CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Inotuzumab Ozogamicin (Besponsa) for Acute Lymphoblastic Leukemia

July 6, 2018

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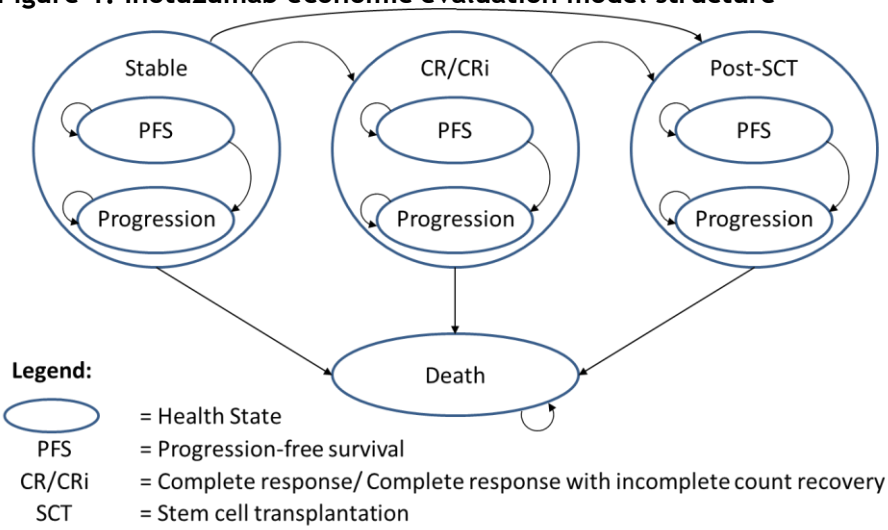
1 ECONOMIC GUIDANCE IN BRIEF

1.2 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Pfizer Canada Inc.** compared Inotuzumab Ozogamicin [Inotuzumab] (Besponsa) to standard of care represented by chemotherapy with hyper-CVAD) for patients with acute lymphoblastic leukemia (ALL). An alternative scenario where Inotuzumab is compared to Blinatumomab (Blincyto) is also presented.

Table [1]. Submitted Economic Model

Funding Request/Patient Population Modelled	The funding request is for the treatment of patients aged 18 years and over, having relapsed or refractory CD22 positive ALL, and being due to receive either Salvage 1 or Salvage 2 therapy (reflecting the population from the INO-VATE ALL trial), which is similar to the patient population in the model except that the model assumes a patient starts at the age of 46.
Type of Analysis	*CUA, along with CEA and CCA (for comparison with blinatumomab)*
Type of Model	*Markov cohort*
Comparator	*Chemotherapy (hyper-CVAD)* *Blinatumomab*
Year of costs	*CAD$2017*
Time Horizon	*Lifetime*
Perspective	Canadian publicly funded health care system
Cost of Inotuzumab *Accessed IMS Brogan on April 9, 2018	At the list price, inotuzumab ozogamicin costs $14,405.85 per 0.9mg vial. At the recommended dose of 1.8 mg/m^2 for cycle 1 (see dosing details per day and cycle below), with a BSA of 1.7 m^2, the cost of inotuzumab ozogamicin is $2,743.97 per day or $57,623.40 per 21 day course (accounting for wastage). At the recommended dose of 1.5 mg/m^2 for cycle 2 onwards for patients who achieved a complete response [CR] (see dosing details per day and cycle below), with a BSA of 1.7 m^2, the cost of inotuzumab ozogamicin is $1,543.48 per day or $43,217.55 per 28 day course (accounting for wastage). At the recommended dose of 1.8 mg/m^2 for cycle 2 onwards for patients who did not achieve CR (see dosing details per day and per cycle), with a BSA of 1.7 m^2, the cost of inotuzumab ozogamicin is $2,057.98 per day or $57,623.40 per 28 day course (accounting for wastage). In the submitted model, the average cost per patient for complete treatment (average use of 10.2 vials per patient), based on a BSA of 1.88m^2 is $149,008.68 (accounting for wastage and average number of cycles in the trial) Dosing details for intozumab ozogamicin: Cycle 1 = 21 days. Day 1 = 0.8 mg/m^2, Day 8 and Day 15 = 0.5 mg/m^2 Cycle 2 and onwards = 28 days

	Day 1 = 0.8 mg/m^2 if no CR/CRi, 0.5 mg/m^2 if CR/CRi Day 8 and Day 15 = 0.5 mg/m^2 Maximum of 6 cycles.
Cost of HYPER-CVAD *as per* blinatumomab for ALL (Resubmission to pCODR). Cost of blinatumomab (as reported in the blinatumomab submission to pCODR) *Accessed IMS Brogan on April 9, 2018	HYPER CVAD consists of multiple agents. In the submitted model, the cost of HYPER CVAD is $2,049 per 28-day cycle (average of 1.23 cycles in the INO-VATE ALL trial.) The average cost per patient treated is $2,522.62. At the list price, blinatumomab costs $2,978.26 per 38.5 mcg. Assuming 2 cycles, the recommended dose of 9 mcg/day for 7 days, then 28 mcg/day for 21 days for cycle 1, and 28mcg/day for 28days for cycle 2, the cost of blinatumomab is $1,978.38 per day or $55,394.59 per 28 day course or $83,091.89 per 6 week cycle (accounting for wastage and administration costs), which is assumed in the model.
Model Structure	A state transition Markov model was developed. Patients enter the model in the health state "stable disease", and can either remain in that health state, experience disease progression, achieve a complete remission (CR)/complete remission with incomplete hematologic response (CRi), proceed to hematopoietic stem cell transplantation (HSCT) or die. Patients who experience disease progression remain in that health state until they die. The model structure is presented below: **Figure 1. Inotuzumab economic evaluation model structure**  Patients start in the model at the age of 46. Patients who survived the SCT, after the trial period were assumed to have a mortality risk 4 times above the general population (RR=4).
Key Data Sources	• INO-VATE ALL study[1,2,3] (trial PFS and OS Kaplan-Meier (K-M) curves were fit with several candidate hazard functions), • TOWER trial for blinatumomab – no head-to-head clinical data, MAIC was performed by Pfizer for the indirect comparison.

	• For on-treatment utilities, the value set from a Canadian published study that used the time trade-off technique (Bansback ***et al***. 2012)[4] was applied to the EQ5D-3L data collected in the INO-VATE ALL study. • Utility of progressed disease and utility for patients undergoing HSCT was sourced from published literature as quality of life was not captured in the INO-VATE trial for these health states. • Hospitalization costs, HSCT costs and adverse events were obtained from the Ontario Case Costing Initiative and/or published literature.

1.1 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), there is a net clinical benefit from treatment with inotuzumab ozogamicin in patients with with relapsed or refractory CD22+ pre-B ALL compared to chemotherapy. Relevant issued identified included:

Overall survival did not differ between the groups once corrections were made for multiple comparisons.[1,2,3] The difference in PFS was clinically meaningful and a small subset (approximately 20%) of patients treated with inotuzumab enjoyed very long survival. Patients who survived for more than 14 months from the start of treatment were likely cured.

A greater proportion of patients in the inotuzumab group received definitive therapy with hematopoietic cell transplantation (47% vs. 20.4%),[2] although it is unclear whether the difference in HCT rates explains the improved survival noted in the InO group.

The primary definition of progression-free survival (PFS) in the INO-VATE ALL trial included patients who withdrew due to global deterioration of health status or starting new induction therapy or post-therapy HSCT without achieving CR/CRi (protocol definition). This definition was different from 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). Since there were more patients in the control arm who proceeded to HSCT after a new induction therapy, under the protocol definition these patients might be considered as being in the progressed disease state which led to greater effect size in hazard ratio favoring Inotuzumab. 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.

The submitter has provided a clinically relevant indirect comparison of inotuzumab and blinatumomab 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 inotuzumab groups and the resulting substantial reduction in the sample size once non-overlapping patient subsets were excluded, the CGP believes this comparison is only hypothesis-generating. The economic analysis compared inotuzumab to blinatumomab used this indirect comparison estimates to reflect the differences in remission and transplant rates, and after the transplant, assumed the same survival for both inotuzumab or blinatumomab-treated patients, based on data from the inotuzumab arm in the pivotal trial. The lack of direct evidence of comparative efficacy and the indirectly derived estimates may create considerable uncertainty around the cost-effectiveness of inotuzumab and blinatumomab.

Summary of registered clinician input relevant to the economic analysis
According to the pCODR Clinical Guidance Panel (CGP) the base-case comparison with hyper-CVAD is appropriate. 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. All regimens are quite toxic and often ineffective.

The economic model compared to chemotherapy used the costs of hyper-CVAD but the clinical data from the chemotherapy arm from the pivotal trial that includes other regimes used in Canada (FLAG, cytarabine plus mitoxantrone, high dose cytarabine). Survival after transplant was assumed treatment independent and used pooled data from both arms of the pivotal trial.

The clinicians providing input noted that the advantage of inotuzumab is the better toxicity profile considered manageable, and the option to have this treatment as outpatient. The key disadvantage is the potential for liver toxicity. Both side effects and in-hospital/outpatient treatment were appropriately reflected in the cost-utility analysis.

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.

Summary of patient input relevant to the economic analysis

Input was received from patients and caregivers for the review of inotuzumab but no patients or caregivers had direct experience with inotuzumab. In terms of experience with the ALL they were unanimous in how important it is to have better treatment options with less side effects, and the majority of the respondents stated the available therapies were not able to manage their ALL symptoms. Adverse events and quality of life during treatment with inotuzumab were appropriately reflected in the economic analysis.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

PAG considered the following factors important to consider if implementing a funding recommendation for inotuzumab which are relevant to the economic analysis:

Clinical factors:

- Whether there is data for use in pediatric ALL: The pivotal trial did not include pediatric ALL and the economic analysis assumed patients started the model at 46 years of age.
- Clarity on whether treatment is for patients with first relapse, second relapse, or either: The economic analysis included patients in 1st and 2nd salvage therapic, and allowed to isolate the ICER for those in 1st salvage therapy, but not for 2nd salvage therapy.
- For patients with Philadelphia chromosome positive ALL, clarity that treatment is with oral tyrosine kinase inhibitors first, then inotuzumab ozogamicin or vice versa. Sequencing of treatment was not explicited in the model, although it did include the costs of tyrosine kinase inhibitors for those who failed to respond to inotuzumab, but not the contrary.
- For patients with Philadelphia chromosome negative ALL, appropriate sequencing of inotuzumab ozogamicin and blinatumomab. Sequencing of treatment was not explicited in the model, although it did include the costs of blinatumomab for those who failed to respond to inotuzumab, but not the contrary.

Subgroup analysis were presented for Philadelphia negative patients, <55 years patients , ≥55 years patients,patients with no prior HSCT, salvage 1 patients, patients with a prior duration of

remission of ≥12 months, patients with a prior duration of remission of <12 months, patients with CD22≥90%, HSCT ineligible patients (Inotuzumab versus BSC), and patients without HSCT.

Economic factors:

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

All three factors were incorporated into the economic analysis and extensively subject of reanalysis by EGP. The amount of drug extracted from one vial and the average BSA of ALL in Canada are the two most important factors impacting the cost-effectiveness of the drug after the time horizon assumed in the model.

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. However, 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. PAG also noted that the time and resources required to prepare and administer inotuzumab ozogamicin is less than that required for blinatumomab.

The economic analysis used the number of inpatient days in the trial to account for the costs of administration and management of side effects (10 days per patient).

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 a 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 EGP would like to clarify that the use and cost of defibrotide to manage veno-occlusive disease was not considered in the pharmacoeconomic model. In the submitted PE report, the Submitter states that "the cost of treating VOD is based on the cost of acute hepatic failure reported by the OCCI. Defibrotide has recently received a Notice of Compliance (NOC) from Health Canada but has currently not been assessed by CADTH. It is therefore not reimbursed on the Canadian market. It is not expected to be publicly reimbursed in Canada at the time of the inotuzumab pCODR recommendation. As the number of options to treat VOD in Canada is limited, the cost of acute liver failure is representative of best supportive care".

1.2 Submitted and EGP Reanalysis Estimates

The Submitter commented on the pCODR Expert Review Committee's (pERC) Initial Recommendation that pERC may have deliberated on the cost-effectveness of inotuzumab ozogamicin based on results of probabilistic analyses that were run using an influential parameter that was incorrect. The Submitter explained that this error occurred because of an error in the submitted pharmacoecnommic model. Specifically, the body surface area (BSA) parameter needed to be manually modified in two places when running the probabilistic sensitivity analyses. As a

result, pERC concluded that substantial uncertainty exists in the economic model. The Submitter believes that the probabilistic analysis results should have been more consistent with the determinisitic analysis results. This error applies to both the comparison with chemotherapy (Hyper-CVA) and blinatumomab.

Table [2]. Submitted and EGP Reanalysis Estimates Inotuzumab Ozogamicin Compared to Hyper-CVAD (Reference Case) – deterministic results

Estimates (range/point)	Submitted	Lower Bound (BSA 1.70)	Best Guess (BSA 1.70)	Upper Bound (BSA 1.80)
ΔE (LY)	1.683	0.612	0.547	0.419
ΔE (QALY)	1.316	0.754	0.669	0.669
ΔC ($)	$120,883.05	$109,370.39	$109,745,88	$140,559.56
ICER estimate ($/QALY)	$91,840.63	$178,800.89	$200,596,80	$335,752.14

In response to the Submitter's feedback, the EGP acknowledge the error in the submitted pharmacoeconomic model regarding the BSA parameter. As a result, the EGP re-ran the probabilistic analysis, manually modifying the BSA in two places in the pharmacoecnomic model as instructed by the Submitter for the comparison of inotuzumab ozogamicin to hyper-CVAD. For the best guess deterministic scenario (ICER $200,596.80/QALY), the EGP re-ran the probabilistic analysis for 5000 iterations and the ICER result was $202,556.66/QALY. The greatest uncertainity that remained was around the amount of QALYs gained (Figure 9: horizontal cloud dispersion) from the treatment which was highly influenced by the assumptions on the source of utilities, data for survival extrapolations and time horizon (rather than parameter uncertainty). Uncertainty around incremental costs were more related to the assumptions around average BSA and extractable amount per vial and their direct effect on wastage.

Table [3]. Submitted and EGP Reanalysis Estimates Inotuzumab Ozogamicin Compared to Blinatumomab (Scenario Analysis) – deterministic results

Estimates (range/point)	Submitted	Lower Bound (BSA 1.70)	Upper Bound (BSA 1.88)
ΔE (LY)	1.531	0.604	0.651
ΔE (QALY)	1.151	0.447	0.483
ΔC ($)	-$8,799.53	-$9,404.97	$54,504.46
ICER estimate ($/QALY)	-$7,642.65	-61,195.10	112,898.91

In response to the Submitter's feedback, the EGP acknowledge the error in the submitted pharmacoeconomic model regarding the BSA parameter. As a result, the EGP re-ran the probabalstic analysis manually modifying the BSA in two places in the pharmacoecnomic model as instructed by the Submitter for the comparison of inotuzumab ozogamicin to blinatumomab. For the best guess deterministic scenario (ICER -$61,195,10/QALY), the EGP re-ran the probabilistic analysis for 5000 iterations and the ICER result was -$63,902.38/QALY. The greatest uncertainity that remained was around the amount of QALYs gained (Figure 10: horizontal cloud dispersion), and a few instances when the treatment was not cost-saving but had an incremental cost associated. However, it is worth noting that this comparison was generated by indirect evidence and no studies directly comparing these two drugs have been conducted. The lack of direct evidence of comparative efficacy and the indirectly derived estimates may create considerable uncertainty around the cost-effectiveness of inotuzumab and blinatumomab.

The main assumptions and limitations with the submitted economic evaluation were:
Some concerns remain with a combination of factors such as the incompatibility of PFS data collection (due to the trial design) with the model structure, and the use of different utility values for progression in the post-HSCT state. The EGP recognizes the limitations of the PFS data with the model structure and that this might justify the use of another source of utility data for progression, however, because the impact on ICERS when using the classic "same utility value for progression states" is significant, and cannot be addressed within this model structure, extrapolations far beyond the trial period will amplify overestimations of QALYS.

The economic model assumes that patients enter at 46 years of age. The base case then assumes a time horizon of 60 years. The likelihood of any person in the general Canadian population living to 106 years is very low. In cases where extrapolation is required to estimate long-term effect, external data sources, biology or clinical expert judgement may be used to justify the plausibility of extrapolation (CADTH guidelines, Page 43). Due to the remaining incompatibility of PFS data with the model structure and the use of different source of utility data, in addition to the highly censored data from the trial after 2 years, the uncertainty around the survival of ALL patients in the long term, and remaining parameter uncertainty (PSA results demonstrates that there is a 50% chance that the ICER will be lower than 100K/QALYs), EGP recommends that the base case be limited to 10-years and every other sensitivity analysis to be performed on the same time horizon to reduce uncertainty around the best estimate of the real ICER.Furthermore, the CGP suggested that based on clinical experience, a 10 year time horizon is more clinically plausible in this patient population.

Beyond the limitations with the model structure, the number of vials necessary per patient - which is directly affected by the assumptions on the extractable amount per vial and the BSA of ALL patients - are the main drivers of the cost-effectiveness results. The EGP reduced the average extractable amount for the reanalysis to 0.90 mg based on the approved Health Canada product monograph.

Extrapolations of survival after the trial period were also a concern since the results submitted demonstrates that extrapolations based on the pivotal trial data were more similar to a RR=10 over the general population mortality rather than the RR=4 used in the base-case.

1.3 Detailed Highlights of the EGP Reanalysis

EGP further performed extensive sensitivity analysis (one-way and multiple-way) in the parameters:

- Actual n. vials used in the trial
- Extractable amount at 0.90mg per vial
- Extrapolations after trial period using pooled survival after HSCT (parametric Gen gamma) or RR of 10 compared to general population
- Attributing costs to every patient entering the model (including those who died in the first cycle, when treatment costs incur in the model)
- Adjusted utility values for VOD
- Unit cost price reductions
- Equal utility values for progression states

Table [4]: Detailed Description of EGP Reanalysis Estimates of Inotuzumab compared to HYPER-CVAD (Reference Case) – Deterministic Results

		Costs	QALYs	LYs	ICER	Difference from base-case lifetime	Difference from base-case with a 10-year time horizon
BSA of 1.88 as per base-case	Base case (lifetime)	$120,883.05	1.316	1.683	$91,840.63		
	Base case (lifetime) + All grade 3+4 AE rates (not only treatment related)	$121,630.93	1.316	1.683	$92,408.83	1%	
	Base-case (lifetime)+ 25% price reduction	$86,494.14	1.316	1.683	$65,713.73	-28%	
	Base-case (lifetime)+ 50% price reduction	$52,105.23	1.316	1.683	$39,586.83	-57%	
	Base-case (lifetime)+ 75% price reduction	$17,716.31	1.316	1.683	$13,459.93	-85%	
	Base-case (10-years)	$120,220.50	0.612	0.754	**$196,538.88**	114%	
	Base-case (10-years)+ 25% price reduction	$85,831.59	0.612	0.754	$140,319.20	53%	-29%
	Base-case (10-years)+ 50% price reduction	$51,442.68	0.612	0.754	$84,099.52	-8%	-57%
	Base-case (10-years)+ 75% price reduction	$17,053.76	0.612	0.754	$27,879.83	-70%	-86%
	Base-case (10-years) + Utilities in progression 0.30 regardless of transplant	$120,220.50	0.472	0.754	$254,696.98	177%	30%
	Base-case (10-years) + Same utilities in progression regardless of transplant U_PD =0.30 Allocation of Prop_noCR_HSCT to Prop_CR_HSCT	$120,220.50	0.469	0.754	$256,110.79	179%	30%
	Base-case (10-years) + Utility for progression after transplant from Kurosawa (as in the base case) Utility of VOD as 0.35 instead of 0.50	$120,220.50	0.611	0.754	$196,907.13	114%	0%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model	$122,369.51	0.612	0.754	$200,052.12	118%	2%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial	$127,286.03	0.612	0.754	$208,089.75	127%	6%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg	$191,934.54	0.612	0.754	$313,778.43	242%	60%
BSA of 1.80	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.80	$140,224.06	0.612	0.754	$229,241.10	150%	17%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.80+	$140,288.80	0.603	0.743	$232,637.43	153%	18%

	Extrapolation after trial period for HSCT survivors using RR 10 vs general population						
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.80+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled - treatment independent)	$140,599.56	0.547	0.669	$256,992.07	180%	31%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.80+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled - treatment independent)+ 25% price reduction	$101,073.05	0.547	0.669	$184,744.34	101%	-6%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.80+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled - treatment independent)+ 50% price reduction	$61,546.54	0.547	0.669	$112,496.61	22%	-43%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.80+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled - treatment independent)+ 75% price reduction	$22,020.03	0.547	0.669	$40,248.88	-56%	-80%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.80+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled - treatment independent)+ 57.5% price reduction	$49,688.59	0.547	0.669	$90,822.29	-1%	-54%

	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.80+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled - treatment independent)+ Utilities for progression 0.30	$140,599.56	0.419	0.669	$335,752.14	266%	71%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.80+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled - treatment independent)+ Utilities for progression 0.30+ 25% price reduction	$101,073.05	0.419	0.669	$241,362.73	163%	23%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.80+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled - treatment independent)+ Utilities for progression 0.30+ 50% price reduction	$61,546.54	0.419	0.669	$146,973.32	60%	-25%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.80+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled - treatment independent)+ Utilities for progression 0.30+ 75% price reduction	$22,020.03	0.419	0.669	$52,583.91	-43%	-73%
BSA of 1.70	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.70	$109,370.39	0.612	0.754	$178,800.89	95%	-9%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.70+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled – treatment independent)	$109,745.88	0.547	0.669	$200,596.80	118%	2%

	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.70+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled – treatment independent)+ 25% price reduction	$77,932.79	0.547	0.669	$142,447.89	55%	-28%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.70+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled – treatment independent)+ 50% price reduction	$46,119.71	0.547	0.669	$84,298.97	-8%	-57%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.70+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled – treatment independent)+ 75% price reduction	$14,306.62	0.547	0.669	$26,150.06	-72%	-87%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.70+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled – treatment independent)+ 47% price reduction	$49,937.28	0.547	0.669	$91,276.84	-1%	-54%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.70+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled – treatment independent)+ Utilities for progression 0.30	$109,745.88	0.419	0.669	$262,073.48	185%	33%

	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.70+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled – treatment independent)+ Utilities for progression 0.30+ 25% price reduction	$77,932.79	0.419	0.669	$186,103.73	103%	-5%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.70+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled – treatment independent)+ Utilities for progression 0.30+ 50% price reduction	$46,119.71	0.419	0.669	$110,133.99	20%	-44%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.70+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled – treatment independent)+ Utilities for progression 0.30+ 75% price reduction	$14,306.62	0.419	0.669	$34,164.24	-63%	-83%
	Base-case (10-years) + Treatment costs attributed to every patient entering the model+ Actual n. vials used in the trial+ Extractable amount per vial 0.90mg+ BSA 1.70+ Extrapolation after trial period for HSCT survivors using Gen Gamma (pooled – treatment independent)+ Utilities for progression 0.30+ 44% price reduction	$38,484.56	0.419	0.669	$91,901.25	0%	-53%

The best guess for the deterministic estimate for the *ICER was generated assuming a **10-year time horizon** (with the use of KM data for the first 15 months + pooled fitted curves for extrapolation up to 50 months + pooled fitted curves for extrapolation after the trial period for HSCT survivors), an average extractable amount of the drug of 0.90mg per vial, an average BSA of 1.70m^2 (This was chosen to be consistent with previous submissions to pCODR, including blinatumomab.), the actual average number of vials used in the trial (9.3 vials), and incurred treatment costs for every patient entering the model (including those who died at cycle 1).* The best guess deterministic scenario ICER was $200,596.80/QALY. The EGP re-ran the probabilistic analysis for 5000 iterations and the ICER result was $202,556.66/QALY. The greatest uncertainity

that remained was around the amount of QALYs gained from the treatment which was highly influenced by the assumptions on the source of utilities, data for survival extrapolations and time horizon (rather than parameter uncertainty). Uncertainty around incremental costs were more related to the assumptions around average BSA and extractable amount per vial and their direct effect on wastage.

Table [5]. EGP Reanalysis Estimates Inotuzumab compared to Blinatumomab (Scenario Analysis) – deterministic results

		Costs	QALYs	Lys	ICER	Difference from base-case lifetime	Difference from base-case with a 10-year time horizon
BSA of 1.88 as per base-case	Blinatumomab (lifetime)	-$8,799.53	1.151	1.531	-$7,642.65		
	Blinatumomab (10-year)	-$9,404.97	0.483	0.651	-$19,481.18	155%	
	Blinatumomab (10-year) + 0.90 mg per vial	$54,504.46	0.483	0.651	$112,898.91	-1577%	-680%
BSA of 1.70	Blinatumomab (10-year) + 0.90 mg per vial	-$27,553.17	0.483	0.651	-$57,072.81	647%	193%
	Blinatumomab (10-year) + 0.90 mg per vial+ Extrapolation after trial period for HSCT survivors using Gen Gamma+	-$27,343.79	0.447	0.604	-$61,195.10	701%	214%

The best guess deterministic scenario using a 10 year time horizon, 0.90 mg per vial, BSA 1.70m^2 and extrapolation after trial period for HSCT survivors using Gen Gamma is an ICER -$61,195,10/QALY). The EGP re-ran the probabalastic analysis for 5000 iterations and the ICER result was -$63,902.38/QALY. The greatest uncertainity that remained was around the amount of QALYs gained, and a few instances when the treatment is not cost-saving but has an incremental cost associated. However, it is worth noting that this comparison was generated by indirect evidence and no studies directly comparing these two drugs have been conducted. The lack of direct evidence of comparative efficacy and the indirectly derived estimates may create considerable uncertainty around the cost-effectiveness of inotuzumab and blinatumomab.

1.4 Evaluation of Submitted Budget Impact Analysis

The budget impact of implementing inotuzumab to the market is estimated for three years; 2019-2021 from a Canadian perspective. In the base case, the model includes the costs of salvage treatments (including inotuzumab). Scenario analyses explore the effect of including, hospitalization costs and administration cost.

The estimated number of patients 18 years old or older with relapsed/refractory (R/R) ALL in Canada was based on projections of population growth, incidence of ALL, and relapse rates). 100% of the calculated R/R ALL population was considered eligible for treatment with Inotuzumab. It was assumed that inotuzumab would capture some of blinatumomab and ponatinib market shares.

The factors that most influence the budget impact analysis include the number of vials (which is dependent on the extractable amount per vial and the BSA of a patient) necessary per patient and the market share.

Key limitations of the BIA model include the fact that the reference case considered an impact of implementation of the drug alone (compared to blinatumomab and ponatimib) without hospital costs, or costs of future HSCT. The BIA contains assumptions regarding epidemiology, current treatment patterns, costs, and market assumptions, but did not include hospital admissions for inotuzumab patients as seen in the trial, and did not take into account the costs of future HSCT, which is claimed benefit of this drug. The trial showed an average of 10 inpatient days in the inotuzumab arm that is not accounted for in the BIA (which would somehow account for AE costs). Also, no discussion of the future costs of HSCT is incorporated into the BIA which will be higher in the inotuzumab arm if the benefits of bridge to transplant from the clinical trials are confirmed in clinical practice.

These parameters were not able to be modified and explored by the EGP. However, the probabilistic CUA compared to blinatumomab presented earlier showed that the option can still have an incremental cost when other costs and benefits are factored in (hospitalization, AE, HSCT, etc).

1.5 Conclusions

The EGP's best estimate of ΔC and ΔE for Inotuzumab when compared to SoC (Hyper-CVAD) is:

- Between $178K/QALY and $335K/QALY (deterministic results)
- The extra cost of Inotuzumab is between $109K and $140K (deterministic results).
- The extra clinical effect of Inotuzumab is between 0.66 and 0.75 QALYS (deterministic results).
- The main factors affecting the results are the time horizon, number of vials necessary to treat a patient (which is dependent on BSA and extractable amount per vial),and the assumption on survival extrapolation beyond the trial period.
- Within this range, the best estimate for the deterministic ICER estimate would likely be an average of $200K/QALY.
- The greatest uncertainity that remained was around the amount of QALYs gained from the treatment which is highly influenced by the assumptions on the source of utilities, data for survival extrapolations and time horizon. Uncertainty around incremental costs are more related to the assumptions around average BSA and extractable amount per vial and their direct effect on wastage.

The EGP's best estimate of ΔC and ΔE for Inotuzumab when compared to Blinatumomab is:

- Between -$61K/QALY [cost saving] and $112K/QALY [incremental] (deterministic results).
- The extra cost of Inotuzumab is between -$27K and $54K.
- The extra clinical effect of Inotuzumab is between 0.44 and 0.48 QALYS.
- A great amount of uncertainty remains for this comparison as there are no studies directly comparing these two drugs.
- Within this range, the best estimate for the deterministic ICER would be -$61K/QALY. *This ICER was generated assuming a **10-year time horizon** (with the use of KM data for the first 15 months + pooled fitted curves for extrapolation up to 50 months + pooled fitted curves for extrapolation after the trial period for HSCT survivors), an average extractable amount of the drug of 0.90mg per vial, an average BSA of 1.70m^2.*
- The greatest uncertainity remaining is around the amount of QALYs gained from the treatment which is highly influenced by the assumptions on the source of utilities, data for survival extrapolations and time horizon. Uncertainty around incremental costs are more

related to the assumptions around average BSA and extractable amount per vial and their direct effect on wastage.

Overall conclusions of the submitted model:

- *The major factor affecting the results is the time horizon (increase in 114%). The costs of this new treatment in the first year (cost of new drug + additional costs with HSCT since more patients reached transplant) requires long time horizon to offset the overall incremental costs. The original trial had a 50-month duration. Differences in survival between treatment options play a more important role only after 15 months, but the data are highly censored after 24 months. The submitted base case model used extrapolations of survival after the trial period applying a RR=4 over the general population mortality. The lifetime horizon had a 50% chance of producing ICERS below $100k/QALY. Extrapolations of inconclusive results on safety and survival after transplant may underestimate the ICERs and magnifies the uncertainty around this outcome. When extrapolating survival after HSCT using the trial data, the results were very similar to a RR=10 or Gen gamma pooled survival curves after HSCT. This would be the conservative approach to avoid overestimation of the long term benefits.*
- *The second factor affecting the ICER (increase in 60%) is the average number of vials per patient, which in turn is directly affected by a combination of the average extractable amount of the drug per vial and the average BSA of an ALL patient. Given the evidence from the submitter that patients would require an extra vial in 30% of the cases (at a BSA of 1.88 m^2), the EGP reduced the average extractable amount for the reanalysis to 0.90mg based on the approved Health Canada product monograph, but also decreased the BSA to reflect the BSA of the Canadian population to 1.70 m^2 and 1.80 m^2 (as per previous submissions to pCODR) to avoid overestimation on the number of vials.*
- *Other factors such as the source of data/assumption for extrapolation of survival after HSCT (pooled parametric curves) and the use of different utility values for progressive states depending whether the patients progressed after a HSCT have equal impact in the ICER (increase in 30%)*
- *The use of a modified PFS definition in the trial design limits the use of the data to more accurately estimate the progression of disease after the HSCT, which in turn limits the use of the model structure and the classic use of same utility values for patients in progression regardless of which treatment they have received.*
- *Given the remaining uncertainties, the EGP's best guess is that in order for Inotuzumab to have an ICER closer to the Submitter's best estimate ($91k/QALY) it would require more than a 50% price reduction.*
- *For patients who did not reach transplant or were not eligible for HSCT, the ICER is above $600k/QALY without changing any assumptions from the base-case. It is not specified in the model nor in the INO-VATE ALL trial what proportion of patients nor the reasons for why some patients were considered ineligible for HSCT.*

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Leukemia Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of inotuzumab ozogamicin (Besponsa) for ALL . A full assessment of the clinical evidence of inotuzumab ozogamicin (Besponsa) for ALL is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR 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 Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

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

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

REFERENCES

1. pan-Canadian Oncology Drug Review manufacturer submission: BESPONSA™ (inotuzumab ozogamicin), lyophilized powder for solution for infusion, 1 mg single-dose vial. Company: Pfizer Canada Inc. Pointe-Claire/Dorval (PQ): Pfizer Canada Inc; 2017 Nov 13.

2. Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med. 2016 Aug 25;375(8):740-53.

3. Kantarjian HM, DeAngelo DJ, Stelljes M, Liedtke M, Stock W, Gökbuget N, et al. Inotuzumab ozogamicin (InO) vs standard of care (SC) in patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL): long-term results of the phase 3 INO-VATE study. Blood [Internet]. 2017 [cited 2017 Dec 14];130(Suppl 1):2574. Available from: http://www.bloodjournal.org/content/130/Suppl_1/2574

4. Bansback N, Tsuchiya A, Brazier J, Anis A. Canadian valuation of EQ-5D health states: preliminary value set and considerations for future valuation studies. PLoS One. 2012;7(2):e31115.

5. NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. Final appraisal determination Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (2017). Available from: https://www.nice.org.uk/guidance/gid-ta10091/documents/final-appraisal-determination-document.

6. NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia (2018). Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10091