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Review

Targeted inhibitors and antibody immunotherapies: Novel therapies for paediatric leukaemia and lymphoma

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Abstract Despite improved outcomes achieved in the last decades for children with newly diagnosed leukaemia and lymphoma, treatment of patients with refractory/relapsed disease remains a challenge. The cure rate is still unsatisfactory and often achieved at the cost of

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Targeted inhibitors;
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significant morbidity. Exploring treatment with novel agents should offer less toxic therapeutic options, without compromising efficacy. Bispecific and antibody–drug conjugates targeting CD19 and CD22 (blinatumomab and inotuzumab ozogamicin) play an important role in the treatment of relapsed and refractory B-cell precursor acute lymphoblastic leukaemia (BCP-ALL); antibodies targeting CD123 and CD38 are also under investigation for acute myeloid leukaemia (AML) and T-ALL, respectively. Targeted therapy with small molecules is of primary importance for specific genetic subtypes, such as BCR-ABL-positive ALL, *FLT3*-ITD AML and anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma. *KMT2A*-directed targeted therapy with menin inhibitors holds promise to be of relevance in *KMT2A*-rearranged leukaemias, known to have dismal prognosis. Target inhibition in cellular pathways such as BCL-2, RAS, MEK, Bruton's tyrosine kinase, JAK-STAT or CDK4/CDK6 inhibition may be suitable for different diseases with common mutated pathways. Nevertheless, development and approval of new agents for paediatric cancers lags behind adult therapeutic options. New regulations were implemented to accelerate drug development for children. Considering the number of oncology medicinal products available for adults and the rarity of paediatric cancers, prioritisation based on scientific evidence and medical need, as well as international collaboration, is critical. Herein, we review the current status of drug development for children with leukaemia and lymphoma, excluding cellular therapy despite its well-known significance.

1. Introduction

Leukaemias and lymphomas in children are heterogeneous diseases comprising roughly one-third of paediatric cancers. Although in acute lymphoblastic leukaemia (ALL), mature B-cell ALL and lymphoblastic lymphoma (LL) outcomes have increased to over 85% event-free survival (EFS), outcomes in anaplastic large-cell lymphoma (ALCL) and acute myeloid leukaemia (AML) still lag behind with EFS rates in the range of 55–75% [1,2]. Salvage treatment options for patients with B-cell precursor ALL (BCP-ALL) have increased significantly with the market authorisation of blinatumomab and chimeric antigen receptor T cells (CAR T cells), changing the landscape for treatment options and resulting in a new relapse category after immunotherapy [3,4]. For T-cell ALL, despite current high survival rates in complete remission 1 (CR1), the first relapse salvage remains dismal, and there is no unified approach to relapse [5]. In paediatric AML, first-relapse salvage rates have improved with retreatment with intensive chemotherapy and stem cell transplantation [4], with an overall survival (OS) of about 40–50%, but there is a paucity of options for the second or later relapse [6]. CAR T-cell therapy in AML is hampered by the problem of identifying antigens selective for the leukaemia cell population, while sparing haematopoietic stem cells, and thus avoiding the risks of prolonged myelosuppression. In paediatric non-Hodgkin lymphoma (NHL), progress is highly dependent on the subtype of NHL. In mature B-cell NHL, prognosis after relapse remains dismal, similar to T-cell LL. Progress has been made in ALCL with the availability of vinblastine, brentuximab vedotin and anaplastic lymphoma kinase (ALK) inhibitors, although crizotinib was approved only recently by the United States Food and Drug Administration (FDA) and not yet in Europe [7–9]. Relapses of BCP NHL are approached in a similar way as in BCP-ALL [1]. Table 1 summarises recent results of paediatric trials in relapsed/refractory haematological malignancies.

Improved outcomes have often been at the expense of significant acute morbidity and mortality as well as late effects [10,11]. Replacing therapy elements with less toxic, but equally effective, drugs therefore remains an important goal. Haematopoietic stem cell transplantation (HSCT) is almost inevitably part of salvage treatment after relapse and is also associated with the risk of transplant-related mortality and long-term morbidity, and the long-term safety of CAR T-cell therapy as an alternative needs to be awaited [12]. Development and approval of new agents for paediatric cancers lags behind adult development. New regulations in Europe and the United States are enacted to ensure commitment of companies to develop drugs in children [13]. The new Research Acceleration for Cure and Equity for Children Act requires paediatric investigation of new agents if directed at a relevant molecular target for paediatric cancer, even when the drug is intended for the treatment of an adult cancer. Considering the rarity of paediatric cancers, prioritisation based on science and medical need is of primary importance, as discussed at paediatric forum meetings organised by ACCELERATE, an international multistakeholder network involving clinicians,

Table 1
Recent results of paediatric trials in relapsed/refractory haematological malignancies.

Disease category	Study title	N. relapse	Era	Nr of patients	Overall survival	Event-free survival	References
Paediatric ALL							
B/T ALL	TACL retrospective data	2nd relapse	2005–2013	325	–	In CR3: 2 y: 41% ± 6%	Sun et al., Leukaemia 2018
	TACL retrospective data	1st relapse	1995–2004	225	–	2 y: 40% ± 4% 5-y 27% ± 4% In CR3: 2 y: 31% ± 7%; 5 y 15% ± 7%	Ko et al. JCO 2010
	NOPHO retrospective data	1st relapse	2002–2011	239	5 y: 57.5% ± 3.4%	5 y: 51% ± 3%	Oskarsson et al. Haematologica 2016
	ALLR3 MITOXANTRONE arm only	1st relapse	2003–2009	103	3 y: 69.0% (95% CI 58.5–77.3)	3 y: 64.6% (95% CI 54.2–73.2)	Parker et al., Lancet 2010; 376:1968–1970
B ALL	AALL1331 Blinatumomab arm only	1st relapse	2014–2019	105	2 y: 71.3%	2 y: 54.4%	[Brown et al. JAMA. 2021
	NCT02393859 Blinatumomab arm only	1st relapse	2015–2019	54	2 y: 80%	2 y: 66.2% (95% CI, 50.1%–78.2%)	Locatelli et al. JAMA 2021
B ALL	Austrian BFM	1st relapse	1981–1999	150	10 y: 37% ± 4%	10 y: 40% ± 4%	Reismuller et al., 2009. Br J Haematol. 2009
T ALL	Austrian BFM	1st relapse	1981–1999	28	10 y: 21% ± 8%	10 y: 21% ± 8%	Reismuller et al., 2009. Br J Haematol. 2009
Paediatric AML							
	Relapsed AML 2001/01	1st relapse	2001–2009	394	4 y: 38% ± 3% Early 1st rel. 28% ± 3%; Late 1st rel. 48% ± 4%	–	Kaspers et al. JCO 2013
	TACL retrospective data	1st relapse	1995–2004	99	5 y: 29% ± 5%	5 y: 24 ± 5%	Gorman et al. Pediatr Blood Cancer.2010
	AAML1421	1st relapse	2016–2018	38	In CR2 2 y 52.7% ± 21.1%	–	Cooper et al., JCO 2020
	BFM registry	1st relapse	2005–2010	155	5 y: 45 ± 4%	–	Rasche et al., Leukaemia 2018
	ITCC-020/I-BFM 2009-02	Early 1st relapse or ≥2nd relapse	2010–2014	34	2 y: 32.4 ± 8.0%	2 y: 26.5% ± 7.6%	van Eijkelenburg et al. Haematologica 2018
Paediatric NHL							
ALCL	ALCL relapse study	–	2004–2014	118	3 y: 78% ± 4%	3 y: 59% ± 5%	Ruf S. et al. BJH 2015 (Abstract)
	ALCL99-vinblastine (vinblastine arm only)	–	1999–2006	110	–	2 y: 73%	Le Deley et al. J Clin Oncol 2010
	ALCL-relapse trial (NCT00317408)	Progression/relapse	2005–2014	105	5 y: 78% ± 4%.	5 y: 53% ± 5%	Knörr et al., JCO 2020
B-NHL	CCLG retrospective data	–	2000–2010	33	4 y: 27.3%	–	Anoop et al. leukaemia&Lymphoma 2012
	JPLSG retrospective data	–	2004–2011	33	5 y: 48.5%	–	Osumi et al. Pediatr Blood Cancer 2016
	SFCE retrospective data	–	1989–2007	67	5 y: 29.9%	–	Jourdain A et al. Haematologica 2015
T LL	BFM retrospective data	–	1990–2003	28	5 y:14% ± 6%	–	Burkhardt B et al. JCO 2009
T/B LL	JPLSG retrospective data	–	1996–2004	48 (9 B LL, 32 TLL)	3 y 43.2 ± 7.4% T LL: 32.8 ± 8.6% B LL: 72.9 ± 16.5%	3 y 37.0 ± 7.3%	Mitsui e al. Pediatr. Blood Cancer 2009

ALCL, anaplastic large-cell lymphoma; AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; BFM, Berlin-Frankfurt-Münster; CI, confidence interval; CR3, complete remission 3; ITCC, European Innovative Therapies for Children with Cancer; NHL, non-Hodgkin lymphoma.

regulators, industry and patient advocates (https://www.accelerate-platform.eu/) [14–16].

We aim to review the current status of drug development for leukaemia and lymphoma in children, excluding Hodgkin lymphoma (HL) (a summary of the discussed drugs is provided in Table 2). Figs. 1–3 provide an overview of actionable targets with agents currently in development in paediatric settings, in AML, ALL and NHL, respectively. Cellular therapies including CAR T-cells, while transformational for some patients, are outside the scope of this article and reviewed elsewhere.

Table 2
Drugs in development for paediatric haematological malignancies.

Drug class	Compound	Disease	Trial number and Reference, if applicable
Immunotherapy			
Bispecific antibodies	Blinatumomab	ALL	COG AALL1331 (NCT02101853) [26] COG ALL1731 (NCT03914625) NCT02187354 [25] NCT02393859 [27] Interfant-06 NL7937 AIEOP-BFM ALL 2017 (NCT03643276) ALLTogether (NCT03911128)
	Blinatumomab + nivolumab	ALL	COG AALL1821 (NCT04546399)
	Flotetuzumab	AML	COG ADVL1812 (NCT0215956)
Monoclonal antibodies	Daratumumab	ALL	NCT03384654
	Isatuximab	AML/ALL	NCT03860844
	Rituximab	NHL	Inter B-NHL Ritux 2010 (NCT01516580) [1]
Antibody–drug conjugates	Inotuzumab ozogamicin	ALL	ITCC-059 (EudraCT 2016-000227-71) [38,39] COG AALL1621 (NCT02981628) [40] COG AALL1732 (NCT03959085) ALLTogether (NCT03911128)
	Anetumab ravtansine	AML	PedAL
	IGMN632	AML	PedAL/EupAL
	Brentuximab	HL/ALCL	NCT01492088 [8]
Immune checkpoint inhibitors	Nivolumab	HL/ALCL	NCT03703050
	Pembrolizumab	HL	NCT03407144
Targeted therapy			
FLT3 inhibition	Midostaurin	AML	NCT03591510 [50]
	Sorafenib	AML	COG AAML1031 (NCT 01371981)
	Quizartinib	AML	COG ADVL1822 (NCT03793478)
	Crenolanib	AML	NCT02270788
	Gilteritinib	AML	COG AAML1831 (NCT04293562)
ALK inhibition	Crizotinib	NHL	ITCC-053 (EudraCT 2015-005437-53)
	Ceritinib	NHL	NCT01742286 [57]
	Brigatinib	NHL	ITCC-098
BCR-ABL inhibition	Ponatinib	ALL/AML/CML	NCT03934372
	Dasatinib	ALL	NCT01460160
	Bosutinib	CML	ITCC-054/COG AAML1921 (EudraCT 2015-002916-34)
MEK inhibition	Selumetinib	ALL	ITCC-063 (NCT03705507)
BTK inhibition	Ibrutinib	NHL	(NCT02703272) [95]
JAK-STAT inhibition	Ruxolitinib	ALL	COG AALL1521 (NCT02723994)
CDK4/CDK6 inhibition	Ribociclib	ALL	DFCI 18–328 (NCT03740334)
	Palbociclib	ALL	COG AINV18P1 (NCT03792256)
IDH inhibition	Enasidenib	AML	ITCC-057 (NCT02813135)
Proteasome inhibition	Carfilzomib	ALL	ITCC/TACL CFZ2008 (NCT02303821) [81]
BCL2 inhibition	Venetoclax	AML/ALL	NCT03236857 [83]
	Venetoclax + idasanutlin	AML	NCT04029688)
KMT2A inhibition	SNDX-5613 (Menin inhibition)	AML/ALL	PedAL/EupAL
	Pinometostat (DOT1L inhibition)	AML/ALL	NCT03724084
Other			
Arginine depletion/enzyme therapy	BCT-100 (recombinant arginase)	AML/ALL	ITCC-062 (NCT03455140)

AIEOP-BFM, associazione italiana emato-oncologia pediatrica – Berlin-Frankfurt-Münster; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; CML, chronic myeloid leukaemia; COG, Children's Oncology Group; HL, Hodgkin lymphoma; ITCC, European Innovative Therapies for Children with Cancer; NHL, non-Hodgkin lymphoma; PedAL/EupAL, Paediatric Acute Leukaemia/European Paediatric Acute Leukaemia; TACL, therapeutic advances in childhood leukemia & lymphoma.

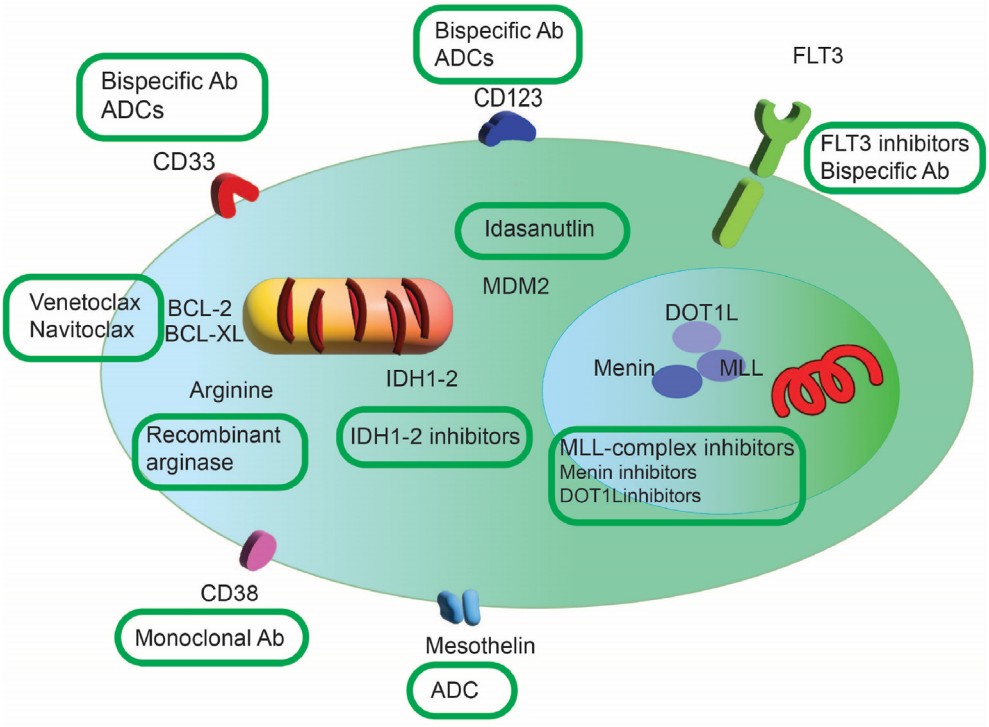

Fig. 1. Overview of current targets in paediatric acute myeloid leukaemia. The figure shows actionable targets with agents currently in development in paediatric AML and discussed in this overview, excluding CAR T cells products. Ab, antibody; ADC, antibody–drug conjugate. AML, acute myeloid leukaemia; CAR T, chimeric antigen receptor T.

2. Immunotherapy

2.1. Monoclonal antibodies

2.1.1. Anti-CD38

Therapeutic CD38-targeting monoclonal antibodies (daratumumab; isatuximab) have recently been approved to treat adults with multiple myeloma (MM). Preclinical data show that CD38 is expressed in many paediatric haematological malignancies, with a strong expression in ALL and more variable expression in AML [17]. Based on promising preclinical data and the high CD38 expression at diagnosis and relapse, targeting CD38 could have utility in ALL and AML [17,18].

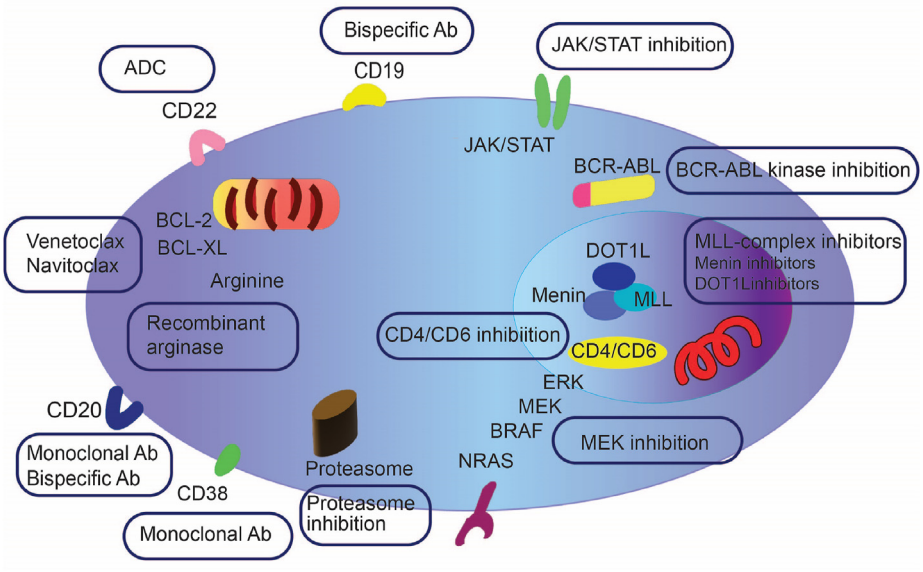

Fig. 2. Overview of current targets in paediatric acute lymphoblastic leukaemia. The figure shows actionable targets with agents currently in development in paediatric ALL, excluding CAR T cells products. BCR-ABL kinase inhibitors can target additional ABL-class fusions involving ABL1, ABL2, CSF1R and PDGFRB (not shown in the figure). Ab, antibody; ADC, antibody–drug conjugate. ALL, acute lymphoblastic leukaemia; CAR T, chimeric antigen receptor T.

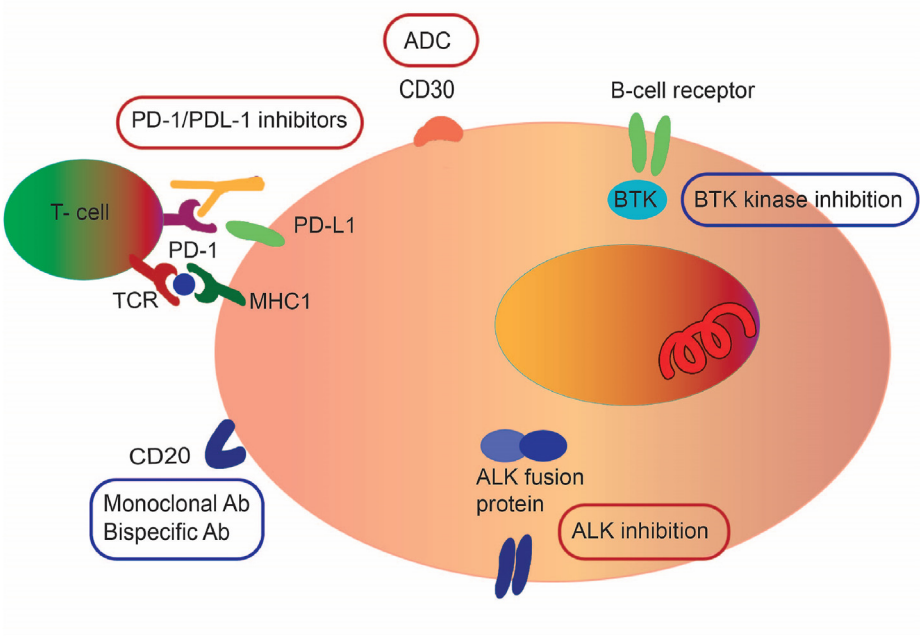

Fig. 3. Overview of current targets in paediatric non-Hodgkin lymphoma. The figure shows actionable targets with agents currently in development in paediatric NHL, excluding CAR T cells products. The figure includes actionable targets for ALCL and other types of NHL. Red circles highlight targets actionable for ALCL, blue circles for Burkitt lymphoma, diffuse large cell lymphoma or other NHL. Ab, antibody; ADC, antibody–drug conjugate. ALCL, anaplastic large-cell lymphoma; CAR T, chimeric antigen receptor T; NHL, NHL, non-Hodgkin lymphoma.

Daratumumab induces lysis through cytotoxic mechanisms (complement-dependent, cell-mediated and antibody-dependent cellular phagocytosis). A phase I–II trial of daratumumab with standard 4-drug reinduction in children and young adults with relapsed or refractory (R/R) BCP or T-cell ALL and LL is ongoing (National Clinical Trial number – NCT03384654). Isatuximab is an immunoglobulin G1 class monoclonal antibody, also binding CD38, that exerts its activity by the same mechanisms as daratumumab [19]. The NCT03860844 study, ongoing for paediatric BCP/T-ALL and AML, observed CR + CRi (complete remission with incomplete count recovery) in 3/7 (42.9%) in the B-ALL cohort, 2/6 (33.3%) in the T-cell ALL (T-ALL) cohort and 2/4 (50.0%) in the AML cohort. In this study, patients receive isatuximab in combination with chemotherapy (modified UKALL R3 for ALL and FLAG, fludarabine, cytarabine, granulocyte colony-stimulating factor, for AML). Pharmacokinetic (PK) parameters in children (>2 y) are consistent with those observed in adult ALL [20]. Similar to other monoclonal antibodies, infusion reactions have been reported as the most common adverse event for both compounds.

2.1.2. Anti-CD20

Rituximab, a monoclonal antibody that binds to CD20, is currently the standard of care in addition to chemotherapy in mature B-cell NHL and also as single agent in post-transplant lymphoproliferative disease, especially in case of EBV-positive disease [21]. Its role in ALL is less established, with only 30 to 50% of BCP-ALL blasts expressing CD20. A French trial in adults (NCT00327678), adding rituximab to the ALL chemotherapy protocol, demonstrated an improved outcome for younger adults with CD20-positive, Philadelphia chromosome (Ph)-negative ALL [22]. CD20 expression has an adverse prognostic significance in adult ALL, whereas its impact in paediatric ALL is controversial [23]. Owing to these characteristics, CD20 is a potential target that has not been widely used to treat R/R paediatric BCP-ALL. Novel anti-CD20 antibodies, such as obinutuzumab an anti-CD20 monoclonal antibody with greater affinity for CD20, and the bispecific T-cell engagers glofitamab and mosunetuzumab, may be of interest for future studies in mature B-cell ALL/NHL, as well as in CD20-positive BCP-ALL [24].

2.2. Bispecific antibodies

Bispecific antibodies bind two distinct antigens simultaneously, linking antigens on target cells to immune effector cells (i.e. T cells, natural killer (NK) cells or macrophages).

2.2.1. Blinatumomab

Blinatumomab directs CD3-positive effector T cells to CD19-positive target cells. It is currently approved by the FDA as monotherapy for the treatment of children with R/R BCP-ALL, or in the first or second CR with persisting positive minimal residual disease (MRD) [25].

In Europe, blinatumomab is indicated for paediatric patients above the age of 1 year, with second or greater R/R BCP-ALL, or with high-risk first relapse BCP-ALL as part of the consolidation therapy. In the single-agent trial in overt relapse, neurological toxicity and cytokine release syndrome (CRS) were noticed as a result of high tumour burden, which occurs at a much lower frequency in MRD setting [3]. For example, the results of an expanded access trial of blinatumomab in R/R ALL showed a good safety profile and high MRD response rate (NCT02187354) [25]. Two randomised trials have highlighted the superiority of blinatumomab as post-reinduction consolidation treatment compared with chemotherapy. This was owing both to enhanced anti-leukaemic activity as well as less haematologic toxicity and infections. In the phase III trial in intermediate and high-risk first relapse of BCP-ALL NCT02101853, two cycles of blinatumomab as postreinduction consolidation treatment demonstrated higher disease-free survival at two years (54.4% vs 39.0%) compared with conventional chemotherapy [26]. The NCT02393859 randomised trial demonstrated superior EFS for children with high-risk first relapse of BCP-ALL treated with blinatumomab as compared with those given the third block of consolidation chemotherapy before HSCT [27]. Based on these results, blinatumomab seems to be best positioned in MRD setting in postinduction therapy, rather than for remission re-induction. Novel strategies to overcome mechanisms of blinatumomab resistance are under investigation, including the combination with immune checkpoint inhibitors (NCT04546399/AALL1821) [28]. Currently, research is focused on moving blinatumomab to upfront treatment. Infants with ALL have a poor prognosis compared with older children, with a 4-year EFS rate of 47% and a survival rate after relapse of approximately 20% [29]. A pilot study adding blinatumomab to the Interfant-06 backbone for infants with *KMT2A*-rearranged (*KMT2A*-r) ALL (NCT03643276) is ongoing. Trials including newly diagnosed children above 1 year of age with BCP-ALL are also aiming to determine how to optimally incorporate blinatumomab. The Children's Oncology Group (COG) NCT03914625/AALL1731 trial and the Berlin-Frankfurt-Münster, BFM/Associazione Italiana Emato-oncologia pediatrica, AIEOP NCT03643276 trial include randomised questions of blinatumomab during consolidation. The ALLTogether1 trial (NCT03911128) evaluates blinatumomab as consolidation treatment in patients with Down syndrome, who have poor tolerance to chemotherapy. Nevertheless, a recent warning about increased risk of seizures during blinatumomab infusion in patients with Down syndrome >10 years has been raised by the COG group [30].

2.2.2. Flotetuzumab

Flotetuzumab is a CD123xCD3 bispecific antibody. CD123 is overexpressed in AML and other disease subsets, such as BCP-ALL, early-T precursor ALL (ETP-ALL) and mixed phenotype acute leukaemia (MPAL), as compared with normal haematopoietic stem cells, and has been associated with chemotherapy resistance and high-risk genetic alterations, including FLT3 internal tandem duplication (FLT3-ITD) in AML [31,32]. A phase I/II study in adults with R/R AML (NCT02152956) established the maximum tolerated dose (MTD) at 500 ng/kg/day, the most frequent adverse events being infusion-related reactions and CRS. Complete response after flotetuzumab positively correlated with 'immune infiltration' profiles, that were mainly noted in patients with primary induction failure (PIF) or early relapse, leading to a clinical benefit for this specific patient group (overall response rate, ORR 30% vs 20%) [33]. A COG phase I trial of flotetuzumab in paediatric patients with refractory or second or later relapse AML is currently open for recruitment (NCT04158739).

Besides flotetuzumab, a variety of other CD123-targeted agents have been tested in preclinical models and translated into human clinical trials, including antibodies with enhanced antibody-dependent cellular cytotoxicity ([34]) and antibody–drug conjugates (ADCs) such as IMGN632 (see section on ADCs) [35].

2.3. Antibody–drug conjugates

2.3.1. Inotuzumab ozogamicin

Inotuzumab ozogamicin (InO) is an anti-CD22 antibody linked to calicheamicin, a potent cytotoxic antitumour antibiotic. The INO-VATE adult phase III study (NCT01564784), with a CR rate of 80.7% in the InO arm as compared with 29.4% in the standard intensive chemotherapy control arm, led to the approval of InO for adults with R/R CD22-positive BCP-ALL [36]. In a compassionate use program in children with R/R BCP-ALL, treatment with single-agent InO resulted in CR in 67% of patients [37]. A phase I/II study is currently ongoing in children with R/R BCP ALL (study European Innovative Therapies for Children with Cancer [ITCC]-059) within the ITCC group. The phase I study established the recommended phase II dose (RP2D) at 1.8 mg/m^2, similar as in adults, with an ORR of 80%, which was confirmed in the phase II part of the study [38,39]. An additional phase 1b cohort is ongoing to test the combination of InO with a modified R3 reinduction regimen. The study also includes a cohort of patients with very high-risk first relapse of CD22-positive ALL, who will receive single-agent InO (NTR57360), followed by consolidation with stem cell transplantation (SCT) or CAR T-cells once in CR. The COG is performing two additional studies on InO in paediatric ALL, the AALL1621 phase II study, using the adult RP2D, and a phase III randomised trial of InO for newly diagnosed high-risk CD22-positive BCP-ALL, which is currently open for recruitment (AALL1732 study; NCT03959085). AALL1621 demonstrated an

ORR of 58.6% in children and young adults with R/R CD22-positive BCP-ALL [40] and is proceeding with InO combined with chemotherapy in a manner to complement the ITCC-059 study. InO experience in infants is limited: a retrospective study showed a CR rate of 47% in R/R ALL [41]. InO is also being studied during consolidation in the ALLTogether1 protocol for newly diagnosed patients with ALL with persistent high MRD (NCT03911128). A particular concern with the use of InO is sinusoidal obstruction syndrome, likely owing to the calicheamicin component. Warnings were raised by studies in adults, showing a relatively high incidence in the transplant population (30% of transplanted patients after InO), similar to gemtuzumab ozogamicin (GO) [36,37,39]. Current recommendations, as per the summary of product characteristics, are to limit InO to 2–3 cycles if a patient is a candidate for HSCT and to use non-alkylating chemotherapy.

The available data suggest that InO may be a very efficient drug for remission induction and may be less toxic than conventional multi-agent (re-)induction chemotherapy. A comparative study between InO single-agent and chemotherapy as re-induction therapy will be performed by the IntReALL (International study for treatment of childhood relapsed ALL) group, to further provide evidence for this.

2.3.2. IMGN632

As mentioned previously, CD123 represents an attractive candidate for targeted therapy approach in different disease subsets, and various CD123-targeted agents are in development. IMGN632 is a humanised anti-CD123 antibody linked to a novel DNA-alkylating payload of the novel indolinobenzodiazepine pseudodimer (IGN) class [35]. IMGN632 has demonstrated promising activity in a phase I–II trial in adults with R/R AML and blastic plasmacytoid dendritic cell neoplasms (BPDCN), which led to FDA approval for the treatment of BPDCN at the recommended dose of 0.045 mg/kg once every 21 days (NCT03386513) [42]. A phase I-II study in paediatric AML is in development in the international Paediatric Acute Leukaemia/European Paediatric Acute Leukaemia (PedAL/EuPAL) program, which is a global precision medicine clinical trial with the aim to improve outcome in paediatric AML (see Future directions section in the following) [43]. Another CD123-targeting compound, with a truncated diphtheria toxin payload, tagraxofusperzs, was approved in December 2018 by the FDA for treatment of BPDCN in adult and paediatric patients.

2.3.3. Anetumab ravtansine: a mesothelin-directed antibody-drug conjugate

Anetumab ravtansine (AR) is a mesothelin (MSLN)-directed antibody linked to the maytansinoid tubulin inhibitor DM4. MSLN is a cell surface glycoprotein normally expressed on mesothelial cells, and it is overexpressed in several human cancers, including in 23–35% of paediatric AML samples, with a significantly higher expression in patients with inv (16), t (8; 21) and *KMT2A* translocations. The phase I study in adults with advanced solid tumours showed a favourable safety profile [44]. AR showed a survival benefit and synergy with conventional chemotherapy in mouse models with disseminated MSLN + leukaemia [45]. A study in paediatric AML is in development.

2.3.4. Brentuximab vedotin

Brentuximab vedotin is a CD30-directed ADC linked to the cytotoxic payload monomethyl auristatin E, approved for adult patients with HL and ALCL. A paediatric phase I–II trial recently established the RP2D at 1·8 mg/kg once every three weeks, showing an ORR of 53% for R/R ALCL and 47% for classical HL [8]. COG ANHL12P1 tested brentuximab vedotin with chemotherapy in children with newly diagnosed ALCL, reporting a two-year EFS of 79.1% (95% confidence interval [CI], 67.2%–87.1%) and a two-year OS of 97.0% (95% CI, 88.1%–99.2%), without significant additional toxicity compared with standard chemotherapy [46].

2.3.5. Gemtuzumab ozogamicin

GO is a humanised anti-CD33 antibody conjugated to calicheamicin approved in combination with chemotherapy for the treatment of patients of 15 years and above with newly diagnosed AML by the European medicines agency (EMA) and for all age groups by the FDA. A large randomised COG trial in newly diagnosed AML showed that GO added to chemotherapy improved EFS through a reduction in relapse risk [47].In Europe, GO is studied in a fractionated schedule in newly diagnosed paediatric AML in a French-United Kingdom collaboration, still ongoing (NCT02724163). As most relevant toxicities, veno-occlusive liver disease and prolonged cytopenia have been observed. During the past few years, several additional CD33-targeting antibody-based drugs were developed (i.e. the ADC IMGN779, the bispecific antibodies AMG330 and AMG673), but no paediatric trials are currently ongoing.

3. Small-molecule inhibitors

3.1. FLT3 inhibition

The incidence of *FLT3*-ITD in AML increases with age, occurring in approximately 10–15% of children and 20–30% of adults with *de novo* AML, conferring a poor prognosis in patients with AML harbouring this lesion [48]. To date, two FLT3 inhibitors have been approved for adult AML: midostaurin in combination with chemotherapy for newly diagnosed patients and gilteritinib as monotherapy for patients with R/R. No drugs are approved for paediatric AML as yet, but paediatric studies are ongoing.

3.1.1. Midostaurin

Midostaurin was initially developed as an inhibitor of protein kinase C, but was subsequently recognised to have strong inhibitory effects on FLT3, and various other targets as well. It was approved by the FDA and EMA for use in adults with *de novo FLT3*-mutated AML in combination with chemotherapy, after a randomised study demonstrating improved median EFS and OS compared with patients treated with chemotherapy [49]. A phase I trial of midostaurin monotherapy was conducted in children with leukaemia by the ITCC, establishing the paediatric recommended dose at 30 mg/m^2 twice daily; five of nine patients with AML and three of 13 patients with *KMT2A*-rearranged ALL had partial or complete responses [50]. A phase II study is open to evaluate midostaurin combined with standard chemotherapy and as a single agent after consolidation therapy in children with *FLT3*-mutated AML (NCT03591510).

3.1.2. Sorafenib

Sorafenib is a first-generation pan-kinase inhibitor with activity against RAF, c-KIT, PDGFR, VEGFR and FLT3 and is FDA-approved for the treatment of adults with solid tumours. A COG phase III trial AAML1031 (NCT01371981) was conducted to assess the efficacy of sorafenib in addition to chemotherapy for children and young adults with *de novo FLT3*−ITD AML. Owing to concerns for cardiac toxicity, the study was amended to start sorafenib only between cycles of chemotherapy rather than concurrently. In addition, one year of sorafenib maintenance therapy was added. This resulted in improved remission rates and an improved 3-year EFS, compared with historical controls (57.5% vs 34.3%, $p = 0.007$) [51]. A randomised trial against a placebo arm in adults showed that sorafenib maintenance therapy reduced the risk of relapse and death after HSCT for FLT3-ITD-positive AML [52].

3.1.3. Quizartinib

Quizartinib is a second-generation FLT-3 inhibitor and has 10−50 times greater *in vivo* potency than first-generation inhibitors against *FLT3*-ITDs and demonstrates preclinical activity against overexpression of *FLT3*-wilde type (*FLT3*-WT) and c-KIT [53]. Recently, the QuANTUM-first trial in adults with newly diagnosed AML met its primary end-point of increased OS (press release). Next to FLT3-mutated AML, in paediatric ALL, the highest levels of *FLT3*-WT expression occur in patients with *KMT2A*-r. Based on this observation, a phase I study tested quizartinib in combination with chemotherapy in 17 children with R/R AML or *KMT2A*-r ALL, and the optimal dose level was set at 60 mg/m^2 once daily [54]. Three of the seven patients with *FLT3*-ITD AML achieved complete response. Remissions were not achieved in wild-type *FLT3* AML or *KMT2A*-r ALL. An industry-sponsored phase I/II trial has opened in R/R AML combining quizartinib with chemotherapy, followed by consolidation therapy and/or HSCT, and maintenance treatment with quizartinib for one year (NCT03793478). *FLT3*-ITD + cells with secondary *FLT3*-tyrosine kinase domain (TKD) mutations may become resistant to the first-generation FLT3 inhibitors and to quizartinib but may retain sensitivity to the other second-generation inhibitors crenolanib and gilteritinib [55]. When combined with chemotherapy, developing resistance mutations may be less relevant, as known from Philadelphia-chromosome-positive ALL and BCR-ABL inhibitors.

3.1.4. Crenolanib

Crenolanib was originally designed as a PDGFR inhibitor, although data suggest that this second-generation TKI has robust activity against both *FLT3*-ITD and *FLT3*-TKD mutations, including those that confer resistance to quizartinib. Tolerable paediatric dosing of crenolanib monotherapy was established at 170 mg/m^2 once daily in a phase I trial conducted at St Jude Children's Research Hospital (SJCRH) in children with central nervous system gliomas, which have activated PDGFR signalling. The current SJCRH RELHEM2 phase I trial (NCT02270788) is assessing the safety of combined crenolanib and sorafenib in children with R/R haematologic malignancies.

3.1.5. Gilteritinib

Gilteritinib is a potent second-generation FLT3 inhibitor, with moderate additional activity against AXL, and is also active against *FLT3*-TKD resistance mutations (96). Gilteritinib recently received FDA approval as monotherapy for treatment of adult patients with R/R *FLT3 mutant* AML, based on improved OS for the gilteritinib arm compared with standard chemotherapy in a phase III trial. This trial reported good tolerability and a 34% (vs 15.3%) CR/Cri rate in heavily pretreated patients [56]. In the COG AAML1831 study for newly diagnosed AML, patients with FLT3 mutations are treated with gilteritinib plus chemotherapy. An industry-sponsored international study is also open for paediatric patients with R/R AML (NCT04240002).

3.2. Anaplastic lymphoma kinase inhibition

ALK inhibitors are investigated in the treatment of malignancies that are *ALK* or *ROS* fusion gene-driven, including ALCL. A variety of ALK inhibitors are available, including crizotinib, ceritinib, lorlatinib, alectinib, entrectinib and brigatinib. A Paediatric Strategy Forum meeting in 2017 and a follow-up meeting this year focused on ALK inhibition, highlighting its role in achieving remission in relapsed ALCL. Prospects for the future are establishing its role in curing newly diagnosed children, while reducing treatment toxicity, and combination approaches (i.e.

brentuximab or vinblastine in combination with crizotinib or other ALK inhibitors) [57].

A phase I/II study of crizotinib in 26 children with relapsed ALK-positive ALCL showed an ORR of 83% and 90% for patients treated at 165 mg/m^2 and 280 mg/m^2 twice daily [7]. In January 2021, the FDA approved crizotinib for paediatric patients (1 year of age and older) and young adults, with R/R ALK-positive ALCL at the 280 mg/m^2 oral dose twice daily. This dose is higher compared with the adult-approved flat dose of 250 mg twice daily (500 mg daily). An ITCC phase I/II basket trial tested crizotinib at a fixed dose of 150 mg/m^2 twice daily in combination with a dose escalation of vinblastine in relapsed ALK-positive ALCL (ITCC053/CRISP, European Union Drug Regulating Authorities Clinical Trials (EudraCT) 2015-005437-53); however, this combination raised tolerability issues, and hence the study will generate more data on single-agent activity. The overall ALCL relapse strategy within the European Inter-Group for Childhood Non-Hodgkin Lymphoma consists of the ITCC053/CRISP study in the first relapse, and in the ALCL-Nivo study (NCT03703050) in the second relapse, evaluating the response to nivolumab compared with allo-HSCT [58]. A recently published phase I/II study in 83 paediatric patients established the MTD of ceritinib to be 510 mg/m^2 once daily (fasted) and 500 mg/m^2 once daily (fed) And showed an ORR of 75% for ALCL treated at MTD. The most commonly reported adverse event was transaminase elevation [59]. Although clinically active, crizotinib and ceritinib may not have durable efficacy, and secondary resistance mutations may occur [7,60]. Moreover, these drugs do not penetrate into the central nervous system. In adults with non−small-cell lung cancer, brigatinib (dosed 180 mg once daily) achieved better intracranial response rates, more durable responses and showed better tolerability and quality-of-life scores over crizotinib [61]. Moreover, brigatinib maintained activity against all 17 secondary ALK mutants tested in cellular assays. Brigatinib will be tested in a phase I-II trial for ALCL, inflammatory myofibroblastic tumours (IMT) or other solid tumours (the ITCC-098 study).

3.3. BCR-ABL kinase inhibition

The chromosomal translocation t (9; 22) (q34; q11), Ph, is found in all patients with chronic myeloid leukaemia (CML) and in 3−4% of paediatric patients with ALL. Its resulting product is the fusion protein BCR-ABL with aberrant kinase activity, in two major isoforms: p210, the hallmark of CML, and p190, which occurs in most BCP-ALL cases. Ph-like ALL is an identified high-risk B-lineage ALL subtype. Its gene expression profile is similar to that of Ph + ALL, with ABL-class fusions involving ABL1, ABL2, CSF1R and PDGFRB, and other alterations (not targetable with ABL kinase inhibitors) including CRLF2, JAK2 and EPOR that activate JAK/STAT signalling [62].

Imatinib, dasatinib and nilotinib are the first- and second-generation BCR-ABL inhibitors approved for paediatric patients with CML, whereas the second-generation tyrosine kinase inhibitor (TKI) bosutinib is currently under investigation (NCT04258943). Imatinib and dasatinib in combination with chemotherapy are also approved for paediatric patients with Ph + ALL. The NCT02883049 COG trial is exploring the addition of dasatinib to backbone chemotherapy for ABL-class Ph-like ALL. Recent interesting results obtained in adults with Ph + ALL treated with a combination of dasatinib and blinatumomab as induction therapy may open the possibility of chemotherapy-free induction treatment for Ph + -ALL [69].

Ponatinib is a third-generation kinase inhibitor demonstrating potent ABL kinase inhibition, including activity against the T315I mutation, which leads to resistance to the first- and second-generation TKIs. It is currently approved for second-line treatment in adult CML and Ph + ALL, or first line in case of T315I mutation [63]. In addition, ponatinib has been shown to be a potent inhibitor of other tyrosine kinases, including FLT3, KIT, RET, AKT, ERK1/2, FGFRs and others, implicated in a variety of myeloproliferative disorders and solid tumours. A phase I/II study is evaluating ponatinib single-agent in paediatric patients with CML-resistant or intolerant to a prior TKI-containing therapy, or Ph + ALL with T315I mutation, or any other tumour in which standard therapy is not available or is not indicated (NCT04501614). An important consideration is the vascular toxicity reported at the approved dose of 45 mg ponatinib in adults. Studies with lower dosages of ponatinib for adult CML are ongoing, to see if they are associated with a better vascular safety signal [64]. Two reports on compassionate use of ponatinib in 11 and 21 paediatric patients with CML or Ph + ALL have been published with median doses administered of 21.4 mg/m^2 and 20 mg/m^2 (or 16 mg/m^2 for ALL); treatment efficacy is reported as major molecular response in 50% of cases in one study and as disease burden decrease in 70% of cases in the other [65,66].

Asciminib is a BCR-ABL1 inhibitor specifically targeting the ABL myristoyl pocket recently approved for the treatment of adult patients with CML, previously treated with two or more TKIs or carrying the T315I mutation. No trial in paediatric is currently available or planned.

3.4. MEK inhibition

MEK kinase is a component of the RAS-RAF-MEK-ERK-pathway. Approximately 40% of R/R ALL carry different *RAS* pathway mutations (NRAS, KRAS, PTNP11 and *FLT3*). In a mouse model, selumetinib selectively repressed growth of *RAS*-mutated ALL blasts, also reducing central nervous system (CNS) disease burden [67]. Selumetinib acts synergistically with dexamethasone. Dexamethasone-induced blast

apoptosis is mediated by increasing the pro-apoptotic protein Bim, which is inactivated when phosphorylated by ERK. MEK inhibition prevents this ERK phosporylation, hence inducing synergy. The ITCC-063 trial is evaluating the combination of dexamethasone and selumetinib in paediatric and adult R/R ALL patients (NCT03705507).

The presence of NRAS or KRAS mutations in T-ALL has significant impact on OS, and mutations occur in 9% of T-ALL relapsed patients [68]. MEK inhibitors might be able to re-sensitise patients to steroids, which could be of value in this population with a poor prognosis. [69] Moreover, MEK inhibitors effectively killed *RAS*-mutant infant ALL cells *in vitro*, with trametinib being the most potent compound tested [70]. Trametinib is not yet tested in paediatric patients with acute leukaemia; one trial in R/R juvenile myelomonocytic leukaemia is currently ongoing (NCT03190915).

3.5. Bruton's tyrosine kinase inhibition

Signalling from the BCR is essential for normal B-cell development and controls several cellular functions including proliferation, apoptosis and differentiation. Constitutive activation of the BCR is common in B-cell malignancies, including chronic lymphocytic leukaemia (CLL) and mature B-NHL. Ibrutinib is an oral, potent inhibitor of Bruton's tyrosine kinase (BTK), the kinase responsible for BCR signal transduction [71]. The SPARKLE study (NCT02703272) investigated ibrutinib in paediatric patients with R/R mature B-cell NHL, in combination with either rituximab, ifosfamide, carboplatin, etoposide and dexamethasone (RICE) or rituximab, vincristine, idarubicin, carboplatin, ifosfamide and dexamethasone (RVICI). The phase I part of the study demonstrated that the combination was safe, and preliminary efficacy was promising with 57% response. However, the randomised phase II part stopped enrolment for futility as failed demonstrating the superior EFS in the ibrutinib + RICE/RVICI arm compared with RICE/RVICI alone [72]. In addition, *in vitro* data suggest that deletion of BTK may enhance asparaginase-induced apoptosis, suggesting that therefore ibrutinib combined with asparaginase could enhance efficacy.

3.6. JAK/STAT inhibition

Rearrangements of *CRLF2-R* with frequent concomitant *JAK2* point mutations occur in ~50% of Ph-like ALL cases and induce constitutive JAK/STAT and other kinase signalling. An additional 15–20% of Ph-like ALL carries other JAK pathway alterations that similarly activate JAK/STAT signalling. Ruxolitinib is a potent, selective JAK1/JAK2 inhibitor with demonstrated activity in preclinical Ph-like ALL models. In the ongoing phase II COG AALL 1521 study (NCT02723994), ruxolitinib is administered in combination with multi-agent chemotherapy in patients with Ph-like ALL. The continuous administration of 40 mg/m2/dose × 28 days per cycle was found to be safe and to induce sustained inhibition of phosphorylated STAT5 [73].

3.7. CDK4/CDK6 inhibition

The CDK 4/6-p16-retinoblastoma (Rb) pathway is commonly disrupted in cancer, leading to abnormal cell proliferation. *NOTCH* mutations, a common feature of T-ALL, lead to upregulation of cyclin D3, resulting in CDK4/6 hyperactivation, phosphorylation of Rb and cell cycle progression. Ribociclib and palbociclib are selective inhibitors of CDK4 and CDK6 [74]. Both ribociclib and palbociclib are FDA-approved for hormone receptor-positive/HER2/neu-negative advanced breast cancer when combined with an aromatase inhibitor. A paediatric phase I study with ribociclib in rhabdoid tumours and neuroblastoma has been completed; the most common grade 3-4 adverse event was haematologic toxicity [75]. The phase I COG AINV18P1 trial will test palbociclib in combination with reinduction chemotherapy in children and young adults with relapsed B- or T-lineage ALL (NCT03792256). Another phase I trial (NCT03740334) investigates ribociclib in combination with the mTOR inhibitor everolimus and dexamethasone in R/R paediatric ALL. An important secondary objective is to determine the pharmacokinetic characteristics of ribociclib and everolimus when given in combination with dexamethasone, owing to potential drug–drug interactions related to cytochrome P450 3A4 (CYP3A) metabolism.

3.8. Isocitrate dehydrogenase (IDH) inhibition

Mutations in *IDH1/2* generate high levels of 2-hydroxyglutarate that inhibit various components of the epigenetic machinery including histone and DNA demethylases — impairing cellular differentiation. In adult AML, *IDH1/2* mutations occur in approximately 10% of cases, but in paediatric AML only in 2–4% of cases, mostly in adolescents. [76] Enasidenib is a targeted inhibitor of mutated *IDH2*. In adult AML with *IDH2* mutations, continuous daily enasidenib treatment was generally well-tolerated, with 19.3% of patients with R/R attaining CR [77]. The multicentre, single-arm open-label ESMART trial (NCT02813135) aims to evaluate safety and activity of enasidenib as a single agent in up to 10 R/R AML *IDH2*-mutated paediatric patients. Ivosidenib is an inhibitor of IDH1, currently FDA-approved for adult R/R AML *IDH1*-mutated (or first line in elderly patients with AML). Clinical trials in paediatric AML are not open, but the MATCH trial (NCT04195555) is investigating ivosidenib in paediatric solid tumours and lymphomas with *IDH1* mutations.

3.9. Proteasome inhibition

Bortezomib in combination with chemotherapy has shown an improved CR rate in R/R T/BCP-ALL over historical controls in a COG study [78]. A larger randomised phase III trial in paediatric AML failed to show benefit [79].

Carfilzomib is a second-generation highly selective proteasome inhibitor that showed a better safety profile in terms of peripheral neurotoxicity than that of bortezomib. In 2012, carfilzomib was approved by the FDA and EMA for patients with MM who had received at least two prior therapies. Preclinical models demonstrated that carfilzomib achieved higher levels of proteasome inhibition than bortezomib, suggesting that it may have enhanced clinical activity [80]. The international CFZ2008 study is a phase Ib/II study of carfilzomib in combination with chemotherapy for R/R paediatric ALL (NCT02303821) [81]. During the dose-escalation phase, the UKALLR3 regimen (vincristine, dexamethasone, PEGylated asparaginase and mitoxantrone) was considered too toxic and was replaced with vincristine, dexamethasone, PEGylated asparaginase and daunorubicin (VXLD). The overall remission rate with VXLD-carfilzomib was 67% at the end of consolidation. A phase II study is ongoing (NCT02303821).

3.10. Apoptosis pathway

Venetoclax prevents interaction of the anti-apoptotic protein BCL2 with the pro-apoptotic proteins BIM and BAX, allowing the latter proteins to activate the mitochondrial apoptotic pathway. Venetoclax is FDA- and EMA-approved for adult patients with CLL or small lymphocytic lymphoma, and in combination with hypomethylating agents or low-dose cytarabine for the treatment of newly diagnosed AML in adults not eligible for intensive induction chemotherapy. A phase I/II study of venetoclax in combination with chemotherapy in paediatric patients with different diseases (ALL, AML, NHL, neuroblastoma and other tumours) showed preliminary efficacy in patients with leukaemia at an age or weight-adjusted adult-equivalent target dose of 800 mg [82]. A phase I study of venetoclax in combination with cytarabine, with or without idarubicin, in children and young adults with R/R AML, established the RP2D at 360 mg/m^2 once daily, and overall responses were observed in 69% of the 35 patients [83]. One resistance mechanism to venetoclax may occur through upregulation of the anti-apoptotic protein MCL1. *TP53* activation by the MDM2 inhibitor idasanutlin inhibits intracellular signalling pathways that lead to MCL1 upregulation. Addition of venetoclax to idasanutlin seems to switch the cellular context from the one that favours cell cycle arrest to one that favours cell death [84]. This combination tested in a phase Ib/II study (NCT02670044) enrolling adults with R/R AML led to a CR/Cri rate of 33% [85]. The idasanutlin phase Ib/II paediatric study (NCT04029688) is evaluating idasanutlin in combination with chemotherapy or venetoclax in paediatric AML, ALL and solid tumours including neuroblastoma. Of note, a phase III trial in adults testing idasanutlin in combination with cytarabine in patients with R/R AML was stopped early for futility (NCT02545283). Results of another phase I study in paediatric and adult ALL/LL showed a good safety profile and a promising CR rate of 60%, when venetoclax was combined with low-dose navitoclax, a BCL-XL/BCL-2 inhibitor and chemotherapy [86]. In the PedAL/EuPAL program for R/R AML, a randomised trial between fludarabine-cytarabine (FLA)-GO ± venetoclax will be investigated.

3.11. KMT2A targeting

KMT2A rearrangement occurs both in AML and ALL, involving approximately 15–20% of childhood AML and being particularly common in infant ALL with a prevalence of approximately 75%. Outcomes remain poor for *KMT2A*-r ALL with conventional therapies, and two newer classes of inhibitors have emerged as possible targeted therapies: DOT1L and menin inhibitors. DOT1L is a histone methyltransferase that modifies chromatin of target genes to help maintain the integrity of these genes**.** Preclinical work on cell lines and mice transformed with *KMT2A*-rearranged leukaemia demonstrated activity. However, clinically, the DOT1L inhibitor pinometostat showed only very modest antileukaemic activity as single agent in patients with R/R with *KMT2A-r* acute leukaemia (NCT01684150 and NCT02141828) [87]. Pinometostat is now under investigation in combination with standard chemotherapy (NCT03724084) or zacytidine (NCT03701295) in patients with *KMT2A*-r AML.

Menin inhibitors prevent the binding between MLL and menin, an essential cofactor of the oncogenic component of the *KMT2A* complex that acts as a histone methyltransferase for transcription regulating genes critical to tumour proliferation. Menin inhibitors have demonstrated downregulation of the *Meis-2* and several *HOX*-genes in *KMT2A*-r cell lines, and a survival benefit in *KMT2A*-r leukaemia xenograft mice models across various fusion types [88]. The first in-human trial, NCT04065399, of single-agent SNDX-5613 in adults and children with R/R acute leukaemia showed an ORR of 44% (49% among patients with *KMT2A*-r leukaemia and 30% in patients with *NPM1*-mutated leukaemia) [89]. Another menin-*KMT2A* inhibitor from Kura Oncology-539 has been shown to prolong survival in *KMT2A*-rearranged cell lines and *in vivo* models and has recently entered a phase I/II trial in adults with R/R AML (NCT04067336). *In-vitro* and *ex-vivo* data suggest that combined treatment with a menin inhibitor combined with a DOT1L inhibitor may induce synergy [90].

4. Others

4.1. Recombinant arginase

Arginine is a semi-essential amino acid, with a key role in cell survival and proliferation in both normal and malignant cells. Treatment with BCT-100, a pegylated recombinant human arginase, results in depletion of arginine and starvation of malignant cells in different settings, including leukaemias, hepatocellular carcinoma, melanoma and prostate cancer [91]. The compound was well tolerated in phase 1 trials in adults, with no neutralising antibodies or ammonia formation observed. [92] A phase II trial of BCT-100 in combination with cytarabine for older patients with AML has recently been completed (EudraCT — 2011-000749-19). The phase I/II NCT03455140 trial is currently evaluating the safety and activity of BCT-100 in R/R cancers of children and young adults.

5. Future directions

Immunotherapy in the form of targeted antibodies (and CAR T-cell therapy) represents at present the most promising future direction for haematologic malignancies. InO and blinatumomab are already introduced in front-line treatment for newly diagnosed ALL, as single-agent cycles during consolidation therapy. InO is further tested against regular reinduction therapy in relapsed BCP-ALL and may be more efficacious and less toxic in that setting than regular 4 drug reinduction chemotherapy. Whether similar results may be obtained with anti-CD38 or anti-CD123 (conjugated) antibodies for other subsets of leukaemia needs to be awaited. With the focus on immunotherapy, the urge to develop targeted agents is somewhat diminished; however, for example, BCR-ABL inhibitors have an established role in Ph + -ALL. The development and approval (at least in Europe) of ALK inhibitors is lagging behind despite clear activity in ALCL. The role of MEK-inhibitors, FLT3 inhibitors, menin inhibitors and venetoclax needs to be studied further to assess their added value.

Meetings of the ACCELERATE platform have accelerated paediatric drug development and resulted in the set-up of umbrella trials for AML and NHL lymphoma, respectively, referred to as the PedAL project and the Glo-BNHL project [16,43]. The PedAL project is further initiated and supported by the Leukaemia Lymphoma Society, to mirror the Beat-AML project for adults [93]. Both projects are collaborative initiatives between Europe and the United Statesfacilitating recruitment in these rare patient populations. Another umbrella protocol is in the final stages of design (HemiSMART), and focuses primarily on T-cell ALL with persisting MRD post re-induction therapy, and multiple relapses of BCP-ALL, often after CART and after SCT. Molecular profiling and international tumour boards to facilitate allocation of patients to the best suitable target-based trial or therapy are implemented, and in leukaemia, need to take surface marker expression and potentially also drug response profiling into account.

Considering the growing partnership between collaborative groups in Europe and North America, harmonisation of regulatory incentives on both sites of the Atlantic Ocean is a prerequisite for timely initiation of these early-phase studies [94]. Further development of the academic networks, including sponsorship capabilities, for early phase studies in children with cancer, is needed to accommodate the regulatory requirements associated with ‘intent-to-file’ studies sponsored by academia.

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Conflict of interest statement

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