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Zanubrutinib and Venetoclax as Initial Therapy for CLL with Obinutuzumab Triplet Consolidation in Patients with Detectable Minimal Residual Disease (BruVenG): Trial in Progress

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Study Rationale

Bruton's tyrosine kinase inhibitors (BTKi), anti-CD20 antibodies, and B cell lymphoma 2 inhibitors (BCL-2i) are essential therapeutic drug classes in the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Current evidence demonstrates clinical synergy between BTKi and BCL-2i, which allows for an all-oral regimen, that can be safely administered in a clinic setting for most patients (Tam et al., 2022; Wierda et al., 2021). This combination can achieve high rates of minimal residual disease (MRD) negativity and offer a fixed duration therapeutic approach (Kater et al., 2022).

Still, it remains uncertain if anti-CD20 therapy meaningfully adds to the effectiveness of oral combination therapy. Recent reports of triplet regimens demonstrate modest improvement in MRD negativity with similar overall response rates when compared to oral doublets (Davids et al., 2021; Soumerai et al., 2021; Wierda et al., 2021).

Therefore, anti-CD20 therapy may not be required for all patients and might be best utilized within a response-adapted strategy seeking to maximize response and minimize toxicity. This trial has been developed to assess efficacy of a response adapted consolidative treatment approach utilizing obinutuzumab triplet consolidation in CLL/SLL patients who remain MRD positive after completion of an oral doublet fixed duration treatment with zanubrutinib and venetoclax.

This study will utilize once daily zanubrutinib for which there is limited data in regard to safety and efficacy particularly in combination with venetoclax.

Study Design & Objectives

Study Design: Open label, Phase II, Single Center, Investigator initiated clinical trial

Study Population: Treatment naïve patients with CLL/SLL with treatment indications per the International Workshop on CLL 2018 Guidelines.

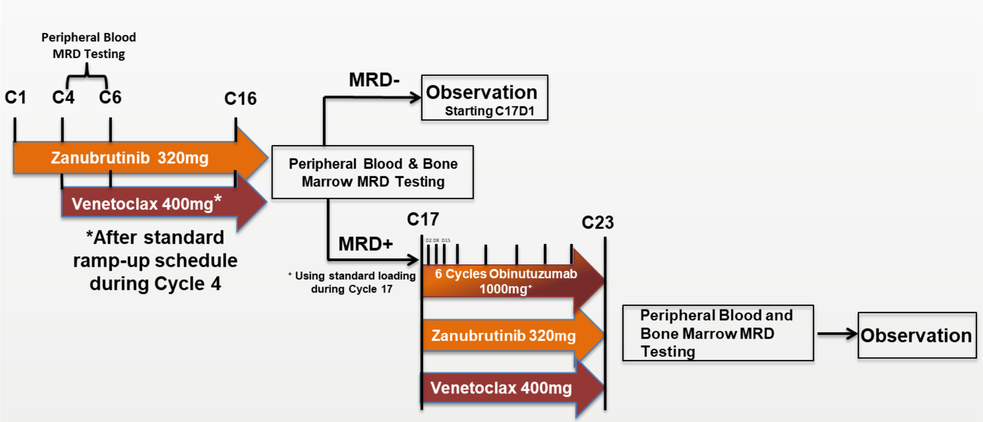
Sample Size: N = 50 subjects

1º Objectives: To determine peripheral blood and bone marrow MRD negativity rate ($1x10^{-4}$) for the doublet combination at Cycle 16 and to determine the peripheral blood and bone marrow MRD negativity rate ($1x10^{-4}$) at the beginning of cycle 23 for subjects who were MRD positive at cycle 16 assessment.

2º Objectives: To evaluate safety during doublet and triplet therapy, 36 month progression free survival (PFS), 36 month overall survival (OS), 24 and 36 months peripheral blood MRD rates in patients treated with doublet therapy, 36 month peripheral blood MRD rates in subjects treated with triplet therapy, 36 month time to next treatment (TTNT), and tumor lysis risk reduction rates at cycle 4.

Exploratory Objectives: Validation of Δ400 (400-fold reduction in MRD from baseline) after 2 cycles of combination therapy to predict MRD negativity at cycle 16.

Study Schema



Key Inclusion Criteria:

1. Subject must be able to voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study specific procedures.
2. Subject must be ≥ 18 years of age.
3. Subject must have confirmed diagnosis of CLL/SLL based upon 2018 iwCLL Guidelines.
4. Subject must have indications for treatment per the 2018 iwCLL Guidelines.
5. Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
6. Subject must have adequate organ function defined as:
   a. Creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation
   b. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase, and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase ≤ 2.5 × upper limit of normal (ULN) unless due to CLL/SLL.
   c. Serum total bilirubin < 3.0 × ULN (unless documented Gilbert's syndrome)
7. Subject must have adequate bone marrow function and meet the below thresholds unless approved by sponsor if cytopenias are felt to be due to significant marrow involvement of CLL:
   a. Absolute neutrophil count ≥ 1.0 x10³/μL
   b. Hemoglobin ≥ 7 g/dL (can be transfused up to 1 week prior to study enrollment)
   c. Platelets ≥ 75,000 cells/μL OR platelets ≥ 30,000 cells/μL if clearly due to disease
8. Subjects of childbearing potential must be willing to comply with pregnancy prevention interventions

Key Exclusion Criteria:

1. Previous exposure to any systemic anti-cancer therapy as a treatment for CLL/SLL, including but not limited to chemotherapy, immunotherapy, radiotherapy, hormone therapy (other than contraceptives, hormone-replacement therapy or megestrol acetate) or investigational therapy.
2. Subject with a history of malignancy except for non-melanoma skin cancers. Subjects treated with curative intent via methods of local resection and or locally targeted anticancer treatment and are free of malignancy for at least 5 years from treatment end will be allowed to enroll.
3. Subjects with active autoimmune hemolytic anemia or immune thrombocytopenia purpura.
4. Subject with prolymphocytic leukemia or Richter's Transformation.
5. Subject requires warfarin or equivalent vitamin K antagonist.
6. Uncontrolled or active significant infection requiring systemic treatment, subjects are eligible if they have completed antibiotic therapy 2 weeks prior to study enrollment.
7. Clinically significant cardiovascular disease including the following:
8. Patients with stroke or CNS hemorrhage within 6 months.
9. Pregnant or breastfeeding.
10. Subject is known to be positive for human immunodeficiency virus (HIV).
11. Active hepatitis C, as confirmed by being positive for Hep C RNA by PCR.
12. Active hepatitis B infection documented by a positive PCR for Hep B DNA. If hepatitis B serology is positive for hepatitis B core antibody, but Hep B DNA PCR is negative, patient is eligible to enroll.
13. Known hypersensitivity reactions (e.g., anaphylaxis) to obinutuzumab or any of the excipients, including serum sickness with prior obinutuzumab use.

Study Definitions, Endpoints, & Statistical Methods

Study Definitions and Endpoints

MRD Negativity:
Subjects that complete 15 cycles of therapy or follow-up regardless of dose reductions, drug discontinuations and have not progressed, died, or withdrawn from the study must undergo Cycle 16 peripheral blood and bone marrow assessments for MRD. Subjects that are found to be MRD negative by NGS via clonoSEQ® in the peripheral blood AND bone marrow will be considered MRD negative and will stop therapy starting at C17D1. Minimal residual disease negativity will be defined by a sensitivity cutoff of 1 x 10-4 or < 0.01% CLL cells present out of minimum of 1 million cells analyzed.

Response Rate:
Response rates will be assessed by investigator using IWCLL 2018 response definitions

Progression Free Survival:
PFS will be measured from the start of the treatment to the date of documentation of either disease progression or death until 3 years of follow-up is completed.

Overall Survival:
OS will be measured from the start of treatment to the date of death from any cause until 3 years of follow-up is completed.

Time to Next Treatment:
TTNT will be measured from the start of treatment to the date of next line of treatment after stopping therapy. Obinutuzumab consolidation will not be considered a second line of treatment. Any treatment directed at CLL after stopping therapy will be considered a next therapy. Subjects will be followed prospectively and for 36 months from start of initial therapy to calculate a 3 year TTNT. Subjects that die will be censored at time of death.

Tumor Lysis Risk Reduction:
Tumor lysis risk of high, medium, or low will be collected at baseline/screening. After 3 cycles of zanubrutinib debulking, TLS risk will be reassessed prior to Cycle 4 day 1. Subjects will have their new assessment, high, medium, or low recorded.

MRD Kinetics
Fold reduction of MRD between baseline, Cycle 4, Cycle 6, and Cycle 16 will be collected

Safety Monitoring
Safety will be assessed using CTCAE 5.0. This study will employ a Weill Cornell Medicine DSMC. The monitoring committee will review periodic reports of safety and toxicity every 6 months at convened DSMC meetings. AE reporting will be compiled and submitted for DSMC review prior to every 6-month review. Following comprehensive review of trial safety data, the DSMC will issue guidance regarding whether it is safe for the trial to continue and whether any modifications are required.

Statistical Methods
With a sample size of 50 patients in the study, assuming the historical MRD negativity rate is 70%, we can accept an equivalence proportion between 53% - 87% at C16 with at least 80% power at alpha level of 0.1 using an exact binomial test. It is hypothesized that some patients initially found to be MRD positive will be become MRD negative after receipt of additional consolidation therapy, resulting in an overall MRD negativity proportion of at least 83%. This total sample size allows us to achieve at least 80% power at alpha level of 0.1 to declare superiority of the observed 83.1% negativity at C23 against 70% using an one-sided binomial test.

Analysis of Primary Endpoint
The primary endpoint of C16 peripheral blood and bone marrow MRD negativity as defined by clonoSEQ® will be represented as a percentage of total patients. The co-primary endpoint of C23 peripheral blood and bone marrow MRD negativity rate as defined by clonoSEQ® will be presented as a percentage of patients that achieve undetectable MRD at C23, who were found to be MRD positive at C16 and went on to receive at least one dose of obinutuzumab. These will be calculated on both efficacy evaluable and intention to treat basis. These will be estimated with a 90% confidence interval using Clopper-Pearson method based on exact binomial distribution.

Analysis of Secondary & Correlative Endpoints
Secondary endpoints measuring toxicity will be tabulated using CTCAE 5.0. Numbers of participants experiencing AEs will be represented as a percentage through cycle 16. Exact 90% confidence intervals around the toxicity proportions will be calculated to assess the precision of the obtained estimates.

Twenty-four month and 36-month peripheral blood MRD negativity rates will be assessed by clonoSEQ® and represented as percentage of subjects that remain MRD negative at those time points on intention to treat basis. Overall response rate including all categories of response will be tabulated and calculated as total percentage of patients achieving a specific response on an intention to treat basis. Thirty-six-month PFS, 36-month OS, and 36-month TTNT will be determined via Kaplan-Meier methods. Patients who do not experience an event or lost to follow-up will be censored at last follow-up prior to data cutoff. TLS high risk reduction rates at C4D1 will be represented as a percentage change. Positive predictive value of the Δ400 biomarker will be calculated. MRD concordance between compartments will be assessed using Lin's concordance coefficient. The Youden Index will be used to establish an optimal ΔMRD cutoff measured from baseline to C6D1 to predict MRD negativity at C16D1.

Trial Registry, Enrollment Status, & Funding Sources

Trial Registry: Clinicaltrials.gov
NCT #: NCT05650723
Study Activation: May 1st 2023
First Patient In: May 16th 2023
Total Current Enrollment: 10 subjects (as of Sept 5th 2023)
Industry Funding Sources: BeiGene (trial funding and drug; zanubrutinib), Genentech (drug only; venetoclax and obinutuzumab), Adaptive Biotechnologies (research pricing on clonoSEQ® assay), NeoGenomics Inc. (research pricing on Neotype Lymphoid Discovery Panel®)
Foundation Grant Support: Conquer Cancer Foundation of the American Society of Clinical Oncology
Grant #: ASCO 221054-01 (Daniel Helbig, Awardee)

BeiGene Genentech A Member of the Roche Group Adaptive biotechnologies NEO GENOMICS CONQUER CANCER THE ASCO FOUNDATION YOUNG INVESTIGATOR AWARD

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