

6.01 BLINATUMOMAB, Powder for I.V. infusion 38.5 micrograms, Blincyto[®], Amgen

1 Purpose of Application

- 1.1 The submission requested a Section 100 Authority Required (Efficient Funding of Chemotherapy) listing for blinatumomab for the treatment of patients with B-cell precursor acute lymphoblastic leukaemia (B-ALL) in haematological complete remission with minimal residual disease (MRD) following chemotherapy. This was the first consideration by the PBAC of blinatumomab for this indication.
- 1.2 Listing was requested on a cost-effectiveness basis compared to consolidation chemotherapy.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Patients with B-ALL in haematological complete remission with minimal residual disease after induction/consolidation chemotherapy.
Intervention	Blinatumomab continuous intravenous infusion 28 micrograms daily for 28 days followed by 14 days treatment free (one treatment cycle). Patients may have up to four treatment cycles per complete remission.
Comparator	Standard of care chemotherapy, i.e. consolidation/maintenance chemotherapy.
Outcomes	Relapse-free survival, overall survival and safety.
Clinical claim	Blinatumomab is superior in terms of efficacy and non-inferior in terms of safety compared to standard of care chemotherapy.

Source: Table 13, p.2 of the submission.

- 1.3 Blinatumomab was recommended for listing for relapsed/refractory Ph- B-ALL under a managed entry scheme in July 2016, following a rejection in November 2015 due to uncertainties in comparative clinical effectiveness and a high and uncertain ICER. A minor resubmission in November 2016 requested that the July 2016 recommendation be revised to remove the managed entry scheme (as the data requested could not be provided) and included a price reduction. The minor resubmission was recommended and blinatumomab was listed on the PBS for patients with relapsed/refractory Ph- B-ALL in May 2017.

2 Requested listing

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BLINATUMOMAB 38.5 µg, injection, 1 vial	784 µg	3-1	\$81417.39 (public)	Blincyto® Amgen Pty Ltd Australia
BLINATUMOMAB 38.5 µg, injection, 1 vial	784 µg	3-1	\$82594.79 (private)	Blincyto® Amgen Pty Ltd Australia

Category / Program	Section 100 – Efficient funding of Chemotherapy (S100 EFC Public) Section 100 – Efficient funding of Chemotherapy (S100 EFC Private)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Acute lymphoblastic leukaemia (ALL)
PBS Indication:	B-cell precursor acute lymphoblastic leukaemia (B-ALL) in complete haematological remission with minimal residual disease (MRD) <i>Minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL) in patients in complete haematological remission</i>
Treatment phase:	Initial and Continuing treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Patient Must be treated by a physician experienced in the treatment of haematological malignancies.
Clinical criteria:	The condition must be B-cell precursor acute lymphoblastic leukaemia with an Eastern Cooperative Oncology Group (ECOG) performance status of less than 2, AND The condition must not be present in the CNS central nervous system or testis, AND Patient must have received intensive combination chemotherapy for initial treatment of ALL or for subsequent salvage therapy, AND Patient The condition must have less than 5% blasts in bone marrow, AND Patient must have minimal residual disease defined as at least 10 ⁻⁴ (0.01%) blasts based on measurement in bone marrow, documented after an interval of at least 2 weeks from last systemic chemotherapy, AND Minimal residual disease must be measured using polymerase chain reaction or flow cytometry, AND The treatment must not be more than 2 treatment cycles under this restriction in a lifetime. The treatment must not be more than 4 treatment cycles in this current remission.

<p>Prescriber Instructions</p>	<p>According to the proposed TGA-approved Product Information, hospitalisation is recommended at 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 (e.g. if treatment is interrupted for 4 or more hours), supervision by a health care professional or hospitalisation is recommended.</p> <p>MRD testing sites should attempt to use the most stringent measure available.</p> <p>An amount of 784 microgram will be sufficient for a continuous infusion of blinatumomab over 28 days in each cycle.</p> <p>Blinatumomab is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.</p> <p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> (1) a completed authority prescription form; (2) a completed Minimal residual disease positive Acute Lymphoblastic Leukaemia PBS Authority Application - Supporting Information Form; (3) proof of complete remission; (4) date of most recent chemotherapy, and if this was the initial chemotherapy regimen or salvage therapy; and (5) a copy of the most recent MRD results and bone marrow biopsy report of no more than one month old at the time of application. <p>Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time when an assessment is required must cease PBS-subsidised therapy with this agent.</p> <p>A patient may only qualify for PBS-subsidised initiation treatment with blinatumomab once in a lifetime under either this restriction or the induction treatment restriction for relapsed or refractory B-precursor cell ALL.</p>
<p>Administrative Advice</p>	<p>A complete remission is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a full recovery of peripheral blood counts with platelets of greater than 100,000 per microliter, and absolute neutrophil count (ANC) of greater than 1,000 per microliter.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

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Caution	Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome, neurological toxicities and reactivation of John Cunningham virus (JC) viral infection.
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Category / Program	Section 100 – Efficient funding of Chemotherapy (S100 EFC Public) Section 100 – Efficient funding of Chemotherapy (S100 EFC Private)
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Condition:	Acute lymphoblastic leukaemia (ALL)
PBS Indication:	B-cell precursor acute lymphoblastic leukaemia (B-ALL) in complete haematological remission with minimal residual disease (MRD) Minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL) in patients in complete haematological remission
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Patient Must be treated by a physician experienced in the treatment of haematological malignancies.
Clinical criteria:	Patient must have previously received PBS-subsidised initial treatment with this drug for this condition, AND Patient must have achieved a complete remission, AND Patient must be MRD negative defined as either undetectable using the same assay as used to determine original eligibility or less than 10 ⁻⁴ (0.01%) blasts based on measurement in bone marrow, AND Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition, AND The treatment must not be more than 2 treatment cycles under this restriction in a lifetime.
Prescriber Instructions:	Per Initial restriction

<p>Administrative Advice</p>	<p><i>A complete remission is defined as bone marrow blasts of less than or equal to 5%, no evidence of disease and a full recovery of peripheral blood counts with platelets of greater than 100,000 per microliter, and absolute neutrophil count (ANC) of greater than 1,000 per microliter.</i></p> <p><i>Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time when an assessment is required must cease PBS-subsidised therapy with this agent.</i></p> <p><i>No increase in the maximum quantity or number of units may be authorised.</i></p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i></p> <p><i>Special Pricing Arrangements apply.</i></p>
<p>Caution</p>	<p><i>Careful monitoring of patients is required due to risk of developing life-threatening Cytokine Release Syndrome, neurological toxicities and reactivation of John Cunningham virus (JC) viral infection.</i></p>

- 2.2 The submission proposed that the existing rebate specified in the current Special Pricing Arrangement for blinatumomab (in the relapsed/refractory setting), comprising a ██████% rebate on the published AEMP per vial of \$2,904.77, would remain unchanged. The submission further proposed that the subsidisation caps specified in the risk sharing arrangement be adjusted to account for the additional use.
- 2.3 The PBAC considered that a continuing restriction would be required to limit PBS-subsidised use of blinatumomab to patients who have responded to the drug (i.e. are MRD negative and in complete remission) after two cycles, noting that all patients in the BLAST study who became MRD negative did so within two cycles. The PBAC considered this would require a maximum of one repeat for each of the initial and continuing restrictions.
- 2.4 The ESC noted that the requested restriction did not limit use based on patient age (i.e. use in adult and paediatric patients would be allowed). Further, the restriction did not specify Philadelphia chromosome status, which differs from the existing blinatumomab restriction which is for Ph- patients only. Data for paediatric, adolescent or Ph+ patients was either absent or limited in the submission.
- 2.5 Patients achieving multiple remission periods would be eligible for multiple courses of blinatumomab therapy under the requested restriction (i.e. the submission requested blinatumomab be available for re-use in subsequent periods of complete remission in patients who are MRD positive under the proposed restriction, and requested that patients with relapsed/refractory Ph- B-ALL be eligible for re-use under the existing blinatumomab restriction). However, the submission did not present any evidence for re-use of blinatumomab in subsequent periods of complete remission, and did not

account for multiple courses of blinatumomab in the economic model and financial estimates. The pre-PBAC response acknowledged the lack of evidence to support re-use of blinatumomab, but considered that re-use would be uncommon given “the rarity of the disease and available treatment options”.

- 2.6 The PBAC noted that the requested restriction would allow use of blinatumomab in any line of complete remission. The PBAC considered that the clinical data indicated that blinatumomab may be more effective in the first complete remission (CR1) setting than in later remissions, but that, over time, blinatumomab would predominantly be used in CR1 (i.e. in incident patients, and also because remissions may become less common in the presence of effective earlier-line therapies). The PBAC considered that it is currently uncommon for patients to get to a third period of complete remission, but considered that this may change in the future with the availability of blinatumomab and other novel treatments.
- 2.7 The requested restriction defines MRD as at least 10^{-4} (0.01%) blasts based on measurement in bone marrow, documented at least 2 weeks after the last systemic chemotherapy, and recommends MRD should be assessed using the most stringent measure available. The methodology (polymerase chain reaction (PCR) or flow cytometry), procedure and sensitivity of the tests used to determine MRD was not defined in the proposed restriction. The evaluation and the PBAC considered that, given differences between methods in terms of sensitivity and analytic variability, the eligible population under the requested restriction may vary with the method of MRD assessment because:
- The requested restriction enables use when MRD is detected at a lower level ($\geq 10^{-4}$ blasts, or 0.01%) than is supported by the key study presented in the submission, BLAST, which enrolled patients with MRD at or above 0.1% ($\geq 10^{-3}$). Thus, the proposed PBS population may include patients with less severe disease or a lower risk of relapse than in the key study.
 - Key evidence presented in the submission from the BLAST study used assays with a minimum sensitivity of 10^{-4} (by rearrangement of immunoglobulin (Ig) measured by PCR; or flow cytometry marker profile). The submission acknowledged that some methods used in current practice have higher assay sensitivity (e.g. sensitivity of 10^{-4} to 10^{-6} for 6 to 9 colour flow cytometry).
- 2.8 The Pre-Sub-Committee Response (PSCR) stated that it would not expect the treatment effect of blinatumomab to vary with the MRD cut-off used. To support this it cited a meta-analysis that investigated the association of MRD with clinical outcomes in patients with ALL (regardless of treatment received), based on studies published between 2000 and 2014 (Berry et al, 2017). While this analysis suggested that baseline MRD is an important negative prognostic determinant regardless of the MRD threshold used, it did not inform whether the relative treatment effect of blinatumomab would be consistent across different MRD levels. The PBAC also noted that subgroup analyses from the BLAST study indicated that blinatumomab was

similarly effective if the MRD level was above or below 10^{-2} . However, the Committee considered that this observation could not be extrapolated to lower MRD thresholds (e.g. above or below 10^{-3} or 10^{-4}).

- 2.9 The ESC and PBAC advised that a MRD level of $\geq 10^{-4}$, as proposed in the restriction, is the threshold used in current clinical practice to define MRD (though noting it was lower than the threshold used in the key clinical study of $\geq 10^{-3}$), however the PBAC noted that this threshold was based on consensus (clinical opinion) rather than strong evidence.
- 2.10 The ESC and the PBAC considered that more sensitive assays are being developed, and if lower MRD thresholds were to be used in the future then the risk profile and number of eligible patients may change. Further, the ESC and PBAC considered that the clinical relevance of thresholds below 10^{-4} was not established.
- 2.11 The submission stated that MRD assessment in adult patients with ALL is evolving and is increasingly being adopted as routine, and that it is routinely undertaken in paediatric patients. Timing of MRD assessment is recommended on completion of initial induction chemotherapy, with follow up assessment guided by treatment regimen and clinician discretion on a patient-by-patient basis. However, MRD testing is not currently subsidised under the Medicare Benefits Schedule (MBS). The submission stated that it anticipated that fewer than 300 patients would be assessed for eligibility for blinatumomab each year and that many of these patients are already being tested under current arrangements. The submission did not provide further information as to how these tests were being funded and whether consistent access was available throughout Australia.
- 2.12 The ESC considered that MRD testing is routinely conducted in Australian clinical practice at multiple time points in the clinical pathway, with patients generally being tested at the end of each cycle (e.g. at intervals of around 28 days). The ESC considered that this would align with the proposed restriction which requires patients to have MRD testing at least two weeks after their last systemic chemotherapy.
- 2.13 The PBAC considered that access to MRD testing was not consistently available throughout Australia.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 Blinatumomab was TGA registered for the treatment of patients with B-ALL in haematological remission with MRD on 18 May 2018.
- 3.2 The approved TGA indications are for:

“the treatment of minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL) in patients in complete haematological remission”; and “the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukaemia,” (i.e. including both Ph+ and Ph- patients);

Note to indication: the indications in Philadelphia positive, MRD positive and paediatric patients were approved based on phase II, non-randomised evidence. An improvement in clinical outcomes by direct prospective comparison in a randomised setting relative to other standard-of-care salvage therapies has not been established.”

4 Population and disease

- 4.1 Acute lymphoblastic leukaemia (ALL) is a rare malignant disease of the bone marrow in which lymphoid precursor cells proliferate (approximately 1-1.5/100,000 of the general population). The incidence of ALL is highest in children under 5 years of age, declines slowly until the mid-20s and then begins to rise again slowly after 50 years of age. ALL may be related to either B-cell or T-cell precursors, with the majority of diagnoses identified as B-cell precursor ALL (B-ALL).
- 4.2 ALL is characterised by the emergence of haematological deficiencies, anaemia, thrombocytopenia and neutropenia, that give rise to the distinctive symptoms of fatigue, bruising, bleeding, enlarged lymph nodes, fever, and infections. Hepatomegaly, splenomegaly, and lymphadenopathy may also be observed, as well as symptoms related to central nervous system or testicular involvement (headache, weakness, seizures, vomiting, testicular enlargement).
- 4.3 While most patients achieve haematological complete remission or partial remission after intensive induction chemotherapy, the risk of relapse is strongly correlated with the level of post-induction residual disease detectable in bone marrow or peripheral blood. Prognosis is generally positive in children, and less favourable with increasing age.
- 4.4 Relapse in B-ALL is believed to result from residual leukaemic blast cells persisting in haematological complete remission, at levels not detected in conventional morphologic assessments (<5% blast cells in bone marrow). The presence of residual leukaemic blast cells (in patients who have been assessed as having complete remission as assessed by conventional morphology analyses) is referred to as minimal residual disease (MRD).
- 4.5 More sensitive assays such as multicolour flow cytometry and PCR provide detection of lower concentrations of MRD at levels of prognostic significance strongly correlated with risk of relapse. A meta-analysis of MRD and clinical outcomes in adults and children with ALL (Berry et al. 2017) found MRD detected by multicolour flow cytometry or polymerase chain reaction correlated with risk of relapse, and that reduction or eradication of MRD provided clinically important patient benefits, regardless of cytogenetic subgroups.

- 4.6 Different techniques have different sensitivities. Real-time quantitative PCR targeting immunoglobulin (Ig) can amplify a DNA or cDNA sequence unique to the leukemic clone cell resulting in assay sensitivity of 10^{-4} to 10^{-5} . Multicolour flow cytometry based on aberrant antigen expressions has an assay sensitivity of approximately 10^{-4} , or about 1 log less than PCR. While MRD assessment by multi-parametric flow cytometry and PCR are highly correlated, differences in methodology and sensitivity may influence results and therapeutic decisions (Berry et al. 2017).
- 4.7 The submission stated that access to blinatumomab may increase the probability (but not affect eligibility) that a patient will receive an allogeneic HSCT as it may provide a “bridge” to HSCT. The ESC considered that this would represent an appropriate use of blinatumomab, but noted that this was not fully accounted for in the economic model or financial estimates.
- 4.8 The proposed clinical algorithm positions blinatumomab as an alternative to consolidation chemotherapy in patients with MRD following achievement of haematological complete remission after induction chemotherapy. Following treatment with blinatumomab or consolidation chemotherapy, patients may receive either maintenance chemotherapy (low risk patients in first complete remission) or allogeneic HSCT (high risk patients in first complete remission or all patients in any subsequent complete remission).
- 4.9 The proposed clinical management algorithm includes the addition of a sub-algorithm for the assessment of MRD following achievement of haematological complete remission after initial induction chemotherapy. This sub-algorithm also introduces the use of blinatumomab as a treatment option for molecular relapse in patients who are initially MRD negative. No data were provided in the submission to support the use of blinatumomab as a treatment for molecular relapse.

For more detail on PBAC’s view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated standard of care post-induction chemotherapy regimens for the consolidation and/or maintenance of haematological complete remission, as the main comparator.
- 5.2 The submission noted that there are currently no specific treatments available for patients with B-ALL in haematological complete remission with MRD post-induction chemotherapy, but acknowledged that patients achieving complete remission post induction may continue treatment with consolidation/maintenance chemotherapy or HSCT.
- 5.3 The evaluation considered that the appropriate comparator for blinatumomab was unclear due to its uncertain place in therapy. One of the reasons for the uncertain place in therapy was because blinatumomab may be initiated at many points along the treatment algorithm. The evaluation considered that, as such, it was unclear

whether blinatumomab is likely to target a new place in therapy as a primary or adjunctive therapy to improve or delay other treatment options, or to directly replace existing therapies. Thus the evaluation considered that HSCT or placebo may also be relevant comparators.

- 5.4 The PSCR reiterated that the submission's nominated comparator was appropriate, and argued that while the response to blinatumomab may alter the next therapeutic action (e.g. bridge to transplant) this would be a consequence of use rather than a comparator.
- 5.5 The ESC considered that blinatumomab may be used in a number of discrete therapeutic roles including as a primary treatment, disease suppression until HSCT (bridge to transplant), optimisation of HSCT (by eliminating MRD) and treatment of molecular relapse. The ESC and the PBAC considered that standard of care chemotherapy, as nominated by the submission, was the appropriate comparator in all these settings.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed that MRD status is correlated with improved health outcomes, with MRD positivity being an accepted prognostic factor in paediatric patients and becoming more widely accepted in adult patients. The clinician discussed that emerging tests for detecting the presence of MRD are improving in sensitivity (e.g. next-generation sequencing). The sponsor also indicated that randomised controlled trials were ongoing for blinatumomab in this condition.

Consumer comments

- 6.2 The PBAC noted the advice received from health care professionals (2) outlining the likely use of blinatumomab in clinical practice. The comments described the benefits of treatment with blinatumomab in achieving complete MRD response, and described the use of blinatumomab as either a bridge to HSCT or as a primary treatment in patients for whom transplantation is not possible. The PBAC noted that this advice was consistent with the evidence provided in the submission.

Clinical trials

- 6.3 The submission was based on a propensity score indirect analysis of one single arm blinatumomab study (BLAST; N=116) and one retrospective historical control cohort study of patients receiving treatment with standard of care chemotherapy (Study 20120148; N=287) in patients with B-ALL in haematological remission with MRD. One additional supporting single arm blinatumomab study (MT103-202; N=21) was presented, but was not included in the propensity score-adjusted analysis.

6.4 Details of the studies presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Key single arm study		
BLAST (MT103-203) NCT01207388	<p>A confirmatory multicenter, single-arm study to assess the efficacy, safety, and tolerability of the BiTE® antibody blinatumomab in adult subjects with minimal residual disease (MRD) of B-precursor acute lymphoblastic leukemia.</p> <p>Gökbuget, N., et al. Blinatumomab for minimal residual disease in adults with B-precursor acute lymphoblastic leukemia.</p> <p>Gökbuget, N., et al. Long-term outcomes after blinatumomab treatment: Follow-up of a phase 2 study in patients (PTS) with minimal residual disease (MRD) positive b-cell precursor acute lymphoblastic leukemia (ALL).</p> <p>Gökbuget, N., et al. BLAST: A confirmatory, single-arm, phase 2 study of blinatumomab, a bispecific T-cell engager (BiTE®) antibody construct, in patients with minimal residual disease B-precursor acute lymphoblastic leukemia (ALL).</p>	<p>Report date: 24 September 2014.</p> <p>Blood First Edition Paper, online January 22, 2018. Blood 2015; 126(23): 680.</p> <p>Blood 2014; 124(21): 379.</p>
Retrospective historical control cohort study		
20120148 NCT02010931	<p>A retrospective analysis of haematological relapse free survival and overall survival in adult patients with Philadelphia-negative B-precursor acute lymphoblastic leukemia in complete haematological remission with minimal residual disease.</p> <p>Propensity score analysis of relapse free survival and overall survival among adult patients with minimal residual disease (MRD) in study 20120148.</p>	<p>Report date: 12 December 2014.</p> <p>Report date: 30 January 2017 (updated 19 February 2018).</p>
Supportive single arm study		
MT103-202 NCT00560794	<p>An open-label, multicenter phase 2 study to investigate the efficacy, safety, and tolerability of the Bi-specific T-cell engager (BiTE®) MT103 in patients with minimal residual disease (MRD) of positive B-precursor acute lymphoblastic leukemia (ALL).</p> <p>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.</p> <p>Klinger, M., et al. Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell-engaging CD19/CD3-bispecific BiTE antibody blinatumomab.</p> <p>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.</p>	<p>Report date: 7 November 2013.</p> <p>Blood 2012; 120(26): 5185-5187.</p> <p>Blood 2012; 119(26): 6226-6233.</p> <p>Journal of Clinical Oncology 2011; 29(18): 2493-2498.</p>

Source: Tables 21 and 22, pp.27-29 of the submission.

Abbreviations: ALL, acute lymphoblastic leukaemia; MRD, minimal residual disease.

6.5 The key features of the studies are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design	Risk of bias	Intervention	Patient population	Outcome	Use in model
BLAST	116	Phase II, open label, multicentre, single arm	High	Blinatumomab IV 15 mcg/m ² /day (4 wks), Treatment free (2 wks), Up to 4 cycles.	B-ALL ≥18 years, haematological complete remission, MRD ≥10 ⁻³ in an assay with minimum sensitivity of 10 ⁻⁴ by PCR or flow cytometry, ECOG performance status ≤1.	MRD response rate, haematological RFS at 18 months, overall survival from first blinatumomab dose, 100-day mortality after alloHSCT; EQ-5D, EORTC-QLQ-C30	Propensity score-adjusted hazard ratios (ATT in base case).
MT103-202	21	Phase II, exploratory, open label, multicentre, single arm	High	Blinatumomab IV 15 mcg/m ² /day (4 weeks), Treatment free (2 weeks), Increased to 30 ug/m ² /day if no response cycle 1, increased for all non-responders cycle 2.	B-ALL ≥18 years, Haematological complete remission, MRD ≥10 ⁻⁴ in an assay with minimum sensitivity of 10 ⁻⁴ by PCR, ECOG performance status ≤1.	MRD response rate, haematological RFS, MRD progression.	Not used
20120148	287	Retrospective historical cohort	High	Non-interventional, Standard-of-care treatment as per site study protocols.	Ph- B-ALL ≥15 years, Haematological complete remission, MRD ≥10 ⁻⁴ by PCR or ≥10 ⁻³ by flow cytometry.	Haematological RFS, overall survival from MRD detection, 100-day mortality after alloHSCT,	Propensity score-adjusted survival curve (ATT in base case)

Source: Table 23, p.31 of the submission.

Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplantation; ATE, average treatment effects; ATT, average treatment effect of the treated weights; B-ALL, B-cell precursor acute lymphoblastic leukaemia; ECOG, Eastern Cooperative Oncology Group; MRD, minimal residual disease; Ph-, Philadelphia chromosome negative; PCR, Polymerase chain reaction; RFS, relapse free survival.

- 6.6 Both blinatumomab studies presented in the submission included adult patients only. No data were presented to support the use of blinatumomab in paediatric and adolescent patients, who would be eligible for blinatumomab under the requested restriction. Further, the product information does not provide guidance on dosing of paediatric patients with MRD (i.e. patients <45 kg). The 20120148 study (historical control) excluded Philadelphia positive patients and patients exposed to blinatumomab within the prior 18 months.
- 6.7 The PBAC also noted that the blinatumomab dose used in the studies differed to that requested for PBS-listing (15 mcg/m²/day in BLAST versus a fixed dose of 28 µg/day requested). Further, the PBAC noted that the recommended duration of hospitalisation for the first cycle differed from that recommended in the relapsed/refractory Ph– setting, and considered that the basis that this difference was not clear.
- 6.8 There were substantial differences between the study populations of the two studies compared in the propensity score indirect analysis: the BLAST and 20120148 studies.

Patients in the BLAST study (of blinatumomab) were older (46 years at screening vs 34 years at diagnosis), reported shorter mean time from diagnosis (6 months vs 20 months) and were more likely to be in second or third remissions (35.3% vs 1%) compared to Study 20120148 (historical control). There were differences between study inclusion criteria in terms of age (≥ 18 years in BLAST, ≥ 15 years in Study 20120148) and MRD assessment threshold ($\geq 10^{-3}$ or $\geq 10^{-4}$ in bone marrow detected by PCR or flow cytometry).

- 6.9 In addition, most patients in Study 20120148 (89.5%) were assessed for MRD and treated between 2000-2010, while patients in the BLAST study were assessed and treated after 2010. Age, relapse history, and MRD level are known prognostic factors that affect patient outcomes and the absolute treatment effect of blinatumomab. While the selection of patients for the indirect analysis and propensity score adjustments lead to better matching of patient characteristics between studies, the evaluation and the PBAC considered that it may have reduced the applicability of results to the proposed PBS population.
- 6.10 Chemotherapy regimens used in Study 20120148 were poorly reported, and were described in the submission as standard of care chemotherapy regimens consistent with protocols and practice by site, at the time of administration (GMALL, GIMEMA, GRAALL, PETHEMA, UKALL, NILG). Treatment regimens were not described in the submission and therefore the chemotherapy regimens used in Study 20120148 (historical control) are unknown. The PSCR stated that survival outcomes are unlikely to have improved since Study 20120148 was conducted (2000 to 2010) as MRD represents disease that is insensitive to the multi-agent therapy used for induction and/or consolidation. However, the ESC noted that improvements have been reported in chemotherapy regimens and disease management for B-ALL patients since 2000 (Pulte et al. 2013; Ma et al. 2014), and considered that this may confound survival outcomes between the BLAST and 20120148 studies. The pre-PBAC response considered that the studies referred to by the ESC, Pulte and Ma, might not be applicable as they were based on male patients and children (aged 0-14 years), respectively.
- 6.11 The pre-PBAC response stated that Study 20120148 is the only large scale observational study that has reported outcomes in this patient population, and that patients in the study had received at least three intense blocks of age-appropriate standard or investigational chemotherapy regimens. Further, the pre-PBAC response stated that 65.5% of patients in the historic control study had their initial ALL diagnosis in 2005 or later, and 10.5% of patients were diagnosed post-2010. The PBAC considered that, as the majority of patients were treated more than a decade ago, the regimens may not reflect current practice and that differences in chemotherapy regimens and disease management may account for some of the differences in outcomes observed between BLAST and the historical control study.

6.12 Further the PBAC noted that Study 20120148 was conducted in the UK, Europe and Russia in order to match patients in the BLAST study. The PBAC considered that this may have further reduced the applicability to the current Australian PBS population.

Comparative effectiveness

6.13 Table 4 summarises the results of the primary outcome of the BLAST study, MRD response in cycle 1.

Table 4: BLAST Complete MRD response (Primary endpoint FAS)

Complete MRD response	Primary endpoint full analysis set (N=113)	
	N (%)	95% CI
Complete MRD response cycle 1	88 (77.9%)	(69.1, 85.1)
MRD non-responders cycle 1	25 (22.1%)	(14.9, 30.9)
Complete MRD response overall	90 (79.6%)	(71.0, 86.6)

Source: Table 34, p.59 of the submission.

Abbreviations: CI, confidence interval; FAS, full analysis set; MRD, minimal residual disease.

NOTE: the primary endpoint full analysis set excluded 3 patients: 1 with no MRD assay results; and 2 with MRD assay $<5 \times 10^{-4}$.

6.14 In the BLAST study complete MRD response was achieved within one treatment cycle in 77.9% of patients, and an additional two patients achieved complete MRD response overall (both in cycle 2).

6.15 Table 5 and Figure 1 summarise the results of the BLAST study for haematological relapse free survival at 18 months, censored and not censored at allogeneic HSCT (alloHSCT) or after post-blinatumomab chemotherapy. Philadelphia chromosome positive patients were excluded from the analysis.

Table 5: BLAST haematological relapse free survival, events at 18 months (Key secondary endpoint FAS; not censored or censored at alloHSCT or post-blinatumomab chemotherapy)

Relapse free survival	Key secondary endpoint full analysis set (N=110)	
	Not censored at alloHSCT or chemotherapy ^a	Censored at alloHSCT or chemotherapy ^a
Haematological relapse events, N (%)	62 (56.4%)	21 (19.1%)
- Relapse	37 (33.6%)	18 (16.4%)
- Secondary leukaemia	1 (0.9%)	1 (0.9%)
- Deaths	24 (21.8%)	2 (1.8%)
Censored, N (%)	48 (43.6%)	89 (80.9%)
Kaplan-Meier estimate, 18 months (95% CI)	0.53 (0.44, 0.62)	0.54 (0.33, 0.70)
RFS median, months (95% CI)	18.9 months (12.3, 35.2)	NE months (6.3, NE)

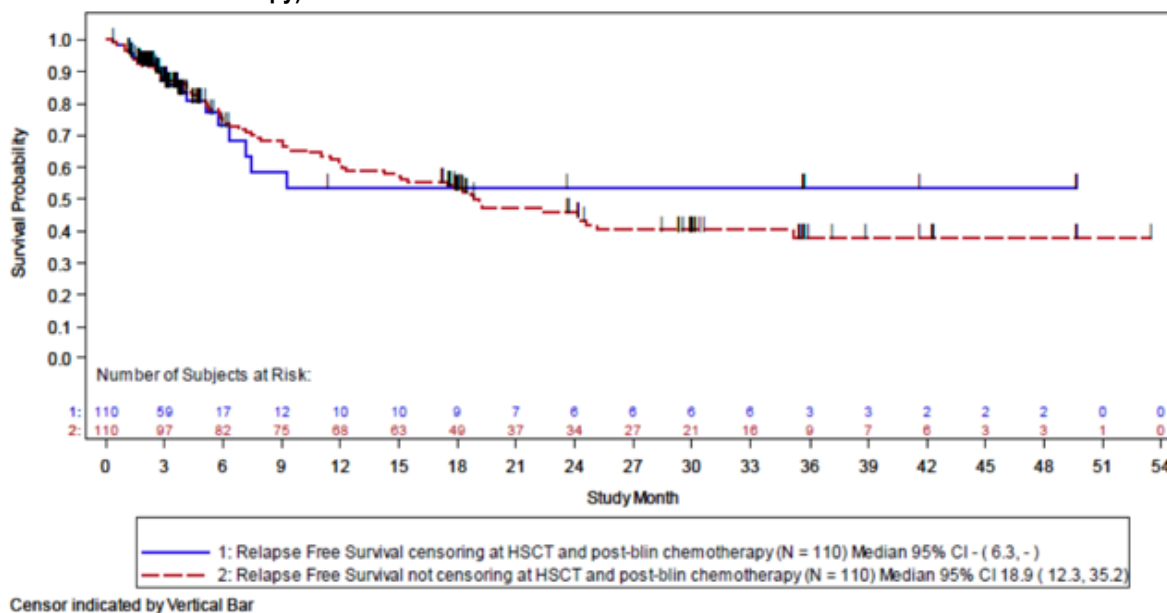
Source: Table 35, p.61 of the submission.

Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplantation; CI, confidence interval; FAS, full analysis set; NE, not estimable; RFS, relapse free survival.

^a Chemotherapy following treatment with blinatumomab.

NOTE: the key secondary endpoint full analysis set excluded 6 patients: 5 Philadelphia positive patients; and 1 patient with MRD assay $<5 \times 10^{-4}$.

Figure 1: BLAST Kaplan-Meier curves for haematological RFS (FAS, not censored or censored at alloH SCT or post-blinatumomab chemotherapy)



Source: Figure 11, p.62 of the submission; Figure 10.1, p.71 of MT103-203 CSR Jan 2016.
 Abbreviations: HSCT, haematopoietic stem cell transplantation; RFS relapse free survival.

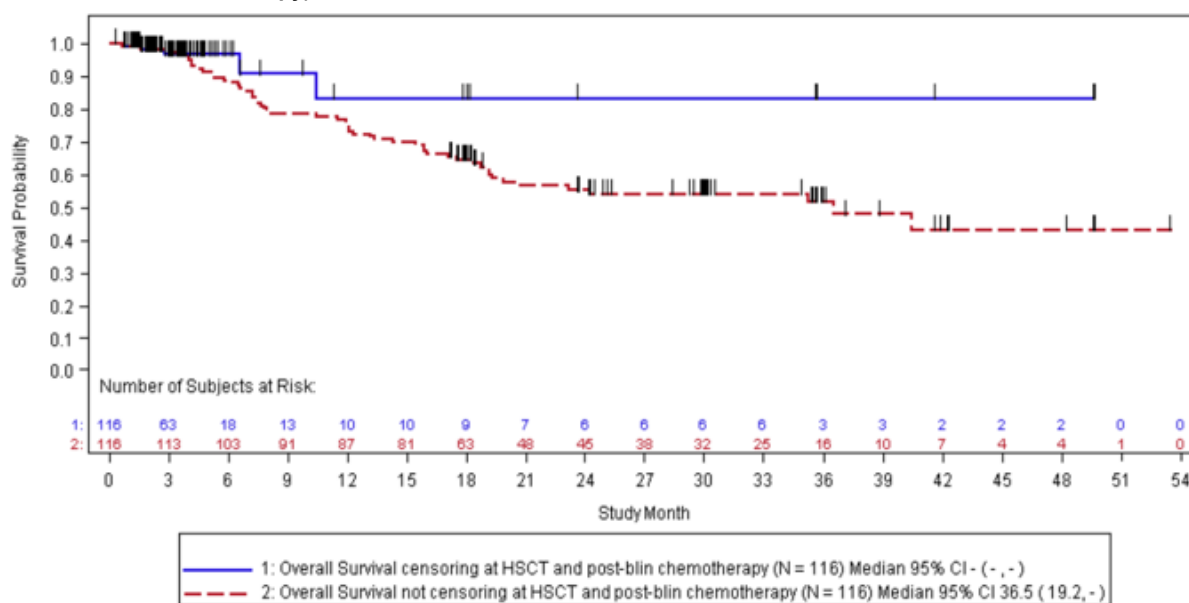
- 6.16 Median relapse free survival was 18.9 months without censoring at alloH SCT or after post-blinatumomab chemotherapy. When censored for alloH SCT and post-blinatumomab chemotherapy, median relapse free survival was not reached.
- 6.17 Table 6 and Figure 2 summarise the results of the BLAST study for overall survival for analyses censored and not censored at alloH SCT or after post-blinatumomab chemotherapy.

Table 6: BLAST overall survival (FAS; not censored or censored at alloH SCT or post-blinatumomab chemotherapy)

Overall survival	Full analysis set (N=116)	
	Not censored at alloH SCT or chemotherapy ^a	Censored at alloH SCT or chemotherapy ^a
Survival events (deaths), N (%)	53 (45.7%)	5 (4.3%)
Censored, N (%)	63 (54.3%)	111 (95.7%)
OS median months (95% CI)	36.5 (19.2, NE)	NE

Source: Table 35, p.61 of the submission and Table 14-4.3.1, p.189 of MT103-203 CSR Jan 2016.
 Abbreviations: alloH SCT, allogeneic haematopoietic stem cell transplantation; CI, confidence interval; FAS, full analysis set; NE, not estimable; OS, overall survival.
^a Chemotherapy following treatment with blinatumomab.

Figure 2: BLAST Kaplan-Meier curves for overall survival (FAS; not censored or censored at alloHSCt or post-blinatumomab chemotherapy)



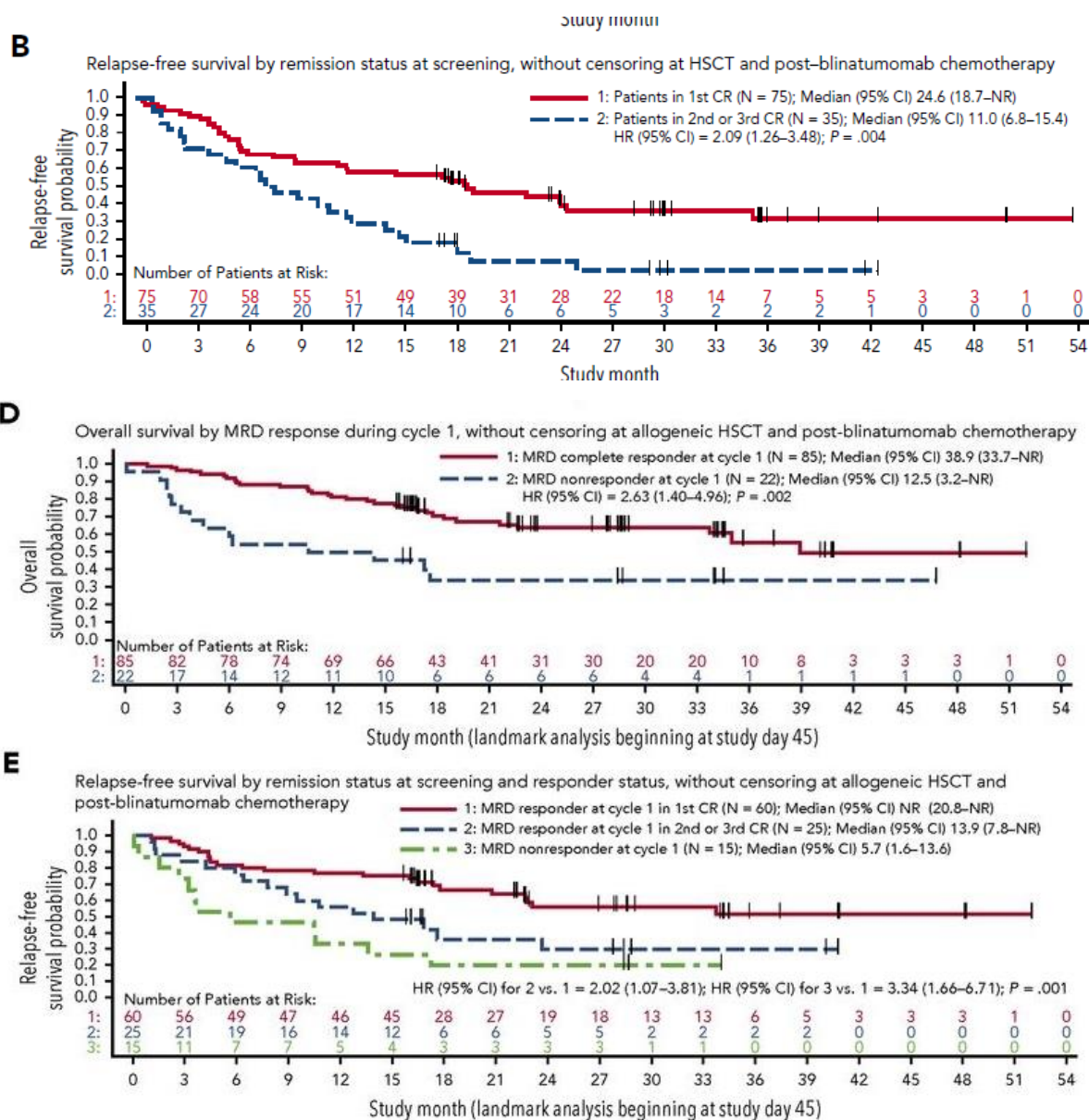
Censor indicated by Vertical Bar

Source: Figure 12, p.63 of the submission; Figure 10.6, p.78 of MT103-203 CSR Jan 2016.

Abbreviations: HSCT, haematopoietic stem cell transplantation.

- 6.18 Median overall survival was 36.5 months without censoring at alloHSCt or post-blinatumomab chemotherapy. With censoring for alloHSCt or post-blinatumomab chemotherapy, median overall survival was not reached.
- 6.19 The overall incidence of alloHSCt following blinatumomab was 77.6% (90/116). In patients who received alloHSCt after treatment with blinatumomab prior to relapse (N=74), overall survival at 100 days after alloHSCt was 93%. Median overall survival after alloHSCt was 30.6 months.
- 6.20 Mean change in EQ-5D was small across all five domains and not meaningful. Overall EQ-5D was not reported. Similarly, in the EORTC-QLQ-C30 there was a small improvement in the Global health status from baseline (3.9), with improvements in social, emotional, physical and role functioning and reductions in scores associated with the fatigue, nausea/vomiting and pain symptom scales.
- 6.21 The PBAC noted that subgroup analyses conducted in the BLAST study (presented in the figure below) suggested that blinatumomab may be more effective if used in CR1 (rather than CR2 or CR3) and/or if the patient was an “MRD responder” after Cycle 1.

Figure 3: RFS and OS among Ph+ patients (B) RFS by relapse history (D) OS by MRD response status in Cycle 1; (E) RFS by both relapse history and MRD response will status in Cycle 1^a



Source: Gökbuğet et al, Blinatumomab for minimal residual disease in adults with B-precursor acute lymphoblastic leukemia. *Blood*, 2018. 131(14), 1522-1531.

^a The three analyses were in evaluable patients (landmark analysis, excluding patients who were censored or had relapsed or died within 45 days of beginning treatment), without censoring at allogeneic HSCT or post-blinatumomab chemotherapy. Also only included evaluable patients, i.e. excluded 3 patients without MRD results or insufficient sensitivity of the assay.

Indirect comparison

6.22 The submission presented a propensity score indirect analysis comparing blinatumomab with standard of care chemotherapy in patients with B-ALL in

haematological complete remission with MRD, based on the BLAST study and Study 20120148 (historical control).

- 6.23 A direct comparison analysis set (DCAS) was defined post-hoc to minimise the differences in patient characteristics between the BLAST and 20120148 studies prior to the propensity score analysis. The DCAS only included patients who were Ph negative, ≥ 18 years of age, in haematological complete remission with a detectable MRD $\geq 10^{-3}$ and excluded patients in second or third remission, and those who relapsed within 14 days of baseline MRD detection in the historical control. Adjustments to improve the comparability between studies resulted in substantial data loss from the BLAST study (full analysis set N=116, DCAS N=73).
- 6.24 The submission presented an attachment titled “Propensity Score Analysis of Relapse Free Survival and Overall Survival among Adult Patients with MRD of B—ALL”. The primary propensity score-based weight chosen in this Analysis Report was the average treatment effects (ATE) approach, which estimates the average treatment effect of moving the entire population from untreated to treated. The Analysis Report also conducted what it described as an “exploratory sensitivity analysis” using the average treatment effect of the treated weights (ATT) approach, which estimates the average effect of treatment in those patients who were ultimately treated (this is further discussed in Paragraph 6.37 and 6.38 below).
- 6.25 Relapse free survival and overall survival were analysed using weighted Cox proportional hazard models with the treatment indicator as a baseline covariate and including a time-varying covariate for HSCT.
- 6.26 Table 7 and Figure 4 summarise the indirect comparison of blinatumomab and standard of care chemotherapy for relapse free survival, in the primary ATE analysis.

Table 7: Propensity scoring analysis (ATE) haematological relapse free survival (PAS; stabilised IPTW)

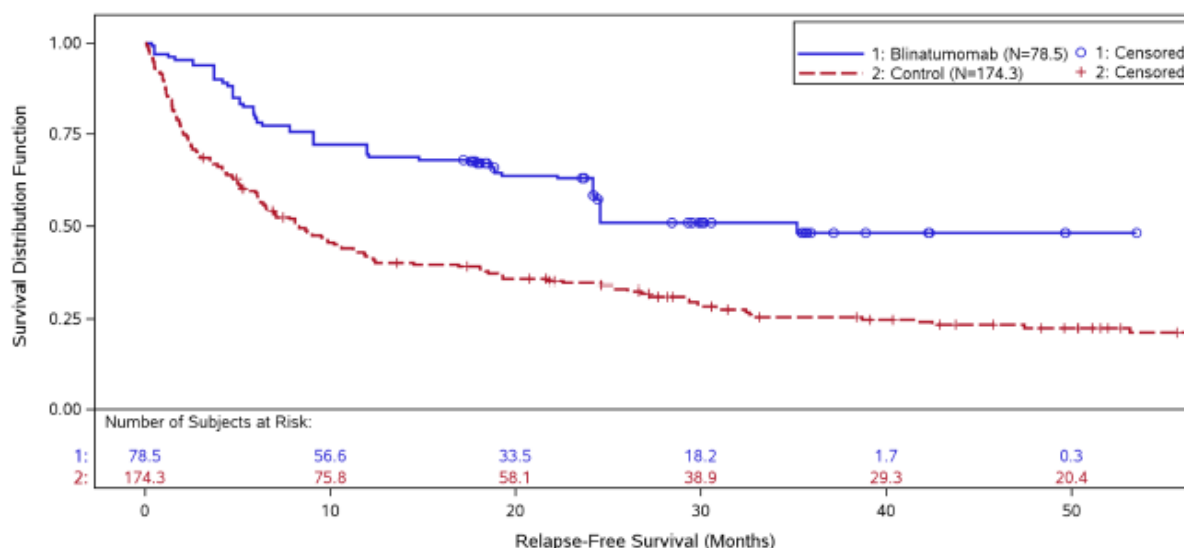
	Blinatumomab (N=78.5) Kaplan-Meier estimate (95% CI)	Historical control (N=174.3) Kaplan-Meier estimate (95% CI)
ATE stabilised IPTW Kaplan-Meier estimates (not adjusted for alloHSCT)		
18 months	0.67 (0.58, 0.78)	0.39 (0.33, 0.48)
RFS median months (95% CI)	35.2 months (24.2, NE)	8.3 months (6.2, 11.8)
ATE stabilised IPTW		Hazard ratio (95% CI)^a
not adjusted for alloHSCT	0.47 (0.30, 0.73)	
adjusted for alloHSCT	0.50 (0.32, 0.78)	

Source: Table 53, p.94 of the submission.

Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplantation; ATE, average treatment effect; CI, confidence interval; IPTW, inverse probability of treatment weight; NE, not evaluable; PAS, primary analysis set; RFS, relapse free survival.

^a Results <1 favour blinatumomab. Statistically significant results in bold.

Figure 4: ATE stabilised IPTW Kaplan-Meier curve of relapse free survival (PAS)



Source: Figure 22, p.95 of the submission.

Abbreviations: ATE, average treatment effect; IPTW, inverse probability of treatment weight; PAS, primary analysis set.

6.27 In the primary ATE analysis, blinatumomab showed a statistically significant increase in median relapse free survival of 26.9 months compared with standard of care chemotherapy (not adjusted for alloHSCT). Similar results were reported for the exploratory ATT analysis; median relapse free survival of 28.7 months (not adjusted for alloHSCT).

6.28 Table 8 and Figure 5 summarise the indirect comparison of blinatumomab and standard of care chemotherapy for overall survival, in the primary ATE analysis.

Table 8: Propensity scoring analysis (ATE) overall survival (PAS; stabilised IPTW)

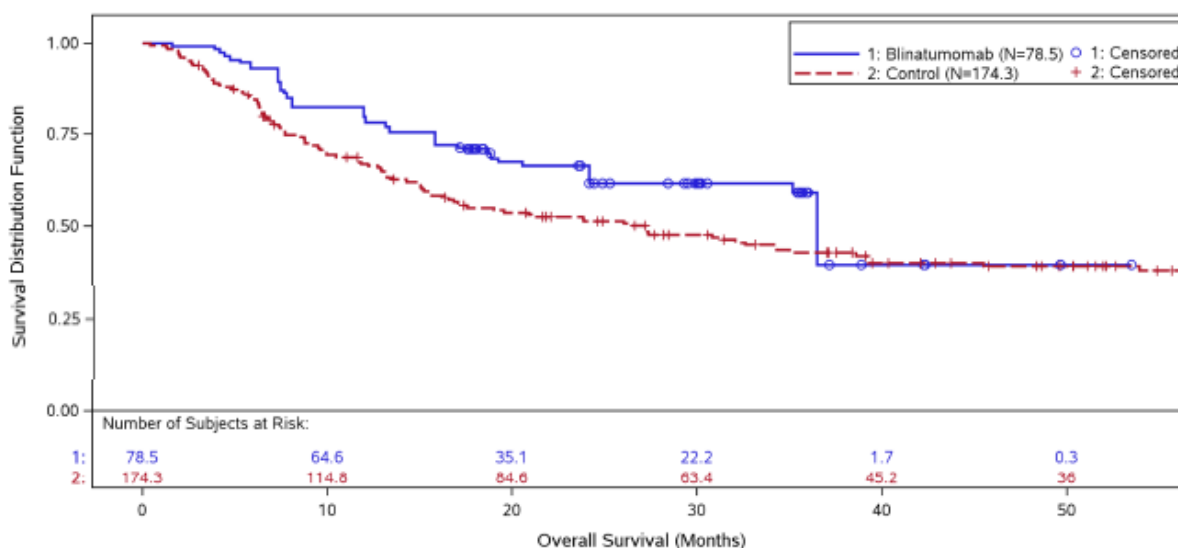
	Blinatumomab (N=78.5) Kaplan-Meier estimate (95% CI)	Historical control (N=174.3) Kaplan-Meier estimate (95% CI)
ATE stabilised IPTW Kaplan-Meier estimates (not adjusted for alloHSCT)		
18 months	0.71 (0.62, 0.81)	0.55 (0.48, 0.63)
OS median months (95% CI)	36.5 months (24.2, NE)	27.2 months (16.4, 38.6)
ATE stabilised IPTW Hazard ratio (95% CI)^a		
not adjusted for alloHSCT	0.68 (0.42, 1.09)	
adjusted for alloHSCT	0.76 (0.47, 1.24)	

Source: Table 54, p.97 of the submission.

Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplantation; ATE, average treatment effect; CI, confidence interval; IPTW, inverse probability of treatment weight; NE, not evaluable; OS, overall survival.

^a Results <1 favour blinatumomab.

Figure 5: ATE stabilised IPTW Kaplan-Meier curve of overall survival (PAS)



Source: Figure 25, p.97 of the submission.

Abbreviations: ATE, average treatment effect; IPTW, inverse probability of treatment weight; PAS, primary analysis set.

6.29 In the primary ATE analysis blinatumomab showed no statistically significant difference in overall survival compared to standard of care chemotherapy (hazard ratio 0.68; 95% CI 0.42, 1.09). However, results from the exploratory ATT analysis showed a statistically significant increase in median overall survival (median not reached for blinatumomab vs 19.6 months for standard of care chemotherapy; HR 0.58; 95% CI 0.37, 0.91; not adjusted for alloHSCT).

6.30 Investigation of an interaction term for treatment effect and the time-dependent HSCT covariate showed evidence of an interaction effect (p=0.0795). The impact of HSCT on overall survival was further explored using a Cox proportional hazards model with an interaction term for treatment and the time-dependent HSCT covariate, with stabilised inverse probability of treatment weighting (Table 9).

Table 9: Treatment effect / time dependent HSCT covariate interaction for overall survival (stabilised IPTW)

	HSCT status	Hazard ratio (95% CI) ^a
Blinatumomab vs control	No HSCT	0.405 (0.165, 0.995)
	After HSCT	1.033 (0.611, 1.748)

Source: Table 10-1, p.50 of the 203-148 MRD Propensity Score Analysis Report: Feb18.

Abbreviations: HSCT, haematopoietic stem cell transplantation; CI, confidence interval; IPTW, inverse probability of treatment weight.

^a Results <1 favour blinatumomab. Statistically significant results in bold.

6.31 Blinatumomab was associated with a statistically significant improvement in overall survival prior to or in the absence of HSCT, but there was no difference in overall survival following HSCT.

6.32 Overall, the propensity score analysis showed blinatumomab was associated with a statistically significant improvement in relapse free survival compared to standard of care chemotherapy, but there was no statistically significant difference between blinatumomab and standard of care chemotherapy in overall survival in the ATE

analysis, possibly due to a treatment-by-HSCT interaction. After accounting for this interaction, there was a statistically significant overall survival benefit associated with blinatumomab prior to, or in the absence of, HSCT while there was no difference in overall survival following HSCT.

6.33 The ESC noted that the propensity score analyses were conducted post hoc, but acknowledged this was an expected limitation of this type of analysis. Given the differences between the populations included in the two studies, the ESC considered that, in this case, propensity score analyses may have been more appropriate than an unadjusted analysis or a multivariate analysis on the unmatched sample. However, the ESC and the PBAC considered that the results of the propensity score analyses were at a high risk of bias because:

- The ESC noted that the propensity score analysis re-balanced the sample for the following variables: age at primary diagnosis; gender; country; MRD at baseline; time from diagnosis to baseline; white blood cells at diagnosis; T(4;11)MLL-AF4 mutation; and prior chemotherapy. However the ESC considered that some potential confounding variables (which may correlate with survival) were not included, such as frequency of assessment and length of follow up. The pre-PBAC response argued that the covariates considered in the propensity score model were key for the analyses (as determined by a logistic regression model), and that including additional variables would have further reduced the sample size.
- The matching algorithm can only account for known confounders measured in both studies and cannot account for known confounders that are not common to both studies, or unknown confounders.
- There were underlying differences between studies in study design and differences in clinical management due to the time period over which the studies were conducted that were not addressed by the propensity score analysis.
- Adjustments to improve the comparability between studies resulted in substantial data loss (e.g. for blinatumomab full analysis set N=116; DCAS N=73; ATE N=78.5; and ATT N=20.9).
- It was unclear to what extent the larger proportion of patients undergoing alloHSCT prior to relapse in BLAST was due to blinatumomab enabling alloHSCT versus clinical advances in alloHSCT treatment/assignment over time and/or more aggressive current treatment practices.

6.34 Further, the ESC and the PBAC considered that while the propensity score adjustments led to better matching of known patient characteristics, it may have reduced the applicability of results to the broader target population. The propensity score analyses excluded patients with Philadelphia chromosome positive B-ALL, subsequent complete remissions, or a smaller extent of minimal residual disease (MRD $\geq 10^{-4}$ but less than 10^{-3}); however, these patient groups would be eligible for blinatumomab under the proposed PBS restriction. In particular, the ESC noted that patients in subsequent complete remissions comprised 35% of the BLAST study population, but were excluded from the analysis. The PBAC acknowledged that the proportion of

patients in complete remission 2 or 3 treated with blinatumomab would gradually reduce over time. However, overall the PBAC considered that the population included in the propensity score analysis was likely to be significantly different to the PBS population.

- 6.35 The ESC requested that the sponsor provide, in its Pre-PBAC Response, an analysis comparing the patients excluded from the matched analysis to the a) overall population and b) matched population. The ESC considered that this would help inform the applicability of the analyses to the intended PBS population (i.e. to better inform a judgement as to whether the matched population substantially differs from the real-world or expected population, and if so the extent of the differences). The pre-PBAC response (pp. 1-2) instead compared survival outcomes across the different analysis sets which had different inclusion criteria (full analysis set, primary analysis set, DCAS, ATT and ATE), which the pre-PBAC response claimed may help to assess the impact of patient exclusions. The pre-PBAC response stated that the survival outcomes were relatively consistent across the different methods of analysis with their differing inclusion criteria. However, this analysis did not address the ESC's concerns about the applicability of the analyses to the intended PBS population.
- 6.36 The submission used the results from the ATT approach (which resulted in a statistically significant difference in overall survival) in the base case of the economic model, despite this being described as an exploratory sensitivity analysis in the Analysis Report. The submission argued that the ATT approach was more appropriate than ATE as the results could be generalised to the population of patients in the BLAST study rather than the combined populations of BLAST and the historical control cohort. The submission argued that it cannot be assumed that the historical controls were drawn from the same homogeneous population as the treated group in the BLAST study, which is a strong assumption when performing ATE analyses. However, the Analysis Report chose the ATE approach as the primary analysis because it mirrors the objective of a randomised study.
- 6.37 The ESC and the PBAC considered that the submission's use of the ATT results in the base case of the economic evaluation may not have been appropriate due to the substantial data loss in the ATT analysis relative to the pre-matched sample (for the blinatumomab full analysis set N=116; DCAS N=73; ATE N=78.5; and ATT N=20.9). The ESC considered that this meant that only the most similar patients across the two groups were able to be matched in the ATT analysis (e.g. the analysis may have adjusted for factors that were not likely to be important predictors of outcome), which may further limit the applicability to the intended PBS population. The ESC considered that this would therefore increase the uncertainty in applying the treatment effect seen in the ATT population to the expected effect in the more variable PBS population. Further, the ESC and the PBAC noted that the ATT analysis may have been less balanced for some covariates, with white blood cell count at baseline and time from diagnosis both being outside the ± 0.15 standardised difference range in the ATT

analysis while only gender was outside this range in the ATE analysis (per Tables 11-2 and 11-5 of the Analysis Report).

- 6.38 The rationale provided in the pre-PBAC response for using the ATT analyses was that it adjusts the control population so it looks similar to the treated population which it stated was “more likely to reflect the treated population in the real-world setting”. However the PBAC considered that this was not a reasonable premise for using the ATT analysis given that the proposed population is much broader than the patients selected for inclusion in the analysis. Overall, the PBAC considered that using the ATT approach resulted in less well-matched covariates after weighting and a greater loss of data compared with the ATE approach.

Comparative harms

- 6.39 Treatment emergent adverse events were reported in 97% of patients in the BLAST study, with substantial proportions of patients reporting serious treatment emergent adverse events (52%) and Grade ≥ 3 events (52%). The most frequently reported adverse events were pyrexia, headache, tremor, chills and fatigue.

- 6.40 Table 10 shows the adverse events of interest reported in the BLAST study.

Table 10: Adverse events of interest reported in BLAST

Event n (%)	BLAST (N=116)	
	Any grade severity	Severity grade ≥ 3
Any event of interest	111/116 (95.6%)	61/116 (52.6%)
Neurologic events	61/116 (52.69%)	14/116 (12.1%)
Infections	48/116 (41.4%)	12/116 (10.3%)
Cytokine release syndrome	4/116 (3.4%)	2/116 (1.7%)
Drug related hepatic events	17/116 (14.7%)	10/116 (8.6%)
Infusion reaction	100/116 (86.2%)	10/116 (8.6%)
Tumour lysis syndrome	8/116 (6.9%)	2/116 (1.7%)
Thromboembolic events	5/116 (4.3%)	3/116 (2.6%)
Medication errors	6/116 (5.2%)	0
Cytopenias	32/116 (27.6%)	29/116 (25.0%)
Decreased immunoglobulins	8/116 (6.9%)	2/116 (1.7%)
Capillary leak syndrome	19/116 (16.4%)	NR

Source: Table 46, p.81 of the submission.

- 6.41 In the BLAST study, 96% of patients reported an adverse event of interest and 53% reported an adverse event of interest of Grade ≥ 3 . The most frequently reported event of interest was neurological events (53%), with 12% of patients reporting a neurological event of interest of Grade ≥ 3 . The most frequently identified neurologic events were tremor, aphasia, dizziness, ataxia and paraesthesia, and encephalopathy. Four patients (3%) experienced cytokine release syndrome.
- 6.42 The submission acknowledged the lack of comparative safety data for blinatumomab versus standard of care chemotherapy in the MRD positive setting, and stated that Study 20120148 did not capture adverse events so a naïve comparison of safety outcomes was not provided in the submission. Instead, the submission presented a

comparative safety analysis in the relapsed/refractory setting from the TOWER study. The proportions of patients reporting any adverse events or serious adverse events were similar between blinatumomab and standard of care chemotherapy treated patients, but there were statistically significantly larger proportions of patients receiving standard of care chemotherapy reporting Grade ≥ 3 events. Statistically significantly larger proportions of patients treated with blinatumomab reported neurologic events, cytokine release syndrome, infusion reaction, pyrexia, tremor and cough compared to standard of care chemotherapy. The ESC and the PBAC considered that comparative safety outcomes from the relapsed/refractory setting are unlikely to reflect the circumstances of use in the MRD population (the relapsed/refractory setting includes longer blinatumomab treatment length, less fit patients and more aggressive chemotherapy regimens).

- 6.43 Important risks associated with blinatumomab identified in the expanded assessment of harms include neurologic events, infections, cytokine release syndrome, infusion reactions, tumour lysis syndrome, capillary leak syndrome, elevated liver enzymes, medication errors, febrile neutropenia and neutropenia and decreased immunoglobulin.

Benefits/harms

- 6.44 Blinatumomab was estimated to result in an increase in progression free survival of approximately 27 months compared with standard of care post-induction chemotherapy regimens for consolidation and/or maintenance, however this estimate is highly uncertain given it is based on a comparison of separate studies.
- 6.45 No data were presented in the submission comparing adverse events associated with blinatumomab and standard of care chemotherapy in the MRD positive population.

Clinical claim

- 6.46 The submission described blinatumomab as superior in terms of effectiveness compared with standard of care chemotherapy (post induction) and non-inferior in terms of safety, in the treatment of B-ALL in haematological complete remission with minimal residual disease.
- 6.47 The PBAC considered that the claim of superior efficacy may be reasonable in terms of relapse free survival, but may not be reasonable in terms of overall survival. There were insufficient data to support a claim of non-inferior safety. The PBAC considered that the magnitude of the incremental effectiveness was uncertain due to the following issues:
- the results of the standard of care arm are were not necessarily applicable to Australian clinical practice, given that most of the regimens were over 10 years old and there were limited details provided on the treatments administered as part of the historical control Study 20120148.

- the propensity score analysis had a high risk of bias because: some of the underlying differences between the studies were not addressed by the analysis; some potential confounding variables were not accounted for; and adjustments to improve comparability resulted in substantial data loss, particularly for the ATT analysis.
 - the population included in the propensity scoring analysis was likely to be significantly different to the eligible population under the requested restriction (in terms of age, Philadelphia chromosome status, remission history, MRD level and HSCT use), which the PBAC considered may affect incremental survival gains associated with blinatumomab treatment.
 - the data study did not adequately support an improvement in overall survival with blinatumomab treatment, given the lack of statistically significant overall survival gain reported in the ATE analysis, the immaturity of the BLAST study data (median follow-up of 18.3 months), and potential confounding by alloHSCT use.
 - No comparative adverse event data for the MRD population were provided in the submission. Instead, the submission relied on comparative safety outcomes from the relapsed/refractory setting which are unlikely to reflect circumstances of use in the MRD population (longer blinatumomab treatment length, less fit patients, more aggressive chemotherapy regimens).
- 6.48 The ESC considered that, as blinatumomab may be used in a number of discrete therapeutic roles depending on when MRD occurs or is diagnosed in the disease pathway, the true comparative effect of blinatumomab throughout the treatment algorithm was difficult to determine based on the evidence available.
- 6.49 The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data, though the magnitude of the incremental effectiveness was uncertain.
- 6.50 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.51 The submission presented a stepped economic evaluation (based on a partitioned survival analysis) of blinatumomab compared to consolidation chemotherapy for the treatment of patients with B-ALL in haematological complete remission with minimal residual disease. A summary is presented in Table 11.

Table 11: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Outcomes	Relapse-free life years; life years; quality-adjusted life years
Time horizon	30 years
Methods used to generate results	Partitioned survival analysis
Treatments	Blinatumomab, consolidation chemotherapy
Health states	Relapse-free disease, relapsed disease, death
Cycle length	3 months (with half cycle corrections)
Transition probability	<p><u>Consolidation chemotherapy arm</u> As outlined in Table 13:</p> <ul style="list-style-type: none"> - Kaplan-Meier curves for relapse-free survival and overall survival from 0 to 4 years based on the propensity score analysis population from the historical control (Study 20120148). - Kaplan-Meier curves for relapse-free survival and overall survival from 4 to 10 based on the direct comparison analysis set from the historical control (Study 20120148). - Kaplan-Meier curve for relapse-free survival beyond 10 years based on the assumption that there is no further risk of recurrence after 10 years. Kaplan-Meier curve for overall survival beyond 10 years for consolidation chemotherapy based on Australian life tables adjusted using a mortality factor to account for the potential long-term age-related increase in mortality in ALL patients. <p><u>Blinatumomab arm</u> Kaplan-Meier curves for relapse-free survival and overall survival from 0 to 4 years based on the estimated hazard ratio from the propensity score indirect comparison using ATT weights (base case) or ATE weights (sensitivity analysis). Relapse-free survival and overall survival beyond 4 years based on the assumption of no difference in hazards between treatments.</p>
Discount rate	5% for costs and outcomes, applied annually
Software package	Excel 2013

Source: Table 66, p.123 of the submission.

Abbreviations: ALL, acute lymphoblastic leukaemia; ATE, average treatment effect; ATT, average treatment effect of the treated

6.52 Key drivers of the economic model are summarised in Table 12 below.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Modelled patient population	The modelled patient population was based on adult patients with Philadelphia chromosome negative B-ALL in first haematological complete remission with minimal residual disease (MRD $\geq 10^{-3}$). The modelled patient population was narrower than the proposed PBS population which would also include children, chromosome positive B-ALL, subsequent complete remissions and patients with a smaller extent of minimal residual disease (MRD $\geq 10^{-4}$). Age, Philadelphia chromosome status, disease history and extent of MRD are well known prognostic factors that will influence underlying survival and therefore will also affect the potential incremental benefit associated with blinatumomab treatment.	High, direction unclear
Modelled circumstances of use	<p>The model estimated HSCT use in the blinatumomab arm based on the BLAST study and HSCT use in the consolidation chemotherapy arm based on the historical control. The submission noted that differences in HSCT use between arms may be due to blinatumomab treatment but acknowledged they could also be due to advances in HSCT and/or more aggressive treatment practices over time. It was unclear whether either of these estimates were representative of current Australian clinical practice. The level of HSCT use is likely to have a substantial impact on the cost-effectiveness of blinatumomab given that HSCT use was a treatment effect modifier.</p> <p>The model assumed that the circumstances of blinatumomab use in the BLAST trial would be representative of Australian clinical practice. It was unclear whether this assumption was reasonable as it will depend on a number of unknown factors such as the similarity of patient populations and the availability of downstream treatment options (particularly HSCT).</p> <p>The model synthesised the circumstances of use for consolidation chemotherapy based on survival data from the historical control and treatment details from the ALLG ALL6 protocol. The submission did not present any details on the treatments administered as part of the historical control and therefore it is unclear whether they are representative of consolidation chemotherapy protocols used in Australian clinical practice. It was also unclear whether the ALLG ALL6 protocol was a reasonable proxy for protocols used in Australia given the treatment regimens are likely to be individualised which may lead to substantial variation between protocols.</p>	High, direction unclear
Consolidation chemotherapy survival curve	The estimated survival in the consolidation chemotherapy arm was synthesised from the propensity score analysis population in the historical control study (0 to 4 years), the direct comparison analysis set from the historical control (4 to 10 years), and Australian life tables adjusted by a mortality factor to account for the potential long-term age-related increase in mortality in ALL patients (10 to 30 years). The ESC and the PBAC considered that the three-phase estimation of survival may not be reliable due to underlying differences in patient characteristics and survival trends between data sources as well as the limited availability of long-term patient data. In particular, the PBAC considered that long-term B-ALL survivorship assumptions should not have been applied to relapsed disease patients in the model. The synthesis approach resulted in apparent structural anomalies within the model (see Markov trace figure below).	Unclear (structural uncertainty)
Blinatumomab survival curve	The estimated survival in the blinatumomab treatment arm was derived by applying the estimated blinatumomab treatment effect to the extrapolated consolidation chemotherapy survival curves (ATT weights in base case; ATE weights in sensitivity analysis). The PBAC considered that the magnitude of benefit in terms of relapse-free survival was highly uncertain due to the limitations of the propensity-adjusted indirect comparison, and the current available data do not adequately support an improvement in overall survival with blinatumomab treatment. The submission did not test the proportional hazards assumption for any of the extrapolated data.	High, favours blinatumomab

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Description	Method/Value	Impact
Adjustment for cure assumption	The submission implements the assumption of cure in the model by preventing patients in the relapse-free health state experiencing relapse beyond 54 months ¹ . The model also prevents patients dying in the relapse-free state between 54 to 78 months in the blinatumomab arm and between 54 months to 22 years in the consolidation chemotherapy arm. The adjustment to allow for cure was inappropriately implemented in the model as it prevented patients from being able to die due to any cause in the relapse-free state. This adjustment resulted in apparent structural anomalies within the model (see Markov trace figure below). Further, the PBAC considered that the clinical evidence were not sufficiently mature or reliable to support any cure assumptions.	Unclear (structural uncertainty)
Adjustment for RFS ≤OS	The model prevents relapse-free survival exceeding overall survival, which would otherwise occur at 78 months for the blinatumomab arm and at 22 years for the consolidation chemotherapy arm based on the underlying independent curves. The evaluation and the ESC considered that the need for adjustments to the survival curves suggested that the underlying data did not adequately reflect the implicit relationships between survival estimates and therefore suggested that a partitioned survival analysis may not provide reliable estimates in these circumstances. This adjustment resulted in apparent structural anomalies within the model (see Markov trace figure below).	Unclear (structural uncertainty)
Time on treatment	The economic model did not include a time on treatment curve and therefore treatment use was not linked to survival estimates. This resulted in a series of implausible costing estimates in which patients were receiving costs that were not appropriate for that stage of the model (e.g. patients were receiving consolidation chemotherapy costs after relapse or death). The PSCR (p. 3) argued that a time on treatment curve would not be informative as blinatumomab and the comparator (chemotherapy) are finite courses of treatment. However, the ESC noted that the submission assumed that all patients received a full course of comparator chemotherapy (even if dead) which overestimated the drug and administration costs of the comparator arm.	Unclear (structural uncertainty)
HSCT utilisation	The submission only included HSCT as a cost item in the economic model. The ESC and the PBAC considered that this was inappropriate as blinatumomab may increase the probability of patients receiving a HSCT and the clinical evidence presented in the submission indicated that HSCT use was a treatment effect modifier. Additionally, HSCT is a major clinical event with its own risks, benefits and costs.	Unclear (structural uncertainty)
Utility values	The submission used a complex, multi-step approach to derive utilities included in the economic model (propensity-adjusted EQ-5D from BLAST, regression analysis of EQ-5D from BLAST, mapping of EORTC to EQ-5D from TOWER, propensity-adjusted EQ-5D from BLAST and TOWER). The estimated utilities were 0.806 for relapse free disease and 0.692 for relapsed disease. The estimation of utility values was poorly documented in the submission with no validation against other sources. The PSCR (p. 4 and attachment) provided additional documentation regarding the calculation of the utility values used in the submission. However, overall EQ-5D results for the BLAST study were not provided and the explanation of methods was incomplete. The ESC noted that the utility values had a moderate impact on the ICER. The submission did not estimate utility values associated with adverse events or HSCT use.	Moderate, direction unclear

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Description	Method/Value	Impact
Treatment costs	<p>Blinatumomab drug and administration costs were estimated based on the BLAST study. It was unclear whether blinatumomab use in the BLAST study was representative of clinical practice and/or the subgroup of patients used to derive comparative efficacy estimates. It was also unclear whether blinatumomab will be co-administered with imatinib for Ph+ disease in clinical practice. The submission inappropriately excluded the cost of co-administered therapies (which were in the comparator arm). The ESC also considered that the submission inappropriately estimated hospitalisations based on the minimum recommended time stated in the Product Information rather than the observed time in the BLAST study. The submission did not estimate adverse event costs which may have been inappropriate given the frequent incidence of treatment-related serious adverse events in the BLAST study.</p> <p>Consolidation chemotherapy drug and administration costs were estimated based on a full course of therapy under the ALLG ALL6 protocol. It was unclear whether consolidation therapy using the ALLG ALL6 protocol was representative of clinical practice and/or the subgroup of patients used to derive comparative efficacy estimates. The submission inappropriately assumed all patients would undergo the full treatment course (which was not consistent with the blinatumomab arm). The submission did not estimate adverse event costs which may have been inappropriate given that these regimens may be associated with serious treatment-related adverse events.</p>	Moderate, favours blinatumomab
Downstream costs	<p>The economic model assumed that all relapse-free patients would receive maintenance therapy for 2 years based on the ALLG ALL6 protocol. These costs were inappropriately implemented in the model as it did not adjust for the duration of blinatumomab or consolidation chemotherapy and therefore lead to substantial overlap between treatment regimens.</p> <p>The model estimated HSCT use in the blinatumomab arm based on the BLAST trial and HSCT use in the consolidation chemotherapy arm based on the historical control. It was unclear whether HSCT use for the BLAST study and historical control are representative of practice.</p> <p>The costs of HSCT were based on a published costing study in New South Wales hospitals. Costing estimates were based on data captured from 2004 to 2007 and it was unclear whether they were representative of current clinical practice given the constantly evolving management of B-ALL. The estimated costs were based on the direct costs of the HSCT procedure, related hospitalisations and outpatient care for two months prior to the procedure and twelve months after the procedure. These are likely to overlap with some of the cost estimates for chemotherapy as well as disease management costs.</p>	High, favours comparator
Salvage costs	<p>The economic model assumed that all patients would receive 1.76 cycles of salvage chemotherapy prior to death based on the FLAG-ida protocol. The submission did not include the use of more costly therapies such as blinatumomab or imatinib in the relapsed/refractory setting. The expected health resource use (particularly hospitalisations) associated with salvage chemotherapy was poorly documented in the submission. The costs of salvage chemotherapy were inappropriately applied to patients who died in the relapse-free state.</p>	High, direction unclear

Description	Method/Value	Impact
Health state costs	<p>The economic model estimated relapse-free health state costs based on expert advice on health resource use by MRD status. The submission estimated MRD response with blinatumomab based on the BLAST study. The submission assumed patients could not achieve an MRD response with consolidation chemotherapy. Health resource use was based on interviews with two UK physicians and may not be representative of Australian clinical practice. The estimated health resource use for patients who were MRD positive appeared implausible (particularly the extended hospital stays) given that patients who are MRD positive are still in complete remission. The assumption that consolidation chemotherapy could not affect MRD status was not adequately justified in the submission. Additionally, the estimates did not account for changes in MRD status over time.</p> <p>The submission assumed that patients with relapsed disease had the same resource use as patients who were MRD positive. This assumption did not appear reasonable as patients with relapsed disease would be expected to have higher costs associated with the management of disease symptoms.</p>	High, favours blinatumomab

Source: Constructed during the evaluation

Abbreviations: B-ALL, B-cell lymphoblastic leukaemia; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQoL- 5 dimension questionnaire; HSCT, haematopoietic stem cell transplant; MRD, minimal residual disease; Ph+, Philadelphia chromosome positive.

¹ The assumption of cure is explicitly incorporated into survival estimates at 10 years. However, the impact of cure on survival estimates is effectively implemented earlier in the model at 54 months based on a small number of patients from the direct comparison analysis set who do not apparently experience death or relapse (16 patients with follow-up data on relapse-free survival between 54 to 78 months) contributing to mid-term extrapolations (4 to 10 years).

6.53 The ESC noted that survival in the consolidation chemotherapy (comparator) arm was estimated based on three phases: from the propensity score analysis population of the historical control study (0 to 4 years), the direct comparison analysis set of the historical control study (4 to 10 years), and long-term B-ALL survivorship assumptions (10 to 30 years). This is outlined in the table below. The estimated treatment effect of blinatumomab compared with consolidation chemotherapy was based on the results of the propensity score analysis indirect comparison using the ATT method in the base case (0 to 4 years) and the assumption of no difference in hazards between treatments beyond 4 years. The submission did not test the proportional hazards assumption for any of the extrapolated data.

Table 13: Input data and extrapolation in the comparator arm

Years	RFS	OS
0-4	Estimated from KM curves of RFS from the historical control study of the propensity score analysis (ATT weighted methods in the base case)	Estimated from KM curves of OS from the historical control study of the propensity score analysis (ATT in base case)
4-10	Estimated assuming same probability of events in the KM curves of RFS from the historical control study (DCAS); that is, before the ATT weightings	Estimated from KM curves of OS from the historical control study (DCAS). That is, same approach as described for RFS
10+	Assumed to remain constant (i.e. no risk of recurrence after 10 years). ¹ This assumption is based on RFS data from the historical control study (20120148 study) which demonstrates that patients who are alive at 5 years do not experience a relapse of ALL over the duration of follow-up. ¹ RFS was assumed to equal OS from the point of curve intersection.	Extrapolated using age-matched general Australian population mortality data (Australian life tables), adjusted using a mortality factor (base case = 4) to account for the potential long-term age-related increase in mortality in ALL patients.

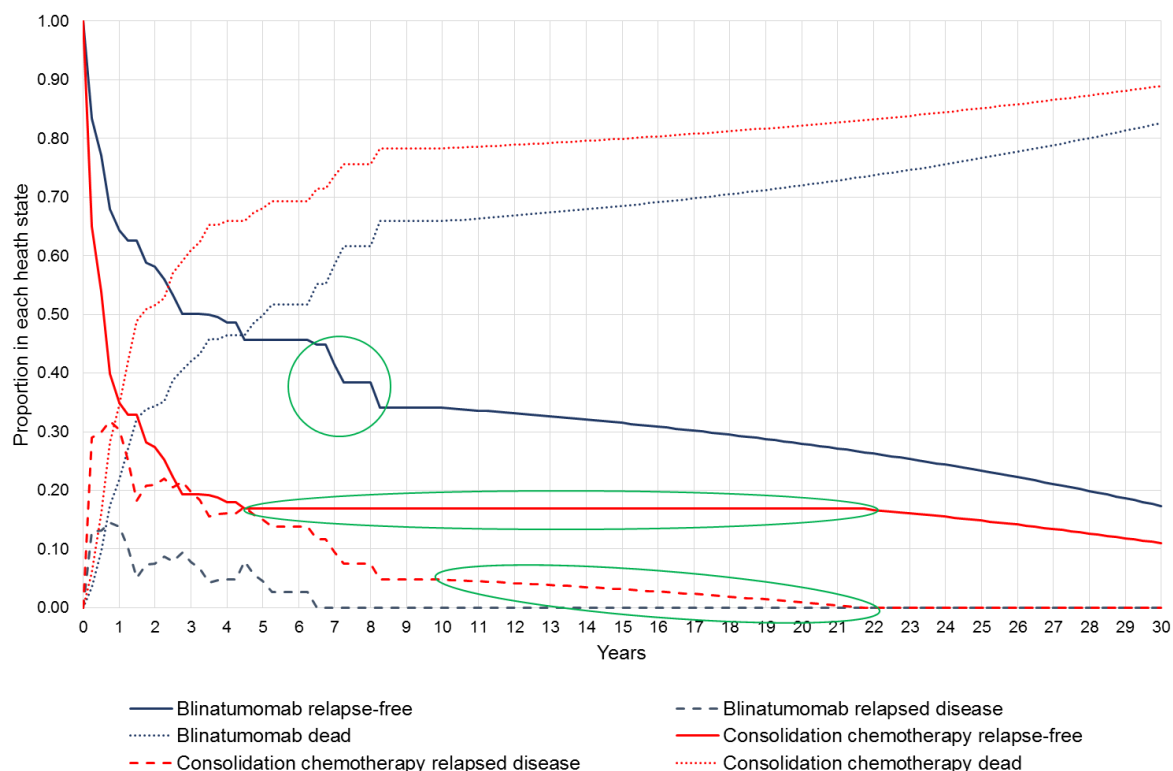
Abbreviations: DCAS, direct comparison analysis set; KM, Kaplan-Meier; OS, overall survival; RFS, relapse free survival
Source: Table 71, p 137 of the submission

¹ The assumption of cure is explicitly incorporated into survival estimates at 10 years. However, the impact of cure on survival estimates is effectively implemented earlier in the model at 54 months based on a small number of patients from the direct comparison analysis set who do not apparently experience death or relapse (16 patients with follow-up data on relapse-free survival between 54 to 78 months) contributing to mid-term extrapolations (4 to 10 years).

6.54 The ESC considered that the three-phase estimation of survival curves may not be reliable due to underlying differences in patient characteristics and survival trends between data sources as well as the limited availability of long-term patient data. The ESC also considered that the assumption of cure (for patients remaining in the relapse free health state, effectively implemented at 4.5 years) was not adequately justified in the submission. The PBAC considered that the clinical evidence was not sufficiently mature or reliable to strongly support any cure assumptions.

6.55 A Markov trace of the proportion of patients in each health state over time is presented below.

Figure 6: Markov trace of relapse-free, relapsed disease and dead health states



Source: adapted during the evaluation based on Figure 35, p.162 of the submission

6.56 A number of anomalies were apparent in the Markov trace for the model (circled in green in the figure above):

- A substantial proportion of 'cured' patients in the blinatumomab relapse-free state died between 6 to 8 years;
- No patients in the consolidation chemotherapy relapse-free state died between 5 to 22 years; and
- A small proportion of patients in the consolidation chemotherapy arm with relapsed disease (who cannot recover) continued to survive for up to 22 years, primarily due to declining risk of death as the model switches to risks observed in the DCAS population (4-10 years) and even lower risks based on the long term ALL survivor assumption (>10 years).

6.57 The PSCR argued that the anomalies identified in the model were a minor consequence of the partitioned survival analysis approach. However the ESC considered that the anomalies are associated with underlying structural uncertainty, with an unknown impact on the ICER.

6.58 The results of the modelled economic evaluation are summarised below.

Table 14: Results of the economic evaluation of blinatumomab versus consolidation chemotherapy

Type of resource item	Blinatumomab	Consolidation chemotherapy	Incremental difference
Costs			
QALYs	5.3820	3.6086	1.7734
Incremental cost per QALY gained			

Source: Table 91, p163 of the submission

Abbreviations: QALYs, quality-adjusted life years

The redacted table shows ICERs in the range of \$45,000/QALY – \$75,000/QALY.

6.59 Based on the economic model, treatment with blinatumomab was associated with an incremental cost per QALY gained of \$45,000/QALY – \$75,000 compared to consolidation therapy for the treatment of patients with B-ALL in haematological complete remission with minimal residual disease. The ESC and the PBAC considered that the cost-effectiveness estimate was not reliable given major applicability issues, structural limitations and parameter uncertainties outlined in Table 12.

6.60 The ESC and the PBAC considered that the key issues with the model were:

- the clinical evidence did not adequately support or reliably quantify an improvement in overall survival with blinatumomab treatment compared to consolidation chemotherapy. The ESC and the PBAC considered that the model was sensitive to the choice of analysis method, with the potentially less appropriate method (ATT) being used in the base case. The ESC and the PBAC noted that the ICER increased from \$45,000/QALY – \$75,000 (base case with ATT analysis) to \$45,000/QALY – \$75,000 when the ATE analysis was used.
- the results of the modelled population (adult patients with Philadelphia chromosome negative B-ALL in first haematological complete remission with MRD $\geq 10^{-3}$) may not be applicable to the broader proposed PBS population. The PBAC also considered that the modelled circumstances of use for both blinatumomab and consolidation chemotherapy were not representative of Australian clinical practice.
- The ESC and the PBAC considered that the modelled estimates may not be reliable given structural issues associated with: the extrapolation of underlying survival based on a three-phase estimate from different sources; implementing the cure assumption; the need to adjust relapse-free survival estimates to not exceed overall survival; and the lack of a time on treatment curve.
- The submission only included HSCT as a cost item in the economic model. The ESC and the PBAC considered this was inappropriate and that HSCT should have been explicitly included in the economic model given blinatumomab would increase the likelihood of HSCT in some patients. The ESC and the PBAC acknowledged there may be limited data available to inform assumptions relating to HSCTs, but considered inclusion would be appropriate given that HSCT was a treatment effect

modifier (blinatumomab was not associated with any improvement in overall survival in patients undergoing HSCT) and is a major clinical event with its own risks, benefits and costs, and therefore should have been explicitly modelled.

- The ESC and the PBAC considered that the treatment, downstream management, salvage therapy and health state costs may not be reliable given substantial uncertainties with the sources and calculations of all costs.
- There was a lack of adequate documentation or validation to support utility values estimated through a complex multi-step approach. The PSCR provided additional documentation regarding the calculation of the utility values used in the submission. However, overall EQ-5D results for the BLAST study were not provided and the explanation of methods was incomplete. The ESC and the PBAC considered that the utility values had a moderate impact on the ICER.
- The ESC and the PBAC also considered that the submission had underestimated costs in the blinatumomab arm as hospitalisation costs were based on the minimum recommended time stated in the Product Information (3 days for the first cycle, 2 days in subsequent cycles) rather than the observed time in the BLAST study (average of 9 days in the first cycle and 3 to 6 days in subsequent cycles).
- Further, the PBAC noted that the submission did not address the costs, accuracy and likely impacts on health outcomes due to MRD testing.

6.61 The results of key sensitivity analyses are summarised below.

Table 15: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case		1.7734	
Time horizon (base case 30 years)			
20 years		1.5632	
10 years		1.0866	
5 years		0.6303	
Blinatumomab treatment effect (base case ATT weighting with fixed HR of 0.42 (RFS) and 0.58 (OS) for blinatumomab vs. consolidation chemotherapy)			
ATE weighting with fixed HR of 0.47 (RFS) and 0.68 (OS)		1.2814	
ATE weighting with fixed HR of 0.30 (RFS) and 0.42 (OS) ^a		2.6220	
ATE weighting with fixed HR of 0.73 (RFS) and 1.09 (OS) ^b		-0.1525	Dominated
ATT weighting with fixed HR of 0.29 (RFS) and 0.37 (OS) ^a		2.9012	
ATT weighting with fixed HR of 0.60 (RFS) and 0.91 (OS) ^b		0.4262	
Drug administration costs (base case blinatumomab \$8,491, consolidation chemotherapy \$26,756)			
No administration costs in both arms		1.7734	
Overall survival extrapolation (base case curves do not converge at model endpoint of 30 years)			
Convergence starts at 4 years and ends at 10 years		0.8506	
Convergence starts at 4 years and ends at 20 years		1.3511	
Convergence starts at 4 years and ends at 30 years		1.7010	
Difference in total relapse-free disease management costs due to MRD response (base case blinatumomab, 79.6% with MRD response; consolidation chemotherapy, 0% with MRD response; difference of \$23,032) ^c			
No difference between arms		1.7734	
5% response consolidation chemotherapy (\$21,586)		1.7734	
10% response consolidation chemotherapy (\$20,141)		1.7734	
20% response consolidation chemotherapy (\$17,249)		1.7734	
Proportion receiving stem cell transplant (base case blinatumomab 72.6%, consolidation chemotherapy 38.4%)			
No difference between arms		1.7734	
Quarter of proportional difference between arms		1.7734	
Half of proportional difference between arms		1.7734	
Three quarters of proportional difference between arms		1.7734	

Source: Table 96, pp167-169 and compiled during evaluation using 'BlinMRD_Section3model_March2018_revised' Excel workbook of the submission

Abbreviations: ATE, average treatment effect; ATT, average treatment effect of the treated, average ICER, incremental cost-effectiveness ratio; MRD, minimal residual disease; OS, overall survival; QALY, quality adjusted life year; RFS, relapse-free survival

^a Based on lower limits of the 95% confidence interval of the hazard ratios for the blinatumomab vs. historical control ATE/ATT analysis

^b Based on the upper limits of the 95% confidence interval of the hazard ratios for the blinatumomab vs historical control ATE/ATT analysis

^c Proportion with MRD response was used to estimate the average cost of relapse-free disease management weighted by relapse-free MRD+ and relapse-free MRD- disease

The redacted table shows ICERs in the range of dominate to more than \$200,000/QALY

6.62 The ESC and the PBAC considered that the model is most sensitive to the treatment effect associated with blinatumomab on survival outcomes compared with consolidation chemotherapy. The PBAC noted that the model was also sensitive to time horizon, survival extrapolation approach, relapse-free health state costs (primarily due to MRD response rates) and the proportion of patients undergoing HSCT.

6.63 The ESC considered that the sensitivity analyses for HSCT use were non-informative as the model included HSCT as a cost item only and it did not include the risks, benefits

and treatment effect modification associated with the procedure. The model was insensitive to salvage chemotherapy costs but this may be an artefact of the costing approach which is unlikely to reflect the actual incremental difference between treatments (see Table 12).

Drug cost/patient/course

- 6.64 The estimated drug cost for blinatumomab per patient per course was \$ [REDACTED] (based on 53 treatment days using the effective price of \$ [REDACTED] per vial per day).
- 6.65 The estimated drug cost for consolidation chemotherapy per patient per course for Ph- patients was \$4,094 (based on ALLG ALL6 consolidation protocol, assuming 135 treatment days, using current DPMQ/DPMA: \$4,094).
- 6.66 The estimated drug cost for consolidation chemotherapy per patient per course for Ph+ patients was \$26,783 (based on ALLG ALL6 consolidation protocol, assuming 135 treatment days, using current DPMQ/DPMA: \$4,094 plus imatinib 600 mg daily, assuming 183 treatment days, using current DPMQ for imatinib 400 mg packs: \$22,690).

Estimated PBS usage & financial implications

- 6.67 This submission was not considered by DUSC. The submission used an epidemiological approach, using a number of published sources, to estimate the utilisation and financial implications of PBS listing blinatumomab for the treatment of patients with B-ALL in haematological complete remission with minimal residual disease.
- 6.68 Table 15 summarises the estimated extent of use and costs of listing blinatumomab for the treatment of patients with B-ALL in haematological complete remission with minimal residual disease in the first 6 years of listing.

Table 16: Estimated utilisation and cost to the PBS in the first six years of listing (per the submission)

	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
Estimated eligible patient population						
Incidence of ALL	██████████	██████████	██████████	██████████	██████████	██████████
- Adults	██████████	██████████	██████████	██████████	██████████	██████████
- Paediatrics	██████████	██████████	██████████	██████████	██████████	██████████
Proportion B-cell lineage	██████████	██████████	██████████	██████████	██████████	██████████
- Adults (76%)	██████████	██████████	██████████	██████████	██████████	██████████
- Paediatrics (80%)	██████████	██████████	██████████	██████████	██████████	██████████
Proportion B-cell which is immature B-cell precursor	██████████	██████████	██████████	██████████	██████████	██████████
- Adults (93%)	██████████	██████████	██████████	██████████	██████████	██████████
- Paediatrics (93%)	██████████	██████████	██████████	██████████	██████████	██████████
Proportion of patients with complete remission after induction treatment	██████████	██████████	██████████	██████████	██████████	██████████
- Adults (88%)	██████████	██████████	██████████	██████████	██████████	██████████
- Paediatrics (96%)	██████████	██████████	██████████	██████████	██████████	██████████
Proportion of patients with complete remission who are MRD positive	██████████	██████████	██████████	██████████	██████████	██████████
- Adults (40%)	██████████	██████████	██████████	██████████	██████████	██████████
- Paediatrics (13%)	██████████	██████████	██████████	██████████	██████████	██████████
Estimated extent of use and cost of blinatumomab on the PBS						
Expected utilisation of blinatumomab (80% uptake rate)	██████████	██████████	██████████	██████████	██████████	██████████
Total number of blinatumomab vials (1 course per patient, 53 vials per course)	██████████	██████████	██████████	██████████	██████████	██████████
Total expenditure (at published price \$2,922.39)	██████████	██████████	██████████	██████████	██████████	██████████
Patient co-payments (\$21.95 per patient)	██████████	██████████	██████████	██████████	██████████	██████████
Total rebates for SPA (\$██████████ per vial)	██████████	██████████	██████████	██████████	██████████	██████████
Total PBS cost at effective price	██████████	██████████	██████████	██████████	██████████	██████████
Substituted chemotherapy costs	██████████	██████████	██████████	██████████	██████████	██████████
Avoided relapse treatment costs	██████████	██████████	██████████	██████████	██████████	██████████
Net financial impact to PBS (effective, less substitution for chemotherapy and relapse)	██████████	██████████	██████████	██████████	██████████	██████████

Source: pp.171-182 of the submission; and 'BlinMRD_Section4model_March2018' Excel workbook of the submission.

Abbreviations: ALL, acute lymphocytic leukaemia; MRD, minimal residual disease; SPA, special pricing arrangement (published versus effective price).

The redacted table shows that at year 6, the estimated number of patients was less than 10,000.

6.69 The submission estimated that the proposed listing would be associated with a net cost to the PBS of up to less than \$10 million per year less than \$10 million per year (\$8.7 million based on published prices) in the sixth year of listing. The estimated net cost to the PBS over the first six years of listing was \$30 – \$60 million per year (\$30 – \$60 million per year based on published prices).

6.70 The evaluation, ESC and PBAC considered that the estimated utilisation and financial

implications were highly uncertain and most likely underestimated for the following reasons:

- The submission applied a simple extrapolation to the AIHW incident ALL data (4-5 patients per year) to estimate the annual growth in the ALL population. A source was not provided for this estimate, which may underestimate growth in the population.
- The proportion of patients with MRD was based on two small, older publications (2008-2009) reporting relatively low proportions (32-48%). A number of alternative estimates were available, which estimate that up to 60% or more patients will have MRD after complete haematological remission. The proportion of patients with MRD may change over time with the availability of new technologies (e.g. increased assay sensitivity will detect lower levels of MRD).
- The estimates only consider MRD positive patients in complete remission following initial induction. Additional patients will be eligible for blinatumomab under the requested restriction (i.e. patients in second or subsequent remission; patients initially MRD negative who experience molecular relapse). The ESC and PBAC considered that patients in second or subsequent remission should have been included in the financial estimates.
- No justification was provided for the assumed uptake rate of 80%. The uptake rate may be affected by the perceived clinical need for blinatumomab. The PBAC considered that the uptake rate was likely underestimated.
- The submission assumed that each patient will receive 53 vials of blinatumomab, based on blinatumomab use in the BLAST study. It is unclear whether this will be representative of Australian clinical practice. Patients are eligible for up to four cycles of blinatumomab (112 vials) under the requested restriction.
- Some of the drug costs, administration costs, and hospitalisation costs (for transplant and relapse) were based on the economic evaluation and therefore incorporate all the uncertainties associated with this analysis (outlined under “Economic analysis” above).
- The submission claimed that there may be an increase in HSCT use due to the availability of blinatumomab. This may result in additional costs to government at the state and federal level.
- It is unclear whether there is potential for leakage outside the requested restriction in patients who have complete remission but experience molecular relapse after earlier blinatumomab treatment.

6.71 Other issues identified by the evaluation and the ESC included:

- The submission assumed that the PBS would fund all inpatient treatment with blinatumomab. The PSCR acknowledged that this was inconsistent with the

current PBS listing for blinatumomab in the relapsed/refractory setting, and confirmed that it intended for current subsidy arrangements to apply (i.e. that blinatumomab will not be PBS-subsidised if administered to a public hospital inpatient). The pre-PBAC response (pp. 3-4) updated the financial estimates to reflect this revised assumption. The pre-PBAC response estimated that an average of 3.27 doses per patient would be dispensed in a public hospital inpatient setting (based on the recommended duration of hospitalisation in the Product Information, the proportion of patients treated in each cycle in the BLAST study, and the estimated proportion of public versus private hospital use) and excluded these doses from the revised estimated cost to the PBS/RPBS.

- The financial estimates assume patients receive a single course of blinatumomab, despite the requested restriction not limiting patients to a single course of blinatumomab. The PBAC considered that a once-in-a-lifetime restriction would be more appropriate, and thus this assumption was reasonable.

Quality Use of Medicines

- 6.72 The submission did not raise any quality use of medicines issues.
- 6.73 There are no data to inform the use of blinatumomab in the relapsed setting following use in MRD in an earlier line of therapy, which the PBAC considered would be addressed by limiting use of blinatumomab to once-per-lifetime.

Financial Management – Risk Sharing Arrangements

- 6.74 The cover letter accompanying the submission stated that “Special pricing and financial cap arrangements are in place for blinatumomab. It is proposed with the listing that the rebate in the blinatumomab deed would not need to be altered. Amgen is willing to agree to revised financial caps for blinatumomab which reflect forecast utilisation under the recommended restrictions which, along with the requirements of the written authority, will serve to address uncertainty and provide an absolute limit on the cost of blinatumomab to the PBS”.
- 6.75 The PBAC considered that use of blinatumomab in the MRD positive B-ALL setting would likely, over time, reduce or delay use in the existing listing for relapsed/refractory Ph- patients. The impact of these reductions would need to be accounted for (i.e. with corresponding reductions in the risk sharing arrangement caps in the relapsed/refractory setting).

For more detail on PBAC’s view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the proposed Section 100 Authority Required (Efficient Funding of Chemotherapy) listing of blinatumomab for the treatment of patients with MRD-positive B-ALL due to the patient population in the Australian setting not being

well defined, the difficulty in estimating the incremental benefit and comparative safety versus standard of care chemotherapy, and the high and uncertain incremental cost-effectiveness ratio.

- 7.2 The PBAC considered that there is a high clinical need for more effective treatments for B-ALL, particularly in the first-line setting where there is the greatest potential for impact on cure rates.
- 7.3 The PBAC noted that the submission had requested a broad place in therapy, which included MRD-positive patients in complete haematological remission regardless of line-of-therapy or age, and allowed blinatumomab to be used multiple times. However, the PBAC considered that use of blinatumomab should be restricted to once-per-lifetime as no evidence had been provided for re-use of blinatumomab in subsequent periods of complete remission. Further, the PBAC considered that the appropriate eligible population should include patients:
- in any line of complete remission. The PBAC considered that the clinical data indicated that blinatumomab is likely to be more effective in patients in first complete remission (CR1) than in later remissions, but that, over time, blinatumomab would predominantly be used in CR1 (i.e. in incident patients);
 - of any age (i.e. including children and adolescents);
 - regardless of Philadelphia chromosome status (i.e. including Ph⁺ patients); and
 - with an MRD level of $\geq 10^{-4}$ measured using PCR or flow cytometry (as discussed further below).
- 7.4 The PBAC acknowledged that this would be broader than the population included in the comparative efficacy data provided in the submission (which only included adult patients in CR1, who are Ph⁻, with MRD $\geq 10^{-3}$).
- 7.5 The PBAC considered that the restriction should be Authority Required (written) and would need to include proof of complete remission and MRD status.
- 7.6 The PBAC noted that MRD testing is not subsidised on the MBS and considered that access to MRD testing is not consistently available throughout Australia.
- 7.7 The PBAC noted that that the key study (BLAST) recruited patients with an MRD level of $\geq 10^{-3}$, while the threshold proposed in the restriction was $\geq 10^{-4}$. The PBAC noted that a threshold of $\geq 10^{-4}$ is currently used in clinical practice to define MRD, but noted this was based on a consensus of clinical opinion rather than a strong evidence base. Notwithstanding this, the PBAC considered that an MRD level of $\geq 10^{-4}$ was appropriate for inclusion in the blinatumomab restriction. The PBAC also considered that, as testing technology improves over time, the level of residual disease detected would decrease which may further lessen the applicability of the study data. Thus, the PBAC considered that the level of MRD should be explicitly stated in the PBS restriction.
- 7.8 The PBAC noted that the requested restriction recommended that MRD should be measured using the most stringent measure available. However, there may be

differences in sensitivity and analytic variability depending on the test methodology (with PCR or flow cytometry being the most commonly used methods in current Australian practice) which may impact the level of residual disease detected. Thus, the PBAC considered that the methodology should also be explicitly stated in the PBS restriction.

- 7.9 The PBAC considered that standard of care chemotherapy, as nominated by the submission, was the appropriate comparator.
- 7.10 The PBAC noted the advice given at the sponsor hearing that there are ongoing randomised controlled trials (RCT) of blinatumomab in this patient population, and considered that it would be useful to know when RCT data are expected to be available. The PBAC acknowledged the limitations of conducting an RCT in this patient population (e.g. the difficulty in accruing patients), but considered that RCT data would be particularly useful in this case, given the difficulty estimating the incremental benefit due to the significant limitations of the indirect comparison that had been submitted.
- 7.11 The PBAC noted that the comparative effectiveness was based on a propensity score indirect analysis comparing blinatumomab (based on the BLAST study) with standard of care chemotherapy (based on Study 20120148, a historical control). The PBAC noted and agreed with the key issues raised by the commentary and the ESC about the reliability of the indirect comparison, notably:
- the lack of applicability of the standard of care chemotherapy arm to Australian clinical practice. In particular, the PBAC noted that the majority of patients in the historical control study were treated more than a decade ago, limited details were provided about the treatments administered, and the study was conducted in the UK, Europe and Russia;
 - the high risk of bias of the propensity score analysis;
 - the population included in the propensity score analysis was likely to be significantly different to the PBS population; and
 - the results from the ATT method were used as the primary analysis in the submission (and economic model) despite the alternative method, ATE, resulting in better-matched covariates and a smaller extent of data loss. The PBAC noted that the rationale provided in the pre-PBAC response for using the ATT analyses was that it adjusts the control population so it looks similar to the treated population, which the pre-PBAC response stated was “more likely to reflect the treated population in the real-world setting”. However, the PBAC considered that this was not a reasonable premise for using the ATT analysis given that the proposed restriction is much broader than the patients selected for inclusion in the analysis. The PBAC considered that, of the two methods presented, the ATE analysis would have been the more appropriate primary analysis, and to inform the economic model.

- 7.12 The PBAC considered that blinatumomab is effective in eliminating MRD and is associated with durable relapse-free survival, especially in first-line therapy (CR1), patients with an MRD response after Cycle 1 and those who proceed to alloHSCT. However, the PBAC considered that the magnitude of any improvement in overall survival could not be determined from the data presented due to the immaturity of the BLAST study data (median follow-up of 18.3 months), confounding by alloHSCT use, the limitations and lack of applicability of the propensity score analysis (outlined above), and the lack of statistically significant overall survival gain reported in the ATE analysis.
- 7.13 The PBAC noted that no comparative adverse event data were provided for the MRD population, with the submission instead relying on comparative safety outcomes in the relapsed/refractory setting. The PBAC considered these were unlikely to reflect the circumstances of use in the MRD population (the relapsed/refractory setting includes longer blinatumomab treatment length, less fit patients, more aggressive chemotherapy regimens). The PBAC considered that more recent safety data for the intended population would have been more informative.
- 7.14 The PBAC considered that blinatumomab and standard of care chemotherapy have different safety profiles, with both therapies being associated with potentially life-threatening complications.
- 7.15 The PBAC considered that the largest source of uncertainty in economic model was the uncertainties in the underpinning clinical data, noting that the model was most sensitive to the survival gains associated with blinatumomab compared with consolidation chemotherapy. The PBAC also noted and agreed with the other issues raised by the evaluation and the ESC regarding the economic evaluation, as outlined in the 'Economic analysis' section (Paragraph 6.60).
- 7.16 The PBAC noted that the ICER presented in the base case of the submission was \$45,000/QALY – \$75,000/QALY, which it considered was high and significantly underestimated.
- 7.17 The PBAC noted that the submission estimated that ■ patients would use blinatumomab in Year 6 of listing, which the PBAC considered was underestimated. Further, the PBAC considered that this did not seem consistent with estimates in previous submissions for the relapsed/refractory Ph- population (which the PBAC considered was likely to be a much smaller patient population) which estimated that ■ patients would use blinatumomab in Year 6 (Table 6, blinatumomab November 2016 PBAC Public Summary Document).
- 7.18 The PBAC noted and agreed with the issues raised by the evaluation and the ESC regarding the financial estimates, as outlined in the 'Estimated PBS usage & financial implications' section (Paragraph 6.71). In particular, the PBAC considered that the uptake rate was underestimated.

- 7.19 The PBAC considered that use of blinatumomab in the MRD positive B-ALL setting would likely, over time, reduce or delay use in the existing listing for blinatumomab in relapsed/refractory Ph- patients. The PBAC considered that the impact of these reductions would need to be accounted for (i.e. with corresponding reductions in the risk sharing arrangement caps in the relapsed/refractory setting).
- 7.20 The PBAC considered that any resubmission would need to be a major submission, and would need to address the following issues:
- update the proposed restriction;
 - address the uncertainties identified in the clinical data arising from the indirect comparison and include any RCT data, if available; and
 - update the economic model and financial estimates as outlined above. The PBAC considered that, in the absence of any RCT data, conservative assumptions would need to be applied in the economic model.
- 7.21 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Amgen is pleased that the PBAC acknowledged the clinical need for effective treatment for B-ALL. The elimination of MRD with blinatumomab is an important and effective treatment option for these patients. As such, Amgen will continue to work with the PBAC with the aim to make blinatumomab available for these patients.