LA RIVOLUZIONE NEL MONDO DEL
LINFOMA MANTELLARE!

Milano, Hilton Milan Hotel
27 gennaio 2025

Responsabili Scientifici
Paolo Corradini, Pier Luigi Zinzani

Risultati del trapianto autologo nel giovane

Maurizio Martelli

Ematologia Univ. Sapienza Roma

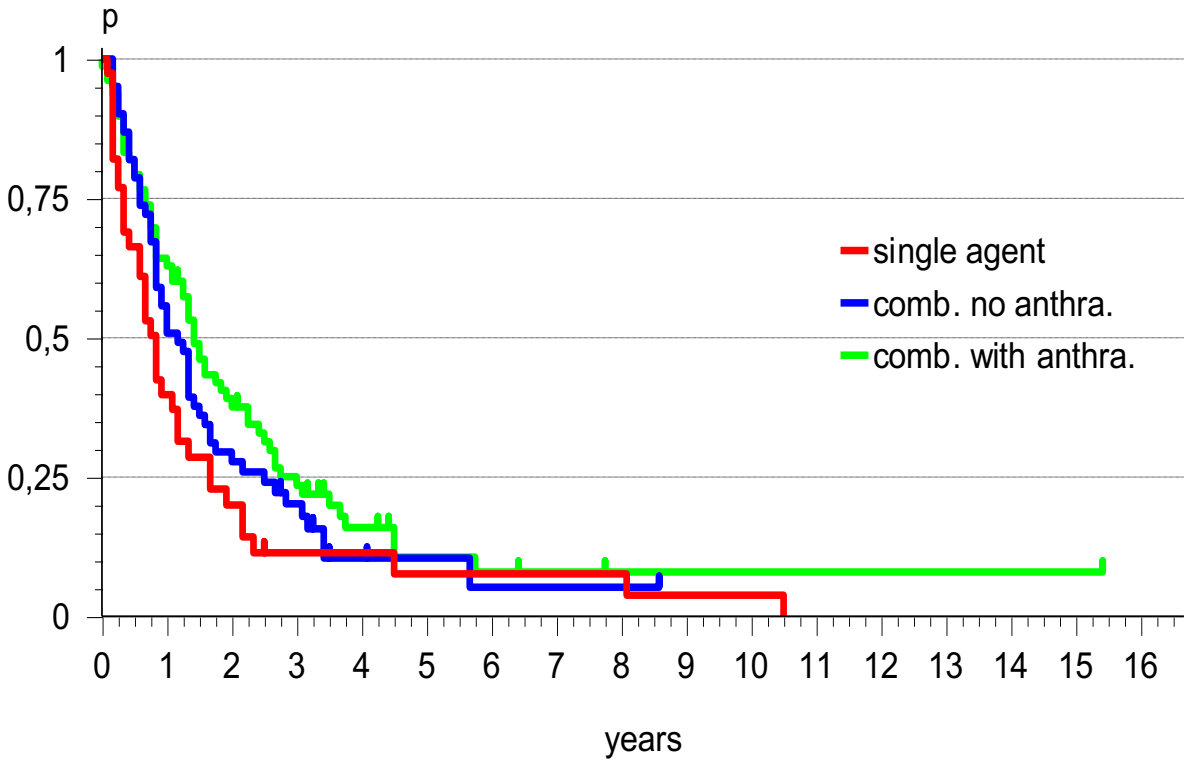
Disclosures of Maurizio Martelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche					X	X	
Gilead					X	X	
Novartis						X	
Takeda						X	
Eusapharma					X	X	
Incyte					X	X	
Janssen					X	X	
BMS						X	
Beigene					X	X	
Alexion	x						

Multicenter Evaluation of MCL

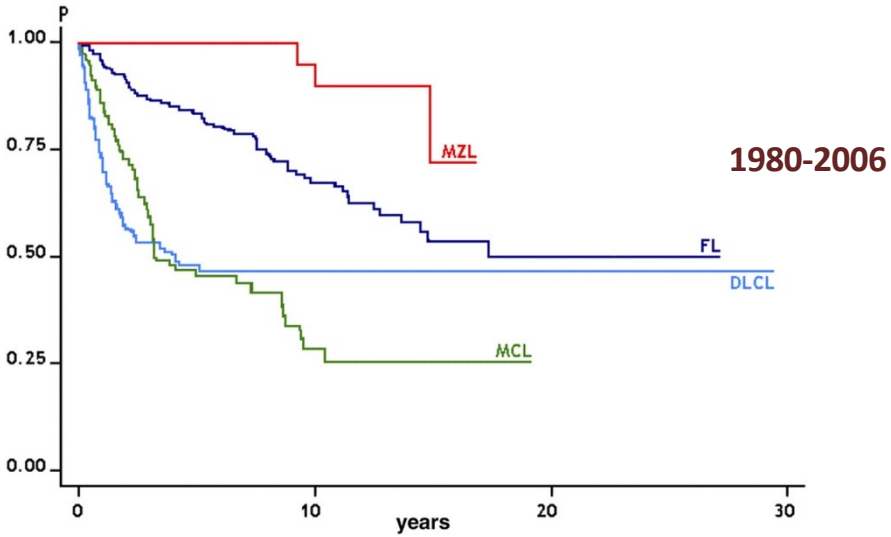
Annency Criteria fulfilled

event free interval after chemotherapy in stages III + IV



Dreyling, ASCO 1999

Cause-specific survival of the main B-cell lymphoma subtypes



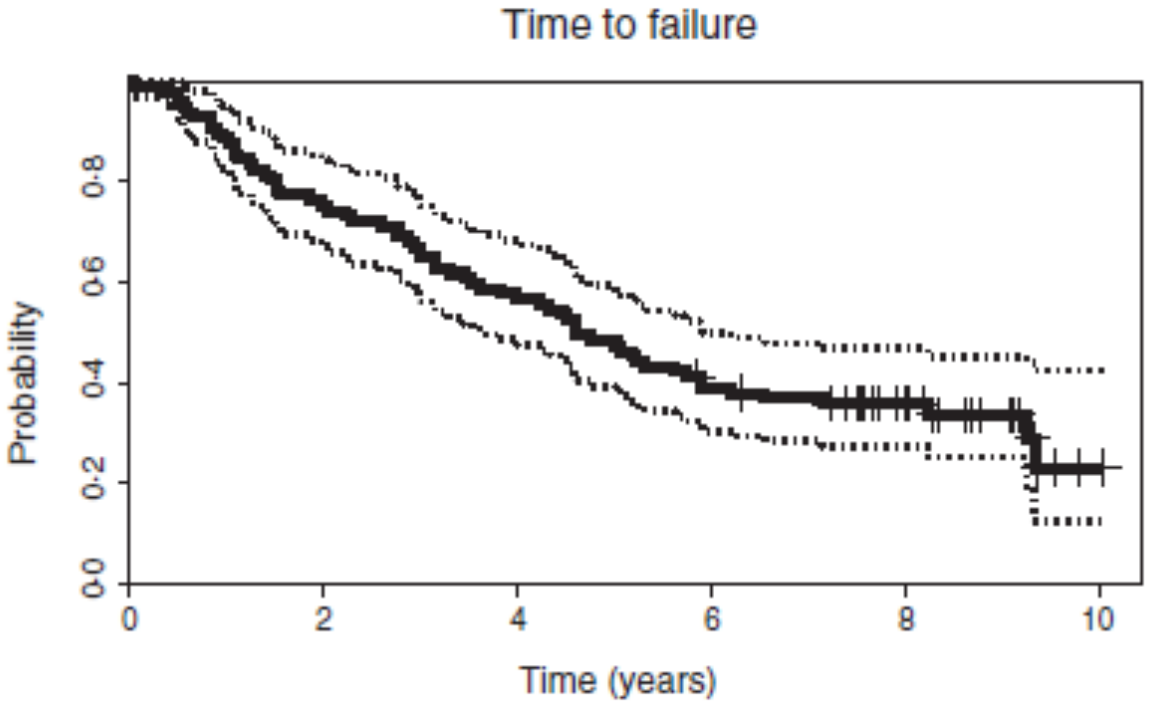
1980-2006

Significant improvement in OS in the last 10 years:

1) introduction of dose-intensive strategies upfront in younger patients
2) availability of novel agents in older patients or in the r/r setting.

Oncology Institute of Southern Switzerland, Ghielmini and Zucca, Blood 2009

Regimens not including ASCT R-HyperCVAD+MTX-Ara-C



<65 , 65 pts: 8-year TTF 46%
>65 , 32 pts: 8-year TTF 16%

Romaguera J et al , BJH 2010

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, et al.

N Engl J Med 2012; 367:520-531

June,2012

Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network

Olivier Hermine*, Eva Hoster*, Jan Walewski, André Bosly, Stephan Stilgenbauer, Catherine Thieblemont, Michal Szymczyk, Reda Bouabdallah, Michael Kneba, Michael Hallek, Gilles Salles, Pierre Feugier, Vincent Ribrag, Josef Birkmann, Roswitha Forstpointner, Corinne Haioun, Matthias Hänel, René Olivier Casasnovas, Jürgen Finke, Norma Peter, Kamal Bouabdallah, Catherine Sebban, Thomas Fischer, Ulrich Dührsen, Bernd Metzner, Georg Maschmeyer, Lothar Kanz, Christian Schmidt, Richard Delarue, Nicole Brousse, Wolfram Klapper, Elizabeth Macintyre, Marie-Hélène Delfau-Larue, Christiane Pott, Wolfgang Hiddemann, Michael Unterhalt, Martin Dreyling, on behalf of the European Mantle Cell Lymphoma Network

The Lancet. VOLUME 388, ISSUE 10044, P565-575, AUGUST 06, 2016

June,2016

The NEW ENGLAND JOURNAL of MEDICINE

Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma

Michael L. Wang, M.D., Wojciech Jurczak, M.D., Ph.D., Mats Jerkeman, M.D., Ph.D., Judith Trotman, F.R.A.C.P., Pier L. Zinzani, M.D., Ph.D., David Belada, M.D., Ph.D., Carola Boccomini, M.D., Ian W. Flinn, M.D., Ph.D., Pratyush Giri, F.R.A.C.P., Andre Goy, M.D., Paul A. Hamlin, M.D., Olivier Hermine, M.D., Ph.D., et al., for the SHINE Investigators*

June 30, 2022
N Engl J Med 2022; 386:2482-2494
DOI: 10.1056/NEJMoa2201817

January, 2022

September, 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Steven Le Gouill, M.D., Ph.D., Catherine Thieblemont, M.D., Ph.D., Lucie Oberic, M.D., Anne Moreau, M.D., Krimo Bouabdallah, M.D., Caroline Dartigeas, M.D., Gandhi Damaj, M.D., Ph.D., Thomas Gastinne, M.D., Vincent Ribrag, M.D., Ph.D., Pierre Feugier, M.D., Ph.D., Olivier Casasnovas, M.D., Hacène Zerazhi, M.D., et al., for the LYSA Group*

N Engl J Med 2017; 377:1250-1260

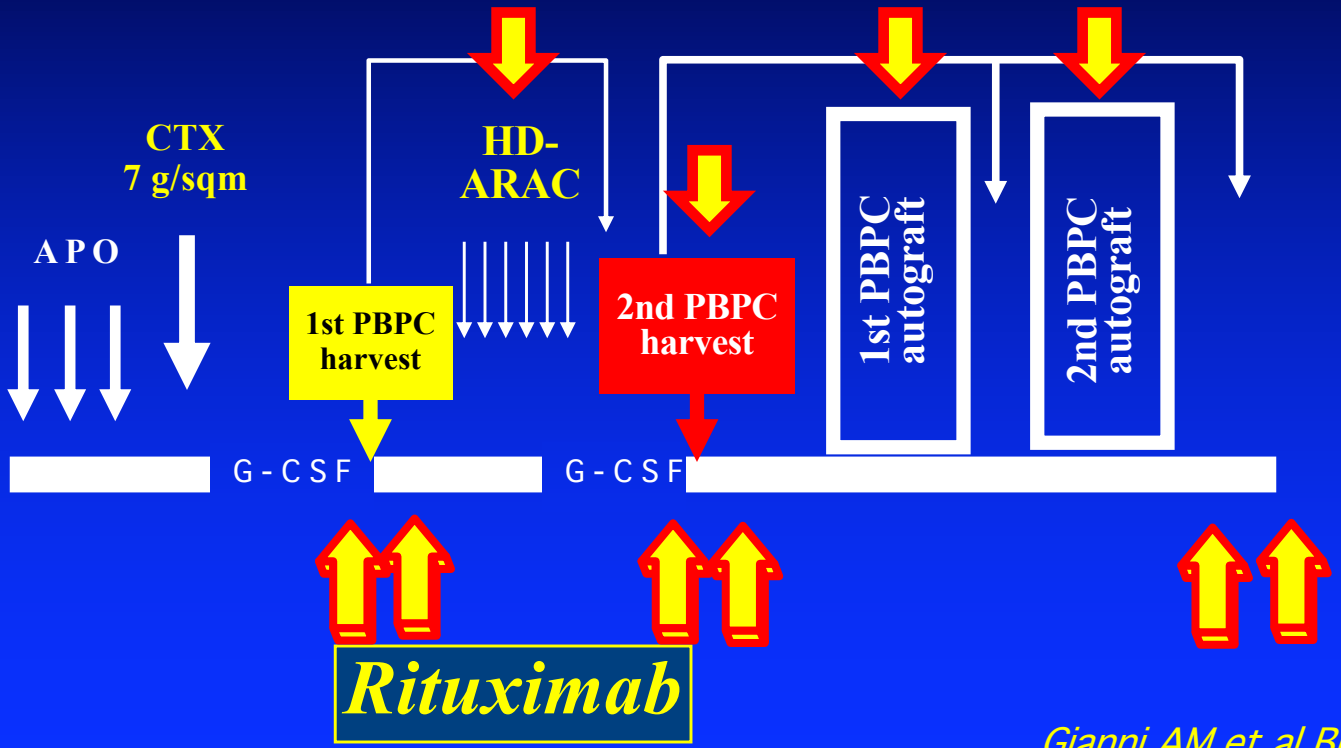
January, 2020

Lenalidomide maintenance after autologous haematopoietic stem-cell transplantation in mantle cell lymphoma: results of a Fondazione Italiana Linfomi (FIL) multicentre, randomised, phase 3 trial

Marco Ladetto*, Sergio Cortelazzo*, Simone Ferrero, Andrea Evangelista, Michael Mian, Rita Tavarozzi, Manuela Zanni, Federica Cavallo, Alice Di Rocco, Vittorio Stefoni, Chiara Pagani, Alessandro Re, Annalisa Chiappella, Monica Balzarotti, Vittorio R Zilioli, Maria Gomes da Silva, Luca Arcaini, Anna L Molinari, Filippo Ballerini, Andrés J M Ferreri, Benedetta Puccini, Fabio Benedetti, Piero M Stefani, Franco Narni, Ivana Casaroli, Caterina Stelitano, Giovannino Ciccone, Umberto Vitolo, Maurizio Martelli

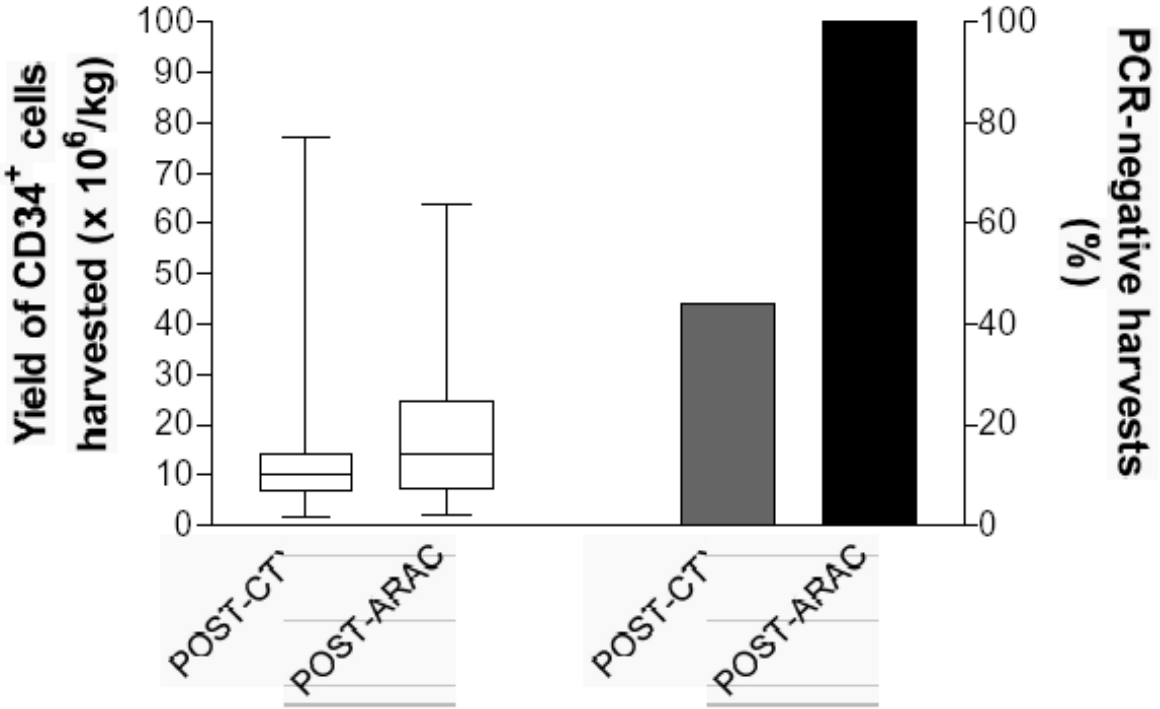
The Lancet Haematology.VOLUME 8, ISSUE 1, E34-E44, JANUARY 01, 2021

Modified HDS with rituximab (R-HDS) given prior to PBC collections for MCL



Gianni AM et al Blood 2003

Quantity and quality of PBPC harvests after CT and AraC + Rituximab

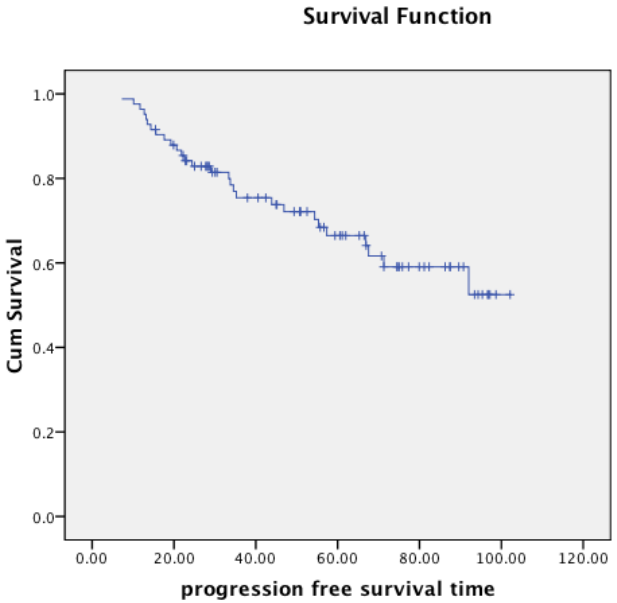


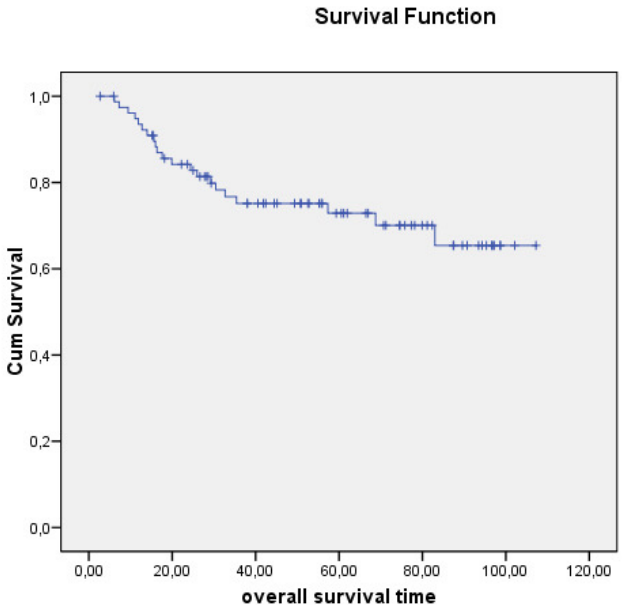
Gianni AM et al Blood 2003

Update of 83 MCL Patients Treated with R-HDS

(Median follow-up 44 months, range 3-96 months)

ORR= 100% CR= 94% PR= 6%



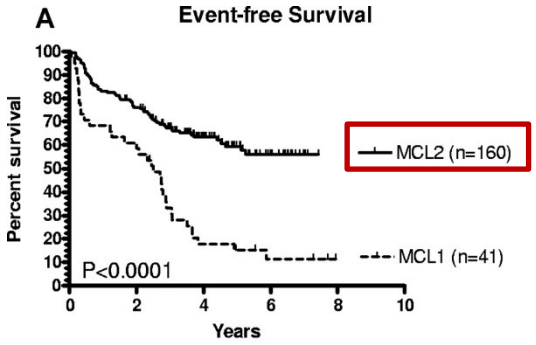


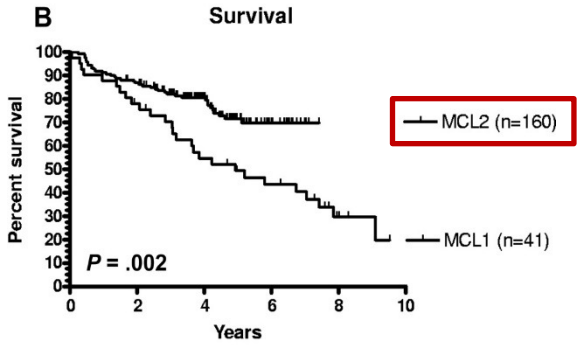
PFS at 2 yrs 84.4%; at 5yrs 66.3%

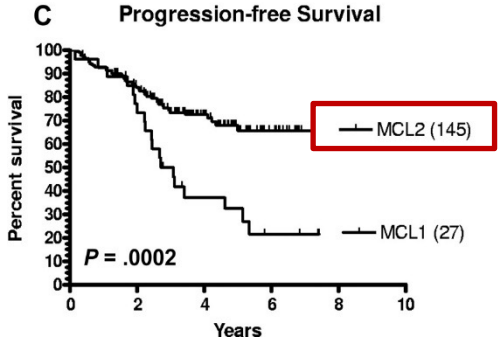
OS at 5 yrs 73%

Courtesy of Sergio Cortelazzo

Nordic Lymphoma Study Group
MCL1 vs MCL2



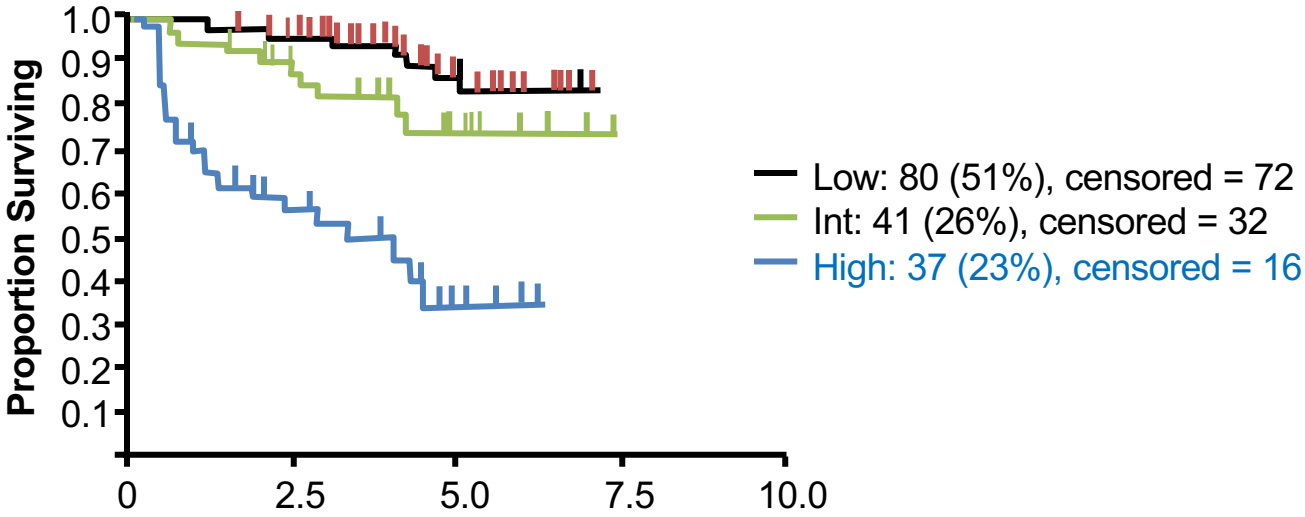




	No Ara-C	R-Ara-C
NORDIC MCL PROTOCOL #	MCL1 (1996-2000) (-CHOP⇒ASCT)	MCL2 (2000-2006)
Number of cases included	41	160
ORR pre-transplant	76%	96%
CR/CRu pre-transplant	27%	54%

Geisler et al, Blood. 2008

Nordic Group: Survival of MCL 2 by MIPI (N = 158)



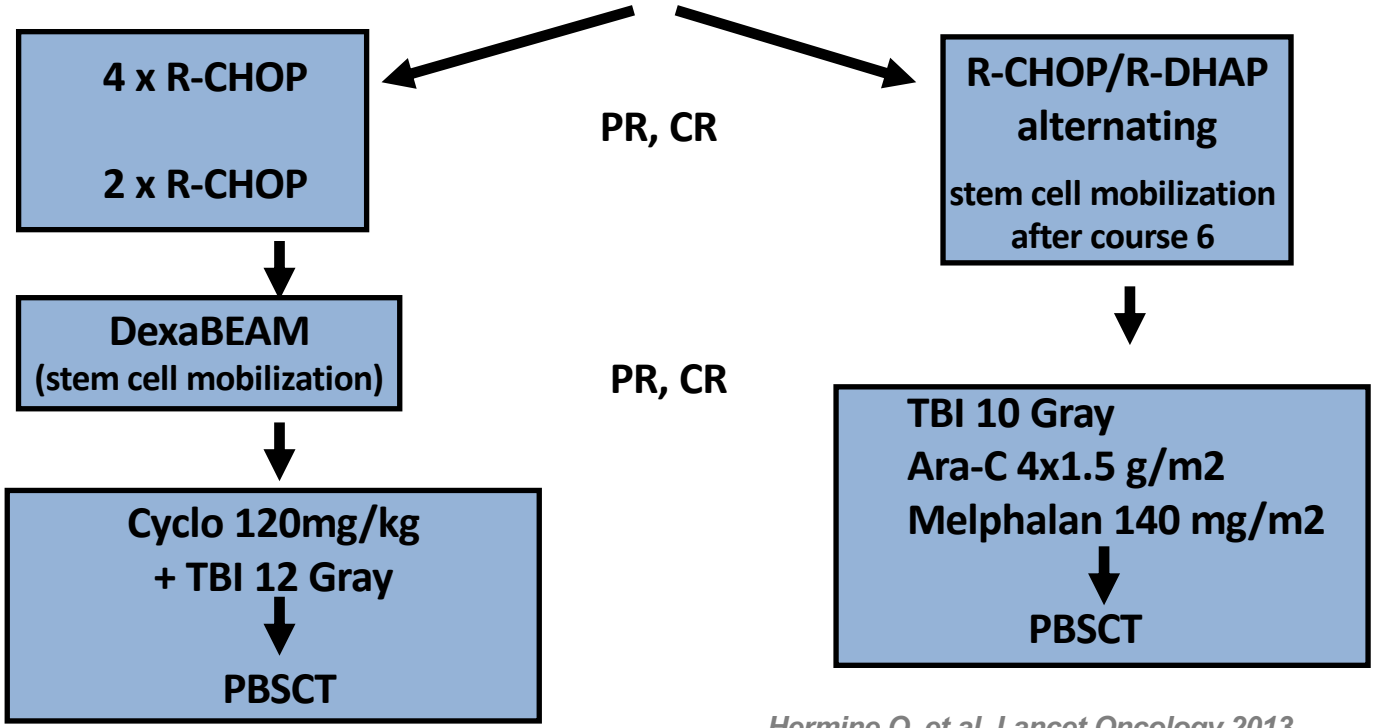
Geisler CH, et al. Blood. 2010;115:1530-1533.

Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network

Olivier Hermine, Eva Hoster*, Jan Walewski, André Bosly, Stephan Stilgenbauer, Catherine Thieblemont, Michal Szymczyk, Reda Bouabdallah, Michael Kneba, Michael Hallek, Gilles Salles, Pierre Feugier, Vincent Ribrag, Josef Birkmann, Roswitha Forstpointner, Corinne Haioun, Mathias Hänel, René Olivier Casasnovas, Jürgen Finke, Norma Peter, Kamal Bouabdallah, Catherine Sebban, Thomas Fischer, Ulrich Dührsen, Bernd Metzner, Georg Maschmeyer, Lothar Kanz, Christian Schmidt, Richard Delarue, Nicole Brousse, Wolfram Klapper, Elizabeth Macintyre, Marie-Hélène Delfau-Larue, Christiane Pott, Wolfgang Hiddemann, Michael Unterhalt, Martin Dreyling, on behalf of the European Mantle Cell Lymphoma Network*

Intensive schemes including ASCT

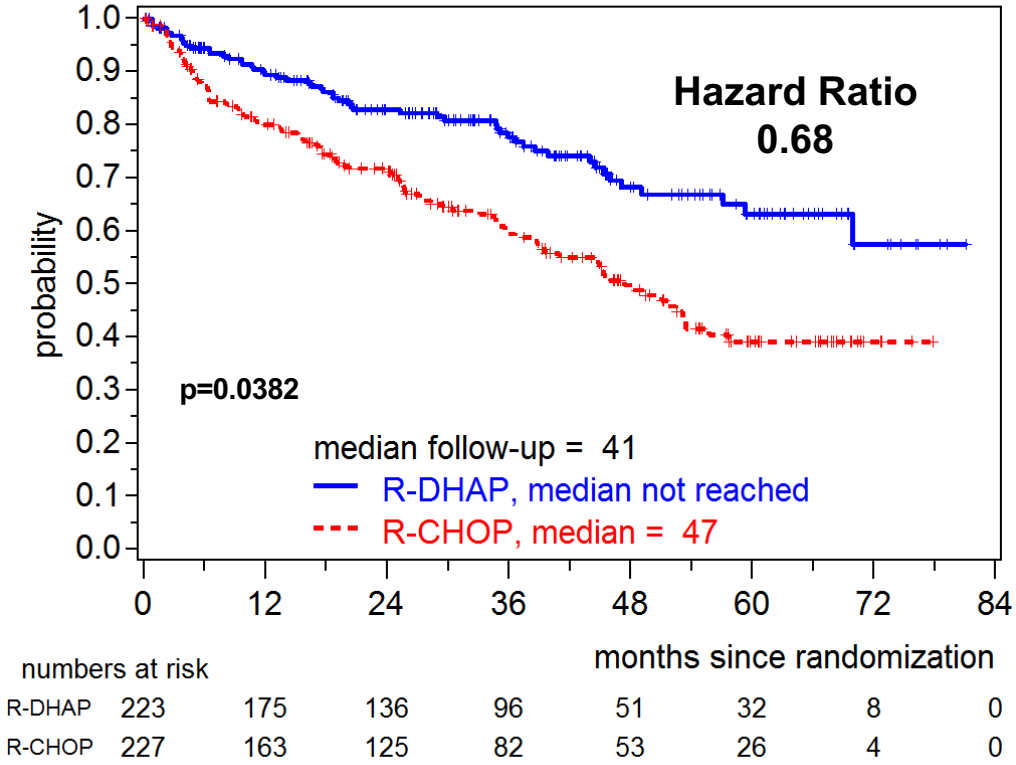
MCL Network younger Trial



Hermine O, et al. Lancet Oncology 2013.

Intensive schemes including ASCT

MCL Network younger Trial

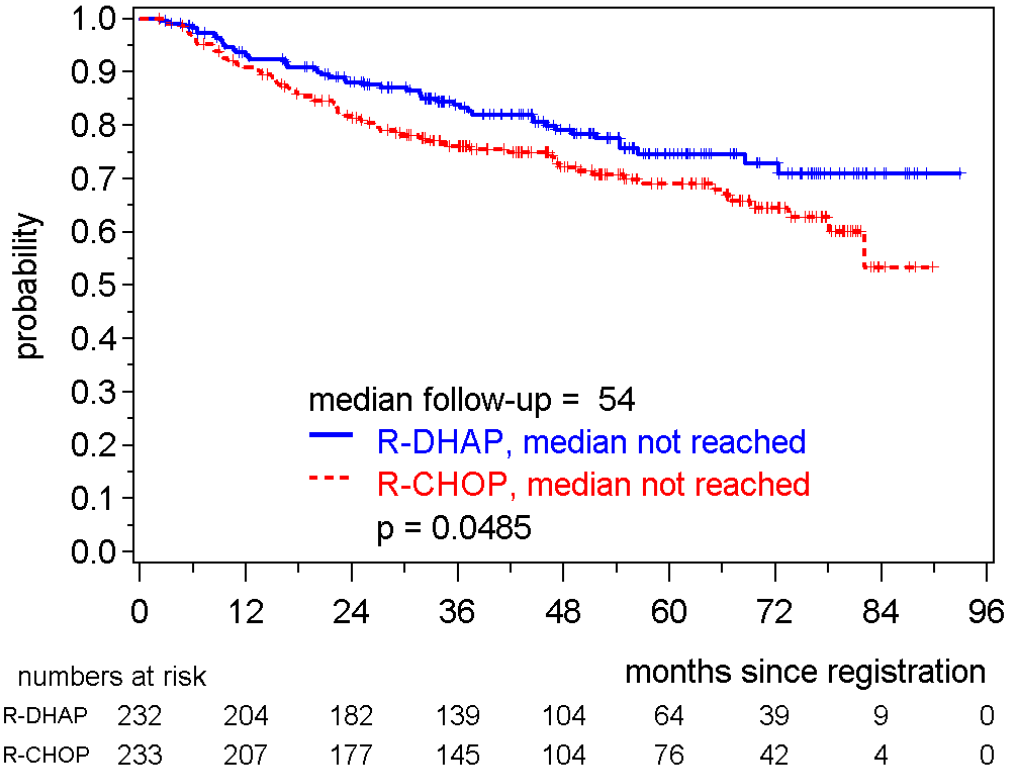


PFS

Hermine O, et al. Lancet Oncology 2013.

Intensive schemes including ASCT

MCL Network younger Trial

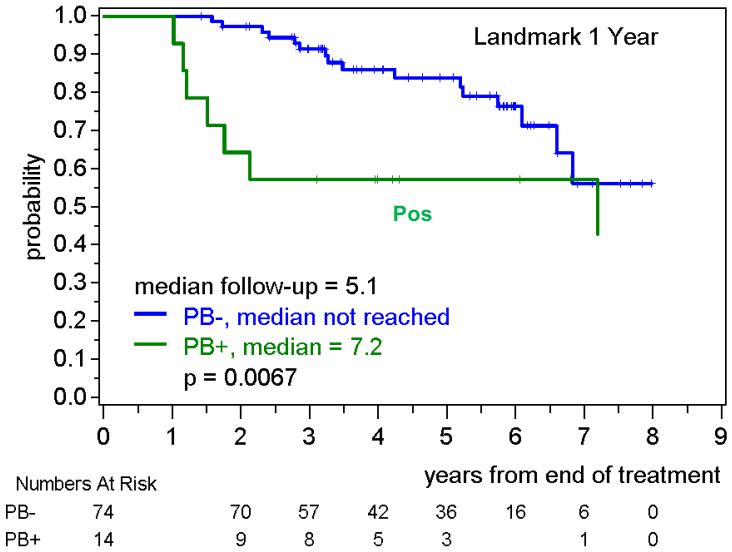


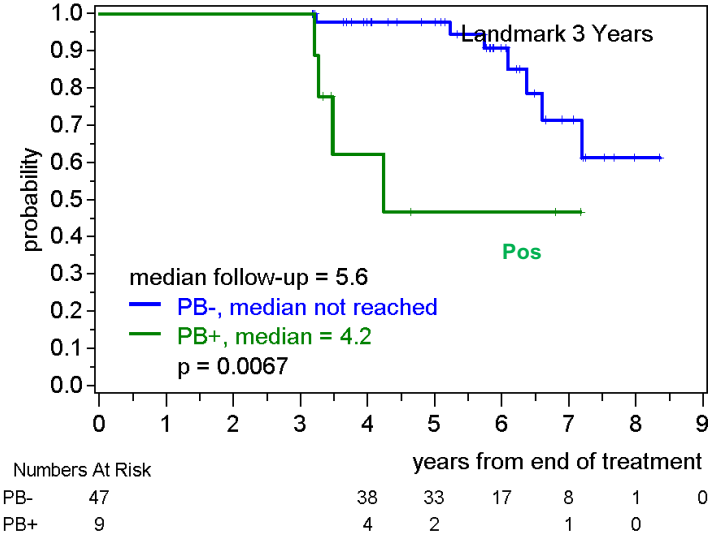
OS

Hermine O, et al. Lancet Oncology 2013.

MRD Landmark analyses for PFS in remission

After R-CHOP/R-DHAP/ASCT younger





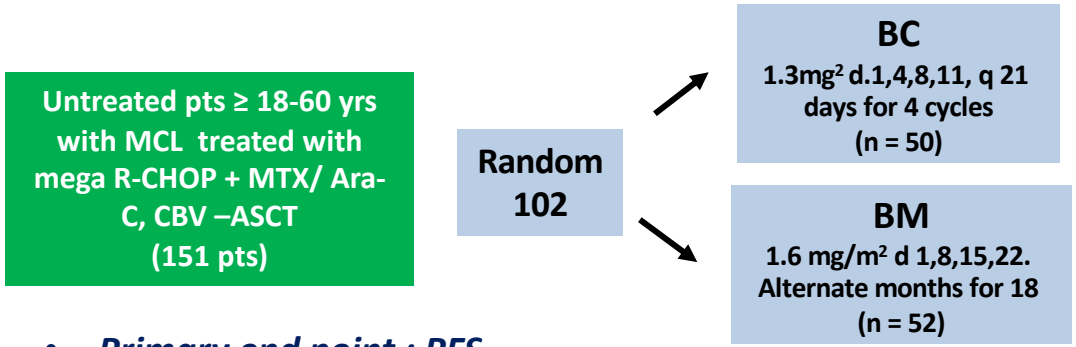
Achievement and preservation of MRD response is a strong independent predictor of prognosis in MCL and correlates significantly with long-term survival

Cox regression: independent of MIPI, trial and treatment arm

Pott et al., ASH 2014; abstract 147 (oral presentation)

Bortezomib maintenance (BM) versus Consolidation (BC) after induction therapy and ASCT in younger MCL: CALGB (Alliance 50403)

- **Multicenter, prospective randomized phase II study**



- ***Primary end point : PFS***

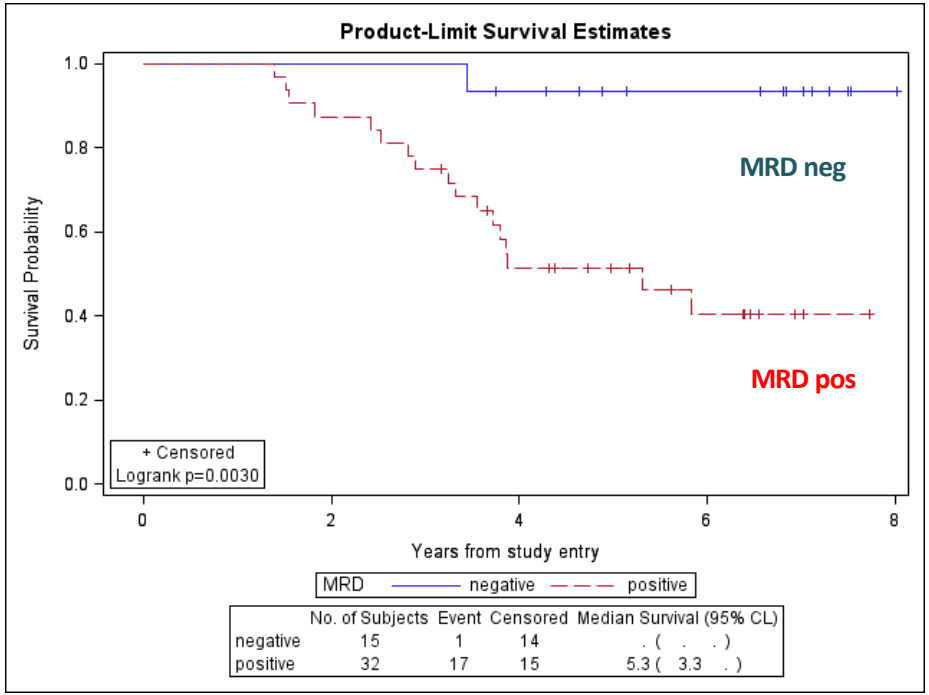
	BM (52)	BM (52)	BC (50)	BC (50)	Tot (102)	
Transplant	**Pre %**	**Post %**	**Pre %**	**Post %**	**Pre %**	**Post %**
CR+PR	63.5	82.7	52.0	82.0	57.8	81.4

	BM	BC
6 yrs PFS	**58 %**	**64 %**

	50403	59909	P value
5 yrs PFS	**64 %**	**52 %**	**0.0026**

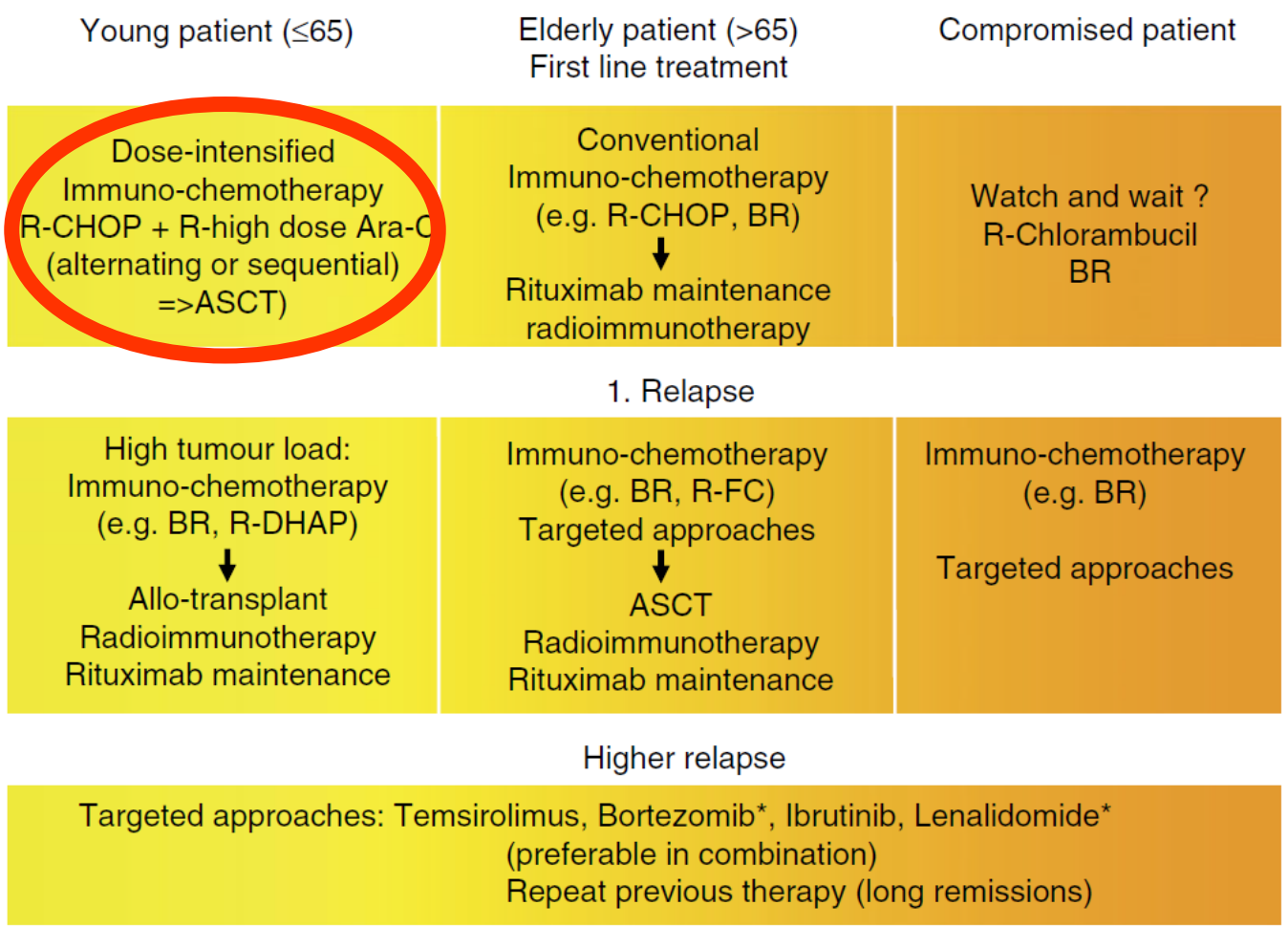
Kaplan D et al ASH 2015 oral session abs 337

Bortezomib maintenance (BM) versus Consolidation (BC) after induction therapy and ASCT in younger MCL: CALGB (Alliance 50403)



MRD negative is associate with an improved PFS

Kaplan D et al ASH 2015 oral session abs 337



Dreyling, ESMO CR MCL 2014

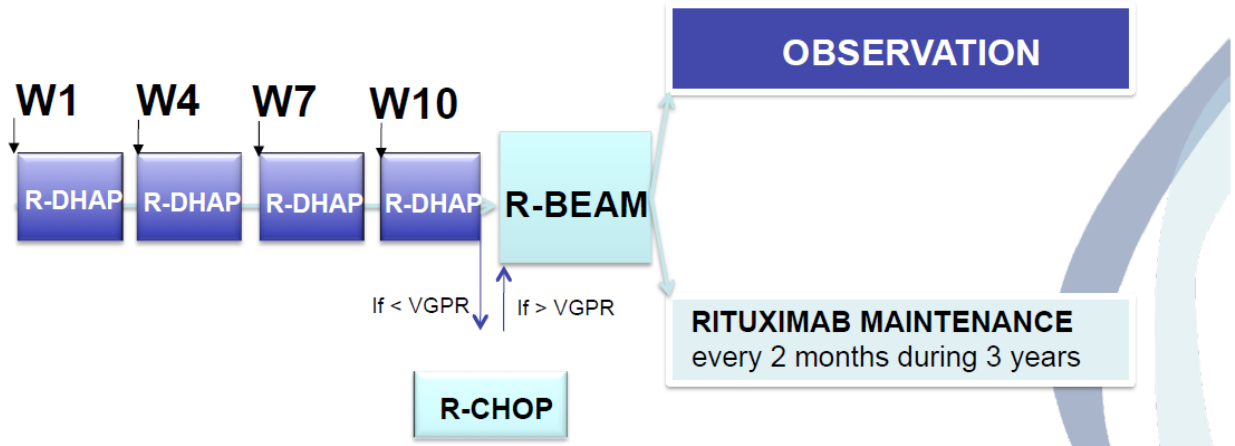
The NEW ENGLAND JOURNAL of MEDICINE

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*

Rituximab maintenance after R-DHAP and ASCT in young untreated MCL: LyMa trial

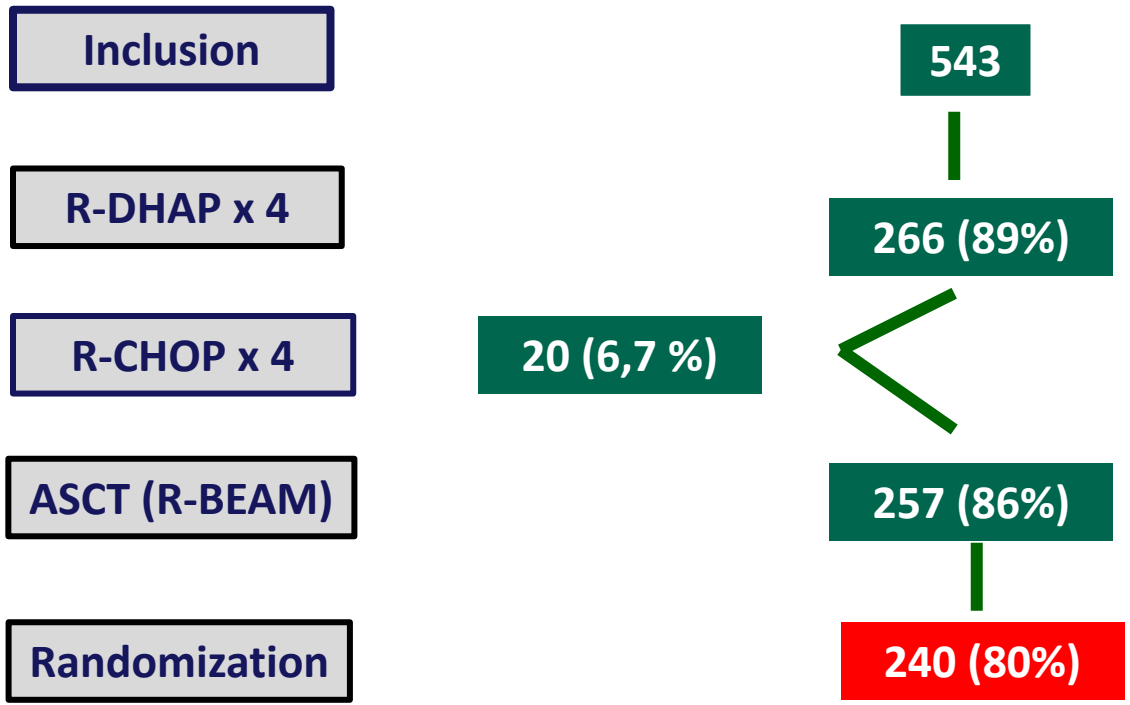


R-DHAP: Rituximab 375mg/m2; aracytine 2g/m2 x2 IV 3 hours injection 12hours interval; dexamethasone 40mg d1-4; Cisplatin 100mg/m2 d1 (or oxaliplatin or carboplatin)

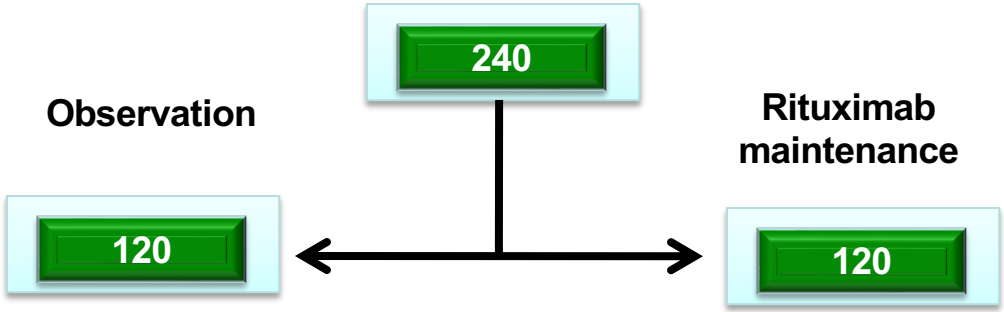
R-BEAM: Rituximab 500mg/m2 d-8; BCNU 300mg/m2 d-7; Etoposide 400mg/m2/d d-6 to -3; aracytine 400mg/m2/d d-6 to d-3; melphalan 140mg/m2 d-2

N Engl J Med 2017; 377:1250-1260

Study Flow Chart



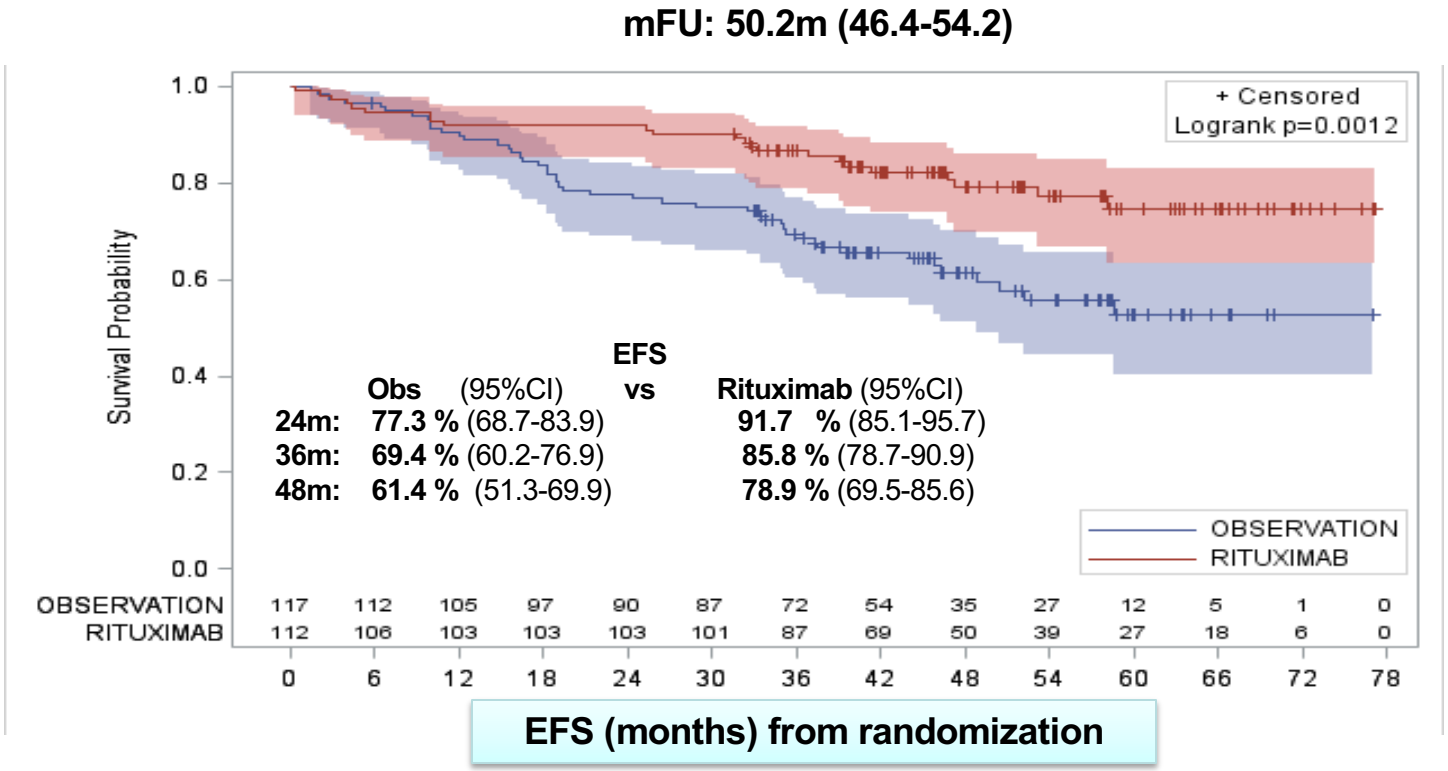
Flow chart of randomized patients



37 Progressions
25 Deaths
4 severe Infections

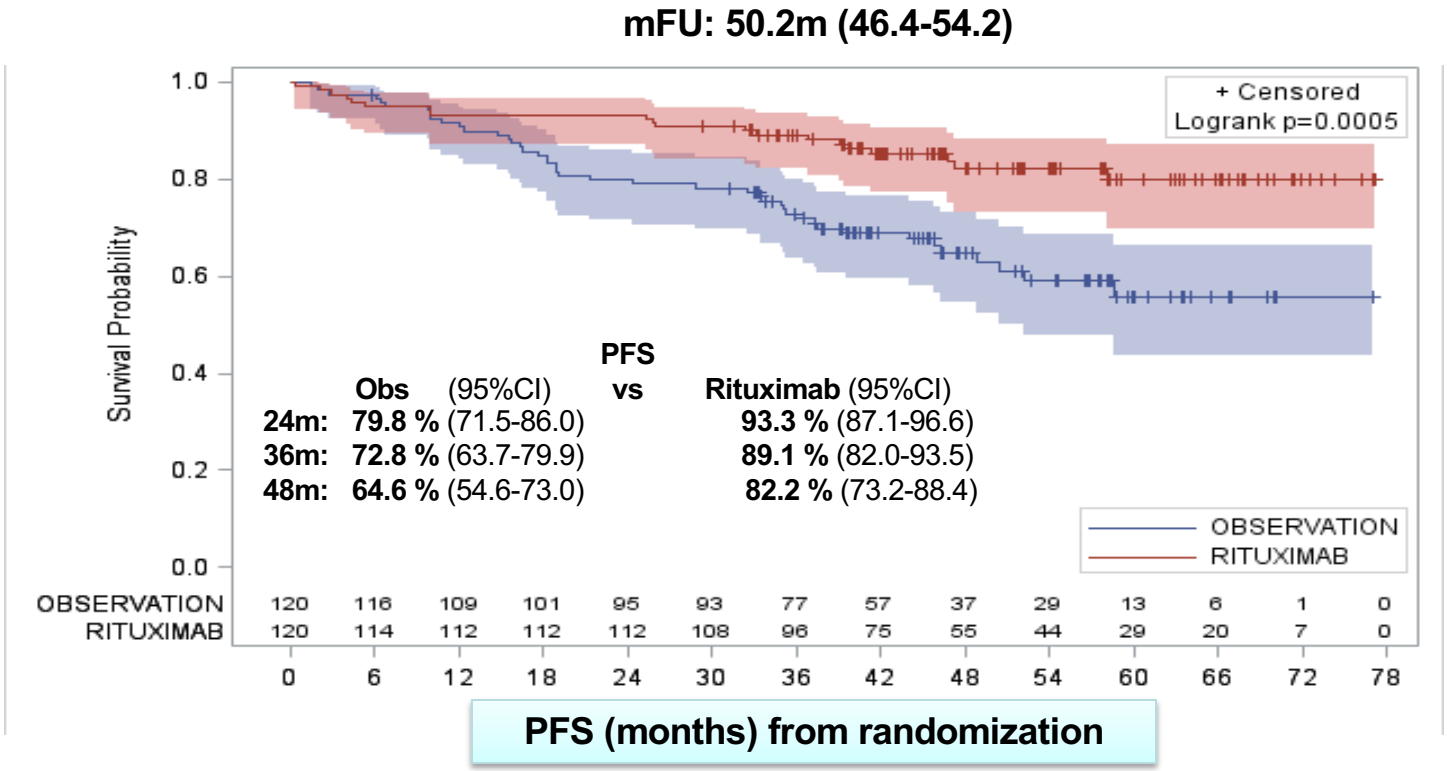
16 Progressions
14 Deaths
4 Severe infections
83 pts completed maintenance

EFS from Randomization



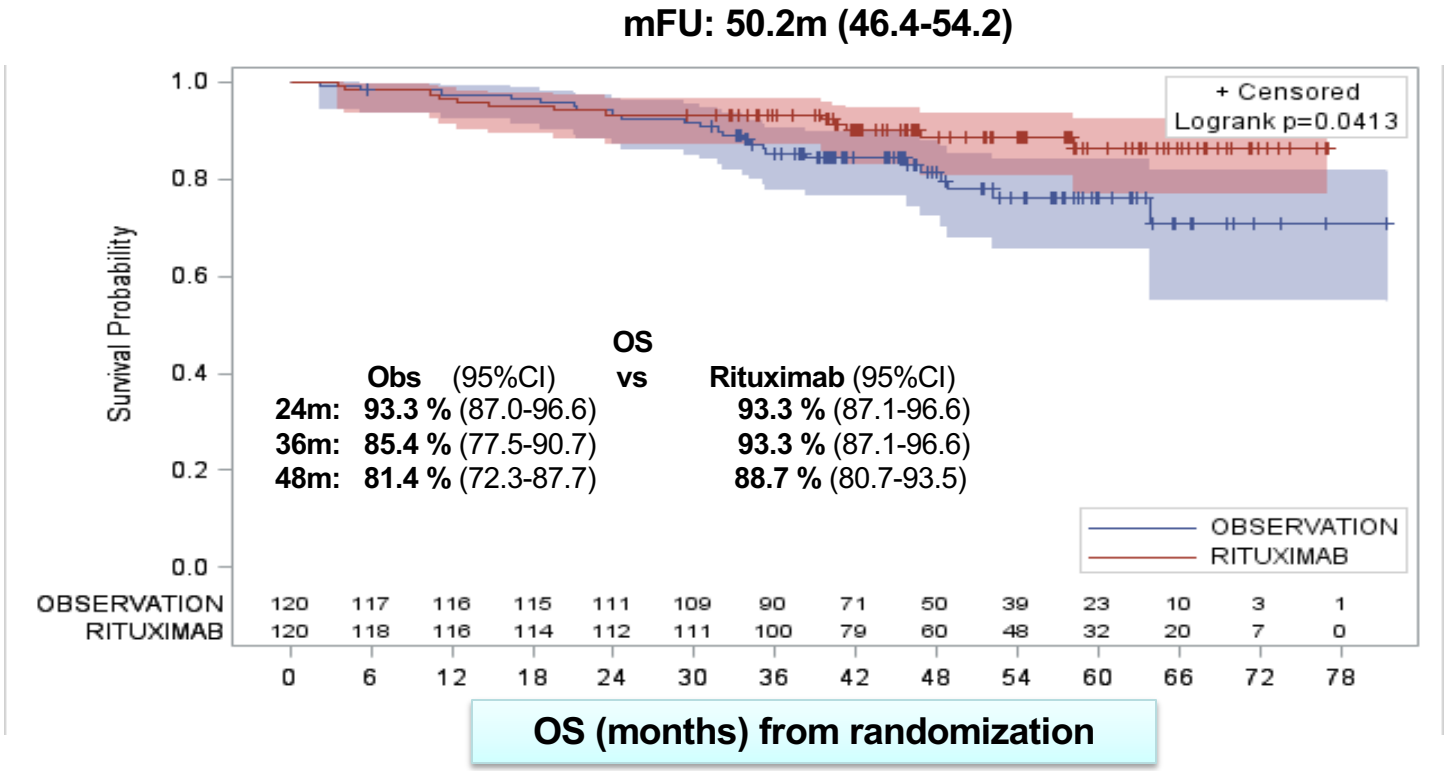
N Engl J Med 2017; 377:1250-1260

PFS from Randomization



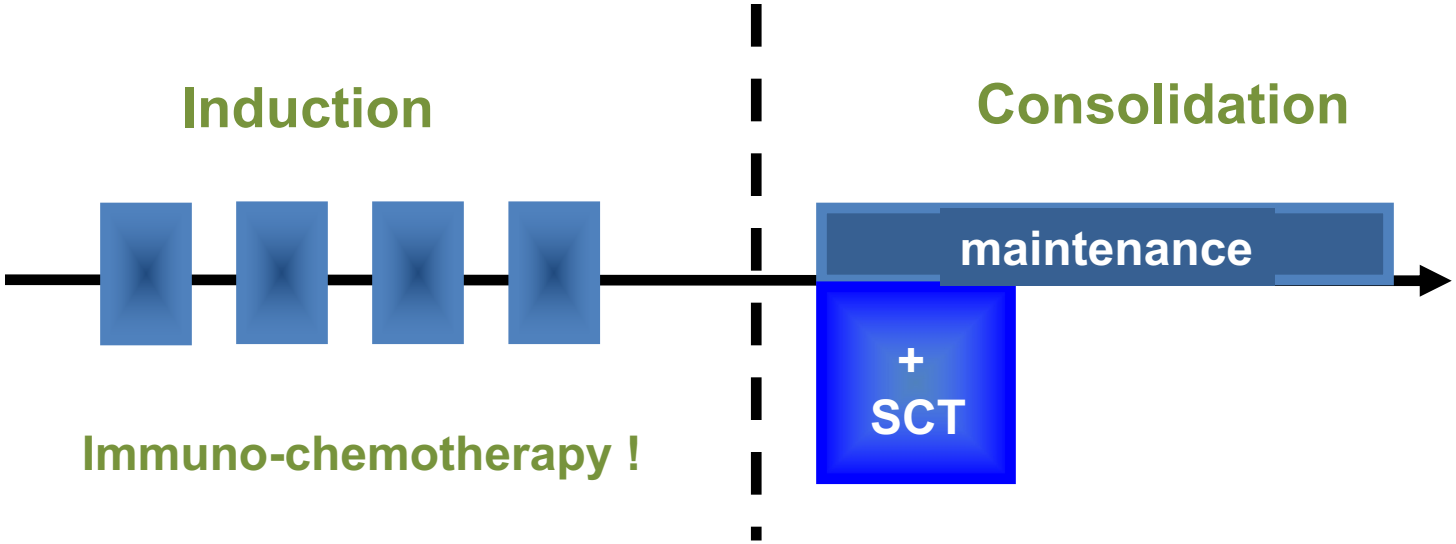
N Engl J Med 2017; 377:1250-1260

OS from Randomization



N Engl J Med 2017; 377:1250-1260

Optimal treatment for younger MCL



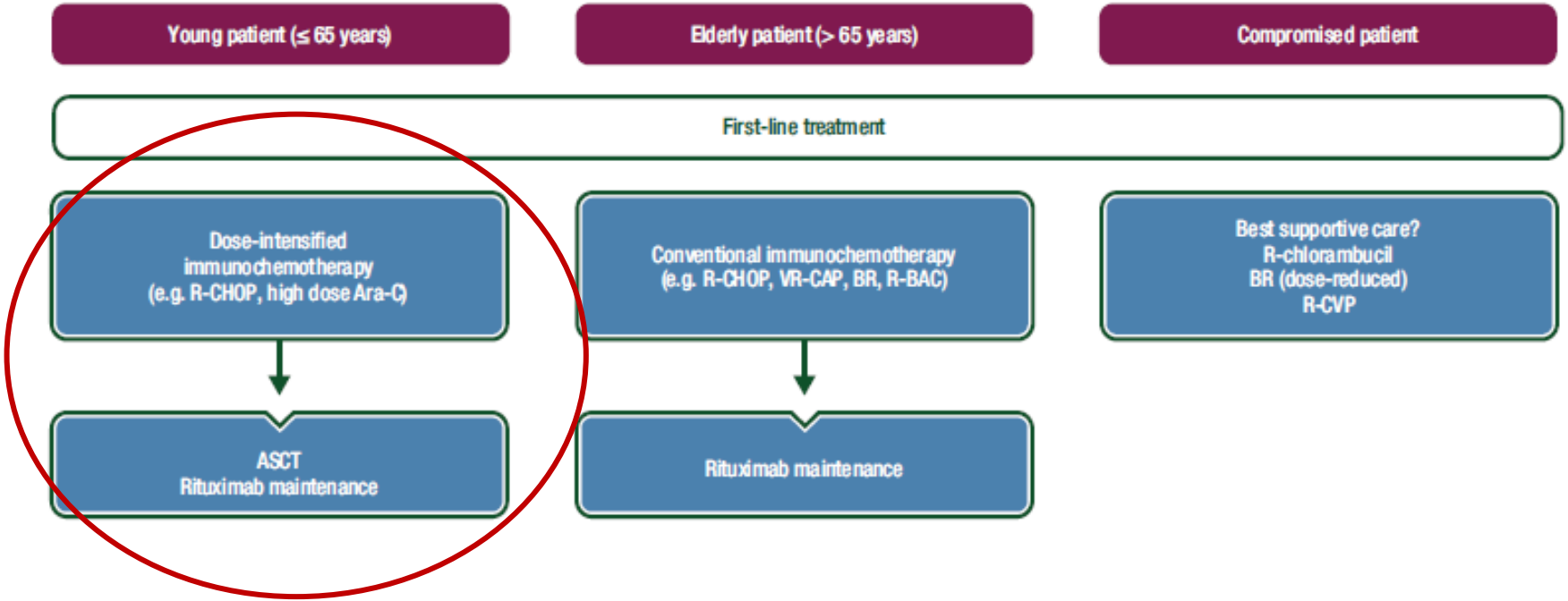
ESMO

Annals of Oncology 28 (Supplement 4): iv62–iv71, 2017
doi:10.1093/annonc/mdx223

CLINICAL PRACTICE GUIDELINES

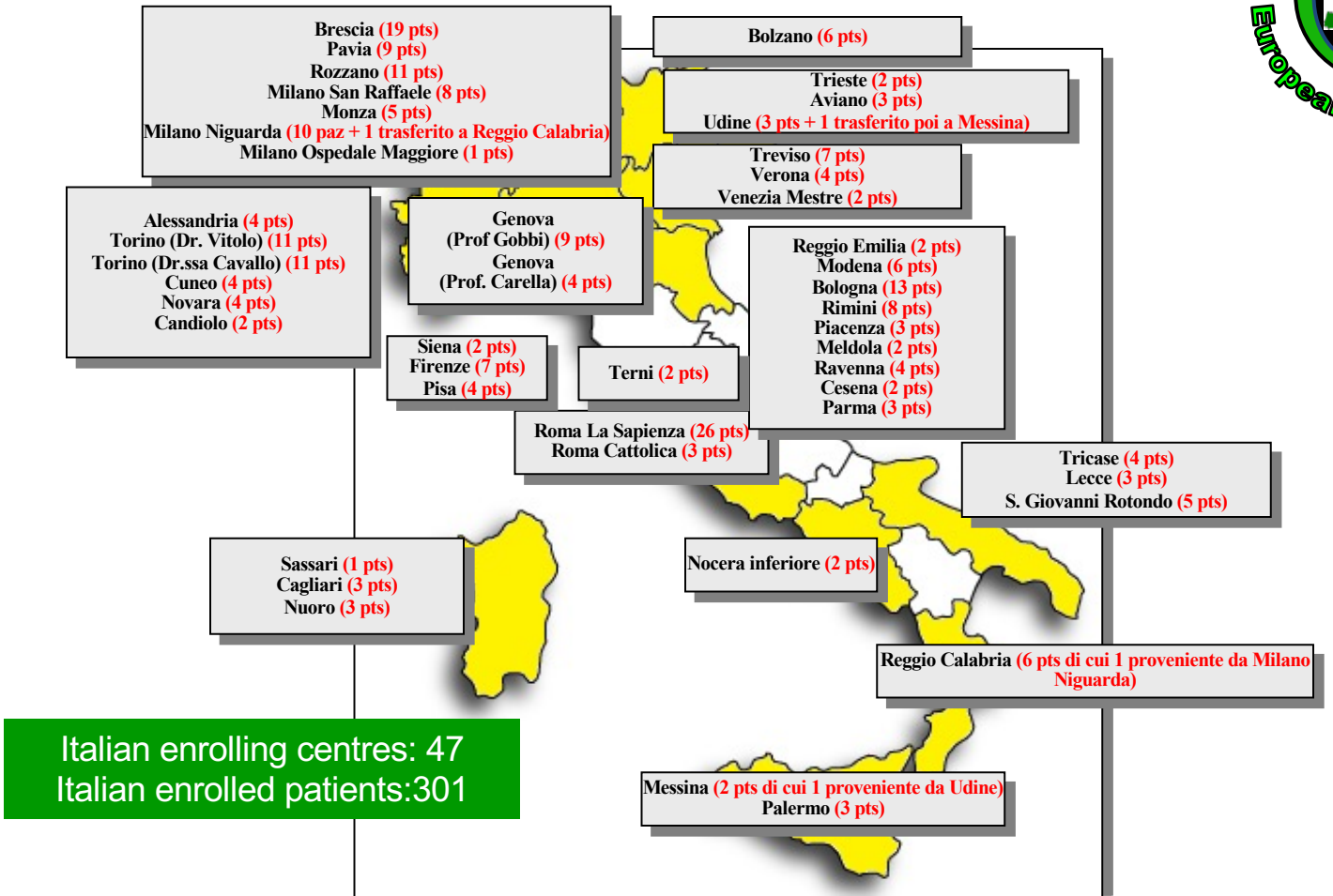
Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

M. Dreyling[1], E. Campo[2], O. Hermine[3], M. Jerkeman[4], S. Le Gouill[5], S. Rule[6], O. Shpilberg[7], J. Walewski[8] & M. Ladetto[9], on behalf of the ESMO Guidelines Committee*



Annals of Oncology 2017

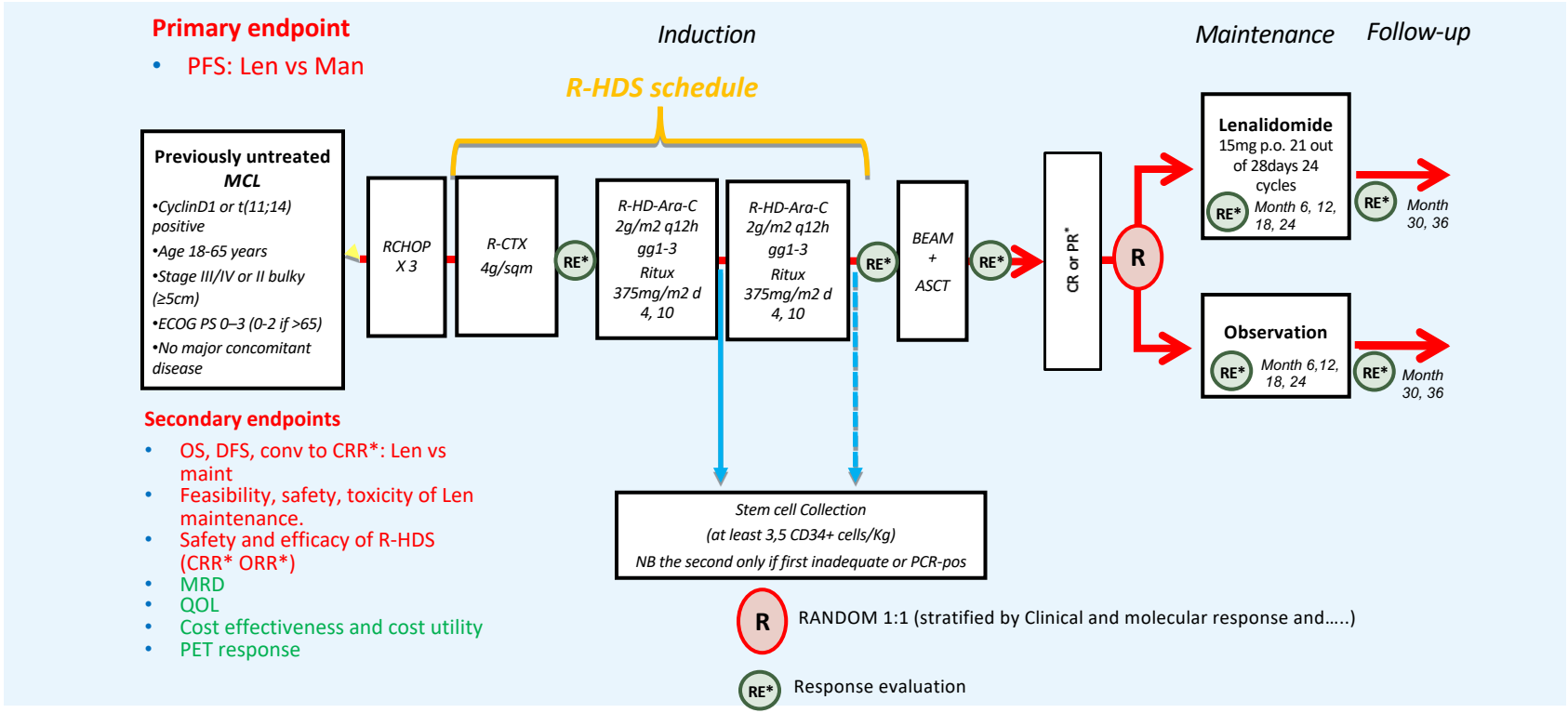
FIL MCL 0208

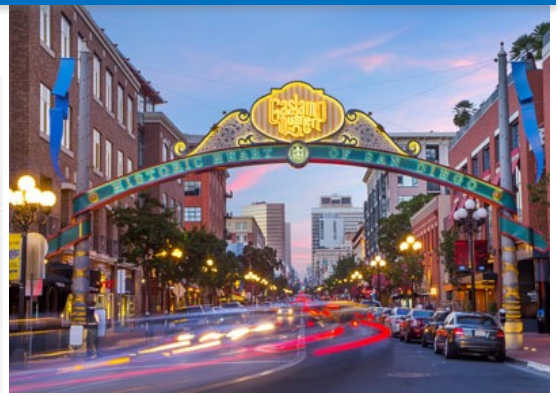


Italian enrolling centres: 47
Italian enrolled patients:301

STUDY DESIGN

Open-label, randomised Phase III study (NCT02354313)





Lenalidomide Maintenance after Autologous Transplantation Prolongs PFS in Young MCL Patients: Results of the Randomized Phase III MCL0208 Trial from Fondazione Italiana Linfomi (FIL) (NCT02354313)

ASH Meeting, San Diego CA USA 2nd December 2018

Marco Ladetto*, *Simone Ferrero, Andrea Evangelista, Michael Mian, Alice Di Rocco, Angela Coggi, Giuseppe Rossi, Alessandro Re, Vittorio Stefoni, Federica Cavallo, Annalisa Chiappella, Armando Santoro, Chiara Rusconi, Maria Gomes da Silva, Manuel Gotti, Anna Lia Molinari, Filippo Ballerini, Andrés J.M. Ferreri, Alberto Bosi, Franco Narni, Caterina Stelitano, Albrto Zamò, Gianni Ciccone, Umberto Vitolo, Maurizio Martelli, Sergio Cortelazzo*

On behalf of Fondazione Italiana Linfomi (FIL) and European Mantle Cell Lymphoma Network

**A.O. S.S. Antonio e Biagio e Cesare Arrigo, Alesssandria, Italy EU*

STUDY POPULATION

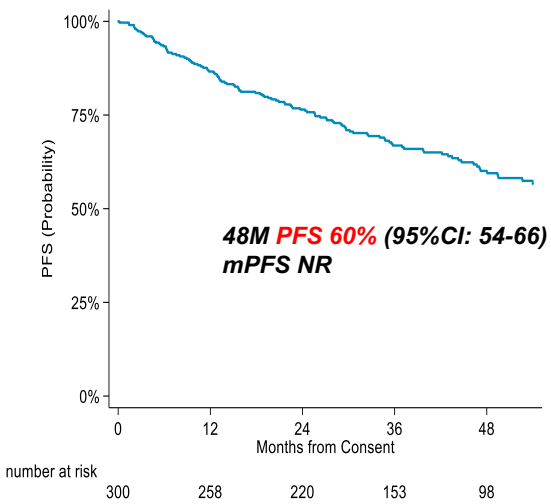
	Enrolled population (N=300)	Non-randomised population (N=95)	Randomised population (N=205)	Lenalidomide maintenance group (N=104)	Observation group (N=101)
Age, years	57 (51–62)	58 (54–62)	57 (49–61)	57 (51–61)	57 (49–61)
Sex					
Female	65 (22%)	20 (21%)	45 (22%)	19 (18%)	26 (26%)
Male	235 (78%)	75 (79%)	160 (78%)	85 (82%)	75 (74%)
Lactate dehydrogenase >ULN	98 (33%)	45 (47%)	53 (26%)	25 (24%)	28 (28%)
ECOG-PS score >1	69 (23%)	29 (31%)	40 (20%)	18 (17%)	22 (22%)
Ann Arbor Stage III–IV	295 (98%)	95 (100%)	200 (98%)	102 (98%)	98 (97%)
MIPI score					
Low	162 (54%)	38 (40%)	124 (60%)	60 (58%)	64 (63%)
Intermediate	93 (31%)	38 (40%)	55 (27%)	29 (28%)	26 (26%)
High	45 (15%)	19 (20%)	26 (13%)	15 (14%)	11 (11%)
Bulky disease (>5 cm)	98 (33%)	39 (41%)	59 (29%)	29 (28%)	30 (30%)
Bone marrow involvement	233 (78%)	82 (86%)	151 (74%)	72 (69%)	79 (78%)
Ki67 index >30%	84/271 (31%)	30/81 (37%)	54/190 (28%)	24/94 (26%)	30/96 (31%)
MIPI-c					
Low risk	133/271 (49%)	32/81 (40%)	101/190 (53%)	46/94 (49%)	55/96 (57%)
Low–intermediate risk	79/271 (29%)	25/81 (31%)	54/190 (28%)	32/94 (34%)	22/96 (23%)
High–intermediate risk	36/271 (13%)	14/81 (17%)	22/190 (12%)	12/94 (13%)	10/96 (10%)
High risk	23/271 (8%)	10/81 (12%)	13/190 (7%)	4/94 (4%)	9/96 (9%)
Blastoid histology	26 (9%)	13 (14%)	13 (6%)	7 (7%)	6 (6%)
TP53[mut] or del(17p)	31/186 (17%)	14/62 (23%)	17/124 (14%)	8/55 (15%)	9/69 (13%)
Clinical or molecular randomisation strata					
Group 1: CR with PCR negative	NA	NA	89 (43%)	42 (40%)	47 (47%)
Group 2: PR or CR with PCR positive	NA	NA	116 (57%)	62 (60%)	54 (53%)

Data are median (IQR), n (%), or n/total available (%). ULN=upper limit of normal. ECOG-PS=Eastern Cooperative Oncology Group Performance Status. MIPI=Mantle Cell Lymphoma International Prognostic Index. MIPI-c=combined Mantle Cell Lymphoma International Prognostic Index and Ki67 index.[11] CR=complete response. NA=not applicable. PR=partial response.

Table 1: **Demographic and clinical characteristics of patients at inclusion**

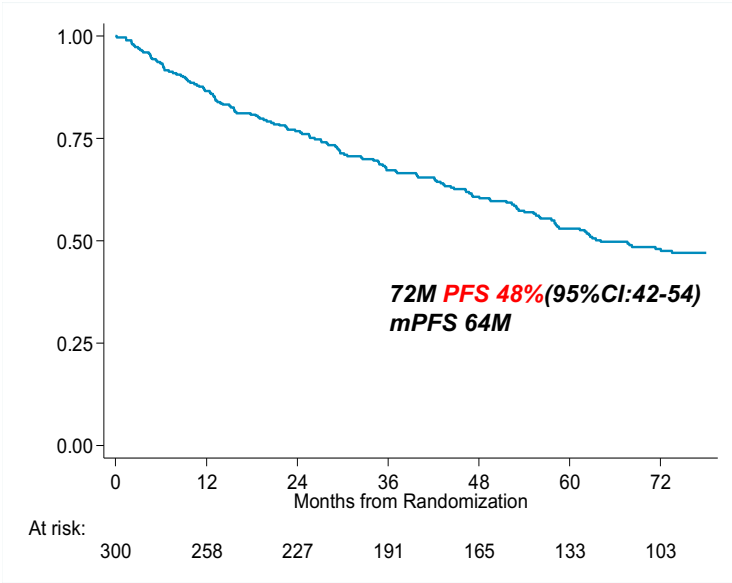
PFS FROM ENROLLMENT:ENROLLED POPULATION

mFU TIME FROM CONSENT-- 51 M



PRIMARY ENDPOINT ANALYSIS

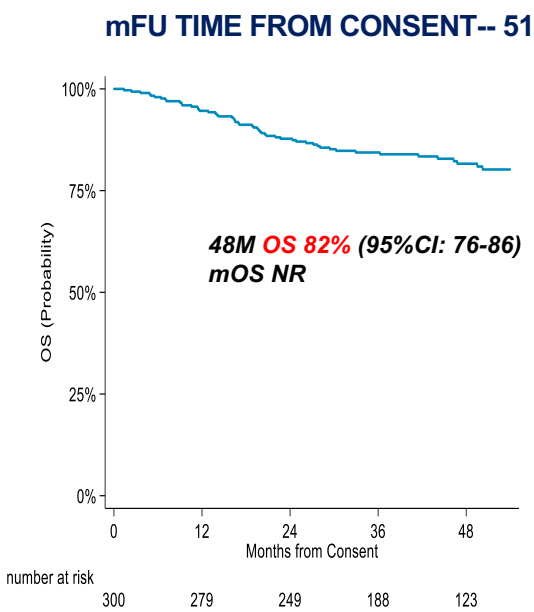
mFU TIME FROM CONSENT-- 84 M

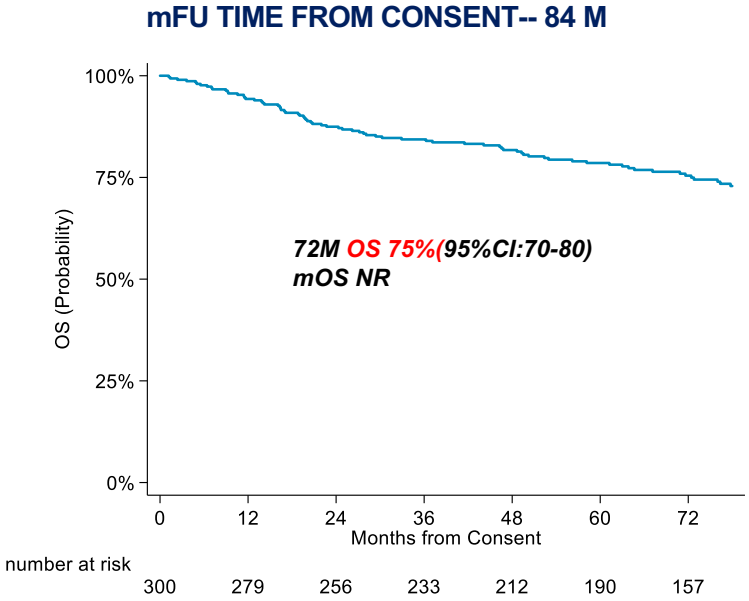


LONG-TERM ANALYSIS

Ladetto M et al., Lancet Hematol. 2020

OS FROM ENROLLMENT:ENROLLED POPULATION





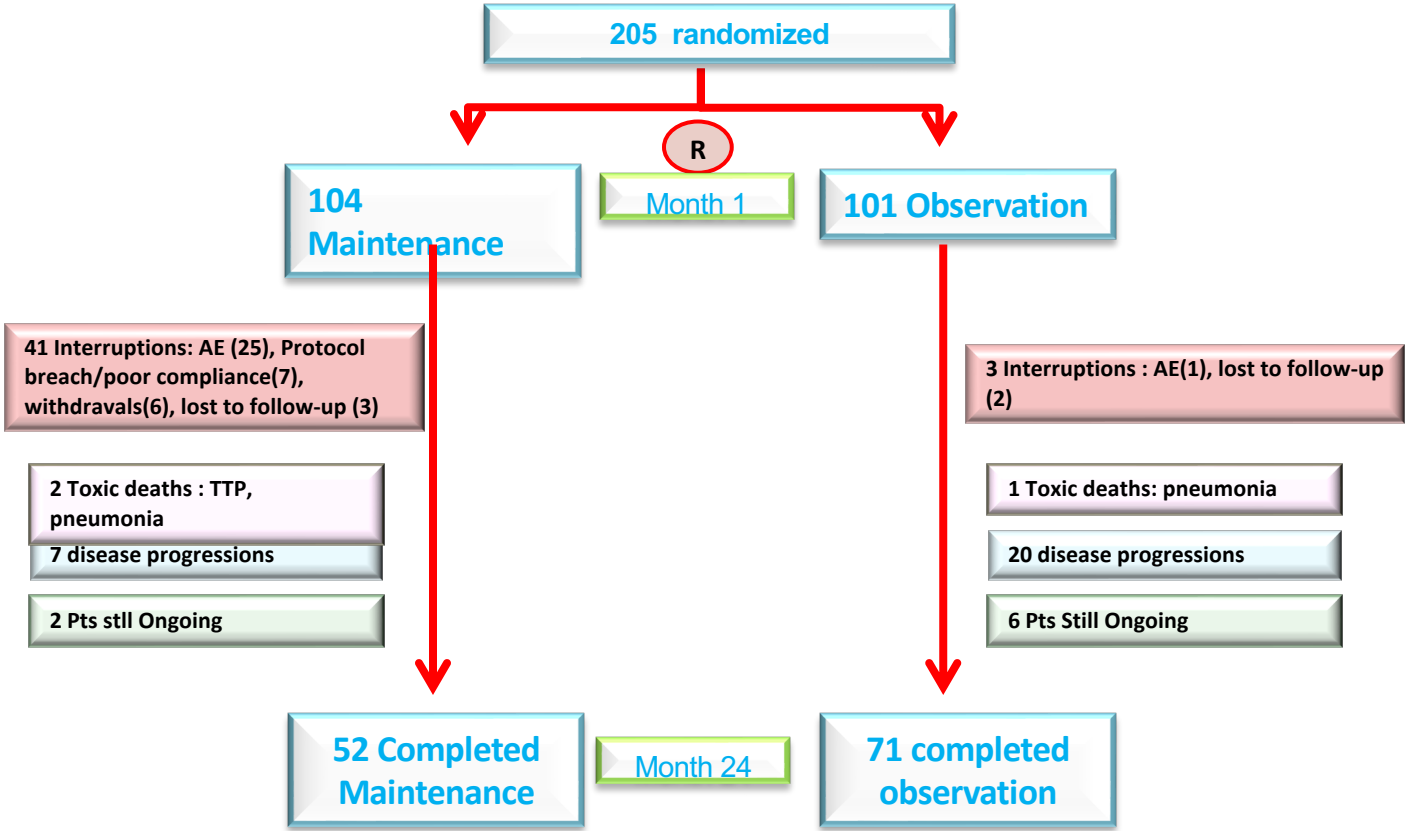
PRIMARY ENDPOINT ANALYSIS

LONG-TERM ANALYSIS

Ladetto M et al., Lancet Hematol. 2020

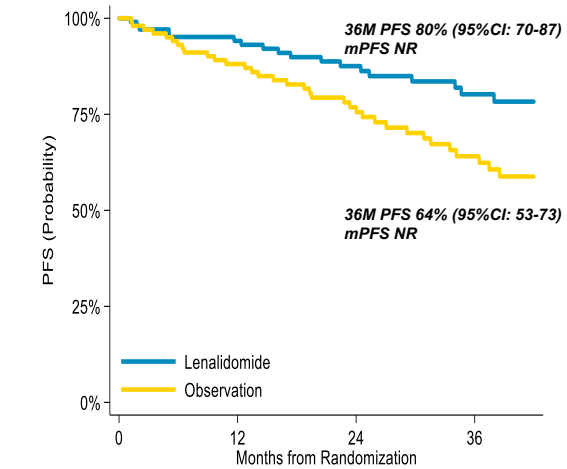
RANDOMIZED POPULATION

PATIENT FLOW



RANDOMIZED POPULATION
PFS FROM RANDOMIZATION (ITT ANALYSIS)

mFU TIME FROM RANDOMIZATION-- 38 M

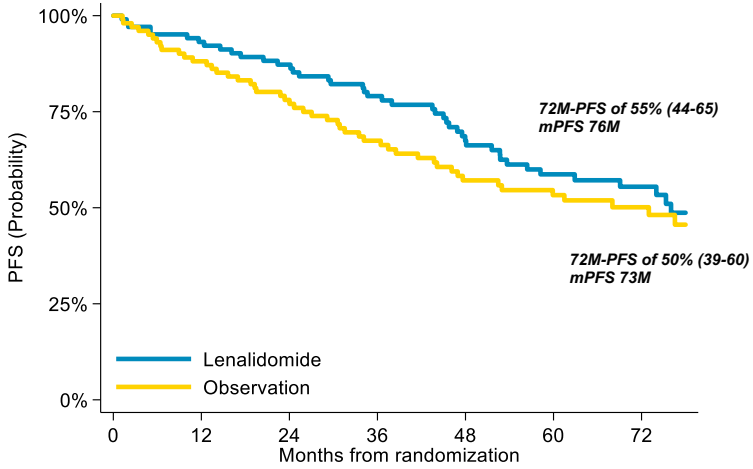


number at risk

Lenalidomide	104	93	69	44
Observation	101	87	60	40

PRIMARY ENDPOINT ANALYSIS

mFU TIME FROM RANDOMIZATION-- 74 M



number at risk

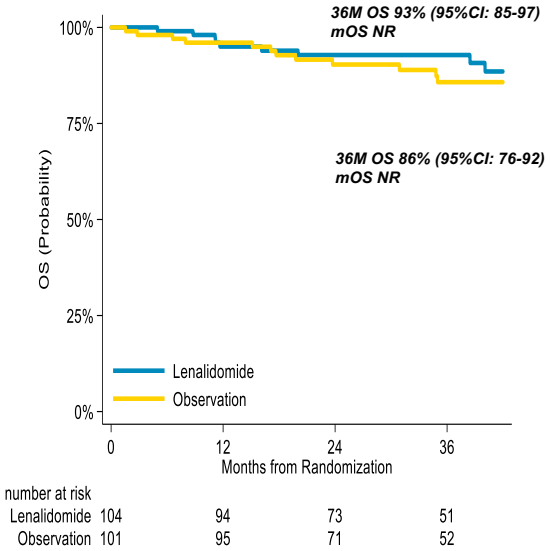
Lenalidomide	104	95	86	73	57	43	32
Observation	101	89	75	61	49	40	26

LONG-TERM ANALYSIS

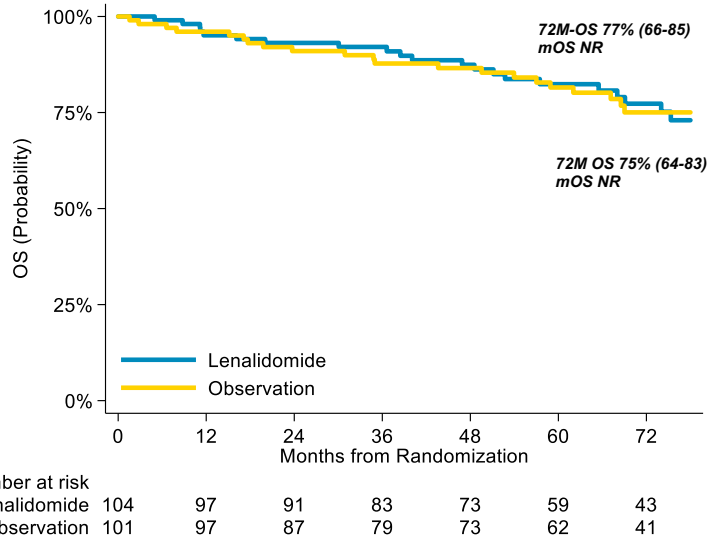
Ladetto M et al., Lancet Hematol. 2020

RANDOMIZED POPULATION
OS FROM RANDOMIZATION (ITT ANALYSIS)

mFU TIME FROM RANDOMIZATION-- 38 M



mFU TIME FROM RANDOMIZATION-- 74 M

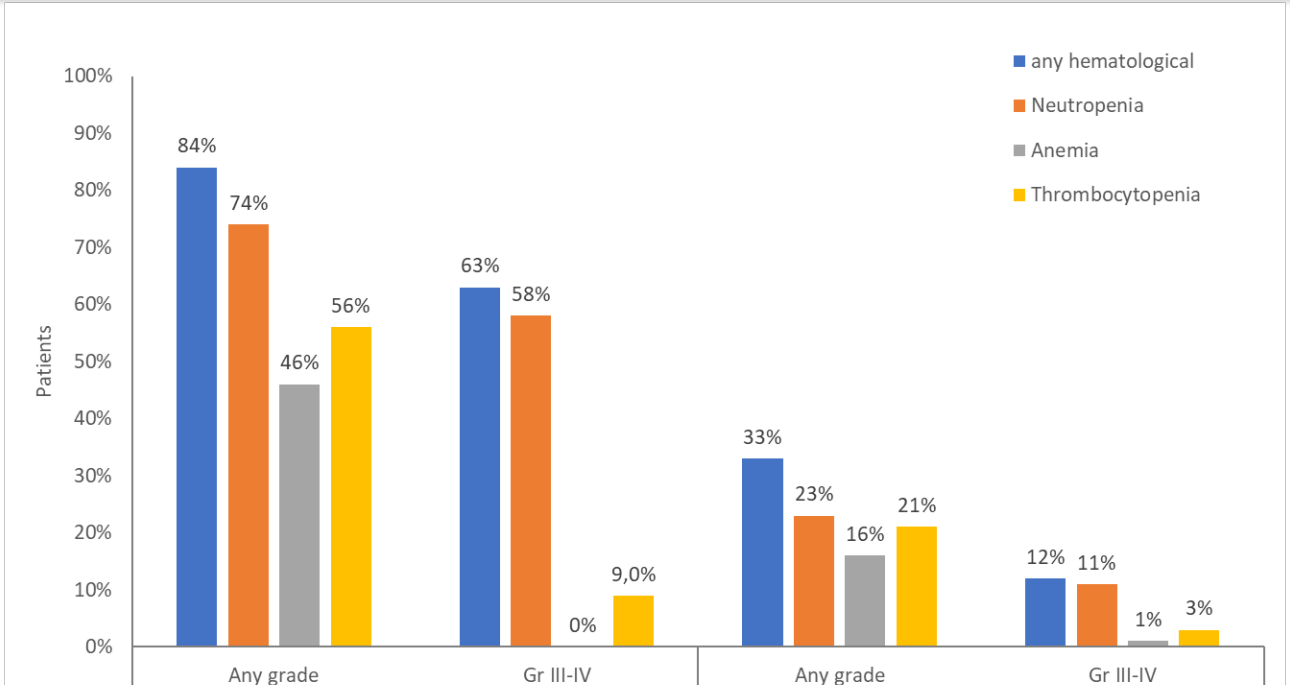


PRIMARY ENDPOINT ANALYSIS

LONG-TERM ANALYSIS

11 (11%) of 104 patients randomly assigned to lenalidomide did not start the study drug.
52 (50%) of 104 patients completed the maintenance treatment

HEMATOLOGICAL TOXICITY (by patient)



Lenalidomide Maintenance

Observation

Ladetto M et al., Lancet Hematol. 2020

blood®
1378 22 SEPTEMBER 2022 | VOLUME 140, NUMBER 12
Regular Article

LYMPHOID NEOPLASIA

Punctual and kinetic MRD analysis from the Fondazione Italiana Linfomi MCL0208 phase 3 trial in mantle cell lymphoma

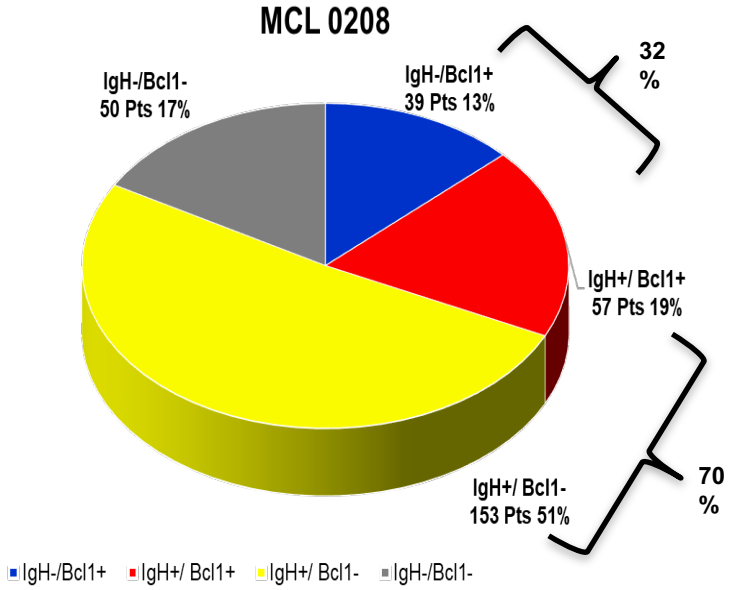
Simone Ferrero,[1,2] Daniele Grimaldi,[1,3] Elisa Genuardi,[1] Daniela Drandi,[1] Gian Maria Zaccaria,[1,4] Beatrice Alessandria,[1] Marco Ghislieri,[5,6] Martina Ferrante,[1] Andrea Evangelista,[7] Barbara Mantoan,[1] Gabriele De Luca,[1] Piero Maria Stefani,[8] Fabio Benedetti,[9] Ivana Casaroli,[10] Manuela Zanni,[11] Claudia Castellino,[3] Vincenzo Pavone,[12] Mario Petrini,[13] Francesca Re,[14] Stefan Hohaus,[15] Gerardo Musuraca,[16] Nicola Cascavilla,[17] Chiara Ghiggi,[18] Anna Marina Liberati,[19] Sergio Cortelazzo,[20] and Marco Ladetto[11]

[1]Department of Molecular Biotechnologies and Health Sciences, University of Torino, Torino, Italy; [2]AOU Città della Salute e della Scienza di Torino, Torino, Italy; [3]Hematology Division, AO S.Croce e Carle, Cuneo, Italy; [4]Hematology and Cell Therapy Unit, IRCCS Istituto Tumori Giovanni Paolo II, Bari, Italy; [5]PoliToBIOMed Lab, Politecnico di Torino, Torino, Italy; [6]Department of Electronics and Telecommunications, Politecnico di Torino, Torino, Italy; [7]Unit of Cancer Epidemiology, CPO, AOU Città della Salute e della Scienza di Torino, Torino, Italy; [8]Hematology Unit, General Hospital Ca' Foncello, Treviso, Italy; [9]Department of Medicine, Section of Hematology and Bone Marrow Transplant Unit, University of Verona, Verona, Italy; [10]Hematology Unit, Ospedale San Gerardo, Monza, Italy; [11]Division of Hematology, Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy; [12]Hematology, Card. G. Panico Hospital, Tricase, Italy; [13]Santa Chiara University Hospital, Pisa, Italy; [14]Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; [15]Hematology Unit, Università Cattolica S.Cuore; Roma, Italy; [16]Department of Hematology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS; [17]Hematology, Casa Sollievo della Sofferenza IRCCS Hospital, San Giovanni Rotondo, Italy; [18]Department of Hematology, San Martino Hospital and University, Genova, Italy; [19]Department of Hematology, A.O. Santa Maria Terni, University of Perugia, Perugia, Italy; and [20]Oncology Unit, Clinica Humanitas Gavazzeni, Bergamo, Italy

FIL-MCL0208
MRD MARKER IDENTIFICATION RATE

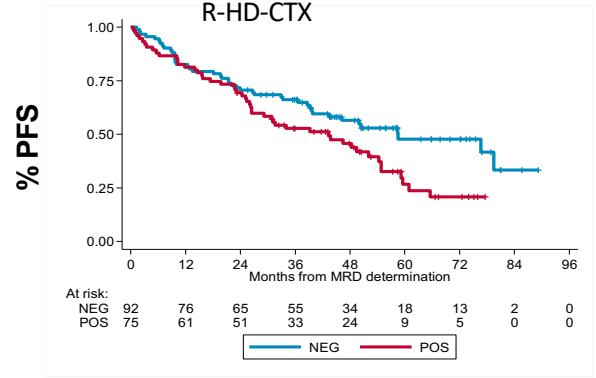
Molecular markers for MRD detection: 250/300 (83%)

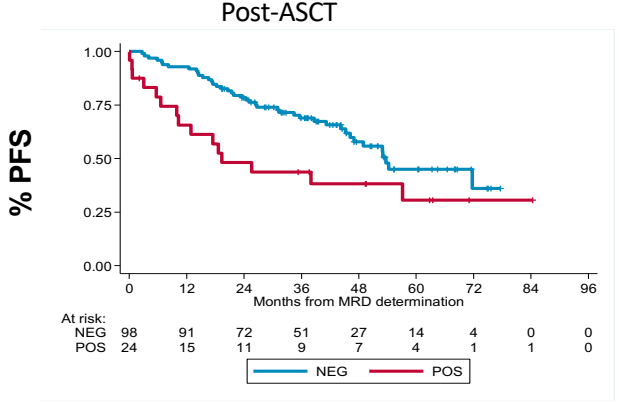
IGH+ 70%
BCL1/IGH+ 32%

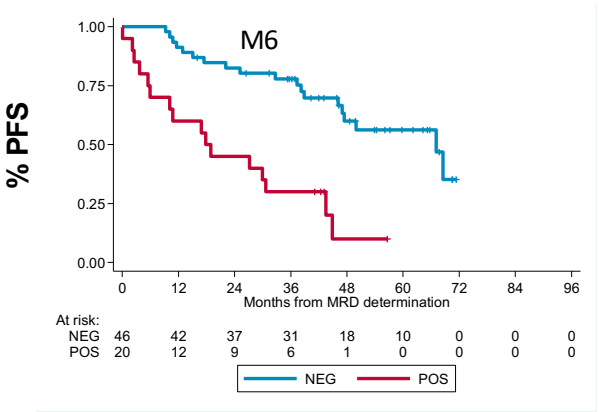


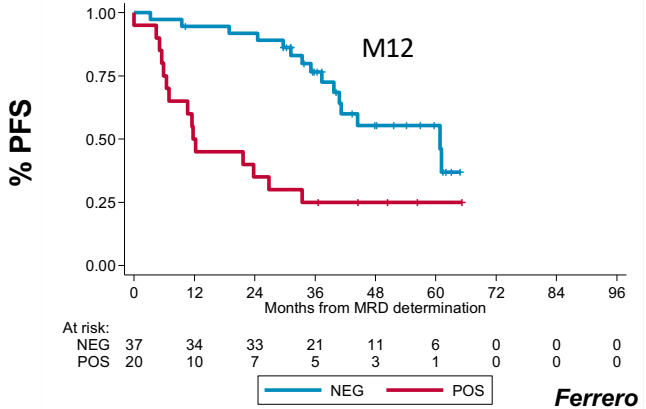
MRD TIME POINTS COMPARISON: PFS BY RQ-PCR RESULTS ON BM

FONDAZIONE ITALIANA LINFOMI





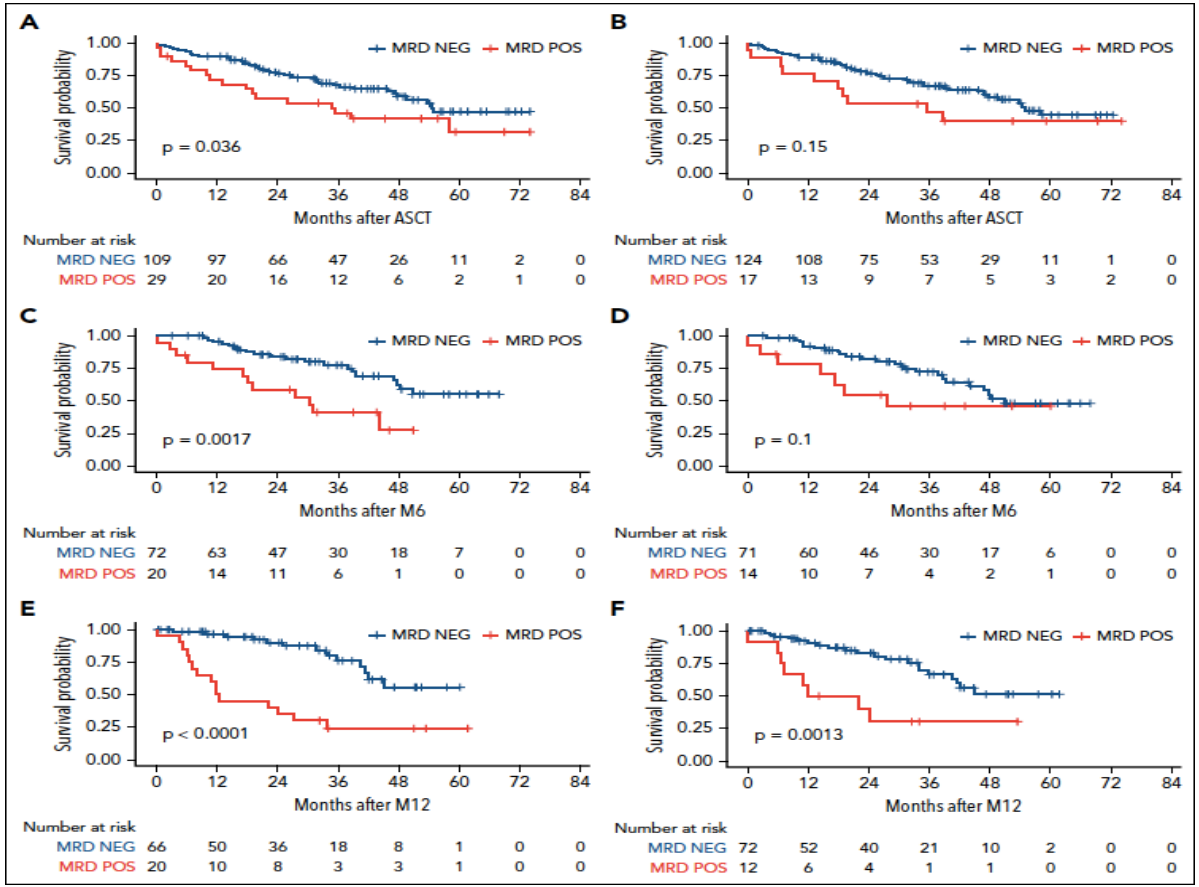




Ferrero S., Blood 2022

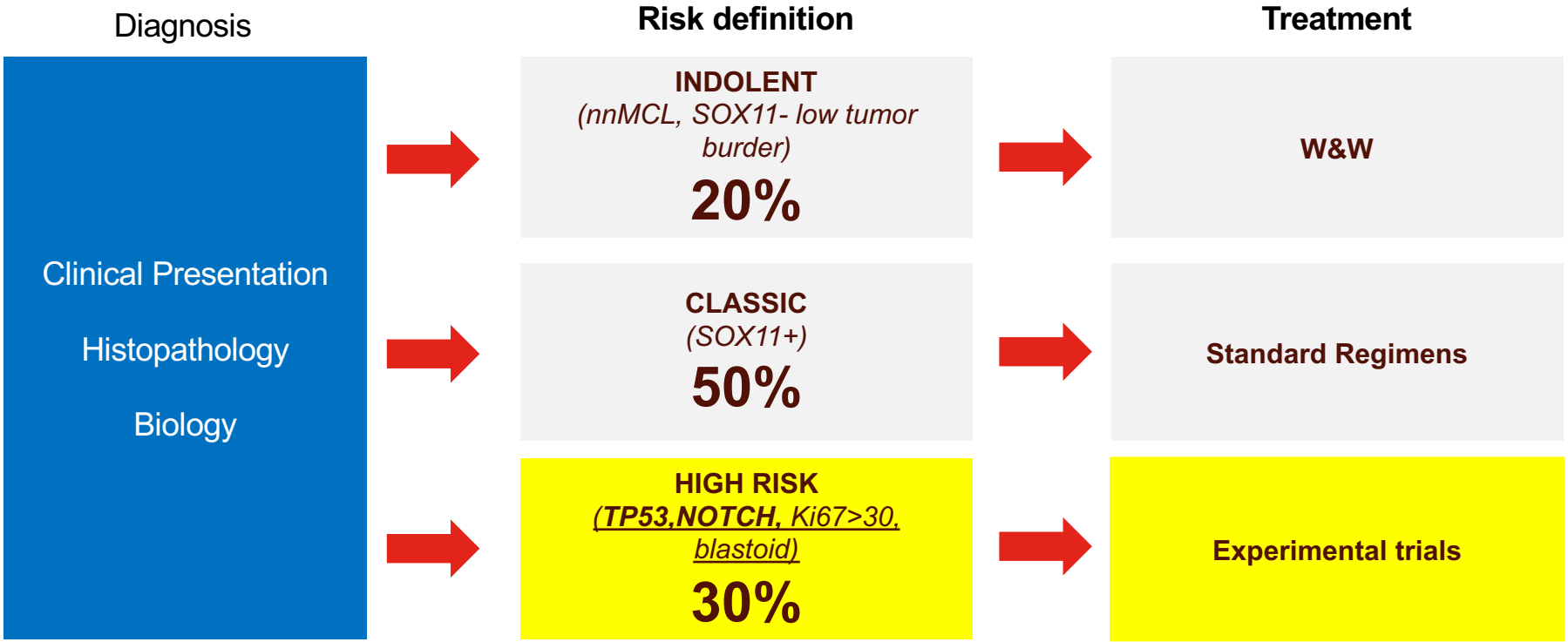
MCL0208: MRD peripheral blood Landmark analysis for PFS

FONDAZIONE ITALIANA LINFOMI



Ferrero S., Blood 2022

New therapeutic approach in MCL



Courtesy of Carlo Visco

High risk features distribution

	Young (MCL-0208)	Nordic (MCL2-3)	Elderly (VR-BAC)
All patients	190	183	140
Ki67>30%	50 (28%)	68 (43%)	34 (24%)
TP53 mut	15 (8%)	20 (11%)	28 (20%)
TP53 del	25 (13%)	29 (16%)	19 (14%)
TP53 mut/del	31 (17%)	37 (20%)	34 (24%)
Blastoid	16 (8%)	31 (17%)	13 (9%)

Ferrero S et al, Haematologica 2020;
Visco C et al, partial at ASH 2021;
Eskelund et al, Blood 2017

ESMO

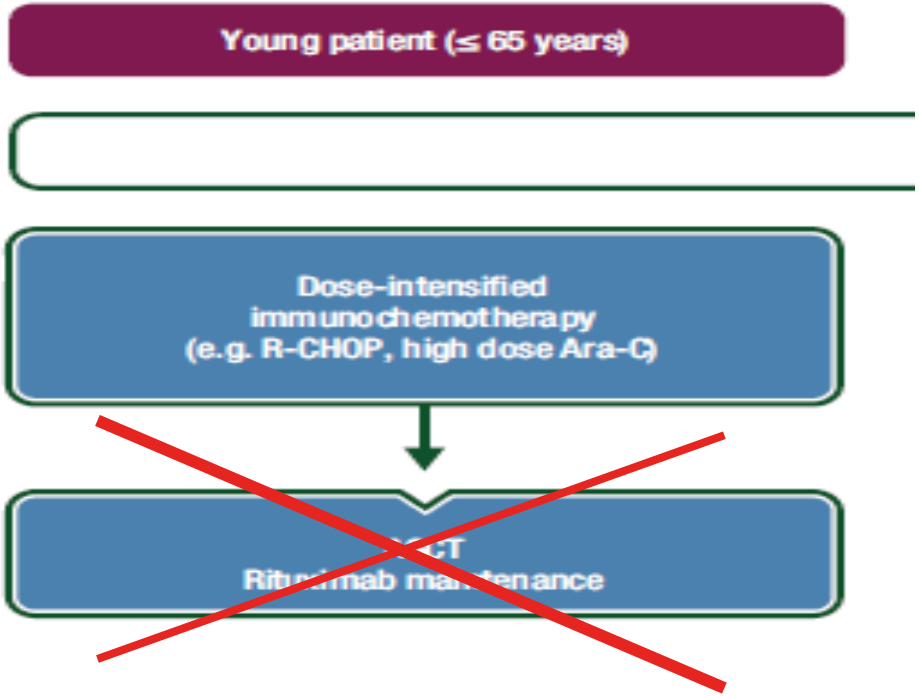
Annals of Oncology 28 (Supplement 4): iv62–iv71, 2017
doi:10.1093/annonc/mdx223

CLINICAL PRACTICE GUIDELINES

Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

M. Dreyling[1], E. Campo[2], O. Hermine[3], M. Jerkeman[4], S. Le Gouill[5], S. Rule[6], O. Shpilberg[7], J. Walewski[8] & M. Ladetto[9], on behalf of the ESMO Guidelines Committee*

TRIANGLE ERA



Gruppo per la terapia dei linfomi non Hodgkin
Ematologia Sapienza Roma

SAPIENZA
UNIVERSITÀ DI ROMA

SISTEMA SANITARIO REGIONALE
AZIENDA OSPEDALIERO-UNIVERSITARIA
POLICLINICO UMBERTO I

FONDAZIONE
ITALIANA
LINFOMI

Grazie!

… a voi tutti per l'attenzione