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First-Line Ibrutinib + Venetoclax Shows Benefit Across Genomic Subgroups in Patients With Chronic Lymphocytic Leukemia: Results From Phase 2 CAPTIVATE Study and Phase 3 GLOW Study

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OBJECTIVES

To report outcomes in subgroups by genomic alterations in patients treated with fixed-duration (FD) ibrutinib + venetoclax in the phase 2 CAPTIVATE study and in those treated with FD ibrutinib + venetoclax or chlorambucil + obinutuzumab in the phase 3 GLOW study

To assess the impact of the 4-gene signature (*BCOR*, *CCND2*, *NRAS*, and *XPO1*; BCNX)[4] in patients with previously untreated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) who were treated with FD ibrutinib + venetoclax in the CAPTIVATE FD cohort and GLOW, and with minimal residual disease (MRD)–guided ibrutinib + venetoclax in the CAPTIVATE MRD cohort

CONCLUSIONS

Similar incidences of genomic alterations were observed in CAPTIVATE and GLOW, with generally consistent associations with IGHV mutations status

These robust analyses from CAPTIVATE and GLOW showed that FD ibrutinib + venetoclax provided clinical benefit across subgroups of patients with and without genomic alterations

The proposed BCNX mutation signature[4] had no impact on progression-free survival (PFS) or overall survival (OS) in patients treated with FD ibrutinib + venetoclax in CAPTIVATE and in GLOW

The BCNX mutation signature appeared to impact PFS and OS in patients treated with MRD -guided ibrutinib + venetoclax in the CAPTIVATE MRD cohort

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https://www.congresshub.com/ASH2025/Oncology/Ibrutinib/Cheung

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INTRODUCTION

- Genomic alterations, including IGHV mutation status, are predictive for outcomes on chemoimmunotherapy in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)[1-3]
- Recently, a 4-gene signature (*BCOR*, *CCND2*, *NRAS*, and *XPO1*; BCNX) was found to be predictive of progression-free survival (PFS) and overall survival (OS) with minimal residual disease (MRD)–guided ibrutinib + venetoclax in patients with relapsed/refractory CLL in the VISION study[4]
- Ibrutinib + venetoclax is approved for first-line treatment of CLL in 50+ countries across Asia, Europe, the Middle East, and South America, as well as in Canada, Australia, and New Zealand
- Approvals were based on results from the phase 3 GLOW and phase 2 CAPTIVATE studies, in which fixed-duration (FD) treatment with ibrutinib + venetoclax demonstrated durable treatment-free remissions in patients with previously untreated CLL/SLL[5-7]

METHODS

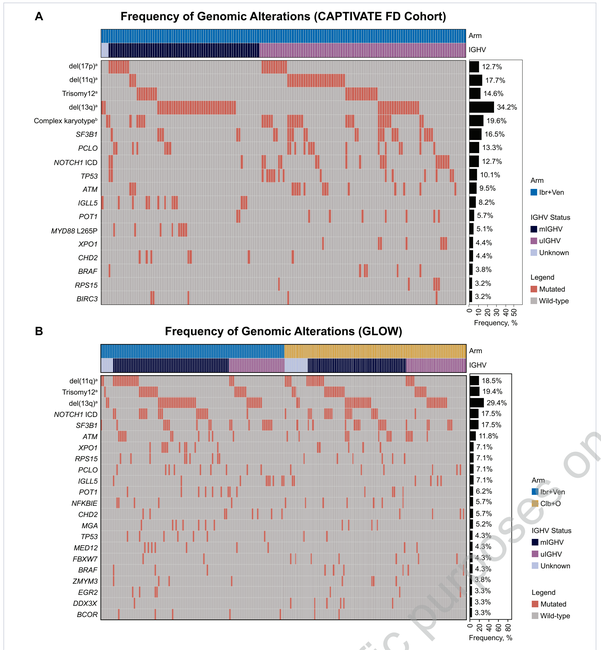
- The phase 2 CAPTIVATE study evaluated first-line ibrutinib + venetoclax in patients with previously untreated CLL in 2 cohorts: MRD–guided randomized discontinuation (MRD cohort) and Fixed Duration (FD cohort)[5,6]
- The randomized phase 3 GLOW study evaluated first-line ibrutinib + venetoclax versus chlorambucil + obinutuzumab in patients with previously untreated CLL aged ≥65 years or 18 to 64 years with comorbidities[7]
- In CAPTIVATE, mutational analysis was performed using targeted next-generation sequencing (NGS) covering >1400 genes (Personalis ACE panel) in CD19+-enriched peripheral blood mononuclear cells (PBMCs) collected at baseline from 322 patients treated with ibrutinib + venetoclax (FD cohort, n=158; MRD cohort, n=164)
- In GLOW, mutational analysis was performed using whole exome sequencing (Personalis ImmunoID NeXT) in PBMCs collected at baseline from 211 patients (ibrutinib + venetoclax, n=106; chlorambucil + obinutuzumab, n=105)
- Efficacy outcomes of interest for the current analyses were complete response (CR) rate, overall response rate (ORR), undetectable MRD (<10^{-4}; uMRD4) rate in peripheral blood at 3 months after end of treatment (EOT+3), PFS, and OS
  - MRD was assessed by 8-color flow cytometry in CAPTIVATE and by NGS in GLOW
- Time-to-event end points were analyzed using Cox proportional hazards models, Kaplan-Meier estimates, and log-rank tests
- Fisher exact test was used to test for associations between binary variables, with no adjustment for multiple tests; nominal *P* values are reported

RESULTS

Incidence of Genomic Alterations

- Except for del(17p) or known *TP53* mutations, which were an exclusion for GLOW, incidences of genomic alterations were similar in patients treated with FD ibrutinib + venetoclax in CAPTIVATE and GLOW

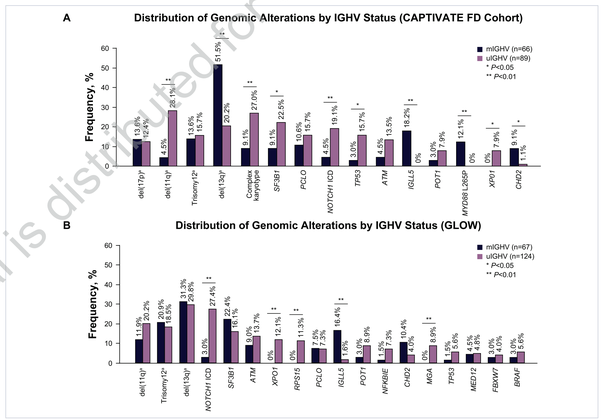
Figure 1: Incidences of Genomic Alterations Were Similar in Patients Treated With FD Ibrutinib + Venetoclax in CAPTIVATE FD Cohort and GLOW



Clb, chlorambucil; Ibr, ibrutinib; ICD, intracellular domain; O, obinutuzumab; Ven, venetoclax.
*Chromosomal abnormalities were assessed per Döhner hierarchy; †Complex karyotype was defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.

- Mutations in *NOTCH1* ICD, *XPO1* (CAPTIVATE and GLOW), *TP53*, *SF3B1* (CAPTIVATE only), and *RPS15* (GLOW only) were more frequent in patients with unmutated IGHV (uIGHV; *P*<0.05), whereas mutations in *IGLL5* (CAPTIVATE and GLOW) and *MYD88* L265P (CAPTIVATE only) were more frequent in patients with mutated IGHV (mIGHV; *P*<0.05)

Figure 2: Distribution of Genomic Alterations by IGHV Status Was Similar in CAPTIVATE and GLOW

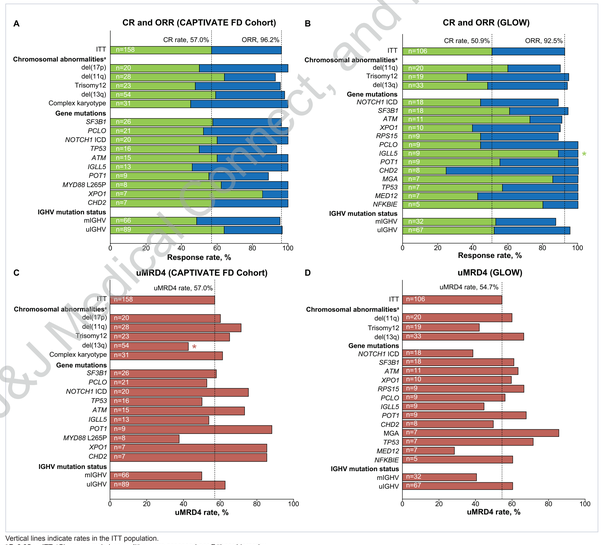


*Chromosomal abnormalities were assessed per Döhner hierarchy.

Outcomes in Subgroups by Genomic Alterations

- In patients treated with FD ibrutinib + venetoclax in both CAPTIVATE and GLOW, CR, ORR, and uMRD rates at EOT+3 across genomic subgroups were generally similar to those observed in all patients treated with FD ibrutinib + venetoclax (intention-to-treat [ITT])

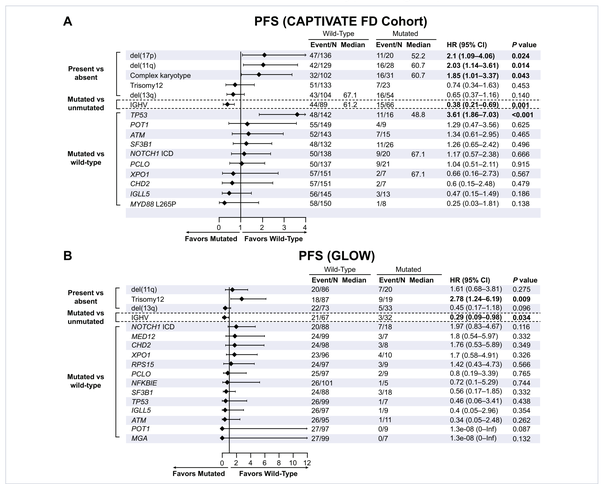
Figure 3: CR, ORR, and uMRD4 Rates With FD Ibrutinib + Venetoclax Were Not Significantly Different Across Genomic Subgroups



Vertical lines indicate rates in the ITT population.
*P<0.05 vs ITT; *Chromosomal abnormalities were assessed per Döhner hierarchy.

- There were no statistically significant differences in PFS between mutant versus wild-type subgroups, except for shorter PFS in patients with uIGHV versus mIGHV (CAPTIVATE and GLOW; *P*<0.05), shorter PFS in patients with del(17p), del(11q), complex karyotype or *TP53* mutant versus wild type (CAPTIVATE only; *P*<0.05), and shorter PFS in patients with Trisomy 12 mutant versus wild type (GLOW only; *P*<0.05)
- There were no statistically significant differences in OS between mutant versus wild-type subgroups, except for shorter OS in patients with uIGHV, *TP53* mutated, complex karyotype (CAPTIVATE only; *P*<0.05), and shorter OS in patients with Trisomy 12 (GLOW only; *P*<0.05) (data not shown)

Figure 4: PFS With FD Ibrutinib + Venetoclax Was Generally Similar Between Mutant and Wild-Type Subgroups

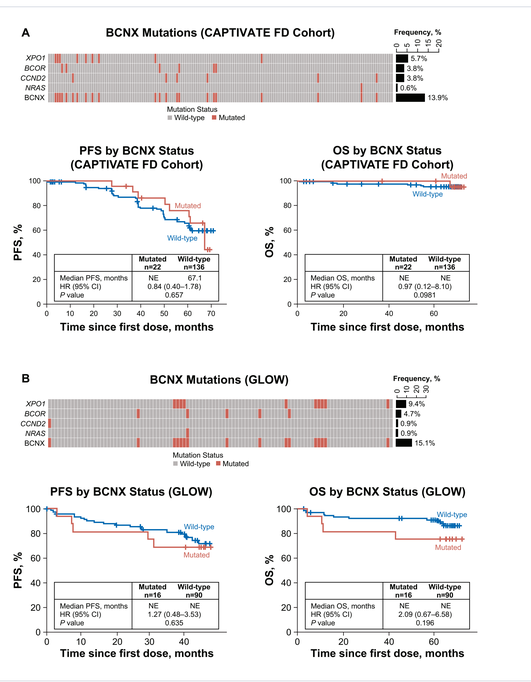


HR, hazard ratio.

Impact of BCNX Mutations on Outcomes

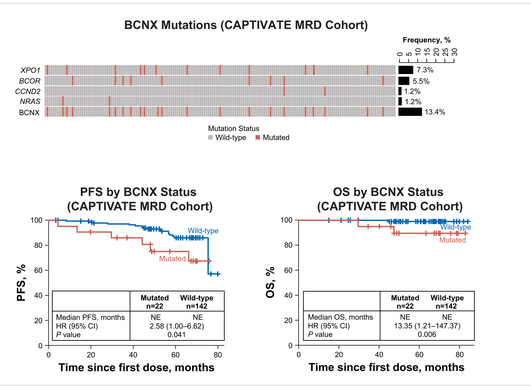
- At baseline, mutations in any of the 4 genes in the proposed BCNX signature (*BCOR*, *CCND2*, *NRAS*, or *XPO1*)[4] were found in 13.9% of patients in the CAPTIVATE FD cohort, 15.1% of patients in GLOW, and 13.4% of patients in the CAPTIVATE MRD cohort
- There were no statistically significant differences in PFS or OS between BCNX mutated versus wild-type subgroups in the CAPTIVATE FD cohort or GLOW
- By contrast, in the CAPTIVATE MRD cohort, PFS and OS were significantly longer in the BCNX wild-type versus mutated subgroup (both *P*<0.05)

Figure 5: Incidence and Predictive Value of BCNX Signature Mutations With FD Ibrutinib + Venetoclax



NE, not estimable.

Figure 6: Incidence and Predictive Value of BCNX Signature Mutations With MRD–Guided Ibrutinib + Venetoclax



Pbo, placebo.