

# Regulatory Reforms Offer Renewed Hope for Pediatric Cancer Patients Who are in Urgent Need for Therapeutic Innovations

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There is an unmet and urgent need to improve the survival outcomes of adolescents with cancer.<sup>[1-3,5-7,8-10,14,23,25-27,29,30]</sup> Limited numbers of available clinical trials offering new treatment strategies and poor accrual to available clinical trials have been among the main hurdles globally impeding the desired improvements in cancer survival rates for adolescents.<sup>[4,5,16,18,25,27,29]</sup> While this may be rational in settings where the pediatric and adult manifestations of a cancer type differ, there is now broad recognition that in well-defined cancers (e.g. melanoma<sup>[24]</sup>, acute myeloid leukemia<sup>[32]</sup>) it may be more appropriate to include adolescents in adult trials - with appropriate consent and safety provisions.

In Europe, there has been concern that the clinical trial landscape may delay the evaluation of promising new therapies in adolescents, and this led to the European Pediatric Medicine Regulation ((EC)-No1901/2006)] mandating the establishment of the European Medicines Agency's Pediatric Committee to provide guidance to pharmaceutical companies regarding their pediatric investigation plans for drugs in active development.<sup>[23]</sup> Recently, the multi-stakeholder platform ACCELERATE (<http://www.accelerate-platform.eu>) presented a consensus expert opinion in support of early drug access for adolescents with cancer indicating that enrollment of adolescents of 12 years and over in adult early-phase clinical drug trials would represent a safe and efficient strategy in drug development. The expert opinion cited documented similarities between adults and adolescents in regard to drug maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) levels and pharmacokinetics (PK)

parameters,<sup>[21]</sup> regulatory obligations in the context of ICH-E6 as well as oversight of clinical trials.<sup>[10]</sup> Several changes were proposed by ACCELERATE that should facilitate access for adolescents to early drug development programs. The key recommendations of ACCELERATE included that (i) there should be no set upper or lower age limit criteria for Phases II and III trials for cancers that are present in both pediatric and adult populations with similar biology and (ii) adolescents over 12 years of age should be included from the onset of the cancer drug development process in adults.<sup>[10]</sup> These suggestions of ACCELERATE were in accord with the 2016 ICH-E11 guidance, stipulating that data from pediatric clinical trials should be included in adult marketing authorization applications for promising drugs that may significantly alter the therapeutic landscape for difficult to treat illnesses.

The importance of adolescent participation in clinical trials and design of "adolescent"-enriched clinical trials is especially evident for sarcomas because more than half of all sarcomas occur in adolescents and young adults which has already prompted the initiation of hybrid AA clinical trials.<sup>[7]</sup> The lessons and insights learned from the study start-up experience for the NCI Cancer Treatment program-sponsored NCT02180867/PAZNTIS study of pazopanib in neoadjuvant settings were very important and actionable. This first collaborative sarcoma trial enrolled both adults and children with sarcoma, revealed a series of challenges in overcoming the practical barriers between NCI-funded adult and pediatric cooperative groups and underscored the importance of multi-stakeholder collaboration for success.

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The recently published June 2018 Draft Guidance from FDA, “Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials”<sup>[8]</sup> in the US can be viewed as a strong endorsement of the ACCELERATE proposal<sup>[12]</sup> regarding inclusion of adolescent patients in adult early phase clinical drug trials in Europe. FDA recommendations are based in part on the observed similarities in disposition and PK of drugs in adolescents and adults<sup>[21,31]</sup> combined with the fact that many malignancies encountered by adolescents such as leukemias, lymphomas, melanoma, and sarcomas also occur in adults, as previously noted both in a 2017 CCR publication<sup>[5]</sup> and the above referenced 2018 ACCELERATE expert opinion.<sup>[10]</sup> These recommendations would certainly expand the options available for adolescent cancer patients who have relapsed after or are refractory to standard therapeutic strategies with no curative options, or for whom no standard therapies with curative intent exist. The suggestion that adolescent patients may be enrolled in first-in-human clinical trials after initial adult PK and toxicity data are obtained is aimed at providing significant risk mitigation for adolescents.<sup>[8]</sup> While the recommendations in the draft guidance are intended to facilitate earlier access to promising new anticancer drugs for adolescent patient populations, the inclusion of adolescents on all disease and target-appropriate adult oncology trials carries several risks if adolescents were to be enrolled simultaneously with adults in activity estimating or confirmatory trials.

Pediatric oncology trials traditionally have incorporated the best standard of care regimens as comparator arms and adolescent patients have therefore enjoyed protection from poorly performing new treatment strategies due to carefully designed trial stopping rules based on the interim comparison of the outcome on experimental treatment arms to the outcome on the best available standard treatment regimen. For example, if a new agent is being added to a combination chemotherapy backbone for newly diagnosed high-risk acute lymphoblastic leukemia (ALL) patients that has not yet been fully evaluated in adolescent patient populations, the enrollment of newly diagnosed adolescent ALL patients on such a protocol could have the unintended consequence that adolescent patients are not promptly treated with a time-tested and effective standard regimen developed through decades of high-quality clinical research for pediatric ALL patients. Likewise, a retrospective meta-analysis of adolescents and young adults with acute myeloid leukemia showed that patients treated on pediatric trials had better outcomes than those treated on adult trials:<sup>[32]</sup> The 10-year event-free survival (EFS) of the Children’s Oncology Group (COG) cohort was superior to that of the combined adult cohorts as was overall survival (OS), with a 10-year estimate comparison of  $P = 0.026$ . Younger adolescent-young adult patients with Hodgkin’s lymphoma (HL) also appear to have better outcomes when treated on a pediatric trial than patients of similar age on an adult trial.<sup>[12]</sup> EFS and

OS were compared between 114 patients ages 17–21 years with HL who were treated on the Eastern Cooperative Oncology Group - American College of Radiology Imaging Network Intergroup adult E2496 study and 391 similarly patients ages 17–21 years with HL who were treated on the pediatric COG AHOD0031 study. The 5-year EFS and OS rates were statistically superior for the COG patients ( $P = 0.001$ ).<sup>[12]</sup> Therefore, it will be critically important to first reach consensus on chemotherapy backbones for adult and adolescent patient populations and define the efficacy and toxicity targets before launching hybrid AA trials. Additional safeguards are needed to ensure that adolescents are not treated with frontline experimental regimens designed for adults for which there is no compelling evidence that they are likely to be at least as effective as standard pediatric regimens. Any trial including adolescents should carefully document that there is a concordance of control treatments with accepted standards of care and that such standards are evidence-based from evaluations in adolescent populations. Adolescents should be allowed on adult trials only after failing a standard pediatric regimen that is considered the best regimen by a pediatric cooperative group such as the COG and the eligibility criteria even for late stage efficacy trials designed for adults should exclude newly diagnosed therapy-naïve adolescent cancer patients for whom there is a high probability to have long-term survival after treatment on an existing pediatric treatment regimen. The pediatric and adult cooperative groups in collaboration with other stakeholders across the entire drug development enterprise should carefully consider and develop standard inclusion and exclusion criteria for hybrid AA cancer trials.

As with adult cancer patients, the participation rate in the adolescent population is alarmingly low. Strategies should be developed to address the major challenge of traditionally very poor accrual of, especially, older adolescent cancer patients in clinical trials that have had arguably a much greater impact than the lack of access to relevant trials. In the US, older adolescent patients with cancer have the lowest clinical trial participation rate of all age groups.<sup>[9,18,29]</sup> It has been shown that factors other than clinical trial availability are important enrollment barriers and should be addressed. According to a well-designed prospective observational study, significantly fewer adolescents were enrolled when a clinical trial was available than children.<sup>[29]</sup> It is unclear how allowing adolescents to have access to experimental treatments designed for adult cancer patients will address the challenge that only 10–15% of older adolescent cancer patients between ages 15 and 19 have participated in clinical trials that were available to them.<sup>[29]</sup> In this context, it is noteworthy that the recent NCT01696045 trial aiming at evaluating the tolerability and efficacy of ipilimumab in adolescent melanoma patients aged 12–<18 years had to be stopped prematurely due to poor accrual.<sup>[11]</sup> It is desirable to open a discussion if the establishment of harmonization of key inclusion/exclusion criteria for adolescent patients with cancer

is feasible. We must consider all available options and strategies about how all stakeholders (FDA, industry, institutions and MDS, as well as support services, and advocacy groups) can increase access to, acceptance of, and entry into clinical trials for adolescent cancer patients. Organizations associated with advocacy groups such as Teen Cancer America (TCA, [www.teencanceramerica.org](http://www.teencanceramerica.org)) and Critical Mass ([criticalmass.org](http://criticalmass.org)) provide many resources for adolescent cancer patients at major medical centers. Major efforts have been launched by cancer centers to improve the access of their adolescent cancer patient population to clinical trials. Innovative social media and electronic messaging platforms for educating adolescent patients about available clinical trial options are also being explored.

Effective start-up and execution of the hybrid AA clinical trials require that they are conducted at experienced study sites with established pediatric and adult oncology units providing age-appropriate and specialized treatment centers, such as the NCI-funded comprehensive cancer centers of academic institutions. In addition, the participation of both pediatric and adult hematologists-oncologists as investigators and members of key oversight committees and close collaboration with national and international groups supporting adolescents with cancer and/or facilitating their treatment to ensure the best possible outcomes is needed. The profound impact of the institutional infrastructure on treatment outcomes of cancer clinical trials and survival outcomes of participants with cancer types affecting adolescents was recently demonstrated by Muffly *et al.* who used the California Cancer Registry to describe patterns of care and outcomes for almost 1500 adolescents and young adults with ALL over the past decade.<sup>[19]</sup> In a multivariate analysis, front-line treatments in a pediatric (vs. adult) setting and at a NCI-designated cancer center were associated with significantly superior survival. Results were similar for younger adolescents. Therefore, we believe a listing of minimum site criteria should be developed for participation in hybrid AA clinical trials. We must ensure that institutions, sponsors, and other participating stakeholders such as CROs, carefully select and qualify - with appropriate training and documentation - investigators, and sites that are experienced in the management of adolescent cancer patients. Unique care, counseling and ethics considerations must be closely observed. We strongly agree with the recent FDA recommendations that safety data collected during the trial should be examined for any age-related differences and that sponsors should develop a plan for longitudinal evaluation of potential developmental toxicities when it is feasible, particularly in trials enrolling patients in earlier lines of therapy. To ensure a consistent monitoring approach and highest quality standards in hybrid AA studies, effective communication and coordinated training will also be essential. A uniquely-tailored and risk-based monitoring strategy and a data-driven monitoring frequency should be used in hybrid AA clinical trials.

In this context, there should also be an open discussion about the pros and cons of alternative strategies such as a parallel path of clinical development in adolescent patient populations as soon as the first in human dose escalation trial is completed in adult patients. More recently, there has been an effort to initiate early phase trials of targeted therapies in children and adolescents with cancer. For example, umbrella trial initiatives aimed at allowing children and adolescents with relapsed or refractory pediatric cancers early access to promising targeted precision medicines such as the NCT03155620 COG–NCI Pediatric Molecular Analysis for Therapy Choice (MATCH) trial “Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphomas, or Histiocytic Disorders (The Pediatric MATCH Screening Trial)” provide a unique opportunity for new therapeutic innovations through mechanistic hypothesis-driven studies. Treatment arms are selected for inclusion in the pediatric COG–NCI Pediatric MATCH if there is already existing evidence from a clinical trial linking gene variants to response to the targeted therapy or compelling proof of concept from nonclinical studies. Likewise, the European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors (NCT02813135) is designed for children and adolescents aged 0–18 years with relapsed or refractory solid tumors and leukemias as part of the Innovative Therapies for Children with Cancer Precision Cancer Medicine Program, a European academic consortium.<sup>[28]</sup> Lessons and insights learned from these trials are likely to provide the foundation for more advanced precision medicine “basket trials” for children and adolescents with cancer. Dramatic and durable responses were observed in pediatric patients with anaplastic large-cell lymphoma and inflammatory myofibroblastic tumors harboring anaplastic lymphoma kinase (ALK) fusions who were treated in a Phase 1/2 setting with the ALK inhibitor crizotinib.<sup>[28]</sup> Likewise, the Phase 1 testing of the tropomyosin receptor kinase (TRK) inhibitor larotrectinib for TRK fusion positive malignancies generated an exciting ORR of >90% in pediatric and adult patients.<sup>[15]</sup>

We further note that the recommended path of including adolescents in adult clinical trials might arguably add only marginally to the advantages provided by a responsible and effective implementation of the important provisions of the Race for Children Act, which is incorporated as Title V of the FDA Reauthorization Act (FDARA) that was enacted in 2017 (FD&C Act Sec. 505B (a)(3), 21 USC 355c (a)(3), Public Law 115-52).<sup>[22]</sup> Title V requires evaluation of new molecularly targeted drugs and biologics “intended for the treatment of adult cancers and directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer” in molecularly targeted pediatric cancer investigation to generate clinically meaningful study data, “using appropriate formulations, regarding dosing, safety,

and preliminary efficacy to inform potential pediatric labeling” by designing and executing earlier rational dose finding and signal-seeking trials.<sup>[22]</sup> FDARA has thus created a mechanism to expedite the evaluation of novel medicines with the potential to address the unmet need in the pediatric population by requiring pediatric investigation of appropriate new drugs intended for adults with cancer.<sup>[22]</sup>

We, therefore, believe a discussion is urgently needed about how hybrid AA trials can best provide a strong rationale for inclusion of adolescent patients, as opposed to initiating a parallel adolescent development pathway. These discussions and documentation should be (a) tumor and (b) drug unique plans that are included in pre-IND and other FDA-Sponsor interactions that seek alignment on a drug’s regulatory and clinical development pathway.

FDA-regulated clinical trials that enroll adolescents with cancer must comply with the Additional Safeguards for Children in Clinical Investigations found at 21 C.F.R. 50, Subpart D.<sup>[8]</sup> Due to the risks associated with oncology drug treatment, pediatric studies must be evaluated under 21 C.F.R. Sect. 50.52, which requires that the prospect of direct benefit is sufficient to justify the known and unknown risks of the proposed experimental treatment strategy and is at least comparable to the assessed benefit of alternative strategies.<sup>[13,17]</sup> These additional safeguards provide a strong rationale for our recommendations of further considerations outlined hereinabove. Additional assurances are needed that adolescent patients will not only observe protocol I/E criteria for contraception/pregnancy - items standard in protocols but also will receive substantive counseling about fertility impact/preservation and considerations for ova/sperm banking. Hybrid AA trials should take into consideration the 2018 ASCO Clinical Practice Update regarding fertility preservation in patients with cancer. The informed consent process associated with the hybrid AA protocols should include a candid and fact-based discussion on the possibility of infertility as well as various fertility preservation options, which is particularly relevant for adolescents with cancer and their parents/guardians.<sup>[20]</sup> The study committees of hybrid AA protocols should also include reproductive specialists with experience in counseling adolescents with cancer. Informed consent forms should take into consideration, the summary recommendations regarding the informed consent process and the ethics of including adolescents in clinical research.<sup>[33]</sup>

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