APSHO Regional Lecture Series

Accredited Educational Activities for Advanced Practitioners in Oncology

Collaborative Practice in the Management of Patients With Cancer

Relapsed or Refractory Chronic Lymphocytic Leukemia and the Management of CLL Patients Treated With Immunotherapy

Program Chair

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APSHO Regional Lecture Series

Disclosures

Faculty

Ms. Kurtin has served as consultant for Amgen, BMS, Celgene, Genentech, Incyte, Janssen, Novartis, Takeda, and Pharmacyclics.

Planning Committee

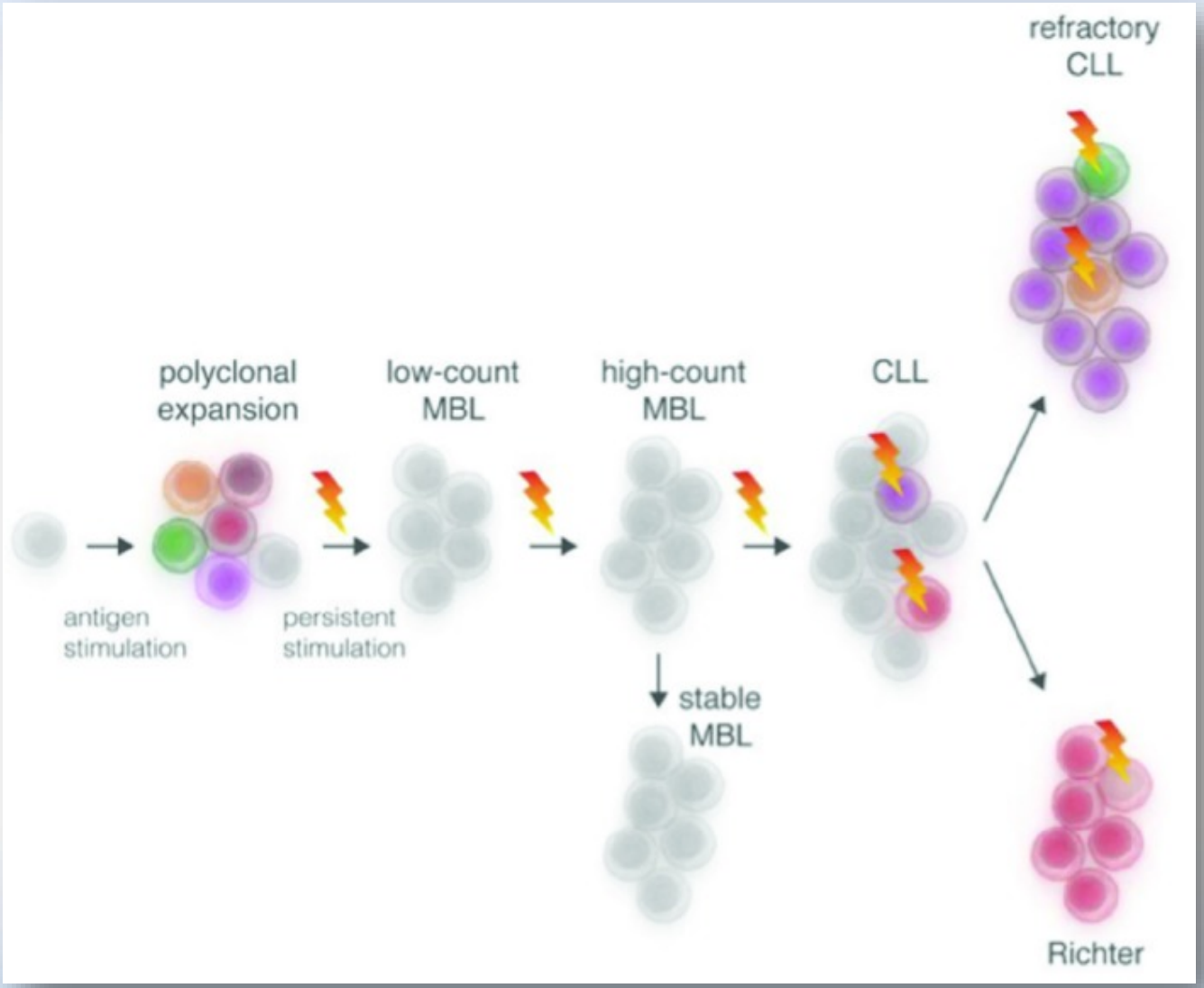
Moshe C. Ornstein, MD, MA, Cleveland Clinic Taussig Cancer Institute (Reviewer) has nothing to disclose. Alana Brody, Terry Logan, Lynn Rubin, and Wendy Smith (MEI) have nothing to disclose. Sandy Leatherman, Annamarie Luccarelli, and Jessica Tamasi (APSHO) have nothing to disclose. Claudine Kiffer and Annie Yueh (Harborside Press) have nothing to disclose.

Learning Objectives

- Apply the principles of risk-adapted treatment using case-based scenarios to illustrate the impact of patient attributes and disease-specific attributes
- Manage toxicities associated with newer agents used to treat CLL
- Describe the role of oral therapies in treating patients with CLL

RELAPSED OR REFRACTORY CLL

CLL Pathobiology: From MBL to Richter's



Sutton & Rosenquist (2015). *Haematologica* 100(1):7-16

Case Study 2: Clinical Decision-Making

- 46-year-old male with a history of small lymphocytic leukemia
- Treatment history and outcome: 2012-2014
  - Bendamustine x 4 cycles: minimal response
  - Fludarabine/cyclophosphamide: no response
  - Pentostatin/cyclophosphamide/rituximab: progression

How would you characterize his disease?

Progression, Relapse, Refractory: Definitions

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

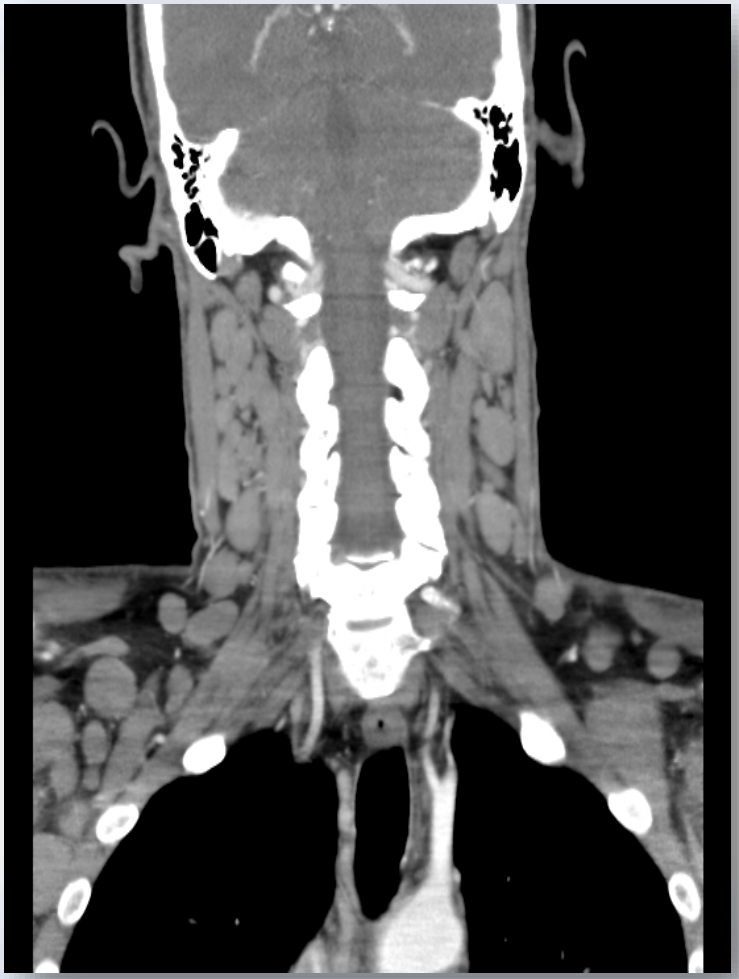
Hallek M, et al. (2008). *Blood* 111(12):5446-5456

Case Study 2: Continued

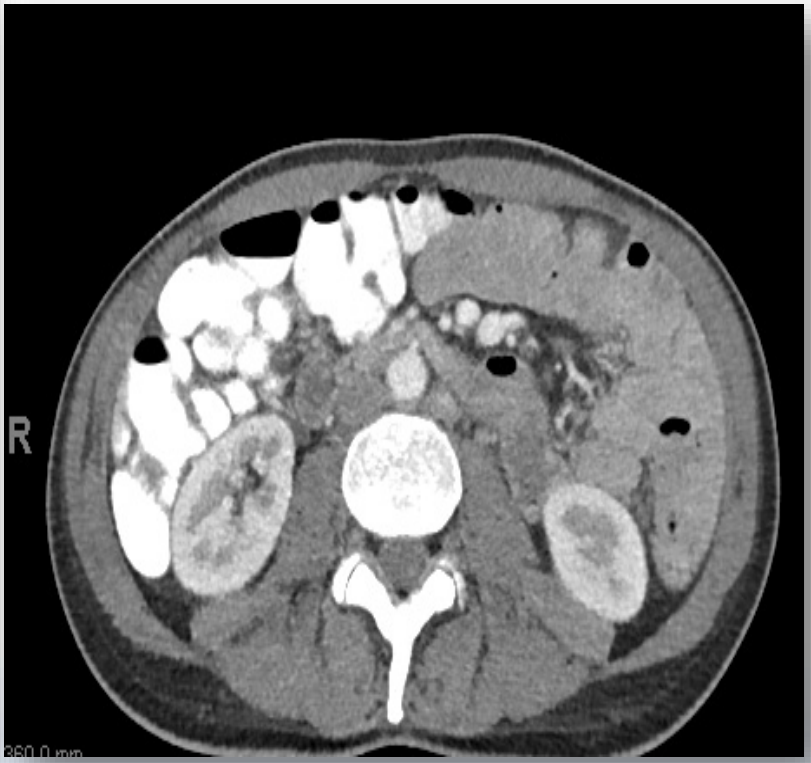
- The patient is started on a clinical trial
  - Venetoclax – near CR 7/9/13 – 7/2/14
- He now presents with rapidly increasing adenopathy on exam and progressive thrombocytopenia

What would your next recommendation be?

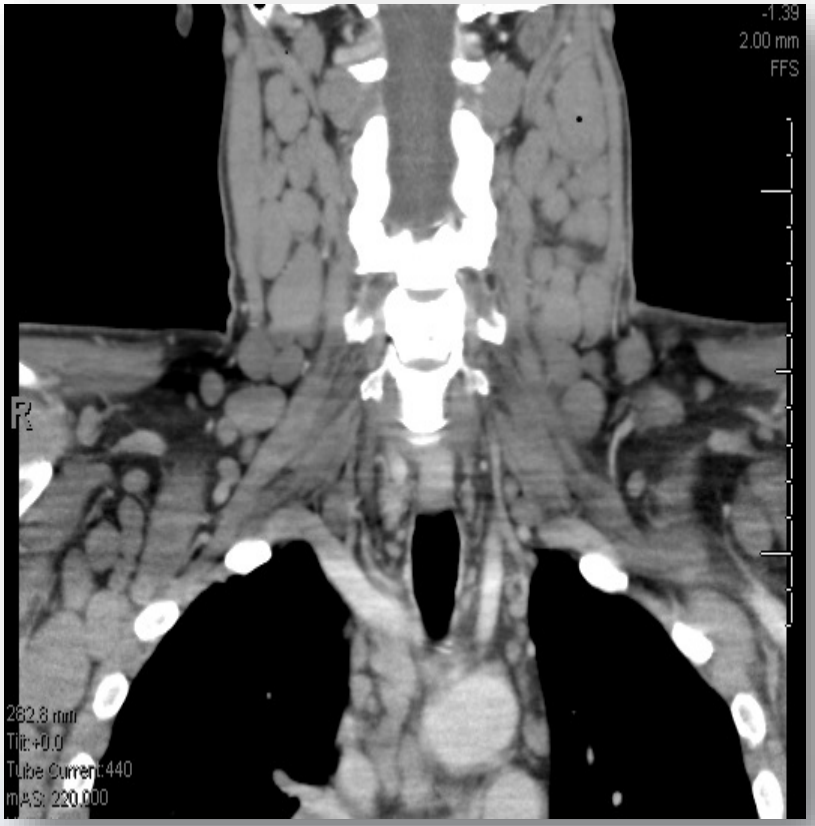
Diagnostic Profile: Diagnostic Radiology



CT Neck, Chest, Abdomen and Pelvis
Diffuse adenopathy



Rapid Progression Within 6 Weeks



Biopsy of a large retroperitoneal node causing back pain shows no evidence of Richter's transformation

Diagnostic Profile: Hematopathology

Bone Marrow Biopsy and Aspirate

1) 90% BONE MARROW INVOLVEMENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA
2) MARKEDLY DECREASED TRILINEAGE HEMATOPOIESIS (SEE COMMENT)

Peripheral Blood

1) Leukocytosis (WBC 16,300/uL) with 77% lymphocytes
2) Normocytic, normochromic anemia (Hgb 12.0 g/dL, MCV 96 fL, MCHC 32.5 g/dL)

Bone Marrow

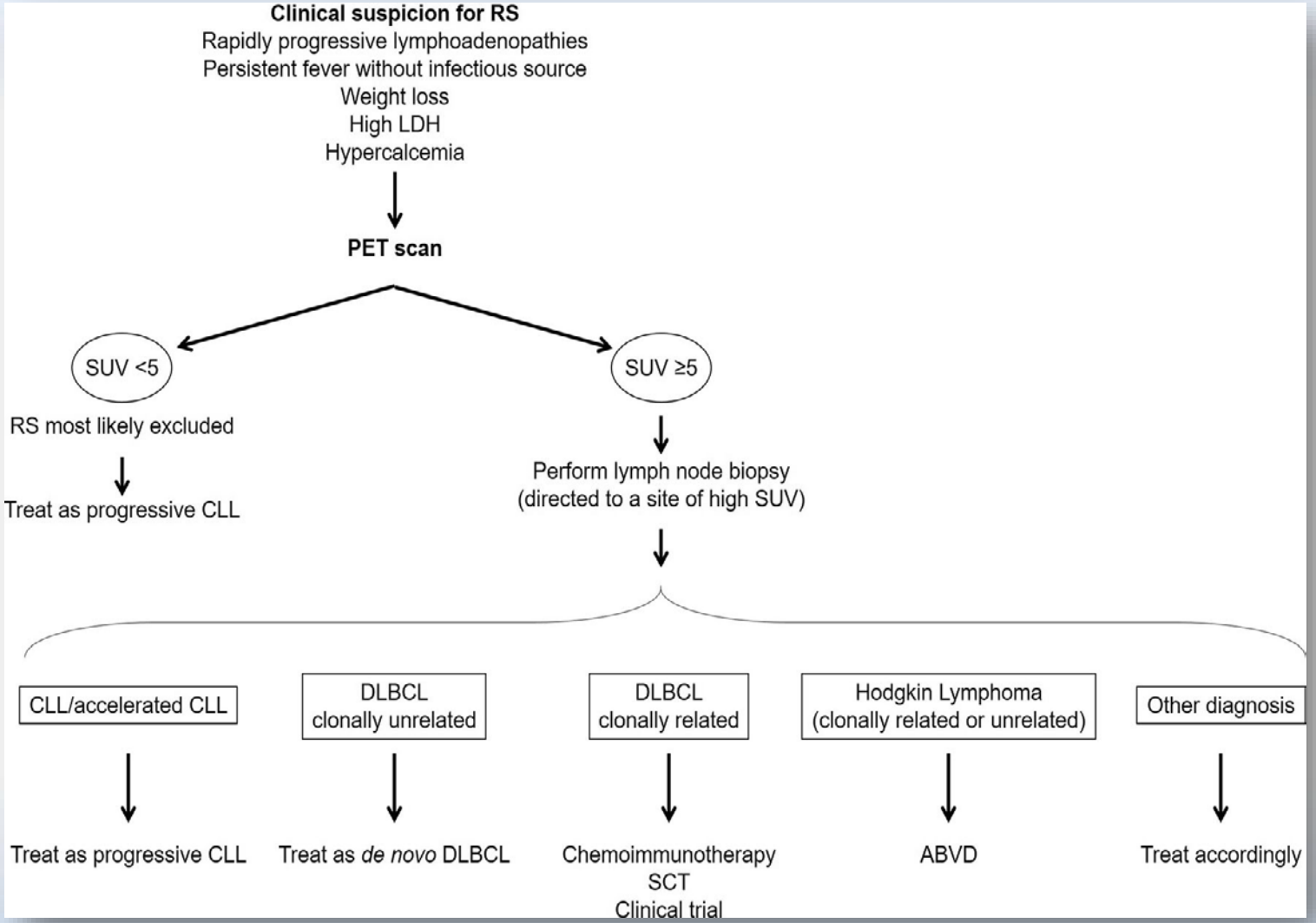
1) 92% lymphocytes
2) Cellularity 90%
3) M:E ratio: 0.56
4) Megakaryocytes 0.2/hpf

By **flow cytometry**, a lambda light chain restricted B-cell population (CD19+) is detected that coexpresses CD5 and CD23 with subset expression of CD2 and CD8. This population **does not express CD20**. Approximately 40% of the abnormal B cells express CD38

Cytogenetics: Normal male karyotype: 46XY [20]

CLL panel **FISH** studies indicated a 17p13 deletion in 138/200 cells (69%).
This finding may represent the previously reported clone with an isochromosome 17q with subsequent loss of the short arm of 17.

Richter's Transformation



Vitale C, Ferrajoli A (2016). *Curr Hematol Malig Rep* 11(1):43-51.

CLL Second-Line Treatment

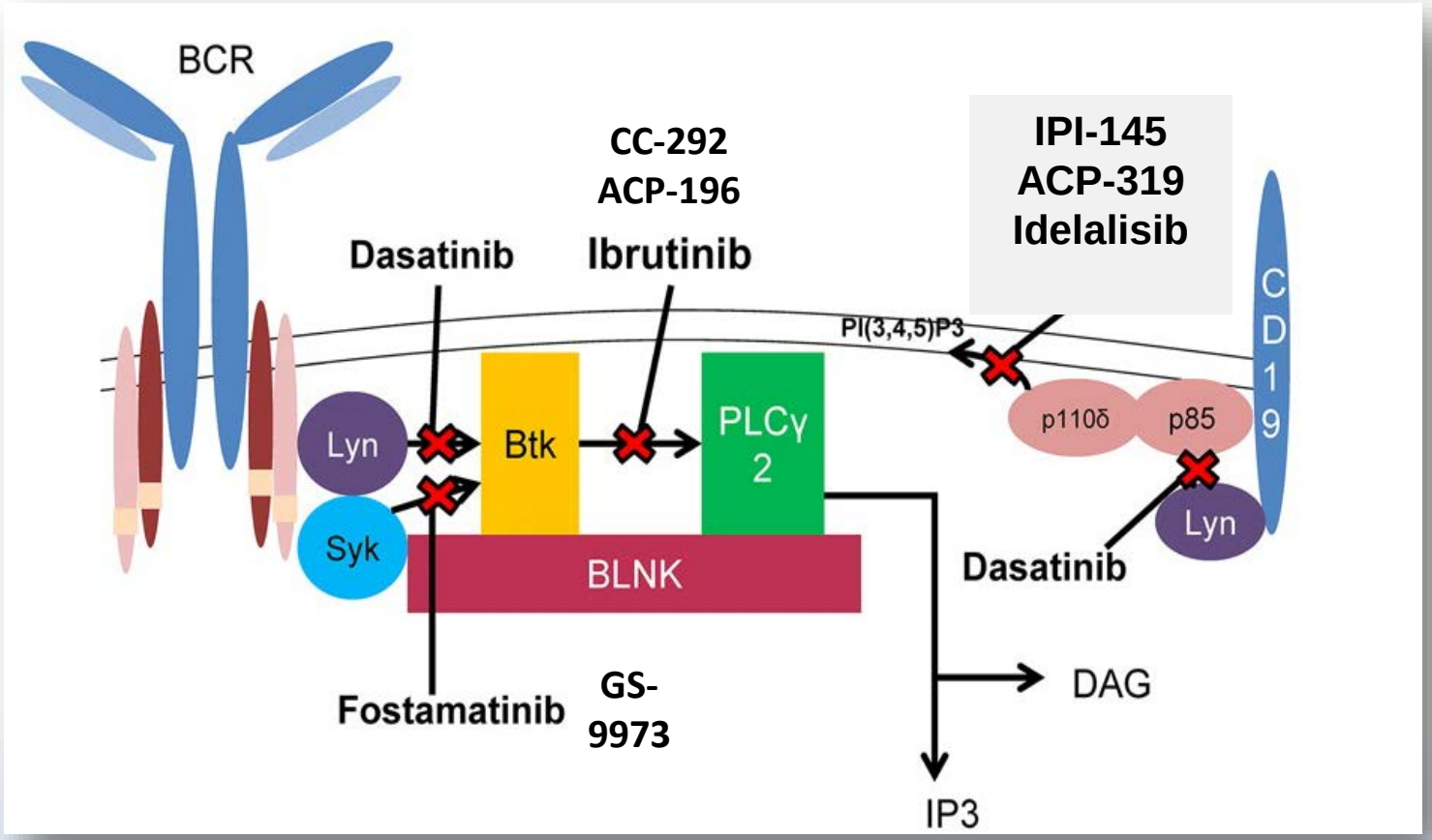
Response to First-Line therapy	Fitness	Therapy	
		Standard	Alternatives
Refractory or progression within 2 years	Fit and low co-morbidity index (Go-Go)	Ibrutinib* Idelalisib + Rituximab* Venetoclax (17p) Chemoimmunotherapy Allogeneic SCT (?)	Lenalidomide BR Other kinase inhibitors
	Unfit and/or Complex co-morbidities (Slow-Go)	Change therapy (include in trial)	Ibrutinib * Idelalisib + Rituximab* Venetoclax (17p) Alemtuzumab (del 17p) Rituximab Ofatumumab Lenalidomide FCR-lite HD Rituximab
Progression after 2 years	All	Repeat first-line therapy	

*NCCN category 1

Hallek, M. (2015). *Am J Hematol* 90(5):446-460; NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas (v.3.2016).

SMALL-MOLECULE ORAL THERAPIES FOR CLL

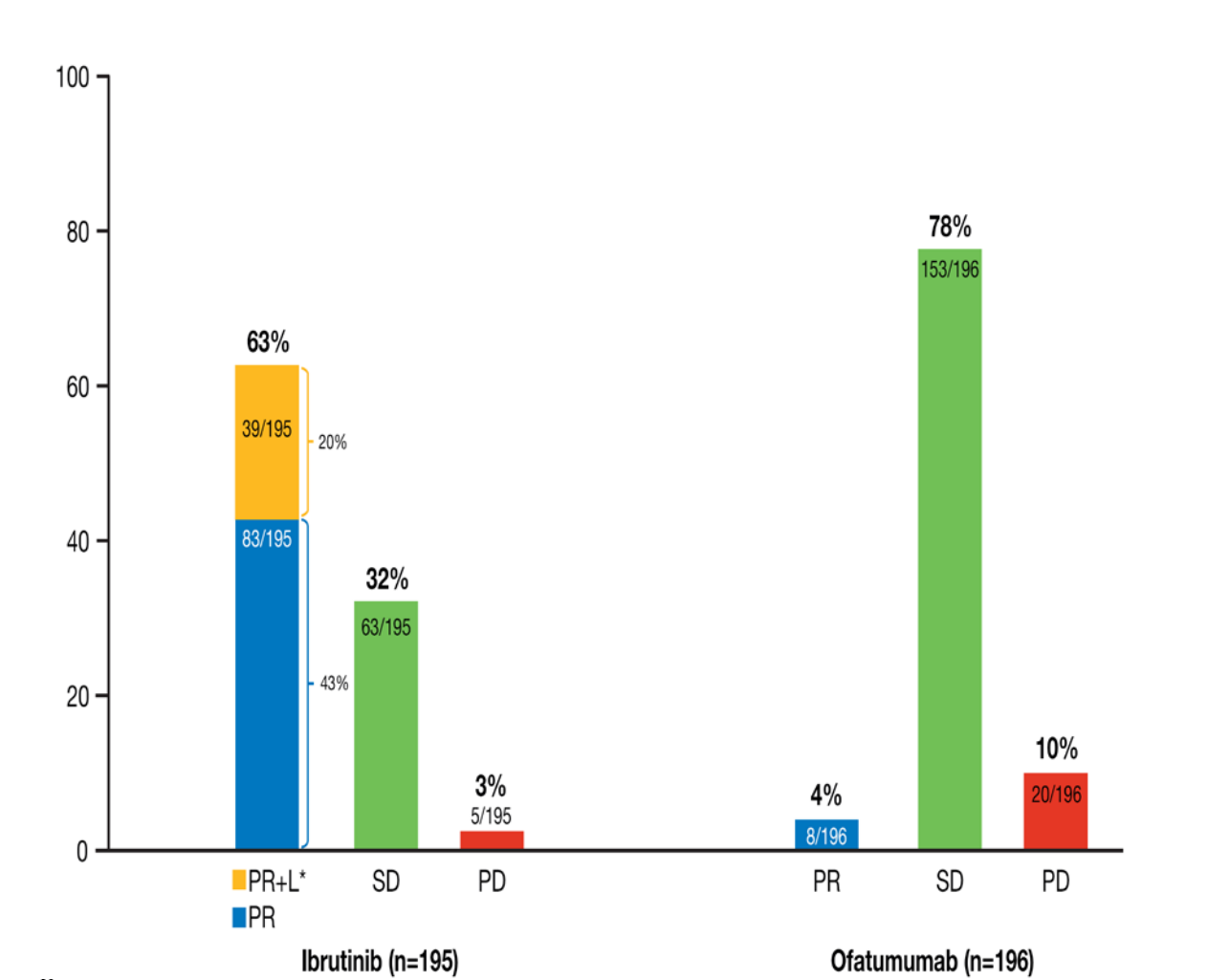
Kinase Inhibitors in Clinical Development for CLL



Woyach JA et al. *Blood* 2012;120:1175-1184

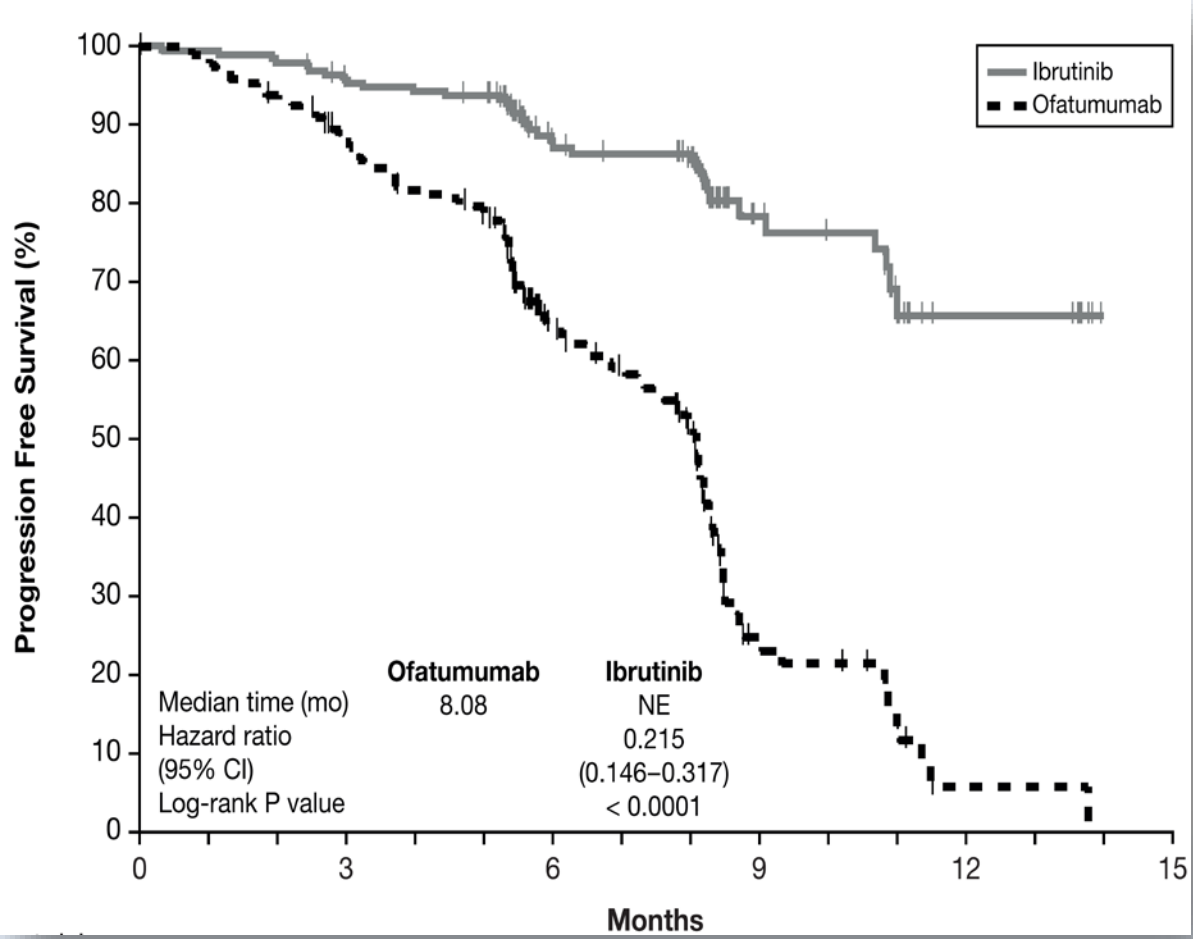
RESONATE Trial: Ofatumumab vs. Ibrutinib

Response



Byrd JC, et al. (2014). *N Engl J Med* 371(3):213-223

RESONATE Trial: Ofatumumab vs. Ibrutinib Progression-Free Survival



Byrd JC, et al. (2014). *N Engl J Med* 371(3):213-223

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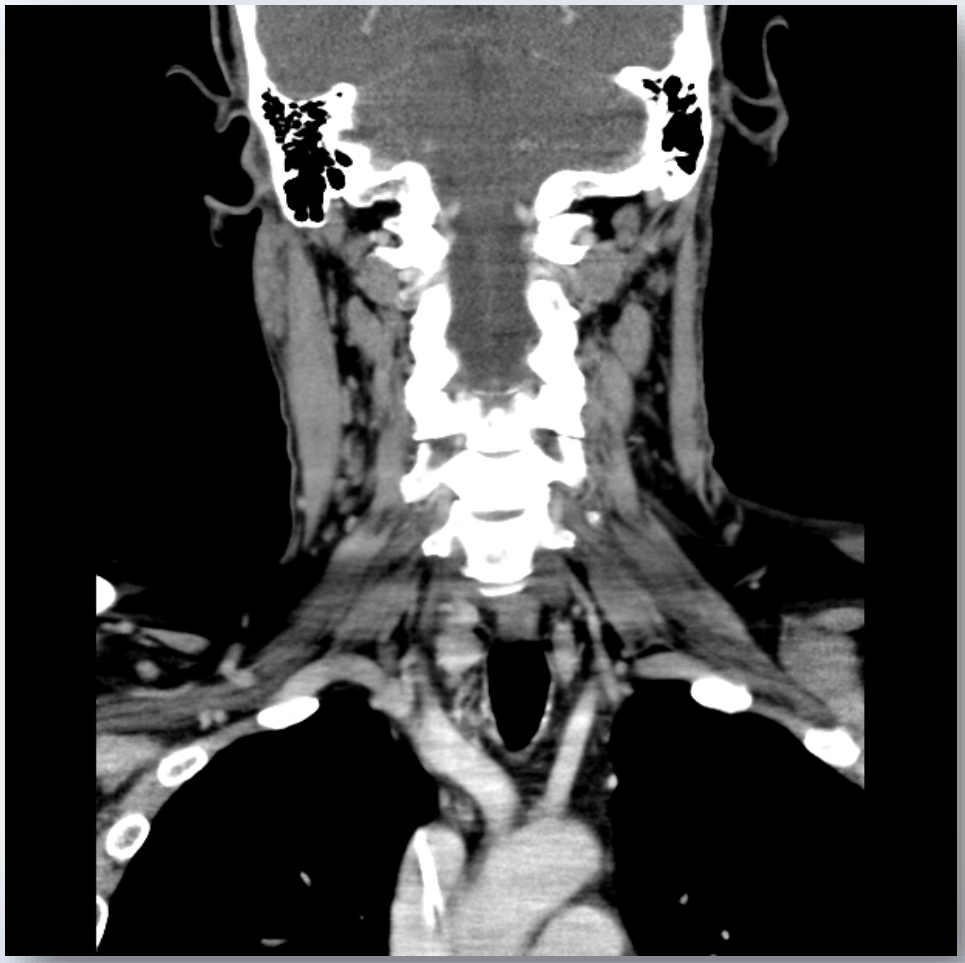
Case Study Continued

Response to ibrutinib after 3 months of treatment



RESONATE Safety: Adverse Events (≥ 15%)

	Ibrutinib (N=195)		Ofatumumab (N=191)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TEAE, %	99	51	98	39
Diarrhea	48	4	18	2
Fatigue	28	2	30	2
Nausea	26	2	18	0
Pyrexia	24	2	15	1
Anemia	23	5	17	8
Neutropenia	22	16	15	14
Cough	19	0	23	1
Thrombocytopenia	17	6	12	4
Arthralgia	17	1	7	0
Upper respiratory tract infection	16	1	10	2
Constipation	15	0	9	0
Infusion-related reaction	0	0	28	3

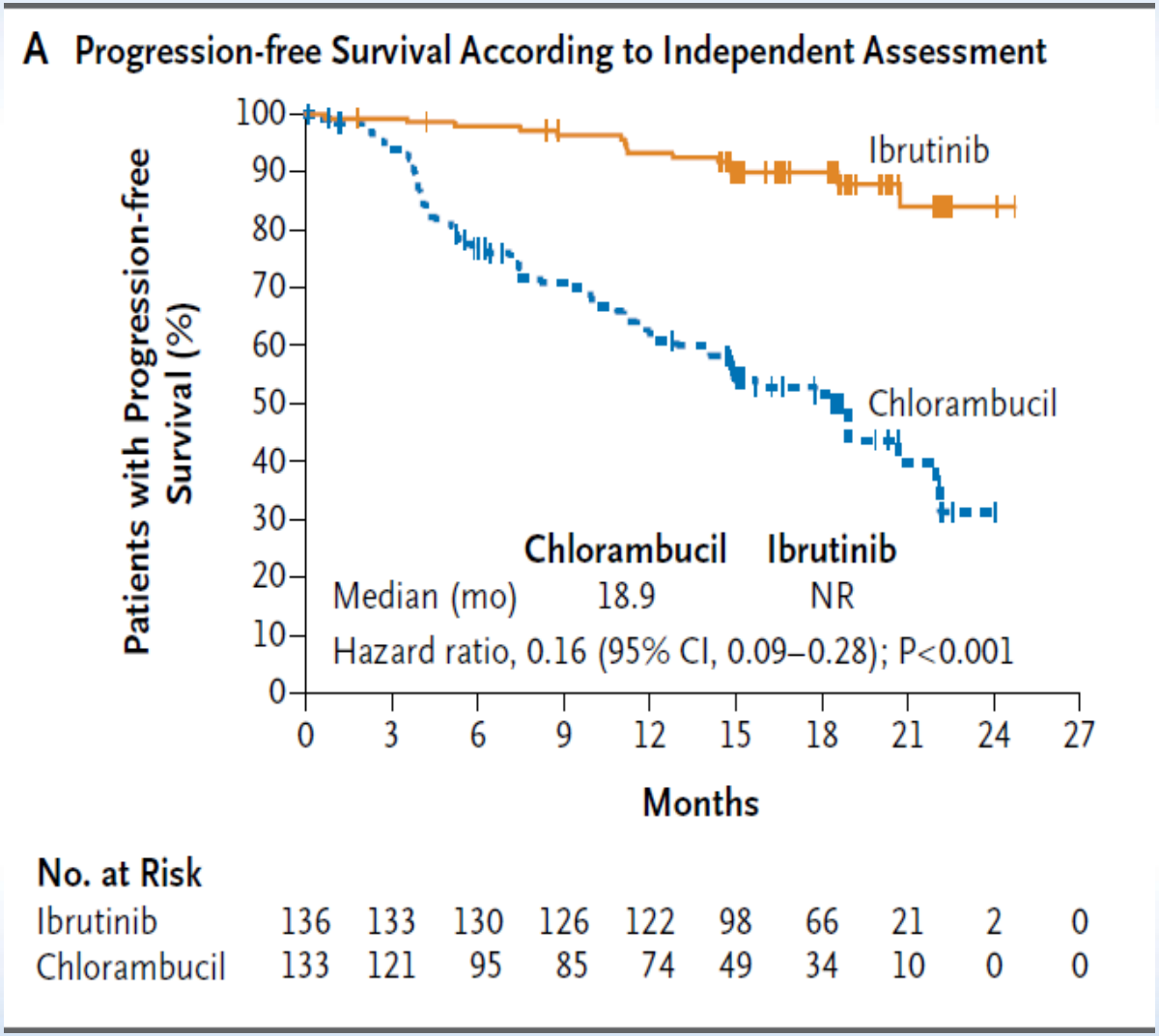
[a]Patients in the ibrutinib arm had a >50% longer AE reporting period than those on ofatumumab (median of treatment duration 8.6 vs. 5.3 months, respectively); there was no adjustment for exposure duration; [b]TEAE, treatment-emergent AEs reported in all patients who received study drug.

Byrd JC, et al. (2014). *N Engl J Med* 371(3):213-223

Resonate-2 Trial: CLL ≥ 65, Treatment Naive

Phase III, open label, randomized, multicenter, international trial

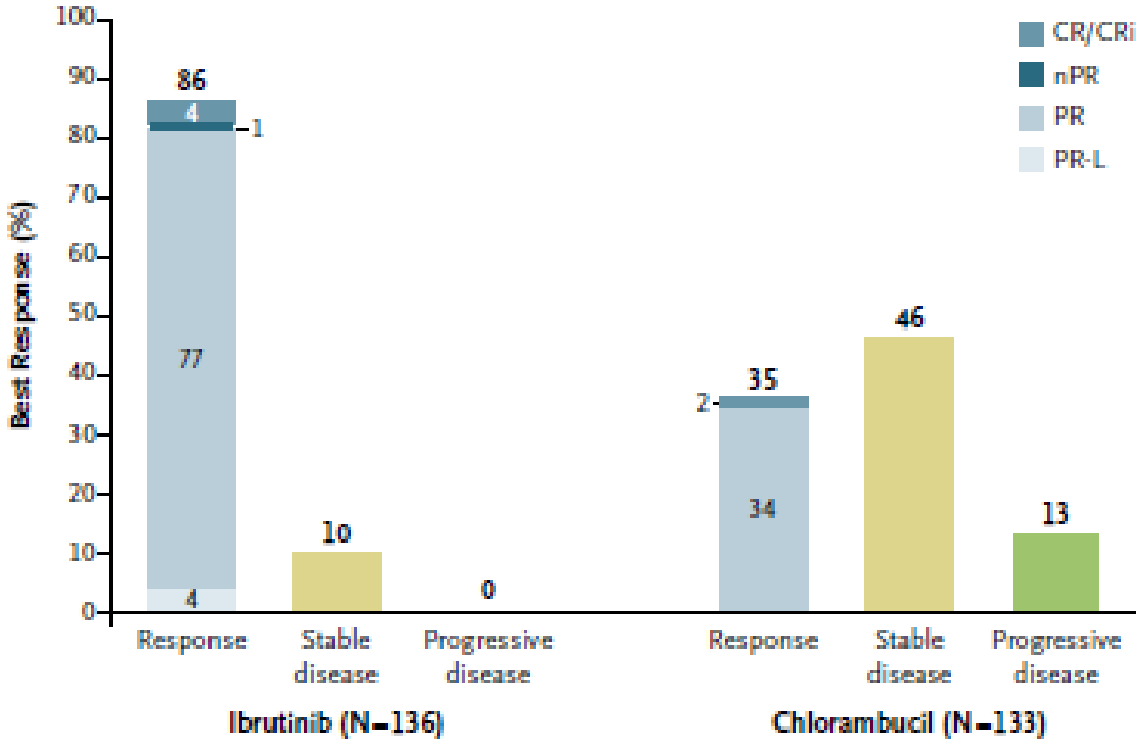
- Chlorambucil vs. ibrutinib



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

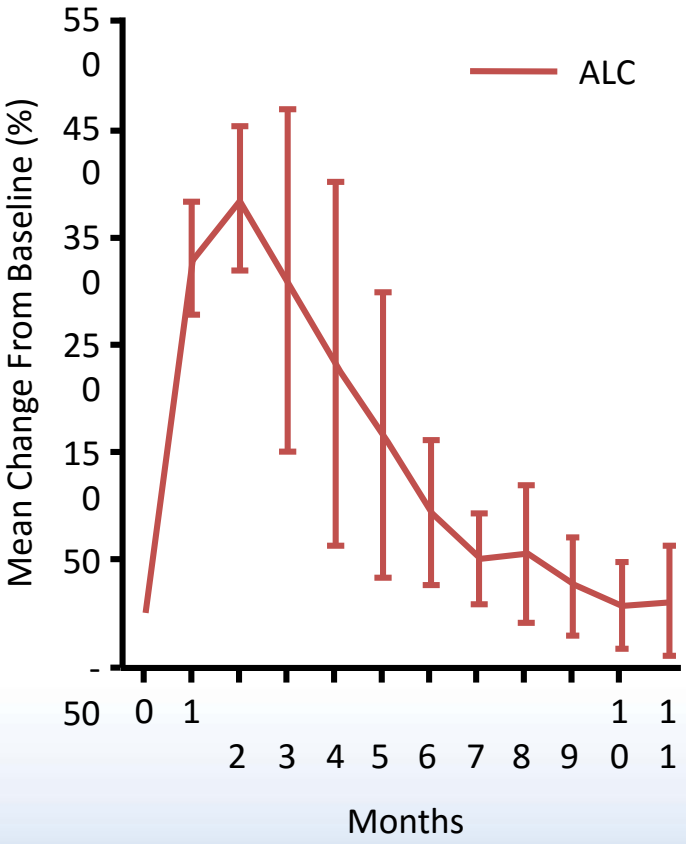
B Best Response

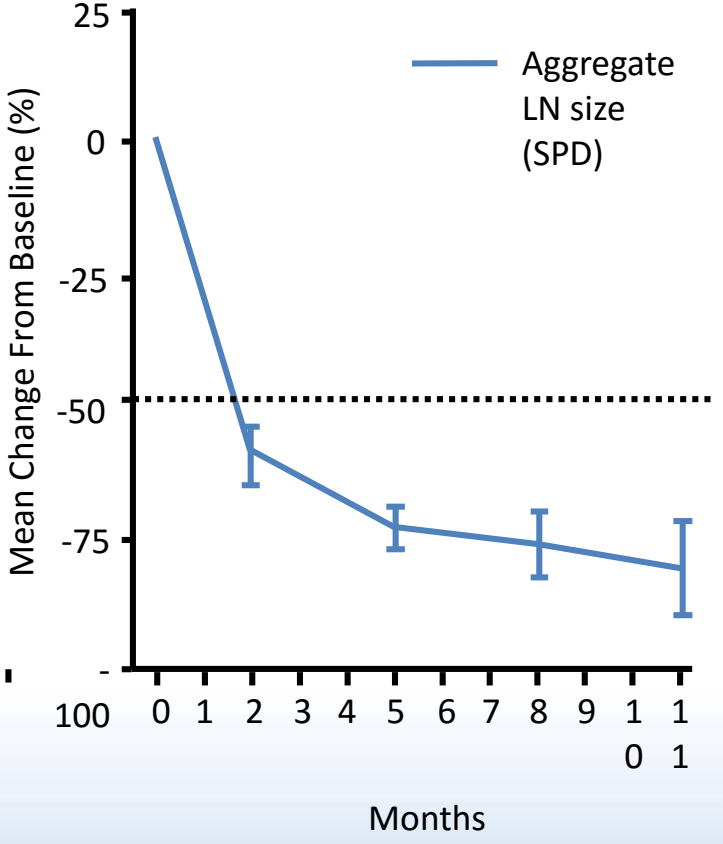
Overall Response Rate	Ibrutinib	Chlorambucil	Rate Ratio (95% CI)	P Value
	% of patients			
With PR-L	86	35	2.42 (1.91–3.07)	<0.001
Without PR-L	82	35	2.32 (1.82–2.95)	<0.001



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

Ibrutinib Pattern of Response: Blood Lymphocytes vs Lymph Nodes





O'Brien S, et al. ASH 2011. Abstract 983.

Lymphocytosis With Ibrutinib

- Analysis of blood from 59 CLL patients 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
  - Progression-free survival is not inferior for patients with prolonged lymphocytosis vs those with traditional responses

Woyach JA, et al. (2014). *Blood* 123(12):1810-1817

Case Study 3:
82-year-old Retired Hematologist, Rai Stage IV CLL

- Originally diagnosed in 2004
- WBC ranging from 275,000 to 400,000
- No treatment until 2014 when the patient developed progressive thrombocytopenia (80,000) and recurrent infections (pneumonia x 2)
- PMH: Hypertension, gout, A-fib
- After a long discussion with the patient, he was started on ibrutinib 420 mg daily

What discussions would you have with this patient at this time?

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 pts

Ibrutinib package insert

RESONATE Safety: A-Fib 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 randomized 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 anti-platelet agents (excluding NSAIDs) or anticoagulants

Byrd JC, et al. (2014). *N Engl J Med* 371(3):213-223

Ibrutinib and Atrial Fibrillation

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

Ibrutinib prescribing information, Pharmacyclics, Inc. 2014.

Case Study Continued

- The patient presents with a “bad tooth” and believes he needs to have a root canal or an extraction.

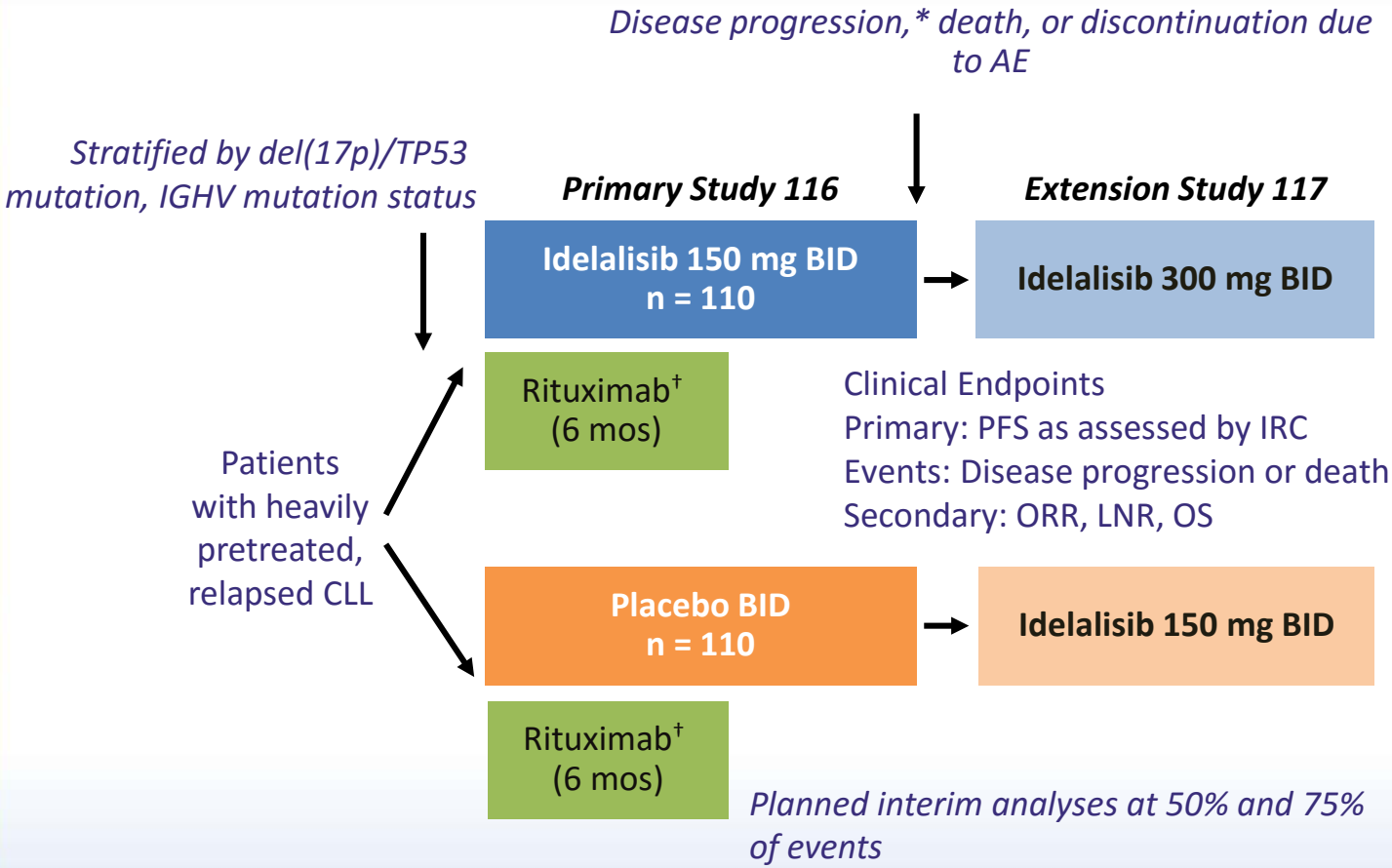
What recommendations would you have for this patient?

Bleeding and Holding Ibrutinib

- 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 upon the type of surgery and the risk of bleeding

Ibrutinib prescribing information, Pharmacyclics, Inc. 2014.

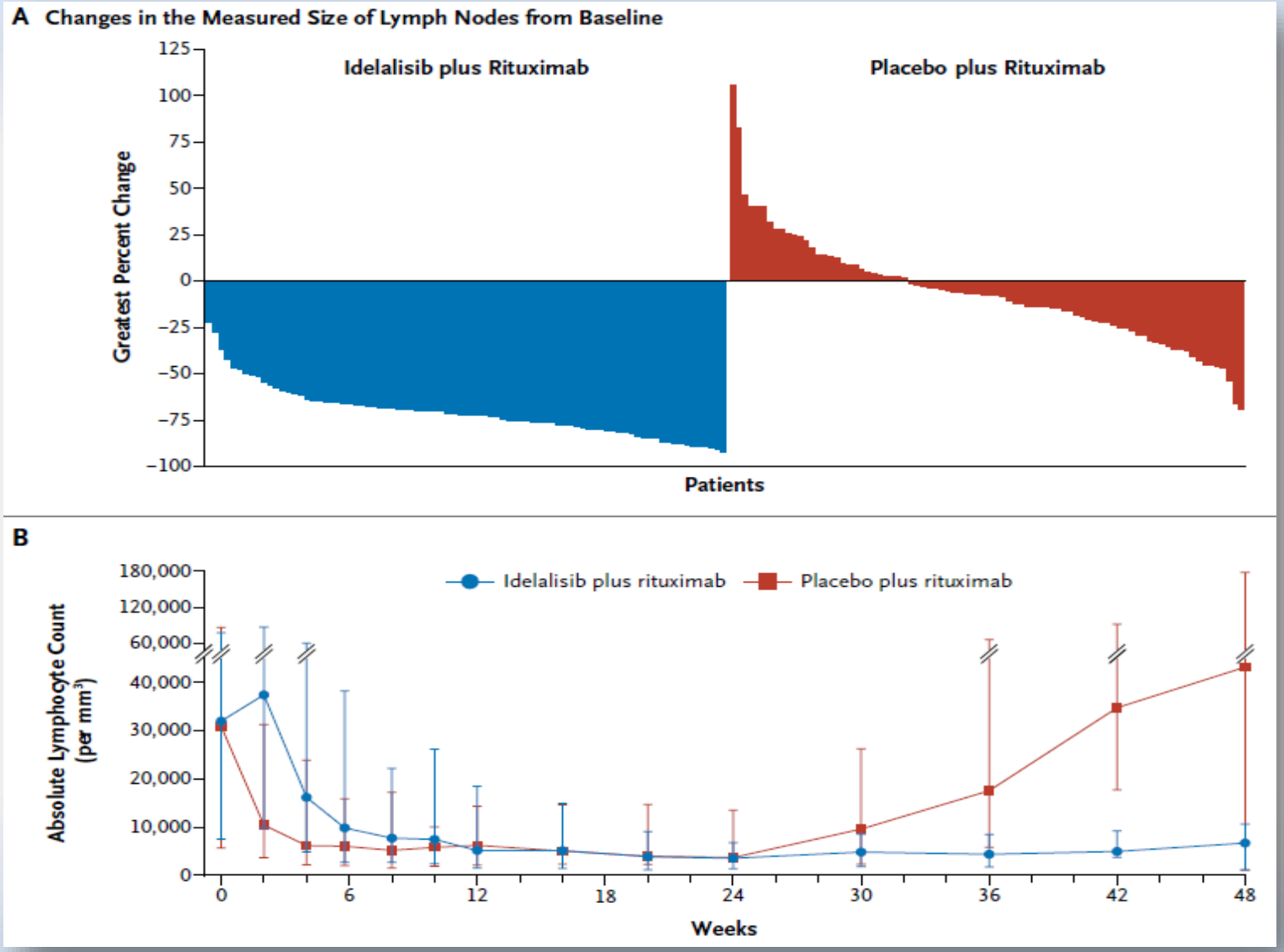
Idelalisib and Rituximab for Relapsed CLL



*Patients with disease progression continued on idelalisib Extension Study 117.
†Rituximab schedule: 375 mg/m^2, then 500 mg/m^2 every 2 wk x 4, then 500 mg/m^2 every 4 wk x 3.

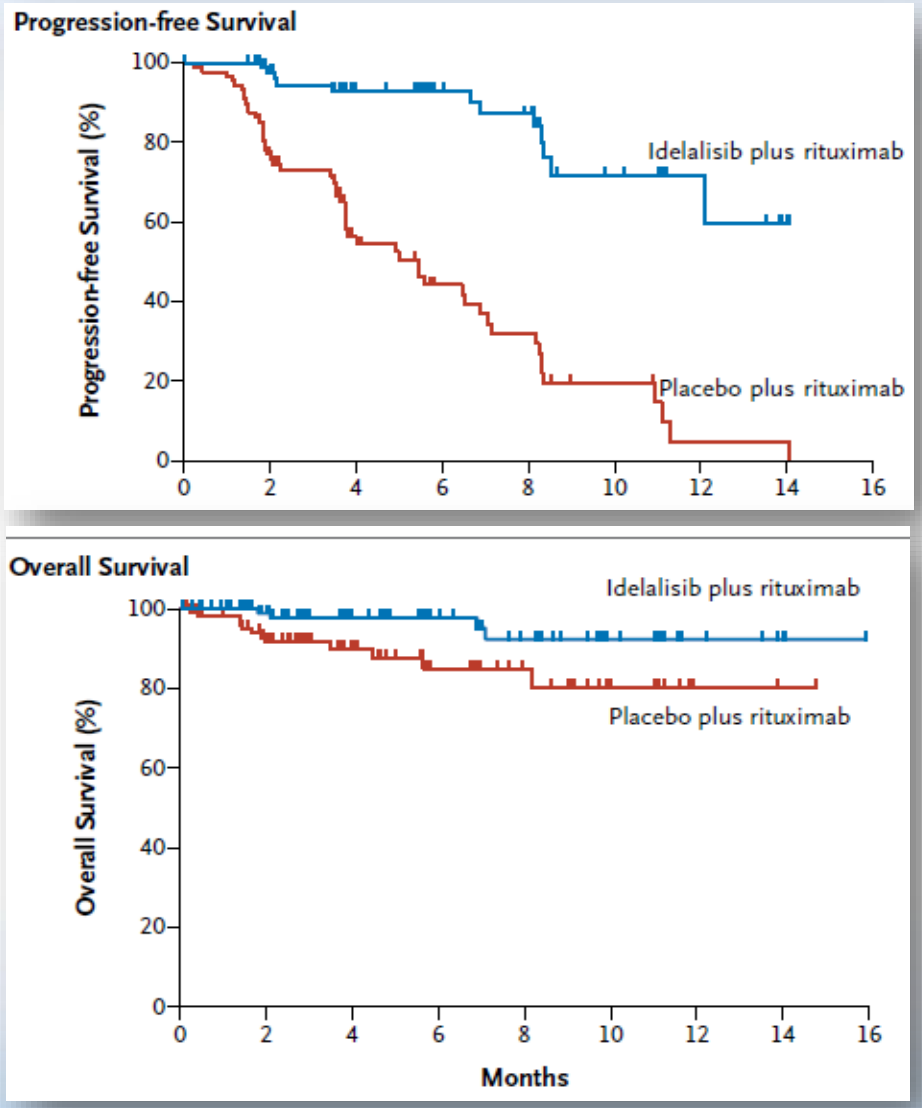
Furman RR et al. *N Engl J Med* 2014;370:997-1007.

R-Idelalisib for Relapsed CLL: Response



Furman RR, et al. *N Engl J Med* 2014;370:997-1007.

R-Idelalisib for Relapsed CLL: Survival



Placebo = 5.5 months
Idelalisib = NR
(hazard ratio for progression or death in the idelalisib group, 0.15; P<0.001)

Furman R et al. (2014) *N Engl J Med* 370(11):997-1007

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)

Furman RR, et al. *N Engl J Med*. 2014;370:997-1007.

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 bid	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 bid	Discontinue idelalislib
Diarrhea	**Moderate**	**Severe or Hospitalized**	**Life Threatening**
	-Continue idelalisib -Monitor until resolved	-Hold idelalisib -Monitor weekly until resolved -Resume at 100 mg bid	Discontinue idelalisib

Gilead Sciences, Inc. Idelalisib (Zydelig) Prescribing Information (2014)

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 pts with R/R CLL
  - ORR for R/R CLL with del(17p): 71% (95% CI: 52% to 86%)
- A single dose of ABT-199 in three patients enrolled in the phase I trial with refractory CLL resulted in tumor lysis within 24 h

Souers AJ, et al. (2013). *Nat Med* 19(2):202-208; Roberts AW, et al. (2016). *N Engl J Med* 374(4):311-322.

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:

- 20 mg QD day 1
- 50 mg QD days 2-7
- 100 mg QD wk 2
- 200 mg QD wk 3
- 400 mg QD wk 4+

- **Risk-based TLS prophylaxis used**
- Primary endpoint: ORR (IRC assessment)
- Secondary endpoints: CR/PR, time to first response, DoR, PFS, OS, safety
- Exploratory endpoint: Minimal residual disease (MRD)

Stilgenbauer S, et al. ASH 2015. Abstract LBA-6.

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

- Overall response: 79% (20% CR)
- 15-month progression-free survival 69%
- Among 87 pts 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 pts 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. (2016). *N Engl J Med* 374(4):311-322.

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%)

Roberts AW, et al. (2016). *N Engl J Med* 374(4):311-322.

Tumor Lysis Syndrome (TLS) Risk Stratification

- **TLS risk category, % 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 tumor lysis syndrome 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* 374(4):311-322.

Tumor Lysis Syndrome
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; see below for monitoring in hospital

Roberts AW, et al. *N Engl J Med* 374(4):311-322; Venclexta prescribing information

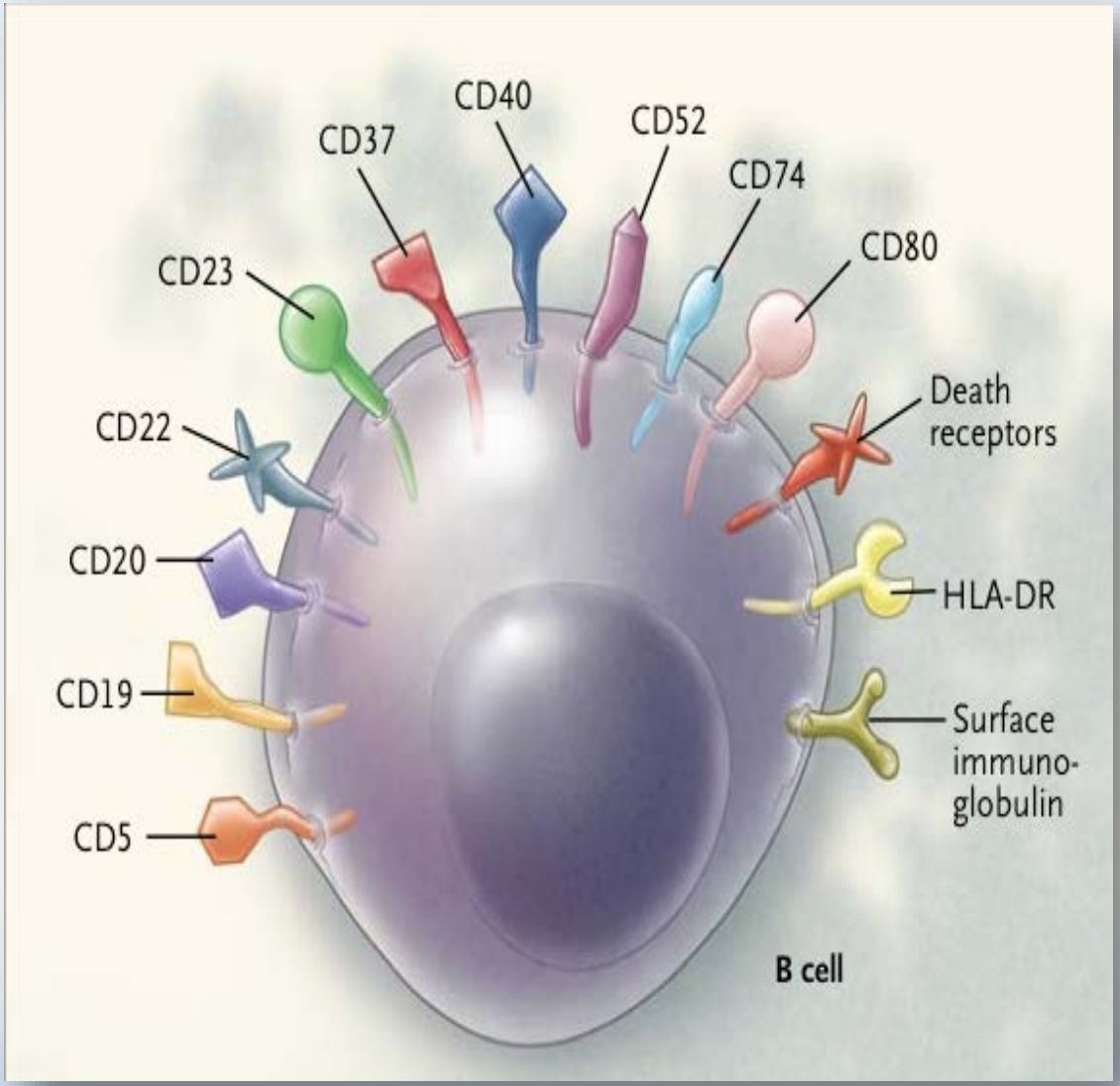
Tumor Lysis Syndrome Risk Stratification and Prophylaxis

HIGH Tumor Burden	Any LN ≥10 cm OR ALC ≥25 x 10^9/L AND Any LN ≥5 cm
Prophylaxis	Oral (1.5-2L) and intravenous (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* 374(4):311-322; Venclexta prescribing information

MONOCLONAL ANTIBODIES USED TO TREAT CLL

Antigen Targets on B Cells



Cheson BD, & Leonard JP (2008). *N Engl J Med* 359:613-626

Ofatumumab

- Fully human anti-CD20 monoclonal antibody
- FDA-approved in 2009 for use in CLL patients with disease refractory to fludarabine and alemtuzumab
- Premedicate with acetaminophen, antihistamine, and corticosteroid
- Dosing is variable

Ofatumumab (Arzerra) prescribing information, 2011.

Ofatumumab (cont.)

- No Black Box warnings
- Warnings and precautions include
  - Infusion reactions (44% w/first infusion; 29% w/second infusion)
  - Cytopenias
  - Progressive multifocal leukoencephalopathy
  - Hepatitis B reactivation

Results in Fludarabine and Alemtuzumab Refractory	%
Overall response rate (%)	42
Complete response rate (%)	0
Median duration of response (mos)	6.5

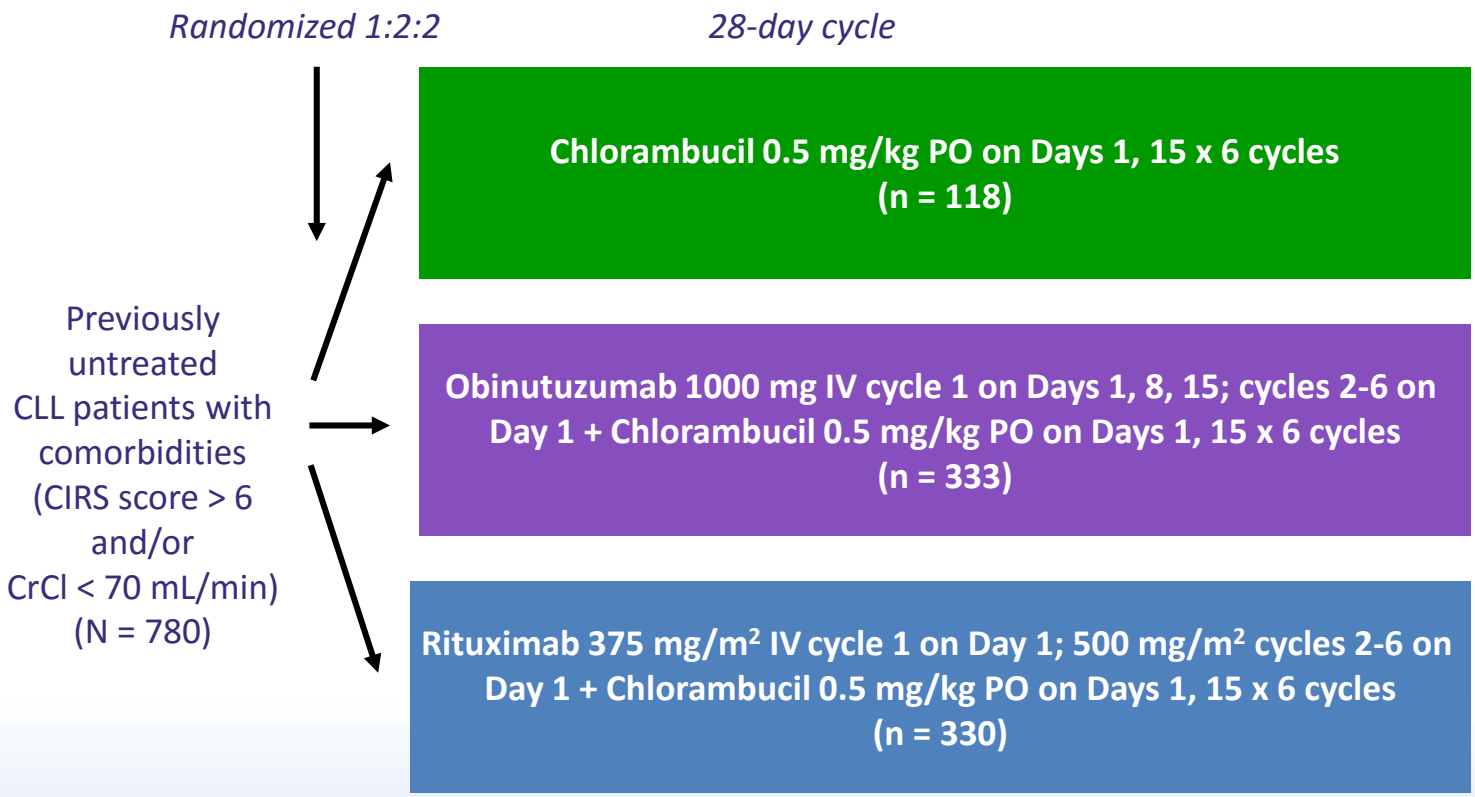
Ofatumumab (Arzerra) prescribing information, 2011.

Ofatumumab Side Effects

Adverse event	Total population (n = 154; %)
Neutropenia	60
Pneumonia	23
Fever	20
Cough	19
Diarrhea	18
Anemia	16
Fatigue	15
Rash	14
Dyspnea	14
Nausea	11
Upper respiratory tract infection	11
Bronchitis	11

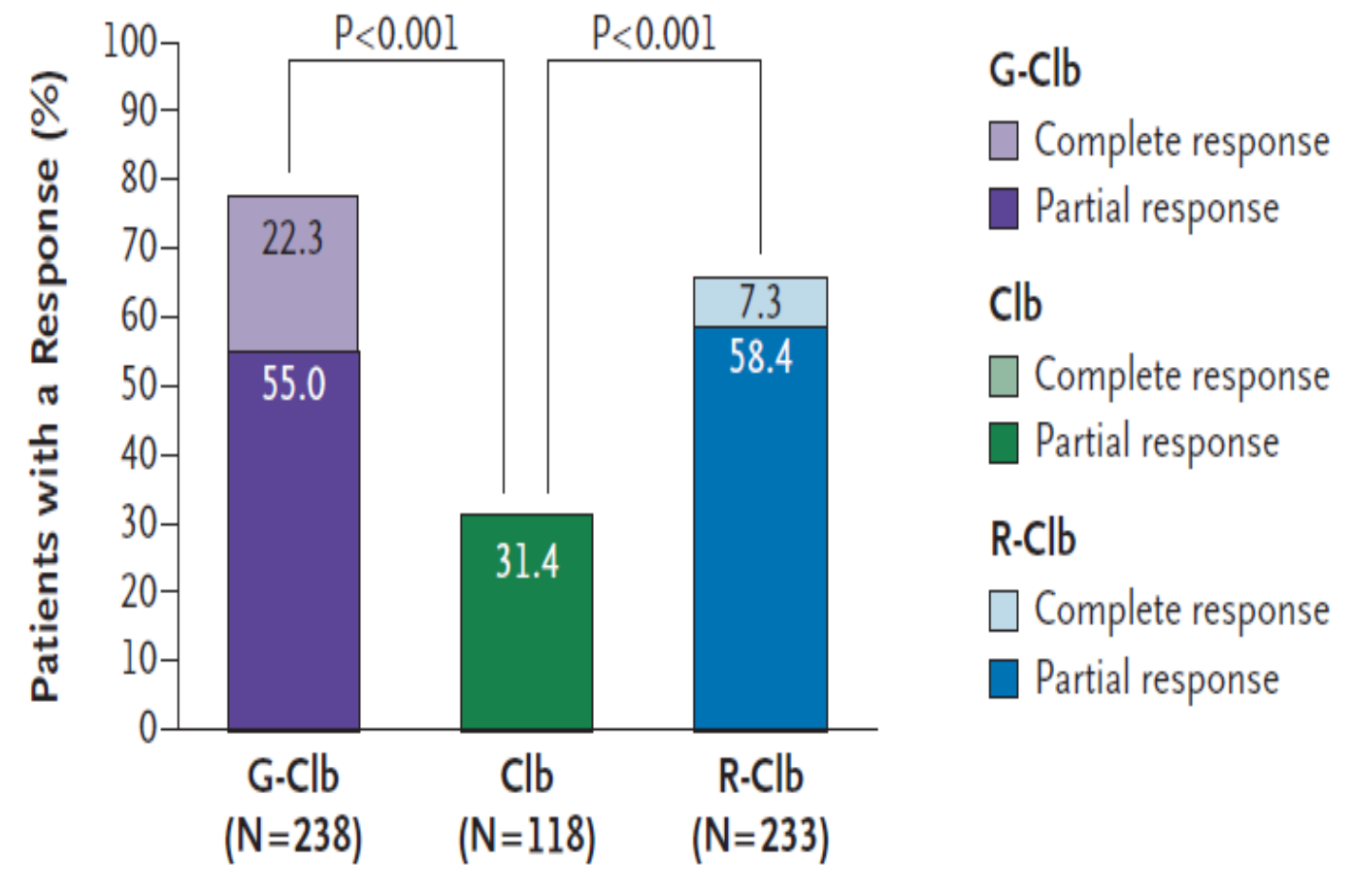
Ofatumumab (Arzerra) prescribing information, 2011.

CLL11 Trial: Obinutuzumab + Chl vs. Rituximab + Chl



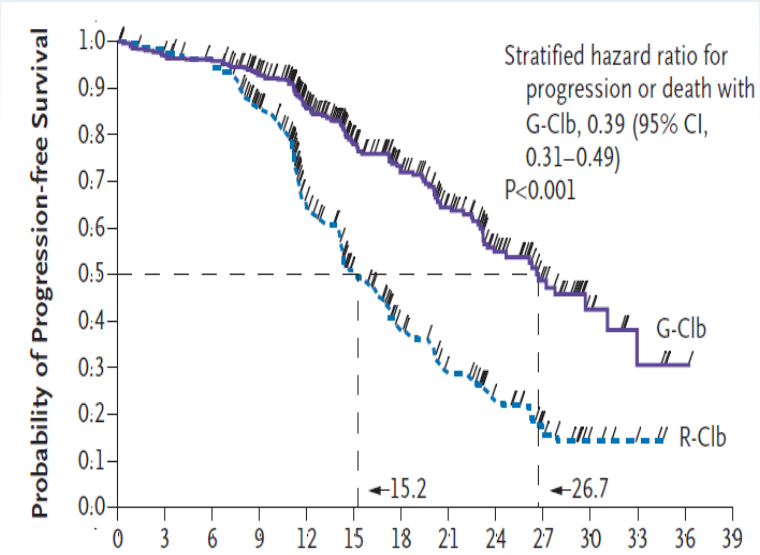
Goede V, et al. (2014). *N Engl J Med* 370(12):1101-1110

CLL11 Trial:
Obinutuzumab + Chl vs. Rituximab + Chl



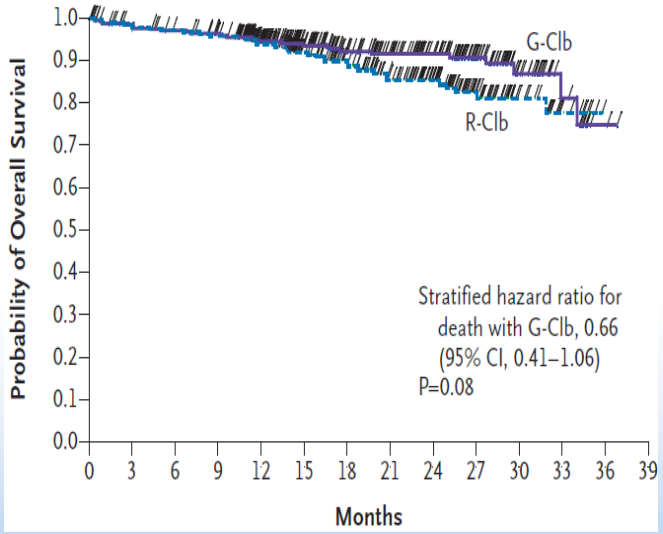
Goede V, et al. (2014). *N Engl J Med* 370(12):1101-1110

CLL11 O-Chl vs. R-Chl: Survival



O-Chl improved PFS by 11.5 months vs. R-Chl

BUT
OS was similar in both groups



Goede V, et al. (2014). *N Engl J Med* 370(12):1101-1110

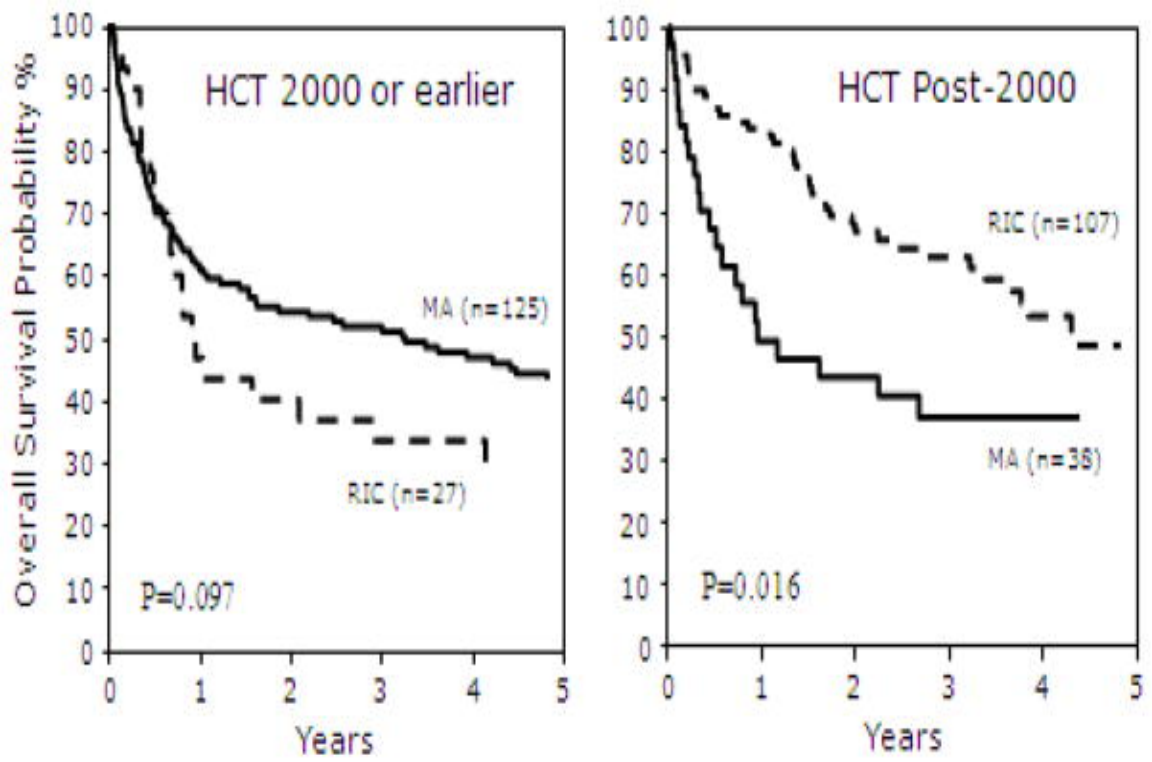
THE ROLE OF HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CLL

Allogeneic Transplant in CLL

- Only curative option for CLL due to graft-vs-leukemia effect
- Considered mainly in patients with
  - del(17p)
  - Fludarabine-refractory disease
  - Relapse within 2 years of autologous BMT
- Myeloablative approaches carry high toxicity and mortality
- Reduced intensity/non-myeloablative/mini transplant
- Developed in the 1990s
- Allow allogeneic transplant in elderly or young with comorbidities
- Many studies show lower non-relapse mortality than myeloablative allogeneic BMT
- Graft-vs-leukemia effect seen

Sobecks RM, et al. (2014) *Biol Blood Marrow Transplant* 20(9):1390-1398

Allogeneic Transplant in CLL



Comparison of overall survival between MA and RIC allogeneic HCT for CLL
(A) performed in 2000 or earlier
(B) performed after 2000

Sobecks RM, et al. (2014) *Biol Blood Marrow Transplant* 20(9): 1390-1398

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)

www.clinicaltrials.gov