BSH2020-615

Inotuzumab ozogamicin vs. blinatumomab for adults with Philadelphia chromosome-negative relapsed/refractory B-cell acute lymphoblastic leukaemia in Scotland: cost-effectiveness and relative treatment effect estimates.

T. Alexander Russell-Smith* [1], Miranda Cooper[2], Ilse van Oostrum[3], Verna Welch[1], Simone Critchlow [2]

[1]Pfizer Inc, New York, United States; [2]BresMed Health Solutions, Sheffield, United Kingdom; [3]Ingress Health, Rotterdam, Netherlands

Objective

To explore the relative treatment effect and subsequent cost-effectiveness estimates of inotuzumab ozogamicin vs blinatumomab in the treatment of Philadelphia chromosome-negative relapsed/refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL).

Conclusion

All methods explored indicated that inotuzumab ozogamicin is associated with longer modelled survival than blinatumomab. Inotuzumab ozogamicin was highly cost effective compared with blinatumomab, with incremental cost-effectiveness estimates well below £20,000 per quality-adjusted life year.

Context

Given that R/R ALL is terminal if left untreated, bridging to potentially curative therapy (such as stem cell transplant [SCT]) may lead to long-term survival or a functional cure. The ability of a treatment to provide complete response/complete response with incomplete count recovery, a typical prerequisite for SCT, and thus act as a bridge to future SCT, is imperative to patients. Doing so in a cost-effective manner is imperative to payers.

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Introduction

- Relapsed/refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL) is associated with poor diagnosis and a low life expectancy. Patients with Philadelphia chromosome-negative (Ph-) B-cell ALL lack an irregularity in chromosome 22 that is present in patients with Philadelphia chromosome-positive (Ph+) B-cell ALL, the latter of which is more common in older patients and is linked to worse outcomes. [1]
- At present, stem cell transplant (SCT) is the only potentially curative therapy for patients with R/R B-cell ALL in the UK [1]. However, treatment-induced remission, defined as complete response/complete response with incomplete count recovery (CR/CRi), is a typical SCT pre-requisite. Consequently, the most crucial treatment-related outcomes are:
  1. Achieving a response (CR/CRi)
  2. The likelihood of reaching SCT (SCT rate)
  3. Overall survival (OS)
- Inotuzumab ozogamicin (InO) – investigated in a Phase III open-label randomized control trial (RCT), INO-VATE – and blinatumomab (Blina) have both been approved as R/R B-cell ALL treatments and are recommended by the Scottish Medicines Consortium (SMC) for reimbursement. [2, 3, 4]
- Blina, a monoclonal antibody, was recommended for SMC reimbursement first, but only in the Ph- indication. Results of a Phase 3 trial (TOWER), show the safety and efficacy of Blina compared to chemotherapy. INO-VATE data are presented alongside TOWER in Table 1. [2,5]
- During InO's SMC appraisal, the costs and effects of InO were compared to those of Blina. Owing to a lack of head-to-head trial evidence, the treatments were compared via indirect treatment comparisons (ITCs) within a UK-based cost-effectiveness model. [3]
  - Specific model outputs for each treatment were: quality-adjusted life years (QALYs), life years (LYs) and incremental cost-effectiveness ratios (ICERs).
- The ITCs and cost-effectiveness analysis results used in the SMC-appraisal for InO, submitted in 2017, which compared InO and Blina are presented in this poster.

Materials and Methods

Study design

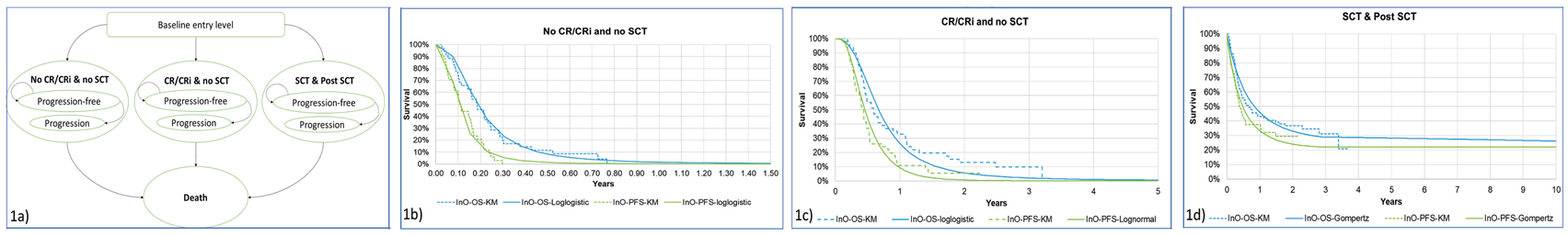
- The cost-effectiveness model was constructed using a Markov health-state structure with four main health states which were based on whether response was achieved and whether SCT was received (Figure 1a). The probability of death for InO (based on the INO-VATE trial) was specific to each state. Progression-free survival (PFS) was also modelled within each state (Figure 1).
- A 3.5% discount rate, a lifetime time horizon and 28-day cycle length were used in the model. A UK costing perspective was taken, with 2017 sources and UK drug costs sources used where possible.
- Quality-of-life data for the health states were derived from either the INO-VATE trial ('No CR/CRi & no SCT' and 'CR/CRi and no SCT') or the literature ('SCT & Post SCT').[6]
- Dosing for InO was informed by the INO-VATE trial, whereas dosing for Blina was assumed to be that from the Phase 2 Blina trial. [7]
- Data on length of stays were used to derive hospital costs; for InO, data were taken from INO-VATE (and determined by how many cycles patients received), and for Blina data were taken from the SMC detailed advice document.[6]
- UK costs were used to capture adverse events with incidences taken from the respective InO or Blina trials. InO and Blina's published UK list prices were used.
- InO's PFS and OS estimates were derived from INO-VATE and were previously published. [1,2]
- Additional details of InO-related model inputs are also in the existing literature.[1]

Table 1: Comparison of the INO-VATE and TOWER trials

Component	INO-VATE		TOWER	
	InO (n=164)	IC (n=162)	Blina (n=271)	IC (n=134)
Age (years)	46.5 (18–78)	47.5 (18–79)	37 (18–80)	
Ph- (n [%])	142 (86.6)	134 (82.7)	100%	
Median PFS (months)	5.0 (3.7–5.6)	1.8 (1.5–2.2)	Not reported	
Median OS (months)	7.7 (6.0–9.2)	6.7 (4.9–8.3)	7.7 (5.6–9.6)	4.0 (2.9–5.3)
CR/CRi/CRh (n [%])	120 (73.2)	50 (30.9)	119 (43.9)	33 (24.6)
SCT (n [%])	79 (48.2)	36 (22.2)	65 (24.0)	32 (23.9)

Key for figures and tables: Blina, blinatumomab; CR, complete response; CRh, complete response with partial hematologic recovery; CRi, complete response with incomplete count recovery; HR, hazard ratio; HSCT, haematopoietic stem cell transplant; IC, investigator's choice; ICER, incremental cost-effectiveness ratio; InO, inotuzumab ozogamicin; ITC, indirect treatment comparison; KM, Kaplan–Meier; LY, life year; OS, overall survival; MAIC, matched-adjusted indirect comparison; OR, odds ratio; PFS, progression-free survival; Ph-, Philadelphia chromosome-negative; QALY, quality-adjusted life year; SCT, stem cell transplant; STC, simulated treatment comparison.

Figure 1: Model structure diagram and health-state survival for InO



InO vs Blina

- Relative effectiveness of InO versus Blina was determined for important treatment-related outcomes (CR/CRi, SCT rate and OS).
- Due to a lack of PFS data from the TOWER trial at the time of analysis, an assumption was needed to estimate PFS hazard ratios (HRs): OS HRs were used as a proxy for PFS HRs.
- As achieving CR/CRi generally precedes SCT, these treatment-related outcomes are not mutually exclusive. Therefore, ITC results for these outcomes could not be used to directly populate the model. Instead, to model the Blina health state, it was assumed that the proportions of patients with CR/CRi and without CR/CRi who undergo SCT in each of the TOWER trial arms was the same as that observed in the INO-VATE trial.
- The investigated anchored ITC methods were: Bucher ITCs, matching-adjusted indirect comparisons (MAICs) and simulated treatment comparisons indirectly estimate relative treatment effect using a common comparator (IC). The latter two adjust for differences in trial patient populations.
- To determine CR/CRi and SCT rate outcomes:
  - Both MAICs and standard Bucher ITCs were carried out to generate odds ratios (ORs; Table 2) as relative treatment effects. These enabled the proportions of Blina-treated patients achieving CR/CRi and SCT to be re-estimated as though they had originally been assessed as part of the INO-VATE trial. These re-estimates, combined with the assumptions stated previously, enabled estimation of the health state proportions.
  - A multinomial ITC was also conducted because of the link between CR/CRi and SCT (CR/CRi being a typical pre-requisite for SCT). Following the application of the above assumption, a multinomial logistic regression, with covariates for treatment and trial, was used to simultaneously model the health state proportions from each trial. Consequently, the proportions of Blina-treated patients were estimated as though they had been assessed as part of the INO-VATE trial (Table 3).
- To determine OS relative efficacy:
  - A MAIC, a simulated treatment comparison and unadjusted ITCs were all conducted. The relative OS between InO vs Blina was only compared in the entire intention-to-treat population, as this was the only survival data available from TOWER (i.e. there were no subgroup data corresponding to the model health states).
  - Relative effectiveness for OS between InO and Blina was assumed to hold within each health state, although this assumption was explored. CR/CRi and SCT rates were the key model drivers; SCT drove long-term OS in the model.

Table 2: Relative treatment effect estimates of InO vs blinatumomab for response and SCT rates

InO vs Blina	Bucher ITC	MAIC* (adjusted)	Estimated Blina rates†	
	OR (95% CI)	OR (95% CI)	Bucher ITC	MAIC
Achieving CR/CRi	3.38 (1.67, 6.86)	2.81 (1.12, 7.05)	45.64%	50.25%
Achieving SCT	3.24 (1.59, 6.60)	4.11 (1.85, 9.12)	23.06%	19.13%

*MAICs were conducted to adjust the patient population of the INOVATE-ALL trial to the aggregate patient characteristics of the TOWER trial for any characteristics that were identified as potential treatment effect modifiers based on subgroup analyses and clinical expert opinion. †As though assessed within the INOVATE-ALL trial.

Table 3: Proportion of patients in each health state

Health state proportions	No CR/CRi	CR/CRi & no SCT	SCT/Post SCT *	
			No CR/CRi & SCT	CR/CRi & SCT
InO (Ph- population)				
Observed	20.42%	30.28%	49.29% (100%)	
			5.63% (11%)	43.66% (89%)
Blinatumomab †				
MAIC	47.57%	33.30%	19.13%	
			2.19% (11%)	16.94% (89%)
Bucher ITC	51.73%	25.21%	23.06%	
			2.64% (11%)	20.42% (89%)
Multinomial ITC	51.12%	26.42%	22.46%	
			2.57% (11%)	19.89% (89%)

*The distribution of Blina SCT patients with CR/CRi versus No CR/CRi was assumed to be consistent with the corresponding patient distribution for InO (as shown in brackets) † As though assessed within the INOVATE-ALL trial.

Results

InO versus Blina: Relative efficacy

- The ITCs associate InO with greater odds of CR/CRi and SCT versus Blina (Table 2).
- Blina was consistently associated with reduced likelihood of reaching both SCT and achieving CR/CRi:
  - Estimated Blina SCT rates show a lower likelihood of Blina-treated patients reaching SCT compared to the rates reported in TOWER (23.06–19.13% vs 24.0% observed).
  - Given the dependence of SCT and CR/CRi outcomes, InO was associated with a greater chance of achieving CR/CRi (79.58%) vs Blina (48.88–52.43%) (Table 3).
- All ITCs consistently suggest that observed OS for InO and Blina was similar within the observed period:
  - HRs spanned 0.96 (95% CI: 0.61, 1.50) to 1.06 (95% CI: 0.65, 1.59).

Cost-effectiveness results

- The mean incremental QALYs, LYs and ICERs for InO versus Blina are presented in Table 4.
- The cost-effectiveness model explored all ITC combinations and showed that InO consistently resulted in incremental QALY gains (range: 0.91–1.14) over Blina.
- The cost-effectiveness model showed that, because of increased SCT rate which was modelled as a key driver of long-term survival, InO results in increases in incremental LYs gained (i.e. mean survival gain; range: 2.03–2.59 years) over Blina.
- In all scenarios explored, InO was repeatedly cost effective versus Blina, consistently falling under a willingness-to-pay threshold of £20,000 per QALY; the ICER ranged from £3,700–£7,010 per QALY gained.

Table 4: Cost-effectiveness of InO vs Blina at list prices (Incremental, Incr.)

Survival options: ICER (InO vs Blina)	Method to derive the HR informing each health state: No CR/CRi, CR/CRi, and SCT	MAIC			ITC			Multinomial		
		Incr. QALY	Incr. LY	ICER (incr. cost per QALY)	Incr. QALY	Incr. LY	ICER (incr. cost per QALY)	Incr. QALY	Incr. LY	ICER (incr. cost per QALY)
	NMA	1.03	2.31	£7,010	0.91	2.03	£3,773	0.92	2.08	£4,322
	MAIC	1.14	2.59	£6,607	1.03	2.34	£3,700	1.05	2.38	£4,182
	STC	1.08	2.45	£6,794	0.97	2.19	£3,728	0.99	2.23	£4,242
	HR=1	1.09	2.48	£6,754	0.98	2.22	£3,721	1.00	2.26	£4,228

Discussion

- The modelled OS benefit of InO versus Blina is most evident when considering the mean (modelled LYs gained) rather than directly comparing the observed trial medians which fail to tell the whole story:
  - The ITCs suggest that InO provides patients with a higher chance of experiencing CR/CRi and SCT versus Blina, with the proportion of patients achieving SCT with InO more than double that of patients receiving Blina across all scenarios (Table 3). This results in a modelled survival gain.
  - Survival differs by health state (Figure 1b–d), and the health state proportions show a clear difference between InO and Blina (Table 3); therefore, higher CR/CRi and SCT increase modelled survival
- This analysis investigated various ways to indirectly compare InO and Blina. In all the methods investigated, InO was shown to be a highly cost-effective treatment, with ICERs falling well below the UK recommended level of £20,000–30,000 per QALY.
- It should be noted that:
  - To capture the benefit of InO as a SCT-facilitating treatment, it was essential to separate patients into subgroups that capture this; however, this meant that randomization was lost as these were not pre-specified subgroups.
  - Due to limited TOWER trial data, especially model health state survival outcomes and PFS data, assumptions were necessary to model Blina. Additionally, it was assumed that CR/CRi in INO-VATE was equivalent to CR/CRh (complete response with partial hematologic recovery, as defined in TOWER).
  - The survival gains and differences between therapies are modelled, and are not from any head-to-head clinical comparison.
- There is a lack of evidence suggesting that long-term survival is possible in patients with R/R B-cell ALL without CR/CRi and SCT treatment. Therefore, the mean OS gain (based on the cost-effectiveness model and cited in the SMC recommendation) aligns with the increased chances of CR/CRi and SCT provided by InO. However, our outcomes and model rely on the assumption that SCT is the main driver of long-term OS in R/R ALL..
- Longer-term outcomes are available for the INO-VATE trial but not for the TOWER trial. However, neither trial was designed to specifically explore the long-term effects of SCT; therefore, further investigation is needed to fully understand this potentially curative therapy for R/R B-cell ALL.

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Presented at the BSH 2020 Virtual • November 9–14, 2020

BSH2020 EP-008-A

ALL and AML

Alexander Russell-Smith

Poster presented at: British Society for Haematology

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