special articles

Combination Early-Phase Trials of Anticancer Agents in Children and Adolescents

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abstract

PURPOSE There is an increasing need to evaluate innovative drugs for childhood cancer using combination strategies. Strong biological rationale and clinical experience suggest that multiple agents will be more efficacious than monotherapy for most diseases and may overcome resistance mechanisms and increase synergy. The process to evaluate these combination trials needs to maximize efficiency and should be agreed by all stakeholders.

METHODS After a review of existing combination trial methodologies, regulatory requirements, and current results, a consensus among stakeholders was achieved.

RESULTS Combinations of anticancer therapies should be developed on the basis of mechanism of action and robust preclinical evaluation, and may include data from adult clinical trials. The general principle for combination early-phase studies is that, when possible, clinical trials should be dose- and schedule-confirmatory rather than dose-exploratory, and every effort should be made to optimize doses early. Efficient early-phase combination trials should be seamless, including dose confirmation and randomized expansion. Dose evaluation designs for combinations depend on the extent of previous knowledge. If not previously evaluated, limited evaluation of monotherapy should be included in the same clinical trial as the combination. Randomized evaluation of a new agent plus standard therapy versus standard therapy is the most effective approach to isolate the effect and toxicity of the novel agent. Platform trials may be valuable in the evaluation of combination studies. Patient advocates and regulators should be engaged with investigators early in a proposed clinical development pathway and trial design must consider regulatory requirements.

CONCLUSION An optimized, agreed approach to the design and evaluation of early-phase pediatric combination trials will accelerate drug development and benefit all stakeholders, most importantly children and adolescents with cancer.

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INTRODUCTION

There is an urgent need to develop new therapies for children and adolescents with cancer, both to improve outcome for poor prognosis malignancies[1] and to reduce acute and long-term adverse effects of current treatments.[2,3] Biological rationale and published experience indicate that combination approaches, particularly those that use agents with robust single-agent activity,[4–6] will be more efficacious than the same agents used alone. Therefore, there is an increasing need to evaluate innovative drugs for childhood cancer using combinatorial strategies. The adult drug development landscape has radically evolved over the past decade, moving away from a traditional approach to seamless-design, phase I/II trials for single agents.[7] Seamless trials can address multiple objectives under the heading of early-phase investigation and allow for rapid completion.

Consensus articles have described the conduct of early-phase trials in children to bring beneficial innovative agents more rapidly to the clinic.[8,9] With the increasing evaluation of agents in combination, there is a need for a consensus to combination early-phase trials. New combinations may be developed with existing standard-of-care chemotherapy regimens or with other new agents (novel-novel combinations). The goal should be to evaluate drug combinations rapidly and efficiently, without compromising identification of safety signals or assuming unnecessary risks of toxicity. Ideally, this should require the smallest number of patients to enroll to determine safe dose(s) and schedule, identify early signals of activity, and reach a go/no-go decision in a tumor or target-specific population.

In addition to efficient trial designs, three changes are needed to accelerate evaluation of innovative medicines in children. The first change requires that the

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CONTEXT

Key Objective

To achieve an international consensus among stakeholders on the process to design and deliver early-phase combination trials in children and adolescents with cancer.

Knowledge Generated

An efficient, effective approach on the basis of mechanism of action and robust preclinical evaluation is recommended to evaluate new combinations of anticancer agents and identify the efficacy and toxicity of each novel agent. The very early involvement of patient advocates and regulators in a proposed clinical development pathway and trial design is crucial.

Relevance *(S. Bhatia)*

This paper provides general guidance to accelerate the availability of optimized treatments for children and adolescents with cancer.*

*Relevance section written by *JCO* Associate Editor Smita Bhatia, MD, MPH, FASCO.

development of anticancer medicines and combinations for children be based on the biology of childhood cancers and the mechanism of action of the drug(s) investigated rather than the adult indication.[10,11] The second requires that new drugs with high potential for benefit be assessed quickly and early in the context of the development in adults. A third improvement is expanding in vivo preclinical testing using genomically characterized pediatric models to provide the strongest possible data set for prioritizing specific combinations among the multitude of potential combinations that could be evaluated clinically.[12] These changes can reduce the unacceptable delay (median 6.5 years) from the initiation of first-in-human trials to first-in-child trials.[13] Legislation in Europe,[14,15] and more recently in the United States,[16] prioritizes science-driven, patient-oriented, pediatric oncology drug development over adult-indication approaches. These regulatory advances, together with the international multistakeholder organization ACCELERATE, promote children having greater access to innovative, safe, and effective treatments.[17,18]

Early engagement of regulators in the clinical development of agents for pediatric cancers is critical. Trial design needs to consider regulatory requirements (pediatric investigation plan and initial pediatric study plans) along a full clinical development pathway including early- and late-phase combination trials for novel agents, and for all drugs included in the combination. By aligning scientific, regulatory, and payer (eg, European health technology assessment bodies) requirements from the inception of a clinical trial, the fewest number of patients will need to be enrolled to obtain sufficient evidence for scientific and regulatory purposes.[18] Similarly, involving patient advocates early and throughout discussions is important for both pragmatic and principled reasons.[19] Doing so ensures the patient voice is heard and that specific unmet needs are accounted for in all phases of pediatric oncology drug development.[18]

Herein, we report a consensus opinion among invested stakeholders and discuss salient points that should be considered in the development of early-phase combination trials for pediatric oncology, presenting best practices whenever possible.

SUMMARY OF RECOMMENDED PRACTICE FOR GENERAL PEDIATRIC ONCOLOGY EARLY-PHASE TRIALS

Prior position statements have strongly advocated that the pediatric clinical evaluation of a new anticancer drug follows an early-phase seamless trial design rather than individual phase I and II trials.[10,20–22] An early-phase clinical trial has two components: (1) a dose-finding or dose-confirmation phase and (2) expansion cohort(s) (Table 1) in which optimal dosing, toxicity profile, pharmacokinetic (PK) parameters, pharmacodynamic (PD) effects, and early signals of antitumor activity are obtained. The therapeutic agent is then transitioned to late-stage trials to determine antitumor efficacy and comparison with current standard(s) of care. Avoiding the distinction between different phases of development can reduce the numbers of exposed patients and as well limit cost, resource requirements, trial development timelines, and trial duration. Monotherapy or combination platform trials[23] with several parallel arms[24–28] are examples of potential frameworks with many advantages (Table 2).

In practice, no differences have been observed in the PK of cytotoxic drugs between patients age 5-11 and 11-16 years, or between 12-16 and 16-21 years.[29–33] Furthermore, the median age of enrollment was 12 years or younger in 15 of 20 recent Innovative Therapies for Children with Cancer (ITCC)–published phase I trials (F. Bautista, personal communication, January 2023). Therefore, to expedite dose-finding for pediatric patients, age-specific cohorts for the majority of pediatric patients are discouraged. Additional PK/PD data can be collected in infants age 2 years and younger, who are anticipated to have different metabolism, using dedicated PK/PD expansion cohorts at the recommended phase II dose (RP2D) and in later-phase studies.

TABLE 1. General Principles of Pediatric Early-Phase Clinical Trials

Early-Phase Clinical Trial		
Component	**Recommendations**	**Rationale**
Dose-finding or dose-confirmation phase	Starting dose: If a drug has neither serious dose-related toxicities nor a narrow therapeutic index: Adult RP2D (if known) corrected for patient size (BSA or weight) Objectives: Confirm toxicity profile, RP2D, and preliminary PK parameters with minimal dose ranging Extrapolation from data in adults should be considered, when possible[22]	Pediatric RP2D of most molecularly targeted drugs range between 90% and 130% of the BSA-adjusted RP2D for adults and, in the absence of DLT, is often based on PKs[20,21]
Expansion cohorts	Early signals of antitumor activity Additional PK, PD, and safety data including young children and infants Opportunity to evaluate a child-friendly oral formulation that was not available at the start of trial	Generate activity data to inform potential late-phase trials in target population of interest

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

Early-phase trials should also avoid defining a lower age limit for inclusion, unless biologically justified. To this end, developing age-appropriate formulations is critical. However, this development should not delay the start of the first-in-child trial. Rather, trials should begin using tablets or capsules, feasible to reliably deliver a pediatric dose with adult formulations. When a child-friendly formulation becomes available with bioequivalence data, this should be used and PK data for the new formulation collected subsequently.

A mechanism of action, tumor-agnostic development approach provides more opportunities for rapid and focused pediatric and adult drug development, if the relevant biomarker is also age-agnostic.[34,35]

CONSIDERATIONS FOR PEDIATRIC COMBINATION TRIALS

General Principles

Early-phase combination trials, like monotherapy trials, should be seamless and encompass both a dose-finding/confirmation and an activity evaluation phase. Different approaches are required for safely combining agents on the basis of prior clinical experience with the agent or agents-in-class.

TABLE 2. Advantages of Platform Trials for Clinical Drug Development in Children With Cancer

Advantage
Share molecular profiling across arms[a]
Standardize data management and biological samples
Accelerate the introduction of new combination arms
Facilitate joint analyses of two arms with a common investigational agent and different backbone
Facilitate joint analyses of specific tumor types
Facilitate translational research across cohorts
Maximize the probability that a child enters one of the arms, as prevalence of molecular abnormalities is often low
Improve operational efficiency rather than opening multiple individual trials

[a]It is frequently mandatory to have molecular screening of subjects when partial or complete enrichment is required to evaluate activity.

Combinations may contain agents previously studied in children as monotherapy, or those for which there are only adult data. When agents are combined, new toxicities can occur that are not present when agents are administered individually, and overlapping toxicity is possible. For combinations of a novel drug with standard-of-care chemotherapy, scenarios depend on whether the pediatric PK and safety profile of the new drugs is known, and if overlapping toxicities or PK interactions are expected. Novel-novel combinations are indicated when there is a strong biological rationale with robust preclinical data and are particularly compelling if early proof-of-principle clinical data exist.[36] For novel-novel combinations, scenarios depend on whether the products have (1) known pediatric PK and safety profiles; (2) known adult PK and safety profiles; (3) metabolism that is expected to contribute to PK interactions; and (4) observed or expected interactions or overlapping toxicities (Table 3, Fig 1).

Parents enroll their children on early-phase clinical trials in the hope that participation will directly benefit them.[37,38] Although the goal of a trial is to address a scientific question, therapeutic intent (ie, the potential for patient benefit, balanced against potential or real short- and long-term toxicity) should guide trial design considerations. This means conducting appropriate patient selection during dose-finding to maximize chances of benefit, avoiding subtherapeutic doses, minimizing single-agent evaluations, except when necessary, and rapidly assessing agent efficacy. To limit the number of patients who receive a dose less than a potentially beneficial treatment, intrasubject dose escalation should be considered. Maximum dose escalation may also not be required if the dose used in adults (if any) provides evidence of biological activity and is supported by PK. A unique aspect of combination trials is to demonstrate signals of improved activity over either monotherapy or standard of care. Randomization is of value and follows the European Medicine Agency (EMA) guidelines for combination development.[36]

TABLE 3. Clinical Scenarios and Proposed Design and Starting Dose Strategies

Clinical Scenario	Proposed Strategies (Design/Starting Dose)	
Novel Drug Added to Standard of Care (2 or 3 drugs) and New Drug. Only One Novel Drug Escalated		
PK, RP2D, and Safety Profile	**Overlapping Toxicities or Drug-Drug Interaction**	
	Not Expected	**Expected**
Known in children	Dose confirmation/pediatric RP2D	Dose escalation[a]/maximum 80% pediatric RP2D
Known in adults only	Dose confirmation/equivalent to adult RP2D	Dose escalation[a]/80% equivalent adult RP2D
Not known	Dose escalation[a]/per regulatory guidance for first-in-human study	Dose escalation[a]/per regulatory guidance for first-in-human study
Novel-Novel Combination		
Pediatric data available for both agents	Dose confirmation/pediatric RP2D of both agents	Dose escalation (two drugs)[b]/maximum 80% pediatric RP2D of both agents
One drug first-in-child[c]/one with pediatric data	Dose escalation (two drugs)[b]/pediatric RP2D of one agent and equivalent to adult RP2D for second agent	Dose escalation (two drugs)[b]/maximum 80% pediatric RP2D of one agent and 80% equivalent adult RP2D for second agent
Both drugs are first-in-child,[c] combination has not been evaluated in adults	Dose escalation (two drugs)[b]/80% equivalent adult RP2D for both agents	Dose escalation (two drugs)[b]/80% equivalent adult RP2D for both agents
Both drugs are first-in-child,[c] one drug with known adult PK, safety profile, and RP2D, and one drug with no knowledge of PK, safety profile and RP2D in adults	Dose escalation (two drugs)[b]/80% equivalent adult RP2D for first agent and follow regulatory guidance for first-in-human dosing for second agent	Dose escalation (two drugs)[b]/80% equivalent adult RP2D for first agent and follow regulatory guidance for first-in-human dosing for second agent

Abbreviations: CRM, continual reassessment method; DLT, dose-limiting toxicity; PK; pharmacokinetic; RP2D, recommended phase II dose.

[a]Dose escalation: escalation using a design to escalate one drug, for example, rolling six or CRM, depending on number of dose levels and targeted DLT rate.

[b]Dose escalation (two drugs): using a design to escalate two drugs, or rolling six if few and well-ordered combined dose levels, or partial ordering CRM, for unknown order.

[c]Limited monotherapy evaluation of the agent, before proceeding to combination.

Therapeutic intent is also enhanced in the context of combination studies of existing plus novel drugs if there is benefit with existing drug(s) alone. Randomized evaluation of a new agent plus standard therapy versus standard therapy is the most effective approach to isolate the effect and toxicity of the novel agent.[36] Early-phase platform studies,[24–28] where arms of different drugs can be evaluated, provide an efficient way for combinations to be evaluated for efficacy in relatively small patient populations and dropped rapidly if there is no early signal. Continual dialogue is required to challenge the perception that a phase I study has no realistic potential for benefit.[37,38] Early-phase testing must be designed with an eye toward where the combination might ultimately fit into existing treatment paradigms for newly diagnosed patients.[10]

As with all pediatric clinical trials, incorporating translational correlative research is a crucial element of early-phase trials, so that knowledge can be increased to guide future evaluation of more biologically rational combination regimens. Moreover, this approach will facilitate the detailed retrospective molecular analyses of responders and nonresponders to generate a revised or new hypothesis.

Rationale for Combinations

Selection of combinations with compelling biological and clinical rationale for evaluation in children is essential, given the rarity of pediatric cancers and the mismatch between the immense numbers of combinations that are available for testing compared with the number of clinical trials that can be conducted. Prioritization of agents should be based on knowledge of tumor biology, molecular drivers of disease, a drug's mechanism of action, robust activity of the combination in relevant in vivo preclinical models that exceeds that of the component agents used alone, and therapeutic unmet needs.[10] Another important factor is the single-agent activity of the drugs used in the combination, as it is uncommon for meaningful clinical benefit to be observed for combinations in which an agent lacking evidence of single-agent activity is evaluated.[4,39,40] Recent advances from positive pediatric phase III trials highlight the importance of the activity of the agent added to standard-of-care regimens, as illustrated by rituximab for non-Hodgkin lymphoma,[41] brentuximab vedotin for high-risk Hodgkin lymphoma,[42] arsenic trioxide for acute promyelocytic leukemia,[43] blinatumomab for

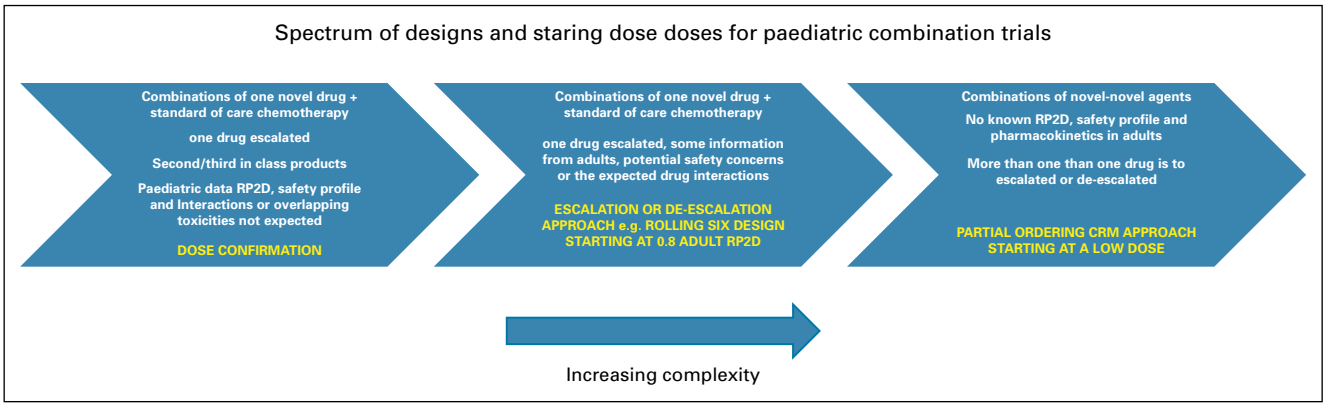

FIG 1. Spectrum of designs and starting dose for pediatric combination trials. The design depends on the amount of known existing data relating to the drug and the target/entity in pediatrics and in adults, expectations for interactions or overlapping toxicities, and the number of drugs for which dose and schedule will be explored. At one end, there are second- or third-in-class products where there are pediatric data on the class and the emphasis is on dose confirmation. In the middle of the spectrum, only one drug is escalated for which there is some information from trials in adults, but some potential safety concerns or expected drug interactions—here, dose finding is required but could potentially start at the adult recommended dose for the same combination with planned escalation or de-escalation using an approach such as a rolling six design if the number of dose levels is smaller (only 2-3.) At the other end of the spectrum, there are combinations of novel-novel agents studied where there is no experience in adults and more than one drug is to be escalated or de-escalated; in this case, a partial ordering CRM approach is appropriate starting at a lower dose than adult equivalent RP2D. CRM, continual reassessment method; RP2D, recommended phase II dose.

B-cell acute lymphoblastic leukemia (ALL),[44,45] nelarabine for T-ALL,[46] and imatinib[47]/disatinib[48] for Philadelphia chromosome–positive ALL and dinutuximab with chemotherapy for neuroblastoma.[49]

Evidence generated nonclinically is of paramount importance with the objective that the activity of the combination is at least additive or synergistic. Although synergy observed in preclinical studies may highlight combinations of potential interest, it is important to consider that the synergy observed for cancer cell lines in vitro may also apply to one or more critical normal tissues when combinations are tested in patients and translate into toxicity, with the result that there is little or no therapeutic window for the combinations. For this reason, in vivo studies with appropriate controls are required. An example is O^6-benzylguanine plus nitrosoureas for high-grade gliomas. Remarkable preclinical synergy was observed for O^6-benzylguanine plus nitrosourea combinations,[50] but in patients, the synergistic effect also applied to normal hematopoietic cells leading to excessive myelosuppression that required reduced doses of nitrosourea when biologically relevant doses of O^6-benzylguanine were administered.[51] A phase III trial comparing O^6-benzylguanine plus reduced-dose bischloronitrosourea, carmustine (BCNU) to full-dose BCNU for adults with high-grade glioma was stopped early for futility.[52] Other examples of preclinical synergy with excessive clinical toxicity are the combination of CHK1 inhibitors with gemcitabine,[53] MEK inhibitors with pan-HER inhibitors,[54–57] imatinib/dasatinib with high-dose chemotherapy,[58] and crizotinib with vinblastine in anaplastic large-cell lymphoma.[59]

The extent and depth of the preclinical studies required for support of combinations depend on the strength of the underlying biological hypothesis. For example, if the target of an agent that is being incorporated into a combination is a well-defined oncogenic driver, then less evidence may be required. Conversely, in the majority of instances, when the agent lacks a predictive biomarker of response, robust preclinical evidence for a substantial combination effect is warranted before moving forward to clinical testing. Prioritization should be given to combinations with evidence of synthetic lethality, where inhibiting two targets together results in cell death, but inhibiting one target alone does not.[60] The ITCC-P4 and Pediatric Preclinical Testing Consortium[12,61,62] consensus on minimum preclinical testing requirements for the development of investigational therapies can facilitate combination strategies.

Design Considerations

Inclusion criteria. Depending on preclinical and adult trial data, the pediatric dose-confirmation/finding phase may include an enriched selected population[24,63] or all-comers.[64] Another approach is to include all-comers in the dose-confirmation/finding phase and an enriched population for histology-/genomic-specific expansions to determine activity.[65,66] If there is biological rationale and potential benefit for the individual patient, such as non–biomarker-driven agents, all-comers may facilitate accrual and quickly ascertain a safe and adequate drug exposure dosing schedule. If preclinical or adult data suggest that antitumor activity is highly unlikely in an unselected population, eligibility criteria should be restricted to the relevant target population.[63] Biomarker-positive or histology-specific patients may be permitted to enter the study at any time at the best current estimate of a safe dose when there is no available slot in the main open cohort.[67,68] To maximally

use these data flexibly, statistical methods such as model-guided methods[69] (continual reassessment method [CRM]-type) may be used. When determining antitumor activity, the population should be restricted by disease or by biomarker to the target population for future clinical development or there should be partial enrichment to enroll a proportion of patients whose tumor has the target of interest. Patients who have prior exposure to single-agent therapy may be permitted, as this may reveal the benefit of the combination, by demonstrating response in a previously resistant population.[70]

Defining the starting dose. Confirmation of the adult body surface area (BSA)– or weight-adjusted RP2D should be the preferred strategy rather than dose finding. More conservative dose finding, starting at 20%-30% lower than the adult RP2D, may be warranted if there are safety concerns, a narrow therapeutic index, overlapping toxicities, or expected drug-drug interactions. The dose-confirmation approach will enable shorter studies.[71–73]

The sample size of the dose-confirmation cohort should enable the estimation of PK parameters and the determination of the recommended dose for the combination (RDC) for children.

Dose and schedule finding. In line with EMA guidelines,[36] studies should aim to identify the product(s) causing the observed adverse reactions to guide dose reductions in relation to observed toxicity. For example, if one agent is particularly likely to cause an observed adverse event (eg, rash), it should be de-escalated first. Generally, the novel product should be dose escalated/de-escalated first when a novel agent is combined with a known active agent or backbone. In addition, preclinical evidence of mechanism-based synergistic toxicity should be considered, for example, that seen with talazoparib and temozolomide.[65] Designs to de-escalate each component of the combination regimen if there is toxicity, or escalate if the exposure is less than occurring in adults or inadequate target inhibition, need to be pre-specified, so that trials are not halted unnecessarily.[31,74]

The concept of an *acceptable* toxicity should be considered, independently of its grade as per Common Terminology Criteria for Adverse Events. For example, reversible hematologic toxicity could be *acceptable*, in contrast to a permanent cardiac toxicity, which would be *unacceptable*. Class effects should be considered; for example, dose-limiting toxicity (DLT) definitions should exclude known class-related side effects easily manageable with supportive care. The concept of *tolerability* is also important, but potentially subjective, and might be measured as a quality-of-life metric. Increasing input from advocates and use of patient-reported outcomes is also encouraged, particularly for symptom-based toxicities for which concordance is poor between patient and clinician or caregiver reports.[75–77]

Preclinical evaluations for additivity and synergy can guide optimal exposures for combinations. However, optimal combination dose and schedule finding in patients may require simultaneous exploration of dose for each drug and multiple schedules. A CRM design for unknown toxicity ordering (partial ordering) is efficient in exploring dose combinations with as few patients as possible.[78] Dose-escalation strategies may include either cohorts that use alternate increases of each drug (or changes in schedule) or use of one drug in its standard single-agent dose and schedule and increase only the dose of the novel drug(s). Generally, if there are only two or three dose levels, then the rolling six design[79] can be acceptable. However, if there are more dose levels for the combination, a partial ordering CRM (POCRM) approach[78] (Table 3) is typically more accurate in identifying the combination dose and schedule and allows for tailoring which drug is escalated or de-escalated at completion of each cohort.[80] The POCRM can also be designed to avoid waiting lists, testing multiple doses and schedules in parallel.

RDC. It is not always possible to establish an optimal biological dose (eg, dose generating an adequate PD response without excessive toxicity) on the basis of PD data.[81] Despite a strong biological rationale and convincing preclinical work, generating exposure/PD response data in the target population may not be feasible if there are no relevant/validated biomarkers. Preclinical data and response data from clinical trials in adults may provide information to determine the RDC in pediatrics. Dose optimization and dose-finding rely on toxicity, tolerability,[36] and interpatient variability in exposure to target adult PK exposure with therapeutic drug monitoring whenever feasible.

Traditionally, the maximum tolerated dose (MTD) is defined on DLTs observed during cycle one of the dose-escalation phase, but the RDC should incorporate all information (eg, severe or chronic cumulative toxicity after cycle 1, dose modifications, PD and PK data, and toxicities that have significant impact on quality of life) since repeated dose reductions at cycles ≥2 are often because of chronic toxicity/intolerability that are not accounted in the definition of the MTD.[82] Dose optimization might also enable intrapatient dose escalation (after achieving steady-state drug exposure or completion of two cycles and response evaluation) in patients who tolerate drugs and when therapeutic drug monitoring suggests a higher dose would be preferable.[83,84]

It is highly important to characterize doses and schedules of molecularly targeted therapy before initiating registration trials, as has been highlighted by Project Optimus of the US Food and Drug Administration (FDA).[85] An inadequately characterized dose and schedule of one or more combination agents may lead to more toxicity without additional efficacy, resulting in unwanted consequences, for example, persistent or irreversible toxicities and

inappropriate discontinuation of a potentially effective medicinal product.[86] Given the size of clinical trials needed to reliably optimize dose and schedule, this optimization generally needs to occur in adult cancer populations with extrapolation of the optimal dosage- and exposure-response relationships for efficacy and toxicity to pediatric patients.[22]

Designs of trials with an initial monotherapy phase. It is proposed that if a product is included in the combination where there are no previous pediatric data, a limited monotherapy evaluation, including an appropriate single-agent window, is included before proceeding to combination to better characterize dose, PK, toxicity, and, in some cases, single-agent activity. The starting dose for the monotherapy component should, in the absence of agent-specific toxicity, pharmacologic considerations, or a narrow therapeutic index, be 100% of the BSA-adjusted adult RP2D.[9,21] Designs should allow for transition from monotherapy to combination therapy in the same patient as soon as possible (after one or two courses) unless substantial single-agent activity is observed. The need to determine efficacy of monotherapy will depend upon whether its preclinical mechanism of action is only to enhance the activity of other agents in the combination, or it is active on its own, with the caveat that there are few examples of successful development of agents without single-agent activity that are used only to enhance the activity of other agents. The minimum possible number of patients should receive monotherapy[87,88] unless there is good evidence of single-agent activity and lack of evolving resistance to single-agent therapy.

Summary of approach for selection of starting dose and dose-finding designs. Table 3 and Figure 1 illustrate potential scenarios for early-phase combination trials depending upon a range of agent characteristics.

An FDA guidance on the codevelopment of two or more new investigational drugs for use in combination[89] is relevant to the developmental and regulatory pathways of novel-novel combinations in children, where there are no known pediatric data for at least one agent. This guidance also emphasizes the crucial importance of determining the contribution of each individual new investigational drug.

Evaluation of antitumor activity in early-phase combination trials. Randomized evaluation of a new agent plus standard therapy versus standard therapy is most effective to isolate the effect of the addition of the novel agent in a combination.[36,71] An underpowered randomization is considered acceptable and already agreed by the EMA.[22,90] Crossover from standard to combination regimen after progression of disease may be allowed.[91] This approach provides more robust evidence to identify promising regimens to take forward to later-stage trials and reduces the confounding effects of trial outcomes with unknown and uncontrollable trial effects such as patient selection, prior treatment, age, sex, comorbidities, referral bias, and differences in supportive care,[72] compared with single-arm phase II trials. Relatively small, randomized expansion phases, randomized selection, or screening designs[92,93] can be very valuable in screening for activity of a novel agent added to standard therapy. Novel designs (such as Bayesian or two-stage minimax Jung designs)[94,95] can be used to minimize the sample size to 25-35 patients per cohort depending on the objectives and assumptions used in sample size determination. In this setting, controlling type I error (false positive) is less relevant than controlling type II error (false negative), as the goal of such trials is to ensure that if one regimen is superior, then there is a high probability that it will be selected. Pick-the-winner phase II randomized trial designs are another approach.[96] Randomization of patients two to one to receive the arm combined with the innovative agent versus standard of care, respectively, could be considered to accelerate accrual if patients are more willing/inclined to enroll. However, this approach might lower the power or increase the total sample size to maintain the same power[97] and should only be used if the activity of the investigational agent is expected to be high. The success or failure criteria generally are defined by clinically acceptable response rate or progression-free survival[98] that would lead to further evaluation of the drug. Intercontinental studies are required to recruit sufficient numbers of patients in studies with low incidence.

Evaluating activity using Ensign (3-stage design allowing for two interim analyses implemented)[99] or Simon's two-stage design[100] via a single-arm trial using robust historical control or population known to be resistant to the single agent has several disadvantages, particularly in the absence of meaningful control data.

Patients in the dose-confirmation portion of the study can be included in the expansion cohort if they received the pediatric RDC and have disease status appropriate for assessment of the response endpoint. All responses and nonresponses (even those observed at lower dose level) should be reported, and prolonged disease stabilizations in some instances may be relevant.

Existing pediatric combination early-phase trials. From a total of 287 trials including children in the ClinicalTrials.gov database, examples of published or presented pediatric combination early-phase trials are shown in Table 4.[110]

The phase I study of regorafenib in combination with vincristine and irinotecan was an amendment to single-agent regorafenib trial (ITCC-047). The combination used sequential dosing, had liberal DLT definitions,[70] and moved rapidly to a second-line treatment in rhabdomyosarcoma (compared with standard of care) in a platform trial (FaR-RMS).[111]

The phase I/II study lenvatinib with etoposide plus ifosfamide (ITCC-050) included a combination dose-finding phase and a combination expansion in patients with osteosarcoma.[101,102]

TABLE 4. Selected Published or Presented Pediatric Combination Early-Phase Trials Reviewed to Identify Key Themes in Combination Trial Design

Trial	Type of Study	Known PK and Safety of Novel Agent in Pediatrics	Adult Combination Data Available	Design	Outcome	Age of Eligibility	Disease	DLT Definition	Drug-Drug Interaction	RDC
Regorafenib + VI[70]	1	Yes	No	Rolling six dose finding; sequential dosing as first de-escalation; studied only two dose levels	RDC and preliminary activity established	Six months to younger than 18 years; different doses of regorafenib for very young children; suspension formulation available	All-comer solid tumors, but ≥50% required to have rhabdomyosarcoma	Liberal DLT definitions; allowance for substantial individualized dose modifications	CYP3A4 UGT1A9	Regorafenib at 100% RP2D: 82 mg/m^2 once every day combined sequentially with standard-dose VI
Lenvatinib + etoposide and ifosfamide[101,102]	1	Yes	No	Rolling six dose-finding phase; lenvatinib 80% of single-agent RP2D; combination expansion	RDC and preliminary activity established	2-25 years; no suspension available	Osteosarcoma	Standard	No	Lenvatinib 14 mg/m^2 (cap 24 mg) once daily; etoposide 100 mg/m^2 and ifosfamide 3,000 mg/m^2 days 1-3
Pazopanib + IT[103]	1	Yes	No	3 + 3 dose finding; pazopanib at 77% single-agent RPD2; no sequential dosing	RDC not determined because of DLT; class-specific; overlapping toxicity	6-21 years; no suspension available	All-comer sarcoma; difficult to decipher an efficacy signal	Strict DLT definitions for expected side effects (diarrhea, neutropenia, and ALT/AST). Many might not have been called DLT in regorafenib study	CYP3A4	Not determined even when de-escalated to 50% MTD doses of pazopanib and irinotecan
Alisertib + IT[104]	1	Yes	No	Rolling six dose-finding; alisertib at 56% single-agent MTD with standard IT	RDC and preliminary activity established	1-30 years	Neuroblastoma	Standard; amendment required to add myeloid growth factor	No	Alisertib at 75% single-agent MTD: 60 mg/m^2 with standard IT
Temsirolimus or dinutuximab + IT[105]	1	Yes	No	Dose confirmation/safety run-in; randomized phase II selection design	Confirmed tolerability of both regimens; showed higher response rate in chemoimmunotherapy arm, promoting that combination for further development	No age restriction	Neuroblastoma	Not specified, although unacceptable toxicity monitoring rule included	No	Confirmed tolerability of full-dose dinutuximab with standard doses of IT
Vorinostat as a radiation sensitizer with 131I-MIBG[106]	1	Yes	No	3 + 3 design; alternating dose escalation of vorinostat and MIBG; six dose levels	RDC and preliminary activity established	2-30 years	Neuroblastoma	Standard	No	Vorinostat at 180 mg/m^2 once every day with 18 mCi/kg MIBG
Venetoclax + TC[86]	2	No	No	Venetoclax monotherapy to confirm PK at equivalent dose to adult RP2D; separate combination dose finding with appropriate backbones in leukemias and solid tumors (TC); cohort expansions in combination	RDC could not be determined for continuous venetoclax in solid tumors with TC because of cytopenias; amended to include discontinuous schedule	Initially < 18 years; suspension available; TC combo cohort <25	ALL, AML, NHL All-comer solid tumors, with expansion in neuroblastoma	Standard	No	Determination of RDC for leukemias with continuous and solid tumors with discontinuous schedule (trial ongoing)

(continued on following page)

TABLE 4. Selected Published or Presented Pediatric Combination Early-Phase Trials Reviewed to Identify Key Themes in Combination Trial Design (continued)

Trial	Type of Study	Known PK and Safety of Novel Agent in Pediatrics	Adult Combination Data Available	Design	Outcome	Age of Eligibility	Disease	DLT Definition	Drug-Drug Interaction	RDC
Talazoparib + temozolomide[65]	3	No	No	3 + 3 design; started with 80% of adult MTD of talazoparib and escalated talazoparib before escalating temozolomide dose, which started at 40% of RP2D; six dose levels; PK and expansion cohort at the RP2D	RDC determined; synergistic toxicity, particularly neutropenia and thrombocytopenia; no objective responses in Ewing despite achieving talazoparib exposure active in adults	1-21 years for phase I; <30 years for phase II	All-comer solid tumors, with expansion in Ewing sarcoma with EWS-ETS fusions	Standard	Temozolomide Cmax increased with increasing doses of talozoparib	Talazoparib 600 $\mu g/m^2$ twice a day on day 1 and 600 $\mu g/m^2$ once every day days 2-6 (maximum 1,000 μg) and temozolomide 30 mg/m^2 once every day days 2-6
Dabrafenib and trametinib[63]	3	No	Yes (melanoma)	Seamless trial design. Part 1/2: single-agent trametinib escalation/ expansions. Part 3: combination dose finding with trametinib at RP2D and limited dose escalation of dabrafenib in biomarker selected patients naive to MAPK pathway-targeted therapy. Part 4: histology (LGG) and biomarker cohort expansion	RDC determined and preliminary activity established in V600E mutant LGG	1-18 years Suspension formulation available for both agents	BRAF V600E mutant tumors, expansion in V600E mutant LGG and LCH	Not available	Not reported/not found	Trametinib 0.025 mg/kg once every day + dabrafenib 5.25 mg/kg once every day (<12 years) or 4.5 mg/kg once every day (≥12 years) orally continuously
Vorinostat +13 cis retinoic acid[107]	3	Yes	No	Seamless trial design. Single-agent vorinostat studied, then dose confirmation in combination with CisRA; only two dose levels studied: The second DL was a schedule de-escalation of vorinostat (four times per week *v* daily)	RDC determined and signal of efficacy in neuroblastoma	12 months-21 years	All-comer solid tumors; with combination in neuroblastoma, medulloblastoma, CNS PNET, or ATRT	Standard	Not reported No data on CisRA PK	13-CisRA 80 mg/m^2/dose twice a day + vorinostat 180 mg/m^2 once every day, four times per week
Durvalumab ± tremelimumab[108]	4	No (but, yes using analogous agents)	Yes	Dose finding: cycle 1 durvalumab monotherapy; cycles 2-5 durvalumab/ tremelimumab combination; cycle 6 + durvalumab monotherapy Dose expansion: cycles 1-4 combination and then durvalumab monotherapy	Trial ongoing	Younger than 18 years	Non-CNS solid tumors or lymphoma	Not available	Not anticipated	Ongoing trial

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TABLE 4. Selected Published or Presented Pediatric Combination Early-Phase Trials Reviewed to Identify Key Themes in Combination Trial Design (continued)

Trial	Type of Study	Known PK and Safety of Novel Agent in Pediatrics	Adult Combination Data Available	Design	Outcome	Age of Eligibility	Disease	DLT Definition	Drug-Drug Interaction	RDC
Cixutumumab (IMC-A12) + temsirolimus (CCI-779)[61]	5	Yes	Yes	Modified 3 + 3 design; four dose levels, which included two dose reductions and a subsequent intermediate dose escalation	RDC determined but children unexpectedly tolerated the combo less well than adults because of severe mucositis; temsirolimus decreased to nearly 50% single-agent MTD (and 50% adult RDC)	12 months-21 years	All-comer solid tumors; separate sequential phase II	Standard	Overlapping toxicity (vertical pathway inhibition)	Cixutumumab 6 mg/kg + and temsirolimus 8 mg/m^2 weekly; strong PK/PD to validate dose/target inhibition
Lenvatinib + everolimus[109]	5	Yes	Yes (renal cell carcinoma)	Rolling 6 design; dose confirmation of adult RDC; DL-1 for dose de-escalation of lenvatinib only; planned escalations if needed; 3 planned expansions.	RDC determined; 2/3 DLTs in DL1 (one overturned by DSMC); de-escalated to DL-1 with 0/5 DLTs, then re-escalated to DL1; total 2/12 DLTs in DL1	2-18 years No suspension available	All-comer solid tumors; expansions in Ewing, HGG, and rhabdomyosarcoma	Standard	Not found	Lenvatinib 11 mg/m^2 once every day (cap 14 mg) + everolimus 3 mg/m^2 once every day (cap 5 mg) continuously
Ribociclib + everolimus[24]	5	Yes	Yes	Dose escalation using continuous reassessment method targeting a dose associated with 25% risk of DLT; 3 dose levels: ribo 25%/eve 50%; ribo 50%/eve 50%; ribo 50%/eve 75% (alternating dose escalation)	RDC was defined as DL2 (after DLTs occurring in DL3, and DL2 expanded)	Younger than 18 years	Biomarker-selected patients with activating alterations in CDK4/6 pathway and/or PI3K/AKT/mTOR pathway (eg, PIK3CA, TSC mutations, and loss of PTEN)	Standard	CYP3A4 Study showed ribociclib coadministration inhibited clearance of everolimus, increasing its exposure	Ribociclib 175 mg/m^2 once every day + everolimus 2.5 mg/m^2 once every day

NOTE. Type of study: standard of care (two or three drugs) and new drug (known PK, RP2D, and safety profile in pediatrics); standard of care (two or three drugs) and new drug (PK, RP2D, and safety profile not known in pediatrics); one innovative drug with no knowledge of PK, safety profile, and RP2D, and a drug with known PK, RP2D, safety profile; two innovative drugs with no knowledge of PK, safety profile, and RP2D, and two products, both with known pediatric PK, RP2D, and safety profiles.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATRT, atypical teratoid rhabdoid tumor; CNS, central nervous system; DLT, dose-limiting toxicity; EWS-ETS, EWS gene–ETS transcription factor; HGG, high-grade glioma; IT, irinotecan and temozolomide; LGG, low-grade glioma; MIBG, metaiodobenzylguanidine; MTD, maximum tolerated dose; NHL, non-Hodgkin's lymphoma; PK, pharmacokinetic; PNET, peripheral neuroectodermal tumor; RDC, recommended dose for the combination; RP2D, recommended phase II dose; TC, topotecan and cyclophosphamide; VI, vincristine and irinotecan.

TABLE 5. Key Principles for Early-Phase Combination Trials in Pediatric Oncology

Principle
Regulatory
Importance of early engagement of regulators in clinical development of agents for pediatric cancers, including a full clinical development pathway comprising the design of early- and late-phase combination trials for novel agents
The trial design needs to consider regulatory requirements (PIPs and initial pediatric study plans) for all drugs included in the combination trial, so that it is fit for filing—the data set that meets the expectations for inclusion in a regulatory package
Designs need to isolate the effects of novel agent (both toxicity and antitumor effects)
Purpose of the trial
A robust biological rationale for the combination and clinical pharmacology and pharmacodynamics for targeted agents are paramount to design novel combinations
Extrapolation from adults may aid the design of the pediatric combination trials, but some combinations may also be first studied in children
There should be therapeutic intent in the combinations evaluated with potential patient benefit. This includes thoughtful/appropriate patient selection even in early-phase trials and the avoidance of subtherapeutic doses or trials that have many dose levels, or treat many patients below a potentially beneficial treatment dose
There needs to be a strategy designed for the combination's ultimate subsequent role in frontline therapy
Specific PK/toxicity studies in the very young (eg, younger than 2 years) may be appropriate depending upon the ultimate target population
Trial design
The trial design for early evaluation of combinations should be as simple and short as possible, as long as it adequately addresses the question
The general principle for combination early-phase studies is that if possible, they should be dose- and schedule-confirmatory, rather than exploratory
Go/no-go decisions should be incorporated early in the development of the combination trial to identify lack of activity in expansion cohorts, for excess toxicity, or interactions during dose escalation/confirmation
If not previously evaluated as monotherapy, limited evaluation of monotherapy (one cycle or less for one cohort, if single-agent activity is predicted to be low) should be included in the same clinical trial/protocol as the combination
Depending upon the combination of interest, the trial design may prioritize exposure to one agent over the other agent(s) in the combination, while other designs may be guided solely by toxicity or other considerations. Generally, if a novel agent is being added to standard of care, the dose and schedule of the new product will be escalated/de-escalated, while the dose and schedule of the standard regimen remains constant at the known therapeutic exposure
In expansion cohorts or subsequent trials, randomized determination of the activity of a new agent when combined with known active agent(s) should be considered. Recruiting patients previously known to be resistant to one of the agents could be considered
Platform trials have a major role in this setting as they share molecular analysis, standardize data management and biological sampling, accelerate the introduction of new combination arms, facilitate joint analyses of two arms with common investigational agent and different backbone and specific tumor types, and operationally are more efficient

Abbreviations: PIP, paediatric investigation plan; PK, pharmacokinetic.

This trial was followed by the OLIE (ITCC-082) randomized study evaluating the combination of lenvatinib with ifosfamide and etoposide compared with ifosfamide and etoposide alone (in relapsed/refractory osteosarcoma[112]). This efficient design could have been further accelerated if the randomized comparison had been integrated into the initial protocol and followed the phase I/II component.

The dabrafenib and trametinib combination trial began with a single-agent cohort to determine the RP2D of trametinib. This led to a limited dose escalation of dabrafenib and trametinib, followed by an expansion of the combination in patients with *BRAF* V600-mutant low-grade glioma.[63] The combination was demonstrated to have a superior overall response rate and median progression-free survival when randomized against standard of care (carboplatin and vincristine) in pediatric low-grade gliomas.[113]

In conclusion, children and adolescents with cancer deserve early access to innovative drugs in clinical trials, and those agents that are potentially beneficial need to be evaluated expeditiously. Clinical trials should maximize the potential for benefit in the greatest possible proportion of patients contributing to such trials. Combinations should be developed on the basis of mechanism of action, cancer biology, robust preclinical evaluation, and clinical activity for the agent when known (Table 5). We propose that optimally efficient early-phase combination trials combine dose-confirmation/finding and randomized expansion cohorts in the tumor or target of interest.

Very early discussion of trial designs with regulators is essential so that trials fulfill both scientific and regulatory purposes. Including parent advocates meaningfully in these early stages will help reveal potential points of confusion and misinformation, help shape strategies to increase recruitment and educate study participants, and help raise the likelihood of on-time completion of planned enrollment. Furthermore, this approach would allow

children with rare conditions available to participate in clinical trials to be evaluated in the most parsimonious way possible.

A fit-for-purpose approach to the design of early-phase pediatric combination trials will benefit all stakeholders, especially children and adolescents with cancer.

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