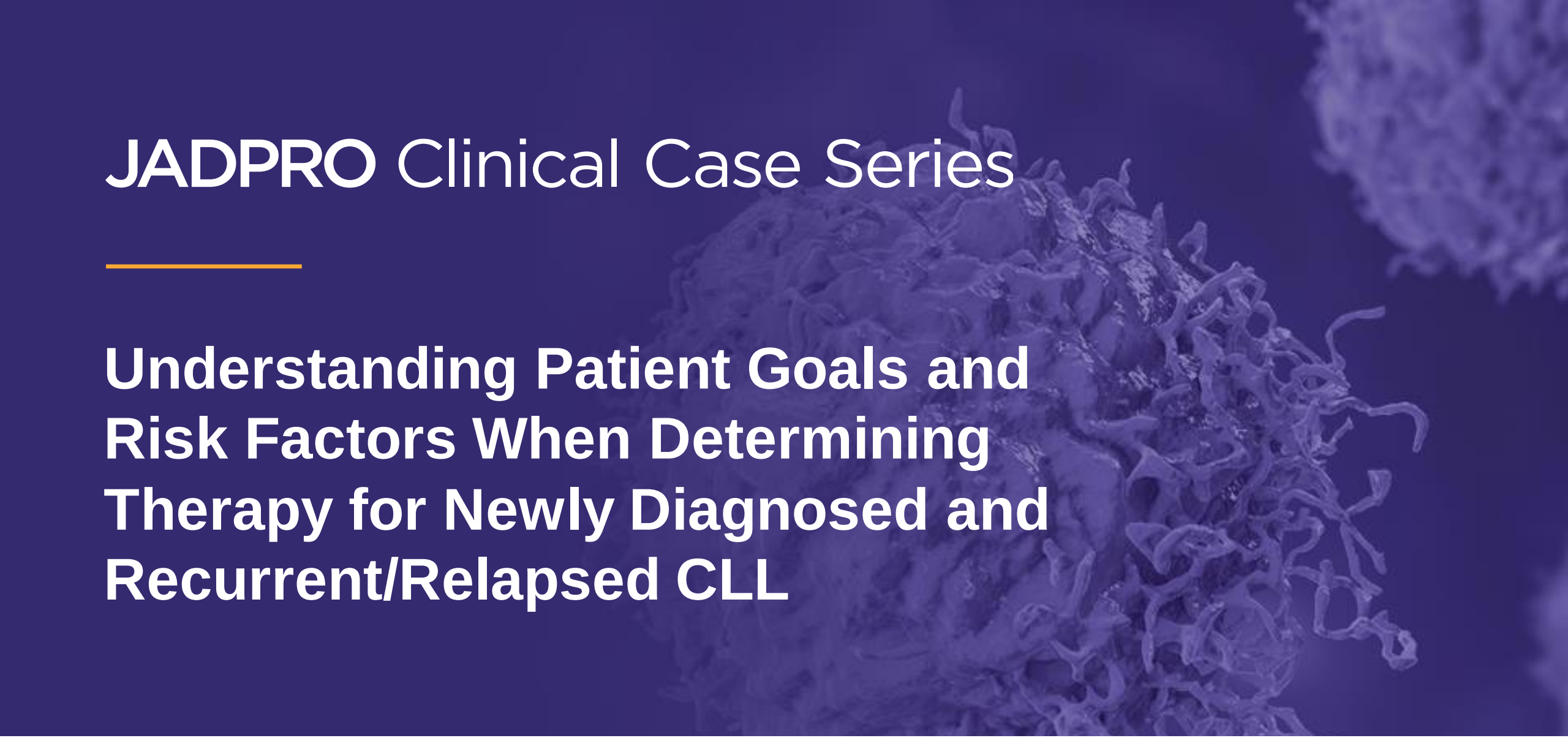

JADPRO Clinical Case Series

Understanding Patient Goals and Risk Factors When Determining Therapy for Newly Diagnosed and Recurrent/Relapsed CLL

SUPPORTED BY abbvie

PRESENTER

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Program Agenda

- Identification of patient and family goals when determining optimal treatment for newly diagnosed and recurrent/relapsed CLL
- Recognition of high-risk features and atypical presentations of CLL
- Exploration of treatment options for durable responses in recurrent/relapsed CLL

Introduction to CLL

- In 2020, more than 200,000 people were living with CLL in the United States
- In 2022, ~20,000 adults were diagnosed with CLL
- Most prevalent adult leukemia in Western countries
- Characterized by progressive accumulation of leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues
- Staged by the Rai and Binet systems
- Prognostic information and staging used to tailor treatment to disease characteristics
- Patient characteristics important, including goals, fit/frail, comorbidities, social support, insurance

Siegel RL et al. Cancer statistics, 2022. CA Cancer J Clin. 2022;72:7-33.

Question

Regarding the care of newly diagnosed patients with CLL, how confident are you in your knowledge regarding optimal management of the disease?

a. Extremely confident
b. Somewhat confident
c. Not confident at all

Question

Regarding the care of patients with recurrent/relapsed CLL, how confident are you in your knowledge regarding optimal management of the disease?

a. Extremely confident
b. Somewhat confident
c. Not at all confident

Case 1: Polling Question

In your practice, is it routine to perform a bone marrow biopsy at baseline when seeing a patient with suspected CLL?

a. Yes **38%**

b. No **54%**

c. I do not see patients with CLL **4%**

Case 1: Endurance Athlete With CLL Recurrence After Chemotherapy

At Diagnosis

- 60 years old
- Asymptomatic
- Routine labs
- WBC: 14.9 x 10^3/µL
  - Hb: 15.9 g/dL
  - Platelets: 218,000/µL, 70% lymphocytes
- No lymphadenopathy or hepatosplenomegaly

Bone Marrow Biopsy + Aspiration

- Normocellular marrow with 30% to 40% infiltration with CLL
- Cytogenetics positive for 13q deletion
- Flow cytometry positive for CD20, CD19, and CD5
- Rai stage 0
- IgVH unmutated

Recommendations

Observation Every 3 Months

- Remained without the need for CLL treatment for 8 years
- Active with competitive cycling and ocean kayaking all over the world
- Expressed desire to stay active
- Treatment needed to fit into his schedule

…and Then

- WBCs increased to 274,000/µL
  - Absolute lymphocyte count of 260,000/µL
  - Hb of 12 g/dL
  - Platelet count: 135,000/µL
  - Lymphadenopathy in the neck, axilla, and inguinal region, splenomegaly

Meets Criteria for Treatment

- Deferred treatment
- Began treatment once bulky lymphadenopathy (8.6-cm inguinal) interfered with ability to compete in rowing
- Widespread bulky lymphadenopathy by CT scans, splenomegaly
- FISH for CLL with 13q deletion only
- WBC 306,000/µL, Hb 12.5 g/dL, platelets 119,000/µL
- Treated with 6 cycles of fludarabine, cyclophosphamide, and rituximab without complications
- Achieved a complete response
- No evidence of CLL for 6 years

Treatment Decision for Relapse

- Developed pneumonia requiring hospitalization
- Rapid lymphocyte doubling time
- PET/CT performed with non-bulky lymphadenopathy
- Repeat FISH for CLL with 13q deletion, and new 17p deletion
- Platelets dropped to 56,000/µL
- Discussed treatment: bendamustine + rituximab vs fixed-duration venetoclax with rituximab according to MURANO trial
- Shared in the decision to start venetoclax and rituximab

MURANO Trial

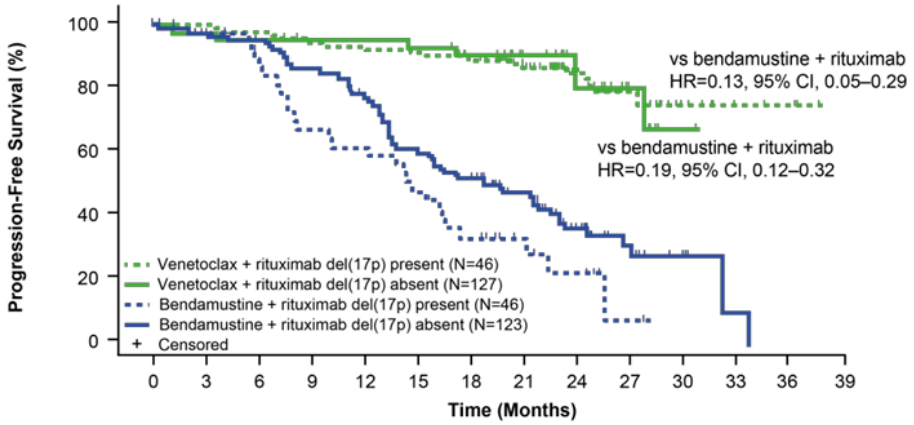
- Randomized clinical trial of 389 patients (VEN+R: n = 194; BR: n = 195)
- Previously treated CLL
- Median follow-up of 23.8 months
- 2-year progression-free survival in the VEN+R arm was 84.9% vs BR arm of 36.3% ($p < .001$ by log-rank test)
- 2-year rate in patients with 17p deletion 85.9% vs 41.0%

VEN+R: venetoclax + rituximab; BR, bendamustine + rituximab.

Seymour JF et al. *N Engl J Med.* 2018;378:1107-1120.

MURANO Trial (cont'd)

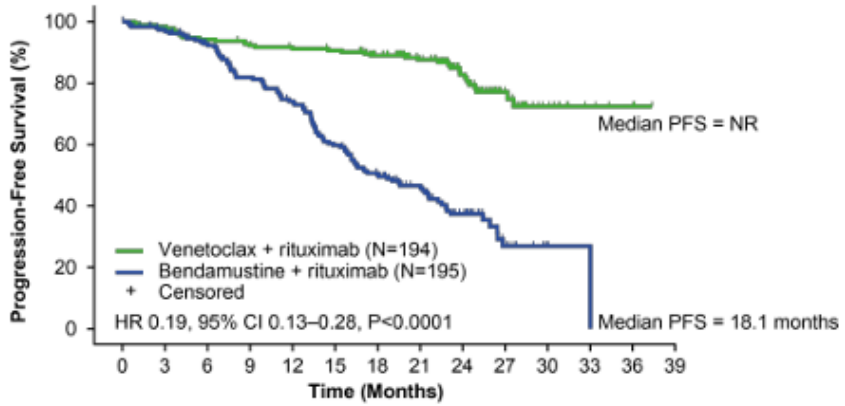
Figure S2. Kaplan–Meier estimates of investigator-assessed progression-free survival by del(17p) status as centrally assessed (Vysis CLL FISH probe kit) using a 7% cutoff value



No. of patients at risk

Venetoclax + rituximab del(17p) present	46	44	43	43	43	42	36	25	17	7	2		
Venetoclax + rituximab del(17p) absent	127	127	124	118	116	114	105	76	48	20	10	4	3
Bendamustine + rituximab del(17p) present	46	40	34	27	25	20	14	8	5	1			
Bendamustine + rituximab del(17p) absent	123	114	108	99	88	70	60	44	26	10	3	1	

Figure S1. Kaplan–Meier estimates of independent review committee-assessed progression-free survival for venetoclax plus rituximab compared with bendamustine plus rituximab (intention-to-treat population)

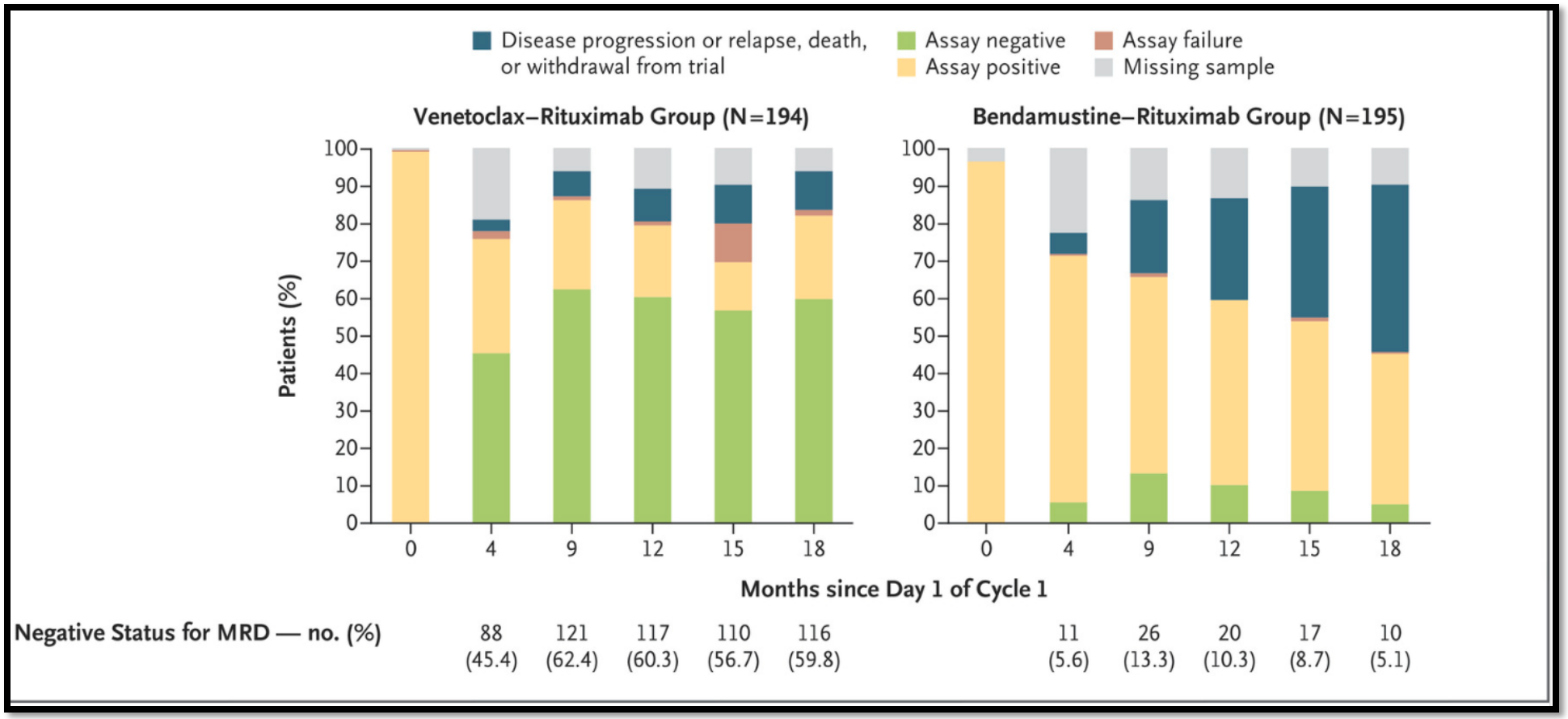


No. of patients at risk

Venetoclax + rituximab	194	190	182	177	173	171	157	116	75	34	14	5	3
Bendamustine + rituximab	195	178	162	138	124	100	82	56	34	11	2	1	

Seymour JF et al. N Engl J Med. 2018;378:1107-1120.

Rate of Clearance of Minimal Residual Disease



Seymour JF et al. N Engl J Med. 2018;378:1107-1120.

The Nuts and Bolts: How to Treat Safely

- Venetoclax titrated gradually over a 5-week period
  - 20 mg per day week 1
  - 50 mg per day week 2
  - 100 mg daily week 3
  - 200 mg daily week 4
  - 400 mg daily week 5
  - Continue recommended daily dose of 400 mg for 24 months
- Rituximab (375 mg/m^2) starts after patient has received venetoclax 400 mg for 7 days
  - Continue rituximab (500 mg/m^2) on day 1 of each (28-day) cycle for a total of 6 cycles

https://www.venclextahcp.com/cll/dosing-and-administration/ven-r-dosing.html

Educational Points for Discussion

- Accurate medication list is important
- Call office with any planned changes in medications
- Take daily, same time if possible
- Swallow whole with meal and water
- Stay hydrated with 6-8 glasses of fluids daily
- Important to keep all appointments, especially in the ramp-up phase
- Need for careful monitoring, both physical examination and bloodwork to monitor for tumor lysis syndrome (risk of death/renal failure)

Question

What features of a CLL diagnosis are concerning for more aggressive disease, resistant to traditional chemotherapy?

a. Bulky lymphadenopathy
b. 13q deletion
c. Development of 17p deletion
d. Recurrent infections

Case 2: Polling Question

In your practice, do you refer patients with CLL who are diagnosed younger than the median age for diagnosis (65-70 years) for genetic counseling?

a. Yes **32%**

b. No **45%**

c. Sometimes **23%**

Case 2: Young Patient With High-risk Disease Characteristics

At Diagnosis

- 36 years old
- Symptomatic
  - 40-lb weight loss
  - Fevers
  - Enlarged tonsils
  - Drenching night sweats
- Labs
  - WBC 15.95 x 10^3/µL, Hb 14.5 g/dL,
  - Platelets 157,000/µL, 60% lymphocytes
- No lymphadenopathy, hepatosplenomegaly

High-risk Features

- Diagnosed by flow cytometry with CLL
- Flow cytometry positive for CD19, CD23, and CD5
- Unmutated IgVH
- FISH positive for 17p deletion in 47% of cells, 13q deletion
- Rai Stage 0, high risk molecular features
- Worked up for infectious etiologies

WBC, white blood cell count; Hb, hemoglobin

Atypical Progression

6 Months Later

- Pulmonary infiltrates concerning for infectious etiology
- Tonsillar enlargement, airway concerns
- Drenching night sweats and fevers

Recommendations

- Referred to pulmonary colleagues
  - Underwent bronchoscopy
- Referred to head and neck
- No antibiotics initiated
- Checked quantitative immunoglobulins

Pathology From Bronchoscopy

Lung, Right Lower Lobe, Forceps Biopsy:

Non-necrotizing epithelioid granulomas admixed with a dense lymphocytic proliferation involving bronchial submucosa and alveolated lung parenchyma

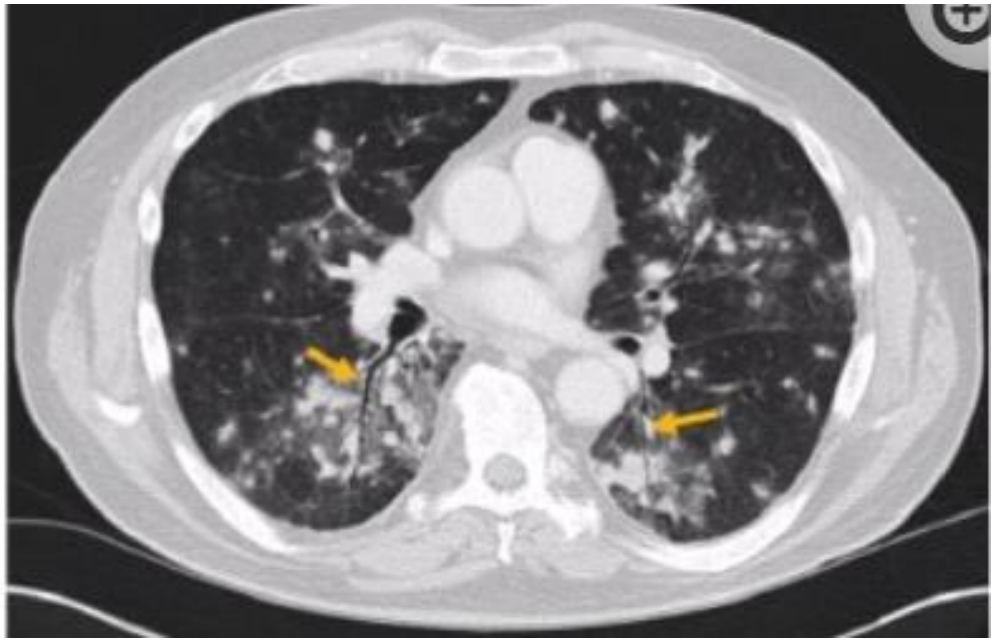
- No acid-fast bacilli or fungal microorganisms identified
- No necrosis or epithelial malignancy identified

<u>Negative infectious work-up</u>

- IgG level greater than 600

<u>Head and neck consultation</u>

- Tonsillar enlargement attributed to CLL



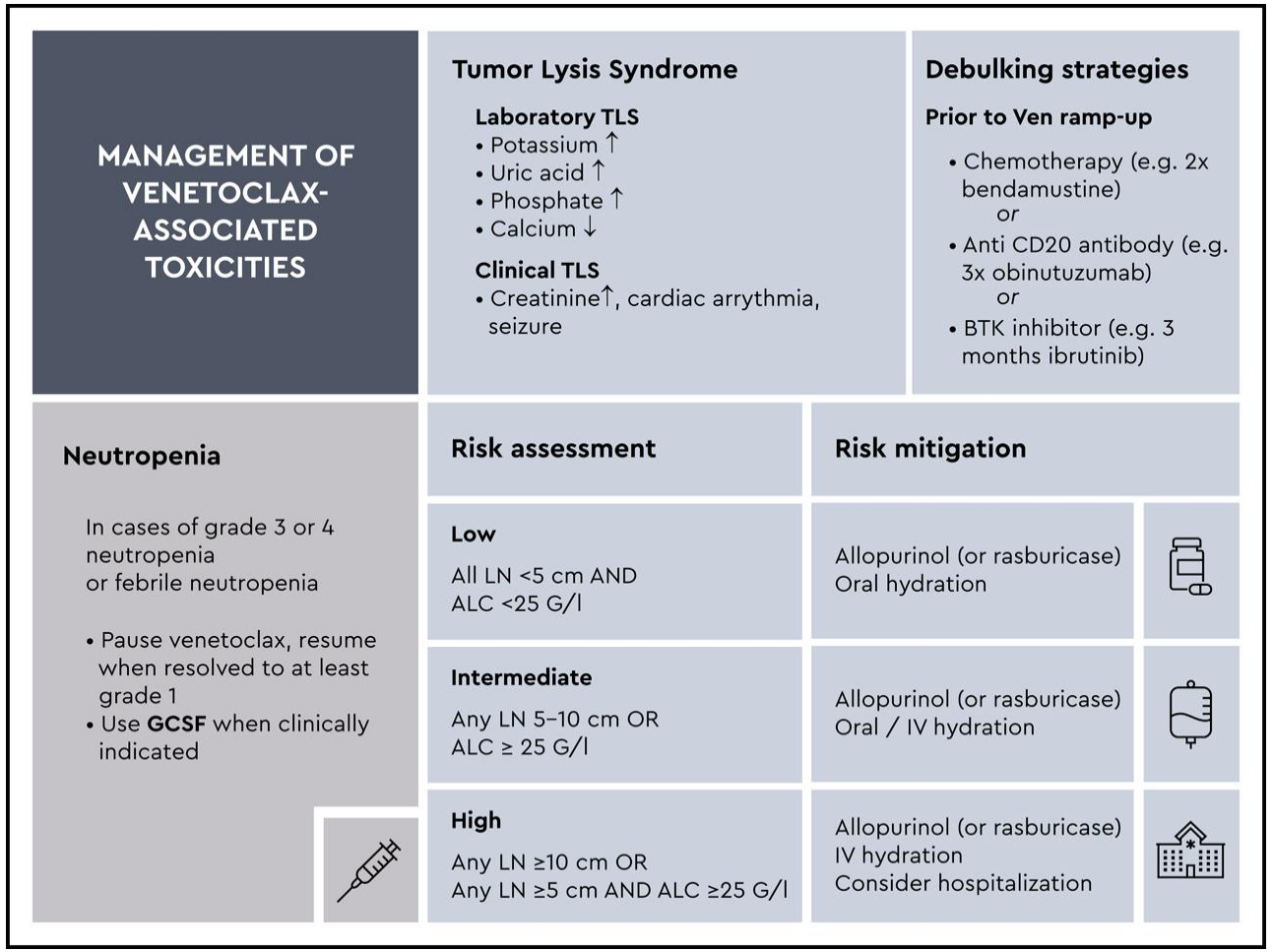
Treatment Decision

- Family present for discussion
- Disease-related factors
  - High-risk features with 17p deletion
  - Rapid progression within 6 months goal of diagnosis
  - Airway concerns
  - Coughing, symptomatic
- Patient specific factors
  - Healthy prior to diagnosis
  - Wants to be cured

- Shared decision with discussion
  - Since goal is to be cured, moved forward with plans for transplant after remission achieved
  - Referred for consultation with blood and marrow transplant
  - Began obinutuzumab and venetoclax
  - ClonoSEQ ordered for following minimal residual disease

Assess Risk for Tumor Lysis Syndrome

- CT scans to determine risk for tumor lysis syndrome
  - Size of lymph nodes
- CBC with differential
  - Absolute lymphocyte count
- Assess blood chemistry
  - Potassium
  - Uric acid
  - Phosphorus
  - Calcium
  - Creatinine



Kirsten Fischer, Othman Al-Sawaf, Michael Hallek; Hematology Am Soc Hematol Educ Program 2020; 2020 (1): 357–362. doi:

Venetoclax + Obinutuzumab

- Cycle 1, Day 1
  - Start with obinutuzumab IV for debulking (risk mitigation strategy for tumor lysis syndrome) 100 mg
- Cycle 1, Day 2
  - Obinutuzumab 900 mg IV
- Cycle 1, Day 8
  - Obinutuzumab 1000 mg IV
- Cycle 1, Day 15
  - Obinutuzumab 1000 mg IV

Venetoclax + Obinutuzumab (cont'd)

- Cycle 1, Day 22
  - Begin venetoclax ramp-up 20 mg daily for 1 week
- Cycle 2, Day 1
  - Obinutuzumab 1000 mg IV
  - Venetoclax 50 mg daily for 1 week
- Cycle 2, Day 8
  - Venetoclax 100 mg daily
- Cycle 2, Day 15
  - Venetoclax 200 mg daily
- Cycle 2, Day 22
  - Venetoclax 400 mg daily until the last day of cycle 12
- Cycle 3 D1 every 28 days through D6, D1 obinutuzumab 1000 mg IV daily

Why the Slow Ramp-up?

- With the 5-week dose ramp-up and tumor lysis prophylaxis and monitoring, rate of TLS was 2%
- With a 2- to 3-week ramp-up and higher starting dose, the TLS rate was 13% and included deaths and renal failure

Slow and steady is the key to success to minimizing TLS in patients with CLL!

Back to Our Patient

- After 6 months, no measurable disease
- Proceeded to matched unrelated donor stem cell transplant
- Remains in remission with excellent quality of life and no evidence of CLL
- Just gave birth to daughter from eggs harvested prior to starting treatment (almost unbelievable!)

Case 3: Achieving a Complete Response After Multiple Lines of Treatment

At Diagnosis

- 62-year-old presented with upper respiratory tract infection
- Routine labs
  - WBC of 20,000 x 10^3/µL
  - Lymphocytosis
  - Normal hemoglobin
  - Normal platelets
- Splenomegaly

Prognostic Indicators

- Flow cytometry cytologically and phenotypically consistent with CLL
- FISH
  - 5.3% of cells positive for deletion 13q14.3
  - 71.0% positive for a partial or complete deletion of chromosome 11q22.3 (ATM)
  - No abnormalities of chromosomes 17p13.1 (p53) or chromosome 12
- 91% of lymphocytes neoplastic B cells
- Cells expressed CD19 and CD20, co-expressing CD23 and weak CD5
- Rai stage 1

Question

What measures are recommended for mitigating the risk of tumor lysis syndrome (TLS) in patients with CLL who are initiating treatment with venetoclax?

a. Pre-initiation scans to identify patients at high risk for TLS
b. Frequent monitoring of blood chemistry
c. Administration of allopurinol
d. All of the above

When to Treat?

Observation for Years

- Anxiety wondering which visit will be “the time” to start treatment
- Ongoing discussions regarding indications for treatment
- Counseling for anxiety (for patient) and patience (for APP)

“The Time” to Start Treatment

- WBC 240,000, hemoglobin (Hb) 12.6 g/dL, platelets 300,000…*not quite yet*. Minimal symptoms.
- WBC 428,000, hemoglobin 6.7 g/dL, platelets 238,000; just 3 days prior, the patient’s Hb level was 8.6 g/dL, LDH 1321 U/L, Coombs positive (4+), acute hemolytic anemia
- Initial treatment high-dose steroids, transfusion, and then fludarabine and rituximab for 6 cycles with CR achieved

Relapses and Remissions

- Treatments
  - Bendamustine and rituximab
  - Pentostatin, cyclophosphamide, and rituximab
- Extended 2-year hospitalization for infection and developed extensive bulky lymphadenopathy in the abdominal area, retroperitoneal, and pelvis
- Expressed a desire to improve quality of life and minimize hospitalizations

Quality of Life With Single-Agent Venetoclax

- Venice II open-label, single-arm, phase 3b study
- Assessed improvements in health-related quality of life (HRQOL) in patients with relapsed/refractory CLL receiving single-agent venetoclax
- Quality of life measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30)
- Trial met the primary HRQOL endpoint at week 48 with a mean improvement in EORTC QLQ-C30 global health status of + 9.3 points (p = .004)

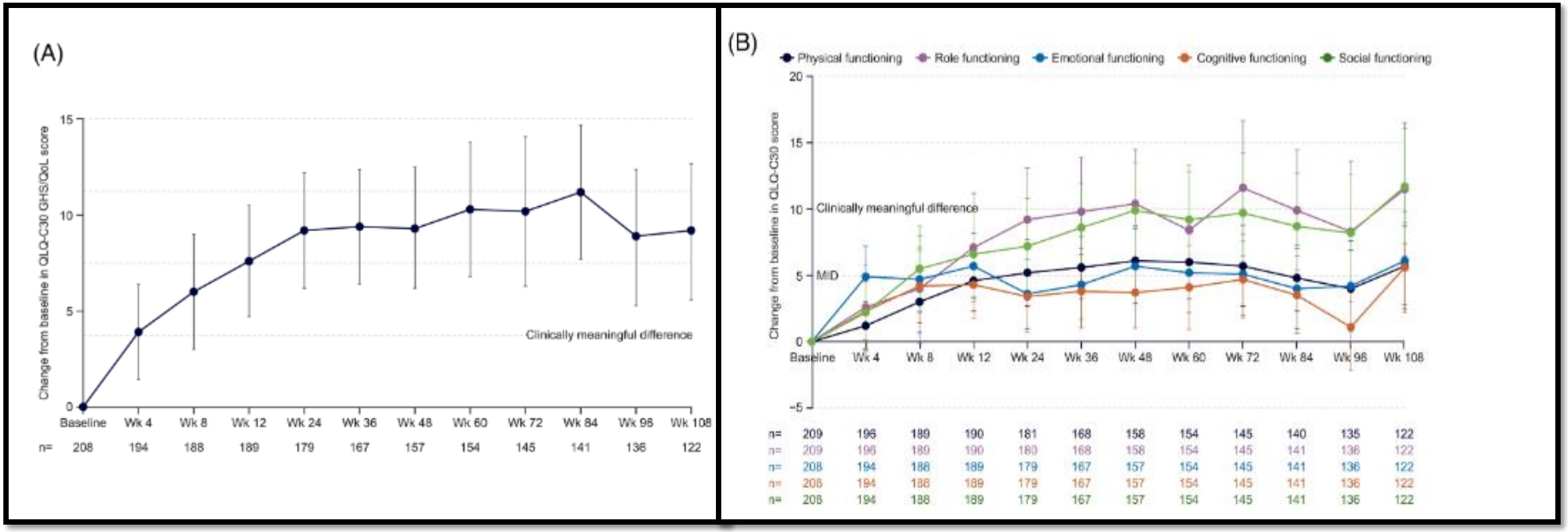
Cochrane T, Enrico A, Gomez-Almaguer D, et al. Leuk Lymphoma. 2023. DOI: 10.1080/10428194.2023.2247511

Quality of Life With Single-Agent Venetoclax

- Clinically meaningful improvements in:
  - Role functioning
  - Fatigue
  - Insomnia
- This study provides encouragement for anticipating improvement in quality of life, identified as an important goal for the patient, to start single-agent venetoclax

Cochrane T, Enrico A, Gomez-Almaguer D, et al. Leuk Lymphoma. 2023. DOI: 10.1080/10428194.2023.2247511

Quality-of-Life Improvements



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Single-Agent Venetoclax

- Starter ramp-up kit for 5 weeks with labs and visits to monitor for tumor lysis syndrome
- Slow and steady to prevent tumor lysis syndrome
- Continue at 400 mg daily until disease progression or unacceptable toxicity

Back to Our Patient

- Began venetoclax with the 5-week ramp-up starter pack
- No evidence of tumor lysis syndrome despite bulky disease
- Achieved a complete response
- Remains in remission 9 years later
- Able go camping and hiking with family, and that's what means the most with treatment: spending time with family, not feeling ill

Case 3: Polling Question

In your practice, what percentage of patients present with Rai Stage 0?

a. Up to 25% **29%**

b. 25% to 50% **14%**

c. 50% to 75% **29%**

d. I don't know **29%**

Q & A

Please type your questions for Sara M. Tinsley-Vance into the **question box**.

Thank You