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6-YEAR TIME TO NEXT TREATMENT (TTNT) EXTRAPOLATION CURVE FOR GLOW STUDY: FIRST-LINE IBRUTINIB + VENETOCLAX (I+V) OFFERS LONG TREATMENT-FREE PERIOD FOR ELDERLY/UNFIT CLL PATIENTS

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Objective

6-year extrapolation curve: to estimate the number of patients who would be free from subsequent therapy after 6 years of I+V treatment in the GLOW study.

Conclusions

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

These findings suggest a promising long treatment-free period for previously untreated elderly and/or unfit CLL patients.

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 to use these results as a valid estimation.

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Joris Diels, Claudio A. Schioppa, Ana Alfayate and Teresa Domínguez Lubillo are employees of Janssen Pharmaceuticals. Joris Diels and Claudio A. Schioppa hold Johnson & Johnson stock.

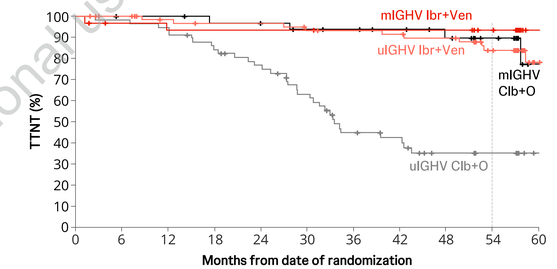
INTRODUCTION

- GLOW is a phase 3 trial evaluating the efficacy and safety of fixed-duration (FD) ibrutinib plus venetoclax (I+V) in elderly patients and/or those 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 to chlorambucil plus obinutuzumab, as well as an advantage in overall survival (OS) within this population.
- 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 (HR 0,155 [95% CI 0,072–0,333]; p<0·0001). The median TTNT was not reached in both treatment groups. The estimated 46-month TTNT rate was 91,4% for I+V and 57,3% for chlorambucil plus obinutuzumab.
- At latest data cut, 57-month follow-up, the majority of patients treated with I+V did not initiate a second line of treatment regardless of IGHV mutational status. Estimated percentage of patients not requiring second-line treatment at 54 months by IGHV status (Figure 1). This data was not available at the moment of this extrapolation.

– Ibr+Ven:	– Clb+O:
▪93.5% for mIGHV	▪89.8% for mIGHV
▪83.9% for uIGHV	▪35.1% for uIGHV

- Based on RESONATE-2 trial, the median duration of treatment with Bruton's Tyrosine Kinase inhibitor ibrutinib, given until disease progression, was 6 years (74 months). However, long-term evidence regarding the duration of therapeutic effect associated with this FD therapy (15 cycles) in previously untreated elderly and/or unfit patients with CLL is still limited.

Figure 1: TTNT by IGHV status



Patients at risk

mIGHV Ibr+Ven	32	29	28	28	28	28	27	27	27	23	6
uIGHV Ibr+Ven	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

AIMS

- This study aimed to estimate the number of patients who would be free from subsequent treatment after 6 years from randomization in the GLOW study and receiving the combination of I+V. In the absence of observed data, extrapolation beyond the available observed TTNT data from the study was performed.
- We used parametric models to simulate 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 anticancer 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-cancer therapy) by a given time point. Exponential, Weibull, Log-normal, Log-logistic, Generalized Gamma, 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. 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 1)

Table 1: Time to Next Treatment GLOW study (I+V arm)

	I+V (n=106)
Median follow-up (months)	46
Events (%)	8 (7.55%)
Censored (%)	98 (92.45%)
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%

RESULTS

- At the time of data cut-off (September 2022), there were 8 patients (7.55%) who 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, Loglogistic, and Gamma (Table 2).
- 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-years extrapolations. Based on this analysis it is expected that 6-year TTNT would be in the range of 87.0% - 88.5%.

Figure 2: TTNT 6-year extrapolation

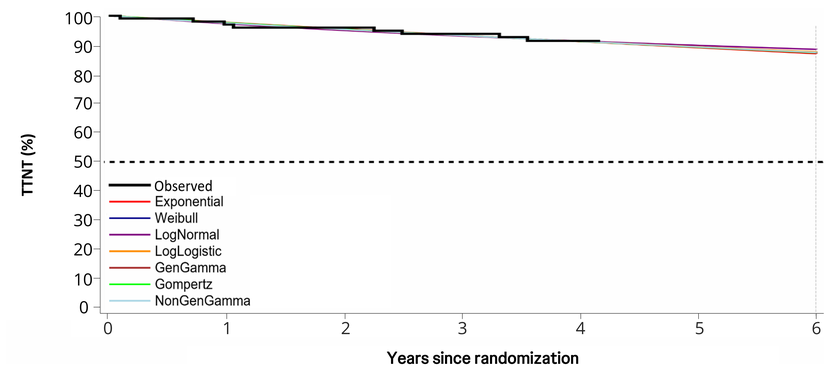


Table 2: Percentage of patients free of subsequent therapy at 6 years with survival distributions used and AIC/BIC values

Survival distributions	Exponential	Weibull	Log-Normal	Log-logistic	Gen 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

CONCLUSIONS

- In conclusion, the extrapolation based on the observed TTNT data for the combined treatment of ibrutinib and venetoclax indicates that at 6 years approximately 87% of patients treated with this combination will not require a second line of treatment. These findings suggest a promising long treatment-free period for previously untreated elderly and/or unfit CLL patients. 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.

References

1. Niemann CU, Munir T, Moreno C, et al. Fixed-duration ibrutinib-venetoclax versus chlorambucil-obinutuzumab in previously untreated chronic lymphocytic leukaemia (GLOW): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2023 Dec;24(12):1423-1433; 2. Barr PM, Owen C, Robak T, et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. Blood Adv. 2022 Jun 14;6(11):3440-3450; 3. Latimer N, NICE DSU TECHNICAL SUPPORT DOCUMENT 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS - EXTRAPOLATION WITH PATIENT-LEVEL DATA. June 2013. Accessed: DDMM2023. Available: https://www.ncbi.nlm.nih.gov/books/NBK395885/pdf/Bookshelf_NBK395885.pdf

B-cell Malignancies

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