Updates in Mantle Cell Lymphoma: What's old is new and what's new is old

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Disclosures

Consulting advice:

Abbvie, Astellas, AstraZeneca, Bayer, Beigene, BMS, Calithera, Constellation, Eisai, Lilly, Epizyme, Genmab, Grail, Incyte, Janssen, Karyopharm, Merck, Mustang Bio, Novartis, Pfizer, Roche/Genentech, Seattle Genetics, Second Genome, Sutro, Caribou Biosciences

Topics

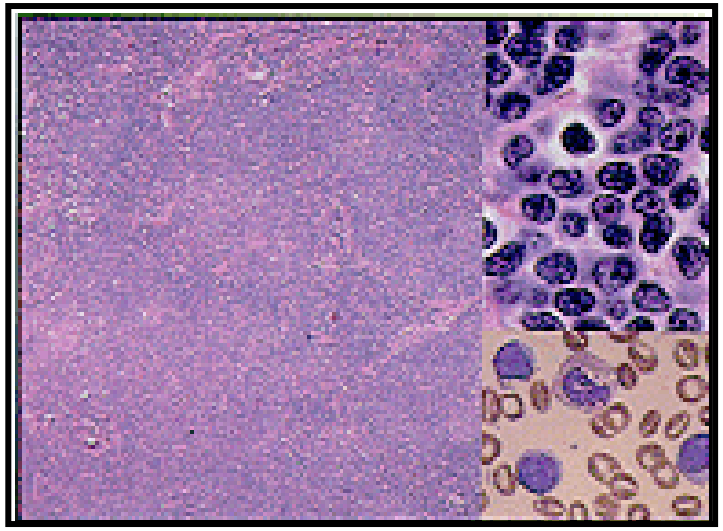
- Mantle cell lymphoma is about 40 years old – is that old or new?
- Old ideas are new
  - Bendamustine based therapy – tough to beat
  - Auto transplant may not be needed in first remission
  - Maintenance rituximab makes a difference
- New ideas are old
  - Watch and wait for asymptomatic patients accepted
  - “chemotherapy-free” regimens may be better for some (? many) patients
  - BTK inhibitors are aging fairly well
  - Accumulating data and followup on CAR-T and bispecific antibodies

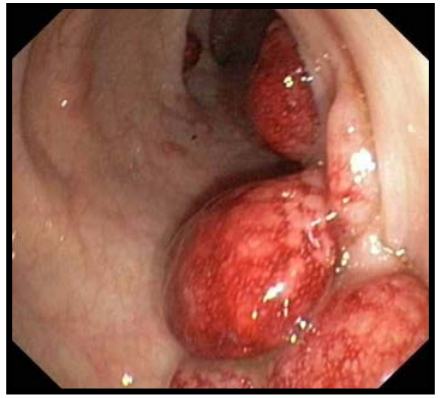
Mantle cell lymphoma: basic features

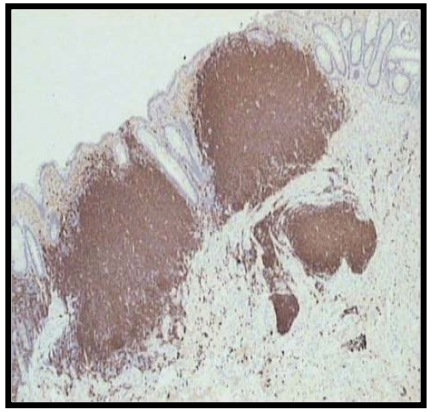
Clinical Features

- M:F ratio 4:1, median age 64
- Advanced stage
- Leukemic phase up to 30%
- Extranodal sites common
- GI tract 80% (polyps)
- Variable clinical course

  (indolent to aggressive)







Fisher RI, et al. Hematology. 2004;221-236.

Lymphoma Classification 1974-1982

Kiel (1974) MCL = “Centrocytic lymphoma” (Lennert)

1982

National Cancer Institute Sponsored Study of Classifications of Non-Hodgkin’s Lymphomas

Summary and Description of a Working Formulation for Clinical Usage

THE NON-HODGKIN'S LYMPHOMA PATHOLOGIC CLASSIFICATION PROJECT*

Low Grade	Intermediate Grade	High Grade
Small lymphocytic	Follicular large cell	Large cell immunoblastic
Follicular small-cleaved cell	Diffuse small cleaved cell	Lymphoblastic
Follicular mixed small-cleaved and large cell	Diffuse mixed small and large cell	Small non-cleaved cell (Burkitt and non-Burkitt type)
	Diffuse large cell	

Cancer, 1982

Early descriptions of MCL (“mantle zone”)

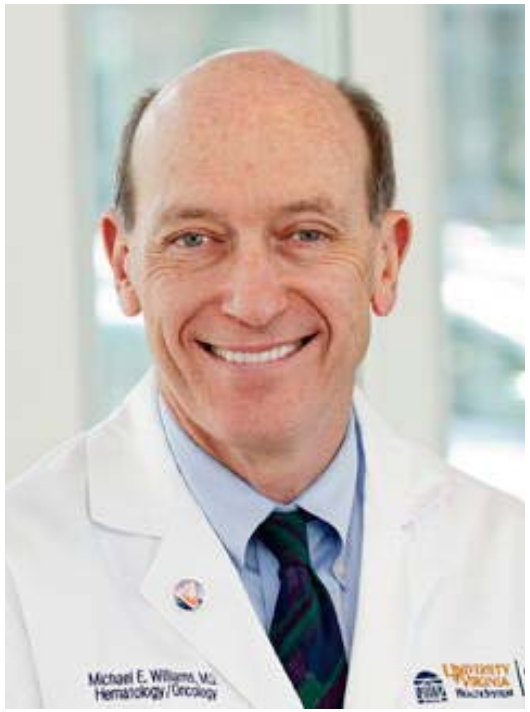
Dennis Weisenburger
(“Mantle zone lymphoma”)
1982

Steven Swerdlow
(“Centrocytic lymphoma”)
1983

Stefano Pileri
(Mantle cell vs Marginal zone)
1985

Better classification of MCL

Elaine Jaffe
(Blastoid variant)
1987



Michael Williams
(11;14 translocation in MCL)
1990

Francesc Bosch
(Cyclin D1 overexpression specificity)
1994

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Lymphoma Classification 1994

Revised European-American Lymphoma (REAL) Classification of Lymphoid Neoplasms

Morphology, immunophenotype, genetics, and clinical features

B-cell neoplasms in the R.E.A.L./WHO Classification
Precursor B-cell neoplasm
- Precursor B-lymphoblastic leukemia/lymphoma (B-ALL/LBL)

Mature (peripheral) B-cell neoplasms
- B-cell chronic lymphocytic leukemia /small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Splenic marginal zone B-cell lymphoma (+/— villous lymphocytes)
- Hairy-cell leukemia
- Plasma cell myeloma /plasmacytoma
- Extranodal marginal zone B-cell lymphoma of MALT type
- Mantle-cell lymphoma
- Follicular lymphoma
- Nodal marginal zone B-cell lymphoma (+/ - monocytoid B cells)
- Diffuse large B-cell lymphoma
- Burkitt lymphoma

Harris NL, et al, Blood 1994

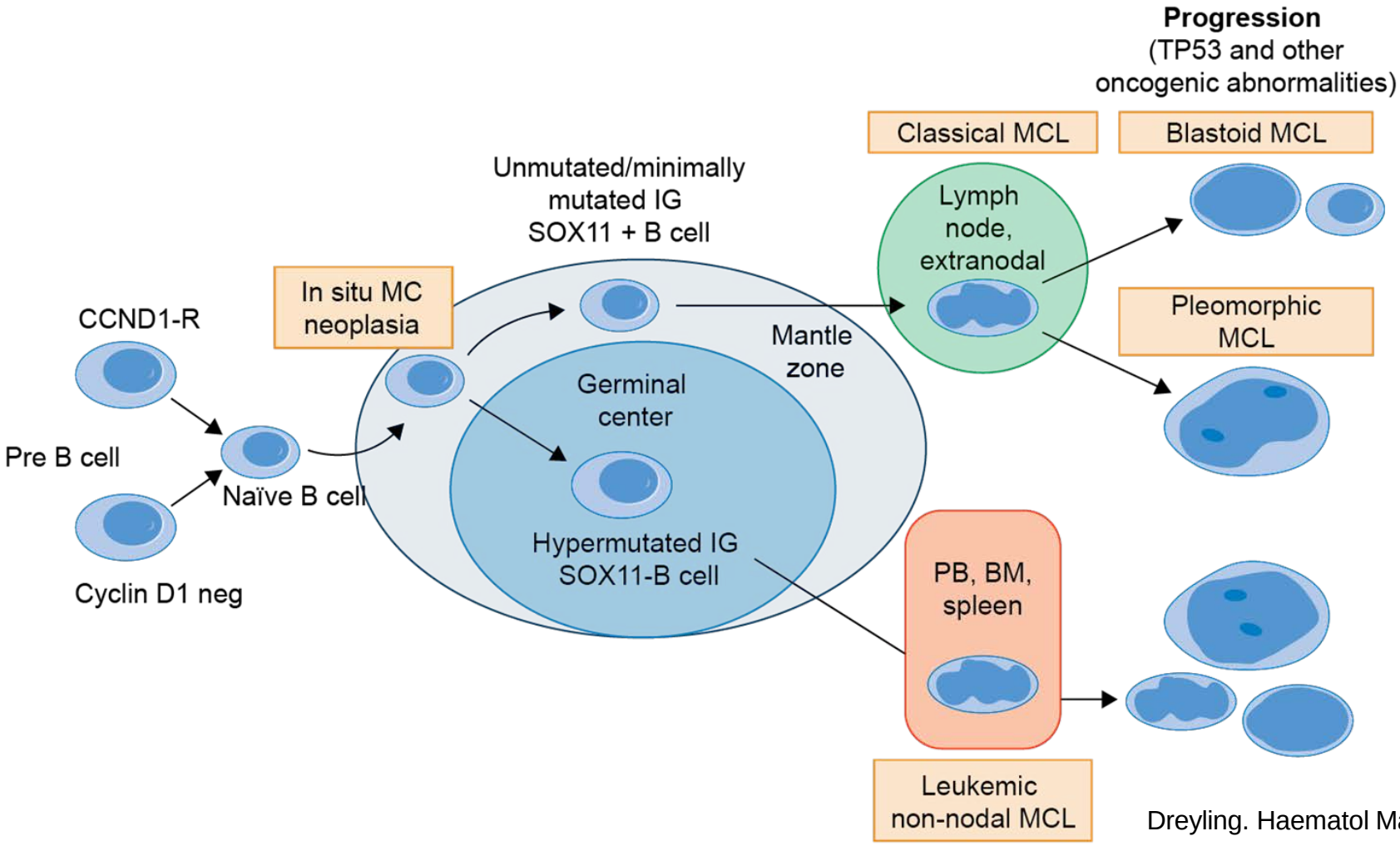
Lymphoma Classification 2022
Mantle cell lymphoma subtypes

WHO 5th edition
International Consensus Classification

In situ mantle cell neoplasm
Mantle cell lymphoma
Leukaemic non-nodal mantle cell lymphoma

Alaggio et al, Leukemia 2022
Campo et al, Blood 2022

MCL Pathogenesis



Dreyling. Haematol Malig. 2017;28(suppl 4):IV62

MCL: Risk factors

- Risk factors are heterogeneous within a patient and between patients
- MCL is biologically heterogeneous, and risk stratification incorporates multiple biologic factors

Low Risk

- Low Ki-67 (≤10%)
- SOX-11 negative
- IGHV hypermutated
- Stable karyotype

High Risk

- Blastic/blastoic/pleomorphic
- High Ki-67 (>30%)
- Complex karyotype
- *TP53* alterations

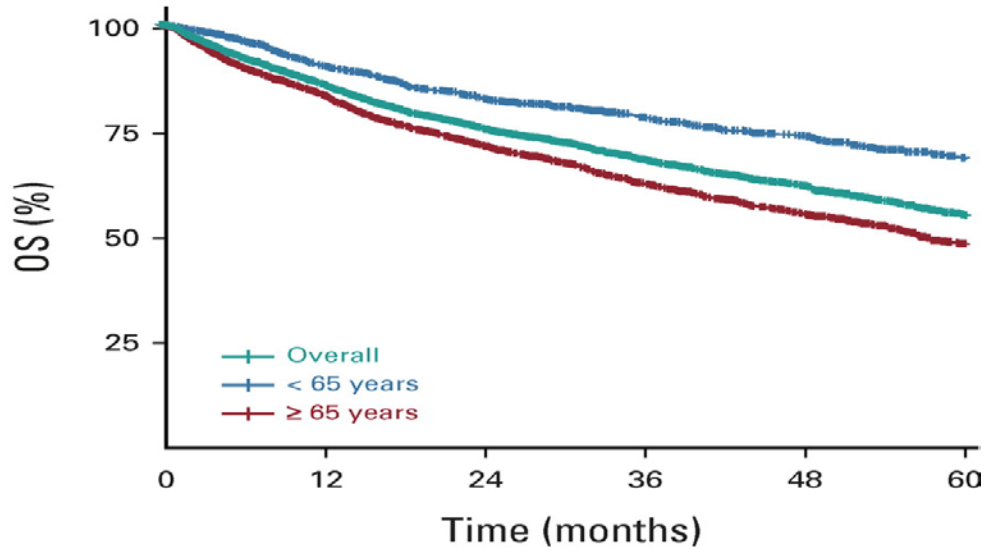
Indolent MCL

Classic MCL

Blastic MCL

Hoster. Blood. 2008;111:558-565.

“Real world” MCL overall survival has improved to > 5 years (and longer in “study populations”)



Patients at risk:

Overall	3,614	2,613	1,964	1,439	1,071	783
< 65 years	1,274	958	753	571	445	332
≥ 65 years	2,340	1,655	1,211	868	626	451

	Overall n = 3,614	< 65 Years n = 1,274	≥ 65 Years n = 2,340
Median OS (95% CI), months	69.6 (66.6 to 74.3)	105 (99.0 to NE)	56 (53.2 to 60.6)
OS rate at 3 years, % (95% CI)	68 (66 to 69)	78 (75 to 81)	62 (60 to 65)

Martin, Cohen et al, JCO 2022

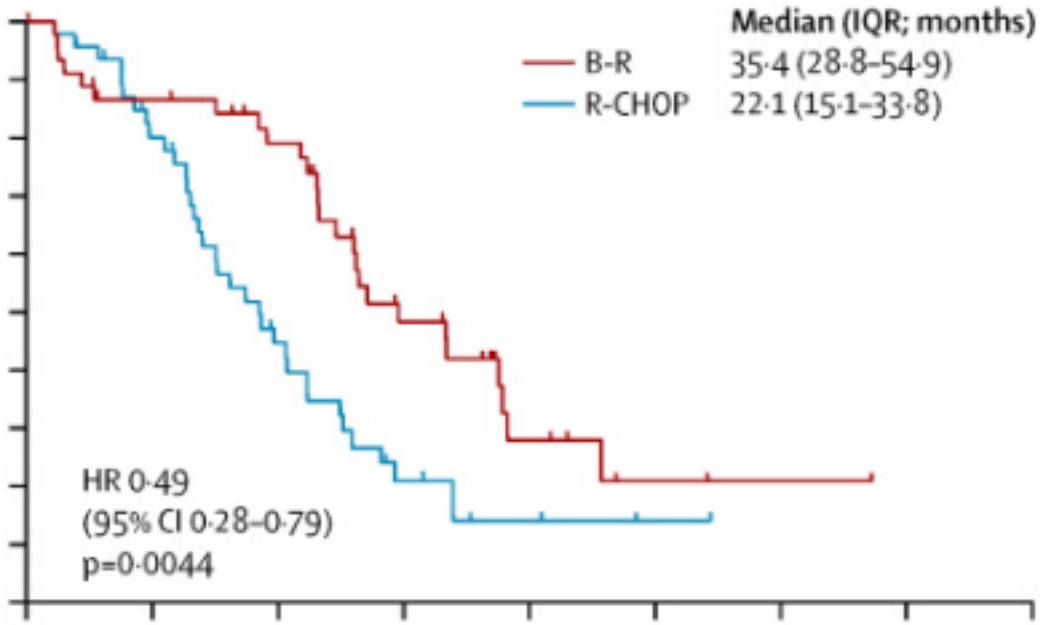
Mantle cell lymphoma: Old ideas are new

Bendamustine + Rituximab-based therapy is tough to beat

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

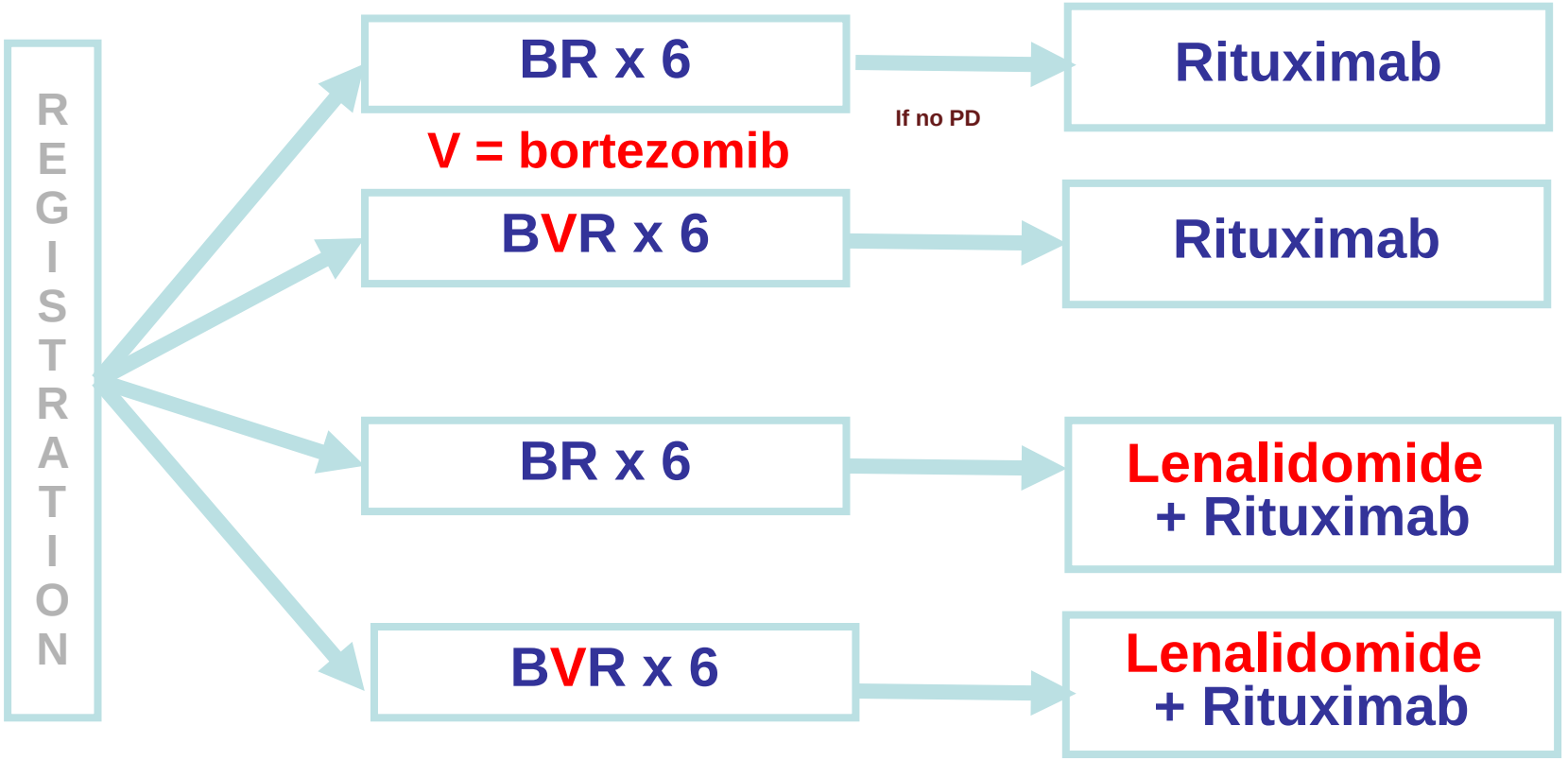
Mathias J Rummel, Norbert Niederle, Georg Maschmeyer, G Andre Banat, Ulrich von Grünhagen, Christoph Losem, Dorothea Kofahl-Krause, Gerhard Heil, Manfred Welslau, Christina Balser, Ulrich Kaiser, Eckhart Weidmann, Heinz Dürk, Harald Ballo, Martina Stauch, Fritz Roller, Juergen Barth, Dieter Hoelzer, Axel Hinke, Wolfram Brugger, on behalf of the Study group indolent Lymphomas (StiL)

PFS with B-R vs R-CHOP



Rummel et al, Lancet 2013

E1411 Schema



Induction:

BR = bendamustine 90 mg/m^2/d days 1, 2 + rituximab 375 mg/m^2 day 1, every 28 days x 6

BVR = BR + bortezomib 1.3 mg/m^2 days 1, 4, 8, 11 (later amended to 1.6 mg/m^2 days 1, 8), IV or SQ

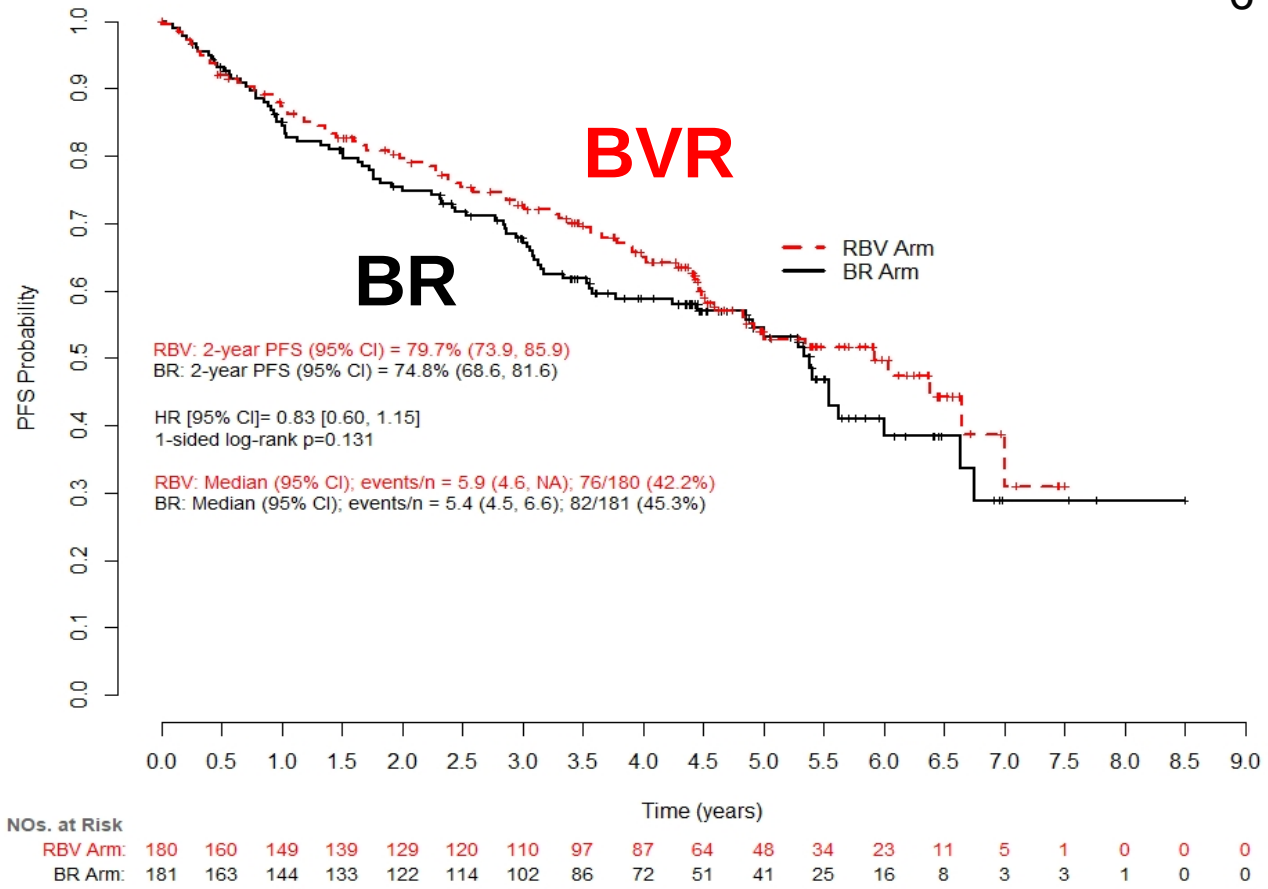
Consolidation:

Rituximab 375 mg/m^2 every 8 weeks x 12 doses ± Lenalidomide 15 mg/d 21/28 days x 24 cycles

Smith et al, ASH 2022

E1411: PFS by induction arm

373 patients (187 BR; 186 BVR) enrolled 2012–2016
6 protocol ineligible in each arm

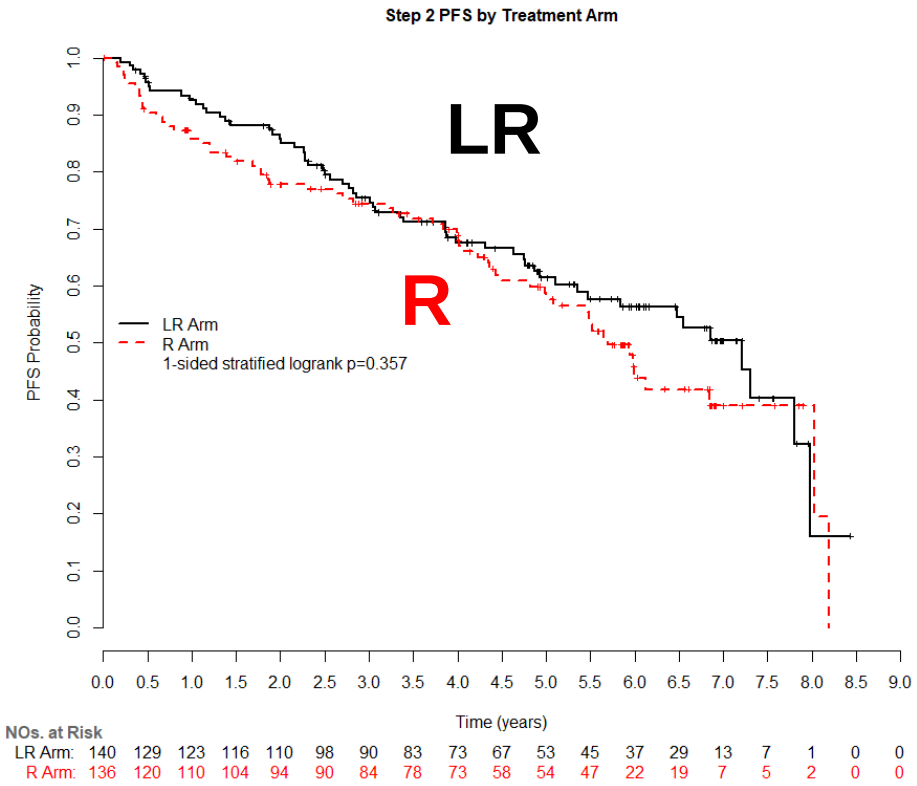


	BR	BVR
# of patients	181	180
2 year PFS % (95% CI)	74.8% (68.6-81.6)	79.7% (73.9-85.9)
Median PFS (years)	5.4	5.9
Hazard Ratio	0.83 (0.60 -1.15)	
MRD < 10^{-4}	92%	91%

Smith et al, ASH 2022

Weill Cornell Medicine NewYork-Presbyterian

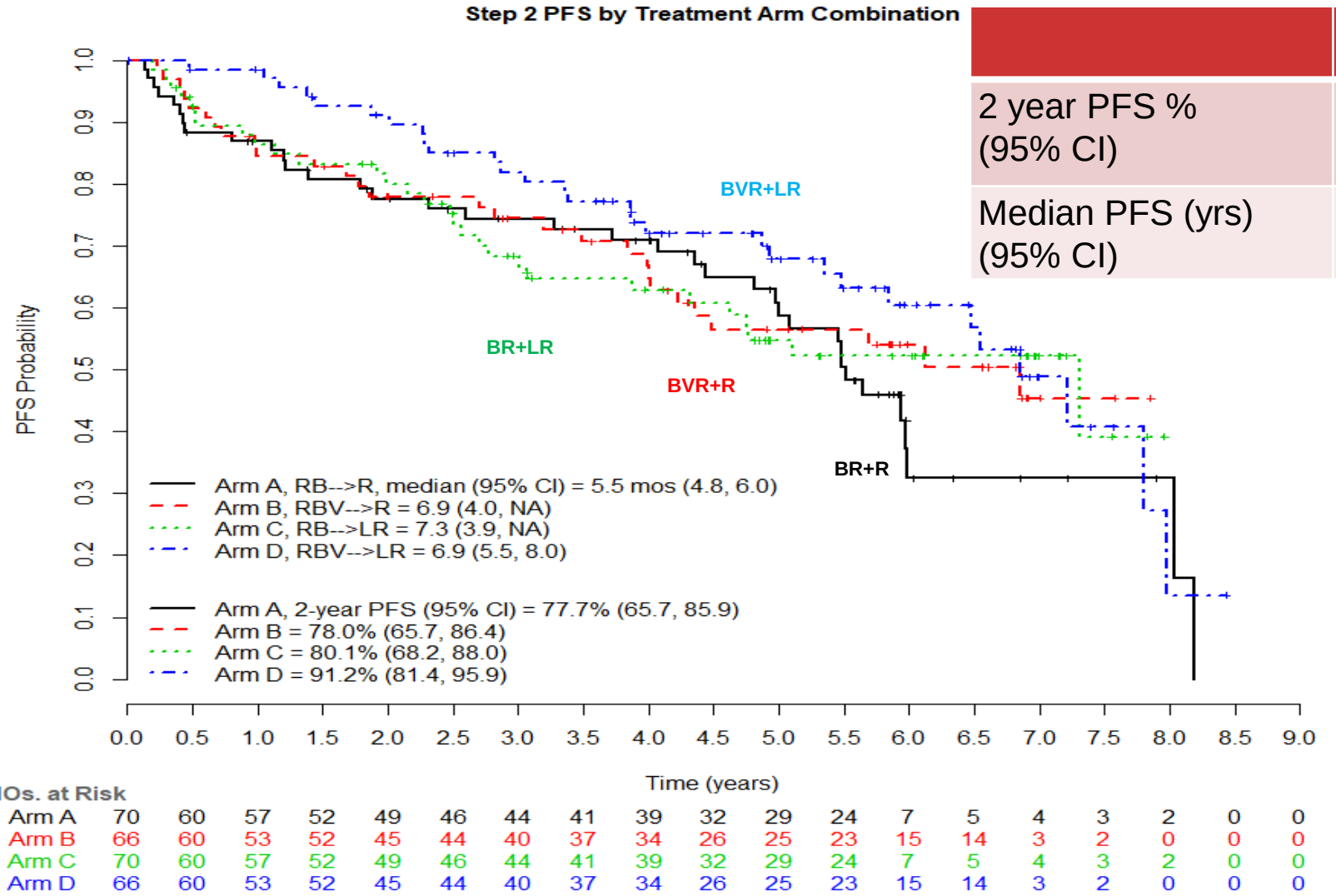
E1411: PFS by consolidation arm



	BR/BVR + R	BR/BVR + LR
2 year PFS (95% CI)	78% (70-84%)	86% (79-91%)
p = NS		
Complete Response	87%	84%
P = NS		

Smith et al, ASH 2022

E1411: PFS by overall treatment



	BR + R	BVR + R	BR + LR	BVR + LR
2 year PFS % (95% CI)	78% (66-86)	78% (66-86)	80% (68-88)	91 (81-96)
Median PFS (yrs) (95% CI)	5.5 (4.8-6.0)	6.9 (4.0-NR)	7.3 (3.9-NR)	6.9 (5.5-8.0)

Smith et al, ASH 2022

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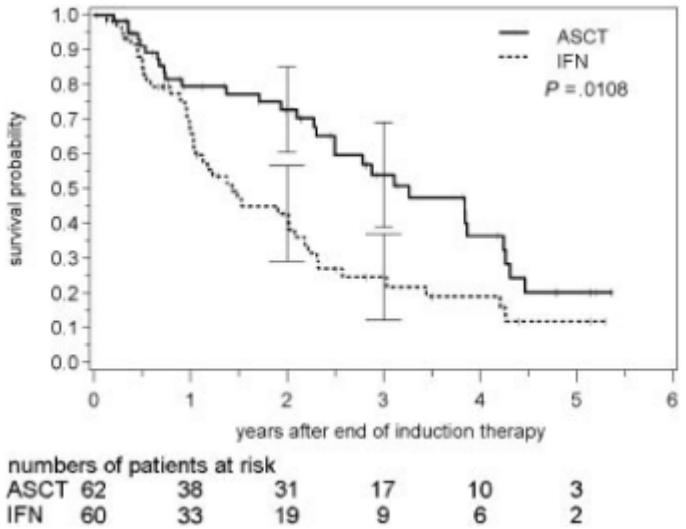
Autotransplant in first remission improves PFS

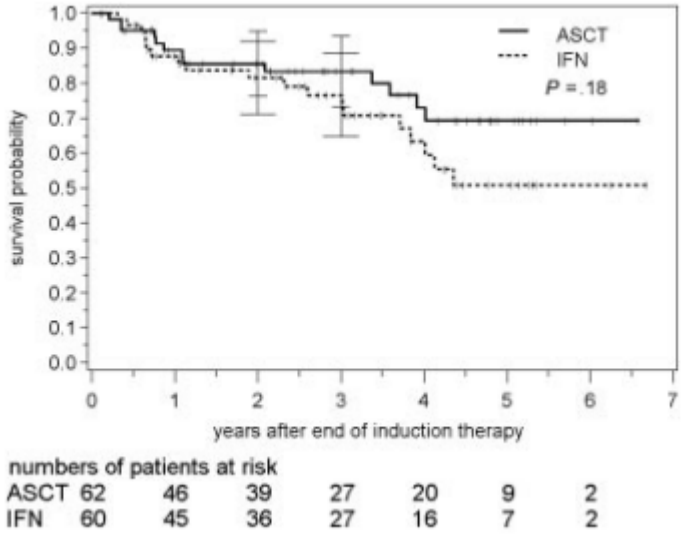
Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network

Martin Dreyling, Georg Lenz, Eva Hoster, Achiel Van Hoof, Christian Gisselbrecht, Rudolf Schmits, Bernd Metzner, Lorenz Truemper, Marcel Reiser, Hjalmar Steinhauer, Jean-Michel Boiron, Marc A. Boogaerts, Ali Aldaoud, Vittorio Silingardi, Hanneke C. Kluin-Nelemans, Joerg Hasford, Reza Parwaresch, Michael Unterhalt, and Wolfgang Hiddemann

PFS

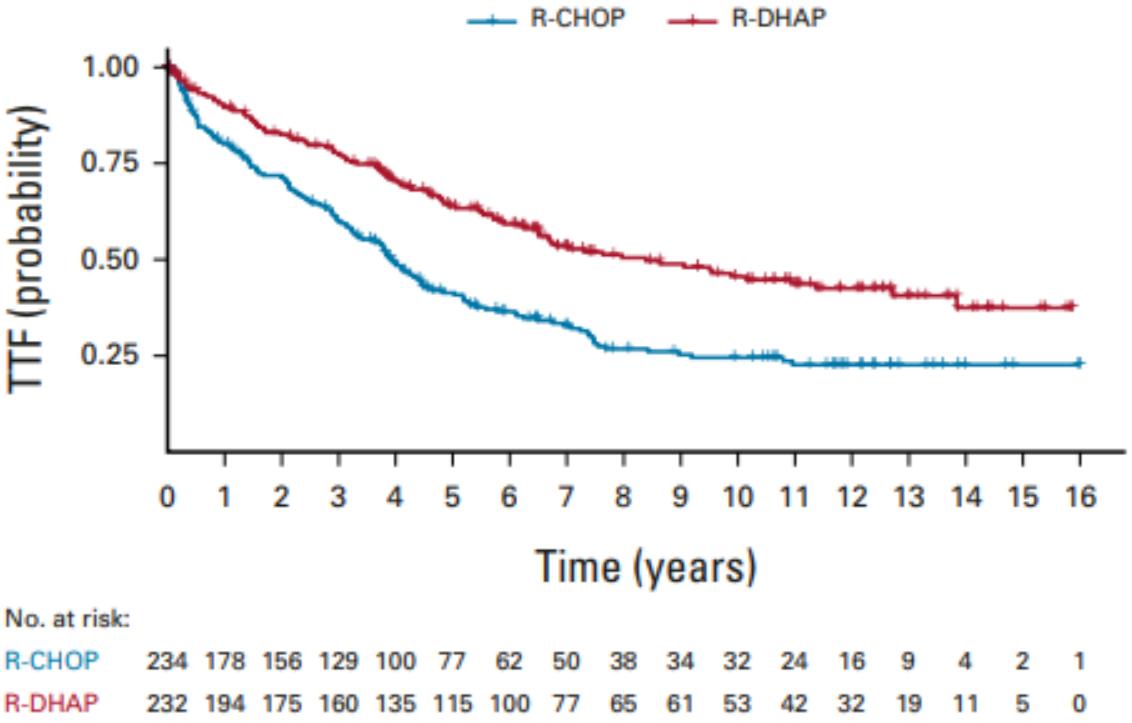


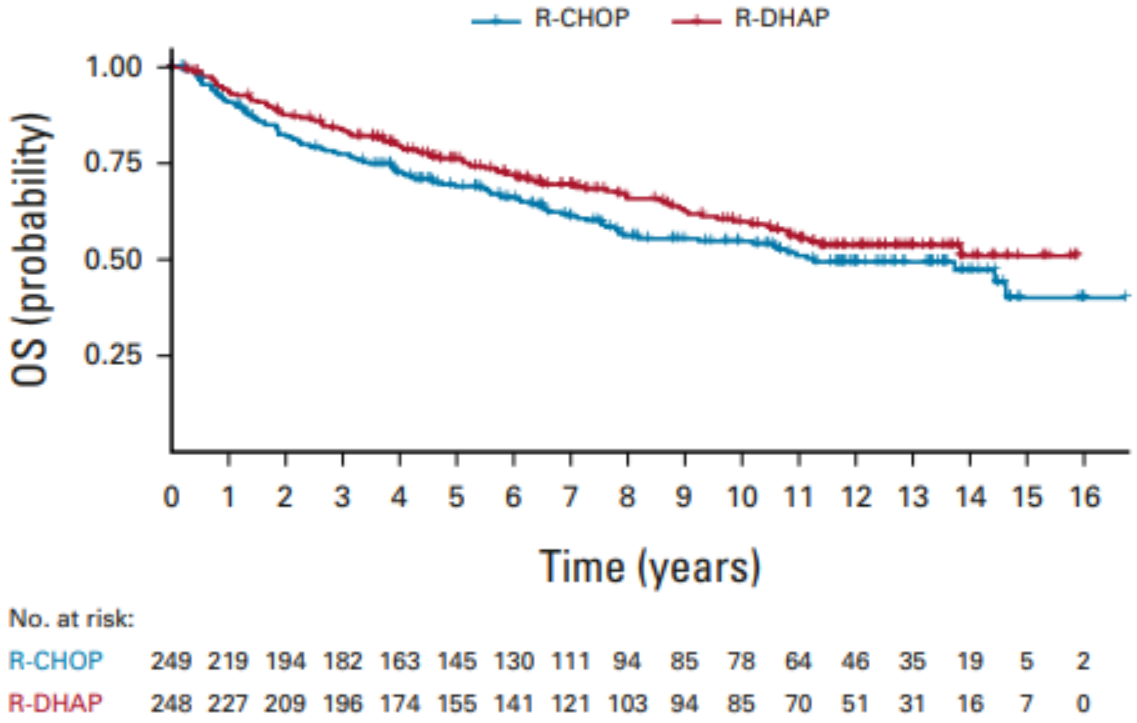
OS



Dreyling et al, Blood 2005

R-CHOP/AutoSCT vs R-CHOP/R-DHAP/AutoSCT





Hermine et al, JCO 2022

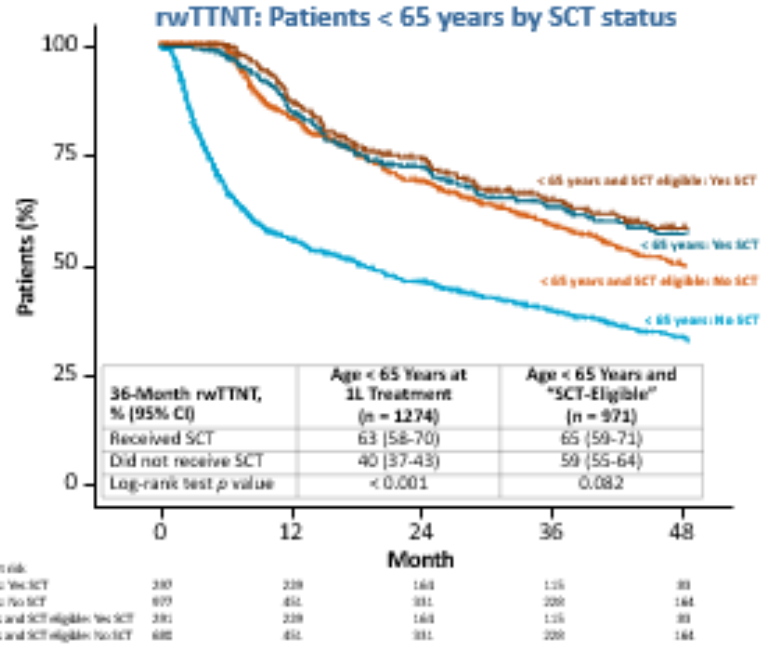
R-CHOP/AutoSCT vs R-CHOP/R-DHAP/AutoSCT

Outcome	Control Group		Cytarabine Group		Cytarabine *v* Control	
	5-Year Rate (95% CI)	10-Year Rate (95% CI)	5-Year Rate (95% CI)	10-Year Rate (95% CI)	MIPI-Adjusted HR (95% CI)	*P*[a]
TTF						
Primary analysis (modified ITT)	41% (35 to 49)	25% (19 to 32)	64% (58 to 71)	46% (39 to 54)	0.59 (NA)[b]	.0380[b]
Secondary analysis (ITT)	43% (37 to 50)	27% (21 to 34)	63% (57 to 70)	43% (37 to 51)	0.56 (0.44 to 0.71)	< .0001
PFS						
From random assignment	45% (39 to 52)	27% (21 to 34)	64% (58 to 70)	44% (37 to 51)	0.57 (0.45 to 0.72)	< .0001
From the end of successful induction	46% (39 to 53)	30% (24 to 37)	67% (61 to 73)	45% (38 to 53)	0.56 (0.44 to 0.72)	< .0001
From ASCT	47% (40 to 56)	32% (25 to 40)	74% (68 to 81)	51% (44 to 61)	0.50 (0.37 to 0.66)	< .0001
OS	69% (63 to 75)	55% (48 to 62)	76% (71 to 82)	60% (53 to 67)	0.74 (0.56 to 0.98)	.0380

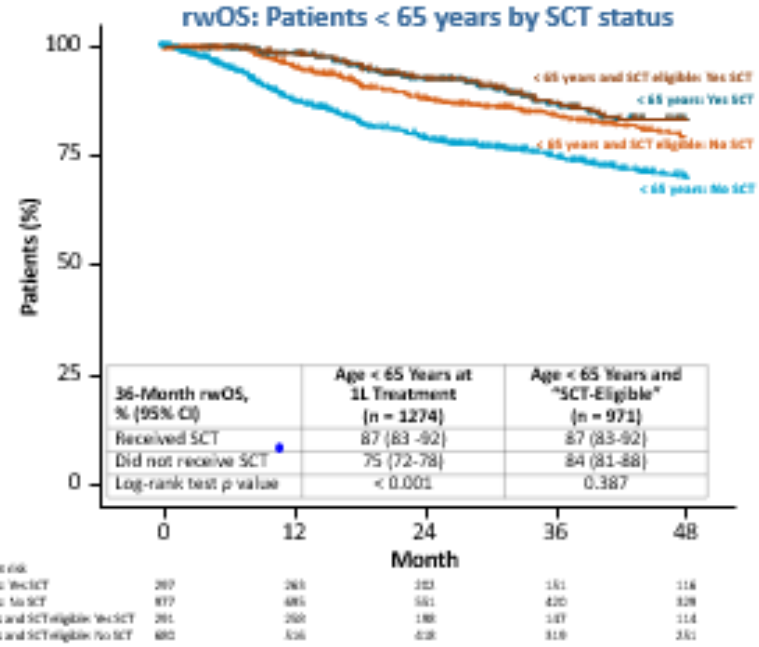
Hermine et al, JCO 2022

“Real world” data on 1274 MCL pts < 65yo SCT vs no SCT

- In the “SCT-eligible”[a] cohort (N = 971), 36-month rwTTNT was comparable for patients with SCT (65 [95%CI 59-71]) compared with those who did not receive SCT (59% [95% CI, 55-64])



36-Month rwTTNT, % (95% CI)	Age < 65 Years at 1L Treatment (n = 1274)	Age < 65 Years and "SCT-Eligible" (n = 971)
Received SCT	63 (58-70)	65 (59-71)
Did not receive SCT	40 (37-43)	59 (55-64)
Log-rank test *p* value	< 0.001	0.082



36-Month rwOS, % (95% CI)	Age < 65 Years at 1L Treatment (n = 1274)	Age < 65 Years and "SCT-Eligible" (n = 971)
Received SCT	87 (83 -92)	87 (83-92)
Did not receive SCT	75 (72-78)	84 (81-88)
Log-rank test *p* value	< 0.001	0.387

[a]Given the potential for treatment response to impact the receipt of SCT in the real world, only patients < 65 years who were alive and did not initiate subsequent treatment within 6 months of starting the 1L treatment were considered “SCT-eligible.”
rwTTNT is defined as time from start of 1L treatment to subsequent treatment or death, whichever comes first; rwOS is defined as time from start of 1L treatment to death.

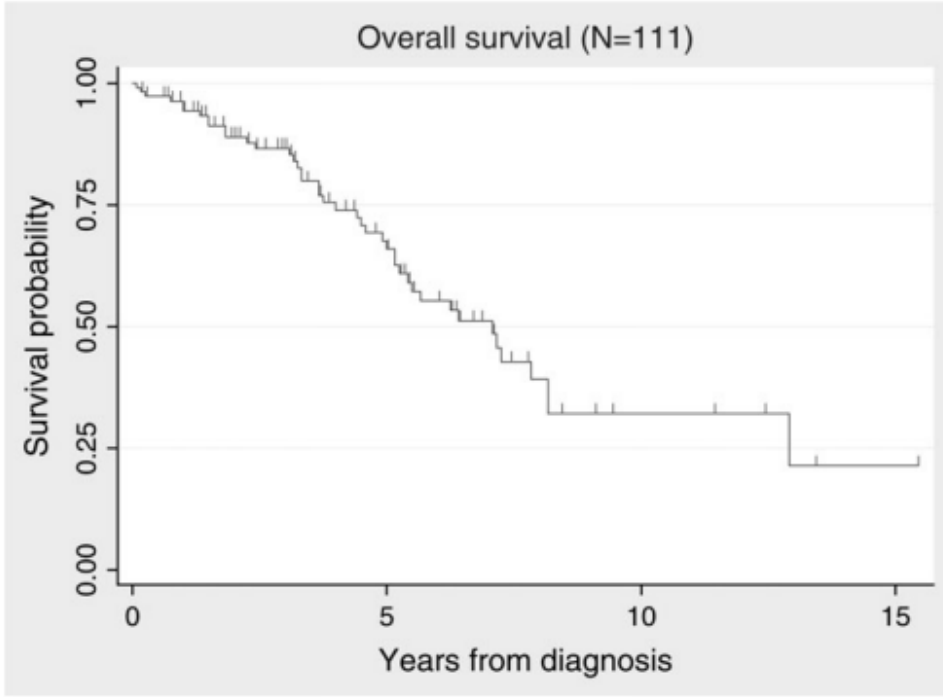
Martin et al, ASCO 2021

Weill Cornell Medicine NewYork-Presbyterian

What's old is new

Intensive treatment strategies may not provide superior outcomes in mantle cell lymphoma: overall survival exceeding 7 years with standard therapies

P. Martin[1], A. Chadburn[2], P. Christos[3], R. Furman[1], J. Ruan[1], M. A. Joyce[1], E. Fusco[1], P. Glynn[1], R. Elstrom[1], R. Niesvizky[1], E. J. Feldman[1], T. B. Shore[1], M. W. Schuster[1], S. Ely[2], D. M. Knowles[2], S. Chen-Kiang[2], M. Coleman[1] & J. P. Leonard[1]*



Study	Treatment	*n*	Three-year OS (%)	Five-year OS (%)	Median OS
Cornell	Conservative	111	86	66	85 months
Romaguera	Hyper-CVAD	97	82	–	–
Ganti	ASCT	80	–	56	–

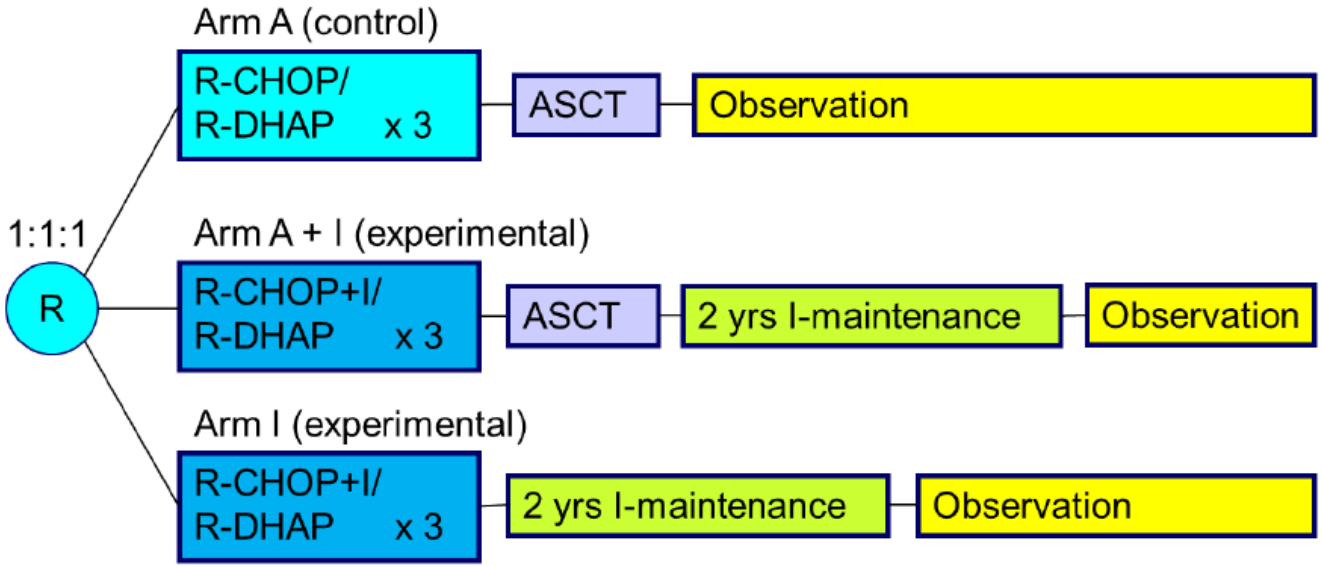
Martin et al, Ann Oncol 2008

Triangle study: Induction/Auto vs Induction/Ibrutinib vs Induction/Ibrutinib/Auto

- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2

- Primary outcome: FFS

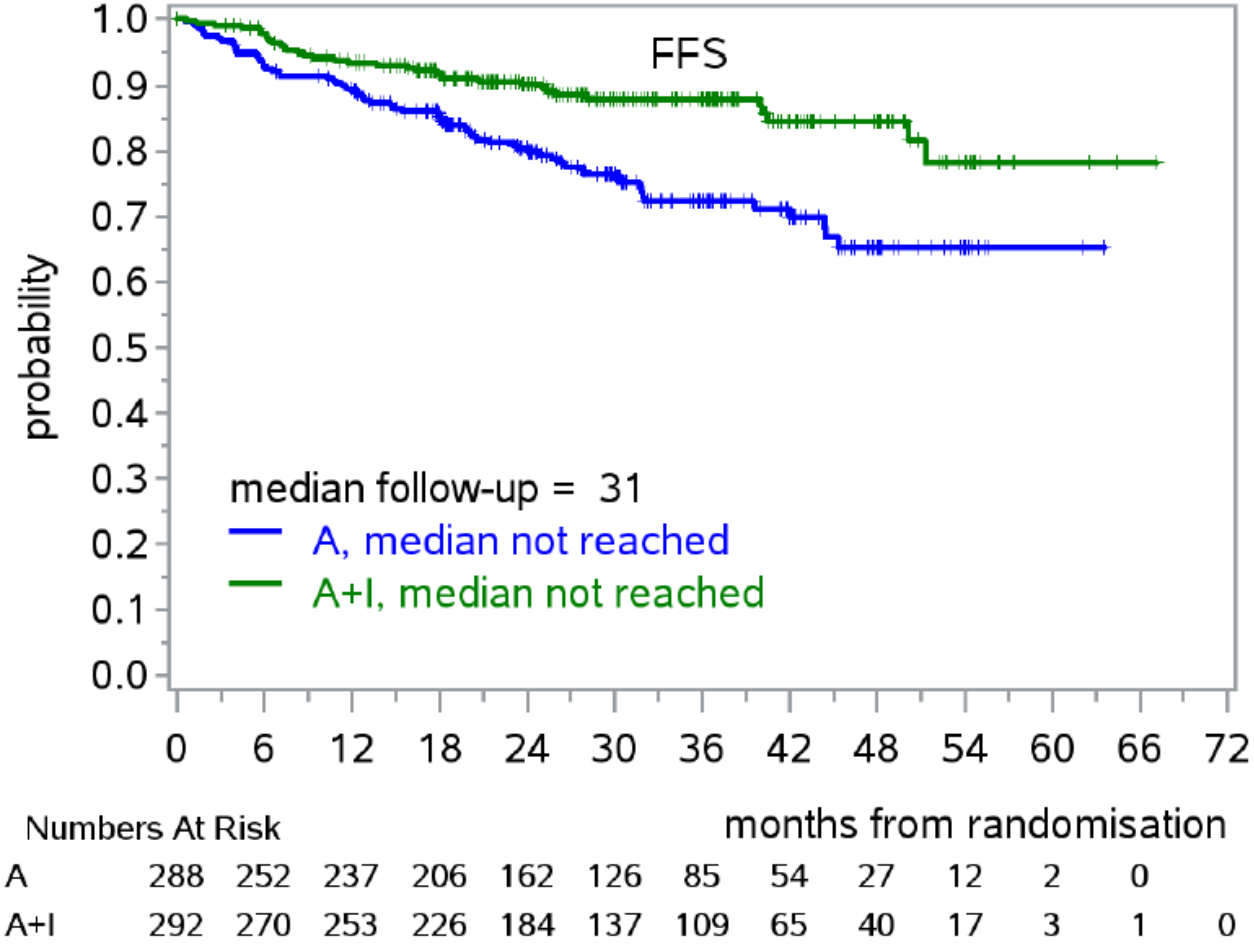
- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety



- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

Dreyling et al, ASH 2022

Triangle study: Induction/Auto vs Induction/Ibrutinib

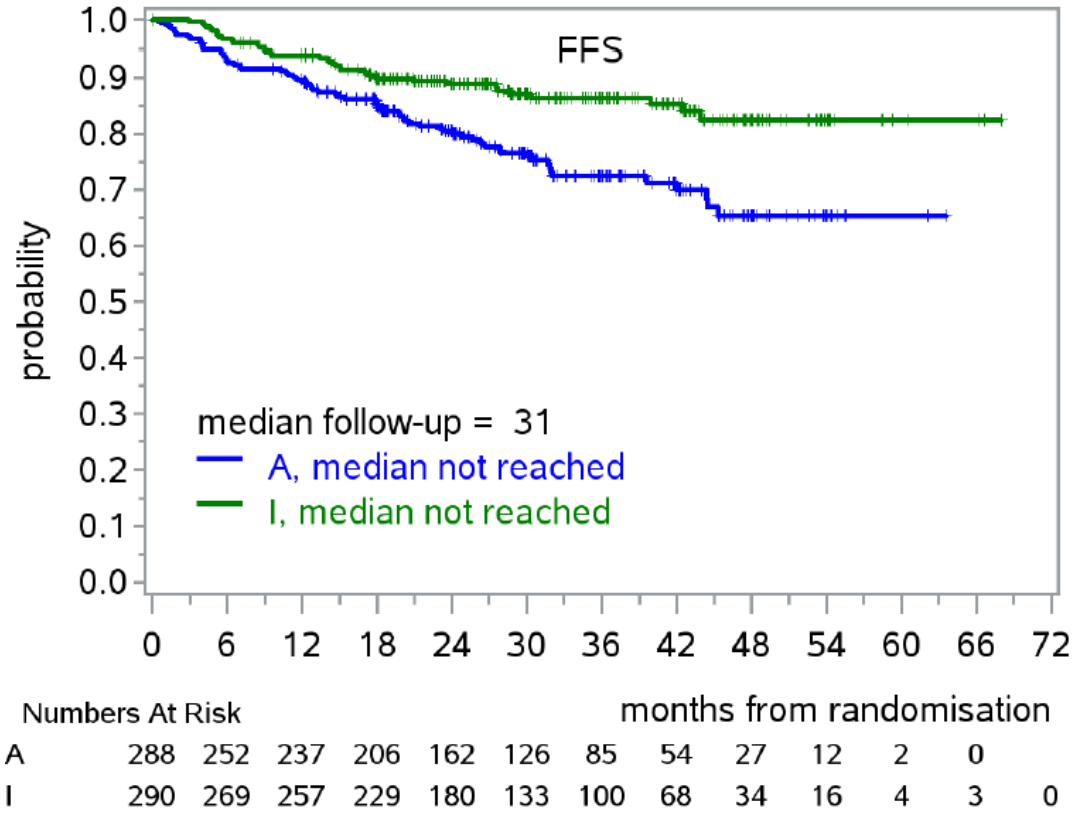


- Superiority of A+I vs. A (FFS) is confirmed
- Kaplan-Meier plots:
  - 3-year FFS A+I: 88%
  - 3-year FFS A: 72%
- p-value (corrected for sequential design) p=0.0008
- HR (A+I vs. A): HR=0.52

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I

Dreyling et al, ASH 2022

Triangle study: Induction/Auto vs Induction/Ibrutinib vs Induction/Ibrutinib/Auto

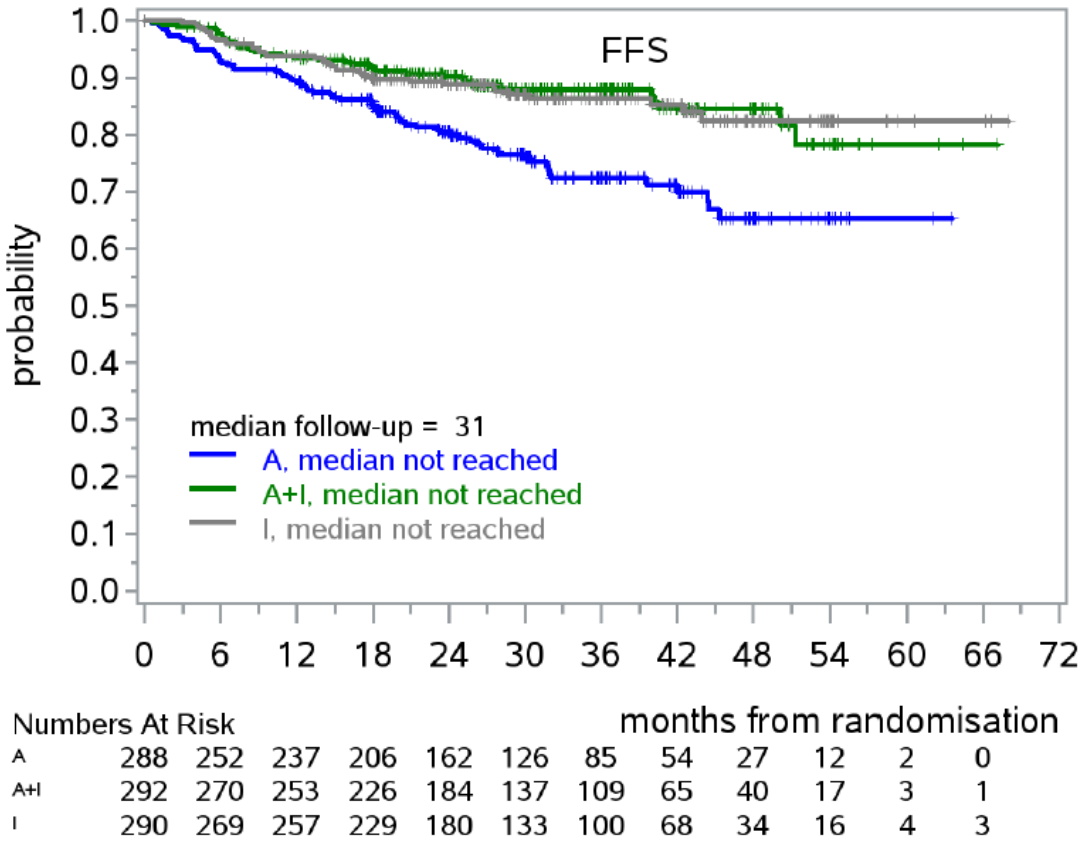


- Superiority of A vs. I (FFS) was rejected
- Kaplan-Meier plots:
  - 3-year FFS A: 72% (MCL Younger: 75%)
  - 3-year FFS I: 86%
- p-value corrected for sequential design: p=0.9979
- HR (A vs. I): HR=1.77

A arm: R-CHOP/R-DHAP+ASCT; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Dreyling et al, ASH 2022

Triangle study: Induction/Auto vs Induction/Ibrutinib vs Induction/Ibrutinib/Auto



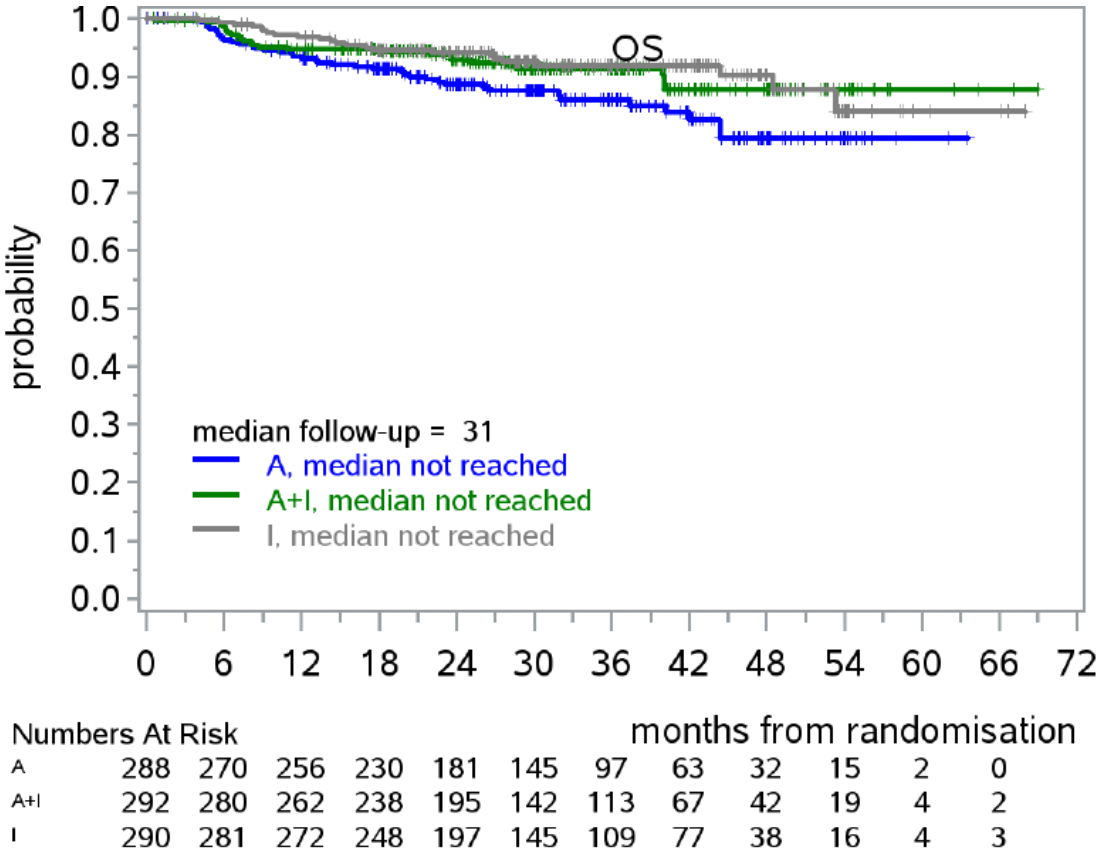
- Test A+I vs. I ongoing, no decision yet

Next lymphoma treatment (among patients with first treatment failure)	A (n=68)		A+I (n=35)		I (n=37)	
Treatment with Ibrutinib	34	79%	4	24%	3	11%
Treatment without Ibrutinib	9	21%	13	76%	24	89%
No treatment	25		18		10	

A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Dreyling et al, ASH 2022

Triangle study: Induction/Auto vs Induction/Ibrutinib vs Induction/Ibrutinib/Auto



- 3-year OS:
  - A: 86% (MCL Younger exp.: 84%)
  - A+I: 91%
  - I: 92%
- Too early to evaluate statistical significance

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Dreyling et al, ASH 2022

Triangle study: Induction/Auto vs Induction/Ibrutinib vs Induction/Ibrutinib/Auto

Based on FFS (primary endpoint):

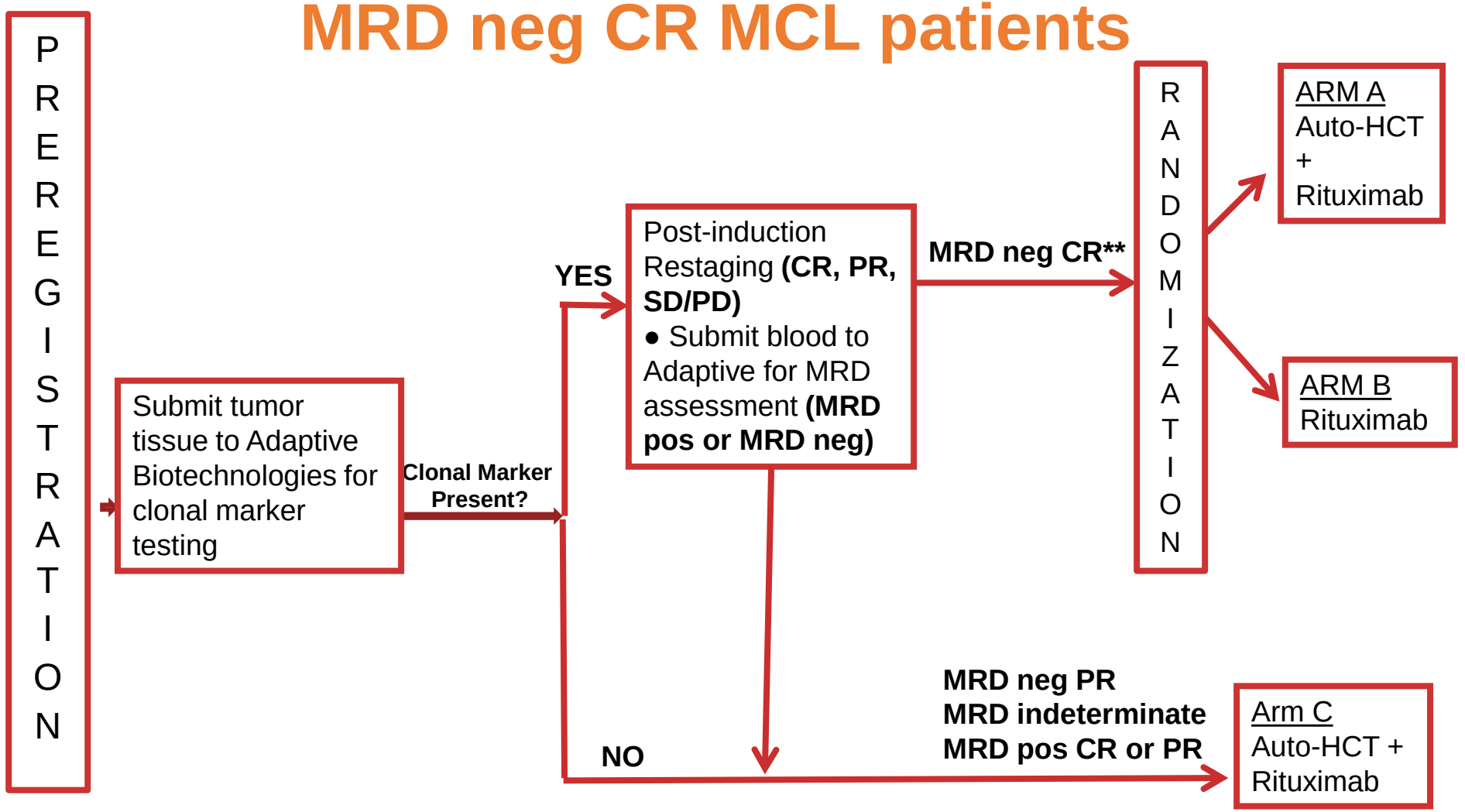
- **A+I (auto SCT + ibrutinib) is superior to A (auto SCT only)**
- **A (auto SCT) is not superior to I (ibrutinib without auto SCT)**
- **currently, no decision whether autologous SCT adds to I (ibrutinib) but toxicity favors Ibru only**

numerical overall survival benefit in the ibrutinib arms (I, A+I)

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Dreyling et al, ASH 2022

E4151: Randomized trial of SCT/R vs R in MRD neg CR MCL patients



Maintenance rituximab makes a difference

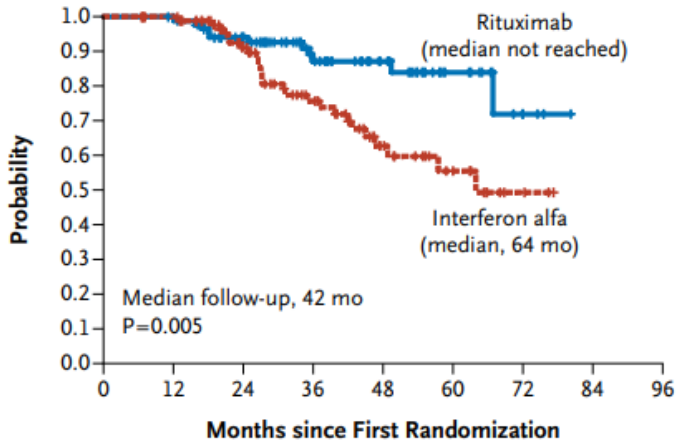
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Older Patients with Mantle-Cell Lymphoma

H.C. Kluin-Nelemans, E. Hoster, O. Hermine, J. Walewski, M. Trneny, C.H. Geisler, S. Stilgenbauer, C. Thieblemont, U. Vehling-Kaiser, J.K. Doorduijn, B. Coiffier, R. Forstpointner, H. Tilly, L. Kanz, P. Feugier, M. Szymczyk, M. Hallek, S. Kremers, G. Lepeu, L. Sanhes, J.M. Zijlstra, R. Bouabdallah, P.J. Lugtenburg, M. Macro, M. Pfreundschuh, V. Procházka, F. Di Raimondo, V. Ribrag, M. Uppenkamp, M. André, W. Klapper, W. Hiddemann, M. Unterhalt, and M.H. Dreyling

D Overall Survival, Patients Assigned to R-CHOP



No. at Risk

Rituximab	87	86	71	46	30	13	3	0
Interferon alfa	97	92	65	43	22	11	3	0

The NEW ENGLAND JOURNAL of MEDICINE

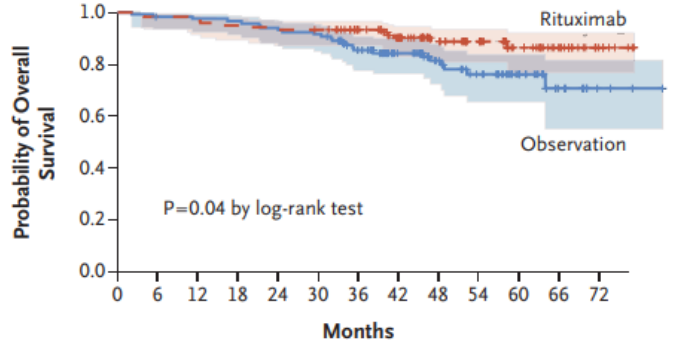
ORIGINAL ARTICLE

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*

C Overall Survival

	No. of Patients	Patients with Event	Patients with Censored Data	Median Survival
		no. (%)		
Rituximab	120	13 (11)	107 (89)	Not reached
Observation	120	24 (20)	96 (80)	Not reached



No. at Risk

Rituximab	120	118	116	114	112	111	100	79	60	48	32	20	7
Observation	120	117	116	115	111	109	90	71	50	39	23	10	3

Kluin-Nelemans et al, NEJM 2012
LeGouill et al, NEJM 2017

Weill Cornell Medicine NewYork-Presbyterian

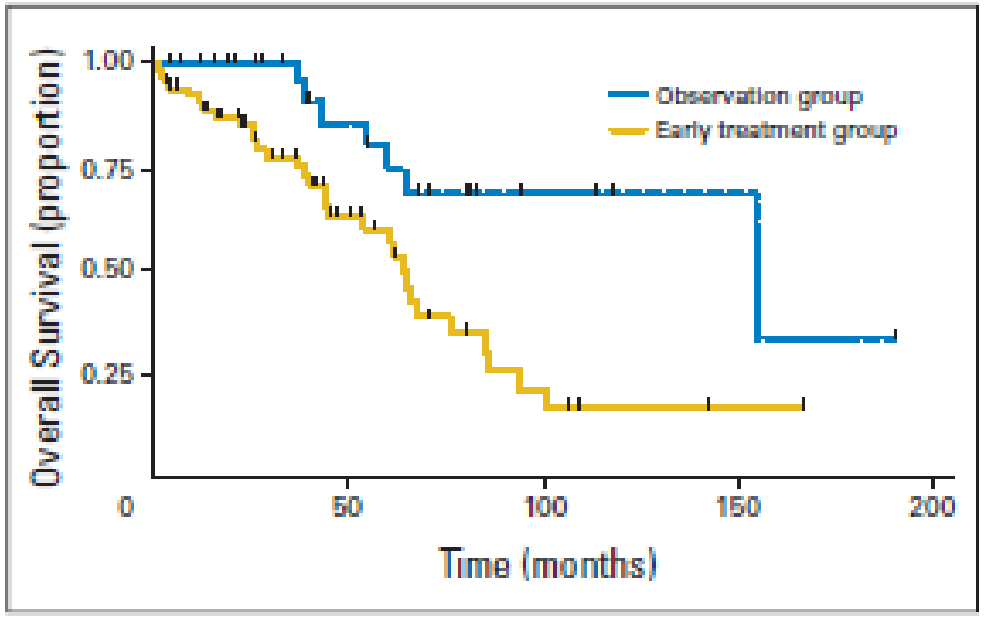
Mantle cell lymphoma: New ideas are old

Watch and wait is a reasonable approach in MCL

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Outcome of Deferred Initial Therapy in Mantle-Cell Lymphoma

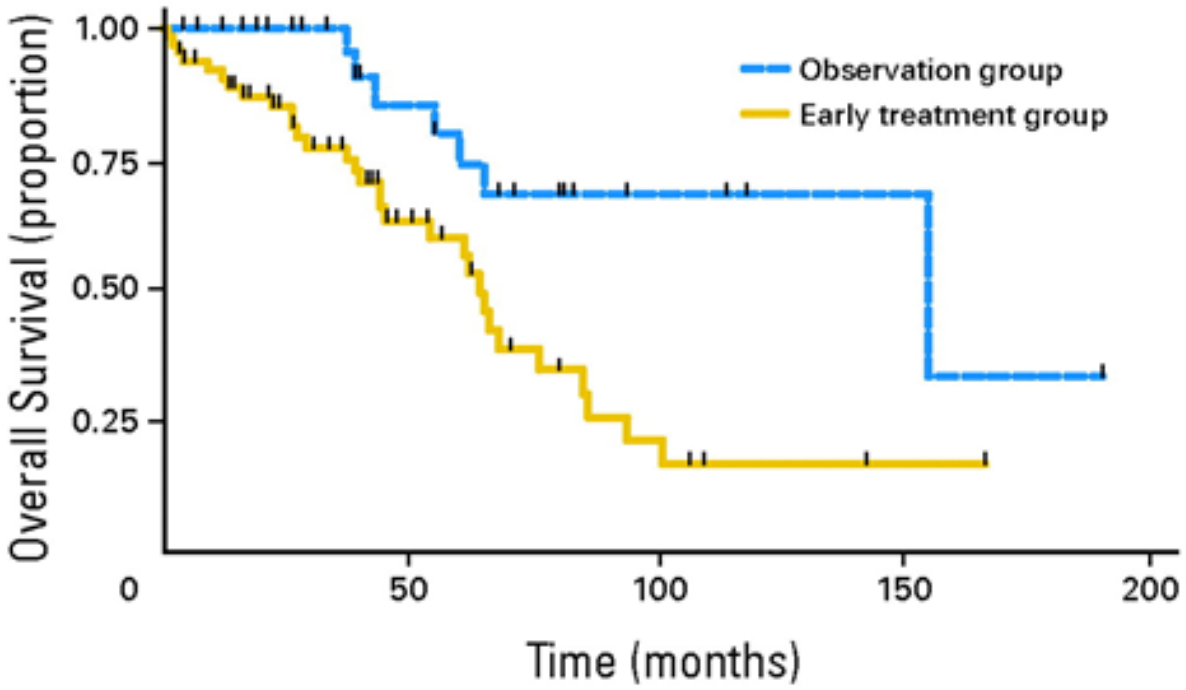
Peter Martin, Amy Chadburn, Paul Christos, Karen Weil, Richard R. Furman, Jia Ruan, Rebecca Elstrom, Ruben Niesvizky, Scott Ely, Maurizio DiLiberto, Ari Melnick, Daniel M. Knowles, Selina Chen-Kiang, Morton Coleman, and John P. Leonard



Martin et al, JCO 2009

Who can watch and wait in MCL?

Not blastoid morphology[1]
Normal LDH[2]
Ki67 <30%[3]
No B symptoms[4]
Mutated IGHV[5]
Non-nodal[6]
MIPI is NOT a defining characteristic



1-Martin JCO 2009, 7-Eve JCO 2009, 8-Budde JCO 2010, 2-Abrahamsson Blood 2014, 3-Abrisqueta ASH abstract 2015, 4-Cohen ASH abstract 2015, 5-Orchard Blood 2003, 6-Ondrejka Haematologica 2011

Outcomes of deferred therapy (retrospective)

Series	Number of Deferred Patients (%)	Median time to treatment (Range)	Median OS (Deferred Pts)	Median OS (Immediate Pts)
Martin 2009 (Cornell)	31 / 97 (32)	12 months (4-128)	Not Reached (4.6 years)	5.3 years
Abrisqueta 2015 (B.C.)	74 / 439 (17)	35.5 months (5-79)	5.5 years	4.2 years
Cohen 2016 (NCDB)	492 / 8029 (6)	4 months (3-38)*	6.6 years	-
Kumar 2015 (MSKCC)	91 / 404 (23)	23 months	10.6 years	9.4 years
Calzada 2016 (Multicenter)	72 / 395 (18)	7.8 months (3-121)*	11.8 years	11.6 years

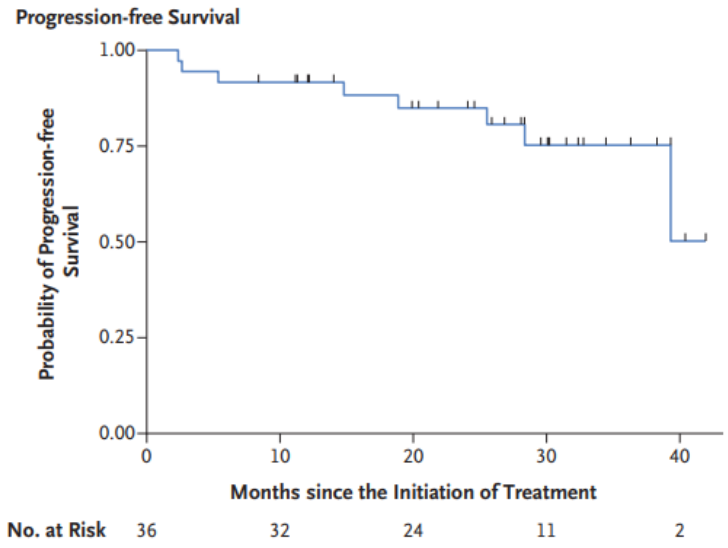
Chemotherapy is not necessary in MCL

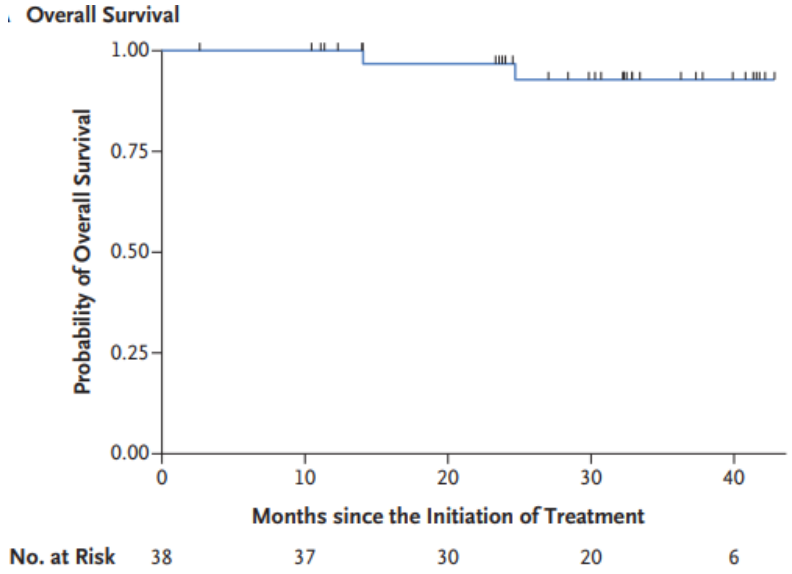
The NEW ENGLAND JOURNAL of MEDICINE

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., Paul Christos, Dr.P.H., Amelyn Rodriguez, R.N., Jakub Svoboda, M.D., Jessica Lewis, P.A., Orel Katz, P.A., Morton Coleman, M.D., and John P. Leonard, M.D.





Ruan et al, NEJM 2015

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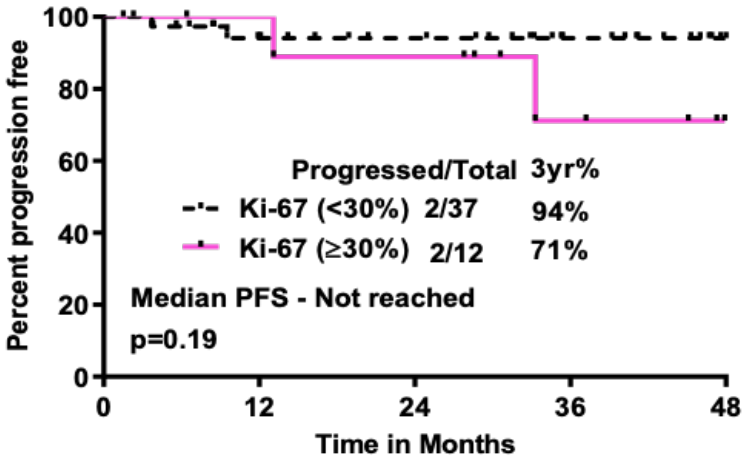
Ibrutinib plus rituximab in frontline setting

WINDOW-1 (<65y)

Response	All patients
Part A week 16*	N (%)
Part A Best response	
ORR	50 (100)
CR	46 (92)
PR	4 (8)
Part B Best response**	
ORR	48 (96)
CR	47 (94)
PR	1 (2)

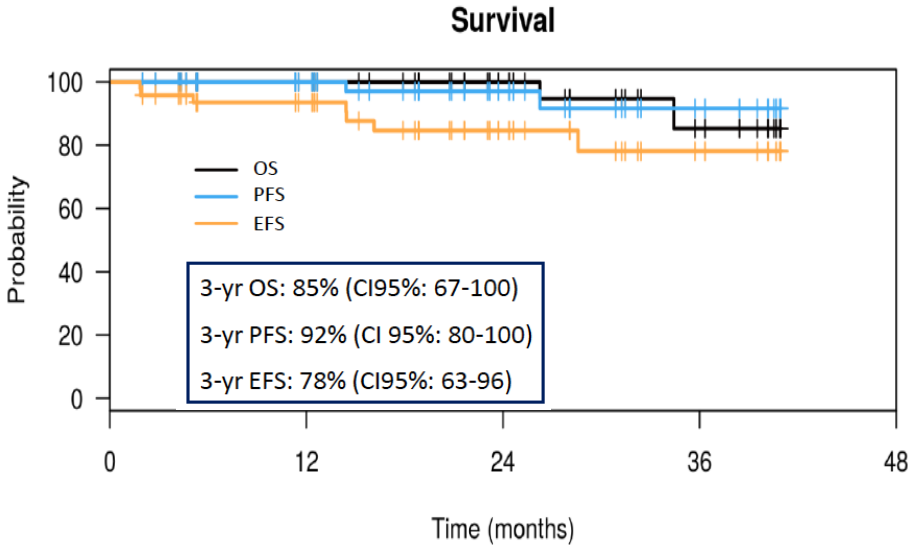
I+R x up to 12 cycles followed by R-hyperCVAD

MDACC (>65y)



ORR 100%, CR 60%
57% required dose reduction
20/50 stopped study tx (15 for a.fib)

IMCL-15 (indolent)



2-years of treatment for MRD- cases
ORR 83%, CR 77%, MRD- 74%
57% required dose reduction

Wang, ASH 2018, Jain et al. ICML 2019, Gine ASH 2019

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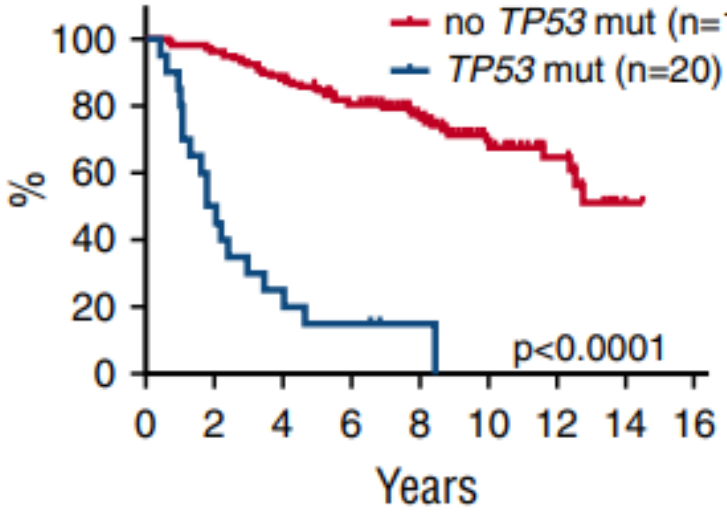
Chemotherapy is ineffective in MCL patients with p53 mutations

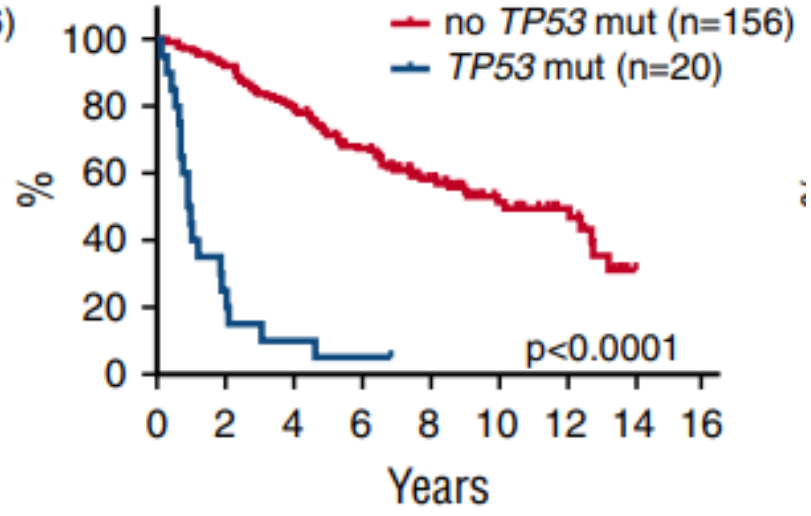
TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy

Christian W. Eskelund,[1,2] Christina Dahl,[3] Jakob W. Hansen,[1,2] Maj Westman,[4] Arne Kolstad,[5] Lone B. Pedersen,[1] Carmen P. Montano-Almendras,[1,2] Simon Husby,[1,2] Catja Freiburghaus,[6] Sara Ek,[6] Anja Pedersen,[1,2] Carsten Niemann,[1] Riikka Räty,[7] Peter Brown,[1] Christian H. Geisler,[1] Mette K. Andersen,[4] Per Guldberg,[3] Mats Jerkeman,[8] and Kirsten Grønbæk[1,2]

OS



PFS

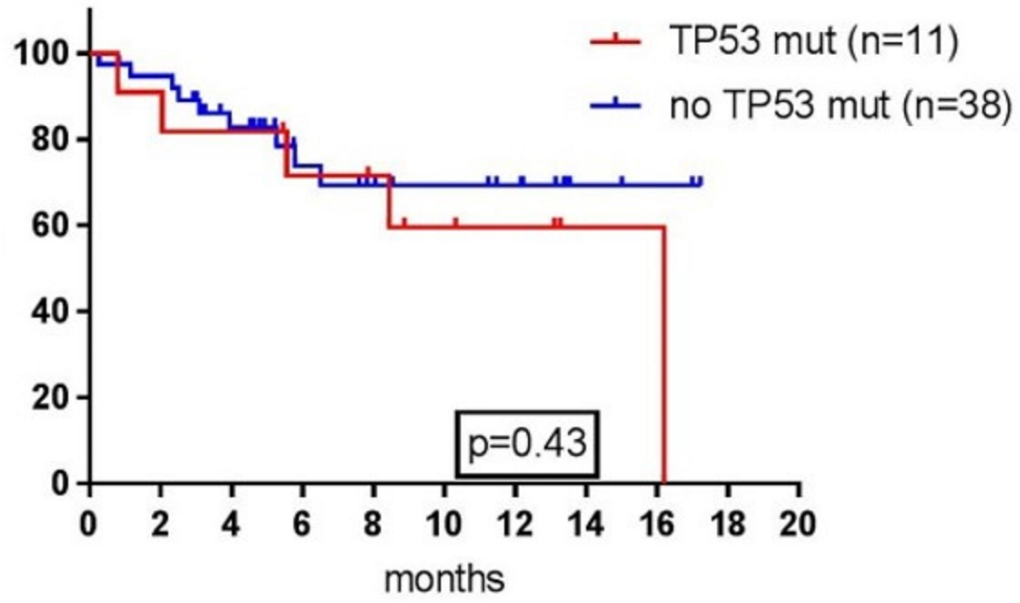


Eskelund et al, Blood 2017

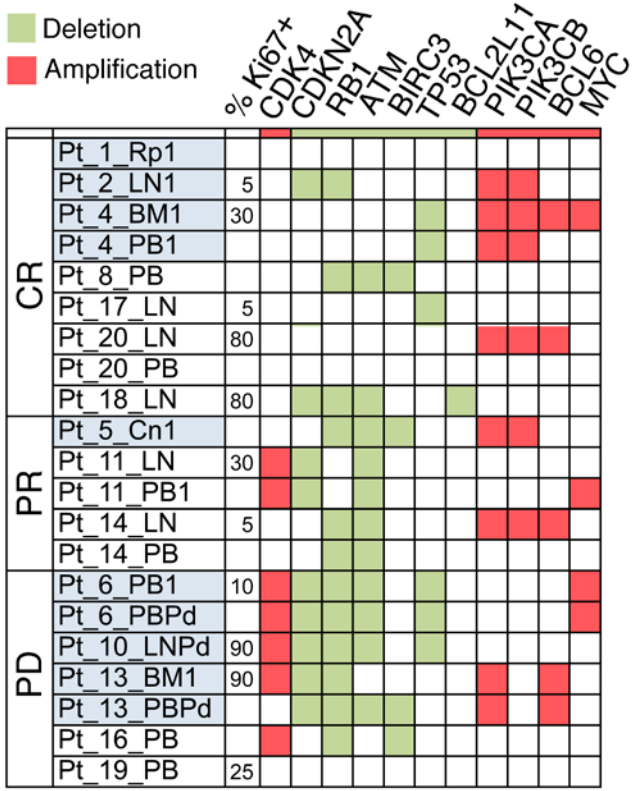
TP53 was not associated with prognosis in studies with novel agents in relapsed/refractory MCL

Ibrutinib-lenalidomide-rituximab

PFS by TP53



Ibrutinib-palbociclib



Jerkman et al. ASH 2016
Martin et al. ASH 2016

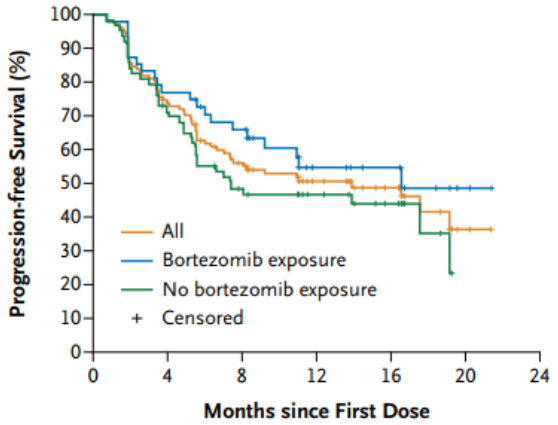
BTK inhibitors are an essential option for MCL patients

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 8, 2013 VOL. 369 NO. 6

Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

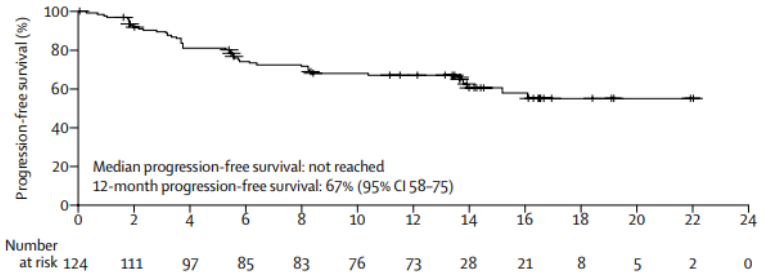
Michael L. Wang, M.D., Simon Rule, M.D., Peter Martin, M.D., Andre Goy, M.D., Rebecca Auer, M.D., Ph.D., Brad S. Kahl, M.D., Wojciech Jurczak, M.D., Ph.D., Ranjana H. Advani, M.D., Jorge E. Romaguera, M.D., Michael E. Williams, M.D., Jacqueline C. Barrientos, M.D., Ewa Chmielowska, M.D., John Radford, M.D., Stephan Stilgenbauer, M.D., Martin Dreyling, M.D., Wieslaw Wiktor Jedrzejczak, M.D., Peter Johnson, M.D., Stephen E. Spurgeon, M.D., Lei Li, Ph.D., Liang Zhang, M.D., Ph.D., Kate Newberry, Ph.D., Zhishuo Ou, M.D., Nancy Cheng, M.S., Bingliang Fang, Ph.D., Jesse McGreivy, M.D., Fong Clow, Sc.D., Joseph J. Buggy, Ph.D., Betty Y. Chang, Ph.D., Darrin M. Beaupre, M.D., Ph.D., Lori A. Kunkel, M.D., and Kristie A. Blum, M.D.



No. at Risk							
No bortezomib exposure	63	44	28	19	12	0	0
Bortezomib exposure	48	37	29	14	10	2	0
All	111	81	57	33	22	2	0

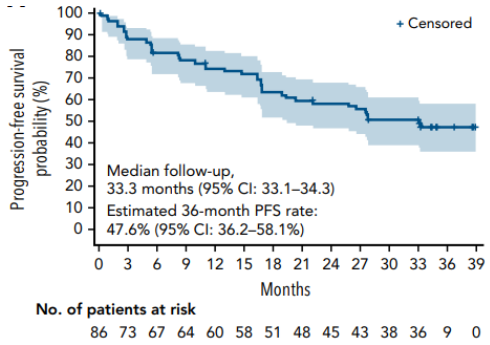
Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial

Michael Wang, Simon Rule, Pier Luigi Zinzani, Andre Goy, Olivier Casasnovas, Stephen D Smith, Gandhi Damaj, Jeanette Doorduijn, Thierry Lamy, Franck Morschhauser, Carlos Panizo, Bijal Shah, Andrew Davies, Richard Eek, Jehan Dupuis, Eric Jacobsen, Arnon P Kater, Steven Le Gouill, Lucie Oberic, Taduesz Robak, Todd Covey, Richa Dua, Ahmed Hamdy, Xin Huang, Raquel Izumi, Priti Patel, Wayne Rothbaum, J Greg Slatter, Wojciech Jurczak



Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study

Yuqin Song,[1] Keshu Zhou,[2] Dehui Zou,[3] Jianfeng Zhou,[4] Jianda Hu,[5] Haiyan Yang,[6] Huilai Zhang,[7] Jie Ji,[8] Wei Xu,[9] Jie Jin,[10] Fangfang Lv,[11] Ru Feng,[12] Sujun Gao,[13] Haiyi Guo,[14] Lei Zhou,[15] Jane Huang,[16] William Novotny,[16] Pil Kim,[16] Yiling Yu,[14] Binghao Wu,[14] and Jun Zhu[1]



Wang et al, NEJM 2013
Wang et al, Lancet 2018
Song et al, Blood 2022

Weill Cornell Medicine NewYork-Presbyterian

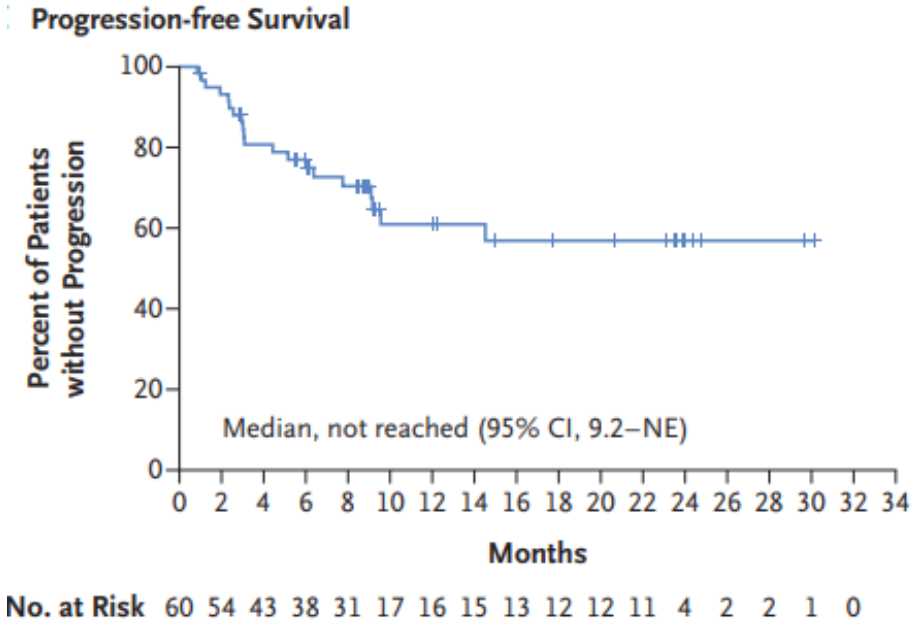
CAR-T cell therapy can be valuable

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan



Wang et al, NEJM 2020

Weill Cornell Medicine NewYork-Presbyterian

Key questions for the future

- Rational selection of therapy (beyond age/fitness)
- Chemotherapy vs novel combinations as initial therapy?
- Does autoSCT improve OS?
- What are best therapies for patients with p53 mutations?
- Role of novel BTKi (pirtobrutinib, BTK degraders) and the best ways to overcome BTK resistance
- Can we improve efficacy and tolerability of CAR-T
- Role of bispecific antibodies and other novel agents
- When should we perform alloSCT?
- Can we cure MCL and if so, how will we know we have done it?