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

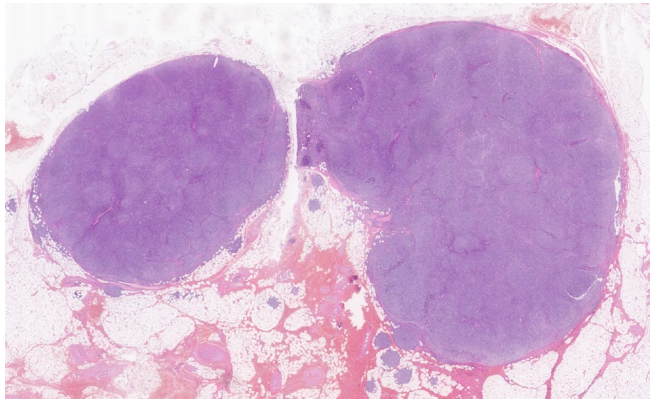
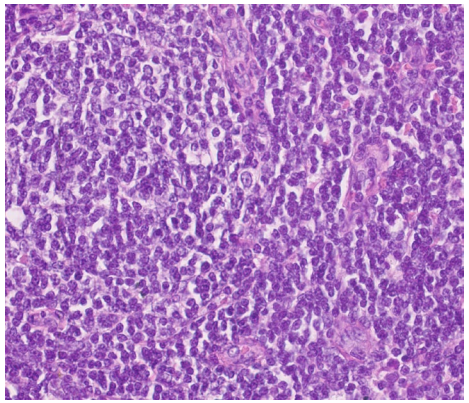
Self-assessment case 1
Session **Indolent Non-Hodgkin Lymphoma**

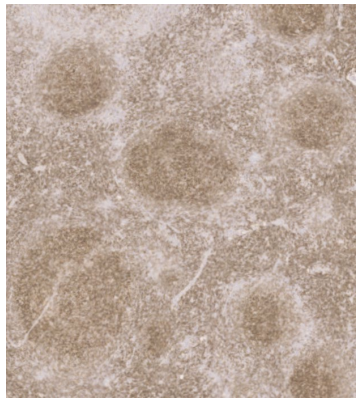
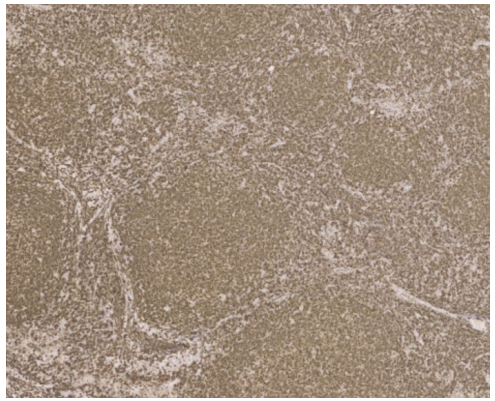
Maria Gomes da Silva

October 18th 2024

Introduction

- A 37-year-old female patient presented in August 2016 with fatigue, lower left limb edema and abdominal pain
- Physical examination
  - → lymphadenopathy (cervical, axillar and left inguinal)
  - → no organomegaly
- Histology of the cervical node:

HE IHC staining

CD2
0

CD1
0

BCL2

Q1) What is the most likely diagnosis?

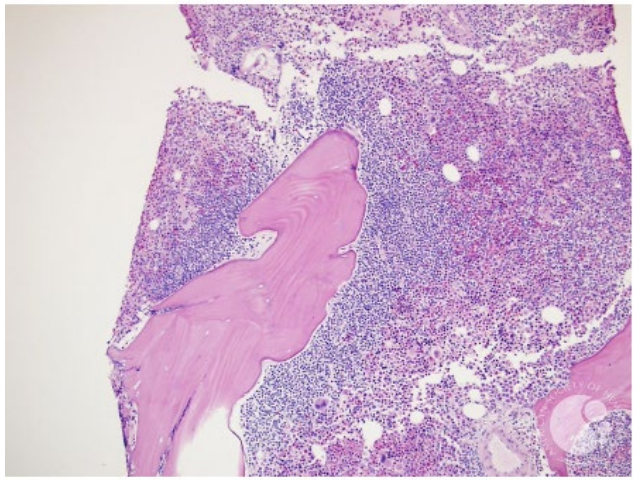
1. Infectious mononucleosis (EBV)
2. Hodgkin lymphoma
3. Follicular lymphoma
4. Diffuse large B-cell lymphoma
5. Peripheral T cell lymphoma

Q1) What is the most likely diagnosis?

1. Infectious mononucleosis (EBV)
2. Hodgkin lymphoma
3. Follicular lymphoma
4. Diffuse large B-cell lymphoma
5. Peripheral T cell lymphoma

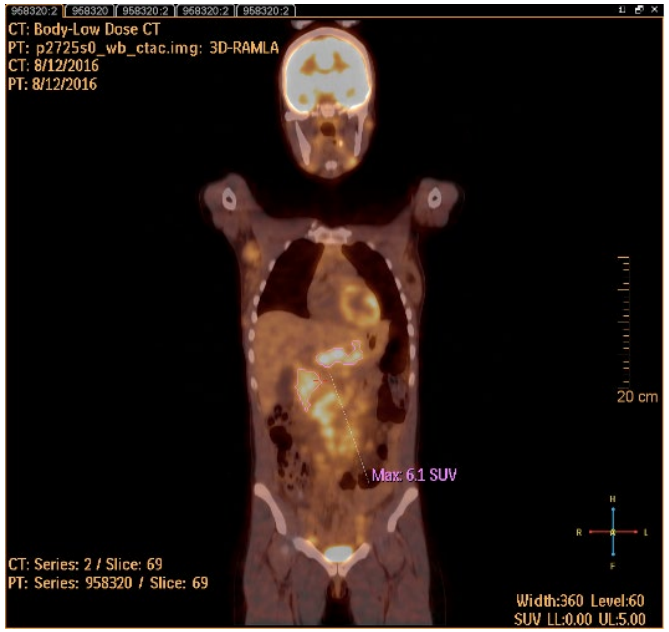
Staging

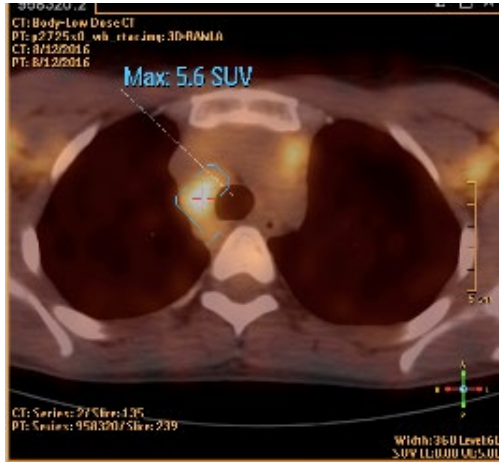
Bone marrow trephine biopsy

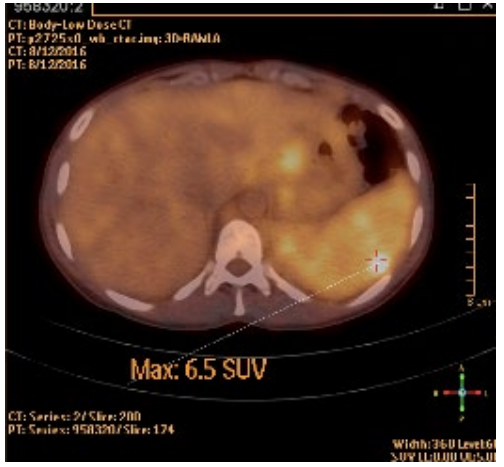


ASH image bank

PET/CT







Ann Arbor stage IV: Based on lymph nodes above and below diaphragm and BM infiltration

Q2) How can prognosis be assessed in this patient?

1. Using the FLIPI index
2. Using the FLIPI 2 index
3. Using the PRIMA-Prognostic index
4. Assessing the disease status at 24 months after treatment initiation
5. All of the above

FLIPI, Follicular Lymphoma International Prognostic Index; PRIMA,

Q2) How can prognosis be assessed in this patient?

1. Using the FLIPI index
2. Using the FLIPI 2 index
3. Using the PRIMA-Prognostic index
4. Assessing the disease status at 24 months after treatment initiation
5. All of the above

Prognostic Indexes in Folicular Lymphoma

Table 4. FLIPI and PRIMA-PI risk factors

Parameter	Definition of risk factors		
	FLIPI 1	FLIPI 2	PRIMA-PI
Nodal sites	>4 LN regions (definition in[5])	Long diameter of largest LN >6 cm	—
Age	>60 years	>60 years	—
Serum marker	Elevated LDH	Elevated B2M	Elevated B2M
Stage	Advanced stage III-IV (Ann Arbor classification)	Bone marrow involvement	Bone marrow involvement
Haemoglobin	<12 g/dl	<12 g/dl	—

FLIPI:
- low risk: 0-1 risk factor.
- intermediate risk: 2 risk factors.
- high risk: 3-5 risk factors.

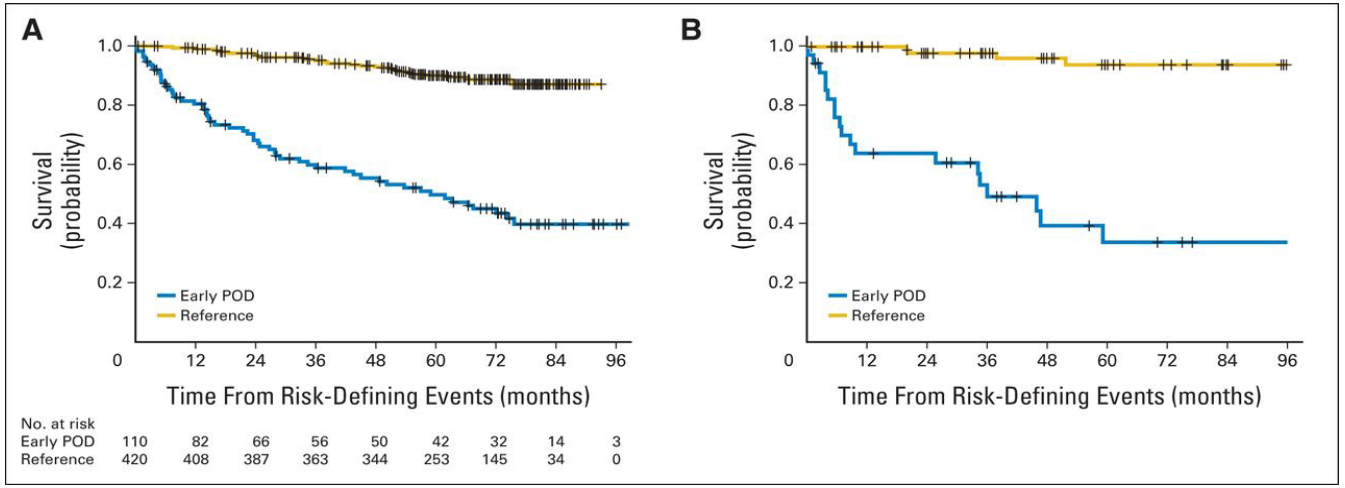
PRIMA-PI:
- low risk: B2M normal and bone marrow not involved.
- intermediate risk: B2M normal and bone marrow involved.
- high risk: B2M elevated.

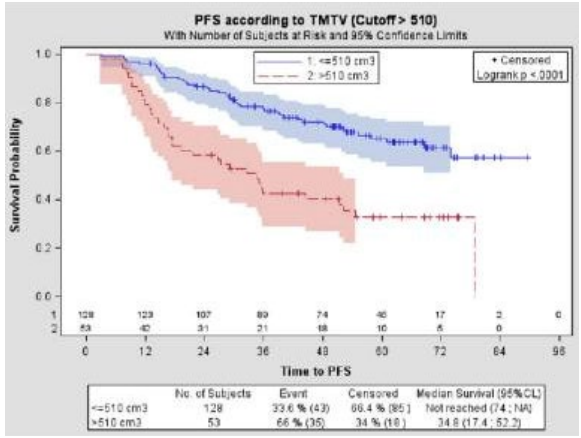
B2M, β2-microglobulin; FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; LN, lymph node; PRIMA-PI, PRIMA prognostic index.

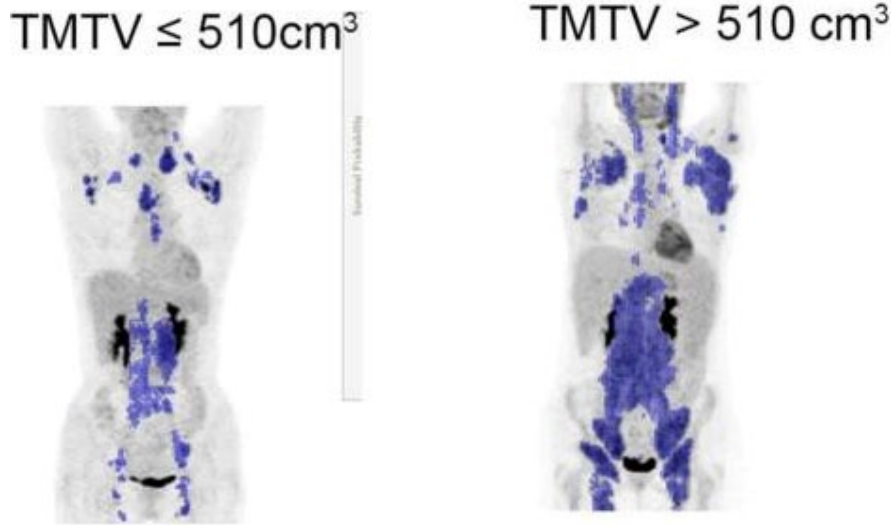
Treatment is not decided on the basis of prognostic indexes
Criteria to start treatement are clinical and related to symptoms and tumor burden (eg. GELF criteria, BNLI criteria)

Dreyling M et al. Ann Oncol 2021, 32(3): 298-308

Other factors affecting the course of follicular lymphoma







Casulo C; Byrtek; M, Dawson KL; et al *Journal of Clinical Oncology* 2015 332516-2522.

Meignan M et al, Br J Radiol. 2021 Nov 1; 94(1127): 20210448.

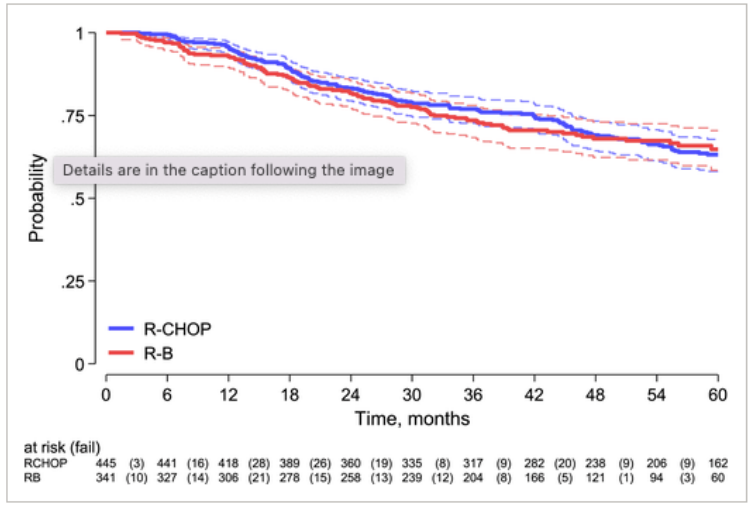
Q3) What treatment do you recommend in this patient (stage IV symptomatic follicular lymphoma)?

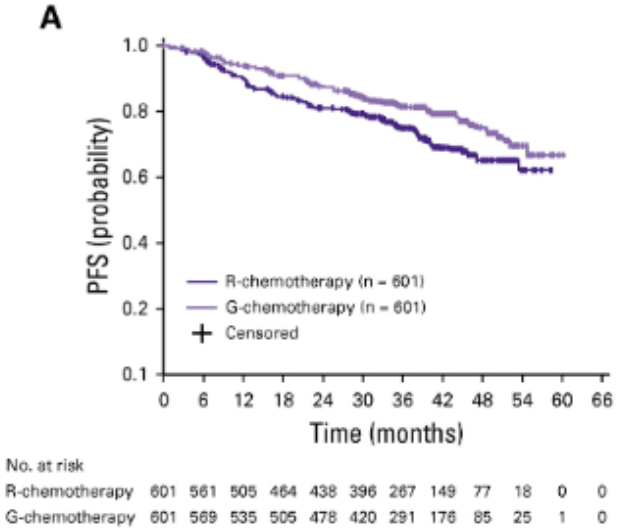
1. Watch and wait
2. Rituximab monotherapy, 4 weekly administrations
3. Oral PI3K (idelalisib) treatment until progression
4. 6 cycles of immunochemotherapy followed by rituximab maintenance
5. Consolidation of first response with high dose chemotherapy and autologous transplant

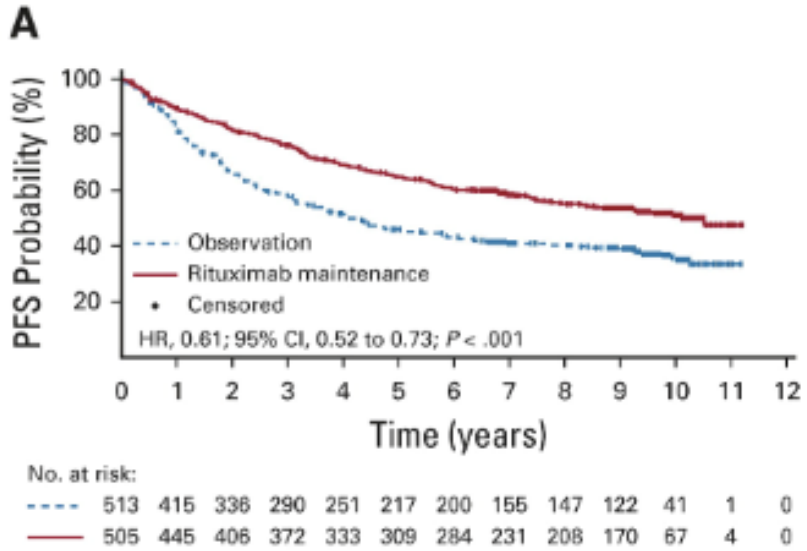
Q3) What treatment do you recommend in this patient (stage IV symptomatic follicular lymphoma)?

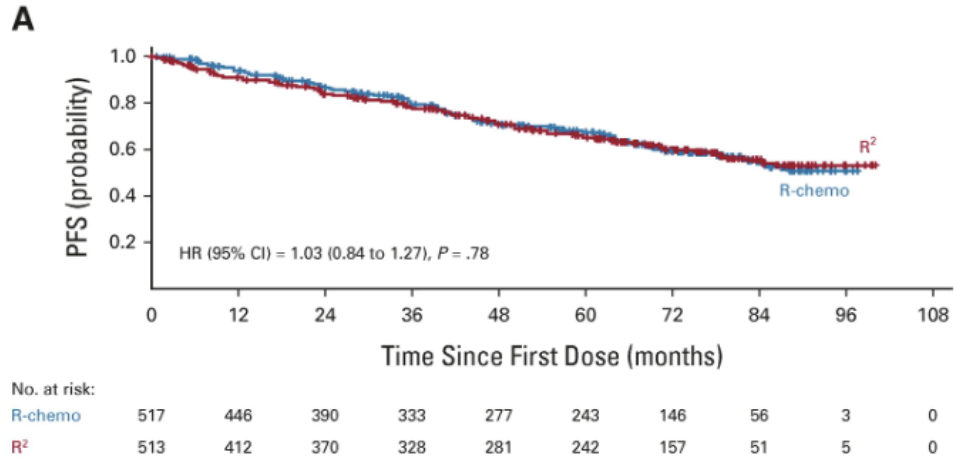
1. Watch and wait
2. Rituximab monotherapy, 4 weekly administrations
3. Oral PI3K (idelalisib) treatment until progression
4. 6 cycles of immunochemotherapy followed by rituximab maintenance
5. Consolidation of first response with high dose chemotherapy and autologous transplant

Treatment outcomes with different regimens









Nizzoli ME, Manni M, Ghiggi C et al. Hematol Oncol. 2023 Oct;41(4):655-662.

Hiddemann W, Barbui AM, Canales MA et al. J Clin Oncol. 2018 Aug 10;36(23):2395-2404..

Bachy E, Seymour JF, Feugier P, et al J Clin Oncol. 2019 Nov 1;37(31):2815-2824.

Morschhauser F, Nastoupil L, Feugier P et al. J Clin Oncol. 2022 Oct 1;40(28):3239-3245.

Q4) How should response be evaluated?

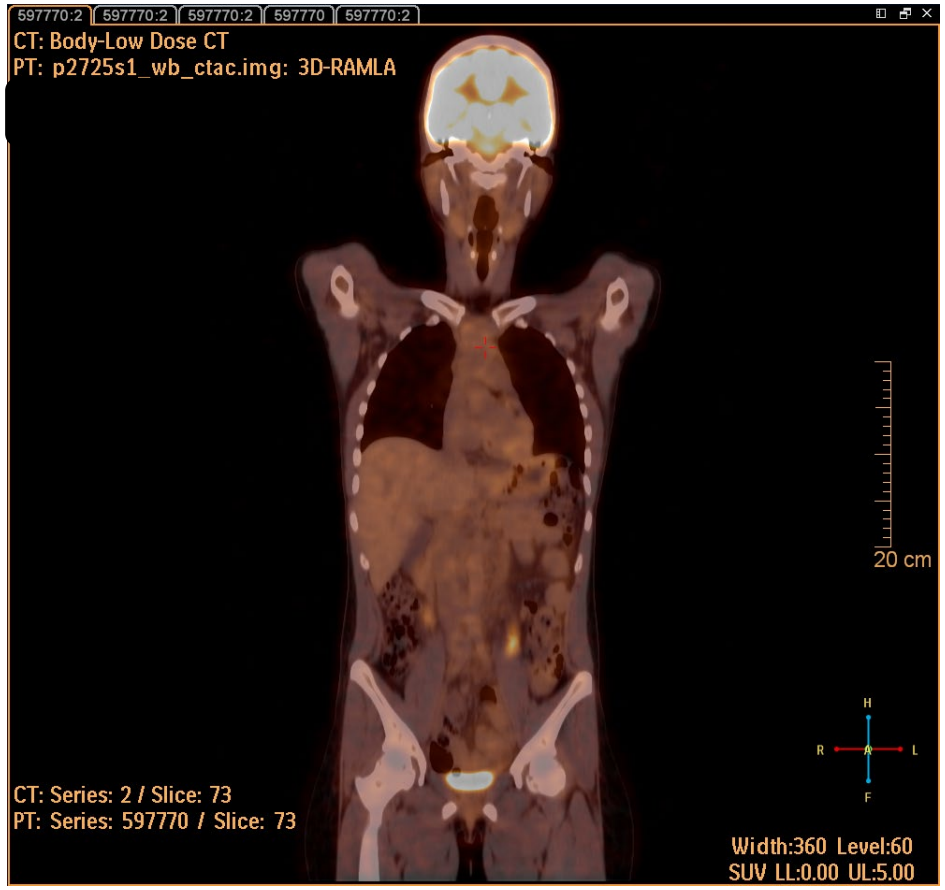
1. Clinically, by physical examination
2. By PET CT (using Deauville score) at the end of induction therapy
3. By CT scan and bone marrow aspirate
4. At regular intervals using CT scan after final response evaluation
5. By ctDNA quantification

Q4) How should response be evaluated?

1. Clinically, by physical examination
2. By PET CT (using Deauville score) at the end of induction therapy
3. By CT scan and bone marrow aspirate
4. At regular intervals using CT scan after final response evaluation
5. By ctDNA quantification

Feedback:
The Lugano classification says that FDG- avid lymphomas (including FL) should be staged and response-evaluated by PET CT
Regular CT scans are are not indicated during surveillance; BM aspirate is not sufficient to assess BM infiltration
ctDNA is not routinely used

Evaluation 6 week after 6 cycles of R CHOP



Deauville score 2:
Complete metabolic remission

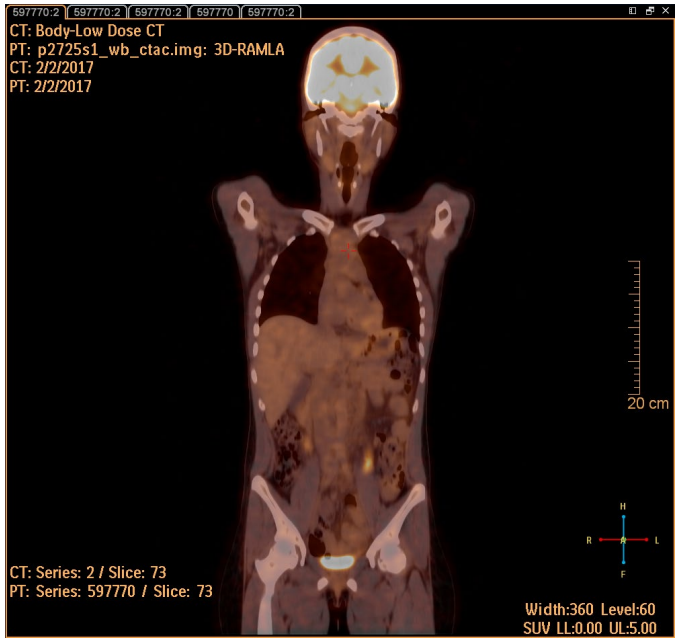
8/2016 1/2017 12/2018 4/2021

Diagnosis

End of induction

End of maintenance

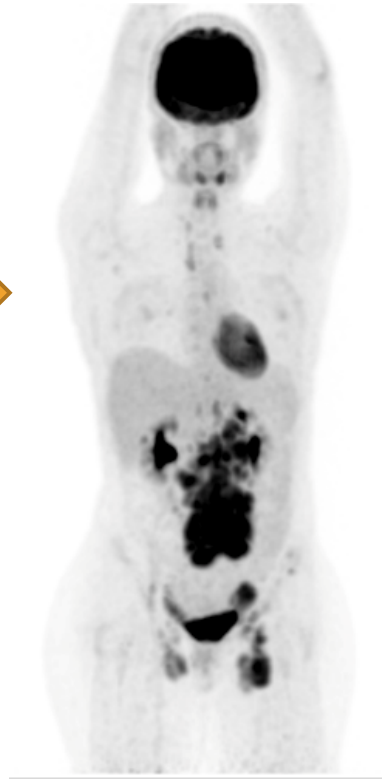
Fatigue
Abdominal pain



Palpable inguinal node
No organomegaly
PS1

Labs
Hb 105 g/L
WBC 6.5 x10^9L
Platelets 230 x10^9L

LDH 350 IU/L
B2M 3.5 mg/dL



Q5) How should we proceed in this patient?

1. Watch and wait
2. Lymph node biopsy
3. Start second line treatment with a platinum-based regimen aiming to autologous stem cell transplant (ASCT)
4. Start second line treatment with rituximab lenalidomide
5. Initiate ibrutinib 420 mg daily until progression

Q5) How should we proceed in this patient?

1. Watch and wait
2. Lymph node biopsy
3. Start second line treatment with a platinum-based regimen aiming to autologous stem cell transplant (ASCT)
4. Start second line treatment with rituximab lenalidomide
5. Initiate ibrutinib 420 mg daily until progression

Feedback:
The patient is symptomatic ⇒ W+W is not an option
Intensive chemotherapy and ASCT has now a limited role and may be discussed in early (<24 months) progressors
Biopsy should be repeated at each relapse due to risk of transformation
Rituximab lenalidomide is approved for relapsed FL (but biopsy should be performed before) while ibrutinib has low acti

8/2016 1/2017 12/2018 4/2021 6/2022

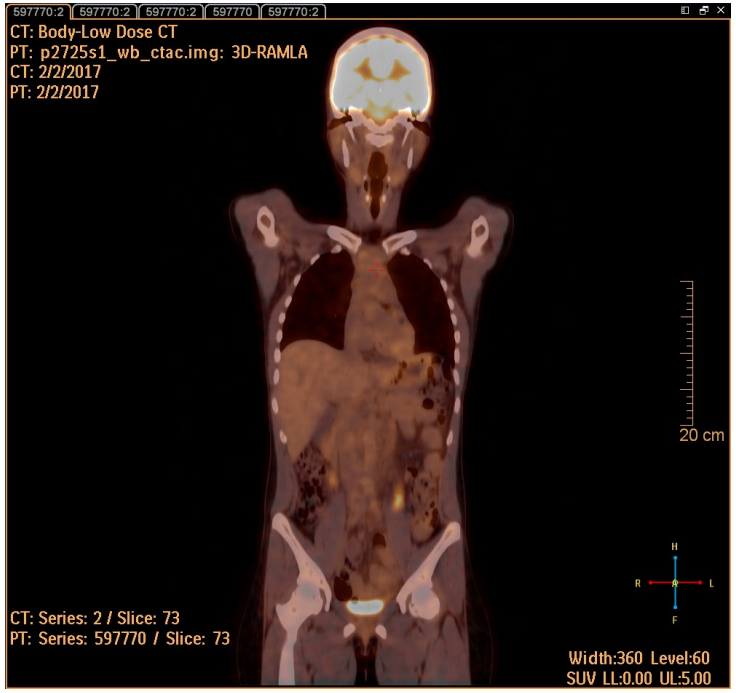
Diagnosis

End of induction

End of maintenance

Fatigue
Abdominal pain

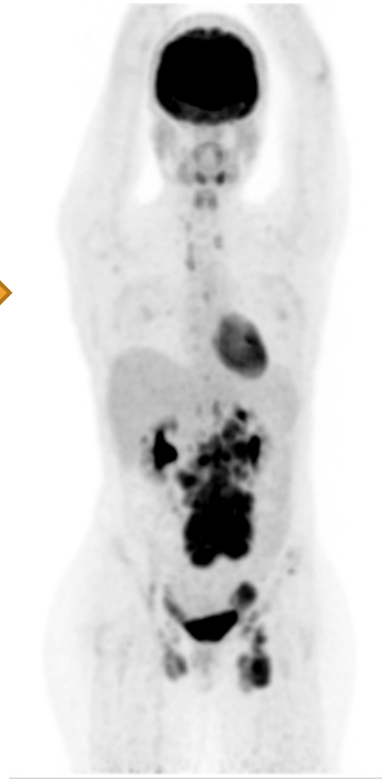
Asymptomatic
Persistant inguinal lymph node
PS1



Palpable inguinal node
No organomegaly
PS1

Labs
Hb 105 g/L
WBC 6.5 $x10^9L$
Platelets 230 $x10^9L$

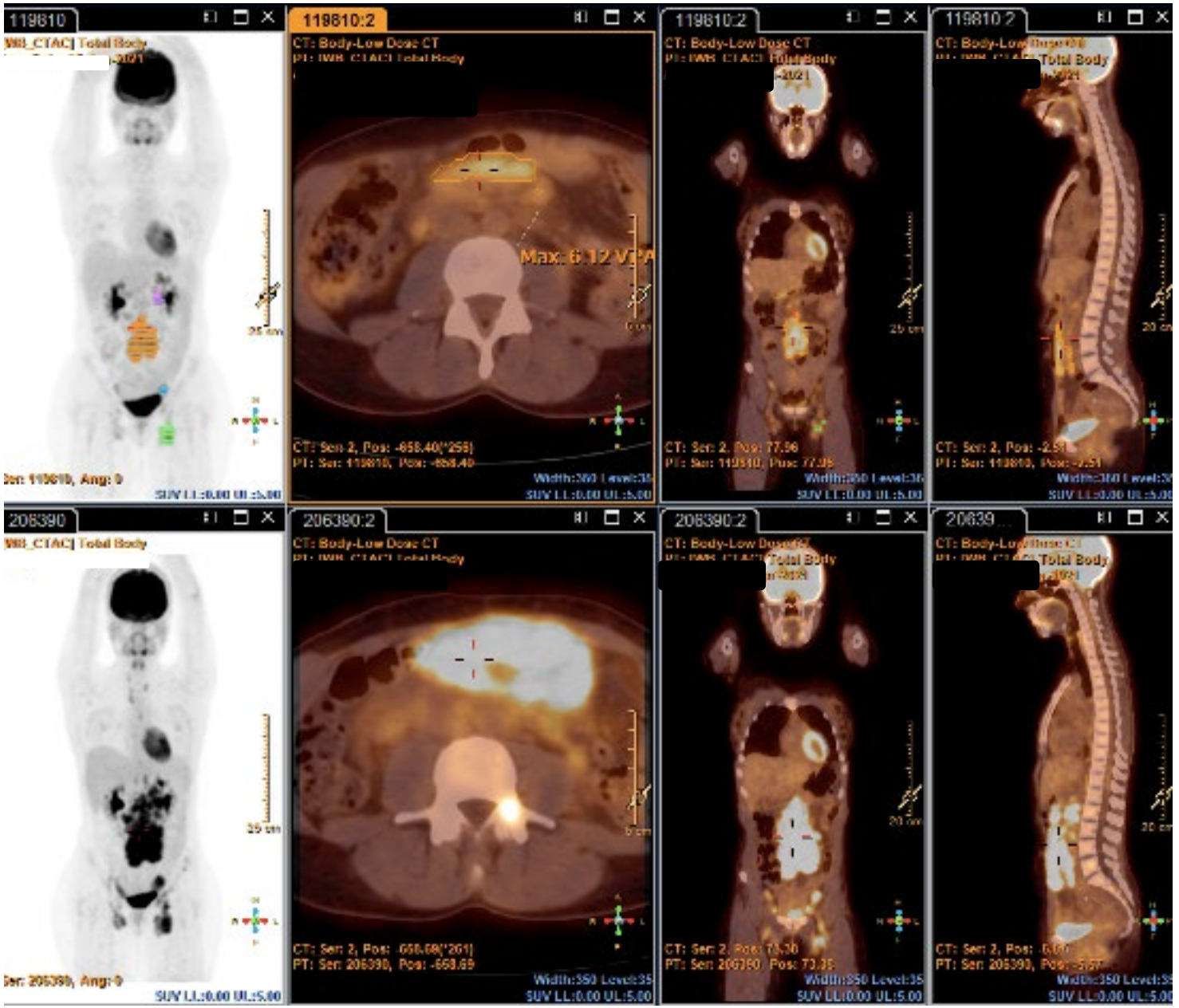
LDH 350 IU/L
B2M 3.5 mg/dL



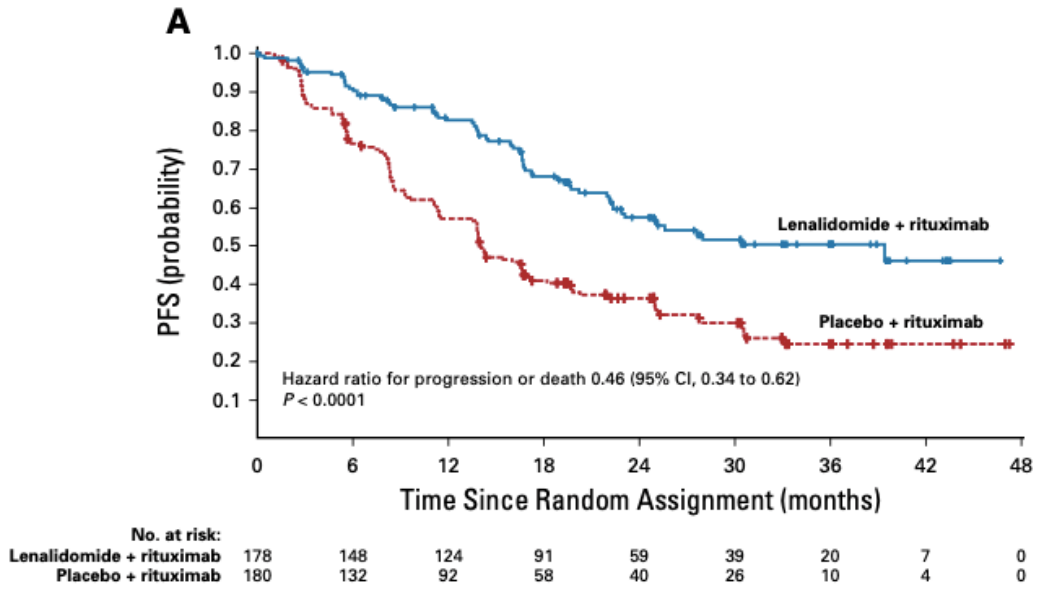
2L treatment:
Rituximab plus lenalidomide x 1 year (AUGMENT trial)

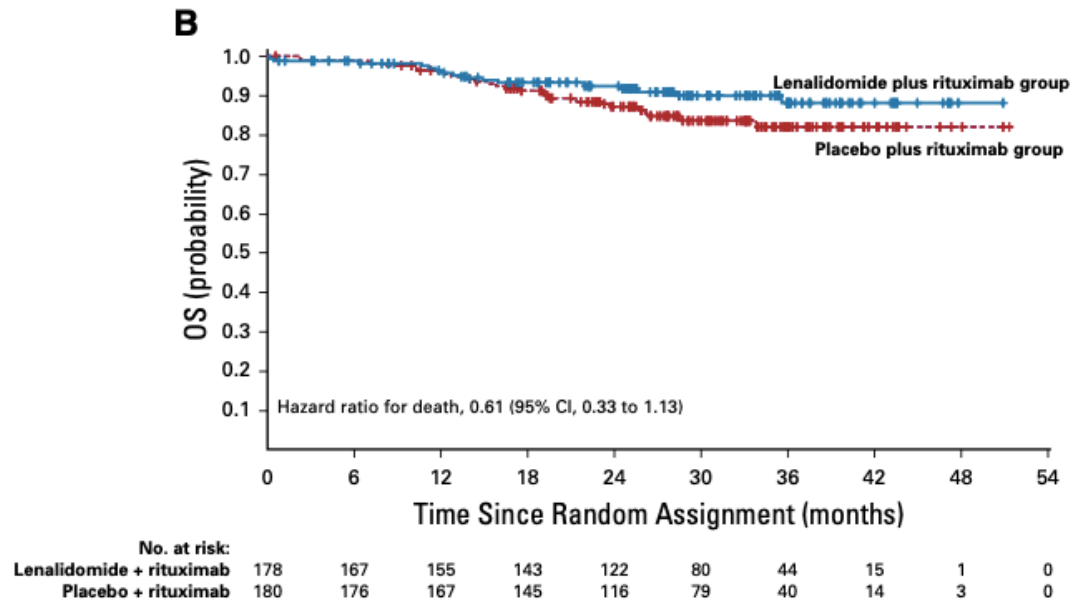
Before rituximab lenalidomide

After rituximab lenalidomide



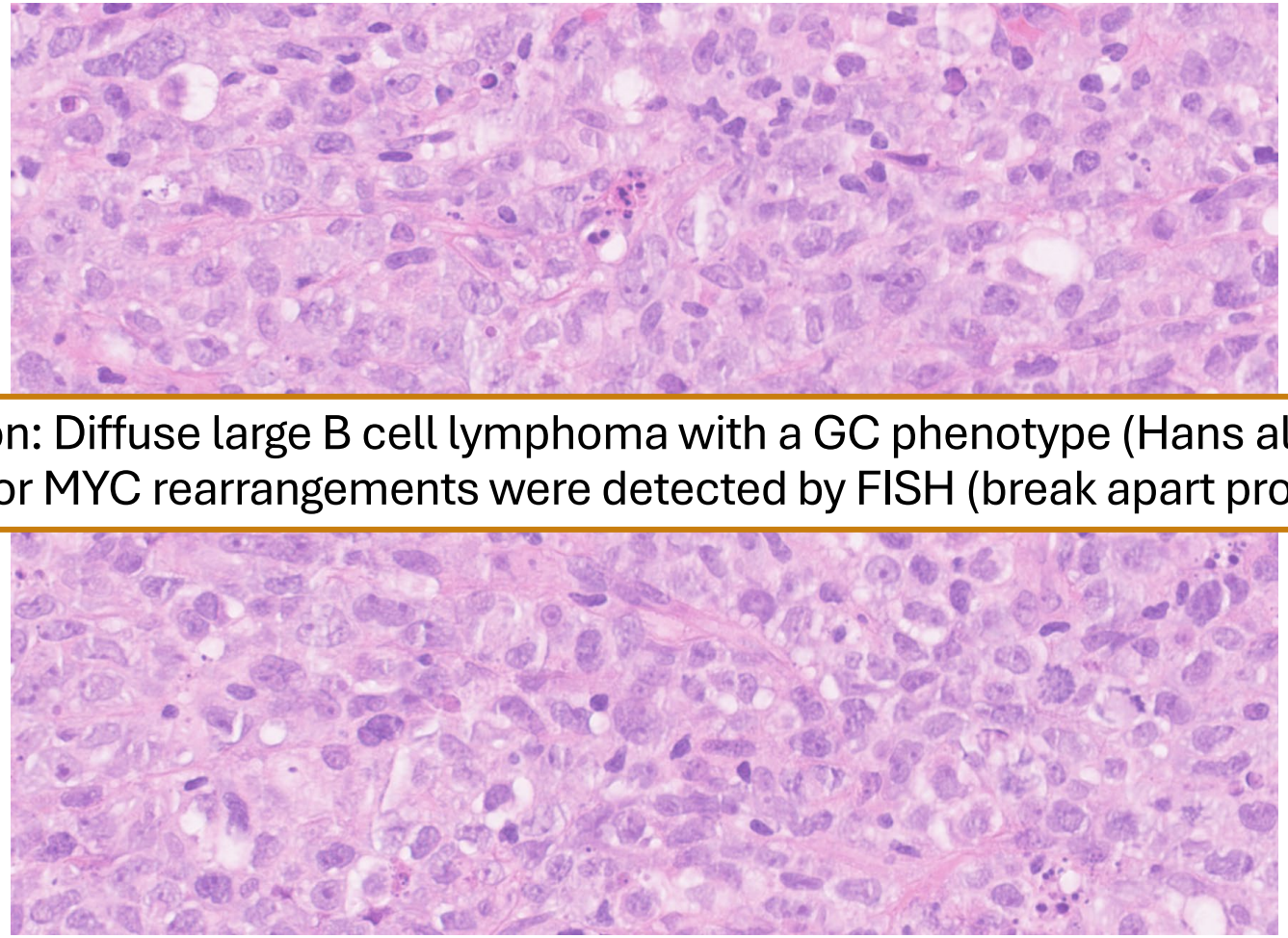
Rituximab lenalidomide in iNHL at relapse





Leonard JP et al. J Clin Oncol. 2019 May 10;37(14):1188-1199.

Histology of the celiac lymph node



Conclusion: Diffuse large B cell lymphoma with a GC phenotype (Hans algorithm)
No BCL2 or MYC rearrangements were detected by FISH (break apart probes)

Q6) Transformation of follicular lymphoma after two lines of therapy (already treated with anthracycline)

How should we proceed?

1. Salvage with anti CD20 antibody and bendamustine
2. R DHAP and BEAM followed by ASCT if chemosensitive
3. Cellular therapy with CAR T if available
4. Bispecific antibody (glofitamab or epcoritamab) if available

Q6) Transformation of follicular lymphoma after two lines of therapy (already treated with anthracycline)

How should we proceed?

1. Salvage with anti CD20 antibody and bendamustine
2. R DHAP and BEAM followed by ASCT if chemosensitive
3. Cellular therapy with CAR T if available
4. Bispecific antibody (glofitamab or epcoritamab) if available

Feedback: Current treatment options for transformed lymphoma with prior treatment with anthracyclines are similar to Diffuse Large B Cell Lymphoma including chemotherapy and ASCT

6/2022 7/2022 9/2022

Asymptomatic
PS 0
Persistant inguinal node

LN biopsy: Diffuse large B cell lymphoma
No BCL2 or MYC rearrangements (FISH)

PET CT shows < partial response

Proposed for CAR T

Dec 2022 | January 2022 | March 2023 | March 2023

Leukapheresis → Bridging: R**ituximab**
Polatuzumab
Bendamustine (1 cycle) → Lymphodepletion → CAR T cell infusion

Fludarabine 30mg/m2/d x 3
+ Cyclophosphamide
500mg/m2/d x 3

6/2022

7/2022

9/2022

3/2023

6/2023

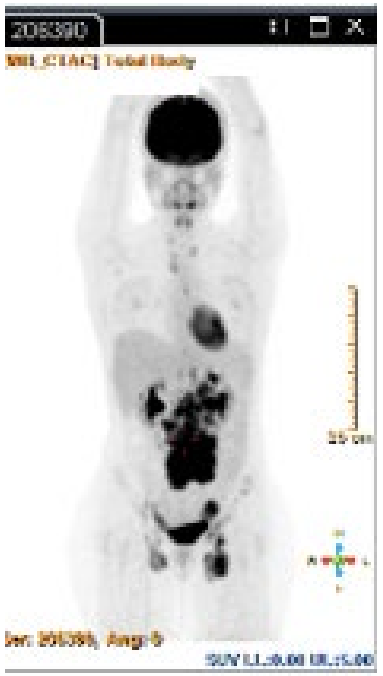
No symptoms
PS 0
Persistant inguinal node

LN biopsy: Diffuse large B cell lymphoma
No BCL2 or MYC rearrangements (FISH)

PET CT shows < partial response

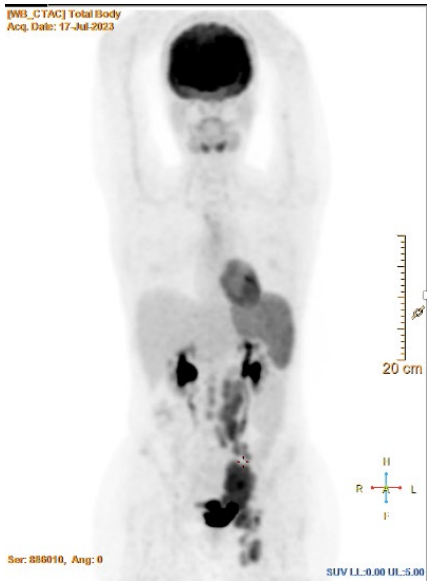
CAR T infused

Response evaluation

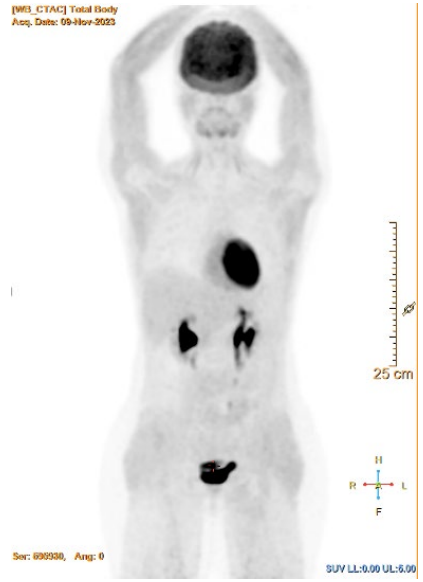


R DHAP x 2

Proposed for CAR T



March 2023 (after R DHAP, before CAR T)



June 2023 (3M after CAR T)

Discussion and conclusions

- First line treatment for advanced follicular lymphoma is based on immunochemotherapy, with maintenance prolonging PFS
- Relapses are frequent and difficult to predict in individual cases
- Biopsy should be repeated at each relapse due to the risk of transformation
- Multiple options exist for relapsed disease, with responses progressively shorter
- Intensive chemotherapy and autologous stem cell transplant have a limited role in FL
- Currently, in young patients who may be candidates to cellular therapy bendamustine should be used with caution at relapse
- Transformed disease is treated as DLBCL, including HDT and ASCT and cellular therapy as indicated
- Cellular therapy with CAR T-cells has a role in 3rd or further line of treatment of FL in selected cases and in countries with regulatory approval

CAR T cell trial results in diffuse and follicular B cell lymphoma

1. Locke FL, Ghobadi A, Jacobson CA et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019 Jan;20(1):31-42. doi: 10.1016/S1470-2045(18)30864-7.
2. Locke FL, Miklos DB, Jacobson CA, Perales MA et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022 Feb 17;386(7):640-654.
3. Abramson JS, Palomba ML, Gordon LI, et al. Two-year follow-up of lisocabtagene maraleucel in relapsed or refractory large B-cell lymphoma in TRANSCEND NHL 001. Blood. 2024 Feb 1;143(5):404-416.
4. Kamdar M, Solomon SR, Arnason J, Johnston PB, et al. TRANSFORM Investigators. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet. 2022 Jun 18;399(10343):2294-2308
5. Schuster SJ, Tam CS, Borchmann P, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2021 Oct;22(10):1403-1415.
6. Neelapu SS, Chavez JC, Sehgal AR et al. Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). Blood. 2024 Feb 8;143(6):496-506.
7. Dreyling M, Fowler NH, Dickinson M et al. Durable response after tisagenlecleucel in adults with relapsed/refractory follicular lymphoma: ELARA trial update. Blood. 2024 Apr 25;143(17):1713-1725
8. Morschhauser F, Dahiya S, Palomba ML, et al Lisocabtagene maraleucel in follicular lymphoma: the phase 2 TRANSCEND FL study. Nat Med. 2024 Aug;30(8):2199-2207.

References

1. Kurz KS, Kalmbach S, Ott M et al. Follicular lymphoma in the 5th edition of the WHO classification of Hematolymphoid neoplasms – updated classification and new biological data. Cancers 2023, *15*, 785.
2. Barrington SF, et al. Role of imaging in the staging and response assessment of lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014; 32: 3048-3058
3. Cheson BD. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014; 32: 3059-3068
4. Dreyling M, Ghielmini M, Rule S et al. Newly diagnosed and relapsed folicular lymphoma. ESMO clinical practice guidelines for diagnosis, treatment and follow up. Ann Oncol 2021, 32(3): 298-308
5. Nizzoli ME, Manni M, Ghiggi C et al. Impact of immunochemotherapy with R Bendamustine or R CHOP for treatment naive advanced stage folicular lymphoma. A subset analysis of the FOLL12 trial by Fundazione Italiana Linfomi. Hematol Oncol. 2023 Oct;41(4):655-662.
6. Bachy E, Seymour JF, Feugier P, et al Sustained Progression-free survival benefit of Rituximab Maintenance in Patients With Follicular Lymphoma: Long-Term Results of the PRIMA Study J Clin Oncol. 2019 Nov 1;37(31):2815-2824.
7. Casulo C; Byrtek; M, Dawson KL; et al Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. *Journal of Clinical Oncology* 2015 332516-2522.
8. Leonard JP, Trneny M, Izutsu K, ET AL. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. J Clin Oncol. 2019 May 10;37(14):1188-1199.
9. Rodgers TD, Casulo C, Boissard F, et al. Early Relapse in First-Line Follicular Lymphoma: A Review of the Clinical Implications and Available Mitigation and Management Strategies. Oncol Ther. 2021 Dec;9(2):329-346
10. Florindez JA, Chihara D, Reis IM, Lossos IS, Alderuccio JP. Risk of transformation by frontline management in follicular and marginal zone lymphomas: a US population-based analysis. Blood Adv. 2024 Aug 27;8(16):4423-4432.
11. Federico M, Caballero Barrigón L, , Marcheselli L et al. Aristotle Consortium. Rituximab and the risk of transformation of follicular lymphoma: a retrospective pooled analysis. Lancet Haematol. 2018 Aug;5(8):e359-e367
12. Alonso-Álvarez S, Manni M, Montoto S, et al. Primary refractory follicular lymphoma: a poor outcome entity with high risk of transformation to aggressive B cell lymphoma. Eur J Cancer. 2021 Nov;157:132-139. doi: 10.1016/j.ejca.2021.08.005. Epub 2021 Sep 8. PMID: 34508995.

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

Self-assessment case 2
Session **Indolent Non-Hodgkin Lymphoma**

Maria Gomes da Silva

October 18th 2024

Introduction

- A 49-year-old male patient presents in May 2016 with fatigue, slight jaundice and low grade fever
- Physical examination
  - → no lymphadenopathy or organomegaly
  - → pallor, jaundice
  - → Bilateral malleolar edema
- Labs:

Hb 121 g/L WBC 10.4 x10^9/L Platelets 295 x10^9/L

LDH 225 IU/L B2 M 4.13 mg/L CPR 2.04 mg/dL

AST 60 IU/L ALT 80 IU/L

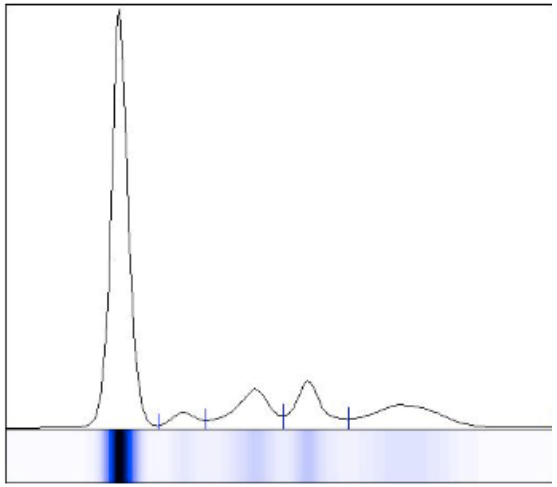
ALP 300 UI/L (UNL 150) GGT 200 UI/L(UNL 34)

Bilirubin (2.5 mg/dL/1.8 mg/dL)

Hepatitis B and C and HIV serologies: negative

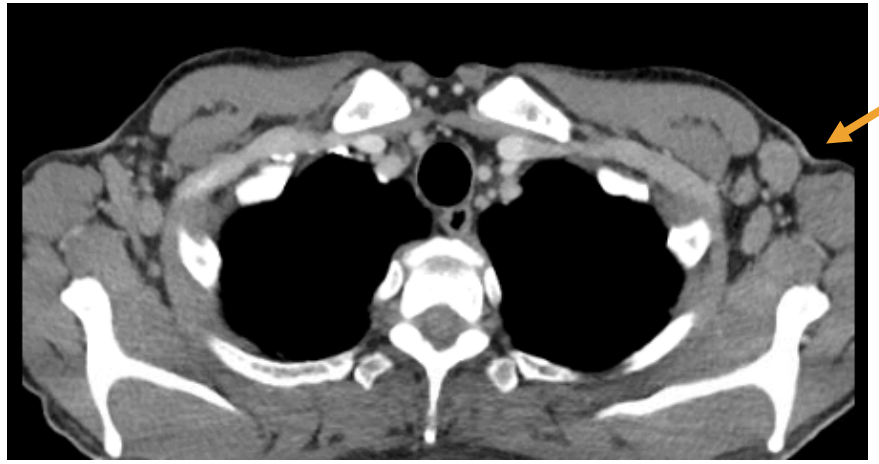
Total protein 7g/dL Albumin 3.5 g/L

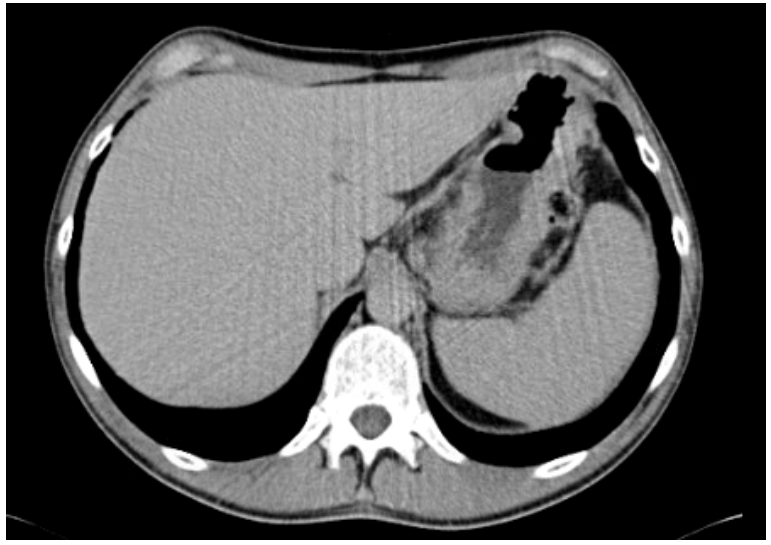
IgM 107 mg/dL IgG 1196 mg/dL IgA 67 mg/dL

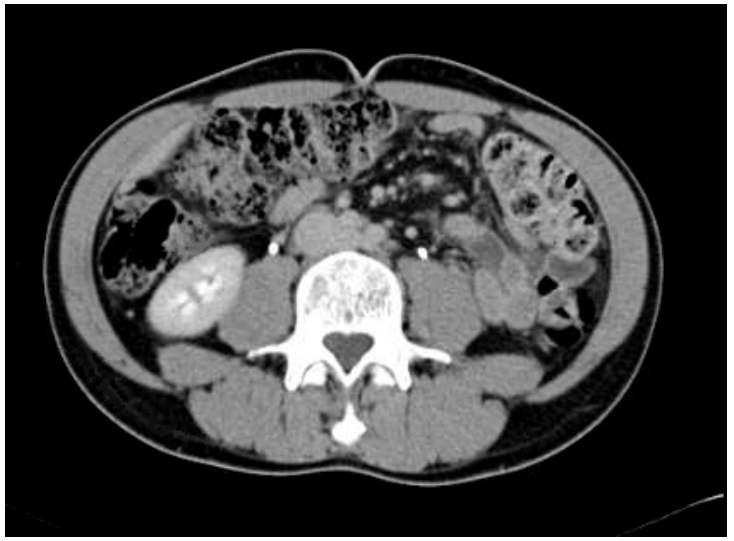


Immunofixation: biclonal IgM lambda and IgG K discrete peaks

Body CT scan

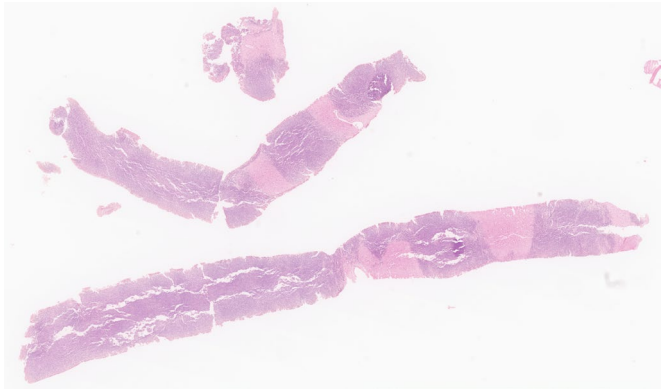


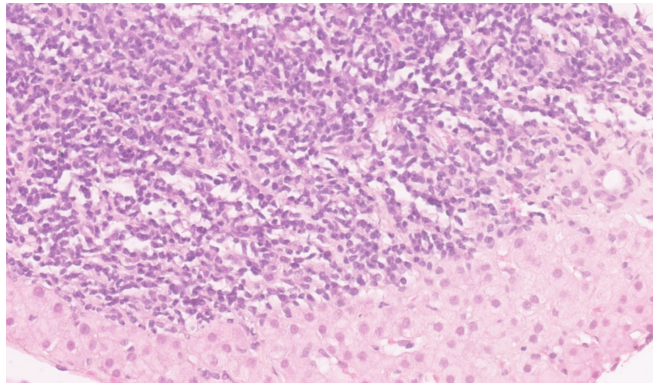


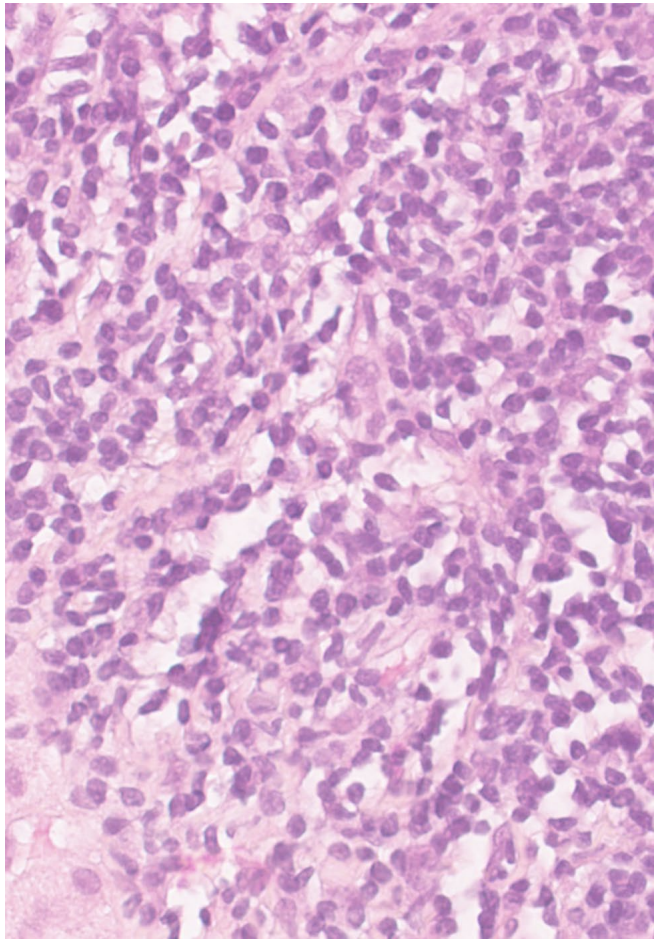


Liver biopsy

The liver is infiltrated by small lymphoid cells with irregular nuclei and clear cytoplasm, staining for CD20 but not for CD10, CD5 or BCL6. A diagnosis of marginal zone lymphoma is made.

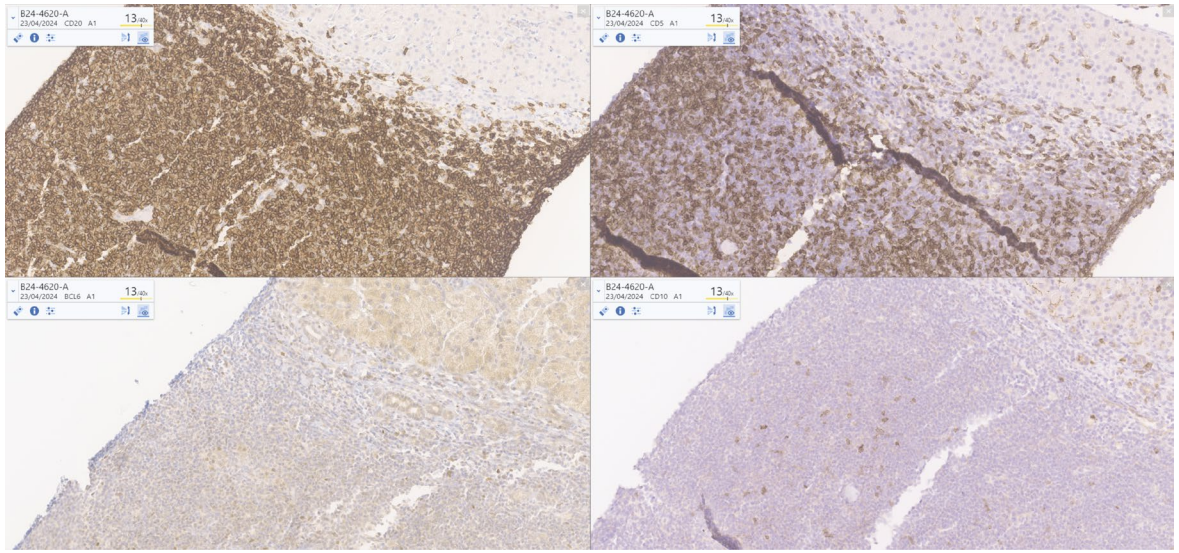






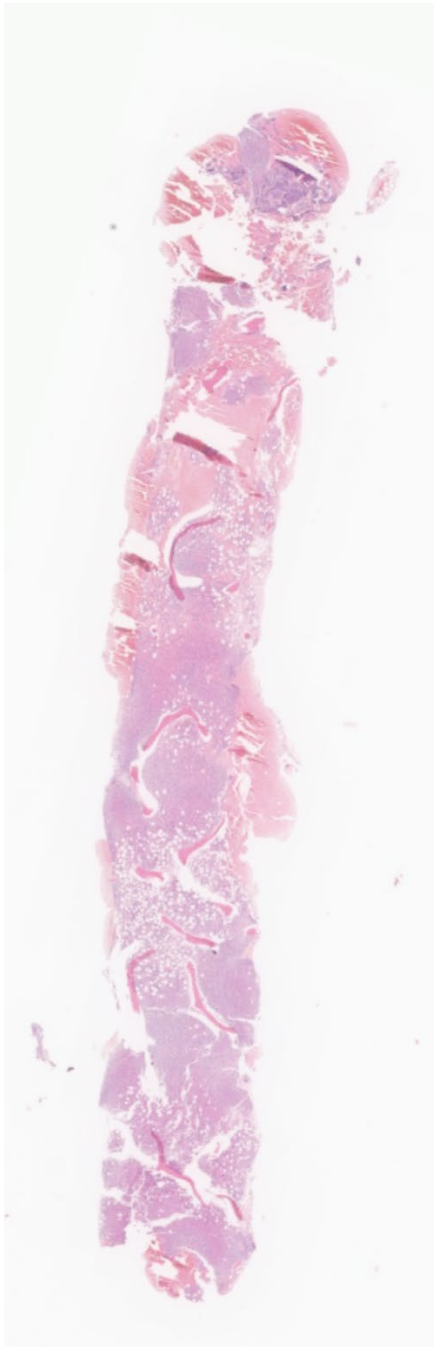
CD20

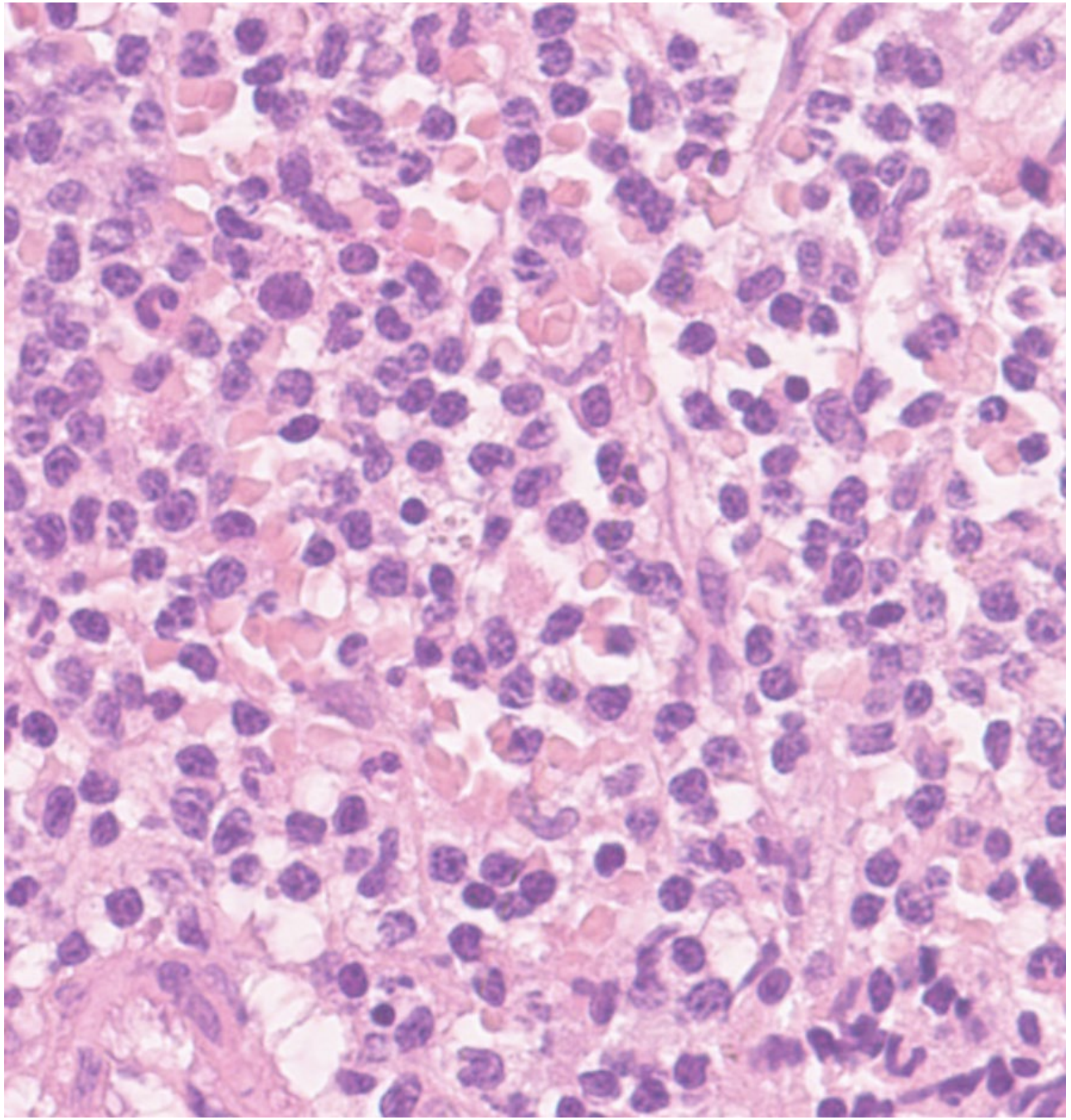
CD5



BCL6

CD10

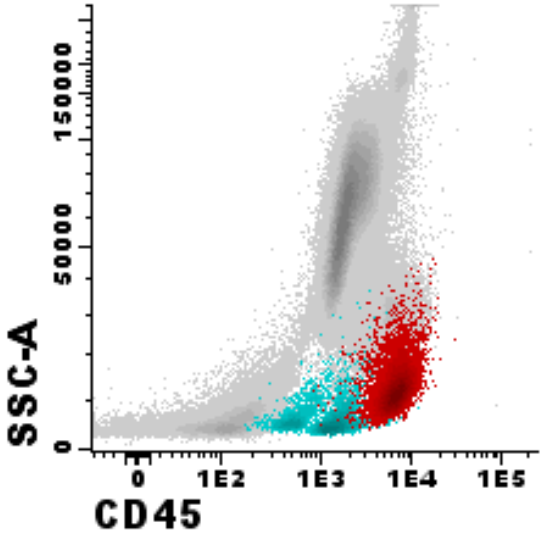


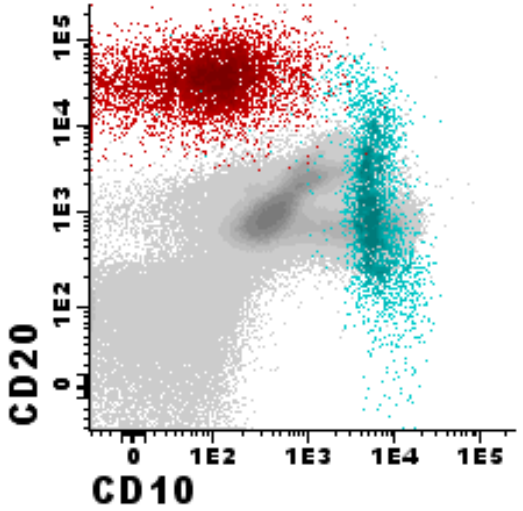


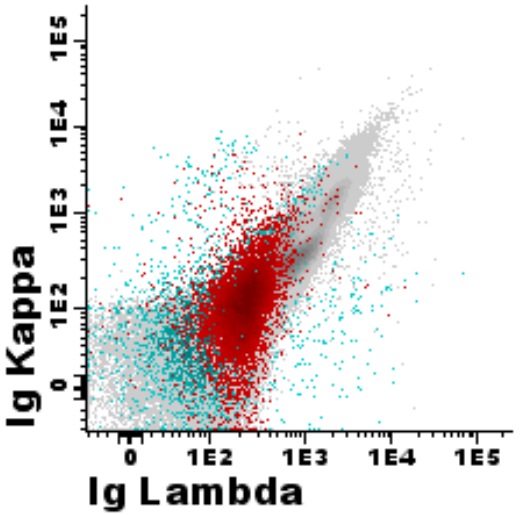
BM trephine biopsy shows a nodular and interstitial infiltrate by small, irregular lymphoid cells, without plasma cell differentiation

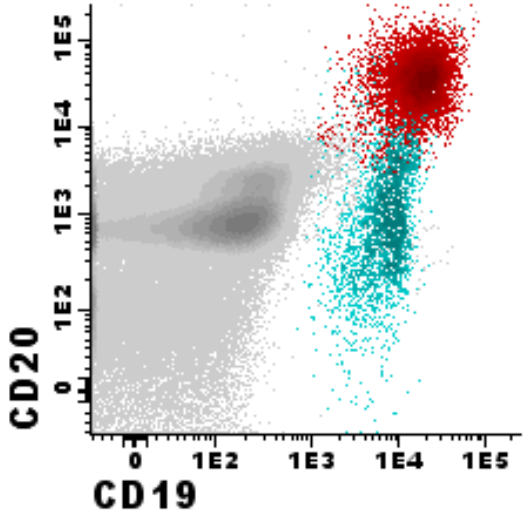
Bone marrow biopsy

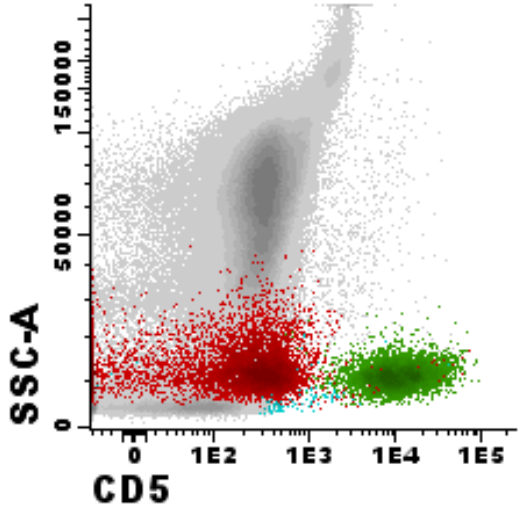
Bone marrow aspirate: flow cytometry











- T cells
- Immature B cells
- Neoplastic B cells

Q1) What other test would you order at this time?

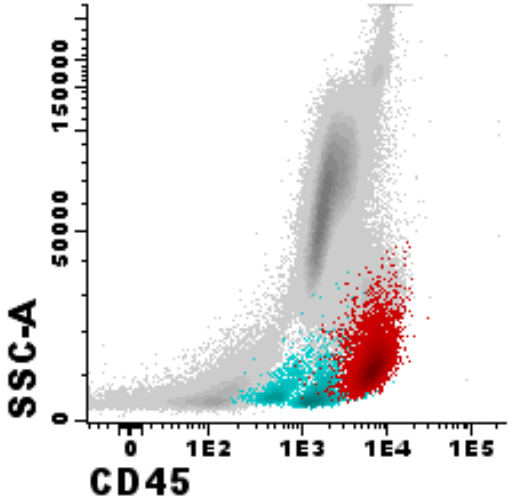
1. PET CT
2. Abdominal MRI
3. PCR for MYD88 L265P mutations in bone marrow
4. FISH for t(14;18) translocation in bone marrow
5. FISH for t(11;14) translocation in bone marrow

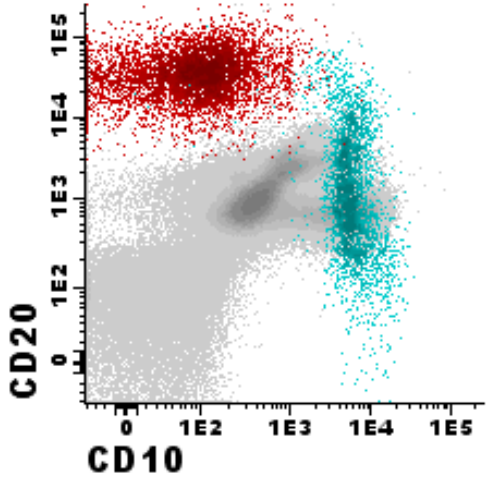
Q1) What other test would you order at this time?

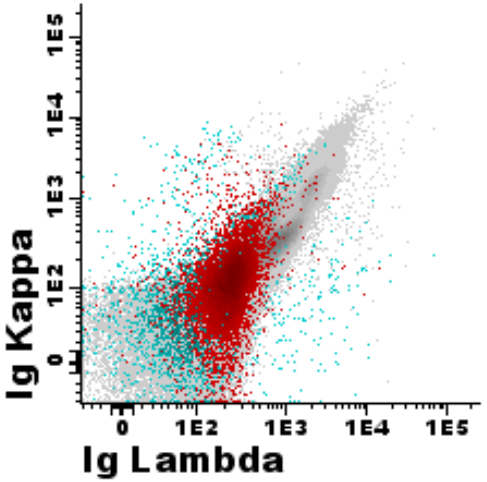
1. PET CT
2. Abdominal MRI
3. PCR for MYD88 L265P mutations in bone marrow
4. FISH for t(14;18) translocation in bone marrow
5. FISH for t(11;14) translocation in bone marrow

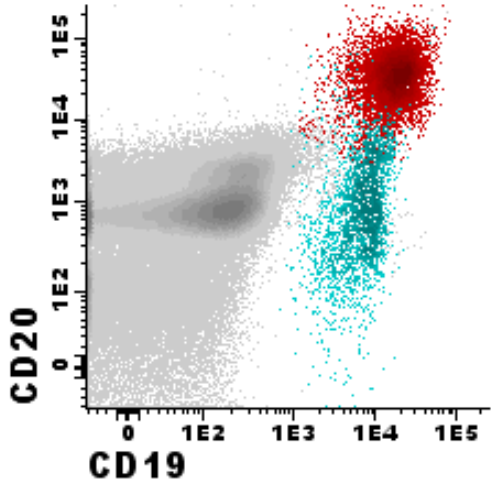
Feedback:
PET CT and abdominal MRI are not mandatory to stage MZL; PET CT may be useful if transformation is suspected and to stage localized disease
MYD88 L265P mutations are found in >90% cases of Waldenstrom's Macroglobulinemia and <10% marginal zone Lymphoma and may help in differential diagnosis
t(14;18) is most frequently found (85%) in follicular lymphoma cells
t(11;14) is most frequently found (95%) in mantle cell lymphoma cells

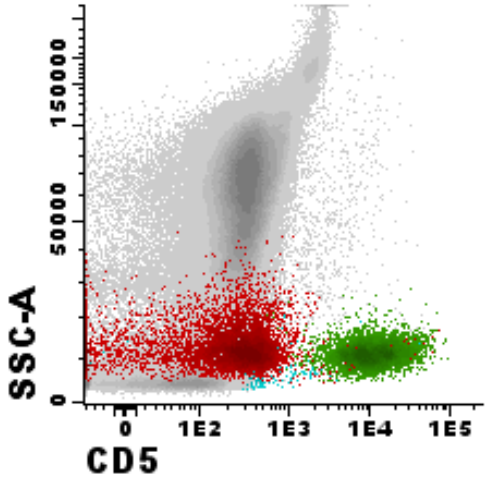
Bone marrow aspirate: flow cytometry











T cells

Immature B cells

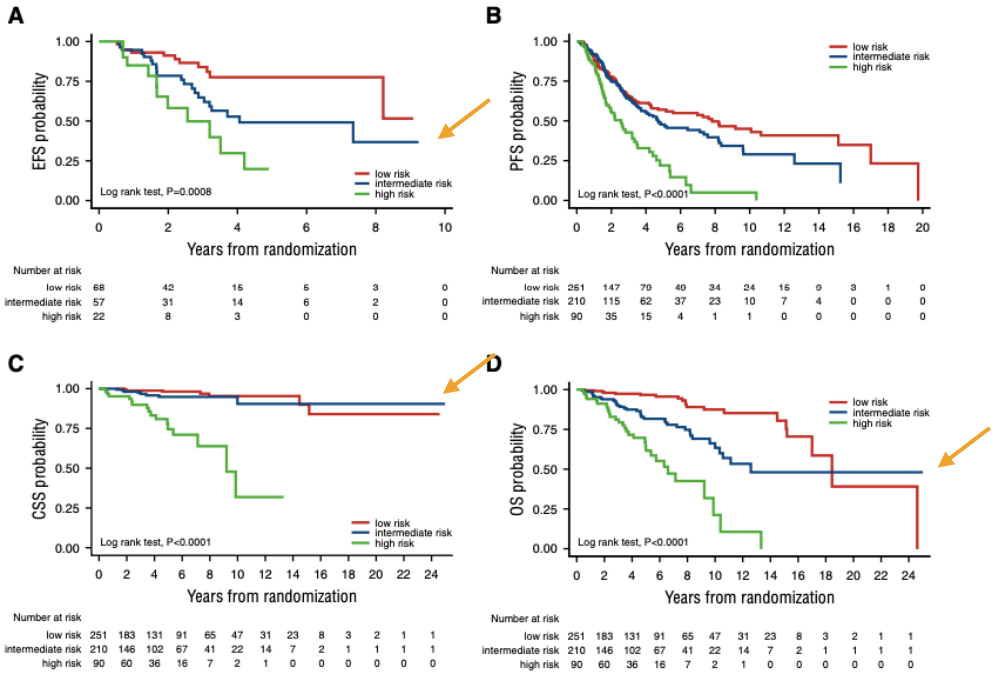
Neoplastic B cells

MYD L265P mutation present (quantitative PCR)

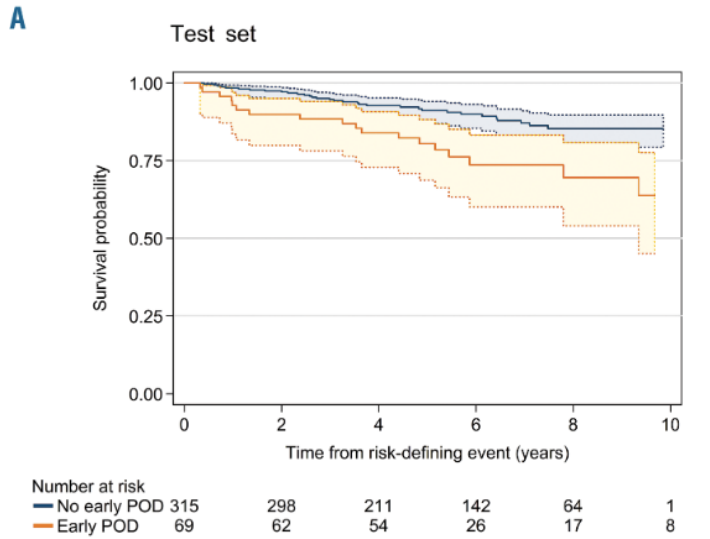
Prognostic assessment

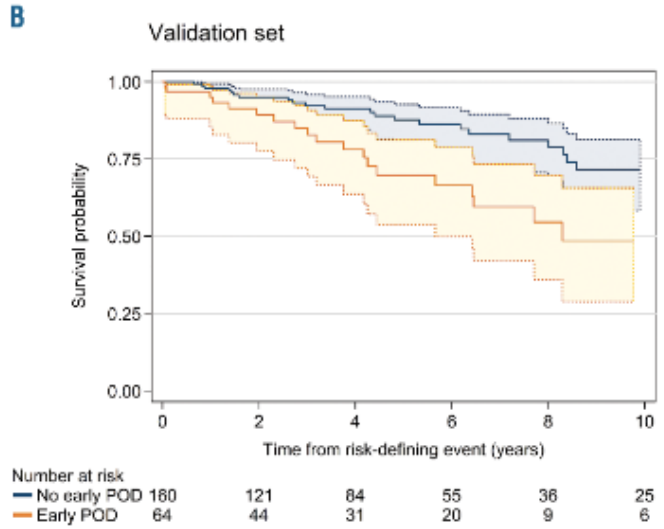
MALT IPI

Age >70 yo
LDH> Upper Normal Limit
Stage (III-IV)



Early progression





Thieblemont C et al. Blood. 2017;130(12):1409-1417

Conconi A et al. Haematologica 2020, 105(11): doi.org/10.3324/haematol.2019.237990

Q2) What treatment would you recommend for this patient?

1. Watch and wait
2. Rituximab monotherapy, 4 weekly administrations
3. Oral ibrutinib 560 mg/day until progression
4. 4 to 6 cycles of immunochemotherapy with R bendamustine
5. High dose chemotherapy with autologous stem cell transplantation after first line response

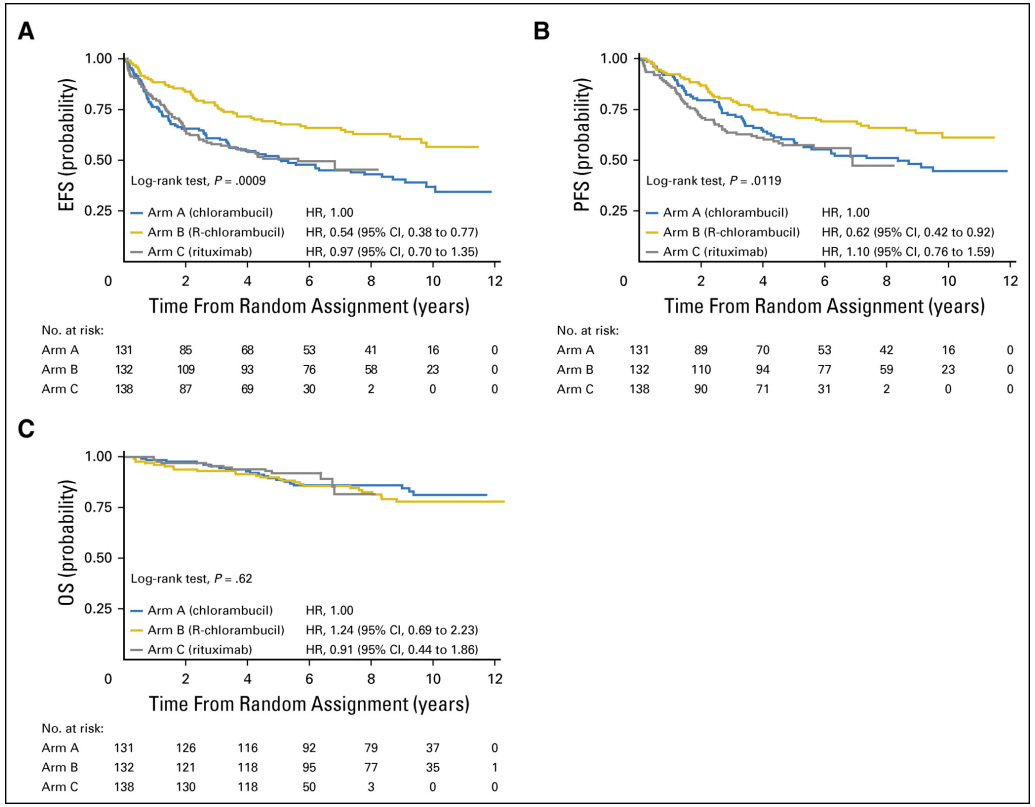
Q2) What treatment would you recommend for this patient?

1. Watch and wait
2. Rituximab monotherapy, 4 weekly administrations
3. Oral ibrutinib 560 mg/day until progression
4. 4 to 6 cycles of immunochemotherapy with R bendamustine
5. High dose chemotherapy with autologous stem cell transplantation after first line response

Feedback:
Rituximab bendamustine is effective therapy for advanced marginal zone lymphoma
Rituximab monotherapy is less effective than immunochemotherapy in marginal zone lymphoma in need of systemic therapy
BTK inhibitors are not approved for first line treatment of marginal zone lymphoma
High dose chemotherapy is not indicated as consolidation for first response in indolent lymphomas

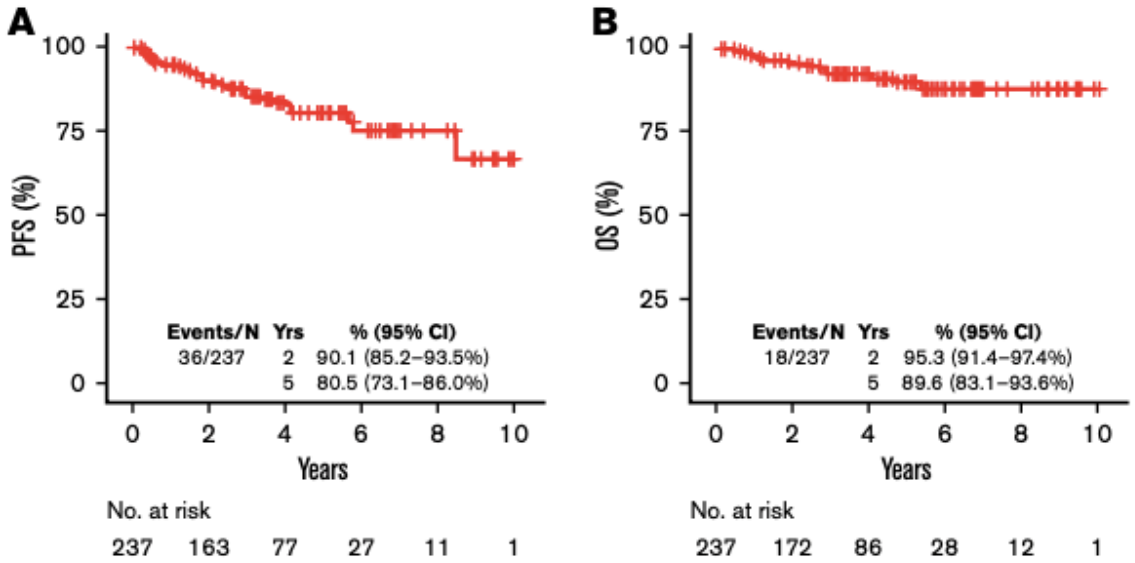
Outcomes of immunochemotherapy in advanced MZL

R-chlorambucil vs R mono vs chlorambucil



Zucca E, Conconi A, Martinelli G et al. *Journal of Clinical Oncology* 2017 351905-1912.

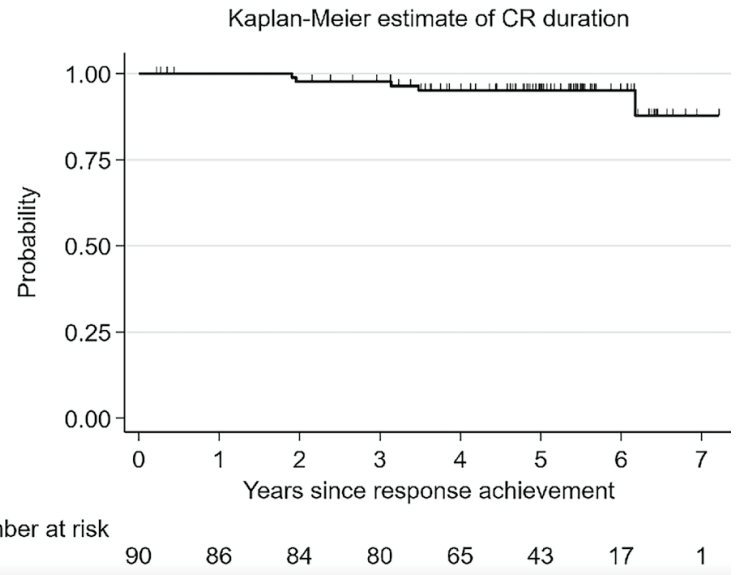
Retrospective analysis
237 patients receiving **6 cycles of BR**
Overall Response rate 93.2%
Complete response rate 81%

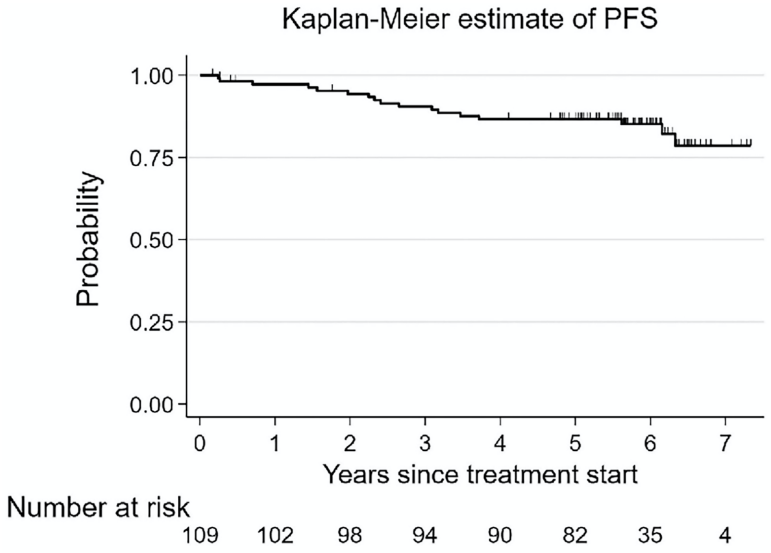


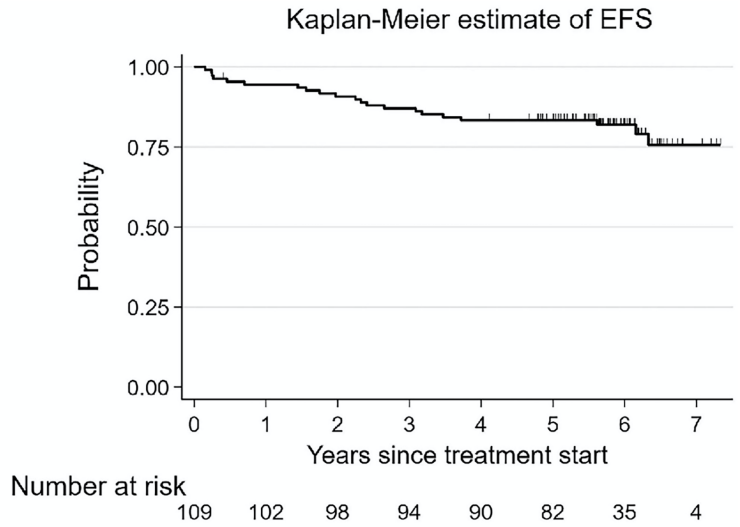
Alderuccio JP, Arcaini L, Watkins MP et al. *Blood Adv* 2022; 6 (7): 2035–2044

Should rituximab maintenance be used after immunochemotherapy?

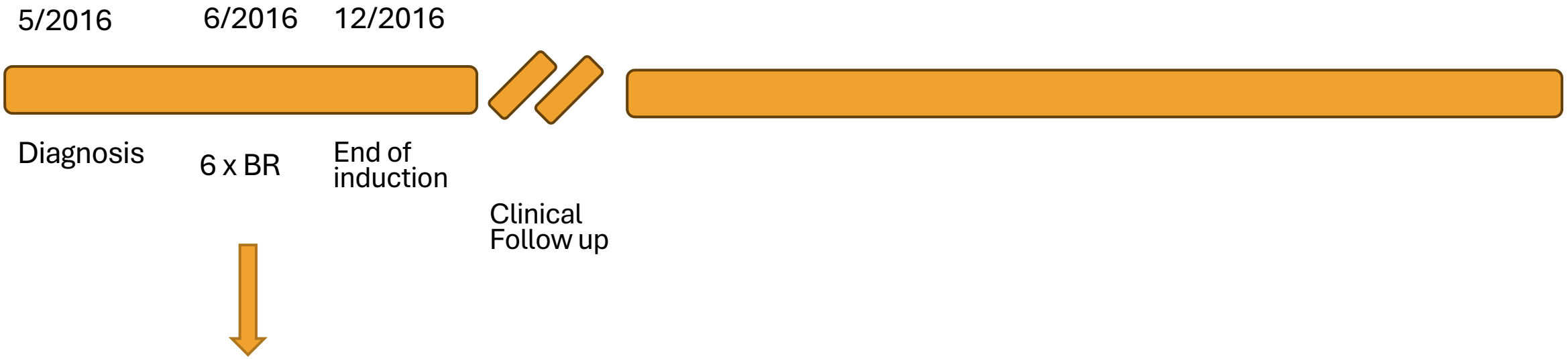
Response	Planned restaging timepoints						Additional restaging	
	After induction (month 6)		After 1 year of maintenance (month 18)		After 2 years of maintenance (month 30)		During follow-up (up to month 60)	
	N	%	N	%	N	%	N	%
CR	57	52	66	61	76	70	81	74
PR	37	34	21	19	8	7	8	7
SD	3	3	2	2	1	1	2	2
PD	2	2	2	2	1	1	6	5
NA	10	9	18	17	23	21	12	11







Stathis A, Pirosa MC, Orsucci L et al Haematologica. 2024 Aug 1;109(8):2564-2573



No symptoms

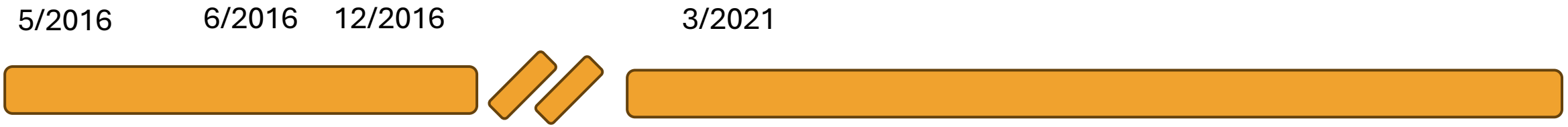
Normal **labs,** Hb 14.5 g/dL

CT scan

No adenopathy, no organomegaly

BM biopsy: normal hematopoiesis

Complete remission



No symptoms
Normal **labs,** Hb 14.5 g/dL

CT scan
No adenopathy, no organomegaly
BM biopsy: normal hematopoiesis

Complete remission

Hb 114 g/L
WBC 6.29 $x10^9$/L
Platelets 225 $x10^9$/L

AST, ALT: Normal
ALP, GGT, bilirubin: Normal
LDH 232 IU/L

B2M 3.98 mg/dL
CPR 3.02 mg/dL

IgG 1116 mg/dL
IgM 85 mg/dL

BM biopsy:
50% lymphocytes
(nodular infiltrate)

Body CT scan

PET CT

5/2016 6/2016 12/2016 3/2021

Diagnosis 6 x BR End of induction

Clinical Follow up

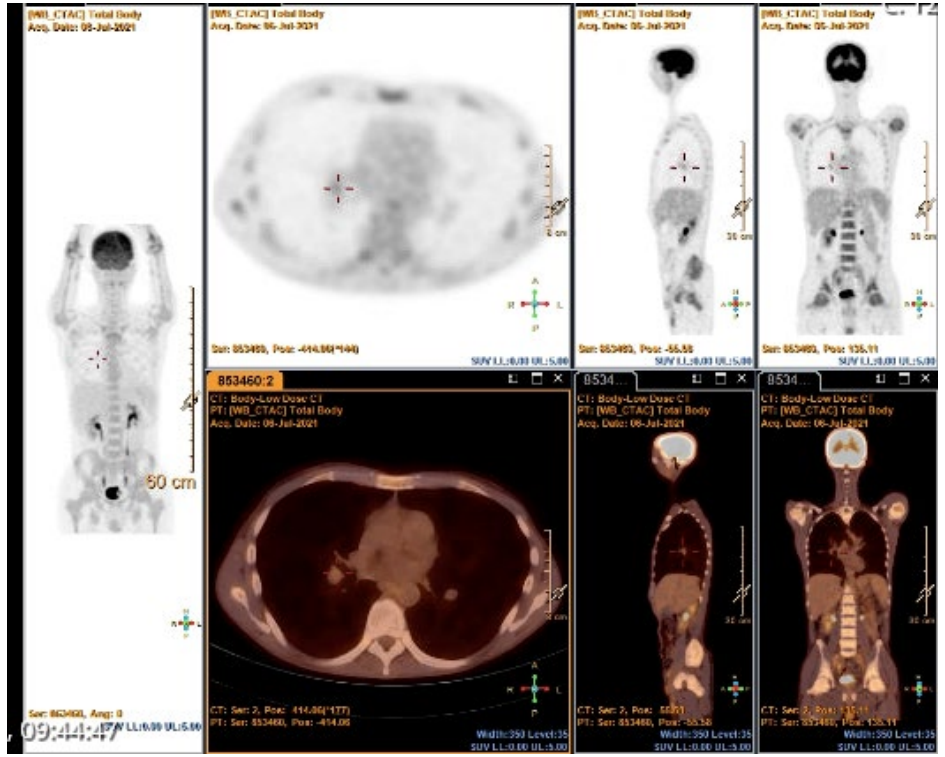
Hb 11.4 mg/dL
Fatigue

Body CT scan

PET CT

No symptoms
Normal **labs,** Hb 14.5 g/dL

CT scan
No adenopathy, no organomegaly
BM biopsy: normal hematopoiesis



Complete remission

Q3) What treatment do you recommend for this patient at first relapse?

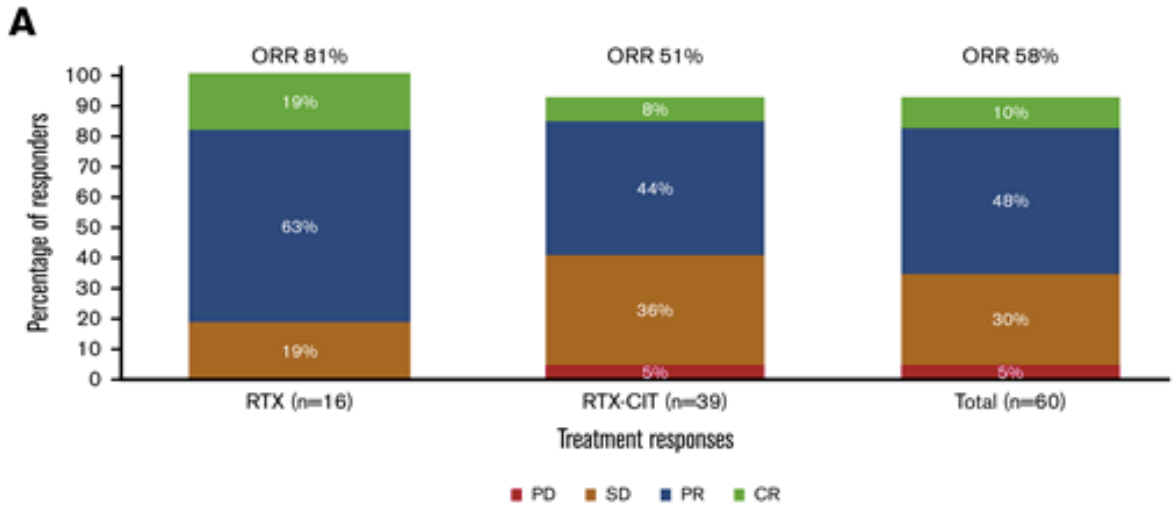
1. Watch and wait
2. Plasmapheresis
3. Repeat R bendamustine
4. 6 cycles of R CHOP
5. Oral idelalisib 150 mg twice a day until progression

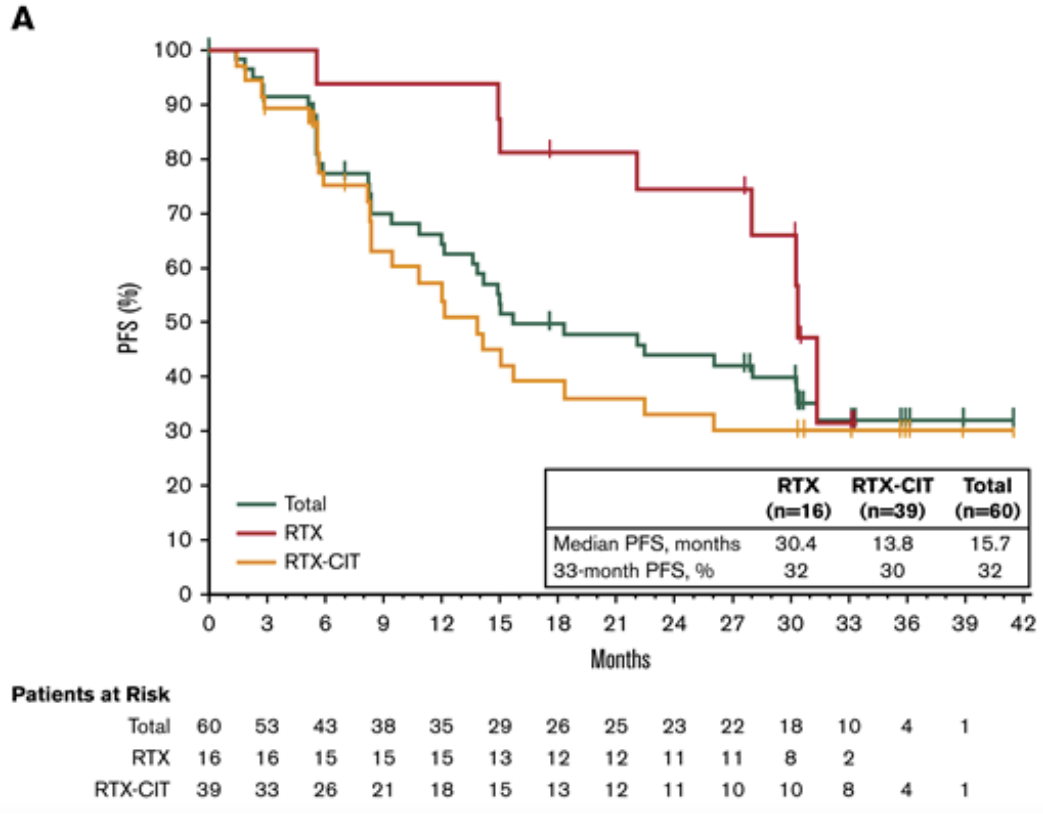
Q3) What treatment do you recommend for this patient at first relapse?

1. Watch and wait
2. Plasmapheresis
3. Repeat R bendamustine
4. 6 cycles of R CHOP
5. Oral idelalisib 150 mg twice a day until progression

Feedback:
According to ESMO guidelines, if systemic treatment is required chemoimmunotherapy can be repeated if remission ≥24 months. However, due to potencial toxicity BR is usually not repeated.
In other cases, an alternate chemoimmunotherapy regimen can be used. ASCT may be considered in fit patients with clinically aggressive relapse.
Idelalisb is effective in indolent lymphomas at ≥ 3rd line but toxicities are of concern

Role of BTK inhibitors: ibrutinib for the treatment of marginal zone lymphoma





Noy A, de Vos S, Coleman M et al. Blood Adv. 2020 Nov 24;4(22):5773-5784

Safety and efficacy of **zanubrutinib in relapsed/refractory marginal zone lymphoma:** final analysis of the **MAGNOLIA study**

Zanubrutinib demonstrated durable disease control in patients with relapsed/refractory marginal zone lymphoma

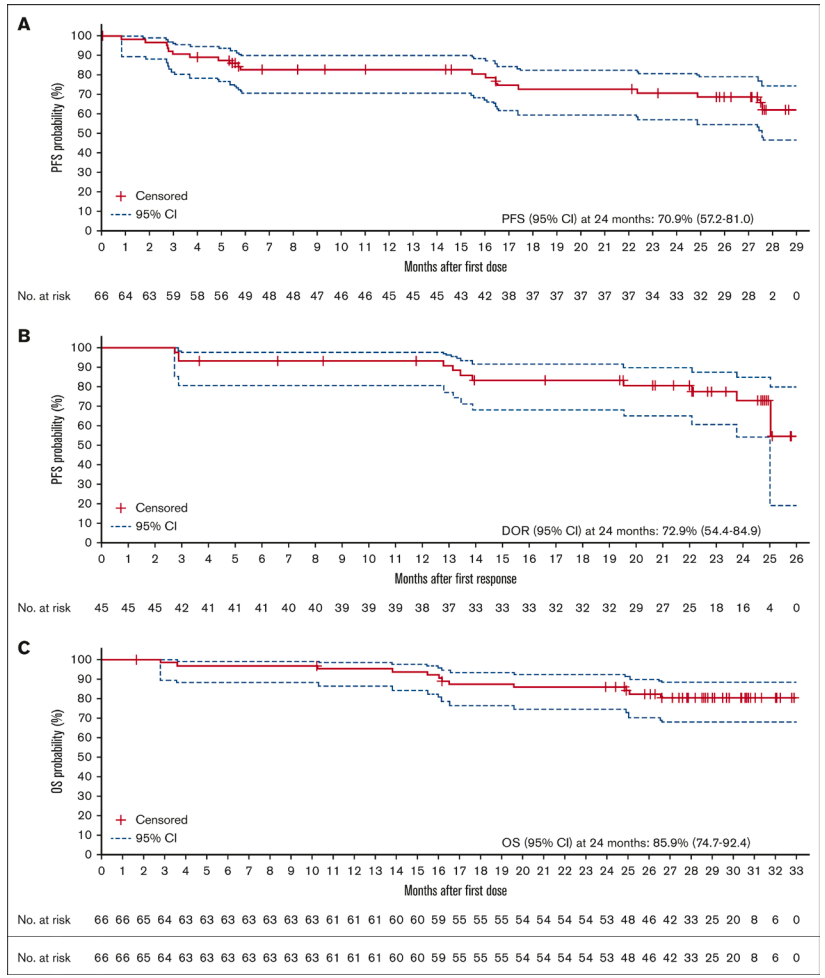
MZL subtype	Response	2-Year Rates		
		Response Duration	PFS	OS
Nodal (n = 25)	ORR 76%; CR 20%; PR 56%	78%	73%	80%
Splenic (n = 12)	ORR 67%; CR 8%; ORR 58%	Not estimable	64%	92%
MALT (n = 25)	ORR 64%; CR 40%; PR 24%	75%	77%	92%

HRQOL

Patients experienced sustained improvements from baseline in HRQOL with greatest benefits at 18 to 24 months

High-risk patients
- Stage III/IV disease: 87%
- Bulky (>5 cm) disease: 37%
- Age ≥75 years: 28%

Zanubrutinib had a favorable safety profile
- Most common grade ≥3 TEAE: neutropenia/neutrophil count decreased (12%)
- Cardiac TEAEs (any grade) uncommon: atrial fibrillation/flutter (3%), hypertension (4%)
- Grade ≥3 bleeding: 1 patient
- No new safety signals observed



Opat S, Tedeschi A, Hu B, Linton KM et al. Blood Adv. 2023 Nov 28;7(22):6801-6811

3/2021

4/2021

8/2021

RCHOP x 6

Hb 11. 4mg/dL
Fatigue

Relapse
Stage IV disease

Hb 114 g/L
WBC 6.29 x10^9/L
Platelets 225 x10^9/L

AST, ALT: Normal
ALP, GGT, bilirubin: Normal
LDH 232 IU/L

B2M 3.98 mg/dL
CPR 3.02 mg/dL

IgG 1116 mg/dL
IgM 85 mg/dL

PET CT

BM biopsy

BM biopsy: normal hematopoesis

PET CT: negative

Complete remission

Q4) How should this patient be managed after remission?

1. Imaging surveillance with periodic PET CT
2. Clinical surveillance with regular laboratory evaluation
3. Lenalidomide maintenance
4. BTK inhibitor maintenance

Q4) How should this patient be managed after remission?

1. Imaging surveillance with periodic PET CT
2. Clinical surveillance with regular laboratory evaluation
3. Lenalidomide maintenance
4. BTK inhibitor maintenance

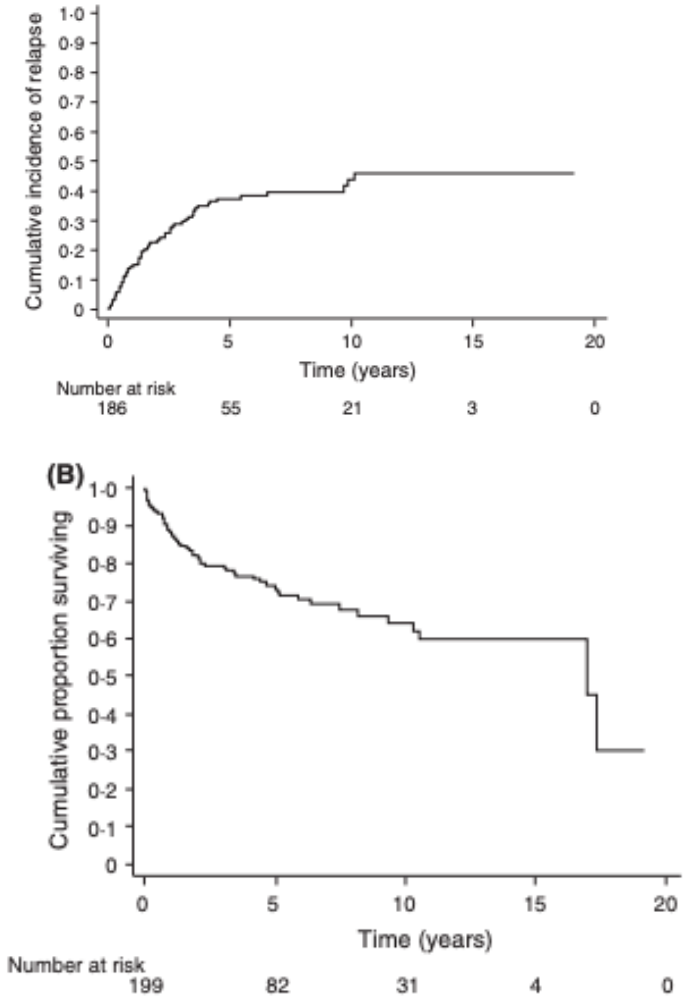
Feedback:
Imaging surveillance is not indicated in indolent lymphoma
Neither lenalidomide nor BTK inhibitor maintenance are indicated in marginal zone lymphoma. Both agents may be useful at relapse but only BTK inhibitors are approved in that setting.

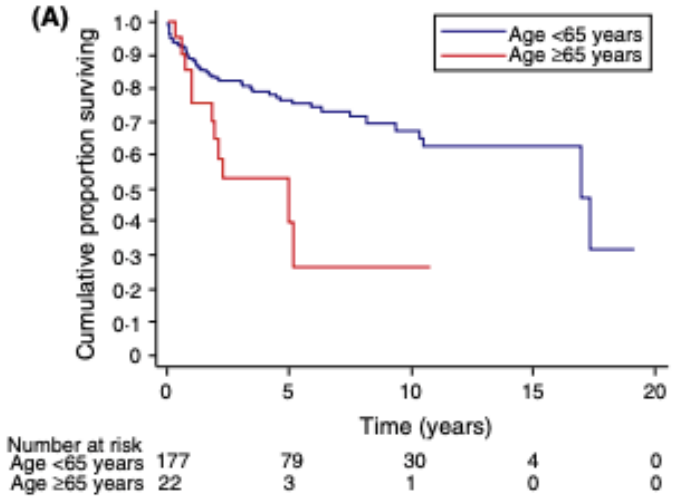
Should ASCT have been considered as consolidation?

199 patients

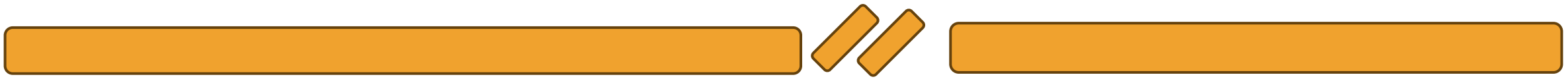
- Registered in EBMT, FIL, GELTAMO
- EMZL, SMZL, NMZL
- Median 57 yo
- Median 2y from diagnosis to ASCT

Median 5 y follow up
29% pts died (33 due to PD, 22 in remission)





Avivi I et al, Br J Haematol 2018, doi: 10.1111/bjh.15454



Hb 11.5 mg/dL
IgG 1116 mg/dL

Fatigue

Relapse
Stage IV disease

RCHOP x 6

Labs

PET CT

BM biopsy

Complete remission

Headache
Back pain
Fatigue
Absence seizures

Hb 139 g/L
WBC 6.85 $x10^9$/L
Platelets 191 $x10^9$/L

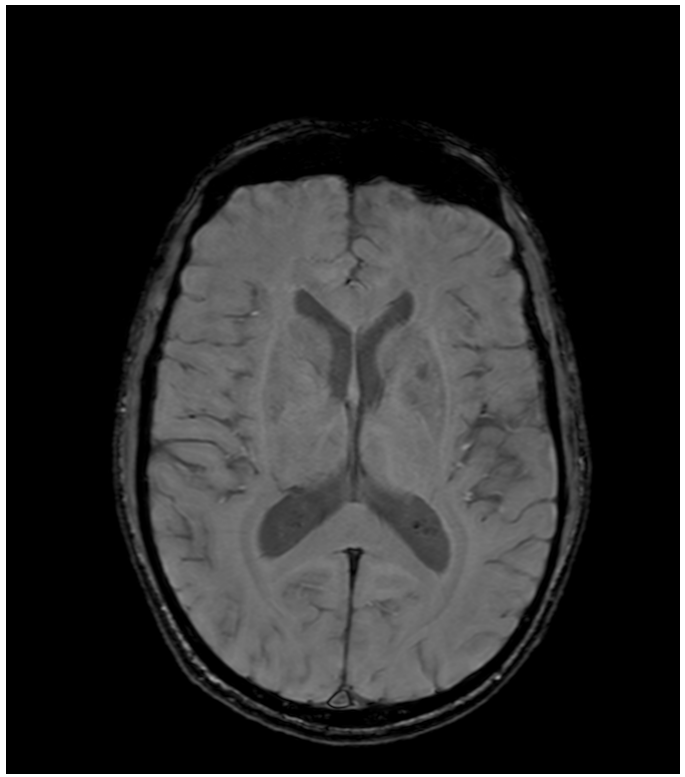
LDH 135 IU/L
B2 M 2.44mg/dL
Liver tests
IgG 1459 mg/dL
IgM 55 mg/dL

Neurology consultation

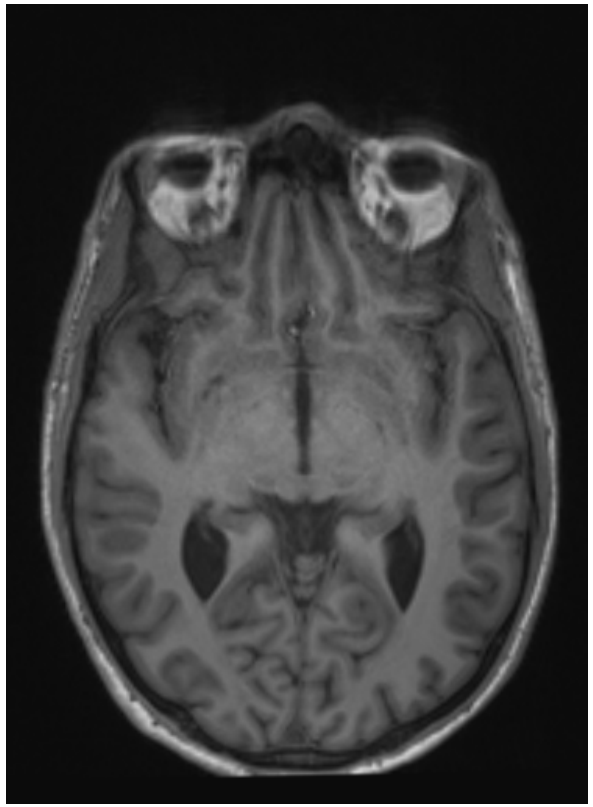
Craneal MRI

Lumbar puncture

Craneal MRI and Cerebrospinal Fluid



Normal MRI



Cell count: 90/μL
- 54% neutrophils
- 38% lymphocytes
- 8% monocytes

Proteins 5.49 g/L
Albumin 40 g/L
IgA 64 mg/dL
IgG 1234 mg/dL
IgM 50 mg/dL
Glucose 51 mg/dL
Cl 116 mmol/L
LDH 43 IU/L

Viral DNA
- HSV1, HSV2 – undetectable
- VZV, CMV – undetectable
- HHV6 – undetectable
- BK vírus – undetectable
- JC vírus - undetectable

Q5) What other tests can be useful?

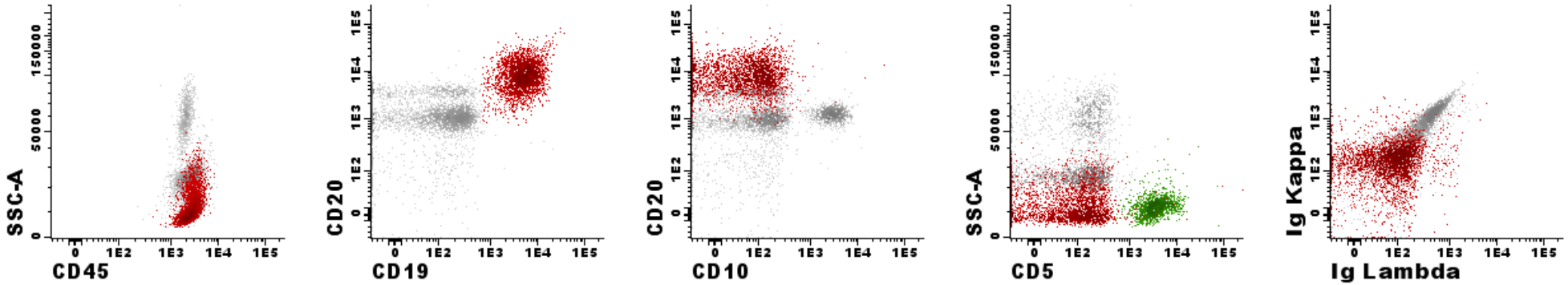
1. Flow cytometry of the cerebrospinal fluid
2. PCR for MYD88 L265P mutation in the cerebrospinal fluid
3. Bone marrow aspirate and biopsy
4. PET CT
5. All of the above

Q5) What other tests can be useful?

1. Flow cytometry of the cerebrospinal fluid
2. PCR for MYD88 L265P mutation in the cerebrospinal fluid
3. Bone marrow aspirate and biopsy
4. PET CT
5. All of the above

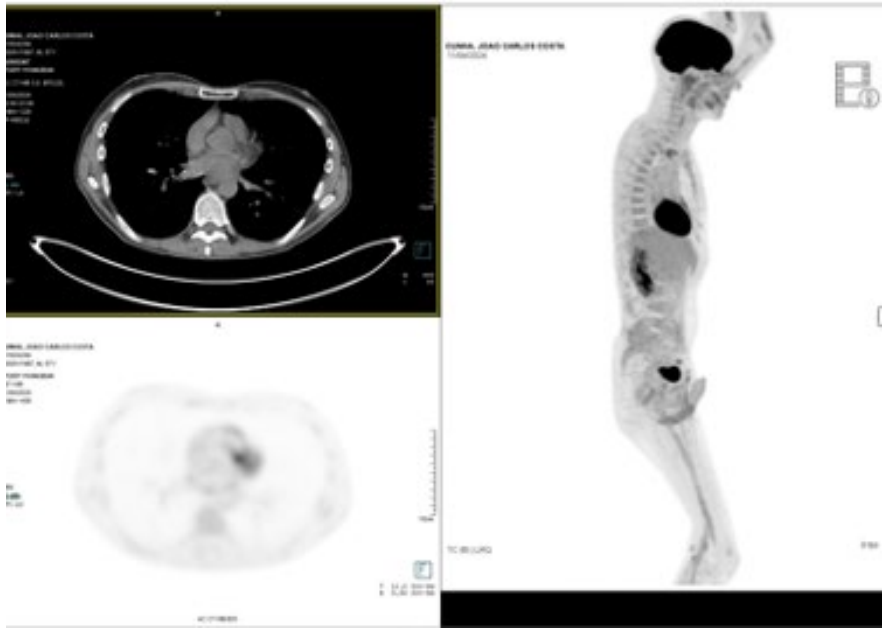
Feedback:
Flow cytometry helps to confirm B cell lymphoma infiltration in CSF
MYD88 L265P mutation is expected to be present in neoplastic cells in this patient
Bone marrow evaluation and PET CT are part of the staging of relapsed disease; PET CT helps to evaluate possible transformation into high grade lymphoma

Cerebrospinal fluid: **flow cytometry**



Cerebrospinal fluid: **MYD L265P mutation present**

Staging PET CT
(transformation?)



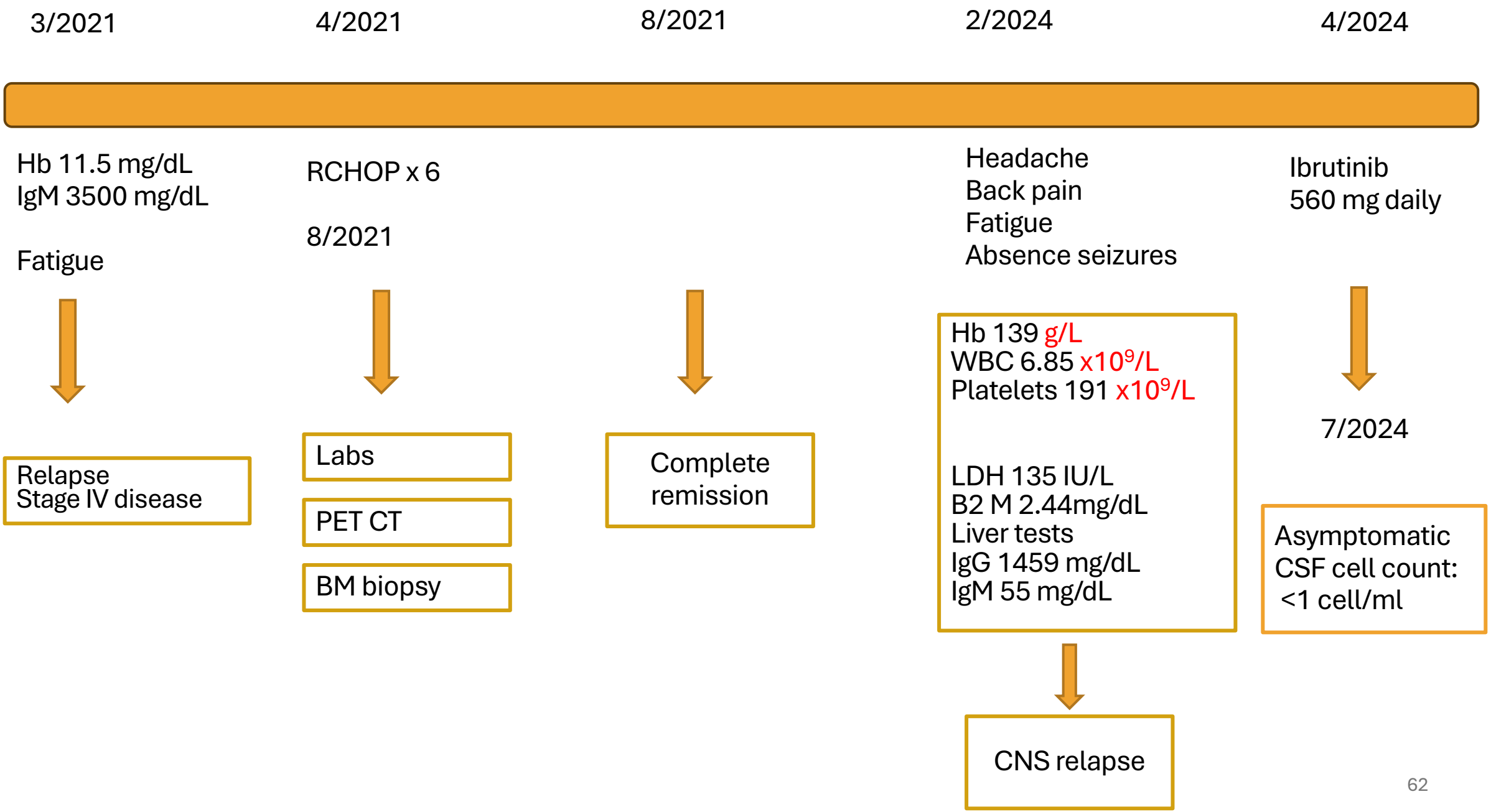
Q6) What treatment would you recommend at this time?

1. High dose systemic methotrexate
2. Repeated administrations of intrathecal methotrexate
3. Oral covalent BTK inhibitor (ibrutinib or zanubrutinib)
4. Oral pirtobrutinib
5. Oral lenalidomide

Q6) What treatment would you recommend at this time?

1. High dose systemic methotrexate
2. Repeated administrations of intrathecal methotrexate
3. Oral covalent BTK inhibitor (ibrutinib or zanubrutinib)
4. Oral pirtobrutinib
5. Oral lenalidomide

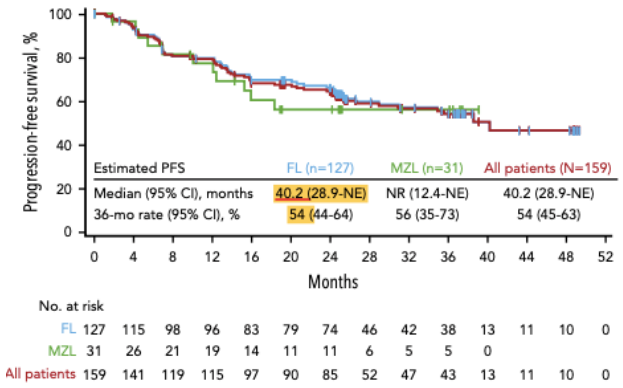
Feedback:
Although systemic and intrathecal methotrexate may be used to treat CSF infiltration by MZL, covalent BTK inhibitors penetrate well the blood brain barrier and lead to remission in patients presenting with this rare complication, as well as Waldenstrom's Macroglobulinemia patients with Bing Neel syndrome
No data are available regarding the non-covalent BTK inhibitor pirtobrutinib or lenalidomide in this setting.

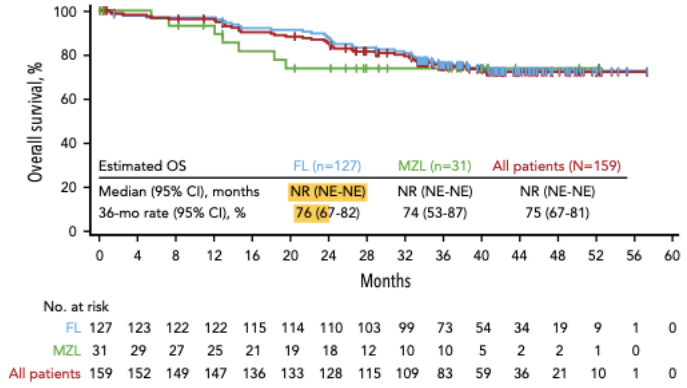

3/2021
4/2021
8/2021
2/2024
4/2024
Hb 11.5 mg/dL
IgM 3500 mg/dL
Fatigue
Relapse
Stage IV disease
RCHOP x 6
8/2021
Labs
PET CT
BM biopsy
Complete remission
Headache
Back pain
Fatigue
Absence seizures
Hb 139 g/L
WBC 6.85 x10^9/L
Platelets 191 x10^9/L
LDH 135 IU/L
B2 M 2.44mg/dL
Liver tests
IgG 1459 mg/dL
IgM 55 mg/dL
CNS relapse
Ibrutinib
560 mg daily
7/2024
Asymptomatic
CSF cell count:
<1 cell/ml

New treatments for marginal zone lymphomas

CAR T-cells

31 MZL pts included in ZUMA 5 (axi cel)
Median 64 yo, median 3 prior treatment lines
ORR 77% || CR 65%
Median DOR at 36 months 64%

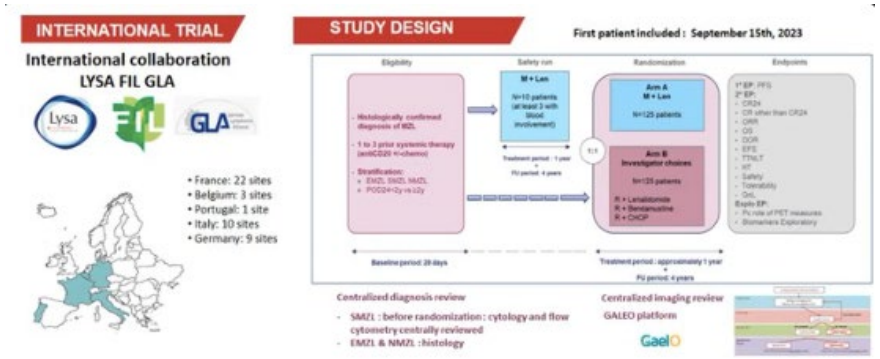




Neelapu et al. Blood 2024, 143(6): 496-506

Bispecific antibodies

- Mosunetuzumab
- Epcoritamab
- Odronextamab
- New trials



Radhakrishnan VS, Davies AJ. Front Immunol. 2024 Jan 11;14:1295599.
Thieblemont C et al. Blood, 2023, 142, 3055

Discussion and conclusions

- Marginal zone lymphomas are indolent but heterogeneous
- Prognosis is usually good but may be difficult to ascertain in individual cases
- Molecular characterization may contribute to the differential diagnosis but distinction from lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia can be difficult in disseminated disease
- In advanced, symptomatic patients first line immunochemotherapy is indicated
- Uncertain remains about optimal treatment sequencing in relapsed/refractory advanced disease
- Relapses in need of systemic therapy may be candidates to new agents including BTK inhibitors
- Intensive chemotherapy and autologous stem cell transplant have a limited role in marginal zone lymphoma
- New treatments in the horizon include cellular and other immunotherapies

References

1. Du MQ. MALT lymphoma: a paradigm of NF-kappaB dysregulation. Semin Cancer Biol. 2016;39:49-60
2. de Leval L, Alizadeh AA, Bergsagel PL et al. Genomic profiling for clinical decision making in lymphoid neoplasms. Blood. 2022 Nov 24;140(21):2193-2227
3. Thieblemont C, Cascieone L, Conconi A et al. A MALT lymphoma prognostic index. Blood. 2017;130(12):1409-1417
4. Kiesewetter B, Raderer M. How can we assess and measure prognosis for MALT lymphoma? A review of current findings and strategies. Expert Rev Hematol. 2021 Apr;14(4):391-399
5. Alderuccio JP, Arcaini L, Watkins MP et al. An international analysis evaluating frontline Bendamustine with Rituximab in extranodal marginal zone lymphoma. *Blood Adv* 2022; 6 (7): 2035–2044
6. Salar A, Doming E, Panizo C et al. First-line response-adapted treatment with the combination of bendamustine and rituximab in patients with mucosa-associated lymphoid tissue lymphoma (MALT2008-01): a multicentre, single-arm, phase 2 trial. Lancet 2014, 1(3) E104-E111
7. Zucca E, Conconi A, Martinelli G et al. Final results of IELSG-19 randomized trial of mucosal associated lymphoide tissue lymphoma: improved event-free survival with Rituximab plus Chlorambucil versus either Chlorambucil or Rituximab monotherapy. J Clin Oncol 2017, 35. DOI: 10.1200/JCO.2016.70.6994
8. Zucca E, L Arcaini, Buske C et al. Marginal Zone Lymphomas: ESMO practice guidelines for diagnosis, treatment and follow up. Ann Oncol 2020, Jan;31(1):17-29
9. Walewska R, Eyre T, Barrington S et al. Guideline for the diagnosis and management of marginal zone lymphomas. A British Society of Haematology guideline. Br J Haematol 2023, DOI: 10.1111/bjh.19064
10. Noy A, de Vos S, Thieblemont C, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood. 2017;129(16):2224–32.
11. Opat S, Tedeschi A, Linton K et al. The MAGNOLIA trial: zanubrutinib, a next-generation Bruton ty- rosine kinase inhibitor, demonstrates safety and efficacy in relapsed/refractory marginal zone lymphoma. Clin Cancer Res. 2021;27(23):6323–32.
12. Avivi I, Arcaini L, Ferretti V et al. High dose therapy and autologous stem cell transplantation in marginal zone lymphoma: a retrospective study by the EBMT Lymphoma Working Party and FIL-GITMO. Br J Hameatol 2018, doi: 10.1111/bjh.15454
13. Albano D, Durmo R, Treglia G et al. ^{18}F-FDG PET/CT or PET Role in MALT Lymphoma: An Open Issue not Yet Solved-A Critical Review. Clin Lymphoma, Myeloma and Leukemia 2019. doi.org/10.1016/j.clml.2019.10.006
14. Grunenberg A, Buske C. How to manage Waldenstrom Macroglobulinemia in 2024. Cancer Treatment Reviews 2024, doi.org/10.1016/j.ctrv.2024.102715