**Venetoclax/Obinutuzumab Continues to Demonstrate Superior Efficacy**

Long-term results from the CLL14 trial continue to show that fixed-duration venetoclax/obinutuzumab (VenG) continues to improve progression-free survival (PFS) compared with chlorambucil/obinutuzumab (ClbG) in patients who have previously untreated chronic lymphocytic leukemia (CLL).

For the open-label phase 3 trial, Dr Othman Al-Sawaf and colleagues randomly assigned 432 patients with previously untreated CLL and coexisting conditions to receive 6 cycles of obinutuzumab (Gazyva, Genentech) plus 12 cycles of either venetoclax (Venclexta, AbbVie; n=216) or chlorambucil (Leukeran, Aspen Global; n=216).

After a median follow-up of 39.6 months, median PFS in the VenG group continued to be superior to that in the ClbG group (not reached vs 35.6 months; hazard ratio [HR], 0.31 [95% CI, 0.22-0.44]; \( P < .001 \)). The estimated 3-year PFS rate was 81.9% in the VenG arm and 49.5% in the ClbG arm. This benefit was consistently observed across all clinical and biological risk groups, including patients with a \( TP53 \) mutation and those with an unmutated immunoglobulin heavy chain variable region gene (\( IGHV \)). PFS was also significantly longer for VenG-treated patients with mutated \( IGHV \) status than for those with unmutated \( IGHV \) status.

The rate of undetectable minimal residual disease 18 months after the end of treatment was 47.2% in the VenG arm and 7.4% in the ClbG arm. Median overall survival (OS) was not reached in either group. Second primary malignancies occurred in 11% of patients. Serious AEs, which included pneumonia (n=4) and sepsis (n=3), were reported in 38% of patients.

The overall response rate (ORR) was 97%, with 7% of patients achieving a complete response (CR) and 90% a partial response. The median time to response was 3.7 months. The median duration of response and median event-free survival were not reached.

**Acalabrutinib Safer, More Effective Than Certain Rituximab-Based Regimens in CLL**

Acalabrutinib (Calquence, AstraZeneca) produces durable remissions and has long-term tolerability in patients who have treatment-naive CLL, according to results from the phase 2 ACE-CL-001 study. The results of this study provide the longest safety and efficacy follow-up to date in patients with symptomatic triple-negative CLL, according to the investigators.

The trial included 99 patients with treatment-naive CLL or small lymphocytic lymphoma who were considered ineligible for or declined standard chemotherapy and had an Eastern Cooperative Oncology Group performance status of 0 through 2. Dr John C. Byrd and colleagues randomly assigned patients to acalabrutinib at 100 mg twice a day (n=62) or at 200 mg once a day with a later switch to 100 mg twice a day (n=37). Treatment continued until progressive disease or unacceptable toxicity.

At a median follow-up of 53 months, 85 of the patients (86%) remained on treatment. Most of the discontinuations were due to adverse events (AEs) or progressive disease, which occurred in 6 and 3 patients, respectively. The most common AEs of any grade were diarrhea (52%), headache (45%), upper respiratory tract infection (44%), arthralgia (42%), and contusion (42%). All-grade and grade 3 or higher events of clinical interest included infection (84% and 15%), bleeding (66% and 3%), and hypertension (22% and 11%). All-grade atrial fibrillation occurred in 5% of patients. Second primary malignancies, excluding nonmelanoma skin cancer, occurred in 11%. Serious AEs, which included pneumonia (n=4) and sepsis (n=3), were reported in 38% of patients.

The overall response rate (ORR) was 97%, with 7% of patients achieving a complete response (CR) and 90% a partial response. The median time to response was 3.7 months. The median duration of response and median event-free survival were not reached.

**Acalabrutinib Demonstrates Durable Remissions in Treatment-Naive CLL**

Acalabrutinib (Calquence, AstraZeneca) produces durable remissions and has long-term tolerability in patients who have treatment-naive CLL, according to results from the phase 2 ACE-CL-001 study. The results of this study provide the longest safety and efficacy follow-up to date in patients with symptomatic triple-negative CLL, according to the investigators.

The trial included 99 patients with treatment-naive CLL or small lymphocytic lymphoma who were considered ineligible for or declined standard chemotherapy and had an Eastern Cooperative Oncology Group performance status of 0 through 2. Dr John C. Byrd and colleagues randomly assigned patients to acalabrutinib at 100 mg twice a day (n=62) or at 200 mg once a day with a later switch to 100 mg twice a day (n=37). Treatment continued until progressive disease or unacceptable toxicity.

At a median follow-up of 53 months, 85 of the patients (86%) remained on treatment. Most of the discontinuations were due to adverse events (AEs) or progressive disease, which occurred in 6 and 3 patients, respectively. The most common AEs of any grade were diarrhea (52%), headache (45%), upper respiratory tract infection (44%), arthralgia (42%), and contusion (42%). All-grade and grade 3 or higher events of clinical interest included infection (84% and 15%), bleeding (66% and 3%), and hypertension (22% and 11%). All-grade atrial fibrillation occurred in 5% of patients. Second primary malignancies, excluding nonmelanoma skin cancer, occurred in 11%. Serious AEs, which included pneumonia (n=4) and sepsis (n=3), were reported in 38% of patients.

The overall response rate (ORR) was 97%, with 7% of patients achieving a complete response (CR) and 90% a partial response. The median time to response was 3.7 months. The median duration of response and median event-free survival were not reached.


**Acalabrutinib Safer, More Effective Than Certain Rituximab-Based Regimens in CLL**

Monotherapy with acalabrutinib is safer and more effective than 2 rituximab-based regimens in CLL, according to final results from the ASCEND trial.
Venetoclax Plus R-EPOCH Shows Activity in Richter Syndrome

A combination of venetoclax and rituximab plus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (VR-EPOCH) shows activity in Richter syndrome, according to a phase 2 study.

For the study, which Dr Matthew S. Davids presented orally, 27 patients at 3 US sites who had CLL with biopsy-confirmed diffuse large B-cell lymphoma received VR-EPOCH for 1 cycle. After blood cell count recovery, the patients underwent 5 inpatient days of accelerated ramp-up of venetoclax, followed by VR-EPOCH for up to 5 more 21-day cycles. Patients who responded to treatment went on to allogeneic hematopoietic cell transplant (alloHCT) or to daily venetoclax maintenance.

After a median follow-up of 9.3 months, the intention-to-treat analysis revealed an ORR of 59%, with 48% of patients having a CR as their best response. Among the 21 patients who started combination therapy, the ORR was 76% and the CR rate was 62%. Only 1 patient who achieved a CR experienced disease progression. The patient who has been on venetoclax maintenance for the longest remains in CR 2 years after chemotherapy. Eight patients went on to alloHCT. The median PFS and median OS were both 16.3 months.

Grade 3 or higher hematologic toxicities were neutropenia (58%), anemia (50%), and thrombocytopenia (50%). Grade 3 or higher nonhematologic toxicities included febrile neutropenia (38%) and hypophosphatemia (23%). No patients had tumor lysis syndrome with the daily ramp-up of venetoclax. Ten patients have died; causes of death were disease progression (7), sepsis (1), sudden death (1), and graft-versus-host disease following alloHCT (1).


Addition of Ublituximab to Ibrutinib Improves PFS in High-Risk CLL

The addition of ublituximab to ibrutinib (Imbruvica, Pharmacyclics) improves PFS in high-risk CLL, according to final results from the GENUINE study. Ublituximab is a glyco-engineered monoclonal antibody that has enhanced antibody-dependent cellular cytotoxicity.

For the study, Dr Jeffrey Sharman and colleagues randomly assigned 117 patients who had high-risk relapsed or refractory CLL with del(17p), del(11q), and/or a TP53 mutation to receive ibrutinib alone (n=58) or ublituximab plus ibrutinib (n=59).

After a median follow-up of 3.5 years, all efficacy endpoints favored ublituximab/ibrutinib over ibrutinib; these included ORR without and with partial response with lymphocytosis (90%-93% vs 69%-78%; P<.05), CR/CR with incomplete blood cell count recovery (20% vs 5%; P=.024), measurable residual disease negativity (46% vs 7%; P=.0001), and PFS (not reached vs 35.9 months; HR, .455; P=.016). The difference in PFS was driven by patients with del(17p) or mutated TP53, in whom PFS was not reached vs 18.9 months (HR, .253; P=.004). No meaningful difference in PFS was observed for patients with del(11q). The 4-year OS rate with ublituximab/ibrutinib was 82% vs 70% with ibrutinib alone, but the difference was not statistically significant.

AEs were comparable in the 2 arms, with the exception of more infusion reactions and neutropenia in the ublituximab/ibrutinib group.