

# CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL) TREATMENT REGIMENS (Part 1 of 3)

**Clinical Trials:** The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are provided only to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

## CLL/SLL Without del(17p)/TP53 Mutation<sup>1</sup>

**Note:** All recommendations are Category 2A unless otherwise indicated.

### First-line therapy for frail patients with significant morbidities

REGIMEN	DOSING
<b>Obinutuzumab + chlorambucil (Category 1)<sup>2</sup></b>	<b>Day 1:</b> Obinutuzumab 100mg IV + chlorambucil 0.5mg/kg orally <b>Day 2:</b> Obinutuzumab 900mg IV <b>Day 8:</b> Obinutuzumab 1,000mg IV <b>Day 15:</b> Obinutuzumab 1,000mg IV + chlorambucil 0.5mg/kg orally. Repeat cycle every 28 days for 6 cycles with obinutuzumab given at a dose of 1,000mg IV on day 1 of subsequent cycles.
<b>Ibrutinib (Category 1)<sup>3</sup></b>	Ibrutinib 420mg orally once daily until disease progression or unacceptable toxicity.
<b>Ofatumumab + chlorambucil<sup>4</sup></b>	<b>Cycle 1</b> <b>Day 1:</b> Ofatumumab 300mg IV <b>Days 1–7:</b> Chlorambucil 10mg/m <sup>2</sup> orally <b>Day 8:</b> Ofatumumab 1,000mg IV <b>Subsequent Cycles</b> <b>Day 1:</b> Ofatumumab 1,000mg IV <b>Days 1–7:</b> Chlorambucil 10mg/m <sup>2</sup> orally. Repeat cycle every 28 days for a maximum of 12 cycles.
<b>Rituximab + chlorambucil<sup>5</sup></b>	<b>Cycle 1</b> <b>Days 1–7:</b> Chlorambucil 8mg/m <sup>2</sup> /day orally <b>Cycle 3</b> <b>Day 1:</b> Rituximab 375mg/m <sup>2</sup> IV <b>Days 1–7:</b> Chlorambucil 8mg/m <sup>2</sup> /day orally <b>Cycle 4–8</b> <b>Day 1:</b> Rituximab 500mg/m <sup>2</sup> IV <b>Days 1–7:</b> Chlorambucil 8mg/m <sup>2</sup> /day orally. Repeat cycle every 28 days; administer rituximab at dose of 375mg/m <sup>2</sup> IV every 2 months for 2 years as maintenance therapy.
<b>Obinutuzumab (Category 2B)<sup>6</sup></b>	<b>Cycle 1</b> <b>Day 1:</b> Obinutuzumab 100mg IV <b>Day 2:</b> Obinutuzumab 900mg IV <b>Day 3:</b> Obinutuzumab 1,000mg IV <b>Days 8 and 15:</b> Obinutuzumab 2,000mg IV <b>Cycles 2–8</b> <b>Day 1:</b> Obinutuzumab 2,000mg IV. Repeat cycle every 21 days.
<b>Rituximab (Category 3)<sup>7</sup></b>	<b>Day 1, 8, 15, and 22:</b> Rituximab 375mg/m <sup>2</sup> /day IV.
<b>Chlorambucil (Category 3)<sup>8,9</sup></b>	<b>Days 1–28:</b> Chlorambucil 0.4mg/kg/day with an increase to 0.8mg/kg orally daily. Repeat cycle every 28 days for 12 cycles.
<b>First-line therapy for patients age ≥65 with significant comorbidities</b>	
<b>Obinutuzumab + chlorambucil (Category 1)<sup>2</sup></b>	<b>Day 1:</b> Obinutuzumab 100mg IV + chlorambucil 0.5mg/kg orally <b>Day 2:</b> Obinutuzumab 900mg IV <b>Day 8:</b> Obinutuzumab 1,000mg IV <b>Day 15:</b> Obinutuzumab 1,000mg IV + chlorambucil 0.5mg/kg orally. Repeat cycle every 28 days for 6 cycles with obinutuzumab given at a dose of 1,000mg IV on day 1 of subsequent cycles.
<b>Ibrutinib (Category 1)<sup>3</sup></b>	Ibrutinib 420mg orally once daily until disease progression or unacceptable toxicity.
<b>Ofatumumab + chlorambucil<sup>4</sup></b>	<b>Cycle 1</b> <b>Day 1:</b> Ofatumumab 300mg IV <b>Days 1–7:</b> Chlorambucil 10mg/m <sup>2</sup> orally <b>Day 8:</b> Ofatumumab 1,000mg IV <b>Subsequent Cycles</b> <b>Day 1:</b> Ofatumumab 1,000mg IV <b>Days 1–7:</b> Chlorambucil 10mg/m <sup>2</sup> orally. Repeat cycle every 28 days for a maximum of 12 cycles.

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## CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL) TREATMENT REGIMENS (Part 2 of 3)

### CLL/SLL Without del(17p)/TP53 Mutation<sup>1</sup> (continued)

#### First-line therapy for patients age ≥65 with significant comorbidities (continued)

REGIMEN	DOSING
Rituximab + chlorambucil <sup>5</sup>	<p><b>Cycle 1</b> Days 1–7: Chlorambucil 8mg/m<sup>2</sup>/day orally</p> <p><b>Cycle 3</b> Day 1: Rituximab 375mg/m<sup>2</sup> IV Days 1–7: Chlorambucil 8mg/m<sup>2</sup>/day orally</p> <p><b>Cycle 4–8</b> Day 1: Rituximab 500mg/m<sup>2</sup> IV Days 1–7: Chlorambucil 8mg/m<sup>2</sup>/day orally. Repeat cycle every 28 days; administer rituximab at dose of 375mg/m<sup>2</sup> IV every 2 months for 2 years as maintenance therapy.</p>
Bendamustine ± rituximab <sup>10-12</sup>	<p>Day 0: Rituximab 375mg/m<sup>2</sup> IV Days 1 and 2: Bendamustine 70mg/m<sup>2</sup> IV. Repeat cycle every 28 days for 6 cycles with rituximab given at a dose of 500mg/m<sup>2</sup> on day 1 and bendamustine at a dose of 90mg/m<sup>2</sup> of subsequent cycles.</p>
Obinutuzumab (Category 2B) <sup>6</sup>	<p><b>Cycle 1</b> Day 1: Obinutuzumab 100mg IV Day 2: Obinutuzumab 900mg IV Day 3: Obinutuzumab 1,000mg IV Days 8 and 15: Obinutuzumab 2,000mg IV</p> <p><b>Cycles 2–8</b> Day 1: Obinutuzumab 2,000mg IV. Repeat cycle every 21 days.</p>
Chlorambucil (Category 3) <sup>8,9</sup>	<p>Days 1–28: Chlorambucil 0.4mg/kg/day with an increase to 0.8mg/kg orally daily. Repeat cycle every 28 days for 12 cycles.</p>
Rituximab (Category 3) <sup>7</sup>	<p>Day 1, 8, 15, and 22: Rituximab 375mg/m<sup>2</sup>/day IV</p>

#### First-line therapy for patients age <65 without significant comorbidities

Fludarabine + cyclophosphamide + rituximab (FCR) (Category 1) <sup>13-15a</sup>	<p>Day 1: Rituximab 375mg/m<sup>2</sup> IV Days 1–3: Fludarabine 25mg/m<sup>2</sup>/day IV plus cyclophosphamide 250mg/m<sup>2</sup>/day IV. Repeat cycle every 28 days for 6 cycles with rituximab given at a dose of 500mg/m<sup>2</sup> on day 1 of subsequent cycles.</p>
Fludarabine + rituximab (FR) <sup>16b</sup>	<p>Days 1–5: Fludarabine 25mg/m<sup>2</sup> IV Day 1: Rituximab 50mg/m<sup>2</sup> IV Day 3: Rituximab 325mg/m<sup>2</sup> IV Day 5: Rituximab 375mg/m<sup>2</sup> IV. Repeat cycle every 28 days for 6 cycles with rituximab given at a dose of 375mg/m<sup>2</sup> on day 1 of subsequent cycles.</p>
Pentostatin + cyclophosphamide + rituximab (PCR) <sup>17</sup>	<p>Day 1: Pentostatin 2mg/m<sup>2</sup> IV plus cyclophosphamide 600mg/m<sup>2</sup> IV, and rituximab 375mg/m<sup>2</sup> IV. Repeat cycle every 21 days for 6 cycles; administer rituximab thrice weekly at a dose of 100mg/m<sup>2</sup> on day 1, followed by 375mg/m<sup>2</sup> on days 3 and 5 of the first week only.</p>
Bendamustine ± rituximab <sup>10-12</sup>	<p>Day 1: Rituximab 375mg/m<sup>2</sup> IV Days 1 and 2: Bendamustine 90mg/m<sup>2</sup> IV. Repeat cycle every 28 days for 6 cycles with rituximab given at a dose of 500mg/m<sup>2</sup> on day 1 of subsequent cycles.</p>
Ibrutinib <sup>3</sup>	Ibrutinib 420mg orally once daily until disease progression or unacceptable toxicity.

### CLL/SLL With del(17p)/TP53 Mutation<sup>1</sup>

#### First-line therapy

Alemtuzumab ± rituximab <sup>18a</sup>	<p>Day 1: Alemtuzumab 3mg IV Day 2: Alemtuzumab 10mg IV Day 3, 10, 12, 17, 19, 24, and 26: Alemtuzumab 30mg IV Days 1, 8, 15, and 22: Rituximab 375mg/m<sup>2</sup> IV. Repeat cycle once depending on response and toxicity.</p>
High-dose methylprednisolone + rituximab <sup>19,20</sup>	<p>Days 1–3: Methylprednisolone 1g/m<sup>2</sup> IV Days 1, 8, 15, and 22: Rituximab 375mg/m<sup>2</sup> IV. Repeat cycle every 28 days for 3 cycles.</p>
Ibrutinib <sup>3</sup>	Ibrutinib 420mg orally once daily until disease progression or unacceptable toxicity.

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# CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL) TREATMENT REGIMENS (Part 3 of 3)

## CLL/SLL With del(17p)/TP53 Mutation<sup>1</sup> (continued)

### First-line therapy (continued)

REGIMEN	DOSING
<b>Obinutuzumab + chlorambucil (Category 3)<sup>2</sup></b>	<b>Day 1:</b> Obinutuzumab 100mg IV and chlorambucil 0.5mg/kg orally <b>Day 2:</b> Obinutuzumab 900mg IV <b>Day 8:</b> Obinutuzumab 1,000mg IV <b>Day 15:</b> Obinutuzumab 1,000mg IV and chlorambucil 0.5mg/kg orally. Repeat cycle every 28 days for 6 cycles with obinutuzumab given at a dose of 1,000mg on day 1.

a Data from the CLL10 study confirm the superiority of FCR over bendamustine plus rituximab (BR) in younger patients. For patients older than 65 years, the outcome was similar for both regimens with less toxicity for BR. BR may be a reasonable alternative for older patients otherwise eligible for chemoimmunotherapy and is associated with fewer myelosuppressive toxicities.

b Not for del(11q).

c While alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use. It is less effective for bulky (>5cm) lymphadenopathy. Monitor for cytomegalovirus reactivation.

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