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THE COMPARATIVE PHARMACOECONOMIC ANALYSIS OF USING BLINATUMOMAB IN RUSSIA

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OBJECTIVES:

- Pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL) is an extremely rare disease, and while it has a high cure rate with first-line therapy, it will relapse in 15% to 20% [1] of patients and a further 2% will have refractory disease [2,3];
- The age-standardized ALL(ICD-10 C91.0) incidence rate using the world standard population as a reference was estimated at 1.59 per 100 000 leading to about 984 new ALL cases in children aged 0-19 in Russia for the year 2017;
- Current treatment options for pediatric relapsed or refractory BCP-ALL (R/R BCP-ALL) are extremely limited, and the disease is considered to be life-threatening and associated with high unmet need;
- Patients with pediatric R/R BCP-ALL experience substantial impairment of HRQL;
- Blinatumomab, which has demonstrated meaningful and consistent efficacy in paediatric patients with R/R Philadelphia chromosome negative BCP-ALL (R/R Ph- BCP-ALL) in the MT 103-205 study [4] vs. historical comparator data, represents a major therapeutic innovation and a pivotal change in the management of young patients with this devastating and highly aggressive disease that responds poorly to current salvage chemotherapy regimens and experience very poor survival.

The main **aim** of this study was to perform cost-utility model comparing blinatumomab with standard of care (SoC) for treating paediatric patients with R/R Ph- BCP-ALL in Russia.

METHODS:

- Health outcomes were expressed in terms of life-years (LYs) and quality-adjusted life-years (QALYs) gained. Cost estimates were presented as aggregated total costs, costs by components (i.e. medication costs (blinatumomab and SoC), inpatient and outpatient costs, allo-SCT-related costs, subsequent treatment costs, adverse events (AE) costs, terminal care costs and indirect costs). Incremental cost-utility ratios (ICURs) were calculated and expressed as ICUR per LY gained and ICUR per QALY gained. The analysis was conducted from the social perspective including direct and indirect costs.
- A lifetime horizon was considered justified, since death reflected the natural course of pediatric R/R Ph- BCP-ALL patients. The base case analysis followed patients until death or for up to 80 years, which corresponds, to the life-time projection for a typical patient with paediatric R/R BCP ALL (in MT 103-205 [4] the median age of patients was 8 years). An annual discount rate of 3.5% was applied to both costs and future outcomes.
- The propensity score analysis was undertaken using inverse probability of treatment weighting (IPTW), which is the most appropriate approach given that overall survival (OS) (a time-to-event endpoint) was the primary endpoint in the propensity score analysis, and the sample sizes of the MT103-205 and historical cohort were small. Endpoint analyses was then conducted using the IPTW, using average treatment effect (ATE) weights to align the control population and the MT103-205 [4] cohort more closely in terms of important baseline characteristics.
- The evaluation uses a partitioned survival model with states defined on the basis of response to treatment, relapse, and death (Figure 1). The model was programmed in Microsoft Excel. All patients enter the model in the "initial" state and remain in this state for 12 weeks (unless they die during that period), after which they may either enter the "refractory/relapsed" state or "response" state, depending on response to therapy. A 12-week duration for the initial period was used to correspond to the point at which response was assessed in the MT 103-205 trial [4] (i.e., after two 6-week cycles).
- Clinical effectiveness inputs to inform health state probabilities for blinatumomab and the relevant comparator (SoC chemotherapy) are based on the ATE analysis of the MT 103-205 trial [4] for blinatumomab and the historical comparator data (study 20120299 and 20140228228) for SoC. The probabilities of response for patients receiving blinatumomab and SoC were based on the proportion of patients achieving a complete remission with full recovery of peripheral blood count from study MT 103-205 [4] and the historical comparator study. For patients achieving a response, the proportion of patients remaining in the response state over time was based on the distribution of relapse-free survival (RFS) among responders.
- Parametric distributions for OS and RFS among responders were estimated by fitting parametric survival distributions to individual patient failure time data using Flexsurv, an R package for fully-parametric modelling of survival data (Figure 2, 3).

Figure 1. Schematic of model structure

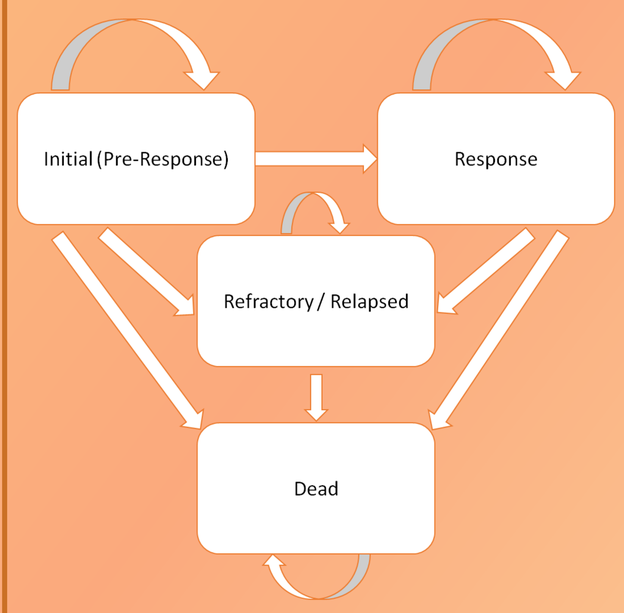

Figure 2. Visual fit of distributions fit to OS for patients receiving blinatumomab and SoC (ATE adjustment)

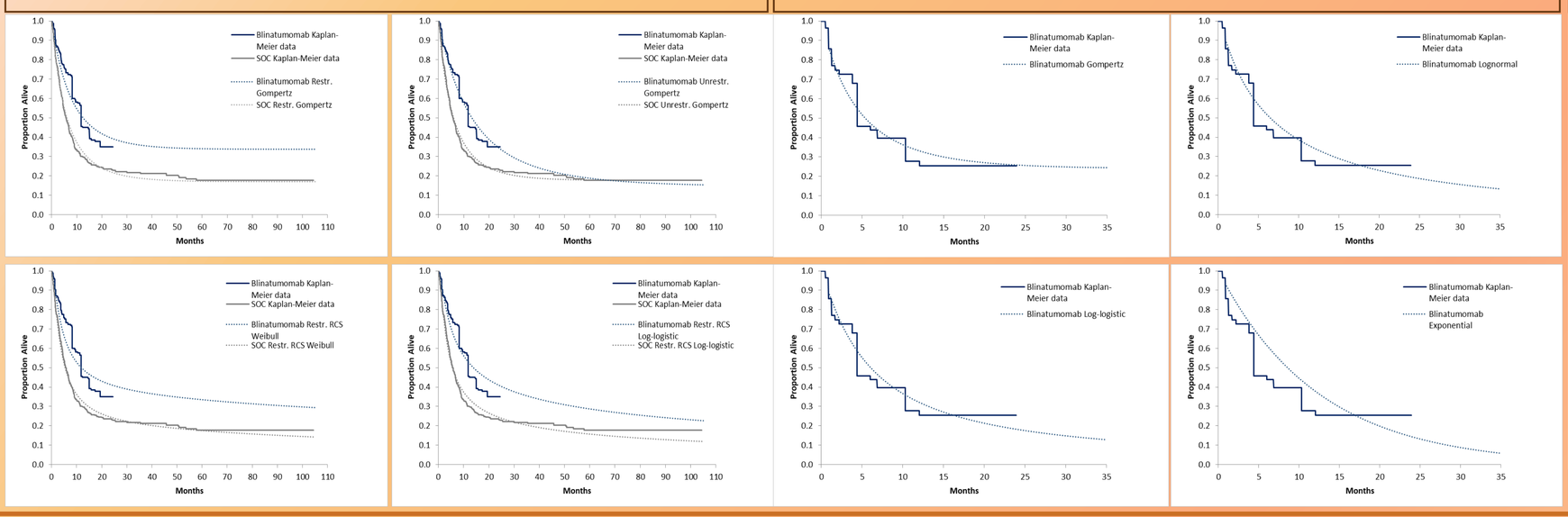

Figure 3. Visual fit of distributions fit to RFS for patients receiving blinatumomab (ATE adjustment)

Table 1. Summary of propensity score analysis results (IPTW, ATE Weights)

	SoC	Blinatumomab	Ratio (95% CI)[a]
Overall Survival			0.60 (0.38, 0.95)
at 3-month	0.70	0.85	
95% CI	(0.66, 0.75)	(0.74, 0.97)	
at 6-month	0.48	0.74	
95% CI	(0.43, 0.54)	(0.61, 0.89)	
Complete response with full recovery			1.79 (0.71, 4.52)
Overall (%)	0.09	0.14	
95% CI	(0.06, 0.13)	(0.07, 0.27)	

[a] Blinatumomab:SoC hazard ratio for OS from a Cox proportional-hazards model with each patient's treatment status as an independent factor; blinatumomab: SoC odds ratio for CR rates from a logistic regression model

- EQ-5D utility values were derived from the TOWER phase III clinical trial [5] of blinatumomab in patients with adult R/R Ph- BCP ALL. Utility values in the model are assumed to be dependent on health state and treatment, mapped EQ-5D utility values from TOWER were analysed using generalised linear model/generalised estimating equations regression.
- Costs of blinatumomab and SoC drug acquisition and administration costs were based on the dosing regimens in the MT 103-205 trial [4] and typical clinical practice. The cost per patient receiving allo-SCT was assumed to be the same for patients receiving blinatumomab and SoC. Information on AE from the TOWER phase III clinical trial [5] of blinatumomab in patients with adult R/R Ph- BCP ALL were used in the base case. The costs of adverse events for patients treated with blinatumomab and SoC were included in the model as a one-off cost. The model includes the expected costs of subsequent salvage therapy (SST) for those patients who do not respond to treatment or relapse during the model time horizon. The cost for terminal care was applied as a one-off cost at death for patients who died within 48 months. Indirect costs were applied per model cycle to patients who died along the modelled time horizon, once patients reach the age of 18 until the official retirement age in Russia (60 years).

RESULTS: Results from the propensity score analysis showed a trend in favor of blinatumomab for OS compared with SoC (hazard ratio [HR]: 0.60; 95% CI: 0.38, 0.95; Table 1). Blinatumomab was associated with a higher rate of complete response (CR) with full recovery of peripheral blood counts (14% vs 9%; odds ratio: 1.79) which is considered a robust surrogate for prolonged OS in ALL [17]. Cost-effectiveness analysis demonstrated that blinatumomab was both more effective (greater life-years and QALYs) and less costly than SoC (Table 2). Blinatumomab was projected to yield 3.97 more (discounted) LYs and 3.51 more (discounted) QALYs than SoC chemotherapy. Total costs were estimated to be $3750 lower with blinatumomab than with SoC chemotherapy. The resulting ICUR was $943.5 per QALY gained and $1068.9 per LY gained. Consequently, blinatumomab is dominant (i.e. less expensive and more efficacious) (rate for September 2019).

Table 2. Base case results for the cost-utility of blinatumomab vs SoC in paediatric patients with R/R Ph– BCP ALL

Cost Category	Blinatumomab	SoC	Incremental
Life years			
Initial	0.21	0.20	0.01
Response	0.86	0.55	0.31
Relapse/refractory	7.58	3.93	3.65
Total	**8.65**	**4.68**	**3.97**
QALYs			
Initial	0.14	0.11	0.03
Response	0.76	0.48	0.28
Relapse/refractory	6.47	3.26	3.21
Total	**7.36**	**3.85**	**3.51**
Costs (USD)			
Drug acquisition	42,746.6	5,033.6	37,713
Hospitalization	1,404.1	9,498.4	-8,094.3
Outpatient visits	68.2	0	68.2
Allo-SCT	22,353.3	22,353.3	0
SST	12,497.5	13,224.1	-726.6
Terminal Care	601.8	752.3	-150.5
AE costs	3,875.5	6,536.3	-2,660.8
Indirect costs	109,395.1	139,294.2	-29,899.1
Total	**192,942.1**	**196,692.2**	**-3,750.1**
ICER per LY Gained			**-943.5**
ICER per QALY Gained			**-1068.9**

DISCUSSION:

- To our knowledge, this is the first economic evaluation comparing blinatumomab versus SoC in paediatric patients with R/R Ph- BCP ALL; therefore, a comparison of cost-effectiveness results with published literature is not possible.
- Additional benefits associated with blinatumomab are unlikely to be captured within the standard incremental cost-utility framework, specifically, the benefits to patients and their families (e.g., informal caregivers) of minimizing hospitalization requirements and to wider society by enabling pediatric patients to achieve long-term remission and survival.
- Blinatumomab is indicated for a rare condition in a very small number of patients who have a huge unmet medical need and who stand to gain substantially from access to this highly innovative treatment.

CONCLUSIONS: Using blinatumomab for treating paediatric patients with R/R Ph- BCP ALL was effective and economically justified treatment option in Russia.

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