HHS Public Access

Author manuscript

Med Res Arch. Author manuscript; available in PMC 2024 July 18.

Published in final edited form as:

Med Res Arch. 2024 January ; 12(1): . doi:10.18103/mra.v12i1.5088.

Considerations on Design and Analysis of External Control in Pediatric Oncology

Jingjing Ye[1,*], **Haitao Pan**[2], **Gregory Reaman**[3], **Satrajit Roychoudhury**[4], **Chengxing Lu**[5], **Lindsay A. Renfro**[6], **Yuan Ji**[7], **Rong Liu**[8], **Ying Yuan**[9], **Weidong Zhang**[10] **Pediatric Oncology subteam of the American Statistical Association (ASA) Biopharmaceutical Session Statistical Methods in Oncology Scientific Working Group**

[1]Global Statistics and Data Sciences (GSDS), BeiGene USA, Fulton, MD

[2]Department of Biostatistics, St Jude Children's Research Hospital, Memphis, TN

[3]National Cancer Institute (NCI), National Institute of Health (NIH)

[4]Statistical Research and Innovation, Pfizer Inc.

[5]Oncology Biometrics, AstraZeneca, Waltham, Massachusetts

[6]Division of Biostatistics, University of Southern California and Children's Oncology Group, Los Angeles, CA

[7]University of Chicago, Chicago, IN

[8]Biostatistics and Data Management, Regeneron Pharmaceuticals, Tarrytown NY 10591

[9]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX

[10]Sana Biotechnology, Cambridge, Massachusetts

Abstract

Pediatric cancer consists of a diverse group of rare diseases. Due to limited patient populations, standard randomized and controlled trials are often infeasible. As a result, single-arm trials are common in pediatric oncology and the use of external controls is often desirable or necessary to help generate actionable evidence and contextualize trial results. In this paper, we illustrate unique features in pediatric oncology clinical trials and describe their impact on the use of external controls. Various types of relevant external control data sources are described in terms of their utility and drawbacks. Statistical methodologies and design implications with external control are discussed. Two recent case studies using external controls to support pediatric oncology drug development are described in detail.

[*]Corresponding author: Jingjing Ye, jingjing.ye@beigene.com.

Conflicts of Interest Statement

Yuan Ji: Co-Founder of Bayesoft Inc., a statistical company providing consultation and software service for pharmaceutical and biotech industry. IDMC member for Astellas, Boehringer Ingelheim and Lyell. Executive Advisor for Cytel Inc. Haitao Pan was partially supported by American Lebanese Syrian Associated Charities (ALSAC).

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health and all other authors' employers

Keywords

Pediatric oncology; external controls; registry; prior clinical trial; combination therapy; Bayesian analysis

1. Introduction

Pediatric cancer consists of a diverse group of rare diseases. The relatively small population of children with multiple disparate tumor types across various age groups presents a significant challenge for drug development programs as compared to those for adults (1). Other known challenges with pediatric oncology include evolving landscapes and consequently inconsistent standards of care during clinical development, complex disease biology, and rarity of natural history data. These elements collectively affect and demand proper trial designs that are suitable for the drug and the indication (2).

Rarity, among all known challenges, makes it infeasible to achieve adequate statistical power and control of type I error rate in traditional randomized clinical trials (RCTs) in a timely manner. Specifically, to recruit the number of patients required in such a trial during a short period of time may simply not exist in the population (3). Furthermore, modern targeted and precision cancer drug development typically are only effective in a subtype of disease which further shrinks the targeted patient population. As a result, pediatric trials targeting multiple but more rare subpopulations, often defined by molecular phenotypes effectively necessitate the use of single-arm trials in pediatric oncology (4).

The compounded reality of small single-arm trials can be enhanced when external data are available to help contextualize single-arm trial results in pediatric oncology (2). Use of external data can largely be classified into three categories: a) informing trial design, patient characteristics and sample size, Standards of Care (SoC), selection of endpoints, etc.; b) assisting trial conduct (e.g., site selection), and c) serving as external controls (either as a fixed value derived from external data or as an external control arm) (5). In this paper, the focus is on the approach to supplement single-arm data with data external to the clinical trial, referred to as an external control arm. Similar to adult drug development, external control arm data may be derived from prior clinical trial data (individual or pooled), or observational, real-world data (RWD) such as from registries, electronic health records (EHRs) and medical or pharmacy claims (6). Unique to pediatric oncology is the relevant adult clinical trial data that can be leveraged, which have implications for trial designs and more broadly the use of external data in interpreting benefit-risk results.

Other unique features of pediatric oncology include, for instance, the fact that most regimens in pediatric oncology are combination regimens (7). Single-arm trials of combinations are unable to isolate the contribution of the new agent to the regimen. External data on the existing regimen may help understand if such a contribution is present (6).

Additionally, indirect comparisons are common for understanding certain features of a treatment regimen although often retrospective. DuBois et al (8) investigated the optimal mode of local control for patients with localized osseous Ewing sarcoma in a retrospective

analysis of three consecutive clinical trials, with patients treated primarily at Children's Oncology Group (COG) centers located in the United States and Canada. Adams et al (9) utilized the Surveillance, Epidemiology, and End Results (SEER) cancer registry to determine the effect of gross total resection (GTR), partial resection (PR), and biopsy (Bx) on overall survival in pediatric glioblastoma patients.

These examples illustrated potential approaches and resources that may be leveraged for pediatric oncology trials. First, pediatric cancer patients are usually treated at children's hospitals (10), where abundant external data are available. Second, it is often the case that one large trial is conducted at a time in pediatric oncology, particularly in early disease settings. Data from such a trial may be leveraged for future studies. Third, in the United States, national databases provide wide coverage of the population. This is particularly salient and timely as there are ongoing efforts to extend the capabilities of these databases (11).

The remainder of the paper proceeds as follows. Section 2 describes the sources of data in pediatric oncology. Sections 3 and 4 discusses the considerations specific to drug development and the corresponding implications for the design and analysis of externally controlled studies, respectively. Section 5 describes selected examples of external controls in pediatric oncology, and Section 6 ends the paper with some discussions.

2. Sources of Data

External data are often available at the design stage for pediatric oncology trials. Using the external data, statistical designs may be developed and refined based on calibration of operating characteristics such as the distribution of the primary endpoint. More directly, the external data it may serve as a formal historical control in a new single-arm trial against which a novel treatment strategy may be compared. Such a design would be rare in a late-phase adult oncology setting. It is possible in pediatric trials because in some disease settings, the historical data represents nearly population-level data.

The following discussions have been grouped by the potential data sources for external controls in pediatric clinical trials: prior pediatric and adult clinical trials, disease registries, archives and national databases and medical records.

Prior Clinical Trials

Pediatric cancer patients are usually treated at children's hospitals through cooperative networks. Examples include the COG, the pediatric cooperative group member of the National Cancer Institute (NCI)'s National Clinical Trials Network (NCTN) and the Beat Childhood Cancer (BCC) Research Consortium. The COG is the largest of all covering major children's hospitals, universities and cancer centers across North America, Australia, New Zealand and several other countries. Collectively, 80–90% of children diagnosed with cancer in the United States are treated at COG member institutions (12). The COG is also responsible for conducting the vast majority of late phase (phase II-III) therapeutic pediatric cancer trials in the US, across all primary cancers affecting children. When a new cancer clinical trial is being designed for a given disease setting within COG, the most recent

completed COG trial(s) in the same setting often directly informs the design of the new trial in the following aspects: feasible annual accrual rates for that disease, specific estimates of the distribution(s) of primary endpoint(s) of interest, the percentage of eligible patients who enrolled on the therapeutic studies, and patient outcomes against which the new trials will be compared, either formally or indirectly.

Adult Clinical Trial as Data Source for Pediatric Trials

In typical drug development, drugs are often approved for adult use or in the process of obtaining approval in adults before pediatric development is initiated. The trials of the same drug studied in adults based on the same mechanism of action (MOA) can serve as valuable external data for pediatric oncology. Key considerations are highlighted in this section with details in section 3: a) Adult trials often include dose-finding studies, which can provide valuable starting points for pediatric dosing. This can streamline the process of determining appropriate dosage regimens for children. b) Utilizing existing adult trial data can help with interpretation of single-arm pediatric trial results. Incorporating efficacy observed in adults into pediatrics can inform the chance of efficacy in pediatrics. c) Adult trials provide a wealth of safety data based on MOA. Especially in on-target effects, which are considered as adverse drug reactions (ADRs) that are reasonably associated with the use of a drug. The on-target effects can be learned from adult development to inform the safety evaluation in pediatrics. An example of this usage will be illustrated in a case study of Blincyto in Section 5.

Disease Registries, Archives and Databases

Pediatric disease registries, which collect data on children with specific medical conditions, can provide valuable external control data. These registries often focus on rare diseases or conditions specific to children. In fact, registries are particularly valuable for studying rare diseases or conditions, as they can provide a larger sample size than individual clinical trials. They also enable the tracking of long-term effects that may not be captured in short-term trials. Pediatric disease registries include many advantages, described in further detail in the following sections describing two registries in greater detail.

National Childhood Cancer Registry

The National Childhood Cancer Registry (NCCR) (13) is a rapidly growing public health surveillance data resource. Its primary goal is to provide a platform to better understand the causes, outcomes, effective treatments, and later effects of cancer among children, adolescents, and young adults in the U.S. Developed under the NCI Childhood Cancer Data Initiative (CCDI), the NCCR contributes to the CCDI data ecosystem by serving as a linked infrastructure of central cancer registry data that will integrate various other childhood cancer data—from hospitals, research centers, heath care administrations, and other sources—to enhance access to and utilization of childhood cancer and survivorship data. The NCCR uses the Virtual Pooled Registry Cancer Linkage System_to link multiple cancer registries and generate an accurate count of childhood cancer cases by combining information that appears in more than one registry. In addition to the SEER registries, NCCR receives data from multiple state-based NPCR registries to currently provide coverage of approximately 70% of childhood cancer, with plans to expand coverage to 100% in the near

future. Multiple pilot projects to enhance patient-level data through electronic extraction from electronic health records to increase the granularity of treatment and outcome data are also in progress.

The NCCR will be updated annually with newly diagnosed cases. NCCR plans to continuously expand its capacity through linkages to externally available patient-level data to enhance its database with genomic (tumor and germline) and tumor characteristics, longitudinal treatment information (chemotherapy, surgery, and radiation), indicators of cancer recurrence, social determinants of health, and coexisting adverse health conditions as well as specimen availability and biorepository localization. The National Clinical Trials Network (NCTN)/The NCI Community Oncology Research Program (NCORP)

Data Archive

The NCI has created a centralized, controlled-access database, called the NCTN/NCORP Data Archive, for storing and sharing datasets generated from clinical trials of NCTN and NCORP. With some exceptions, the NCTN/NCORP Data Archive includes clinical data from:

- Primary publications of phase 3 trials published since January 1, 2015 and
- Selected non-primary publications of phase 3 trials published as of April 1, 2018

Data providers must submit data within 6 months of publication, after which submitted data undergo a review period by NCI and, if applicable, by trial pharmaceutical collaborators.).

The NCTN/NCORP Data Archive also includes clinical data from selected publications of phase 3 trials published prior to January 1, 2015. However, the data available for such legacy publications may include only a limited number of the variables that appeared in the publications.

Currently, data from 55 COG phase 3 and select phase 2 clinical trials for the following diseases: Acute Lymphoblastic Leukemia (ALL), Acute myeloid leukemia (AML), neuroblastoma, Germ cell tumors, retinoblastoma, Wilms tumor, medulloblastoma, and hepatoblastoma from April, 2016 through November, 2022 are available in the Archive.

NCTN/NCORP Data Archive contents supplied for each publication include a clinical dataset, a data dictionary, and limited metadata fields. Datasets are patient-level, de-identified, and include values for all variables used in the published analyses (with minor exceptions that, if present, are explained within the data submission). Data can be used to approximate published study findings, but exact reproduction of previous manuscripts may not be possible in some cases (e.g., when data must be modified for de-identification purposes or have undergone further data cleaning).

For selected trials, imaging data are also available via a link to The Cancer Imaging Archive (TCIA; http://www.cancerimagingarchive.net/), NCI's official imaging repository for NCTN Trials. Requestors seeking both clinical and imaging data must submit requests to the NCTN/NCORP Data Archive.

Other National Databases

Pediatric national databases are extensive collections of medical and health-related information focused specifically on the pediatric population. These databases contain data from various sources, such as hospitals, clinics, healthcare providers, and research studies, and are used to track health outcomes, treatments, and trends in children. For example, Ager et al (14) utilized data from the National Cancer Database (NCDB) to assess the impact of radiotherapy dose on overall survival (OS) in intracranial World Health Organization (WHO) grade II–III ependymoma within hospital-based adult and pediatric cohorts. NCDB captures nearly 70% of new cancer diagnoses made in the United States (15). Some key features of pediatric national databases are: (a) Comprehensive data encompassing a wide range of medical and healthcare information for children across diverse patient populations. (b) Large sample size (c) Real-world representation: reflecting real-world clinical practices and treatment patterns (d) Data on rare conditions and long-term effects.

Pediatric Electronic Health Records (EHRs)

Hospital-based or institution-specific EHRs may include a wide range of medical and health-related information, such as medical history, diagnoses, medications, lab results, and treatment plans. Key uses based on pediatric EHRs include: (a) Real-World Patient Data: Pediatric EHRs contain real-world data captured during routine clinical care, providing a comprehensive picture of a child's health history and treatment journey. (b) Longitudinal Data: EHRs often track patient information over time, allowing researchers to examine trends, disease progression, and treatment outcomes in the pediatric population. (c) Treatment Comparisons: Researchers can compare the outcomes of pediatric patients receiving a new treatment or intervention with those who have received different treatments or standard care documented in the EHRs. (d) Diverse Patient Population: EHRs cover a wide range of patients with varying conditions, backgrounds, and demographics, offering insights into the effects of treatments on diverse groups. (e) Long-Term Follow-Up: EHRs can help track long-term effects of treatments or interventions, which might not be feasible in short-term clinical trials.

All of the aforementioned sources come with limitations, e.g., data quality (accuracy, completeness and consistency in data capturing), selection bias (may not represent general population), confounding factor (e.g., comorbidities, disease severity) and temporal changes (changes in medical practice and standard of care). For EHRs, there are additional limitations: a) Privacy and Security: Ensuring patient privacy and complying with regulations such as HIPAA is crucial when accessing and using EHR data for research purposes. b) Data Accessibility: Gaining access to EHR data might require collaboration with healthcare institutions and compliance with their data-sharing policies. c) Auditability challenges: when use for regulatory purposes, it is often difficult for EHR data to be defensible through regulatory audit.

Other Sources

Data from previously published pediatric studies, especially observational studies, may be used as supportive evidence if the study populations are well-matched and the conditions being studied are comparable. The general use may include: (a) Literature Review:

Researchers can identify relevant studies in the scientific literature that have investigated similar treatments or interventions in pediatric populations. (b) Comparative Analysis: The outcomes of the new treatment group can be compared to the outcomes reported in the published studies' control groups. (c) Diverse Treatment Comparisons: Published studies might provide data on various treatment approaches, allowing researchers to evaluate a range of treatment options. (d) Historical Context: Published studies can provide insights into how treatment outcomes have evolved over time, helping to contextualize the results of the new intervention.

However, there are certain specific challenges and limitations: (a) Heterogeneity of Studies: Published studies might vary in terms of patient populations, methodologies, and outcome measures, making direct comparisons complex. (b) Differences in Study Designs: Studies may have different designs (observational, randomized, etc.) that affect their suitability as external controls. (c) Limited Data Availability: Not all studies provide detailed patient-level data on the control that the new trial is compared, potentially limiting the ability to make meaningful comparisons.

3. Considerations specific to Drug Development in Pediatric Oncology

Due to the prevalence of single-arm trials in pediatric oncology, construction and comparison to an external control arm emerge as a feasible alternative to generate actionable evidence. The weakness and limitations of external controls have been discussed extensively in literature, including subject selection bias, evolving disease and diagnostic definitions, improvements in standards of care over time, changes in disease evaluation criteria, immortal time bias, and other concerns related to the lack of patient-level data (3, 6); these weaknesses often preclude their use in adult drug development, where careful assessment and implementation of the external control are required for fit-for-purpose use to support adult drug development (16). Although many of those concerns are shared with pediatric oncology, the quality of the external data that can aid in external control generation and/or broadly support benefit-risk evaluation in pediatric oncology is often better or more comprehensive than in the adult setting. The reasons and the considerations are discussed in detail below.

We have grouped the discussions into areas of clinical questions, trial conduct and designs to discuss the considerations that have features that are different from adult development.

3.1 CLINICAL QUESTIONS

Development Paradigm—Recent research has reported that 45% of the driver genes in pediatric cancer matched those identified in the adult pan-cancer studies (17). More importantly, in those cancers that have driver genes affecting both adult and children, before the initiation of the pediatric trial, adult data are oftentimes available. Grobner et al (18) reported that ~50% of pediatric tumors may contain an alteration in a gene for which a targeted drug is available or under development. The activities and safety observed in adult may well be served as benchmark to design a pediatric trial or establish its substantial evidence.

Children 12 and older have the same percentages of total body water, extracellular fluid, and intracellular fluid and the same creatinine clearance as adults (19). The drug-metabolizing isoenzymes in the liver and intestine reach full maturation at 12 years of age. Therefore, no PK differences for volume of distribution of drugs and drug clearance would be expected between adolescent and adults (20). The inclusion of adolescent population with adult clinical studies has been endorsed in FDA guidance (21), ACCELERATE (22) and through Innovative Therapy for Children with Cancer Consortium (ITCC) (23). What's unique in pediatric oncology development paradigm for younger age groups is the availability of adolescent data to aid in the design and evaluation in the drug under investigation.

Isolation of Effect—Unlike in adult development, it is not uncommon for pediatric cancer patients to be treated with combination therapies, especially in the relapsed and refractory setting (7), and newer investigational drugs are often added to a current treatment backbone. For example, based on the COG study (CCG-7943, POG-9754, INT-0133, and AOST0121) for Osteosarcoma, the standard of care treatment is a combination of Cisplatin, Doxorubicin and high-dose Methotrexate. For ethical reasons, any new treatments being studied would be added to this current regimen; therefore, isolation of their effects from that of the backbone regimen might be challenging to establish in a single-arm setting. Results from previously conducted trials or other sources with the same existing regimens would aid in interpretation of the contribution of the new therapy.

Prognostic Factors—From the PK perspective, for younger patients, the drug metabolizing isoenzymes in the liver and intestine are immature at birth and take time to mature between ages 2 and 12 (20). Developmental factors also contribute to design considerations when using adolescent and adult data to study younger age patients.

Additionally, over-treatment is often a concern in pediatric patients with cancer when they are still in growth and pre-maturity stages of development. Prognostic factors (such as age or molecular markers) learned or validated in previous trials or external sources often aid in risk stratification and therapeutic intensification or de-intensification of prognostically-defined patient subgroups in future trials.

3.2 TRIAL POPULATION AND STUDY SITES

Clinical Trial Participation—Per Surveillance, Epidemiology and End Results (SEER) data from 2006, 14% of patients aged 15 to 39 years had enrolled onto a clinical trial, with the highest participation in those diagnosed with acute lymphoblastic leukemia (37%) and sarcoma (32%). The rate of participation in clinical trials for patients diagnosed between ages 15 and 19 years (34%) was significantly higher than those in all older age groups (3% in age 35 to 39) (24). Similarly, in a retrospective cohort study in Canada, 27.5% of children with cancer are enrolled onto therapeutic clinical trials with newly diagnosed between 0 and 14 years of age and diagnosed from 2001 to 2012 (25).

An example is COG's AAML0531 trial patients diagnosed with AML. The trial enrolled 1022 patients with 178/198 sites in US. Brown (26) noted that about 70 infants in the US are diagnosed with AML each year. In AAML0531, there were 207 infants with AML (27).

When considering external controls, the higher rate of participation in clinical trials in pediatric patients makes the quality and granularity of data in past clinical trials a better source and a more representative population than would be the same usage of external/prior clinical trials in the adult oncology setting.

Number of Trials in Pediatric Oncology—Unlike the adult trial landscape, many pediatric oncology trials are managed and operationalized through pediatric clinical research networks. Given the relatively limited population of patients diagnosed in the US for any given pediatric cancer, it is not uncommon for only one large Phase III trial at a time to be enrolling to specific 1st line indications; while in the relapsed and refractory setting, multiple trials may be ongoing by multiple companies to fulfill pediatric requirements.

Sites for Trial Conduct—The seminal paper by Pocock (28) has included 6 criteria to combine randomized and historical controls in clinical trials. One of the criteria is that the data are collected in the same setting and by the same investigator. This has been recognized as difficult to achieve in the adult setting.

As previously mentioned, children with cancer are generally seen by pediatric specialists at a limited set of cancer centers that has remained relatively stable over time. Over 80% of children diagnosed with cancer in the US are treated at COG member institutions. Similarly, in Canada, the C17 council comprises programs and 16 administrators that specialize in pediatric oncology across Canada (29). In Europe the Innovative Therapies for Children with Cancer (ITCC) has been a scientific center to gather experts who conduct early phase trials in children with cancer in European countries. In 2011, ITCC was established as a European Category 1 network for pediatric research at the European Medicines Agency (EnprEMA) (30). Across most geographic regions, children with cancer have been treated in the same centers and by the same investigators over time.

3.3 TRIAL DESIGNS

Endpoints—Endpoints to establish the benefit of investigational drugs are more likely to be objectively measured in pediatric oncology. In most pediatric trials, overall response rate (ORR) or the time-to-event endpoint is the primary endpoint. As reported in (31), over 75% of pediatric trials supporting drug label updates via FDA's issued written requests (WRs) between 2001–2019 in pediatric oncology were based on response rate endpoints. The response assessment criteria are based on established criteria, e.g., RECIST (Response Evaluation Criteria in Solid Tumors) in solid tumors, RANO (Response Assessment in Neuro-Oncology criteria) for brain tumors, Lugano or Cheson criteria for Hodgkin's lymphoma, blasts in bone marrow in acute lymphoblastic leukemia (ALL) and response criteria in acute myeloid leukemia (AML). In other poor prognosis diseases (e.g., relapsed neuroblastoma), overall survival (OS) would be the preferred endpoint and is objectively measured.

Dosing—As previously mentioned, pediatric drug development is initiated after adult. Both the starting dose in phase 1 pediatric trials and establishing the MTD (Maximum tolerable dose) and/or RP2D (recommended phase 2 dose) in pediatrics are informed based on the

corresponding adult's pharmacokinetics (PK), safety and activities. For example, in pediatric oncology programs submitted to US FDA between 2001 and 2019 (31), for a starting dose, the majority of the programs was based on empirical approach to match 100% or ~80% body size-adjusted adult dose, or used 50–70% of adult MTD or RP2D adjusted for body-weight or body surface area. Other approaches included allometric scaling of adult PK parameters (i.e., clearance and volume of distribution) based on children's body weight and account development factors such as organ and enzyme maturation, where ontogeny functions were added for dose projection.

For pediatric patients aged < 2 years, allometry alone has limitations to predict the drug clearance or optimal dose. One of the alternative approaches utilizing adult data is physiologically based pharmacokinetics (PBPK) model developed after adult PBPK through incorporating age-related changes in the system and drug-dependent information (32).

Safety Evaluation—Because of limited trial size in most pediatric trials, there is a need to prioritize what safety objectives can be achieved while keeping track of other risks. Two major areas have been identified: growth and maturation domain and on-target effects (33).

Children grow and mature at different paces. For growth evaluation, two prominent sources are from WHO (World Health Organization) and US CDC (Centers for Disease Control and Prevention), which are applicable to normal healthy children. In pediatric trials, reference to growth standards derived from pediatric oncology would be preferred if available. Maturation age can be determined by Tanner signs of sexual maturation in pediatric age groups during or soon to be starting puberty. For a single-arm trial, a shift table to compare the baseline and post-baseline height/weight/BMI SDS (standard deviation score) crossed down or up at least 2 main percentile curves can be used to illustrate potential abnormal growth (34).

For sexual maturity, evaluations can be conducted to compare the proportion of patients with precocious puberty/delayed puberty/hold of puberty to the expected proportion in a similar population that was not exposed to the study intervention. Similarly, age-based neurocognitive development can be evaluated by comparing the rate of development of cognition after treatment initiation and/or in the long term to a similar population that was not exposed to the medication (34).

On-target effects are adverse drug reactions (ADRs) that are reasonably associated with the use of a drug. The pediatric ADRs can be compared to the corresponding adult cohorts (33). When the evaluation is in long-term extension trials, adult information may not be relevant. The proportion of ADRs may be established that is not *f*-fold increased from the background rate, e.g., to a population that was not exposed to the medication. Sexual maturity, neurocognitive development, and ADRs in similar populations can be derived from registries or health claims databases (33).

4. Implications for Design and Analysis

This section provides a brief overview of statistical methodologies and design considerations while considering external control data in pediatric oncology trials. Careful consideration for

controlling potential bias and evaluating operating characteristics is required to understand the implications in decision-making.

4.1 ANALYSIS METHODS

A major concern about the use of external controls is the potential mismatch of external control data and current trial data, which can induce bias in the treatment comparison. Such bias can be caused by different sources, including selecting “relevant” external data, unmeasured confounders, systematic differences in data collection, missing data, and measurement errors. Many statistical approaches are available to borrow external control with a tangible degree of dissimilarity. Next, we describe a few approaches.

Propensity Score Methods—Propensity score methods are commonly used for causal inference on treatment effects in observational studies. The overall goal is to adjust for imbalance to the extent explanatory factors are available in the data. The key assumption for propensity score methods is that baseline covariates explain all differences between external data sources and current trials.

The two-stage propensity score study design proposed by (35) and (36) provides a paradigm for conducting a comparative observational, non-randomized study. Other propensity score-based methods include bias-adjusted (37) and propensity score-integrated composite likelihood methods (38–39). These approaches use stratification to enhance balance and bias adjustment using unmatched populations to reduce the bias in treatment comparison. Other than propensity score methods, other methods such as Bayesian nonparametric method (40) have also been proposed to balance the explanatory factors with minimal assumption.

Bayesian Hierarchical Model—Bayesian hierarchical models (BHM) combine data from multiple sources through prior exchangeability and shrinkage of response parameters. Meta-analytic approaches are the most commonly used BHM method for incorporating external control information in the design and analysis (41). The primary assumption of meta-analytic approaches is “exchangeability” or “similarity” between external control data and current trial data. These methods are flexible enough to adapt different types of source data, including individual subject data and aggregate data from publications. At the planning stage, a random-effects meta-analysis is used to construct a “pseudo-control” using relevant external control data. Once the trial data is observed, statistical inference on the difference between test and control is straightforward using all available data (from trial and relevant external control) and Bayesian inference. The degree of borrowing can be approximated by the “effective sample size” (ESS). Depending on the type of relevant source data, more complex meta-analytic approaches may be needed, including meta-regression, which uses baseline covariate information to explain part of the between-trial heterogeneity. Other BHM approaches such as commensurate prior (42), are conceptually similar as they also discount the external control information for potential heterogeneity.

Power Prior and Propensity Score-Integrated Power Prior—The power prior (43–44) assume the response parameter for the trial is the same as that for the external data. This is the main difference to the meta-analytic prior (MAP) (41), commensurate prior (42) and

BHM approaches. Power prior discounts the likelihood of the external control data using a power parameter with which it forms the prior for the response parameter of the trial. This parameter quantifies the discounting of the contribution to the likelihood from the external control subjects due to heterogeneity between the current study and the external data source. The key assumption of power prior is the "equality" of the parameter of interest between external control data and the current trial. When the "power parameter" is set to zero, no external data are used in the analysis, whereas when the power parameter is set to one, no down-weighting occurs. Thus, the power parameter is often considered the "proportion of the external data" used, which can be fixed or random. Adding a prior on the power parameter will allow for uncertainty in the analysis when the similarity between external control and the current trial is unknown.

Mixture Priors—Mixture priors provide another intuitive approach to addressing potential heterogeneity between the external control and the present study. This approach involves a combination of an informative prior, facilitating the extraction of information from the external control, and a noninformative prior, allowing for the disregard of external control influence. Assigning weights to these two priors achieves varying degrees of information incorporation, akin to the role played by the discount parameter in the power prior. An example of mixture priors is the robust MAP prior (41). A challenge of the robust MAP associated with the robust MAP lies in determining the appropriate weight for the mixture. The self-adaptive mixture prior (SAM) prior (45) has been proposed to address the issue of manually (sometimes arbitrarily) specifying the weight by enabling the data to autonomously determine its optimal value.

Other notable methods to borrow external control include advanced machine learning methods like Bayesian additive regression trees (BART) (46), random forests, neural networks, and cluster analysis. These novel techniques are robust to explore both linear and nonlinear relationships between outcomes and a large number of covariates. Also, these advanced techniques allow better identification of the homogeneous strata for composite likelihood and power prior to application, as described previously.

4.2 DESIGN IMPLICATIONS

Using external control data in the trial design and analysis requires proactive planning, careful implementation of the methodology, evaluation of the operating characteristics, and discussion with regulatory authorities well before the start of a trial.

An important design aspect is using simulations to estimate frequentist operating characteristics (e.g., type I error, power). It is essential to present these operating characteristics in the study protocol to maintain complete transparency about the design and planned analyses. Operating characteristics are also critical for studies intended to use Bayesian designs; both FDA's complex innovative design (47) and adaptive design (48) guidelines suggest the need for trial simulations. Intensive computations are often required to analyze trial data, assess prior probabilities at the design stage, perform simulations to assess the probabilities of various outcomes, and estimate sample size.

Pre-specification of protocol and statistical analysis plans provide confidence that the plan could be independently performed or duplicated. A detailed protocol should be provided with clear objectives, a description of the study population, and details regarding data sources and critical features of the study design and analysis plan, including lack of blinding, missing data, and handling unmeasured confounders. The statistical analysis plan or other companion documents should provide a detailed methodological approach and assumptions associated with operating characteristics. The final statistical analysis and a thorough plan for sensitivity analyses should be pre-specified and consistent with good statistical practice.

Using non-traditional analytic approaches poses an additional challenge regarding communicating trial results to regulatory statisticians and non-statisticians more familiar or comfortable with traditional trial designs. Most clinical team members will have no or minimal experience with such designs or analyses, and it is recommended that the approach's main features be explained using visual illustrations and non-statistical language. Examples include figures of prior and posterior distributions showing the reduction in uncertainty, and illustrating how individual instances of the trial could play out using simple language. Good preparation includes discussion of mock trial analyses with different data scenarios demonstrating possible outcomes.

5. Recent Examples

Two recent examples that use external controls to support pediatric drug programs are discussed below.

5.1 EXTERNAL CONTROLS FOR SUPPORTIVE COMPARATIVE EFFICACY AND SAFETY ANALYSES

In September 2016, the FDA approved the supplemental Biologics License Application (sBLA) under accelerated approval for Blincyto (blinatumomab) to include new data supporting the treatment of pediatric patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Full approval was granted in June 2023 upon verification of clinical benefit in subsequent trials.

The 2016 accelerated approval was based on results from Protocol 205, a single-arm, open-label, combined two-part multicenter study using blinatumomab in children under 18 years of age with Relaspsed/Refractory (R/R) ALL. Eligible patients had at least 25% blasts in the marrow. The primary endpoint for this objective was the CR (Complete Response) rate within the first 2 cycles of treatment. The efficacy of blinatumomab was evaluated in 70 pediatric subjects at the approved dose.

Since Protocol 205 was a single-arm trial, four previously conducted trials (Protocol 20130320, MT103–211, MT103–206, AALL1331) and analysis of two historical studies were submitted as supportive external data to aid evaluation.

Safety evaluations were based on all available safety data from Protocols 205 and 20130320, as well as the 212 adult subjects with R/R ALL treated on Protocols MT103–206 and

MT103–211. To be specific, Protocol 20130320 was an expanded access study in patients >28 days to <18 years with R/R ALL in second or greater BM relapse, any marrow relapse after allogeneic Hematopoietic stem cell transplantation (HSCT), or refractory to other treatments. Protocols MT103–206 and MT103–211 were open label, multicenter single arm studies of blinatumomab in adult patients with R/R ALL. Overall, the death rate in pediatric subjects was not significantly different than that for adult subjects based on the above dataset. The percentage of subjects in the >=45 kg subgroups who experienced Treatment Emergent Adverse Events (TEAEs), and the Standard of Cares (SOCs) represented, are similar to the frequencies in the 212 labeled adults.

There were two additional prospectively planned, retrospective analyses (Study 20140228 and 120521) of outcomes for pediatric patients with R/R ALL treated with conventional chemotherapy. The purpose of these studies was to provide additional support that the CR+CRh (CR with partial recovery of peripheral blood counts) rates in Protocol 205 were at least as good as those to be expected with conventional therapy in this heterogeneous population of patients with various disease states (number of prior therapies, prior HSCT etc.). Study 120521 was a meta-analysis of efficacy endpoints for existing therapies in pediatric patients with relapsed/refractory ALL. It was an application of a model-based meta-analysis to quantify the CR, EFS (Event-Free Survival) and OS (Overall Survival) for existing salvage therapies for the population enrolled in Protocol 205, and to estimate the efficacy of blinatumomab relative to existing salvage therapies with respect to these 3 outcomes. Using studies published after 2006, and covariates similar to those in Protocol 205, the odds ratio was in favor for blinatumomab compared to existing salvage therapies. Study 20140228 was a retrospective cohort study of re-induction treatment outcome among pediatric patients with R/R ALL. Its objective was to estimate CR in pediatric patients with R/R B-cell precursor ALL receiving SoC and to establish a CR rate that could serve as an external comparator to the CR proportion in Protocol 205. One hundred and twenty-one patients were included, and CR was reported for various disease strata. The above two studies' data provided additional supportive evidence that blinatumomab at the proposed dosing regimen for subjects <45 kg does not warrant a limitation of use. A summary of the above evidence has been included in Table 1 (49).

5.2 EXTERNAL CONTROL USED FOR I-OMBURTAMAB FOR CENTRAL NERVOUS SYSTEM (CNS)/LEPTOMENINGEAL (LM) METASTASES FROM NEUROBLASTOMA

On Oct 28, 2022, FDA's Oncology Drugs Advisory Committee unanimously voted against approving I-omburtamab for children with CNS/LM metastases from neuroblastoma. The committee discussed whether "the observed differences in overall survival between the single arm study 03–133 and external control population are due to I-omburtamab" or other factors ((FDA), FDA Briefing Document, BLA 761176 I-omburtamab by Y-mAbs Therapeutics).

^{131}I-omburtamab is an iodine-131 radiolabeled murine monoclonal antibody that binds to the B7-H3 (also known as cluster of differentiation 276, CD276) antigen. It is administered as an intraventricular infusion using an intracerebroventricular access device. The sponsor was seeking approval based on overall survival from an investigator-initiated, single arm,

single center trial (initiated by MSKCC) compared to an external control derived from the Central German Childhood Cancer Registry (CGCCR) and supportive data from a multi-center study (Study 101).

Although the sponsor had done due diligence in identifying the data source to build a comparable external control and conducted various sensitivity analyses to provide robust comparisons, multiple concerns were raised during the review process. Table lists the sponsor's efforts to mitigate potential bias and further concerns from the FDA.

In the pediatric setting using ECA, it is not uncommon to include imperfect Real-world data (RWD) such as single country data and/or data with imbalanced baseline characteristics, yet in this case study, across all sensitivity analyses conducted by FDA, no strong evidence of efficacy from the treated patients were observed. These sensitivity analyses include restricting the treatment era in ECA matching the single arm trial and using new index dates for a conservative comparison and some more. This stresses the importance of planning sensitivity analyses, best prespecified, in a submission using ECA, especially when the sample size is small.

6. Discussions and Conclusions

The US FDA has published regulatory guidance and resources when considering use of external control data to demonstrate efficacy of a drug or biologic (16). Although many of the considerations may be applicable to all oncology trials, context specifically relevant to pediatric oncology has not been discussed. Development of novel pediatric anticancer drugs poses significant obstacles, from biological, societal to economic, especially within the context of today's targeted therapy landscape. The rarity of pediatric cancer renders it impractical to execute gold standard randomized clinical trials in majority of conditions. Additionally, clinical equipoise may be difficult to assess when a drug is already approved for adults and is available on the market (50). Rather than "nice-to-have", external control data emerges to be necessary in many instances to demonstrate efficacy either by supplementing or replacing control data in a prospective clinical trial.

The advantages of external controls in the pediatric setting include availability of patient-level data, higher rate of clinical trial participation, centralized institutes and treating physicians, same or similar endpoints and diagnosis criteria used between external controls and developed trials, and informative adult data in the same drug to inform dose, efficacy and safety evaluations. Those advantages make external controls in pediatric oncology more likely to be fit-for-purpose than in the adult setting.

Statistical methods that borrow external data, especially adults data, for pediatrics trials may need additional model considerations. For example, it is apparent that adults and children are not "exchangeable" or "similar". To what extent or how to discount adults data for pediatric trial design or data analysis is an important and future research topic. Currently, most existing methods assume the response parameters for adults and children are either the same or follow an exchangeable prior distribution. This assumption is most likely violated for pediatric trials. More research is needed in this direction.

Nonetheless, the quality and granularity of external data that is needed to evaluate and control bias in such evaluations can be substantial. Pre-specification regarding the selection of patients and endpoints for protocol analyses, as well as careful analytic methods and examination of assumptions are required. Additionally, it is important to consult with pediatric ethicists, regulatory agencies, and relevant stakeholders to ensure that the chosen data sources and methodologies for establishing external controls align with ethical considerations and scientific rigor. Done well, use of external controls in supporting efficacy and overall benefit-risk evaluations has the potential to accelerate pediatric cancer drug development.

Funding Statement

This research was supported by NCI/NIH NCTN Operations Center Grant U10CA180886 and Statistics & Data Center Grant U10CA180899.

References

1. Ye J, Reaman G, De Claro R, & Sridhara R (2020). A Bayesian approach in design and analysis of pediatric cancer clinical trials. Pharmaceutical Statistics, 1–13. DOI: 10.1002/pst.2039.
2. Cooner F, Ye J, & Reaman G (2023). Clinical trial considerations for pediatric cancer drug development. Journal of Biopharmaceutical Statistics, DOI: 10.1080/10543406.2023.2172424.
3. Renfro L, Ji L, Piao J, Onar-Thomas A, Kairalla J, & Alonzo T (2019). Trial design challenges and approaches for precision oncology in rare tumors: experiences of the Children's Oncology Group (COG). JCO Precision Oncology, DOI 10.1200/PO.19.00060.COG), C. O. (2023). Retrieved from https://www.thecogfoundation.org/
4. Agrawal S, Arora S, Amiri-Kordestani L, & et al. (2023). Use of Single-Arm Trials for US Food and Drug Administration Drug Approval in Oncology, 2002–2021. JAMA Oncol., 9(2):266–272. doi:10.1001/jamaoncol.2022.5985. [PubMed: 36580315]
5. Chen J, Li X, Lu C, Yuan S, Yung G, Ye J, . . . Lin J, (2023). Considerations for Master Protocols Using External Controls. Journal of Biopharmaceutical Statistics.
6. Mishra-Kalyani PS (2022). External control arms in oncology: current use and future directions. Annals of Oncology, 10.1016/j.annonc.2021.12.015.
7. Adamczewska-Wawrzynowicz K, Wiacek A, & et al. (2023). Modern treatment strategies in pediatric oncology and hematology. Discover Oncology, 10.1007/s12672-023-00658-7.
8. DuBois S, Krailo M, Gebhardt M, & et al. (2015). Comparative evaluation of local control strategies in localized Ewing sarcoma of bone: a report from the Children's Oncology Group. Cancer, 121(3):467–75. doi: 10.1002/cncr.29065. [PubMed: 25251206]
9. Adams H, Adams H, Jackson C, Rincon-Torroella J, Jallo G, & Quinones-Hinojosa A (2016). Evaluating extent of resection in pediatric glioblastoma: a multiple propensity score-adjusted population-based analysis. Childs Nerv Syst, 32(3):493–503. doi: 10.1007/s00381-015-3006-x. [PubMed: 26767842]
10. (COG), C. O. (2023). Retrieved from https://www.thecogfoundation.org/
11. Unger J, & Fleury M (2021). Nationally representative estimates of the participation of cancer patients in clinical research studies according to the commission on cancer. Journal of Clinical Oncology, DOI: 10.1200/JCO.2020.39.28_suppl.74.
12. Ward E, DeSantis C, Robbins A, & et al. (2014). Childhood and Adolescent Cancer Statistics, 2014. CA Cancer J Clin, 64:83–103. [PubMed: 24488779]
13. (NCI), N. C. (n.d.). Statistics for cancers in children, adolescents, and young adults. Retrieved from https://nccrexplorer.ccdi.cancer.gov/
14. Ager B, Christensen M, Burt L, & Poppe M (2019). The value of high-dose radiotherapy in intracranial ependymoma. Pediatr Blood Cancer, 66(6):e27697. doi: 10.1002/pbc.27697. [PubMed: 30865382]

15. Bilimoria K, Stewart A, Winchester D, & Ko C (2008). The National Cancer Data Base: A Powerful Initiative to Improve Cancer Care in the United States. Ann Surg Oncol, 15(3): 683–690. doi: 10.1245/s10434-007-9747-3. [PubMed: 18183467]

16. (FDA), U. F. (2018, December). Framework for FDA's Real-world evidence program. Retrieved from https://www.fda.gov/media/120060/download

17. Ma X, Liu Y, Liu Y, & et al. (2018). Pan-cancer genome and transcriptome analyses of 1,699 pediatric leukaemias and solid tumors. Nature, 555:371–6. [PubMed: 29489755]

18. Grobner S, Worst B, Weischendieldt J, & et al. (2018). The landscape of genomic alterations across childhood cancers. Nature, 555:321–7 (FDA), U. F. (2019, November). Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry. Retrieved from https://www.fda.gov/media/78495/download [PubMed: 29489754]

19. Barrett J, Bishai R, & et al. (2018). Challenges and opportunities in the development of medical therapies for pediatric populations and the role of extrapolation. Clin Pharmacol Ther, 103(3):376–378. [PubMed: 29384202]

20. Mohamad S, Menon R, Gibbs J, & et al. (2019). Accelerating Drug Development in Pediatric Oncology With the Clinical Pharmacology Storehouse. The Journal of Clinical Pharmacology, 59(5):625–637. [PubMed: 30562405]

21. (FDA), U. F. (2019, March). Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials. Retrieved from https://www.fda.gov/media/113499/download

22. Gaspar N, Marshall L, Binner D, & et al. (2018). Joint adolescent adult early phase clinical trials to improve access to new drugs for adolescents with cancer proposals from the multistakeholder platform—ACCELERATE. Ann Oncol, 29(3):766–771. [PubMed: 29351570]

23. Moreno L, Pearson A, Paeletti X, & et al. (2017). Early phase clinical trials of anticancer agents in children and adolescents—an ITCC perspective. Nat Rev Clin Oncol, 14(8):497–507. [PubMed: 28508875]

24. Parsons H, Harlan L, Seibel N, Stevens J, & Keegan T (2011). Clinical Trial Pariticipation and Time to Treatment Among Adolescents and Young Adults with Cancer: Does Age at Diagnosis or Insurance Make a Difference? Journal of Clinical Oncology, 29:4045–4053.DOI: 10.1200/JCO.2011.36.2954. [PubMed: 21931022]

25. Pole J, Barber R, Bergeron R, & et al. (2017). Most children with cancer are not enrolled on a clinical trial in Canada: a population-based study. BMC Cancer, 17, 402. 10.1186/s12885-017-3390-6. [PubMed: 28583094]

26. Brown P (2013). Treatment of infant leukemias: challenge and promise. Hematology Am Soc Hematol Educ Program, 596–600. doi:10.1182/asheducation-2013.1.596. [PubMed: 24319237]

27. Gamis A, Alonzo T, & et al. (2014). Gemtuzumab ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Children's Oncology Group trial AAML0531. Journal of Clinical Oncology, 32(27):3021–32. doi: 10.1200/JCO.2014.55.3628. [PubMed: 25092781]

28. Pocock S (1976). The combination of randomized and historical controls in clinical trials. J Chronic Dis, 29(3):175–88. doi: 10.1016/0021-9681(76)90044-8. [PubMed: 770493]

29. Council TC (2023). The C17 Council. Retrieved from https://www.c17.ca/

30. Europe IT (2023). INNOVATIVE THERAPIES FOR CHILDREN WITH CANCER (ITCC). Retrieved from https://www.itcc-consortium.org/

31. Akalu A, Meng X, Reaman G, Ma L, Yuan W, & Ye J (2021). A review of the experience with pediatricwritten requests issued for oncology drug products. Pediatric Bloood & Cancer, Feb;68(2):e28828. doi: 10.1002/pbc.28828.

32. Ye J, Bi Y, & Ting N (2022). How to select the initial dose for a pediatric study? Journal of Biopharmaceutical Statistics, 10.1080/10543406.2022.2149770.

33. Gamalo M, Zhao Y, Gao A, Ye J, Lin J, Eshida E, . . . Nelson R (2023). Extent of safety database in pediatric drug development: types of assessment, analytical precision, and pathway for extrapolation through on-target effects. Journal of Biopharmaceutical Statistics, 10.1080/10543406.2023.2172425.

34. Choi Y, Barbier N, Furst-Recktenwald S, Ye J, Wajsbrot D, Ishida E, & Gamalo M (2022). Analysis and reporting of pediatric growth and development assessment

from clinical trials: overview and challenges. Journal of Biopharmaceutical Statistics, 10.1080/10543406.2022.2154357.

35. Yue LQ LN (2014). Designing premarket observational comparative studies using existing data as controls: challenges and opportunities. J Biopharm Stat, 24(5):994–1010. doi: 10.1080/10543406.2014.926367. [PubMed: 25013971]
36. Li H, Mukhi V, Lu N, & Xu Y (2016). A Note on Good Practice of Objective Propensity Score Design for Premarket Nonrandomized Medical Device Studies with an Example. Statistics in Biopharmaceutical Research, 8(3):DOI:10.1080/19466315.2016.1148071.
37. Stuart E. a. (2007). Best Practices in Quasi-Experimental Designs: Matching methods for causal inference. Chapter 11. In J. O. (Ed.)., Best Practices in Quantitative Social Science (pp. 155–176). Thousand Oaks, CA: Sage Publications.
38. Wang C, L. N. (2020). Propensity score-integrated composite likelihood approach for incorporating real-world evidence in single-arm clinical studies. J Biopharm Stat., 30(3):495–507. doi: 10.1080/10543406.2019.1684309. [PubMed: 31707908]
39. Chen WC WC (2020). Propensity score-integrated composite likelihood approach for augmenting the control arm of a randomized controlled trial by incorporating real-world data. J Biopharm Stat, 30(3):508–520. doi: 10.1080/10543406.2020.1730877. [PubMed: 32370640]
40. Chandra N, Sarkar A, de Groot J, Yuan Y, & Muller P (2023). Bayesian Nonparametric Common Atoms Regression for Generating Synthetic Controls in Clinical Trials. JASA, 10.1080/01621459.2023.2231581.
41. Schmidli HG (2014). Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics, 70(4): 1023–1032. 10.1111/biom.12242. [PubMed: 25355546]
42. Hobbs B CB (2011). Hierarchical commensurate and power prior models for adaptive incorporation of historical information in clinical trials. Biometrics, 67(3):1047–56. [PubMed: 21361892]
43. Chen M, & Ibrahim J (2000). Power prior distributions for regression models. Statist. Sci, 15(1): 46–60 (1 February 2000). DOI: 10.1214/ss/1009212673.
44. Chen M, & Ibrahim J (2006). The Relationship Between the Power Prior and Hierarchical Model. Bayesian Analysis, 1(3):551–574.
45. Yang P, Zhao Y, Nie L, Vallejo J, & Yuan Y (2023). SAM: Self-adapting mixture prior to dynamically borrow information from historical data in clinical trials. Biometrics, 10.1111/biom.13927.
46. Zhou T, & Ji Y (2021). Incorporating external data into the analysis of clinical trials via Bayesian additive regression trees. Statistics in Medicine, 40(28): 6421–6442. 10.1002/sim.9191. [PubMed: 34494288]
47. (FDA), U. F. (2020, December). Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products. Retrieved from https://www.fda.gov/media/130897/download?attachment
48. (FDA), U. F. (n.d.). FDA Briefing Document, BLA 761176 I-omburtamab by Y-mAbs Therapeutics. Retrieved from https://www.fda.gov/media/162614/download
49. Amgen. (2018, March 07). Background Materials for the Oncology Drugs Advisory Committee Meeting (ODAC) on Blinatumomab. Retrieved from https://www.fda.gov/media/111641/download
50. Sridhara R, Marchenko O, Jiang Q, & et al. (2023). Statistical Considerations in Pediatric Cancer Trials: Report of American Staistical Association Biopharmaceutical Section Open Forum Discussions. Statistics in Biopharmaceutical Research, 10.1080/19466315.2023.2238650.

Table 1:

Summary of Clinical Trial Details and Endpoints

Type	Trials	Design	Population	Primary Endpoint*
Pivotal Study	Protocol 205	Single-arm, open-label, Phase I-II dose-escalation -Ph I: Blin 3.75–60 μg/m^2/d × 28 days -Ph II: Blin 5–15 μg/m^2/d step dose	Children with Ph-negative precursor B-cell ALL in 2nd or later relapse -Ph I: 49 subjects - Ph II: 44 subjects	Ph 1: MTD Ph2: CR by 2 cycles
Supporting External Studies for Safety	Protocol 20130320 Protocol AALL 1331 Protocol MT103-206 Protocol MT103-211	Single-arm, open-label expanded access -Blin 5–15 μg/m^2/d step dose Risk-stratified randomized phase 3 - Blin 15 μg/m^2/d × 28 days - Blin 5–15 μg/m^2/d step dose Single-arm, open-label, Phase II dose-ranging trial - Blin 5–30 μg/m^2/d × 28 days Single-arm, open-label, Phase II trial - Blin 59–28 μg/m^2/d × 28 days	Children with precusor B-cell ALL in 2nd or later relapse -41 subjects Patients ≥ 1 year and <31 years in 1st relapse of B-ALL with or without extramedullary disease-37 subjects Adults with Ph-negative R/R precursor B-cell ALL -36 subjects Adults with Ph-negative R/R precursor B-cell ALL -233 subjects	Incidence of TEAEs and TRAEs DFS CR+CRhby 2 cycles CR+CRh by 2 cycles
Supporting External Studies for Efficacy	Study 20140228 Study 20140228	Meta analysis of existing therapies -Using only studies published after 2006, and covariates similar to those in Protocol 205 Retrospective Cohort Study of Re-induction Treatment Outcome - Data collected from patients treated at 14 clinical sites in the TACL Consortium from 2005–2013 -121 patients included in the primary analysis set	Pediatric Patients with Relapsed/ Refractory ALL Among Pediatric Patients with Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia (ALL)	CR EFS OS CR

*CR: Complete Response; EFS: Event-Free Survival; OS: Overall Survival; DFS: Disease-Free Survival; TEAEs: Treatment Emergent Adverse Events; MTD: Maximum Tolerated Dose; CRh=CR with partial recovery of peripheral blood counts; TRAEs: Treatment-related Adverse Events

Table 2:

Efforts made from the sponsor's side to address the validity of External Control Arm (ECA) and further issues identified by FDA

Issues	Sponsor's efforts	Further concerns from FDA
Fit-for-purpose ECA	CGCCR identified; data comparable with single arm trial in • Degree of complete resection • Presence of systemic disease • Treatment intensity	Do not agree with the sponsor that CGCCR is a fit-for- purpose ECA as it is not comparable with the single arm study in the following aspects • 95% in single arm study received craniospinal irradiation (CSI) and none in EC received CSI • Patients in internal single arm study may be healthier patients that are well enough to travel • Treatment era different (2005 – 2018 in single arm study vs 1991– 2020 in ECA) • Unknown factors such as different in clinical care between US and Germany
Index date	proposed 4 index dates and specified multiple sensitivity analyses considering various combinations of modality groups and index dates with and without imputation for missing covariates	Concerned about immortal time bias from any of the sponsor's proposed index dates. Proposed to use start date of Omburtamab treatment in the Study 03–133 population and last post-CNS relapse treatment in the ECA as the index dates for a conservative comparison.
Primary population	Received post-relapse RT and at least one other therapy (surgery or chemo)	Received post-relapse RT and at least one other therapy (surgery or chemo) and complete case
Propensity score method	Down-weigh external control	Down weight seemed to be arbitrary