Updates in the Management of Chronic Lymphocytic Leukemia: A Focus on Targeted Therapies

A presentation for HealthTrust Members
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Chris Franzese, PharmD, MHS

PGY1 Pharmacy Resident

Preceptor, Christina Howlett, PharmD, BCOP

Speaker & Preceptor Disclosures

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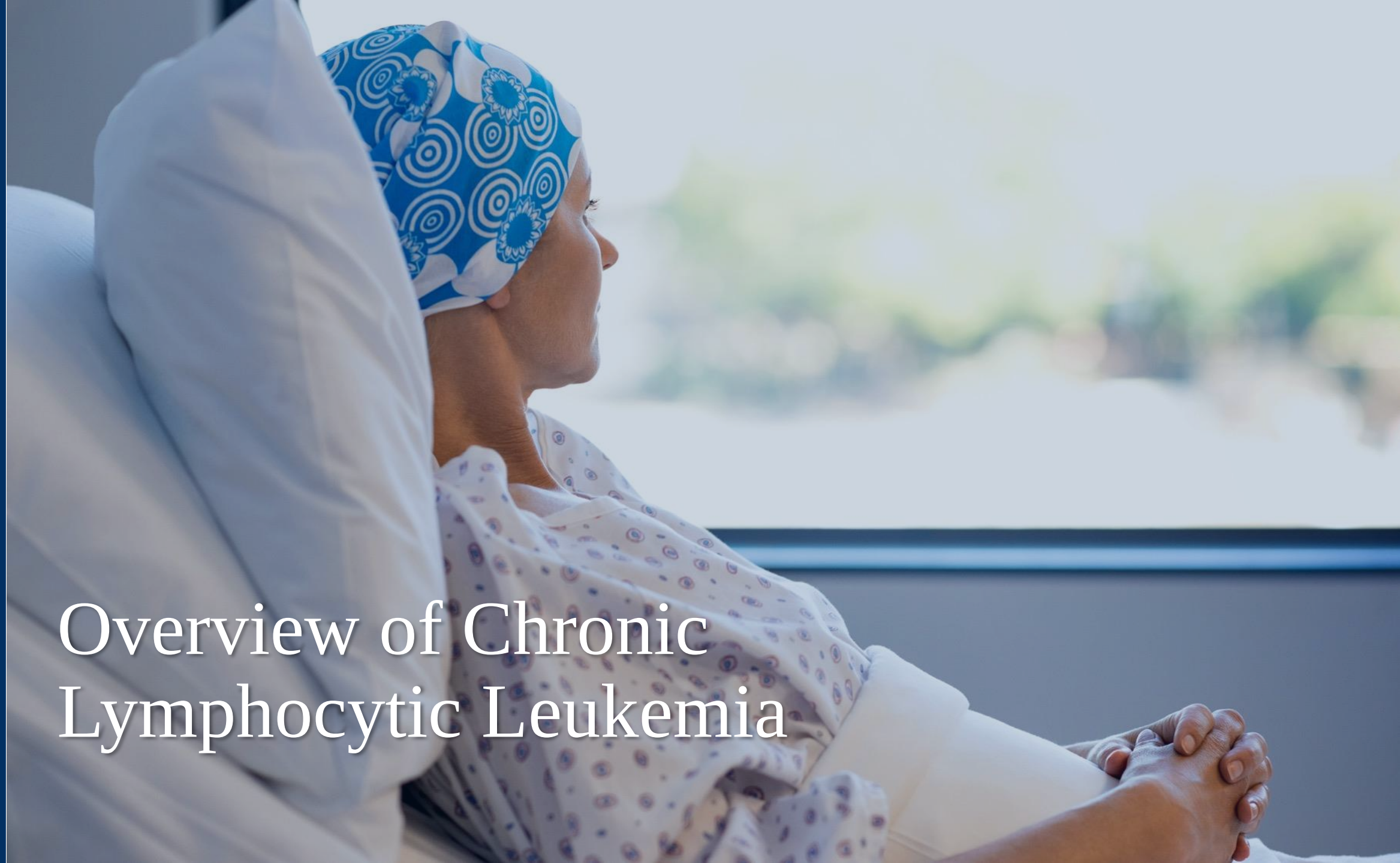
Learning Objectives

At the end of this session, participants should be able to:

- List the currently preferred regimens for treatment of chronic lymphocytic leukemia according to disease- and patient-specific factors
- Describe the considerations for selecting one regimen over another
- Provide appropriate counseling to patients taking targeted therapies, drawing attention to potential side effects, drug interactions, and treatment durations



Overview of Chronic Lymphocytic Leukemia

Background & Epidemiology

- Chronic lymphocytic leukemia (CLL) is a disease of neoplastic mature B-lymphocytes
- Most common type of leukemia in western countries – age-adjusted incidence of 4.1/100,000 inhabitants in the United States
- Median age at diagnosis is 72 years – more males are affected than females
- Proportion of younger patients with early stage CLL and minimal symptoms seems to be increasing, likely due to more frequent blood testing

Source: National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 2.2019); Hallek M et al. *Am J Hematol*. 2019;94(11):1266-1287.

Pathophysiology

- Characterized by the clonal proliferation and accumulation of mature, typically CD5-positive B-cells within the blood, bone marrow, lymph nodes and spleen
- Capacity to generate clonal malignant B-cells may be acquired at the hematopoietic stem cell stage
- Disease thought to be initiated by loss or addition of large amounts of chromosomal material (e.g. deletion 13q, deletion 11q, trisomy 12), followed later by additional mutations that render the leukemia more aggressive

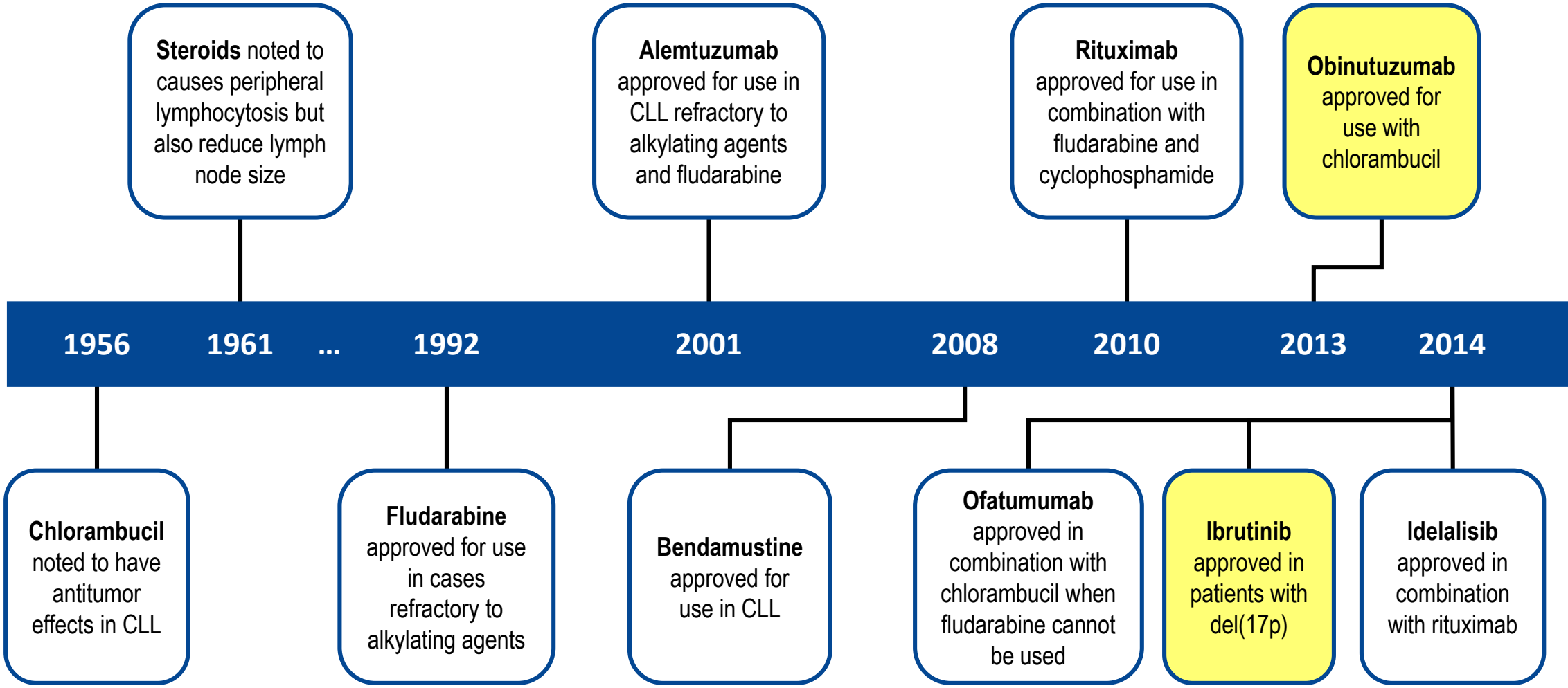
Source: National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 2.2019); Hallek M et al. *Am J Hematol*. 2019;94(11):1266-1287.

Genetic Landscape

Deletions on chromosome 13 (del[13q])	• Most frequently observed cytogenetic aberration in CLL, occurring in approximately 55% of all cases • Typically involve band 13q14 (del[13q14])
Deletions on chromosome 11 (del[11q])	• Can be found in approximately 25% of chemotherapy-naïve CLL patients with advanced disease stages, and 10% of patients with early stage disease • Patients carrying a del(11q) clone typically show a bulky lymphadenopathy, rapid progression, and reduced overall survival • Some of the poor prognostic features of of del(11q) seem to be overcome with chemoimmunotherapy
Trisomy 12	• Observed in 10% to 20% of CLL patients • Genes involved in the pathogenesis of CLL carrying a trisomy 12 are largely unknown, and the prognostic relevance of trisomy 12 is unclear
Deletions on chromosome 17 (del[17p])	• Found in 5% to 8% of chemotherapy-naïve CLL patients • Almost always include band 17p13, where the prominent tumor suppressor gene *TP53* is located • Associated with marked chemotherapy resistance that cannot be overcome with the addition of anti-CD20 antibodies
***TP53* mutations**	• Found in 4% to 37% of patients with CLL • Associated with very poor prognosis

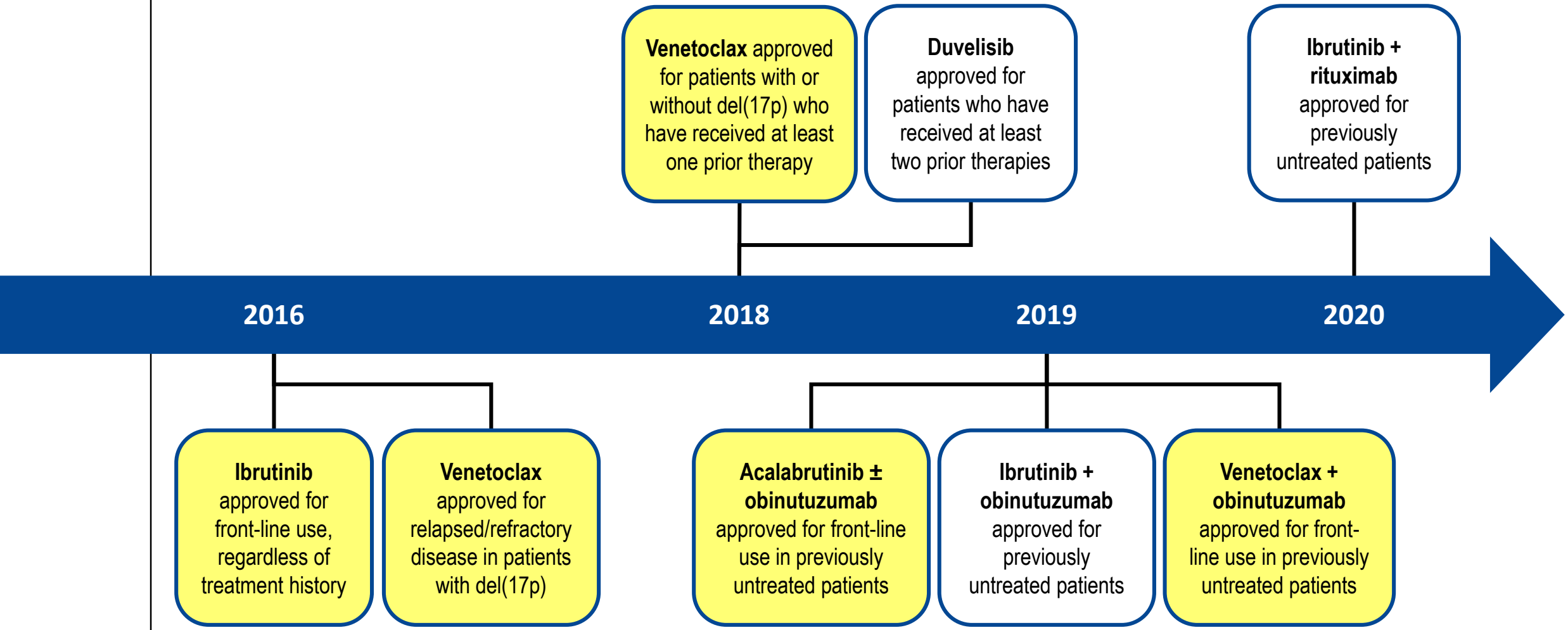
Source: National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 2.2019); Hallek M et al. *Am J Hematol*. 2019;94(11):1266-1287.

Evolution of Treatment



Source: National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 2.2019); Mato A et al. *Am J Hematol*. 2015;90(7):657-664.

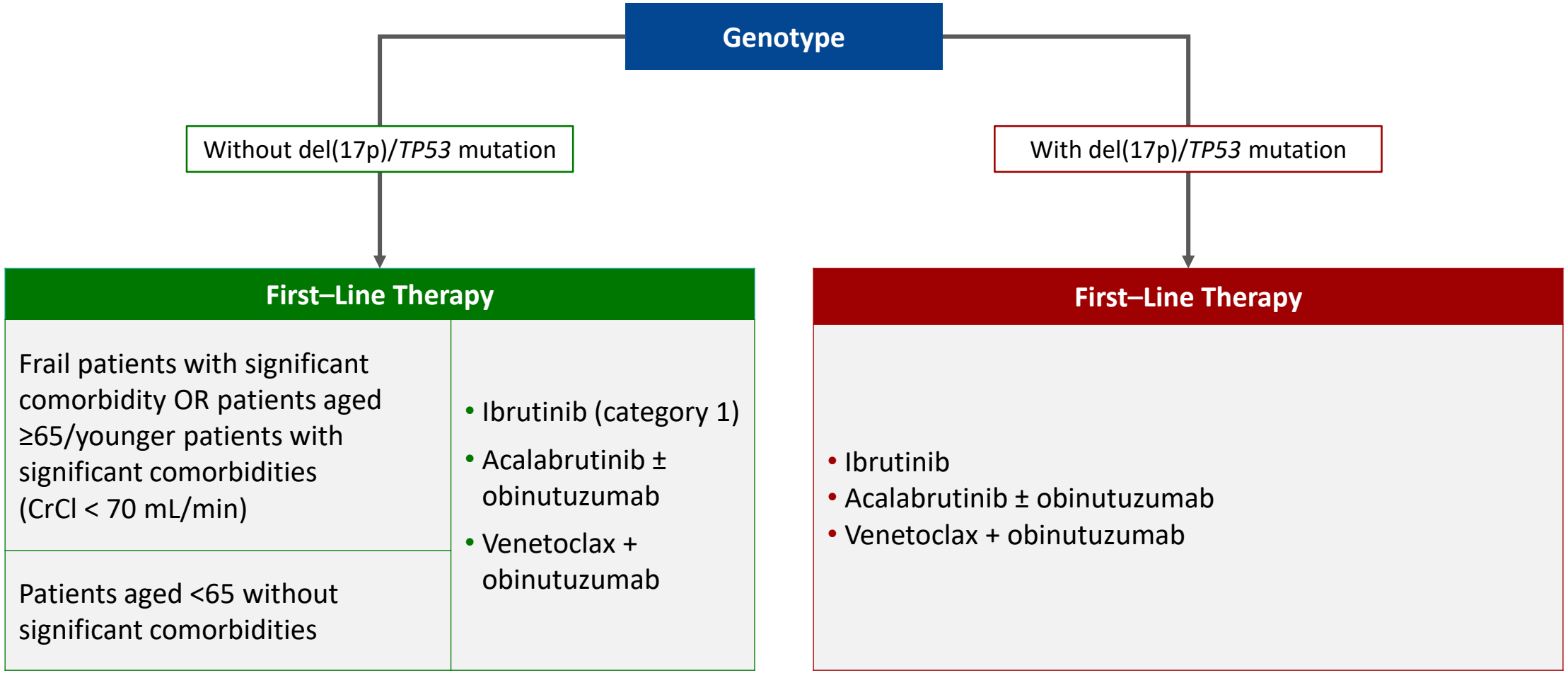
Evolution of Treatment



Source: National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 2.2019); Mato A et al. *Am J Hematol*. 2015;90(7):657-664.

Current First-Line Regimens

Current First-Line Regimens



Source: National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 2.2019).

Ibrutinib (Imbruvica®)

Mechanism of action	• Inhibits Bruton's tyrosine kinase (BTK), which decreases downstream activation of cell survival pathways, such as NF-κB and MAP kinases, and induces apoptosis of malignant B-cells	
Dosing	• Monotherapy: 420 mg orally once daily until disease progression or unacceptable toxicity	
Toxicities	Common • Anemia, neutropenia, thrombocytopenia • Peripheral edema • GI adverse effects (nausea, vomiting, diarrhea) • Myalgia • Rash • Hypertension	Serious • Bleeding • New-onset atrial fibrillation and rare ventricular tachycardias • Secondary malignancies, including skin cancers • Infections, including invasive fungal infections
How supplied	• Capsules: 70 mg (28-count bottle); 140 mg (90- or 120-count bottle) • Tablets: 140 mg, 280 mg, 420 mg, 560 mg (all supplied in two 14-count blisters)	

Source: Imbruvica [package insert]. Sunnyvale, CA: Janssen Biotech, Inc; 2020.

Ibrutinib (Imbruvica®)

Clinical pearls	• Transient lymphocytosis is expected in most patients within the first few weeks of treatment and does not signify disease progression • Ibrutinib should be held 3-7 days prior to surgery • Treatment resistance may develop due to mutations at the ibrutinib binding site (via PLCG2) – transition to next therapy as soon as possible after disease progression on ibrutinib, as progression can accelerate after discontinuation • Avoid concomitant use of strong/moderate inhibitors and strong inducers of CYP3A4 • Administer at the same time each day with a glass of water • Swallow capsules and tablets whole; do not open, break, chew, cut, or crush

Source: Imbruvica [package insert]. Sunnyvale, CA: Janssen Biotech, Inc; 2020.

Acalabrutinib (Calquence®)

Mechanism of action	• Inhibits BTK by covalently bonding to a cysteine residue at the active BTK site, which prevents activation of the signaling proteins CD86 and CD69, as well as inhibits proliferation and survival of malignant B-cells	
Dosing	• Monotherapy or in combination with obinutuzumab: 100 mg orally every 12 hours until disease progression or unacceptable toxicity	
Toxicities	Common • Anemia, neutropenia, thrombocytopenia • Headache (typically resolves over 1-2 months of therapy) • Diarrhea • Myalgia	Serious • Bleeding • New-onset atrial fibrillation • Secondary malignancies, including skin cancers • Infections
How supplied	• Capsules: 100 mg (60-count bottle)	

Source: Calquence [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.

Acalabrutinib (Calquence®)

Clinical pearls	• Transient lymphocytosis is expected in most patients within the first few weeks of treatment and does not signify disease progression • Headaches can generally be managed with analgesics such as acetaminophen and caffeine supplements • Consider the benefit-risk of withholding acalabrutinib for 3 days pre-post surgery • Treatment resistance may develop due to mutations at the acalabrutinib binding site (via PLCG2) – transition to next therapy as soon as possible after disease progression on acalabrutinib, as progression can accelerate after discontinuation • Avoid concomitant use of strong inhibitors and strong inducers of CYP3A4 • Avoid co-administration with proton pump inhibitors (PPIs), and stagger dosing with H2-receptor antagonists and antacids by 2 hours • Swallow capsules and tablets whole; do not open, break, chew, cut, or crush

Source: Calquence [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.

Obinutuzumab (Gazyva®)

Mechanism of action	• Binds to the CD20 antigen on the surface of pre-B- and mature B-cells and causes lysis. Also activates polymorphonuclear neutrophils, produces radical oxygen, and mediates phagocytosis by binding to CD16A and CD16B	

Dosing	• In combination with acalabrutinib:
	  • Cycle 2: 100 mg on day 1, followed by 900 mg on day 2, followed by 1,000 mg weekly for 2 doses (days 8 and 15) (cycle 1 is acalabrutinib only; obinutuzumab begins with cycle 2)
	  • Cycles 3 through 7: 1,000 mg on day 1 every 28 days for 5 doses (continue acalabrutinib until progression or unacceptable toxicity)
		• In combination with venetoclax:
		  • Cycle 1: 100 mg on day 1, followed by 900 mg on day 2 (or 1,000 mg on day 1), followed by 1,000 mg weekly for 2 doses (days 8 and 15)
		  • Cycles 2 through 6: 1,000 mg on day 1 every 28 days for 5 doses (continue venetoclax until the end of cycle 12)

Toxicities	Common • Anemia, neutropenia, thrombocytopenia • Diarrhea • Arthralgia • Cough • Fever	Serious • Infections, including hepatitis B virus reactivation • Infusion reactions and hypersensitivity • Tumor lysis syndrome (TLS) • Gastrointestinal perforation • Progressive multifocal leukoencephalopathy
How supplied	• Single-dose vials: 1,000 mg/40 mL (25 mg/mL)	

Source: Gazyva [package insert]. South San Francisco, CA: Genentech, Inc; 2020.

Obinutuzumab (Gazyva®)

Clinical pearls	• All patients should receive pre-medication with acetaminophen, an antihistamine, and a glucocorticoid prior to cycle 1, day 1 and day 2 obinutuzumab infusions, and acetaminophen prior to all subsequent infusions. Antihistamines and/or glucocorticoids should be added thereafter depending on occurrence of infusion reactions and pre-treatment lymphocyte count • Initial infusion given over 4 hours; infusion rate may be increased incrementally for subsequent infusions based on tolerability • Neutropenia may warrant antimicrobial, antiviral, and/or antifungal prophylaxis

Source: Gazyva [package insert]. South San Francisco, CA: Genentech, Inc; 2020.

Venetoclax (Venclexta®)

Mechanism of action	• Inhibits B-cell lymphoma 2 (Bcl-2), an antiapoptotic protein, thus restoring apoptosis in leukemia cells by triggering mitochondrial outer membrane permeability and activating caspases		
Dosing	• <u>In combination with obinutuzumab</u>: initial 5-week ramp-up (20 mg x 1 week, 50 mg x 1 week, 100 mg x 1 week, 200 mg x 1 week, 400 mg x 1 week), followed by 400 mg once daily for a total treatment duration of 12 cycles (28 days each). Obinutuzumab begins on day 1 of cycle 1 and venetoclax is initiated on day 22 of cycle 1.		
Toxicities	• Anemia, neutropenia, thrombocytopenia • GI adverse effects (nausea, vomiting, diarrhea)	<u>Common</u> • Peripheral edema • Rash • Myalgia	• Cough • Dizziness • Fever	<u>Serious</u> • TLS • Bleeding • Autoimmune hemolytic anemia • Infections

How supplied	• <u>Tablets</u>:
	  • Starter pack (four weekly wallet blisters corresponding to the ramp-up schedule and containing 10 mg, 50 mg, and 100 mg tablets)
	  • Unit dose blister (10 mg x 2 tablets and 50 mg x 1 tablet)
	  • Bottle (100 mg x 120 tablets and 100 mg x 180 tablets)		

Source: Venclexta [package insert]. North Chicago, IL: AbbVie Inc; 2020.

Venetoclax (Venclexta®)

Clinical pearls	• Pre-hydration and pre-medication with an anti-hyperuricemic agent is required before initiating venetoclax. Agent selection and treatment setting (i.e. inpatient vs. outpatient) is dependent on tumor burden • If treatment is interrupted for >1 week during escalation, consider re-initiating at a lower dose • Accelerated dose escalation with close inpatient monitoring can be initiated in patients with high tumor burden where there is concern for rapid disease progression on or following BTK inhibitor therapy • Reduced renal function (CrCl <80 mL/min) increases the risk of TLS • Avoid concomitant use of strong CYP3A inhibitors or inducers • Swallow capsules and tablets whole; do not open, break, chew, cut, or crush

Source: Venclexta [package insert]. North Chicago, IL: AbbVie Inc; 2020.

BEFORE 1ST DOSE

PREP DAY 1	PREP DAY 2
56 oz	56 oz

Prep Day 1 and Prep Day 2 are the 2 days before the first dose of VENCLEXTA® (venetoclax tablets), as directed by your healthcare provider.

How do I take VENCLEXTA?

Take your dose once a day with a meal and water at about the same time each day. Swallow each tablet whole. Do not chew, crush, or break the tablets. Write the day of the week and the date you take your dose in each calendar box.

Your healthcare provider may delay, decrease your dose, or stop treatment with VENCLEXTA if you have side effects. If your healthcare provider changes your dosing schedule, the information in this calendar may no longer apply.

What if I miss my dose?

If it has been **less than 8 hours**, take your dose as soon as possible. If it has been **more than 8 hours**, skip the missed dose. Take the next dose at your usual time.

If you vomit after taking your dose, do not take an extra dose. Take the next dose at your usual time the next day.

It is important to stay hydrated. Drink water every day when taking VENCLEXTA.

Pay special attention on:

- Prep Day 1
- Prep Day 2
- The days marked with a blue water bottle

Drink at least 7 cups of water throughout the day.

For more information, click here for full Prescribing Information, including Medication Guide.

VENCLEXTA CLL Starting Pack

Color-coded weekly blister packs for Weeks 1-4 of treatment.

Keep VENCLEXTA in the original packaging during the first 4 weeks of treatment, and do not transfer the tablets to a different container.

Tablets shown are not actual size.

Take VENCLEXTA tablets by mouth once daily

	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
WEEK 1	Take two 10 mg tablets	Take two 10 mg tablets	Take two 10 mg tablets	Take two 10 mg tablets	Take two 10 mg tablets	Take two 10 mg tablets	Take two 10 mg tablets
WEEK 2	Take one 50 mg tablet	Take one 50 mg tablet	Take one 50 mg tablet	Take one 50 mg tablet	Take one 50 mg tablet	Take one 50 mg tablet	Take one 50 mg tablet
WEEK 3	Take one 100 mg tablet	Take one 100 mg tablet	Take one 100 mg tablet	Take one 100 mg tablet	Take one 100 mg tablet	Take one 100 mg tablet	Take one 100 mg tablet
WEEK 4	Take two 100 mg tablets	Take two 100 mg tablets	Take two 100 mg tablets	Take two 100 mg tablets	Take two 100 mg tablets	Take two 100 mg tablets	Take two 100 mg tablets
WEEK 5	Take four 100 mg tablets	Take four 100 mg tablets	Take four 100 mg tablets	Take four 100 mg tablets	Take four 100 mg tablets	Take four 100 mg tablets	Take four 100 mg tablets

VENCLEXTA pill bottle

The medicine you will need for your 5th week of treatment and beyond is in a pill bottle.

WEEK 5 and beyond

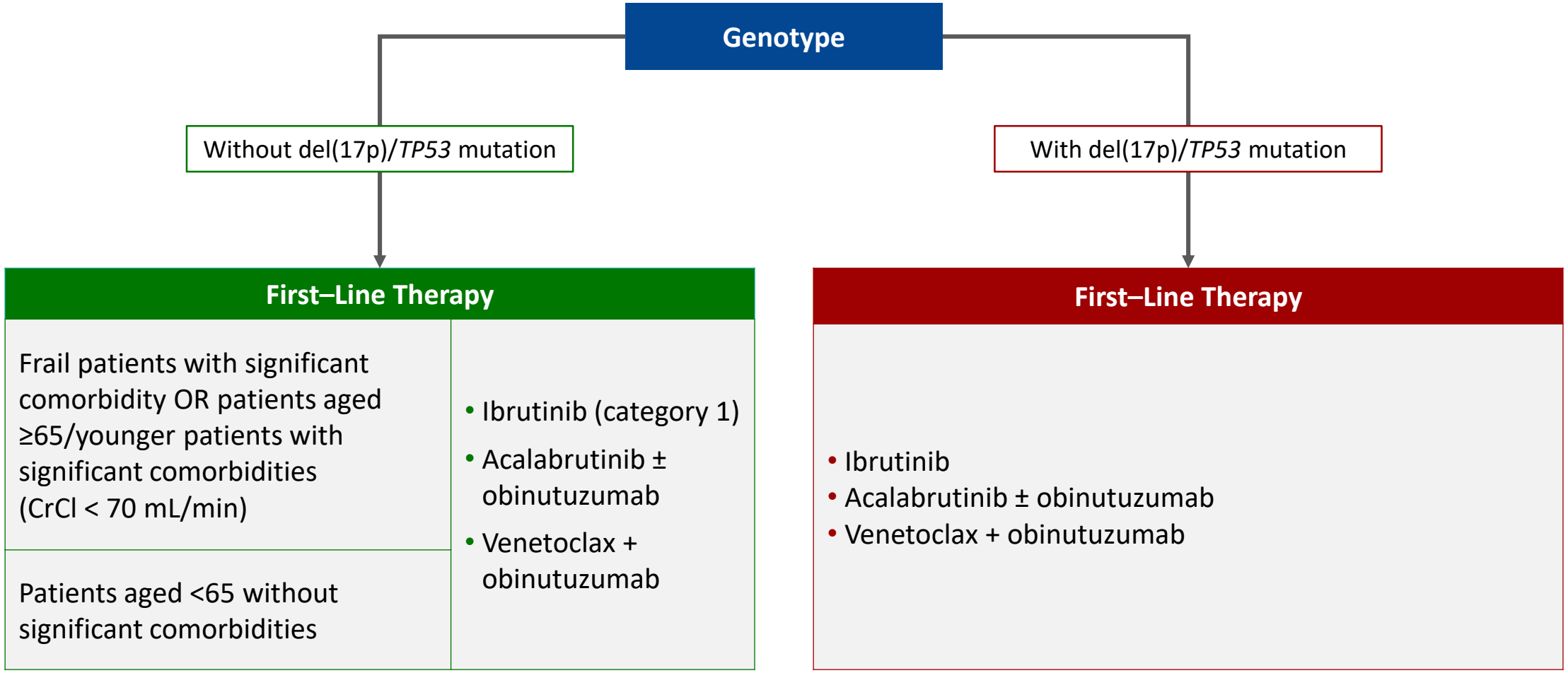
Safety Considerations

- **VENCLEXTA can cause serious side effects, including tumor lysis syndrome (TLS).** TLS can cause kidney failure, the need for dialysis treatment, and may lead to death. Your healthcare provider will do tests for TLS. It is important to keep your appointments for blood tests. Tell your healthcare provider right away if you have any symptoms of TLS during treatment with VENCLEXTA, including fever, chills, nausea, vomiting, confusion, shortness of breath, seizures, irregular heartbeat, dark or cloudy urine, unusual tiredness, or muscle or joint pain. **Drink plenty of water during treatment with VENCLEXTA to help reduce your risk of getting TLS.**

Please see Use and Important Safety Information on page 3

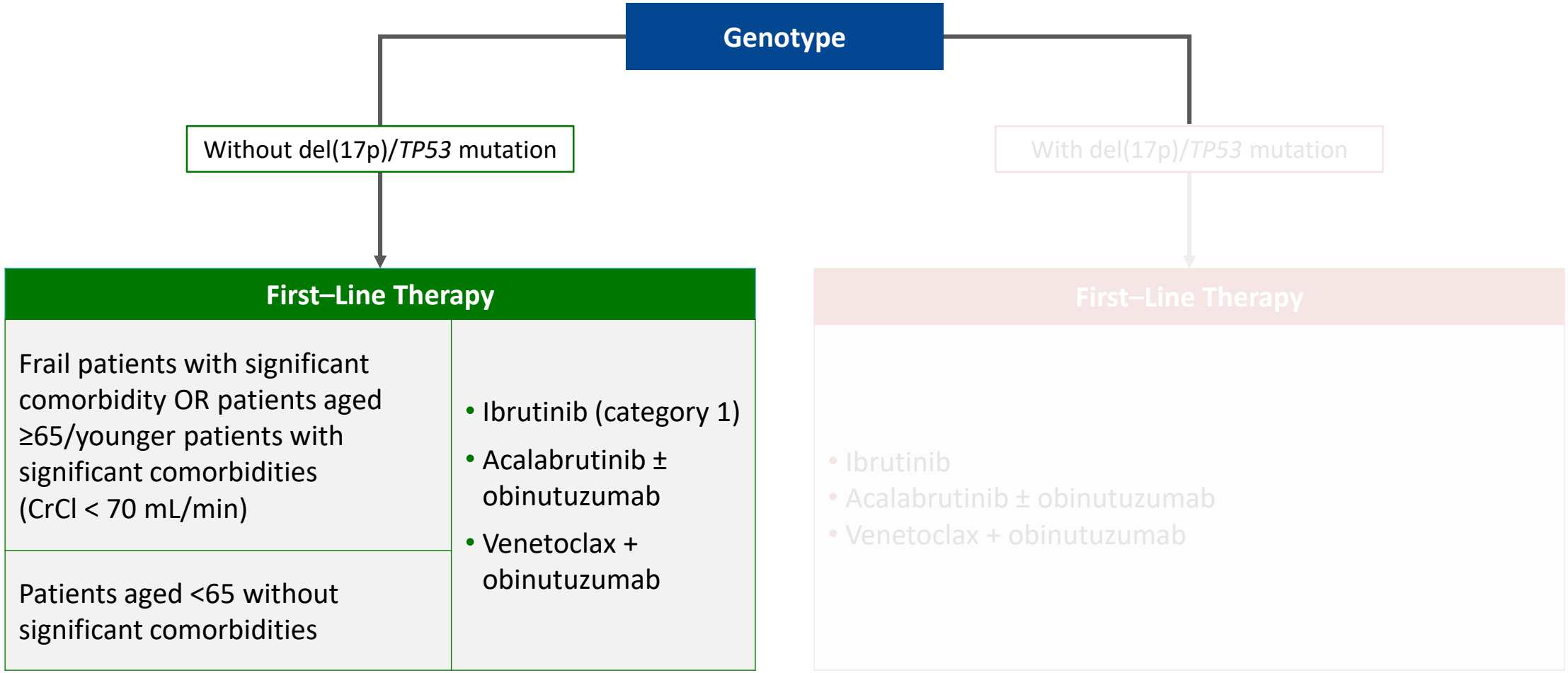
Landmark Trials for First-Line Treatments

Current First-Line Regimens



Source: National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 2.2019).

Current First-Line Regimens



Source: National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 2.2019).

Landmark Trials: del(17)/*TP53*-negative

Ibrutinib monotherapy in older patients

RESONATE-2

Population	• 269 patients 65 years of age or older with previously untreated CLL or small lymphocytic lymphoma
Intervention	• Study group (n = 136): ibrutinib 420 mg daily (n = 136) • Control group (n = 133): twelve 28-day cycles of chlorambucil 0.5 mg/kg on days 1 and 15 of each 28-day cycle, which could be increased to a maximum of 0.8 mg/kg
Outcomes	• Primary outcome: PFS as assessed by an independent review committee

Abbreviations: PFS: progression-free survival

Source: Burger JA et al. *N Engl J Med*. 2015;373(25):2425-2437.

Landmark Trials: del(17)/*TP53*-negative

Ibrutinib monotherapy in older patients

RESONATE-2

Results: Efficacy	• Median follow-up period: 18.4 months • PFS: significantly longer with ibrutinib (median not reached vs. 18.9 months) • Risk of progression or death: 84% lower with ibrutinib than with chlorambucil (HR 0.16, 95% CI 0.09-0.28; P <0.001) • OS: significantly prolonged with ibrutinib at 24 months (98% vs. 85%) (HR 0.16, 95% CI 0.05-0.56; P = 0.001) • OR: higher with ibrutinib than with chlorambucil (86% vs. 35%, rate ratio 2.42, 95% CI 1.91-3.07; P <0.001)
Results: Safety	• Most frequent all grades: ibrutinib – diarrhea (42%), chlorambucil – nausea (39%) • Most frequent grade 3-4: ibrutinib – neutropenia (10%); chlorambucil – neutropenia (18%) • Discontinuation of treatment due to adverse events occurred less frequently in the ibrutinib group than in the chlorambucil group (9% vs. 23% of the patients) • Major hemorrhage and atrial fibrillation occurred in 4% and 6% of patients in the ibrutinib group, respectively
Conclusion	• In patients ≥65 years old with previously untreated CLL, treatment with ibrutinib resulted in significantly longer PFS and higher rates of OS and OR compared to chlorambucil, with fewer patients discontinuing treatment due to toxicity
Comments	• Patients with del(17p) were excluded and only 12 patients had *TP53* mutations

Abbreviations: PFS: progression-free survival; OS: overall survival; OR: overall response; HR: hazard ratio; CI: confidence interval

Source: Burger JA et al. *N Engl J Med*. 2015;373(25):2425-2437.

Landmark Trials: del(17)/*TP53*-negative

Ibrutinib monotherapy in younger patients

ECOG-ACRIN research group (E1912)

Population	• 529 patients 70 years of age or younger with previously untreated CLL
Intervention	• Study group (n = 354): ibrutinib 420 mg daily + rituximab (50 mg/m^2 on day 1 of cycle 2; 325 mg/m^2 on day 2 of cycle 2; and 500 mg/m^2 on day 1 of cycles 3 through 7 • Control group (n = 175): six 28-day cycles of intravenous fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 on days 1 through 3 with rituximab 50 mg/m^2 on day 1 of cycle 1; 325 mg/m^2 on day 2 of cycle 1; and 500 mg/m^2 on day 1 of cycles 2 through 6
Outcomes	• Primary outcome: PFS • Secondary outcome: OS

Abbreviations: PFS: progression-free survival; OS: overall survival

Source: Shanafelt TD et al. *N Engl J Med*. 2019;381(5):432-443.

Landmark Trials: del(17)/*TP53*-negative

Ibrutinib monotherapy in younger patients

ECOG-ACRIN research group (E1912)

Results: Efficacy	• Median follow-up period: 33.6 months • PFS: significantly longer with ibrutinib-rituximab (89.4% vs. 72.9% at 3 years; HR 0.35, 95% CI 0.22-0.56; P <0.001) • OS: favored ibrutinib-rituximab (98.8% vs. 91.5% at 3 years; HR 0.17, 95% CI 0.05-0.54; P <0.001)
Results: Safety	• The incidence of adverse events of grade 3 or higher was similar in the two groups (80.1% treated with ibrutinib-rituximab vs. 79.7% who received fludarabine-cyclophosphamide-rituximab, P = 0.91) • Most frequent grade 3-4: ibrutinib-rituximab – neutropenia (25.6%); chemoimmunotherapy – lymphopenia (47.5%)
Conclusion	• In patients ≤70 years of age with previously untreated CLL, the combination of ibrutinib with rituximab resulted in superior PFS and OS compared to chemoimmunotherapy without a significant difference in adverse events
Comments	• Despite this being a study of the combination of ibrutinib + rituximab, these results combined with others suggesting no OS benefit with the addition of rituximab to ibrutinib were sufficient for NCCN to change ibrutinib monotherapy from category 2A to category 1 for treatment of younger patients (<65 years old) • Patients with del(17p) and those taking concomitant warfarin were excluded • Patients with unmutated immunoglobulin heavy-chain variable region (*IGHV*) had particularly good response

Abbreviations: PFS: progression-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval

Source: Shanafelt TD et al. *N Engl J Med*. 2019;381(5):432-443.

Landmark Trials: del(17)/*TP53*-negative

Acalabrutinib ± obinutuzumab

ELEVATE TN

Population	• 675 patients 65 years of age or older, or 18-65 years of age with creatinine clearance of 30-69 mL/min or Cumulative Illness Rating Scale for Geriatrics score greater than 6 with previously untreated CLL
Intervention	• Study group 1 (n = 179): acalabrutinib 100 mg twice daily plus obinutuzumab on days 1 (100 mg), 2 (900 mg), 8 (1000 mg), and 15 (1000 mg) of cycle 2 and on day 1 (1000 mg) of cycles 3-7 • Study group 2 (n = 179): acalabrutinib 100 mg twice daily • Control group (n = 177): oral chlorambucil 0.5 mg/kg on days 1 and 15 plus obinutuzumab on days 1 (100 mg), 2 (900 mg), 8 (1000 mg), and 15 (1000 mg) of cycle 1 and on day 1, (1000 mg) of cycles 2-6
Outcomes	• Primary outcome: PFS between the two combination therapy groups, assessed by independent review committee

Abbreviations: PFS: progression-free survival

Source: Sharman JP et al. *Lancet*. 2020;395(10232):1278-1291.

Landmark Trials: del(17)/*TP53*-negative

Acalabrutinib ± obinutuzumab

ELEVATE TN

Results: Efficacy	• Median follow-up period: 28.3 months • Median PFS: significantly longer with acalabrutinib-obinutuzumab and acalabrutinib monotherapy, compared with obinutuzumab-chlorambucil (median not reached with acalabrutinib-obinutuzumab vs. 22.6 months with obinutuzumab-chlorambucil, HR 0.1, 95% CI 0.06-0.17; P <0.0001; and not reached with acalabrutinib monotherapy vs. 22.6 months with obinutuzumab-chlorambucil, HR 0.20, 95% CI 0.13-0.3; P <0.0001) • Estimated PFS at 24 months: 93% (95% CI 87-96%) with acalabrutinib-obinutuzumab, 87% (95% CI 81-92%) with acalabrutinib monotherapy, and 47% (95% CI 39-55%) with obinutuzumab-chlorambucil
Results: Safety	• Most frequent all grades: acalabrutinib-obinutuzumab – headache (39.9%); acalabrutinib monotherapy – headache (36.9%) obinutuzumab-chlorambucil – neutropenia (45%) • Most frequent grade 3-4: acalabrutinib-obinutuzumab – neutropenia (30%); acalabrutinib monotherapy – neutropenia (9%) obinutuzumab-chlorambucil – neutropenia (4%)
Conclusion	• In patients with previously untreated CLL, acalabrutinib with or without obinutuzumab significantly improved PFS compared to obinutuzumab-chlorambucil chemoimmunotherapy and had a manageable safety profile
Comments	• Del(17)(p13.1) was present in 49 (9%) patients, del(11)(q22.3) was present in 95 (18%) patients, and *TP53* mutation was present in 61 (11%) patients – improvements in PFS were consistently observed across each of these patient subgroups • Patients taking concomitant warfarin were excluded

Abbreviations: PFS: progression-free survival; HR: hazard ratio; CI: confidence interval

Source: Sharman JP et al. *Lancet*. 2020;395(10232):1278-1291.

Landmark Trials: del(17)/*TP53*-negative

Venetoclax + obinutuzumab

CLL14

Population	• 432 patients with previously untreated CLL and coexisting conditions with a score of greater than 6 on the Cumulative Illness Rating Scale or a calculated creatinine clearance of less than 70 mL/min
Intervention	• Study group (n = 216): venetoclax initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week), thereafter continuing at 400 mg daily until completion of cycle 12 plus six cycles of obinutuzumab starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on day 8 and 1000 mg on day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles 2 through 6 • Control group (n = 216): oral chlorambucil 0.5 mg/kg on days 1 and 15 of each cycle until completion of 12 cycles plus obinutuzumab (same dosing and schedule as above)
Outcomes	• Primary outcome: investigator-assessed PFS

Abbreviations: PFS: progression-free survival

Source: Fischer K et al. *N Engl J Med*. 2019;380(23):2225-2236.

Landmark Trials: del(17)/*TP53*-negative

Venetoclax + obinutuzumab

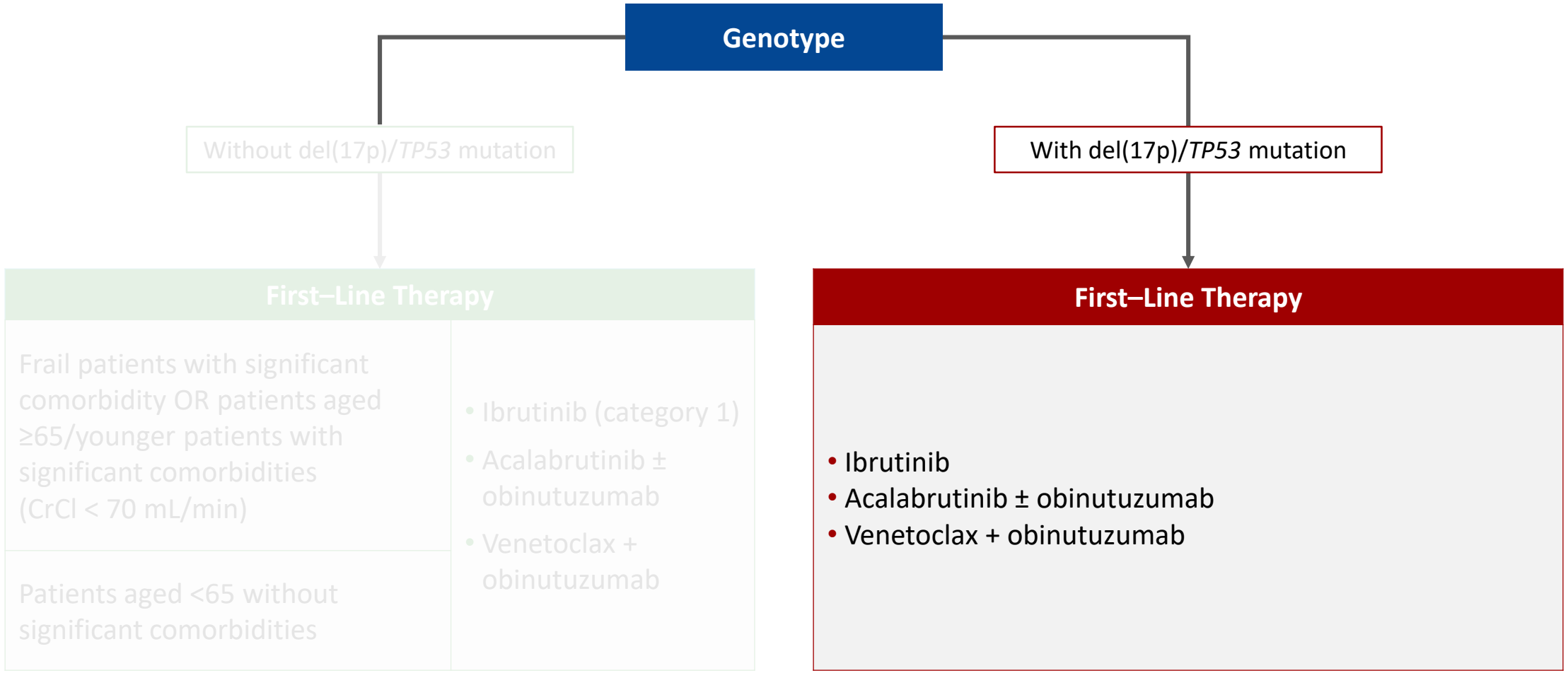
CLL14

Results: Efficacy	• Median follow-up period: 28.1 months • Median PFS: significantly higher in the venetoclax-obinutuzumab group (30 events vs. 77 events); HR 0.35, 95% CI 0.23-0.53; P <0.001) • Estimated PFS at 24 months: significantly higher in the venetoclax-obinutuzumab group than in the chlorambucil-obinutuzumab group (88.2% [95% CI 83.7-92.6] vs. 64.1% [95% CI 57.4 to 70.8])
Results: Safety	• Most frequent grade 3-4: venetoclax-obinutuzumab – neutropenia (52.8%); chlorambucil-obinutuzumab – neutropenia (48.1%) • TLS was reported in three patients in the venetoclax-obinutuzumab group – venetoclax–obinutuzumab was not associated with a higher frequency of tumor lysis syndrome
Conclusion	• In patients with previously untreated CLL and coexisting conditions, fixed-duration venetoclax-obinutuzumab was associated with significantly higher percentage of patients with PFS than treatment with chlorambucil-obinutuzumab without an overall increased risk of adverse effects, including TLS
Comments	• Del(17) was present in 31 patients and TP53 mutation was present in 32 patients • The observed benefit was also seen in patients with *TP53* deletion, mutation, or both

Abbreviations: PFS: progression-free survival; HR: hazard ratio; CI: confidence interval

Source: Fischer K et al. *N Engl J Med*. 2019;380(23):2225-2236.

Current First-Line Regimens



Source: National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 2.2019).

Landmark Trials: del(17)/*TP53*-positive

Ibrutinib monotherapy

Farooqui et al. 2015 and Ahn et al. 2018 (follow-up study)

Population	• 51 Patients with active CLL with *TP53* aberrations (47 had deletion 17p13.1 and 4 carried a *TP53* mutation in the absence of deletion 17p13.1); 35 enrolled patients had previously untreated CLL and 16 had relapsed or refractory disease
Intervention	• Study group (n = 51): ibrutinib 420 mg orally once daily
Outcomes	• Primary outcome: OR to treatment at 24 weeks in all evaluable patients

Abbreviations: OR: overall response

Source: Farooqui MZ et al. *Lancet Oncol*. 2015;16(2):169-176; Ahn IE et al. *Blood*. 2018;131(21):2357-2366.

Landmark Trials: del(17)/*TP53*-positive

Ibrutinib monotherapy

Farooqui et al. 2015 and Ahn et al. 2018 (follow-up study)

Results: Efficacy	• Median follow-up period: 24 months
	• OR:
	  • Untreated CLL: 32 (97% [95% CI 86-100]) of 33 previously untreated patients achieved an objective response, including partial response in 18 patients (55%) and partial response with lymphocytosis in 14 (42%).
	  • Relapsed-refractory: 12 (80% [95% CI 52-96]) of the 15 patients with relapsed or refractory CLL had an objective response: six (40%) achieved a partial response and six (40%) achieved a partial response with lymphocytosis; the remaining three (20%) patients had stable disease

Results: Safety	• Most frequent all grades: diarrhea (49%) • Most frequent grade 3-4: neutropenia (22%)
Conclusion	• In patients with CLL with *TP53* aberrations, treatment with single-agent ibrutinib induced durable responses. Clones with deletion 17p13.1 were equally sensitive to ibrutinib as were those not carrying the mutation.
Comments	• After a median follow-up of 57 months, the estimated 5-year PFS and OS were 74% and 85%, respectively

Abbreviations: PFS: progression-free survival; OS: overall survival; OR: overall response; CI: confidence interval

Source: Farooqui MZ et al. *Lancet Oncol*. 2015;16(2):169-176; Ahn IE et al. *Blood*. 2018;131(21):2357-2366.

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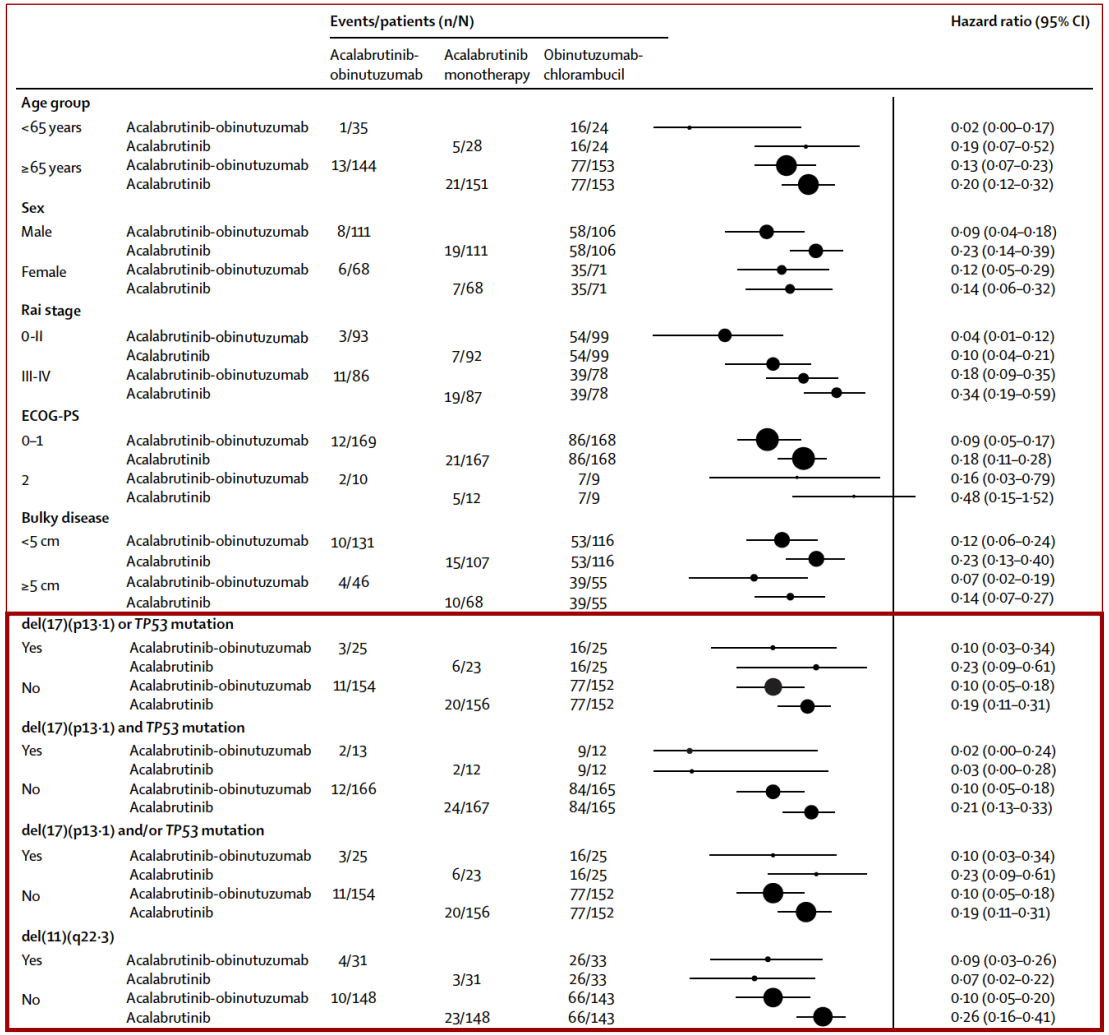
Acalabrutinib ± obinutuzumab

ELEVATE TN

	Acalabrutinib-obinutuzumab (n=179)	Acalabrutinib monotherapy (n=179)	Obinutuzumab-chlorambucil (n=177)
Age (years)			
Median (IQR)	70·0 (65·0–75·0)	70·0 (66·0–75·0)	71·0 (67·0–76·0)
≥75	53 (29·6%)	50 (27·9%)	52 (29·4%)
≥65	144 (80·4%)	151 (84·4%)	153 (86·4%)
<65*	35 (19·6%)	28 (15·6%)	24 (13·6%)
Creatinine clearance 30–69 mL/min†	2 (1·1%)	4 (2·2%)	7 (4·0%)
CIRS-G >6†	30 (16·8%)	21 (11·7%)	15 (8·5%)
Any of the above†	31 (17·3%)	24 (13·4%)	20 (11·3%)
Sex			
Female	68 (38·0%)	68 (38·0%)	71 (40·1%)
Male	111 (62·0%)	111 (62·0)	106 (59·9%)
ECOG PS			
0–1	169 (94·4%)	165 (92·2%)	167 (94·4%)
2	10 (5·6%)	14 (7·8%)	10 (5·6%)
CLL-IPI score			
0–1 (low risk)	9 (5·0%)	4 (2·2%)	5 (2·8%)
2–3 (intermediate risk)	27 (15·1%)	18 (10·1%)	25 (14·1%)
4–6 (high risk)	115 (64·2%)	134 (74·9%)	119 (67·2%)
7–10 (very high risk)	23 (12·8%)	20 (11·2%)	23 (13·0%)
Rai stage			
0	3 (1·7%)	0	1 (0·6%)
I	54 (30·2%)	48 (26·8%)	50 (28·2%)
II	36 (20·1%)	44 (24·6%)	48 (27·1%)
III	48 (26·8%)	50 (27·9%)	40 (22·6%)
IV	38 (21·2%)	37 (20·7%)	38 (21·5)
High-risk features			
Chromosome 17p13·1 deletion	17 (9·5%)	16 (8·9%)	16 (9·0%)
Chromosome 11q22·3 deletion	31 (17·3%)	31 (17·3%)	33 (18·6%)
Unmutated *IGHV*	103 (57·5%)	119 (66·5%)	116 (65·5%)
Mutated *TP53*	21 (11·7%)	19 (10·6%)	21 (11·9%)
Complex karyotype	29 (16·2%)	31 (17·3%)	32 (18·1%)
Including chromosome 17p13·1 deletion	8 (4·5%)	8 (4·5%)	7 (4·0%)
Without chromosome 17p13·1 deletion	21 (11·7%)	23 (12·8%)	25 (14·1%)
Chromosome 17p13·1 deletion or mutated *TP53*	12 (6·7%)	11 (6·1%)	13 (7·3%)
Chromosome 17p13·1 deletion and mutated *TP53*	13 (7·3%)	12 (6·7%)	12 (6·8%)



Source: Sharman JP et al. *Lancet*. 2020;395(10232):1278-1291.

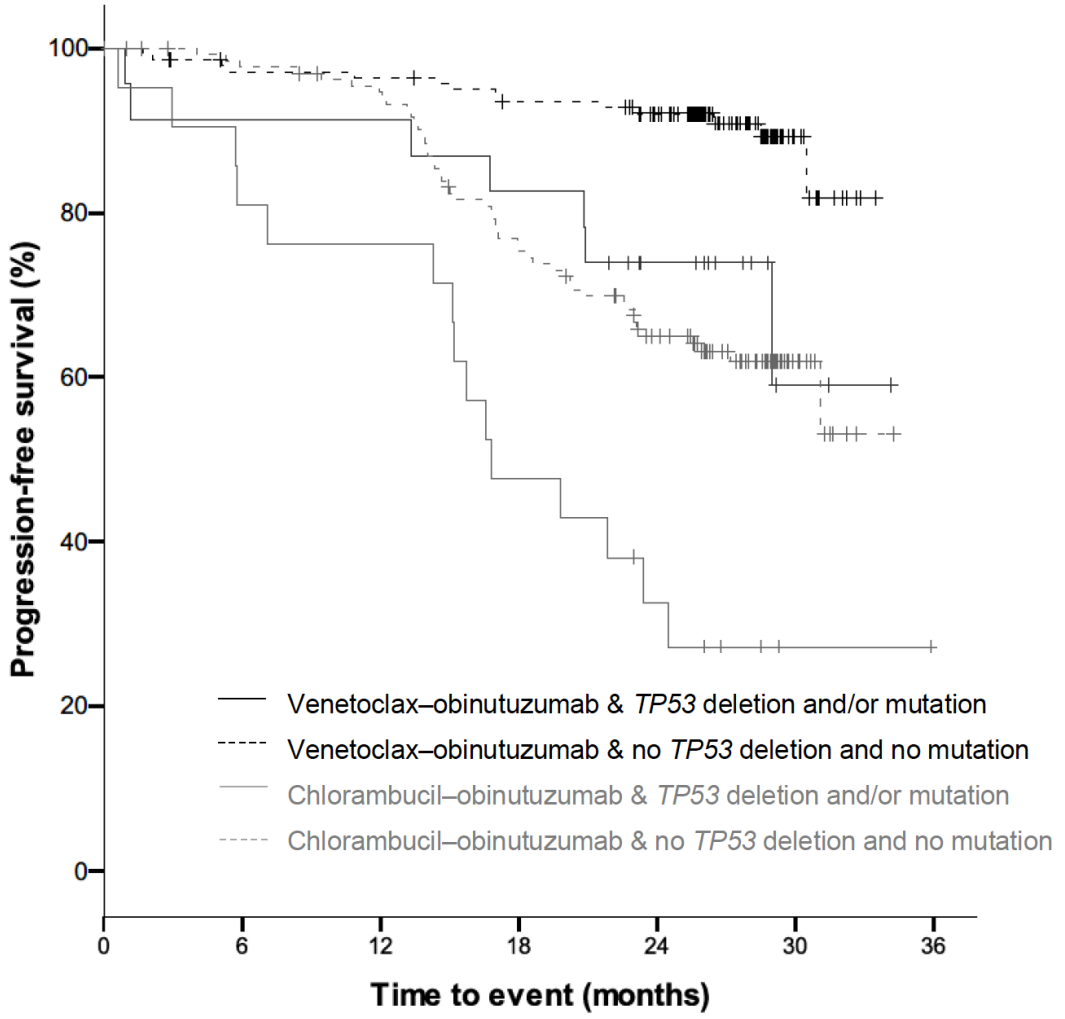
Landmark Trials: del(17)/*TP53*-positive

Venetoclax + obinutuzumab

CLL14

Table 1. Selected Patient Demographic and Disease Characteristics at Baseline (Intention-to-Treat Population).*

Characteristic	Venetoclax–Obinutuzumab (N=216)	Chlorambucil–Obinutuzumab (N=216)
Age ≥75 yr — no. (%)	72 (33.3)	78 (36.1)
Male sex — no. (%)	146 (67.6)	143 (66.2)
Binet stage — no. (%)†		
A	46 (21.3)	44 (20.4)
B	77 (35.6)	80 (37.0)
C	93 (43.1)	92 (42.6)
Tumor lysis syndrome risk category — no. (%)		
Low	29 (13.4)	26 (12.0)
Intermediate	139 (64.4)	147 (68.1)
High	48 (22.2)	43 (19.9)
Total CIRS score >6 — no. (%)‡	186 (86.1)	177 (81.9)
Calculated creatinine clearance <70 ml/min — no./total no. (%)	128/215 (59.5)	118/213 (55.4)
Cytogenetic subgroup — no./total no. (%)§		
Deletion in 17p	17/200 (8.5)	14/193 (7.3)
Deletion in 11q	36/200 (18.0)	38/193 (19.7)
Trisomy 12	36/200 (18.0)	40/193 (20.7)
No abnormalities	50/200 (25.0)	42/193 (21.8)
Deletion in 13q alone	61/200 (30.5)	59/193 (30.6)
IGHV mutational status — no./total no. (%)		
Mutated	76/200 (38.0)	83/208 (39.9)
Unmutated	121/200 (60.5)	123/208 (59.1)
Could not be evaluated	3/200 (1.5)	2/208 (1.0)
TP53 mutational status — no./total no. (%)		
Mutated	19/171 (11.1)	13/157 (8.3)
Unmutated	152/171 (88.9)	144/157 (91.7)



Source: Fischer K et al. *N Engl J Med*. 2019;380(23):2225-2236.

Considerations for Treatment Selection

Patient-Specific Factors

Cardiac abnormalities:

- Use caution with ibrutinib or acalabrutinib and monitor closely, as both agents may cause supraventricular arrythmias

Underlying bleeding risk or concomitant anticoagulation:

- Evaluate risk-benefit of ibrutinib or acalabrutinib treatment, and monitor for signs of bleeding if treatment is initiated
- Avoid concomitant use of warfarin if possible

Hypertension:

- Monitor blood pressure in patients taking ibrutinib or acalabrutinib and consider alternative therapy if hypertension is not controllable

High tumor burden:

- Initiate venetoclax slowly and cautiously with appropriate hydration and anti-hyperuricemic agents to reduce the risk of TLS, and monitor closely

Underlying hepatitis B

- Obinutuzumab may cause reactivation of hepatitis B virus – HBV-positive patients should be monitored closely during and after treatment, and obinutuzumab should be discontinued if reactivation does occur

Source: National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 2.2019); Hallek M et al. *Am J Hematol*. 2019;94(11):1266-1287.

Patient-Specific Factors

Treatment burden:

- Ibrutinib and acalabrutinib (whether given with or without obinutuzumab) are both administered indefinitely until disease progression or unacceptable toxicity, whereas venetoclax + obinutuzumab is given for a fixed duration of twelve 28-day cycles – patients may prefer one dosing schedule to another depending on their circumstances
- Risks of medication non-adherence should be considered as well, given varying oral dosing schedules (i.e. twice daily acalabrutinib vs. once daily ibrutinib vs. complex venetoclax ramp-up schedule)

Site of care:

- Patients receiving obinutuzumab would need to travel to a facility for intravenous administration. Depending on the patient, this could be infeasible or inconvenient, and oral monotherapy regimens may be preferred
- For patients at particularly high risk of TLS (e.g. high tumor burden, renal impairment), venetoclax may need to be initiated in an inpatient setting

Drug-drug interactions:

- Ibrutinib, acalabrutinib, and venetoclax all have the potential for clinically significant drug interactions when combined with agents that induce or inhibit CYP3A4
- Drugs that alter the gut pH (e.g. PPIs, H2-receptor antagonists, and antacids) can potentially reduce plasma concentrations of acalabrutinib. PPIs should not be co-administered and other agents should be separated by ≥2 hours

Source: National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 2.2019); Hallek M et al. *Am J Hematol*. 2019;94(11):1266-1287.

Nursing Pearls

- Monitor blood pressure, heart rate, and for any ECG changes in patients receiving ibrutinib or acalabrutinib
- Patients who do develop new-onset atrial fibrillation on ibrutinib or acalabrutinib may ultimately require anticoagulation, depending on risk-benefit. Warfarin should be avoided if possible due to increased bleeding risk and exclusion from ibrutinib and acalabrutinib clinical trials
- Ibrutinib, acalabrutinib, and venetoclax must all be swallowed whole and cannot be crushed, opened, broken, chewed, or cut
- Tumor lysis syndrome prophylaxis is required with a minimum of oral hydration and an anti-hyperuricemic drug (e.g. allopurinol) in all patients receiving venetoclax. Depending on tumor burden, IV hydration, other anti-hyperuricemic drugs (e.g. febuxostat, rasburicase), and inpatient initiation may be required
- The laboratory hallmarks of tumor lysis syndrome include high potassium, high uric acid, high phosphorous, low calcium, and high lactate dehydrogenase – these labs are critical to trend during venetoclax treatment

Nursing Pearls

- Ibrutinib, acalabrutinib, and venetoclax may all interact with CYP3A4 inhibitors (e.g. HIV protease inhibitors, azole antifungals, macrolide antibiotics, verapamil/diltiazem, amiodarone) or CYP3A4 inducers (phenobarbital, phenytoin, carbamazepine, rifampin, St. John's wort)

- Acalabrutinib should not be co-administered with PPIs and must be separated by ≥2 from administration of H2-receptor antagonists or antacids

- Obinutuzumab is associated with infusion reactions. The initial infusion is given over 4 hours and infusion rates may be increased incrementally for subsequent infusions based on tolerability. Pre-medication with acetaminophen, an antihistamine, and a glucocorticoid is required prior to the initial infusion, and a minimum of acetaminophen is required prior to all subsequent infusions

- Obinutuzumab must be administered via a dedicated line and should not be mixed with other drugs

Assessment Question 1

- Which of the following is NOT a preferred regimen in CLL patients with cancers that express the del(17p)/TP53 mutation?

    A. Ibrutinib monotherapy
    B. Venetoclax monotherapy
    C. Acalabrutinib ± obinutuzumab
    D. Venetoclax + obinutuzumab

Assessment Question 1: Response

- Which of the following is NOT a preferred regimen in CLL patients with cancers that express the del(17p)/TP53 mutation?

A. Ibrutinib monotherapy
B. Venetoclax monotherapy
C. Acalabrutinib ± obinutuzumab
D. Venetoclax + obinutuzumab

Assessment Question 2

- New-onset arrhythmia is a side effect most commonly associated with which of the following agents?

A. Ibrutinib
B. Chlorambucil
C. Obinutuzumab
D. Venetoclax

Assessment Question 2: Response

- New-onset arrhythmia is a side effect most commonly associated with which of the following agents?

A. Ibrutinib
B. Chlorambucil
C. Obinutuzumab
D. Venetoclax

Assessment Question 3

- Tumor lysis syndrome is a side effect most commonly associated with which of the following agents?

    A. Ibrutinib
    B. Chlorambucil
    C. Acalabrutinib
    D. Venetoclax

Assessment Question 3: Response

- Tumor lysis syndrome is a side effect most commonly associated with which of the following agents?

A. Ibrutinib
B. Chlorambucil
C. Acalabrutinib
D. Venetoclax

Assessment Question 4

- Which of the following regimens is/are recommended to be administered continuously until progression of disease or intolerable side effects?

I. Ibrutinib monotherapy
II. Fludarabine-cyclophosphamide-rituximab
III. Venetoclax + obinutuzumab
IV. Acalabrutinib monotherapy

A. II only
B. I and IV
C. I, III, and IV
D. III only

Assessment Question 4: Response

- Which of the following regimens is/are recommended to be administered continuously until progression of disease or intolerable side effects?

I. Ibrutinib monotherapy
II. Fludarabine-cyclophosphamide-rituximab
III. Venetoclax + obinutuzumab
IV. Acalabrutinib monotherapy

A. II only
B. I and IV
C. I, III, and IV
D. III only

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Thank you!

Chris Franzese, PharmD, MHS
PGY1 Pharmacy Resident, Atlantic Health System
Christopher.Franzese@atlantichealth.org