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Paediatric Strategy Forum for medicinal product development for acute myeloid leukaemia in children and adolescents☆

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Contribution

Study conceptsdADJP, GV, KN, DK, GR, CM, EAK and HH. Manuscript preparationdADJP, CM, EAK, GV, DK, GR, LVM, MS, SKT, TC, AM, FL and GL and. Study design, data acquisition, quality control of data analysis and algorithms, data analysis and interpretation, manuscript editing and manuscript review—All authors.

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Conflict of interest statement

PA is an employee of Sanofi. BB is an employee of Celgene. FB is an employee of Servier. AB is an employee of Jazz Pharmaceuticals. RC is an employee of Novartis. DD is an employee of Astellas Pharma Global Development, Inc. DF is an employee of Takeda Pharmaceuticals. LF has participated in advisory boards for Astellas. PGF is an employee of Sanofi. MK is an employee of BMS. SYK is an employee of AbbVie. SM is an employee of Helsinn Healthcare. HM is an employee FORMA Therapeutics. JM is an employee of Amgen. LVM has participated in advisory boards for AstraZeneca, Merck, Tesaro, Bayer and Celgene. JN is an employee, Janssen Research & Development. ADJP has participated in advisory boards for Novartis, Takeda, Merck, Lilly and Celgene. SS is an employee of Roche/Genentech. TW is an employee of Agios Pharmaceuticals. CMZ has received institutional research funding from Pfizer, Daiichi-Sankyo, BMS and Celgene. Consultancy was provided for Agios, Takeda, Janssen, Sanofi, Servier, AbbVie and Forma therapeutics. Travel support was obtained from Jazz Pharmaceuticals.

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Abstract

Purpose: The current standard-of-care for front-line therapy for acute myeloid leukaemia (AML) results in short-term and long-term toxicity, but still approximately 40% of children relapse. Therefore, there is a major need to accelerate the evaluation of innovative medicines, yet drug development continues to be adult-focused. Furthermore, the large number of competing agents in rare patient populations requires coordinated prioritisation, within the global regulatory framework and cooperative group initiatives.

Methods: The fourth multi-stakeholder Paediatric Strategy Forum focused on AML in children and adolescents.

Results: CD123 is a high priority target and the paediatric development should be accelerated as a proof-of-concept. Efforts must be coordinated, however, as there are a limited number of studies that can be delivered. Studies of FLT3 inhibitors in agreed paediatric investigation plans present challenges to be completed because they require enrolment of a larger number of patients than actually exist. A consensus was developed by industry and academia of optimised clinical trials. For AML with rare mutations that are more frequent in adolescents than in children, adult trials should enrol adolescents and when scientifically justified, efficacy data could be extrapolated. Methodologies and definitions of minimal residual disease need to be standardised internationally and validated as a new response criterion. Industry supported, academic sponsored platform trials could identify products to be further developed. The Leukaemia and Lymphoma Society PedAL/EUpAL initiative has the potential to be a major advance in the field.

Conclusion: These initiatives continue to accelerate drug development for children with AML and ultimately improve clinical outcomes.

Keywords

Paediatric oncology; Acute myeloid leukaemia; Paediatric Strategy Forum; Drug development; Cancer therapeutics

1. Introduction

The fourth multi-stakeholder Paediatric Strategy Forum was organised by ACCELERATE [1] in collaboration with the European Medicines Agency (EMA) with the participation of the Food and Drug Administration (FDA) and focused on acute myeloid leukaemia (AML) in children and adolescents.

Multi-stakeholder Paediatric Strategy Forums [2–4] have been created to evaluate science, facilitate dialogue and provide an opportunity for constructive interactions between relevant stakeholders (patient advocates, clinicians, academics, biotechnology/pharmaceutical companies and regulators) on specific topics requiring open discussion on the development of medicines in the best interest of children and adolescents with cancer. The aim of the Forums is to share information and advance learning, in a pre-competitive setting, which may inform subsequent clinical investigation strategies and regulatory decisions on the development of medicines for children with cancer [5].

The 5-year overall survival (OS) for paediatric AML is currently greater than 70% [6]. The standard-of-care for front-line therapy for many decades has been an anthracycline (mostly daunorubicin) or the anthracenedione mitoxantrone and cytarabine [6–18] resulting in significant risk for short-term infectious complications, due to therapy intensity, and long-term cardiotoxicity due to anthracyclines and mitoxantrone. The liposomal formulation of daunorubicin, which was used off-label mainly in Europe in anticipation of reduced cardiotoxicity, has become unavailable. Most children with AML in Europe, North America, Japan, Australia and New Zealand are enrolled on international cooperative group clinical trials, with a peak enrolment estimated at approximately 900 patients per year.

AML is more frequent under the age of 3 years and its incidence declines during childhood with subsequent increases throughout young adulthood with a peak incidence in the elderly [19,20]. The occurrence of specific genetic alterations differs in AML in children compared to adults and the elderly, yet drug development continues to be adult-focused. *NPM1, FLT3* and *CEBPA* single-gene mutations occur less frequently in children than in adults, and *IDH1, IDH2, RUNX1* and *DNMT3A* mutations are extremely rare in children [21]. Conversely, NRAS pathway mutations occur more commonly in children with AML [22]. Gene fusions involving *KMT2A* (previously *MLL*) or *NUP98* and core binding factor (CBF) leukaemias are also more common in children [21].

Although there are many novel medicinal products being evaluated in adults with AML (8 EMA authorisations and FDA approvals since 2018), there are three main factors that make clinical development of adult AML drugs in children problematic: i) children and adults have vastly differing profiles of genetic abnormalities and underlying disease (including myelodysplastic syndromes (MDS) and secondary AML in the elderly), and targeted agents are thus often not applicable across all ages; ii) children and adults, especially the elderly, exhibit different tolerability to new drugs; and iii) the relative rarity of AML in children presents challenges for enrolment. There is clearly a need for a drug development process specific for the paediatric population. The challenge is how to make the best choices of innovative medicines for children with AML, how to prioritise their inclusion in clinical trials and ultimately introduce these medicines into clinical practice. As most newly-diagnosed patients are already treated on international cooperative group trials for front-line therapy, prioritising novel agents for paediatric assessment within the global regulatory framework and international cooperative group initiatives requires coordination. The goal of this meeting was to facilitate development of innovative medicines for the treatment of children and adolescents with AML and to ultimately incorporate these medicines into the standard-of-care for children [5].

The Paediatric Strategy Forum was held over 2 days at Erasmus University, Rotterdam, The Netherlands in April 2019, with an emphasis on facilitating discussion and consensus among the participants. The Forum was structured with first an outline by academic experts of the current therapeutic landscape of newly diagnosed and relapsed AML and potential therapeutic targets for AML in children and adolescents. An overview of pre-clinical testing programs and models was presented, as well as proposals for the Leukaemia and Lymphoma Society (LLS) paediatric acute leukaemia (PedAL)/European paediatric acute myeloid leukaemia (EUpAL) protocol. This discussion was followed by a review of paediatric investigation plans (PIPs) of medicinal products for AML, which gave context to the subsequent presentation by pharmaceutical companies of the pharmacological and clinical information on 29 medicinal products being developed for AML and grouped by the mechanism of action of the drugs. Finally, overall recommendations emerged, after discussion among all participants.

The Forum was advertised, and expressions of interest were sought from the pharmaceutical industry (if they wished to present data on relevant medicinal products, a condition for their participation), academic clinicians and patient advocates.

At the Paediatric Strategy Forum, the 71 participants (14 by remote access) included international experts in paediatric AML and drug development; representatives from 18 pharmaceutical companies and the LLS; patient advocates from Target Paediatric AML, KickCancer, Zoé4life and CCI Europe, regulators from the EMA (including Paediatric Committee) and the US FDA.

2. Current therapy of AML in children and adolescents at presentation

In newly diagnosed paediatric patients with none–high-risk disease, front-line therapy comprises 4 or 5 courses of intensive cytarabine-/anthracycline-based chemotherapy [6–18]. There is heterogeneity in the chemotherapy backbones among international paediatric oncology cooperative groups with different anthracycline drugs, different doses of anthracycline or cytarabine and variable inclusion of etoposide and fludarabine. A very important consequence of this heterogeneity is the resultant difficulty in cross-cooperative group trial design and it is frequently impossible to define a control arm that satisfies all sites or regions; however, despite these differences in backbone therapies, the outcome is similar [6]. Risk stratification has become more comprehensive in recent years and is now based on both cytogenetic and molecular characteristics and measurable/minimal residual disease (MRD) in most collaborative group trials [6,23,24]. Allogeneic haematopoietic stem cell transplantation in first remission is the standard-of-care in selected high-risk patients [6]. Although the efficacy of gemtuzumab ozogamicin has been demonstrated in subgroups of AML, particularly those with high CD33 expression, CC genotype and/or FLT3 mutation [10,25,26], this drug has only very recently received regulatory approval for children under 15 years of age in newly-diagnosed patients. New or planned trials are addressing the role of CPX-351 (liposomal cytarabine and daunorubin in a fixed ratio [27–29]), clofarabine [30], FLT3 inhibitors [31] and azacytidine [32,33]. Owing to differences in biology and more favourable outcomes, there are distinct therapeutic approaches and trials for AML associated with Down syndrome [34] and acute promyelocytic leukaemia [35,36]. Arrangements for

the laboratory diagnosis and assessment of AML (in terms of diagnosis, risk group stratification and response assessment) are relatively similar across the cooperative groups, which has allowed meaningful comparison of results [23]. However, certain methodologies require harmonisation and some of these definitions are somewhat outdated (e.g. morphological complete response [CR] without flow confirmation or molecular genetics [37]) and may need revision. These issues are currently under consideration by the collaborative groups.

3. Current therapy of AML in children and adolescents at relapse

Approximately, 40% of children with AML relapse and another 5% of patients have disease refractory to initial induction therapy [38]. On average, a total of 250 patients under the age of 19 years present with relapsed/progressive disease in Europe, North America, Australia, New Zealand and Japan each year. Contrary to newly diagnosed patients, fewer than 20% of patients in relapse have generally been treated on trials. Only 70% of relapsed patients achieve a morphological CR and 5-year OS is 30–40% [38]. Duration of first remission is the most important prognostic factor and is related to molecular and cytogenetic risk groups. There are a variety of chemotherapy regimens used at relapse with fludarabine and high-dose cytarabine with or without granulocyte colony stimulating factor and an anthracycline being the most commonly used, and the role of gemtuzumab ozogamicin in combination is being evaluated [39,40]. Allogeneic haematopoietic stem cell transplantation, in second remission, is the therapeutic standard for all relapsed patients [41]. Liposomal daunorubicin had held promise of reducing cardiotoxicity and improving efficacy in the relapsed setting, but its unavailability has limited further clinical trials [38]. CPX-351 may be an attractive alternative liposomal agent as ‘backbone’ chemotherapy for patients in relapse given the relatively high cumulative anthracycline dose that most patients will have received during front-line therapy and the associated risk of late cardiotoxicity [27–29]. Another promising approach to prevent late cardiotoxicity is the use of dexrazoxane concurrent with administration of anthracyclines [42].

4. Therapeutic targets for AML in children and adolescents

4.1. Paediatric and adult AML cell lineage targets

Gemtuzumab ozogamicin targeting CD33 has improved event-free survival in major subgroups of patients with high expression of CD33, CC genotype and those with FLT3 mutations [9,25,26,43]. Gemtuzumab ozogamicin will be incorporated into the forthcoming Children’s Oncology Group (COG) phase III front-line trial (AML1831) as part of the backbone therapy and is also being evaluated in newly diagnosed patients in the United Kingdom, Europe, Australia and New Zealand in the MyeChild 01 [44] phase II/III trial.

CD123 is the interleukin-3 (IL-3) receptor alpha-chain, which mediates signalling stimulating multi-lineage haematopoiesis in bone marrow and endothelial cell proliferation. The IL-3 cytokine (ligand for the receptor) is known to stimulate AML cell proliferation. In normal cellular populations, CD123 expression varies according to cell lineage, being absent on CD34+/CD38-cells, with low expression in T-cells and CD34+ B-cell precursors and highest expression in basophils and plasmacytoid dendritic cells [45]. In malignancy, CD123

is expressed on the surface of cells >80% of adult and childhood AML and leukaemia-initiating cells [46–51]. CD123 is also expressed on a subset of B acute lymphoblastic leukaemia (ALL), blastic plasmacytoid dendritic cell neoplasm and hairy cell leukaemia. The exclusive expression of CD123 on leukaemia-initiating cells but not at high levels on undifferentiated haematopoietic progenitor cells is potentially advantageous for the tolerability of immunotherapeutic targeting and therefore CD123 is an ideal 'near-universal' immunotherapeutic target across the age spectrum. In univariate and multivariate analyses, inferior outcomes are associated with higher CD123 expression [46,49]. CD123 is a robust flow cytometric MRD marker and can also be detected by immunohistochemical analysis, which may aid in selection of patients in whom to test CD123 immunotherapies [46]. As CD123 is expressed at a lower level on normal myeloid precursor cells, there is a risk of severe myelosuppression. CD123 is currently being targeted in adults by monoclonal antibodies, antibody–drug conjugates (ADCs), protein–drug conjugates, T cell engagers and chimeric antigen receptor T cells (CAR T-cells). Preliminary data from phase I clinical trials of CD123xCD3 bispecific T cell engager/dual affinity retargeting antibodies (DARTs) [52] and CD123CART [53,54] have not reported significant aplasia in patients, although the goal of current therapies is rapid haematopoietic stem cell rescue for responding patients.

4.1.1. Tyrosine kinase inhibitors—*FLT3* mutations occur in 10–15% of paediatric AML [21,55]. In a recent study, *KIT* exon 17 mutations were demonstrated to confer a worse prognosis [56] and are potentially targetable by multi-kinase inhibitor agents such as crenolanib and dasatinib. NRAS pathway mutations are more common in children (11% [23% in infants]) compared to adults (6%) [21] and may be subclonal and lost between diagnosis and relapse [21,57]. MEK inhibitors have not been systematically studied in children with RAS-mutant leukaemia, although this is an area of major interest in paediatric AML with some studies ongoing. IDH1/IDH2 mutations occur in 1% and 2% of patients [21] and trials exist or are opening for this ultra-rare population with paediatric AML with these mutations.

4.1.2. Additional pathways—*KMT2A* (*MLL1*) is another important target for paediatric AML and ALL, and specific inhibitors of the menin–KMT2A complex are available and entering clinical evaluation [58,59]. Pevonedistat is a first in class NEDD8 activating enzyme inhibitor that targets the ubiquitin proteasome system [60]. Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death [61]. Idasanutlin and other MDM2 inhibitors promote cell cycle block and apoptosis by inhibiting MDM2, a negative regulator of p53 [62]. Mesothelin is a cell surface glycoprotein expressed on mesothelial cells (including the pleura and peritoneum), but not expressed on normal bone marrow [63,64].

4.1.3. Immune modulation—TIM-3 is an inhibitory receptor expressed on T cells and innate immune (myeloid and dendritic) cells. It is not expressed on normal haematopoietic stem cells but is highly expressed on leukaemia stem cells [65].

4.1.4. Specific paediatric targets—

CBFA2T3-GLIS2 is cryptic fusion occurring exclusively in the very young paediatric population. This AML subtype is associated with high CD56 surface protein expression and a dismal prognosis [66].

5. PIPs

A PIP is a development plan aimed at ensuring that the necessary data to support the authorisation of a medicine for children are obtained through studies in children. According to Paediatric Regulation (EC) No 1901/2006, all applications for marketing authorisation for new medicines must include the results of studies carried out as part of an agreed PIP or information on a PIP deferral (for studies planned to be initiated and/or completed after the submission of the marketing authorisation in adults) or a waiver.

There have been (as of April 2019) 16 PIPs agreed for medicines for a condition related to the treatment of AML: gemtuzumab ozogamicin, CPX-351, pevonedistat, idasanutlin, isatuximab, venetoclax, volasertib, decitabine, azacitidine, guadecitabine, midostaurin, quizartinib, gilteritinib, enasidenib, elacytarabine and ivosedinib. As of 12th April 2019, none of these PIPs have been completed, and no final compliance check has yet been conducted. Trials with some of these drugs are currently ongoing in children, whereas some agents are no longer under development for AML.

Details of initial paediatric study plans (iPSPs) and proposed paediatric study requests (PPSRs) are confidential and could not be reviewed.

6. New medicinal products

Eight classes of medicinal products were discussed at the Forum: FLT3, IDH1&2, immune-checkpoint, cell signalling and HDAC inhibitors, monoclonal antibodies, bispecific T cell engagers and ADCs as well as cytotoxics (Table 1).

7. LLS PedAL/EUpAL initiative

This is a systematic approach [67] for the treatment of childhood AML comprising the following: i) preclinical assessment using *in vitro/in vivo* models, validating drug–target activity, target dependency mapping and rational combinations; ii) biomarkers using diagnostic assays, response assessments and new target discovery; iii) informatics with an AML common data model, data commons and sponsor/investigator data interface; and iv) clinical trials with diagnostic assays, safety and efficacy assessments, pharmacokinetics and pharmacodynamics as well as monitoring. A major component of the initiative is a platform trial with key concepts, including the fact that relapsed AML in children is often more aggressive than in adults and that therapy needs to be started early after relapse with curative intent for all patients, even those in second or greater relapse. The goal is for simple, common clinical trial designs to answer highly clinically relevant questions in paediatric AML whilst efficiently addressing industry priorities for their new agents, informed by evolving science, and meeting the United States of America and European regulatory requirements. The aim of the trial is to ultimately benefit more children. Given the rarity of paediatric AML, the PedAL/EUpAL initiative will seek international collaboration with the

European and COG study groups (including Australia and New Zealand) to deliver the program and is due to open first or second quarter of 2021. To coordinate the European cooperative study groups, and to organise the standardisation and quality management of diagnostics, the data management and European research institutions, the EUpAL consortium and foundation were initiated (Zwaan, Reinhardt and Kolb, personal communication, April 2020).

8. Discussion

Frequently there has been a long interval between a potentially valuable drug being evaluated in adults and then in children. Efforts should be focused on accelerating the evaluation of the most promising of these products in children, and prioritisation of these novel agents within the global regulatory framework and cooperative group initiatives is critical. Although many novel drugs for AML are developed in older adults as monotherapy or in combination with lower-intensity chemotherapy regimens due to co-morbidities, there is a need to alter this approach in children who are much more likely to tolerate, and benefit from, combinations with more intensive chemotherapy. Moreover, some drugs that are discarded in the elderly population because of lack of efficacy or excess toxicity may be of value to children given their differences in AML biology and higher tolerance for toxicity. Consensus approaches between clinical trial cooperatives and biopharmaceutical companies are necessary to achieve these goals.

Although there are many approaches for children with AML at presentation, it is not considered, at present, essential for progress or for conducting clinical trials that there is only one standardised front-line chemotherapy regimen internationally, as results have been similar across large co-operative group trials despite minor differences in regimens. However, it is critical that biological data are obtained from all patients at diagnosis and that there is an international consensus regarding definitions for treatment response and relapse.

A common chemotherapy backbone in relapsed or refractory disease to which novel agents can be added and/or new treatment regimens can be compared would improve efficiency compared to the current diversity of approaches. Close collaboration between international clinical trial cooperative groups and the biopharmaceutical industry is essential, as it will increase the number of patients enrolled into relapse trials. Master protocols with a common screening platform to identify all trials for which a patient is eligible and an evaluation of multiple treatment strategies within the same overall trial structure have an important role in the relapsed AML population. It is envisaged that the trials would be industry supported, academically sponsored with compounds from different pharmaceutical companies and different mechanisms of action, using an adaptive design and conducted with ‘intent to file’, that is, collecting data that can be reliably used for regulatory submissions. The trials would be an international collaborative effort to enrol the necessary number of patients in a rare setting and in a timely manner. Hitherto opening academic trials on both sides of the Atlantic has been challenging. These protocols could be part of a regulatory package in Europe (i.e. included in a PIP) and fulfil FDA regulatory requirements in response to the Paediatric Research Equity Act (PREA) including planned amendments brought about via the Research to Accelerate Cures and Equity (RACE) for Children Act FDARA amendments

to section 505B of the FD&C Act–which comes into force in August 2020, and/or the Best Pharmaceuticals for Children Act (BPCA). Data generated by a master protocol could be part of *early* development (dose finding and efficacy signal seeking) and included in PIPs for the individual drugs. As PIPs require studies generating pivotal evidence sufficient enough for marketing authorisation, such studies, if considered necessary for the intended target population with all the relevant known details, should be included at high level into each of the individual PIPs, iPSPs and PPSRs. For any such pivotal study, it is important to uniformly define success criteria allowing the product to move forward (and will possibly be product-specific). Companies should plan to submit their individual PIPs at the same time to the EMA for assessment, as they submit their iPSPs to the FDA and engage in early interactions with regulatory agencies (e.g. through the request of PIP pre-submission meetings and/or the Committee for Medicinal Products for Human Use scientific advice). In parallel, early discussions with the FDA should occur requesting a Common Commentary from EMA and FDA. The LLS PedAL/EUpAL initiative meets the requirements of a platform trial as it aims to collect all data on all patients, with central screening to permit efficiency in target identification, treatment recommendations and response assessment. Its flexibility to engage the biopharmaceutical industry early and the intent to meet regulatory objectives provides a strong potential to standardise and unite global efforts in paediatric AML drug development.

MRD is currently used for risk stratification in some protocols and MRD-negative CR is often added as a primary or secondary end-point in paediatric clinical phase III trials, although there is as yet no consensus on the definition of MRD-negativity. Analysis of MRD can today be performed with flow cytometry (assessed as ‘different from normal’ or as ‘leukaemia-associated immunophenotype’, or a combination) or with quantitative PCR of recurrent mutations and fusion transcripts or next-generation sequencing. Various techniques are available and under further development/evaluation in the study groups, but consensus is currently lacking. There are major international initiatives ongoing to standardise MRD-CR for adult AML [68,69] and to validate it as a new response criterion. MRD may have the potential to become a surrogate marker of long-term outcome in AML, although the rigor required to establish true surrogacy may be challenging to meet in the paediatric AML setting [70]. Furthermore, it is well known that children in MRD-negative CR can later relapse. A further challenge is the variability in the definition of molecular remission and relapse. Harmonisation, cross-validation of technology platforms, data-sharing, meta-analysis of patient-level data from ongoing or completed studies and openness of standards and communication with FDA and EMA are essential to establish MRD as a surrogate marker of long-term outcome. There are many ongoing academic initiatives investigating MRD and a major biopharmaceutical company alliance with the COG is currently working with regulators [71] to evaluate the acceptability of MRD as a surrogate clinical trial endpoint.

Concerns were raised at the Forum by the clinicians, pharmaceutical companies and patient advocates present about the number of agreed PIPs (16) in view of the relatively small number of eligible paediatric patients available for study (900 patients in Europe, North America, Japan, Australia and New Zealand for first-line studies and 250 in the relapsed setting). However, a PIP and its obligations, in the context of its mechanism of action can be

re-assessed at any time based on scientifically justified arguments, such as, for example, early results of a clinical study. Similarly, if an early clinical trial fails to show promising results, a PIP can be modified accordingly and the need for the agreed pivotal trial can be reconsidered. Discussions among clinicians, cooperative groups and pharmaceutical companies should take place *before* PIPs are proposed to decide which compounds are most likely to be relevant for evaluation in the paediatric population with AML. Relevant scientific arguments from these discussions should be incorporated into the clinical study design and relevant regulatory applications. An academic–industry consensus would be of great benefit to regulators. Where a medicinal product is being developed in adult AML, but thought to be less relevant for children, an upfront product-specific waiver could be submitted in the EU. This waiver should be supported by clinical trial cooperative groups based on scientific evidence or lack of therapeutic benefit, over existing authorised products (for children), or safety grounds. An example is the paediatric development of the sonic hedgehog inhibitor glasdegib, which was waived due to concern for skeletal toxicity as a class-effect [72]. At the same time, it was considered important to see the high number of agreed PIPs in context of the known high failure rate of novel compounds in early development. If there is substantial uncertainty, rather than agreeing to waive products prematurely, deferrals could be considered where needed, to maintain feasible product development. However, this requires consolidated efforts by academia and industry, to agree to defer paediatric development of those products that are considered to be of sufficient interest, but not highest priority based on current scientific knowledge.

Table 2 is an overview of classes of compounds prioritised at the Forum, based on pre-clinical and clinical data available at the time of the Forum. For a number of classes, insufficient data were available at that time, and prioritisation may change. The prioritisation is only truly relevant at the time of the Forum, and not all companies with relevant medicinal products or academic groups representative of all regions were present at the Forum. Therefore, consideration must be given towards developing an inclusive, transparent and sustainable process to address prioritisation challenges for paediatric malignancies with high unmet medical needs.

CD123 is a high priority target in paediatric AML and it was proposed that CD123 should be a proof-of-concept of how to accelerate the paediatric evaluation of products with greatest probability of being beneficial in view of their mechanism of action. This would comprise a consensus between the relevant biopharmaceutical companies and academics about prioritisation (particularly within the same class of agent, but also among agents with different mechanisms of action) and then discussion with regulatory agencies. It was suggested that combining ADCs with chemotherapy has the advantage of not being reliant on a competent immune environment and may be particularly advantageous for patients in relapse. A follow-up meeting was held with the relevant biopharmaceutical companies and academics that proposed a strategy whereby agents targeting CD133 would be sequentially evaluated, taking into account geographical considerations.

At the time of the Forum, there were two FLT3 inhibitors with FDA approval in adults and three agreed PIPs for FLT3 inhibitors with three front-line and two relapse paediatric studies. It is highly unlikely that these trials could be completed in view of the numbers of

available patients. A follow-up meeting was held with the relevant biopharmaceutical companies and academics to discuss the studies with FLT3 inhibitors and develop a consensus to propose to the regulatory agencies. The meeting concluded that the cohort sizes of the current relapsed studies should be reduced to describe preliminary safety data and pharmacokinetics without requirements to enrol specific age groups. There should be exploration of the possibility of extrapolation from adolescent and adult data, to avoid full efficacy determination in this rare paediatric subset. In addition, it was proposed that front-line studies of FLT3 inhibitors should recruit from distinct geographical areas to minimise issues of competing trials for the same patient population.

IDH1 mutations occur in <1% of children with AML (approximately 10 patients per year in trials in North America, Europe, Australia, New Zealand and Japan), although incidence increases in adolescence. The incidence of *IDH2* mutations is similarly low at approximately 2% of paediatric AML. It was concluded that the future approach for inhibitors of mutations, which are very rare in children, but more frequent in adolescents, is to include adolescent patients in adult trials and discuss with regulators the possibility of extrapolating efficacy to younger children from adolescent data. The inclusion of 'real world' adult data is another approach, although this may be scant.

9. Conclusion

There is a major need to accelerate the introduction of innovative medicines into the therapy of children and adolescents with AML. A number of competing agents of the same class in a rare population present a challenge, and prioritisation is thus required. The LLS PedAL/EUpAL master clinical trial with compounds from different pharmaceutical companies could fulfil the requirements for an industry-supported, academic-sponsored study, which could collect relevant data to identify the products to be further developed in paediatric AML. The paediatric development of CD123 (high priority)-targeted drugs should be accelerated as a proof-of-concept. Through the AML Paediatric Strategy Forum, a consensus was developed by industry and academia to propose to the regulatory agencies using formal regulatory pathways. Finally, there is a need to standardise internationally methodologies and definitions of MRD in order that it can be recommended as a new response criterion.

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Key conclusions of the Paediatric Strategy Forum

- There is a major need to accelerate the introduction of innovative medicines into the therapy of children and adolescents with AML.
- A number of competing agents of the same class in a rare population present a challenge, and prioritisation is thus required.
- The PedAL/EUpAL Master Trial with compounds from different pharmaceutical companies should fulfil many of the requirements for an industry-supported, academic-sponsored study, which could collect relevant data to identify the products to be further developed in paediatric AML.
- In the future, trials of novel agents in front-line AML should be embedded in cooperative group trials and not stand-alone trials, as this will aid in standardisation across trials and recruitment.
- CD123 is a high priority target for ADC, DART and CAR T-cell. The paediatric development of CD123-targeted drugs should be accelerated as a proof-of-concept. There is a need for coordination, as there are a limited number of studies that can be delivered.
- Currently, the three front-line and two relapse studies of FLT3 inhibitors in paediatrics, as part of PIPs, are highly unlikely to be completed as approximately 90 children present at diagnosis and 30 children relapse each year with *FLT3* mutations in North America, Europe, Australia, New Zealand and Japan. The objective is to develop a consensus to propose to the regulatory agencies using formal regulatory pathways (e.g. pre-submission meetings). This would be a proof-of-concept for cleaning the landscape of approved PIPs to focus on most promising developments.
- In the future, if rare mutations are more frequent in adolescents than in children, adult trials of inhibitors of these mutations should include adolescents, and data extrapolated from adolescent and adult data (if scientifically justified).

Table 1

Medicinal products discussed at the Paediatric Strategy Forum.

Class of medicinal product	Product	Target	Company
FLT3 inhibitors	Midostaurin	FLT3	Novartis Pharmaceutical Industry AG
	Gilterinib	FLT3	Astellas Pharma Global Development, Inc.
IDH1&2 inhibitors	FT-2102	IDH1	FORMA Therapeutics
	Ivosidenib	IDH1	Agios
	Enasidenib	IDH2	Celgene
Monoclonal antibodies, T cell engager and ADC	Flotetuzumab (bispecific CD123xCD3 DART)	CD123	Les Laboratoires Servier
	XmAb®14045 (SQZ622) (bispecific CD123xCD3) (intermittent dosing)	CD 123	Novartis Pharmaceutical Industry AG
	SAR440324 (CD3xCD123 T cell engager) with weekly dosing	CD 123	Sanofi
	Gemtuzumab ozogamicin (ADC)	CD33	Pfizer
	AMG 330 & AMG 673 (BITE CD33)	CD33	Amgen
	AMG 427 (BITE FLT3)	FLT3	Amgen
	Anetumab ravtansine (ADC)	Mesothelin	Bayer
	Cusatuzumab (monoclonal antibody)	CD70	Janssen
	Isatuximab (monoclonal antibody)	CD38	Sanofi
Checkpoint inhibitors	MBG453	TIM-3	Novartis Pharmaceutical Industry AG
	Nivolumab, ipilimumab with azacytidine	PD-L1	BMS
Cell signalling & HDAC inhibitors and combinations	Venetoclax	BCL2	Abb Vie jointly with Roche-Genentech
	Idasanutlin	MDM2	Roche-Genentech
	Siremadlin (HDM201) & MIK665/ S64315	MDM2 and MCL-1	Novartis Pharmaceutical Industry AG
	BMS-986158	BET	BMS
	AMG 176 and AMG 397	MCL1	Amgen
	Alisertib	Aurora A kinase	Takeda Ltd
	Pevonedistat	NEDD8-activating enzyme	Takeda Ltd

Class of medicinal product	Product	Target	Company
	Pracinostat	HDAC	Helsinn Healthcare
Cytotoxic	Vyxeos (CPX-351)	Liposomal cytarabine and daunorubin	Jazz Pharmaceuticals

ADC, antibodyedrug conjugate; DART, dual affinity retargeting antibody.

Table 2

Rationale for prioritised class of compounds.

High priority targets in childhood AML	Scientific rationale
Immunotherapy targets for cytotoxic therapy	**CD123**—Greatest probability. Expressed in nearly all AML subsets and leukaemia stem cells [46–51]. Robust preclinical data and clinical studies ongoing of various CD 123 immunotherapies in relapse.
	CD33—Previous studies with gemtuzumab ozogamicin confirm that CD33 is a good target [10,25,26,43,50,73–75]. Robust clinical data with new studies ongoing in *de novo* and relapsed settings.
	FLT3—Commonly expressed receptor on paediatric AML cells [76]. Robust preclinical data and clinical studies ongoing of various FLT3 inhibitors in *de novo* and relapsed settings.
	Mesothelin—Phase I trial of an anti-mesothelin ADC planned in COG. This is a proof-of-concept for this novel target [63,64], and a paediatric clinical study is in development.
Targeting mutational gene products	**Menin**—Strong preclinical rationale. Phase I/II development underway [58,59].
	MEK—NRAS and KRAS mutations are among the most common SNVs in childhood AML [21,57].
	There is no clinical proof-of-principle to date for MEK inhibition as an effective strategy for RAS-mutant cancers and leukaemias.
	FLT3—The FLT3 ITD mutation is a high priority target with clear efficacy signal in children [31,77].
	There is preclinical evidence for targeting the FLT3 activating mutations in children [78].
	CBFA2T3-GLIS2—CD56 is overexpressed (‘RAM phenotype’), as well as other potential targets [66]. Targeting downstream products of this catastrophic fusion is a high priority as there are currently few survivors.
Other categories	**NEDD8—**An NEDD8 activating enzyme inhibitor [60] trial is underway in COG to meet PIP requirements. The future of this target in childhood AML is uncertain.
	BCL2—Preliminary clinical experience is promising [79]. A definitive phase II efficacy determination is needed.
	E-selectin ligand—Uproleselan is a specific antagonist of E-selectin binding currently in phase II/III development in adults with AML.
High priority targets in childhood AML—requiring more data	
Immunotherapy targets for cytotoxic therapy	**CCL-1**—Commonly expressed in paediatric AML while being absent in normal haematopoietic stem cells makes it an attractive target [80].
Immunotherapy targets for blocking antibodies	**CD70**—Cusatuzumab development on going. Mechanism of effect is unknown in paediatric AML.
	CD47—Phase I development planned for paediatrics. Minimal preclinical rationale at the moment.
	Tim-3—Phase I development planned for paediatrics. Minimal preclinical rationale at the moment.
Other categories	**MDM2 and MCL-1**—Phase I/II development is underway in children. Combination therapy with BCL2 inhibition has compelling potential based on preliminary preclinical data, but further preclinical and clinical testing are needed to identify relevant potential target subpopulations [60].

ADC, antibodyedrug conjugate; AML, acute myeloid leukaemia; COG, Children’s Oncology Group; PIP, paediatric investigation plan; SNV, single nucleotide variant.