Cost-effectiveness of Blinatumomab Versus Chemotherapy in Adult Patients With Acute Lymphoblastic Leukemia in First Hematological Complete Remission With Minimal Residual Disease Using a Markov Cohort Approach

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BACKGROUND AND OBJECTIVE

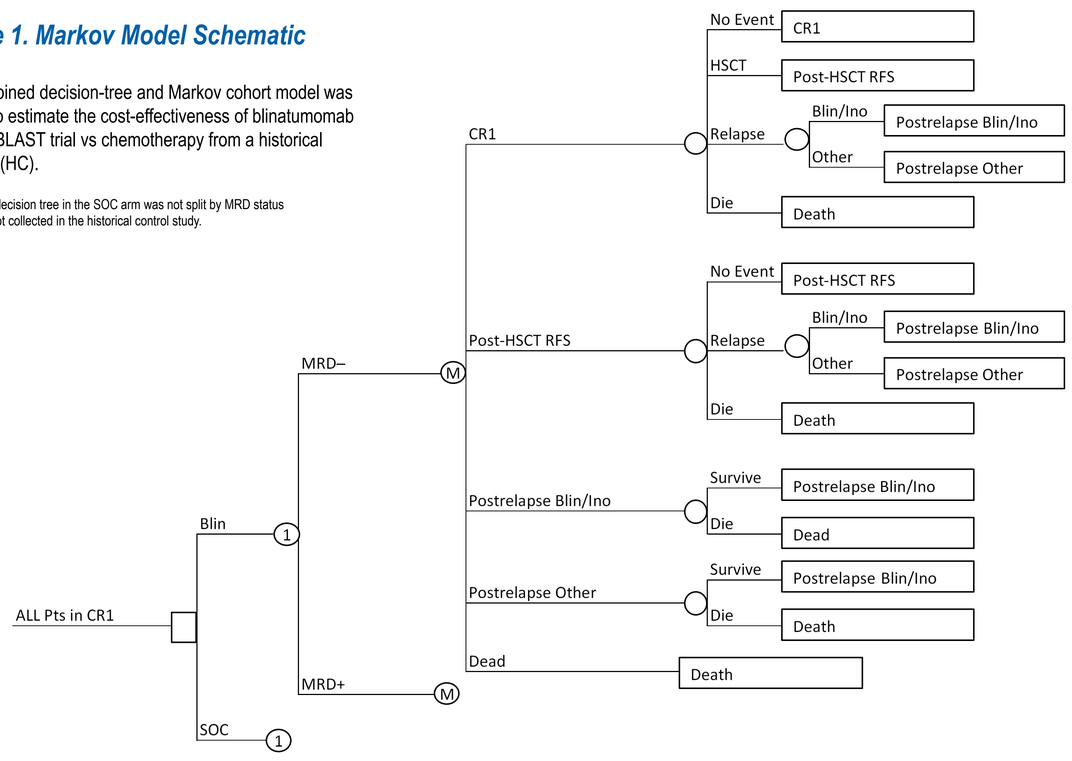
- Minimal residual disease (MRD) refers to residual acute lymphoblastic leukemia (ALL) that is below the sensitivity of standard microscopy, but detectable by molecular techniques such as flow cytometry or polymerase chain reaction .
- MRD is a strong prognostic factor for patients with Philadelphia chromosome-negative (Ph–) B-cell precursor acute lymphoblastic leukemia (BCP-ALL).[1]
- Blinatumomab is a CD19/CD3 (bispecific T-cell engager) antibody construct that is indicated in the US for the treatment of
  - Relapsed or refractory BCP-ALL
  - Adults and children with BCP-ALL in first or second complete remission (CR) with MRD greater than or equal to 0.1%
- In the BLAST trial, an open-label, multicenter, single-arm, phase 2 study of blinatumomab in patients with MRD BCP-ALL in hematological CR, blinatumomab resulted in complete MRD response (no target amplification with a minimum sensitivity of 10^{-4}) in cycle 1 in 78% of patients.[2]
- The cost-effectiveness of blinatumomab vs chemotherapy was demonstrated from a US healthcare payer perspective using a partitioned survival analysis framework.
- The objective of this study is to estimate the cost-effectiveness of blinatumomab vs chemotherapy in patients with MRD using a Markov cohort modeling approach from a US payer perspective.

METHODS

Figure 1. Markov Model Schematic

- A combined decision-tree and Markov cohort model was used to estimate the cost-effectiveness of blinatumomab in the BLAST trial vs chemotherapy from a historical cohort (HC).

Note: The decision tree in the SOC arm was not split by MRD status as it was not collected in the historical control study.



ALL: acute lymphoblastic leukemia, Blin: blinatumomab, CR1: first complete remission, HSCT: hematopoietic stem cell transplant, Ino: inotuzumab, MRD: minimal residual disease, PRS: postrelapse survival, RFS: relapse-free survival, SOC: standard of care, 1: node 1, M: Markov node

Table 1. Summary of Distribution Used for Transition Probabilities

Population	From	To	Distribution	Comment
BLAST MRD Responders	CR1	HSCT	Lognormal Cure	Lowest BIC, Excellent visual fit Reasonable to assume no risk after ~6 months
		Relapsed	Exponential	Lowest BIC, Good visual fit
		Dead	Exponential	Only one event so constant probability assumed
	HSCT	Relapsed	Exponential Cure	Good statistical fit, Excellent visual fit Reasonable to assume cure with HSCT
		Dead	Exponential Cure	Lowest BIC, Excellent visual fit Reasonable to assume long-term cure with HSCT
BLAST MRD NonResponders	CR1	HSCT	Lognormal	Lowest BIC, Excellent visual fit Yields 100% probability of HSCT at ~12 months
		Relapsed	Gompertz	Lowest BIC, Excellent visual fit Consistent with assumed distribution for SOC
		Dead	Exponential	Only one event so constant probability assumed
	HSCT	Relapsed	Exponential	Since no events, set to zero by specifying exponential distribution with approximately zero probability of event in model time horizon
		Dead	Gompertz	Good statistical fit, Excellent visual fit Reasonable to assume long-term cure with HSCT
SOC	CR1	HSCT	Gompertz	Best statistical fit, Excellent visual fit Reasonable to assume no risk after ~6 months
		Relapsed	Gompertz	Best statistical fit, Excellent visual fit Reasonable to assume no risk after ~6 months
		Dead	Exponential	Curve fitting difficult due to small number of events Constant hazard assumed
	HSCT	Relapsed	Exponential Cure	Good statistical fit, Good visual fit Reasonable to assume cure after HSCT
		Dead	Lognormal	Good statistical fit, Good visual fit, Decreasing hazard with lognormal yields long tail approximating cure model, which is reasonable post-HSCT
TOWER S0 Not Primary Refractory ATT-IPTW	Relapsed Blin/Ino	Dead	Restricted Gompertz	Good statistical fit, Excellent visual fit
	Relapsed Other	Dead	Restricted Gompertz	Adjusted to match overall survival observed in BLAST (H=0.5993)

- MRD status was used to allocate transition probabilities for receiving hematopoietic stem cell transplant (HSCT), relapse, and death.
  - CR1 to HSCT
  - CR1 to relapsed
  - CR1 to dead
  - HSCT to relapsed
- After relapse, the transition probabilities were estimated based on the data from patients receiving chemotherapy in TOWER .
- Probability calculations were based on a competing risk framework.
  - Survival distribution for particular patients who experience other competing risks were censored at the time of the event
- Patients from the HC study were matched to patients from BLAST using propensity score weighting.

Figure 2. Observed and Predicted Survival for Relapse Free and Overall Survival

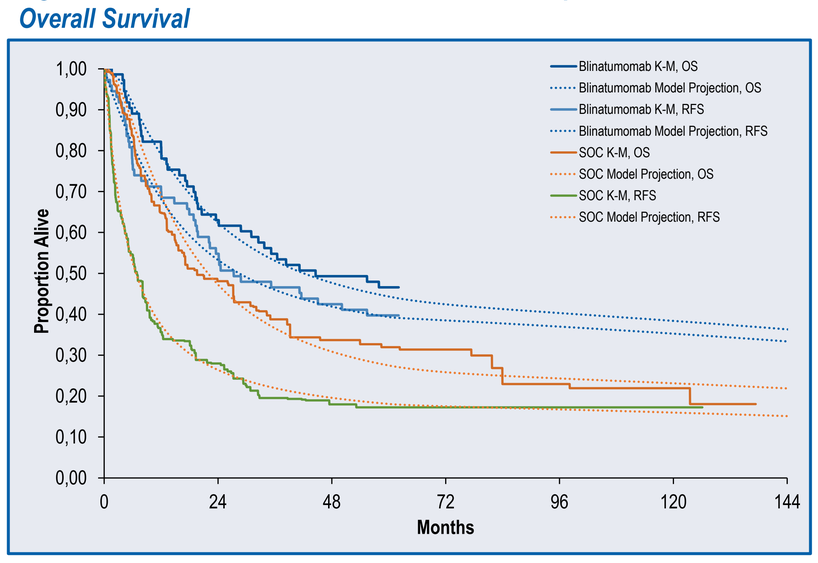


Table 2. Utility Values Used in the Model

State	Utility value mean
Blinatumomab on-treatment relapse-free	
Cycle 1	0.824
Cycle 2+	0.859
Blinatumomab off-treatment relapse-free	
Cycle 1[a]	0.832
Cycle 2+	0.859
SOC relapse-free >6 months prior to death	0.836
Postrelapse >6 months prior to death	0.762
Decrement in utility for ≤6 months prior to death	–0.093
Patients who survive for 5 years	Age and sex-matched norms accounting for long-term decrement due to long-term effects of exposure to radiotherapy, chemotherapy, and HSCT on health- related quality of life (0.02)
Decrement in utility value post-HSCT[b]	Year 1: 0.17 Year 2: 0.01 Years 3–5: 0.02

[a]All patients start cycle 1, so this utility value is not used in the model.
[b]These values were not captured in either trial and are from the study by Kurosawa et al.[4]

Table 3. Costs Used in the Model

Parameter	Point Estimate	Source
Medication costs		
Blinatumomab ($, cost per mg)	113.344	[3]
Blinatumomab dose per day: (mcg/day for 28 days / 14-day treatment-free interval)	28	Blinatumomab (BLINCYTO®) prescribing information [4]
SOC (total cost of therapy): Vincristine / Prednisolone / Mercaptopurine / Methotrexate	2,247.44	[3]
Administration costs		
Blinatumomab: inpatient days per cycle received		
Cycle 1	3	Blinatumomab (BLINCYTO®) prescribing information [4]
Cycle 2	2	Blinatumomab (BLINCYTO®) prescribing information [4]
Cycles 3–4	0	Blinatumomab (BLINCYTO®) prescribing information [4]
Cost per inpatient day ($)	6,498	MarketScan Claims Database Analysis.[5]
Blinatumomab: outpatient care		
Days per bag change	2	Assumption.
Cost per day of home infusion therapy ($)	68	BCBS of Michigan. Medicare Advantage PPO Enhanced Benefits Fee Schedule (2017).[6,8]
Cost per outpatient visit, refill of infusion pump ($)	142	CMS (2017).[7]
Standard of care: outpatient costs ($)	1,872	
MRD response – Blinatumomab	83.6%	BLAST Trial.[2]
MRD response – Standard of care	8%	Assumption
Inpatient costs by MRD status		
Number of days / month - MRD+	1.9	Rose et al. ASH 2018.[8]
Number of days / month - MRD-	0.6	Rose et al. ASH 2018.[8]
Cost per inpatient day ($)	5,450	Marketscan Claims Database Analysis.[5]
Outpatient costs by MRD status		
Number of visits / month - MRD+	0.13	Rose et al. ASH 2018.[8]
Number of visits / month - MRD-	0.09	Rose et al. ASH 2018.[8]
Cost per outpatient visit ($)	109	CMS (2017).[7]
Probability of undergoing HSCT		
Blinatumomab patients	72.6%	BLAST Trial.[2]
SOC patients	38.4%	BLAST Trial.[2]
Cost of HSCT ($)	394,069	Zhang et al. 2017.[9]
Cost per course of subsequent salvage therapy ($)		
Multi-agent chemotherapy	62,061	Delea et al. 2017.[10]
Cost of terminal care ($)	26,193	Chastek et al. 2012.[11]

- One-way sensitivity analyses, scenario analyses, and probabilistic sensitivity analyses were conducted to test model robustness.

RESULTS

- Blinatumomab yields an additional 2.47 life years and 2.05 quality-adjusted life years (QALYs) vs chemotherapy.
- Blinatumomab has higher incremental costs vs chemotherapy of $242,940; higher medication costs in the blinatumomab arm are partially offset by reduced postrelapse costs of $58,499.
- The incremental cost-effectiveness ratio (ICER) for blinatumomab vs chemotherapy is $118,659/QALY gained.

Table 4. Results of the Cost-effectiveness Analysis

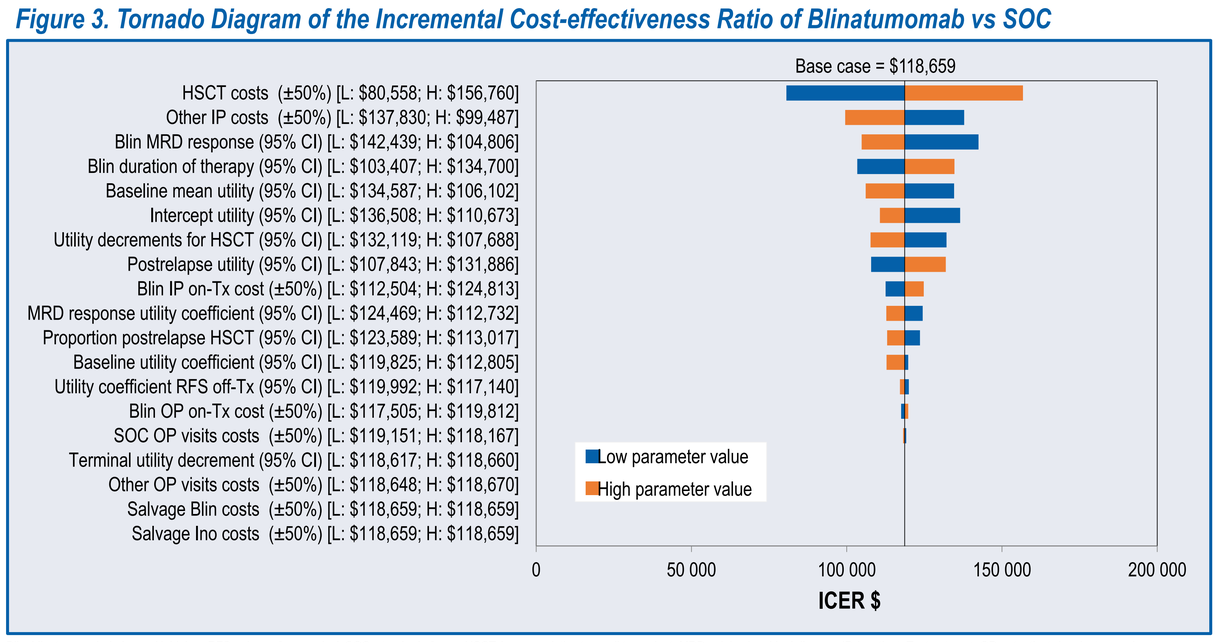
	Blinatumomab	SOC	Blinatumomab vs SOC
Effectiveness, discounted			
Relapse-free life years	1.54	1.24	0.30
Allo-SCT	5.41	2.21	3.20
Postrelapse life years	0.75	1.78	–1.03
Total life years	7.70	5.23	2.47
Total QALYs	6.32	4.27	2.05
Costs, discounted ($)			
Medication and administration	200,780	3,499	197,282
HSCT	297,259	110,232	187,028
Other inpatient	138,110	216,613	–78,503
Other outpatient	301	257	44
Postrelapse	46,123	104,621	–58,499
Terminal care	14,239	18,651	–4,412
Total	696,812	453,872	242,940
Cost-effectiveness			
Cost per life year ($/LY)			98,479
Cost per QALY ($/QALY)			**118,659**

Table 5. Scenario Analysis Results

Scenario	Blinatumomab vs SOC			
	Cost ($)	LYs	QALYs	ICER ($)
Base case	242,940	2.47	2.05	118,659
ATE weights	214,184	1.92	1.62	131,860
Use SOC survival curves to inform survival in MRD+ receiving blinatumomab	235,572	2.67	2.22	106,164
SOC estimated based on BLAST data (0% response rate)	198,245	3.82	3.17	62,452
SOC estimated based on BLAST data (8% response rate)	196,855	3.45	2.87	68,604
SOC estimated based on BLAST data (15% response rate)	195,639	3.13	2.60	75,170
2-fold increase in long-term mortality	243,929	2.86	2.36	103,244
6-fold increase in long-term mortality	242,721	2.23	1.86	130,812
Annual discount rate for costs and QALYs=0%	240,271	3.77	3.13	76,835

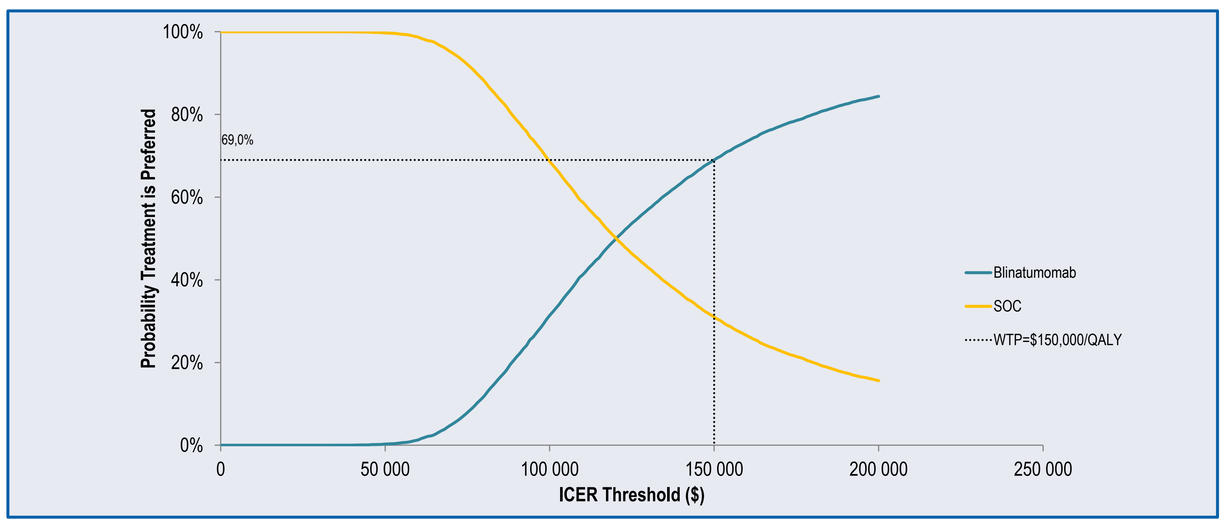
- Assumptions that most affected cost-effectiveness results were
  - The discount rate,
  - The methods used for the propensity score analysis for the historical control comparison
  - The long-term mortality estimation.
- The cost-effectiveness remained below the willingness-to-pay (WTP) threshold value of $150,000/QALY gained in all scenarios tested.

Figure 3. Tornado Diagram of the Incremental Cost-effectiveness Ratio of Blinatumomab vs SOC



Blin, blinatumomab; L, lower; H, higher; RFS, relapse-free survival; SOC, standard of care; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease; IP, inpatient; Tx, treatment; OP, outpatient; Ino, inotuzumab

Figure 4. Cost-effectiveness Acceptability Curve



DISCUSSION

- Model projections of relapse-free survival and overall survival were very similar to Kaplan-Meier estimates throughout the duration of the BLAST trial.
- Results of the model were relatively insensitive to changes in model parameters and assumptions.
- The numbers of patients with events were small for several of the events included in the Markov model, which made selection of survival distributions for these events challenging.

CONCLUSIONS

- **Blinatumomab is cost-effective vs chemotherapy in ALL patients with MRD from a US healthcare payer perspective.**
- **Achieving MRD negativity with blinatumomab therapy is associated with better survival and improved QALYs.**
- **The results of these analyses may be useful for US healthcare payers in their deliberations regarding reimbursement decisions for this vulnerable population with limited treatment options.**

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DISCLOSURE

- The study was funded by Amgen.