EHA-GBMTA-AHA Hematology Tutorial: New aspects in diagnostic choices and treatment options of hematological malignancies

Session 6: CLL

Self assessment case 1

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Disclosures

Scientific Advisory Board: AbbVie, AstraZeneca, BeiGene, Incyte, Johnsson & Johnsson, Eli-Lilly

Speakers Bureau: Abbvie, AstraZeneca, BeiGene, Hikma, Incyte, Johnsson & Johnsson

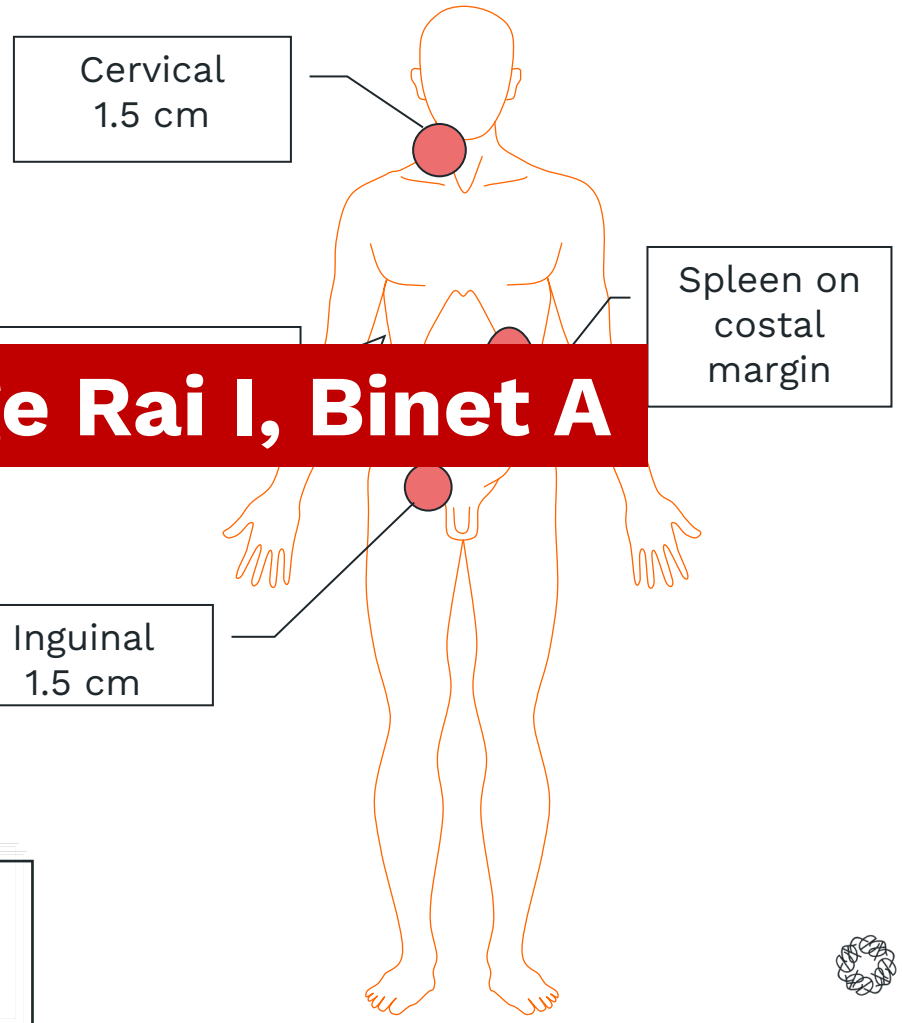
Clinical history: diagnosis

- ✓ Male, 66-years-old at diagnosis
- ✓ Hypertension, hypothyroidism, right carotid artery stenosis
- ✓ Oral daily therapy: ramipril, levothyroxine, cardioaspirin
- ✓ The last routine blood tests prescribed by his general practitioner show lymphocytosis. He is referred to the Hematology division of his town.

Laboratory tests and physical examination

Parameters	Values	Reference values
WBC	19.1 x10^9/l	4.0-10.0 x10^9/l
ALC	**14.3 x10^9/l**	1.0-4.5 x10^9/l
Hb	151 g/l	135-175 g/l
PLT	301 x10^9/l	150-450 x10^9/l
Total bilirubin	11 ∝mol/l	3-22 ∝mol/l
LDH	320 IU/l	208-450 IU/l
IgG	10.61 g/l	6-16 g/l
IgA		
IgM		
B2M	1.8 mg/l	0-2.3 mg/l
HCV serology	Negative	
HIV serology	Negative	
HBsAg	Negative	
HBcAb/HBsAb	Negative	
DAT/IAT (Coombs)	Negative	

Physical examination: no B symptoms, small lymphadenopathies, no hepatosplenomegaly



Asymptomatic CLL, stage Rai I, Binet A

PB film: typical lymphocytes, several smudge cells (Gumprecht)
Markers: CD19+, CD5+, CD23+, CD200+
with low expression of surface Ig

Question 1

Which other tests could be performed to complete the diagnostic assessment in this patient?

1. CT scan

2. Abdominal Ultrasound and chest radiography

3. *TP53* and *IGHV* mutational status

4. Marrow aspiration and biopsy

5. All previous options are correct

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4. Marrow aspiration and biopsy
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Question 2

Which should be the management of this CLL Rai I, Binet A patient?

1. Treat the patient with BTKi immediately

2. Watch and wait strategy

3. Start chemoimmunotherapy with within the next 2 months

4. Discharge the patient

5. All the previous options are incorrect

Question 2

Which should be the management of this CLL Rai I, Binet A patient?

1. Treat the patient with BTKi immediately
2. Watch and wait strategy
3. Start chemoimmunotherapy with within the next 2 months
4. Discharge the patient
5. All the previous options are incorrect

iwCLL guidelines

	General practice
Treat with Rai stage 0	NGI*
Treat with Binet stage A	NGI*
Treat with Binet stage B or Rai stage I or II	Possible*
Treat with Binet stage C or Rai stage III or IV†	Yes
Treatment of active/progressive disease	Yes
Treat without active/progressive disease	No

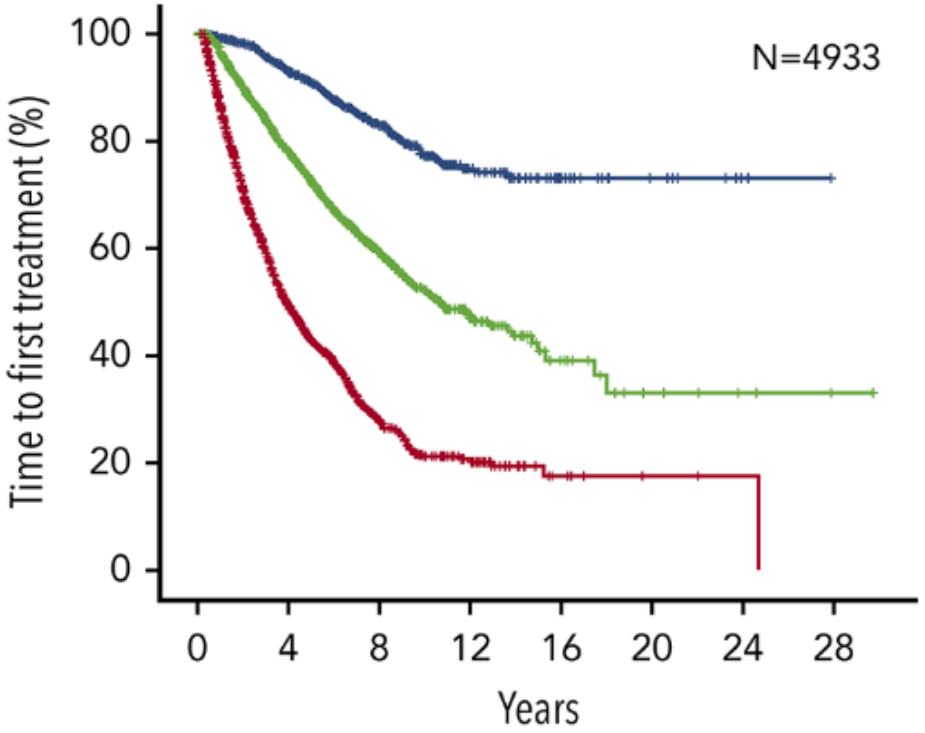
Abbreviations: NGI, not generally indicated

Hallek *et al., Blood*. 2018

IPS-E: a prognostic tool for the assessment of risk of progression in early stage CLL

Variable	Points
IGHV unmutated	1
Lymphocytes >15x10^9/L	1
Nodal involvement	1

Risk group	Score
Low risk	0
Intermediate risk	1
High risk	2-3



Cumulative incidence of treatment

	1 year	5 years
Low risk	<1%	8%
Intermediate risk	3%	28%
High risk	14%	61%

The IPS-E is a simple and robust prognostic model that predicts the **likelihood of treatment requirement** in patients with early-stage CLL and can be used in clinical management and in the design of clinical trials

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Condoluci *et al., Blood*. 2020

Clinical history: progression after watch and wait

Asymptomatic CLL, stage Rai I, Binet A

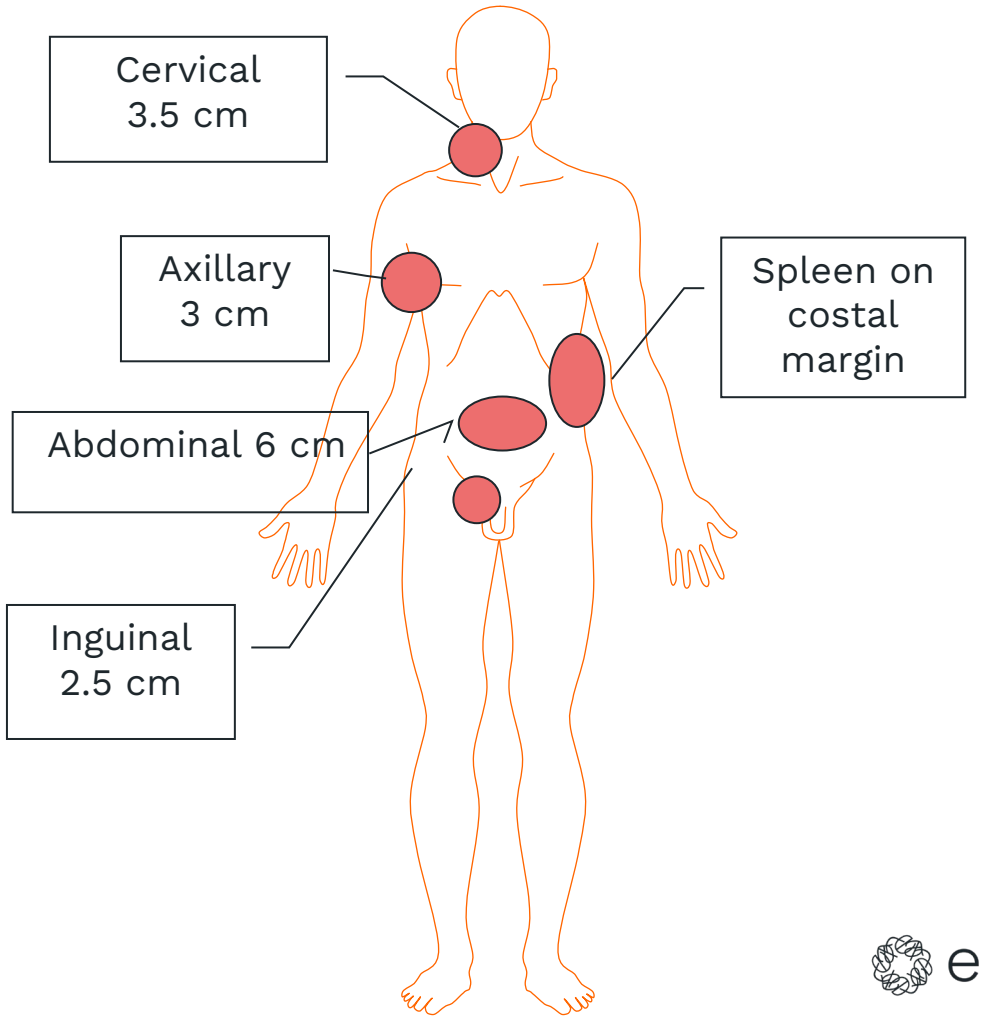
Watchful waiting

5 years later: progressive lymphadenopathies and lymphocytosis, anemia, thrombocytopenia, high LDH, fatigue and weight loss developed

Laboratory tests and physical examination

Parameters	Values	Reference values
WBC	60.5 x10^9/l	4.0-10.0 x10^9/l
ALC	**55.4 x10^9/l**	1.0-4.5 x10^9/l
Hb	104 g/l	135-175 g/l
PLT	**69 x10^9/l**	150-450 x10^9/l
Total bilirubin	10 ∝mol/l	3-22 ∝mol/l
LDH	**651 IU/l**	208-450 IU/l
IgG	7.42 g/l	6-16 g/l
IgA	1.2 g/l	0.9-4.5 g/l
IgM	0.8 g/l	0.5-2 g/l
B2M	3.8 mg/l	0-2.3 mg/l
HCV serology	Negative	
HIV serology	Negative	
HBsAg	Negative	
HBcAb/HBsAb	Negative	
DAT/IAT (Coombs)	Negative	

Physical examination and US of the abdomen



Question 3

Considering lab tests and physical examination, which other tests is useful to perform?

1. Only CT scan to exclude Richter Syndrome
2. Only *TP53* and *IGHV* mutational status
3. CT scan and *TP53* and *IGHV* mutational status
4. CT/PET scan and *TP53* and *IGHV* mutational status
5. No further tests are required: immediate treatment with BTKi

Question 3

Considering lab tests and physical examination, which other tests is useful to perform?

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3. CT scan and *TP53* and *IGHV* mutational status
4. CT/PET scan and *TP53* and *IGHV* mutational status
5. No further tests are required: immediate treatment with BTKi

Question 4

How would you analyse *TP53* status in this patient?

1. by flow cytometry
2. by DNA sequencing only
3. by FISH only
4. by FISH and DNA sequencing
5. by immunistochemistry on the bone marrow biopsy

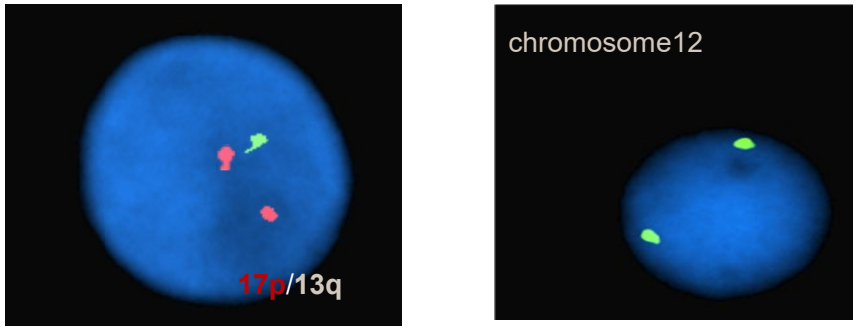
Question 4

How would you analyse *TP53* status in this patient?

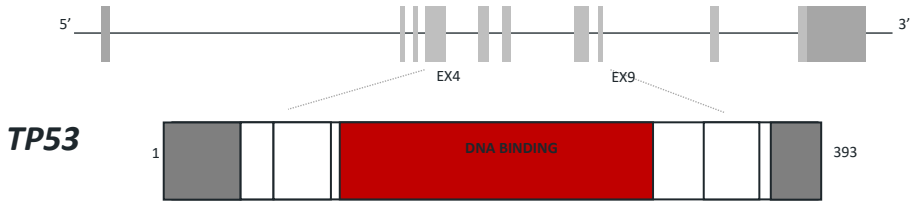
1. by flow cytometry
2. by DNA sequencing only
3. by FISH only
4. by FISH and DNA sequencing
5. by immunistochemistry on the bone marrow biopsy

Biological parameters

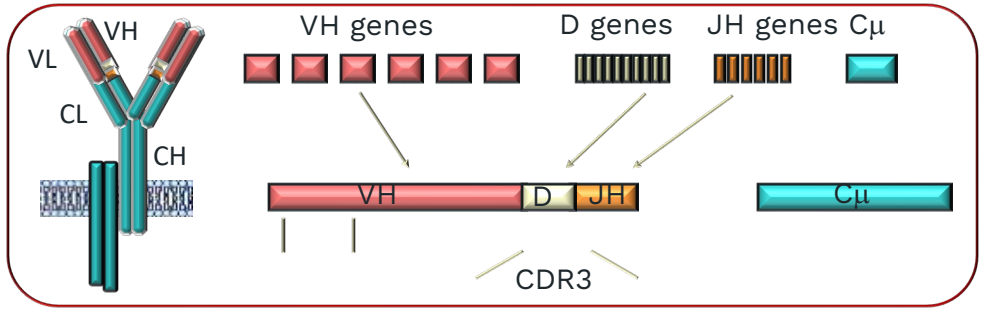
- ✓ Fluorescence *in situ* hybridisation (FISH):
  - ✓ 13q deletion



- ✓ ***TP53* mutational status:**
  - ✓ **Mutated**



- ✓ **Unmutated *IGHV* 4-34*01**



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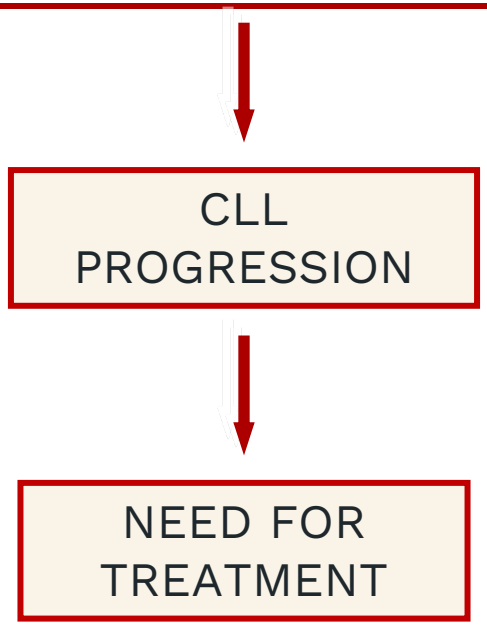
Clinical history: indication for treatment

- 72-years-old CLL patient, Rai IV, Binet C, symptomatic for fatigue, weight loss, progressive lymphadenopathies and thrombocytopenia
- **IGHV unmutated, *TP53* mutated**
- SUVmax at PET/CT scan 3.4



Question 5

Which treatment option for this patient?

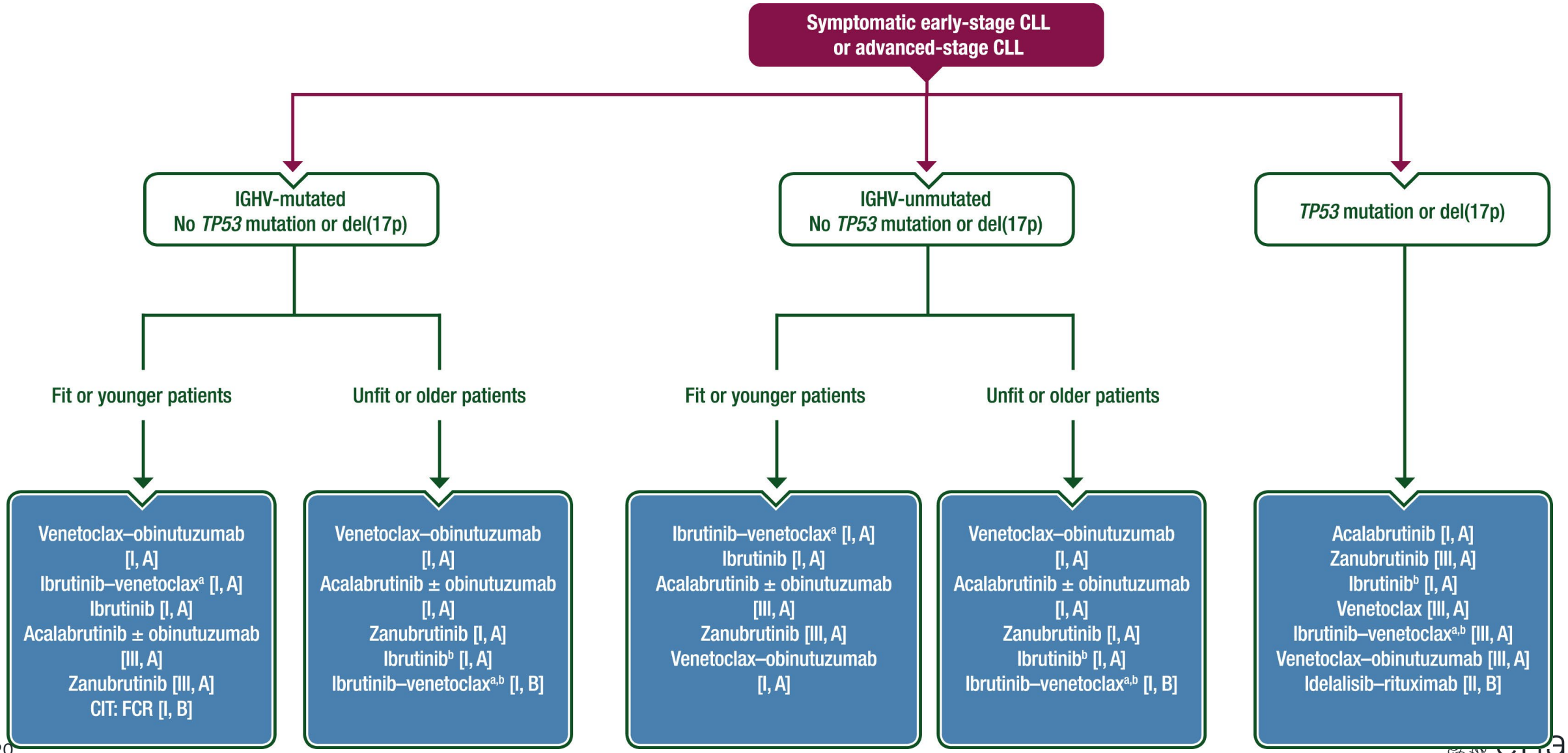
1. Continue watch and wait
2. Obinutuzumab-Venetoclax (Fixed Duration)
3. Ibrutinib – Venetoclax (Fixed Duration)
4. Obinutuzumab-Chlorambucil
5. BTK inhibitor (continuous treatment)

Question 5

Which treatment option for this patient?

1. Continue watch and wait
2. Obinutuzumab-Venetoclax (Fixed Duration)
3. Ibrutinib – Venetoclax (Fixed Duration)
4. Obinutuzumab-Chlorambucil
5. BTK inhibitor (continuous treatment)

ESMO guidelines for first-line treatment



Eichhorst *et al., Ann Oncol*. 2024.

Clinical history: treatment choice

- 72-year old CLL patient, Rai IV, Binet C, symptomatic for fatigue, weight loss, progressive lymphadenopathies and thrombocytopenia
-
- **IGHV unmutated, *TP53* mutated**
- SUVmax at PET/CT scan 3.4

Acalabrutinib 100 mg BID

Laboratory tests and physical examination after 6 months of acalabrutinib

Parameters	Values	Reference values
WBC	8.5 $x10^9$/l	4.0-10.0 $x10^9$/l
ALC	4.4 $x10^9$/l	1.0-4.5 $x10^9$/l
Hb	134 g/l	135-175 g/l
PLT	150 $x10^9$/l	150-450 $x10^9$/l
Total bilirubin	10 ∝mol/l	3-22 ∝mol/l
LDH	230 IU/l	208-450 IU/l
IgG	7.42 g/l	6-16 g/l
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IgM	0.8 g/l	0.5-2 g/l
B2M	3.8 mg/l	0-2.3 mg/l
HCV serology	Negative	
HIV serology	Negative	
HBsAg	Negative	
HBcAb/HBsAb	Negative	
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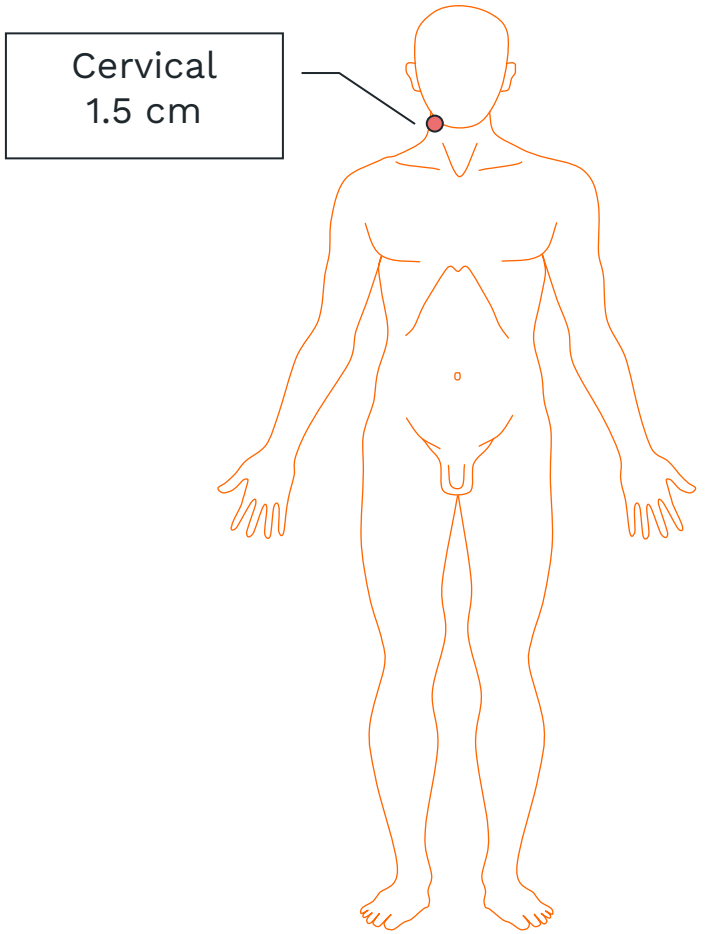
Physical examination and ultrasound of the abdomen



Partial response was obtained

After 12 months of acalabrutinib

- 72-year old CLL patient, Rai IV, Binet C, symptomatic for fatigue, weight loss, progressive lymphadenopathies and thrombocytopenia
-
- **IGHV unmutated, *TP53* mutated**
- SUVmax at PET/CT scan 3.4

Acalabrutinib 100 mg BID

12 months later: gingival bleeding and petechiae (grade 3)

Question 6

Which is your option in this case?

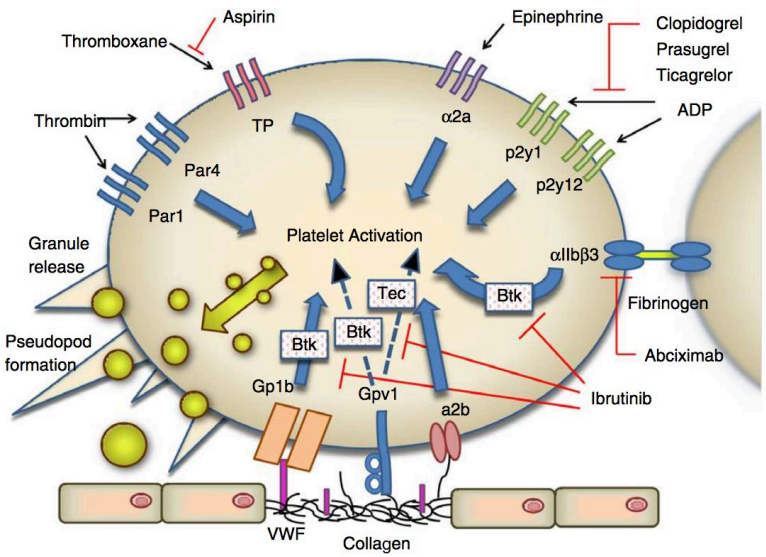
1. Stop Acalabrutinib and switch to Obinutuzumab-Venetoclax
2. Consider acalabrutinib temporary interruption and dose reduction
3. Switch to Obinutuzumab-Chlorambucil
4. Switch to Zanubrutinib
5. Other options

Question 6

Which is your option in this case?

1. Stop Acalabrutinib and switch to Obinutuzumab-Venetoclax
2. Consider acalabrutinib temporary interruption and dose reduction
3. Switch to Obinutuzumab-Chlorambucil
4. Switch to Zanubrutinib
5. Other options

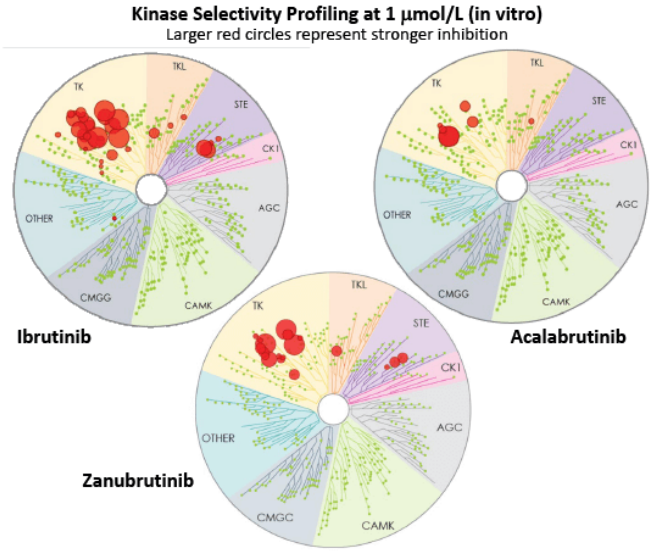
BTKi and bleeding



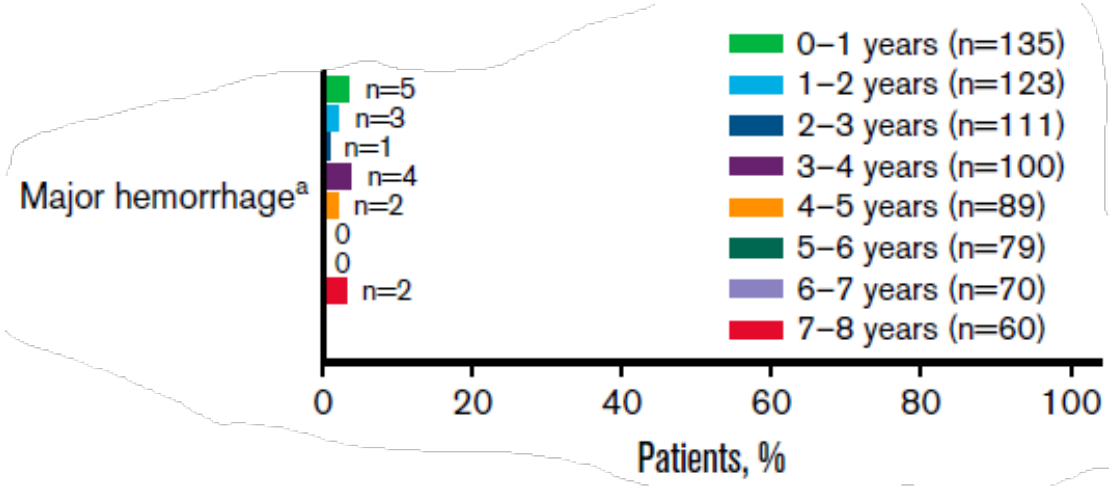
IC_{50}/EC_{50} (nM)

Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	>1000	50
BMX	0.8	46	1.4
EGFR	5.3	>1000	21
ERBB4	3.4	16	6.9
JAK3	32	>1000	1377
BLK	0.1	>1000	2.5

Kaptein. ASH 2018. Abstr 1871.



The increased risk of bleeding is related to the role of BTK and TEC kinases in platelet activation downstream of the collagen receptor glycoprotein VI



Major hemorrhage episodes are uncommon in patients under BTKi. 2nd generation BTKi causes less bleeding. **Vast majority of bleeding events represent minor grade AEs**

Concurrent medication with a single direct oral anticoagulant or antiplatelet agent does not represent a contraindication for acalabrutinib administration

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Schatzel *et al., J Thromb Haemost*. 2017; Barr *et al.*, *Blood Adv*. 2022.

Acalabrutinib: Recommended Dose Adjustments for Adverse Reactions

Dose modifications are specified for occurrence of the following Grade ≥3 adverse events

- Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia
- Grade 4 neutropenia lasting longer than 7 days
- Grade 3 or greater non-haematological toxicities

	Dose Modification
First and second occurrence	• Interrupt Acalabrutinib • Once toxicity has resolved to Grade 1 or baseline, Acalabrutinib may be resumed at 100 mg approximately every 12 hours
Third occurrence	• Interrupt Acalabrutinib • Once toxicity has resolved to take Grade 1 or baseline, Acalabrutinib may be resumed at a reduced frequency of 100 mg once daily
Fourth occurrence	• Discontinue Acalabrutinib

Discussion points

- ✓ CLL staging according to iwCLL guidelines is based on history, physical examination, and CBC
- ✓ Chest X-ray and abdominal US at diagnosis are optional, though used in many centers
- ✓ Trials anticipating treatment have shown no overall survival benefit
- ✓ Second generation BTK inhibitors should be preferred over ibrutinib for continuous treatment
- ✓ Access (availability + affordability) to novel medicines may prevent full implementation of ESMO guidelines in specific geographic contexts

Take home messages

- ✓ Indications for starting CLL treatment should be according to iwCLL guidelines
- ✓ Biomarkers (IGHV, *TP53*) represent decisional nodes for choosing first line treatment
- ✓ Chemoimmunotherapy has no longer a role in CLL provided that access to pathway inhibitors is fully granted

References

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EHA-GBMTA-AHA Hematology Tutorial: New aspects in diagnostic choices and treatment options of hematological malignancies

Session 6: CLL

Self assessment case 2

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Speakers Bureau: Abbvie, AstraZeneca, BeiGene, Hikma, Incyte, Johnsson & Johnsson

Clinical history

- ✓ Male, 45-years-old
- ✓ Asymtomatic. Unremarkable medical history
- ✓ He was a blood donor till the identification of lymphocytosis before one blood donation. He was referred to our institution for further work up. Flow cytometry identified 7 x 10^9/l monoclonal CD19+, CD5+, CD23+ lymphocytes
- ✓ Diagnosis of CLL (Rai 0/Binet A) in 2007

Clinical history: 3 years later

Asymptomatic CLL, stage Rai 0/Binet A

Watchful waiting

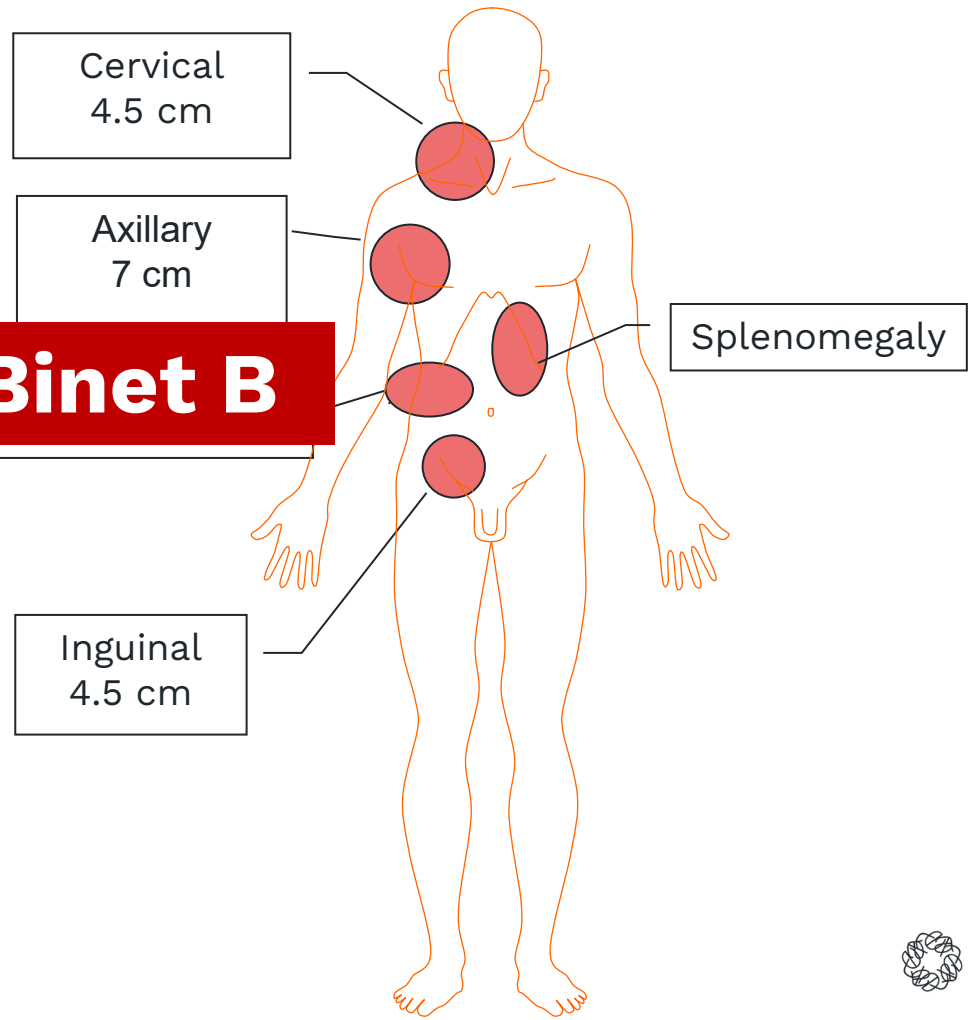
3 years later: lymphadenopathy, splenomegaly, hepatomegaly, night sweats, fatigue, weight loss

Laboratory tests and physical examination

Laboratory tests

Parameters	Values	Reference values
WBC	94.8 x10^9/l	4.0-10.0 x10^9/l
ALC	**88.8 x10^9/l**	1.0-4.5 x10^9/l
Hb	120 g/l	135-175 g/l
PLT	**115 x10^9/l**	150-450 x10^9/l
Total bilirubin	12 µmol/l	3-22 µmol/l
LDH	600 IU/l	
IgG	10.6 g/l	
IgA	0.5 g/l	0.9-4.5 g/l
IgM	0.2 g/l	0.5-2 g/l
B2M	**3.2 mg/l**	0-2.3 mg/l
HCV serology	negative	
HIV serology	negative	
HBsAg	negative	
HBcAb/HBsAb	Negative	
DAT/IAT (Coombs)	negative	

Clinical examination: lymphadenopathy, hepatosplenomegaly



stage Rai II, Binet B

Question 1

Which condition would you consider in your diagnostic reasoning at this time?

1. CLL progression
2. Richter transformation
3. Second neoplasms (solid cancer)
4. All of the above
5. None of the above

Question 1

Which condition would you consider in your diagnostic reasoning at this time?

1. CLL progression
2. Richter transformation
3. Second neoplasms (solid cancer)
4. All of the above
5. None of the above

Question 2

Would you perform a lymph node biopsy in this patient?

1. Yes, at the most accessible site independent of other considerations
2. Yes, preferentially at the site with the highest SUV after performing PET
3. Yes, but only if LDH is elevated
4. Possibly yes, but only in young and fit patients
5. No, because the patient is treatment naïve

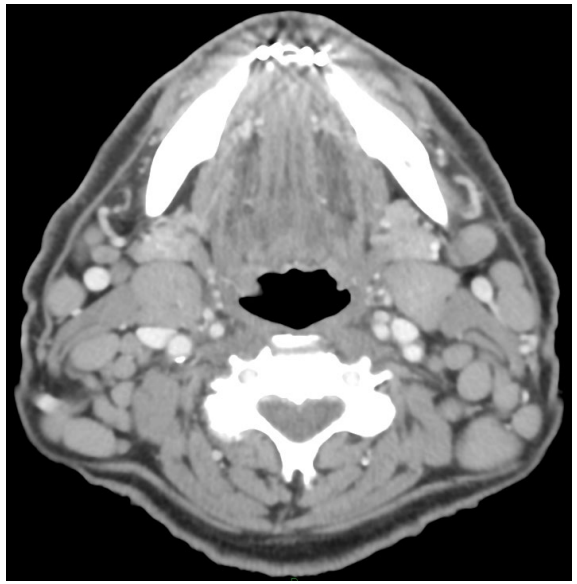
Question 2

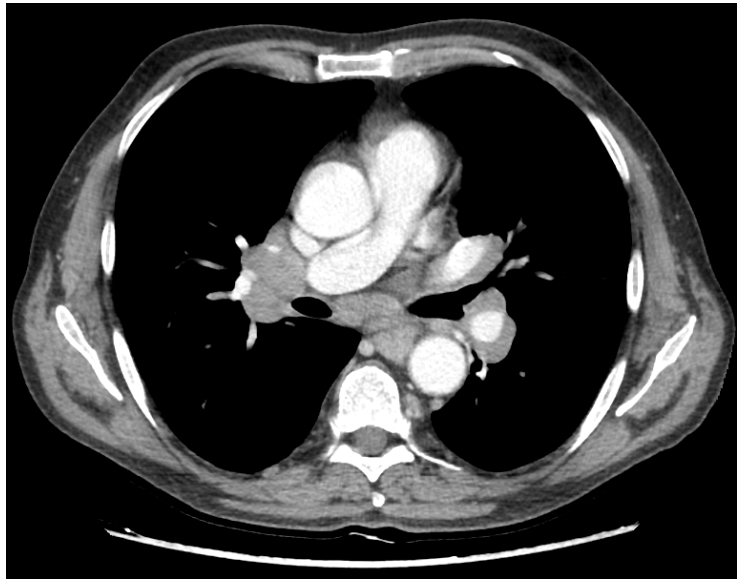
Would you perform a lymph node biopsy in this patient?

1. Yes, at the most accessible site independent of other considerations
2. Yes, preferentially at the site with the highest SUV after performing PET
3. Yes, but only if LDH is elevated
4. Possibly yes, but only in young and fit patients
5. No, because the patient is treatment naïve

Diagnostic imaging evaluation

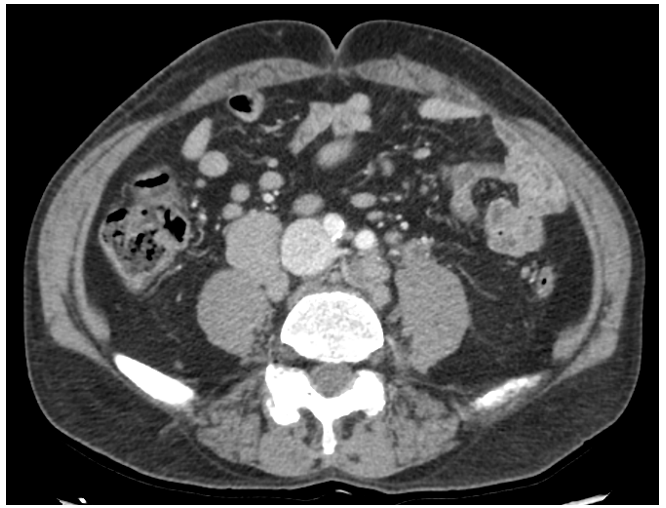
Lymph node biopsy: massive infiltration by small B lymphocytes CD5+CD23+





CT-PET: SUV <10; no evidence of transformation to aggressive disease

CT: lymphadenopathy – 5-8 cm nodes at multiple sites, hepatosplenomegaly



Clinical history: indication for treatment

CLL Rai II/Binet B, symptomatic with B symptoms, nodal progression, hepatomegaly and splenomegaly

NEED FOR TREATMENT

iwCLL guidelines for treatment initiation

	General practice
Treat with Rai stage 0	NGI*
Treat with Binet stage A	NGI*
Treat with Binet stage B or Rai stage I or II	Possible* If active disease
Treat with Binet stage C or Rai stage III or IV†	Yes
Treatment of active/progressive disease	Yes
Treat without active/progressive disease	No

Abbreviations: NGI, not generally indicated

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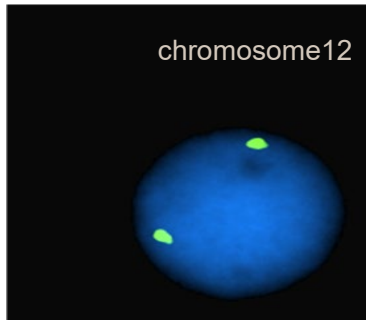
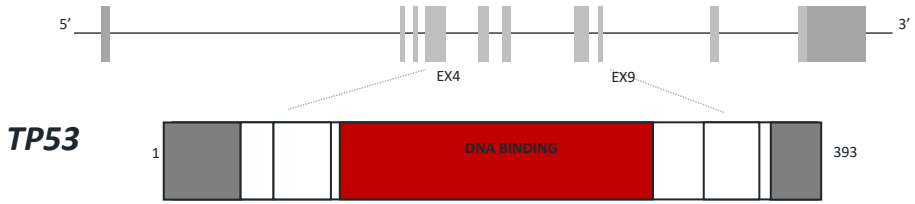
Hallek *et al., Blood*. 2018

Biomarkers status in the patient

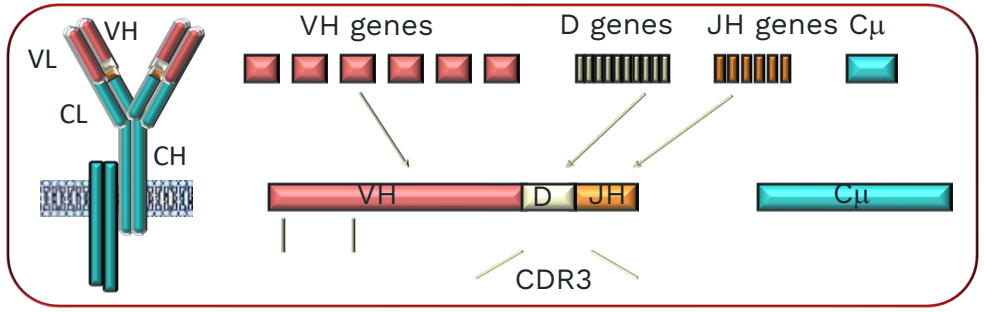
- ✓ Fluorescence *in situ* hybridisation (FISH):
  - ✓ Negative



- ✓ *TP53* mutational status:
  - ✓ Wild type (no mutation)



- ✓ Unmutated *IGHV* 4-39/IGHD6-13/IGHJ5 (subset #8)



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Question 3

What would be your treatment choice in this patient in the pathway inhibitor era?

1. BR (bendamustine + rituximab)
2. Idelalisib + rituximab
3. A 2nd generation BTKi (e.g. acalabrutinib or zanubrutinib)
4. Ibrutinib + venetoclax (fixed duration)
5. None of the above

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What would be your treatment choice in this patient in the pathway inhibitor era?

1. BR (bendamustine + rituximab)
2. Idelalisib + rituximab
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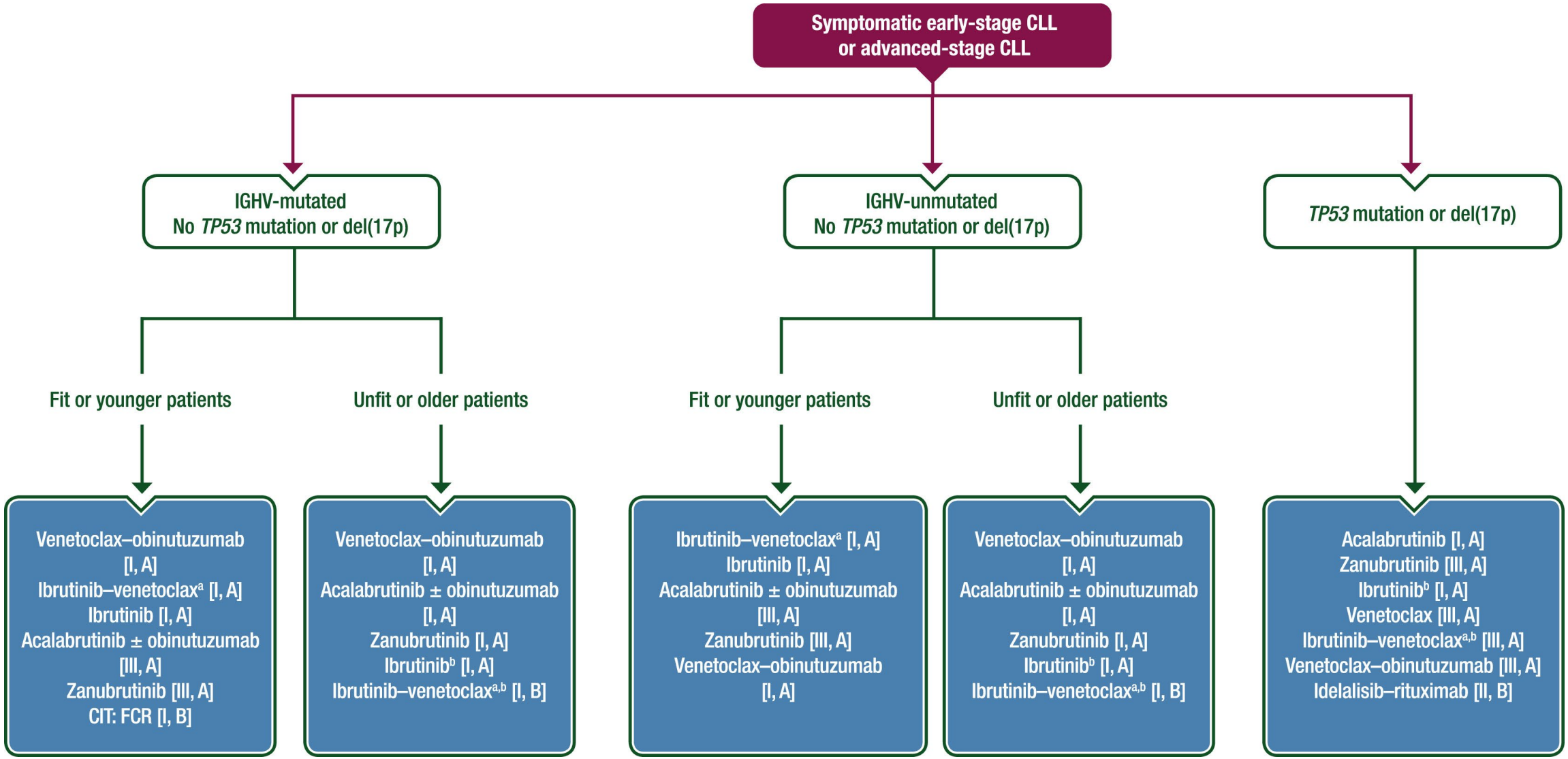
4. Ibrutinib + venetoclax (fixed duration)
5. None of the above

ESMO guidelines for first-line treatment

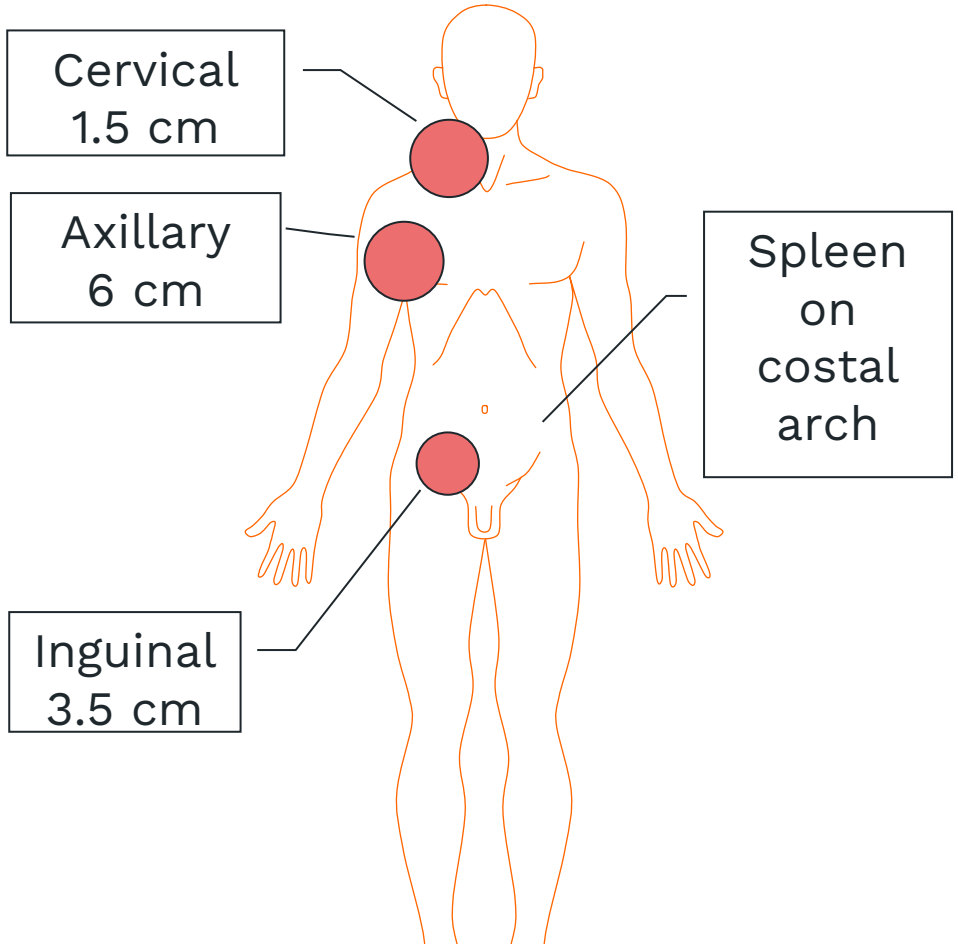


eha

Eichhorst *et al., Ann Oncol*. 2024.

Clinical history

The patient was in remission for two years. At restaging during follow up, presence of progressive and symptomatic axillary lymphadenopaty; presence of elevated LDH



Question 4

When Richter transformation is suspected, what is the best approach?

1. Perform a lymph node FNA
2. Perform a CT/PET scan
3. Treat the patient with high dose therapy without performing a biopsy
4. Any of the above
5. None of the above

Question 4

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Question 5

Which test may be important to evaluate the prognosis and may help in the choice of the correct therapy for Richter transformation?

1. Define the Rai stage of the CLL phase
2. Test for the presence of t(8:14) in the Richter biopsy
3. Define the clonal relationship between Richter transformation and the CLL phase
4. Test the percentage of Ki-67 expression in the Richter biopsy
5. None of the above

Question 5

Which test may be important to evaluate the prognosis and may help in the choice of the correct therapy for Richter transformation?

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3. Define the clonal relationship between Richter transformation and the CLL phase
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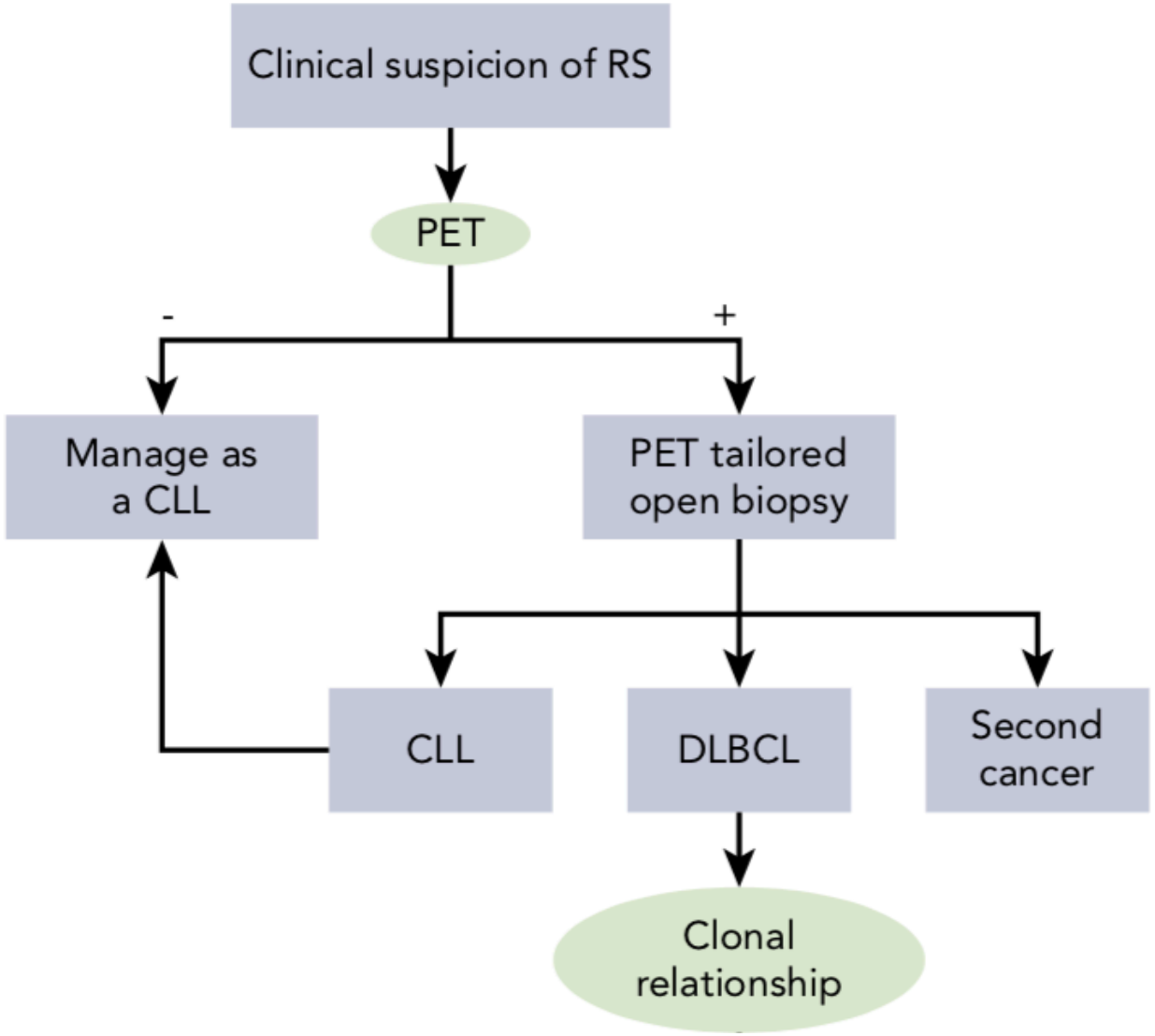
5. None of the above

Management of Richter transformation

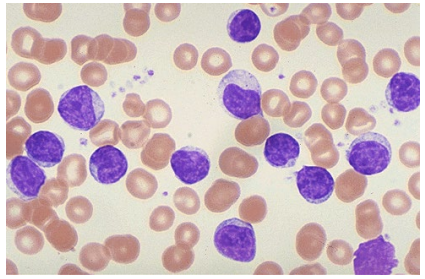


DLBCL, diffuse large B-cell lymphoma

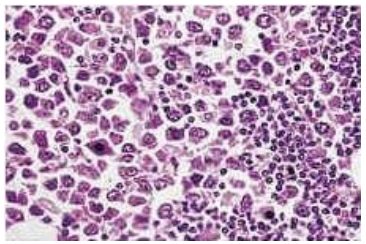
eha

Gaidano and Rossi, *Hematology* 2017; Rossi *et al.*, *Blood*. 2018

Management of RS

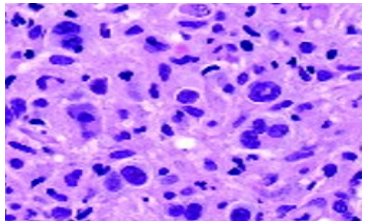


95-99%

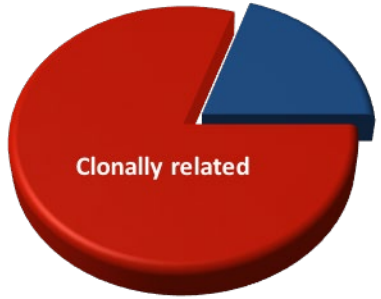


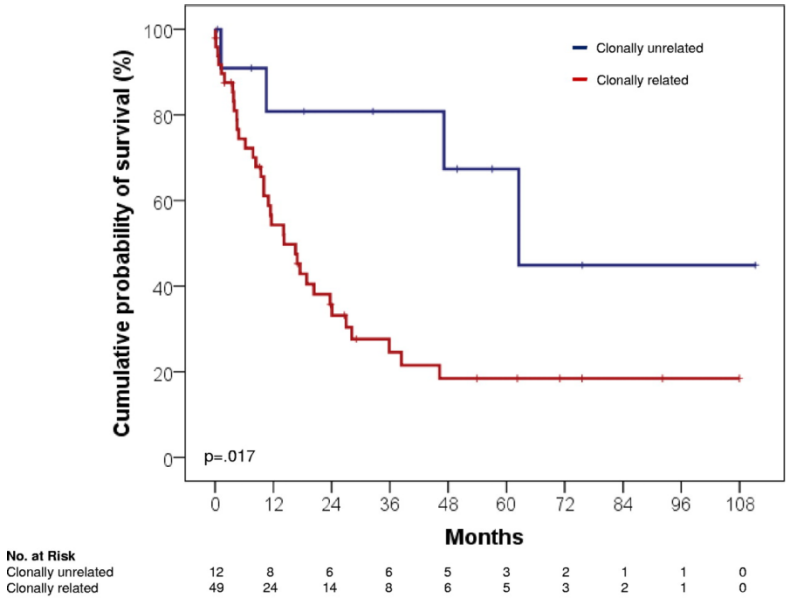
DLBCL

1-5%



HL



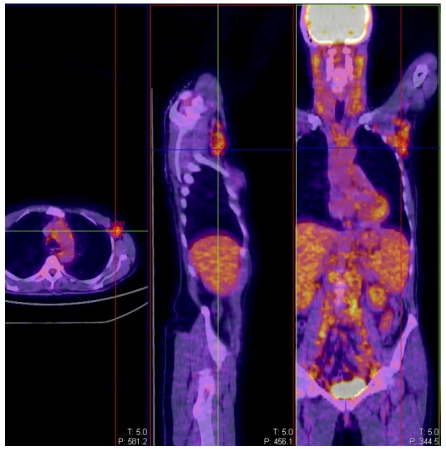


HL, Hodgkin lymphoma

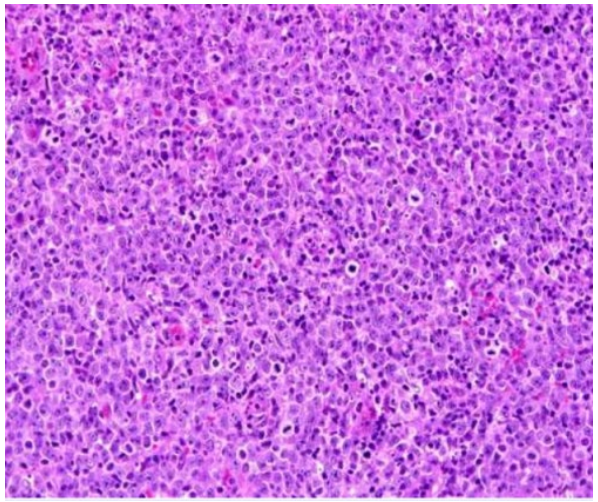
Rossi *et al*., 2011; Swerdlow *et al*., 2016; Gaidano and Rossi, 2017; Rossi *et al,* 2018; Moia *et al*., 2022

Clinical history: diagnosis of Richter transformation

CT/PET documents the presence of axillary lymphadenopathy with SUV = 12



A biopsy of the lymph node was performed and revealed transformation into DLBCL



Immunoglobulin analysis on lymph node biopsy demonstrates the same *IGHV* rearrangement found in the CLL phase

Question 6

In a young patient with clonally-related DLBCL Richter syndrome, the preferred treatment option is:

1. Treat with R-CHOP, followed by a *watch and wait* strategy
2. Treat with venetoclax
3. Treat with bendamustine-rituximab (BR)
4. Treat with a BTKi
5. Enrollment in a clinical trial, followed by transplant if feasible

Question 6

In a young patient with clonally-related DLBCL Richter syndrome, the preferred treatment option is:

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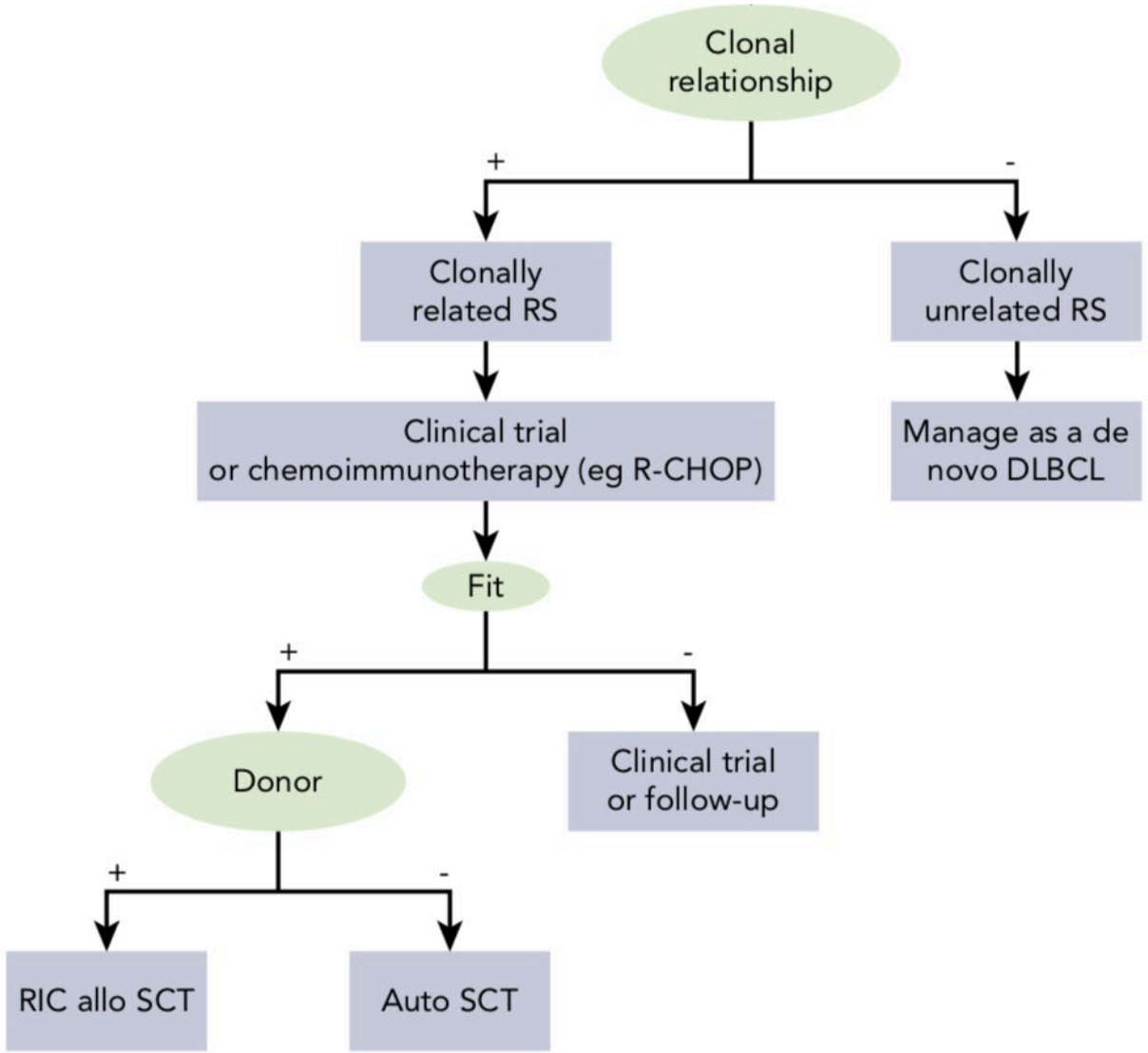
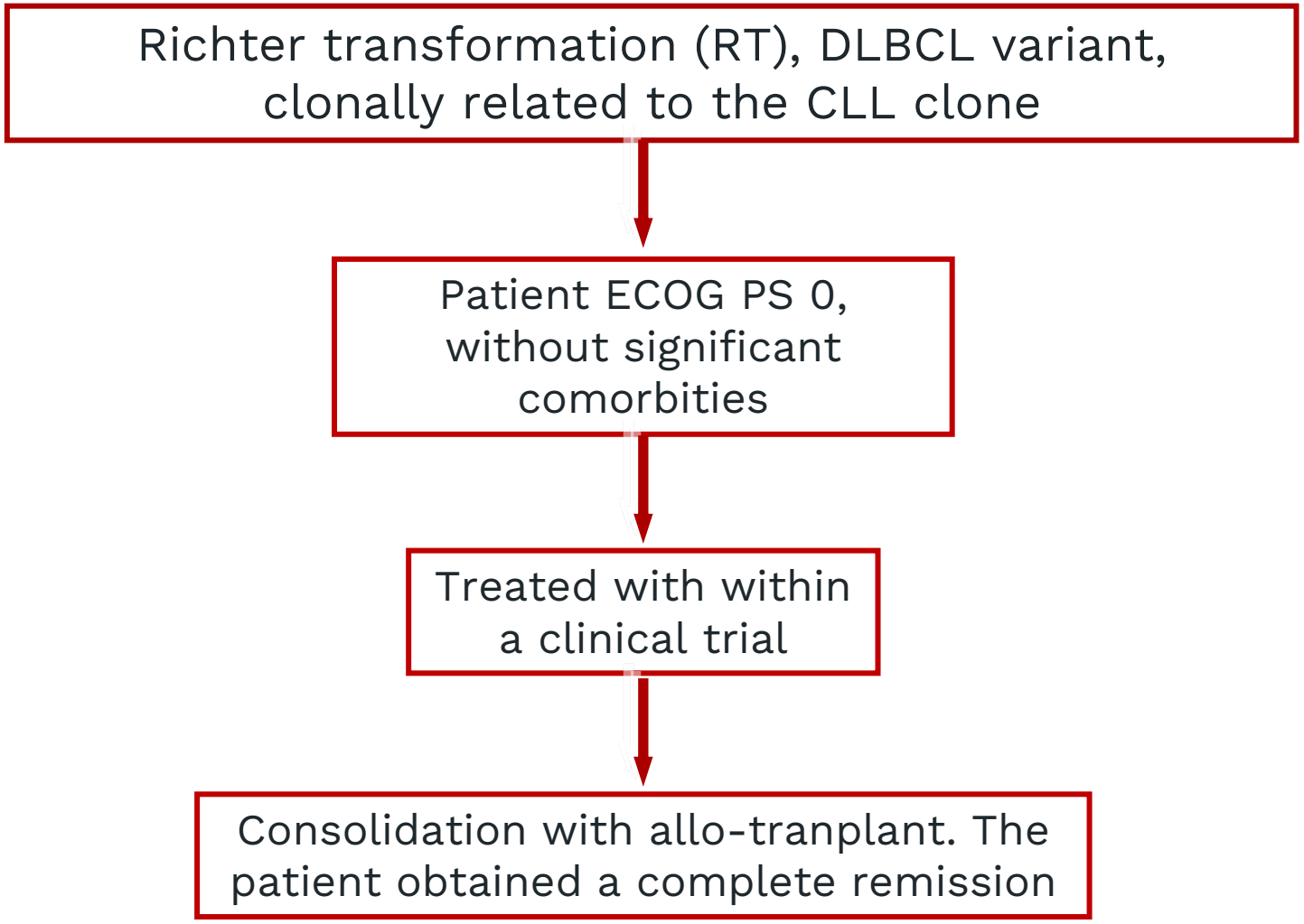
Management of DLBCL-type RS



RIC, reduced intensity conditioning; SCT, stem cell transplant

Gaidano and Rossi, *Hematology* 2017; Rossi *et al., Blood.* 2018, Moia *et al, Br J Haematol.* 2022

Clinical history: management of clonally related RT



Discussion points

- ✓ Need to be suspect and rule out Richter transformation whenever appropriate at CLL progression
- ✓ Importance of testing CLL biomarkers at the time of treatment requirement
- ✓ Role of patients' preferences for continuous versus fixed duration treatment
- ✓ Relevance of pathological review by experienced hematopathologists for the diagnosis of Richter transformation

Take home messages

- ✓ Fixed duration regimens are an emerging option in treatment-naïve CLL requiring treatment
- ✓ The choice of first line treatment is based on molecular predictors, fitness and age
- ✓ PET should guide tissue biopsy whenever Richter transformation is suspected
- ✓ Assessment of clonal relationship between CLL and Richter phase is important for patient management

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