



Cost-Effectiveness of Inotuzumab Ozogamicin Compared to Standard of Care Chemotherapy for Treating Relapsed or Refractory Acute Lymphoblastic Leukaemia Patients in Norway and Sweden

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Abstract

Objective The aim was to estimate the cost-effectiveness of inotuzumab ozogamicin (InO) versus standard of care chemotherapy (SoC) for adults with relapsed or refractory B cell acute lymphoblastic leukaemia (R/R ALL) in Sweden and Norway, and compare this to evaluations made by the health technology assessment (HTA) authorities *Tandvårds- och läkemedelsförmånsverket* (TLV) and the Norwegian Medicines Agency (NoMA).

Materials and methods A partitioned survival model was developed to determine incremental cost-effectiveness ratios (ICERs) for InO versus SoC. Parametric survival models were fit to overall survival and progression-free survival Kaplan-Meier data from the INO-VATE ALL phase III trial. Two base cases were run using (1) Swedish and (2) Norwegian inputs (costs and discount rates). Core clinical inputs and utilities did not differ between countries. Analyses were then conducted to reflect the preferred assumptions of TLV and NoMA. Univariate and multivariate sensitivity analyses were performed.

Results The base case deterministic ICERs for InO versus SoC were €16,219/quality-adjusted life years (QALY) in Sweden (probabilistic €19,415) and €44,405/QALY in Norway (probabilistic €47,305). The ICERs using our model but applying the preferred assumptions of TLV or NoMA were €74,061/QALY (probabilistic €77,484) and €59,391/QALY (probabilistic €63,632), respectively. Differences between our base cases and the ICERs with TLV and NoMA settings were mainly explained by the exclusion of productivity costs and use of pooled post-haematopoietic stem-cell transplant (post-HSCT) survival in Sweden and use of higher HSCT costs in Norway. All ICERs remained below the approximated willingness-to-pay thresholds. The probability of InO being cost-effective ranged from 77 to 99% versus SoC.

Conclusions InO can likely be considered cost-effective versus SoC under our and the HTA-preferred settings.

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Key Points for Decision Makers

In the INO-VATE acute lymphoblastic leukaemia (ALL) phase III trial, inotuzumab ozogamicin (InO) demonstrated improved overall survival and remission rate, favourable patient-reported outcomes, and a manageable safety profile versus standard of care chemotherapy (SoC) for relapsed or refractory acute lymphoblastic leukaemia (R/R ALL).

Prior to public reimbursement, in Sweden and Norway, a health technology assessment (HTA) including a cost-effectiveness analysis is conducted.

This article explores the cost-effectiveness of InO versus SoC and examines the differences between our preferred set of cost-effectiveness analyses and the evaluations made by the Swedish and Norwegian HTA authorities in order to aid future decision making on where and how to use InO for the treatment of R/R ALL.

1 Introduction

Acute lymphoblastic leukaemia (ALL) is a malignant disorder of lymphoid progenitor cells that affects children and adults [1]. In Sweden and Norway around 50 and 44 adults are diagnosed with ALL annually, respectively [2–4]. Upon diagnosis, patients are stratified by a number of factors to help understand the prognosis and guide therapeutic decisions (e.g. T vs B cell leukaemia; Philadelphia-negative vs Philadelphia-positive leukaemia). For patients newly diagnosed with ALL, treatment consists of an induction phase, a consolidation phase, and a maintenance phase [2, 5, 6]. Chemotherapy is typically administered in the induction phase with the aim of achieving a complete remission (CR) or complete remission with incomplete haematological recovery (CRi), with treatment in the following consolidation and maintenance phases aiming to keep the leukaemia in remission [7]. If remission is achieved following previous conditioning pharmacological treatment, a subsequent allogeneic haematopoietic stem-cell transplant (HSCT) [8] currently offers the best opportunity for long-term disease-free survival [7, 9–12]. Only around 30–40% of adults with ALL achieve long-term disease-free survival, with the primary reason for failure being disease recurrence [13]. If a patient relapses following treatment or HSCT or if they are refractory to treatment (R/R ALL), the aim of salvage treatment is again to induce haematological remission (CR/CRi) so that patients might be able to bridge to subsequent HSCT. To

induce haematological remission in the R/R setting, patients have historically been treated with a salvage regimen consisting of combination chemotherapy [2, 6].

Over recent years, new options have been added to the R/R treatment arsenal, with the targeted therapy inotuzumab ozogamicin (InO) (Besponsa®) now indicated for adults with B cell R/R ALL, [14] based on results versus standard of care chemotherapy (SoC) in the INO-VATE 1022 ALL trial [15, 16]. The INO-VATE ALL trial was a multicentre, parallel, open-label, phase 3 trial that randomised 326 adults with R/R ALL to InO ($n = 164$) or SoC ($n = 162$). The study demonstrated that patients in the InO arm versus the SoC arm experienced a significantly higher CR/CRi rate (73.8% vs 30.9%; $P < 0.0001$), improved minimal residual disease rate (78.4% vs 28.1% in the initially studied population; $P < 0.001$), and longer duration of remission (median 5.4 months vs 4.2 months; $P = 0.0071$). Median overall survival (OS) was 7.7 months with InO and 6.2 months with SoC, with 2-year OS rates of 22.8% and 10.0%, respectively (overall hazard ratio [HR] 0.75; $P = 0.0105$). Correlated with these improvements, the percentage of patients reaching HSCT after achieving CR/CRi was higher for InO versus SoC (39.6% vs 10.5%; $P < 0.0001$) [15, 16].

Prior to public reimbursement in many countries covered by the European Medicines Agency, health technology assessments (HTAs) must often be conducted, including in Norway and Sweden. Such HTAs typically include a cost-effectiveness analysis to assess whether an intervention brings value for money. Based on HTAs conducted by *Tandvårds- och läkemedelsförmånsverket* (TLV) and the Norwegian Medicines Agency (NoMA), InO was considered to be cost-effective and recommended for use by the New Therapies (NT) council in Sweden and publicly reimbursed in Norway [4, 17, 18].

The aim of this paper was to estimate the cost-effectiveness of InO compared to SoC for the treatment of B cell R/R ALL in Sweden and Norway, and to compare the results of our two base cases to the results when applying to our model the preferred assumptions stated by TLV and NoMA in their recent appraisals of InO [4, 18]. Whilst in most part the models were similar between our base cases and the preferred base cases of the two agencies, we have sought to highlight where assumptions differed and provide justification and rationale for our preferences. By presenting a full set of assumptions, where they differed, and then the resulting impact these have on cost-effectiveness estimates via a side-by-side examination, we aim to provide future decisions makers with transparent and full information to aid their choices and decisions.

2 Methods

The cost-effectiveness for InO versus SoC was assessed using a health economic model. The following sections describe the model structure and incorporation of clinical and economic inputs. Two sets of base case analyses were performed, specific to the perspective of each country: (1) using Swedish and (2) using Norwegian cost inputs and annual discount rates. These base case analyses were then compared to analyses using the preferred assumptions of TLV and NoMA. Both TLV and NoMA appraised InO using fundamentally the same model as the one presented in this study, although some assumptions differed.

2.1 Model Structure

The cost-effectiveness analysis used a time-dependent, partitioned survival model with states defined based on treatment response (CR/CRi), HSCT, progression, and death (Fig. 1). A comparable model structure has been used in the National Institute of Health and Care Excellence (NICE) appraisal of InO (appraisal TA541) and was deemed appropriate for decision-making [19].

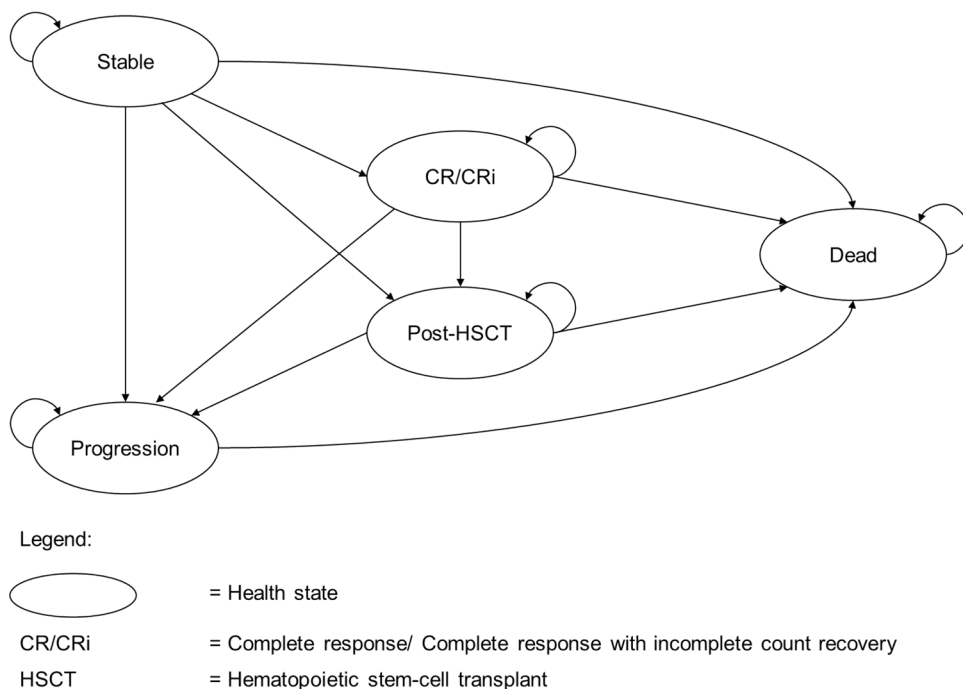
All patients entered the model in the ‘stable’ state. The average age of the patient cohort at the start of the model was 46 years, based on the INO-VATE ALL trial [16, 20]. A monthly model cycle length (30.4375 days) was used. From the ‘stable’ health state, patients could move to the ‘CR/CRi’ state after one cycle (the average time to response in INO-VATE ALL was 1 month) or to the ‘post-HSCT’

state. Almost all patients in INO-VATE ALL who underwent HSCT did so having first achieved CR/CRi; however, a small number of patients underwent HSCT without CR/CRi. Transition to ‘post-HSCT’ from either the ‘stable’ or ‘CR/CRi’ state occurred after 4 and 5 months for InO and SoC, respectively, mirroring the average time to HSCT in the INO-VATE ALL trial’s respective arms [20]. This transition at 4 and 5 months was considered appropriate as alternatively allowing patients to transition to HSCT in different cycles through tunnel states led to similar results but over-complicated the model. From all health states, patients were at risk of disease progression and/or death. This risk was specific to each arm and each state and was determined by progression-free survival (PFS) and OS Kaplan-Meier data from INO-VATE ALL’s latest cut (April 2017) [16, 20]. To capture all relevant costs and effects, a life-time time horizon was used. Discount rates for future costs and effects of 3.0% per annum for Sweden and 4.0% for Norway were applied in line with TLV and NoMA guidelines [21, 22].

2.2 Model Estimation

Health-state specific PFS and OS were based on the intention-to-treat (ITT) population from the INO-VATE ALL trial (patient characteristics were presented in the trial publications) [16, 20]. PFS and OS for InO and SoC were estimated by fitting parametric survival distributions to Kaplan-Meier data using Flexsurv [23] (Gompertz and generalised gamma) and Survival [24] (exponential, Weibull, lognormal, and log-logistic) R packages. Base case distributions were selected according to fit statistics (Akaike information criterion

Fig. 1 Visual representation of the survival partitioned model



[AIC] and Bayesian information criterion [BIC]), visual inspection, hazard functions, time-dependent HRs, diagnostic plots for treatment effects, and clinical plausibility.

Parametric survival curves were fitted for each health state (stable, CR/CRi, and post-HSCT) separately.

If the proportional hazards assumption was violated, individually fitted curves were applied; otherwise, survival curves with treatment as a covariate were used [25]. For PFS, the log-logistic and generalised gamma function with treatment as a covariate were used for stable and CR/CRi patients, respectively. For OS, a lognormal distribution was used for stable patients and a generalised gamma was used for CR/CRi patients (both using treatment as a covariate). For post-HSCT survival, generalised gamma and log-logistic distributions were fitted individually for the InO and SoC arms, respectively (the proportional hazards assumptions were violated).

Some patients that receive an HSCT will be long-term survivors [7, 9–12]. For patients who survived until the end of the maximum follow-up of the INO-VATE ALL trial (approximately 50 months), it was assumed that the HSCT was successful and therefore a lower mortality risk was applicable from 50 months onwards. This risk was estimated by applying a standardised mortality ratio (SMR) to general population mortality data. This way, the model reflects that patients surviving longer term after successful HSCT have survival prospects closer to, yet still lower than, the general population [26]. The use of a point in time post-transplant where the model's probability of survival moves from using shorter-term clinical trial data to data adjusted from the general population (a 'functionally cured' point) has been accepted in other models in the literature [26–30]. To calculate longer-term survival, general population mortality for Norway and Sweden was taken from national life tables [31, 32]. An SMR of 4 from the study of Martin et al. [33] was then applied to elevate the general population mortality risk (implying a risk of death four times higher in any future year than a similarly aged person from the general population). This estimated SMR was preferred by NICE in the United Kingdom (UK) HTA of InO [34]. The model applies the same SMR for both treatment arms, implying an HR of 1 for InO versus SoC is applied from 50 months onwards, i.e. if a patient survived past this point, then they have had a successful HSCT and there was no assumed difference in their survival expectations going forwards whether they had received InO or SoC pre-HSCT.

Based on the PFS and OS extrapolations for stable, CR/CRi, and post-HSCT patients, the time in each health state was determined. The PFS and OS Kaplan-Meier data from the ITT population, the base case parametric survival curves, and parametrisation are summarised in Supplementary Table 1 and Supplementary Figures 1–3 (see the electronic supplementary material). In Supplementary Figures 4 and

5, the long-term modelled OS and PFS are compared to the Kaplan-Meier data from the INO-VATE ALL trial.

2.3 Clinical Inputs

Table 1 presents an overview of the applied clinical inputs and their corresponding uncertainty distributions. The SoC comparator was informed by the INO-VATE ALL trial, in which it was a choice of one of FLAG (fludarabine, cytarabine, and granulocyte colony-stimulating factor), cytarabine plus mitoxantrone, or high-dose cytarabine (HIDAC), from which the majority received FLAG. Whilst SoC in our Norwegian base case mirrored the trial, the base case in Sweden assumed 50% FLAG-Asp (fludarabine, cytarabine, pegylated-asparaginase plus granulocyte colony-stimulating factor) and 50% MEA (mitoxantrone, etoposide and cytarabine) based on key opinion leader (KOL) opinion. Other inputs informed by the INO-VATE ALL trial included probabilities of response (CR/CRi) and HSCT, adverse event rates, hospitalisation days, and subsequent induction therapy after treatment with InO or SoC (chemotherapy regimens FLAG, HIDAC, and cytarabine plus mitoxantrone based, tyrosine kinase inhibitors [TKIs], or innovative anti-cancer treatments blinatumomab and InO) [16, 20]. Overall, patients in the InO arm used fewer subsequent induction therapies than those in the SoC arm.

Hospitalisation days were measured while patients were on their primary treatment in the INO-VATE ALL trial. For subsequent treatment with InO (which was relevant to the SoC arm), the same number of hospitalisation days as observed on primary induction therapy with InO were applied. For other subsequent treatments, the number of bed-days for SoC from the INO-VATE ALL trial was applied. This was assumed more reflective than using InO's bed-days as InO can be administered in an outpatient setting. One exception applied for the Swedish subsequent chemotherapy costs, with these estimated using a national healthcare cost code that already included hospitalisation costs (as discussed in the "Cost Inputs" section below). Post-HSCT hospitalisation was assumed to be already captured in the follow-up costs applied after HSCT.

2.4 Utility Inputs

The utilities at baseline and in the stable and CR/CRi health states (see Table 1) were based on the safety population from the INO-VATE ALL trial [16, 20]. In the INO-VATE ALL trial, patients completed the EuroQoL 5 Dimensions Questionnaire (EQ-5D-3L) at baseline, on day 1 of each cycle, and at the end of treatment. The EQ-5D-3L UK value set was applied to determine the utility values [20]. At the time of TLV and NoMA's appraisals of InO, the UK value set was the preferred set for HTAs in both countries due to

Table 1 Overview of country-independent parameter values, standard errors, and distributions

Parameter	Mean (SE)—base case		Distribution	Source	
	InO	SoC			
Response and HSCT rates, %					
Stable	0.213	0.611	Dirichlet	INO-VATE ALL [16, 20]	
CR/Cri	0.305	0.167	Dirichlet		
No CR/Cri and HSCT	0.049	0.080	Dirichlet		
CR/Cri and HSCT	0.433	0.142	Dirichlet		
Adverse events, %					
Neutropenia	0.360	0.378	Beta	INO-VATE ALL [16, 20]	
Thrombocytopenia	0.244	0.490	Beta		
Leukopenia	0.177	0.252	Beta		
Febrile neutropenia	0.140	0.455	Beta		
Anaemia	0.122	0.350	Beta		
Lymphopenia	0.116	0.168	Beta		
WBC decreased	0.055	0.049	Beta		
VOD before HSCT	0.031	0.000	Beta		
VOD post-HSCT	0.228	0.083	Beta		
GVHD post-HSCT	0.110	0.110	Beta		
Hospitalisation					
Number of bed-days	21 (2)	27 (1)	Normal		INO-VATE ALL [16, 20]
Subsequent treatments, %					
Blina	0.073	0.142	Beta	INO-VATE ALL [16, 20]	
TKI	0.024	0.111	Beta		
Chemotherapy	0.762	0.667	Beta		
InO	0.006	0.056	Beta		
Utilities					
Stable—baseline	0.694 (0.022)	0.675 (0.029)	Beta	INO-VATE ALL [16, 20]	
Stable—from cycle 1	0.586 (0.080)	0.511 (0.056)	Beta		
CR/Cri	0.756 (0.023)	0.761 (0.045)	Beta		
Stable—baseline (pooled)	0.686 (0.018)		Beta	INO-VATE ALL [20]	
Progressed disease	0.300 (0.040)		Beta	Aristides et al. [37]	
0–1 years post-HSCT	0.590 (0.097)		Beta	Kurosawa et al. [35]	
1–2 years post-HSCT	0.750 (0.033)		Beta	Kurosawa et al. [35]	
3–5 years post-HSCT	0.740 (0.020)		Beta	Kurosawa et al. [35]	
> 5 years post-HSCT	0.760 (0.026)		Beta	Kurosawa et al. [35]	
VOD for 1 month	0.503 (0.026)		Beta	INO-VATE ALL [20]	
CRS for 1 week	0.000 (0.000)		Beta	Hettle et al. [26]	

ALL acute lymphoblastic leukaemia, *Blina* blinatumomab, *CR*, complete remission, *CRi* complete remission with incomplete haematological recovery, *CRS* cytokine release syndrome, *GVHD* graft-versus-host disease, *HSCT* haematopoietic stem-cell transplant, *InO* inotuzumab ozogamicin, *SE* standard error, *SoC* standard of care chemotherapy, *TKI* tyrosine kinase inhibitor, *VOD* veno-occlusive disease, *WBC* white blood cell count

the lack of a formally adopted Swedish or Norwegian value set. Given the baseline utility was similar in both arms, a pooled baseline utility of 0.69 was applied for InO and SoC. In the stable and CR/Cri health states, treatment specific utilities were used (stable: InO 0.51, SoC 0.47; CR/Cri: InO 0.73, SoC 0.75). As utilities were not measured past the end of treatment, post-HSCT utilities were not available from the INO-VATE ALL trial; hence, post-HSCT utilities (Table 1) were taken from a study by Kurosawa et al. [35],

which estimated utilities of 0.59 for < 1 year after HSCT, 0.75 at 1–2 years after HSCT, 0.74 at 3–5 years after HSCT, and finally 0.76 at 5 + years post-HSCT. The utilities from Kurosawa et al. [35] were estimated from a cross-sectional questionnaire study that administered SF-36, FACT-Leukaemia, and EuroQOL5D to 524 acute leukaemia survivors in Japan [36]. Although they were not from a UK population, at the time of our analyses, these were deemed the best available data. For the progressed disease health state, a utility

score of 0.30 was applied, taken from the study by Aristides et al. [37], in which utility values were assigned to R/R ALL health states from the perspective of the UK general population ($n = 123$) using the time trade-off method for preference elicitation. All utilities were decreased over time to reflect the aging of patients in the model [38].

2.5 Cost Inputs

Table 2 presents an overview of the applied country-specific costs and the corresponding uncertainty distributions. All costs were converted to 2017 Euros to make the results easy to compare, using 31-12-2017 conversion rates of 0.10185 for Sweden [39] and 0.10159 for Norway [40]. Drug costs for InO and SoC were determined by multiplying the average number of vials/tablets used with the costs per vial/tablet (wastage was included). For InO and SoC, the number of vials/tablets used were determined based on the actual doses in the INO-VATE ALL trial (dosing schedules were previously published [15]) and the average body surface area (1.88 m² [2]) and weight (76.9 kg) of the INO-VATE ALL patients [20]. As the Summary of Product Characteristics (SmPC) restricted the use of InO for patients who either do not achieve a CR/CRi or were planning to bridge to an HSCT to a maximum of three cycles, an average of 8.9 InO vials was used for our models' population, corresponding to these SmPC recommendations. Although the trial allowed treatment up to six cycles, all CR/CRi was first achieved during the first three cycles. Therefore, the CR/CRi rate and subsequent HSCT rate associated with only three cycles of InO can be assumed to be similar to that observed in the trial. The costs per vial/tablet were based on Swedish and Norwegian list prices [41, 42].

The costs per inpatient bed-day were higher for Norway (€4376) [43] than for Sweden (€2163) [44]. The costs of HSCT we applied were comparable for both countries (Norway €51,893 [45], Sweden €59,788 [46]); in Norway, our base case used a cost estimate based on reported cost for autologous HSCT, which was the most relevant cost we identified from the literature. Follow-up costs after HSCT were converted from the UK National Health Service Blood and Transplant study (NHSBT) [47] for Sweden as no Swedish data were available, and were based on studies conducted by public institutions for Norway [45].

For subsequent TKIs, drug costs were based on the national list prices of Sweden and Norway [41, 42, 48, 49] and a median treatment duration for ponatinib of 83 days [50]. Hospitalisation associated with TKIs was assumed to be equal to SoC [20]. For subsequent chemotherapy costs, in Sweden, a national healthcare cost code was applied that covered the costs of providing chemotherapy, including hospitalisation in acute leukaemia [51]. For Norway, the cost of subsequent chemotherapy consisted of standard

chemotherapy drug costs based on national list prices [41] and hospitalisation costs (INO-VATE ALL SoC bed-days [16, 20] multiplied with the cost per inpatient bed-day in Norway [43]).

Adverse event costs (excluding veno-occlusive disease [VOD], cytokine release syndrome [CRS], and graft-versus-host disease [GVHD]) were sourced from national cost data for Sweden [52, 53] and Norway [54, 55]. For VOD, in Sweden, a weighted average of cost of defibrotide (47.8%) and ursodeoxycholic acid (52.2%) [49, 56] was applied, in line with VOD treatment in the INO-VATE ALL trial [16, 20]. In Norway, VOD was assumed to be treated with defibrotide only [41]. CRS costs were converted from a UK source for Sweden [26] and were assumed to be equal to haematological adverse events in Norway [54]. GVHD costs were estimated based on Esp  rou et al. in both countries as no country-specific data were available [57]. End-of-life costs were higher in Norway ( 16,335) [58] versus Sweden ( 8046) [59].

In both countries, costs from a societal perspective were included that reflected the cost of time lost due to travelling to, and staying in, the hospital. The time value per hour for 'leisure time' was higher in Norway ( 28) [60] versus Sweden ( 6) [61]. The travelling time was 1 h in Sweden and 37 h in Norway (average of 0 h for residents of the Oslo/Bergen regions [24%] and 48 h for all other residents [76%] [62]). For Sweden, the costs of lost productivity were included as well. Based on expert opinion from Swedish KOLs, 50% of the HSCT patients were assumed to go back to work after 12 months post-HSCT and the remaining 50% after 18 months post-HSCT. The production value per patient was estimated to be  4390 per month [63, 64], and the general employment rate was 81% [65].

2.6 Analyses

Four sets of analyses are presented: our modelled base cases from the Swedish and Norwegian perspectives, and TLV's and NoMA's base cases from their country's perspective. All four analyses used the same model structure, core clinical inputs, and utility inputs (Table 1). Our two base cases and the two HTA authorities' all used their respective country's input costs and discount rates (Table 2). There were some differences between TLV's and NoMA's preferred assumptions versus our base case assumptions (Table 3). In summary, TLV's preferred type of SoC chemotherapy differed slightly to our base case and the population assessed by TLV was more limited than in our base case (TLV selected a subgroup of the INO-VATE ALL trial [the no prior HSCT population], which represents 81% of the full INO-VATE ALL population). The extrapolation of long-term survival post-HSCT also varied in that there were slight differences in the time horizons

Table 2 Overview of country-specific parameter values, standard errors, and distributions

Parameter name	Mean (SE) Sweden	Mean (SE) Norway	Distribution	Source Sweden	Source Norway
Discount rates					
Cost discount rate	3.0%	4.0%	Fixed	TLV 2017 [21]	Statens legemiddelverk 2017 [22]
Outcome discount rate	3.0%	4.0%	Fixed		
Survival HSCT patients > 50 months					
SMR HSCT patients vs general population	4.0 (0.38)	4.0 (0.38)	Lognormal	Martin et al. [33] and NICE appraisal InO (TA541) [34]	Martin et al. [33] and NICE appraisal InO (TA541) [34]
Healthcare costs (2017 euros)					
Costs: general costs					
Costs per bed-day	2163 (55)	4376 (112)	Gamma	Karolinska US [44]	Regjeringen [43]
End-of-life costs	8036 (205)	16,335 (417)	Gamma	Region skåne, out of county price list [59]	Innsatsstyrt finansiering [58]
Costs: treatments					
InO	90,513	84,086	Gamma	Apoteket.se AUP 171025 [42], list price per vial = 99,348.97 SEK, 8.9 vials	SLV 2017 maximum pharmacy selling price excluding VAT [41], list price per vial = 92,530.48 NOK, 8.9 vials
SoC	7267	2229	Gamma	FLAG-asp and MEA costs, dosing: FASS. se 2017 [67] costs: medicmpriser.se 2017 [48]	Drug price from SLV 2017 [41]
Blina	103,176	144,537	Gamma	Apoteket.se 171019 [42], list price per vial = 27,178.50 SEK, 37.3 vials (no wastage)	Drug price from SLV 2017 [41], list price per vial = 27,360.56 NOK, 52 vials (wastage included)
TKI (ponatinib)	19,951	16,686	Gamma	TLV.se and apoteket.se October 2017 [42, 49]	Drug price from SLV 2017 [41]
Subsequent chemotherapy (incl. hospitalisation)	11,941	129,333	Gamma	Region skåne, out of county price list [51]	Drug price from SLV 2017 [41], Regjeringen [43], INO-VATE ALL [16, 20]
Costs: HSCT					
Costs at time of HSCT	59,788 (1525)	51,893 (1324)	Gamma	Region skåne, out of county price list [46]	The Knowledge Centre [45]
Monthly costs post-HSCT					
1–6 months post-HSCT	5181 (132)	501 (13)	Gamma	NHSBT [47]	The Knowledge Centre [45]
6–12 months post-HSCT	3558 (91)	501 (13)	Gamma	NHSBT [47]	The Knowledge Centre [45]
12–24 months post-HSCT	1284 (33)	–	Gamma	NHSBT [47]	The Knowledge Centre [45]
Costs: adverse events					
Neutropenia	157 (4)	226 (6)	Gamma	Region skåne, out of county price list [52]	Innsatsstyrt finansiering [54]
Thrombocytopenia	157 (4)	226 (6)	Gamma	Region skåne, out of county price list [52]	Innsatsstyrt finansiering [54]
Leukopenia	157 (4)	226 (6)	Gamma	Innsatsstyrt finansiering [54]	Innsatsstyrt finansiering [54]
Febrile neutropenia	6406 (163)	9286 (237)	Gamma	Socialstyrelsen [53]	Innsatsstyrt finansiering [55]
Anaemia	157 (4)	226 (6)	Gamma	Region skåne, out of county price list [52]	Innsatsstyrt finansiering [54]
Lymphopenia	157 (4)	226 (6)	Gamma	Region skåne, out of county price list [52]	Innsatsstyrt finansiering [54]
Costs WBC decreased	157 (4)	226 (6)	Gamma	Region skåne, out of county price list [52]	Innsatsstyrt finansiering [54]

Table 2 (continued)

Parameter name	Mean (SE) Sweden	Mean (SE) Norway	Distribution	Source Sweden	Source Norway
Costs VOD	40,661 (1037)	84,455 (2154)	Gamma	Weighted average defibrotide and ursodeoxycholic acid costs from FASS.se [56] and TLV.se [49] October 2017	Defibrotide costs, Drug price from SLV 2017 [41]
Costs GVHD	24,495 (625)	19,564 (499)	Gamma	Espérou et al. [57]	Espérou et al. [57]
Costs CRS	3129 (80)	226 (6)	Gamma	Hettle et al. [26]	<i>Imssatsstyrt finansiering</i> [54]
Societal costs (2017 euros)					
Time value per hour	6 (0.20)	28 (1)	Gamma	Valuation of leisure time, <i>Trafikverket</i> 2012 [61]	SSB 2017 [60], <i>Gjennomsnittlig timelønn</i> 2016
Number of hours spent	24 per bed-day 1 for travelling*	24 per bed-day 48 for travelling*	Normal	Assumption	Calculated using population statistics [62]
Monthly production value	€ 4,390 (112)	Not applicable	Gamma	SCB 2017 [63] and <i>Ekonomifakta</i> 2017 [64]	Not applicable
Employment rate	81.0% (2.1%)	Not applicable	Beta	SCB 2017 [65]	Not applicable
Part-time rate	50.0% (1.3%)	Not applicable	Beta	Assumption	Not applicable
Retirement age	65	Not applicable	Fixed	<i>Pensjonsskydds-centralen</i> [68]	Not applicable

ALL acute lymphoblastic leukaemia, AUP apotekets pris [pharmacy selling price], *Blixa* blinatumomab, CRS cytokine release syndrome, GVHD graft-versus-host disease, FLAG-Asp fludarabine, cytarabine, pegylated-asparaginase plus granulocyte colony-stimulating factor, HSCT haematopoietic stem-cell transplant, *inO* inotuzumab ozogamicin, NOK Norwegian Krone, MEA mitoxantrone, etoposide, and cytarabine, NHSBT National Health Service Blood and Transplant study, NICE National Institute of Health and Care Excellence, SCB Statistics Sweden, SE standard error, SEK Swedish Krona, SLV Statens Legemiddelverk [Norwegian Medicines Agency], SMR standardised mortality ratio, SoC standard of care chemotherapy, SSB Statistics Norway, TA technology appraisal, TKI tyrosine kinase inhibitor, TLV Tandvårds- och läkemedelsförmånsverket, VOD veno-occlusive disease, WBC white blood cell count

*Travelling hours only apply for residents outside the Oslo and Bergen regions (76% of the population) [62]

Table 3 Differences in assumptions between our base case versus those preferred by TLV and NoMA

	Base case	TLV (Sweden) [18]	NoMA (Norway) [4]
Comparator	SoC (Sweden: 50% FLAG-Asp and 50% MEA; Norway: INO-VATE ALL SoC)	SoC (25% FLAG-Asp and 75% MEA)	ND*
Time horizon	Lifetime	ND*	40 years
Patient population	R/R ALL patients	R/R ALL patients with no prior HSCT***	ND*
Survival HSCT patients > 50 months	SMR of 4 vs general population	SMR of 9 versus general population	Parametric survival curve survival probabilities
Treatment-(in)dependent survival after HSCT	Treatment-independent survival after HSCT	Pooled trial survival from 20 m after HSCT	ND*
Cost of HSCT (2017 euros)	Sweden: 59,788 Norway: 51,893	ND*	Norway: 105,686 [69]
Societal perspective	Yes**	No	ND*

ALL acute lymphoblastic leukaemia, *FLAG-Asp* fludarabine, cytarabine, pegylated-asparaginase plus granulocyte colony-stimulating factor, *HSCT* haematopoietic stem-cell transplant, *HTA* health technology assessment, *InO* inotuzumab ozogamicin, *MEA* mitoxantrone, etoposide, and cytarabine, *ND* no difference, *NoMA* Norwegian Medicines Agency, *R/R ALL* relapsed or refractory acute lymphoblastic leukaemia, *SMR* standardised mortality ratio, *SoC* standard of care chemotherapy, *TLV* Tandvårds- och läkemedelsförmånsverket

*ND vs our base case

**In Sweden, both leisure time costs and costs of lost productivity fall within the societal perspective, whereas for Norway, costs of lost productivity were not included, in line with Norwegian HTA guidelines [22]

***In Sweden, TLV selected a subgroup of the INO-VATE ALL population consisting of patients with no prior HSCT. This subgroup represents 81% of the total INO-VATE ALL population and has a slightly more favourable outcome for InO vs SoC with respect to incremental survival

used. Furthermore, societal costs were not included by TLV [4, 18]. NoMA chose to apply a higher cost for HSCT than our preferred cost, using an estimate based on a Diagnosis Related Group (DRG) code for allogeneic HSCT for patients older than 17 years [4].

Lifetime costs, life years (LYs), and quality-adjusted life years (QALYs) were estimated for each treatment. Scenario analyses were performed to estimate the impact of using the lower or upper limit of the 95% confidence interval of the PFS and OS curves and the impact of applying general population utilities beyond 5 years post-HSCT. Additionally, deterministic sensitivity analyses (DSAs) and probabilistic sensitivity analyses (PSAs) with 1000 simulations were conducted. Where data on distributions were unavailable, a $\pm 5\%$ or $\pm 10\%$ range was assumed for costs and utilities, respectively. The DSA findings are presented in a tornado diagram including the ten parameters with the largest influence on the outcomes. Results of the PSA were used to generate acceptability curves for InO versus SoC, showing the probability that InO would be preferred over SoC given a range of willingness-to-pay (WTP) thresholds. Approximate WTP for severe disease, such as R/R ALL, were estimated at €102,000 per QALY in Sweden (corresponding to 1,000,000 Swedish Krona) and €84,000 per QALY (corresponding to 825,000 Norwegian Krone) in Norway [66].

3 Results

Table 4 displays the incremental LYs, QALYs, costs, and resulting incremental cost-effectiveness ratio (ICERs) for our Swedish and Norwegian base cases, alongside the results when TLV's and NoMA's preferred assumptions were applied. Our base case ICERs for InO versus SoC were €16,219 and €44,405 per QALY gained for Sweden and Norway, respectively. If costs of lost productivity are excluded, the base case ICER for Sweden was €50,361 per QALY gained, closer to the Norwegian ICER.

Using our model but applying the preferred assumptions of TLV and NoMA, we estimated the ICERs for InO versus SoC to be €75,127 per QALY gained for Sweden (reported as 733,577 Swedish Krona [€74,715] in TLV's documentation [18]) and €59,391 per QALY gained for Norway (reported as 584,615 Norwegian Krone [€59,391] in NoMA's documentation [4]). These ICERs all remained below the approximated WTP thresholds.

The results of the scenario analyses are presented in Supplementary Tables 2 and 3 (see the electronic supplementary material). The ICERs did not change substantially for most of the scenarios and generally remained below the approximated WTP thresholds. Applying the lower and upper 95% confidence interval limits of the post-HSCT curve had the biggest impact on the ICERs, as it influenced the number

Table 4 Base case and HTA results for Sweden and Norway

Country	Scenario	Incr. costs	Incr. LYs	Incr. QALYs	ICER InO vs SoC
Sweden (3% discounting)	Base case	€26,163	2.079	1.613	€16,219*
	TLV preferred settings (No prior HSCT patients, pooled survival post-HSCT, SMR = 9 post-HSCT, 25/75% FLAG-Asp/MEA, exclude societal costs)	€86,083	1.482	1.146	€75,127
Norway (4% discounting)	Base case	€63,220	1.829	1.424	€44,405
	NoMA preferred settings (Time horizon 40 years, parametric curves post-HSCT, higher HSCT costs)	€77,123	1.665	1.299	€59,391

FLAG-Asp fludarabine, cytarabine, pegylated-asparaginase plus granulocyte colony-stimulating factor, *HSCT* haematopoietic stem-cell transplant, *HTA* health technology assessment, *ICER* incremental cost-effectiveness ratio, *Incr.* incremental, *InO* inotuzumab ozogamicin, *LY* life year, *MEA* mitoxantrone, etoposide, and cytarabine, *NoMA* Norwegian Medicines Agency, *QALY* quality-adjusted life year, *SMR* standardised mortality ratio, *SoC* standard of care chemotherapy, *TLV* Tandvårds- och läkemedelsförmånsverket

*The base case ICER for Sweden was lower compared to Norway mainly due to the inclusion of productivity costs. If these costs are excluded, the Swedish ICER was more comparable, at €50,361 per QALY gained vs SoC

of patients who would be long-term survivors after HSCT. ICERs decreased if general population utilities were applied beyond 5 years post-HSCT, as this increased the quality of life post-HSCT, with InO having bridged more patients to HSCT.

The results of the PSA are presented in Fig. 2. Probabilistic ICERs are presented in Supplementary Table 4. Convergence tests confirmed a sufficient number of PSA iterations were performed (Supplementary Figure 6). The cost-effectiveness acceptability curves showed that the probability of InO being cost-effective versus SoC at the approximated Swedish WTP threshold was 99% in our base case and 81% if TLV's preferred assumptions were used (Fig. 3). At the approximated Norwegian WTP threshold, the probability of our base case being cost-effective was 93%, or 77% under NoMA's preferred assumptions.

The DSA for our base case (Fig. 4a) shows that, in Sweden, the three parameters with the highest influence on the ICER were the number of bed-days for InO, the HSCT rate for InO, and the proportion of patients receiving blinatumomab as a subsequent treatment after SoC. Under TLV's preferences, the HSCT rate for InO, HSCT rate for SoC, and the number of bed-days for InO were the three main drivers (Fig. 4b). For Norway, in both our base case and NoMA's, the number of bed-days for InO, the number of bed-days for SoC, and the proportion of patients receiving blinatumomab as subsequent treatment after SoC had the highest influence (Fig. 4c and d).

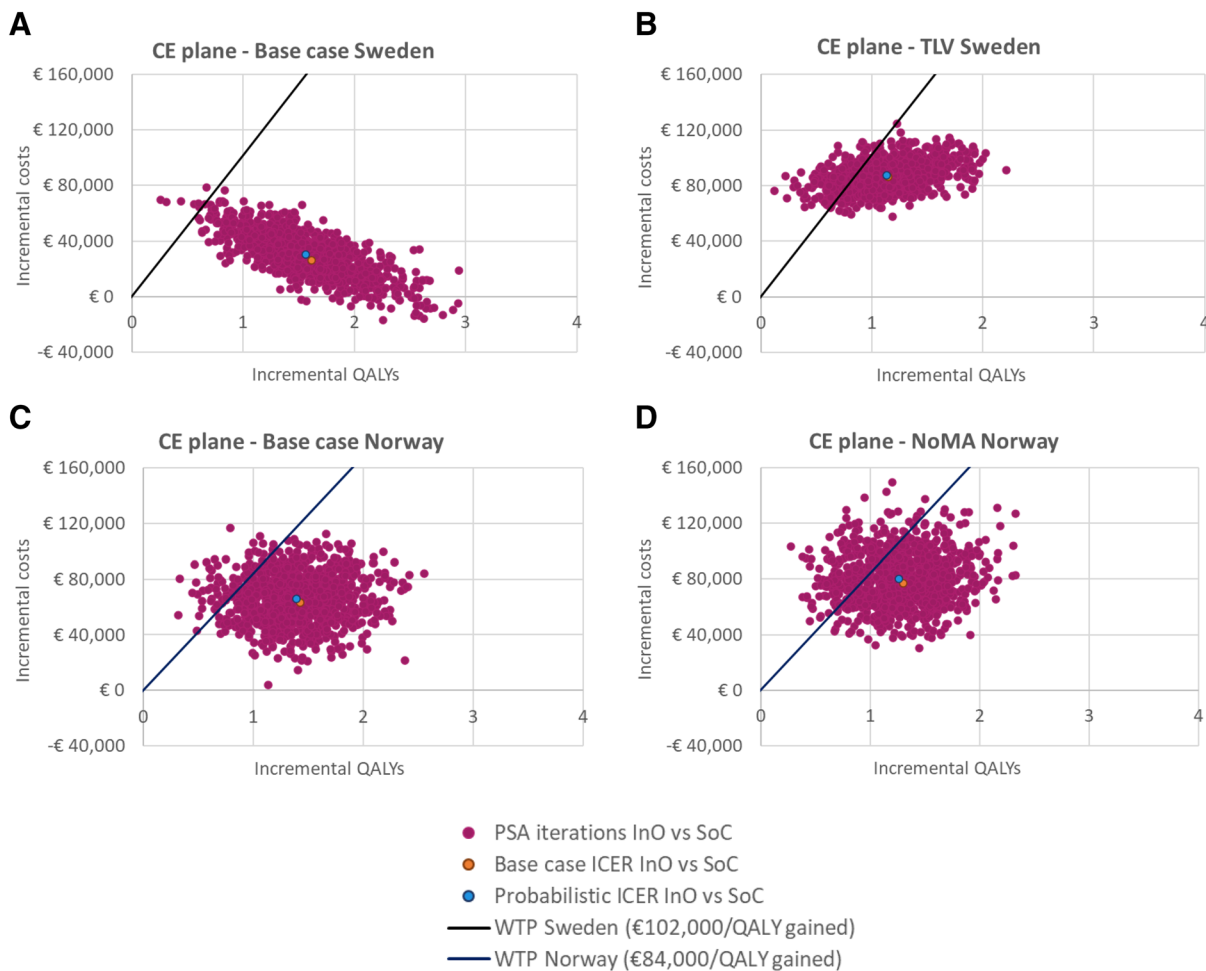
4 Discussion

The aim of this paper was to assess the cost-effectiveness of InO compared to SoC for treatment of B cell R/R ALL in Sweden and Norway, comparing our base case assumptions to those preferred by TLV and NoMA. We sought to

present the model's assumptions and justify our base case preferences. Table 3 presents where the perspectives of NoMA and TLV differed to ours (noting that assumptions not highlighted were implicitly agreed upon). In Table 4, the paper then aimed to present the differing estimates of cost-effectiveness side by side, allowing an examination of the impact of the differing perspectives.

Our base case and HTA ICERs were below the approximated WTP thresholds for both countries. Incremental QALYs and LYs were similar for InO versus either SoC. The difference in our base case ICERs for Sweden (€16,219 per QALY gained) and Norway (€44,405 per QALY gained) was mainly driven by the inclusion of productivity costs in Sweden, but higher bed-day costs in Norway, and the use of different discount rates also was a factor; removing these three differences would bring our base case ICERs for the two countries to within €200 of each other.

TLV's preferred assumptions increased the Swedish ICER by €58,908 per QALY gained versus our base case. However, the majority of this difference is driven by TLV's decision to exclude societal costs. TLV argued these should not be included as there is a risk that patients above the retirement age will be discriminated against for not being able to deliver the expected productivity gains related to treatment with InO [18]. Without societal costs, the difference between our Swedish base case and TLV's preferred assumptions was €24,766 per QALY gained. An important driver in this difference was TLV's preference to pool post-HSCT survival; this eliminated differences between arms upon the point of HSCT, which increased the SoC post-HSCT survival over the course of the model whilst reducing the InO survival versus our base case. No precise argumentation for this assumption was provided except for a general discussion on uncertainty around differences in long-term survival between the two treatment arms [18]. TLV also applied a more conservative SMR than our base



Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; InO, inotuzumab ozogamicin; NoMA; Norwegian Medicines Agency; QALY, quality-adjusted life year; SoC, standard of care chemotherapy; TLV, Tandvårds- och läkemedelsförmånsverket; vs, versus; WTP, willingness-to-pay.

Fig. 2 Cost-effectiveness planes. *CE* cost-effectiveness, *ICER* incremental cost-effectiveness ratio, *InO* inotuzumab ozogamicin, *NoMA* Norwegian Medicines Agency, *PSA* probabilistic sensitivity analysis,

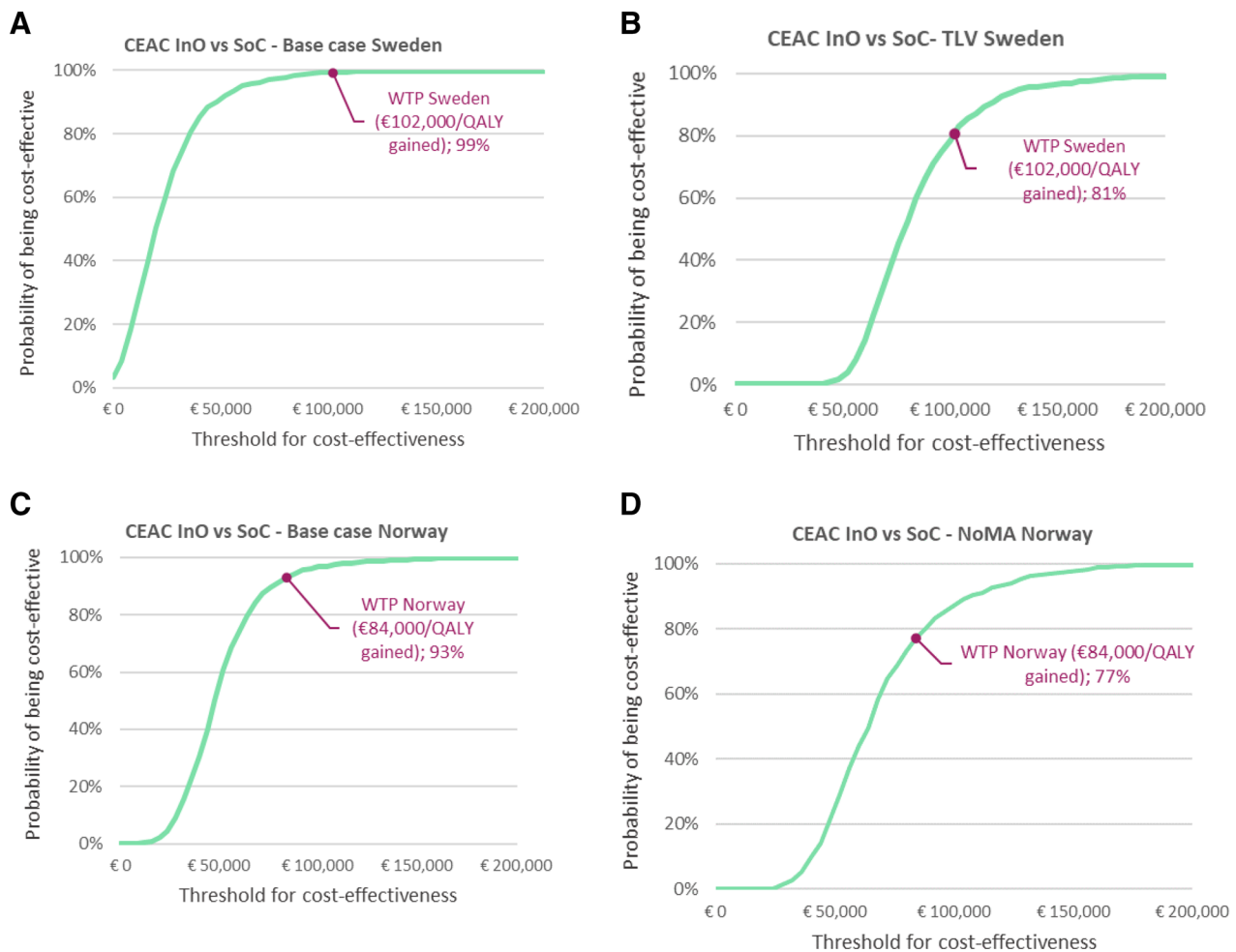
QALY quality-adjusted life year, *SoC* standard of care chemotherapy, *TLV* Tandvårds- och läkemedelsförmånsverket, *WTP* willingness to pay

case, which reduced long-term survival post-HSCT. While we considered an SMR of 4 to already be conservative as transplantation practices and related long-term survival have likely improved compared to the Martin et al. [33] cohort of 30 years ago, TLV argued an SMR of 9 was more applicable [18] as the median age of the INO-VATE ALL trial population was slightly higher than that of the Martin et al. patients [15, 16, 33].

NoMA’s preferred assumptions increased the Norwegian ICER by €14,986 per QALY gained versus our base case. The majority of this difference came from a higher cost used for an HSCT. Our base case used a cost per HSCT of €51,893 in Norway and €59,788 in Sweden. NoMA applied a cost of €105,686 per HSCT, just over twice that in our base case. As InO bridges significantly more patients to HSCT

versus SoC, this increased the incremental cost for InO in the model. NoMA also preferred to use parametric curves to extrapolate long-term post-HSCT instead of an SMR as they felt there was insufficient evidence to justify applying an SMR to general population mortality [4]. However, this only had a small impact on the ICER versus our base case assumption to use an SMR of 4. Changing the time horizon from lifetime (60 years) in our base case to NoMA’s preference of 40 years also had minimal impact on the ICER.

This study had several limitations. Although long-term data from the INO-VATE ALL trial was available, there was still uncertainty on how to model post-HSCT survival as OS and PFS data were only collected up to a final point of follow-up and not beyond. Long-term data collected from R/R post-HSCT ALL patients across a multi-decade period



Abbreviations: CEAC, cost-effectiveness acceptability curve; InO, inotuzumab ozogamicin; NoMA, Norwegian Medicines Agency; QALY, quality-adjusted life year; SoC, standard of care chemotherapy; TLV, Tandvårds- och läkemedelsförmånsverket; WTP, willingness-to-pay.

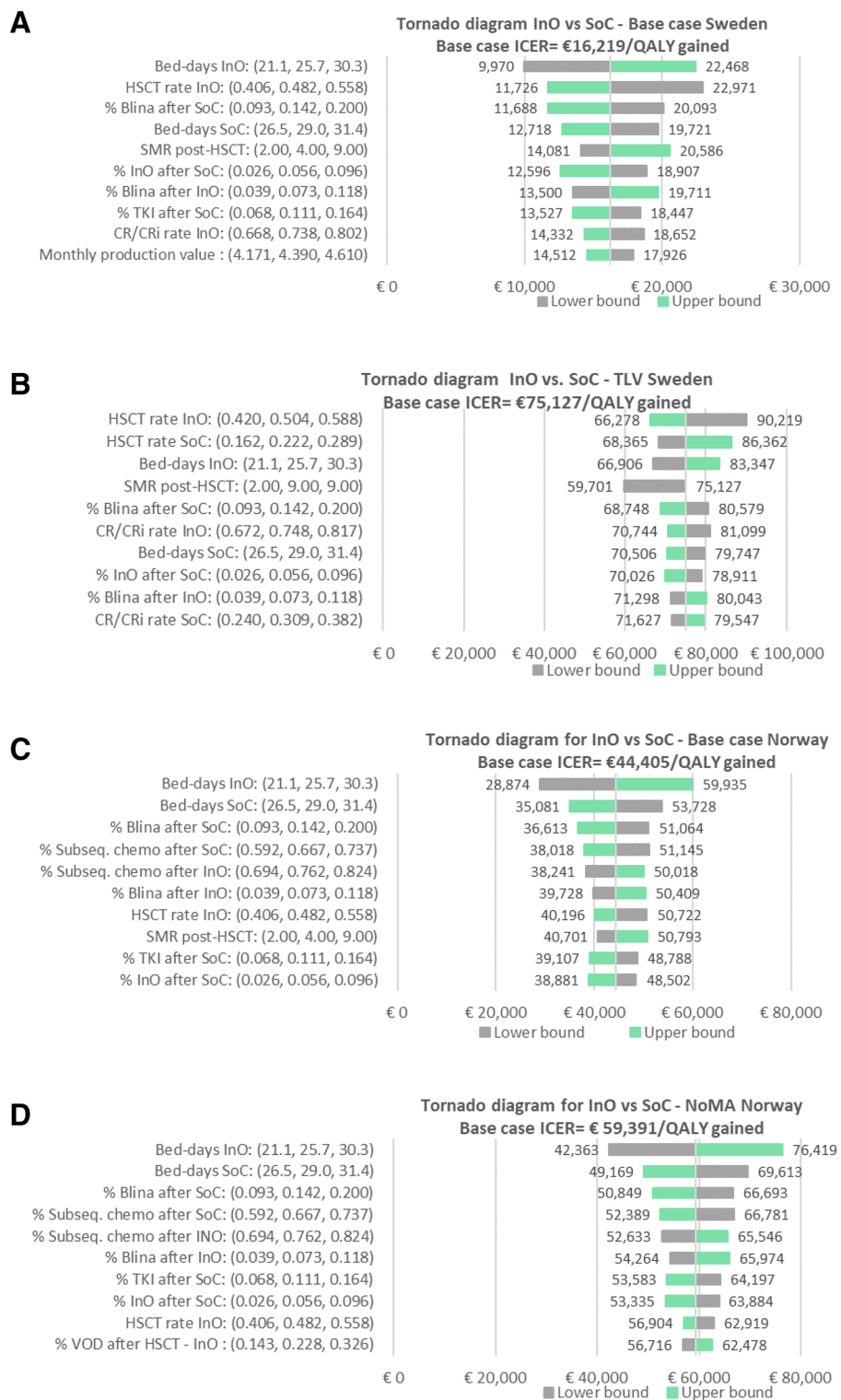
Fig. 3 Cost-effectiveness acceptability curves: InO vs SoC. CEAC cost-effectiveness acceptability curve, InO inotuzumab ozogamicin, NoMA Norwegian Medicines Agency, QALY quality-adjusted life

year, SoC standard of care chemotherapy, TLV Tandvårds- och läkemedelsförmånsverket, WTP willingness to pay

is sparse in the literature; further, improvements in transplant practices may render older registry data inaccurate when predicting long-term survival for those who have had successful transplants. In order to account for future survival uncertainty, multiple differing scenarios informed the various results presented in Table 4. As set out in Table 3, the two HTA authorities applied differing assumptions for post-HSCT survival versus our base case, which, together with our base case, presents a range that helps account for this uncertainty. Although the HTA authorities' assumptions were generally more conservative towards InO than our base case (leading to an increase in the ICERs), both authorities still found InO was associated with acceptable cost-effectiveness in both Norway and Sweden. A further limitation

was the uncertainty around the time spent in the hospital while treated with InO or SoC. The hospitalisation duration is expected to vary in clinical practice, demonstrated through a recent study in the UK real-world setting showing InO patients had a vastly reduced hospitalisation duration in the real world (a median of 5 days) compared to that observed in the INO-VATE ALL trial [70]. Although the time spent in the hospital will likely vary between countries, lower real-world hospitalisation with InO has a strong downward effect on the ICER. Finally, an explanation for differences between our base case assumptions and those of the HTA authorities was sometimes difficult to provide as the HTA documentation did not always include a clear argumentation for deviating from our base case assumptions.

Fig. 4 Tornado diagram on ICER: InO versus SoC



Abbreviations: Blina, blinatumomab; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; HSCT, hematopoietic stem-cell transplant; ICER, incremental cost-effectiveness ratio; InO, inotuzumab ozogamicin; NoMA, Norwegian Medicines Agency; QALY, quality-adjusted life year; SMR, standardized mortality ratio; SoC, standard of care chemotherapy; TKI, tyrosine kinase inhibitor; TLV, Tandvårds- och läkemedelsförmånsverket; VOD, veno-occlusive disease; vs, versus.

By way of external comparison, no previous R/R ALL models in Norway or Sweden were identified. In the UK, however, an adapted version of our described model was used for the NICE appraisal of InO (appraisal TA541) [19]. The model structure was similar to ours and was deemed appropriate for decision-making [19]. The final ICER versus SoC, upon which InO was recommended for use, was £37,497 per QALY gained (approximately €41,000) [19, 71]. The NICE ICER differed slightly from our base case because of confidential UK data on drug costs and a greater real-world hospitalisation advantage for InO over SoC than was observed in INO-VATE ALL; these data would be expected to lower all ICERs for InO versus SoC should it be incorporated into our model [70].

In conclusion, the results presented in this paper highlight our base cases in Sweden and Norway versus estimates informed by TLV and NoMA. All results use the same model structure, core clinical inputs, utility inputs, and similar country-specific input costs and discount rates. We have attempted to provide justification and rationale for our choices and preferences whilst acknowledging the differing preferences of the HTA authorities on specific assumptions. Key differences between our base case and those of the HTA authorities were preferences on the inclusion of societal costs, assumptions for survival post-HSCT, and the cost of HSCT. Based on all the different ICERs presented in this paper, InO is likely to be a cost-effective treatment versus SoC. The transparency reflected in this paper and the side-by-side examination of results will aid future decision makers in making informed choices on where and how to use InO for the treatment of R/R ALL.

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Declarations

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Conflict of interest IvO and BH were employees of Ingress-Health BV, who were paid consultants to Pfizer in connection with the development of this article. At the time of the study, TARS, JTO, and MJ were employees of Pfizer Inc.

Author contributions All authors were involved in the conceptualisation and the design of the study and interpretation of the data. IvO and TARS analyzed the data and drafted the manuscript. All authors critically reviewed the article and made substantial contributions to the finalisation of the manuscript and have given their final approval of the version to be submitted.

Data availability statement The authors declare that the data supporting the findings of this study are available within the article and its supplementary information files, and within the referenced studies.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication All authors have provided their consent for publication.

Code availability An overview of the model structure has been published in this article to allow replication; however, the coded model itself has not been published. Further details are available via the corresponding author upon reasonable request.

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