First-Line Ibrutinib Plus Venetoclax Versus Chlorambucil Plus Obinutuzumab in Elderly or Comorbid Patients With Chronic Lymphocytic Leukemia: GLOW Study 67-Month Follow-up and Adverse Event-Free Progression-Free Survival Analysis

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Progression-Free Survival (1 of 2)

- With a median follow-up of 67 months, Ibr+Ven prolonged PFS, reducing the risk of progression or death by 73% versus Clb+O (HR 0.273 [95% CI, 0.186-0.401], nominal $p < 0.0001$) (**Figure 1A**)
  - Estimated 66-month PFS rates were 51.7% and 18.1% for Ibr+Ven and Clb+O, respectively
- Ibr+Ven prolonged PFS independent of IGHV status (uIGHV: HR 0.273 [95% CI, 0.171-0.434], nominal $p < 0.0001$; mIGHV: HR 0.246 [95% CI, 0.097-0.619], nominal $p = 0.0014$) (**Figure 1B**)
  - Estimated 66-month PFS rates in the Ibr+Ven group were 41.6% and 76.4% for patients with uIGHV (n = 67) and mIGHV (n = 32), respectively
  - Estimated 66-month PFS rates in the Clb+O group were 8.8% for patients with uIGHV (n = 57) and 35.1% of patients with mIGHV (n = 35)

CI, confidence interval; Clb+O, Chlorambucil+Obinutuzumab; HR, hazard ratio; Ibr+Ven, Ibrutinib+Venetoclax; mIGHV, mutated IGHV; PFS, progression-free survival; uIGHV, unmutated IGHV.

Progression-Free Survival (2 of 2)

- Estimated PFS rates at 54 months post treatment in the Ibr+Ven group were 64% for patients with uMRD (n = 58) and 50% for patients with dMRD (n = 31) at EOT+3, whereas estimated PFS rates at 54 months post treatment in the Clb+O group were 41% for patients with uMRD (n = 41) and 0% for patients with dMRD (n = 47) at EOT+3 (**Figure 1C**)
- uMRD at EOT+3 was more critical for long-term PFS in patients with uIGHV versus those with mIGHV treated with Ibr+Ven (**Figure 1D**)
  - uIGHV patients: 54-month posttreatment PFS rates were 60% for uMRD (n = 40) and 28% for dMRD (n = 16)
  - mIGHV patients: 54-month posttreatment PFS rates were 92% for uMRD (n = 13) and 71% for dMRD (n = 14)

Clb+O, Chlorambucil+Obinutuzumab; dMRD, detectable minimal residual disease; EOT+3, end of treatment plus 3 months; Ibr+Ven, Ibrutinib+Venetoclax; mIGHV, mutated IGHV; PFS, progression-free survival; uIGHV, unmutated IGHV; uMRD, undetectable minimal residual disease.

Overall Survival

- Ibr+Ven demonstrated an OS advantage versus Clb+O, reducing relative risk of death by 54% (HR 0.459 [95% CI, 0.271-0.776], nominal *p* = 0.0029) (**Figure 2A**)
  - 66-month OS rates were 79.0% and 60.8% for Ibr+Ven and Clb+O, respectively
- There was a trend toward improved OS observed for Ibr+Ven over Clb+O for both uIGHV and mIGHV groups (**Figure 2B**)
  - In patients with uIGHV, 66-month OS rates were 76.5% (n = 67) and 59.9% (n = 57) for Ibr+Ven and Clb+O, respectively
  - In patients with mIGHV, 66-month OS rates were 89.8% (n = 32) and 61.9% (n = 35) for Ibr+Ven and Clb+O, respectively

CI, confidence interval; Clb+O, Chlorambucil+Obinutuzumab; HR, hazard ratio; Ibr+Ven, Ibrutinib+Venetoclax; mIGHV, mutated IGHV; OS, overall survival; uIGHV, unmutated IGHV.

Time to Next Treatment

- At 67-month median follow-up, Ibr+Ven reduced the risk of needing second-line treatment by 77% compared with Clb+O (HR 0.226 [95% CI, 0.127-0.403], nominal $p < 0.0001$) (**Figure 3A**)
  - At 66 months, 19.3% of patients in the Ibr+Ven group and 52.0% in the Clb+O group required second-line treatment
- Ibr+Ven reduced the risk of needing second-line therapy versus Clb+O in patients with uIGHV (HR 0.171 [95% CI, 0.085-0.344]; nominal $p < 0.0001$); there was no difference in patients with mIGHV (HR 1.199 [95% CI, 0.314-4.585], nominal $p = 0.7905$) (**Figure 3B**)
  - For patients with uIGHV at 66 months, 20.7% (n = 67) in the Ibr+Ven group and 68.1% (n = 57) in the Clb+O group required second-line treatment
  - For patients with mIGHV at 66 months, 19.7% (n = 32) in the Ibr+Ven group and 22.9% (n = 35) in the Clb+O group required second-line treatment

CI, confidence interval; Clb+O, Chlorambucil+Obinutuzumab; HR, hazard ratio; Ibr+Ven, Ibrutinib+Venetoclax; mIGHV, mutated IGHV; uIGHV, unmutated IGHV.

Treatment-Free Survival

- At 67-month median follow-up, Ibr+Ven prolonged treatment-free survival time by 66% compared with Clb+O (HR 0.337 [95% CI, 0.224-0.507], nominal $p < 0.0001$) (**Figure 4**)
- The estimated 66-month rate of treatment-free survival time was 65.7% for Ibr+Ven and 29.8% for Clb+O

CI, confidence interval; Clb+O, Chlorambucil+Obinutuzumab; HR, hazard ratio; Ibr+Ven, Ibrutinib+Venetoclax.

Subsequent Treatment After Disease Progression

Subsequent treatment for patients with PD, n (%)	Ibr+Ven (n = 28)	Clb+O (n = 76)
Patients with subsequent therapy	16 (57.1)	46 (60.5)
Types of subsequent treatments		
High-dose therapy/stem cell transplant	0	0
Radiotherapy	1 (3.6)	2 (2.6)
Surgery	1 (3.6)	1 (1.3)
Systemic therapy	10 (35.7)	26 (34.2)
Antineoplastic agents	9 (32.1)	26 (34.2)
Monoclonal antibodies	6 (21.4)	13 (17.1)
Rituximab	5 (17.9)	13 (17.1)
Brentuximab vedotin	1 (3.6)	0
Nitrogen mustard analogues	4 (14.3)	1 (1.3)
Cyclophosphamide	2 (7.1)	1 (1.3)
Bendamustine	1 (3.6)	1 (1.3)
Chlorambucil	1 (3.6)	0
Other antineoplastic agents	4 (14.3)	12 (15.8)
Venetoclax	3 (10.7)	12 (15.8)
Idelalisib	1 (3.6)	1 (1.3)
Anthracyclines and related substances	3 (10.7)	1 (1.3)
Doxorubicin	3 (10.7)	1 (1.3)
Vinca alkaloids and analogues	3 (10.7)	2 (2.6)
Vinblastine	2 (7.1)	1 (1.3)
Vincristine	1 (3.6)	0
Vincristine sulfate	0	1 (1.3)
Other alkylating agents	1 (3.6)	1 (1.3)
Dacarbazine	1 (3.6)	1 (1.3)
Other cytotoxic antibiotics	1 (3.6)	0
Bleomycin	1 (3.6)	0
Protein kinase inhibitors	9 (32.1)	38 (50.0)
Ibrutinib	8 (28.6)	31 (40.8)
Acalabrutinib	0	7 (9.2)
Zanubrutinib	1 (3.6)	0
Folic acid analogues	0	1 (1.3)
Methotrexate	0	1 (1.3)
Methylhydrazines	0	1 (1.3)
Procarbazine	0	1 (1.3)
Investigational drug	0	1 (1.3)
Corticosteroids for systemic use	0	2 (2.6)
Glucocorticoids	0	2 (2.6)
Dexamethasone	0	1 (1.3)
Prednisolone	0	1 (1.3)
Prednisone	0	1 (1.3)

- Best responses for patients in the Ibr+Ven group (n = 8) who received single-agent ibrutinib: 1 complete response, 3 partial responses; 4 did not have disease assessment at clinical cutoff

Clb+O, Chlorambucil+Obinutuzumab; Ibr+Ven, Ibrutinib+Venetoclax; PD, disease progression.

Total Number of Second Primary Malignancies

n (%)	Ibr+Ven (n = 106)	Clb+O (n = 105)
≥ 1 other malignancies	14 (13.2)	18 (17.1)
Non-melanoma skin cancer	5 (4.7)	4 (3.8)
Melanoma skin cancer	1 (0.9)	2 (1.9)
Non-skin cancer	10 (9.4)	12 (11.4)
Hematologic malignancies	5 (4.7)	1 (1.0)[a]

- 14 patients (13.2%) who received Ibr+Ven and 18 (17.1%) who received Clb+O had second primary malignancies
  - Non-skin cancer: 10 (9.4%) in Ibr+Ven versus 12 (11.4%) in Clb+O
- All patients were past the treatment-emergent period in the previous analysis. Therefore, the safety analysis was limited to overall incidence of second primary malignancies

Clb+O, Chlorambucil+Obinutuzumab; Ibr+Ven, Ibrutinib+Venetoclax.
[a]1 patient had 2 hematologic second primary malignancies in the Clb+O group of the study.
Duration of treatment was 13.8 months for Ibr+Ven and 5.5 months for Clb+O.

Grade 3/4 TEAE-Free PFS

- Compared with Clb+O, patients in the Ibr+Ven group spent more time in the no grade 3/4 TEAEs, no progressive disease health state (**Figure 5**)
- Areas under the curve for grade 3/4 TEAE TOX time, grade 3/4 TEAE-free PFS, and alive postprogression are generated from partition curves for Ibr+Ven and Clb+O (**Figure 6**)
  - Patients treated with Ibr+Ven spent longer time in the grade 3/4 TEAE TOX time state versus Clb+O (1.9 vs 1.1 months, nominal *p* = 0.004)
  - Patients in the Ibr+Ven group spent more than 21 months longer in the grade 3/4 TEAE-free PFS compared with Clb+O (51.6 vs 30.2 months; nominal *p* = 0.0052)

RMST, months (95% CI)	Ibr+Ven	Clb+O	Estimated Difference Between Ibr+Ven and Clb+O, RMST (95% CI) Nominal *p* Value
Grade 3/4 TOX time	1.9 (1.5-2.4)	1.1 (0.8-1.4)	0.9 (0.4-1.4) *p* = 0.0042
PFS	53.5 (48.9-57.3)	31.2 (27.6-35.8)	22.3 (15.6-27.7) *p* = 0.0052
OS	64.7 (61.2-69.5)	59.5 (55.9-63.8)	5.25 (-0.1 to 10.9) *p* = 0.0047
Grade 3/4 TEAE-free PFS	51.6 (46.7-55.3)	30.2 (26.5-34.7)	21.4 (15.0-26.8) *p* = 0.0052
Postprogression survival time	11.2 (9.0-15.4)	28.2 (24.4-34.0)	2.5 (-21.8 to -11.4) *p* = 0.0054

CI, confidence interval; Clb+O, Chlorambucil+Obinutuzumab; Ibr+Ven, Ibrutinib+Venetoclax; OS, overall survival; PFS, progression-free survival; RMST, restricted mean survival time; TEAE, treatment-emergent adverse event; TOX, toxicity.

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