

**ACCELERATE and EMA Paediatric Strategy Forum for  
medicinal product development for mature B-cell malignancies in children**

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## **Abstract**

Paediatric Strategy Forums have been created by the multi-stakeholder organisation, ACCELERATE, and the European Medicines Agency to facilitate dialogue between all relevant stakeholders and suggest strategies in critical areas of paediatric oncology drug development. As there are many medicines being developed for B-cell malignancies in adults but comparatively few in children with these malignancies, a Paediatric Strategy Forum was held to discuss the best approach to develop these products for children. It was concluded that as current frontline therapy is highly successful, despite associated acute toxicity, de-escalation of this or substitution of presently used drugs with new medicines can only be undertaken when there is an effective salvage regimen, which is currently not available. Therefore priority should be given to developing treatment for patients with relapsed and refractory mature B-cell lymphomas. The consensus of the clinicians attending the meeting was that CAR T-cells, T-cell engagers and antibody drug conjugates (excluding those with a vinca alkaloid-like drug) presently have the greatest probability of providing benefit in relapse in view of their mechanism of action. However, as producing autologous CAR T-cells currently takes at least 4 weeks, they are not products which could be quickly employed initially at relapse in rapidly progressing mature B-cell malignancies but only for the consolidation phase of the treatment. Global, industry supported, academic sponsored studies testing simultaneously compounds from different pharmaceutical companies should be considered in rare populations and it was proposed that an international working group be formed to develop an overarching clinical trials strategy for these disease groups. Future Forums are planned for other relevant paediatric oncologic diseases with a high unmet medical need and relevant molecular targets.

**Keywords:** Paediatric oncology, mature B cell malignancies, medicinal product development

## **Introduction**

Currently, there are many developments in the field of oncology medicine with more effective and innovative medicinal products becoming available more rapidly to treat adult patients. Meanwhile, children in need of new therapeutic options still do not have access to early clinical studies leading to paediatric approvals<sup>1</sup> and therefore do not have timely access to many of these innovative drugs. The high unmet medical need remains, and major efforts are being made to accelerate new drug development for children and adolescents with cancer. In parallel there are strong arguments that drug development for children with cancer should not be any different from adults and follow a mechanism of action-based approach rather than being driven by the adult indication for the medicinal product<sup>2</sup>. In light of this, in 2015, the European Medicines Agency revised their decision on class waiver<sup>3</sup> list to allow an early dialogue with pharmaceutical companies on their paediatric development plans based on a mechanism of action approach. This approach is expected to further enhance timely development of paediatric oncology medicines. Highlighting the need of a global effort, the passing of the FDA Reauthorization Act of 2017 by the US Congress (and incorporating the RACE for Children Act), requires that “development of drugs and biological products should be evaluated early in paediatric cancers if the drug is directed at a molecular target substantially relevant to the growth or progression of a paediatric cancer”<sup>4</sup> and is a substantial step along this path.

Within this landscape there is a need to facilitate dialogue and provide an opportunity for constructive interactions between relevant stakeholders (clinicians, academics, patient representatives, pharmaceutical companies and regulators) on topics requiring open discussion, in the best interests of children and adolescents with cancer. To fulfil this need, the ACCELERATE multi-stakeholder forum, which aims to promote innovation in new drug development for children with cancer, and the EMA, have created Paediatric Strategy Forums. The goal of these meetings is to share information between all stakeholders, in a pre-competitive setting, to inform paediatric drug development strategies. This will facilitate the timely development and prioritisation of innovative medicines for the treatment of children with cancer, and make new drugs available for children more rapidly and ultimately introduce these medicines into standard-of-care treatment. The premise that scientific information should underpin these discussions and that no regulatory decisions would be made during the meeting was considered critical to the success of the Forums.

As the objective of the Forum is to provide an opportunity for interaction and discussion between all stakeholders on topics being identified as hurdles or problems in drug development in children and adolescents with malignancy, two types of forum were envisaged; some focusing on a given molecular target and others on a disease. The first Paediatric Strategy Forum was held on 30-31 January 2017 at

the EMA on anaplastic lymphoma kinase inhibition in paediatric malignancies<sup>5</sup>. This pilot Forum demonstrated that the approach taken for the Paediatric Strategy Forums is feasible, can be highly relevant for paediatric cancer drug development and is widely supported by the participating stakeholders.

There are many medicines being developed for B-cell malignancies in adults; however most of the malignancies in adults differ from those in children. Furthermore, the paediatric B-cell malignancy population is rare, with relapsed patients even rarer, as the current four year event free survival rates for children with newly-diagnosed mature B cell malignancies is greater than 90%<sup>6-12</sup>. Thus, ACCELERATE and the EMA agreed that it would be appropriate to dedicate the second Forum to discussing approaches to developing the best medicines for children with mature B-cell malignancies. The main aim of the forum was to share information, in a pre-competitive setting, to facilitate the developments of innovative medicines for the treatment of children with mature B cell malignancies. In the Forum the epidemiology, clinical features, biology, similarities and differences compared to adult mature B cell malignancies, current international standard approaches and therapeutic needs of mature B cell malignancies were presented. The medicines for mature B cell malignancies in development, relevant pre-clinical data and data from paediatric clinical trials completed or in progress, sponsored by industry or academia, were reviewed.

### **The challenge of mature B cell malignancies in children and adolescents**

Mature B-cell malignancies in children and adolescents comprise Burkitt lymphoma, diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBL) and post-transplant lymphoproliferative disorders. The current standard of care for Burkitt lymphoma and DLBCL with standard-risk and high-risk disease results in more than 94% five year event free survival (EFS)<sup>6-12</sup>. Furthermore, similar results are currently observed in the Lymphoma Malignancy B-cell (LMB) and Berlin Frankfurt Munster (BFM) studies for B-cell non-Hodgkin's lymphoma. Future discussions should therefore be on joining efforts for collaborative studies. On the other hand, the probability of survival for refractory and relapsed patients is very poor<sup>13,14</sup>. The acute toxicity (including infection) of current frontline treatment remains substantial, but evidence suggests that most survivors have limited long term sequelae<sup>15,16</sup>. Therefore, the solutions to address the current unmet therapeutic needs for children with mature B-cell malignancies are twofold: i) to develop innovative treatments for incurable patients; predominantly those with disease progression or relapse but also patients with predisposing conditions, including those associated with reduced treatment tolerance, for example post-transplant lymphoproliferative disorders<sup>17</sup> or immunodeficiency, and ii) to reduce the high acute toxicity of

current therapy without jeopardizing rates of cure. There are many medicines being developed for B-cell malignancies in adults; however, most B-cell malignancies in adults differ from those in children making direct extrapolation impossible and therefore specific studies need to be carried out in the paediatric population.

With this background the goals for the Forum were to identify which of the many potential new drugs would have the optimal probability of improving rates of cure in paediatric patients with chemo-resistant disease, and to initiate a dialogue on plans to design and execute scientifically sound studies in a very small international population of children with relapsed mature B-cell malignancies.

### **Format of the Paediatric Strategy Forum**

The Paediatric Strategy Forum was held over two days at the EMA, with an emphasis on facilitating discussion and consensus amongst the participants. A comprehensive overview of the epidemiology, biology, standard therapy, therapeutic needs and future therapeutic strategies for paediatric patients with mature B-cell malignancies was provided by European and North American academic speakers. This gave context to the subsequent presentation of non-clinical and clinical information by pharmaceutical companies on medicinal products being developed, mainly in adults, for the treatment of B-cell malignancies.

Prior to the Forum, the meeting preparation (over six months) included multiple planning phone calls with academic speakers and representatives of the pharmaceutical industry, ensuring an aligned approach to the meeting and its objectives.

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

At the Forum, there were seventy three participants including European and North American experts in mature B-cell malignancies in children; drug development experts, representatives from fourteen pharmaceutical companies; patient representatives (from Childhood Cancer International, Unite2Cure, Children's Cause for Cancer Advocacy); regulators from EU national competent authorities, EMA (including Paediatric Committee [PDCO]), Committee for Medicinal Products for Human Use [CHMP], Committee for Orphan Medicinal Products [COMP] and Scientific Advice Working Party [SAWP] members) and the US Food and Drug Administration (FDA).

## **Mature B-cell malignancies in children**

### *Mature B-cell malignancies in children compared to adults*

Generally the spectrum, biology and nature of non-Hodgkin lymphoid malignancies in children differ from those in adults with the exception of PMBL. In children and adolescents younger than 14 years of age, 38-49% are Burkitt lymphoma, 7-20% DLBCL (with two subtypes – germinal centre [the majority] B-cell-like and activated B-cell-like), 21-29% lymphoblastic lymphoma, 10% anaplastic large cell lymphoma (ALCL), 1% follicular lymphoma and 2-11% other types<sup>18,19,20</sup>. In adolescents from 14 years to younger than 19 years, 21-27% are Burkitt lymphoma, 21-37% DLBCL, 15-19% lymphoblastic lymphoma, 17-20% ALCL, 1% follicular lymphoma and 5-17% other types<sup>18,19,20</sup>. In total, mature B cell malignancies in children and adolescents (including Burkitt lymphoma, DLBCL and PMBL) comprise 58% of all lymphomas with 98% being aggressive, and Burkitt lymphoma accounts for more than 80% of childhood B-cell malignancies. By contrast, in adults, 40% of non-Hodgkin lymphoid malignancies are follicular lymphoma, 30% DLBCL, 5% Burkitt lymphoma, 5% small lymphocytic lymphoma, 5% ALCL, 5% lymphoblastic lymphoma and 10% other. Eighty percent of all lymphomas are B-cell lymphomas with 57% of those being indolent and the remainder being aggressive. In Europe and the US there are approximately just 1680 patients under the age of 19 years presenting each year with mature B-cell lymphomas, in contrast to about 200,000 adults<sup>18</sup>. Furthermore, there is good evidence that the biology and clinical behaviour of DLBCL in children differs from that in adults<sup>21</sup>. The evidence is less clear that the biology and clinical behaviour of Burkitt lymphoma differs and probably is the same to the age of around 25 years<sup>22</sup>.

### *Therapeutic targets for paediatric mature B-cell malignancies*

CD20, CD79a/b, CD19, CD22 and CD37 are pan B-cell markers which are expressed in essentially all mature B-cell malignancies. CD30 is expressed in a subset of mature B-cell malignancies, mostly DLBCL, and is associated with a better outcome in adult patients but not in children. CD30 is also expressed in PMBL, although more weakly than in Hodgkin disease. BCL2 and MCL1 could be targets in DLBCL and Burkitt lymphoma, respectively<sup>23</sup>. While chronic active B cell receptor (BCR) signalling is an activated B-cell-like DLBCL phenomenon, tonic BCR signalling (via the PI3K/AKT pathway) has a role in Burkitt lymphoma and some germinal centre-DLBCL. P53 pathway re-activation could in theory be effective in improving outcomes. PMBL has attractive targets such as PDL1/PDL2, with published experience of the efficacy with anti-PD1 immune checkpoint inhibitors<sup>24</sup> (Table 1).

### *Current therapy of mature B-cell malignancies in children and adolescents at presentation*

In newly-diagnosed paediatric patients with standard-risk disease, frontline therapy is very effective and similar excellent results have recently also been achieved for patients with high-risk disease. The current therapy for paediatric high-risk mature B-cell malignancies (Burkitt lymphoma and DLBCL) consists of multi-agent chemotherapy and rituximab. The Inter B non-Hodgkin's lymphoma (NHL) Ritux 2010 study, which recruited 310 children and adolescent patients from Europe, the US and Asia, randomised patients to LMB chemotherapy with or without six doses of rituximab. The trial resulted in one year EFS of 94.2% (88.5% - 97.2 %; 95%CI), which is similar to other first-line protocols in standard risk B-cell NHL and for lower stage disease<sup>10</sup>. The NHL-BFM experience with rituximab added to chemotherapy has a very similar EFS >90%<sup>12</sup>. Acute toxicity is, however, high for both the Inter B NHL Ritux 2010 and NHL-BFM regimens. The future objectives for the treatment of these types of lymphomas are therefore to reduce toxicity and identify patients who are at high risk of recurrence or treatment failure. The results from three international groups for PMBL all demonstrate an inferior survival of 65-70% for children with PMBL<sup>24,25,26</sup>. More recently, the Inter B NHL Ritux 2010 phase II trial reported a similar EFS of 72% with DA-EPOCH-R<sup>27</sup>. Since PMBL harbours 9p21.1 alterations, this makes them vulnerable to PD1 blockade, and a randomised trial of a checkpoint inhibitor could, therefore, be a rational therapeutic approach in PMBL.

#### *Therapeutic needs of mature B-cell malignancies in children at relapse*

Based on the success of current first-line therapy discussed above, it is expected that in Europe and the US, there are only approximately 90 patients under the age of 19 years with relapsed/progressive disease, potentially eligible for early phase clinical studies each year; approximately 56 with Burkitt lymphoma, 17 with DLBCL and 14 with PMBL<sup>28</sup>. As the numbers of patients are so small, only international studies can generate useful data. As young adults and children with relapsed Burkitt's lymphoma may have a similar biology<sup>29</sup>, they could be included in the same trials. Generally, following relapse, disease progresses quickly, response rates are between 50-60%, with very low probability of survival (EFS <30%)<sup>13,14</sup>. Single agent studies are challenging as patients who do not respond usually die rapidly and may have significant morbidity at the time of relapse. Disease refractory to or progressing on front-line therapy occurs very rarely (for DLBCL/Burkitt lymphoma <2.5%)<sup>7,30</sup> with a very low survival rate, and the clinical consensus is that the biology in such patients is probably different from that seen in patients with relapsed disease, though biological studies comparing relapsed and refractory disease are lacking<sup>31</sup>. New medicinal products are being tested<sup>31</sup> in patients with relapsed or refractory mature B-cell NHL. For example SPARKLE (NCT02703272), a randomised study of ibrutinib, a Bruton's tyrosine-kinase (BTK) inhibitor, opened in July 2016 and aims to recruit 93 subjects. Patients are being randomised to three courses of rituximab, ifosfamide, carboplatin and

etoposide with dexamethasone (RICE) or rituximab, vincristine, ifosfamide, carboplatin and idarubicin with dexamethasone (RVICI) with or without ibrutinib<sup>32</sup>. Results are expected by June 2021.

### *Medicinal products for mature B cell malignancies developed for adults and relevant for treatment of malignancies in children*

In adults with DLBCL, rituximab has made a major impact<sup>33</sup>; however, dose escalation has not improved results in the majority of subtypes<sup>34</sup>. Furthermore, the benefit of second generation anti-CD20 antibodies has not been clearly demonstrated<sup>35</sup>. Many new medicinal products have been demonstrated to be beneficial in low grade tumours<sup>36</sup>, and antibody conjugates and CAR-T cells have been demonstrated to be effective in higher grade tumours<sup>37</sup>.

Within the Forum, eight classes of medicinal products were discussed: antibody drug conjugates, CAR T-cells, monoclonal antibodies, T-cell engagers, checkpoint inhibitors, cell signalling inhibitors, immunomodulatory imide drugs (IMiDs) and CELMoDs and cytotoxics (Table 2).

### *Paediatric Investigation Plans (PIPs)*

According to Paediatric Regulation (EC) No 1901/2006 all applications for marketing authorisation (MA) 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 performed after the MA in adults) or a waiver. A PIP is a development plan aimed at ensuring that the necessary data are obtained through studies in children to support the authorisation of a medicine for children.

By November 2017 there were 13 PIPs agreed or under assessment for medicines for a condition related to the treatment of mature B-cell neoplasms. These medicines are: ibrutinib, acalabrutinib, idelalisib, nivolumab, obinutuzumab, pixantrone, pembrolizumab, pralatrexate, rituximab, venetoclax and three cellular therapies with autologous T-cells genetically modified to express a chimeric antigen receptor targeting CD19 (CD19 CAR T cell therapies) (tisagenlecleucel [CTL019], axicabtagene ciloleucel [KTE-C19] and JCAR017 [lisocabtagene maraleucel]). None of these PIPs have been completed and no final compliance check yet conducted.

## **Discussion**

The data presented demonstrated that the frequency of the types of B-cell malignancies differs between adults and children and in many instances the biology varies. The number of patients in Europe and the US eligible for clinical trials is substantially less for children and adolescents (1680 versus 200,000 adults per year), especially those with relapsed or progressive disease (in the region of 90 patients per year). Furthermore, the number of patients with relapsed or progressive disease can be expected to fall significantly as a result of the decreased treatment failures with rituximab therapy for high risk disease.

As a general principle, it was agreed that depending on the target, whenever possible, knowledge and protocols should be shared between related diseases in adults and children. However, with the exception of PMBL (where the disease is similar in adults and children), paediatric-specific studies are considered necessary. As mature B-cell lymphomas occurring in adults and children have different molecular pathologies, extrapolation of efficacy from adult to children is not appropriate in most cases and extrapolation of safety is not possible. Additionally, since children can tolerate higher doses, there is a risk of under-treating children if 'adult' doses are used or of increasing toxicity in adults, if 'paediatric' doses are used. Therefore, the only opportunities may be for combined paediatric and adult frontline and relapsed clinical trials in PMBL, since the proposal is to add a checkpoint inhibitor to "adult" and "paediatric" standard of care for each relevant age population. It should be noted that the logistics of conducting a joint frontline adult and paediatric study would not be without challenges.

The inclusion of adolescents (aged 12 to 17 years) in adult trials of B-cell malignancies, where appropriate, is very strongly encouraged in this context, as adolescents demonstrate similar toxicity profiles, maximum tolerated doses and pharmacokinetic parameters to adults<sup>38</sup>. Furthermore, young adults with relapsed Burkitt's lymphoma should be included in strategies and trials for "paediatric" relapsed disease, as Burkitt's lymphoma has a similar biology at least up to 25 years of age<sup>22</sup> and adolescent and young adults have a similar tolerance of chemotherapy as children. Drugs that are highly effective in small biomarker based selected subpopulations of patients, for example germinal centre DLBCL, may not be amenable to classical randomised trials in unselected patient populations; under such circumstances biomarkers should first be identified and randomised trials in enriched populations should be considered.

The consensus of the clinicians present at the Forum was that it was not feasible to have a joint approach to clinical trials for leukaemia and lymphoma given differences in disease biologies and therapeutic approaches. Furthermore, the results of a trial including both leukaemia and lymphoma

would not be informative to investigators and/or regulators (e.g. due to difference in biology of disease). In addition the distinct (and often separate) organisation of leukaemia and lymphoma treating clinicians and services, or the significant undersupply of some options (especially in the case of CAR T-cells) for leukaemia patients, means that introducing competition within the same trial for patients with different disease would not be acceptable.

As current frontline therapy results in high rates of survival, de-escalation of treatment or substitution of drugs with new medicines can generally only be undertaken when there is an effective salvage regimen, which is currently not available. Priority should therefore be given to developing new treatment for patients with relapsed mature B-cell lymphomas. A further factor supporting this approach is that there is no validated biomarker predicting relapse. Therefore new drugs for mature B cell malignancies in children and adolescents should be first evaluated in relapsed patients who have the highest unmet need, and not frontline. At the same time, studies should continue to aim to identify and validate biomarkers predictive of relapse.

In view of the very small numbers of patients available for enrolment in studies at relapse, a global strategy for the development of products for relapsed mature B-cell malignancies in children and adolescents is required. Other challenges in designing trials in these relapsed mature B- cell lymphomas are the rapid progression of the disease, availability of very few pre-clinical models (and uncertainty about the optimal model), and limited opportunity for extrapolation from adults. Therefore, unless there are agents with outstanding activity (overall response rate >80%, given that an overall response rate with conventional chemotherapy of ~60% only translates to EFS of <30%) in a given early phase study, a single agent study in the relapsed setting is unlikely to be appropriate. Whilst it is thus more appropriate that a new agent is evaluated in combination rather than as monotherapy, the probable contributory benefit of each drug within the combination needs to be established. However, sequencing of an experimental agent evaluated immediately at relapse followed by experimental consolidation/maintenance could facilitate a quicker introduction of new drugs into first-line therapy. To advance knowledge and facilitate the choice of rational therapy based on the mechanism of action, trials for relapsed disease must integrate correlative biology studies to investigate resistance to therapy. Moreover, longitudinal relevant correlative studies are required as these will facilitate a better understanding of mechanisms of resistance and response.

Based on lack of significant therapeutic benefit and/or concerns around safety, the consensus of the clinicians attending the Forum was that CAR T-cells, T-cell engagers and antibody drug conjugates

(potentially excluding those carrying a vinca alkaloid-like drug) had the greatest probability of being beneficial in relapsed/refractory patients in view of their mechanism of action. It was furthermore the experts' opinion that given the uncertainties on their efficacy, new additional trials of cell signalling inhibitors, including BTK inhibitors, should not commence until the results of the SPARKLE trial<sup>33</sup> were known (Table3), especially in view of the very small numbers of available patients. This should however not preclude discussions on the placing of any such novel compound within the evolving treatment landscape. Additionally, as currently autologous CAR T-cells take at least 4 weeks for production, they are not products which could be quickly employed initially at relapse in rapidly progressing mature B-cell malignancies but only for the consolidation phase of the treatment. However, third party products, such as "off-the-shelf" modalities with streamlined manufacturing and distribution may circumvent these limitations. This prioritised approach to trials of new agents will reduce the probability of multiple trials competing for the same patients and increase the likelihood of recruitment.

Optimal drug development for new anti-cancer medicines demands collaboration and interaction between all stakeholders, with each contributing substantially to the process. Proposals for industry sponsored early phase studies should be developed by pharmaceutical companies in collaboration and conjunction with clinicians, who have expertise in the clinical context and the available populations for clinical evaluation. The input of international clinical trial cooperative groups is particularly valuable. These proposals should be for appropriate paediatric clinical studies, based on scientific rationale and should form the basis of PIPs<sup>38</sup> in Europe. Clinicians and pharmaceutical companies further considered that an iterative, 'life cycle' approach could be adapted for mechanism of action-driven drug development, with the direction of drug development continually being reviewed following evolution of the data and science. Changes could be made to the PIP by modification procedures supported by scientific arguments.

In Europe and the US serious concerns were also raised by the clinicians and pharmaceutical companies present about the number of agreed PIPs, in view of the small number of eligible patients, and about the source of information provided to sponsors submitting PIPs as to numbers of patients eligible for enrolment and number of committed study sites. This may result in a surfeit of medicinal products developed for a very small group of paediatric patients and therefore limited availability of patients for clinical trials participation and duplication of effort. Discussions among clinicians, cooperative groups and pharmaceutical companies should take place before PIPs are proposed, to decide which compounds are most likely to succeed in the paediatric population with mature B-cell

malignancies. Relevant points from these discussions should be incorporated into the clinical study design and relevant regulatory applications. This will result in a better alignment between the required number of patients for proposed clinical trials, potentially available eligible patients and regulatory requirements. On the other hand it should be taken into account that oncology medicines have an extremely high attrition rate (only 5.1% of the drugs tested in Phase I studies were approved in 2006-2015)<sup>39</sup> and that reducing the number of medicines tested in paediatric clinical trials too much could result in no new drugs being approved for children. Parent representatives stressed the importance of a global strategy and this proposed approach.

European, US and other international academic clinical cooperative groups should work closely together, guide pipeline discussions with industry to identify those products able to address the unmet medical need and undertake collaborative clinical studies (due to low patient number) in those products considered most promising to accelerate the development of new drugs. In addition to industry-initiated drug development, there are many benefits of conducting industry supported, academic sponsored studies with compounds from different pharmaceutical companies and different mechanisms of action using an adaptive design; however academic clinical trials supported by industry should be designed and conducted to a very high quality standard with “intent to file”, in order that clinical trial data can be used for licensing purposes and early input should be sought from regulators (through available procedures with the EMA’s PDCO and/or SAWP and FDA). A global industry supported academic sponsored study with compounds from different pharmaceutical companies using a master protocol in rare populations should ideally be considered. These principles may also be highly applicable to other rare paediatric cancers where international collaborative studies are necessary. As a result of the Forum, highlighting the need for continuous exchange beyond the Forum, an international working group is being formed by ACCELERATE, with academic and industry participants, to develop an overarching clinical trials strategy for medicinal products for the treatment of relapsed mature B cell malignancies in children and adolescents.

Finally, this Paediatric Strategy Forum has demonstrated that it is feasible for clinicians and industry to reach agreement, in the presence of supportive regulators and parent/patient representatives, about the prioritisation of classes of compounds for relapsed or progressive mature B-cell malignancies in children. Continual dialogue between industry and academia is critical for optimal drug development of new anti-cancer medicines in children. Future Forums are planned for other oncologic paediatric diseases with a high unmet medical need and possible relevant targeted agents.

## **Contribution**

Study concepts - ADJP, GV, KN, GL and FL. Manuscript preparation - ADJP, GV, AB, VMC and LVM. Study design, data acquisition, quality control of data analysis and algorithms, data analysis and interpretation, manuscript editing and manuscript review - All authors.

## **Conflicts of interest**

DC is an employee of Acerta Pharma; ABa was an employee of Merck & Co, Inc and is now an employee of Allogene Therapeutics; BBe is an employee of Celgene Corporation; PB is an employee of Gilead Sciences International Limited; EB is an employee of Bayer Healthcare; HC is an employee of Hoffman-La Roche Limited; AE is an employee of Servier; MF is an employee of Debiopharm International SA; GZ is an employee of Amgen Research; KN is an employee of Janssen; LP is an employee of Novartis; RR is an employee of Bristol-Myers Squibb Pharma EEIG; RV is an employee of Kite Pharma and SYK is an employee of AbbVie Limited. AB provides consultancy for Merck, Roche and Janssen. CMB is on the advisory board for Cellectis and has stock or ownership in Mana Therapeutics, Torque and Neximmune. JB is on advisory boards for Novartis and Pfizer. RM receives honoraria and consultancy fees from Roche and Gilead.

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## Tables

Table 1 - Therapeutic targets for paediatric mature B-cell malignancies

Table 2 - Medicinal products discussed at the Paediatric Strategy Forum

Table 3 – Rationale for the consensus of the clinicians regarding the medicinal products which have the greatest probability of being beneficial in relapse

Text box of key conclusions of the Paediatric Strategy Forum

## Table

Table 1 - DLBCL - diffuse large B cell lymphoma, PMBL - primary mediastinal B cell lymphoma

Table 2 - \*Approved in the US for paediatric/ young adult relapsed/refractory B-cell acute lymphoblastic leukaemia; \*\*Approved in the US for adult relapsed/refractory large B-cell lymphoma; \*\*\* Marketing Authorization Holder for Pixuvri® (pixantrone) is CTI Life Science Limited; Servier is the local representative of CTI Life Science Limited in EU.

Table 3 - PMBL - primary mediastinal B cell lymphoma,

## Tables

**Table 1**

	<b>Target</b>	<b>Type of B Cell Malignancy</b>
<b>Cell surface markers</b>	CD20, CD79a/b, CD19, CD22 and CD37	All mature B-cell malignancies
	CD30	PMBL and some DLBCL
<b>Cell signalling</b>	B-cell lymphoma (BCL)-2 and MCL1	DLBCL and Burkitt lymphoma
	Phosphoinositide 3-kinase (PI3-K)/AKT pathway	Burkitt lymphoma and some germinal centre-DLBCL.
<b>Immunological Checkpoint</b>	PDL1/PDL2	PMBL

**Table 2**

<b>Class of medicinal product</b>	<b>Product</b>	<b>Target</b>	<b>Company</b>
Antibody drug conjugates	Polatuzumab vedotin	CD79b	Roche
	Debio 1562l	CD37	Debiopharm International
CAR T-Cells	CTL019 (tisagenlecleucel)	CD19	Novartis*
	KTE-C19 (axicabtagene ciloleucel)	CD19	Kite pharma**
Monoclonal antibodies	Obinutuzumab	CD20	Roche
T-cell engagers	Blinatumomab	CD3-CD19	Amgen
	RG6026	CD20-CD3 TCB	Roche
	RG7828	CD20-CD3 TDB	Roche
Checkpoint inhibitor	Pembrolizumab	PD-1 receptor	Merck
	BMS-986016	LAG-3	BMS
Cell signalling inhibitors	Ibrutinib	Bruton's tyrosine-kinase	Jansen
	Acalabrutinib	Bruton's tyrosine-kinase	Acerta Pharma
	BAY1895344	ATR	Bayer
	BMS986158	BET	BMS
	Idelalisib	Phosphoinositide 3-kinase (PI3-K)	Gilead
	Venetoclax	B-cell lymphoma (BCL)-2	AbbVie
	Navitoclax	BCL-2	AbbVie
IMiDs and CELMoD	CC-122		Celgene
	CC-220		Celgene
Cytotoxic	Pixantrone		Servier ***

Table 3

<b>Medicinal products with greatest probability of being beneficial in relapse in mature B-cell malignancies in children</b>	<b>Scientific rationale</b>
CAR T-cells	Mechanism of action with a rapid onset of effect Significant advance in relapsed/refractory leukaemias with same target. Potential to replace high dose therapy, which is required for cure of relapsed/refractory B-cell non-Hodgkin's lymphoma.
T-cell engagers	Mechanism of action with a rapid onset of effect. Immune cellular therapy with significant promise in leukaemias with shared targets for B-cell non-Hodgkin's lymphoma.
Antibody drug conjugates	Mechanism of action with a rapid onset of effect. Immuno-chemotherapy has shown substantial efficacy in frontline high risk B-cell non-Hodgkin's lymphoma in adults. Antibody-conjugates could provide increased efficacy in relapsed/refractory patients who may have received naked antibody as frontline therapy.
Checkpoint inhibitors	Biology of PMLBL associated with enhanced target for checkpoint inhibitors similar to Hodgkin's lymphoma
<b>Medicinal products with lower probability of being beneficial in relapse in mature B-cell malignancies in children</b>	<b>Scientific rationale</b>
Monoclonal antibodies	Mechanism of action with a slow onset of effect - lack of significant therapeutic benefit. In future most relapsed/refractory patients will have received naked monoclonal antibodies as part of frontline therapy. Adult studies do not suggest that changes of antibody against the same target in relapsed/refractory setting are effective.
Cell signalling inhibitors	Mechanism of action with a slow onset of effect demonstrated in adults - lack of significant therapeutic benefit and uncertainty about activity of Bruton's tyrosine-kinase inhibitors (ongoing trial)
IMiDs and CELMoD	Mechanism of action with a slow onset of effect demonstrated in adults - lack of significant therapeutic benefit
Cytotoxics	Mechanism of action not different from established cytotoxics used in therapy of mature B-cell malignancies in childhood



## Text Box

- Except for Primary Mediastinal B cell lymphoma and potentially relapsed Burkitt's Lymphoma, specific paediatric studies are needed primarily due to different biology
- Inclusion of adolescents (aged 12 to 17 years) in adult trials is very strongly encouraged
- Joint leukaemia-lymphoma clinical trials are not feasible
- Current frontline therapy is very successful and de-escalation can only be undertaken with an effective salvage regimen
- Priority should be directed at developing treatment for relapse
- Single-agent studies are not feasible
- As there are very small numbers of patients with relapsed disease, a global strategy is required
- Trials for relapsed disease must integrate correlative biology studies
- The consensus of clinicians is that antibody drug conjugates (excluding a vinca alkaloid drug); CAR-T cells (as takes 4 weeks for production - not products for initial use but only for consolidation) and T-cell engagers have the greatest probability of being beneficial in relapse
- In view of very small numbers of patients, new additional trials of cell signalling inhibitors should not commence until the results of the ongoing SPARKLE trial known; yet discussion need to continue on the placing of any novel therapy
- Clinicians and pharmaceutical companies expressed concerns about the number of 13 related Paediatric Investigation Plans (PIPs) agreed / under assessments, in view of the small number of eligible patients and proposed that PIPs being adapted in response to new data ('PIP development Life-cycle' approach)
- Benefits of conducting academic sponsored clinical trials with adaptive design of compounds from *different* pharmaceutical companies and *different* mechanism of action - designed with "intent to file" with early input from regulators
- Patient representatives stressed the importance of a global strategy in order to limit the possibility of having too many PIPs for too few children