Comparison of Partitioned Survival Versus Markov Cohort Modeling Approaches in the Evaluation of Cost-effectiveness of Blinatumomab Versus Chemotherapy in Adult Patients With Acute Lymphoblastic Leukemia in First Hematological Complete Remission With Minimal Residual Disease

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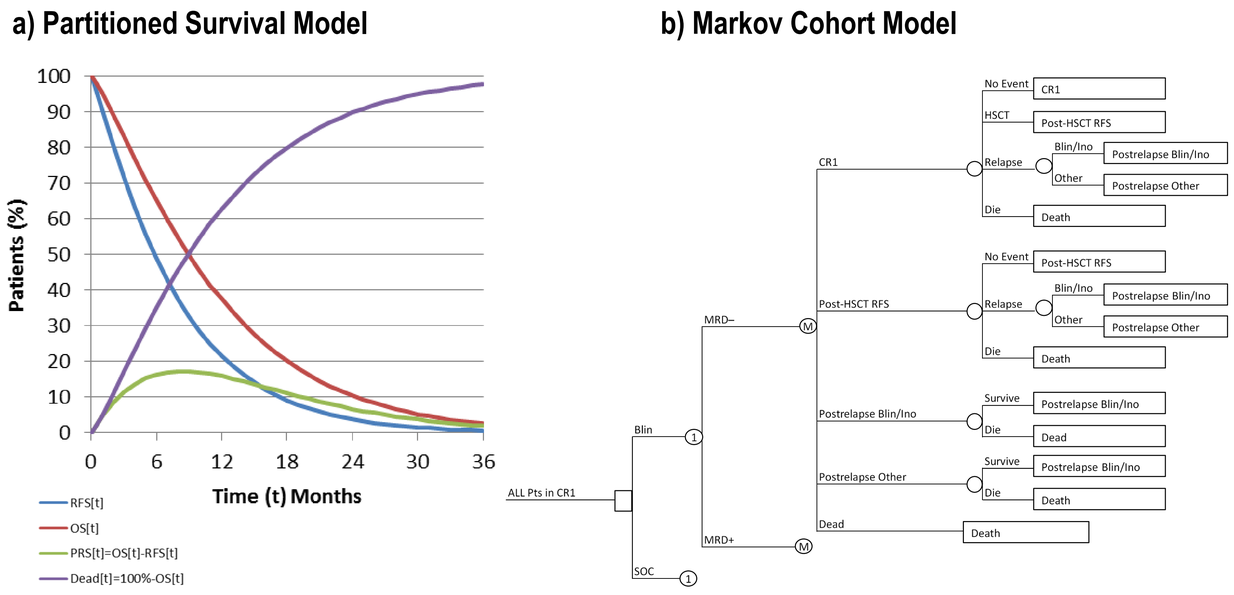
BACKGROUND AND OBJECTIVE

- For rare diseases like B-cell precursor acute lymphoblastic leukemia (BCP-ALL), trials frequently present limitations including small samples and single-arm design.
- The BLAST trial is an open-label, multicenter, single-arm, phase 2 study that evaluated the efficacy of blinatumomab in patients with minimal residual disease (MRD) BCP-ALL in hematological complete remission (CR).[1]
- Blinatumomab resulted in complete MRD response in cycle 1 in 78% of patients and was associated with an overall survival (OS) of 36.5 months.[1]
- The cost-effectiveness of blinatumomab vs chemotherapy was demonstrated from a US healthcare payer perspective using a partitioned survival analysis framework.
- Partitioned Survival Models (PSMs)
  - Are relatively simple, transparent, and require relatively few assumptions
  - But are unable to link MRD response and survival or model explicitly the impact of subsequent treatment/interventions such as hematopoietic stem cell transplant (HSCT)
- Markov cohort models (MCMs)
  - Can include intermediate endpoints affecting survival
  - But require more assumptions and more parameter estimates
- In this context, we propose to assess the value of using a MCM instead of a PSM that only relies on relapse-free survival (RFS) and OS evaluating the cost-effectiveness of blinatumomab vs chemotherapy.

METHODS

- Clinical data from BLAST study (blinatumomab) and historical control study (chemotherapy) adjusted using inverse probability of treatment weighting were used to populate both cost-effectiveness models.
- In the PSM, RFS and OS were based on parametric distributions fit to patient level failure-time data from the BLAST trial and the historical comparator study.
  - MRD response was included to estimates its consequences on resource use, but its impact on survival was not modelled
  - HSCT was included in the model to estimate its impact on costs and utilities, but its potential impact on survival was not included
- To validate PSM findings, an MCM, which explicitly estimated the contribution of MRD and HSCT on survival, was developed.
  - Time to HSCT, time to relapse conditional on HSCT, time to death conditional on HSCT were added to the model
  - All survival functions were derived according to MRD response; MRD response was applied only to the blinatumomab group since it was not available in the historical cohort
  - Transition probabilities for HSCT, relapse, and death were estimated using BLAST
- We evaluated the sensitivity of both models around parameters and assumptions.

Figure 1. Model Schematics

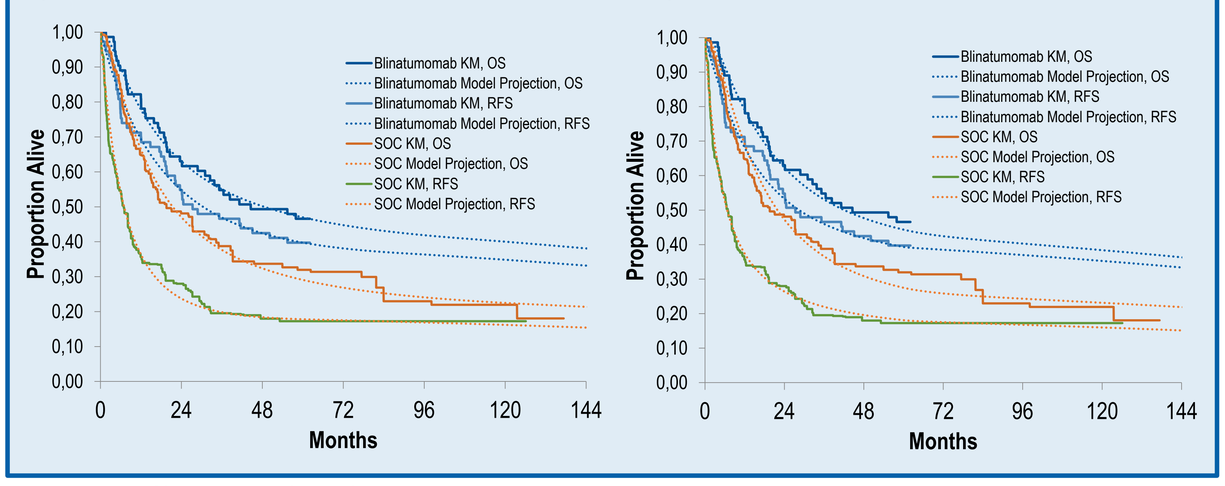


ALL: acute lymphoblastic leukemia, Blin: blinatumomab, CR1: first complete remission, HSCT: hematopoietic stem cell transplant, Ino: inotuzumab, MRD: minimal residual disease, OS: overall survival, PRS: postrelapse survival, RFS: relapse-free survival, SOC: standard of care; 1, Node 1; M, Markov node

RESULTS

- Survival predictions in the base case were similar between the two models and provided a good fit to the Kaplan–Meier data (Figure 2).
- Both models led to similar incremental cost-effectiveness ratios for blinatumomab vs chemotherapy: $102,016/QALY in the PSM and $118,659/QALY in the MCM.
- Incremental costs (PSM: $261,876; MCM: $242,940) and QALYs (PSM: 2.57; MCM: 2.05) were comparable.
- The lower QALY difference in MCM vs PSM is due to lower estimations of postrelapse survival for blinatumomab in MCM model.
- The lower incremental cost in MCM is due to the explicit allocation of MRD-related costs (other inpatient costs, other outpatient costs), leading to higher cost offsets.

Figure 2. Model Predictions



K-M, Kaplan-Meier; OS, overall survival; RFS, relapse-free survival

RESULTS (Continued)

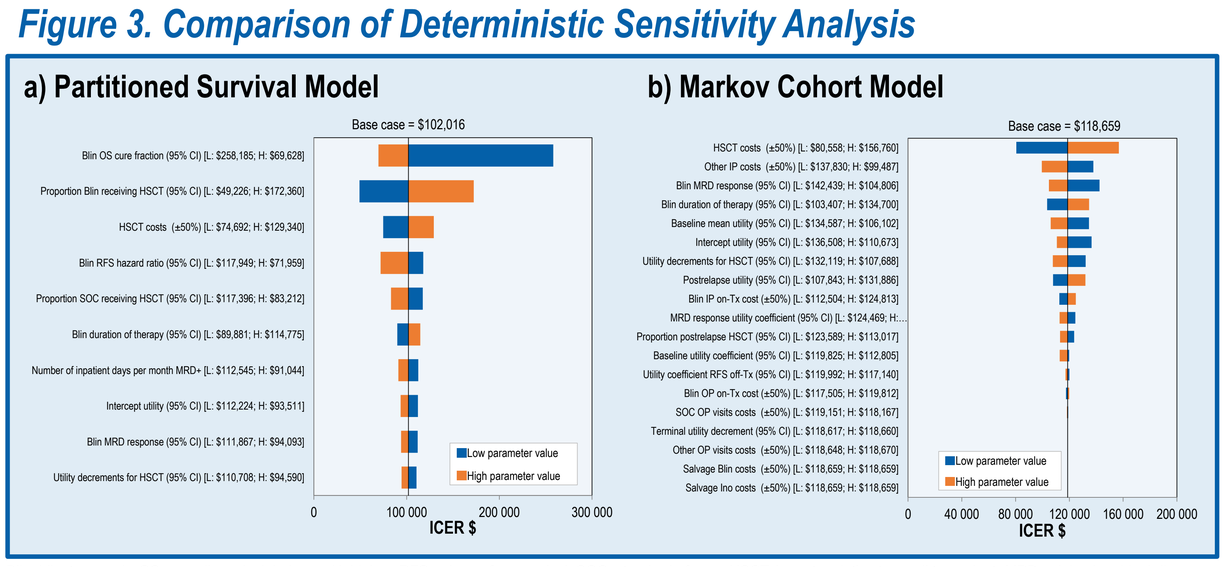
Table 1. Cost-effectiveness Results Comparison

	PSM			MCM		
	Blinatumomab	SOC	Blinatumomab vs SOC	Blinatumomab	SOC	Blinatumomab vs SOC
Effectiveness, discounted						
Relapse-free life years/Allo-SCT	7.34	3.57	3.77	6.95	2.45	3.50
Postrelapse life years	1.08	1.86	–0.78	0.75	1.78	–1.03
Total life years	8.42	5.43	2.99	7.70	5.23	2.47
Total QALYs	6.94	4.37	2.57	6.32	4.27	2.05
Costs, discounted ($)						
Medication and administration	200,455	4,552	195,904	200,780	3,499	197,282
HSCT	271,851	97,009	174,843	297,259	110,232	187,028
Other inpatient	161,050	202,408	–41,359	138,110	216,613	–78,503
Other outpatient	345	240	105	301	257	44
Postrelapse	42,200	105,102	–62,902	38,526	99,185	–60,659
Terminal care	13,728	18,442	–4,715	12,453	17,872	–5,419
Total	689,629	427,753	261,876	697,011	448,084	248,926
Cost-effectiveness						
Cost per life year ($/LY)			87,481			98,479
Cost per QALY ($/QALY)			**102,016**			**118,659**

PSM, partitioned survival model; MCM, markov cohort model; SOC, standard of care; HSCT, hematopoietic stem cell transplant; QALY, quality adjusted life year; LY, life year

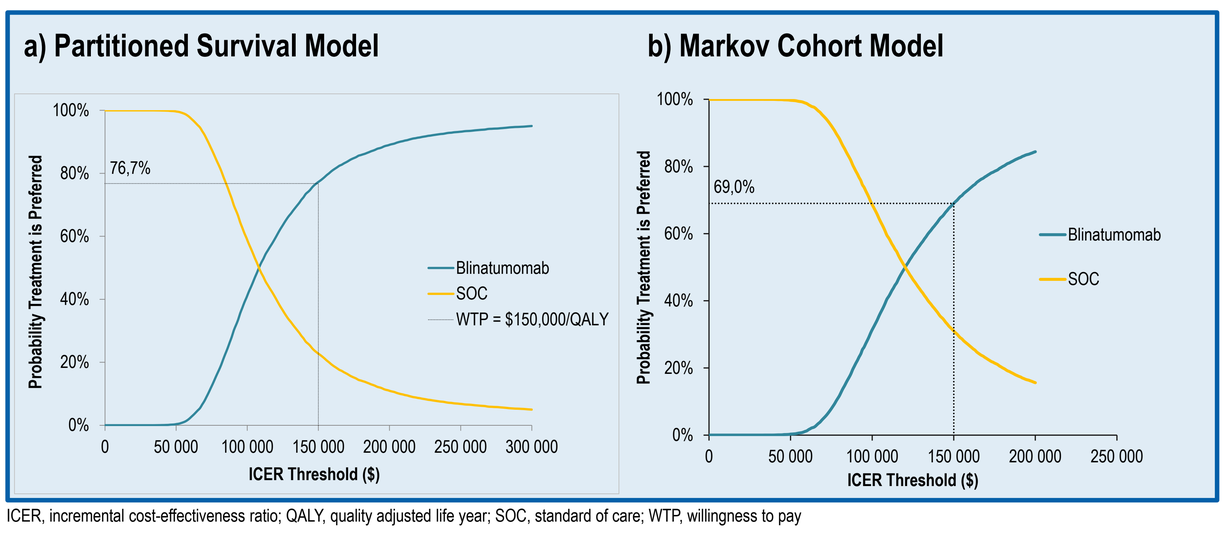
- Deterministic sensitivity analysis was consistent between the two models, but sometimes different model drivers were identified due to differences in the model structure
  - Cost of HSCT was an important driver in both models
  - Proportion of patients receiving HSCT was an important driver in PSM – it was captured in the time to HSCT estimation in MCM, so the uncertainty around this parameter could not be evaluated in the tornado
  - Other inpatient days (based on MRD response) and blinatumomab MRD response rate were important drivers in MCM – this is directly related to the MCM structure where MRD response is linked to higher survival and lower costs
- Probabilistic sensitivity analyses showed little and comparable variability due to parameter uncertainty in both models (see Figure 4).

Figure 3. Comparison of Deterministic Sensitivity Analysis



Blin, blinatumomab; OS, overall survival; 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. Comparison of Probabilistic Sensitivity Analysis



ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SOC, standard of care; WTP, willingness to pay

CONCLUSIONS

- **In both models, blinatumomab is cost-effective vs chemotherapy in ALL patients with MRD for US healthcare payers.**
- **Whether to use PSM vs MCM likely depends on a number of factors including sample size, duration of follow-up, nature of the clinical problem, strength of the association between intermediate and final outcomes, and availability of long-term observational data.**
- **In the context of blinatumomab, the PSM structure is simple, widely accepted, and can be based on a limited amount of data with few assumptions. However, it cannot explicitly account for treatment effects on survival mediated by MRD response or HSCT.**
- **However, MCM requires more assumptions due to limited data for estimating transition probabilities**
  - **MRD response was available only for one treatment arm**
  - **The link between HSCT and survival independent of treatment was not well established from the BLAST trial**
- **Based on these elements, PSM is recommended as the primary approach to estimate the cost-effectiveness on blinatumomab in ALL.**

REFERENCES

1. Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood*. 2018;131(14):1522-31.

DISCLOSURE

- The study was funded by Amgen.