Hämatologie im Wandel 2019

Mantelzell-Lymphom:

## *Behandlungsstrategien und Studien*
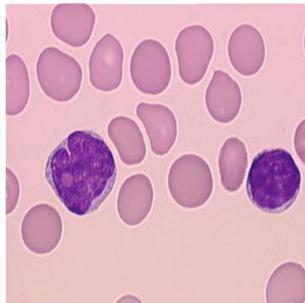
Prof. Dr. Martin Dreyling

Medizinische Klinik III

LMU München
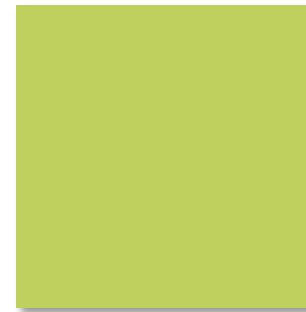
European MCL Network

German Lymphoma Alliance

MANTLE CELL LYMPHOMA

- **molecular pathogenesis**

- **chemotherapy standards in first line**

- **targeted approaches**

MCL: *two kind of diseases*

Dreyling, ESMO CR 2017
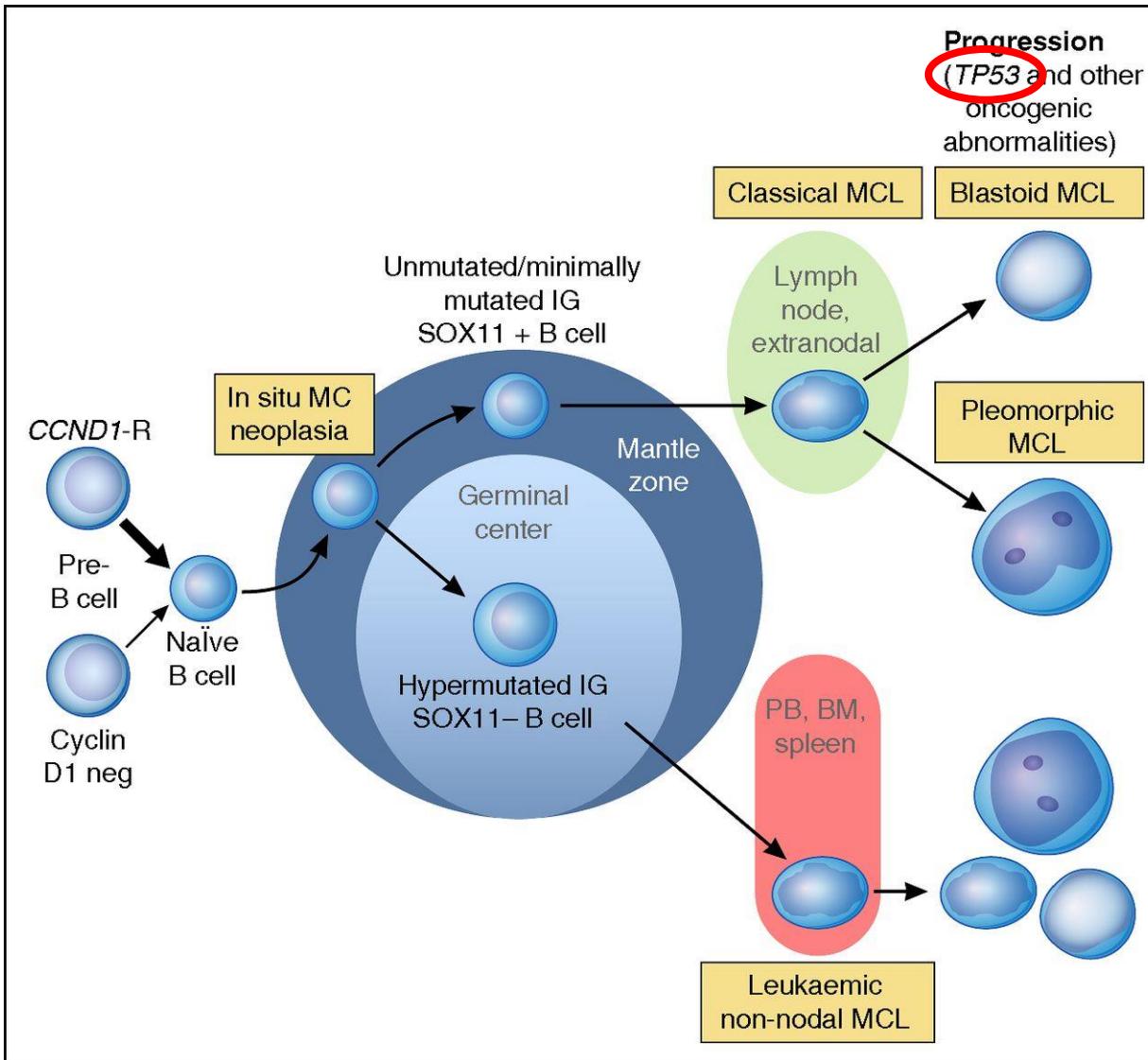
Risk factor proliferation: MCL 35

Scott, JCO 2017
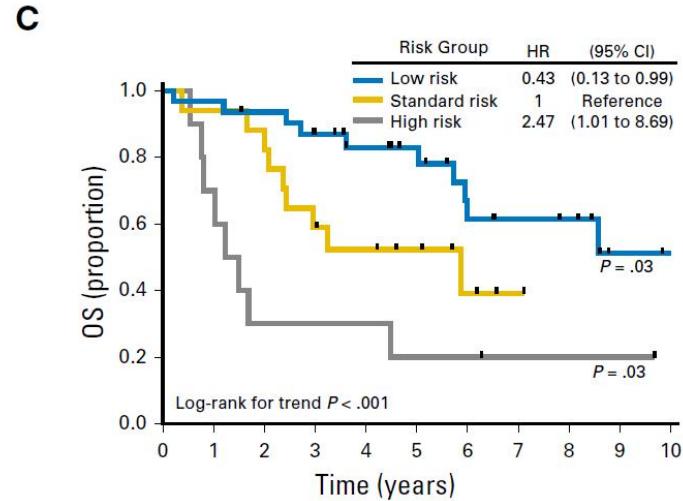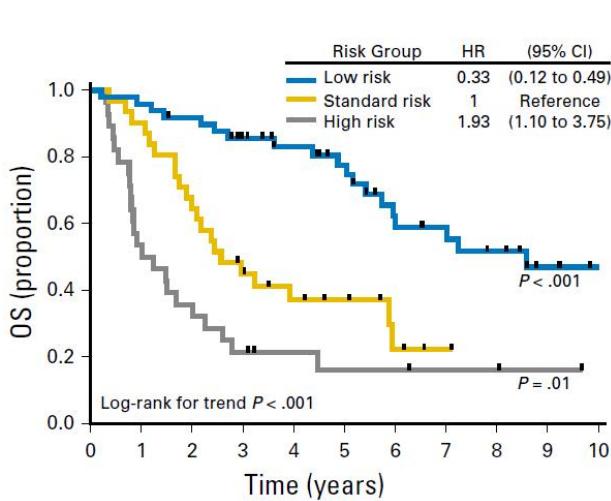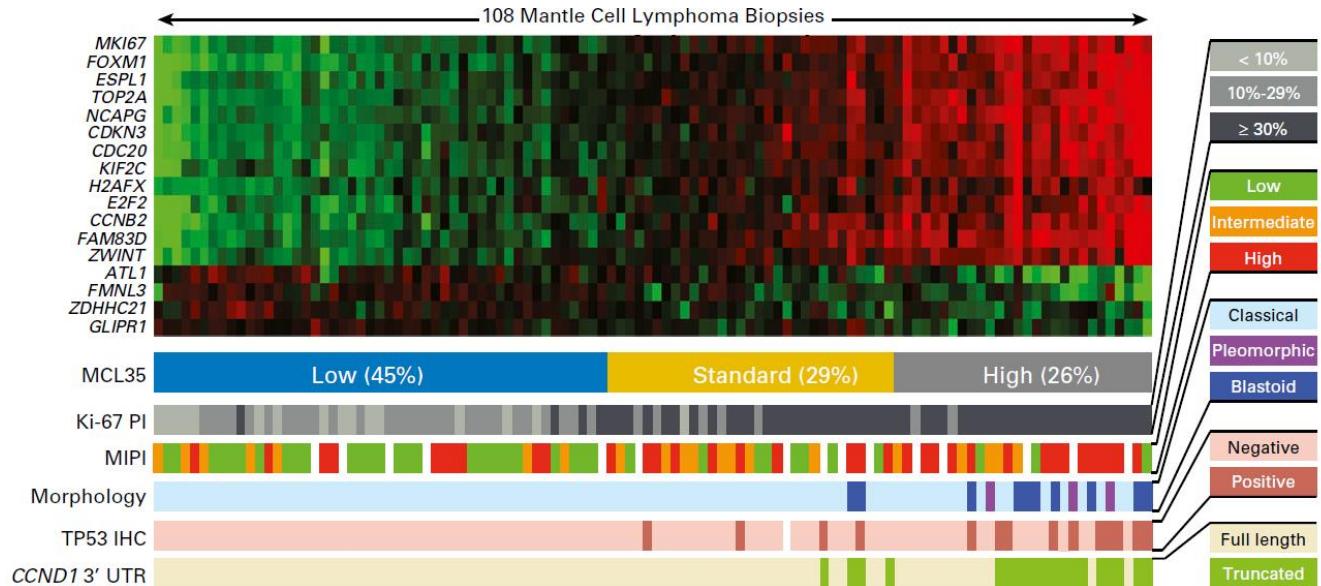
MCL immunohistochemistry
SOX11 and p53 deletion/mutation
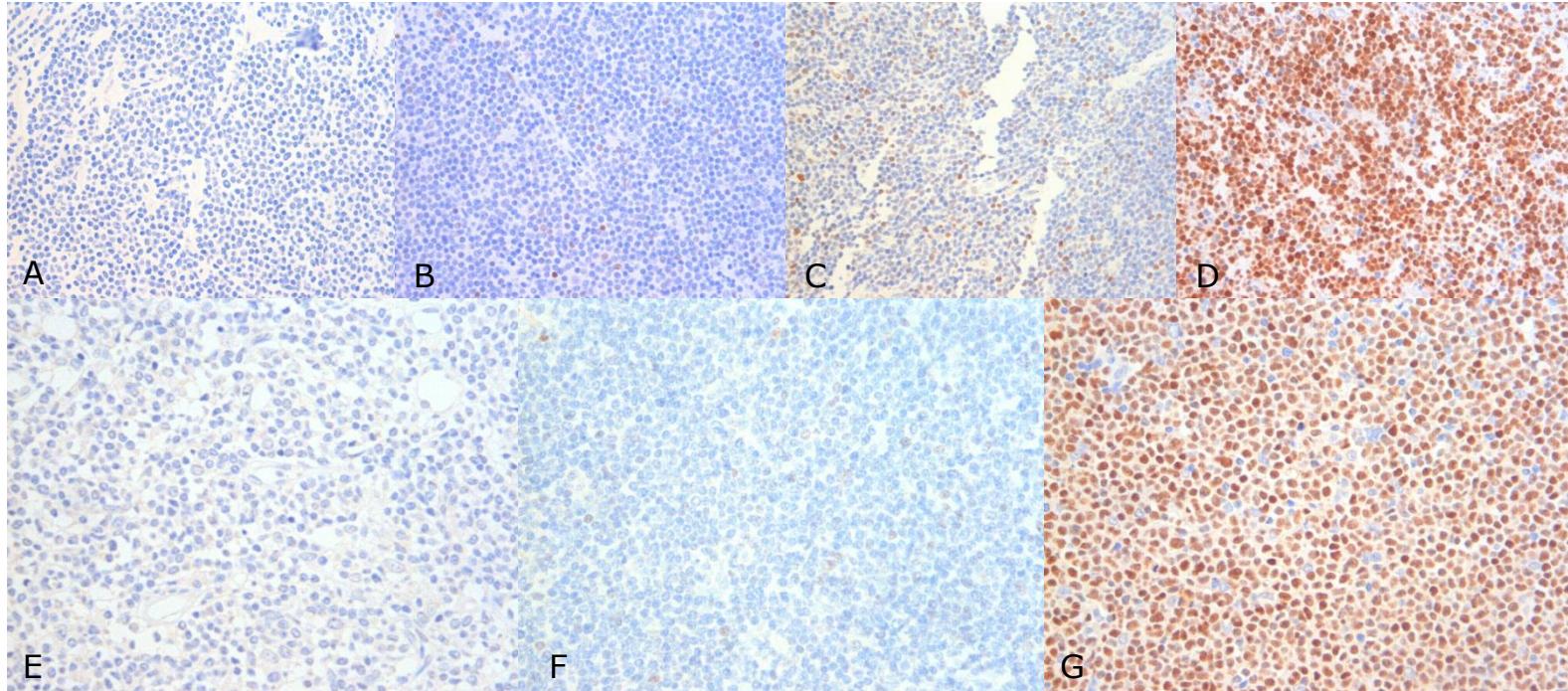
(A) p53 0%, (B) p53 1-10%, (C) p53 11-50%, (D) p53 >50%,
(E) SOX11 0%, (F) SOX11 1-10% and (G) SOX11 >10%

MCL immunohistochemistry
p53 deletion/ mutation
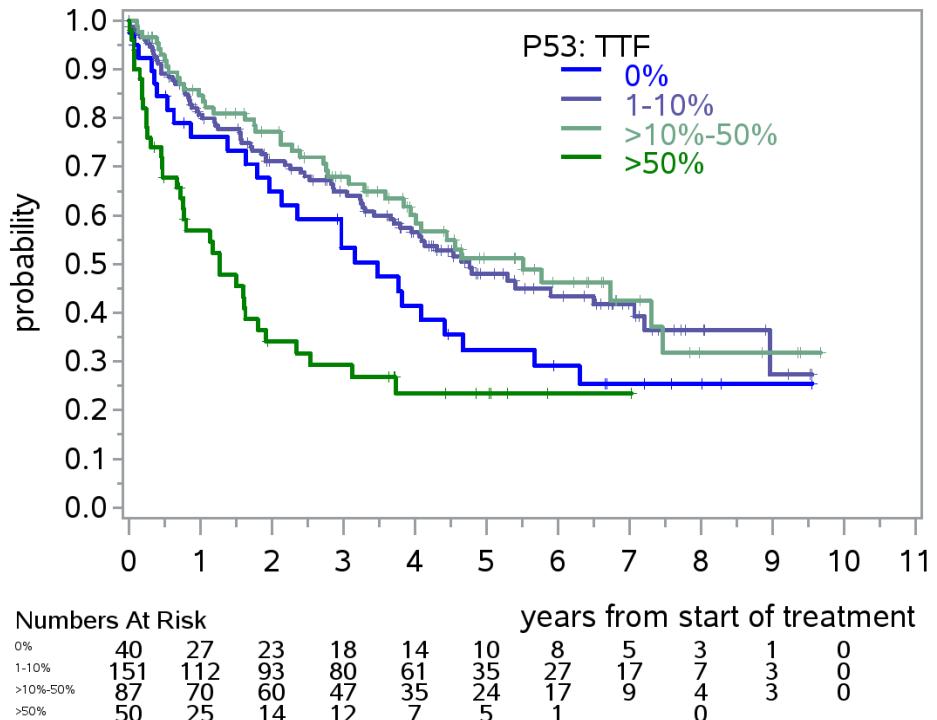
p = 0.10; HR 1.45 / <0.0001; HR 2.47
(adjusted: 0.22; HR 1.38 / 0.0083; HR 1.91)
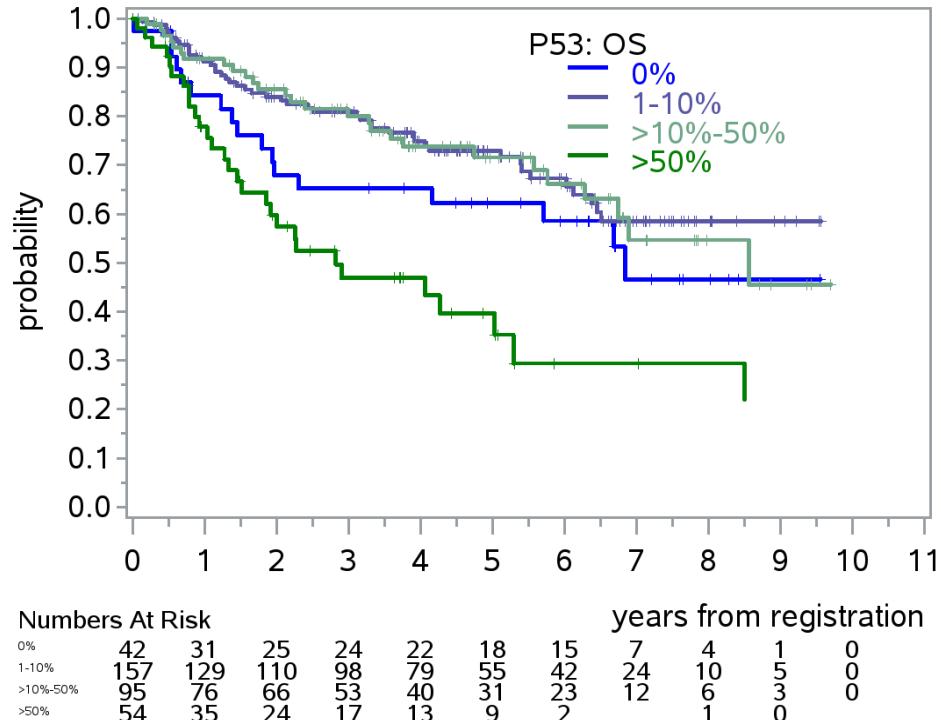
p = 0.18; HR 1.46 / <0.0001; HR 3.00
(adjusted: 0.18; HR 1.54 / <0.010; HR 2.00)

Aurema, Blood 2018

Combined MIPI-c
Overall survival

Patients >65 years — Patients <65 years
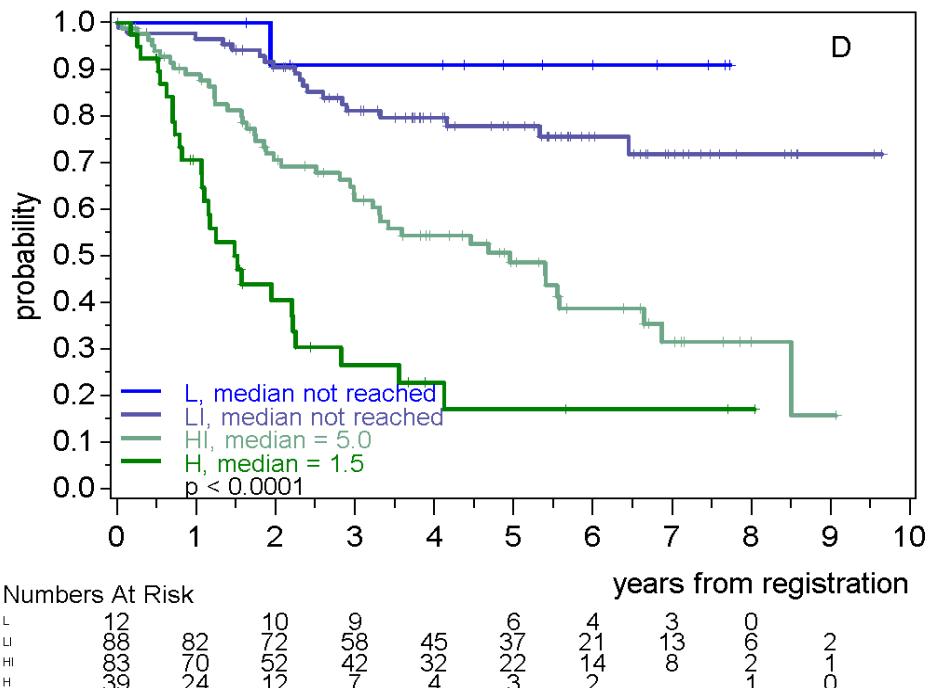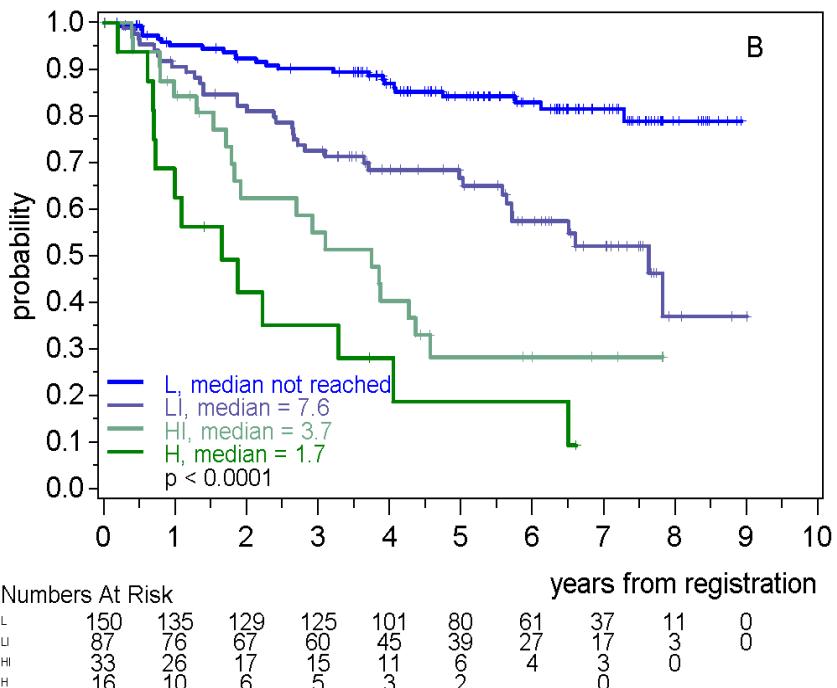
Hoster, JCO 2016

MANTLE CELL LYMPHOMA

- **molecular pathogenesis**

- **chemotherapy standards in first line**

- **targeted approaches**

young patient (≤65)	elderly patient (>65)	compromised patient

First line treatment

dose-intensified immuno-chemotherapy (R-CHOP, high dose Ara-C) ⟹ Autologous SCT ⟹ Rituximab maintenance	conventional immuno-chemotherapy (VR-CAP, R-CHOP, BR, R-BAC) ↓ Rituximab maintenance	Best supportive care? R-Chlorambucil BR (dose-reduced) R-CVP

1. relapse

immuno-chemotherapy (R-BAC, BR) or targeted approaches ↓ discuss: - allogeneic SCT	immuno-chemotherapy (BR, R-BAC) or targeted approaches ↓ discuss: - Rituximab maintenance - radioimmunotherapy	Immuno-chemotherapy (BR) or targeted approaches

higher relapse

Targeted approaches: Ibrutinib, Lenalidomide,
Temsirolimus, Bortezomib (preferable in combination)
Alternatively: repeat previous therapy (long remissions)

Dreyling, ESMO CR MCL 2017 (updated)

European MCL Network
patients <65 years

3 x R-CHOP

↓

PR, CR!

3 x R-CHOP

↓

PR, CR!

DexaBEAM
(stem cell mobilization)

↓

Cyclo 120 mg/kg
+ TBI 12 Gy

↓

PBSCT

---

3 x R-CHOP
3 x R-DHAP
alternating

(stem cell mobilization after course 4)

↓

TBI 10 Gy
Ara-C 4 x 1.5 g/m^2
Melphalan 140 mg/m^2

↓

PBSCT

Hermine, Lancet 2016

MCL YOUNGER
TIME TO TREATMENT FAILURE

Hermine, Lancet 2016

young patient (≤65) elderly patient (>65) compromised patient

First line treatment

young patient (≤65)	elderly patient (>65)	compromised patient
dose-intensified immuno-chemotherapy (R-CHOP, high dose Ara-C) ⇒ Autologous SCT ⇒ Rituximab maintenance	conventional immuno-chemotherapy (VR-CAP, R-CHOP, BR, R-BAC) ↓ Rituximab maintenance	Best supportive care? R-Chlorambucil BR (dose-reduced) R-CVP

1. relapse

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higher relapse

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Alternatively: repeat previous therapy (long remissions)

Immuno-chemotherapy in MCL
Progression-free survival

PFS: mantle cell (n=93)

	Median (months)
B-R	35.4
CHOP-R	22.1

HR, 0.50
(95% CI 0.29 - 0.81)
p = 0.0061

Overall survival

	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs
B-R	89.7%	85.6%	82.3%	80.1%	80.1%	75.9%
CHOP-R	89.5%	86.7%	84.2%	77.8%	75.5%	59.5%

Rummel, Lancet 2013
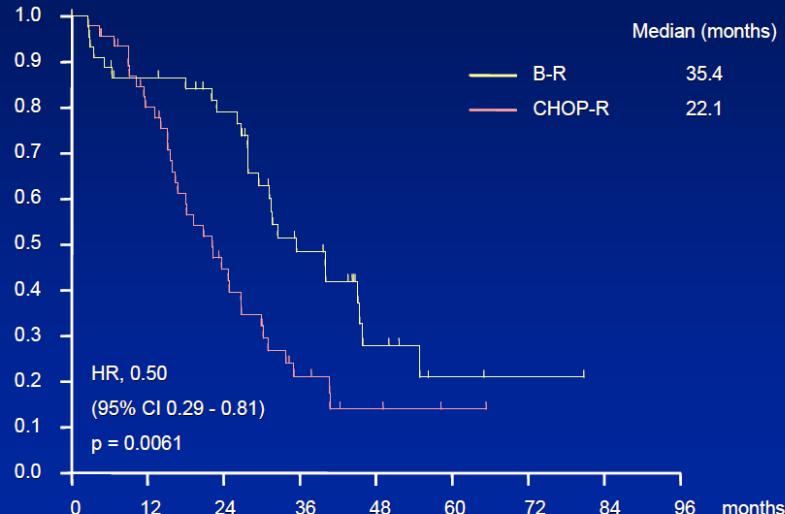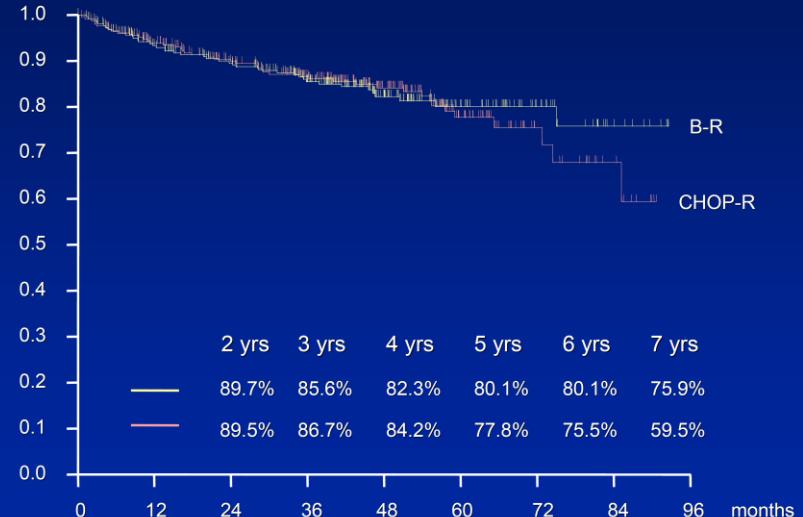
Mantle cell lymphoma
R-BAC 500: Efficacy

Visco, Lancet Haematol 2017
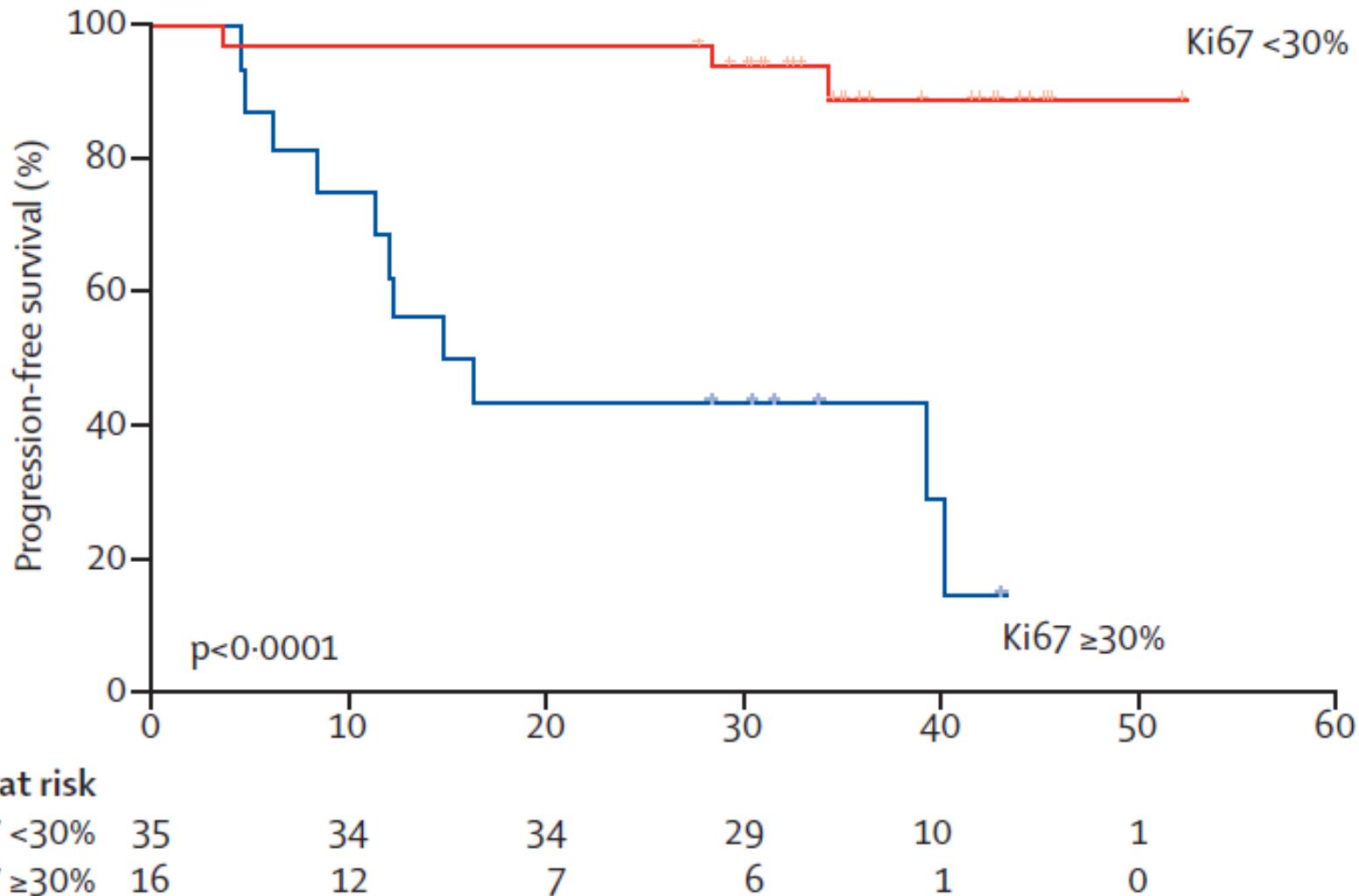
VR-CAP vs. R-CHOP
Study scheme

Recruitment at 128 centers in 28 countries (Europe, Asia, North America, South America) between 26 May 2008 and 05 December 2011

Newly diagnosed MCL patients
- Measurable stage II–IV MCL
- ECOG PS 0–2
- Ineligible or not considered for BMT

Central laboratory confirmation of MCL diagnosis Concordance: 97%

(N=487)

Randomization 1:1
Stratified by IPI (0-1, 2, 3, 4-5) and disease stage at diagnosis (II, III, IV)

R-CHOP (n=244)

Rituximab 375 mg/m² IV day 1
Cyclophosphamide 750 mg/m² IV day 1
Doxorubicin 50 mg/m² IV day 1
Prednisone 100 mg/m² PO days 1–5
Vincristine 1.4 mg/m² (max 2 mg) IV day 1

6–8 x 21-day cycles

VR-CAP (n=243)

Rituximab 375 mg/m² IV day 1
Cyclophosphamide 750 mg/m² IV day 1
Doxorubicin 50 mg/m² IV day 1
Prednisone 100 mg/m² PO day 1–5
Bortezomib 1.3 mg/m² IV days 1, 4, 8, 11

Study Limitation
Rituximab maintenance therapy not established when study initiated

MUNICH 2018 ESMO congress

Key: BMT, bone marrow transplant; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, International Prognostic Index; MCL, Mantle Cell Lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; VR-CAP, bortezomib plus rituximab, cyclophosphamide, doxorubicin, and prednisone

Cavalli, ESMO 2018

VR-CAP vs. R-CHOP
Survival Rates

Progression-free Survival
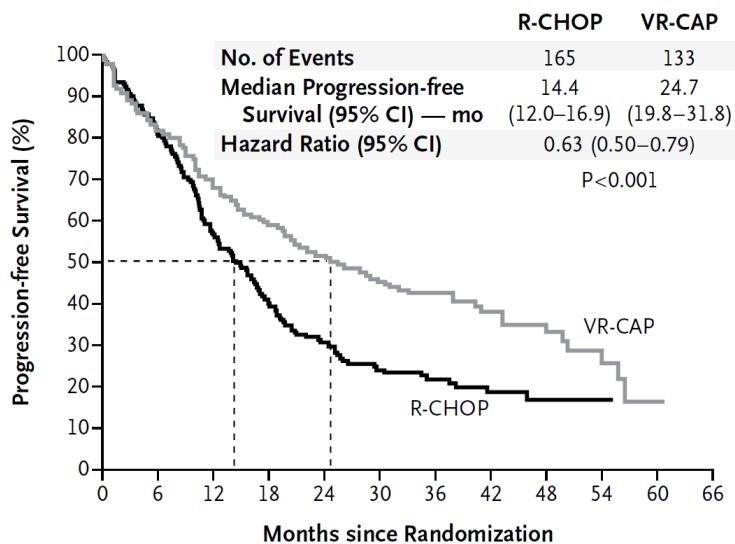
Overall Survival
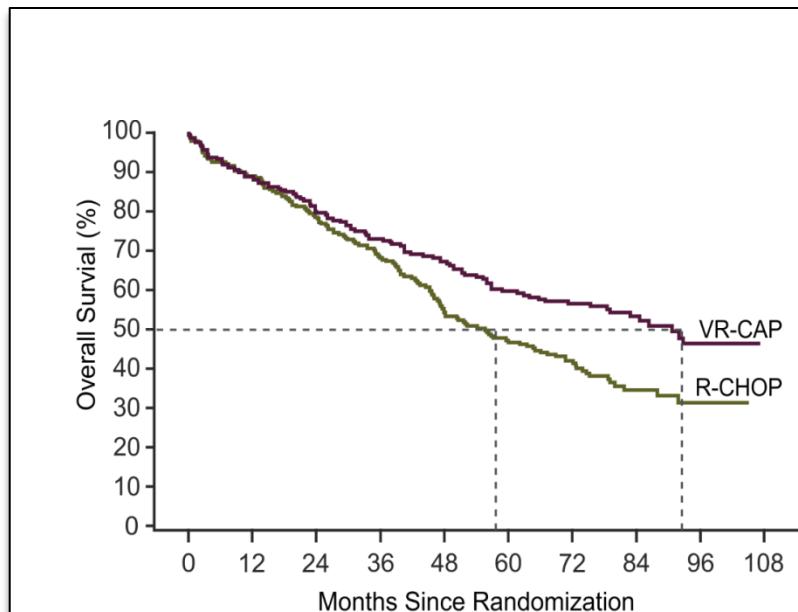
Median follow-up: approx. 80 months

Robak, NEJM 2015

Robak, Lancet Oncol 2019

Optimal treatment for elderly MCL ?

Induction

Consolidation

maintenance

+/- SCT

Immuno-chemotherapy !

=> *lymphoma remission*

=> *MRD elimination*
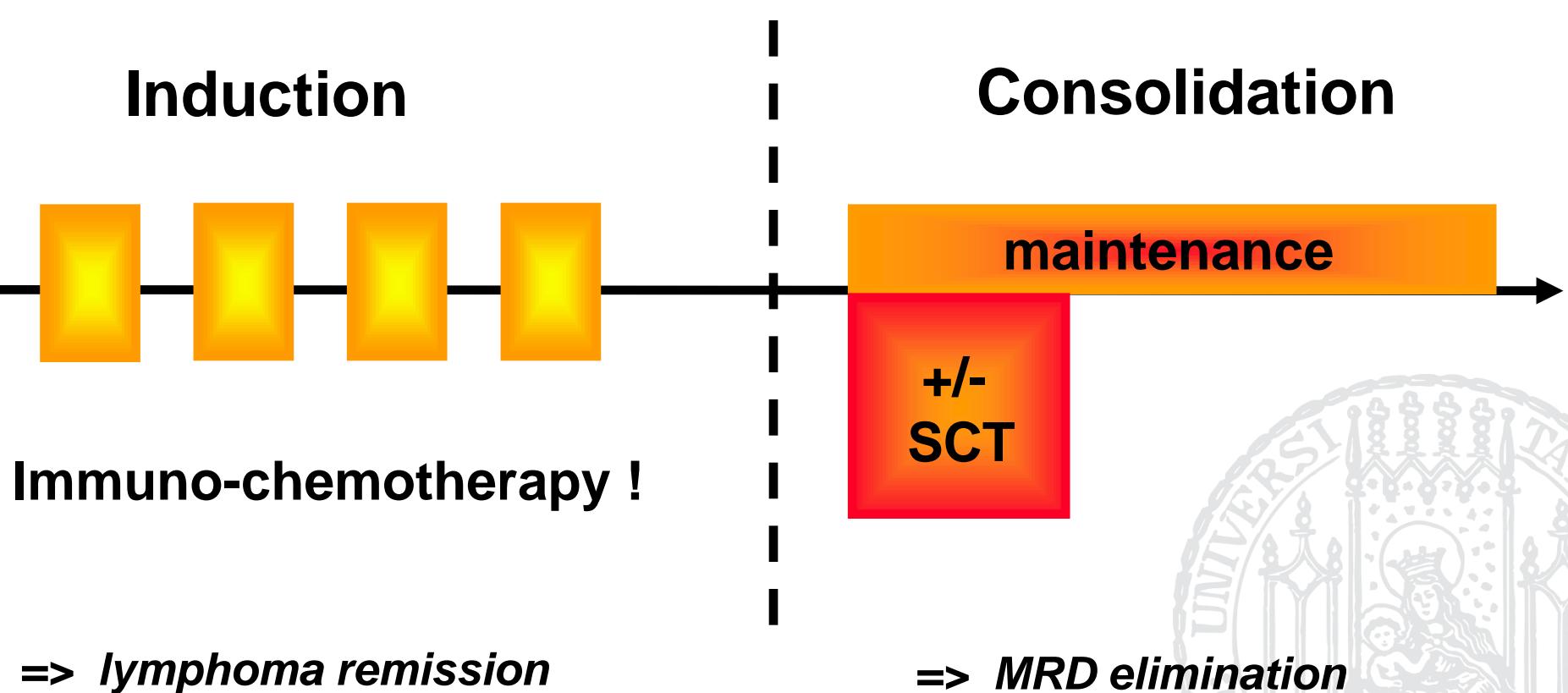
MCL elderly
R-CHOP +/- R maintenance

Updated results 2017: Maintenance part (R2) – after R-CHOP
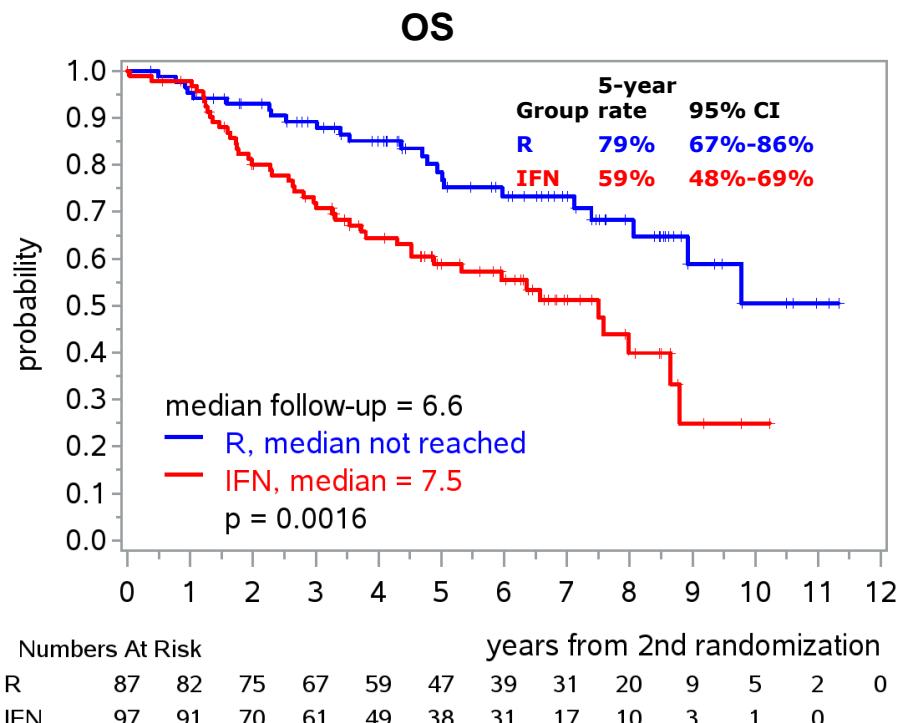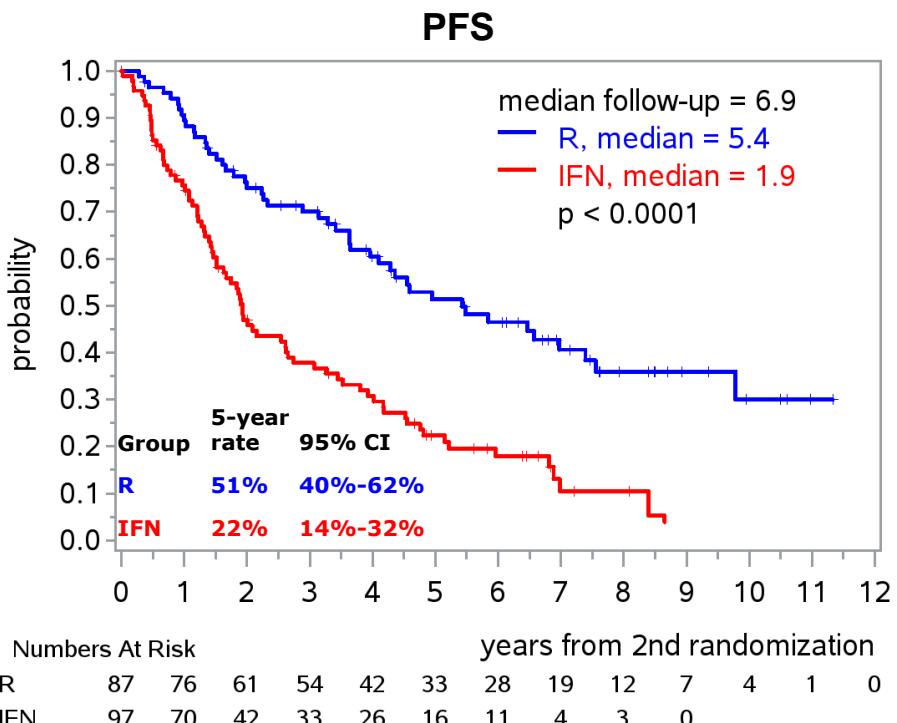
Hoster, ASH 2017: #153

MANTLE CELL LYMPHOMA

- **molecular pathogenesis**

- **chemotherapy standards in first line**

- **targeted approaches**

New

Bortezomib

Ibrutinib

Temsirolimus

Lenalidomide

young patient (≤65)	elderly patient (>65)	compromised patient

First line treatment

dose-intensified immuno-chemotherapy (e.g. R-CHOP, high dose Ara-C) ⇒ **Autologous SCT** ⇒ **Rituximab maintenance**	**conventional immuno-chemotherapy** (e.g. R-CHOP, VR-CAP, BR, R-BAC) ↓ **Rituximab maintenance**	**Best supportive care? R-Chlorambucil BR (dose-reduced) R-CVP**

1. relapse

| **immuno-chemotherapy** (e.g. R-BAC, BR) **or targeted approaches** ↓ discuss: - allogeneic SCT	**immuno-chemotherapy** (e.g. BR, R-BAC) **or targeted approaches** ↓ discuss: - Rituximab maintenance - radioimmunotherapy	**Immuno-chemotherapy** (e.g. BR) **or targeted approaches**

higher relapse

Targeted approaches: Ibrutinib, Lenalidomide, Temsirolimus, Bortezomib (preferable in combination) Alternatively: repeat previous therapy (long remissions)

Dreyling, ESMO CR MCL 2017

Lenalidomide
Mechanisms of action

T-Cell Effects
Activation and proliferation
↑ Immune synapse formation
↑ CD8+ T-effector cell activity
Stimulation of cytotoxic CD8+ and helper CD4+ T cells
↑ Dendritic cell antigen presentation
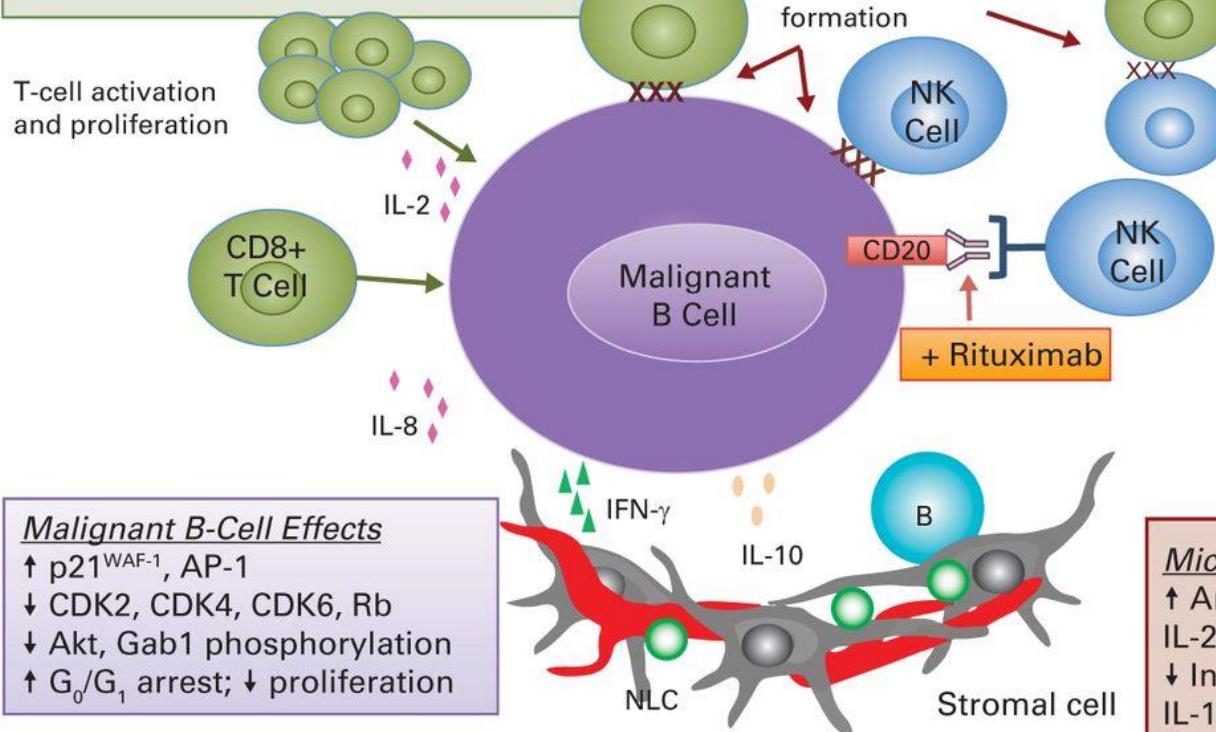
NK-Cell Effects
↑ Number and activity of NK cells
↑ Enhanced ADCC
↑ Immune synapse formation and direct NK killing

T-cell activation and proliferation

IL-2

CD8+ T Cell

IL-8

T Cell

Immune synapse formation

NK Cell

NK Cell

CD20

+ Rituximab

ADCC and enhanced cytotoxicity

Malignant B-Cell Effects
↑ $p21^{WAF-1}$, AP-1
↓ CDK2, CDK4, CDK6, Rb
↓ Akt, Gab1 phosphorylation
↑ G_0/G_1 arrest; ↓ proliferation

Malignant B Cell

IFN-γ
IL-10
B
NLC
Stromal cell

Microenvironment Effects
↑ Anti-inflammatory cytokines: IL-2, IL-8, IL-10, IFN-γ, TNF-α
↓ Inflammatory cytokines: IL-1, IL-6, IL-12, TNF-α

Gribben, JCO 2015

Relapsed Mantle cell lymphoma
Lenalidomide

	Lenalidomide (n = 170)	IC (n = 84)
Median PFS, mo (95% CI)	8.7 (5.5-12.1)	5.2 (3.6-6.9)
HR (95% CI)	0.61 (0.44-0.84); *P* = 0.004	

Lenalidomide 8.7 mo

Control 5.2 mo

IC

Lenalidomide

Survival Probability

Progression-Free Survival, months

Number of patients at risk

|	0	5	10	15	20	25	30	35	40	45	50	55
Lenalidomide	170	86	63	36	27	20	16	12	7	1	1	0
IC	84	31	15	7	5	4	4	2	0			
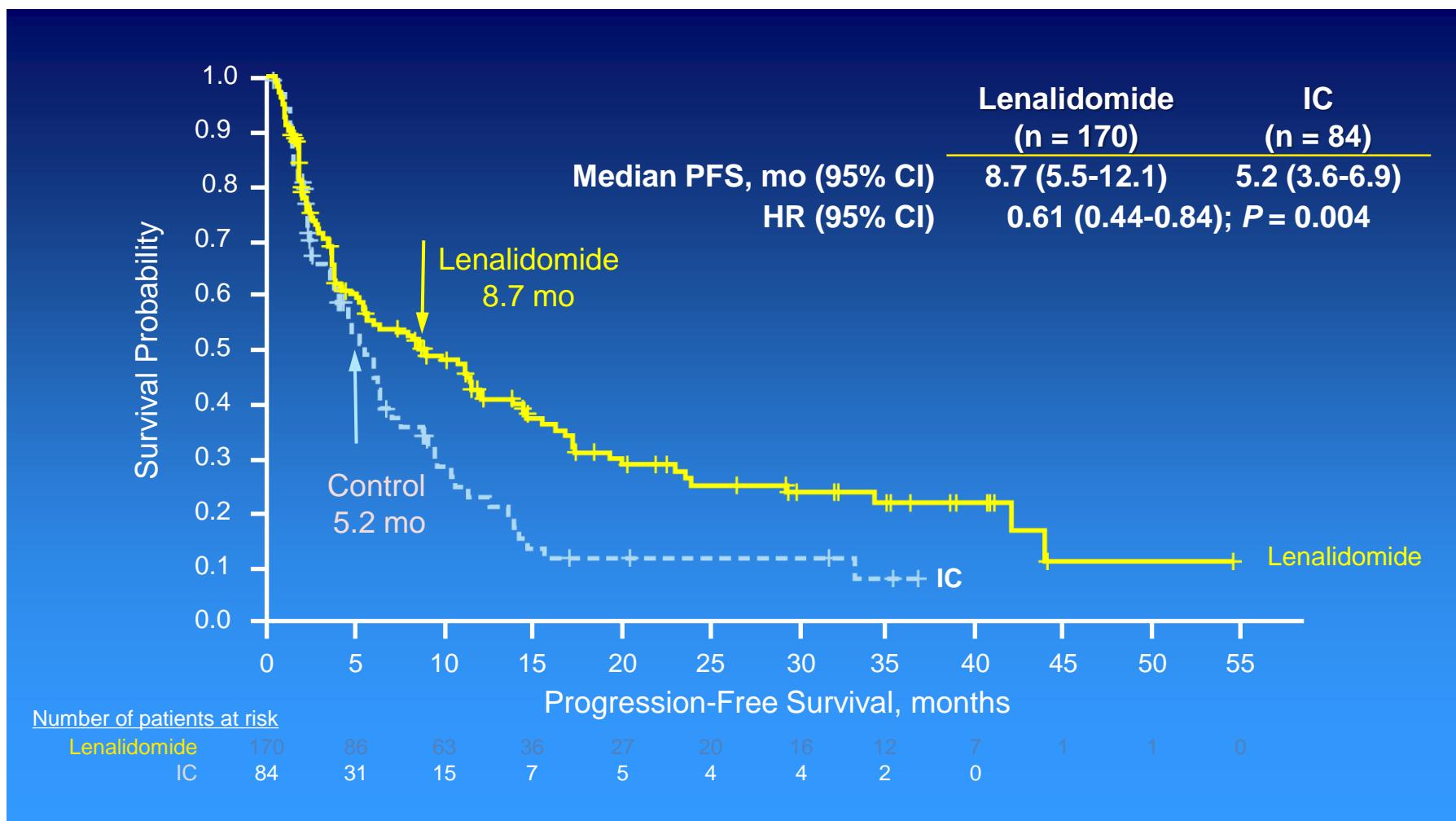
Study Design

Induction (cycles 1-12)

Rituximab 375 mg/m²

Lenalidomide 20 mg*
Days 1-21 q 28

* Dose escalation to 25 mg allowed

Time (months): 1 2 3 4 5 6 7 8 9 10 11 12
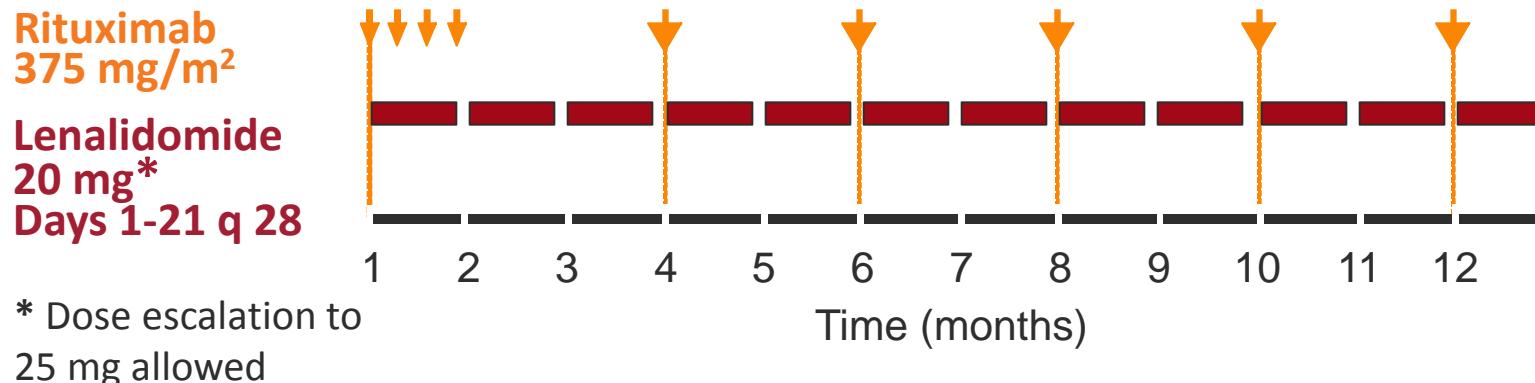
Maintenance (cycle 13 - POD)

Rituximab 375 mg/m²

Lenalidomide 15 mg
**Days 1-21 q 28**

Time (months): 13 14 15 16 17 18 19 20 21 22 23 24 POD
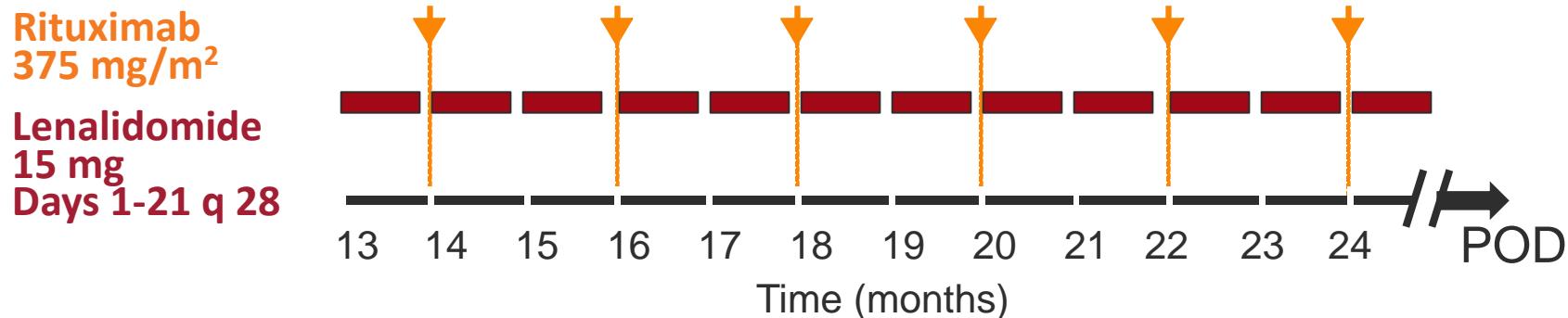
Response assessment: Cheson 2007; DVT prophylaxis: ASA
Scan frequency: every 3 months Y1-2, every 6 month Y3 & beyond

Weill Cornell Medicine

24

*Ruan, Blood 2018*

Survival

Progression-Free Survival

36-month PFS = 80.3% (95% CI = 63.0%, 90.1%)
48-month PFS = 70.6% (95% CI = 52.0%, 83.1%)

Median follow-up = 61 months (range 21-74)

Number at risk
36   33   30   28   23   16   12   2

Overall Survival

36-month OS = 91.9% (95% CI = 76.9%, 93.7%)
48-month OS = 83.0% (95% CI = 65.9%, 92.0%)

Median follow-up = 61 months (range 21-74)

Number at risk
38   37   36   34   33   26   19   7   0
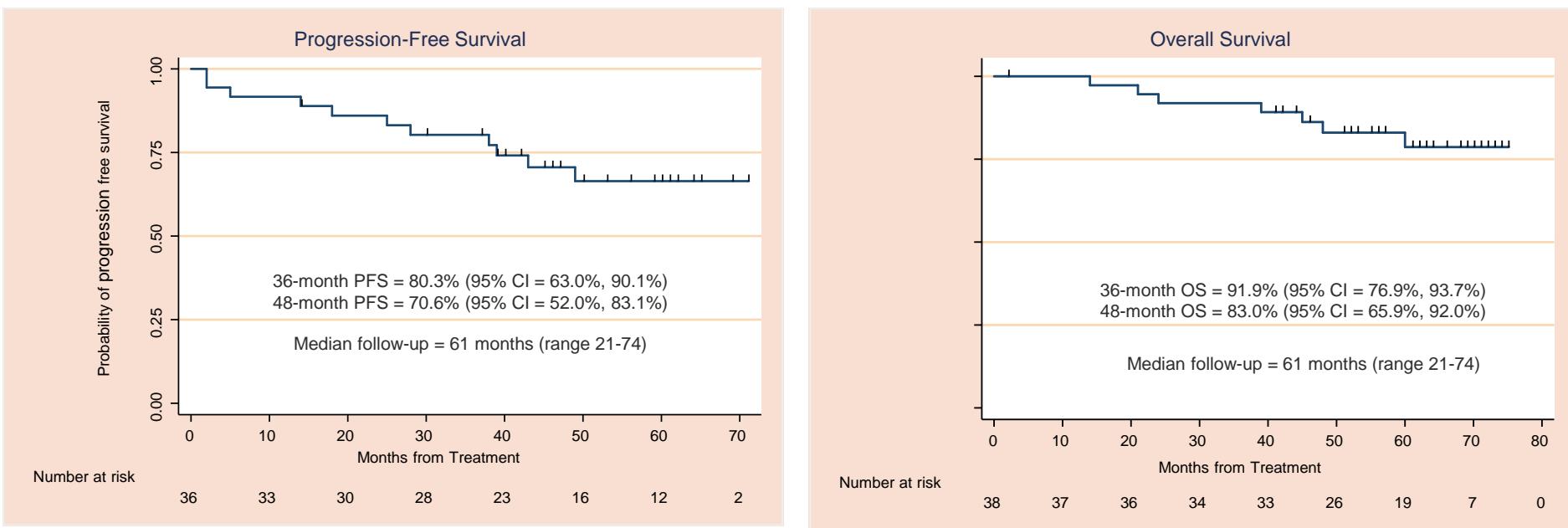
EUROPEAN MCL NETWORK
MCL R2 ELDERLY

1st line induction: 8x R-CHOP

®

1st line induction: 6x R-CHOP/Ara-C

PR/CR ~80%

®

Rituximab maintenance + Lenalidomide 15 mg daily d1-21, q28 days

Treatment: max. 2 years

Rituximab maintenance
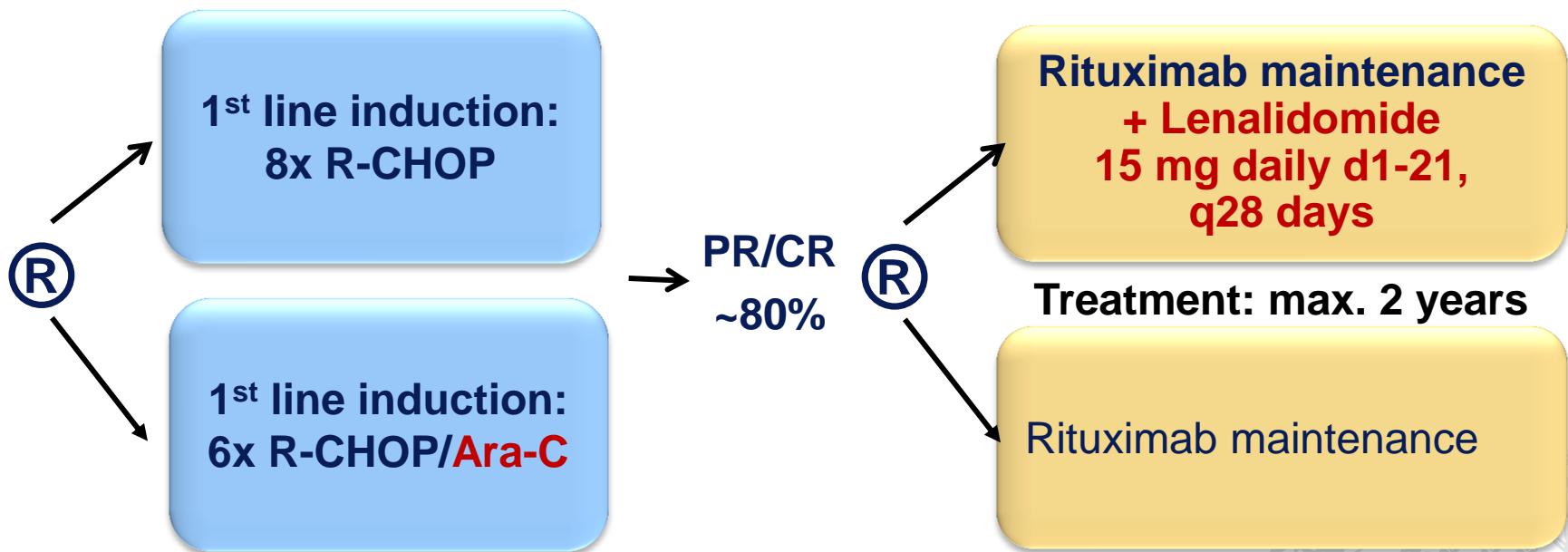
sponsor: LYSARC
central pathology: W. Klapper
MRD diagnostics: M. Ladetto, C. Pott, MH Delfau

Recruitment status (02/2019)


MCL-R2 Elderly - Global Recruitment
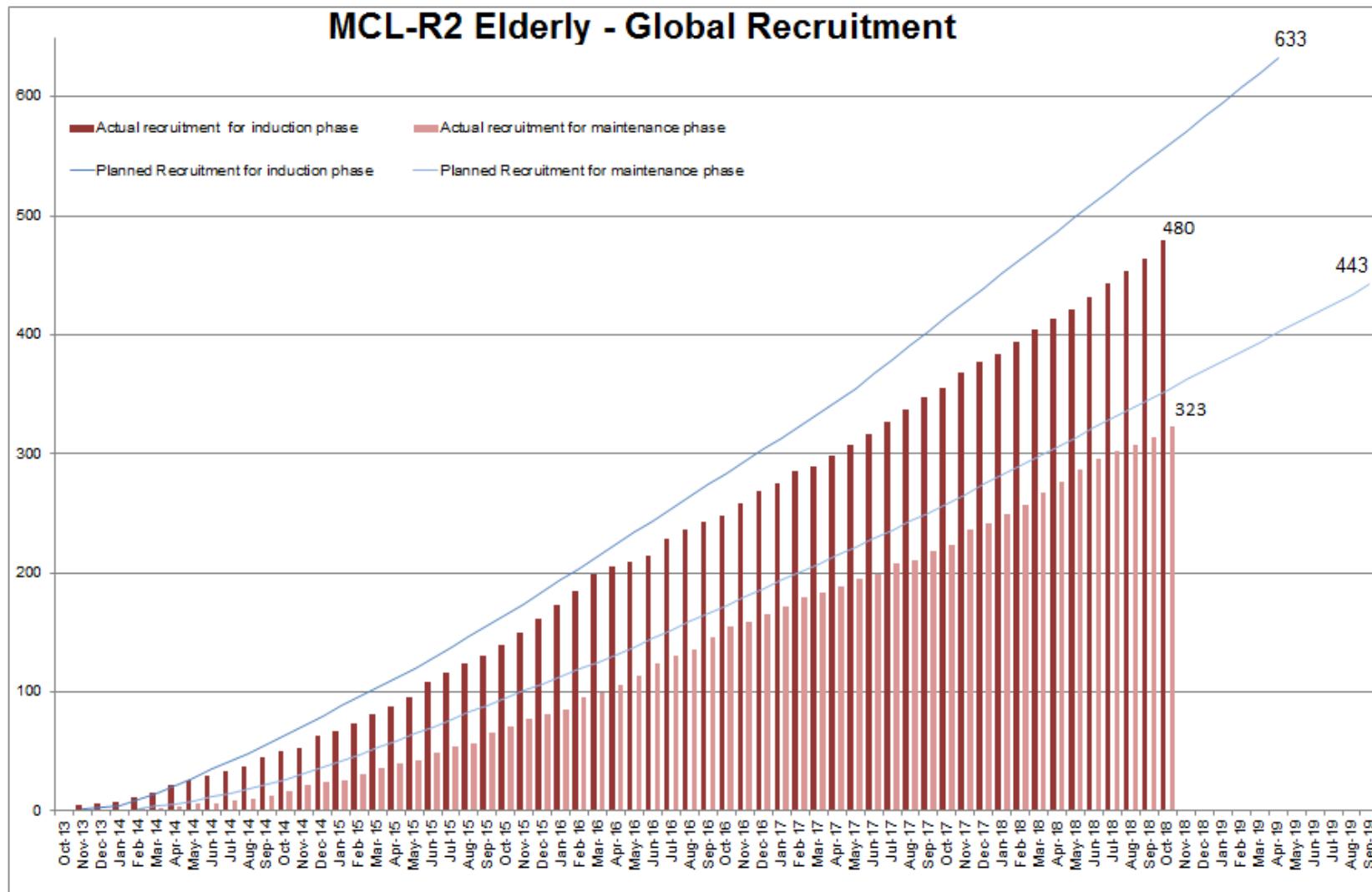
Recruitment status (02/2019)

MCL-R2 Elderly - Germany - Recruitment per centre

Number of patients randomized for induction
Number of patients randomized for maintenance
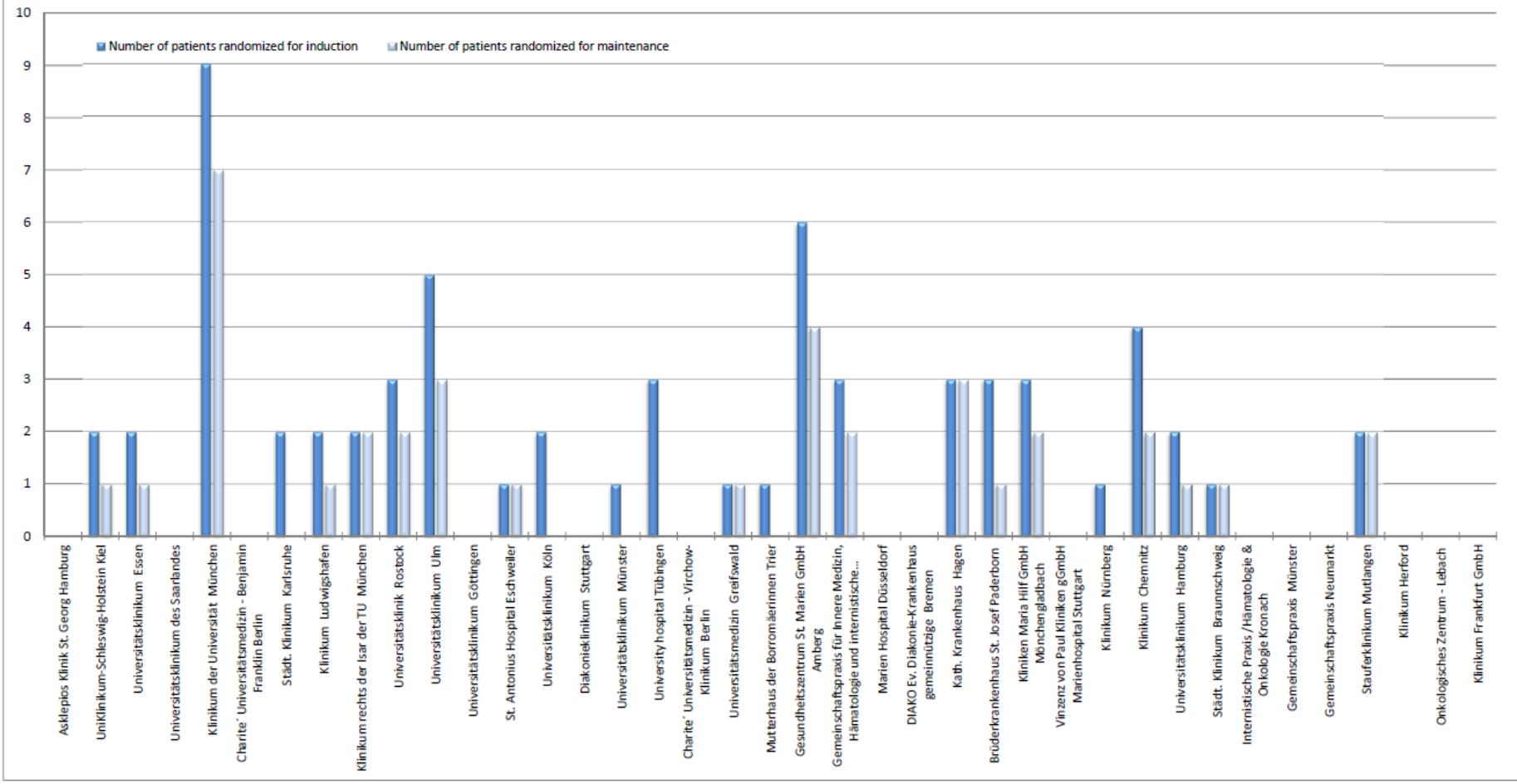
BTK inhibition in lymphoma
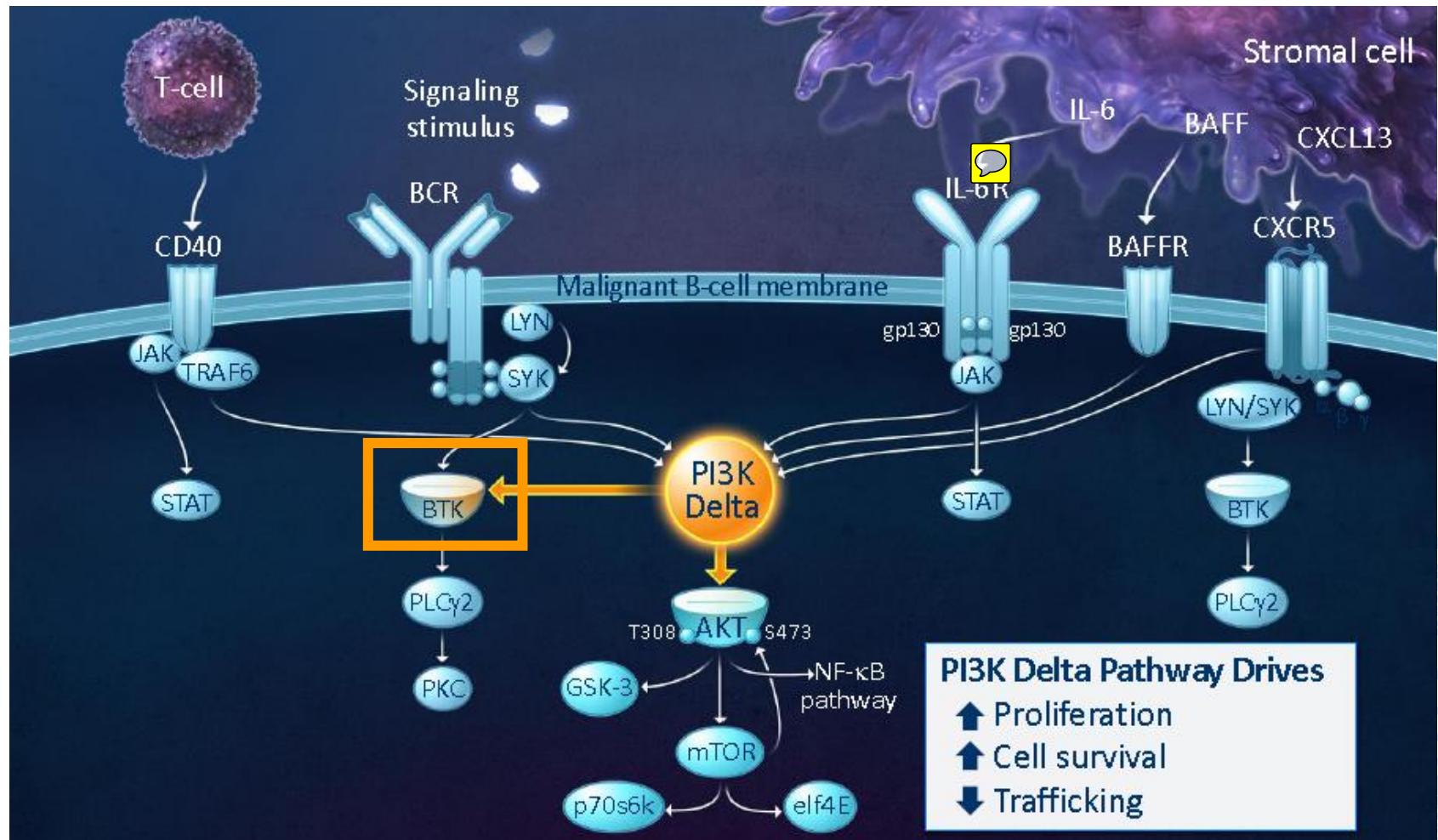
Ibrutinib vs Temsirolimus
Progression-free survival

ITT population
Median follow-up: 20 months

|	Ibrutinib	Temsirolimus
Median PFS (months)	14.6	6.2
Hazard ratio (HR)	0.43	
95% confidence interval (CI)	0.32-0.58	
Log-rank *p* value	< 0.0001	

Patients at risk

Ibrutinib	139	114	101	83	77	45	34	8	5	0	0
Temsirolimus	141	93	69	45	33	19	11	3	1	0	0
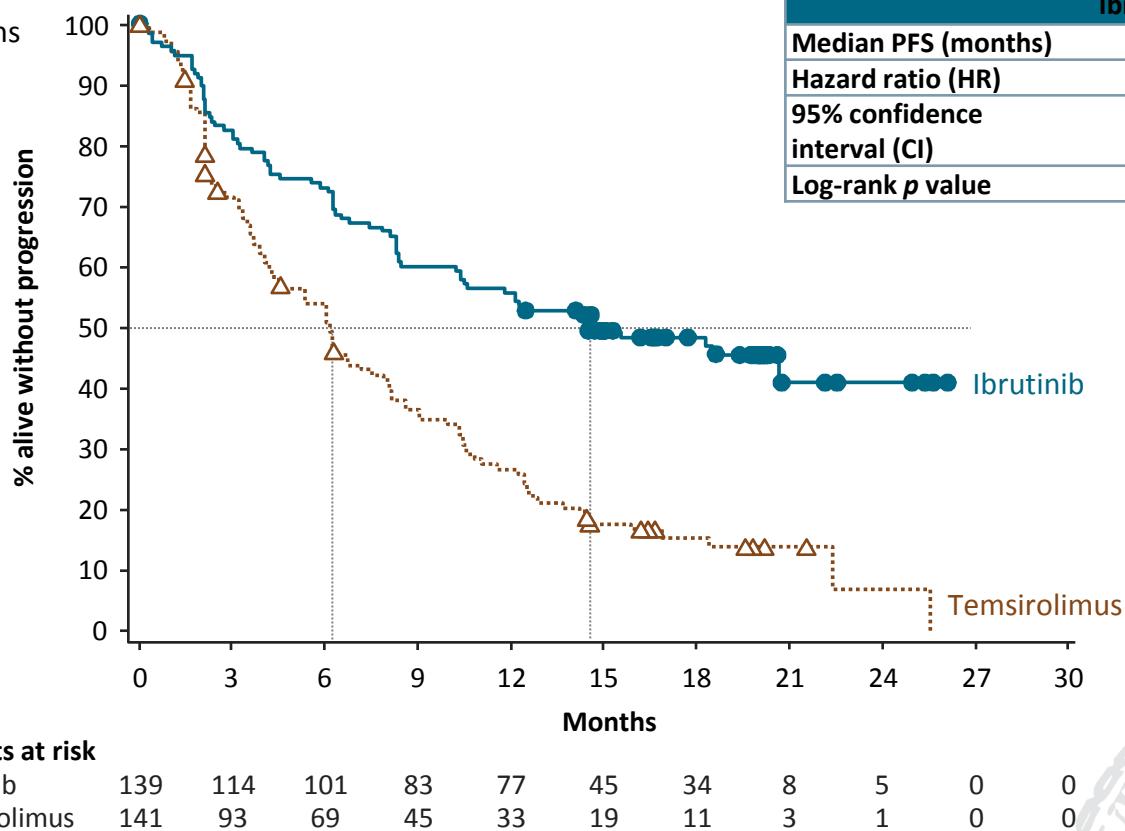
At a 2-year landmark, the PFS rate was 41% for ibrutinib versus 7% for temsirolimus

Investigator-assessed HR for ibrutinib versus temsirolimus was 0.43 (95% CI, 0.32-0.58)

Ibrutinib in relapsed MCL
Survival rates

Rule, Haematologica 2018
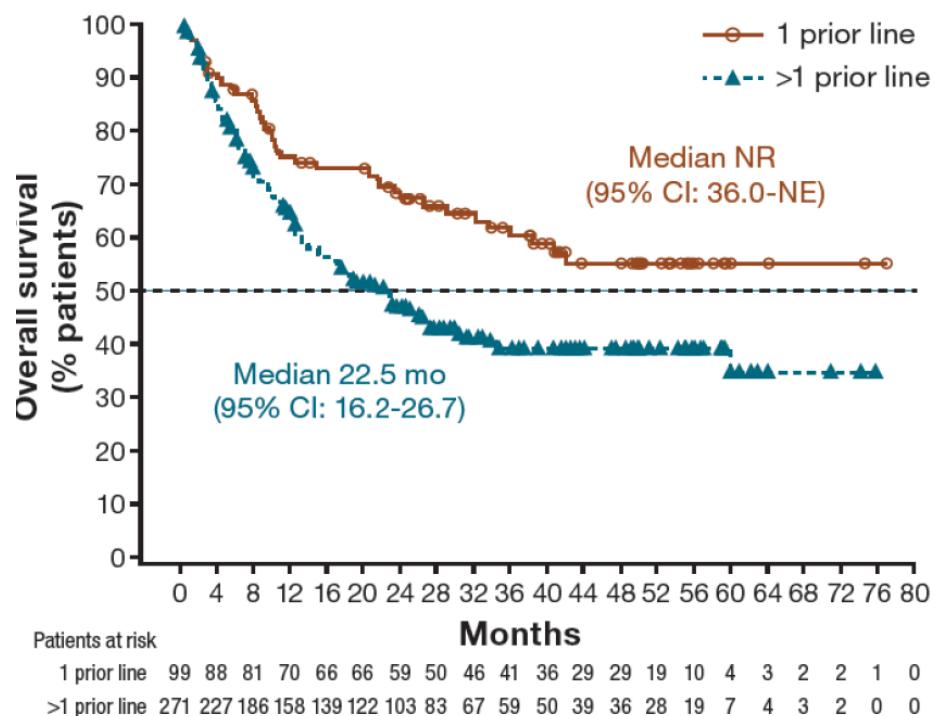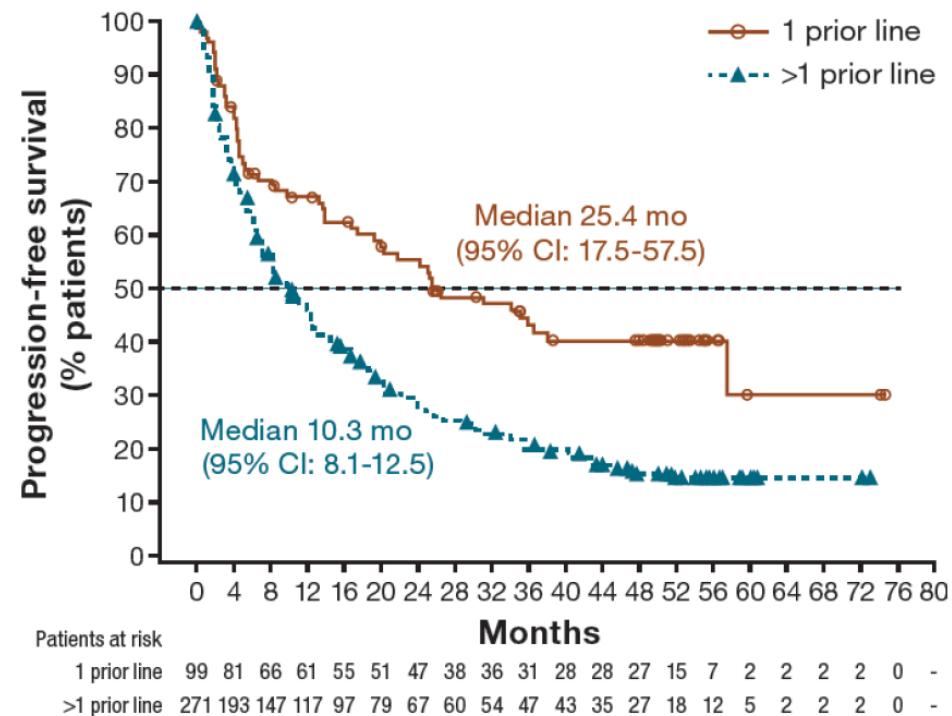
Independent Predictors of PFS and OS With Ibrutinib: Multivariate Analysis

PFS

		HR	p value
Age, yrs	< 65 vs ≥ 65	0.947	0.7177
ECOG PS	≥ 2 vs 0-1	1.884	0.0093
Extranodal disease	Yes	1.293	0.0724
sMIPI	High vs low risk	1.987	0.0015
	Intermediate vs low risk	1.501	0.0309
Prior lines of therapy	> 1 vs 1	1.585	0.0073
MCL stage	IV vs I-III	0.658	0.0667
Bone marrow involvement	Yes	1.127	0.3876
Bulky disease, cm	≥ 5	1.612	0.0005
Blastoid history	Yes	2.308	<0.0001

0.25 0.5 1 2 4

Lower risk of progression — Higher risk of progression

OS

		HR	p value
Age, yrs	< 65 vs ≥ 65	0.744	0.0937
ECOG PS	≥ 2 vs 0-1	2.316	0.002
Extranodal disease	Yes	1.208	0.2432
sMIPI	High vs low risk	2.118	0.0024
	Intermediate vs low risk	1.565	0.0417
Prior lines of therapy	> 1 vs 1	1.361	0.1084
MCL stage	IV vs I-III	0.859	0.5611
Bone marrow involvement	Yes	1.38	0.0422
Bulky disease, cm	≥ 5	1.645	0.0014
Blastoid history	Yes	2.421	<0.0001

0.25 0.5 1 2 4

Lower risk of death — Higher risk of death

- **Clinical risk factors and number of prior lines predict outcome in R/R MCL**

HR, hazard ratio.

Relapsed mantle cell lymphoma
Failure under ibrutinib

Martin, Blood 2016
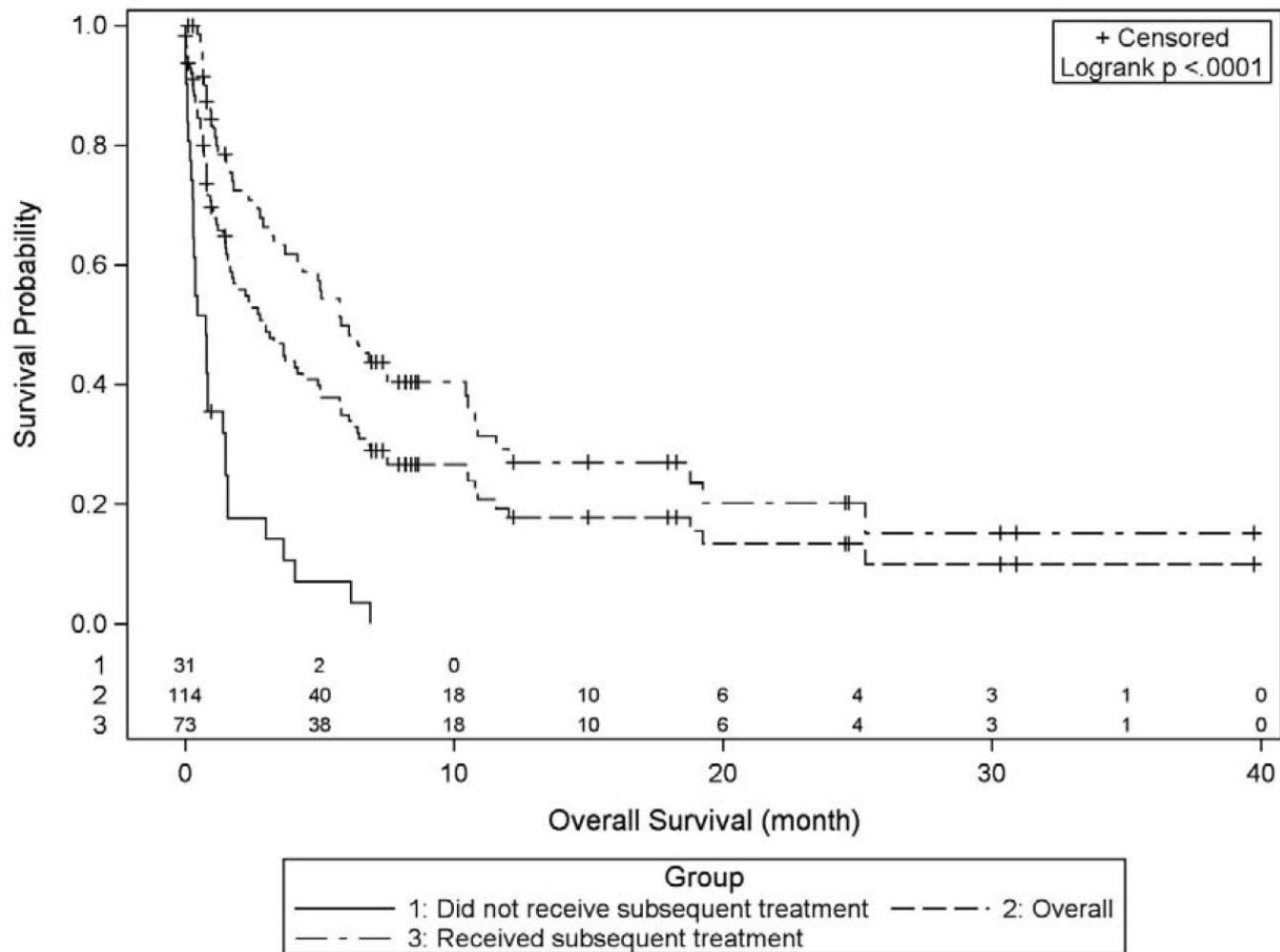
THE ERA OF COMBINATIONS

copyright: A. Viardot

TRIANGLE
ADD ON VS HEAD TO HEAD COMPARISON

A:

3x R-CHOP/
3x R-DHAP → ASCT → Observation

R maintenance (3 years)

A + I:

3x R-CHOP + I/
3x R-DHAP → ASCT → 2 yrs I-maintenance → Observation

R maintenance (3 years)

I:

3x R-CHOP + I/
3x R-DHAP → 2 yrs I-maintenance → Observation

R maintenance (3 years)
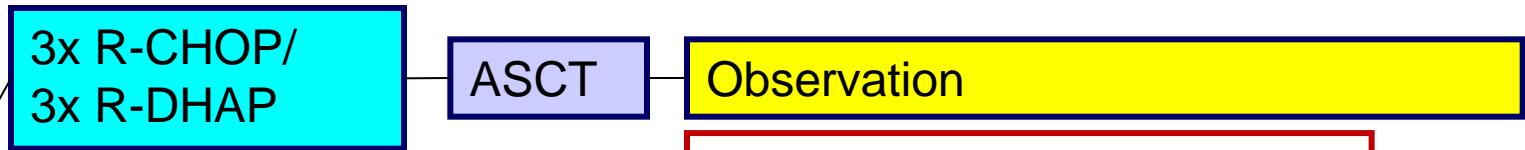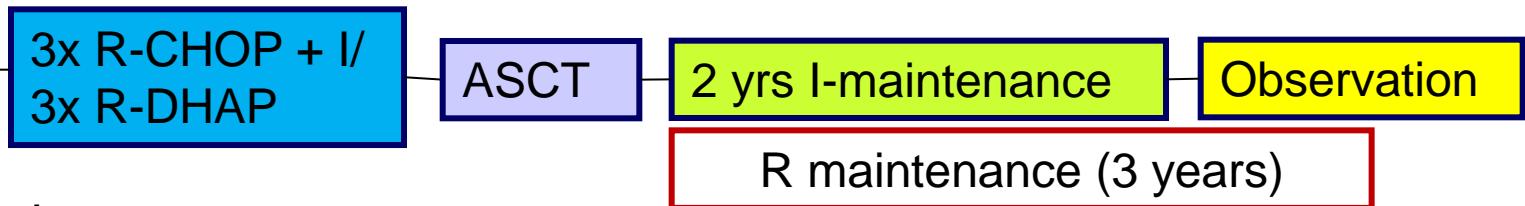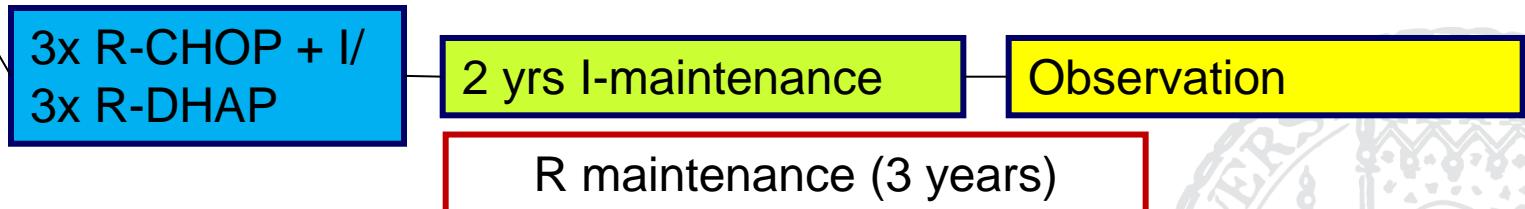
superiority/non-inferiority: time to treatment failure
HR: 0.60; 65% vs. 77% vs. 49% at 5 years

TRIANGLE
RECRUITMENT

Patients randomized: 412

Planned randomization   Actual randomization
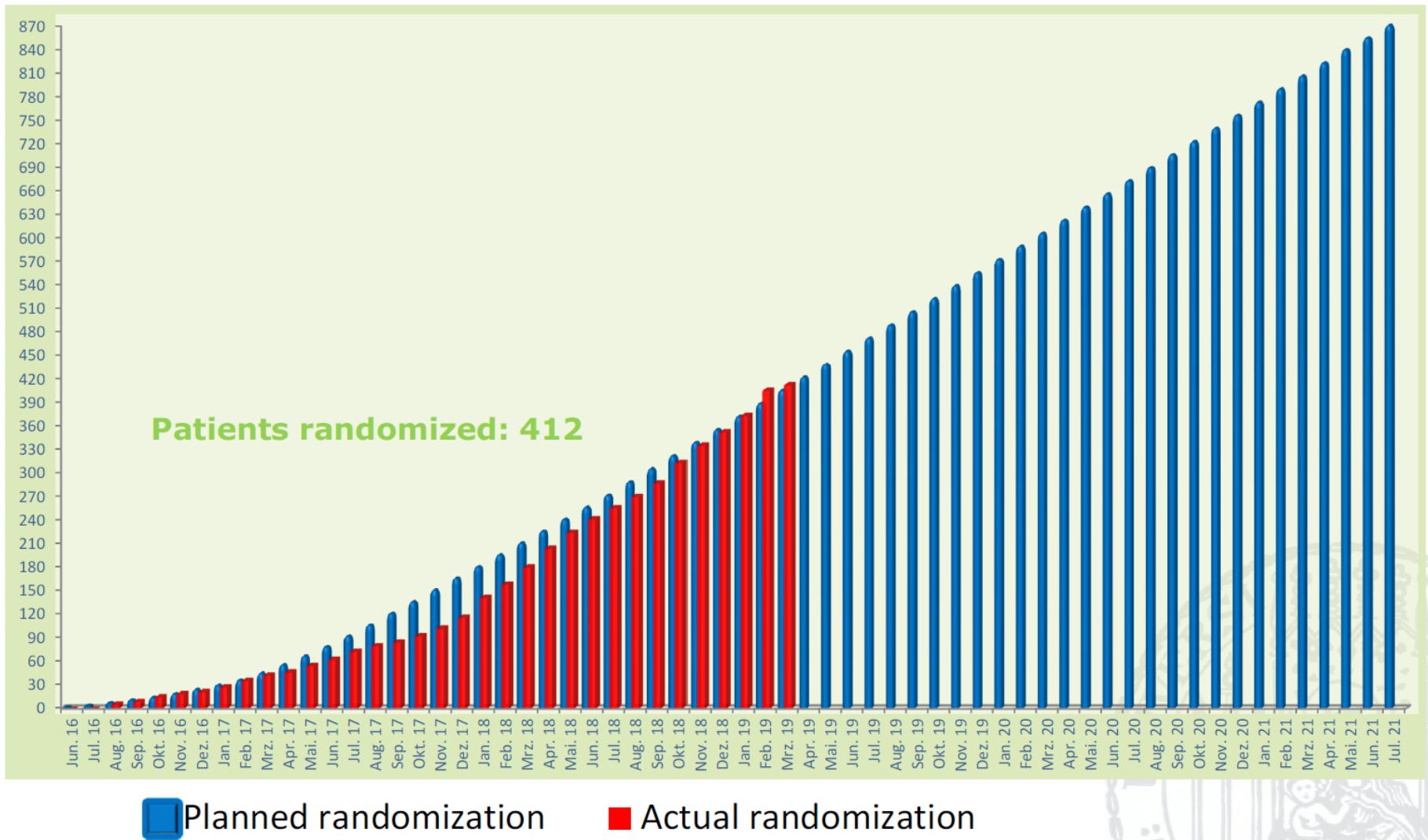
SITE INITIATION, ACTIVATION AND PATIENT RECRUITMENT

Number of ....

Countries	Sites				Patients
active	planned	initiated	active	recruiting	randomized
Belgium	8	7	7	3	4
Denmark	6	6	6	4	7
Germany	**60**	**60**	**59**	**38**	**151**
Italy	34	31	31	28	69
Netherlands	25	19	19	10	20
Norway	5	3	3	2	7
Poland	7	7	7	5	7
Spain	14	13	13	10	22
Sweden	8	8	8	7	22
Switzerland	13	13	13	6	10
10 countries	180	167	166	113	319

KLINIKUM DER UNIVERSITÄT MÜNCHEN®
MEDIZINISCHE KLINIK UND POLIKLINIK III

TRIANGLE
RANDOMIZATION PER SITE IN GERMANY
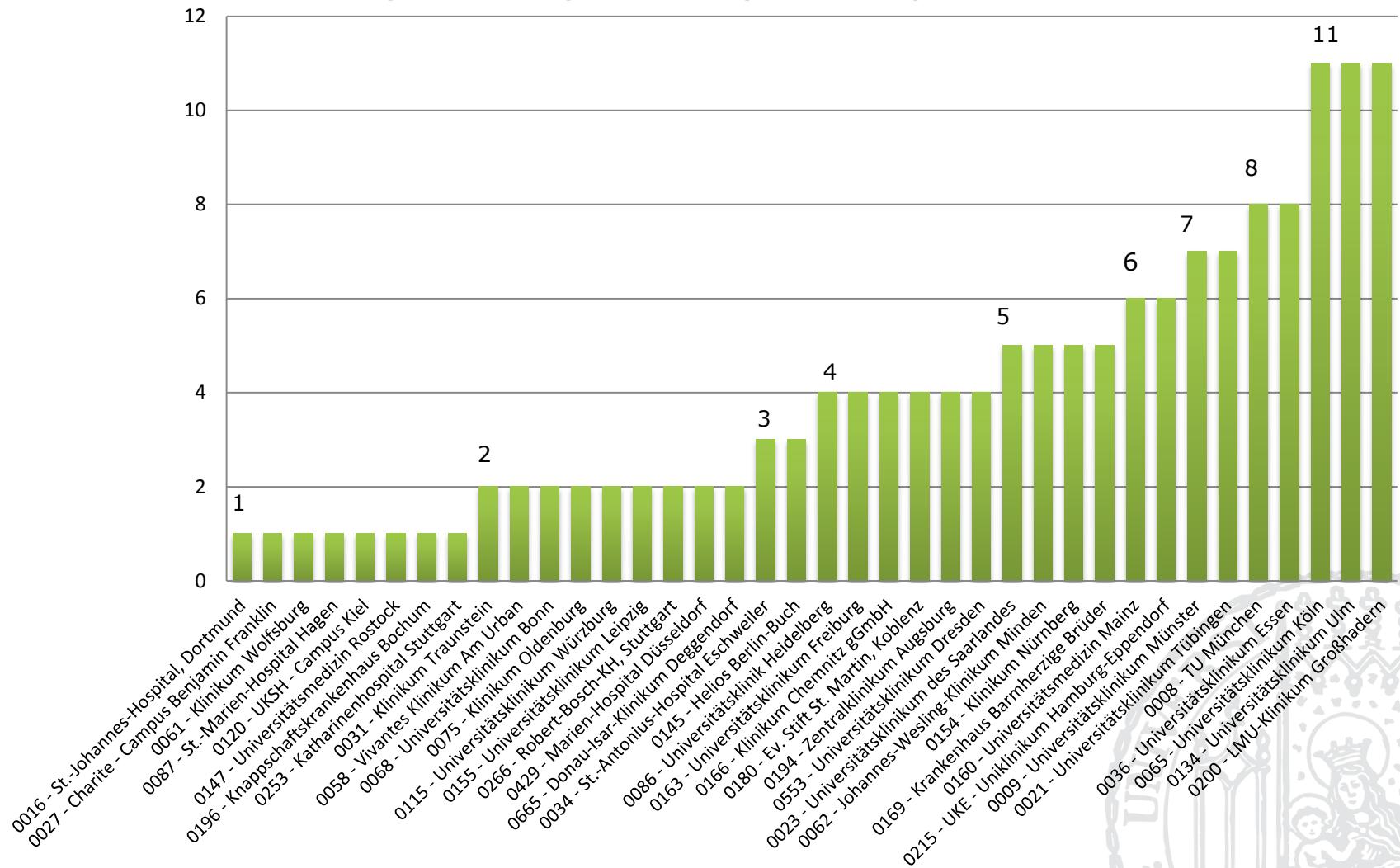
VENETOCLAX
MECHANISM OF ACTION

1 An Increase in BCL-2 Expression Allows the Cancer Cell to Survive

Pro-apoptotic Proteins (BAX, BAK)

Anti-apoptotic Proteins (BCL-2)

Mitochondria

2 Venetoclax Binds to and Inhibits Overexpressed BCL-2

Venetoclax

BH3-only

BAX

BAK

BCL-2

BCL-2
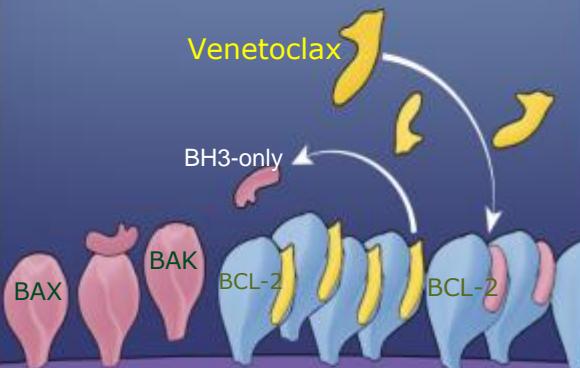
Mitochondria

3 Apoptosis is Initiated

Apoptosome

APAF-1

Cytochrome C

Active Caspase

Procaspase

Mitochondria

Davids, JCO 2017

Objective responses
ABT-199 (Venetoclax)

Davids, JCO 2017
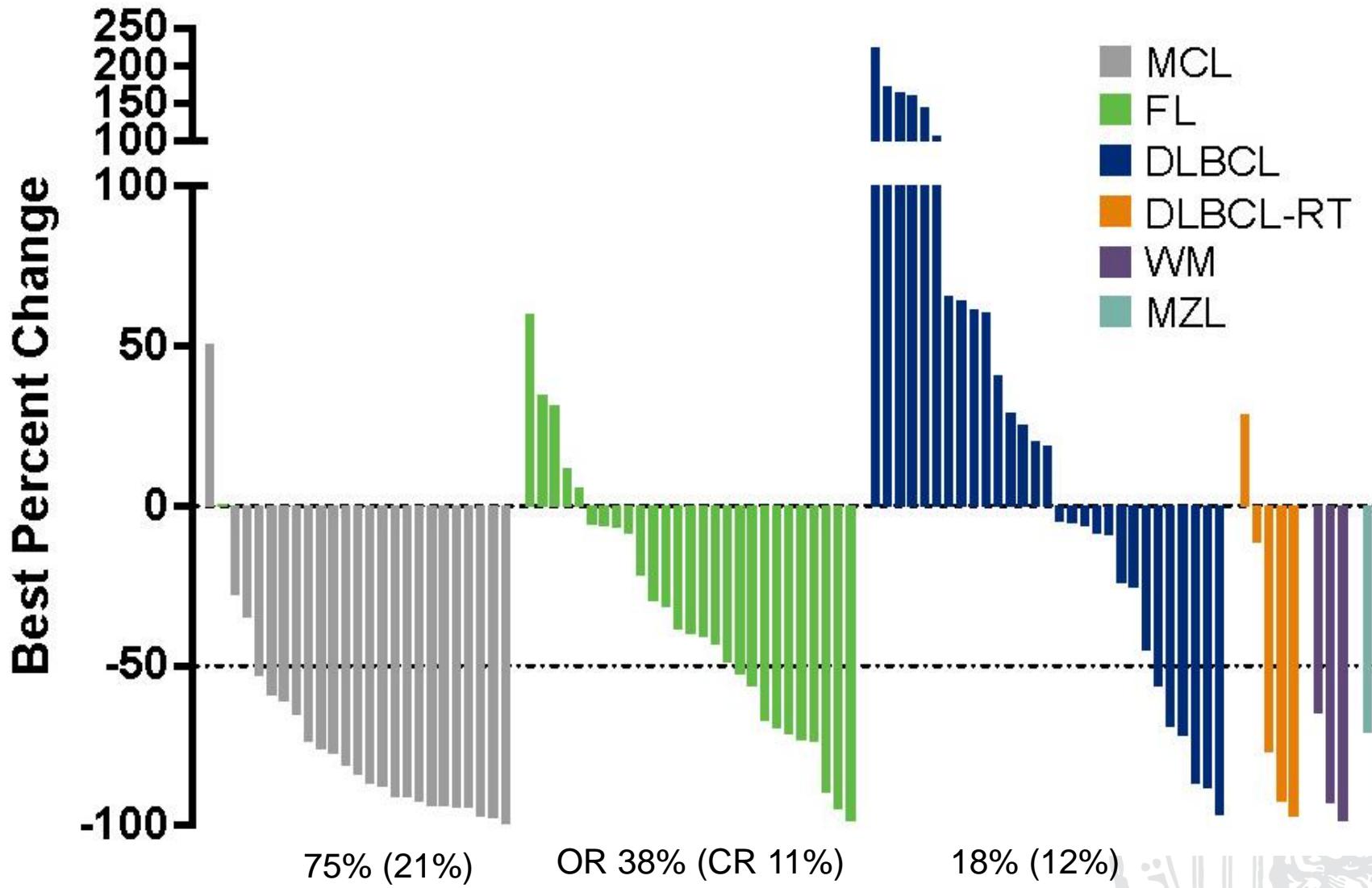
AIM: PROGRESSION FREE & OVERALL SURVIVAL

KLINIKUM DER UNIVERSITÄT MÜNCHEN®

MEDIZINISCHE KLINIK UND POLIKLINIK III
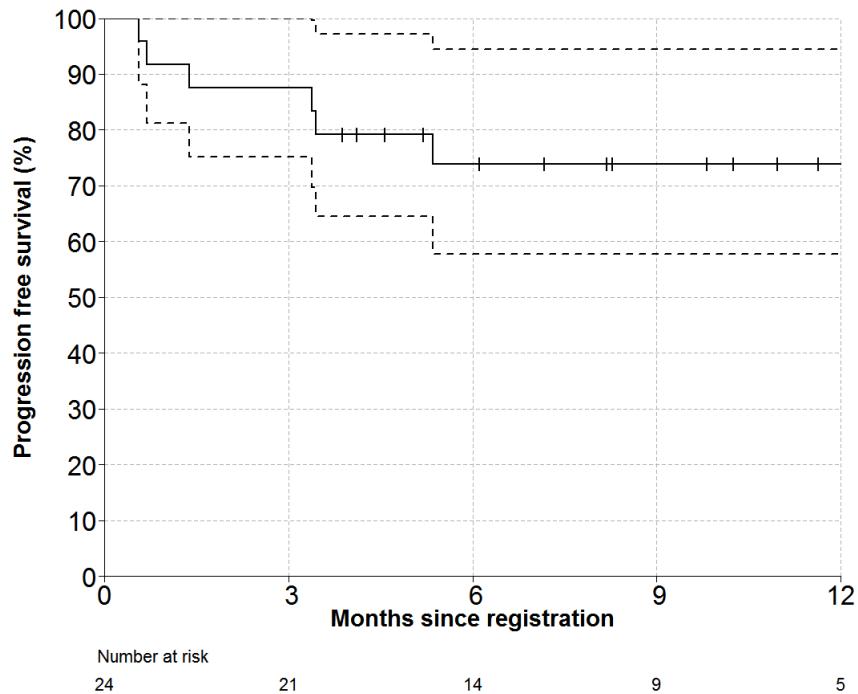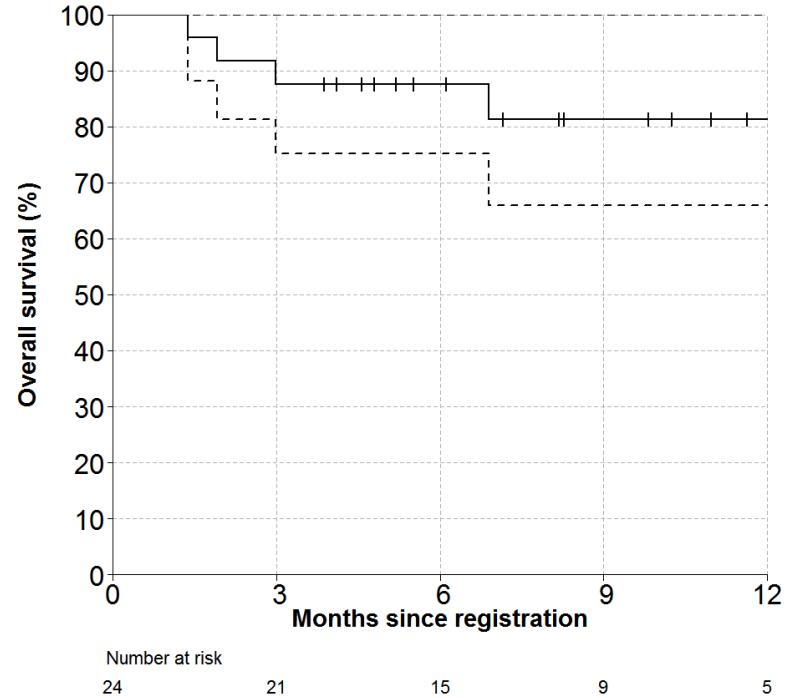
RELAPSED MANTLE CELL LYMPHOMA
IBRUTINIB-LENALIDOMIDE-R

NORDIC MCL6 PHILEMON
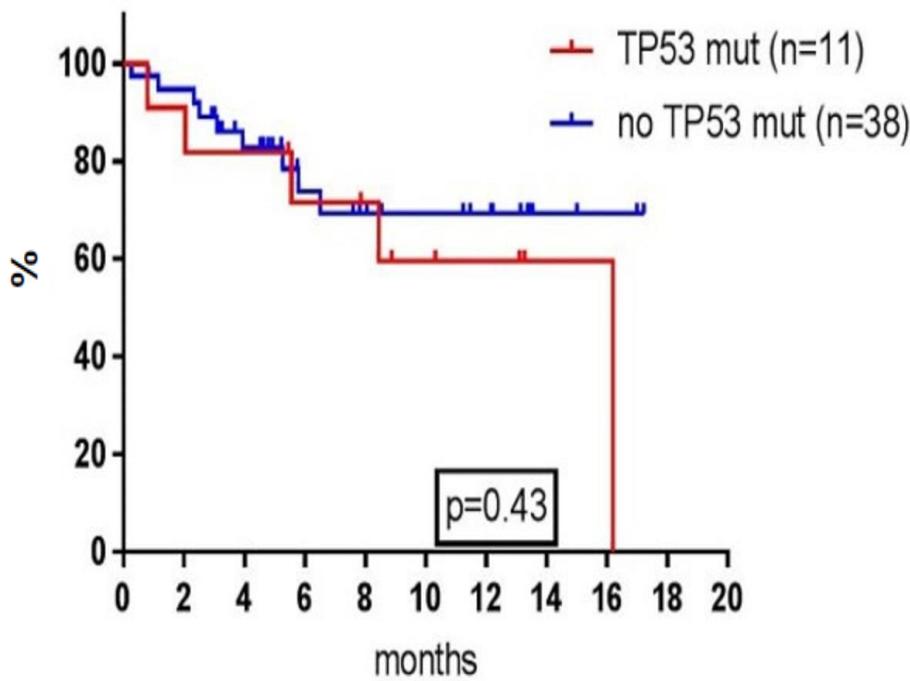
NORDIC MCL2/3

Eskelund, Blood 2017

Jerkeman, Lancet Haematology 2018
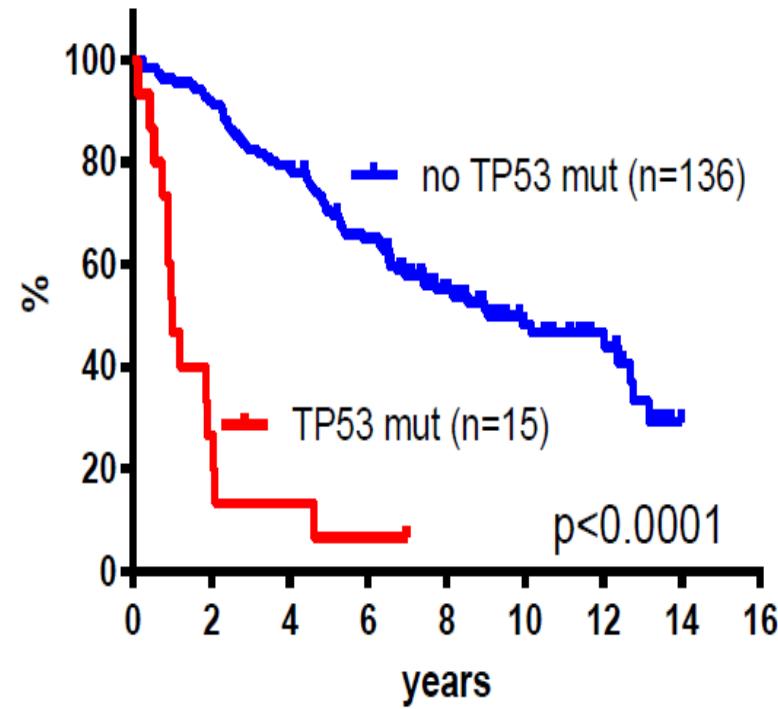
European MCL Network
Study generation 2019

< 65 years	> 60 years	> 65 years
MCL younger: R-CHOP/DHAP =>ASCT R-CHOP/DHAP+I =>ASCT => I R-CHOP/DHAP + I => I	**MCL elderly R2:** R-CHOP vs R-CHOP/Ara-C => Rituximab M +/- Lenalidomide	**MCL elderly I:** BR +/- Ibrutinib => Rituximab M +/- Ibrutinib

Relapse

Ibrutinib/ Bortezomib	R-HAD +/- Bortezomib	*Ibrutinib +/-* ABT-199