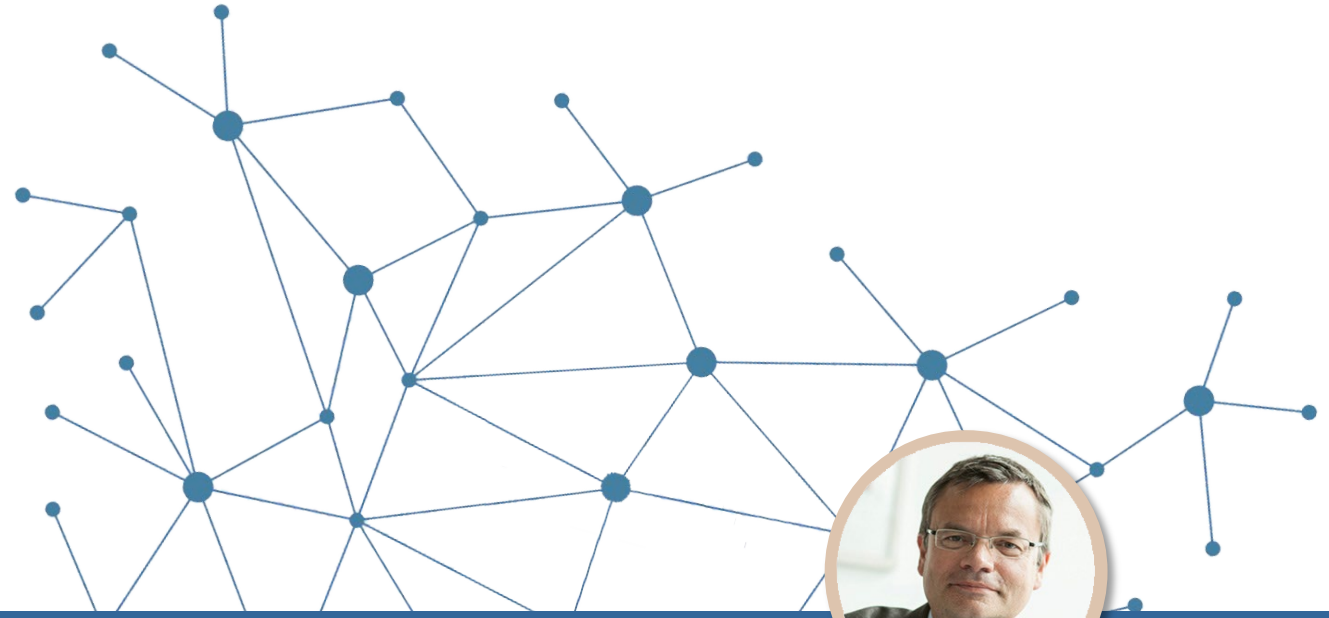
Lymphom Kompetenz KOMPAKT

EHA2020 VIRTUAL
11. – 14. Juni 2020

Kompetenznetz Maligne Lymphome

Vernetzt forschen.
Gut informiert entscheiden.



Prof. Dr. med. Christian Buske

Indolente Lymphome

- Ärztlicher Direktor, CCC Ulm, Universitätsklinikum Ulm
- Präsident der German Lymphoma Alliance e.V.
- Vorstandsmitglied im KML

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT **EHA2020** wird in Kooperation mit fünf unterstützenden Firmen durchgeführt.
Diese Firmen haben keinen Einfluss auf die Inhalte dieses Vortrags. Meine weiteren Disclosures betreffen:

Art	Verbundenheit
Anstellungsverhältnis, Führungsposition	---
Beratungs-/Gutachtertätigkeit	Roche, AbbVie, Janssen, Regeneron, Beigene, Celgene
Besitz von Geschäftsanteilen, Aktien, Fonds	----
Patent, Urheberrecht, Verkaufslizenz	----
Honorare	Roche, AbbVie, Janssen, Regeneron, Beigene
Finanzierung wissenschaftlicher Untersuchungen	Roche, Janssen, MSD, Celltrion
Andere (auch immaterielle)	----

Kapitel 1

Follikuläres Lymphom

Wirksamkeit von CAR-T Zellen auch beim FL?

Mögliche Salvage – Therapie bei schwer vorbehandelten Patienten mit FL?

Interim Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

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C Jacobson

EHA25

ZUMA-5 Study Design

Phase 2 (N ≈ 160 planned for enrollment)

R/R iNHL	FL: n ≈ 125 (with n ≥ 80 evaluable for efficacy) MZL: n ≈ 35

Key eligibility criteria

- R/R FL (Grade 1 – Grade 3a) or MZL (nodal or extranodal)[a]
- ≥ 2 prior lines of therapy—must have included an anti-CD20 mAb combined with an alkylating agent

Conditioning regimen

- Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, −3

Axi-cel: 2 × 10^6 CAR+ cells/kg

Primary endpoint

- ORR (IRRC-assessed per the Lugano classification[1])

Key secondary endpoints

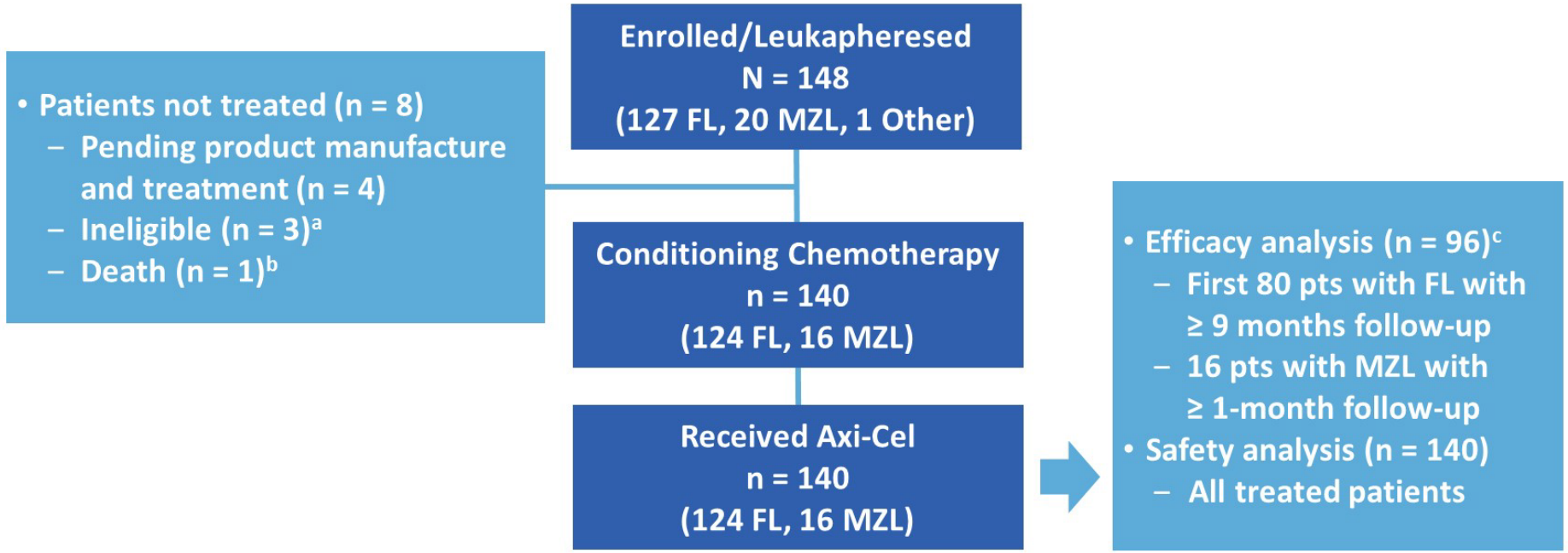
- CR rate (IRRC-assessed)
- DOR, PFS, OS
- AEs
- CAR T cell and cytokine levels

1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.

[a] Patients with stable disease (without relapse) > 1 year from completion of last therapy were not eligible.

AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; FL, follicular lymphoma; IRRC, Independent Radiology Review iNHL, indolent non-Hodgkin lymphoma; IV, intravenous; mAb, monoclonal antibody; MZL, marginal zone lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, R/R, relapsed/refractory.

ZUMA-5 Disposition



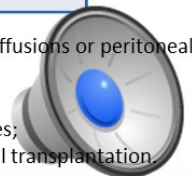
- As of December 16, 2019, the median follow-up for the efficacy analysis was 15.3 months (range, 1.9 – 28.8)
  - The median follow-up for the safety analysis was 12.8 months (range, 1.9 – 28.8)

[a] Ineligible due to low platelet levels (n = 1), CR prior to conditioning chemotherapy (n = 1), and preinfusion biopsy showing transformation to DLBCL (n = 1). [b] Death due to cardiac arrest before the start of conditioning chemotherapy. [c] All enrolled pts who met the eligibility criteria for the pivotal cohort in the primary analysis and were treated with any dose of axi-cel (inferential analysis set) were evaluable for efficacy.
Axi-cel, axicabtagene ciloleucel; CR, complete response; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; pt, patient; MZL, marginal zone lymphoma.

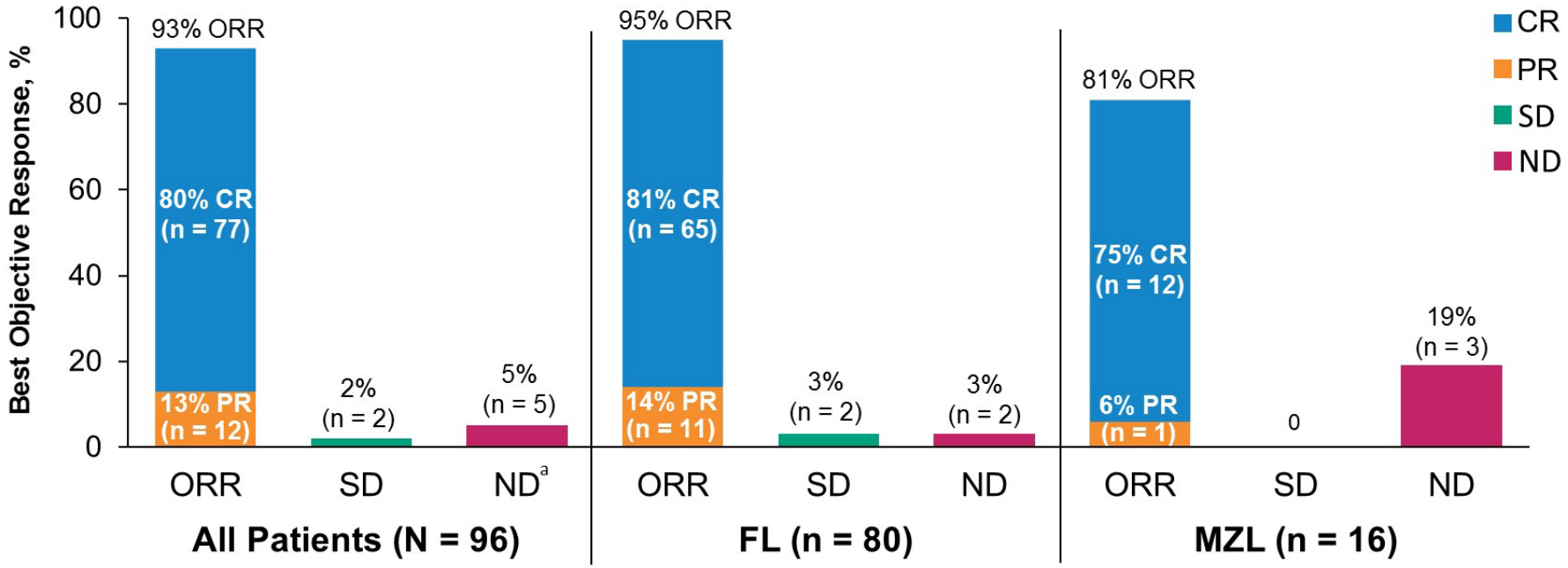
Baseline Disease Characteristics

Characteristic	FL n = 80	MZL n = 16	All Patients N = 96
Median age (range), years	62 (34 – 79)	67 (52 – 77)	63 (34 – 79)
≥ 65 years, n (%)	29 (36)	11 (69)	40 (42)
Male, n (%)	43 (54)	4 (25)	47 (49)
ECOG PS 1, n (%)	33 (41)	6 (38)	39 (41)
Stage IV disease, n (%)	37 (46)	13 (81)	50 (52)
≥ 3 FLIPI, n (%)	38 (48)	11 (69)	49 (51)
High tumor bulk (GELF criteria), n (%)[a]	40 (50)	7 (44)	47 (49)
Median no. of prior therapies (range)	3 (2 – 9)	3 (2 – 8)	3 (2 – 9)
≥ 3, n (%)	56 (70)	11 (69)	67 (70)
Prior PI3Ki therapy, n (%)	26 (33)	6 (38)	32 (33)
Refractory disease, n (%)[b]	59 (74)	11 (69)	70 (73)
POD24 from first anti-CD20 mAb-containing therapy, n (%)[c]	45 (56)	7 (44)	52 (54)
Prior autologous SCT, n (%)	19 (24)	3 (19)	22 (23)

[a] Disease burden, as defined by GELF criteria: involvement of ≥ 3 nodal sites (≥ 3 cm diameter each); any nodal or extranodal tumor mass with a diameter of ≥ 7 cm; B symptoms; splenomegaly; pleural effusions or peritoneal ascites; cytopenias; or leukemia. [b] Patients with iNHL who progressed within 6 months of completion of the most recent prior treatment. [c] POD24 defined as 24 months from initiation of the first line of anti-CD20–containing immunochemotherapy to progression. Percentages are based on the number of patients who ever received anti-CD20–chemotherapy combination therapy.
ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; iNHL, indolent non-Hodgkin lymphoma; mAb, monoclonal antibody; MZL; marginal zone lymphoma; PI3Ki, phosphoinositide 3-kinase inhibitor; POD24, progression of disease < 24 months; SCT, stem cell transplantation.



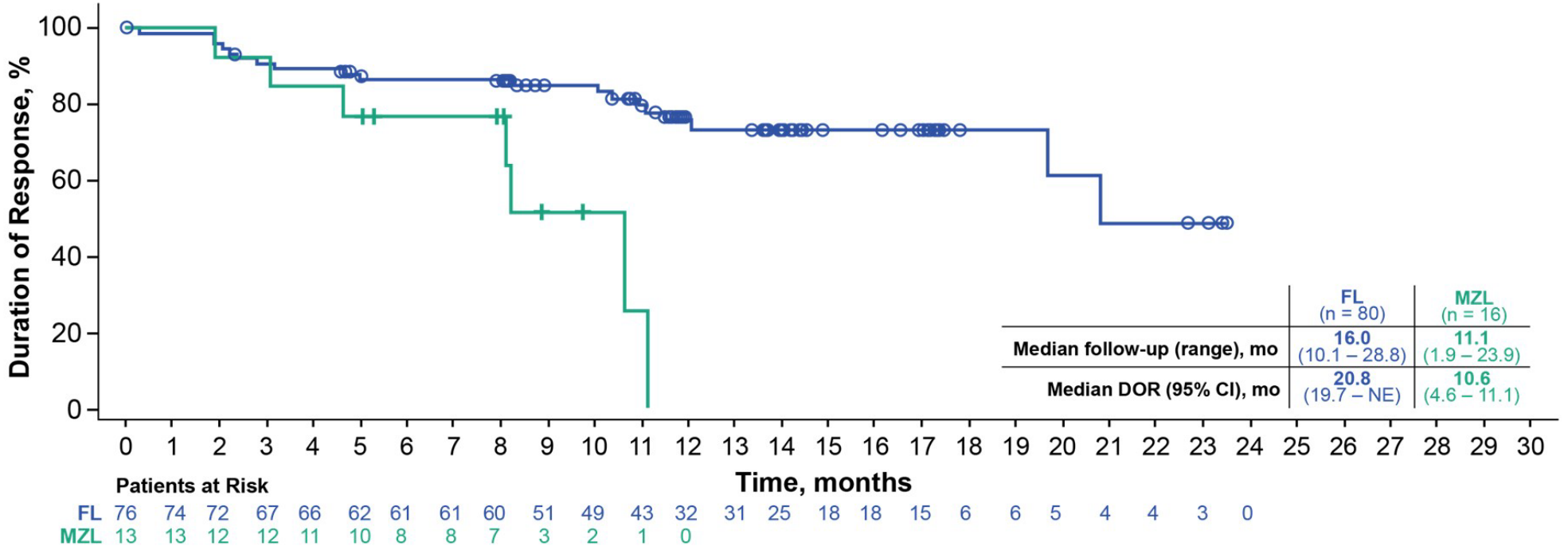
Overall ORR by IRRC Assessment Was 93% (95% CI, 86 – 97), and CR Rate Was 80% (95% CI, 71 – 88)



- The median time to first response was 1 month (range, 0.8 – 3.1)
- Of the 80 patients with FL, 10 (13%) had an initial response of PR at Week 4 and later converted to CR

The investigator-assessed ORR (N = 96) was 95%, with a CR rate of 80%.
[a] For the 5 patients reported as ND, 4 (1 with FL and 3 with MZL) had no disease at baseline and postbaseline assessments by IRRC; 1 patient with FL died prior to the first scheduled assessment.
CR, complete response; FL, follicular lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; ND, undefined/not done; ORR, objective response rate; PR, partial response; SD, stable disease.

Duration of Response

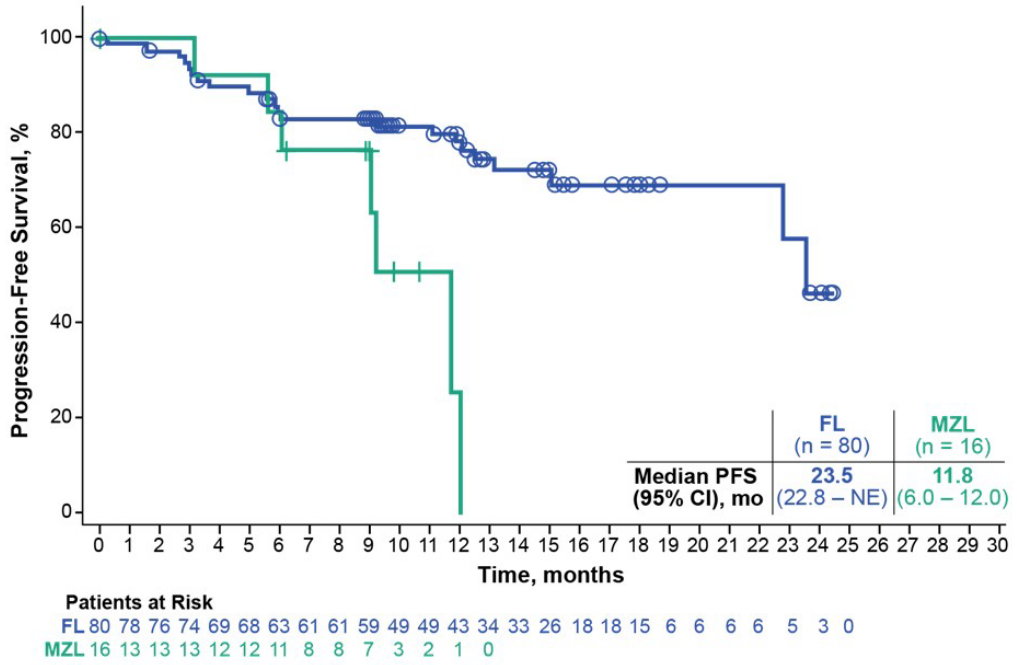


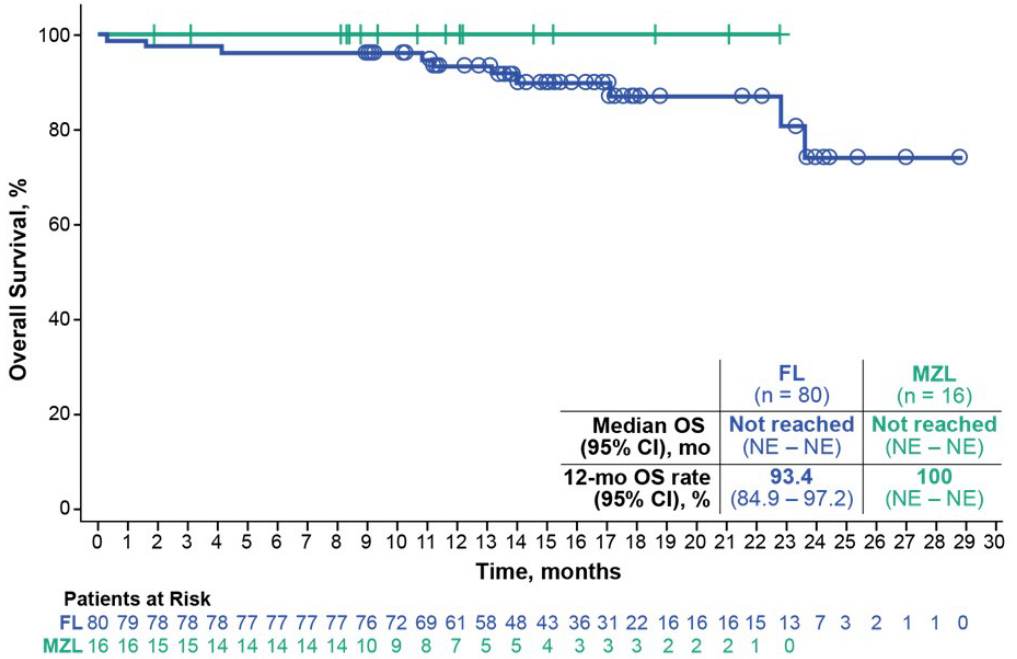
	FL (n = 80)	MZL (n = 16)
Median follow-up (range), mo	16.0 (10.1 – 28.8)	11.1 (1.9 – 23.9)
Median DOR (95% CI), mo	20.8 (19.7 – NE)	10.6 (4.6 – 11.1)

- With a median follow-up of 15.3 months, estimated median DOR in all patients was 20.8 months, and 68% of patients with FL had an ongoing response
  - Among patients with FL, responses were ongoing in 80% of patients with a CR and 18% of patients with a PR

CR, complete response; DOR, duration of response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; PR, partial response.

Progression-Free Survival and Overall Survival





- With a median follow-up of 15.3 months, median PFS was 23.5 months (95% CI, 22.8 – NE) in all patients, and the median OS was not reached
  - The 12-month OS rate was 94.3% (95% CI, 86.8 – 97.6) for all patients

FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Follikuläres Lymphom – ZUMA 5

Schlussfolgerungen?

- Beeindruckende Ansprechraten
- Gute Verträglichkeit
- ABER: enttäuschende PFS und Ansprechdauer – kein Plateau?

→ Längeres Follow-up nötig, noch zu früh für eine sichere Beurteilung
→ Viele andere Alternativen, bispezifische AK?

Kapitel 2

Morbus Waldenström

Alternative BTK – Inhibitoren?
Bessere Verträglichkeit?
Bessere Wirksamkeit?

ASPEN: Results of A Phase 3 Randomized Trial of Zanubrutinib Versus Ibrutinib For Patients With Waldenström Macroglobulinemia

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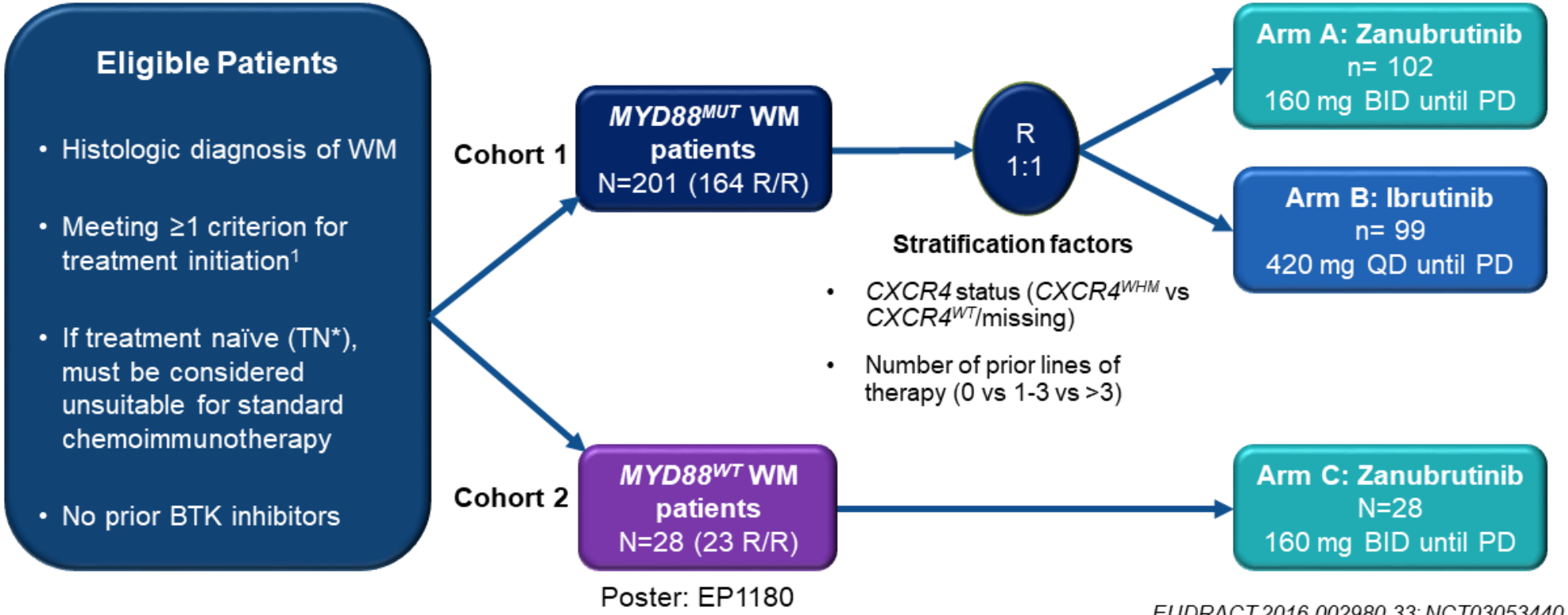
Presented at the 25th Congress of the European Hematology Association (EHA25 Virtual), June 11-14, 2020
Abstract: S225

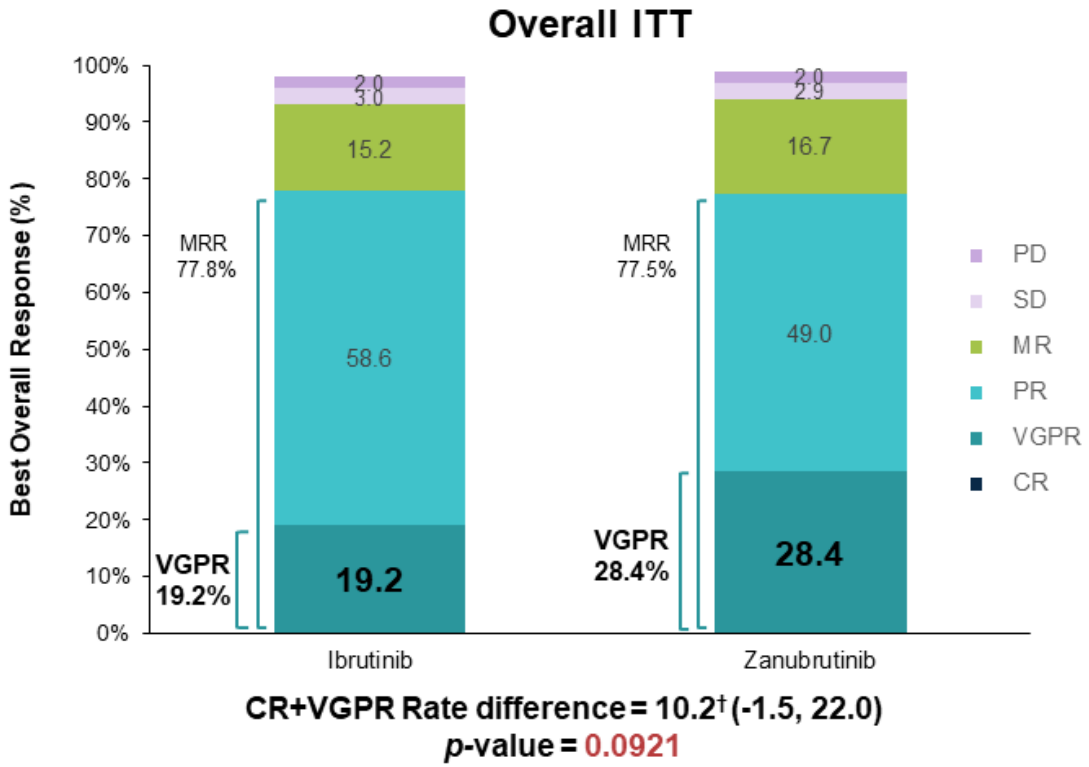
ASPEN Study Design: Zanubrutinib vs Ibrutinib in *MYD88*^{MUT} WM



BID, twice daily; BTK, Bruton tyrosine kinase; CXCR4, C-X-C Motif Chemokine Receptor 4; MYD88^{MUT}, myeloid differentiation primary response gene 88 mutant; PD, progressive disease; QD, daily; R, randomization; R/R, relapsed/refractory; TN, treatment naïve; WM, Waldenström Macroglobulinemia; WT, wild-type.
*Up to 20% of the overall population.
1. Dimopoulos MA, et al. *Blood*. 2014;124:1404-1411.

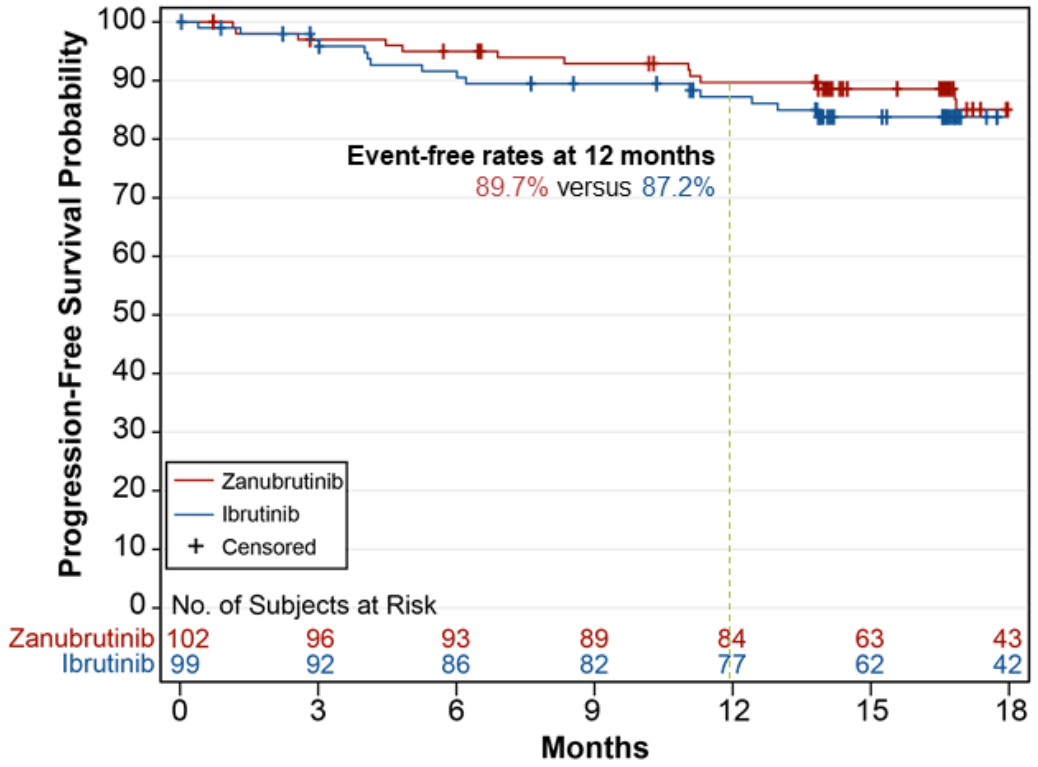
ASPEN: Efficacy – Response by IRC (Data cutoff: 31 August 2019)

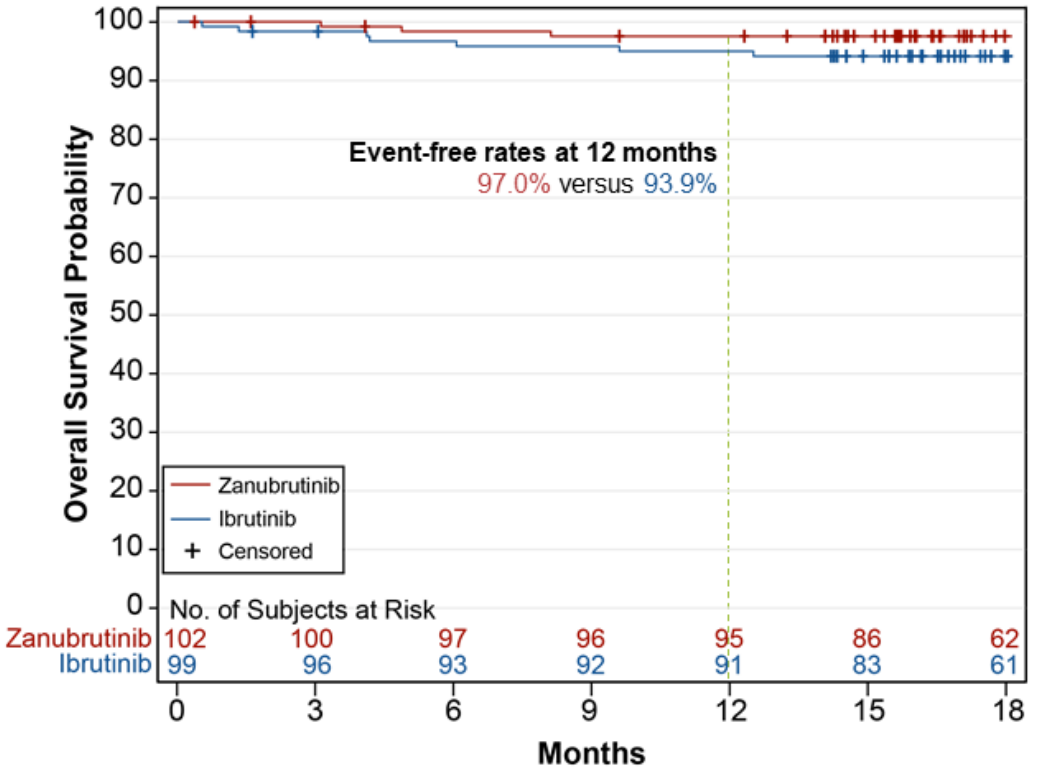
- Superiority in CR+VGPR rate compared to ibrutinib in relapsed/refractory population (primary study hypothesis) was not significant*



CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MRR, major response rate; MR, minor response; ; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; VGPR, very good PR.
Overall concordance between Independent review and investigators = 94%
* All other *P* values are for descriptive purposes only. †Adjusted for stratification factors and age group.

ASPEN: Progression-Free and Overall Survival in ITT population





IRC, independent review committee; VGPR, very good partial response.
Disease progression determined by IRC.

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ASPEN: AE Categories of Interest (BTKi Class AEs) with additional 5 months follow-up (Data cutoff: 31 January 2020)

- **An additional 5 patients had discontinued ibrutinib treatment due to AEs versus 0 in the zanubrutinib arm (14.3% vs 4%)**

AE *Categories*, n (%) *(pooled terms)*	All Grades		Grade ≥ 3	
	Ibrutinib (n = 98)	Zanubrutinib (n = 101)	Ibrutinib (n = 98)	Zanubrutinib (n = 101)
Atrial fibrillation/ flutter†	**18 (18.4)**	3 (3.0)	**7 (7.1)**	0 (0.0)
Diarrhea (PT)	**32 (32.7)**	22 (21.8)	2 (2.0)	3 (3.0)
Hemorrhage	**59 (60.2)**	51 (50.5)	9 (9.2)	6 (5.9)
Major hemorrhage[a]	10 (10.2)	6 (5.9)	9 (9.2)	6 (5.9)
Hypertension	20 (20.4)	13 (12.9)	**15 (15.3)**	8 (7.9)
Neutropenia[b]†	15 (15.3)	**32 (31.7)**	8 (8.2)	**23 (22.8)**
Infection	70 (71.4)	70 (69.3)	23 (23.5)	19 (18.8)
Second Malignancy	12 (12.2)	13 (12.9)	1 (1.0)	3 (3.0)

Higher AE rate in bold blue with ≥ 10% difference in any grade or ≥ 5% difference in grade 3 or above.
[a]Defined as any grade ≥ 3 hemorrhage or any grade central nervous system hemorrhage.
[b]Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.
† Descriptive two-sided *P*-value < 0.05.

Morbus Waldenström - ASPEN

Schlussfolgerungen?

- Zanubrutinib hocheffektiver und nebenwirkungsarmer BTK Inhibitor beim WM
- Aber: neuer Standard im Vergleich zu Ibrutinib?
- Eher nein, aber sinnvolle weitere Therapiealternative bei Patienten, die mit einem BTK – Inhibitor behandelt werden sollten (anderes NW – Profil).

Kapitel 3

MCL
Chemotherapiefreie Ansätze bereits in der Erstlinie?

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Ibrutinib, Venetoclax Plus Obinutuzumab in Newly Diagnosed Mantle Cell Lymphoma Patients: OAsIs phase I/II trial.

Steven Le Gouill, MD, PhD[1], Franck Morschhauser, MD[2], Kamal Bouabdallah, MD, Guillaume Cartron, MD, PhD, Olivier Casasnovas, MD[5], Thomas Gastinne, MD*, Patrice Chevallier, MD, PhD, Cédric Rossi, MD, PhD[5], Emmanuelle Tchernonog, MD[8], Rory McCulloch[9], Charles Herbaux, MD[10], David Chiron, PhD[11], Mary Callanan, PhD[12] and Simon Rule[13]

[1]CHU DE NANTES, Université de Nantes, CIC, CRCINA INSERM, NANTES, FRA; [2]Centre Hospitalier Régional Universitaire De Lille, Nord, France; [3]Hematology Clinic, University Hospital of Bordeaux, Pessac, France; [4]Centre Hospitalier Universitaire de Montpellier, Montpellier, France; [5]Hematology Department, University Hospital F. Mitterrand and Inserm UMR 1231, Dijon, France; [6]Clinical Hematology, Nantes University Hospital, Nantes, France; [7]Service d'Hématologie, CHU Nantes, Nantes, France; [8]Service d'hématologie, Département d'hematologie clinique, CHU Montpellier, Montpellier, FRA; [9]Plymouth University Medical School, Plymouth, United Kingdom; [10]Service des Maladies du Sang, Université de Lille, CHU Lille, Lille, France; [11]CRCINA, INSERM, CNRS, Angers University and Nantes University, Nantes, France; [12]Hematology Biology Department, University Hospital F. Mitterrand and Inserm UMR 1231, DIJON, France; [13]University of Plymouth, Plymouth, United Kingdom

14th May 2020
Session- Indolent and mantle-cell non-Hodgkin lymphoma – Clinical

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S Le Gouill

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INCLUSION CRITERIA FOR COHORT C

- Age ≥18for French patients, Age ≥16 for English patients
- **Cohort C: Untreated patients with histologically confirmed mantle cell lymphoma (within 3 months before baseline) in need of treatment**
- Stage II-IV in need of treatment
- ECOG performance status of 0 – 2
- Hematology values must be within the following limits: Absolute neutrophil count (ANC) ≥1000/mm^3; Platelets≥75,000/mm^3 or ≥ 50,000/mm^3 if bone marrow involvement and independent of transfusion support in either situation, Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN), Total bilirubin ≤ 1.5 x ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin, Serum creatinine ≤ 2 x ULN or estimated Glomerular Filtration Rate (Cockroft Gault11) ≥ 50 mL/min/1.73m2
- HIV, anti-HBc, HbsAg test negative

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TREATMENT SCHEDULLED

	Cycle 1				Cycle 1 bis				Cycle 2				cycles	Maintenance	
Baseline	W1	W2	W3	W4	W1	W2	W3	W4	W1	W2	W3	W4	C3-C6	C7-C23	until prog
Ibrutinib (560mg/d)	D2	→	→	→	→	→	→	→	→	→	→	→	→	→	- - - →
Obinutuzumab (1g)	D1	D8	D15		D1				D1				D1 each cycle	D1 every 2 cycles from C8	
Venetoclax (mg/d)					20	50	100	200	400	400	400	400	→	→	

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AEs from C1 to C6

	Grade 1-2 (>20% patients)	All Grade 3	All Grade 4
ANY ADVERSE EVENT	15 (100)	5 (33)	3 (20)
THROMBOCYTOPENIA	3 (20)	0	0
NEUTROPENIA	3 (20)	2 (13)	1 (7)
MUSCULOSKELETAL PAIN	5 (33)	0	0
DIARRHOEA	6 (40)	0	0
NAUSEA	3 (20)	0	0
HEADACHE	3 (20)	0	0
UPPER RESP. INFECT	3 (20)	0	0
ASTHENIA	4 (27)	0	0
LYMPHOPENIA	0	1 (7)	0
RASH	1 (7)	1 (7)	0
ALAT INCREASED	0	0	1 (7)
ASAT INCREASED	0	1 (7)	0
HEPATIC CYTOLYSIS	0	0	1 (7)
HYPERLYMPHOCYTOSIS	0	1 (7)	0

SAEs from C1 to C6

	Grade 1-2	All Grade 3	All Grade 4
ANY SAE	2 (13)	1 (7)	0
TLS	1 (7)	0	0
APPENDICITIS	0	1 (7)	0
BASAL CELL CARCINOMA	1 (7)	0	0

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Response rates: MRD by ASO-PCR

	CHESON (99)			LUGANO		MRD		
Cycles	C2	C4	C6	C6		PB C3	PB C6	BM C6
CR/CRu	8 (53%)	12 (80%)	12 (80%)	13 (86%)	Neg	12 (80) (100)*	11 (73) (100)*	10 (67) (100)*
PR	7 (47%)	2 (13%)	2 (13%)	1 (7%)	Pos	-	-	-
Prog		1 (7%)	1 (7%)	1 (7%)	Not Eval for MRD	3 (20)	2 (13)	2 (13)

- *% of MRD neg in patients evaluable for MRD*
- *1 sample missing, 1 progression before C6*
- *3 MRD not evaluable patients*

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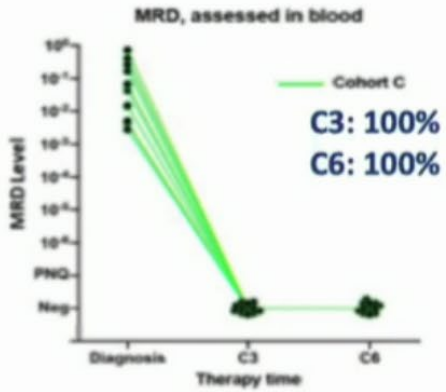
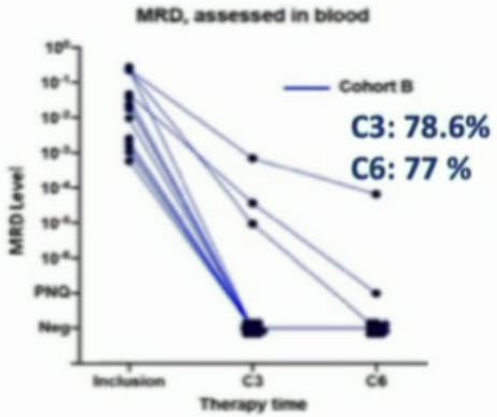
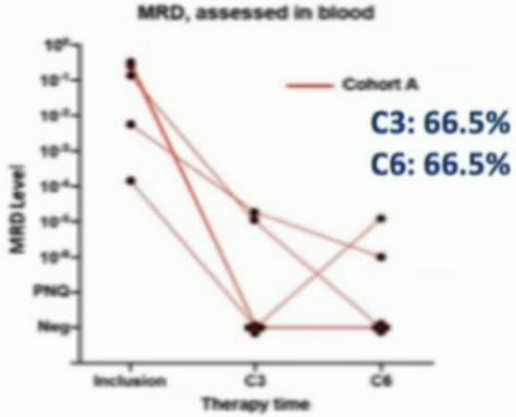
MRD by ASO-PCR in each cohort

Patients	Newly-diagnosed	Relapsed	Relapsed
	Ibrutinib Obinutuzumab Venetoclax	Ibrutinib Obinutuzumab Venetoclax	Ibrutinib Obinutuzumab







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MCL – Chemotherapiefreie Ansätze

Schlussfolgerungen?

- Sehr frühe Studiendaten
- ABER: beeindruckende Ansprechraten und MRD – Daten!
- Randomisierte Studie Erstlinie geplant!

→ OASIS (Phase II): Ibrutinib/α-CD20 vs. Venetoclax/Ibrutinib/α-CD20

Kapitel 4

MCL
Welche Therapie bei ZNS – Befall?

EHA25 VIRTUAL

Ibrutinib Compared to Immuno-chemotherapy for Central Nervous System Relapse of Mantle Cell Lymphoma: A Report from Fondazione Italiana Linfomi (FIL) and the European Mantle Cell Lymphoma Network (EMCLN)

Chiara Rusconi, Chan Y. Cheah, David Tucker, Toby A. Eyre, Pavel Klener, Eva Giné Soca, Lara Crucitti, Cristina Muzi, Sophie Bernard, Rebecca L. Auer, Chiara Pagani, Wojciech Jurczak, Heidi Mocikova, Hanneke C. Kluin-Nelemans, Emanuele Cencini, Ana Marin-Niebla, Michael E. Williams, Piera Angelillo, Paolo Nicoli, Annalisa Arcari, Lucia Morello, Donato Mannina, Orsola Vitagliano, Roberto Sartori, Annalisa Chiappella, Roberta Sciarra, Piero M. Stefani, Martin Dreyling, John Seymour, Carlo Visco

June 12th 2020

Indolent and mantle-cell non-Hodgkin lymphoma – Clinical; abs S229

C. Rusconi

EHA25 VIRTUAL

Background

Central Nervous System (CNS) involvement in Mantle Cell Lymphoma (MCL):

- Uncommon: 57/1396 pts (4.1%, 0.9% at initial diagnosis)
- Risk factors at diagnosis: elevated LDH, blastoid histology, high MIPI, ECOG ≥ 2, B symptoms
- Median time to CNS relapse: 15.2 ms
- Median survival after CNS relapse: 3.7 ms

Cheah CY et al, Ann Oncol 2013

A standard of care is lacking and therapeutic strategies are borrowed from Diffuse Large B-cell Lymphoma

Study design

Retrospective multi-center analysis of consecutive patients with **CNS relapse of systemic MCL** after at least one therapeutic line

Aim: to evaluate outcome of pts receiving ibrutinib (Ibrutinib cohort, IbC) compared to pts treated with a standard therapy (Standard Cohort, SC)

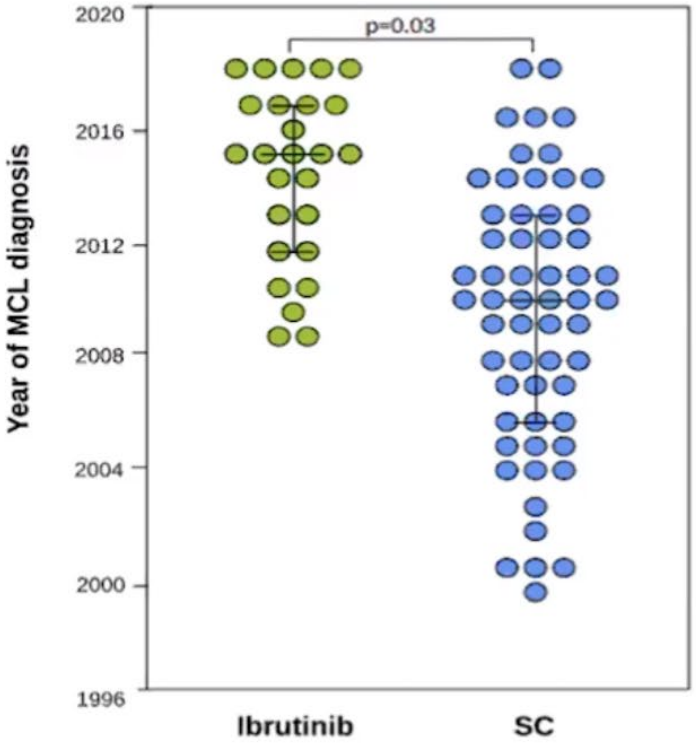
Primary objective: Overall Survival (OS)

Secondary objectives: Progression-free Survival (PFS), Response rate, Safety, efficacy of additional intratechal therapy (IT)

OS and PFS estimated from the time of initiation of therapy for CNS-MCL

Study population

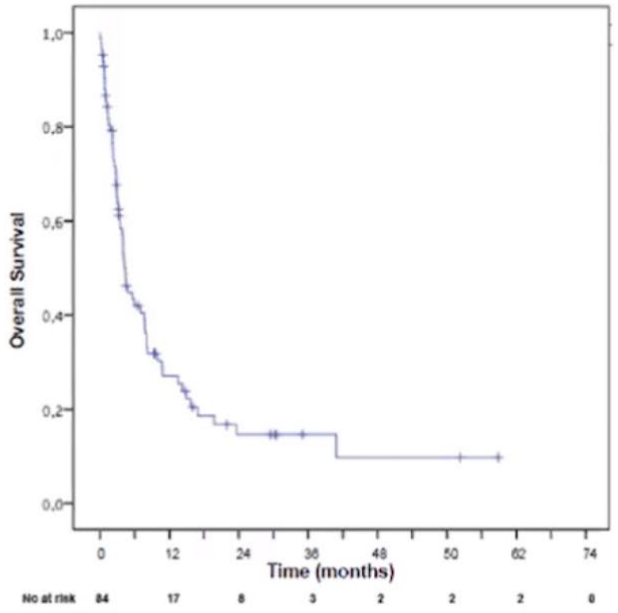
- 38 Centers involved, 20 international and 18 from FIL
- 84 consecutive cases with CNS relapse of systemic MCL occurred between 2000 and 2019 were included
- 58 patients received standard therapy and 26 patients ibrutinib
- 39 patients receiving standard chemotherapy in the present study have been described in previous reports [EMCLN study: Cheah CY et al, Ann Oncol 2013; MANTLE-FIRST study: Visco C et al, Br J Haematol 2019]



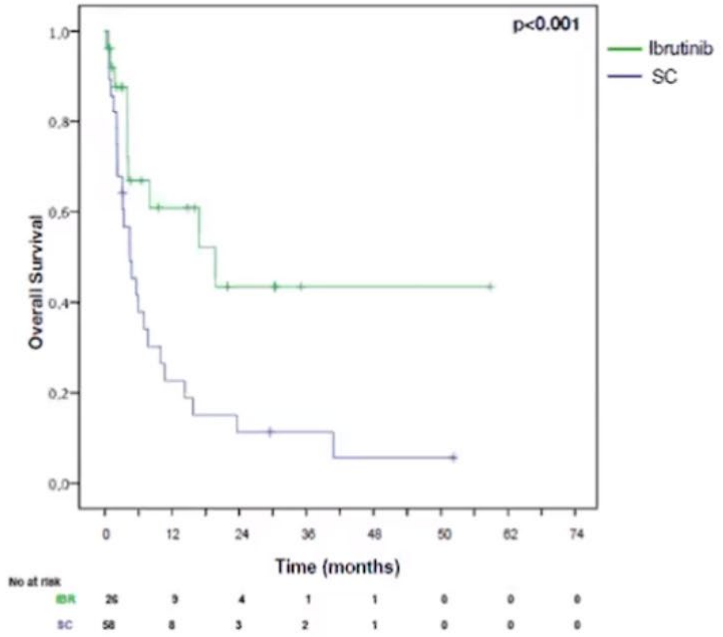
Overall Survival

Median follow-up: 4.3 months (range: 0.1-68)

Entire study population:
1-year OS: 27%



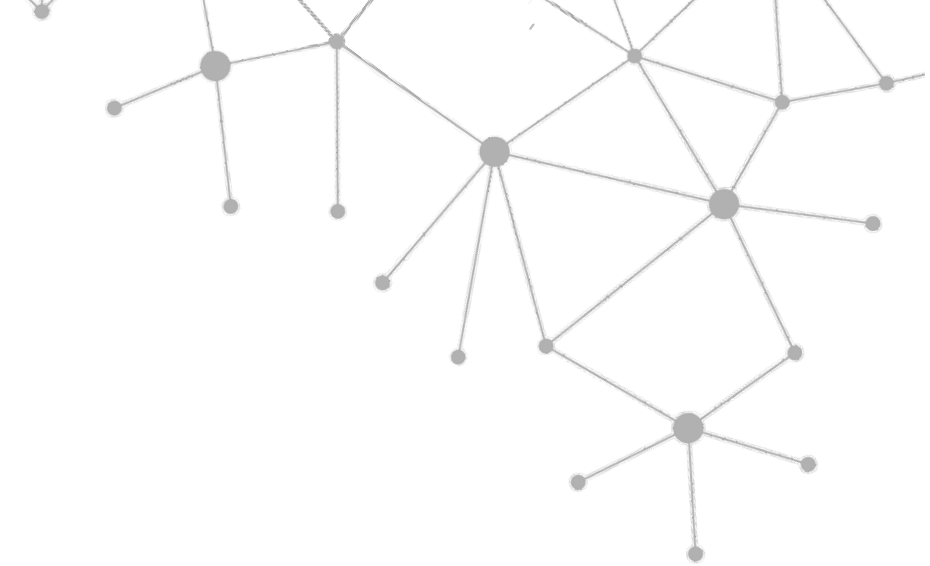
IbC vs SC:
1-year OS: 61% vs 16%;
HR=0.29-p<0.001



MCL – ZNS Befall

Schlussfolgerungen?

- Bestätigung kleinerer Fallserien und Fallberichte
- Ibrutinib konventioneller ZNS – gängiger Chemotherapie überlegen



Die Kurzpräsentationen sind online unter

www.lymphome.de/eha2020

Für den Inhalt verantwortlich:

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CCC Ulm • Universitätsklinikum Ulm

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