Chronic Lymphocytic Leukemia Clinical Trials

The following clinical trials are currently open and accruing for patients with CLL.

Contact Kalin Morrell (Assistant Clinical Research Manager), kalin_morrell@dfci.harvard.edu, 617-582-8713 to discuss a patient.

FRONTLINE TRIALS – NEWLY-DIAGNOSED PATIENTS

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See the following pages for more information about these trials.

These trials are offered through Dana-Farber/Harvard Cancer Center, an NCI-designated Comprehensive Cancer Center.
FRONTLINE TRIALS FOR NEWLY-DIAGNOSED PATIENTS

18-226: A phase 2 study of acalabrutinib, venetoclax, and obinutuzumab (AVO) for initial therapy of chronic lymphocytic leukemia

Rationale: The purpose of this phase 2 frontline trial is to assess the rate of bone marrow MRD-negative complete response after 15 cycles of treatment with AVO in CLL patients, as well as to study the safety and tolerability of the AVO combination. The rationale for combining these three novel agents is that the combination may lead to deeper responses and achievement of deeper responses may lead to longer remissions. The achievement of deeper responses may also allow for discontinuation of therapy, lessening toxicities, improving adherence and decreasing financial burden on patients. Finally, the combination of novel agents may reduce toxicities compared to each agent given as monotherapy.

Key Eligibility Criteria:
- Patients must not have received any prior systemic therapy for CLL or SLL due to previously meeting IWCLL 2018 guidelines and must currently have an indication for treatment as defined by the IWCLL 2018 guidelines.
- Participants who have a history of other malignancies except:
  - Malignancy treated with curative intent and with no known active disease present and felt to be at low risk for recurrence by treating physician
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
  - Adequately treated carcinoma in situ without evidence of disease
  - Low risk prostate cancer on active surveillance
- Currently active, clinically significant cardiovascular disease such as controlled arrhythmia or class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction unstable angina or acute coronary syndrome within 6 months prior to randomization

Treatment Schedule:
Patients will start on cycle 1 day 1 with one month of acalabrutinib monotherapy. Obinutuzumab will be introduced on day 1 of cycle 2 and will be administered at standard dosing for six monthly cycles with acalabrutinib continued. Venetoclax will be introduced at the beginning of cycle 4 for triplet combination therapy. Venetoclax will be initiated in a ramp-up stepwise dosing strategy with frequent tumor lysis syndrome monitoring. After the completion of obinutuzumab, venetoclax, and acalabrutinib, combination therapy will continue through cycle 15. At the conclusion of cycle 15, patients who have achieved a complete remission with MRD-negativity in the peripheral blood and bone marrow will discontinue acalabrutinib and venetoclax and will be monitored for disease recurrence with peripheral blood MRD testing by flow cytometry every three cycles.

Principal Investigator: Matthew Davids, MD, MMsc

Slots Available at Last Update: Slots will vary. Please email us for the latest slot availability.

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17-544: An international, phase 3, open-label, randomized study of BGB-3111 compared with bendamustine plus rituximab in patients with previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma

**Rationale:** This is a randomized, phase 3 study of BGB-3111 versus B+R in patients with previously untreated CLL or SLL. This study’s purpose is to examine the effects of the BGB-3111 (zanubrutinib) versus B+R therapy in patients without del(17p), which will be measured by progression-free survival.

**Key Eligibility Criteria:**
- Patients must be diagnosed with CD-20 positive CLL or SLL, Binet Stage C disease, or Binet Stage B or A disease requiring treatment as defined by at least one of the following: progressive marrow failure; massive, progressive or symptomatic splenomegaly; massive, progressive or symptomatic lymphadenopathy; progressive lymphocytosis with rapid doubling time; autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids; or constitutional symptoms
- Patients must be ≥ 65 years of age at time of informed consent, or < 65 years of age and unsuitable for chemoimmunotherapy with FCR, per physician opinion

**Treatment Schedule:**
In Arm A/C, the patient will present once for cycles 1-7 and then once every three cycles after cycle 7 (10, 13, etc.). The drug will be administered orally twice per day for as long as the patient is on trial and not progressing. In Arm B, the patient will present three days in cycle 1, and then one day in cycles 2-6. They will then come in every 3 cycles for follow up visits after the completion of drug (7, 10, 13 etc.). The patient will receive drug intravenously on days 1 and 2 of cycles 1-6.

**Principal Investigator:** Jennifer Brown, MD, PhD

**Slots Available at Last Update:** 21. Please email us for the latest information.
16-596: CRC043: A phase 2 study of venetoclax in combination with dose-adjusted EPOCH-R for the therapy of patients with Richter’s syndrome

**Rationale:** The purpose of this phase 2 trial is to analyze the rate of complete response (CR) of venetoclax plus dose-adjusted R-EPOCH for patients with Richter’s syndrome (RS) of chronic lymphocytic leukemia (CLL). In addition, the study aims to closely access the overall survival and the safety of this regimen. This study seeks to garner an effect of treating RS using a unique and promising approach.

**Key Eligibility Criteria:**
- Confirmed diagnosis of CLL or SLL with a biopsy showing transformation to DLBCL
- Age greater than or equal to 18 years
- Patient must have adequate coagulation, renal, and hepatic function

**Treatment Schedule:**
The first cycle (28 days) begins with just the chemotherapy and then the venetoclax is ramped up daily at the end of the cycle. This is used to determine if the patient could tolerate the regimen. Cycles 2-6 (21 days) are known as the combination phases which involve both R-EPOCH and venetoclax simultaneously. Cycle 7 to the off-treatment cycle (28 days/cycle) are known as the maintenance phases and patients are only on venetoclax. The patient is monitored carefully, and the trial’s efficacy is analyzed by PET/CT scans. At this point, the window for the patients’ visit dates are increased so patients could come in earlier or later as needed. As the patients progress through the phase, they start coming in less frequently. At present, the trial has accrued 18 of 24 total patients who require subsequent survival follow-up visits or are currently in the early stages of the study.

**Principal Investigator:** Matthew Davids, MD, MMSc

**Slots Available at Last Update:** Slots will vary. Please email us for the latest slot availability.

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**TRIALS FOR PATIENTS WITH RELAPSED/REFRACTORY DISEASE**

17-558: A phase 1, open-label, multicenter study to assess the safety, tolerability, pharmacokinetics and preliminary antitumor activity of ascending doses of AZD5991 in patients with relapsed or refractory hematologic malignancies

**Rationale:** The purpose of this phase 1, open-label multicenter study is to assess the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of ascending doses of AZD5991 in patients with relapsed/refractory hematologic malignancies. Hematologic malignancies include: non-Hodgkin’s lymphoma, Richter’s syndrome, CLL/SLL, T-cell lymphoma (including cutaneous), multiple myeloma, acute myeloid leukemia, acute lymphoblastic leukemia, and myelodysplastic syndrome. The study is broken up into two arms: The first arm includes NHL, CLL, and MM patients; the second arm includes AML, ALL, and MDS patients. Additionally, the study aims to assess the urine pharmacokinetic parameters, pharmacodynamics, and assess the biomarkers that may correlate with response or resistance of AZD5991.

**Key Eligibility Criteria:**

- Diagnosis of any of the following hematologic malignancies and histologically proven based on criteria established by the World Health Organization (WHO) as documented by medical records:
  - Non-Hodgkin lymphoma
  - Richter’s syndrome
  - CLL/small lymphocytic lymphoma (SLL)
  - T-cell lymphoma including cutaneous
- Must have received at least 2 prior lines of therapy for the treatment of current histology; there are no treatment options available known to provide clinical benefit. Refer to National Comprehensive Cancer Network (NCCN) guidelines of each respective histology for guidance.
- Documented active disease requiring treatment per respective NCCN guideline that is relapsed or refractory defined as:
  - Recurrence of disease after response to prior line(s) of therapy
  - Or progressive disease after completion of the treatment regimen preceding entry into the study

**Treatment Schedule:**
Patients will be assigned to either a weekly or daily dose escalation schema where they will be admitted at Brigham and Women’s Hospital. After the patients escalate to the cohort specified dose, patients will present to clinic for treatment once a week over the course of nine 21-day cycles. After completing all nine cycles of treatment, patients will continue to present to clinic every 3 months for follow up.

**Principal Investigator:** Matthew Davids, MD, MMSc

**Slots Available at Last Update:** Slots will vary. Please email us for the latest slot availability.

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**CLL Clinical Trials, Dana-Farber/Brigham and Women’s Cancer Center.**
These trials are conducted through Dana-Farber/Harvard Cancer Center, an NCI-designated Comprehensive Cancer Center.
18-089: A phase 1/2 study of duvelisib and venetoclax in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma

**Rationale:** The purpose of the phase 1 portion of this open-label study will be to determine the maximum tolerated dose, schedule, safety and tolerability of duvelisib in combination with venetoclax. The phase 2 portion of this study will serve to determine the rate of complete response in combination with the maximum tolerated dose of venetoclax. Additionally, the phase 1 portion of this study aims to evaluate the pharmacokinetics of both duvelisib and venetoclax. The phase 2 portion of this study also aims to evaluate primary efficacy, including objective response rate, duration of response among those patients who have achieved a partial or complete response, progression free survival, and overall survival. The objective is to determine the rate of minimal residual disease in the bone marrow at 6-months, one and two years, or every 3 months if MRD -negativity is achieved in the blood, and to determine the association of FISH abnormalities, TP53, NOTCH1, or SF3B1 mutations, ZAP70 expression, and IGHV mutational status with ORR and CR rate.

**Key Eligibility Criteria:**
- Must have a confirmed diagnosis of chronic lymphocytic leukemia or small lymphocytic lymphoma requiring therapy, as per IW-CLL 2008 criteria
- Disease that has progressed during or relapsed after at least one previous CLL/SLL therapy
- Must not have any previous treatment with venetoclax or duvelisib

**Treatment Schedule:**
Patients will be admitted at Brigham and Women’s hospital once per week during the dose escalation portion of the trial, then weekly for 1 month, monthly for 3 months, every 2 months for 8 months, and then every 3 months until disease progression.

**Principal Investigator:** Matthew Davids, MD, MMSc

**Slots Available at Last Update:** 38. Please email us for the latest information.

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18-164: A phase 1, open-label, study of voruciclib in patients with relapsed and/or refractory B-cell malignancies after failure of prior standard therapies

Rationale: The purpose of this phase 1, open label study is to determine the safety and tolerability of voruciclib and determine the maximum tolerated dose in patients with relapsed/refractory B-cell malignancies. B-cell malignancies in this study include follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, CLL/SLL, and diffuse large B-cell lymphoma. Additionally, the study aims to evaluate the potential efficacy of voruciclib as assessed by overall response rate, the sum of complete response/remission, complete remission with incomplete marrow recovery, and partial response; duration of response; rate of CR/CRi; and progression free survival. The study also aims to evaluate the pharmacokinetics of voruciclib, determine the effect of voruciclib on expression and function of proteins in the apoptotic pathway in patients with CLL, and correlate anti-tumor activity with baseline tumor characteristics.

Key Eligibility Criteria:
- Histologically-confirmed diagnosis of FL, MCL, marginal zone lymphoma (MZL), SLL, CLL, or DLBCL, and patients must have disease that has relapsed or is refractory to 2 or more prior regimens and in need of treatment due to progressive disease (PD).
- Patient must NOT have (for CLL only) known histological transformation to an aggressive lymphoma (e.g., Richter transformation).
- Presence of measurable disease defined per the 2008 International workshop on CLL guidelines, or by 2014 Lugano criteria for non-Hodgkin lymphoma

Treatment Schedule:
Patients will present to clinic once a week for 1 month, then every other week for one month, then monthly for 6 months. Currently, there is no follow-up period defined in the protocol.

Principal Investigator: Matthew Davids, MD, MMSc

Slots Available at Last Update: Slots will vary with the sponsor. Please email us for the latest information.
17-662: A two-arm, phase 1b, open-label, dose escalation study of ME-401 in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or follicular lymphoma (FL) and an open-label study of ME-401 in combination with rituximab in patients with relapsed/refractory CLL/SLL or B-cell non-Hodgkin’s lymphoma

Rationale: This is a phase 1b dose escalation study of ME-401 in patients with relapsed/refractory CLL/SLL or FL as well as a study of ME-401 in combination with rituximab in patients with relapsed/refractory CLL/SLL or B-cell non-Hodgkin’s lymphoma. This study serves to determine the biologically effective dose, maximally tolerated dose and dose limiting toxicities of ME-401. In the ME-401 with rituximab combination therapy, the purpose is to determine the safety of the combination therapy.

Key Eligibility Criteria:
- In ME-401 alone study: the patients need to be diagnosed with relapsed or refractory CLL/SLL or FL, have no prior therapy with PI3Kδ inhibitors, and have not had any prior BTK inhibitor therapies, unless the subject was intolerant of the BTK therapy
- Patients must also be ≥ 65 years of age at time of informed consent, or < 65 years of age and unsuitable for chemoimmunotherapy with FCR, per physician opinion
- In ME-401+Rituximab study: patients need to be diagnosed with relapsed/refractory CLL or relapsed/refractory SLL or FL, MZL, or DLBCL, have no prior therapy with PI3Kδ inhibitors, and have not had any prior BTK inhibitor therapies, unless the patient was intolerant of the BTK therapy

Treatment Schedule:
Patients will present for five visits in cycle 1, two visits in cycles 2 and 3, one visit in cycles 4-7, 9, 11, 13 and then one visits every three cycles starting at 16 (16, 19, 22 etc.). Patients receiving ME-401 will be administered the drug orally in the dose depending on the cohort they are assigned, and those in the ME-401 +Rituximab will require a combination of oral ME-401 and intravenous rituximab.

Site Principal Investigator: Jennifer Brown, MD, PhD

Slots Available at Last Update: 22. Please email us for the latest information.

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17-139: A phase 1B/2 dose-escalation and cohort-expansion study of the noncovalent, reversible Bruton’s tyrosine kinase inhibitor, SNS-062, in patients with B-lymphoid malignancies

**Rationale:** This is a phase 1b/2 dose escalation study of the noncovalent, reversible BTK inhibitor SNS-062 in patients with B-lymphoid malignancies. The purpose of this study is to examine the safety and pharmacology of a range of SNS-062 dose levels administered to patients with previously treated B-lymphoid malignancies, including: CLL/SLL, LPL/WM, MCL, diffuse large B-cell lymphoma of the activated B-cell subtype (DLBCL-ABC), and follicular lymphoma (FL). SNS-062 is a novel BTK inhibitor that maintains potent inhibitory activity against C481S-mutated BTK that is resistant to inhibition by ibrutinib.

**Key Eligibility Criteria:**
- Patients must have confirmed relapsed/refractory disease after ≥2 lines of standard systemic therapy including prior BTK inhibitor therapy in CLL, LPL/WM or MCL and after ≥2 lines of standard systemic therapy in DLBCL-ABC or FL
- For the 1b/2 portion, patients need to be determined to have a functional BTK C481 mutation (i.e., BTK C481S) or a resistance or gain of function mutation(s) (i.e., PLCγ2 R665W).
- For the phase 2 portion patients need to meet the following criteria depending on the disease:
  - CLL: the presence of a functional BTK C481 mutation (i.e., ≥1% BTK C481 mutation), and absence of a different resistance or gain of function mutation (i.e., PLCγ2 R665W) or the absence of a functional BTK C481mutation alone
  - LPL/WM: no mutational requirement
  - MCL: no mutational requirement

**Treatment Schedule:**
Patients will present for five visits in cycle 1, two visits in cycles 2 and 3, one visit in cycles 4-7, 9, 11, 13 and then one visits every three cycles starting at 16 (16, 19, 22 etc.). Patients receiving ME-401 will be administered the drug orally in the dose depending on the cohort they are assigned, and those in the ME-401 +Rituximab will require a combination of oral ME-401 and intravenous rituximab.

**Site Principal Investigator:** Jennifer Brown, MD, PhD

**Slots Available at Last Update:** 10. Please email us for the latest information.