European Journal of Cancer 160 (2022) 112–133

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Paediatric Strategy Forum for medicinal product development of chimeric antigen receptor T-cells in children and adolescents with cancer ACCELERATE in collaboration with the European Medicines Agency with participation of the Food and Drug Administration[2]

Andrew DJ. Pearson [a,*,1], Claudia Rossig [b,1], Crystal Mackall [c,1], Nirali N. Shah [d,1], Andre Baruchel [e,1], Gregory Reaman [f], Rosanna Ricafort [g], Delphine Heenen [h], Abraham Bassan [i], Michael Berntgen [j], Nick Bird [k], Eric Bleickardt [l], Najat Bouchkouj [f], Peter Bross [f], Carrie Brownstein [m], Sarah Beaussant Cohen [n], Teresa de Rojas [a], Lori Ehrlich [f], Elizabeth Fox [o], Stephen Gottschalk [o], Linda Hanssens [p], Douglas S. Hawkins [q], Ivan D. Horak [r], Danielle H. Taylor [s], Courtney Johnson [f], Dominik Karres [t], Franca Ligas [t], Donna Ludwinski [u], Maksim Mamonkin [v], Lynley Marshall [w], Behzad K. Masouleh [x], Yousif Matloub [y], Shannon Maude [z], Joe McDonough [aa], Veronique Minard-Colin [ab], Koen Norga [ac], Karsten Nysom [ad], Alberto Pappo [o], Laura Pearce [ae], Rob Pieters [af], Martin Pule [ag], Alfonso Quintás-Cardama [ah], Nick Richardson [f], Martina Schüßler-Lenz [ai,as], Nicole Scobie [aj], Martina A. Sersch [ak], Malcolm A. Smith [al], Jaroslav Sterba [am], Sarah K. Tasian [z], Brenda Weigel [an], Susan L. Weiner [ao], Christian Michel Zwaan [af,ap,ar], Giovanni Lesa [t], Gilles Vassal [a,aq]

[a] *ACCELERATE, Europe*
[b] *University Childreńs Hospital Muenster, Pediatric Hematology and Oncology, Germany*
[c] *Department of Pediatrics and Medicine, Stanford University, Center for Cancer Cell Therapy, Stanford Cancer Institute, Stanford, CA, USA*
[d] *Pediatric Oncology Branch, National Cancer Institute, USA*

* *Corresponding author*:
E-mail address: andy1pearson@btinternet.com, gynette.cook@icr.ac.uk (A.DJ. Pearson).
[1] Joint first authors. [2] The participants are given in Appendix section.

https://doi.org/10.1016/j.ejca.2021.10.016

[e] Hôpital Universitaire Robert Debré (APHP) and Université de Paris, France
[f] US Food and Drug Administration, USA
[g] Bristol Myers Squibb Company/Celgene, a BMS Company, USA
[h] KickCancer, Belgium
[i] Syncopation Life Sciences, USA
[j] Scientific Evidence Generation Department, Human Medicines Division, European Medicines Agency (EMA), Amsterdam, Netherlands
[k] Solving Kids' Cancer, UK
[l] Novartis, USA
[m] Cellectis, USA
[n] CRISPR Therapeutics, Switzerland
[o] St Jude Children's Research Hospital, USA
[p] Miltenyi Biomedicine, Germany
[q] Seattle Children's Hospital, USA
[r] Tessa Therapeutics, Singapore
[s] Paediatric Oncology Reference Team (PORT), London, UK
[t] Paediatric Medicines Office, Scientific Evidence Generation Department, Human Medicines Division, European Medicines Agency (EMA), Amsterdam, Netherlands
[u] Solving Kids' Cancer, USA
[v] Baylor College of Medicine, USA
[w] The Royal Marsden Hospital and the Institute of Cancer Research, London, UK
[x] Kite, a Gilead Company, USA
[y] Takeda Pharmaceuticals International, USA
[z] Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, Philadelphia, USA
[aa] The Andrew McDonough B+ Foundation, USA
[ab] Department of Pediatric and Adolescent Oncology, INSERM U1015, Gustave Roussy, Université Paris-Saclay, Villejuif, France
[ac] Antwerp University Hospital, Paediatric Committee of the European Medicines Agency, Federal Agency for Medicines and Health Products, Belgium
[ad] Rigshospitalet, Denmark
[ae] GlaxoSmithKline, USA
[af] Princess Maxima Center for Pediatric Oncology, Netherlands
[ag] Autolus Limited, UK
[ah] TCR^2 Therapeutics, USA
[ai] Chair of CAT (Committee for Advanced Therapies), European Medicines Agency (EMA), Amsterdam, Netherlands
[aj] Zoe4Life, Switzerland
[ak] Gracellbiotechnologies Inc, China
[al] National Cancer Institute, USA
[am] University Hospital Brno, Masaryk University, Brno, Czech Republic
[an] University of Minnesota, USA
[ao] Children's Cancer Cause, USA
[ap] Haematological Malignancies Co-Chair Innovative Therapies for Children with Cancer Consortium (ITCC), Europe
[aq] Department of Pediatric and Adolescent Oncology, Gustave Roussy, Université Paris-Saclay, Villejuif, France
[ar] Erasmus University Medical Center Rotterdam, Netherlands
[as] Paul-Ehrlich-Institut, Germany

Received 28 September 2021; accepted 13 October 2021
Available online 25 November 2021

KEYWORDS
Paediatric oncology;
CAR T-cell;
Adoptive cellular immunotherapy;
Paediatric Strategy Forum;
Drug development;
Cancer therapeutics

Abstract The seventh multi-stakeholder Paediatric Strategy Forum focused on chimeric antigen receptor (CAR) T-cells for children and adolescents with cancer. The development of CAR T-cells for patients with haematological malignancies, especially B-cell precursor acute lymphoblastic leukaemia (BCP-ALL), has been spectacular. However, currently, there are scientific, clinical and logistical challenges for use of CAR T-cells in BCP-ALL and other paediatric malignancies, particularly in acute myeloid leukaemia (AML), lymphomas and solid tumours. The aims of the Forum were to summarise the current landscape of CAR T-cell therapy development in paediatrics, too identify current challenges and future directions, with consideration of other immune effector modalities and ascertain the best strategies to accelerate their development and availability to children.

Although the effect is of limited duration in about half of the patients, anti-CD19 CAR T-cells produce high response rates in relapsed/refractory BCP-ALL and this has highlighted previously unknown mechanisms of relapse. CAR T-cell treatment as first- or second-line

therapy could also potentially benefit patients whose disease has high-risk features associated with relapse and failure of conventional therapies. Identifying patients with very early and early relapse in whom CAR T-cell therapy may replace haematopoietic stem cell transplantation and be definitive therapy versus those in whom it provides a more effective bridge to haematopoietic stem cell transplantation is a very high priority. Development of approaches to improve persistence, either by improving T cell fitness or using more humanised/fully humanised products and co-targeting of multiple antigens to prevent antigen escape, could potentially further optimise therapy.

Many differences exist between paediatric B-cell non-Hodgkin lymphomas (B-NHL) and BCP-ALL. In view of the very small patient numbers with relapsed lymphoma, careful prioritisation is needed to evaluate CAR T-cells in children with Burkitt lymphoma, primary mediastinal B cell lymphoma and other NHL subtypes. Combination trials of alternative targets to CD19 (CD20 or CD22) should also be explored as a priority to improve efficacy in this population. Development of CD30 CAR T-cell immunotherapy strategies in patients with relapsed/refractory Hodgkin lymphoma will likely be most efficiently accomplished by joint paediatric and adult trials.

CAR T-cell approaches are early in development for AML and T-ALL, given the unique challenges of successful immunotherapy actualisation in these diseases. At this time, CD33 and CD123 appear to be the most universal targets in AML and CD7 in T-ALL. The results of ongoing or planned first-in-human studies are required to facilitate further understanding. There are promising early results in solid tumours, particularly with GD2 targeting cell therapies in neuroblastoma and central nervous system gliomas that represent significant unmet clinical needs. Further understanding of biology is critical to success.

The comparative benefits of autologous versus allogeneic CAR T-cells, T-cells engineered with T cell receptors T-cells engineered with T cell receptor fusion constructs, CAR Natural Killer (NK)-cell products, bispecific T-cell engager antibodies and antibody-drug conjugates require evaluation in paediatric malignancies.

Early and proactive academia and multi-company engagement are mandatory to advance cellular immunotherapies in paediatric oncology. Regulatory advice should be sought very early in the design and preparation of clinical trials of innovative medicines, for which regulatory approval may ultimately be sought. Aligning strategic, scientific, regulatory, health technology and funding requirements from the inception of a clinical trial is especially important as these are very expensive therapies.

The model for drug development for cell therapy in paediatric oncology could also involve a 'later stage handoff' to industry after early development in academic hands. Finally, and very importantly, strategies must evolve to ensure appropriate ease of access for children who need and could potentially benefit from these therapies.

1. Introduction

The goal of a multi-stakeholder Paediatric Strategy Forum1 [2–5] is to share information between all stakeholders in a pre-competitive setting to inform paediatric drug development strategies and subsequent decisions. This is achieved by providing a unique opportunity to facilitate dialogue and enable constructive interactions between all stakeholders (regulators, pharmaceutical companies, clinical academics and patient advocates) on topics requiring discussion in drug development in children and adolescents with malignancy. In this way, novel drugs with a similar mechanism of action can then be 'compared' in a non-competitive space, such that precious resources are not wasted, and paediatric patients are not enrolled on sub-optimal clinical studies. These Forums provided unprecedented opportunities for meaningful interaction between all stakeholders on topics that might cause a feasibility problem from an industry or academic standpoint in paediatric or adolescent cancer drug development. They facilitate the development of and scientifically driven discussion about the best choices of innovative medicines for the treatment of children with cancer and ultimately accelerate the introduction of these medicines into the standard of care for children.

The development of chimeric antigen receptor (CAR) T-cell immunotherapy [6] for patients with cancer over the last 11 years has been dramatic and rapid [7–9]. CAR T-cells were first used to treat advanced non-Hodgkin lymphoma (NHL) in 2010, chronic lymphocytic leukaemia in 2011, paediatric and adolescent/young adult (AYA) B-cell precursor acute lymphoblastic leukaemia (BCP-ALL) in 2012 and most recently multiple myeloma. The first agency-approved CAR T-cell therapy was tisagenlecleucel for the treatment of

paediatric/AYAs with relapsed/refractory BCP-ALL (approved by the FDA in 2017 and EMA in 2018). This was followed by the approvals by the EMA and FDA for tisagenlecleucel for adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), axicabtagene ciloleucel for adults with relapsed/refractory large B-cell lymphoma or follicular lymphoma, brexucabtagene autoleucel for adults with relapsed/refractory mantle cell lymphoma, lisocabtagene maraleucel for adults with relapsed/refractory large B-cell lymphoma and idecabtagene vicleucel for adults with relapsed/refractory multiple myeloma. Over 1100 trials of CAR T-cells have now been completed or are ongoing in children and adults with high-risk cancers [10]. However, numerous biological, clinical and manufacturing challenges exist in the use of CAR T-cells in the treatment of cancer and specifically in paediatric malignancies [11]. To develop CAR T-cell therapy effectively and efficiently for the benefit of children with cancer, there is a need for close cooperation between academia, industry, regulators and patient advocates. It was, therefore, considered timely to hold a Paediatric Strategy Forum focussing on CAR T-cell therapies in children and adolescents with cancers. The aims of the Forum were to summarise the current landscape of CAR T-cell therapy development in paediatrics to identify current challenges and future directions, with consideration of other immune effector modalities, such as T-cell receptor (TCR)-engineered T-cells, TCR fusion construct T-cells (TRuC) and CAR-NK cell products, and ascertain the best strategies to accelerate their development and availability to children.

The meeting was organised by ACCELERATE in collaboration with the European Medicines Agency (EMA) with participation of the United States Food and Drug Administration (FDA) and was held virtually on 25th, 26th and 27th 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, Gracellbiotechnologies Inc, GlaxoSmithKline, Kite – a Gilead company, Miltenyi Biomedicine, Novartis, Syncopation Life Sciences, Takeda Pharmaceuticals, TCR [2] 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 (Paediatric Oncology Reference Team), Solving Kids' Cancer, Solving Kids' Cancer UK, World Duchenne Organization and European Patients Forum, Zoé4life 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 BCP-ALL, T-ALL, acute myeloid leukaemia (AML) and lymphomas was presented by academic experts, as well as emerging approaches for CAR T-cell strategies in solid tumours and remaining challenges. Details of thirteen CAR T-cell, TCR T-cell, TRuC T-cell and CAR NK-cell products that are or will be under evaluation specifically in paediatric trials were also highlighted by industry representatives. The Forum concluded with the patient advocate perspective and a multi-stakeholder strategic discussion.

2. CAR T-cells in BCP-ALL

Ten percent of children with BCP-ALL relapse following standard chemotherapy regimens and many relapses cannot be effectively rescued even with allogeneic haematopoietic stem cell transplantation (HSCT) [12,13]. BCP-ALL thus remains a major cause of death from childhood malignancy given its relatively common incidence. Furthermore, deaths from therapy, acute toxicity and long-term adverse events, especially in those patients who have received HSCT, need to be prevented [14]. The outcome of patients is particularly poor for those patients with BCP-ALL with (a) adverse genetic features at initial presentation; (b) high levels of minimal residual disease after initial induction and particularly after consolidation therapy; (c) early medullary relapse and (d) multiple relapses. CAR T-cell therapy could potentially benefit these patients for whom conventional therapies fail. A long-term vision is that CAR T-cell therapy could replace many components of toxic standard treatment and, in the future, substantially shorten the duration of therapy needed to cure children with BCP-ALL.

The ELIANA (Novartis) trial of the autologous anti-CD19 CAR T-cell product, tisagenlecleucel, in children and AYAs with relapsed/refractory BCP-cell ALL (with central manufacturing and global distribution to 25 sites across 11 countries) reported a complete response (CR)/complete response with incomplete cell count recovery (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-nine of 92 patients enrolled had CAR T-cells infused [15,16], highlighting critical factors of cell manufacturing difficulties or leukaemia progression and clinical instability that precluded infusion. Although the response is of limited durability in about half of the patients, other academic paediatric and adult studies of autologous CD19 CAR T-cell therapy products have confirmed their high initial response rates [17–22]. Multiple studies have now shown that post-CD19 CAR T-cell relapse often occurs because of antigen escape with the loss of CD19

by acquired somatic gene mutations in the leukaemic clone [23]. Failure of expansion and persistence [24,25] of CAR T-cells is another mechanism of relapse. Recent studies have also reported that prior treatment with other CD19-targeted therapy (e.g. blinatumomab) [26–28] and a higher medullary tumour burden before CAR T-cell treatment are factors associated with higher relapse rates after CD19 CAR T-cell therapy in this population [25,29]. CAR T-cells containing costimulatory domains of CD28 (versus 4-1BB, as in tisagenlecleucel) have also been shown to be effective at inducing remissions and can effectively be a bridge to subsequent HSCT, but do not persist *in vivo* beyond a few weeks and are unlikely to be curative as a stand-alone therapy in children with relapsed/refractory B BCP-ALL [17,18].

To improve CAR-T cell persistence and RFS, humanised [25] or fully human products and/or products with improved T cell fitness are under evaluation. Alternative targets in BCP-ALL have also shown promise, including CD22, CD20 [30,31] and CRLF2 [32,33]. A clinical trial in paediatric and AYA patients with relapsed/refractory disease of CD22 CAR T-cells showed robust remission induction, including those with CD19-negative relapse after CD19 CAR T-cells. This has facilitated subsequent HSCT in some patients [34–36]. It is currently thought that relapse via antigen escape mechanisms could be potentially prevented by co-targeting multiple antigens (e.g. dual CD19 × CD22 CAR T-cells) [37] either in bivalent or bicistronic constructs or by sequential or concomitant co-infusion of monovalent anti-CD19 and anti-CD22 CAR-T cells [17,22]. Multi-antigen targeting is under active preclinical and clinical investigation, including dual- and even triple-antigen targeting strategies [38]. To date, it has not yet been clearly demonstrated that a multi-antigen approach will improve RFS nor whether a simultaneous or sequential approach of co-targeting may be superior.

2.1. Role of CAR T-cells in BCP-cell ALL in front-line therapy

The therapeutic benefit of CAR T-cells in patients with newly-diagnosed National Cancer Institute high-risk BCP-ALL with persistent minimal residual disease after two cycles of chemotherapy [39] (induction and consolidation) is currently being investigated in the CASSIOPEIA (Novartis) trial, given the documented poor clinical outcomes of this population with 5-year event-free survival of 39% [40]. The primary outcome of this single-arm study of 140 patients is 5-year RFS compared with historical control patients treated with chemotherapy. To account for the capacity of CAR T-cells to replace HSCT in this population, in addition to the primary end-point of RFS, a secondary end-point of disease-free survival without allogeneic HSCT is being explored [41]. The trial is expected to report the first results in approximately 2025.

2.2. Role of CAR T-cells in B-cell ALL at very early/early relapse

The role of CAR T-cells in an early and very early relapse in a landscape of chemotherapy (+/-blinatumomab) and HSCT requires clarification. This is especially important after recent randomised trials established a clear benefit with substantially superior RFS after blinatumomab as a bridge to HSCT [12,13] in patients in first early relapse of BCP-ALL or late relapse with minimum residual disease (MRD) positivity after reinduction chemotherapy. Two strategies are currently being followed, some centres use CAR T-cell therapy as a bridge to HSCT, other centres use CAR T-cell therapy followed by careful monitoring of MRD reappearance and use HSCT only in those cases. The first strategy is focused on the prevention of relapses, and the second strategy is the prevention of HSCT with its late effects. Which one leads to better survival is unknown. Determining if CAR T-cell therapy is a bridge to HSCT or if it is curative and could replace HSCT in some patients is a very high priority. Ideally, this question 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, and which optimal product(s) should be investigated. Given the high priority of this research question, a partnership between academia and industry will be needed as it is unlikely this will be a solely industry-sponsored study due to timelines, cost and feasibility of enrolment. Furthermore, regulatory involvement will be required on trial design to fulfil potentially regulatory requirements 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 to answer this question efficiently and definitively. The design of any randomised study is not trivial as not only all patients would have a CAR T-cells product manufactured effectively but also because patients proceeding to allogeneic HSCT need to be in a CR, which is not the case for CAR T-cells.

3. CAR T-cells in AML

Approximately 30% of children with AML will die from their disease despite maximally intensive chemotherapy and HSCT, often in the first remission. Early relapse (<12 months from diagnosis) and any relapse after HSCT are associated with $\leq$ 20% survival [42]. A key challenge is that there are no known AML-specific antigens that are uniquely expressed on the malignant clone, but not on normal myeloid precursors, as a basis

for immunotherapy [43–45]. The best-studied, most validated and most selective immunotherapeutic targets currently for childhood AML are CD123 [46–54] and CD33 [55–58]. Hence, most of the CAR T-cell clinical development, to date, has focused on CD33 or CD123 targeting given that the targets are expressed in >85% of AML, and clinical safety data with several antibody-based immunotherapies are now available [59–61]. Other targets under active exploration include mesothelin [62], CD56 [63] (expressed by the important rare *CBFA2T3-GLIS2* fusion subgroup, occurring exclusively in the very young paediatric population with a high risk acute megakaryoblastic leukaemia subtype and associated with a dismal prognosis), FLT3, CD38, CD44v6 [64] and CLEC12A/CLL-1 [65]. Early phase studies with paediatric enrolment are ongoing with CAR T-cells targeting CD33, CD123, CD44v6, and CLL-1 [59–61,64,65]. The challenges with these trials are a heavily pretreated relapsed/refractory AML patient population, which has made autologous T-cell apheresis quite difficult, rapid AML progression while awaiting CAR T-cell manufacturing, lack of effective bridging chemotherapy options during CAR T-cell manufacturing, and difficulty in enrolling patients ≥16 years with relapsed/refractory AML at paediatric institutions. Because of the nature of the target antigens which are co-expressed on normal haematopoietic progenitor cells, current CAR T-cell therapy in AML may be associated with appreciable on-target/off-tumour toxicity. At this time, most AML CAR T-cell immunotherapy does not aim to provide long-term persistence of CAR T-cells but rather aims to provide effective remission reinduction and bridge to subsequent transplant which in itself may be important for chemo-refractory patients. Early results of clinical studies demonstrate that the safety of AML CAR T-cell immunotherapy has been reasonable without as much 'bystander' toxicity as initially feared with some deep responses that have been transplant-enabling.

3.1. Role of CAR T-cells in the therapy of AML

It remains unknown whether novel improved CAR T-cell designs will allow AML immunotherapy without subsequent HSCT in the future. Evaluation of the relative value of more readily-available bispecific T-cell engager antibodies and antibody-drug conjugates (ADCs) targeting myeloid antigens, which also provide preliminary antigen-redirected T cell responses as a bridge to HSCT is also of paramount importance. The potential efficacy of dual targeting CAR T-cells with two or more different AML antigens, the optimal immunotherapy combination with small molecule inhibitors and optimal indication and/or sequence of CAR T-cells and T-cell engagers requires clarification. Because persistence of CAR T-cells is currently not the aim for a bridge-to-transplant strategy, allogeneic CAR T-cells (including multiple administrations), allogeneic NK cells, CAR NK-cells and other adoptive cellular therapy may have specific roles in treating some 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-cell therapy in AML. Further engineered T cell therapies targeting AML-restricted antigens in 'boutique' subtypes with a high expression on leukaemic blasts but with low to no expression in normal haematopoiesis (e.g. mesothelin), warrants clinical investigation.

4. CAR T-cells in T-cell ALL

Immune-targeted therapy options in patients with relapsed/refractory T-ALL are limited because most targetable antigens are expressed on normal T cells [66]. This results in two challenges using 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 currently be compensated in patients. In addition, similar to BCP-cell ALL, subclones or mutants with low or lost antigen expression can escape and produce antigen-negative relapses [66]. There are two groups of T-ALL antigens that are currently being targeted with CAR T-cell therapies, (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; and (ii) subset-restricted (CD1a, TRBC1) antigens with which fratricide/aplasia are easier to overcome, but the expression is restricted to smaller subgroups of T-ALL [66]. Clinical development of CAR T-cells for T-ALL to date has been most advanced for CD5 [67]. These clinical studies show that CD5-specific CAR T-cells can be manufactured despite fratricide. Because of 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 [67]. Evidence suggests that fratricide by CD7 CAR T-cells can be overcome by gene-editing because CD7 expression appears not to be a prerequisite for T cell function [66,68–70]. In addition, the adoptive transfer of gene-edited CD7-negative T-cells could also overcome *in vivo* T-cell depletion by CD7-specific CAR T-cells [67]. There are ongoing clinical studies of CD7-modified CAR T-cells demonstrating promising activity in relapsed/refractory T-ALL [71–75], including durable remissions in a subset of patients [75]. Investigating additional T-ALL targets and/or co-targeting strategies, allogeneic CAR T-cells or CAR NK-cells is also warranted. As with AML, the results of ongoing or planned first-in-child studies are required to facilitate further understanding and clinical progress.

5. CAR T-cells and other adoptive cell therapies in solid tumours

Cellular immunotherapies are currently being evaluated in solid tumours by numerous academic research teams and industry with some promising early results recently reported. CAR T-cells targeting the non-protein ganglioside GD2 have been developed over many years [76–80]. Clinical activity in neuroblastoma has been recently reported, including complete remissions with no evidence of on-target neurotoxicity. This is consistent with a therapeutic window for on-target/on-tumour targeting GD2 without deleterious effects on normal tissues, where GD2 can be present at low densities [78,81]. Pre-clinical studies of GD2-CAR T-cells have shown potent eradication of H3K27M diffuse midline glioma tumours in murine models [82]. CAR T-cells administered directly into the central nervous system in murine models were also found to be more potent than those administered intravenously [83,84]. An ongoing investigator-initiated Phase I clinical trial has reported manageable toxicity without on-target neurotoxicity, improved clinical symptoms and decreased tumour size in response to GD2-specific CAR T-cells, administered intravenously, in patients with diffuse midline glioma [85]. These responses are particularly notable as these tumours have one of the worst prognoses of all paediatric malignancies, with no known curative strategies despite decades of research and many trials. Innovative approaches aiming to improve the antitumour activity of GD2-specific CAR T-cells include engineering cytokine genes to allow optimal expansion (e.g. C7R-GD2 CAR T-cells) and the use of alternative effector cells, such as autologous NKT cells [86–90]. Glypican 3 (GPC3)-specific CAR T-cells have also shown some early response signals in patients with hepatocellular carcinoma [91] and are now being evaluated in combination with interleukin-15 [92] and -21 [93]. This work provides important feasibility for ongoing and planned studies of CAR T-cells targeting an alternative glypican, such as GPC2, in neuroblastoma [94]. In addition, HER2 CAR T-cells for glioblastoma and with or without PD1-blockade for paediatric sarcomas [95,96], L1CAM for neuroblastoma [97], EGFR806-specific CAR T-cells in glioblastoma [98] and B7H3-specific CAR T-cells [84,99] for various solid cancers of childhood are showing potential.

Overall, targetable antigens in paediatric solid cancers are rare and may be 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 currently include GD2 and B7H393 [84] and NY-ESO-1 as a target for TCR. Novel CAR designs, for example, 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 used. The challenges in developing CAR T-cells in solid tumours include the fact that targets lack either tumour specificity or homogeneous expression or both and that there are various mechanisms contributing to T-cell dysfunction in the tumour microenvironment, which makes it difficult for CAR T-cells to infiltrate the tumour, expand and persist. TCR engineering is an alternative approach that targets antigens both on the cell surface and within the cell but requires peptide presentation on MHC, which may be defective in cancer cells, and which restricts patient eligibility by human leukocyte antigens (HLA) type. NY-ESO-1- and MAGEA4-specific T cells for the treatment of synovial sarcoma are a promising example currently evaluated in both adults and the paediatric population [100,101]. Engineered T cell platforms that leverage the power of the entire TCR complex (as opposed to just the CD3 zeta chain used in CAR-T constructs) while avoiding HLA restriction, so-called TRuC T-cells, may improve T cell trafficking and persistence and therefore should be investigated in paediatric solid cancers [102].

Generally, the development of CAR T-cell and other adoptive cell therapy products for adults is not a clearly defined route for meaningful paediatric studies. Because of the distinct biologies and cells of origin of paediatric and adult solid cancers, only a small overlap exists for antigens of interest. However, the inclusion of adolescents in adult programs, if scientifically justified (as with NY-ESO-1 specific T-cells), is strongly encouraged. There are various potential models for development (i) development in children first by academia then to industry; (ii) joint development by academia and industry; (iii) standalone academic development within a business model.

In summary, early clinical trials with CAR T-cells in solid tumours demonstrate that they are safe, show promising evidence of clinical activity in very poor prognosis tumours but require further optimisation. TCR-engineered 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.

6. CAR T-cells in lymphoma

6.1. Paediatric B-NHL

Paediatric mature B-NHL and BCP-ALL are distinct diseases. Most paediatric B-NHLs are Burkitt lymphomas, which are rare and have an excellent prognosis with an RFS of 94% and overall survival (OS) of 95% for patients with high-risk disease and an

RFS of 97–98% and >98% OS for standard-risk disease [104]. The acute toxicity of therapy is substantial but there are few expected long-term side effects [103]. Relapses are very rare, with just 50–70 paediatric patients per year, in North America and Europe [1]. The relapsed disease has poor chemosensitivity and a very poor prognosis; however, there are many potential medicinal products for B-NHL, and in view of the very small population, randomised studies are not feasible, and prioritisation is needed. At the ACCELERATE and EMA Paediatric Strategy Forum for mature B cell malignancies based on the mechanism of action and disease specificity, B-cell antigen-targeting CAR T-cells, T-cell engagers and ADC were prioritised for development [1]. Resulting from that Forum, a 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 an efficient 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 the non-frequentist metho dology but offers potential solutions for prioritisation strategies.

CD19 CAR T-cells have produced durable responses in adult B NHL [104–106]. Low tumour burden may correlate with a response as in BCP-ALL, but the relationship between CD19 CAR T-cell expansion and response is less than with B- ALL, and durable responses in B-NHL do not require long term persistence of functional CAR T-cells, at least detectable in peripheral blood [104–107]. Many trials, including combination studies in the adult population, are ongoing or upcoming.

Based on biology, the best targets for paediatric B-NHL are the B-lineage markers CD19, CD20 and CD22, and combinatorial targeting may be superior. Pre-clinical studies confirm that BCMA is probably not an optimal target because it is only expressed in late memory B cells committed to plasma cell differentiation and has very limited expression on paediatric Burkitt and DLBCL that arise from earlier stage B cell differentiation. CD19 CAR T-cells have been demonstrated to elicit some activity against paediatric Burkitt lymphoma [108].

The BIANCA (C2202) Novartis Study is a phase II study of tisagenlecleucel in paediatric patients with relapsed/refractory B-NHL [109]. Apheresis, manufacturing and bridging were found feasible, and primary analysis is planned in late 2021 [41]. Outside the trial, in contrast to BCP-ALL and also adult DLBCL, 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 are the mechanisms of resistance, and how could they be overcome? (ii) what are the best targets, and is dual or triple targeting required to optimise therapeutic responses? (iii) what are the comparative benefits of CAR T-cells versus T-cell engagers and ADCs? and (iv) should subsequent HSCT (essentially autologous in this setting) be utilised to consolidate responses?

There is a major difference between BCP-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 is very small, and it is thus not feasible for all CAR T-cell products, even if they are biologically relevant, to be evaluated. Further development requires the results of ongoing paediatric clinical trials (BIANCA [109], ZUMA-4 [41] and JCAR [110] studies), in addition to early and thoughtful prioritisation which is essential in view of limited patient numbers.

6.2. Hodgkin and anaplastic large cell lymphoma

Both Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL) have outstanding OS rates (>95%), although 5y EFS is approximately 75% in ALCL. Many patients with relapsed disease can be salvaged, with targeted therapies, including anti-CD30 immunotoxins, anti-PD1 checkpoint inhibitors, and ALK inhibitors for ALCL. The early activity of CD30 CAR T-cells has been also reported (60% CR; 1-year PFS 36%) [111]. The optimal approach looking forward is the prioritisation of agents with joint paediatric and adult trials as the disease biology is the same. Consideration should be given to evaluate CD30 CAR T-cells in front-line therapy for Hodgkin and other CD30-expressing lymphomas and combination with immune checkpoint anti-PD1 inhibitors due to >90% overexpression of PDL1 and the potential for synergistic activity.

7. Allogeneic therapies and CAR NK-cells

There is increasing evidence that allogeneic CAR T-cells or CAR NK-cells obtained from healthy donors may have roles in childhood malignancies, but the relative utility of these approaches varies by indication. The use of allogeneic CAR T-cells from unrelated, unmatched donors relies on gene-editing to remove TCR genes along with genes that allow at least temporary protection from rejection by host T cells [112]. The main benefit of allogeneic CAR T-cells is their easy 'off-the-shelf' availability that may also provide a

bridge to other therapies, as their lack of persistence is the main challenge for use as stand-alone agents. Allogeneic CAR T-cells could also overcome challenges in an inability to apheresis and/or manufacture CAR T-cells in patients in whom autologous products are not feasible. Currently, the utility of allogeneic CAR T-cell therapy is relatively less in BCP-ALL, given the success to date of autologous products, but could have an increased role in the treatment of T-ALL, B-NHL, AML and solid tumours.

Cytokine-induced memory-like CAR NK-cells is an alternative approach. CAR NK-cells derive from the innate immune system and recognise targets via CAR with contributions by a complex array of activating and inhibitory receptors [113–116]. There is no relevant risk of graft-versus-host disease given the lack of TCRs on NK cells. Adoptively transferred NK cells have short persistence and cannot establish immune memory, although they have induced potent anti-cancer responses with multi-dose infusions. Investigators at the MD Anderson Cancer Center recently demonstrated that CAR NK-cells derived from cord blood achieved a CR rate of 64% in adults with relapsed/refractory CD-19-positive NHL and chronic lymphocytic leukaemia. In this study, the infused CAR NK-cells expanded and persisted at low levels for at least a year [115]. 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-ALL, lymphomas and solid tumours. Combination approaches with cytokine stimulation or adjunctive therapy to prolong CAR NK-cell survival and persistence *in vivo* are being investigated [115].

8. Products discussed at the Forum

Ten autologous CAR T-cell products, 5 allogeneic CAR T-cell, 1 TCR T-cell, 1 TRuC T-cell and 1 CAR NK-cell product were discussed at the Forum (Table 1). Amongst these, there are currently 5 published paediatric investigation plans (PIPs) agreed with the EMA PDCO for CAR T-cells as of May 2021 (Table 2), all of which target CD19 for BCP-ALL and/or B-NHL.

9. Discussion (Box 1)

9.1. Discussion and conclusions

9.1.1. Patient advocates perspective

Patient advocates believed that the conundrum of how to optimally advance CAR T-cell therapies for paediatric patients with BCP-ALL for relapsed/refractory disease will require additional tightly coordinated regular and ongoing discussion among clinicians. CAR T-cell or other adoptive cell therapeutic options for solid tumours, AML, and T-ALL 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 first-in-child trials when appropriate and enrolling children in adult trials, as well as adaptive designs. Advocates were concerned about potential low enrolment in randomised trials for cell therapies because families may perceive these novel therapies as superior to HSCT or other options. There are concerns that studies may fail to successfully accrue or that evidence will be insufficiently robust as a result, and there are opportunity costs in terms of the time required to

Table 1
Medicinal products discussed at the Paediatric Strategy Forum.

Class of medicinal product	Product	Target	Company
Autologous CAR T-cell	JCAR017/lisocabtagene maraleucel (liso-cel) Breyanzi®	CD19	BMS/Celgene
Autologous CAR T-cell	Tisagenlecleucel, Kymriah®	CD19	Novartis
Allogenic CAR T-cell	CTX110	CD19	CRISPR Therapeutics
Autologous CAR T-cell	KTE-X19	CD19	Kite Pharma/Gilead
Autologous CAR T-cell	AUTO1	CD19	Autolus
Autologous CAR T-cell	AUTO1/22	CD19 & CD22	Autolus
Allogenic CAR T-cell	UCART22	CD22	Cellectis
Autologous CAR T-cell	Syncopation CD22	CD22	Syncopation Life Sciences
TCR-T cell	Letetresgene autoleucel (lete-cel); GSK3377794	NY-ESO-1	GlaxoSmithKline
NK CAR	TAK-007		Takeda
Allogenic CAR T-cell	GC027	CD7	Gracellbio
Allogenic CAR T-cell	UCART 123	CD123	Cellectis
T cell receptor fusion construct (TRuC)	Gavocabtagene autoleucel/gavo-cel (formerly TC-210)	Anti-mesothelin.	TCR^2 Therapeutics
Allogenic CAR T-cell	CTX130	CD70	CRISPR Therapeutics
Autologous CAR T-cell	TT11	CD30	Tessa Therapeutics
Autologous CAR T-cell	MB-CART2019.1	CD19 & CD20	Miltenyi Biomedicine
Autologous CAR T-cell	MB-CART2219.1	CD19 & CD22	Miltenyi Biomedicine
Autologous CAR T-cell	MB-CART19.1	CD19	Miltenyi Biomedicine

Box 1. Text box of key conclusions of the Paediatric Strategy Forum.

- Chimeric antigen receptor (CAR) T-cell therapy has substantial promise for children and adolescents with cancer, but there are biological, clinical and manufacturing challenges, as well as significant challenges to access for many children
- Anti-CD19 CAR T-cells produce high response rates in relapsed/refractory B-cell ALL, although the effect is of limited duration in half of the patients
- Targeting multiple antigens to prevent antigen escape and the use of humanised products to improve persistence could optimise therapy for B-cell ALL
- CAR T-cell treatment could potentially benefit children and adolescents with very high-risk B-cell ALL who ultimately fail conventional therapies
- Identifying patients with B-cell ALL with very early and early relapse or those with the persistent initial disease in whom CAR T-cell therapy can replace haematopoietic stem cell transplantation and those patients in whom it can be a more effective bridge to haematopoietic stem cell transplantation than current options is a very high priority
- Prioritisation is needed to evaluate CAR T-cells in Burkitt lymphoma
- Combination trials of additional or alternative targets (CD20 or CD22) should be considered in Burkitt lymphoma
- Development of CD30 CAR T-cells in Hodgkin lymphoma and ALCL should be by joint paediatric and adult trials
- CAR T-cells are early in development for AML and T-ALL now in phase 1 clinical trial testing
- CD33 and CD123 appear to be good targets in AML and CD7 in T-ALL; other targets are under evaluation
- There are promising early results in solid tumours, particularly with GD2 targeting, and there is substantial potential to address a significant unmet clinical need
- Novel CAR T-cell designs, for example, allow T-cell activation only in the presence or absence of an additional marker, and combinations of targets and (immuno)therapies need to be investigated in solid tumours
- The comparative benefits of autologous versus allogeneic CAR T-cells, T-cell receptor-engineered T-cells, TRuCs, NK cells and CAR NK-cell products, T-cell engager antibodies, and antibody-drug conjugates require evaluation
- Global academic collaboration, very early involvement of regulators in studies seeking registration, early academia-multi company-patient advocacy engagement are critical factors
- The model for drug development for cancer cell therapy in paediatrics could involve a 'later stage handoff' to industry after first clinical evaluation in the academic arena
- To facilitate greater access for children and adolescents with malignancy to CAR T-cell products and allow for the performance of academic multicentre studies establishing a new standard of care, a decentralised model of manufacture potentially has advantages
- Continued development is required for many CAR T-cells after the first approved indication. However, currently, there is neither requirement nor any incentives for a company to continue to support innovation in the same patient population once a PIP or iPSP has been completed, or an approved indication obtained
- Patient advocates urged investigators to agree and drive forward key research questions strategically for BCP-ALL and solid tumours, strongly emphasised the need to broaden access to these novel treatments, and a common data registry to be used by both academia and industry to capture important long-term follow-up information.
- Strategies must evolve to ensure appropriate access (including cross-border access) for children who could potentially benefit from these therapies

undertake them. Patient advocates were also very concerned about the high cost of cell therapy products, associated reimbursement uncertainties, availability and equitable global access. Cost, location 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 pharma companies, funding and health technology assessment (HTA) agencies and advocates. Such partnerships will also be necessary through Paediatric Strategy Forums to help determine which, among a large number of products in development, should be evaluated in rare paediatric cancers. Patient advocates highlighted that, apart from regulatory obligations, long-term toxicities of cell therapies have not been systematically studied [117] and urged industry and academia to establish a registry to document these going forward. They also continued to urge the 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.

9.2. Disease-specific discussion

9.2.1. BCP-ALL

The international academic 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/inotuzumab ozogamicin) and HSCT require elucidation. Identifying those patients in whom CAR T-cell therapy can replace HSCT and those patients in whom it may effectively bridge to HSCT is a **very high priority** and requires a randomised study. The TRANSCEND PEDAL study (lisocabtagene maralucel) [110] and the

Table 2
Published PIPs agreed for CAR T-cells.

Product	Brexucabtagene Autoleucel - *Tecartus* KTE-X19 (Kite-Gilead)	Axicabtagene ciloleucel – YESCARTA (Kite-Gilead)	Tisagenlecleucel (Novartis)	Tisagenlecleucel (Novartis)	JCAR017, lisocabtagene maraleucel (Celgene)
PIP	EMEA-001862-PIP01-15-M02 Decision No P/0142/2020; date 18/04/2020	EMEA-002010-PIP01-16-M02 Decision No P/0132/2020; date 15/04/2020	EMEA-001654-PIP02-17-M01 (Decision No P/0323/2019; date 11/09/2019)	EMEA-001654-PIP01-14-M03 (Decision No P/0008/2019; date 03/01/2019)	EMEA-001995-PIP01-16-M02 (Decision No P/0198/2019; date 12/06/2019)
MoA	CD19	CD19	CD19	CD19	CD19
Condition	Acute lymphoblastic leukaemia	Mature B-cell neoplasms	Treatment of mature B-cell neoplasms	Treatment of B cell ALL/NHL	Treatment of ALL/NHL
PIP Indication	Paediatric patients with r/r B-ALL	Paediatric patients with r/r B-NHL	Treatment of paediatric patients with CD19+ relapsed or refractory NHL	Treatment of CD19+ refractory/relapsed B-ALL in paediatric patients	Treatment of paediatric patients with CD19+ relapsed or refractory B-ALL/DLBCL, BL or PMLBCL
Waiver	Paediatric population weighing less than 6 kg				
Deferral	Yes. For completion by **December 2023.** No published compliance check yet.	Yes. For completion by **December 2023.** No published compliance check yet.	Yes. For completion by March 2022. No published compliance check yet.	Yes. For completion by November 2026. No published compliance check yet.	Yes. For completion by November 2023. No published compliance check yet.
Formulation	Dispersion for infusion; intravenous use.				
Clinical	Safety and activity **r/r B-ALL or B NHL**	Safety and activity **r/r B-ALL or B NHL**	Safety and activity with **CD19+ relapsed or refractory B-NHL**	1. Safety and feasibility **chemotherapy-resistant or refractory CD19+ leukaemia or lymphoma** 2. Safety and activity **refractory/relapsed CD19+ + B-ALL/NHL** 3. Safety and activity **refractory/relapse CD19+ B-ALL** 4. Efficacy and safety in paediatric patients with *de novo* **high-risk 1–18 years of age B-ALL MRD+.**	1. Activity and safety **relapsed or refractory CD19 + B-ALL or B-NHL** 2. Safety, feasibility and efficacy with **relapsed or refractory CD19+ B-ALL**

KTE-X19 study (brexucabtagene autoleucel) [41] are evaluating CD19-targeting CAR T-cells, in paediatric patients with relapsed/refractory BCP-ALL and include patients with first marrow relapse. However, more trials need to be initiated in this setting given demonstrated success in second or greater relapse. The results of the CASSIOPEIA trial for patients who are newly-diagnosed with high-risk persistent MRD [40] may clarify the role of CAR T-cells in this scenario, although it is unclear if these results will alter the standard of care. Although not yet proven, dual targeting CD19 and CD22 is the currently most advanced approach for hypothetical prevention of 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 compared to existing products. Development of CAR T-cells with improved persistence and more favourable immunologic properties (e.g. human or humanised CAR constructs, use of advanced culture conditions and manufacturing technologies enriching for T cells with superior fitness and longevity) 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.

9.2.2. AML and T-ALL

CAR T-cells are early in development for AML and T-ALL. CD33 and CD123 appear to be current optimal targets in AML and CD7 in T-ALL. The results of ongoing or planned first-in-child studies of autologous products are required to facilitate further understanding. Allogeneic CAR T-cells, TCR T-cells, NK and CAR NK-cells, and antibody-based immunotherapies may also be beneficial in these heavily pre-treated populations in which autologous T cell apheresis may be suboptimal and require further study.

9.2.3. Solid Tumours

Promising early results have been reported, particularly with GD2 targeting, and there is substantial potential to address a significant unmet clinical need. It is critical to understand the biology of the solid tumour microenvironment with its barriers against T cells and improve targeting efficacy and selective targeting to rationally evaluate CAR T-cells in solid tumours. Alternatives such as CAR NK-cells and engineered T cells that use the entire TCR must also be considered. Cell therapies may require a combination with other immuno-oncology agents to be active against solid cancers.

9.2.4. Lymphoma: B-NHL

There are many differences between paediatric B-NHL and BCP-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 early experience with CAR T-cells in this situation comprises, mostly, no responses or early relapses. 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. Mechanisms of resistance must be understood to inform further development and combination trials with alternative targets (CD20 or CD22) should also be explored as a priority to improve efficacy in this population.

9.2.5. Hodgkin lymphoma and ALCL

The optimal approach for product development of CD30 CAR T-cells in Hodgkin disease and ALCL is joint paediatric and adult trials. CAR T-cells targeting other antigens may also be relevant for these patients.

9.3. General discussion

9.3.1. Combinatorial regimens

In many paediatric malignancies, a combinatorial approach with cell therapies may be warranted, including multi-antigen targeting. Other combinations may include cell therapies in conjunction with (i) immune checkpoint inhibitors; (ii) anti-tumour vaccines; (iii) cytokine stimulation; (iv) therapies to up-regulate target antigen expression; (v) modulators of the tumour micro-environment; (vi) chemotherapy; (vii) kinase or other small molecule inhibitors to prevent CAR T-cell tonic signalling and subsequent exhaustion; (viii) bispecific, trispecific, quad specific T-cell engager antibodies to extend the target spectrum. Decisions of the appropriate combinations should be based on the biology of the individual cancers, sufficient pre-clinical and clinical data and identification of the contribution of each component based on an appropriate study design.

9.3.2. Access for children to cell therapies

Currently, many children who could potentially benefit from such therapy, either through the approved product or a clinical trial, do not have access to this innovation. Strategies must evolve to ensure appropriate access.

9.3.3. Decentralised academic and non-academic manufacturing

The challenges of access to CAR T-cell products in Europe was highlighted in 2017, when it was apparent that <10% of CAR T-cell clinical trials worldwide were conducted in Europe [8]. To facilitate greater access for children and adolescents with malignancy to CAR T-cell products, a decentralised model of manufacture potentially has advantages, including improved logistics with manufacturing closer to the patient. Semi-automated closed-system manufacturing devices now allow in-

house manufacturing of standardised products by academic institutions upon product-specific licences. Academic manufacturing, with qualification of both at the manufacturing facility and the sites, could provide access to products within investigator-initiated multicentre trials for rare conditions where academia has the scientific lead. Realistic requirements for decentralised manufacturing that is now occurring in terms of quality control assays and release criteria need to be agreed upon by regulators, industry and academia.

9.3.4. CAR T-cell trial design

The regulatory/ethical aspects of executing first-in-human CAR T-cell studies in children and adults need to be considered. The general dogma is that first-in-human dose-finding studies should be carried out in adults first and then in children. However, there is a lack of precedence in study designs that take into account that age is a continuum, and in general, children tolerate T-cell therapies much better than adults and there are, for instance, more BCP-ALL cases in childhood than in adulthood. Therefore, new clinical study designs are needed for early phase clinical studies enrolling both children and adults; data from either group could be used to inform the other, as long as subentities of disease are comparable. 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 CAR T-cell therapy, to date, has largely induced fewer or more manageable toxicities in children than in adults. The use of novel trial designs should be used to reduce the required number of patients and evaluate new cell therapies most efficiently.

Generally, CAR T-cell products being developed for adults are not a route for meaningful paediatric studies. Because of, sometimes, distinct biologies and cells of origin of paediatric and adult malignancies, only a limited overlap exists for cancers and antigens of interest. However, the inclusion of adolescents in adult programs, if scientifically justified, is highly encouraged to improve the efficiency of trial enrolment and maximise access to novel therapies for older paediatric patients.

An additional challenge is ensuring access to clinical trials, especially where the disease is very rare, and there is a very small trial population. Referral of patients, including cross-border referrals, should be strongly encouraged. Patient advocates, academia, and industry should work together to ensure adequate cost coverage in these situations. The model where studies determining the dose and toxicity profile are carried out in a limited number of centres, but then there is a rapid expansion of sites, would allow greater access to children to innovative therapies and is strongly supported.

9.3.5. 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 because in the B-cell directed leukaemia/lymphoma setting, CAR T-cell persistence may be feasible. In the solid tumour setting, persistence has not yet been achieved, and multiple infusions seem likely to be required for a sustained effect. Conceptual advantages of gene-engineered T-cells over engagers or ADCs in solid tumours, such as improved trafficking to metastatic sites of disease and infiltration into tumours, have not yet been demonstrated in clinical therapy. There are ADCs and/or T-cell engaging products for many of the solid tumour antigens also targeted by CAR T-cells, including HER2 and B7-H3/CD276 that are under early clinical evaluation. As shown in acute childhood leukaemias for blinatumomab and inotuzumab and adult solid tumours (trastuzumab deruxtecan for HER2-positive advanced-stage breast cancer [118] and trastuzumab deruxtecan against HER2-positive gastric cancer [119]), response rates for these agents, in general, can be substantial. Decisions on prioritising 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 'off-the-shelf' ADC and T-cell engaging products.

9.3.6. Development plan for cell therapies

Very early planning of the development pathway is critical for optimal efficiency. Regulators should be involved from the inception agreeing with the design of clinical trials of innovative medicines for which regulatory approval may ultimately be sought. Also, early academia-multi-company discussion and potential collaboration may be beneficial. By aligning academic, 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 purposes will be generated. Trial design (randomised versus non-randomised), identification of appropriate 'control' populations (historical versus contemporaneous) and comparisons with the standard of care are critical issues. It is important to define the final target population, for example, very high-risk front-line

disease and design studies that 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 may also help align scientific, regulatory and HTA requirements; however, a focussed and sequential approach must be adopted to ensure an appropriately sized population is available for each trial. The challenge occurs when trials are required to determine the standard of care after registrational studies. Treatment optimisation is essential for paediatric cancers and is long-established, cooperative international clinical studies. An additional challenge is establishing the 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 and the published common commentary document was applauded [120–122]. Harmonisation of different countries within the European Union would be of great benefit to both academia and industry.

9.3.7. Development of cell therapy products by academia

In general, the industry should be encouraged to partner with academia to help support rare disease indications in paediatric oncology. However, there are scenarios when it is anticipated that the industry will not be willing to develop a CAR T-cell or TCR T-cell product, for example, for very small paediatric populations, and where trials are required to determine the 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 and have been 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 the conduction of first studies in the academic arena. This approach could enable more rapid/efficient yet robust testing of the most promising products, targets and combinations. The optimal position is one in which there is a partnership with the industry through innovative collaborative platforms. A flexible model is needed, as 'one size does not fit all'. Co-development and funding are other options. An academic development model for cell therapy products relies on academic manufacturing of uniform products by good manufacturing practice standards upon local licences, along with potential distribution to additional academic trial sites (decentralised academic manufacturing). In this model, the academic manufacturing centre would ensure quality to good manufacturing practice levels and take responsibility for all regulatory related actions. However, this model would require substantial financial investments by the government, foundations and academic medical centres, which have some track record of experience and success and requires further discussions moving forward. It is also critical that access for all children with relevant diseases is available when development is finalised and drugs are validated.

10. Conclusion

The development of CAR T-cell therapy and adoptive cellular therapies is very rapidly progressing and evolving and hold much promise. This is a field where first-in-human CAR T-cell studies have occurred in children in the past and this needs to continue in the future. For the benefit of children and adolescents with cancer, close partnerships between academia and industry are essential. The relative utility of different approaches (autologous and allogeneic CAR T-cell, TCR T-cell, TRuC T-cells, CAR NK-cell ADCs and T-cell engaging products) varies by indication. Therefore, intense discussion between academia and industry, with early regulatory advice, will be required to obtain a consensus. As these are very expensive therapies, aligning strategic, scientific, regulatory and funding requirements from the inception of a clinical trial is of critical importance. It is also imperative that strategies evolve to ensure appropriate ease of access for children who need and could potentially benefit from these therapies.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of, or reflecting the position of, the agencies or organisations with which the authors are affiliated. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services nor does mention of trade names, commercial products, or organisations imply endorsement by the U.S. Government.

Role of funding source

Andrew McDonough B+ Foundation for financial support of ACCELERATE.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ABassan is an employee of Syncopation Life Sciences. EB is an employee of

Novartis. CB is an employee of Cellectis. SBC is an employee of CRISPR Therapeutics and has stock ownership in CRISPR. DSH has participated in advisory boards for AstraZeneca and Bayer and has received institutional funding from Incyte, Pfizer, Bristol Myers Squibb, Merck Sharpe Dohme, Lilly. LH is an employee of Miltenyi Biomedicine. IDH is an employee of Tessa Therapeutics. BKM is an employee of Kite, a Gilead company. YM is an employee of Takeda Pharmaceuticals International. SM has participated in advisory boards for Novartis and Wugen and received clinical trial support from Novartis. LP is an employee of GlaxoSmithKline. ADJP has participated in advisory boards for Novartis, Takeda, Merck, Lilly and Celgene and consulted for Lilly and Developmental Therapeutics Consortium Limited MP is an employee of Autolus Limited. AQ-C is an employee of TCR2 Therapeutics. RR is an employee of Celgene/Bristol Myers Squibb. CR has participated in advisory boards for Amgen, BMS, Celgene, Novartis and Pfizer. MAS is an employee and stock ownership of Gracellbiotechnologies Inc. SKT receives research funding from Incyte Corporation and Beam Therapeutics and as participated in advisory boards of Aleta Biotherapeutics and Kura Oncology. MCZ has been a constant for Incyte, Sanofi, BMS, Novartis, Pfizer, Jazz, Abbvie, Roche and Takeda; has received institutional funding from Jazz, Pfizer, Takeda, Abbvie and funding for travel from Jazz. All remaining authors have declared no conflicts of interest.

Acknowledgements

The authors very gratefully acknowledge Andrea Demadonna for his dedication, efficiency, enthusiasm and very substantial work in preparation of the Forum, Michael Vranken and Samira Essiaf for their pivotal roles in organising the Forum, and Gynette Cook for preparation of the manuscript.

Appendix

Participants

Silvijus Abramavičius	Lithuanian University of Health Sciences, Lithuanian
Peter Adamson	Sanofi, USA
Laurence Adegeest	Bristol Myers Squibb Company/ Celgene, a BMS Company, USA
Srini Akkaraju	Syncopation Life Sciences, USA
Persis Amrolia	Great Ormond St Children's Hospital, London, UK
Oezlem Anak	Novartis
Dimitrios Athanasiou	World Duchenne Organisation/ UPPMD and European Patients Forum/EPF
Andishe Attarbaschi	St. Anna Children's Hospital & CCRI
Boryana Avramova	University Hospital "Tzaritza Joanna" - Sofia, Department of Pediatric Hematology and Oncology
Kristin Baird	US Food and Drug Administration,
Claudia Baldazzi	GlaxoSmithKline,
Sinan Bardakci	Chair of Oncology Working Party
Immanuel Barth	Paul Ehrlich Institut, Germany
Andre Baruchel	Hôpital Universitaire Robert Debré (APHP) and Université de Paris
Abraham Bassan	Syncopation Life Sciences
Caroline M Batemen	Sydney Children's Hospitals Network, The Children's Hospital at Westmead
Carly Bergstein	The Andrew McDonough B + Foundation
Michael Berntgen	Human Medicines Division, European Medicines Agency (EMA), Amsterdam, Netherlands
Michael Bethune	Syncopation Life Sciences
Ettore Biagi	Bristol Myers Squibb Company/ Celgene, a BMS Company
Andrea Biondi	Dept. of Pediatrics Univ. Milano-Bicocca, Found. MBBM/Hosp. S.Gerardo
Nick Bird	Solving Kids' Cancer, UK
Eric Bleickardt	Novartis
Estera Boeriu	Universitar of Medicine and Pfarmacy VBabes Timisoara
Najat Bouchkouj	US Food and Drug Administration
Peter Bross	US Food and Drug Administration
Patrick Brown	Johns Hopkins University
Carrie Brownstein	Cellectis
Jochen Buechner	Oslo University Hospital, Department of Pediatric Hematology and Oncology, Oslo, Norway
Michael Burgess	Bristol Myers Squibb Company/ Celgene, a BMS Company
Amos Burke	Cambridge University Hospitals NHS Foundation Trust
Andrea Buzzi	Human Medicines Division, European Medicines Agency (EMA), Amsterdam, Netherlands
Friso Calkoen	Princess Maxima Center for Paediatric Oncology
Danielle Carreon	Bristol Myers Squibb Company/ Celgene, a BMS Company
Monica Cellini	Oncoematologia Pediatrica Azienda ospedaliero universitaria modena
Valeria Ceolin	Princess Maxima Center for Pediatric Oncology
Antony Ceraulo	Institute of Pediatric Hematology and Oncology, Lyon, Fr
Mwe Mwe Chao	CRISPR Therapeutics
Jonelle Champan	Autolus Limited
Susan Chi	Dana-Farber Cancer Institute
Andre Choulika	Cellectis

(*continued*)

	Group (ANZCHOG)
Stephen Gottschalk	St Jude Children's Research Hospital
Tomasz Grybek	Foundation of Borys the Hero, Poland, PDCO member
Dalia Hammouche	Birmingham Children's Hospital
Linda Hanssens	Miltenyi Biomedicine
Doug Hawkins	Seattle Children's Hospital
Niklas Hedberg	TLV (Health Technology Assessment Agency)
Delphine Heenen	KickCancer
Blanca Herrero	Hospital Infantil Universitario Del Niño Jesŭs Madrid Spain
Ana Hidalgo-Simon	Human Medicines Division, European Medicines Agency (EMA), Amsterdam, Netherlands
Larissa Higgins	Member of SAWP/HPRA
Lars Hjorth	Skåne University Hospital
Ivan David Horak	Tessa Therapeutics, Singapore
Danielle Horton Taylor	PORT (Paediatric Oncology Reference Team)
Marianne Ifversen	Copenhagen University Hospital
Miron Ingrith	Crengta Pediatric Hematology and Oncology Unit, Emergency Children's Hospital.
Antonella Isgrò	AIFA
Sae Ishimaru	National Cancer Center
Shai Izraeli	Schneider Children's Medical Center of Israel
Adnan Jaigirdar	US Food and Drug Administration
Yuxia Jia	US Food and Drug Administration
Abigail Johnson	US Food and Drug Administration
Courtney Johnson	US Food and Drug Administration
Edita Kabickova	University Hospital Motol and Charles University Prague, Czech Republic
Dominik Karres	Paediatric Medicines Office, Scientific Evidence Generation Department, Human Medicines Division, European Medicines Agency (EMA), Amsterdam, Netherlands
Rejin Kebudi	Istanbul University, Oncology Institute
Mark Kieran	Bristol Myers Squibb Company/ Celgene, a BMS Company
Lin Khaw	Royal Children's Hospital
Olga Kholmanskikh	Federal Agency for Medicines and Health Products (BE)
Rune Kjeken	Member of SAWP
E. Anders Kolb	Nemours/Alfred I duPont Hospital for Children
Alexandra Kolenova	National Institute of Children's Diseases
Miriam Kremser	Miltenyi Biomedicine
Koerg Krueger	Sickkids, Toronto, Canada
Theodore Laetsch	UT Southwestern Medical Center
Pablo Landgraf	University Hospital of Cologne
Cecilia Langenskiöld	Children's cancer ward, Drottning Silvias Barnsjukhus, Gothenburg
Rita Lankester	European Medicines Agency (EMA), Amsterdam, Netherlands

(*continued*)

Sarah Cohen	CRISPR Therapeutics
Valentina Conti	AIFA
Vítor Costa	Instituto Português de Oncologia FG Porto
Francis Crawley	Good Clinical Practice Alliance –Europe (GCPA) & Strategic Initiative for Developing Capacity in Ethical Review (SIDCER Monika Csóka)Semmelweis University, 2nd Department of Pediatrics
Alysha Croker	Health Canada
Asha Das	US Food and Drug Administration
Sara Davis	CRISPR Therapeutics
Zoe Davison	Bone Cancer Research Trust
Boris Decarolis	University Hospital of Cologne, Pediatric Oncology
Andrea Demadonna	ACCELERATE
Victoria Demby	GlaxoSmithKline
Teresa de Rojas	ACCELERATE
Barbara De Moerloose	Ghent University Hospital
Cristina Diaz-de-Heredia	Hospital Universitari Vall d'Hebron, Barcelona, Spain
Elizabeth de Somer	Medicines Australia
Martha Donoghue	US Food and Drug Administration
Peter Downie	Monash Children's Hospital; Monash Health
Ximo Duarte	Instituto Português de Oncologia de Lisboa, Portugal
Lori Ehrlich	US Food and Drug Administration
Samira Essiaf	ACCELERATE
María Estela Moreno Martín	Spanish Agency of Medicines and Medical Devices (AEMPS)
Matthias Eyrich	University Children's Hospital Würzburg
Patrick Fandja	Health Canada
Fei Fei	FAGG
Elizabeth Fox	St. Jude
Stanley Frankel	Autolus Limited
Mark Frattini	Cellectis
Lisa Freeman	CRISPR Therapeutics
Miriam Fuchs	Novartis
Caroline Furness	The Royal Marsden Hospital, London, UK
José L Fuster	Hospital Clínico Universitario Virgen de la Arrixaca
Sara Galluzzo	PDCO and SAWP Member
Miklos Garami	Semmelweis University, Budapest, Hungary
Rebecca Gardner	Seattle Children's Hospital
Carmen Garrido	Gregorio Marañőn
Sara Ghorashian	UCL Great Ormond Street Institute of Child Health
Rocio Gonzalo Ruiz	Human Medicines Division, European Medicines Agency (EMA), Amsterdam, Netherlands
Nancy Goodman	Kids v Cancer, USA
Nick Gottardo	Princess Margaret Hospital for Children and Telethon Kids Institute, Perth, Australia, Australian and New Zealand Children's Haematology/Oncology

(*continued on next page*)

(*continued*)

David Lee	HealthCanada
Amaury Leruste	Institut Curie, Paris
Giovanni Lesa	Paediatric Medicines Office, Scientific Evidence Generation Department, Human Medicines Division, European Medicines Agency (EMA), Amsterdam, Netherlands
John Lewandowski	Bristol Myers Squibb Company/ Celgene, a BMS Company
Franca Ligas	Paediatric Medicines Office, Scientific Evidence Generation Department, Human Medicines Division, European Medicines Agency (EMA), Amsterdam, Netherlands
Effie Liu	Gracell
Franco Locatelli	Sapienza, University of Rome, Bambino Gesù Children's Hospital
Thalia Loka	Agia Sophia Children's Hospital
Chrystal Louis	CRISPR Therapeutics
Donna Ludwinski	Solving Kids' Cancer, USA
Crystal Mackall	Stanford
Lauren MacMullen	TCR^2 Therapeutics
Maksim Mamonkin	Baylor College of Medicine
Helen Mao	Health Canada
Anacarmina Mariategue	Syncopation Life Sciences
Dana Marin	National Agency for Medicines and Medical Devices, Bucharest, Romania
Lynley Marshall	The Royal Marsden Hospital and The Institute of Cancer Research, London, UK
Lydia Martynec	US Food and Drug Administration
Aisha Masood	Novartis
Behzad Kharabi Masouleh	Kite, a Gilead company
Yousif Matloub	Takeda Pharmaceuticals
Shannon Maude	Children's Hospital of Philadelphia
Geoff McCowage	Westmead at Sydney Children's Hospitals Network, Australia
Joe McDonough	The Andrew McDonough B + Foundation
Margret Merino	US Food and Drug Administration
Anne Miermont	AFMPS
Veronique Minard-Colin	Department of Pediatric and Adolescent Oncology, INSERM U1015, Gustave Roussy, Université Paris-Saclay, Villejuif, France
Francis Mussai	University of Birmingham
Viera Muzithras	TCR^2 Therapeutics
Swati Naik	St Jude Children's Research Hospital
Koen Norga	Antwerp University Hospital, PDCO member
Karsten Nysom	Righospitalet
Odoardo Olimpieri	AIFA
Antonia Palmer	Ac2orn
Vassilios Papadakis	Dept of Ped Hem – Onc, Agia Sofia Children's Hospital
Michael Papadimitrious	Miltenyi Biomedicine
Alberto Pappo	St Jude
Simona Paratore	Novartis
Julie R Park	Seattle Children's Hospital

(*continued*)

Alpesh Patel	Cellectis
Meera Patturajan	Bristol Myers Squibb Company/ Celgene, a BMS Company
Laura Pearce	GlaxoSmithKline
Andy Pearson	ACCELERATE
Rob Pieters	Princess Maxima Center for Pediatric Oncology
Martina Pigazzi	University of Padova, Oncohematology Clinic and Lab
Laurent Poirot	Cellectis
Apostolos Pourtsidis	Pediatric and Adolescent Oncology Clinic Children's Hospital MITERA
Martin Pule	Autolus Limited
Alfonso Quintás-Cardama	TCR^2 Therapeutics
Eduardo Quiroga	Hospital infantil virgen del rocio
Manuel Ramírez	Hospital Infantil Universitario Niño Jesús
Shiva Ramroop	Medicines and Healthcare Products Regulatory Agency;
Gregory Reaman	US Food and Drug Administration
Marleen Renard	University Hopsital Leuven, PDCO member
Stephan Reynier	Cellectis
Rosanna Ricafort	Bristol Myers Squibb Company/ Celgene, a BMS Company
Nick Richardson	US Food and Drug Administration
Susana Rives	Hospital Sant Joan de Déu de Barcelona
Carmelo Rizzari	Pediatric Hem Onc Unit, University of Milano Bicocca, Monza, Italy
Kelly Robinson	HealthCanada
Kaye Robertson	Therapeutic Goods Administration, Australia
Jelena Roganovic	Clinical Hospital Centre Rijeka
Claudia Rossig	University Children's Hospital Muenster
Michael Rosu-Myles	Health Canada
Anja Schiel	Chair of Scientific Advice Working Party (SAWP)
Kjeld Schmiegelow	Rigshospitalet, Copenhagen University Hospital
Martina Schüßler-Lenz	Chair of CAT (Committee for Advanced Therapies), Paul-Ehrlich-Institute, Germany
Lenneke Schrier	Princess Maxima Center for Paediatric Cancer
Petra Schuberth	Gilead
Nicole Scobie	Zoe4Life
Bradley Scott	Health Canada
Heidi Segers	University Hospital Leuven
Senada Serifi	Clinical Hospital Center Rijeka
Martina Sersch	Gracell
Nirali Shah	National Cancer Institute
Deepak Sharma	Health Canada
Angeliki Siapkara	Medicines and Healthcare Products Regulatory Agency
Peter Šišovský	State Institute for Drug Control, Slovakia, PDCO member
Jodi Skiles	Riley Hospital for Children at IU Health
Malcolm Smith	National Cancer Institute
Karin Straathof	University College London Great

(*continued*)

	Ormond Street Institute of Child Health
Kerstin Sollerbrant	The Swedish Childhood Cancer Fund
Arend Stackelberg	Ped Oncology/Hematology, Charité Berlin
Eileen Stark	Cellectis
Jaroslav Sterba	University Hospital Brno, Masaryk University, Brno Czech Republic, PDCO Member
Alexandra Stoicescu	Regional Oncology Institute Lasi
Tim Stonehouse	Autolus Limited
Violeta Stoyanova-Beninska	Medicines Evaluation Board, Netherlands, Chair of Committee of Orphan Medicines (COMP), EMA
Robyn Strong	Australian and New Zealand Children's Haematology/Oncology Group (ANZCHOG)
Tomasz Szczepanski	Medical Univeristy of Silesia
Aimee Talleur	St Jude Children's Research Hospital
Sarah Tasian	Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine
Denise Thomas	Cellectis
Markus Vallaster	Takeda Pharmaceuticals
Maaike van Dartel	Medicines Evaluation Board, Netherlands, PDCO Member
Gilles Vassal	ACCELERATE
Pablo Velasco	Hospital Universitario Vall D'Hebron
Paulina Velasquez	St. Jude Children's Research Hospital
Jaime Verdu	Hospital Clinico Universitario Valencia
Arend von Stackelberg	Charité University Medicine Berlin
Ajay Vora	Great Ormond Street Hospital
Josef Vormoor	Princess Maxima Center for Pediatric Oncology
Adam Z. Walker	GlaxoSmithKline
Siri Wang	Norwegian Medicines Agency, PDCO Member
Xinxin Wang	Gracell
Brenda Weigel	University of Minnesota
Susan L. Weiner	Children's Cancer Cause
Peter Wejbora	Children's Cancer Institute, Australia
Dovilė Zacharkienė	State Medicines Control Agency under ministry of Health of the Republic of Lithuania
Kevin Zikaras	TCR^2 Therapeutics
Megan Zimmerman	US Food and Drug Administration
Michel Zwaan	Princess Maxima Center for Pediatric Oncology

References

[1] Pearson ADJ, Scobie N, Norga K, Ligas F, Chiodin D, Burke A, et al. ACCELERATE and European Medicine Agency Paediatric Strategy Forum for medicinal product development for mature B-cell malignancies in children. Eur J Cancer 2019;110:74–85.

[2] Pearson ADJ, Rossig C, Lesa G, Diede SJ, Weiner S, Anderson J, et al. ACCELERATE and European medicines agency paediatric strategy Forum for medicinal product development of checkpoint inhibitors for use in combination therapy in paediatric patients. Eur J Cancer 2020;127:52–66.

[3] Pearson ADJ, Kolb EA, Zwaan CM, Karres D, Guillot J, Kim SY, et al. Paediatric strategy Forum for medicinal product development for acute myeloid leukaemia in children and adolescents. Eur J Cancer 2020;136:116–29.

[4] Pearson AD, Stegmaier K, Bourdeaut F, Reaman G, Heenen D, Meyers ML, et al. Paediatric Strategy Forum for medicinal product development of epigenetic modifiers for children: ACCELERATE in collaboration with the European Medicines Agency with participation of the Food and Drug Administration. Eur J Cancer 2020;139:135–48.

[5] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/06/WC500228940.pdf (Accessed 26 September 2021).

[6] Gross G, Waks T, Eshhar Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. Proc Natl Acad Sci U S A 1989;86:10024–8.

[7] Blanc V, Bousseau A, CaronA, Carrez C, Lutz RJ, Lambert JM. SAR3419: an anti-CD19-Maytansinoid Immunoconjugate for the treatment of B-cell malignancies. Clin Cancer Res 2011;17:6448–58.

[8] Hartmann J, Schüßler-Lenz M, Bondanza A, Buchholz CJ. Clinical development of CAR T cells-challenges and opportunities in translating innovative treatment concepts. Rev EMBO Mol Med 2017;9:1183–97.

[9] Majzner RG, Mackall CL. Clinical lessons learned from the first leg of the CAR T cell journey. Nat Med 2019;25:1341–55.

[10] Hou AJ, Chen LC, Chen YC. Navigating CAR-T cells through the solid-tumour microenvironment. Nat Rev Drug Discov 2021;20:531–50.

[11] Schultz L, Mackall C. Driving CAR T cell translation forward. Sci Transl Med 2019;11. eaaw2127 https://doi.org/10.1126/scitranslmed.aaw2127.

[12] Brown PA, Ji L, Xu X, Devidas M, Hogan LE, Borowitz MJ, et al. Effect of postreinduction therapy consolidation with blinatumomab vs chemotherapy on disease-free survival in children, adolescents, and young adults with first relapse of B-cell acute lymphoblastic leukemia: a randomized clinical trial. J Am Med Assoc 2021;325:833–42.

[13] Locatelli F, Zugmaier G, Rizzari C, Morris JD, Gruhn B, Klingebiel T, et al. Effect of blinatumomab vs chemotherapy on event-free survival among children with high-risk first-relapse B-cell acute lymphoblastic leukemia: a randomized clinical trial. J Am Med Assoc 2021;325:843–54.

[14] Dixon SB, Chen Y, Yasui Y, Pui CH, Hunger SP, Silverman LB, et al. Reduced morbidity and mortality in survivors of childhood acute lymphoblastic leukemia: a report from the childhood cancer survivor study. J Clin Oncol 2020;38:3418–29.

[15] Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378:439–48.

[16] Grupp SA, Maude SL, Rives S, Baruchel A, Boyer MW, Bittencourt H, et al. Updated analysis of the efficacy and safety of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory (r/r) acute lymphoblastic leukemia. Blood 2018;132(Supplement 1):895.

[17] Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507–17.

[18] Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, DelbrookC, Feldman SA, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015;385:517–28.

[19] Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood 2017;129:3322–31.
[20] Ghorashian S, Kramer AM, Onuoha S, Wright G, Bartram J, Richardson R, et al. Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. Nat Med 2019;25:1408–14.
[21] Hay KA, Gauthier J, Hirayama AV, Voutsinas JM, Wu Q, Li D, et al. Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy. Blood 2019;133:1652–63.
[22] Pasquini MC, Hu Z-H, Curran K, Laetsch T, Locke F, Rouce R, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. Blood Adv 2020;4:5414–24.
[23] Sotillo E, Barrett DM, Black KL, Bagashev A, Oldridge D, WuG, et al. Convergence of acquired mutations and alternative splicing of CD19 enables resistance to CART-19 immunotherapy. Cancer Discov 2015;5:1282–95.
[24] Finney OC, Brakke HM, Rawlings-Rhea S, Hicks R, Doolittle D, Lopez M, et al. CD19 CAR T cell product and disease attributes predict leukemia remission durability. J Clin Invest 2019;129:2123–32.
[25] Myers RM, Li Y, Leahy AB, Barrett DM, Teachey DT, Callahan C, et al. Humanized CD19-targeted chimeric antigen receptor (CAR) T cells in CAR-naive and CAR-exposed children and young adults with relapsed or refractory acute lymphoblastic leukemia. J Clin Oncol 2021;39:3044–55.
[26] Pillai V, Muralidharan K, Meng W, Bagashev A, Oldridge DA, Rosenthal JN, et al. CAR T-cell therapy is effective for CD19-dim B-lymphoblastic leukemia but is impacted by prior blinatumomab therapy. Blood Adv 2019;3:3539–49.
[27] Taraseviciute A, Steinberg SM, Myers RM, Gore L, Lamble AJ, Brown PA, et al. Pre-CAR blinatumomab is associated with increased post-CD19 CAR relapse and decreased event free survival. Blood 2020;136(Supplement 1):13–4.
[28] Dourthe M-E, Rabian F, Yakouben K, Chevillon F, Cabannes-Hamy A, Méchinaud F, et al. Determinants of CD19-positive vs CD19-negative relapse after tisagenlecleucel for B-cell acute lymphoblastic leukemia. Leukemia 2021 May 17. https://doi.org/10.1038/s41375-021-01281-7.
[29] Kadauke S, Myers RM, Li Y, Aplenc R, Baniewicz D, Barrett DM, et al. Risk-adapted preemptive tocilizumab to prevent severe cytokine release syndrome after CTL019 for pediatric B-cell acute lymphoblastic leukemia: a prospective clinical trial. J Clin Oncol 2021;39:920–30.
[30] Qin H, Ramakrishna S, Nguyen S, Fountaine TJ, Ponduri A, Stetler-Stevenson M, et al. Preclinical development of bivalent chimeric antigen receptors targeting both CD19 and CD22. Mol Ther Oncolytics 2018;11:127–37.
[31] Shah NN, Johnson BD, Schneider D, Zhu F, Szabo A, Keever-Taylor CA, et al. Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial. Nat Med 2020;26:1569–75.
[32] Tasian SK, Pollard JA, Aplenc R. Molecular therapeutic approaches for pediatric acute myeloid leukemia. Front Oncol 2014;4:55. https://doi.org/10.3389/fonc.2014.00055.
[33] Qin H, Cho M, Haso W, Zhang L, Tasian SK, Oo H, et al. Eradication of B-ALL using chimeric antigen receptor-expressing T cells targeting the TSLPR oncoproteins. Blood 2015;126:629–39.
[34] Fry TJ, Shah NN, Orentas RJ, Stetler-Stevenson M, Yuan CM, Ramakrishna S, et al. CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. Nat Med 2018;24:20–8.
[35] Shah NN, Highfill SL, Shalabi H, Yates B, Jin J, Wolters PL, et al. CD4/CD8 T-Cell selection affects chimeric antigen receptor (CAR) T-cell potency and toxicity: updated results from a phase I anti-CD22 CAR T-cell trial. J Clin Oncol 2020;38:1938–50.
[36] Pan J, Niu Q, Deng B, Liu S, Wu T, Gao Z, et al. CD22 CAR T-cell therapy in refractory or relapsed B acute lymphoblastic leukemia. Leukemia 2019;33:2854–66.
[37] Haso W, Lee DW, Shah NN, Stetler-Stevenson M, Yuan CM, Pastan IH, et al. Anti -CD22-chimeric antigen receptors targeting B-cell precursor acute lymphoblastic leukemia. Blood 2013;121:1165–74.
[38] Fousek K, Watanabe J, Joseph SK, George A, An X, Byrd TT, et al. CAR T-cells that target acute B-lineage leukemia irrespective of CD19 expression. Leukemia 2021;35:75–89.
[39] Borowitz MJ, Wood BL, Devidas M, Loh ML, Raetz EA, Salzer WL, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. Blood 2015;126:964–71.
[40] Study of efficacy and safety of tisagenlecleucel in HR B-all EOC MRD positive patients (CASSIOPEIA). https://clinicaltrials.gov/ct2/show/NCT03876769 (Accessed 26 September 2021).
[41] Study evaluating brexucabtagene autoleucel (KTE-X19) in pediatric and adolescent participants with relapsed/refractory B-precursor acute lymphoblastic leukemia or relapsed/refractory B-cell non-hodgkin lymphoma (ZUMA-4). https://clinicaltrials.gov/ct2/show/NCT02625480 (Accessed 26 September 2021).
[42] Rasche M, Zimmermann M, Borschel L, Bourquin J-P, Dworzak M, Klingebiel T, et al. Successes and challenges in the treatment of pediatric acute myeloid leukemia: a retrospective analysis of the AML-BFM trials from 1987 to 2012. Leukemia 2018;32:2167–77.
[43] de Rooij JE, Zwaan CM, van den Heuvel-Eibrink M. Pediatric AML: from biology to clinical management. J Clin Med 2015;4:127–49.
[44] Perna F, Berman SH, Soni RK, Mansilla-SotoJ, Eyquem J, Hamieh M, et al. Integrating proteomics and transcriptomics for systematic combinatorial chimeric antigen receptor therapy of AML. Cancer Cell 2017;32:506–19.
[45] Tasian SK, Bornhäuser M, Rutella S. Targeting leukemia stem cells in the Bone marrow niche. Biomedicines 2018;6:22. https://doi.org/10.3390/biomedicines6010022.
[46] Testa U, Pelosi E, Frankel A. CD 123 is a membrane biomarker and a therapeutic target in hematologic malignancies. Biomark Res 2014;2:4. https://doi.org/10.1186/2050-7771-2-4.
[47] Mardiros A, Santos CD, McDonald T, Brown CE, Wang X, Budde LE, et al. T cells expressing CD123-specific chimeric antigen receptors exhibit specific cytolytic effector functions and antitumor effects against human acute myeloid leukemia. Blood 2013;122:3138–48.
[48] Gill S, Tasian SK, Ruella M, Shestova O, Li Y, Porter DL, et al. Preclinical targeting of human acute myeloid leukemia and myeloablation using chimeric antigen receptor-modified T cells. Blood 2014;123:2343.
[49] Bonifant CL, Szoor A, Torres D, Joseph N, Velasquez MP, Iwahori K, et al. CD123-Engager T cells as a novel immunotherapeutic for acute myeloid leukemia. Mol Ther 2016;24:1615–26.
[50] Bras AE, de Haas V, van Stigt A, Jongen-Lavrencic M, Beverloo HB, Marvelde JG, et al. CD123 expression levels in 846 acute leukemia patients based on standardized immunophenotyping. Cytometry B Clin Cytom 2019;96:134–42.
[51] Tasian SK, Kenderian SS, Shen F, Ruella M, Shestova O, Kozlowski M, et al. Optimized depletion of chimeric antigen receptor T cells in murine xenograft models of human acute myeloid leukemia. Blood 2017;129:2395–407.
[52] Riberdy JM, Zhou S, Zheng F, KimY -I, Moore J, Vaidya A, et al. The art and science of selecting a CD123-specific chimeric antigen receptor for clinical testing. Mol Ther Methods Clin Dev 2020;18:571–81.

[53] Baroni ML, Sanchez Martinez D, Gutierrez Aguera F, Roca Ho H, Castella M, Zanetti SR, et al. 41BB-based and CD28-based CD123-redirected T-cells ablate human normal hematopoiesis in vivo. J Immunother Cancer 2020;8:e000845. https://doi.org/10.1136/jitc-2020-000845.
[54] Qin H, Yang L, Chukinas JA, Shah N, Tarun S, Pouzolles M, et al. Systematic preclinical evaluation of CD33-directed chimeric antigen receptor T cell immunotherapy for acute myeloid leukemia defines optimized construct design. J Immunother Cancer 2021;9:e003149.
[55] Gamis AS, Alonzo TA, Meshinchi S, Sung L, Gerbing RB, Raimondi SC, et al. Gemtuzumab ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Children's Oncology Group trial AAML0531. J Clin Oncol 2014;32:3021–32.
[56] Pollard JA, Alonzo TA, Loken M, Gerbing RB, Ho PA, Bernstein ID, et al. Correlation of CD33 expression level with disease characteristics and response to gemtuzumab ozogamicin containing chemotherapy in childhood AML. Blood 2012;119:3705–11.
[57] Pollard JA, Loken M, Gerbing RB, Raimondi SC, Hirsch BA, Aplenc R, et al. CD33 expression and its association with gemtuzumab ozogamicin response: results from the randomized phase III Children's oncology group trial AAML0531. J Clin Oncol 2016;34:747–55.
[58] Lamba JK, Chauhan L, Shin M, Loken MR, Pollard JA, Wang Y, et al. CD33 splicing polymorphism determines gemtuzumab ozogamicin response in de novo acute myeloid leukemia: report from randomized phase III Children's oncology group trial AAML0531. J Clin Oncol 2017;35:2674–82.
[59] Study of anti-CD33 chimeric antigen receptor-expressing T cells (CD33CART) in children and young adults with relapsed/refractory acute myeloid leukemia. https://clinicaltrials.gov/ct2/show/NCT03971799 (Accessed 26 September 2021).
[60] CD123-Directed autologous T-cell therapy for acute myelogenous leukemia (CATCHAML). https://clinicaltrials.gov/ct2/show/NCT04318678 (Accessed 26 September 2021).
[61] CD123 redirected T cells for AML in pediatric subjects. https://clinicaltrials.gov/ct2/show/NCT04678336 (Accessed 26 September 2021).
[62] Kaeding A, Tarlock K, Kolb EA, Meshinchi S. Immunotherapeutic targeting of mesothelin in acute myeloid leukemia in vitro with anetumab ravtansine and a novel antibody-drug conjugate. Blood 2018;132(Supplement 1):1448.
[63] Smith JL, Ries RE, Santaguida MT, Gekas C, Alonzo TA, Gerbing RB, et al. Comprehensive transcriptome profiling of cryptic CBFA2T3-GLIS2 fusion-positive AML defines novel therapeutic options — a COG and target pediatric AML study. Blood 2018;132(Supplement 1):881.
[64] Study of CAR T-cell therapy in acute myeloid leukemia and multiple myeloma https://clinicaltrials.gov/ct2/show/NCT04097301 (Accessed 26 September 2021).
[65] Chimeric antigen receptor T-cells for the treatment of AML expressing CLL-1 antigen https://clinicaltrials.gov/ct2/show/NCT04219163 (Accessed 26 September 2021).
[66] Scherer LD, Brenner MK, Mamonkin M. Chimeric antigen receptors for T-cell malignancies. Front Oncol 2019;9:126. https://doi.org/10.3389/fonc.2019.00126.
[67] Mamonkin M, Rouce RH, Tashiro H, Brenner MK. A T-cell-directed chimeric antigen receptor for the selective treatment of T-cell malignancies. Blood 2015;126:983–92.
[68] Gomes-Silva D, Srinivasan M, Sharma S, Lee CM, Wagner DL, Davis TH, et al. CD7-edited T cells expressing a CD7-specific CAR for the therapy of T-cell malignancies. Blood 2017;130:285–96.
[69] Png YT, Vinanica N, Kamiya T, Shimasaki N, Coustan-Smith E, Campana D. Blockade of CD7 expression in T cells for effective chimeric antigen receptor targeting of T-cell malignancies. Blood Adv 2017;1:2348–60.
[70] Cooper ML, Choi J, Staser K, Ritchey JK, Devenport JM, Eckardt K, et al. An "off-the-shelf" fratricide-resistant CAR-T for the treatment of T cell hematologic malignancies. Leukemia 2018;32:1970–83.
[71] CD7 CAR-T cells for patients with R/R CD7+ NK/T cell Lymphoma,T-lymphoblastic lymphoma and acute lymphocytic leukemia. https://clinicaltrials.gov/ct2/showNCT04004637.
[72] Anti-CD7 U-CAR-T cell therapy for T/NK cell hematologic malignancies. https://clinicaltrials.gov/ct2/showNCT04264078 (Accessed 26 September 2021).
[73] CD7 CAR-T cells for patients with R/R CD7+ NK/T cell Lymphoma,T-lymphoblastic lymphoma and acute lymphocytic leukemia. https://clinicaltrials.gov/ct2/showNCT04004637 (Accessed 26 September 2021).
[74] Pan J, Tan Y, Wang G, Deng B, Ling Z, Song W, et al. Donor-derived CD7 chimeric antigen receptor T cells for T-cell acute lymphoblastic leukemia: first-in-human, phase I trial. J Clin Oncol 2021:JCO2100389. https://doi.org/10.1200/JCO.21.00389.
[75] Li S, Wang X, Yuan Z, Liu L, Luo L, Li Y, et al. Eradication of T-ALL cells by CD7-targeted universal CAR-T cells and initial test of ruxolitinib-based CRS management. Clin Cancer Res 2021;27:1242–6.
[76] Rossig C, Bollard CM, Nuchtern JG, Merchant DA, Brenner MK. Targeting of G(D2)-positive tumor cells by human T lymphocytes engineered to express chimeric T-cell receptor genes. Int J Cancer 2001;94:228–36.
[77] Pule MA, Savoldo B, Myers GD, Rossig C, Russell HV, Dotti G, et al. Virus-specific T cells engineered to coexpress tumor-specific receptors: persistence and antitumor activity in individuals with neuroblastoma. Nat Med 2008;14:1264–70.
[78] Straathof K, Flutter B, Wallace R, Jain N, Loka T, Depani S, et al. Antitumor activity without on-target off-tumor toxicity of GD2-chimeric antigen receptor T cells in patients with neuroblastoma. Sci Transl Med 2020;12:eabd6169. https://doi.org/10.1126/scitranslmed.abd6169.
[79] Long AH, Haso WM, Shern JF, Wanhainen KM, Murgai M, Ingaramo M, et al. 4-1BB costimulation ameliorates T cell exhaustion induced by tonic signaling of chimeric antigen receptors. Nat Med 2015;21:581–90.
[80] Quintarelli C, Orlando D, Boffa I, Guercio M, Polito VA, Petretto A, et al. Choice of costimulatory domains and of cytokines determines CAR T-cell activity in neuroblastoma. OncoImmunology 2018;7:e1433518. https://doi.org/10.1080/2162402X.2018.1433518.
[81] Anti-GD2 CAR T cells in pediatric patients affected by high risk and/or relapsed/refractory neuroblastoma or other GD2-positive solid tumors. https://clinicaltrials.gov/ct2/show/NCT03373097 (Accessed 26 September 2021).
[82] Mount CW, Majzner RG, Sundaresh S, Arnold EP, Kadapakkam M, Haile S, et al. Potent antitumor efficacy of anti-GD2 CAR T cells in H3-K27M + diffuse midline gliomas. Nat Med 2018;24:572–9.
[83] Donovan LK, Delaidelli A, Joseph SK, Bielamowicz K, Fousek K, Holgado BL, et al. Locoregional delivery of CAR T cells to the cerebrospinal fluid for treatment of metastatic medulloblastoma and ependymomas. Nat Med 2020;26:720–31.
[84] Theruvath J, Sotillo E, Mount CW, Graef CM, Delaidelli A, Heitzeneder S, et al. Locoregionally administered B7-H3-targeted CAR T cells for treatment of atypical teratoid/rhabdoid tumors. Nat Med 2020;26:712–9.
[85] GD2 CAR T cells in diffuse intrinsic pontine gliomas(DIPG) & spinal diffuse midline glioma(DMG) https://clinicaltrials.gov/ct2/show/NCT04196413 (Accessed 26 September 2021).
[86] Heczey A, Liu D, Tian G, Courtney AM, Wei J, Marinova E, et al. Invariant NKT cells with chimeric antigen receptor provide

a novel platform for safe and effective cancer immunotherapy. Blood 2014;124:2824–33.
[87] Song L, Asgharzadeh S, Salo J, Engell K, Wu HW, Sposto R, et al. Valpha24-invariant NKT cells mediate antitumor activity via killing of tumor-associated macrophages. J Clin Invest 2009; 119:1524–36.
[88] Liu D, Song L, Wei J, Courtney AN, Gao X, Marinova E, et al. IL-15 protects NKT cells from inhibition by tumor-associated macrophages and enhances antimetastatic activity. J Clin Invest 2012;122:2221–33.
[89] Heczey A, Courtney AN, Montalbano A, Robinson S, Liu K, Li M, et al. Anti-GD2 CAR-NKT cells in patients with relapsed or refractory neuroblastoma: an interim analysis. Nat Med 2020; 26:1686–90.
[90] C7R-GD2.CART cells for patients with relapsed or refractory neuroblastoma and other GD2 positive cancers (GAIL-N). https://clinicaltrials.gov/ct2/show/NCT03635632.
[91] Glypican 3-specific chimeric antigen receptor expressed in T cells for patients with pediatric solid tumors (GAP). https://clinicaltrials.gov/ct2/show/NCT02932956 (Accessed 26 September 2021).
[92] Interleukin-15 armored glypican 3-specific chimeric antigen receptor expressed in T cells for pediatric solid tumors. https://clinicaltrials.gov/ct2/show/NCT04377932 (Accessed 26 September 2021).
[93] Interleukin-15 and -21 armored glypican-3-specific chimeric antigen receptor expressed in T cells for pediatric solid tumors. https://clinicaltrials.gov/ct2/show/NCT04715191 (Accessed 26 September 2021).
[94] Li N, Fu H, Hewitt SM, Dimitrov DS, Ho M. Therapeutically targeting glypican-2 via single-domain antibody-based chimeric antigen receptors and immunotoxins in neuroblastoma. Proc Natl Acad Sci U S A 2017;114:E6623–31.
[95] Ahmed N, Brawley V, Hegde M, Bielamowicz K, Kalra M, Land D, et al. HER2-Specific chimeric antigen receptor-modified virus-specific T cells for progressive glioblastoma: a phase 1 dose-escalation trial. JAMA Oncol 2017;3:1094–101.
[96] Hegde M, Joseph SK, Pashankar F, DeRenzo C, Sanber K, Navai S, et al. Tumor response and endogenous immune reactivity after administration of HER2 CAR T cells in a child with metastatic rhabdomyosarcoma. Nat Commun 2020;11:3549. https://doi.org/10.1038/s41467-020-17175-8.
[97] Künkele A, Taraseviciute A, Finn LS, Johnson AJ, Berger C, Finney O, et al. Preclinical assessment of CD171-directed CAR T-cell adoptive therapy for childhood neuroblastoma: CE7 epitope target safety and product manufacturing feasibility. Clin Cancer Res 2017;23:466–77.
[98] Ravanpay AC, Gust J, Johnson AJ, Rolczynski LS, Cecchini M, Chang CA, et al. EGFR806-CAR T cells selectively target a tumor-restricted EGFR epitope in glioblastoma. Oncotarget 2019;10:7080–95.
[99] Majzner RG, Theruvath JL, Nellan A, Heitzeneder S, Cui Y, Mount CW, et al. CAR T cells targeting B7-H3, a pan-cancer antigen, demonstrate potent preclinical activity against pediatric solid tumors and brain tumors. Clin Cancer Res 2019;25: 2560–74.
[100] D'Angelo SP, Melchiori L, Merchant MS, Bernstein D, Glod J, Kaplan R, et al. Antitumor activity associated with prolonged persistence of adoptively transferred NY-ESO-1 c259 T cells in synovial sarcoma. Cancer Discov 2018;8:944–57.
[101] Hong DS, Van Tine BA, Olszanski AJ, Johnson ML, Liebner DA, Trivedi T, et al. Phase I dose escalation and expansion trial to assess the safety and efficacy of ADP-A2M4 SPEAR T cells in advanced solid tumors. J Clin Oncol 2020; 38(15 suppl). abstr 102.
[102] Hong DS, Johnson MS, Tanyi JL, MacMullen L, Tighe R, Jalbert L, et al. Preliminary safety and efficacy of gavocabtagene autoleucel (gavo-cel, TC-210), a T cell receptor fusion construct (TRuC), in patients with treatment refractory mesothelin overexpressing solid tumors. Cancer Res 2021;81(13 Supplement): CT105.
[103] Minard-Colin V, Aupérin A, Pillon M, Burke GAA, Barkauskas DA, Wheatley K, et al. European intergroup for childhood non-hodgkin lymphoma; children's oncology group rituximab for high-risk, mature B-cell non-hodgkin's lymphoma in children. N Engl J Med 2020;382:2207–19.
[104] Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20: 31–42.
[105] Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2019;380: 45–56.
[106] Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet 2020;396:839–52.
[107] Locke FL, Rossi JM, Neelapu SS, Jacobson CA, Miklos DB, Ghobadi A, et al. Tumor burden, inflammation, and product attributes determine outcomes of axicabtagene ciloleucel in large B-cell lymphoma. Blood Adv 2020;4. 4898-491.
[108] Zhang W, Yang J, Zhou C, Hu B, Jin L, Deng B, et al. Early response observed in pediatric patients with relapsed/refractory Burkitt lymphoma treated with chimeric antigen receptor T cells. Blood 2020;135:2425–7.
[109] Phase II open label trial to determine safety & efficacy of tisagenlecleucel in pediatric non-hodgkin lymphoma patients (BIANCA). https://clinicaltrials.gov/ct2/show/NCT03610724 (Accessed 26 September 2021).
[110] A study to evaluate the safety and efficacy of JCAR017 in pediatric subjects with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (B-all) and B-cell non-hodgkin lymphoma (B-NHL). https://clinicaltrials.gov/ct2/show/NCT03743246 (Accessed 26 September 2021).
[111] Ramos CA, Grover NS, Beaven AW, Lulla PD, Wu MF, Ivanova A, et al. Anti-CD30 CAR-T cell therapy in relapsed and refractory Hodgkin lymphoma. J Clin Oncol 2020;38:3794–804.
[112] Benjamin R, Graham C, Yallop D, Jozwik A, Mirci-Danicar OC, Lucchini G, et al. Genome-edited, donor-derived allogeneic anti-CD19 chimeric antigen receptor T cells in paediatric and adult B-cell acute lymphoblastic leukaemia: results of two phase 1 studies. Lancet 2020;396:1885–94.
[113] Romee R, Rosario M, Berrien-Elliott MM, Wagner JA, Jewell BA, Schappe T, et al. Cytokine-induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia. Sci Transl Med 2016;8. 357ra123 https://doi.org/10.1126/scitranslmed.aaf2341.
[114] Berrien-Elliott MM, Cashen AF, Cubitt CC, Neal CC, Wong P, Wagner JA, et al. Multidimensional analyses of donor memory-like NK cells reveal new associations with response after adoptive immunotherapy for leukemia. Cancer Discov 2020;10: 1854–71.
[115] Liu E, Marin D, Banerjee P, Macapinlac HA, Thompson P, Basar R, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. N Engl J Med 2020;382:545–53.
[116] Parihar R, Rivas C, Huynh M, Omer B, Lapteva N, Metelitsa LS, et al. NK cells expressing a chimeric activating receptor eliminate MDSCs and rescue impaired CAR-T cell activity against solid tumors. Cancer Immunol Res 2019;7:363–75.
[117] Shalabi H, Gust J, Taraseviciute A, Wolters PL, Leahy AB, et al. Beyond the storm — subacute toxicities and late effects in children receiving CAR T cells. Nat Rev Clin Oncol 2021;18: 363–78.

[118] Tamura K, Tsurutani J, Takahashi S, Iwata H, Krop IE, Redfern C, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. Lancet Oncol 2019;20:816–26.

[119] Shitara K, Bang Y-J, Iwasa S, Sugimoto N, Ryu M-H, Sakai D, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med 2020;382. 2419–243.

[120] Reaman G, Karres D, Ligas F, Lesa G, Casey D, Ehrlich L, et al. Accelerating the global development of pediatric cancer drugs: a call to coordinate the submissions of pediatric investigation plans and pediatric study plans to the European medicines agency and US Food and drug administration. J Clin Oncol 2020;38:4227–30.

[121] Common Commentary - EMA/FDA Common issues requested for discussion by the respective agency (EMA/PDCO and FDA) concerning paediatric oncology development plans (Paediatric Investigation Plans [PIPs] and initial Pediatric Study Plans [iPSPs]). https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans#joint-ema-/-fda-guidance-on-cancer-medicines-for-use-in-children-section (Accessed 26 September 2021).

[122] Common Commentary - EMA/FDA Common issues requested for discussion by the respective agency (EMA/PDCO and FDA) concerning paediatric oncology development plans (Paediatric Investigation Plans [PIPs] and initial Pediatric Study Plans [iPSPs]). https://www.fda.gov/media/147197 (Accessed 26 September 2021).