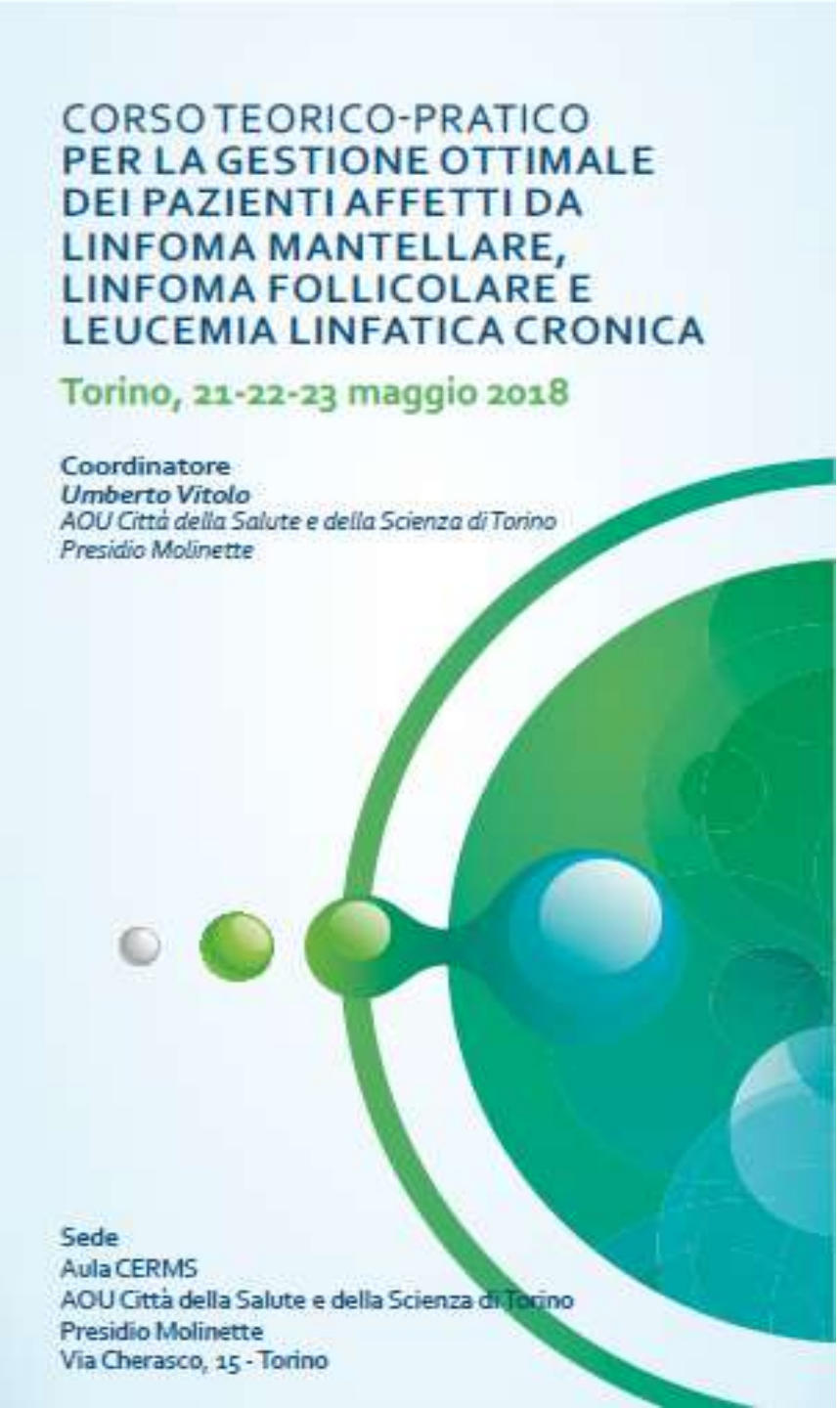


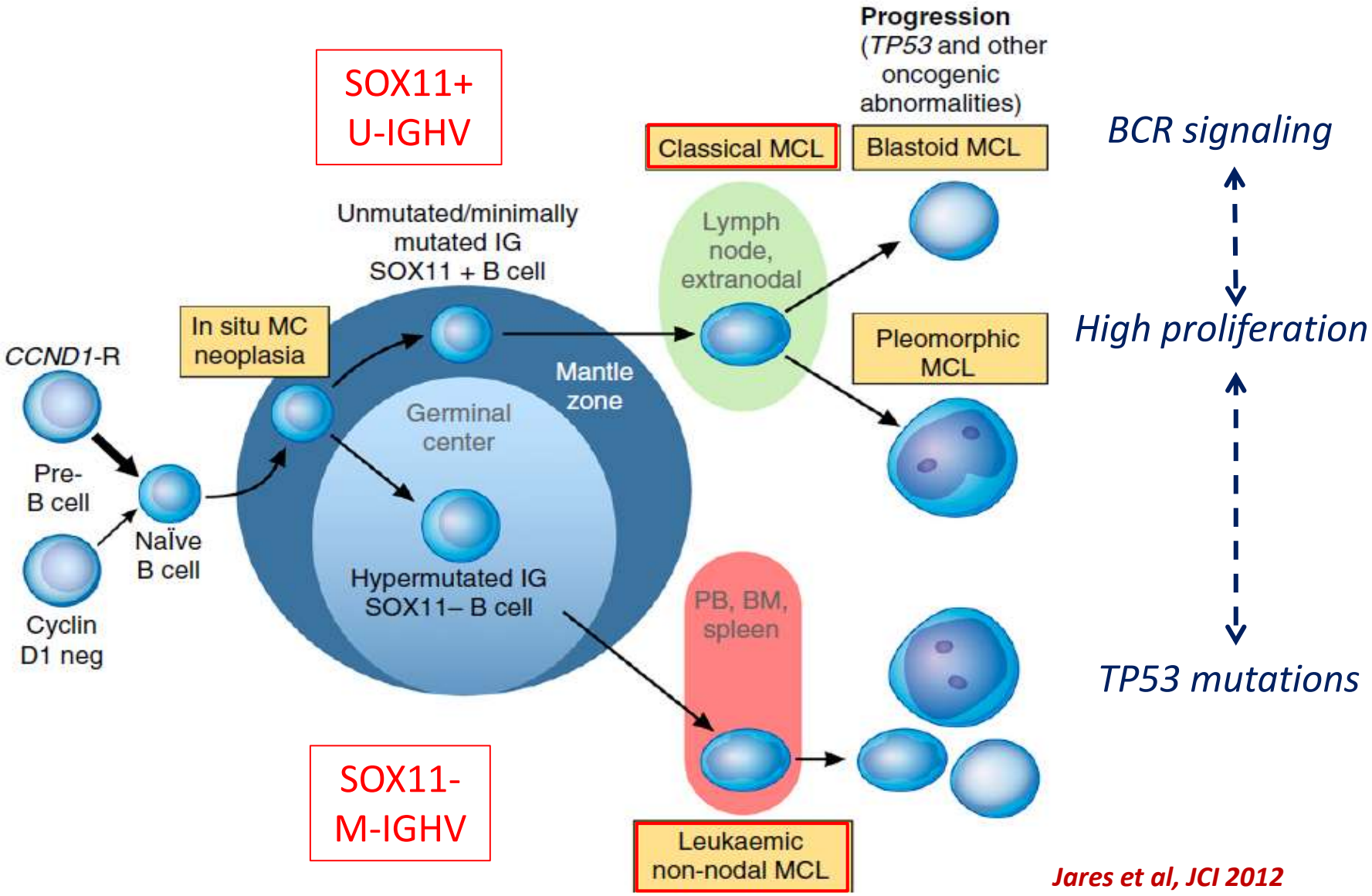
Linfoma mantellare: terapia di prima linea

Maurizio Martelli
Dip. Biotecnologie Cellulari ed Ematologia
Università "Sapienza" Roma

Mantle cell lymphoma (MCL)

- About 6% of non Hodgkin's lymphomas
- Predominantly elderly (>60), male patients
- Advanced Ann Arbor stage
- Extranodal involvement (bone marrow, **gastrointestinal tract**, liver, spleen)

Molecular pathogenesis of MCL



Jares et al, JCI 2012
Swerdlow SH et al, Blood 2016

How to predict the outcome in MCL ?

MCL OS and TTF according to MIPI

MIPI score

0.03535 age (years)

+

+

+

Points	Age (years)	ECOG Performance Status	LDH/ULN	Leukocytes ($x10^9$/L)
0	<50	0-1	<0.670	6700
1	50-59	-	0.670-0.999	6700-9999
2	60-69	2-4	1.000-1.499	10000-14999
3	>69	-	>1.499	>14999

For each prognostic factor, 0 to 3 points are given to each patient and points are summed up to define a category of risk

Risk stratification	
0-3 points	low-risk
4-5 points	intermediate-risk
6-11 points	high-risk

Low-Risk: <5.7

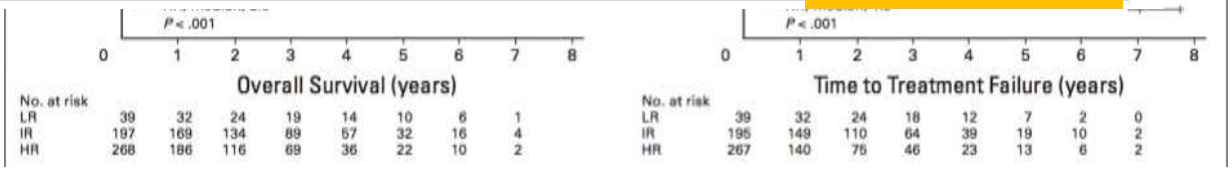
Intermed. Risk: ≥5.7 <6.2

.2

5

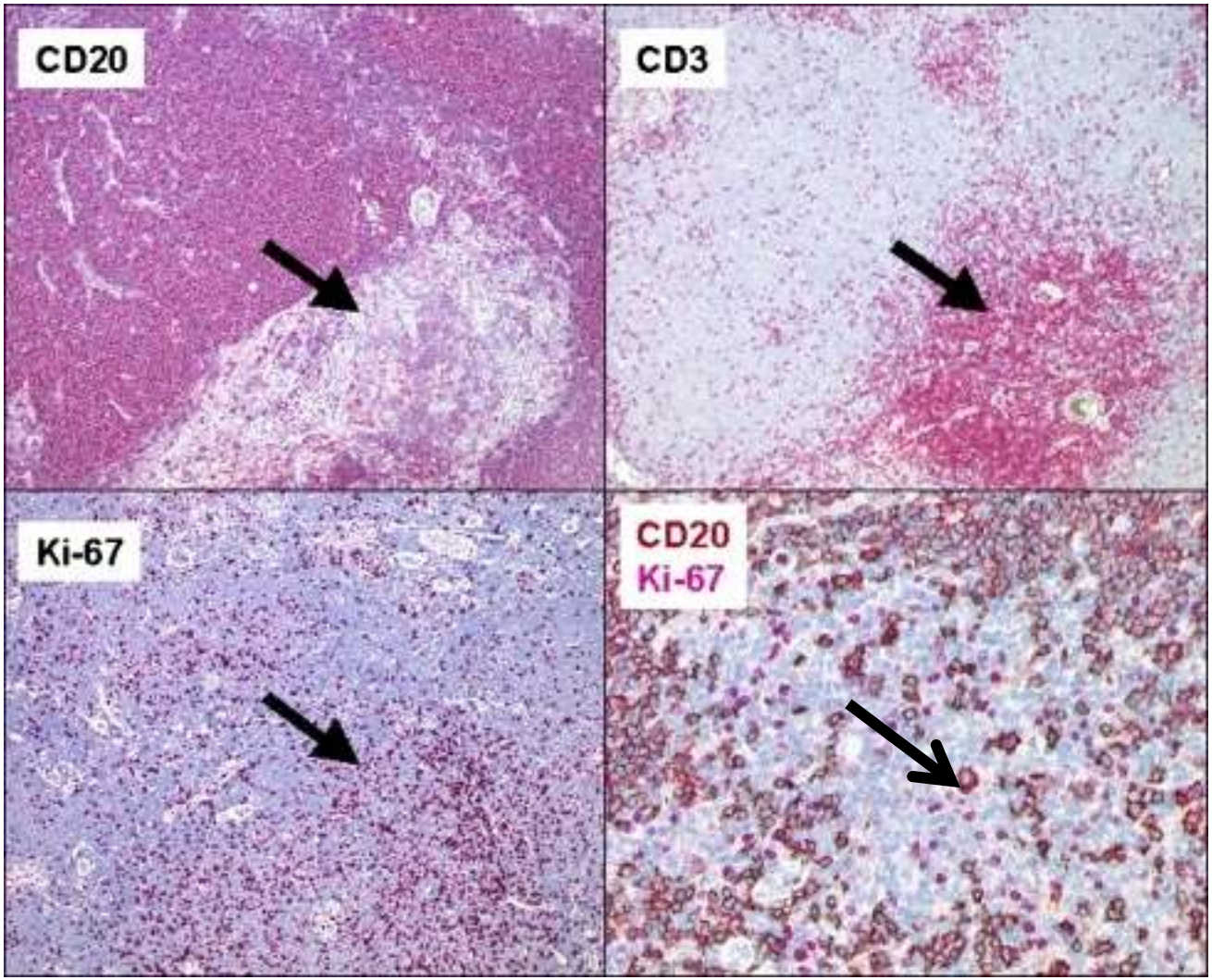
5

sMIPI



Hoster et al. JCO 2014

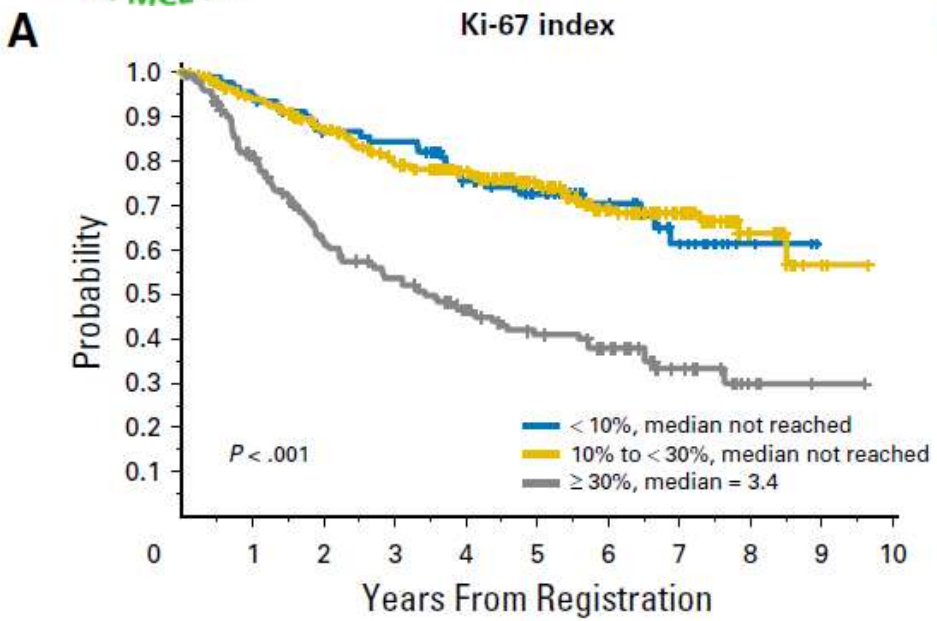
KI-67 as prognostic factor in MCL

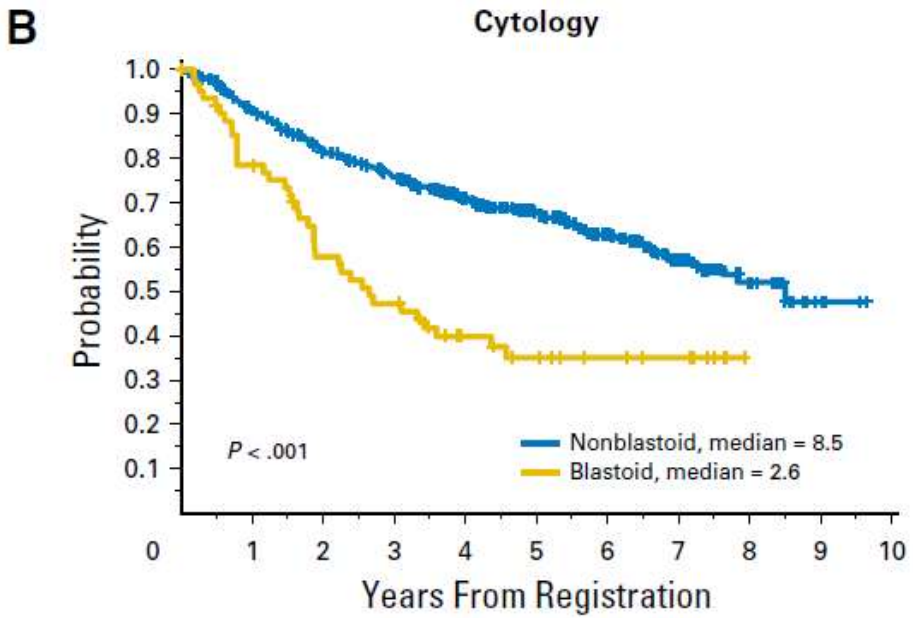


1. Before Tx
2. LN>BM
3. Avoid residual GC, hot spots, T-cells

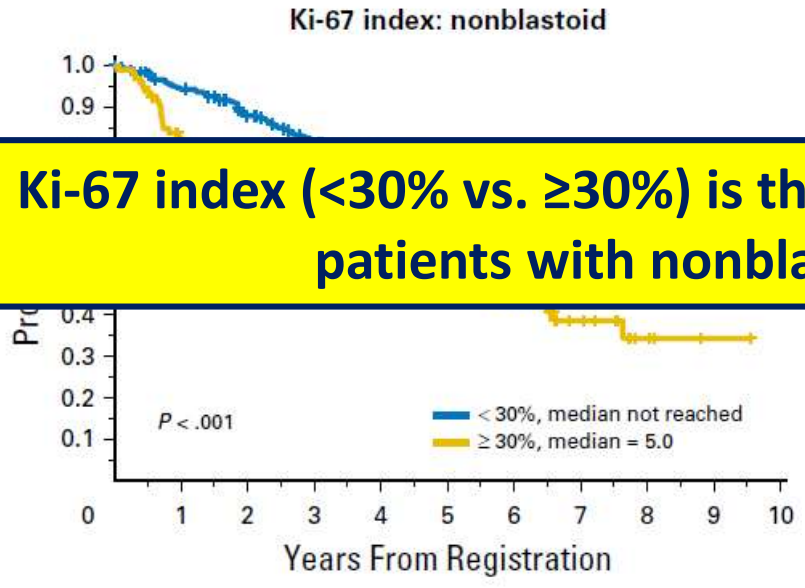
Klapper W et al, J Hematop 2009

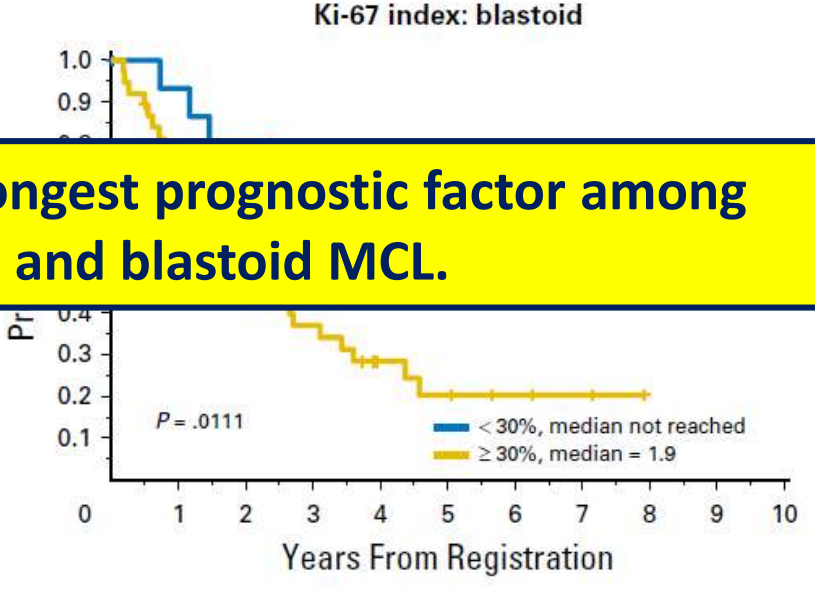
OS according to KI-67- Cytology





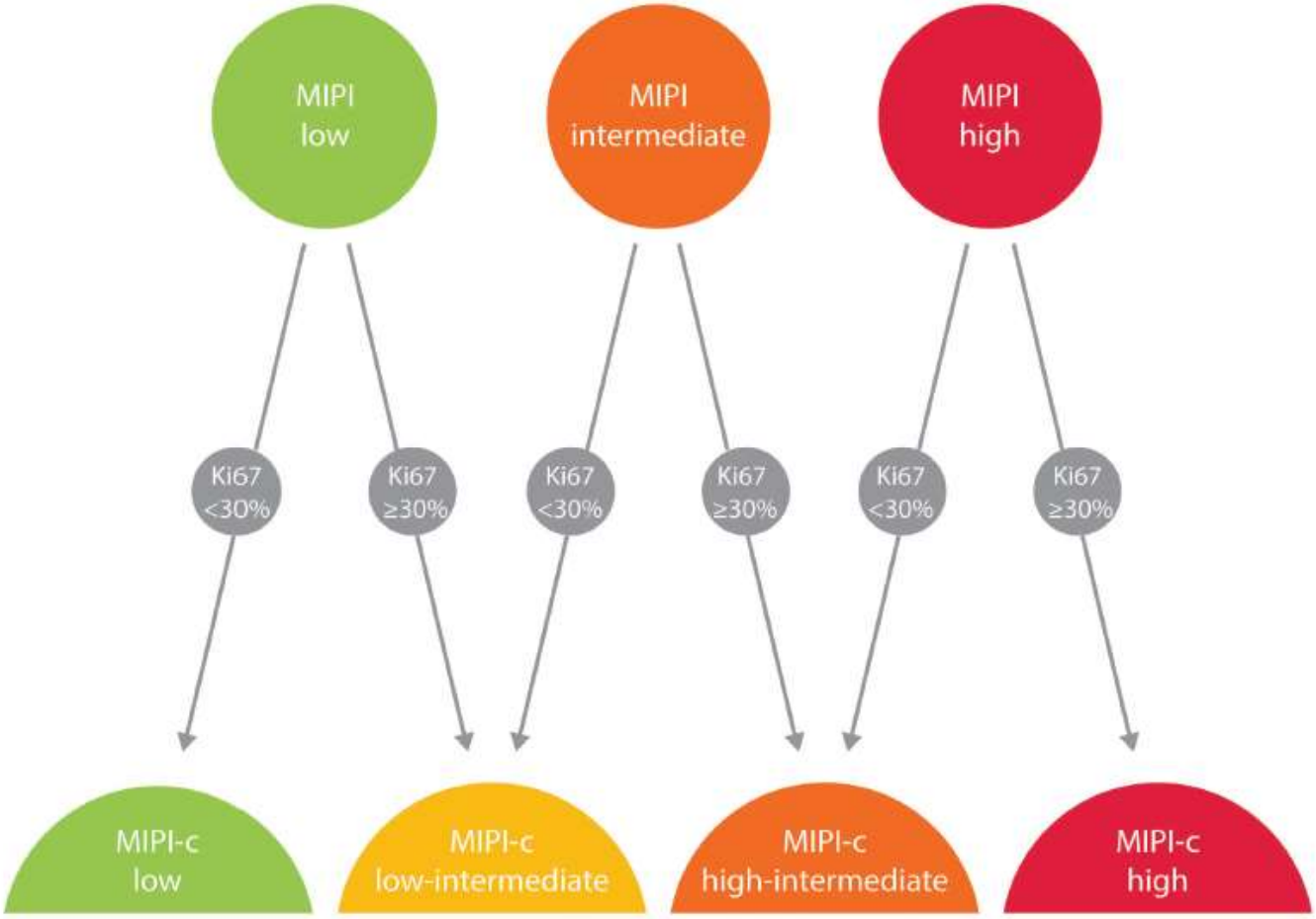
Hoster et al. JCO 2016



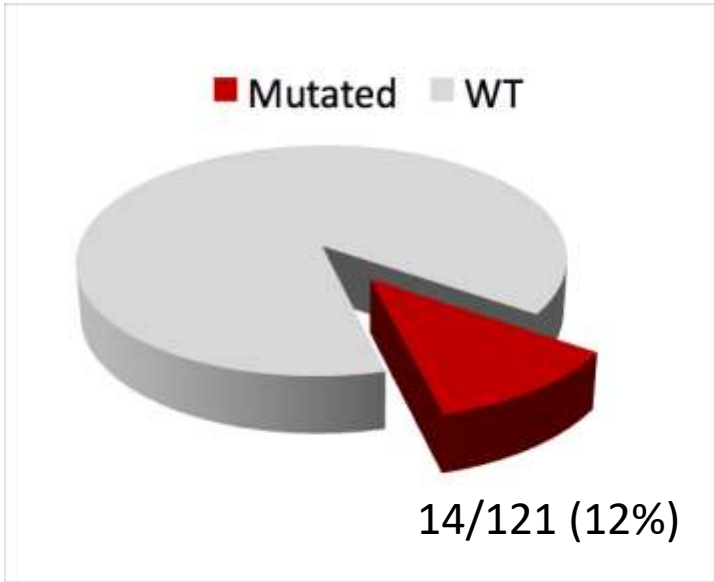


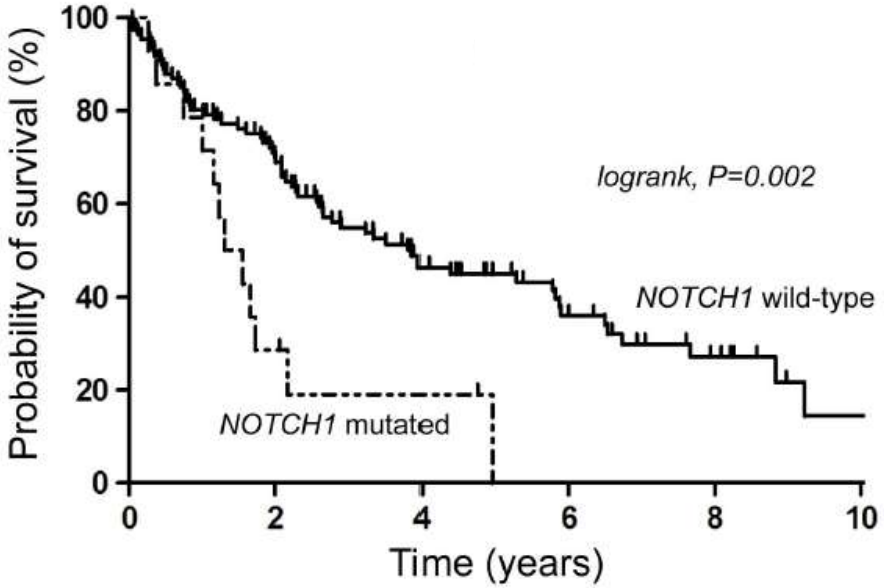
Ki-67 index (<30% vs. ≥30%) is the strongest prognostic factor among patients with nonblastoid and blastoid MCL.

Combined MIPI



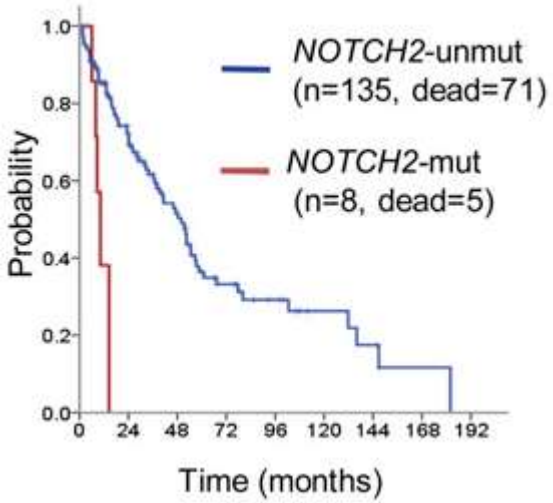
NOTCH 1-2 mutations in MCL





Kridel R, et al. Blood 2012

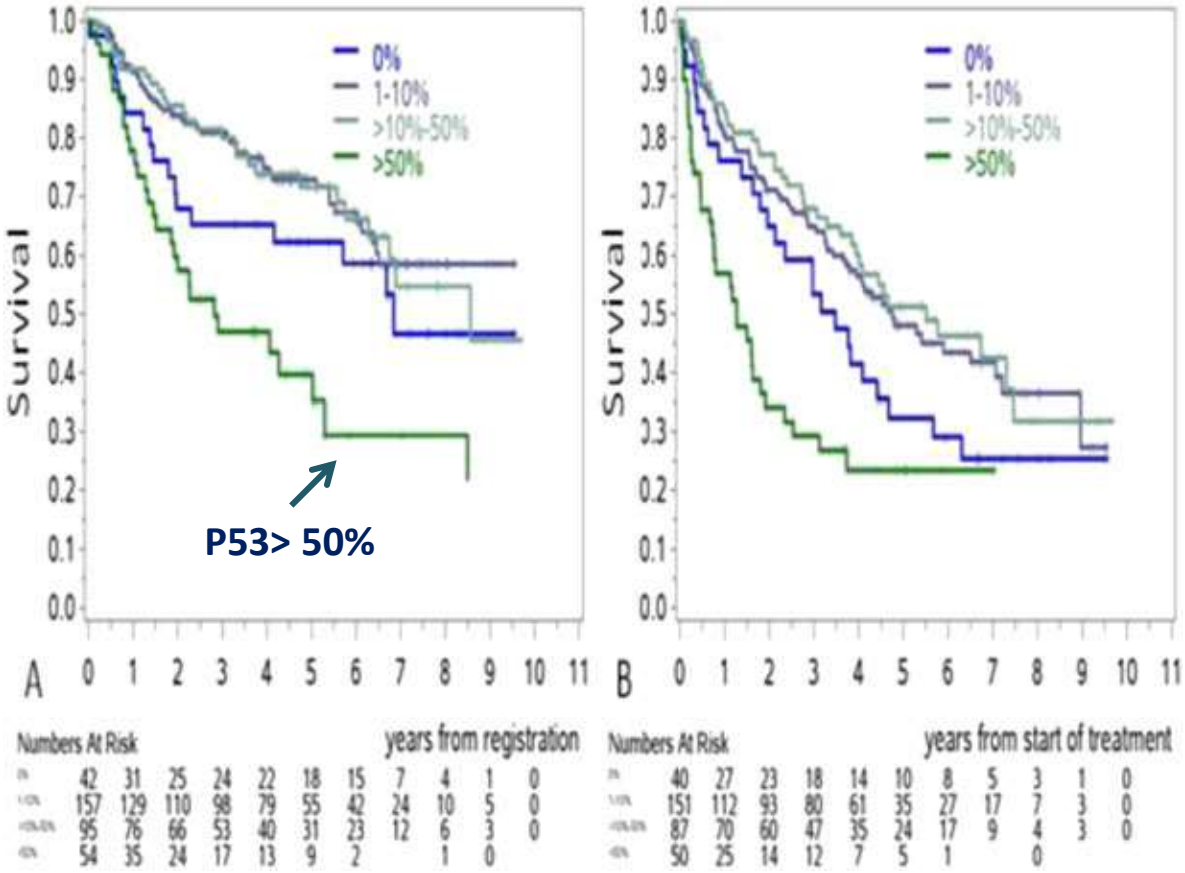
- ++blastoid/pleomorphic
- Occur in different subsets: 1/16 had mutations in both



Beà S et al. PNAS 2016

P53 protein expression by IHC has a prognostic value in prospective trials of the MCL

Figure 1: Prognostic value of p53 IHC score for overall survival (A) and time to treatment failure (B)



P53 expression >50% had a shorter TTFT and OS independent of MIPI and Ki-67.

Aukema SM et al, ICML 2017, Abst 130

KMT2D AND TP53 MUTATIONS PREDICT POOR PFS AND OS IN MANTLE CELL LYMPHOMA RECEIVING HIGH-DOSE THERAPY AND ASCT: THE FONDAZIONE ITALIANA LINFOMI (FIL) MCL0208 PHASE III TRIAL

S. Ferrero[1], D. Rossi[2], A. Bruscaggin[3], A. Evangelista[4], A. Di Rocco[5], V. Spina[3], V. Stefoni[6], P. Ghione[1], D. Barbero[1], L. Monitillo[1], M. Gomes da Silva[7], A. Santoro[8], A. Molinari[9], A. Ferreri[10], A. Piccin[11], S. Cortelazzo[12], M. Ladetto[13], G. Gaidano[14]

1 Molecular Biotechnologies and Health Sciences - Hematology Division,, Università di Torino, Torino, Italy, 2 Hematology, Oncology, Institute of Southern Switzerland and Institute of Oncology Research, Bellinzona, Switzerland, 3 Hematology, Institute of Oncology Research, Bellinzona, Switzerland, 4 Clinical Epidemiology, Città della Salute e della Scienza and CPO Piemonte, Torino, Italy, 5 Department of Cellular Biotechnologies and Hematology, Policlinico Umberto I, "Sapienza" University of Rome, Roma, Italy, 6 University of Bologna, Institute of Hematology "L. e A. Seràgnoli, Bologna, Italy, 7 Department of Hematology, Instituto Português de Oncologia de Lisboa, Lisbona, Portugal, 8 Humanitas Clinical and Research Center, Humanitas Cancer Center, Rozzano, Italy, 9 Hematology, Ospedale degli Infermi, Rimini, Italy, 10 Unit of Lymphoid Malignancies, Department of Onco-Haematology, IRCCS San Raffaele Scientific Institute, Milano, Italy, 11 Department of Hematology, Ospedale Generale, Bolzano, Italy, 12 Gavazzeni, Clinica Humanitas, Bergamo, Italy, 13 Azienda Ospedaliera Santi Antonio e Biagio e Cesare Arrigo, SC Ematologia, Alessandria, Italy, 14 Department of Translational Medicine, University of Eastern Piedmont, Division of Hematology, Novara, Italy.

Dipartimento di Biotecnologie Molecolari e Scienze per la Salute

DIVISIONE DI EMATOLOGIA
LABORATORIO DI BIOLOGIA MOLECOLARE
Prof. Mario Boccadoro

Simone Ferrero, MD

Lugano (CH), 15.06.2017

FIL MCL0208 phase III trial:

All the enrolled patients
N=300

DATA CUT OFF
January 2017
(II interim analysis)

Fulfilling the inclusion criteria
N=174

Not fulfilling the inclusion criteria
N=126

Somatic analysis
(paired GL + tumor samples)
N = 95

CNS analysis
(only tumor samples)
N = 79

Filter out:

- Variants <10% VAF
- SNPs from dbSNP (IARC for *TP53* SNV)
- Intronic and synonymous variants
- Variants occurring in the paired GL ($p=3.2 \times 10^{-8}$ by Bonferroni-corrected Fisher exact test)

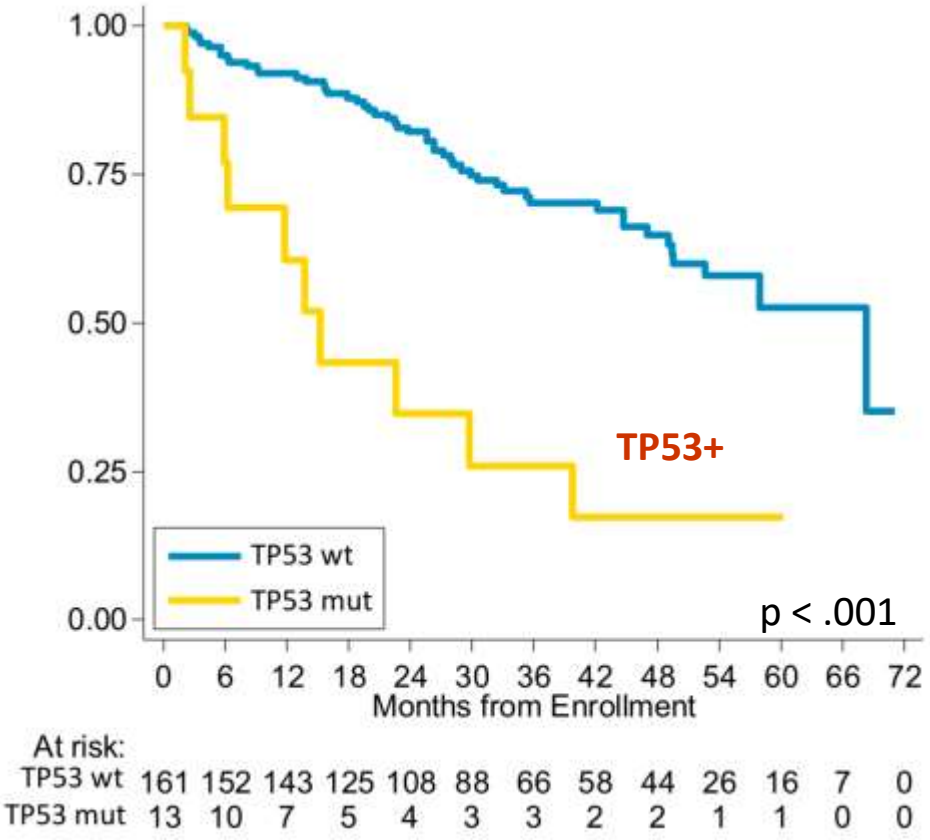
Filter out:

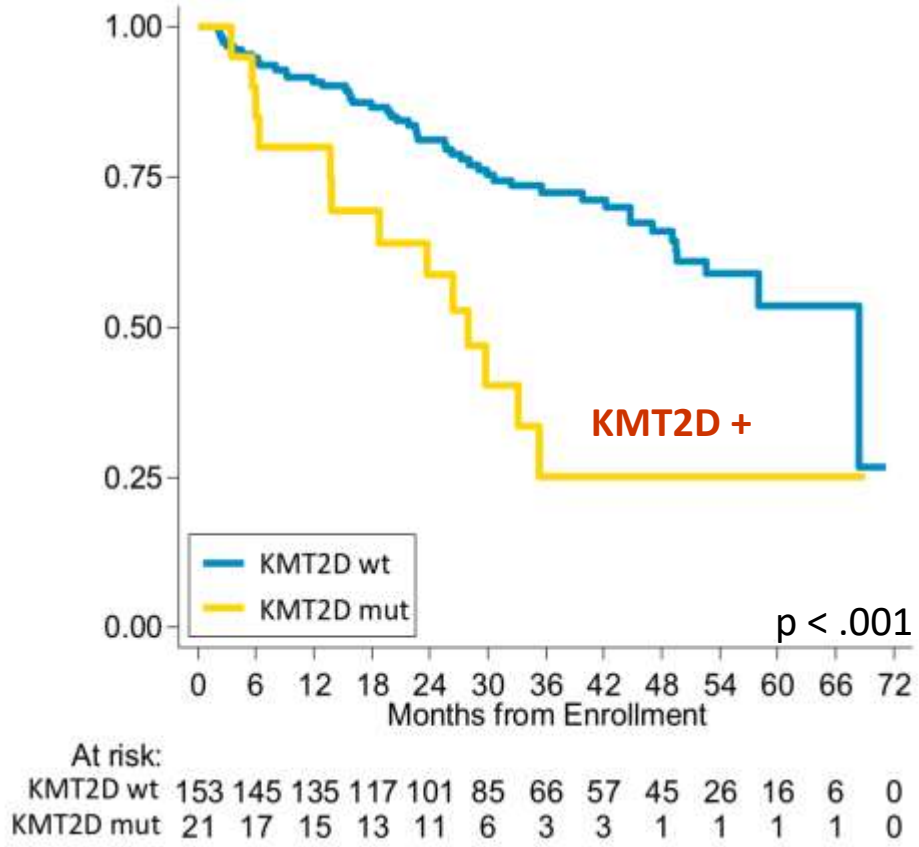
- Variants <10% VAF
- SNPs from dbSNP (IARC for *TP53* SNV)
- Intronic and synonymous variants
- Variants occurring in unpaired GL
- Missense substitutions non reported in COSMIC

INCLUSION CRITERIA

Availability of DNA from purified tumor cells

Clinical impact of TP53 and KMT2D in terms of PFS





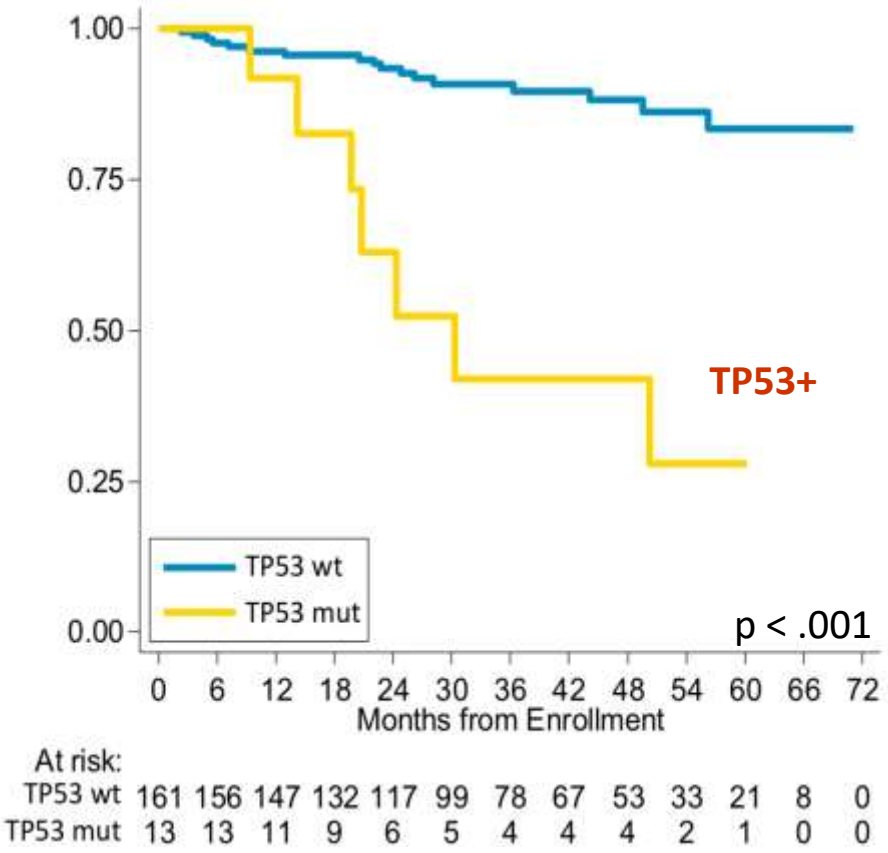
36 months PFS:

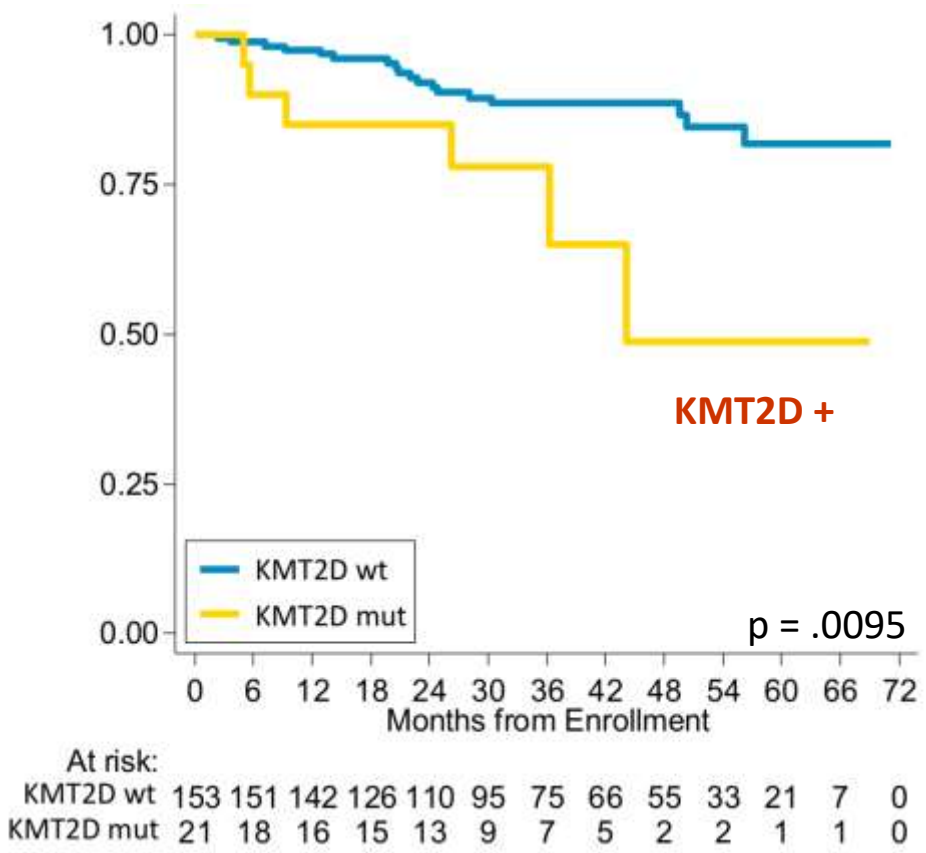
- ***TP53*** **wild type 70%**
- ***TP53*** **mut 26%**

36 months PFS:

- ***KMT2D*** **wild type 74%**
- ***KMT2D*** **mut 25%**

Clinical impact of TP53 and KMT2D in terms of OS





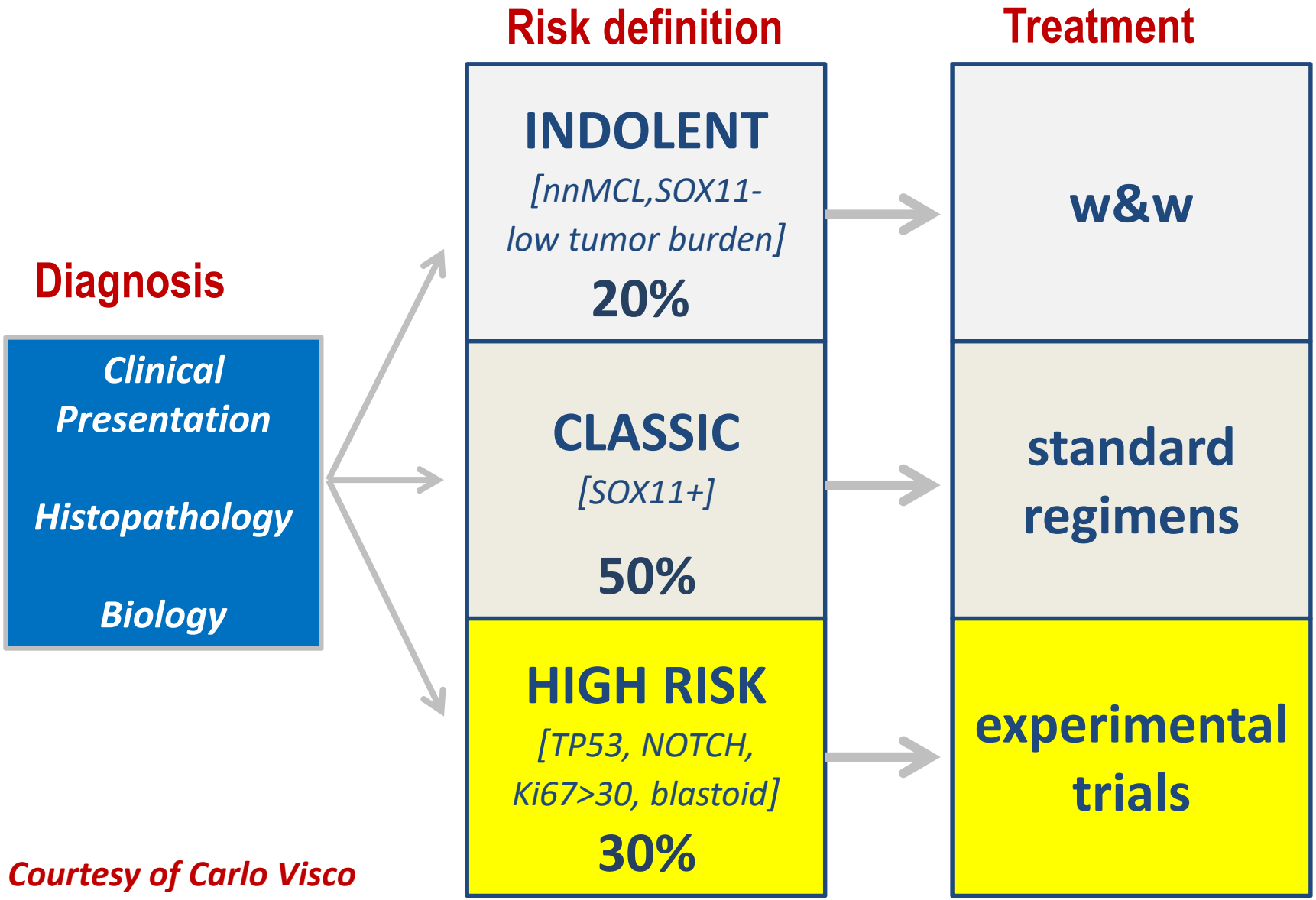
36 months OS:

- ***TP53*** **wild type 90%**
- ***TP53*** **mut 46%**

36 months OS:

- ***KMT2D*** **wild type 89%**
- ***KMT2D*** **mut 65%**

New therapeutic approach in MCL



Courtesy of Carlo Visco

Patients in whom treatment may be postponed (indolent MCL)

- Long history of asymptomatic disease
- Non-nodal leukemic disease (++ spleen)
- Low proliferation rate (Ki-67< 20%)
- Hypermutated IGHV
- Non complex karyotypes
- SOX11-negative

Fernandez V, Cancer Res 2010
Seto M, Blood 2013
Ferrando A, Blood 2013
Vegliante et al, Blood 2013

Patients in whom treatment may be postponed (indolent MCL)

- ***Long history of asymptomatic disease***
- ***Non-nodal leukemic disease (++ spleen)***
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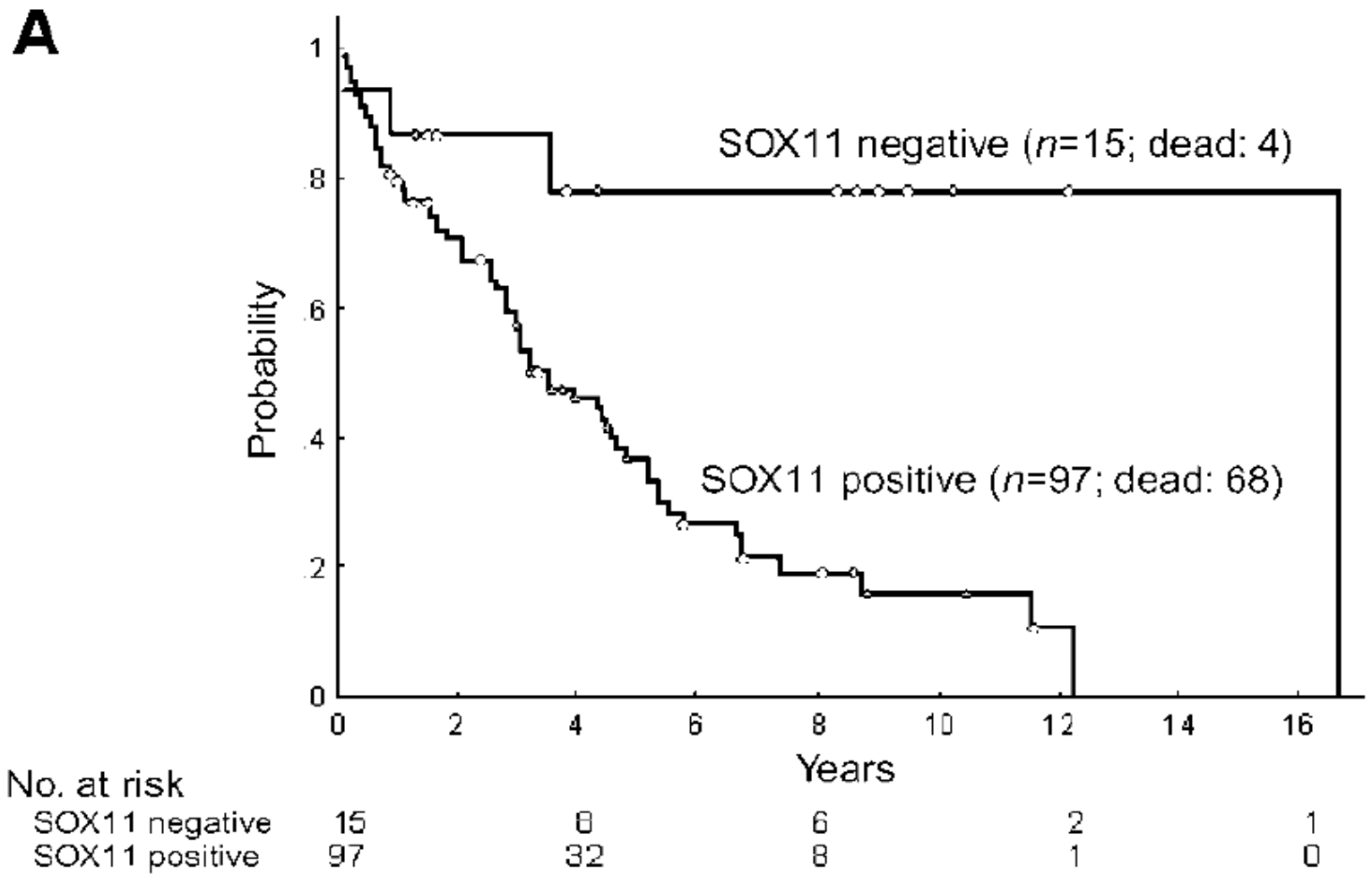
- ***SOX11-negative ????***

Fernandez V, Cancer Res 2010
Seto M, Blood 2013
Ferrando A, Blood 2013
Vegliante et al, Blood 2013

Indolent mantle cell lymphoma (iMCL)

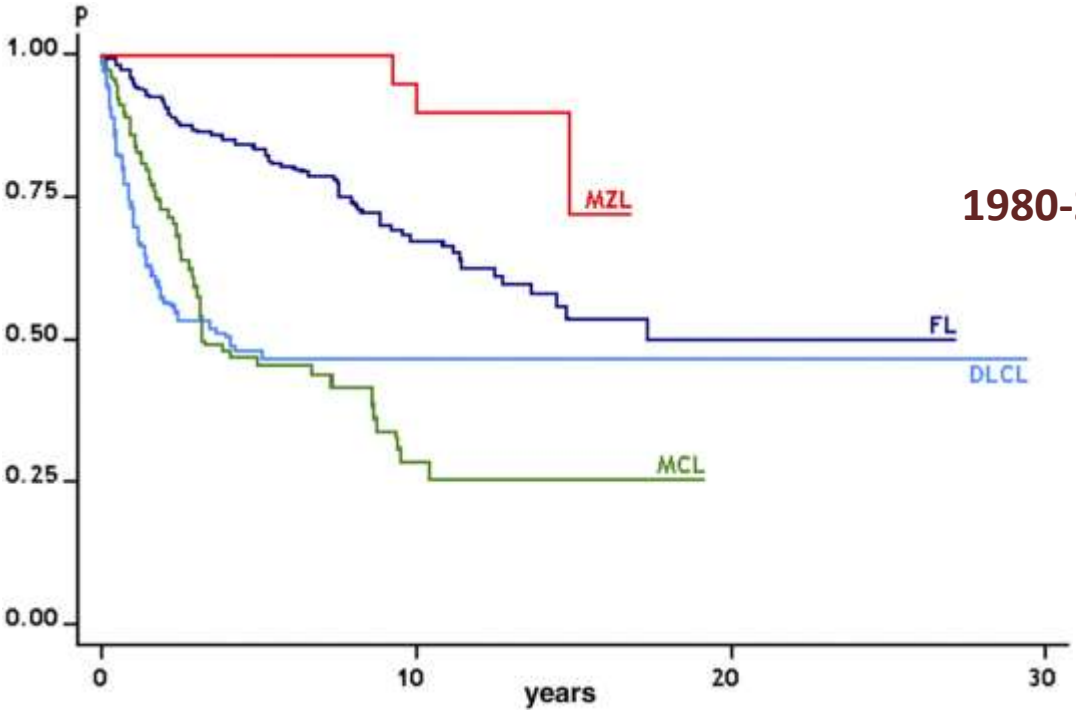
Risk factor clinical presentation



Fernandez, Cancer Research 2010

Therapy of younger (<65 year)

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



1980-2006

Significant improvement in OS in the last 10 years:

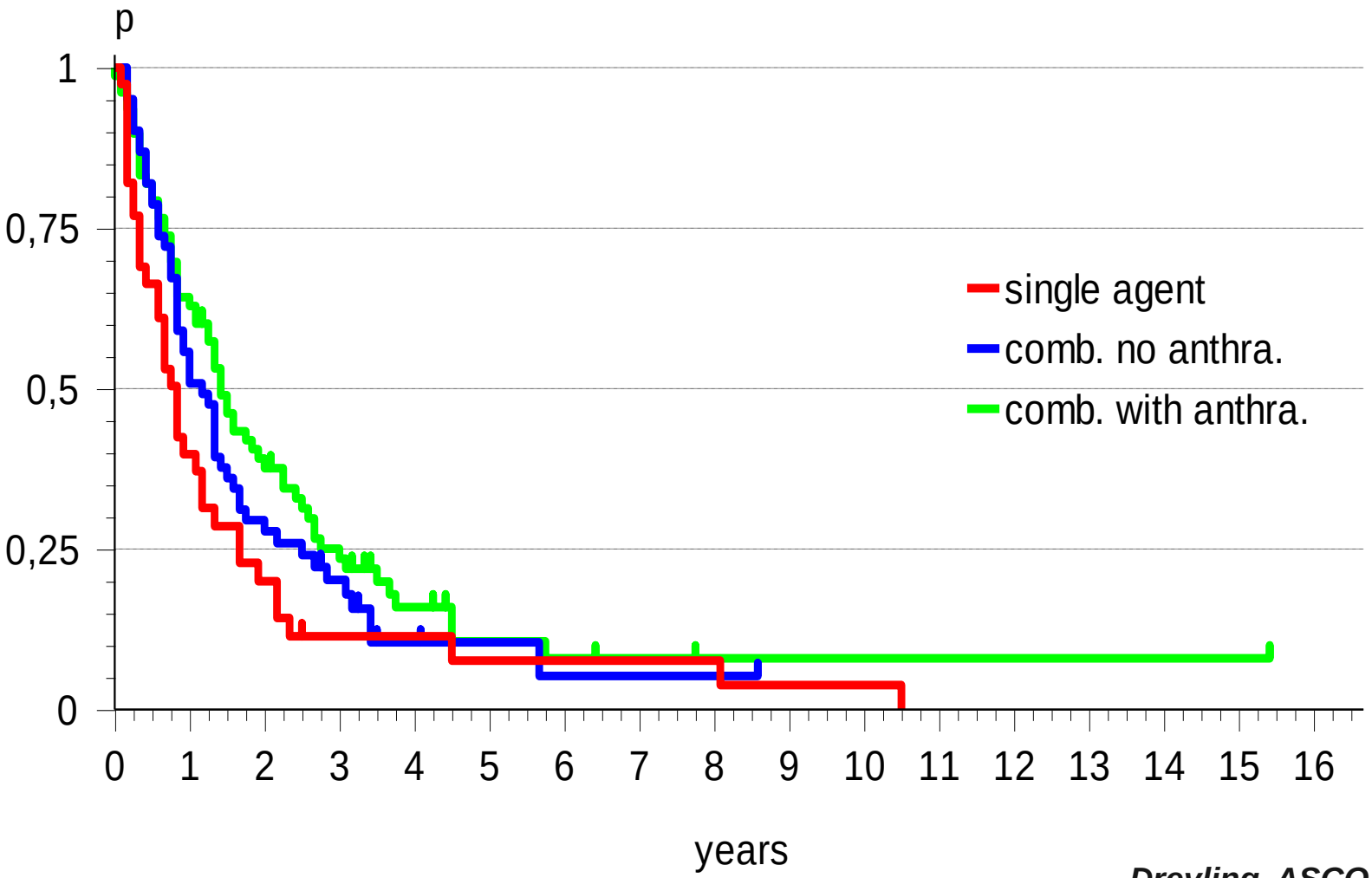
1) introduction of dose-intensive strategies upfront in younger patients
2) availability of novel agents in older patients or in the r/r setting.

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

Multicenter Evaluation of MCL

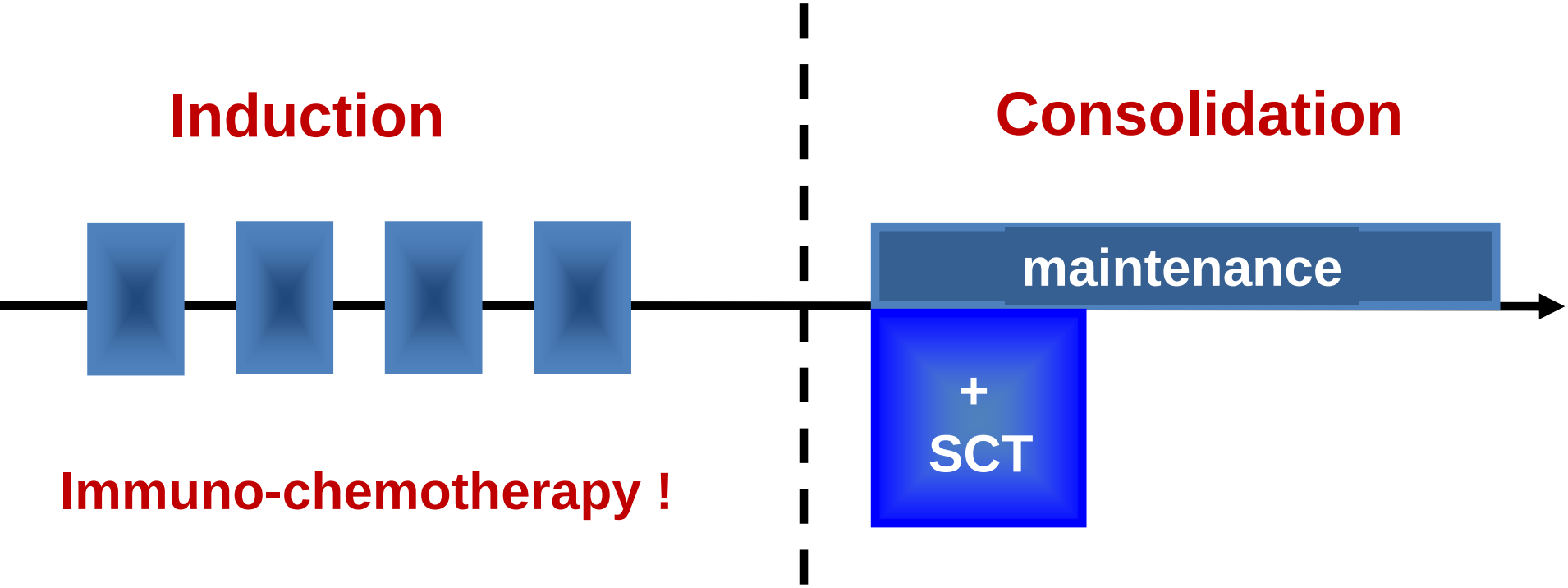
Annency Criteria fulfilled

event free interval after chemotherapy in stages III + IV



Dreyling, ASCO 1999

Current optimal treatment for MCL



Young patient (≤65)	Elderly patient (>65) First line treatment	Compromised patient
Dose-intensified Immuno-chemotherapy R-CHOP + R-high dose Ara-C (alternating or sequential) =>ASCT)	Conventional Immuno-chemotherapy (e.g. R-CHOP, BR) ↓ Rituximab maintenance radioimmunotherapy	Watch and wait ? R-Chlorambucil BR
1. Relapse		
High tumour load: Immuno-chemotherapy (e.g. BR, R-DHAP) ↓ Allo-transplant Radioimmunotherapy Rituximab maintenance	Immuno-chemotherapy (e.g. BR, R-FC) Targeted approaches ↓ ASCT Radioimmunotherapy Rituximab maintenance	Immuno-chemotherapy (e.g. BR) Targeted approaches
Higher relapse		
Targeted approaches: Temsirolimus, Bortezomib*, Ibrutinib, Lenalidomide* (preferable in combination) Repeat previous therapy (long remissions)		

Dreyling, ESMO CR MCL 2014

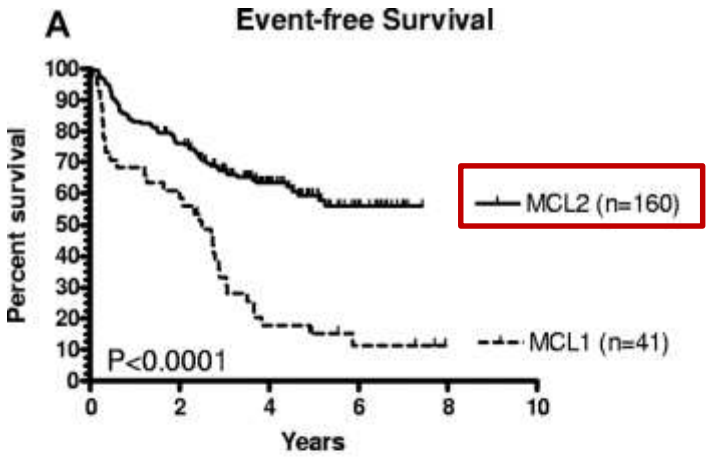
Dose-intensified immuno-chemotherapy

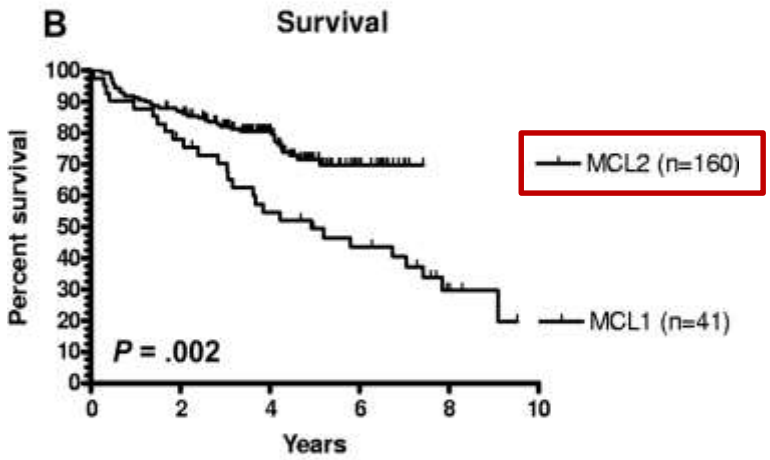
Younger MCL patients

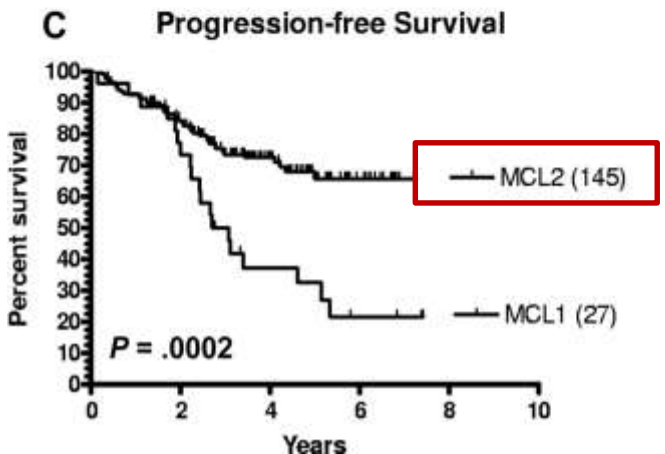
	Author	Study Features	Evaluable Patients	Therapeutic Regimen	ORR% (CR%)	Median PFS (Years)	Median OS (Years)	Dropout Rate	TRM	Secondary Tumors Rate
ASCT-Based Regimens	Dreyling et al. 2005	Phase III, randomized	122	R-CHOP + ASCT vs. R-CHOP + interferon-α	98 (81) vs. 99 (37)	3.3 vs. 1.4	NR (83% 3-yr OS) vs. NR (77% 3-yr OS)	13% vs. na	5% vs. 0%	5%
	Hermine et al. 2012	Phase III, randomized	455	R-CHOP + ASCT vs. R-CHOP/R-DHAP + ASCT	98 (63) vs. 97 (61)	3.8 vs. 7.3	6.8 vs. NR	na	4%	na
	Damon et al. 2009	Phase II	77	R-CHOP + methotrexate + HD-araC/ etoposide + ASCT	88 (69)	NR (56% 5-yr PFS)	NR (64% 5-yr OS)	13%	3%	na
	Van't Veer et al. 2009	Phase II	87	R-CHOP + HD-araC + ASCT	70 (64)	NR (36% 4-yr PFS)	NR (66% 4-yr OS)	30%	5%	na
	Geisler et al. 2012	Phase II	160	R-Maxi-CHOP + HD-araC + ASCT	96 (54)	7.4	NR 58% (10-yr OS)	9%	5%	4%
	Delarue et al. 2013	Phase II	60	R-CHOP/R-DHAP + ASCT	100 (96)	6.9	NR (75% 5-yr OS)	18%	1.5%	18%
	Touzeau et al. 2013	Retrospective	396	ASCT-based schedules	83 (77)	NR (67% 3-yr PFS)	NR (83% 3-yr OS)	ne	2.5%	6%
Non-ASCT-Based Regimens	Romaguera et al. 2010	Phase II, monocentric	97	R-HyperCVAD	97 (87)	4.6	NR (64% 10-yr OS)	29%	8%	5%
	Merli et al. 2012	Phase II, multicentric	60	R-HyperCVAD	83 (72)	NR (73% 5-yr PFS)	NR (61% 5-yr OS)	63%	6.5%	1.5%
	Bernstein et al. 2013	Phase II, multicentric	49	R-HyperCVAD	86 (55)	4.8	6.8	39%	2%	4%

ASCO Educational 2014

Nordic Lymphoma Study Group
MCL1 vs MCL2



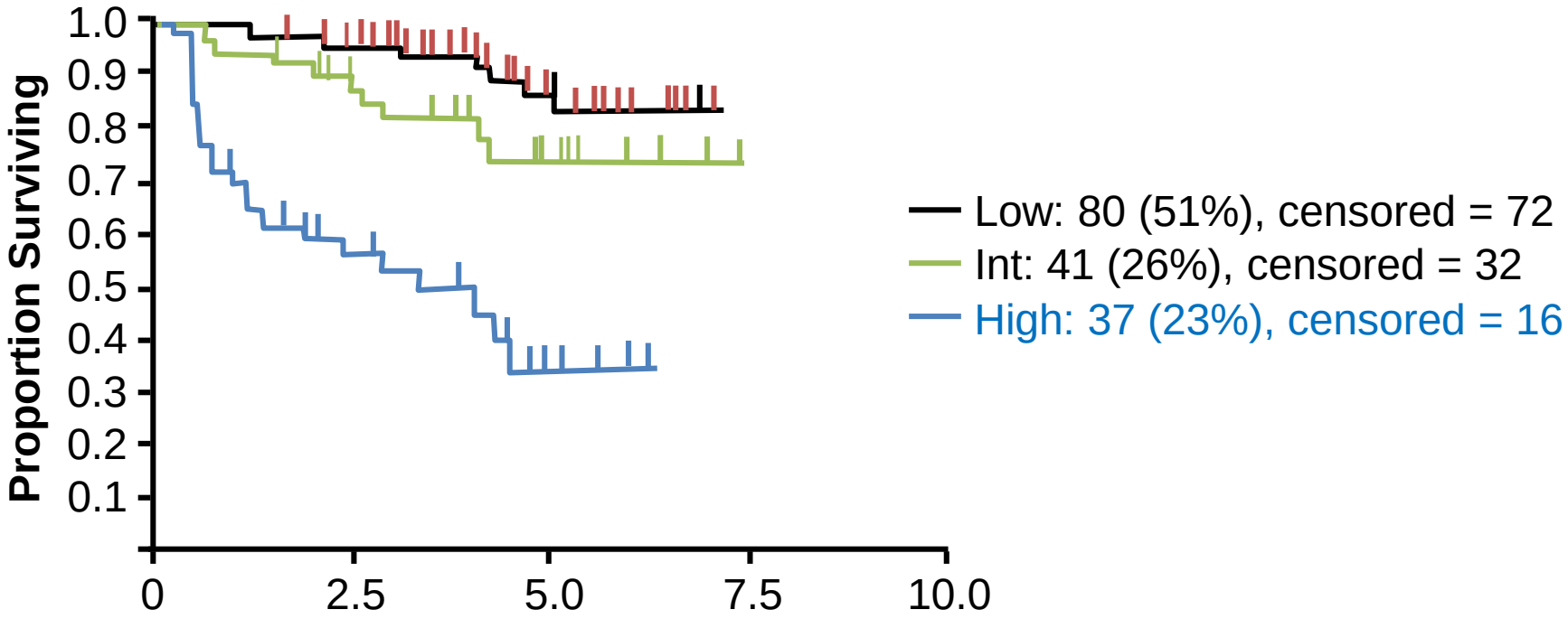




	No Ara-C	R-Ara-C
NORDIC MCL PROTOCOL #	MCL1 (1996-2000) (-CHOP⇒ASCT)	MCL2 (2000-2006)
Number of cases included	41	160
ORR pre-transplant	76%	96%
CR/CRu pre-transplant	27%	54%

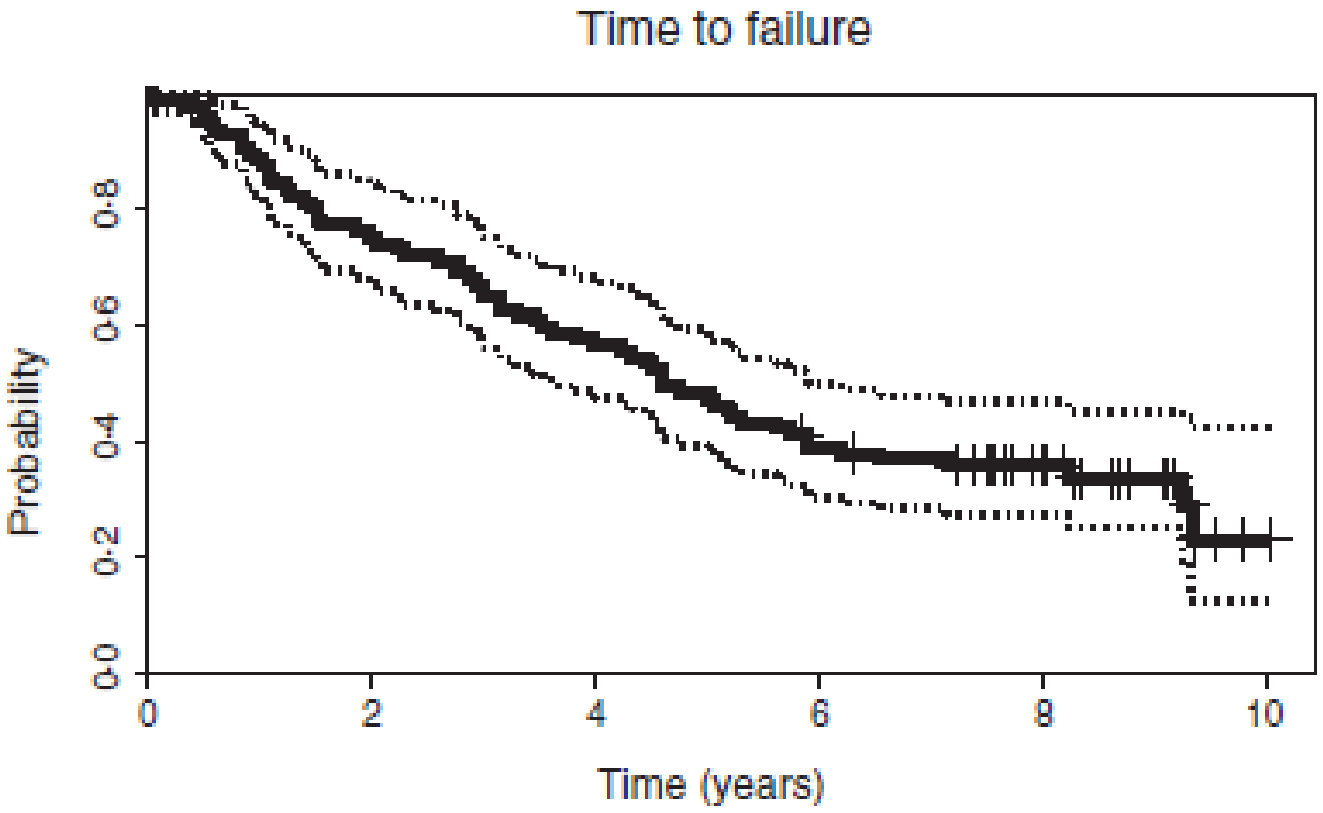
Geisler et al, Blood. 2008

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



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

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



<65 , 65 pts: 8-year TTF 46%

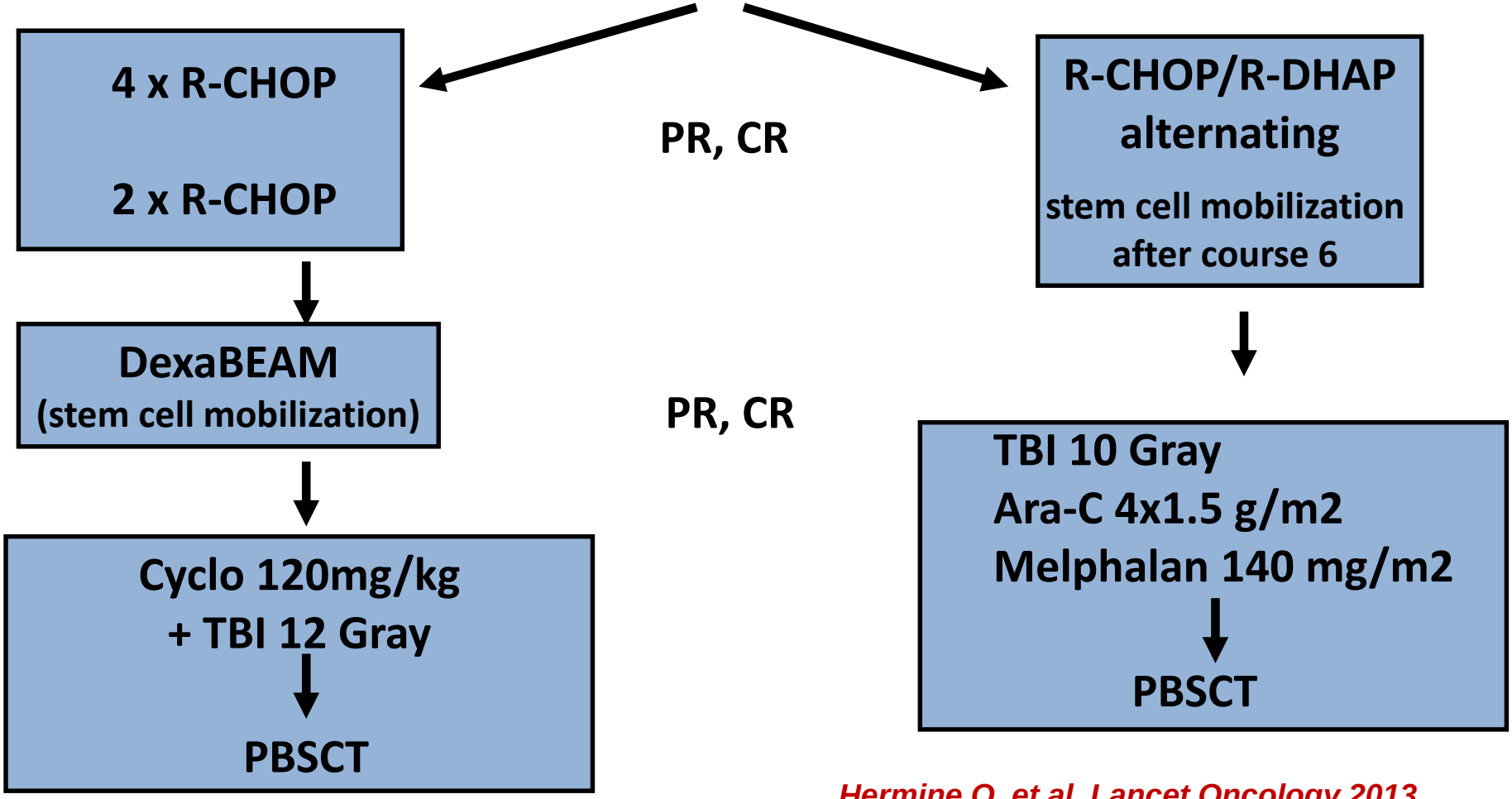
>65 , 32 pts: 8-year TTF 16%

Romaguera J, JCO 2005

Romaguera J, BJH 2010

Intensive schemes including ASCT

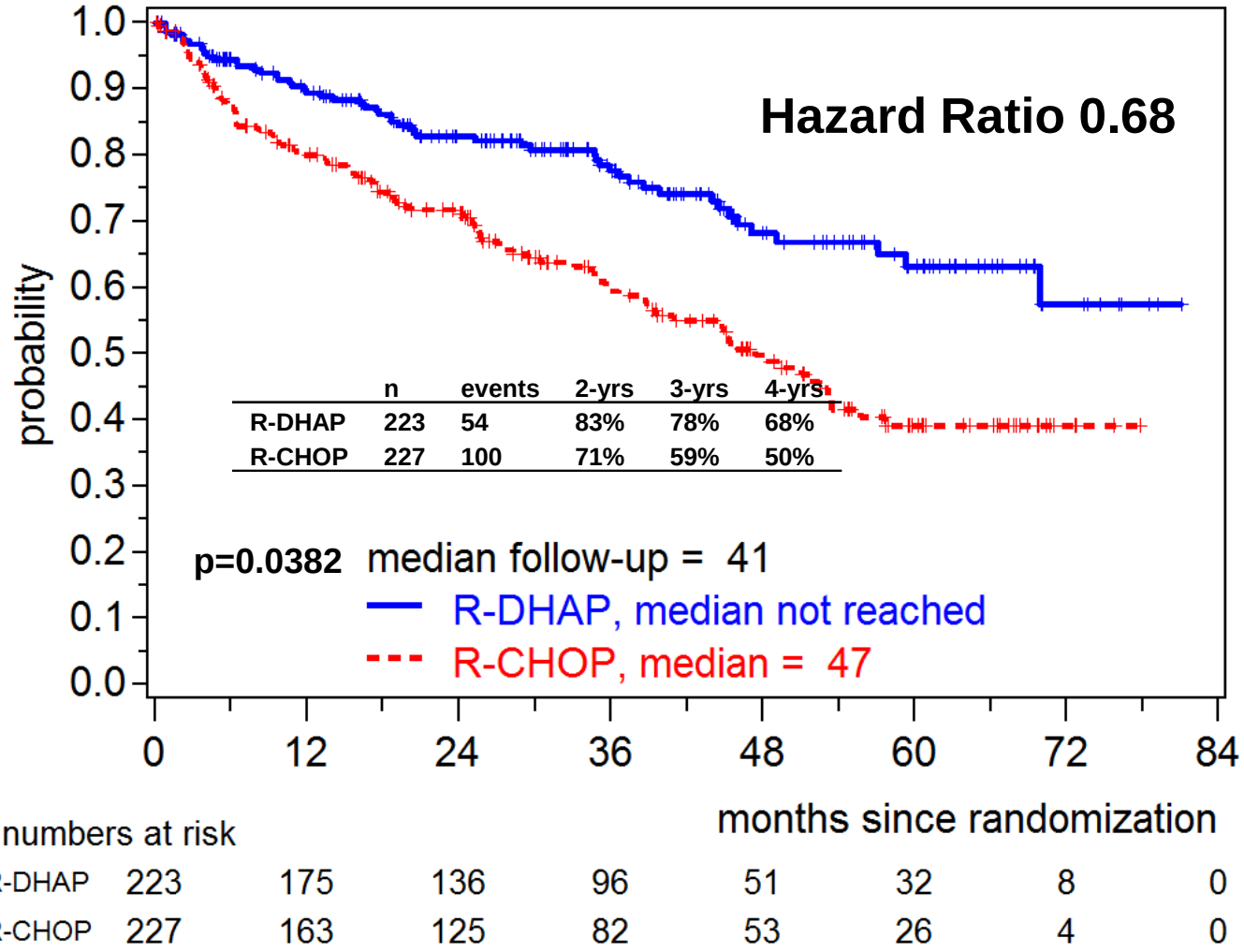
MCL Network younger Trial



Hermine O, et al. Lancet Oncology 2013.

Intensive schemes including ASCT

MCL Network younger Trial

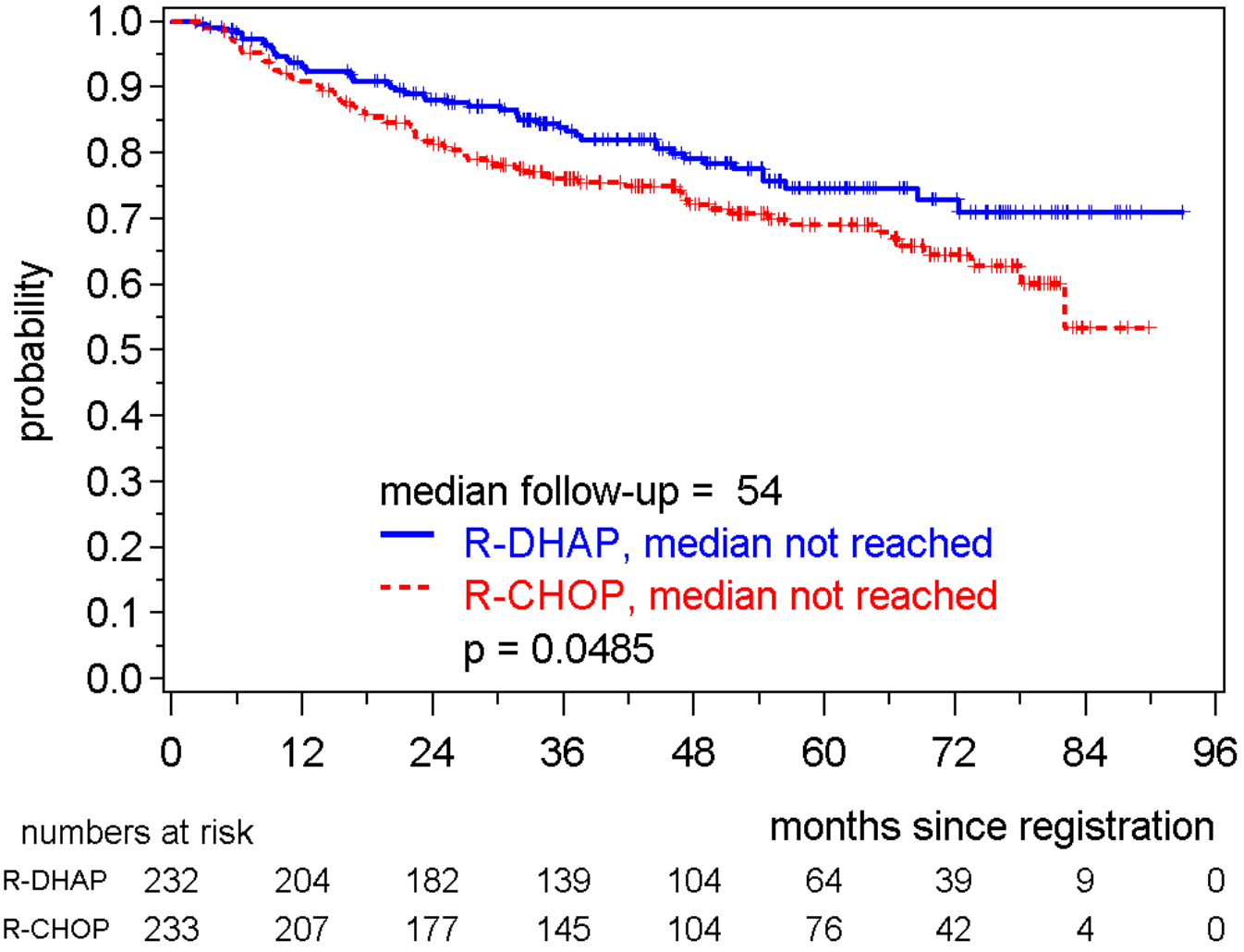


PFS

Hermine O, et al. Lancet Oncology 2013.

Intensive schemes including ASCT

MCL Network younger Trial



OS

Hermine O, et al. Lancet Oncology 2013.

MRD as the therapeutic goal in MCL: results of the Intergroup Trials of the European MCL Network

- MRD was prospectively monitored in the randomized intergroup trials of the European MCL Network

- The trials focused on
  - immunochemotherapy followed by autologous stem cell transplantation (ASCT) for younger patients (<65 y)
  - rituximab or interferon maintenance for elderly patients (> 65 y)

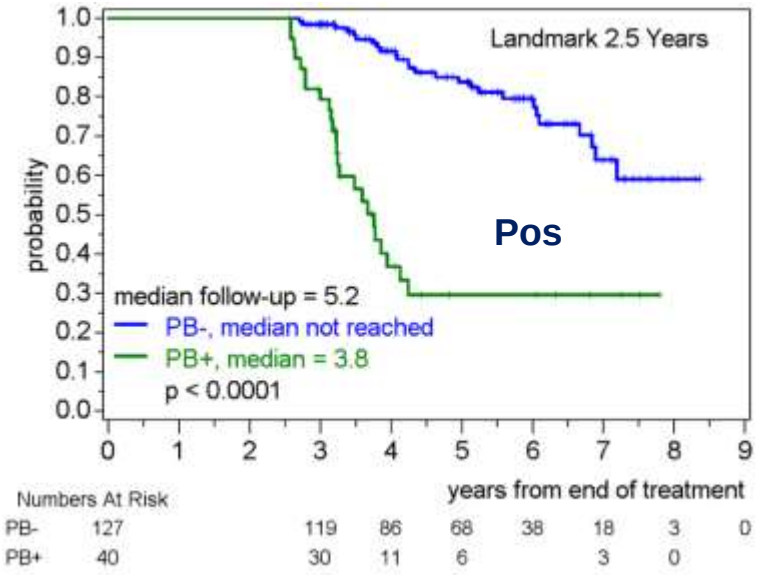
- MRD analyses were performed after induction then every 3-months after ASCT or every 2-months during maintenance until progression (n=406)

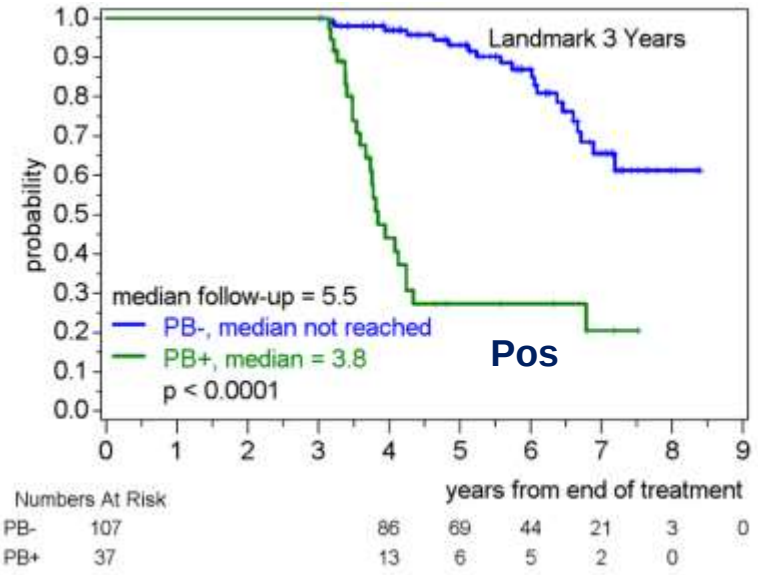
- ***602 patients in remission 6 months after induction, 334 younger or 268 elderly***

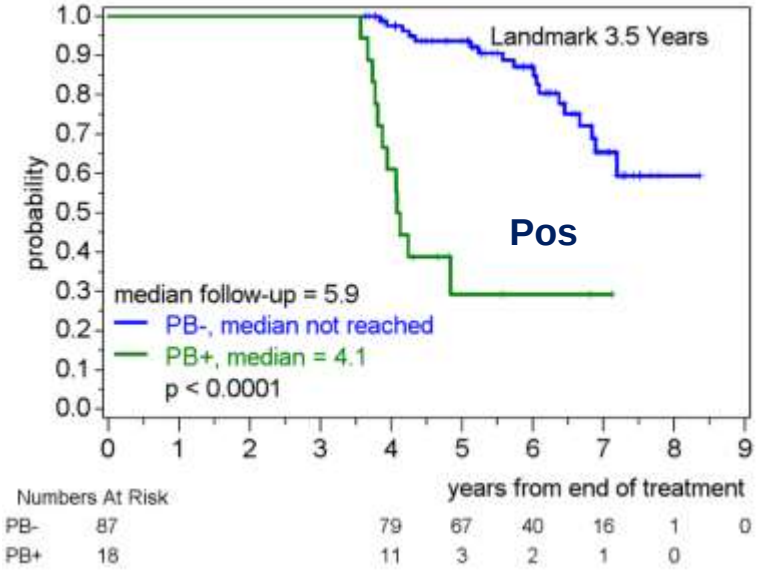
European MCL Network

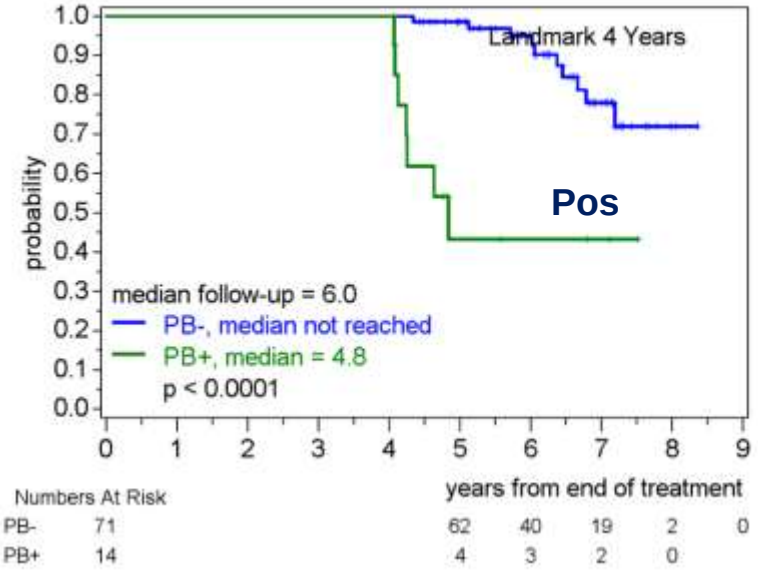
Pott et al., ASH 2014; abstract 147 (oral presentation)

MRD Landmark analysis Pos. vs Neg. Pooled trials





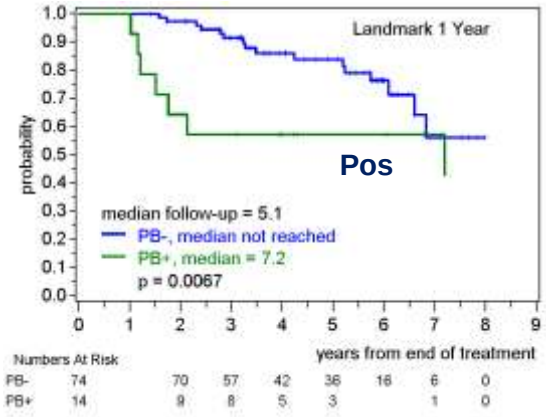


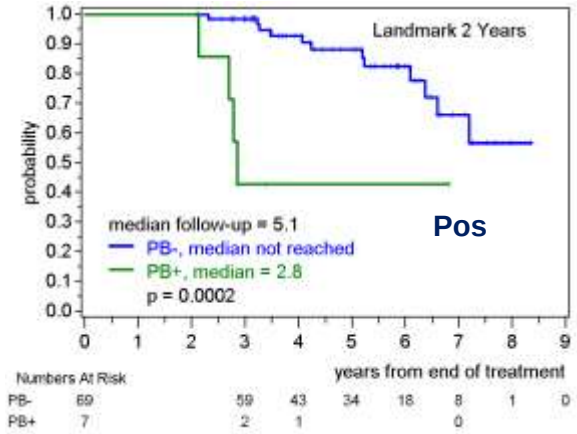


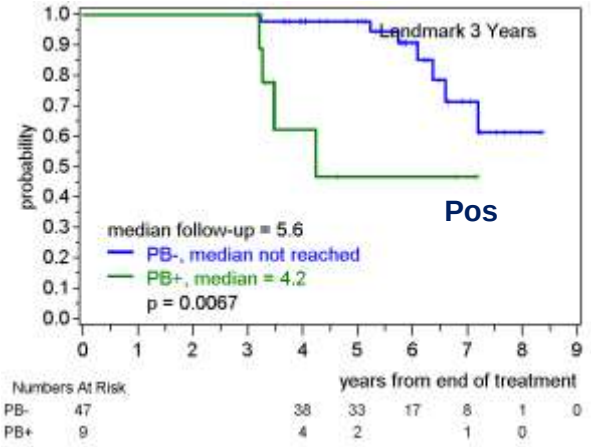
Pott et al., ASH 2014; abstract 147 (oral presentation)

MRD Landmark analyses for PFS in remission

After R-CHOP/R-DHAP/ASCT younger

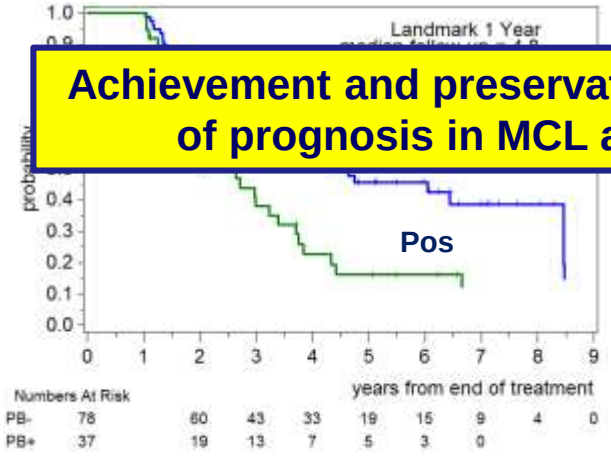


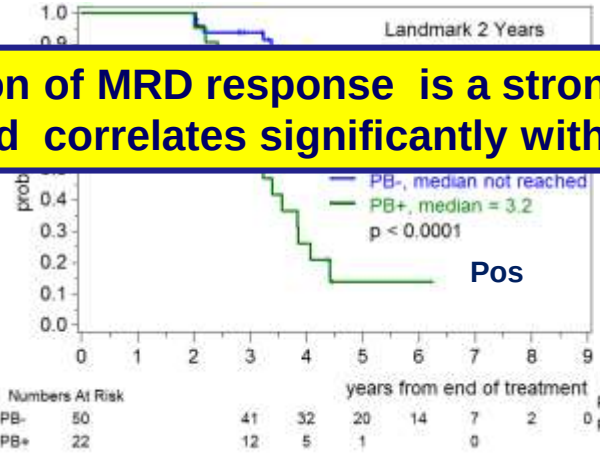


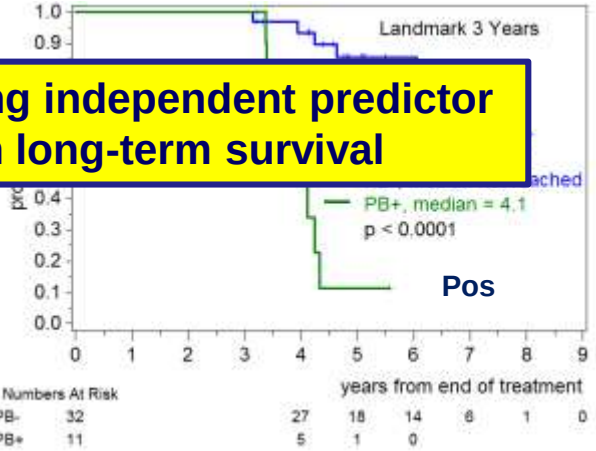


After induction/maintenance therapy elderly

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

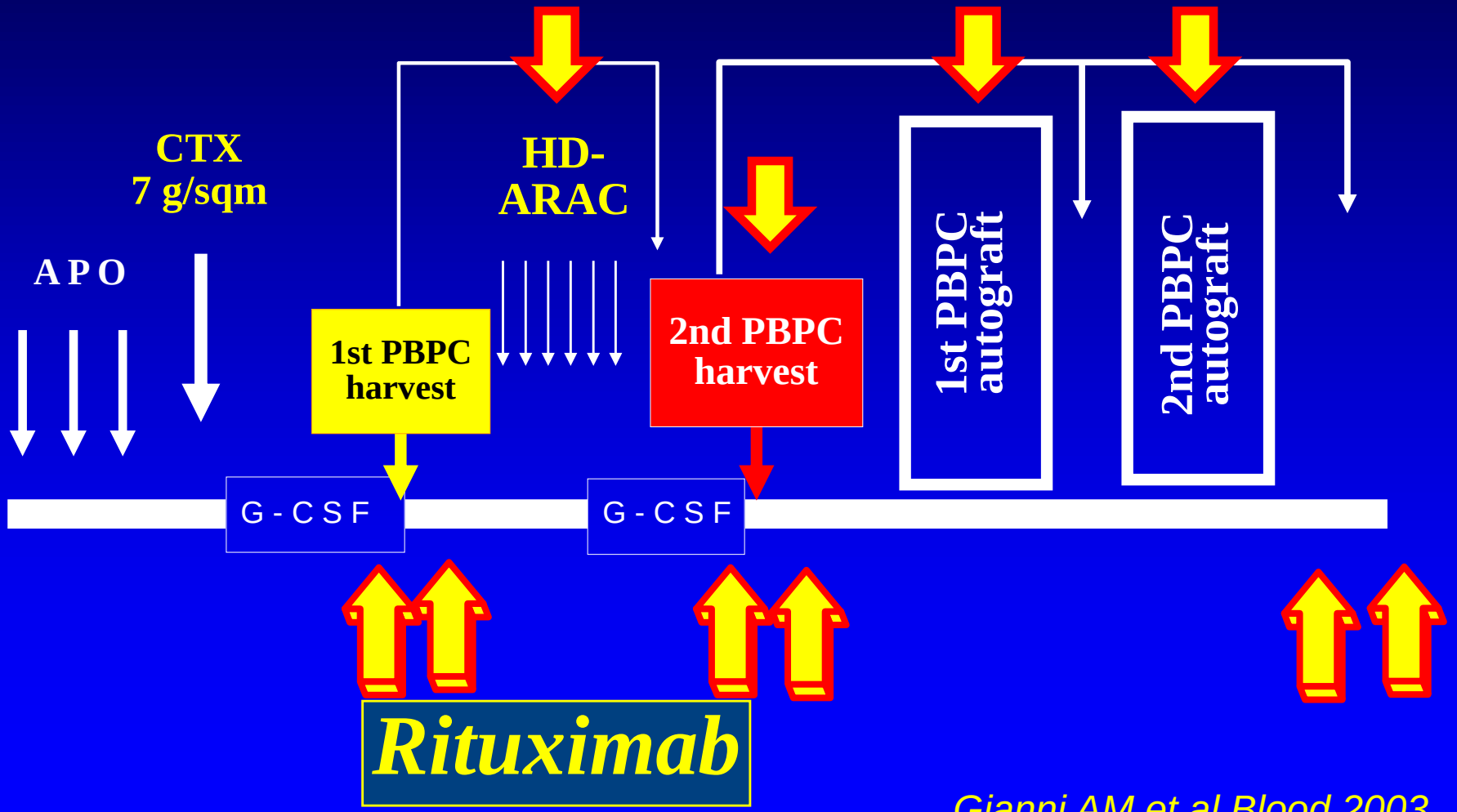






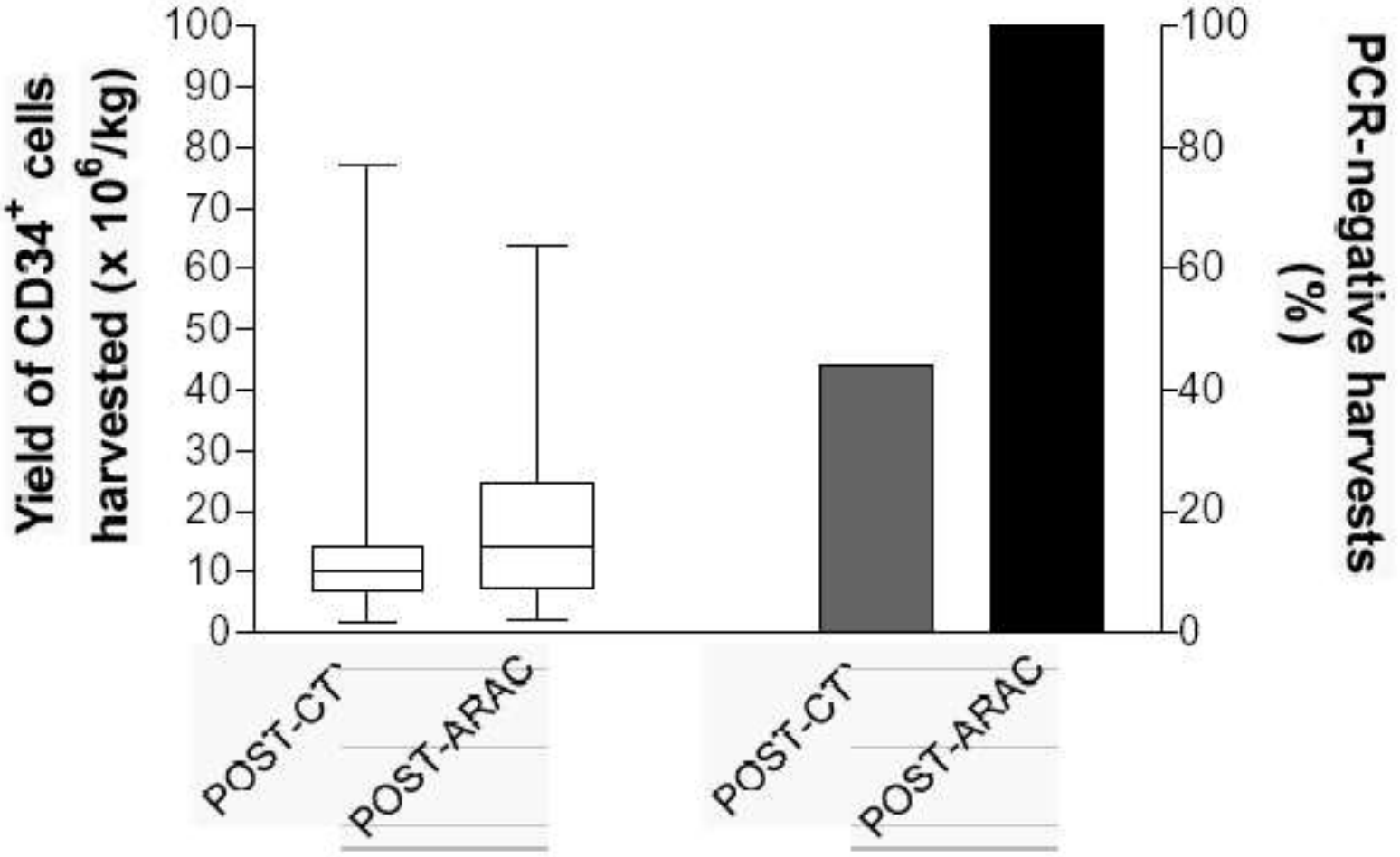
Cox regression: independent of MIPI, trial and treatment arm

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



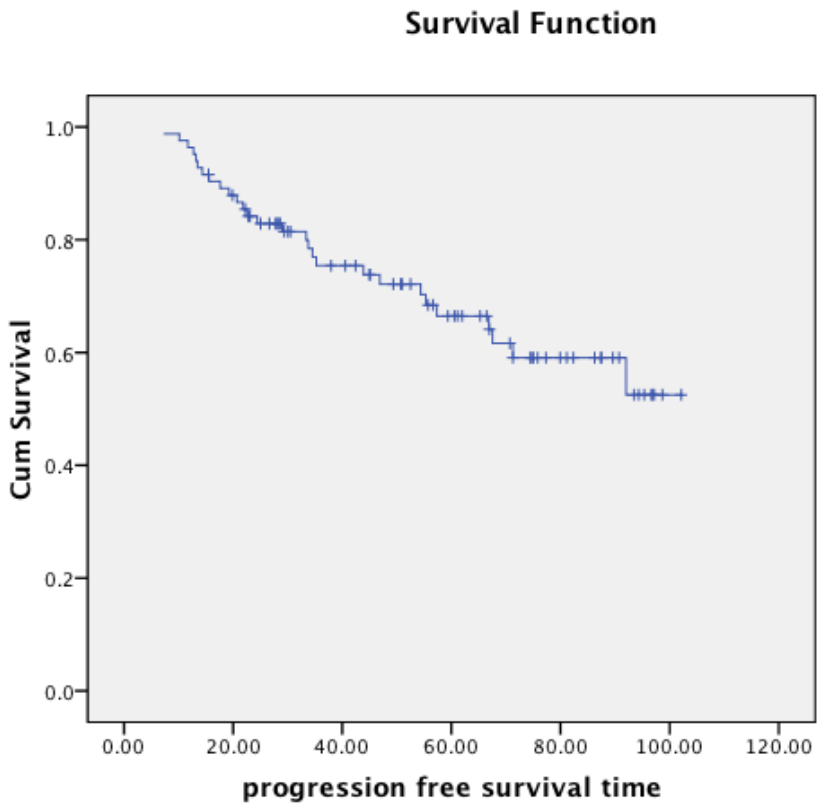
Gianni AM et al Blood 2003

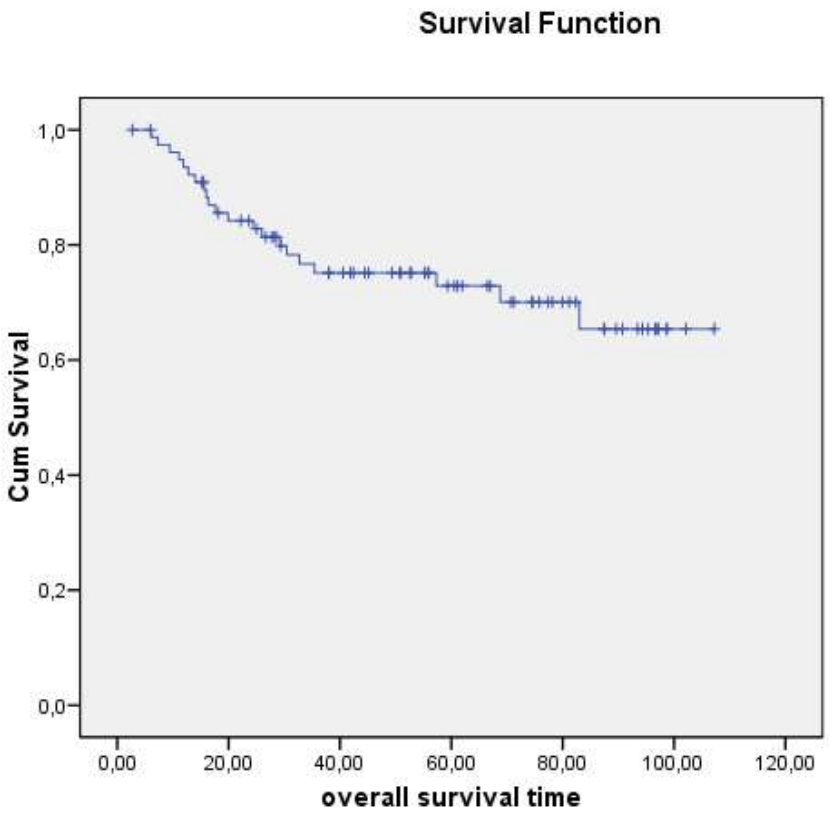
Quantity and quality of PBPC harvests after CT and AraC + Rituximab



Update of 83 MCL Patients Treated with R-HDS (Median follow-up 44 months, range 3-96 months)

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



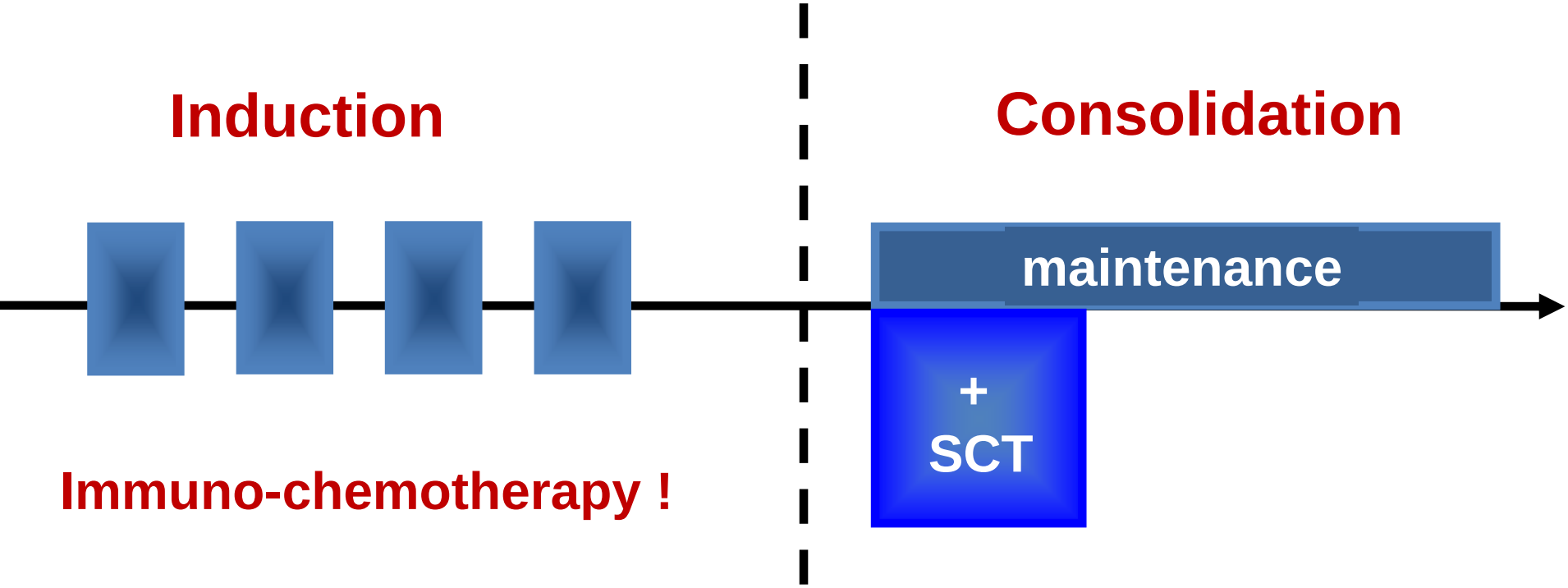


PFS at 2 yrs 84.4%; at 5yrs 66.3%

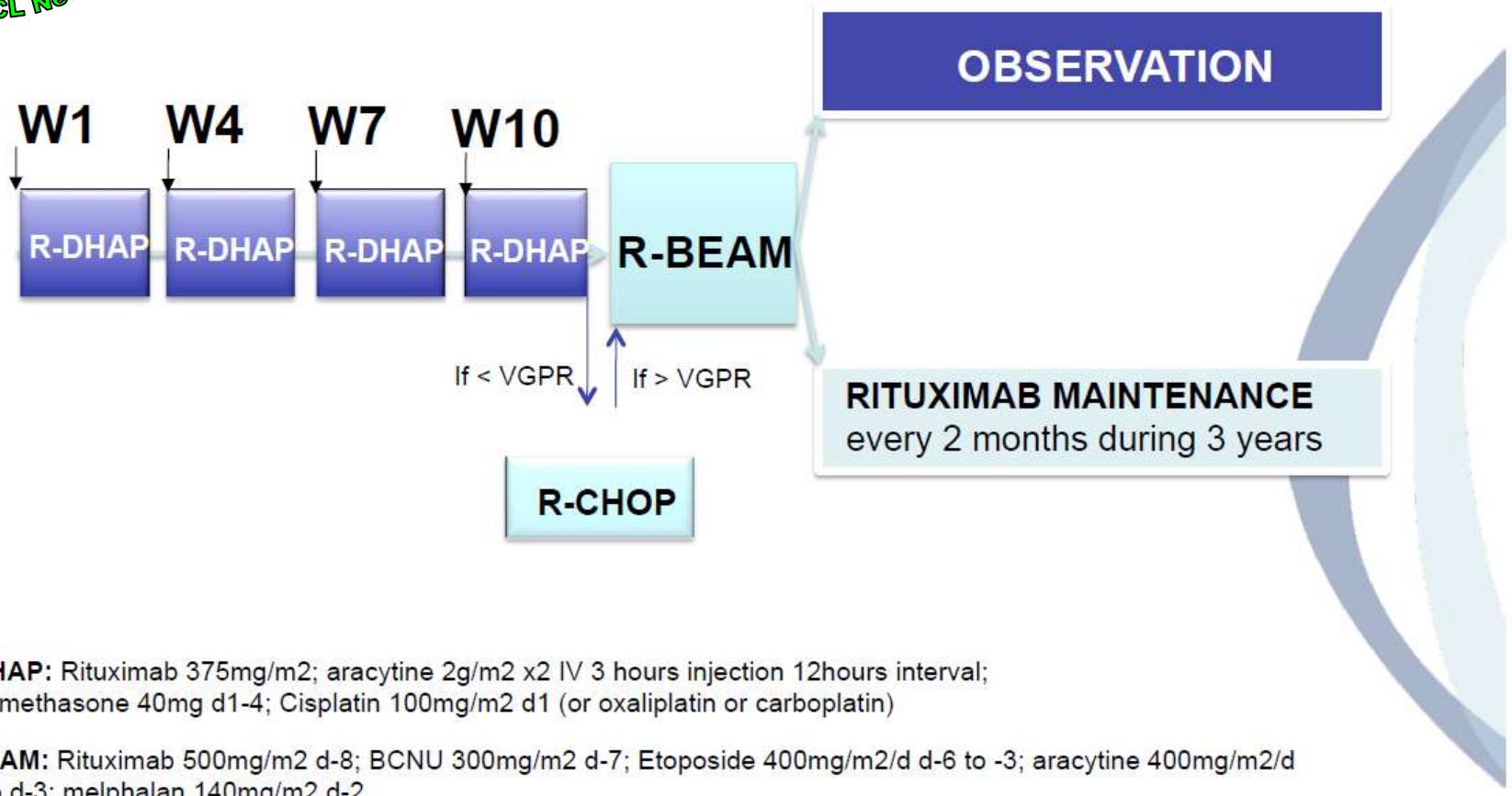
OS at 5 yrs 73%

Courtesy of Sergio Cortelazzo

Current optimal treatment for MCL



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

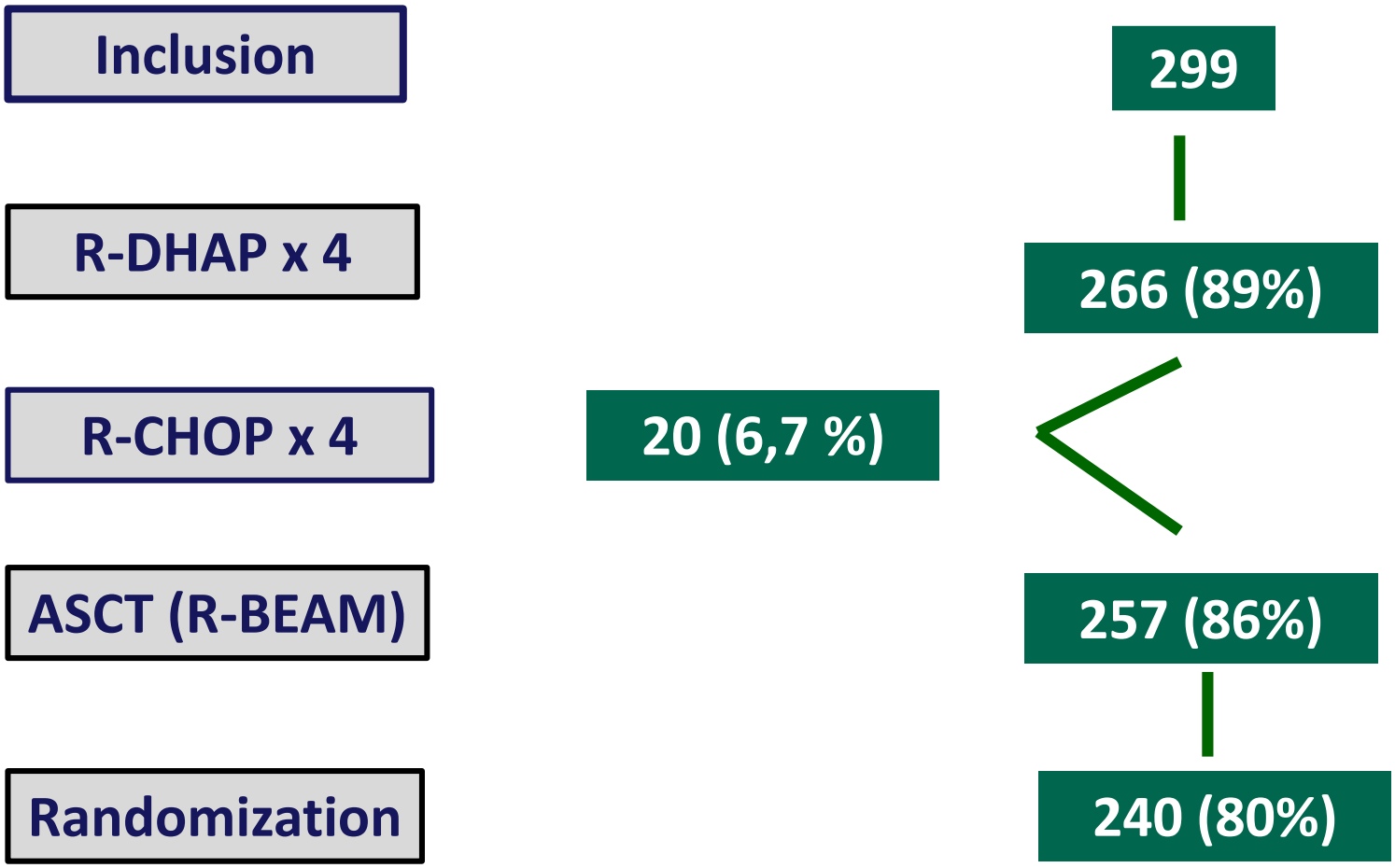
Le Gouill et al., ASH 2014; abstract 146 (oral presentation)

Objectives of the LyMa trial

- Primary objective is to demonstrate the superiority in terms of 4-years EFS of a rituximab maintenance compared to surveillance after ASCT for MCL patients aged 18-65y inclusive.

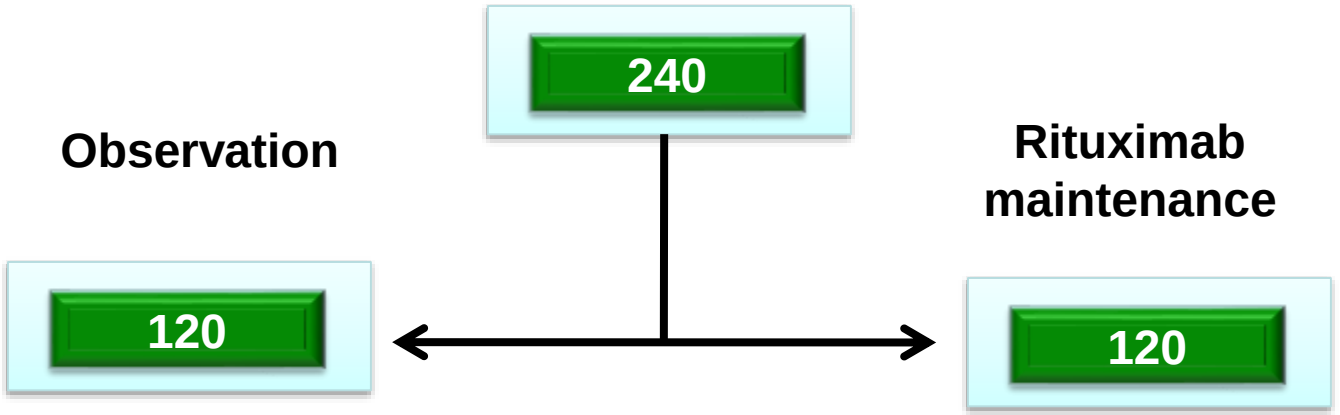
- Secondary objectives:
  - To evaluate PFS and OS
  - To evaluate response rates (CR, PR, SD, prog) after 4 courses of R-DHAP and after ASCT by Cheson 99 criteria, FDG-PET and MRD by molecular biology.

Study Flow Chart



Le Gouill et al., ASH 2014; abstract 146 (oral presentation)

Flow chart of randomized patients

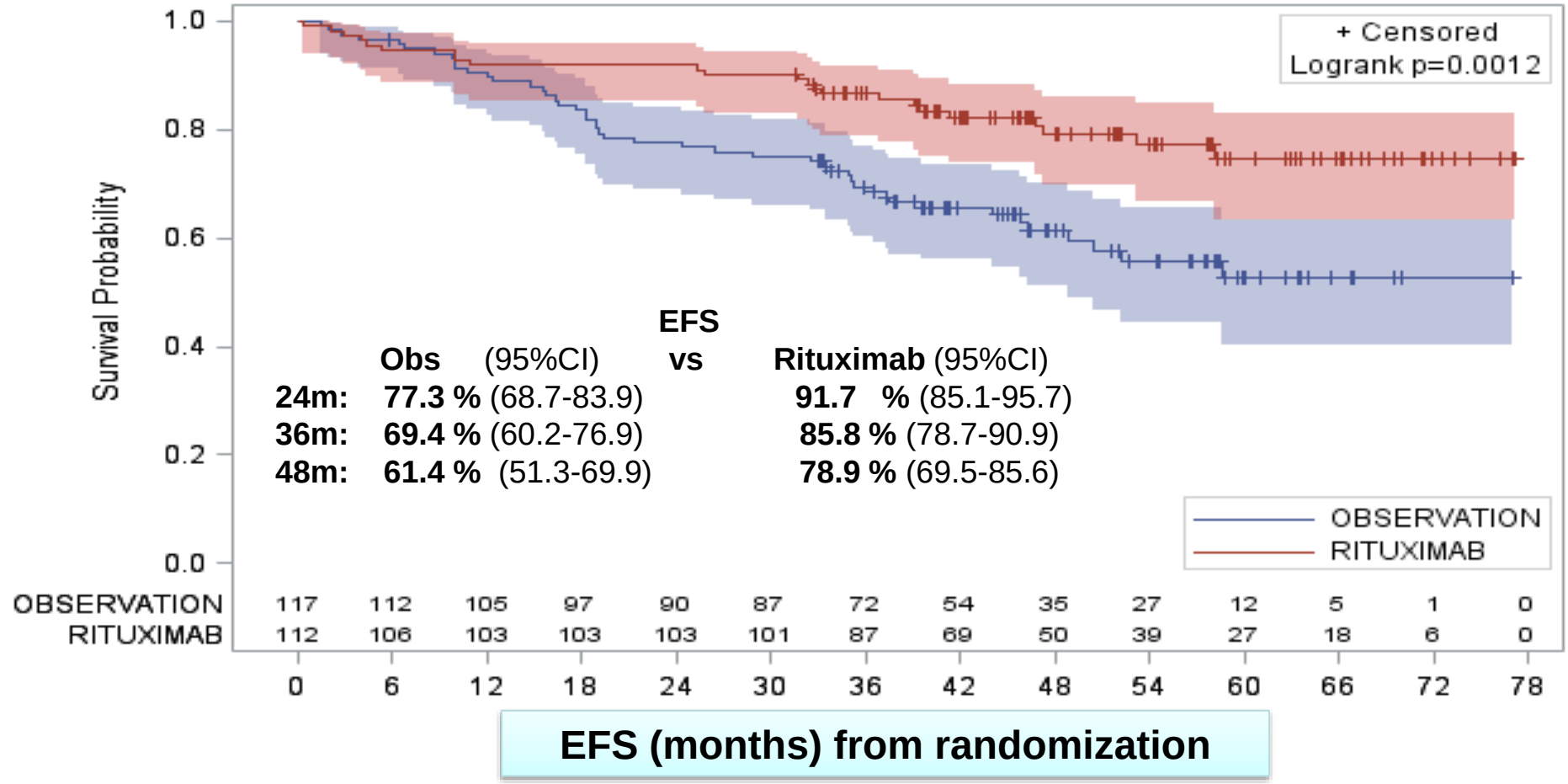


37 Progressions
25 Deaths
4 severe Infections

16 Progressions
14 Deaths
4 Severe infections
83 pts completed maintenance

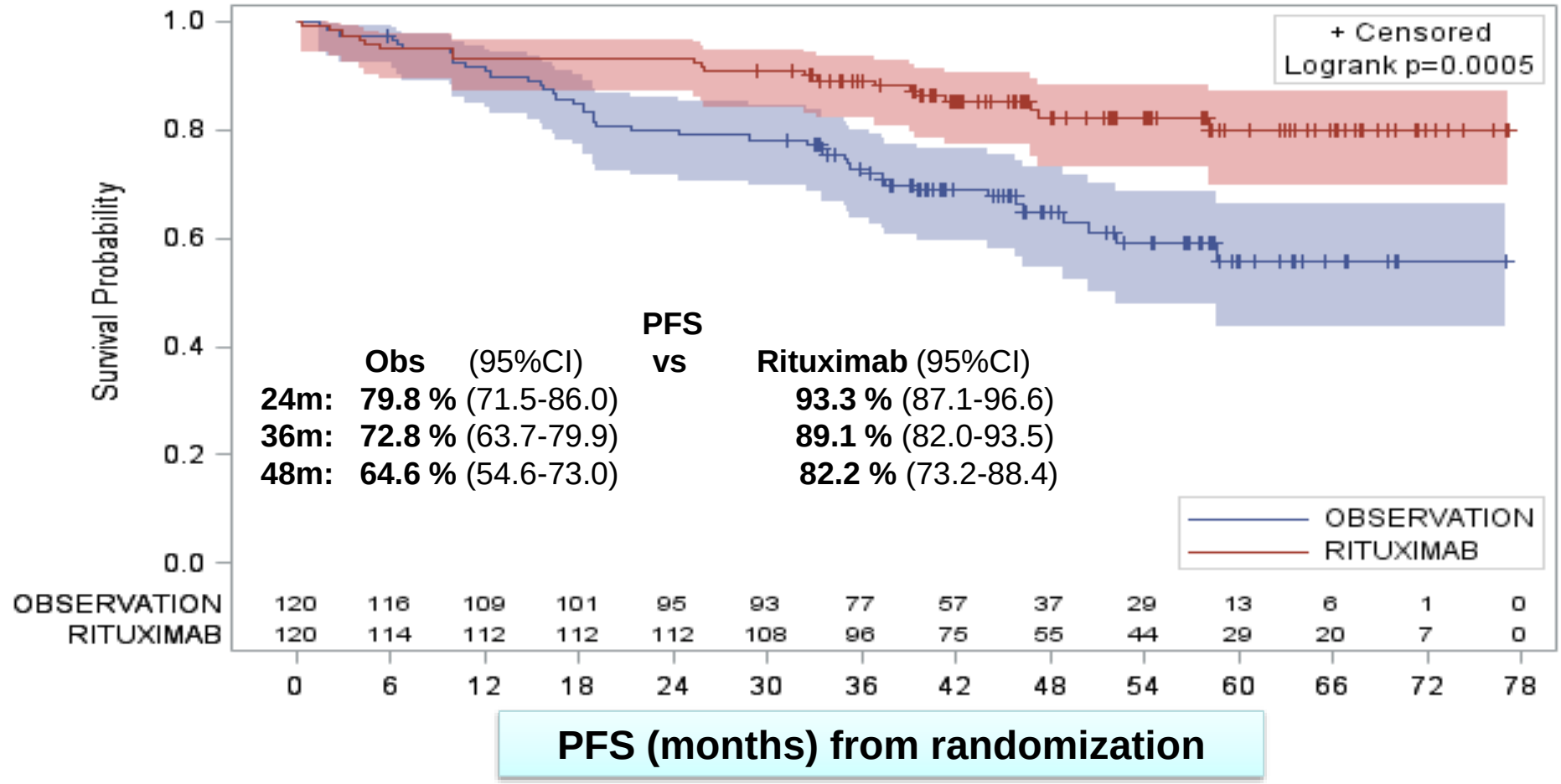
EFS from Randomization

mFU: 50.2m (46.4-54.2)



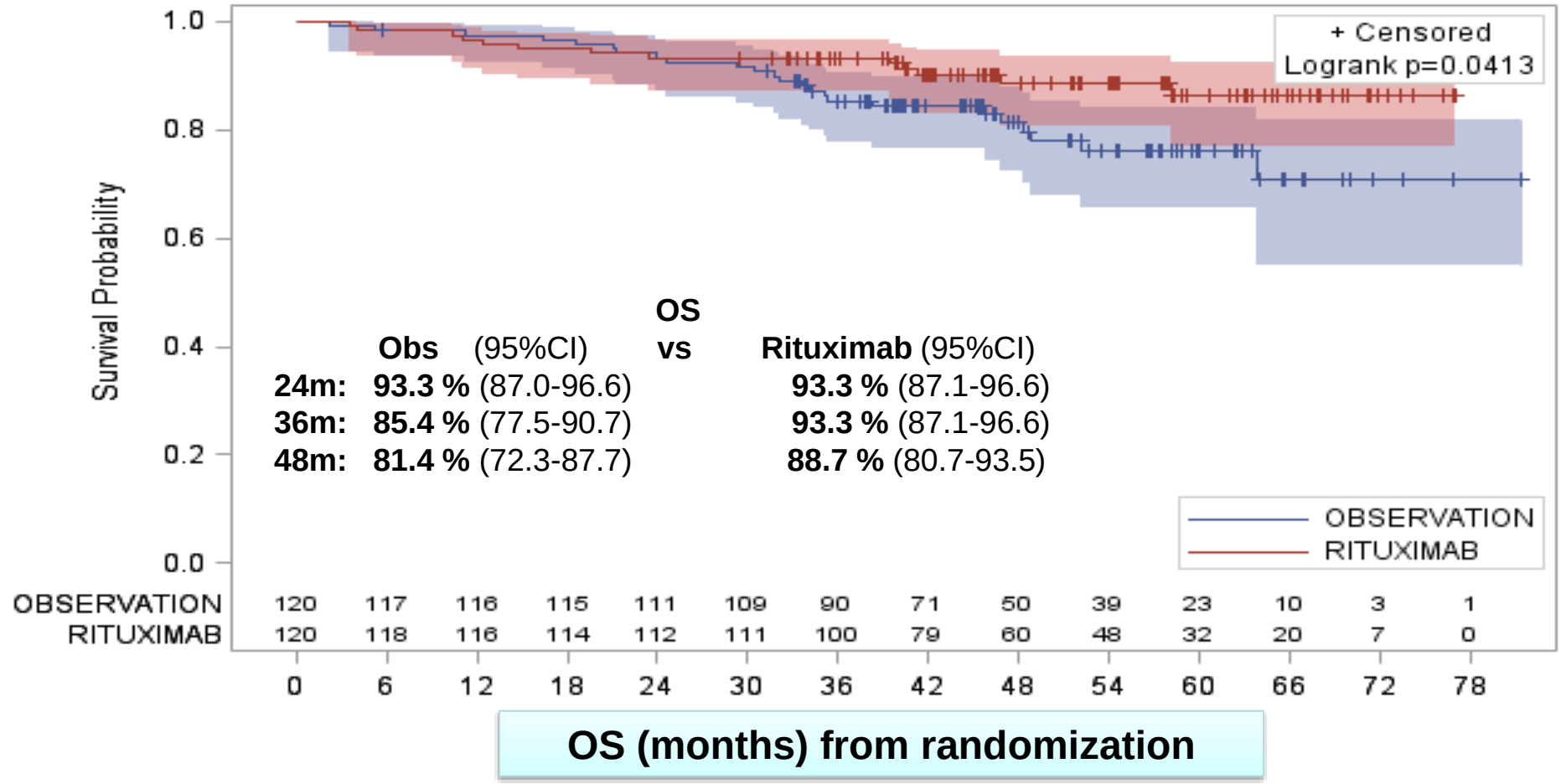
PFS from Randomization

mFU: 50.2m (46.4-54.2)



OS from Randomization

mFU: 50.2m (46.4-54.2)



CONCLUSIONS

- **The LyMa design (R-DHAP/R-BEAM) provides:**

  - high CR/CRu before and after ASCT (Le Gouill et al. ASH 2013)
  - Longterm disease control (PFS and EFS)
  - Prolonged OS

- **The final analysis demonstrates that Rituximab maintenance after ASCT prolongs:**

  - EFS: 78.9% vs 61.4% at 4 years (HR=0.457; 0.27-0.74; p= 0.0016)
  - PFS: 82.2% vs 64.6 % at 4 years (HR=0.4; 0.23-0.68; p= 0.0007)
  - OS : 88.7% vs 81.4 % at 4 years (HR=0.502; 0.25-0.98; p= 0.0454)

- **Rituximab maintenance (375mg/m2 every 2 months for 3 years) should be recommended to transplanted MCL patients**

- **Ancilary studies:**
  - Genomic (Le Bris et al. ASH 2016 Saturday, abstract 1745)

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

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

Untreated pts ≥ 18-60 yrs with MCL treated with mega R-CHOP + MTX/ Ara-C, CBV –ASCT (151 pts)

Random 102

BC
1.3mg^2 d.1,4,8,11, q 21 days for 4 cycles (n = 50)

BM
1.6 mg/m^2 d 1,8,15,22. Alternate months for 18 (n = 52)

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

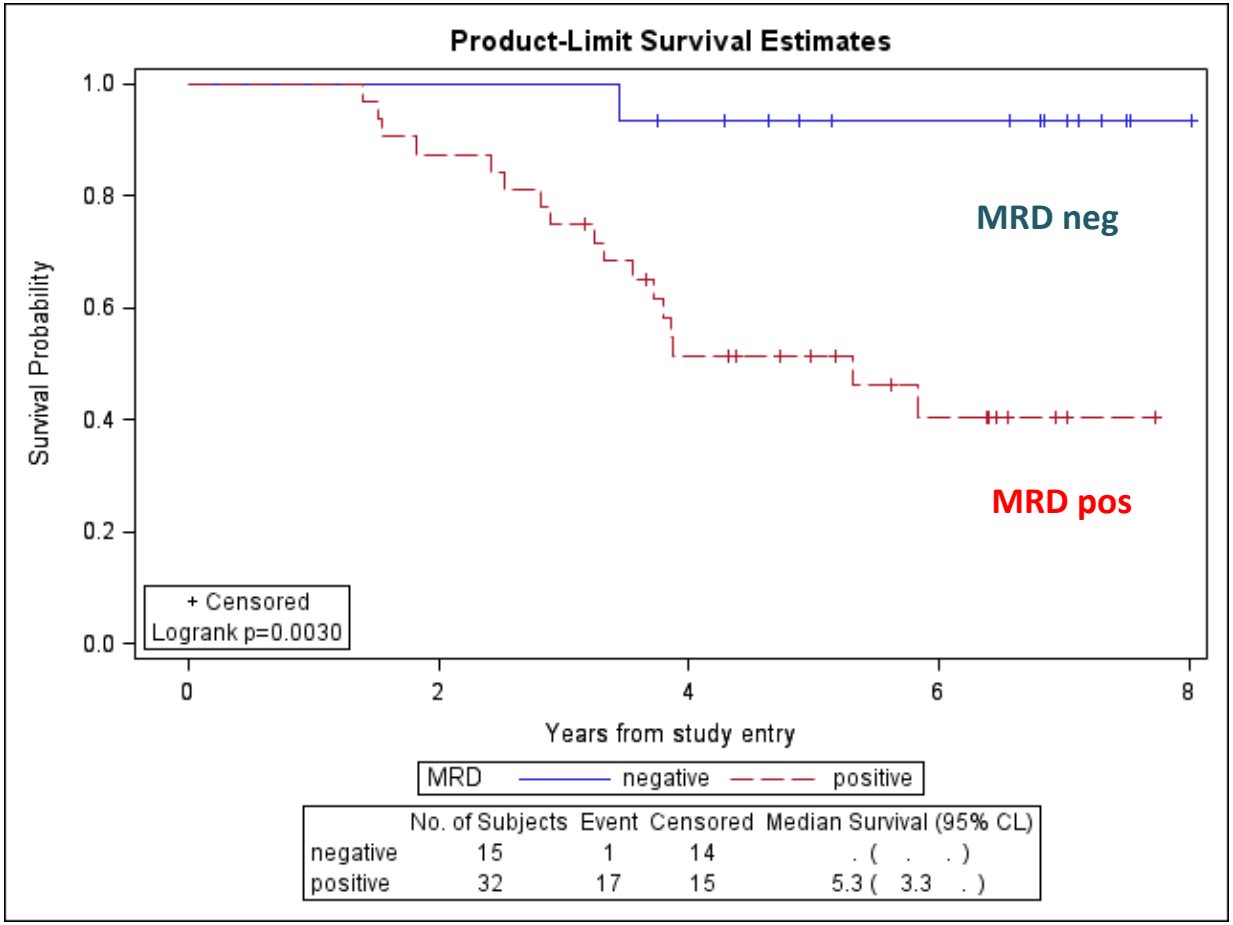
	BM (52)	BM (52)	BC (50)	BC (50)	Tot (102)	
Transplant	**Pre %**	**Post %**	**Pre %**	**Post %**	**Pre %**	**Post %**
CR+PR	63.5	82.7	52.0	82.0	57.8	81.4

	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) fater induction therapy and ASCT in younger MCL: CALGB (Alliance 50403)



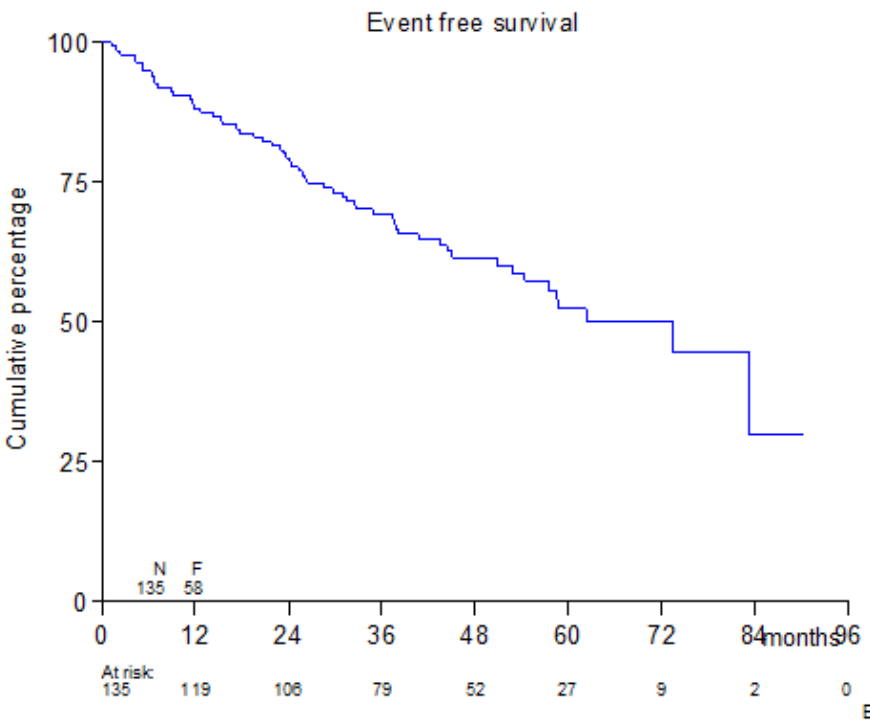
MRD negative is associate with an improved PFS

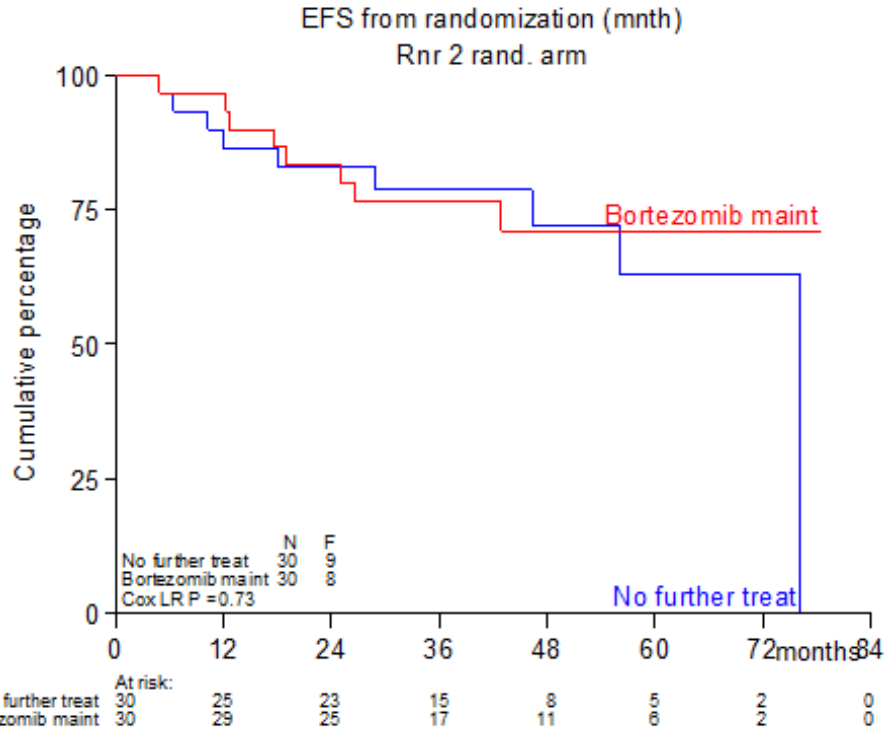
Kaplan D et al ASH 2015 oral session abs 337

Bortezomib maintenance therapy after induction with R-CHOP, ARA-C and ASCT in younger MCL patients

Tot MCL pts= 60

- **Bortezomib = 30**
- **No therapy = 30**

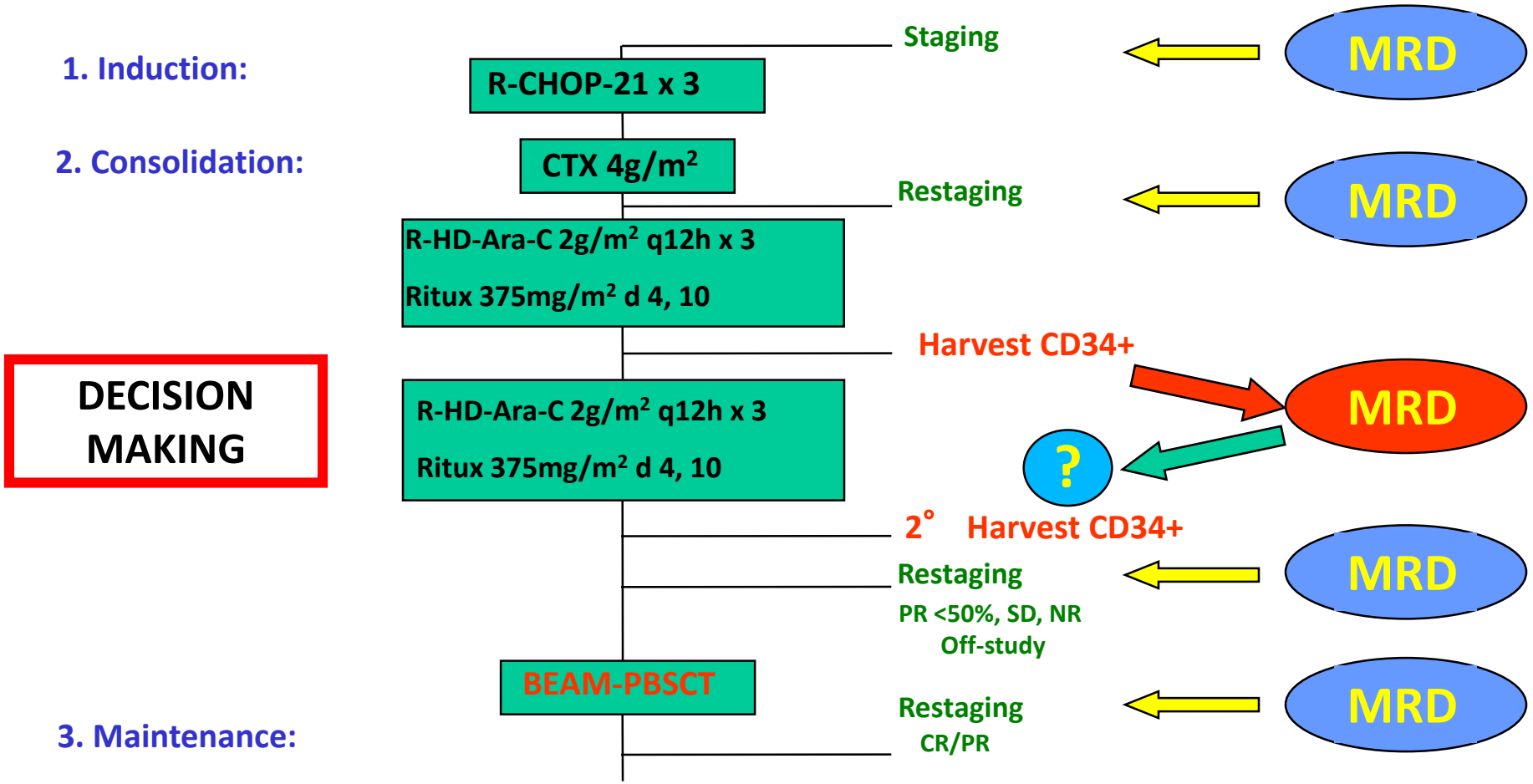




Doorduijn JK et al ASH 2015 oral session abs 339

MCL 0208: a new protocol for first line therapy

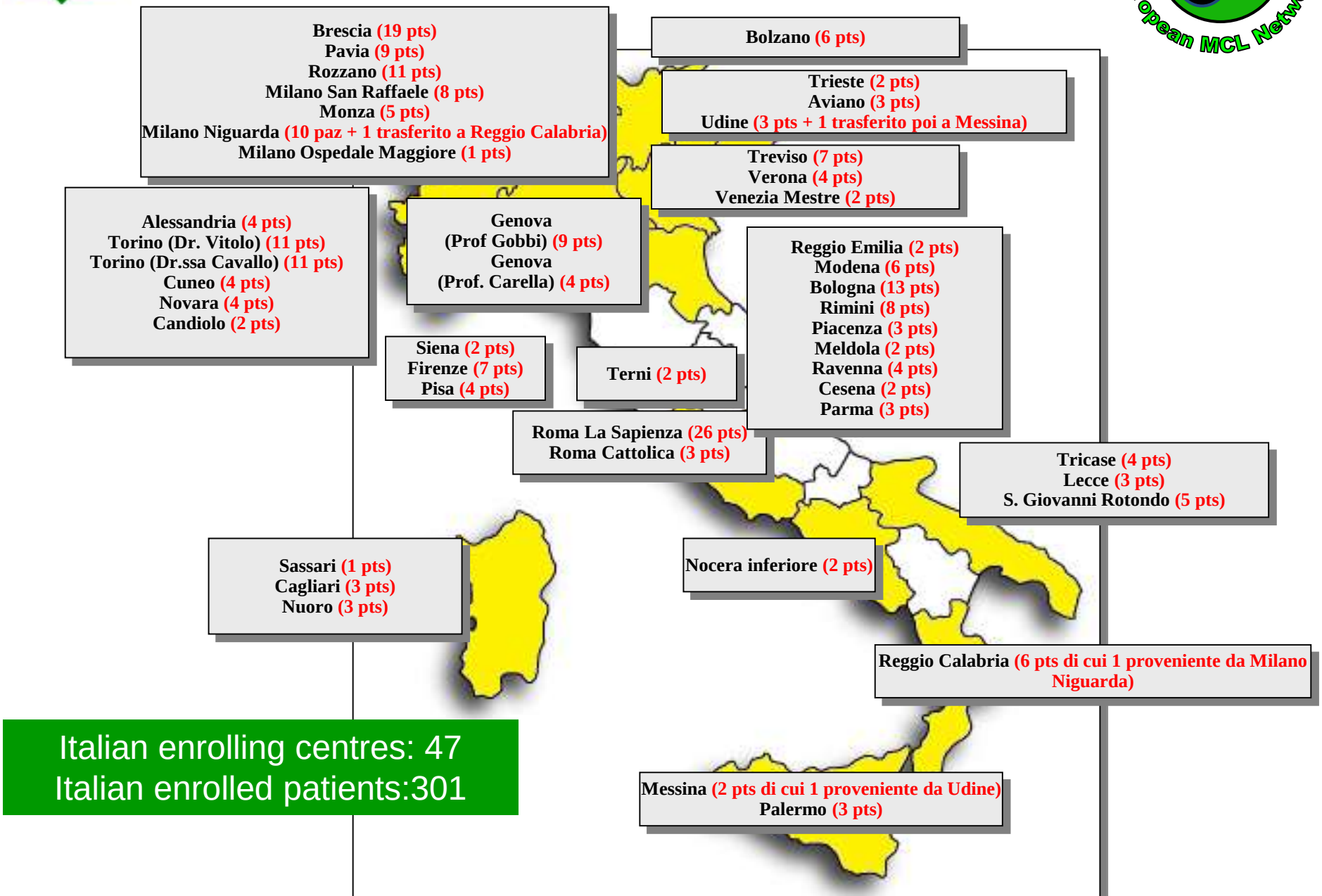
Phase 3, 1:1 Randomized, comparative, observation-controlled study after completion of intensive immunochemotherapy followed by ASCT



RANDOM observation vs. lenalidomide

15 mg (plts >100x10^9/ L) or 10 mg (plts 60-100x10^9/L) once daily on days 1-21 every 28 day cycle) for 24 months.

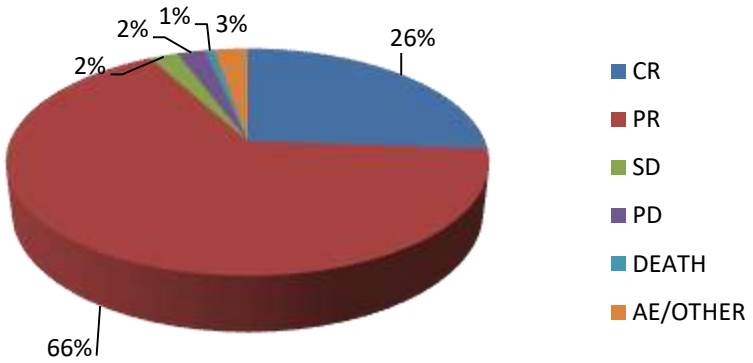
FIL MCL 0208



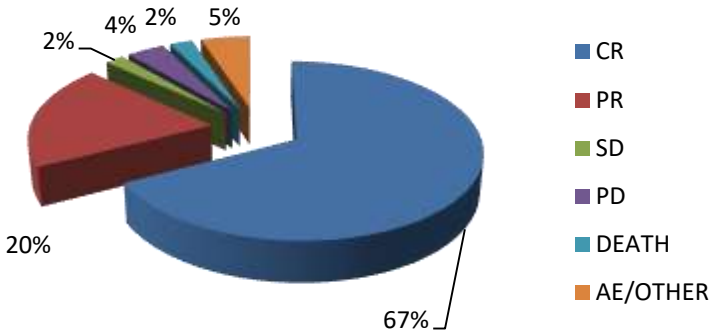
Italian enrolling centres: 47
Italian enrolled patients:301

MCL0208: response

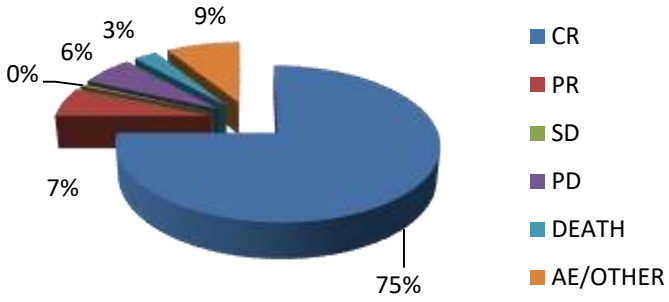
Restaging 1



Restaging 2



Restaging 3

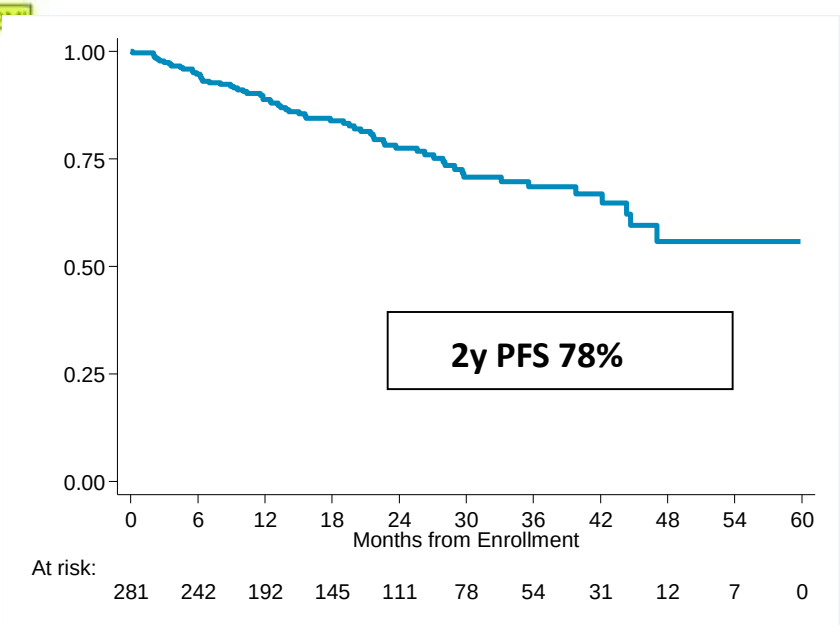


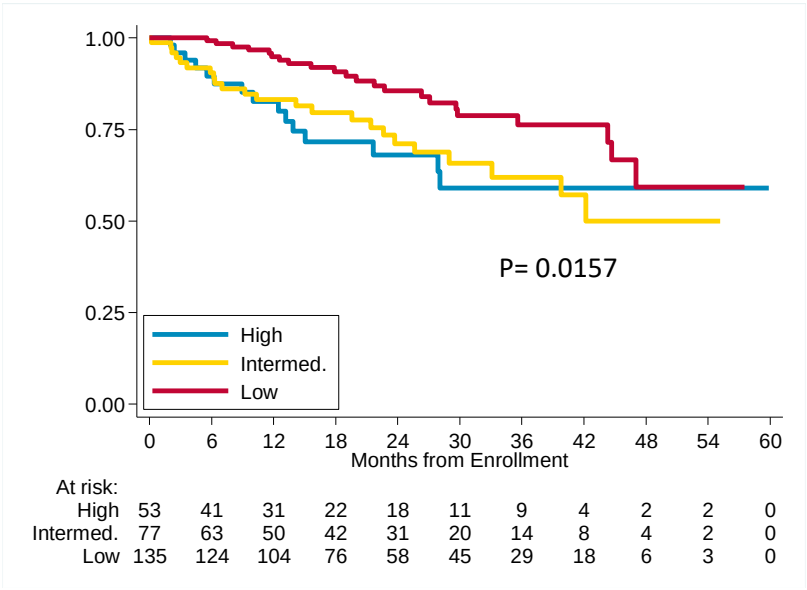
Final Response (including Intermediate+Final Response)	R-HDS+ASCT n = 248
CR/CRu	193(78%)
PR	22 (9%)
SD	3 (1%)
NR/PG	16 (6%)
Deaths during treatment*	7 (3%)
Interruption not due to PD or death	7(3%)

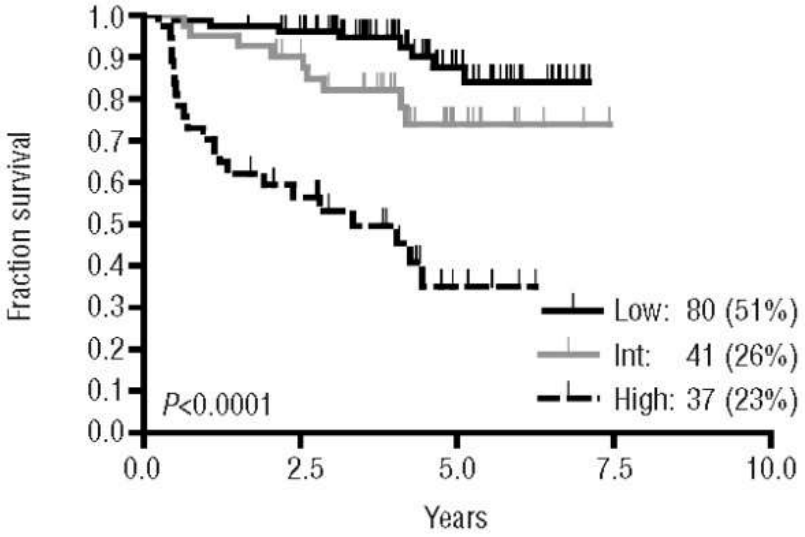
Cortelazzo et al EHA 2015 oral session

** One not related to treatment: road accident*

2-year PFS for MIPI low, intermediate and high





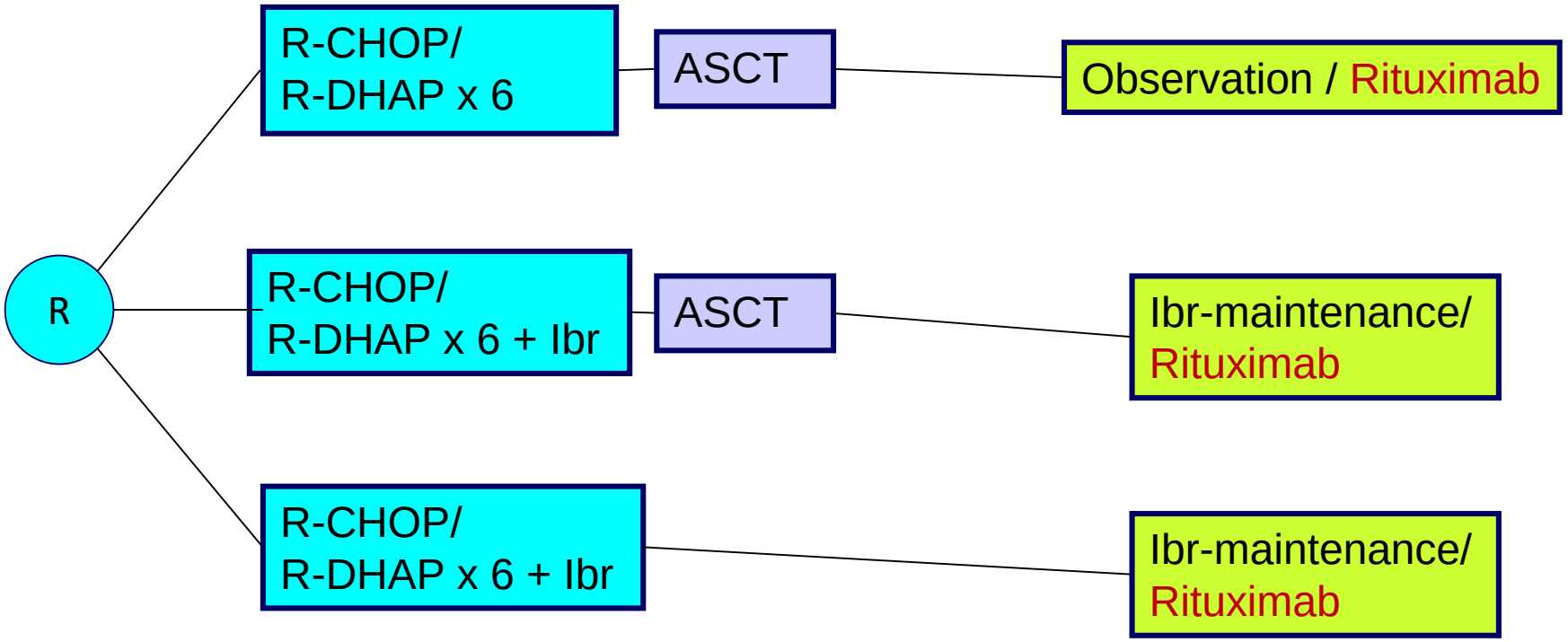


CG Gaisler, Haematologica, 2010

Cortelazzo et al EHA 2015 oral session

TRIANGLE Phase III Trial

MCL, 18 to 65 years old



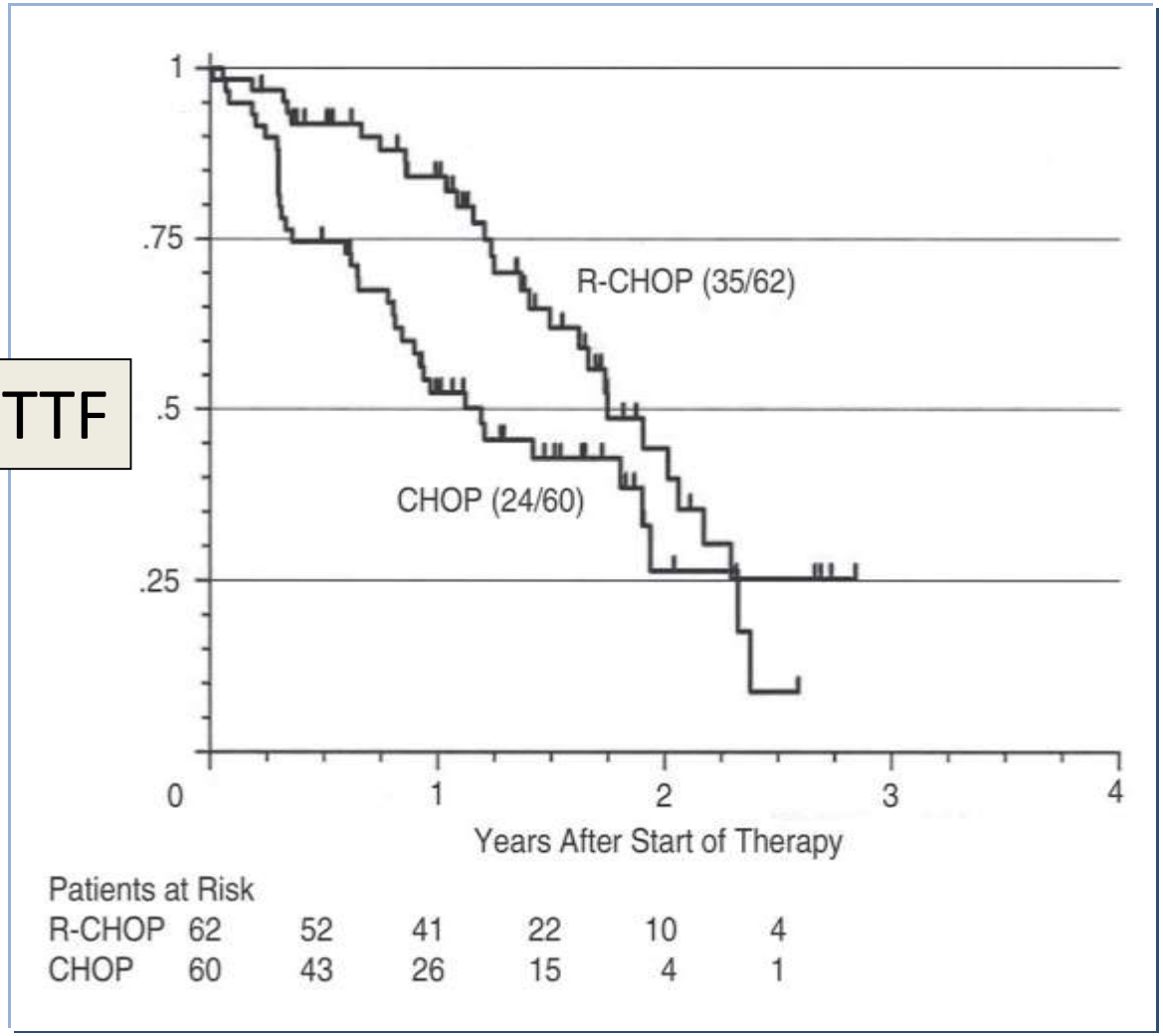
on behalf of European MCL Network

Key issues (1st line younger)

- Intensified protocols containing Rituximab HD-Ara-C are the standard and ensure prolonged remissions
- ASCT remains the standard outside HyperCVAD or investigational therapies
- Maintenance after auto seems feasible and improve overall survival.
- New targeted therapies to be integrated soon

Therapy of elderly (≥65 year)

CHOP vs Rituximab-CHOP



	ORR (%)	CR (%)
R-CHOP	**94**	**34**
CHOP	**75**	**7**

Median age 61 (1/3>65)

No difference in DOR or OS*

Lenz et al, JCO 2005

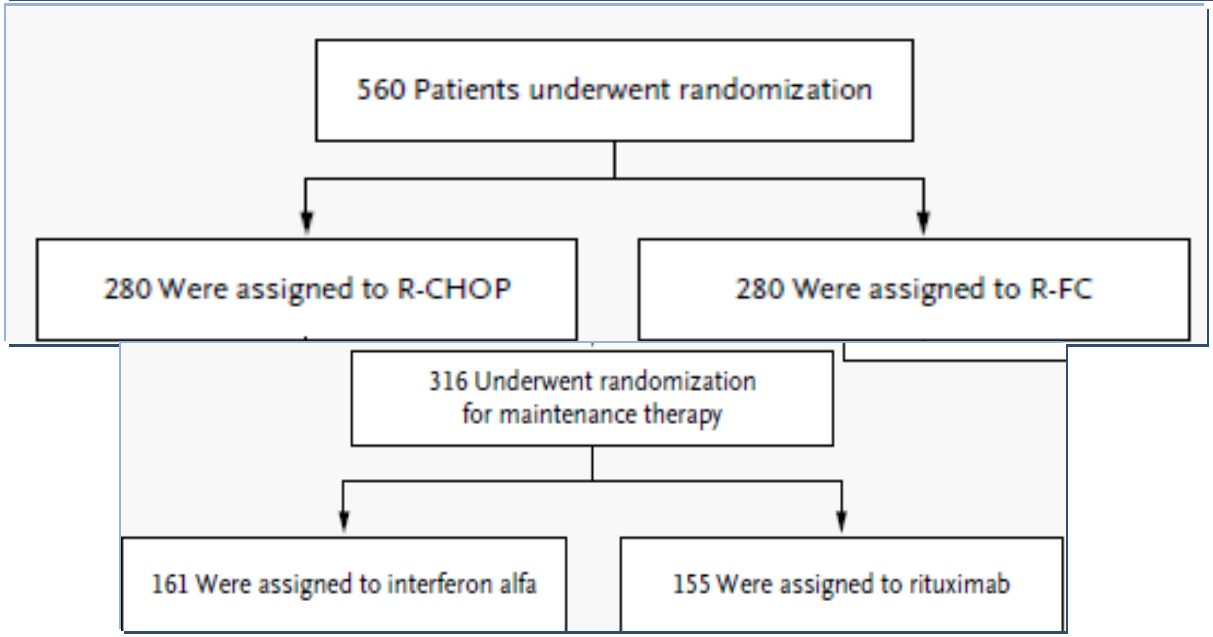
The NEW ENGLAND JOURNAL of MEDICINE

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

≥60 years



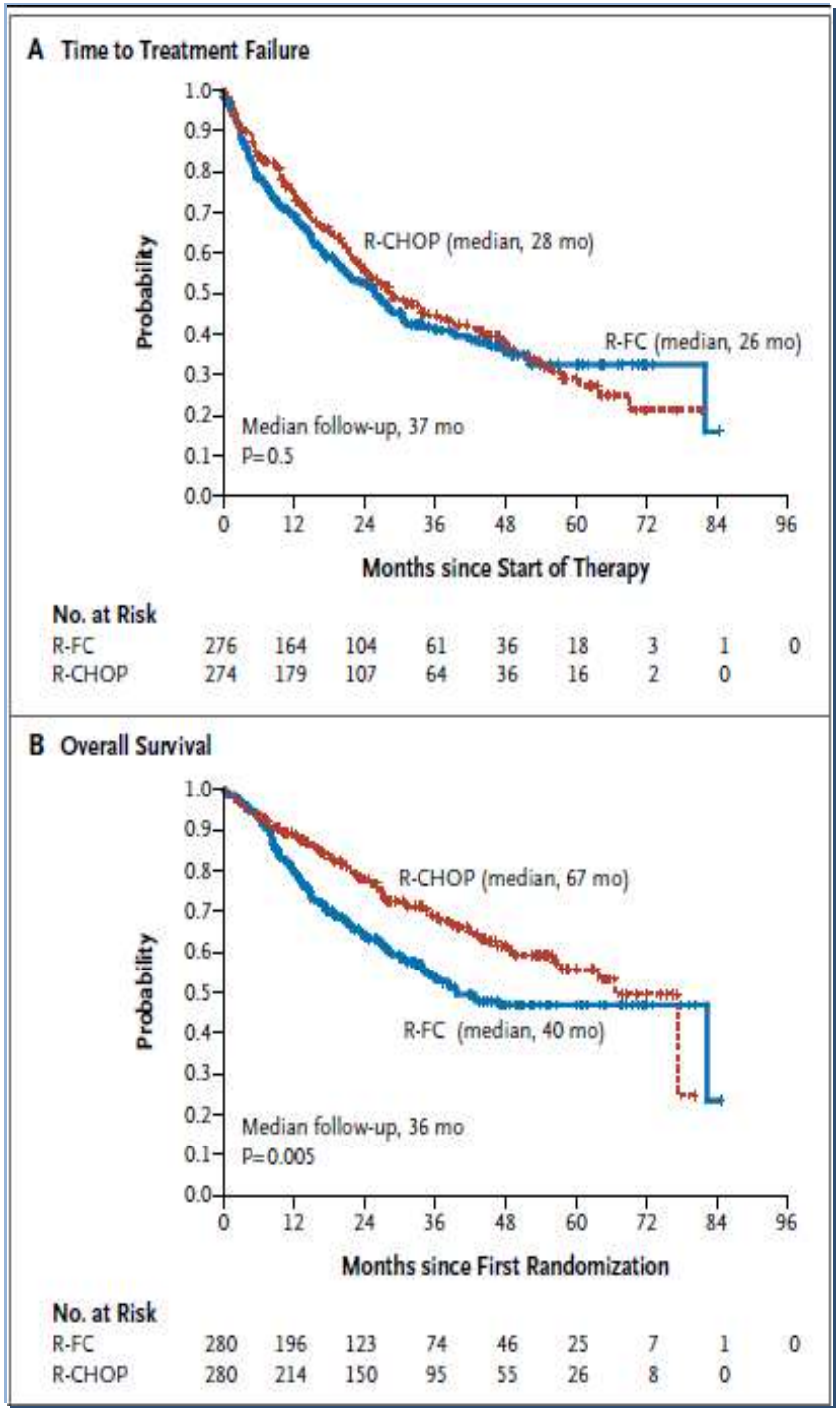
1st: is Flu-regimen better than CHOP?

2nd: does maintenance with Rituximab prolong remission?

R-CHOP vs R-FC in elderly patients with MCL

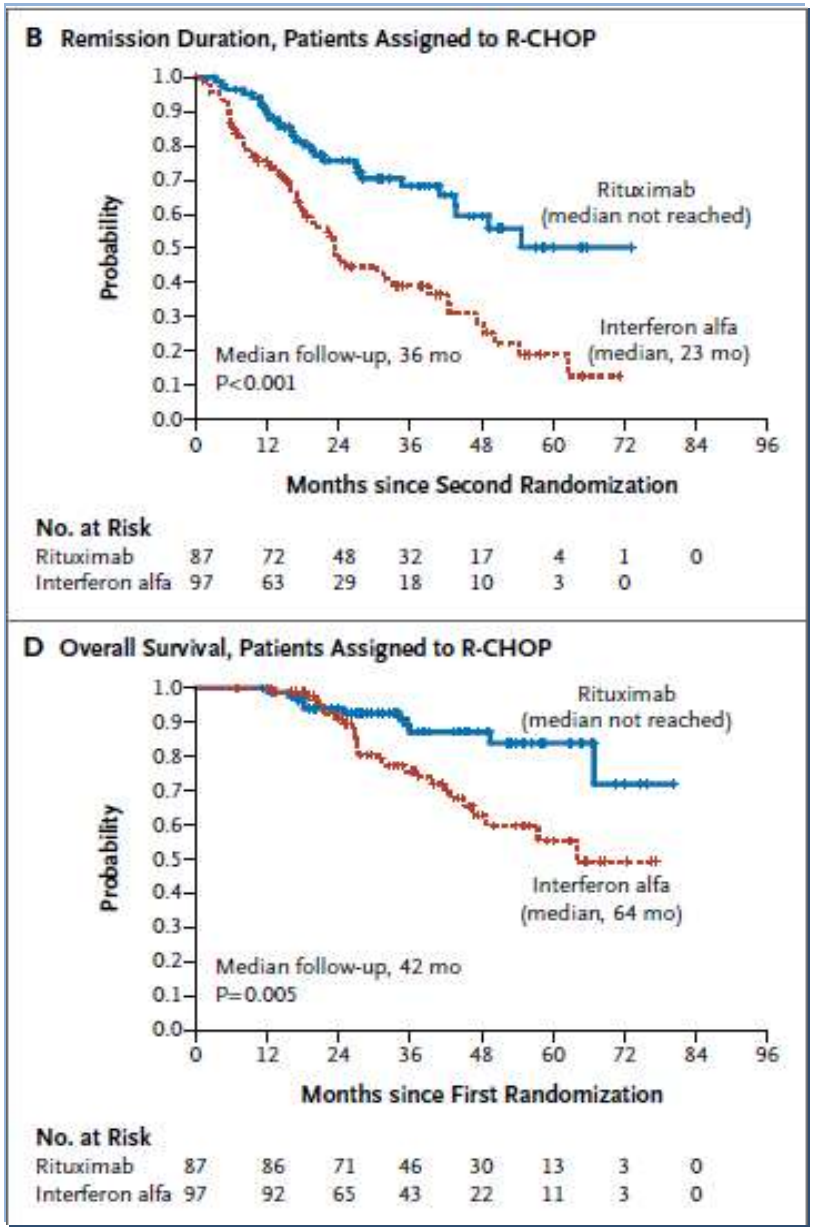
	ORR (%)	CR (%)
R-CHOP	**86**	**34**
R-FC	**78**	**40**
	P=0.06	P=0.10

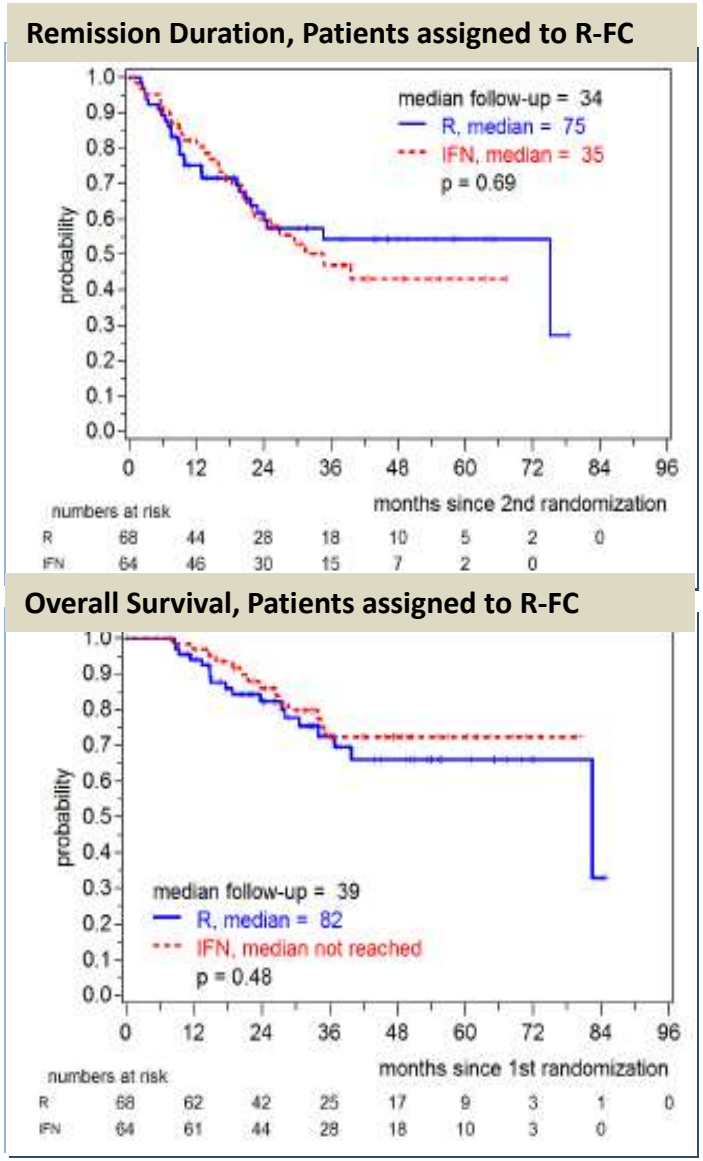
Cause of death	R-FC	R-CHOP
Died in CR/PR	10%	4%
Infections	7%	4%
Second cancer	3%	1%



Kluin-Nelemans HC et al. NEJM 2012;367:520-31

Maintenance therapy: Rituximab vs Interferon α





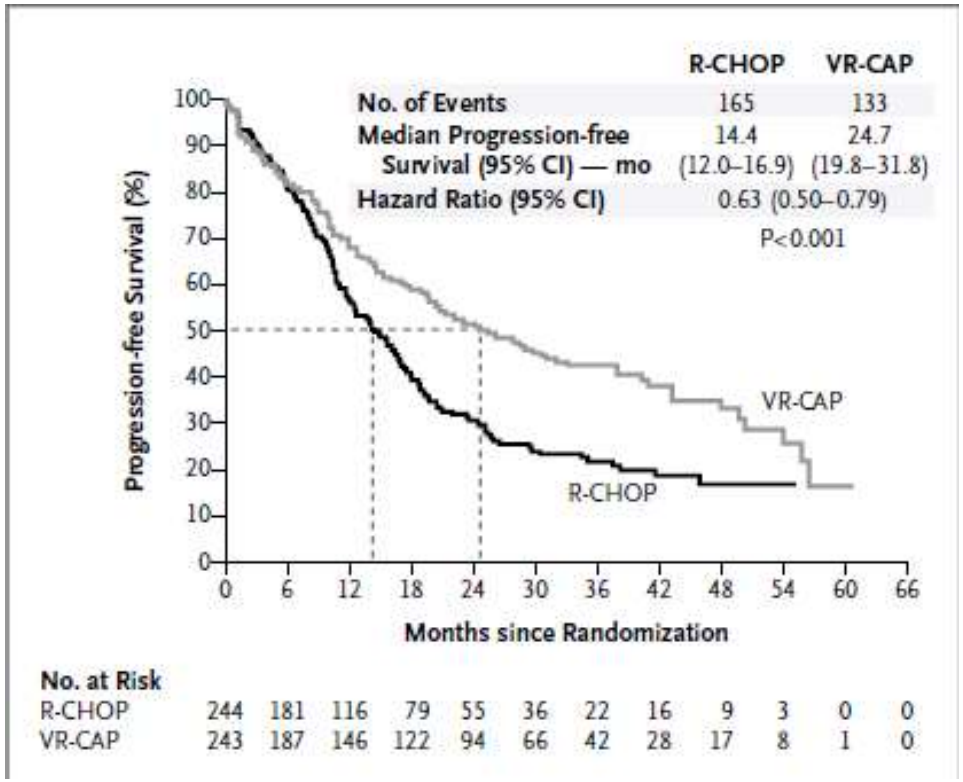
Kluin-Nelemans HC et al. NEJM 2012;367:520-31

The NEW ENGLAND JOURNAL of MEDICINE

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., Ting Liu, M.D., Olga Samoilova, M.D., Halyna Pylypenko, M.D., Gregor Verhoef, M.D., Ph.D., Noppadol Siritanaratkul, M.D., Evgenii Osmanov, M.D., Ph.D., Julia Alexeeva, M.D., Ph.D., Juliana Pereira, Ph.D., Johannes Drach, M.D., Jiri Mayer, M.D., Xiaonan Hong, M.D., Rumiko Okamoto, M.D., Lixia Pei, Ph.D., Brendan Rooney, Ph.D., Helgi van de Velde, M.D., Ph.D., and Franco Cavalli, M.D., for the LYM-3002 Investigators*



	ORR (%)	CR (%)
R-CHOP	89	42
VR-CAP	92	53

No difference in OS.

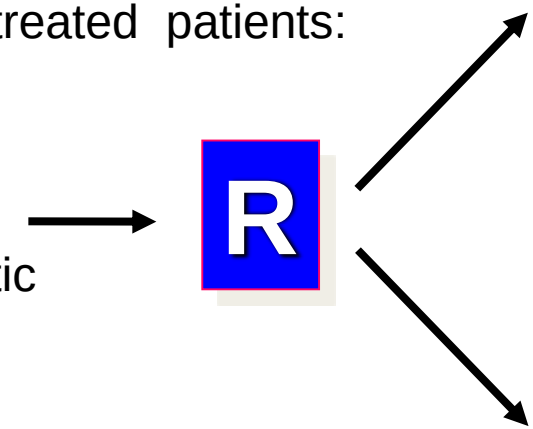
VR-CAP was more effective than R-CHOP in patients with newly diagnosed MCL but at the cost of increased hemo-toxicity.

Robak T et al, NEJM 2015

Bendamustine-Rituximab (B-R) *vs* *R*-CHOP

StiL NHL 1-2003

In previously untreated patients:
Follicular
Waldenströms
Marginal zone
Small lymphocytic
Mantle cell



Bendamustine-Rituximab

CHOP-Rituximab

Studiengruppe Indolente Lymphome

Bendamustine 90 mg/m^2 day 1+2 + R day 1, max 6 cycles, q 4 wks.

CHOP-R, max 6 cycles, q 3 wks.

Rummel MJ et al. Lacet Oncology 2013

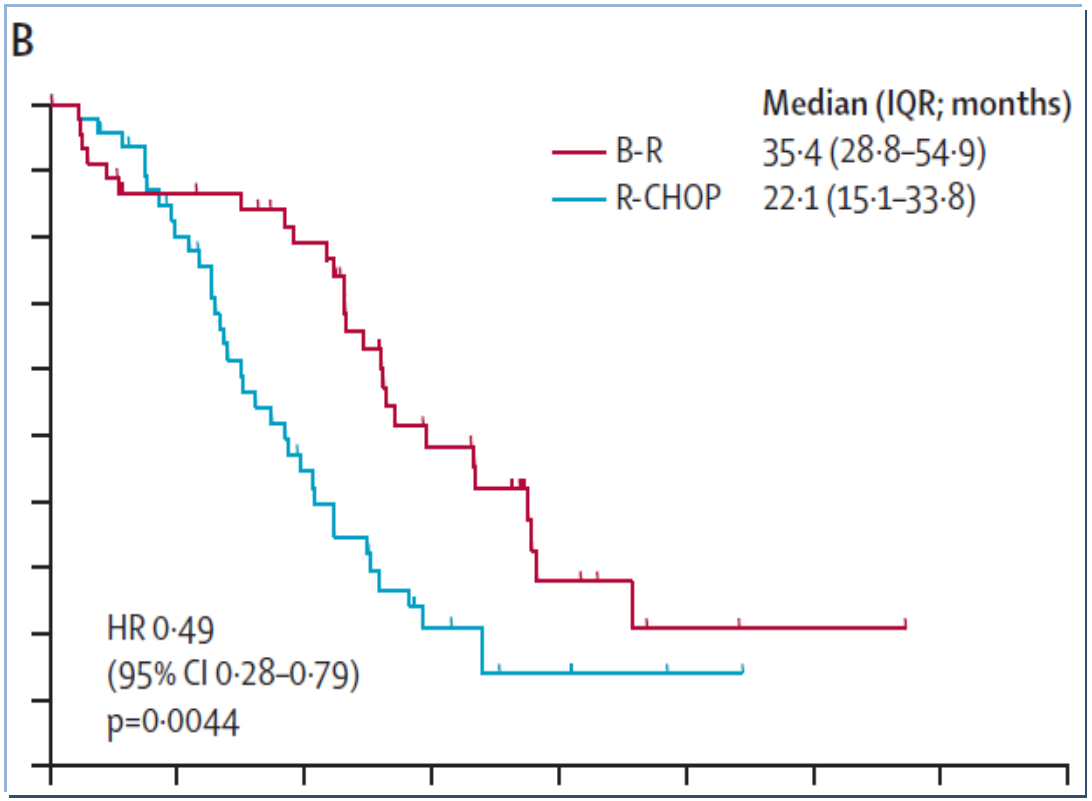
Bendamustine-Rituximab (B-R) *vs.R-* CHOP

549 patients randomized. 513 patients evaluable for response and toxicity

		B-R	CHOP-R	Age (median)
Total	**n**	**260**	**253**	**64**
Follicular	**54 %**	**139**	**140**	**60**
Mantle cell	**18 %**	**45**	**48**	**70**
Marginal zone	**13 %**	**37**	**30**	**66**
Waldenströms	**8 %**	**22**	**19**	**64**
SLL	**4 %**	**10**	**11**	**68**
Unclassifiable	**2 %**	**7**	**5**	**69**

Rummel MJ et al. Lancet 2013

Bendamustine-Rituximab (B-R) *vs. R-* CHOP

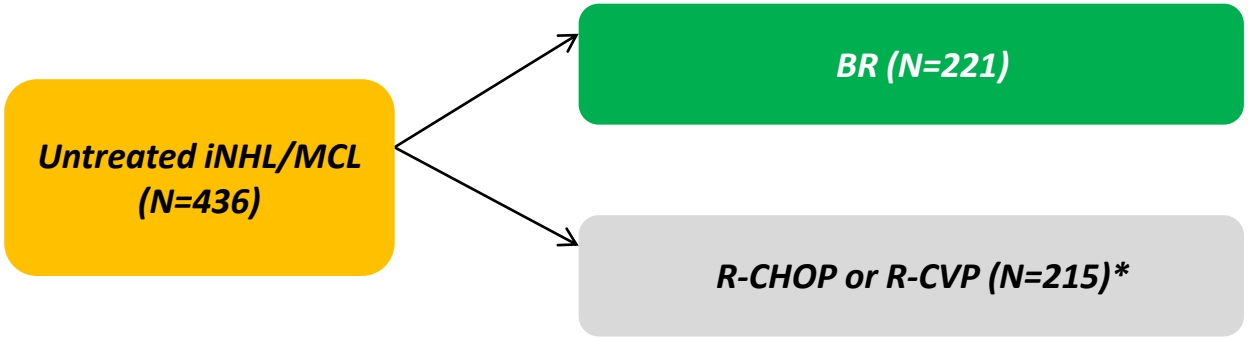


	B-R (n=261)	R-CHOP (n=253)	p value
Alopecia	0	245 (100%)*	<0·0001
Paresthesia	18 (7%)	73 (29%)	<0·0001
Stomatitis	16 (6%)	47 (19%)	<0·0001
Skin (erythema)	42 (16%)	23 (9%)	0·024
Skin (allergic reaction)	40 (15%)	15 (6%)	0·0006
Infectious episodes	96 (37%)	127 (50%)	0·0025
Sepsis	1 (<1%)	8 (3%)	0·019

Rummel MJ et al. Lancet 2013;381:1203-10

BR vs R-CHOP/R-CVP for untreated iNHL/MCL: phase III study (BRIGHT)

Design



Baseline characteristics:

Median age: 60/58 yrs

Histology: 83% iNHL; 17% MCL

Ann Arbor: 63% stage IV

**R-CHOP n=99; R-CVP n=116*

Regimens:

BR:	***Bendamustine 90 mg/m^2, d1 & 2, q28d*** ***Rituximab 375 mg/m^2, d1, q28d***
R-CHOP/R-CVP:	***Standard dosing (q21d)***

Adapted from Flinn IW et al. ASH 2012; abstract 902.

BR vs R-CHOP/R-CVP for untreated iNHL/MCL: phase III study (BRIGHT)

Results

Response rates (%)	BR	R-CHOP/R-CVP	p value
ORR	94	84	–
CR	31	25	0.0225*
iNHL	27	23	0.1289*
MCL	51	24	0.0180†
Most common AEs (N)			
Nausea	139	102	–
Fatigue	113	107	–
Alopecia	8	74	–
Most common grade 3–4 haematological AEs (N)			
Lymphopenia	137	64	–
Neutropenia	98	151	–

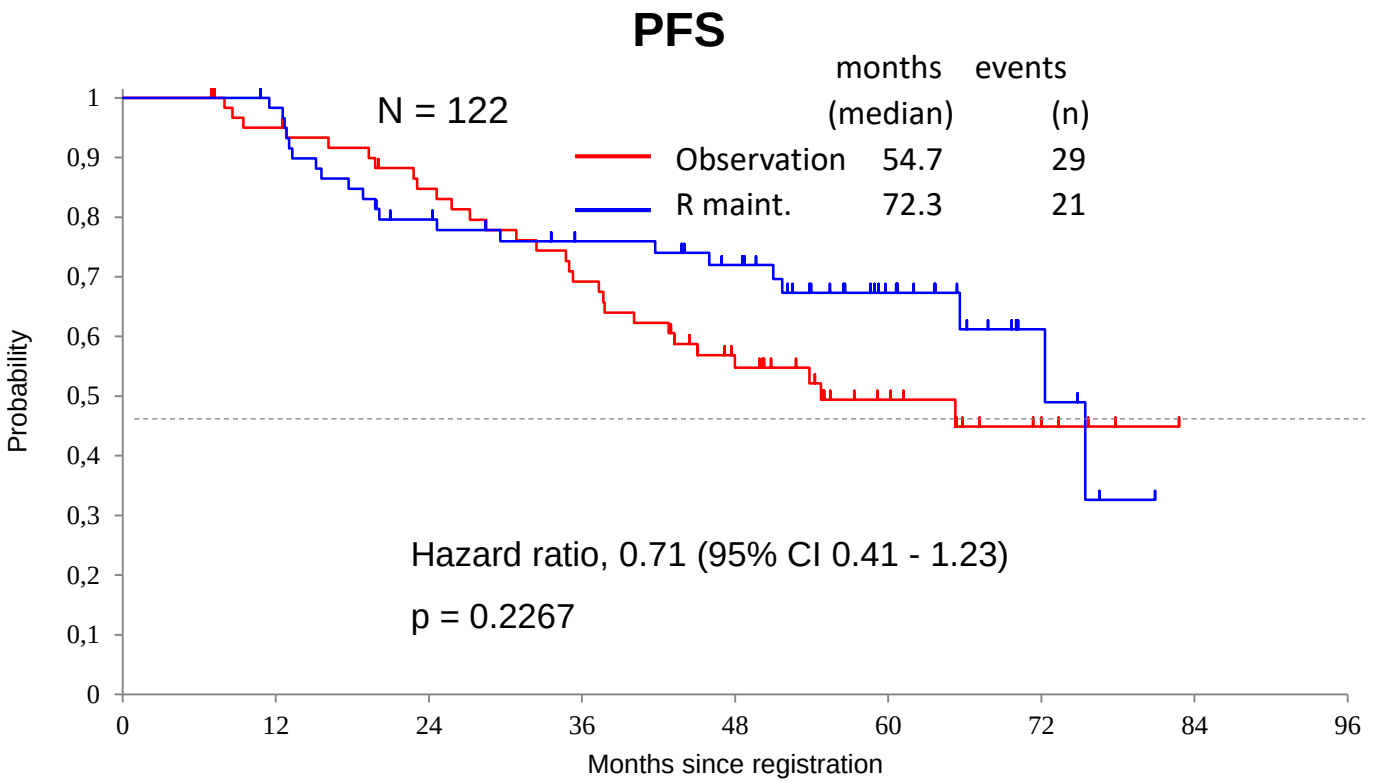
Adapted from Flinn IW et al. ASH 2012; abstract 902.

MAINTAIN Trial

Subgroup Analysis, randomized Phase 2

Rituximab maintenance vs. Observation following B-R in Patients with Mantle Cell Lymphoma

(58.6 months median follow-up)

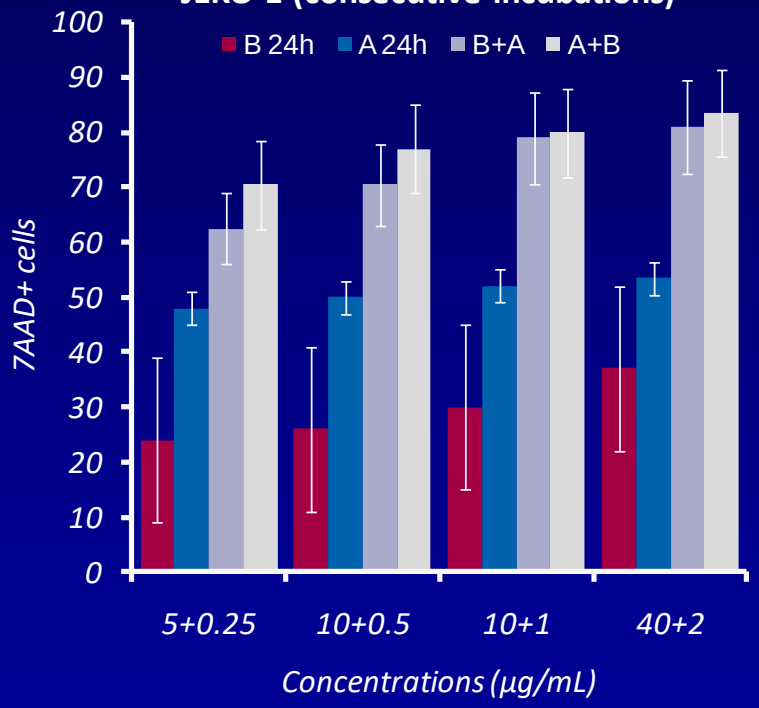


Rummel et al, ASCO 2016

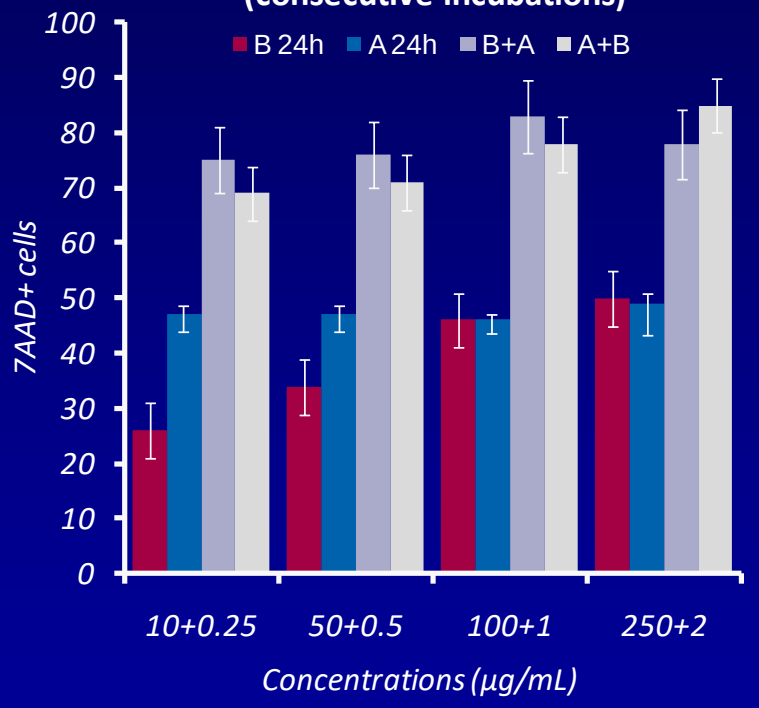
R-BAC in elderly MCL pts: background

Bendamustine (B) and cytarabine (A) are strongly synergistic *in-vitro* (CI<0.01)

Classic MCL

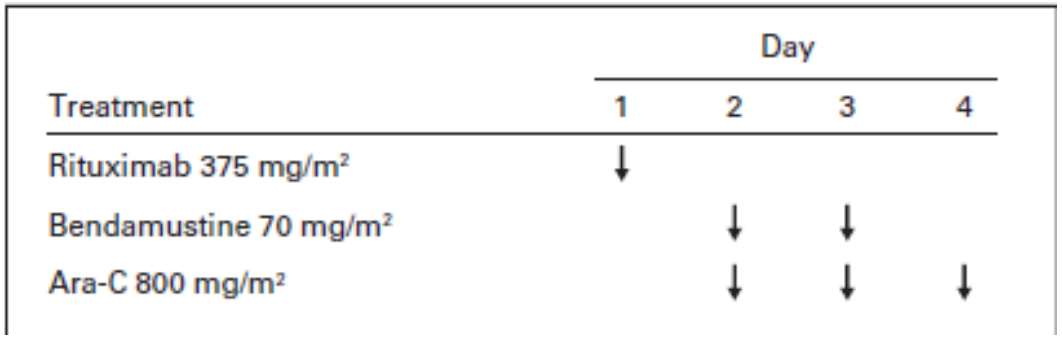


Blastoid variant



Visco C et al BCMD 2011

Rituximab, Bendamustine, Cytarabine (R-BAC)



	ORR (%)	CR (%)
Untreated	100	95

	Overall			
	Cycles (N = 182)		Patients (N = 40)	
Grade 3 or 4 Event	No.	%	No.	%
Leukopenia	87	48	23	57
Neutropenia	56	31	16	40
Febrile neutropenia	7	4	5	12
Thrombocytopenia	138	76	35	87
Anemia	48	26	18	45

R-BAC PROTOCOL VI-1903

Treatment schedule R-BAC

	1	2	3	4	+1	+2..	..+5
Rituximab 375 mg/m²	↓						
Bendamustine 70 mg/m²		↓	↓				
Ara-C 500 mg/m²		↓	↓	↓			
G-CSF 10 µg/kg							→

4 cycles (2+2) if CR or PR after 2 cycles. Stop if NR after 2 cycles.
6 cycles only if 1st line and good tolerance. Recycle every 28 days.

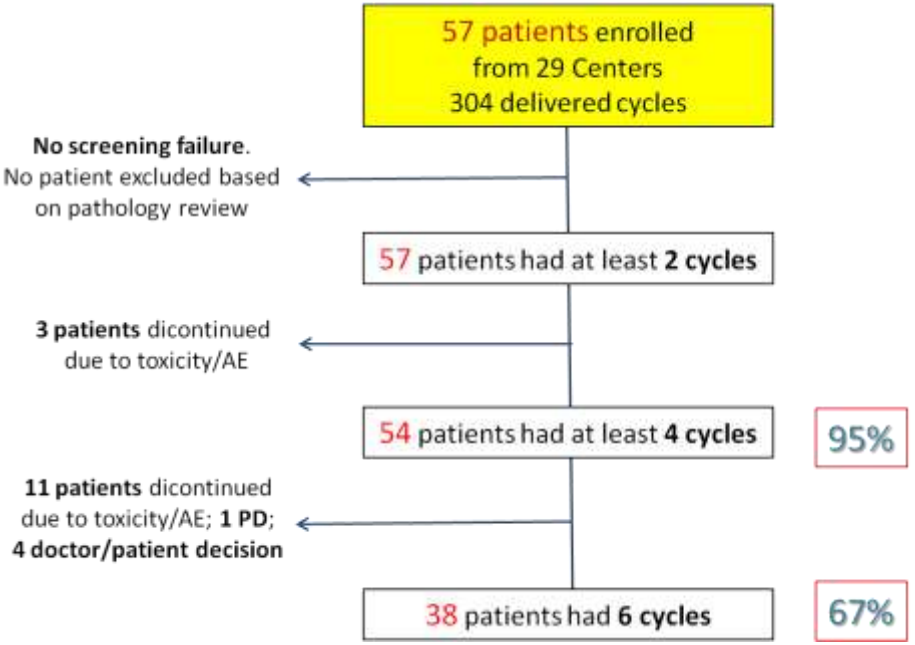
Visco et al, J.Clin. Oncol 2013

FIL RBAC 500 trial

✓ Patients' characteristics at inclusion

	Overall (57)	%
Age, years median (range)	71 (61-79)	
Gender male	43	75
Performance Status 0-1	54	94
AAS III-IV	52	91
MIPI risk category low intermediate high	9 23 25	16 40 44
BM involvement	36	63
Histology classical pleomorphic blastoid	43 8 6	75 14 11
Ki-67 (%) ≥30% median (range)	16 20 (5-85)	31

✓ Trial profile



Visco C. et al JCO 2017

Hematological Toxicity

Delivered cycles: 304

	Overall					R-BAC JCO 2013
Grade	0	1	2	3	4	Grade 4
Leukopenia	-	30%	26%	17%	27%	28%
Neutropenia	-	15%	36%	14%	35%	17%
Febrile neutropenia				5%	1%	4%
Thrombocytopenia	-	14%	34%	16%	36%	64%
Anemia	21%	24%	43%	12%	<1%	12%
Platelet transfusion	89 of 304 (29%)					62%

41 patients (72%) had at least one dose reduction over treatment courses.

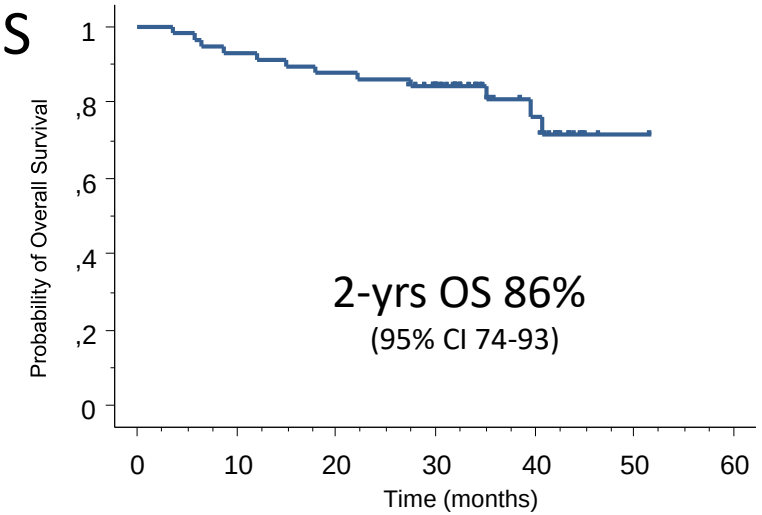
23 patients (40%) had at least one episode of “relevant toxicity”, which exceeded our predefined safety boundaries (<18 of 57).

Visco C. et al JCO 2017

Survival curves

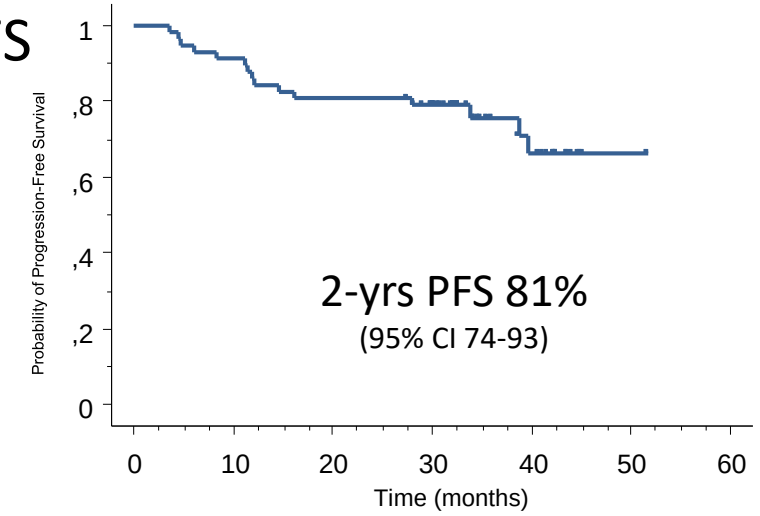
Median follow-up 35 months (28-52)

OS



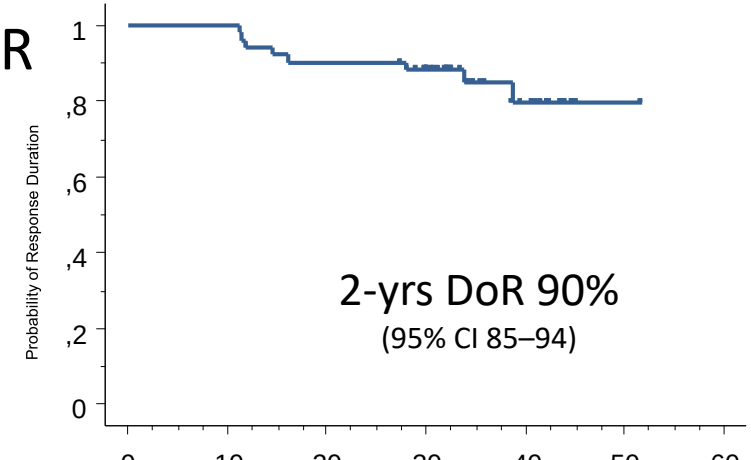
Number at risk	57	53	50	44	17	1

PFS



Number at risk	57	52	46	41	14	1

DoR



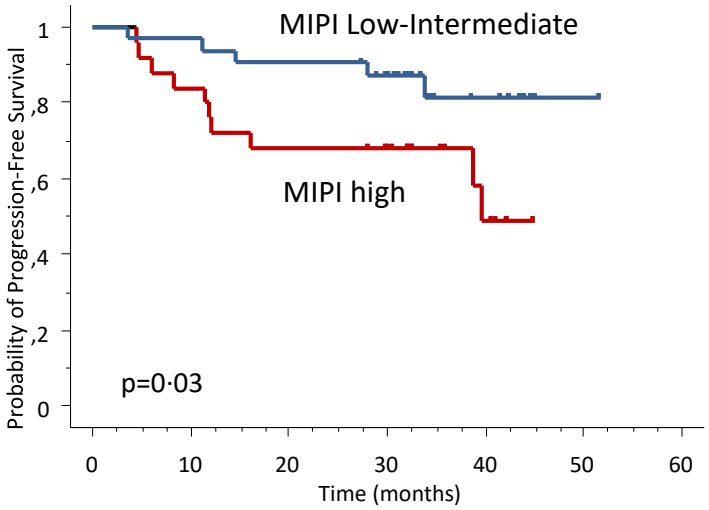
Number at risk	52	52	47	43	14	1

Visco C. et al JCO 2017

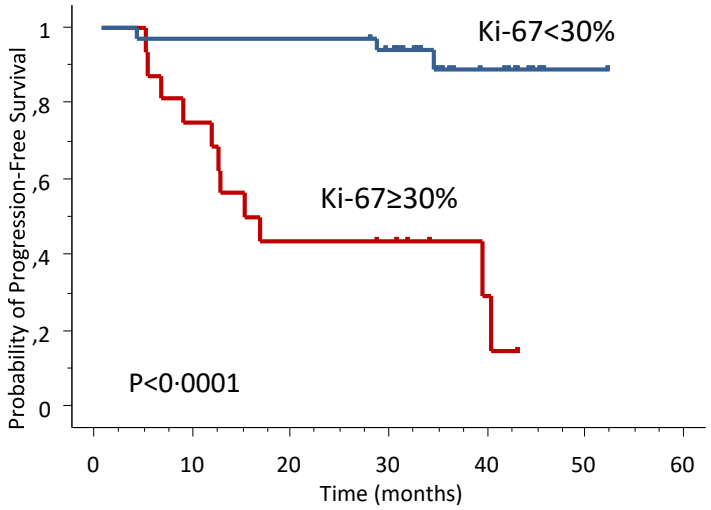
Survival curves

Univariate analysis for PFS

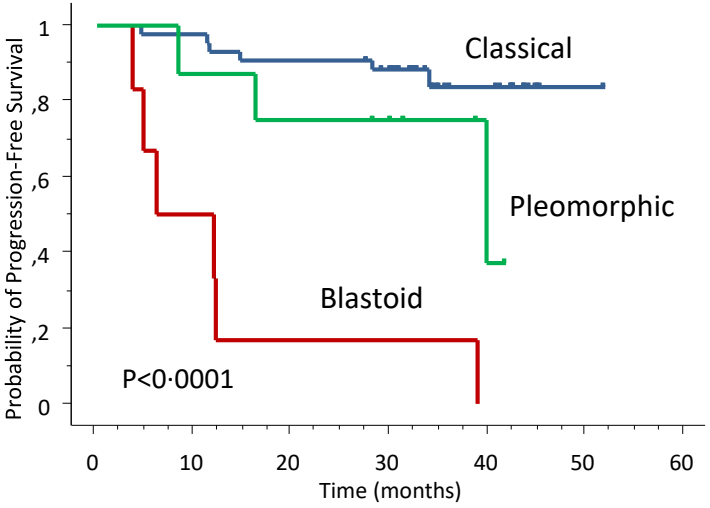
Grouping Variable: **MIPI**



Grouping Variable: **Ki-67**



Grouping Variable: **Morphology**



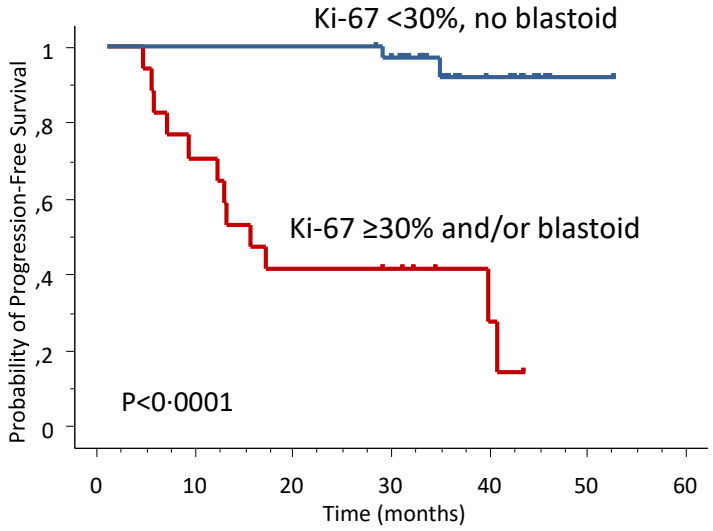
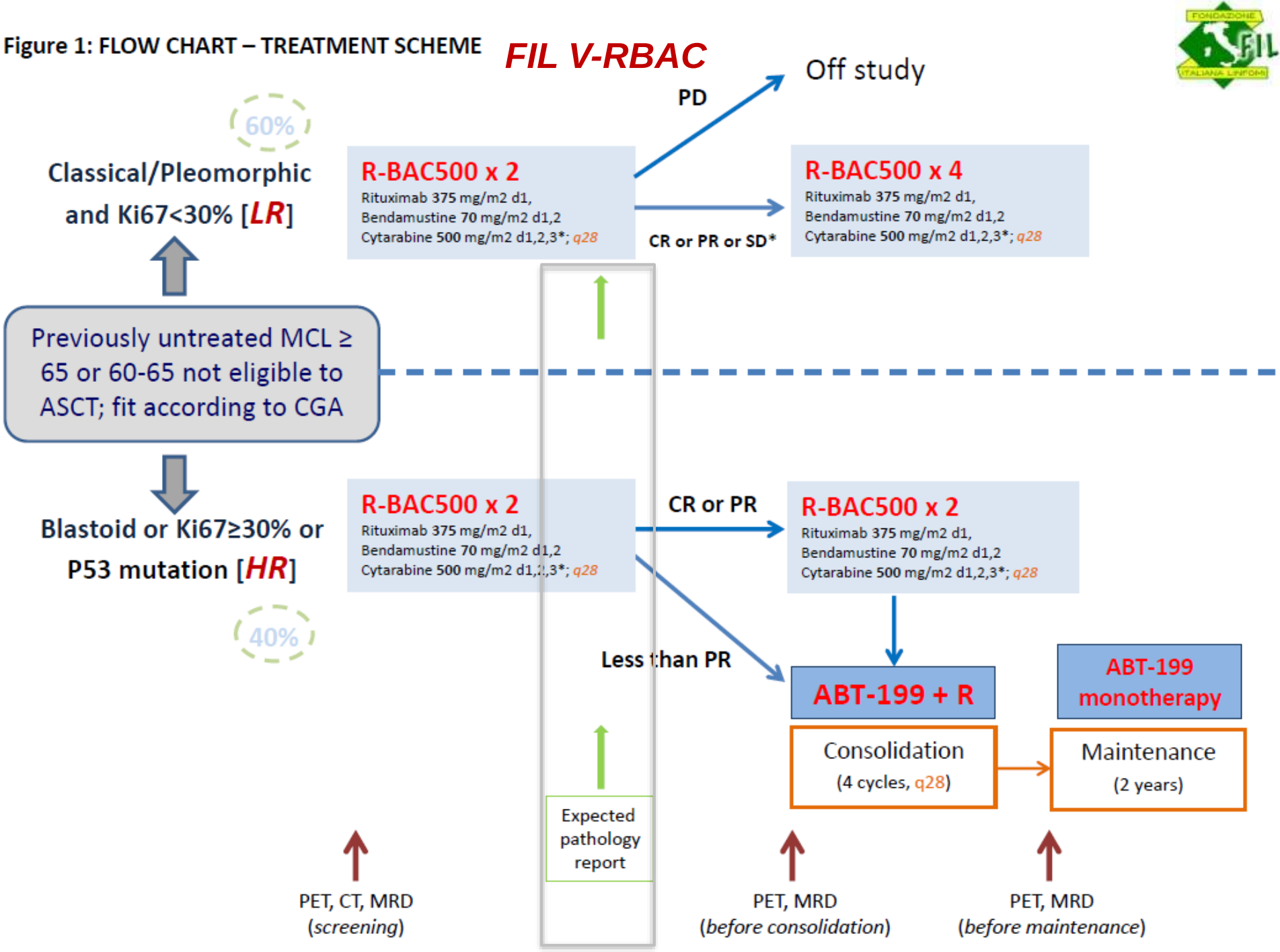


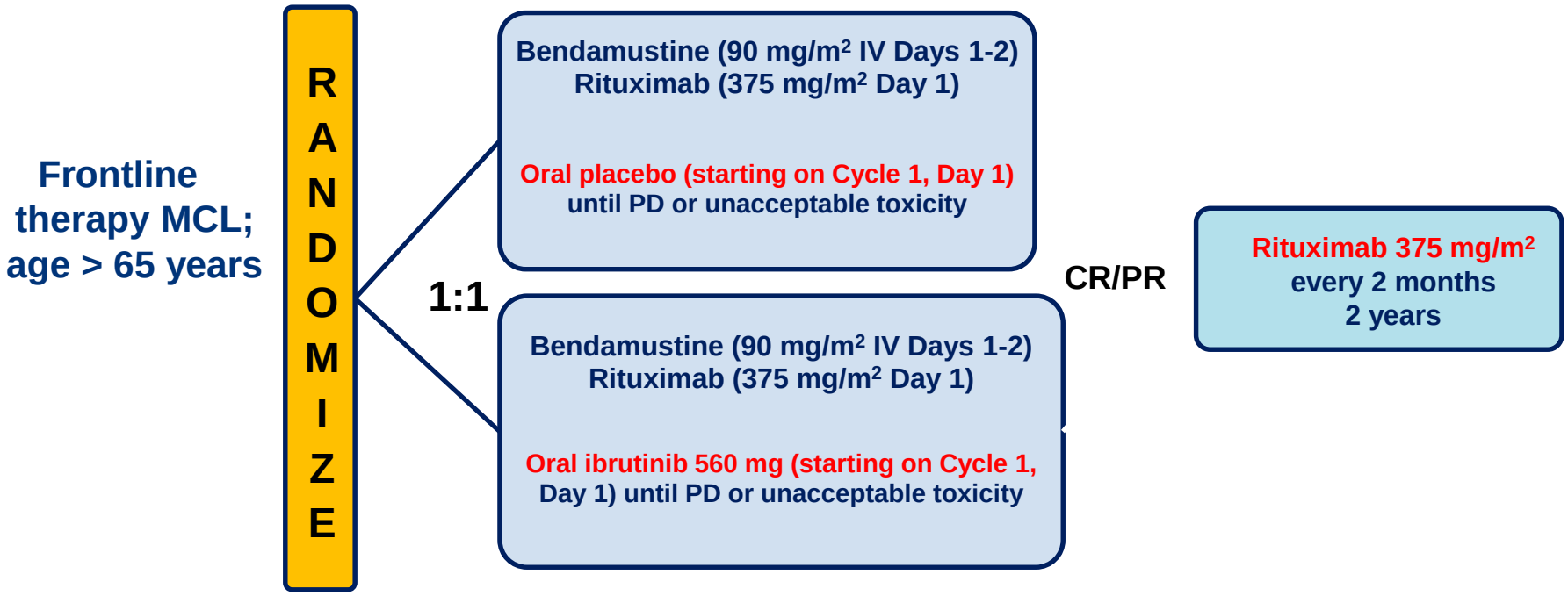
Figure 1: FLOW CHART – TREATMENT SCHEME



MCL3002 - study design (SHINE study)

Phase 3, randomized, double-blind, placebo-controlled study

N=520

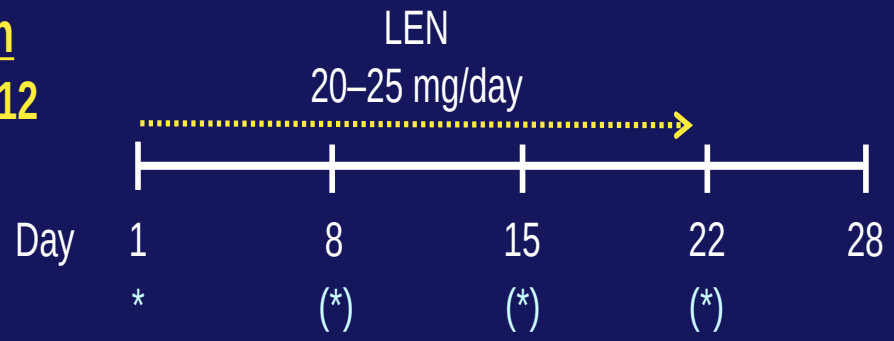


Chemo-free approach

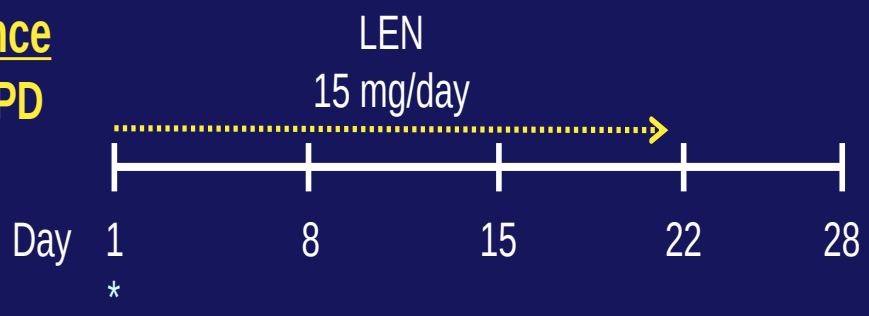
Combination Biologic Therapy Without Chemotherapy As Initial Treatment For Mantle Cell Lymphoma: Multi-Center Phase II Study Of ***Lenalidomide Plus Rituximab***

Sustained Remission with the Combination of Lenalidomide Plus Rituximab As Initial Treatment for MCL: A Multi-Center Phase II Study Report

Induction
Cycle 1–12



Maintenance
Cycle 13–PD



Induction

* Rituximab 375 mg/m^2
  Cycle 1: weekly x 4
  Cycles 2 and 3: no rituximab
  Cycles 4–12: once every other cycle

LEN starting dose of 20 mg/day could be escalated to 25 mg/day as tolerated

Maintenance

* Rituximab every other cycle (starting cycle 14)

DVT prophylaxis: aspirin

DVT, deep venous thrombosis; PD, progressive disease.

Ruan J et al. ASH 2014 Abs 625

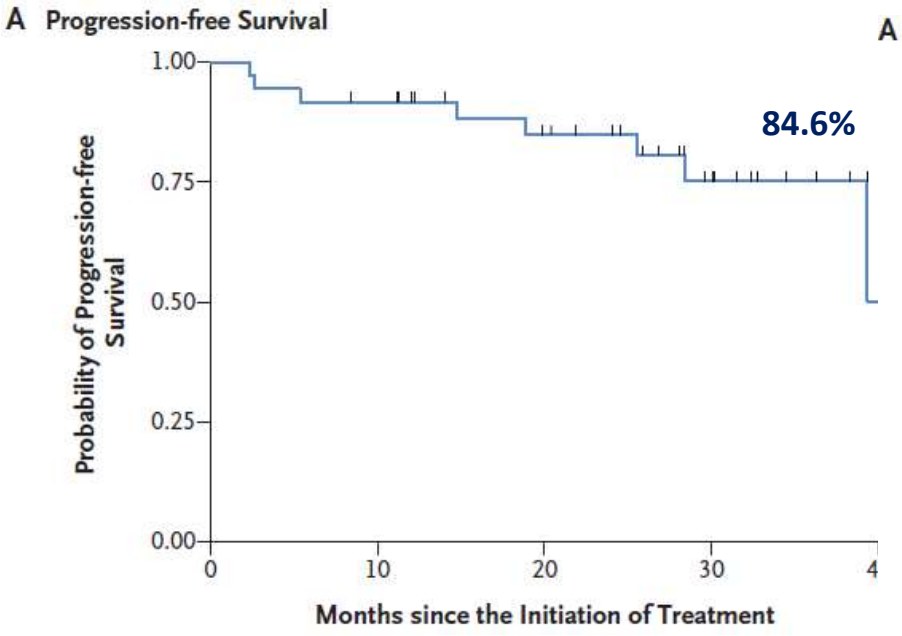
The NEW ENGLAND JOURNAL of MEDICINE

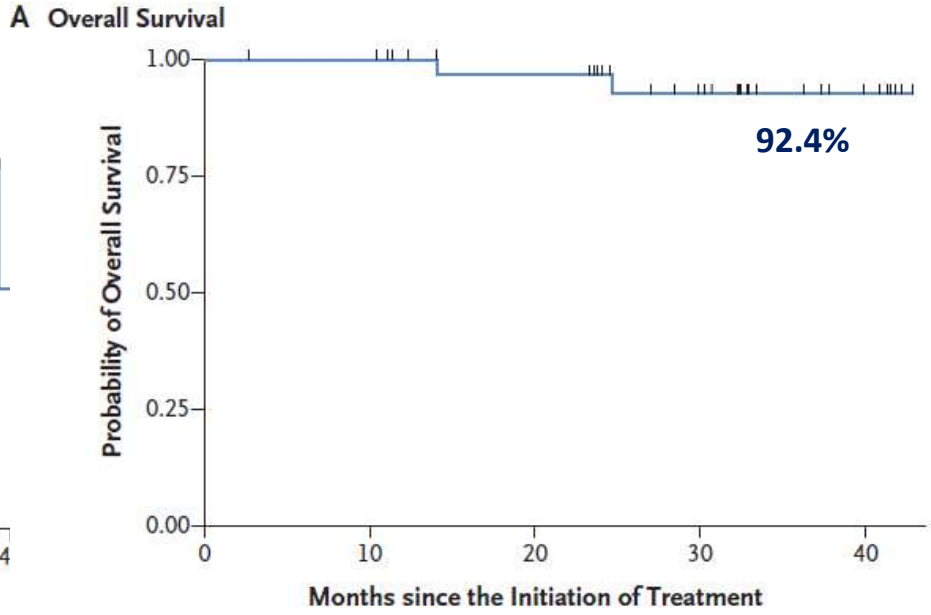
ORIGINAL ARTICLE

N ENGL J MED 373;19 NEJM.ORG NOVEMBER 5, 2015

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.





Initial treatment with lenalidomide plus rituximab for MCL: 5-year follow-up from a multi-center phase II study

Sample size = 38

Key eligibility

- Untreated MCL: CD20+CD5+CD23- Cyclin D1+
- Tumor mass ≥ 1.5 cm
- Low to intermediate risk MIPI
- High risk MIPI if decline or non-candidate for chemotherapy
- Adequate organ function

Objectives

- 1st: Overall response rates
- 2nd: Survival, safety, QoL assessment

- The study includes both induction and maintenance
- **Lenalidomide was administered at 20 mg daily on days 1-21 of a 28-day cycle for 12 cycles during induction, followed by dose reduction to 15 mg during maintenance**
- Standard dose rituximab was administered weekly x 4 during cycle 1, then once every other cycle
- **Treatment was continuous until progression, with option to stop therapy after 3 years.**

Ruan et al., ASH 2017 (abstract 154, oral presentation)

Initial treatment with lenalidomide plus rituximab for MCL: 5-year follow-up from a multi-center phase II study: best responses

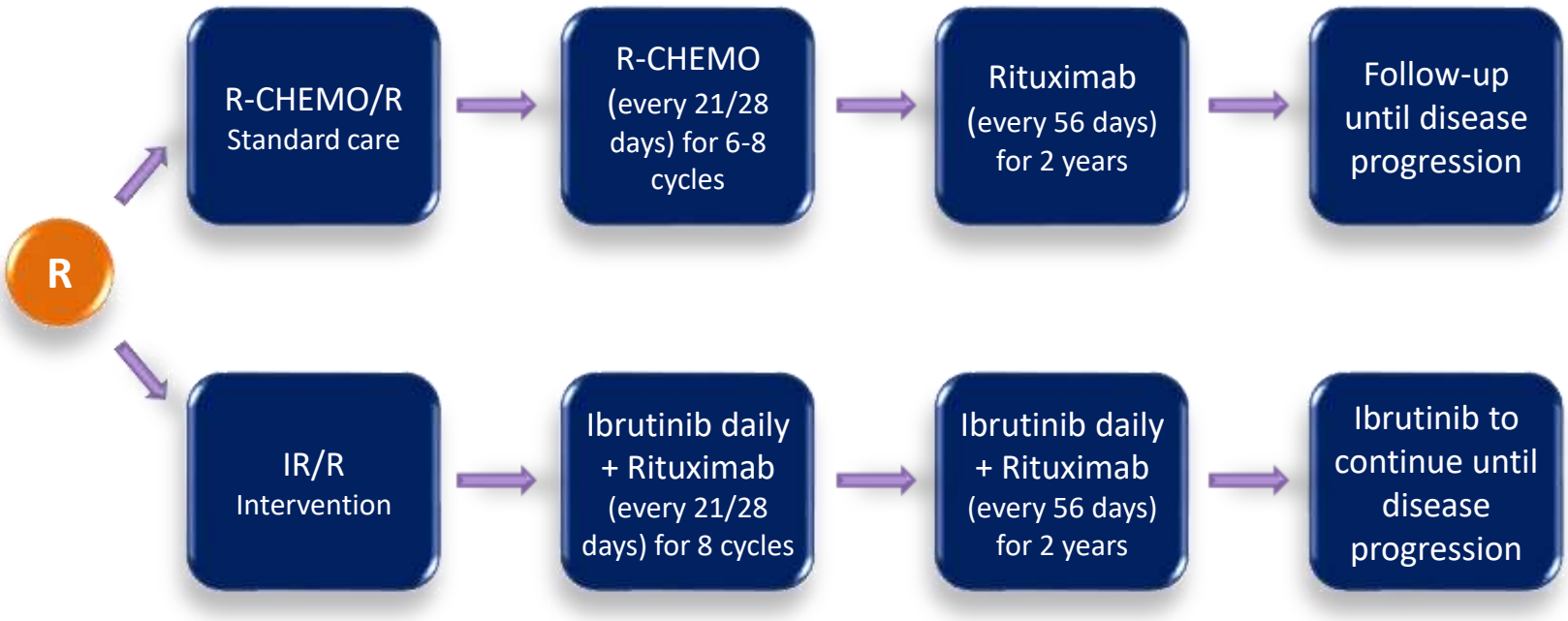
Response	No. of patients	ITT (n=38)	Evaluable (n=36)
Overall response	33	87%	92%
CR	23	61%	64%
PR	10	26%	28%
SD	1	3%	3%
PD	2	5%	6%
Inevaluable*	2		
Median follow-up	61 months (range 21-74)		
Median time to PR	3 months (range 3-13)		
Median time to CR	11 months (range 3-22)		
36-month PFS	80.3%		
48-month PFS	70.6%		

Ruan et al., ASH 2017 (abstract 154, oral presentation)

Initial treatment with lenalidomide plus rituximab for MCL: 5-year follow-up from a multi-center phase II study: AEs

Events	Induction		Maintenance	
	Any (%)	Grade ≥ 3 (%)	Any (%)	Grade ≥ 3 (%)
Hematologic				
Neutropenia	68	42	66	42
Anemia	47	8	32	3
Thrombocytopenia	29	11	37	5
Febrile neutropenia	3	3	5	5
Infectious				
URI	24	0	45	0
UTI	11	0	21	5
Sinusitis	5	0	13	0
Cellulitis	5	0	11	3
Pneumonia	3	3	8	8

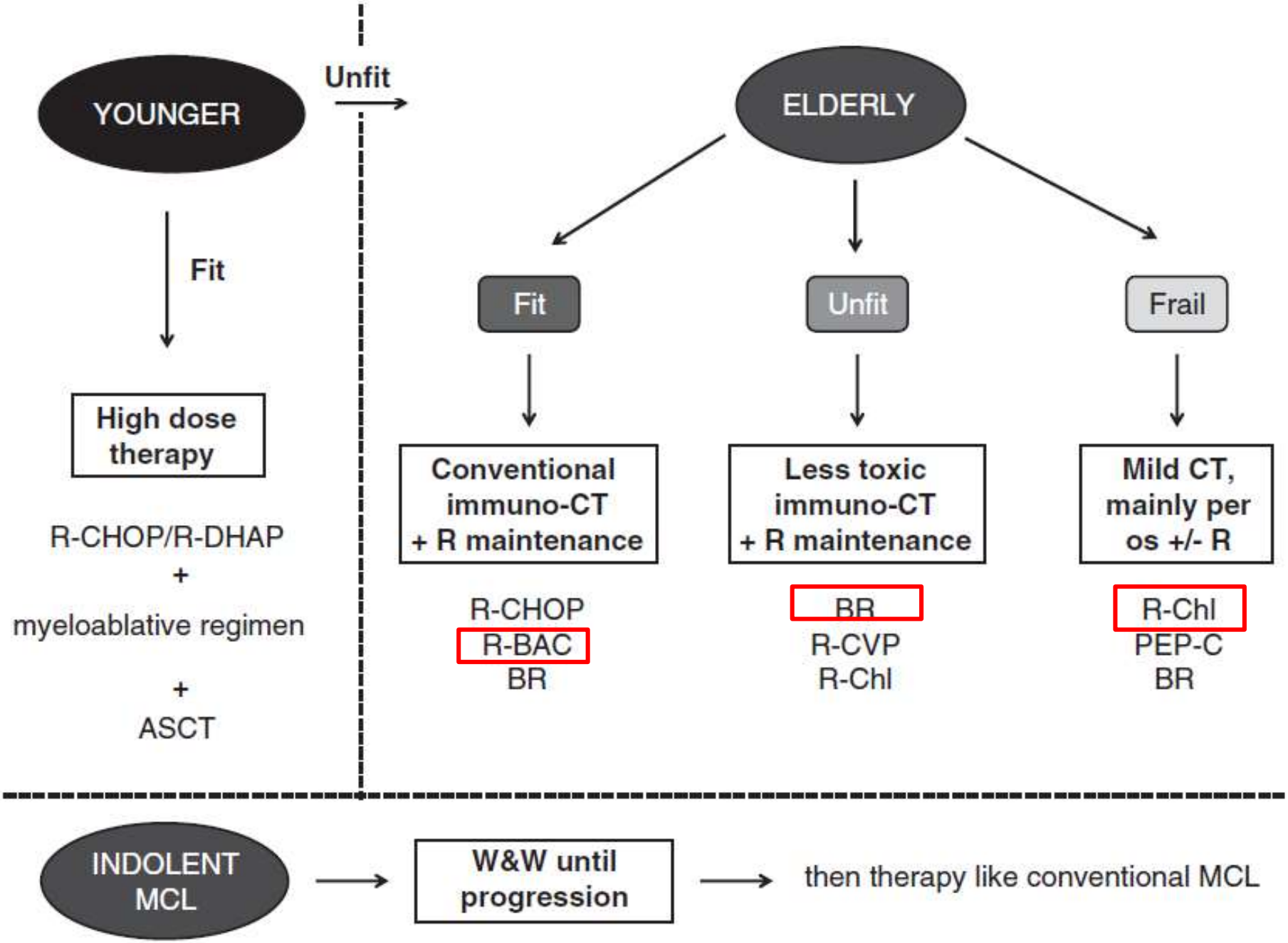
ENRICH – NCRI multicentre Randomised open label phase II/III trial of Rituximab & Ibrutinib *vs* Rituximab & CHemotherapy in Elderly mantle cell lymphoma



Principal Investigator : S. Rule

Key issues (1st line elderly)

- R-CHOP + R maintenance standard therapy for many groups
- R-Benda seems better than R-CHOP in 2 randomized trials
- R-Benda + R maintenance ?
- R-BAC represents an attractive alternative
- Several oral compounds soon available for monotherapy or association in less fit patients


YOUNGER
Unfit
ELDERLY
Fit
Fit
Unfit
Frail
High dose therapy
Conventional immuno-CT + R maintenance
Less toxic immuno-CT + R maintenance
Mild CT, mainly per os +/- R
R-CHOP/R-DHAP
+
myeloablative regimen
+
ASCT
R-CHOP
R-BAC
BR
BR
R-CVP
R-Chl
R-Chl
PEP-C
BR
INDOLENT MCL
W&W until progression
then therapy like conventional MCL

Ringraziamenti

SAPIENZA
UNIVERSITÀ DI ROMA

Alice Di Rocco
Luigi Petrucci
Clara Minotti
Michela Ansuinelli
Fulvio Massaro
Emilia Scalzulli

FONDAZIONE FIL ITALIANA LINFOMI

Robin Foà

Grazie per l'attenzione