phase I clinical trials: comparison by simulations in a realistic timeline framework. *Control. Clin. Trials* **33**, 657–665 (2012).
54. Doussau, A., Geoerger, B., Jiménez, I. & Paoletti, X. Innovations for phase I dose-finding designs in pediatric oncology clinical trials. *Contemp. Clin. Trials.* **47**, 217–227 (2016).
55. Simon, R. *et al.* Accelerated titration designs for phase I clinical trials in oncology. *J. Natl Cancer Inst.* **89**, 1138–1147 (1997).
56. Manji, A. *et al.* Evolution of clinical trial design in early drug development: systematic review of expansion cohort use in single-agent phase I cancer trials. *J. Clin. Oncol.* **31**, 4260–4267 (2013).
57. Ensign, L. G., Gehan, E. A., Kamen, D. S. & Thall, P. F. An optimal three-stage design for phase II clinical trials. *Stat. Med.* **13**, 1727 (1994).
58. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02813135 (2016).
59. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02432274 (2017).
60. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02124772 (2017).
61. Moroz, V., Wilson, J. S., Kearns, P. & Wheatley, K. Comparison of anticipated and actual control group outcomes in randomised trials in paediatric oncology provides evidence that historically controlled studies are biased in favour of the novel treatment. *Trials* **15**, 481 (2014).

62. Saad, E. D., Paoletti, X., Burzykowski, T. & Buyse, M. Precision medicine needs randomized clinical trials. *Nat. Rev. Clin. Oncol.* http://dx.doi.org/10.1038/nrclinonc.2017.8 (2017).
63. Billingham, L., Malottki, K. & Steven, N. Research methods to change clinical practice for patients with rare cancers. *Lancet Oncol.* **17**, e70–e80 (2016).
64. Jung, S. H. Randomized phase II trials with a prospective control. *Stat. Med.* **27**, 568–583 (2008).
65. Jakacki, R. *et al.* Single-agent erlotinib versus oral etoposide in patients with recurrent or refractory pediatric ependymoma: a randomized open-label study. *J. Neurooncol.* **129**, 131–138 (2016).
66. Mody, R. *et al.* Phase II randomized trial of irinotecan/temozolomide (I/T) with temsirolimus (TEM) or dinutuximab plus granulocyte colony stimulating factor (DIN/GMCSF) in children with refractory or relapsed neuroblastoma: a report from the Children's Oncology Group (COG) [abstract]. *J. Clin. Oncol.* **34** (Suppl.), 10502 (2016).
67. Moreno, L. *et al.* A randomised phase IIb trial of bevacizumab added to temozolomide ± irinotecan for children with refractory/relapsed neuroblastoma — BEACON-Neuroblastoma, a European Innovative Therapies for Children with Cancer (ITCC) — International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) trial [abstract]. *J. Clin. Oncol.* **33** (Suppl.), TPS10082 (2015).
68. Corbacioglu, S. *et al.* The RIST design: a molecularly targeted multimodal approach for the treatment of patients with relapsed and refractory neuroblastoma [abstract]. *J. Clin. Oncol.* **31** (Suppl.), 10017 (2013).
69. Kager, L. *et al.* The ENCCA-WP7/EuroSarc/EEC/PROVABES/EURAMOS 3rd European Bone Sarcoma Networking Meeting/Joint Workshop of EU Bone Sarcoma Translational Research Networks; Vienna, Austria, September 24–25, 2015. Workshop Report. *Clin. Sarcoma Res.* **6**, 3 (2016).
70. Malempati, S. *et al.* Early results from Children's Oncology Group (COG) ARST08P1: pilot studies of cixutumumab or temozolomide with intensive multiagent chemotherapy for patients with metastatic rhabdomyosarcoma [abstract]. *J. Clin. Oncol.* **33** (Suppl.), 10015 (2015).
71. Yap, T. A., Sandhu, S. K., Workman, P. & de Bono, J. S. Envisioning the future of early anticancer drug development. *Nat. Rev. Cancer* **10**, 514–523 (2010).
72. Biomarkers Definition Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin. Pharmacol. Ther.* **69**, 89–95 (2001).
73. Fouladi, M. *et al.* A phase I trial of MK-2206 in children with refractory malignancies: a Children's Oncology Group study. *Pediatr. Blood Cancer* **61**, 1246–1251 (2014).
74. Moreno, L. *et al.* Phase I trial of AT9283 (a selective inhibitor of aurora kinases) in children and adolescents with solid tumors: a Cancer Research UK study. *Clin. Cancer Res.* **21**, 267–273 (2015).
75. Smith, J. R. *et al.* Novel pharmacodynamic biomarkers for MYCN protein and PI3K/AKT/mTOR pathway signaling in children with neuroblastoma. *Mol. Oncol.* **10**, 538–552 (2016).
76. Siravegna, G., Marsoni, S., Siena, S. & Bardelli, A. Integrating liquid biopsies intro the management of cancer. *Nat. Rev. Clin. Oncol.* http://dx.doi.org/10.1038/nrclinonc.2017.14 (2017).
77. Glade Bender, J. L. *et al.* Phase I pharmacokinetic and pharmacodynamic study of pazopanib in children with soft tissue sarcoma and other refractory solid tumors: a Children's Oncology Group Phase I Consortium report. *J. Clin. Oncol.* **31**, 3034–3043 (2013).
78. Sedlacik, J. *et al.* MR imaging assessment of tumor perfusion and 3D segmented volume at baseline, during treatment, and at tumor progression in children with newly diagnosed diffuse intrinsic pontine glioma. *AJNR Am. J. Neuroradiol.* **34**, 1450–1455 (2013).
79. Schleiermacher, G. *et al.* Emergence of new ALK mutations at relapse of neuroblastoma. *J. Clin. Oncol.* **32**, 2727–2734 (2014).
80. Hill, R. M. *et al.* Combined MYC and P53 defects emerge at medulloblastoma relapse and define rapidly progressive, therapeutically targetable disease. *Cancer Cell* **27**, 72–84 (2015).
81. Carr-Wilkinson, J. *et al.* High frequency of p53/MDM2/p14ARF pathway abnormalities in relapsed neuroblastoma. *Clin. Cancer Res.* **16**, 1108–1118 (2010).
82. Chicard, M. *et al.* Genomic copy number profiling using circulating free tumor DNA highlights heterogeneity in neuroblastoma. *Clin. Cancer Res.* **22**, 5564–5573 (2016).
83. Combaret, V. *et al.* Detection of tumor ALK status in neuroblastoma patients using peripheral blood. *Cancer Med.* **4**, 540–550 (2015).
84. Geoerger, B. *et al.* Molecular screening for cancer treatment optimization (MOSCATO 01) in pediatric patients: first feasibility results of a prospective molecular stratification trial [abstract]. *J. Clin. Oncol.* **32** (Suppl.), 10500 (2014).
85. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02613962 (2017).
86. Worst, B. C. *et al.* Next-generation personalised medicine for high-risk paediatric cancer patients — the INFORM pilot study. *Eur. J. Cancer* **65**, 91–101 (2016).
87. Netherlands Trial Register. Towards individualized therapy for patients with pediatric tumors. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5915 (2016).
88. National Cancer Institute. NCI-MATCH trial (molecular analysis for therapy choice). *Cancer* https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match (2017).
89. Harris, M. H. *et al.* Multicenter feasibility study of tumor molecular profiling to inform therapeutic decisions in advanced pediatric solid tumors: the Individualized Cancer Therapy (iCat) study. *JAMA Oncol.* **2**, 608–615 (2016).
90. Kearns, G. L. *et al.* Developmental pharmacology — drug disposition, action, and therapy in infants and children. *N. Engl. J. Med.* **349**, 1157–1167 (2003).
91. Veal, G. J. *et al.* Adaptive dosing of anticancer drugs in neonates: facilitating evidence-based dosing regimens. *Cancer Chemother. Pharmacol.* **77**, 685–692 (2016).
92. Food and Drug Administration, HHS. International Conference on Harmonisation; guidance on E11 clinical investigation of medicinal products in the pediatric population; availability. Notice. *Fed. Regist.* **65**, 78493–78494 (2000).
93. Momper, J. D. *et al.* Adolescent dosing and labeling since the Food and Drug Administration Amendments Act of 2007. *JAMA Pediatr.* **167**, 926–932 (2013).
94. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01353625 (2016).
95. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02304458 (2017).
96. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01524926 (2016).
97. Voss, S. D. *et al.* Growth plate abnormalities in pediatric cancer patients undergoing phase 1 anti-angiogenic therapy: a report from the Children's Oncology Group Phase I Consortium. *Pediatr. Blood Cancer* **62**, 45–51 (2015).
98. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01390948 (2016).
99. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01956669 (2017).
100. Kimura, H., Ng, J. M. & Curran, T. Transient inhibition of the Hedgehog pathway in young mice causes permanent defects in bone structure. *Cancer Cell* **13**, 249–260 (2008).
101. Geoerger, B. *et al.* A phase I/II study of LDE225, a smoothened antagonist, in pediatric patients with recurrent medulloblastoma or other solid tumors [abstract]. *J. Clin. Oncol.* **30** (Suppl.), 9519 (2012).
102. Gajjar, A. *et al.* Phase I study of vismodegib in children with recurrent or refractory medulloblastoma: a Pediatric Brain Tumor Consortium study. *Clin. Cancer Res.* **19**, 6305–6312 (2013).
103. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01125800 (2017).
104. Goteke, V. K. R. *et al.* An anthropometric study in children with chronic myeloid leukemia on imatinib [abstract]. *J. Clin. Oncol.* **30** (Suppl.), 6554 (2012).
105. Shima, H. *et al.* Distinct impact of imatinib on growth at prepubertal and pubertal ages of children with chronic myeloid leukemia. *J. Pediatr.* **159**, 676–681 (2011).
106. PanCare. Pan-European network for care of survivors after childhood and adolescent cancer. *PanCare* http://www.pancare.eu (2017).
107. Dupont, J. C., Pritchard-Jones, K. & Doz, F. Ethical issues of clinical trials in paediatric oncology from 2003 to 2013: a systematic review. *Lancet Oncol.* **17**, e187–e197 (2016).
108. Vogelstein, B., Papadopoulos, N., Velculescu, V.E., Zhou, S., Diaz, L.A.Jr & Kinzler, K.W. Cancer genome landscapes. *Science* **339,** 1546–1558 (2013).
109. Trippett, T. M. *et al.* Phase I and pharmacokinetic study of cetuximab and irinotecan in children with refractory solid tumors: a study of the Pediatric Oncology Experimental Therapeutic Investigators' Consortium. *J. Clin. Oncol.* **27**, 5102–5108 (2009).
110. Glade Bender, J. L. *et al.* Phase I trial and pharmacokinetic study of bevacizumab in pediatric patients with refractory solid tumors: a Children's Oncology Group study. *J. Clin. Oncol.* **26**, 399–405 (2008).
111. Daw, N. C. *et al.* Phase I and pharmacokinetic study of gefitinib in children with refractory solid tumors: a Children's Oncology Group study. *J. Clin. Oncol.* **23**, 6172–6180 (2005).

Acknowledgements
L.M. has received funding support from the Oak Foundation. The work of A.D.J.P. has been funded through a Cancer Research UK Life Chair and Programme Grant included within a Cancer Research UK ICR Core Award (C347/A15403), and is supported by the NIHR RM/ICR Biomedical Research Centre. C.M.Z. receives support from a KiKa-foundation (project 113) grant. We thank M. White (freelance editor and medical writer) for editorial support in the preparation of this article and G. Cook for administrative assistance. Editorial support costs have been funded by institutional funds from CNIO–HNJ Clinical Research Unit at Hospital Niño Jesus

Author contributions
All authors discussed the content, researched data for the article, reviewed and edited the manuscript before submission. L. M., A.D.J.P, X.P, B.G., and G.V. wrote the manuscript.

Competing interests statement
The authors declare no competing interests.

Publisher's note
SpringerNature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

SUPPLEMENTARY INFORMATION
See online article: S1 (table) | S2 (table)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF