Initiating First-Line Fixed-Duration Ibrutinib and Venetoclax in Patients With Chronic Lymphocytic Leukemia Improves Overall Survival Outcomes to Rates Approximating an Age-Matched General European Population

Paolo Ghia[1,2], Loic Ysebaert[3], Ann Janssens[4], Mohamed Fouad[5], Claudio A Schioppa[6], José-Ángel Hernández-Rivas[7], Alessandra Tedeschi[8]

[1]Università Vita-Salute San Raffaele, Milan, Italy; [2]IRCCS Ospedale San Raffaele, Milan, Italy; [3]Institut Universitaire du Cancer-Oncopole de Toulouse, Toulouse, France; [4]UZ Leuven Gasthuisberg, Leuven, Belgium; [5]Johnson & Johnson Middle East FZ-LLC, Dubai, UAE; [6]Janssen Pharmaceutica NV, Beerse, Belgium; [7]Hospital Universitario Infanta Leonor, Universidad Complutense, Madrid, Spain; [8]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy

Key Takeaway

This pooled analysis demonstrated that first-line fixed-duration ibrutinib+venetoclax provides patients with CLL a life expectancy comparable to the age-matched general European population, which aligns with previous findings of overall survival benefit in treatment-naive patients with CLL receiving continuous ibrutinib regimens

Conclusions

This pooled analysis showed that overall survival rates for patients with CLL treated with ibrutinib+venetoclax in the first-line setting were comparable to an age-matched general European population

Comparable overall survival rates versus the respective age-matched general European population were observed for subpopulation of patients aged ≥ 65 years and < 65 years

Overall survival rates were also similar to the age-matched general European population, regardless of IGHV mutation status

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Poster

https://www.congresshub.com/ASH2024/Oncology/Ibrutinib/Ghia

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Introduction

- Chronic lymphocytic leukemia (CLL) primarily affects older adults (mean age of diagnosis is approximately 70 years)[1]
- As extending survival is considered the primary goal of cancer treatment, overall survival (OS) is widely regarded as the gold-standard end point in oncology clinical trials[2]
- In the 46-month follow-up analysis of the phase 3 GLOW study, first-line fixed-duration (FD) ibrutinib+venetoclax (Ibr+Ven) demonstrated[3]:
  - Superior progression-free survival over chlorambucil-obinutuzumab (hazard ratio [HR] 0.214, $p < 0.0001$), which was also observed regardless of IGHV mutation status
  - An OS advantage over chlorambucil+obinutuzumab (HR 0.487, $p = 0.021$), establishing it as the first FD combination to show this benefit
- In the FD cohort of CAPTIVATE (CAPTIVATE-FD), Ibr+Ven provided an OS rate of 96% at a median follow-up of 61.2 months[4]
- Previous studies with continuous Ibr-based regimens showed OS rates comparable to age-matched general US[5] and European[6] populations
- The current study explores whether the OS rates of FD Ibr+Ven are comparable to those of an age-matched general European population

Methods

- In this study, OS rates in a pooled analysis of patients with treatment-naive CLL administered FD Ibr+Ven in 2 global trials: GLOW (NCT03462719) and the FD cohort of CAPTIVATE (NCT02910583) were compared with those of an age-matched general European population
- This analysis was performed for the following:
  - Overall population
  - Patients aged ≥ 65 years
  - Patients aged < 65 years
  - Patients with mutated IGHV (mIGHV)
  - Patients with unmutated IGHV (uIGHV)
- Median follow-up: GLOW, 55.1 months; CAPTIVATE-FD, 55.7 months[7]
- GLOW study: Post hoc IGHV reclassification was used for baseline status[3]
- OS rates for FD Ibr+Ven–treated patients were compared with an age-matched simulated survival rate of a general European population
  - Age at randomization was used for analysis
  - World Health Organization 2019 life tables were applied for generation of survival probabilities, as this dataset represents the most recent pre–COVID-19 era information available[8]
  - To avoid immortal time bias within each interval, available probabilities for 5-year age intervals were converted to a daily scale
  - OS was analyzed with the Kaplan-Meier method
  - HRs were derived from a Cox proportional-hazards model

Results

Patients

- 265 patients received first-line FD Ibr+Ven across the GLOW and CAPTIVATE-FD studies (**Table 1**)
- Pooled study population had a balanced distribution of younger and older patients
- Median (first quartile [Q1], third quartile [Q3]) age at randomization was 65 (57, 70) years
  - GLOW: 85% of patients were aged ≥ 65 years
  - CAPTIVATE-FD: 28% of patients were aged ≥ 65 years
- IGHV mutation status: 59% unmutated, 37% mutated, 4% unknown
- Median follow-up was 55.7 months

Table 1: Baseline characteristics of Ibr+Ven–treated patients

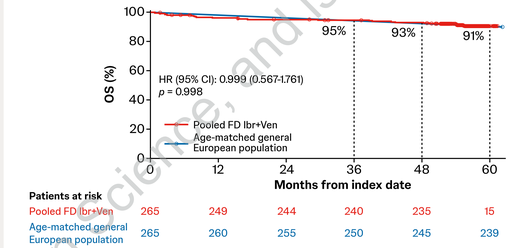
Characteristic	GLOW (n = 106)	CAPTIVATE-FD (n = 159)	Total (N = 265)
Median follow-up, months	55.1	55.7	55.7
Median (Q1, Q3) age at randomization, years	71 (67, 77)	60 (53, 65)	65 (57, 70)
Age, n (%)			
< 65 years	16 (15.1)	114 (71.7)	130 (49.1)
≥ 65 years	90 (84.9)	45 (28.3)	135 (50.9)
Sex, n (%)			
Male	59 (55.7)	106 (66.7)	165 (62.3)
Female	47 (44.3)	53 (33.3)	100 (37.8)
Race, n (%)			
White	101 (95.3)	147 (92.5)	248 (93.6)
Non-White/missing	5 (4.7)	12 (7.5)	17 (6.4)
ECOG PS, n (%)			
0	35 (33.0)	110 (69.2)	145 (54.7)
1	58 (54.7)	49 (30.8)	107 (40.4)
2	13 (12.3)	0	13 (4.9)
Mutated *TP53*, n (%)[a]	7 (6.6)	16 (10.0)	23 (8.7)
del11q, n (%)	20 (18.9)	28 (17.6)	48 (18.1)
IGHV, n (%)[b]			
uIGHV	67 (63.2)	89 (56.0)	156 (58.9)
mIGHV	32 (30.2)	66 (41.5)	98 (37.0)
Unknown IGHV	7 (6.6)	4 (2.5)	11 (4.2)

ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]In CAPTIVATE-FD, 27 (17.0%) patients had either del17p or *TP53* mutations; 20 (13%) patients had del17p mutations. In the GLOW study, only *TP53* mutations were assessed.
[b]Post hoc analysis of IGHV was used for baseline IGHV mutation status for the GLOW study.

Overall survival

- The OS estimates were comparable between the pooled Ibr+Ven–treated patients and the age-matched general European population (HR [95% confidence interval (CI)] 0.999 [0.567-1.761], $p = 0.998$; **Figure 1**)
- Estimated OS rates for the pooled population for the Ibr+Ven–treated patients were 95%, 93%, and 91% at 36, 48, and 60 months, respectively

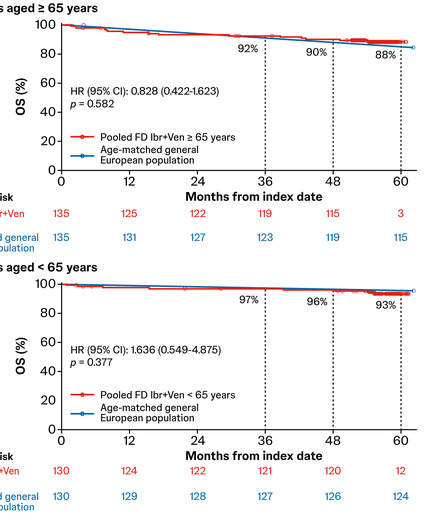
Figure 1: Similar OS estimate for overall pooled Ibr+Ven–treated patients



HR < 1 favored Ibr+Ven.

- OS estimates for FD Ibr+Ven–treated patients in older and younger patient subpopulations were comparable to the age-matched general European population:
  - Aged ≥ 65 years: HR (95% CI) 0.828 (0.422-1.623), $p = 0.582$; estimated OS rates for the Ibr+Ven–treated patients at 36, 48, and 60 months were 92%, 90%, and 88%, respectively (**Figure 2A**)
  - Aged < 65 years: HR (95% CI) 1.636 (0.549-4.875), $p = 0.377$; estimated OS rates for the Ibr+Ven–treated patients at 36, 48, and 60 months were 97%, 96%, and 93%, respectively (**Figure 2B**)

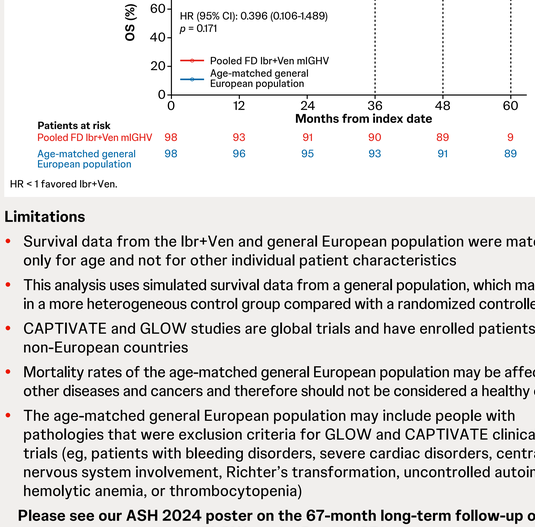
Figure 2: Similar OS estimate for (A) older and (B) younger pooled Ibr+Ven–treated patients versus an age-matched general European population



HR < 1 favored Ibr+Ven.

- Patients with uIGHV treated with FD Ibr+Ven showed OS estimates comparable to the age-matched general European population (HR [95% CI] 1.182 [0.594-2.351], $p = 0.633$); estimated OS rates at 36, 48, and 60 months for the Ibr+Ven–treated patients were 92%, 92%, and 88%, respectively (**Figure 3A**)
- In patients with mIGHV, FD Ibr+Ven showed a numerically favorable OS estimate, but this was not statistically significant (HR [95% CI] 0.396 [0.106-1.489], $p = 0.171$) (**Figure 3B**)
  - Estimated OS rates at 36, 48, and 60 months for the Ibr+Ven–treated patients were 99%, 98%, and 97%, respectively

Figure 3: Similar OS estimate for pooled Ibr+Ven–treated patients based on IGHV mutation status versus an age-matched general European population



HR < 1 favored Ibr+Ven.

Limitations

- Survival data from the Ibr+Ven and general European population were matched only for age and not for other individual patient characteristics
- This analysis uses simulated survival data from a general population, which may result in a more heterogeneous control group compared with a randomized controlled trial
- CAPTIVATE and GLOW studies are global trials and have enrolled patients from non-European countries
- Mortality rates of the age-matched general European population may be affected by other diseases and cancers and therefore should not be considered a healthy control
- The age-matched general European population may include people with pathologies that were exclusion criteria for GLOW and CAPTIVATE clinical trials (eg, patients with bleeding disorders, severe cardiac disorders, central nervous system involvement, Richter's transformation, uncontrolled autoimmune hemolytic anemia, or thrombocytopenia)

Please see our ASH 2024 poster on the 67-month long-term follow-up of the GLOW study (Poster 1871)

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B-cell Malignancies

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