International Consensus on Minimum Preclinical Testing Requirements for the Development of Innovative Therapies For Children and Adolescents with Cancer

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ABSTRACT

Cancer remains the leading cause of disease-related death in children. For the many children who experience relapses of their malignant solid tumors, usually after very intensive first-line therapy, curative treatment options are scarce. Preclinical drug testing to identify promising treatment elements that match the molecular make-up of the tumor is hampered by the fact that (i) molecular genetic data on pediatric solid tumors from relapsed patients and thus our understanding of tumor evolution and therapy resistance are very limited to date and (ii) for many of the high-risk entities, no appropriate and molecularly well-characterized patient-derived models and/or genetic mouse models are currently available. However, recent regulatory changes enacted by the European Medicines Agency (class waiver changes) and the maturation of the RACE for Children act with the FDA, will require a significant increase in preclinical pediatric cancer research and clinical development must occur. We detail the outcome of a pediatric cancer international multistakeholder meeting whose output aims at defining an international consensus on minimum preclinical testing requirements for the development of innovative therapies for children and adolescents with cancer. Recommendations based on the experience of the NCI funded PPTP/C (www.ncipptc.org) and the EU funded ITCC-P4 public private partnership (https://www.itccp4.eu/) are provided for the use of cell-based and mouse models for pediatric solid malignancies, as well as guidance on the scope and content of preclinical proof-of-concept data packages to inform clinical development dependent on clinical urgency. These recommendations can serve as a minimal guidance necessary to jumpstart preclinical pediatric research globally.

Introduction

The 5-year survival rate of children and adolescents with cancer has plateaued at 80% in high-income countries, and cancer remains the primary cause of death by disease after age 1. There is an urgent need to introduce innovative therapies to cure more children and to do so with reduced long-term toxicity. Over the past 20 years, European and US regulatory initiatives have incentivized the pharmaceutical industry to develop medicines in the pediatric population (1, 2), although the impact of these incentives has been limited at best in pediatric oncology (3). Currently, the decision to evaluate a new anticancer drug for children with cancer is typically driven by a drug's adult indication rather than by its mechanism of action (MOA) and thus biological relevance to childhood cancer. For example, lung cancer does not occur in children; however, ALK is altered not only in lung cancer, but in numerous pediatric malignancies such as neuroblastoma and anaplastic large cell lymphoma (4).

Recently, the regulatory environment changed significantly. In 2015, the European Medicines Agency revised the class waiver list, and as a result, the number of adult cancer indications for which companies can apply for an automatic waiver for pediatric development was significantly reduced (5). However, concerns were raised over the impact of this revision to incentivize biology-driven development of anticancer drugs in the pediatric population (6). In August 2017, the RACE for Children Act was signed into law as Title V of the US FDA Reauthorization Act to amend the Pediatric Research Equity Act (PREA; 21 U.S. Code 355c) and entered into force in August 2020 (7). This act requires pediatric evaluation of new molecularly targeted drugs "*intended for the treatment of adult cancers and directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer.*" With this more favorable regulatory environment there must and will be an increase in science-driven pediatric development of anticancer drugs. Recently, knowledge of the biology and heterogeneity of pediatric malignancies has rapidly increased (8, 9), and there is a correspondingly heightened need for thorough preclinical data using better predictive models to develop drugs targeting mechanisms specific to pediatric malignancies.

Research in this space is hampered by the lack of widespread access to comprehensive, well-validated preclinical tools, notably relevant animal models that effectively capture the molecular heterogeneity of pediatric cancer from treatment naïve and relapsed patients. Furthermore, international standards on the development of preclinical data packages necessary to inform clinical decisions do not exist and would greatly facilitate the identification and prioritization of promising agents. Following an international multistakeholder consensus meeting, we propose minimum preclinical testing requirements for

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the development of innovative therapies for children and adolescents with cancer.

Materials and Methods

As part of the Innovative Therapies for Children with Cancer—Pediatric Preclinical Proof-of-Concept Project ITCC-P4 (https://www.itccp4.eu/; ref. 10), an Innovative Medicines Initiative 2 (IMI-2) project, a multi-stakeholder workshop was held in late 2018 to define an international consensus on minimum preclinical testing requirements for the development of innovative therapies for pediatric cancer. This meeting was co-organized with the NCI-funded Pediatric Preclinical Testing Consortium (PPTC; www.ncipptc.org; ref. 11), and was unique in that it brought together academia, industry, regulatory agencies and advocacy groups, the outcome of which is the basis for the recommendations.

Results

Current situation of preclinical testing in pediatric oncology drug development

Most preclinical models of pediatric cancer have been developed by academia, primarily from patient tumor material. As a result, models of pediatric cancer are typically decentralized and neither molecular characterization nor benchmarking to standard of care is consistent, limiting the utility of the models for thorough and rationale drug development. This is especially problematic for companies whose access to these models has been limited due to a myriad of factors. Further complicating matters is preclinical evaluation of anticancer drugs for pediatric indications has generally been anecdotic ("proof-of-concept," POC) rather than systematic.

For 10 years, the forerunner of the PPTC, the NCI Pediatric Preclinical Testing Program (PPTP), attempted a systematic approach to evaluating anticancer compounds using a panel of *in vitro* and *in vivo* models (12). The PPTP tested >60 anticancer compounds as single agents or in combination studies. The seven lessons learnt from PPTP are described in **Table 1**. False-positive results (i.e., preclinical activity without subsequent clinical activity) need to be carefully studied to increase the predictive power of future testing.

Table 1. Seven lessons from the Pediatric Preclinical Testing Program.

1	PDX models can be developed that adequately represent the genomic heterogeneity of pediatric cancers.
2	Essential to address drug scheduling and systemic exposure for accurate clinical translation.
3	Genomic information can be useful for predicting drug sensitivity (BRAF, PALB2, etc.).
4	Models can identify novel efficacious agents (selumetinib, eribulin, OBI-3424) and combinations (eribulin/irinotecan, temsirolimus/cyclophosphamide-vinca, etc.).
5	False-positive results (i.e., preclinical activity without subsequent clinical activity) need to be carefully studied to increase the predictive power of future testing.
6	Single mouse designs will allow more rapid/efficient screening of single agents and possibly combinations if the individual drugs have limited single agent efficacy
7	For screening and orthotopic models, "blinded" experimental design is essential.

Models to be used

The projected value and limitations of current preclinical models are summarized (**Table 2**). Experts concluded that subcutaneous or orthotopically implanted patient-derived xenografts (PDXs), derived from tumors at diagnosis, relapse or following rapid autopsy, as well as genetically engineered mouse models (GEMMs) are the preferred model systems today. Moreover, it is a key to capture intertumor heterogeneity through a saturating repertoire of models/entity rather than relying on "representative models" of a disease (13, 14). Metastatic models should be considered specifically for therapeutics with a MOA targeting the metastatic process; however, such models remain limited. Beyond intrinsic tumor heterogeneity, relapsed disease models are considered important for representation of the evolving tumor milieu and a PDX panel consisting of primary and relapsed tumors is recommended. Although PDX models can impart human context for tumor cell autonomous targets, GEMMs provide an immune-competent setting may confer a more durable desmoplastic component, and enable precise interrogation of discrete genetic events that occur in cancer. Moreover, the use of GEMM-derived tumor material can enable higher throughput testing via syngeneic allografts or in the *ex vivo* setting. Pediatric organoids may also prove valuable for *ex vivo* studies, with their inherent recapitulation of tumor heterogeneity and 3D structure, but translatability is uncertain to date (14). Organoids lack tumor–stroma interaction and are developed mainly from epithelial tumors at this time. Despite the advances in organoid technology, comprehensive 2D cell line panels retain utility, especially if large panels reflective of intertumor heterogeneity and molecular subgroups are used. Other models such as zebrafish may have value for the interrogation of specific MOA, though not enough data exist to definitively assess their translatability (15).

Preclinical evaluation for brain tumors

The preclinical evaluation of treatment innovations for patients with brain tumors poses additional challenges because most drugs (>90%) are developed to not penetrate the brain to prevent neurotoxic side effects. A misconception that brain tumors typically show a disrupted blood–brain/blood–tumor barrier in all parts of the tumor is not backed up by clinical experience, that is, many drugs that show sufficient plasma levels do not reach clinically relevant exposure in brain tumors, especially in the infiltrative zone that is thought to often form the basis for relapses, particularly for high-grade gliomas. This key challenge must be addressed in the minimal preclinical data package to assess a novel therapeutic concept for neurooncology.

There is utility in using orthotopic brain tumor models beyond blood–brain barrier concerns, based on the very specific microenvironment that brain tumors require, and their tropism toward the CNS. As a matter of practicality, the experts concluded that *in vivo* testing in subcutaneous flank models may precede testing in orthotopic brain tumor models as a POC for tumor target relevance and efficacy, unless the MOA of the compound calls for direct testing in an orthotopic setting. It was further concluded that for orthotopic models both event-free survival as well as tumor response as assessed by serial *in vivo* imaging (e.g., by MRI, bioluminescence or PET-CT) were suitable efficacy endpoints, the latter being preferable to monitor objective response rates. Furthermore, pharmacokinetic and pharmacodynamic measurements should ideally occur in an orthotopic setting. There was agreement that negative orthotopic efficacy data should preclude moving forward into a clinical trial. In summary, there was consensus on the mandatory use of several different orthotopic models (preferably a combination of genetically engineered mouse models and PDXs, and preferably utilizing serial *in vivo* imaging) as part of the minimally recommended preclinical dataset for neurooncology indications.

Table 2. Models for pediatric preclinical testing.

	Pros for improving clinical predictability	Issues	Recommendation
In vivo			
PDXs	– Recapitulates heterogeneity of the patients' tumor – Relapse models enable study of tumor evolution – Orthotopic models for brain tumors	Tumorigenicity varies according to histology limited utility for IO compound testing; limited microenvironment context	Mandatory
Non-brain orthotopic models	– Reflects tumor microenvironment and supports metastasis (e.g., neuroblastoma) – successful engraftment rate higher	Model optimization required	Optional
Metastastic models	– Mechanism of action dependent, such as prevention of metastases	– No evidence of clinical predictability – Reproducibility concerns	Recommended with regard to the mechanism of action, if models are available
GEMM	– Immune-competent – Immune and stromal components – Interrogation of specific genetic events	– Lacks heterogeneity of patient tumor – May present cross-species challenges, particularly for biologics	Recommended when genetic drivers are defined in a tumor segment
Zebrafish	– Adult fish: good models for metastasis and angiogenesis – GEMM fish: good models for mechanism of action/on target activity – PDX fish: good models for medium throughput drug screens	Technical issues: larvae versus adult fish, sufficient tumor growth	Optional and translatability to be defined
Other in vivo models	– Large syngeneic models: endogenous tumors in dogs/pigs	– Cost – Experimental tractability and translatability – Drug activity concerns (e.g., antibodies might not work across species)	Optional
In vitro	**Pros for improving clinical predictability**	**Issues**	**Recommendation**
Organoids	– Screening of larger compound panels (prior to mouse PDX model) – Representation of heterogeneity and 3D tumor biology	– Relevance to primary tumors – Experimental reproducibility/ reliability – Not well suited for antibody evaluation	Optional – Could support decision making for tumor types where options are limited (e.g., no PDX)
Other: – 2D – 3D models (spheroids and soft agar) – Thick slice/organotypic – Chick chorioallantoic membane (CAM) assay	– Panels may represent disease/genetic segments underrepresented by in vivo models.	– Translatability	Optional

Abbreviations: GEMM, genetically modified model; PDXs, patient-derived xenografts.

Preclinical evaluation of immunooncology compounds

Immuno-oncology (IO) agents of potential interest for pediatric preclinical testing are divided into two primary groups: IO agents that enhance adaptive immune responses to tumors (e.g., immune checkpoint inhibitors), and IO agents engineered against specific antigens expressed by cancers as exemplified by T-cell bispecific antibodies (TCB), chimeric antigen receptor (CAR) T cells, and antibody–drug conjugates (ADCs). Immune checkpoint inhibitors as a monotherapy appear to have a limited role for pediatric cancers (16–20) that likely reflects the low prevalence of T-cell infiltrate and low tumor mutational burden of childhood cancers and correspondingly low rate of tumor neoantigens (8). Notable exceptions to this limited activity include patients with rare germline mutations in mismatch repair genes, and patients with Hodgkin lymphoma (21, 22).

For engineered IO agents targeting specific antigens, a first requirement for their application for childhood cancers is identifying the tumors that preferentially express the antigen. It is relevant to explore specific pediatric tumors because they are often of embryonal origin and thus express proteins that are no longer relevant/expressed in differentiated tissues. The availability of gene expression databases allows a rapid assessment of mRNA expression (Supplementary Table S1). As engineered IO agents primarily target proteins expressed on the cell surface, and as gene expression at the RNA level does not faithfully mirror protein expression, it is important to develop a detailed understanding of the surface proteome/surfaceome across childhood cancer preclinical models and patient tumor samples and normal tissues. Nonprotein antigens should also be considered as they may also be clinically relevant (e.g., the GD2-targeted agent dinutuximab).

Candidate target antigens for childhood cancers can be credentialed through testing of either ADCs or TCBs in relevant pediatric cancer preclinical models. Methods for testing ADCs are the same as those for testing standard cytotoxic agents, as illustrated by testing of the anti-CD19 ADC coltuximab ravtansine (SAR3419) in pediatric ALL xenograft lines and the testing of the DLL3-targeted ADC rovalpituzumab tesirine in neuroblastoma xenograft lines (22,–24). Methods for

testing TCBs have been developed that use stem cell humanized NSG mice (25), and these can be applied for testing TCBs against relevant pediatric preclinical models, such as PDXs. For IO agents such as checkpoint inhibitors that promote the adaptive immune responses to tumors, GEMMs may generate POC data (26)

Methodology, data, and reporting standards for preclinical testing

It is imperative to generate scientifically sound and comprehensive preclinical data that facilitate the comparison of drugs being considered for evaluation in children, including combinations and conventional radiochemotherapy backbones. In addition to validated and robust platforms using molecularly characterized pediatric preclinical models, careful attention to study design and analysis is critical.

The two primary measures of efficacy used for preclinical testing are "time to event" and "tumor load" (see Supplementary Materials). Methods for assessing prolongation in time to event require defining "event," with the definition dependent upon the type of model being evaluated (subcutaneous tumors, orthotopic tumors, etc.). The ratio of time to event for treated versus control animals is independent of tumor growth rate when defining an event as a multiple of starting tumor volume (e.g., fourfold) and allows for comparison of results across models and experiments. Tumor load results can be categorized by objective response criteria that mirror clinical RECIST or RANO criteria (12). This presentation of agent activity enhances the translational impact of the data package by identifying agents inducing robust regression, with prolonged regression after cessation of treatment being particularly promising. Slowing down of tumor growth over control is, in most cases, insufficient for advancement (as it would be considered inadequate in patients). Statistical significance between treated and control groups for the distribution in time to event or for tumor volume at a defined time point during the experimental phase is determined using standard methods such as the Gehan–Wilcoxon test or RM-ANOVA (preferred "gold standard," with the caveat that a statistically significant difference in preclinical experiments may represent a small treatment effect that is unlikely to imply clinical activity). Interpretation of testing results of experimental agents is facilitated by comparisons with levels of activity of standard agents in the same models.

The Single Mouse Trial (SMT) format uses a single mouse per model and treatment arm, thereby enabling the investigation of efficacy in substantially larger panels of well-characterized models (27, 28). SMTs facilitate the identification of biological factors that may influence response to the tested agent (29, 30). An SMT can optimally support efficacy testing across a panel of tumors that reflect the heterogeneity of a disease in children. Historically, data were generated with 40 to 100 models and up to 62 treatment arms (31, 32). A minimal panel size of 10 models seems to be a fair assumption to mirror inter- and intrapatient heterogeneity. The proposed approach to SMTs focuses on the ability of the tested agents to induce regressions for two reasons: Large treatment effects can be reliably detected and agents able to robustly induce regressions are of greatest value in the childhood cancer clinical setting. The experts concluded that drugs yielding tumor growth delay that do not minimally reach the level of stable disease are of limited utility. A recent publication (33) comparing colorectal patient response to cetuximab to an evaluation of cetuximab across a molecularly characterized panel of colorectal PDX models that faithfully represent tumor heterogeneity showed agreement in response to drug treatment using an SMT. To establish *in vivo* efficacy, this SMTl used three vehicle-treated tumor-bearing mice plus one tumor-bearing mouse per drug treatment. Using this approach, the single mouse PDX trial was a reliable predictor of clinical response. It is worth noting that the authors evaluated 79 PDX tumors representative of the five major known drivers of colorectal cancer and the 6% overall response rate to cetuximab (comparable with clinical reports), was driven by activity only in the subset of KRAS and BRAF WT tumors. In contrast, pediatric tumors typically have far fewer drivers per tumor type (often just a single driver, e.g., a fusion protein) and we are confident that ITCC-P4's goal of upwards of 40 PDX models per tumor type should be more than saturating for the majority of the most common pediatric malignancies.

Table 3. Preclinical proof-of-concept package modules.

Module 1: Target status and patterns in clinical series
Module 2: Molecular validation of target dependence *in vitro models*
Module 3: Molecular validation of target dependence *in vivo* models
Module 4: Drug efficacy patterns *in vitro* models
Module 5: Drug efficacy patterns *in vivo* models
Module 6: Biomarkers (patient selection/PD)
Module 7: Resistance mechanisms
Module 8: Combination testing

Sharing data with the research community is crucial and includes accessibility of the data (access of raw and processed data) and a detailed description of the statistical analyses and evaluation criteria. To this end, visualization and data sharing tools are currently being implemented (e.g., through https://r2.amc.nl and http://www.ncipptc.org/genomics). Finally, feedback from clinical data is an important element of preclinical testing, and preclinical datasets should be retrospectively re-evaluated using clinical data (reverse translation).

Recommendations for preclinical POC data packages

Consistency in preclinical evaluation across drugs and across pediatric tumor types will facilitate prioritization for pediatric clinical development of promising agents, and our experts developed guidance for "Recommended POC data packages" (cancer immunotherapy was excluded here due to time restrictions). We used the description of preclinical POC data packages (separated into data modules developed from the SIOP Preclinical Testing Taskforce (**Table 3**; ref. 34). For drugs selectively targeting kinase-fusions, it was agreed that identification of the kinase-fusion in clinical series of a pediatric tumor type was enough to support clinical testing of the drug. For drugs aimed at nonfusion targets, we agreed on the following three determinants:

Step 1, clinical urgency of the tumor type;
Step 2, availability of profiling data of a series of tumor samples;
Step 3, availability of relevant *in vivo*.

We defined cutoff values for the different subsets in each determinant; see **Table 4** for details.

For each resulting category, we then decided on the extent of POC modules needed for the "Recommended POC data package" (**Table 4**). In some situations, preclinical POC testing is currently not possible due to lack of tumor series with molecular profiling or insufficient availability of relevant models. The level of clinical urgency should influence the extent of POC data packages, for example, for diseases with a very good prognosis, a deeper preclinical POC data package is recommended. The actual extent of the POC data package then depends on the availability of relevant preclinical models.

Table 4. Guidelines for recommended extent of preclinical POC testing packages.

Step 1 Clinical urgency	Step 2 Tumor sample series with molecular profiling	Step 3 Matching vivo model availability	Recommended POC package (for kinase fusion targets consider clinical development without preclinical POC testing[a])
High (<40% survival)	**Insufficient** (<20 samples)	**n/a**	**POC not possible**[b]
	Sufficient (>20 samples)	**No models**	**POC not possible**[b]
		Sufficient models (>1 xeno/PDX, >1 GEMM)	**Mod. 1** Target patterns **Mod. 4** Efficacy vitro[c] **Mod. 5** Efficacy vivo[c]
Medium (40%–80% survival)[d]	**Insufficient** (<100 samples)	**n/a**	**POC not possible**[b]
	Sufficient (>100 samples and >10 in each biological subset)	**No models**	**POC not possible**[b]
		Sufficient models (>1 xeno/PDX, >1 GEMM)	**Mod. 1** Target patterns **Mod. 2** Molecular target validation vitro **Mod. 4** Efficacy vitro[c] **Mod. 5** Efficacy vivo[c] **Mod. 8** Combinations vitro
Low (>80% survival)	**Insufficient** (<100 samples)	**n/a**	**POC not possible**[b]
	Sufficient (>100 samples and >10 in each biological subset)	**No models**	**POC not possible**[b]
		Limited models (1–5 xeno/PDX, 1 GEMM)	**Mod. 1** Target patterns **Mod. 2** Molecular target validation vitro **Mod. 4** Efficacy vitro[c] **Mod. 5** Efficacy vivo[c] **Mod. 8** Combinations vitro
		Sufficient models (>5 xeno/PDX, >1 GEMM)	**Mod. 1** Target patterns **Mod. 2** Molecular target validation vitro[d] (**Mod. 3** Molecular target validation vivo)[d] **Mod. 4** Efficacy vitro[c] **Mod. 5** Efficacy vivo[c] **Mod. 8** Combinations vitro

Abbreviations: GEMM, genetically modified model; Mod, module; POC, proof-of-concept; PDX, patient-derived xenograft; xeno, xenograft.
[a]For kinase fusion genes consider clinical development without preclinical POC testing.
[b]Develop sample series and vivo models.
[c]Module 4 "vitro efficacy testing" used to gate performing module 5 drug efficacy testing in vivo models.
[d]For low urgency disease need to perform module 3 "Target validation in vivo models" is gated on results from module 2 "Molecular target validation *in vitro* models."

With regards to POC module 4, the participants agreed that *in vitro* testing should not factor heavily in determining preclinical POC, but it could be useful as a decision gate for the more complicated module 5 *in vivo* efficacy testing across a saturated repertoire of models representing the disease heterogeneity.

Discussion

To accelerate the development of innovative therapies for children with cancer in the changing regulatory environment, easy access to biological information on pediatric tumors and to high quality pediatric preclinical testing must increase. The capacity to generate relevant preclinical information using comprehensive panels of well characterized pediatric tumor models is a key to prioritizing anticancer drugs for pediatric development. At the same time, this should support academic research to understand the biology of pediatric malignancies, to identify mechanism of sensitivity and resistance, and to inform treatment combinations, including combinations with current standard of care. In addition, identification of pathways specific to pediatric tumors will support the development of agents specific to pediatric cancer.

Currently, there are two publicly funded consortia to generate preclinical pediatric cancer data: ITCC-P4 and PPTC. The ITCC-P4 consortium (https://www.itccp4.eu/) was created to address many of the topics identified in this symposium. This precompetitive, preclinically focused public private partnership brings together academia, industry, and contract research organizations to develop a comprehensive translational research platform of molecularly characterized pediatric solid tumor PDXs (aiming at 40 different PDXs per tumor type, including orthotopic brain tumor models for ten histologies with highest clinical need), organoids and GEMMs. Underpinning the ITCC-P4 platform is a powerful, custom-built informatics suite that enables data handling, visualization and interpretation (https://r2.amc.nl). ITCC-P4 testing also supports biomarker-driven patient tailoring, that is, the right drug for the right patient, based on the tumor's molecular profile. The incorporation of GEMMs allows for testing of drugs in tumors within their "naturally" occurring primary location. In addition, humanized PDXs of neuroblastoma and rhabdomyosarcoma are under development as novel preclinical tools for evaluation of immuno-oncology agents. Compound testing, including disease-relevant standard-of-care drugs and targeted agents, began in 2020. By early 2022, the publicly funded portion of ITCC-P4 will end, and the platform will be available to researchers worldwide.

The NCI has supported a pediatric preclinical testing program since 2004, initially through the PPTP, and since 2015 through the PPTC (www.ncipptc.org), with approximately 130 agents from more than 60

companies and representing a broad range of MOA have been tested (>90 publications are available). The use of a model material transfer agreement that is accepted by all PPTP/PPTC institutions has allowed testing to proceed in a timely manner and not be delayed by extended negotiations. PPTP testing typically involved agnostically evaluating novel single agents across a panel of approximately 40 to 50 xenografts reflecting a range of genomically characterized solid tumors and ALL (https://pedcbioportal.org/study/summary?id = pptc). Activity signals were often pursued with dose–response and/or combination testing. Testing through the PPTC has been more hypothesis-driven, with models selected on the basis of the responder-hypothesis for the agent under evaluation. The genomic data facilitate the selection of models for testing against specific targeted agents and help to relate the preclinical testing results to the clinical context. An important consideration is the ability of agents to induce tumor regression in prioritizing agents or combinations for evaluation in children. Several pediatric clinical trials have been influenced by PPTP/PPTC, including the rationale for phase 3 studies of selumetinib for low-grade glioma and of temsirolimus for rhabdomyosarcoma (35, 36). Negative findings from the PPTP/PPTC have also contributed to pediatric drug development by allowing clinical investigators to focus on more promising research.

In the evolving regulatory environment, the capacity to generate relevant biological and preclinical information is essential to the development of new anticancer assets for the pediatric population. International collaboration for global drug development is needed to best address innovation for the treatment of rare cancers in children and adolescents. International standards on the development of preclinical data packages necessary to inform clinical decisions would greatly facilitate the identification and prioritization of promising agents. The proposed requirements, if adopted, have the potential to impact significantly the movement of promising agents into clinical development.

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Authors' Contributions

G. Vassal: Conceptualization, resources, writing–original draft, writing–review and editing. **P.J. Houghton:** Conceptualization, resources, writing–original draft. **S.M. Pfister:** Conceptualization, resources, supervision, writing–original draft. **M.A. Smith:** Conceptualization, resources, methodology, writing–review and editing. **H.N. Caron:** Conceptualization, resources, supervision, writing–original draft. **X.–N. Li:** Conceptualization, resources, writing–original draft. **D.J. Shields:** Conceptualization, resources, writing–original draft. **O. Witt:** Conceptualization, resources, writing–original draft. **J.J. Molenaar:** Conceptualization, resources, writing–original draft. **S. Colombetti:** Conceptualization, writing–original draft. **J. Schüler:** Conceptualization, resources, methodology, writing–original draft. **L.F. Stancato:** Conceptualization, resources, supervision, writing–original draft, writing–review and editing.

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