National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	The Royal College of Pathologists	possibly - it may be a little early as there is a phase 3 RCT which is as yet incompletely analysed and not yet published so the full potential benefits of this agent compared to SOC may not be clear at the time of consideration	Thank you for your comment. No action required.
	NCRI-RCP-ACP	It may be a little early to refer this topic for appraisal as there is a phase 3 randomised controlled trial which is as yet incompletely analysed and not yet published. Therefore the full potential benefits of this agent compared to standards of care may not be clear at the time of consideration	Thank you for your comment. No action required.
	Pfizer Ltd	Pfizer agrees it is appropriate for this topic to be referred to NICE.	Thank you for your comment. No action required.
Wording	The Royal College of Pathologists	yes	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	NCRI-RCP-ACP	yes	Comment noted. No action required.
	Pfizer Ltd	Pfizer suggests that the wording of the remit should be updated to reflect the wording of the Marketing Authorisation detailed in the Regulatory Issues section of this response.	Comment noted. The wording of the remit was updated following the consultation comments and the scoping workshop.
Timing Issues	Leukaemia CARE	The outlook for acute lymphoblastic leukaemia (ALL) patients varies greatly with age. From Cancer Research UK: • In those aged 14 or younger, more than 90 out of 100 (90%) will survive for 5 years or more after they are diagnosed • In those aged between 15 and 24, more than 66 out of 100 (66%) will survive for 5 years or more after diagnosis • In those aged between 25 and 64, almost 40 out of 100 (40%) will survive for 5 years or more after they are diagnosed • In those aged 65 or older, almost 15 out of 100 (15%) will survive for 5 years or more after diagnosis This demonstrates the fact that adult ALL patients have an extremely poor prognosis. Whilst this may be partly attributable to late diagnosis (with approximately 64% of ALL patients diagnosed via emergency presentation -	Comment noted. No action required.

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		see NCIN Routes to Diagnosis report), there is clearly an urgent need for alternative treatment options for adult ALL patients. With the currently available treatment options, only 20 - 40% of adults with ALL will be "cured". All other patients will eventually relapse. For relapsed patients, the five-year overall survival rate is less than 10% (see Fielding A. et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood. 2006; 944-950). In the cited paper, the author commented that due to a lack of suitable treatment options "We suggest that every eligible adult with recurring ALL be included in a prospective study involving novel therapeutic agents." This demonstrates the urgent need for access to additional treatment options.	
	The Royal College of Pathologists	…However, this will become urgent once the phase 3 data are available as this is likely to lead to a license	Comment noted. No action required.
	NCRI-RCP-ACP	This will become urgent once the phase 3 data noted above are available, as this is likely to lead to a license.	Comment noted. No action required.
	Pfizer Ltd	Pfizer considers it important that clinicians in England and Wales are provided with suitable NICE Guidance on the use of inotuzumab ozogamicin. Pfizer requests that when considering incorporation into the NICE work programme, evidence submission should be no sooner than the time of CHMP Opinion as provided in the Regulatory Issues section of this response.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	The Royal College of Pathologists	largely accurate, doesn't mention that bone marrow transplant is employed as an initial therapy in high risk de novo ALL	Comment noted. The background section of the scope has been updated.
	NCRI-RCP-ACP	The information is largely accurate but should include that bone marrow transplant is employed as an initial therapy in high risk de novo ALL	Comment noted. The background section of the scope has been updated.
	Pfizer Ltd	Pfizer suggests the following points are included at the end of the background section to provide relevant information on the relapsed or refractory B-cell acute lymphoblastic leukaemia (r/r B-ALL) population: Just under half of adults with newly diagnosed B-ALL are expected to relapse or have refractory disease to initial treatment (Fielding et al, 2007). Based on current epidemiology and rate of relapsed and refractory disease, it is estimated that there are around 100 incident adults with r/r B-ALL in England and Wales per year.	Comment noted. The background section of the scope has been updated.
The technology/ intervention	The Royal College of Pathologists	doesn't mention that it is an antibody directed at CD22 antigen. CD22 is expressed on the surface of B cells and is commonly expressed on ALL cells but not invariably doesn't make it clear that this is a therapy only for patients with B (as opposed to T) precursor ALL	Comment noted. The technology section of the scope has been updated to accurately

Section	Consultee/ Commentator	Comments [sic]	Action
			reflect the mechanism of action.
	NCRI-RCP-ACP	The description of the technology should include mention that it is an antibody directed at CD22 antigen. CD22 is expressed on the surface of B cells and is commonly expressed on ALL cells but not invariably Furthermore it does not make it clear that this is a therapy only for patients with B (as opposed to T) precursor ALL	Comment noted. The technology section of the scope has been updated to accurately reflect the mechanism of action.
	Pfizer Ltd	None.	Comment noted. The technology section of the scope has been updated to accurately reflect the mechanism of action.
Population	The Royal College of Pathologists	yes	Comment noted. The population section of the scope has been updated to reflect the proposed marketing authorisation wording for inotuzumab ozogamicin.
	NCRI-RCP-ACP	Yes	Comment noted. The population section of the scope has been updated to reflect the

Section	Consultee/ Commentator	Comments [sic]	Action
			proposed marketing authorisation wording for inotuzumab ozogamicin.
	Pfizer Ltd	Pfizer suggests this is reworded to read: "Adults with relapsed or refractory B-cell acute lymphoblastic leukaemia."	Comment noted. The population section of the scope has been updated to reflect the proposed marketing authorisation wording for inotuzumab ozogamicin.
Comparators	Leukaemia CARE	At present, there is currently no agreed standard of care for relapsed or refractory ALL patients. Patients in this setting are generally treated with re-induction therapy (with various chemotherapy regimens) followed by a stem cell transplant. It is clear that whatever option is chosen from currently available treatments, the outcomes are less than satisfactory.	Comment noted. Following consultation comments and the scoping workshop the comparators have been updated to: For people who are able to take salvage chemotherapy: fludarabine, cytarabine and granulocyte colony-stimulating factor (GCSF) based combination chemotherapy

Section	Consultee/ Commentator	Comments [sic]	Action
			For people who are unable to take a salvage chemotherapy the: best supportive care (including palliative care)
	The Royal College of Pathologists	there isnt an established clinical management for patients with relapsed ALL - usually we give salvage chemotherapy (no one regimen is clearly defined but FLAG-Ida is commonly used in UK) to achieve a second complete remission or enroll patients into trials Beyond CR2 we do our best to enroll patients into trials	Comment noted. Following consultation comments and the scoping workshop the comparators have been updated to: For people who are able to take salvage chemotherapy: fludarabine, cytarabine and granulocyte colony-stimulating factor (GCSF) based combination chemotherapy For people who are unable to take a salvage chemotherapy the:

Section	Consultee/ Commentator	Comments [sic]	Action
			best supportive care (including palliative care)
	NCRI-RCP-ACP	There is not an established clinical management for patients with relapsed ALL - usually we give salvage chemotherapy (no one regimen is clearly defined but FLAG-Ida is commonly used in UK) to achieve a second complete remission or enroll patients into trials Beyond CR2 we do our best to enroll patients into trials	Comment noted. Following consultation comments and the scoping workshop the comparators have been updated to: For people who are able to take salvage chemotherapy: fludarabine, cytarabine and granulocyte colony-stimulating factor (GCSF) based combination chemotherapy For people who are unable to take a salvage chemotherapy the: best supportive care (including palliative care)
	Pfizer Ltd	• FLAG-based (fludarabine plus cytarabine plus granulocyte-colony stimulating factor) combination chemotherapy (majority of patients).	Comment noted.

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		• Palliative care.	Following consultation comments and the scoping workshop the comparators have been updated to: For people who are able to take salvage chemotherapy: fludarabine, cytarabine and granulocyte colony-stimulating factor (GCSF) based combination chemotherapy For people who are unable to take a salvage chemotherapy the: best supportive care (including palliative care)
Outcomes	The Royal College of Pathologists	cytogenetic response is not relevant to ALL time to response is not relevant to ALL	Comment noted. Following the scoping workshop, the outcomes section of the scope has been updated. Cytogenetic response was removed

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			as an outcome. Minimal residual disease and rate of stem cell transplant were added as outcomes to the scope.
	NCRI-RCP-ACP	Cytogenetic response is not relevant to ALL time to response is not relevant to ALL	Comment noted. Following the scoping workshop, the outcomes section of the scope has been updated. Cytogenetic response was removed as an outcome. Minimal residual disease and rate of stem cell transplant were added as outcomes to the scope.
	Pfizer Ltd	Haematologic response (i.e. complete remission (CR) or complete remission with incomplete haematologic recovery (CRi)), is necessary to be eligible for subsequent stem cell transplant (SCT), and is therefore of key clinical importance. Cytogenetic evaluation is integral to the minimal residual disease (MRD) response assessment, and serves as an important baseline covariate, rather than the response rate per se. In the 1022 trial, cytogenetic findings of Philadelphia chromosome positivity (Ph+ ALL) and any complex cytogenetic abnormalities were performed at baseline for all patients. The post-baseline assessment of cytogenetics as a secondary endpoint of the trial was	Comment noted. Following the scoping workshop, the outcomes section of the scope has been updated. Cytogenetic response was removed as an outcome. Minimal residual disease and rate of stem cell transplant were added

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		performed only in patients who achieved a CR/CRi and whose baseline results were abnormal. As cytogenetic response is not commonly used as a primary outcome for trials assessing treatment efficacy in r/r B-ALL, Pfizer requests that it is removed from the scope. Pfizer notes that the following outcomes are of clinical relevance, and requests they are included in the appraisal: • Rate of stem cell transplant in treated patients. • Minimal residual disease in patients who achieve a CR/CRi.	as outcomes to the scope.
Economic analysis	The Royal College of Pathologists	be careful to take into account time spent in hospital espeically time spent being neutropaenic - usually 4-6 weeks for SOC salvage	Comment noted. No action required.
	NCRI-RCP-ACP	It is important to take into account time spent in hospital especially time spent being neutropaenic. It is usually 4-6 weeks for SOC salvage	Comment noted. No action required.
	Pfizer Ltd	No comments.	Comment noted. No action required.
Equality and Diversity	The Royal College of Pathologists	nothing to add	Comment noted. No action required.
	NCRI-RCP-ACP	Nothing to add	Comment noted. No action required.
	Pfizer Ltd	Not applicable.	Comment noted. No action required.

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Innovation	The Royal College of Pathologists	yes - see also this Q within consultatation	Comment noted. The innovative nature of inotuzumab ozogamicin will be considered by the committee during the appraisal. No action required.
	NCRI-RCP-ACP	Yes - see also this Q within consultatation	Comment noted. The innovative nature of inotuzumab ozogamicin will be considered by the committee during the appraisal. No action required.
	Pfizer Ltd	Inotuzumab ozogamicin is an antibody-drug conjugate (ADC), that uses an anti-CD22 antibody to selectively deliver a potent derivative of the DNA-damaging antibiotic calicheamicin, to cancer cells in patients with B-cell ALL. This innovative treatment has the potential to create a step change in the care of adults with r/r B-ALL, in terms of greatly increased efficacy (as measured by CR/CRi) and the potential to administer treatment in the outpatient setting. **Inotuzumab ozogamicin more than doubled the rate of CR/CRi compared with investigator's choice**: 81% vs 33% respectively, based on mITT analysis using an endpoint adjudication committee assessment of first 218 patients randomized to treatment (Pfizer, 2015).	Comment noted. The innovative nature of inotuzumab ozogamicin will be considered by the committee during the appraisal. No action required.

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		CR/CRi is an important clinical end point in r/r B-ALL. It is correlated with improved OS (Gökbuget et al, 2012) and is one of the requirements for subsequent stem cell transplant, which remains the only potentially curative treatment for these patients. **Inotuzumab ozogamicin increases the numbers of patients going on to receive a SCT, compared with investigator's choice:** 48 (40%) vs 20 patients (11%) respectively (DeAngelo et al, 2012). **Inotuzumab ozogamicin has the potential to be administered in the outpatient setting.** The rapid and selective binding of the anti-CD22 antibody to its target allows inotuzumab ozogamicin to be administered in less time than current intensive chemotherapy regimens. Inotuzumab ozogamicin is delivered as a one hour intravenous infusion on days 1, 8 and 15 of a three to four week cycle, for a maximum of six cycles (Kantarjian et al, 2013). This means inotuzumab ozogamicin can potentially be delivered in the outpatient setting, with no recommendations for patients to be hospitalised to receive inotuzumab ozogamicin, unless the patients' clinical condition requires in-patient care.	
Other considerations	The Royal College of Pathologists	nothing to add	Following the scoping workshop, the other considerations section of the scope has been updated with potential subgroups.
	NCRI-RCP-ACP	Nothing to add	Following the scoping workshop, the other considerations section

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			of the scope has been updated with potential subgroups.
	Pfizer Ltd	None.	Following the scoping workshop, the other considerations section of the scope has been updated with potential subgroups.
Questions for consultation	The Royal College of Pathologists	What proportion of the population of people with acute lymphoblastic leukaemia will experience refractory or relapsed acute lymphoblastic leukaemia? Approximately 50% of the adult population Would inotuzumab ozogamicin be expected to be used in combination with specific chemotherapy drugs or regimens? If so, which chemotherapy combinations? At present as a single agent as this is what has been studied in the pivotal trial (a phase 3 RCT vs SOC) Have all relevant comparators for inotuzumab ozogamicin been included in the scope? Which treatments are considered to be established clinical practice in the NHS for relapsed or refractory acute lymphoblastic leukaemia? Should stem cell and bone marrow transplants be included as comparators? NO	Comment noted. No action required. Comment noted. No action required. Following consultation comments and the scoping workshop the comparators have been updated to: For people who are able to take salvage chemotherapy:

			Fludarabine, cytarabine and granulocyte colony-stimulating factor (GCSF) based combination chemotherapy For people who are unable to take a salvage chemotherapy the: best supportive care (including palliative care) Comment noted. No action required.
		Would inotuzumab ozogamicin be expected to be used in combination with specific chemotherapy drugs or regimens? If so, which chemotherapy combinations should be included in this appraisal?	
		See comment above – presently insufficient information to appraise in combination	Comment noted. No action required.
		Would the population included in the scope require testing for CD22? If so, what proportion of the population is routinely tested for CD22?	
		Yes and this is usually a routine test and if not, easily and relatively cheaply done	
		Are the outcomes listed appropriate?	Following the scoping workshop, the outcomes section of the scope has been updated. Cytogenetic
		Not all – I have commented in this in the consultation comment form	

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			response was removed as an outcome. Minimal residual disease and rate of stem cell transplant were added as outcomes to the scope.
		Are there any subgroups of people in whom inotuzumab ozogamicin is expected to be more clinically effective and cost effective or groups that should be examined separately? Yes ; consideration of higher risk relapse (soon after initial therapy, relapses on therapy) or second or subsequent relapse and harder to treat (eg after bone marrow transplant)	Comment noted. No action required. The subgroups in the other considerations section of the scope has been updated.
		Where do you consider inotuzumab ozogamicin will fit into the existing NICE pathway Blood and bone marrow cancers? Not really relevant to ALL	Comment noted. No action required.
		NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which inotuzumab ozogamicin will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider	Comment noted. No action required.

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		population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. Nothing to add re the above except to consider children and young people who may benefit from this agent but for whom there are fewer suppoting data as trials largely conducted in adults Do you consider inotuzumab ozogamicin to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes, this is a non-chemotherapy agent with a mechanism of action which has not been studied before in ALL. The abstract data presented so far indicate a vastly higher CR rate than comparator although survival data are not yet available. The toxicity is low compared to so-called SOC and therapy can be given as an outpatient unlike 'SOC' chemotherapy regimens commonly used in this situation which result in weeks of hospitalisation. Do you consider that the use of inotuzumab ozogamicin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Potentially much less time in hospital Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.	Comment noted. No action required. NICE will appraise inotuzumab ozogamicin within its marketing authorisation. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

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		Various published early phase studies and a forthcoming large international phase 3 RCT not yet analysed	
	NCRI-RCP-ACP	What proportion of the population of people with acute lymphoblastic leukaemia will experience refractory or relapsed acute lymphoblastic leukaemia? Approximately 50% of the adult population Would inotuzumab ozogamicin be expected to be used in combination with specific chemotherapy drugs or regimens? If so, which chemotherapy combinations? At present as a single agent as this is what has been studied in the pivotal trial (a phase 3 RCT vs SOC) Have all relevant comparators for inotuzumab ozogamicin been included in the scope? Which treatments are considered to be established clinical practice in the NHS for relapsed or refractory acute lymphoblastic leukaemia? Should stem cell and bone marrow transplants be included as comparators? No	Comment noted. No action required. Comment noted. No action required. Following consultation comments and the scoping workshop the comparators have been updated to: For people who are able to take salvage chemotherapy: Fludarabine, cytarabine and granulocyte colony-stimulating factor (GCSF) based combination chemotherapy

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			For people who are unable to take a salvage chemotherapy the: best supportive care (including palliative care)
		Would inotuzumab ozogamicin be expected to be used in combination with specific chemotherapy drugs or regimens? If so, which chemotherapy combinations should be included in this appraisal? See comment above – presently insufficient information to appraise in combination	Comment noted. No action required.
		Would the population included in the scope require testing for CD22? If so, what proportion of the population is routinely tested for CD22? Yes and this is usually a routine test and if not, easily and relatively cheaply done	Comment noted. No action required.
		Are the outcomes listed appropriate? Not all – see comments above.	Following the scoping workshop, the outcomes section of the scope has been updated. Cytogenetic response was removed as an outcome. Minimal residual disease and rate of stem cell transplant were added

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			as outcomes to the scope.
		Are there any subgroups of people in whom inotuzumab ozogamicin is expected to be more clinically effective and cost effective or groups that should be examined separately? Yes ; consideration of higher risk relapse (soon after initial therapy, relapses on therapy) or second or subsequent relapse and harder to treat (eg after bone marrow transplant)	Comment noted. No action required. The subgroups in the other considerations section of the scope have been updated.
		Where do you consider inotuzumab ozogamicin will fit into the existing NICE pathway Blood and bone marrow cancers? Not really relevant to ALL	Comment noted. No action required.
		NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which inotuzumab ozogamicin will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities.	Comment noted. No action required.

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		Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. Nothing to add regarding the above except to consider children and young people who may benefit from this agent but for whom there are fewer supporting data as trials largely conducted in adults	Comment noted. No action required. NICE will appraise inotuzumab ozogamicin within its marketing authorisation.
		Do you consider inotuzumab ozogamicin to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes, this is a non-chemotherapy agent with a mechanism of action which has not been studied before in ALL. The abstract data presented so far indicate a vastly higher CR rate than comparator although survival data are not yet available. The toxicity is low compared to so-called SOC and therapy can be given as an outpatient unlike 'SOC' chemotherapy regimens commonly used in this situation which result in weeks of hospitalisation.	Comment noted. No action required.
		Do you consider that the use of inotuzumab ozogamicin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Potentially much less time in hospital	Comment noted. No action required.
		Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. Various published early phase studies and a forthcoming large international phase 3 RCT not yet analysed	Comment noted. No action required.

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	Pfizer Ltd	1. What proportion of the population of people with acute lymphoblastic leukaemia will experience refractory or relapsed acute lymphoblastic leukaemia? Fielding et al (2007) provides the largest retrospective analysis of patients with r/r B-ALL from the UK. Based on an initial cohort of 1508 patients with newly diagnosed B-ALL, 44.5% (671/1508) were either refractory to initial treatment or relapsed. The vast majority of the relapsed or refractory population were relapsed (609 patients), with a median time of relapse after initial treatment of 11 months. 2. Would inotuzumab ozogamicin be expected to be used in combination with specific chemotherapy drugs or regimens? If so, which chemotherapy combinations? Inotuzumab ozogamicin is not expected to be used in combination with other chemotherapy drugs; the anticipated license will be for use as a monotherapy. 3. Have all relevant comparators for inotuzumab ozogamicin been included in the scope? Which treatments are considered to be established clinical practice in the NHS for relapsed or refractory acute lymphoblastic leukaemia? Pfizer's previous comments in the comparators section of this response identify the relevant comparators for the appraisal. With respect to current clinical practice in the treatment of r/r B-ALL, it is important to recognise the lack of a robust evidence base for existing treatments in this population. Few randomised controlled trials exist due to the combination of the high fatality rate (Gökbuget et al, 2010) (median OS of 24 weeks;	Comment noted. No action required. Comment noted. No action required. Following consultation comments and the scoping workshop the comparators have been updated to: For people who are able to take salvage chemotherapy: Fludarabine, cytarabine and granulocyte colony-stimulating factor (GCSF) based

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		Fielding et al, 2007) and the very small patient population. Pfizer estimates there are around 100 incident patients in England and Wales per year, falling well within the definition of ultra-orphan used by NICE (ie <1000 people in England and Wales). Feedback from UK clinicians and the available literature commenting on treatment practices (eg Marks et al, 2010) indicates FLAG-based regimens are established clinical practice in the UK for the majority of adults with r/r B-ALL. Pfizer notes that whilst clofarabine was also identified as a treatment for some patients, the lack of routine access means that it cannot be considered established clinical practice. The lack of RCTs means that clinical practice is not underpinned by a strong comparative evidence base. Consequently, there is very limited evidence to support the use of any specific FLAG-based regimen in r/r B-ALL. Due to the ultra-orphan patient population and the restricted number of RCTs for current treatments, appraisals of new therapies in r/r B-ALL in the UK will face potential challenges in performing comparative clinical and economic assessments versus established clinical practice. The most robust evidence base available for the comparison between inotuzumab ozogamicin and a FLAG-based regimen is from the 1022 trial. In this trial, approximately two thirds (64.5%) of the first 138 patients randomised to chemotherapy received FLAG from a possible choice of three (FLAG, cytarabine plus mitoxantrone, or high dose cytarabine).	combination chemotherapy For people who are unable to take a salvage chemotherapy the: best supportive care (including palliative care)

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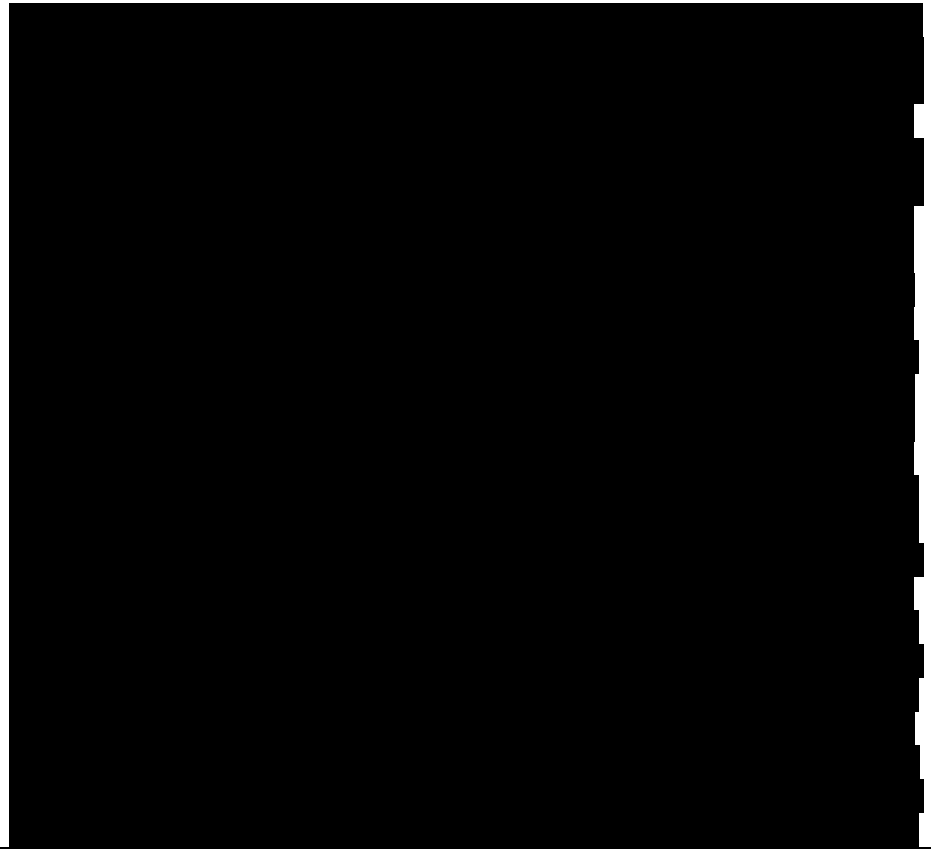
		4. Should stem cell and bone marrow transplants be included as comparators? Stem cell and bone marrow transplants currently provide the only potentially curative treatment for adults with r/r B-ALL. There is little evidence to support the efficacy of transplants in patients who do not achieve remission. The goal of therapy in relapsed B-ALL is therefore to achieve remission whilst minimising undue toxicity. Once in remission, the patient would be moved as quickly as possible onto a transplant, if clinically feasible (Marks et al, 2010). The 1022 trial shows that inotuzumab ozogamicin can increase the number of patients who achieve CR/CRi compared to standard of care (81% vs 33%). Consistent with this, the 1022 trial also shows a greater number of patients treated by inotuzumab ozogamicin compared with investigator's choice went on to receive a transplant (48 vs 20 patients) (DeAngelo et al, 2015). The role of inotuzumab ozogamicin is complementary to transplant. Furthermore, in clinical practice the use of inotuzumab ozogamicin would precede transplant. Consequently, stem cell and bone marrow transplants should not be considered to be a comparator for inotuzumab ozogamicin in the appraisal. 5. Would the population included in the scope require testing for CD22? If so, what proportion of the population is routinely tested for CD22? As part of the EMA regulatory submission, Pfizer has performed a series of analyses of trial data (detailed below) that show a companion	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		diagnostic to evaluate CD22 expression on leukemic blasts is not necessary for the safe and effective use of inotuzumab ozogamicin in the treatment of patients with r/r B-ALL. Therefore, the population in the scope does not require testing for CD22. 	

Section	Consultee/ Commentator	Comments [sic]	Action
		[redacted] 6. Are the outcomes listed appropriate? Please see comments given above in response to the section on outcomes on the scope.	Following the scoping workshop, the outcomes section of the scope has been updated. Cytogenetic response was removed as an outcome. Minimal residual disease and rate of stem cell transplant were added

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			as outcomes to the scope.
		7. Are there any subgroups of people in whom inotuzumab ozogamicin is expected to be more clinically effective and cost effective or groups that should be examined separately? [redacted]	Comment noted. No action required.
		8. Where do you consider inotuzumab ozogamicin will fit into the existing NICE pathway Blood and bone marrow cancers? Currently the NICE pathway does not include an appropriate pathway for patients diagnosed with B-cell acute lymphoblastic leukaemia.	Comment noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
The Royal College of Nurses