Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

15-ICML

15th International Conference on Malignant Lymphoma
Palazzo dei Congressi, Lugano, Switzerland, June 18-22, 2019

18.–22. Juni 2019

KML-Experten berichten vom 15-ICML 2019 in Lugano

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT 15-ICML 18.–22. Juni 2019

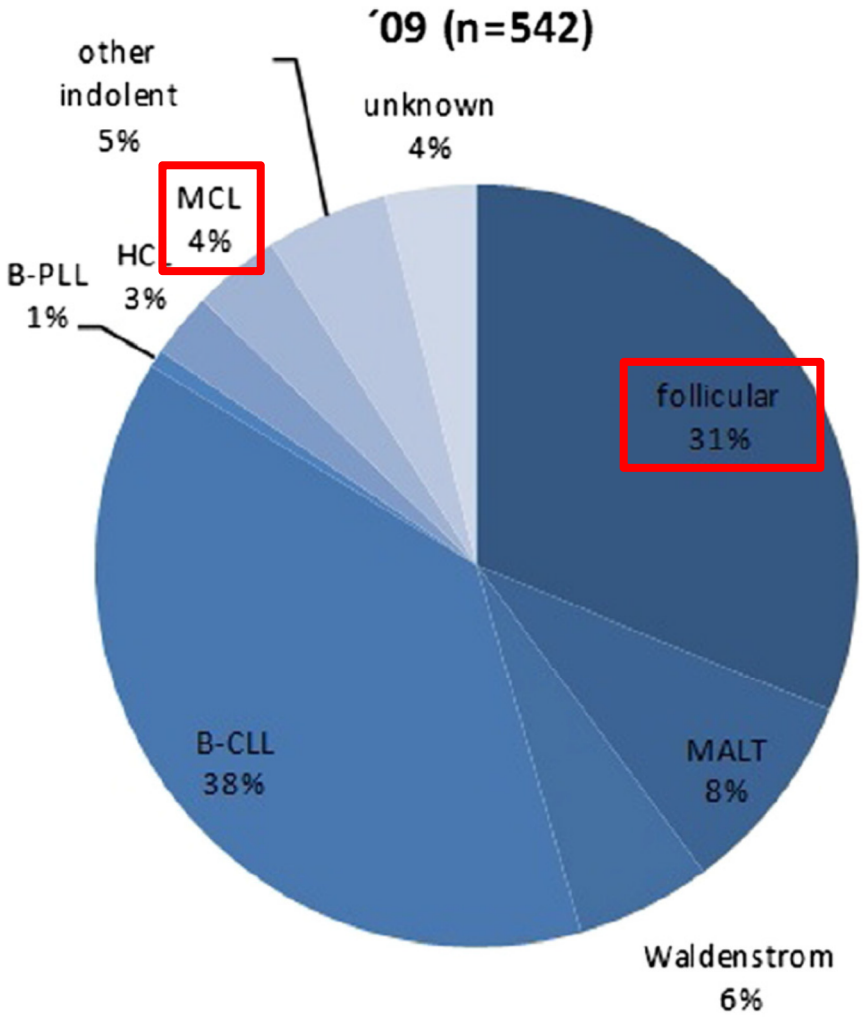
Prof. Dr. med. Martin Dreyling
Indolente Lymphome

Medizinische Klinik III der Universität München-Großhadern|
Koordinator des Europäischen MCL Netzwerks (EMCLN)

Disclosures

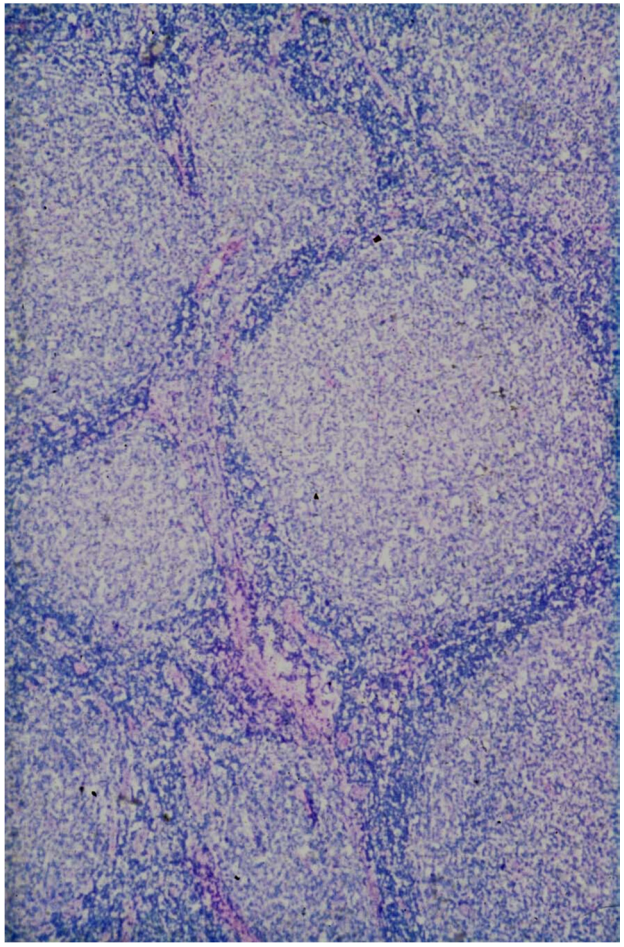
Research Support (institution)	**Celgene, Janssen, Mundipharma, Roche**
Employee	**-**
Major Stockholder	**-**
Speakers Bureau	**-**
Speakers Honoraria	**Bayer, Celgene, Gilead, Janssen, Roche**
Scientific Advisory Board	**Acerta, Bayer, Celgene, Gilead, Janssen, Mundipharma, Roche, Sandoz**

Indolent Lymphoma
Frequency of Subtypes



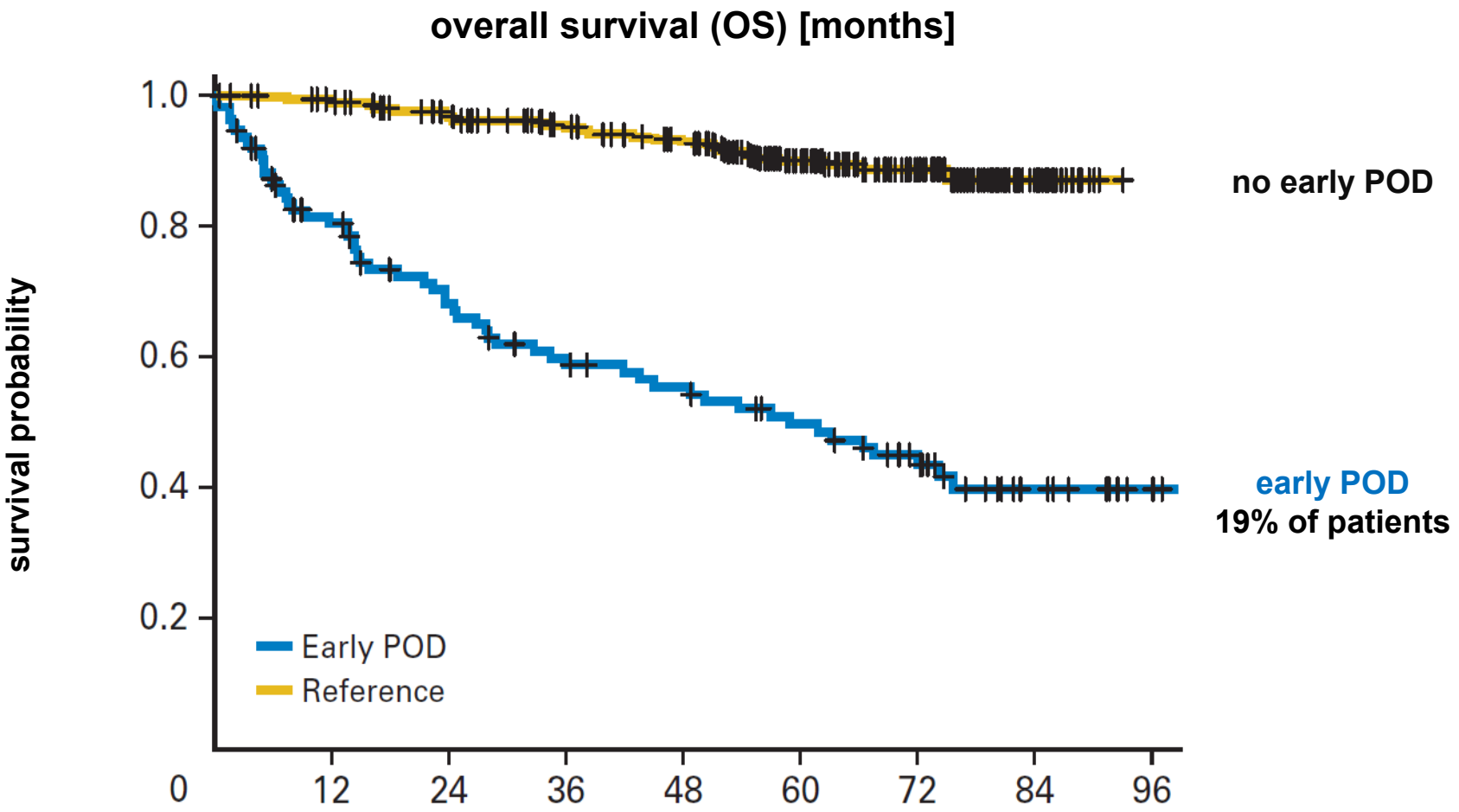
Schmidt, Leuk Lymph 2014

Follicular Lymphoma: Clinical Characteristics



- about 25% of lymphoma
- Median age 60-65 years
- 85% advanced stage III/IV
- Indolent clinical course
  (median survival 15-20 years)
- In relapse still sensitive to therapy

Early Progression of Disease (POD)



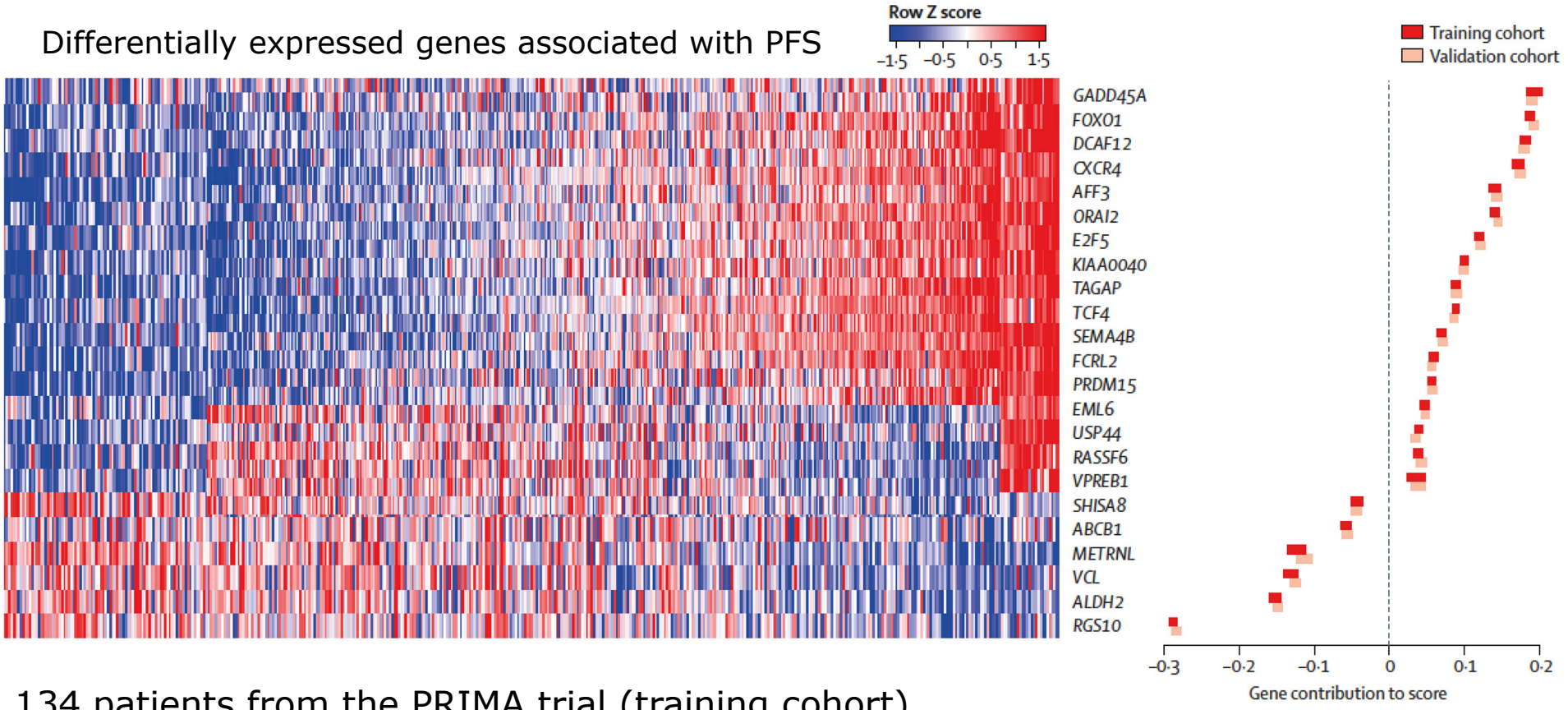
Casulo, JCO 2015

Kapitel 1

Follikuläres Lymphom
Molekulare Risikofaktoren

Follicular Lymphoma
Gene Expression Profiling (n=149/488)

Differentially expressed genes associated with PFS



134 patients from the PRIMA trial (training cohort)

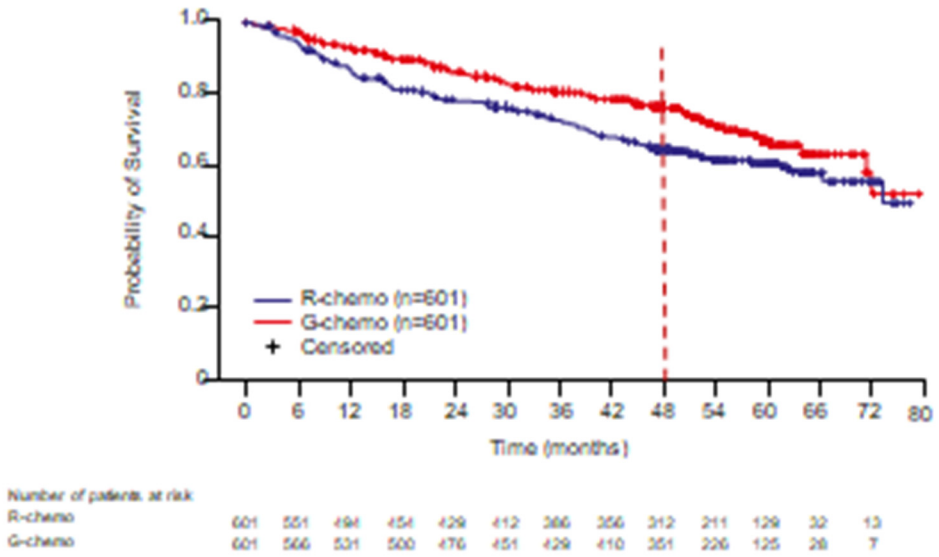
Huet, Lancet Oncol 2018

Treatment-dependence of high-risk Gene Expression Signatures in de novo Follicular Lymphoma

Christopher R. Bolen,[1] Wolfgang Hiddemann,[2] Robert Marcus,[3] Michael Herold,[4] Sarah Huet,[5,6,7] Gilles Salles,[5,8] Federico Mattiello,[9] Tina Nielsen,[9] Farheen Mir,[10] Jeffrey M. Venstrom,[1] Mikkel Z. Oestergaard[9]

[1]Bioinformatics & Computational Biology, Genentech Inc., South San Francisco, United States; [2]University Hospital, LMU Munich, Munich, Germany; [3]Kings College Hospital, London, United Kingdom; [4]HELIOS-Klinikum Erfurt, Erfurt, Germany; [5]Equipe labellisée Ligue Contre le Cancer, Cancer Research Centre of Lyon, Oullins; [6]Laboratoire d'hématologie, Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, Pierre Bénite, France; [7]Faculté de Pharmacie Rockefeller, Université Claude Bernard Lyon-1, Lyon, France; [8]Service d'Hématologie Clinique, Hospices Civils de Lyon et Université Claude Bernard Lyon-1, Pierre-Benite, France; [9]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [10]Royal Marsden Hospital, Sutton, United Kingdom

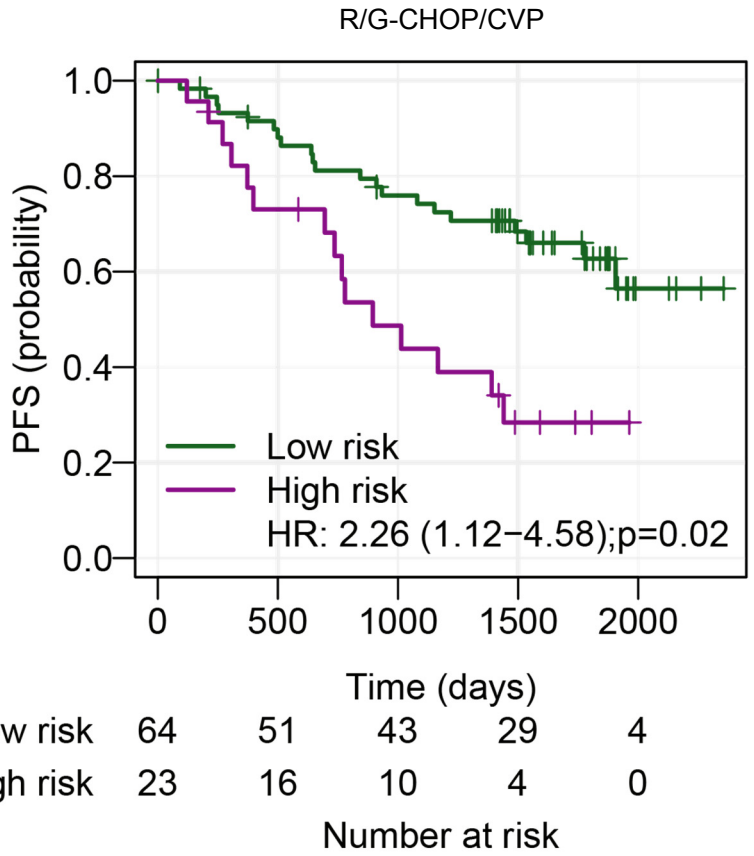
GALLIUM: G-CHEMO vs R-Chemo
Progression-free Survival (Primary Endpoint)

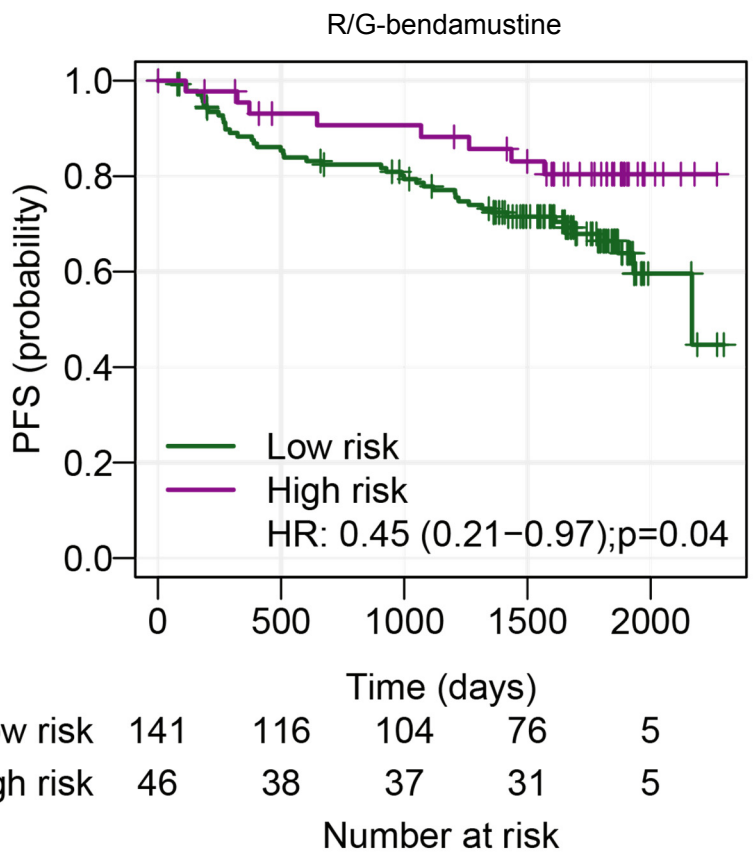


	R-chemo (n=601)	G-chemo (n=601)
4-year PFS, % (95% CI)	67.2 (63.1, 71.0)	78.1 (74.4, 81.3)
HR (95% CI), p-value	0.73 (0.59, 0.90) p=0.0034	

Townsend, ASH 2018: #1507

The 23-Gene Signature was prognostic for PFS (INV) when split by Chemotherapy Regimen





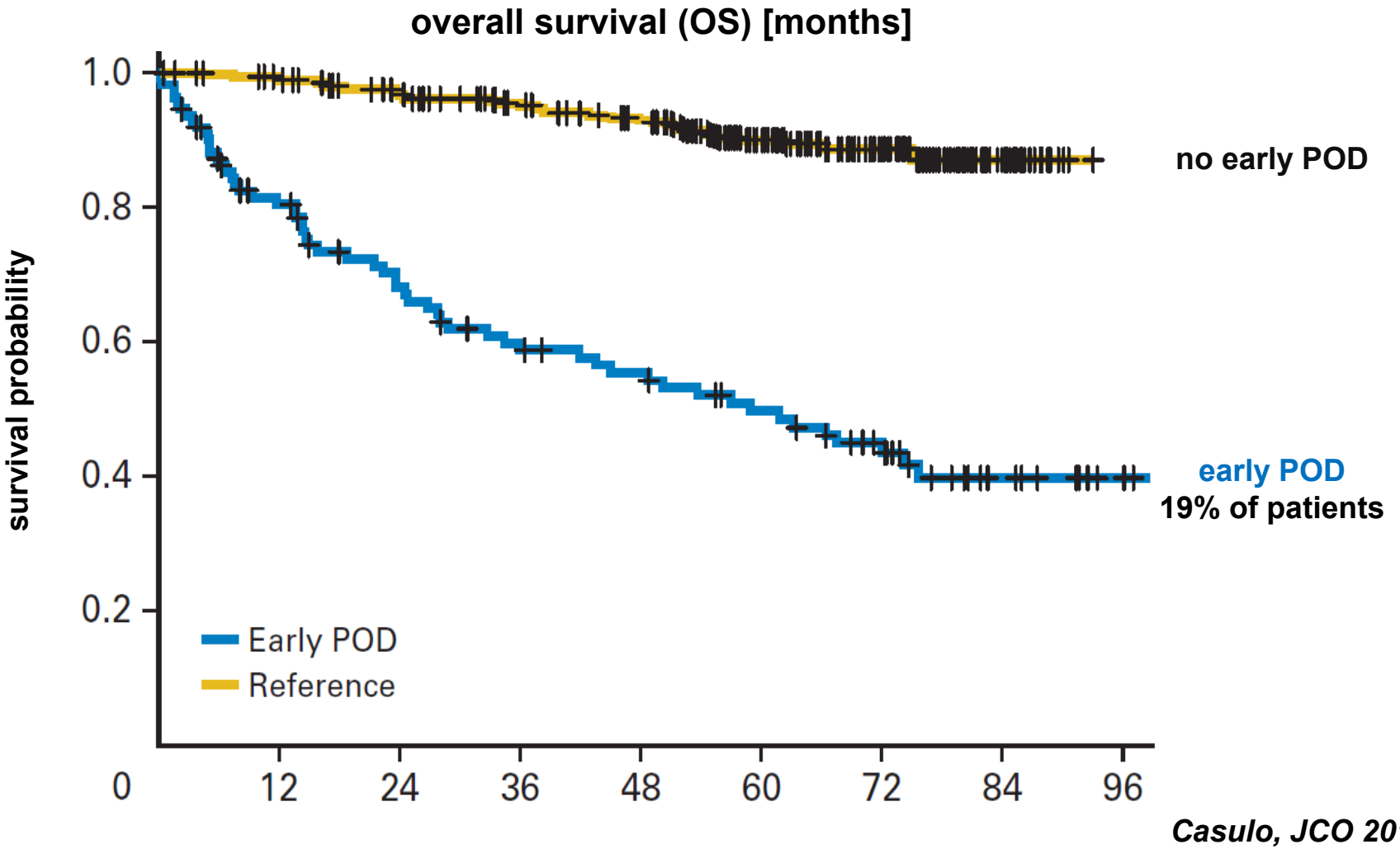
- A differential PFS response was observed according to CHOP/CVP and bendamustine
- Significant interactions between high-risk status and PFS with bendamustine (interaction HR: 0.17, 95% CI: 0.063–0.48; p=0.00074)

Kapitel 2

Follikuläres Lymphom

Frührezidive

Early Progression of Disease (POD)



Casulo, JCO 2015

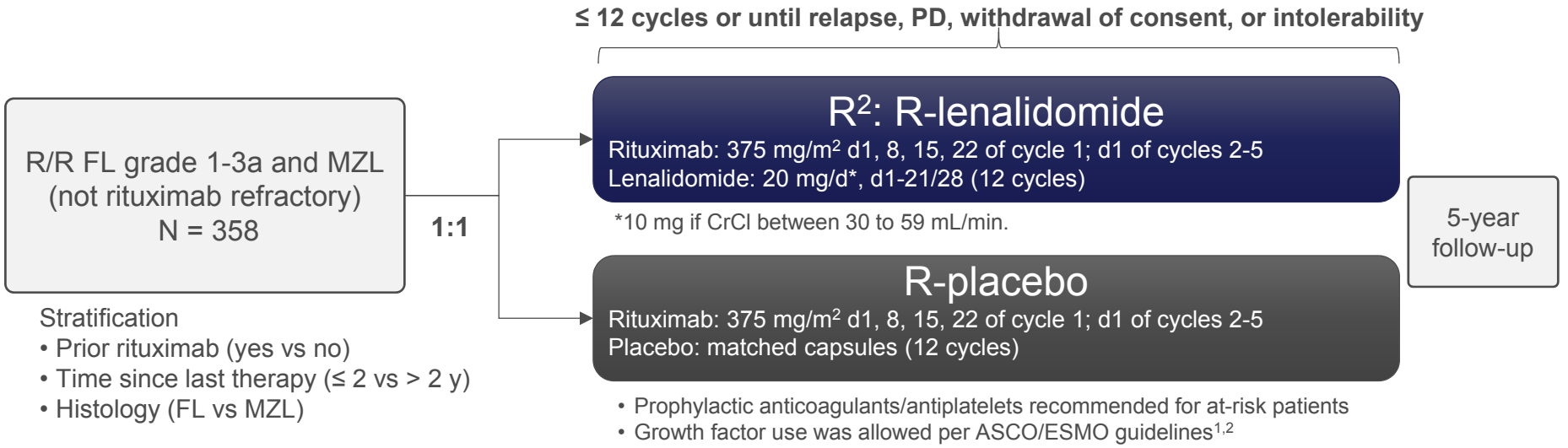
ICML 2019: ABSTRACT 069

AUGMENT Phase III Study: Lenalidomide/Rituximab (R2) Improved Efficacy Over Rituximab/Placebo in Relapsed/Refractory Follicular Lymphoma Patients Irrespective of POD24 Status

John P. Leonard,[1] Marek Trneny,[2] Koji Izutsu,[3] Nathan H. Fowler,[4] Xiaonan Hong,[5] Huilai Zhang,[6] Fritz Offner,[7] Adriana Scheliga,[8] Grzegorz Nowakowski,[9] Antonio Pinto,[10] Francesca Re,[11] Laura Maria Fogliatto,[12] Phillip Scheinberg,[13] Ian Flinn,[14] Claudia Moreira,[15] Myron Czuczman,[16] Stacey A. Kalambakas,[16] Pierre Fustier,[17] Chengqing (Alan) Wu,[16] and John Gribben,[18] on behalf of the AUGMENT study investigators

[1]Meyer Cancer Center, Weill Cornell Medicine and New York Presbyterian Hospital, New York, NY, USA; [2]Charles University, General Hospital, Prague, Czech Republic; [3]National Cancer Center Hospital, Tokyo, Japan; [4]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]Fudan University Shanghai Cancer Center, Shanghai, China; [6]Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [7]UZ Gent, Gent, Belgium; [8]INCA Instituto Nacional De Câncer, Rio de Janeiro, Brazil; [9]Mayo Clinic, Rochester, MN, USA; [10]Istituto Nazionale Tumori, Fondazione 'G. Pascale', IRCCS, Naples, Italy; [11]Azienda Ospedaliero Universitaria di Parma, Parma, Italy; [12]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; [13]Hospital A Beneficência Portuguesa de São Paulo, São Paulo, Brazil; [14]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [15]Instituto Português de Oncologia Do Porto Francisco Gentil Epe, Porto, Portugal; [16]Celgene Corporation, Summit, NJ, USA; [17]Celgene International Sarl, Boudry, Switzerland; and *[18]Centre for Haemato-Oncology, Barts Cancer Institute, London, United Kingdom*

AUGMENT Phase III, Multicenter, randomized Study



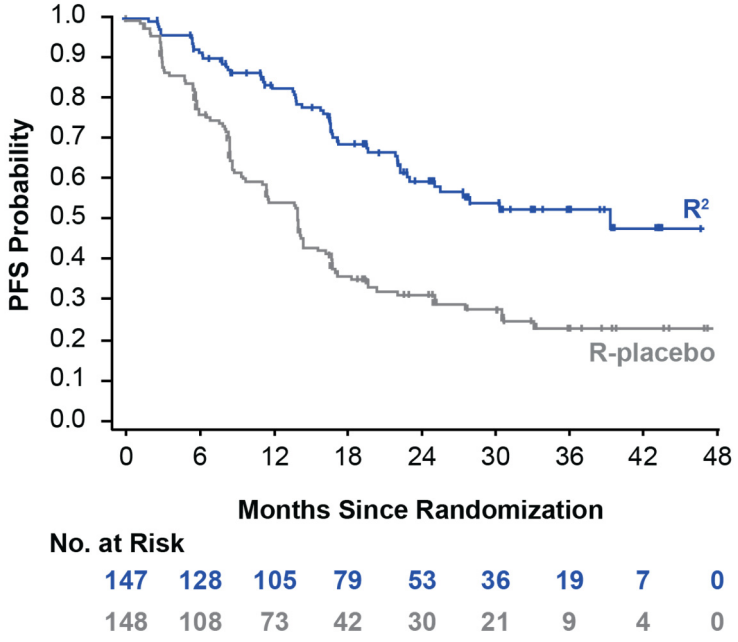
- **Primary endpoint**: PFS by IRC (2007 IWG criteria[3] without PET)
- **Secondary endpoints**: ORR, CR, DOR, OS, EFS, TTNLT

NCT01938001, EudraCT 2013-001245-14.
1. Crawford et al. *Ann Oncol.* 2010;21 Suppl 5:248-251. 2. Smith et al. *J Clin Oncol.* 2015;33:3199-3212. 3. Cheson et al. *J Clin Oncol.* 2007;25:579-586.

AUGMENT: Progression-Free and Overall Survival in FL Patients

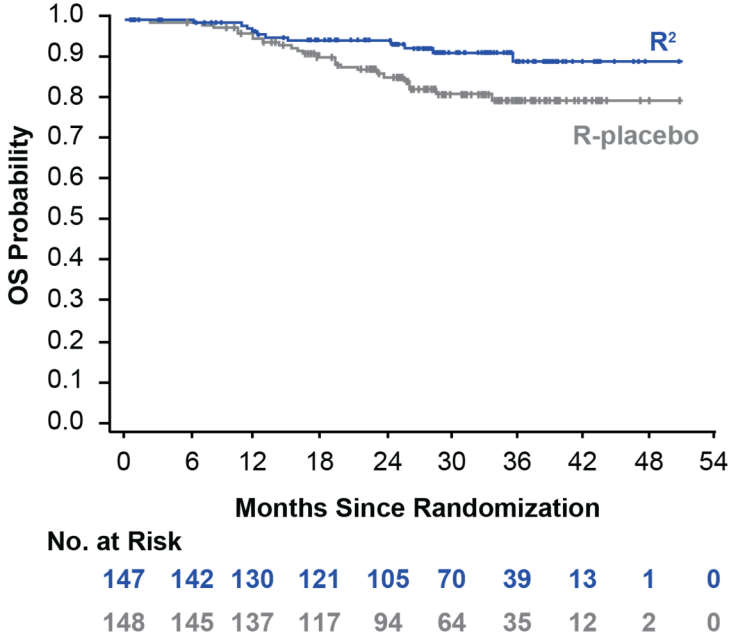
Progression-Free Survival in FL patients

- 2-year PFS: 59% for R^2 and 32% for R-placebo



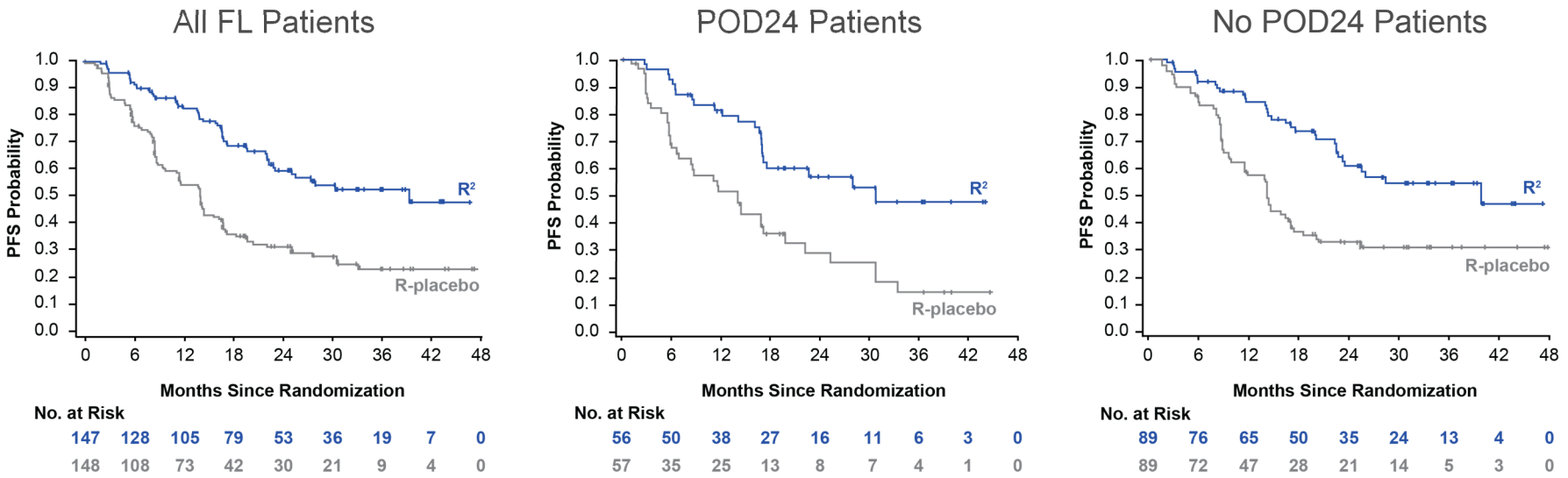
Overall Survival in FL patients

- 2-year OS: 95% for R^2 and 86% for R-placebo



1. Leonard et al. *J Clin Oncol.* 2019;37:1188-1199.

PFS for All FL Patients and by POD24 Status



Median PFS, mo (95% CI) *(n R²/n R-placebo)*	All FL Patients *(n = 147/148)*	POD24 *(n = 56/57)*	No POD24 *(n = 89/89)*
R²	39.4 (23.1-NR)	30.4 (16.8-NR)	39.4 (22.9-NR)
R-placebo	13.9 (11.2-16.0)	13.8 (6.7-16.9)	13.9 (11.2-16.6)
HR (95% CI)	0.40 (0.29-0.56)	0.41 (0.24-0.68)	0.43 (0.28-0.65)
***P* value**	< 0.0001	0.0004	< 0.0001

Data cutoff June 22, 2018. *Censoring rules were based on FDA guidance.

Kapitel 3

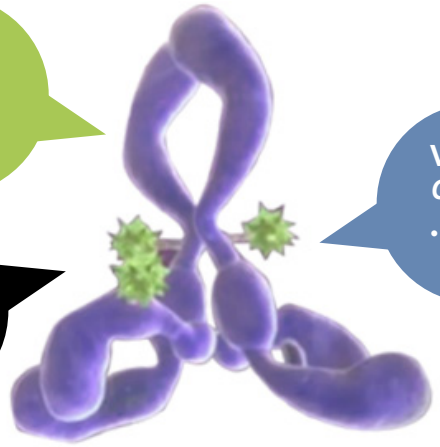
Follikuläres Lymphom
Zukünftige Perspektiven

Polatuzumab vedotin

Polatuzumab vedotin (pola) is the only ADC targeted to CD79b expressed on B-cell malignancies, and is designed to provide delivery of a potent microtubule-disrupting agent, MMAE, directly to tumour cells[1]

Anti-CD79b[2]
Targets to B-cell malignancies
- Not expressed on vital tissue
- Highly internalised

MMAE[3,4]
Microtubule disrupter
- Highly potent
- Non-immunogenic



VC Linker[1]
Cleaved by lysosomal proteases
- Stable in circulation

Dornan D, et al. Blood 2009;114:2721–29; Polson A, et al. Expert Opin Invest Drug 2011;20:75–85
Beckwith M, et al. J Natl Cancer Instit 1993;85:483–88; Doronina SO, et al. Nat. Biotechnol 2003;21:778–84
ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT01691898. Morschhauser F, et al. ASH 2014. Abstr 4457

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POLATUZUMAB VEDOTIN (POLA) + OBINUTUZUMAB (G) + LENALIDOMIDE (LEN) IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL): PHASE IB/II INTERIM ANALYSIS

C. Diefenbach[1] | B. Kahl[2] | L. Banerjee[3] |
A. McMillan[4] | R. Ramchandren[5] | F. Miall[6] |
J. Briones[7] | R. Cordoba[8] | E. Gonzalez-Barca[9] |
C. Panizo[10] | J. Hirata[11] | N. Chang[12] |
L. Musick[13] | P. Abrisqueta[14]

TABLE 1 Responses at end of induction (efficacy-evaluable population; recommended phase II dose; N=18)

Best overall response, n (%)	Modified Lugano 2014		Lugano 2014	
	INV	IRC	INV	IRC
Objective response rate	16 (89)	16 (89)	16 (89)	16 (89)
CR	11 (61)[1]	12 (67)[2]	14 (78)	14 (78)
PR	5 (28)	4 (22)	2 (11)	2 (11)
SD	1 (6)	1 (6)	1 (6)	1 (6)
PD	0	0	0	0
Missing/unevaluable	1 (6)[3]	1 (6)[3]	1 (6)[3]	1 (6)[3]

Follicular Lymphoma
GLSG Studies 2019

Alternative 1:
G-Ibru
↓
G-Ibru maintenance

Alternative 2:
G-Copanilisib
↓
G-Copanlisib maintenance

medically non-fit:
G +/- Bendamustine
↓
G maintenance

Relapse

FLAZ:
ASCT vs. RIT

BeRT:
R-BendaTemsirolimus

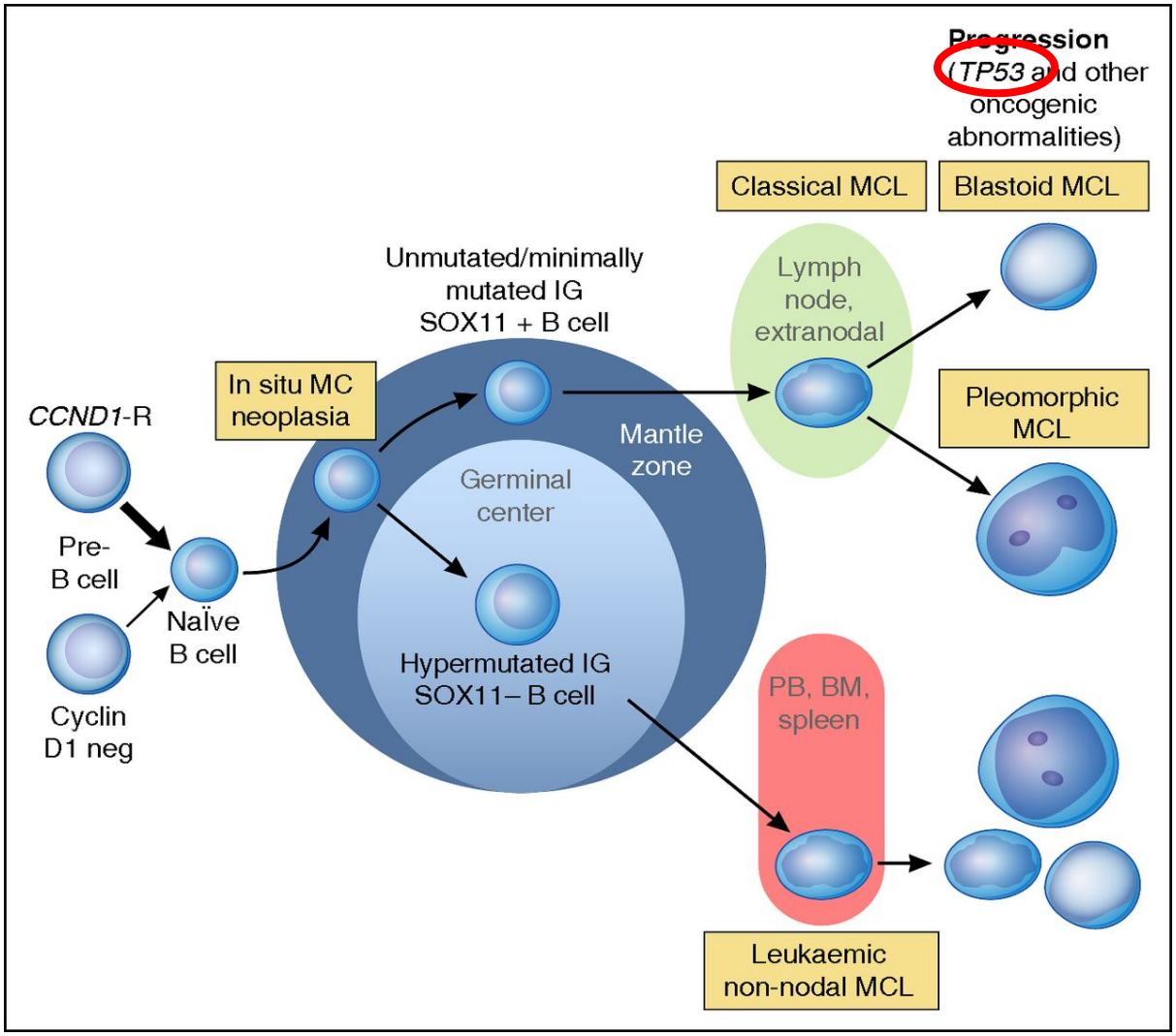
ReBeL:
R2 +/- Benda
↓
R-maintenance

Kapitel 4

Mantelzell-Lymphom

Erstlinientherapie (jüngere Patienten)

MCL: Two Kind of Diseases



Dreyling, ESMO CR 2017

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) ↓ 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

AUTOLOGOUS STEM CELL TRANSPLANTATION IN FIRST REMISSION SIGNIFICANTLY PROLONGS PROGRESSION-FREE AND OVERALL SURVIVAL IN MANTLE CELL LYMPHOMA

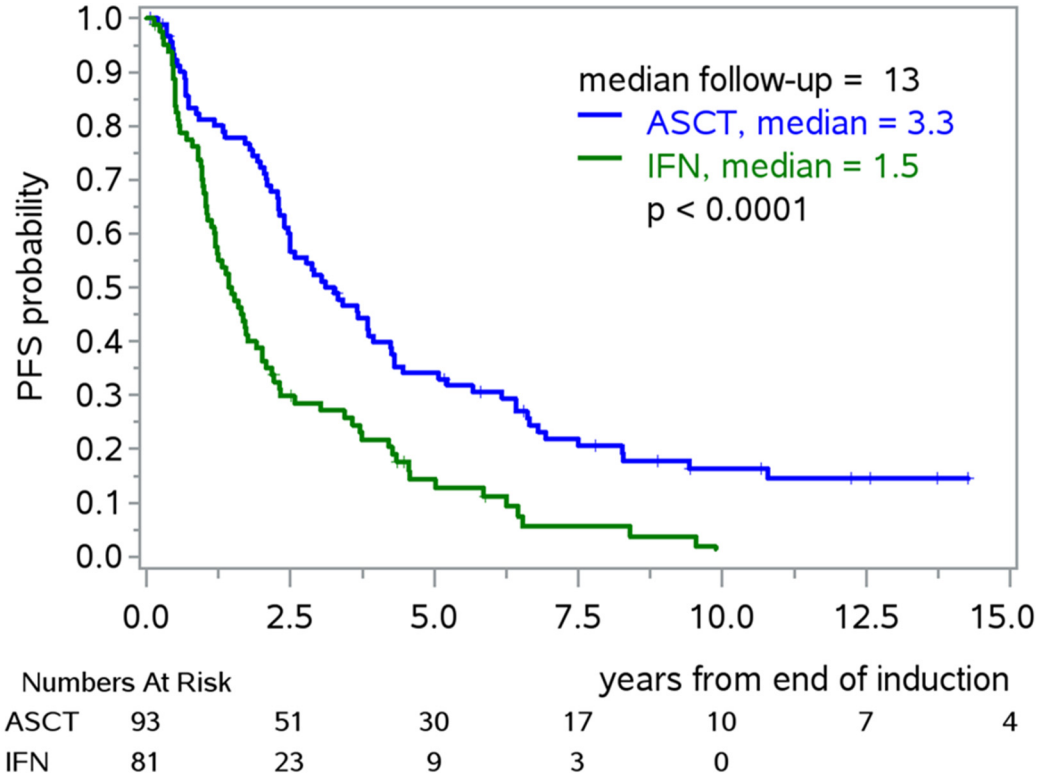
A. ZOELLNER[1], M. UNTERHALT[1], S. STILGENBAUER[2], K. HÜBEL[3], C. THIEBLEMONT[4], B. METZNER[5], H. KLUIN-NELEMANS[6], W. HIDDEMANN[1], M. DREYLING[1] AND E. HOSTER[1].

[1] DEPARTMENT OF MEDICINE III, UNIVERSITY HOSPITAL, LMU MUNICH, MUNICH, GERMANY, [2] DEPARTMENT OF INTERNAL MEDICINE I, UNIVERSITY HOSPITAL OF HOMBURG, HOMBURG, GERMANY, [3] DEPARTMENT OF MEDICINE I, UNIVERSITY HOSPITAL OF COLOGNE, COLOGNE, GERMANY, [4] HEMATO-ONCOLOGY DEPARTMENT, DIDEROT UNIVERSITY, HÔPITAL SAINT-LOUIS, PARIS, FRANCE, [5] DEPARTMENT OF HEMATOLOGY/ONCOLOGY, UNIVERSITY HOSPITAL OLDENBURG, OLDENBURG, GERMANY, [6] HEMATOLOGY, FACULTY OF MEDICAL SCIENCES, GRONINGEN, NETHERLANDS.

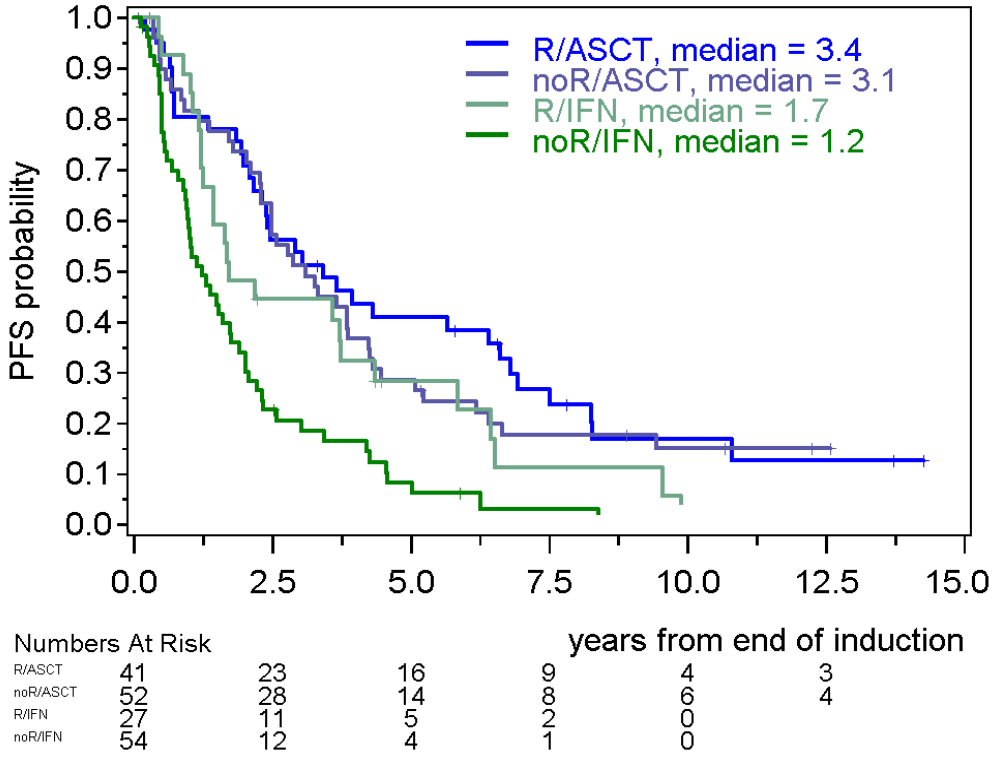
PFS (responding patients)

HR 0.50
0.3-0.69

MIPI,+/- R adjusted



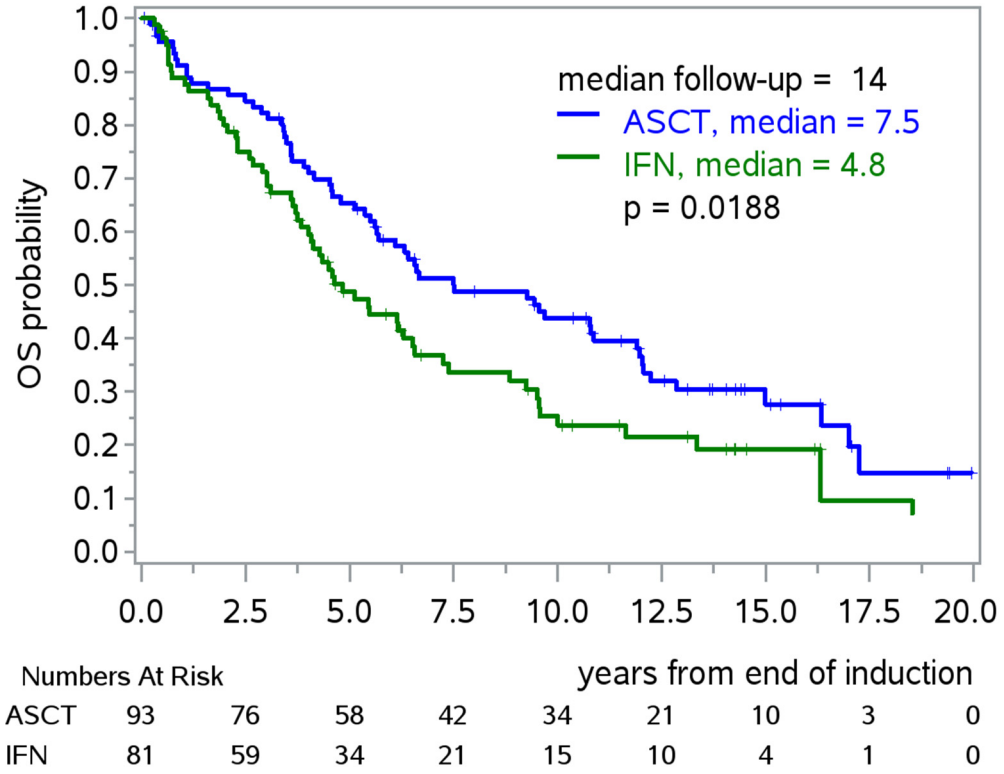
Chemo vs R-Chemo



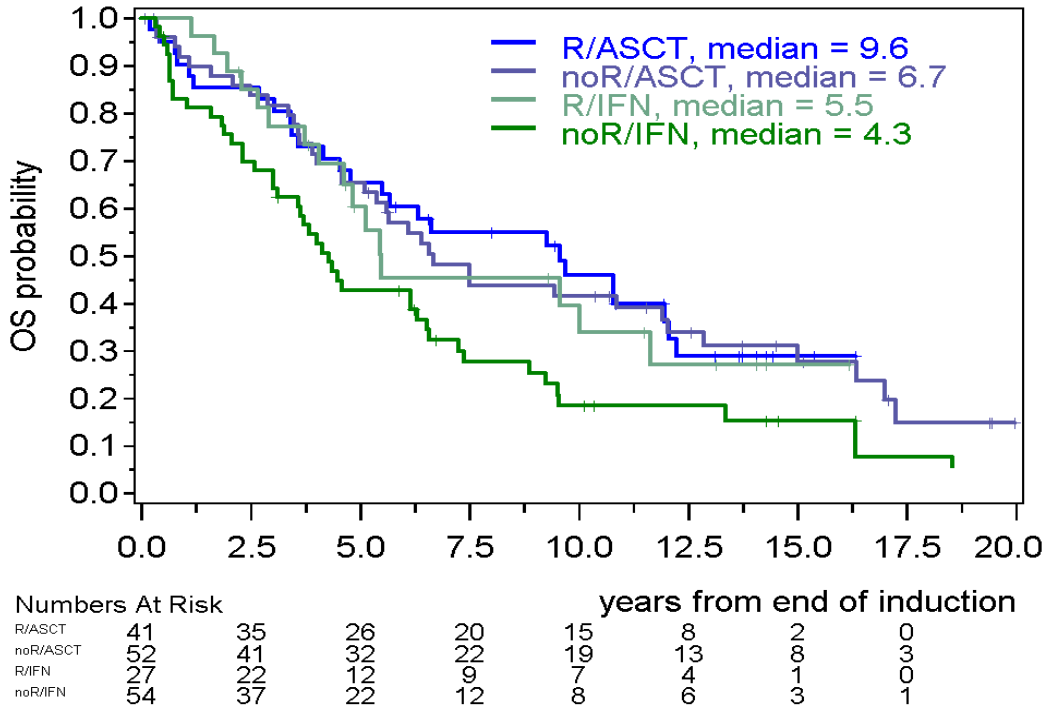
OS (responding patients)

HR 0.66
0.46-0.95

MIPI,+/- R adjusted



Chemo vs R-Chemo



Kapitel 5

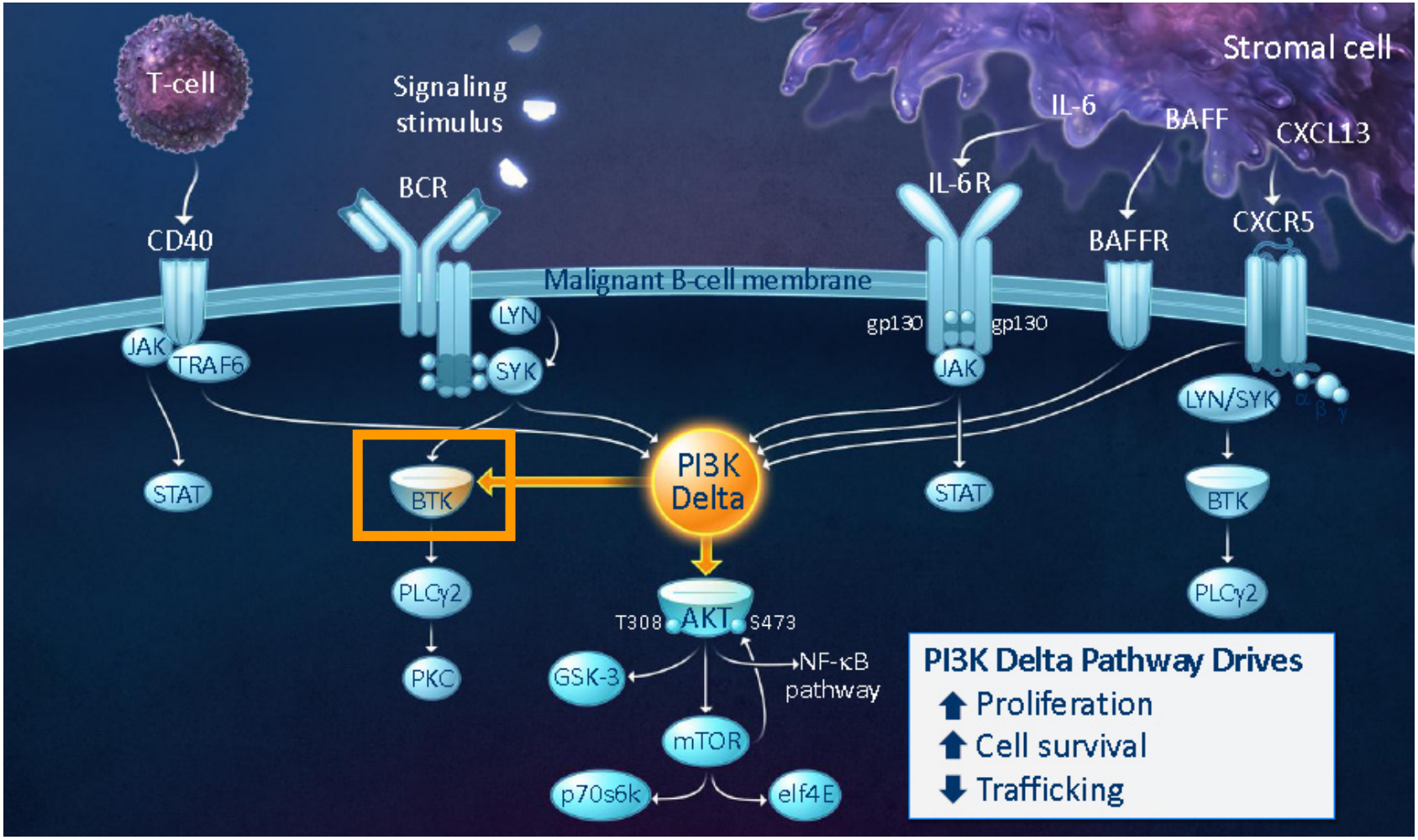
Mantelzell-Lymphom

Frührezidive (jüngere Patienten)

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. VR-CAP, BR, R-CHOP,) ↓ 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

Mantle-Cell Lymphoma
B-Cell Receptor Pathway



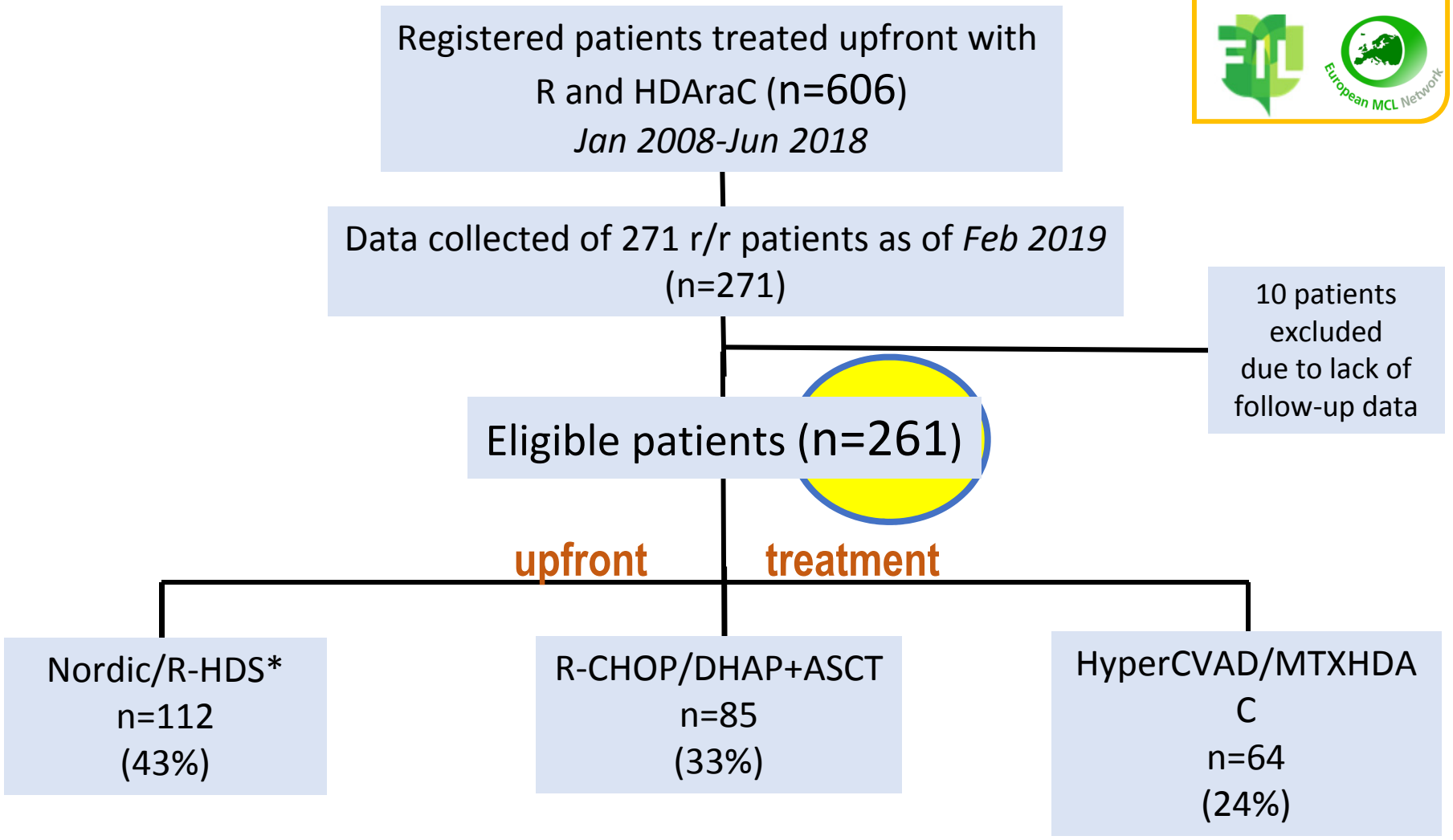
Outcomes in first relapsed-refractory younger Patients with Mantle-Cell Lymphoma: the MANTLE-FIRST Study

Carlo Visco

University of Verona, Italy

ICML Lugano, 19-6-2019

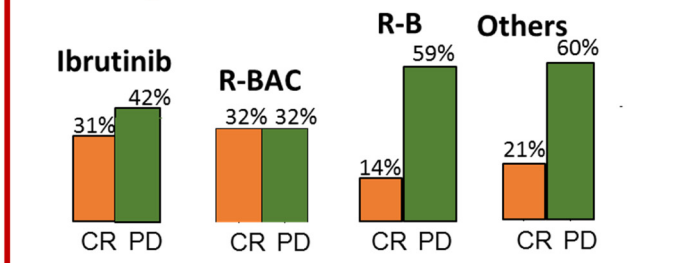
Study Flow

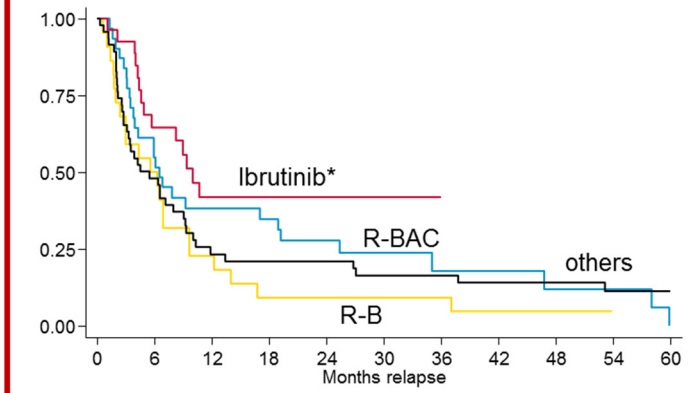

MANTLE-FIRST
European MCL Network
Registered patients treated upfront with R and HDAraC (n=606)
Jan 2008-Jun 2018
Data collected of 271 r/r patients as of Feb 2019 (n=271)
10 patients excluded due to lack of follow-up data
Eligible patients (n=261)
upfront
treatment
Nordic/R-HDS* n=112 (43%)
R-CHOP/DHAP+ASCT n=85 (33%)
HyperCVAD/MTXHDAC n=64 (24%)

Response and PFS, early vs late POD

MANTLE-FIRST

Early POD



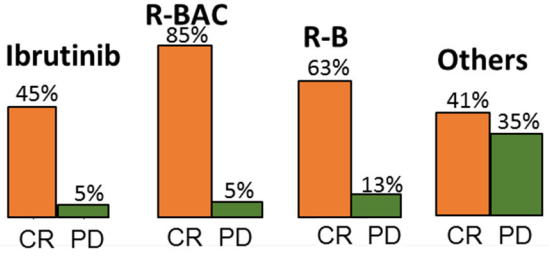


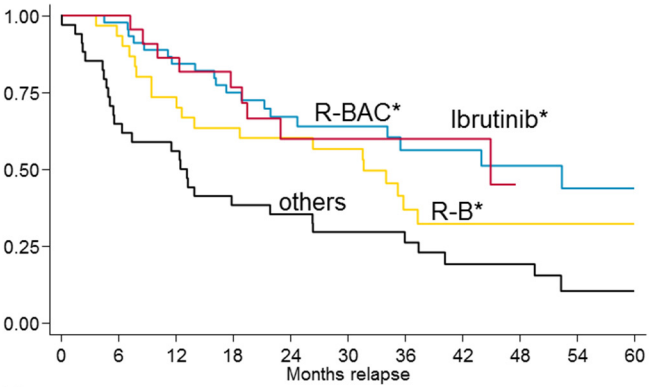
At risk:

BAC	31	17	11	10	7	6	3	3	2	2	0
BR	22	11	5	2	2	2	2	1	1	0	0
ibru	27	16	8	4	2	1	0	0	0	0	0
other	47	22	10	9	9	7	7	5	5	4	3

*Ibru vs R-B (P=0.01); vs others (P=0.02)

Late-POD





At risk:

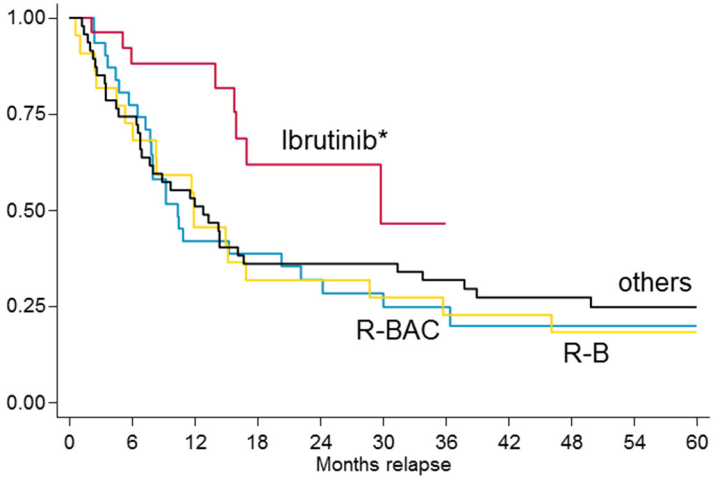
BAC	45	44	37	30	22	20	13	11	10	5	5
BR	32	28	22	19	18	16	8	7	7	6	5
ibru	22	22	19	15	8	6	6	4	0	0	0
other	34	22	19	13	12	10	9	5	5	2	2

*Ibru (P=0.008), R-BAC (P<0.0001) and R-B (P=0.02) vs others

OS, early versus late POD

MANTLE-FIRST

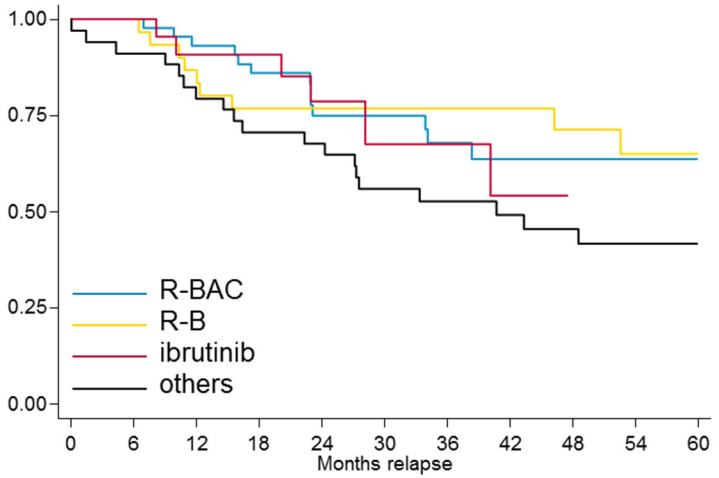
Early POD



At risk:											
BAC	31	24	13	12	9	8	5	4	3	3	3
BR	22	16	10	7	7	6	5	5	4	3	2
ibru	27	21	16	8	5	3	0	0	0	0	0
other	47	35	24	17	17	17	15	11	11	10	6

*Ibru vs R-B and R-BAC (P=0.02); vs others (P=0.03)

Late-POD



At risk:											
BAC	45	45	40	35	26	23	16	14	12	8	7
BR	32	30	26	23	22	20	16	15	13	10	9
ibru	23	22	20	18	10	6	6	4	0	0	0
other	34	31	27	24	23	19	16	13	12	8	7

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

Kapitel 6

Take-Home-Messages
Zusammenfassung

Take Home Messages Indolente Lymphome

Follikuläres Lymphom

- G/R-CHOP oder B-G/R: unterschiedliche Risikogruppen
- Frührezidiv: Rituximab-Lenalidomid zusätzliche Therapieoption

Mantelzell-Lymphome

- Jüngere Patienten: autologe SCT bleibt Standardtherapie
- Frührezidiv: Ibrutinib überlegen (cave: Ki-67 hoch, blastoid, p53)

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Die Kurzpräsentationen sind online unter

www.lymphome.de/15-icml

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abbvie Celgene HEXAL janssen PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Diese hatten keinen Einfluss auf die Inhalte.