

# Predictors of Success of Phase II Pediatric Oncology Clinical Trials

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Disclosures of potential conflicts of interest may be found at the end of this article.

**Key Words.** Phase II • Pediatric • Oncology • Success • Predictors

## ABSTRACT

**Background.** There are limited data to predict which novel childhood cancer therapies are likely to be successful. To help rectify this, we sought to identify the factors that impact the success of phase II clinical trials for pediatric malignancies.

**Materials and Methods.** We examined the impact of 24 preclinical and trial design variables for their influence on 132 phase II pediatric oncology clinical trials. Success was determined by an objective assessment of patient response, with data analyzed using Fisher's exact test, Pearson's chi-square test, and logistic regression models.

**Results.** Trials that evaluated patients with a single histological cancer type were more successful than those that assessed multiple different cancer types (68% vs. 47%, 27%, and 17% for 1, 2–3, 4–7, and 8+;  $p < .005$ ). Trials on liquid or extra-cranial solid tumors were more successful than central nervous system or combined trials (70%, 60%, 38%, and 24%;  $p < .005$ ), and trials of combination therapies were more

successful than single agents (71% vs. 28%;  $p < .005$ ). Trials that added therapies to standard treatment backbones were more successful than trials testing novel therapies alone or those that incorporated novel agents ( $p < .005$ ), and trials initiated based on the results of adult studies were less likely to succeed ( $p < .05$ ). For 61% of trials (80/132), we were unable to locate any relevant preclinical findings to support the trial. When preclinical studies were carried out (52/132), there was no evidence that the conduct of any preclinical experiments made the trial more likely to succeed ( $p < .005$ ).

**Conclusion.** Phase II pediatric oncology clinical trials that examine a single cancer type and use combination therapies have the highest possibility of clinical success. Trials building upon a standard treatment regimen were also more successful. The conduct of preclinical experiments did not improve clinical success, emphasizing the need for a better understanding of the translational relevance of current preclinical testing paradigms. *The Oncologist* 2019;24:e765–e774

**Implications for Practice:** To improve the clinical outcomes of phase II childhood cancer trials, this study identified factors impacting clinical success. These results have the potential to impact not only the design of future clinical trials but also the assessment of preclinical studies moving forward. This work found that trials on one histological cancer type and trials testing combination therapies had the highest possibility of success. Incorporation of novel therapies into standard treatment backbones led to higher success rates than testing novel therapies alone. This study found that most trials had no preclinical evidence to support initiation, and even when preclinical studies were available, they did not result in improved success.

## INTRODUCTION

The survival rates for childhood cancer have improved dramatically over the last 50 years, with approximately 80% of children now cured with standard therapy [1]. There has, however, been a recent plateau in the rate of increase in cure rates. This has occurred at the same time hundreds of novel anticancer compounds have been developed. The relative

rarity of childhood cancer, and high cure rates, mean only a limited number of these novel therapies can be effectively tested in patients with relapsed or refractory disease [2]. Unfortunately, the majority of these novel therapeutic strategies fail in early-phase trials and do not get incorporated into standard treatment protocols [3, 4]. Although every clinical

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trial increases the knowledge base, it is important to develop strategies to help maximize the success rate of future studies.

The ultimate goal of cancer research is the successful translation of preclinical findings into clinical applications [4]. However, anecdotally, there are conflicting data on the utility of preclinical studies to predict clinical success [5]. One of the earliest and most active therapies for pediatric leukemia, VAMP (vincristine, amethopterin, mercaptopurine, and prednisone), was not shown to be effective in *in vivo* models [6]. Despite this, the first 13 patients with leukemia treated with VAMP rapidly entered complete remission [7]. The VAMP protocol has since been successfully applied to other pediatric cancers with the same significant improvements in survival seen [7–9]. Conversely, cytarabine was shown to inhibit the therapeutic target in Ewing's sarcoma, with compelling preclinical activity both *in vitro* and *in vivo* [10], yet no activity was observed in a subsequent phase II trial [11]. Despite the specificity of cytarabine toward EWS-FLI1 [10], subsequent preclinical studies in an extended *in vivo* panel inferred a lack of activity in this cancer type [12]. Although it has been suggested that more rigorous preclinical testing may have predicted this clinical outcome prior to trial initiation [11], there are no objective data to help guide preclinical researchers and trialists as to how much preclinical evidence is needed before a trial should be initiated, which preclinical studies best predict clinical success, or the translational relevance of current preclinical testing paradigms [5, 13, 14].

Similarly, there may be clinical factors that predict which trial may be successful. Phase I response rates have recently been found to significantly correlate with subsequent phase II response [15]. However, it is unknown whether a trial supported by prior adult or pediatric early-phase studies will have a higher possibility of attaining clinical success compared with trials supported by preclinical research. Likewise, there is little understanding of the influence of trial design variables including single agents versus combination therapies, the number of cancer types included, or the type of cancer assessed [16].

Given the limitations in our understanding of how preclinical research and trial design influences trial success, we assessed potential factors that may predict the success of phase II pediatric oncology clinical trials. We systematically identified published phase II pediatric oncology clinical trials, sought and analyzed the preclinical data supporting each trial, and assessed each trial to measure the impact of 24 preclinical research and trial design parameters on success.

## MATERIALS AND METHODS

### Study Design

We conducted database searches of PubMed and Google Scholar using the search terms “Phase 2,” “cancer,” “pediatric,” “tumor,” and “clinical trial” and their spelling variants for phase II pediatric oncology clinical trials. Manuscripts meeting the inclusion criteria were reviewed in full ( $n = 169$ ). Thirty-seven trials were excluded because of insufficient information provided to allow an objective assessment of response rates, or because the trial assessed the activity of a chemo-protectant rather than antitumor activity.

### Variable Assessment

For each trial that met the inclusion criteria ( $n = 132$ ), we assessed 24 preclinical and trial design variables for their impact on trial success (supplemental online Table 1).

To identify relevant preclinical studies, we obtained all references to preclinical findings within each phase II manuscript. We also conducted PubMed and Google Scholar searches to identify preclinical, phase I, and clinical manuscripts relevant to each of the 132 trials. To find these manuscripts, we searched for each individual agent and/or combination therapy assessed in the trial against each cancer type enrolled in the trial along with the search terms “*in vitro*” or “*in vivo*” or “Phase 1.” To account for publication delays [17], database searches were carried out until December 31, 2015.

Preclinical data were classified as “relevant” to the clinical trial if the preclinical studies were performed on models representing the same tumor type(s) included in the trial using the same therapeutic drug(s) as the trial. To limit the number of references, we have not cited these publications. Each trial manuscript and all acquired publications were then reviewed and relevant information extracted to answer each variable. Where available, we also reviewed the trial protocol for references, unpublished preclinical data, and trial design parameters.

### Establishing Success

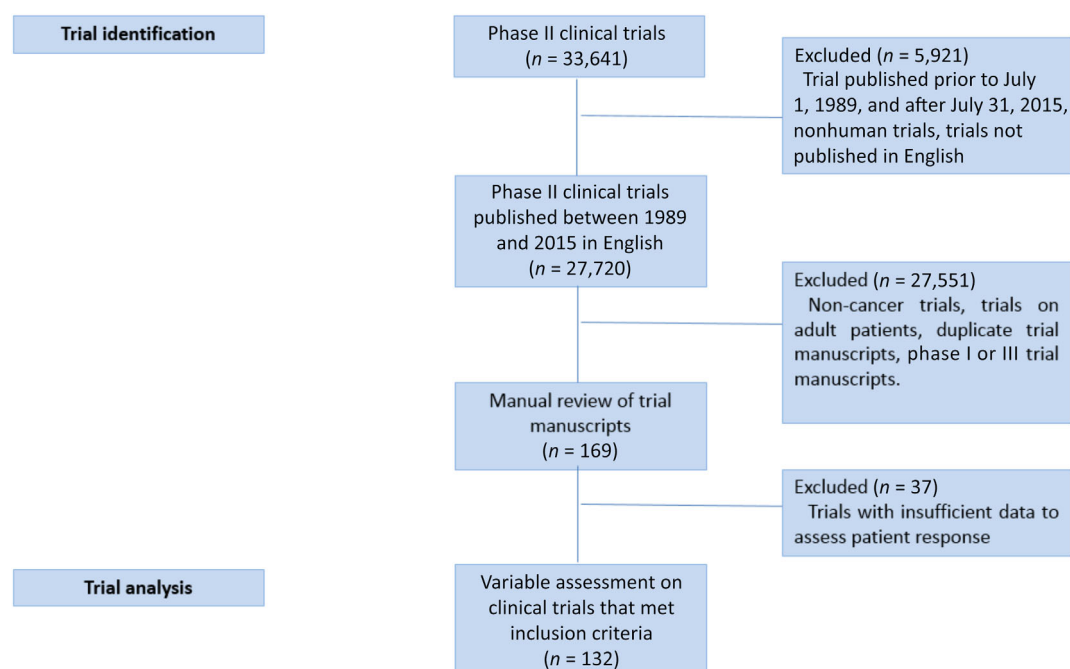
Each trial was then categorized as “successful” or “unsuccessful” based on an independent assessment of response. For extracranial solid and central nervous system (CNS) trials, an overall response rate (complete + partial response)  $\geq 20\%$  was defined as successful, based on the 19.6% response rate observed in Pediatric Oncology Group clinical trials [18]. For liquid tumor trials, a response rate  $\geq 40\%$  was defined as successful, based on the Therapeutic Advances in Childhood Leukemia guidelines reported by Ko et al. [19]. Secondary measures of success included whether the trial investigators (the authors) concluded the trial was successful and whether the phase II results led to the conduct of a phase III trial.

### Statistical Analysis

Upon completion of data collection, each categorical variable was transformed to a numerical format and examined independently to determine its individual influence on successful trial outcome. Statistical analysis was performed using IBM-SPSS Statistics version-22 (IBM, Armonk, NY). Pearson's chi-square and Fisher's exact tests were used to determine the individual association between each variable and successful trial outcome, whereas multivariate logistic regression models were used to determine the grouped influence on trial outcome. All variables with a  $p < .2$  were included in the regression models.  $p$  values and 95% confidence intervals were extracted for each identified predictor.

## RESULTS

Using a search of the keywords, we identified 33,641 manuscripts (Fig. 1). Of these, 5,921 were outside the inclusion timeframe, not performed on humans, or not available in English. We then excluded trials of noncancer diagnoses,



**Figure 1.** Consolidated Standards of Reporting Trials (CONSORT) diagram depicting the process of pediatric oncology trial identification.

trials on adult patients, and manuscripts that discussed the findings of phase I or III results alone. A detailed review of the eligible manuscripts ( $n = 169$ ) led to the exclusion of 37 trials that contained insufficient data for an objective assessment of response rates or that assessed a chemo-protectant.

In total, 132 trials met all criteria for inclusion in this study (supplemental online data). The clinical trial characteristics of each trial are summarized in Table 1. Sixty-nine trials (52%) included patients with a single histological cancer type only, whereas 19 (14%), 26 (20%), and 18 trials (14%) included 2–3, 4–7, and  $\geq 8$  cancer diagnoses, respectively. Patients with liquid tumors were included in 23 trials (17%), extracranial solid tumors in 50 trials (38%), and CNS tumors in 42 trials (32%). Seventeen trials (13%) included patients from at least two of these tumor categories. Sixty-four trials (48%) studied the activity of single agents compared with 68 trials (52%) that examined combination therapies (two or more agents). Anti-tumor activity was demonstrated in a corresponding phase I trial in 71 cases (54%). Seventeen trials tested targeted therapies (13%), and the remainder tested conventional cytotoxic agents. Only three trials (2%) selected patients based on the presence or absence of a biomarker. Ninety-three trials (71%) studied the activity of a novel agent(s), whereas 23 trials (17%) tested a modification of an established standard therapy through the addition of one or more agents. Sixteen trials (12%) examined the activity of an established drug or regimen through a dose or schedule change.

We found 52 trials (39%) that had preclinical research available to support trial initiation. For 36 of these trials, the *in vitro* studies used the same therapy or therapies against one or more of the same target cancer(s) as the phase II trial. In 12 of these cases, the *in vitro* experiments used primary patient-derived samples; the remainder used established tumor cell lines. Of the 36 studies with *in vitro* data, in 35 cases, the treatment regimen was shown to be active against one or more of the tumor type(s) tested in

the phase II trial. In the remaining case, the treatment was inactive *in vitro*. In 12 of the 36 trials (33%), the treatment regimen included in the trial had been tested against cell samples that represented all the tumor types included in the phase II trial.

Relevant *in vivo* studies were identified for 40 trials. In 36 cases, the treatment was shown to have activity *in vivo*. In four cases, the treatment regimen was concluded to be inactive against at minimum one of the same tumor types later assessed in the phase II trial. The types of *in vivo* models used included xenografts in 38 trials (28%) and transgenic models in 2 trials (2%). Subcutaneous xenografts were used for 35 trials (26%) compared with orthotopic models in 3 trials (2%).

### Trial Justification

We examined the reasons stated by the investigators for initiating each of the trials. In total, 90 of the trial manuscripts (67%) referred to preclinical data to support trial initiation. Of these, 47 manuscripts (52%) discussed preclinical data that either used different drugs than those used in the trial or discussed preclinical studies using the same drug(s) but on different tumor types than those included in the trial.

Trial investigators stated that their decision to launch the trial was based on preclinical data (published or unpublished *in-house* testing) in 58 cases (44%) and/or the results of previous pediatric trials and/or the results of previous adult trials. In total, 73 trials (55%) used therapies that had previously been examined in other early-phase pediatric clinical trials (e.g., phase I or smaller phase II trials in subgroups of patients); however, only 49 trials (37%) stated that the trial was initiated based on the conduct of prior pediatric trials. We found that 39 trials (30%) involved therapies previously tested in adult patients with the same cancer type(s); however, only 20 trials (15%) stated that their decision to launch was based on supporting data in an adult population.

**Table 1.** Characteristics of the 132 phase II pediatric oncology trials

Variable	No. of trials	(%)
No. of cancer types included		
1	69	(52)
2–3	19	(14)
4–7	26	(20)
8+	18	(14)
Tumor type		
Liquid	23	(17)
Solid	50	(38)
CNS	42	(32)
Combination	17	(13)
Therapeutic approach		
Single agent	64	(48)
Combination therapy	68	(52)
Were previous trials conducted in a pediatric population?		
Yes	73	(55)
No	59	(45)
Were previous trials conducted in an adult population?		
Yes	39	(30)
No	93	(70)
Targeted therapies		
Targeted therapy	17	(13)
Cytotoxic agent	115	(87)
Patients selected based on the detection of a biomarker		
Yes	3	(2)
No/No biomarker assessed	129	(98)
Demonstration of antitumor activity in phase I trial(s)		
Yes	71	(54)
No	61	(46)
Relevant preclinical research conducted		
Yes	52	(39)
No	80	(61)
Type of preclinical research conducted ( <i>n</i> = 76)		
In vitro	36	(47)
In vivo	40	(53)
In vitro testing ( <i>n</i> = 36)		
Primary patient samples	12	(33)
Cell lines	24	(67)
In vitro antitumor activity ( <i>n</i> = 36)		
Yes	35	(97)
No	1	(3)
In vitro: therapies tested against cell samples representing all the cancers assessed in the trial ( <i>n</i> = 36)		
Yes	12	(33)
No	24	(67)

(continued)

**Table 1.** (continued)

Variable	No. of trials	(%)
In vivo antitumor activity ( <i>n</i> = 40)		
Yes	36	(90)
No	4	(10)
In vivo models ( <i>n</i> = 40)		
Xenograft	38	(95)
Transgenic	2	(5)
Xenograft type ( <i>n</i> = 38)		
Subcutaneous	35	(92)
Orthotopic	3	(8)
Preclinical research supportive of phase II trial initiation		
Yes	47	(36)
No/No preclinical	85	(64)
Was trial initiation based on preclinical research?		
Yes	58	(44)
No	74	(56)
Was trial initiation based on previous adult trials?		
Yes	20	(15)
No	112	(85)
Was trial initiation based on previous pediatric trials?		
Yes	49	(37)
No	83	(63)
Trial sponsor		
Pharmaceutical industry	11	(8)
Clinical trial group	121	(92)
Did the trial build on a standard therapy?		
New drug/New indication	93	(71)
Standard therapy + one or more agents	23	(17)
Old drug/Change of schedule	16	(12)

Abbreviation: CNS, central nervous system.

**Trial Success Rates**

Based on an objective assessment of response rates, 66/132 trials (50%) were classed as successful. Trial investigators were significantly more likely to rate the trial as being successful compared with the independent assessment of response rates (63% vs. 50%;  $p = .037$ ). Conversely, eight trials (6%) appeared successful based on response rate but were deemed unsuccessful by the investigators because of significant toxicities or no observed benefit above standard therapy. Only 8/132 trials (6%) had progressed to phase III studies at the time of analysis, making statistical analysis of this measure not feasible.

**Predictors of Success**

Trials that included patients with a single histological cancer type were significantly more likely to achieve success than trials examining multiple tumor types (Table 2; Fig. 2A). Of the 69 trials that examined patients with a single cancer type, 68% were successful. As the number of cancers included in each trial increased to 2–3, 4–7, and 8+, the success rate

**Table 2.** The influence of clinical trial design characteristics on pediatric oncology clinical trial success rates.

Variable	Successful (n = 66)		Unsuccessful (n = 66)		p value <sup>a</sup>
	No. of trials	(%)	No. of trials	(%)	
No. of cancer types included					9.6 × 10 <sup>-7</sup>
1	47	(68)	22	(32)	
2–3	9	(47)	10	(53)	
4–7	7	(27)	19	(73)	
8+	3	(17)	15	(83)	
Tumor type					3.8 × 10 <sup>-4</sup>
Liquid	16	(70)	7	(30)	
Solid	30	(60)	20	(40)	
CNS	16	(38)	26	(62)	
Combination	4	(24)	13	(76)	
Therapeutic approach					3.9 × 10 <sup>-7</sup>
Single therapy	18	(28)	46	(72)	
Combination therapy	48	(71)	20	(29)	
Were previous trials conducted in a pediatric population?					.29
Yes	40	(55)	33	(45)	
No	26	(44)	33	(56)	
Were previous trials conducted in an adult population?					.036
Yes	14	(36)	25	(64)	
No	52	(56)	41	(44)	
Targeted therapies					.99
Targeted therapy	8	(47)	9	(53)	
Cytotoxic agent	58	(50)	57	(50)	
Patients selected for based on detection of a biomarker					.99
Yes	2	(67)	1	(33)	
No/No biomarker assessed	64	(49)	65	(51)	
Demonstration of antitumor activity in phase I trial(s)					.12
Yes	31	(44)	40	(56)	
No	35	(57)	26	(43)	
Trial sponsor					.53
Pharmaceutical industry	7	(64)	4	(36)	
Clinical trial group	59	(49)	62	(51)	
Did the trial build on a standard therapy?					.012
New drug/New indication	37	(40)	56	(60)	
Standard therapy + one or more agents	19	(83)	4	(17)	
Old drug/Change of schedule	10	(63)	6	(37)	

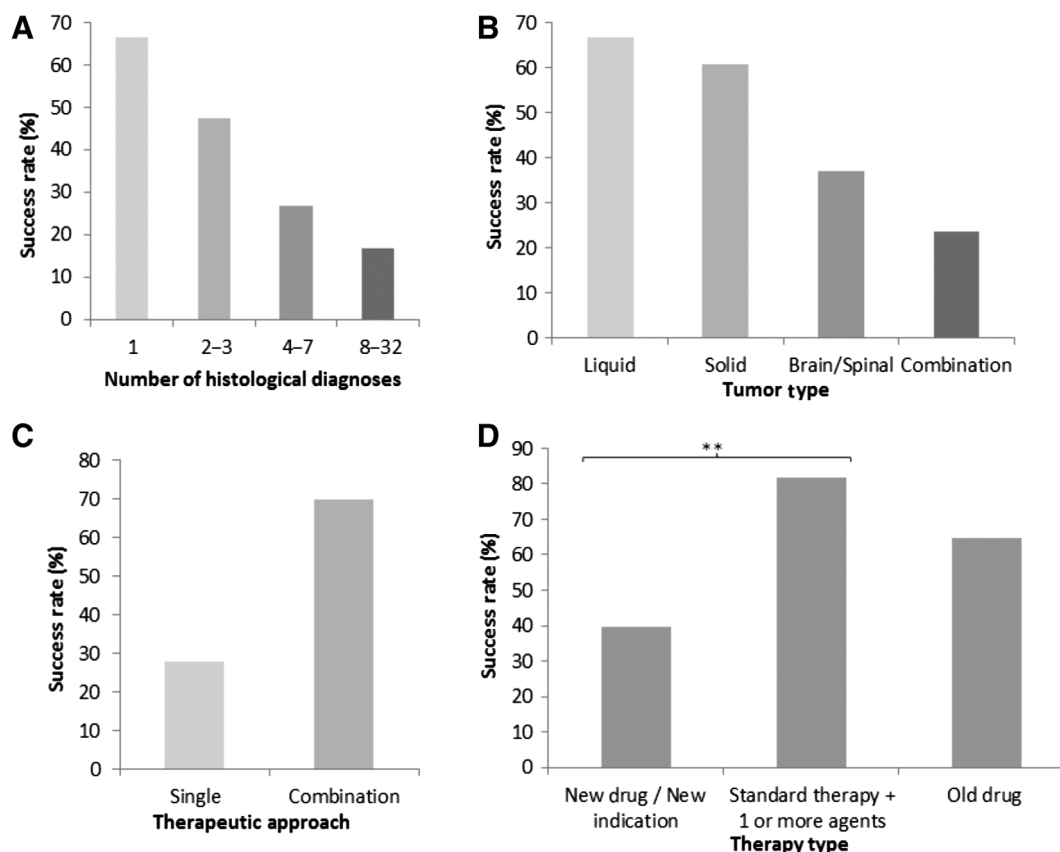
<sup>a</sup>Fisher's exact or Pearson's chi-square tests.

Abbreviation: CNS, central nervous system.

decreased to 47%, 27%, and 17%, respectively ( $p < .0005$ ). The type of cancer assessed also significantly influenced success. Trials in patients with liquid tumors had the highest success rate at 70%, compared with 60%, 38%, and 24% for trials of extracranial solid tumors, CNS tumors, or combined trials ( $p < .0005$ ; Fig. 2B). The type of therapeutic approach used also significantly influenced success rates. The 68 trials that tested combination therapies had a higher likelihood of achieving success (71%) compared with single-agent studies with a success rate of 28% ( $p < .0005$ ; Fig. 2C). For each of these variables, similar results were observed when the investigators' assessment of success was used as the marker of success (supplemental online Table 3).

Trials sponsored by a pharmaceutical company were no more successful than trials sponsored by cooperative groups; however, the investigators on pharmaceutical-sponsored trials were more likely to conclude that the trial was successful (91% vs. 60%;  $p = .05$ ). There was no significant difference in trial success when prior relevant pediatric trials had been conducted (Table 2); however, when prior adult trials had been conducted using the same agent(s) on the same cancer type(s), the pediatric trial was significantly less likely to be successful (36% vs. 56%;  $p = .036$ ).

For 52/132 trials (39%), relevant in vitro and/or in vivo had been conducted, and in 47/52 cases (90%), the preclinical results were positive. However, we found that trials



**Figure 2.** The influence of trial design factors on clinical success. Success rates were assessed according to the number of cancer types included in each trial (**A**;  $p < .0005$ ), the category of tumors assessed in each trial (**B**;  $p < .0005$ ), the therapeutic approach used, that is, single agent versus combination therapy (**C**;  $p < .0005$ ), and the type of therapy used (**D**;  $** = p < .005$ ). Statistical analysis was carried out using Fisher's exact or Pearson's chi-square tests.

with supportive preclinical results were significantly less likely to be successful than those with unsupportive or no preclinical findings ( $p < .001$ ; Table 3). To further understand this finding, we examined multiple preclinical factors but could not identify any preclinical experiments that positively influenced trial success (Table 3). For example, experiments on primary patient-derived cultures were no more predictive of success than experiments on established cells lines. Similarly, the conduct of in vivo studies in any model type did not influence trial success rates. The reasons stated by investigators for initiating the trial were also assessed for their influence on success rates. Trials in which investigators used preclinical data or adult trials as their rationale were less likely to succeed (supplemental online Table 2).

To understand why trials with preclinical data were less likely to succeed, we examined the relationship between the types of therapies tested and trial success. We found that trials that examined the activity of a completely novel therapeutic regimen were significantly less likely to be successful compared with trials that added treatments to a standard therapy backbone (40% vs. 83%;  $p < .0006$ ; Fig. 2D). Importantly, trials of novel regimens were 5 times more likely to have preclinical data prior to initiation compared with trials that built on a standard therapy or trials that did not incorporate novel agents (49% vs. 9% and 12%, respectively). We also found that 67% of novel-agent trials tested the activity of single agents, compared with 12% for trials of old drugs.

Given the lower clinical success rates for single novel-agent studies (27%) versus combination studies (65%;  $p < .0005$ ), this may partly explain the low success rate of both novel-agent trials and trials with supportive preclinical data. However, trials of novel agents that had supportive preclinical findings were still less likely to be successful (28%) compared with those with no preclinical or negative findings (52%;  $p = .02$ ). To further understand these findings, we looked in depth into the preclinical studies for each of the trials that had supportive preclinical data but were unsuccessful in trial ( $n = 35$ ). We found that eight of these trials that assessed novel agents had preclinical indicators that may have suggested the trial was unlikely to succeed. In six cases, we found that the drug(s) used in the trial had little to no efficacy in vitro or in vivo against at least one of the cancer types included in the trial [20–25]. In one trial, in vivo doses resulted in high mouse mortality rates [26], whereas for two trials, the preclinical studies concluded that the treatment was less effective than existing standard therapies [27, 28].

### Multivariate Analysis

Using logistic regression models, four clinical variables were predictive of trial success (Table 4): The number of cancers assessed during the trial influenced success, with an identified decrease in the likelihood of achieving success as the number of cancer types assessed increased; the type of



**Table 3.** The influence of preclinical research characteristics on pediatric oncology phase II trial success rates

Variable	Successful		Unsuccessful		p value <sup>a</sup>
	No. of trials	(%)	No. of trials	(%)	
Relevant preclinical research conducted					.0003
Yes	16	(31)	36	(69)	
No	50	(62)	30	(38)	
Type of preclinical research conducted					.80
In vitro	9	(25)	27	(75)	
In vivo	12	(30)	28	(70)	
In vitro testing					.99
Primary patient samples	3	(25)	9	(75)	
Cell lines	6	(25)	18	(75)	
In vitro antitumor activity demonstrated					.99
Yes	9	(26)	26	(74)	
No	0	(0)	1	(100)	
In vitro: therapies tested against cell samples representing all the cancers assessed in the trial					.69
Yes	4	(33)	8	(67)	
No	5	(21)	19	(79)	
In vivo antitumor activity					.57
Yes	10	(28)	26	(72)	
No	2	(50)	2	(50)	
In vivo models					.99
Xenograft	11	(29)	27	(71)	
Transgenic	1	(50)	1	(50)	
Xenograft type					.54
Subcutaneous	11	(31)	24	(69)	
No in vivo activity	2	(18)	2	(7)	
Orthotopic	0	(0)	3	(100)	
Preclinical research supportive of phase II trial initiation?					.001
Yes	14	(30)	33	(70)	
No/No preclinical	52	(61)	33	(39)	

<sup>a</sup>Fisher's exact or Pearson's chi-square tests.**Table 4.** Logistic regression analysis for the variables predictive of phase II success

Prognostic variable	95% CI	p value
No. of cancers assessed <sup>a</sup>	0.047–0.190	$1.3 \times 10^{-3}$
Therapeutic approach <sup>b</sup>	0.494–0.171	$8.1 \times 10^{-5}$
Investigator rationale: Prior relevant pediatric trials <sup>c</sup>	0.028–0.333	$2.1 \times 10^{-2}$
Investigator rationale: Adult trials <sup>c</sup>	0.339–0.018	$3.0 \times 10^{-2}$

<sup>a</sup>Quantitative measure 1–32.<sup>b</sup>Single versus combination.<sup>c</sup>Yes versus no.

Abbreviation: CI, confidence interval.

therapeutic approach (trials using combination therapies were more successful than single-agent trials); trials that did not base initiation on prior clinical data in adults; and investigators using previous pediatric trials as their rationale for trial initiation.

## DISCUSSION

Although the majority of children with cancer are cured, there remains an urgent need to develop novel treatment strategies for patients with tumors refractory to standard therapies. There are, however, enormous challenges around conducting trials in this patient population, given their low numbers, heterogeneity of tumor types, high clinical trial costs, lengthy patient accrual timeframes, and the reluctance of pharmaceutical companies to support pediatric trials [16, 29, 30]. Thus, despite the development of hundreds of new anticancer agents, only a small number can be effectively tested in children with cancer. Although many of these trials are successful, and cure rates continue to increase, a large proportion of phase II trials remain unsuccessful, showing insufficient antitumor activity, excessive toxicity, or no benefit above current treatment strategies [31, 32].

To our knowledge, this is the first study to examine the factors that predict the success of phase II pediatric oncology trials, and until now, much has remained unknown. What

preclinical information is needed before starting a trial? Do different preclinical models better predict clinical activity? How should phase II trials be designed to maximize the chance of success? Should drugs be tested as single agents or in combination? The results here provide a first step in answering these questions. Our findings suggest that studies using combination therapies and focusing on a limited number of tumor types were significantly more likely to succeed.

Given that preclinical studies of drug activity are meant to guide the inclusion of novel treatment strategies in clinical trials [4], it is concerning that for the majority of trials initiated (61%), we were unable to locate any preclinical data to support the trial. Surprisingly, even when supporting preclinical findings were available, we found no positive association between the conduct of preclinical experiments and trial success. Although the reasons for this remain unclear, the results emphasize the pressing need for a better understanding of the reliability and clinical relevance of preclinical research. We identified several cases in which even when there was supportive clinical data, there were indications that the clinical trials were unlikely to succeed because of, for example, tumor types being included where little to no activity was seen preclinically.

It is also possible that a lack of control for tumor heterogeneity and limitations of molecular subtyping may have influenced the reliability of preclinical data in the past. Preclinical studies sometimes use poorly characterized xenograft models [33]. Another potential confounder is the inability to model the impact of immune responses or mimic the human condition, as preclinical testing usually occurs in immunocompromised animals. Doses used *in vitro*, and sometimes *in vivo*, are often not achievable in the clinic, or drugs may not penetrate into the tumor or past biological barriers such as the blood-brain barrier [34, 35]. Negative preclinical results are usually not published, and it has also been proposed that up to 50% of preclinical findings cannot be reproduced [31, 36, 37]. Preclinical target validation may not be considered robust enough to warrant further investigation, or the results may not consider each potential variable that may be causing the result including off-target effects [38].

Although our results suggest that the gap between the laboratory and the clinic was wider than expected, there are current attempts to strengthen the bridge between scientific justification and patient care [39]. It has been suggested that clinical translation can be enhanced through pharmacokinetic and pharmacodynamics studies, randomization and double blinding of preclinical analysis, the use of clinically relevant drug dosages, scheduling *in vivo* treatment regimens to mimic clinically relevant regimes, and the application of early-phase studies in mice directly comparable to the clinical environment [33, 39]. The aim of this new preclinical archetype is to increase the reliability of research findings and ease the transition of novel therapies from the laboratory to the clinic. Whether this will increase the successful translation of laboratory experiments to the clinic will hopefully be established in time.

An additional concern may be the relevance of prior clinical trials to support phase II initiation in a pediatric population. The rationale for trial initiation is often supported by results of prior early-phase studies in both adult and pediatric populations. Given that the approval for a new therapy in a

pediatric population generally occurs following approval for its use in adults [29], prior adult trials are often used as the rationale for trial initiation in pediatric patients. Our study, however, showed that trials initiated based on activity data from adult trials were less likely to succeed. This may be because most pediatric malignancies are biologically distinct from adult cancers, even if histologically they bear similarities [29, 40]. For example, glioblastoma (GBM) in adults and children is histologically identical; however, molecular aberrations found in adult tumors (e.g., *IDH1*) are rarely found in childhood GBM, and mutations identified in pediatric GBM (e.g., H3-K27 M mutations) are rarely found in adult tumors [40, 41]. In agreement, logistic regression models identified both prior activity in a pediatric population and not using proof of principle in an adult population as rationale for trial initiation as predictors of clinical success.

Overall, clinical trial design factors were the only variables that best predicted clinical success. The number of cancer types examined was one of the most important factors identified. Although widening patient enrollment to include different cancer types may allow for more rapid patient enrollment, our data suggest this reduces response rates and the possibility of attaining success. Similarly, the type of cancer examined significantly impacted success rates, with trials involving liquid or extracranial solid tumors having the highest possibility of success. CNS tumors had the lowest response rates, possibly related to poor penetration of the blood-brain barrier [34, 35].

Combination therapies were also almost 3 times more likely to be active compared with single agents. Notably, half the studies included in this review tested drugs as single agents. The necessity to use combination therapies to improve cure rates in both child and adult cancers has been theorized for decades [15]. There may, however, be reasons trialists opt for single-agent studies, including the reticence of pharmaceutical companies to work with competitors and difficulty in understanding which agents are active when using combination therapies. Novel trial designs, such as randomized phase II trials testing, for example, a novel agent added to a standard treatment backbone can address the latter concern while facilitating a more rapid progression to a combination therapeutic approach.

Importantly, trials that added therapies to standard treatment backbones were more successful than trials testing novel therapies alone or trials that did not incorporate novel agents. This in part may relate to the fact that trials of novel therapeutic strategies were more often tested as single agents, which we found were less active than combination therapies. This finding suggests that future trials should focus on this strategy of building on successful therapies in order to lift success rates. It is also possible that clinicians who used therapies containing standard therapies were more likely to use these treatments at earlier timepoints, when response rates may be expected to be higher.

Although these results have the potential to impact clinical success moving forward, there are limitations to this study. Most importantly, our analysis should not be interpreted to imply that preclinical research is unnecessary or that treatment strategies should enter clinical development without a solid foundation of supportive preclinical findings. The majority of trials did not have any supportive preclinical



data, and when preclinical studies had been performed, the methodology was variable, often with significant differences in dose and tumor types compared with the clinical trial that was performed. Greater emphasis should be placed on preclinical studies that take into account clinically achievable concentrations and treatment schedules.

We also recognize that because of the retrospective nature of the review there are factors we could not control, or assess adequately, including the percentage of trial responders, exposure to prior therapies, and the tumor types assessed. Despite our best attempts, literature searches may not have uncovered all of the preclinical manuscripts available, and we may not have been able to account for the presence of in-house or unpublished preclinical testing if the data were not readily available. The small number of studies that involved the use of targeted therapies, transgenic models, and biomarkers may have also influenced the ability to detect the impact of these variables on trial outcome. Therefore, the lack of influence of these variables on clinical outcome may not be a reflection of their lack of impact on clinical success but rather the small sample sizes. Further investigation into the impact of these factors on clinical outcome is warranted. Finally, only published clinical findings were reviewed. The number of trials in the timeframe assessed may be greater than that identified [17, 42]. The small number of agents progressing to phase III trials was surprising. This may reflect the difficulty in conducting large randomized phase III studies in many pediatric cancers, because of the relatively small number of patients with what is essentially a rare disease. Activity in phase II trials may be a surrogate that is being used to guide the development of treatment regimens, especially for those cancers with poor outcomes.

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## CONCLUSION

Overall, we identified key variables that significantly influence and/or enhance the success rate of phase II trials for patients with childhood cancer. The results suggest that phase II trials should focus on one cancer type and on the development of combination therapies. Preclinical studies should be focused on drug doses that are achievable in patients, and trialists should rigorously assess preclinical data to help generate the best and most effective trials.

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## DISCLOSURES

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