# Mantle cell lymphoma
## *How I treat high risk MCL in first line*

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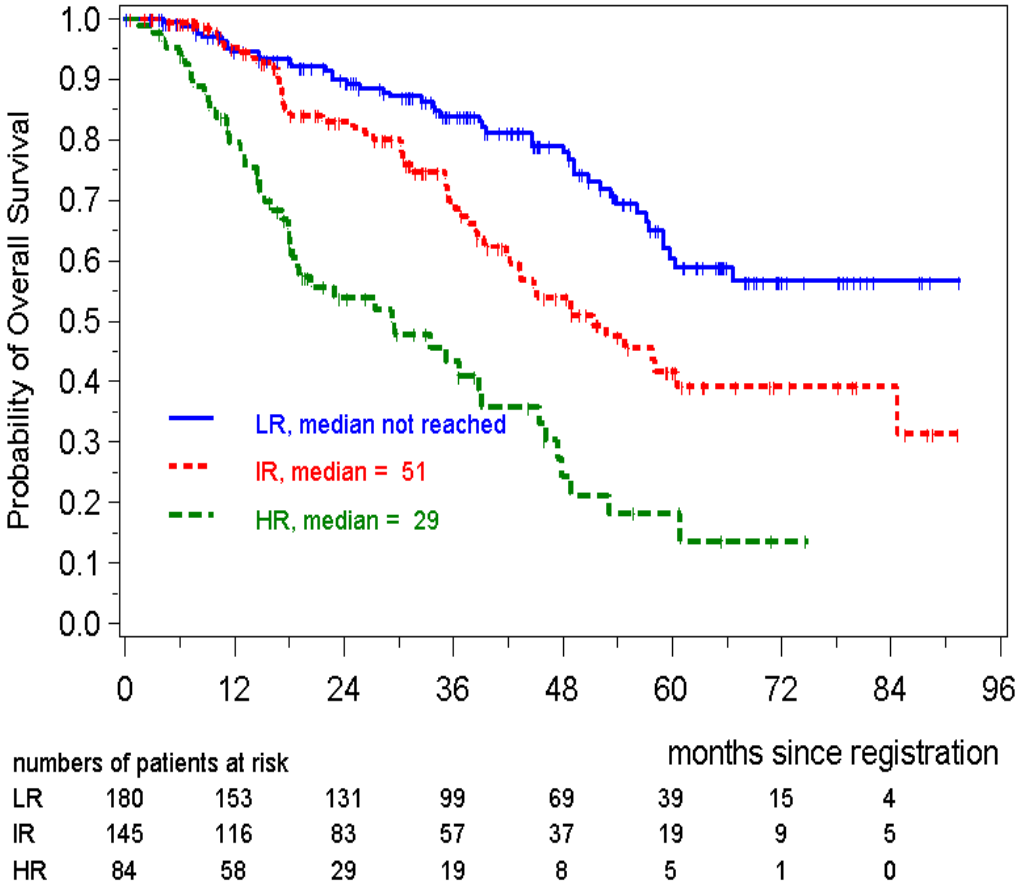
# Clinical risk factors: MIPI

*Univariate risk factors*

- age
- ECOG performance status
- B-symptoms
- spleen involvement
- tumor size
- leukocyte or lymphocyte count
- LDH
- hemoglobin
- albumin
- beta2-microglobulin




**(PALL: PS, age, LDH, leucocyte count, Ki67)**

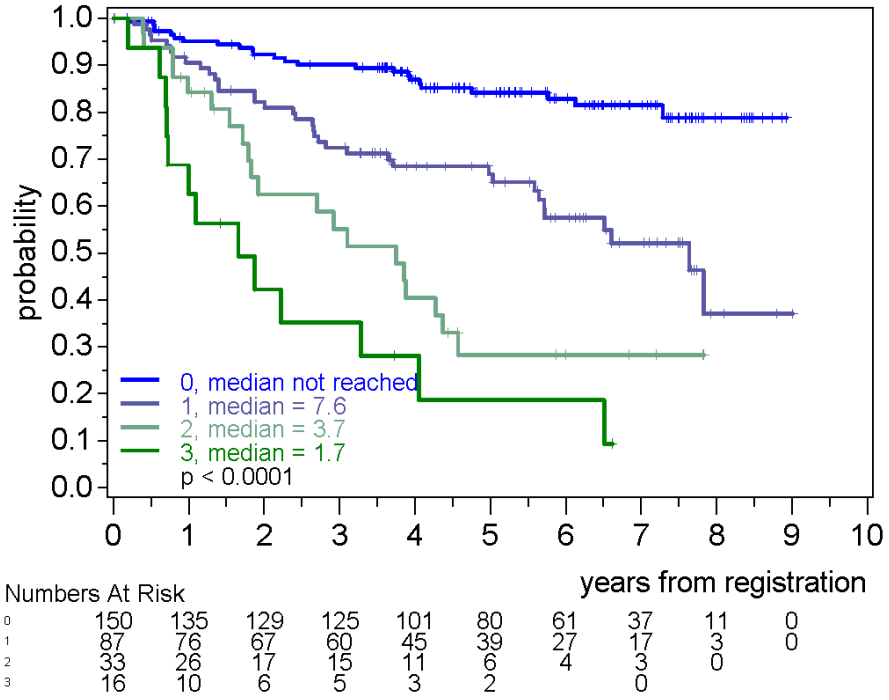
*Hoster, Blood 2008*

# New combined Biological MIPI
# MIPI-c

| MIPI Group | Ki-67 Index | MIPI-c Group |
|---|---|---|
| Low Risk | <30% | Low Risk |
| Low Risk | ≥30% | Low Intermediate Risk |
| Intermediate Risk | <30% | Low Intermediate Risk |
| Intermediate Risk | ≥30% | High Intermediate Risk |
| High Risk | <30% | High Intermediate Risk |
| High Risk | ≥30% | High Risk |

# OS according to MIPI-C
# In Age groups

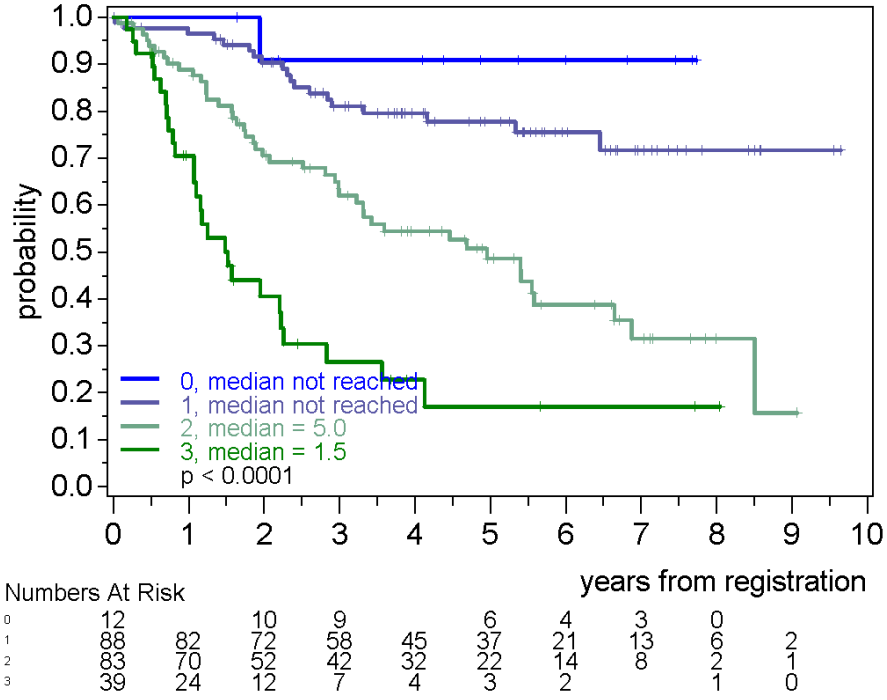
**< 65 years**




Numbers At Risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 150 | 135 | 129 | 125 | 101 | 80 | 61 | 37 | 11 | 0 |
| 1 | 87 | 76 | 67 | 60 | 45 | 39 | 27 | 17 | 3 | 0 |
| 2 | 33 | 26 | 17 | 15 | 11 | 6 | 4 | 3 | 0 | |
| 3 | 16 | 10 | 6 | 5 | 3 | 2 | | 0 | | |

**>= 65 years**



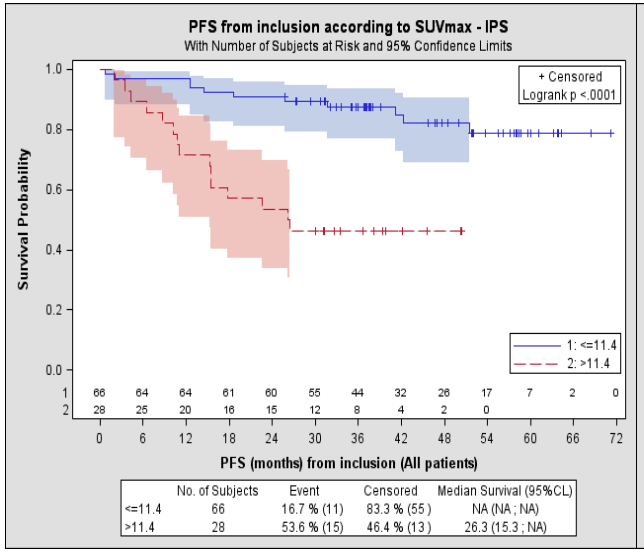

Numbers At Risk

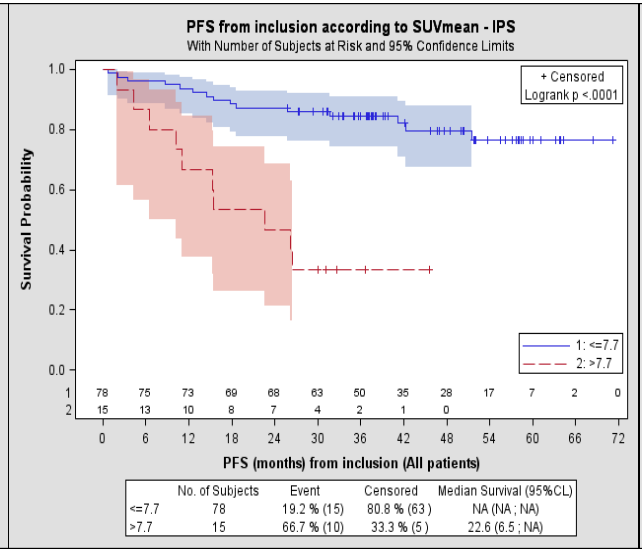
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 12 | | 10 | 9 | | 6 | 4 | 3 | 0 | |
| 1 | 88 | 82 | 72 | 58 | 45 | 37 | 21 | 13 | 6 | 2 |
| 2 | 83 | 70 | 52 | 42 | 32 | 22 | 14 | 8 | 2 | 1 |
| 3 | 39 | 24 | 12 | 7 | 4 | 3 | 2 | | 1 | 0 |

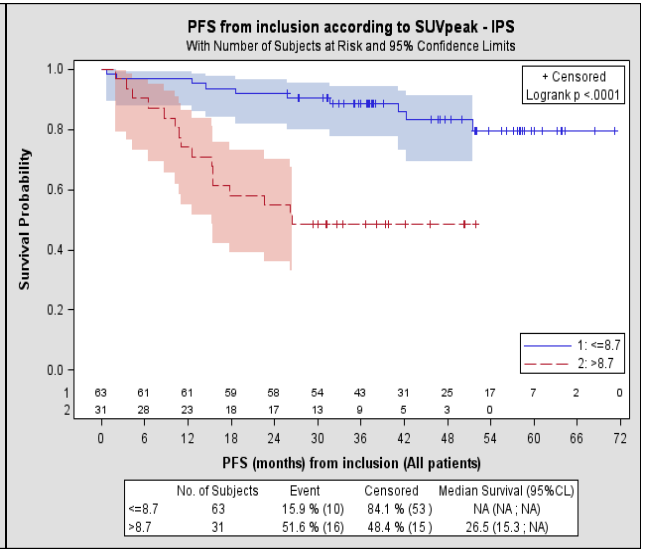
# Prognostic value of FDG-PET parameters at time of diagnosis

Univariate analysis showed a strong prognostic value on PFS of 3 metrics:

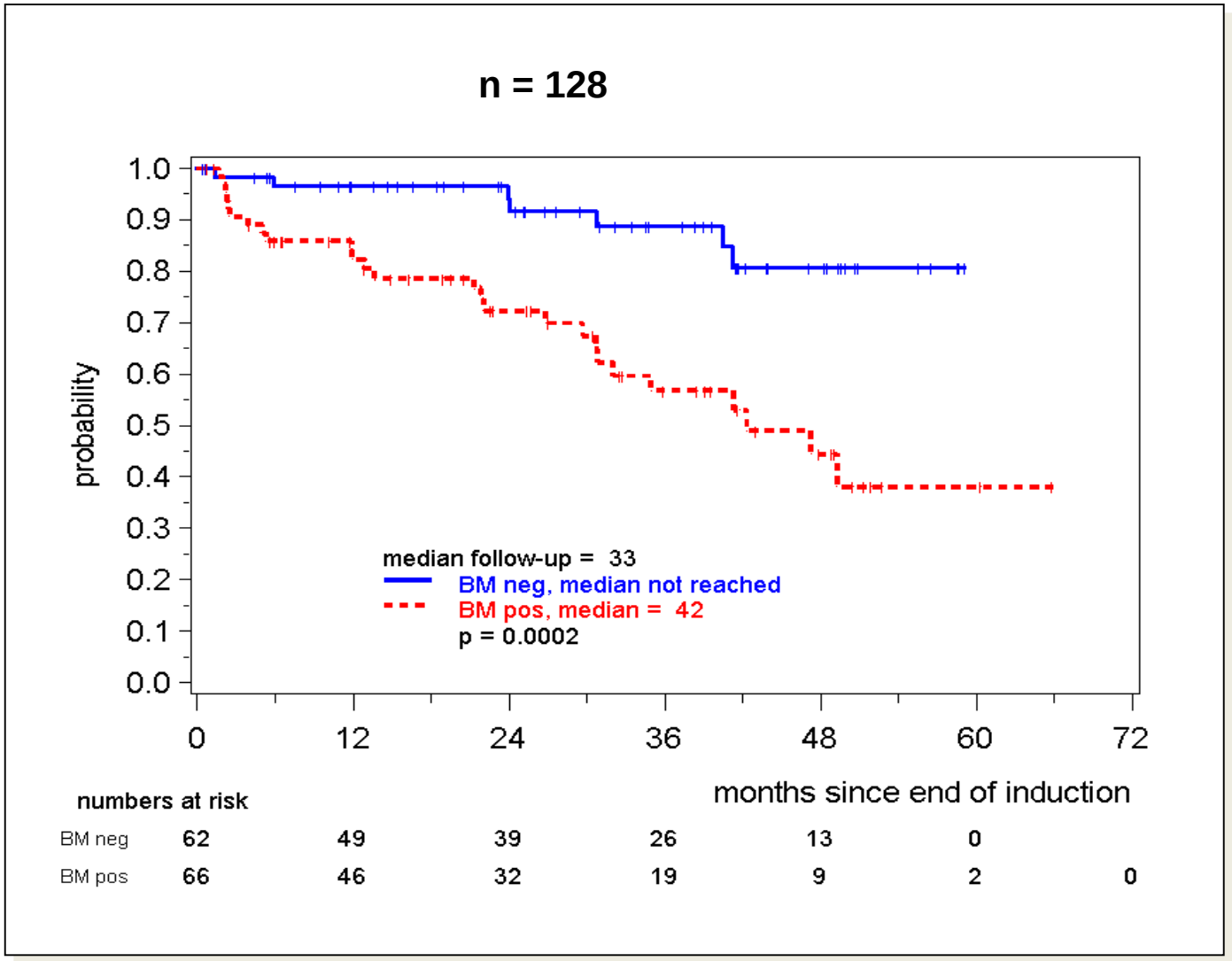
| $SUV_{max}$ (p<0.001, cutoff=11.4) | $SUV_{mean}$ (p<0.001, cutoff=7.7) | $SUV_{peak}$ (p<0.001, cutoff=8.7) |
|---|---|---|



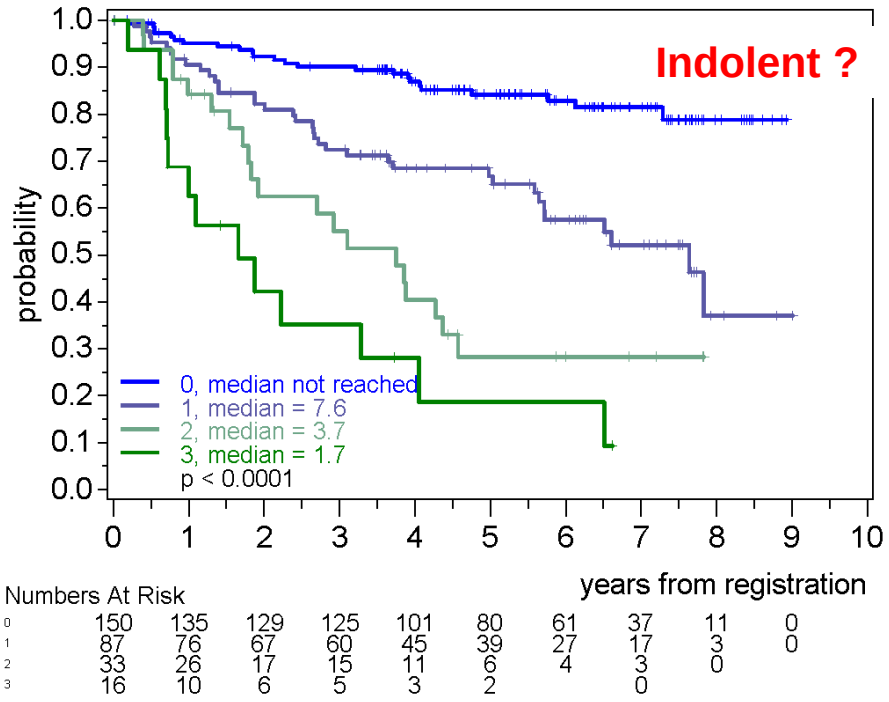



# Remission Duration according to MRD Status after Induction - pooled Arms -

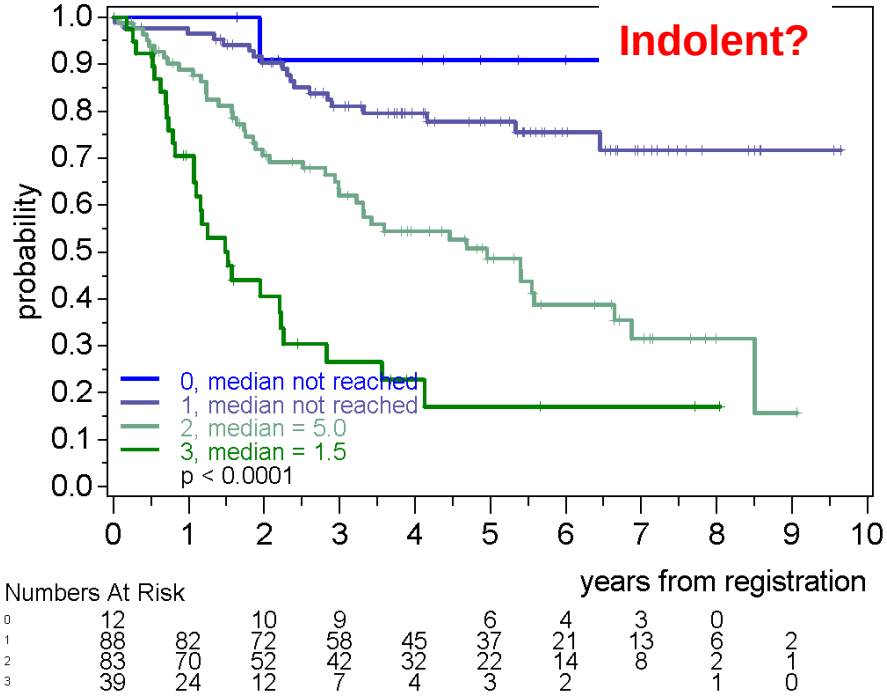


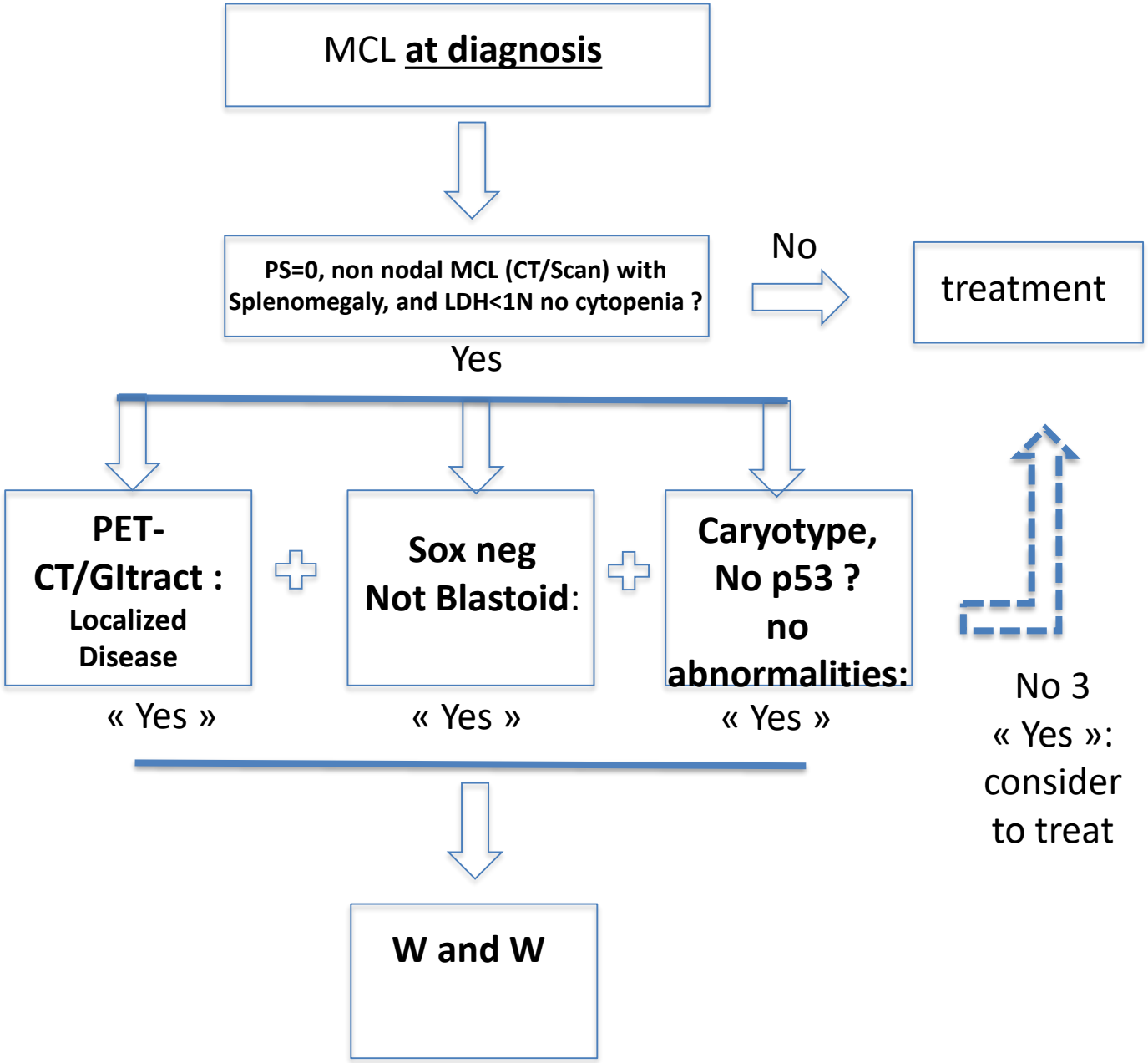
# OS according to MIPI-C
# In Age groups

**< 65 years**

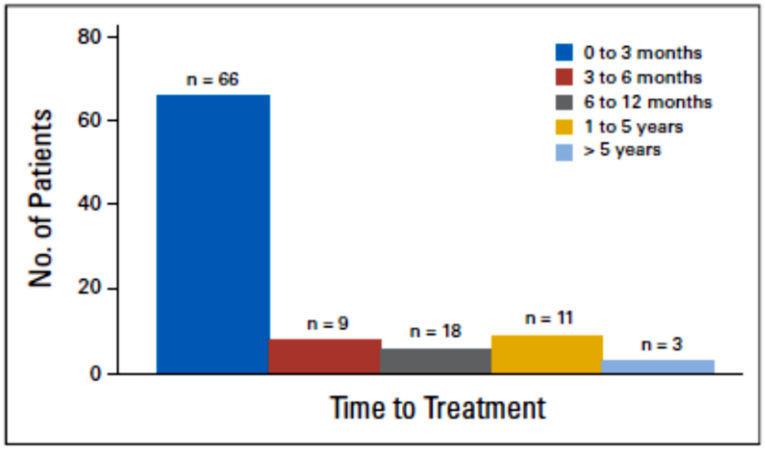


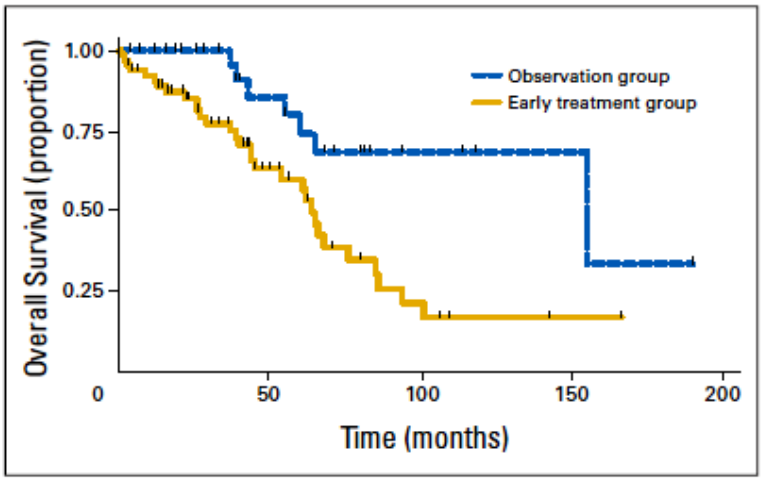

**>= 65 years**



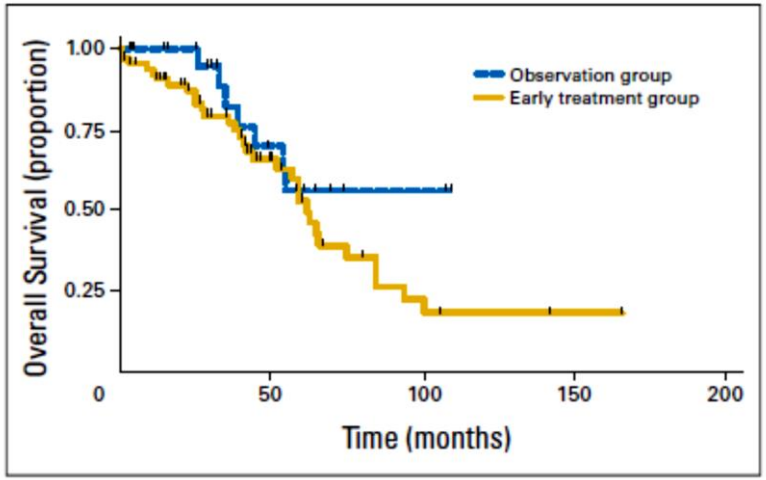

MCL at diagnosis
PS=0, non nodal MCL (CT/Scan) with Splenomegaly, and LDH<1N no cytopenia ?
No
treatment
Yes
PET-CT/GItract : Localized Disease
« Yes »
Sox neg Not Blastoid:
« Yes »
Caryotype, No p53 ? no abnormalities:
« Yes »
No 3 « Yes »: consider to treat
W and W

# MCL with Indolent Clinical Behavior



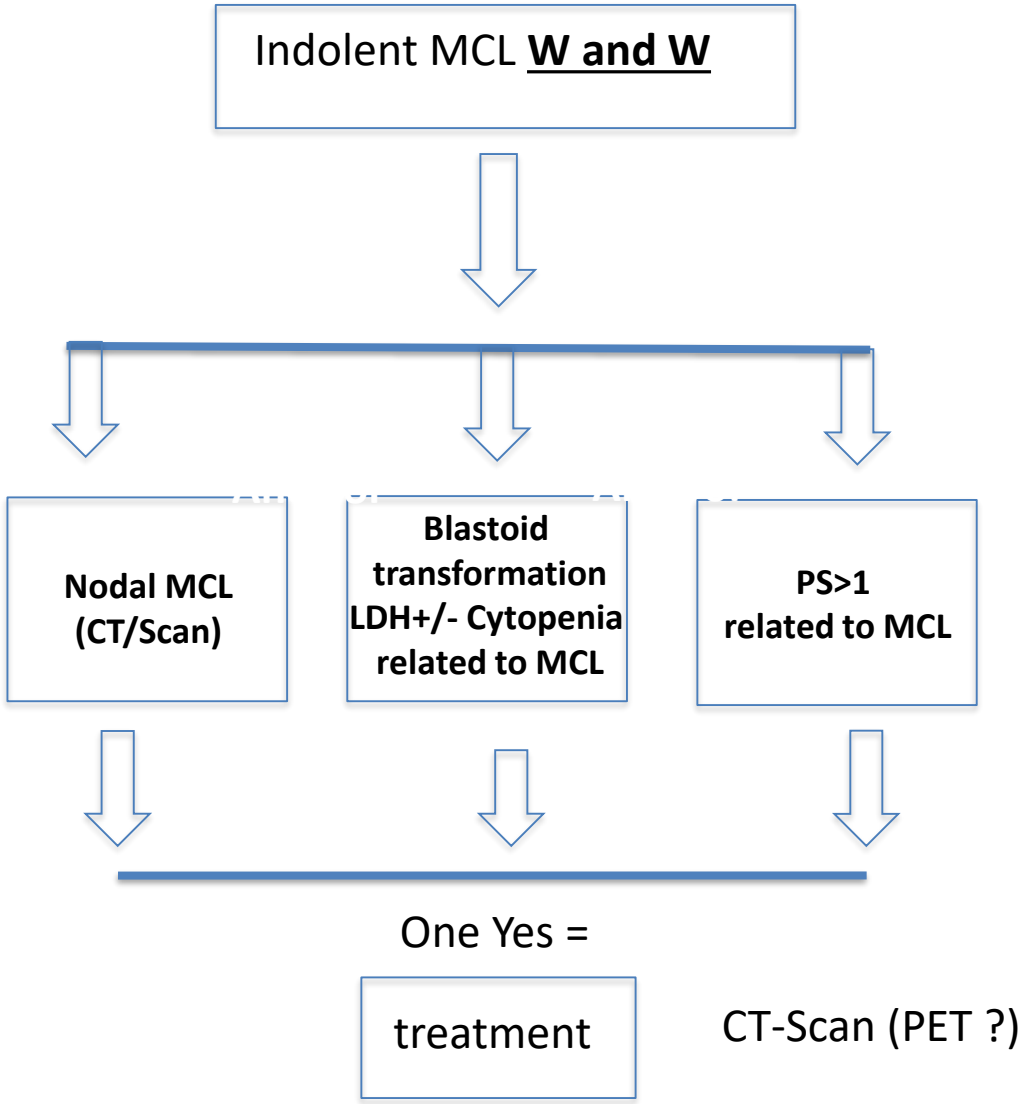



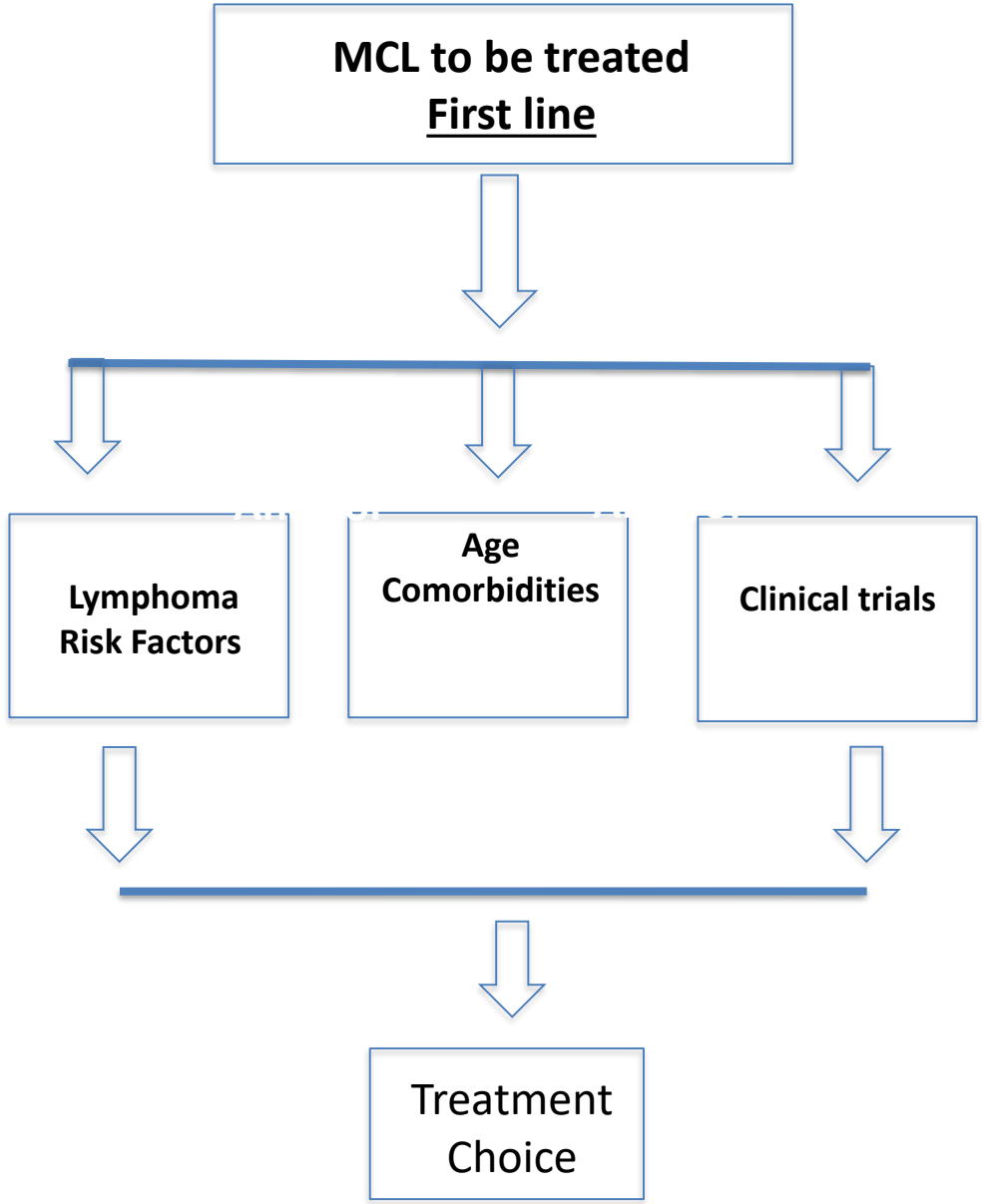

**OS from diagnosis**

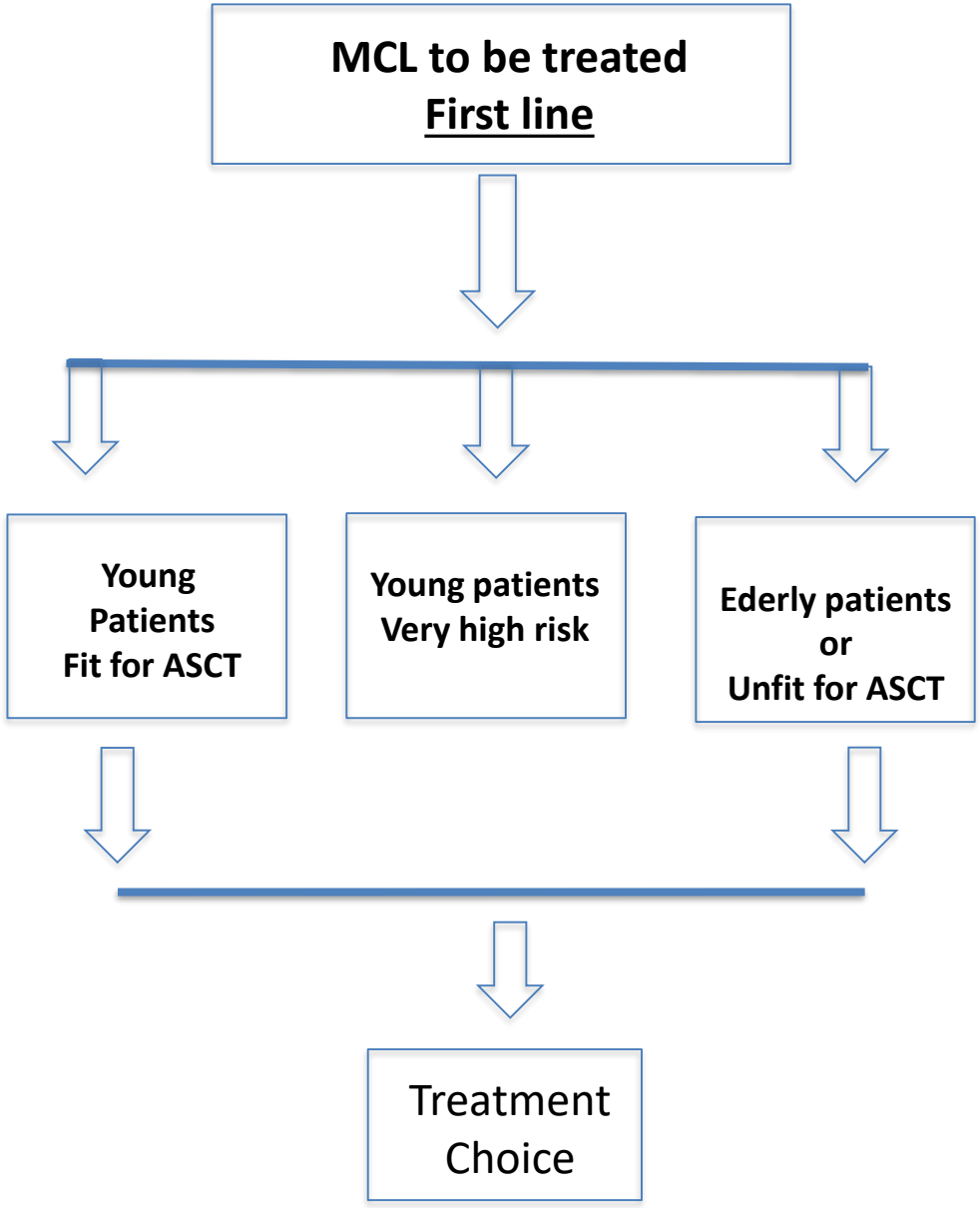


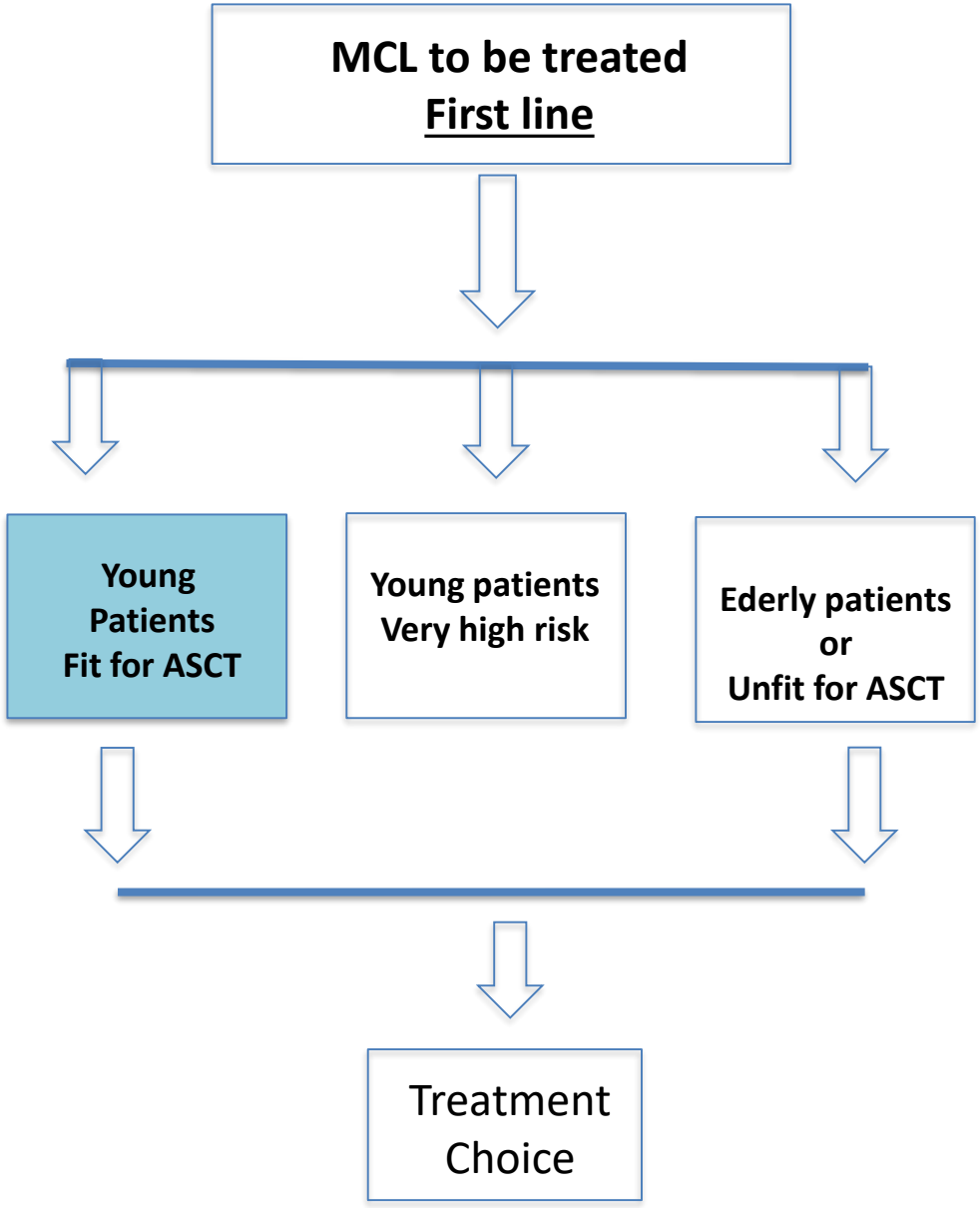

**OS from treatment**

***Martin P et al JCO 2009***


Indolent MCL **W and W**
**Nodal MCL (CT/Scan)**
**Blastoid transformation LDH+/- Cytopenia related to MCL**
**PS>1 related to MCL**
One Yes =
treatment
CT-Scan (PET ?)


MCL to be treated
First line
Lymphoma Risk Factors
Age Comorbidities
Clinical trials
Treatment Choice


MCL to be treated
First line
Young
Patients
Fit for ASCT
Young patients
Very high risk
Ederly patients
or
Unfit for ASCT
Treatment
Choice


MCL to be treated
First line
Young
Patients
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Young patients
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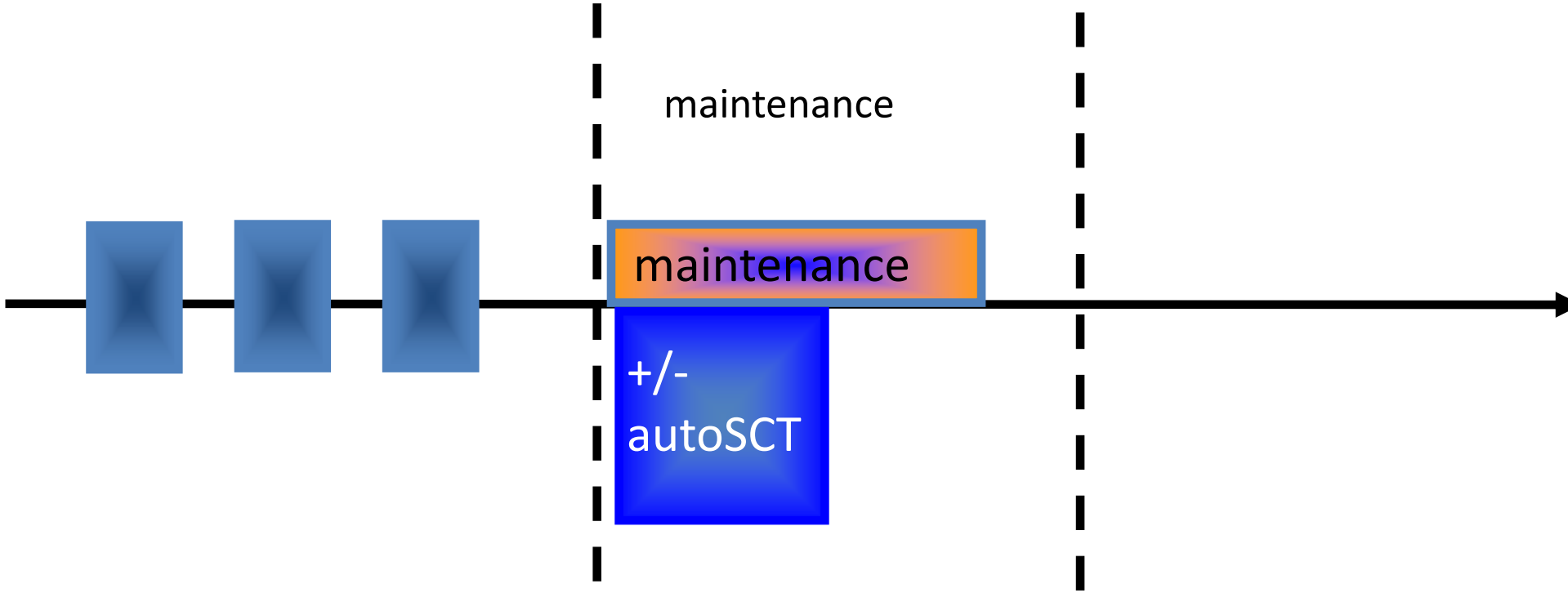
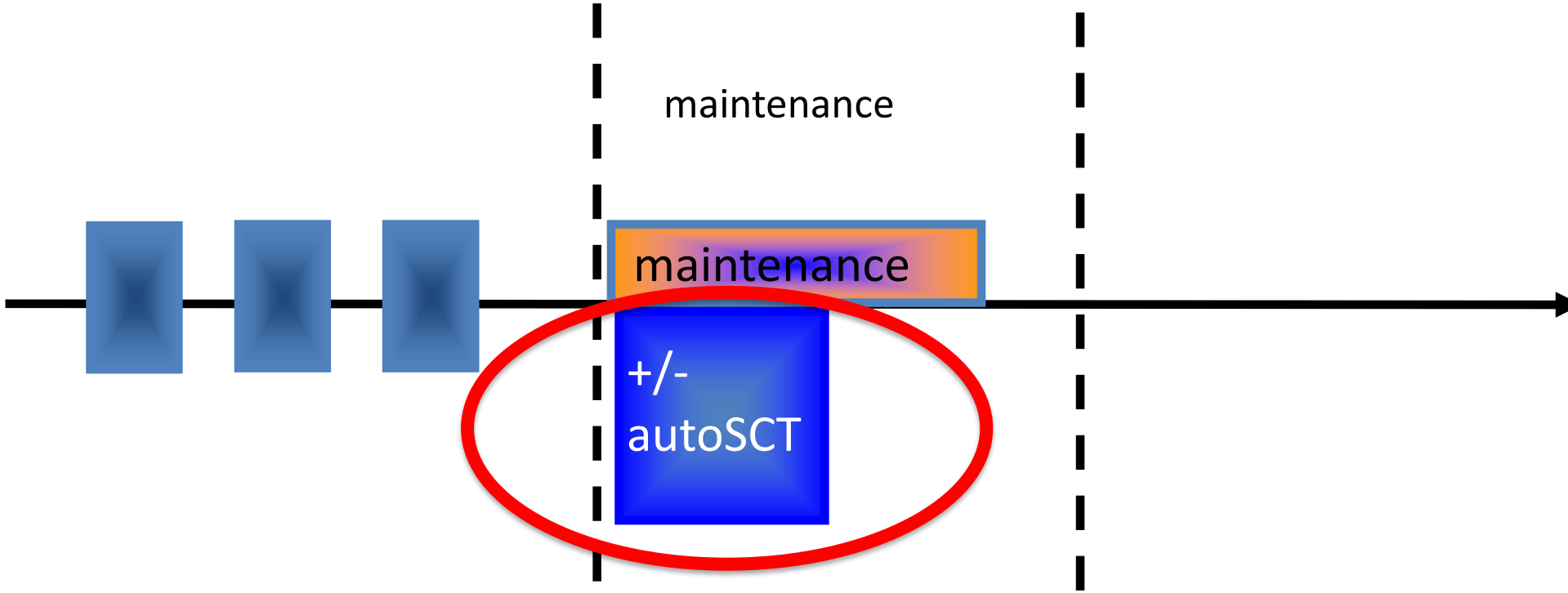
Treatment
Choice

# Treatment strategy in MCL
# First line/young (<65y/Fit)




*=> lymphoma remission*

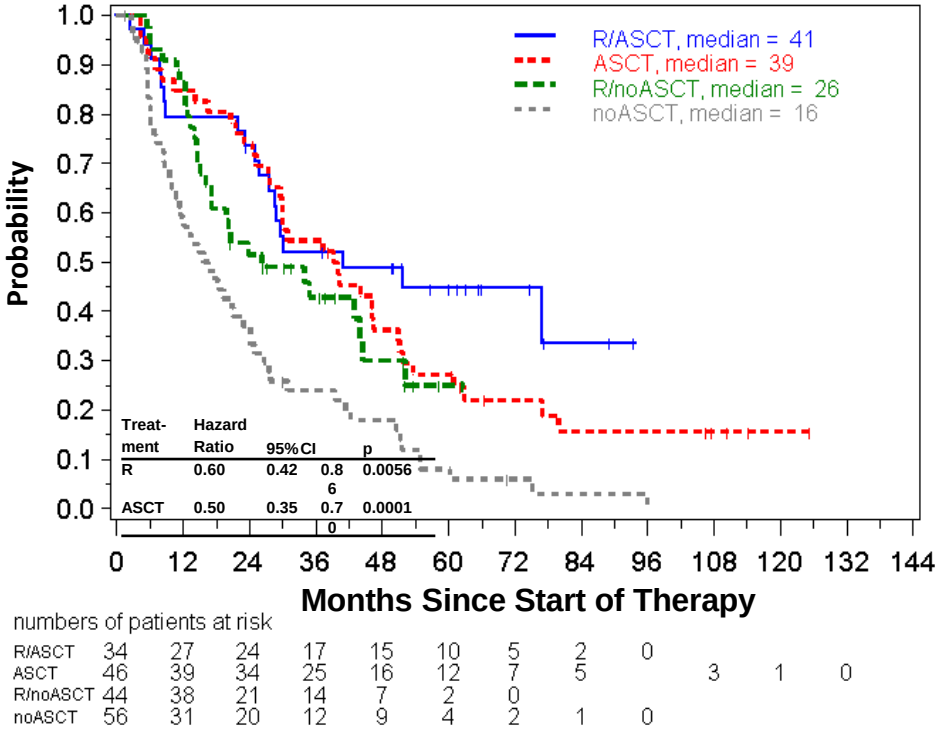
# Treatment strategy in MCL
# First line/young (<65y/Fit)



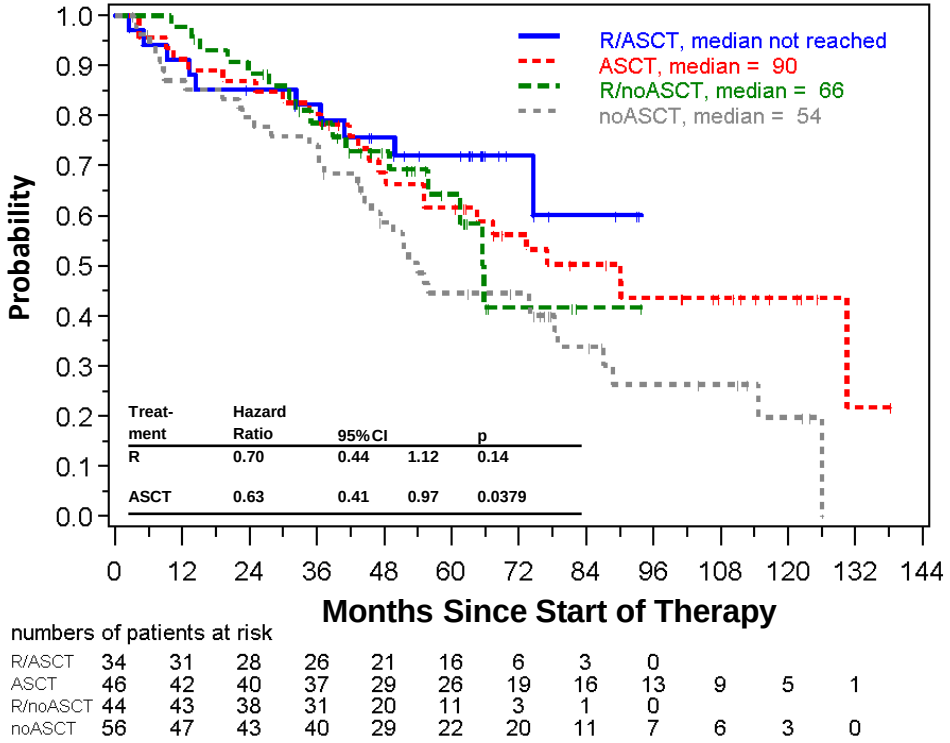

*=> lymphoma remission*

# Meta-Analysis: Autologous SCT and IFN Survival Rates

## Remission Duration




## Overall Survival




IFN, interferon; R, rituximab; SCT, stem cell transplant

Hoster E, *Blood.* 2009;114(22): Abstract 880.

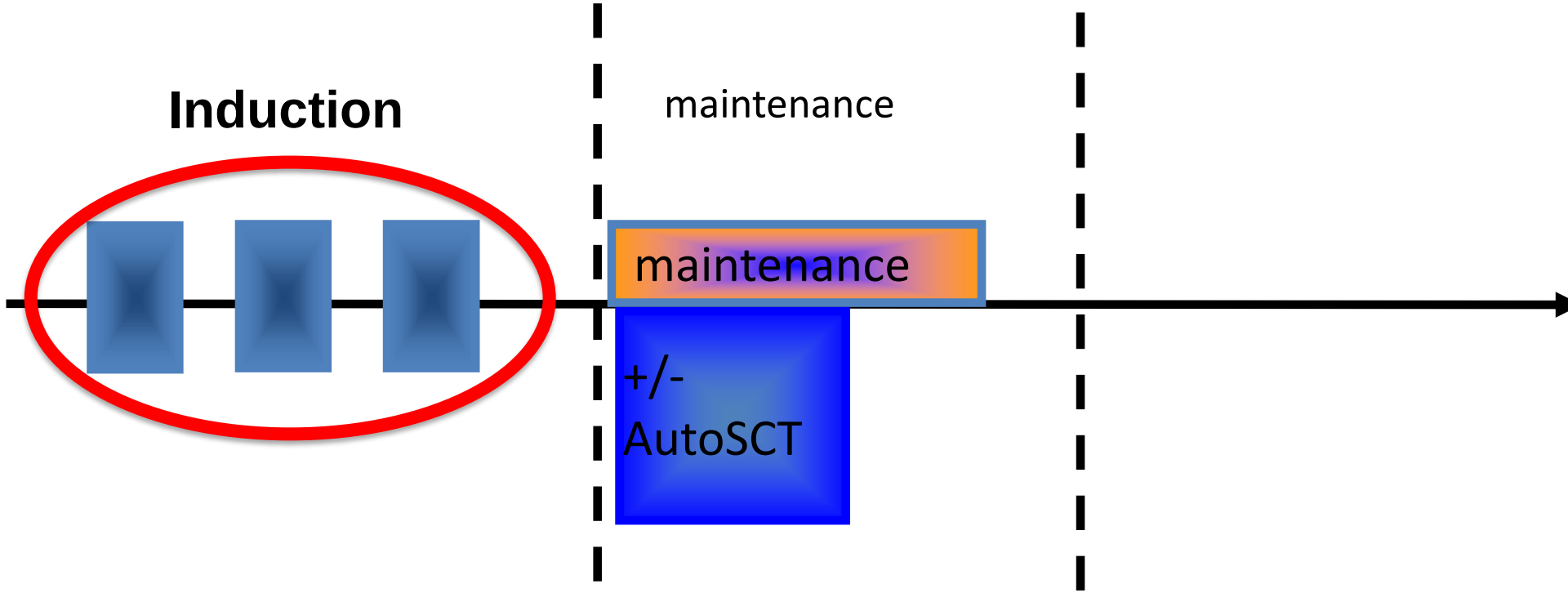
# Autologous Stem Cell Transplantation Improves Overall Survival in Young Patients with Mantle Cell Lymphoma in the Rituximab Era.

*Gerson JN, Handorf E, Villa D, et al. Blood.2017;ASH Annual Meeting*

- Multi-center retrospective study of 1007 transplant-eligible
- MCL patients ≤ 65, in which 64% of patients received upfront ASCT and 94% received rituximab with induction
- ASCT at median follow-up 76.8 months (6.4 years)

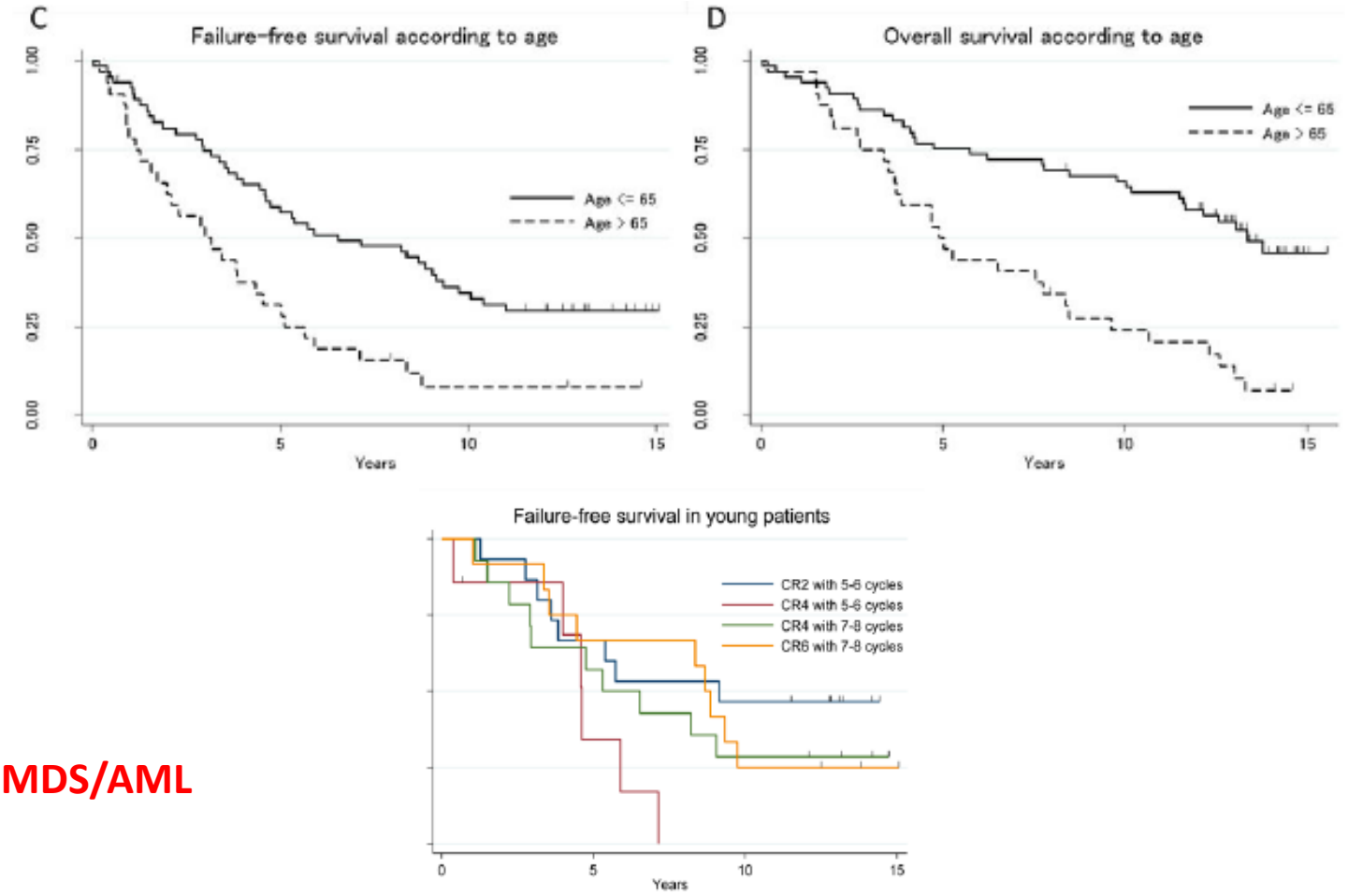
- **PFS (median 44 vs 75 months, p<0.01)**
- **OS (median 115 vs 147 months, p=0.02)**

# Treatment strategy in MCL
# First line/young (<65y/Fit)




*=> lymphoma remission*

# Rituximab plus hyper-CVAD alternating with MTX/Ara-C in patients with newly diagnosed mantle cell lymphoma: 15 year follow up of a phase II study from MD Anderson Cancer Center

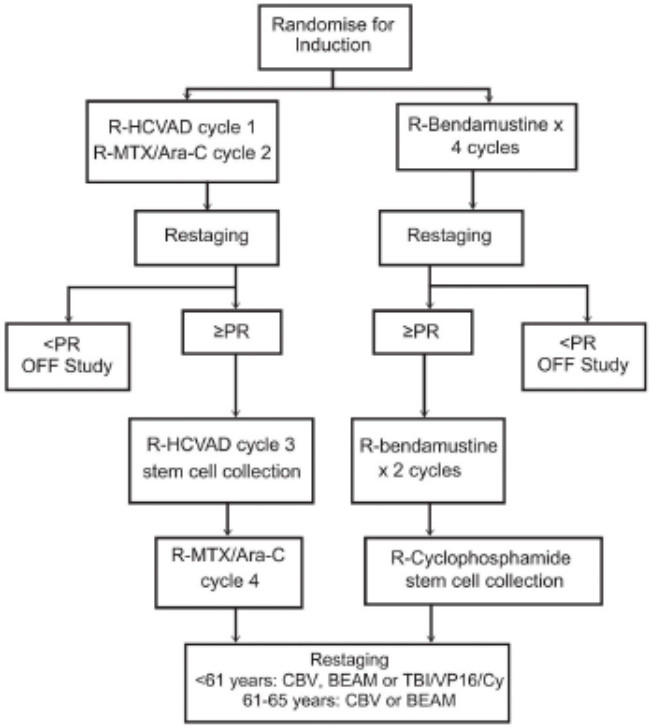


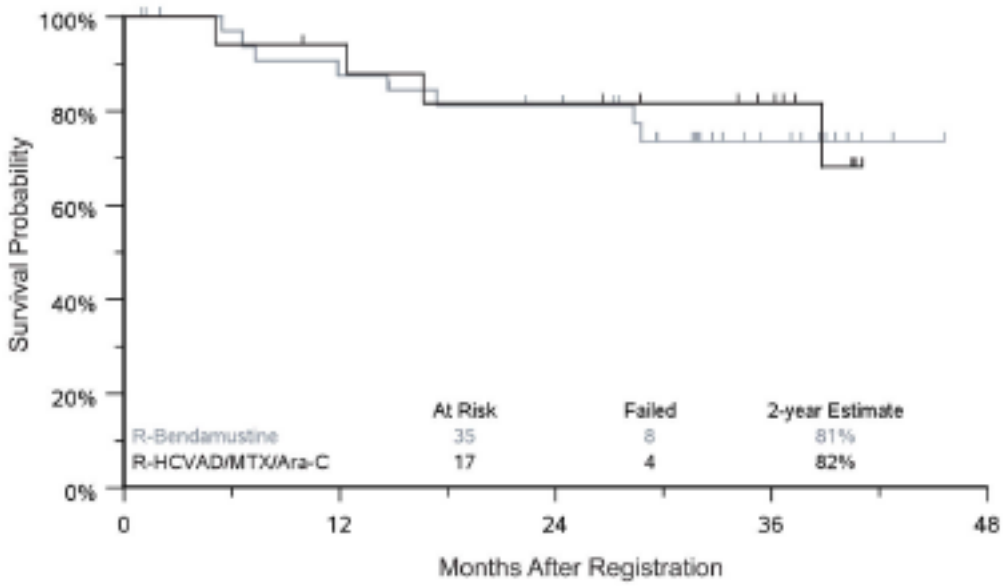

**6.2% MDS/AML**

*Chihara et al* *Br J Haematol.* 2016 January ; 172(1): 80–88. doi:10.1111/bjh.13796.

# RB but not R-HCVAD is a feasible induction regimen prior to auto-HCT in frontline MCL: results of SWOG Study S1106

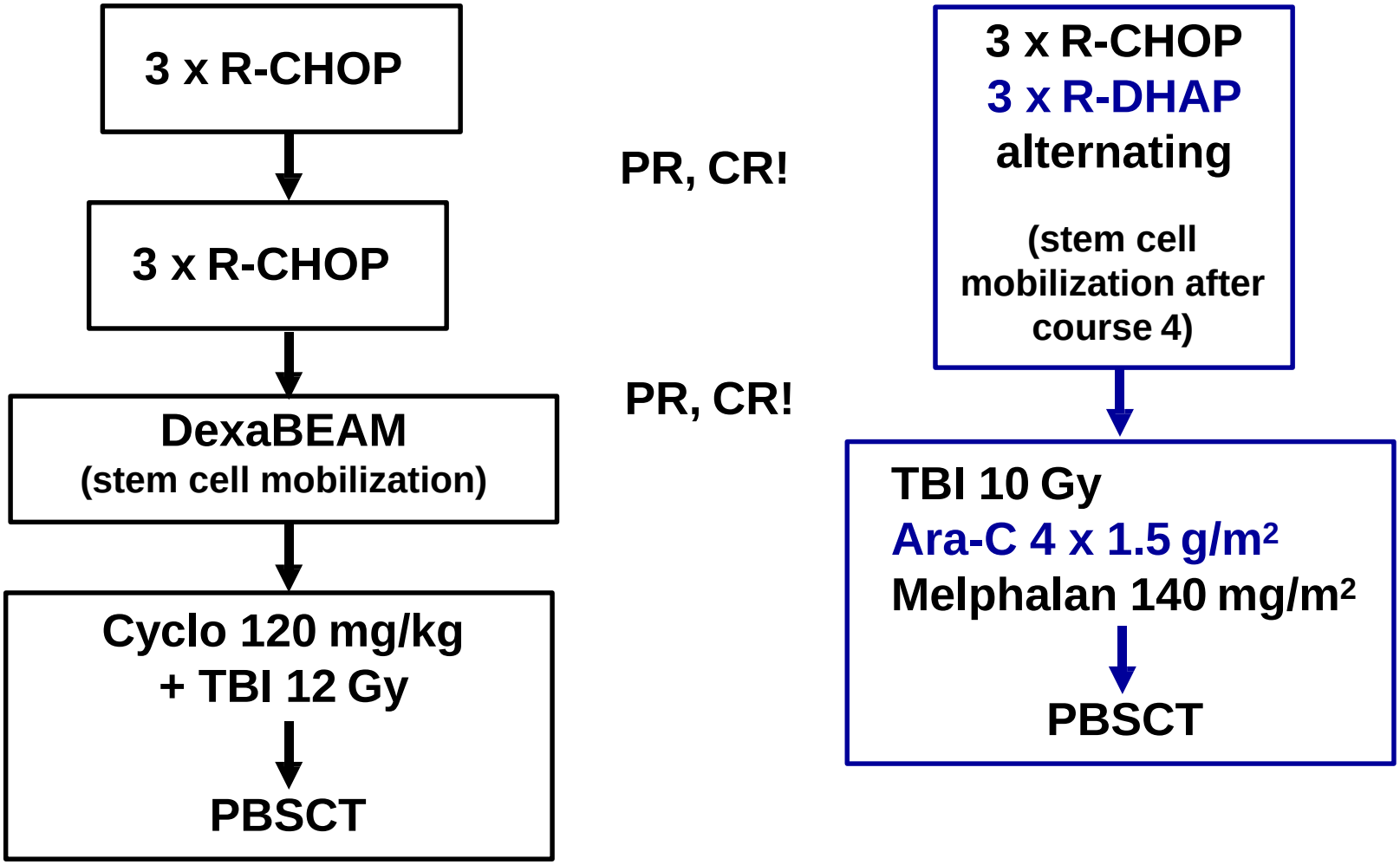
**Early stop of the study 30% SC collection failure**




*Robert W. Chen*

# European MCL Network
# Patients <65 Years

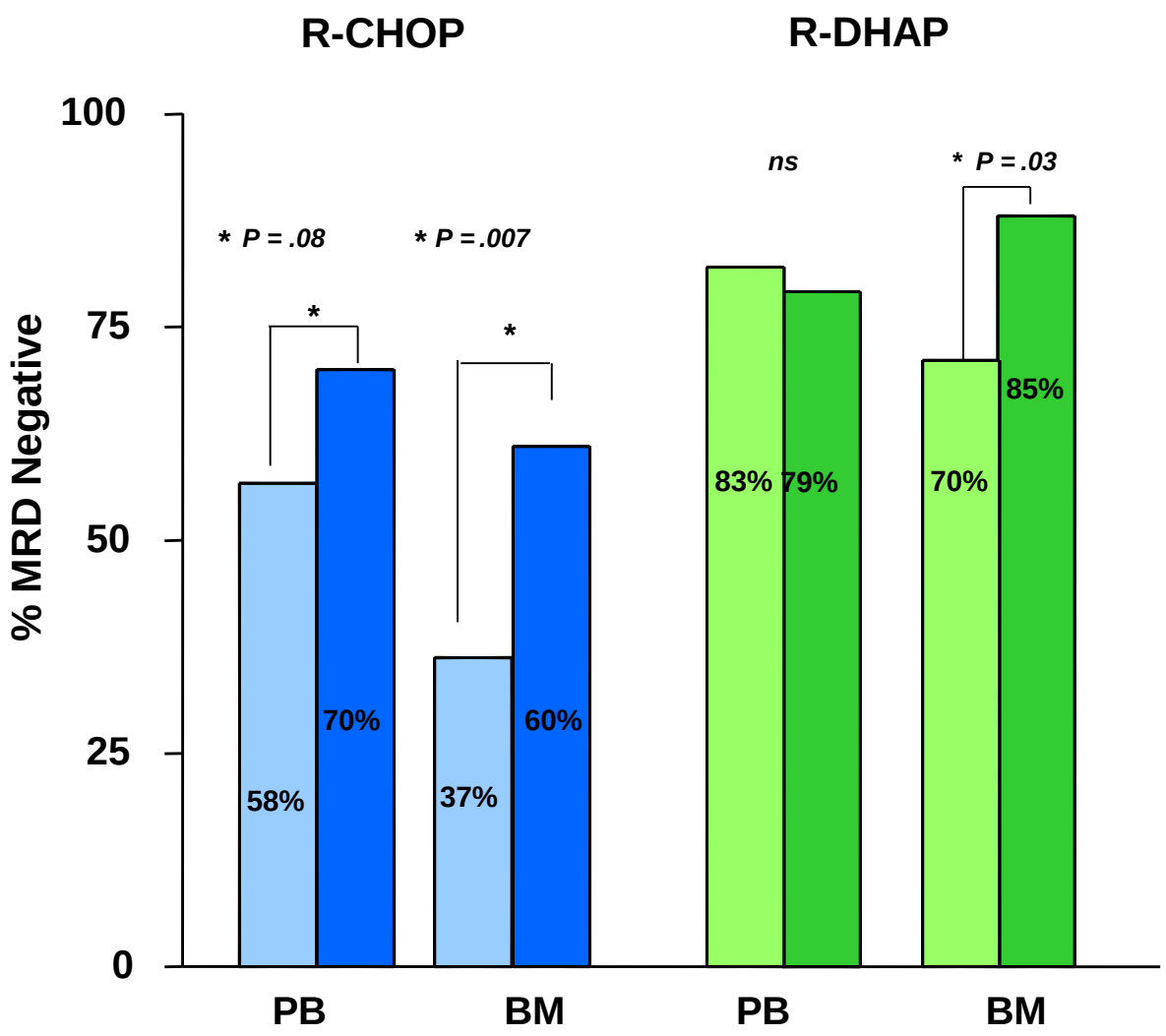



PBSCT, peripheral blood stem cell transplantation; TBI, total body irradiation

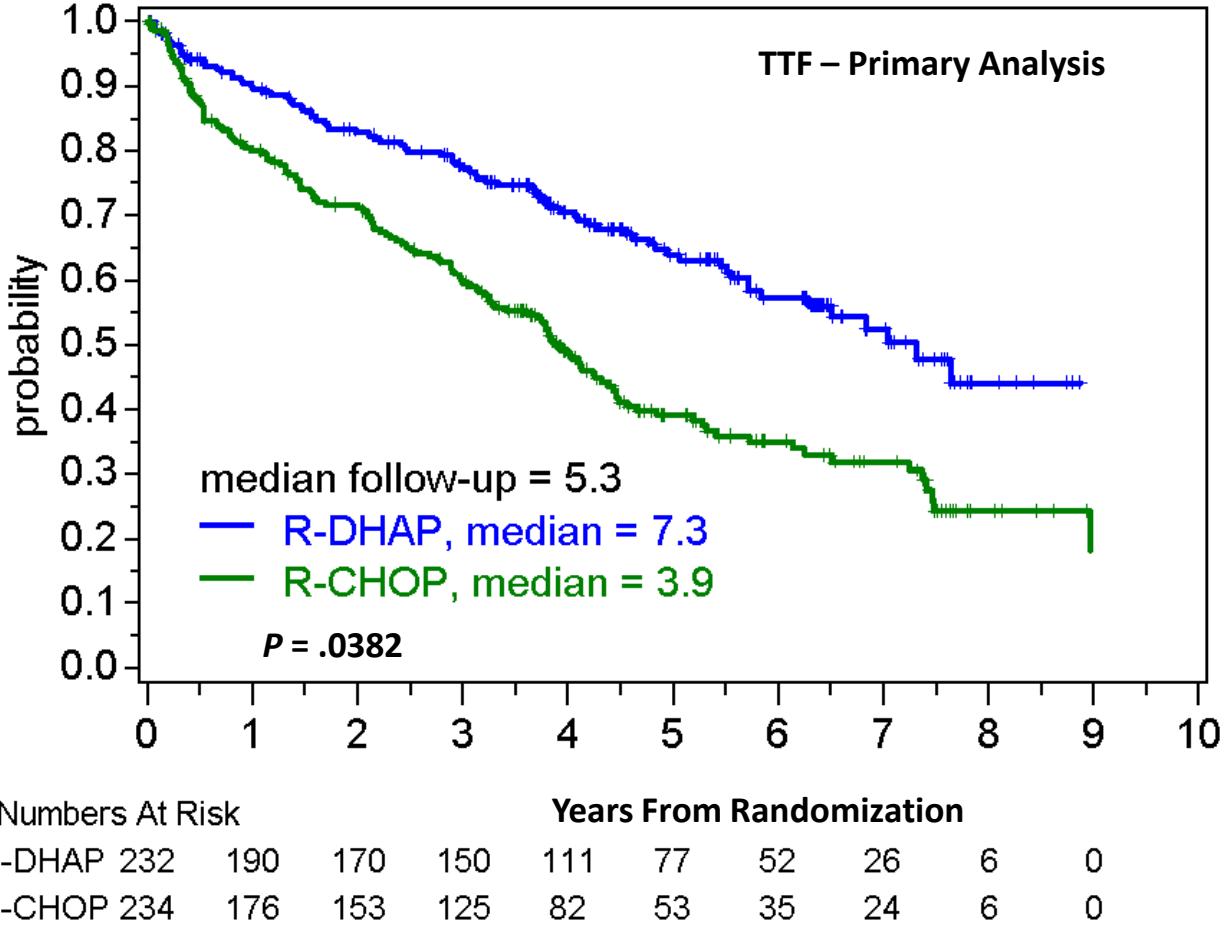
Hermine O. *Lancet.* 2016. *In press.*

*Hermine O, et al. Lancet 2016 388;565-75*

# MRD at End of Induction: Effect of ASCT



# MCL Younger:
# Time to Treatment Failure (TTF)

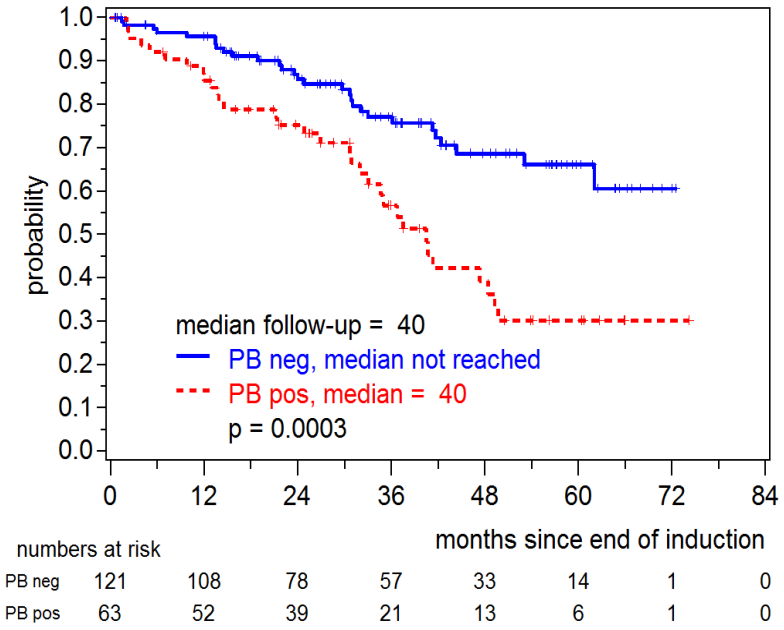



| Numbers At Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| R-DHAP | 232 | 190 | 170 | 150 | 111 | 77 | 52 | 26 | 6 | 0 |
| R-CHOP | 234 | 176 | 153 | 125 | 82 | 53 | 35 | 24 | 6 | 0 |

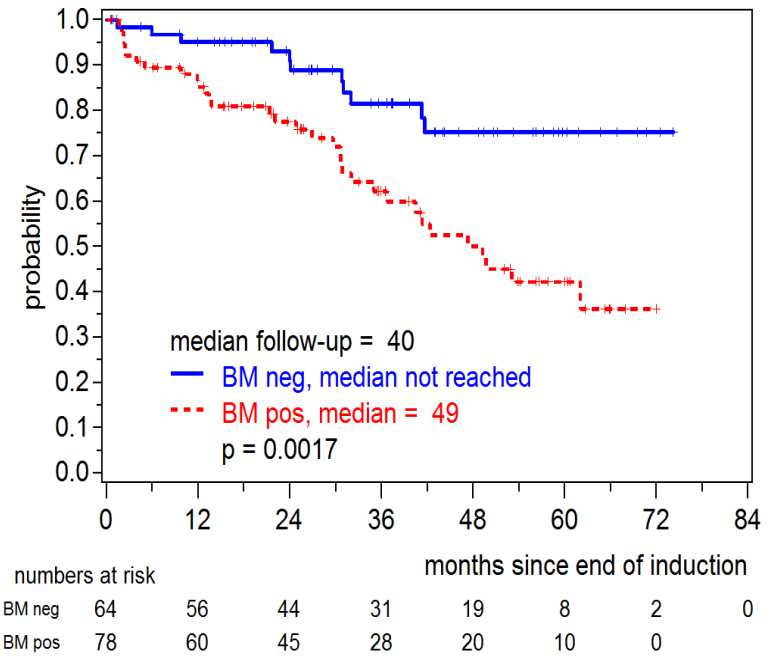
**Hermine O. *Lancet.* 2016. *In press.***

# *MCL Younger study:* Remission duration after Induction according to MRD response

PB
n=164

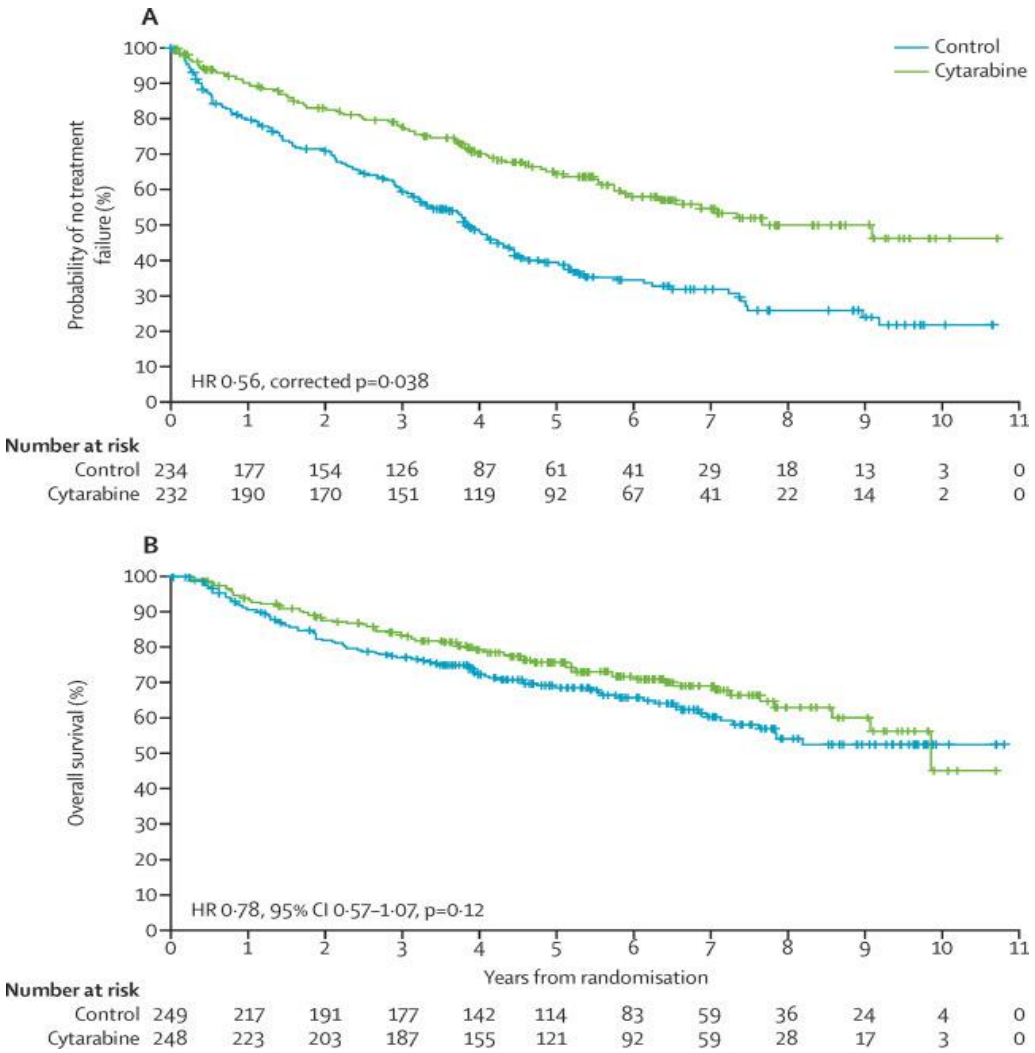



BM
n = 143



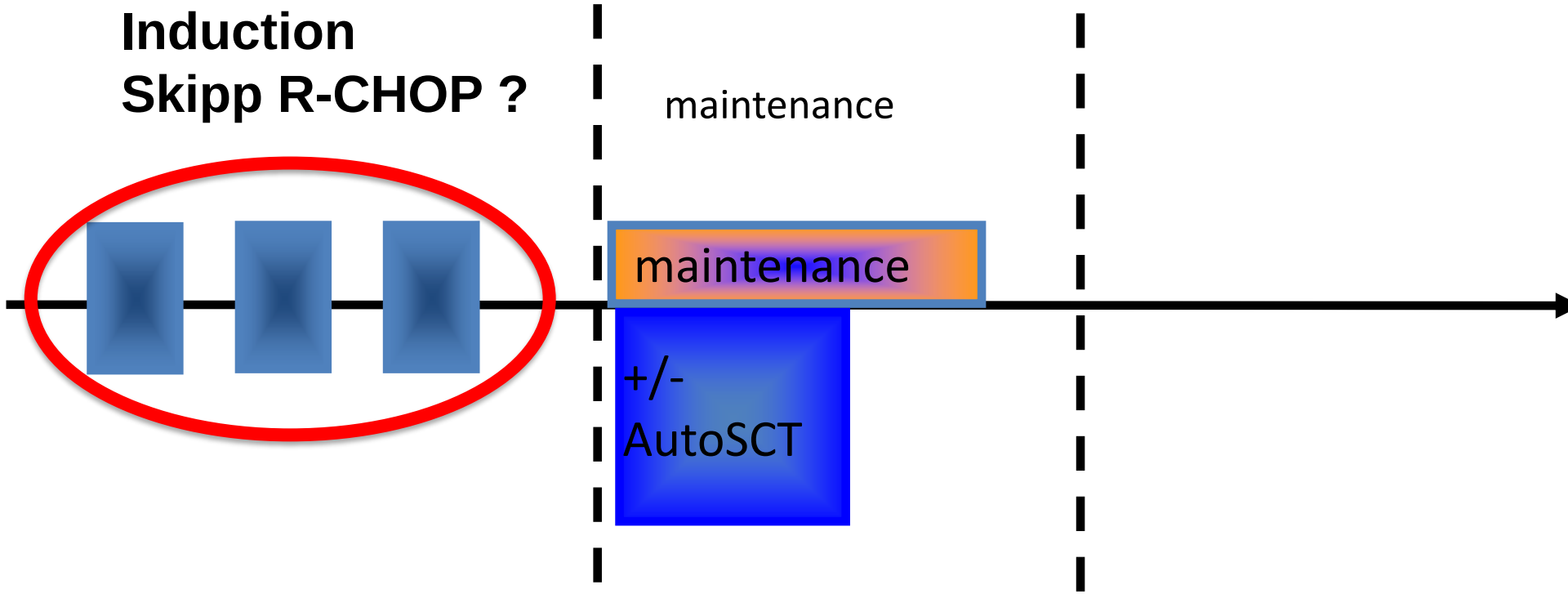

| Variable | HR | 95% CI | p |
|---|---|---|---|
| Molecular Response | 2.4 | (1.4-3.9) | 0.001 |
| MIPI score | 1.7 | (1.2-2.5) | 0.008 |
| Treatment arm | 0.6 | (0.3-1.1) | 0.1 |
| CR | 0.9 | (0.5-1.6) | 0.68 |

# MCL Younger: Overall Survival (OS)




Olivier Hermine et al. Lancet 2016;388:565-575

# Treatment strategy in MCL
# First line/young (<65y/Fit)




*=> lymphoma remission*

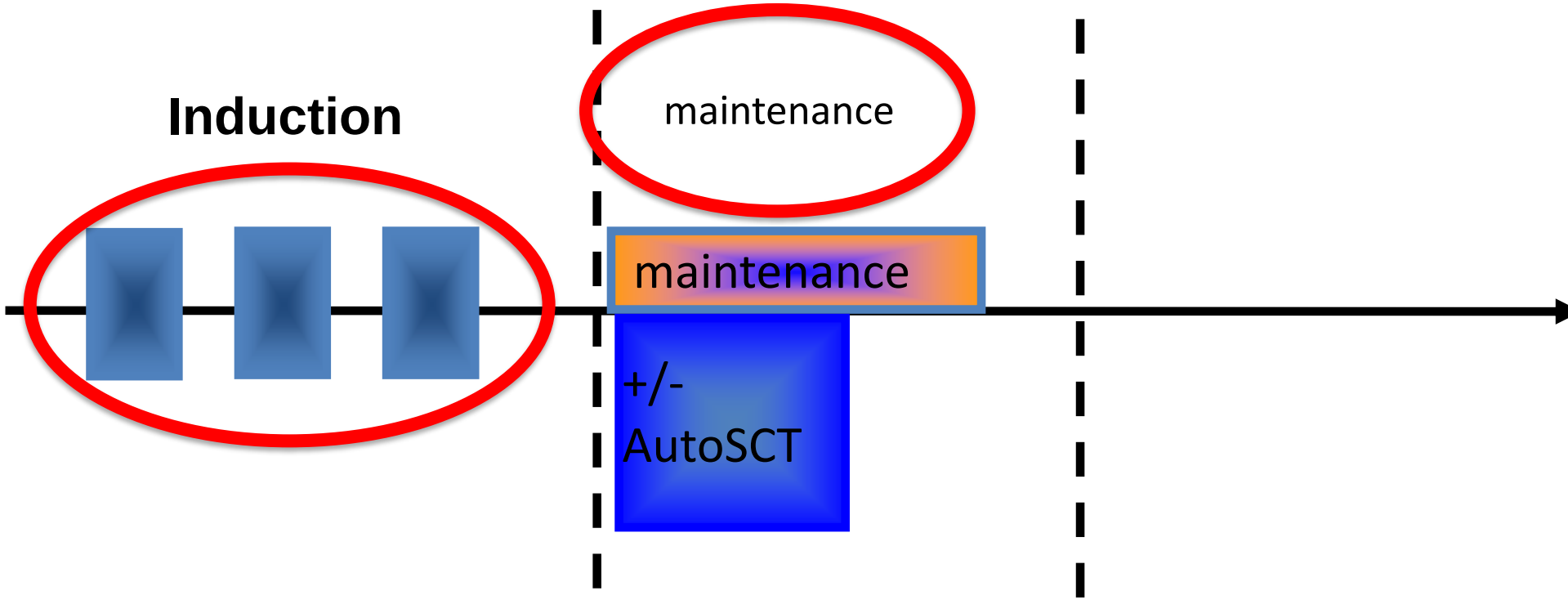
# Bendamustine pre-autograft and Stem cell collection

- BR x 3 followed by Ritux / Cytarabine x3
- 23 patients
- 96% CR/Cru
- 21/23 had a subsequent autograft

- BR Might be a good platform for further studies

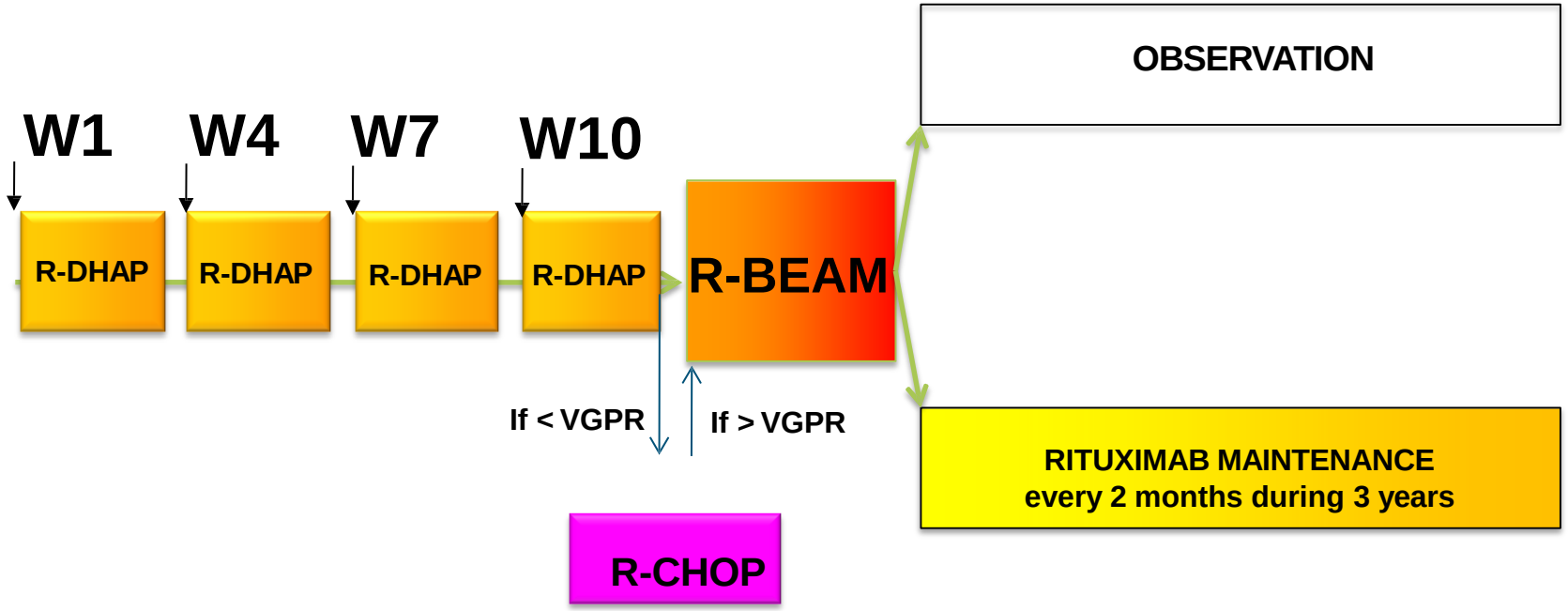
Armand et al. BJ Haematol 2016 173;89-95

# Treatment strategy in MCL
# First line/young (<65y/Fit)




*=> lymphoma remission*

# LyMa Trial



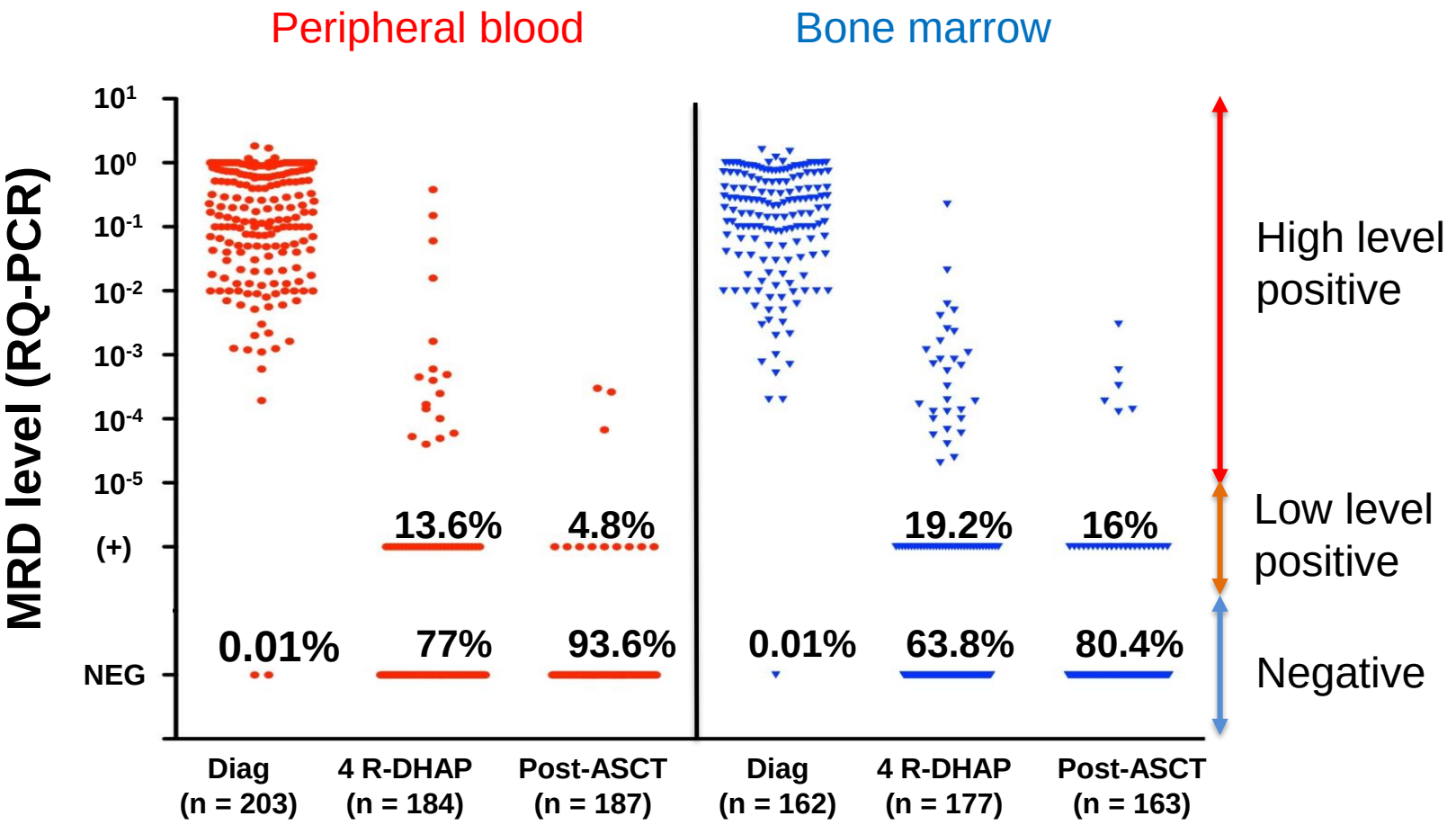

R-DHAP: Rituximab 375 mg/m$^2$; cytarabine 2 g/m$^2$ x2 IV 3 hours injection 12 hours interval; dexamethasone 40 mg days 1-4; cisplatin 100 mg/m$^2$ day 1 (or oxaliplatin or carboplatin)

R-BEAM: Rituximab 500 mg/m$^2$ day 8; BCNU 300 mg/m$^2$ day 7; Etoposide 400 mg/m$^2$/d day 6 to day 3; cytarabine 400 mg/m$^2$/d day 6 to day 3; melphalan 140 mg/m$^2$ day 2

Le Gouill S, et al. *Hematol Oncol.* 2015;22(s1): Abstract 61.

# Response rates according (Cheson 99) after 4 x R-DHAP and after ASCT

| | After R-DHAP | After R-CHOP | After ASCT |
|---|---|---|---|
| n | 299 | 20 | 257 |
| CR/CRu (%) | 81.4% | 42% | 92.7% |
| PR (%) | 15.5% | 37% | 6.9% |
| SD/prog (%) | 3.2% | 21% | 0.4% |
| Missing (n) | 15 | 1 | 10 |

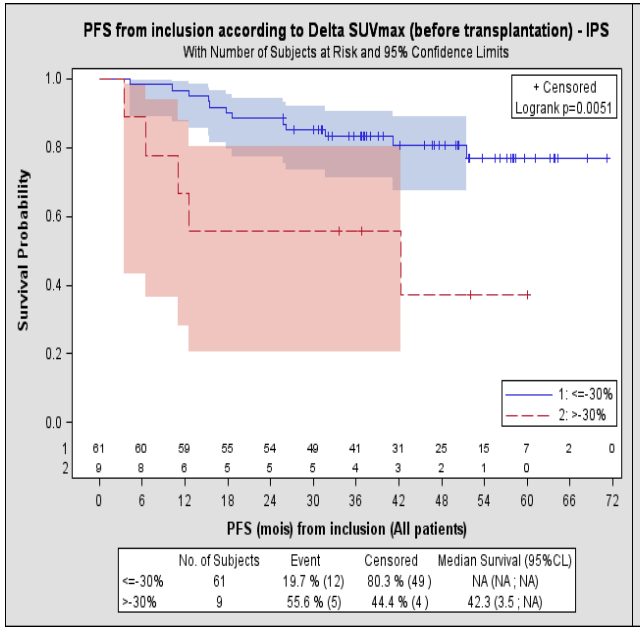


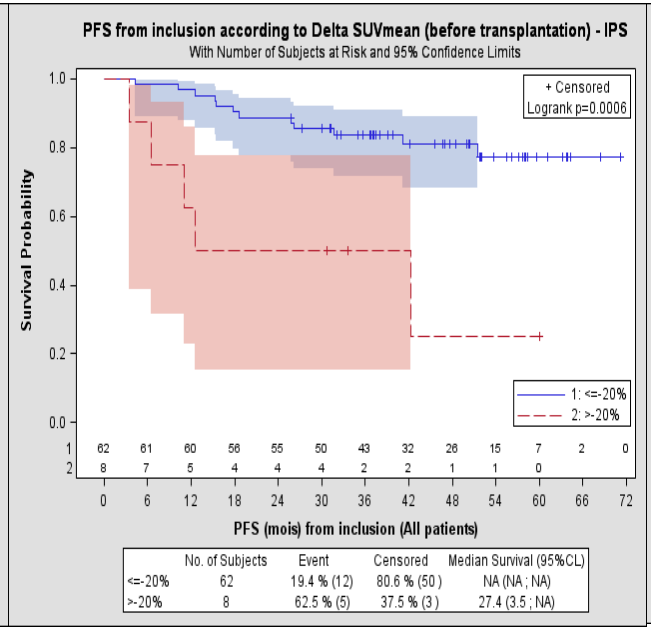

(Interim analysis samples ; n = 711)

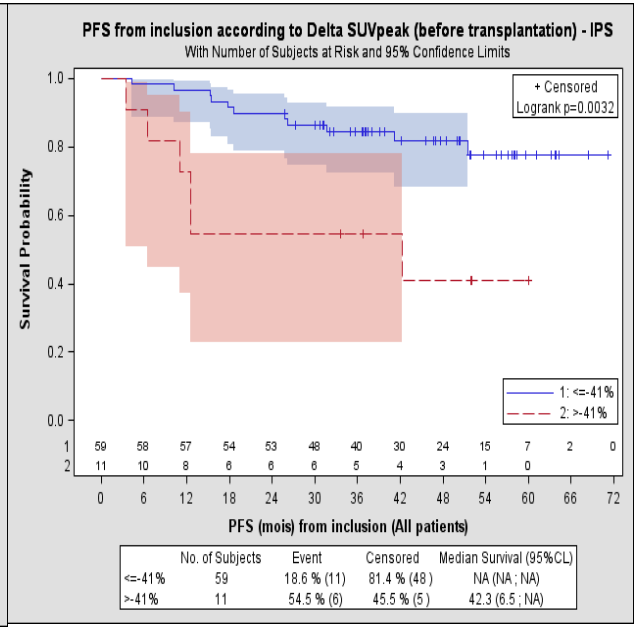
EURO-MRD : ASO *IGH* qPCR
Minimal assay sensitivity 10-4

# Prognostic value of DSUV parameters at the end of induction

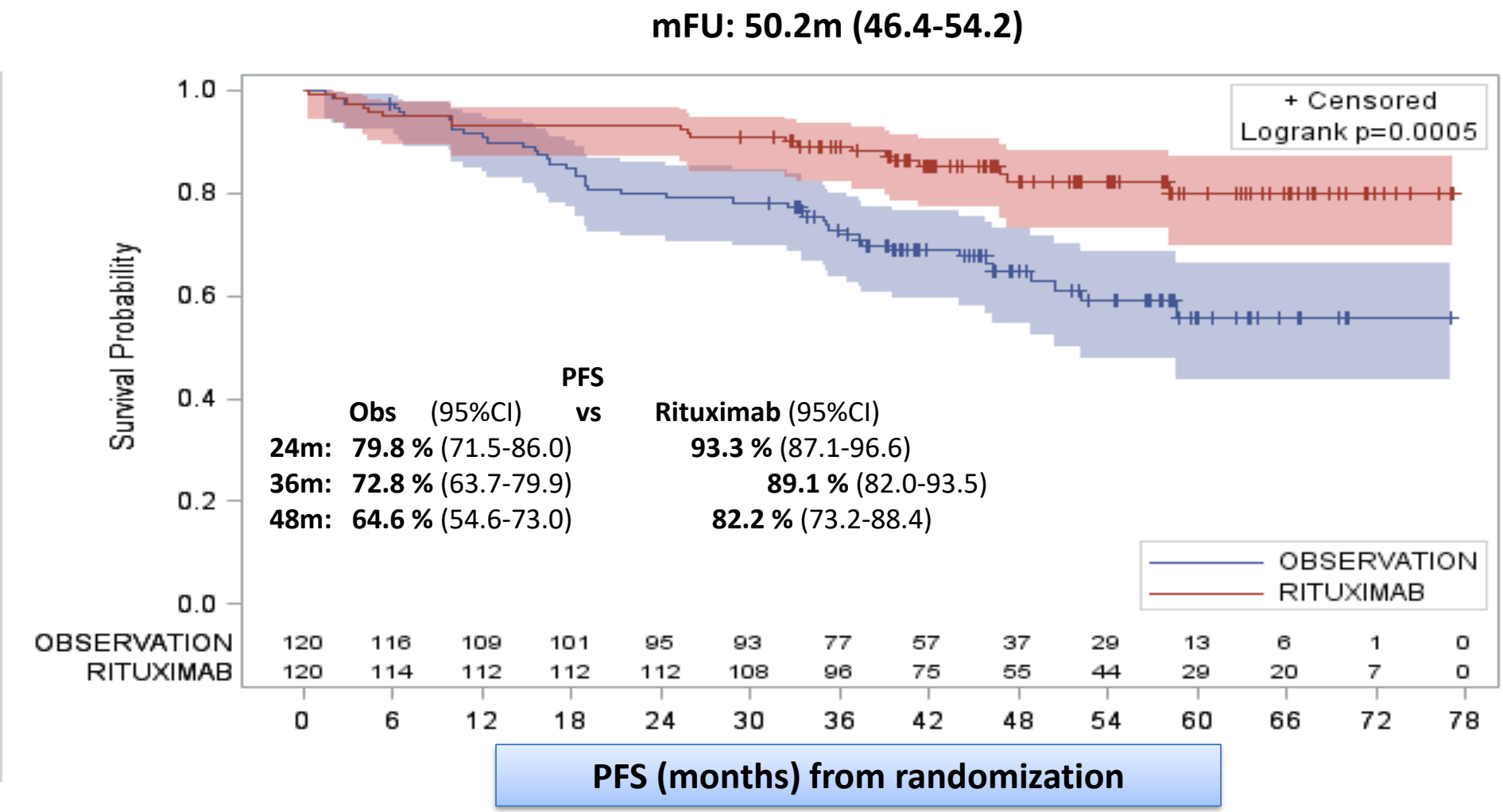
| $\Delta SUV_{max}$ (p=0.005, cutoff=-30%) | $\Delta SUV_{mean}$ (p=0.0006, cutoff=-20%) | $\Delta SUV_{peak}$ (p=0.003, cutoff=-41%) |
|---|---|---|



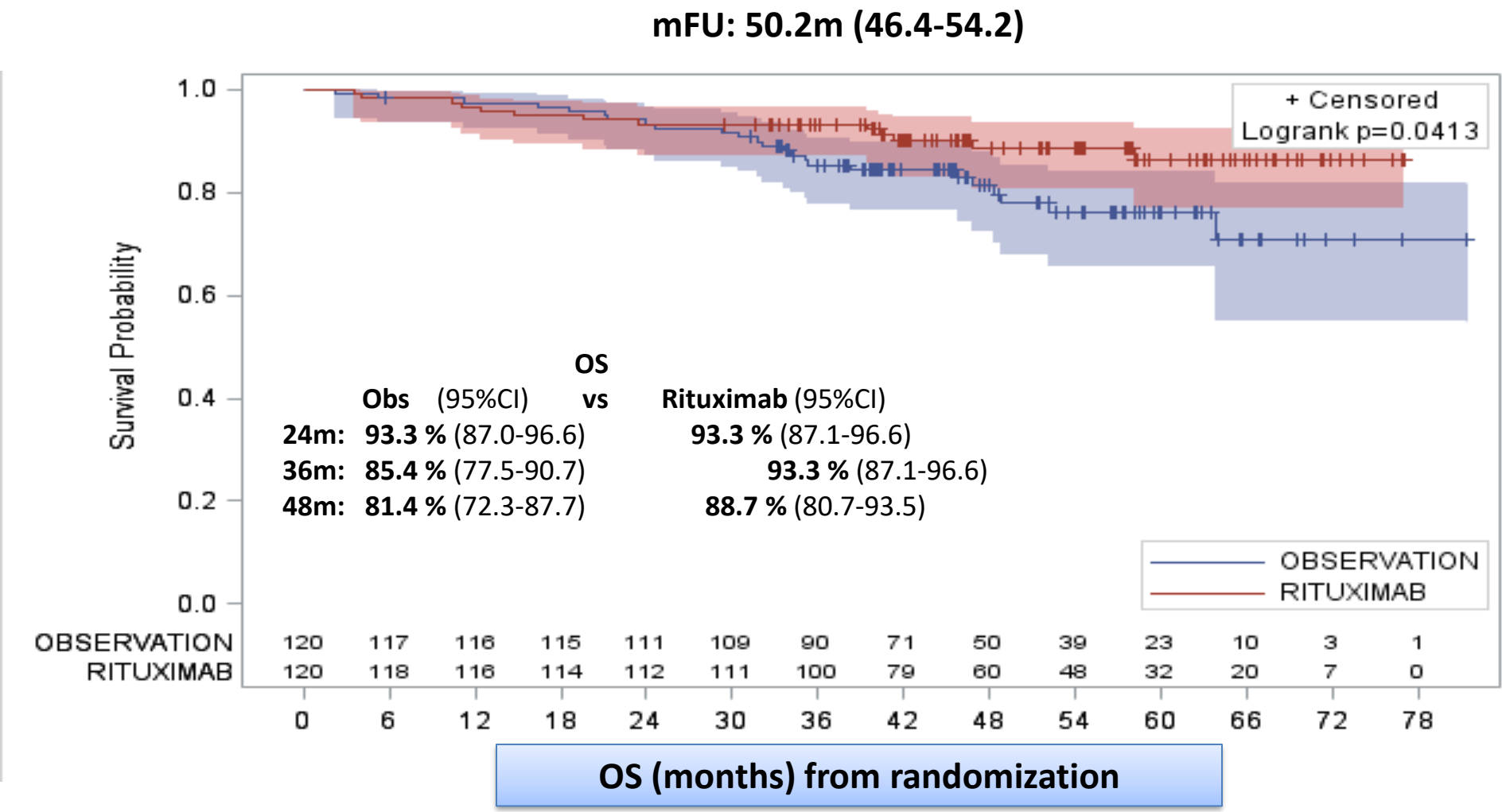



# PFS from Randomization



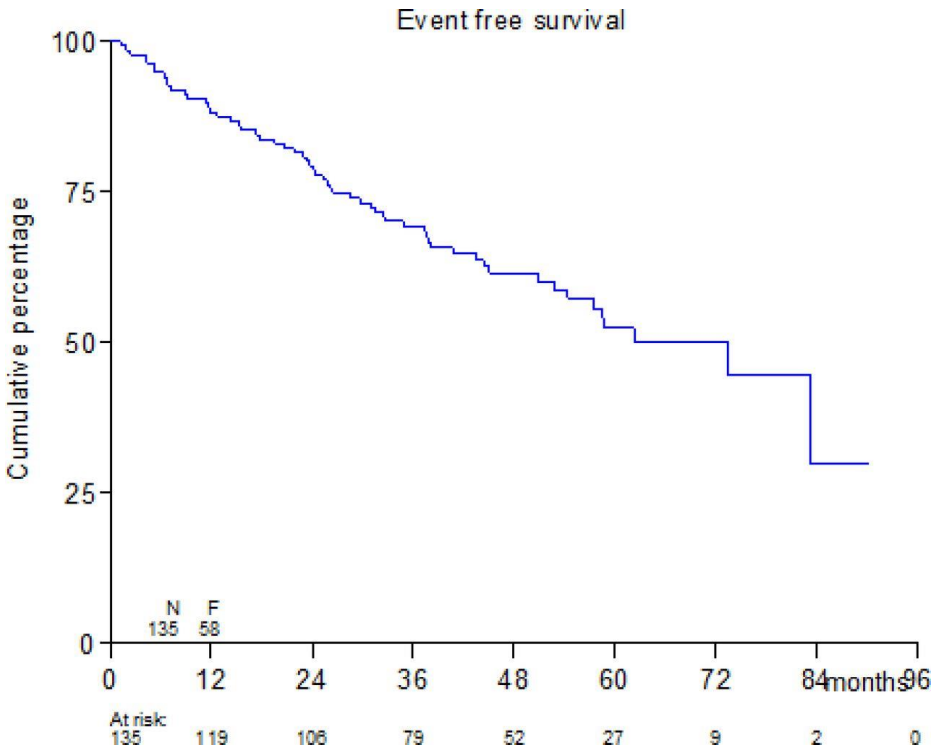
# OS from Randomization

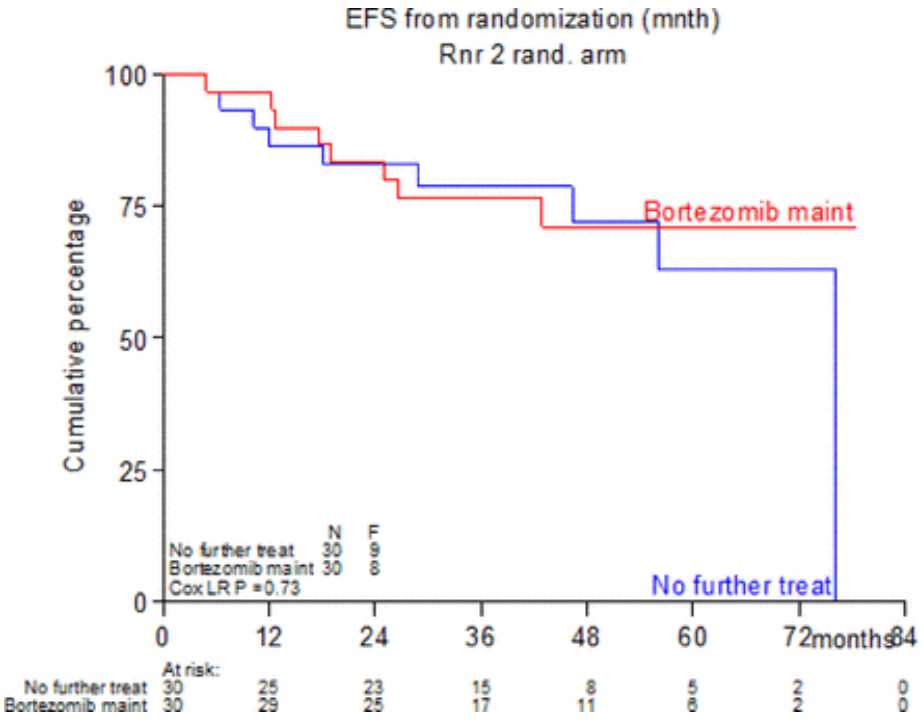


# Bortezomib maintenance therapy after induction with R-CHOP, ARA-C and ASCT in younger MCL patients

**MCL pts= 60**

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




*Doorduijin JK et al ASH 2015 oral session abs 339*

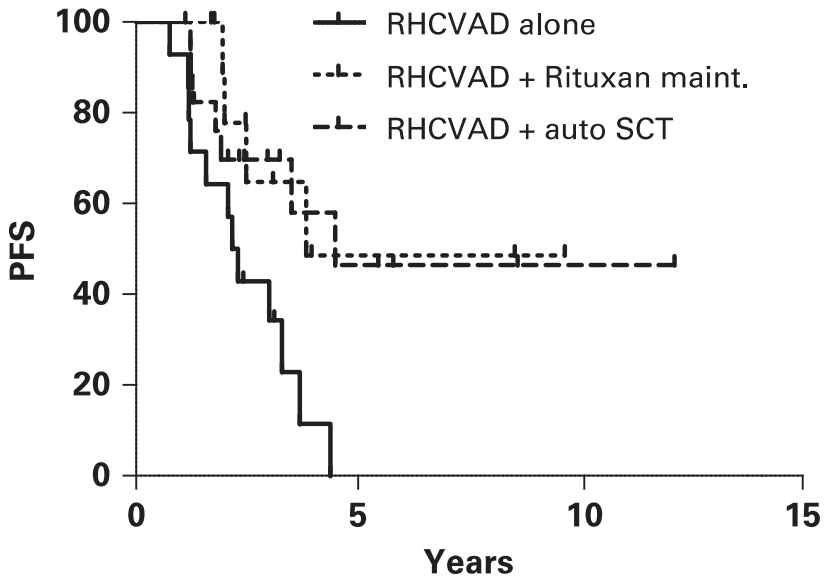
**ORIGINAL ARTICLE**

# Potential prolongation of PFS in mantle cell lymphoma after R-HyperCVAD: auto-SCT consolidation or rituximab maintenance

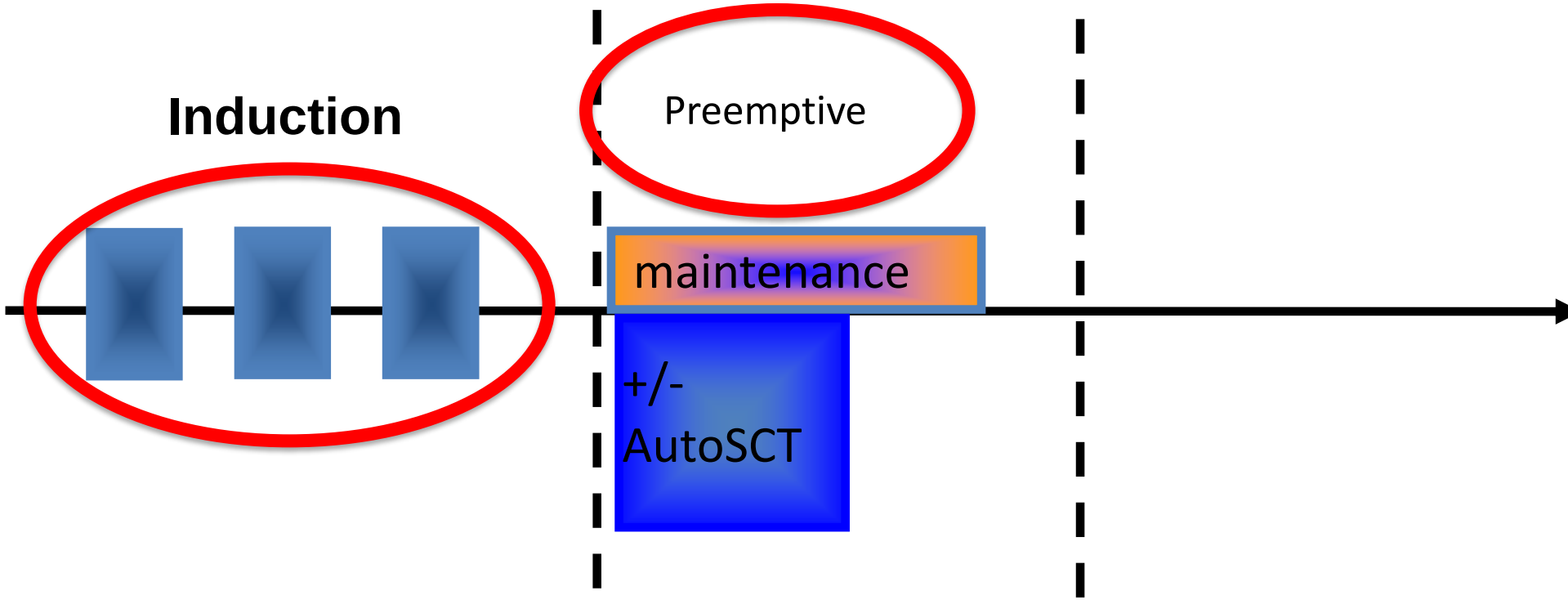
T Ahmadi[1], J McQuade[2], D Porter[1], N Frey[1], AW Loren[1], SC Goldstein[1], J Svoboda[1], E Stadtmauer[1], SJ Schuster[1] and SD Nasta[1]

Bone Marrow Transplantation (2012) **47**, 1082–1086



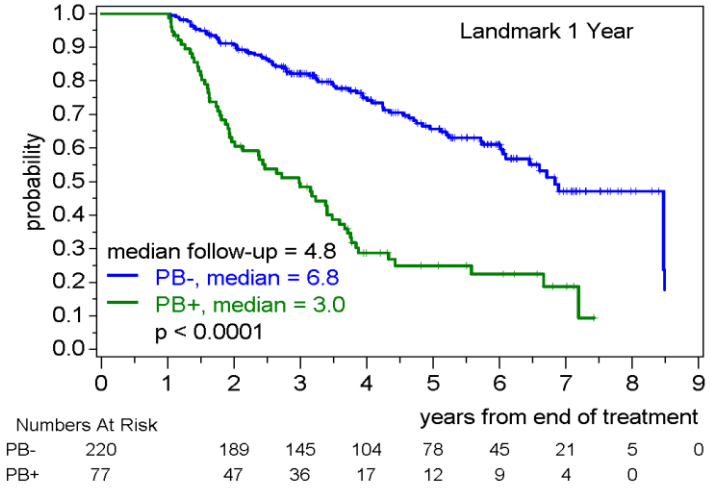


# Treatment strategy in MCL
# First line/young (<65y/Fit)

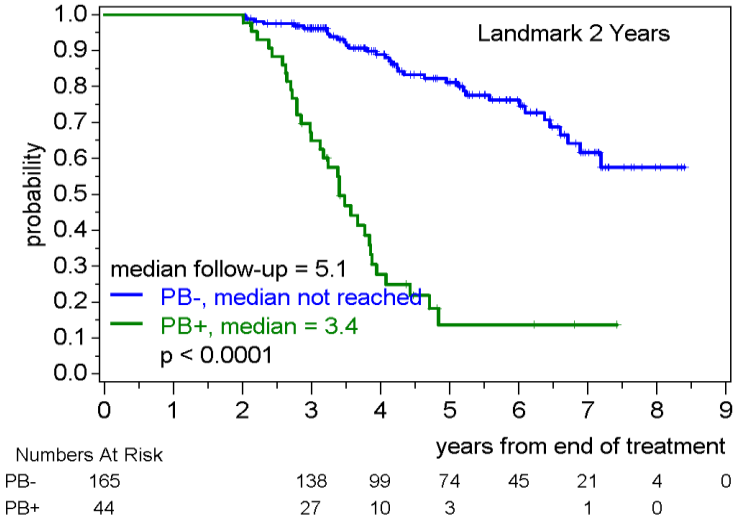



*=> lymphoma remission*

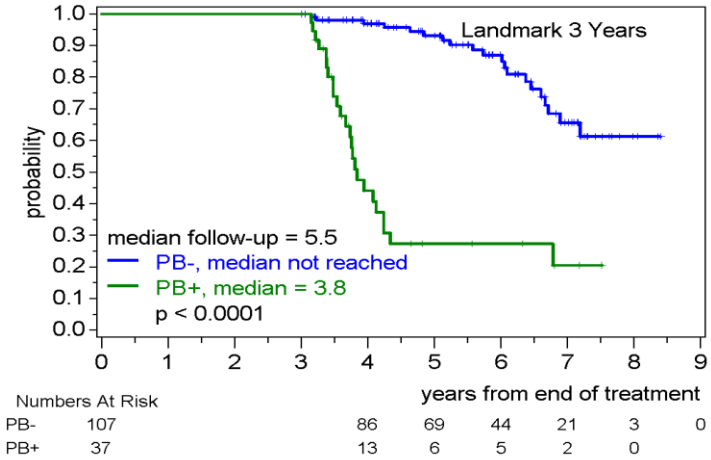
# Landmark analyses for PFS in remission after ASCT (MCL Younger) or end of induction (MCL Elderly).

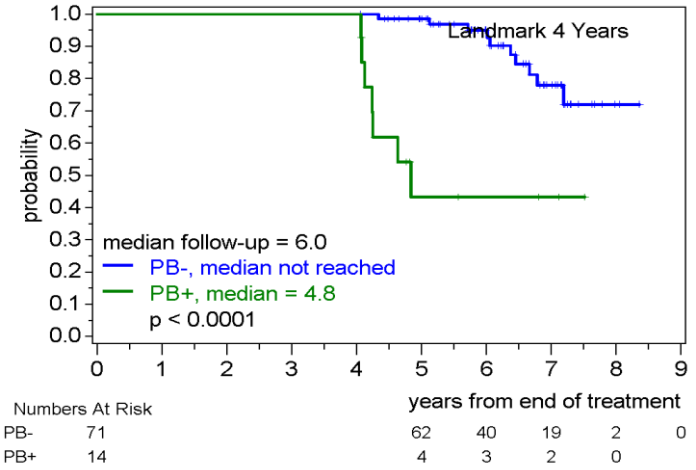



P <0.0001 HR 3,26 (95%CI 2,3-4,61)



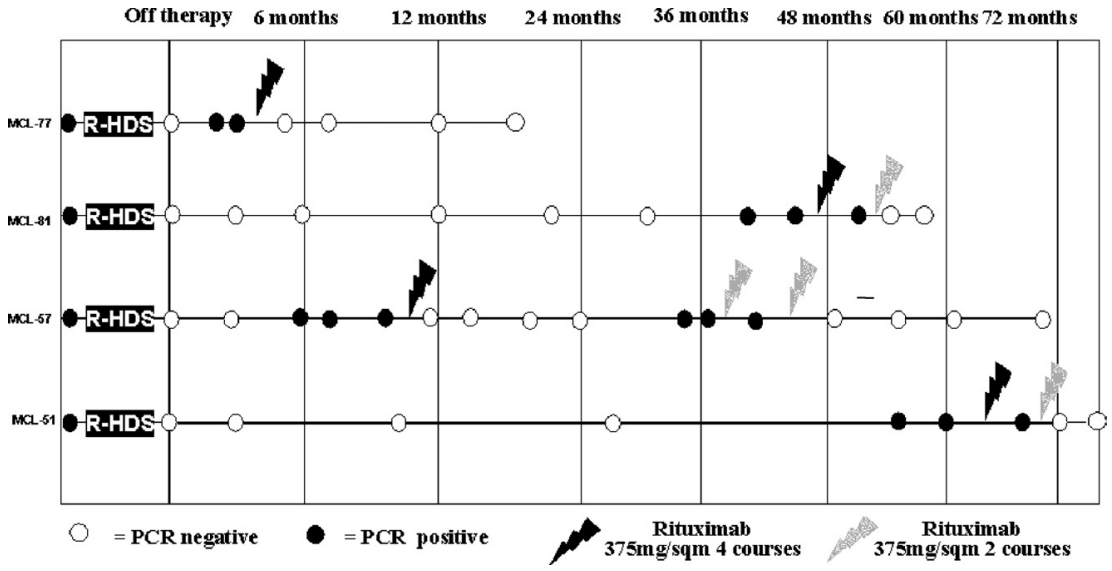

p= 0.0148 HR 1.55 (95%CI 1.1.-2.2)



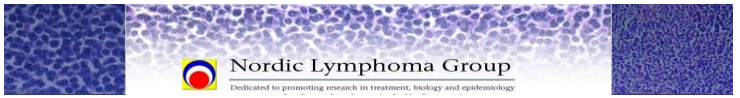



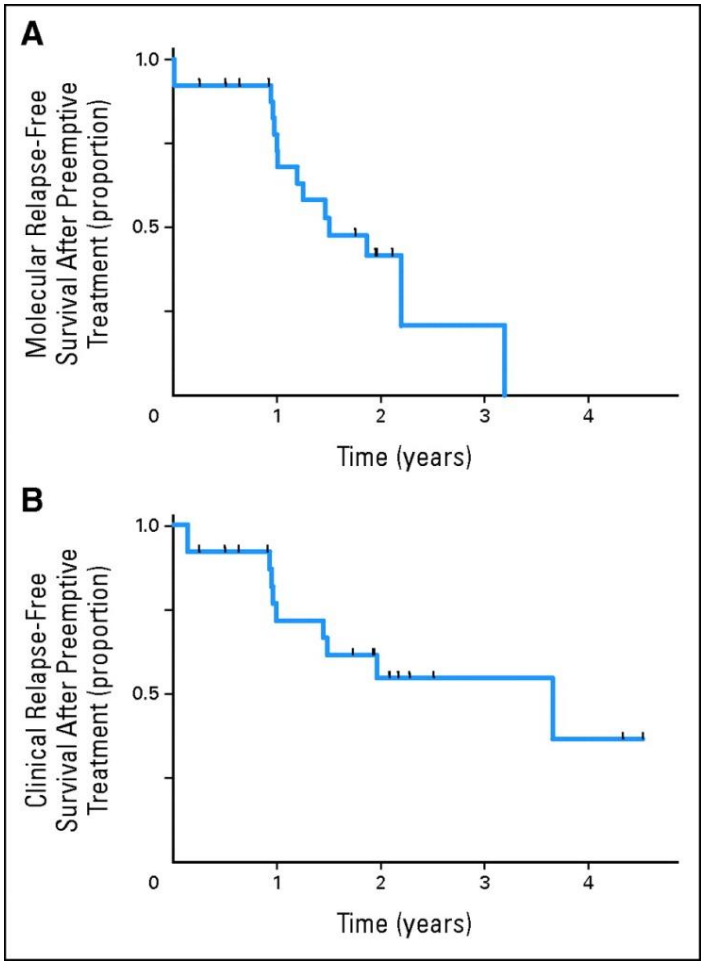

**Cox regression: independent of MIPI, trial and treatment arm**

# Preemptive treatment with Rituximab of molecular relapse in MCL




Ladetto M et al Biol Blood and Marrow Transpl. 2006

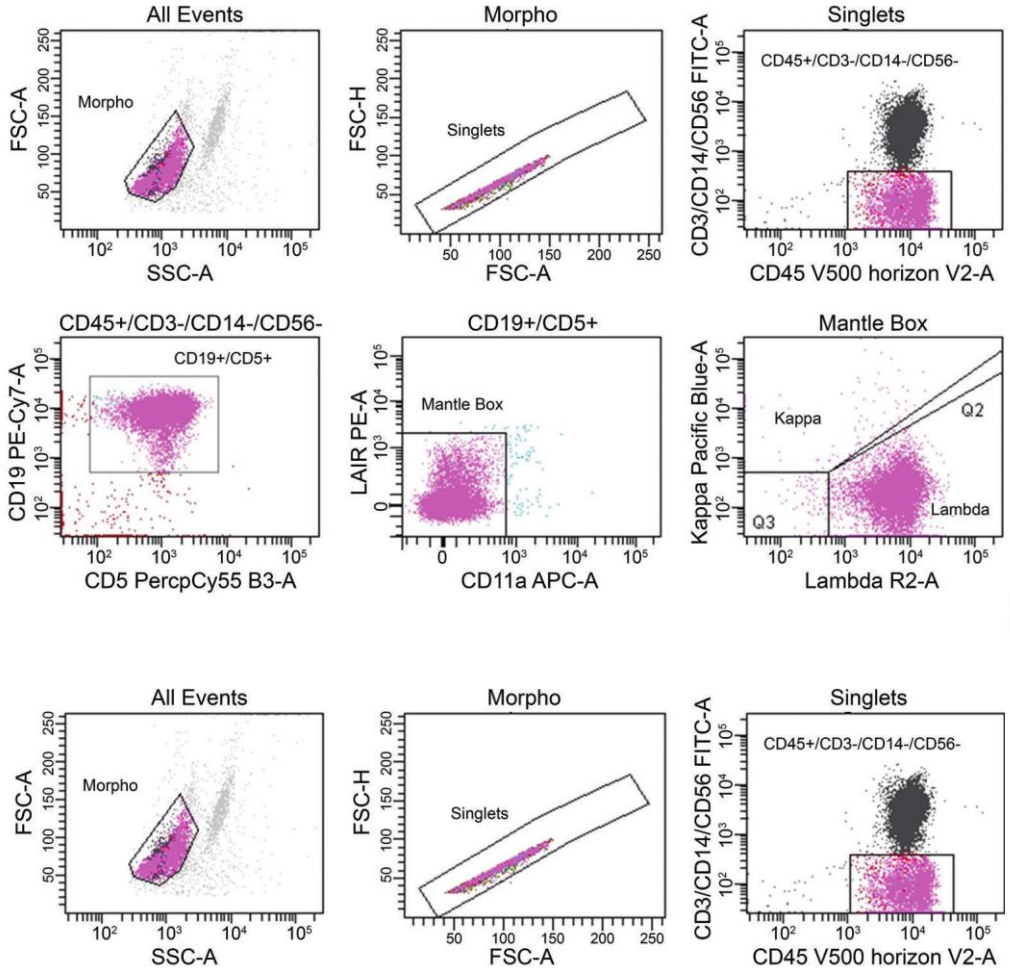


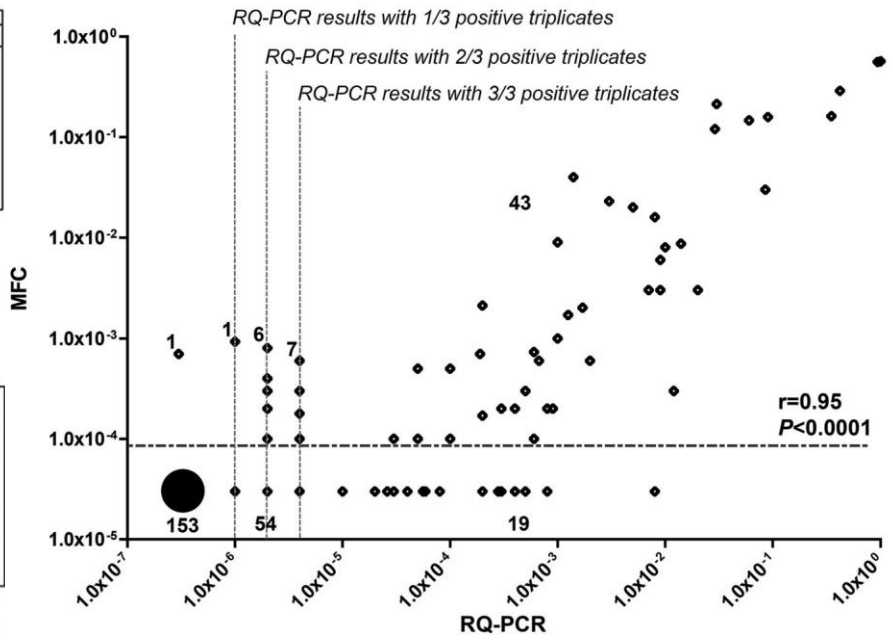



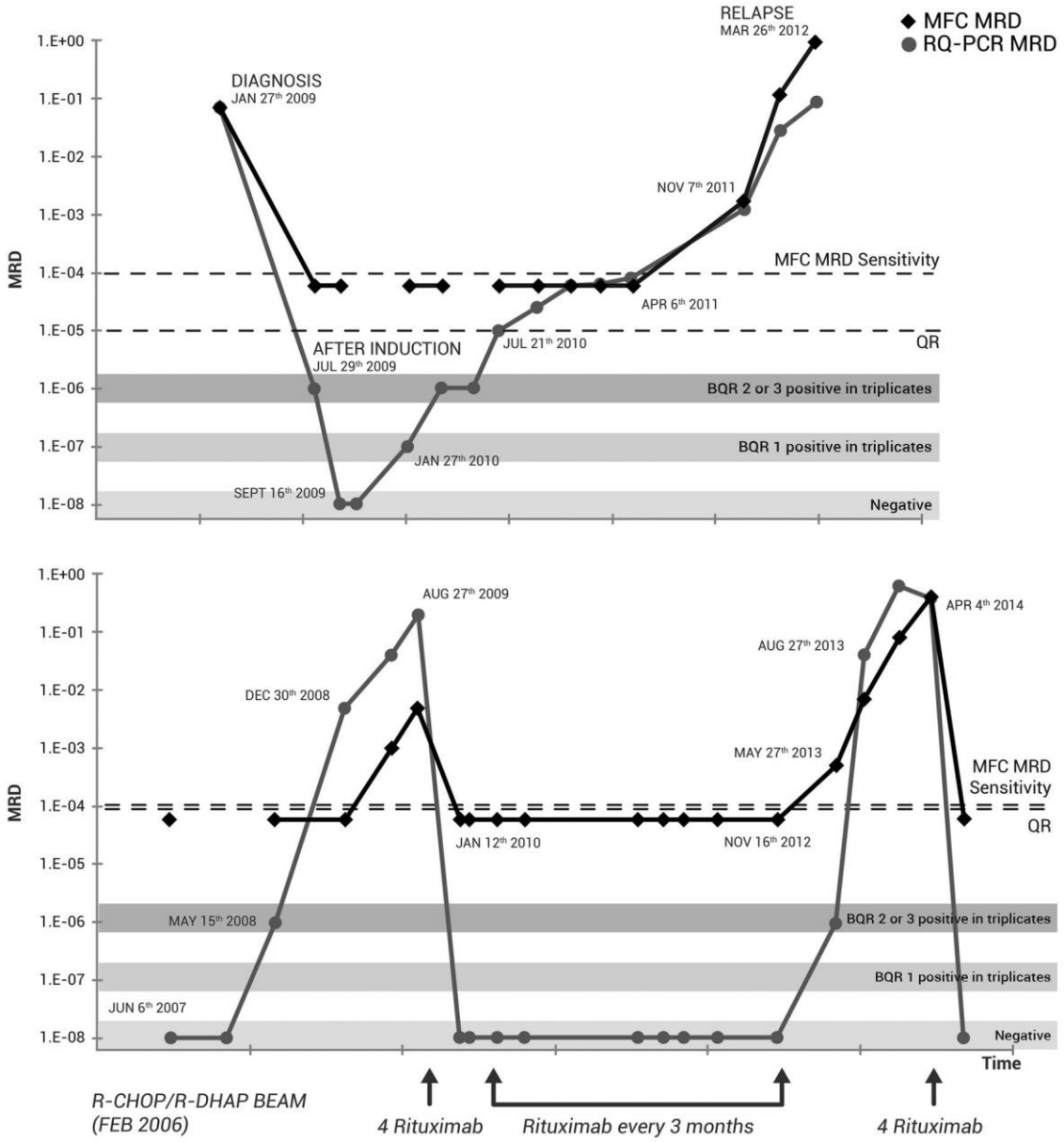

Andersen, N. S. et al. J Clin Oncol. 2009

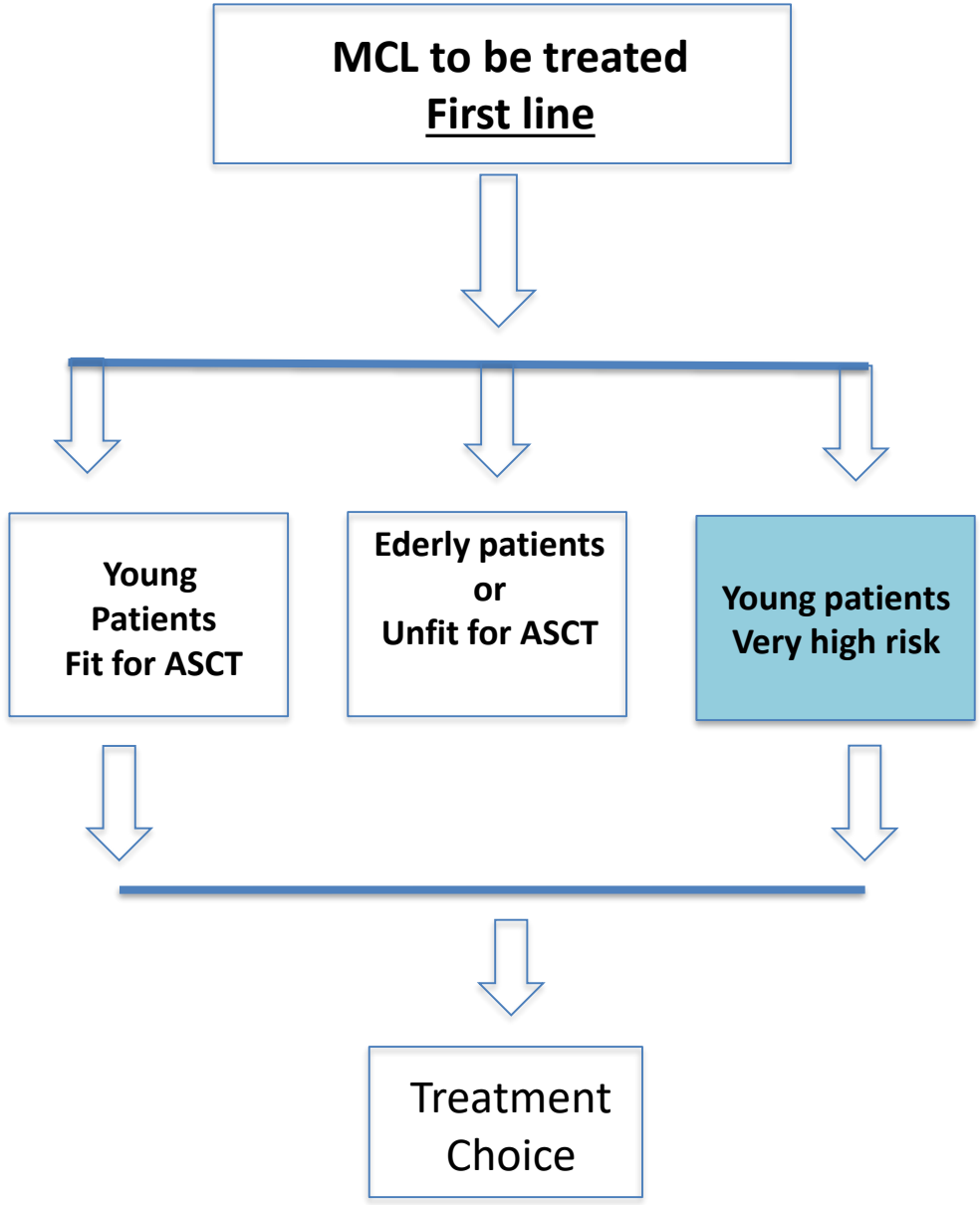
# Minimal residual disease monitoring by 8-color flow cytometry in mantle cell lymphoma: an EU-MCL and LYSA study

Morgane Cheminant,[1,2] Coralie Derrieux,[1] Aurore Touzart,[1] Stéphanie Schmit,[1] Adrien Grenier,[1] Amélie Trinquand,[1] Marie-Hélène Delfau-Larue,[3] Ludovic Lhermitte,[1] Catherine Thieblemont,[4] Vincent Ribrag,[5] Stéphane Cheze,[6] Laurence Sanhes,[7] Fabrice Jardin,[8] François Lefrère,[2] Richard Delarue,[2] Eva Hoster,[9,10] Martin Dreyling,[10] Vahid Asnafi,[1] Olivier Hermine,[2] and Elizabeth Macintyre[1]




MFC MRD
RQ-PCR MRD
RELAPSE
MAR 26th 2012
DIAGNOSIS
JAN 27th 2009
NOV 7th 2011
MFC MRD Sensitivity
APR 6th 2011
QR
AFTER INDUCTION
JUL 29th 2009
JUL 21th 2010
BQR 2 or 3 positive in triplicates
BQR 1 positive in triplicates
JAN 27th 2010
SEPT 16th 2009
Negative
MRD
1.E+00
1.E-01
1.E-02
1.E-03
1.E-04
1.E-05
1.E-06
1.E-07
1.E-08
AUG 27th 2009
APR 4th 2014
AUG 27th 2013
DEC 30th 2008
MAY 27th 2013
MFC MRD Sensitivity
QR
JAN 12th 2010
NOV 16th 2012
MAY 15th 2008
BQR 2 or 3 positive in triplicates
BQR 1 positive in triplicates
JUN 6th 2007
Negative
Time
R-CHOP/R-DHAP BEAM
(FEB 2006)
4 Rituximab
Rituximab every 3 months
4 Rituximab


MCL to be treated
First line
Young
Patients
Fit for ASCT
Ederly patients
or
Unfit for ASCT
Young patients
Very high risk
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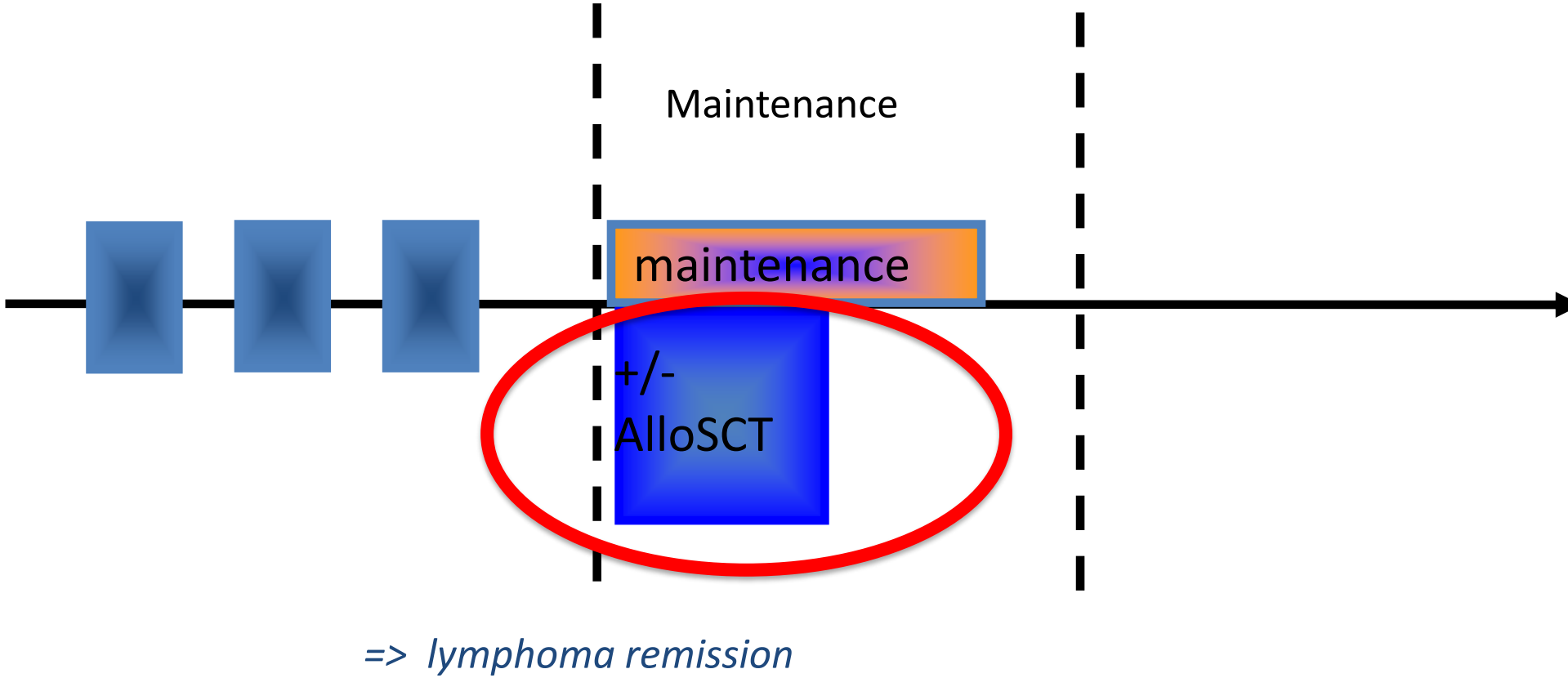
# Treatment strategy in MCL
# First line/young (<65y/Fit)

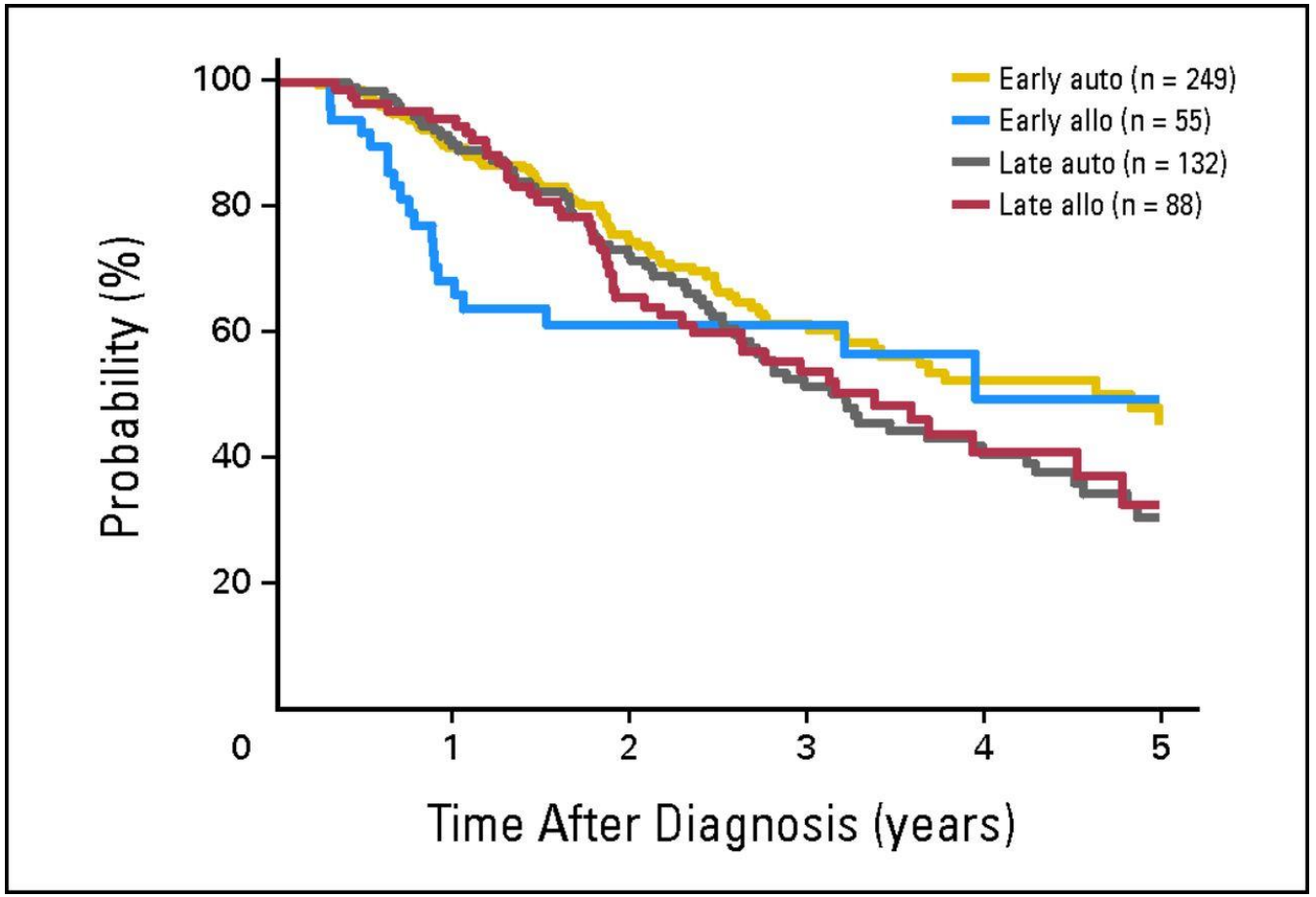



*=> lymphoma remission*

# RIC Allo SCT in MCL

**Early= 1st CR/PR**
**<3 Lines**

**Late= all others**

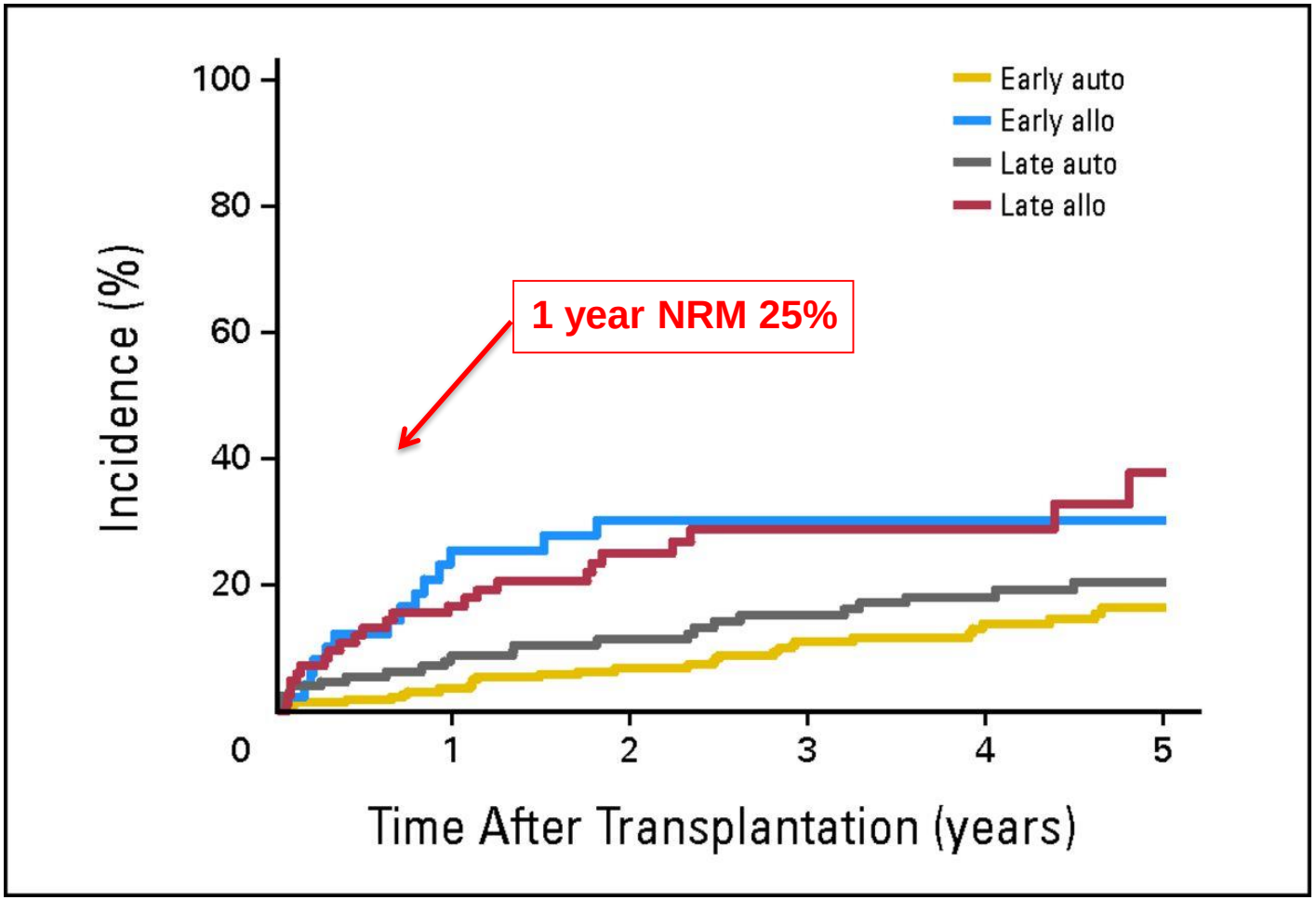



Fenske T S et al. JCO 2014;32:273-281



JOURNAL OF CLINICAL ONCOLOGY ASCO

# NRM Following Reduced Intensity Allogeneic Stem Cell Transplantation and Autologous Stem Cell Transplantation



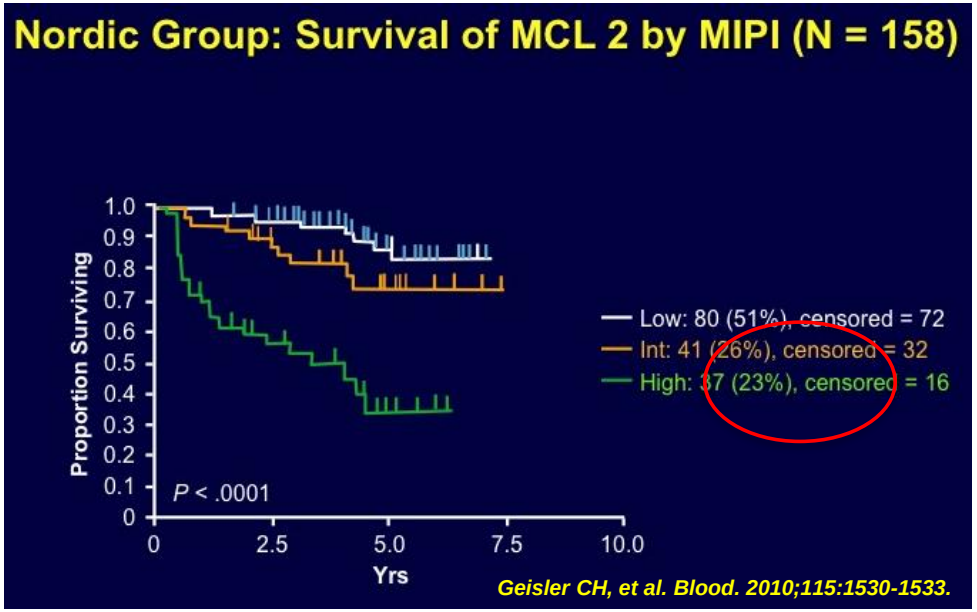

Fenske T S et al. JCO 2014;32:273-281

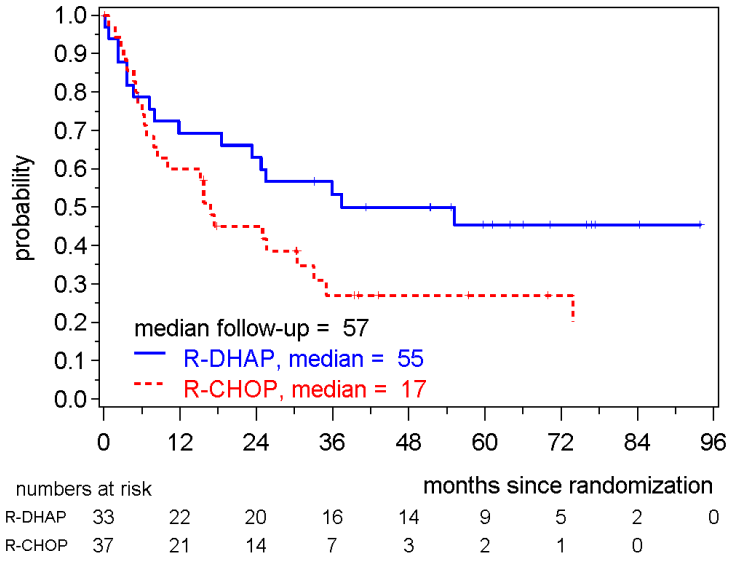


JOURNAL OF CLINICAL ONCOLOGY ASCO

# Possible role for an early Allo SCT?

- ✓ PR pre ASCT?
- ✓ Blastoid variant?
- ✓ 17p/p53, P16, NOTCH ?
- ✓ High MIPI?
- ✓ MRD + Pet + after induction?



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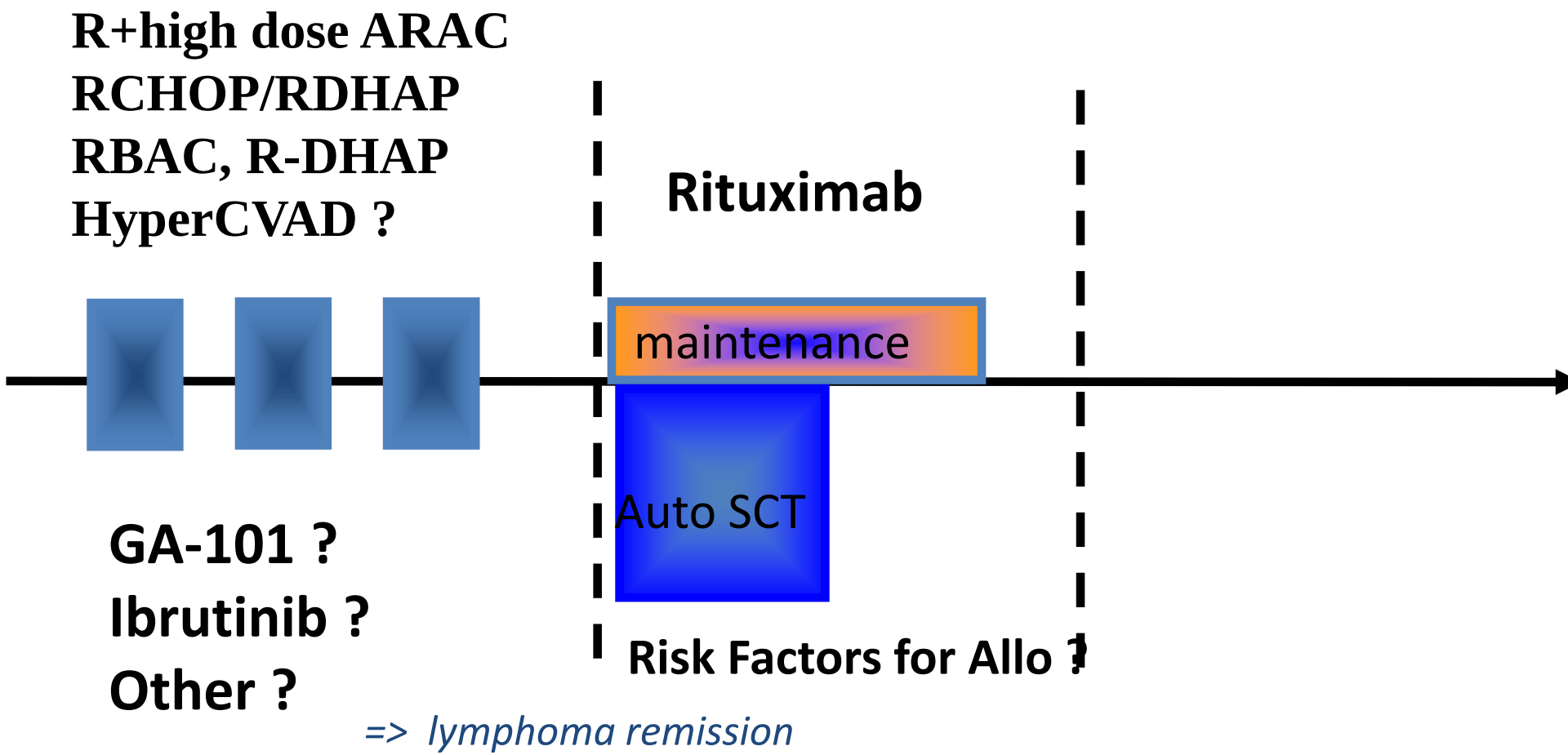
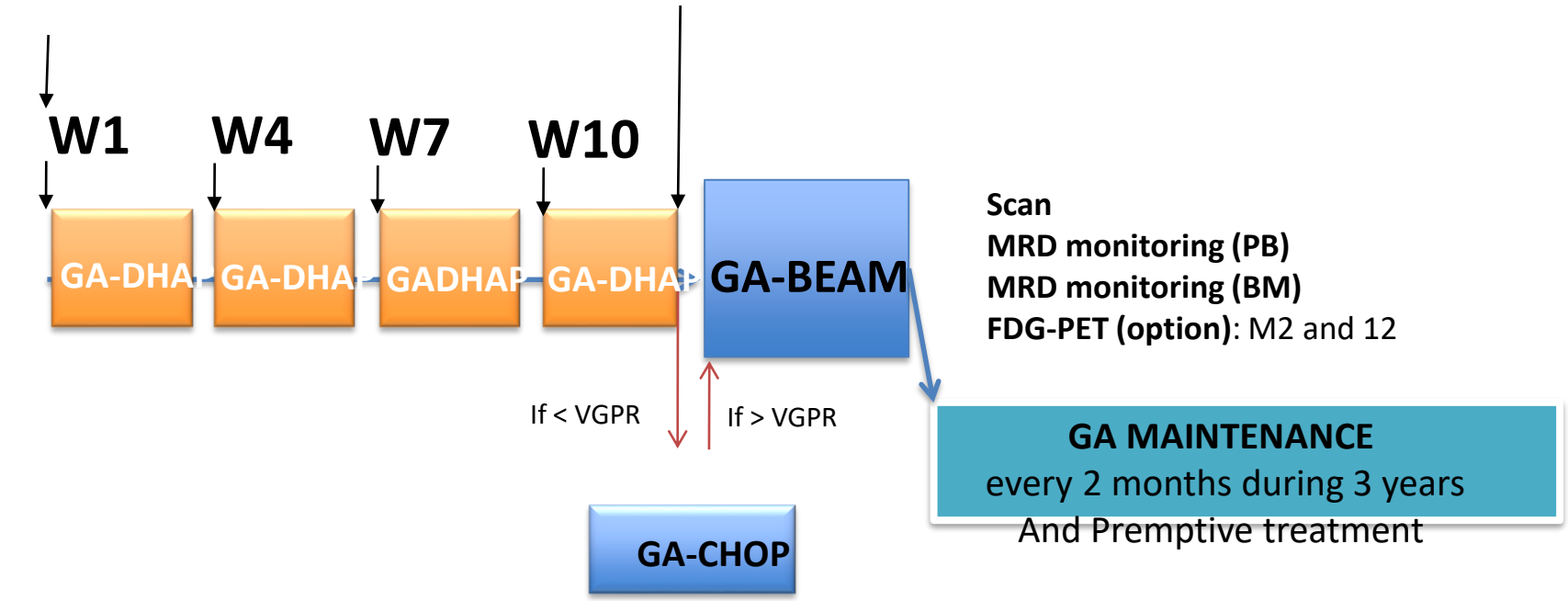
# First line/young (<65y/Fit)

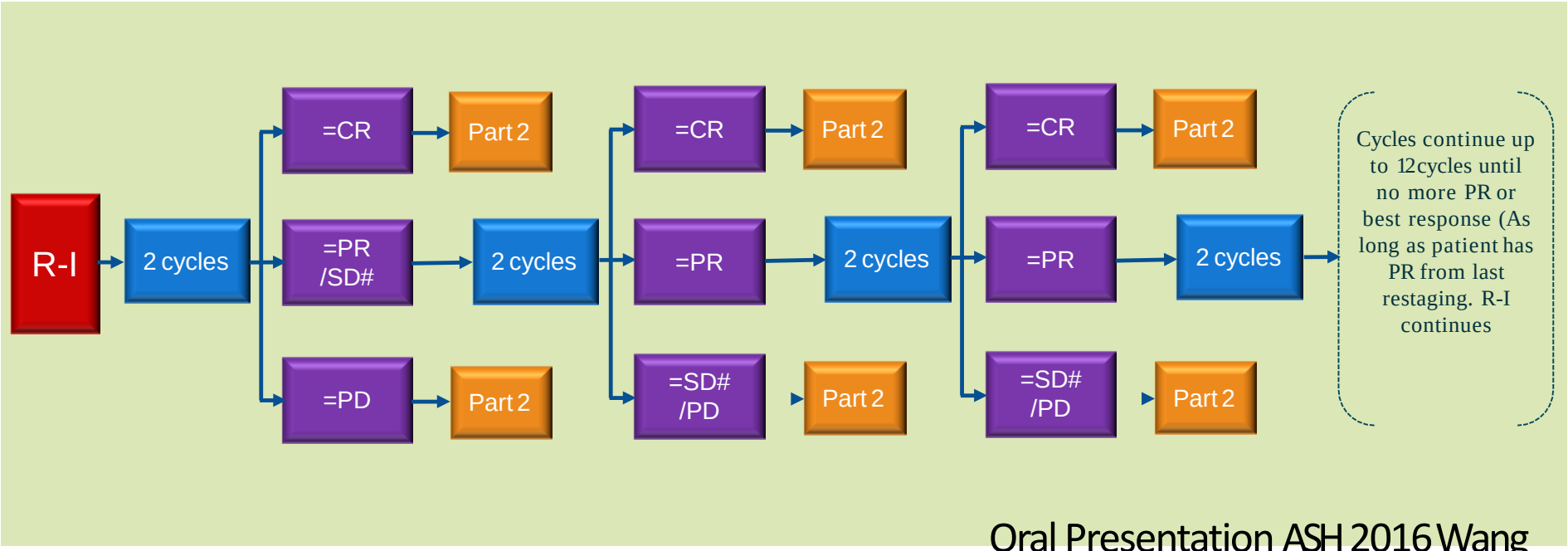


# Lyma 101 trial (France)



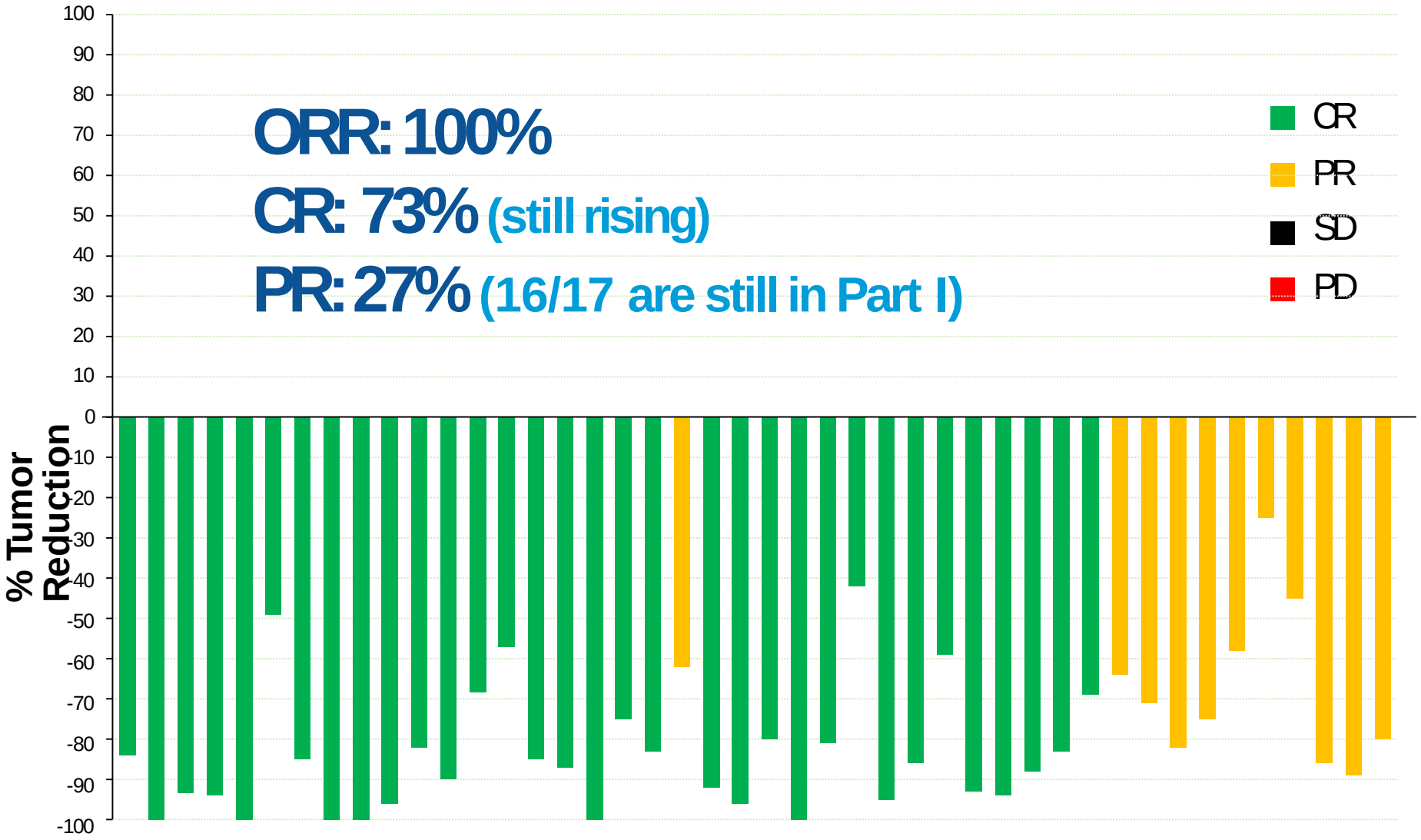
# Study Therapy PART I: Chemo-free Ibrutinib + Rituximab

- Oral ibrutinib at 560 mg daily, each cycle is 28 days
- 4 weekly loading doses IV rituximab at 375 mg/m² in Cycle 1, then 1 dose/cycle in Cycles 3-12
- Restage every 2 cycles
- Any time CR in PART I, will enter PART II
- Up to 12 months to reach best response.



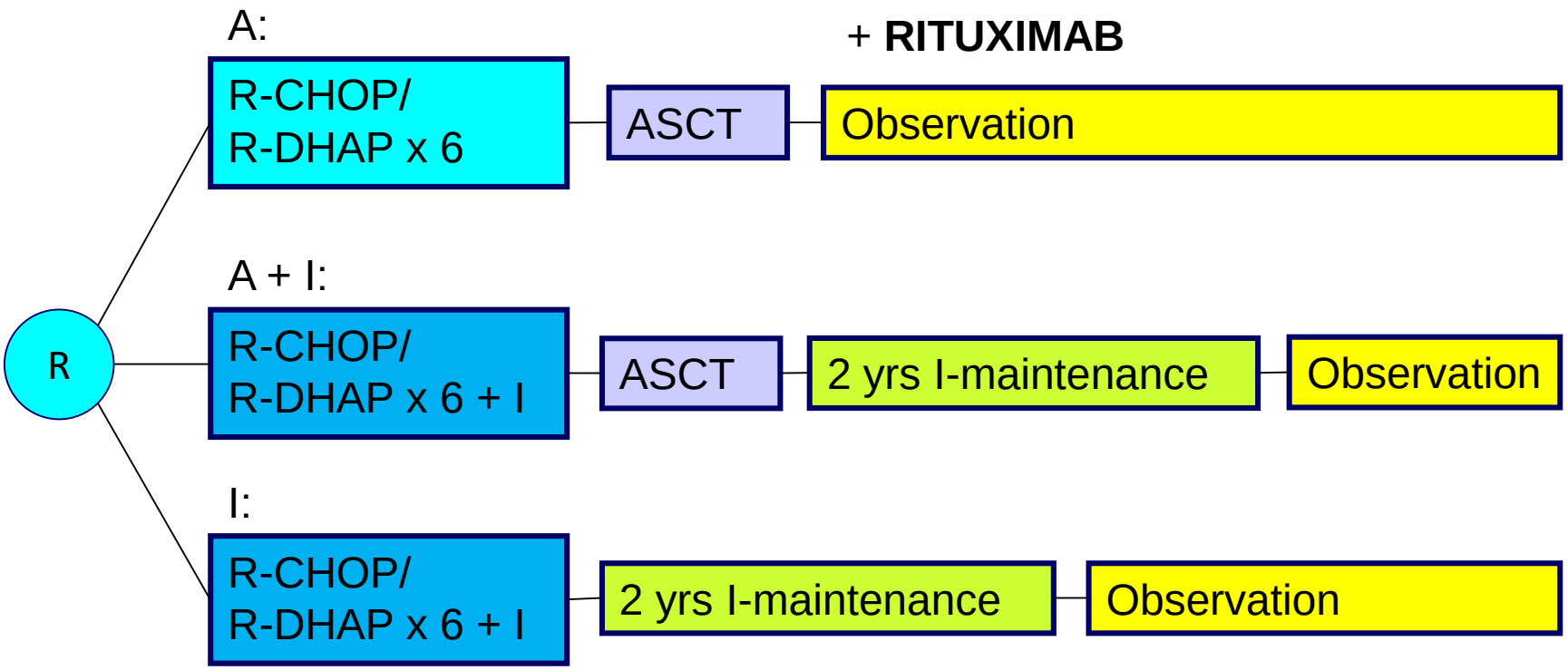

Oral Presentation ASH 2016 Wang

# Best Response: IR by chemo-free alone in PART I before chemo consolidation



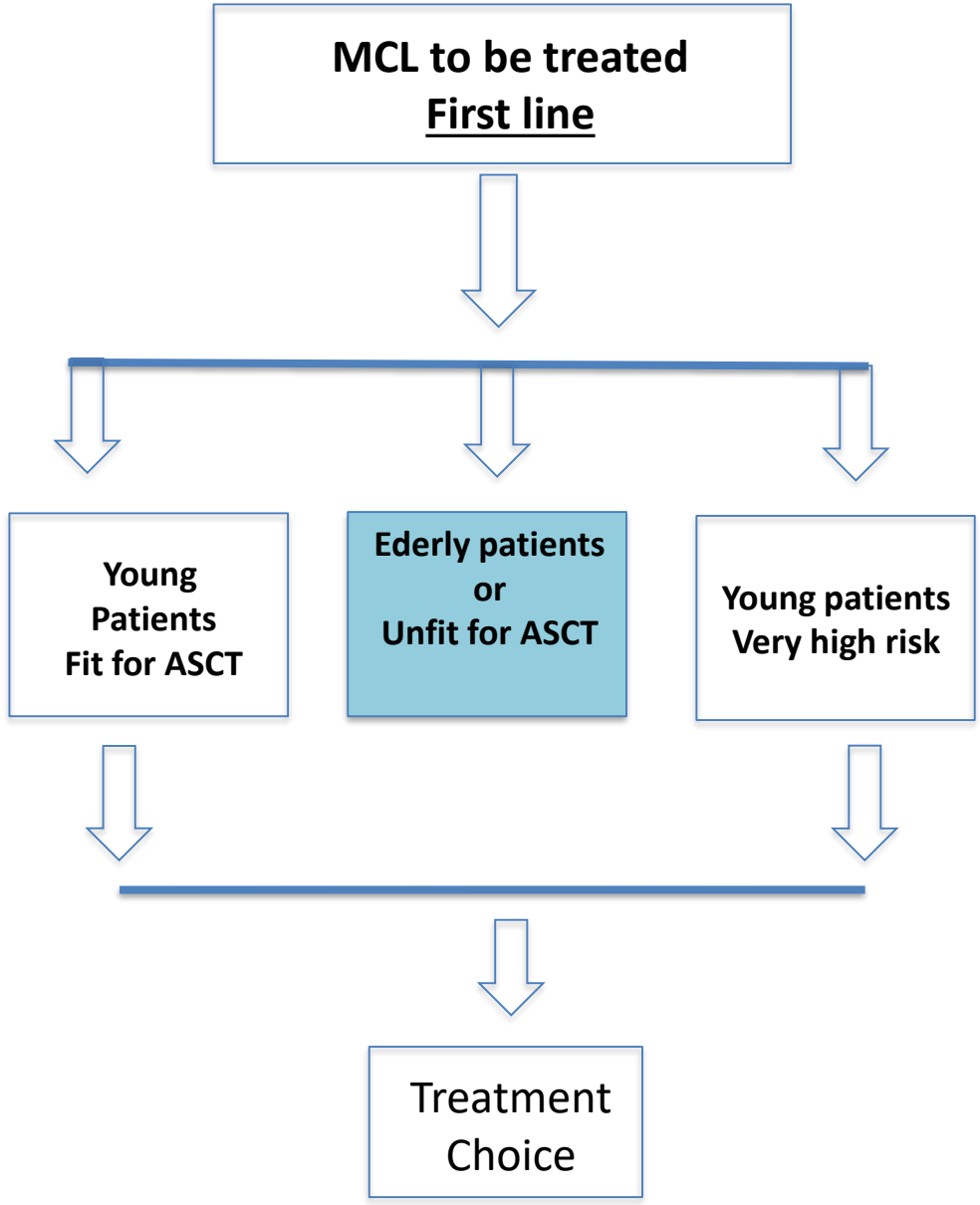

Oral Presentation ASH2016 Wang

# Trial Design: TRIANGLE (EMCL)




**Bras A+I et I, faisabilité du I-R-DHAP ? BIBLOS …**

13.01.2014 Dr. Eva Hoster, University Hospital Munich, on behalf of the European MCL Network


MCL to be treated
First line
Young
Patients
Fit for ASCT
Ederly patients
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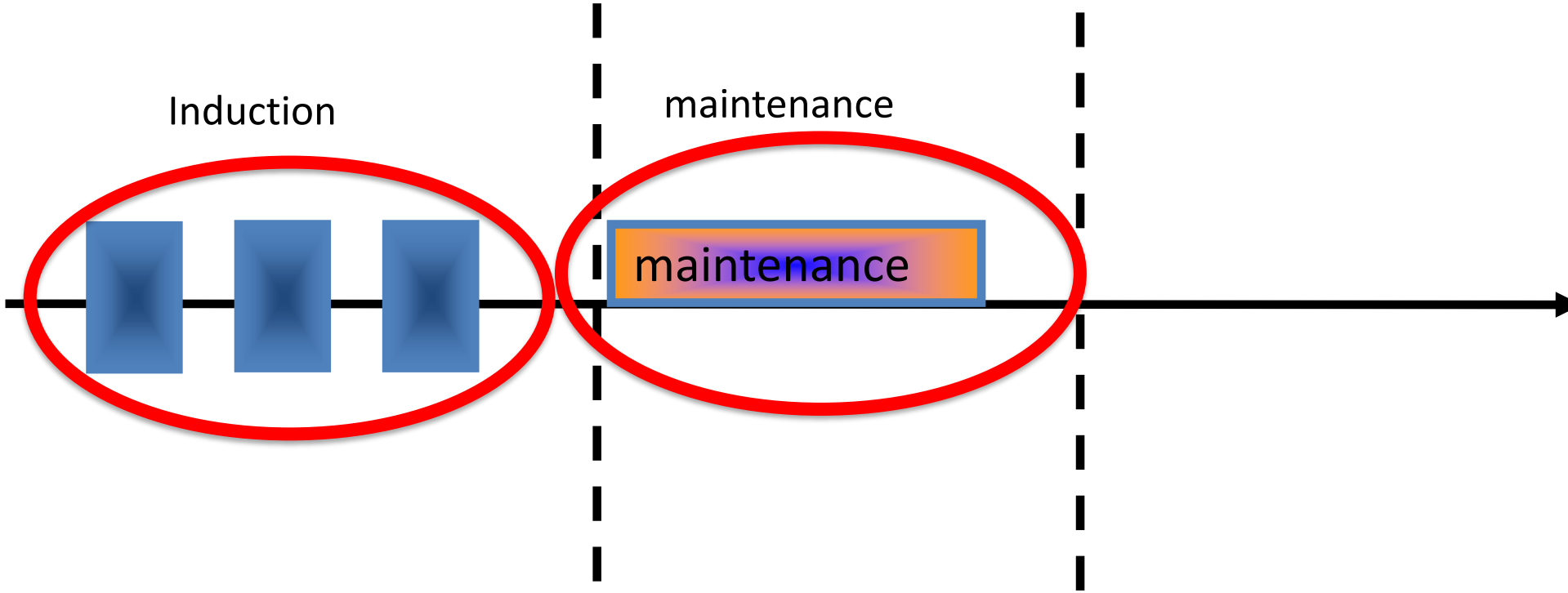
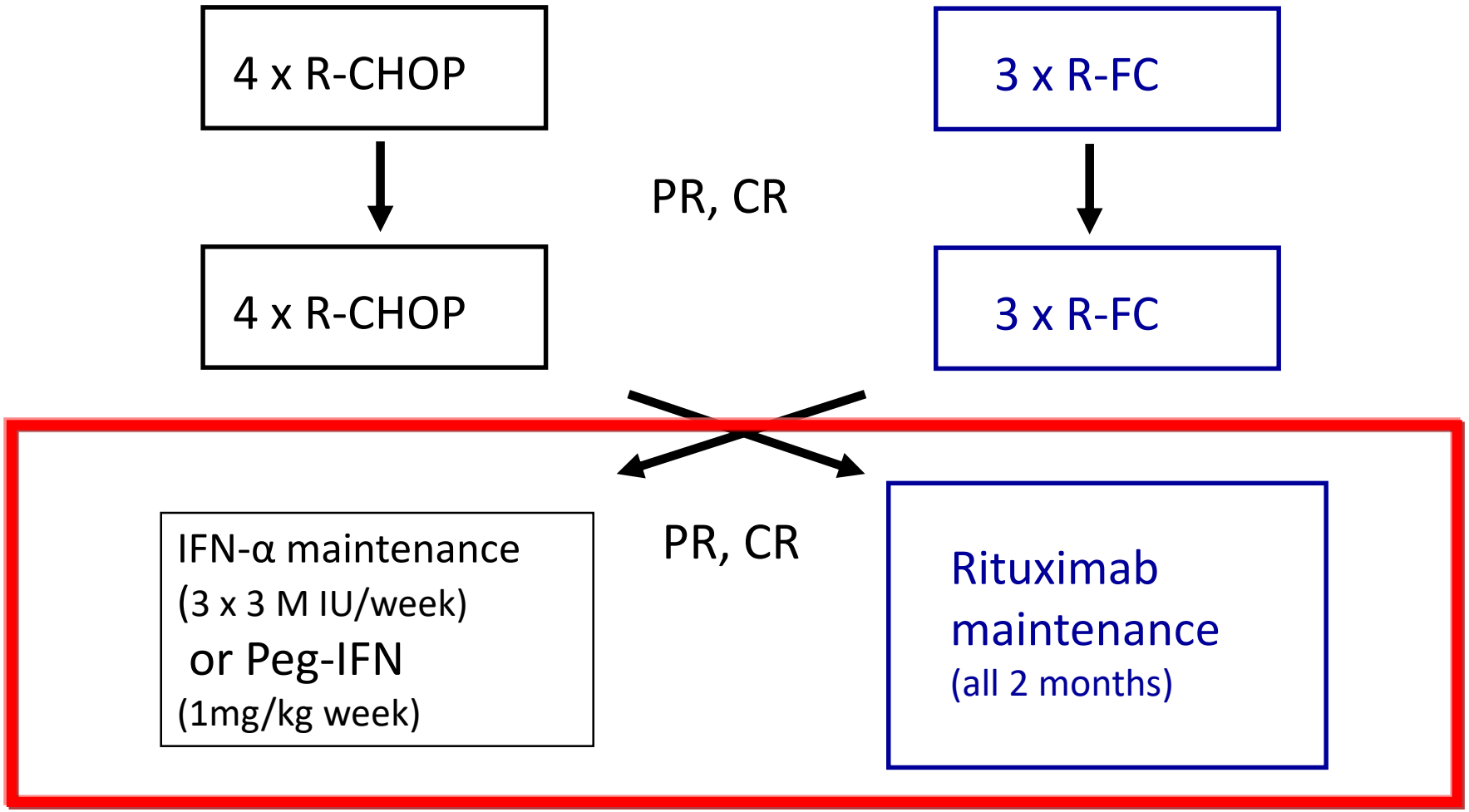
Unfit for ASCT
Young patients
Very high risk
Treatment
Choice

# Treatment strategy in MCL
# First line/Ederly (>65y/Not Frail)




*=> lymphoma remission*

# *European MCL network* studies
# patients >60 years




***Kluin-Nelemans, NEJM 2012***

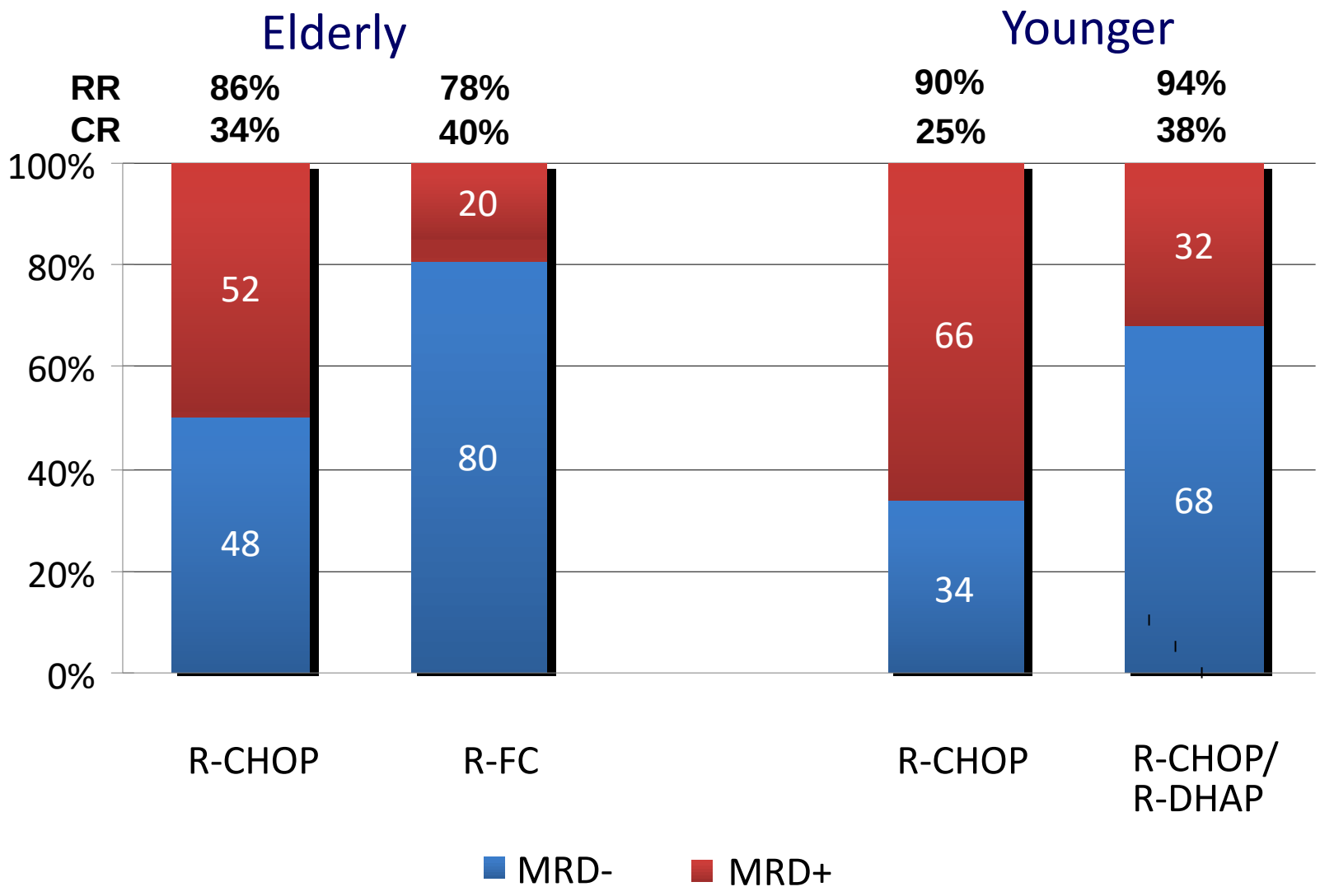
# R-CHOP vs R-FC in elderly patients with MCL

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

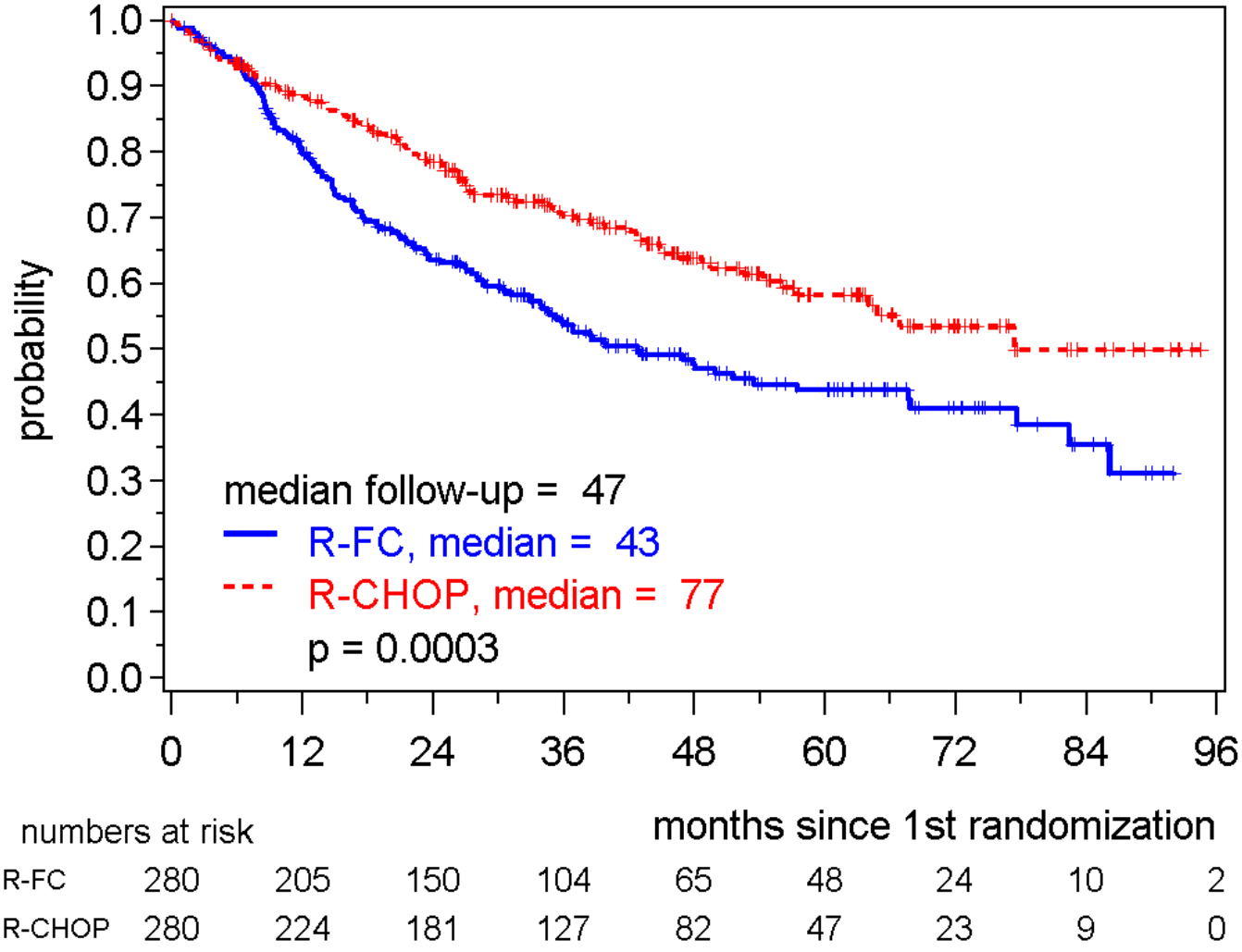
| Cause of death | R-FC | R-CHOP |
|---|---|---|
| Died in CR/PR | 10% | 4% |
| Infections | 7% | 4% |
| Second cancer | 3% | 1% |

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

# MRD response after induction



# MCL Elderly: Overall survival ITT

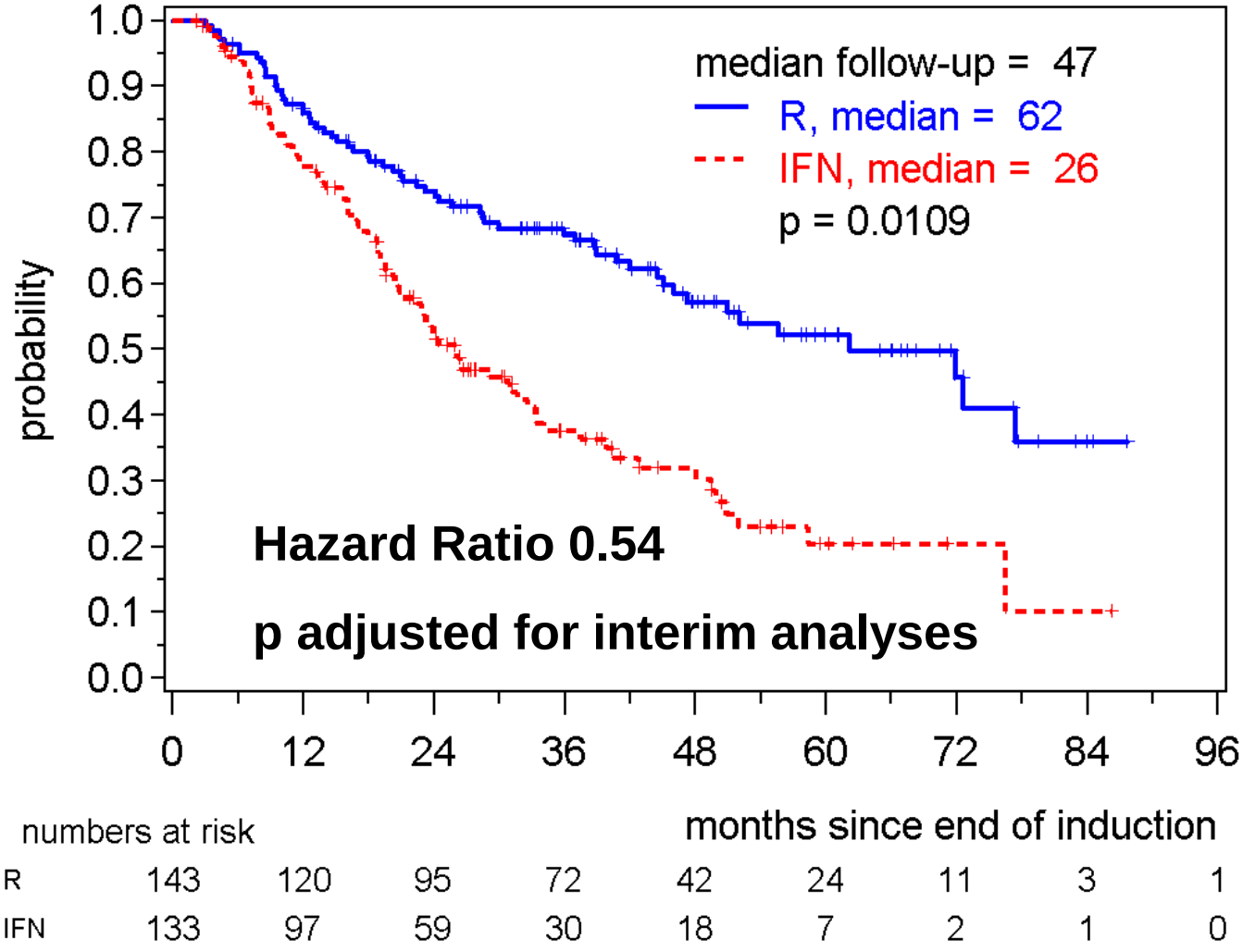



numbers at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| R-FC | 280 | 205 | 150 | 104 | 65 | 48 | 24 | 10 | 2 |
| R-CHOP | 280 | 224 | 181 | 127 | 82 | 47 | 23 | 9 | 0 |

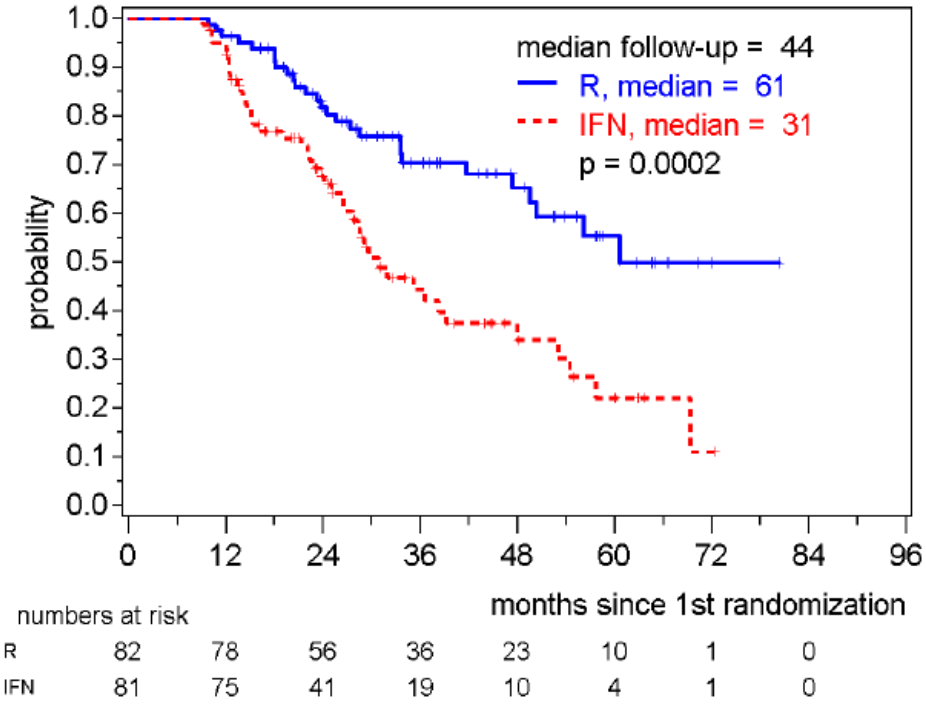
**Update April 7, 2013, European MCL Network, V1.0, 23.05.2013**

# MCL Elderly: RD R vs. IFN - PP

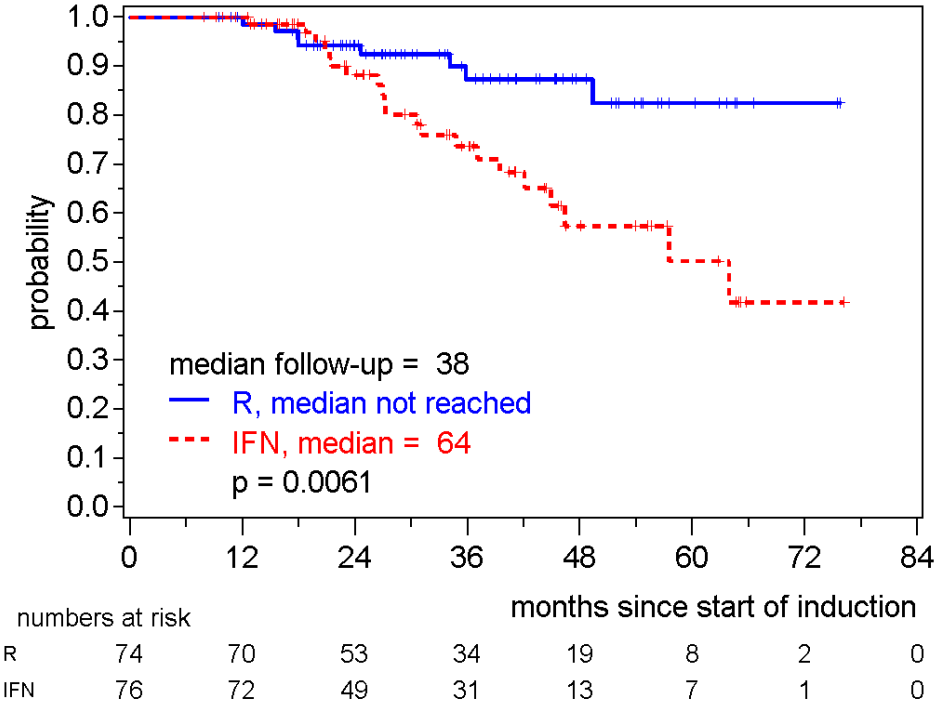


# *MCL Elderly:*
# R-CHOP => maintenance

## Progression-free survival

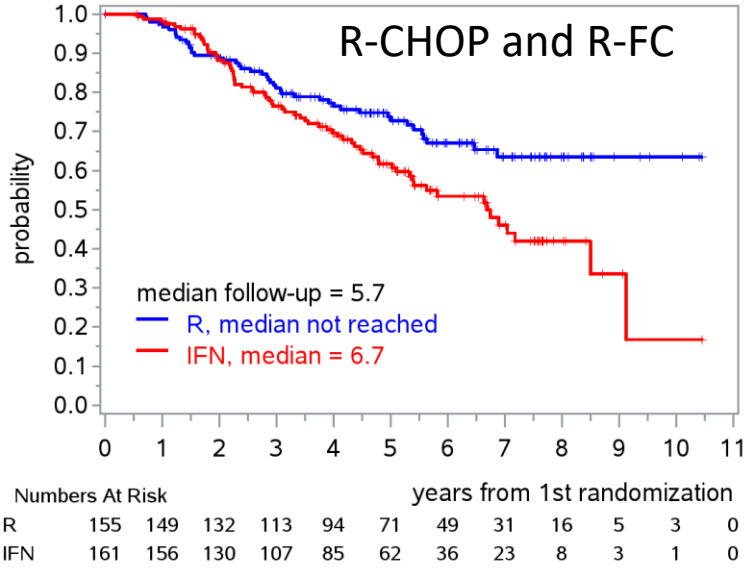


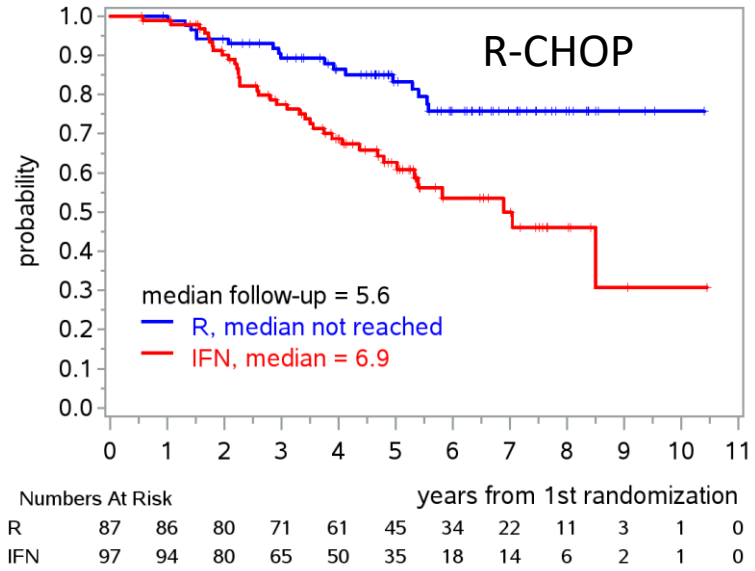

## Overall survival

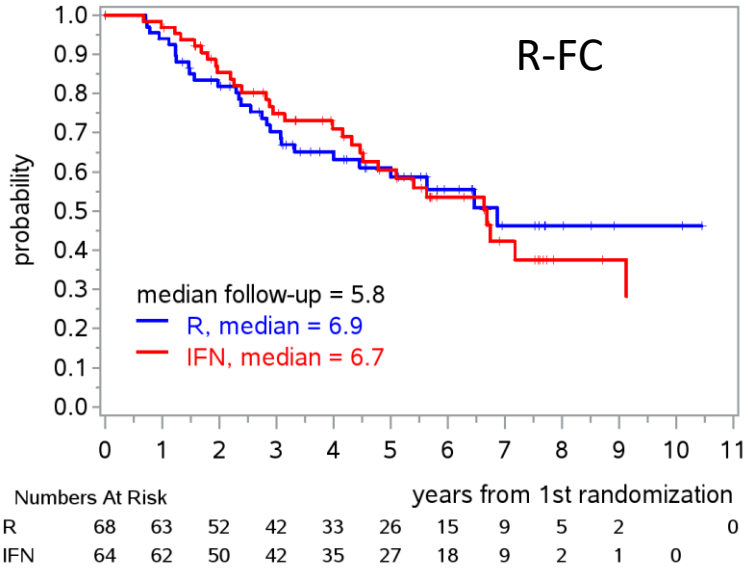



***Kluin-Nelemans, NEJM 2012***

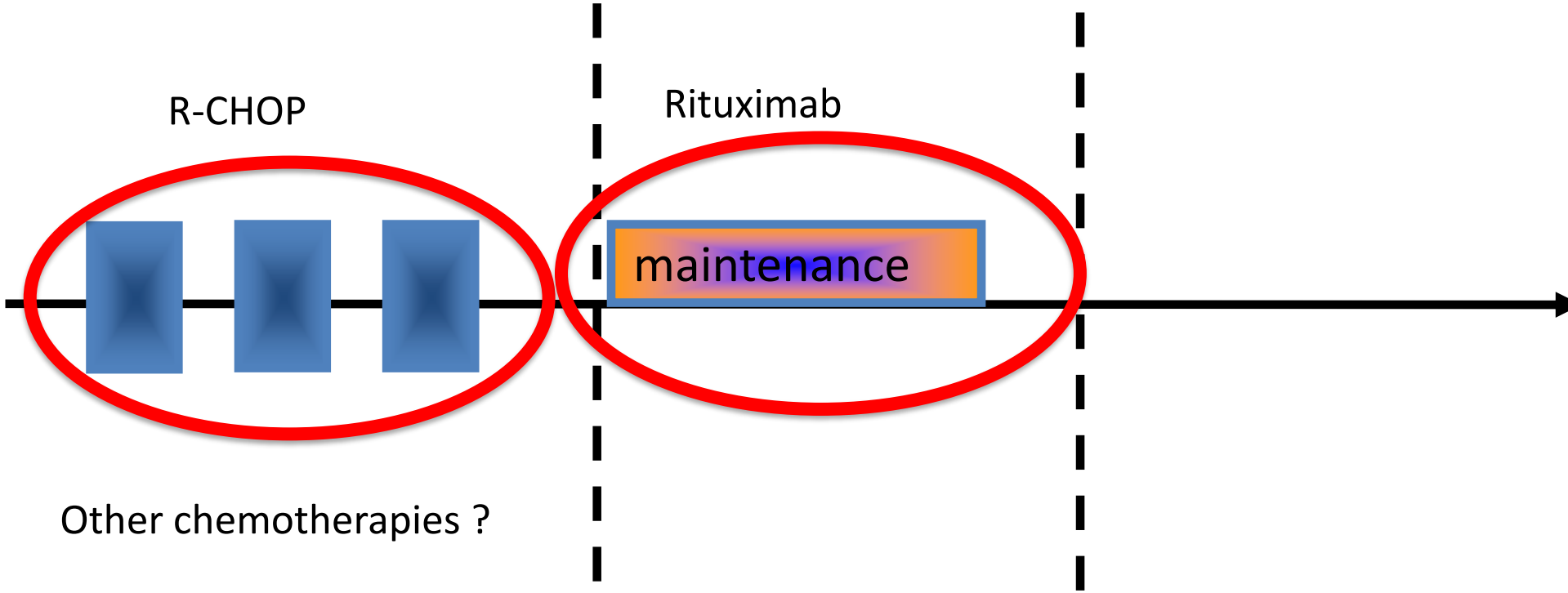
# Clinical Results: Maintenance, OS



# Treatment strategy in MCL
# First line/Ederly (>65y/Not Frail)

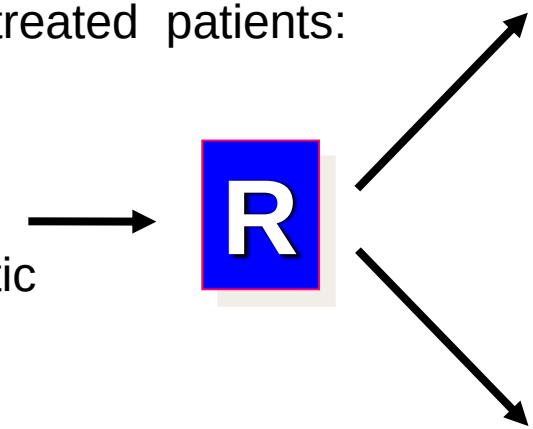



*=> lymphoma remission*

# 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**

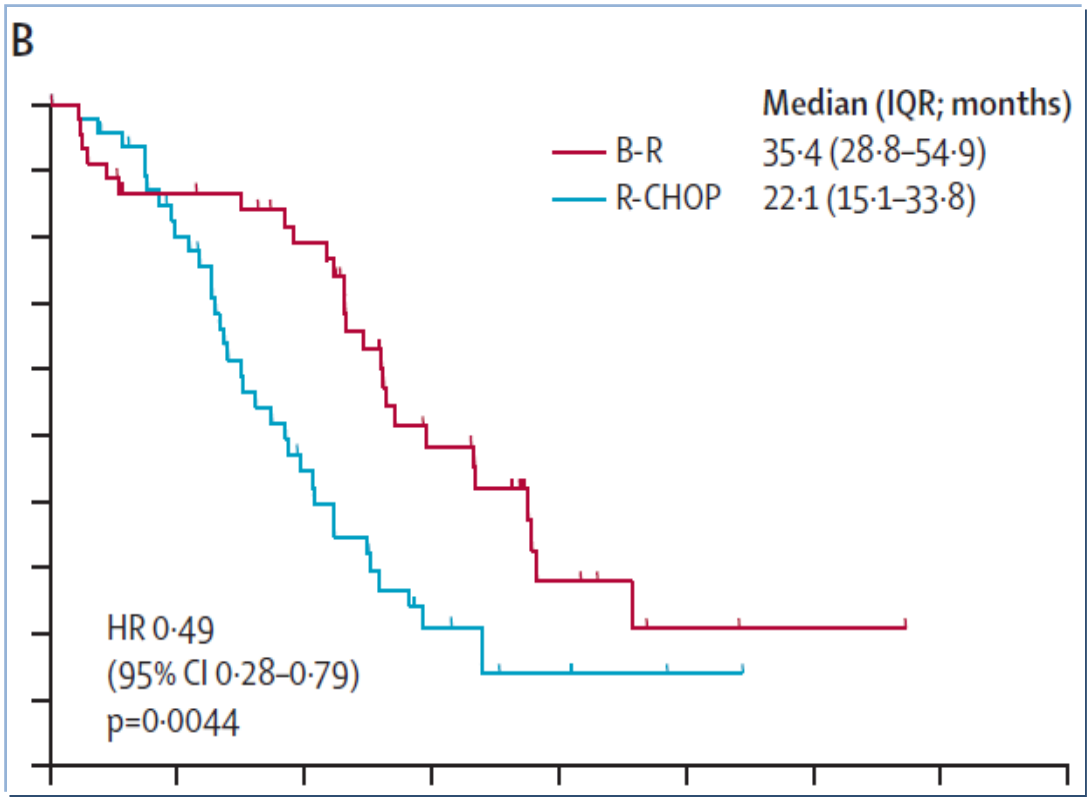
**CHOP-Rituximab**

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. Lancet Oncology 2013*

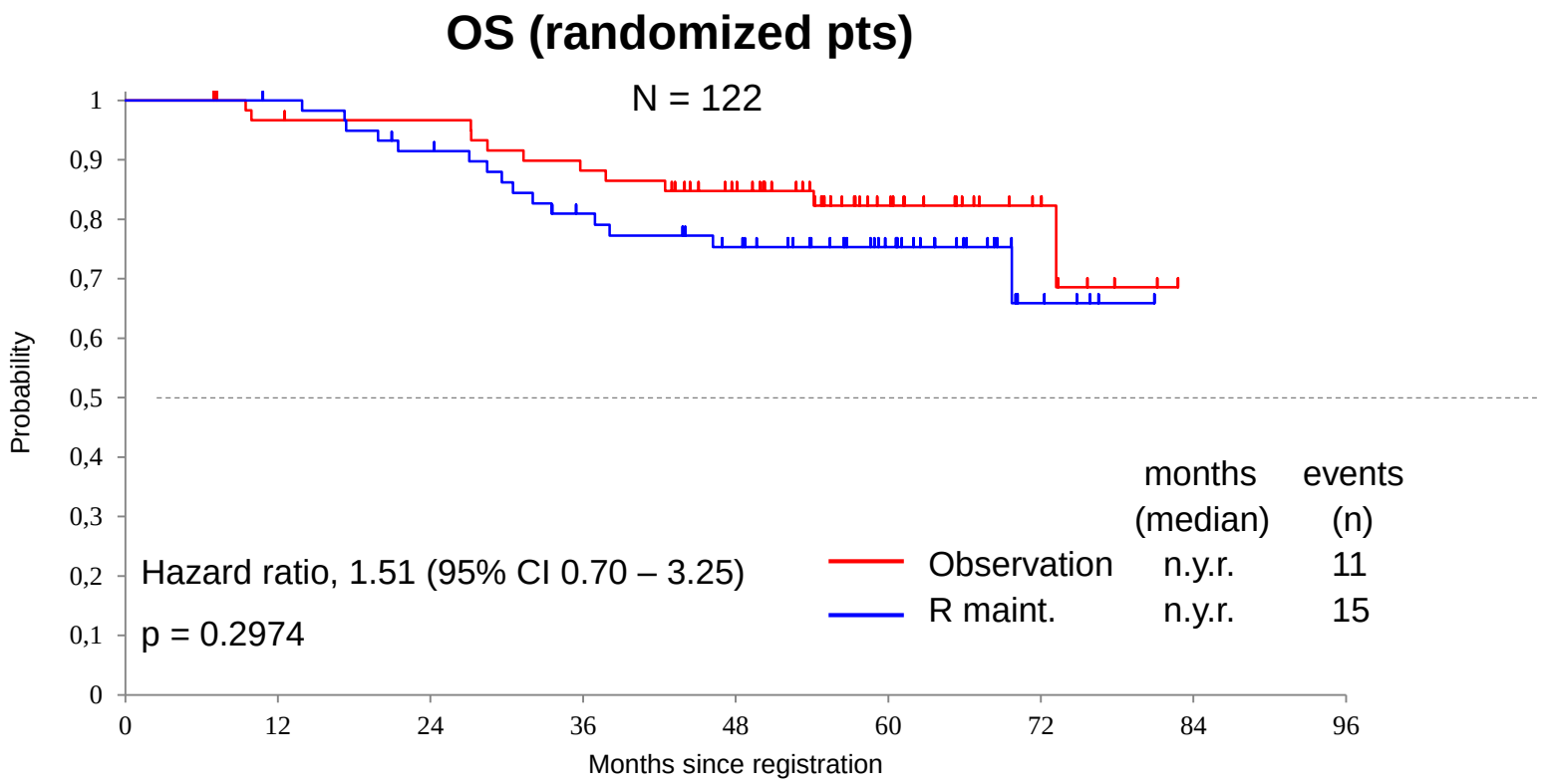
# Bendamustine-Rituximab (B-R) *vs.R-* CHOP




| | 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***

# Overall survival (58.6 months median follow-up)




| Pts at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Observ | 62 | 58 | 57 | 52 | 43 | 21 | 8 |
| R maint | 60 | 59 | 53 | 44 | 38 | 23 | 5 |

# Cross study comparison

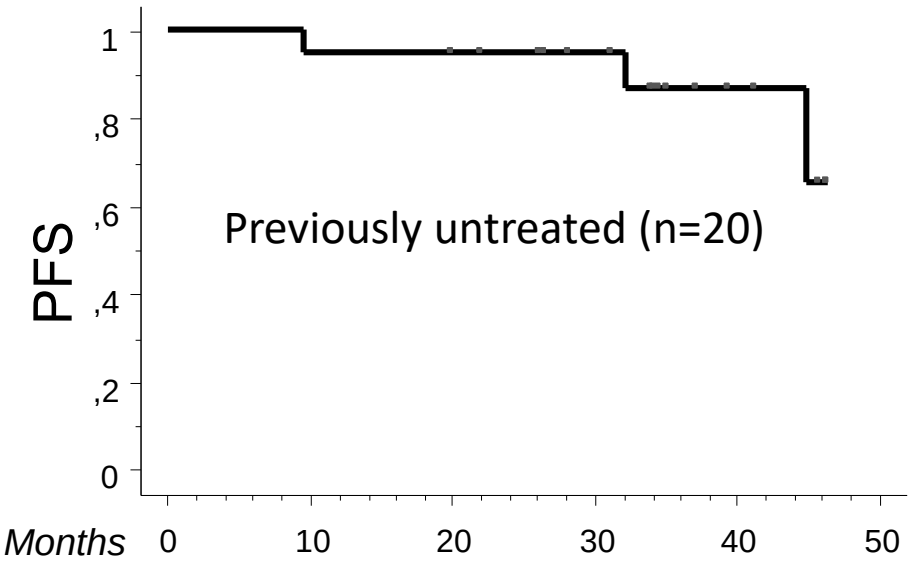
| | StiL NHL 7-2008 | | Kluin-Nelemans et al | |
|---|---|---|---|---|
| | n = 122 (of 168) | | n = 184 (of 280) | |
| Rate of randomized patients | 73 % | | 66 % | |
| | B-R | B-R + R | CHOP-R + INF | CHOP-R + R |
| **Remission duration** | | | | |
| median (months) since randomization | 57 | 68 | 23 | n.y.r |
| rate at 72 months (estimated) | 49% | 40% | 12% | 50% |
| **OS** | | | | |
| median (months) since randomization | n.y.r. | n.y.r. | 64 | n.y.r. |
| rate at 72 months (estimated) | 70% | 66% | 50% | 71% |

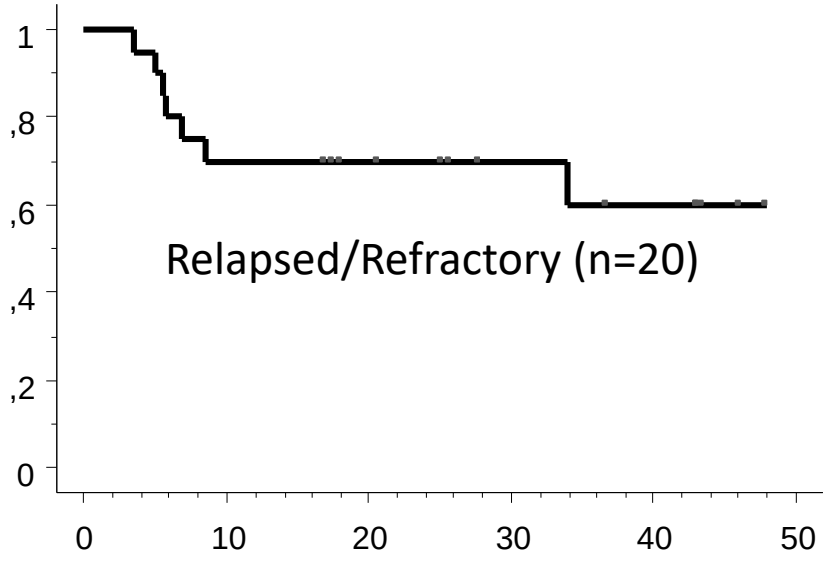
# Rituximab, Bendamustine, Cytarabine (R-BAC)

| Treatment | Day 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Rituximab 375 mg/m² | ↓ | | | |
| Bendamustine 70 mg/m² | | ↓ | ↓ | |
| Ara-C 800 mg/m² | | ↓ | ↓ | ↓ |

| | ORR (%) | CR (%) |
|---|---|---|
| Untreated | 100 | 95 |
| R/R | 80 | 70 |

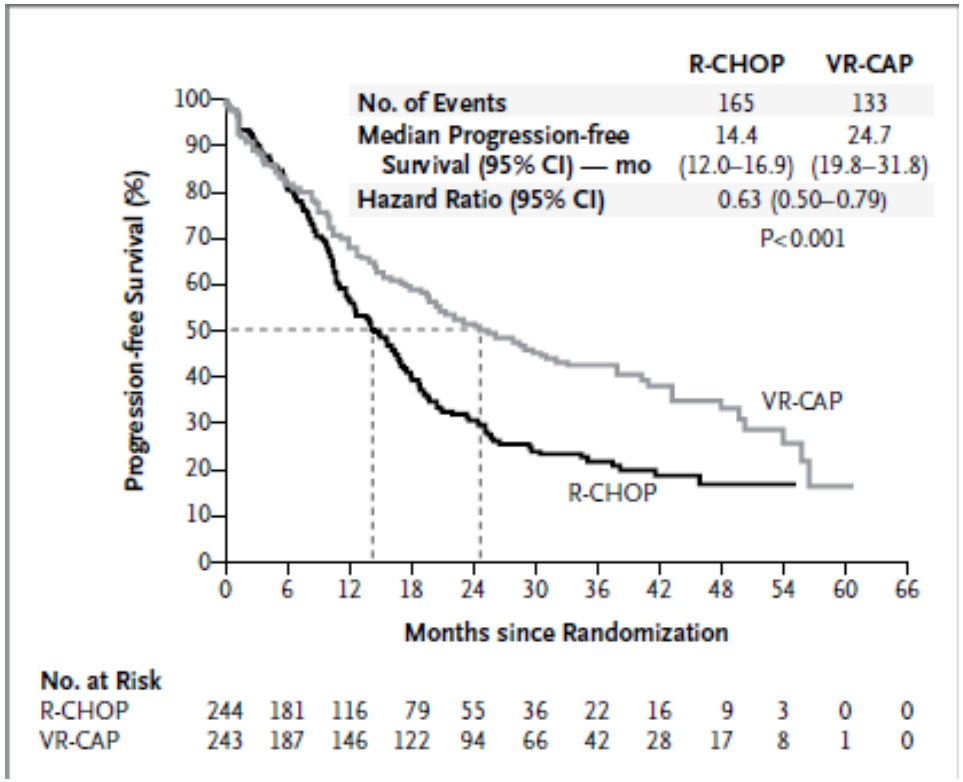
Median F/U 35 months (17-49)




Updated (june 2013) from Visco et al, JCO 2013

# Bortezomib as induction therapy for elderly/unfit for ASCT patients

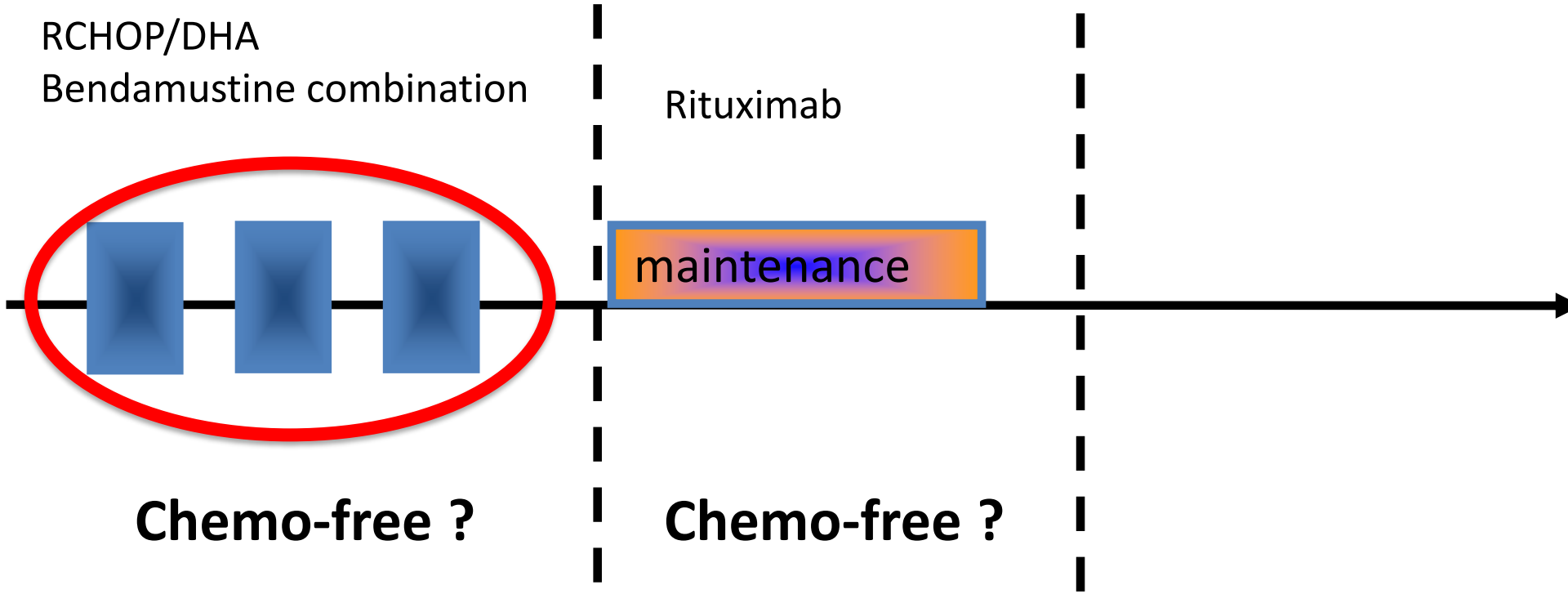



| | ORR (%) | CR (%) |
|---|---|---|
| R-CHOP | 89 | 42 |
| VR-CAP | 92 | 53 |

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***

# Treatment strategy in MCL
# First line/Ederly (>65y/Not Frail)

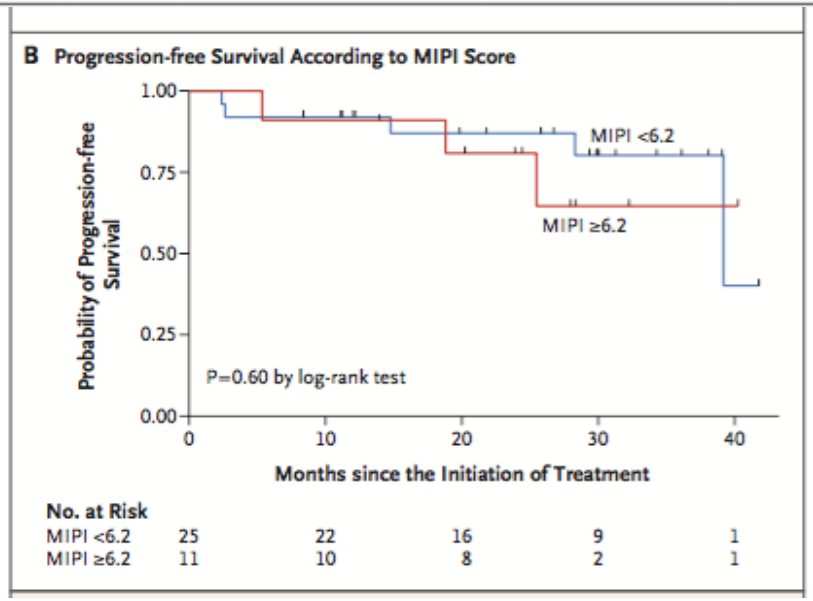



*=> lymphoma remission*

# Lenalidomide Rituximab
# First line/Ederly (>65y/Unfit for chemotherapy)

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

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

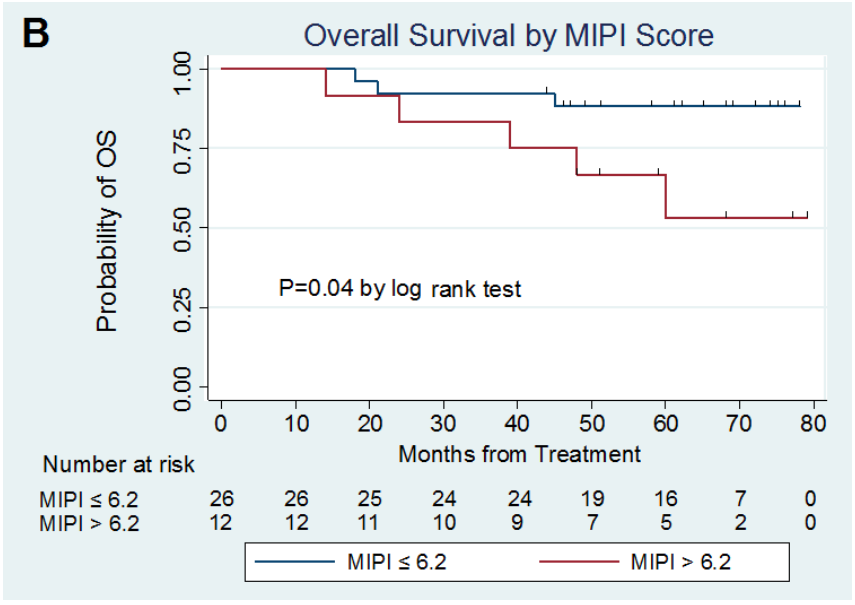


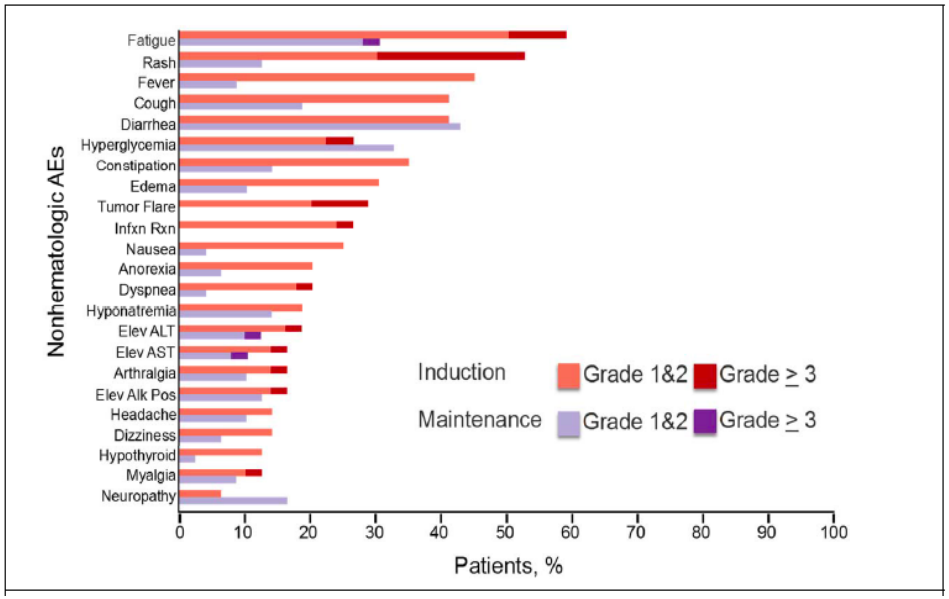

*Ruan J et al. NEJM 2016*

blood®
Prepublished online September 4, 2018;
doi:10.1182/blood-2018-07-859769

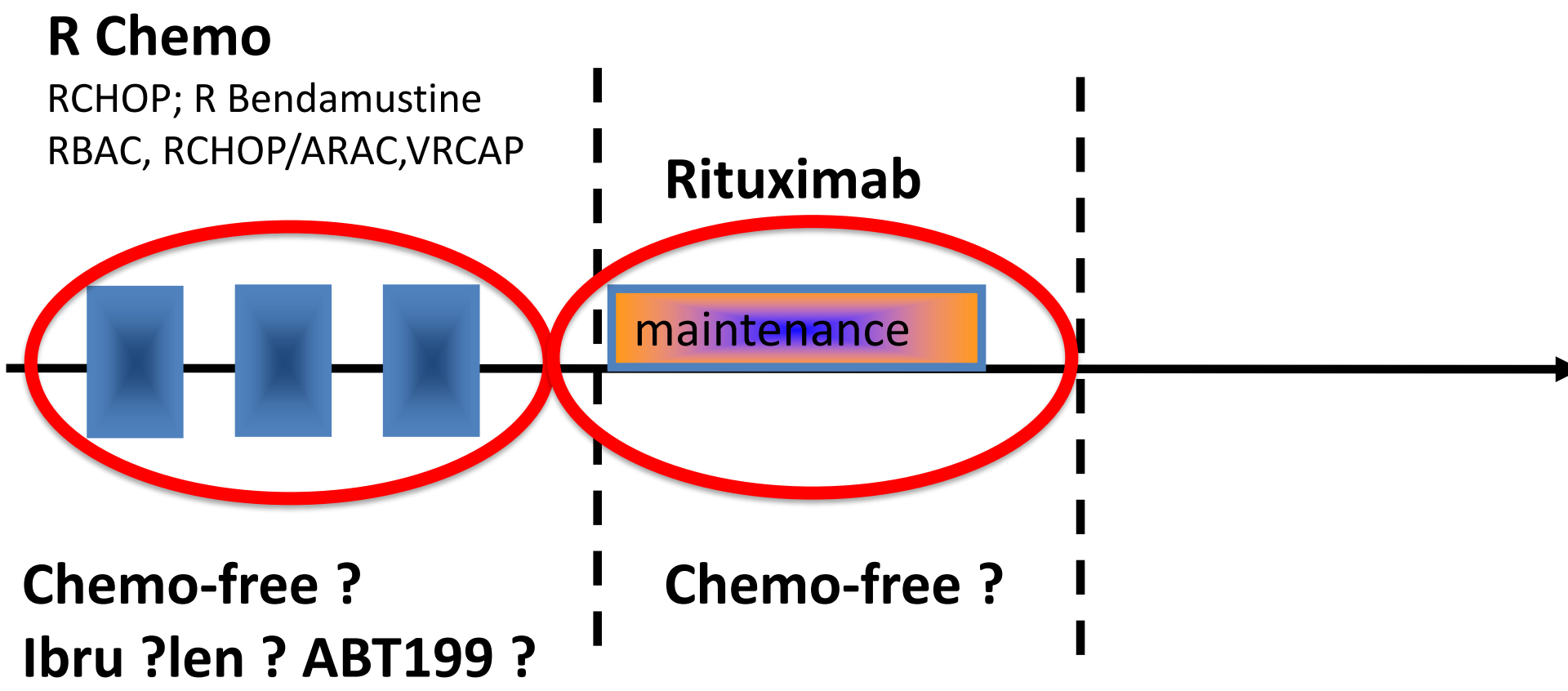
# Five-year follow-up of lenalidomide plus rituximab as initial treatment for mantle cell lymphoma

Jia Ruan, Peter Martin, Paul Christos, Leandro Cerchietti, Wayne Tam, Bijal Shah, Stephen J. Schuster, Amelyn Rodriguez, David Hyman, Maria Nieves Calvo-Vidal, Sonali M. Smith, Jakub Svoboda, Richard R. Furman, Morton Coleman and John P. Leonard



# Treatment strategy in MCL
# First line/Ederly (>65y/Not Frail)

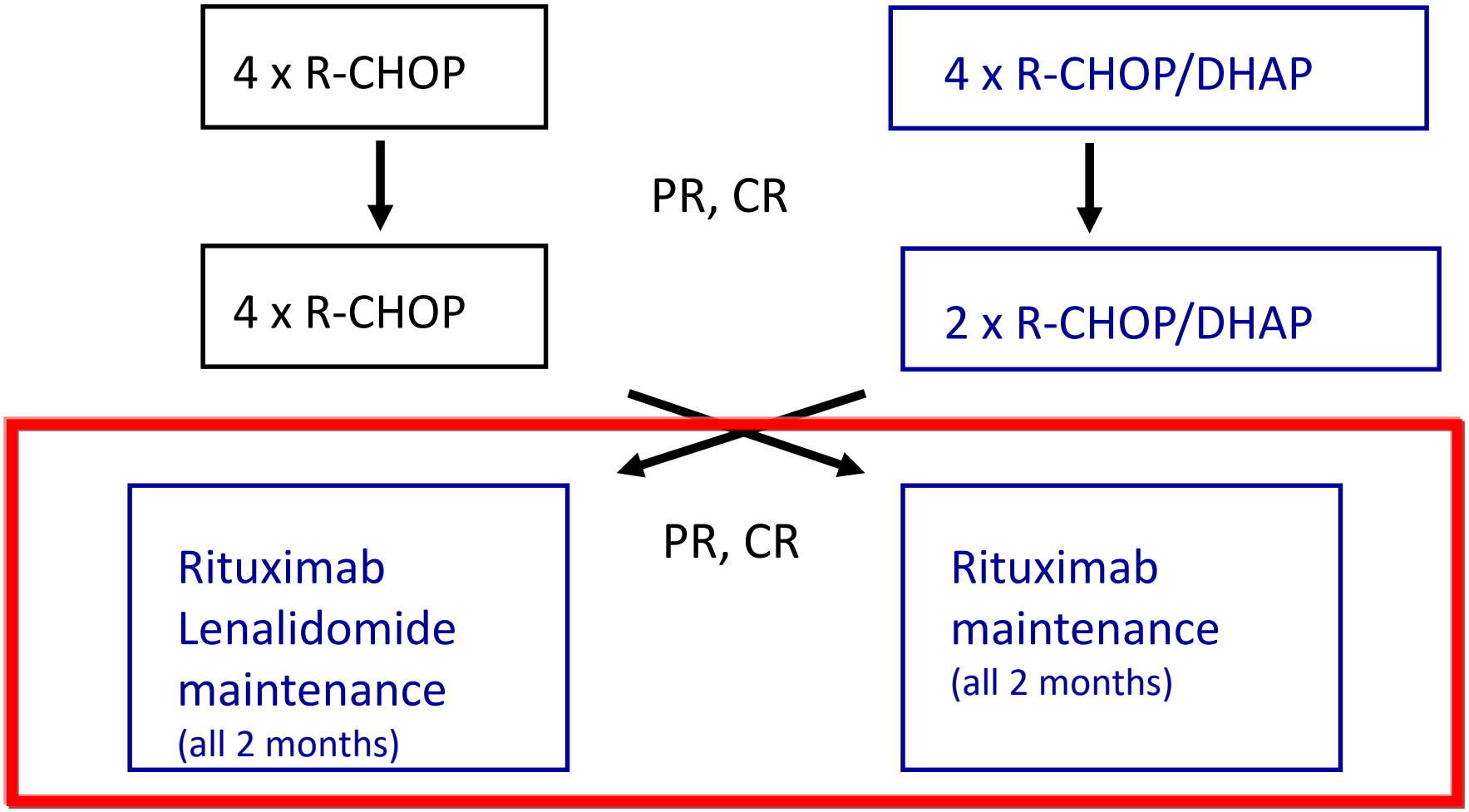



*=> lymphoma remission*

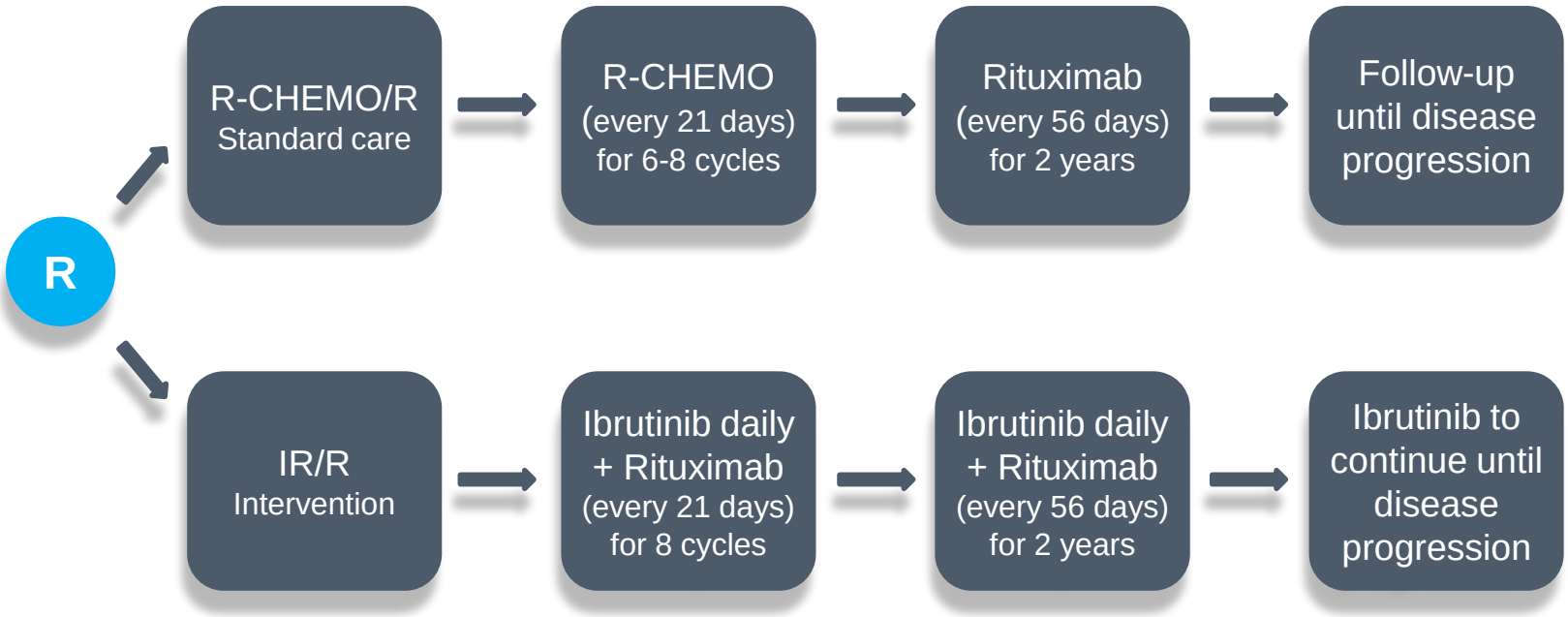
# *European MCL network* studies

## patients >60 years

## MCL R2 elderly



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

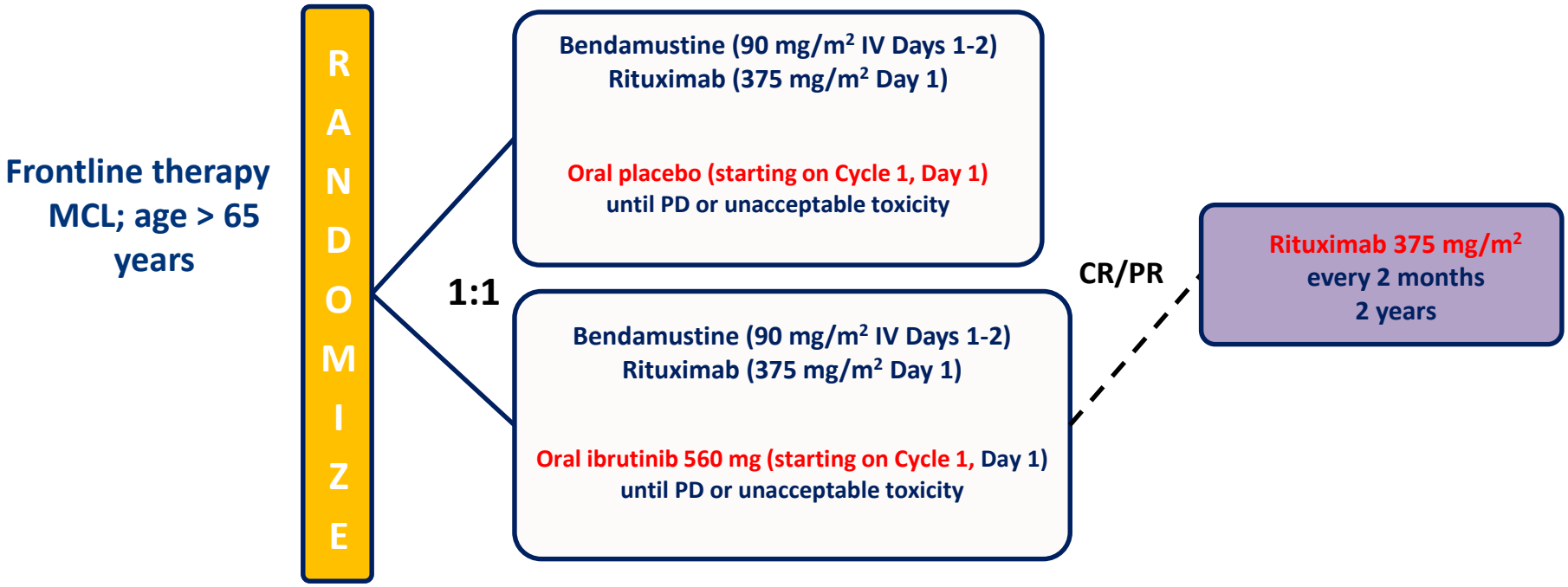



CI S Rule

# MCL3002 - study design ( SHINE study)

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

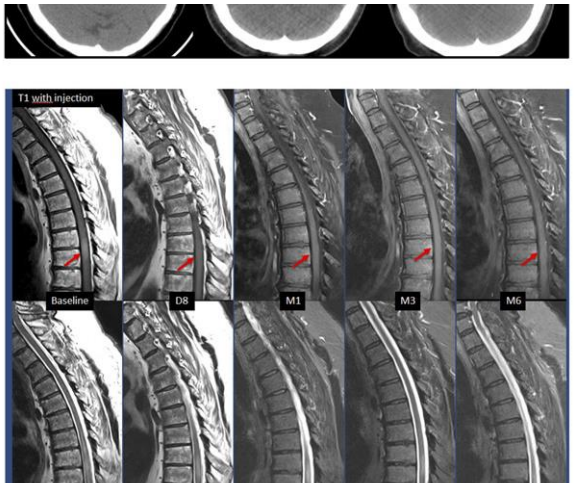
**N=520**

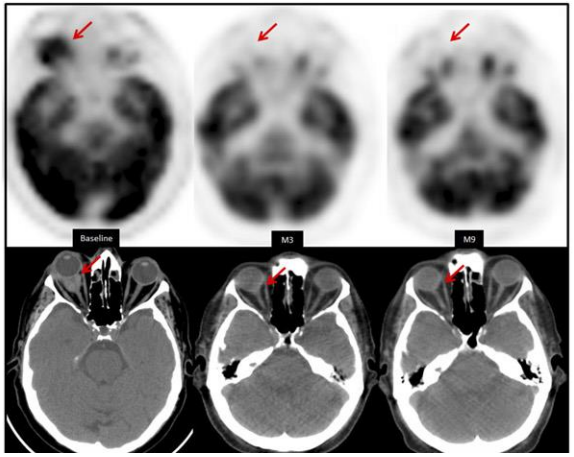


LYMPHOID NEOPLASIA

# Activity of ibrutinib in mantle cell lymphoma patients with central nervous system relapse

Sophie Bernard,[1,2] Lauriane Goldwirt,[3] Sandy Amorim,[1,2] Pauline Brice,[1] Josette Brière,[4] Eric de Kerviler,[5] Samia Mourah,[2,6,7] Hélène Sauvageon,[3] and Catherine Thieblemont[1,2]



# New Drugs

- Good efficacy+++
- Determine molecular parameters of responses
- No cure
- Best use in combination with or without chemotherapy ?
- Sequential increase OS (no cross resistance)
- Best strategy : first line (cure) relapse (Combo +/- Auto or allo)
- Maintenance ? Preemptive ?

# Study Generation 2018

**< 65 years**

***MCL younger:***
**R-CHOP/DHAP =>ASCT**
**R-DHAP/OX=>ASCT**
**R-CHOP/DHAP+I =>ASCT => I**
**R-CHOP/DHAP + I => I**
**GA101/Ibru/Venetoclax**

**> 60 years**

***MCL elderly R2:***
**R-CHOP vs R-CHOP/Ara-C**
**=> Rituximab M**
**+/-Lenalidomide**
**Rev-Ritux**
**R-BAC=>R**

**> 65 years**

***MCL elderly I:***
**BR +/- Ibrutinib**
**=> Rituximab M**
**+/- Ibrutinib**
**R-BAC=>R**

# Aknowledgement


- LYSA (G Salles, H Tilly, Th Lamy, C Gisselbrecht, B Coiffier)
- LYSARC (G Salles, B Coiffier, P Deschaseaux)
- LYSA path (F Berger, N Brousse)
- LYSA Biology (MH Delfau, EA MacIntyre)
- MCL LYSA subcommitte (S Legouill, V Ribrag)
- EMCL (M Dreyling, E Hoster, M Unternhalt, H Kluis Nuelemans, C Geisler, U Vitoto, M Ladetto, C Visco, C Pott, W Klapper)
- EBMT (A Sureda, S Robinson, S Dietrich, P Dreger)