Diagnosis of Chronic Lymphocytic Leukemia (CLL)

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Overview

- Evaluation of lymphocytosis
- Diagnostic criteria for CLL and related conditions
- Rai staging of CLL
- Health implications of CLL patients

Case 1: Ms. Smith

- 70-year-old female
- Planned to undergo hip surgery
- CBC for pre-operative work up

Complete Blood Count

WBC*	11.92 k/uL	H
Hgb	12.2 g/dL	
Plt	160 k/uL	

Differential

Neu	3.22	
Lym*	7.99	H
Mono	0.6	
Eos	0.0	
Baso	0.12	

Case 1- continued

- She feels well. No night sweats, fevers, severe fatigue, weight loss, or new masses.
- Physical exam with no adenopathy. No enlarged spleen or liver
- No other medical problems, medications, or prior surgeries.
- She leads an active life-style and is up to date on her vaccinations and health maintenance

What is the diagnosis?

A. Chronic lymphocytic leukemia (CLL)

B. Small lymphocytic lymphoma (SLL)

C. Monoclonal B-cell lymphocytosis (MBL)

D. Normal findings, recheck in a year

E. Not enough information

Differential Diagnosis of Lymphocytosis

- Infectious mononucleosis (EBV or CMV)
- Viral infections (eg. HIV, influenza)
- Some non-viral infections (eg. *bartonella henselae*, tuberculosis)
- Inflammation or trauma
- Splenectomy
- Lymphoproliferative disorders (eg. T-LGL, CLL, lymphomas)

Clues from the CBC

- Determine if relative (%) or absolute (cells/uL)
- Determine the duration of lymphocytosis
- Review any comments from the technologist or pathologist
- Review the peripheral blood smear
- Are there other abnormalities such as anemia, thrombocytopenia, or neutropenia?

What should I look for?

- Lymphadenopathy or splenomegaly on exam (size matters!)
- Constitutional symptoms
  - Rapid or unintentional weight loss
  - Drenching night sweats
  - Fatigue limiting daily activities without other cause
- Signs of bone marrow failure such as anemia or thrombocytopenia
- Abnormal circulating cells in the peripheral blood

Ms. Smith returns in 6 weeks

- She feels well with no fatigue. She is anxious about the findings

Complete Blood Count

WBC*	17.2 k/uL	H
Hgb	15.1 g/dL	
Plt	247 k/uL	

Differential

Neu	2.1	
Lym*	14.4	H
Mono	0.4	
Eos	0.2	
Baso	0.1	

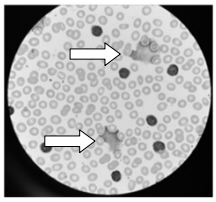

Photo credit to Dr. Kerry Rogers

What should I do next?

A. Send peripheral blood flow cytometry
B. Perform bone marrow biopsy
C. Start treatment
D. No additional testing needed

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What is flow cytometry ?

- Technique for immunophenotyping of blood cells
- WBC are marked with antibodies linked to fluorochromes to detect specific antigen markers (eg. CD20 or CD5)
- Cells are passed by a laser to determine which fluorescent markers are present
- Determines the types of white blood cells
  - T-cells
  - B-cells
  - Myeloid cells
  - Blasts, leukemic cells, or other abnormal cells

Ms. Smith flow cytometry results

- The majority of B-cells were clonal with a "CLL- like" immunophenotype: (CD19+, CD5+, CD20^{dim}, CD23+, kappa light chain+, FMC7-)
- The clonal lymphocyte count was 11.2 k/uL
- Impression says "consistent with chronic lymphocytic leukemia"
- She asks if he has leukemia and what to do next

Diagnostic Criteria for CLL

- Presence of ≥5,000 u/L clonal B-lymphocytes in the blood
  - Persistent for >3 months
  - Clonality confirmed by light chain restriction
- Clonal cells have a "CLL immunophenotype"
  - B-cell antigens (CD19, CD20, and CD23) with CD5
  - Low/dim surface immune globulin, CD20, and CD79b
  - Restricted to kappa or lambda light chain expression

Hallek et al., Blood 2018

What is the diagnosis?

A. Chronic lymphocytic leukemia (CLL)

B. Small lymphocytic lymphoma (SLL)

C. Monocloncal B-cell lymphocytosis (MBL)

D. Normal findings, recheck in a year

E. Not enough information

Chronic Lymphocytic Leukemia (CLL)

- Chronic B-cell lymphoid malignancy
- Median age at diagnosis late 60s
- Most prevalent leukemia in adults in the US
- Median survival is good and can be predicted by cytogenetic testing
- Survival today is likely improved over historical estimates with newer more effective treatments such as oral targeted agents

Hallek et al., Blood 2018; Dohner et al., NEJM 2000

Chronic Lymphocytic Leukemia (CLL)

- People who are asymptomatic are typically observed.
- Some patients may never require treatment.
- Signs and symptoms that may develop over the disease course:
  - Enlarging lymph nodes
  - Increasing lymphocyte count
  - Anemia, thrombocytopenia, neutropenia
  - B- symptoms

Hallek et al., Blood 2018

Small Lymphocytic Lymphoma (SLL)

- The lymphoma version of CLL
- Has the same immunophenotype as CLL but without ≥5,000 /uL CLL-cells in the blood and has enlarged lymph nodes
- Prognostic features and outcomes are the same as with CLL
- Treated with the same therapies as CLL
- Can generally be considered together with CLL

Hallek et al., Blood 2018

Monoclonal B-lymphocytosis (MBL)

- Not a cancer. Often found incidentally
- Common in the elderly
  - Incidence increases with age (5.1% of people age 60-80)
- Can have a "CLL-like" or "non-CLL-like" immunophenotype
  - More is known about "CLL-like" MBL
  - "Non-CLL-like" may eventually progress to other lymphomas
- Can be low-count (<0.5 k/uL) or high-count (≥0.5 k/uL)
  - High-Count progresses to CLL requiring treatment at a rate of ~1-2% per year
  - Low-count almost never progresses to CLL

Rawstron et al., NEJM 2008; Strati et al., Blood 2015

Diagnostic distinctions

- MBL:
  - Lymphocytes < $5x10^9$/L
  - No LAD or organomegaly
  - No cytopenia related to disease
  - 1-2% per year progress to CLL needing treatment
- SLL:
  - Lymphocytes < $5x10^9$/L+ lymphadenopathy
  - NO cytopenia due to marrow involvement
  - Confirm diagnosis with biopsy
- CLL:
  - Clonal lymphocytes > $5x10^9$/L or < $5x10^9$/L + cytopenia due to marrow involvement
  - Could be symptomatic or asymptomatic

CLL & Related Diagnoses

Diagnosis	CLL Clone ≥5k	Enlarged Lymph Nodes	Enlarged Liver or Spleen	Cytopenias due to Marrow Infiltration
CLL	Required	+/-	+/-	+/-
SLL	-	Required	+/-	-
MBL	-	-	-	-

MBL = Monoclonal B-Lymphocytosis, SLL = Small Lymphocytic Lymphoma

Hallek et al., Blood 2018

What do I tell my patient?

- You tell Ms. Smith that she has chronic lymphocytic leukemia
- You make sure to tell her:
  - The expected survival is many years to potentially decades
  - She may <u>not</u> need treatment right now
  - Treatments for CLL are highly successful and often have only mild side effects
  - This is the most prevalent leukemia in adults in the US, so she is not alone

Implications for Health Maintenance

- People with CLL have inherent immune dysregulation
- Higher risk for autoimmune disease <u>and</u> complications from decreased immune function
- Since CLL-specific survival is generally good therefore these other risks are an important cause of morbidity and mortality

Visentin et al., European Journal of Cancer 2017

Risk of Second Cancers is Increased

- CLL increases risk for other types of cancer
- In large cohort studies overall risk for second cancer was increased compared to general population
- Highest risk for
  - Squamous cell carcinoma
  - Melanoma
  - Myeloid neoplasms – particularly if prior chemotherapy
  - Solid tumors and soft tissue sarcoma
- 2-10% risk of Richter transformation

Zheng et al., BJH 2018; Royle et al., British Journal of Cancer 2011; Thompson et al., Blood 2016 . Der Straten et al, Blood Cancer, 2023

Approach to Cancer Screening in CLL Patients

- Recommend all age-appropriate cancer screenings
- Should be based on the individual patient's risk factors
- If you are considering stopping screening based on age or lower risk, take the CLL into account
- **Annual skin exam** is recommended due high risk of non-melanoma skin cancers and increased risk for melanoma

Vaccination Recommendations

- Vaccines have decreased efficacy in CLL patients but should still be given
- CDC has recommendations for vaccination in immune compromised individuals
- Live vaccines should be avoided

Dagnew et al., Lancet Infectious Diseases 2019

NCCN Guidelines for Immunizations for Patients with CLL

- Avoid all live vaccines
- Recommended vaccines:
  - Annual influenza vaccine
  - Pneumococcal vaccine
  - Zoster vaccine recombinant, adjuvenated for all patients treated with Bruton's tyrosine kinase inhibitors
  - Respiratory syncytial virus (RSV)
  - COVID-19 vaccine

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): CLL Guidelines 2.2025. [https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed 3.24.2025

Considerations for MBL Patients

- Patients are followed at least annually as they may progress to CLL
- At increased risk for
  - Infections and hospitalizations from infections
  - Hematological and non-hematological malignancies
- We also recommend vaccinations and cancer screening similar to patients with CLL

Rawstron et al., NEJM 2008; Strati et al., Blood 2015; Moreira et al., Leukemia 2013; Solomon et al., Leukemia 2016

Take Home Points

- Patients with persistent absolute lymphocytosis and/or “red flag” features should be further evaluated, usually with flow cytometry
- CLL is the most prevalent leukemia in adults in the U.S
- Expected survival for CLL patient is many years
- CLL is a heterogeneous disease; genomic factors can better refine prognosis for individual patients
- CLL does not always need treatment at diagnosis
- CLL, SLL, and MBL patients have a higher risk for second cancers and infections and need strategies to manage this risk

How do We Approach CLL Treatment?

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Objectives

- To understand Staging & Risk Stratification for CLL
- To discuss Rationale for Observation in early-stage asymptomatic patients
- To discuss Treatment Indications
- To understand Approach to Selecting Initial Treatment

Case

- Ms. Jones is a 66 y/o female with hypertension and atrial fibrillation who was diagnosed with CLL in 2019 when a routine CBC showed a WBC of 21k with 85% lymphocytes. Hb and platelets were normal, and patient was asymptomatic. Flowcytometry confirmed CLL
- Patient was recommended observation
- She is worried about the “cancer” diagnosis and wants to do her estate planning. She asks you, what should I expect, how much time do I have?

CLL: Disease Course

- People who are asymptomatic should be observed
- Treating people at diagnosis does not improve survival
- Over the course of the disease people develop
  - Enlarging lymph nodes
  - Increasing lymphocyte count – *even up to 300-400 k/uL can be ok*
  - Cytopenias due to marrow infiltration with leukemia
  - Constitutional symptoms in some cases
- If these become a problem treatment is started
- Some people never require treatment!

Hallek et al., Blood 2018

CLL Presentation

- Heterogeneous disease with survival ranging from months to 25+ years from diagnosis
- No signs or symptoms (25-50%)
- Fatigue
- Lymph node enlargement (10-20%)
- Spleen or liver enlargement
- Frequent infections
- Weight loss, fever, or night sweats (5-10%)

Rai Staging of CLL

- Requires a physical exam and CBC
- Bone marrow biopsy and CT scans are not needed for staging
- Both should only be used to evaluate symptoms or findings
  - Bone marrow biopsy to evaluate unexplained cytopenias
  - CT scans for abdominal pain or palpable masses
- Higher stage correlates with shorter overall survival

Rai Stage	Finding	Median Survival (Mo)	Modified Rai Classification
0	Lymphocytosis	>150	Low Risk
I	Lymphadenopathy	101	Intermediate Risk
II	Splenomegaly and/or Hepatomegaly	71	
III	Anemia (<11 g/dL)	19	High Risk
IV	Thrombocytopenia (<100 k/uL)	19	
Category is assigned based on highest risk finding			

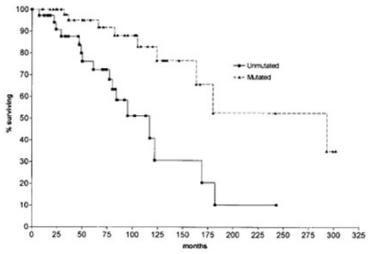
Rai et al., Blood 1975; Hallek at al., Blood 2018

Immune Globulin Heavy Chain Variable (IGHV) Mutational Status

- IGHV region undergoes somatic mutation during B-cell development
- This is a marker of B-cell maturity
- IGHV sequence in CLL cells is compared to germline
  - ≥2% difference from germline = mutated
  - <2% different from germline = unmutated
- Unmutated status is associated with
  - Earlier therapy,
  - Lower response rates esp. to chemoimmunotherapy
  - Inferior survival

Hamblin et al., Blood 1999

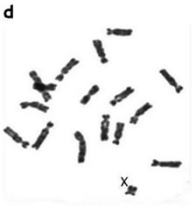
Survival by IGHVs Mutational Status



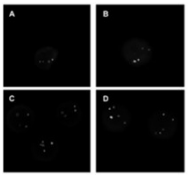
Median Survival (months)	
Mutated	293
Unmutated	95
P=0.001	

Hamblin et al., Blood 1999

Cytogenetics & Fluorescence In Situ Hybridization



Metaphase spread



A. Normal
B. Trisomy
C. Deletion
D. Translocation

FISH Testing & Hierarchical Risk Categories

- Prior to interphase FISH trisomy 12 most common recurrent abnormality
- FISH identifies more aberrations than karyotype (82% vs 40-50%)
- OS determined by highest risk finding
- Patients with 17p deletions had the worst prognosis, followed by patients with 11q deletions, those with 12q trisomy, and those with normal karyotypes
- Patients with 13q deletions had the longest estimated survival times
- Can change with disease progression, clonal evolution

FISH	%	Median Survival (months)
Del17p	7	32
Del11q	18	79
Tri12	16	114
None	18	111
Del13q	55	133

Dohner et al, NEJM 2000

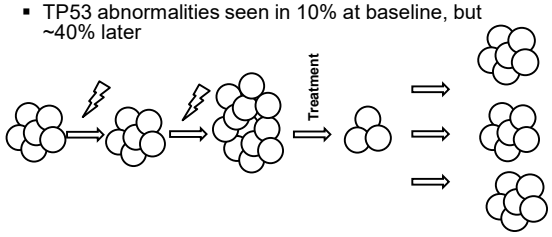
Complex Karyotype

- Complex defined as ≥3 independent chromosomal abnormalities
- Karyotype should be stimulated
- Abnormalities MUST be in karyotype – FISH findings do not count
- Correlates with del17p
- Poor prognostic feature
- Predicts worse survival in untreated, relapsed/refractory, and post-allogeneic stem cell transplant patients

Haferlach et al., Leukemia 2007; Juliusson et al., NEJM 1990; Woyach et al., Leukemia 2012; Jaglowski et al., BJH 2012

Can Prognosis Change Over Time?

- IGHV mutational status does not change
- Cytogenetic abnormalities and gene mutations can, a process called clonal evolution
  - TP53 abnormalities seen in 10% at baseline, but ~40% later



The CLL-IPI Score & Risk Groups

- Patient level data from 8 CLL studies analyzed
- Takes into account stage, biologic, and patient demographic factors
- Points are assigned for each feature present
- Has been extensively validated in other cohorts
- Predicts survival and time to first treatment

Feature	Points
TP53 Deleted or Mutated	4
IGHV Unmutated	2
β2-microglobulin >3.5 mg/L	2
Rai I-IV or Binet B or C	1
Age >65	1

Score	Risk Group	5-year Survival
0-1	Low	93%
2-3	Intermediate	79%
4-6	High	63%
7-10	Very High	23%

International CLL-IPI Working Group, Lancet Oncology 2016

Why Don't We Treat at Diagnosis?

- CLL is frequently asymptomatic and cannot be cured so why expose patients to treatment side effects sooner than needed?
- Early treatment with chemotherapy does not help patients with CLL live any longer or any better
- Multiple clinical trials have investigated this question—none yet have shown a survival advantage to early treatment
- This remains a question of interest, especially with advances in prognosis (so high-risk patients can be targeted) and with newer better tolerated therapies

Ms. Jones after 5 years

- Ms. Jones has done well over the last 5 years. Disease assessment at diagnosis had shown Trisomy 12 and IGHV was unmutated
- She is feeling fatigued and has early satiety. Exam reveals a palpable spleen 8 cm below costal margin
- Blood work, besides showing continued increase in WBC count, now shows a low Hb of 8.9g/dL

Indications for Therapy

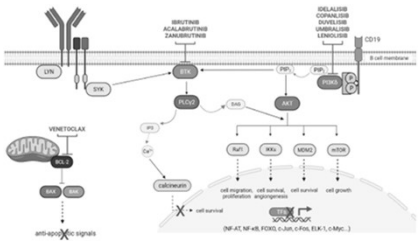
Category	Reasons for Treatment
CLL-related symptoms	• Significant B symptoms (eg, night sweats, weight loss, fever without infection, severe fatigue)
Tumor burden	• Progressive lymphadenopathy • Progressive splenomegaly Lymphocyte doubling time <6 months (if ALC >30 x 10^9/L) • Threatened end-organ function (eg, enlarged lymph node obstructing biliary tree)
Bone marrow failure	• Progressive anemia (Hgb <11 mg/dL) • Progressive thrombocytopenia (platelets <100K)
Immune dysfunction	• Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy

How to Approach Selecting Initial Treatment

- Disease features and predicted benefit from therapy
  - Del17p
  - IGHV mutation status
- Consider patient fitness
  - Age and performance status
  - Medical comorbidities and organ function
  - Specific toxicities of relevance to that person

NO CHEMOTHERAPY ANYMORE

Major Mechanisms of Action of Current CLL Therapies

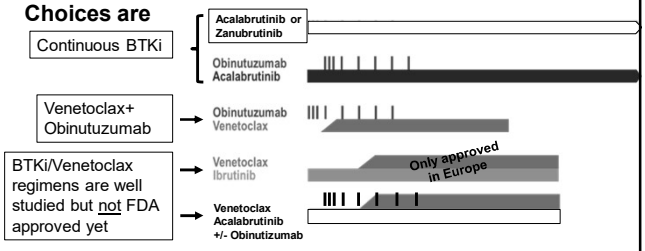


Two major classes of drugs:

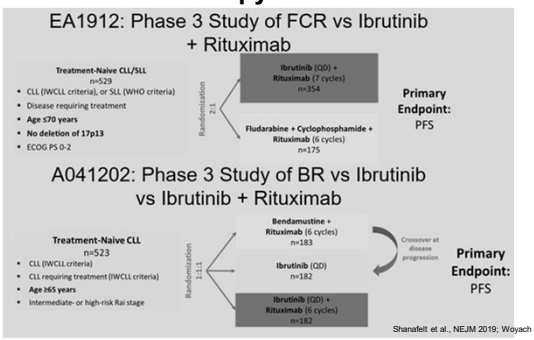
- **BTK inhibitors (ibrutinib, acalabrutinib and zanubrutinib**)
  - ✓ Inhibits B-cell receptor signaling as a pro-survival signal
  - ✓ Need to be taken long-term
- **BCL2 inhibitors (venetoclax)**
  - ✓ Induces apoptosis by inhibiting an anti-apoptotic protein
  - ✓ Causes acute TLS but eliminates disease more rapidly

First-line Regimens in CLL

Choices are



Chemoimmunotherapy vs Ibrutinib



Shanafelt et al., NEJM 2019; Woyach et al., NEJM 2018

Outstanding Efficacy

EA1912 Progression-Free Survival

- With a median follow-up of >8 years, median PFS has not been reached for the ibrutinib arm
- IR improved PFS relative to FCR in patients with both IGHV gene mutated CLL and IGHV unmutated CLL
- Among the 352 patients randomized to IR, 149 (42.3%) currently remain on ibrutinib

A041202 Progression-Free Survival

- With a median follow-up of 55 months, the median PFS was 44 months for BR and not yet reached in either ibrutinib-containing arm
- The 48-month PFS estimates were 47%, 76%, and 76% for BR, ibrutinib, and IR, respectively
- The benefit of ibrutinib regimens over chemoimmunotherapy was consistent across subgroups of patients defined by *TP53* abnormalities, del(11q), complex karyotype, and IGHV mutation

Shanafelt et al., Blood Advances 2025, Woyach et al. Blood 2024

FCR vs IR in IGHV Mutated Patients: E1912

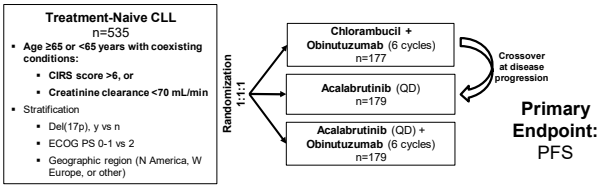
Progression-Free Survival

- After 6 years of median follow up the PFS with IR was significantly longer in IGHV mutated patients with an HR of 0.27 and a P value of 0.001
- This means FCR should not really be used

Shanafelt et al., Blood 2022

ELEVATE-TN: Randomized Phase 3 with Acalabrutinib

- Older and less fit patients
- Randomized comparison to chlorambucil/obinutuzumab
- Compared acalabrutinib to acalabrutinib/obinutuzumab



Sharman et al., Lancet 2020

ELEVATE-TN: Frontline Acalabrutinib ± Obinutuzumab vs Chlorambucil + Obinutuzumab

- At a median follow-up of 74.5 months, PFS was significantly prolonged with acalabrutinib monotherapy versus obinutuzumab/chlorambucil (not reached vs 27.8 months) and acalabrutinib/obinutuzumab (NR vs 27.8 months) versus obinutuzumab/chlorambucil; and significantly prolonged with acalabrutinib/obinutuzumab versus acalabrutinib monotherapy
- The estimated 72-month PFS rates were 78% for acalabrutinib/obinutuzumab, 62% for acalabrutinib, and 17% obinutuzumab/chlorambucil. For the 79 patients who crossed over from obinutuzumab/chlorambucil to acalabrutinib monotherapy, median PFS2 (time to second disease progression or death) was NR; estimated 72-months PFS2 rate was 54%
- ORR and complete response (CR) rates were significantly higher with acalabrutinib/obinutuzumab and acalabrutinib monotherapy compared to obinutuzumab/chlorambucil
- ORR and CR rates were also significantly higher with acalabrutinib/obinutuzumab compared to acalabrutinib alone
- Acalabrutinib-treated patients who achieved a CR had longer PFS

Sharman. ASH 2023. Abstr 636.

SEQUOIA: Frontline Zanubrutinib vs Bendamustine/Rituximab

- Open-label, part-randomized phase III trial of **zanubrutinib** for pts with untreated CLL/SLL requiring treatment; aged ≥65 yr or ≥18 yr with comorbidities; unsuitable for FCR treatment-cohort 1, randomized vs **BR** for CLL without del17p
- Zanubrutinib was found to be superior to BR regardless of evaluated cytogenetic abnormalities
- Patients with del(11q), del(13q), trisomy 12, and CKT of at least 3 - all experienced a PFS benefit with zanubrutinib vs the combination

Munir. EHA 2023. Abstr P639. Shadman. ICML 2023. Abstr 154.

CLL14: First-line Obinutuzumab + Venetoclax or Chlorambucil (Time Limited)

- Randomized phase III trial of **venetoclax + obinutuzumab** vs **chlorambucil + obinutuzumab** for patients with previously untreated CLL and coexisting medical conditions (CIRS >6 and/or CrCl <70 mL/min) (N = 432)
- Long-term results of the CLL14 trial show that 53% of previously untreated patients who received fixed duration of the combination of the BCL2 inhibitor venetoclax plus obinutuzumab are still in remission after more than 6 years without therapy
- More than 60% of patients treated with fixed-duration venetoclax plus obinutuzumab have not required the next line of treatment

Al-Sawaf. Nature Commun. 2023;14:2147. Al-Sawaf. EHA 2023. Abstr S145.

Rationale for Combining BTK inhibitor and Venetoclax

- Distinct mechanism of action
- Non-overlapping toxicity profile
- Act on CLL cells in different compartments
- Synergy in preclinical studies

AMPLIFY Study: AV/AVO vs CIT

- AMPLIFY enrolled fit adults with treatment-naive CLL without del(17p) or *TP53* mutation
- Patients were randomly assigned to receive 14 cycles of acalabrutinib plus venetoclax (AV), 14 cycles of AV plus 6 cycles of obinutuzumab (AVO), or investigator's choice of FCR or BR for 6 cycles
- The primary endpoint was IRC-assessed PFS for AV versus FCR/BR
- At a median follow-up of 40.8 months, the trial met its primary endpoint with a statistically significant difference in IRC-assessed PFS observed between the AV arm and the FCR/BR arm
- A significant difference in PFS was also observed for the AVO arm versus FCR/BR
- With censoring of COVID-19 deaths, there still was a significant difference in PFS favoring AV and AVO, compared with FCR/BR

Brown et al., ASH 2024. Abs 1009

Comparison: Firstline Treatment Options

Continuous BTKi

Pros:
- Easy to start and take (oral, limited initial monitoring)
- Highly effective in TP53 disrupted disease
- Number of approved agents provides options

Cons:
- Indefinite duration (adherence)
- Cardiovascular and bleeding adverse events

Venetoclax/Obinutuzumab

Pros:
- 1 year duration
- Less concern for long-term adherence
- Potential for cost saving if 1 yr of therapy is durable
- No cardiovascular side effects

Cons:
- Difficult to start (TLS risk)
- Unsuitable for those with renal disease or unable to tolerate hydration
- Anti-CD20 antibody has risks

Venetoclax/BTKi

Pros:
- Fixed duration + all oral
- Less concern for long-term adherence
- Potential for cost saving if 1 yr of therapy is durable
- ~~No cardiovascular side effects~~

Cons:
- Difficult to start (TLS risk)
- Unsuitable for those with renal disease or unable to tolerate hydration
- ~~Anti-CD20 antibody has risks~~

Which Therapy Is Best Initial Therapy in CLL?

- **There is no single best initial therapy**
- **Multiple factors are important in this evaluation:**
- **Patient-specific factors:** comorbidities: arrhythmia, renal insufficiency; concurrent medications (Drug interactions and overlapping toxicities: ongoing anticoagulation/antiplatelet therapy), Comfort/convenience of administration, Cost, Patient preference, available resources
- **Disease-specific factors**: Disease biology: cytogenetic/molecular features (*TP53* aberrations) and disease presentation (eg, bulky disease, cytopenias)
- **Regimen-specific factors:** continuous vs fixed duration, oral vs combination, Toxicities with specific drugs

1. Shanafelt. Blood. 2022;140:112. 2. Sharman. ASCO 2022. Abstr 7539.
3. Al-Sawaf. EHA 2021. Abstr S146. 4. Tam. Lancet Oncol. 2022;23:1031.