A COST-EFFECTIVENESS EVALUATION OF BLINATUMOMAB USE IN THE MEASURABLE RESIDUAL DISEASE NEGATIVE REMISSION STATE TO TREAT ADULTS WITH PHILADELPHIA-CHROMOSOME-NEGATIVE B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA IN FRANCE

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INTRODUCTION

- B-cell precursor acute lymphoid leukemia (B-ALL) is characterized by the excessive proliferation of lymphoblastic B-cells and rapid onset of disease.[1]
- First-line treatment of adult patients with Philadelphia negative (Ph-) and minimal residual disease (MRD) negative B-ALL consists of three successive phases of intensive chemotherapy-based regimens : induction, consolidation +/- hematopoietic stem cell transplantation (HSCT), and maintenance (in patients without prior HSCT).[2-3]
- Despite achieving hematological complete remission (CR), defined as the absence of leukemia cells in the blood/bone marrow after induction therapy, MRD may remain detectable using flow cytometry or polymerase chain reaction (PCR).[4-6]
- Thus, among patients achieving CR after 1st line treatment, 15% to 20% of patients will relapse[7] and the 5-year overall survival (OS) is estimated to range between 60% to 70%.[8]
- In the E1910 ECOG phase III randomized, controlled trial, blinatumomab in addition to consolidation regimen demonstrated a significative increase in OS versus standard consolidation chemotherapy (chemo) alone (hazard ratio [HR]: 0.44; 95% confidence interval [CI]: [0.25; 0.76]; p= 0.003).[9]

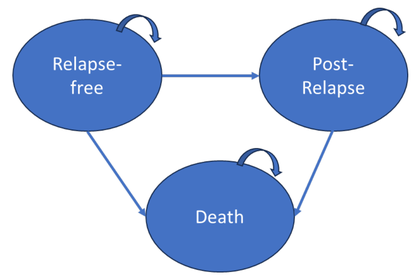
OBJECTIVE

- **To assess the cost-effectiveness of blinatumomab + chemotherapy versus standard chemo in France in line with French HTA guidelines and methodology.**

METHOD

- **The incremental cost-effectiveness ratio (ICER)** was estimated using a three-state (relapse-free, post-relapse and death) partitioned survival model that was developed to extrapolate clinical outcomes, quality of life, and treatment-related costs for patients with Ph- B-ALL who received consolidation with blinatumomab + chemo-versus standard chemo over a 50-year lifetime horizon (Figure 1).

Figure 1 : Structure of the partitioned survival model



- **Costs of drug** acquisition and administration in consolidation, maintenance, and upon relapse; medical follow-up; and adverse event-related hospitalizations were estimated from the French payer perspective in 2024 Euros (€).
- **Health state utilities** were estimated from a French real-world study that collected quality of life (EQ-5D-3L with French tariffs) between 30 March 2018 and 18 January 2019 in 219 French patients with B-ALL.[10] Patients remaining relapse-free after 5 years were assumed to have the same utility as the general population.
- **Extrapolations of relapse-free survival (RFS)** and OS data for both treatment arms were performed using patient-level data from the E1910 trial.[9] Extrapolation selection was done according to NICE decisions support unit (DSU).[12]
- **Mixture-cure models (MCMs) were used** for both arms :
  - MCMs are useful to describe survival data where a subgroup of patients experiences long-term survival, as treatment of B-ALL can induce deep remission thereby leading to improved OS. This was the case in E1910 trial as a plateau in the Kaplan-Meier curves of RFS of Blinatumomab plus chemo and chemo alone emerges from 48 and 72 months onwards, respectively, where patients are no longer relapsing and dying.
  - Long-term survival was modelled by estimating an implicit 'cure fraction' (i.e. the proportion of cured patients). Cured patient survival was then modelled assuming age- and sex-matched general population mortality. To account for any residual ALL complications and treatments (e.g. allogeneic SCT), a standardized mortality ratio (SMR) of 1.09[11] was applied to the general population mortality.
  - **This model was previously submitted to the French HTA (CEESP, Comité Economique et de Santé Publique) in February 2025.**

RESULTS

- The incremental cost-utility ratio (ICUR) of blinatumomab + chemo *vs* standard chemo was €39,273 per quality adjusted life year (QALY) gained (Table 1). The ICER was €29,300 per life year (LY). Blinatumomab + chemo was associated with 4.30 additional QALYs compared to standard chemo alone (13.80 *vs* 9.50), and an incremental cost of €168,754 (€327,581 *vs* €158,827) over a lifetime horizon (50 years).

Table 1 : Total costs and QALYs (main analysis)

Intervention	Total costs (€)	Total LY	Total QALYs	ICER (€/Life year)	ICUR (€/QALY)
Standard chemo	€158,827	19.50	9.50	-	-
Blinatumomab + chemo	€327,581	13.48	13.80	€29,300	€39,273
Difference	€168,754	5.76	4.30	-	-

- Among the total cost associated with blinatumomab + chemo, the drug acquisition costs (59%) were the main drivers, followed by administration cost of consolidation treatments (15%), and costs of subsequent post-relapse treatments (10%). For standard chemo, the main driver was the cost of treatments used after relapse (46% of the total cost), cost of HSCT pre- and post-relapse (14%), and administration costs of consolidation treatments (12%). Breakdowns of costs are shown in Table 2.
- Acquisition cost of chemotherapy was close to zero (€75, due to the dispensing fee in the hospital pharmacy) because chemotherapy cost used in consolidation are included in hospital administration tariffs. Savings were observed with blinatumomab + chemo treatment, mainly on costs associated with post-relapse subsequent therapy drug acquisition (- 36,400€), administration (- 5,541€) and HSCT costs (- 2,359€ pre-relapse and -980€ post-relapse), not compensating costs expense in 1st line.

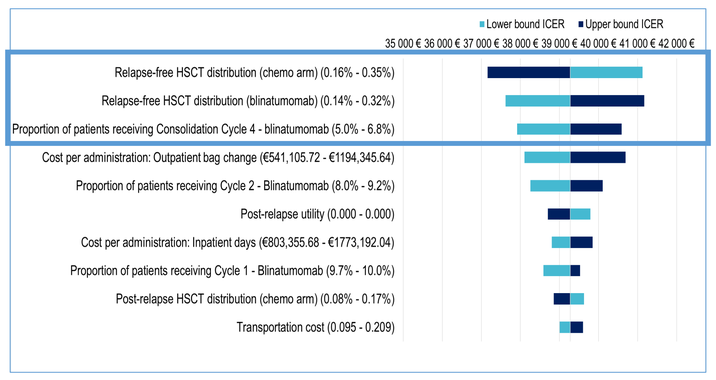
Table 2 : Cost breakdown (main analysis)

Costs item	Blinatumomab + chemo	Chemo	Difference
Costs in relapse-free state (1st line consolidation)			
Total costs in relapse free-state include:	**€268,862**	**€59,023**	**€209,839**
Drug acquisition costs	€184,395	€75	€184,320
Administration costs for consolidation treatment	€47,817	€19,368	€28,448
Administration and acquisition costs in maintenance	€5,047	€5,426	- €380
Adverse events costs	€11,956	€12,147	- €191
Pre-relapse HSCT costs	€19,648	€22,007	- €2,359
Costs in relapse state			
Total costs in relapse state include:	**€41,992**	**€86,234**	**- €44,242**
Acquisition costs of subsequent post-relaspe treatment	€31,045	€67,445	- €36,400
Administration costs of subsequent treatment	€6,484	€12,025	- €5,541
Post-relapse HSCT costs	€3,264	€4,244	- €980
Other cost items			
End of life costs	€1,198	€2,519	- €1,321
Follow up costs	€16,727	€13,570	€3,158

SENSITIVITY AND SCENARIO ANALYSES

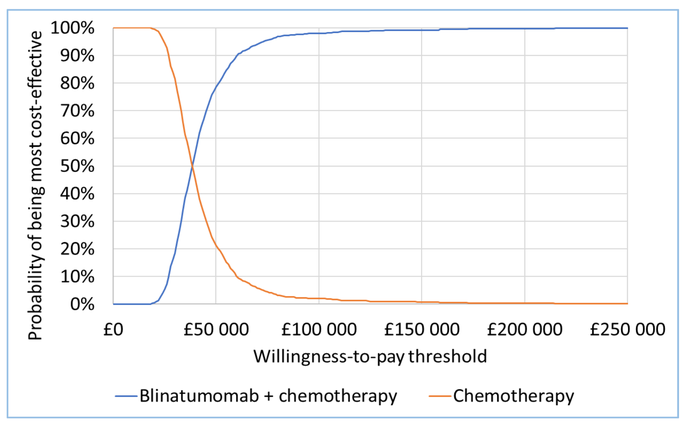
- **The deterministic sensitivity analysis** (64 parameters tested) showed that parameters with the most impact on the ICUR were the distribution of HSCT in the relapse-free state (for both treatment arms) and the proportion of patients receiving blinatumomab (Figure 2). Overall, ICUR variations were acceptable and did not exceed +/- 5% (€37,158; €41,171).

Figure 2 : Tornado diagram



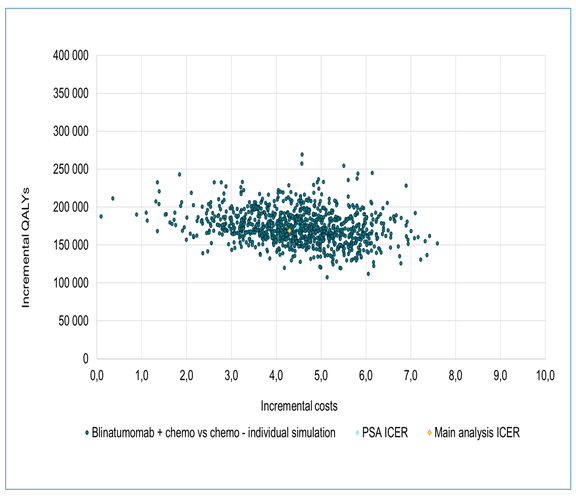
- Acceptability curve representation of probabilistic results shows that blinatumomab plus chemo versus chemo alone has an 80% probability of being cost-effective at a willingness-to-pay threshold of €52,000 per QALY (Figure 4).

Figure 4 : Acceptability curves



- **In the probabilistic sensitivity analysis (PSA),** blinatumomab + chemo is more effective and more costly than standard chemo alone across all simulations (1000 iterations), with a mean probabilistic ICUR of 30,543 (Figure 3).

Figure 3 : Cost-effectiveness plan



- **Several scenario analyses** were also conducted. Scenarios having the most impact on ICER were:
  - Reduction of time horizon to 30 years (€48,059/QALY; +22%)
  - Actualization rate of costs and health benefits set to 4.5% instead of 2.5% (€26,388/QALY; -33%)
  - Actualization rate of costs and health benefits set to 0.0% instead of 2.5% (€56,679/QALY +44%)
  - A 7-year relapse-free delay (instead of 5) to consider patients cured (€39,760 /QALY; +1%)
  - Exclusion of post-relapse treatments (€49,034/QALY; +25%)

CONCLUSIONS

- Blinatumomab added to consolidation chemotherapy for the treatment of Ph- MRD- B-ALL is a cost-effective option compared to standard chemotherapy with the recently published ICUR in France (€147,093/QALY to € 201,398/QALY).[13] Incremental costs were €90,839 in the relapse-free state, partially offset by a saving of €44,242 in the relapse state, due to blinatumomab preventing relapse and subsequent costly treatments.
- Consistency across the results of the sensitivity analyses supports the robustness of the model and the estimated long-term survival extrapolations. Long-term outcomes (up to 4.5 years of follow-up) showing an important proportion of long-term survivors in the blinatumomab + chemo arm restrain uncertainty around lifetime extrapolation.
- While no quality-of-life data were collected in the E1910 trial, health state utilities were not identified as major drivers of uncertainty in the sensitivity analyses. Uncertainty was further reduced by leveraging real-world quality of life data in a French population, with similar patient characteristics to the E1910 trial population.
- **This cost-effectiveness analysis demonstrated that the addition of blinatumomab to consolidation chemotherapy compared to consolidation chemotherapy alone is a cost-effective option in adult patients in MRD-negative remission from B-ALL from the French healthcare and societal perspective.**

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