# Oncology Clinical Pathways

## Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)

March 2025 – V1.2025

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# CLL and SLL – Presumptive Conditions

VA automatically presumes that certain disabilities were caused by military service. This is because of the unique circumstances of a specific Veteran's military service. If a presumed condition is diagnosed in a Veteran within a certain group, they can be awarded disability compensation.

Atomic Veterans – Exposure to Ionizing Radiation

- Lymphomas, other than Hodgkin's disease

Vietnam Veterans – Agent Orange Exposure or Specified Locations

- Chronic lymphocytic leukemia

Gulf War and Post 9/11 Veterans

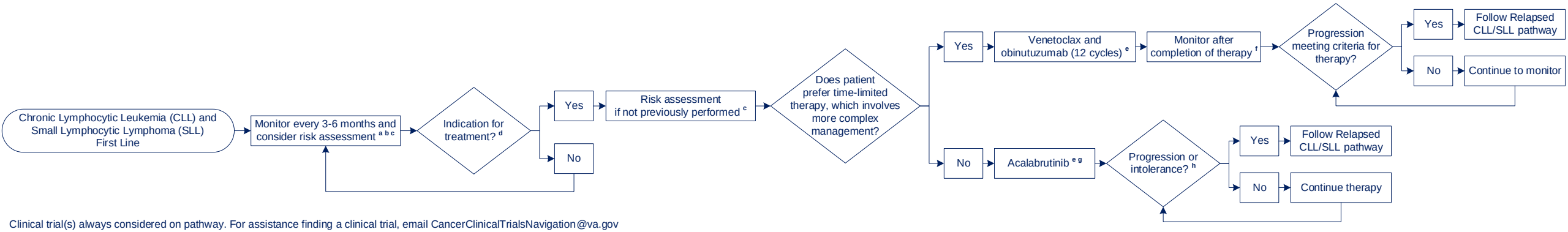
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if the patient served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- Lymphatic cancer of any type
- Lymphoma of any type
- Chronic leukemias

* The Southwest Asia theater of operations refers to Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above these locations.

For more information, please visit U.S. Department of Veterans Affairs - Presumptive Disability Benefits (va.gov); VA makes several cancers presumptive for service connection Jan 08 2025; eCFR :: 38 CFR 3.320b -- Presumptive service connection for leukemias, multiple myelomas, myelodysplastic syndromes, and myelofibrosis.

# CLL and SLL – First Line




Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov

[a] **General Supportive Care for CLL/SLL** includes IVIG for hypogammaglobulinemia and frequent infections, vaccinations (e.g. COVID, influenza, pneumococcus, and varicella-zoster virus); do not administer live attenuated vaccines; screen for secondary malignancies, particularly non-melanoma skin cancers

[b] **Monitor** consider hepatitis B and C and HIV testing at baseline; monitoring frequency dependent on current symptoms, patient preference, absolute lymphocyte doubling time

[c] **Risk Assessment** using CLL/SLL IPI score which includes CLL/SLL FISH panel, TP53 mutation status, serum beta-2-microglobulin, IGHV mutation status, Rai or Binet staging, and age; also consider checking FISH t(11;14) to rule out mantle cell lymphoma, and CpG-stimulated karyotype; CLL FISH panel should include probes for: 13q, 17p, 11q, and 12

[d] **Indications for Treatment** include anemia (Hgb <10 g/dL) hemoglobin < 10 g/dL, platelets < 100,000/mm3, thrombocytopenia/anemia must be non-immune and not related to alternate causes, B-symptoms, and symptomatic adenopathy; consider cross-sectional imaging prior to initiation of therapy

[e] **Supportive Care and Pre-Treatment Evaluation During Therapy Includes**: 1) Hepatitis B serologies if not already checked, particularly with anti-CD20 antibodies (rituximab, obinutuzumab, ofatumumab), 2) TLS risk stratification prior to Venetoclax initiation, with prevention strategies as recommended by manufacturer, 3) provide COVID prophylaxis dependent on availability, and 4) consider HSV/VZV prophylaxis

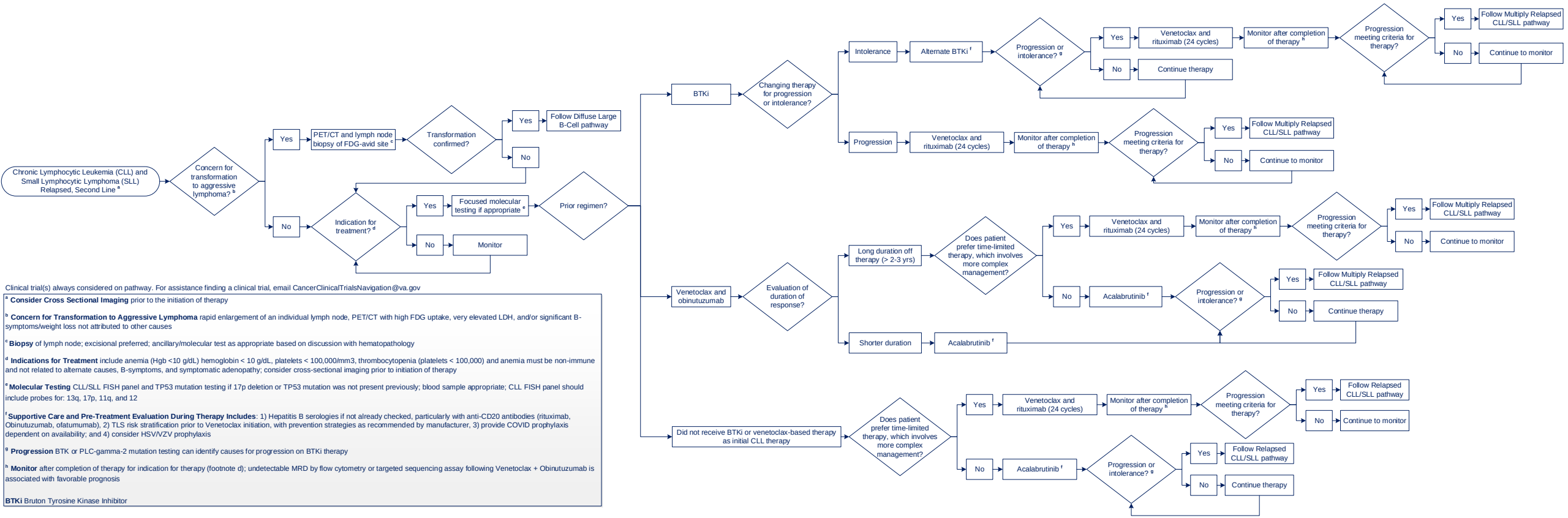
[f] **Monitor** after completion of therapy for indication for therapy (footnote d); undetectable MRD by flow cytometry or targeted sequencing assay following venetoclax + obinutuzumab is associated with favorable prognosis

[g] **BTK Inhibitor** avoid BTKi in severe hepatic impairment

[h] **Progression** BTK or PLC-gamma-2 mutation testing can identify causes for progression on BTKi therapy but is not recommended

**BTKi** Bruton Tyrosine Kinase Inhibitor

# CLL and SLL – Relapsed, Second Line




Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov

[a] **Consider Cross Sectional Imaging** prior to the initiation of therapy

[b] **Concern for Transformation to Aggressive Lymphoma** rapid enlargement of an individual lymph node, PET/CT with high FDG uptake, very elevated LDH, and/or significant B-symptoms/weight loss not attributed to other causes

[c] **Biopsy** of lymph node; excisional preferred; ancillary/molecular test as appropriate based on discussion with hematopathology

[d] **Indications for Treatment** include anemia (Hgb <10 g/dL) hemoglobin < 10 g/dL, platelets < 100,000/mm3, thrombocytopenia (platelets < 100,000) and anemia must be non-immune and not related to alternate causes, B-symptoms, and symptomatic adenopathy; consider cross-sectional imaging prior to initiation of therapy

[e] **Molecular Testing** CLL/SLL FISH panel and TP53 mutation testing if 17p deletion or TP53 mutation was not present previously; blood sample appropriate; CLL FISH panel should include probes for: 13q, 17p, 11q, and 12

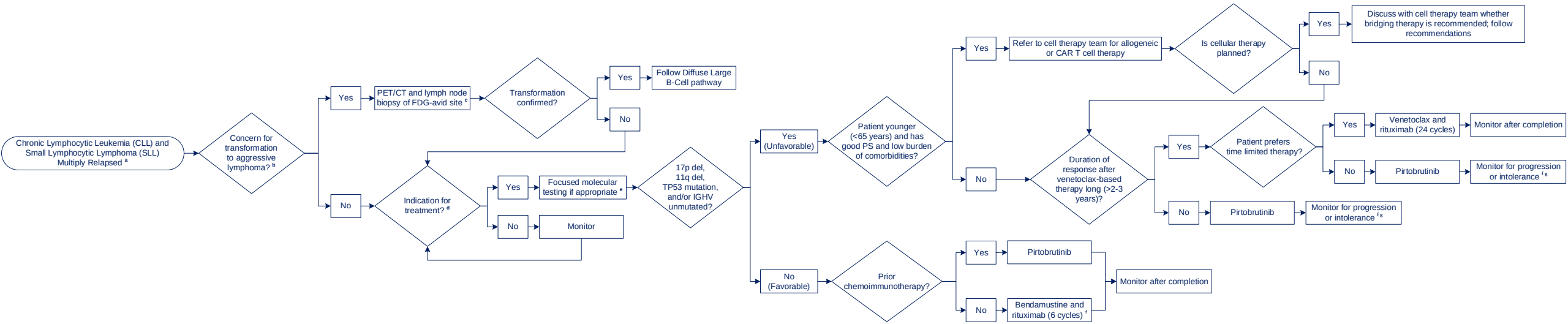
[f] **Supportive Care and Pre-Treatment Evaluation During Therapy Includes**: 1) Hepatitis B serologies if not already checked, particularly with anti-CD20 antibodies (rituximab, Obinutuzumab, ofatumumab), 2) TLS risk stratification prior to Venetoclax initiation, with prevention strategies as recommended by manufacturer, 3) provide COVID prophylaxis dependent on availability; and 4) consider HSV/VZV prophylaxis

[g] **Progression** BTK or PLC-gamma-2 mutation testing can identify causes for progression on BTKi therapy

[h] **Monitor** after completion of therapy for indication for therapy (footnote d); undetectable MRD by flow cytometry or targeted sequencing assay following Venetoclax + Obinutuzumab is associated with favorable prognosis

**BTKi** Bruton Tyrosine Kinase Inhibitor

# CLL and SLL – Multiply Relapsed




Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov

[a] **Relapsed** defined as previously treated with both BTKi and venetoclax-based therapy

[b] **Concern for Transformation to Aggressive Lymphoma** rapid enlargement of an individual lymph node, PET/CT with high FDG uptake, very elevated LDH, and/or significant B- symptoms/weight loss not attributed to other causes

[c] **Biopsy of Lymph Node** excisional preferred; ancillary/molecular test as appropriate based on discussion with hematopathology

[d] **Indications** include anemia (Hgb <10 g/dL) hemoglobin < 10 g/dL, platelets < 100,000/mm3, thrombocytopenia (platelets < 100,000) and anemia must be non-immune and not related to alternate causes, B-symptoms, and symptomatic adenopathy; consider cross-sectional imaging prior to initiation of therapy

[e] **Molecular Testing** IGHV mutation status and CLL/SLL FISH panel and TP53 mutation testing if 17p deletion or TP53 mutation was not present previously; blood sample appropriate; CLL FISH panel should include probes for: 13q, 17p, 11q, and 12

[f] **Supportive Care and Pre-Treatment Evaluation During Therapy Includes**: 1) Hepatitis B serologies if not already checked, particularly with CD20 antibodies (rituximab, Obinutuzumab, ofatumumab), 2) TLS risk stratification prior to Venetoclax initiation, with prevention strategies as recommended by manufacturer, 3) provide COVID prophylaxis dependent on availability, and 4) consider HSV/VZV prophylaxis

**BTKi** Bruton Tyrosine Kinase Inhibitor

# CLL and SLL – Molecular Testing Table

| Eligibility | Test Category | Test Type | Recommended Vendors | NPOP Coverage | Specimen Type |
|---|---|---|---|---|---|
| Initial Diagnosis of Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) | FISH | FISH panel should include probes for chromosomes 13q, 17p, 11q, and 12, t(11;14) | Local VA or locally contracted vendor | No | Bone Marrow Biopsy, Lymph Node Biopsy, Blood |
| | Molecular Testing | TP53 sequencing | Local VA or locally contracted vendor | No | Bone Marrow Biopsy, Lymph Node Biopsy, Blood |
| | Molecular Testing | IGHV hyper mutation status | Local VA or locally contracted vendor | No | Bone Marrow Biopsy, Lymph Node Biopsy, Blood |
| | Karyotyping | CpG-stimulated karyotype | Local VA or locally contracted vendor | No | Bone Marrow Biopsy, Lymph Node Biopsy, Blood |
| Relapsed Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) | FISH | FISH panel should include probes for chromosomes 13q, 17p, 11q, and 12 | Local VA or locally contracted vendor | No | Bone Marrow Biopsy, Lymph Node Biopsy, Blood |
| | Molecular Testing | TP53 (If alteration not detected previously) | Local VA or locally contracted vendor | No | Bone Marrow Biopsy, Lymph Node Biopsy, Blood |
| | Molecular Testing | BTK and PLCG2 sequencing (if BTK inhibitor resistant) | Local VA or locally contracted vendor | No | Bone Marrow Biopsy, Lymph Node Biopsy, Blood |
| Monitoring After Completion of Therapy | MRD Test | MRD detection by flow cytometry or NGS (if clinically indicated) | Local VA or locally contracted vendor | No | Bone Marrow Biopsy, Lymph Node Biopsy, Blood |