Paediatric Strategy Forum for Medicinal Product Development of CAR T-cells in children and adolescents with cancer

Context: The development of CAR T-cells for patients with cancer over the last 11 years has been dramatic and rapid. CAR T-cells were first evaluated to treat advanced non-Hodgkin’s lymphoma (NHL) in 2010, chronic lymphocytic leukaemia in 2011, and then paediatric, adolescent and adult acute lymphoblastic leukaemia (ALL) and multiple myeloma. The first approved CAR T-cell therapy was tisagenlecleucel for the treatment of relapsed/refractory paediatric, adolescent and young adult ALL. This was followed by approvals for tisagenlecleucel for adult diffuse large B-cell lymphoma (DLBCL), axicabtagene ciloleucel for adult large B-cell lymphoma and follicular lymphoma, brexucabtagene autoleucel for relapsed or refractory adult mantle cell lymphoma and lisocabtagene maraleucel for adult large B-cell lymphoma. Now over 300 trials of CART-cells have been completed or are ongoing. Currently there are biological, clinical and manufacturing challenges for use of CAR T-cells in paediatric malignancies. To effectively and efficiently develop CAR T-cell therapy for the benefit of children with cancer, there is a need for close cooperation between academia, industry, regulators and patient advocates. The aims of the Forum were to summarise the current status of the development of CAR T-cells in paediatrics, to identify current challenges and future directions, including other approaches such as T Cell Receptor Engineering (TCR) T-cells and to ascertain the best strategies to accelerate their development and availability to children.

Meeting: The meeting was organised by ACCELERATE, in collaboration with the European Medicines Agency (EMA), with participation of the Food and Drug Administration (FDA) of the US and was held virtually on 25, 26 and 27 May 2021 with 226 participants: 95 international paediatric haematology-oncology and immunotherapy experts from Europe, US, Canada and Australia; 54 representatives from 13 pharmaceutical companies in Europe, US, China and Singapore (Autolus Limited, Celgene/BMS, Cellectis, CRISPR Therapeutics, GSK, Gracell, Kite – a Gilead company, Miltenyi Biomedicine, Novartis, Syncophication Life Sciences, Takeda Pharmaceuticals, TCR Therapeutics and Tessa Therapeutics); 13 patient advocates from Europe, US and Canada (representatives from Andrew McDonough B Foundation, Ac2orn, Bone Cancer Research Trust, Children’s Cancer Cause, KIDS V CANCER, KickCancer, PORT/PanCare, Solving Kids’ Cancer, Solving Kids’ Cancer UK, World Duchenne Organization and European Patients Forum, Zoë4life and Childhood Cancer International); 61 regulators from the EMA (including Paediatric Committee [PDCO] and Committee for Advanced Therapies [CAT]) and national competent authorities within the EU regulatory network, Health Technology Assessment (HTAs) bodies; US FDA; UK Medicines and Healthcare Products Regulatory Agency; Health Canada as observers, and three organisers. A comprehensive overview of the development of CAR T-cells in B-cell ALL, T-cell ALL, acute myeloid leukaemia (AML) and lymphomas was presented by academic experts as well as emerging approaches for CART-cells in solid tumours, new CAR T-cell strategies and remaining challenges. Details of thirteen CAR T-cell, TCR-T, T cell receptor fusion constructs (TRuC) cell and NK CAR products were highlighted by industry representatives. The Forum concluded with the patient advocate perspective and a multi-stakeholder strategic discussion.

CAR T-cell and TCR-T cell products: JCAR017/ lisocabtagene maraleucel (liso-cell) /tisagenlecleucel, Kymriah®, CTX110, KTE-X19, AUTO1 - targeting CD19; CART22, Syncophication CD22 - targeting CD22; AUTO1/22 targeting CD19 and CD22; letetresgene autoleucel (lete-cell); TCR-T cell - GSK3377794 targeting NY-ESO-1; TAK-007 – NK CAR; GC027 targeting CD7; UCART123 targeting CD123 and gavocabtagene autoleucel / gavo-cell (T cell receptor fusion constructs (TRuC) T-cell product formerly known as TC-210) targeting mesothelin were discussed.

Paediatric Investigation Plans: There are currently (May 2021) 5 published PIPs agreed for CAR T-cells; brexucabtagene autoleucel (Tecartus) (Kite-Gilead); axicabtagene ciloleucel (YESCARTA) (Kite-Gilead); two for tisagenlecleucel (Kymriah) (Novartis); JCAR017, lisocabtagene maraleucel (Breyanzi) (Celgene). All these medicinal products target CD19 for B-cell ALL and/or B-NHL. The clinical trials associated with the PIPs relate to B-cell ALL (4), B-NHL (3) and both B-cell ALL and NHL (3). Amongst these studies, there is only one study for children at initial presentation in B-cell ALL.
**CAR T-cells in B-cell ALL:** Fifteen percent of children with B-cell ALL still relapse following standard chemotherapy regimens and many relapses cannot be effectively rescued even with allogeneic haematopoietic stem cell transplantation (HSCT). B-cell ALL thus remains a major cause of death from childhood malignancy. Furthermore, deaths from therapy, acute toxicity and long-term adverse events, especially in those patients who have received HSCT, need to be prevented. The outcome of patients is particularly poor for B-cell ALL patients with adverse genetic features or high levels of minimal residual disease after initial induction therapy and for patients with a very early or early relapse. In the immediate future, CAR T-cell therapy could potentially benefit these patients who are destined to have the worst outcomes with conventional therapies. A long-term vision is that CAR T-cell therapy may replace many components of toxic standard treatment and in the future shorten substantially the duration of therapy needed for B-ALL.

The ELIANA (Novartis) trial of the autologous anti-CD19 CAR T-cell product tisagenlecleucel in relapsed/refractory B-cell ALL (with central manufacturing and global distribution to 25 sites across 11 countries) first demonstrated a complete response (CR)/CRi rate of 81% in patients who had T cells infused with a probability of relapse-free survival (RFS) of 59% among responders at 12 months post therapy. Seventy five of 92 patients enrolled had CAR T-cells infused. Other studies of autologous CD19 CAR T-cell therapy products have confirmed the high response rate, although the effects are of limited durability in many patients. Relapse occurs either due to antigen escape with loss of CD19 and/or failure of persistence (due to immunological reasons) of CAR T-cells. Some recent studies have also reported that prior therapy with other CD19-targeted therapy (for example blinatumomab) and a higher tumour burden prior to CAR T-cell treatment are emerging as factors associated with a higher relapse rate after CAR T-cell therapy.

To improve RFS, CAR T-cell persistence may be optimised with humanized or fully human products and/or products with improved fitness. Relapse through antigen escape could be potentially prevented by targeting multiple antigens (for example, CD19 and CD22) either in sophisticated constructs or by applying sequential use of anti-CD19 and anti-CD22 CAR-T Cells. Indeed CD22 CAR T-cells (alone or in combination with CD19-directed CAR T-cells) have also been demonstrated to be active at inducing remissions in patients with relapsed/refractory disease, including following CD-19 CAR T-cells, but not long term remissions. Multi-antigen targeting is under active investigation and include, for example CD20 or CRLF2 or tri-targeting CD19-20-22. However, it has not yet been clearly demonstrated that a multi-antigen approach will improve RFS nor whether a simultaneous or sequential approach is superior.

**Role of CAR T-cells in B-cell ALL in front-line therapy:** The therapeutic benefit of CAR T-cells in newly diagnosed, high risk patients with B-cell ALL with persistent minimal residual disease after two cycles of chemotherapy (induction and consolidation therapy) is currently being investigated in the CASSIOPEIA (Novartis) trial for NCI high-risk patients (patients with age above 10 years and/or initial WBC above 50X10^9/L, persistence of minimal residual disease after several months of chemotherapy). This single arm study of 140 patients with a 5-year RFS endpoint compared to historical controls is expected to report first results in approximately in 2025. To account for the capacity of CAR T-cells to replace HSCT in this population, in addition to the primary endpoint of RFS, a secondary endpoint of disease-free without allogeneic HSCT is being explored.

**Role of CAR T-cells in B-cell ALL at very early/early relapse:** The role of CAR T-cells in very early and early relapse in a landscape of chemotherapy (+/−blinatumomab) and HSCT requires clarification. Determining if CAR T-cell therapy is a bridge to HSCT or if it is curative and it could replace HSCT is a very high priority. Ideally this should be assessed within a randomised study. It is to be decided if such a trial should target CD19 alone or use an advanced product co-targeting CD19 and CD22. Given the high-priority of this research question, partnership with academia and industry will be needed to answer this critical question as it is unlikely this will be an industry-sponsored study, due to timelines, cost, feasibility of enrolment and regulatory agreement on trial design. An academic sponsored study within the framework of an international childhood leukaemia cooperative study group with industry support is the favoured option.
CAR T-cells in AML: Approximately 40% of children with AML will die from their disease. Early relapse (<12 months from diagnosis) and any relapse after HSCT are associated with ≤20% survival. A key challenge is that there are limited AML-specific antigens as a basis for immunotherapy. The best studied, most validated and selective immunotherapeutic targets currently for childhood AML are CD123 and CD33. Mesothelin and CD56 (an important rare subgroup, occurring exclusively in the very young paediatric population with a high risk AMKL subtype and associated with a dismal prognosis) and others are being evaluated. The majority of CAR T-cell clinical development to date has focused upon CD33 or CD123 targeting, given that the targets are expressed in >85% of AML and clinical safety data with antibody-based immunotherapies are available. Other targets under active exploration include FLT3, CD38, CD44v6 and CLEC12A/CLL-1. Early phase studies are ongoing with CAR T-cells targeting CD33, CD123, CD44v6, and CLL-1. The challenges with these trials are bridging chemotherapy options, low enrolment of patients ≥16 years and heavily pre-treated relapsed/refractory AML patient population, which has made T-cell apheresis difficult. Due to the nature of the target antigens which are co-expressed on normal hematopoietic progenitor cells, current CAR T-cell therapy in AML does not aim, at this time, to provide long term persistence of CAR T-cells but rather aims to provide an effective bridge to subsequent transplant. The early results of clinical studies demonstrate that safety is similar to that seen in B-cell ALL and there may be good responses.

Role of CAR T-cells in the therapy of AML: If subsequent HSCT after AML immunotherapy is required and the relative value of T-cell engagers compared to CAR T-cells are unknown. In the future, dual targeting CAR T-cells with two or more different antigens and determining the optimal immunotherapy combination with small molecule inhibitors and sequencing of CAR T-cells and T-cell engagers requires clarification. Since persistence of CAR T-cells is not the aim for a bridge-to-transplant strategy, allogeneic CAR T-cells (including multiple administrations) CAR-NK cells and adoptive cellular therapy may have specific roles in treating patients with high-risk/relapsed AML. The results of ongoing or planned first-in-child studies are required to understand the role of CAR T-cells in AML. Further, engineered T cell therapies targeting AML-restricted antigens with high expression on leukemic blasts, but low to no expression in normal haematopoiesis (e.g. mesothelin) warrants clinical investigation.

CAR T-cells in T-cell ALL: Immune-targeted therapy options in patients with relapsed/refractory T-ALL are limited, since most targetable antigens are expressed on normal T cells. This results in three challenges utilising CAR T-cells in T-cell ALL: i) fratricide of CAR T-cells resulting in impaired expansion during manufacturing; ii) targeting normal T cells resulting in immunodeficiency, which in contrast to B-cell depletion cannot be compensated; and iii) similar to B-cell ALL, antigen escape by antigen-low subclones. There are two groups of antigens: i) pan-T antigens (CD5, CD7) which are widely expressed in T-ALL and are therefore likely to allow benefit for most patients; however fratricide and T-cell aplasia need to be overcome; ii) subset-restricted (CD1a, TRBC1) antigens with which fratricide/aplasia are easier to overcome but expression is restricted to subgroups of T-ALL. Clinical development of CAR T-cells for T-ALL is most advanced for CD5. The clinical studies to date show that CD5-specific CAR T-cells can be manufactured despite fratricide, due to down-regulation of CD5 on CAR T-cells during in vitro expansion, endogenous T cells are reduced but not eliminated post CD5 CAR T-cell infusion, therapy is safe, but responses are (currently) suboptimal. There are ongoing clinical studies of CD7-modified CAR T-cells demonstrating promising potency in relapsed/refractory T-ALL. Investigating additional T-ALL targets and/or co-targeting strategies and allogeneic CAR T-cells is warranted. As with AML, the results of ongoing or planned first-in-child studies are required to facilitate further understanding.

CAR T-cells and other adoptive cell therapies in Solid Tumours: CAR T-cells and other adoptive cell therapies are currently being evaluated in solid tumours by academic research teams and there are some promising early results. GD2-specific CAR T-cells have recently demonstrated activity in clinical studies in neuroblastoma, including complete remissions with no evidence of on-target neurotoxicity, consistent with a therapeutic window for GD2 between tumour and normal tissue. H3K27M diffuse midline gliomas also massively overexpress GD2 and in a murine model GD2-CAR T-cells eradicated established tumours. An ongoing investigator-initiated Phase I clinical trial (NCT04196413) that commenced two years after publication of the pre-clinical results demonstrates manageable toxicity, without on-target
neurotoxicity, improved clinical symptoms and decreased tumour size in response to GD2-specific CAR T-cells in glioma patients. CAR T-cells administrated directly into the CNS were found to be more potent than those administrated intravenously in these patients. Glypican 3 (GPC3)-specific CAR T-cells have also shown some early response signals in patients with hepatocellular carcinoma and are now being evaluated in combination with interleukin-15 and -21. This work provides important feasibility for ongoing and planned studies of GPC2 CAR T-cells for neuroblastoma. In addition, HER2 CAR T-cells with or without PD1-blockade for sarcoma, L1CAM for neuroblastoma, EGFR806-specific CAR T-cells in glioblastoma and B7H3-specific CAR T-cells for various solid cancers of childhood are showing potential.

Overall, targetable antigens in paediatric solid cancers so far are rare and often complicated by co-expression on normal tissues and/or heterogeneous expression in tumours. It is important to identify and prioritise the most promising antigens which include those that are well known e.g. GD2and NYESO-1 and those from recent studies e.g. B7H3. Novel CAR T-cell designs, e.g. allowing T-cell activation only in the presence or absence of an additional marker, and combinations need to be investigated and novel trial designs, such as pick the winner, drop the loser should be utilised. The challenges in developing CAR T-cells in solid tumours include the fact that targets lack tumour specificity and homogeneous expression and that there are various mechanisms contributing to T-cell dysfunction in the tumour microenvironment, which makes it more difficult for CAR T-cells to infiltrate the tumour, expand and persist. TCR is an alternative approach given ability to target antigens both on surface and within the cell.

Generally, CAR T-cell and other adoptive cell therapy products being developed for adults are not a clearly defined route for meaningful paediatric studies. Due to the distinct biologies and cells of origin of paediatric and adult solid cancers, only a small overlap may exist for antigens of interest. However, inclusion of adolescents in adult programs if scientifically justified is encouraged. There are various, potential models for development: i) development as child first by academia then to industry; ii) joint development by academia and industry; iii) standalone academic development. Engineered T cell platforms that leverage the power of the entire T cell receptor complex (as opposed to just the CD3 zeta chain utilized in CAR-T constructs) may improve T cell trafficking and persistence and therefore should be investigated in paediatric solid cancers.

In summary, early clinical trials with CAR T-cells in solid tumours are safe, show impressive evidence of clinical activity in very poor prognosis tumours, but require further optimization. TCR-T cells and other adoptive cell therapy products have shown preliminary safety and evidence of clinical activity in solid tumours. However none of these have yet received approvals. It is critical to understand the biology and improve efficacy for the rational evaluation of CAR T-cells and other adoptive cell therapies.

**CAR T-cells in Lymphoma: Paediatric B-NHL.** Paediatric mature B-NHL and precursor B-cell ALL are distinct diseases. The majority of paediatric B-NHLs are Burkitt’s lymphoma, which is rare and has an excellent prognosis with a RFS of 94% and overall survival of 95% for high-risk and a RFS of 97-98% and >96% overall survival for standard-risk disease. The acute toxicity of therapy is substantial but there are few expected long-term side effects. Relapses are very rare with just 50-70 patients per year in North America and Europe. Relapsed disease has poor chemosenstivity and a very poor prognosis. There are many potential medicinal products for B-NHL and in view of a very small population, prioritisation is needed and randomised studies are not feasible. At the ACCELERATE and EMA Paediatric Strategy Forum for mature B cell malignancies based on the mechanism of action and disease specificity, CAR T-cells, T-cell engagers and antibody drug conjugates (ADC) were prioritised for development. Resulting from the Forum the global academic-led early phase clinical trial to rapidly assess multiple novel agents in paediatric patients with relapsed and refractory B-NHL (GloBNHL) was designed. There are currently three cohorts: bispecific T-cell engager, ADC with standard chemotherapy and CAR T-cells or HSCT. The trial aims to recruit 210 patients over seven years and with an efficient, novel (Bayesian) design will be able to evaluate multiple agents, rejecting those that offer no advantage with as few children exposed to an ineffective agent as possible. The trial illustrates the challenge for initial funding of an academic sponsored industry
supported platform trial, using non-frequentist methodology, but offers potential solutions for prioritisation strategies.

CD19 CAR T-cells have produced durable responses in adult B NHL. Low tumour burden may correlate with response as in pre-B-cell ALL, but the relationship between CD19 CAR T-cell expansion and response is less than with pre-B-cell ALL and durable responses in B-NHL do not require long term persistence of functional CAR T-cells, at least detectable in peripheral blood. Many trials including combination studies are ongoing or upcoming.

Based on biology, the best targets for paediatric B-NHL are the B-lineage markers CD19, CD20 and CD22 and combinations of target may be superior. Pre-clinical studies confirm that BCMA is probably not relevant as it is only expressed in late memory B cells committed to plasma cell differentiation and has very limited expression on paediatric Burkitt and DLBCL cells since these arise from earlier stage B cell differentiation. CD19 CAR T-cells have been demonstrated to elicit some activity in paediatric Burkitt’s lymphoma.

The BIANCA (C2202) Novartis Study is a phase II study in relapsed/refractory B-NHL. Currently 33 patients have been infused; apheresis, manufacturing and bridging were found feasible and primary analysis is planned in late 2021. In contrast to B-ALL, the general picture of early experience with CAR T-cells in relapsed/refractory Burkitt lymphoma is of no response or early partial response followed by rapid progression in a majority of patients. The key questions for future development are: i) what is the mechanism of resistance? ii) what are the best targets, and is dual or triple targeting required? iii) what are the comparative benefits of CAR T-cells versus T-cell engagers and ADCs? iv) should there be a consolidation of response with HSCT?

There is a major difference between pre-B-cell ALL and B-NHL in terms of unmet needs and patient numbers. The number of eligible patients for CAR T-cell studies in paediatric B-NHL are very small and therefore it is not feasible for all CAR T-cells products, even if they are biologically relevant, to be evaluated. Further development requires the results of the BIANCA study, although early and thoughtful prioritization is essential in view of limited patient numbers.

Hodgkin and anaplastic large cell lymphoma (ALCL) both have outstanding survival rates (>95%) even if 5y-EFS is approximately 75% in ALCL. Patients with relapsed disease can be salvaged with innovative drugs (ALCL: anaplastic lymphoma kinase inhibitors, anti CD30, anti-PD1; Hodgkin: anti CD30, anti PD1). Early activity of CD30 CAR T-cells has been reported (60% CR; 1-year PFS 36%). The optimal approach is joint paediatric and adult trials as the disease biology is the same, with prioritisation of agents. Consideration should be given to evaluating CD30 CAR T-cells in front-line therapy for Hodgkin lymphoma.

Allogeneic therapies and CAR-NK: There is increasing evidence that allogeneic CAR T-cells and CAR-NK cells obtained from human donors may have roles in childhood malignancies, but this varies according to the disease, and “one size does not fit all”. The use of allogeneic CAR T-cells from unrelated, unmatched donors relies on gene-editing to remove T cell receptor genes along with genes that allow at least temporary protection from rejection by host T cells. The main benefit of allogeneic CAR T-cells is their easy availability and therefore they can act as a bridge to other therapies, whereas their lack of persistence is the main challenge for their use as stand-alone agents. Allogeneic CAR T-cells have very few indications for pre-B-cell ALL, but could have potential roles in T-cell ALL, B-NHL, AML and solid tumours. Allogeneic CAR T-cells could also overcome challenges in inability to manufacture CAR T-cells in patients where an autologous product is not feasible.

CAR-NK cells derive from the innate immune system and recognize targets via CAR, with contributions by a complex array of activating and inhibitory receptors. There is no relevant risk of GVHD. Adoptively transferred NK cells have short persistence. The main benefit from CAR-NK cells is their ‘off-the-shelf’
availability (overcoming the issues with autologous CAR T-cells of limited access and a complex supply chain) and multiple mechanisms of tumour recognition beyond the CAR alone. CAR-NK cells could have potential roles in AML, T-cell ALL, lymphomas and solid tumours. Combination approaches e.g. with IL-15 to prolong CAR NK-cell survival and persistence in vivo require investigation.

CAR T-cell trial design
The regulatory/ethical aspects of executing first in man CAR T-cell studies in children and adults needs to be considered. Although the general dogma is that first-in-man dose finding studies should be carried out in adults first and then in children, there is a lack of precedence in study designs which take into account that age is a continuum and that in general children tolerate T-cell therapies much better than adults. Therefore, new clinical study designs are needed for early phase clinical studies enrolling both children and adults and in these studies data from either group is used to inform the other, so the total number of patients treated in a study with children and adults is essentially the same as for an exclusively adult or paediatric study. For paediatric studies of CAR T-cells the requirement to demonstrate safety in adults and teenagers first before enrolling younger patients is not logical because children tolerate toxicities of CAR T-cell therapy better than adults. The use of novel trial designs, such as pick the winner, drop the loser should be utilised, to reduce the required number of patients required.

Generally, CAR T-cell products being developed for adults are not a route for meaningful paediatric studies. Due to the distinct biology and cells of origin of paediatric and adult malignancies, only a small overlap exists for antigens of interest. However, inclusion of adolescents in adult programs if scientifically justified is encouraged.

An additional challenge is ensuring access to clinical trials, especially where the disease is very rare and there is a very small trial population. Innovative options including referral of patients and rapid opening of centres should be considered.

CAR T-cells, ADCs and T-cell engaging products
CAR T-cell products for specific diseases based on relevant antigen expression will be directly competitive with both ADCs and T-cell engaging products directed against the same target. Therefore a key question is to determine the comparative benefits of CAR T-cells versus T-cell engagers and ADCs in specific situations. The ease with which the T-cell engagers and ADCs can be administered to patients, in comparison to the challenges required to administer CAR T-cell products, will make them highly attractive if they have reasonably comparable activity. The issue of competition with T-cell engaging products and ADCs applies perhaps even more in the solid tumour setting, since in the leukaemia/lymphoma setting CAR T-cell persistence may be feasible, whereas in the solid tumour setting persistence is not yet achieved and multiple infusions seem likely to be required for achieving a maintained effect. There are ADC and/or T-cell engaging products for many of the solid tumour antigens including HER2 and B7-H3/CD276. Response rates for these agents can be substantial Decisions on prioritizing and designing clinical trials for CAR T-cell products targeting these antigens will need to take into consideration plans for and results from clinical trials for the comparable ADC and T-cell engaging products.

Discussion and Conclusions
Patient Advocate’s Perspective: Patient advocates believed that the conundrum of how to optimally advance CAR T-cell therapies for B-cell ALL for relapsed/refractory disease will require additional tightly coordinated discussion among clinicians. CAR T-cell or other adoptive cell therapy therapeutic options for solid tumours, AML, T-cell leukaemia are insufficient at this time, and research should be directed to these unmet therapeutic needs. To help address these and other complex clinical strategies, patient advocates urge the use of innovative trial designs, including, child first trials and when appropriate and enrolling children in adult trials, as well as adaptive designs. They were concerned about enrolment in randomized trials for cell therapies, as these novel therapies may be seen as offering better therapeutic options over HSCT or other options. Patient advocates were very concerned about the high cost of cell therapy products, associated reimbursement uncertainties, availability, and equitable access. Cost and
manufacturing time affect patients’ access to these novel therapies. While these challenges are outside the purview of clinical research, their solution will require partnerships among researchers and other stakeholders including funding agencies, HTAs and advocates. Such partnerships will also be necessary through Paediatric Strategy Forums to help determine which, among the large number of products in development, should be evaluated in rare paediatric cancers. Patient advocates highlighted that long-term toxicities of cell therapies have not been systematically studied, and urged industry and academia to establish a common entity to document these going forward. They also continued to urge industry to engage survivors and patient advocates early in drug development, trial design, treatment implementation and patient follow-up to improve the chances that novel scientific insights can offer patients the best valid treatment options.

**Disease-specific discussion**

**B-cell ALL:** The results of the CASSIOPEIA trial for newly-diagnosed high-risk patients may contribute to clarifying the role of CAR T-cells in this scenario. It is unclear if these results will alter standard of care. The international experts, representatives from industry and patient advocates, all believed that the role of CAR T-cells in very early and early relapse in a landscape of chemotherapy (+/- blinatumomab) and HSCT requires elucidation. Identifying those patients in whom CAR T-cell therapy can replace HSCT and those patients it is a bridge to HSCT is a very high priority and requires a randomized study. Additionally, there are no CAR T-cell trials for patients with first relapse of B-ALL, and CAR T-cells need to be studied in this setting. Although not yet proven, dual targeting CD19 and CD22 is the currently the most advanced approach for hypothetical prevention of prevent antigen escape. However, the benefits of this approach need to be established. Therefore, additional products targeting CD19 alone should only be developed in paediatrics if the product has a substantial benefit (demonstrated from adult and/or preliminary paediatric studies) in terms of efficacy, persistence and/or toxicity comparable or superior to existing products. Development of CAR T-cells with improved persistence and more favourable immunologic properties for example the development of human or humanized CAR constructs, is another priority, but does not address the problem of antigen escape. In addition strategies must evolve to ensure appropriate access for children who could potentially benefit from this therapy.

**AML and T-cell ALL:** CAR T-cells are early in development for AML and T-cell ALL. CD33 and CD123 appear to be good targets in AML and CD7 in T-cell ALL. The results of ongoing or planned first-in-child studies are required to facilitate further understanding.

**Solid Tumours:** There are promising early results particularly in midline gliomas and neuroblastoma with GD2 targeting and there is substantial potential for a significant unmet clinical need. It is critical to understand the biology and improve selective targeting and efficacy to rationally evaluate CAR T-cells as well as engineered T cells that employ the entire T cell receptor either alone or in combination with other immuno-oncology agents.

**Lymphoma: B-NHL:** There are many differences between paediatric B-NHL and pre-B-cell ALL. Prioritisation is needed and randomised studies are not feasible to evaluate CAR T-cells in Burkitt lymphoma in view of the very small patient numbers. The BIANCA phase II study is expected to demonstrate the feasibility and initial efficacy of CD19 CAR T-cells in paediatric relapsed/refractory B-NHL. The early experience with CAR T-cells in this setting comprises mostly no responses or early relapses. Mechanisms of resistance must be understood to inform further development and Combination trials of alternative targets (CD20 or CD22) should also be explored as a priority to improve efficacy in this population.

**Hodgkin’s disease and ALC:** The optimal approach for product development of CD30 CAR T-cells in Hodgkin’s disease and ALC is joint paediatric and adult trials.

**General discussion**

**Combinatorial regimens:** In many paediatric malignancies a combinatorial approach with cell therapies is warranted, (for example bispecific CD19 x CD22 CAR T-cells in B-cell ALL). Other combinations will
include cell therapies with i) immunomodulators - anti-PD1; ii) vaccines; iii) cytokines such as IL-15; iv) bryostatin to up regulate CD22; v) modulators of the tumour micro-environment; vi) chemotherapy; vii) small molecules e.g. dasatinib and other multi-targeted kinase inhibitors to prevent CAR T-cell tonic signalling and subsequent exhaustion; viii) bispecific, trispecific, quadspecific T-cell engagers to extend the target spectrum. Decisions of the appropriate combination based on biology of the individual cancers are therefore critical.

**Access for children to cell therapies (CAR T-cell B-cell ALL example):** Currently many children who could potentially benefit from such a therapy, either through the approved product or a clinical trial, do not have access to this innovation. Strategies must evolve to ensure appropriate access.

**Development plan for cell therapies:** Very early planning of the development pathway is critical for optimal efficiency with involvement of regulators in clinical trials of innovative medicines for which regulatory approval may ultimately be sought. Also, early academia-multi-company engagement is mandatory. By aligning scientific, regulatory and HTA (in the EU) requirements from the inception of a clinical trial, drug development will be accelerated, the patients with the greatest need will be prioritised and evidence for scientific and regulatory purpose will be generated. Trial design (randomised versus non-randomised), identification of appropriate “control” populations (historical versus contemporaneous) and comparisons with standard of care are critical issues. It is important to define the target population (e.g. high-risk front-line or first relapse) and have study designs to allow for early decision making of development plans to continue or not, while overall ensuring clinically relevant endpoints and robust comparative data are generated to also inform HTAs. The inclusion of front-line trials in PIPs will align scientific, regulatory and HTA requirements. The challenge occurs when trials are required to determine standard of care, but these are not registrational studies. An additional challenge is establishing contribution of components for regulatory support when seeking to develop CAR T-cell in combination with other agents. There needs to be a dynamic process for prioritisation.

The current approach for increasing trans-Atlantic regulatory (EMA and FDA) alignment, for example the simultaneous submission of PIPs and iPSPs was applauded. Further alignment would be of great benefit to both academia and industry as would harmonisation different countries within the European Union.

**Development of cell therapy products by academia:** There are scenarios when it is anticipated that industry will not be willing to develop a CAR T-cell or TCR-T cell product, (for example for very small or ‘boutique’ paediatric populations), and where trials are required to determine standard of care, but these are not registrational studies. Unlike small molecules and protein therapeutics where the timing of first-in-child trials is generally determined by industry, first-in-child trials of cell therapies can be launched without private sector investments. The model for drug development for cancer cell therapy in paediatrics could involve a “later stage handoff” to industry after derisking in the academic arena. This could enable more rapid/efficient testing of the most promising products, targets, combinations. The optimal position is where there is a partnership with industry. A flexible model is needed, “one size does not fit all”. Co-sponsorship is another option. An academic development model relies on academic manufacturing of uniform products by good manufacturing practice (GMP) standards upon local licenses, along with distribution to additional academic trial sites (decentralized academic manufacturing). In this model, the academic manufacturing centre would ensure quality to GMP levels and take responsibility for all regulatory related actions. However, the business model requires substantial financial investments by government, foundations and academic medical centres which have some track record of experience and success. It is also critical that access to all relevant children is available when development is finalized and drugs are validated. Generally industry should be encouraged to partner with academia to help support these rare disease indications.