eha

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

Self-assessment case 1

Speaker: Kamila Polgárová, Prague, Czech Republic

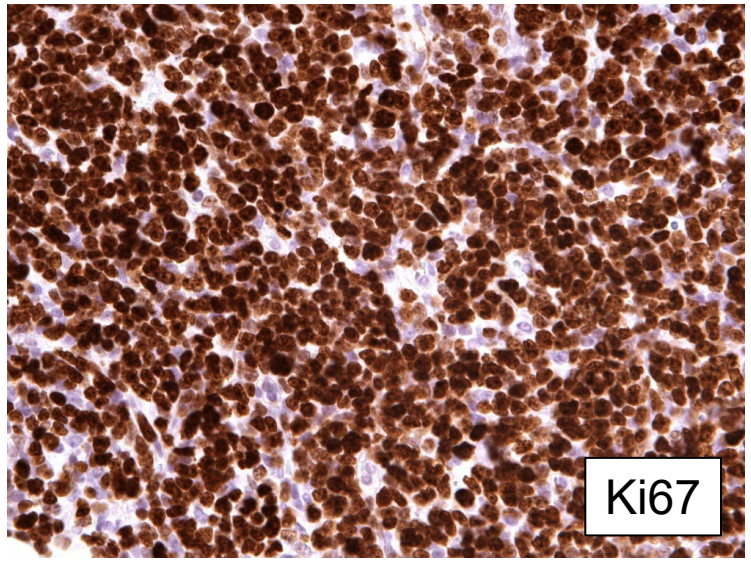
Tbilisi, Georgia

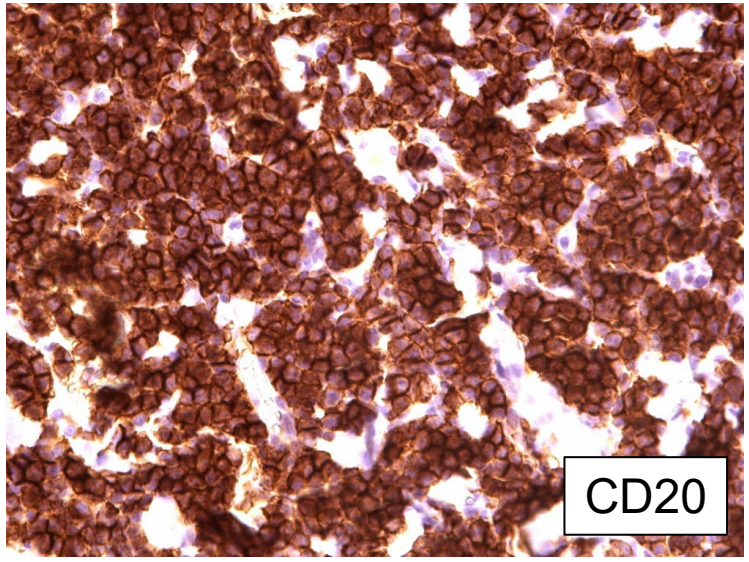
October 18-20, 2024

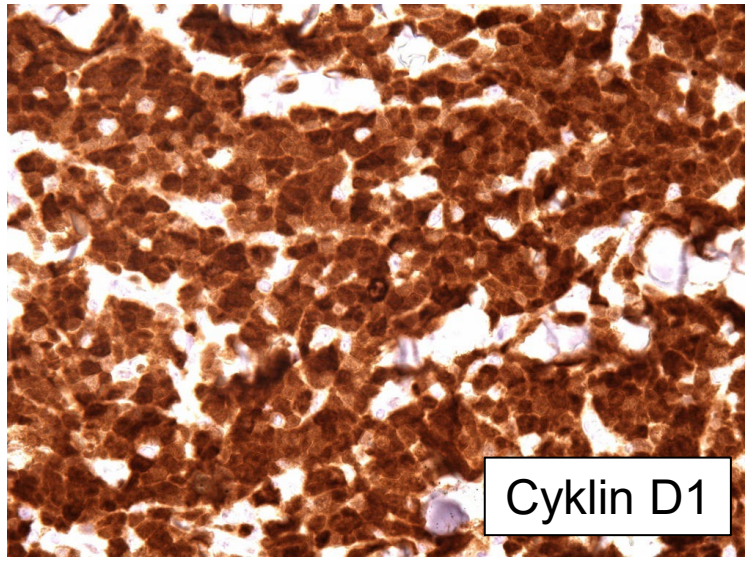
Introduction

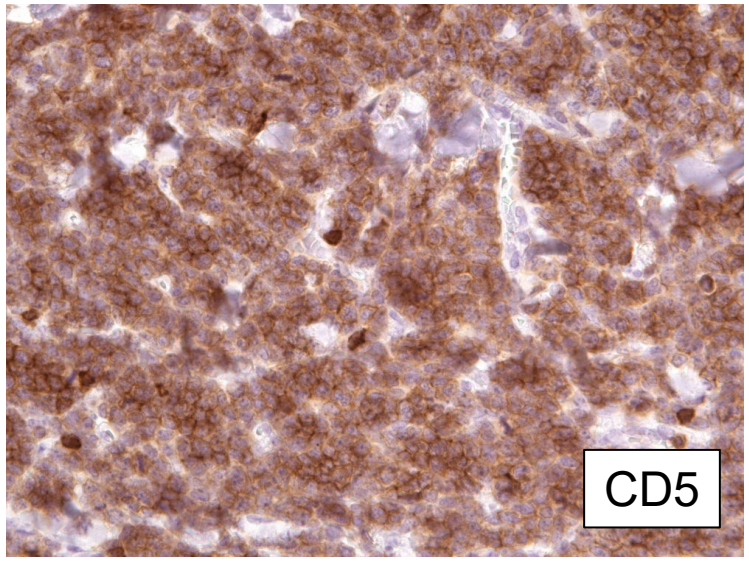
- male, 63 years with history of hypertension and no other significant comorbidities
- History of colorectal carcinoma within parental family
- Presented with cervical and inguinal palpable and painless masses and subcutaneous nodular lesions
- fevers and night sweats appeared soon after masses were observed followed by rapid unintended weight loss
- Fine needle aspiration was indicated by general practitioner with inconclusive results
- Core-cut biopsy from cervical mass showed:

Immunohistochemistry









Q1) What is the diagnosis?

1. Diffuse large B-cell lymphoma
2. Follicular lymphoma
3. Anaplastic large cell lymphoma
4. Mantle cell lymphoma
5. Burkitt lymphoma
6. Small cell lymphoma

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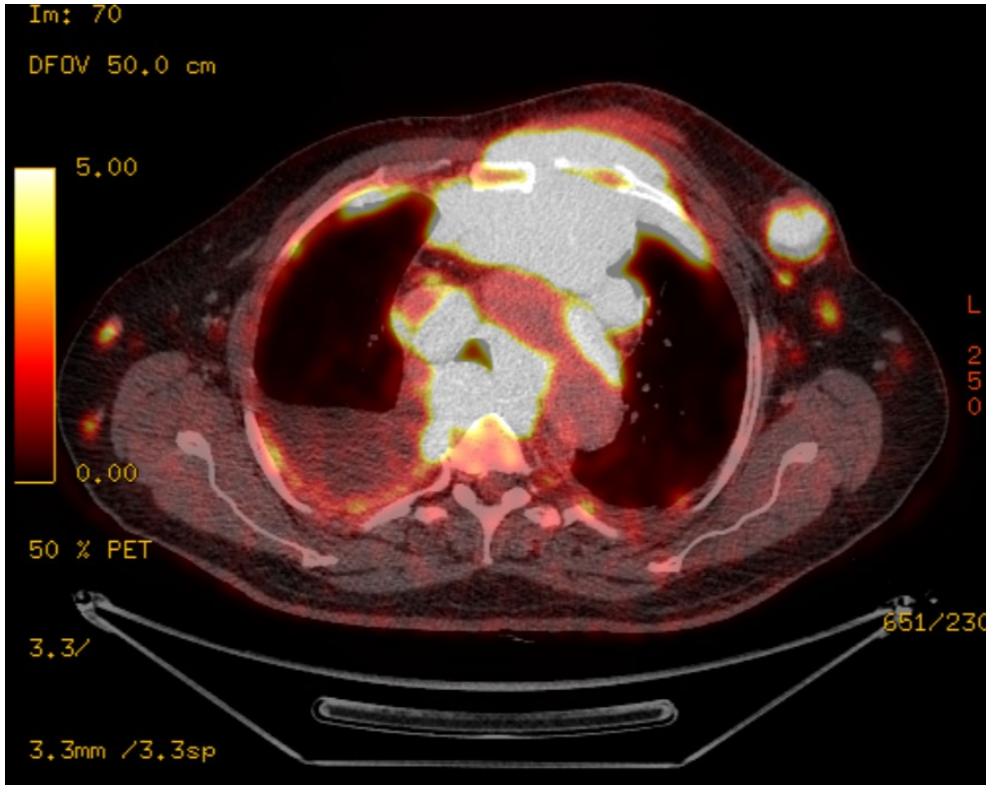
Staging and risk scoring



Clinical stage (Ann Arbor): IVB – generalized lymphadenopathy, liver, spleen and kidneys infiltration, bone marrow infiltration, intramuscular and subcutaneous nodules, CNS (leptomeningeal) involvement

- MIPI(c) score 9.1
  - Age: 63 yrs
  - LDH: 10.1 µkat/L (upper limit: 3.8 µkat/L)
  - WBC: 5.8×10^9/L
  - ECOG 2
  - Ki67 100%

Q2) What is the prognosis?

1. Failure-free survival 5-8 months, OS 11-16 months
2. Failure-free survival 9-13 months, OS 24-30 months
3. Failure-free survival 36 months, OS 5 years
4. Failure-free survival 5 years, OS 10 years

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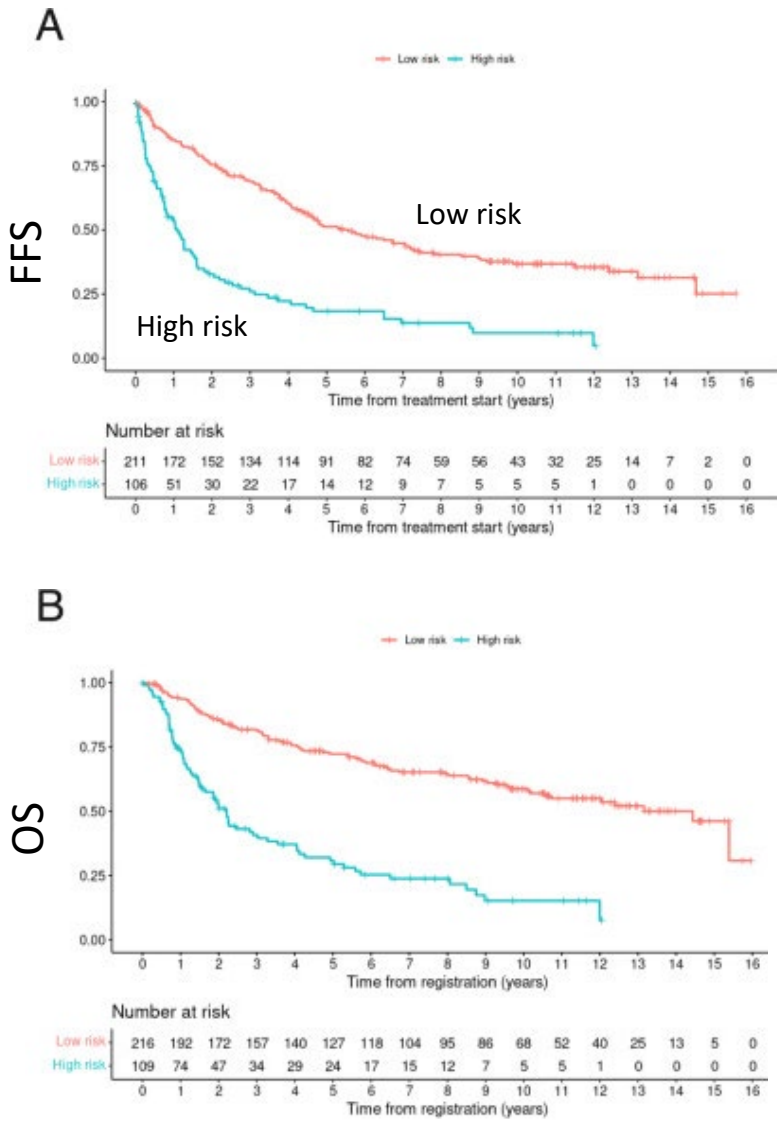
Survival of high-risk MCL



1183 MCL pts with Ann Arbor stage II-IV

- + validation cohorts

High risk: MIPIc high risk or p53 expression > 50%

High-risk x low risk:

- FFS 1.1 yrs x 5.6 yrs, HR 2.97, $p < 0.0001$
- OS 2.2 yrs x 13.2 yrs, HR 3.69, $p < 0.0001$
- Discriminatory power confirmed in subgroup analyses in elderly and younger MCL groups
- R-CHOP+R-DHAP vs. R-CHOP partially mitigates the dismal prognosis

Scheubeck G et al. Leukemia 2023

Q3) What other factors define the prognosis?

1. TP53 and CDKN2A mutation
2. BCL2 and BCL6 expression
3. Superficial CD5 expression
4. IgG rearrangement
5. Response to corticoid pretreatment

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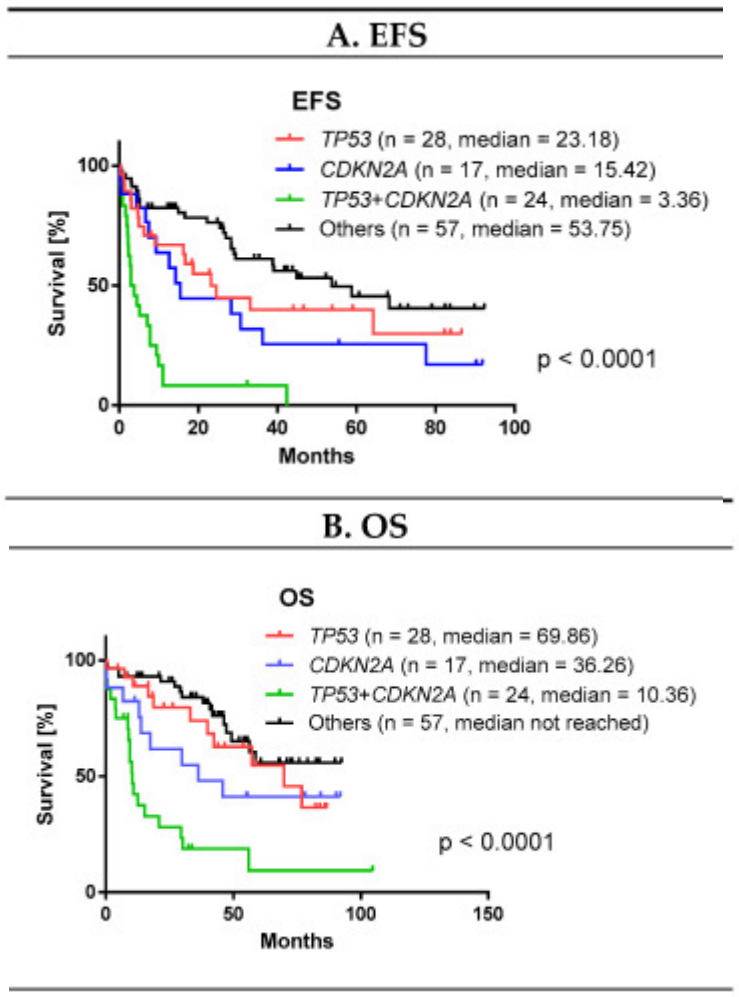
Factors defining prognosis of MCL patients



- **CDKN2A aberrations** are probably a late event (described exclusively in the context of other gene aberrations)
- **TP53 + CDKN2A aberrations** – independent marker of chemoresistance
  - EFS 3 months; OS 10 months
  - Addition of HD AraC regimen does not mitigate the dismal prognosis
  - New modalities, intensified treatment and upfront HSCT should be considered

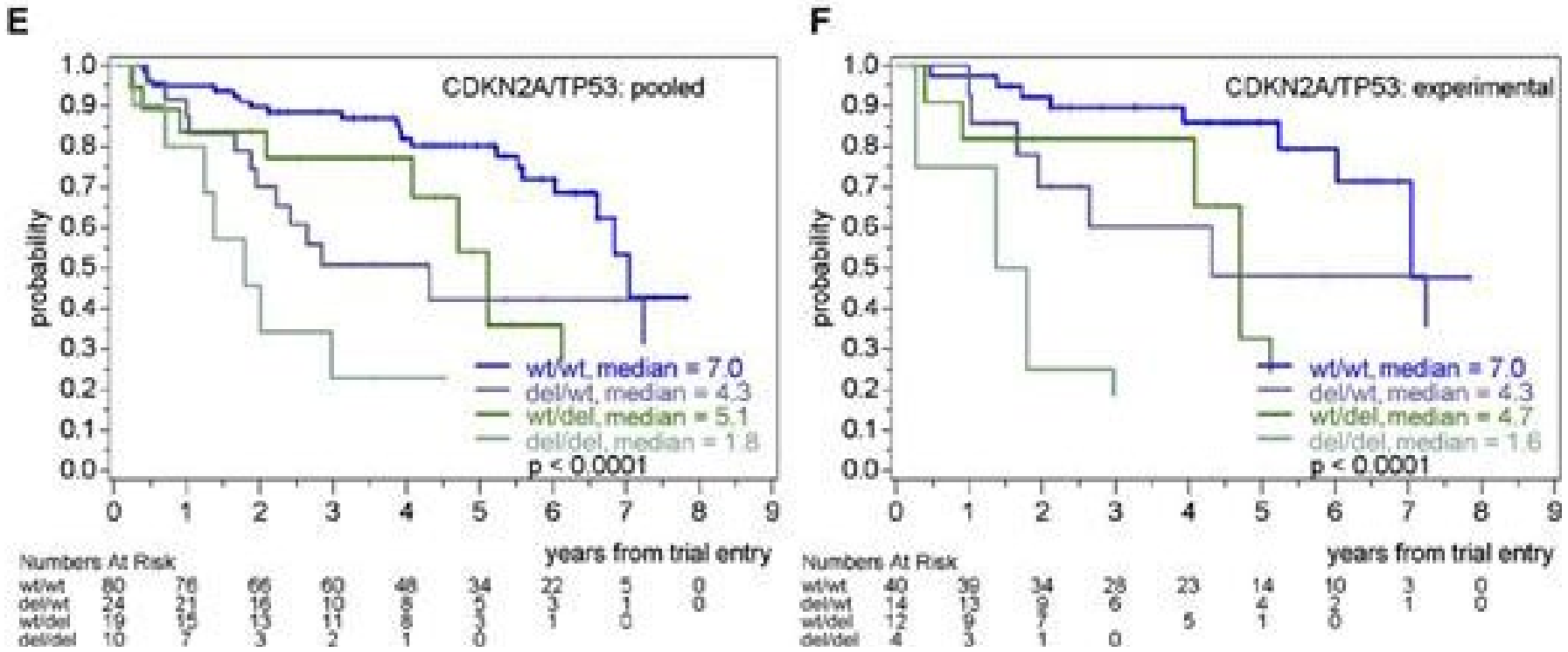
Other aberrations with negative impact:

- RB1 deletion
- CDKN1B deletion
- (ATM del, cMYC gain – contradicting data)

Malarikova D et al. Cancers 2020
Delfau-Larue MH et al. Blood 2015
Koff LJ et al. Blood 2022 suppl. Abstr. No 140

Case report: prognostic factors and FISH and NGS findings

- Clinical stage: IVB
- MIPI(c) score 9.1
- Ki67 100%
- TP53 deletion ATM deletion
- RB1 deletion
- CDKN2A deletion



Time to treatment failure in patients from European MCL Younger trial treated by chemoimmunotherapy (R-CHOP (E) or R-CHOP/R-DHAP) followed by ASCT

Delfau-Larue MH et al. Blood 2015

Q4) What is the preferred first line treatment

1. R-CHOP
2. R-Bendamustin
3. R-DHAP + venetoclax
4. R-(maxi)CHOP alt. R-DHAP + ibrutinib
5. R-hyperCVAD alt. R-HD-MTX

Q4) What is the preferred first line treatment

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2. R-Bendamustin
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4. R-(maxi)CHOP alt. R-DHAP + ibrutinib
5. R-hyperCVAD alt. R-HD-MTX

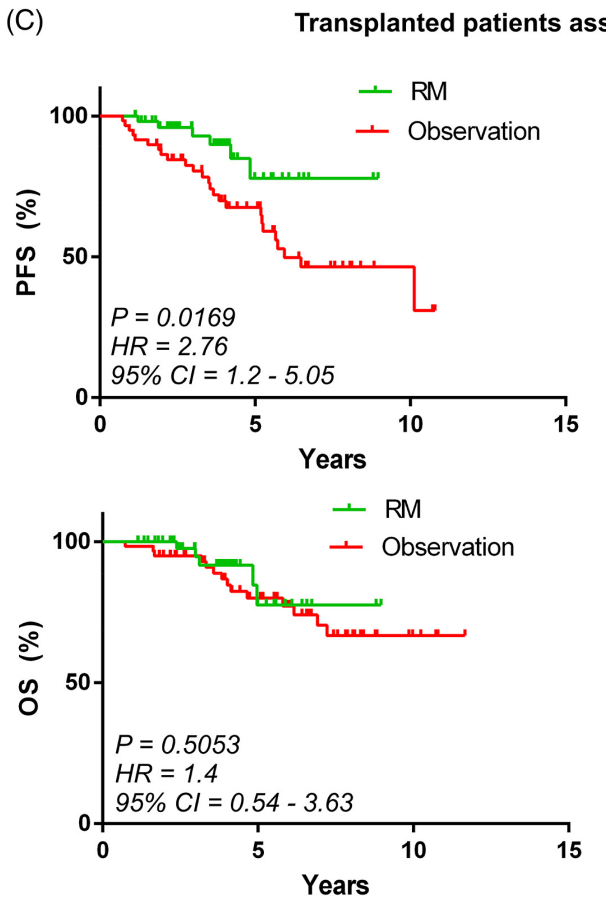
Treatment choices in Mantle Cell Lymphoma

1. **Decision making factors**:
   - Biological age / eligibility for intensive treatment
   - Disease associated factors – MIPI, Ki67, TP53, CDKN2A
2. **Aggressive induction regimens**:
   - Nordic protocol
   - R-CHOP+covalent BTKi/R-DHAP
   - (consolidation by ASCT)
   - Maintenance: rituximab + covalent BTKi
   - (Zanubrutinib+venetoclax+obinutuzumab in TP53 mutated)
   - Clinical trial

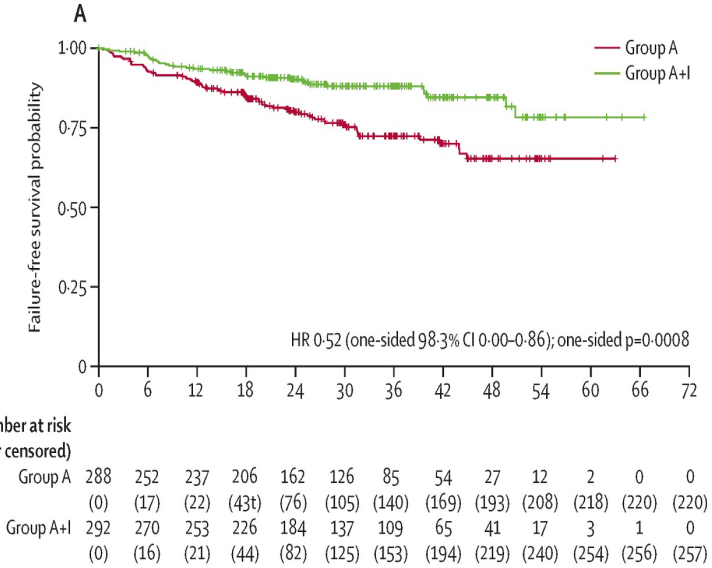
NCCN guidelines 2024

Treatment choices in Mantle Cell Lymphoma

Nordic protocol (incl ASCT) +/- RM



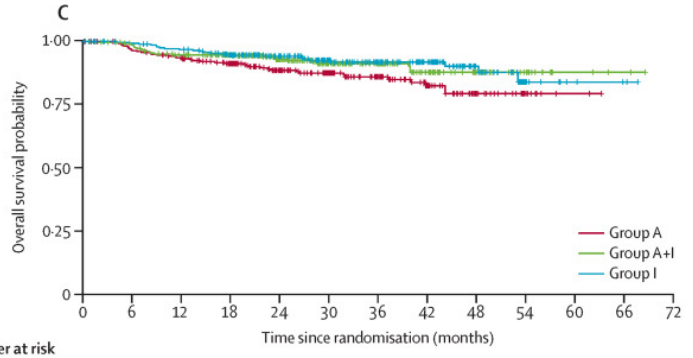
TRIANGLE: (I)R-CHOP/R-DHAP+ASCT +RM +/- IM



Number at risk (number censored)

Group A	288	252	237	206	162	126	85	54	27	12	2	0	0
	(0)	(17)	(22)	(43t)	(76)	(105)	(140)	(169)	(193)	(208)	(218)	(220)	(220)
Group A+I	292	270	253	226	184	137	109	65	41	17	3	1	0
	(0)	(16)	(21)	(44)	(82)	(125)	(153)	(194)	(219)	(240)	(254)	(256)	(257)

TRIANGLE: (I)R-CHOP/R-DHAP+/-ASCT +RM +/- IM



Number at risk (number censored)

Group A	288	270	256	230	181	145	97	63	32	15	2	0	0
	(0)	(8)	(13)	(34)	(77)	(111)	(157)	(188)	(217)	(234)	(247)	(249)	(249)
Group A+I	292	280	262	238	195	142	113	67	43	19	4	2	0
	(0)	(8)	(15)	(38)	(78)	(128)	(157)	(200)	(225)	(248)	(263)	(265)	(267)
Group I	290	281	272	248	197	145	109	77	39	16	4	3	0
	(0)	(7)	(9)	(27)	(77)	(126)	(161)	(193)	(231)	(251)	(263)	(264)	(267)

Klener P et al. Am J Hematol 2019
Dreyling M et al. Lancet 2024

Addressing CNS involvement

- Rare complication (< 5%) with dismal prognosis (median PFS after CNS directed Th 2.4m)
- HD MTX/AraC
- Intrathecal chemotherapy
- Ibrutinib
- Radiotherapy
- (CAR T-ly)

Figure 1. Overall Survival from CNS diagnosis

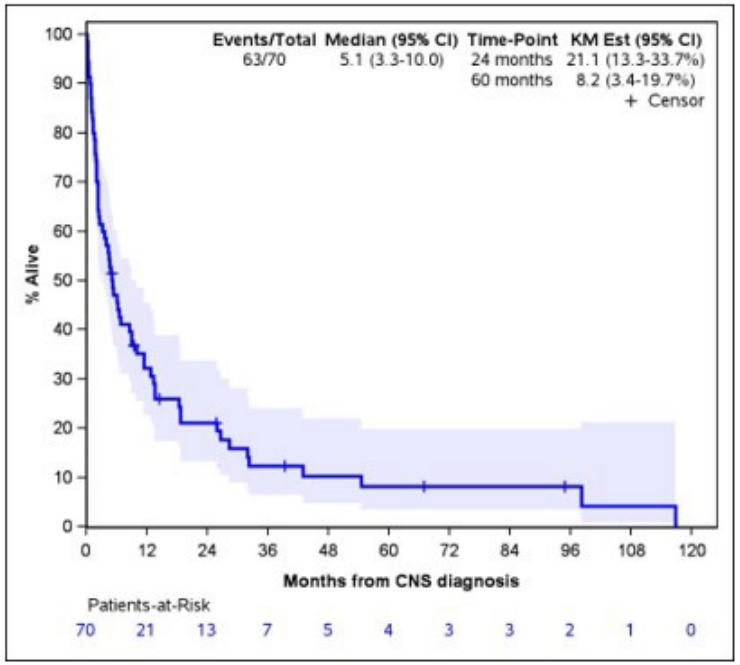
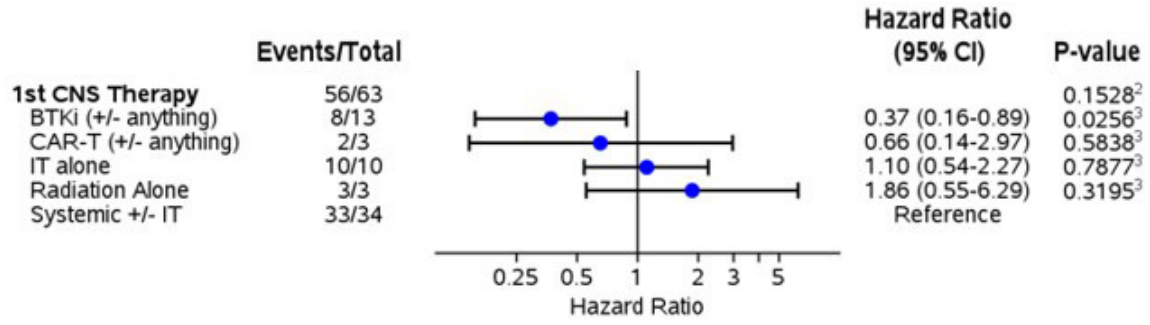


Figure 2. Univariable Cox models of OS from CNS diagnosis

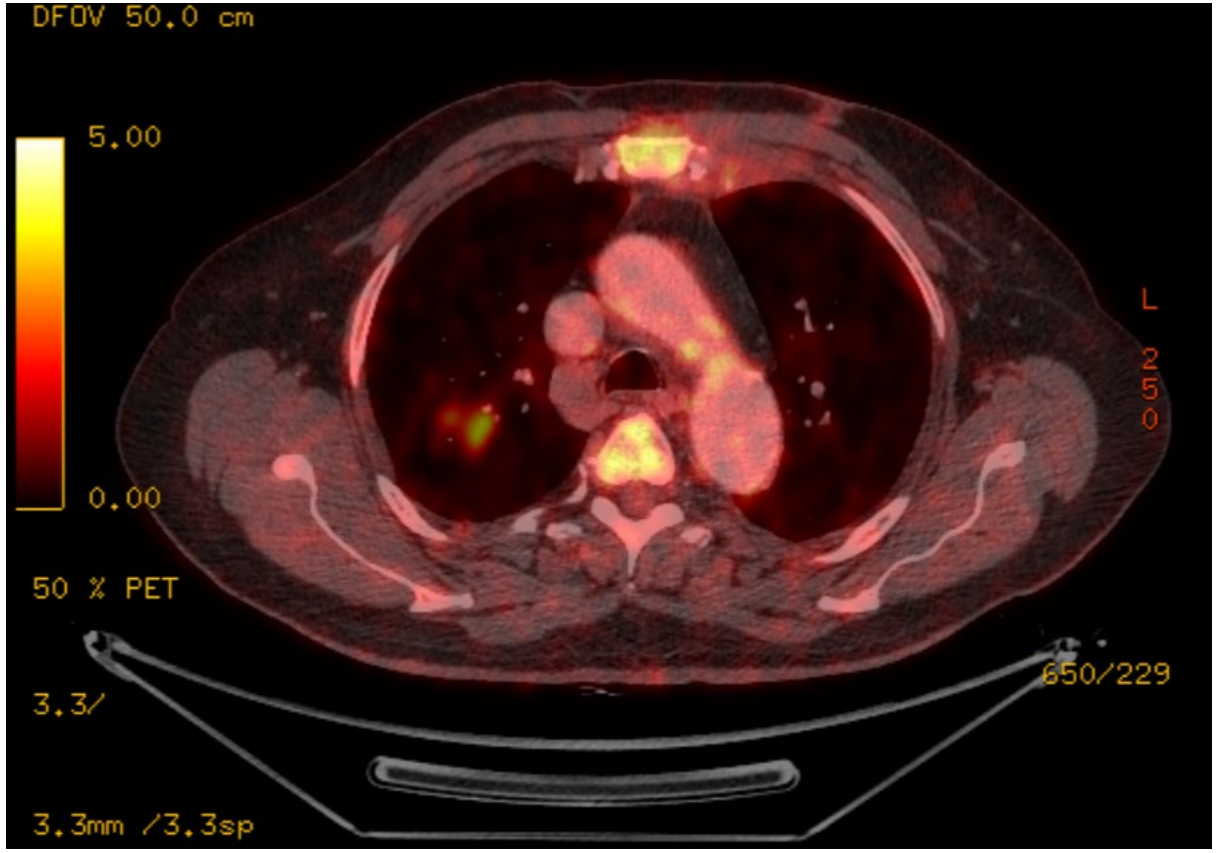


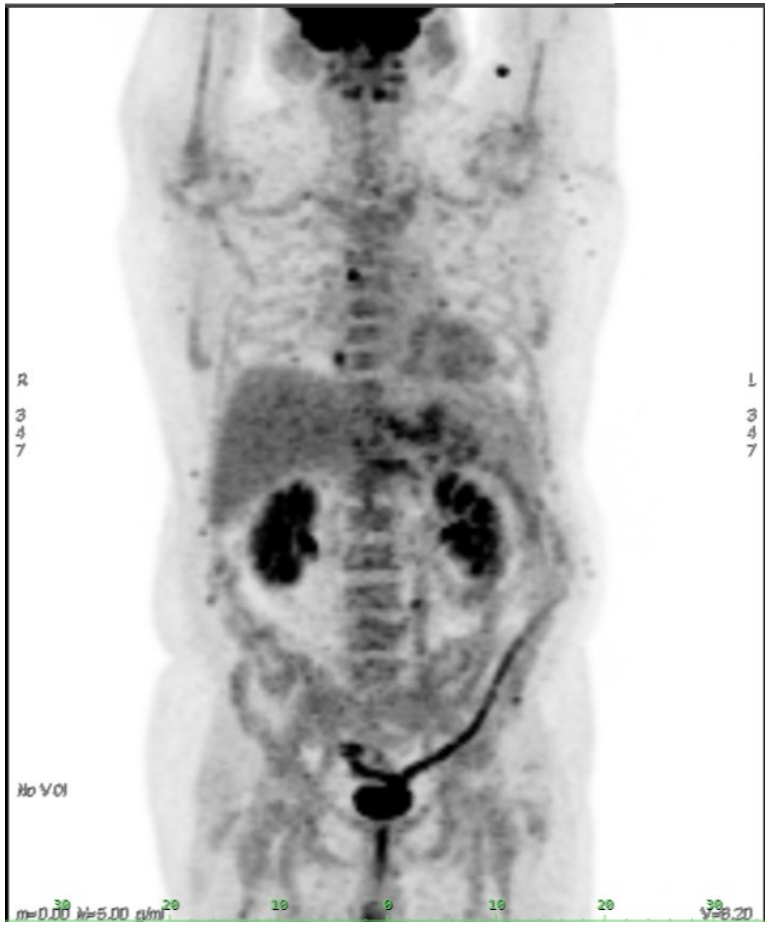
[1]Stratified covariate Wald p-value; [2]Stratified type 3 Wald p-value; [3]Covariate Wald p-value;

McLaughlin N et al. Blood 2023 Supp 142

Case report: treatment response

The patient achieved complete metabolic remission with MRD positivity in BM after R-maxiCHOP/R-DHAP + triple i.t. chemotherapy (ibrutinib was not available at the time (2017))





Q5) What would be nowadays the preferred subsequent treatment after the induction, if any?

1. none
2. Rituximab maintenance
3. +/- ASCT followed by rituximab + ibrutinib maintenance
4. ASCT, no maintenance
5. Mercaptopurin maintenance

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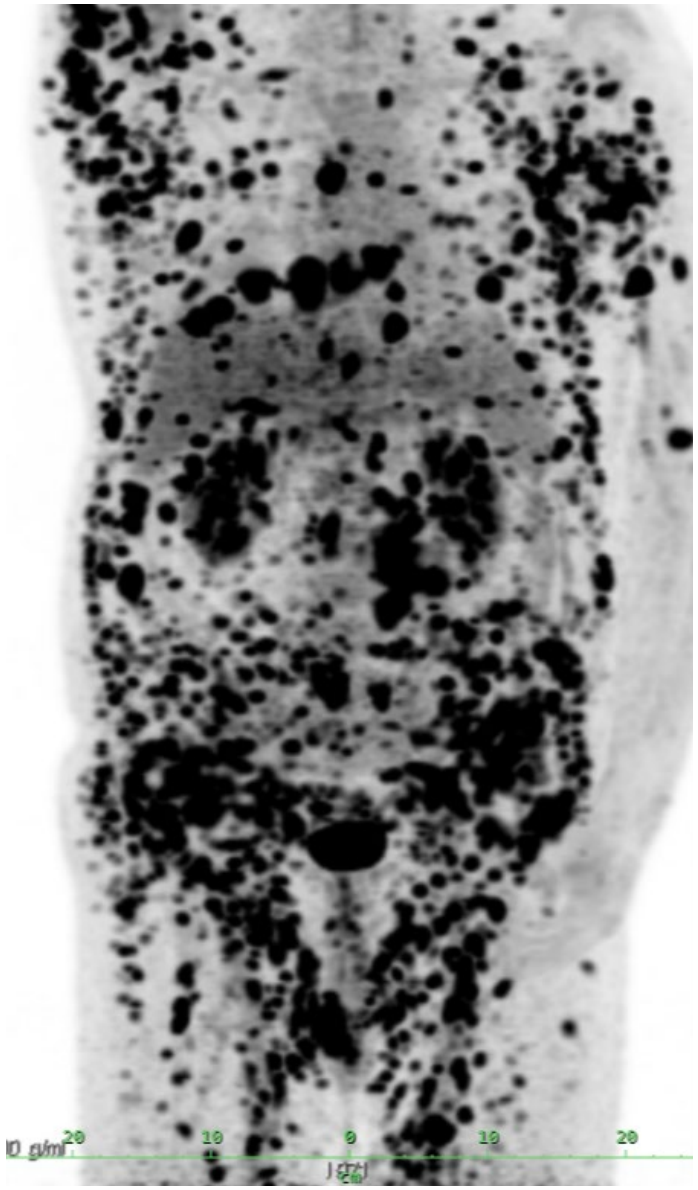
Case report: early progressing disease



The patient fulminantly progressed - before ASCT

- multiple subcutaneous and intramuscular lesions
- Liver, spleen and kidney infiltration
- Bone marrow involvement
- No prove of CNS relapse

Q6) What is the preferred next line treatment option after an early relapse after BTKi containing regimen

1. Rituximab-lenalidomide
2. Polatuzumab-vedotin+bendamustin+rituximab
3. CAR T-cell Therapy
4. Idelalisib
5. Epcoritamab

Q6) What is the preferred next line treatment option after an early relapse after BTKi containing regimen

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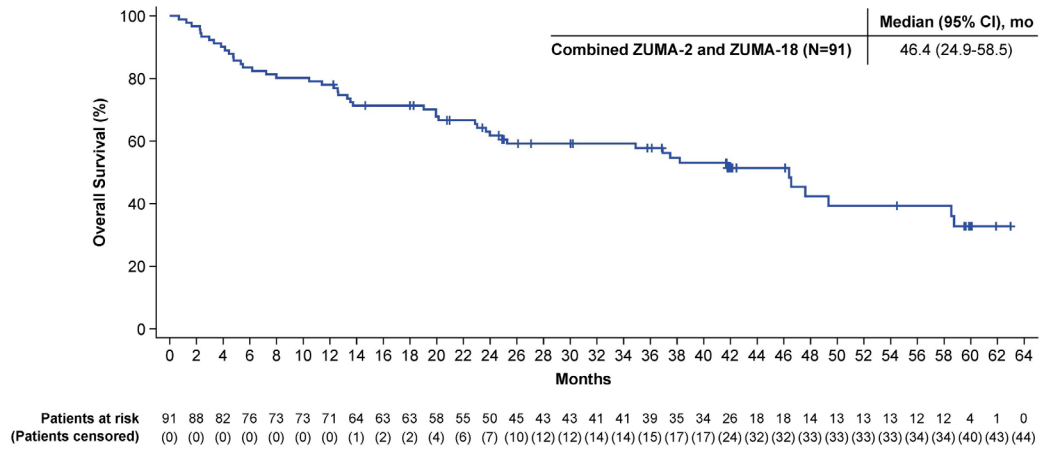
Relapse after BTKi treatment

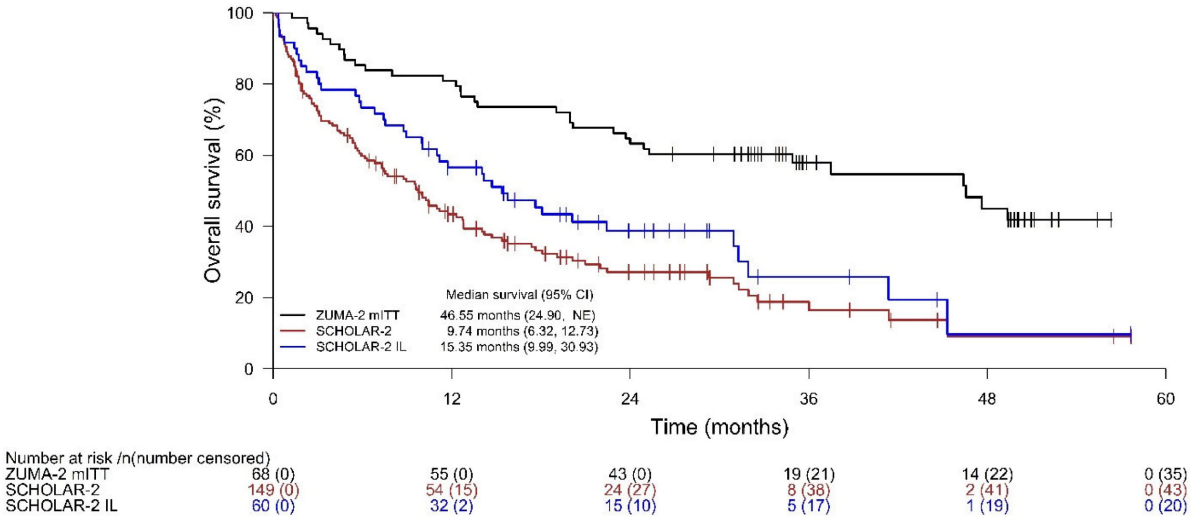
Brexu-cel in R/R MCL after BTKi failure

- incl. 17% of pts with confirmed TP53 mut
- ORR 91%, CR 68%
- PFS 26m, OS 47m

	ZUMA-2	SCHOLAR-2
No. patients	68	60
Mean age	63.2 ± 7.8 years	69.5 ± 9.5 years
Median lines th	3 (range, 1-5)	3 (range, 1-6)
After ASCT	43%	37%
Median OS	46.6 months	15.4 months
	HR 0.43 (95% CI, 0.26-0.68, p < 0.001)	

Figure 2. Combined Overall Survival in ZUMA-2 and ZUMA-18





Hess G et al, Leuk Lymp 2024
Wang M et al. NEJM 2020

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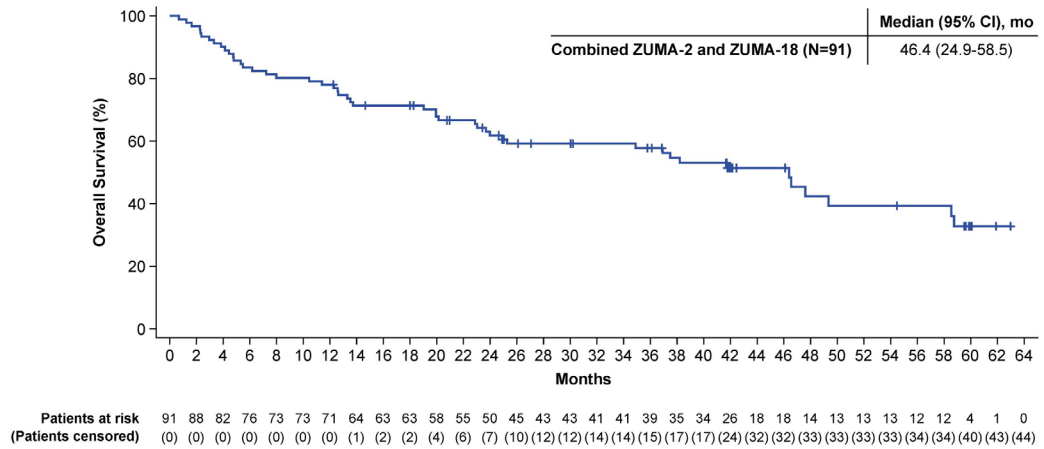

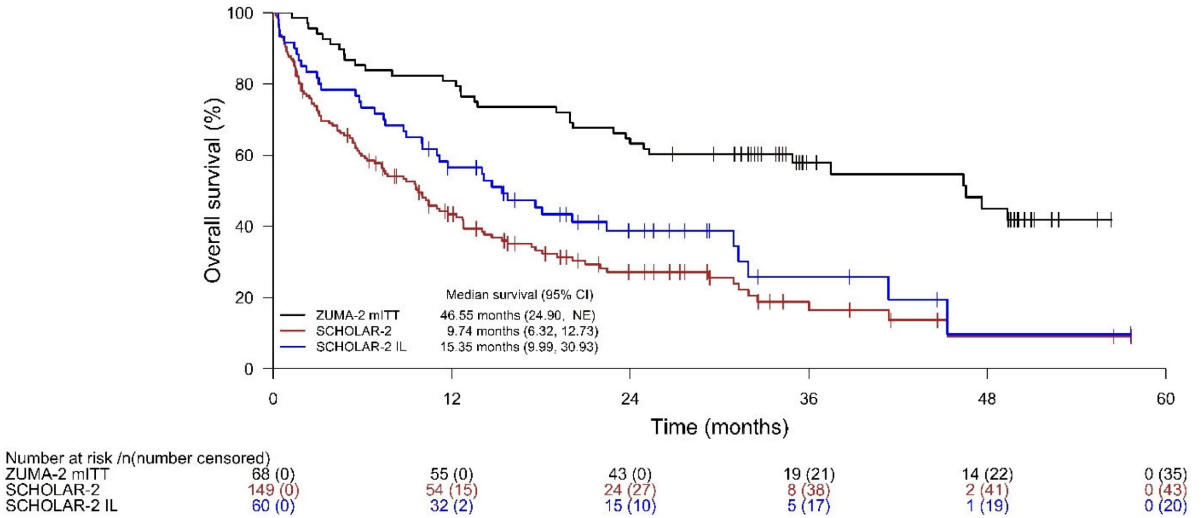

Hess G et al, Leuk Lymp 2024
Wang M et al. NEJM 2020

Discussion

- Mantle cell lymphoma is an aggressive B-NHL with variable course and prognosis depending on different factors including
  - Tumor volume
  - Proliferation index
  - Cytogenetic/mutation profile
- R-CHOP is usually not suficient to control the disease - more intensive regimens incl. HD AraC are needed
- Upfront ASCT should be discussed for eligible patients
- Considering the proven benefit, BTKi should optimally be included in the 1st line treatment and maintenace therapy, particularly for high risk patients

Thank you for your attention

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eha

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

Self-assessment case 2

Speaker: Kamila Polgárová, Prague, Czech Republic

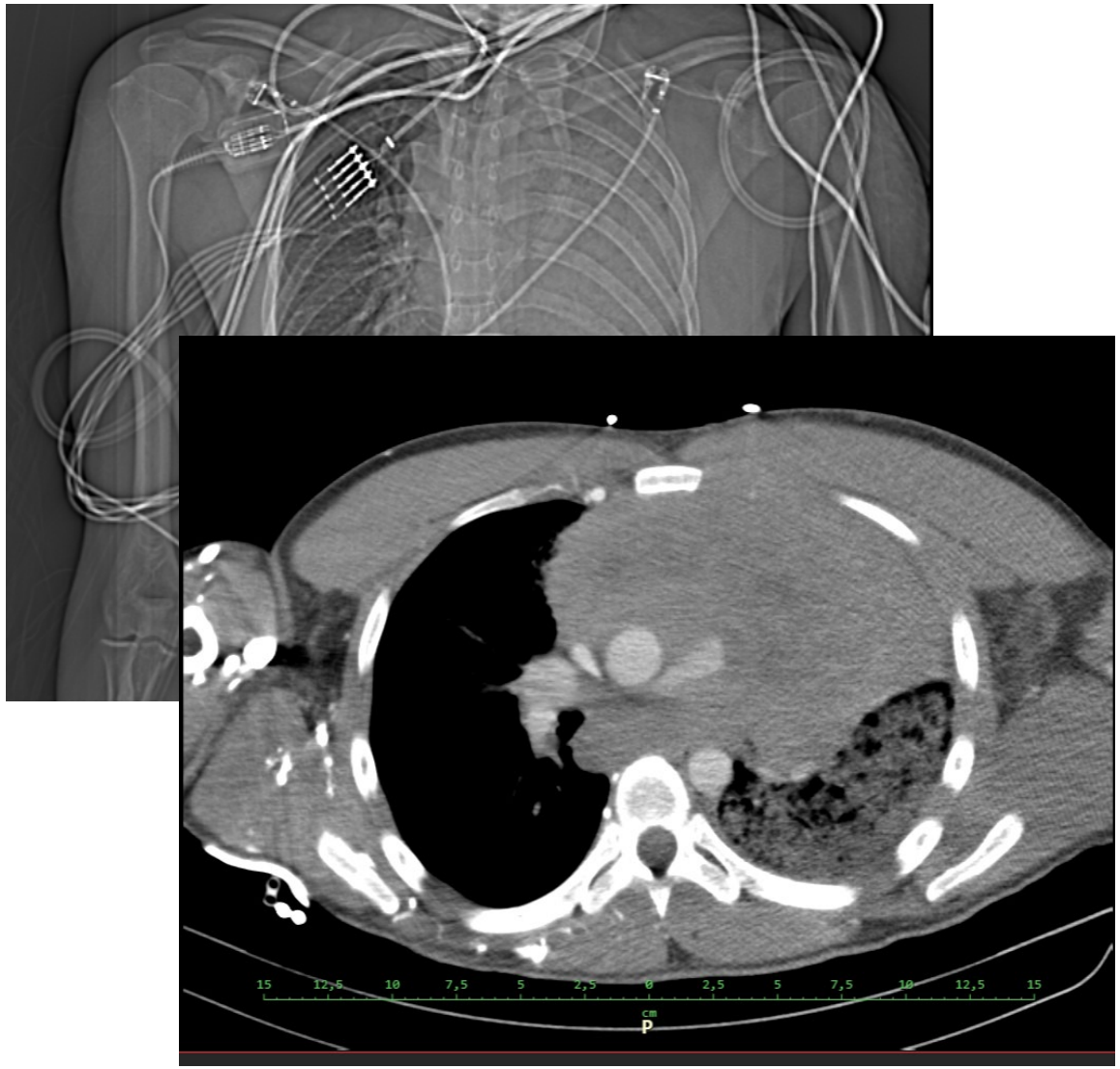
Tbilisi, Georgia

October 18-20, 2024

Introduction

- male, 22 years with no significant history of severe diseases/comorbidities
- Presented with rapidly progressing shortness of breath and cough during SARS-CoV-2 pandemic
- Examination: swelling of the head, neck and partially upper limbs; absent breathing sounds on the left side
- Vital signs at first presentation at the emergency department:
  - BP 115/70mmHg; P 135/min (sinus tachycardia on ECG); satO2 spont. 89%; Temp 37.1°C
- LAB tests: WBC $11x10^9$/L, Hb 124g/L, Plt $480x10^9$/L, ANC $7.2x10^9$/L; CRP 145mg/L; lactate 3.8mmol/L; LDH nor PCT were not tested at the time of admission
- COVID-19 PCR testing was negative

Imaging studies



- X-ray showed massive left-side fluidothorax and mediastinal mass
- Bed-side chest ultrasound confirmed massive pleural effusion
    - A drain was placed – 2.5L of fluidothorax was evacuated with characteristics of exsudate
- Bed-side ECHO showed pericardial effusion and D-shaped left ventricle

Q1) What would be the next diagnostic/therapeutic step after stabilizing the patient?

1. PET/CT scan
2. Cytology of the fluidothorax
3. Fine needle biopsy
4. Bioptic verification
5. Antibiotics and observation
6. Pretreatment by cyclofosfamide

Q1) What would be the next diagnostic/therapeutic step after stabilizing the patient?

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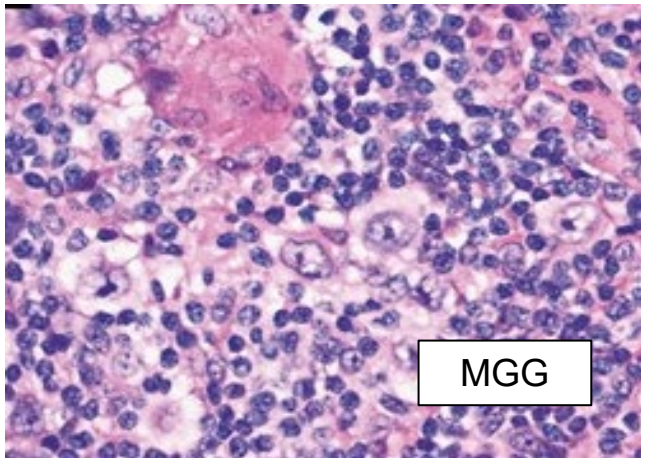
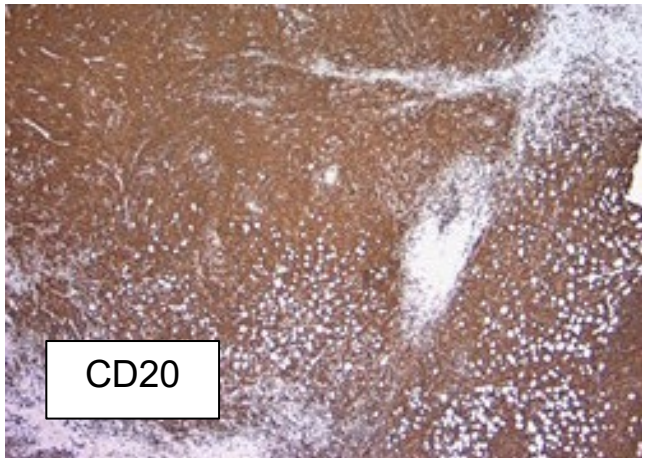
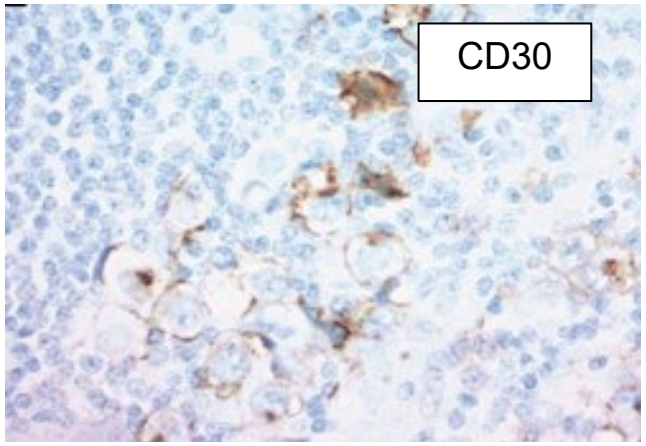
Case report

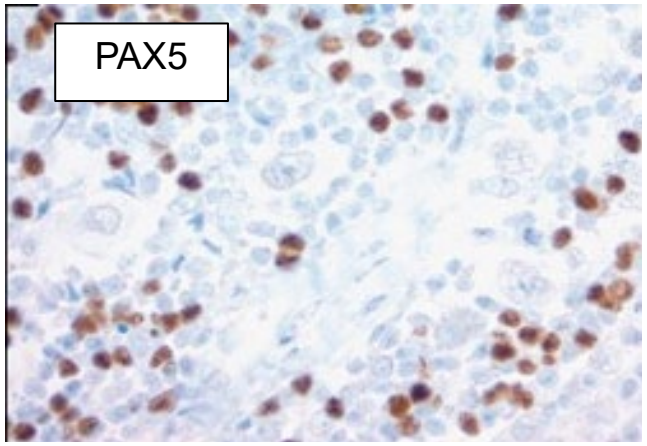
- The patient underwent transparietal CT navigated biopsy
  - Right after the procedure, corticosteroids were started
- Flow cytometry and cytology of the pleural effusion were performed at the same time
  - Came out negative for pathologic/clonal population

Q2) What is the diagnosis?









Ondrejka SL, Ott G. American Journal of Clinical Pathology. 2021

Q2) What is the diagnosis?

1. Classic Hodgkin lymphoma
2. Gray zone lymphoma
3. Anaplastic large cell lymphoma
4. Primary mediastinal B-cell lymphoma
5. Burkitt’s lymphoma

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Primary mediastinal B-cell lymphoma

- Specific large B-cell neoplasm with unique clinical and biological properties
- Affects mainly young adults
- Generaly better prognosis comparing to other DLBCL subtypes

	Localization/Growth	Histology	Immunophenotype
PMBL	Anterior-superior mediastinal mass in thymic area, occasionally other extranodal sites or locoregional lymph nodes	Diffuse growth of medium- to large-sized cells, with pale to clear cytoplasm and compartmentalizing alveolar sclerosis, occasional pleomorphic cells	Strong B-cell antigen expression (CD20, CD79a, CD22, PAX5, BOB1, OCT2, PU.1, CD30 weak/partial, CD23, CD200, cREL, TRAF, MAL
CHL	Mediastinal involvement occurs in approximately 78% of cases, involves lymph nodes with contiguous spread	Nodules of inflammatory cells and HRS cells separated by broad collagen bands	CD30, PAX5 (weak), CD15, sometimes EBV positive, CD20 is typically negative or weak, OCT2 and BOB1 are variable/weak
MGZL	Most patients have mediastinal involvement (approximately 73%); can include systemic disease	Sheet-like growth of pleomorphic tumor cells; can be CHL like or PMBL/DLBCL like; paucity of inflammatory cells	Divergent from morphology: CHL-like patterns have strong CD20 and B-cell markers, weak/absent CD30, variable CD15; PMBL-like patterns have CD30 and inconsistent or negative CD20 and CD79a and other B-cell markers

Ondrejka SL, Ott G. American Journal of Clinical Pathology. 2021

Q3) What would be the first line treatment?

1. 4x R-CHOP
2. R-CHOP / R-AraC
3. R-CHOEP or R-DA-EPOCH
4. Pola-R-CHP
5. GMALL protocol

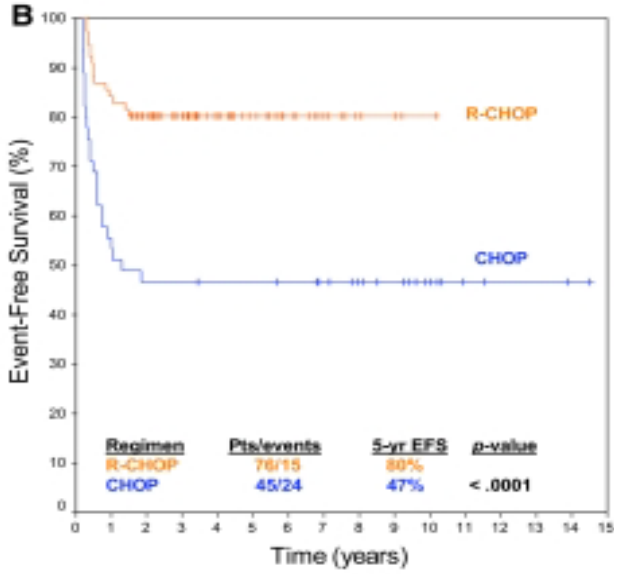
Q3) What would be the first line treatment?

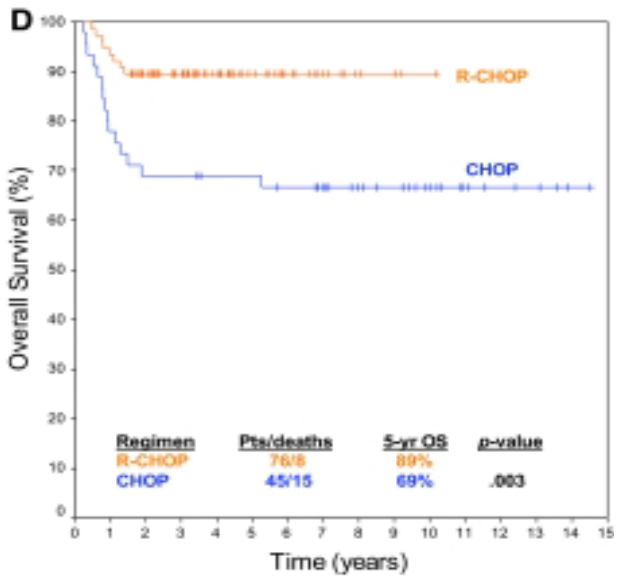
1. 4x R-CHOP
2. R-CHOP / R-AraC
3. R-CHOEP or R-DA-EPOCH
4. Pola-R-CHP
5. GMALL protocol

Treatment options

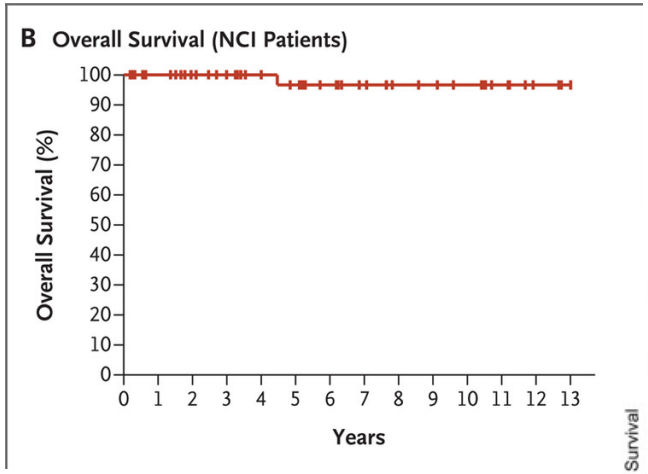
- 6x R-CHOP21
- 4-6x R-CHOP14
- 6x R-DA-EPOCH
- 6x R-CHOEP14/21
- +/- radiotherapy

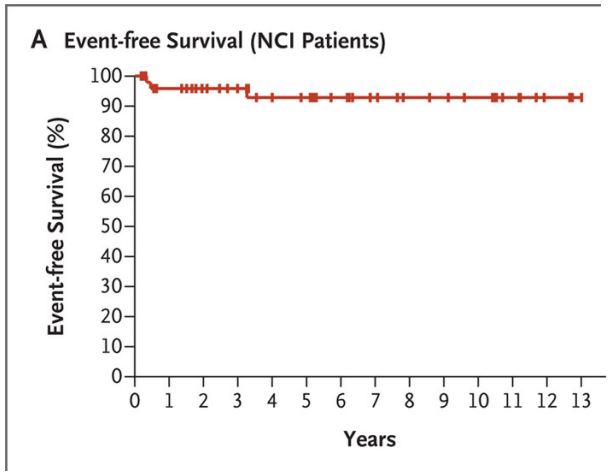
R-CHOP+/-RT



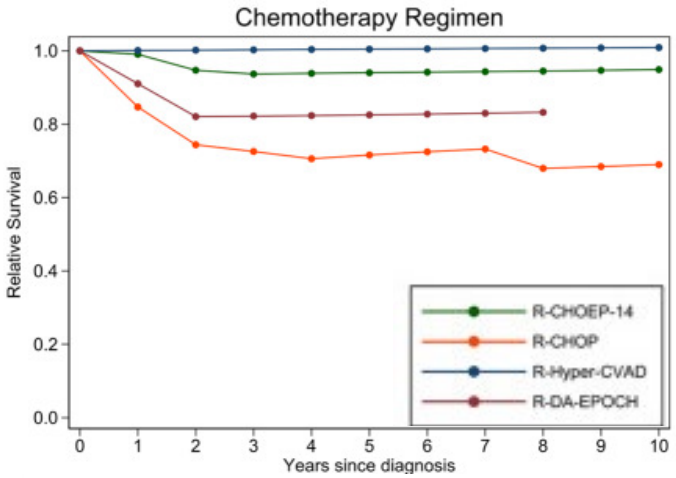


R-DA-EPOCH (no RT)





RWE – different regimens (+/- RT)



NCCN guidelines 2024
Wasterlid T et al. Blood Cancer J 2021
Vassilakopoulos T et al. Oncologist 2012
Dunleavy K et al. NEJM 2013

Q4) How would you asses the treatment response

1. PET/CT scan during (after 2-3 cycles) and after (6 cycles) the chemoimmunotherapy
2. PET/CT scan after finishing the 6 cycles of chemoimmunotherapy
3. CT scan during (after 2-3 cycles) and after(6 cycles) the chemoimmunotherapy
4. CT scan after finishing the 6 cycles of chemoimmunotherapy
5. X-ray during the treatment and PET/CT scan after finishing chemoimmunotherapy

Q4) How would you asses the treatment response

1. PET/CT scan during (after 2-3 cycles) and after (6 cycles) the chemoimmunotherapy
2. PET/CT scan after finishing the 6 cycles of chemoimmunotherapy
3. CT scan during (after 2-3 cycles) and after(6 cycles) the chemoimmunotherapy
4. CT scan after finishing the 6 cycles of chemoimmunotherapy
5. X-ray during the treatment and PET/CT scan after finishing chemoimmunotherapy

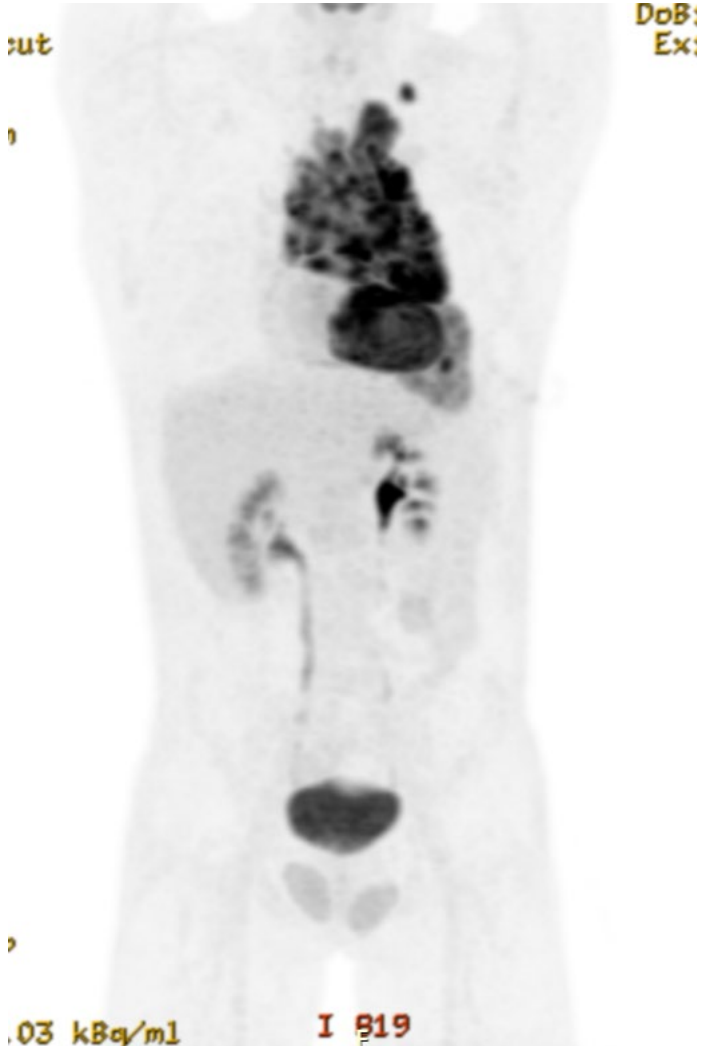
Evaluating response during and after therapy

For **FDG avid** neoplasms:

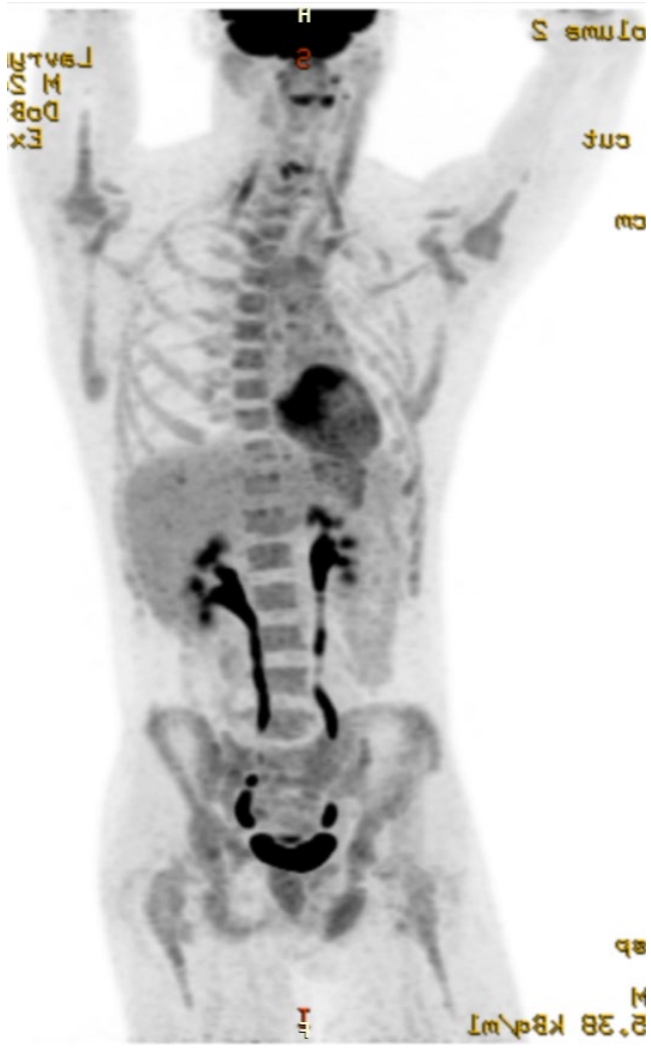
- PET/CT at time of dg – to asses the extent of the disease
- PET/CT interim (after 2-3 treatment cycles) + final (after finishing the therapy) – to asses response of the disease
- Response criteria:
  - Lugano criteria – Deauville five-point scale
  - LYRIC criteria (for immunomodulatory drugs)

Cheson BD et al. JCO 2014
Cheson BD et al. Blood 2016

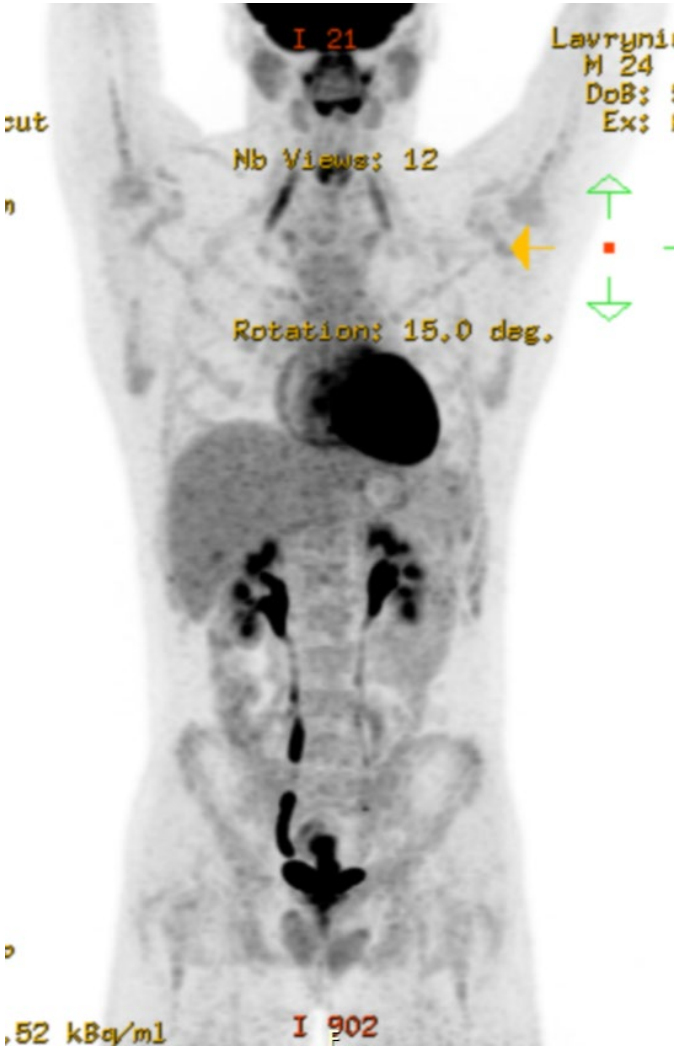
Case report – residual mass with Deauville PS3



Diagnosis



Interim



Final

Q5) What, if any, would be the proper consolidation?

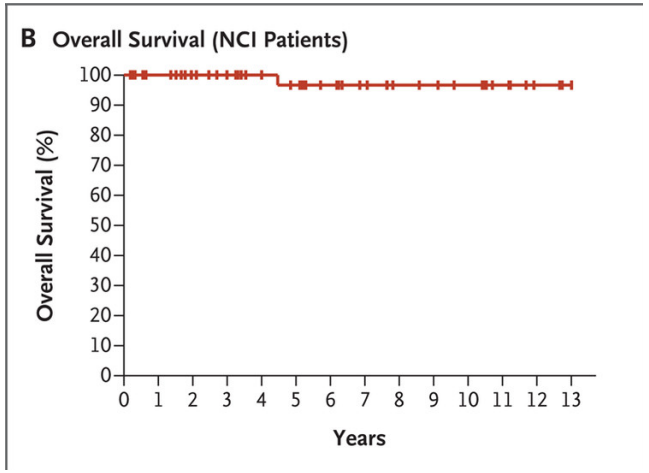
1. Rituximab maintenance
2. Brentuximab vedotin maintenance
3. Radiotherapy
4. ASCT
5. None

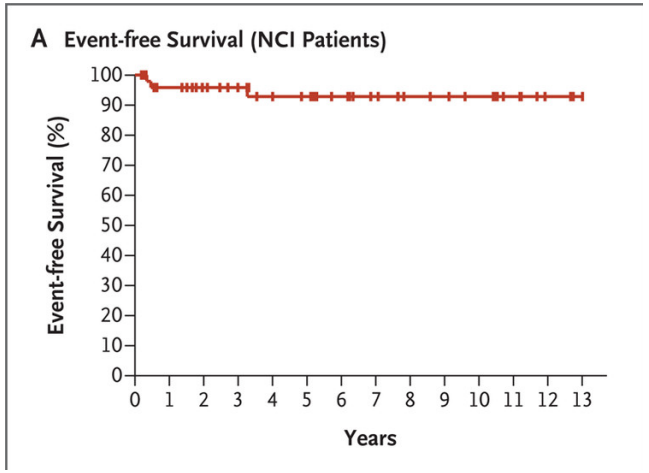
Q5) What, if any, would be the proper consolidation?

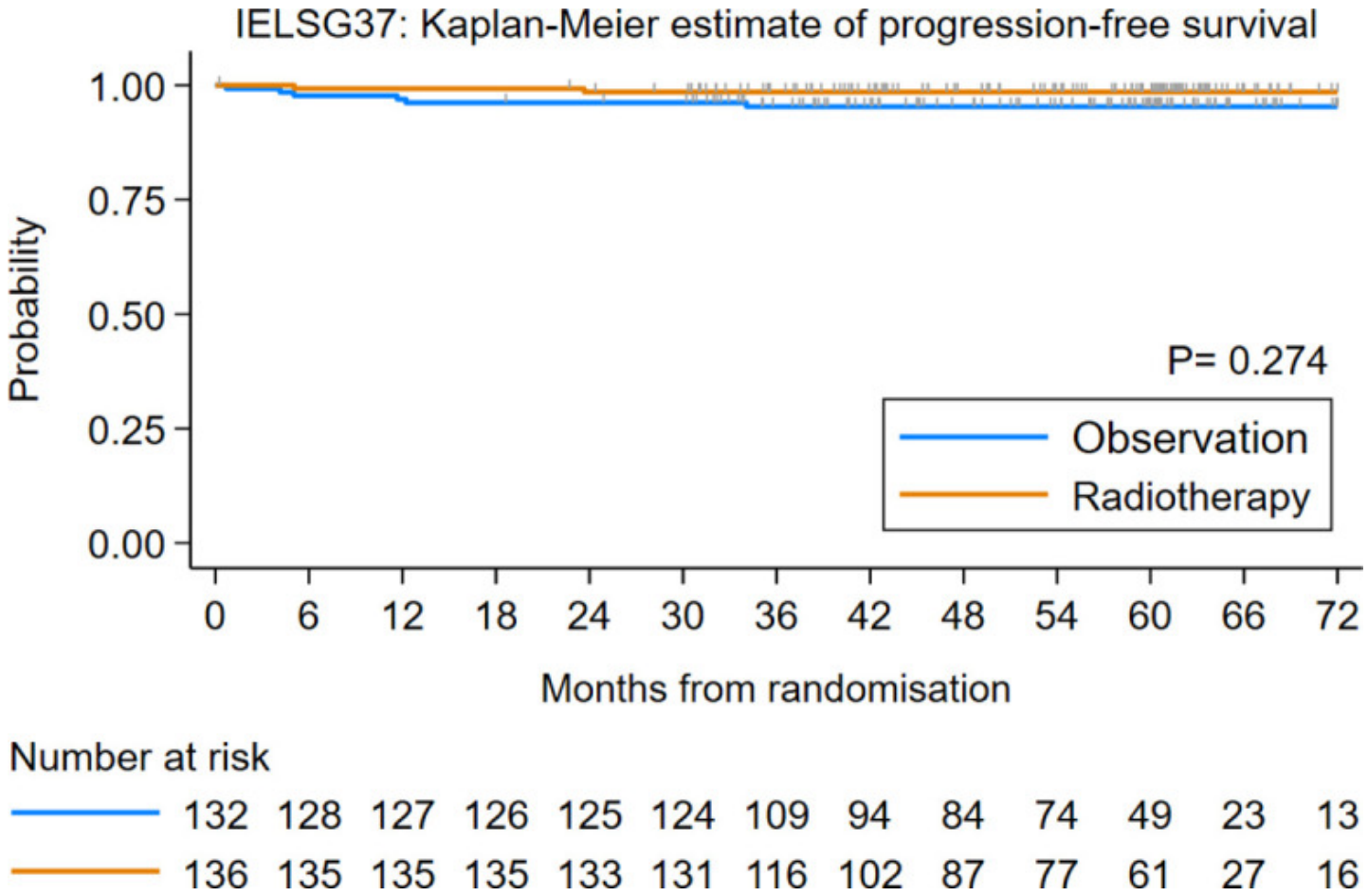
1. Rituximab maintenance
2. Brentuximab vedotin maintenance
3. Radiotherapy
4. ASCT
5. None

Role of radiotherapy after achieving CR

R-DA-EPOCH (**no** RT)







Dunleavy K et al. NEJM 2013
Martelli M et al. Hemasphere 2023. Suppl

Q6) What would be your treatment suggestion in case of progression/relapse?

1. Loncastuximab-tesirin
2. Ibrutinib+venetoclax
3. Salvage platinum regimen + ASCT
4. Tisagenlecleucel
5. Single agent nivolumab

Q6) What would be your treatment suggestion in case of progression/relapse?

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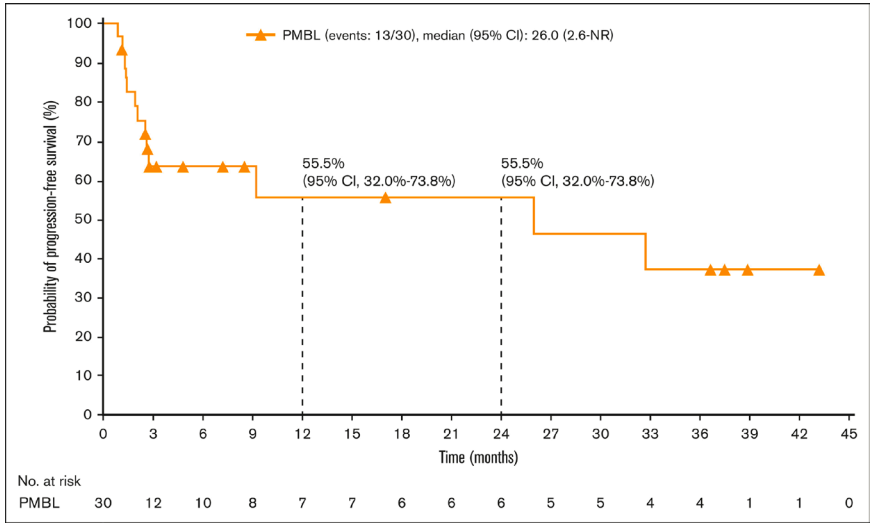
5. Single agent nivolumab

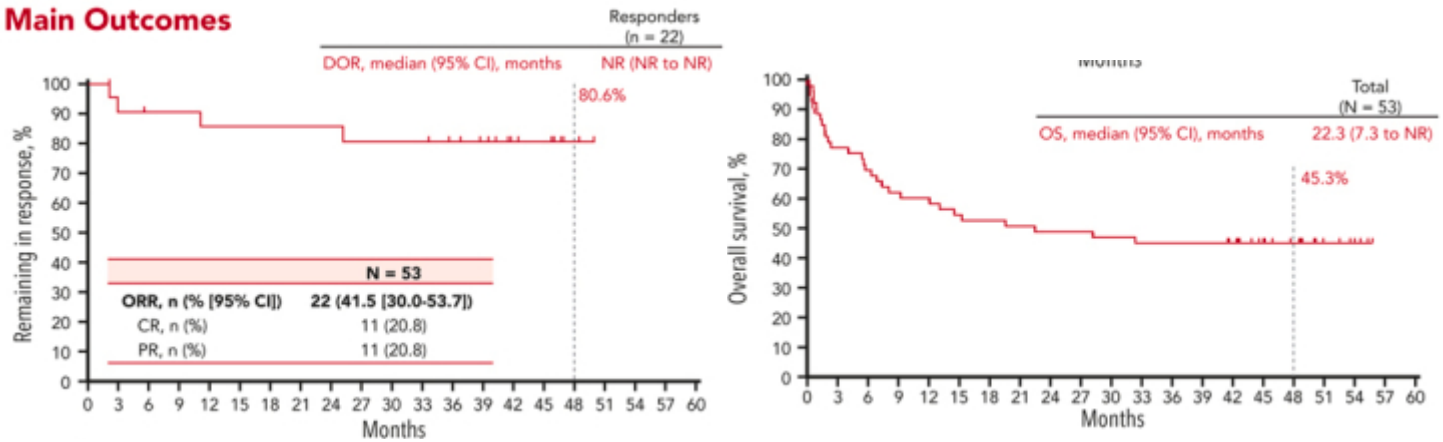
Treatment options in relapsed / refractory disease

- Salvage platinum + ASCT
- Pembrolizumab (KEYNOTE-170)
  - R/R disease with relapse after ASCT or not eligible for ASCT
- Nivolumab+brentuximab-vedotin (CheckMate 436)
  - R/R disease with relapse after ASCT or not eligible for ASCT after ≥2 therapeutic lines
- CAR T-ly:
  - axicabtagene ciloleucel (3rd + line)
  - lisocabtagene maraleucel (2nd line in early relapse or 3rd + line)

CheckMate 436



KEYNOTE-170



Aoki T et al. Blood Cancer J 2015
Neelapu SS et al. NEJM 2017
Zinzani PL et al. Blood Adv 2023
Zinzani PL et al. Blood 2023
Abramson LS et al. Lancet 2020
Kamdar M et al. Lancet 2022

Discussion

- PMBL is specific type of B-NHL affecting mostly young adults
- The therapy is based on rituximab + anthracyclin regimen, mostly CHOP or DA-EPOCH
- Radiotherapy consolidation can mostly be ommited in patients achieving metabolic complete remission (DS 1-3 on final PET/CT scan)
- Treatment options in relapsed settings include check-point inhibitors, brentuximab vedotin, CAR T-cell therapy or salvage chemoimmunotherapy with ASCT

Thank you for your attention

VFN PRAHA
VŠEOBECNÁ FAKULTNÍ NEMOCNICE

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