

7.06 GEMTUZUMAB OZOGAMICIN, Powder for injection 5 mg, Mylotarg[®], Pfizer Australia Pty Ltd.

1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a Section 100 Authority Required (Efficient Funding of Chemotherapy) listing for gemtuzumab ozogamicin in combination with standard intensive chemotherapy (an anthracycline and cytarabine) for the treatment of patients with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia, who have favourable/intermediate/unknown cytogenetic risk. The PBAC had previously considered gemtuzumab ozogamicin for the same indication in March 2021.
- 1.2 Any further reference to gemtuzumab in this document refers to gemtuzumab ozogamicin.
- 1.3 Listing was requested on the basis of a cost-effectiveness analysis versus standard intensive chemotherapy (an anthracycline and cytarabine).

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

Component	Description
Population	Patients with previously untreated, de novo CD33-positive acute myeloid leukaemia, except acute promyelocytic leukaemia who do not have known unfavourable cytogenetic profile (i.e. favourable, intermediate, or unknown risk).
Intervention	1-2 induction cycles: gemtuzumab ozogamicin 3 mg/m ² /dose (maximum 5 mg) via intravenous infusion in combination with standard intensive chemotherapy on Day 1, 4 and 7 for one cycle only. If required, a second induction cycle may be administered with standard intensive chemotherapy alone. 2 consolidation cycles: gemtuzumab ozogamicin 3 mg/m ² /dose (maximum 5 mg) via intravenous infusion in combination with standard intensive chemotherapy on Day 1 only.
Comparator	Standard intensive chemotherapy for induction and consolidation therapy (an anthracycline and cytarabine).
Outcomes	Event-free survival, haematological response, relapse-free survival, overall survival, and potential for functional cure.
Clinical claim	Gemtuzumab ozogamicin in addition to standard intensive chemotherapy is superior in terms of effectiveness (for event-free survival and relapse-free survival, "with a trend towards improved OS") and inferior in terms of safety compared to standard intensive chemotherapy.

Source: Table 1.1.1, p30 of the resubmission

2 Background

Registration status

- 2.1 Gemtuzumab was approved by the TGA on 9 April 2020 for the following indication: combination therapy with standard anthracycline and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive AML, except acute promyelocytic leukaemia.

- 2.2 The approved indication is agnostic to which anthracycline is used whereas the key trial data was based on daunorubicin only. The sponsor indicated that the rationale for an anthracycline agnostic indication was to allow broader treatment options for clinicians. Idarubicin, which is the more commonly used anthracycline in Australia, is PBS funded. Daunorubicin is not PBS funded.
- 2.3 The TGA-approved Product Information includes special warnings and precautions for use of gemtuzumab including the risk of veno-occlusive disease (VOD). Gemtuzumab is also included in the Black Triangle Scheme for additional monitoring and identification of new safety information.

Previous PBAC consideration

- 2.4 The outstanding matters of concern from the previous March 2021 PBAC meeting are summarised in the table below. Overall, the PBAC considered a resubmission for gemtuzumab should address issues with the economic model and present updated utilisation and financial estimates (para 7.16, gemtuzumab Public Summary Document (PSD), March 2021 PBAC meeting).

Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
The PBAC considered that the economic model structure was overly complex making it difficult to determine the flow of patients through the model. The PBAC identified a number of issues with the model which meant the base case ICER per QALY gained of \$██████ ¹ was highly uncertain and likely optimistic (para 7.13, gemtuzumab PBAC PSD, March 2021 PBAC meeting).	The resubmission presented the same economic model structure as the previous submission. However, the resubmission attempted to address a number of PBAC's concerns, as below.
The PBAC considered the 40-year time horizon applied in the model was optimistic given the baseline age of patients of 62 years (para 7.13, gemtuzumab PBAC PSD, March 2021 PBAC meeting).	The time horizon in the resubmission was revised to 25 years.
The PBAC considered that the model relied on transition probabilities that were informed by subgroups consisting of small patient numbers, unsubstantiated assumptions and unverifiable expert opinion, which resulted in highly uncertain outcomes (para 7.13, gemtuzumab PSD, March 2021 PBAC meeting).	The transition probabilities in the resubmission were informed by the same data.
The PBAC considered that relative treatment effects for gemtuzumab in terms of EFS and OS were derived from a subset of patients in the favourable/intermediate/unknown cytogenetic risk subgroup who achieved an overall response. The PBAC noted that the submission did not adequately justify the use of the subgroup results over the ITT results or provide the relative and absolute treatment effect measures for the subgroups or their complements (para 7.13, gemtuzumab PSD, March 2021 PBAC meeting).	The model in the resubmission relied on the same relative treatment effects based on the favourable/intermediate/unknown cytogenetic risk subgroup. The resubmission conducted multiple interaction tests for subgroup analyses of EFS, RFS and OS as additional justification for the use of this subgroup's estimates over the ITT results. The resubmission also provided the treatment effect estimates used in the economic model.

Matter of concern	How the resubmission addresses it
<p>The PBAC considered that the assumption of increased OS for patients in the gemtuzumab arm, which was a key driver of the model, was highly uncertain as the clinical evidence did not suggest a statistically significant difference in the mITT population of the ALFA-0701 trial and the OS difference in the proposed PBS population was difficult to interpret. The PBAC considered that RFS and OS curves only converged towards the end of the 40-year time horizon. The PBAC considered that the differences, particularly the difference in OS, were not adequately supported by the clinical data (para 7.13, gemtuzumab PSD, March 2021 PBAC meeting).</p>	<p>The model in the resubmission maintained an overall survival benefit, however, the magnitude of benefit was more conservative as the resubmission applied forced convergence of OS curves at the end of the 25-year time horizon.</p>
<p>The PBAC considered that the extrapolated survival curves in both arms were driven by patients achieving a functional cure. The PBAC considered that it was unclear whether the plateaus at the tail-end of the Kaplan-Meier data for EFS and OS were sufficiently robust representations of functional cure which would translate into ongoing survival benefits, particularly as there were substantial differences in the estimated cure fractions for RFS and OS. The PBAC noted that higher cure fractions were estimated for OS than for RFS, which was not clinically plausible unless patients who relapsed became functionally cured due to subsequent therapies and/or HSCT, which is relatively rare in AML. In addition, the PBAC considered that the cure fractions based on overall survival (52.1% in the gemtuzumab arm and 40.0% in the comparator arm) were high compared to the estimated cure fraction due to HSCT (42.2%) (para 7.13, gemtuzumab PSD, March 2021 PBAC meeting).</p>	<p>The same methods of extrapolation were employed in the resubmission; however, the resubmission claimed the inclusion of forced convergence of OS reduced the impact of the cure fraction assumptions in the model.</p>
<p>The PBAC considered the model assumed a higher proportion of patients in the standard of care arm would receive HSCT after relapse. The PBAC noted that this was a key offset in the economic model and considered that the rate should be equal in both arms (para 7.13, gemtuzumab PSD, March 2021 PBAC meeting).</p>	<p>The resubmission used revised transition probabilities to HSCT based on an updated analysis of individual patient data from the trial, however, the resubmission maintained the use of individual arm HSCT rates in relapsed patients. Pooled rates were presented as a sensitivity analysis during evaluation, and in the pre-PBAC response.</p>
<p>The PBAC considered that the majority of use of gemtuzumab would be in the public hospital setting, but that the financial impact was highly dependent on the public hospital/private hospital split of 83%/17% presented in the PSCR (para 7.14, gemtuzumab PSD, March 2021 PBAC meeting).</p>	<p>The estimated financial impact was updated based on a public hospital versus private hospital ratio of 83%/17%, as presented in the PSCR for the March 2021 submission.</p>
<p>The PBAC considered that the utilisation and financial impact estimations were uncertain and that a resubmission should present updated estimates to address a number of issues concerning key inputs to determine the size of the eligible and treated populations, and additional costs to the PBS/MBS associated with the use of gemtuzumab (para 7.15 and 7.16, gemtuzumab PSD, March 2021 PBAC meeting)</p>	<p>The resubmission presented updated utilisation and financial estimates, with multiple revisions including the size of the eligible and treated populations and additional costs to Government associated with gemtuzumab treatment.</p>

Source: adapted from Table OV, p20 of the resubmission.

EFS, event-free survival; HSCT, haematopoietic stem cell transplant; OS, overall survival; PSCR, Pre-Sub-Committee Response; RFS, relapse-free survival

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

3 Requested listing

3.1 The resubmission claimed the administration of gemtuzumab would occur primarily in the public hospital inpatient setting. Therefore, the funding of gemtuzumab is

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expected to largely fall within the budget of public hospitals and not the Australian Government. The PBAC had previously considered the majority of use would be in the public hospital setting (para 7.14, gemtuzumab PSD, March 2021 PBAC meeting).

3.2 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack (MPP)	PBS item code	Dispensed Price for Max. Amt	Max. Amount	№.of Rpts
GEMTUZUMAB OZOGAMICIN gemtuzumab ozogamicin 5 mg injection, 1 vial	<i>NEW (Public)</i> <i>NEW (Private)</i>	\$ (public) \$ (private)	4.5 mg	2
Available brands				
Mylotarg				
Restriction Summary [new] / Treatment of Concept: [new]				
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals				
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Telephone <input checked="" type="checkbox"/> Authority Required – Electronic <input checked="" type="checkbox"/> Authority Required – Telephone/electronic via Online PBS Authorities				
Condition: Previously untreated de novo Acute Myeloid Leukaemia (AML)				
Indication: Acute Myeloid Leukaemia				
Treatment Phase: Induction treatment				
Clinical criteria:				
AND				
Patient must have confirmed CD33-positive AML prior to initiation of treatment,				
Clinical criteria:				
AND				
<i>The condition must be de novo,</i>				
Clinical criteria:				
AND				
<i>The condition must be previously untreated,</i>				
Clinical criteria:				
AND				
Patients must not have confirmed unfavourable cytogenetic risk, <i>Patient must have confirmed intermediate/favourable cytogenetic risk,</i> OR <i>Patient must have unknown cytogenetic risk due to inconclusive test results.</i>				
Clinical criteria:				
AND				
Patient must have an ECOG performance status of 0-3 <i>an Eastern Cooperative Oncology Group (ECOG) performance status score of 3 or less,</i>				
Clinical criteria:				
AND				
<i>The condition must not be acute promyelocytic leukaemia,</i>				
Clinical criteria:				
AND				
<i>The treatment must be in combination with standard intensive remission induction chemotherapy for this condition,</i>				
Clinical criteria:				

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	AND
	<i>The treatment must not be used in combination with a tyrosine kinase inhibitor.</i>
	The treatment must not be used in combination with other therapies, including tyrosine kinase inhibitors. A maximum of 1 induction cycle will be authorised under this restriction in a lifetime. Standard intensive remission induction combination chemotherapy must include cytarabine and an anthracycline. A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.
	Treatment criteria:
	This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.
	Prescribing Instructions: <i>This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.</i>
	Prescribing Instructions: <i>Patients will still be considered eligible despite receiving prior, but essential treatment with hydroxyurea or leukapheresis.</i>
	Prescribing Instructions: <i>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.</i>
	Prescribing Instructions: <i>Standard intensive remission induction combination chemotherapy must include cytarabine and an anthracycline.</i>
	Prescribing Instructions: <i>Progressive disease is defined as the presence of any of the following:</i> <ul style="list-style-type: none"> •Leukaemic cells in the CSF; •Re-appearance of circulating blast cells in the peripheral blood, not attributable to overshoot following recovery from myeloablative therapy; •Greater than 5 % blasts in the marrow not attributable to bone marrow regeneration or another cause; •Extramedullary leukaemia.
	Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>
	Administrative Advice: <i>No increase in the maximum amount or number of units may be authorised.</i>
	Administrative Advice: <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</i>
	Definitions: Progressive disease is defined as the presence of any of the following: <ul style="list-style-type: none"> •Leukaemic cells in the CSF; •Re-appearance of circulating blast cells in the peripheral blood, not attributable to overshoot following recovery from myeloablative therapy; •Greater than 5 % blasts in the marrow not attributable to bone marrow regeneration or another cause; •Extramedullary leukaemia.

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Available brands				
Mylotarg				
Restriction Summary [new] / Treatment of Concept: [new]				
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals				
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Telephone <input checked="" type="checkbox"/> Authority Required – Electronic <input checked="" type="checkbox"/> Authority Required – Telephone/electronic via Online PBS Authorities				

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	Condition: Previously untreated de novo Acute Myeloid Leukaemia (AML)
	Indication: Acute Myeloid Leukaemia
	Treatment Phase: Consolidation treatment
	Clinical criteria:
	The treatment must be for consolidation treatment following induction treatment with gemtuzumab-ozogamicin in combination with chemotherapy; Patient must have achieved a complete remission following induction treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be in combination with standard intensive remission consolidation chemotherapy for this condition,
	AND
	Clinical criteria:
	Patient must have achieved a complete remission A maximum of 2 consolidation cycles will be authorised under this restriction in a lifetime. A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. Standard intensive remission induction combination chemotherapy must include cytarabine and an anthracycline.
	Treatment criteria:
	This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.
	Prescribing Instructions: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.
	Prescribing Instructions: A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.
	Prescribing Instructions: Standard intensive remission consolidation combination chemotherapy must include cytarabine and an anthracycline.
	Prescribing Instructions: Complete remission following induction is defined as fewer than 5% blasts in a normocellular marrow and an absolute neutrophil count of more than 1.0×10^9 cells/L with a platelet count of 100×10^9/L or more in the peripheral blood in the absence of transfusion.
	Prescribing Instructions: Progressive disease is defined as the presence of any of the following: <ul style="list-style-type: none"> •Leukaemic cells in the CSF; •Re-appearance of circulating blast cells in the peripheral blood, not attributable to overshoot following recovery from myeloablative therapy; •Greater than 5 % blasts in the marrow not attributable to bone marrow regeneration or another cause; •Extramedullary leukaemia.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: No increase in the maximum amount or number of units may be authorised.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Definitions: For patients experiencing a complete remission (CR) following induction, this is defined as fewer than 5% blasts in a normocellular marrow and an absolute neutrophil count (ANC) of more than 1.0×10^9 cells/L with a platelet count of 100×10^9/L or more in the peripheral blood in the absence of transfusion. Progressive disease is defined as the presence of any of the following: <ul style="list-style-type: none"> •Leukaemic cells in the CSF; •Re-appearance of circulating blast cells in the peripheral blood, not attributable to overshoot following recovery from myeloablative therapy;

<ul style="list-style-type: none">• Greater than 5 % blasts in the marrow not attributable to bone marrow regeneration or another cause;• Extramedullary leukaemia.
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- 3.3 The proposed price was an AEMP of \$ [REDACTED] per vial. This represented a 9.7% reduction compared to the previous submission (AEMP \$ [REDACTED] per vial). The pre-PBAC response offered a further 14% price reduction, which the PBAC noted resulted in an AEMP of \$ [REDACTED] per vial.
- 3.4 Key changes to the requested restrictions compared to the previous submission were the exclusion of use of gemtuzumab with other therapies including tyrosine kinase inhibitors and clarification of the clinical criteria that the condition must be CD33-positive prior to treatment.
- 3.5 The clinical criteria limit use of gemtuzumab to patients without confirmed unfavourable cytogenetic risk, which is narrower than the TGA indication that was agnostic to cytogenetic risk classification, and narrower than the previous submission which had also permitted use in patients awaiting cytogenetic test results.
- 3.6 The resubmission also removed the request for a grandfathering provision for gemtuzumab. The sponsor anticipated that the likelihood of patients requiring grandfathering was low given the dosing and administration schedule of gemtuzumab.
- 3.7 The requested restriction was broader than the TGA indication as it allows use in the paediatric population less than 15 years old. The eligible population in the financial estimates of the resubmission was based on patients aged 15 years and above. In June 2020, the FDA extended the indication of gemtuzumab for newly diagnosed CD33-positive AML to include paediatric patients 1 month and older based on data from the AAML0531 trial (completed September 2020), a phase 3, randomised open-label study in newly diagnosed AML patients aged 0 to 29 years. Patients were randomised to 5-cycle combination chemotherapy alone (including asparaginase, cytarabine, daunorubicin, etoposide and mitozantrone) or with gemtuzumab, which was different to the treatment regimen used in the ALFA-0701 trial for adults.
- 3.8 The ESC noted that the resubmission had clarified that patients with confirmed FLT3 mutations would not be treated with gemtuzumab, and ESC considered that the restriction should specifically exclude these patients, given the lack of evidence to support concomitant use of gemtuzumab and FLT3 inhibitors. The pre-PBAC response agreed, noting that these patients were already excluded from the financial estimates.

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

4 Population and disease

- 4.1 AML is a type of blood cancer which develops when the body makes too many immature white blood cells known as myeloid blasts. This condition usually occurs suddenly and develops quickly, as the myeloid blasts multiply out of control, continue to divide but never mature into normal cells. These immature and abnormal blast cells are also known as leukaemia cells. They do not perform the usual infection-fighting

function of white blood cells, and also crowd out normal white blood cells, impairing their function. When the bone marrow is filled with leukaemia cells, there is less room for healthy red blood cells and platelets to be produced. Patients with AML typically experience fatigue, weakness or breathlessness, memory loss, bruising, bleeding, and frequent infections.

- 4.2 AML is the most common type of acute leukaemia in adults. The disease becomes more common with age, mostly occurring after 65 years, and affects more males than females. AML is associated with rapid progression and poor prognosis, with a 5-year relative survival in all ages of 26.3% (2013-2017 period, AIHW Cancer data in Australia, 2021). Relative survival at 5 years is higher in younger adults and adolescents (above 70%), decreasing to approximately 50% from age 50 years and becoming worse among older patients age 60 years and above (30% or less) (AIHW Cancer data in Australia, 2021). The majority of cases occur de novo, however, there are a minority of cases with subtypes of AML, including acute promyelocytic leukaemia and secondary AML, which are associated with prior myelodysplastic syndrome or myeloproliferative disease or prior cytotoxic chemotherapy or radiation for an unrelated malignancy. These subtypes are biologically and clinically distinct variants, which are associated with relatively poorer treatment response and prognosis and are treated differently to de novo AML.
- 4.3 Diagnosis of AML is typically confirmed using blood tests, bone marrow examination (to determine cell morphology and degree of bone marrow infiltration with disease), immunophenotyping (to determine cell lineage, e.g. whether AML blasts are CD33 positive), cytogenetics profile and molecular genetics.
- 4.4 The previous submission intended for gemtuzumab to be used in patients awaiting confirmation of their cytogenetic profile. However, the resubmission stated that this scenario was unlikely based on a survey of experts, suggesting that clinicians would rather wait for confirmation of cytogenetic risk before commencing treatment due to potential impacts of using gemtuzumab on subsequent treatment decisions and use of alternative treatment options (e.g. adverse risk patients may have a prolonged wait for HSCT due to veno-occlusive disease risk following gemtuzumab, alternative therapies for FLT3 and IDH mutation positive patients, and no treatment benefit with gemtuzumab in some patients) (Expert Opinion June 2021, Attachment 11 of the resubmission). The ESC considered that it may not be practical to wait for cytogenetic test results in locations with longer wait times (e.g. 5 days) if patients required immediate treatment.
- 4.5 The target population in the resubmission was patients with previously untreated, de novo CD33-positive AML, except acute promyelocytic leukaemia, who have favourable, intermediate, or unknown cytogenetic risk. The resubmission noted that while all patients would receive cytogenetic test results prior to treatment initiation, not all patients would have a confirmed cytogenetic risk classification, as some patients would be classified as having unknown cytogenetic risk due to inconclusive test results. In practice, the ESC considered it was possible that few of these patients

would be treated with gemtuzumab. The ESC recognised that some patients with inconclusive test results would have demonstrated intermediate/favourable cytogenetics had their tests been successful, and the ESC considered that it may be reasonable not to exclude this group from subsidy (which would be a pragmatic decision based on small expected patient numbers and despite the lack of evidence to support use in patients with “unknown” cytogenetic risk).

- 4.6 While the pivotal trial included patients with unknown cytogenetic risk, the magnitude of benefit in this subgroup, if any, was unclear as the results were based on *post hoc* analyses in a relatively small number of patients.
- 4.7 The resubmission provided additional clarification on the goals of induction treatment and whether it is to achieve remission or to bridge patients to HSCT. A survey of clinicians provided in the resubmission suggested that the primary use of gemtuzumab is in patients with favourable risk and some patients with intermediate risk who are not being considered for HSCT (i.e. not a bridging therapy to HSCT).
- 4.8 Based on published international guidelines and local expert opinion, the ESC advised that the place in therapy for gemtuzumab appears to be in patients with favourable/intermediate cytogenetic risk, who are not FLT3-mutation positive and who are not being considered for HSCT. This role was smaller than the requested listing and proposed target population in the resubmission. The ESC noted that the proposed listing would restrict use in patients requiring immediate treatment (i.e. in settings with longer waiting times for cytogenetic test results). The ESC also considered that the clinical place of gemtuzumab would be further limited to those in good prognosis AML subgroups (e.g. core binding factor AML), and advised that there may be some clinical hesitancy to use with anthracyclines other than daunorubicin. The ESC considered it may be appropriate for the PBAC to seek additional advice from expert clinical groups around the expected clinical place of gemtuzumab (see ‘Consumer comments’ below).

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

5 Comparator

- 5.1 The resubmission nominated standard of care as the main comparator. The PBAC had previously considered that standard of care, which consisted of intensive induction and consolidation chemotherapy with an anthracycline and cytarabine, was appropriate (para 7.2, gemtuzumab PSD, March 2021 PBAC meeting).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. Comments were received from the Leukaemia Foundation, Rare Cancers Australia, and the Australasian Leukaemia and Lymphoma Group (ALLG). The comments supported the PBS listing of gemtuzumab, and described a likely small population with a clear clinical need for additional benefits above those provided by standard care, given the overall poor prognosis for AML. The health care professional and the ALLG considered that gemtuzumab would likely be used in patients with CD33-positive AML with favourable/intermediate cytogenetic risk disease, who are fit for chemotherapy, and that use would be limited in patients considered candidates for HSCT due to the potential AEs associated with gemtuzumab. The comments further expected that clinicians would favour use with daunorubicin (rather than another anthracycline), because the key clinical evidence supported use of this combination.
- 6.3 The PBAC sought additional clinical advice from the Haematology Society of Australia and New Zealand (HSANZ) and the ALLG. Among other matters, the PBAC noted that:
- HSANZ advised that AML was a poor prognosis aggressive blood cancer, and that gemtuzumab has shown benefits in terms of event-free survival and overall survival, thus addressing an unmet clinical need. HSANZ commented that the benefit in event-free survival was related to a reduction in relapsed leukaemia, and corresponded to a small benefit in overall survival. HSANZ noted no evidence to support the use of gemtuzumab in combination with midostaurin, and also did not support use in combination with novel low-intensity regimens (except in the context of a clinical trial).
 - ALLG also again emphasised that gemtuzumab would likely be used in patients with CD33-positive de novo AML with either favourable or intermediate cytogenetic disease (and was not expected to be used extensively outside those with core binding factor AML). It was again commented that clinicians would likely favour use in combination with daunorubicin, as the clinical literature was predominantly with this anthracycline. ALLG considered that if remission is not achieved in a first cycle of therapy, it is highly unlikely that gemtuzumab would be used for a second cycle of therapy. There may also be a hesitancy to use during consolidation for patients expected to proceed to HSCT, due to concerns around veno-occlusive disease risk of gemtuzumab. Clinicians are unlikely to use gemtuzumab until cytogenetic results are confirmed, in order to select better prognosis patients for treatment. ALLG also considered that patients with unknown cytogenetics should not necessarily be excluded from PBS subsidy, as molecular testing could also identify better prognosis disease in patients whose cytogenetic test results were inconclusive. ALLG considered that there is not currently sufficient evidence to support use in FLT3-mutation positive patients. Finally, ALLG advised that there was an expected survival benefit over standard of care, and highlighted that paediatric

populations should have access to such novel oncological therapies (although noted that the benefit in this population was observed in relation to event-free survival, rather than overall survival).

- 6.4 The PBAC noted that the expert advice from HSANZ, ALLG and the ESC was broadly aligned, and considered that gemtuzumab would likely be used in a smaller, more defined population of patients most likely to see benefit, than that which had been assumed by the resubmission.

Clinical trials

- 6.5 The resubmission was based on the following clinical evidence, previously considered by the PBAC at the March 2021 PBAC meeting:
- A head-to-head trial, ALFA-0701, comparing gemtuzumab with standard intensive remission chemotherapy (cytarabine and daunorubicin) versus standard intensive remission chemotherapy (cytarabine and daunorubicin) alone in induction and consolidation chemotherapy.
 - A supportive meta-analysis of individual patient data (IPD) of 5 trials including the pivotal trial, ALFA-0701, and 4 other trials (MRC AML15, SWOG S0106, NCRI AML16, GOELAMS AML 2006 IR) comparing gemtuzumab as add-on to induction chemotherapy versus induction chemotherapy alone. The resubmission noted that this analysis was considered supportive only as the 4 other trials employed dosage regimens for gemtuzumab that were inconsistent with the Product Information. These trials were also based on broader patient populations (including secondary AML and high-risk myelodysplastic syndrome), used varying dosing regimens of gemtuzumab and varying backbone chemotherapy regimens.
 - Supportive data from a published systematic review (Li 2014) and network meta-analysis (Ashaye 2019) assessing gemtuzumab as add-on to standard induction chemotherapy. Another relevant systematic review (Kharfan-Dabaja 2013) was identified during the evaluation of the previous submission and included in the March 2021 commentary.
- 6.6 Details of the key trial and supportive studies presented in the resubmission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Key clinical trial		
ALFA-0701	<p>Multicentre, randomized, phase 3 study of fractionated doses of the monoclonal antibody Gemtuzumab Ozogamicin (Mylotarg) in addition to Daunorubicin + Cytarabine for induction and consolidation therapy in patients with Acute Myeloid Leukaemia (AML) aged 50-70 years. (NCT00927498).</p> <p>Castaigne, Pautas, Terre et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study.</p> <p>Fournier, Duployez, Ducourneau et al. Mutational profile and benefit of gemtuzumab in acute myeloid leukemia.</p> <p>Lambert, Pautas, Terre et al. Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase II ALFA-0701 trial.</p> <p>Olombel, Guerin, Guy et al. The level of blast CD33 expression positively impacts the effect of gemtuzumab ozogamicin in patients with acute myeloid leukemia.</p> <p>Renneville, Abdelali, Chevret et al. Clinical impact of gene mutations and lesions detected by SNP-array karyotyping in acute myeloid leukemia patients in the context of gemtuzumab ozogamicin treatment: Results of the ALFA-0701 trial.</p> <p>Othus, Wood, Stirewalt et al. Effect of measurable (“minimal”) residual disease (MRD) information on prediction of relapse and survival in adult acute myeloid leukemia.</p>	<p>Clinical Study Report, 26 July 2016</p> <p><i>Lancet</i> 2012; 379(9825):1508-16</p> <p><i>Blood</i> 2020; 135(8):542-546</p> <p><i>Haematologica</i> 2019; 104(1):113-119</p> <p><i>Blood</i> 2016; 124(17):2157-60</p> <p><i>Oncotarget</i> 2014; 5(4):916-932</p> <p><i>Leukemia</i> 2016; 30(10):2080-83</p>
Systematic reviews and meta-analyses		
Ashaye 2019	Ashaye, Khankel, Xu et al. A comparative evaluation of gemtuzumab ozogamicin + daunorubicin-cytarabine and other treatments for newly diagnosed acute myeloid leukemia.	<i>Future Oncology</i> 2019; 15(6):663-81
IPD meta-analysis	<p>Hills, Castaigne, Appelbaum et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials.</p> <p>Pfizer. Section 2.5.4.2. Individual patient data meta-analysis. Module 2.5 clinical overview gemtuzumab ozogamicin (Mylotarg) for the treatment of acute myeloid leukaemia.</p>	<p><i>Lancet Oncology</i> 2014; 15(9):986-96</p> <p>Mylotarg Clinical Overview, 2016, attached in the submission</p>
Kharfan-Dabaja 2013 ^a	Kharfan-Dabaja, Hamadani, Reljic et al. Gemtuzumab ozogamicin for the treatment of newly diagnosed acute myeloid leukaemia: a systematic review and meta-analysis.	<i>British Journal of Haematology</i> 2013; 163:315-25
Li 2014	Li, Su, Qin et al 2014. Effect of adding gemtuzumab ozogamicin to induction chemotherapy for newly diagnosed acute myeloid leukemia: a meta-analysis of prospective randomized phase III trials.	<i>Annals of Oncology</i> 2014; 25:455-61

Source: 'Section 2 Literature Searches Report and Annotated Results' Excel workbook, Attachment 1 of the resubmission.

^a Identified during the evaluation.

6.7 The key features of the ALFA-0701 trial are summarised in the table below.

Table 4: Features of the key trial included in the submission

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
ALFA-0701	271	Phase 3, multi-centre, open label, parallel group RCT 1 August 2011 data cut: median follow-up duration 14.8 months; 30 April 2013 data cut: 47.6 months for gemtuzumab and 41.0 months in control arm	High	Adults aged 50 to 70 years with previously untreated morphologically documented AML, normal cardiac function, ECOG PS 0 to 3. Excluded patients with acute promyelocytic leukaemia and secondary AML.	Primary: EFS Secondary: CR/CRp, RFS, OS	CR/CRp, RFS, OS, time to HSCT, RMST for patients receiving subsequent therapies, post-HSCT cure rates, adverse events, age, gender, BSA, weight, treatment courses received in induction and consolidation.

Source: Section 2.3.1, p86 of the resubmission.

AML, acute myeloid leukaemia; BSA, body surface area; CR/CRp, complete remission with or without incomplete platelet recovery; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS, event-free survival; HSCT, haematopoietic stem cell transplant; OS, overall survival; RCT, randomised controlled trial; RFS, relapse-free survival; RMST, restricted mean survival time.

- 6.8 The open-label trial design for ALFA-0701 had the potential to introduce bias as knowledge of treatment assignment may have affected disease management decisions as well as the reporting of subjective outcomes (e.g. response, relapse) that were not centrally-assessed during the trial.
- 6.9 There was some attrition of data following data acquisition by the current sponsor in March 2013, and the safety analysis set was based on the ‘As Treated’ population who were grouped by whether or not any gemtuzumab was received and not as per randomisation.
- 6.10 A retrospective collection of additional safety and efficacy data was performed by an independent research organisation at the sponsor’s request (1 November 2013 data cut-off date). A concordance analysis of investigator assessment and independent review indicated an overall discordance rate of 21.4% for event-free survival. The results suggest differential discordance between the gemtuzumab arm (19.2%) and the comparator arm (23.5%), primarily driven by timing and occurrence of an event.
- 6.11 Adverse events in this study were not collected as per usual industry standards that typically include an extensive review of any untoward or unplanned events. During the initial study conduct, safety information was captured using a predefined checklist developed by the original sponsor (Centre Hospitalier de Versailles) rather than open-ended solicitation of all-causality treatment-emergent adverse events. Notable omissions were that Grade 1 or 2 events were not recorded, nor adverse events leading to dose reduction or temporary discontinuation. A retrospective safety data collection via review of individual patient records was conducted to capture this missing information.
- 6.12 The trial report noted a number of protocol deviations including 8 patients who had a treatment allocation deviation, 30 patients with a gemtuzumab dosing error, 68 patients with a chemotherapy dosing error, 2 patients with source data missing during

retrospective data collection, and 31 patients who had eligibility criteria deviations. The impact of protocol deviations was unclear as the proportion of patients with deviations in each treatment arm was not reported.

Comparative effectiveness

- 6.13 The majority of patients in both arms achieved complete remission (CR) or complete remission with incomplete platelet recovery (CRp) (74.1% in gemtuzumab arm and 70.6% in the control arm).
- 6.14 The PBAC had previously noted there was no statistically significant difference in overall response rate between arms when assessed either by the investigator (HR = 1.58; 95% CI: 0.86, 2.96) or by independent review (HR = 1.19; 95% CI: 0.67, 2.10) (para 7.6, gemtuzumab PSD, March 2021 PBAC meeting).
- 6.15 Subgroup analysis results (favourable/intermediate/unknown cytogenetic risk) were consistent with the overall results, with no statistically significant differences in response rates between treatment arms.
- 6.16 In terms of event-free survival, the PBAC had noted that gemtuzumab plus standard intensive chemotherapy versus standard intensive chemotherapy alone was associated with a modest statistically significant benefit in the modified Intention to Treat (mITT) population (independent review committee dataset) (5.7 months; HR = 0.705, 95% CI: 0.536, 0.928). The PBAC had noted that the result in the favourable/intermediate/unknown cytogenetic risk subgroup was also statistically significant (7.2 months; HR = 0.630, 95% CI: 0.459, 0.866) (para 7.5, gemtuzumab PSD, March 2021 PBAC meeting).
- 6.17 In the economic model, relative treatment effects for gemtuzumab were derived from event-free survival observed in the subset of patients in the subgroup with favourable/intermediate/unknown cytogenetic risk, who achieved an overall response. The resubmission clarified that event-free survival assessed in patients achieving response would be the same as relapse-free survival. This was consistent with outcomes definitions in the trial protocol.
- 6.18 The clinical input data used in the economic model was unchanged compared to the previous submission, however, the resubmission provided new Kaplan-Meier figures and treatment effect estimates for these inputs that were not available in the previous submission.
- 6.19 The table below presents the results of *post hoc* analyses of relapse-free survival by cytogenetic risk. These estimates had not previously been considered by the PBAC.

Table 5: Post hoc analysis of relapse-free survival by cytogenetic risk subgroups (30 April 2013 cut off)

	GO+DA	DA
mITT population		
Number of patients	100	96
Number of events, n (%)	63 (63.0)	72 (75.0)
- Relapse	58 (58.0)	60 (62.5)
- Death	5 (5.0)	12 (12.5)
Kaplan-Meier estimate of median RFS, months (95% CI)	21.7 (14.1, 33.0)	12.1 (10.2, 15.9)
Hazard ratio vs DA (95% CI)	0.656 (0.466, 0.922)	
Favourable/intermediate cytogenetic risk subgroup		
Number of patients	76	74
Number of events, n (%)	48 (63.2)	56 (75.7)
- Relapse	44 (57.9)	48 (64.9)
- Death	4 (5.3)	8 (10.8)
Kaplan-Meier estimate of median RFS, months (95% CI)	23.5 (14.1, 42.9)	14.4 (10.6, 17.0)
Hazard ratio vs DA (95% CI)	0.630 (0.427, 0.931)	
Unknown cytogenetic risk subgroup		
Number of patients	10	7
Number of events, n (%)	3 (30.0)	5 (71.4)
- Relapse	3 (30.0)	3 (42.9)
- Death	0 (0.0)	2 (28.6)
Kaplan-Meier estimate of median RFS, months (95% CI)	NE (9.9, NE)	10.5 (2.2, NE)
Hazard ratio vs DA (95% CI)	0.284 (0.067, 1.206)	
Unfavourable cytogenetic risk subgroup		
Number of patients	14	15
Number of events, n (%)	12 (85.7)	11 (73.3)
- Relapse	11 (78.6)	9 (60.0)
- Death	1 (7.1)	2 (13.3)
Kaplan-Meier estimate of median RFS, months (95% CI)	7.0 (3.6, 17.0)	11.1 (4.2, 20.8)
Hazard ratio vs DA (95% CI)	1.195 (0.526, 2.719)	
Favourable/intermediate/unknown cytogenetic risk subgroup		
Number of patients	86	81
Number of events, n (%)	51 (59.3)	61 (75.3)
- Relapse	47 (54.7)	51 (63.0)
- Death	4 (4.7)	10 (12.3)
Kaplan-Meier estimate of median RFS, months (95% CI)	27.9 (16.7, 49.2)	14.1 (10.5, 16.1)
Hazard ratio vs DA (95% CI)	0.578 (0.397, 0.842)	

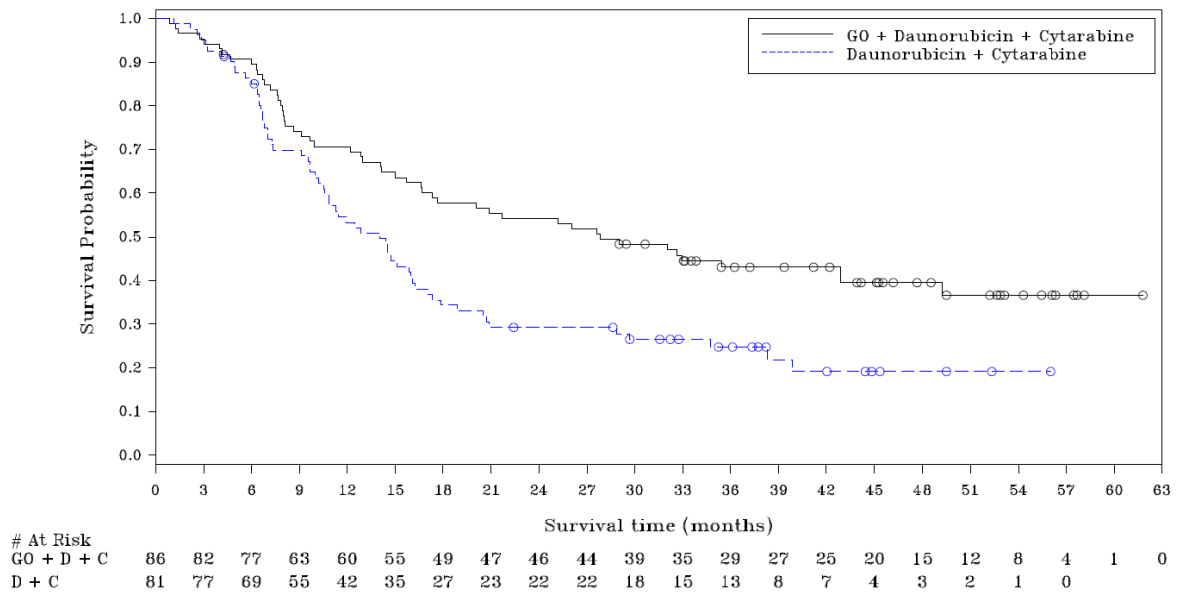
Source: Tables 14.2.10.7 and 14.2.10.36 of the resubmission

CI, confidence interval; DA, daunorubicin; GO, gemtuzumab; NE, not estimable; RFS, relapse-free survival

- 6.20 In patients with favourable/intermediate cytogenetic risk, relapse-free survival was consistent with the whole trial population. There was no apparent treatment benefit in patients with unknown or unfavourable cytogenetic risk.
- 6.21 Results based on the combined subgroup with favourable/intermediate/unknown cytogenetic risk were also consistent with the whole trial population, with a numerical improvement in median relapse-free survival and hazard ratio compared to the favourable/intermediate subgroup due to the inclusion of patients with unknown risk. It was difficult to interpret these results given the relatively small size of the subgroup with unknown risk and the lack of subgroup characteristics in the resubmission.

6.22 The figure below represents the Kaplan-Meier data for relapse-free survival in the subgroup with favourable/intermediate/unknown cytogenetic risk (patients who achieve response). The data were previously considered by the PBAC at the March 2021 PBAC meeting, but the figure previously presented used a different scale (X-axis based on days).

Figure 1: Kaplan-Meier curve for relapse-free survival in the subgroup with favourable/intermediate/unknown risk, who achieve an overall response (independent review, 30 April 2013 cut-off).



Notes: Circles indicate censored observations.
D + C stands for Daunorubicin + Cytarabine.

Source: Figure 3.4.1, p214 of the resubmission

- 6.23 Based on the new figure, relapse-free survival was similar initially and then diverged from approximately 4.5 months. The reason for the delay in divergence was unclear.
- 6.24 The resubmission claimed the plateaus occurring at the tail-end of the plots represents patients who achieved functional cure. The resubmission suggested there is a substantial difference in the proportion of patients achieving functional cure of around 40% in the gemtuzumab arm versus 20% in the control arm. The plateaus appear to be based on a small number of patients and less than four years follow-up in the trial.
- 6.25 The PBAC had previously noted that the difference in overall survival, at a median follow up of 47.6 months in the gemtuzumab arm and 41.0 months in the control arm, was not statistically significant in the mITT population (HR = 0.807; 95% CI: 0.596, 1.093) (para 7.7, gemtuzumab PSD, March 2021 PBAC meeting).
- 6.26 The PBAC had also previously noted that overall survival was potentially confounded as 22.1% of patients in the control arm subsequently received gemtuzumab, and due to the use of salvage therapies and HSCT. The PBAC had further noted that more

patients in the control arm (39.0%) underwent HSCT compared to in the gemtuzumab arm (23.7%) (para 7.8, gemtuzumab PSD, March 2021 PBAC meeting).

- 6.27 The Pre-Sub-Committee Response (PSCR) considered that the lack of significance for overall survival in the mITT population was likely because the study was not powered to detect statistically significant differences between arms for this outcome, in addition to confounding by subsequent therapies, and also because the mITT results included patients with unfavourable cytogenetics, who are outside the proposed PBS population.
- 6.28 Subgroup results for overall survival were broadly consistent with whole trial population results, with no statistically significant improvement in overall survival with gemtuzumab treatment.
- 6.29 The PSCR noted that the overall survival benefit was greater in the gemtuzumab arm than the control arm in the favourable/intermediate cytogenetic subgroup (HR = 0.747; 95% CI: 0.511, 1.091).
- 6.30 The PBAC had previously noted that overall survival results based on the favourable/intermediate/unknown cytogenetic risk subgroup were difficult to interpret (HR = 0.697; 95% CI: 0.486, 0.999) (para 7.7, gemtuzumab PSD, March 2021 PBAC meeting).
- 6.31 In the economic model, overall survival was modelled based on the subgroup with favourable/intermediate/unknown cytogenetic risk, stratified by response and refractory groups. The same data were used in the economic model of the previous submission, however, the resubmission provided new treatment effect estimates not previously considered by the PBAC (summarised in the table below).

Table 6: Post hoc analysis of overall survival by response in the favourable/intermediate/unknown cytogenetic risk subgroup (independent review, 30 April 2013 cut off)

	GO+DA	DA
Patients with response		
Number of patients	86	81
Number of deaths, n (%)	37 (43.0)	43 (53.1)
Kaplan-Meier estimate of median OS, months (95% CI)	NE (37.6, NE)	35.5 (24.5, NE)
Hazard ratio vs DA (95% CI)	0.659 (0.424, 1.025)	
Patients without response		
Number of patients	22	25
Number of deaths, n (%)	19 (86.4)	21 (84.0)
Kaplan-Meier estimate of median OS, months (95% CI)	14.8 (3.6, 22.7)	6.9 (5.2, 13.2)
Hazard ratio vs DA (95% CI)	0.797 (0.426, 1.492)	

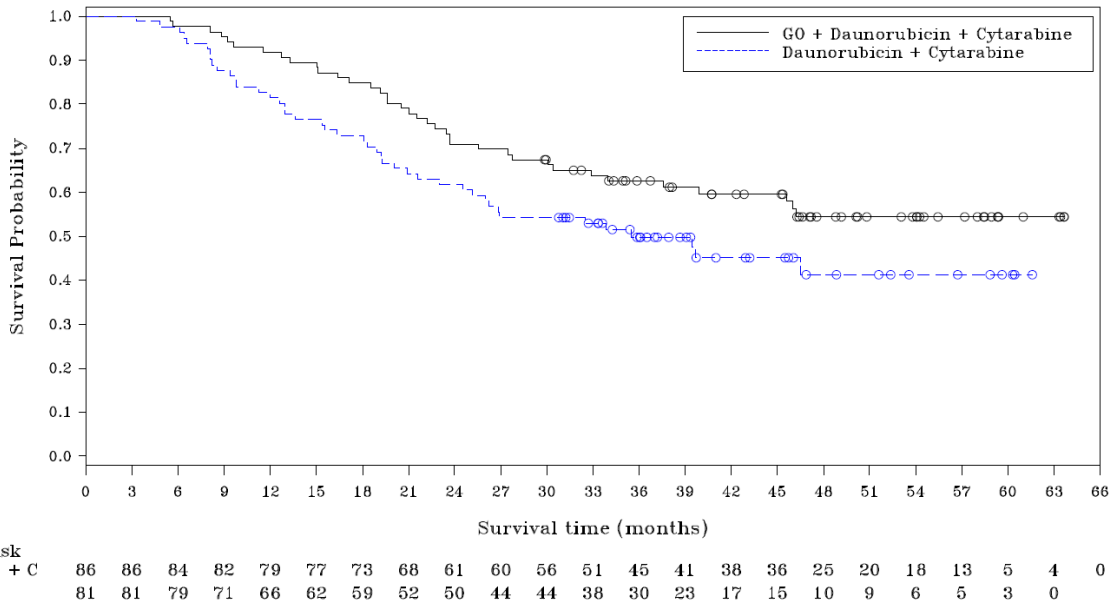
Source: Table 2.6.2, p152 of the resubmission; Table 14.2.7.7, p635 of the trial report
 CI, confidence interval; DA, daunorubicin; GO, gemtuzumab; NE, not estimable; OS, overall survival

- 6.32 There was no apparent treatment benefit in either subgroup, with results of borderline statistical significance in patients with response. The resubmission claimed no difference in overall survival between treatment arms in patients with favourable/intermediate/unknown cytogenetic risk, who did not achieve an overall

response. The Kaplan-Meier estimates suggest a lack of maturity and/or statistical power in the overall survival data.

- 6.33 The figure below presents the Kaplan-Meier curves for overall survival in the subgroup with favourable/intermediate/unknown cytogenetic risk, who achieved response. This figure was previously considered by the PBAC in March 2021; however, the previous figure was constructed using a different scale (X-axis based on days).

Figure 2: Kaplan-Meier curves for overall survival in the subgroup with favourable/intermediate/unknown cytogenetic risk, who achieved an overall response (independent review, April 2013 cut-off).



Source: Table 14.2.6.29.1 of the resubmission

- 6.34 Based on the new figure, overall survival was initially similar between arms until the curves started to diverge from around 6 months. The resubmission claimed the plateaus at the tail-end of the plots represent patients who achieved a functional cure. The plateaus appear to be based on relatively few patients with follow-up extending beyond 3 years.
- 6.35 The PBAC had previously considered that the results of *post hoc* subgroup analyses should be interpreted with caution due to differences in definitions of cytogenetic risk used in the key trial and more recent risk classifications, the lack of interaction testing, and the large number of analyses conducted without adjustment for multiplicity (para 7.4, gemtuzumab PSD, March 2021 PBAC meeting).
- 6.36 The resubmission conducted multiple *post hoc* tests for interaction to address uncertainties with the magnitude of benefit for event-free survival, relapse-free survival and overall survival in patients with favourable/intermediate/unknown cytogenetic risk.
- 6.37 Overall, the evaluation considered that the results of the analyses should be interpreted with caution due to the following reasons:

- The analyses were conducted *post hoc* and therefore subject to potential risk of bias and confounding. Statistical findings due to chance could not be ruled out given the large number of analyses that were not adjusted for multiplicity.
 - While interaction testing was performed for cytogenetic risk grouping based on the favourable/intermediate/unknown risk and unfavourable risk subgroups, there were no corresponding results for the pre-specified subgroups with favourable/ intermediate risk, unfavourable risk, and unknown risk.
 - There were several analyses that were difficult to interpret, in particular, tests for overall survival benefit in various subgroups by cytogenetic risk, response status, HSCT status and by cytogenetic risk and response status. The majority of the results based on hazard ratios did not achieve statistical significance, except in the subgroup who did not receive HSCT. However, interaction p-value results suggested statistically significant differences in overall survival benefit between subgroups by cytogenetic risk, and by cytogenetic risk within subgroups with and without response. The reliability of these results was uncertain and the evaluation advised that they should be interpreted within the context of no apparent difference in overall survival between treatment arms in the mITT population.
- 6.38 The PBAC had previously noted concerns with the applicability of the magnitude of benefit observed in the key trial to the PBS population due to potential differences in age, CD33 expression levels, cytogenetic and molecular risk distribution, treatment regimens used as consolidation chemotherapy and use of subsequent therapies including HSCT. Data from the key trial were relatively old and may not adequately reflect changes in the diagnostic work-up, assessment of response (e.g. increasing use of minimal residual disease (MRD) status to determine molecular relapse) and subsequent treatment decisions in current practice (para 6.52, gemtuzumab PSD, March 2021 PBAC meeting).
- 6.39 To address PBAC’s concerns with the applicability of the trial to the PBS population, the resubmission presented new data from the Australasian Leukaemia and Lymphoma Group National Blood Cancer Registry (ALLG NBCR) 2020 report prepared for sponsors associated with the registry. The registry is active in 38 treatment centres in Australia and is an opt-in registry. A broad range of measures are collected including baseline demographics, diagnostic laboratory assessments, treatments received (including HSCT) and related outcomes.
- 6.40 The report included a “pre-publication” analysis comparing the characteristics and outcomes of the ALFA-0701 trial population and a matched cohort enrolled in the registry between 2012 and 2018 (summarised in the table below).

Table 7: Characteristics and outcome of patients enrolled in the ALFA-0701 study or ALLG NBCR aged 50-70 years with de novo AML receiving induction chemotherapy

	ALFA-0701 ITT population ^a		NBCR subset N=418
	GO+DA N=139	DA N=139	
Baseline characteristics			
Age, years, median (IQR)	62.8 (59.3, 66.8)	61.7 (57.4, 65.6)	61.0 (56.0, 66.0)
- Age ≥60, n (%)	100 (72)	86 (62)	246 (58)
Male, n (%)	77 (55)	61 (44)	235 (56)
WBC (x 10 ⁹ /L), median (IQR)	6.9 (2.3, 30.4)	5.0 (1.9, 26.7)	5.2 (2.1, 21.4)
Platelet count (x 10 ⁹ /L), median (IQR)	66.0 (36.5, 118.5)	67.5 (36.3, 125.5)	65.0 (38.0, 127.5)
NCCN cytogenetic risk, n (%) ^b			
- Favourable	3/122 (2.5)	6/127 (4.7)	36/394 (9.1)
- Intermediate	91/122 (74.6)	91/127 (71.7)	273/394 (69.3)
- Adverse	28/122 (23.0)	30/127 (23.6)	85/394 (21.6)
FLT3-ITD, n (%)	22/137 (16.1)	27/138 (19.6)	76/366 (20.8)
NPM1 mutation positive, n (%)	45/136 (33.1)	48/138 (34.8)	113/307 (36.8)
Favourable ELN 2010, n (%)	24/119 (20.2)	24/125 (19.2)	61/360 (16.9)
Treatments received			
Induction courses >1, n (%)	25 (18.0)	35 (25.2)	42 (10.0)
Allogeneic HSCT, n (%)			
- All patients	32 (23.7)	53 (39.0)	109 (26.1)
- Upfront	17/135 (12.6)	22 (16.2)	87/417 (20.9)
Outcomes			
Treatment response, n (%)			
- CR	102 (73.4)	100 (71.9)	260/396 (65.7)
- CRp	11 (7.9)	4 (2.9)	57/396 (14.4)
- No CR/CRp	17 (12)	29 (21)	65/396 (16.4)
- Death	9 (6.4)	6 (4.3)	14/396 (3.5)
Event-free survival, median (months)	15.6	9.7	15.9
Event-free survival at 2 years (%)	40.8	17.1	42.7
Overall survival, median (months) ^c	27.5	21.8	28.1
Overall survival at 2 years (%)	53.2	41.9	53.5

Source: Table 14 of the ALLG NBCR 2020 Report

CR/CRp, complete remission with or without partial haematological recovery; ELN, European LeukemiaNet; HSCT, haematopoietic stem cell transplant; IQR, interquartile range; NCCN, National Comprehensive Cancer Network; WBC, white blood cell

^a Based on the ITT population analysed in the Castaigne 2012 publication (N=278). The mITT population in the resubmission was based on a slightly smaller population (N=271) due to attrition of data after transfer from the original trial sponsor to current sponsor.

^b Distribution excludes patients with unknown cytogenetic risk.

^c Median overall survival for ALFA-0701 cohort was based on the updated analysis, April 2013 cut off (Lambert 2019 publication).

- 6.41 The study authors noted that baseline median age, cytogenetic and molecular characteristics were similar between the two cohorts.
- 6.42 In terms of outcomes, results in the gemtuzumab arm of the ALFA-0701 trial were similar to the NBCR cohort. The control arm of the ALFA-0701 trial appeared to have similar rates of treatment response but poorer event-free survival and overall survival compared to the gemtuzumab arm and the NBCR cohort. The study authors claimed a number of factors may have contributed to improved outcomes in the NBCR cohort including a higher rate of HSCT in first remission and differing induction and consolidation backbones used in the two cohorts. In the ALLG NBCR cohort, idarubicin was the dominant anthracycline (93%) used in induction, compared to daunorubicin in the ALFA-0701 trial. During consolidation, high dose cytarabine (≥ 2 g/m²) was used

in 17% of the NBCR cohort, compared to intermediate dose cytarabine (≥ 1 g/m²) plus daunorubicin in the ALFA-0701 trial.

- 6.43 The resubmission and PSCR claimed that differences in treatment regimens (i.e. backbone chemotherapy and consolidation regimens) and subsequent therapies including HSCT are unlikely to have an effect on the applicability of the trial to the PBS population. The pre-PBAC response further noted that a recent advisory board meeting held by the sponsor had discussed the data, noting that there is follow up bias in registries due to incomplete data, and so the data should be interpreted with caution.

Comparative harms

- 6.44 The incidence of any serious adverse event was higher in the gemtuzumab arm compared with the control arm. The most common serious adverse events that were more frequent in the gemtuzumab arm were thrombocytopenia, febrile bone marrow aplasia, bacterial sepsis, acute kidney injury, VOD, and hepatocellular injury.
- 6.45 Treatment-related deaths were identified based on the serious adverse events retrospective analysis and fatal events (or infection events indicating study withdrawal) considered related to study treatments. The most common fatal adverse events were haemorrhage, sepsis, and VOD/liver toxicity. There were more treatment-related deaths in the gemtuzumab arm (n=7, 5.3%) compared with the control arm (n=5, 3.6%), most of them occurring during the induction phase.
- 6.46 More patients in the gemtuzumab arm had unplanned hospitalisations (including re-admission or prolonged stay due to adverse events, n=58, 44.3%) compared with the control arm (n=48, 35.0%), with the difference observed in both the induction and consolidation 1 treatment phases.
- 6.47 The majority of patients in both treatment arms required at least one platelet transfusion and one red blood cell transfusion. Mean red blood cell transfusions were similar between treatments (15.3 versus 14.3 in gemtuzumab and control arms, respectively), while platelet infusions were higher in the gemtuzumab arm (25.8) than the control arm (12.6). This difference was observed across all phases of treatment.
- 6.48 The resubmission presented the incidence of any serious adverse event in the subgroup with favourable/intermediate/unknown cytogenetic risk. The frequency of serious adverse events was higher in the gemtuzumab arm (69.5%) compared to the control arm (55.7%).
- 6.49 The resubmission presented an expanded assessment of harms for gemtuzumab. Important identified risks were severe (Grade ≥ 3) and/or serious hepatotoxicity including VOD/sinusoidal obstruction syndrome (SOS), myelosuppression (severe [Grade ≥ 3] and/or serious infection and haemorrhage), tumour lysis syndrome, and infusion-related reactions (including anaphylaxis) from start of infusion to within 24 hours of end of infusion. Important potential risks were renal toxicity, reproductive and developmental toxicity (post exposure during pregnancy, including

breastfeeding), neurotoxicity, second primary malignancy, immunogenicity, and off-label use in paediatric patients. Missing information included use in patients with severe hepatic impairment, use in patients with severe renal impairment and effect on cardiac conduction. During the reporting interval, no new safety information was identified.

Benefits/harms

- 6.50 On the basis of direct evidence presented in the resubmission (ALFA-0701 whole trial population), after approximately 4 years, patients treated with gemtuzumab with standard intensive chemotherapy compared to standard intensive chemotherapy alone have:
- No apparent difference in response rates;
 - Longer event-free survival of approximately 5.7 months;
 - No apparent difference in overall survival.
- 6.51 On the basis of direct evidence presented in the resubmission (ALFA-0701 whole trial population), over a median duration of follow-up of approximately 4 years, for every 100 patients treated with gemtuzumab with standard intensive chemotherapy compared to standard intensive chemotherapy alone:
- Approximately 12 additional patients would experience a serious adverse event that is life-threatening or requires hospitalisation;
 - There would be a similar incidence of severe infections;
 - Approximately 12 additional patients would experience a severe haemorrhage (blood loss) and 2 additional patients would die from haemorrhage;
 - Approximately 2 additional patients would experience severe veno-occlusive disease (blocked veins in the liver that may lead to liver damage), and 2 additional patients would die from veno-occlusive disease.
- 6.52 On the basis of direct evidence presented in the resubmission (ALFA-0701) in the subgroup of patients with favourable, intermediate or unknown cytogenetic risk (the requested PBS population), patients treated with gemtuzumab with standard intensive chemotherapy compared to standard intensive chemotherapy alone have:
- No apparent difference in response rates;
 - Longer event-free survival of 7.2 months.
- 6.53 The PBAC had previously considered that overall survival results in the favourable/intermediate/unknown cytogenetic risk subgroup were difficult to interpret (para 7.7, gemtuzumab PSD, March 2021 PBAC meeting).

Clinical claim

- 6.54 The resubmission described gemtuzumab as superior in terms of effectiveness compared to standard of care.

- 6.55 The PBAC had previously considered that the claim of superior comparative effectiveness was reasonable in terms of event-free survival in both the mITT and the favourable/intermediate/unknown cytogenetic risk subgroup. In terms of overall survival, the PBAC considered that the clinical claim of superior effectiveness was not supported (para 7.10, gemtuzumab PSD, March 2021 PBAC meeting).
- 6.56 The resubmission provided additional treatment effect estimates and conducted multiple interaction tests to provide additional certainty on the magnitude of treatment benefit in the subgroup with favourable/intermediate/unknown cytogenetic risk. The data were difficult to interpret and were limited given the large number of analyses conducted that were not adjusted for multiplicity.
- 6.57 The evaluation remained concerned with the applicability of the magnitude of benefit observed in the trial to the PBS population. New data based on a matched Australian cohort in the ALLG NBCR registry suggested patients receiving standard of care achieved similar event-free survival and overall survival at 2 years compared to the gemtuzumab arm in the ALFA-0701 trial.
- 6.58 The PBAC had previously considered that there were no data provided to support long-term survival benefit in the proposed population. The PBAC considered a study by Breems 2005 claiming that increased length of remission is positively correlated with overall survival, however, the same study also identified three other clinically relevant parameters linked to overall survival (cytogenetic profile, age at relapse and prior HSCT). The PBAC noted the claim of functional cure was based on observed plateaus at the tail-end of Kaplan-Meier data for event-free survival and overall survival. The PBAC considered that as the plateaus were informed by small numbers of patients with follow-up durations of less than four years, the likely proportion of patients achieving functional cure was unclear (para 7.9, gemtuzumab PSD, March 2021 PBAC meeting).
- 6.59 The PSCR claimed that the concept of functional cure is accepted in AML; patients who have been in complete remission for 3 consecutive years have little risk of relapsing (Kumar 2011, Watts 2014). Clinical experts in the UK and Australia consider patients to be 'functionally cured' when they have been in CR for 3–5 years (Expert Opinion, September 2020).
- 6.60 The pre-PBAC response acknowledged some residual uncertainty remained, but noted that no further clinical trial data is pending.
- 6.61 The resubmission described gemtuzumab as inferior in terms of safety compared to standard of care. The PBAC had previously considered the claim of inferior safety was reasonable (para 7.11, gemtuzumab PSD, March 2021 PBAC meeting), and remained of this view during its consideration of this resubmission.
- 6.62 The PBAC remained of the view that the claim of superior comparative effectiveness was reasonable in terms of event-free survival, however it considered that the overall survival claim was uncertain. At the same time, it also recognised that no further

clinical data was expected and that the cure claim itself was not implausible, although the magnitude of the benefit had been poorly supported.

Economic analysis

6.63 The resubmission presented a modelled economic evaluation of gemtuzumab in combination with standard intensive chemotherapy compared to standard intensive chemotherapy alone for the treatment of patients with previously untreated, de novo, CD33-positive AML, except acute promyelocytic leukaemia who do not have unfavourable cytogenetic risk (i.e. favourable, intermediate or unknown risk). The economic evaluation was based on data from the key ALFA-0701 trial as well as other modelled variables. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

Table 8: Key components of the economic evaluation

Component	Summary
Treatments	Gemtuzumab in combination with standard intensive chemotherapy (daunorubicin and cytarabine) versus standard intensive chemotherapy alone (daunorubicin and cytarabine), for induction and consolidation therapy
Time horizon	25 years in the model base case versus median follow-up of 4 years in the gemtuzumab arm and 3.4 years in the control arm in the trial
Outcomes	Life years, quality-adjusted life years
Methods used to generate results	Markov cohort expected value analysis
Health states	6 main health states including sub-states described in brackets: induction phase, response (remission, relapse), refractory, HSCT (procedure, CR without GVHD, CR with GVHD), functional cure, dead
Cycle length	1 month

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Component	Summary
Allocation to health states	<p>Pooled response rates from the ALFA-0701 trial used to determine treatment pathway (response or refractory) in the induction phase.</p> <p>Overall survival and relapse-free survival in patients achieving response, based on individual treatment arm Kaplan-Meier curves from the ALFA-0701 trial over a median duration of follow-up (3-4 years), followed by parametric extrapolation using mixture cure models (survival curves for cured and uncured fractions, weighted by statistical estimates of cure). The resubmission assumed convergence of the overall survival curves would occur at the end of the model. This was implemented using forced linear convergence of the extrapolated survival curve for gemtuzumab with the extrapolated survival curve of the control arm, starting at 5 years and ending at 25 years in the base-case model.</p> <p>Overall survival for refractory patients based on Kaplan-Meier curves using pooled data from the ALFA-0701 trial, median duration of follow-up unreported, followed by parametric extrapolation.</p> <p>Transition probabilities to HSCT based on time to HSCT data from the ALFA-0701 trial (pooled for response and refractory patients; individual arms for relapsed patients). Overall survival and relapse-free survival for response sub-states based on underlying survival curves; overall survival for refractory patients based on underlying overall survival curve.</p> <p>The resubmission assumed that patients are functionally cured after remaining in response health states for 5 years in the model. Transitions to the functionally cured health state occurred from response sub-states at fixed time points in the model (after 5 years in patients with remission, with or without HSCT; after 5 years in post-HSCT states in relapsed or refractory patients). Survival and relapse in the functionally cured health states were still determined by underlying overall survival and relapse-free survival curves (which had underlying cure fraction estimates).</p> <p>In the model, 3% of incremental costs and 65% of incremental QALYs were generated in the extrapolated period.</p>
Health state and event costs	<p>First-line drug costs based on proportions receiving induction and consolidation treatment cycles in the ALFA-0701 trial.</p> <p>Subsequent therapy (salvage, non-curative, and best supportive care) costs based on local guidelines and UK expert opinion. The duration of treatment of salvage therapy was assumed to be 1.5 months. The durations of non-curative therapies and best supportive care were based on a restricted means survival time (RMST) analysis for newly relapsed (13.8 months) and refractory patients (10.98 months) in the ALFA-0701 trial. The duration of terminal care of 2 months was assumed with corresponding costs applied in the last 2 months of survival.</p> <p>Administration costs based on AR-DRG items or MBS items applied using the following proportions: 100% inpatient cost for induction cycles; 80% inpatient/20% outpatient costs for consolidation cycles; 100% inpatient costs for salvage therapies; mixed settings (depending on treatment administered, but largely outpatient) for non-curative therapies.</p> <p>Adverse event costs assumed captured in treatment administration costs. Additional costs for unplanned hospitalisations were based on incidence of adverse events in the ALFA-0701 trial and hospitalisation costs plus the cost of defibrotide for the treatment of VOD. Blood transfusion costs were included as a proxy for additional adverse events costs.</p> <p>Other disease management costs in the model included diagnostic and disease monitoring tests (MBS items), inpatient attendance costs in patients receiving non-curative therapy or best supportive care (4 hospitalisations), outpatient attendance, and antifungal and antibiotic prophylaxis.</p> <p>HSCT costs and acute GVHD event costs were based on AR-DRG items. Post-HSCT costs were applied over 2 years based on assumed frequencies of hospitalisation and outpatient visits.</p>

Component	Summary
Health related quality of life	<p>Based on multiple published sources:</p> <p>Induction phase: 0.16 (midostaurin PSD, July 2018)</p> <p>CR/CRp (consolidation 1 and 2): 0.57 (midostaurin PSD, July 2018)</p> <p>CR/CRp (off treatment): 0.74 (NICE 2016 appraisal of azacitidine)</p> <p>Relapse (salvage therapy): 0.16 (midostaurin PSD, July 2018)</p> <p>Relapse (non-curative therapy): 5 years or less: 0.51 (midostaurin PSD, July 2018); after 5 years: 0.798 decreasing over time (age- and gender-adjusted EQ-5D UK general population utility)</p> <p>Refractory (salvage therapy): 0.16 (midostaurin PSD, July 2018)</p> <p>Refractory (non-curative therapy): 0.51 (midostaurin PSD, July 2018)</p> <p>HSCT procedure: 0.613 (Forsythe 2018)</p> <p>Post-HSCT CR/CRp without GVHD: 0.74 (NICE 2016 appraisal of azacitidine)</p> <p>Post-HSCT CR/CRp with GVHD: 0.67 (Forsythe 2018)</p> <p>Functionally cured: 0.821 decreasing over time (age- and gender-adjusted EQ-5D UK general population utility)</p> <p>Adverse event disutility (all events except VOD): 0.0207 (NICE 2016 appraisal of azacitidine)</p> <p>VOD disutility: 0.208 (defibrotide SMC submission, 2014)</p>

Source: Table 3.1.1, p188 of the resubmission

AR-DRG, Australian refined diagnosis related groups; CR/CRp, complete remission with or without incomplete platelet recovery; GVHD, graft versus host disease; HSCT, haematopoietic stem cell transplant; VOD, veno-occlusive disease

6.64 Compared to the March 2021 submission, the main changes to the economic model were:

- Model time horizon has been revised to 25 years (previously 40 years).
- Overall survival curves were forced to converge at the end of the modelled duration.
- Revised gemtuzumab drug costs based on a new proposed price.
- Revised HSCT transition probabilities based on a new *ad hoc* analysis.
- Removal of additional gemtuzumab induction costs, adverse event costs and consequences associated with patients with unknown risk who initiate gemtuzumab and are later confirmed as having unfavourable cytogenetic risk.
- Increased non-curative therapy costs.

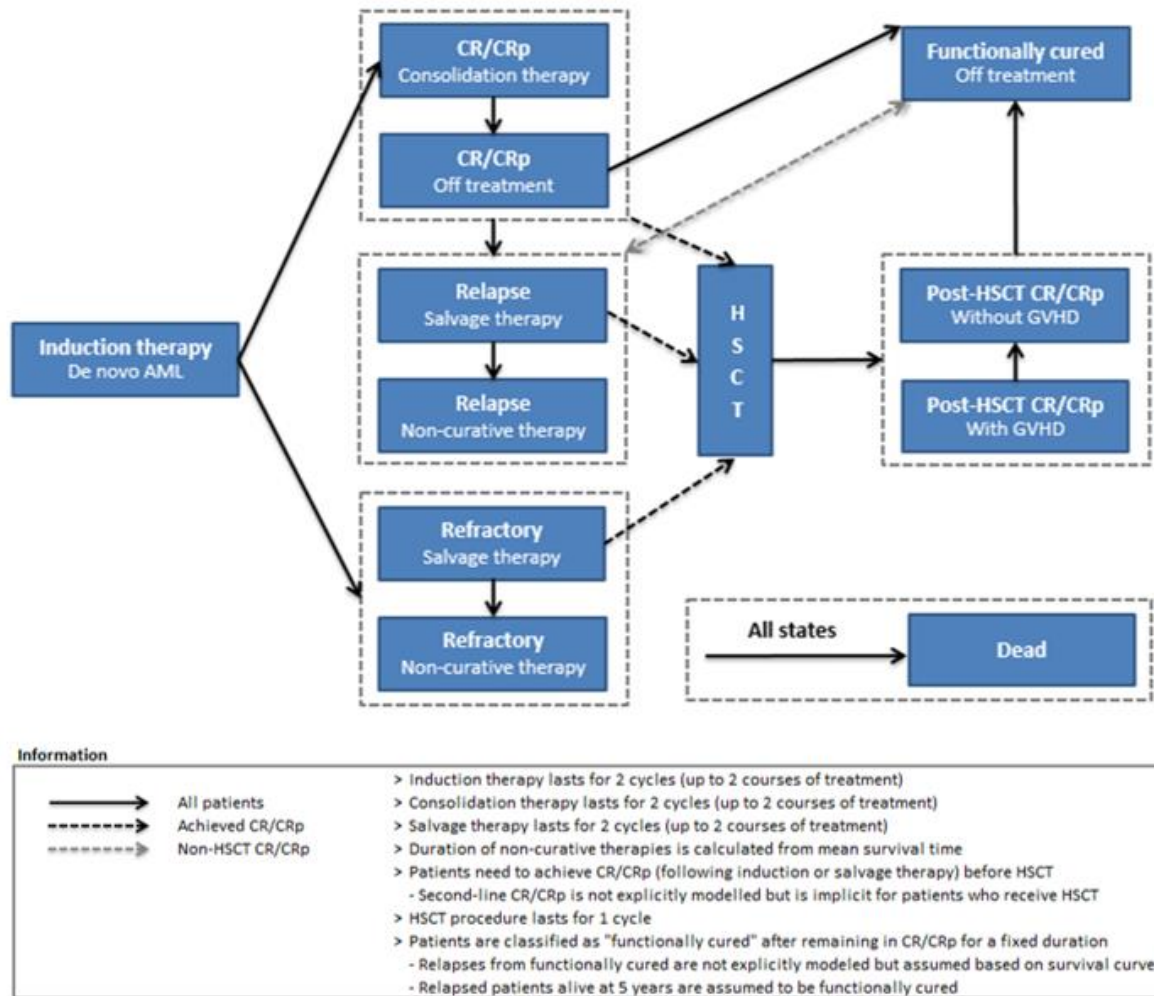
6.65 There were also relatively minor changes to selected cost inputs based on issues raised in the March 2021 commentary and use of a revised public hospital/private hospital split to determine drug costs and other disease management costs. All cost inputs based on AR-DRG codes, PBS item codes and MBS item codes were also updated to the most recently published estimates.

6.66 Administration costs in the resubmission were revised using a public/private hospital split of 88%/12%. During the evaluation, the sponsor clarified that these estimates were calculated in error and that the public/private hospital split should have been 83%/17%. This was not corrected during the evaluation given the minimal impact on the results of the economic evaluation (ICER per QALY gained of \$45,000 to < \$55,000 versus \$45,000 to < \$55,000 in the base case).

6.67 It was noted during the evaluation of the economic analysis that many of the changes to the model in the resubmission compared to the previous submission were poorly documented.

- 6.68 The structure of the economic model was unchanged from the previous submission; it was a semi-Markov cohort state-transition model. The model used separate survival analyses based on the response status of patients (response or refractory). Transitions to relapse and death for patients in the response pathway were determined by relapse-free survival and overall survival curves that were separate to overall survival curves used to determine transitions to death in refractory patients. Subsequent transitions to downstream health states (and sub-states) were dependent on probabilities derived from these underlying survival curves. This approach appeared more similar to a partitioned survival analysis rather than a state-transition modelling approach, which uses explicit structural links between health states, such that differences in survival outcomes are determined by the combined effect of each treatment on individual health states and conditional transition probabilities.
- 6.69 The diagram below presents the model structure (unchanged from previous submission).

Figure 3: Model structure diagram



Source: Figure 3.2.1, p195 of the resubmission

AML, acute myeloid leukaemia; CR, complete remission; CRp, complete remission with incomplete platelet recovery; GVHS, graft versus host disease; HSCT, haematopoietic stem cell transplant

6.70 The PBAC had previously considered that the model structure was overly complex making it difficult to determine the flow of patients through the model (para 7.13, gemtuzumab PSD, March 2021 PBAC meeting). The ESC considered that the complex model structure resulted in a need to rely on transition probabilities informed by subgroups consisting of small patient numbers, unsubstantiated assumptions and unverifiable expert opinion, all of which had made the outcomes highly uncertain (para 6.6, gemtuzumab PSD, March 2021 PBAC meeting).

6.71 Additional structural assumptions were included in the model in an attempt to limit the complexity of the state transition model by including relapse and HSCT as sub-states within the response, relapse and refractory health states respectively; and applying structural assumptions to the HSCT health state to avoid the need for separate states to capture patient 'history' and to ensure the internal validity of the model predictions. This approach was unchanged from the previous submission,

which limited the ability of the model to fully capture the impact of alternative assumptions regarding HSCT rates (see sensitivity analysis section below).

- 6.72 Despite the use of a complex structure and simplifying assumptions, the resubmission claimed the internal validity of the model was maintained and produced outcomes that were similar to results from the key trial. While internal validity is important, the absence of an explicit structural link between relapse and HSCT and mortality rates significantly limited the flexibility of the model to fully reflect longer-term uncertainties. The lack of an explicit structural link between key states also resulted in the same independence assumption between clinical events that underpins the partitioned survival analysis approach. The ESC previously considered that any gains in clinical accuracy were offset by input uncertainty, particularly relating to the fact that although clinical data did not demonstrate a survival benefit for gemtuzumab patients, these benefits were applied in the model (para 6.63. gemtuzumab PSD, March 2021 PBAC meeting).
- 6.73 Overall, modelled outcomes remained largely dependent on statistical cure fractions used to extrapolate survival beyond the trial duration and assumptions underpinning the functional cure health state. The validity of statistical cure fractions and the functional cure health state assumptions appeared more critical than the route by which patients achieved functional cure.
- 6.74 The table below presents the estimated cure fractions informing long-term survival extrapolations in the model.

Table 9: Estimated cure fractions used in the economic model

Survival curve	Statistical cure fractions from MCM log-normal function		HSCT cure rate
	GO+DA	DA	
Overall survival (response)	52.1%	40.0%	42.2%
Relapse-free survival	34.3%	20.6%	-

Source: Adapted from Table 3.7.3, p 254 of the resubmission

DA, daunorubicin; GO, gemtuzumab; HSCT, haematopoietic stem cell transplant; MCM, mixture cure model

- 6.75 The PBAC had previously considered that it was unclear whether the trial-based data were sufficiently robust representations of functional cure that would translate into ongoing survival benefits, particularly as there were substantial differences in the estimated cure fractions for relapse-free survival and overall survival. The PBAC had previously noted that higher cure fractions were estimated for overall survival than for relapse-free survival, which was not clinically plausible unless patients who relapsed became functionally cured due to subsequent therapies and/or HSCT, which is relatively rare in AML. In addition, the PBAC had considered that the cure fractions based on overall survival (52.1% in the gemtuzumab arm and 40.0% in the comparator arm) were high compared to the estimated cure fraction due to HSCT (42.2%) (para 7.13, gemtuzumab PSD, March 2021 PBAC meeting).
- 6.76 The resubmission argued that it is clinically plausible that relapsed patients receiving subsequent therapies (particularly HSCT), have the potential to achieve functional cure, therefore justifying the higher cure fraction for overall survival compared to

relapse-free survival. Moreover, the resubmission claimed that the application of forced convergence of overall survival reduced the impact of the cure fractions used in survival extrapolation.

- 6.77 The resubmission stated that the difference in cure fractions between arms was similar for both outcomes. The resubmission claimed that this difference was more important in the determination of the cost-effectiveness results rather than absolute cure fractions as the incremental difference in survival benefit was the driver of QALY differences between arms. While modelled survival benefit was a key driver of cost-effectiveness results, differences in costs and QALYs were also driven by assumptions underpinning transitions, costs, and consequences in the functional cure health state. Based on expert opinion, the resubmission assumed that all patients are functionally cured after remaining in remission for 5 years. These patients transitioned to the functional cure health state with no ongoing costs and were attributed general population health utility values.
- 6.78 The PSCR and pre-PBAC response maintained the appropriateness of the mixture cure model methodology, and argued that applying standard parametric curves showed poor fit to the data based on visual inspection; all curves would cut through the plateau observed in the data. It reiterated that the magnitude of the cure fractions applied in the model were clinically plausible.
- 6.79 The table below was constructed during the evaluation to illustrate modelled outcomes based on the use of mixture cure models to extrapolate overall survival and relapse-free survival (in patients with response), functional cure health state assumptions and to determine the impact of forced convergence of overall survival.

Table 10: Model trace of proportion of patients remaining in health states over time

Years	1	2	3	4	5	10	15	20	25
Base case with OS convergence (sensitivity analysis without OS convergence)									
GO+DA									
OS	81%	63%	52%	47%	44%	37% (39%)	30% (34%)	22% (28%)	15% (19%)
- Remission	58%	42%	35%	31%	29%	25%	22%	18%	12%
- Relapsed	13%	15%	14%	13%	13%	10% (12%)	6% (11%)	3% (9%)	2% (6%)
- Refractory	10%	5%	4%	3%	2%	2%	2%	2%	1%
Functional cure	0%	0%	0%	0%	29%	25%	22%	18%	12%
- No HSCT	0%	0%	0%	0%	23%	19%	17%	14%	9%
- HSCT	0%	0%	0%	0%	6%	5%	5%	4%	3%
DA									
OS	74%	53%	43%	38%	35%	31%	27%	22%	15%
- Remission	47%	25%	18%	17%	16%	15%	13%	10%	7%
- Relapsed	18%	23%	20%	18%	17%	14%	12%	10%	7%
- Refractory	10%	5%	4%	3%	2%	2%	2%	2%	1%
Functional cure	0%	0%	0%	0%	16%	15%	13%	10%	7%
- No HSCT	0%	0%	0%	0%	10%	9%	8%	7%	4%
- HSCT	0%	0%	0%	0%	6%	5%	5%	4%	3%

Source: constructed during the evaluation using the '210701_Mylotarg CEM_v7.2_Australia_PBAC_RESUBMISSION' Excel workbook

DA, daunorubicin and cytarabine; GO, gemtuzumab; HSCT, haematopoietic stem cell transplant; OS, overall survival

Note: estimates highlighted in orange changed with the removal of OS convergence. All other estimates remained the same as the base case.

- 6.80 There was an overall survival benefit in the gemtuzumab arm compared to the standard of care arm. This was apparent from the start of the model, with convergence towards the end of the model. The majority of survival benefit was due to more patients in the gemtuzumab arm maintaining remission compared to standard of care. There was no difference in overall survival between arms in refractory patients.
- 6.81 All patients in remission transitioned to the functional cure health state at 5 years in the model. A greater proportion of patients achieved functional cure due to induction therapy rather than HSCT in both the gemtuzumab (23% no HSCT, 6% with HSCT) and standard of care (10% no HSCT, 6% with HSCT) arms. Effectively, the model assumed gemtuzumab was associated with a 13% increase in functional cure compared to standard of care. This assumption was in favour of gemtuzumab given these patients accrue no ongoing costs and were assumed to have the same quality of life as the general population.
- 6.82 The use of a mixture cure model to extrapolate relapse-free survival and overall survival resulted in long-term survival being driven by cured fractions that were attributed general population mortality (adjusted for excess mortality due to AML). The effect of this approach was particularly apparent in the standard of care arm, given very similar rates of survival in both remission and relapsed patients from 4 years onwards.

- 6.83 The resubmission claimed that the application of forced convergence of overall survival reduced the impact of the cure fractions used in survival extrapolation. Based on the tabled estimates, the approach resulted in an increase in deaths of relapsed patients in the gemtuzumab arm without impacting the proportion of patients maintaining remission who then enter the functional cure health state. The convergence scenario resulted in a more conservative overall survival benefit attributed to gemtuzumab, however, the difference in functional cure of 13% versus standard of care was maintained.
- 6.84 The application of forced convergence of the overall survival curves was difficult to interpret from a clinical perspective as no corresponding adjustments were made to relapse-free survival. This approach also assumed no relationship between disease status and overall survival. Moreover, the increased rate of death in the gemtuzumab arm was applied to relapsed patients, of whom the vast majority had achieved cure based on statistical cure fractions in the mixture cure model.
- 6.85 The resubmission claimed that the functional cure assumption was not applied to refractory patients. This appeared inconsistent with survival estimates in the model, suggesting a small proportion of patients continue to survive up to 25 years following induction therapy.
- 6.86 Overall, the model structure and use of individual patient data may have reliably reproduced results observed in the trial, with a median follow up of less than 4 years. However, predictions beyond this timeframe were highly uncertain and reliant on the robustness of tail-end Kaplan-Meier data which informed statistical cure fractions in the log-normal mixture cure model and assumptions underpinning the functional cure health state.
- 6.87 Key drivers of the economic model are summarised in the table below.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Treatment benefit	The PBAC had previously noted that the use of treatment benefit based on the subgroup with favourable/intermediate/unknown cytogenetic risk over the ITT results was inadequately justified (para 7.13, gemtuzumab PSD, March 2021 PBAC meeting). The magnitude of benefit in the nominated subgroup, particularly in terms of OS, remained uncertain, as did this applicability of the trial data.	High, favours gemtuzumab
Extrapolation	The resubmission maintained the use of log-normal mixture cure models to extrapolate OS and RFS curves (in patients with response). Long-term survival based on the mixture cure model was driven by the cured fraction in both OS and RFS curves who were attributed general population mortality (adjusted for excess mortality due to AML). During the evaluation, modelled outputs were assessed to determine the impact of extrapolation using mixture cure model with forced OS convergence and functional cure rates (see Table 10 above).	High, favours gemtuzumab

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Description	Method/Value	Impact
HSCT rates	<p>The PBAC had previously stated that the model assumed a higher proportion of patients in the standard of care arm would receive a HSCT after relapse. The PBAC noted that this was a key offset in the economic model and considered that the rate should be equal in both arms (para 7.13, gemtuzumab PSD, March 2021 PBAC meeting). HSCT rates used in the resubmission were revised and appeared to be a re-analysis of data used in the March 2021 submission.</p> <p>The resubmission argued for the use of individual arm estimates in relapsed patients. The resubmission clarified that HSCT transition probabilities in the model were not conditional probabilities (i.e. not linked to disease status) and were applied to the whole model cohort. The resubmission claimed the use of a pooled rate would imply that patients who relapse after receiving gemtuzumab have a higher probability of receiving HSCT than those who relapse after standard of care, which is clinically implausible and not supported by the clinical evidence. During the evaluation, HSCT model outputs were compared with trial-based HSCT rates. The use of pooled rates resulted in the same proportion of relapsed patients undergoing HSCT in each arm, which was inconsistent with the resubmission's claim. The comparison of HSCT rates in the model versus the trial also indicated that in the base case, the rate of HSCT in the gemtuzumab arm (28.4%) was overestimated compared to the trial (25.9%) and the rate of HSCT in the control arm (34%) was underestimated compared to the trial (39.6%). This suggested potential issues with the internal validity of HSCT transitions in the model.</p> <p>The model appeared sensitive to the use of a pooled HSCT rate in relapsed patients based on the assumption of no difference in HSCT rates between arms. However, this analysis should be interpreted with caution as HSCT events in the model primarily impacted costs only. OS and RFS in the model were dependent on underlying survival curves, without explicit structural links to HSCT events. The model structure also preserved the overall proportion of patients achieving functional cure. Overall, the model structure limited the ability to fully capture the impact of alternative assumptions regarding the use of HSCT.</p>	High, direction unclear
Subsequent line therapies costs	<p>The attribution of costs in the model was difficult to determine due to the complexity of the model structure and use of multiple health states and sub-states. Costs associated with subsequent line therapies were applied as a once off fixed cost, not linked to time spent in the health states. The cost-effectiveness of gemtuzumab was sensitive to the use of alternative non-curative therapy and best supportive care costs based on individual arm estimates instead of pooled estimates in the base case of the economic model. The available estimates suggested patients in the gemtuzumab arm received, on average, longer durations of treatment compared to best supportive care. The robustness of the restricted means survival time analysis used to inform these inputs was uncertain due to limited documentation in the resubmission. The economic analysis was sensitive to alternative non-curative therapy and best supportive care costs.</p>	High, favours gemtuzumab

Source: constructed during the evaluation

EFS, event-free survival; HSCT, haematopoietic stem cell transplant; OS, overall survival; RFS, relapse-free survival

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

Table 12: Results of the economic evaluation

Component	GO+DA	DA	Increment
Costs (\$)		\$261,749	
LYs	6.12	5.30	0.82
QALYs	4.35	3.71	0.65
Incremental cost per LY gained			¹
Incremental cost per QALY gained			²
March 2021 submission			
Costs (\$)		\$265,942	
LYs	6.68	5.49	1.19
QALYs	4.77	3.86	0.91
Incremental cost per LY gained			³
Incremental cost per QALY gained			¹

Source: Table 3.8.6, p265 of the resubmission

DA, daunorubicin; GO, gemtuzumab; LY, life year; QALY, quality-adjusted life year

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$45,000 to < \$55,000

³ \$25,000 to < \$35,000

- 6.89 Based on the economic model, treatment with gemtuzumab in addition to standard intensive chemotherapy was associated with a cost of \$45,000 to < \$55,000 per QALY gained compared to standard intensive chemotherapy alone. The difference in the incremental cost per QALY gained compared to the previous submission (\$35,000 to < \$45,000) was primarily due to the revised time horizon, forced overall survival convergence and the use of the revised price of gemtuzumab.
- 6.90 The difference in cost between treatment arms was primarily driven by gemtuzumab drug costs which were partially offset by costs of salvage therapy, non-curative therapy, best supportive care and HSCT procedures in relapsed patients.
- 6.91 The difference in health outcomes was primarily driven by time spent in the response health states, particularly the 'no HSCT functional cure' sub-state. Compared to standard of care, more patients in the gemtuzumab arm achieved functional cure following sustained remission (i.e. achieved response and did not relapse) after induction therapy. The difference was partially offset by time spent in the relapse health states.
- 6.92 The results of key sensitivity analyses are summarised below.

Table 13: Results of sensitivity analyses

Analysis	Incremental cost (\$)	Incremental QALYs	ICER per QALY gained
Base case		0.65	⁴
Administration costs (base case 88% public hospital and 12% private hospital administration for induction) ^a			
83% public hospital and 17% private hospital		0.65	⁴
Time horizon (base case 25 years) ^a			
5 years		0.29	⁶
10 years		0.52	³
15 years		0.62	⁴
Treatment effect (base case subgroup with favourable/intermediate/unknown cytogenetic risk) ^a			
mITT population (independent review dataset)		0.42	⁵
mITT population (investigator assessed dataset)		0.32	⁶

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Analysis	Incremental cost (\$)	Incremental QALYs	ICER per QALY gained
Modelled overall survival benefit (base case extrapolated survival using individually fitted MCM log-normal functions with linear convergence starting from 5 years and converging at 25 years)			
Individually fitted MCM log-normal functions without convergence	██████	0.88	██████ ¹
GO+DA survival based on HR 0.659 applied to DA arm, fixed over 25 years	██████	1.19	██████ ²
GO+DA survival based on HR 0.659 applied to DA arm, fixed in first 5 years. Beyond 5 years to 25 years, variable HR assuming linear increase to HR of 1.000 at 25 years was applied.	██████	0.79	██████ ¹
Overall survival convergence (base case linear convergence starting from 5 years and converging at 25 years, applied to MCM log-normal survival curves) ^a			
Start at 4 years, converge by 10 years	██████	0.43	██████ ³
Start at 4 years, converge by 15 years	██████	0.58	██████ ⁴
Start at 4 years, converge by 20 years	██████	0.68	██████ ⁴
Start at 4 years, converge by 25 years	██████	0.70	██████ ⁴
Start at 5 years, converge by 10 years	██████	0.43	██████ ³
Start at 5 years, converge by 15 years	██████	0.56	██████ ³
Start at 5 years, converge by 20 years	██████	0.63	██████ ⁴
HSCT rates (base case: pooled rates in remission and refractory patients, individual arm rates in relapsed patients) ^a			
Pooled rates in all patients	██████	0.67	██████ ³
Overall survival convergence and HSCT rates (base case: linear convergence starting from 5 years and converging at 25 years, applied to MCM log-normal survival curves; pooled HSCT rates in remission and refractory patients, individual arm rates in relapsed patients) ^a			
Pooled HSCT rates and OS convergence starting at 4 years and converging by 10 years	██████	0.46	██████ ⁵
Pooled HSCT rates and OS convergence starting at 4 years and converging by 15 years	██████	0.61	██████ ³
HSCT cure rate (base case: 42.2%) ^a			
Halved (21.1%)	██████	0.64	██████ ⁴
Doubled (84.4%)	██████	0.63	██████ ⁴
Non-curative therapy and BSC costs in relapsed or refractory patients (base case using pooled trial data: relapsed patients receive 11.8 months non-curative therapy and 10.3 months BSC; refractory patients receive 9.0 months non-curative therapy and 7.5 months BSC)			
Based on individual arm data GO+DA: relapsed patients (12.5 months non-curative therapy and 11.0 months BSC); refractory patients (11.7 months non-curative therapy and 10.2 months BSC) DA: relapsed patients (11.1 months non-curative therapy and 9.6 months BSC); refractory patients (5.9 months non-curative therapy and 4.4 months BSC)	██████	0.65	██████ ³
Discount rate (base case 5%)			
0%	██████	0.88	██████ ¹
3.5%	██████	0.70	██████ ¹

Source: Tables 3.92 and 3.93, p 269 of the resubmission and additional analyses conducted during the evaluation using the '210701_Mylotarg CEM_v7.2_Australia_PBAC_RESUBMISSION' Excel workbook

BSC, best supportive care, DA, daunorubicin; Go, gemtuzumab; HSCT, haematopoietic stem cell transplant; RFS, relapse-free survival; ICER, incremental cost-effectiveness ratio; MCM, mixture cure model; OS, overall survival; QALY, quality adjusted life year; RMST, restricted means survival time

^a Analyses undertaken during evaluation and for the ESC advice.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$25,000 to < \$35,000

³ \$55,000 to < \$75,000

⁴ \$45,000 to < \$55,000

⁵ \$75,000 to < \$95,000

⁶ \$95,000 to < \$115,000

- 6.93 The results were most sensitive to treatment effect (based on the whole trial population) and time horizon.
- 6.94 The results were also sensitive to alternative start and end times for overall survival convergence. These analyses should be interpreted with caution given concerns with adjustments to overall survival without corresponding adjustments to relapse-free survival, and a clinically implausible interaction with statistical cure estimates underpinning the mixture cure models used for extrapolation.
- 6.95 The ESC considered that additional sensitivity analyses using pooled HSCT rates and adjusting the start and end times for overall survival convergence may be informative for the PBAC (see table above, analyses resulting in ICERs of \$75,000 to < \$95,000/QALY gained and \$55,000 to < \$75,000/QALY gained). The pre-PBAC response claimed that at the reduced price offered, the ICER for the scenario “Pooled HSCT rates and OS convergence starting at 4 years and converging by 15 years”, reduced from \$55,000 to < \$75,000/QALY gained to \$45,000 to < \$55,000/QALY gained. The PBAC also noted that at the reduced price, the ICER for the scenario “Pooled HSCT rates and OS convergence starting at 4 years and converging by 10 years”, reduced from \$75,000 to < \$95,000/QALY gained to approximately \$55,000 to < \$75,000/QALY gained.

Drug cost/patient/course

- 6.96 The drug cost per patient per course shown and discussed below was based on the resubmission’s proposed price, and not the revised price offered in the pre-PBAC response.

Table 14: Drug cost per patient per course for gemtuzumab component

	ALFA-0701	Economic model	Financial estimates
Gemtuzumab costs			
Proportion receiving:			
-Induction Day 1	98.5%	100%	93.9%
-Induction Day 4	96.9%	100%	93.9%
-Induction Day 7	95.4%	100%	93.9%
Induction vials/patient ^a	2.91	3.00	2.82
Proportion receiving:			
-Consolidation 1	69.5%	74.0%	69.5%
-Consolidation 2	48.9%	62.6%	48.9%
Consolidation vials/patient ^a	1.18	1.37	1.20
Cost per 5 mg vial ^b (\$)	-		
Cost/patient/course (\$)	-		

Source: Table 32, pp117 of the ALFA-0701 clinical study report; 'Cost calcs' worksheet of the '201103_Mylotarg CEM_v7.2_Australia' Excel workbook; Table 4.1.1, pp234-236 of the submission.

Note: Gemtuzumab is not administered in patients requiring a second induction (backbone chemotherapy only)

^a One 5 mg vial required per treatment.

^b Weighted price based on assumed 6.25%/93.75% public/private split (based on idarubicin PBS dispensing data for January 2020 to December 2020).

6.97 In the economic model, the estimated drug cost for induction and consolidation chemotherapy with gemtuzumab was \$ [REDACTED] (gemtuzumab: \$ [REDACTED], daunorubicin: \$11,029, cytarabine: \$5,241; using trial-based drug exposure of 100% induction 1, 14.5% induction 2, 74% consolidation 1 and 62.6% consolidation 2).

6.98 The estimated drug cost for induction and consolidation chemotherapy for standard of care was \$16,275 (daunorubicin: \$11,056, cytarabine: \$5,219; using trial-based drug exposure of 100% induction 1, 14.5% induction 2, 70.8% consolidation 1 and 65% consolidation 2).

6.99 The drug costs in the resubmission were revised compared to the March 2021 submission primarily due to the use of a lower proposed price for gemtuzumab and removal of the additional cost of gemtuzumab for induction therapy in patients subsequently confirming with unfavourable risk.

Estimated PBS usage & financial implications

6.100 Compared to the March 2021 submission, the main changes to this section were:

- Revised eligible population estimates accounting for the proportion of patients with acute promyelocytic leukaemia who would not be eligible for treatment with gemtuzumab.
- Revised size of the treated population including the assumption that 100% of patients would have cytogenetic test results prior to treatment initiation.
- Removed grandfathering provision, previously estimated as 3 patients in Year 1.
- Updated number of vials of gemtuzumab used in induction based on the trial.
- Updated cost of gemtuzumab based on the new proposed price.
- Updated cost of gemtuzumab to the PBS/RPBS based on proportions of use in public (non-admitted) and private hospitals (admitted and non-admitted), separately estimated for induction and consolidation settings.

- Updated split of private and public hospital PBS prescriptions to determine the cost of gemtuzumab scripts and average co-payments.
- The inclusion of costs to the MBS due to additional blood transfusions for the management of gemtuzumab adverse effects.
- The inclusion of costs to the National Blood Authority due to additional blood products used for the management of gemtuzumab adverse effects.

- 6.101 The financial estimates in the resubmission were revised using a public/private hospital split of 88%/12%. During the evaluation, the sponsor clarified that these estimates were calculated in error and that the public/private hospital split should be 83%/17%. The financial estimates were corrected during the evaluation.
- 6.102 The PBAC had previously considered that the majority of use would be in the public hospital setting, but that the estimated financial impact was highly dependent on the public hospital versus private hospital ratio of use, estimated to be 83% public hospital versus 17% private hospital in the March 2021 PSCR (para 7.14, gemtuzumab PSD, March 2021 PBAC meeting).
- 6.103 This submission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the utilisation and financial impact of gemtuzumab. Key inputs used to determine the size of the eligible population are summarised in the table below.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
AML incidence	4.2 per 100,000. AIHW Cancer Data in Australia (2021). Fixed incidence over 6 years, applied to Australian population ≥15 years.	The resubmission inappropriately applied a rate based on the whole Australian population to the Australian population ≥15 years. This may result in an underestimate of the size of the incident population; however, the difference is likely to be small. Moreover, the PBAC considered it not unreasonable for the PBS listing to be silent on age.
Proportion of AML patients without APL	92%. Based on an average of 8% with APL using data from the ALLG NBCR AML registry (6%) and the proportion listed on the Leukaemia Foundation website (10%).	This estimate was uncertain. The authors of the ALLG NBCR Report noted the dataset was limited by low population coverage (approximately 30% of all AML cases), which may limit its applicability to the whole AML population. No reference could be identified as the basis of the proportion noted on the Leukaemia Foundation website.
Proportion of patients with de novo AML	70%. Krauss et al. (2018) reported that 10% of AML related to prior therapies and 20% due to antecedent haematological disorder. Juliusson et al. (2009) reported that 4% of patients had therapy-related AML and 24% secondary to previous haematologic disease.	This estimate appeared reasonable.
Proportion of AML patients 'fit' or eligible for intensive chemotherapy	62%. Based on an analysis of the Swedish Acute Leukemia Registry (2,767 patients diagnosed with non-APL AML leukaemia January 1997 to September 2005; median age 72 years, range 16-97 years), by Juliusson et al. (2009).	Included patients across all WHO categories (I-IV), and the PBAC considered that the listing should be restricted to patients with WHO status 0-2.
Proportion of patients that have CD33-positive AML	90%. Assumption based on O'Hear et al., 2015 (90%); Linenberger, 2005 (85-95%); Ehninger et al., 2014 (87.8%).	This appeared to be reasonable.
Proportion of patients with cytogenetics results available at induction	100%. Assumption. The resubmission claimed that based on expert opinion, all patients would receive cytogenetic results prior to induction treatment with gemtuzumab (Expert opinion June 2021, Attachment 11 of the resubmission).	This appeared to be reasonable.
Proportion of patients with favourable/intermediate/unknown cytogenetic risk	78.9%. Based on ALFA-0701, 21.0% of patients had unfavourable cytogenetics (3.3% favourable, 66.4% intermediate, 9.2% unknown).	Changes in the methods used to characterise cytogenetic risk suggest that the ALFA-0701 trial population may not be representative of the proposed PBS population.
Proportion of patients who are not FLT3-mutation positive	70%. Expert opinion (Sept 2020) indicating that midostaurin is the treatment of choice for patients with FLT3-positive AML. The assumption of 70% represents the proportion of patients that do not have FLT3-positive AML (Daver et al., 2019).	The estimated proportion of patients who are FLT3-mutation positive was based on all newly diagnosed cases, which was inappropriately applied to the subgroup with favourable/intermediate/unknown risk only. FLT3 mutation is associated with intermediate/adverse risk and so the proportion may be higher than 70% in the subgroup.

Source: Table 4.1.1, p277 of the resubmission.

AIHW, Australian Institute of Health and Welfare; AML, acute myeloid leukaemia; APL, acute promyelocytic leukaemia; CD, cluster of differentiation; ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; Yr, Year.

6.104 The table below presents the estimated utilisation and financial impact of listing gemtuzumab on the PBS/RPBS, based on the resubmission’s proposed price, not the price offered in the pre-PBAC response.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Eligible population						
Favourable/intermediate/unknown cytogenetics	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
March 2021 submission, eligible population	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Gemtuzumab induction treatment utilisation						
Patients without FLT3 mutation receiving induction (70%)	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Private hospital admitted (17%)	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Induction scripts (2.82/patient)	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
March 2021 submission, induction scripts	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Gemtuzumab consolidation treatment utilisation						
Patients receiving induction	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Consolidation 1 uptake (69.5%)	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Consolidation 2 uptake (48.9%)	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Total patients (both consolidation cycles)	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Private hospital admitted and non-admitted, and public hospital non-admitted (34%)	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Consolidation scripts (1/patient)	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
March 2021 submission, consolidation scripts	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Cost of gemtuzumab to the PBS/RPBS						
Total scripts	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
March 2021 submission, total scripts	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Net PBS/RPBS cost (less copay)	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
March 2021 submission, Net PBS/RPBS cost (less copay)	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Blood transfusions procedure (MBS item 13706)	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Cost of blood products (National Blood Authority, NBA) ^a	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Total cost to PBS/RPBS/MBS/NBA	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²

Source: Sections 4.2-4.4, pp281-298 of the resubmission

^a The resubmission assumed the full cost of blood products is borne by the Australian Government. Funding of blood and blood products is shared between the Australian Government (63%) and the States and Territories (37%).

There was an error in the public hospital/private hospital split presented in the resubmission. Italicised estimates were calculated based on corrected estimates provided by the sponsor during the evaluation.

The redacted values correspond to the following ranges:

¹ < 500

² \$0 to < \$10 million

- 6.105 The estimated net cost to the PBS/RPBS was \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6, a total cost of \$10 million to < \$20 million over 6 years. The March 2021 submission estimated a net cost to the PBS/RPBS of \$10 million to < \$20 million over 6 years. The pre-PBAC response claimed that at the reduced price offered, the financial impact to the PBS would reduce by \$0 to < \$10 million over 6 years. The difference in RPBS/PBS budget implications was primarily due to a smaller eligible population that excluded patients with acute promyelocytic leukaemia, and a smaller treated population that excluded the initiation of gemtuzumab treatment in patients who are awaiting cytogenetic test results. Net costs to the PBS/RPBS in the March 2021 submission were also based on a slightly higher proportion of use of gemtuzumab in private hospital settings (20%).
- 6.106 The resubmission estimated additional costs to Government due to increased blood transfusions associated with gemtuzumab treatment. The total cost to Government including additional costs to MBS and the National Blood Authority was \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6, a total cost of \$10 million to < \$20 million over 6 years.
- 6.107 Based on expert opinion, the resubmission clarified that all patients would receive confirmation of cytogenetic risk prior to initiation of treatment with gemtuzumab.
- 6.108 The size of the eligible population remained uncertain given concerns with key inputs related to cytogenetic risk distribution and the proportion of patients who are not FLT3-mutation positive.
- 6.109 The uptake of gemtuzumab in the eligible population was likely overestimated due to the following reasons:
- The uptake of gemtuzumab in patients with unknown cytogenetic risk is likely to be relatively low. The PSCR argued that cytogenetic analysis is only unsuccessful in a small proportion of AML cases, with no correlations to defined biological/genetic aspects of AML or established risk groups. It also considered that this small group of patients (estimated as 9%, i.e. 4 of 31) should not be excluded from subsidy as it claimed that they also have favourable evidence of clinical benefit with treatment with gemtuzumab. In practice, the ESC considered it was possible that few of these patients would be treated with gemtuzumab. The ESC recognised that some of these patients would have demonstrated intermediate/favourable cytogenetics had their tests been successful.
 - Based on published international guidelines and local expert opinion, the role of gemtuzumab is primarily for the treatment of patients with favourable risk and some patients who have intermediate risk, who are not FLT3-mutation positive and are otherwise not being considered for HSCT. This is a smaller role than was proposed in the resubmission.
- 6.110 The majority of costs associated with gemtuzumab are expected to be derived from use in the public hospital inpatient setting, based on 83% of patients receiving induction treatment and 66% of patients receiving consolidation treatment. An

estimate of gemtuzumab drug costs to State/Territory Governments was calculated during the evaluation (based on utilisation assumptions in the resubmission and the proposed gemtuzumab AEMP). The estimated cost to State/Territory Government budgets was \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6, a total of \$30 million to < \$40 million over 6 years. This impact would be less when based on the reduced price offered in the pre-PBAC response.

- 6.111 The resubmission assumed that gemtuzumab would be added to current therapy and would not result in changes in the use of the backbone chemotherapy regimen. There may be additional costs should daunorubicin (the backbone therapy in ALFA-0701) be used instead of idarubicin given that daunorubicin is more expensive than idarubicin. These costs are likely to impact State/Territory Government budgets given that daunorubicin is not listed on the PBS.

Quality Use of Medicines

- 6.112 The resubmission noted a range of activities initiated to support the quality use of medicines including a patient access program, patient support materials, healthcare professional guidelines, expert presentations, and post-marketing surveillance.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of gemtuzumab ozogamicin, in combination with standard intensive chemotherapy (an anthracycline and cytarabine), for the treatment of patients with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML) except acute promyelocytic leukaemia, who have favourable/intermediate/unknown cytogenetic risk (where the unknown risk is due to inconclusive test results). The PBAC recommended that gemtuzumab ozogamicin should be available only under special arrangements under Section 100 (Efficient Funding of Chemotherapy Program). The PBAC is satisfied that gemtuzumab ozogamicin provides, for some patients, a significant improvement in efficacy over standard of care.
- 7.2 The PBAC remained of the view that the exact magnitude of the overall survival benefit was difficult to determine, and that the economic model was complex and difficult to assess. Although the resubmission had not addressed all areas of uncertainty, nonetheless, the PBAC considered that the cost-effectiveness of the listing would be acceptable, in the context of the reduced price offered in the pre-PBAC response and a high clinical need in a smaller, more defined population of patients most likely to see benefit, than that which had been assumed by the resubmission.
- 7.3 The PBAC acknowledged the clinical input received from the Haematology Society of Australia and New Zealand and the Australasian Leukaemia and Lymphoma Group (ALLG), as well as the advice from the ESC and other consumers, which confirmed that gemtuzumab ozogamicin would most likely be used for treatment in patients with

favourable/intermediate cytogenetic risk, who are not FLT3-mutation positive and who are not being considered for HSCT. The PBAC also agreed with the ESC that use would be limited in settings with longer wait times for cytogenetic tests and where daunorubicin was not available.

- 7.4 The PBAC remained of the view that the nominated comparator of standard of care was appropriate, noting that this comprised intensive induction and consolidation chemotherapy with an anthracycline and cytarabine.
- 7.5 The PBAC reiterated that the clinical claim of inferior comparative safety was reasonable, in view of the higher incidence of serious adverse events (para 7.11, gemtuzumab, PSD, March 2021 PBAC meeting).
- 7.6 The PBAC recalled that it had previously considered the key trial AFLA-0701, and various *post hoc* subgroup analyses by cytogenetic risk, and although it had considered the clinical claim of superior effectiveness was reasonable in terms of event-free survival, the claim was not adequately supported in terms of overall survival, and there were also applicability concerns (para 7.9 and 6.52, gemtuzumab, PSD, March 2021 PBAC meeting). The PBAC noted new clinical evidence presented including revised Kaplan-Meier figures, new treatment effect estimates, *post hoc* tests for interaction, and a comparison with ALLG National Blood Cancer Registry data. The PBAC considered that the new evidence alone did not address its uncertainties with respect to the clinical claim. However, it also recognised that no further clinical data was expected and that the cure claim itself was not implausible, although the magnitude of the benefit had been poorly supported.
- 7.7 In terms of the economic model, the PBAC recalled that it had previously considered that the economic model structure was overly complex making it difficult to determine the flow of patients through the model, and that a range of issues meant that the base case ICER of \$35,000 to < \$45,000/QALY gained was highly uncertain and likely optimistic (para 7.13, gemtuzumab, PSD, March 2021 PBAC meeting). The PBAC noted the changes made to the new model (see paragraph 6.64-6.66), and although some issues had been adequately addressed (e.g. shortened time horizon), it considered that there remained uncertainties with respect to the clinical data and application of cure fractions, the verification of some model inputs and assumptions, and the HSCT transition probabilities. At the same time, with the reduced price offered in the pre-PBAC response, and in the more conservative sensitivity analyses (using pooled HSCT rates and adjusting the start and end times for overall survival convergence, see paragraph 6.95), the PBAC considered that, based on the resulting incremental cost-effectiveness ratios, gemtuzumab ozogamicin was likely cost-effective.
- 7.8 The PBAC recollected that it had considered the previous submission's financial estimates were uncertain for reasons to do with the assumed split between public and private hospital use, the size of eligible population, and assumed uptake rates. The PBAC noted the resubmission's revisions to the utilisation and financial estimates (see paragraph 6.100), and agreed with the evaluation that specific inputs to the financial

model remained somewhat uncertain, but that the likely overall impact had been overestimated as the uptake was likely to be in a smaller, more defined population than had been assumed in the resubmission. That is, use would be primarily in patients with favourable cytogenetic risk and some patients with intermediate risk, who are not FLT3-mutation positive and not otherwise being considered for HSCT. The PBAC considered that the uptake would be further limited in settings where daunorubicin was not used, given the clinical hesitancy to use with alternative anthracyclines. The PBAC noted also that updates to the estimates would be required in terms of limiting to patients with WHO status 0-2 (see next paragraph).

7.9 With respect to the PBS listing, the PBAC:

- Recommended an Authority Required listing for both induction and consolidation phases.
- Agreed with the ESC and ALLG that patients with unknown cytogenetic results due to inconclusive results should not be excluded from PBS subsidy (a pragmatic decision, given expected small patient numbers and likelihood that some of these patients would in fact have had intermediate/favourable cytogenetics if testing had been successful).
- Recommended that gemtuzumab must not be used in combination with a tyrosine kinase inhibitor, and that FLT3-mutation positive patients should be excluded from using gemtuzumab.
- Recommended that gemtuzumab should be initiated in patients who are previously untreated, except for essential treatment hydroxyurea or leukapheresis (consistent with the TGA PI recommendation for patients with hyperleukocytic AML).
- Recommended that the listing should be silent on age, noting that although the magnitude of benefit in the paediatric population had not been demonstrated by the resubmission, it had been approved in the US based on phase III trial data and there was strong support for equity of access in the consumer comments. Moreover, the PBAC considered that any PBS use in this population would be minor, given the size of the population.
- Recommended a maximum amount of 5 mg and 2 repeats for induction, and 5 mg and 1 repeat for consolidation, to align with dosage intervals, with no increases in maximum amounts or units permitted. It agreed with the resubmission that 1 induction cycle and 2 consolidation cycles should be permitted per lifetime.
- Recommended that the listing should be restricted to patients with an ECOG performance status of 0-2, given that the vast majority of patients in ALFA-0701 were in this range.
- Noted that the proposed induction criteria had stated that patients with progressive disease would no longer be eligible for PBS-subsidised therapy, however the PBAC considered this was unnecessary in the context of only 1 induction cycle being permitted. The PBAC considered that the same

requirement and definitions of progressive disease on the consolidation phase listing were appropriate.

- Recommended that to access consolidation therapy, a patient must have achieved a complete remission following induction chemotherapy. The PBAC noted that the definition of complete remission in the proposed Prescribing Instructions was consistent with the TGA PI, and advised that there was no need to specify a timeframe between assessment of remission and accessing consolidation therapy as prescribers would be expected to consolidate therapy as clinically appropriate.

- 7.10 The PBAC advised that gemtuzumab ozogamicin should not be treated as interchangeable with any other drugs.
- 7.11 The PBAC advised that gemtuzumab ozogamicin is not suitable for prescribing by nurse practitioners.
- 7.12 The PBAC recommended that the Early Supply Rule should not apply.
- 7.13 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for gemtuzumab ozogamicin:
- a) The treatment is expected to provide an improvement in efficacy, over alternative therapies, on the basis of improved event-free survival, although uncertainty remained with respect to the magnitude of overall survival benefit;
 - b) The treatment is not expected to address a high and urgent unmet clinical need as, although the PBAC recognised a high clinical need for the subset of patients expected to be treated with gemtuzumab ozogamicin, there are currently therapies available on the PBS for AML;
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item:

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MEDICINAL PRODUCT medicinal product pack (MPP)	PBS item code	Max. Amount	No. of Rpts
GEMTUZUMAB OZOGAMICIN gemtuzumab ozogamicin 5 mg injection, 1 vial	NEW (Public) NEW (Private)	5 mg	2
Available brands			
Mylotarg			
Restriction Summary [new] / Treatment of Concept: [new]			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners			
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Telephone/electronic via Online PBS Authorities			
Condition: Acute Myeloid Leukaemia			
Indication: Acute Myeloid Leukaemia			
Treatment Phase: Induction treatment			
Clinical criteria:			
AND			
Patient must have confirmed CD33-positive AML prior to initiation of treatment,			
Clinical criteria:			
AND			
The condition must be de novo,			
Clinical criteria:			
AND			
The condition must be previously untreated (except for prior essential treatment with hydroxyurea or leukapheresis for patients with hyperleukocytic AML).			
Clinical criteria:			
AND			
Patient must have confirmed intermediate/favourable cytogenetic risk, OR Patient must have unknown cytogenetic risk due to inconclusive test results.			
Clinical criteria:			
AND			
Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less,			
Clinical criteria:			
AND			
The condition must not be acute promyelocytic leukaemia,			
Clinical criteria:			
AND			
The treatment must be in combination with standard intensive remission induction chemotherapy for this condition, which must include cytarabine and an anthracycline.			
Clinical criteria:			
AND			
The treatment must not be used in combination with a tyrosine kinase inhibitor.			
Clinical criteria:			
AND			
The condition must not be internal tandem duplication (ITD) or tyrosine kinase domain (TKD) FMS tyrosine kinase 3 (FLT3) mutation positive.			
Clinical criteria:			
AND			
Patient must not receive more than 1 induction cycle under this restriction in a lifetime.			

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	Prescribing Instructions: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: No increase in the maximum amount or number of units may be authorised.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

MEDICINAL PRODUCT medicinal product pack (MPP)	PBS item code	Max. Amount	No. of Rpts
GEMTUZUMAB OZOGAMICIN gemtuzumab ozogamicin 5 mg injection, 1 vial	NEW (Public) NEW (Private)	5 mg	1
Available brands			
Mylotarg			
Restriction Summary [new] / Treatment of Concept: [new]			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners			
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Telephone/electronic via Online PBS Authorities			
Condition: Acute Myeloid Leukaemia			
Indication: Acute Myeloid Leukaemia			
Treatment Phase: Consolidation treatment			
Clinical criteria:			
Patient must have achieved a complete remission following induction treatment with this drug for this condition.			
AND			
Clinical criteria:			
The treatment must be in combination with standard intensive remission consolidation chemotherapy for this condition, which must include cytarabine and an anthracycline.			
AND			
Clinical criteria:			
Patient must not receive more than 2 consolidation cycles under this restriction in a lifetime.			
Prescribing Instructions: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.			
Prescribing Instructions: A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.			
Prescribing Instructions: Complete remission following induction is defined as fewer than 5% blasts in a normocellular marrow and an absolute neutrophil count of more than 1.0×10^9 cells/L with a platelet count of 100×10^9 /L or more in the peripheral blood in the absence of transfusion.			
Prescribing Instructions: Progressive disease is defined as the presence of any of the following: •Leukaemic cells in the CSF; •Re-appearance of circulating blast cells in the peripheral blood, not attributable to overshoot following recovery from myeloablative therapy; •Greater than 5 % blasts in the marrow not attributable to bone marrow regeneration or another cause; •Extramedullary leukaemia.			
Administrative Advice: No increase in the maximum number of repeats may be authorised.			
Administrative Advice: No increase in the maximum amount or number of units may be authorised.			
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.			

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.