Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Context: The Bruton tyrosine kinase (BTK) inhibitor, zanubrutinib, was designed for high BTK specificity and minimal toxicity. SEQUOIA (NCT03336333) is a global, open-label, randomized phase 3 study in treatment-naïve patients with CLL/SLL without *del(17p)* who were unsuitable for fludarabine/cyclophosphamide/rituximab. **Design:** Patients were randomized to receive zanubrutinib (160 mg twice daily) or bendamustine (day 1-2: 90 mg/m^2) and rituximab (cycle 1: 375 mg/m^2; cycles 2-6: 500 mg/m^2); stratification factors were age (<65 years vs ≥65 years), Binet Stage, *IGHV* mutation, and geographic region. **Main Outcome Measures:** Primary endpoint was an independent review committee (IRC)-assessed progression-free survival (PFS). Secondary endpoints included investigator-assessed (INV) PFS, overall response rate (ORR), overall survival (OS), and safety. **Results:** From October 31, 2017, to July 22, 2019, 479 patients were enrolled (zanubrutinib=241; BR=238). Baseline characteristics (zanubrutinib vs BR): median age, 70.0 years versus 70.0 years; unmutated *IGHV*, 53.4% versus 52.4%; *del(11q)*, 17.8% versus 19.3%. With median follow-up of 26.2 months, PFS was significantly prolonged with zanubrutinib by IRC (HR 0.42; 2-sided P<.0001) and INV (HR 0.42; 2-sided P=.0001). Zanubrutinib treatment benefit occurred across age, Binet stage, bulky disease, *del(11q)* status, and unmutated *IGHV* (HR 0.24; 2-sided P<.0001), but not mutated *IGHV* (HR 0.67; 2-sided P=.1858). For zanubrutinib versus BR, 24-month PFS-IRC=85.5% versus 69.5%; ORR-IRC=94.6% versus 85.3%; complete response rate=6.6% versus 15.1%; ORR-INV=97.5% versus 88.7%; and 24-month OS=94.3% versus 94.6%. Select adverse event (AE) rates (zanubrutinib vs BR): atrial fibrillation (3.3% vs 2.6%), bleeding (45.0% vs 11.0%), hypertension (14.2% vs 10.6%), infection (62.1% vs 55.9%), and neutropenia (15.8% vs 56.8%). Treatment discontinuation due to AEs (zanubrutinib vs BR)=20 patients (8.3%) versus 31 patients (13.7%); AEs leading to death=11 patients (4.6%) versus 11 patients (4.8%). No sudden deaths occurred. **Conclusions:** In summary, zanubrutinib significantly improved PFS-IRC versus BR and was well tolerated, supporting the potential utility of frontline zanubrutinib in treatment-naïve CLL/SLL. **Keywords:** CLL, BTK inhibitor; BGB-3111-304; NCT03336333, Phase III

CLL-140

Booster and BTKi Interruption Improve Response to SARS-CoV-2 Vaccine in Patients With CLL

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Introduction: Patients with chronic lymphocytic leukemia (CLL) have inadequate responses to vaccination, including SARS-CoV-2 mRNA vaccines. Treatment with anti-B-cell therapies, such as anti-CD20 monoclonal antibodies (mAb) and Bruton's tyrosine kinase inhibitors (BTKi), further suppress the antibody response to vaccines. Here, we aimed to evaluate clinical and laboratory parameters associated with vaccine response and the effect of BTKi interruption around the time of booster. **Methods:** A single-institution cohort study of patients with CLL was conducted at the National Institutes of Health. Treatment-naïve (TN) patients as well as those receiving treatment with a BTKi or venetoclax (VEN) were included. Patients who received IVIG, anti-SARS-CoV-2 mAb, or convalescent plasma within 3 months of vaccination were excluded. Anti-spike antibody titers were measured after completion of the primary series (two

doses of Pfizer-BioNTech/Moderna vaccines or one dose of Janssen vaccine) and the first booster. **Results:** There were 86 patients in total (54 BTKi, 14 VEN, and 18 TN). The median age was 68.0, and 97.7% of patients received mRNA vaccine. After the primary series, seroconversion (anti-spike >0.8 U/mL) was detected in 53% of BTKi-treated patients, 43% of patients on single-agent VEN, and 67% of TN patients. After booster, seroconversion was detected in 87% of BTKi-treated patients, 50% of patients on single-agent VEN, and 83% of TN patients. Anti-spike antibodies increased after booster in 90% of patients who responded to the primary series. No patients who received anti-CD20 mAb within 12 months of vaccination (in combination with VEN) responded to the primary series or booster. Seroconversion was associated with higher serum IgM (P=0.023 after the primary series and P=0.039 after booster). Twelve patients interrupted BTKi for a median of 19 days (range 8–23) around the time of booster. Patients who interrupted BTKi had higher anti-spike antibodies (median 7,148 U/mL) than those who continued therapy (median 1,198 U/mL, P=0.018). Of the 12 patients who interrupted BTKi, 3 experienced lymph node pain and swelling and resumed BTKi earlier than intended. **Conclusions:** Increasing anti-spike antibodies with subsequent vaccinations support additional boosters in this population. BTKi interruption at the time of vaccination results in a more robust antibody response. **Keywords:** CLL, chronic lymphocytic leukemia, SARS-CoV-2, vaccine response, BTKi, venetoclax

CLL-152

The Significance of Rai and Binet Clinical Staging on the Survival of CLL Patients in the Kurdistan Region of Iraq

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Background: Chronic lymphocytic leukemia is an uncommon type of leukemia in Iraq, although many reported cases of chronic lymphocytic leukemia in the Iraqi Kurdistan region are of high risk stage. Staging of chronic lymphocytic leukemia is essential in treatment planning and for disease prognosis. **Aim of Study:** To find out the difference in patients' survival with early and late clinical stages, and to evaluate CLL outcome in relation to the Rai and Binet staging **Patients and Methods:** This retrospective cross-sectional analysis studied 250 patients, 170 male and 80 female, with chronic lymphocytic leukemia who were registered in three hemato-oncology centers in Iraqi Kurdistan for the last 10 years. The diagnosis of the disease was made according to the guideline of the International Workshop Chronic Lymphocytic Leukemia update of the National Cancer Institute. The patients' clinical staging was determined by a senior hematologist based on the clinical and laboratory findings. **Results:** The mean age of the patients was 63(±11.8) years, 40% were >65 years. The median survival was 27 months. Elderly patients >65 years had significantly lower mean survival. The Rai staging was distributed as follows: stage 0 (24.8%), stage I (12.8%), stage II (30.8%), stage III (9.6%) and stage IV (22%). The median survival was significantly higher among patients with Rai stage 0 comparing to patients with advanced stages (p<0.001). The Binet stage was distributed as follows: stage A (47.2%), stage B (26.4%) and stage C (26.4%). The median patients' survival was significantly higher among patients with Binet stage A comparing to those with Binet stage C (p<0.001). **Conclusions:** The survival of patients with chronic lymphocytic leukemia strongly related to the clinical stages of both staging systems. **Keywords:** CLL, survival, Rai staging, Binet staging

CLL-162

PTX3 is Constitutively Active in CLL Cells

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The pentraxin-related PTX3, commonly produced by myeloid and endothelial cells, is a humoral pattern-recognition protein of the innate immune system. Because CLL patients' PTX3 plasma levels are high and most circulating cells in patients with chronic lymphocytic leukemia (CLL) are CLL cells, we reasoned that CLL cells produce PTX3. Western immunoblotting revealed that low-density cells from 7 out of 7 CLL patients produce high levels of PTX3, flow cytometry analysis revealed that the PTX3-producing cells are B lymphocytes co-expressing CD19 and CD5, and confocal microscopy demonstrated that PTX3 co-localized with STAT3. Because signal transducer and activator of transcription (STAT)-3 is constitutively activated in CLL cells and we identified putative STAT3 binding sites within the PTX3 gene promoter, we postulated that phosphorylated STAT3 triggers transcriptional activation of PTX3. Immunoprecipitation analysis of CLL cells' chromatin fragments showed that STAT3 antibodies precipitated PTX3 DNA. STAT3 knockdown induced a marked reduction in PTX3 expression, indicating a STAT3-induced transcriptional activation of the PTX3 gene in CLL cells. Using an electromobility shift assay that we established and a dual-reporter luciferase assay, we confirmed that STAT3 binds the PTX3 gene promoter. Downregulation of PTX3 induced apoptotic disassembly of CLL cells, suggesting that inhibition of PTX3 might benefit patients with CLL. **Keywords:** CLL, STAT3, PTX3