Chronic Lymphocytic Leukemia Clinical Trials

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

Contact Jillian Foreman (Clinical Research Manager), jillianm_foreman@dfci.harvard.edu, 617-582-8713 to discuss a patient.

**FRONTLINE TRIALS – NEWLY-DIAGNOSED PATIENTS**

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**TRIALS FOR RELAPSED/REFRACTORY PATIENTS**

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To discuss a patient, email jillianm_foreman@dfci.harvard.edu

### RICHTER’S SYNDROME

| 18-089  | A phase 1/2 study of duvelisib and venetoclax in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma |
| 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 |

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.

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*CLL Clinical Trials, Dana-Farber/Brigham and Women’s Cancer Center.*

These trials are conducted through Dana-Farber/Brigham 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 the risk of resistance 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
- Must have either del(17p) or \TP53 mutation
- Patients with B-prolymphocytic leukemia are also eligible

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 have the option to discontinue acalabrutinib and venetoclax and will be monitored for disease recurrence with peripheral blood MRD testing by flow cytometry every three cycles. Those who have not achieved such a remission or choose to stay on therapy will be re-evaluated at the conclusion of cycle 24, with similar guidelines for treatment discontinuation at that time.

Principal Investigator: Matthew Davids, MD, MMSc

Slots Available at Last Update: 35 slots are currently open for patients with del(17p), \TP53 mutations, or B-PLL. 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.
19-196: A randomized, multicenter, open-label, phase 3 study to compare the efficacy and safety of acalabrutinib (ACP-196) in combination with venetoclax with and without obinutuzumab compared to investigator’s choice of chemoimmunotherapy in patients with previously untreated chronic lymphocytic leukemia without del(17p) or TP53 mutation

**Rationale:** This randomized, open-label, phase 3 study will evaluate the efficacy and safety of AV (acalabrutinib + venetoclax) and AVG (AV + obinutuzumab) versus chemoimmunotherapy (FCR or BR) in patients with previously untreated CLL without del(17p) or TP53 mutation. Despite the potential for prolonged PFS with MRD negativity with chemoimmunotherapy, both FCR and BR are still associated with toxicities due to the nonspecific mechanism of action of conventional chemotherapeutic agents. There currently exists a need for frontline chemotherapy-free regimens in patients with few comorbidities that can offer improved outcomes with less toxicity and fixed duration of treatment. This study will evaluate the efficacy of AV and AVG compared with chemoimmunotherapy (FCR or BR).

**Key Eligibility Criteria:**
- Confirmed diagnosis of CLL that meets published diagnostic criteria
- No detected del(17p) or TP53 mutation
- No prior CLL-specific therapies
- No disease transformation of CLL

**Treatment Schedule:**

Arm A (AV)
- The AV treatment regimen consists of 12 cycles of venetoclax (oral) and 14 cycles of acalabrutinib (oral), with each cycle having a duration of 28 days. Acalabrutinib will start on cycle 1 day 1 and venetoclax will begin on cycle 3 day 1. Patients will present in clinic once during the first two cycles, 4 times during the 3rd cycle and one day per cycle thereafter.

Arm B (AVG)
- The AVG treatment regimen consists of 6 cycles obinutuzumab (infusion), 12 cycles of venetoclax (oral), and 14 cycles of acalabrutinib (oral), with each cycle having a duration of 28 days. Acalabrutinib will start on cycle 1 day 1, obinutuzumab will start on cycle 2 day 1 and venetoclax will begin on cycle 3 day 1 and continue for 12 cycles. Patients will present in clinic once during the first cycle, 4 times during the second cycle, 4 times during the third cycle (with a possibility for admission) and one day per cycle thereafter.

Arm C (BR or FCR)
- FCR - Fludarabine and Cyclophosphamide will be administered as an IV infusion on Days 1–3 of a 28-day cycle for a maximum of 6 cycles. Rituximab will be administered as an IV infusion on day 1 of a 28-day cycle for a maximum of 6 cycles.
- BR - Bendamustine will be administered as an IV infusion on Days 1–2 of a 28-day cycle. Rituximab will be administered as an IV infusion on day 1 of a 28-day cycle for a max. of 6 cycles.

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

**Slots Available at last update:** Please email 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 Bcl-2 inhibitor venetoclax is highly effective in CLL, but resistance to this drug may develop due to increasing reliance on a different anti-apoptotic protein, Mcl-1. 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 a novel MCL-1 inhibitor, 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.

Key Eligibility Criteria:
- Diagnosis of any of the following hematologic malignancies
  - 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.
- 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 a daily dose escalation schema where they will be admitted at Brigham and Women’s Hospital for dosing of this intravenous drug. After the patients escalate to the cohort specified dose, patients will present to clinic for treatment once or twice 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.

To discuss a patient, email jillianm_foreman@dfci.harvard.edu
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 2 portion of this open-label study is to determine the rate of complete response (CR) of duvelisib in combination with the MTD of venetoclax, as defined by the IWCLL 2008 criteria for CLL/SLL or Lugano 2014 Criteria for RS. The phase 2 portion of this study also aims to evaluate 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, and every 3 months 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
- Patients with Richter’s Syndrome are now also eligible for the trial and will be accrued in a separate cohort from the CLL/SLL patients

**Treatment Schedule:**
Patients will receive one week of duvelisib monotherapy as an outpatient and in week 2 will continue the duvelisib and begin the venetoclax dose ramp-up, with the schedule and monitoring plan based on the individual patient’s risk for TLS based on the venetoclax FDA label. High TLS risk patients will be admitted each week for venetoclax dose ramp-up, and medium or low risk patients can be escalated in the outpatient setting. Study visits then occur monthly for 3 months, every 2 months for through the first 8 months, and then every 3 months thereafter until disease progression or unacceptable toxicity. Patients who achieve MRD-negative CR after 1 year of therapy will have the option to discontinue therapy and may resume therapy if they later progress.

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

**Slots Available at Last Update:** Phase 2 cohort recently opened with initial availability of 12 slots. 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, complete response, and partial response; duration of response; 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 intrinsic 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 known histological transformation of CLL to an aggressive lymphoma (e.g., Richter transformation).
- Presence of measurable disease defined per 2008 CLL criteria, or by 2014 Lugano criteria for non-Hodgkin lymphoma

**Treatment Schedule:**
Voruciclib is an oral medication that patients take daily at the dose assigned to their particular cohort. Patients will present to clinic once a week for 1 month, then every other week for one month, then monthly for 6 months, and every 2 months thereafter until disease progression or unacceptable toxicity.

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

**Slots Available at Last Update:** Slots availability will vary. 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 (vecabrutinib) in patients with B-lymphoid malignancies. The purpose of this study is to examine the safety and pharmacology of a range of vecabrutinib 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). Vecabrutinib 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 during active treatment with a BTK inhibitor; those who stop for adverse events and subsequently progress are not eligible.
  - After ≥2 lines of standard systemic therapy including prior BTK inhibitor therapy in CLL, LPL/WM or MCL
  - After ≥2 lines of standard systemic therapy in DLBCL-ABC or FL

Treatment Schedule:
Patients will present weekly for two cycles, monthly for cycles 3-5, every other cycle for cycles 5-9 and then every 3 cycles from cycle 12 onwards. Patients receiving vecabrutinib will be administered the drug orally, twice per day. Each cycle is 28 days.

Site Principal Investigator: Jennifer Brown, MD, PhD

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

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To discuss a patient, email jillianm_foreman@dfci.harvard.edu

18-636: A phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in adult patients with relapsed/refractory chronic lymphocytic leukemia

**Rationale:** Evaluate the safety of the CD19-targeted CAR-T therapy KTE-C19 in patients with R/R CLL and to evaluate the efficacy of KTE-C19 as measured by the objective response rate (ORR) per independent review in patients with R/Rr/r CLL treated with KTE-C19.

**Key Eligibility Criteria:**
- Documentation of relapsed or refractory CLL AND a minimum of two prior treatment regimens with progression on treatment with ibrutinib
- Patients with Richter’s transformation are excluded.
- No evidence, suspicion and/or history of central nervous system (CNS) involvement of lymphoma
- No prior CAR T-cell therapy

**Treatment Schedule:**
Patients will undergo leukapheresis for collection of T cells. After successful manufacturing of CAR T-cells, patients will receive 3 days of outpatient conditioning chemotherapy followed by a single infusion of axicabtagene ciloleucel KTE-C19 in the hospital, where they will remain for a minimum of 7 additional days, or until CAR T-cell related toxicities resolve to grade 1 or better. Initial re-staging occurs 30 days after CAR-T infusion. Protocol visits and restaging subsequently occur every 6 months until month 60, then yearly through year 15.

**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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19-021: A phase 1/2 study of oral LOXO-305 in patients with previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or non-Hodgkin lymphoma (NHL)

Rationale: LOXO is a phase 1/2 study using the drug, LOXO-305, which is a small molecule that binds to the ATP site of the BTK kinase, prevents ATP from binding and inhibits BTK’s kinase activity. LOXO-305 causes potent dose-dependent inhibition of BTK kinase activity and tumor growth in multiple biologically relevant BTK-dependent model systems in vitro and in vivo, including B-cell lymphoma cell lines. The primary objective for the phase 1 study is to determine the maximum tolerated dose of oral LOXO-305 with previously treated chronic lymphocytic leukemia/ small lymphocytic lymphoma and non-Hodgkin’s lymphoma. The primary objective for the phase 2 study is to assess the preliminary anti-tumor activity of LOXO-305 based on ORR as assessed by an Independent Review committee.

Key Eligibility Criteria:
- Adequate hematologic status, defined as the following on C1D1 prior to treatment
  - Absolute neutrophil count (ANC) 0.75 x 10^9/L and not requiring growth factors; if there is documented bone marrow involvement, growth factors (pegfilgastrim preferred) may be used at any time prior to C1D1 to achieve this ANC threshold
  - Platelet count 50 x 10^9/L not requiring transfusion support; if there is documented bone marrow involvement, platelet transfusion may be used prior to 7 days before C1D1 to achieve this ANC threshold
  - Hemoglobin (Hb) 8 mg/dL not requiring transfusion support or growth factors; if there is documented bone marrow involvement, growth factors (e.g., epoetin alpha) may be used at any time prior to C1D1 to achieve this Hb threshold
- At least 2 prior lines of therapy
- No more than 2 prior chemotherapy-containing treatment regimens
- Patients must have prior BTK inhibitor exposure but may have discontinued for adverse events or had disease progression.

Treatment Schedule:
Patients will receive the assigned LOXO-305 dose on C1D1 in clinic. Patients will continue dosing daily and will return to clinic on days 8 and 15 of cycle 1. Patients will then return to clinic on day 1 of each subsequent cycle until EOT. Patients will continue LOXO-305 dosing until PD, unacceptable toxicity other reason for treatment discontinuation. Patients with documented PD may be allowed to continue LOXO-305 if the patient is tolerating study drug and in the opinion of the Investigator, the patient is deriving clinical benefit from continuing study drug.

Principal Investigator: Jennifer Brown, MD PhD

Slots Available at Last Update: Slots will vary but are continuously available as we can add patients to older cohorts. Please email us for the latest slot availability.

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19-073: A phase 3, randomized study of zanubrutinib (BGB-3111) compared with ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma

Rationale: B-cell receptor signaling plays a major role in B-cell development and survival of CLL cells. BTK has a relevant role in the signal transduction of the B-cell receptor and inhibiting its function can lead to reduced growth of CLL cells. Both ibrutinib and zanubrutinib have been shown to be effective BTK inhibitors with zanubrutinib being better tolerated across studies. This study seeks to compare the efficacy and safety of zanubrutinib versus ibrutinib in treating CLL/SLL as measured by the ORR (Overall Response Rate) determined by independent central review.

Key Eligibility Criteria:
- Relapsed or refractory to ≥1 prior systemic therapy for CLL/SLL
- Last dose of prior therapy for CLL/SLL more than 14 days before randomization
- Measurable disease (≥1 lymph node that’s >1.5 cm in longest diameter, and measurable in 2 perpendicular diameters)
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy

Treatment Schedule:
Patients will present to clinic every 4 weeks (monthly) for the first six cycles for assessments. The patients will then come in every three cycles (C7, C10, C13, etc.) until cycle 25. After cycle 25, the patients will be scheduled to come in every six cycles (C25, C31, C37, etc.) until off treatment. The Zanubrutinib arm (Arm A) will receive drug at site and will take it orally twice daily. The Ibrutinib arm (Arm B) will receive drug commercially from the site (reimbursed by the study) and will take it orally once daily.

Principal Investigator: Jennifer Brown, MD PhD

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

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