Crossing Oceans: Preclinical Collaboration to Improve Pediatric Drug Development

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overview

Changes in the regulatory environment affecting pediatric cancer drug development in the United States and the European Union provide unprecedented opportunity to advance the concept of precision medicine to children with cancer. Increasing evidence suggests that new drugs and biologic products directed at molecular targets presumed to be etiologically associated with many adult cancers may well provide therapeutic options for selected subsets of children with cancer despite their histologic and biologic differences. Regulatory requirements for early evaluation of appropriate new drugs for children based on their molecular mechanism of action, rather than the specific clinical indications for which they are developed and/or approved, will shorten the unacceptable time lag between first-in-human and first-in-children studies. The relative scarcity of pediatric patients eligible for biomarker-directed studies and the ever-expanding compendium of new targeted agents mandate rational, science-based decision-making in selecting and prioritizing appropriate drugs to study early in development. A critical component of the evidence base in such decision-making includes preclinical testing of relevant drugs in pediatric tumor-specific in vitro and in vivo models. Established preclinical testing programs with academic investigator–industry collaborations are actively engaged in such activities. International collaboration is required to address the resource constraints and increasing number of potential products to be tested in a timely, efficient, nonduplicative, and cost-effective manner.

BACKGROUND AND CASE STATEMENT: THE EVOLVING REGULATORY ENVIRONMENT

Despite the substantial advances in childhood cancer outcomes during the past 5 decades, cancer remains the leading cause of death from disease among children, largely owing to the initial refractoriness of some cancers or the development of resistance mechanisms and disease recurrence.[1,2] Although the current overall 5-year survival rates approach 85%, the cost of cure is high, because 30% to 50% of long-term survivors experience serious long-term, life-altering, and life-threatening sequelae.[3,4] The need for more effective and less toxic drugs for childhood cancer remains substantially unmet. Cancer drug development for children has largely leveraged adult cancer drug discovery and development; however, the demonstration of effectiveness and approval for use of new anticancer agents for children has lagged seriously behind development and approval of new drugs for cancers that occur predominantly among adults. A recent report demonstrated a median lag time from first-in-human studies of those new agents ultimately approved by the U.S. Food and Drug Administration (FDA) during the period from 1997 to 2017 to first-in-child studies of 6.5 years (range, 0–28 years).[5] The explanation for the delay is multifactorial but attributable only to a minimal extent by a scientific rationale for why a drug should not be evaluated with children. In both the United States and the European Union, drug development for children is subject to legislation that was intended to foster and support the development and ultimately approval of effective new drugs for children. The effect of this legislation on the timely assessment and approval of effective new drugs for children has been markedly more obvious in nearly all clinical conditions compared with cancer.

The Pediatric Research Equity Act was enacted in 2003 and authorizes the FDA to require pediatric assessment of efficacy and safety of any new drug that is the subject of a New Drug or Biologics Licensing Application for any indication that also exists for children unless the requirement is waived for study feasibility, likelihood of use, or toxicity concerns; products developed for orphan-designated indications are exempt from the Pediatric Research Equity Act requirements.[6] There have never been Pediatric Research Equity Act–required studies of an oncology drug for children. A pediatric exclusivity provision was enacted under the Food and Drug Administration Modernization Act in 1997 and reauthorized as the Best Pharmaceuticals for Children Act in 2002, which provides a financial incentive to industry sponsors for voluntarily evaluating drugs among the pediatric population through fulfillment of a Written Request.[7]

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Accepted on February 28, 2020 and published at ascopubs.org on March 24, 2020: DOI https://doi.org/10.1200/EDBK_278893

PRACTICAL APPLICATIONS

- Changes in the regulatory environment in the United States and European Union have the potential to advance the concept of precision medicine to children with cancer.
- Preclinical testing of targeted drug products developed for cancers that occur among adults and potentially relevant to cancers that occur predominantly among children can contribute to the science-based rationale for pediatric assessment.
- Functional but insufficiently resourced industry–academic investigator collaborations exist in the United States and European Union to address this need.
- The large number of molecules in development for which evaluation with children may be appropriate and the existing resource limitations mandate timely, efficient, and cost-effective preclinical testing.
- International collaboration is necessary to provide acceptable preclinical data packages to inform decisions regarding the justification and prioritization of pediatric clinical evaluations.

Both laws were permanently reauthorized in 2012. The European Pediatric Regulation (EC 1901/2006), which came into force in 2007,[8] requires pharmaceutical companies seeking a marketing authorization for a new drug or a new indication for adults to create a pediatric development program in the form of a Pediatric Investigation Plan. The regulation allows for waivers of pediatric studies by the Pediatric Committee of the European Medicines Agency based on adult indication, safety, and potential efficacy. The regulation provided for a list of class waivers serially modified in 2008, 2010, 2015, and 2017. Removing class waivers permits changes to the requirement for pediatric assessment from merely clinical indication to mechanism of action.

Section 504 of the Food and Drug Administration Reauthorization Act of 2017 amended the Pediatric Research Equity Act in Section 505B of the Food, Drug, and Cosmetic Act[9] to require the sponsor of an original New Drug Application or Biologics Licensing Application submitted on or after August 18, 2020, to conduct an early pediatric clinical trial of a new drug, intended for the treatment of an adult cancer and directed at a molecular target that the FDA determines to be substantially relevant to the growth or progression of a pediatric cancer to yield meaningful data regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling.

Advances in the understanding of the molecular biology and genetic epidemiology of human cancer have transformed the overall paradigm for cancer drug discovery and development.[10] The advent of molecularly targeted drugs has advanced the concept of precision medicine in oncology. Although the science of precision medicine development is less mature for children, increasing evidence implicates established molecular drivers of certain cancers prevalent among adults as having a causative role in childhood cancers across a spectrum of histologies.[11,12] The evidence for considering that a specific molecular target may be substantively relevant to convey the same vulnerability to a molecule directed at that target and effective in a cancer among adults varies considerably among specific targets and across a variety of tumor types. The relevance of a target and decision-making about early investigation of drugs directed at a target are further complicated by the differences in the degree of unmet clinical need across pediatric cancer diagnoses. There is, therefore, a need to critically evaluate and expand, when possible and necessary, the evidence base supporting the concept that a molecular target is relevant to the etiology or progression of a pediatric cancer and that a new drug product directed at such a target may exert a deleterious effect on a pediatric cancer.

The FDA and the National Cancer Institute (NCI) were legislatively mandated to create an initial list of relevant molecular targets, which was published on the FDA website in August 2018, consists of more than 200 distinct entities, and is likely to change with emerging scientific discovery.[13] The Relevant Pediatric Molecular Target list is intended to guide rather than dictate decision-making related to development of specific targeted drugs for children based on molecular mechanism of action. This list is essentially based on peer-reviewed publications and publicly available databases of broad pediatric cancer genomic sequencing results demonstrating associations with both hematologic and solid tumor malignant neoplasms.[13] The framework used to construct the list included the following: genomic data indicating an association of a specific gene perturbation/mutation, deletion, copy number variation, or protein overexpression in one or more pediatric cancers irrespective of frequency; functional genomic evidence that a gene defect relates with another cellular pathway to result in synthetic lethality; nonclinical evidence or adult clinical evidence that target modulation effects tumor cell sustainability or growth; and the existence of predictive and/or response biomarkers. Target actionability and the consequence of target inhibition in specific pediatric cancers is incomplete. The preclinical evaluation of specific target-directed therapeutics using pediatric-specific models (e.g., cell lines and organoids for high throughput in vitro screening, patient-derived xenografts [PDXs], orthotopic xenografts, and human-engineered xenografts, particularly

for targets applicable to immune-directed therapy approaches) can add substantially to the existing evidence base of target relevance and rational decision-making regarding the appropriateness of early pediatric clinical assessment. Many established targets in tumor cells, innate immune cells, and other cellular elements of the tumor microenvironment may feasibly direct drug development strategies, including early evaluation, and provide a rationale for therapeutic intervention. Practically speaking, this creates many therapeutic possibilities that greatly exceed the number of children both within specific and across cancer diagnoses that can be allocated to specific biomarker-enriched populations for clinical trials in which new targeted drugs can be adequately tested for effectiveness and safety. Cancer drug development is a global enterprise, and early assessment of relevant new drugs for children mandates international coordination and clinical trial collaboration, given the increasingly small number of patients available for clinical trials, particularly in the context of biomarker-directed trials. Building the scientific rationale for assessing specific new drugs for children requires a strengthened evidence base achievable in part through robust preclinical testing of drug products of interest that similarly mandates international collaboration.

SETTING THE STAGE FOR INDUSTRY COLLABORATION

The hurdles to developing drugs specifically for pediatric patients with cancer (listed in Table 1) are well known and have remained relatively unchanged for years.[14] However, as described above, the evolving regulatory environment creates an important opportunity for the biopharmaceutical industry (henceforth "industry") to markedly increase pediatric oncology research and development, commensurate with its position as the major funder of biomedical research in the United States.[14,15] Industry, with clinical pipelines well stocked with targeted agents with unlocked pediatric potential, must be an active participant in identifying safer and more effective therapies for children with cancer, but how? Unfortunately, even with a supportive regulatory environment, the path toward the development of compelling preclinical data packages in support of clinical development is muddled at best. Unlike counterparts in adult cancer development, there is a paucity of tools readily available to the industry researcher interested in assessing drug activity in the pediatric setting. Outside of the NCI-funded Preclinical Pediatric Testing Consortium (PPTC),[16] which provides access to efficacy testing in a wide range of pediatric cancer in vivo models (albeit with limited budget and capacity), options are extremely limited, and what is available is often scattered across academic centers globally. In a recent survey of industry conducted by the ITCC-P4 (Innovative Therapies for Children With Cancer Pediatric Preclinical Proof-of-Concept Platform) consortium, most of the industry representatives cited the lack of available, well-characterized, and relevant pediatric models as a major hurdle for pediatric development (pediatric evaluation not being a company priority and insufficient resources/funding were also cited).[17] Furthermore, the expertise (and frankly, the will) required to efficiently develop drugs for children with cancer is often lacking across industry. As a result, it is imperative that stronger ties develop between industry and academia to effectively address the unmet medical need in pediatric oncology, particularly in the relapsed/refractory setting. The development of robust preclinical data packages matching tumor vulnerabilities with targeted agents is a necessary first step in addressing this need.

As the molecular drivers of pediatric tumors are identified, opportunities will continue to arise to match targeted therapies with corresponding pediatric tumor drivers.[18,19] Examples such as dasatinib in Philadelphia chromosome–

TABLE 1. Challenges to Pediatric Cancer Drug Development

Pediatric Challenge	Practical Considerations
Most prevalent of the known driver mutations may be the nondruggable fusion oncoproteins/transcription factors	Bold, fresh approaches to drug targeting needed
Lack of clarity of short-term/long-term developmental consequences of signaling pathway disruption in young children	Clinical data must be generated and evaluated
Concerns about off-target toxicities of agents with less than highly specific activity	Clinical data must be generated and evaluated
Formulation concerns	Begin formulation discussions much earlier in development.
Limited number of patients—must prioritize	Preclinical data key to decision-making and global cooperation for clinical evaluation
Limited number of patients—not profitable or attractive to industry	Patient need, not market size, needs to be a driver; additional incentives to sponsors?
Development expertise primarily found within academic centers; industry has little experience	Stronger industry ties with academia

positive acute lymphoblastic leukemia (ALL); crizotinib treatment of anaplastic lymphoma kinase–mutated neuroblastoma and anaplastic lymphoma kinase fusion–positive anaplastic large cell lymphoma and inflammatory myofibroblastic tumor; and larotrectinib in neurotrophic tyrosine receptor kinase fusion–positive pediatric tumors reduce to practice the concept of precision medicine in pediatric oncology and offer hope for the future while also highlighting collaborative efforts between industry and academia.[20-22] Unfortunately, the pace of discovery of tumor drivers is clearly outstripping industry's development of potentially promising agents, creating a deadly clinical gap. To fill this gap, there is a recent and steady increase in collaboration between industry and the public sector (both academia and government) on the individual institution level all the way up to precompetitive public-private partnerships (PPPs), such as the ITCC-P4 consortium (explained in the next section) and a burgeoning PPP spearheaded by the Foundation for the National Institutes of Health. The unique challenges associated with pediatric drug development all but ensure that multistakeholder collaboration is required for success, and they provide the rationale for the importance of preclinical testing using pediatric-specific models for new drugs that may be potentially relevant (Table 1). Furthermore, fresh approaches to data sharing and transparency, a willingness to prioritize drugs for clinical development based on scientific merit, and a streamlining of the legal agreement/technology transfer process are all elements critical to advancing promising therapies to the clinic.

In an ideal world, pediatric cancer research would be best served in a precompetitive setting, whereby data generated are shared publicly; however, the desire to protect *current* intellectual property while ensuring that *future* intellectual property is secured is omnipresent across both industry and academia and can be a substantial barrier to collaboration. Unlike adult cancers, in which patient populations can run into the hundreds and even thousands, pediatric cancers are orphan diseases, and the corresponding market for treatment is exceptionally small. This creates an interesting paradox, whereby small patient populations can deter industry from clinical development, yet, when a positive development decision is considered, it may be held up by perceived or potential intellectual property considerations despite dealing with the same small population. Industry and academia must find common ground on the issue of intellectual property and concentrate on advancing a field that has been neglected for too long, particularly in the generation and sharing of preclinical data. Fortunately, the regulatory realities are encouraging industry to adjust pediatric development strategy (and, in some cases, develop a strategy), which will almost certainly fuel greater collaboration with academia. From any point of view, this development can only be viewed as a positive, especially as preclinical evaluation of promising drugs in industry pipelines, for which mechanisms of action may match known pediatric cancer vulnerabilities, remains one of the best options for identifying newer agents for clinical development (with the potential exception of immuno-oncology agents, for which there are few relevant preclinical pediatric models).

Clearly, academia is industry's best option for the expertise necessary to effectively identify and target pediatric tumor vulnerabilities. The payoff in terms of safer and more effective medicines from years of academic research will most likely be realized through a merging of the in-depth academic science with the drug development expertise of industry. For example, novel approaches to targeting "nondruggable" targets, such as fusions (e.g., EWS-FLI1), are more likely to arise out of academic rather than industry laboratories, where development timelines are hastened and the need for quick go/no-go decisions is greater. In cases such as these, leveraging academia's scientific know-how with industry's unique ability to identify and develop targeted agents is key to success and should result in compelling preclinical data packages that serve as substrates for clinical trial decisions. When used appropriately, preclinical data should help identify the best molecules to advance to clinical trials, which is of importance in pediatric development, in which the number of patients available for clinical trials is exceedingly small. From a clinical standpoint, many academic researchers are often associated with pediatric hospitals and are therefore able to move promising treatment options from bench to bedside in a way not easily accessible to industry; all that these researchers are lacking is systematic access to promising new therapies. These are just a couple of the many reasons why industry is beginning to develop deeper ties with the pediatric research community. This deepening relationship is already contributing to advances in the understanding of target biology in pediatric cancers (e.g., "target actionability reviews"),[23] led to the development of an international consensus on the depth and breadth of preclinical data required for moving a promising agent into pediatric clinical development,[24] and resulted in the creation of precompetitive PPPs that bring academia and industry together to identify promising drugs for children dying from cancer. Of note regarding PPPs is the formal voice given to the critical but often overlooked contribution of patient advocacy, which plays a vital role in building bridges to all stakeholders while maintaining a patient focus. Depending on how they are structured, PPPs can bring in government funding, further supporting the depth and breadth of the PPP (e.g., the E.U. IMI2 [Innovative Medicines Initiative 2] program). Overall, in the past few years, there has been an increase in pediatric clinical development across industry as a result of the growing number of collaborative efforts, and this trend must continue.

Between 2000 and 2015, two drugs from Eli Lilly and Company ("Lilly") were evaluated in the pediatric cancer setting. Since 2015, six targeted Lilly oncology agents (nearly one dozen clinical trials) have entered the clinic, with many of the trials enabled through collaboration with both academia and the NCI/PPTC. Underpinning many of these trials were preclinical data packages that suggested compelling preclinical activity and a mechanism of action deemed relevant to one or more pediatric cancers. A poignant example is the *CHEK 1* (checkpoint kinase 1) small molecule inhibitor prexasertib, currently in clinical testing for multiple pediatric malignancies (ClinicalTrials.gov identifiers: NCT02808650, NCT04095221, and NCT04023669). The collaborative development of prexasertib was a model of data sharing and transparency across multiple academic and government programs, which enabled rational, data-based decisions on progression to the clinic.[25] In the absence of extensive collaboration, which entailed co-development of robust preclinical data packages and the development of clinical protocols, it is unlikely that prexasertib would currently be in pediatric clinical testing.

The development of innovative therapies for children with cancer begins with the identification of tumor vulnerabilities that can be matched with corresponding targeted agents, with preclinical research serving as the bridge to the clinic. With so many agents currently in clinical development, preclinical pediatric data will continue to increase in importance as we search for the "best" molecules to advance to clinical trials. More than ever, success requires close, transparent collaboration between industry and academia, with completely transparent and open data sharing and communication, a willingness to challenge the old conventions, and a spirit of collegiality that will ultimately benefit our youngest patients with cancer.

E.U. PERSPECTIVE ON ACADEMIA–INDUSTRY COLLABORATION: DEVELOPMENT AND STATUS OF THE ITCC-P4

In 2017, the 5-year ITCC-P4 project was launched as part of the European IMI2 PPP, with the goal to build a sustainable preclinical testing platform in pediatric oncology for both commercial and academic use. This European project was designed to address the anticipated increased needs for pediatric preclinical evaluation to rationalize and facilitate prioritization of anticancer compounds for pediatric development within the new international regulatory environment. ITCC-P4 aims to provide quality-assured, upfront preclinical testing of novel mechanism of action–based compounds in a (saturating) repertoire of molecularly and pharmacologically well-characterized models to establish the basis for increasing therapeutic success of new drugs for children with solid tumors (and leukemias within a currently planned extension).

ITCC-P4 is a PPP with 14 academic institutions, five pharmaceutical companies (namely, Lilly, Roche, Pfizer, Bayer, and Pharma Mar), and three preclinical contract research organizations (namely, Charles River/Oncotest, XenTech, and EPO). The aim is to establish a representative collection of 400 PDX models of pediatric high-risk malignant solid and brain tumors, as well as leukemias, including a substantial proportion of models from relapsed cancers as well as genetically engineered mouse models for each indication (target: 15–20 models). A pilot evaluation of humanized mouse models of neuroblastoma and rhabdomyosarcoma is ongoing, as is a pilot evaluation on the development of organoids. All PDX models and their matching primary tumor samples and germline controls are fully molecularly characterized (low-coverage whole-genome and high-coverage whole-exome sequencing, RNA sequencing, methylation). Each model is further pharmacologically characterized by in vivo testing that includes two standard-of-care drugs, one standard-of-care combination, and six targeted agents, selected by entity experts. Testing is also being conducted in an organoid pilot study. As of December 2019, 150 models have been established and fully characterized. An open access repository of the data generated from the project via the IMI-funded R2 database has been established (https://hgserver1.amc.nl/cgi-bin/r2/main.cgi).

ITCC-P4 has also established a methodology for the systematic in silico evaluation of selected compounds and corresponding actionable molecular targets and pathways in the different pediatric solid tumor entities (target actionability reviews) before the in vitro and in vivo testing phases to comprehensively assess relevant literature and the existing (epi)genomic and transcriptomic data sets of all entities in question.[23] To facilitate the design of preclinical packages for regulatory purposes, a joint ITCC-P4 and PPTC multistakeholder workshop with representatives from regulatory networks and industry, patient advocates, and academia established an international consensus on minimum preclinical testing requirements for the evaluation of compounds in pediatric oncology.[24]

The ultimate goal is to deliver a sustainable high-quality preclinical testing platform with unique, fully characterized models and access to molecular information to serve the needs of both the biopharmaceutical industry as part of the new regulatory environment and the academic research community in an effort to continue to gain knowledge on pediatric malignancies and to drive pediatric oncology drug development through science in a much more rigorous and systematic way. Companies will have access to compound testing on ITCC-P4 models performed by contract research organizations as well as to biologic data and academic expertise to best design preclinical evaluation. Data generated by the contract research organizations for a company will be owned by the company, and data generated by

academic groups will be owned by those groups. In addition, companies and academic groups will be encouraged to share all or part of their testing results anonymously to continuously increase the value and relevance of the panel of models for the sake of science and relevance of any additional testing.

PEDIATRIC PRECLINICAL TESTING IN A PUBLICLY FUNDED ACADEMIC CONSORTIUM

The concept for a childhood cancers preclinical testing academic collaborative research initiative was formulated during and after an NCI and Children's Oncology Group–sponsored meeting cochaired by Drs. Peter Houghton, Malcolm Smith, and Peter Adamson in 2001.[26] The major outcome of the meeting was identification of the key scientific issues and infrastructural requirements to establish a program focused on testing novel anticancer agents in credentialed models of childhood cancers. The Pediatric Preclinical Testing Program (PPTP) was established in 2003 through an NCI federal contract with five testing sites in the United States and one in Australia. The program included a moderate-throughput in vitro cellular cytotoxicity screening program and PDX models of ALL, neuroblastoma, osteosarcoma, brain cancers, and soft tissue sarcomas. The PPTP evaluated 116 drugs during a decade, including standard-of-care drugs in the initial year of the program, to document sensitivity or resistance to commonly used chemotherapeutics. The PPTP was organized in a "top-down" manner, in which program leaders negotiated with industry to procure drugs, and testing was done in a blinded fashion by research sites in a model similar to a contract research organization.

The NCI subsequently moved from a contract to cooperative agreement funding mechanism, with investigative teams competing for histology-centric research testing. The resulting PPTC was established in 2015 and is organized as shown in Table 2.

The PPTC has tested 43 agents to date (several are still being tested). Unlike the PPTP, in which the majority of agents were screened for antitumor activity across all models in the program, the PPTC performs hypothesis-driven testing of agents, which means that many of the agents are tested in subsets of cases based on known molecular aberrations. To realize this goal, the PPTC sought to dramatically expand the number of PDX models available to the consortium, and investigators performed whole-exome sequencing, RNA sequencing, single nucleotide polymorphism arrays, and simple tandem repeat genotyping on 261 PDXs[27] available in the pediatric component of the cBIO Portal, which is housed alongside genomic data generated on 151 overlapping models from the PPTP (https://pedcbioportal.kidsfirstdrc.org/study/summary?id=pptc%2Cmixed_target_pptp). Although many of the agents tested in the PPTP/PPTC have been targeting specific activating mutations, allowing models to be selected based on exome sequencing data, increasing numbers of candidate molecules are immuno-oncology agents directed against plasma membrane proteins. Hence, RNA sequencing data, especially compared with normal tissues, is increasingly used to select models for testing. The PPTC is currently generating reverse-phase protein array data, data for cell membrane proteins utilizing sucrose gradient ultracentrifugation coupled to mass spectrometry, and whole-genome sequences from the osteosarcoma models.

Although the list is certainly not comprehensive, major take-home points from the PPTP/PPTC experience to date include the following:

- PPPs to engage pharmaceutical and biotechnology companies in testing their later-stage drugs in ultrarare childhood cancers can be accomplished with moderate throughput (approximately 10 compounds evaluated annually across a wide range of cancer).
- PDX models are robust for testing drugs targeting tumor cell intrinsic mechanisms on childhood cancer oncogenesis.
- The majority of the compounds screened across PDX models agnostic to a mechanism of action show little if any antitumor efficacy, which allows decision-making to limit additional time and effort in the pediatric setting for these agents so that investigators can focus on more promising agents.

TABLE 2. The Pediatric Preclinical Testing Consortium

Role	Institution	Principal Investigator
Coordinating Center	RTI International (formerly Research Triangle Institute)	Greg Gatto, PhD
Sarcoma and Renal Cancer	Greehey Children's Cancer Research Institute	Peter Houghton, PhD
		Raushan Kurmasheva, PhD
Neuroblastoma	Children's Hospital of Philadelphia	John Maris, MD
		Yaël Mossé, MD
Osteosarcoma	MD Anderson Cancer Center	Richard Gorlick, MD
		Andy Kolb, MD
Leukemia	Children's Cancer Institute Australia	Richard Lock, PhD
Brain Tumors	Northwestern University	Xiao-Nan Li, MD, PhD
Sponsorship and Funding	National Cancer Institute	Malcolm Smith, MD, PhD
		Beverly Teicher, PhD

- Multiple agents have proceeded to pediatric clinical testing based in part on PPTP/PPTC results, including selumetinib for low-grade gliomas; temsirolimus in combination with chemotherapy for rhabdomyosarcoma; OBI-3424 for T-cell ALL; lorvotuzumab mertansine (IMGN901); SNDX-5613 in mixed-lineage leukemia, rearranged ALL, and acute myelogenous leukemia; alisertib; and eribulin. The comparison of the level of preclinical activity to the activity of the agents observed among patients allows ongoing refinement of the use of preclinical data to prioritize agents for clinical testing.
- Comparative pharmacokinetics and pharmacodynamics between adult early-phase trials and pediatric cancer PDX mouse models can be critical to the success or failure of early-phase childhood cancer trials. A noted example was robust activity of the Aurora kinase A inhibitor alisertib in neuroblastoma and ALL PDX models, followed by limited single-agent activity in the clinic when the same dose and schedule modeled in the mice could not be achieved with patients.[28-30]
- Robust proteogenomic characterization of models allows for careful preclinical testing design, allowing for identification of molecular subsets that might be enriched in biomarker-directed clinical trials.

The pediatric cancer community has a paucity of credentialed models to properly study immuno-oncology agents. To address the anticipated increased bandwidth for preclinical testing of anticancer agents as industry plans for the Research to Accelerate Cures and Equity for Children Act, a broader PPP to further modernize and expand the PPTC model is under discussion through the Foundation for the National Institutes of Health and may be launched in 2020.

The challenges and opportunities provided by changes in the regulatory environment in both the United States and European Union and the reality of the global context of cancer drug development require international coordination and collaboration at multiple levels, including both clinical trial design and conduct and pediatric preclinical investigations. Meaningful transformation of regulatory change to improved therapeutics for childhood cancer mandates data sharing, rational priority setting, maximum efficiency, and avoidance of needless duplication. Collaboration across the Atlantic is mandatory.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_278893.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7-30.
2. Jemal A, Ward EM, Johnson CJ, et al. Annual report to the nation on the status of cancer, 1975-2014, featuring survival. J Natl Cancer Inst. 2017;109:djx030.
3. Landier W, Armenian S, Bhatia S. Late effects of childhood cancer and its treatment. Pediatr Clin North Am. 2015;62:275-300.
4. Bhakta N, Liu Q, Ness KK, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). Lancet. 2017;390:2569-2582.
5. Neel DV, Shulman DS, DuBois SG. Timing of first-in-child trials of FDA-approved oncology drugs. Eur J Cancer. 2019;112:49-56.
6. U.S. Food and Drug Administration. Pediatric Research Equity Act, Pub. L. No. 108–155, 117 Stat. 1936 (2003). www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077853.pdf. Accessed January 6, 2020.
7. U.S. Congress. Best Pharmaceuticals for Children Act (2002). www.congress.gov/107/plaws/publ109/PLAW-107publ109.pdf. Accessed January 6, 2020.
8. European Union. EU Regulation on Medicinal Products for Paediatric Use [Regulation (EC) No 1901/2006 of the European Parliament and of the Council of December 12, 2006 on Medicinal Products for Paediatric Use and Amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004e]. https://op.europa.eu/en/publication-detail/-/publication/2b688364-769b-4529-ab41-ba530e266466/language-en. Accessed January 14, 2020.
9. U.S. Food and Drug Administration. Food and Drug Administration Reauthorization Act (FDARA) of 2017. www.fda.gov/regulatory-information/selected-amendments-fdc-act/fda-reauthorization-act-2017-fdara. Accessed January 14, 2020.
10. Vogelstein B, Papadopoulos N, Velculescu VE, et al. Cancer genome landscapes. Science. 2013;339:1546-1558.

11. Gröbner SN, Worst BC, Weischenfeldt J, et al; ICGC MMML-Seq Project. The landscape of genomic alterations across childhood cancers [published correction appears in *Nature*. 2018;559:E10]. Nature. 2018;555:321-327.
12. Ma X, Liu Y, Liu Y, et al. Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. Nature. 2018;555:371-376.
13. U.S. Food and Drug Administration. OCE Pediatric Oncology Program. Relevant Pediatric Molecular Target List. www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology. Accessed January 14, 2020.
14. Adamson PC, Houghton PJ, Perilongo G, et al. Drug discovery in paediatric oncology: roadblocks to progress. Nat Rev Clin Oncol. 2014;11:732-739.
15. Dorsey ER, de Roulet J, Thompson JP, et al. Funding of US biomedical research, 2003-2008. JAMA. 2010;303:137-143.
16. Houghton PJ, Morton CL, Tucker C, et al. The pediatric preclinical testing program: description of models and early testing results. Pediatr Blood Cancer. 2007;49:928-940.
17. ITCC-P4. ITCC-P4 International Multistakeholder Workshop: Improving Pediatric Oncology Drug Development Through Preclinical Research. www.itccp4.eu/files/itcc-p4_international-workshop-2018-in-amsterdam.pdf. Accessed January 15, 2020.
18. Adamson PC. Improving the outcome for children with cancer: development of targeted new agents. CA Cancer J Clin. 2015;65:212-220.
19. Jones DTW, Banito A, Grünewald TGP, et al. Molecular characteristics and therapeutic vulnerabilities across paediatric solid tumours. Nat Rev Cancer. 2019;19:420-438.
20. Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. Lancet Oncol. 2012;13:936-945.
21. Bresler SC, Weiser DA, Huwe PJ, et al. ALK mutations confer differential oncogenic activation and sensitivity to ALK inhibition therapy in neuroblastoma. Cancer Cell. 2014;26:682-694.
22. Laetsch TW, DuBois SG, Mascarenhas L, et al. Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. Lancet Oncol. 2018;19:705-714.
23. Schubert NA, Lowery CD, Bergthold G, et al. Systematic target actionability reviews of preclinical proof-of-concept papers to match targeted drugs to paediatric cancers. Eur J Cancer. , In press.
24. Vassal G, Houghton PJ, Pfister SM, et al. International consensus on minimum preclinical testing requirements for the development of innovative therapies for children and adolescents with cancer. Mol Cancer Ther. In press.
25. Lowery CD, Dowless M, Renschler M, et al. Broad spectrum activity of the checkpoint kinase 1 inhibitor prexasertib as a single agent or chemopotentiator across a range of preclinical pediatric tumor models. Clin Cancer Res. 2019;25:2278-2289.
26. Houghton PJ, Adamson PC, Blaney S, et al. Testing of new agents in childhood cancer preclinical models: meeting summary. Clin Cancer Res. 2002;8:3646-3657.
27. Rokita JL, Rathi KS, Cardenas MF, et al. Genomic profiling of childhood tumor patient-derived xenograft models to enable rational clinical trial design. Cell Rep. 2019;29:1675-1689.
28. Carol H, Boehm I, Reynolds CP, et al. Efficacy and pharmacokinetic/pharmacodynamic evaluation of the Aurora kinase A inhibitor MLN8237 against preclinical models of pediatric cancer. Cancer Chemother Pharmacol. 2011;68:1291-1304.
29. Maris JM, Morton CL, Gorlick R, et al. Initial testing of the Aurora kinase A inhibitor MLN8237 by the Pediatric Preclinical Testing Program (PPTP). Pediatr Blood Cancer. 2010;55:26-34.
30. Mossé YP, Fox E, Teachey DT, et al. A phase II study of alisertib in children with recurrent/refractory solid tumors or leukemia: Children's Oncology Group Phase I and Pilot Consortium (ADVL0921). Clin Cancer Res. 2019;25:3229-3238.