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REVIEW ARTICLE

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The pharmacology of blinatumomab: state of the art on pharmacodynamics, pharmacokinetics, adverse drug reactions and evaluation in clinical trials

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Abstract

What is known and objective: Bispecific drugs (BDs) belong to the family of immunotherapies along with checkpoint inhibitors and CAR-T cells. In the field of oncology, BDs are designed to simultaneously bind a tumour antigen on the one side and an antigen present on the surface of effector cells on the other. This review summarizes the information available to date on the first marketed BiTE-format bispecific antibody, blinatumomab BLINCYTO® in acute lymphoblastic leukaemia.

Methods: A literature search was conducted in the PubMed database by including studies published in English using the term blinatumomab. Furthermore, bibliographies of selected references were also evaluated for relevant articles. Clinical trial (CT) data were retrieved from clinicaltrials.gov (ongoing trials, adverse events [AEs]) and global pharmacovigilance data were retrieved from VigiBase®.

Results and discussion: Blinatumomab is a fusion protein which consists of two single-chain variable fragments arranged in tandem: the first binds the CD19 surface antigen of all B cells and the second targets the CD3 antigen of T cells. Binding of blinatumomab to B and T cells induces apoptosis of B cells after secretion of granzymes and perforins by T cells. T-cell activation results in secretion of pro-inflammatory cytokines and upregulation of activation markers and adhesion molecules on the surface of T cells. The major CTs that led to an indication show increased overall survival with blinatumomab with better efficacy in patients in haematological remission with minimal residual disease $\geq 10^{-3}$. The major AEs are cytokine release syndrome, neurotoxicity and hypogammaglobulinemia. The three most frequent system organ classes in CTs are haematological, gastrointestinal and general disorders. These results are also found in VigiBase® but neurological disorders and infections appear more frequently in real life.

What is new and conclusion: This review summarizes the current knowledge of blinatumomab in the literature. The subject of many CTs is to improve the route of administration and expand the indications for treatment.

KEYWORDS
acute lymphoblastic leukaemia, bispecific antibody, blinatumomab, pharmacovigilance

1 | WHAT IS KNOWN AND OBJECTIVE

Research into the development of treatments that act on the modulation of the immune response for anti-cancer purposes dates back several decades, in particular with the intratumoral injections of *Streptococcus pyogenes* by Dr. William COLEY.[1] However, the advent of the term immunotherapy came with the first checkpoint inhibitors in the 2010s. Immunotherapy strategies are now complemented by CAR-T (chimeric antigen rforeceptor-T) cells and bispecific drugs. These drugs use a cell of the immune system (T cell, NK cell, etc.) as a direct or indirect target to promote the recognition of tumour cells as a foreign body.

Bispecific drugs are genetically engineered proteins. They are antibody sequences of interest capable of recognizing two or more different epitopes simultaneously. They are designed to bind an antigen expressed by the tumour tissue on one side and an antigen present on the surface of the effector cells on the other (often the CD3 of T cells). These antibodies recruit effector cells and concentrate the activity of the immune system in the tumour environment. Such binding abilities bring the T cell physically closer to the tumour cell. The family of bispecific drugs is composed of two main types, according to the presence or absence of the crystallizable fragment (Fc) of the antibodies from which they are derived. Several formats are being developed with complex constructs and a wide variety of targets are being evaluated. Blinatumomab is the first BiTE-format drug in the bispecific class to obtain a marketing authorization. It is indicated for the treatment of acute lymphoblastic leukaemia (ALL).

This drug has been the subject of many clinical trials and the scientific data are scattered across different works. Therefore, the objective of this work was to collect and summarize the information available to date on the first bispecific antibody marketed, blinatumomab BLINCYTO®.

2 | METHODS

A literature search was conducted in the PubMed database for studies published in English between 2006 and 2021 having the word blinatumomab. The bibliographies of the selected articles were also assessed for relevant articles. Collection for this review was limited to the most recent available human data and only with the pathology ALL.

The referenced clinical trials that evaluate blinatumomab were identified from the ClinicalTrials website: www.clinicaltrials.gov. Data from each trial were analysed to investigate the following parameters: phase, status (active, not recruiting, recruiting, completed, suspended, and terminated), study results, pathology and estimated number of patients enrolled. Adverse event (AE) data from the three main trials that led to the first marketing approvals were examined.[2–5] Considering that the referencing of AEs was different from one trial to another in the articles, we chose to study AEs via the ClinicalTrials website. An analysis was performed by selecting the serious AEs, defined as 'an adverse event that results in death, is life-threatening, requires inpatient hospitalization or extends a current hospital stay, results in an ongoing or significant incapacity or interferes substantially with normal life functions, or causes a congenital anomaly or birth defect. Medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered serious adverse events if they put the participant in danger or require medical or surgical intervention to prevent one of the results listed above'. The data presented for serious AEs were selected for AEs that occurred with a frequency of more than 1% for all the patients exposed in the three trials. An analysis of data from serious and non-serious AEs was carried out by presenting only AEs that occurred with a frequency of more than 10% for all patients exposed in the three trials.

Pharmacovigilance data were analysed from the World Pharmacovigilance Bank: VigiBase®. In May 2022, VigiBase® contained >30 million individual case safety reports (ICSRs) from 127 countries. Each ICSR consists of a description of the drugs that are suspected of causing adverse drug reactions and contains information on patient age, gender, medical history, country, drugs taken, and drug initiation and stop dates. The 10 most common system organ classes (SOC) for blinatumomab were examined.

3 | RESULTS AND DISCUSSION

3.1 | Drug composition

Blinatumomab is a member of the bispecific family of drugs, specifically the Bispecific T-cell Engager (BiTE) antibodies.[6] During the development evaluation studies, it was described as MT103, MEDI-538,[7] bscCD19xCD3[6] or AMG103.[8] It was named according to the World Health Organization (WHO) rules, which resulted in blinatumomab, which stands for 'B-lineage-specific antitumor mouse monoclonal antibody'.[7] The size is 504 amino acids,[9] approximately one-third of a traditional antibody[7] with a molecular weight of approximately 55 kDa.[10] The fact that it is smaller than an antibody is presented as an advantage for better intra-tumour penetration.[11] It is a non-glycosylated fusion protein[12] consisting of two single-chain variable fragments (scFv) arranged in tandem.[13] The first scFv fragment is directed against the CD19 surface antigen of all B cells (healthy or malignant[6]), except haematopoietic stem cells and plasma cells which do not display this antigen.[14] The second scFv fragment targets the

epsilon subunit of the CD3 invariant antigen of the T-cell TCR[13,15,16] (Figure 1). Each scFv fragment consists of a large binding sequence. The fragments are linked together by a flexible, non-immunogenic, non-glycosylated linkage of 5 amino acids (4 glycine and 1 serine[11]).[10,17] The sequence that links the two fragments must allow a high degree of rotational flexibility so that each epitope present on the cells of interest can be bound simultaneously.[10]

Blinatumomab is genetically engineered using the recombinant DNA technique (requiring the respective cDNAs of the four variable domains and three binding sequences). The CD19-targeting scFv is derived from the parental murine monoclonal antibody HD37 and is placed N-terminally in the final molecule. The CD3-binding scFv is produced from the parental murine monoclonal antibody L2K-07 and is located on the C-terminal to the final molecule.[10,18] The drug is produced in hamster ovary cells in both monomeric and dimeric forms (biologically active forms): only the monomeric form is purified due to its superior biological and pharmaceutical properties.[10,19]

3.2 | Pharmacodynamics and effects of blinatumomab

After infusion, blinatumomab is thought to bind preferentially to B cells (due to a higher affinity) and then to T cells.[11] This binding forces B and T cells to come together and form a structurally normal cytolytic immune synapse similar to that found in physiological situations.[16,20] In T cells, activation events trigger the migration of vesicles containing granzymes and perforins to the cell membrane to deliver these cytotoxic contents[20] into the synaptic space. Perforins create pores in the membrane of target cells in the presence of extracellular calcium. These pores allow the penetration of granzymes which will induce apoptosis of the targeted B cells. In fact, granzyme B cleaves pro-caspases (3 and 7[21]) and itself acts as a caspase by cleaving substrate proteins such as activated caspases.[20] The consequences could be DNA fragmentation, membrane damage and cleavage of poly-ADP ribose polymerases, resulting in the release of the cytosolic contents of B cells.[20]

It is important to note the following:

- Recruitment of polyclonal T cells and their activation only occur when the second arm of blinatumomab binds to the target cell antigen. A single binding of blinatumomab to the T cell is not sufficient to activate it.[12,22]
- The major histocompatibility complex (MHC) is not required to activate T cells, so antigen presentation is not required,[12] nor is TCR specificity or the presence of co-stimulatory molecules (interleukin-2 [IL-2], CD28).[11,14] This is advantageous because MHC is often absent or down-regulated in tumour cells.[23]
- Cytotoxic T cells have a high lytic potential because few CD3 receptors are engaged, the lytic mode is rapidly established and proliferation occurs following binding to the activation site.[24] In fact, an activated T cell can kill several target B cells.[25]
- There is a low incidence of immunogenicity with less than 1% of patients developing neutralizing anti-drug antibodies.[26]
- The therapeutic effect depends on 3 key points: T-cell activity, T-cell to target B-cell ratio and time to form a cytolytic synapse.[27]

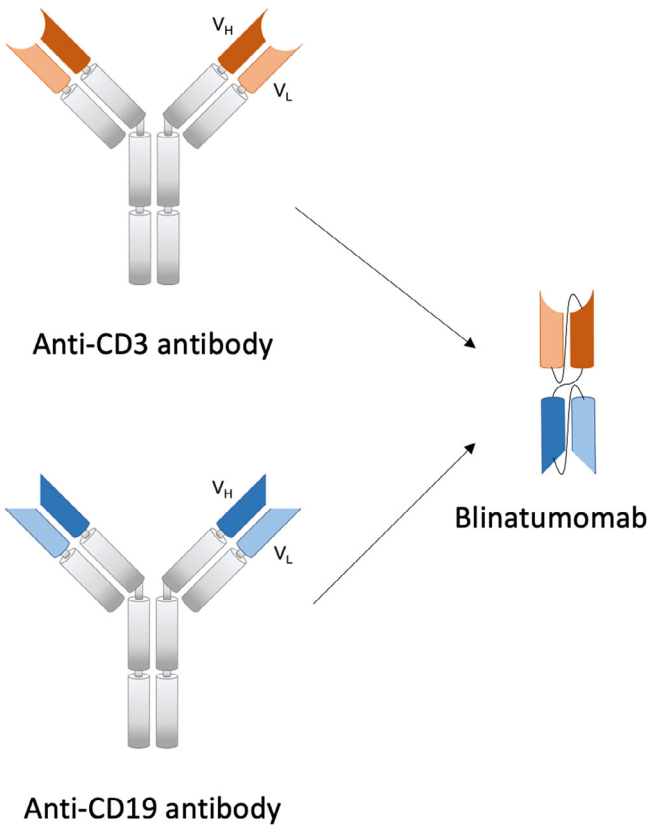

FIGURE 1 Structure of blinatumomab

3.3 | Blinatumomab effects on blood cells

After administration of blinatumomab, T cells disappear from the bloodstream (between 2 and 6 h after the start of the blinatumomab infusion). They then return to basal levels within 7–10 days[28] and exceed this threshold within a few days.[7] Such kinetics suggests redistribution rather than elimination.[12]

The early disappearance of T cells may be due to either increased adhesion to the vascular endothelium or their extravasation triggered by monovalent blinatumomab-$CD3^+$ T-cell binding.[7] The phenomenon of cell expansion can be explained by the proliferation of memory effector T cells[24] following stimulation by cytokines. This proliferation would occur locally to increase the level of T cells in the target tissue.[20]

The T-cells that predominantly expand after blinatumomab binding are the $CD8^+$ and $CD4^+$ memory effector cells that have a $CD45RA^-/CCR7^-$ phenotype (CCR7 also known as CD197[29]).[20,24] $CD8^+$ cells with a naive, central memory phenotype and $CD45RA^+$ memory effectors have more or less constant levels.[24]

T-cell activation is mediated by the binding of blinatumomab to these cells and to B cells.[6] This activation is accompanied by the upregulation of activation markers such as CD69 and CD25 and adhesion molecules CD2 and LFA-1 (lymphocyte function-associated antigen-1) on the surface of T cells.[6] The markers CD69 and CD25 have peak levels in 2 and 3 days, respectively, and both persist for up to 6 days.[6] CD2 has a maximum expression 72 hours after administration and LFA-1 has a level that increases up to 6 days. LFA-1 is thought to switch from a low affinity to an intermediate conformation, which favours binding to ICAM (intercellular adhesion molecule).[28]

In addition, angiotensin-2 (a marker of endothelial activation) levels were shown to increase 6 hours after the start of blinatumomab infusion and to return to normal within 7 days.[28] T-cell activation is also thought to induce the production of granzymes and perforins to fill the vesicles required for serial lysis by T cells.[20]

When patients are treated with higher doses of the drug, T-cell levels increase several-fold from baseline, which correlates with the expression of the activation markers CD69 and CD25 with a higher proportion for $CD8^+$ T-cells.[24]

It is important to note that:

- On the subsequent treatments, patients show a transient decrease in T-cell count with an accelerated return to basal status compared to the first treatment cycle.[29]
- Despite constant exposure to blinatumomab for several months, there was no evidence of uncontrolled T-cell activation or signs of T-cell anergy.[15]
- A low level of circulating regulatory T cells is thought to be associated with a better response to blinatumomab in patients with B-precursor ALL.[30]
- T-cell parameters are not different between responders and non-responders.[29]

On the first day of infusion, the B-cell count decreases rapidly: it falls by 50% within 1 hour and then by 90% within 4 hours,[11] and below the detection limit within 2 days (less than one B-cell per microliter[11]). The B-cell level remains undetectable throughout the infusion period.[7] The absence of B cells during continuous infusion of blinatumomab is mainly explained by their death by apoptosis rather than by redistribution.[29]

This decrease in $CD19^+$ B-cell count is also thought to be accompanied by an increase in annexin V, which is a marker of early apoptosis.[24,29] In addition, it is important to note that B cells are not cleared from the bloodstream in many non-responders.[31]

3.4 | Blinatumomab effects on cytokines

Binding of blinatumomab to T and B cells induces secretion of pro-inflammatory cytokines such as IL-2, TNF-alpha (tumour necrosis factor–alpha), IFN-gamma (interferon–gamma), IL-6 and IL-10, by peripheral T cells[6] (IL-4 is not detectable[29]). The three cytokines with the highest blood concentrations are, in descending order, IL-10, IL-6 and IFN-gamma.[29] These cytokine peaks are transient, short-lived and self-limiting.[32] This massive secretion of cytokines is detectable during the first 2 days with maximum concentrations obtained on the first day. After these 2 days, the concentrations decrease rapidly until they become undetectable. These peaks would not be repeated in the subsequent cycles.[29] However, it is important to note that there is significant inter-individual variability in the levels of cytokines measured during blinatumomab administration and that the cytokine peaks obtained do not correlate with the clinical response to blinatumomab.[29]

3.5 | Mechanisms of resistance

Several mechanisms of resistance are described in the literature. It is still difficult to establish the degree of involvement of each of the mechanisms:

- Target antigen density,[33] variation in target antigen expression,[34] disruption of CD19 membrane export to the post-endoplasmic reticulum compartment responsible for loss of CD19 surface expression,[35] the presence of a partial deletion of exon 2 of the CD19 gene, CD19 ex2part,[36] a low level of CD19 RNA expression and the presence of a mutation in the CD19 chaperone protein, CD81.[36]
- Expression of proteins that block perforin/granzyme and caspase-induced apoptosis (e.g., concanamycin A and calcium chelating agents are perforin inhibitors[16,37]; aprotinin is a granzyme inhibitor[37]; caspase inhibitors[37]).
- Secretion of molecules that interfere with T-cell adhesion,[33] formation of anti-drug antibodies,[34] increased expression of PD-L1 present on blasts,[34,38] increased expression of inhibitory proteins such as TIM-3, LAG-3, PD-1 and CTLA-4 on T-cells.[38]
- Expression of signalling molecules that induce apoptosis or anergy in T cells or prevent their differentiation.[33]
- Extramedullary relapse[39] (the presence of extramedullary ALL at the time of treatment is predictive of poor response to blinatumomab[40]).
- Activation of other signalling pathways.[34]
- Increase in the number of $CD3^+$ $CD4^+$ $CD25^{high}$ $FoxP3^+$ regulatory T cells that provide immunosuppression through IL-10 production[41] and suppress T-cell proliferation and cytotoxicity.[30]
- Alteration of the ratio of regulatory T cells to effector T cells.[42]
- Switch from lymphoid to myeloid lineage.[42]

3.6 | Pharmacokinetics of blinatumomab

The route of administration is intravenous (IV). The steady-state serum concentration found in the literature is 500–700 pg/mL with an IV dosage of 28 μg/day.[43] The subcutaneous route is being evaluated in various clinical trials.

3.7 | Distribution

The volume of distribution is estimated to be 1.61 ± 0.74 L/m[27] or 4.5 L[8] which shows tissue distribution close to the plasma compartment.[44]

3.8 | Metabolism

The metabolism of blinatumomab is still poorly understood. It is assumed that blinatumomab is degraded to small peptides and amino acids by cellular catabolic pathways common to all antibodies.[45]

3.9 | Elimination

The half-life of the drug is relatively short. It is estimated to be 1.25 ± 0.63 hour[7] or 2.1 hours.[8] This half-life is due to the lack of recycling of the antibody as it does not contain an Fc fragment in its structure.[46] Therefore, continuous IV infusions are required in order to obtain constant serum concentrations.[12] The average renal clearance is 22.3 ± 5 L/day/m^2.[7] According to *Buie et al.*, the urinary excretion of unchanged blinatumomab is 0.2% and therefore negligible.[26] However, it has been shown that in bilaterally nephrectomized mice, the systemic exposure and half-life of blinatumomab were increased compared to the control group.[46] Consequently, the mechanisms of elimination may be quite complex.

3.10 | Variation factors

The pharmacokinetic parameters of blinatumomab are independent of age, gender, weight, body surface area, pathology and disease state.[26,43,45]

The equilibrium dissociation constant (K_D) for CD19 is approximately 1 x 10^{-9} M compared to 1 x 10^{-7} M for CD3.[10]

Blinatumomab induces B-cell lysis at very low concentrations[6] (10–100 pg/mL), and at an effector-to-target cell ratio as low as 2:1.[47] The low dose required to achieve a response is probably related to the high lytic potential of cytotoxic T cells.[7]

3.11 | Drug interactions

The increase in cytokines, primarily IL-6, following administration of blinatumomab is thought to induce the inhibition of cytochrome P450 (CYP) activity. Substrates metabolized by CYP3A4, CYP2C9 and CYP1A2 in the presence of blinatumomab have a less than 2-fold increase in concentration.[47] This increase in IL-6 levels also results in an increase in C-reactive protein (CRP) levels, so there is an inverse correlation between CRP levels and CYP3A4 activity. The duration of suppression of CYP3A4 enzyme activity can therefore be estimated from the duration of CRP elevation.[47] As a result, close monitoring is necessary for drugs with a narrow therapeutic range.[47] The risk of interactions is greatest during the first nine days of treatment and the first two days of cycle 2.[45] Mild to moderate renal impairment has been shown to have little or no effect on the clearance of blinatumomab and therefore no dose adjustment is required.[26] For patients with renal insufficiency with a glomerular filtration rate of less than 30 mL/min/1.73m^2 or on dialysis, no recommendation has yet been made.[26] Hepatic impairment does not affect the clearance of blinatumomab.[48]

3.12 | Dosage adjustment and methods of administration

The daily dose is calculated according to the patient's weight.[49]

- For patients who weigh 45 kg or more, the recommended dose is 9 μg/day by continuous infusion from day 1 (D1) until day 7 (D7) and 28 μg/day from day 8 (D8) until day 28 (D28). For the subsequent cycles, the recommended dose is 28 μg/day.[49,50]
- If the patient weighs less than 45 kg, then the dose is adapted to the body surface area: from D1 to D7, the dose is 5 μg/m^2/day and from D8 to D28, the dose is 15 μg/m^2/day. For the subsequent cycles, the dose is 15 μg/m^2/day. Note that the dose of 28 μg/day should not be exceeded for this patient group.[49]

The dose levels are valid for the treatment of refractory or relapsed B-precursor ALL. For the treatment of B-precursor ALL with minimal residual disease (MRD), there is no dose escalation: the dose is 28 μg/day or 15 μg/m^2/day depending on patient weight.[51]

B-cell depletion and objective response are obtained from 15 μg/m^2/day. Adverse events (mainly neurological) limit the dose to be administered.[14,52] The maximum tolerated dose is 60 μg/m^2/day.[14]

The drug is supplied in a 35-μg vial of lyophilized blinatumomab and a 10 mL vial of stabilizing solution used for the final bag. In any case the stabilizing solution should be used to reconstitute the vial of blinatumomab.[50]

The infusion should be prepared under aseptic conditions.[49,53] The different steps of preparation are:

- Reconstitute the blinatumomab vial with 3 mL of water for injection by running the water down the sides of the vial to avoid foaming.[49,54]
- Gently shake the vial to avoid excessive foaming: the resulting solution has a concentration of 12.5 μg/mL with a final volume of 3.08 mL.[49,55]
- Add 5.5 mL of stabilizing solution to a pre-filled 250 mL bag of 0.9% sodium chloride.[49,54,55]

Note: the infusion bags, pump cassettes and tubing used must be made of polyolefin or polyvinyl chloride (PVC) without diethylhexylphthalate (DEHP) or ethyl vinyl acetate (EVA).[49,55,56]

- Gently mix this bag.[49,54,55] The stabilizing solution prevents blinatumomab from sticking to IV bags and tubing.[26]

- Transfer the appropriate volume of blinatumomab to the infusion bag containing the stabilizer and shake gently.[49,55]
- Connect tubing with a sterile, non-pyrogenic 0.2 micron filter to the bag.[8,49,55]
- Remove air from the bag and prime the infusion line with the final blinatumomab solution.[49]
- The infusion bag can be stored for 10 days at 2–8°C and 96 hours at room temperature (27°C maximum) if prepared under controlled and validated aseptic conditions.[49]

Blinatumomab is administered through a central venous line as a continuous IV infusion over 4 weeks followed by a 2-week break. Some clinical trials on the administration of blinatumomab over 2 or 4 hours revealed a significant rate of adverse events, such as neurological effects, cytokine release syndromes and infections, which led to these trials being stopped.[7] A portable pump (programmable, lockable, non-elastomeric with an alarm[49]) is used for administration which ensures a continuous and uniform flow rate.[57] Therefore, it allows for sustained, predictable and linear blood levels of blinatumomab.[7] Dexamethasone 20 mg IV is administered in pre-medication 1 hour before each start of infusion, before dose escalation or before reintroduction after an interruption of infusion of 4 hours or more.[11,50] Dexamethasone has been reported to have only a weak effect on cell proliferation and no effect on blinatumomab-induced cell lysis.[6] It is important to note that when changing bags or at the end of the infusion, the infusion line should not be flushed as there is a risk of overdosing and the consequent development of adverse effects.[58]

Hospitalization is required for the first few days of the first cycle and for the first 2 days of the subsequent cycles to monitor for treatment-related adverse events.[50] Further infusions can be administered at home[17] using a portable pump.[57] Infusion bags can be changed either in the hospital or at home by an external company.[57]

3.13 | Clinical development of blinatumomab

The three main clinical trials that made it possible to compile the data to obtain the first marketing authorizations are presented in Table 1.

Of these three trials, only the TOWER trial compares blinatumomab with chemotherapy. The primary endpoint for both TOWER and ALCANTARA was overall survival. These two studies show a similar overall survival (7.7 months and 9 months, respectively). In contrast, the BLAST trial showed a longer overall survival (36.5 months, almost 4 times the overall survival obtained by the other 2 trials). MRD of less than 10^{-4} is therefore a predictive factor for longer overall survival. Complete response to blinatumomab in MRD (the primary endpoint for BLAST) averaged 78% (after weighting each outcome against the number of patients who received blinatumomab in each trial). The endpoints '12-month remission rate', 'duration of remission' and 'allogeneic stem-cell transplantation' are similar in TOWER and ALCANTARA. The BLAST study again showed better results with 54% of patients being event-free within 18 months of blinatumomab administration. In addition, a higher percentage of patients reached haematopoietic stem-cell transplantation (67% of patients included in BLAST).

Therefore, these three studies show the clinical efficacy of blinatumomab in ALL with much better results in patients in haematological remission with an MRD ≥10^{-3}. Different clinical trials evaluating blinatumomab are presented in Table 2. Clinical trials are referenced with varying degrees of progress (extracted on April 2022 on clinicaltrials.gov).

In addition to the data from the referenced clinical trials, various publications are available, in particular on case reports or small series studies. In fact, patients with Down's syndrome and ALL have achieved a negative MRD after one cycle of treatment and without significant toxicity.[59] Some patients with genetically altered ALL have also responded favourably to blinatumomab (CRLF2 rearrangement,[36] T315I or E255K mutations,[60] ABL1 mutations,[61] presence of transcription factor TCF3-HLF[62]). For some patients, blinatumomab has been shown to be again effective in the retreatment of patients with relapsed or refractory ALL who have previously responded to blinatumomab with a relapse within 12 months with $CD19^{+}$.[63] In clinical trials, the use of blinatumomab is extensively examined prior to stem-cell transplantation but it is reported to be effective post-transplant by restoring the effects of graft-versus-leukaemia (GVL) in relapsed post-allograft patients.[64] Due to the mechanism of action (recruitment of T cells), blinatumomab may not be indicated in patients with lymphopenia due to previous treatments. *Ramdeny et al* showed that blinatumomab was effective in patients with congenital or acquired T-cell lymphopenia. This suggests that blinatumomab is able to activate and expand a small fraction of functional T cells.[65] In addition, other findings such as the lower efficacy of blinatumomab on high tumour loads (greater than 50% blasts in the bone marrow) should lead to changes in treatment regimens. Reduction therapy would be recommended in such cases.[66] Finally, in order to monitor response to blinatumomab, bone marrow MRD at D15 and CD19 ex2part levels would be markers of complete response and non-response to blinatumomab, respectively.[36,67]

3.14 | Adverse event profile

In the TOWER study, 271 patients were included in the blinatumomab arm. A total of 267 received protocol-specified treatment and were therefore analysed in the following tables.

To classify the adverse events (AE) reported in the clinical trials, we added the number of patients who reported an AE in each clinical trial. We then calculated the proportion of patients who reported an AE out of the total number of patients who received blinatumomab in the three trials (expressed as a percentage).

Only AEs with a frequency greater than 1% (all trials combined) are presented in Table 3. The full list of adverse events collected during these trials can be found in online Appendix 1.

Table 4 represents the overall AEs (serious and non-serious) reported in the three clinical trials on clinicaltrials.gov. Only AEs with

TABLE 1 Outcomes in three clinical trials of blinatumomab

Name of clinical trial (NCT)	TOWER (NCT02013167)[2]	ALCANTARA (NCT02000427)[3,4]	BLAST (NCT01207388)[5]
Design	Phase 3 trial Prospective Randomly assigned with a 2:1 ratio	Phase 2 trial Open-label Single-arm study	Phase 2 trial Open-label Single-arm study
Pathology	Heavily pretreated B-cell precursor ALL	Relapsed or refractory Ph^+ ALL	B-cell precursor ALL in complete hematologic remission with MRD ($\geq 10^{-3}$)
Population concerned	18 years of age or older	18 years of age or older	18 years of age or older
Dose of blinatumomab	9 μg/day for 7 days (in cycle 1) and 28 μg/day thereafter 1 cycle = 4 weeks of continuous IV infusion followed by a 2-week treatment-free interval	9 μg/day for 7 days (in cycle 1) and 28 μg/day thereafter 1 cycle = 4 weeks of continuous IV infusion followed by a 2-week treatment-free interval	15 $\mu g/m^2$ per day by continuous IV infusion for up to 4 cycles 1 cycle = 4 weeks of continuous IV infusion followed by a 2-week treatment-free interval
Treatment	Blinatumomab versus SOC	Blinatumomab	Blinatumomab
Number of patients	271 versus 134	45	116
Overall survival (median)	7.7 versus 4.0 months (HR for death: 0.71; 95% CI: [0.55–0.93]; $p = 0.01$)	9.0 months (95% CI: [5.7–13.5] months)	36.5 months
Complete MRD response	76% versus 48%	88% (95% CI: [62–98] %)	78%
Remission rates within 12 weeks	With full hematologic recovery: 34% versus 16% ($p < 0.001$) With full, partial or incomplete hematologic recovery: 44% versus 25% ($p < 0.001$)	With full, partial or incomplete hematologic recovery: 36% (95% CI[22–51]: %)	NA
Survival analysis: Event-free survival Relapse-free survival	6-month estimates: 31% versus 12% (HR[a]: 0.55; 95% CI: [0.43–0.71]; $p < 0.001$)	6.8-month estimates: 50% (95% CI: [4.4-NE])	18-month estimates: 54%
Duration of remission (median)	7.3 versus 4.6 months	6.8 months (95% CI: [4.5-NE] months)	NA
Allogeneic stem-cell transplantation	24% for each group	20%	67%

Abbreviations: ALL, acute lymphoblastic leukaemia; 95% CI, 95% confidence interval; HR, hazard ratio; IV, intravenous; MRD, minimal residual disease; NA, not applicable; NCT, national clinical trial; NE, not estimable; p, *p*-value; Ph^+, Philadelphia chromosome positive; SOC, standard-of-care.
[a]For a relapse after achieving complete remission with full, partial, or incomplete hematologic recovery, or death.

a frequency of more than 10% (all trials combined) are presented in Table 4. All the AEs noted during these trials can be found in online Appendix 2.

3.15 | Specific adverse drug reactions (ADR)

3.15.1 | Cytokine release syndrome (CRS)

This ADR is characterized by symptoms such as fever, chills,[68] shortness of breath, hypotension[19] and other constitutional symptoms.[68]

These symptoms appear rapidly after the start of the infusion.[68] CRS can range from mild to life-threatening.[69,70] It may be due to rapid destruction of leukaemic cells by T-cells,[19] resulting in a massive influx of cytokines into the bloodstream. The risk of developing high-grade CRS appears to be correlated with tumour mass and the initial dose of blinatumomab.[70] In addition, older people are at greater risk of developing CRS compared to a younger population.[71] In order to prevent the development of CRS, particularly in patients with a large tumour mass, the starting dose should be 5 $\mu g/m^2$/day with dose escalation to 15 $\mu g/m^2$/day in subsequent weeks depending on the tolerability.[70,72]

Corticosteroids may also be given as premedication in order to avoid the development of CRS.[19,70]

When CRS occurs with blinatumomab, 2 treatments can be given to improve symptoms: corticosteroids (methylprednisolone) and tocilizumab (8 mg/kg IV).[73,74] It is important to note that tocilizumab, which is an IL-6 receptor antagonist, does not have an inverse activity to the anti-leukaemic activity.[26] Discontinuation of treatment may also be considered until symptoms resolve (grades 3–4) and then be resumed with a gradual increase in dose starting with 9 μg/day.[51] According to the US Food and Drug Administration (FDA), a grade 4 CRS should lead to permanent discontinuation of treatment.[51] *Marini et al* report a patient with a grade 4 CRS for whom they reintroduced blinatumomab. The dose was escalated (9 μg/day for 5 days,

TABLE 2 All ongoing clinical trials on *clinicaltrials.gov*

Phase	Status	Study results	Pathology	Number of clinical trials	Estimated number of patients enrolled
Phase 1	Active, not recruiting	Results available	Diffuse large B-cell lymphoma	1	31
		No results available	Diffuse large B-cell lymphoma	1	14
			Indolent non-Hodgkin lymphomas/Chronic lymphocytic leukaemia	1	19
	Completed	Results available	Non-Hodgkin's lymphoma	1	76
		No results available	Non-Hodgkin's lymphoma	1	36
	Recruiting	No results available	Acute lymphoblastic leukaemia (ALL)	4	137
			ALL/Mixed phenotype acute leukaemia	1	30
			Myeloid leukaemia/Chronic myeloid leukaemia/ALL/B-cell precursor type acute leukaemia	1	62
	Suspended	No results available	Recurrent B-cell lymphoma, unclassifiable	1	44
	Terminated	No results available	Multiple myeloma	1	6
Phase 1/Phase 2	Completed	Results available	ALL	2	159
	Not yet recruiting	No results available	ALL	1	90
	Recruiting	No results available	ALL	4	375
		No results available	ALL/B-cell non-Hodgkin lymphoma	1	64
Phase 2	Active, not recruiting	No results available	ALL	6	467
			Non-Hodgkin lymphoma	1	13
			Richter syndrome	1	41
	Completed	Results available	ALL	5	443
			Diffuse large B-cell lymphoma	2	72
		No results available	ALL	2	29
			Haematopoietic and lymphoid cancer/Richter's transformation	1	10
	Not yet recruiting	No results available	ALL	1	180
	Recruiting	No results available	ALL	10	438
			ALL/Acute myeloid leukaemia/Myelodysplastic syndromes/NK-cell leukaemia/Hodgkin lymphoma/Non-Hodgkin lymphoma/Juvenile myelomonocytic leukaemia/Chronic myeloid leukaemia	1	140
			ALL/Acute myeloid leukaemia/Myeloid sarcoma/Chronic myeloid leukaemia/Juvenile myelomonocytic leukaemia/Myelodysplastic syndrome/Non-Hodgkin lymphoma	1	52
			ALL/B lymphoblastic lymphoma	1	80
			Chronic myelogenous leukaemia/ALL/Acute myeloid leukaemia	2	120
			Down's syndrome/ALL	1	550
			Mixed phenotype acute leukaemia	1	5
	Terminated	Results available	Diffuse large B-cell lymphoma	1	10
		No results available	B-cell adult ALL/Stem-cell leukaemia/Minimal residual disease	1	8
	Unknown status	No results available	ALL	2	72
Phase 2/Phase 3	Completed	Results available	Non-Hodgkin lymphoma	1	41
	Recruiting	No results available	ALL	1	1000

TABLE 2 (Continued)

Phase	Status	Study results	Pathology	Number of clinical trials	Estimated number of patients enrolled
Phase 3	Active, not recruiting	Results available	ALL	1	111
		No results available	ALL	2	1158
	Completed	Results available	ALL	1	121
	Not yet recruiting	No results available	ALL	1	80
			ALL/Mixed phenotype acute leukaemia	1	160
	Recruiting	No results available	ALL	5	12,283
			Down's syndrome/ALL	1	6720
	Terminated	Results available	ALL	1	405
Phase 4	Recruiting	No results available	ALL	1	45
Unknown phase	Active, not recruiting	No results available	Blincyto use in routine clinical practice	1	279
	Completed	No results available	ALL	1	212
	Not yet recruiting	No results available	ALL	1	60
	Recruiting	No results available	ALL	1	180
	Unknown status	No results available	ALL	1	92

Note: 'Estimated number of patients enrolled' is the target number of participants that the researchers need for the study.

TABLE 3 Serious adverse events in three clinical trials of blinatumomab

	TOTAL Serious adverse events $N = 428$ patients (%)	TOWER Serious adverse events $n = 267$ patients (%)	ALCANTARA Serious adverse events $n = 45$ patients (%)	BLAST Serious adverse events $n = 116$ patients (%)
Preferred term				
• Pyrexia	35 (8.18%)	16 (5.99%)	2 (4.44%)	17 (14.66%)
• Febrile neutropenia	29 (6.78%)	23 (8.61%)	4 (8.89%)	2 (1.72%)
• Sepsis	17 (3.97%)	13 (4.87%)	3 (6.67%)	1 (0.86%)
• Overdose	14 (3.27%)	8 (3.00%)	1 (2.22%)	5 (4.31%)
• Device-related infection	12 (2.80%)	6 (2.25%)	3 (6.67%)	3 (2.59%)
• Tremor	12 (2.80%)	1 (0.37%)	3 (6.67%)	8 (6.90%)
• Pneumonia	11 (2.57%)	10 (3.75%)	1 (2.22%)	0 (0.00%)
• Encephalopathy	11 (2.57%)	4 (1.50%)	1 (2.22%)	6 (5.17%)
• Cytokine release syndrome	10 (2.34%)	7 (2.62%)	1 (2.22%)	2 (1.72%)
• Aphasia	10 (2.34%)	3 (1.12%)	1 (2.22%)	6 (5.17%)
• Septic shock	9 (2.10%)	8 (3.00%)	1 (2.22%)	0 (0.00%)
• Neutropenia	7 (1.64%)	2 (0.75%)	0 (0.00%)	5 (4.31%)
• Bacterial sepsis	6 (1.40%)	6 (2.25%)	0 (0.00%)	0 (0.00%)
• Multi-organ failure	5 (1.17%)	4 (1.50%)	1 (2.22%)	0 (0.00%)
• Bronchopulmonary aspergillosis	5 (1.17%)	4 (1.50%)	0 (0.00%)	1 (0.86%)
• Leukocytosis	5 (1.17%)	3 (1.12%)	2 (4.44%)	0 (0.00%)
• Staphylococcal infection	5 (1.17%)	2 (0.75%)	0 (0.00%)	3 (2.59%)

Abbreviation: n, total number of patients.
Note: The percentages represent the number of patients who reported the adverse reaction.

TABLE 4 All adverse events in three clinical trials of blinatumomab

	TOTAL Adverse events $N = 428$ patients (%)	TOWER Adverse events $n = 267$ patients (%)	ALCANTARA Adverse events $n = 45$ patients (%)	BLAST Adverse events $n = 116$ patients (%)
Preferred term				
• Pyrexia	313 (73.13%)	169 (63.30%)	28 (62.22%)	116 (100.00%)
• Headache	137 (32.01%)	77 (28.84%)	14 (31.11%)	46 (39.66%)
• Febrile neutropenia	92 (21.50%)	71 (26.59%)	19 (42.22%)	2 (1.72%)
• Anaemia	90 (21.03%)	70 (26.22%)	13 (28.89%)	7 (6.03%)
• Diarrhoea	90 (21.03%)	58 (21.72%)	9 (20.00%)	23 (19.83%)
• Nausea	86 (20.09%)	52 (19.48%)	7 (15.56%)	27 (23.28%)
• Neutropenia	75 (17.52%)	53 (19.85%)	3 (6.67%)	19 (16.38%)
• Hypokalemia	72 (16.82%)	46 (17.23%)	8 (17.78%)	18 (15.52%)
• Fatigue	68 (15.89%)	34 (12.73%)	6 (13.33%)	28 (24.14%)
• Tremor	66 (15.42%)	27 (10.11%)	3 (6.67%)	36 (31.03%)
• Vomiting	65 (15.19%)	33 (12.36%)	6 (13.33%)	26 (22.41%)
• Cough	59 (13.79%)	39 (14.61%)	5 (11.11%)	15 (12.93%)
• Thrombocytopenia	58 (13.55%)	47 (17.60%)	10 (22.22%)	1 (0.86%)
• Constipation	54 (12.62%)	34 (12.73%)	7 (15.56%)	13 (11.21%)
• Chills	53 (12.38%)	19 (7.12%)	4 (8.89%)	30 (25.86%)
• Hypotension	52 (12.15%)	32 (11.99%)	6 (13.33%)	14 (12.07%)
• Back pain	49 (11.45%)	35 (13.11%)	4 (8.89%)	10 (8.62%)
• Cytokine release syndrome	48 (11.21%)	42 (15.73%)	4 (8.89%)	2 (1.72%)
• Insomnia	48 (11.21%)	28 (10.49%)	3 (6.67%)	17 (14.66%)
• Peripheral edema	47 (10.98%)	39 (14.61%)	8 (17.78%)	0 (0.00%)

Abbreviation: n, total number of patients.
Note: The percentages represent the number of patients who reported the adverse reaction.

then an unconventional dose of 18 μg/day for 3 days and then 28 μg/day) which led to complete molecular remission.[75]

3.15.2 | Neurological adverse reactions

Commonly reported neurological AEs include the following:

- Headache. Severe and frequent AEs are headache.[8,45,68]
- Movement disorders. Severe and frequent AEs are tremors.[8,45]
- Encephalopathy is a frequent and serious AE.[45,76]
- Neurological disorders. Cerebellar symptoms are frequent AEs (15–20% of cases[76]). Confusional state is a frequent and serious effect.[8,45,68] Serious AEs include altered consciousness, aphasia, ataxia and neurotoxicity.[8] Other effects such as diminished consciousness and impaired coordination and balance are less frequent but clinically significant.[45]
- Epileptic seizures such as convulsions are frequent (15–20% of cases), worrying and serious.[8,19,76]

The mechanism of action of neurotoxicity could be explained by the migration of T cells through the cerebral microvascular endothelium. In fact, blinatumomab is detected in cerebrospinal fluid (CSF) despite an intact blood–brain barrier.[28] Endothelial adhesion molecules (ICAM-1, P-selectin, VCAM-1 [vascular cell adhesion molecule-1]) were shown to be upregulated once blinatumomab was administered into the bloodstream. This could induce a decrease in T-cell turnover, an increase in endothelial adhesion[28] and an activation of the endothelium.[77]

To confirm this hypothesis, three agents with anti-adhesive properties were tested: sodium pentosan to block P-selectin, the antibiotic minocycline to interfere with LFA-1 - ICAM-1 binding (by calcium ion chelation) and the humanized antibody natalizumab to block the interaction between VLA-1 (very late antigen–1) and VCAM-1 on endothelial cells. All 3 agents showed a decrease in T-cell adhesion to the endothelium and consequently a reduction in neurotoxicity.[28] T cells adhere and then cross the vascular endothelium by extravasation[77] to the CSF. Blinatumomab is thought to activate T cells in the presence of B target cells, which induces secretion of cytokines and chemokines. This massive influx could thus cause transient local neuroinflammation which could in turn attract circulating leukocytes.[28,77]

A B cell to T-cell ratio of less than 1:8 could be one of the predictive factors of neurotoxicity.[11,78] In addition, parameters such as advanced age, pre-existing or previous signs of neurotoxicity, non-Caucasian race, and number of post-relapse treatments greater than

2 are risk factors for neurotoxicity.[79,80] Neurological side effects appear early in the course of treatment (first week) but unlike CRS, neurotoxicity can occur regardless of dose, tumour burden and pathology.[70] In order to prevent the development of neurological disorders, corticosteroids can be administered before the first dose of blinatumomab and before each dose escalation and retreatment.[68] Seizures can be treated with levetiracetam.[11]

3.15.3 | Hypogammaglobulinemia

Hypogammaglobulinemia is a frequently reported AE.[48,68] This effect is related to the mechanism of action of blinatumomab, which induces a depletion of B-cell levels. Therefore, immunoglobulin level could be reduced during and after treatment. Immunoglobulin M would be the first to reappear due to the generation of new naive B cells.[81] Immunoglobulin G and A levels could increase in a second phase due to the later reappearance of memory B cells and plasma cells after treatment.[81] It is important to note that non-responders do not show a suppressive effect of immunoglobulin G and that this side effect is more significant with blinatumomab compared to other conventional chemotherapies.[81] The consequence of this adverse effect is the risk of infection. Therefore, immunoglobulin replacement therapy may be necessary.[81]

In the various publications, we also found several prominent cases of adverse events with blinatumomab:

- Bone marrow necrosis. It was suggested that the high tumour burden induced a major CRS which in turn led to this necrosis (associated with cytopenia and persistent bone pain).[82]
- Pancreatitis on blinatumomab but lack of data to establish a causal link between the drug and pancreatitis.[83]
- Pneumatosis of the bowel from the ascending colon to the hepatic flexure that started at D28 after the start of the infusion, with no complaints expressed by the patient. The second cycle of blinatumomab was therefore postponed. The condition resolved despite the resumption of treatment.[84]
- Neurotoxicity with blinatumomab and concomitant intrathecal chemotherapy.[85]
- Neurotoxicity 9 days after completion of cycle 1 blinatumomab infusion with intrathecal methotrexate injections at D15 and D29. Toxicity was non-reversible despite numerous treatments (corticosteroids, anticonvulsants, etc.).[86]
- Development of a Horner-type syndrome with hypoesthesia of the face, associated with a negative CSF, due to infiltration of the basilar artery by a fungal hyphae *Rhizopus* sp. An antifungal prophylaxis such as posaconazole has therefore been implemented for patients at high risk of invasive fungal infection.[87]
- Trichosporonosis disseminated to the skin and lung at D24 of the first treatment.[88]
- Periungual and subungual pyogenic granuloma occurring 6 weeks after the start of the first blinatumomab infusion.[89]
- Fulminant mucormycosis infection in a child. Thrombi in the right and left heart ventricles, multiple systemic thromboembolic lesions with ischemia, haemorrhage and infarction in the lungs, heart, liver, both kidneys, intestines and muscles. The patient was already in a chronically diminished general condition and had left flank pain before the introduction of blinatumomab. At D5 of the infusion, the pain worsened. At D6, the patient became drowsy and sleepy.[90]
- Cardiac dysfunction induced by elevated cytokine levels following treatment with blinatumomab.[21]
- Development of mid-vessel vasculitis in the feet at D15 of the first course. Blinatumomab was stopped and then restarted 1 week later at lower doses.[91]

There are cases of patients who had disabling symptoms due to the disease that resolved after administration of blinatumomab. For example, one case of decreased visual acuity due to leukaemic cell infiltration of the optic nerves[92] improved on blinatumomab. There is also a case of severe liver failure (due to chemotherapy treatments) that resolved on blinatumomab (transaminase increase at the beginning of the infusion and then resolution).[93]

3.16 | Adverse reactions in the Vigibase® global pharmacovigilance database

Data were extracted from the VigiBase® global pharmacovigilance database on April 10, 2022: on this date, a total of 8534 adverse reactions were reported for 4541 patients. This population is of median age [45–64 years] with a minimum age of 0–27 days and a maximum age above 75 years (with a proportion of 35.4% of unknown patient age). The male–female distribution is 44.3%–35.6%, respectively (with a proportion of 20.1% of unknown data). Figure 2 shows the 10 most represented SOCs (system organ classes) in terms of occurrence of adverse events (number of adverse events of the SOC out of the total number of adverse events).

These results are consistent with those found in the clinical trials (Tables 3 and 4). The 3 most frequent SOCs in the clinical trials are haematological disorders, gastrointestinal disorders and general disorders. However, it is important to note that neurological disorders and infections occur more frequently in real life than in clinical trials.

3.17 | Administrative status of blinatumomab

Blinatumomab is the first BiTE antibody approved in the USA It was accepted by the FDA on December 3, 2014 for the indication of ALL.[94] It was accepted by the European Medicines Agency (EMA) on November 23, 2015. Blinatumomab is marketed under the name BLINCYTO®.

3.18 | Indications

Blinatumomab, BLINCYTO®, is indicated[49,51]:

- As monotherapy for the treatment of adult patients with relapsed or refractory CD19-expressing B-precursor ALL. Patients with

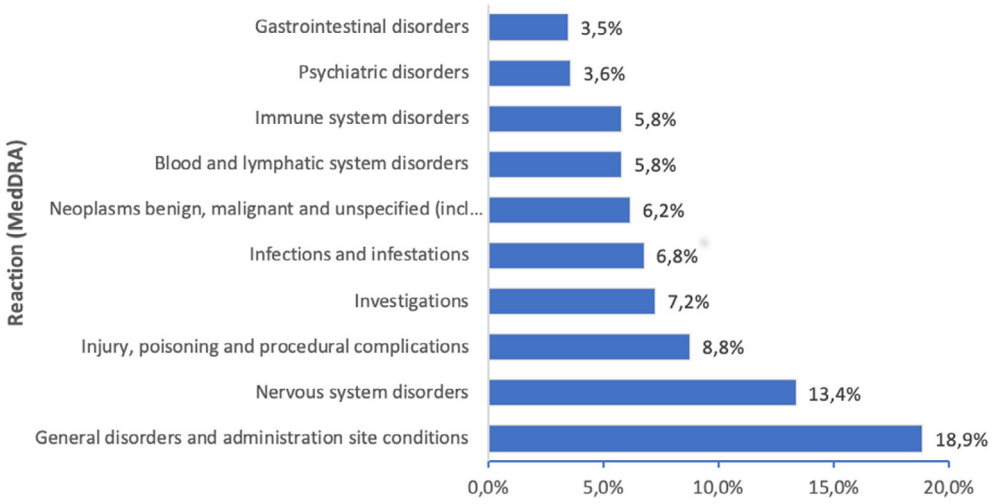

FIGURE 2 The 10 most frequent system organ classes (SOC) found in VigiBase® for blinatumomab

Philadelphia chromosome-positive B-precursor ALL must have failed at least two tyrosine kinase inhibitor (TKI) regimens and have no other treatment options.

- As monotherapy for the treatment of adult patients with Philadelphia chromosome-negative CD19-expressing B-cursor ALL in first or second complete remission with MRD of 0.1% or greater.
- As a single agent for the treatment of paediatric patients from 1 year of age with CD19-expressing Philadelphia chromosome-negative B-precursor ALL refractory to or having relapsed after at least two prior therapies or having relapsed after a prior haematopoietic stem-cell allograft.
- As monotherapy in the treatment of paediatric patients from 1 year of age with Philadelphia chromosome-negative CD19-expressing B-precursor ALL in a first relapse at high risk in the consolidation setting.

4 | WHAT IS NEW AND CONCLUSION

Blinatumomab is the first bispecific drug in BiTE-format to be marketed worldwide. Despite potentially life-threatening side effects, blinatumomab is generally well tolerated. Due to a fairly short half-life, different administration methods are being studied in order to improve the practical use of this drug whilst maintaining the same efficacy. In fact, currently the administration constraints concern continuous infusion for 28 days. The route of administration could be an area for improving administration. Modifying the BiTE-format by adding an Fc fragment is a second way of improvement that allows for an increased elimination half-life. Indeed, *Lorenczewski et al* showed that this new generation of BiTE antibodies, called 'half-life extended (HLE) BiTE molecules', allowed to increase the half-life to 210 hours after a single IV injection.[95]

The number of clinical trials on diseases other than ALL is constantly increasing, which gives hope that the indications for blinatumomab will be extended in the coming years.

CONFLICT OF INTEREST

The authors report no financial relationships or conflict of interests regarding the content herein.

DATA AVAILABILITY STATEMENT

Data is openly available in a public repository that issues datasets with DOIs.

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