Oncology Grand Rounds

New Agents and Strategies in Chronic Lymphocytic Leukemia

Thursday, June 4, 2020

5:00 PM – 6:30 PM ET

Faculty

Amy Goodrich, CRNP
Brad S Kahl, MD
Robin Klebig, APRN, CNP, AOCNP
Jeff Sharman, MD

Moderator

Neil Love, MD

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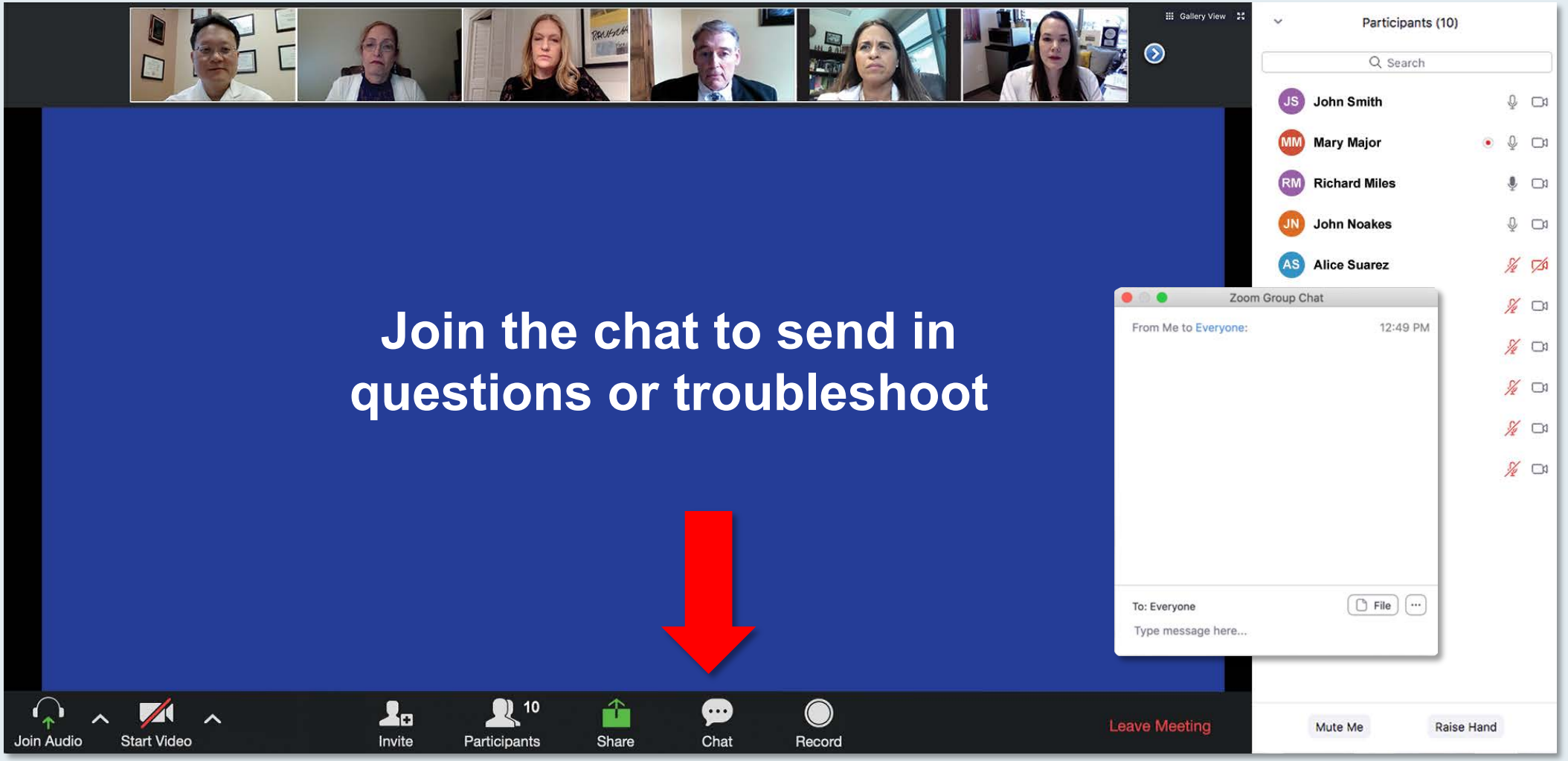
Familiarizing yourself with the Zoom interface

How to participate in the chat



RTP Live Webinar Nursing Series

Monday	Tuesday	Wednesday	Thursday	Friday
25	26 **Breast Ca** **5:00 PM**	27	28 **GI Ca** **5:00 PM**	29
Jun 1	2 **Lymphoma** **5:00 PM**	3	4 **CLL** **5:00 PM**	5
8	9 **GYN** **5:00 PM**	10	11 **Metastatic Lung Ca** **5:00 PM**	12
15	16 **Locally Advanced Lung Ca** **5:00 PM**	17	18 **Bladder Ca** **5:00 PM**	19
22	23 **CAR-T** **5:00 PM**	24	25 **PARP** **5:00 PM**	26
29	30 **Prostate Ca** **5:00 PM**	Jul 1 9 AM	2	3
6	7	8	9	10

Oncology Grand Rounds

New Agents and Strategies in Gynecologic Cancers

Tuesday, June 9, 2020

5:00 PM – 6:30 PM ET

Faculty

Paula J Anastasia, RN, MN, AOCN
Jennifer Filipi, MSN, FNP-C
David M O'Malley, MD
Shannon N Westin, MD, MPH

Moderator

Neil Love, MD

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About the Enduring Program

- This webinar is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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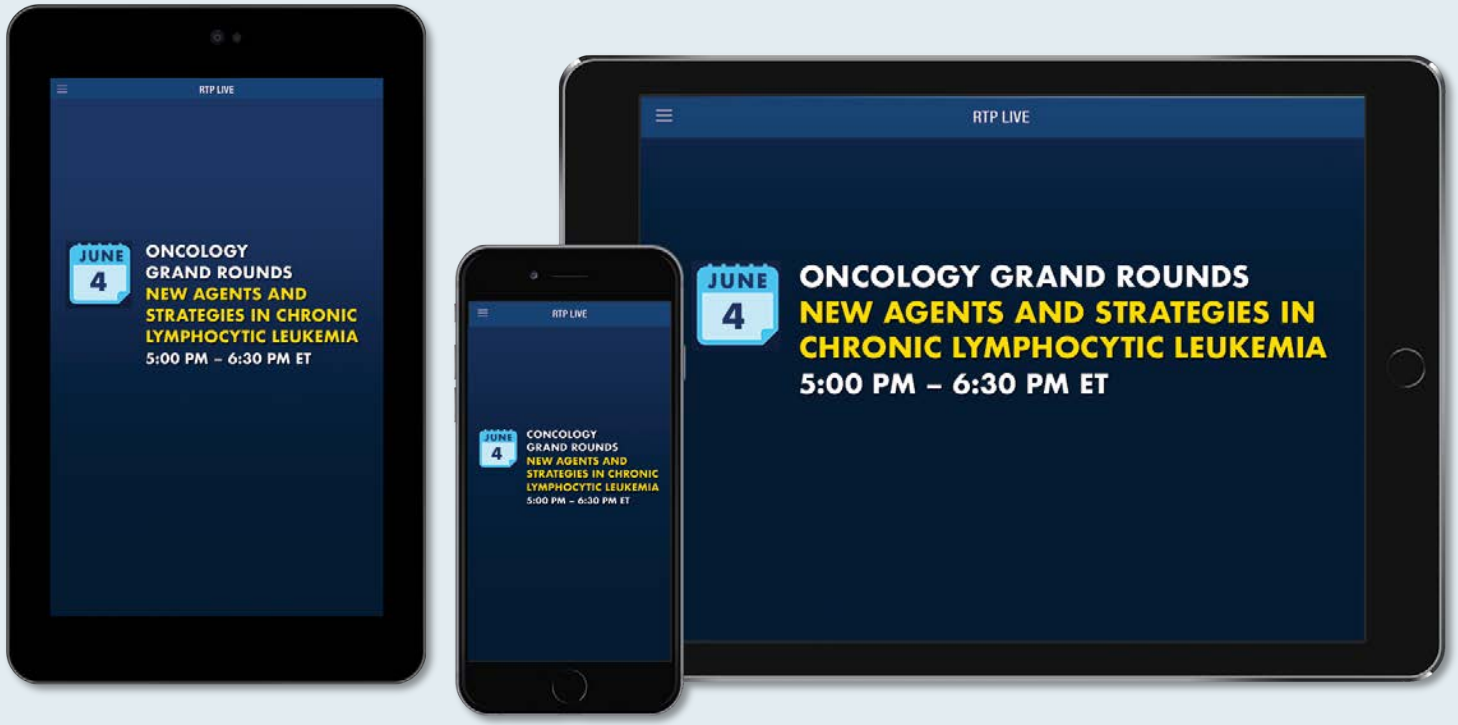


Agenda

Module 1: Biology, Clinical Presentation and Workup

- Case Presentation: Ms Klebig — 69-year-old man

Module 2: New Agents/Regimens

- Case Presentation: Ms Goodrich — 58-year-old man

Module 3: Key Clinical Trials

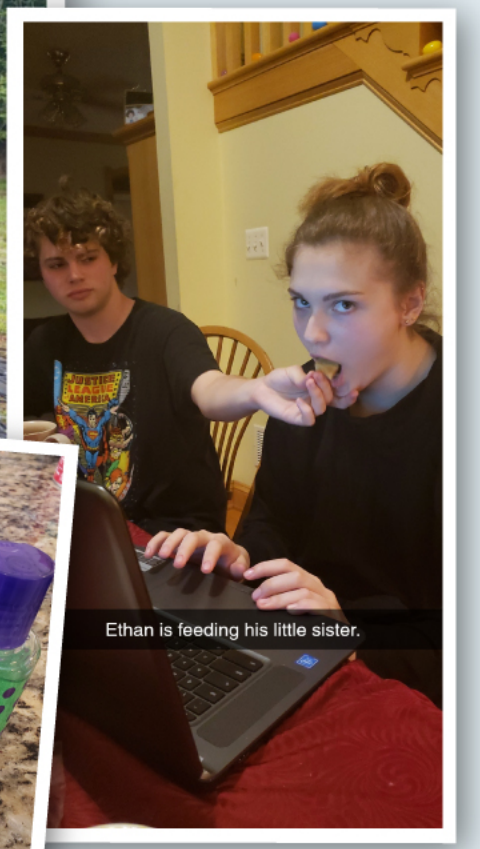
- Case Presentation: Ms Klebig — 76-year-old woman

Module 4: First-Line Treatment Decision-Making

- Case Presentation: Ms Goodrich — 84-year-old woman

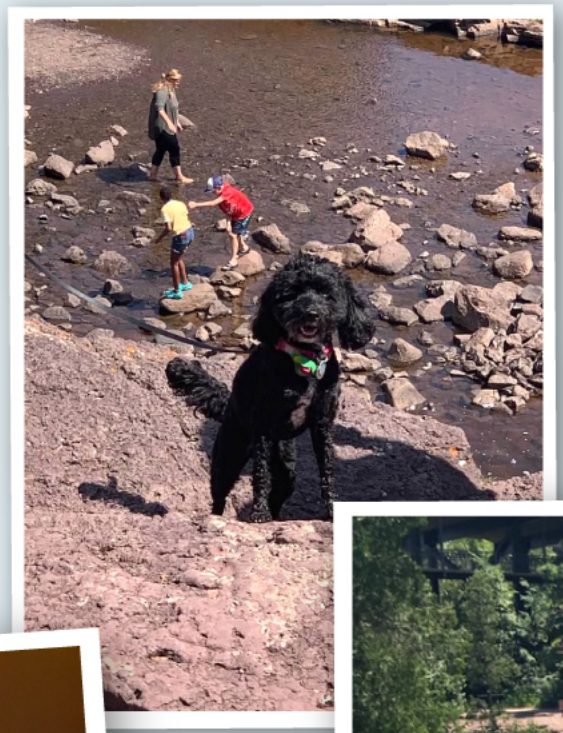
Module 5: Use of Oncologic Agents to Treat COVID-19

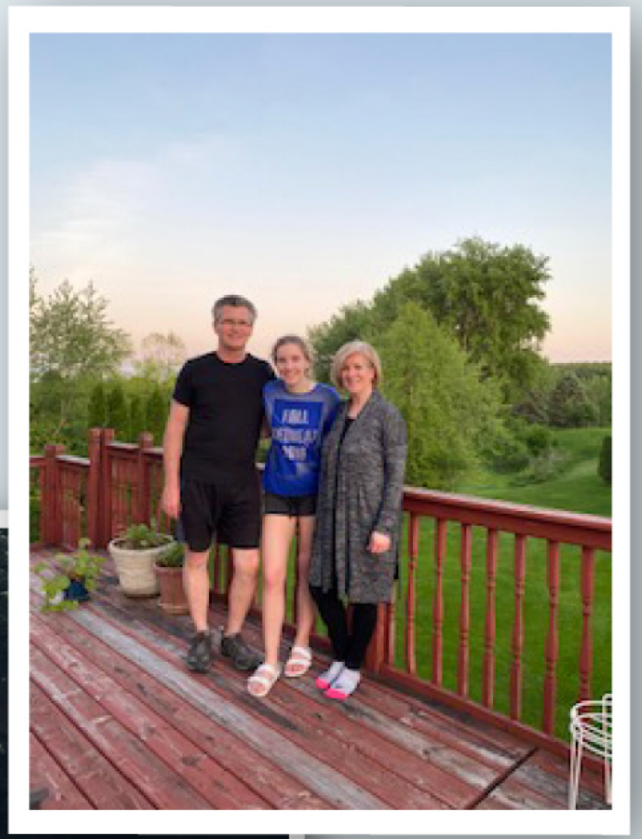
Amy Goodrich, CRNP
The Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins Medicine
Baltimore, Maryland



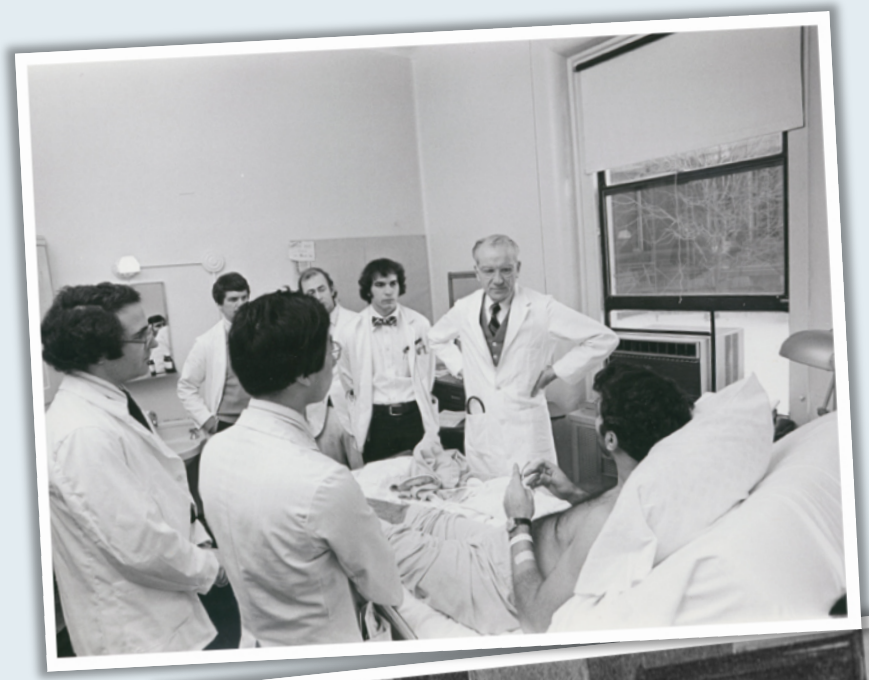
Brad S Kahl, MD
Siteman Cancer Center
St Louis, Missouri

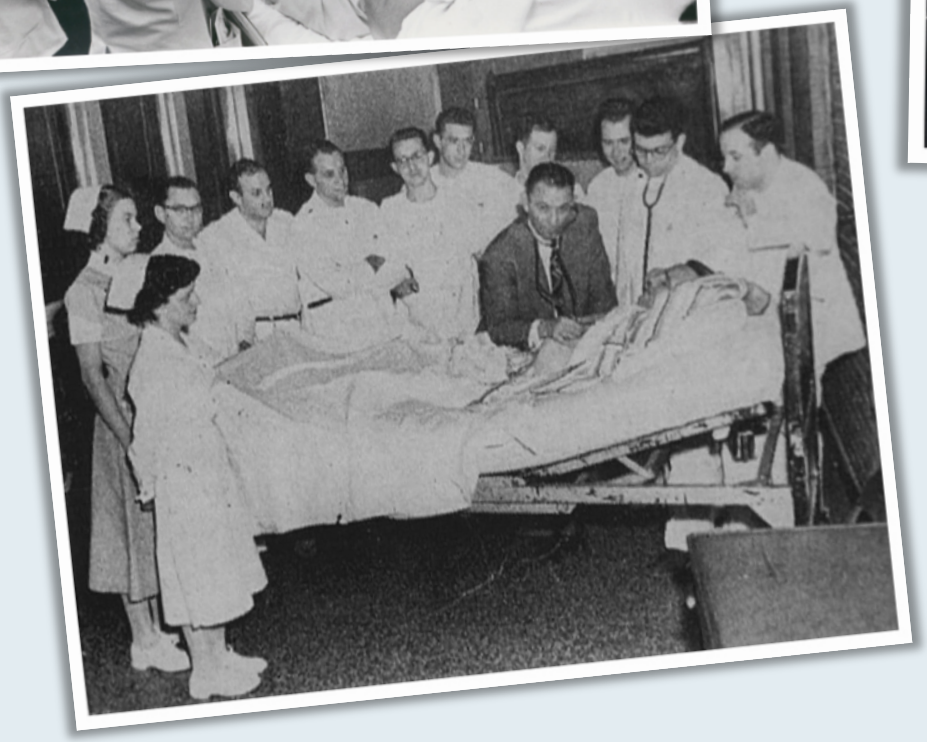
Robin Klebig, APRN, CNP, AOCNP
Mayo Clinic
Rochester, Minnesota





Jeff Sharman, MD
Willamette Valley Cancer Institute
and Research Center
Eugene, Oregon

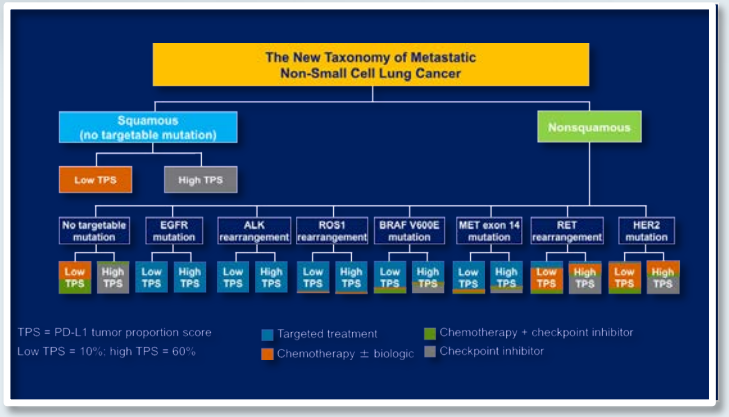


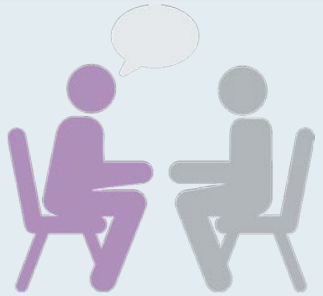



The Birmingham News

Oncology Grand Rounds: Format

- **Personalized oncology strategy**
  - New markers and agents
- **Patient counseling and education as a component of that strategy**
  - Symptom management
- **Discussion of actual cases from nurse faculty**
  - The bond that heals; trust and integrity
  - Supporting family and loved ones





The Core Oncology Triad
Developing an Individualized Oncology Strategy

Day in the Life: NURSE 8

- 72 M, Lung cancer, Pemetrexed, carboplatin, Socioeconomic status
- 31 F, Benign hematology, transfusion exchange, Depression
- 72 F, AML and HCC, Pembrolizumab, Acceptance of disease
- 73 F, Mantle Cell Lymphoma, Study drug, Acceptance of disease
- 30 F, Breast cancer, AC, Young age
- 61 F, Colorectal cancer, completed FOLFOX, Language barrier
- 63 F, Multiple myeloma, Daratumumab, Language barrier
- 56 F, Head and neck cancer, Pembrolizumab, Socioeconomic status
- 79 F, Multiple myeloma, Surveillance, Culture
- 58 M, Multiple myeloma, Zoledronic acid, poor attitude
- 85 F, Ovarian cancer, will receive study drug, had multiple lines of therapy

Day in the Life: NURSE 8

- 80 F, AML and Lung cancer, Pembrolizumab, venetoclax, azacitidine, family support
- 70 F, Lung cancer, Pemetrexed/carbo/pembrolizumab, Acceptance of disease
- 37 F, Benign hematology, Opioid addiction
- 26 F, Hodgkin lymphoma, Nivolumab, Family support
- 63 M, Colorectal cancer, Surveillance, Socioeconomic status
- 91 M, Myeloproliferative neoplasm, Surveillance, ETOH use
- 31 M, Testicular cancer, Surveillance, Anxiety/depression
- 67 F, Multiple myeloma, Bortezomib, Positive outlook
- 50 F, Breast cancer, AC, Family support

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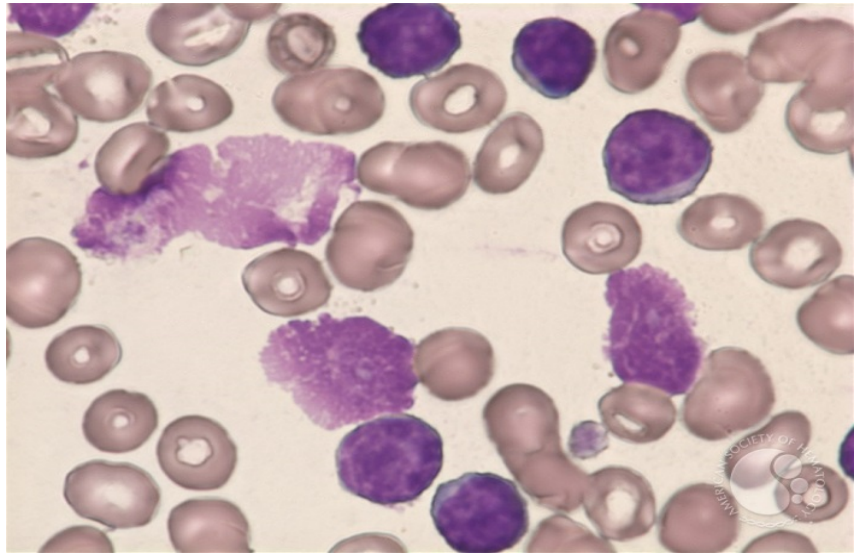
Module 1: Biology, Clinical Presentation and Workup

Chronic Lymphocytic Leukemia

- US Epidemiology:
  - Incidence: ~19,000/year
  - US Prevalence: ~130,000 cases
- Median age at diagnosis: 71 years
- Male to female ratio: 2 to 1
- Diagnosis usually made from blood
  - Less common: lymph node, marrow
- Immunophenotype
  - sIg(dim) (light chain restricted)
  - CD5+
  - CD20 (dim)
  - CD23+(bright)



Courtesy of Brad S Kahl, MD

Potential clinical manifestions of CLL

1. None
2. Marrow failure syndrome
    1. Anemia, Thrombocytopenia
3. Autoimmune cytopenias
    1. Anemia, thrombocytopenia, neutropenia
4. Immunodeficiency (low Ig levels)
    1. Recurrent infections
5. Symptoms
    1. Fatigue, night sweats, weight loss, fevers, pain

Courtesy of Brad S Kahl, MD

Summary: diagnosis & initial work up

- Flow cytometry
- Laboratory testing
  - CBC, CMP
  - LDH
  - B2M
  - FISH (CLL Panel)
  - IGHV mutation analysis
  - Consider TP53 mutation
- Imaging
  - Not needed for most patients
  - Worth considering CT scan if starting treatment or if significant adenopathy or splenomegaly detected on exam
  - Need if starting venetoclax
  - Obtain PET scan if worried about Richter's Transformation
- Bone marrow
  - Not needed at diagnosis but worth considering if starting treatment

Courtesy of Brad S Kahl, MD

Patients with CLL and which of the following prognostic factors generally do not respond well to chemoimmunotherapy?

a. Del(17p)

b. TP53 mutation

c. IGHV mutation

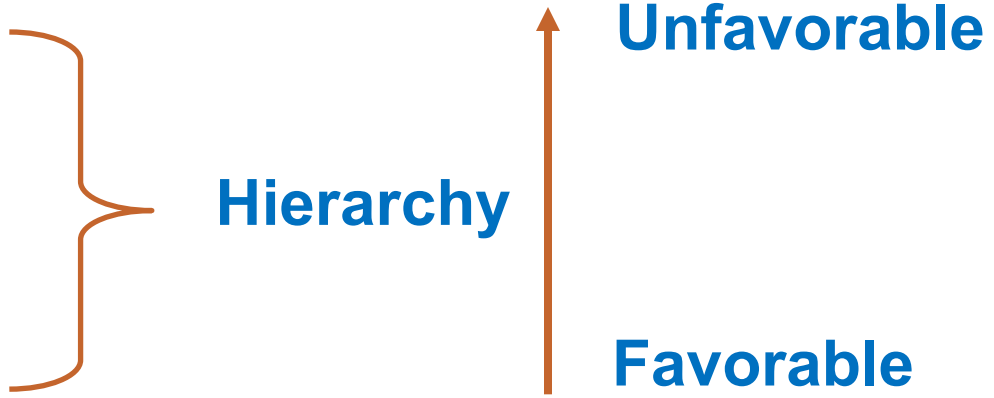
d. All of the above

e. Only a and b

f. I don’t know

(Brief) Summary of Genomic/Molecular Prognostic Factors

- **FISH defects**
  - 17p deletion
  - 11q deletion
  - 12q trisomy
  - Normal
  - 13q deletions



- **Immunoglobulin heavy chain variable region *(IGHV)***
  - Mutated: better prognosis
  - Unmutated: worse prognosis

- **CD38 status (≥ 30% = higher risk)**
- **ZAP-70 status (≥ 20% = higher risk)**

Often included with flow but *IGHV* more important and less variable

Courtesy of Brad S Kahl, MD

CLL special consideration

- High frequency of AI complications
  - ITP, AIHA, neutropenia
- High frequency of infections
  - Check Ig levels
  - Consider IVIg replacement therapy if recurrent infections and IgG < 300
- High rate of skin cancer
  - Low threshold to send to Dermatology

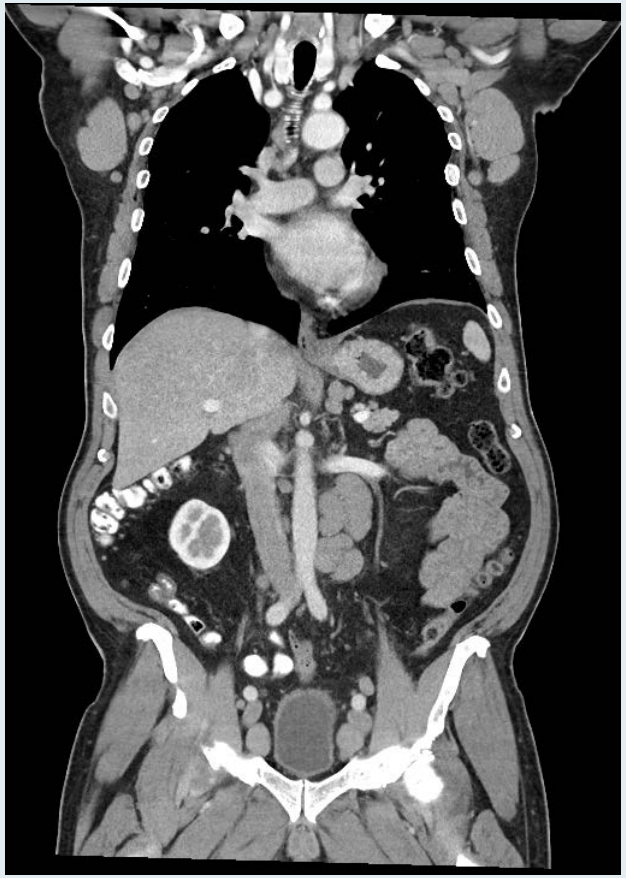
Courtesy of Brad S Kahl, MD

69-year-old man with a PMH of DJD, anxiety and BPH (from the practice of Ms Klebig)

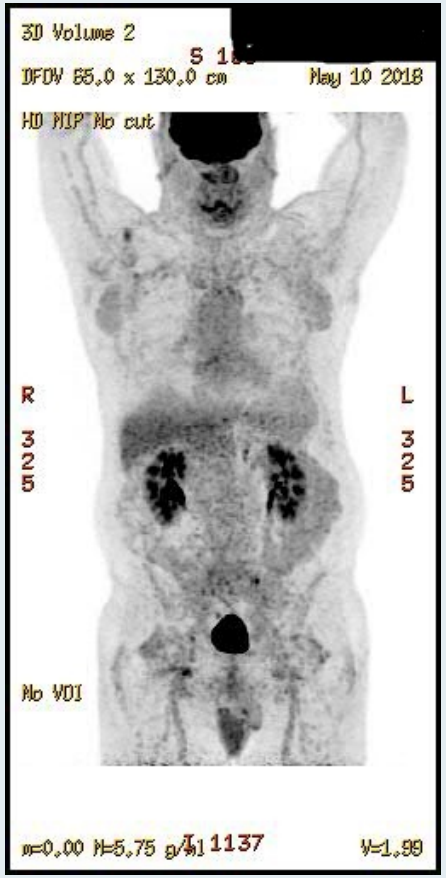
- 5/2018: Worsening chronic low back pain, no B-symptoms, diffuse adenopathy
  - Left inguinal LN biopsy: SLL/CLL
  - Hypercellular marrow (70%) with 70% involvement by CLL
  - RAI stage I, CLL-IPI: 4 (high risk), 13q deletion, TP53: Negative, IGH-V unmutated, CD49d: Positive
  - Hgb: 13.3, Plts: 197,000, WBC: 17,800, ANC: 4,090, ALC: 12,638, LDH: 172, B2M: 2.40
- **Observation** → 1/2019: Disease progression
- 2/2019: **Acalabrutinib/obinutuzumab** on clinical trial
  - 1/2020 Response assessment
    - Bone marrow: Normocellular marrow, no morphologic features of lymphoma involvement
    - Small CD5-positive kappa-restricted B-cell population detected on flow cytometry consistent with CLL/SLL (MRD=0.07%)
    - CT chest/abdomen/pelvis: Near to complete resolution of lymphadenopathy

69-year-old man (from the practice of Ms Klebig)
Baseline imaging at diagnosis

CT (5/3/2018)



PET (5/10/2018)

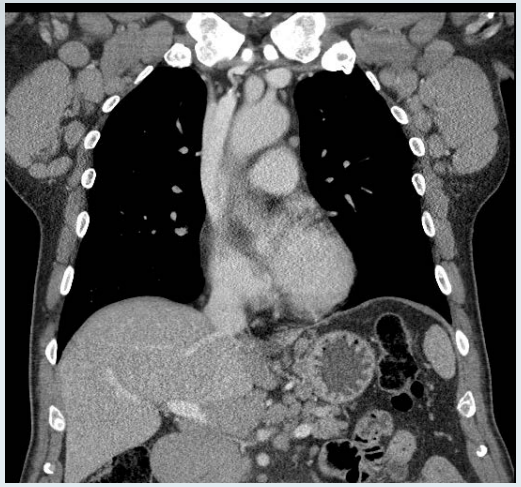


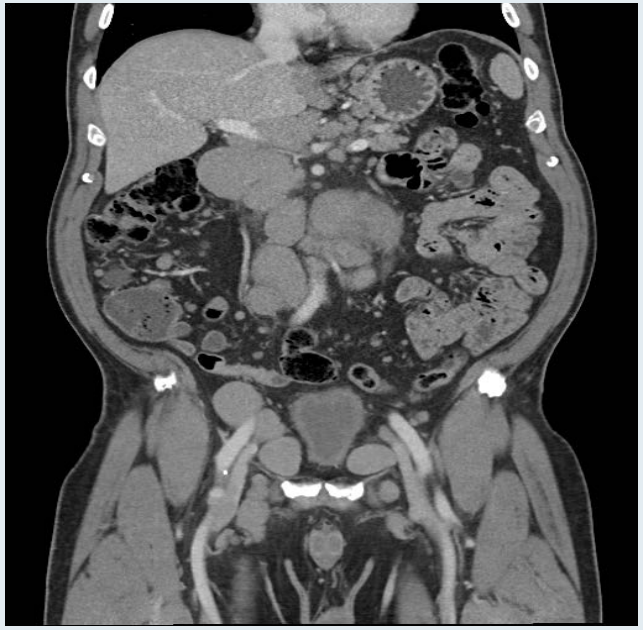
69-year-old man (from the practice of Ms Klebig)
Disease Progression (1/2019)

- CT chest/abd/pelvis:
  - Progression with bulky adenopathy

- Bone marrow:
  - CLL involving 70% of bone marrow cellularity (90% hypercellular marrow)

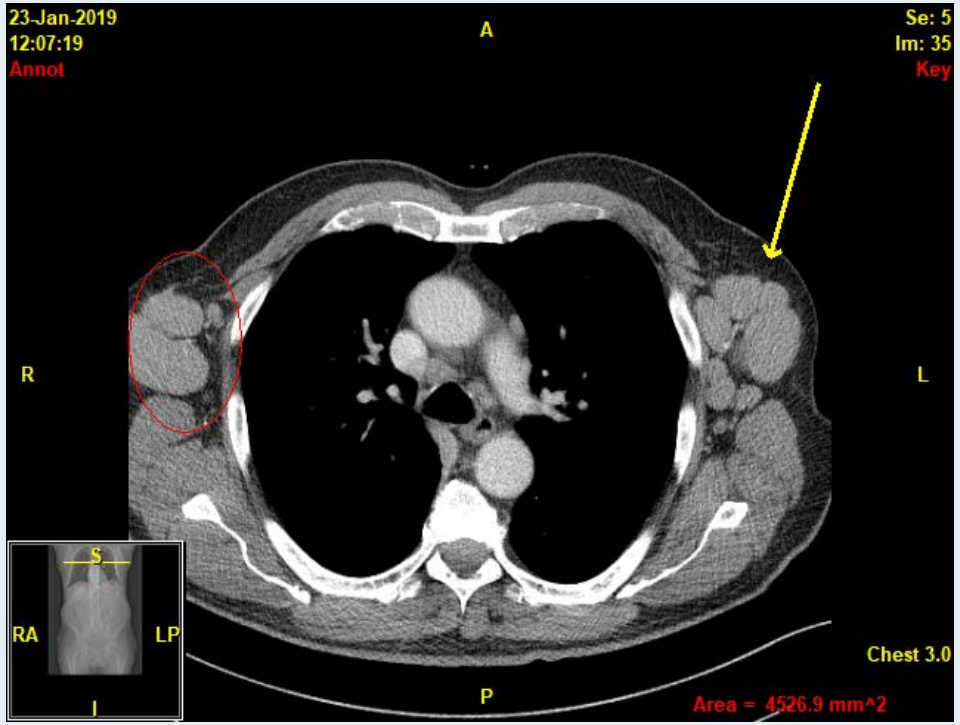
- Hgb 13.1
- Plts 198,000
- WBC 56,600
- ANC 6,790
- ALC 45,320
- Chem, LDH WNL



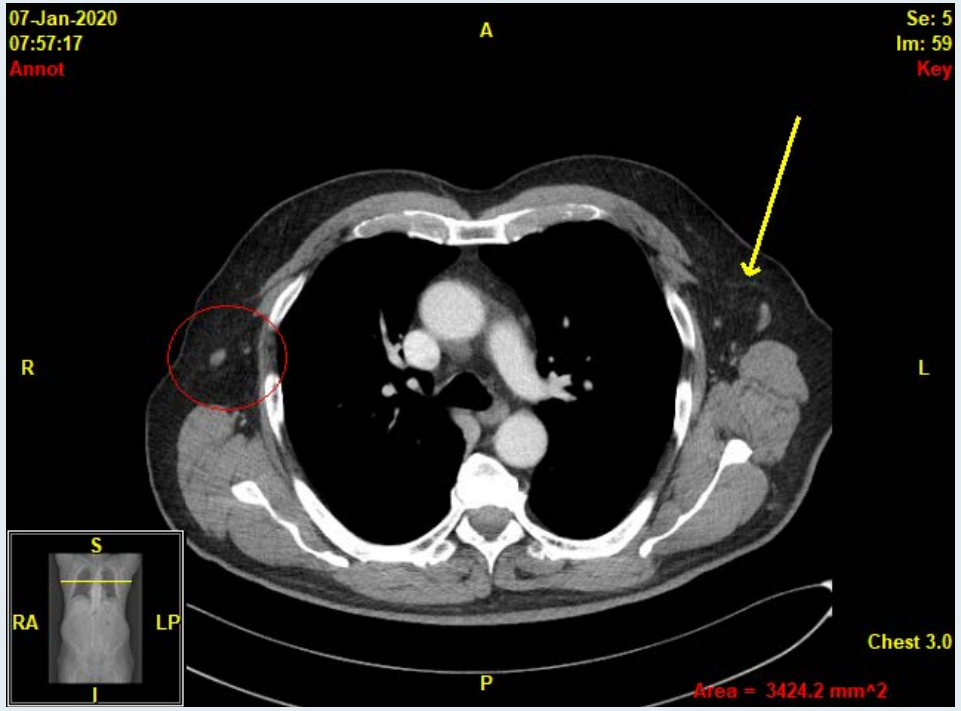


69-year-old man (from the practice of Ms Klebig)
Response to acalabrutinib/obinutuzumab therapy

Before (1/23/2019)



After (1/7/2020)



69-year-old man (from the practice of Ms Klebig)
Patient Education

Pharmacy consultation re potential drug interactions

- CYP3A4 interactions - Avoid strong inhibitors & inducers
  - Azole antifungals, -mycin antibiotics, protease inhibitors, etc
  - Moderate – consider dose adjustment
  - Avoid grapefruit/juice and Seville oranges
- Avoid antacids or calcium supplements and H2 receptor antagonists for 2 hours before and after acalabrutinib
- Avoid proton pump inhibitors due to potential decrease in drug exposure

Take with water, with or without food

Possible tumor lysis syndrome

- Allopurinol x 10 days at start of therapy

69-year-old man (from the practice of Ms Klebig)
Patient Education

Acalabrutinib is typically very well tolerated

Bleeding tendency with BTK inhibitors

- May note easy bleeding/bruising/petechiae
- Avoid NSAIDs, ASA, vitamin E, fish oil
- Hold acalabrutinib 3 days prior to and 3 days following minor procedure; 7 days for major procedure

Headache is likely

- Usually temporary, first month or so
- Typically easily managed with acetaminophen

69-year-old man (from the practice of Ms Klebig)
Patient Education

Risk for atrial fibrillation

- Watch for palpitations, lightheadedness, syncope, dyspnea, irregular rapid pulse

Risk for hypertension

Diarrhea

- Loperamide prn
- Record # stools per day at baseline

Myalgia/arthralgia

- Recommend increase activity, movement, stretching
- Treat symptomatically

Nausea

Rash

Cytopenias

- Anemia
  - Typically not transfusion requiring
- Leukopenia, neutropenia, lymphocytopenia
  - Increased infection risk
- Thrombocytopenia
- Monitor weekly during 1st month
- Consider dose adjustment if limiting

Take acalabrutinib *indefinitely*, as long as responding if no CR

I really wish I could find words meaningful enough to express how thankful I am for all that you and everybody at Mayo has done for me. I was very sick just 18 month ago and today I feel great and extremely grateful for the program you put me in.

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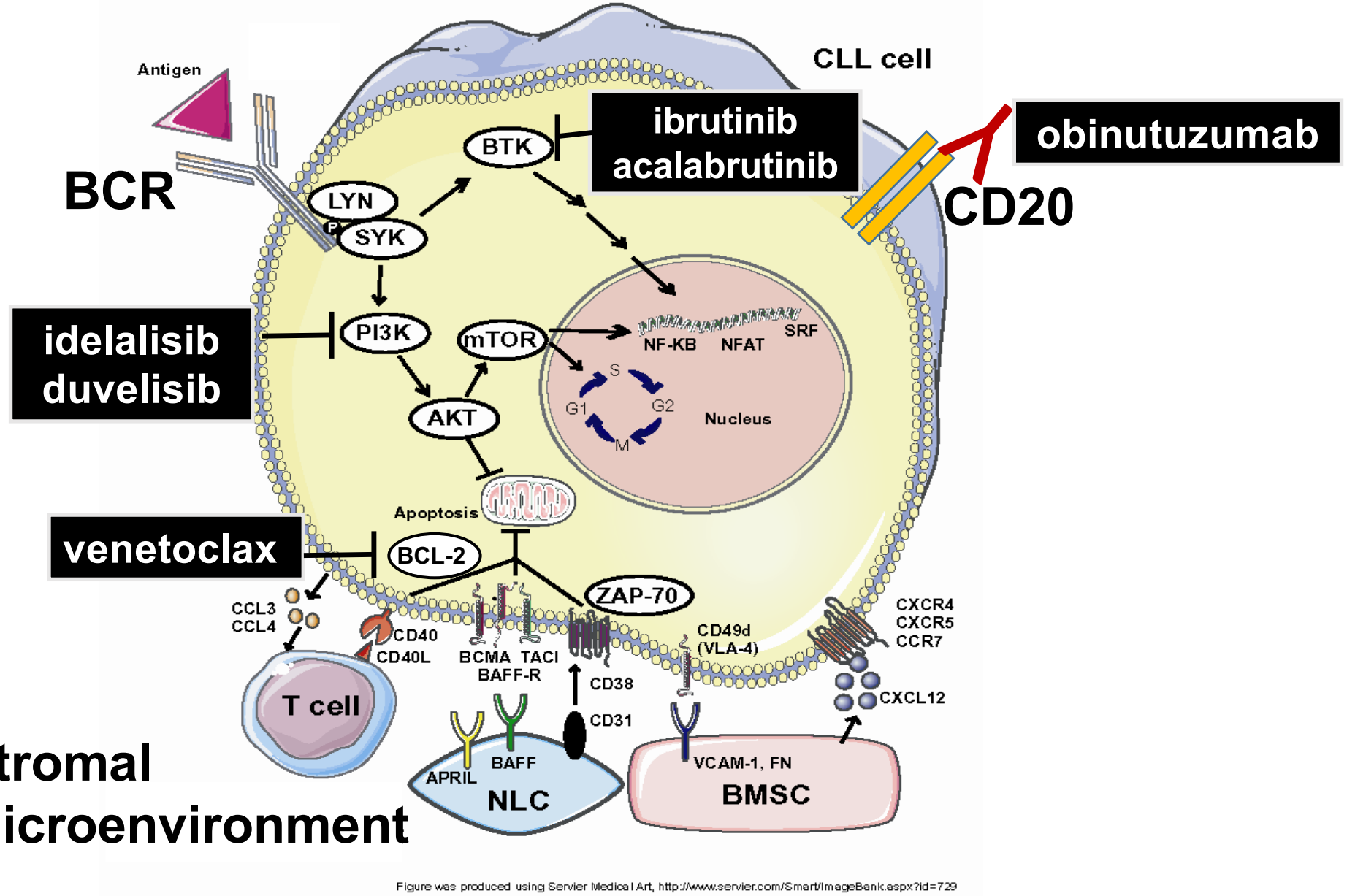
Module 2: New Agents/Regimens

Novel agents in CLL have recently revolutionized therapy



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Courtesy of Matthew S Davids, MD

Adapted from Davids and Brown, *Leuk Lymphoma*, 2012

Newer options for 1st line CLL

- BTK inhibitors
  - Ibrutinib (FDA approved 2016)
  - Acalabrutinib (FDA approved 2019)
  - Zanubrutinib (TBD)
- BCL-2 inhibitors
  - Venetoclax (FDA approved 2019)
- New anti-CD20 MoAbs
  - Obinutuzumab (FDA approved 2019)
    - Combination with Venetoclax (yes)
    - Combination with Ibrutinib or Acalabrutinib (optional)

Courtesy of Brad S Kahl, MD

Ibrutinib

- 1st generation BTK inhibitor
  - Associated with lymphocytosis
- Highly effective
  - Response rate ~ 90%, 75% still in remission at 5 years
  - 420 mg/day
  - Beat FCR and BR head to head in phase III clinical trials
    - No major difference in IgHV mutated patients
  - Remissions shallow – need for indefinite therapy
- Generally well tolerated
  - Arthralgias/myalgias tend to improve with time
  - Rash/skin issues can be nagging
  - Hypertension (can be hard to manage)
  - Atrial fibrillation 10-15%
  - Bleeding (need to hold for surgery)
    - No warfarin. Careful with other agents.

Courtesy of Brad S Kahl, MD

The use of anticoagulant therapy is an absolute contraindication to the use of ibrutinib in patients with CLL.

a. Agree

b. Disagree

c. I don’t know

Ibrutinib should be temporarily discontinued in patients scheduled to undergo surgical procedures.

a. Agree

b. Disagree

c. I don’t know

Acalabrutinib

- 2nd Generation BTK inhibitor
  - More selective kinase inhibitor = less AE's
- Highly effective
  - Activity appears comparable to ibrutinib
  - No 5 year follow up at this point
- Better tolerated (my opinion)
  - Less arthralgia, myalgia, HTN, Afib, Bleeding
  - Does cause headache – caffeine helps
- Other issues
  - 100 mg po BID
  - Can't be on proton pump inhibitor
  - Should take on empty stomach

Courtesy of Brad S Kahl, MD

Venetoclax

- BCL-2 inhibitor
  - No lymphocytosis
- Highly effective
  - Remission “deeper" than with BTKi’s
    - More complete responses. More MRD negativity.
  - Developed as a 12-month “time limited therapy” when used with obinutuzumab in 1st line
  - Responses in ~90%. No 5-year data yet.
- Generally well tolerated
  - GI side effects, cytopenias
- Tumor Lysis Syndrome

Courtesy of Brad S Kahl, MD

Which of the following disease-related factors is critical in attempting to determine an individual's risk of developing tumor lysis syndrome from treatment with venetoclax for CLL?

a. White blood cell count

b. Size of lymph nodes

c. Tumor grade

d. All of the above

e. Only a and b

f. Only a and c

g. Only b and c

h. I don't know

Which of the following patient-related factors is most important in attempting to determine an individual's risk of developing tumor lysis syndrome from treatment with venetoclax for CLL?

a. Hepatic function

b. Renal function

c. Body mass index

d. I don't know

venetoclax

- Toxicity profile different from other targeted agents: TLS risks

Figure 1. **Intrapatient dose ramp-up scheme for CLL patients initiating venetoclax**

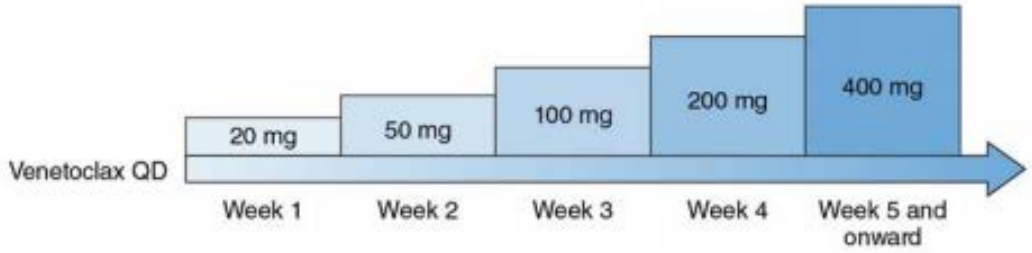


Figure 2. **Tumor lysis syndrome risk stratification, prophylaxis, and monitoring for CLL patients initiating venetoclax**

LOW RISK Nodal mass <5 cm and ALC <25,000 K/μL	**MEDIUM RISK** Nodal mass ≥5 cm and <10 cm or ALC ≥25,000 K/μL	**HIGH RISK** Nodal mass ≥10 cm or Nodal mass ≥5 cm but <10 cm and ALC ≥25,000 K/μL
Oral hydration (1.5-2L), allopurinol	Oral hydration (1.5-2L), consider IV hydration, allopurinol	Oral hydration (1.5-2L) and IV hydration (150-200 mL/hr as tolerated), allopurinol, consider rasburicase if elevated baseline uric acid
Outpatient administration	–Outpatient administration –Consider inpatient if CrCl <80 mL/min	–Inpatient administration for initial dose of 20 mg and 50 mg –Outpatient administration for subsequent dose escalations
Labs pre-dose, then 6-8 and 24 hours post-dose after initial dose of 20 mg and 50 mg	Labs pre-dose, then 6-8 and 24 hours post-dose after initial dose of 20 mg and 50 mg	**Inpatient:** Labs pre-dose, then 4, 8, 12, and 24 hours post-dose **Outpatient:** Labs pre-dose, then 6-8 and 24 hours post-dose

Courtesy of Brad S Kahl, MD

Obinutuzumab

- Anti-CD20 MoAb
  - Designed to be a new and improved rituximab
  - Better than rituximab for CLL
- Dosing: 1000 mg flat dose
  - Cycle 1: Day 1 (100mg), 2 (900mg), 8, 15
  - Cycle 2-6 Day 1
- When to use it
  - If using venetoclax 12-month time limited therapy, combine with obinutuzumab
  - If using BTKi obinutuzumab, use is optional
    - Improves outcomes marginally
    - Adds some toxicity (mostly infections)

Courtesy of Brad S Kahl, MD

Approved PI3K Inhibitors for CLL: Indication and Dosing

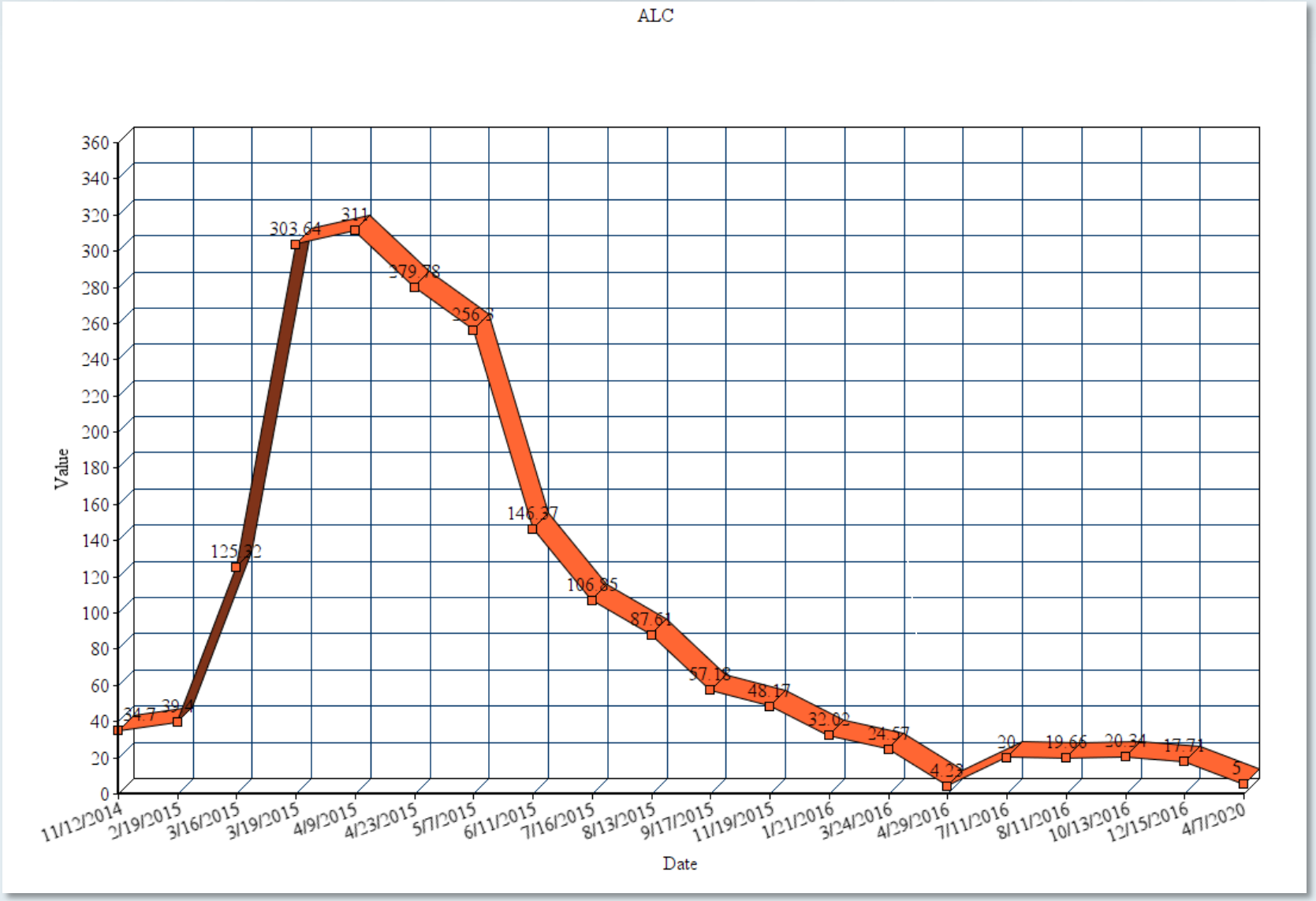
	Idelalisib[1]	Duvelisib[2]
Mechanism of action	Selective PI3Kδ inhibitor	Dual inhibitor of PI3Kδ,γ
Indication	Relapsed CLL in combination with rituximab for patients with comorbidities	R/R CLL after at least 2 prior systemic therapies
Dosing	150 mg orally, twice daily	25 mg orally, twice daily

[1] Idelalisib package insert, October 2018; [2] Duvelisib package insert, September 2018.

58-year-old man with a history of anxiety, recent depression, and 2 divorces since diagnosis (from the practice of Ms Goodrich)

- **4/2001:** Diagnosed with asymptomatic Stage IVA SLL in 4/2001 at age 39
  - Prognostic factors: 13q and 11q deletions, mutated IGHV
- **Observed until 2008** → Bulky adenopathy and lymphocytosis
- Thrice weekly rituximab (PR) → PD in 2010
- **Clinical trial: FCR + ABT-263** (BCL-2 inhibitor) x 6 (PR) → PD 7/2013
- Observed until early 2015: Bulky adenopathy, symptomatic splenomegaly (continued 13q and 11q deletions)
- **3/2015: Ibrutinib**
  - Nausea and diarrhea (ondansetron and Imodium for the first two years) → tapered off
- Summer 2016: Kidney cancer → partial nephrectomy
  - ALC rose upon holding drug, trended down over months/years
- Currently, remains on ibrutinib at full dose

58-year-old man (from the practice of Ms Goodrich)



58-year-old man (from the practice of Ms Goodrich)

Teaching points

- Common side effects
  - Nausea, diarrhea, arthralgias, fatigue, minor bleeding
  - Prescription and OTC meds to manage; lifestyle/diet changes; holding for procedures
- Uncommon side effects
  - Major bleeding
  - A-fib/flutter
- Potential for lymphocytosis
- Contact/emergency numbers
- Monitoring schedule
  - I see/touch base weekly until good symptom management
  - Frequent initial labs, we did TLS monitoring due to bulky adenopathy


AMERICAN HAULER

Agenda

Module 1: Biology, Clinical Presentation and Workup

- Case Presentation: Ms Klebig — 69-year-old man

Module 2: New Agents/Regimens

- Case Presentation: Ms Goodrich — 58-year-old man

Module 3: Key Clinical Trials

- Case Presentation: Ms Klebig — 76-year-old woman

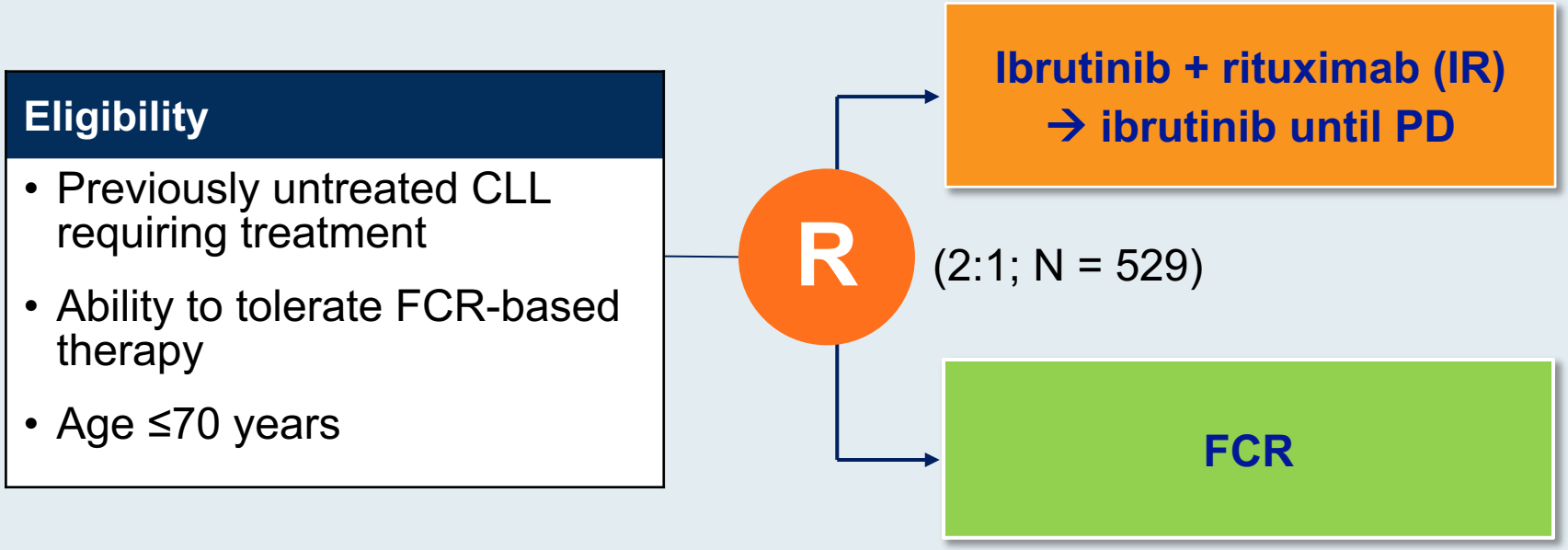
Module 4: First-Line Treatment Decision-Making

- Case Presentation: Ms Goodrich — 84-year-old woman

Module 5: Use of Oncologic Agents to Treat COVID-19

Module 3: Key Clinical Trials

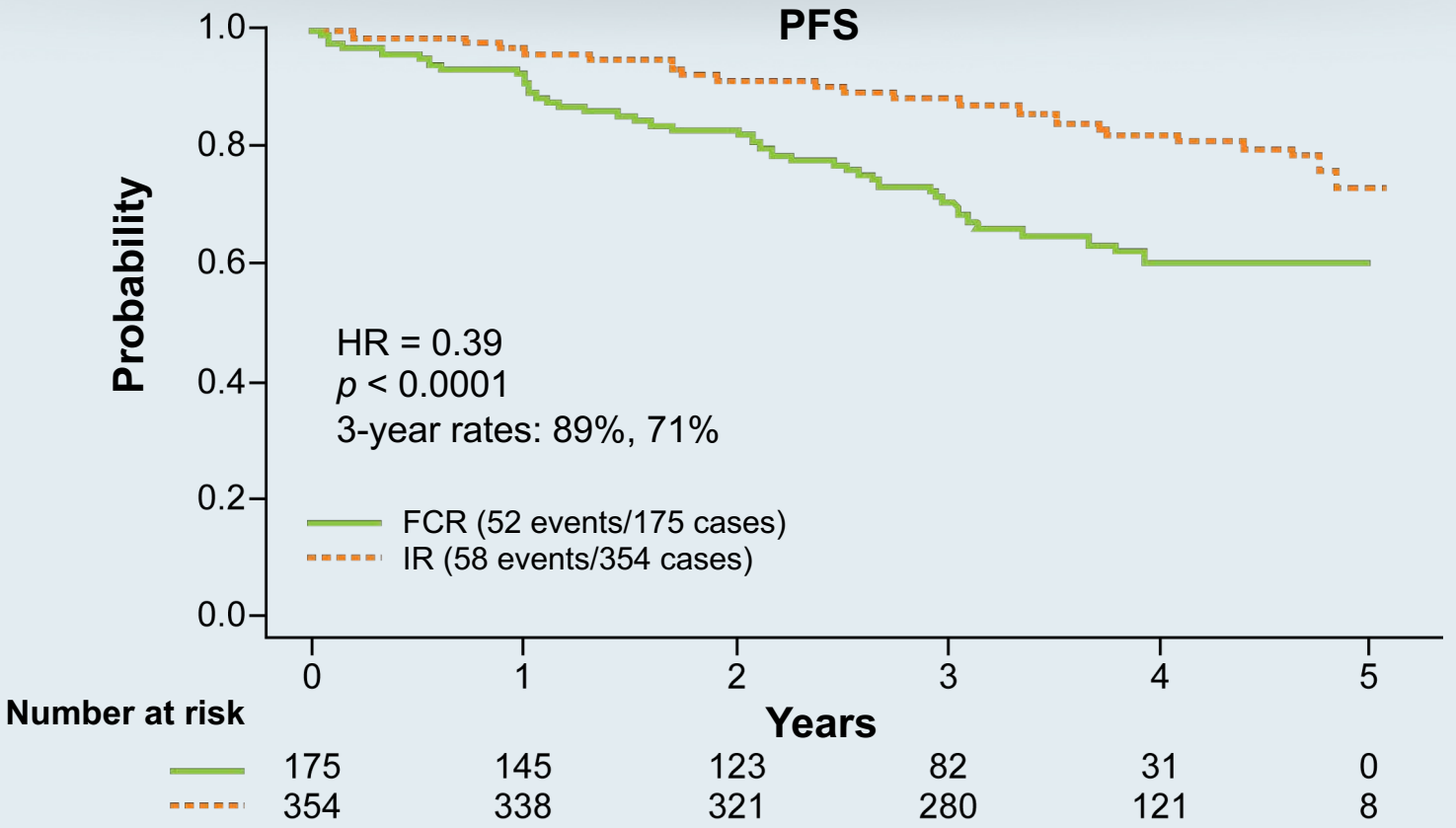
Phase III ECOG-ACRIN E1912 Study Design



Primary endpoint: PFS
Secondary endpoints: OS, ORR, Toxicity and Tolerability

ECOG-ACRIN E1912 Physician Fact Sheet, version 01/15/16;
www.clinicaltrials.gov (NCT02048813); Shanafelt TD et al. *Proc ASH* 2018;Abstract LBA-4.

ECOG-ACRIN E1912 Extended Follow-Up: Up-Front IR Compared to FCR for Younger Patients with CLL

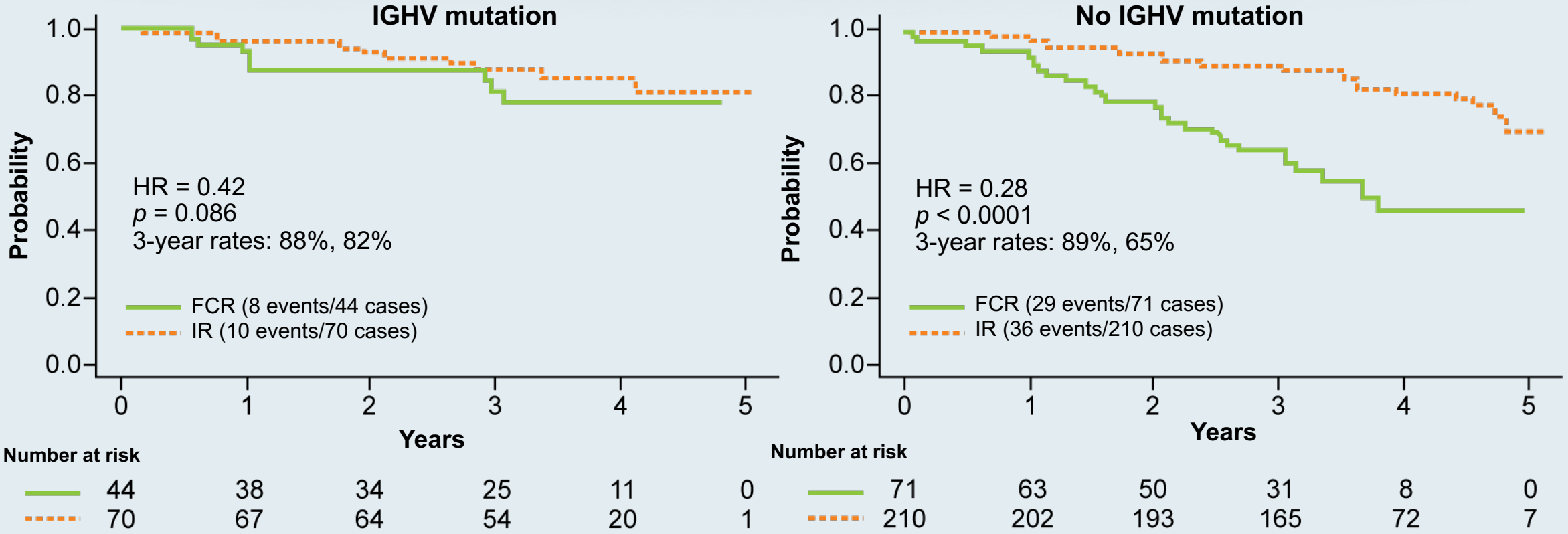


Grade ≥3 treatment-related AEs were reported in 70% of patients receiving IR and 80% of patients receiving FCR (odds ratio = 0.56; $p = 0.013$).

Among the 95 patients who discontinued ibrutinib, the most common cause was AE or complication.

Shanafelt TD et al. ASH 2019;Abstract 33.

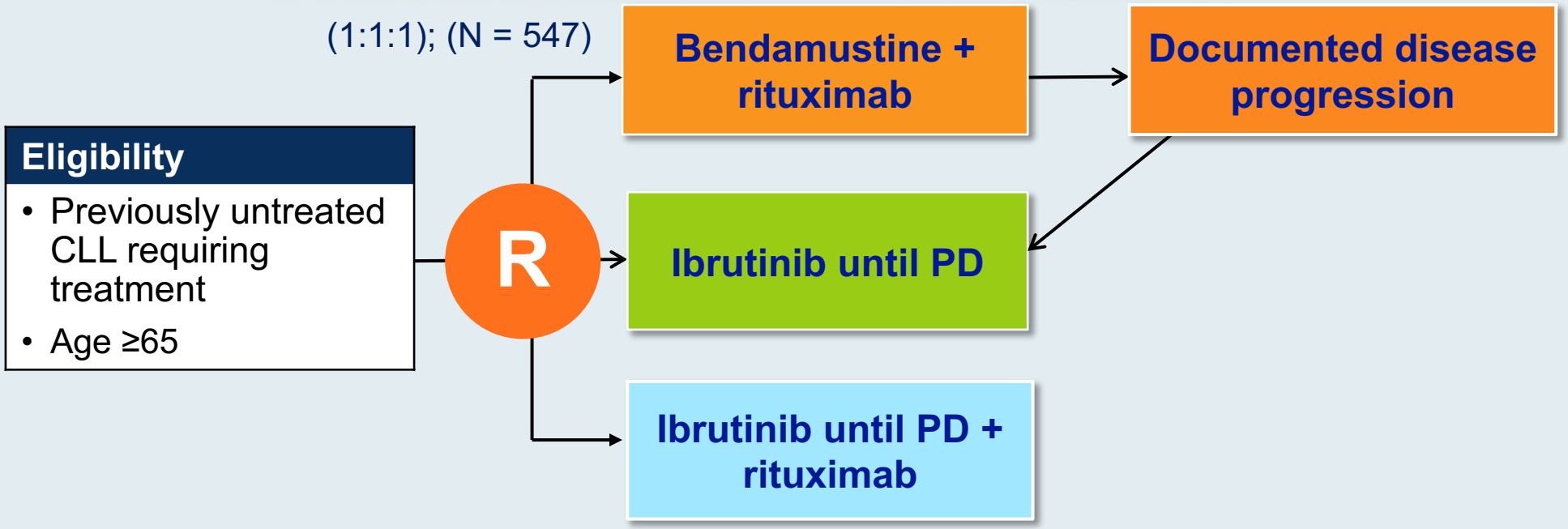
ECOG-ACRIN E1912 Extended Follow-Up: PFS by IGHV Mutation Status



On subgroup analysis by IGHV mutation status, IR was superior to FCR for CLL with no IGHV mutation (HR = 0.28; $p < 0.0001$). With current follow-up the difference between IR and FCR is not significant for CLL with IGHV mutation (HR = 0.42; $p = 0.086$).

Shanafelt TD et al. ASH 2019;Abstract 33.

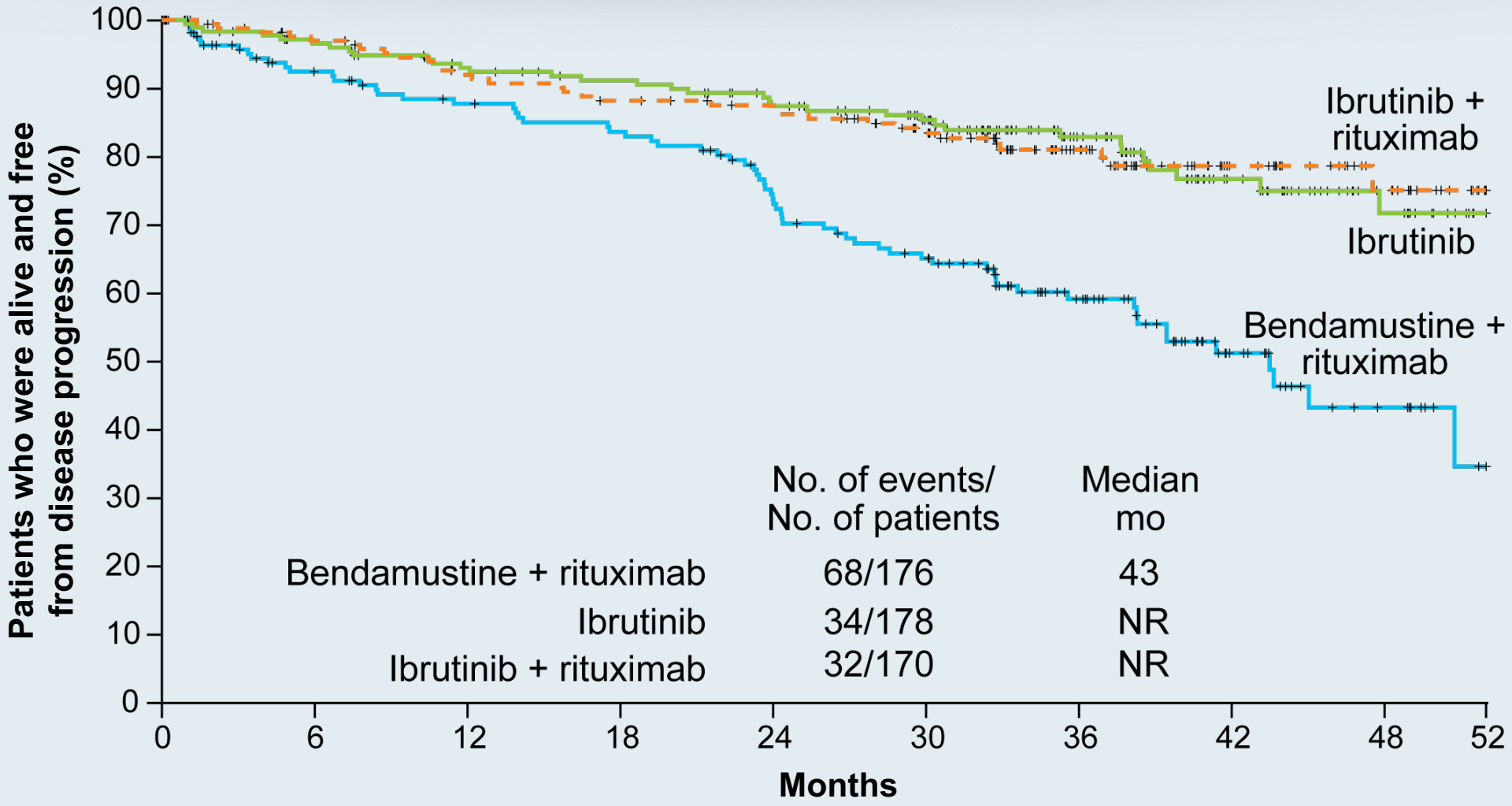
Phase III Alliance A041202 Study Design



Primary endpoint: Progression-free survival (PFS)
Secondary endpoints: OS, ORR, Impact of MRD on PFS and OS, Duration of response, Toxicity and Tolerability

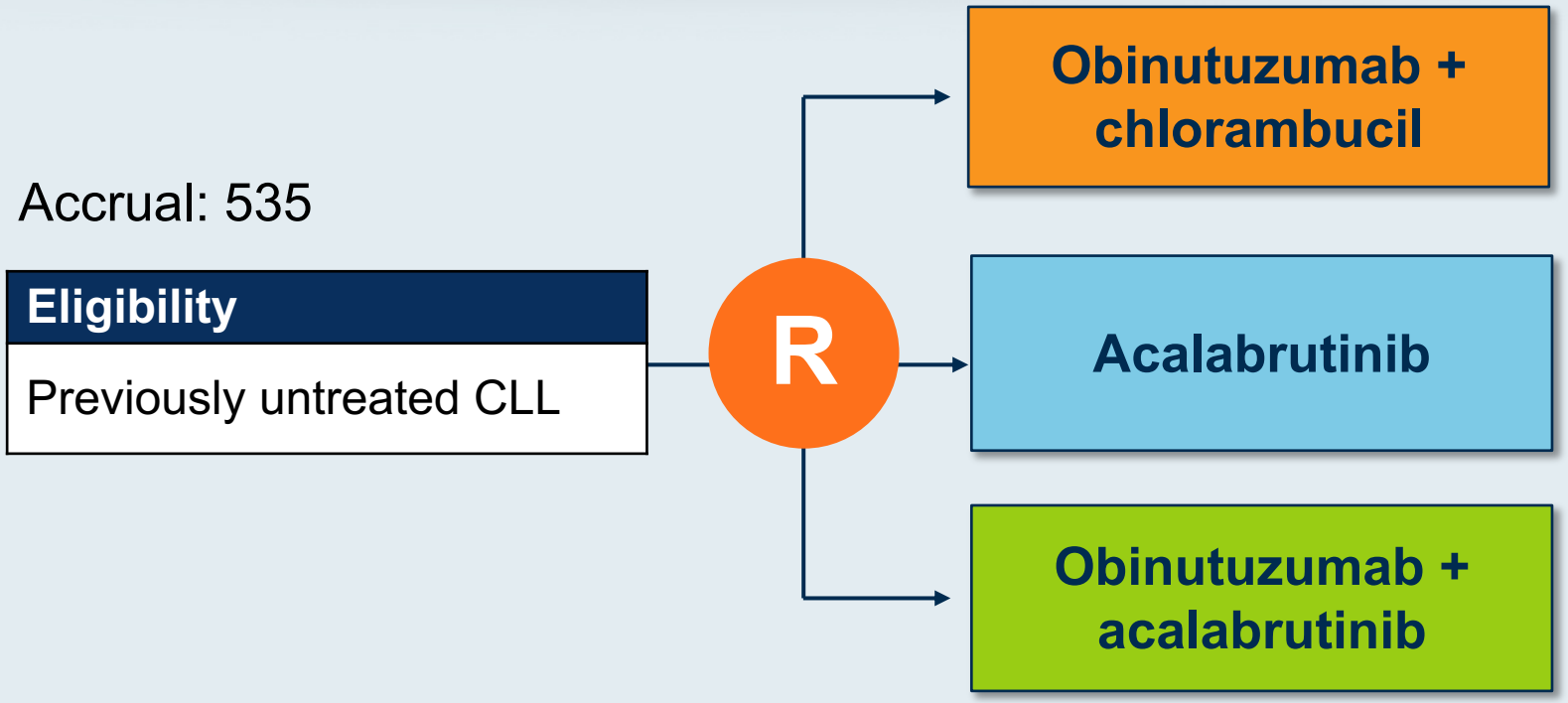
Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.
Woyach J et al. Alliance Fall Group Meeting, November 5, 2015.

Alliance A041202: Efficacy with Ibrutinib Alone or in Combination with Rituximab Compared to Bendamustine/Rituximab



Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.

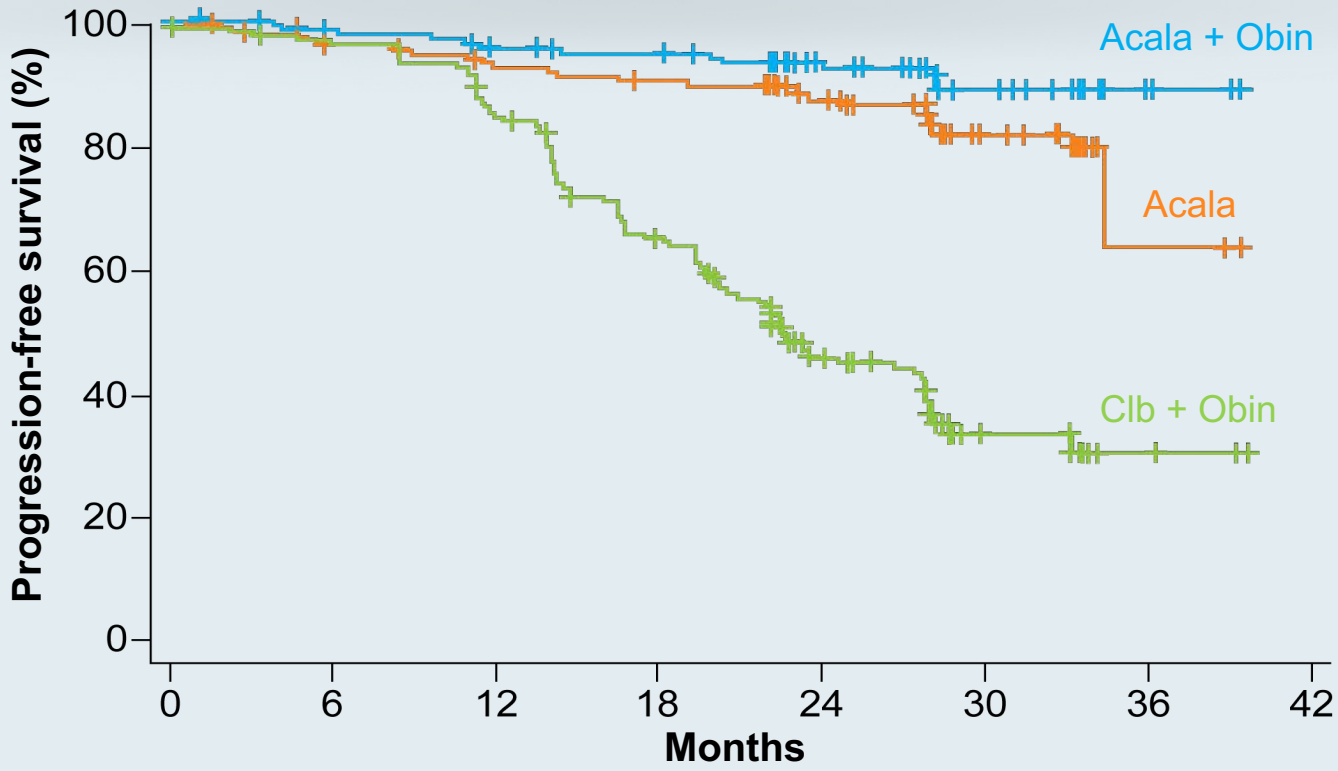
ELEVATE-TN: Phase III Trial Schema



Primary endpoint: Progression-free survival

www.clinicaltrials.gov. (NCT02475681) Accessed October 2019.

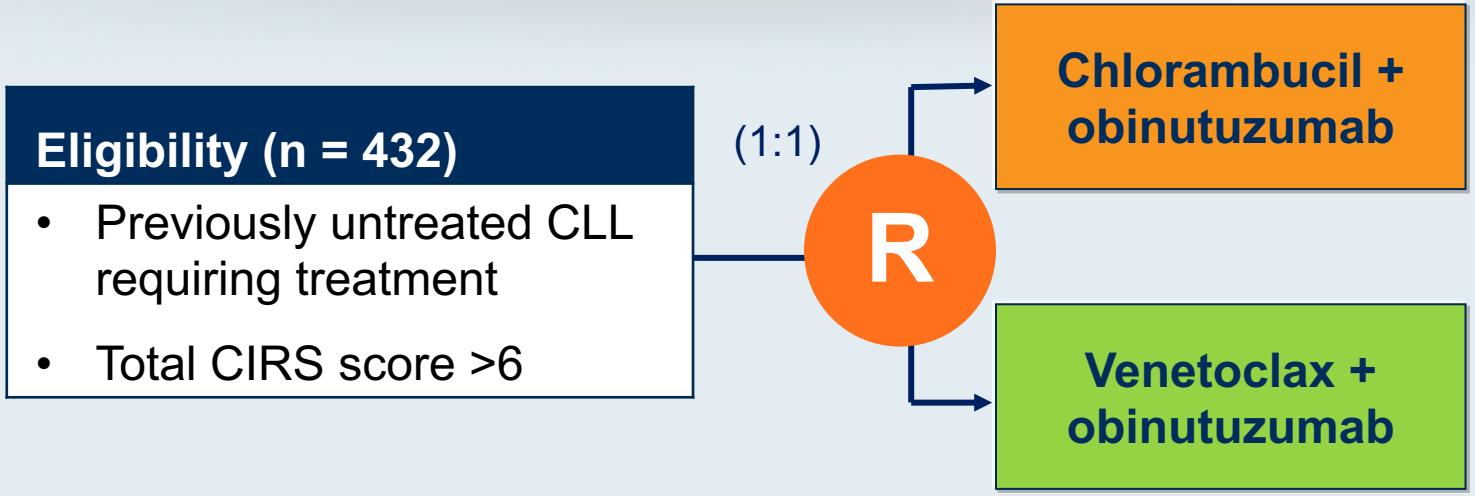
ELEVATE-TN: PFS (IRC)



Endpoint	Acala + Obin (n = 179)	Clb + Obin (n = 177)	Acala (n = 179)
Median PFS	Not reached	22.6 mo	Not reached
HR (*p*-value)	0.10 (<0.0001)		—
	—	0.20 (<0.0001)	

Sharman JP et al. ASH 2019;Abstract 31.

CLL14 Phase III Study Schema

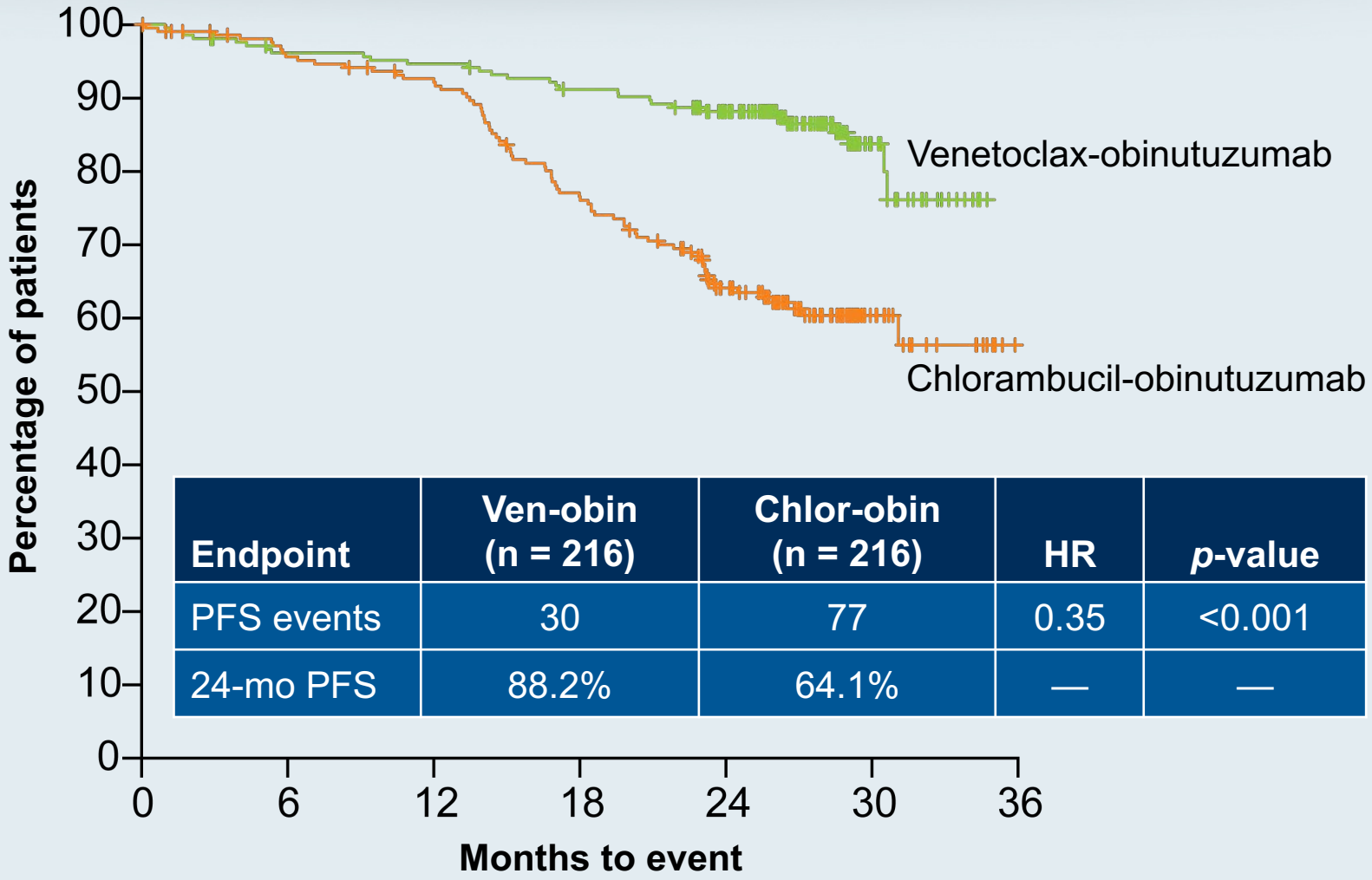


Primary endpoint: Progression-free survival

- Treatment duration in both groups: 12 cycles, 28 days each
- No crossover was allowed
- The trial started with an initial cycle of obinutuzumab followed by the 5-week venetoclax dose ramp-up to help reduce tumor burden and decrease the risk of TLS
- Daily oral venetoclax regimen:
  - Initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100 and 200 mg, then 400 mg daily for 1 week)
  - Thereafter continuing at 400 mg daily until completion of cycle 12

www.clinicaltrials.gov. Accessed October 2019 (NCT02242942).
Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

CLL14: Investigator-Assessed Progression-Free Survival



Endpoint	Ven-obin (n = 216)	Chlor-obin (n = 216)	HR	*p*-value
PFS events	30	77	0.35	<0.001
24-mo PFS	88.2%	64.1%	—	—

Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

CLL14: Minimal Residual Disease 3 Months After Treatment

MRD 3 months after treatment	MRD-negative		MRD responders	
	Veneto-obin (N = 216)	Chloram-obin (N = 216)	Veneto-obin (N = 216)	Chloram-obin (N = 216)
MRD in bone marrow	56.9%	17.1%	33.8%	10.6%
Odds ratio, *p*-value	OR: 6.4, $p < 0.0001$		OR: 4.3, $p < 0.0001$	
MRD in peripheral blood	75.7%	35.2%	42.1%	14.4%
Odds ratio, *p*-value	OR: 5.7, $p < 0.0001$		OR: 4.3, $p < 0.0001$	

Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

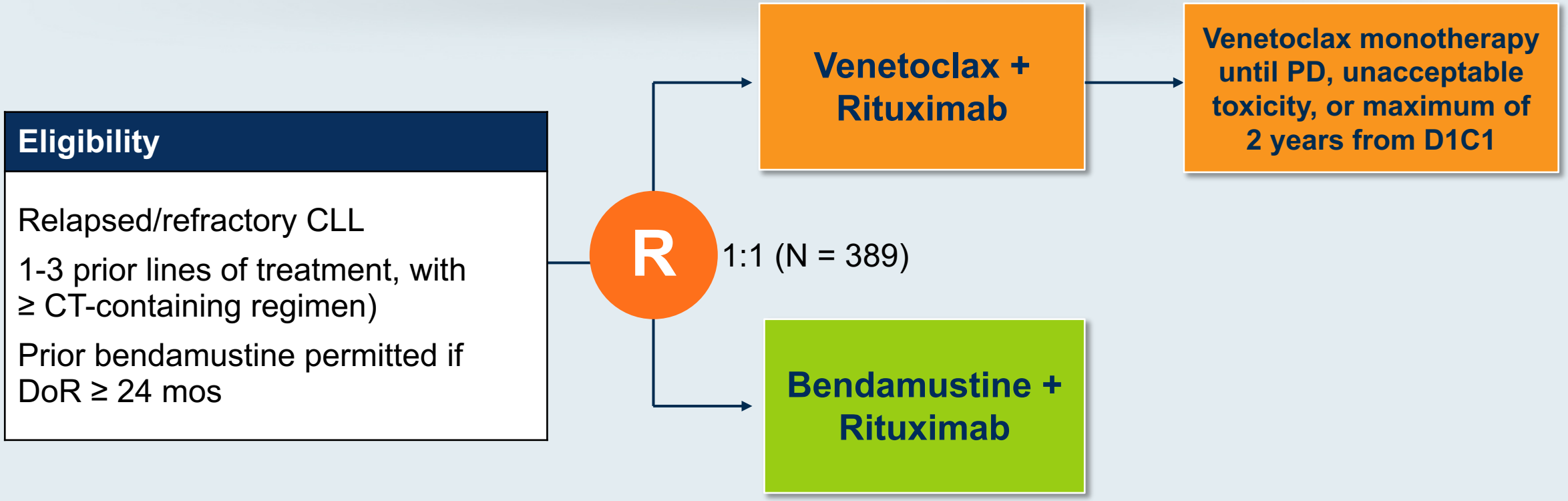
There is evidence to support the use of minimal residual disease assessment to evaluate the need for continued treatment in patients with CLL.

a. Agree

b. Disagree

c. I don’t know

MURANO Phase III Trial Schema



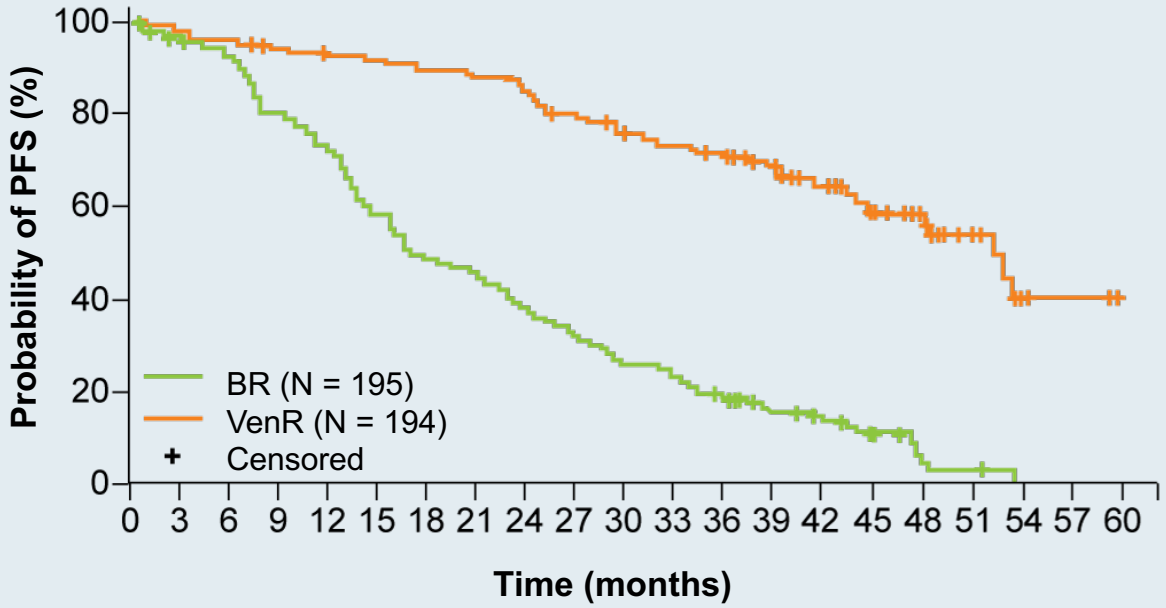
Primary endpoint: Investigator-assessed progression-free survival

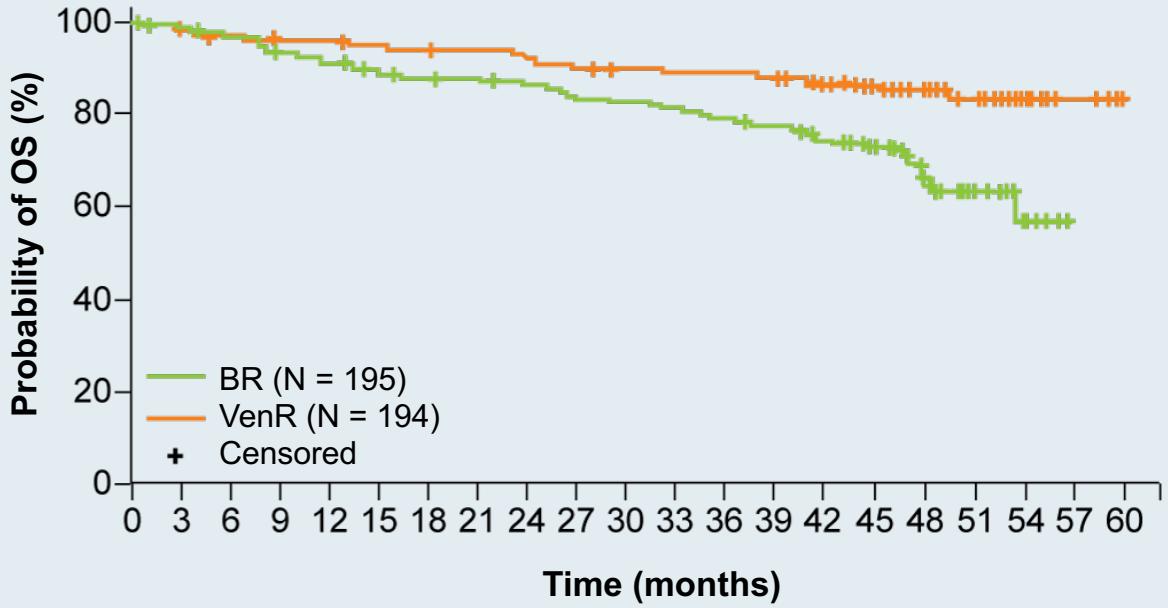
- Daily oral venetoclax regimen:
  - Starting with a 5-week dose ramp-up (1 week each of 20, 50, 100 and 200 mg, then 400 mg daily)
- Rituximab was administered after the initial venetoclax dose ramp-up for 6 cycles

Seymour JF et al. ASH 2019;Abstract 355.

MURANO Trial: Survival Analyses with Venetoclax/ Rituximab for R/R CLL (48-Month Median Follow-Up)

	VenR (n = 194)	BR (n = 195)	Hazard ratio	*p*-value
Four-year PFS	57.3%	4.6%	0.19	<0.0001
Four-year OS	85.3%	66.8%	0.41	<0.0001





Seymour JF et al. ASH 2019;Abstract 355.

Select Ongoing Phase III Studies of First-Line Therapy in CLL

Study	Target N	Randomization	Primary endpoints
FLAIR (ISRCTN01844152)	754	• Ibrutinib • Ibrutinib + rituximab • Ibrutinib + venetoclax • FCR	PFS
GLOW/CLL3011 (NCT03462719)	211	• Ibrutinib + venetoclax • Chlorambucil + obinutuzumab	PFS
GAIA/CLL13 (NCT02950051)	920	• Standard chemo (FCR/BR) • Venetoclax + rituximab • Venetoclax + obinutuzumab • Ibrutinib + venetoclax + obinutuzumab	PFS, MRD negativity rate

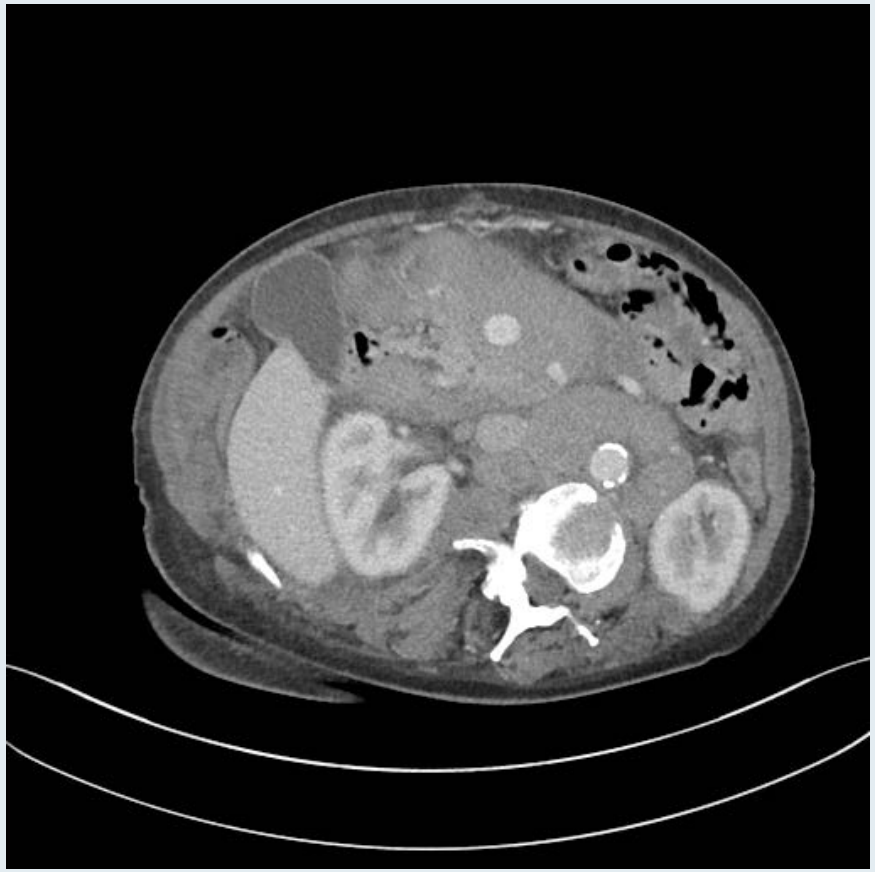
www.clinicaltrials.gov. Accessed October 2019.
www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-ibrutinib-rituximab-chronic-lymphocytic-leukaemia-flair#undefined

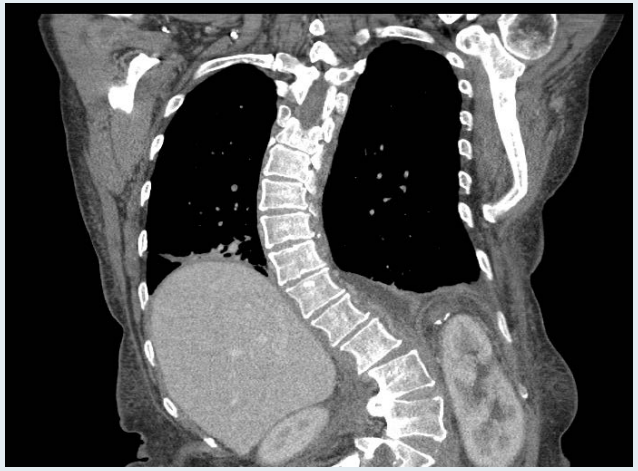
76-year-old woman with a PMH of depression/anxiety, hypothyroidism, osteoporosis, thyroid cancer, and DVT/PE after hip ORIF (from the practice of Ms Klebig)

- **2008:** Diagnosed with CLL (age 64)
- 2010: R-CVP x 8 → 2012: Rituximab/methylprednisolone → 2014: Bendamustine/rituximab x 4 → 2015: Ibrutinib
- May 2018: Progression
  - RAI stage I, CLL-IPI: 8 (very high risk), 17p deletion, TP53 mutated, IGH-V unmutated
  - Hypercellular marrow (80%) with 80% involvement by CLL
  - Hgb: 12.0, Plts: 229,000, WBC: 39,200, ANC: 10,580, ALC: 26,600, LDH: 270 (122-222)
- **6/2018: Venetoclax initiated**
  - Added to ibrutinib, which was then tapered off
- 8/2018 – 1/2019: Rituximab added x 6 months
- Single-agent venetoclax continued

76-year-old woman (from the practice of Ms Klebig)
Baseline imaging: May 2018

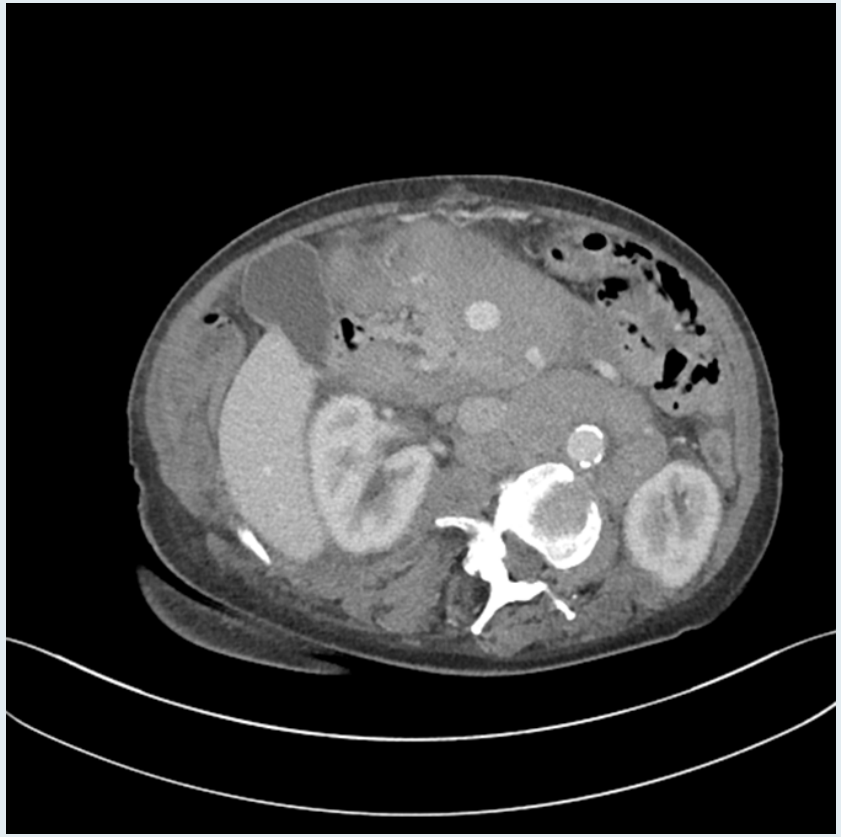
- CT: extensive confluent adenopathy



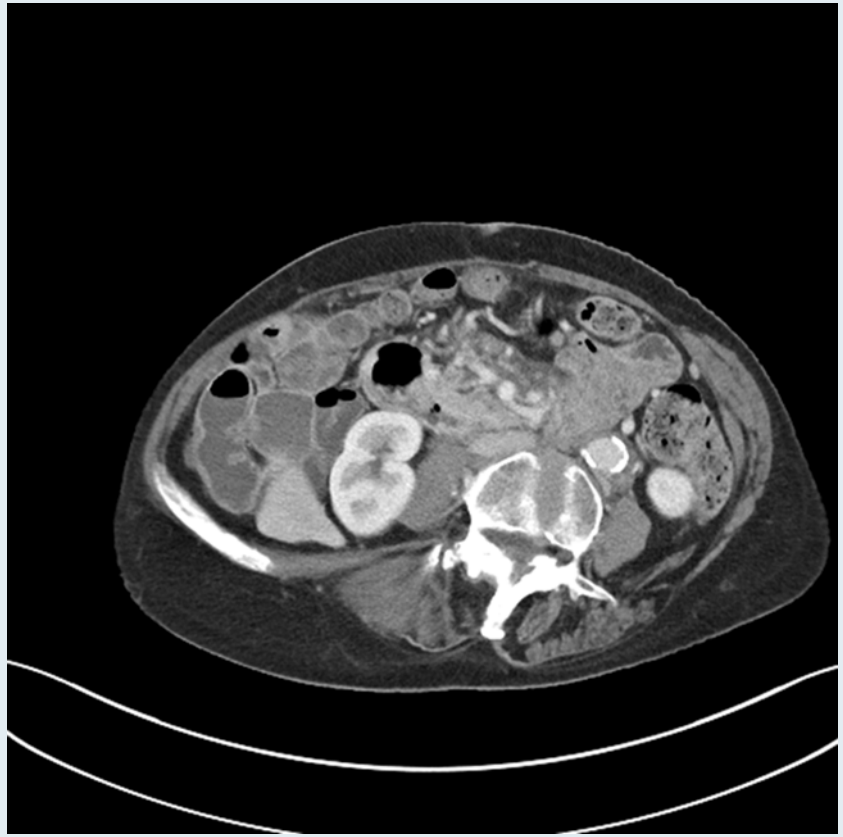


76-year-old woman (from the practice of Ms Klebig)
Response to therapy

May 2018



February 2019



76-year-old woman (from the practice of Ms Klebig)
Patient Education

- Pharmacy consultation re potential drug interactions
  - CYP3A4 interactions - Avoid strong inhibitors & inducers
    - Azole antifungals, -mycin antibiotics, protease inhibitors, etc
    - Moderate – consider dose adjustment
    - Avoid grapefruit/juice, Seville oranges, and starfruit
- Take with food and water, same time each day

76-year-old woman (from the practice of Ms Klebig)
Patient Education

Potential for tumor lysis syndrome

- 5 week ramp up to goal dose
- Hospitalization for weekly ramp up (bulky)
- TLS lab monitoring q8h x 24 hours
- Allopurinol
- Hydration

Nausea

- prn antiemetic

Diarrhea

- Loperamide prn
- Record # stools per day at baseline

Cytopenias

- Neutropenia
  - Increased infection risk
- Thrombocytopenia
  - Bleeding risk
- Anemia
  - Typically not transfusion requiring

76-year-old woman (from the practice of Ms Klebig)
Change in patient over time

- Very anxious, subdued at appts
- 6 weeks to decide on treatment

- Worried about each step; did she even want treatment?

- Now less anxious, more sociable, enjoys coming to appts, shopping with daughter

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Module 4: First-Line Treatment Decision-Making

Patients with newly diagnosed chronic lymphocytic leukemia (CLL) who feel well and are asymptomatic require treatment if…

a. Del(17p)/TP53 mutation is detected

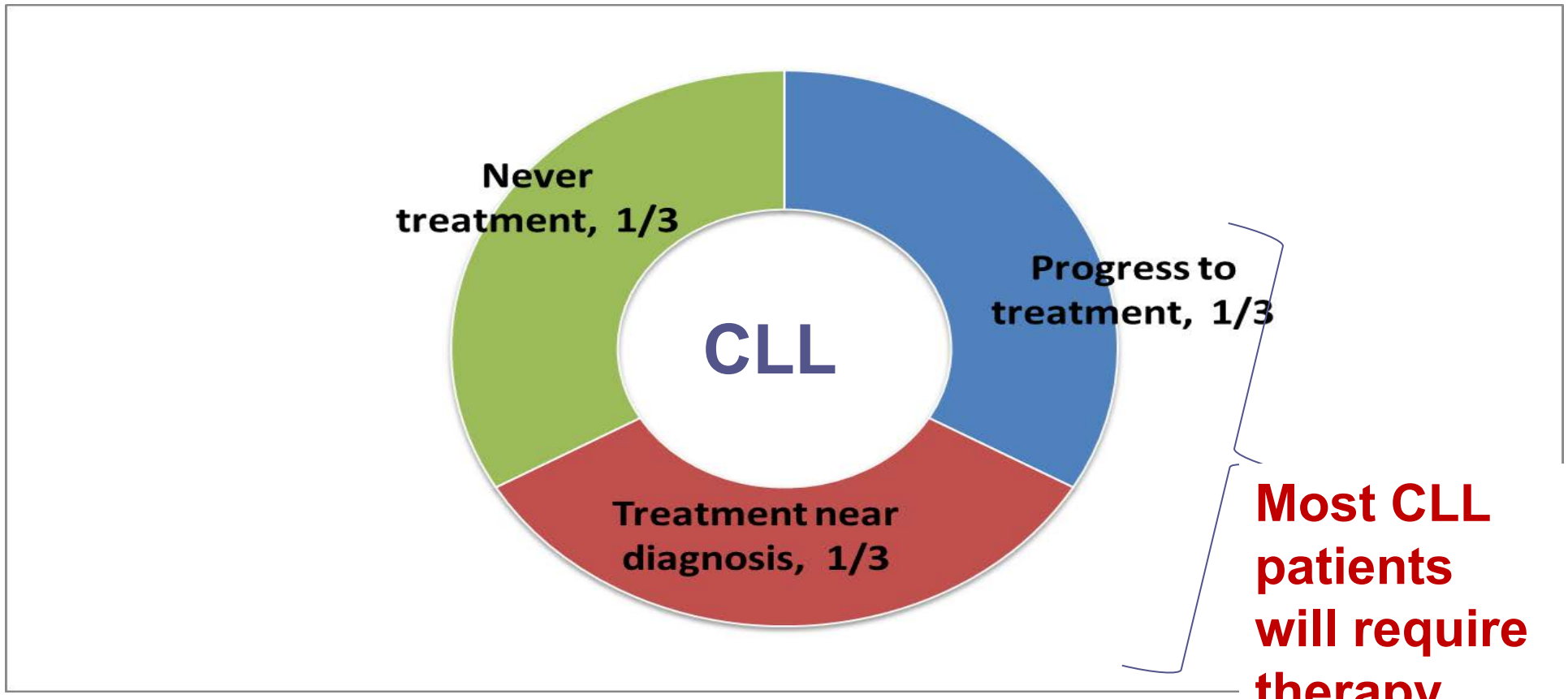
b. White blood cell count exceeds 200,000

c. Both a and b

d. Neither a nor b

e. I don’t know

CLL: Dynamic Monitoring vs Treatment



- Rationale against treatment on diagnosis for asymptomatic patients (unless in a clinical trial)

Courtesy of Brad S Kahl, MD

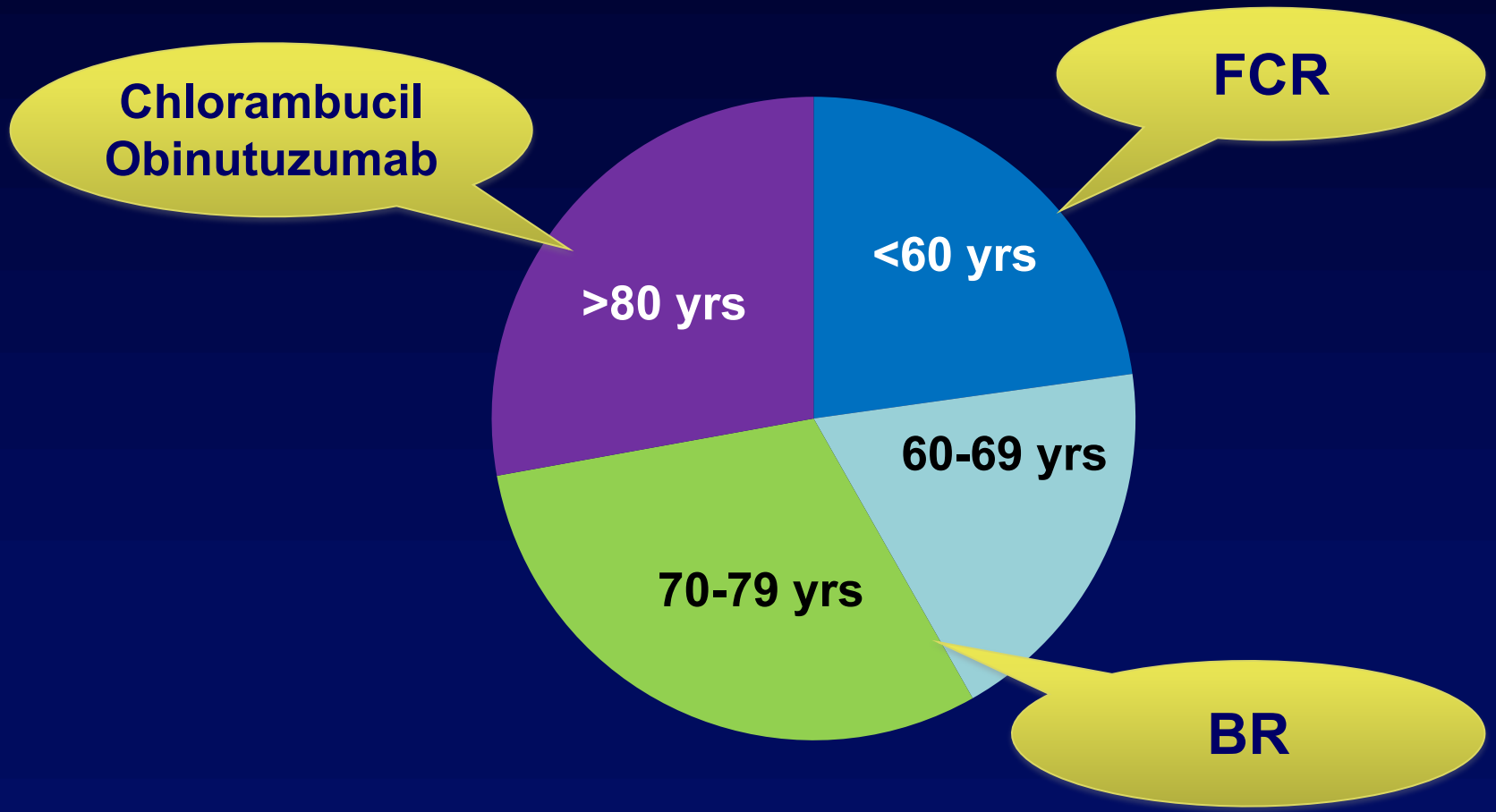
Indications for treatment:

- Disease-related symptoms
  - Fatigue can by tricky
- Progressive bulky disease
  - spleen > 6 cm below costal margin; LN > 10 cm
- Progressive bone marrow failure, manifesting as anemia or thrombocytopenia
- Autoimmune complications poorly responsive to steroids
- Progressive lymphocytosis: Lymphocyte doubling time < 6 months, or increase in ≥ 50% in a two-month period

*Note: Absolute lymphocyte count alone not an indication for treatment

Courtesy of Brad S Kahl, MD

A simplistic (and outdated) approach to CLL



Courtesy of Brad S Kahl, MD

Available clinical trial data demonstrate that younger patients with CLL with IGHV mutation but without del(17p) or TP53 mutation can experience prolonged remissions after the completion of short-term therapy with which of the following regimens?

a. Ibrutinib

b. Venetoclax

c. FCR (fludarabine/cyclophosphamide/rituximab)

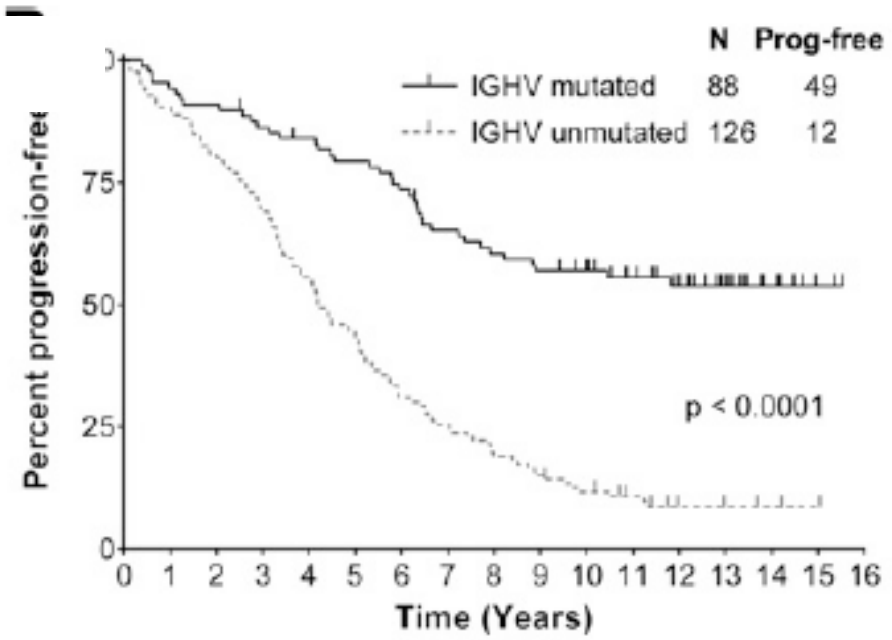
d. Obinutuzumab/chlorambucil

e. I don’t know

Rationale for frontline chemoimmunotherapy (CIT): durable remissions for some patients

FCR (fludarabine/cyclophosphamide/rituximab)

- **MDACC:** 300pts received treatment with FCR frontline
  - Plateau in PFS: no relapses beyond 10.4 years in 42 patients with favorable risk (mutated IGHV, no del17p or del11q)



Blood. 2008;112:975-980.
Blood. 2015;126(16):1921.
Blood. 2016;127(3):303.
Blood. 2016;127(2):208.
Blood. 2015;126(16):1921.

- Similar plateau in CLL8 and Rossi et al FCR studies
- Bendamustine and Rituximab (BR) frontline: lower CR, PFS but not OS

Courtesy of Brad S Kahl, MD

How to select a treatment for an individual patient?

Menu

- Immunochemotherapy
  - FCR
  - BR
  - Chlorambucil/Obinutuzumab
- Novel Agents
  - Ibrutinib ± obinutuzumab
  - Acalabrutinib ± obinutuzumab
  - Venetoclax + Obinutuzumab

Considerations

- If deletion 17p or p53 mutation
  - Chemo not very effective, better off with novel agents
- If IgHV unmutated
  - Chemo less effective than novel agents
- If IgHV mutated
  - Chemo and novels agents are similarly effective

Courtesy of Brad S Kahl, MD

Scenario #1

- 52 yo man with CLL requiring treatment.
  - No p53 mutation or 17p deletion.
  - IgHV unmutated.

- Best options include
  1. Venetoclax plus obinutuzumab
  2. BTKi plus obinutuzumab

- Pro's and Con's to each

Courtesy of Brad S Kahl, MD

Scenario #2

- 52 yo man with CLL requiring treatment.
  - No p53 mutation by sequencing
  - No 17p deletion or 11q deletion by FISH.
  - IgHV mutated.

- Best options include
  1. FCR
  2. Venetoclax plus obinutuzumab
  3. BTKi plus obinutuzumab
- Pro's and Con's to each

Courtesy of Brad S Kahl, MD

Scenario #3

- 72 yo man with CLL requiring treatment.
  - No p53 mutation.
  - No 17p deletion or 11q deletion.
  - IgHV unmutated.

- Best options include
  1. Venetoclax plus obinutuzumab
  2. BTKi

- Pro's and Con's to each.

Courtesy of Brad S Kahl, MD

Scenario #4

- 72 yo man with CLL requiring treatment.
  - No p53 mutation or 17p deletion.
  - IgHV mutated.

- Best options include
  1. Venetoclax plus obinutuzumab
  2. BR
  3. BTKi

- Pro's and Con's to each.

Courtesy of Brad S Kahl, MD

Scenario #5

- 72 yo man with CLL requiring treatment.
- 17p deletion by FISH

- BTKi plus obinutuzumab

- This is the one scenario where I favor indefinite therapy over time limited therapy

Courtesy of Brad S Kahl, MD

Take home points

1) CLL is not primarily “chemo-free” in frontline and r/r disease

2) BTK inhibitors have beaten FCR / BR / Clb-Obi

3) Two approved BTK inhibitors ibrutinib / acalabrutinib

4) Venetoclax approved in both frontline and r/r disease allows for fixed duration therapy

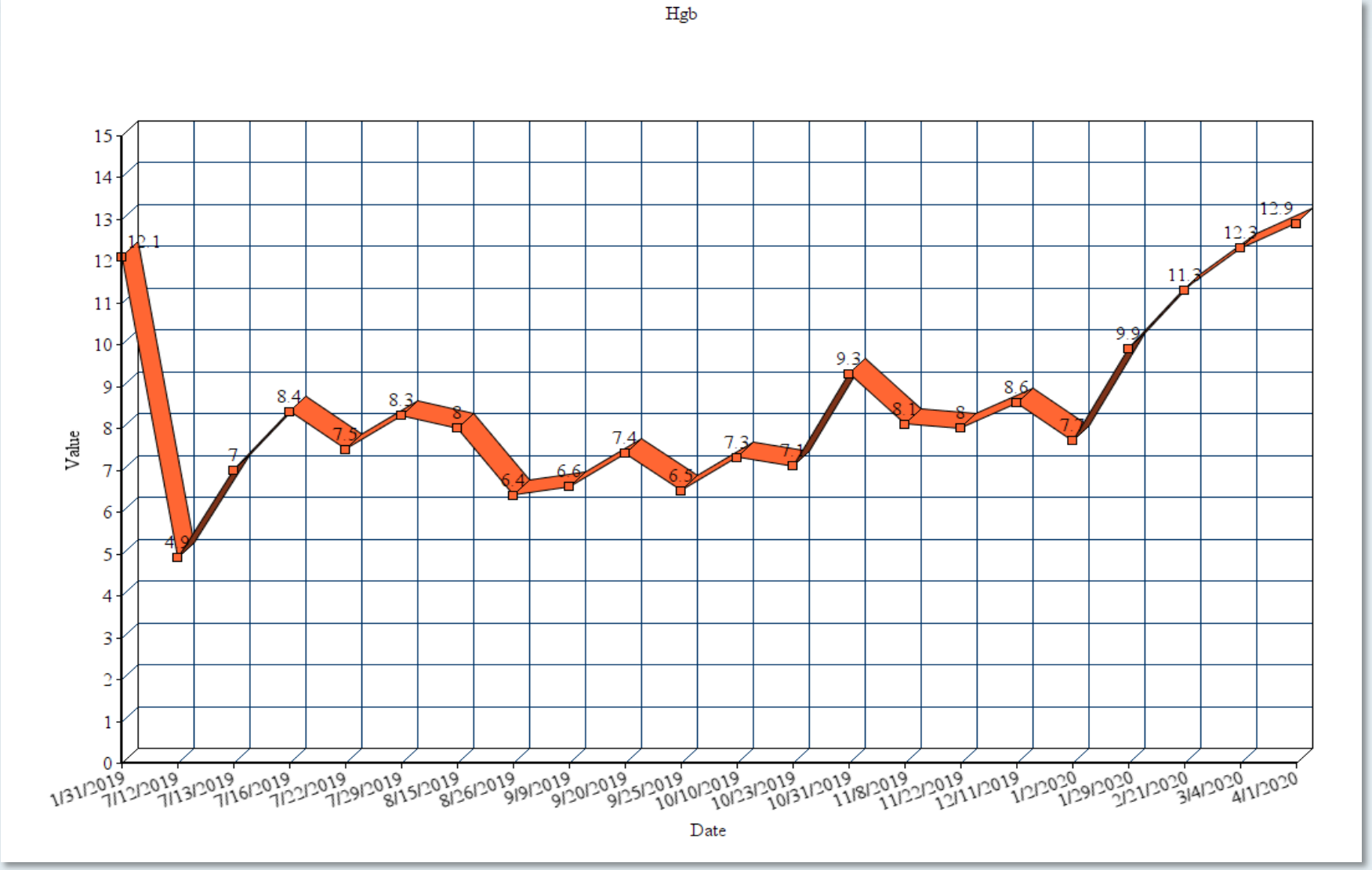
5) In r/r disease – targeted agents have beaten chemotherapy

Courtesy of Jeff Sharman, MD

53-year-old single mother of 3 teenagers with PMH of hypertension and GERD (from the practice of Ms Goodrich)

- 2015: Diagnosed with asymptomatic SLL, when adenopathy noted on routine mammogram
  - WBC 7.9, Hgb 12, Plts 259K, ALC 2.3
  - CT scans revealed adenopathy in chest, abd and pelvis, up to 3.4 cm
- Observed
- Mid-2019: Significant anemia (transfusion dependent, hemolysis work up: Negative)
  - WBC 68.4K, Hgb 4.6, Plts 188K, ALC 64.6K
  - FISH: Normal, IGHV mutated
  - CT: Nodes up to 5.5 cm
  - Declines marrow
- **Obinutuzumab + venetoclax** (1 year of therapy attractive) → Good WBC and nodal response
  - Tolerates well, no TLS
  - Transfusion independent after 2 months on full-dose venetoclax
  - Very late response

53-year-old single mother (from the practice of Ms Goodrich): Hgb



53-year-old single mother (from the practice of Ms Goodrich)

Teaching points and challenges

- Obinutuzumab toxicity (infusion reaction, cytopenias, infection risk)
- Venetoclax toxicity (mainly TLS, some nausea)
- Relatively new combination regimen, health care teams still gaining expertise on patterns of toxicity and management, not typically using obinutuzumab widely
- Mother and children were unaware of diagnosis
- Continuing to work full time was a priority
- Symptomatic anemia
- Daughter active in travel sports, timed transfusions around tournaments


PhotoGrid

84-year-old widow with no significant PMH who lives in an independent living facility (from the practice of Ms Goodrich)

- 1999: Lymphocytosis → 2004: Diagnosed with CLL → 2009: BR (bulky adenopathy)
- Developed Stevens-Johnson Syndrome with allopurinol
- 9/2017: First seen at JH (daughter 5 hours away, transports and accompanies to all visits)
  - Asymptomatic, with extensive adenopathy, largest node < 4 cm
  - 13q, 11q and 17p and TP53 abnormalities, Unmutated IGHV
  - WBC 59.6, Hgb 13.2, Plts 170K, ANC 5.9
- Observed
- Early 2020: Increasing adenopathy to 6 cm in multiple areas
  - WBC 120K, Hgb 7.5, Plts 134K, creat 1.2 with creat clearance 31
- **Venetoclax + rituximab** (2-year finite therapy)
  - Admitted for first two doses due to allopurinol allergy, elevated ALC, tumor burden and creatinine clearance

84-year-old widow (from the practice of Ms Goodrich)

- COVID19 quarantine, patient cannot leave ILF
  - Collaborated with facility's health care staff to obtain TLS monitoring labs around dose escalations
- Main teaching point for this patient- HYDRATE
  - No TLS!
- Developed rash on 400 mg, tolerating 200 mg well
- Current labs: WBC 5.2, Hgb 9.6, Plts 112K
- Patient reports palpable adenopathy resolved
- Will start rituximab when travel is possible

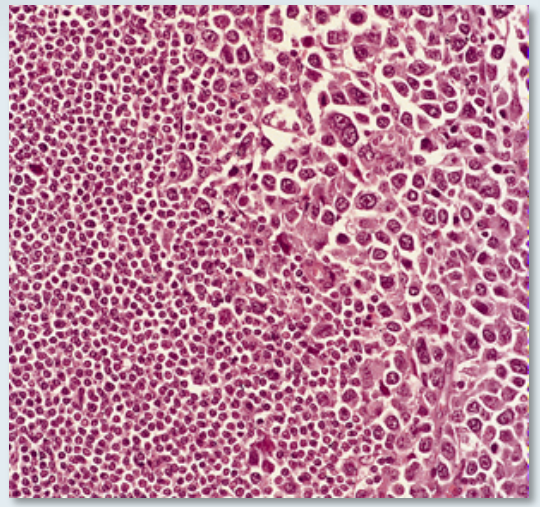
84-year-old widow (from the practice of Ms Goodrich)

COVID 19 and Telemedicine challenges

- No computer in apartment, had relied on using computers in a common area
- Smart phone novice
- All communication via phone only
- Patient unable to transmit photos of rash
- Had to shift dose escalation days to be able to do any TLS monitoring
- Took 24-48 hours to receive lab results
- Allopurinol allergy
- Has not started rituximab
- Fortunately, quarantining well!

Richter's Transformation

- Transformation of CLL into aggressive lymphoma, often diffuse large B-cell lymphoma
- Occurs in 5-10% of patients
- Poor prognosis (median OS = 5-8 months)
- Clinical presentation:
  - Sudden deterioration (increased lymphadenopathy, splenomegaly, worsening B symptoms)
  - Elevated LDH
  - Anemia, thrombocytopenia



Warnke RA et al. Tumors of the lymph nodes and spleen. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 14, 1995, Washington, DC. Armed Forces Institute of Pathology

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Module 5: Use of Oncologic Agents to Treat COVID-19

Module 6: Use of Oncologic Agents to Treat COVID-19

Thank you for joining us!

CNE (NCPD) credit information will be emailed to each participant tomorrow morning.