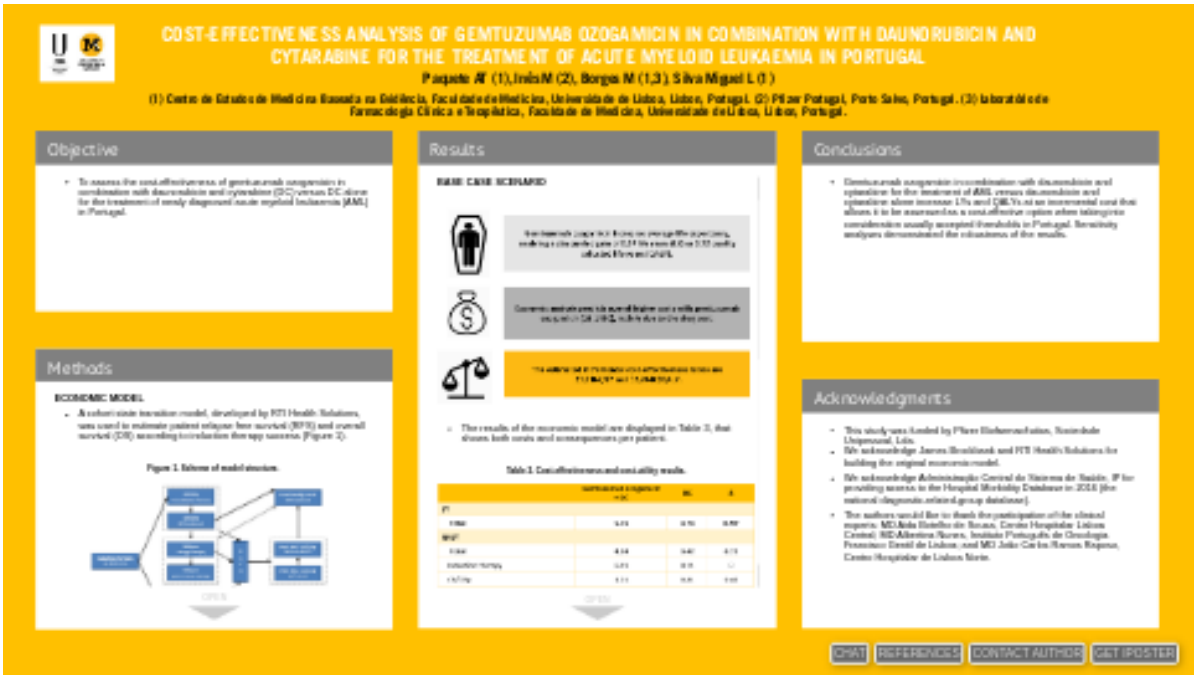
COST-EFFECTIVENESS ANALYSIS OF GEMTUZUMAB OZOGAMICIN IN COMBINATION WITH DAUNORUBICIN AND CYTARABINE FOR THE TREATMENT OF ACUTE MYELOID LEUKAEMIA IN PORTUGAL



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PRESENTED AT:

OBJECTIVE

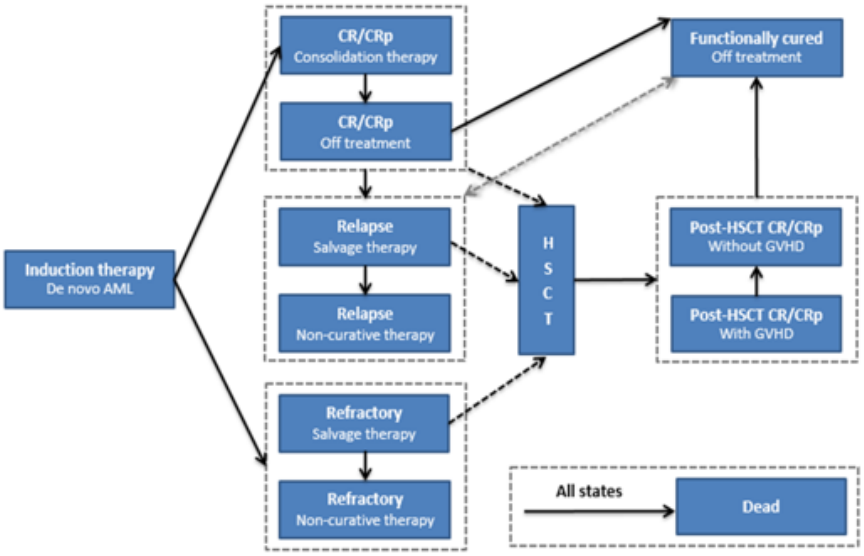
- To assess the cost-effectiveness of gemtuzumab ozogamicin in combination with daunorubicin and cytarabine (DC) versus DC alone for the treatment of newly diagnosed acute myeloid leukaemia (AML) in Portugal.

METHODS

ECONOMIC MODEL

- A cohort state transition model, developed by RTI Health Solutions, was used to estimate patient relapse free survival (RFS) and overall survival (OS) according to induction therapy success (Figure 1).

Figure 1. Scheme of model structure.



AML: Acute myeloid leukaemia; CR/CRp: Complete response/complete remission with incomplete platelet recovery; GVHD: Graft versus host disease; HSCT: Hematopoietic stem-cell transplant.

- Costs, life years (LYs) and quality-adjusted life years (QALYs) were estimated for treatment with gemtuzumab ozogamicin in combination with DC and DC alone in patients with AML.
- The analysis was conducted from a payers' perspective, assuming a lifetime horizon and a 5% annual discount rate for both costs and effects. The model uses monthly cycles and half-cycle correction was implemented.

CLINICAL DATA

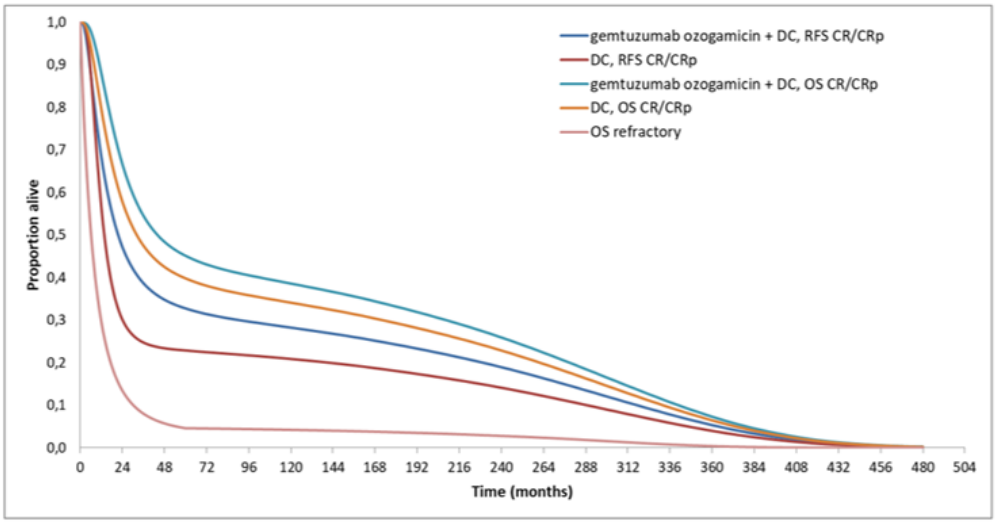
- The model was parameterized using clinical data from ALFA-0701, a head-to-head phase III, open-label, randomized controlled trial [1,2].
- The cohort was firstly separated according to response to induction treatment: complete response / complete remission with incomplete platelet recovery (CR/CRp) and refractory patients. This separation was based on the CR/CRp rates retrieved from ALFA-0701 trial, which were 81,5% for gemtuzumab ozogamicin + DC and 73,5% for DC alone [1,2].
- RFS and OS for both cohorts were also derived from the ALFA-0701 trial and long-term estimates were extrapolated using parametric models (Table 1 and Figure 2). Time to HSCT was also based on ALFA-0701 and mortality of post-HSCT patients was based on OS pooled data from the overall population in the trial [1-3].

Table 1. Models fit to extrapolate survival.

Cohort	Outcome	Treatment	
		Gemtuzumab ozogamicin + DC	DC
CR/CRp	RFS	Lognormal mixture cure model	Lognormal mixture cure model
	OS	Lognormal mixture cure model	Lognormal mixture cure model
Refractory	OS	Gompertz parametric model (Pooled data)	

CR/CRp: Complete response / complete remission with incomplete platelet recovery; DC: Daunorubicin and cytarabine; OS: Overall survival; RFS: Relapse-free survival

Figure 2. Extrapolated RFS and OS curves for CR/CRp and refractory patients.



CR/CRp: Complete response / complete remission with incomplete platelet recovery; DC: daunorubicin and cytarabine; OS: overall survival; RFS: relapse-free survival

- The impact of grade 3/4 adverse events (AE) with at least 1% incidence observed in the trial was incorporated in the model, as well as of graft versus host disease (GVHD) after hematopoietic stem-cell transplant (HSCT).

UTILITIES

- Utilities per health state and disutilities due to AE were based on an economic evaluation study regarding azacitidine (NICE TA 399), in which EORTC-QLQ-C30 results were mapped to EQ-5D-3L according to UK tariffs [4,5]. Utilities of those undergoing HSCT were based on the literature [6,7] and those with veno-occlusive disease on defibrotide's economic evaluation (SMC No. 967; NICE ID) [8,9]. For those considered functionally cured, utilities from UK general population were used [10].

Table 2. Mean utility/disutility scores per health states and adverse events.

Description	
Health state	**Utilities**
Induction therapy and subsequent therapy (high-intensity chemotherapy)	0.657
CR/CRp (consolidation therapy)	0.657
HSCT procedure	0.657
CR/CRp (after HSCT, with GVHD)	0.670
CR/CRp (off treatment)	0.740
Relapse disease	0.568
Refractory disease	0.568
Functionally cured	0.820
Adverse event / Disease	**Disutilities**
Adverse events (grade 3/4)	0.021
Veno-occlusive disease	0.208

CR/CRp: Complete response/complete remission with incomplete platelet recovery; GVHD: Graft versus host disease; HSCT: Hematopoietic stem-cell transplant.

COSTS

- Portuguese-specific disease management resource use was based on a panel of clinical experts on AML and on Portuguese 2016 diagnosis related group (DRG) microdata (ACSS, 2016). Resources were valued according to national legislation (Portaria 234/2015 and Portaria 254/2018) and on an official drug cost database (SPMS Catalog).

- Transportation costs were considered for outpatient visits, emergency visits and radiotherapy treatment being valued according to a study that estimated costs borne by patients in Portugal [11].

RESULTS

BASE CASE SCENARIO

Gemtuzumab ozogamicin increases average life expectancy, enabling a discounted gain of 0.97 life years (LY) or 0.72 quality adjusted life years (QALY).

Economic analysis predicts overall higher costs with gemtuzumab ozogamicin (23,145€), mainly due to the drug cost.

The estimated incremental cost-effectiveness ratios are 23,916€/LY and 32,244€/QALY.

- The results of the economic model are displayed in Table 3, that shows both costs and consequences per patient.

Table 3. Cost-effectiveness and cost-utility results.

	Gemtuzumab ozogamicin + DC	DC	Δ
LY			
Total	**5.71**	**4.74**	**0.97**
QALY			
Total	**4.14**	**3.42**	**0.72**
Induction therapy	0.11	0.11	0
CR/CRp	1.21	0.81	0.40
Relapsed disease	0.44	0.37	0.08
Refractory disease	0.05	0.07	-0.02
HSCT and after-HSCT	0.38	0.49	-0.11
Functionally cured	1.99	1.60	0.38
Adverse events	-0.05	-0.03	-0.01
Costs			
Total	**€85,602**	**€62,457**	**€23,145**
Therapy and follow-up (CR/CRp, Relapse and refractory disease)	€62,616	€37,305	€25,311
HSCT and after-HSCT	€11,050	€14,322	-€3,271
Adverse events	€4,916	€3,727	€1,190
Indirect costs	€7,019	€7,104	-€85
		ICER (€/LY)	**€23,916**
		ICUR (€/QALY)	**€32,244**

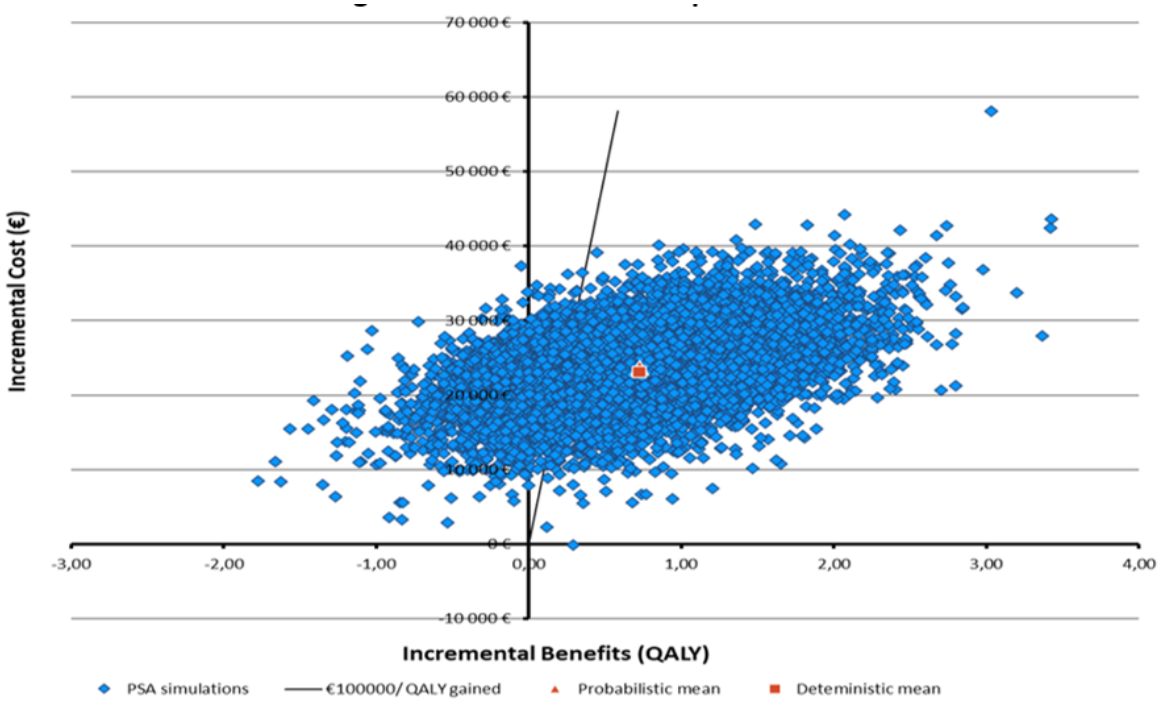
Note: Due to rounding of numerical values, the sum of QALY values can be different from the total values.

DC: Daunorubicin and cytarabine; ICER: Incremental cost-effectiveness ratio; ICUR: Incremental cost-utility ratio; LY: Life-year; QALY: Quality-adjusted life-year.

SENSITIVITY ANALYSIS

- Deterministic sensitivity analyses show that results are robust to most scenarios but slightly sensitive to utilities per health state. Probabilistic sensitivity analysis was also conducted (Figure 3).

Figure 3. Cost-effectiveness plane.



PSA: Probabilistic sensitivity analysis; QALY: Quality-adjusted life-year.

CONCLUSIONS

- Gemtuzumab ozogamicin in combination with daunorubicin and cytarabine for the treatment of AML versus daunorubicin and cytarabine alone increase LYs and QALYs at an incremental cost that allows it to be assessed as a cost-effective option when taking into consideration usually accepted thresholds in Portugal. Sensitivity analyses demonstrated the robustness of the results.

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REFERENCES

[1] Castaigne S, Pautas C, Terré C, Raffoux E, Bordessoule D, Bastie JN, Legrand O, Thomas X, Turlure P, Reman O, de Revel T, Gastaud L, de Gunzburg N, Contentin N, Henry E, Marolleau JP, Aljijakli A, Rousselot P, Fenaux P, Preudhomme C, Chevret S, Dombret H; Acute Leukemia French Association. Effect of gemtuzumab ozogamicin on survival of adult patients with denovo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet. 2012;379(9825):1508-16.;

[2] European Medicines Agency. Summary of product characteristics - Mylotarg® (2018);

[3] Battipaglia G, Labopin M, Candoni A, Franin R, El Cheikh J, Blasie D, et al. Risk of sinusoidal obstruction syndrome in allogeneic stem cell transplantation after prior gemtuzumab ozogamicin treatment: a retrospective study from the Acute Leukemia Working Party of the EBMT. Bone Marrow Transplant. 2017;52:592-9;

[4] National Institute for Health and Care Excellence (NICE). Technology appraisal No. 399. Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts. Company evidence submission. Data on file (provided by Pfizer). November 25, 2015.;

[5] McKenzie L, van der Pol M. Mapping the EORTC QLQ C-30 onto the EQ-5D instrument: the potential to estimate QALYs without generic preference data. Value Health. 2009 Jan-Feb;12(1):167-71.

[6] Kurosawa S, Yamaguchi T, Mori T, Kanamori H, Onishi Y, Emi N, et al. Patient-reported quality of life after allogeneic hematopoietic cell transplantation or chemotherapy for acute leukemia. Bone Marrow Transplant. 2015;50(9):1241–9.

[7] Kurosawa S, Yamaguchi H, Yamaguchi T, Fukunaga K, Yui S, Wakita S, et al. Decision analysis of postremission therapy in cytogenetically intermediate-risk acute myeloid leukemia: the impact of FLT3 internal tandem duplication, nucleophosmin, and CCAAT/enhancer binding protein alpha. Biol Blood Marrow Transplant. 2016;22(6):1125–32.

[8] Scottish Medicines Consortium. Defibrotide, 80mg/mL, concentrate for solution for infusion (Defitelio®). SMC No. (967/14). 9 May 2014.;

[9] National Institute for Health and Care Excellence (NICE). Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia [ID893]. Committee Papers. 18 August 2017.

[10] Ara, R., & Brazier, J. E. (2010). Populating an economic model with health state utility values: moving toward better practice. Value in Health, 13(5), 509-518.

[11] Barros, PP., et al. Políticas Públicas em Saúde: 2011–2014, Avaliação do Impacto [Health Public Policies: 2011–2014. Impact Assessement. NOVA Healthcare Initiative Research] Universidade NOVA de Lisboa, 2015.