Mantle Cell Lymphoma Management in North Carolina: Updates for 2020

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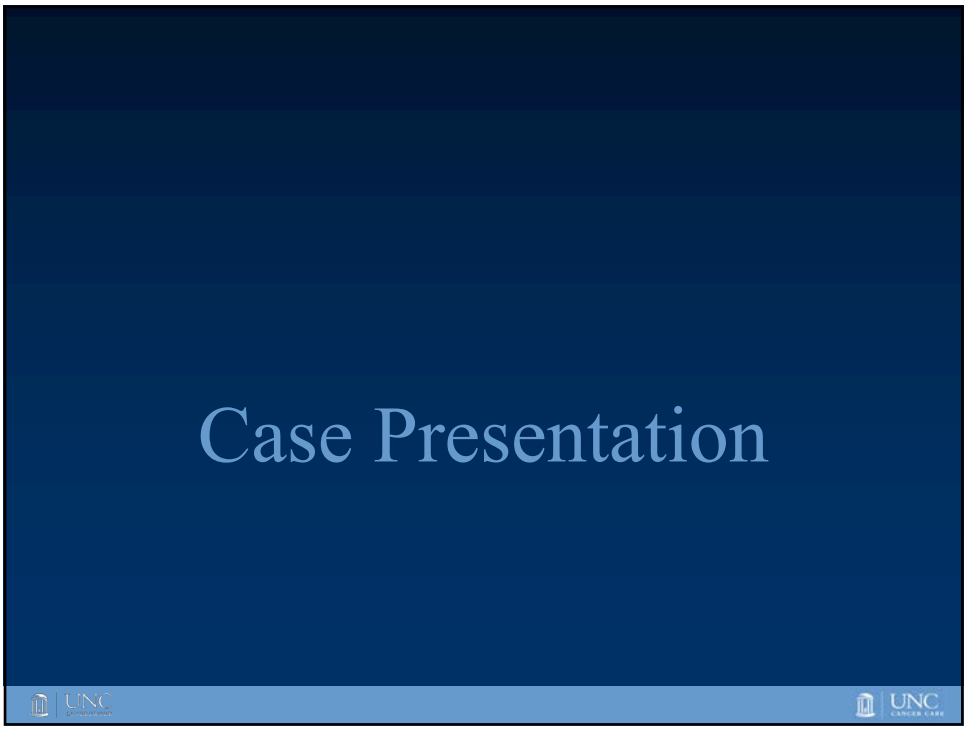
November 18, 2020

1

Outline

- Case Presentation
- Background
- Diagnosis & Workup
- Treatment

2



3

MCL Case

- 82y F with no PMH presents with palpable lymphadenopathy and fatigue.
- ECOG: 0 (patient is very active)
- Palpable LAD on exam (axilla, inguinal)
- Had excisional inguinal LN biopsy:
  - Pathology c/w non-blastoid MCL
  - Ki67 Proliferation Index=10%
  - Translocation (11;14)

4

Labwork

- WBC: 8.8
- Hg: 15.3
- Plats: 196

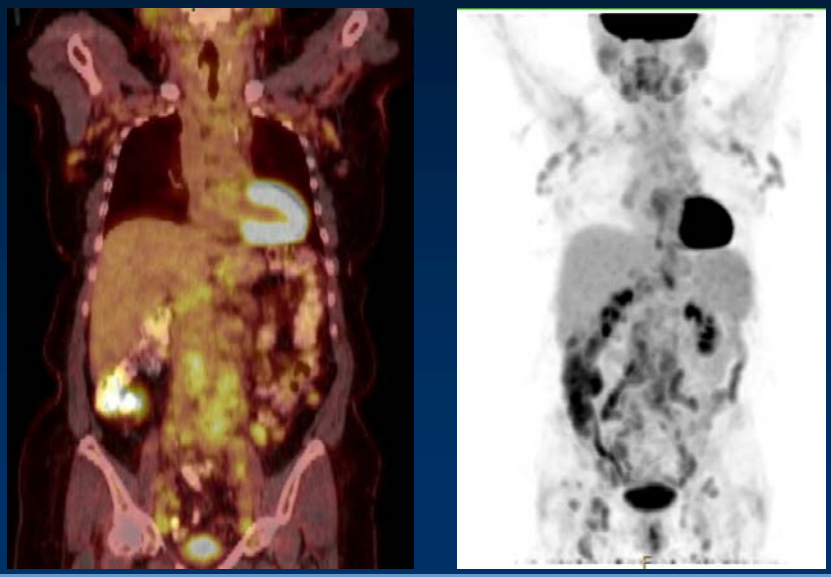
- CMP: Normal

- LDH: 763

- HBV/HIV: Negative

5

Staging PET-CT



6

MCL Case

- The patient started surveillance, which lasted for 1 year
- Her LAD progressed, and she had worsening fatigue.
- Decision was made to proceed with further workup and treatment.

7

Background

8

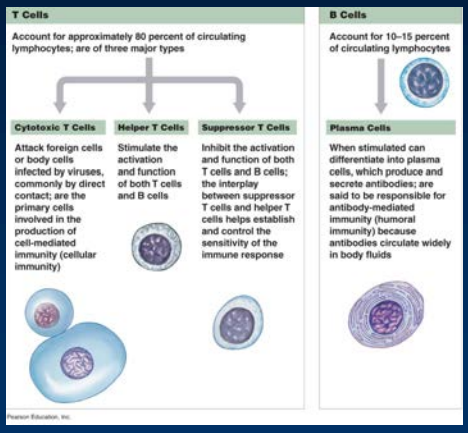
What is Lymphoma?

Adaptive Immune System:

- B Cells (Humoral immunity)
- T Cells (Cell-mediated immunity)

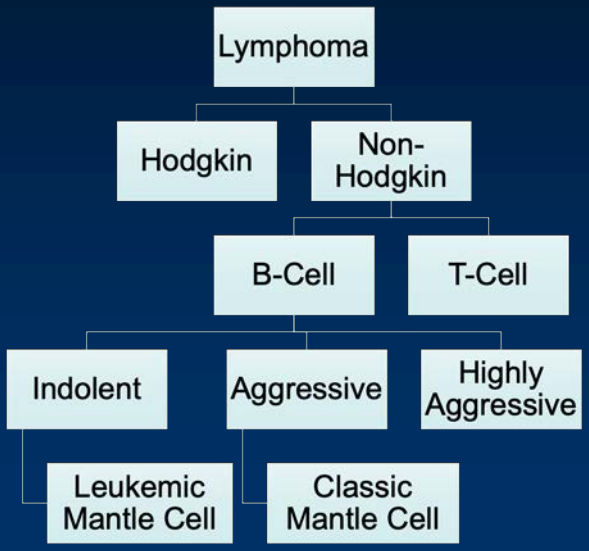
Lymphoma = Cancer of *mature* B-cells and T-cells

Generally in Lymph Nodes



9

Lymphoma Classification



10

Lymphoma Epidemiology

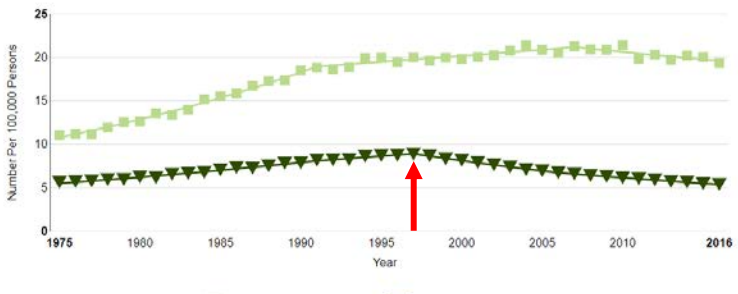
	Common Types of Cancer	Estimated New Cases 2019	Estimated Deaths 2019
1.	Breast Cancer (Female)	268,600	41,760
2.	Lung and Bronchus Cancer	228,150	142,670
3.	Prostate Cancer	174,650	31,620
4.	Colorectal Cancer	145,600	51,020
5.	Melanoma of the Skin	96,480	7,230
6.	Bladder Cancer	80,470	17,670
7.	**Non-Hodgkin Lymphoma**	**74,200**	**19,970**
8.	Kidney and Renal Pelvis Cancer	73,820	14,770
9.	Uterine Cancer	61,880	12,160
10.	Leukemia	61,780	22,840

Non-Hodgkin lymphoma represents 4.2% of all new cancer cases in the U.S.

SEER Cancer Statistics Factsheets: Non-Hodgkin Lymphoma. NCI. Bethesda, MD, http://seer.cancer.gov/statfacts/html/nhl.html

11

Non-Hodgkin Lymphoma: SEER



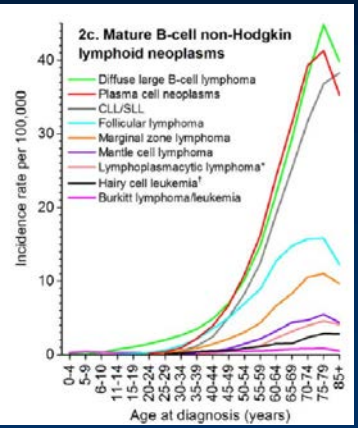
New cases come from SEER 9 Incidence. Deaths come from U.S. Mortality. 1975-2016, All Races, Both Sexes. Rates are Age-Adjusted.
Modeled trend lines were calculated from the underlying rates using the Joinpoint Trend Analysis Software.

SEER Cancer Statistics Factsheets: Non-Hodgkin Lymphoma. NCI. Bethesda, MD, http://seer.cancer.gov/statfacts/html/nhl.html

12

MCL Background

- Usually **aggressive**, but **NOT** considered curable
- Rare disease:
  - 3-6% of NHL
  - Incidence: 0.8 cases/100,000 pop
  - **3,320 cases/year** in US
- Median Age: 68; Men (3:1)



Teras, Ca Cancer J Clin, 2016

13

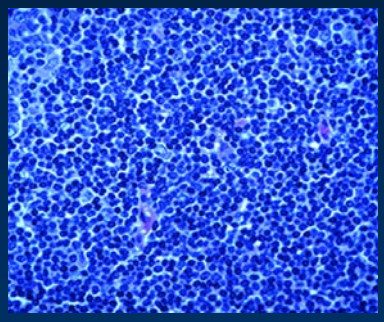
Diagnosis and Workup

14

Diagnosis

Morphology:

- Small-med cells; slightly irregular nucleus



Flow/IHC:

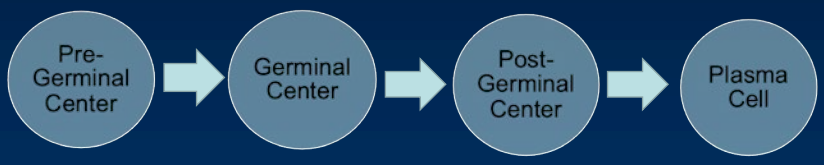
- B-cell Markers: CD19, CD20, PAX5
- Aberrant T-cell Expression: CD5+
- CD23-, FMC7+ (opposite of CLL)

Confirm:

- **CyclinD1 +**
- **t(11;14)** (leads to overexpression of Cyclin D1)

15

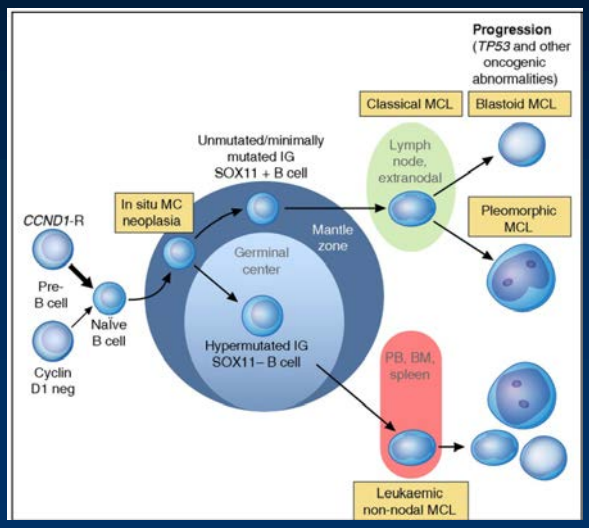
B-cell Maturation



Pre-Germinal Center	Germinal Center	Post-Germinal Center	Plasma Cell
Mantle Cell CLL	Follicular Burkitt DLBCL-GC	Marginal Zone Waldenstrom DLBCL-ABC Plasmablastic	Myeloma

16

MCL Development and Progression



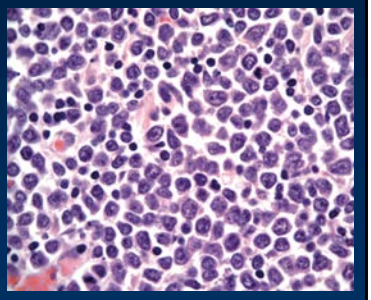
Leukemic Non-Nodal MCL:
-PB, BM, Spleen
-SOX11-, IgHV Mut
-ki67<10%

Swerdlow, Blood, 2016

17

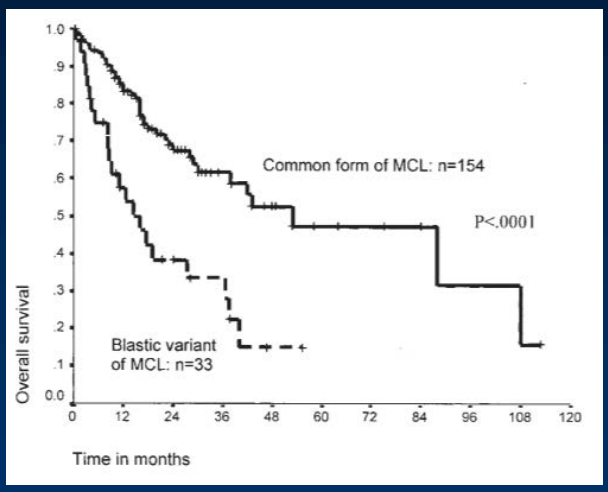
High Risk Features

- Morphology:
  - **Blastoid or Pleomorphic**
  - Medium cells; large irregular nuclei
  - Increased risk of CNS relapse
- IHC: Ki67 >30%
  - Increased risk of CNS relapse
- Molecular: TP53 mutated
- Prognostic Score: MIPI



18

Blastic (Blastoid) Variant Survival



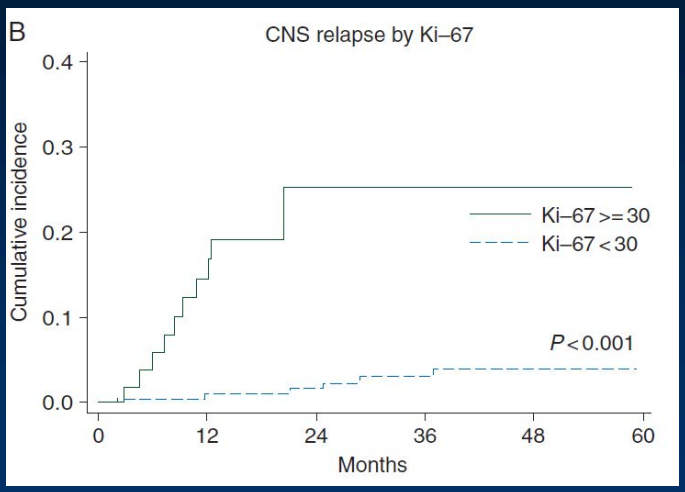
OS Common: 53mo

OS Blastic: 14.5mo

Landmark Study: Bernard, Leukemia, 2001

19

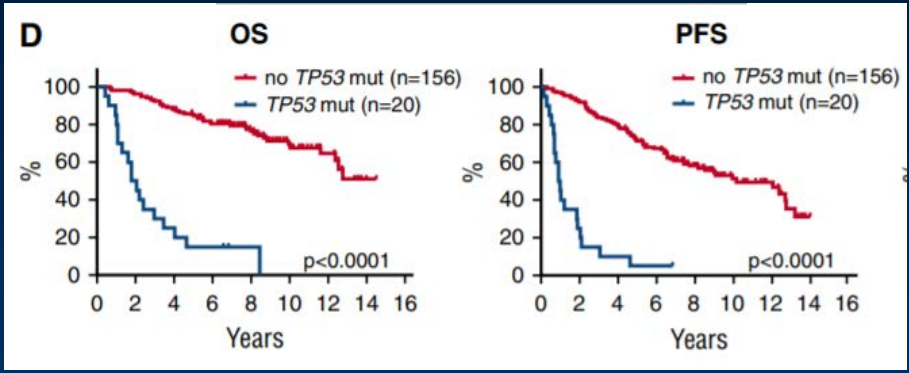
Ki67 >30%: CNS Relapse



Chihara, Ann Oncol, 2015

20

TP53 Mutations and Survival



mOS no TP53: 12.7 yrs

mOS TP53: 1.8 yrs

Eskelund, Blood, 2017

21

Prognosis: MIPI

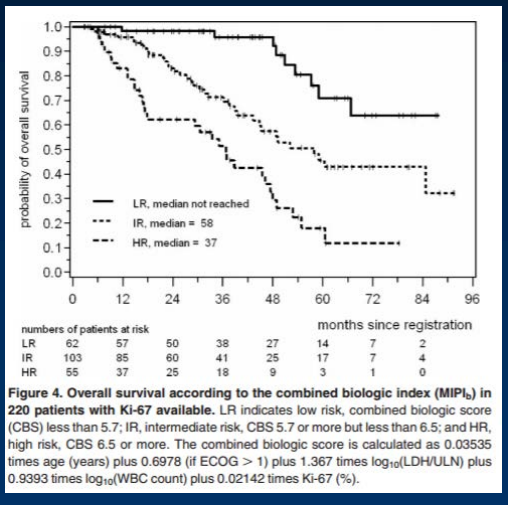


Figure 4. Overall survival according to the combined biologic index (MIPI$_b$) in 220 patients with Ki-67 available. LR indicates low risk, combined biologic score (CBS) less than 5.7; IR, intermediate risk, CBS 5.7 or more but less than 6.5; and HR, high risk, CBS 6.5 or more. The combined biologic score is calculated as 0.03535 times age (years) plus 0.6978 (if ECOG > 1) plus 1.367 times $\log_{10}$(LDH/ULN) plus 0.9393 times $\log_{10}$(WBC count) plus 0.02142 times Ki-67 (%).

Factors:
- Age
- ECOG
- LDH
- WBC
- Ki-67

Landmark Study: Hoster, Blood, 2008

22

Risk Factor Summary

Clinical Course	Newly Diagnosed MCL
Ultra-high risk	De novo blastoid/pleomorphic histology
	Ki-67 ≥ 30%/50% in involved tissues with blastoid/pleomorphic histology[b]
	TP53 mutated with other high-risk gene mutations (*KMT2D, NSD2, CCND1, NOTCH1, CDKN2A, NOTCH2, SMARCA4*)
	CNS involvement
High risk	Blastoid/pleomorphic histology
	Ki-67 ≥ 30%/50% in involved tissues with classic histology[b]
	TP53 mutated with high variant allele frequency (≥ 10%) or del(17p) by FISH
	Complex kartyyope
	Simplified high-risk MIPI score (≥ 6.2)
	Bulky disease[c]
Standard risk	Classic histology
	Ki-67 < 30% in involved tissues
	Presence of B symptoms
	Bulky or nonbulky disease[c]
	No other features of high-risk disease
Generally smoldering or indolent	Classic histology
	Ki-67 < 30% in involved tissues
	Low-risk MIPI score
	No B symptoms
	Nonnodal leukemic MCL type
	Low tumor burden
	No other features of high-risk disease

Jain, JCO, 2020

23

Workup

- Labs: CBC, CMP, LDH, TLS, HBV, HIV, +/- peripheral flow, +/- BM bx
- Imaging: PET-CT
- TTE: pre-transplant
- GI Involvement Common
  - Endoscopy/Colonoscopy to confirm stage I/II
- CNS Workup for Blastoid/Pleomorphic, Ki67>30%
  - Lumbar Puncture with CSF for flow
  - MRI brain if symptoms

24

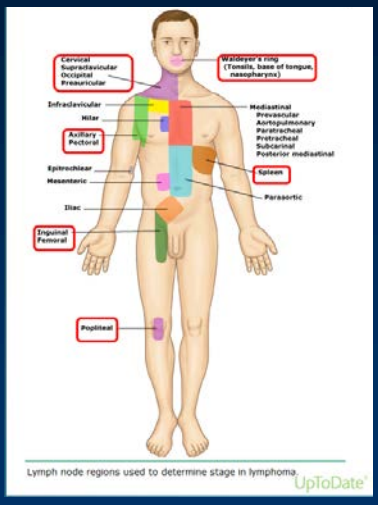
Ann Arbor/Lugano Staging

Revised staging system for primary nodal lymphomas (Lugano classification)

Stage	Involvement	Extranodal (E) status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

Extent of disease is determined by positron emission tomograph/computed tomography (PET/CT) for avid lymphomas and CT for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

* Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.



Cheson et al, JCO, 2014

25

Lugano Response Criteria

Response	Site	PET-CT (Metabolic response)
Complete response	Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5 point scale (5-PS)[b,c]
	Non-measured lesion	Not applicable
	Organ enlargement	Not applicable
	New Lesions	None
	Bone Marrow	No evidence of FDG-avid disease in marrow
Partial response	Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline. No new or progressive lesions. At interim these findings suggest responding disease. At end of treatment these findings may indicate residual disease.
	Non-measured lesion	Not applicable
	Organ enlargement	Not applicable
	New Lesions	None

PET Five Point Scale (5-PS)

1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately > liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Cheson, JCO, 2014; NCCN, 2017

26

27

Intensive vs Less Intensive

- Clinical Trial if available
- **<75yrs: Intensive Approach**
  - **R-DHAX(P) x4 to AutoSCT + mRituximab x3 yrs (preferred)**
  - Nordic Regimen (R-maxiCHOP/HD-cytarabine) to AutoSCT
  - R-HyperCVAD +/- AutoSCT
- **>75yrs: Less Intensive Approach**
  - **BR** (w/o mRituximab; Rummel, ASCO, 2016)
  - R-BAC500: 2yr OS: 86%; PFS: 81% (Visco, Lancet H, 2017)
  - VR-CAP
  - Lenalidomide + Rituximab
  - Ibrutinib or Acalabrutinib

28

Role for High Dose Cytarabine

Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma

- Ph. III RCT
- N=497
- Age<65
- St II-IV
- R-CHOP x6 → Auto
- R-CHOP/R-DHAP x6 → Auto

Hermine, Lancet, 2016

29

Patient Characteristics

	Control group (n=234)	Cytarabine group (n=232)
Age (years)	55 (48–60)	56 (50–60)
Male sex	186 (79%)	183 (79%)
Ann Arbor stage		
II	7 (3%)	10 (4%)
III	31 (13%)	31 (13%)
IV	196 (84%)	191 (82%)
MIPI		
Score	5·60 (5·29–5·93)	5·56 (5·31–5·88)
Low risk	141 (60%)	150 (65%)
Intermediate risk	60 (26%)	51 (22%)
High risk	33 (14%)	31 (13%)
Blastoid mantle cell lymphoma*	14/159 (9%)	14/169 (8%)
Ki67 index*		
Median (IQR)	20% (12–34%)	21% (11–32%)
≥30%	38/132 (29%)	34/129 (26%)
Biological MIPI*		
Low risk	35/132 (27%)	45/129 (35%)
Intermediate risk	64/132 (48%)	58/129 (45%)
High risk	33/132 (25%)	26/129 (20%)

Hermine, Lancet, 2016

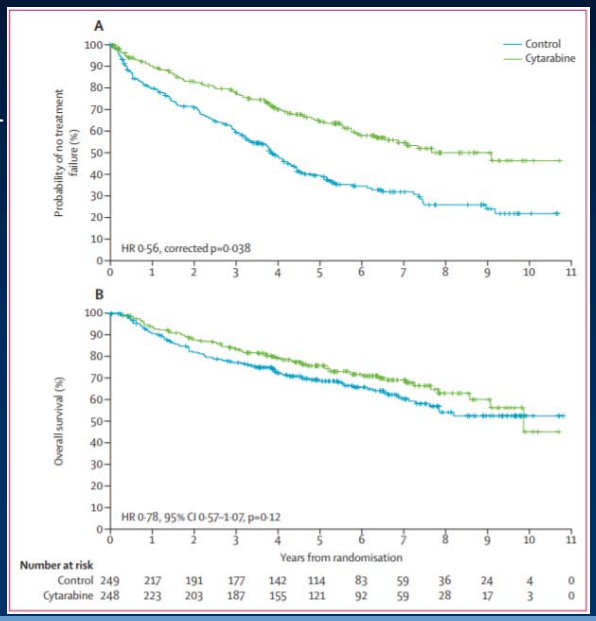
30

No Treatment Failure and OS

Median TTF:
Control: 3.9yr
Cytarabine: 9.1yr

5-yr TTF:
Control: 40%
Cytarabine: 65%

5-yr OS:
Control: 69%
Cytarabine: 76%



Hermine, Lancet, 2016

31

R-DHAX: Intensive Approach

Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma

S. Le Gouill, C. Thieblemont, L. Oberic, A. Moreau, K. Bouabdallah, C. Dartigeas, G. Damaj, T. Gastinne, V. Ribrag, P. Feugier, O. Casasnovas, H. Zerazhi, C. Haioun, H. Maisonneuve, R. Houot, F. Jardin, E. Van Den Neste, O. Tournilhac, K. Le Dû, F. Morschhauser, G. Cartron, L.-M. Fornecker, D. Canioni, M. Callanan, M.C. Béné, G. Salles, H. Tilly, T. Lamy, R. Gressin, and O. Hermine, for the LYSA Group*

Phase 3 Trial
-N=299
-Age<66yrs
-All R-DHAP (or DHAX) x4 → AutoSCT
-Randomize to q2mo mRitux for 3 yrs vs observation

Le Gouill, NEJM, 2017

32

Patient Characteristics

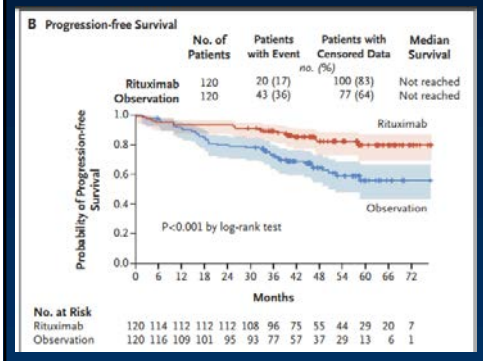
Table 1. Demographic and Clinical Characteristics of the Patients at the Time of Inclusion in the Trial.*

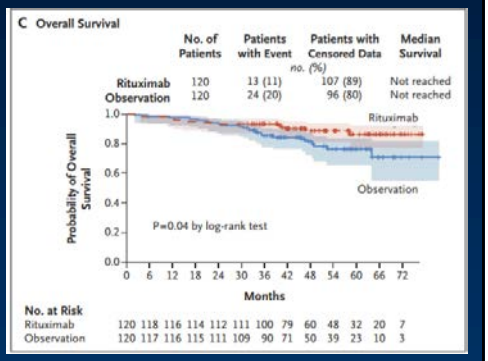
Characteristic	Patients Who Underwent Randomization (N=240)	Observation Group (N=120)	Rituximab Maintenance Group (N=120)
Age — yr			
Median	57	56	58
Range	27–65	29–65	27–65
MIPI score — no. (%)¶			
Low risk	133 (55)	63 (52)	70 (58)
Intermediate risk	65 (27)	31 (26)	34 (28)
High risk	42 (18)	26 (22)	16 (13)
Percent of Ki-67–positive cells >30% — no./total no. (%)	61/175 (35)	29/83 (35)	32/92 (35)
Variant mantle-cell lymphoma — no./total no. (%)‖			
On local review			
Blastoid	24/239 (10)	12/119 (10)	12/120 (10)
Pleomorphic	6/239 (3)	5/119 (4)	1/120 (1)

Le Gouill, NEJM, 2017

33

PFS and OS benefit





4-yr PFS:
mRitux: 83%
Observ: 64%

4-yr OS:
mRitux: 89%
Observ: 80%

Le Gouill, NEJM, 2017

34

Front-Line Therapy: Less Intensive

Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

Mathias J Rummel, Norbert Niederle, Georg Maschmeyer, G Andre Banat, Ulrich von Grünhagen, Christoph Losem, Dorothea Kofahl-Krause,

Phase III
N=514
BR x6
RCHOPx6

Rummel et al, Lancet, 2013

35

Table 1: Histology

Phase III
N=514
BR x6
RCHOPx6

	B-R (n=261)	CHOP-R (n=253)
Age (years)	64 (34–83)	63 (31–82)
<60	94 (36%)	90 (36%)
61–70	107 (41%)	105 (42%)
>70	60 (23%)	58 (23%)
Stage		
II	9 (3%)	9 (4%)
III	50 (19%)	47 (19%)
IV	202 (77%)	197 (78%)
Histology		
Follicular	139 (53%)	140 (55%)
Mantle cell	46 (18%)	48 (19%)
Marginal zone	37 (14%)	30 (12%)
Lymphoplasmacytic*	22 (8%)	19 (8%)
Small lymphocytic	10 (4%)	11 (4%)
Low grade, unclassifiable	7 (3%)	5 (2%)

Rummel et al, Lancet, 2013

36

BR vs. RCHOP

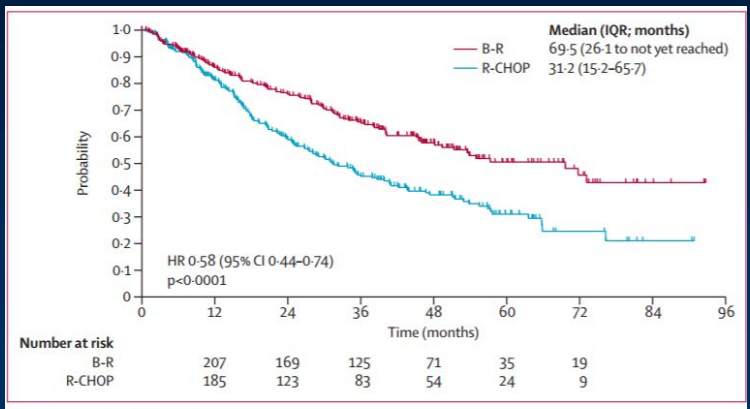


Figure 2: Progression-free survival

Rummell et al, Lancet, 2013

37

BR vs. RCHOP by Subtype

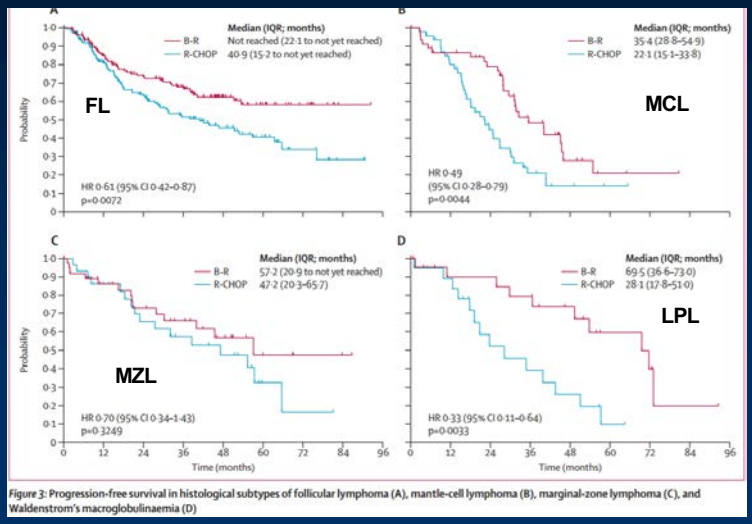


Figure 3: Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia (D)

MCL: N=94

BR PFS: 35.4mo

RCHOP PFS: 22.1mo

Rummel et al, Lancet, 2013

38

VR-CAP: Less Intensive Approach

ORIGINAL ARTICLE

Bortezomib-Based Therapy for Newly Diagnosed Mantle-Cell Lymphoma

Tadeusz Robak, M.D., Huiqiang Huang, M.D., Jie Jin, M.D., Jun Zhu, M.D.,

Phase III trial
N=487
R-CHOP x6-8
VR-CAP x6-8

Robak, NEJM, 2015

39

VR-CAP vs. R-CHOP: PFS and OS

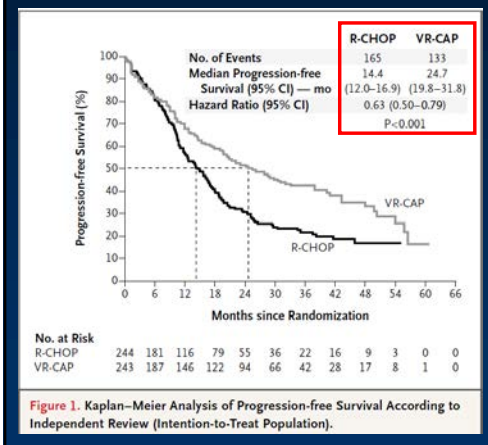


Figure 1. Kaplan–Meier Analysis of Progression-free Survival According to Independent Review (Intention-to-Treat Population).

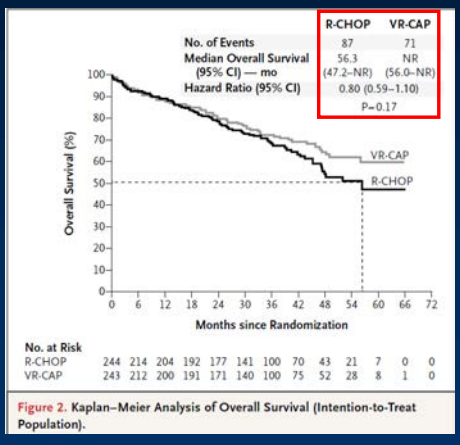


Figure 2. Kaplan–Meier Analysis of Overall Survival (Intention-to-Treat Population).

Robak, NEJM, 2015

40

R^2: Least Intensive Approach

ORIGINAL ARTICLE

Lenalidomide plus Rituximab as Initial Treatment for Mantle-Cell Lymphoma

Jia Ruan, M.D., Ph.D., Peter Martin, M.D., Bijal Shah, M.D., Stephen J. Schuster, M.D., Sonali M. Smith, M.D., Richard R. Furman, M.D.,

Phase II
N=38
Med Age:
65yrs

Schedule:
-Len 20mg D1-21/28d Cycle x12C, then:
-Len 15mg D1-21/28d Cycle maintenance
-Ritux x4 weekly then every other month

Ruan, NEJM, 2015

41

Excellent response rates

Table 2. Rates of Best Response at the Median Follow-up of 30 Months.

Response	Patients	Intention-to-Treat Population (N=38)	Patients Who Could Be Evaluated (N=36)
	no.	%	
Overall response	33	87	92
Complete response*	23	61	64
Partial response	10	26	28
Stable disease	1	3	3
Progressive disease†	2	5	6
Could not be evaluated‡	2	5	

Ruan, NEJM, 2015

42

Excellent 2-Year PFS and OS

Table 3. Survival and Follow-up Data.

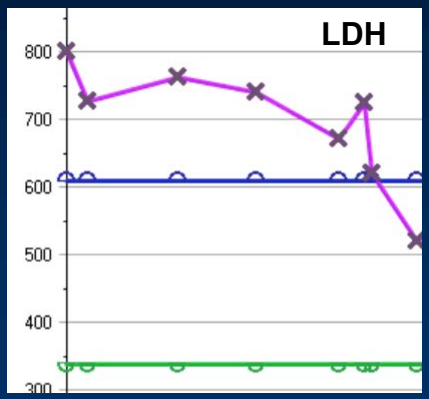
Variable	Value
Median progression-free survival	Not reached
2-Yr progression-free survival — % of patients (95% CI)	85 (67–94)
2-Yr overall survival — % of patients (95% CI)	97 (79–99)
Follow-up time — mo	
Median	30
Range	10–42
Time to partial response — mo	
Median	3
Range	3–13
Time to complete response — mo*	
Median	11
Range	3–22

Ruan, NEJM, 2015

43

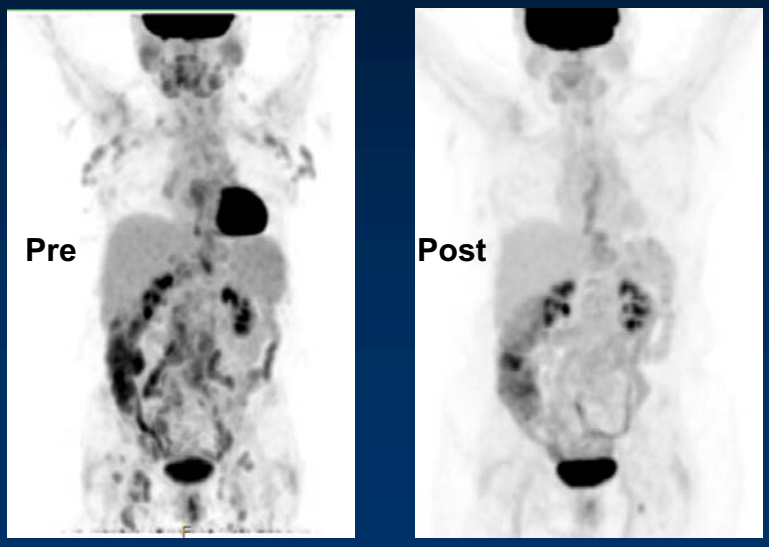
MCL Case

- Pt started on Bendamustine/ Rituximab (BR)
- Bendamustine was dose reduced 20%
- 6 cycles completed



44

MCL Case: Response



45

MCL Case

- Patient remained in Complete Remission for 3 years.
- Now at age 86, she developed severe night sweats, fevers, weight loss.
- PET showed diffuse LAD
- Diagnosed with relapsed MCL

46

Approach to Relapsed MCL

- Clinical trial if available.
- More Intensive:
  - Any frontline or salvage regimens that have not been used (VR-CAP, R-BAC, R-ICE, etc)
  - If no prior transplant: consider autoSCT
  - If prior autoSCT: consider alloSCT
  - **CD19 CAR-T:** Brexucabtagene autoleucel (Tecartus)
- Less Intensive:
  - BTK inhibitor
  - Lenalidomide/Rituximab (R^2): ORR=57%, CR=36%*
  - Venetoclax: ORR=75%, CR=21%**

*Wang, Lancet Oncol, 2012
**Davids et al, JCO, 2017

47

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney,

Phase II study
N=74
N=68 (received CAR-T)
All w/ prior BTKi
Dose=2x10^6 cells/kg
Flu/Cy Lymphodepletion

Wang, NEJM, 2020

48

Baseline Characteristics

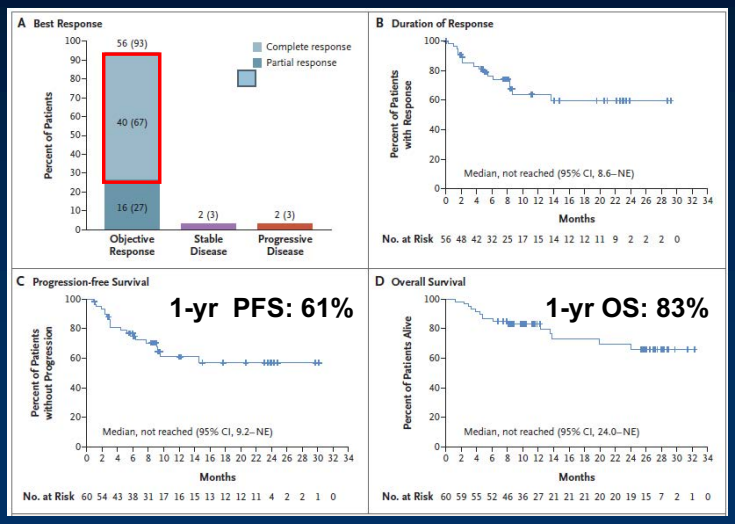
Table 1. Baseline Characteristics of All 68 Treated Patients.*

Characteristic	Patients
Median age (range) — yr	65 (38–79)
Intermediate or high risk according to Simplified MIPI — no. (%)†‡	38 (56)
Blastoid or pleomorphic morphologic characteristics of MCL — no. (%)	21 (31)
Ki-67 proliferation index ≥30% — no./total no. (%)‡	40/49 (82)
TP53 mutation — no. (%)	6/36 (17)
Positive CD19 status — no./total no. (%)	47/51 (92)
Median no. of previous therapies (range)§	3 (1–5)
≥3 Previous lines of therapy — no. (%)	55 (81)
Previous autologous stem-cell transplantation — no. (%)	29 (43)
Previous BTK inhibitor therapy — no. (%)§	68 (100)
Ibrutinib	58 (85)
Acalabrutinib	16 (24)
Both	6 (9)
Relapsed or refractory disease — no. (%)	
Relapse after autologous stem-cell transplantation	29 (43)
Refractory to most recent previous therapy	27 (40)
Relapse after most recent previous therapy	12 (18)
Disease that relapsed or was refractory to BTK inhibitor therapy — no. (%)	68 (100)
Refractory to BTK inhibitor therapy	42 (62)
Relapse during BTK inhibitor therapy	18 (26)
Relapse after BTK inhibitor therapy	5 (7)
Could not take BTK inhibitor therapy because of adverse events¶	3 (4)

Wang, NEJM, 2020

49

Results



Wang, NEJM, 2020

50

Adverse Events

Table 2. Adverse Events among All 68 Treated Patients.*

Event	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			number of patients (percent)			
Any adverse event	68 (100)	0	1 (1)	11 (16)	54 (79)	2 (3)
Pyrexia	64 (94)	14 (21)	41 (60)	9 (13)	0	0
Neutropenia	59 (87)	0	1 (1)	11 (16)	47 (69)	0
Thrombocytopenia	50 (74)	9 (13)	6 (9)	11 (16)	24 (35)	0
Anemia	46 (68)	0	12 (18)	34 (50)	0	0
Hypotension	35 (51)	4 (6)	16 (24)	13 (19)	2 (3)	0
Chills	28 (41)	17 (25)	11 (16)	0	0	0
Hypoxemia	26 (38)	2 (3)	10 (15)	8 (12)	6 (9)	0
Cough	25 (37)	14 (21)	11 (16)	0	0	0
Hypophosphatemia	25 (37)	2 (3)	8 (12)	15 (22)	0	0
Fatigue	24 (35)	10 (15)	13 (19)	1 (1)	0	0
Headache	24 (35)	15 (22)	8 (12)	1 (1)	0	0
Tremor	24 (35)	19 (28)	5 (7)	0	0	0
Hypoalbuminemia	23 (34)	5 (7)	17 (25)	1 (1)	0	0
Hyponatremia	22 (32)	15 (22)	0	7 (10)	0	0

Wang, NEJM, 2020

2 Deaths d/t conditioning
-Organizing PNA
-Staph bacteremia

51

CRS and Neurotoxicity

Event	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			number of patients (percent)			
Symptom of cytokine release syndrome						
Any	62 (91)	20 (29)	32 (47)	8 (12)	2 (3)	0
Pyrexia	62 (91)	15 (22)	40 (59)	7 (10)	0	0
Hypotension	35 (51)	4 (6)	16 (24)	14 (21)	1 (1)	0
Hypoxemia	23 (34)	1 (1)	10 (15)	8 (12)	4 (6)	0
Chills	21 (31)	12 (18)	9 (13)	0	0	0
Tachycardia	16 (24)	11 (16)	5 (7)	0	0	0
Headache	15 (22)	7 (10)	8 (12)	0	0	0
Alanine aminotransferase increased	10 (15)	5 (7)	1 (1)	3 (4)	1 (1)	0
Aspartate aminotransferase increased	9 (13)	4 (6)	0	5 (7)	0	0
Fatigue	9 (13)	6 (9)	2 (3)	1 (1)	0	0
Nausea	9 (13)	5 (7)	4 (6)	0	0	0
Neurologic event	43 (63)	13 (19)	9 (13)	15 (22)	6 (9)	0

Wang, NEJM, 2020

52

Relapsed Oral Agents: BTK Inhibition

- **Ibrutinib** (Wang, NEJM, 2013)
  - Relapsed (N=111): ORR=68%; CR=21%
- **Ibrutinib/Palbociclib** (Martin, Blood, 2020)
  - Relapsed (N=27): ORR=67%; CR=37%; 2-yr PFS=59.4%
- **Acalabrutinib** (Wang, Lancet, 2017)
  - Relapsed (N=124): ORR=80%; CR=40% (no prior BTKi)
- **Zanubrutinib** (Song, CCR, 2020)
  - Relapsed (N=86): ORR=84%; CR=68.6 (no prior BTKi)

53

MCL Case

- Pt started on **Acalabrutinib**
- In first month, symptoms resolved
- Awaiting restaging PET-CT.

54

Clinical Trials at UNC

- Frontline:
  - EA4151: A Randomized Phase III Trial of Consolidation w/ autoSCT followed by mRituximab vs. mRituximab Alone for Patients w/ ***MRD-Negative*** First CR.
  - EA4181: A Randomized 3-Arm Phase II Study in ≤70 Untreated MCL Comparing:
    1.) Benda/Rituximab/HD Cytarabine
    2.) Benda/Rituximab/HD Cytarabine/Acalabrutinib
    3.) Benda/Rituximab/Acalabrutinib

55

Clinical Trials at UNC

- Relapsed:
  - A Phase II Study of Palbociclib in Combination With Ibrutinib in Patients With Previously Treated Mantle Cell Lymphoma
  - LOXO-BTK-18001: A Phase 1/2 Study of Oral LOXO-305 in Patients with Previously Treated CLL or NHL
  - LCCC1813-ATL: CD19 CAR-T for lymphoma (w/ "suicide gene" – antidote for toxicity).

56

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57

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58


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59