JADPRO CE Regional Lectures

Clinical Management of Novel Therapies for Hematologic Malignancies: Targeted Therapies, CAR-T, and Beyond

Risk-Adapted Treatment of Indolent B-Cell Lymphomas: Application of Novel Agents

Program Chair

Sandra E. Kurtin
PhDc, ANP-C, AOCN®
Arizona Cancer Center

Faculty

Amy Goodrich
MSN, CRNP
Johns Hopkins Kimmel Cancer Center

Patrick J. Kiel
PharmD, BCPS, BCOP
IU Simon Cancer Center

Jean A. Ridgeway
DNP, APN, NP-C, AOCN®
The University of Chicago Medicine

Barbara Rogers
CRNP, MN, AOCN®, ANP-BC
Fox Chase Cancer Center

Faculty Financial Disclosures

- Ms. Kurtin has served as a consultant for AbbVie, Celgene, Genentech, and Pharmacyclics.
- Ms. Goodrich has served on the speakers bureau for Gilead.
- Dr. Kiel has served on speakers bureaus for Celgene, Genentech, Gilead, and Takeda.
- Ms. Ridgeway has served on the speakers bureau for Abbvie and Phamacyclics
- Ms. Rogers has served on advisory boards for Gilead, Merck, and Takeda, and has served on speakers bureaus for Bristol-Myers Squibb, Genentech, Seattle Genetics, and Teva Pharmaceuticals.

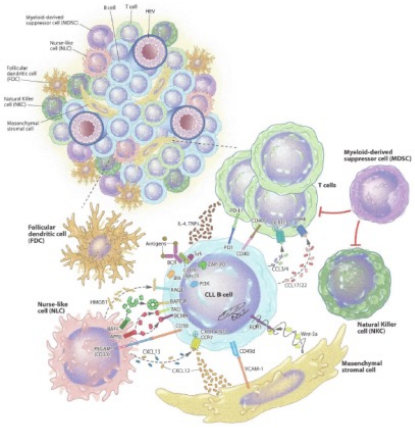
Planning Committee Financial Disclosures

- Moshe C. Ornstein, MD, MA, Cleveland Clinic Taussig Cancer Institute (Reviewer) has served as a consultant for Pfizer and Eisai.
- Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has nothing to disclose.
- Annenberg Center for Health Sciences at Eisenhower
  - John Bayliss, VP, Business Development, spouse is an employee of Amgen, Inc.; Charles Willis, Director, Continuing Education, consults for Pfizer Inc.; all other staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.
- Alana Brody, Lynn Rubin, and Patti McLafferty (Harborside Medical Education) have nothing to disclose.
- Sandy Leatherman, Annamarie Luccarelli, and Jessica Tamasi (APSHO) have nothing to disclose.
- Claudine Kiffer and Annie Yueh (Harborside) have nothing to disclose.

This activity is supported by educational grants provided by Amgen, AstraZeneca, Celgene Corporation, Incyte Corporation, Merck Sharp & Dohme Corp., Takeda Oncology, Pharmacyclics LLC, an AbbVie Company, and Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC.

Learning Objectives: Chronic Lymphocytic Leukemia

- Recall high-risk CLL determinants, including clinical factors, biologic and genetic factors, and complex karyotypes
- Incorporate emerging therapies into treatment plans for patients with CLL, based upon an evaluation of efficacy and safety, as well as patient age, performance status, and comorbidities
- Integrate mitigation strategies into treatment planning for managing adverse events such as patient education, prophylactic measures, and dose adjustments in CLL



Chronic Lymphocytic Leukemia

Audience Response Question #5

Mr. G is a 72-year-old male with a PMH of COPD, type 1 diabetes, coronary artery disease (Hx of MI x2 with CABG and stent placement), atrial fibrillation, and chronic renal insufficiency (CrCl = 45). He is taking clopidogrel and aspirin 81 mg, as well as insulin. He has CLL, 17p negative, 11q negative, mIgHV, WBC of 90 x 10^9/L, Hgb 9.5 g/dL, platelets of 78 x 10^9/L. He has developed progressive fatigue and exertional dyspnea. Which of the following approaches to treatment would be best for Mr. G?

A. No treatment is indicated, as the symptoms are likely unrelated to his CLL.

B. He meets criteria for treatment and would benefit most from a fludarabine/rituximab-based regimen. He will need prophylaxis for tumor lysis syndrome.

C. He meets criteria for treatment and should be considered for a monoclonal antibody +/- chlorambucil, or ibrutinib. He will need prophylaxis for tumor lysis syndrome.

D. He meets criteria for treatment and should be considered for venetoclax. He will need prophylaxis for tumor lysis syndrome.

E. Unsure

PMH = past medical history; COPD = chronic obstructive pulmonary disease; Hx = history; MI = myocardial infarction; CABG = coronary artery bypass graft; CrCl = creatinine clearance; mIgHV = mutated immunoglobulin heavy-chain variable-region gene; WBC = white blood cell count; Hgb = hemoglobin.

Clinical Staging Predicts Outcome

Staging system		Clinical features	Median survival
Rai stage	0 (low risk)	Lymphocytosis in blood and marrow only	> 150 mo (12.5 yr)
	I and II (intermediate risk)	Lymphadenopathy, splenomegaly ± hepatomegaly	71–101 mo (5.9-8.4 yr)
	III and IV (high risk)	Anemia (Hgb < 11.0 g/dL) thrombocytopenia (Plt < 100 × 10^9/L) ± lymphadenopathy and splenomegaly	19 mo
Binet group	A	Lymphocytosis < 3 areas of lymphadenopathy; no anemia or thrombocytopenia	Similar to age-matched controls
	B	Lymphocytosis ≥ 3 areas of lymphadenopathy; no anemia or thrombocytopenia	7 yr
	C	Lymphocytosis Anemia (Hb < 10 g/dL) or thrombocytopenia (Plt < 100 × 10^9/L) ± ≥ 3 areas of lymphadenopathy	2 yr

Plt = platelets.

Rai KR, et al. *Blood* 1975;46:219-34; Binet J, et al. *Cancer* 1981;148:198-206.

CLL International Prognostic Index

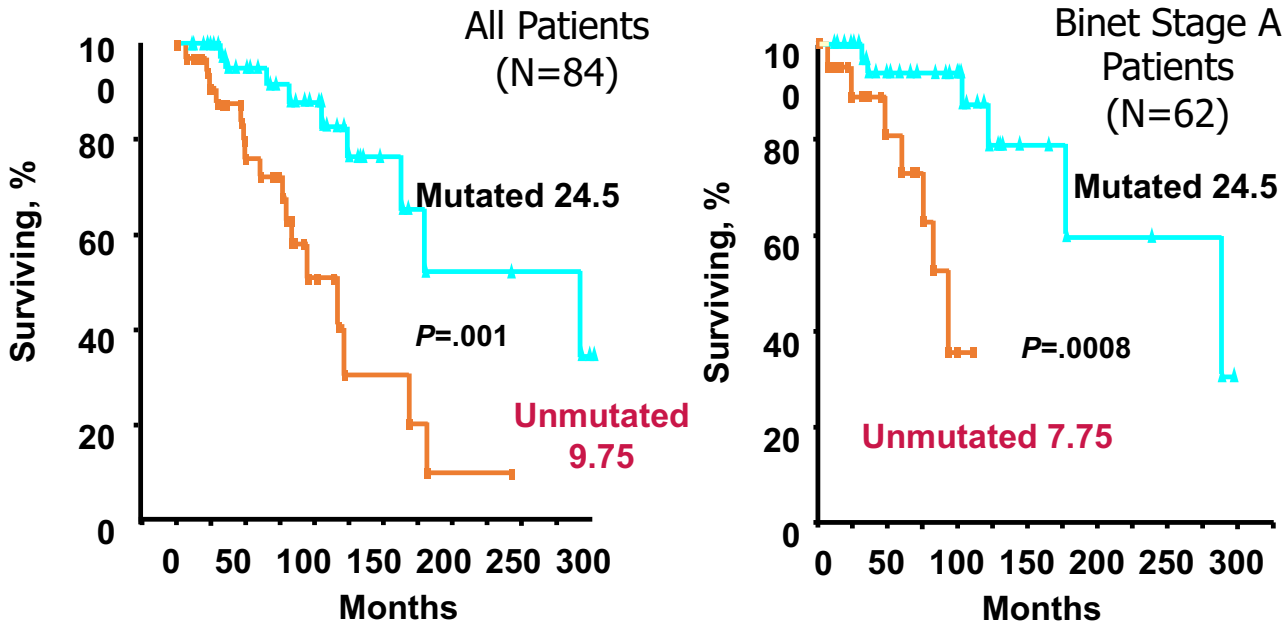
Prognostic factor	Results	Points
FISH	del17p/*TP53* mutation	4
Serum β_2	> 3.5 mg/dL	2
Rai stage	I–IV	1
IgHV	Unmutated	2
Age, years	> 65	1

Risk category	Composite risk score	5-yr OS
Minimal risk	0–1	93%
Low risk	2–3	79%
Intermediate risk	4–6	64%
High risk	7–10	23%

FISH = fluorescence in situ hybridization; OS = overall survival.

Parikh SA, et al. *Semin Oncol* 2016;42(2):233-40.

CLL Prognostic Markers
Mutated vs. Unmutated IgHV Genes



Overall Survival

ZAP70 is a surrogate for uIgHV

uIgHV = unmutated IgHV.

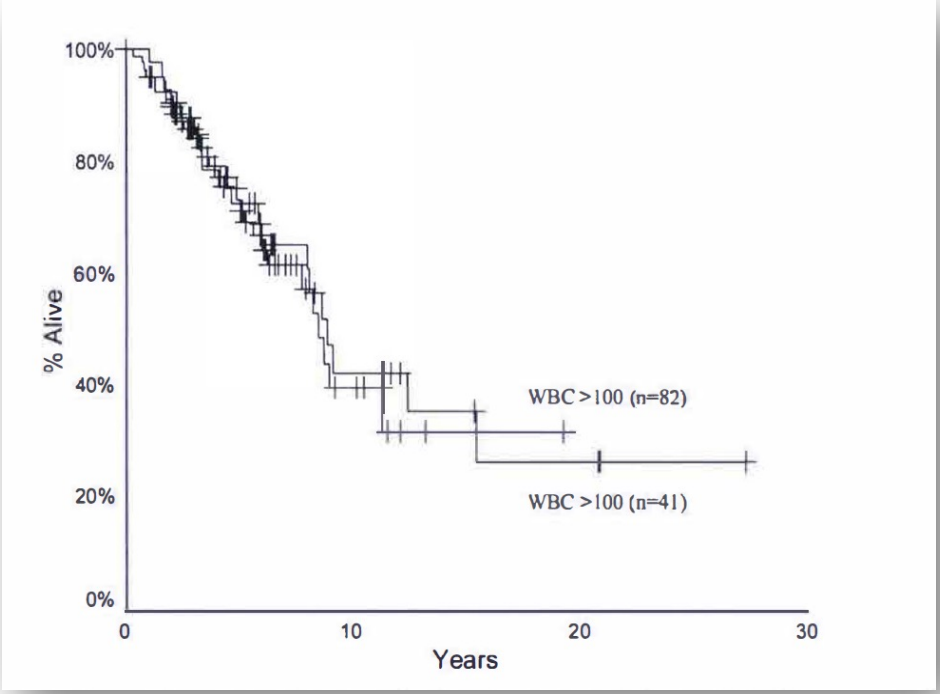
Genomic Alterations in CLL

Alteration	Risk (with sole abnormality)	Median survival	Median TFS
13q deletion	Favorable	133 mo (11 yr)	92 mo (7.6 yr)
Normal	Neutral	111 mo (9.25 yr)	49 mo (4.1 yr)
Trisomy 12	Neutral	114 mo (9.5 yr)	33 mo (2.75 yr)
11q deletion	**Unfavorable**	**79 mo (6.5 yr)**	**13 mo**
17p deletion	**Unfavorable**	**32 mo (2.6 yr)**	**9 mo**

TFS = treatment-free survival.

Cramer P, et al. *Nat Rev Clin Oncol* 2011;8(1):38-47.

Elevated WBC Alone Is Not a Significant Adverse Prognostic Factor



Silverman JA, et al. *Leuk Lymphoma* 2002;43(6):1245-51.

CLL: To Treat or Not to Treat?

1. The clinical stage of the disease
2. The symptoms of the patient
3. The fitness of the patient
4. The genetic risk of the leukemia
5. The treatment situation (first vs. second line, response vs. nonresponse to the last treatment)

Hallek, M. *Am J Hematol* 2015;90(5):446-60.

Indications for Therapy Include the Extent and Severity of Disease Manifestations

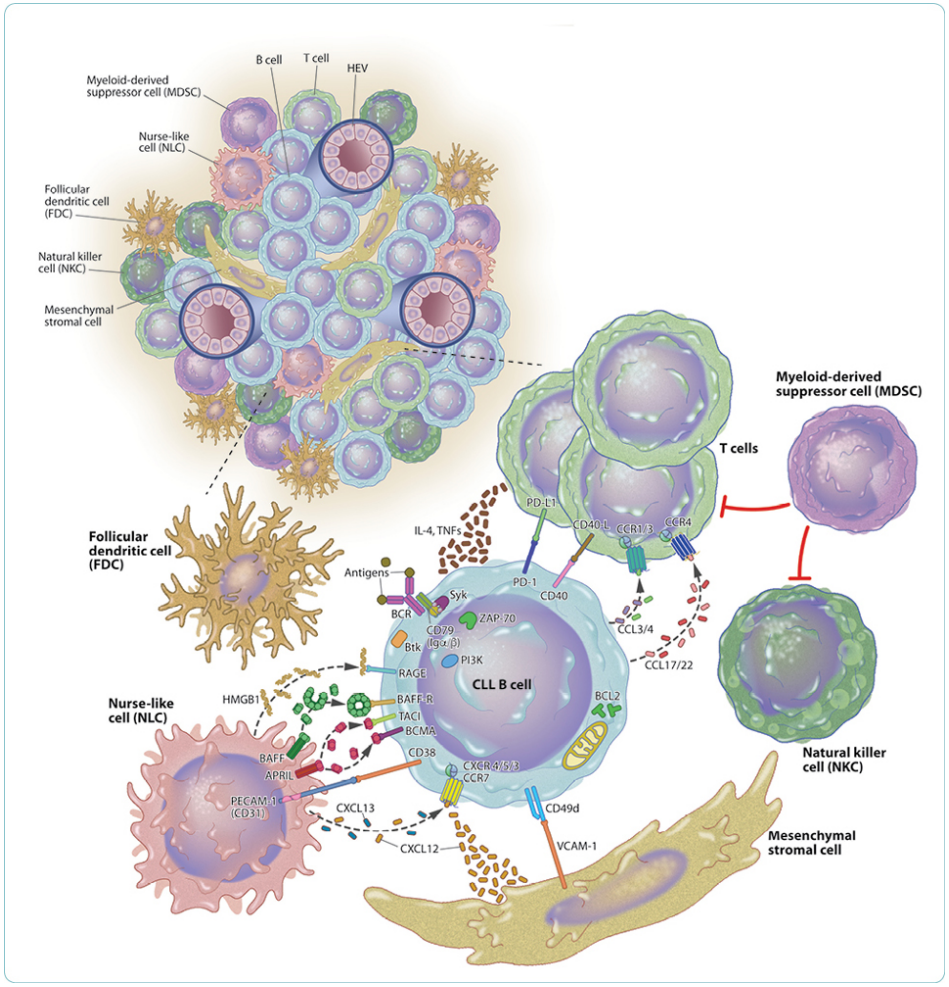
Category	Reasons for Treatment
CLL-related symptoms	• Significant B symptoms (e.g., night sweats, fever without infection, severe fatigue, unintentional weight loss)
Tumor burden	• Massive nodes (i.e.,10 cm in longest diameter) or progressive or symptomatic lymphadenopathy • Massive (i.e., 6 cm below the left costal margin) or progressive or symptomatic splenomegaly • Progressive lymphocytosis with an increase of > 50% over a 2-mo period • Lymphocyte doubling time < 6 mo (if ALC > 30 x 10^9/L) • Threatened end-organ function (e.g., enlarged lymph node obstructing bowel) • Richter's transformation
Bone marrow failure	• Progressive anemia (Hgb < 11 mg/dL) • Progressive thrombocytopenia (Plt < 100K)
Immune dysfunction	• Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy

ALC = absolute lymphocyte count.

Hallek, M. *Am J Hematol* 2015;90(5):446-60; Hallek M, et al. *Blood* 2008;111(12):5446-56.

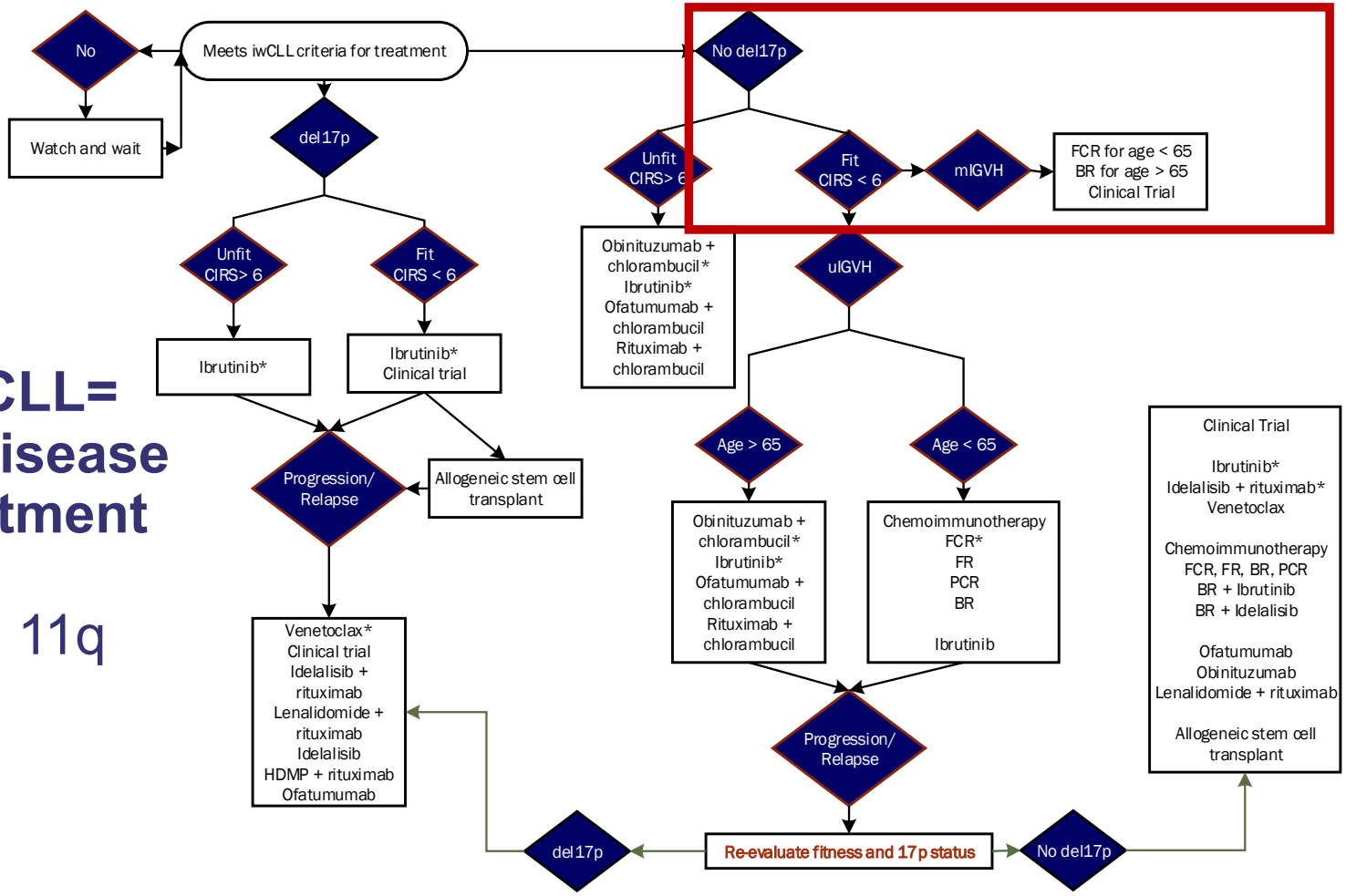
Pathways and Targets in CLL

- CD20
- CD52
- BTK
- PI3K
- BCL2



Risk Adapted Treatment of CLL= Fitness/Age/Disease Adjusted Treatment

Fit, No 17p, No 11q abnormality
mIgHV



Kurtin et al. *Journal of the Advanced Practitioner in Oncology* 2017;8(7):721–728. https://doi.org/10.6004/jadpro.2017.8.7.5

Fludarabine in CLL

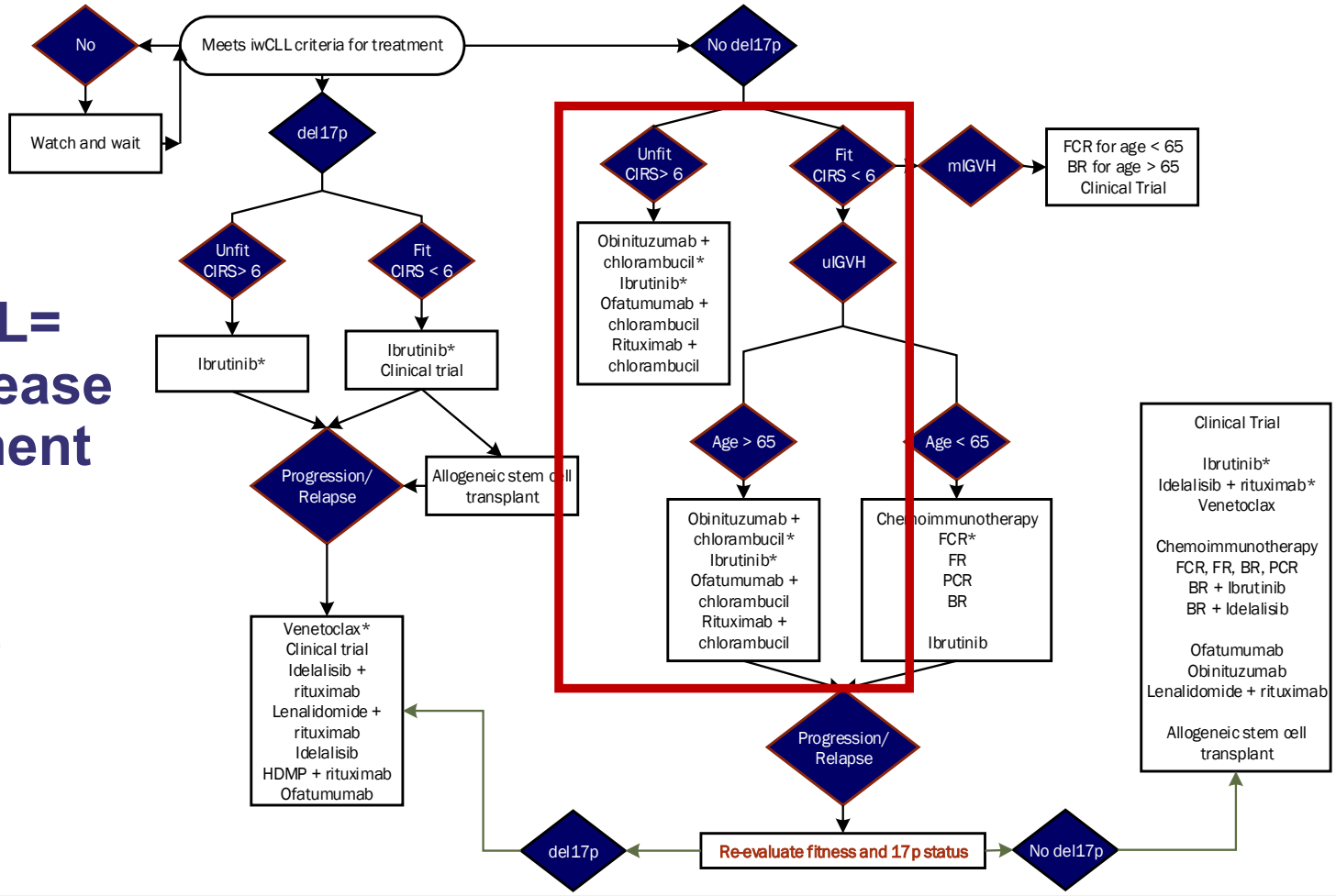
- FDA approved in 1991 for use in CLL
- Remains a preferred regimen in younger, fit patients with mIgHV and NO 17p or 11q abnormalities
  - Response rate 80% in previously untreated patients
- Hematologic and infectious toxicities common
  - ANC ≤ 500 in 59%
  - Long-term depletion of CD4+ T lymphocytes
  - ≥ 2-g drop in Hgb in 60%
  - ≥ 50% drop in platelets in 55%

ANC = absolute neutrophil count.

NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas, v.1.2018;
Fludarabine package insert, Sagent Pharmaceuticals, 201,
https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020038s033lbl.pdf.

Risk Adapted Treatment of CLL= Fitness/Age/Disease Adjusted Treatment

- **Frontline**
- **Unfit and/or age > 65**
- **No del17p**
- **No 11q abnormality**
- **uIgHV**



Guidelines for Determining Fitness for Treatment for Older Adults (Age > 65–70) With CLL

Robust/fit: go-go	Vulnerable/unfit: slow-go	Terminally ill/frail: no-go
CIRS–G ≤ 6 and preserved creatinine clearance (i.e., glomerular filtration rate ≥ 70 mL/min, Cockcroft-Gault formula)	• CIRS-G score > 6 (but without individual organ impairment score of 4) or CrCl between 30 and 69 mL/min based on CLL11 • Consider geriatric impairments including IADLs, physical capacity, nutritional status, cognitive capacity	• Age-adjusted life expectancy < 3 mo • CrCl <30 • Multimorbidity (CIRS > 6 with individual organ impairment score of 4)
Consider for intensive therapy	• Unsuitable for intensive therapy • Consider for adapted therapy	• Unsuitable for antileukemic therapy • Consider for best supportive care

Note. CIRS-G = Cumulative Illness Rating Scale for Geriatrics; CrCl = creatinine clearance; IADLs = instrumental activities of daily living. Information from Cramer, Eichhorst, Reinhardt, & Hallek (2016); Eichhorst, Hallek, & Goede (2016); Merli, Mammi, & Ilariucci (2015); Rai (2015); Stauder et al. (2016).

From Kurtin, S. *J Adv Pract Oncol* 2017;8:113-122.

Audience Response Question #5

Mr. G is a 72-year-old male with a PMH of COPD, type 1 diabetes, coronary artery disease (Hx of MI x2 with CABG and stent placement), atrial fibrillation, and chronic renal insufficiency (CrCl = 45). He is taking clopidogrel and aspirin 81 mg, as well as insulin. He has CLL, 17p negative, 11q negative, mIgHV, WBC of 90 x 10^9/L, Hgb 9.5 g/dL, platelets of 78 x 10^9/L. He has developed progressive fatigue and exertional dyspnea. Which of the following approaches to treatment would be best for Mr. G?

A. No treatment is indicated, as the symptoms are likely unrelated to his CLL.

B. He meets criteria for treatment and would benefit most from a fludarabine/rituximab-based regimen. He will need prophylaxis for tumor lysis syndrome.

C. He meets criteria for treatment and should be considered for a monoclonal antibody +/- chlorambucil, or ibrutinib. He will need prophylaxis for tumor lysis syndrome.

D. He meets criteria for treatment and should be considered for venetoclax. He will need prophylaxis for tumor lysis syndrome.

E. Unsure

PMH = past medical history; COPD = chronic obstructive pulmonary disease; Hx = history; MI = myocardial infarction; CABG = coronary artery bypass graft; CrCl = creatinine clearance; mIgHV = mutated immunoglobulin heavy-chain variable-region gene; WBC = white blood cell count; Hgb = hemoglobin.

Obinutuzumab/Chlorambucil vs. Rituximab/Chlorambucil vs. Chlorambucil Alone

- 781 previously untreated patients with CLL/SLL with comorbidities: median age 73, median CrCl 62 mL/min, median CIRS score of 8

Regimen	ORR	PFS	OS
G/Clb (n = 238)	78.4% (CR 20.7%)	26.7 mo	20%
R/Clb (n = 233)	65.1% (CR 7%)	16.3 mo	
Clb (n = 118)		11.1 mo	9%
G/Clb vs. Clb		HR, 0.18; 95% CI: 0.13–0.24; $p < .001$	HR, 0.41; 95% CI: 0.23–0.74; $p = .002$
R/Clb vs. Clb		HR, 0.44; 95% CI: 0.34–0.57; $p < .001$	NR
G/Clb vs. R/Clb	HR, 0.39; 95% CI: 0.31–0.49; $p < .001$	HR, 0.39; 95% CI: 0.31–0.49; $p < .001$	NR

G/Clb = obinutuzumab/chlorambucil; R/Clb = rituximab/chlorambucil (R/Clb); Clb = chlorambucil alone; CIRS = Cumulative Illness Rating Scale; CI = confidence interval; HR = hazard ratio; NR = not reported; ORR = overall response rate; PFS = progression-free survival.

Goede V, et al. *N Engl J Med* 2014;370(12):1101-10.

Obinutuzumab (Initial Approval 2013)

- **Mechanism:** CD20-directed cytolytic antibody
- **Indications**
  - In combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia
  - In combination with bendamustine followed by obinutuzumab monotherapy, for the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen
  - In combination with chemotherapy followed by obinutuzumab monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma
- **Dosing**
  - CLL: 100 mg on day 1 and 900 mg on day 2 of cycle 1, 1000 mg on day 8 and 15 of cycle 1, and 1000 mg on day 1 of cycles 2–6
  - FL: 1000 mg on day 1, 8 and 15 of cycle 1, 1000 mg on day 1 of cycles 2-6 or cycles 2-8, and then 1000 mg every 2 months for up to 2 years

Goede V, et al. *N Engl J Med* 2014;370(12):1101-10.

Obinutuzumab

- **Warnings and precautions**
  - Infusion reactions: Premedicate patients with glucocorticoid, acetaminophen, and antihistamine. Monitor patients closely during infusions. Interrupt or discontinue infusion for reactions.
  - Hypersensitivity reactions, including serum sickness, have been reported
    - Standard premedications and supportive care
  - Tumor lysis syndrome (TLS)
    - Patients with high tumor burden or more aggressive disease (high ALC, leukocytosis, bulky adenopathy) are at increased risk for TLS
    - Start allopurinol, adequate hydration, frequent laboratory monitoring with appropriate supportive care
  - Infections (may be atypical)
    - Hepatitis B reactivation: Test all patients prior to initiation of therapy, monitor LFTs, refer to hepatology, discontinue obinutuzumab in the event of hepatitis B reactivation
    - Posterior multifocal leukoencephalopathy (PML) (rare)
  - Neutropenia: Monitor for infection and promptly treat
  - Thrombocytopenia: Monitor platelet counts, assess risk of bleeding. Supportive care as indicated.
  - Do not administer live virus vaccines prior to or during obinutuzumab treatment
- **Common adverse events** (> 20%)
  - Infusion-related reactions: more common with obinutuzumab (21%) then rituximab (4%) in this study
  - Cytopenias including leukopenia
  - Infections: pneumonia is most common
  - HSV infection

LFT = liver function test; HSV = herpes simplex virus.

Goede V, et al. *N Engl J Med* 2014;370(12):1101-10.

Ofatumumab

- **Mechanism**
  - Fully human anti-CD20 monoclonal antibody
  - FDA approved in 2009 for use in patients with CLL refractory to fludarabine and alemtuzumab
- **Indications**
  - In combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate
  - In combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL
  - For extended treatment of patients who are in complete or partial response after at least 2 lines of therapy for recurrent or progressive CLL
  - For the treatment of patients with CLL refractory to fludarabine and alemtuzumab
- **Dosing**
  - Variable based on indication
  - Premedicate with acetaminophen, antihistamine, and corticosteroid

Ofatumumab prescribing information, Novartis, 2011, https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/arzerra.pdf.

Ofatumumab (cont.)

- **Warnings and precautions**
  - Infusion reactions: Premedicate patients with corticosteroid, acetaminophen, and antihistamine. Monitor patients closely during infusions. Interrupt or discontinue infusion for reactions.
  - Tumor lysis syndrome (TLS)
    - Patients with high tumor burden or more aggressive disease (high ALC, leukocytosis, bulky adenopathy) are at increased risk for TLS
    - Start allopurinol, adequate hydration, frequent laboratory monitoring with appropriate supportive care
  - Infections (may be atypical):
    - Hepatitis B reactivation: Test all patients prior to initiation of therapy, monitor LFTs, refer to hepatology, discontinue ofatumumab in the event of hepatitis B reactivation
  - Neutropenia: Monitor for infection and promptly treat
  - Thrombocytopenia: Monitor platelet counts, assess risk of bleeding. Supportive care as indicated.
  - Do not administer live virus vaccines prior to or during ofatumumab treatment
  - Cytopenias
  - Progressive multifocal leukoencephalopathy
  - Hepatitis B reactivation
- **Common adverse events** (> 20%):
  - Infusion-related reactions
  - Neutropenia
  - Upper respiratory tract infections

Ofatumumab prescribing information, Novartis, 2011, https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/arzerra.pdf.

Ibrutinib

- **Mechanism:** BTK Inhibitor
- **Indication for CLL**
  - Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
  - CLL/SLL with 17p deletion
- **Dosing**
  - CLL/SLL, WM, and cGVHD: 420 mg taken orally once daily (three 140-mg capsules once daily)
  - New formulation of 70 mg tablets released February, 2018 to allow for dose modifications
- **Drug interactions**
  - CYP3A inhibitors: Dose adjustments may be recommended
  - CYP3A inducers: Avoid coadministration with strong CYP3A inducers

WM = Waldenström macroglobulinemia; cGVHD = chronic graft-vs.-host disease.

Ibrutinib package insert, Janssen Pharmaceuticals, 2013, https://www.janssenmd.com/pdf/imbruvica/PI-Imbruvica.pdf.

Ibrutinib Toxicity

Common adverse events (≥ 20%)

- Thrombocytopenia
- Diarrhea
- Neutropenia
- Anemia
- Fatigue
- Musculoskeletal pain
- Peripheral edema
- Upper respiratory tract infection
- Nausea

Common grade 3/4 nonhematologic adverse events (≥ 5%)

- Pneumonia
- Abdominal pain
- **Atrial fibrillation**
- Diarrhea
- Fatigue
- Skin infections (5%)

- Treatment-emergent grade ≥ 3 cytopenias reported in nearly half of patients

Ibrutinib

RESONATE (n = 391)

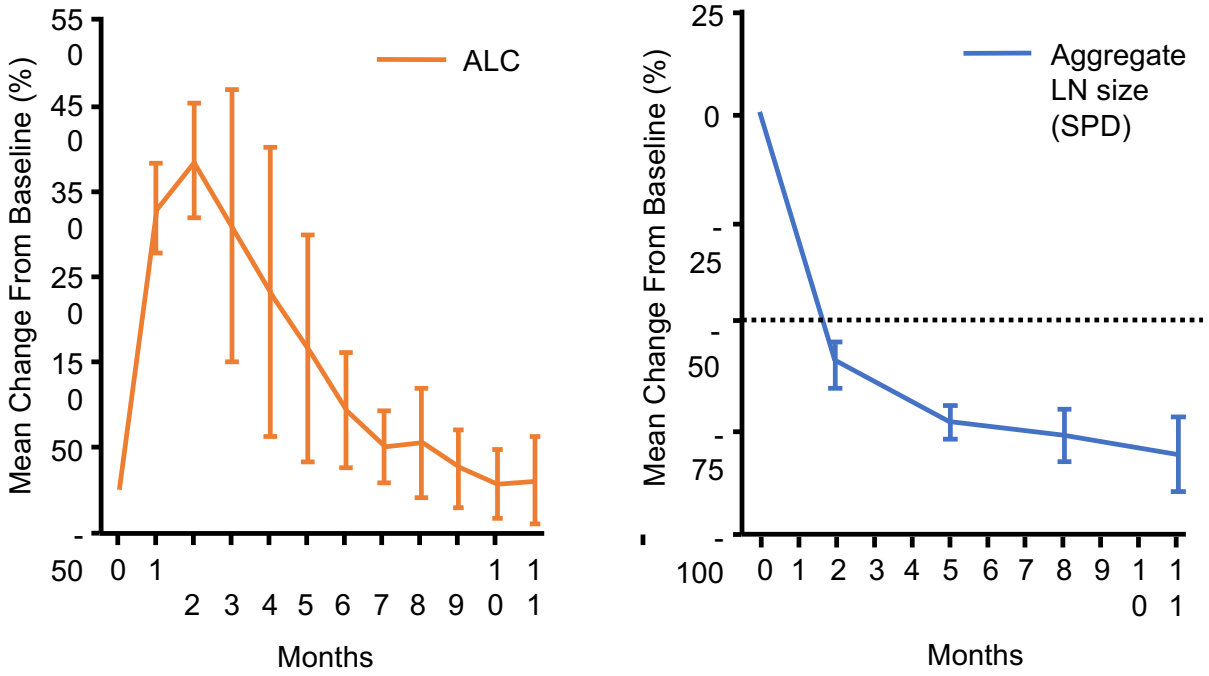
- Ibrutinib vs. ofatumumab in previously treated CLL/SLL
- At median 9.4 months of follow-up ibrutinib vs. ofatumumab:
  - ORR: 42.6% vs. 4.1%, $p < .001$
  - PFS: NR vs. 8.1 months (HR 0.22; $p < .001$)
  - OS: 90% vs. 81% at 9.4 months of follow-up (HR 0.43; $p = .005$)

RESONATE 2 (n = 269)

- Ibrutinib vs. chlorambucil in treatment-naive CLL/SLL age > 65
- At median 18.4 months of follow-up ibrutinib vs. chlorambucil
  - ORR: 86% vs. 35%, $p < .001$
  - PFS: NR vs. 18.9 months (HR 0.16; $p = .001$)
  - OS: 98% vs. 85% at 24 months (HR 0.16; $p = .001$)

Byrd JC, et al. *N Engl J Med* 2014;371(3):213-23; Burger JA, et al. *N Engl J Med* 2015;373(25):2425-37.

Ibrutinib Pattern of Response: Blood Lymphocytes vs. Lymph Nodes



LN = lymph node; SPD = sum of the products of the greatest transverse diameters.

Lymphocytosis With Ibrutinib

Analysis of blood from 59 patients with CLL treated with ibrutinib on clinical trials

- Lymphocytosis is common
- Related to the egress from nodal compartments
- Resolves within 8 months in the majority of patients
- A subgroup had lymphocytosis lasting > 12 months
- Persistent lymphocytes do not represent clonal evolution
- PFS is not inferior for patients with prolonged lymphocytosis vs. those with traditional responses

Woyach JA, et al. *Blood* 2014;123(12):1810-7.

RESONATE Safety: Atrial Fibrillation and Bleeding Events

- **Atrial fibrillation of any grade was noted more frequently in patients receiving ibrutinib (n = 10) compared with ofatumumab (n = 1)**
  - Led to discontinuation of ibrutinib in only 1 patient; patients were ≥ 60 years old (median age 73); most had predisposing risk factors (a prior history of atrial fibrillation or occurrence in the setting of a pulmonary infection)
- **Bleeding-related AEs of any grade, most commonly petechiae, and including ecchymoses, were more common with ibrutinib than with ofatumumab (44% vs. 12%)**
  - The vast majority of ibrutinib events were grade 1
  - **No difference in severe/major bleeding events** (reported in 2 patients randomly assigned to ibrutinib and 3 patients receiving ofatumumab, including 1 ibrutinib patient with a subdural hematoma)
  - **Only 1 patient discontinued ibrutinib due to a bleeding AE**
  - 37% of patients on the ibrutinib arm and 28% of patients on the ofatumumab arm received either concomitant antiplatelet agents (excluding NSAIDs) or anticoagulants

AE = adverse event; NSAIDs = nonsteroidal anti-inflammatory drugs.

Byrd JC, et al. *N Engl J Med* 2014;371(3):213-23.

Ibrutinib and Atrial Fibrillation

- Risk of atrial fibrillation and atrial flutter
  - Patients with cardiac risk factors
  - Acute infections
  - History of atrial fibrillation
- Monitor closely for atrial fibrillation
- If symptomatic atrial fibrillation, consider discontinuation of ibrutinib

Ibrutinib package insert, Janssen Pharmaceuticals, 2013, https://www.janssenmd.com/pdf/imbruvica/PI-Imbruvica.pdf.

Ibrutinib and Bleeding Risk

- Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients
- Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with ibrutinib
- The mechanism for the bleeding events is not well understood
- Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies
- Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre- and post-surgery depending on the type of surgery and the risk of bleeding

Ibrutinib package insert, Janssen Pharmaceutical, 2013, https://www.janssenmd.com/pdf/imbruvica/PI-Imbruvica.pdf.

Audience Response Question #6

Mrs. J is a 66-year-old female with relapsed CLL, 17p+, uIgHV. WBC 88 x 10^9/L, ALC 18 x 10^9/L, platelets 85 x 10^9/L, LDH 400 (250 = ULN). CT shows multiple nodes throughout the chest, abdomen, and pelvis. The largest node measures 5.5 x 2.5 cm. She lives 1 hour from the clinic. She drinks ~1.5 liters of fluid a day. You are assessing her risk for tumor lysis syndrome prior to starting her on venetoclax. You let her know that:

A. She will start allopurinol and will be admitted to the hospital for rasburicase and fluids the first 2 weeks of the 5-week ramp-up; she is at high risk for TLS.

B. She will start allopurinol and will be treated in the clinic. She will need to come in 2 days a week for the first 2 weeks and may receive additional IV fluids, then weekly to complete the 5-week ramp-up; she is at moderate risk for TLS.

C. She will start allopurinol and will be admitted to the hospital for the first week of the 5-week ramp-up; she is at high risk for TLS.

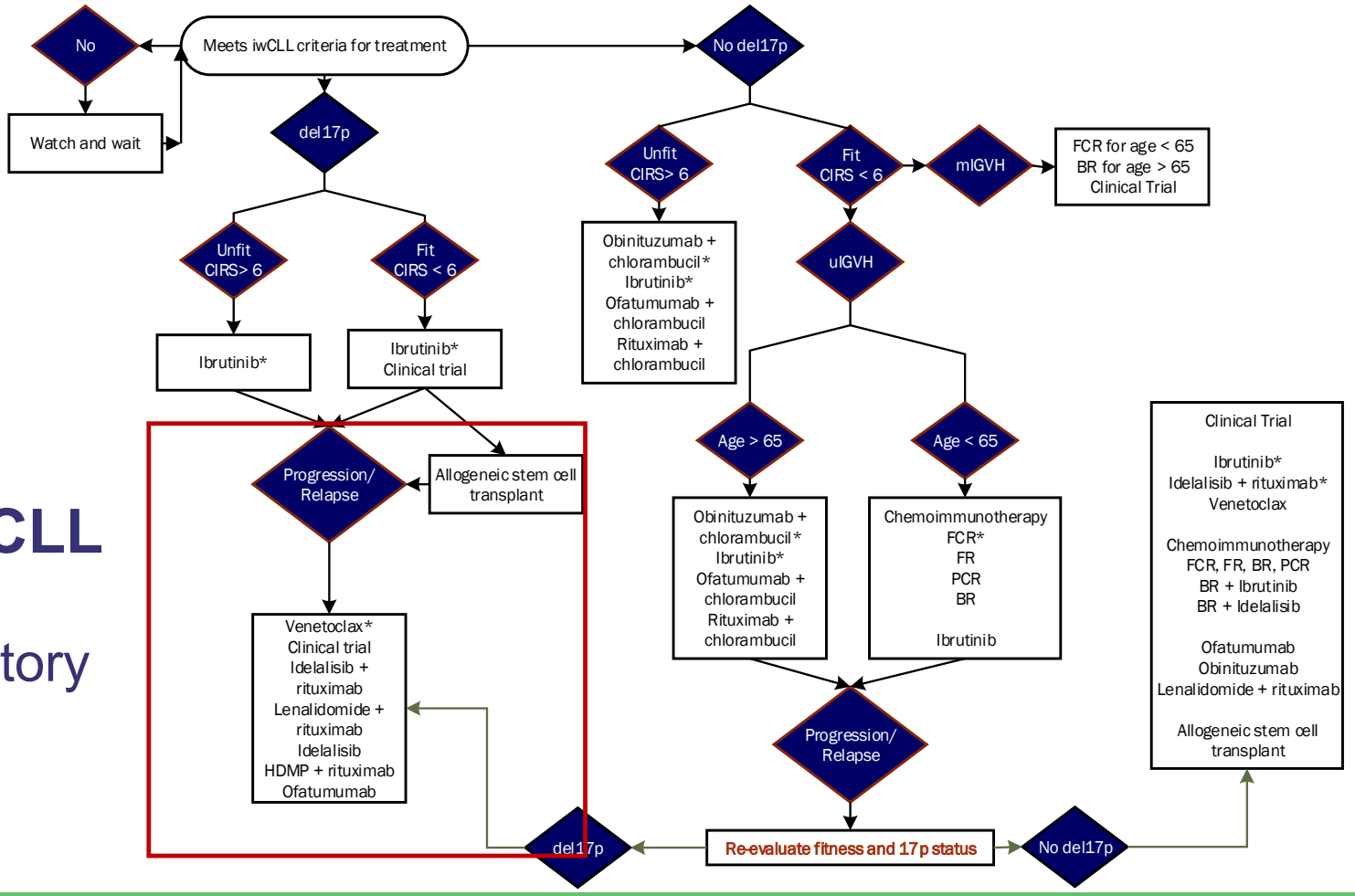
D. She will start allopurinol and will be treated in the clinic. She will need to come in weekly for the first 2 weeks of the 5-week ramp-up and may receive additional IV fluids, then monthly; she is at low risk for TLS.

E. Unsure

LDH = lactate dehydrogenase; ULN = upper limit of normal.

Risk-Adapted Treatment of CLL

Relapsed/Refractory with 17p



Definitions: Progression, Relapse, Refractory

Progression of disease

- Lymphadenopathy: Increase ≥ 50%
- Hepatomegaly: Increase ≥ 50%
- Splenomegaly: Increase ≥ 50%
- Blood lymphocytes: Increase ≥ 50% over baseline
  - ***Isolated progressive lymphocytosis in the setting of reduce lymph node size organomegaly or improvement in hemoglobin or platelets will not be considered progressive disease***
- Platelets: Decrease ≥ 50% over baseline secondary to CLL
- Hemoglobin: Decrease > 2 g/dL from baseline secondary to CLL

Relapse: Evidence of disease progression after a period of 6 months or more following an initial CR or PR

Refractory: Failure to achieve a response for having disease progression within 6 months of the last treatment

CR = complete response; PR = partial response.

Hallek M, et al. *Blood* 2008;111(12):5446-56.

Clonal Evolution and RR CLL

- Clonal evolution (CE): The acquisition of new cytogenetic abnormalities during the disease course
  - Disease characteristics at relapse may be different that at initial diagnosis
- Acquired mutations drive CLL relapse
- CE in CLL by FISH has implications for overall survival:
  - Acquisition of high-risk abnormalities: (deletion 17p or 11q) associated with inferior overall survival
  - Acquisition of low/intermediate abnormalities: (trisomy 12, deletion 13q, and IGH translocation) had no difference in OS
- Richter's transformation is not clearly associated with known mutations

Woyach JA, et al. *N Engl J Med*. 2014;370:2286-2294; Huang SJ, et al, *Cancer Genet*. 2017;210:1-8.

Idelalisib

- Phase II, multicenter, randomized, double-blind, placebo-controlled, study comparing idelalisib/rituximab vs. rituximab/placebo
- 220 patients (↓ CrCl, myelosuppression, or major coexisting illnesses)
- Median PFS: NR in I/R vs. 5.5 months in R/P (HR 0.15; *p* <.001)
- ORR: 81% (I/R) vs. 13% (R/P) (odds ratio, 29.92; *p* <.001) at 12 months of follow-up
- OS: 92% (I/R) vs. 80% (R/P) (HR 0.28; *p* =.02) at 12 months of follow-up
- Serious adverse events occurred in 40% of the patients receiving idelalisib and rituximab and in 35% of those receiving placebo and rituximab

I/R = idelalisib/rituximab; R/P = rituximab/placebo.

Idelalisib + Rituximab: Adverse Events

Adverse Event	Any Grade n (%)	Grade ≥ 3 n (%)
Pyrexia	32 (29)	3 (3)
Fatigue	26 (24)	3 (3)
Chills	24 (22)	2 (2)
Diarrhea	21 (19)	4 (4)
Dyspnea	12 (11)	2 (2)
Rash	11 (10)	2 (2)
ALT/AST elevation	38 (35)	6 (5)
Anemia	28 (25)	6 (5)
Neutropenia	60 (55)	37 (34)
Thrombocytopenia	19 (17)	11 (10)

Serious Adverse Event	Any Grade n (%)
Pneumonia	7 (6)
Pyrexia	7 (6)
Febrile neutropenia	5 (5)
Sepsis	4 (4)
Pneumonitis	4 (4)
Diarrhea	3 (3)
Neutropenia	3 (3)
Pneumocystis pneumonia	3 (3)
Neutropenic sepsis	3 (3)
Dyspnea	1 (1)
Cellulitis	1 (1)

ALT = alanine transaminase; AST = aspartate transaminase.

Idelalisib: Considerations for Patient Management

Manufacturer-Recommended Dose Modifications			
Toxicity	**Recommended Management**		
Pneumonitis, severe skin rash	Any symptomatic occurrence, discontinue idelalisib		
ALT/AST	> 3-5 x ULN	5-20 x ULN	> 20 x ULN
	• Continue idelalisib • Monitor weekly until ≤1 x ULN	• Hold idelalisib • Monitor weekly until ≤ 1 x ULN • Resume at 100 mg twice/day	Discontinue idelalisib
Bilirubin	> 1.5-3 x ULN	> 3-10 x ULN	> 10 x ULN
	• Continue idelalisib • Monitor weekly until ≤1 x ULN	• Hold idelalisib • Monitor weekly until ≤ 1 x ULN • Resume at 100 mg twice/day	Discontinue idelalisib
Diarrhea	Moderate	Severe or Hospitalized	Life Threatening
	• Continue idelalisib • Monitor until resolved	• Hold idelalisib • Monitor weekly until resolved • Resume at 100 mg twice/day	Discontinue idelalisib

Idelalisib prescribing information, Gilead Sciences, Inc. 2014, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf.

Venetoclax in Relapsed CLL With del(17p)

- Proteins in the B-cell CLL/lymphoma 2 (BCL-2) family are key regulators of the apoptotic process
- Venetoclax induces p53-independent apoptosis of CLL cells
- Phase I study showed 79% response rate to venetoclax in patients with R/R CLL
  - ORR for R/R CLL with del(17p): 71% (95% CI: 52%-86%)
- A single dose of ABT-199 in 3 patients enrolled in the phase I trial with refractory CLL resulted in tumor lysis within 24 hours

R/R = relapsed/refractory.

Souers AJ, et al. *Nat Med* 2013;19(2):202-8; Roberts AW, et al. *N Engl J Med* 2016;374(4):311-22.

Venetoclax in R/R CLL With del(17p): Study Design

- Single-arm, multicenter phase II study, 107 patients with R/R CLL with del(17p)
- Titrated dosing of venetoclax (5-week ramp-up)*
  - 20 mg QD week 1
  - 50 mg QD week 2
  - 100 mg QD week 3
  - 200 mg QD week 4
  - 400 mg QD week 5+
- **Risk-based TLS prophylaxis used**
- Primary endpoint: ORR (IRC assessment)
- Secondary endpoints: CR/PR, time to first response, DoR, PFS, OS, safety
- Exploratory endpoint: **MRD**

QD = once per day; IRC = independent review committee; DoR = duration of response; MRD = minimal residual disease.
* FDA-approved dosing – ramp up dosing schedule was different in this clinical trial.

Phase II Trial Venetoclax Monotherapy in CLL With del(17p)

- Overall response: 79% (20% CR)
- 15-month PFS: 69%
- Among 87 patients with baseline lymphocytosis, only 4 failed to normalize ALC count to < 4 x 10^9/L
  - Median time to normalization: 22 days (range: 2-122)
- Among 96 patients with baseline lymphadenopathy, 89 had ≥ 50% reduction in nodal size of the largest target lesion (by SPD)
  - Median time to ≥ 50% reduction: 2.7 mo (range: 0.7-8.4 mo)

Roberts AW, et al. *N Engl J Med* 2016;374(4):311-22.

Venetoclax in R/R CLL With del(17p): Adverse Events

- Grade 3 or 4 neutropenia (in 41%)
  - Manageable with dose interruption or reduction, G-CSF, and/or antibiotics
- Mild diarrhea (52%)
- Upper respiratory tract infection (48%)
- Nausea (47%)

G-CSF = granulocyte colony-stimulating factor.

Roberts AW, et al. *N Engl J Med* 2016;374(4):311-22.

TLS Risk Stratification

- **TLS risk category, percent in the phase II study**
  - High: 42%
  - Medium: 40%
  - Low: 18%
- TLS occurred in 3 of 56 patients in the dose-escalation cohort, with 1 death
- After adjustments to the dose-escalation schedule, clinical TLS did not occur in any of the 60 patients in the expansion cohort
- The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS

Roberts AW, et al. *N Engl J Med* 2016;374(4):311-22.

TLS Risk Stratification and Prophylaxis

LOW Tumor Burden	All LN < 5 cm AND ALC < 25 x 10^9/L
Prophylaxis	Allopurinol Oral hydration (1.5-2 liters/day)
Setting	Outpatient
TLS Monitoring	Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg Pre-dose at subsequent ramp-up doses

MEDIUM Tumor Burden	LN 5 cm to < 10 cm OR ALC ≥ 25 x 10^9/L
Prophylaxis	Allopurinol Oral hydration (1.5-2 liters/day) Consider supplemental hydration for at risk patients
Setting	Outpatient*
TLS Monitoring	Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg Pre-dose at subsequent ramp-up doses

*Consider hospitalization for patients with CrCl < 80 mL/min at first dose of 20 mg and 50 mg.

Roberts AW, et al. *N Engl J Med* 2016;374(4):311-22; Venetoclax prescribing information, AbbVie and Genentech, 2016, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf.

TLS Risk Stratification and Prophylaxis (cont.)

HIGH Tumor Burden	Any LN ≥ 10 cm OR ALC ≥ 25 x 10^9/L AND Any LN ≥ 5 cm
Prophylaxis	Oral (1.5-2 liters) and IV (150-200 mL/hr as tolerated) Allopurinol; consider rasburicase if baseline uric acid is elevated
Setting	First dose at 20 mg and 50 mg inpatient Subsequent doses given outpatient
TLS Monitoring	20-mg and 50-mg dosing: Pre-dose, 4, 8, 12, and 24 hours Subsequent dosing: Pre-dose, 6 to 8 hours, 24 hours

Roberts AW, et al. *N Engl J Med* 2016;374(4):311-22; Venetoclax prescribing information, AbbVie and Genentech, 2016, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf.

Venetoclax Combinations in Relapsed/Refractory CLL

Agents	Phase	Setting	Results
Venetoclax + rituximab	Ib	Patients with R/R CLL/SLL (n = 49)	• ORR: 86% (MRD- in 53%) • PFS at 1 year: 87%; OS at 1 year: 94% • Tolerable safety profile
Venetoclax + obinutuzumab	Ib	Patients with R/R or treatment-naive CLL (n = 32)	• ORR: 100% (24% CR/CRi) • AEs appear to be manageable • Cytopenia is most frequent AE, but no patient discontinued treatment due to AEs • TLS prophylaxis effective even in patients with higher disease burden
Venetoclax + BR	Ib	Patients with R/R or treatment-naive CLL (n = 30)	• ORR: 100% (10% CR) • AEs appear to be manageable • Most common AEs: neutropenia and nausea

CRi = CR with incomplete blood count recovery.

Ma S, et al. ASH 2015. Abstract 830; Flinn IW, et al. ASH 2015. Abstract 494; Salles GA, et al. ASH 2015. Abstract 829.

Selected Studies Combining Ibrutinib and Venetoclax

Ongoing Studies	Study Investigator	Study Design	Estimated Date for Data Reporting
ML29533 (R/R, 1L)	Jones (OSU)	Phase Ib dose escalation of venetoclax + obinutuzumab/ibrutinib up to 14 cycles in the absence of unacceptable toxicity/PD followed by phase II	Phase Ib: ASH 2016
CLL13 (1L fit)	German CLL Study Group	Phase II open-label study of ibrutinib + venetoclax/obinutuzumab to 12 cycles	Pending finalization
10915/A15-746: CLARITY (R/R)	Hillmen (UK)	Phase II study of ibrutinib + venetoclax	Interim: pre-2021

PD = progressive disease.

https://clinicaltrials.gov/ct2/show/NCT02427451; https://clinicaltrials.gov/ct2/show/NCT02758665; Cancer Research UK, A study of venetoclax and ibrutinib for chronic lymphocytic leukemia (CLARITY), http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-of-venetoclax-and-ibrutinib-for-chronic-lymphocytic-leukaemia-clarity.

Second-Generation Bruton Kinase Inhibitors

- Acalabrutinib (ACP-196)
  - Acalabrutinib was granted Breakthrough Therapy Designation by the FDA August 2, 2017, for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy based on results of the ACE-LY-004 clinical trial
- BGB-3111
- Both drugs are more selective for BTK and are designed to minimize off-target activity with minimal effects on other kinases such as TEC, EGFR, or ITK
- Expect limited utility in patients with mutations conveying resistance to ibrutinib

BTK = Bruton tyrosine kinase

Byrd JC, et al. *N Engl J Med* 2016;374:323-32; Tam C, et al. ASH 2015. Abstract 832.

Ongoing Clinical Trials and Emerging Agents in CLL

Agent	Mechanism of Action	Initial Therapy	Relapsed Therapy
Duvelisib	PI3K-δ,γ inhibitor		Duvelisib vs. ofatumumab (phase III) Duvelisib/obinutuzumab after BTK inhibitor
Acalabrutinib (ACP-196)	Bruton tyrosine kinase inhibitor	Acalabrutinib alone vs. acalabrutinib plus obinutuzumab vs. obinutuzumab plus chlorambucil (phase III)	Acalabrutinib vs. Ibrutinib (phase III)
Pembrolizumab	PD-1 inhibitor		Relapsed/refractory CLL (phase II)
CAR-T cells	Adoptive T-cell therapy		Relapsed/refractory CLL (phase I/II)

Audience Response Question #6

Mrs. J is a 66-year-old female with relapsed CLL, 17p+, uIgHV. WBC 88 x 10^9/L, ALC 18 x 10^9/L, platelets 85 x 10^9/L, LDH 400 (250 = ULN). CT shows multiple nodes throughout the chest, abdomen, and pelvis. The largest node measures 5.5 x 2.5 cm. She lives 1 hour from the clinic. She drinks ~1.5 liters of fluid a day. You are assessing her risk for tumor lysis syndrome prior to starting her on venetoclax. You let her know that:

A. She will start allopurinol and will be admitted to the hospital for rasburicase and fluids the first 2 weeks of the 5-week ramp-up; she is at high risk for TLS.

B. She will start allopurinol and will be treated in the clinic. She will need to come in 2 days a week for the first 2 weeks and may receive additional IV fluids, then weekly to complete the 5-week ramp-up; she is at moderate risk for TLS.

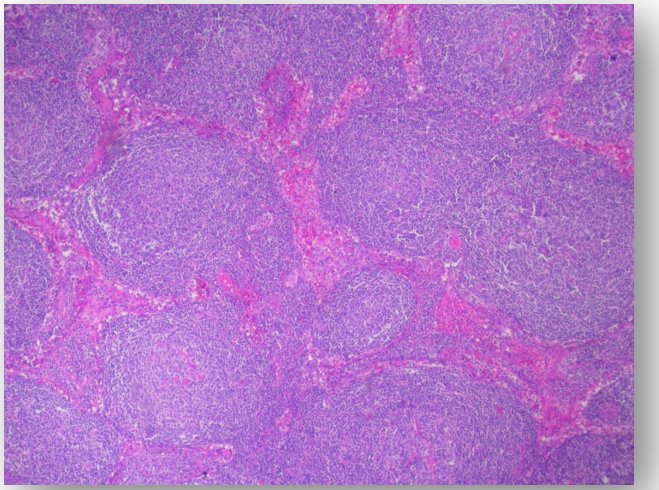
C. She will start allopurinol and will be admitted to the hospital for the first week of the 5-week ramp-up; she is at high risk for TLS.

D. She will start allopurinol and will be treated in the clinic. She will need to come in weekly for the first 2 weeks of the 5-week ramp-up and may receive additional IV fluids, then monthly; she is at low risk for TLS.

E. Unsure

LDH = lactate dehydrogenase; ULN = upper limit of normal.

Follicular Lymphoma



Learning Objectives: Follicular Lymphoma

- Describe prognostic factors and risk adaptive strategies for treatment decisions in follicular lymphoma (FL)
- Discuss the latest data on efficacy and safety of newly approved agents for primary, relapsed, and refractory FL
- Formulate strategies to manage treatment side effects for patients with FL
- Recall clinical trials of novel targeted therapies for the management of newly diagnosed and relapsed/refractory FL

Audience Response Question #7

Which of the following patients would meet the GELF criteria for treatment of follicular lymphoma?

A. A 45-year-old female with widespread adenopathy (largest 2.5 cm) in the neck and groin, mild splenomegaly, LDH 280 (ULN = 280) normal, anxiety
B. A 66-year-old male with a single nodal conglomerate measuring 4.5 cm in the periaortic region, mild fatigue, normal LDH 225 (ULN = 280)
C. A 75-year-old male with a single nodal conglomerate measuring 4.0 cm in the retroperitoneal region abutting the right ureter, mild hydronephrosis, mild fatigue, LDH 315 (ULN = 280)
D. A 75-year-old male with widespread adenopathy, largest (4.5 cm) in the right axilla, mild fatigue, LDH 275 (ULN = 280)
E. Unsure

GELF = Groupe d'Etude des Lymphomes Folliculaires; LDH = lactate dehydrogenase; ULN = upper limit of normal.

Follicular Lymphoma: Grades 1–3

- Cytogenetic demonstrates t(14;18) in 90%
- Molecular analysis: Bcl-6 positive and Bcl-2 positive in 70%–95%

Grade 1	Grade 2	Grade 3
Predominantly small cells (centrocytes predominate few centroblast present 0–5/hpf)	Mixture of small and large cells (both centrocytes and centroblast present approximately 5–15/hpf)	Predominantly large cells Two subtypes: ▪FL3A—composed of centroblasts and centrocytes (> 15 /hpf) ▪FL3B—mainly centroblasts; often does not have t(14;18)/BCL2 rearrangement but has a BCL-6 rearrangement that is more closely like a DLBCL
40%–45% of FL	30% of FL	20% of FL
Indolent	Indolent	Clinically aggressive
Generally incurable	Generally incurable	May be curable

hpf = high power field; DLBCL = diffuse large B-cell lymphoma.

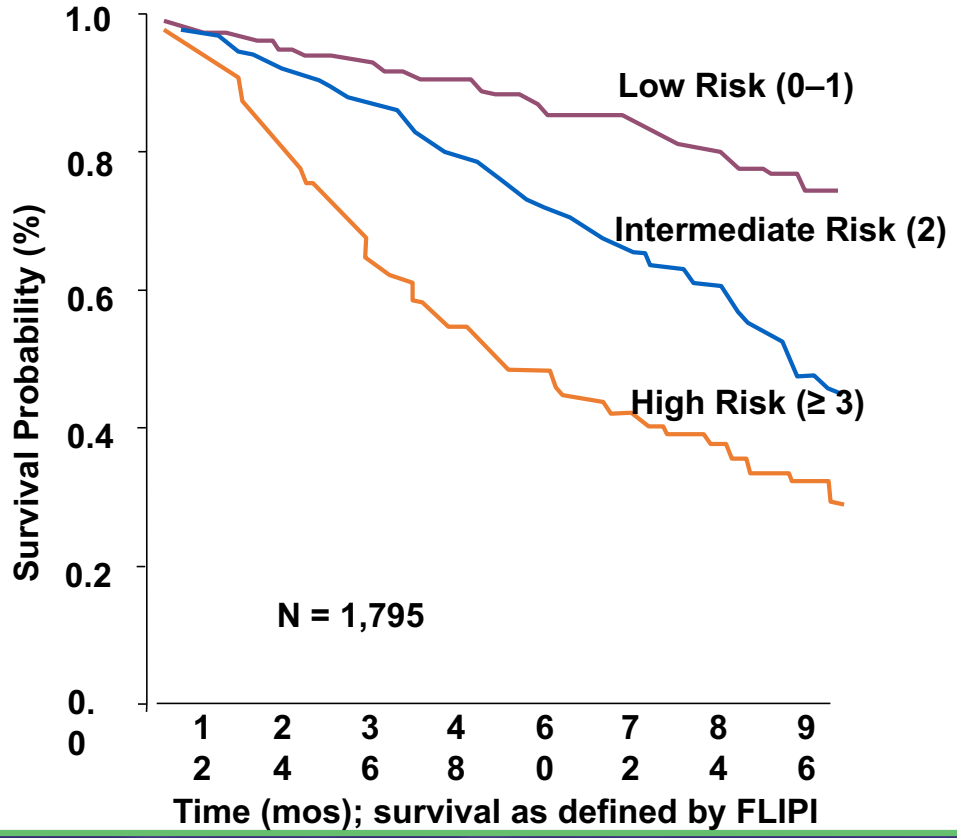
Friedberg JW, et al. *J Clin Oncol* 2009;27:1202-8; Tan D, et al. *Hematol Oncol Clin N Am* 2008;22:863-82; Vilol U, et al. *Crit Rev Oncol Hematol* 2008;66:248-61.

Follicular Lymphoma IPI

FLIPI risk factors (1 point each)

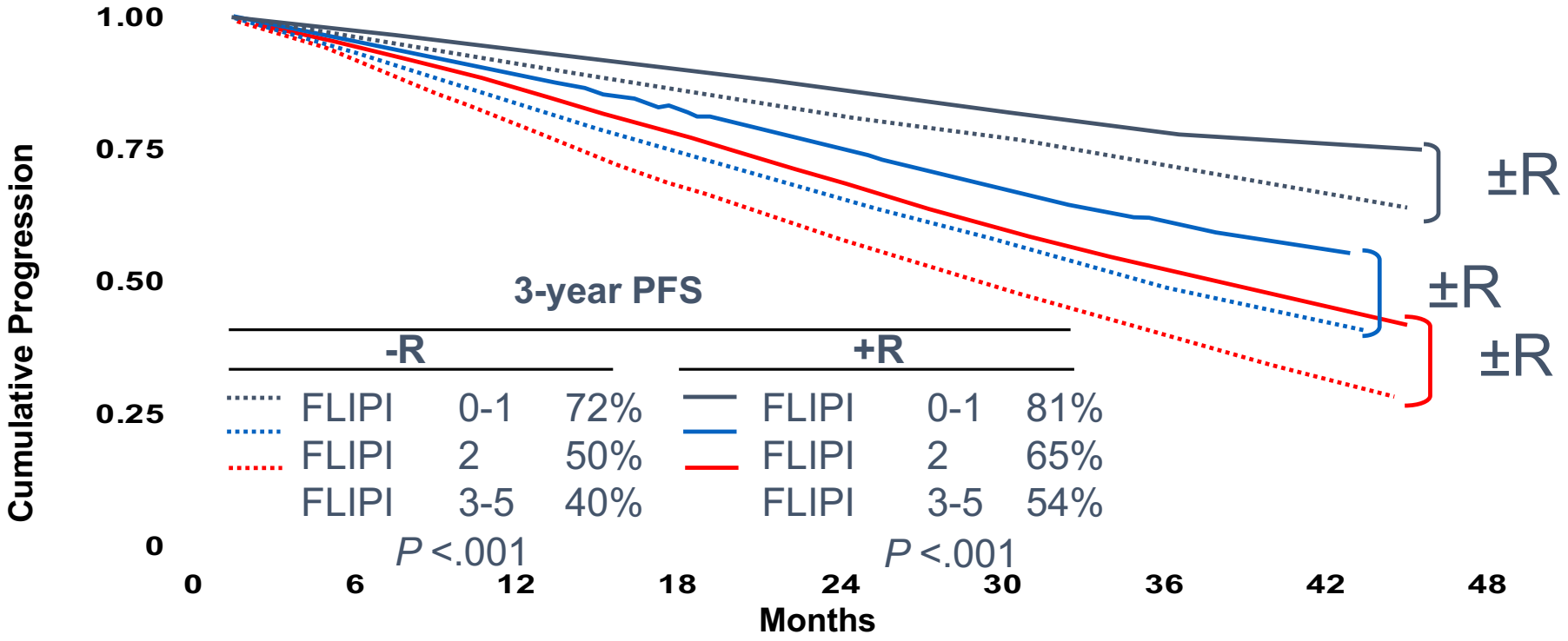
- Age > 60 years
- LDH > ULN
- Hgb < 12 g/dL
- Ann Arbor stage III/IV
- > 4 involved node regions

Risk group	# of factors	5-year OS (%)	10-year OS (%)
Low	0–1	90.6	70.7
Intermediate	2	77.6	50.9
High	> 3	52.5	35.5



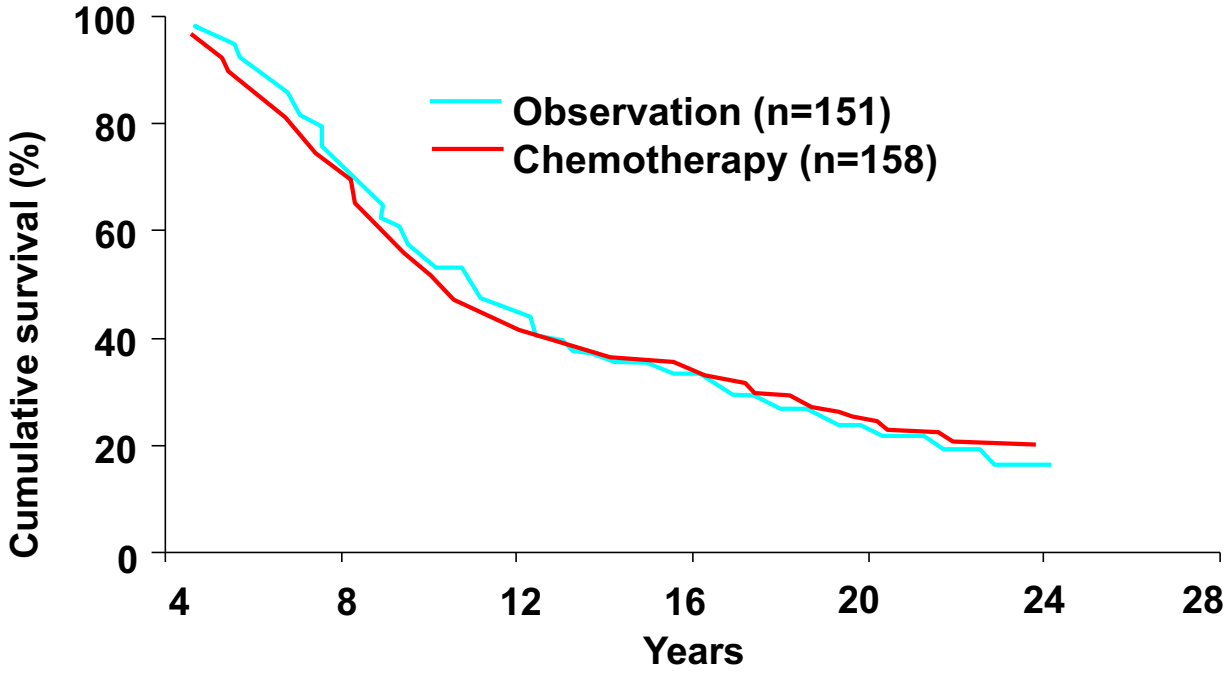
FLIPI = Follicular Lymphoma International Prognostic Index.

Revalidation of FLIPI in Patients With Follicular Lymphoma Treated With R-Chemo: PFS by FLIPI (Cox Stratified by Rituximab)



Federico M, et al. *J Clin Oncol* 2007;25 (suppl; abstr 8008).

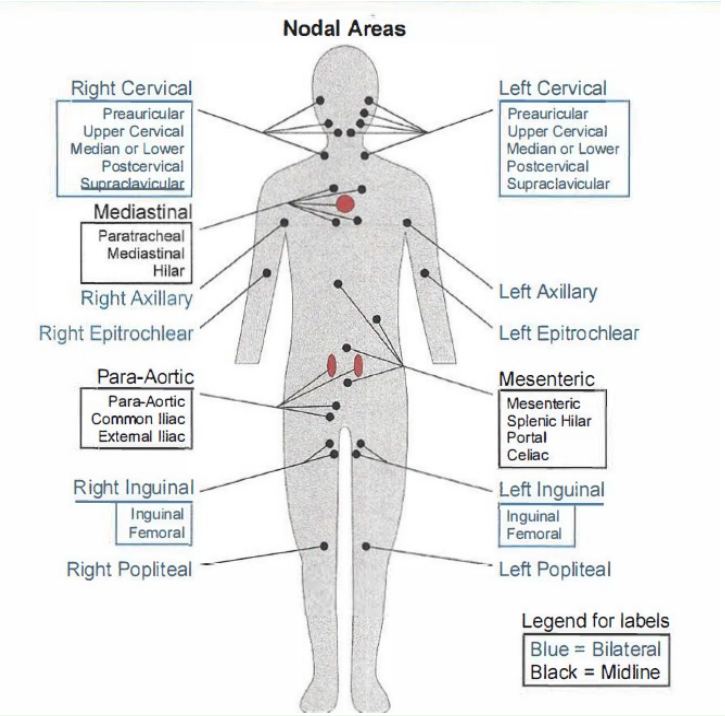
Watchful Waiting vs. Immediate Treatment in Indolent Lymphoma



GELF Criteria for When to Start Treatment in Follicular Lymphoma

Any of the following criteria indicate a need to initiate therapy:

- High tumor bulk
  - > 7 cm
  - 3 nodes in 3 distinct areas each > 3 cm
  - Symptomatic splenic enlargement
  - Organ compression
  - Ascites or pleural effusions
- Presence of systemic symptoms
- ECOG performance status > 1
- LDH or β_2-microglobulin > ULN



ECOG = Eastern Cooperative Oncology Group.

Brice P, et al. *J Clin Oncol* 1997;15:1110-7; NCCN V1, 2018, Non-Hodgkin Lymphoma.

Audience Response Question #7

Which of the following patients would meet the GELF criteria for treatment of follicular lymphoma?

A. A 45-year-old female with widespread adenopathy (largest 2.5 cm) in the neck and groin, mild splenomegaly, LDH 280 (ULN = 280) normal, anxiety
B. A 66-year-old male with a single nodal conglomerate measuring 4.5 cm in the periaortic region, mild fatigue, normal LDH 225 (ULN = 280)
C. A 75-year-old male with a single nodal conglomerate measuring 4.0 cm in the retroperitoneal region abutting the right ureter, mild hydronephrosis, mild fatigue, LDH 315 (ULN = 280)
D. A 75-year-old male with widespread adenopathy, largest (4.5 cm) in the right axilla, mild fatigue, LDH 275 (ULN = 280)
E. Unsure

GELF = Groupe d'Etude des Lymphomes Folliculaires; LDH = lactate dehydrogenase; ULN = upper limit of normal.

First-Line Therapy for Grade 1-2 FL

NCCN-preferred regimens

- Rituximab (category 1)
- Bendamustine + obinutuzumab
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- CHOP + obinutuzumab
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- CVP + obinutuzumab
- Rituximab (375 mg/m^2 weekly for 4 doses) (consider for low tumor burden)
- Lenalidomide + rituximab (category 2B)

Unfit/elderly

- Rituximab (preferred) (375 mg/m^2 weekly for 4 doses)
- Single-agent alkylators (e.g., chlorambucil or cyclophosphamide) ± rituximab
- Radioimmunotherapy (category 2B)

Consolidation/extended dosing

- Rituximab maintenance 375 mg/m^2 one dose every 8 weeks for 12 doses for patients initially presenting with high tumor burden (category 1)
- Obinutuzumab maintenance (1,000 mg every 8 weeks for 12 doses)
- If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m^2 one dose every 8 weeks for 4 doses
- Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy) (category 2B)

NCCN = National Comprehensive Cancer Network.

GELA PRIMA Phase III Study: Rituximab Maintenance in FL

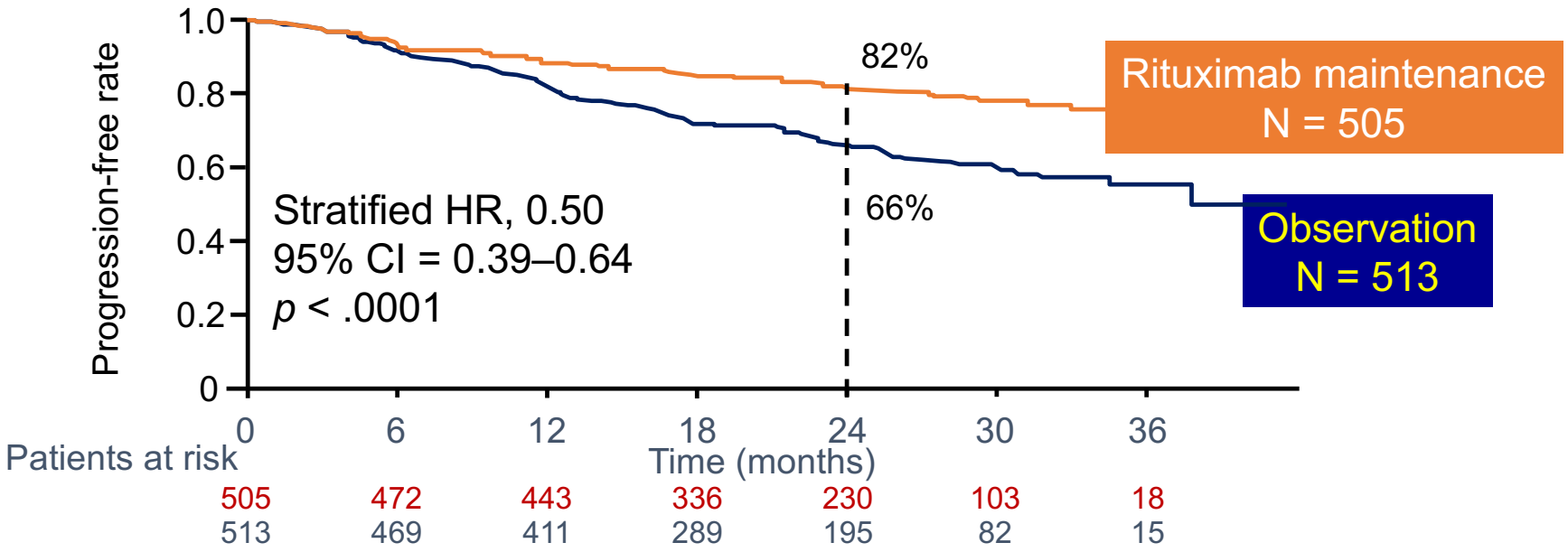
- Primary endpoint: PFS
- Secondary endpoints: EFS, OS

EFS = event-free survival.

Salles G, et al., *Lancet*. 2011;377(9759), 42-51.

Primary Endpoint (PFS) Met at the Planned Interim Analysis

- Rituximab maintenance significantly reduced the risk of progression by 50%, but OS the same



Hyaluronidase and Subcutaneous Tissue

- Hyaluronan (hyaluronic acid)
  - Carbohydrate polymer that forms an extracellular matrix in subcutaneous tissue
  - Forms tight junctions and barriers to interstitial fluid flow
- Hyaluronidase
  - Cleaves hyaluronan through depolymerization
  - Allows for large volume injections and systemic absorption

Rituximab SC With Hyaluronidase

- **Mechanism:** Hyaluronidase (an endoglycosidase) cleaves hyaluronan; anti-CD20 monoclonal antibody
- **Indications:** Newly diagnosed diffuse large B-cell lymphoma with CHOP, chronic lymphocytic leukemia with FC, follicular lymphoma single agent or with chemotherapy
- **Key points**
  - Patients must have had at least 1 prior rituximab IV infusion
  - Not indicated for nonmalignant disorders

SC = subcutaneous; FC = fludarabine, cyclophosphamide.

Rituximab and hyaluronidase product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761064s000lbl.pdf.

Rituximab SC With Hyaluronidase

- **Dosing:** premedicate with acetaminophen and antihistamine (and corticosteroid)
- Inject into abdomen
  - FL/DLBCL: 1,400 mg/23,400 units (1,400 mg rituximab and 23,400 units hyaluronidase) – 11.7 mL over approx. 5 min
  - CLL: 1,600 mg/26,800 units (1,600 mg rituximab and 26,800 units hyaluronidase) – 13.4 mL over approx. 7 min
- Observe 15 minutes following administration

CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FC = follicular lymphoma.

Rituximab and hyaluronidase product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761064s000lbl.pdf.

Rituximab SC With Hyaluronidase

- **Warnings and precautions**
  - Hypersensitivity and local administration reactions
  - Tumor lysis syndrome
  - Infections
  - Hepatitis B reactivation
- **Common adverse events (> 20%):** infections, neutropenia, nausea, injection site erythema
- **Grade 3/4 adverse reactions (≥ 10%)**: neutropenia

Rituximab and hyaluronidase product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761064s000lbl.pdf.

Audience Response Question #8

Mr. Y is here to start treatment with copanlisib for R/R FL. PMH includes HTN and type 2 diabetes. He is taking lisinopril and glucophage. What should you emphasize with Mr. Y?

A. You do not anticipate any problems for Mr. Y, with the exception of possible cytopenias in the first few weeks of treatment
B. You instruct Mr. Y that he may experience hyperglycemia within 12 hours of the infusion. He may need to be started on insulin.
C. You instruct Mr. Y that he may experience hyperglycemia within 5 to 8 hours of his infusion. It should return to normal by the following morning.
D. You instruct Mr. Y that he will have his blood pressure checked prior to each infusion, and his infusion may be held if his systolic pressure is > 140 mmHg or his diastolic pressure is > 80 mmHg.
E. Unsure

R/R = relapsed/refractory; FL = follicular lymphoma; PMH = past medical history; HTN = hypertension.

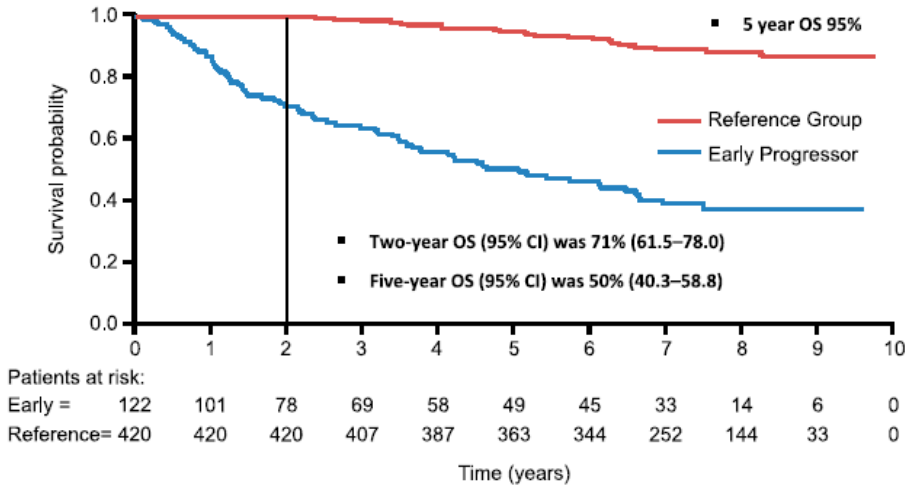
Clinical Factors Associated With Prognosis in FL

Factor	Prognostic impact	PET scan/ Deauville Score
Early disease progression after first-line chemoimmunotherapy (within 2 years) with R-CHOP, R-CVP, R-fludarabine	OS of 34%–50% in early-relapse group; OS of 90% in reference group without early relapse	N/A
Early disease progression after first-line chemoimmunotherapy (within 1 year)	Standard mortality ratio, 3.90; 95% CI = 2.89–5.25; $p < .001$	N/A
PET response	4-year PFS, 63%; OS, 95%	Positive 4–5

PET = positron emission tomography.

Early Relapse After R-CHOP Associated With Inferior Survival

- 122 patients were classified as early progressors (n=110 PD and n=12 non-PD death within 2 years)



NCCN Guidelines Version 2.2017 B-cell Lymphomas; Casulo C. Hematology Am Soc Hematol Educ Program 2016;2016:269-76.

Follow-up After First-Line Therapy

End of treatment evaluation

- PET/CT is preferred at end of treatment to evaluate residual disease
  - PET+ PR is associated with inferior PFS
- Consider consolidation therapy/extended dosing

Follow-up visits

- Visits with labs and physical exam every 3–6 months for 5 years, then annually or as clinically indicated
- Routine surveillance imaging is not recommended in the absence of symptoms or physical findings

CT = computed tomography.

Second-Line/Subsequent Therapy for Grade 1-2 FL

Preferred regimens

- Bendamustine + obinutuzumab or rituximab
- CHOP + obinutuzumab or rituximab
- CVP + obinutuzumab or rituximab
- Rituximab
- Lenalidomide + rituximab

Other recommended regimens

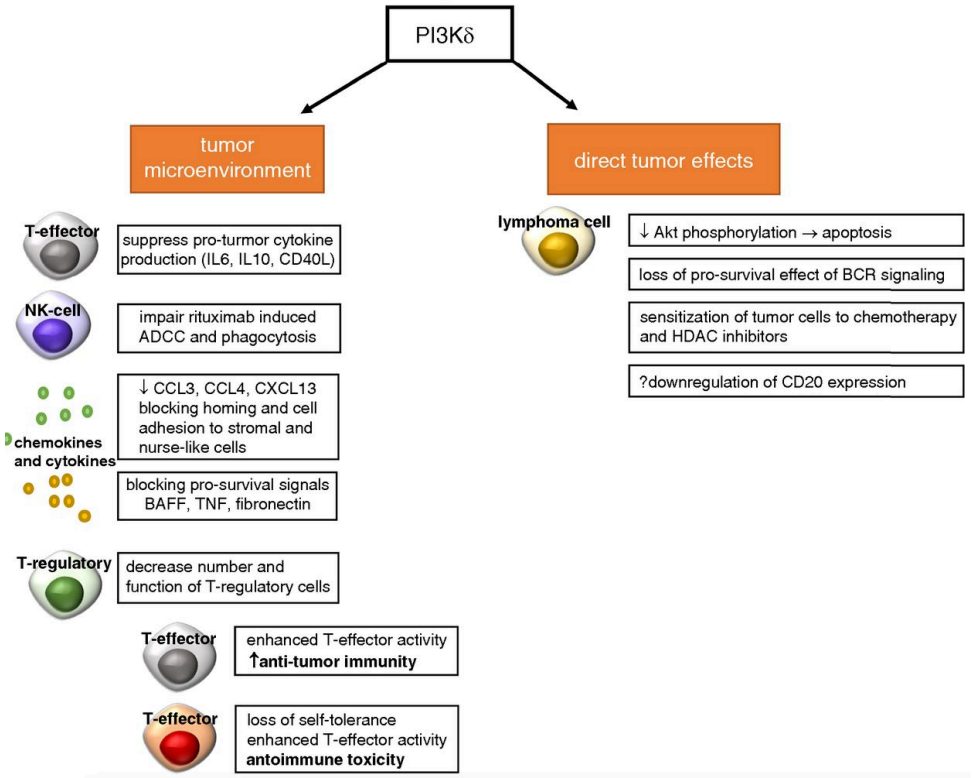
- Ibritumomab tiuxetan
- Idelalisib (refractory to both an alkylator and rituximab)
- Copanlisib (refractory to at least 2 prior therapies)

Consolidation/extended dosing

- Rituximab maintenance 375 mg/m^2 one dose every 12 weeks for 2 years (category 1)
- Obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 weeks for total of 12 doses)
- High-dose therapy with autologous stem cell rescue
- Allogeneic stem cell transplant for highly selected patients

PI3K in Follicular Lymphoma

- PI3K regulates
  - Proliferation
  - Differentiation
  - Trafficking
- Four isoforms: α, β, γ, δ
- Copanlisib
  - Inhibits PI3K-α and PI3K-δ isoforms
  - Induces apoptosis and inhibits proliferation of primary malignant B cells
  - Inhibits several key cell-signaling pathways, including BCR signaling, CXCR12 mediated chemotaxis of malignant B cells, and NFκB signaling in lymphoma cell lines



CHRONOS-1 Study

- R/R lymphoma (FL grades 1–3a [73.2%], MZL, SLL, WM)
- Failure of at least 2 prior lines of therapy
  - N = 142
  - Median age 63
  - Median time since the most recent progression 8.3 mo
  - Median number or prior therapies = 3
    - All patients had prior rituximab exposure and 1 or more alkylating agents
    - 60.6% had disease that was refractory to the last regimen received
    - 80.3% of the patients had advanced disease (stage III or IV) at enrollment
    - Median duration of treatment = 22 wk
    - Median number of cycles = 5.5
- All but a few patients had some degree of target lesion shrinkage in response to treatment with copanlisib
- Patients with all lymphoma subtypes had lesion shrinkage

MZL = marginal zone lymphoma; SLL = small lymphocytic lymphoma; WM = Waldenström macroglobulinemia.

Cheah CY, et al. *Blood* 2016;128:331-6.

Copanlisib

- **Mechanism:** PI3Kα and δ inhibitor
- **Indications:** Adult patients with relapsed FL who have received at least 2 prior systemic therapies (accelerated approval)
- **Dosing:** 60 mg administered as a 1-hour IV infusion on days 1, 8, and 15 of a 28-day treatment cycle (3 weeks on, 1 week off)
- **Drug interactions**
  - Avoid concomitant use with strong CYP3A inducers
  - Strong CYP3A inhibitors: reduce dose to 45 mg

Copanlisib package insert. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209936s000lbl.pdf.

Copanlisib (cont.)

- **Warnings and precautions**
  - Infections: Withhold treatment for grade 3 and higher infections until resolution
  - Hyperglycemia: Start each infusion once optimal blood glucose control is achieved; withhold treatment, reduce dose, or discontinue treatment depending on the severity and persistence of hyperglycemia
  - Hypertension: Withhold treatment in patients until both the systolic less than 150 mmHg and the diastolic less than 90 mmHg; consider reducing dose if antihypertensive treatment is required; discontinue in patients with blood pressure that is uncontrolled or with life-threatening consequences
  - Non-infectious pneumonitis (NIP): Treat NIP and reduce dose; discontinue treatment if grade 2 NIP recurs or in patients experiencing grade 3 or higher NIP
  - Neutropenia: Monitor blood counts at least weekly while under treatment; withhold treatment until ANC ≥ 500
  - Severe cutaneous reactions: Withhold treatment, reduce dose, or discontinue treatment depending on the severity and persistence of severe cutaneous reactions
- **Common adverse events (> 20%):** Hyperglycemia, diarrhea, decreased general strength and energy, hypertension, leukopenia, neutropenia, nausea, lower respiratory tract infections, thrombocytopenia

Copanlisib package insert. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209936s000lbl.pdf.

Audience Response Question #8

Mr. Y is here to start treatment with copanlisib for R/R FL. PMH includes HTN and type 2 diabetes. He is taking lisinopril and glucophage. What should you emphasize with Mr. Y?

A. You do not anticipate any problems for Mr. Y, with the exception of possible cytopenias in the first few weeks of treatment
B. You instruct Mr. Y that he may experience hyperglycemia within 12 hours of the infusion. He may need to be started on insulin.
C. You instruct Mr. Y that he may experience hyperglycemia within 5 to 8 hours of his infusion. It should return to normal by the following morning.
D. You instruct Mr. Y that he will have his blood pressure checked prior to each infusion, and his infusion may be held if his systolic pressure is > 140 mmHg or his diastolic pressure is > 80 mmHg.
E. Unsure

R/R = relapsed/refractory; FL = follicular lymphoma; PMH = past medical history; HTN = hypertension.