

# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treatment Regimens

**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 only provided 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 National Comprehensive Cancer Network 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 NCCN 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.

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

## ► First-Line Therapy Without del (17p)/TP53 Mutation<sup>1</sup>

REGIMEN	DOSING
<b>Patients age ≥65 years OR &lt;65 years with significant comorbidities (creatinine clearance [CrCl] &lt;70mL/min)</b>	
<b>Preferred Regimens</b>	
Acalabrutinib (Category 1) <sup>2,5,a</sup>	<b>Days 1-28:</b> Acalabrutinib 100mg orally every 12 hours. Repeat cycle every 4 weeks.
Acalabrutinib + Obinutuzumab (Category 1) <sup>2,4,6,a,b</sup> <i>Obinutuzumab requires premedication.</i>	<b>Days 1-28:</b> Acalabrutinib 100mg orally twice daily Administer for one 4-week cycle, <b>followed by:</b> <b>Day 1 (Cycle 2):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 2):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 2):</b> Obinutuzumab 1,000mg, <b>followed by:</b> <b>Day 1 (Cycle 3-7):</b> Obinutuzumab 1,000mg IV <b>Days 1-28:</b> Acalabrutinib 100mg orally twice daily. Repeat cycle every 4 weeks for 6 cycles, <b>followed by:</b> Days 1-28: Acalabrutinib 100mg orally twice daily. Repeat cycle every 4 weeks.
Ibrutinib (Category 1) <sup>7,10,c</sup>	<b>Day 1-28:</b> Ibrutinib 420mg orally once daily. Repeat cycle every 4 weeks.
Venetoclax + Obinutuzumab (Category 1) <sup>6,11,13,b,d,e</sup> <i>Obinutuzumab requires premedication.</i>	<b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Obinutuzumab 1000mg IV. Repeat cycle every 4 weeks for 6 cycles, <b>with:</b> <b>Days 22-28 (Cycle 1):</b> Venetoclax 20mg orally once daily, <b>followed by:</b> <b>Days 1-7 (Cycle 2):</b> Venetoclax 50mg orally once daily, <b>followed by:</b> <b>Days 8-14 (Cycle 2):</b> Venetoclax 100mg orally once daily, <b>followed by:</b> <b>Days 15-21 (Cycle 2):</b> Venetoclax 200mg orally once daily, <b>followed by:</b> <b>Days 22-28 (Cycle 2):</b> Venetoclax 400mg orally once daily, <b>followed by:</b> <b>Days 1-28 (Cycle 3 and beyond):</b> Venetoclax 400mg orally once daily. Repeat cycle every 4 weeks for 12 cycles
<b>Other Recommended Regimens</b>	
Bendamustine + Obinutuzumab (not recommended for frail patients) <sup>6,14,15,b,f</sup> <i>Obinutuzumab requires premedication.</i>	<b>Days 1-2 (Cycle 1):</b> Bendamustine 70mg/m <sup>2</sup> IV over 10-30 minutes (based on product selection) daily, <b>followed by (if tolerated):</b> <b>Days 1-2 (Cycles 2-6):</b> Bendamustine 90mg/m <sup>2</sup> IV over 10-30 minutes (based on product selection) daily <b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycles 2-6):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 4 weeks for 6 cycles. <b>OR</b> <b>Days 1-2 (Cycles 1-6):</b> Bendamustine 70mg/m <sup>2</sup> IV over 10-30 minutes (based on product selection) daily <b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycles 2-6):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 4 weeks for 6 cycles.

continued

# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treatment Regimens

## ► First-Line Therapy Without del (17p)/TP53 Mutation<sup>1</sup> (continued)

REGIMEN	DOSING
Patients age ≥65 years OR <65 years with significant comorbidities (creatinine clearance [CrCl] <70mL/min) (continued)	
Other Recommended Regimens (continued)	
Bendamustine + Ofatumumab (not recommended for frail patients) <sup>14,16,17,f,g,h</sup> <i>Ofatumumab requires premedication.</i>	<b>Days 1-2 (Cycle 1):</b> Bendamustine 70mg/m <sup>2</sup> IV over 10-30 minutes (based on product selection) daily, <b>followed by (if tolerated):</b> <b>Days 1-2 (Cycles 2-6):</b> Bendamustine 90mg/m <sup>2</sup> IV over 10-30 minutes (based on product selection) daily <b>Day 1 (Cycle 1):</b> Ofatumumab 300mg IV, <b>followed by:</b> <b>Day 8 (Cycle 1):</b> Ofatumumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycles 2-6):</b> Ofatumumab 1,000mg IV. Repeat cycle every 4 weeks for 6 cycles. <b>OR</b> <b>Days 1-2 (Cycles 1-6):</b> Bendamustine 70mg/m <sup>2</sup> IV over 10-30 minutes (based on product selection) daily <b>Day 1 (Cycle 1):</b> Ofatumumab 300mg IV, <b>followed by:</b> <b>Day 8 (Cycle 1):</b> Ofatumumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycles 2-6):</b> Ofatumumab 1,000mg IV. Repeat cycle every 4 weeks for 6 cycles.
Bendamustine + Rituximab (not recommended for frail patients) <sup>14,18,21,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-2 (Cycle 1):</b> Bendamustine 70mg/m <sup>2</sup> IV over 10-30 minutes (based on product selection) daily, <b>followed by (if tolerated):</b> <b>Days 1-2 (Cycles 2-6):</b> Bendamustine 90mg/m <sup>2</sup> IV over 10-30 minutes (based on product selection) daily <b>Day 1 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycles 2-6):</b> Rituximab 500mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 6 cycles.
Chlorambucil (Category 3) <sup>22-24,k</sup>	<b>Day 1:</b> Chlorambucil 40mg/m <sup>2</sup> orally Repeat cycle every 4 weeks. <b>OR</b> <b>Day 1:</b> Chlorambucil 0.4-0.8mg/kg orally. Repeat cycle every 2 weeks.
Chlorambucil + Obinutuzumab <sup>6,13,22,25,26,b,k</sup> <i>Obinutuzumab requires premedication.</i>	<b>Days 1,15:</b> Chlorambucil 0.5mg/kg orally <b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Obinutuzumab 1,000mg IV. Repeat every 4 weeks for 6 cycles
High-dose Methylprednisolone (HDMP) + Obinutuzumab (Category 2B) <sup>6,27,b</sup> <i>Obinutuzumab requires premedication.</i>	<b>Days 1-3 (Cycles 1-4):</b> HDMP 1,000mg/m <sup>2</sup> IV over 90 minutes <b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 4 weeks for 6 cycles.
High-dose Methylprednisolone (HDMP) + Rituximab (Category 2B) <sup>18,28,29,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-3:</b> HDMP 1,000mg/m <sup>2</sup> IV over 90 minutes <b>Day 1 (Cycle 1):</b> Rituximab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> minus 100mg IV, <b>followed by:</b> <b>Days 8,15,22 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Days 1,8,15,22 (Cycles 2-3):</b> Rituximab 375mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 3 cycles
Ibrutinib + Obinutuzumab (Category 2B) <sup>5,7,26,b,c</sup> <i>Obinutuzumab requires premedication.</i>	<b>Days 1-28:</b> Ibrutinib 420mg orally once daily <b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 4 weeks for 6 cycles, <b>followed by:</b> <b>Days 1-28:</b> Ibrutinib 420mg orally once daily. Repeat cycle every 4 weeks.
Obinutuzumab <sup>6,30,31,b</sup> <i>Obinutuzumab requires premedication.</i>	<b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV. Administer for one 3-week cycle, <b>followed by:</b> <b>Days 1 (Cycle 2-8):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 3 weeks for 7 cycles.
Rituximab (Category 3) <sup>18,32,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Days 1,8,15,22:</b> Rituximab 375mg/m <sup>2</sup> IV. Administer for one 4-week cycle.

continued

# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treatment Regimens

## ► First-Line Therapy Without del (17p)/TP53 Mutation<sup>1</sup> (continued)

REGIMEN	DOSING
<b>Patients Age &lt;65 Years Without Significant Comorbidities</b>	
<b>Preferred Regimens</b>	
Acalabrutinib (Category 1) <sup>2,5,a</sup>	<b>Days 1-28:</b> Acalabrutinib 100mg orally every 12 hours. Repeat cycle every 4 weeks.
Acalabrutinib + Obinutuzumab (Category 1) <sup>2,4,6,a,b</sup> <i>Obinutuzumab requires premedication.</i>	<b>Days 1-28:</b> Acalabrutinib 100mg orally twice daily Administer for one 4-week cycle, <b>followed by:</b> <b>Day 1 (Cycle 2):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 2):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 2):</b> Obinutuzumab 1,000mg, <b>followed by:</b> <b>Day 1 (Cycle 3-7):</b> Obinutuzumab 1,000mg IV <b>Days 1-28:</b> Acalabrutinib 100mg orally twice daily. Repeat cycle every 4 weeks for 6 cycles, <b>followed by:</b> <b>Day 1-28:</b> Acalabrutinib 100mg orally twice daily. Repeat cycle every 4 weeks.
Ibrutinib (Category 1) <sup>7-10,c</sup>	<b>Days 1-28:</b> Ibrutinib 420mg orally once daily. Repeat cycle every 4 weeks.
Venetoclax + Obinutuzumab <sup>6,11-13,b,d,e</sup> <i>Obinutuzumab requires premedication.</i>	<b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 4 weeks for 6 cycles, <b>with:</b> <b>Days 22-28 (Cycle 1):</b> Venetoclax 20mg orally once daily, <b>followed by:</b> <b>Days 1-7 (Cycle 2):</b> Venetoclax 50mg orally once daily, <b>followed by:</b> <b>Days 8-14 (Cycle 2):</b> Venetoclax 100mg orally once daily, <b>followed by:</b> <b>Days 15-21 (Cycle 2):</b> Venetoclax 200mg orally once daily, <b>followed by:</b> <b>Days 22-28 (Cycle 2):</b> Venetoclax 400mg orally once daily, <b>followed by:</b> <b>Days 1-28 (Cycle 3 and beyond):</b> Venetoclax 400mg orally once daily. Repeat cycle every 4 weeks for 12 cycles.
<b>Other Recommended Regimens<sup>o</sup></b>	
Bendamustine + Obinutuzumab <sup>6,14,15,b,f</sup> <i>Obinutuzumab requires premedication.</i>	<b>Days 1-2 (Cycles 1-6):</b> Bendamustine 90mg/m <sup>2</sup> IV over 10-30 minutes <b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycles 2-6):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 4 weeks for up to 6 cycles.
Bendamustine + Ofatumumab <sup>14,16,17,f,h</sup> <i>Ofatumumab requires premedication.</i>	<b>Days 1-2 (Cycles 1-6):</b> Bendamustine 90mg/m <sup>2</sup> IV over 10-30 minutes (based on product selection) daily <b>Day 1 (Cycle 1):</b> Ofatumumab 300mg IV, <b>followed by:</b> <b>Day 8 (Cycle 1):</b> Ofatumumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycles 2-6):</b> Ofatumumab 1,000mg IV. Repeat cycle every 4 weeks for 6 cycles.
Bendamustine + Rituximab <sup>18-21,f,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-2 (Cycles 1-6):</b> Bendamustine 90mg/m <sup>2</sup> IV over 10-30 minutes (based on product selection) daily <b>Day 1 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycles 2-6):</b> Rituximab 500mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 6 cycles.
FCR (Fludarabine, Cyclophosphamide, Rituximab) (preferred for patients with IGHV-mutated CLL) <sup>18,21,33-35,i,j,l</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-3:</b> Fludarabine 25mg/m <sup>2</sup> IV over 30 minutes daily <b>Days 1-3:</b> Cyclophosphamide 250mg/m <sup>2</sup> IV over 30 minutes daily <b>Day 1 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Rituximab 500mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 6 cycles.
FR (Fludarabine + Rituximab) (Category 3) <sup>18,33,36,37,i,j,l</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-5:</b> Fludarabine 25mg/m <sup>2</sup> IV over 30 minutes <b>Day 1 (Cycle 1):</b> Rituximab 50mg/m <sup>2</sup> IV over 4 hours, <b>followed by:</b> <b>Day 3 (Cycle 1):</b> Rituximab 325mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 5 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Rituximab 375mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 6 cycles.

continued

# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treatment Regimens

## ► First-Line Therapy Without del (17p)/TP53 Mutation<sup>1</sup> (continued)

REGIMEN	DOSING
<b>Patients Age &lt;65 Years Without Significant Comorbidities (continued)</b>	
<b>Other Recommended Regimens<sup>9</sup> (continued)</b>	
High-dose Methylprednisolone (HDMP) + Obinutuzumab (Category 3) <sup>6,27b</sup> <i>Obinutuzumab requires premedication.</i>	<b>Days 1-3 (Cycles 1-4):</b> HDMP 1,000mg/m <sup>2</sup> IV over 90 minutes <b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 4 weeks for 6 cycles.
High-dose Methylprednisone (HDMP) + Rituximab (Category 3) <sup>18,28,29,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-3:</b> HDMP 1,000mg/m <sup>2</sup> IV over 90 minutes <b>Day 1 (Cycle 1):</b> Rituximab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> minus 100mg IV, <b>followed by:</b> <b>Days 8,15,22 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Days 1,8,15,22 (Cycles 2-3):</b> Rituximab 375mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 3 cycles.
Ibrutinib + Rituximab (Category 2B) <sup>18,28,39,c,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-28 (Cycles 1-6):</b> Ibrutinib 420mg orally once daily <b>Days 1,8,15,22 (Cycle 2):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycle 3-6):</b> Rituximab 375mg/m <sup>2</sup> IV Repeat cycle every 4 weeks for 6 cycles, <b>followed by:</b> <b>Days 1-28:</b> Ibrutinib 420mg orally once daily. Repeat cycle every 4 weeks.

## ► Second/Subsequent-Line Therapy Without del (17p)/TP53 Mutation<sup>1</sup>

<b>Patients Age ≥65 Years OR Patients Age &lt;65 Years With Significant Comorbidities (Creatinine Clearance [CrCl] &lt;70 mL/min)</b>	
<b>Preferred Regimens</b>	
Acalabrutinib (Category 1) <sup>2-5,a</sup>	<b>Days 1-28:</b> Acalabrutinib 100mg orally every 12 hours. Repeat cycle every 4 weeks.
Ibrutinib (Category 1) <sup>7,10,c</sup>	<b>Days 1-28:</b> Ibrutinib 420mg orally once daily. Repeat cycle every 4 weeks.
Venetoclax + Rituximab (Category 1) <sup>11,18,40,41,d,e,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-7:</b> Venetoclax 20mg orally once daily, <b>followed by:</b> <b>Days 8-14:</b> Venetoclax 50mg orally once daily, <b>followed by:</b> <b>Days 15-21:</b> Venetoclax 100mg orally once daily, <b>followed by:</b> <b>Days 22-28:</b> Venetoclax 200mg orally once daily, <b>followed by:</b> <b>Days 29-35:</b> Venetoclax 400mg orally once daily. Administer for one 5-week cycle, <b>followed by:</b> <b>Days 1-28 (Cycle 2 and beyond):</b> Venetoclax 400mg orally once daily Repeat cycle every 4 weeks for a maximum of 2 years, <b>with:</b> <b>Day 1 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycle 2 and beyond):</b> Rituximab 500mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 6 cycles.
<b>Other Recommended Regimens</b>	
Bendamustine + Rituximab (Category 2B) <sup>18-21,f,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-2 (Cycles 1-6):</b> Bendamustine 70mg/m <sup>2</sup> IV over 10-30 minutes (based on product selection) daily <b>Day 1 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycles 2-6):</b> Rituximab 500mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 6 cycles.
Chlorambucil + Rituximab <sup>18,22,42,j-k</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-7:</b> Chlorambucil 10mg/m <sup>2</sup> orally daily <b>Day 1 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Rituximab 500mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 6 cycles.
Duvelisib <sup>43-46,m</sup>	<b>Days 1-28:</b> Duvelisib 25mg orally twice daily Repeat cycle every 4 weeks.

continued

# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treatment Regimens

## ▶ Second/Subsequent-Line Therapy Without del (17p)/TP53 Mutation<sup>1</sup> (continued)

REGIMEN	DOSING
Patients Age ≥65 Years OR Patients Age <65 Years With Significant Comorbidities (Creatinine Clearance [CrCl] <70 mL/min) (continued)	
Other Recommended Regimens (continued)	
High-dose Methylprednisolone (HDMP) + Obinutuzumab (Category 2B) <sup>6,27b</sup> <i>Obinutuzumab requires premedication.</i>	<b>Days 1-3 (Cycles 1-4):</b> HDMP 1,000mg/m <sup>2</sup> IV over 90 minutes <b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 4 weeks for 6 cycles.
High-dose Methylprednisolone (HDMP) + Rituximab (Category 2B) <sup>18,28,29,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-3:</b> HDMP 1,000mg/m <sup>2</sup> IV over 90 minutes <b>Day 1 (Cycle 1):</b> Rituximab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> <b>minus 100mg</b> IV, <b>followed by:</b> <b>Days 8,15,22 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Days 1,8,15,22 (Cycles 2-3):</b> Rituximab 375mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 3 cycles.
Idelalisib <sup>47,48,n</sup>	<b>Days 1-28:</b> Idelalisib 150mg orally twice daily. Repeat cycle every 4 weeks.
Idelalisib+ Rituximab <sup>18,47-49,g,i,j,n</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-28 (Cycles 1-6):</b> Idelalisib 150mg orally twice daily <b>Day 1 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 15 (Cycle 1):</b> Rituximab 500mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Days 1,15 (Cycle 2):</b> Rituximab 500mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycle 3-6):</b> Rituximab 500mg/m <sup>2</sup> IV Repeat every 4 weeks for 6 cycles, <b>followed by:</b> <b>Days 1-28:</b> Idelalisib 150mg orally twice daily. Repeat cycle every 4 weeks.
Lenalidomide <sup>50-52,o</sup>	<b>Days 1-28:</b> Lenalidomide 10mg orally once daily (escalate dose every 14-28 days as tolerated up to a maximum dose of 25mg daily). Repeat cycle every 4 weeks for 4 cycles. <b>OR</b> <b>Days 1-21:</b> Lenalidomide 10mg orally once daily (escalate dose every 14-28 days as tolerated up to a maximum dose of 25mg daily). Repeat cycle every 4 weeks.
Lenalidomide + Rituximab <sup>18,50,53,i,j,o</sup> <i>Rituximab requires premedication.</i>	<b>Days 9-28 (Cycle 1):</b> Lenalidomide 10mg orally once daily, <b>followed by:</b> <b>Days 1-28 (Cycle 2-12):</b> Lenalidomide 10mg orally once daily <b>Days 1,8,15,22 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycle 2-12):</b> Rituximab 375mg/m <sup>2</sup> IV Repeat cycle every 4 weeks for 12 cycles, <b>followed by:</b> <b>Days 1-28:</b> Lenalidomide 10mg orally once daily. Repeat cycle every 4 weeks.
Obinutuzumab <sup>6,30,31,b</sup> <i>Obinutuzumab requires premedication.</i>	<b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV. Administer for one 3-week cycle, <b>followed by:</b> <b>Day 1 (Cycle 2-8):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 3 weeks for 7 cycles.
Ofatumumab <sup>16,54-56,g,h</sup> <i>Ofatumumab requires premedication.</i>	<b>Day 1 (Week 1):</b> Ofatumumab 300mg IV, <b>followed by:</b> <b>Day 1 (Beginning with Week 2):</b> Ofatumumab 2,000mg IV Repeat cycle weekly for 7 doses, <b>followed by:</b> <b>Day 1 (Beginning with Week 12):</b> Ofatumumab 2,000mg IV Repeat cycle every 4 weeks for 4 doses.
Rituximab (Dose-dense) (Category 3) <sup>18,57,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Day 1:</b> Rituximab 100mg/m <sup>2</sup> IV over 4 hours (do not titrate infusion rate), <b>followed by:</b> <b>Day 3,5,8,10,12,15,17,19,22,24,26:</b> Rituximab 375mg/m <sup>2</sup> IV. Administer for one 4-week cycle.

continued

# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treatment Regimens

## ► Second/Subsequent-Line Therapy Without del (17p)/TP53 Mutation<sup>1</sup> (continued)

REGIMEN	DOSING
Patients Age ≥65 Years OR Patients Age <65 Years With Significant Comorbidities (Creatinine Clearance [CrCl] <70 mL/min) (continued)	
Other Recommended Regimens (continued)	
Venetoclax <sup>1,58,59,d,e</sup>	<p><b>Days 1-7:</b> Venetoclax 20mg orally once daily, <b>followed by:</b>  <b>Days 8-14:</b> Venetoclax 50mg orally once daily, <b>followed by:</b>  <b>Days 15-21:</b> Venetoclax 100mg orally once daily, <b>followed by:</b>  <b>Days 22-28:</b> Venetoclax 200mg orally once daily, <b>followed by:</b>  <b>Days 29-35:</b> Venetoclax 400mg orally once daily.            Administer for one 5-week cycle, <b>followed by:</b>  <b>Days 1-28 (Cycle 2 and Beyond):</b> Venetoclax 400mg orally once daily.            Repeat cycle every 4 weeks.</p>
Zanubrutinib (for patients with intolerance or contraindication to other BTK inhibitor) <sup>60-63,p</sup>	<p><b>Days 1-28:</b> Zanubrutinib 160mg orally twice daily.            Repeat cycle every 4 weeks.  <b>OR</b>  <b>Days 1-28:</b> Zanubrutinib 320mg orally twice daily.            Repeat cycle every 4 weeks.</p>
Patients Age <65 Years Without Significant Comorbidities	
Preferred Regimens	
Acalabrutinib (Category 1) <sup>2-5,a</sup>	<p><b>Days 1-28:</b> Acalabrutinib 100mg orally every 12 hours.            Repeat cycle every 4 weeks.</p>
Ibrutinib (Category 1) <sup>7,10,c</sup>	<p><b>Day 1-28:</b> Ibrutinib 420mg orally once daily.            Repeat cycle every 4 weeks.</p>
Venetoclax + Rituximab (Category 1) <sup>11,18,30,41,d,e,i,j</sup> Rituximab requires premedication.	<p><b>Days 1-7:</b> Venetoclax 20mg orally once daily, <b>followed by:</b>  <b>Days 8-14:</b> Venetoclax 50mg orally once daily, <b>followed by:</b>  <b>Days 15-21:</b> Venetoclax 100mg orally once daily, <b>followed by:</b>  <b>Days 22-28:</b> Venetoclax 200mg orally once daily, <b>followed by:</b>  <b>Days 29-35:</b> Venetoclax 400mg orally once daily.            Administer for one 5-week cycle, <b>followed by:</b>  <b>Days 1-28 (Cycle 2 and beyond):</b> Venetoclax 400mg orally once daily            Repeat cycle every 4 weeks for a maximum of 2 years, <b>with:</b>  <b>Day 1 (Cycle 1):</b> Rituximab 375mg/m<sup>2</sup> IV, <b>followed by:</b>  <b>Day 1 (Cycle 2 and beyond):</b> Rituximab 500mg/m<sup>2</sup> IV.            Repeat cycle every 4 weeks for 6 cycles.</p>
Other Recommended Regimens <sup>o</sup>	
Alemtuzumab (Category 3) <sup>64-67,q,r</sup> Alemtuzumab requires premedication.	<p><b>Day 1 (Week 1):</b> Alemtuzumab 3mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b>  <b>Day 2 (Week 1):</b> Alemtuzumab 10mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b>  <b>Day 3 (Week 1):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous.            Dose titration followed by three times weekly administration of Alemtuzumab (on alternate days) for a maximum of 12 weeks (including dose-escalation phase).</p>
Alemtuzumab + Rituximab (Category 3) <sup>18,64,68,69,i,j,q,r</sup> Alemtuzumab requires premedication. Rituximab requires premedication.	<p><b>Day 1 (Week 1):</b> Alemtuzumab 3mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b>  <b>Day 2 (Week 1):</b> Alemtuzumab 10mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b>  <b>Day 3 (Week 1):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b>  <b>Days 3,5 (Weeks 2-4):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous twice weekly  <b>Days 1,8,15,22:</b> Rituximab 375mg/m<sup>2</sup> IV            Administer for one 4-week cycle (if WBC &lt;50,000/mcL), <b>followed by:</b>  <b>Days 3,5 (Weeks 1-4):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous twice weekly  <b>Days 1,8,15,22:</b> Rituximab 375mg/m<sup>2</sup> IV.            Administer for one 4-week cycle (if WBC &lt;50,000/mcL).  <b>OR</b>  <b>Day 1 (Week 1):</b> Alemtuzumab 3mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b>  <b>Day 2 (Week 1):</b> Alemtuzumab 10mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b>  <b>Day 3 (Week 1):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b>  <b>Day 3,5 (Weeks 2-4):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous twice weekly  <b>Day 1 (Week 1):</b> Rituximab 100mg/m<sup>2</sup> IV, <b>followed by:</b>  <b>Day 2 (Week 1):</b> Rituximab 275mg/m<sup>2</sup> IV, <b>followed by:</b>  <b>Days 8,15,22:</b> Rituximab 375mg/m<sup>2</sup> IV            Administer for one 4-week cycle (if WBC ≥50,000), <b>followed by:</b>  <b>Days 3,5 (Weeks 1-4):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous twice weekly  <b>Days 1,8,15,22:</b> Rituximab 375mg/m<sup>2</sup> IV.            Administer for one 4-week cycle (if WBC ≥50,000).</p>

continued

# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treatment Regimens

## ► Second/Subsequent-Line Therapy Without del (17p)/TP53 Mutation<sup>1</sup> (continued)

REGIMEN	DOSING
Patients Age ≥65 Years OR Patients Age <65 Years With Significant Comorbidities (Creatinine Clearance [CrCl] <70 mL/min) (continued)	
Other Recommended Regimens <sup>o</sup> (continued)	
Bendamustine + Rituximab <sup>14,18-21,f,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-2 (Cycles 1-6):</b> Bendamustine 70mg/m <sup>2</sup> IV over 10-30 minutes (based on product selection) daily <b>Day 1 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycles 2-6):</b> Rituximab 500mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 6 cycles.
Bendamustine + Rituximab + Ibrutinib (Category 3) <sup>7,14,18,70,c,f,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-28:</b> Ibrutinib 420mg orally once daily <b>Days 2-3 (Cycle 1):</b> Bendamustine 70mg/m <sup>2</sup> IV over 10-30 minutes (based on product selection), <b>followed by:</b> <b>Days 1-2 (Cycles 2-6):</b> Bendamustine 70mg/m <sup>2</sup> IV over 30 minutes (based on product selection) <b>Day 1 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycles 2-6):</b> Rituximab 500mg/m <sup>2</sup> IV Repeat cycle every 4 weeks for 6 cycles, <b>followed by:</b> <b>Days 1-28:</b> Ibrutinib 420mg orally once daily. Repeat cycle every 4 weeks.
Duvelisib <sup>43-46,n</sup>	<b>Day 1-28:</b> Duvelisib 25mg orally twice daily Repeat cycle every 4 weeks.
FC (Fludarabine + Cyclophosphamide) + Ofatumumab (Category 3) <sup>6,33,71,g,h,l</sup> <i>Ofatumumab required premedication.</i>	<b>Days 1-3:</b> Fludarabine 25mg/m <sup>2</sup> IV over 30 minutes <b>Days 1-3:</b> Cyclophosphamide 250mg/m <sup>2</sup> IV over 30 minutes <b>Day 1 (Cycle 1):</b> Ofatumumab 300mg IV, <b>followed by:</b> <b>Day 8 (Cycle 1):</b> Ofatumumab 1,000mg, <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Ofatumumab 1,000mg IV. Repeat cycle every 4 weeks for 6 cycles.
FCR (Fludarabine + Cyclophosphamide + Rituximab) <sup>18,21,34,35,i,j,l</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-3:</b> Fludarabine 25mg/m <sup>2</sup> IV over 30 minutes daily <b>Days 1-3:</b> Cyclophosphamide 250mg/m <sup>2</sup> IV over 30 minutes daily <b>Day 1 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Rituximab 500mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 6 cycles.
High-dose Methylprednisolone (HDMP) + Obinutuzumab (Category 2B) <sup>6,27,b</sup> <i>Obinutuzumab requires premedication.</i>	<b>Days 1-3 (Cycles 1-4):</b> HDMP 1,000mg/m <sup>2</sup> IV over 90 minutes <b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 4 weeks for 6 cycles.
High-dose Methylprednisolone (HDMP) + Rituximab (Category 2B) <sup>18,28,29,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Day 1-3:</b> HDMP 1,000mg/m <sup>2</sup> IV over 90 minutes <b>Day 1 (Cycle 1):</b> Rituximab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> minus 100mg IV, <b>followed by:</b> <b>Day 8,15,22 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1,8,15,22 (Cycles 2-3):</b> Rituximab 375mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 3 cycles.
Idelalisib <sup>47,48,n</sup>	<b>Days 1-28:</b> Idelalisib 150mg orally twice daily. Repeat cycle every 4 weeks.
Idelalisib + Rituximab <sup>18,47-49,i,j,n</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-28 (Cycles 1-6):</b> Idelalisib 150mg orally twice daily <b>Day 1 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 15 (Cycle 1):</b> Rituximab 500mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Days 1,15 (Cycle 2):</b> Rituximab 500mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycle 3-6):</b> Rituximab 500mg/m <sup>2</sup> IV Repeat every 4 weeks for 6 cycles, <b>followed by:</b> <b>Days 1-28:</b> Idelalisib 150mg orally twice daily. Repeat cycle every 4 weeks.
Lenalidomide <sup>50-52,o</sup>	<b>Days 1-28:</b> Lenalidomide 10mg orally once daily (escalate dose every 14-28 days as tolerated up to a maximum dose of 25mg daily). Repeat cycle every 4 weeks for 4 cycles. <b>OR</b> <b>Days 1-21:</b> Lenalidomide 10mg orally once daily (escalate dose every 14-28 days as tolerated up to a maximum dose of 25mg daily). Repeat cycle every 4 weeks.

continued

# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treatment Regimens

## ► Second/Subsequent-Line Therapy Without del(17p)/TP53 Mutation<sup>1</sup> (continued)

REGIMEN	DOSING
Patients Age ≥65 Years OR Patients Age <65 Years With Significant Comorbidities (Creatinine Clearance [CrCl] <70 mL/min) (continued)	
Other Recommended Regimens <sup>o</sup> (continued)	
Lenalidomide + Rituximab <sup>18,50,53,i,j,o</sup> <i>Rituximab requires premedication.</i>	<b>Days 9-28 (Cycle 1):</b> Lenalidomide 10mg orally once daily, <b>followed by:</b> <b>Days 1-28 (Cycle 2-12):</b> Lenalidomide 10mg orally once daily <b>Days 1,8,15,22 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycle 2-12):</b> Rituximab 375mg/m <sup>2</sup> IV Repeat cycle every 4 weeks for 12 cycles, <b>followed by:</b> <b>Days 1-28:</b> Lenalidomide 10mg orally once daily. Repeat cycle every 4 weeks.
Obinutuzumab <sup>6,30,31,b</sup> <i>Obinutuzumab requires premedication.</i>	<b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV. Administer for one 3-week cycle, <b>followed by:</b> <b>Day 1 (Cycle 2-8):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 3 weeks for 7 cycles.
Ofatumumab <sup>16,54-56,g,h</sup> <i>Ofatumumab requires premedication.</i>	<b>Day 1 (Week 1):</b> Ofatumumab 300mg IV, <b>followed by:</b> <b>Day 1 (Beginning with Week 2):</b> Ofatumumab 2,000mg IV Repeat cycle weekly for 7 doses, <b>followed by:</b> <b>Day 1 (Beginning with Week 12):</b> Ofatumumab 2,000mg IV Repeat cycle every 4 weeks for 4 doses.
Venetoclax <sup>11,58,59,d,e</sup>	<b>Day 1-7:</b> Venetoclax 20mg orally once daily, <b>followed by:</b> <b>Days 8-14:</b> Venetoclax 50mg orally once daily, <b>followed by:</b> <b>Days 15-21:</b> Venetoclax 100mg orally once daily, <b>followed by:</b> <b>Days 22-28:</b> Venetoclax 200mg orally once daily, <b>followed by:</b> <b>Days 29-35:</b> Venetoclax 400mg orally once daily. Administer for one 5-week cycle, <b>followed by:</b> <b>Days 1-28 (Cycle 2 and Beyond):</b> Venetoclax 400mg orally once daily. Repeat cycle every 4 weeks.
Zanubrutinib (for patients with intolerance or contraindications to other BTK inhibitor) <sup>60-63,p</sup>	<b>Days 1-28:</b> Zanubrutinib 160mg orally twice daily. Repeat cycle every 4 weeks. <b>OR</b> <b>Days 1-28:</b> Zanubrutinib 320mg orally twice daily. Repeat cycle every 4 weeks.

## ► First-Line Therapy With del(17p)/TP53 mutation<sup>1</sup>

Preferred Regimens	
Acalabrutinib <sup>2-5,a</sup>	<b>Days 1-28:</b> Acalabrutinib 100mg orally every 12 hours. Repeat cycle every 4 weeks.
Acalabrutinib + Obinutuzumab <sup>2,4,6,a,b</sup> <i>Obinutuzumab requires premedication.</i>	<b>Days 1-28:</b> Acalabrutinib 100mg orally twice daily Administer for one 4-week cycle, <b>followed by:</b> <b>Day 1 (Cycle 2):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 2):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 2):</b> Obinutuzumab 1,000mg, <b>followed by:</b> <b>Day 1 (Cycle 3-7):</b> Obinutuzumab 1,000mg IV <b>Days 1-28:</b> Acalabrutinib 100mg orally twice daily. Repeat cycle every 4 weeks for 6 cycles, <b>followed by:</b> <b>Days 1-28:</b> Acalabrutinib 100mg orally twice daily. Repeat cycle every 4 weeks.
Ibrutinib <sup>7-10,c</sup>	<b>Days 1-28:</b> Ibrutinib 420mg orally once daily. Repeat cycle every 4 weeks.

continued



# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treatment Regimens

## ► First-Line Therapy With del(17p)/TP53 mutation<sup>1</sup> (continued)

REGIMEN	DOSING
<b>Preferred Regimens (continued)</b>	
Venetoclax + Obinutuzumab <sup>6,11-13,b,d,e</sup> <i>Obinutuzumab requires premedication.</i>	<b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV, <b>followed by:</b> <b>Day 1 (Cycle 2-6):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 4 weeks for 6 cycles, <b>with:</b> <b>Days 22-28 (Cycle 1):</b> Venetoclax 20mg orally once daily, <b>followed by:</b> <b>Days 1-7 (Cycle 2):</b> Venetoclax 50mg orally once daily, <b>followed by:</b> <b>Day 8-14 (Cycle 2):</b> Venetoclax 100mg orally once daily, <b>followed by:</b> <b>Day 15-21 (Cycle 2):</b> Venetoclax 200mg orally once daily, <b>followed by:</b> <b>Day 22-28 (Cycle 2):</b> Venetoclax 400mg orally once daily, <b>followed by:</b> <b>Day 1-28 (Cycle 3 and beyond):</b> Venetoclax 400mg orally once daily. Repeat cycle every 4 weeks for 12 cycles
<b>Other Recommended Regimens</b>	
Alemtuzumab <sup>64-67,q,r</sup> <i>Alemtuzumab requires premedication.</i>	<b>Day 1 (Week 1):</b> Alemtuzumab 3mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 2 (Week 1):</b> Alemtuzumab 10mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 3 (Week 1):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous. Dose titration followed by three times weekly administration of Alemtuzumab (on alternate days) for a maximum of 12 weeks (including dose-escalation phase).
Alemtuzumab + Rituximab <sup>18,64,68,69,i,j,q,r</sup> <i>Alemtuzumab requires premedication.</i> <i>Rituximab requires premedication.</i>	<b>Day 1 (Week 1):</b> Alemtuzumab 3mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 2 (Week 1):</b> Alemtuzumab 10mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 3 (Week 1):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Days 3,5 (Weeks 2-4):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous twice weekly <b>Days 1,8,15,22:</b> Rituximab 375mg/m <sup>2</sup> IV Administer for one 4-week cycle (if WBC <50,000/mcL), <b>followed by:</b> <b>Days 3,5 (Weeks 1-4):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous twice weekly <b>Days 1,8,15,22:</b> Rituximab 375mg/m <sup>2</sup> IV. Administer for one 4-week cycle (if WBC <50,000/mcL). <b>OR</b> <b>Day 1 (Week 1):</b> Alemtuzumab 3mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 2 (Week 1):</b> Alemtuzumab 10mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 3 (Week 1):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 3,5 (Weeks 2-4):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous twice weekly <b>Day 1 (Week 1):</b> Rituximab 100mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 2 (Week 1):</b> Rituximab 275mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Days 8,15,22:</b> Rituximab 375mg/m <sup>2</sup> IV Administer for one 4-week cycle (if WBC ≥50,000), <b>followed by:</b> <b>Days 3,5 (Weeks 1-4):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous twice weekly <b>Days 1,8,15,22:</b> Rituximab 375mg/m <sup>2</sup> IV. Administer for one 4-week cycle (if WBC ≥50,000).
High-dose Methylprednisolone (HDMP) + Rituximab <sup>18,28,29,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Day 1-3:</b> HDMP 1,000mg/m <sup>2</sup> IV over 90 minutes <b>Day 1 (Cycle 1):</b> Rituximab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> minus 100mg IV, <b>followed by:</b> <b>Days 8,15,22 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> <b>followed by:</b> <b>Days 1,8,15,22 (Cycles 2-3):</b> Rituximab 375mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 3 cycles
Obinutuzumab <sup>6,30,31,b</sup> <i>Obinutuzumab requires premedication.</i>	<b>Day 1 (Cycle 1):</b> Obinutuzumab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Obinutuzumab 900mg IV, <b>followed by:</b> <b>Days 8,15 (Cycle 1):</b> Obinutuzumab 1,000mg IV. Administer for one 3-week cycle, <b>followed by:</b> <b>Day 1 (Cycle 2-8):</b> Obinutuzumab 1,000mg IV. Repeat cycle every 3 weeks for 7 cycles.
Zanubrutinib (for patients with intolerance or contraindication to other BTK inhibitors) <sup>60-63,p</sup>	<b>Days 1-28:</b> Zanubrutinib 160mg orally twice daily. Repeat cycle every 4 weeks. <b>OR</b> <b>Days 1-28:</b> Zanubrutinib 320mg orally twice daily. Repeat cycle every 4 weeks.

continued

# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treatment Regimens

## ► Second/Subsequent-Line Therapy With del(17p)/TP53 mutation<sup>1</sup>

REGIMEN	DOSING
<b>Preferred Regimens</b>	
Acalabrutinib (Category 1) <sup>2,5,a</sup>	<b>Days 1-28:</b> Acalabrutinib 100mg orally every 12 hours. Repeat cycle every 4 weeks.
Ibrutinib (Category 1) <sup>7,10,c</sup>	<b>Days 1-28:</b> Ibrutinib 420mg orally once daily. Repeat cycle every 4 weeks.
Venetoclax <sup>11,58,59,d,e</sup>	<b>Days 1-7:</b> Venetoclax 20mg orally once daily, <b>followed by:</b> <b>Days 8-14:</b> Venetoclax 50mg orally once daily, <b>followed by:</b> <b>Days 15-21:</b> Venetoclax 100mg orally once daily, <b>followed by:</b> <b>Days 22-28:</b> Venetoclax 200mg orally once daily, <b>followed by:</b> <b>Days 29-35:</b> Venetoclax 400mg orally once daily. Administer for one 5-week cycle, <b>followed by:</b> <b>Days 1-28 (Cycle 2 and Beyond):</b> Venetoclax 400mg orally once daily. Repeat cycle every 4 weeks.
Venetoclax + Rituximab (Category 1) <sup>11,18,40,41,d,e,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-7:</b> Venetoclax 20mg orally once daily, <b>followed by:</b> <b>Days 8-14:</b> Venetoclax 50mg orally once daily, <b>followed by:</b> <b>Days 15-21:</b> Venetoclax 100mg orally once daily, <b>followed by:</b> <b>Days 22-28:</b> Venetoclax 200mg orally once daily, <b>followed by:</b> <b>Days 29-35:</b> Venetoclax 400mg orally once daily. Administer for one 5-week cycle, <b>followed by:</b> <b>Days 1-28 (Cycle 2 and beyond):</b> Venetoclax 400mg orally once daily Repeat cycle every 4 weeks for a maximum of 2 years, <b>with:</b> <b>Days 1 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Days 1 (Cycle 2 and beyond):</b> Rituximab 500mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 6 cycles.
<b>Other Recommended Regimens</b>	
Alemtuzumab <sup>64-67,q,r</sup> <i>Alemtuzumab requires premedication.</i>	<b>Day 1 (Week 1):</b> Alemtuzumab 3mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 2 (Week 1):</b> Alemtuzumab 10mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 3 (Week 1):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous. Dose titration followed by three times weekly administration of Alemtuzumab (on alternate days) for a maximum of 12 weeks (including dose-escalation phase).
Alemtuzumab + Rituximab <sup>18,64,68,69,i,j,q,r</sup> <i>Alemtuzumab requires premedication.</i> <i>Rituximab requires premedication.</i>	<b>Day 1 (Week 1):</b> Alemtuzumab 3mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 2 (Week 1):</b> Alemtuzumab 10mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 3 (Week 1):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Days 3,5 (Weeks 2-4):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous twice weekly <b>Days 1,8,15,22:</b> Rituximab 375mg/m <sup>2</sup> IV Administer for one 4-week cycle (if WBC <50,000/mcL), <b>followed by:</b> <b>Days 3,5 (Weeks 1-4):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous twice weekly <b>Days 1,8,15,22:</b> Rituximab 375mg/m <sup>2</sup> IV. Administer for one 4-week cycle (if WBC <50,000/mcL). <b>OR</b> <b>Day 1 (Week 1):</b> Alemtuzumab 3mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 2 (Week 1):</b> Alemtuzumab 10mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 3 (Week 1):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous, <b>if tolerated followed by:</b> <b>Day 3,5 (Weeks 2-4):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous twice weekly <b>Day 1 (Week 1):</b> Rituximab 100mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 2 (Week 1):</b> Rituximab 275mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Days 8,15,22:</b> Rituximab 375mg/m <sup>2</sup> IV Administer for one 4-week cycle (if WBC ≥50,000), <b>followed by:</b> <b>Days 3,5 (Weeks 1-4):</b> Alemtuzumab 30mg IV over 2 hours <b>OR</b> subcutaneous twice weekly <b>Days 1,8,15,22:</b> Rituximab 375mg/m <sup>2</sup> IV. Administer for one 4-week cycle (if WBC ≥50,000).
Duvelisib <sup>43-46,m</sup>	<b>Days 1-28:</b> Duvelisib 25mg orally twice daily Repeat cycle every 4 weeks.

continued

# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treatment Regimens

## ► Second/Subsequent-Line Therapy With del(17p)/TP53 mutation<sup>1</sup> (continued)

REGIMEN	DOSING
<b>Other Recommended Regimens (continued)</b>	
High-dose Methylprednisolone (HDMP) + Rituximab <sup>18,28,29,i,j</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-3:</b> HDMP 1,000mg/m <sup>2</sup> IV over 90 minutes <b>Day 1 (Cycle 1):</b> Rituximab 100mg IV, <b>followed by:</b> <b>Day 2 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> minus 100mg IV, <b>followed by:</b> <b>Days 8,15,22 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Days 1,8,15,22 (Cycles 2-3):</b> Rituximab 375mg/m <sup>2</sup> IV. Repeat cycle every 4 weeks for 3 cycles.
Idelalisib <sup>47,48,n</sup>	<b>Days 1-28:</b> Idelalisib 150mg orally twice daily. Repeat cycle every 4 weeks.
Idelalisib + Rituximab <sup>18,47-49,i,j,n</sup> <i>Rituximab requires premedication.</i>	<b>Days 1-28 (Cycles 1-6):</b> Idelalisib 150mg orally twice daily <b>Day 1 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 15 (Cycle 1):</b> Rituximab 500mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Days 1,15 (Cycle 2):</b> Rituximab 500mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycle 3-6):</b> Rituximab 500mg/m <sup>2</sup> IV Repeat every 4 weeks for 6 cycles, <b>followed by:</b> <b>Days 1-28:</b> Idelalisib 150mg orally twice daily. Repeat cycle every 4 weeks.
Lenalidomide <sup>50-52,o</sup>	<b>Days 1-28:</b> Lenalidomide 10mg orally once daily (escalate dose every 14-28 days as tolerated up to a maximum dose of 25mg daily). Repeat cycle every 4 weeks for 4 cycles. <b>OR</b> <b>Days 1-21:</b> Lenalidomide 10mg orally once daily (escalate dose every 14-28 days as tolerated up to a maximum dose of 25mg daily). Repeat cycle every 4 weeks.
Lenalidomide + Rituximab <sup>18,50,53,i,j,o</sup> <i>Rituximab requires premedication.</i>	<b>Days 9-28 (Cycle 1):</b> Lenalidomide 10mg orally once daily, <b>followed by:</b> <b>Days 1-28 (Cycle 2-12):</b> Lenalidomide 10mg orally once daily <b>Days 1,8,15,22 (Cycle 1):</b> Rituximab 375mg/m <sup>2</sup> IV, <b>followed by:</b> <b>Day 1 (Cycle 2-12):</b> Rituximab 375mg/m <sup>2</sup> IV Repeat cycle every 4 weeks for 12 cycles, <b>followed by:</b> <b>Days 1-28:</b> Lenalidomide 10mg orally once daily. Repeat cycle every 4 weeks.
Ofatumumab <sup>16,54-56,g,h</sup> <i>Ofatumumab requires premedication.</i>	<b>Day 1 (Week 1):</b> Ofatumumab 300mg IV, <b>followed by:</b> <b>Day 1 (Beginning with Week 2):</b> Ofatumumab 2,000mg IV Repeat cycle weekly for 7 doses, <b>followed by:</b> <b>Day 1 (Beginning with Week 12):</b> Ofatumumab 2,000mg IV Repeat cycle every 4 weeks for 4 doses.
Zanubrutinib (for patients with intolerance or contraindication to other BTK inhibitors) <sup>60-63,p</sup>	<b>Days 1-28:</b> Zanubrutinib 160mg orally twice daily. Repeat cycle every 4 weeks. <b>OR</b> <b>Days 1-28:</b> Zanubrutinib 320mg orally twice daily. Repeat cycle every 4 weeks.

<sup>a</sup> Acalabrutinib has multiple drug-drug interactions and/or drug-food interactions.

<sup>b</sup> For Obinituzumab, premedication for hypersensitivity is required. The recommended dosing is: diphenhydramine 50mg IV or orally at least 30 minutes pre-Obinituzumab for doses 1 and 2. For subsequent doses, diphenhydramine should be administered to patients with grade  $\geq 1$  infusion-related reactions with the previous infusion AND acetaminophen 650-1,000mg orally at least 30 minutes pre-Obinituzumab AND dexamethasone 20mg or methylprednisolone 80mg IV at least 60 minutes pre-Obinituzumab for doses 1 and 2. Hydrocortisone is not recommended. For subsequent doses, corticosteroid should be administered to patients with grade 3 infusion-related reactions with the previous infusion or with a lymphocyte count  $>2.5 \times 10^9/L$  prior to next treatment.

<sup>c</sup> Ibrutinib has multiple drug-drug interactions and/or drug-food interactions.

<sup>d</sup> Venetoclax has multiple drug-drug interactions and/or drug-food interactions.

<sup>e</sup> Venetoclax should be taken with food.

<sup>f</sup> Bendamustine has multiple drug-drug interactions and/or drug-food interactions.

<sup>g</sup> While Ofatumumab is no longer commercially available for CLL, it may be obtained for clinical use.

<sup>h</sup> For Ofatumumab: Premedication for hypersensitivity and/or infusion reaction is required. The recommended dosing is: diphenhydramine 50mg IV or orally 30-120 minutes pre-Ofatumumab AND acetaminophen 1,000mg orally 30-120 minutes pre-Ofatumumab AND prednisolone 50-100mg (or equivalent) 30-120 minutes pre-Ofatumumab.

<sup>i</sup> For Rituximab: Premedication is required. The recommended dosing is: diphenhydramine 12.5-50mg IV or orally 30-60 minutes pre-Rituximab AND acetaminophen 650mg orally 30-60 minutes pre-Rituximab.

<sup>j</sup> Rituximab and Hyaluronidase Human (Rituxan Hycela) for subcutaneous injection may be substituted for Rituximab in patients who have received one dose of Rituximab product by IV route without experiencing severe adverse reactions.<sup>72</sup> A biosimilar agent may be substituted for Rituximab if clinically appropriate.

continued

# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treatment Regimens

- <sup>k</sup> Chlorambucil should be taken on an empty stomach.
- <sup>l</sup> Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing Fludarabine; however, patients should be observed carefully and fludarabine should be avoided in those where a history of Fludarabine-associated AIHA is suspected.
- <sup>m</sup> Duvelisib has multiple drug-drug interactions and/or drug-food interactions.
- <sup>n</sup> Idelalisib is indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities/reduced renal function as measured by CrCl <60ml/min or NCI CTCAE grade ≥3 neutropenia or grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.
- <sup>o</sup> Lenalidomide can be given as continuous or interim dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Andritsos L, et al. *J Clin Oncol*. 2008;26:2518-2525; Wendtner C, et al. *Leuk Lymphoma*. 2016;57:1291-1299.
- <sup>p</sup> Zanubrutinib has multiple drug-drug interactions and/or drug-food interactions.
- <sup>q</sup> While Alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use.
- <sup>r</sup> For Alemtuzumab: Premedication for infusion reactions is required prior to initial dose and dose escalations, then as clinically indicated. The recommended dosing is: diphenhydramine 50mg orally or IV 30 minutes pre-Alemtuzumab AND acetaminophen 500-1,000mg orally 30 minutes pre-Alemtuzumab.

## References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V1.2022. Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/b-cell.pdf](https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf). Accessed December 6, 2021.
2. Acalabrutinib (Calquence). [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2019.
3. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: Results of the first randomized phase III trial. *J Clin Oncol*. 2021;39(31):3441-3452.
4. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet*. 2020; 395(10232):1278-1291.
5. Awan FT, Schuh A, Brown JR, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. *Blood Adv*. 2019; 3(9):1553-1562.
6. Obinutuzumab (Gazyva). [package insert]. South San Francisco, CA: Genentech, Inc.; January 2021.
7. Ibrutinib (Imbruvica). [package insert]. Horsham, PA: Janssen Biotech, Inc.; December 2020.
8. Burger JA, Tedeschi A, Bar PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437.
9. O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicenter study. *Lancet Oncol*. 2016;17(10):1409-1418.
10. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019;94(12):1353-1363.
11. Venetoclax (Venclexta). [package insert]. North Chicago, IL: AbbVie Inc.; October 2021.
12. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380(23):2225-2236
13. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(9):1188-1200.
14. Bendamustine (Bendeka). [package insert]. Parsippany, NJ: Teva Pharmaceuticals; October 2021.
15. Stilgenbauer S, Leblond V, Foa R, et al. Obinutuzumab plus bendamustine in previously untreated patients with CLL: a subgroup analysis of the GREEN study. *Leukemia*. 2018;32(8):1778-1786.
16. Ofatumumab (Kesimpta). [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2020.
17. Flinn IW, Panayiotidis P, Afanasyev B, et al. A phase 2, multicenter study investigating ofatumumab and bendamustine combination in patients with untreated or relapsed CLL. *Am J Hematol*. 2016;91(9):900-906.
18. Rituximab (Rituxan). [package insert]. South San Francisco, CA: Genentech, Inc.; December 2021.
19. Michallet AS, Aktan M, Hiddemann W, et al. Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study. *Haematologica*. 2018;103(4):698-706.
20. Fischer K, Cramer P, Bush R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol*. 2011;29(26):3559-3566.
21. Eichhorst B, Fink AM, Bhalo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016;17(7):928-942.
22. Chlorambucil (Leukeran) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; November 2006.
23. Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. *Blood*. 2009 114(16):3382-3391.
24. Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *N Engl J Med*. 2000;343(24): 1750-1757.
25. Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. *Leukemia*. 2015;29(7):1602-1604.
26. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(1):43-56.
27. Castro JE, Amaya-Chanaga CI, Lujan JV, et al. Obinutuzumab (Gazyva) and high-dose methylprednisone (HDMP) combination for patients with chronic lymphocytic leukemia (CLL) – a phase Ib/II study. [abstract]. *Blood*. 2017;130(Suppl\_1):1730.
28. Castro JE, James DF, Sandoval-Sus JD, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of chronic lymphocytic leukemia. *Leukemia*. 2009;23(10):1779-1789.
29. Bowen DA, Call TG, Jenkin GD, et al. Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. *Leuk Lymphoma*. 2007;48(12): 2412-2417.
30. Byrd JC, Flynn JM, Kipps TJ, et al. Randomized phase 2 study of obinutuzumab monotherapy in symptomatic, previously untreated chronic lymphocytic leukemia. *Blood*. 2016;127(1):79-86.
31. Cartron G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. *Blood*. 2014;124(14):2196-2202.
32. Huhn D, von Schilling C, Wilhelm M et al. Rituximab therapy of patients with B-cell chronic lymphocytic leukemia. *Blood*. 2001;98(5):1326-1331.
33. Fludarabine (Fludara). [package insert]. Princeton, NJ: Sandoz; December 2010.
34. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood*. 2016;127(2):208-215.
35. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood*. 2016;127(3):303-309.

continued

# Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treatment Regimens

## References (continued)

36. Byrd JC, Peterson BL, Morrison VA, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). *Blood*. 2003;101(1):6-14.
37. Woyach JA, Ruppert AS, Heerema NA, et al. Chemoimmunotherapy with fludarabine and rituximab produces extended overall survival and progression-free survival in chronic lymphocytic leukemia: long-term follow-up of CALGB study 9712. *J Clin Oncol*. 2011;29(10):1349-1355.
38. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. *N Engl J Med*. 2019;381(5):432-443.
39. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. *N Engl J Med*. 2018;379(26):2517-2528.
40. Kater AP, Wu JQ, Kipps T, et al. Venetoclax plus rituximab in relapsed chronic lymphocytic leukemia: 4-year results and evaluation of impact of genomic complexity and gene mutations from the MURANO phase III study. *J Clin Oncol*. 2020;38(34):4042-4054.
41. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2018;378(12):1107-1120.
42. Hillmen P, Gribben JG, Follows GA, et al. Rituximab plus chlorambucil as first-line treatment for chronic lymphocytic leukemia: Final analysis of an open-label phase II study. *J Clin Oncol*. 2014;32(12):1236-1241.
43. Duvelisib (Copiktra). [package insert]. Las Vegas, NV: Secura Bio, Inc.; October 2021.
44. Flinn IW, O'Brien S, Kahl B, et al. Duvelisib, a novel oral dual inhibitor of PI3K- $\delta$ , is clinically active in advanced hematologic malignancies. *Blood*. 2018;131(8):877-887.
45. Flinn IW, Miller CB, Ardeshtna KM, et al. DYNAMO: A phase II study of duvelisib (IPI-145) in patients with refractory indolent non-Hodgkin lymphoma. *J Clin Oncol*. 2019;37(11):912-922.
46. Davids MS, Kuss BJ, Hillmen P, et al. Efficacy and safety of duvelisib following disease progression on ofatumumab in patients with relapsed/refractory CLL or SLL in the DUO crossover extension study. *Clin Cancer Res*. 2020;26(9):2096-2103.
47. Idelalisib (Zydelig) [package insert]. Foster City, CA: Gilead Sciences, Inc.; October 2020.
48. Gopal AK, Kahl BS, de Vos S, et al. PI3K $\delta$  inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370(11):1008-1018.
49. Sharman JP, Coutre SE, Furman RR, et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. *J Clin Oncol*. 2019;37(16):1391-1402.
50. Lenalidomide (Revlimid) [package insert]. Summit, NJ: Celgene Corporation; 2021.
51. Ferrajoli A, Lee BN, Schlette EJ, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. *Blood*. 2008;111(11):5291-5297.
52. Chanan-Khan A, Miller KC, Musial L, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. *J Clin Oncol*. 2006;24(34):5343-5349.
53. Badoux XC, Keating MJ, Wen S, et al. Phase II study of lenalidomide and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2013;31(5):584-591.
54. Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2010;28(10):1749-1755.
55. Miklos U, Strugov V, Lewerin C, et al. Five-year survival follow-up of a phase III randomised trial comparing ofatumumab versus physicians' choice for bulky fludarabine-refractory chronic lymphocytic leukaemia: a short report. *Br J Haematol*. 2020;189(4):689-693.
56. Osterborg A, Jewell RC, Padmanabhan-Iyer S, et al. Ofatumumab monotherapy in fludarabine-refractory chronic lymphocytic leukemia: final results from a pivotal study. *Haematologica*. 2015;100(8):e311-e314.
57. Byrd JC, Murphy T, Howard RS, et al. Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. *J Clin Oncol*. 2001;19(8):2153-2164.
58. Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. *Blood*. 2018;131(15):1704-1711.
59. Stilgenbauer S, Eichhorst B, Schtelig J, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: Results from the full population of a phase II pivotal trial. *J Clin Oncol*. 2018;36(19):1973-1980.
60. Zanubrutinib (Brukinsa). [Package Insert]. San Mateo, CA: BeiGene USA, Inc.; November 2019.
61. Tam CS, Robak T, Ghia P et al. Zanubrutinib monotherapy for patients with treatment naive chronic lymphocytic leukemia and 17p deletion. *Haematologica*. 2020;106(9):2354-2363.
62. Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood*. 2019;134(11):851-859.
63. Xu W, Yang S, Zhou K, et al. Treatment of relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma with the BTK inhibitor zanubrutinib: phase 2, single-arm, multicenter study. *J Hematol Oncol*. 2020;13(1):48.
64. Alemtuzumab (Campath) [package insert]. Cambridge, MA: Genzyme Corporation; September 2007.
65. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood*. 2002;99(10):3554-3561.
66. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2007;25(35):5616-5623.
67. Lozanski G, Heerema NA, Flinn IW, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. *Blood*. 2004;103(9):3278-3281.
68. Faderl S, Thomas DA, O'Brien S, et al. Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. *Blood*. 2003;101(9):3413-3415.
69. Faderl S, Ferrajoli A, Wierda W, et al. Alemtuzumab by continuous intravenous infusion followed by subcutaneous injection plus rituximab in the treatment of patients with chronic lymphocytic leukemia recurrence. *Cancer*. 2010;116(10):2360-2365.
70. Fraser G, Cramer P, Demirkan F, et al. Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leukemia*. 2019;33(4):969-980.
71. Robak T, Warzocha K, Babu KG, et al. Ofatumumab plus fludarabine and cyclophosphamide in relapsed chronic lymphocytic leukemia: results from the COMPLEMENT 2 trial. *Leuk Lymphoma*. 2017;58(5):1084-1093.
72. Rituximab/hyaluronidase human (Rituxan Hycela). [package insert]. South San Francisco, CA: Genentech, Inc.; June 2021.

(Revised 12/2021; NCCN CLL/SLL Guidelines V1.2022) © 2021 by Haymarket Media, Inc.