HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2016 June 15.

Published in final edited form as:

Cancer. 2015 June 15; 121(12): 1927–1936. doi:10.1002/cncr.29267.

Improving Access To Novel Agents For Childhood Leukemia

Weili Sun, MD, PhD, **Paul S. Gaynon, MD**, **Richard Sposto, PhD**, and **Alan S. Wayne, MD**

Children's Center for Cancer and Blood Diseases, Division of Hematology, Oncology and Blood and Marrow Transplantation, Children's Hospital Los Angeles, USC Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California

Abstract

Leukemia is the most common pediatric cancer. Despite great progress in the development of curative therapy, leukemia remains a leading cause of death from disease in childhood and survivors are at life-long risk of complications of treatment. New agents are needed to further increase cure rates and decrease treatment-associated toxicities. The complex biology and aggressive nature of childhood leukemia, coupled with the relatively small patient population available for study, pose specific challenges to the development of new therapies. In this review, we discuss strategies and initiatives designed to improve access to new agents in the treatment of pediatric leukemia.

Keywords

Leukemia; Pediatric cancer; Childhood; Clinical trials; Developmental therapeutics; Targeted therapy

INTRODUCTION

Leukemia is the most common malignancy of childhood, representing approximately 25% of cancer diagnosed in children younger than 20 years of age.[1] Although survival rates have improved dramatically over the past several decades, leukemia remains one of the leading causes of death from disease in children. Additionally, the majority of those who are cured are at risk of short- and long-term complications of therapy.[2-9] Thus, there is a need to develop safe and effective new treatments to increase the cure rate for children with high-risk disease, optimize therapy for children with low-risk disease and minimize associated toxicities.

There are a large number of challenges that serve to impede the development of new therapies for children with leukemia. This includes the multiple phenotypic and molecular subtypes, the commonly aggressive nature of relapse with rapid disease progression and the complex array of medical co-morbidities frequently encountered in individuals with relapsed/refractory leukemia. Compounding these difficulties are the growing number of novel therapeutics in the face of the relatively small numbers of patients available for study.

Corresponding Author: Weili Sun, MD, PhD Children's Hospital Los Angeles 4650 Sunset Blvd., Mailstop #54 Los Angeles, CA 90027 Tel: 323-361-2601, Fax: 323-361-3837 wsun@chla.usc.edu.

Despite the many common clinical and biologic features of leukemias in children and adults, there are important differences that must be considered in regard to pediatric therapeutic development. For example, there is marked age-related variation in the frequency of specific genotypes of acute lymphoblastic leukemia (ALL).[10] Similarly, drugs used to treat leukemia may have variable effects based on age-associated pharmacokinetic and pharmacogenetic variation with impact on efficacy and toxicity.[2, 7, 9, 11-13] The high cost of new agent development in the context of the limited pediatric market, and the possible need for a different oral formulation for young children, pose additional deterrents for the pharmaceutical industry. Consequently, testing new agents in a high-risk pediatric leukemia patient population is extremely complex, challenging and resource intensive. Additionally, new drugs often need to be tested not only as single agents, but also in combination, which further complicates and extends clinical development.

In this review, we discuss strategies and initiatives designed to improve access to new agents and to speed the development of new therapies for pediatric leukemia.

BIOLOGIC AND PRECLINICAL STUDIES

Critical to new drug development in the era of molecularly targeted oncologic therapy are biologic and preclinical studies designed to define “druggable” targets and pathways. The National Cancer Institute (NCI) has established two programs to specifically foster preclinical study of childhood cancer in support of new agent development.

- The Therapeutically Applicable Research to Generate Effective Treatments (TARGET*) Program* (http://ocg.cancer.gov/programs/target). This is a program that uses genomic and epigenomic approaches to facilitate the discovery of new molecular targets for childhood cancers.
- *The Pediatric Preclinical Testing Program* (PPTP, http://pptp.nchresearch.org/). This initiative utilizes well-characterized xenograft mouse models and cell lines for preclinical testing to facilitate new drug selection for study in Phase I clinical trials.[14]

As examples of some initial successes, the TARGET project identified new genetic alterations in high-risk ALL including *IKZF1* deletion, *JAK* mutation, *CRLF2* rearrangement and Philadelphia chromosome (Ph) like subtype, which could lead to identification of new targeted treatment strategies.[15-23] The potential relevance of preclinical studies is exemplified by the study of dasatinib (Bristol-Myers Squibb Company Princeton, NJ), which was shown to induce complete remissions (CR) in Ph+ ALL murine xenograft models by the PPTP.[24] In a Phase I trial, this agent showed substantial activity in Ph+ ALL and CML.[25, 26] Further evidence of the possible clinical importance of such studies is illustrated by the successful use of the bcr-abl kinase inhibitor imatinib (Novartis, East Hanover, NJ) in a child with Ph-like ALL that was resistant to chemotherapy.[27]

These approaches need to be further validated and all data carefully analyzed in relation to clinical results. Misinterpretation and low reproducibility of preclinical data are common and can result in the termination of the development of oncology drugs.[28, 29] Importantly, the predictive power of *in vitro* and animal model testing for drug screening should never be

assumed. For example, although aurora kinase inhibitors showed activity in various preclinical cancer models,[30-32] clinical trial results in solid tumors and hematologic malignancies have been disappointing.[33] The lack of activity in patients may be due in part to the much longer doubling time of cancer cells in humans compared to *in vitro* cell lines and xenograft models.[33]

CLINICAL STUDIES

Early phase clinical trial groups

The international pediatric oncology community has worked together effectively through multi-center clinical trial consortia, the first of which was formed in 1955 (www.childrensoncologygroup.org). By treating children in carefully designed and executed clinical studies, the cure rate for childhood ALL has increased from about 10% fifty years ago to approximately 90% today.[34] A number of pediatric early phase clinical trial consortia have been established that are helping to advance the development of new therapies for children with leukemias (Table 1). The member institutions of these early phase clinical trial groups comprise large premier academic pediatric oncology centers working closely together to rapidly test new agents in childhood cancer. Since most of the members participate in the large cooperative groups, the trials conducted by these consortia often provide data in support of subsequent Phase II and III studies.

Selecting agents for pediatric clinical trials

New therapies are almost always first studied in relapsed/refractory patients for whom there are no standard therapies available. Since most pediatric leukemia patients are cured by frontline chemotherapy, there are only about 600 first relapse cases annually in the US.[1] Typically, Phase I studies require an average of 20-40 patients to complete[35] and currently, there are more than 380 new agents and more than 600 first-in-class medicines in various stages of study for hematologic malignancies.[36] Selected agents that are recently tested in pediatric leukemia see table 2 and 3. Unlike many solid tumor patients who might be able to move from one Phase I trial to another, children with leukemia often progress rapidly and become ineligible for subsequent study. How to strategically choose and prioritize agents for study from the large array of available therapies and potential targets remains a great challenge. As discussed above, there are limitations to selecting agents purely on the basis of target identification and/or preclinical data, although this is commonly utilized as a starting point. Loong and Siu listed favorable characteristics for a drug to enter Phase I testing[37] including:

- Robust, reproducible preclinical data verified in multiple models by independent resources.
- Established correlative biology studies that can be used as biomarkers of efficacy and resistance.
- Potentially better efficacy and/or safety profile in comparison to licensed drugs with similar mechanisms of action that justifies clinical testing.

Even if all of these criteria are adhered to, there are not enough pediatric patients with leukemia to study all such agents. Thus, the portfolio of available agents should be strategically examined and prioritized to determine which should be tested and in what order.

Notably, based on historical experience, most candidate agents fail and disappear from further development. In a recent study of drug development data from 835 companies from 2003-2011, the success rate for oncology drugs was the lowest among all diseases: only 1 in 15 drugs entering Phase 1 trial achieved FDA approval.[38] Investing scarce pediatric patients in trials of agents where future supply is uncertain may prove to be futile and wasteful. To reduce this risk, assessment of whether to continue or abandon agent development should be determined as rapidly as possible based on early results, positive or negative, and ongoing consideration of the security of drug supply.

To deal with many of the challenges noted above, and in order to increase the likelihood that an agent will be active, have an acceptable toxicity profile and ultimately be developed for commercial use, many drugs are selected for study in children only after they have undergone initial evaluation in adults. Although this by definition leads to a delay in pediatric development, in many cases this approach improves the chances of successful pediatric development and long term availability for use in children.

Phase I trial design

As discussed previously, among the challenges to conducting Phase I trials in pediatric leukemia are the limited number of patients, and therefore the limited amount of information that can inform the selection of a best dose and schedule. The most prevalent Phase I design is the standard 3+3,[39] but alternative designs have been developed and studied.[40, 41] One recently popular alternative, the rolling six design,[42] has been incorporated in many COG and TACL Phase I trials. It is a modification to the standard 3+3 design in an attempt to shorten the duration of the Phase I trial. The main difference is that patients are continually accrued based on the data available at the time of enrollment to allow up to six patients on a given dose cohort. In comparison to the standard 3+3 cohort design, the periods of time that studies are suspended to accrual are reduced,[42] the trial duration on average is somewhat shorter and the number of patients required is on average larger, with statistical properties equivalent to that of the 3+3.[43] Continuous reassessment designs have also been used in pediatric studies.[44] Phase I studies are of necessity small in patient numbers, and hence imprecise. While certain designs may be somewhat more precise or efficient in identifying a maximum-tolerated dose (MTD) in specific situations, these differences will not be large and there is not a uniformly “best design” to use in all scenarios. Hence it is important to screen agents rigorously in preclinical studies and also to extract as much information as possible about the *efficacy* of agents from Phase I studies.

When trials in adults have already been completed, one approach to shorten the time it takes to conduct a pediatric Phase I trial is to utilize limited dose levels based on the adult recommended Phase II dose.[45] In that regard, limiting pediatric Phase I trials to the study of no more than four doses levels at 0.7, 1.0, 1.3, and 1.6 times the adult MTD has been

proposed an a method to significantly shorten the study timeline without compromising the outcome.

Notably, parallel rather than sequential study in adults and children has been conducted in an effort to shorten the lag time to pediatric investigations. For example, pediatric and adult Phase I studies of clofarabine (Sanofi US, Bridgewater, CT) were conducted simultaneously. In this case, a modified 3+3 design was utilized in the pediatric study in anticipation of slower accrual such that children were allowed to enter at 1 dose level below a determined safe dose level in adults in order to speed dose escalation.[41] Similarly, an accelerated titration design has been incorporated in some pediatric Phase I studies in attempt to shorten the dose escalation time, speed trial completion and reduce the number of patients who are under-treated.[35] This approach was employed in a pediatric Phase I trial of moxetumomab pasudotox (MedImmune, Gaithersburg, MD), which was conducted in parallel with adult studies.[46]

Increasingly, early phase trials incorporate correlative biologic studies aimed to identify and assess biomarkers for target validation.[47] When a new compound has a well-characterized molecular target and compelling preclinical data in a biologically-defined patient population, it may be justified to enroll the specific subpopulation in Phase I trials to probe for an early signal about the possible response.[37] The right “stuff”,[48] (i.e., the right drug, target, and patient population) could be tested as early as a Phase I trial. For example, the TACL consortium recently completed a Phase I study testing the FLT3 inhibitor AC220 in combination with chemotherapy in childhood leukemia. Since a small subset of pediatric ALL (those with *MLL* rearrangement or hyperdiploid > 50 chromosomes) has been found to have over-expression of FLT3 and respond to FLT3 inhibitors *in vitro*,[49] these two ALL subtypes were also included in the Phase I trial and this upfront enrichment strategy enhanced accrual and biomarker evaluation.[50]

The traditional approach to test single agents can be problematic for patient accrual in childhood leukemia. Single-agent Phase I trials have historically often reported CR rates below 10%,[51] whereas multi-agent chemotherapy regimens have CR rates of approximately 25-40% in the setting of multiply relapsed ALL and AML[48, 52, 53] Physicians, patients and families may be hesitant to enroll onto single agent trials. For example, a Phase II trial of the anti-CD52 monoclonal antibody alemtuzumab (Genzyme Corporation, Cambridge, MA) in children with relapsed ALL conducted by the COG was closed prematurely due to poor accrual.[54] Since many new agents have completed Phase I evaluation in adults before testing is conducted in children, the TACL consortium encourages the study of new agents on multi-agent “backbone” chemotherapy regimens. This approach may reduce the difficulties in enrolling to and completing early phase leukemia trials because the backbone chemotherapy offers the possibility of additional disease control even if a CR is not achieved. This approach is also clinically relevant since any active novel agent is likely to eventually be used in the context of multi-agent chemotherapy. Carefully defining the toxicity profile of the novel agent in the background of a combination regimen is both challenging and important. A proposed approach is to compare the observed adverse events against the expected safety profile for the backbone alone, while also considering the known toxicities uniquely associated with the new and standard agents.[55]

Funding clinical trials

New drug development is costly. The average cost to bring an oncology drug to market is estimated to be approximately $1 billion U.S.[56, 57] In contrast, funding from the NCI for childhood leukemia in fiscal year 2013 was approximately $77 million U.S. (www.nih.gov). The financial market for pediatric oncology is very small. Each year, the number of children diagnosed with leukemia is a tiny fraction of the more common adult cancers. Thus, from the standpoint of the for-profit industry, it is not practical to develop new agents specifically for pediatric diseases. Pediatric oncology relies heavily on a “co-development” model of agents that share similar pathways or targets in cancers of adulthood and childhood. For example, the anti-CD22 immunotoxin moxetumomab pasudotox is very active in hairy cell leukemia, a disease encountered only in adult populations.[58] Since CD22 is expressed in almost all childhood B-lineage ALL, this agent is now being tested in children with relapsed ALL (ClinicalTrials.gov NCT00659425, NCT02227108).[46] Similarly, crizotinib (Pfizer, New York, NY), now approved by the U.S. Food and Drug Administration (FDA) for the treatment of anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer, is being tested in ALK+ neuroblastoma (ClinicalTrials.gov NCT00939770). Such agents are much less likely to be developed in the absence of an indication in adults. Identifying an industrial collaborator is even more difficult for agents with a limited patent duration. Consequently, it is recommended that pediatric trials begin early in the development process, although sponsors commonly wait until the medical oncology indications and market are defined.

U.S. FEDERAL AGENCY INITIATIVES

The U.S. government has recognized the challenges in pediatric drug development. In 2005, the Institute of Medicine and the National Research Council of the National Academies issued a report: *Making Better Drugs for Children with Cancer* (Washington DC: National Academies Press, 2005).[59] This report made three primary recommendations designed to reduce the delays in pediatric testing of new cancer drugs under development for adult cancers:

1. A new public–private partnership, involving government, industry, academic and other research institutions, advocacy groups, philanthropies, and others, should be formed to lead pediatric cancer drug discovery and development.
2. The NCI should assume responsibility as the developer of last resort for agents that show promise only in children if companies decide not to proceed with full-scale development.
3. The pharmaceutical industry, NCI, and FDA should act to reduce the delay in beginning pediatric clinical studies of agents in development for adult cancers.

As an example of the success of this approach, in 2009 the NCI allocated $8 million to produce a two-year supply of the anti-GD2 monoclonal antibody ch14.18 based on results of a Phase III clinical trial in neuroblastoma.[60] Through the NCI's Biopharmaceutical Development Program, sufficient product was manufactured to treat neuroblastoma patients as a transition to commercial production and licensing.

Additional federal initiatives have been designed to improve access to new agents and accelerate pediatric drug research.

- The Pediatric Oncology Subcommittee of FDA's Oncologic Drugs Advisory Committee (ODAC) (http://www.fda.gov/AdvisoryCommittees/) is an advisory committee that holds annual public meetings to discuss issues related to the development of pediatric oncology drugs and that provides guidance to facilitate pediatric studies.
- *ClinicalTrials.gov* (https://clinicaltrials.gov/) is a web-based registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. This resource provides public access to clinical trials information, including negative results that may be low priority for publication.

In addition, a number of legislative acts have been passed to accelerate pediatric drug development.

- *The Orphan Drug Act* was passed in 1983 to give financial incentives to stimulate the development of products for rare diseases.[61] It has led to an increasing number of pediatric marketing approvals over the past decade[62] with modest impact in childhood leukemia. Under the Act, clofarabine and asparaginase *Erwinia chrysanthemi* (Cigna, Bloomfield, CT) have been approved as orphan drugs in pediatrics. Notably, these were also the only oncology drugs that have been approved for pediatric indications in advance of adult approvals.
- *The Best Pharmaceuticals for Children Act (BPCA)*, which was signed into law in 2002, is a program that directs the FDA to request pediatric studies from sponsors to address public health needs in children. If the sponsor fulfills the request, the FDA will grant an additional 6 months of exclusivity on the drug. However, this is a voluntary program and the incentives do not apply to biologic agents such as immunotherapy, generic agents or off-patent drugs.[63]
- *The Pediatric Research Equity Act (PREA)*, which was enacted in 2003, gives the FDA the authority to require pediatric studies of drugs or biologics when other approaches are insufficient to ensure safety and efficacy in children. PREA is triggered and a pediatric assessment is required when sponsors file a New Drug Application.[63]
- *The Creating Hope Act*, which was passed in 2012, expands the cost-neutral FDA priority review voucher (PRV) program for rare pediatric diseases including childhood cancer.[64] When a company develops a drug exclusively for a pediatric rare disease, if qualified, the company can obtain a voucher that can be used to obtain priority review for another product, which could decrease the target time for FDA review from 10 to 6 months.[65]

The BPCA and PREA, which were signed into law permanently in 2012, have greatly accelerated pediatric drug development. They require that drug companies submit pediatric plans at the end of Phase II.[66] However, of note, the PREA applies to drugs developed for

diseases that occur in both children and adults and it does not address pediatric-specific conditions (e.g. juvenile myelomonocytic leukemia).

Access to investigational drugs outside of a clinical trial (Single-patient / Compassionate Use)

Expanded access, also sometimes known as “compassionate use”, is mechanism to provide an investigational drug outside of a clinical trial to treat a patient with a serious or immediately life-threatening disease.[67] This allows occasional use of an investigational agent for patients who do not meet protocol eligibility criteria. For example, the first pediatric use of the anti-CD3/anti-CD19 bi-specific T-cell engager blinatumomab (Amgen, Thousand Oaks, CA) was via a compassionate use mechanism in Germany for three children with relapsed ALL after allogeneic hematopoietic stem cell transplant. The agent was reported to be well tolerated and to induce minimal residual disease (MRD) negative CRs[68]. This experience provided further rationale for and fostered additional interest in pediatric trials of this agent.

CONCLUSIONS

Through the coordinated and collective efforts of the global pediatric oncology community, survival rates for children with leukemia have improved greatly over the past 5 decades. Further progress will require continued investment in preclinical research as new oncology drug development is very much biologically driven. This has proven true in the case of small molecule kinase inhibitors such as imatinib,[69] and has shown great potential based on the initial studies of cellular immunotherapy such as CD19 chimeric antigen receptor (CAR) T cell therapy.[70, 71] New technologies such as Next-Gen sequencing will need to be carefully analyzed and validated as they are used to identify novel agents to target specific pathways or molecules.

Agents should be prioritized for study based on all available data and Phase I trials should be designed to efficiently accrue, probe for response signals, and whenever possible, incorporate biologic studies for target validation and optimum biologic dosing (OBD) assessment, as well as elucidation of mechanisms of resistance. If a new agent appears to be too toxic and/or ineffective, trials should be quickly halted and negative results published.

Multicenter clinical trials greatly facilitate patient access and accrual. Collaboration between pediatric clinical trial consortia in North America, Europe and Australia has further fostered pediatric oncology drug development. Expansion of global collaborations to other regions such as Asia and South America should further increase access to novel agents for children with leukemia, although associated regulatory hurdles will need to be overcome. With the anticipated continued rise in the cost of drug development, partnerships between academia, governmental agencies, industry, philanthropic organizations, and advocacy groups will assume an increasingly important role.

Acknowledgments

Funding source acknowledgement: This work was supported in part by award number P30CA014089 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Financial disclosures: WS: none; PSG: Incyte (consultant), Jazz Pharamceuticals (consultant, honoraria), Novartis (consultant), Sigma Tau Pharmaceuticals (consultant, honoraria, research funding); RS: none; ASW: MedImmune (honorarium, research support, travel support), Co-inventor on investigational products with patents assigned to the NIH.

REFERENCES

1. Gaynon PS, Angiolillo AL, Carroll WL, et al. Long-term results of the children's cancer group studies for childhood acute lymphoblastic leukemia 1983-2002: a Children's Oncology Group Report. Leukemia. 24:285–297. [PubMed: 20016531]
2. Barr RD, Sala A. Osteonecrosis in children and adolescents with cancer. Pediatr Blood Cancer. 2008; 50:483–485. [PubMed: 18064641]
3. Diller L. Clinical practice. Adult primary care after childhood acute lymphoblastic leukemia. N Engl J Med. 2013; 365:1417–1424. [PubMed: 21995389]
4. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. JAMA. 2003; 290:1583–1592. [PubMed: 14506117]
5. Pui CH, Cheng C, Leung W, et al. Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. N Engl J Med. 2003; 349:640–649. [PubMed: 12917300]
6. Razzouk BI, Rose SR, Hongeng S, et al. Obesity in survivors of childhood acute lymphoblastic leukemia and lymphoma. J Clin Oncol. 2007; 25:1183–1189. [PubMed: 17401007]
7. Sala A, Mattano LA Jr. Barr RD. Osteonecrosis in children and adolescents with cancer - an adverse effect of systemic therapy. Eur J Cancer. 2007; 43:683–689. [PubMed: 17169552]
8. Shah A, Stiller CA, Kenward MG, Vincent T, Eden TO, Coleman MP. Childhood leukaemia: long-term excess mortality and the proportion 'cured'. Br J Cancer. 2008; 99:219–223. [PubMed: 18594545]
9. Vora A. Management of osteonecrosis in children and young adults with acute lymphoblastic leukaemia. Br J Haematol. 2011; 155:549–560. [PubMed: 22077340]
10. Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Engl J Med. 2004; 350:1535–1548. [PubMed: 15071128]
11. Rieder MJ, Carleton B. Pharmacogenomics and adverse drug reactions in children. Front Genet. 2014; 5:78. [PubMed: 24795743]
12. Veal GJ, Boddy AV. Chemotherapy in newborns and preterm babies. Semin Fetal Neonatal Med. 2012; 17:243–248. [PubMed: 22464845]
13. Bartelink IH, Rademaker CM, Schobben AF, van den Anker JN. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet. 2006; 45:1077–1097. [PubMed: 17048973]
14. Houghton PJ, Morton CL, Tucker C, et al. The pediatric preclinical testing program: description of models and early testing results. Pediatr Blood Cancer. 2007; 49:928–940. [PubMed: 17066459]
15. Mullighan CG, Zhang J, Harvey RC, et al. JAK mutations in high-risk childhood acute lymphoblastic leukemia. Proc Natl Acad Sci U S A. 2009; 106:9414–9418. [PubMed: 19470474]
16. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med. 2009; 360:470–480. [PubMed: 19129520]
17. Zhang J, Mullighan CG, Harvey RC, et al. Key pathways are frequently mutated in high-risk childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group. Blood. 2011; 118:3080–3087. [PubMed: 21680795]
18. Roberts KG, Morin RD, Zhang J, et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. Cancer Cell. 2012; 22:153–166. [PubMed: 22897847]

19. Loh ML, Zhang J, Harvey RC, et al. Tyrosine kinome sequencing of pediatric acute lymphoblastic leukemia: a report from the Children's Oncology Group TARGET Project. Blood. 2012; 121:485–488. [PubMed: 23212523]
20. Kang H, Chen IM, Wilson CS, et al. Gene expression classifiers for relapse-free survival and minimal residual disease improve risk classification and outcome prediction in pediatric B-precursor acute lymphoblastic leukemia. Blood. 2009; 115:1394–1405. [PubMed: 19880498]
21. Harvey RC, Mullighan CG, Wang X, et al. Identification of novel cluster groups in pediatric high-risk B-precursor acute lymphoblastic leukemia with gene expression profiling: correlation with genome-wide DNA copy number alterations, clinical characteristics, and outcome. Blood. 2010; 116:4874–4884. [PubMed: 20699438]
22. Harvey RC, Mullighan CG, Chen IM, et al. Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. Blood. 2010; 115:5312–5321. [PubMed: 20139093]
23. Maude SL, Tasian SK, Vincent T, et al. Targeting JAK1/2 and mTOR in murine xenograft models of Ph-like acute lymphoblastic leukemia. Blood. 2012; 120:3510–3518. [PubMed: 22955920]
24. Kolb EA, Gorlick R, Houghton PJ, et al. Initial testing of dasatinib by the pediatric preclinical testing program. Pediatr Blood Cancer. 2008; 50:1198–1206. [PubMed: 17914733]
25. Ottmann O, Dombret H, Martinelli G, et al. Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. Blood. 2007; 110:2309–2315. [PubMed: 17496201]
26. Aplenc R, Blaney SM, Strauss LC, et al. Pediatric phase I trial and pharmacokinetic study of dasatinib: a report from the children's oncology group phase I consortium. J Clin Oncol. 2011; 29:839–844. [PubMed: 21263099]
27. Weston BW, Hayden MA, Roberts KG, et al. Tyrosine kinase inhibitor therapy induces remission in a patient with refractory EBF1-PDGFRB-positive acute lymphoblastic leukemia. J Clin Oncol. 2013; 31:e413–416. [PubMed: 23835704]
28. Prinz F, Schlange T, Asadullah K. Believe it or not: how much can we rely on published data on potential drug targets? Nat Rev Drug Discov. 2011; 10:712. [PubMed: 21892149]
29. Begley CG, Ellis LM. Drug development: Raise standards for preclinical cancer research. Nature. 2012; 483:531–533. [PubMed: 22460880]
30. Maris JM, Morton CL, Gorlick R, et al. Initial testing of the aurora kinase A inhibitor MLN8237 by the Pediatric Preclinical Testing Program (PPTP). Pediatr Blood Cancer. 2010; 55:26–34. [PubMed: 20108338]
31. Pollard JR, Mortimore M. Discovery and development of aurora kinase inhibitors as anticancer agents. J Med Chem. 2009; 52:2629–2651. [PubMed: 19320489]
32. Hartsink-Segers SA, Zwaan CM, Exalto C, et al. Aurora kinases in childhood acute leukemia: the promise of aurora B as therapeutic target. Leukemia. 2013; 27:560–568. [PubMed: 22940834]
33. Komlodi-Pasztor E, Sackett DL, Fojo AT. Inhibitors targeting mitosis: tales of how great drugs against a promising target were brought down by a flawed rationale. Clin Cancer Res. 2012; 18:51–63. [PubMed: 22215906]
34. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol. 2012; 30:1663–1669. [PubMed: 22412151]
35. Simon R, Freidlin B, Rubinstein L, Arbuck SG, Collins J, Christian MC. Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst. 1997; 89:1138–1147. [PubMed: 9262252]
36. PhRMA. [March 3, 2014] Medicines in Development, Leukemia & Lymphoma, A Report on Cancers of the Blood. Available from URL: http://www.phrma.org/sites/default/files/pdf/LeukemiaLymphoma2013.pdf
37. Loong HH, Siu LL. Selecting the best drugs for phase I clinical development and beyond. Am Soc Clin Oncol Educ Book. 2013:469–473. [PubMed: 23714572]
38. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. Nat Biotechnol. 2014; 32:40–51. [PubMed: 24406927]

39. Rogatko A, Schoeneck D, Jonas W, Tighiouart M, Khuri FR, Porter A. Translation of Innovative Designs Into Phase I Trials. Journal of Clinical Oncology. 2007; 25:4982–4986. [PubMed: 17971597]
40. Le Tourneau C, Lee JJ, Siu LL. Dose Escalation Methods in Phase I Cancer Clinical Trials. Journal of the National Cancer Institute. 2009; 101:708–720. [PubMed: 19436029]
41. Jeha S, Gandhi V, Chan KW, et al. Clofarabine, a novel nucleoside analog, is active in pediatric patients with advanced leukemia. Blood. 2004; 103:784–789. [PubMed: 14551141]
42. Skolnik JM, Barrett JS, Jayaraman B, Patel D, Adamson PC. Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol. 2008; 26:190–195. [PubMed: 18182661]
43. Sposto R, Groshen S. A wide-spectrum paired comparison of the properties of the Rolling 6 and 3+3 Phase I study designs. Contemp Clin Trials. 2011; 32:694–703. [PubMed: 21554993]
44. Onar-Thomas A, Xiong Z. A simulation-based comparison of the traditional method, Rolling-6 design and a frequentist version of the continual reassessment method with special attention to trial duration in pediatric Phase I oncology trials. Contemporary Clinical Trials. 2010; 31:259–270. [PubMed: 20298812]
45. Lee DP, Skolnik JM, Adamson PC. Pediatric phase I trials in oncology: an analysis of study conduct efficiency. J Clin Oncol. 2005; 23:8431–8441. [PubMed: 16293874]
46. Wayne, A.; Shah, N.; Bhojwani, D., et al. Pediatric phase 1 trial of moxetumomab pasudotox: Activity in chemotherapy refractory acute lymphoblastic leukemia (ALL).. 2014 American Association for Cancer Research Annual Meeting; San Diego, CA. 2014;
47. Goulart BH, Clark JW, Pien HH, Roberts TG, Finkelstein SN, Chabner BA. Trends in the use and role of biomarkers in phase I oncology trials. Clin Cancer Res. 2007; 13:6719–6726. [PubMed: 18006773]
48. Gaynon PS. Childhood acute lymphoblastic leukaemia and relapse. Br J Haematol. 2005; 131:579–587. [PubMed: 16351633]
49. Brown P, Levis M, McIntyre E, Griesemer M, Small D. Combinations of the FLT3 inhibitor CEP-701 and chemotherapy synergistically kill infant and childhood MLL-rearranged ALL cells in a sequence-dependent manner. Leukemia. 2006; 20:1368–1376. [PubMed: 16761017]
50. Cooper, T.; Malvar, J.; Cassar, J., et al. A Phase I Study Of AC220 (Quizartinib) In Combination With Cytarabine and Etoposide In Relapsed/Refractory Childhood ALL and AML: A Therapeutic Advances In Childhood Leukemia & Lymphoma (TACL) Study.. 55th American Society of Hematology (ASH) annual meeting and exposition; New Orleans, LA. 2013;
51. Shah S, Weitman S, Langevin AM, Bernstein M, Furman W, Pratt C. Phase I therapy trials in children with cancer. J Pediatr Hematol Oncol. 1998; 20:431–438. [PubMed: 9787315]
52. Ko RH, Ji L, Barnette P, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. J Clin Oncol. 2009; 28:648–654. [PubMed: 19841326]
53. Gorman MF, Ji L, Ko RH, et al. Outcome for children treated for relapsed or refractory acute myelogenous leukemia (rAML): a Therapeutic Advances in Childhood Leukemia (TACL) Consortium study. Pediatr Blood Cancer. 2010; 55:421–429. [PubMed: 20658611]
54. Angiolillo AL, Yu AL, Reaman G, Ingle AM, Secola R, Adamson PC. A phase II study of Campath-1H in children with relapsed or refractory acute lymphoblastic leukemia: a Children's Oncology Group report. Pediatr Blood Cancer. 2009; 53:978–983. [PubMed: 19637330]
55. Horton TM, Sposto R, Brown P, et al. Toxicity assessment of molecularly targeted drugs incorporated into multiagent chemotherapy regimens for pediatric acute lymphocytic leukemia (ALL): review from an international consensus conference. Pediatr Blood Cancer. 2010; 54:872–878. [PubMed: 20127846]
56. Adams CP, Brantner VV. Estimating the cost of new drug development: is it really 802 million dollars? Health Aff (Millwood). 2006; 25:420–428. [PubMed: 16522582]
57. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ. 2003; 22:151–185. [PubMed: 12606142]
58. Kreitman RJ, Tallman MS, Robak T, et al. Phase I trial of anti-CD22 recombinant immunotoxin moxetumomab pasudotox (CAT-8015 or HA22) in patients with hairy cell leukemia. J Clin Oncol. 2012; 30:1822–1828. [PubMed: 22355053]

59. Institute of Medicine and National Research Council. Making Better Drugs for Children with Cancer. National Academies Press; Washington DC: 2005.
60. Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 2010; 363:1324–1334. [PubMed: 20879881]
61. Designation of drugs for rare diseases or conditions (Orphan Drug Act), 21 USC 360aa. 2010
62. Thorat C, Xu K, Freeman SN, et al. What the Orphan Drug Act has done lately for children with rare diseases: a 10-year analysis. Pediatrics. 129:516–521. [PubMed: 22371464]
63. Institute of Medicine (US) Forum on Drug Discovery D, and Translation. Addressing the barriers to pediatric drug development. 2008
64. The creating hope act. 2012 S 606, HR 3059.
65. Connor E, Cure P. “Creating hope” and other incentives for drug development for children. Sci Transl Med. 2011; 3:66cm61.
66. Pediatrics AAo. [March 14, 2014] Pediatric Drug and Device Laws: Reauthorization Summary, Food and Drug Administration Safety and Innovation Act. Enacted July 9, 2012. Available from URL: http://www.aap.org/en-us/advocacy-and-policy/federal-advocacy/Documents/PediatricDrugDeviceLawsReauthorizationSummary.pdf
67. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014; 371:1507–1517. [PubMed: 25317870]
68. Handgretinger R, Zugmaier G, Henze G, Kreyenberg H, Lang P, von Stackelberg A. Complete remission after blinatumomab-induced donor T-cell activation in three pediatric patients with post-transplant relapsed acute lymphoblastic leukemia. Leukemia. 2011; 25:181–184. [PubMed: 20944674]
69. Bond M, Bernstein ML, Pappo A, et al. A phase II study of imatinib mesylate in children with refractory or relapsed solid tumors: a Children's Oncology Group study. Pediatr Blood Cancer. 2008; 50:254–258. [PubMed: 17262795]
70. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med. 2013; 368:1509–1518. [PubMed: 23527958]
71. Brentjens RJ, Davila ML, Riviere I, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. Sci Transl Med. 2013; 5:177ra138.
72. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2014
73. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med. 2014; 6:224ra225.
74. Haso W, Lee DW, Shah NN, et al. Anti-CD22-chimeric antigen receptors targeting B-cell precursor acute lymphoblastic leukemia. Blood. 2013; 121:1165–1174. [PubMed: 23243285]
75. Hoffman LM, Gore L. Blinatumomab, a Bi-Specific Anti-CD19/CD3 BiTE((R)) Antibody for the Treatment of Acute Lymphoblastic Leukemia: Perspectives and Current Pediatric Applications. Front Oncol. 2014; 4:63. [PubMed: 24744989]
76. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. J Clin Oncol. 2010; 28:3880–3889. [PubMed: 20660823]
77. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Lancet Oncol. 2012; 13:403–411. [PubMed: 22357140]
78. Raetz EA, Cairo MS, Borowitz MJ, et al. Chemoimmunotherapy reinduction with epratuzumab in children with acute lymphoblastic leukemia in marrow relapse: a Children's Oncology Group Pilot Study. J Clin Oncol. 2008; 26:3756–3762. [PubMed: 18669463]
79. Herrera L, Bostrom B, Gore L, et al. A phase 1 study of Combotox in pediatric patients with refractory B-lineage acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2009; 31:936–941. [PubMed: 19875969]
80. Gamis AS, Alonzo TA, Meshinchi S, et al. 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. J Clin Oncol. 2014; 32:3021–3032. [PubMed: 25092781]

81. Cooper TM, Franklin J, Gerbing RB, et al. AAML03P1, a pilot study of the safety of gemtuzumab ozogamicin in combination with chemotherapy for newly diagnosed childhood acute myeloid leukemia: a report from the Children's Oncology Group. Cancer. 2012; 118:761–769. [PubMed: 21766293]
82. Zwaan CM, Reinhardt D, Zimmerman M, et al. Salvage treatment for children with refractory first or second relapse of acute myeloid leukaemia with gemtuzumab ozogamicin: results of a phase II study. Br J Haematol. 2010; 148:768–776. [PubMed: 19995399]
83. Aplenc R, Alonzo TA, Gerbing RB, et al. Safety and efficacy of gemtuzumab ozogamicin in combination with chemotherapy for pediatric acute myeloid leukemia: a report from the Children's Oncology Group. J Clin Oncol. 2008; 26:2390–3295. [PubMed: 18467731]
84. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol. 2009; 27:5175–5181. [PubMed: 19805687]
85. Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. Lancet Oncol. 2012; 13:936–945. [PubMed: 22898679]
86. Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia. 2014; 28:1467–1471. [PubMed: 24441288]
87. Witt O, Milde T, Deubzer HE, et al. Phase I/II intra-patient dose escalation study of vorinostat in children with relapsed solid tumor, lymphoma or leukemia. Klin Padiatr. 2012; 224:398–403. [PubMed: 22915450]
88. Burke MJ, Lamba JK, Pounds S, et al. A therapeutic trial of decitabine and vorinostat in combination with chemotherapy for relapsed/refractory acute lymphoblastic leukemia. Am J Hematol. 2014; 89:889–895. [PubMed: 24891274]
89. Messinger YH, Gaynon PS, Sposto R, et al. Bortezomib with chemotherapy is highly active in advanced B-precursor acute lymphoblastic leukemia: Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) Study. Blood. 2012; 120:285–290. [PubMed: 22653976]
90. Messinger Y, Gaynon P, Raetz E, et al. Phase I study of bortezomib combined with chemotherapy in children with relapsed childhood acute lymphoblastic leukemia (ALL): a report from the therapeutic advances in childhood leukemia (TACL) consortium. Pediatr Blood Cancer. 2010; 55:254–259. [PubMed: 20582937]
91. Horton TM, Pati D, Plon SE, et al. A phase 1 study of the proteasome inhibitor bortezomib in pediatric patients with refractory leukemia: a Children's Oncology Group study. Clin Cancer Res. 2007; 13:1516–1522. [PubMed: 17332297]

PRECIS

The complex biology and aggressive nature of childhood leukemia, coupled with the relatively small patient population available for study, pose specific challenges to the development of new therapies. In this review, we discuss strategies and initiatives designed to improve access to new agents and early phase clinical trials for pediatric leukemia.

Table 1

Early phase clinical trial consortia in pediatric oncology

	Brief Description	Website
COG Phase 1 and Pilot Consortium	21 institution consortium in North America that conducts Phase I trials in both solid tumors and leukemias of childhood	http://www.childrensoncologygroup.org/index.php/phase-1-home
POETIC	10 institution association in North America that conducts Phase I trials for both solid tumors and leukemia	http://poeticphase1.org/
TACL	35 institution early phase clinical trial group in North America and Australia; the only clinical trial group focused solely on childhood hematologic malignancies	https://ipcr.chla.usc.edu/tacl/
ITCC	43 pediatric oncology program and 9 research laboratories in 10 European countries that conducts Phase I trials for both solid tumors and leukemia	http://www.itcc-consortium.org/
ACTT	7 institution early phase clinical trial group in Australia and New Zealand focuses on both solid tumors and leukemias.	http://www.anzchogtrials.org/site/index.php/page/about-ACCT

ACTT, The Australian Children's Cancer Trials; COG, The Children's Oncology Group; ITCC, The Innovative Therapies for Children with Cancer Consortium; POETIC, The Pediatric Oncology Experimental Therapeutics Investigator's Consortium; TACL, The Therapeutic Advances in Childhood Leukemia and Lymphoma Consortium

Table 2

Recent studies using immunotherapies to treat pediatric acute leukemia (ClinicalTrials.gov and Pubmed, accessed 12/31/2014)

Class	Target	Name	Mechanism	Studies in pediatric acute leukemia
Cell therapy	CD19	CD19CART cells	Genetic modified T cells expressing CD19 specific CAR	[67, 70-73], NCT02028455,NCT 01864889, NCT01853631, NCT01593696, NCT01683279, NCT00840853, NCT01195480, NCT01864889
		CD19 CAR EBV-CTL	Allogeneic EBV specific cytotoxic T-lymphocytes (CTL) genetically modified to express CD19 specific CAR	NCT01430390
	CD22	CD22 CAR T cells	Genetic modified T cells expressing CD22 specific CAR	[74], NCT02315612
	CD33	CART-33	Modified autologous or donor-derive T cells expressing CD33 specific CAR	NCT01864902
Antibody therapy	CD19/CD3	Blinatumomab	Bispecific T cell engager Ab	[68, 75], NCT0210853, NCT02187354
	CD19	SGN-CD19A	mAb conjugated with monomethyl auristatin F	NCT017860
		SAR-3419	mAb conjugated with tubulin inhibitor maytasine derivative	NCT01440179 (terminated by sponsor)
		MOR00208	Fc-Optimized mAb	NCT01685021
	CD20	Rituximab	mAb	[76], NCT01700946, NCT02259348, NCT1595048, NC01429610
	CD22	Moxetumomab	mAb conjugated with pseudomonas exotoxin	NCT02227108, NCT00659425
		Inotuzumab	mAb conjugated with calicheamicin	[77]
		Epratuzumab	mAb	[78], NCT01279707, NCT00098839, NCT01802814
	CD19/CD22	Combotox	Bispecific mAb conjugated with ricin A chain	[79]NCT01408106
	CD33	Gemtuzumab	mAb conjugated with calicheamicin	[80-83], NCT02221310
	CD45	AHN-12	mAb conjugated to the radioisotope yttrium 90	
	CD52	Alemtuzumab	mAb	[54], NCT00089349 (completed)

CAR, chimeric antigen receptor; EBV, Epstein-Barr virus; mAb, monoclonal antibody

Table 3

Recent studies targeting cellular pathways in pediatric acute leukemia (ClinilTrial.gov and Pubmed, accessed 12/31/2014)

Class	Target	Name	Mechanism	Studies in pediatric acute leukemia
Tyrosine	BCR-ABL	Imatinib	Abl kinase inhibitor	[84-86], N00287105, NT01491763, NCT 01883219
		Dasatinib	Dual Src and Abl kinase inhibitor, penetrates CSF	NCT00720109, NCT01004497, NCT01460160
		Nilotinib	Inhibits imatinib resistant BCR-ABL mutations (not T351I), c-Kit, PDGFR	N01844764, NCT001219740, NCT01077544
	FLT3	Midostaurin	Multikinase inhibitor for FLT3, PKC, VEGFR, PDGFR, c-Kit	NCT00866281 (completed), NCT00977782 (completed)
		Quizartinib	Inhibits Class III TK including FLT3, CSF1R, c-Kit, PDGFR	NCT01411267 (completed)
		Lestaurtinib	Inhibits autophosphorylation of FLT3	NCT00557193 (not recruiting), NCT00469859 (not recruiting)
		Sorafenib	Inhibits FLT-ITD, RAF, VEGFR	NCT01371981, NCT01445080 (completed), NCT00908167, NCT02270788
		Crenolanib	Inhibits FLT3, PDGFRα	NCT02270788
	JAK	Ruxolitinib	Inhibits JAK1 and 2	NCT01164163 (completed), NCT01251965 (not recruiting)
Serine/Thre onine kinase	mTOR	Sirolimus	Binds to FKBP-12 to generate a complex to inhibit mTOR	NCT01658007, NCT00874562 (not recruiting)
		Everolimus	Derivative of the natural macrocyclic lactone sirolimus	NCT01523977
		Temsirolimus	Derivative of rapamycin	NCT01403415 (not recruiting)
	AKT	MK2206	Binds to AKT and inhibit PI3K/AKT signaling pathway	NCT01231919 (completed)
	Aurora Kinase	Alisertib	Aurora kinase A inhibitor	NCT01154816 (completed)
		AT9283	Multikinase inhibitor: Aurora Kinase A, B, JAK, BCR-ABL	NCT01431664 (completed)
	Polo-like Kinase	Volasertib	Competitive inhibitor of Polo-like kinase 1	NCT01971476
Epigenetics	DNMTs	Azacitidine	Nucleoside analog causes DNA hypomethylation	NCT01861002 (completed), NCT01995578, NCT01700673
		Decitabine	Nucleoside analog causes DNA hypomethylation	NCT02264873, NCT01853228, NCT01177540
	HDACi	Panobinostat	Binds to and inhibits histone deacetylase	NCT01321346
		Vorinostat	Binds to and inhibits histone deacetylase	[87]
		FR901228		NCT00090531963 (completed)
	DNMT + HDACi	Decitabine + Vorinostat or AR-42	See above	[88], NCT01483690, NCT01798901

Class	Target	Name	Mechanism	Studies in pediatric acute leukemia
	DOT	EPZ-5676	Inhibits protein methyltransferase DOT1L	NCT02141828
Protein Degradation	Proteasome	Bortezomib	Reversible inhibitor of proteasome	[89-91], NCT02112916, NCT01371981
		Carfilzomib	Irreversible inhibitor of proteasome	NCT02303821
NOTCH	Ysecretase	PF-03084014	Blocks proteolytic activation of NOTCH receptor	NCT00878189 (not recruiting)
		BMS-906024	Pan NOTCH inhibitor	NCT01363817
Cellular trafficking	Exportin 1 (XPO1)	Selinexor (KPT-330)	Selective inhibitor of nuclear export XPO1	NCT02212561, NCT02091245
DNA repair	PARP	BMN-673	Inhibits DNA repair and cause apoptosis	NCT02116777

CSF, cerebrospinal fluid; DNMT, DNA methyltransferase; HDACi, histone deacetylase inhibitor