Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2234

blinatumomab 38.5 micrograms powder for concentrate and solution for solution for infusion (Blincyto®)

Amgen Ltd

7 February 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the end of life and orphan equivalent process:

blinatumomab (Blincyto®) is accepted for restricted use within NHSScotland.

Indication under review: As monotherapy for the treatment of adults with Philadelphia chromosome negative, CD19 positive, B-precursor acute lymphoblastic leukaemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.

SMC restriction: to patients who are in first complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.

In a single arm phase II study of patients with B-cell precursor ALL in first or later complete remission and with persistent or recurrent MRD, blinatumomab was associated with clinically relevant complete MRD response rates.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Vice Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor acute lymphoblastic leukaemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.[1]

Dosing Information

Blinatumomab for the treatment of Philadelphia chromosome negative MRD positive B-precursor ALL consists of one induction cycle and up to 3 additional consolidation cycles. A single cycle of treatment of blinatumomab (induction or consolidation) is 28 days of continuous intravenous infusion at a dose of 28mcg/day (for patients ≥45kg) followed by a 14 day treatment-free interval (total 42 days). The majority of patients who respond to blinatumomab achieve a response after one cycle. Consequently, the potential risk/benefit ratio associated with continued therapy in patients who do not show haematological and/or clinical improvement after one treatment cycle should be assessed by the treating physician.[1]

In the event of severe or life-threatening toxicities, blinatumomab treatment may be interrupted (potentially in conjunction with dose adjustments) or discontinued. Detailed information on the management of adverse events, premedication (and recommended additional medication), and dose adjustments for patients who weigh <45kg can be found in the Summary of Product Characteristics (SPC).[1]

Treatment should be initiated under the direction of and supervised by physicians experienced in the treatment of haematological malignancies. For the treatment of Philadelphia chromosome negative MRD positive B-precursor ALL, hospitalisation is recommended at a minimum for the first 3 days of the first cycle and the first 2 days of subsequent cycles. For all subsequent cycle starts and re-initiation (that is treatment interruption of ≥4 hours), supervision by a healthcare professional or hospitalisation is recommended.[1]

Product availability date

25 January 2019

Blinatumomab meets SMC end of life and orphan criteria for this indication

Summary of evidence on comparative efficacy

Blinatumomab is a bi-specific T-cell engager antibody. It activates T-cells by binding to both CD3 (expressed on the surface of T-cells) and to CD19 (expressed on the surface of malignant and benign cells of B-lineage origin). The resulting activation of T-cells leads to the elimination of CD19-expressing tumour cells. Blinatumomab is the first medicine to be licensed for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete response (CR) with positive MRD. Blinatumomab has previously been accepted by SMC for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-

precursor ALL (SMC 1145/16). The indication under consideration, if accepted, would result in patients receiving blinatumomab earlier in the treatment pathway.[1]

The evidence supporting the efficacy and safety of blinatumomab comes from BLAST, an open-label, multicentre, single-arm, uncontrolled phase II study. Patients aged ≥18 years with B–precursor ALL in CR (defined as less than 5% blasts in bone marrow after at least three intense chemotherapy blocks, including patients in first, second, and third CR) and an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 were required to have presence of MRD at a level of $\geq 10^{-3}$ (≥0.1%) after an interval of at least 2 weeks from last systemic chemotherapy, in addition to presence of at least one molecular marker for evaluation.[2]

Patients received blinatumomab 15mcg/m^2/day by continuous IV infusion for up to four cycles (n=116). Each cycle consisted of 28 days of blinatumomab infusion and a 14-day treatment-free period. Patients could undergo HSCT after the first cycle of treatment at discretion of the investigator; patients eligible for HSCT could continue to receive blinatumomab until transplantation took place (maximum four cycles). Intrathecal cerebrospinal fluid (CSF) prophylaxis was given to patients prior to cycle 1, and at the end of cycles 2 and 4; corticosteroid pre-treatment (prednisone 100mg IV or equivalent) was given at the start of each cycle for the prophylaxis of neurological events and cytokine release syndrome. In the event of haematological relapse during the study period, blinatumomab was discontinued.[2, 3]

The primary outcome was the proportion of patients who achieved a complete MRD response after one cycle of blinatumomab treatment. Complete MRD response was defined as no polymerase chain reaction (PCR) amplification of individual rearrangements of Ig- or T-cell receptor (TCR)-genes detected after completion of the first cycle. The primary outcome was assessed in the primary end point full analysis set (n=113), defined as all patients who received one dose of blinatumomab except those that did not have a central MRD assay result or did not use a sufficiently sensitive test.[2]

At a data cut-off on 21 February 2014 all patients had been evaluated for the primary outcome. Key and other secondary outcomes were evaluated at the second data cut-off on 5 August 2015 (median follow-up 29.9 months). Details of the primary and key secondary outcomes are shown in Table **1** below.[2, 3]

Table 1. Primary and key secondary outcome results from the BLAST study.[2, 3]

Complete MRD response following 1 cycle of blinatumomab (cut-off 21 February 2014)		
Primary end point full analysis set[A] (n)	113	
Proportion of responders	78% (n=88)	
Haematologic RFS at 18 months after initiation of blinatumomab (cut-off 5 August 2015)		
	Uncensored at HSCT*	Censored at HSCT**
Key secondary end point full analysis set[B] (n)	110	110
Events (n)	62	21
Median RFS	18.9 months	NE
KM estimate for RFS at 18 months	53%	54%

HSCT = haematopoietic stem cell transplant; KM = Kaplan-Meier; MRD = minimal residual disease; RFS = relapse-free survival; NE = not estimable; * = uncensored at HSCT or post-blinatumomab chemotherapy; ** = censored at HSCT or post-blinatumomab chemotherapy; A = primary end point full analysis set excluded patients in the full analysis set who either did not have a central MRD assay result or used a test that was not sufficiently sensitive ($>10^{-4}$); B = key secondary end point full analysis set excluded Philadelphia positive patients

Other secondary outcomes assessed included overall survival, time to haematological response, and duration of complete MRD response, the results of which are presented in Table **2**. The results from the final data cut-off (January 2019, median follow-up of 5 years) were broadly consistent with previous analyses.[2, 3]

Table 2. Other secondary outcome results from the BLAST study (cut-off 5 August 2015).[2, 3]

	Uncensored at HSCT*	Censored at HSCT**
Overall survival (FAS population)[A]		
N	116	116
Events (n)	53	5
Median overall survival	36.5 months	NE
KM estimate at 18 months	65% (95% CI: 55% to 73%)	83% (95% CI: 55% to 94%)
Time to haematological relapse (KSEPFAS population)[B]		
N	110	110
Events (n)	39	19
Median TTHR	NE	NE
KM estimate at 18 months	67% (95% CI: 57% to 76%)	55% (95% CI: 34% to 72%)
Duration of complete MRD response (KSEPFAS population)[C]		
N	85	85
Events (n)	45	16
Median duration	17.3 months	45.0 months
KM estimate at 18 months	46% (95% CI: 33% to 57%)	51% (95%CI: 28% to 69%)

HSCT = haematopoietic stem cell transplant; KM = Kaplan-Meier; MRD = minimal residual disease; NE = not estimable; RFS = relapse-free survival; A = full analysis set, defined as every patient who received any infusion of blinatumomab; B = key secondary end point full analysis set included all enrolled patients except from Philadelphia positive patients; C = the same population as described in B but only included patients who achieved complete MRD response at cycle 1; * = uncensored at HSCT or post-blinatumomab chemotherapy; ** = censored at HSCT or post-blinatumomab chemotherapy

The submitting company conducted an unanchored matched adjusted indirect comparison to indirectly compare blinatumomab with historical control in adult patients with Philadelphia negative B-cell precursor ALL who had MRD positivity following treatment. Two studies, BLAST and a retrospective cohort study (Study 20120148), were used to assess RFS and overall survival which were used to inform the economic model. The submitting company concluded that blinatumomab was superior to standard of care (SoC) for both RFS and overall survival.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

No comparative safety data are available. Refer to the SPC for details.[1]

The EMA concluded that despite the limitations of BLAST, such as small sample size and open-label design, the safety profile of blinatumomab in this setting was generally comparable to what has previously been reported in relapsed/refractory ALL. There remains some uncertainty on the outcome of HSCT in patients who have been treated with blinatumomab, but this will be addressed at a later date following the submission of the results of two phase III studies.[2]

In the BLAST study at data cut-off 5 August 2015, the median duration of blinatumomab treatment was 55 days (range 1 to 113 days). Any treatment-emergent adverse event (AE) was reported by 100% of patients (n=116); patients reporting a grade 3 or higher treatment-emergent AE was 61%; the proportion of treatment-emergent AEs that led to dose interruptions was 31%, patients with a reported serious AE were 63%; treatment-emergent AEs that lead to permanent discontinuation of blinatumomab were 17%.[2]

The most frequently reported treatment-emergent AEs of any grade with a incidence >10% were: pyrexia (89%), headache (38%), tremor (30%), chills (26%), fatigue (24%), nausea (23%), vomiting (22%), diarrhoea (20%), hypokalaemia (16%), neutropenia (16%), insomnia (15%), aphasia (13%), arthralgia (13%), cough (13%), hypotension (12%), and constipation (11%). Treatment-emergent serious adverse events reported in ≥5% of patients were pyrexia (15%), tremor (6.9%), aphasia (5.2%) and encephalopathy (5.2%).[2]

Summary of clinical effectiveness issues

ALL is an aggressive form of cancer that specifically affects immature lymphocytes that are derived from T- or B- lymphocyte stem cells. It is a rare condition, with an estimated prevalence in the EU of 27 cases per 100,000 persons, 40% of which occur in adults. The predisposing risk factors for adult ALL are not well understood. However, incidence increases with age. The majority of patients are diagnosed with B-lineage, Philadelphia chromosome-negative ALL. Prognosis for patients with ALL remains poor, with 5 year overall survival rates of 30-40%.[2, 4, 5]

Treatment is administered to patients with the aim of inducing CR, which can lead to patients receiving potentially curative HSCT. In Scotland, newly diagnosed patients with ALL are typically enrolled into one of the UKALL studies, and treatment is directed by the age and fitness of the patient. Blinatumomab meets SMC end of life and orphan criteria.[2, 4, 5]

In the BLAST study, complete MRD response following one cycle of treatment with blinatumomab was achieved by a large majority (78%) of the primary end point analysis set. This result was supported by positive secondary outcome results; KM 18 month RFS estimate was 53% (uncensored at HSCT) in Philadelphia chromosome negative patients, and a median duration of

response of 17.3 months suggests that the treatment effect is sustainable. Median overall survival was 36.5 months (uncensored at HSCT). The primary outcome, complete MRD response, is not an established surrogate outcome for overall survival in ALL. However, the EMA concluded that demonstrating formal surrogacy with respect to overall survival was unnecessary as MRD is a strong and independent prognostic indicator for relapse risk. The high proportion of complete MRD response achieved by patients receiving blinatumomab was considered clinically meaningful and significant.[2]

There are substantial limitations to the evidence. BLAST was a small, open-label, non-randomised, uncontrolled phase II study. This type of study is associated with a greater risk of confounding in addition to various other biases. The unblinded administration of treatment makes interpretation of safety and patient reported outcomes particularly difficult to interpret.

There is uncertainty around the outcomes for patients who receive HSCT following blinatumomab treatment. In BLAST, increased mortality was observed in patients that received HSCT compared with those who did not; 26% (23/90) of patients who received HSCT after starting blinatumomab died, compared with 12% (3/26) of patients who did not undergo HSCT. The EMA stated that a harmful effect from HSCT in patients treated with blinatumomab could not be clearly ruled out. Phase III studies are ongoing and are expected to further characterise the long-term effects of blinatumomab treatment, providing data on outcomes for post-HSCT, post-blinatumomab patients.[2]

The definitions of RFS and overall survival in BLAST differed from the definitions outlined in EMA guidance. RFS and overall survival were calculated from the time of initiation of blinatumomab, rather than the time of first detection of CR. There was substantial variation between patients in the time intervals between first CR detection and initiation of blinatumomab; time from last anti-ALL treatment to first dose of blinatumomab ranged from 0 months to 55 months. RFS and overall survival results using the more appropriate definitions are not available, and the results presented should be interpreted with caution.[2]

There is no direct evidence comparing blinatumomab with SoC, which typically involves patients receiving treatment in a UKALL study. This was addressed through the use of an unanchored matched adjusted indirect comparison, which had several important limitations: the two studies included in the comparison were non-randomised and differed in study design (interventional versus observational); the cohort study included patients who had been diagnosed with ALL between 2000 and 2013 (one third of patients had been diagnosed pre-2004) and outcomes for patients with ALL may have improved since then; the population was narrower than the licensed indication (first CR patients only); there were differences in the timing of MRD assessments; transplant status/number of prior treatments were not adjusted for in the analysis, and the effective sample size was markedly reduced post-matching. Despite these limitations, the conclusion that blinatumomab is superior to SoC in terms of RFS, and in terms of overall survival prior to HSCT or in those who did not receive HSCT seems credible, but the effect size is highly uncertain. However, there was no statistical difference between blinatumomab and SoC in patients who received HSCT.

Clinical experts consulted by SMC considered that blinatumomab is a therapeutic advancement due to poor prognosis with current treatment and the improved MRD response reported in the literature. The introduction of blinatumomab in this setting is anticipated to have a substantial impact on the service, mainly due to the administration and toxicity profile of blinatumomab. Administrations require short in-patient stays in hospital, and ambulatory pumps have to be available to allow the rest of the continuous infusion to be delivered as an outpatient. Monitoring and management of adverse events associated with blinatumomab are also expected to impact on the service. Blinatumomab is already available to patients in Scotland with relapsed/refractory ALL. The approval for this indication would be expected to displace some of the blinatumomab use in later settings.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of blinatumomab, as an orphan and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- ALL is a rare, relapsing, aggressive illness that is associated with significant mortality. Patients on average are diagnosed relatively young, and therefore may still be working or caring for younger or older family members. Presence of MRD and fear of relapse has a major psychological toll on patients and carers alike.

- The presence of MRD following treatment with chemotherapy is the most important prognostic factor for relapse. Furthermore, patients with MRD positivity who undergo bone marrow transplant have worse outcomes than patients who have no signs of MRD. Bone marrow transplants are the goal for most patients in this setting as it is the only intervention that offers a potential cure.

- At present, there are no other options for patients in CR with MRD. Clinicians expressed concerns with prescribing additional chemotherapy, due to limited efficacy and the risk of cumulative toxicity. Patients with MRD would be considered for transplant in a similar way to MRD negative patients despite the fact that they are at higher risk of relapse post-transplant. There is therefore a high unmet need for patients with MRD following intensive chemotherapy.

- Blinatumomab has been shown to be highly effective at eradicating MRD, which is expected to translate into improved relapse-free survival and overall survival benefits for patients. Eliminating MRD gives better control of the disease, which results in more patients receiving potentially curative bone marrow transplants. Additionally, patients who receive bone marrow transplants have better outcomes if they are MRD negative prior to transplant. The majority of patients in the clinical studies achieved complete MRD response after only one cycle of blinatumomab, offering hope for those who wish to undergo transplant or in those who have no other option.

- Blinatumomab is generally well tolerated, and the majority of the administration can be given in an outpatient setting, resulting in less time attending hospital. This would be beneficial for patients, carers and family members alike.

- Blinatumomab is already available in Scotland for patients with relapsed/refractory ALL. The approval of blinatumomab for the indication under review would result in patients receiving this treatment earlier in the treatment pathway, which patients and clinicians feel is preferable as patients will derive the benefits of blinatumomab sooner. Receiving blinatumomab in this setting may reduce the need for further treatments in the future.

Additional Patient and Carer Involvement
We received a patient group submission from Leukaemia CARE, which is a registered charity. Leukaemia CARE has received 12.6% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Leukaemia CARE participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis for the comparison of blinatumomab to SoC, defined as combination chemotherapy (as per UKALL14 treatment protocol) in adult patients with Philadelphia chromosome negative CD19 positive B-precursor ALL in first complete remission (CR1). This population is narrower than the full licensed indication stated by the company which included patients in first and second complete remission (CR1/2).

A de novo partitioned survival analysis model was developed which evaluated relapse-free and overall survival, overall costs and quality-adjusted life years in weekly cycles over a life-time horizon of 50 years. The model included three health states: pre-relapse, post-relapse and dead with all patients assumed to start in the relapse-free state.

The main clinical evidence came from the indirect comparison described above. Patients from a historical study were matched on baseline characteristics to patients from BLAST, using ATT (average treatment effect on the treated) weights. The effect of application of ATE (average treatment effect) weights was explored in the model and it has an impact on the cost-effectiveness. Parametric “cure” models (assumed cure point was 5 years relapse-free survival) for RFS and OS were fitted in order to extrapolate the observed time-to-event data from the matched population. The first five best fitting parametric cure models were selected using BIC statistics, visual inspection and expert opinion. In the base case analysis, the unrestricted Gompertz and the lognormal mixture cure models were selected for the RFS and OS curves, respectively. Parametric models where the RFS and OS curves crossed at any point were not considered regardless of goodness of fit.

Mortality was incorporated into the model by adjusting the RFS and OS curves by age and sex matched general population mortality estimates and then using the maximum of the probability of death from RFS, OS and general population mortality distributions. Mortality rate in the model

was assumed to always fall between the adjusted general population mortality rate and four times that rate.

Data from the matched sample of BLAST and the historical control study were also used to model the proportion of patients receiving pre-relapse HSCT. The rate of post-relapse HSCT was assumed to depend on pre-relapse transplant receipt and was estimated using data from the no prior salvage therapy subgroup from a historical comparator study for patients with Ph-R/R B-precursor ALL. However, the model structure does not allow tracking HSCT patients who subsequently relapse and an approximation of 15.8% and 20.1% of with and without pre-relapse HSCT would receive post-relapse transplantation was used in the model. On request, the results from a semi-Markov decision model that overcome the issue of tracking HSCT patients was submitted (Table 4). However, estimating transition probabilities, dealing with competing risks by censoring patients at the time of event resulted in a very small sample size. All relapsed patients were assumed to receive a first line salvage therapy regimen dependent on their initial treatment.

Treatment-specific health state utility values for the pre-relapse patients were derived through analysing EQ-5D data for the matched population (n=73) from BLAST using GLM/GEE regression models. Utility scores were derived using UK population tariffs. Estimates of pre-relapse health state utility value were adjusted for baseline EQ-5D score, on/off blinatumomab, MRD response and proximity to death (six months). Utility value for the post-relapse state was derived using indirect comparison and mapping techniques. Utility decrements associated with time since HSCT, proximity to death and long-term effects on quality of life due to radiotherapy, chemotherapy, and HSCT after five years relapse-free (cure point) were applied in the model and are shown in table 3.

Table 3 Health state utility values used in the model

Health state	Utility value
Pre-relapse	
Blinatumomab, on treatment in cycle 1, >6 months prior to death	0.792
Blinatumomab, on treatment in cycle 2, >6 months prior to death	0.832
Blinatumomab, off treatment in cycle 1, >6 months prior to death	0.802
Blinatumomab, off treatment in cycle 2, >6 months prior to death	0.842
SoC, >6 months prior to death	0.806
Post-relapse	0.692 (0.002)

Abbreviations: SoC, standard of care

A comprehensive list of costs and resource use was included in the company submission. The treatment-specific cost of blinatumomab treated patients included the acquisition and administration cost of blinatumomab, CSF prophylaxis therapy every three months, salvage therapy with multi-agent chemotherapy or inotuzumab. Cost of patients treated with SoC chemotherapy included medication and administration costs and salvage therapy with inotuzomab or blinatumomab. Further costs included in the model were initial and follow-up cost of HSCT, other MRD response dependent inpatient and outpatient costs, cost of first line of salvage therapy terminal care costs. Two sources of data for the MRD response- dependent inpatient and outpatient resource use were identified in the company submission, one based on a face-to-face interview with two UK based physicians (used in the base case) and an online survey

of 20 UK physicians. The choice of source of data on MRD response- dependent inpatient and outpatient resource use affects the cost-effectiveness (Table 4). Another uncertainty comes from the choice of first-line salvage therapy as the assumed distribution is difficult to verify due to the lack of data and varying clinical practice. Adverse events were not explicitly modelled and the cost of additional inpatient and outpatient resource use was assumed to cover the cost of adverse events indirectly.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

In the base case, the incremental cost-effectiveness ratio (ICER) with PAS was £14,148.

A range of deterministic scenario analyses were presented by the submitting company in order to explore the uncertainty around some of the model parameters. Selected scenario analyses which have the biggest impact on the ICER are presented in table 4 below.

Table 4: Key sensitivity analyses, with PAS

No.	Description	ICER (per QALY)
	Base case	**£14,148**
1	ATE weights	£22,414
2	Salvage treatment with SoC only	£28,192
3	Healthcare resource use (HRU) data from online survey	£26,829
4	Assumed proportion of blinatumomab patients receiving HSCT using 95% CI upper limit	£39, 009
5	Assumed base case salvage costs increased by 50%	£32,199
6	Updated base case using latest data cut (Jan 2019) model	£16, 523
7	Semi-state transition model	£19, 428
8	Updated proportion of SoC patients receiving HSCT (28.5%)	£23, 440
9	Survival projections for SoC increased by 25%	£41,478

The following limitations were noted:

- The clinical evidence which feeds into the economic model comes from an indirect matching comparison of 73 patients from a single-arm, multicentre, open-label trial (BLAST) and a historical study where patients were treated with various regimens of chemotherapy. As noted, there are major limitations with the evidence source used in the model. In response to concerns about the comparative clinical evidence used to inform the economic model, the company provided some additional exploratory sensitivity analysis to show the impact of increasing the efficacy of SoC by 15%- 25%. The impact on the ICER for the 25% increase is provided in table 4, scenario 9 as an example.
- There is uncertainty around the treatment regimens included in the historical study; only vincristine, prednisolone, mercaptopurine and methotrexate were included in the comparator

used in the economic evaluation and also if maintenance chemotherapy is the only relevant comparator. The company provided some additional sensitivity analysis removing the costs associated with the comparator regimen and this increased the ICER to £18,408.

- The population in the economic evaluation defined as adult patients with Ph- MRD+ BCP-ALL in CR1 was narrower than the licensed indication which considered patients in first and second remission.
- There are uncertainties around the outcomes (PFS and OS) for patients who received HSCT. Since a much higher proportion of patients treated with blinatumomab received HSCT (72.6%) compared to SoC (28.5%), the relative treatment effect is potentially biased towards blinatumomab.
- A substantially higher proportion of pre-relapsed patients in the blinatumomab group (47.1%) experienced a RFS event which was death compared to those in the SoC arm (8.5%) following HSCT. Therefore, a lower proportion of patients in the blinatumomab arm would have to opportunity to experience an event (relapse) compared to SoC patients. This would potentially underestimate the proportion of patients who relapse in the blinatumomab group.
- There are uncertainties associated with some of the resource use included in the model such as additional inpatient and outpatient resource use by MRD response as well as the assumed first-line of salvage therapy. Both of these inputs impact the ICER.

The Committee also considered the benefits of blinatumomab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the potential to bridge to a definitive therapy was satisfied; In addition, as blinatumomab is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted blinatumomab for restricted use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

The European Society for Medical Oncology (ESMO) in April 2016 published their clinical guideline for ALL, titled “Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up”. Treatment recommendations are broadly divided into two categories: newly diagnosed ALL and relapsed/refractory ALL. Standard treatment has yet to be established in ALL, however most induction regimens involve use of vincristine, corticosteroids, and anthracycline (daunorubicin, doxorubicin, rubidazone, idarubicin), with or without cyclophosphamide or cytarabine. For B-cell precursor ALL with short first CR or primary refractory disease, the guideline states consideration should be given to blinatumomab or inotuzumab (via entry into a study or otherwise), as both have shown promising results in phase II studies. Further phase III studies are being conducted. It is important to note that inotuzumab is only currently

licensed for relapsed/refractory CD22-positive B-cell precursor ALL. A clinical study investigating CD19 chimeric antigen receptor t-cell (CAR-T) treatment is another potential option.[6]

Additional information: comparators

UKALL14 protocol is the most relevant comparator, but some patients from UKALL2011 and UKALL60+ may also be eligible to receive blinatumomab for the indication under consideration.

Cost of relevant comparators

Medicine	Dose Regimen	Total cost of treatment (£)
blinatumomab	**Patients ≥45kg: 28mcg/day continuous intravenous (IV) infusion for 28 days, followed by a 14 day treatment-free interval (1 cycle)** **Patients can receive up to a maximum of 4 cycles.**	**£56,476 to £225,904 (1 to 4 cycles)**

Costs from BNF online on 4 October 2019. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 5 patients per year to which confidential estimates of treatment uptake were applied**.** SMC clinical experts suggest that patient numbers may be underestimated.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 15 November 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.