Kompetenznetz Maligne Lymphome


Lymphom Kompetenz KOMPAKT

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Expert:innen berichten zu Lymphomen & Leukämien

## KML-Expert:innen berichten

# 17th ICML 2023 LUGANO

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Expert:innen berichten zu Lymphomen & Leukämien

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Universitätsklinikum Ulm

# Morbus Waldenström (WM) & Marginalzonen-Lymphom (MZL)

# Offenlegung potentieller Interessenskonflikte

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# Kapitel 1

Morbus Waldenström –

Bedeutung der autologen und allogenen Stammzelltransplantation in der Ära der „targeted therapies“?

# Autologous and allogeneic stem-cell transplantation for transformed Waldenström macroglobulinemia

**P287**

E.Durot et al.

RESEARCH ARTICLE

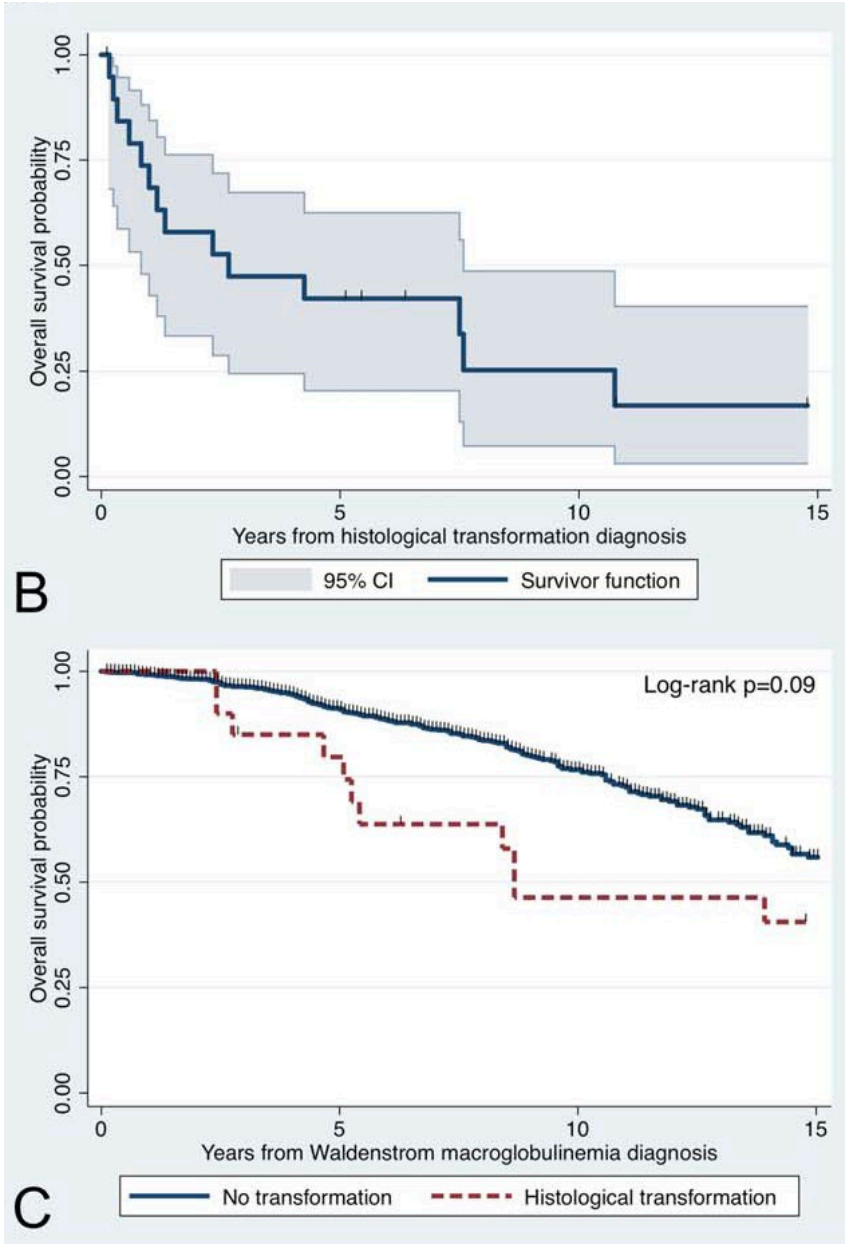
# Histological transformation to diffuse large B-cell lymphoma in patients with Waldenström macroglobulinemia

Jorge J. Castillo,* Joshua Gustine, Kirsten Meid, Toni Dubeau, Zachary R. Hunter, and Steven P. Treon

Histological transformation to diffuse large B-cell lymphoma (DLBCL) rarely occurs in patients with Waldenström Macroglobulinemia (WM). We identified 20 patients out of a cohort of 1,466 WM patients who experienced histologic transformation. The 5, 10, and 15-year cumulative incidence rates were 1, 2.4, and 3.8%, respectively. Approximately half of the patients were naive to nucleoside analogues, and a quarter were previously untreated for WM at the time of transformation. More than 80% of patients presented with extranodal involvement, 65% with high IPI scores. DLBCL cells did not express CD10 but expressed BCL6 and BCL2. All patients were treated with chemoimmunotherapy. The median survival from histological transformation was 2.7 years. The median overall survival was shorter for transformed patients versus those who did not transform (estimated 9 vs. 16 years; $P = 0.09$). Histological transformation to DLBCL is rare, and is associated with inferior survival in WM.

Am. J. Hematol. 91:1032–1035, 2016. 

Nach 10 Jahren Rate an Transformation 2,4 %



# Transformierter WM

**Hintergrund und Methoden**

## METHODS

- ✓ Patients with transformed WM who received autoSCT or alloSCT between 1996 and 2021, identified in an international multicenter database of 285 patients.
- ✓ Primary end-point: overall survival (OS), calculated from the date of SCT to death from any cause
- ✓ Secondary end-points: progression-free survival (PFS), incidence of relapse/progression and non-relapse mortality (NRM).
- ✓ Univariate and multivariate analyses performed using the Cox proportional hazards model for OS and PFS only for the autoSCT cohort, due to the small sample size of the alloSCT cohort.

# Transformierter WM

## Ergebnisse

**RESULTS**

Fifty-six patients were included, 46 had received autoSCT and 10 alloSCT. The median time from HT diagnosis to SCT was 8 months (range, 2 to 76 months) for autoSCT and 7 months (range, 3 to 49 months) for alloSCT. The patients received a median of 2 lines of treatment for HT before SCT (range, 1 to 6 for autoSCT and 1 to 3 for alloSCT), and 89% (complete response (CR): 59%) and 80% (CR: 50%) of the patients had chemosensitive disease at the time of autoSCT and alloSCT, respectively.

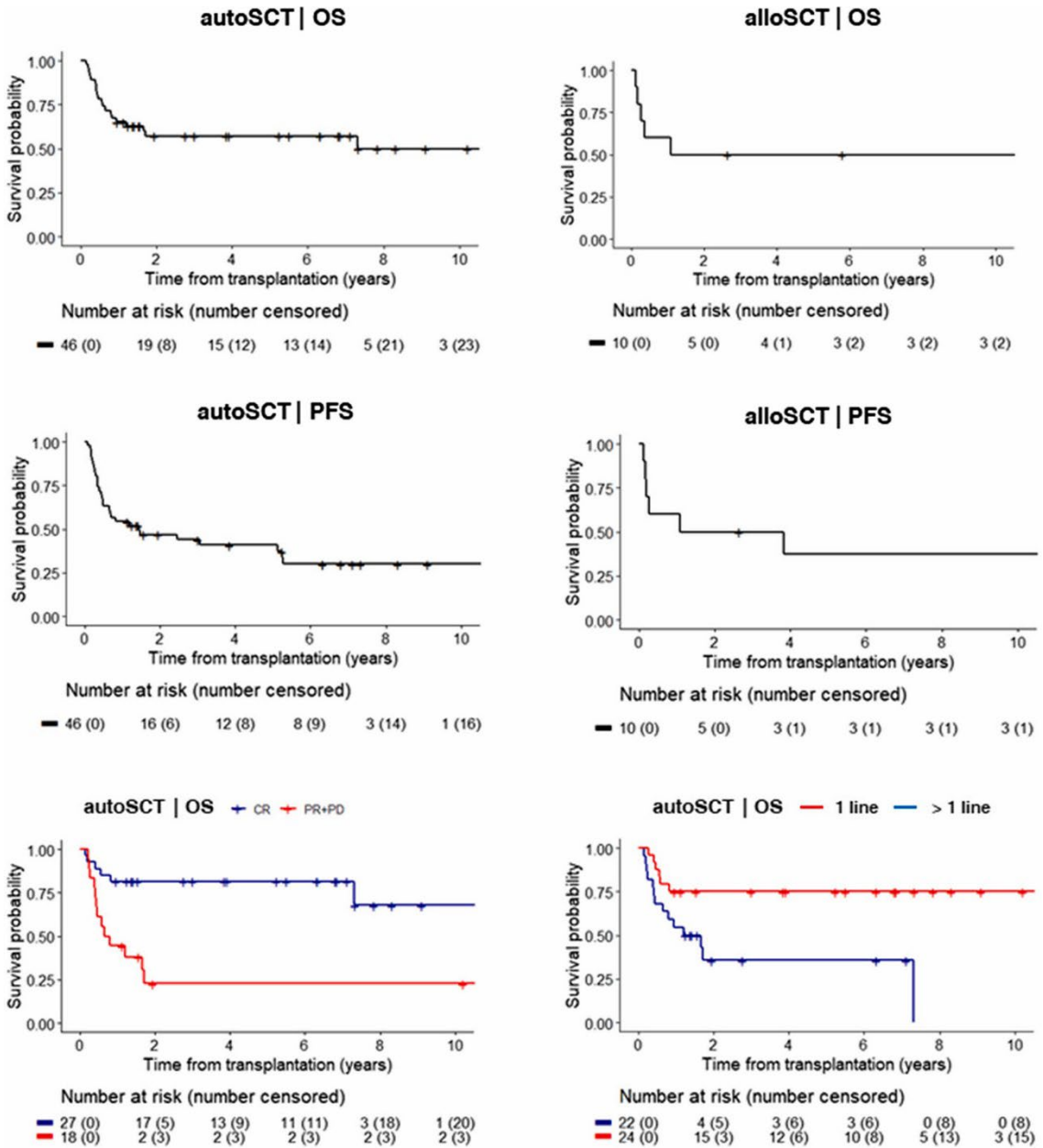
**TABLE 1. PATIENT CHARACTERISTICS**

| Variable | AutoSCT (n = 46) | AlloSCT (n = 10) |
|---|---|---|
| Sex male/female (ratio) | 30/16 (1.9) | 4/6 (0.7) |
| Age at diagnosis of WM (years) | 56 [27-70] | 48 [38-66] |
| Median number of regimens prior to HT | 1 [0-5] | 2 [0-4] |
| Time from WM diagnosis to HT (years) | 4.2 [0-17.2] | 3.3 [0-9.6] |
| Age at diagnosis of HT (years) | 62 [31-75] | 50 [43-69] |
| Advanced Ann Arbor stage | 84% | 100% |
| Elevated LDH | 56% | 67% |
| Prior therapy regimens received for HT | 2 [1-6] | 2 [1-3] |
| Prior autoSCT | N/A | 3 (33%) |
| Time from HT to SCT (months) | 8 [2-76] | 7 [3-49] |
| Year of transplant | | |
| 1996-2005 | 5 (11%) | 1 (10%) |
| 2006-2015 | 28 (61%) | 7 (70%) |
| 2016-2021 | 13 (28%) | 2 (20%) |
| Age at SCT (years) | | |
| > 60 | 29 (63%) | 2 (20%) |
| Median | 63 [31-77] | 51 [43-70] |
| Disease status at SCT | | |
| CR | 27 (59%) | 5 (50%) |
| PR | 14 (30%) | 3 (30%) |
| PD | 4 (9%) | 1 (10%) |
| Unknown | 1 (2%) | 1 (10%) |
| Conditioning regimen | | |
| TBI based | 1 (2%) | 2 (20%) |
| Chemotherapy based | | |
| BEAM protocol | 35 (76%) | |
| BAM | 1 (2%) | |
| Thiotepa + BCNU | 4 (9%) | |
| Thiotepa-Busulfan-Endoxan | 2 (4%) | |
| Tiotepa + carboplatine | 1 (2%) | |
| Busulfan-Endoxan | 1 (2%) | |
| Fludarabine-Busulfan +/- SAL | | 4 (40%) |
| Fludarabine-Campath-melphalan | | 2 (20%) |
| Fludarabine-Busulfan-Endoxan | | 1 (10%) |
| Unknown | 1 (2%) | 1 (10%) |
| Intensity of conditioning | | |
| RIC | N/A | 7 (70%) |
| Myeloablative | N/A | 2 (20%) |
| Unknown | N/A | 1 (10%) |
| Response to SCT | | |
| CR | 35 (76%) | 6 (67%) |
| PR | 4 (9%) | 0 (0%) |
| SD | 0 (0%) | 0 (0%) |
| PD | 7 (15%) | 3 (33%) |
| Unknown | 0 (0%) | 1 (10%) |

# Transformierter WM

## Ergebnisse

The median follow-up time for the surviving patients was 5.5 years (95% CI, 2.8 to 7.1 years) from autoSCT and 12.6 years (95% CI, 2.7 to 14.4 years) from alloSCT. The 3-year estimates of OS, PFS and cumulative incidences of relapse and NRM were 57%, 44%, 54%, and 2% for autoSCT and 50%, 50%, 30%, and 20% for alloSCT, respectively. In the autoSCT cohort, CR at SCT was found to be associated with superior OS and PFS (3-year OS, 81% for CR vs 23% for less than CR, $P = 0.001$ and 3-year PFS, 62% vs 21%, $P < 0.001$) and less than 2 lines of therapy for HT with superior OS (3-year OS, 75% for 1 line vs 36% for > 1 line, $P = 0.01$).



# Kapitel 2

Morbus Waldenström –

Kombination BTK Inhibitor mit R-Chemo beim WM?

# Next generation BTK inhibitor acalabrutinib with bendamustine-rituximab in first line WM: BRAWN Study

**P288**

N. Berinstein et al.

# Kombination BTK Inhibitor mit R-Chemo beim WM?

**Studiendesign**

**Methods:** Symptomatic, previously untreated patients will be treated with bendamustine and rituximab for six 28-day cycles ● acalabrutinib 100 mg BID for 1 year ● CT scans at pre-treatment, 7, 12 & 18 months, unless stable IgM with previous negative CT ● Bone Marrow Aspirate for Standard of Care and MRD analysis pre-treatment, 7, 12 & 18 months; mutational analysis at pre-treatment only ● Active at 9 Canadian cancer centres

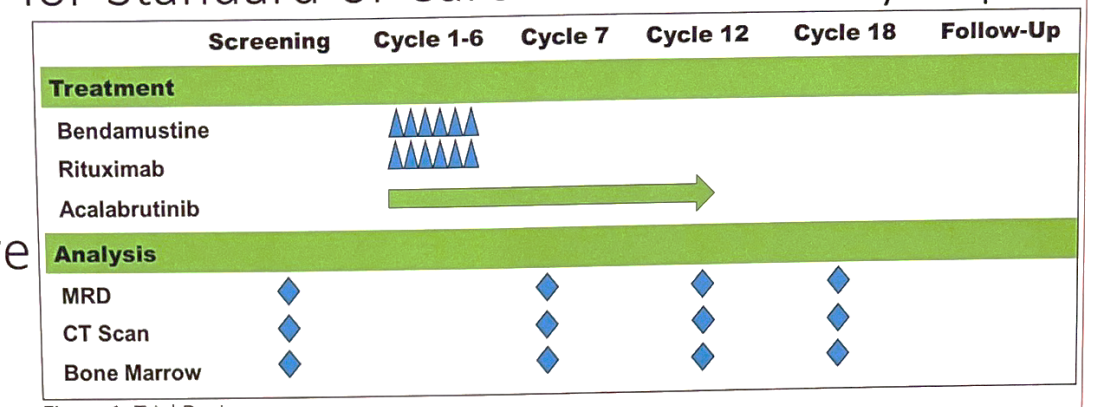



Figure 1: Trial Design

# Kombination BTK Inhibitor mit R-Chemo beim WM?

**Patientencharakteristika**

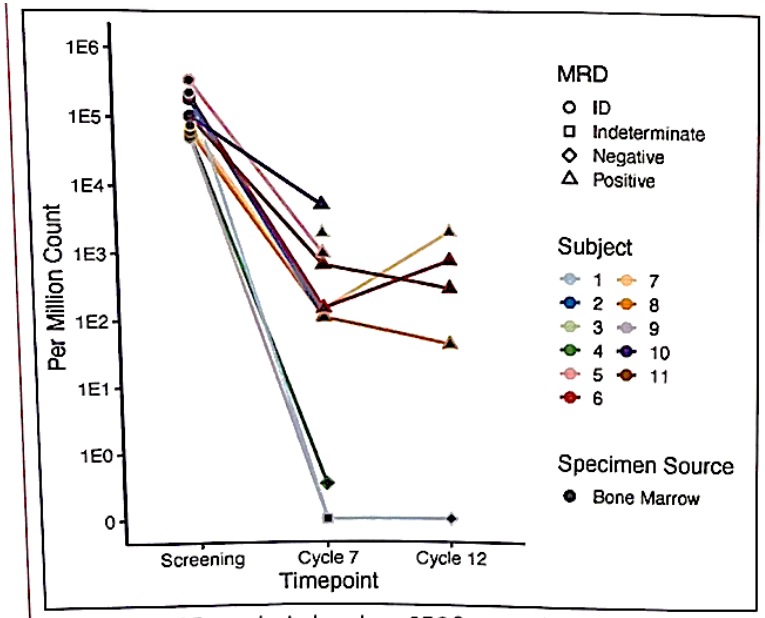
## Interim Results: 38/59 participants have been enrolled.

| | All Participants n = 38 | Mutational Analysis n = 31 | | |
|---|---|---|---|---|
| | | MYD88 n = 29 | CXCR4 n = 9 | TP53 n = 1 |
| Male (%) | 29 (76) | 23 (79) | 7 (78) | 1 (100) |
| Female (%) | 9 (24) | 6 (21) | 2 (22) | 0 (0) |
| Age, median (range) - years | 68 (45-79) | 68 (45-79) | 68 (52-78) | 79 |
| Age > 65 yrs (%) | 26 (68) | 20 (69) | 7 (78) | 1 (100) |
| **IPSSWM Score** | | | | |
| Low Risk (%) | 3 (8) | 3 (10) | 0 (0) | 0 (0) |
| Intermediate Risk (%) | 16 (42) | 12 (42) | 3 (33) | 0 (0) |
| High Risk (%) | 19 (50) | 14 (48) | 6 (67) | 1 (100) |
| **Serum IgM level** | | | | |
| Median (range) - g/L | 36.4 (4.64-75.7) | 36.9 (7.51-75.7) | 38.9 (7.51-59.0) | 60.9 (60.9-60.9) |
| > 40 g/L (%) | 15 (39) | 12 (41) | 4 (44) | 1 (100) |
| **Hemoglobin level** | | | | |
| Median (range) - g/L | 103.5 (69-157) | 103 (69-157) | 96 (69-118) | 77 (77-77) |
| ≤ 115 g/L (%) | 27 (71) | 20 (69) | 7 (78) | 1 (100) |
| **Platelet Count** | | | | |
| Median (range) - x$10^9$/L | 229.5 (56-778) | 236 (68-778) | 171 (68-333) | 251 (251-251) |
| ≤ 100 x$10^9$/L (%) | 2 (5) | 1 (3) | 1 (11) | 0 (0) |
| **Serum β2-microglobulin level** | | | | |
| | **n = 35** | **n = 28** | **n = 9** | **n = 1** |
| Median (range) - g/dL | 3.5 (1.3-15.05) | 3.49 (1.3-15.05) | 3.35 (2.4-3.82) | 3.8 (3.8-3.8) |
| < 3 g/dL (%) | 8 (23) | 7 (25) | 1 (11) | 0 (0) |

Table 1: Baseline demographics for enrolled participants (n=38). 31 participants had samples available

# Kombination BTK Inhibitor mit R-Chemo beim WM?

## MRD unter Therapie



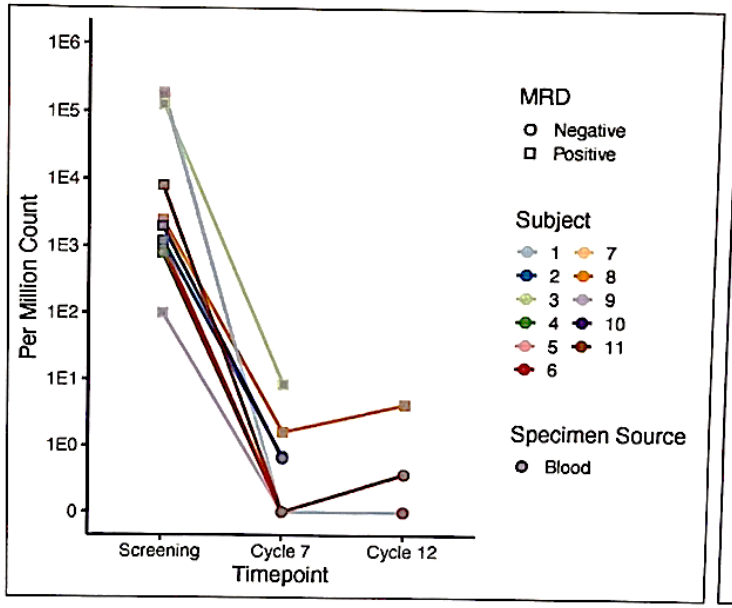




**Figure 2**: MRD analysis by clonoSEQ® using (Left) bone marrow and (Right) peripheral blood for 11 participants with available samples at screening and > 1 time point.

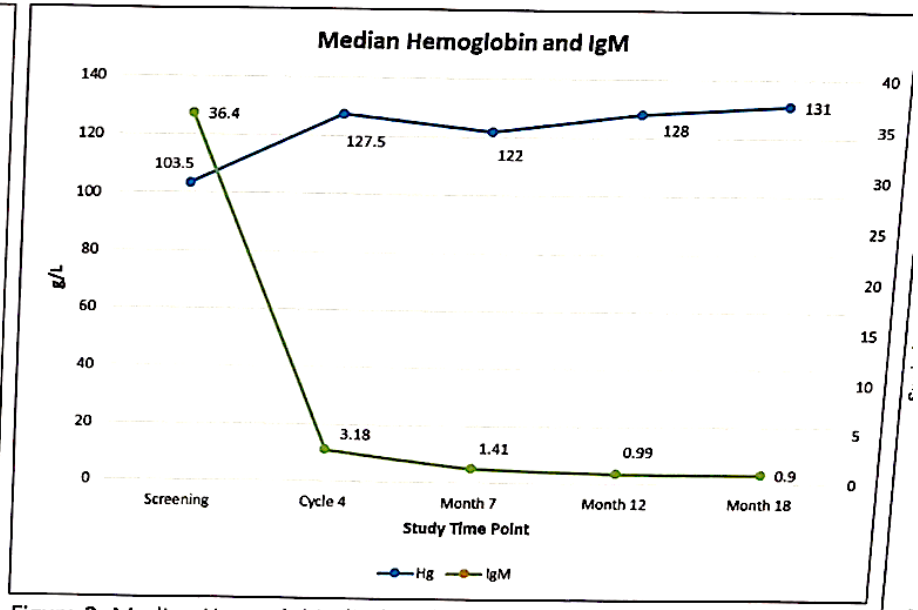



**Figure 3**: Median Hemoglobin (Hg) and IgM at protocol specified time points for enrolled participants.

# Kombination BTK Inhibitor mit R-Chemo beim WM?

**Ansprechen**

| | Cycle 7 n= 24 | Cycle 12 n= 17 | Cycle 18 n= 5 |
|---|---|---|---|
| CR, n (%) | 0 | 2 (12) | 0 |
| VGPR, n (%) | 16 (67) | 11 (65) | 5 (100) |
| PR, n (%) | 8 (22) | 4 (23) | 0 |

Table 3: Clinical Responses using 6th IWWM. 2 participants improved from a VGPR to a CR between cycles 7 and 12. Interim primary endpoint of combined CR and VGPR rate is 13/17 (76%).

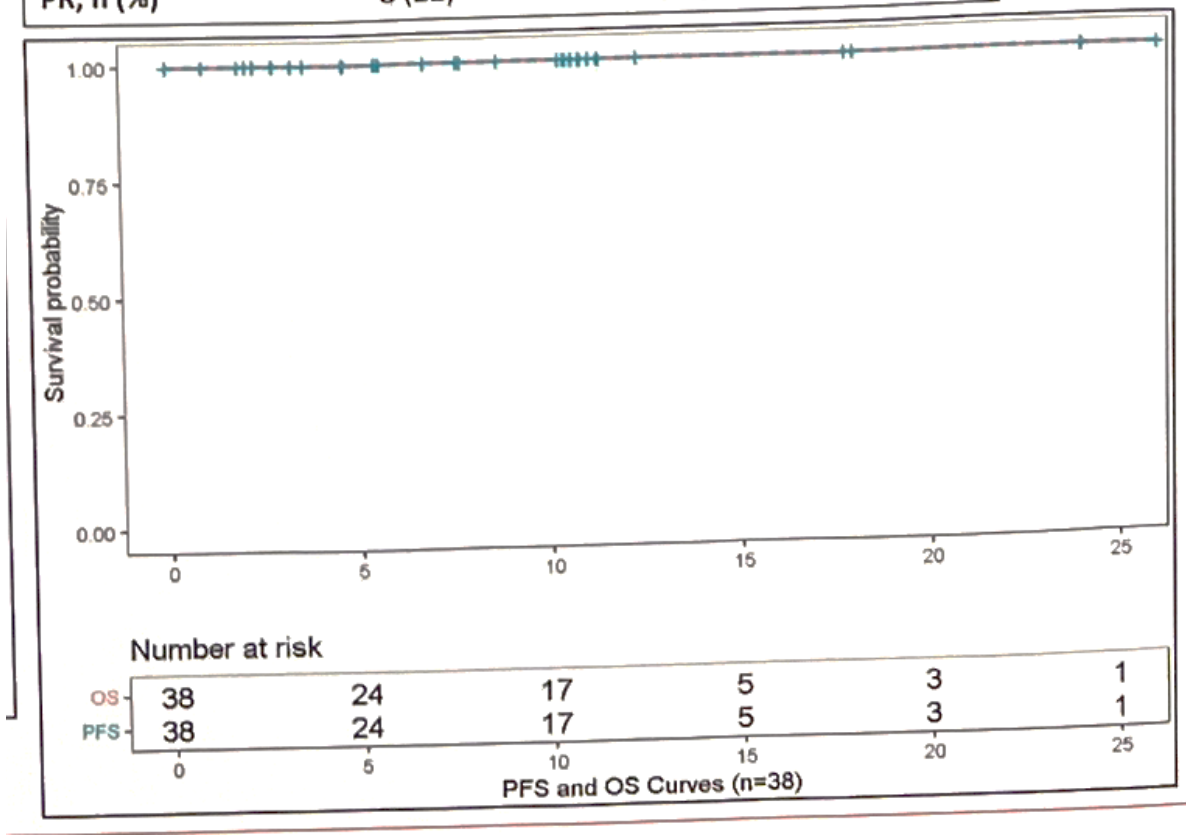



Figure 4: Kaplan Meier curves for Progression Free and Overall Survival for enrolled participants. 24/38 participants have completed combination therapy, 17/38 have completed monotherapy, 5/38 have completed 18 months, and 3/38 have completed 24 months (May 17, 2023). 1 participant discontinued with a VGPR at cycle 7, and 1 discontinued at cycle 3 (response data unavailable), both due to Treatment Related Adverse Events. No participants have died during treatment or during the extended follow-up period. Median follow-up of 7.16 months for all participants.

# Kombination BTK Inhibitor mit R-Chemo beim WM?

## Verträglichkeit

| | Combination | | | Monotherapy | | |
|---|---|---|---|---|---|---|
| | Grade 1/2 | Grade 3/4 | Total | Grade 1/2 | Grade 3/4 | Total |
| **Infections and Infestations** | | | | | | |
| Bronchopneumonia/bronchitis/upper respiratory infection | 2 | - | 2 | 3 | - | 3 |
| Pnemonia | 1, 1* | - | 2 | - | 1* | 1 |
| Fever | 3, 1* | 1* | 5 | - | - | - |
| Mouth/cold Sores/oropharangeal cadidosis | 5 | - | 5 | - | - | - |
| **Central Nervous Sytem Disorders** | | | | | | |
| Headaches/Migraine | 13 | - | 13 | 1 | - | 1 |
| **Gastrointestinal Disorders** | | | | | | |
| Constipation | 6 | - | 6 | 1 | - | 1 |
| Diarrhea | 11 | - | 11 | 1 | - | 1 |
| Nausea | 12 | - | 12 | 1 | - | 1 |
| Vomitting | 6 | - | 6 | 1 | - | - |
| **Skin Disorders** | | | | | | |
| Dry Skin | 6 | - | 6 | - | - | - |
| Infusion/Injection site Reaction | 3 | - | 3 | - | - | - |
| Rash | 6 | - | 6 | - | - | - |
| **Blood & Lymphatic Disorders** | | | | | | |
| Neutropenia | 2 | 9 | 11 | - | 1 | 1 |
| Febrile Neutropenia | - | 3* | 3 | - | - | - |
| Fatigue | 9 | - | 9 | - | - | - |
| Bruising | 8 | - | 8 | - | - | - |
| Anemia | 3 | 1 | 4 | - | - | - |
| Decreased Platelet Count | 5 | - | 5 | - | - | - |
| **Musculoskeletal & Connective Tissue Disorders** | | | | | | |
| Pain | 6 | - | 6 | - | - | - |
| **Total** | **109** | **14** | **123** | **8** | **1** | **9** |

# Kapitel 3

Marginalzonenlymphom –

BTKI weiter auf dem Vormarsch?

# Orelabrutinib for the treatment of relapsed or refractory marginal zone lymphoma: a phase 2 multicenter, open-label study

**P283**

Y. Song et al.

# MZL: BTKi auf dem Vormarsch?

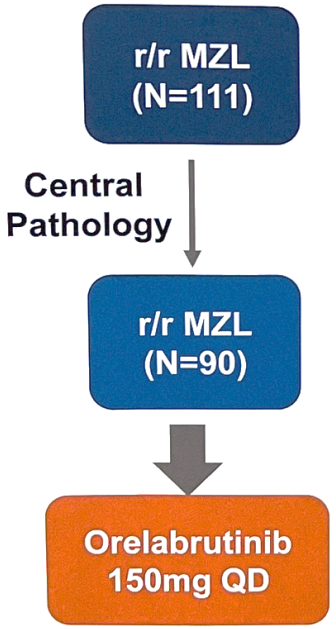
## Studiendesign

### Methods

#### Study Design

- This is a multicenter and open-label phase 2 study of orelabrutinib in r/r MZL patients across 32 sites in China. Orelabrutinib was administered orally at 150 mg QD for 28-day cycles until disease progression, intolerable toxicity, death, or withdrawal of consent (**Figure 1**).

**Fig 1.** Study Schema




***Key Eligibility***

- Age ≥18 and ≤75 years old;
- MZL diagnosis by histology;
- Relapsed or refractory.
- Prior therapies: ≥1 and ≤4, including anti-CD20 mAbs;
- Measurable disease;
- Adequate organ function;
- No prior BTK inhibitor exposure.

➢ **Primary endpoints**: ORR by IRC per 2014 Lugano;

➢ **Secondary endpoints**: ORR by INV, PFS,DOR, TTR, TTP, OS and safety.

- *Data cut-off date: October 8, 2022*
- *Median follow-up time: 24.3 months*

Full analysis set (FAS)

Modified full analysis set (mFAS#) (central pathology confirmed patients)

# MZL: BTKi auf dem Vormarsch?

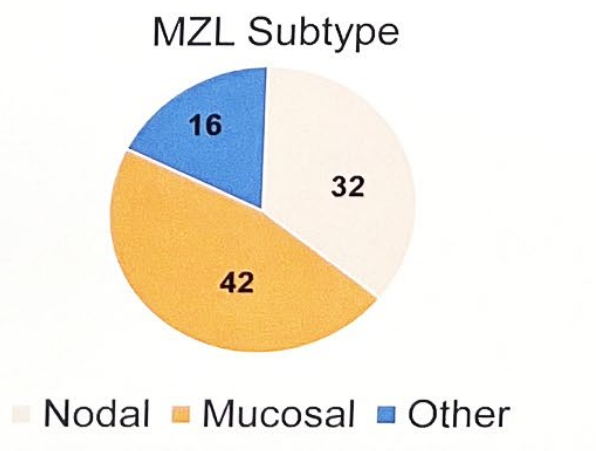
**Patientencharakteristika**

## Results

**Tab 1**. Demographics and disease characteristics

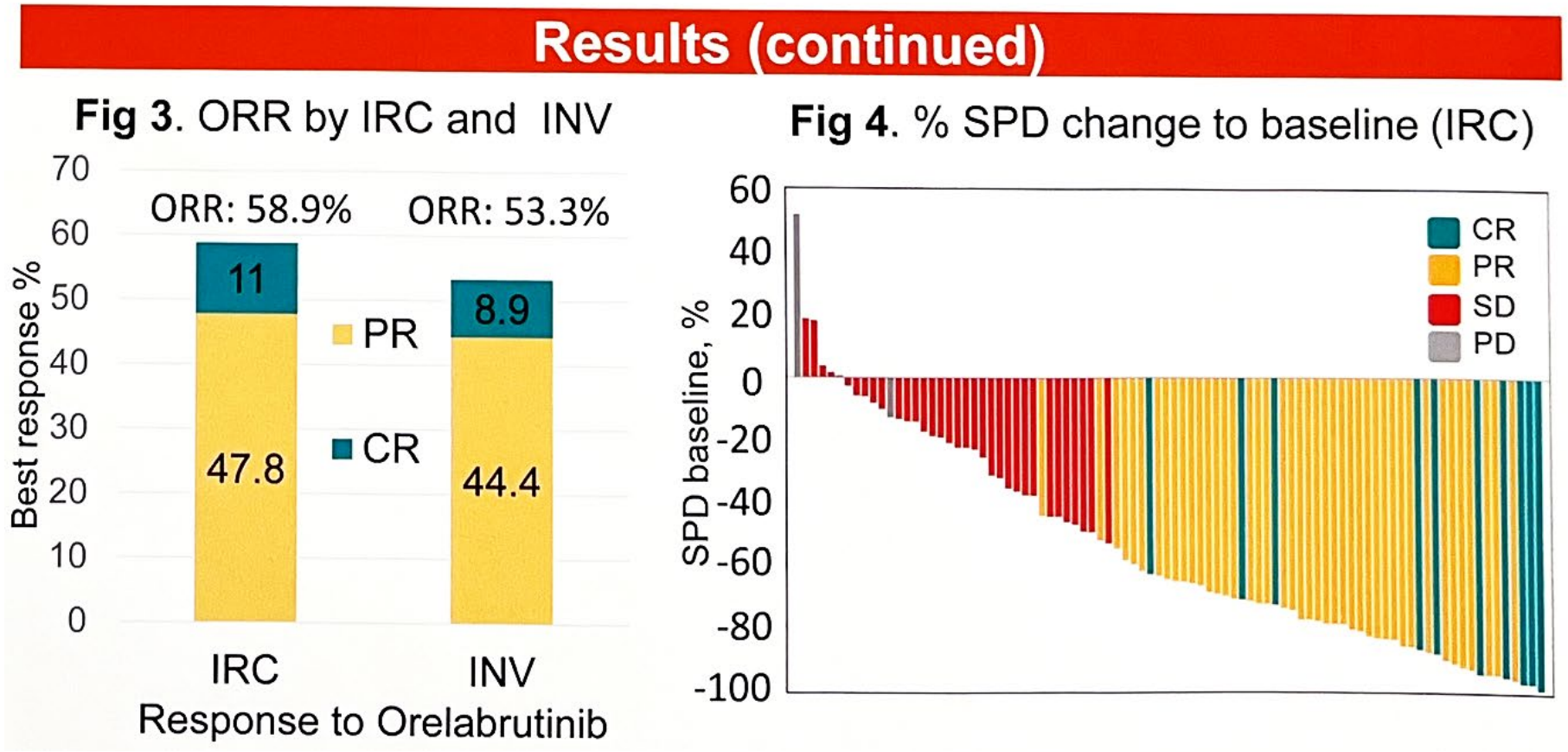
| Characteristic | mFAS (N=90) |
|---|---|
| Median Age (range) | 62.0 (23, 77) |
| Male, n (%) | 49 (54.4) |
| Stage III/IV, n (%) | 74 (82.3) |
| Refractory, n (%) | 32 (35.6) |
| BM involvement, n (%) | 30 (33.3) |
| Median prior lines (range) | 2 (1-3) |
| Prior Anti-CD20, n (%) | 83 (92.2) |

**Fig 2**. Histological subtypes



# MZL: BTKi auf dem Vormarsch?

**Ansprechen**



# MZL: BTKi auf dem Vormarsch?

## Effektivität und Nebenwirkungen

**Conclusions**

- ✓ Orelabrutinib demonstrated robust and sustained efficacy for r/r MZL patients with mDOR of 34.3m. Median PFS has not been reached.
- ✓ High response rates were consistent among patients with different MZL subtypes.
- ✓ Orelabrutinib is well tolerated with no Atrial fibrillation/flutter occurred.
- ✓ The results of this study support orelabrutinib as an effective treatment option for r/r MZL patients.

**Fig 5**. KM curve of DOR (A) and PFS (B) by IRC

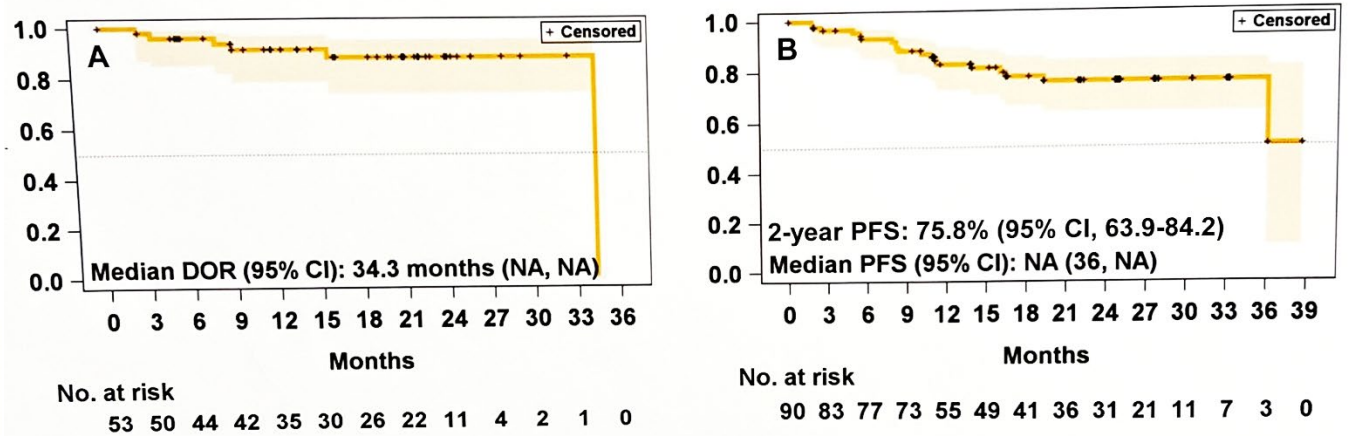
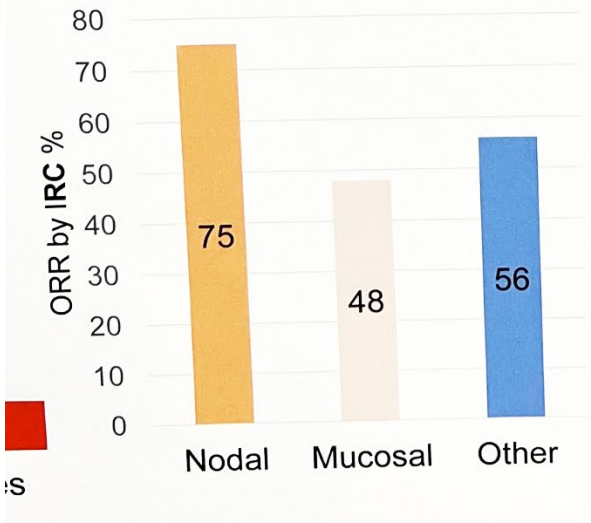



**Fig 6**. ORR per subtypes




**Tab 2**. Treatment-related adverse events

| | FAS (N=111) |
|---|---|
| **All-grade TRAEs in ≥10% of patients (%)** | |
| Anemia | 31 (27.9) |
| Neutrophil count decrease | 26 (23.4) |
| White blood cell count decrease | 20 (18.0) |
| Platelet count decrease | 19 (17.1) |
| Blood present in urine | 18 (16.2) |
| Rash | 16 (14.4) |
| Upper respiratory infection | 12 (10.8) |
| **Grade ≥3 TRAEs in >2 patients (%)** | |
| Neutrophil count decrease | 9 (8.1) |
| Pneumonia | 7 (6.3) |
| Anemia | 5 (4.5) |
| White blood cell count decrease | 4 (3.6) |
| Subcutaneous hemorrhage | 3 (2.7) |

# Kapitel 4

Marginalzonenlymphom –

Zanubrutinib vs Ibrutinib?

# Matching-Adjusted Indirekt Comparison (MAIC) of Zanubrutib vs Ibrutibnib in relapsed/refractory Marginal Zone Lymphoma

**P282**

C. Thieblemont et al.

# MZL: Zanubrutinib vs Ibrutinib (MAIC)

## Hintergrund und Studiendesign

### INTRODUCTION

- Limited effective and tolerable treatment options are available for patients with MZL who have experienced relapse after or whose lymphoma was refractory to prior standard chemoimmunotherapy with anti-CD20 monoclonal antibodies
- Bruton tyrosine kinase inhibitors (BTKi) have shown deep and durable responses in non-Hodgkin lymphoma subtypes, including Waldenstrom macroglobulinemia, chronic lymphocytic leukemia, and mantle cell lymphoma
- Zanubrutinib, a second-generation BTKi, and ibrutinib, a first-generation BTKi, have been assessed in single-arm clinical trials in MZL
- In the absence of head-to-head randomized controlled trials, comparative efficacy estimates must come from unanchored between-trial comparisons of reported treatment effects

### OBJECTIVE

- To assess the comparative efficacy of zanubrutinib vs ibrutinib for the treatment of R/R MZL

### METHODS

#### Data Sources

- Zanubrutinib has been evaluated in 2 single-arm trials in R/R MZL (phase 2 MAGNOLIA trial [NCT03846427]; phase 1/2 BGB-3111-AU-003 trial [NCT02343120])[1,2]
- Ibrutinib has also been evaluated in R/R MZL in a phase 2, single-arm trial (PCYC-1121 [NCT01980628])[3,4]

#### Statistical Analysis

- Propensity score models were used to match baseline characteristics in MAGNOLIA and BGB-3111-AU-003 to those observed in PCYC-1121
- Prognostic factors were ranked by clinical experts (presented in order of importance in **Table 1**)
- In the base-case model, matched variables included number of prior lines of therapy, MZL subtype, response to prior therapy, and age
- In the sensitivity analysis, the following additional variables were considered: lactate dehydrogenase above normal, bulky disease (>5 cm), prior anti-CD20 therapy, time since last therapy, B symptoms, bone marrow involvement, and Eastern Cooperative Oncology Group (ECOG) performance status
- The impact of each covariate in the base-case and scenario models were explored via a leave-one-out analysis
- Logistic regression models for binary outcomes (objective response rate [ORR]) and Cox proportional hazards models for time-to-event outcomes (overall survival [OS], progression-free survival [PFS]) were used to estimate relative treatment effects for zanubrutinib vs ibrutinib

# MZL: Zanubrutinib vs Ibrutinib (MAIC)

## Patientencharakteristika

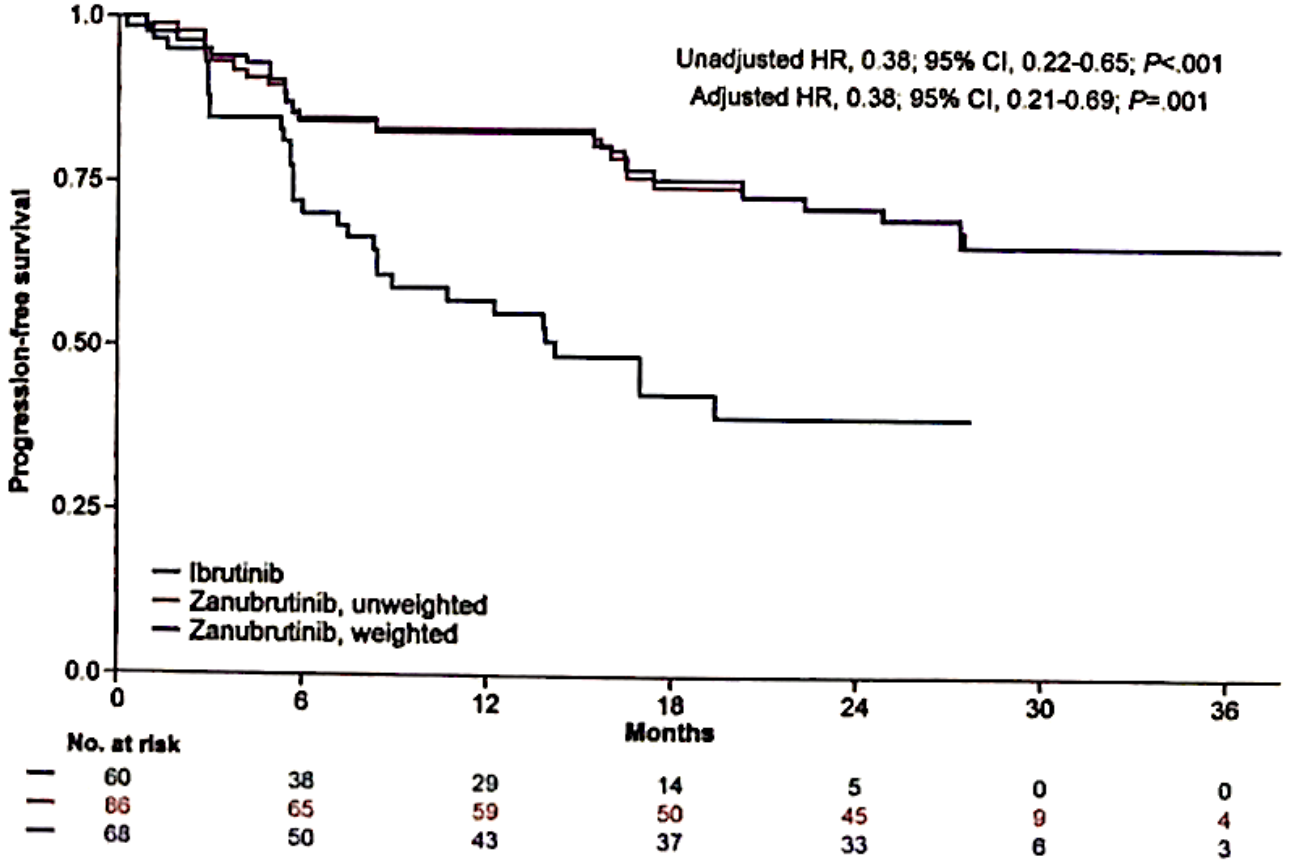
Table 1. Baseline Characteristics in Zanubrutinib Treatment Group Before and After Matching to Ibrutinib Treatment Group

| Covariate | Zanubrutinib | | | Ibrutinib (N=60) |
|---|---|---|---|---|
| | Observed (N=86) | Weighted base-case model (ESS=68) | Weighted sensitivity model (ESS=24) | |
| 2 prior treatment lines, % | 30.2 | 30.0 | 30.0 | 30.0 |
| ≥3 prior treatment lines, % | 25.6 | 33.3 | 33.3 | 33.3 |
| MZL subtype: nodal, % | 36.6 | 28.3 | 28.3 | 28.3 |
| MZL subtype: splenic, % | 22.0 | 21.7 | 21.7 | 21.7 |
| Refractory to last therapy, % | 30.1 | 22.2 | 22.2 | 22.2 |
| Age ≥65 years, % | 65.1 | 60.0 | 60.0 | 60.0 |
| LDH above normal, % | 27.9 | N/A | 19.0 | 19.0 |
| Bulky disease >5 cm, % | 35.4 | N/A | 22.2 | 22.2 |
| Prior anti-CD20 therapy, % | 98.9 | N/A | 100 | 100 |
| Time since last therapy, median, months | 29 | N/A | 45 | 45 |
| B symptoms, % | 19.8 | N/A | 23.8 | 23.8 |
| Bone marrow involvement, % | 50.0 | N/A | N/A | 33.3 |
| ECOG 0-1, % | 91.9 | N/A | N/A | 92.1 |

# MZL: Zanubrutinib vs Ibrutinib (MAIC)

**Ergebnisse – PFS**

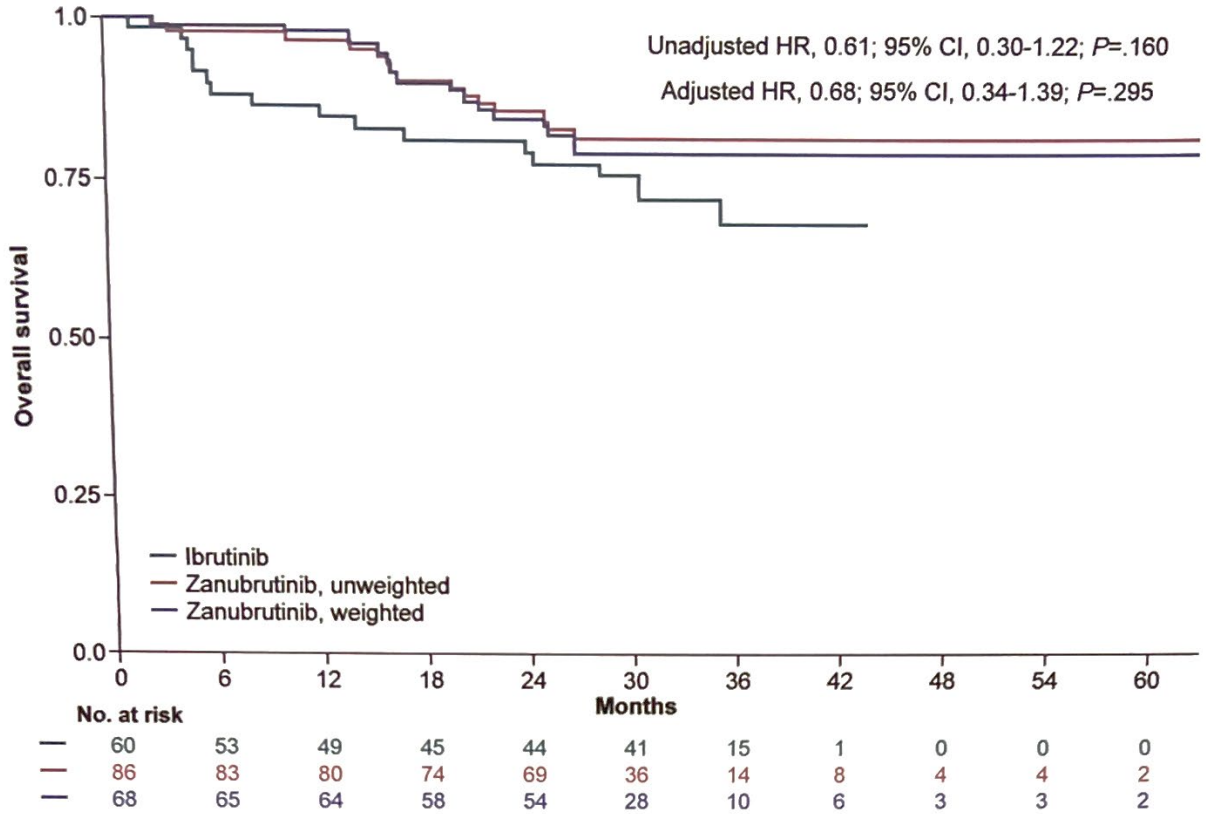
**Figure 1. MAIC of Zanubrutinib and Ibrutinib in Base-Case PFS Analysis (Cox Proportional Hazards Model)**



# MZL: Zanubrutinib vs Ibrutinib (MAIC)

**Ergebnisse – OS**

**Figure 2. MAIC of Zanubrutinib and Ibrutinib in Base-Case OS Analysis (Cox Proportional Hazards Model)**



# Kapitel 5

Marginalzonenlymphom –

Ein neuer Score für alle MZL?

# MARGINAL ZONE LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (MZL-IPI): A PROGNOSTIC SCORE FOR THE ENTIRE SPECTRUM OF MARGINAL ZONE LYMPHOMAS. A FIL AND SPORE-MER STUDY

**Abstract 063**

S. Luminari et al.


# Marginal Zone Lymphoma International Prognostic Index (MZL-IPI): a prognostic score for the entire spectrum of marginal zone lymphomas. A FIL and SPORE-MER study

Stefano Luminari*, Côme Bommier, Nicole Fabbri, Maria Elena Nizzoli , Matthew J Maurer, Vittoria Tarantino6, Simone Ferrero, Sara Rattotti, Michele Merli, Angela Ferrari, Roberta Murru, Arushi Khurana, Raphael Mwangi, Marina Deodato, Ilaria Del Giudice, Emanuele Cencini, Francesca Re, Carlo Visco, Andrew L Feldman, Brian K Link, Marcia Torresan Delamain, Michele Spina, Annibali Ombretta, Alessandro Pulsoni, Donato Mannina, Carola Boccomini, Andrès Ferreri, Thomas M Habermann, Luigi Marcheselli, James R Cerhan, Luca Arcaini

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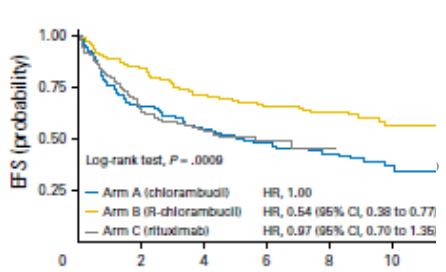
# Background – Marginal Zone Lymphomas

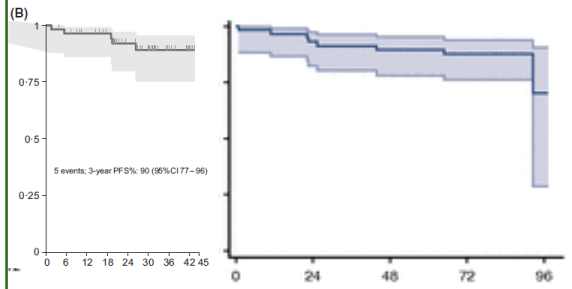
- 6-9% of NHL.
- Splenic, Nodal and Extranodal subtype
- Indolent course improved in the rituximab era
- Missing standard tx but immunochemotherapy required in symptomatic patients (i.e. R-Chl, R-bendamustine)
- Most of recent trials consider MZL as a single entity: Gallium, Augment, Magnify, Magnolia, etc…
- Subtype specific prognostic scores (i.e. HPLL for SMZL, MALT-IPI for ENMZL).
- **A prognostic score validated for all MZLs is missing**

**Alkylating +/-R**




ENMZL- IELSG19 trial(1)
(Chl vs R vs R-Chl)

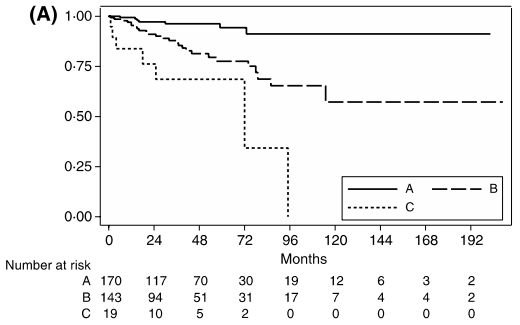
**R-Bendamustine**



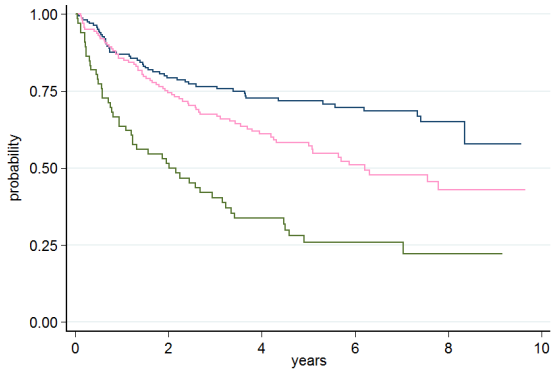

SMZL(2)

ENMZL(3)

**HPLL prognostic score for SMZL (4)**
**(Hb, Plt, LDH, extrahilar LN)**




**MALT-IPI for ENMZL (5)**
**(Age, Stage, LDH)**




(1) Zucca et al. J clin oncol 2017; (2) Iannitto et al Leuk & Lymph 2018; (3) Salar et al. Lancet oncol 2017,
(4) Montalban et al BJH 2012, (5) Thieblemont et al. Blood 2017, (6) Casulo et al. J clin oncol 2015.

# The NF10 study by FIL

- Prospective observational study to investigate the prognosis of Indolent Non-Follicular B-Cell Lymphomas (INFL).

- Adult patients with biopsy-proven INFL
  - **SMZL** (bone marrow and/or splenic histology)
  - **ENMZL** (tissue biopsy)
  - **NMZL** (lymph node biopsy)
  - **Lymphocytic lymphoma** (lymph node biopsy)
  - **Lymphoplasmacytic lymphoma** (bone marrow histology or lymph node biopsy)
  - **CD5-negative leukemia** (bone marrow histology)

- No exclusion criteria

- Started in 2010;
- 47 active centers in Europe and South America
- 1340 patients eligible based on local pathology report


**Study coordinators S.Luminari L.Arcaini**

# Study aims and design

***Study aim:*** to identify and validate a prognostic model for patients with MZLs identified from the prospective NF10 study

## Inclusion criteria

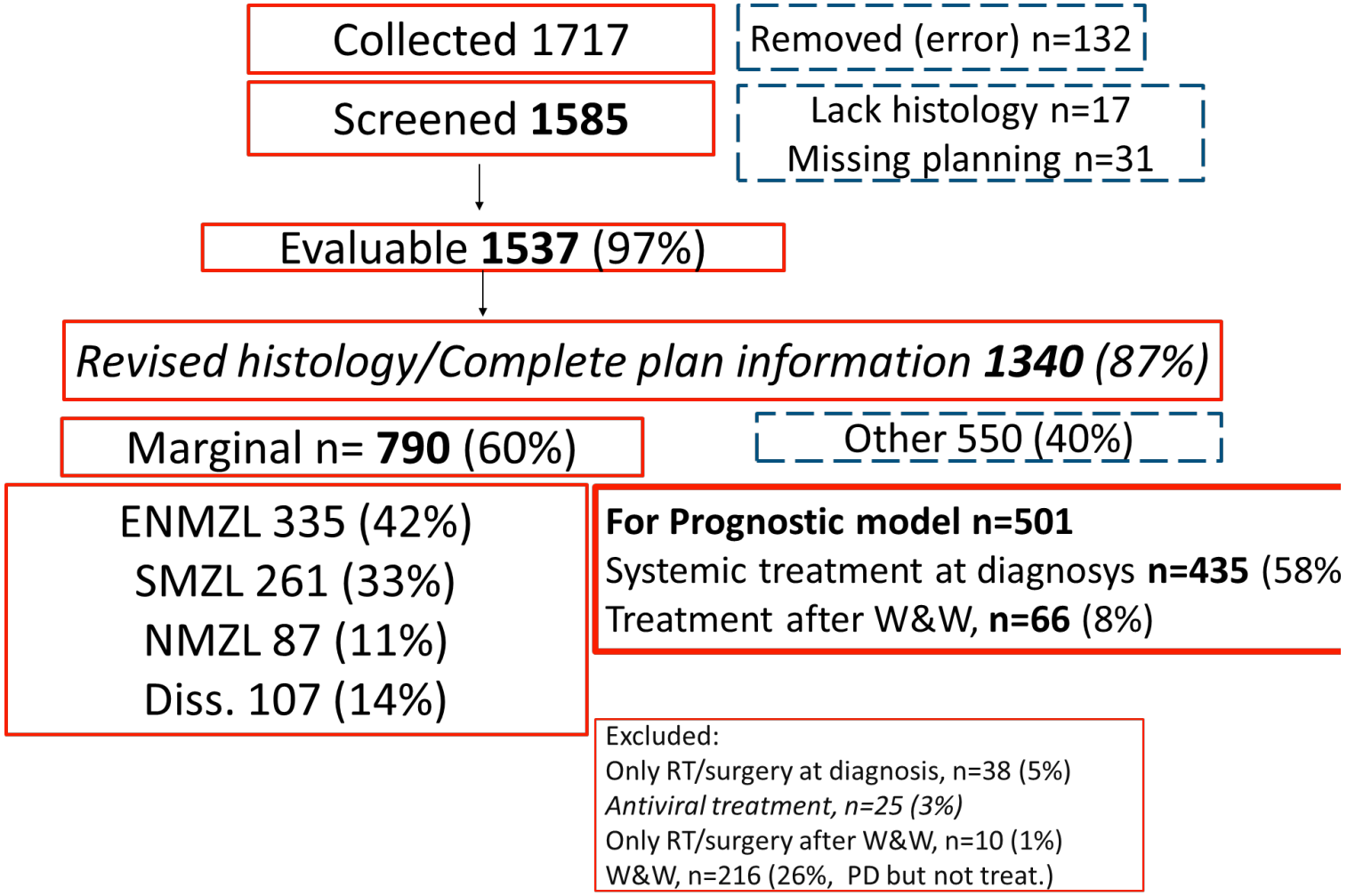
- any MZL,
- adult age,
- start of systemic therapy (at diagnosis or after W&W)

## Exclusion criteria

- histology other than MZL,
- local treatment (RT),
- antibiotics,
- observation without any systemic therapy.

Main study endpoint: ***Progression free survival (PFS)*** calculated for all patients requiring systemic therapy from the date of treatment start to disease progression or death for any cause.

# Patients' flow



# Patient's characteristics and treatment details (n=501)

| Covariate | Status | *Missing (n)* | N | % |
|---|---|---|---|---|
| Age | >70 | | 202 | **40** |
| Sex | M | - | 243 | **49** |
| Stage | III-IV | *8* | 398 | **81** |
| Extranodal sites | >1 | *8* | 90 | **18** |
| Nodal sites | >2 | *9* | 165 | **34** |
| Symptoms | B | *11* | 102 | **21** |
| LDH | >UNL | *18* | 154 | **32** |
| ALC | <1 $10^9$/L | *21* | 99 | **21** |
| Hemoglobin | <12 mg/dL | *12* | 204 | **42** |
| Platelets | <100 $10^9$/L | *12* | 71 | **15** |
| Treatment | At diagnosis | - | 435 | **87** |
| | From W&W | | 66 | **13** |
| MZL subtype | ENMZL | - | 197 | **39** |
| | SMZL | | 166 | **33** |
| | NMZL | | 60 | **12** |
| | Diss.MZL | | 78 | **16** |

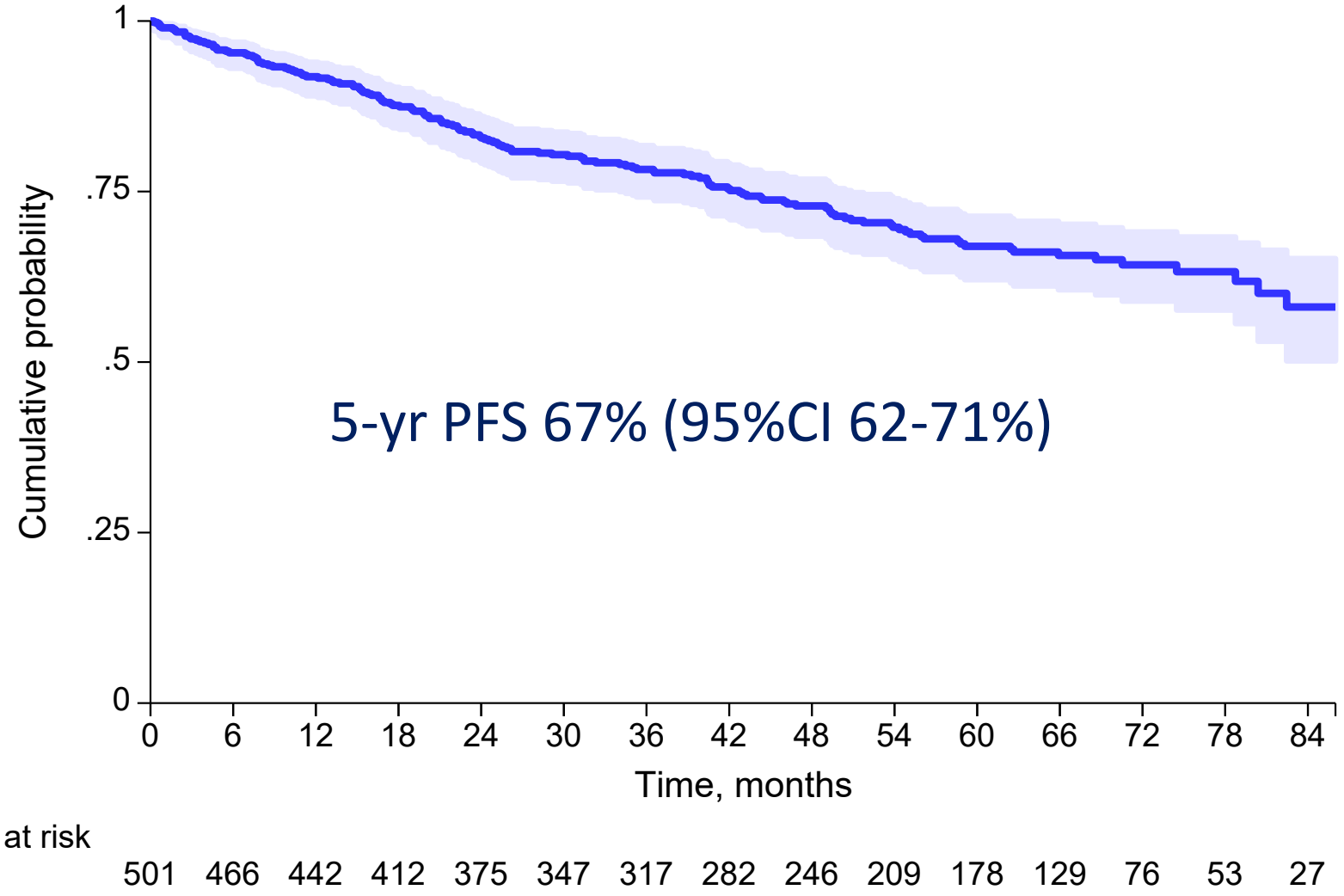
| | At diagnosis | After W&W | Total |
|---|---|---|---|
| Treatment | n (%) | n (%) | n (%) |
| Mono-alkylating | 29 (6.7) | 4 (6.1) | 33 (6.6) |
| Mono-rituximab | 43 (9.9) | 7 (10.6) | 50 (10.0) |
| R-alkylating | 118 (27.1) | 3 (4.6) | 121 (24.1) |
| R-CHOP like | 59 (13.6) | 10 (15.1) | 69 (13.8) |
| R-bendamustine | 179 (41.1) | 29 (43.9) | 208 (41.5) |
| R-fludarabine | 4 (0.9) | 5 (7.6) | 9 (1.8) |
| Others | 3 (0.7) | 8 (12.1) | 11 (2.2) |
| Total | **435** | **66** | **501** |

Rituximab was used in: 91.2%
Immunochemotherapy regimens were used in: 81.2%

**Legend to table:** LDH, Lactic Dehydrogenase; ALC, Absolute Lymphocyte counts; UNL, Upper Normal Limit; SMZL, Splenic Marginal Zone Lymphoma; ENMZL. Extranodal Marginal zone Lymphoma; NMZL, Nodal Marginal Zone Lymphoma; Diss, Disseminated; B2M beta2-microglobuline; LoDLIN, Longest diameter of largest lymphonode

# Progression Free Survival from treatment start

N=501: Median follow up 61 mo (range 1-114) ; # events 150



# Multivariable analysis of PFS

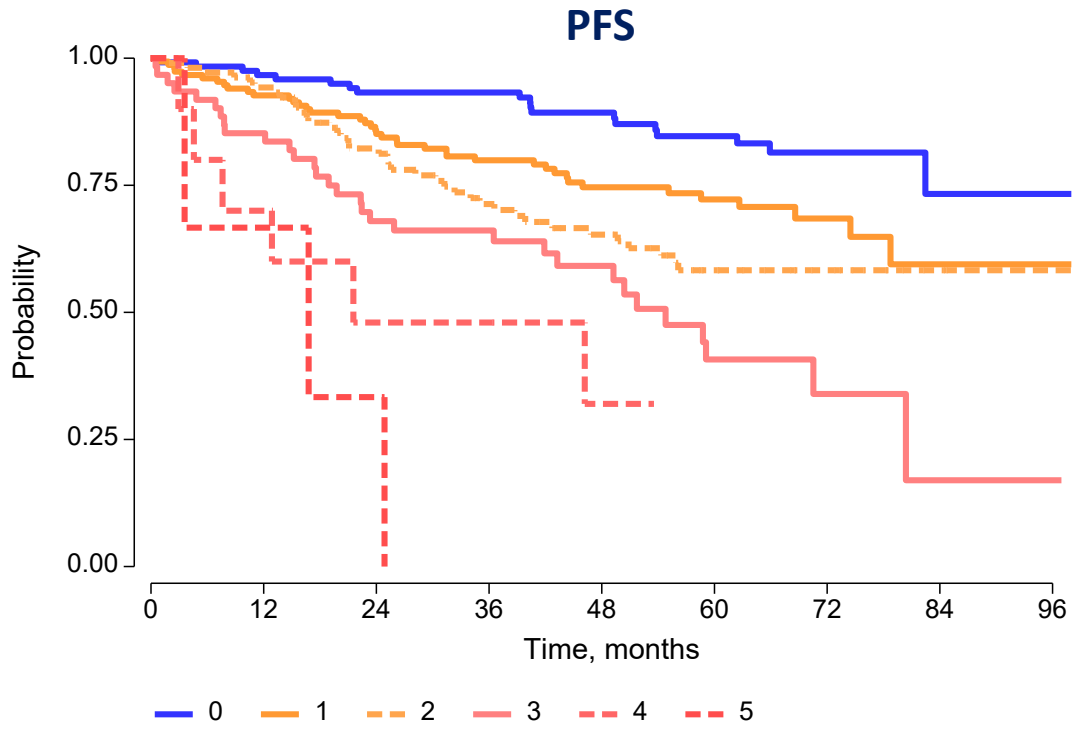
Cases with complete details for 12 covariates (N=456, 138 events)

| Covariate | Status | Multivariable | | Final model | |
|---|---|---|---|---|---|
| | | HR (95%CI) | P | HR (95%CI) | P |
| Age | >70 | 1.40 (0.98-1.99) | 0.061 | | |
| Stage | III-IV | 1.78 (0.97-3.30) | 0.064 | | |
| Extranodal sites | >1 | 0.77 (0.48-1.26) | 0.305 | | |
| Nodal sites | >2 | 1.06 (0.72-1.55) | 0.781 | | |
| Symptoms | B | 1.38 (0.93-2.04) | 0.110 | | |
| **LDH** | >UNL | 1.54 (1.06-2.25) | 0.025 | 1.60 (1.12-2.30) | 0.011 |
| **ALC** | <1 $10^9$/L | 1.58 (1.07-2.35) | 0.022 | 1.72 (1.17-2.53) | 0.006 |
| **Hemoglobin** | <12 g/dL | 1.36 (0.92-2.01) | 0.122 | 1.61 (1.13-2.30) | 0.009 |
| **Platelets** | <100 $10^9$/L | 1.88 (1.17-3.04) | 0.009 | 1.86 (1.18-2.92) | 0.007 |
| **MZL subtype** | ENMZL | 1.00 | | | |
| | SMZL | 0.75 (0.43-1.33) | 0.330 | Ref. EN/S-MZL | |
| | NMZL/Diss. | 1.46 (0.99-2.16) | 0.059 | 1.66 (1.17-2.36) | 0.004 |
| | **AIC** | **1543.4** | | **1540.4** | |
| | | | | **LR test (df 5)** | **0.171** |

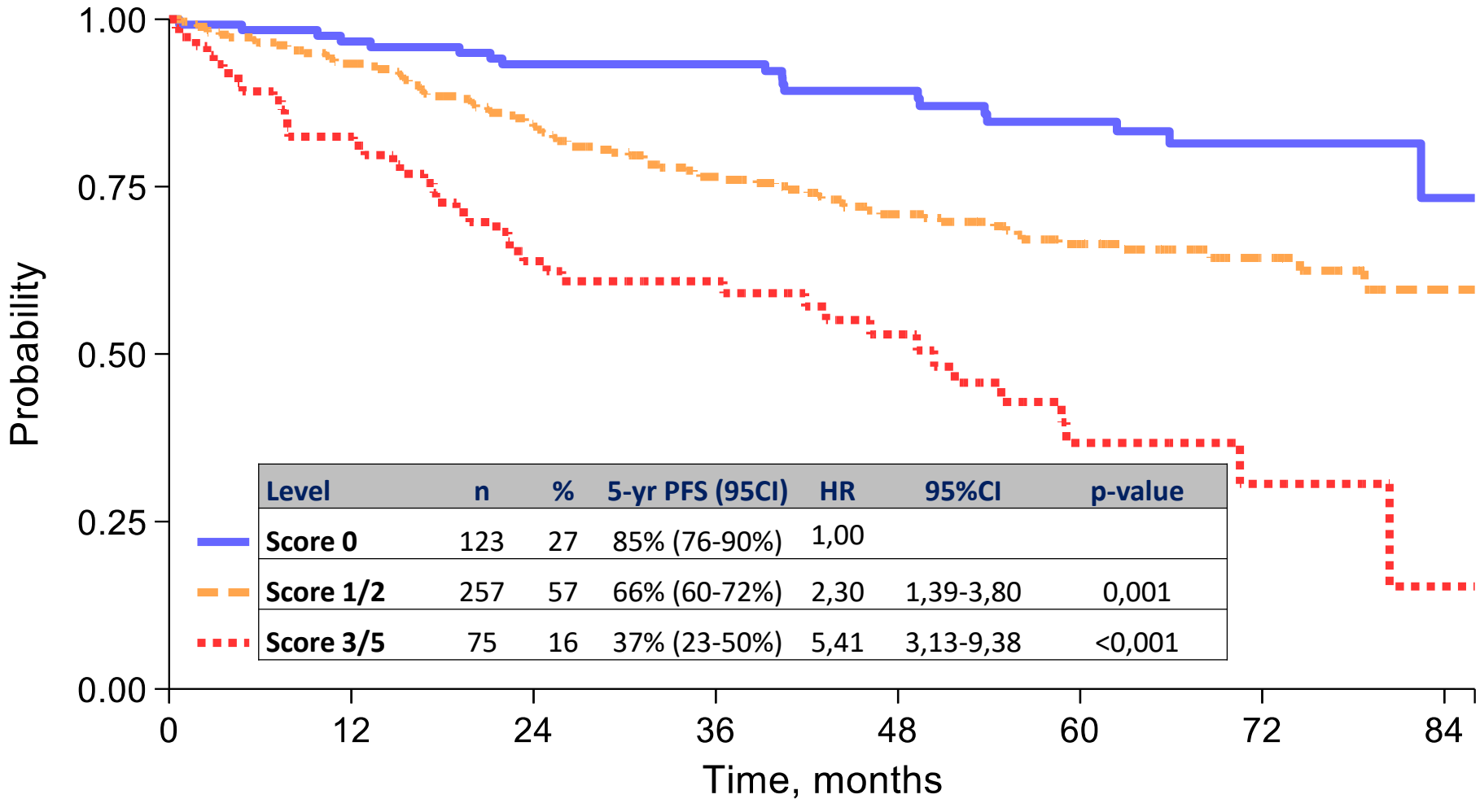
**Legend to table:** LDH, Lactic Dehydrogenase; ALC, Absolute Lymphocyte counts; UNL, Upper Normal Limit, NMZL, Nodal Marginal Zone Lymphoma; Diss, Disseminated;

# Building of the Marginal Zone Lymphoma International Prognostic Index (MZL-IPI)

| Score level | N (%) [#fail] | 5-yr PFS% (95%CI) |
|---|---|---|
| 0 | 123 (27) [19] | 85 (76-90) |
| 1 | 151 (33) [41] | 72 (63-79) |
| 2 | 107 (23) [38] | 58 (47-68) |
| 3 | 61 (13) [31] | 41 (26-55) |
| 4 | 11 (2) [6] | NA |
| 5 | 3 (1) [3] | NA |
| Total | 456 | - |



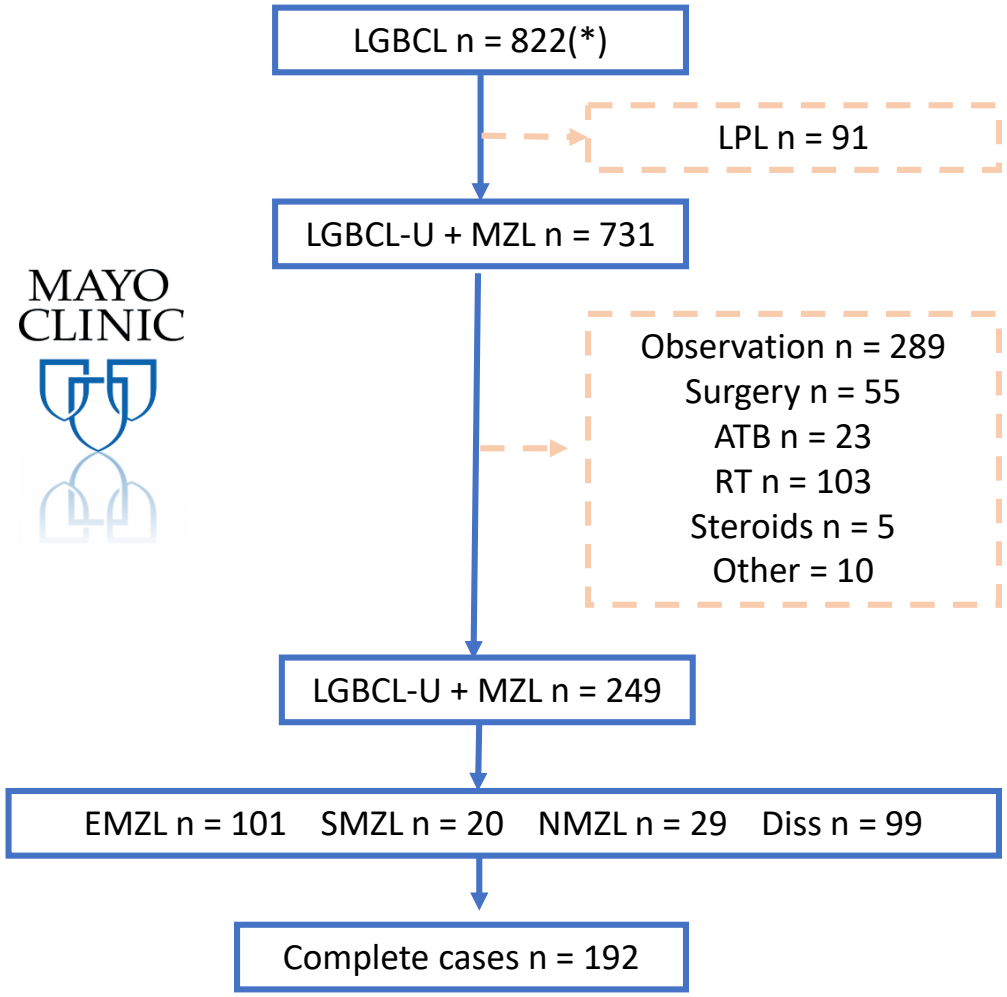
# PFS According to MZL-IPI groups




| Level | n | % | 5-yr PFS (95CI) | HR | 95%CI | p-value |
|---|---|---|---|---|---|---|
| Score 0 | 123 | 27 | 85% (76-90%) | 1,00 | | |
| Score 1/2 | 257 | 57 | 66% (60-72%) | 2,30 | 1,39-3,80 | 0,001 |
| Score 3/5 | 75 | 16 | 37% (23-50%) | 5,41 | 3,13-9,38 | <0,001 |

# Building of the independent validation set

## A Spore/MER database of MZLs

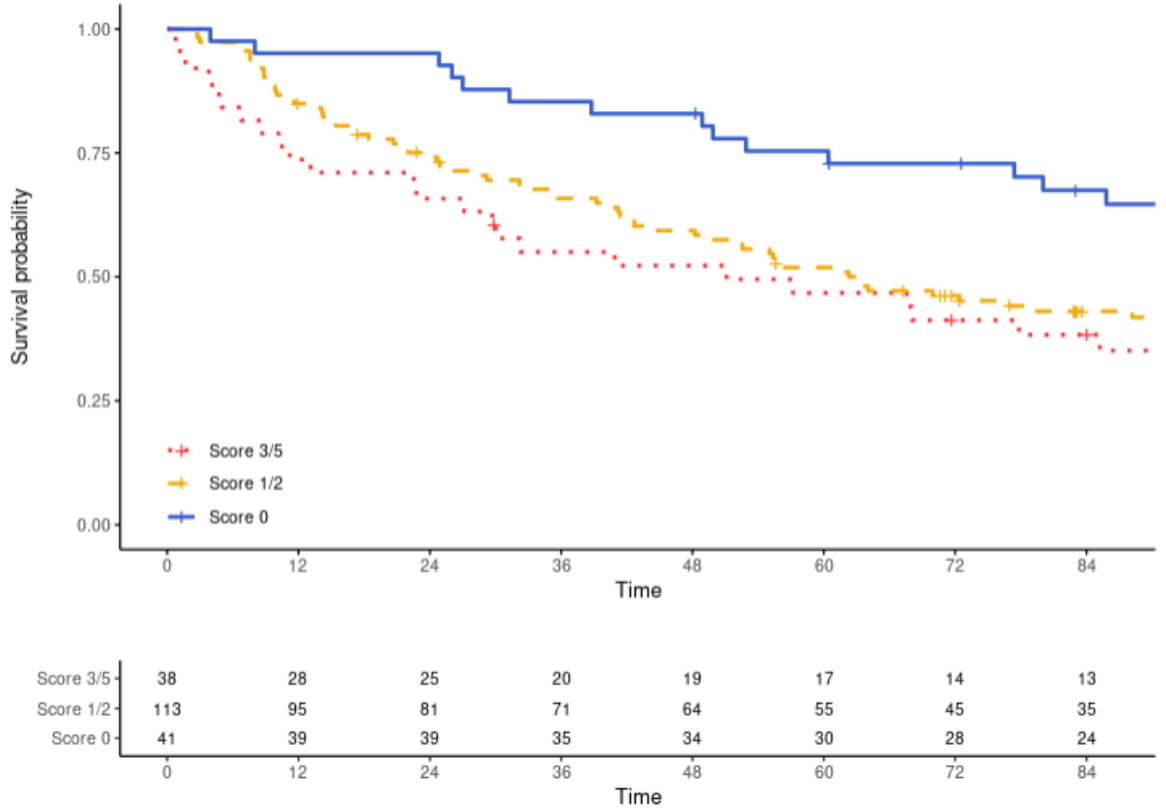



| Covariate | Status | *Missing (n)* | N | % |
|---|---|---|---|---|
| Age | >70 | | 73 | 29 |
| Sex | M | | 120 | 48 |
| Stage | III-IV | *5* | 183 | 75 |
| Extranodal sites | >1 | | 75 | 30 |
| Nodal sites | >4 | *2* | 13 | 13 |
| Symptoms | B | | 39 | 16 |
| LDH | >UNL | *43* | 45 | 22 |
| ALC | <1 $10^9$/L | *31* | 57 | 26 |
| Hemoglobin | <12 mg/dL | *33* | 95 | 44 |
| Platelets | <100 $10^9$/L | *17* | 23 | 10 |
| MZL subtype | SMZL/ENMZL | - | 121 | 49 |
| | NMZL/Diss. | | 128 | 51 |
| Treatment | AntiCD20 | | 99 | 40 |
| | ImmunoCT | | 114 | 46 |
| | Other | | 36 | 14 |

# MZL-IPI validation on the SPORE/MER dataset

5-yr PFS 57% (95%CI 51% - 64%)

| | Total | % | 5-yr PFS% (95%CI) | HR (95% CI) | p |
|---|---|---|---|---|---|
| **Low (0 RF)** | 41 | 21.3 | 75 (63-90) | 1.00 | |
| **Int. (1-2 RF)** | 113 | 58.8 | 52 (43-62) | 1.57 (0.97-2.54) | 0.068 |
| **High (3-5 RF)** | 38 | 19.8 | 47 (33-66) | 2.04 (1.15-3.62) | 0.014 |



# Prognostic role of MZL-IPI for Overall survival

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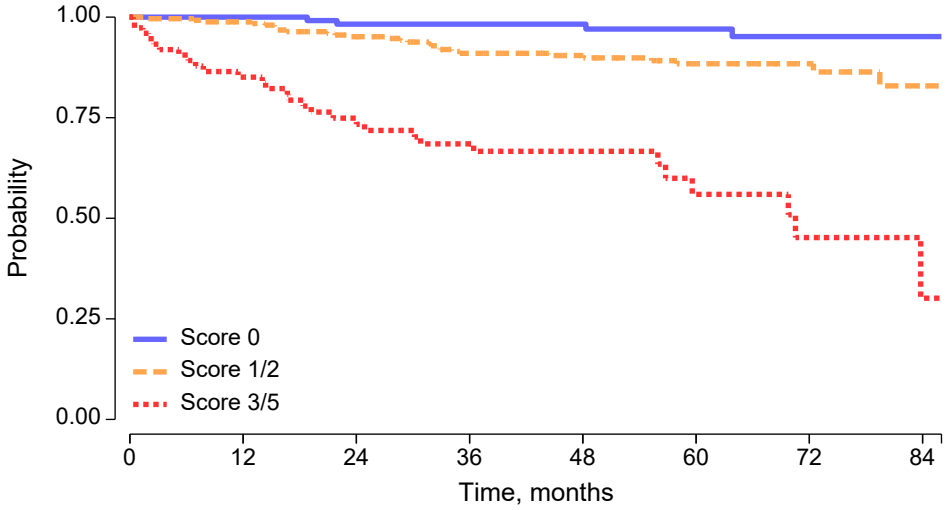


| Score group | 5-yr OS (95%CI) | HR (95%CI | p |
|---|---|---|---|
| Low 0 | 97 (91-99) | 1.00 | |
| Intermediate 1-2 | 88 (83-92) | 3.46 (1.21-9.89) | 0.020 |
| High 3/5 | 56 (40-69) | 17.2 (6.04-49.0) | <0.001 |
| High vs Interm. | | 4.97 (2.94-8.42) | <0.001 |

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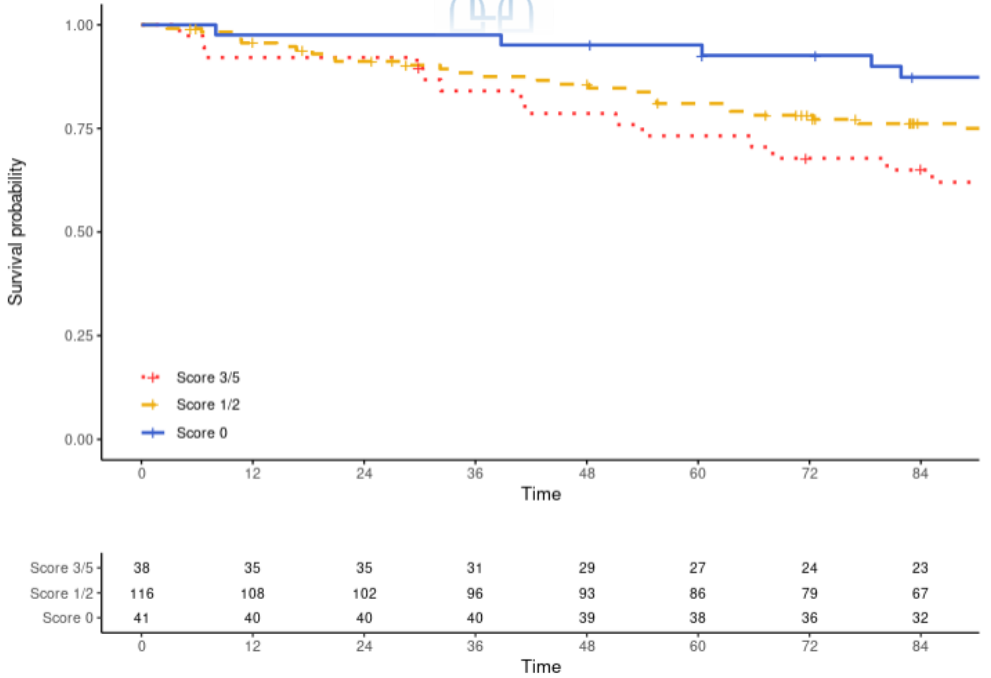


| Score group | 5-yr OS (95%CI) | HR (95%CI | p |
|---|---|---|---|
| Low 0 | 95 (89-100) | 1.00 | |
| Intermediate 1-2 | 81 (74-89) | 1.52 (0.77-3.01) | 0.059 |
| High 3/5 | 73 (60-89) | 2.72 (1.29-5.74) | 0.008 |
| High vs Interm. | | 1.76 (1.007-3.085) | 0.47 |

# Conclusions

- Anemia, Thrombocytopenia, Lymphocytopenia, elevated LDH, and EN or diss MZL subtype are independent risk factors (RF) for shorter PFS in MZL patients in need of therapy.
- Combined together the 5 RFs allow to build the MZL-IPI which identifies 3 patients groups at different risk of PFS
- The MZL-IPI is internally validated and its prognostic role is confirmed on a independent series of MZLs (SPORE-MER cohort)
- The MZL-IPI has better prognostic performance vs conventional prognostic indexes and is prognostic for OS
- We support the use of the MZL-IPI for future studies in MZLs

Die Kurzpräsentationen sind online unter

**www.lymphome.de/icml2023**

Für den Inhalt verantwortlich:

Prof. Dr. med. Christian Buske

Institut für Experimentelle Tumorforschung | Universitätsklinikum Ulm

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