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Original Research

Timing of first-in-child trials of FDA-approved oncology drugs

Dylan V. Neel [a], David S. Shulman [b], Steven G. DuBois [b,*]

[a] *Harvard Medical School, Boston, MA, USA*
[b] *Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA, USA*

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Abstract ***Aim:*** The lag time between initial human studies of oncology agents and the first-in-child clinical trials of these agents has not been defined.
Methods: We conducted a systematic analysis of time from first-in-human trials to first-in-child trials (age of eligibility <18 years) of agents first approved by the US Food and Drug Administration (FDA) for any oncology indication from 1997 to 2017. We used clinical trial registry data, published literature and oncology abstracts to identify relevant trials and start dates.
Results: From 1997 to 2017, 126 drugs received initial FDA approval for an oncology indication. Of these, 117 were non-hormonal agents used in subsequent analyses. Fifteen of 117 drugs (12.8%) did not yet have a paediatric trial, and six of 117 drugs (5.1%) had an initial approval that included children. The median time between the first-in-human trial and first-in-child trial was 6.5 years (range 0–27.7 years). The median time from initial FDA approval to the first-in-child clinical trial was −0.66 years (range −43 to +19 years). These values were stable regardless of year of initial FDA approval, drug class and initial approved disease indication.
Conclusion: The median lag time from first-in-human to first-in-child trials of oncology agents that were ultimately approved by FDA was 6.5 years. These results provide a benchmark against which to evaluate recent initiatives designed to hasten drug development relevant to children with cancer.

Abbreviations: FHCT, first-in-human clinical trial; FCCT, first-in-child clinical trial with eligibility criteria open to patients <18 years; FCCTe, first-in-child clinical trial verified to have enrolled a patient <18 years; EUCTR, European Union Clinical Trials Register.

* *Corresponding author*: Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, USA. Fax: +1617 632 5710.
E-mail address: steven_dubois@dfci.harvard.edu (S.G. DuBois).

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1. Introduction

Progress in treating paediatric malignancies over the last 40 years has largely been driven by advances in conventional cytotoxic chemotherapy regimens, surgery and radiation [1]. Although overall survival for children with cancer now exceeds 80% [2], outcomes remain poor for many patients [3]. Furthermore, treatment-related morbidity remains high for most children treated with chemotherapy-based regimens [4]. Our understanding of cancer genetics, molecular drivers of disease and differences between adult and paediatric malignancies continues to grow [5,6]. Despite this greater understanding of paediatric cancer biology, few targeted therapies are approved by regulatory agencies for children with cancer.

Opportunities exist to spur paediatric drug development at the level of regulatory bodies, the pharmaceutical industry and academic clinical investigators. Although legislation such as the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act in the United States (US) has attempted to mandate and incentivise pharmaceutical companies to develop drugs for children, new strategies are needed to accelerate evaluation of new drugs in children with cancer. Histology-based class waivers to requirements for paediatric testing have been common, with one review of the European experience reporting 147 class waivers over a 3-year span [7]. Several published reports have described additional methods to expand oncology trial eligibility to children [8,9]. For example, in the US, the research to accelerate cures and equity (RACE) for Children Act of 2017, which amends PREA, now allows the FDA to require paediatric evaluation of relevant targeted therapies regardless of histology. Although these initiatives will ideally speed paediatric oncology drug development, the historical and current delays between a first-in-human trial and a first-in-child clinical trial have not been rigorously evaluated. Thus, the scope of the problem remains poorly defined, and we lack a clear baseline to determine the efficacy of current efforts to speed paediatric drug development.

To address this important gap in our knowledge, we performed a systematic evaluation of clinical trial registries, clinical trial publications and a major clinical oncology abstract database. For each drug first approved by the FDA for an oncologic indication between 1997 and 2017, we sought to determine the following: (i) time between first-in-human clinical trial (FHCT) and first-in-child clinical trial (FCCT); (ii) time between initial FDA approval and FCCT and (iii) potential predictors of these time intervals. Furthermore, we evaluated the overall proportion of oncology clinical trials with eligibility criteria open to children. A more precise understanding of these metrics will inform future policies and strategies aimed at accelerating paediatric access to emerging therapeutics.

2. Methods

2.1. FDA-approved oncology drug list

The FDA-approved oncology drug list included all drugs first approved by the FDA for any oncology indication between January 1, 1997, and December 31, 2017. A list of FDA-approved drugs, and corresponding initial approval dates and indications, was generated using multiple sources. Drugs approved between 2006 and 2017 were taken directly from the FDA *Cancer Approvals & Safety Notifications* website [10], whereas drugs from 1997 to 2007 were compiled using an online oncology reference (Hemonc.org), DrugBank [11], FDA archives and previously published reports [12,13].

2.2. Variables and data extraction

For each drug, the following dates were collected. FHCT start dates were obtained by searching clinicaltrials.gov and the EU Clinical Trials Register (EUCTR). Each drug name and the word 'trial' were also used as search terms in PubMed (date of search: April 18–20, 2018). For published studies that did not record a trial start date in the manuscript or registry, a start date of 4.67 years before the first publication of results was used as a proxy (n = 21). This assumption was based on the calculated median time (4.67 years) between the trial start date and first publication of results for agents with a known FHCT start date (n = 96).

The start date of the FCCT was collected and defined as the start date of the first clinical trial with eligibility including patients < 18 years. This date was obtained through a systematic search of clinicaltrials.gov and the EUCTR. Each drug name and the word 'pediatric' were also used as search terms in PubMed and in the American Society of Clinical Oncology (ASCO) abstract database (date of search: March 22–23, 2018). For studies without an available trial start date, a start date of 4.67 years before article publication was used as a proxy (n = 2).

The first clinical trial confirmed as enrolling a patient <18 years (FCCTe) was identified using study results posted on clinicaltrials.gov, results found on PubMed, ASCO abstracts and internet searches (google.com). As opposed to FCCTs which only required that eligibility criteria included children to be coded as a FCCT, the FCCTe metric required that available results demonstrate that a child is enrolled to the trial. In cases in which it was not clear from available data whether a patient < 18 years was enrolled, the lead investigator was contacted.

In all cases, we included only systematic prospective evaluations of the agents of interest as clinical trials.

Off-label use outside of a trial or compassionate use was not included.

2.3. Statistical analysis

The primary end-point was time in years between the first-in-human trial (FHCT) and first trial with eligibility criteria including patients < 18 years (FCCT). This metric was assessed for all non-hormonal drugs, with descriptive statistics (median and range) calculated. The same analysis was repeated using FHCT and FCCTe and also benchmarked to date of first FDA approval for any oncology indication. To assess qualitatively for potential predictors in these intervals, we also plotted data according to specific categories: drug class; initial FDA-approved indication and year of approval.

Recognising that not all FDA-approved agents have been studied in children, we assumed an arbitrary start date for first-in-child studies of January 1, 2018, for all agents without a true first-in-child trial. We repeated each of the aforementioned analyses separately including and excluding these 'censored' trials.

An additional aim of the study was to determine the prevalence of all clinicaltrials.gov registered oncology phase 1 and phase 2 interventional trials that allowed children (<18 years) to enroll. Only trials on clinicaltrials.gov that had a start date between January 1, 1997 and December 31, 2017 were included in this analysis.

3. Results

3.1. Characteristics of FDA-approved drugs

From 1997 to 2017, 126 drugs gained initial FDA approval for an oncologic indication. Forty-seven percent of new agents were small molecules, whereas 22% were antibodies and 14% conventional cytotoxic agents (Fig. 1A). Nine agents were hormonal modulators and were excluded from all subsequent analyses because of lack of relevance to paediatric cancers, leaving 117 agents of interest (Supplemental Table 1). The median time from FHCT to initial FDA approval was 6.9 years (range 1.3–42.8 (Supplemental Fig. 1). Most of these 117 compounds (67%) gained initial approval during the last 10 years (Fig. 1B). Fifty-five percent of the drugs were first approved for use in solid tumours, whereas 44% were first approved to treat haematologic malignancies (Fig. 1C). Only one drug (temozolomide) was first approved for use in a primary central nervous system (CNS) malignancy (glioblastoma). Six of 117 drugs (5.1%) had an initial approval that included children (asparaginase *Erwinia chrysanthemi*, blinatumomab, clofarabine, dinutuximab, nelarabine and tisagenlecleucel).

3.2. Timing of first-in-child oncology trials

The median time between first-in-human trial (FHCT) and FCCT was 6.5 years (range 0–27.7 years; Fig. 2A and Supplemental Table 2). When censored datapoints for drugs that had not yet had a paediatric trial initiated were removed from the analysis (n = 15; highlighted in Supplemental Table 2), the median decreased to 6.3 years (range 0–22 years; n = 102 drugs; Supplemental Fig. 2A). Of these 102 FCCTs, 27 trials (26%) were sponsored by industry, with the remaining sponsored by government agencies, cooperative groups or academia. We then looked at time between FHCT and first trial confirmed to have enrolled a patient < 18 years (FCCTe). The median time from FHCT to FCCTe was 6.6 years (range 0–27.7 years; Fig. 2B). When censored datapoints were removed from the analysis, the median decreased to 6.3 years (range 0–25.8 years; n = 97 drugs; Supplemental Fig. 2B).

We then evaluated time between initial FDA approval for an oncology indication and FCCT. The median time from FDA approval to FCCT was −0.66 years (range −43 to +19 years; Fig. 2C). When censored datapoints were removed from the analysis, the median was −1.1 years (range −43 to +16 years; n = 102 drugs;

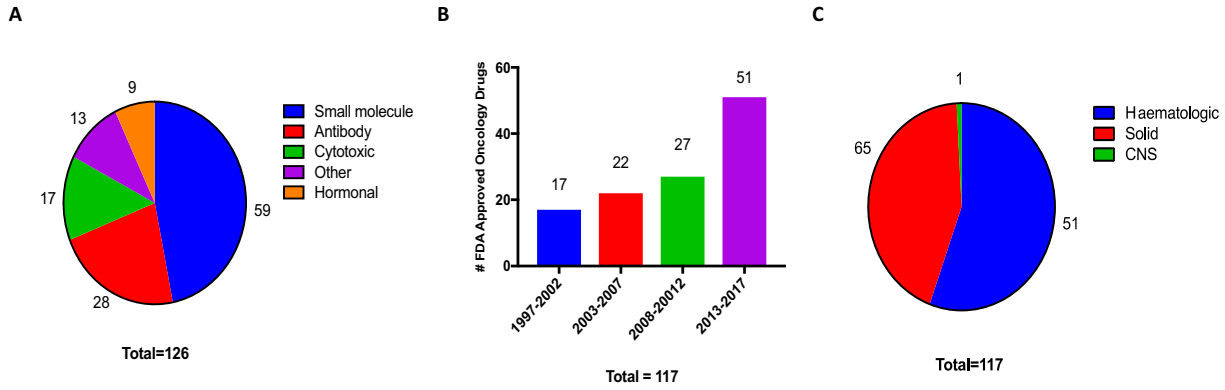

Fig. 1. **(A)** All drugs approved for an oncology indication during 1997–2017 by drug class (n = 126) and after exclusion of hormonal agents (n = 117) showing **(B)** time period of approval from 1997 to 2017 and **(C)** disease group indication. CNS, central nervous system.

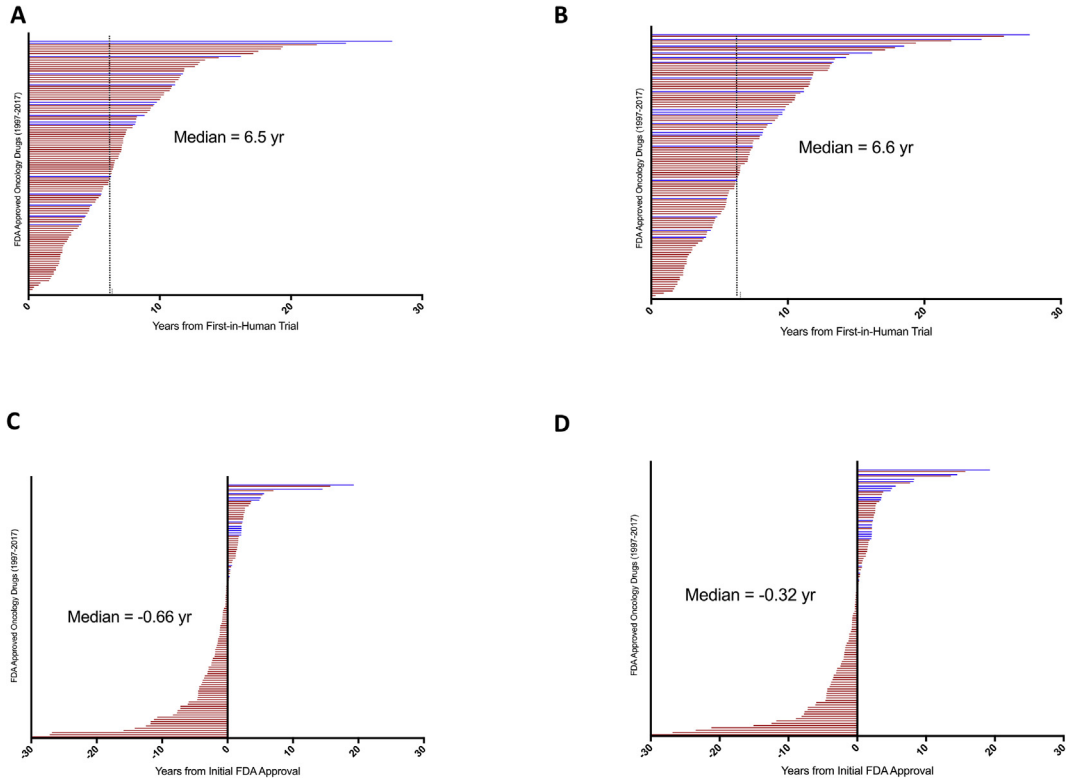

Fig. 2. Analysis of paediatric oncology trial start dates for non-hormonal oncology agents approved by FDA from 1997 to 2017 (n = 117). Each bar represents a single drug. **(A)** Time between the start date of first-in-human clinical trial (FHCT) and first trial eligible to enroll paediatric patients (FCCT). **(B)** Time between FHCT and first trial verified to have enrolled paediatric patients (FCCTe). **(C)** Time between FCCT and FDA approval date for each drug, where negative time (x-axis) indicates an FCCT start date before first FDA approval. **(D)** Time between FCCTe and FDA approval date for each drug, where negative time (x-axis) indicates an FCCTe start date before first FDA approval. Drugs without a paediatric trial starting before January 1, 2018, were censored at that time and are indicated in blue. FCCT, first-in-child clinical trial with eligibility criteria open to patients <18 years; FCCTe, first-in-child clinical trial verified to have enrolled a patient <18 years; FDA, US Food and Drug Administration. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Supplemental Fig. 2C). The median time from FDA approval to FCCTe was −0.32 years (range −31 to +19 years; Fig. 2D). When censored datapoints were removed from the analysis, the median was −0.79 years (range −31 to +15.7 years; n = 97 drugs; Supplemental Fig. 2D).

3.3. Timing of first-in-child oncology trials according to drug characteristics

To identify potential predictors of timing of FCCTs, the aforementioned results were stratified by date of FDA approval, drug class and indication. When results for time between FHCT and FCCT were stratified by FDA approval date, median values and distribution appeared similar across time (Fig. 3A). Similarly, when stratified by drug class and approved disease indication (Fig. 3B and C), similar results were seen. Separate analyses of time between FHCT and FCCTe (Fig. 3D–F) and analyses excluding censored trials (Supplemental Fig. 3) yielded similar results to those of the primary analyses. These results suggest that the time lag separating first-in-child (FCCT and FCCTe) from first-in-human trials is not dependent on the era of FDA approval, drug class or initial disease indication.

We repeated these analyses for time between FDA approval and first-in-child trials. When results were stratified by the initial FDA approval date, median values remained similar across time and clustered around 0 years (equivalent to time of initial FDA approval; Fig. 4A). When stratified by drug class and approved disease indication, median values again clustered around 0 years. Separate analyses of time between FDA approval and FCCTe (Fig. 4D–F) and analyses excluding censored trials (Supplemental Fig. 4) yielded similar results to those of the primary analyses.

We then looked at outlier agents with the top five shortest and longest times from FHCT to FCCT, excluding censored drugs with no known paediatric trial as of January 1, 2018 (Supplemental Table 3). The five drugs with the shortest duration were exclusively for haematologic malignancy indications, whereas the five drugs with the longest duration were approved for a range of oncology indications.

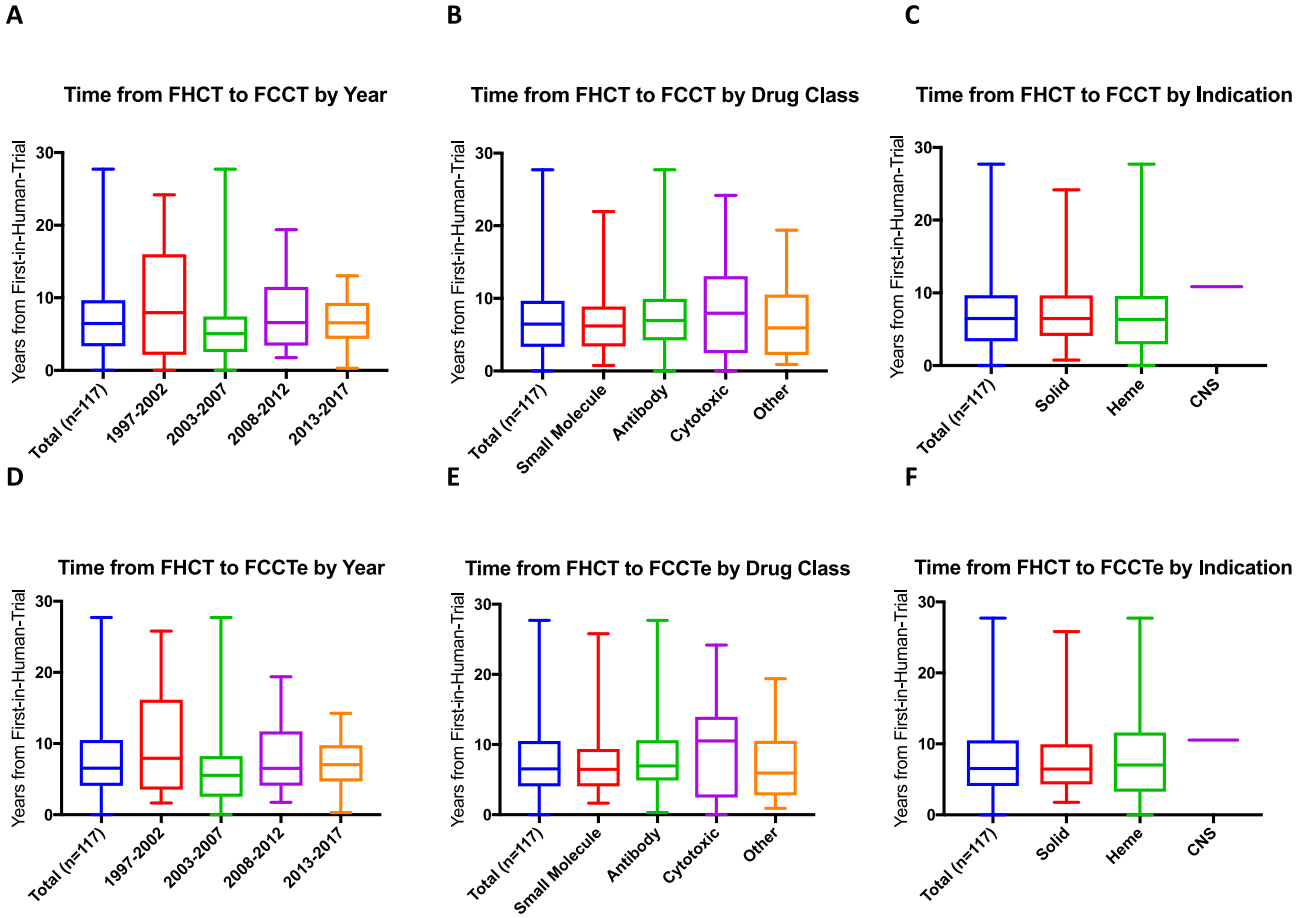

Fig. 3. Analysis of paediatric oncology trial start dates relative to first-in-human trial start dates, with censored datapoints included, stratified by drug characteristic. Box-and-whisker plots display the 25th percentile, median and 75th percentile, along with minimum and maximum values (range). **(A)** Time between the start date of first-in-human trial (FHCT) and first trial eligible to paediatric patients (FCCT) stratified by time period during which the drug first received FDA approval for an oncology indication. **(B)** Analysis of time between the start date of FHCT and FCCT, stratified by drug class. **(C)** Analysis of time between the start date of FHCT and FCCT, stratified by approved disease indication. **(D)** Time between the start date of FHCT and first trial enrolling paediatric patients (FCCTe), stratified by time period during which the drug first received FDA approval for an oncology indication. **(E)** Analysis of time between the start date of FHCT and FCCTe, stratified by drug class. **(F)** Analysis of time between the start date of FHCT and FCCTe, stratified by approved disease indication. FCCT, first-in-child clinical trial with eligibility criteria open to patients <18 years; FCCTe, first-in-child clinical trial verified to have enrolled a patient <18 years; FDA, US Food and Drug Administration.

3.4. Proportion of oncology trials that include children < 18 years

The final aim of the study was to determine the prevalence of paediatric trials in all clinicaltrials.gov registered oncology phase 1 and phase 2 interventional trials, conducted from 1997 to 2017. We found that 84.8% of phase 1 and 84.4% of phase 2 trials registered from 1997 to 2007 were open to adults only (Fig. 5A and C). For this same time period, 14.7% of phase 1 and 15.0% of phase 2 trials were open to both paediatric and adult patients (eligibility open to both <18 years and ≥18 years); whereas only 0.43% of phase 1 and 0.6% of phase 2 were child-only trials (eligibility open only to <18 years). In trials registered during 2008–2017, the proportion of phase 1 (8.47%) and phase 2 (8.40%) trials open to both children and adults decreased relative to the previous decade, although the absolute number of overall trials and those open to children increased (Fig. 5B and D). The proportion of trials open to children only stayed relatively constant across time and was approximately 0.6% for both phase 1 and 2 trials.

4. Discussion

We present a comprehensive analysis of the timing of initiation of FCCTs for 117 non-hormonal oncology drugs first approved by the FDA from 1997 through 2017. Our data show a median 6.5-year lag between FHCT and FCCT for drugs that were ultimately approved for the treatment of cancer. This timing

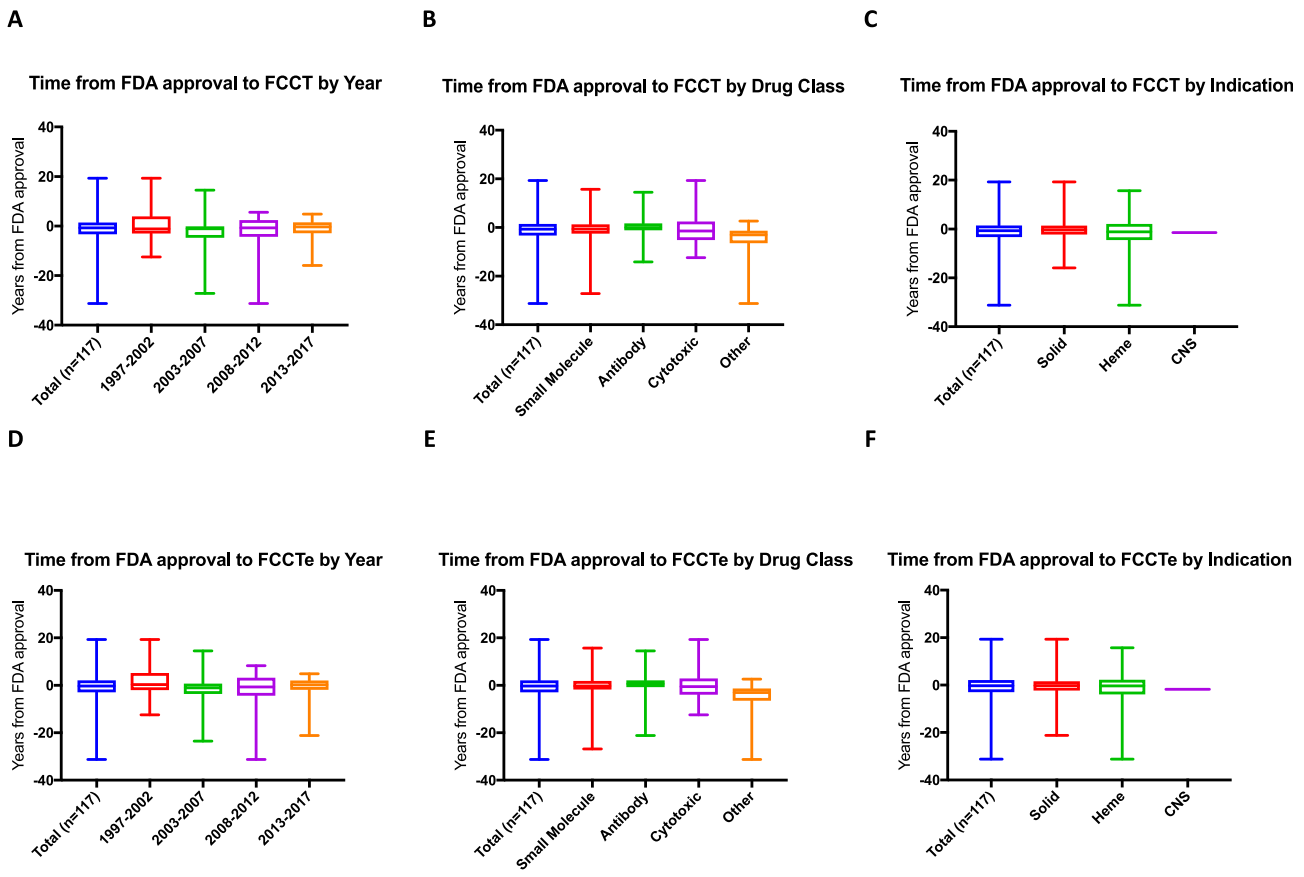

Fig. 4. Analysis of paediatric oncology trial start dates relative to FDA approval, with censored datapoints included, stratified by drug characteristic. Box-and-whisker plots display the 25th percentile, median and 75th percentile, along with minimum and maximum values (range). Negative values indicate a start date of the paediatric trial that was before initial FDA approval for any oncologic indication. Positive values indicate a start date of the paediatric trial that followed initial FDA approval. **(A)** Analysis of time between the start date of first trial eligible to paediatric patients (FCCT) and FDA approval, stratified by time period during which the drug first received FDA approval for an oncology indication. **(B)** Analysis of time between the start date of FCCT and FDA approval, stratified by drug class. **(C)** Analysis of time between the start date of FCCT and FDA approval, stratified by approved disease indication. **(D)** Analysis of time between the start date of first trial enrolling paediatric patients (FCCTe) and FDA approval, stratified by time period during which the drug first received FDA approval for an oncology indication. **(E)** Analysis of time between the start date of FCCTe and FDA approval, stratified by drug class. **(F)** Analysis of time between the start date of FCCTe and FDA approval, stratified by approved disease indication. FCCT, first-in-child clinical trial with eligibility criteria open to patients <18 years; FCCTe, first-in-child clinical trial verified to have enrolled a patient <18 years; FDA, US Food and Drug Administration.

corresponds roughly to the median time of 6.9 years from FHCT to FDA approval for these drugs. The time lag to FCCT remains true across year of initial approval, drug categories and indication, although the agents with the shortest time between FHCT and FCCT were for haematologic malignancies. During this era from 1997 to 2017, only 26% of FCCTs were industry-sponsored and only six oncology drugs had an initial approval that included children. It is noteworthy that all but one of these six agents were approved for acute lymphoblastic leukaemia, the most common paediatric cancer and a malignancy that also impacts adults. The remaining agent was approved for neuroblastoma, the most common non-CNS solid tumour in children and a disease not typically seen in adults. The lack of initial approvals in less common paediatric cancers highlights the challenges of drug development in these rare indications. As CNS tumours make up a greater proportion of paediatric cancers compared with adult cancers, the approval of only one new agent for adult CNS cancers from 1997 to 2017 highlights a population in need for additional innovation.

To assess the robustness of our findings, we analysed the time from FHCT to first paediatric trial in several ways (e.g. using paediatric trial eligibility vs. trial enrolment and using censored and uncensored data). Taken together, our analyses indicate a lag of approximately 6.5 years between FHCT and the start of paediatric development. The optimal timing to begin paediatric development is not defined and not uniform from agent to agent, although regulatory authorities typically request for paediatric study plans early in adult

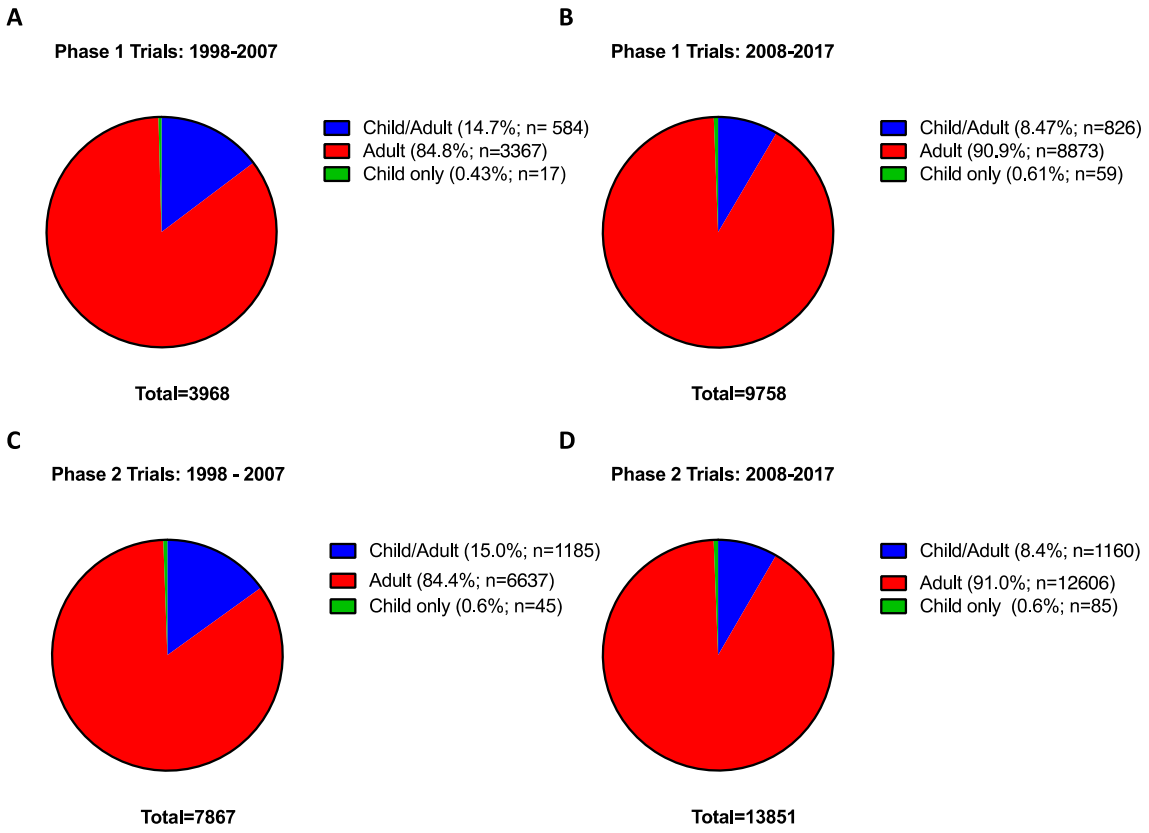

Fig. 5. Prevalence of early-phase oncology clinical trials registered on clinicaltrials.gov open according to age of eligibility: Child/adult (<18 years and ≥18 years); adult (≥18 years) and child only (<18 years). **(A)** Phase 1 trials with registered start dates from 1997 to 2007, **(B)** phase 1 trials with registered start dates from 2008 to 2017, **(C)** phase 2 trials with registered start dates from 1997 to 2007 and **(D)** phase 2 trials with registered start dates from 2008 to 2017. Percentages and absolute trial counts are shown in parentheses.

development. Some may argue that this lag is appropriate to ensure safety of a vulnerable paediatric population and to only study agents in children that are on a path to FDA approval based on activity in adults with cancer. Others may argue that this lag is too long for children with life-threatening diseases and that some agents that fail in adult indications may nevertheless prove to be important drugs for paediatric indications. It will be critical to monitor changes in this metric over time in response to newer initiatives designed to hasten paediatric cancer drug development. There are already recent examples of highly targeted, rationally designed drugs that underwent nearly simultaneous development in children and adults with cancers with shared biology, providing a pathway for closing this gap [14–17]. An approach of age- and histology-agnostic development of rationally designed targeted therapies will be a key step in closing the disparity between adult and paediatric drug development. Similarly, the use of multi-stakeholder meetings to align drug development strategy and master protocols in these rare cancers has been recommended and is already in process [7,18,19].

We found that the absolute number of early-phase oncology clinical trials reported to be open to children in clinicaltrials.gov has increased over the last 20 years. Our data cannot speak to whether this change is in part due to new regulations enacted in the US and Europe during this era. In the US, the recent RACE for Children Act takes a significant step forward from prior versions of PREA, strengthening the requirement that new cancer therapies with potential biological relevance to paediatric cancers be evaluated in children. We note as well that the proportion of trials allowing both children and adults to participate has decreased, although the absolute number of such trials has increased. It will be important to track this metric over time in response to recent position statements seeking to expand the age of eligibility to include adolescents when appropriate [8,9,18].

We acknowledge several limitations in our study. First, our analysis exclusively focuses on FDA-approved agents. We did not assess other agents that may have promise in paediatric oncology but have not yet been FDA approved or may never be approved for an adult indication. Assessing these drugs may provide further insight into the current lag between FHCT and FCCT for newer therapies in the drug development pipeline. Second, given that the exact trial start date was not

always available for trials that predated required reporting on clinicaltrials.gov, estimated start dates were set using a uniform group median for time from FHCT start to publication for some FHCTs and FCCTs. Finally, we defined paediatric populations as < 18 years, which would exclude trials conducted in young adults who may be diagnosed with a cancer more commonly seen in a paediatric population. However, this approach was taken to align our analysis with registry data and the US age of consent.

Our study provides important new data on timing between FHCTs and FCCTs for cancer drugs. The consequences of this observed lag may include the potential for increased off-label prescribing in children without appropriate efficacy, dosing and adverse event data in an age-appropriate population. Increased off-label prescribing in turn may adversely impact rates of paediatric clinical trial enrolment of these agents. Recent policy changes provide an opportunity to facilitate earlier and broader trial evaluation of new compounds in relevant paediatric populations, but will require buy-in from key stakeholders. As the molecular drivers underpinning adult and paediatric cancers are unravelled, and more rationally designed therapies become available, oncology drug development programs inclusive of children will be critical.

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Conflict of interest statement

S.G.D. has received fees for consulting and advisory board roles from Loxo Oncology and has received travel expenses from Loxo Oncology and Roche/Genentech.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.02.011.

References

[1] Armstrong GT, Chen Y, Yasui Y, et al. Reduction in late mortality among 5-year survivors of childhood cancer. N Engl J Med 2016;374:833–42.
[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
[3] 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.
[4] Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355:1572–82.
[5] Vogelstein B, Papadopoulos N, Velculescu VE, et al. Cancer genome landscapes. Science 2013;339:1546–58.
[6] Ma X, Liu Y, Liu Y, et al. Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. Nature 2018;555:371–6.
[7] Pearson ADJ, Pfister SM, Baruchel A, et al. From class waivers to precision medicine in paediatric oncology. Lancet Oncol 2017;18:e394–404.
[8] Chuk MK, Mulugeta Y, Roth-Cline M, et al. Enrolling adolescents in disease/target-appropriate adult oncology clinical trials of investigational agents. Clin Cancer Res 2017;23:9–12.
[9] Gore L, Ivy SP, Balis FM, et al. Modernizing clinical trial eligibility: recommendations of the American society of clinical oncology-friends of cancer Research minimum age working group. J Clin Oncol 2017;35:3781–7.
[10] FDA cancer approvals & safety notifications. 2018.
[11] Law V, Knox C, Djoumbou Y, et al. DrugBank 4.0: shedding new light on drug metabolism. Nucleic Acids Res 2014;42:D1091–7.
[12] Kinch MS. An analysis of FDA-approved drugs for neurological disorders. Drug Discov Today 2015;20:1040–3.
[13] Sun J, Wei Q, Zhou Y, et al. A systematic analysis of FDA-approved anticancer drugs. BMC Syst Biol 2017;11:87.
[14] Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731–9.
[15] 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.
[16] Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507–17.
[17] Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378:439–48.
[18] Gaspar N, Marshall LV, Binner D, et al. Joint adolescent-adult early phase clinical trials to improve access to new drugs for adolescents with cancer: proposals from the multi-stakeholder platform-ACCELERATE. Ann Oncol 2018;29:766–71.
[19] Khan T, Stewart M, Blackman S, et al. Accelerating pediatric cancer drug development: challenges and opportunities for pediatric master protocols. Ther Innov Regul Sci 2018. 2168479018774533.