6-Year Time To Next Treatment (TTNT) Extrapolation Curve For GLOW Study: First-Line Ibrutinib + Venetoclax (I+V) Offers Long Treatment-Free Period For Older Adult/Unfit Patients With Chronic Lymphocytic Leukemia (CLL)

Santiago Osorio Prendes,*[1] Vicente Gimeno,[2] Jose Angel Hernandez Rivas,[3] Francisco Javier Lopez Jimenez,[4] Joris Diels,[5] Claudio A. Schioppa,[5] Ana Alfayate Lobo,[6] Teresa Domínguez-Lubillo[7]

[1]Hospital General Universitario Gregorio Marañón, Department of Hematology, Madrid, Spain; [2]Hospital Universitario Miguel Servet, Pharmacy Department, Zaragoza, Spain; [3]Hospital Universitario Infanta Leonor, Department of Hematology, Madrid, Spain; [4]Hospital Universitario Ramón y Cajal, Department of Hematology, Madrid, Spain; [5]Janssen Pharmaceutica N.V., Beerse, Belgium; [6]Johnson & Johnson company, Janssen Scientific Affairs, Madrid, Spain; [7]Johnson & Johnson company, Health Economics & Market Access, Madrid, Spain

INTRODUCTION

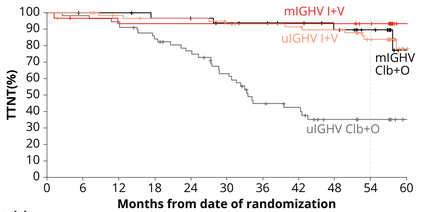
- GLOW is a phase 3 trial evaluating the efficacy and safety of fixed-duration (FD) ibrutinib plus venetoclax (I+V) in older-adult patients and/or patients with comorbidities with previously untreated chronic lymphocytic leukemia (CLL). With a median follow-up of 46 months, this study demonstrated a significantly prolonged progression-free survival (PFS) with I+V compared with chlorambucil plus obinutuzumab (Clb+O), as well as an advantage in overall survival (OS) within this population[1]
- Moreover, time to next treatment (TTNT), defined as time from the date of randomization to the start date of any subsequent anti-leukemic treatment (patients who are alive without subsequent therapy are censored at the date of last visit; patients who died without a subsequent therapy are censored at death) was significantly longer with I+V than Clb+O (HR 0,155 [95% CI 0,072-0,333]; $P < 0.0001$). The median TTNT was not reached in either of the treatment groups. The estimated 46-month TTNT rate was 91.4% for I+V and 57.3% for Clb+O
- At latest data cut, with a median follow-up of 57 months, the majority of patients treated with I+V did not initiate a second-line of treatment regardless of immunoglobulin heavy-chain variable (IGHV) gene mutational status (**Table 1**). Estimated percentage of patients not requiring second-line treatment at 54 months by IGHV status is shown in **Figure 1**. These data were not available at the time of this extrapolation
- Based on RESONATE-2 trial, the median duration of treatment with single-agent ibrutinib, given until disease progression, was 6 years (74 months).[2] However, long-term evidence regarding the duration of therapeutic effect associated with this FD therapy (15 cycles) in previously untreated older-adult and/or unfit patients with CLL is still limited

Table 1. Percentage of patients who did not initiate second-line treatment by IGHV status

I+V	Clb+O
93.5% for mIGHV	89.8% for mIGHV
83.9% for uIGHV	35.1% for uIGHV

Clb+O, chlorambucil plus obinutuzumab; IGHV, immunoglobulin heavy-chain variable; I+V, ibrutinib plus venetoclax; mIGHV, mutated IGHV; uIGHV, unmutated IGHV.

Figure 1: TTNT by IGHV status



Patients at risk

mIGHV I+V	32	29	28	28	28	28	27	27	27	23	6
uIGHV I+V	67	64	59	57	57	54	53	52	50	41	11
mIGHV Clb+O	35	34	34	32	31	29	28	25	22	16	4
uIGHV Clb+O	57	56	52	47	41	32	21	18	11	9	3

Clb+O, chlorambucil plus obinutuzumab; IGHV, immunoglobulin heavy-chain variable; I+V, ibrutinib plus venetoclax; mIGHV, mutated IGHV; TTNT, time to next treatment; uIGHV, unmutated IGHV.

B-cell Malignancies

OBJECTIVES

- To estimate the number of patients in the GLOW study who received the combination of I+V and would remain free from further treatment 6 years after randomization. In the absence of observed data, extrapolation beyond the available observed TTNT data from the study was performed
- To simulate, using parametric models, 6-year TTNT for patients who started FD I+V on the basis of the GLOW trial data, to estimate the expected share of patients who will not have started a subsequent anti-leukemic therapy approximately 5 years after end of I+V treatment

METHODS

- The extrapolation was produced by fitting continuous survival distribution functions to the Kaplan-Meier (KM) estimate for GLOW FD I+V TTNT. Survival distributions describe the probability of not experiencing an event (i.e., start of subsequent anti-leukemic therapy) by a given time point. Exponential, Weibull, Log-normal, Log-logistic, Generalized Gamma, and the Gompertz and Gamma parametric models were applied for this analysis in line with National Institute for Health and Care Excellence (NICE) Technical Decision Support Unit recommendation.[3] For each distribution, the fit to the observed data was assessed by the Akaike Information Criterion (AIC) and Bayes Information Criterion (BIC), as well as the visual inspection
- Extrapolation was performed using longest follow-up available at the time of analysis (46-month median follow-up) (**Table 2**)

Table 2: Time to next treatment in the I+V arm of the GLOW study

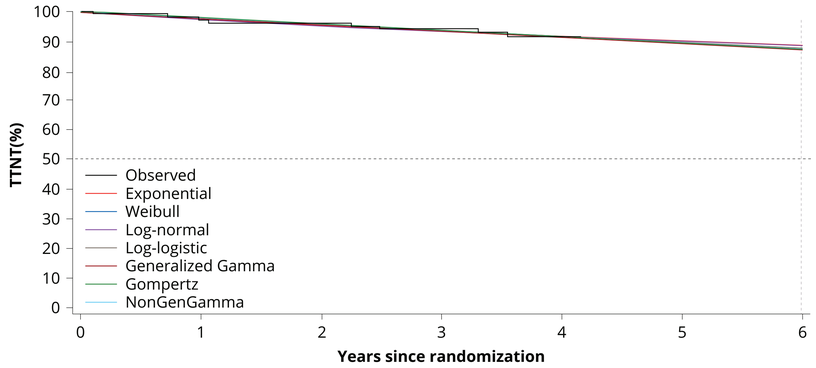
	I+V (n = 106)
Median follow-up, months	46
Events, n (%)	8 (7.5)
Censored, n (%)	98 (92.5)
Time-to-event, months	
25th percentile (95% CI)	NR (NE-NE)
Median (95% CI)	NR (NE-NE)
75th percentile (95% CI)	NR (NE-NE)
12-month event-free rate (95% CI)	97.0%
18-month event-free rate (95% CI)	95.9%
24-month event-free rate (95% CI)	95.9%
30-month event-free rate (95% CI)	93.8%
36-month event-free rate (95% CI)	93.8%
42-month event-free rate (95% CI)	92.7%
48-month event-free rate (95% CI)	91.4%

I+V, ibrutinib plus venetoclax; NE, not estimable; NR, not reached.

RESULTS

- At the time of data cut-off (September 2022), 8 patients (7.5%) had initiated a subsequent therapy after FD I+V. The KM curve for TTNT is provided in **Figure 2**, together with the fitted parametric models. The estimated percentage of patients free of subsequent treatment at the 6-year landmark, based on the different parametric models, ranged from 87.0% to 88.5%
- Small differences in AIC and BIC values were observed between distributions; however, the lowest values for both were reported for Exponential followed by Weibull, Log-logistic, and Gamma (**Table 3**)
- Overall, there was no more than a 1.5% difference between the highest and lowest TTNT estimates (Log-normal and Exponential, respectively) obtained from this analysis, which is not a large variation. Therefore, for the objectives of this analysis, determining the choice of the distribution that best fits the data is not as critical as it would be for 30- or 40-year extrapolations. Based on this analysis, 6-year TTNT ranging from 87.0% to 88.5% would be expected

Figure 2: TTNT 6-year extrapolation



TTNT, time to next treatment.

Table 3: Percentage of patients free of subsequent therapy at 6 years with survival distributions used and AIC/BIC values

Survival distributions	Exponential	Weibull	Log-normal	Log-logistic	Generalized Gamma	Gompertz	Gamma
% of patients without subsequent therapy – 6 years	87.0%	87.5%	88.5%	87.6%	87.3%	87.4%	87.4%
AIC	119.3	121.3	121.4	121.3	123.3	121.3	121.3
BIC	122.0	126.6	126.8	126.6	131.3	126.7	126.6

AIC, Akaike Information Criterion; BIC, Bayes Information Criterion.

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LIMITATIONS

Long-term extrapolations are associated with uncertainty; however, the time horizon for this extrapolation is 6 years, i.e. 2 years longer than the median follow-up of the study (4 years) at the time of this analysis, which could minimize the potential bias of this extrapolation, allowing the use of these results as a valid estimation

CONCLUSIONS

At 6 years, approximately 87% of patients treated with I+V will not require a second line of treatment

These findings suggest a promisingly long treatment-free period for previously untreated older-adult/unfit patients with CLL. However, caution is advised when interpreting these extrapolated results, and prospective long-term studies are needed to further validate the time free of a subsequent therapy after I+V treatment

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