Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: http://www.tandfonline.com/loi/khvi20

Blinatumomab, a bispecific B-cell and T-cell engaging antibody, in the treatment of B-cell malignancies

Richard Burt, Dana Warcel & Adele K. Fielding

To cite this article: Richard Burt, Dana Warcel & Adele K. Fielding (2018): Blinatumomab, a bispecific B-cell and T-cell engaging antibody, in the treatment of B-cell malignancies, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2018.1540828

To link to this article: https://doi.org/10.1080/21645515.2018.1540828

Accepted author version posted online: 31 Oct 2018.

Publisher: Taylor & Francis

Journal: *Human Vaccines & Immunotherapeutics*

DOI: 10.1080/21645515.2018.1540828

Blinatumomab, a bispecific B-cell and T-cell engaging antibody, in the treatment of B-cell malignancies

Richard Burt[1], Dana Warcel[2] and Adele K. Fielding[1],

1, UCL Cancer Institute, 72 Huntley St London WC1E 6DD

2, UCLH, 235 Euston Road London NW1 2BU

Abstract

Blinatumomab (Blincyto, Amgen), a bi-specific antibody, is a first-in-class, targeted immunotherapy agent for treatment of B-cell malignancies with a novel mechanism of action which involves *in-vivo* engagement of the patient's T cells with CD19-expressing tumour cells. Clinical trials have demonstrated its efficacy in relapsed B-cell Acute Lymphoblastic Leukaemia (B-ALL) and B-cell Non-Hodgkin's Lymphoma including in patients who are refractory to chemotherapy. This review summarises the development and design of Blinatumomab, the outcome of clinical studies demonstrating its efficacy and how to manage the administration, practically, including relevant toxicities. We compare and contrast it to other emerging agents for treatment of B-cell malignancies.

Keywords: Blinatumomab; Acute Lymphoblastic Leukaemia; B-cell Non Hodgkin Lymphoma; Immunotherapeutics

Introduction

B-precursor ALL (B-ALL) and diffuse large B cell lymphoma (DLBLC) have historically been treated with multi-agent chemotherapy regimens with notable success in DLBCL with long-term disease free survival of 50-70%[1,2] and paediatric B-ALL with 5 year event free survival of 80-90%[3-5] reported in a number of studies. The addition of the CD20 monoclonal antibody Rituximab over the past 20 years has led to improved outcomes in both B-NHL[6,7] and more recently the addition of rituximab to standard chemotherapy has improved outcome for patients in whom >20% of B-ALL blasts express CD20[8]. However, patients who have a sub-optimal initial response to chemoimmunotherapy or subsequently relapse have poor outcomes[9-11] with stem cell transplant being a pre-requisite for long term disease free survival[12].

Adults with B-ALL have high initial response rates to induction chemotherapy with approximately 80-90% achieving morphological remission however long-term disease-free survival remains poor at approximately 40% due to both relapse and treatment toxicity[13]. It proves challenging to eradicate minimal residual disease (MRD), which represents residual leukaemic cells post treatment, detected by real time quantitative polymerase chain reaction (RQ-PCR) or flow cytometry to a sensitivity of 1x10-4[14,15]. The presence of MRD after induction chemotherapy is a powerful predictor of both relapse and overall survival as demonstrated by a recent meta-analysis of 16 studies including 2076 patients, concluding MRD negativity was associated with a 10-year event free survival of 64% vs 21% for MRD positivity[16]. Although the addition of allogeneic haematopoietic stem cell transplant (HSCT) to chemotherapy improves outcomes[14], not all patients are fit enough for HSCT and it is

associated with significant morbidity and mortality. Furthermore, relapse risk is still considerable in patients with persistent MRD prior to HSCT[17,18].

Although a minority of children with B-ALL have refractory disease or relapsed ALL[3-5], ALL is the most common cancer in childhood and the absolute numbers of children for whom there has been little or no effective treatment in this setting are considerable.

Development and Design

Blinatumomab is a bi-specific antibody belonging to the family of BiTE antibodies. BiTE antibodies function as adapters that physically link T cells and tumour cells triggering the signalling cascade of the T cell receptor complex by binding to the CD3 receptor[19]. The first report of a bi-specific antibody which targeted cells for antibody-dependent cell-mediated cytotoxicty by cytotoxic T-cells was in 1984[20]. The initial limitations of bi-specific antibodies included low yields, a difficult purification process and dependence on pre-activation or co-stimulation of T-cells to achieve adequate T cell function[21].

Blinatumomab was selected from a panel of bi-specific antibody constructs for it optimal biological activity, demonstrating 100- to 10000-fold higher efficacy in tumour cell lysis than previous constructs[21]. CD19 was selected as the tumour target antigen due to its near universal expression on B cells at all stages of maturation and presumed importance for proliferation and survival[22].

Blinatumomab is a fusion protein composed of two single-chain antibodies (scFvs) with a short non-immunogenic linker sequence of 5 amino acids used to recombinantly link the two scFvs in tandem[20]. The V light-chain (VL) and V heavy-chain (VH) domains of the

antibodies are cloned from anti-CD19 HD37 and anti-CD3 TR66 murine hybridomas. The construct is expressed in Chinese hamster ovary cells and purified by its histidine tail[21]. The resulting 55kDa molecule is one third the size of a typical monoclonal antibody. The name is derived from the term B lineage-specific anti-tumour mouse monoclonal antibody.

The small bispecific antibody construct can transiently link CD19-expressing target cells with cytotoxic T cells by bridging to the CD3ε subunit of the T-cell receptor. The scFv fragments rotate and twist at the flexible link to juxtapose cell membranes for synapse formation. This then triggers a signalling cascade in the T-cell for target cell lysis leading to the release of perforin and granzyme and ultimately target cell lysis[20].

Activated T cells are not mutually lysed in the process and are able to move from one CD19+ cell to another in a continued search and destroy mode. T-cells are engaged in a polyclonal fashion, independent of MHC or antigen presentation, side-stepping immune escape mechanisms employed against specific T-cell responses[21]. Blinatumomab recruits T-cells to CD19+ target cells thus activating T cells for further proliferation, cytokine production and granzyme B release. Blinatumomab's mode of action requires neither T-cell receptor or antigen mediation nor co-stimulation from any other membrane receptor. Polyclonal T-cell recruitment and subsequent activation only occurs when the second arm of the BiTE antibody is bound to its target antigen on the tumour cell surface thus ensuring specificity[19].

Pre-clinical studies with blinatumomab

In vitro

The initial in vitro co-culture experiments of Blinatumomab with T cells and CD19+ cells showed remarkable activity, novel for a BiTE antibody at the time[20]. The half maximal concentration of Blinatumomab for redirected lysis of CD19+ cells by T cells was 10-100pg/ml[20]

In vivo (animal models)

Blinatumomab is only cross-reactive in chimpanzees in whom pharmacodynamics was initially studied[20] with subsequent, rapid transition to a murine model using a surrogate/homologous model. A surrogate biTE® antibody called MuS103 was generated to bind to murine CD3 and CD19 (24). It showed similar pharmacodynamic properties and adverse events[20]. For assessment of Blinatumomab efficacy in a murine model, xenograft models established in NOD/SCID mice were supplanted with resting human T cells. Following treatment with Blinatumomab there was complete inhibition of subcutaneous tumour growth and increased survival in a disseminated tumour model was reported at very low doses of daily intravenous Blinatumomab.

Clinical Studies

Blinatumomab in B-cell Lymphoma

The first in human phase I dose-escalation trials (MT103/I/01)[21] were commenced in 2001 on 21 patients with relapsed or refractory B-NHL (R/R B-NHL) and 1 patient with Chronic Lymphocytic Leukaemia who received Blinatumomab via 2-4 hourly intravenous infusions. All three trials were terminated early, based on lack of objective clinical response with neurological adverse events, cytokine release syndrome and infections being observed. Due to this experience and Blinatumomab's short half-life of 2 hours all subsequent trials have used portable pumps for continuous i.v. infusion over 4-8 weeks.

A subsequent multi-centre phase I trial initiated in 2004 (MT103-104)[23] explored the maximum tolerated dose (MTD) of continuous intravenous infusion of Blinatumomab in patients with R/R B-NHL. 42 patients received treatment in the formal dose-escalation phase which included 4-8 weekly cycles at constant flow. 60µg/m2/day was established as the MTD with neurological events being the main dose-limiting toxicity and 34 additional patients were recruited to evaluate anti-lymphoma activity. For patients treated at the target dose, the overall response rate (OR) was 69%, with responses across B-NHL sub-types (follicular lymphoma 80%, mantle cells lymphoma 71% and diffuse large b-cell lymphoma 55%) with complete response/complete response unconfirmed (CR/CRu) 37%. The median response duration was 404 days. Most clinically relevant adverse events (AEs) were neurological events – occurring in 71% of patients (grade 3 22%), with all neurological events resolving clinically to grade 1 or lower on treatment or after discontinuation.

A subsequent phase II trial commenced in 2012 (NCT01741792)[24] evaluated the efficacy of Blinatumomab in relapsed/refractory diffuse large b-cell lymphoma (R/R B-NHL). Response and safety were evaluated with both stepwise dosing (9-28-112µg/day weekly increases, n = 23) or flat dosing (112µg/day n=2) by continuous infusion with dexamethasone prophylaxis

for cytokine release syndrome. Among 21 evaluable patients, OR was 43%, including CR in 19% and three further patients achieved a late CR in follow-up without any further treatment. Median progression free survival (PFS) was 3.7 months and median overall survival (OS) was 5.0 months. Most commonly reported AEs in stepwise dosing were tremor, pyrexia, fatigue and oedema. The two patients who received flat dosing experienced grade 3 neurological events related to Blinatumomab therapy leading to termination of this arm of the trial.

Blinatumomab in adult B-cell Acute Lymphoblastic Leukaemia with Minimal Residual Disease

Following the findings of the Phase I trials in B-NHL, a Phase II trial for adult patients with B-ALL in complete morphological remission but with MRD persistence or MRD relapse after induction and consolidation treatment was commenced by the GMALL study group in 2008[25,26]. The primary objective was to determine efficacy of Blinatumomab in patients with MRD persistence post chemotherapy. Blinatumomab was administered as a 4-weekly continuous infusion at the lower dose of 15µg/m2/24hr. 16/20 (80%) evaluable patients achieved the primary end-point of MRD negativity, which included 12 patients who had never achieved MRD negative status with conventional chemotherapy. 9 patients subsequently had a HSCT. 81% of patients had grade 3-4 AEs, with the most common being lymphopenia. During the first cycle of treatment there was only one discontinuation of treatment due to a grade 3 seizure and no treatment related deaths. At a median follow-up of 50.8 months following blinatumomab treatment 10 patients (50%) were still in remission,

including 5/9 patients who had a subsequent HSCT patients and 5/11 who had no HSCT (ref).

BLAST, a subsequent larger phase II trial of Blinatumomab in the MRD setting was carried out in 46 centres in Europe and Russia commenced in 2010[27,28]. Eligiblity was for adults with B-ALL in morphological CR but with persistent MRD > 10^{-3} after three course of anti-ALL therapy. Patients in second CR were eligible. The treatment schedule was unchanged. Similar responses were achieved with 88/113 (78%) patients achieving the primary end-point of MRD negativity after the first cycle of therapy and two further patients achieving MRD negativity after the second cycle. In a sub-group of 110 patients with Philadelphia-chromosome negative B-ALL, the estimated relapse free survival (RFS) at 18 months was 54%, with a median RFS of 18.9 months. Seventy-four of 110 (67%) patients underwent HSCT in continued remission. The median RFS in 1st CR was 24.6 months versus 11 months in 2nd or later CR suggesting Blinatumomab may have greater efficacy earlier in the course of the disease. Relevant toxicities included neurological AEs with 12 (10%) and 3 (3%) having grade 3 or 4 neurological events respectively. Four (3%) patients had cytokine release syndrome, all occurring in the first cycle of treatment.

Recently published long-term follow-up of the BLAST trial[27] showed the median OS was 36.5 months with a median follow-up of 30 months, which compares favourably to published data for MRD positive ALL. Forty-eight of 110 patients remained in CR, 38 patients relapsed and 24 died in CR (including 20 patients post HSCT). Nine of 36 (25%) patients without HSCT or further chemotherapy remained in CR at a median follow-up of 24.0 months compared to 36/74 (49%) of patients who had a HSCT. Although the data is clearly suggestive of a beneficial effect of HSCT as consolidation in this setting, notably, a proportion of patients

achieved long-term disease free survival without HSCT or further treatment. Thus raising the possibility Blinatumomab may be curative in a proportion of MRD positive patients without the need for consolidation with a HSCT.

Blinatumomab in Adult Relapsed/Refractory B-cell Acute Lymphoblastic Leukaemia –

Following the success of the initial phase II trial in MRD positive B-ALL, the GMALL group established a phase II trial for relapsed/refractory ALL in 2010[29,30]. The initial dosing schedule was based on the BLAST trial but, following the development of grade 4 cytokine release syndrome in one patient during the dose finding run in, dose modifications were made on the assumption that the greater burden of disease in the R/R setting posed a greater risk for cytokine release. The initial infusion rate was lowered to 5µg/m2/day for the first week and then increased to 15µg/m2/day for subsequent weeks and a pre-phase with dexamethasone or cyclophosphamide was allowed. Twenty five of thirty six (69%) of patients achieved the primary end-point of CR (42%) or CR with incomplete haematological recovery (CRh, 28%) within the first 2 cycles. The highest proportion of patients achieving CR/CRh were those in first salvage (11/11, 100%), followed by patients in second salvage (6/10, 60%), with the proportion of responders lower if they had received a prior HSCT (8/15, 53%). Once again, the data suggested that the benefit of Blinatumomab was greater when given earlier in the course of the disease. Among the 25 patients who responded, 22 (88%) of these achieved a MRD response. Of 25 patients achieving CR/CRh, 13 proceeded to HSCT while still in remission. At a median follow-up of 32.6 months, OS was 13.0 months and median RFS was 8.8 months with 28.9 months of follow-up. The most common grade 3+

AE were comparable to earlier Blinatumomab trials but notably 6/36 (17%) patients had nervous system or psychiatric disorders requiring treatment interruption or permanent discontinuation and two patients developed grade 4 cytokine release syndrome.

Further confirmation of the effectiveness on Blinatumomab in relapsed/refractory ALL was provided by a larger phase 2 trial at 37 centres in Europe and North America[31]. Patients received a flat dose of 9μg/day for the first 7 days and 28μg/day thereafter based on the experience of the previous trial. A dexamethasone pre-phase was given to patients with a high burden of disease. After 2 cycles, 81/189 (43%) patients achieved CR/CRh (33%/10%). 73 patients who achieved CR were evaluable for MRD, 60 (82%) achieved an MRD response, 59 in cycle 1 and 1 in cycle 2. 32/81 (40%) patients who achieved CR subsequently underwent HSCT. Median OS for all 189 patients was 6.1 months. These results compared favourably with a weighted analysis of a historical data set of patients with R/R B-ALL treated with standard of care chemotherapy from Europe/US where the CR rate was 24% with a median OS of 3.3 months[32]. Propensity score analysis estimated increased OR CR/CRh (OR 2.68) and improved OS (HR 0.536) with Blinatumomab. Notably, patients had a better response if they had <50% leukaemic blasts in their bone marrow at initiation of treatment. Toxicities observed were comparable to previous trials of Blinatumomab.

A subsequent randomised phase III trial (TOWER) in 21 countries in 2014[33] confirmed the efficacy of Blinatumomab in the relapsed/refractory setting as compared to standard of care chemotherapy (SOC). Patients were randomised to Blinatumomab or SOC at a ratio of 2:1. Two hundred and sixty seven patients received Blinatumomab and 109 received SOC. OS, the primary end-point, was significantly longer in the Blinatumomab group - 7.7 months vs 4 months (HR for death 0.71, p= 0.01) at a duration of follow-up of 11.7 months and 11.8

months respectively. Remission rates were also significantly higher in the Blinatumomab group: CR 34% vs 16% and CR/CRH 44% vs 25% (both $p < 0.001$). Grade 3 or higher AEs occurred at a comparable frequency in the 2 groups and rates of treatment discontinuation were similar in the two groups: blinatumomab 12% vs chemotherapy 8% (4% vs 1% for neurological and 1% vs 0% for cytokine release syndrome). Patients who received blinatumomab also had better post-treatment quality of life based on descriptive mean changes from baseline compared to chemotherapy[34].

To date the focus had been on Philadelphia chromosome negative ALL. A phase II study (ALCANTARA) in 2014 explored the efficacy of Blinatumomab in patients with R/R B-ALL with the Philadelphia chromosome (Ph+ ALL)[35]. Ph+ ALL are a subgroup of B-ALL that historically have a poorer prognosis. However, the introduction of imatinib and other tyrosine kinase inhibitors (TKI) has significantly improved the outcome in this disease. ALCANTATA enrolled patients who were refractory to at least one second-generation TKI. The infusion schedule was identical to the previous refractory/relapsed trial in ALL. Of 45 patients, 16 (36%) achieved CR and patients responded regardless of prior TKI therapy. 14/16 (88%) of responders achieved complete MRD response. The median RFS was 6.7 months and median OS was 7.1 months at median follow-up of 9 months. Toxicities were comparable to previous trials in relapsed/refractory ALL.

Blinatumomab in paediatric B-cell Acute Lymphoblastic Leukaemia

Although the majority of children with B-ALL are cured with conventional chemotherapy, a significant minority (10-15%) relapse with disease that fails to respond to salvage chemotherapy or have primary refractory disease. In this subset of children, treatment

options are limited and there is a need for novel therapeutic approaches. A phase I dose escalation and phase II study[36] explored the efficacy of Blinatumomab in relapsed and refractory paediatric B-ALL patients in 26 USA and European centres. The phase I trial established 15µg/m2/day as the MTD and as per the adult experience, patients were given a lower dose of 5µg/kg/day for the first week. Of the 70 patients who received the recommended dose – 27 (39%) achieved CR within the first 2 cycles and 14 achieved MRD negativity. 24 (34%) patients went on to receive an HSCT. The most frequent dose limiting toxicity was 3 patients who developed cytokine release syndrome but notably neurological events were rare.

Toxicities

The safety profile of blinatumomab has been studied extensively in recent years[29,31,35]. The most common adverse events which have been consistently reported include neurological events, cytokine release syndrome (CRS) as well as cytopenias, elevated liver enzymes, tumour lysis syndrome, acute pancreatitis and gastrointestinal disorders[29,33]. More recent studies confirm this and suggest that most adverse events occur during the first cycle of treatment with a reduction in incidence in subsequent cycles[33,37]. Moreover data to date suggests that although the most significant treatment related toxicities relate to neurological events or CRS, it is infection which primarily accounts for fatal adverse events[37]. Interestingly, the recent randomised phase III TOWER study reported a lower incidence of grade 3 neutropenia in the blinatumomab arm compared to conventional chemotherapy[33]. In addition, lower rates for grade 3 CRS and neurotoxicity were reported

than previously, 5% and 9% respectively, compared to earlier data reporting an incidence of 15-20%.

Blinatumomab related neurotoxicity can affect up to half of patients and presentations include tremor, dizziness, disorientation, aphasia, convulsions and encephalopathy[31]. The mechanism which underlies this remains unclear, although similar effects have been described with other T-cell based therapies including chimeric antigen receptors (CAR) modified T cells. Most reported cases of blinatumomab related neurotoxicity are mild in nature, decrease in incidence over time and can be managed with dexamethasone treatment without the need for infusion interruption[31]. Evidence to date suggests that the incidence of grade 3-4 neurological events ranges from 9-20%[25,29,31,33]. In those who require treatment interruptions, it appears that most symptoms resolve rapidly as blinatumomab has a short serum half-life of 2 hours and most patients are able to resume treatment after resolution of symptoms[27]. Despite infusion interruptions, it seems response can be maintained in some patients as reported in recent data[31,33].

Cytokine release syndrome, a systemic inflammatory response, can present with fevers, chills, infusion reactions as well as haemodynamic and respiratory compromise. The severity of CRS correlates with tumour burden and is associated with raised inflammatory markers such as C-reactive protein, ferritin and interleukin-6[33]. The incidence of blinatumomab related CRS is variable, between 2-35%, but importantly the incidence of grade 3 CRS, is low 2-5%[31,33]. Blinatumomab is given with a dexamethasone prephase of up to five days and in a stepwise dose escalation fashion of 9mcg/day for 6 days and thereafter 28mcg/day. Evidence to date suggest that these measures, introduced following earlier studies, are likely to account for the low incidence of grade 3-4 blinatumomab related CRS[31].

Regulatory Issues

Blinatumomab was first approved by the Food and Drug Administration Agency (FDA) in September 2014 for use in adults with Philadelphia (Ph) negative relapsed/refractory (R/R) precursor B-cell acute lymphoblastic leukaemia (ALL). This was largely based on key studies evaluating the activity and safety of blinatumomab discussed above[26,29]. From September 2016 the FDA expanded the use of blinatumomab to include children with Ph negative R/R B-cell precursor ALL. Further promising results from the phase II Alcantara study discussed above, led to Blinatumomab being approved by the FDA in July 2017 for use in Ph positive B-cell R/R ALL[35]. More recently, since March 2018, the FDA approved the use of Blinatumomab in minimal residual disease positive patients with precursor B-cell ALL, in view of encouraging results from the Blast Phase II clinical trial[27].

Blinatumomab received full marketing authorisation throughout the European Union, for the treatment of Ph negative B-cell R/R ALL on June 18th 2018, having been under conditional marketing authorisation since November 2015. More recently in July 2018, the European Medicines Agency extended the indication of Blinatumomab use to include children aged 1 year or over with Ph negative CD19 positive R/R B-cell precursor ALL either following 2 prior failed therapies or in the relapse setting post-allogeneic haematopoietic stem cell transplantation.

Blinatumomab is currently not FDA or EMA approved for R/R B-NHL.

Other Products Available for R/R ALL

Two other promising novel approaches, Inotuzumab ozogamicin[38-43] and chimeric antigen receptor – engineered T-cells (CAR-T)[44-46], have recently emerged and demonstrated efficacy in relapsed/refractory B-ALL.

Ionotuzumab Ozogamicin (IO) is a humanized anti-CD22 monoclonal antibody bound via a bifunctional linker to calicheamicin, a potent cytotoxic agent. Upon binding to the surface of the target cell (CD22 expression is restricted to B-cell lineage) the antibody is rapidly internalized leading to programmed cell death[47]. IOs efficacy has been demonstrated in relapsed and refractory ALL in a number of phase II trials [40,42,43] and the recent phase III INO-VATE trial[41] where patients were randomized to IO or standard of care chemotherapy. In the INO-VATE trial IO had a great CR rate (80% vs 29.4%, p<0.001), progression free survival (5.0 months vs 1.8 months, p < 0.001) although OS was comparable (7.7 months vs 6.7 months) as compared to chemotherapy. IO has also demonstrated efficacy in up-front treatment of B-ALL in combination with chemotherapy[38]. Advantages of IO over Blinatumomab include its administration as a weekly injection rather than continuous infusion which can be given as an outpatient and the lack of neurotoxicity and cytokine release syndrome, which is associated with Blinatumomab. However, the risk of liver toxicity is greater with IO including venous occlusive disease (VOD), especially in transplant candidates limiting its use in some patients[39,40].

CAR-T cell therapy uses patient-derived T-cells which are then genetically modified ex vivo to target the CD19 antigen on B-ALL cells. Following encouraging results from paediatric trials[44,45] they have recently been FDA approved for children and young adults. A recently reported long-term follow-up of a phase I study of adults[46] (19-28z CAR-T cell therapy) with

R/R ALL reported a CR rate of 83% with a median OS of 12.9 months. Similar response rates were achieved in the phase II 19-41BB CAR-T cell therapy for children with a CR of 81%. Although the response rates of CAR-T therapy in the R/R setting appear superior to Blinatumomab it is notable in the 19-28z CAR-T trial that 30 of 83 patients recruited were unable to receive the CAR-T therapy mainly due to the advanced disease status of the patients and the delay in manufacturing the patient specific CAR-T cells. Whereas, Blinatumomab and IO are 'off the shelf' products and are not patient specific. However to overcome this limitation of CAR-T therapy, several drug companies are currently developing off-the-shelf, or allogeneic, CAR-T therapies[48]. Furthermore CAR-T therapy is associated with significant toxicity with some trials reporting severe CRS rates of up to 77%[45] and significant neurotoxicity including fatal events[45].

It therefore remains unclear what the optimal treatment of R/R ALL is and a clinical trial comparing Blinatumomab, IO and CAR-T therapy in this setting to answer this important question is planned (NCT03628053).

For R/R B-NHL a number of novel agents have emerged in recent years including Bruton's tyrosine kinase inhibitors[49,50], phosphoinositide 3-kinase inhibitors[51,52], BCL2 inhibitors[53,54], immune checkpoint inhibitors[55], antibody drug conjugates[56,57] and CAR-T therapy[58]. Many of these agents have demonstrated superior efficacy than blinatumomab with less toxicity and more straight-forward administration schedule.

Future Direction and Clinical Trials

The benefit of Blinatumomab as a single agent in both the R/R and MRD positive setting in B-ALL has been clearly demonstrated leading to its FDA approval and increasing use in these settings. Ongoing trials (table) are exploring the benefit of adding Blinatumomab to up-front chemotherapy including in older patients (NCT02003222, NCT02143414), combining Blinatumomab with novel agents including Nivolumab, Ipilimumab, Ibrutinib and TKIs (NCT02879695, NCI-2018-01078, NCT03160079) and a trial exploring the benefit of Blinatumomab post HSCT as maintenance therapy (NCT02807883).

The efficacy of Blinatumomab as a single agent in B-NHL in the R/R setting is less clear and future trials are attempting to delineate this further. Ongoing trials (table) for Blinatumomab in B-NHL (table) include a phase II trial for R/R B-NHL as a single agent (NCT02811679), a phase I trial of Blinatumomab in combination with Lenalidomide for relapsed/refractory B-NHL (NCT02568553), a Phase Ib trial of twice daily subcutaneous Blinatumomab for R/R B-NHL (NCT-2017-01857) and a Phase II/III trial in aggressive R/R B-NHL in patients who fail to achieve CR post 2 cycles of standard platinium-based chemotherapy (NCT-2017-00688).

Conclusion

Blinatumomab is an agent with a novel, first-in-class mechanism of action in the treatment of B-cell malignancies. It has notable efficacy in both R/R B-ALL and MRD positive B-ALL and appears superior to conventional chemotherapy, in at least the R/R setting. Although the short half-life necessitates a continuous infusion this can be given as an outpatient and a trial in B-NHL is exploring whether or not twice daily subcutaneous dosing is effective. The toxicities are manageable and the reported neurotoxicity and cytokine release syndrome

occur only in a minority of patients and are almost always reversible. Ongoing trials will investigate its role in upfront treatment in B-ALL and in combination with chemotherapy or other novel agents. The role of Blinatumomab in R/R B-NHL is less well established and it appears less efficacious than in B-ALL despite the use of higher doses. Further trials will explore its role in combination with other agents and in different sub-types on B-NHL.

References

1 Pfreundschuh, M. *et al.* Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. *Blood* **104**, 634-641, doi:10.1182/blood-2003-06-2095 (2004).

2 Wilson, W. H. *et al.* Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. *Blood* **99**, 2685-2693 (2002).

3 Vora, A. *et al.* Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. *Lancet Oncol* **15**, 809-818, doi:10.1016/S1470-2045(14)70243-8 (2014).

4 Moricke, A. *et al.* Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. *Leukemia* **24**, 265-284, doi:10.1038/leu.2009.257 (2010).

5 Hunger, S. P. *et al.* Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol* **30**, 1663-1669, doi:10.1200/JCO.2011.37.8018 (2012).

6 Coiffier, B. *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* **346**, 235-242, doi:10.1056/NEJMoa011795 (2002).

7 Pfreundschuh, M. *et al.* Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol* **9**, 105-116, doi:10.1016/S1470-2045(08)70002-0 (2008).

8 Maury, S. *et al.* Rituximab in B-Lineage Adult Acute Lymphoblastic Leukemia. *N Engl J Med* **375**, 1044-1053, doi:10.1056/NEJMoa1605085 (2016).

9 Fielding, A. K. *et al.* Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood* **109**, 944-950, doi:10.1182/blood-2006-05-018192 (2007).

10 Oriol, A. *et al.* Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. *Haematologica* **95**, 589-596, doi:10.3324/haematol.2009.014274 (2010).

11 Tavernier, E. *et al.* Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. *Leukemia* **21**, 1907-1914, doi:10.1038/sj.leu.2404824 (2007).

12 Fielding, A. K. Current therapeutic strategies in adult acute lymphoblastic leukemia. *Hematol Oncol Clin North Am* **25**, 1255-1279, viii, doi:10.1016/j.hoc.2011.09.008 (2011).

13 Rowe, J. M. *et al.* Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. *Blood* **106**, 3760-3767, doi:10.1182/blood-2005-04-1623 (2005).

14 Bruggemann, M. *et al.* Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. *Blood* **107**, 1116-1123, doi:10.1182/blood-2005-07-2708 (2006).

15 Farahat, N. *et al.* Detection of minimal residual disease in B-lineage acute lymphoblastic leukaemia by quantitative flow cytometry. *Br J Haematol* **101**, 158-164 (1998).

16 Berry, D. A. *et al.* Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. *JAMA Oncol* **3**, e170580, doi:10.1001/jamaoncol.2017.0580 (2017).

17 Bassan, R. *et al.* Different molecular levels of post-induction minimal residual disease may predict hematopoietic stem cell transplantation outcome in adult Philadelphia-negative acute lymphoblastic leukemia. *Blood Cancer J* **4**, e225, doi:10.1038/bcj.2014.48 (2014).
18 Gokbuget, N. *et al.* Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. *Blood* **120**, 1868-1876, doi:10.1182/blood-2011-09-377713 (2012).
19 Nagorsen, D. *et al.* Immunotherapy of lymphoma and leukemia with T-cell engaging BiTE antibody blinatumomab. *Leuk Lymphoma* **50**, 886-891, doi:10.1080/10428190902943077 (2009).
20 Nagorsen, D., Kufer, P., Baeuerle, P. A. & Bargou, R. Blinatumomab: a historical perspective. *Pharmacol Ther* **136**, 334-342, doi:10.1016/j.pharmthera.2012.07.013 (2012).
21 Oak, E. & Bartlett, N. L. Blinatumomab for the treatment of B-cell lymphoma. *Expert Opin Investig Drugs* **24**, 715-724, doi:10.1517/13543784.2015.1021415 (2015).
22 Otero, D. C. & Rickert, R. C. CD19 function in early and late B cell development. II. CD19 facilitates the pro-B/pre-B transition. *J Immunol* **171**, 5921-5930 (2003).
23 Goebeler, M. E. *et al.* Bispecific T-Cell Engager (BiTE) Antibody Construct Blinatumomab for the Treatment of Patients With Relapsed/Refractory Non-Hodgkin Lymphoma: Final Results From a Phase I Study. *J Clin Oncol* **34**, 1104-1111, doi:10.1200/JCO.2014.59.1586 (2016).
24 Viardot, A. *et al.* Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma. *Blood* **127**, 1410-1416, doi:10.1182/blood-2015-06-651380 (2016).
25 Topp, M. S. *et al.* Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. *J Clin Oncol* **29**, 2493-2498, doi:10.1200/JCO.2010.32.7270 (2011).
26 Topp, M. S. *et al.* Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. *Blood* **120**, 5185-5187, doi:10.1182/blood-2012-07-441030 (2012).
27 Gokbuget, N. *et al.* Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood* **131**, 1522-1531, doi:10.1182/blood-2017-08-798322 (2018).
28 Gokbuget, N. *et al.* Long-term relapse-free survival in a phase 2 study of blinatumomab for the treatment of patients with minimal residual disease in B-lineage acute lymphoblastic leukemia. *Haematologica* **102**, e132-e135, doi:10.3324/haematol.2016.153957 (2017).
29 Topp, M. S. *et al.* Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *J Clin Oncol* **32**, 4134-4140, doi:10.1200/JCO.2014.56.3247 (2014).
30 Zugmaier, G. *et al.* Long-term survival and T-cell kinetics in relapsed/refractory ALL patients who achieved MRD response after blinatumomab treatment. *Blood* **126**, 2578-2584, doi:10.1182/blood-2015-06-649111 (2015).
31 Topp, M. S. *et al.* Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol* **16**, 57-66, doi:10.1016/S1470-2045(14)71170-2 (2015).
32 Gokbuget, N. *et al.* Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia. *Blood Cancer J* **6**, e473, doi:10.1038/bcj.2016.84 (2016).
33 Kantarjian, H. *et al.* Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med* **376**, 836-847, doi:10.1056/NEJMoa1609783 (2017).
34 Topp, M. S. *et al.* Health-related quality of life in adults with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab. *Blood* **131**, 2906-2914, doi:10.1182/blood-2017-09-804658 (2018).

35 Martinelli, G. *et al.* Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study. *J Clin Oncol* **35**, 1795-1802, doi:10.1200/JCO.2016.69.3531 (2017).
36 von Stackelberg, A. *et al.* Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. *J Clin Oncol* **34**, 4381-4389, doi:10.1200/JCO.2016.67.3301 (2016).
37 Stein, A. S. *et al.* Exposure-adjusted adverse events comparing blinatumomab with chemotherapy in advanced acute lymphoblastic leukemia. *Blood Adv* **2**, 1522-1531, doi:10.1182/bloodadvances.2018019034 (2018).
38 Kantarjian, H. *et al.* Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study. *Lancet Oncol* **19**, 240-248, doi:10.1016/S1470-2045(18)30011-1 (2018).
39 Kantarjian, H. M. *et al.* Patient-reported outcomes from a phase 3 randomized controlled trial of inotuzumab ozogamicin versus standard therapy for relapsed/refractory acute lymphoblastic leukemia. *Cancer* **124**, 2151-2160, doi:10.1002/cncr.31317 (2018).
40 Jabbour, E. *et al.* Salvage Chemoimmunotherapy With Inotuzumab Ozogamicin Combined With Mini-Hyper-CVD for Patients With Relapsed or Refractory Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: A Phase 2 Clinical Trial. *JAMA Oncol* **4**, 230-234, doi:10.1001/jamaoncol.2017.2380 (2018).
41 Kantarjian, H. M. *et al.* Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. *N Engl J Med* **375**, 740-753, doi:10.1056/NEJMoa1509277 (2016).
42 Kantarjian, H. *et al.* Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. *Cancer* **119**, 2728-2736, doi:10.1002/cncr.28136 (2013).
43 Kantarjian, H. *et al.* Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. *Lancet Oncol* **13**, 403-411, doi:10.1016/S1470-2045(11)70386-2 (2012).
44 Grupp, S. A. *et al.* Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med* **368**, 1509-1518, doi:10.1056/NEJMoa1215134 (2013).
45 Maude, S. L. *et al.* Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med* **378**, 439-448, doi:10.1056/NEJMoa1709866 (2018).
46 Park, J. H. *et al.* Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. *N Engl J Med* **378**, 449-459, doi:10.1056/NEJMoa1709919 (2018).
47 Uy, N., Nadeau, M., Stahl, M. & Zeidan, A. M. Inotuzumab ozogamicin in the treatment of relapsed/refractory acute B cell lymphoblastic leukemia. *J Blood Med* **9**, 67-74, doi:10.2147/JBM.S136575 (2018).
48 The Quest for Off-the-Shelf CAR T Cells. *Cancer Discov* **8**, 787-788, doi:10.1158/2159-8290.CD-ND2018-005 (2018).
49 Maddocks, K. *et al.* A phase 1/1b study of rituximab, bendamustine, and ibrutinib in patients with untreated and relapsed/refractory non-Hodgkin lymphoma. *Blood* **125**, 242-248, doi:10.1182/blood-2014-08-597914 (2015).
50 Wang, M. L. *et al.* Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* **369**, 507-516, doi:10.1056/NEJMoa1306220 (2013).
51 Dreyling, M. *et al.* Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. *Ann Oncol* **28**, 2169-2178, doi:10.1093/annonc/mdx289 (2017).
52 Gopal, A. K. *et al.* PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med* **370**, 1008-1018, doi:10.1056/NEJMoa1314583 (2014).

53 Davids, M. S. *et al.* Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma. *J Clin Oncol* **35**, 826-833, doi:10.1200/JCO.2016.70.4320 (2017).
54 de Vos, S. *et al.* Venetoclax, bendamustine, and rituximab in patients with relapsed or refractory NHL: a phase 1b dose-finding study. *Ann Oncol*, doi:10.1093/annonc/mdy256 (2018).
55 Lesokhin, A. M. *et al.* Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. *J Clin Oncol* **34**, 2698-2704, doi:10.1200/JCO.2015.65.9789 (2016).
56 Trneny, M. *et al.* A phase II multicenter study of the anti-CD19 antibody drug conjugate coltuximab ravtansine (SAR3419) in patients with relapsed or refractory diffuse large B-cell lymphoma previously treated with rituximab-based immunotherapy. *Haematologica* **103**, 1351-1358, doi:10.3324/haematol.2017.168401 (2018).
57 Palanca-Wessels, M. C. *et al.* Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: a phase 1 study. *Lancet Oncol* **16**, 704-715, doi:10.1016/S1470-2045(15)70128-2 (2015).
58 Kochenderfer, J. N. *et al.* Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol* **33**, 540-549, doi:10.1200/JCO.2014.56.2025 (2015).

Table 1 Reported Clinical Trials

Primary Investigator	Indication	Phase	No. of patients	Treatment regimen	Response	Overall Survival
Goebeler et al. 2016[23]	Adult R/R B-NHL	I	76	Continuous infusion, escalating doses. MTD 60µg/m²/day given in n=35	At MTD: ORR FL = 80% MCL = 71% DLBCL = 55% Other = 50%	Not available (Median response duration 404 days)
Viardot et al. 2016[24]	Adult R/R DLBCL	II	25	Continuous infusion with weekly dose escalation, to target 112 µg/day	ORR 43%	5.0 months
Topp et al. 2011[25]	Adult MRD positive B-ALL	II	21	Continuous infusion 15 µg/m²/day	80% MRD response	Not available (At median follow-up 50.8 months 50% still in remission)
Gökbuget et al. 2017[28]	Adult MRD positive B-ALL	II	116	Continuous infusion 15 µg/m²/day	78% MRD response post cycle 1, 80% MRD response overall	36.4 months
Topp et al. 2014[29]	Adult R/R B-ALL	II	36	5-30 µg/m²/day	69% CR/CRh (88% MRD response post cycle 1)	9.8 months
Topp et al. 2015[31]	Adult R/R B-ALL	II	189	9 µg/day for first	43% CR/CRh	6.1 months

				week cycle 1, 28 µg/day thereafter	(82% MRD response)	
Martinelli et al. 2015[35]	Adult Ph-positive R/R B-ALL	II	45	9 µg/day for first week cycle 1, 28 µg/day thereafter	CR/CRh 36% (86% MRD response)	7.1 months
Kantarjian et al. 2017[33]	Adult R/R B-ALL	III	405 (B: 271, SOC 134)	9 µg/day for first week cycle 1, 28 µg/day thereafter	B: 46% CR/CRh SOC: 28% CR/CRh	B: 7.8 months SOC: 4.0 months
Von Stackelberg et al. 2016[36]	Paediatric R/R B-ALL	I/II	70 (at recommended dosage)	In phase II: 5 µg/m²/day for first week, 15 µg/m²/day thereafter	38.6% CR	7.5 months

B-NHL: B-cell non Hodgkin lymphoma, B-ALL: B-cell precursor acute lymphoblastic leukaemia; FL: follicular lymphoma; MCL: mantle cell lymphoma; DLBCL: diffuse large B-cell lymphoma; R/R: relapsed or refractory; MRD: minimal residual disease; Ph: Philadelphia chromosome; ORR: overall response rate; CR: complete response; CRh: complete response with incomplete haematologic recovery; SOC: standard of care;

Table 2 Ongoing/Planned Clinical Trials for B-NHL

Phase	Sponsor	Clinical trial identifier	Condition	Concomitant medication	Primary end point
I	NCI	NCT02568553	R/R B-NHL	Lenalidomide	MTD
I	Washington University School	NCT03072771	DLBCL post ASCT	BEAM ASCT	DLT/AE

	of Medicine				
Ib	Amgen	NCT02961881	R/R indolent B-NHL	None	DLT/AE
Ib	Amgen	NCT03340766	R/R DLBCL	Pembrolizumab	DLTs
II	Amgen	NCT02811679	R/R indolent B-NHL	None	ORR
II	Amgen	NCT03023878	High-risk DLBCL	Following up-front chemotherapy	Incidence/Severity AE
II	MDACC	NCT03121534	Richter's transformation	Dexamethasone	ORR
II	Amgen	NCT03298412	MRD positive DLBCL post ASCT	None	MRD negativity
II/III	Amgen	NCT02910063	R/R aggressive B-NHL	None vs. IC chemotherapy	CMR

B-NHL: B-cell non Hodgkin lymphoma, DLBCL: diffuse large B-cell lymphoma; NCI: National Cancer Institute; MDACC: MD Anderson Cancer Centre; R/R: relapsed or refractory; MRD: minimal residual disease; IC: Investigator's choice; ASCT: Autologous stem cell transplant; MTD: maximum tolerated dose; DLT: dose limiting toxicities; AE: adverse events ORR: overall response rate; CMR: complete metabolic response;

Table 3 Ongoing/Planned Clinical Trials for B-ALL

Phase	Sponsor	Clinical trial identifier	Condition	Concomitant medication	Primary end point
Pilot study	SKCCC John Hopkins	NCT03114865	Adult B-ALL post ASCT	None	OS
I	NCI	NCT02879695	R/R B-ALL	Nivolumab or nivolumab + ipilimumab	Safety MTD
I/II	Amgen	NCT02412306	R/R B-ALL Japanese adults	None	Phase I: DLT Phase II:

					CR
I/II	City of Hope Medical Centre	NCT03512405	R/R adult B-ALL	Pembrolizumab	Phase I: safety Phase II: CR/CRh
I/II	University of California	NCT03160079	R/R B-ALL	Pembrolizumab	Phase I: safety Phase II: ORR
II	MDACC	NCT02877303	De novo B-ALL ≥ 14 yr.	Hyper-CVAD	RFS
II	MDACC	NCT02458014	Adult B-ALL in CR1/CR2 MRD positive	None	RFS
II	MDACC	NCT02807883	B-ALL post ASCT in adults	None	GvHD, NRM, graft failure
II	MDACC	NCT03263572	*de novo* Ph positive B-	Ponatinib	CR

			ALL		
II	NCI	NCT02143414	De novo B-ALL ≥ 65 yr	Combination chemotherapy or dasatinib	CR
II	University of California	NCT02997761	R/R B-ALL	Ibrutinib	CR
II	GIMEMA	NCT02744768	Adults *de novo* Ph positive B-ALL	Dasatinib	CR
II	Goethe University	NCT03480438	De novo older adult B-ALL	Standard chemotherapy	CR MRD
II	JWG University Hospital	NCT03109093	Adults MRD positive B-ALL	None	MRD
II	MDACC	NCT03518112	R/R adult B-ALL	Mini-Hyper-CVD	EFS
II	PETHEMA	NCT03523429	De novo adult B-ALL	Standard chemotherapy	MRD
II	GIMEMA	NCT03367299	De novo	Standard chemotherapy	MRD

			adult B-ALL		
II	HOVON	NCT03541083	De novo adult B-ALL	Standard chemotherapy	MRD
II/III	St Jude Children's Research Hospital	NCT03117751	Refractory B-ALL	Standard combination chemotherapy	EFS
III	Amgen	NCT02393859	Paediatric B-ALL in first relapse	Chemotherapy Comparison with standard chemotherapy	EFS
III	NCI	NCT02101853	Patients 1-30 yr. B-ALL in first relapse	Comparison with standard chemotherapy +/- ASCT	DFS
III	NCI	NCT02003222	De novo adult B-ALL	+/- standard chemotherapy	OS
III	Amgen	NCT03476239	R/R B-ALL Chinese adults	None	CR/CRh

III	Novartis	NCT03628053	R/R adult B-ALL	Tisagenlecleucel vs IC Blinatumomab/Inotuzumab	OS
III	Martin Schrappe	NCT03643276	De novo paediatric B-ALL	Standard chemotherapy	EFS/DFS

NCI: National Cancer Institute; MDACC: MD Anderson Cancer Centre; GIMEMA: Gruppo Italiano Malattie EMatologiche dell'Adulto; SKCCC: Sidney Kimmel Comprehensive Cancer Centre; JWG: Johann Wolfgang Goethe; HOVON: Stichting Hemato-Oncologie Volwassenen Nederland; PETHEMA: Programa para el Tratamiento de Hemopatías Malignas; B-ALL: B-cell precursor acute lymphoblastic leukaemia; R/R: relapsed or refractory; CR: complete response; MRD: minimal residual disease; Ph: Philadelphia chromosome; ASCT: Allogeneic stem cell transplant; IC: Investigator's choice; DLT: dose limiting toxicities; ORR: overall response rate; MTD: maximum tolerated dose; RFS: relapse free survival; GVHD: graft versus host disease; NRM: non-relapse mortality; OS: overall survival; EFS: event free survival; DFS: disease free survival; CRh: complete response with incomplete haematologic recovery