CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Inotuzumab Ozogamicin (Besponsa) for Acute Lymphoblastic Leukemia

July 6, 2018

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding inotuzumab ozogamicin (Besponsa) for acute lymphoblastic leukemia (ALL). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature inotuzumab ozogamicin (Besponsa) for ALL conducted by the Leukemia Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background clinical information provided by the CGP, a summary of submitted Patient Advocacy Group Input on inotuzumab ozogamicin (Besponsa) for ALL, a summary of submitted Provincial Advisory Group Input on inotuzumab ozogamicin (Besponsa) for ALL, and a summary of submitted Registered Clinician Input on inotuzumab ozogamicin (Besponsa) for ALL, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of inotuzumab ozogamicin (Besponsa) as monotherapy on patient outcomes, in the treatment of adult patients with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia (ALL).

The reimbursement request is in line with the approved Health Canada indication. Inotuzumab ozogamicin received its notice of compliance in March 2018. Each inotuzumab ozogamicin carton contains one inotuzumab ozogamicin 0.9-mg single-dose vial containing a sterile, preservative-free, white to off-white lyophilized cake or powder for intravenous infusion.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One RCT (INO-VATE ALL[2-20]) met our inclusion criteria. INO-VATE ALL was a multicenter phase III randomized open-label trial funded by Pfizer, Inc. The primary endpoints of the INO-VATE ALL trial were hematological remission rate (complete remission/incomplete hematologic recovery [CR/CRi]), as assessed by the independent external Endpoint Adjudication Committee (EAC), and overall survival (OS) in patients with relapsed or refractory (≥5% marrow blasts, assessed by morphology; ie, M2 or M3 marrow) CD22-positive B-cell ALL. Patients were randomized to receive inotuzumab ozogamicin (InO) or Investigator's choice of chemotherapy[2]. Secondary outcomes included progression-free survival (PFS), duration of remission, the rate of stem cell transplants, minimal residual disease levels, quality of life, safety and toxicity outcomes. The INO-VATE ALL trial randomized 326 eligible patients, in a 1:1 ratio, to receive either inotuzumab ozogamicin or one of the three defined chemotherapy regimens (either FLAG or cytarabine with mitoxantrone or HIDAC). Randomization was stratified according to

the duration of the first remission (greater or less than 12 months), the salvage treatment phase (first or second salvage) and age (older or younger than 55). Crossover between arms was not allowed during the trial. Investigators and patients were not blinded to the treatment allocation, but the members of the EAC were blinded to the treatment allocation and the result of investigator assessment. Patients who achieved a response to treatment and who had a suitable donor may have undergone stem-cell transplantation at the discretion of the investigator and were followed for disease progression and survival[2].

Efficacy

The key primary and secondary outcomes of the INO-VATE-ALL trial are reported in Table 1 below. At the pre-specified final analysis, the rate of CR/CRi was higher in InO arm (88/109, 80.7%) when compared with control arm (32/109, 29.4%), which was statistically significant (mean difference 51.4%, p<0.001)[2,21,22]. The median duration of remission was 4.6 months in InO arm and 3.1 in the control arm[2]. An updated analysis was carried out for the ITT population on CR/CRi after the data cut-off date of March 8, 2016, which showed consistent results.

At the pre-specified final analysis, the stratified hazard ratio of death was 0.77 (97.5% CI 0.578-1.026,1-sided p=0.0203, 2-sided p=0.04)[2,20,22]. The p-value of the final analysis did not reach the pre-specified level of efficacy at 1-sided p=0.0111 or 2-sided p=0.0208[2,20]. The median survival was 7.7 months in the InO arm and 6.7 months in the control arm[2]. An updated analysis of OS was performed on Jan 4, 2017[20,22]. The stratified hazard ratio of death when comparing InO arm to control arm was 0.751 [97.5% CI 0.568, 0.993, 1-sided p=0.0105][5,22]. This updated analysis was not included in the multiplicity adjustment therefore it was not clear whether the p-value reached the efficacy boundary after multiplicity adjustment. The median survival at the updated OS analysis was 7.7 months in the InO arm and 6.2 months in the control arm[5,22].

PFS was a key secondary outcome. The trial reported PFS using two definitions. Using the definition of PFS in the trial (included treatment discontinuation due to global deterioration of health status and starting new induction therapy or post-therapy HSCT without achieving CR/CRi, the stratified hazard ratio of PFS when comparing InO to control was 0.45 (97.5% CI: 0.336-0.602 p<0.0001)[3,5,20]. The median PFS was 5 months in the InO arm versus 1.7 months in the control arm[5,20]. Using the common definition of PFS (without treatment discontinuation due to global deterioration of health status and starting new induction therapy or post-therapy HSCT without achieving CR/CRi), the stratified hazard ratio of PFS was 0.568 (97.5% CI 0.401-0.804p=0.0001). The median PFS was 5.6 months in the InO arm versus 3.7 months in the control arm.

Health-related quality of life as measured by the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30), v3.0 and the EuroQoL 5 Dimensions questionnaire 3 level version (EQ-5D-3L) were collected from patients in each treatment arm during the treatment cycle period only. A change of 5 to 10 points on the 1-100 point scale of the EORTC-QLQ-C30 or 0.08 in the EQ-5D-3L score are considered estimates of minimally important differences for clinical significant differences in quality of life. There was more than a 5 point difference in three subcatgeories of the EORTC-QLQ-C30 including physical functioning (75.0 vs 68.1, p=0.0139), role functioning (64.7 vs 53.4, p=0.0065) and social functioning (68.1 vs 59.8, p=0.0336) in the InO group compared to the chemotherapy group.[12,22] However, there was no difference in the

EORTC-QLQ-C30 global health status score in the InO arm compared to the control arm (62.1 vs 57.8 (p=0.1572)). Furthermore, there was no difference in the EQ-5D-3L index in the InO arm compared to the control arm,(0.80 vs 0.76 (p=0.1710)).[12,22]

The majority of patients in the INO-VATE ALL trial experienced an adverse event. The most common grade 3 and 4 adverse events in either group were cytopenias, although these were more common among the standard care patients than the InO patients (grade 3 and 4 thrombocytopenia 40.9% vs. 59.4%, grade 3 and 4 febrile neutropenia 26.8% vs. 53.8%).[20] Liver-related adverse events were more common in the patients who received InO and hepatic venoocclusive (11% vs. 2%) of the inotuzumab vs. the standard treatment patients.[20] More patients who received InO required temporary treatment discontinuation (31.1% vs. 8.4%) to deal with adverse events and more of these patients withdrew due to adverse events (18.9% vs. 7.7%).

[Table 1]: Highlights of Key Outcomes

		INO-VATE ALL	
Outcomes	**DCO date**	**InO arm (N=164)**	**Control arm (N=162)**
Overall survival, median[2]	**March 8, 2016**	7.7 months	6.7 months
HR (97.5%CI)		0.77 (0.58-1.03)	
p-value		0.04	
CR/CRi rate[2]	**Oct 2, 2014**	88/109 (80.7%)	32/109 (29.4%)
Mean difference		51.4%	
p-value		<0.0001	
Progression-free survival (trial definition)[3,5,20]			
HR (97.5% CI)	**Jan 4, 2017**	0.45 (0.336-0.602)	
p-value		<0.0001	
Progression-free survival (common definition)[20]	**Jan 4, 2017**		
HR (97.5% CI)		0.568 (0.401-0.804)	
p-value		0.0001	
HrQoL[12,22]	**March 8, 2016**		
EORTC-QLQ-C30		62.1	57.8
p-value		0.1572	
EQ-5D		0.8	0.76
p-value		0.171	
Harms Outcome, n (%)	**Jan 4, 2017**	**InO Arm (N=164)**	**Control Arm (N=143)**
All cause grade 3 & 4 AE		147 (89.6%)	138 (96.5%)
All cause AE (any grade)		163 (99.4%)	143 (100%)
WDAE		31 (18.9%)	11 (7.7%)
TR death		9 (5.5%)	3 (2.1%)
Patients with dose reduction due to TRAE		4 (2.4%)	1 (0.7%)
Patients with temporary discontinuation due to TRAE		51 (31.1%)	12 (8.4%)

AE = adverse event, **CI** = confidence interval, **CR/CRi**= complete remission/complete remission with incomplete hematological recovery, **DCO**= date cut-off, **HR** = hazard ratio, HRQoL = health-related quality of life, **InO**= inotuzumab ozogamicin, **TR** = treatment-related, **WDAE** = withdrawal due to adverse event
*HR < 1 favours InO arm

Key Limitations/Source of Biases

Trial design

- Due to the open-label nature of the study, 19 patients randomized to control arm withdrew from the treatment immediately after

randomization. However, some of the patients still remained in the population allowing follow-up. In addition, since the total number of patients drop-out was small, the risk of attrition bias was low. There was no high risk of bias found in the trial design.

Analysis of effect

- The shape of the Kaplan-Meier plot of the overall survival analysis showed a more profound difference between the two arms after month 14. This might suggest that a subgroup of patients in InO arm who survived after 14 months was the main driver behind the more favourable survival effect. However, the goal of the RCT was not designed to identify the subgroup of patients with a more profound survival benefit. This finding can only be interpreted as hypothesis generating. To minimize the risk of selection bias, the subgroups used in stratification were evaluated. In this case, patients under age 55, with greater than 12 months to their first remission and in their first salvage treatment phase seemed to show a bigger survival difference than patients who were older than 55 years, less than 12 months to the first remission and in their second salvage treatment phase. The p-value of the pre-specified final analysis did not reach the adjusted p-value for efficacy.
- None of the subgroups were adequately powered and the results should only be considered for exploratory reasons.
- The primary definition of PFS in the RCT included patients who withdrew due to global deterioration of health status or starting new induction therapy or post-therapy HSCT without achieving CR/CRi. This definition was different from the common definition of PFS. The PFS analysis using the common definition was also reported. Since there were more patients in the control arm who proceeded to HSCT after an new induction therapy, under the protocol definition these patients might be considered as progressed which led to a greater effect size in hazard ratio favouring InO. The effect size on hazard ratio using the common definition was smaller compared with PFS analysis using the protocol definition in the RCT (0.568 vs 0.450). However, both PFS analyses were consistent.
- More patients achieved a complete remission or complete remission with incomplete hematological recovery in InO arm. This result allowed more patients in the InO arm to proceed to HSCT. However, whether proceeding to HSCT resulted in survival benefit was inconclusive as the sample size for this subgroup was small.
- QoL was a secondary outcome and was not part of the statistical analysis plan for the trial. No multiplicity adjustments were made for QOL analyses. Thus, there is a risk of type one error (false positive finding). Furthermore, QoL was assessed during the treatment period, which was different between the InO arm and chemotherapy arm (median treatment duration of InO was 3 cycles vs 1 cycle in the chemotherapy arm). The temporal effect may have a role in the differences observed between the InO arm and the chemotherapy arm.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient perspective, a diagnosis of ALL results in many disruptions to their daily lives including emotional and physical symptoms. Caregivers experience a huge emotional impact from their loved one going through cancer as well as a complete lifestyle change from the time spent caring for their loved one. The physical symptoms of ALL experienced by all patient respondents to some degree include loss of appetite/and or weight loss, fever/night sweats, fatigue, pain, bruising and/or bleeding, feeling dizzy/light headedness, rashes, numbness and tingly, and other (trauma). Emotional symptoms include anxiety, stress, depression, and a feeling of being overwhelmed (ratings which were considered quantitatively significant). The patient advocacy group noted that the four standard treatments for adult patients with ALL are: chemotherapy, radiation therapy, chemotherapy with stem cell transplant (for patients who do not respond to chemotherapy), and targeted therapy. The patient advocacy group reported that six out of seven patients stated they strongly disagreed with the following statement "my therapy/therapies were able to manage my ALL symptoms" and all identified similar side effects of treatment. Extreme fatigue was the highest ranked side effect of treatment with all patient respondents being impacted to some degree. In addition to fatigue, the highest ranking side effects also included pain, infections/non-cancer illness, and fertility and sexual side effects. According to the patient advocacy group, no patients or caregivers had any knowledge of the drug under review.

Provincial Advisory Group (PAG) Input

Input was obtained from seven provinces (Ministries of Health and/or cancer agencies) and federal drug program participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Whether there are data for use in pediatric ALL
- Clarity on whether treatment is for patients with first relapse, second relapse, or either
- For patients with Philadelphia chromosome positive ALL, clarity that treatment is with oral tyrosine kinase inhibitors first, then inotuzumab ozogamicin or vice versa
- For patients with Philadelphia chromosome negative ALL, appropriate sequencing of inotuzumab ozogamicin and blinatumomab

Economic factors:

- Drug wastage
- Amount of drug extracted from one vial
- Resources to monitor for and treat serious adverse events

Registered Clinician Input

Three clinician inputs were provided: two from individual oncologists and one group input from four oncologists.

The clinicians providing input indicated that the current treatments for relapsed ALL is re-treatment with multi-agent chemotherapy regimens used in first-line and that the regimens are quite toxic and often ineffective. They noted that inotuzumab ozogamicin has better response than chemotherapy and compared to blinatumomab, a better administration schedule and tolerability.

Summary of Supplemental Questions

Objective

To evaluate the clinical effect of inotuzumab ozogamicin when compared with blinatumomab in patients with relapsed/refractory ALL. Blinatumomab is another monoclonal antibody treatment available in Canada for patients with relapsed/refractory ALL. It is the interest of both clinical review and economic review that these two similar drugs be compared to each other.

Findings

No direct head-to-head study comparing inotuzumab ozogamicin (InO) to blinatumomab (Blina) was identified. A technical report of indirect treatment comparison using the INO-VATE ALL study in InO and the TOWER study in Blina was submitted.

Summary

A standard indirect comparison was not appropriate since the baseline characteristics of patients in the control arm were different in several important categories, such as the number of prior stem transplants, number of salvage therapies, and that patients with Philadelphia positive ALL were excluded from the TOWER study[2,23]. Alternative statistical approaches were used in order to address the imbalance in control arms. Matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) were used in the technical report. Each approach presents its own strengths and limitations. MAIC depends on the comparability of the data. The less comparable the data were, the smaller the effective sample size, which leads to greater uncertainty. STC depends on the accurate modeling of the predictive equations and the quality of the input parameters. Results from both approaches were presented for comparison.

The effective sample size was reduced by 50% in most outcomes in the MAIC analysis suggesting a limited overlap of the population in the two RCTs[24]. The loss of a large percentage of effective sample size also introduced a large amount of uncertainty in the results. The results presented in both MAIC and STC were similar. The indirect comparison showed that greater number of patients receiving InO had completed remission or completed remission with incomplete hematological recovery and had a higher stem cell transplant rate. The result was not statistically significant in OS or event-free survival (EFS)[24].

The method presented in the technical report was appropriate and the assumptions were reasonable. In the absence of direct comparison study, and limited comparable indirect data, MAIC and STC can be a useful tool to adjust for baseline imbalance and produce a reasonable prediction of the difference between InO and blaintumomab for economic modeling. As for clinical evaluation, this analysis should only be considered as hypothesis generating.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

[Table 2]: Assessment of generalizability of evidence for inotuzumab ozogamicin for ALL

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(INO-VATE)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>Performance Status</td><td>Patients in the INO-VATE trial had to have ECOG ≤2 to be eligible.

<table><tr><th>ECOG PS</th><th>Inotuzumab Ozogamicin</th><th>Investigator's Choice of Chemotherapy</th></tr><tr><td>0</td><td>62 (37.8)</td><td>61 (37.7)</td></tr><tr><td>1</td><td>81 (49.4)</td><td>80 (49.4)</td></tr><tr><td>2</td><td>21 (12.8)</td><td>20 (12.3)</td></tr></table></td><td>Can the trial results be generalized to patients who have ECOG ≥3?</td><td>The results of the INO-VATE trial cannot be generalized to patients with ECOG ≥3.</td></tr>
<tr><td>Age</td><td>• Patients enrolled in the INO-VATE trial had to be 18 years of age or older.
• The median age of patients in the INO-VATE trial was 47 years and 60% of patients were under the age of 55.</td><td>Does the age restriction in the trial (i.e., patients older than 18 years) limit the interpretation of the trial results with respect to the target population?

Can the trial results be generalized to the pediatric population?</td><td>The results of the INO-VATE ALL trial cannot be generalized into the pediatric age range.</td></tr>
</table>

Domain	Factor	Evidence (INO-VATE)	Generalizability Question	CGP Assessment of Generalizability
	Metastatic Sites	Patients with active CNS, extramedullary, including testicular involvement were excluded from the INO-VATE trial.	Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population? Can the results be generalized to patients with CNS metastases?	Patients with active extramedullary disease were excluded from the INO-VATE trial. The results of this trial cannot be extrapolated into this group. If extramedullary disease can be cleared in another way (intrathecal chemotherapy, testicular radiation) the patient may be considered for treatment with inotuzumab ozogamicin.
	Line of therapy and Sequencing	PAG requested guidance on the following clinical scenarios: • Clarity on whether treatment is for patients with first relapse, second relapse, or either • Primary refractory • patients currently receiving salvage chemotherapy but not tolerating or responding • patients who had three prior lines of therapy, prior to the availability of inotuzumab ozogamicin • patients currently receiving therapy in first or second relapse and who haven't achieved a CR, where a CR is desired as a bridge to a transplant • Patients who have relapsed after a stem cell transplant • Patients being treated with blinatumomab but have not yet progressed, whether it is reasonable to switch to	Are the results of the INO-VATE trial generalizable to these patients?	Patients with relapsed/refractory B-cell ALL were eligible for the INO-VATE trial. Subgroup analysis of this study confirmed that all subgroups appeared to benefit more from treatment with inotuzumab ozogamicin than with investigator's choice. This includes patients with high-risk features and those with more advanced disease. Patients benefiting from their current line of therapy should not be

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(INO-VATE)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>inotuzumab ozogamicin given the easier administration schedule
• For PH+ ALL patients, do they have to fail at least one line of a second generation TKI to be considered for INO?</td><td></td><td>switched to InO for convenience of administration.</td></tr>
<tr><td></td><td>Karyotype</td><td><table><tr><th>Karyotype</th><th>Inotuzumab Ozogamicin</th><th>Investigator's Choice of Chemotherapy</th></tr><tr><td>Ph-</td><td>14 (13)</td><td>18 (17)</td></tr><tr><td>Ph+</td><td>22 (13.4)</td><td>28 (17.3)</td></tr></table>
Patients with Philadelphia positive and Philadelphia negative ALL were included in the study.</td><td>Are the results generalizable to patients with Philadelphia chromosome negative and chromosome positive ALL?</td><td>Yes. Patients with high-risk karyotypes appear to benefit from inotuzumab ozogamicin.</td></tr>
<tr><td>Comparator</td><td>Standard of Care</td><td>The treatment regimen of investigator's choice of chemotherapies in the INO-VATE trial included: FLAG, Cytarabine and mitoxantrone (MXN/Ara-C), and HIDAC.

The comparator in the pharmacoenoncomic evaluation was HYPER-CVAD.

Blinatumomab for Philadelphia chromosome negative ALL.</td><td>Were the comparators in the trial a standard of care in Canada?

Is the comparator in the pharmoeconomic evaluation a standard of care in Canada?</td><td>Yes. All of these regimens, including HYPER-CVAD are used in Canada.</td></tr>
</table>

Domain	Factor	Evidence (INO-VATE)	Generalizability Question	CGP Assessment of Generalizability
Setting	Location of the participating centres	The average number of days in hospital during treatment with INO in the INO-VATE trial was 10 days in the U.S. and 18 days in the EU.	If the trial was conducted only in academic centres are the results applicable in the community setting?	In Canada most patients with ALL are treated in specialized centers. These centers are capable of administering InO and intensive chemotherapy regimens. All would be familiar with appropriate monitoring for adverse effects.
	Supportive medications, procedures or care	Defibrotide was administered in the INO-VATE trial in some pateints who underwent stem-cell transplantation. Of the 48 patients in the inotuzumab ozogamicin group who underwent stem-cell transplantation after the trial, 10 had veno-occlusive disease after transplantation, and 3 of these 10 patients had also received a transplant before the trial. Seven of these 10 patients received defibrotide; 2 of these 7 patients had resolved disease, 4 had ongoing disease, and 1 died.[2]	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	Defibrotide is available for use in Canada. However, the use of defibrotide to manage veno-occlusive disease was not considered in the submitted pharmacoeconomic analysis. The cost of acute liver failure was resepresented as best supportive care in the ecomomic analysis. It is the opinion of the CGP that the efficacy of defibrotide is unclear; however the efficacy and effectiveness of defibrotide was out of scope for this review.

1.2.4 Interpretation

Inotuzumab ozogamicin (InO) is an antibody-drug conjugate consisting of an anti-CD22 monoclonal antibody and calicheamicin. InO has shown clinical activity in B-cell non-Hodgkin lymphoma and in pre-B acute lymphoblastic leukemia (ALL).

The efficacy of InO in pre-B ALL was assessed in a multicenter randomized trial in which it was compared with investigator's choice of therapy (INO-VATE ALL).[2] Treatment allocation was not blinded but the primary outcomes (complete response and overall survival) were evaluated by an Endpoint Adjudication Committee (EAC) that was unaware of the treatment given. Based on the EAC outcome analysis, patients who received InO were significantly more likely to enter complete remission (mean difference in rate of complete remission 51.4%, p<0.001). Remission rates were higher with InO across all subgroups evaluated (first vs. second salvage, age </> 55, pre-study HCT vs. no pre-study HCT) except patients with t(4;11).[2,20,22] Remissions in the InO group were more likely to be negative for measurable residual disease than remissions in the standard care arm (76.7% vs. 38%, p<0.0001).[8,20] A greater proportion of patients in the InO group received definitive therapy with hematopoietic cell transplantation (47% vs. 20.4%),[22] although it is unclear whether the difference in HCT rates explains the improved survival noted in the InO group.

Event-free survival (defined as survival in ongoing complete remission without a requirement to change treatment because of deterioration in health, performance of HCT while not in CR/CRi or requirement to start a new induction therapy) appeared superior among patients who received InO compared with those who received investigator's choice chemotherapy (5 month vs. 1.7 months, HR 0.45 (97.5% CI 0.34-0.61, p<0.001)).[5,20] Using the standard definition of progression-free survival the stratified HR of PFS was 0.568 (97.5% CI 0.401-0.804, p=0.001); the median PFS was 5.6 months in the InO arm vs. 3.7 months in the standard treatment arm. Overall survival did not differ between the groups once corrections were made for multiple comparisons.[2,20] The difference in PFS was clinically meaningful and a small subset (approximately 20%) of patients treated with InO enjoyed very long survival: Patients who survived for more than 14 months from the start of treatment were likely cured.

The harms associated with InO were similar to those of investigator's choice. Adverse events were seen in the majority of patients and in general did not differ between groups. The most common grade III/IV adverse events in either group were cytopenias, although these were more common among the standard care patients than the InO patients (grade III/IV thrombocytopenia 40.9% vs. 59.4%, grade III/IV febrile neutropenia 26.8% vs. 53.8%). Liver-related adverse events were more common in the patients who received InO and hepatic venoocclusive disease was observed up to two years post-randomization and occurred in 11% vs. 2% of the inotuzumab vs. the standard treatment patients, respectively.[20]This was most commonly seen in patients who had undergone HCT previously, or in those who would go on to receive an HCT following treatment with InO. More patients who received InO required temporary treatment discontinuation to deal with adverse events and more of these patients withdrew due to adverse events.

- The Provincial Advisory Group (PAG) commented on the pCODR Expert Review Committee's (pERC's) Initial Recommendation noting that veno-occlusive disease is more common with the use of inotuzumab ozogamicin, especically in patients who received an stem cell transplant. PAG noted that defibrotide may be required to treat VOD. Thus, PAG requested clarification on whether the management of VOD with the potential use of defibrotide was taken into consideration.

- In response to PAG's feedback, the CGP acknowledge that defibrotide is available for use in Canada to manage veno-occlusive disease. However, the use and cost of defibrotide to manage veno-occlusive disease was not considered in the submitted pharmacoeconomic analysis. Rather, the cost of acute liver failure was resepresented as best supportive care.

- The burden of relapsed/refractory ALL on individuals and society is out of keeping with its prevalence. Treating patients with this condition is resource-intensive and requires frequent hospital admissions for treatment of febrile neutropenia and other complications, intensive outpatient supportive care with blood and platelet transfusions and, if not curable, administration of palliative chemotherapy. Patients with this condition are frequently young, often in their prime earning years, with a spouse who has to take time out from the workplace to act as caregiver. In this context the clinically significant differences in the subcategories of the EORTC-QLQ-C30 health-related quality of life favouring patients who received InO in the trial become especially meaningful. Patients in InO arm had a clinically signficant score in physical functioning (75.0 vs. 68.1, p=0.0139), role functioning (64.7 vs. 53.4, p=0.0065) and social functioning (68.1 vs. 59.8, p=0.0336).

1.3 Conclusions

In view of the above, the Clinical Guidance Panel has concluded that there **is a net clinical benefit** from treatment with InO in patients with relapsed or refractory CD22+ pre-B ALL compared to chemotherapy. This opinion is based on its high rate of clinical effectiveness (PFS and response rates) and a manageable rate of adverse events in a high-risk patient population as demonstrated in the phase 3 RCT INO-VATE ALL trial. The superior quality of life in patients treated with InO compared to chemotherapy aligns with values of the patient advocacy group and input from registered clinicians. The simpler administration protocol of InO (shorter infusion time) that may not require hospitalization of patients is in keeping with the input received from the Provincial Advisory Group. In reaching this conclusion the Panel considered the following:

- The majority (73%) of responders achieved complete remission or complete remission with incomplete hematologic recovery with their first cycle of treatment.
- The only subgroup of patients that did not appear to benefit from treatment with InO was the group of patients with the adverse t(4; 11) translocation. The Panel felt that as other high-risk patient groups (such as those with prior HCT or the Philadelphia chromosome positive) appear to benefit from InO and given that there were only three patients with t(4; 11) in the InO cohort the subgroup analyses were underpowered to draw firm conclusions in this regard. This should not be viewed as a criterion on which to deny a patient treatment with InO.
- The submitter has provided a clinically relevant indirect comparison of blinatumomab and InO[24,25] in order to clarify whether there exists a basis to choose one agent over the other. Given the significant differences in the starting populations of the blinatumomab and InO groups and the resulting substantial reduction in the sample size once non-overlapping patient subsets were excluded the Panel believes this comparison is hypothesis generating and is insufficient by itself to settle the question.

2 BACKGROUND CLINICAL INFORMATION

Acute Lymphoblastic Leukemia (ALL) is a highly-aggressive hematological malignancy that presents with signs or symptoms of bone marrow failure (fatigue, dyspnea, bleeding, bruising or infection),

organ infiltration (lymph nodes or central nervous system (CNS)) and systemic complaints (chiefly fevers, fatigue and night sweats). Patients typically present to hospital acutely ill, often with infection in neutropenia, electrolyte disturbances related to tumour lysis syndrome or with neurological abnormalities. The majority of patients have circulating blast at presentation and the diagnosis is confirmed by bone marrow histology and ancillary tests like flow cytometry and immunohistochemistry.

ALL represents the most common malignancy of childhood and with modern treatment protocols pediatric ALL is curable in as many as 90% of cases.[26] ALL represents approximately 15% of adult cases of acute leukemia and adult treatment protocols are based largely on the principles that led to successful outcomes in children. These principles include the use of sequential multi-drug combinations for remission induction. Agents with activity in ALL induction include corticosteroids, cyclophosphamide, methotrexate, anthracyclines and L-asparaginase. Early application of CNS-directed therapy by direct intrathecal administration and whole-brain radiotherapy is intended to address occult CNS disease.[27] Intensification and maintenance phases may last up to 30 months with some protocols and impose significant personal and financial burdens on affected patients and their families.

2.1 Accepted Clinical Practice

A number of factors determine prognosis in ALL. Traditionally, age and cytogenetics have been viewed as the most important prognostic factors in ALL.[28] Newer treatment protocols, however, have proven effective across the spectrum of cytogenetic abnormalities and seem to have abrogated some of the risk associated with high-risk cytogenetics in this disease.[29,30] The presence of the Philadelphia chromosome (which results from a balanced translocation between chromosomes 9 and 22) confers sensitivity to tyrosine kinase inhibitors and while Philadelphia-positive ALL is not curable with conventional treatment the use of TKI's can be associated with durable remissions and good quality of life. In general, however, patients with Philadelphia-positive ALL are still considered for allogeneic hematopoietic cell transplantation in first complete remission.[31] Patients who present with an increased white blood cell count (WBC > 30 x 109/L for B-Cell and > 100 x 109/L for T-Cell) and those over age 34 are at higher risk of adverse outcomes, and patients with both of these risk factors or who fail to achieve complete remission within four weeks of starting treatment are considered for allogeneic HCT in first remission.[30]

The majority of young patients with ALL can expect favourable outcomes with modern chemotherapy protocols. For instance, Storring et al. reported the results of their experience using a modified version of the Dana-Farber Cancer Institute protocol at the Princess Margaret Hospital. This pediatric-inspired protocol resulted in 89% of patients achieving a complete remission, and five-year relapse free survival of 71% was reported.[32] Population-based studies, however, continue to show that the majority of adult patients with ALL with die from their disease.[33] In contrast to initial treatment, where the standard approach is pediatric-inspired protocols, there is no standard treatment for patients with relapsed or refractory ALL. In general patients receive an intensive chemotherapy regimen to induce a remission and, if possible, proceed to an allogeneic hematopoietic cell transplant.[34] Multi-agent chemotherapy regimens appropriate in the Canadian setting may include but are not limited to Hyper-CVAD, FLAG-IDA or Cy VP16. Patients who fail reinduction or for whom HCT is not feasible due to comorbidities or lack of donor have no curative options and are treated with palliative intent. Survival of this cohort of relapsed/refractory patients is limited.

Blinatumomab is a first-in-class bispecific T-Cell engaging (BiTE) antibody with sites to engage CD19 expressed on B-ALL tumour cells and CD3 on T-Lymphocytes. By bringing these two cell types into close approximation a T-Cell mediated immune response is simulated, which results in clearance of malignant cells by the redirected immune system. In 2015, pERC recommended

reimbursement of blinatumomab for adult patients with Ph negative relapsed or refractory B precursor ALL and who have had at least two prior lines of systemic therapy based on evidence from two phase II non-randomized interventional trials (MT 103-211 and MT 103-206).[35,36] However, pERC did not recommend reimbursement in adult patients with Philadelphia Ph- relapsed or refractory B precursor ALL and who have had only one prior systemic chemotherapy, because it was unable to assess the magnitude of benefit of blinatumomab compared to combination chemotherapy in regard to outcomes such as rates of allogeneic stem cell transplant, overall survival, relapse free survival, toxicities, and quality of life. In 2017, a resubmission of blinatumomab based on the results of the TOWER study,[23] evaluating blinatumomab for the treatment of all adult patients with Ph- relapsed or refractory B-precursor ALL including those who have had one prior line of therapy was reviewed by pCODR. At that time, pERC recommended reimbursement of blinatumomab for all adult patients with Ph- relapsed or refractory B-precursor ALL including those who have had one prior line of therapy (i.e., adult patients who are refractory or patients who are in first or later relapse). However, it is currently not publically reimbursed in all jurisdictions in Canada.

2.2 Evidence-Based Considerations for a Funding Population

The management of B-Cell non-Hodgkin lymphoma was revolutionized by the introduction of monoclonal anti-CD20 antibodies into clinical practice. These agents however show only limited activity in ALL. Inotuzumab ozogamicin is the first antibody-drug conjugate to show activity in B-cell ALL. Inotuzumab targets the CD22 antigen expressed on a wide range of hematological malignancies. When inotuzumab ozogamicin administered to preclinical models of CD22+ hematological malignancies (follicular and large B-cell lymphomas) high rates of complete response are observed.[37] Similar results were observed in a phase I/II study of this agent in patients with non-Hodgkin lymphoma.[38] A single-center phase II study of inotuzumab ozogamicin in patients with relapsed-refractory CD22+ ALL demonstrated an overall response rate of 57% (CR 18%, marrow CR 39%) with acceptable rates of toxicity, including raised levels of bilirubin and ALT.[39] A randomized, open-label phase III study comparing inotuzumab ozogamicin with standard chemotherapy in patients with relapsed-refractory B-cell ALL demonstrated a higher rate of complete remission ((80.7% (95% CI 72.1-87.7) vs 29.4 (95% CI 21.0-38.8) months, p<0.001) and improved progression-free (5.0 (95% CI 3.7-5.6) vs. 1.8 (95% CI 1.5-2.2) months, HR 0.45 (0.45 (95% CI 0.34-0.61), p<0.001)) and overall (7.7 (95% HR 6.0-9.2) vs. 6.7 (95% CI 4.9-8.3) months, HR 0.77 (95% CI 0.58-1.03), p=0.04) survival. The use of inotuzumab ozogamicin allowed a greater proportion of patients to proceed to definitive therapy with hematopoietic cell transplantation than did standard chemotherapy (41% vs. 11%, p<0.001).[28]

Compared to blinatumomab, inotuzumab ozogamicin includes treatment of patients with both Ph-positive and Ph-negative karyotypes and is easier to administer in the outpatient setting for patients, pharmacy and nursing staff. Furthermore, there appears to be less acute infusion related reactions and no reported incidence of cytokine release syndrome with the use of inotuzumab ozogamizin.

2.3 Other Patient Populations in Whom the Drug May Be Used

None.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Input on inotuzumab ozogamicin (Besponsa) for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) was provided by The Leukemia & Lymphoma Society of Canada (LLSC). Input provided by LLSC is summarized below.

The information was collected through two online surveys that were posted using Survey Monkey. The first survey was distributed by LLSC staff to patients with ALL to determine their experience dealing with ALL and how therapy has impacted their daily lives. The link to the survey was also distributed to patients through email. There were seven respondents; two patients currently receiving treatment (two females) and five patients currently not receiving treatment (three males and two females). According to LLSC, none of the patients or caregivers surveyed had any knowledge of the drug.

The second online survey was distributed by healthcare professionals and LLSC staff asking for input from current and previous caregivers of patients with ALL. LLSC received input from nine respondents (89% female), all of whom are caregivers for patients that are currently receiving treatment.

Both surveys asked questions about the drug inotuzumab ozogamicin, including whether or not patients or caregivers had heard about the drug, expectations they had about the drug, and what symptoms were most important to them for the drug to manage. According to LLSC, no patients or caregivers had experience with the drug.

Below are tables describing the demographics of respondents who participated in survey 1 and 2:

Survey #1 – Patient Age Range (7 respondents)

Age at Diagnosis	Number of Patients
19 and younger	0
20-29	1
30-39	1
40-49	3
50-59	1
60-69	1
70-79	0
80 and older	0

Survey #2 –Caregiver Age Range (9 respondents)

Age Range	Number of Caregivers
19 and younger	0
20-29	1
30-39	0
40-49	6
50-59	2
60-69	0
70-79	0
80 and older	0

In addition to the surveys, a one-on-one interview with one male patient who was diagnosed with B-cell precursor ALL three times was conducted. The patient discussed his diagnosis and subsequent relapses and how the disease has impacted their life. The discussion was used to substantiate the information gathered in the first survey and provide thorough evidence regarding the effects of an ALL diagnosis.

In brief, LLSC received a total of 16 responses from the online surveys (seven patients and nine caregivers), and supported these findings with one one-on-one interview with a patient with ALL. The 16 responses were from across the country (British Columbia, Alberta, Manitoba, Ontario, Newfoundland, and Nova Scotia). LLSC submits that although they realize this a small sample, since this is a rare disease and there was a great degree of similarity in people's responses, LLSC thinks this information still has value to the pCODR process.

From a patient perspective, a diagnosis of ALL results in many disruptions to their daily lives including emotional and physical symptoms. Caregivers experience a huge emotional impact from their loved one going through cancer as well as a complete lifestyle change from the time spent caring for their loved one. The physical symptoms of ALL experienced by all patient respondents to some degree include loss of appetite/and or weight loss, fever/night sweats, fatigue, pain, bruising and/or bleeding, feeling dizzy/light headedness, rashes, numbness and tingly, and other (trauma). Emotional symptoms include anxiety, stress, depression, and a feeling of being overwhelmed (ratings which were considered quantitatively significant). LLSC noted that the four standard treatments for adult patients with ALL are: chemotherapy, radiation therapy, chemotherapy with stem cell transplant (for patients who do not respond to chemotherapy), and targeted therapy. LLSC reported that six out of seven patients stated they strongly disagreed with the following statement "my therapy/therapies were able to manage my ALL symptoms" and all identified similar side effects of treatment. According to LLSC, extreme fatigue was the highest ranked side effect of treatment with all patient respondents being impacted to some degree. In addition to fatigue, the highest ranking side effects also included pain, infections/non-cancer illness, and fertility and sexual side effects. LLSC learned first-hand how important it is to have better treatment options with less side effects. According to LLSC, no patients or caregivers had any knowledge of the drug under review.

Please see below for a summary of specific input received from LLSC. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Acute Lymphoblastic Leukemia

According to LLSC, acute lymphoblastic leukemia (ALL) is one of the major types of leukemia, a rapidly progressing cancer of the bone marrow and blood. ALL results from either an acquired or genetic injury to the DNA of a developing cell in the bone marrow. When a marrow cell becomes a leukemia cell, the cell multiplies uncontrollably, these cells are known as "leukemic blasts". The presence of these cells blocks the production of normal cells and results in lowering the number of healthy cells. The term "acute" means that the leukemia can progress very quickly, and if not treated quickly, could be fatal within a few months.

According to LLSC, symptoms of ALL are indicative of the reduced production of functional blood cells. These symptoms can include fever, increased risk of infection (especially bacterial infections like pneumonia or neutropenia; symptoms of such infections include shortness of breath, chest pain, cough, and vomiting), increased tendency to bleed (due to thrombocytopenia), anemia, fatigue, and headache. Physical symptoms experienced by patients with ALL often disrupt daily routines and everyday things become more challenging. One respondent equated the challenges of navigating daily routines as having "*a consistent bad hangover or flu*."

LLSC asked patients to rank the following emotional symptoms (anxiety, stress, depression, feeling overwhelmed, and changes in eating habits) of their cancer diagnosis on a scale of 1 (extremely

unimportant) to 7 (extremely important), with 4 or more being quantitatively significant. The following symptoms received a rating of 4 or higher (ratings represent the average rating from all patients):

- anxiety (6.14)
- stress (5.57)
- depression (4.43)
- a feeling of being overwhelmed (5.57)

According to LLSC, all patients indicated that as a result of their diagnosis, they experienced many disruptions to their daily lives. All patients indicated that ALL impacted their "physical functioning" specifically through chronic fatigue and brain fog with one patient claiming that her "*life changed; my new job was treatment… going to daycare, checking blood, chemo or transfusion*". All patients indicated that ALL impacted their "daily routines" such as sleeping and errand running. One patient stated that he had "*not slept properly in over a decade*." All patients indicated that ALL impacted their "financial situation" adversely. With respect to "loss of intimacy", six patients (86%) reported loss of sexual interest and drive. One patient stated that they "*did not have sex for two years*."

Common symptoms of ALL such as loss of appetite/and or weight loss, fever/night sweats, fatigue, pain, bruising and/or bleeding, feeling dizzy/light headedness, rashes, and other (trauma) were experienced in some degree by all patient respondents. Each respondent ranked all the symptoms they were experiencing on a scale of 1 (unimportant) to 7 (extremely important), with 4 or more being quantitatively significant.

Symptom	Percentage of total patients who ranked 4+
Loss of appetite and/or weight loss	42%
Fever/night sweats	28%
Fatigue	42%
Pain	50%
Bruising and/or bleeding	28%
Feeling dizzy/light headedness	42%
Rashes	28%
Numbness and tingling	0%
Other*	14%

*trauma (1 respondent)

3.1.2 Patients' Experiences with Current Therapy for Acute Lymphoblastic Leukemia

LLSC states that while 80-90% of adult patients with ALL will be in complete remission at some point during treatment, about half will relapse. This makes the 5-year survival rate 40%. According to LLSC, the four standards treatment for adult ALL are: chemotherapy, radiation therapy, chemotherapy with stem cell transplant (for patients who do not respond to chemotherapy), and targeted therapy. Treatment is spread over three phases, lasting two years on average. The treatment is usually quite intense, especially during the first phase. The three phases are induction, consolidation (also called "intensification"), and maintenance. Consolidation and maintenance are given after remission.

According to LLSC, two patients surveyed are currently receiving treatment and are in the first phase (induction therapy), one identified that they are currently receiving the Dana Farber consortium protocol (DFCP). Of the five patients who indicated they are no longer receiving treatment, all had received chemotherapy, two had received radiation in addition to

chemotherapy, one had received both chemotherapy and surgery, and one had received chemotherapy and a bone marrow transplant. Numerous chemotherapy drugs were mentioned and included: Doxorubicon, Vincristine, Dexmethasone, Methothrexate, Mercaptopurine, Thiagunine, Ara C, Prednisone, Cyclosphosphamide, Cytarabine, Daunorubican and CNS treatment.

Six out of seven patients stated they strongly disagreed with the following statement "my therapy/therapies were able to manage my ALL symptoms" and all identified similar side effects of treatment.

According to LLSC, chemotherapy affects tissues that normally have a high rate of cell turnover. Therefore, the lining of the mouth, the intestines, the skin and the hair follicles may be affected. Most AML side effects are temporary and subside once the body adjusts to therapy, but some can have long term effects. One patient felt as if the drugs had castrated him and he had "*zero sex for years"*. Another reported joint damage, muscle loss, intimacy issues and numbness and tingling. The most common side-effect of current treatment was identified as fatigue. One patient stated that even though he had been in remission for two years, he "*does not have the physical stamina"* he once had. Another stated that she "*struggled with fatigue during her treatments and for many years following"*.

The highest ranked side effects experienced by the patient sample were:

- Pain
- Fatigue
- Infections/non-cancer illness
- Fertility and sexual side effects

Extreme fatigue was the highest ranked side effect of treatment with all patient respondents being impacted to some degree. In the majority of cases, patients emphasized that they did not have the "physical stamina" they once had. Other side effects mentioned included erectile dysfunction, joint pain, "foot drop", and weight gain.

3.1.3 Impact of Acute Lymphoblastic Leukemia and Current Therapy on Caregivers

LLSC submits that caregivers are essential components of a patient's treatment and recovery. A diagnosis of blood cancer dramatically affects the lives of families and all others who have a relationship with the patient. All of the caregivers who responded to this survey are caring for an immediate family member. These caregivers are a vital extension of the healthcare team and provide emotional and physical support to those suffering from the disease.

Of the nine caregivers surveyed, five indicated that they were caring for a child, three for a spouse/partner, and one for a parent. The survey identified that four of the nine patients were diagnosed with B-cell precursor ALL and that all are currently receiving treatment.

All of the caregivers' surveys expressed some degree of a negative emotional response to their loved one's diagnosis and all had their daily lives/routines severely impacted. In many cases, the emotional response and toll on the caregiver was quite severe. Many stated that they found the cancer experience to be overwhelming and that they "were filled with sadness". One caregiver compared her patient's cancer journey to an amusement park ride stating that they "*are on the world's roughest roller coaster that goes upside down and all over, but without any seatbelts or harnesses….just trying to hang on*". Every facet of life is impacted when caring for a person with cancer and this can result in caregivers "feeling trapped/like a prisoner."

The survey asked caregivers to rank on a scale of 1 (extremely unimportant) to 7 (extremely important), which of the following emotional impacts has the cancer diagnosis and treatment had on their person.

Emotional Impact	Average ranking
Anxiety	6.0
Heightened Stress	6.5
Depression	4.8
Being overwhelmed	6.0
Eating habits	5.4

All caregivers identified challenges in balancing work, family duties (childcare, household maintenance) but maintained that the stress and anxiety of caring for their loved ones was the greatest impact.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Inotuzumab Ozogamicin

One patient surveyed identified as being diagnosed with B-cell precursor ALL. During the one-on-one interview of a patient respondent that had been diagnosed with B-cell precursor ALL three times, LLSC learned first-hand how important it is to have better treatment options with less side effects. LLSC submits that since the survival rate of the disease is so low, symptoms of the disease have to be better managed with drugs that do not adversely impact quality of life. According to this patient, fewer side effects would "*allow him to feel less different and less excluded from the population*".

These patients then responded to questions regarding their expectations for the drug. When asked "what are the most important cancer symptoms for Besponsa to control" the common responses were:[*]

- Fatigue (75% of respondents)
- Pain (50% of respondents)

[*]According to LLSC, five patients answered this question and three skipped this question.

3.2.2 Patient Experiences to Date with Inotuzumab Ozogamicin

According to LLSC, none of the patients or caregivers surveyed had any knowledge of the drug.

3.3 Additional Information

LLSC submits that inotuzumab ozogamicin is indicated for the treatment of adults with relapsed or refractory B-cell precursor ALL whose cancer has not responded to initial treatment or has returned after treatment, and when life expectancy is typically low. LLSC indicated that inotuzumab ozogamicin is an antibody-drug conjugate administered as an IV infusion over a one-hour period. B-Cell ALL is a type of leukemia that affects B lymphocytes, white blood cells that grow in the marrow. The quick reproduction of B lymphocytes can cause infection, anemia, and easy bleeding. LLSC submits that sometimes these cells move from the bone marrow into the central nervous system (brain and spinal cord) through the bloodstream, spreading to other organs. Relapse occurs when patients achieve remission but then have a decreased number of

normal blood cells and a return of leukemia cells in the marrow. For the half of patients that relapse after treatment, these patients have residual leukemic cells in their marrow even after intensive treatment (refractory leukemia).

LLSC submits that the drug under review has been approved by both the FDA and the European Commission. The US carries a black box warning of the risk of the drug causing liver toxicity, in particular hepatic veno-occlusive disease (VOD), which has been fatal in some people. The risk of this is higher in people who take the drug before having hematopoietic stem cell transplantation (HSCT) and more people die who have HSCT following treatment with this drug, than people who have HSCT taking other chemotherapies. The risk gets higher as more rounds of treatment with inotuzumab ozogamicin are administered.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from seven provinces (Ministries of Health and/or cancer agencies) and federal drug program participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Whether there is data for use in pediatric ALL
- Clarity on whether treatment is for patients with first relapse, second relapse, or either
- For patients with Philadelphia chromosome positive ALL, clarity that treatment is with oral tyrosine kinase inhibitors first, then inotuzumab ozogamicin or vice versa
- For patients with Philadelphia chromosome negative ALL, appropriate sequencing of inotuzumab ozogamicin and blinatumomab

Economic factors:

- Drug wastage
- Amount of drug extracted from one vial
- Resources to monitor for and treat serious adverse events

Please see below for more details.

4.1 Currently Funded Treatments

Currently, there is no standard of care for second relapse of Philadelphia chromosome negative ALL in adults. FLAG, high dose Ara-C, cytarabine/mitoxantrone, or other multi-agent chemotherapy may be used.

For Phildelaphia chromosome negative ALL, which is the majority of patients, blinatumomab is the standard of care and would be the appropriate comparator.

4.2 Eligible Patient Population

There is an unmet need for this group of patients and younger patients often seek further treatments. PAG noted that the funding request is for patients with Philadelphia chromosome negative and positive, B precursor ALL who have had one to two prior lines of treatment. PAG noted that the use of inotuzumab ozogamicin in previously untreated ALL and patients with Burkitt's lymphoma would be considered out of scope of the funding request.

PAG is seeking clarity on the patient group who would be eligible for inotuzumab ozogamicin. It would be helpful for implementation to clarify whether inotuzumab ozogamicin is for patients with first relapse or second relapse or either. PAG noted that economic evaluations may be different in each setting and is seeking information on place in therapy and whether there is a preference to use in first relapse or in second relapse.

PAG is seeking clarity on the definition of relapsed and refractory ALL and whether patients who are primary refractory would be considered the same as patients in first relapse and whether patients with Philadelphia chromosome positive ALL must have failed at least one line of a second generation TKI.

In addition, PAG is seeking guidance on whether the following patients would be eligible for treatment with inotuzumab ozogamicin:

- children and adolescents with ALL,
- patients currently receiving salvage chemotherapy but not tolerating or responding,
- patients who had three prior lines of therapy, prior to the availability of inotuzumab ozogamicin,
- patients currently receiving therapy in first or second relapse and who haven't achieved a CR, where a CR is desired as a bridge to a transplant,
- patients who have relapsed after a stem cell transplant.
- Patients being treated with blinatumomab but have not yet progressed, whether it is reasonable to switch to inotuzumab ozogamicin given the easier administration schedule.

4.3 Implementation Factors

PAG indicated that inotuzumab ozogamicin would need to be administered in hospital (in some provinces) or large tertiary care centres that have the resources to monitor and treat serious adverse events that include hepatic veno-occlusive disease. Resources required for in hospital administration and for monitoring adverse events would need to be considered in the economics.

PAG noted that on the pCODR presubmission information, there is one vial size containing 1mg of inotuzumab ozogamicin. However, based on the U.S. prescribing information, 0.9mg is the amount that can be extracted from the vial once reconstituted. This would have an impact on cost and should be included in the economic evaluation.

There are concerns of drug wastage. It is unlikely there will be more than one patient on treatment at any one time, given the low number of adult ALL and the dosed is based on body surface area at either $0.8mg/m^2$ or $0.5mg/m^2$. PAG suggests that the manufacturer consider a second vial strength to minimize drug wastage and improve impact of drug costs.

In addition, as the dose in cycle 2 onwards is based on whether the patient has complete response or not after cycle 1, it is important that the clinicians and the pharmacy staff are clear on the dose being used.

PAG noted that the infusion time is shorter compared to blinatumomab and administration of inotuzumab ozogamicin may not require hospitalization for the majority of patients. PAG also noted that the time and resources required to prepare and administer inotuzumab ozogamicin is less than that required for blinatumomab.

4.4 Sequencing and Priority of Treatments

For Philadelphia chromosome negative ALL, PAG is seeking clarity on the place of therapy of inotozumab ozogamicin and whether it would be for first relapse or second relapse and whether it would be an alternative to treatment with blinatumomab or an additional line of therapy and/or a bridge to transplant independent of first or second relapse. PAG is seeking data on the cost effectiveness of using inotuzumab ozogamicin before or after blinatumomab.

4.5 Companion Diagnostic Testing

CD22 and Philadelphia chromosome are already being tested in ALL. However, MRD negativity is not routinely monitored to assess response.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Three clinician inputs were provided: two from individual oncologists and one group input from four oncologists.

The clinicians providing input indicated that the current treatments for relapsed ALL is re-treatment with multi-agent chemotherapy regimens used in first-line and that the regimens are quite toxic and often ineffective. They noted that inotuzumab ozogamicin has better response than chemotherapy and compared to blinatumomab, a better administration schedule and tolerability.

Please see below for details from the clinician inputs.

5.1 Current Treatment(s) for Acute Lymphoblastic Leukemia

Regimens commonly used for the treatment of relapsed or refractory ALL include: FLAG, cytarabine plus mitoxantrone, high dose cytarabine or hyper-CVAD, and in one province, a pediatric inspired multi-agent chemotherapy regimen based on the Dana Farber Cancer Centre study protocol. The first three regimens were listed in the pivotal trial as comparators to inotuzumab ozogamicin.

One clinician providing input also noted that often the active anthracycline agent has to be omitted as the ceiling dose safe for cardiac function is often exceeded with the original regime from which they relapsed. Hence the regimes are quite toxic and often ineffective.

5.2 Eligible Patient Population

The clinicians providing input indicated that there will be very few patients per year requiring this new treatment but that adult patients with relapsed or refractory CD-22 positive ALL who are either Philadelphia chromosome (Ph)-positive or Ph-negative will be eligible for inotuzumab ozogamicin. This will be a larger patient population than those eligible for blinatumomab, which is limited to Ph-negative patients. However, ALL is a very rare disease to begin with and many are cured by chemotherapy alone or with a stem cell transplant. One clinician in Alberta estimated that less than ten patients who relapse would be eligible for treatment.

The clinicians providing input noted that results of the pivotal trial were underpowered to conclusively show any benefit for patients with t(4;11) translocation.

5.3 Identify Key Benefits and Harms with Inotuzumab Ozogamicin

One clinician indicated that the benefit of this agent is the ability to deliver a better remission (less minimal residual disease) that is longer lived than a repeat of multi-agent chemotherapy, no matter what the regimen. There are some possible toxicities but these are quite manageable and comparable with typical salvage chemotherapy. This can also be administered as an outpatient which typical salvage multi-agent chemotherapy cannot.

Another clinician identified that the key benefit is the high rate of response and complete response compared to standard therapy, with an agent that can be given as an out-patient and with much less acute toxicity like febrile neutropenia that is commonly seen after standard chemotherapy in this situation. Furthermore, even though the median survival does not differ, very importantly there is a significant overall survival benefit with the appearance of a survival plateau approximately 15% higher when compared to standard chemotherapy. This is probably due to two important features: more patients getting to transplant (the only curative modality in this circumstance) in better condition, and with less leukemia (i.e more of the complete

remissions obtained were negative for “minimal residual disease”).

The key disadvantage is the potential for liver toxicity, especially in patients who will go on to receive a transplant, or have previously received a transplant with so-called “double-alkylator” therapy (i.e busulfan with either cyclophosphamide or thiotepa). This is acknowledged to be a risk, but is it really relevant for Canada because most centres in Canada do not use double akylator therapy.

The group of clinicians providing input identified the following benefits and harms:

In the pivotal trial, both first and second salvage-treatment patients who received inotuzumab ozogamicin had a significantly higher rate of remission when compared to the standard therapy (control) group. Among patients with complete remission, patients treated with inotuzumab ozogamicin had a significantly longer duration of remission as well as a higher proportion of individuals with results below the minimal residual disease threshold (0.01% bone marrow blasts). As a result, a significantly higher percentage of patients in the remission-analysis population were able to proceed to transplantation after treatment with inotuzumab ozogamicin versus standard treatment. Inotuzumab ozogamicin also demonstrated an overall survival advantage as well as a superior PFS trend.

Regarding toxicity, inotuzumab ozogamicin patients received fewer platelet transfusions than those in the standard treatment group. Febrile neutropenia was also less common with inotuzumab ozogamicin than with standard therapy. However, inotuzumab ozogamicin was associated with higher rates of veno-occlusive disease (of any grade) when compared to patients who received standard therapy.

5.4 Advantages of Inotuzumab Ozogamicin Over Current Treatments

One clinician providing input identified that most patients with ALL have disease that is quite chemo-sensitive. For the few that relapse, this is clearly not the case and re-treating them with more chemotherapy does not make good clinical sense. There are many treatment and salvage protocols but they all essentially use the same drugs in various doses and schedules. For patients relapsing to chemotherapy, a different modality is required, such as a monoclonal antibody like inotuzumab ozogamicin.

The clinicians providing input noted that there is no direct comparison to blinatumomab but has identified, that when compared to blinatumomab, inotuzumab ozogamicin:

- allows more patients to be eligible as it includes both Ph-positive and Ph-negative karyotypes,
- is easier to administer and more user-friendly in the out-patient setting for patients, staff and pharmacy,
- is simple bolus intravenous infusion as opposed to continuous infusion with frequent pump changes for blinatumomab
- has a higher response rate in a naïve comparison
- has fewer acute infusion related reactions and no reported incidence of cytokine release syndrome.

5.5 Sequencing and Priority of Treatments with Inotuzumab Ozogamicin

Given the indication applied for, inotuzumab ozogamicin would be used as a single agent at first relapse of ALL. Inotuzumab ozogamicin would replace using multi-agent inpatient chemotherapy that is unlikely to work.

One clinician noted that inotuzumab ozogamicin clearly has an improvement over standard chemotherapy. Inotuzumab ozogamicin works with a different mechanism of action than blinatumomab, which would make inotuzumab ozogamicin the preferred agent in certain cases, depending on speed of donor accessibility. Furthermore, inotuzumab ozogamicin would be effective in relapses of ALL that are negative for the "target" seen by blinatumomab (i.e the cell surface marker CD19).

The clinicians providing input noted that sequencing of inotuzumab ozogamicin with newer agents, such as blinatumomab, needs to be determined.

5.6 Companion Diagnostic Testing

No specific companion testing is required other than demonstrating that the "target" for inotuzomab (the cell surface marker CD22) is present on the leukemia cells. This is routinely done as part of standard Flow Cytometry Testing in the diagnosis of ALL across the country (and the vast majority of b linage ALL cases are positive for CD 22).

5.7 Additional Information

One clinician providing input identified that this agent is a breakthrough in a rare disease.

6.1 Objectives

To evaluate the clinical effectiveness of inotuzumab ozogamicin (BESPONSA) on patient outcomes compared with standard therapy in adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

[Table 3]. Selection Criteria

Clinical Trial Design	Published or unpublished RCT
Patient Population	Adult patients with relapsed or refractory B-cell precursor ALL (Ph+ or Ph-)
Intervention	In a 3- to 4-week cycle, give 0.8 mg/m^2 inotuzumab ozogamicin on day 1, then 0.5 mg/m^2 on day 8 and 15, follow by a 7-day treatment-free period. Then depending on the response, the same regimen can be given for the second time or maintained at 0.5 mg/m^2 for the subsequent cycles. Maximum of 6 cycles can be given. Subgroups of interest: • Ph+ vs. Ph- • Age: less than 55 vs. older 55 • Previous transplant vs. no transplant • # of relapses • CD22 expression (less than 90%) vs. greater than 90% • Duration of 1st remission (less than 12 months vs. more than 12 months)
Appropriate Comparators*	Standard chemotherapy • FLAG IDA • RC-HIDAC • HYPER CVAD • High dose cytarabine • High dose Ara-C • Cytarabine/mitoxantrone Blinatumomab (Ph- only)
Outcomes	• Overall survival • Progression-free survival • Complete remission

	• MRD response
	• Quality of life
	• % patient proceed to HSCT
	• Post HSCT survival
	• Grade 3 & 4 adverse events
	  o Grade 3 & 4 hematological toxicities
	• Withdrawal due to adverse events
	• Other adverse effects
	  o veno-occlusive disease
	  o rates of Infection
	  o Cytokine release syndrome rates
	  o Febrile neutropenia

ALL: Acute lymphoblastic leukemia; HSCT: Hematopoietic Stem Cell Transplantation; Ph+ or Ph-: Philadelphia chromosome positive (or negative); RCT: randomized controlled trial	

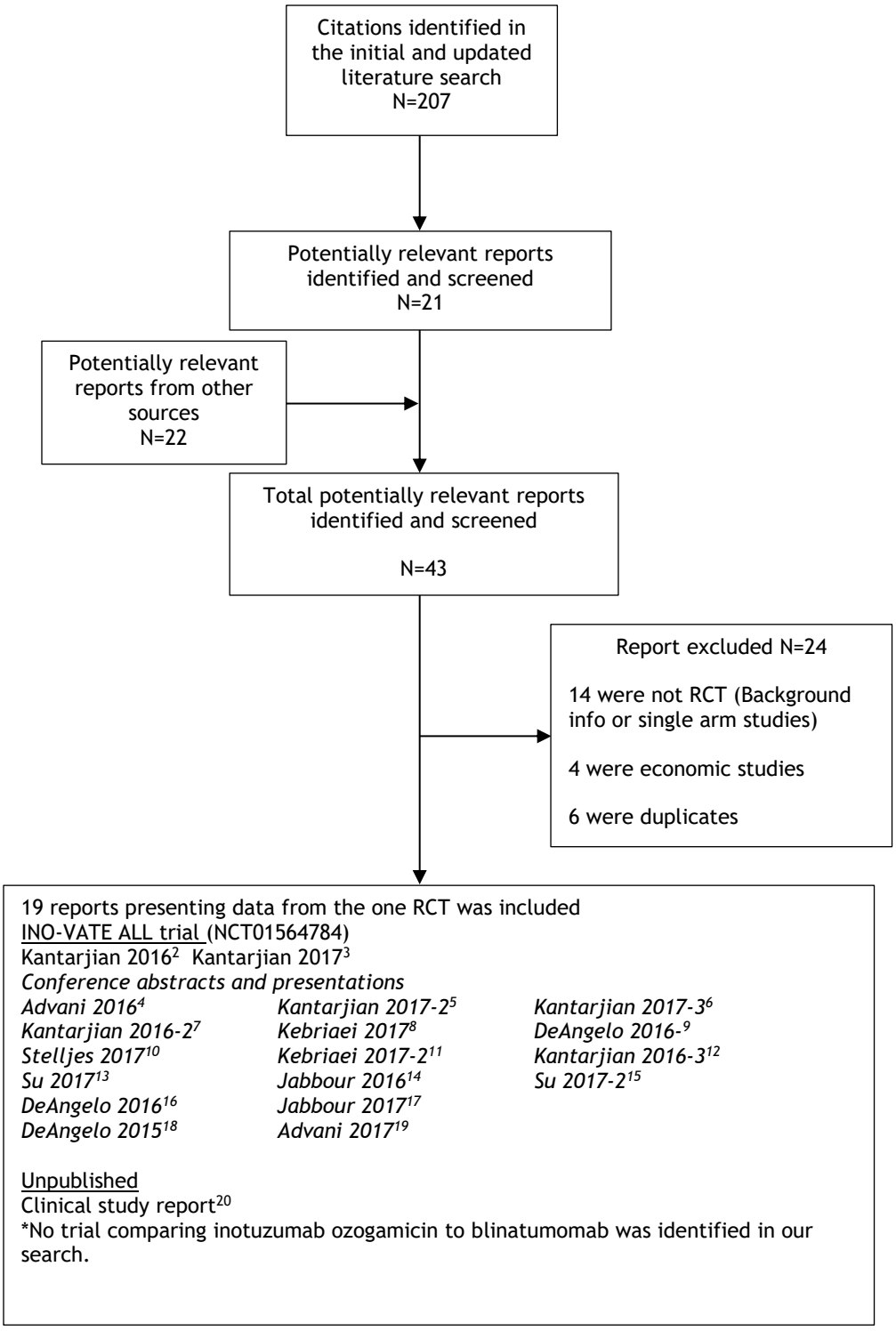
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 43 potentially relevant reports identified, 19 reports from one RCT were included in the pCODR systematic review[2-20] and 24 studies were excluded. Studies were excluded because they were duplicate studies, economic studies or not an RCT.

Figure 1. Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to studies INO-VATE ALL were also obtained through requests to the Submitter by pCODR.

6.3.2 Summary of Included Studies

One RCT (INO-VATE ALL)[2-20] was included in this literature review. The key characteristics of this RCT are summarized in table 4.

6.3.2.1 Detailed Trial Characteristics

[Table 4]: Summary of Trial Characteristics of the Included Studies[2,20-22]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
INO-VATE ALL trial[2-20] Multicenter phase III open label randomization controlled trial N= randomized 326; n= treated 307 129 centres and 25 countries Patient Enrolment Dates Aug 2, 2012 to Jan 4, 2015 Pre-specified final analysis of primary outcomes CR/CRi: First 218 randomized patient followed for 3 months (reached on Oct 2, 2014) OS: After 248 OS events (reached on March 8, 2016) Additional analyses were reported after last patient last visit on Jan 4, 2017 data cut-off Funding: Pfizer	Key Inclusion Criteria: Patients 18 years or older with relapsed or refractory CD22-positive ALL due to receive either salvage 1 or salvage 2 therapy were eligible Key Exclusion Criteria: • Isolated extramedullary relapse • Burkitt's or mixed lineage leukemia • Active central nervous system (CNS) leukemia • Concurrent active malignancy other than non-melanoma skin cancer, carcinoma in situ of the cervix, or localized prostate cancer • History of hepatic veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS)	Intervention A starting dose of 1.8 mg InO per square meter of body-surface via the intravenous route. Repeat the same dose in the second cycle if CR/CRi was not achieved. A third cycle should be considered for those patients who do not achieve a CR or a CRi and MRD negativity after 2 cycles.[1] 1.5 mg/m^2 InO for the subsequent cycles with maximum 6 cycles. For patients with a CR or CRi and MRD negativity not proceeding to HSCT, a maximum of 6 cycles may be administered.[1] Comparators FLAG MXN/Ara-C HIDAC	Primary: Overall survival CR/CRi Secondary: Duration of remission Progression-free survival Number of stem cell transplants Minimal residual disease levels and cytogenetics in patients achieving CR/CRi Pharmacokinetic parameters Quality of life during treatment Safety and toxicity outcomes

[Table 5]: Select quality characteristics of included studies of inotuzumab ozogamicin in patients with acute lymphoblastic leukemia

Study	INO-VATE ALL
Treatment vs. Comparator	Inotuzumab ozogamicin vs investigator's choice chemotherapy[2]
Primary outcome	Overall survival, complete remission and complete remission with incomplete hematological recovery[2]
Required sample size	With 218 patients randomized, the study had at least 88.5% power to detect a difference of response probabilities between 61% in the inotuzumab ozogamicin arm versus 37% in the control arm for 1-sided alpha=0.0125 for the analysis. There was no interim analysis planned for CR/CRi[22].

	The study was also designed to detect a clinically meaningful difference in OS (hazard ratio 0.67 corresponding to 50% improvement in OS, this translated to an improvement in the medians from 4.3 months on defined Investigator's choice of chemotherapy to 6.45 months on inotuzumab ozogamicin) with 80% power for 1-sided alpha=0.0125[2,22]. Assuming accrual of 2 patients per month for the first 6 months and 9.33 patients per month thereafter, 20% drop out within 15 days, 25% dropout total in the defined Investigator's choice of chemotherapy arm, and 5% dropout total in the inotuzumab ozogamicin arm, then a total sample size of 325 patients was required[22].
Sample size	326
Randomization method	1:1 stratified
Allocation concealment	None
Blinding	Investigators and patients were not blinded to the treatment allocation, but the members of the EAC were blinded to the treatment allocation and the result of investigator assessment[2].
ITT Analysis	Yes
Final analysis	Yes
Early termination	No
Ethics Approval	Yes

a) Trials

One RCT (INO-VATE ALL[2-20]) met our inclusion criteria. INO-VATE ALL was a multicenter phase III randomized open-label trial funded by Pfizer, Inc. The primary objective of INO-VATE ALL trial was to compare the hematological remission rate (complete remission/incomplete hematologic recovery [CR/CRi]), as assessed by the independent external Endpoint Adjudication Committee (EAC), and overall survival (OS) in patients with relapsed or refractory (≥5% marrow blasts, assessed by morphology; ie, M2 or M3 marrow) CD22-positive B-cell ALL randomized to receive inotuzumab ozogamicin or Investigator's choice of chemotherapy.[2] Primary refractory patients would not be excluded. The INO-VATE ALL trial randomized 326 eligible patients, in a 1:1 ratio, to receive either inotuzumab ozogamicin or one of the three defined chemotherapy regimens (either FLAG or cytarabine with mitoxantrone or HIDAC). Randomization was stratified according to the duration of the first remission (greater or less than 12 months), the salvage treatment phase (first or second salvage) and age (older or younger than 55). Crossover between arms was not allowed during the trial. Investigators and patients were not blinded to the treatment allocation, but the members of the EAC were blinded to the treatment allocation and the result of investigator assessment. Disease assessments were conducted for all patients whose disease had not progressed for up to 2 years after the first dose of treatment. All patients were followed for survival for up to 2 years from randomization[2]. Survival-status-only follow-up started approximately 12 weeks after relapse (end of disease assessment) and continued every 12 weeks for up to 2 years from the date of randomization[2]. Patients who achieve a response to treatment and who have a suitable donor may undergo stem-cell transplantation at the discretion of the investigator[2].

The two primary endpoints were hematologic remission (CR/CRi), as assessed by EAC, and overall survival. With 218 patients, a one-sided 0.0125 level test had 88.5% power for a difference of 24% in the probability of CR between the treatment arms 61% in the inotuzumab arm vs. 37% in the control arm[22]. The RCT was also designed to detect a clinically meaningful difference in OS (hazard ratio

0.67 corresponding to medians 4.30 months on control and 6.45 months on the experimental arm) with 80% power for one-sided alpha=0.0125[2,22]. The pre-specified final analysis for CR/CRi would be carried out after the first 218 patients had been followed for at least 3 months after randomization which was reached on Oct 2, 2014[2]. An updated analysis was carried out for the ITT population on CR/CRi after the data cut-off date of March 8, 2016. The pre-specified final analysis of OS would be carried out after 248 OS events had occurred which was reached on March 8, 2016[2]. An updated analysis of OS was performed after last patients last visit on Jan 4, 2017[20,22].

The secondary outcomes included the duration of remission, progression-free survival, number of stem cell transplants, minimal residual disease levels and cytogenetics in patients achieving CR/CRi, pharmacokinetic parameters, quality of life and safety and toxicity outcomes[2].

b) Populations

A total of 326 patients were randomized in INO-VATE ALL trial (164 to Inotuzumab ozogamicin arm, 162 to the control arm). Patients 18 years or older with relapsed or refractory CD22-positive ALL due to receive either salvage 1 or salvage 2 therapy were eligible. Other key inclusion criteria included:

1. Bone marrow involvement with ≥ 5% lymphoblasts
2. ECOG performance status 0 – 2
3. Adequate liver function
4. Serum creatinine ≤ 1.5 x upper limit of normal (ULN)
5. Male and female patients of childbearing potential must agree to use a highly effective method of contraception throughout the study and for a minimum of 6 weeks after the last dose of assigned treatment
6. Patients with Ph+ ALL must have failed treatment with at least 1 second or third generation TKI and standard multi-agent induction chemotherapy

Key exclusion criteria included:

1. Isolated extramedullary relapse
2. Burkitt's or mixed lineage leukemia
3. Active central nervous system (CNS) leukemia
4. Prior chemotherapy within ≤2 weeks before randomization with the following exceptions:
    a. Steroids, hydroxyurea, oral mercaptopurine, methotrexate, vincristine, thioguanine, and tyrosine kinase inhibitors are permitted within 2 weeks of randomization as maintenance or to reduce the peripheral blood blast count
    b. Craniospinal radiation is prohibited. However, other concurrent therapies for CNS prophylaxis or treatment of CNS relapse is permitted
    c. Patients must have recovered from acute toxicity of all previous therapy prior to enrollment
5. Prior monoclonal antibodies within 6 weeks of randomization

6. Prior allogeneic hematopoietic stem cell transplant (HSCT) or other anti-CD22 immunotherapy ≤ 4 months before randomization
7. Known systemic vasculitides (eg, Wegener's granulomatosis, polyarteritis nodosa, systemic lupus erythematosus), primary or secondary immunodeficiency (such as HIV infection or severe inflammatory disease)
8. Current or chronic hepatitis B or C infection
9. Major surgery within ≤4 weeks before randomization
10. Unstable or severe uncontrolled medical condition (eg, unstable cardiac function, unstable pulmonary condition or chronic liver disease
11. Concurrent active malignancy other than non-melanoma skin cancer, carcinoma in situ of the cervix, or localized prostate cancer
12. History of hepatic veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS)

The baseline characteristics of randomized patients in INO-VATE ALL can be found in the table below. Baseline characteristics were well balanced between the two arms. Among all randomized patients, the median age was around 47 years with more than 60% of patients under the age of 55. More than 60% of patients were in their first relapse. The investigator's choice chemotherapy arm had 7% more patients who had less than 12-month duration in the first remission.

Table 1: Baseline characteristics[20]

Demographic Characteristic	**Inotuzumab Ozogamicin**	**Defined Investigator's Choice of Chemotherapy**
Number of patients	164	162
Gender (%)		
Male	91 (55.5)	102 (63.0)
Female	73 (44.5)	60 (37.0)
Age		
Mean age (SD)	45.9 years (17.07)	46.0 years (16.60)
Median age (Range)	46.5 years (18-78)	47.5 years (18-79)
<55 years (%)	104 (63.4)	103 (63.6)
≥55 years (%)	60 (36.6)	59 (36.4)
Race, N (%)	164 (100.0)	162 (100.0)
White	112 (68.3)	120 (74.1)
Black	4 (2.4)	3 (1.9)
Asian	31 (18.9)	24 (14.8)
Other	17 (10.4)	15 (9.3)
BMI (kg/m^2)		
Mean (SD)	25.91 (5.639)	26.92 (6.081)
Body surface area (m^2)		
Mean (SD)	1.85 (0.273)	1.90 (0.263)
Primary diagnosis		
B-cell ALL		
Number of patients	153 (93.3)	156 (96.3)
Duration since initial histopathological diagnosis		
Mean (SD)	20.4 months (23.12)	18.6 months (17.86)
Median	12.5 months	13.0 months
B-cell lymphoblastic lymphoma		
Number of patients	11 (6.7)	6 (3.7)

Demographic Characteristic	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy
Duration since initial histopathological diagnosis		
Mean(SD)	19.6 months (16.78)	41.5 months (76.65)
Median	10.5 months	12.9 months
Salvage status		
Salvage 1	111 (67.7)	104 (64.2)
Salvage 2	51 (31.1)	57 (35.2)
Other	2 (1.2)	1 (0.6)
Duration of the first remission		
<12 months	98 (59.8)	108 (66.7)
≥12 months	66 (40.2)	54 (33.3)
ECOG Performance Status		
0	62 (37.8)	61 (37.7)
1	81 (49.4)	80 (49.4)
2	21 (12.8)	20 (12.3)
Missing	0	1 (0.6)
Local CD22 (%)		
≥90	43 (26.2)	47 (29.0)
≥70 - <90	33 (20.1)	33 (20.4)
<70	77 (47.0)	72 (44.4)
Positive	11 (6.7)	10 (6.2)
Central CD22 (%)		
≥90	107 (65.2)	93 (57.4)
≥70 - <90	30 (18.3)	18 (11.1)
<70	5 (3.0)	18 (11.1)
Missing	22 (13.4)	33 (20.4)
Philadelphia chromosome positive	22 (13.4)	28 (17.3)

Note: ALL=Acute lymphoblastic leukemia; BMI=Body Mass index; ECOG=Eastern Cooperative Oncology Group; SD=Standard deviation.

Table 2: Additional baseline characteristics[22]

Demographic Characteristic	Inotuzumab Ozogamicin (n/N)	Defined Investigator's Choice of Chemotherapy (n/N)
Pre-study stem cell transplant	29/164 (17.7%)*	26/143 (18.2%)*
Number of prior TKI containing regiments		
0	3/22 (13.6%)†	2/28 (7.1%)†
1	13/22 (59.1%)	15/28 (53.6%)
2	6/22 (27.3%)	11/28 (39.3%)
Prior TKI	19/22 (86.4%)	26/28 (92.9%)
Dasatinib	18/22 (81.8%)	24/28 (85.7%)
Imatinib	10/22 (45.5%)	14/28 (50.0%)
Ponatinib	4/22 (18.2%)	7/28 (25.0%)
Nilotinib	4/22 (18.2%)	6/28 (21.4%)
Bosutinib	1/22 (4.5%)	0
Prior 2nd or 3rd generation TKI	19/22 (86.4%)	25/28 (89.3%)

Note: TKI= Tyrosine-kinase inhibitors.

* The denominator was the safety population

† The denominator was the number of patients with Philadelphia positive abnormality

c) Interventions

The number of patients randomized to each type of treatments, mean and median cycles, number of patients experienced dose reduction and dose delay can be found in the table below.

Table 3: Proportion of patients receiving difference chemotherapy[20,22]

Chemotherapy	InO arm	Control arm			
		Total	FLAG	MXN/Ara-C	HIDAC
N (%)	164	162	102	38	22
N received at least 1 dose	164	143	93	33	17
Mean cycle	2.8	1.2	1.3	1.1	1.2
Median cycle	3	1	1	1	1
Median duration of treatment (weeks)	8.9	0.9	0.9	1.1	1.0
N (%) with dose reduction	21	5	3	2	0
N (%) with dose delay	73	14	10	2	2

Inotuzumab ozogamicin arm

Patients in the inotuzumab ozogamicin (InO) arm received the trial drug intravenously at a starting dose of 1.8 mg per square meter of body-surface. The treatment regimen of InO can be found in the table below. For patients who achieved a CR or CRi, or to allow recovery from toxicity, the length of Cycle 1 could be extended up to 28 days[20]. For patients proceeding to HSCT, the protocol recommended that InO treatment be limited to 2 cycles or the fewest number of cycles required to achieve CR/CRi[2]. A third cycle should be considered for those patients who do not achieve a CR or a CRi and MRD negativity after 2 cycles. For patients with a CR or CRi and MRD negativity not proceeding to HSCT, a maximum of 6 cycles may be administered.[1] The median cycle administration in the InO arm was 3 cycles.

Table 4: treatment regimen of inotuzumab ozogamicin

Cycle	Day 1 dosage	Day 8 (± 2 days) dosage	Day 15 (± 2 days) dosage	Treatment free period	Total duration
Cycle 1	0.8 mg/m^2 via i.v. over 1 hour	0.5 mg/m^2 via i.v. over 1 hour	0.5 mg/m^2 via i.v. over 1 hour	7 days after last dose of the cycle	Around 3 weeks
Cycle 2	0.8 mg/m^2 via i.v. over 1 hour (if patient still had measurable circulating blasts)	0.5 mg/m^2 via i.v. over 1 hour	0.5 mg/m^2 via i.v. over 1 hour	14 days after last dose of the cycle	Around 4 weeks
	0.5 mg/m^2 (if patients did not have measurable circulating blasts)				
Cycle 3 up to cycle 6	0.5 mg/m^2 via i.v. over 1 hour	0.5 mg/m^2 via i.v. over 1 hour	0.5 mg/m^2 via i.v. over 1 hour	14 days after last dose of the cycle	Around 4 weeks

The control arm

The treatment regimen of investigator's choice chemotherapies can be found in the tables below. There were three different chemotherapy regimens available for the investigators to choose in INO-VATE ALL trial. Dose reduction should be based on institutional guidelines[2]. The median cycle administrated in the control arm was 1 cycle.

Table 5: FLAG regimen (4-week cycle for up to 4 cycles)

Treatment day	Regimen
Pre-treatment	Administer the premedication(s) and check vital signs according to the standard of care at the institution.
Day 1	Administer cytarabine 2.0 g/m^2/day i.v. infusion over 4 hours
Day 2-6 (± 2 days)	1. Administer fludarabine 30 mg/m^2/day by 30 min i.v. infusion 2. Wait 4 hours 3. Administer cytarabine 2.0 g/m^2/day i.v. infusion over 4 hours
Variable days	Administer filgrastim (G-CSF) at 5 µg/kg/day. G-CFS administration first cycle day according to the standard of care at the Institution and continued until neutrophil recovery.
Day 29 (± 2 days)	Begin cycle 2

Table 6: Cytarabine and mitoxantrone (MXN/Ara-C) regiment (15-20 day cycle for up to 4 cycles)

Treatment day	Regimen
Pre-treatment	Administer the premedication(s) and check vital signs according to the standard of care at the institution.
Day 1	1. Administer mitoxantrone at 12 mg/m^2 intravenously over 20 minutes 2. Administer cytarabine at 200 mg/m^2/day intravenously by continuous infusion over 7 days
Day 2-3 (± 2 days)	Administer mitoxantrone at 12 mg/m^2 intravenously over 20 minutes
Day 16-21 (± 2 days)	Begin cycle 2

Table 7: HIDAC regimen

Treatment day	Regimen
Pre-treatment	Administer the premedication(s) and check vital signs according to the standard of care at the institution
Day 1	Administer cytarabine at 3 g/m2 i.v. over 1-3 hours every 12 hours for up to 12 times.*
Comment	A second course is allowed after hematological recovery.

* For patients aged > 55 years the dose of cytarabine can be reduced up to 1.5 g/m^2. In addition a dose reduction according to the standard clinical practice can be done for patients with liver or renal dysfunction

d) Patient Disposition[40]

Category	Inotuzumab ozogamicin	Control
Randomized	164	162
Received treatment	164	143*
Total discontinuation†	164 (100%)	162 (100%)
Discontinued due to death	131 (80.0%)	136 (84.0%)
Discontinued due to completed follow-up‡	30 (18.3%)	11 (6.8%)
Withdrawal consent	1 (0.6%)	13 (8.0%)
Lost to follow-up	1 (0.6%)	1 (0.6%)
Discontinued due to other reasons	1 (0.6%)	1 (0.6%)
ITT population for efficacy	164	162

Population for safety analysis	164	143†

* 19 patients randomized to control arm refused to receive investigator's choice chemotherapy, but some agreed to continue with follow-up
† Discontinuation here meant discontinuation of follow-up in the trial
‡ Completed was considered as discontinuation per CRF. Defined as completed survival follow-up of 5 years from randomization or 2 years from randomization of the last patient, whichever occurred first.

e) Limitations/Sources of Bias

Trial design

- The baseline characteristics were well balanced. Due to the open-label nature of the study, 19 patients randomized to control arm withdrew from the treatment immediately after randomization. However, some of the patients still remained in the population allowing follow-up. In addition, since the total number of patients drop-out was small, the risk of attrition bias was low. There was no high risk of bias found in the trial design. The analysis reported was the final analysis.

Analysis of effect

- The shape of the Kaplan-Meier plot of the overall survival analysis showed a more profound difference between the two arms after month 14. This might suggest that a subgroup of patients in InO arm who survival after 14 months was the main drive behind the more favorable survival effect. However, the goal of the RCT was not designed to identify the subgroup of patients with a more profound survival benefit. One can only hypothesize using the subgroup analysis in overall survival. To minimize the risk of selection bias, the subgroups used in stratification were evaluated. In this case, patients under age 55, with greater than 12 months of the first remission and in salvage 1 therapy seemed to show a bigger survival difference. The p-value of the pre-specified final analysis did not reach the adjusted p-value for efficacy.
- None of the subgroups in OS were adequately powered and the result should only be considered for exploratory reasons.
- The primary definition of progression-free survival in the RCT included patients who withdraw due to global deterioration of health status or starting new induction therapy or post-therapy HSCT without achieving CR/CRi. This definition was different from the common definition of PFS. The PFS analysis using the common definition was also reported. Since there were more patients in the control arm who proceeded to HSCT after an new induction therapy, under the protocol definition these patients might be considered as progression which led to greater effect size in hazard ratio favoring InO. The effect size on hazard ratio using the common definition was smaller compared with PFS analysis using the protocol definition in the RCT (0.568 vs 0.450). However, both PFS analyses were consistent.
- More patients achieved a complete remission or complete remission with incomplete hematological recovery in InO arm. This result allowed more patients in the InO arm to proceed to HSCT. However, whether proceeding to HSCT resulted in survival benefit was inconclusive as the sample size for this subgroup was small.
- QoL was secondary outcome in the trial, however it was not part of the statistical analysis plan and no multiplicity adjustments were made. Thus,

there is an increase risk of type one error (false positive finding). The open-label design of the trial may have influenced patient perceptions, making the interpretation of the QOL data difficult. Furthermore, QoL was assessed during the treatment period, which was different between the InO arm and chemotherapy arm (median treatment duration of InO was 3 cycles vs 1 cycle in the chemotherapy arm). The temporal effect may have a role in the differences observed and therefore the improvement of QoL may be uncertain.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Overall survival (date cut-off date March 8, 2016 and Jan 4, 2017)

Overall survival was defined as the time from randomization to death due to any cause[2]. At the pre-specified final analysis which was reached on the data cut off date on March 8, 2016, there were 252 OS events in the overall population (122 in InO and 130 in control arm)[20,22]. The stratified hazard ratio of death was 0.77 97.5% CI 0.578-1.026,1-sided p=0.0203, 2-sided p=0.04)[2,20,22]. The p-value of the final analysis did not reach the pre-specified level of efficacy at 1-sided p=0.0111 or 2-sided p=0.0208[2,20]. The median survival was 7.7 months in the InO arm and 6.7 months in the control arm[2].

The Kaplan Meier plot of overall survival can be found in the figure below (Figure 1). The difference between the two arms was more profound after month 14.

An updated analysis was performed on January 4th, 2017. The number of deaths reported were 131/164 (79.9%) in the InO arm and 136/162 (84.0%) in the control arm. The stratified hazard ratio of death when comparing InO arm to control arm was 0.751 [95% CI 0.588, 0.959, 97.5% CI 0.568, 0.993, 1-sided p=0.0105][5,22]. This updated analysis was not included in the multiplicity adjustment therefore it was not clear whether the p-value reached the efficacy boundary after multiplicity adjustment. The median survival at the updated OS analysis was 7.7 months in the InO arm and 6.2 months in the control arm[5,22]. The probability of survival in the InO arm and control arm was 33.6% vs 32.0% after one year, 22.8% vs 10.0% after 2 years and 20.3% vs 6.5% after 3 years, respectively.

Subgroup analysis

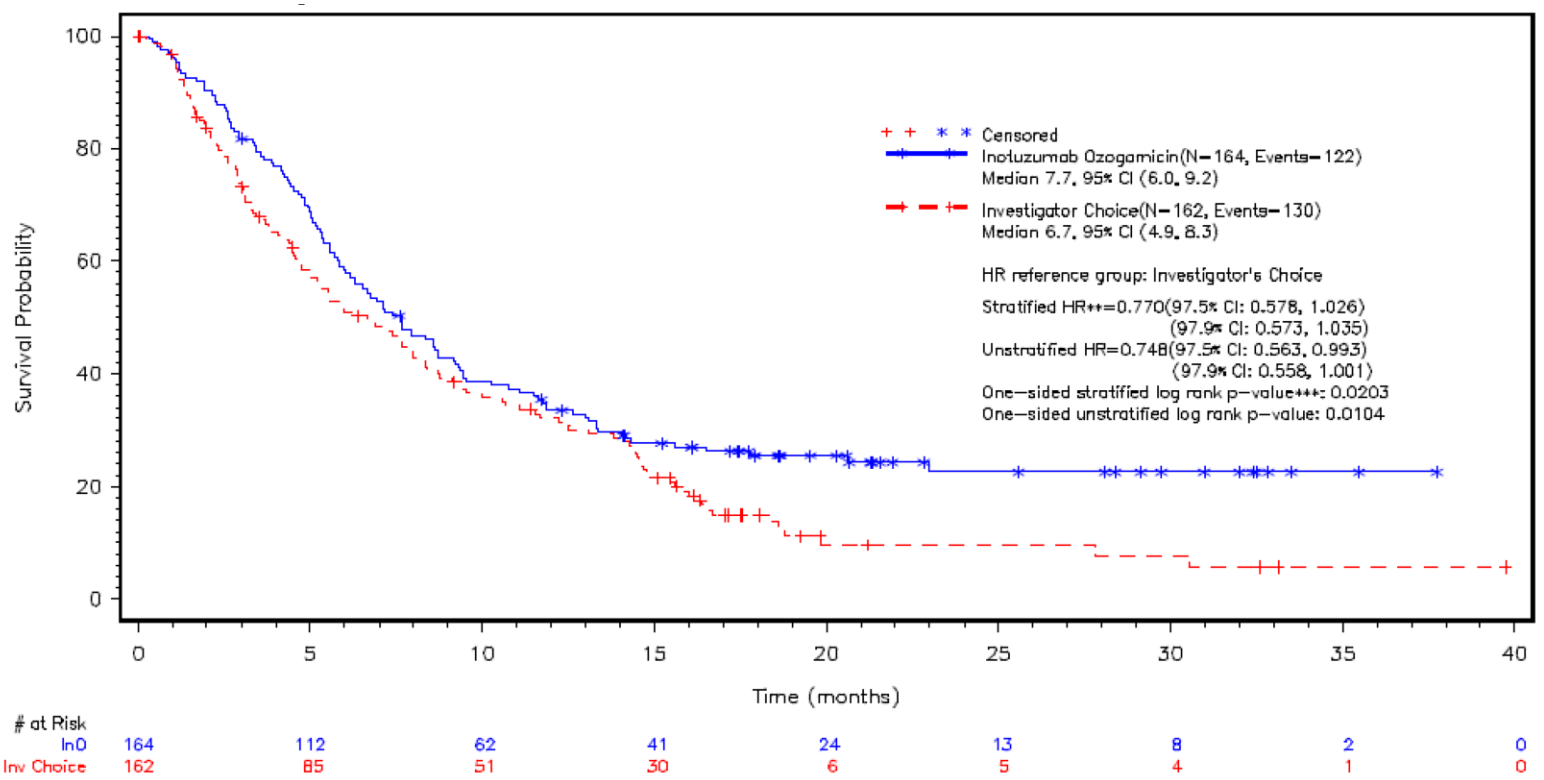
The result from OS subgroup analysis can be found in the tables below. Only OS and remission response rate were shown because they were the primary outcome which the study was powered to show a difference. The most updated subgroup analysis after the Jan 4, 2017 data cut off date is presented below.

Table 8: Subgroup analysis of overall survival (data cut-off date Jan 4, 2017)[20]

Subgroups	InO arm (n/N)	Control arm (n/N)	Stratified hazard ratio of death [97.5% CI]	P value
1st remission<12 months	92/109	93/107	0.801 [0.573-1.118]	0.0669
1st remission≥12 months	39/55	43/55	0.646 [0.387-1.079]	0.0269
Salvage 1	81/108	91/107	0.664 [0.469-0.940]	0.0039
Salvage 2	50/56	45/55	0.942 [0.588-1.510]	0.3887
Age<55	76/104	84/103	0.670 [0.466-0.963]	0.0063

Subgroups	InO arm (n/N)	Control arm (n/N)	Stratified hazard ratio of death [97.5% CI]	P value
Age≥55	55/60	52/59	0.888 [0.572-1.379]	0.2719
CD22≥90%	78/107	81/93	0.511 [0.350-0.746]	<0.0001
CD22<90%	33/35	29/36	1.242 [0.664-2.325]	0.7812
Philadelphia positive	21/22	21/27	1.275 [0.567-2.865]	0.7498
Philadelphia negative	110/142	115/135	0.699 [0.515-0.948]	0.0040
Pre-study HSCT	26/29	21/32	1.508 [0.718-3.168]	0.8948
No Pre-study HSCT	105/135	115/130	0.649 [0.476-0.887]	0.0009

Figure 1: Kaplan Meier plot of overall survival in the ITT population data cut-off date March 8, 2016 [22]



**From stratified Cox proportional hazards model. The stratification factors are Duration of first remission (<12 months or >= 12 months); Salvage treatment (Salvage 1 or 2); Patient age at randomization (<55 or >=55 years). All factors are per IVRS.
***From one sided stratified log-rank test. The stratification factors are Duration of first remission (<12 months or >= 12 months); Salvage treatment (Salvage 1 or 2); Patient age at randomization (<55 or >=55 years). All factors are per IVRS.

Progression-free survival (data cut-off date Jan 4, 2017)

The common definition of progression-free survival (PFS) is the time from date of randomization to earliest date of the following events: death due to any cause, or progressive disease (ie. objective progression, relapse from CR/CRi).

Progression-free survival was defined in the INO-VATE ALL trial as the time from date of randomization to the earliest date of[2]:

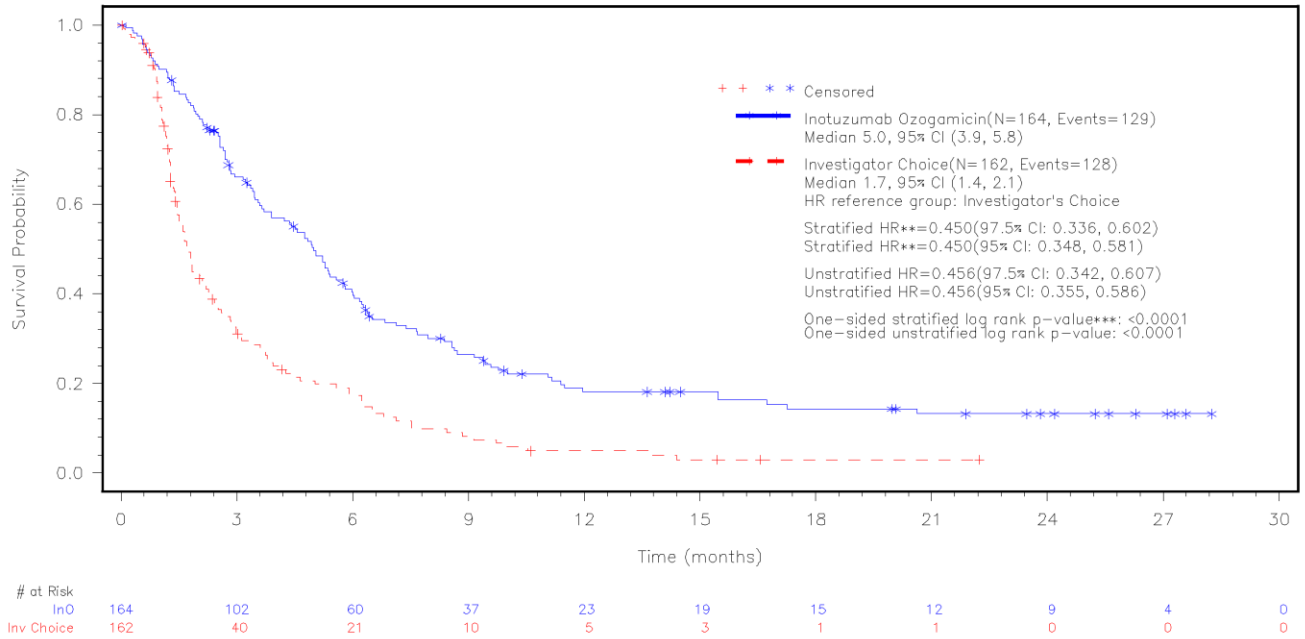
- progressive disease
    - including objective progression
    - relapse from CR/CRi
    - treatment discontinuation due to global deterioration of health status
    - starting new induction therapy or post-therapy HSCT without achieving CR/CRi
- date of death from any cause

The submitter explained that the definition of PFS was different from a standard definition because due to the fact that the patients with ALL who didn't achieve CR/CRi while on study treatment would usually seek a new induction therapy before progression, which was different from the patients in solid tumor studies who usually seek subsequent therapies after progression[20]. However, an additional analysis of PFS using standard definition was also reported.

The data cut off date for PFS was January 4th, 2017. Using the definition of PFS in the protocol, a total of 129/164 (78.7%) of patients in the InO arm and 128/162 (79.0%) in the control arm had a PFS event. In the ITT Population, the stratified hazard ratio of PFS when comparing InO to control was 0.45 (97.5% CI: 0.336-0.602; 95% CI: 0.348-0.581; p<0.0001)[5,20]. The median PFS was 5 months in the InO arm versus 1.7 months in the control arm[5,20].

Using the common definition of PFS (without treatment discontinuation due to global deterioration of health status and starting new induction therapy or post-therapy HSCT without achieving CR/CRi), there were 110/164 PFS events in the InO arm and 75/162 PFS events in the control arm. The stratified hazard ratio of PFS was 0.568 (97.5% CI 0.401-0.804; 95% CI 0.419-0.770; p=0.0001). The median PFS was 5.6 months in the InO arm versus 3.7 months in the control arm. The Kaplan-Meier plot for the PFS can be found in the figures below (Figure 2 and Figure 3).

Figure 2: Kaplan-Meier Plot of Progression-Free Survival using protocol defined PFS (ITT Population)[20]



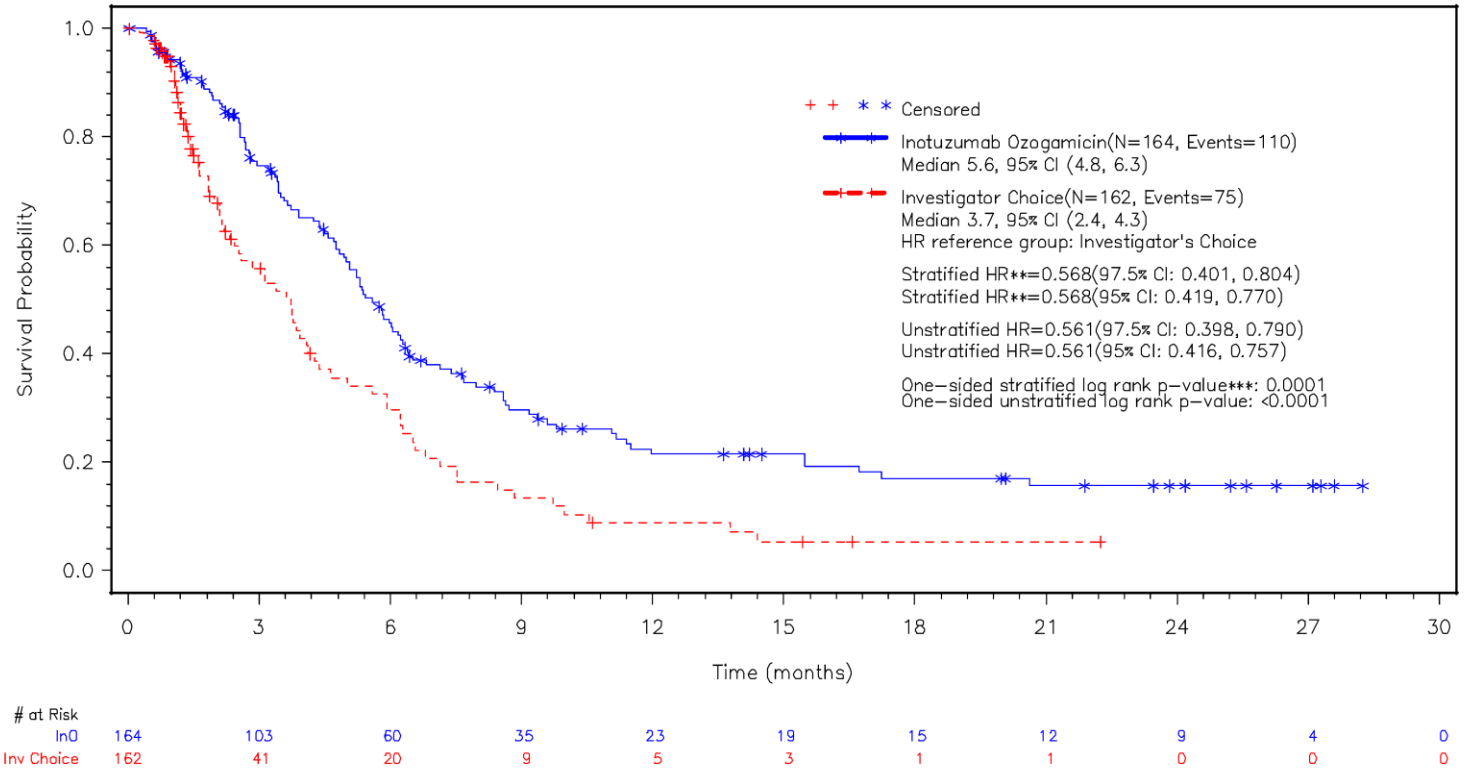
Source: Figure 14.2.3.1

** From stratified Cox proportional hazards model. The stratification factors were duration of first remission (<12 months or ≥12 months); salvage treatment (Salvage 1 or 2); patient age at randomization (<55 years or ≥55 years). All factors were per IVRS.

*** From 1-sided stratified log-rank test. The stratification factors were duration of first remission (<12 months or ≥12 months); salvage treatment (Salvage 1 or 2); patient age at randomization (<55 years or ≥55 years). All factors were per IVRS.

Defined Investigator's choice of chemotherapy (control arm) was 1 of the defined chemotherapy regimens (FLAG, MXN/Ara-C, or HIDAC).
Abbreviations: # at risk=number of patients at risk; CI=confidence interval; FLAG=fludarabine + cytarabine + G-CSF; G-CSF=granulocyte-colony stimulating factor; HIDAC=high-dose cytarabine; HR=hazard ratio; InO=inotuzumab ozogamicin; Inv Choice=defined Investigator's choice of chemotherapy; ITT=intent-to-treat; IVRS=interactive voice response system; MXN/Ara-C=mitoxantrone + cytarabine.

Figure 3: Kaplan-Meier Plot of Progression-Free Survival using common definition (ITT Population)[20]



# at Risk											
InO	164	103	60	35	23	19	15	12	9	4	0
Inv Choice	162	41	20	9	5	3	1	1	0	0	0

Abbreviations: # at Risk = Number of patients at risk; InO = Inotuzumab Ozogamicin; Inv Choice = Investigator Choice.
Note: Investigator Choice is one of the defined chemotherapy regimens (either FLAG (Fludarabine, Cytarabine, and G-CSF), Cytarabine with Mitoxantrone, or HIDAC).
**From stratified Cox proportional hazards model. The stratification factors are duration of first remission (<12 months or >=12 months), salvage treatment (Salvage 1 or 2), patient age at randomization (<55 or >=55 years). All factors are per IVRS.
***From one-sided stratified log-rank test. The stratification factors are duration of first remission (<12 months or >=12 months), salvage treatment (Salvage 1 or 2), patient age at randomization (<55 or >=55 years). All factors are per IVRS.

PFIZER CONFIDENTIAL Source:Table 14.2.3.8 Data Extraction: 23FEB2017 Cutoff Date:04JAN2017 File Generation: 20APR2017:13:22

Complete remission, complete remission with incomplete hematological recovery, duration of remission and minimal residual disease status

Complete remission (CR) was defined as a disappearance of leukemia as indicated by <5% marrow blasts and the absence of peripheral blood leukemic blasts, with recovery of hematopoiesis defined by absolute neutrophil count (ANC) ≥1000/μL, platelets ≥100,000/μL, and resolution of any extramedullary disease (EMD ie, Cycle 1 EMD status). Complete remission with incomplete hematological recovery (CRi) was defined as CR except with ANC <1000/μL and/or platelets <100,000/μL[2].

The pre-specified final analysis of CR/CRi was carried out after the first 218 patients were followed for at least 3 months which was reached on Oct 2, 2014 data cut off date (ITT218 population). The rate of CR/CRi was higher in InO arm (88/109, 80.7%) when compared with control arm (32/109, 29.4%), which was statistically significant (mean difference 51.4%, p<0.001)[2,21,22]. The median duration of remission was 4.6 months in InO arm and 3.1 in the control arm[2]. The number of patients who had bone marrow blast results below the minimal residual disease threshold was higher in the InO arm when compared with the control arm (78.4% vs. 28.1%, p<0.001)[2,22].

The result from the subgroup analysis of the ITT218 population can be found in the table below.

Table 9: subgroup analysis of the ITT218 population[2]

Subgroups	InO arm % CR/CRi	Control arm % CR/CRi	Rate difference [97.5% CI]	P value
1st remission<12 months	77.5%	23.9%	53.5% [37.6-69.4]	<0.001
1st remission≥12 months	86.8%	39.5%	47.7% [25.8-69.0]	<0.001
Salvage 1	87.7%	28.8%	58.9% [44.2-73.6]	<0.001
Salvage 2	66.7%	30.6%	36.1% [11.5-60.7]	0.002
Age<55	80.3%	31.9%	48.4% [31.7-65.1]	<0.001
Age≥55	81.4%	25.0%	56.4% [36.1-76.7]	<0.001
CD22<90%	79.2%	25.0%	54.2% [27.0-81.3]	<0.001
CD22≥90%	82.4%	36.5%	45.9% [29.1-62.8]	<0.001
Philadelphia positive	78.6%	44.4%	34.1% [-1.8-70.1]	0.08
Pre-study HSCT	76.5%	27.3%	49.2% [17.8-80.6]	0.004
No pre-study HSCT	81.5%	29.9%	51.6% [37.4-65.9]	<0.001

The result from ITT population (data cut off date March 8, 2016) can be found in the table below. The Cr/CRi was consistent with the ITT218 results. Please note that the denominators in the MRD negative row were the numbers of the patients achieved CR or CRi status. Therefore, this particular comparison was not ITT.

Table 10: CR/CRi and duration of remission in ITT population[20,22]

Outcome	InO arm	Control arm	Rate difference	P value
CR (%)	55/164 (33.5%)	26/162 (16.0%)	17.5% (95% CI 7.0, 28.0)	0.0001
CRi (%)	65/164 (39.6%)	24/162 (14.8%)	24.8% (95% CI 14.2, 35.4)	<0.0001
CR/CRi (%)	120/164 (73.2%)	50/162 (30.9%)	42.3% (95% CI 31.1, 53.5)	<0.0001
MRD negative in patient achieved CR/CRi	92/120 (76.7%)	19/50 (38.0%)		<0.0001
Median	5.3 months	3.6 months		
Hazard ratio of relapse			0.597 (95% CI 0.4, 0.89)	0.0052

Note: CR=complete remission; CRi= complete remission with incomplete hematological recovery; InO: inotuzumab ozogamicin.

Table 11:Subgroup analysis of complete remission, complete remission with incomplete hematological recovery in ITT population[20]

Subgroups	InO arm (n/N)	Control arm (n/N)	Rate difference [97.5% CI]	P value
1st remission<12 months	76/109	32/107	39.8% [25.8-53.8]	<0.0001
1st remission≥12 months	44/55	18/55	47.3% [28.6-65.9]	<0.0001
Salvage 1	83/108	32/107	46.9% [33.5-60.4]	<0.0001
Salvage 2	37/56	18/55	33.3% [13.3-53.4]	0.0002
Age<55	78/104	29/103	46.8% [33.1-60.6]	<0.0001
Age≥55	42/60	21/59	34.4% [15.1-53.7]	<0.0001
CD22≥90%	83/107	33/93	42.1% [27.8-56.4]	<0.0001
CD22<90%	23/35	11/36	35.2% [10.3-60.0]	0.0015
Philadelphia positive	16/22	15/28	19.2% [-10.8-49.1]	0.0830

Quality of life at the end of treatment cycles(March 8, 2016 data cut-off date)

Health-related quality of lifewas measured by the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30), v3.0 and the EuroQoL 5 Dimensions questionnaire 3 level version (EQ-5D-3L) were collected from patients in each treatment arm during the treatment cycle period only. A change of 5 to 10 points on the 1-100 point scale of the EORTC-QLQ-C30 or 0.08 in the EQ-5D-3L score are considered estimates of minimally important differences for clinical significant differences in quality of life[20]. Analyses were considered supportive, and no multiplicity adjustments were made.[12]

The completion rates of at least one question in the EORTC-QLQ-C30 and EQ-5D were 85% and 65% respectively[12]. There was more than a 5 point difference in three subcategories of the EORTC-QLQ-C30 including physical functioning (75.0 vs 68.1, p=0.0139), role functioning (64.7 vs 53.4, p=0.0065) and social functioning (68.1 vs 59.8, p=0.0336) for the InO arm.[12,22] The EORTC-QLQ-C30 global health status score in the InO arm and control arm was 62.1 and 57.8 respectively (p=0.1572). The EQ-5D-3L index in the InO arm and control arm was 0.80 and 0.76 respectively (p=0.1710)[12,22].

Percentage of patient proceed to hematopoietic stem cell transplantation (March 8 2016 data cutoff date)

The number of patients that proceeded to hematopoietic stem cell transplantation (HSCT) after treatment without a new induction therapy was higher in the InO arm (71/164, 43.3%) when compared with the control arm (18/162, 11.1%, p<0.0001)[20,22]. An additional 6 patients in InO arm and 15 patients in the control arm proceeded to HSCT after a new induction therapy, respectively. This brought the total number of patients proceeding to HSCT after treatment to 77/164 (47.0%) in InO arm and 33/162 (20.4%) in the control arm[22].

Post Hematopoietic Stem Cell Transplantation survival (March 8, 2016 data cut-off date)

Among the patients who received HSCT after study treatment, 46/77 (59.7%) in the InO arm and 19/33 (57.6%) in the chemotherapy arm had died. The stratified hazard ratio of death was 1.376 (p=0.8707), which was inconclusive due to small sample size[22]. Please also note that this is not an ITT analysis.

Harms Outcomes

Grade 3 & 4 adverse events, grade 3 & 4 hematological toxicities, and withdrawal due to adverse events

Please refer to the table below for the number of patients with grade 3 and 4 adverse event, grade 3 and 4 hematological toxicities and withdrawal due to adverse event and specific grade 3 and 4 adverse events (AEs) of interest. The most common grade 3 and 4 hematological AEs in patients receiving InO were neutropenia (47%), thrombocytopenia (40.9%) and febrile neutropenia (26.8%). The most common grade 3 and 4 hepatotoxicity AEs in patients receiving InO were increased GGT (11%), venoocclusive liver disease (11%) and hyperbilirubinaemia (6.1%). The most common grade 3 and 4 infection AEs in patients receiving InO were pneumonia (6.1%), bacteraemia (3.7%), and neutropenic sepsis (3%).

Table 10: Number of patients with at least one all cause grade 3 and 4 AEs and withdrawal due to adverse events (Jan 4th, 2017 data cut off)[20]

Outcomes	InO arm (%)	Control arm (%)
Safety population	164	143
Patients with at least one all cause AE	163 (99.4)	143(100)
Patients with grade 3 or 4 all cause AE	147 (89.6)	138 (96.5)
Patients discontinuation due to all cause adverse events*	31 (18.9)	11 (7.7)
Patients with death due to all cause AE	26 (15.9)	16 (11.2)
Patients with dose reduction due to all cause AE	5 (3.0)	3 (2.1)
Patients with temporary discontinuation due to all cause AE	72 (43.9)	17 (11.9)
Grade 3 & 4 hematological AE		
Neutropenia	77 (47.0)	63 (44.1)
Thrombocytopenia	67 (40.9)	85 (59.4)
Febrile neutropenia	44 (26.8)	77 (53.8)
Leukopenia	44 (26.8)	53 (37.1)
Anaemia	37 (22.6)	63 (44.1)
Lymphopenia	27 (16.5)	36 (25.2)
Hypokalaemia	11 (6.7)	13 (9.1)
WBC count decreased	10 (6.1)	9 (6.3)
Hypophosphataemia	5 (3.0)	6 (4.2)
Haemoglobin decreased	4 (2.4)	6 (4.2)
Hyperuricemia	3 (1.8)	0
Hypocalcaemia	3 (1.8)	5 (3.5)
Hyponatraemia	2 (1.2)	6 (4.2)
Pancytopenia	2 (1.2)	4 (2.8)
Bone marrow failure	0	3 (2.1)
Grade 3 & 4 Hepatotoxicities		
GGT increased	18 (11.0)	7 (4.9)
Venoocclusive liver disease	18 (11.0)	3 (2.1)
Hyperbilirubinaemia	10 (6.1)	9 (6.3)

AST increased	7 (4.3)	5 (3.5)
ALT increased	6 (3.7)	7 (4.9)
Ascites	3 (1.8)	0
Blood alkaline phosphatase increased	3 (1.8)	0
Blood lactate dehydrogenase increased	3 (1.8)	0
Blood albumin decreased	0	3 (2.1)
Grade 3 & 4 infections or infestations		
Pneumonia	10 (6.1)	6 (4.2)
Bacteraemia	6 (3.7)	10 (7.0)
Neutropenic sepsis	5 (3.0)	6 (4.2)
Sepsis	4 (2.4)	11 (7.7)
Staphylococcal bacteraemia	4 (2.4)	3 (2.1)
Septic shock	3 (1.8)	2 (1.4)
Staphylococcal sepsis	3 (1.8)	2 (1.4)
Urinary tract infection	3 (1.8)	1 (0.7)
Clostridium difficile colitis	2 (1.2)	3 (2.1)
Escherichia bacteraemia	2 (1.2)	4 (2.8)
Cellulitis	1 (0.6)	4 (2.8)
Escherichia sepsis	1 (0.6)	3 (2.1)
Klebsiella bacteraemia	1 (0.6)	5 (3.5)
Lung infection	1 (0.6)	3 (2.1)
Pneumonia fungal	1 (0.6)	6 (4.2)
Pseudomonal bacteraemia	1 (0.6)	4 (2.8)
Sinusitis	0	3 (2.1)

Note: AE=Adverse event; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; GGT=Gamma-glutamyl transferase; InO=Inotuzumab ozogamicin; WBC=White blood cells

*Discontinuation here means discontinuation of treatment. Patients discontinued treatment due to AE but were continued to be followed in the trial.

Treatment related adverse events

Table 11: Treatment related adverse events[20]

Outcomes	InO arm (%)	Control arm (%)
Safety population	164	143
Patients with at least one TRAE	144 (87.8)	130 (90.9)
Patients with grade 3 or 4 TRAE	114 (69.5)	114 (79.7)
Discontinuation due to TRAE*	15 (9.1)	6 (4.2)
Patients with treatment related death	9 (5.5)	3 (2.1)
Patients with dose reduction due to TRAE	4 (2.4)	1 (0.7)
Patients with temporary discontinuation due to TRAE	51 (31.1)	12 (8.4)

Note: TRAE= treatment related adverse event

*Discontinuation here means discontinuation of treatment. Patients discontinued treatment due to AE but were continued to be followed in the trial

All grade adverse event occurring in ≥5% of patients

Table 14: All grade adverse event occurring in ≥5% of patients (Jan 4th, 2017 data cut off)

Outcomes	InO arm (%)	Control arm (%)
Safety population	164	143
Patients with at least one AE	163 (99.4)	143(100)
Blood and lymphatic system disorders	135 (82.3)	126 (88.1)
Thrombocytopenia	81 (49.4)	87 (60.8)
Neutropenia	80 (48.8)	66 (46.2)
Anaemia	55 (33.5)	79 (55.2)
Leukopenia	47 (28.7)	54 (37.8)
Febrile neutropenia	44 (26.8)	77 (53.8)
Lymphopenia	31 (18.9))	36 (25.2)
Gastrointestinal disorders	118 (72.0)	113 (79.0)
Nausea	53 (32.3)	68 (47.6)
Diarrhoea	30 (18.3)	56 (39.2)
Constipation	28 (17.1)	34 (23.8)
Vomiting	26 (15.9)	35 (24.5)
Abdominal pain	21 (12.8)	27 (18.9)
Abdominal pain upper	12 (7.3)	12 (8.4)
Abdominal distension	10 (6.1)	2 (1.4)
Stomatitis	6 (3.7)	10 (7.0)
Dyspepsia	3 (1.8)	9 (6.3)
General disorders and administration site conditions	108 (65.9)	112 (78.3)
Pyrexia	52 (31.7)	60 (42.0)
Fatigue	42 (25.6)	24 (16.8)
Chills	18 (11.0)	17 (11.9)
Asthenia	15 (9.1)	14 (9.8)
Oedema peripheral	13 (7.9)	13 (9.1)
Pain	13 (7.9)	8 (5.6)
Mucosal inflammation	6 (3.7)	20 (14.0)
Chest pain	4 (2.4)	9 (6.3)
Investigations	87 (53.0)	62 (43.4)
AST increased	37 (22.6)	16 (11.2)
GGT increased	35 (21.3)	12 (8.4)
ALT increased	25 (15.2)	18 (12.6)
Blood alkaline phosphatase increased	21 (12.8)	10 (7.0)
Lipase increased	15 (9.1)	1 (0.7)
WBC count decreased	10 (6.1)	9 (6.3)
Infections and infestations	81 (49.4)	110 (76.9)
Pneumonia	13 (7.9)	12 (8.4)
Bacteraemia	7 (4.3)	14 (9.8)
Sepsis	5 (3.0)	12 (8.4)
Sinusitis	4 (2.4)	8 (5.6)
Pneumonia fungal	1 (0.6)	8 (5.6)
Nervous system disorders	74 (45.1)	66 (46.2)
Headache	45 (27.4)	38 (26.6)
Dizziness	12 (7.3)	16 (11.2)
Metabolism and nutrition disorders	65 (39.6)	71 (49.7)
Hypokalaemia	25 (15.2)	33 (23.1)
Decreased appetite	19 (11.6)	18 (12.6)
Hyperglycaemia	13 (7.9)	12 (8.4)

Hypocalcaemia	11 (6.7)	15 (10.5)
Hypoalbuminaemia	10 (6.1)	7 (4.9)
Hypomagnesaemia	10 (6.1)	12 (8.4)
Hypophosphataemia	9 (5.5)	10 (7.0)
Hyponatraemia	5 (3.0)	9 (6.3)
Fluid overload	3 (1.8)	8 (5.6)
Respiratory, thoracic and mediastinal disorders	63 (38.4)	68 (47.6)
Epistaxis	24 (14.6)	13 (9.1)
Cough	22 (13.4)	23 (16.1)
Dyspnoea	10 (6.1)	18 (12.6)
Oropharyngeal pain	6 (3.7)	10 (7.0)
Pleural effusion	4 (2.4)	8 (5.6)
Hepatobiliary disorders	55 (33.5)	28 (19.6)
Hyperbilirubinaemia	35 (21.3)	24 (16.8)
Venoocclusive liver disease	23 (14.0)	3 (2.1)
Musculoskeletal and connective tissue disorders	54 (32.9)	49 (34.3)
Back pain	18 (11.0)	10 (7.0)
Pain in extremity	13 (7.9)	16 (11.2)
Arthralgia	10 (6.1)	7 (4.9)
Bone pain	3 (1.8)	10 (7.0)
Skin and subcutaneous tissue disorders	54 (32.9)	61 (42.7)
Rash	14 (8.5)	27 (18.9)
Pruritus	8 (4.9)	10 (7.0)
Erythema	7 (4.3)	9 (6.3)
Psychiatric disorders	37 (22.6)	42 (29.4)
Insomnia	24 (14.6)	22 (15.4)
Anxiety	8 (4.9)	11 (7.7)
Depression	4 (2.4)	9 (6.3)
Injury, poisoning and procedural complications	36 (22.0)	20 (14.0)
Fall	12 (7.3)	4 (2.8)
Contusion	10 (6.1)	3 (2.1)
Cardiac disorders	25 (15.2)	29 (20.3)
Tachycardia	6 (3.7)	16 (11.2)
Vascular disorders	25 (15.2)	40 (28.0)
Hypotension	12 (7.3)	24 (16.8)
Hypertension	9 (5.5)	9 (6.3)
Eye disorders	15 (9.1)	25 (17.5)
Dry eye	1 (0.6)	8 (5.6)

Note: AE=Adverse event; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; GGT=Gamma-glutamyl transferase; InO=Inotuzumab ozogamicin; WBC=White blood cells

6.4 Ongoing Trials

No ongoing trial was found.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during the development of the review protocol as relevant to the pCODR review of Inotuzumab ozogamicin:

- What is the difference in the effect of inotuzumab ozogamicin when compared to the current competitor blinatumomab in patients with relapsed/refractory acute lymphoblastic leukemia?

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.2.1 Objective

To evaluate the clinical effect of inotuzumab ozogamicin when compared with blinatumomab in patients with relapsed/refractory ALL. Blinatumomab is another monoclonal antibody treatment available in Canada for patients with relapsed/refractory ALL. It is the interest of both clinical review and economic review with input from PAG that these two similar drugs be compared to each other.

7.2.2 Findings

No direct head-to-head study comparing inotuzumab ozogamicin (InO) to blinatumomab (Blina) was identified. A technical report of an indirect treatment comparison (ITC) using the INO-VATE ALL study in InO and the TOWER study in Blina was submitted.[23-25]

Patient-level data (cut-off January 4, 2017) from the INO-VATE-ALL study and published summary data for the TOWER study were used in the analyses[25]. Conventional network meta-analysis (NMA), anchored matching-adjusted indirect comparison (MAIC) or simulated treatment comparison (STC) were used in the ITC to estimate the treatment effect of OS, EFS, the rate of CR/CRi and HSCT. Likely effect modifiers were identified in the table below.

Table 15: Likely treatment effect modifier[25]

	Effect modifiers		
Factors	CR/CRi	HSCT	OS/EFS
Age	Yes	Yes	Yes
Philadelphia chromosome status	Yes	No	Yes
Prior HSCT	Yes	Yes	Yes
Duration of first remission	Yes	No	No
Prior number of salvage therapies	Yes	No	No
Maximum of central/local bone marrow	Yes	No	No
Geographic region	No	Yes	Yes

CR=complete remission; CRi=complete remission with incomplete hematologic recovery; EFS=event-free survival; HSCT=hematopoietic stem cell transplant; OS=overall survival

In anchored MAIC, the adjustment for differences between trials on treatment effect modifiers was made through propensity score re-weighting of the patients in the INO-VATE-ALL study to yield a profile matching the TOWER study. The analysis involved 4 key steps[25]:

1. Deriving balanced weights using a logistic regression model — one for the inotuzumab ozogamicin arm and one for the control arm.
2. Re-weighting patients from INO-VATE-ALL trial by their probability of enrollment in the TOWER trial using logistic regression models derived in Step 1.
3. Deriving estimates of relative effect (ie, inotuzumab ozogamicin vs chemotherapy in the TOWER-like population) for outcomes of interest using re-weighted population.
4. Deriving treatment effect for inotuzumab ozogamicin vs blinatumomab using Bucher method.

In anchored STC, the patient-level data from the index trial (INO-VATE-ALL) were used to create a separate predictive equation for each outcome of interest. Cox regression models were used for OS and EFS, and logistic regression models were used for remission rate and HSCT rate.To derive estimates of the comparative effect of inotuzumab ozogamicin vs chemotherapy in the TOWER-like population, treatment indicator (inotuzumab ozogamicin vs IC), potential treatment-effect modifiers, and interaction terms between treatment indicator (inotuzumab ozogamicin vs IC) with treatment-effect modifier variables were included in the model. All factors were centered at the average observed in the overall TOWER population.Treatment effect for inotuzumab ozogamicin vs blinatumomab was derived using Bucher method[25].

In addition to the standard analyses, time-dependent Cox regression and restricted mean survival time (RMST) were used to quantify differences in OS and EFS between inotuzumab ozogamicin and blinatumomab. These approaches account for potential violation of the proportional hazard assumption due to differences in short- and long-term performance of inotuzumab ozogamicin and blinatumomab against SOC, as shown in the published OS and EFS curves in the INO-VATE-ALL and TOWER trials. Truncation time for RMST analyses was 23 and 20 months, ie, maximum follow-up in the TOWER trial for OS and EFS, respectively[25].

There was an imbalance in the baseline characteristics between the INO-VATE ALL and TOWER trials. The characteristics of likely effect modifiers before and after matching can be found in the table below.

Table 16: Characteristics of likely effect modifiers before and after matching[24]

	InO (INO-VATE-ALL) Before Matching	InO (INO-VATE-ALL) After Matching	IC (INO-VATE-ALL) Before Matching	IC (INO-VATE-ALL) After Matching	Blina + SOC (TOWER) Reported
ESS	164	40	162	44	405
Age (years)					
Median	47	36	48	37	37
Range	18-78	18-78	18-79	18-76	18-80
Age - %					
<35	32.9	47.8	31.5	47.7	45.4
≥35	67.1	52.2	68.5	52.3	54.6
Region - %					
Europe	37.2	65.4	40.7	65.4	65.4
US or Canada	45.7	15.8	48.8	15.8	15.8

	InO (INO-VATE-ALL) Before Matching	InO (INO-VATE-ALL) After Matching	IC (INO-VATE-ALL) Before Matching	IC (INO-VATE-ALL) After Matching	Blina + SOC (TOWER) Reported
Rest of World	17.1	18.8	10.5	18.8	18.8
Previous allogeneic SCT - %					
Yes	17.7	34.7	19.7	34.7	34.7
No	82.3	65.3	80.3	65.3	65.3
Ph+ B precursor ALL status					
Yes	13.4	0	16.7	0	0
No	86.6	100	83.3	100	100
Duration of first remission - %					
<12 months	58.5	39.0	65.4	39.0	39.0
≥12 months	41.5	61.0	34.6	61.0	61.0
Salvage treatment phase - % (CRF)					
First	67.7	41.2	63.0	41.2	41.2
Second or later	31.1	58.8	36.4	58.8	58.8
Missing	1.2	0	0.6	0	0
Maximum of central/local bone marrow blasts - %					
<50%	32.3	22.2	30.0	21.4	24.5
≥50%	66.5	77.8	70.0	78.6	75.5
Missing	1.2	0	0.6	0	0.2
Maximum of central/local bone marrow blasts (%)					
n	162	138	161	133	404
Mean	63.1	70.2	63.1	70.2	70.2
SD	28.6	13.9	29.3	15.1	29.1
Median	71.7	82.1	73.0	79.5	81/83
Q1, Q3	38, 90	60, 90	39, 90	60, 90	NR
Min, Max	5, 100	6, 100	5, 100	7, 100	6, 100

Abbreviations: ALL = acute lymphoblastic leukemia; Blina = blinatumomab; CRF = case report form; ESS = effective sample size; IC = investigator's choice; InO = inotuzumab ozogamicin; Ph = Philadelphia chromosome; SCT = stem cell transplantation; SD = standard deviation; SOC = standard of care; US = United States

The effect estimates by the different approaches of ITC can be found in the table below.

Table 17: Effect estimates by different approaches of ITC[24,25]

	ITT		ADJUSTED		Indirect Treatment Comparisons		
	TOWER Blina vs. SOC	INO-VATE-ALL InO vs. SOC	INO-VATE-ALL InO vs. SOC, MAIC	INO-VATE-ALL InO vs. SOC, STC	InO vs. Blina, NMA	InO vs. Blina, MAIC	InO vs. Blina, STC
CR/CRi Remission Rate							
OR (95% CI)	2.40 (1.51, 3.80)	6.30 (3.89, 10.21)	6.75 (3.04, 14.95)	9.38 (4.14, 21.25)	2.63 (1.35, 5.12)	2.81 (1.12, 7.05)	3.91 (1.53, 9.99)
Difference (95% CI)	19.28	42.92	44.40	50.72	23.64	25.12	31.44

	ITT		ADJUSTED		Indirect Treatment Comparisons		
	TOWER Blina vs. SOC	INO-VATE-ALL InO vs. SOC	INO-VATE-ALL InO vs. SOC, MAIC	INO-VATE-ALL InO vs. SOC, STC	InO vs. Blina, NMA	InO vs. Blina, MAIC	InO vs. Blina, STC
	(9.90, 28.67)	(33.12, 52.71)	(28.42, 60.38)	(35.74, 65.70)	(10.10, 37.20)	(6.60, 43.70)	(13.80, 49.10)
HSCT Rate							
OR (95% CI)	1.01 (0.62, 1.63)	3.25 (2.01, 5.26)	4.15 (2.20, 7.85)	3.81 (2.03, 7.18)	3.23 (1.63, 6.40)	4.11 (1.85, 9.12)	3.77 (1.71, 8.35)
Difference (95% CI)	0.10 (-8.72, 8.93)	25.95 (15.98, 35.92)	31.13 (18.40, 43.85)	29.43 (16.59, 42.27)	25.85 (12.50, 39.20)	31.03 (15.50, 46.50)	29.33 (13.70, 44.90)
EFS*,* **							
HR (95% CI)	0.55 (0.43, 0.71)	0.47 (0.36, 0.60)	0.40 (0.28, 0.57)	0.40 (0.28, 0.56)	0.85 (0.60, 1.20)	0.73 (0.47, 1.13)	0.73 (0.48, 1.11)
RMST Difference in months (95% CI)**	2.10 (0.76, 3.43)	4.81 (3.52, 6.11)	5.70 (3.90, 7.49)	NA	2.71 (0.85, 4.57)	3.60 (1.37, 5.83)	NA
RMST Ratio (95% CI)**	1.90 (1.18, 3.07)	3.42 (2.34, 4.98)	4.31 (2.47, 7.54)	NA	1.80 (0.98, 3.31)	2.27 (1.09, 4.74)	NA
Overall Survival*							
Overall HR (95% CI)	0.71 (0.55, 0.93)	0.75 (0.57, 0.99)	0.68 (0.47, 0.97)	0.72 (0.50, 1.03)	1.06 (0.72, 1.56)	0.96 (0.61, 1.50)	1.01 (0.65, 1.59)
0–15-month HR (95% CI)	0.73 (0.55, 0.96)	0.83 (0.64, 1.07)	0.74 (0.51, 1.08)	0.79 (0.55, 1.14)	1.14 (0.78, 1.65)	1.01 (0.64, 1.62)	1.08 (0.69, 1.71)
15+-month HR (95% CI)	1.03 (0.10, 10.23)	0.33 (0.17, 0.67)	0.25 (0.08, 0.79)	0.26 (0.11, 0.65)	0.32 (0.03, 3.54)	0.24 (0.02, 3.17)	0.25 (0.02, 2.99)
RMST Difference in months (95% CI)**	2.05 (0.03, 4.07)	1.68 (-0.03, 3.39)	2.35 (-0.08, 4.78)	NA	-0.37 (-3.02, 2.28)	0.30 (-2.86, 3.46)	NA
RMST Ratio (95% CI)**	1.25 (0.99, 1.57)	1.19 (1.00, 1.42)	1.27 (0.99, 1.64)	NA	0.95 (0.71, 1.27)	1.02 (0.72, 1.43)	NA

***** Restricted set of treatment-effect modifiers

****** 23.25 (20) months of follow-up for OS (EFS)

******* Sensitivity definition of PFS in INO-VATE-ALL trial

Abbreviations: AE = adverse event; Blina = blinatumomab; CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; EFS = event-free survival; HR = hazard ratio; HSCT = hematopoietic stem cell transplantation; InO = inotuzumab ozogamicin; ITT = intent to treat; MAIC = matching-adjusted indirect comparison; NA = not applicable; NMA = network meta-analysis; OR = odds ratio; RMST = restricted mean survival time; SAE = serious adverse event; SOC = standard of care; STC = simulated treatment comparison

7.2.3 Assessment of quality

The quality of the ITC was assessed according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research Task Force on ITC.[41] Details of the critical appraisal are presented in the table below.

Table 18: ISPOR questionnaire to critically appraise the quality of the ITC

ISPOR questions	Assessment and comments
Is the population relevant?	Yes, in general. However, the baseline characteristics of the two included RCTs differed from each other in some area.
Are any relevant interventions missing?	No, all the relevant interventions were included.
Are any relevant outcomes missing?	Yes, quality of life was not a part of the ITC.
Is the context (e.g., settings and circumstances) applicable?	Yes, the setting in the RCT was appropriate to the policy decision.
Did the researchers attempt to identify and include all relevant RCTs?	No search was mentioned in the technical report.
Do the trials for the interventions of interest form one connected network of RCTs?	Yes, in general. But the connection between inotuzumab and blinatumomab did not match well, which require adjustment to allow proper comparison.
Is it apparent that poor quality studies were included, thereby leading to bias?	Both RCTs were good quality RCTs.
Is it likely that bias was induced by selective reporting of outcomes in the studies?	TOWER trial was stopped early at 15 months, therefore, the bias introduced by early termination might affect the comparison.
Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that have an impact on the treatment effects) across the different treatment comparisons in the network?	The baseline characteristics were different in multiple categories including age, duration of remission, number of previous salvage therapies and etc.
If yes (i.e., there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified before comparing individual study results?	Yes. It seemed like patients enrolled in TOWER trials had more severe disease than patients in INO-VATE ALL trial.
Were statistical methods used that preserve within-study randomization? (No naïve comparison)	Bucher method was used to compare the inotuzumab to blinatumomab. However, in order to adjust for the differences in baseline between the RCTs, MAIC and STC were used which selectively included patients that matched the TOWER trial or simulate a control arm that would match the TOWER trial. In this case, the within-study randomization was no longer intact.
If both direct and indirect comparisons are available for pairwise contrasts (i.e. close loops), was an agreement in treatment effects (i.e. consistency) evaluated or discussed?	The network was linear, no direct comparison available.
In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable.

With inconsistency or imbalance in the distrbution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	Yes, MAIC and STC were used to balance out the imbalance caused by treatment effect modifiers.
Was a valid rationale provided for the use of random effect or fixed effect models?	Not applicable.
If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable.
If there are indications of heterogeneity, were subgroup analysis or meta-regression analysis with pre-specified covariates performed?	Not applicable.
Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Not applicable.
Are the individual study result reported?	Yes, result from both INO-VATE ALL and TOWER trial was presented.
Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Not applicable.
Are all pairwise contracts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes, 95% confidence interval was reported for each estimate.
Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Not applicable.
Is the impact of important patient characteristics on treatment effects reported?	Yes, the result of outcomes after adjustments was reported.
Is the conclusion fair and balanced?	The conclusion is fair and did not make excessive extrapolation. In general, OS and EFS did not show any statistical difference between inotuzumab and blinatumomab but the rate of CR/CRi and HSCT favor toward inotuzumab.
Were there any potential conflicts of interest?	The report was prepared for the submitter. Other than that, no conflict of interest was reported.
If yes, were steps taken to address these?	Not applicable.

Note: CR/CRi=complete remission or complete remission with incomplete hematological recovery; EFS=event free survival; HSCT=Hematopoietic stem cell transplantation; ITC=indirect treatment comparison; MAIC=matched adjusted indirect comparison; OS=overall survival; RCT=randomized control trial; STC=simulated treatment comparison

7.2.4 Summary

A standard indirect comparison was not appropriate since the baseline characteristics of patients in the control arm were different in several important categories, such as the number of prior stem transplant, number of salvage therapy, and that Philadelphia positive patients were excluded from TOWER study[2,23]. In addition, the TOWER trial was stopped at month 15 which was shorter than the duration of the INO-VATE ALL trial. Alternative statistical approaches were used in order to address the imbalance in two trials. Each approach presents its own strength and limitations. MAIC depends on the comparability of the data. The less comparable the data were, the smaller the effective sample size, which lead to greater uncertainty. STC depends on the accurate modeling of the predictive equations and the quality of the input parameters. Results from both approaches were presented for comparison.

The effective sample size was reduced by 50% in most outcomes in the MAIC analysis suggesting a limited overlap of the population in the two RCTs[24,25]. The loss of a large percentage of effective sample size also introduced a large amount of uncertainty in the result. In addition, for both MAIC and STC, there were other potential confounders that were not adjusted for, such as CD22 expression, hepatic comorbidity, and the difference in the composition of chemotherapy in control arms. The results presented in both MAIC and STC was similar. The indirect comparison showed that a greater number of patients receiving InO had completed remission or completed remission with incomplete hematological recovery and had proceeded to a stem cell transplant. The result was not statistically significant for OS or EFS[24,25].

The method presented in the submitted technical report was appropriate and the assumptions made were reasonable. In the absence of a direct comparison study, and limited comparable indirect data, MAIC and STC can be a useful tool to adjust for baseline imbalance and produce a reasonable prediction of the difference between InO and blinatumomab for economic modeling. As for clinical evaluation, this analysis should only be considered hypothesis generating.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Leukemia Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on inotuzumab ozogamicin (Besponsa) for ALL . Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Leukemia Clinical Guidance Panel is comprised of three clinicians .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials November 2017, Embase 1974 to 2017 November 17, Ovid MEDLINE(R) ALL 1946 to November 17, 2017

#	Searches	Results
1	(inotuzumab ozogamicin* or Besponsa* or CMC544 or CMC-544 or WAY-207294 or WAY207294 or (CD22 adj10 antibod* adj10 calicheamicin adj10 conjugate)).ti,ab,ot,kf,kw,hw,rn,nm.	735
2	(P93RUU11P7 or 635715-01-4).rn,nm.	465
3	or/1-2	735
4	3 use medall	124
5	3 use cctr	32
6	*inotuzumab ozogamicin/ or (inotuzumab ozogamicin* or Besponsa* or CMC544 or CMC-544 or WAY-207294 or WAY207294 or (CD22 adj10 antibod* adj10 calicheamicin adj10 conjugate)).ti,ab,kw.	351
7	6 use oemezd	214
8	7 and conference abstract.pt.	99
9	limit 8 to yr="2012 -Current"	80
10	limit 9 to english language	80
11	7 not conference abstract.pt.	115
12	4 or 5 or 11	271
13	limit 12 to english language	263
14	remove duplicates from 13	153
15	10 or 14	233
16	remove duplicates from 15	217

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#4	Search #1 AND #2 Sort by: PublicationDate Filters: English	2
#3	Search #1 AND #2 Sort by: PublicationDate	2
#2	Search publisher[sb] Sort by: PublicationDate	526767
#1	Search inotuzumab ozogamicin*[tiab] OR Besponsa*[tiab] OR CMC544[tiab] OR CMC-544[tiab] OR WAY-207294[tiab] OR WAY207294[tiab] OR (CD22[tiab] AND antibod*[tiab] AND calicheamicin[tiab] AND conjugate[tiab]) Sort by: PublicationDate	94

3. Cochrane Central Register of Controlled Trials (Central)

Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: BESPONSA/inotuzumab ozogamicin, relapsed or refractory B-cell precursor acute lymphoblastic leukemia

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: BESPONSA/inotuzumab ozogamicin, relapsed or refractory B-cell precursor acute lymphoblastic leukemia

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology (ASH)
www.hematology.org/

European Society for Medical Oncology (ESMO)
http://oncologypro.esmo.org/Meeting-Resources

Search: Search: BESPONSA/inotuzumab ozogamicin, relapsed or refractory B-cell precursor acute lymphoblastic leukemia - last 5 years

Detailed Methododolgy

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (November 2017) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was BESPONSA/inotuzumab ozogamicin.

No filters were applied to limit the retrieval by study type. The search was limited to English-language documents, but not limited by publication year.

The search is considered up to date as of April 5, 2018.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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