Kompetenznetz Maligne Lymphome


Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

## KML-Expert:innen berichten

# 17th ICML 2023 LUGANO

Kompetenznetz Maligne Lymphome

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Expert:innen berichten zu Lymphomen & Leukämien

**Prof. Dr. med. Martin Dreyling**
Klinikum der Universität München

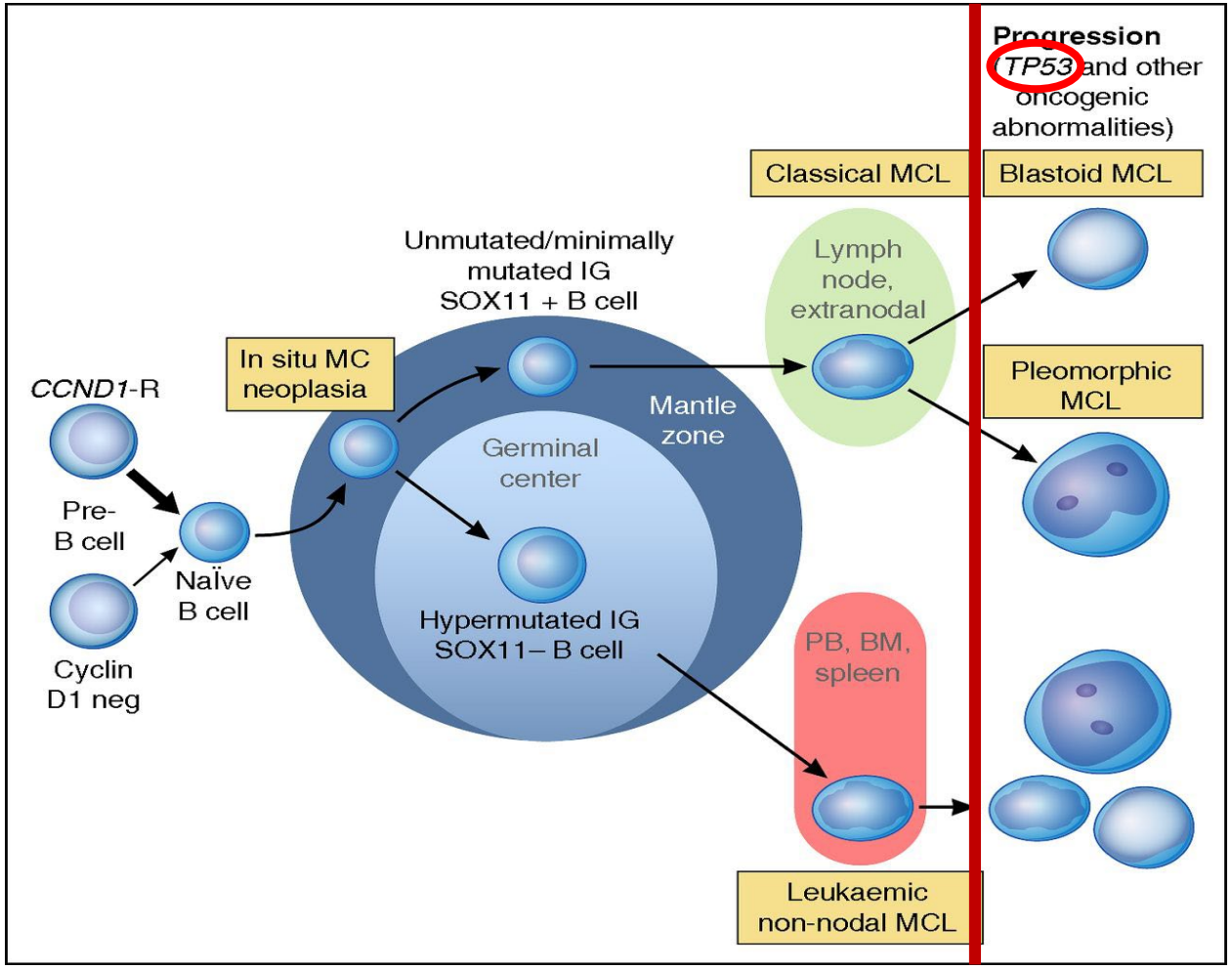
# Mantelzell-Lymphom (MCL)

# Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ICML2023 wird in Kooperation mit fünf unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

| | |
|---|---|
| **Research Support (institution)** | **Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche** |
| **Employee** | **-** |
| **Major Stockholder** | **-** |
| **Speakers Bureau** | **-** |
| **Speakers Honoraria** | **Astra Zeneca, Beigene, Gilead/Kite, Janssen, Lilly, Novartis, Roche** |
| **Scientific Advisory Board** | **Abbvie, Astra Zeneca, Beigene, BMS/Celgene, Gilead/Kite, Janssen, Lilly/Loxo, Novartis, Roche** |

# Mantle cell Lymphoma
## Spectrum of disease




***Dreyling, Ann Oncol 2017***

# Kapitel 1

First line MCL (younger patients)

# Mantle cell lymphoma
## Therapeutic algorithm

LMU KLINIKUM

| 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)*

# Very Long-term follow-up of rituximab maintenance in young patients with mantle cell lymphoma included in the LYMA trial, a LYSA study

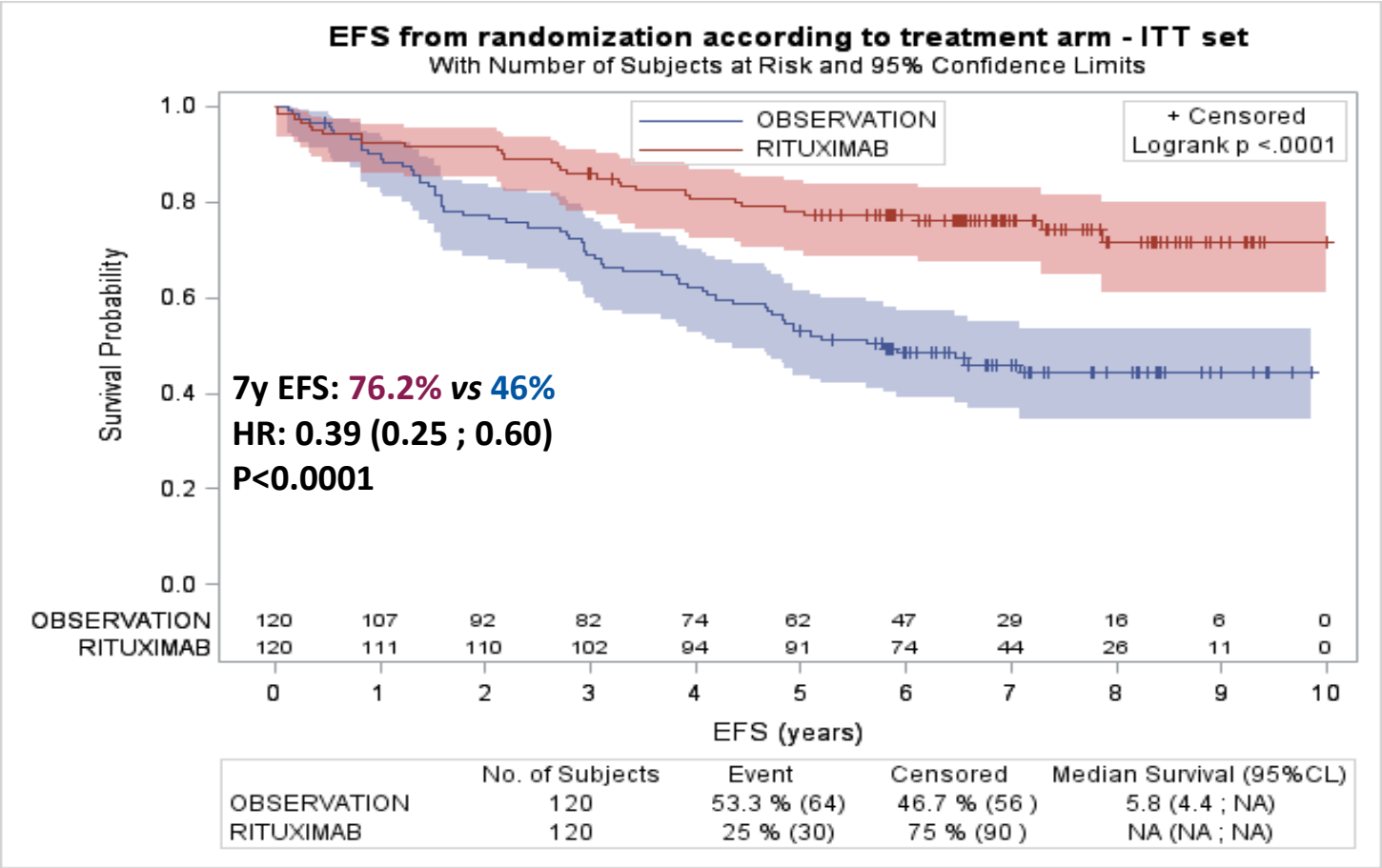
Clémentine Sarkozy, Catherine Thieblemont, Lucie Oberic, Anne Moreau, Krimo Bouabdallah, Gandhi Damaj, Thomas Gastinne, Vincent Ribrag, Olivier Casasnovas, Corinne Haioun, Roch Houot, Fabrice Jardin, Eric Van Den Neste, Morgane Cheminant, Franck Morschhauser, Mary Callanan, Hervé Guesquières, Remy Gressin, Olivier Hermine, and Steven Le Gouill.

ICML, Abstract 100, June 14th 2023

# EFS from randomization

**Median FU for living patients:**

- **from inclusion: 7.5 y (95% CI 7.4-7.7)**
- **from randomization: 7 y (95% CI 6.8-7.2)**



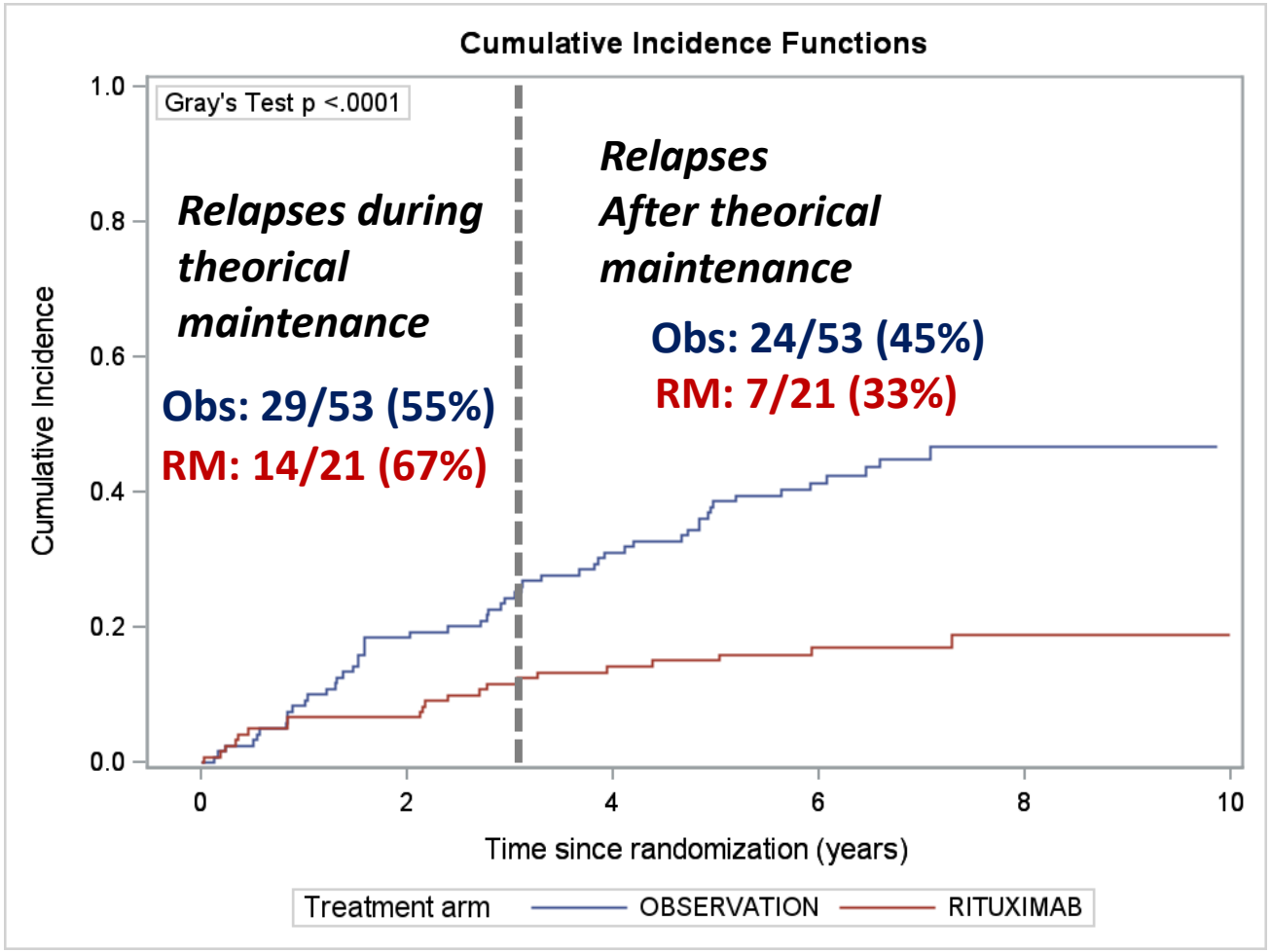

| Nature of first Event | Observation, N=64/120 (53%) | Rituximab N=30/120 (25%) |
|---|---|---|
| Relapse | 51 (80%) | 19 (63%) |
| Death w/o relapse | 9 (14%) | 6 (20%) |
| Serious infections | 4 (6%) | 4 (13%) |
| Life threatening allergy to R | 0 | 1 (4%) |



ICML, Abstract 100, June 14th 2023

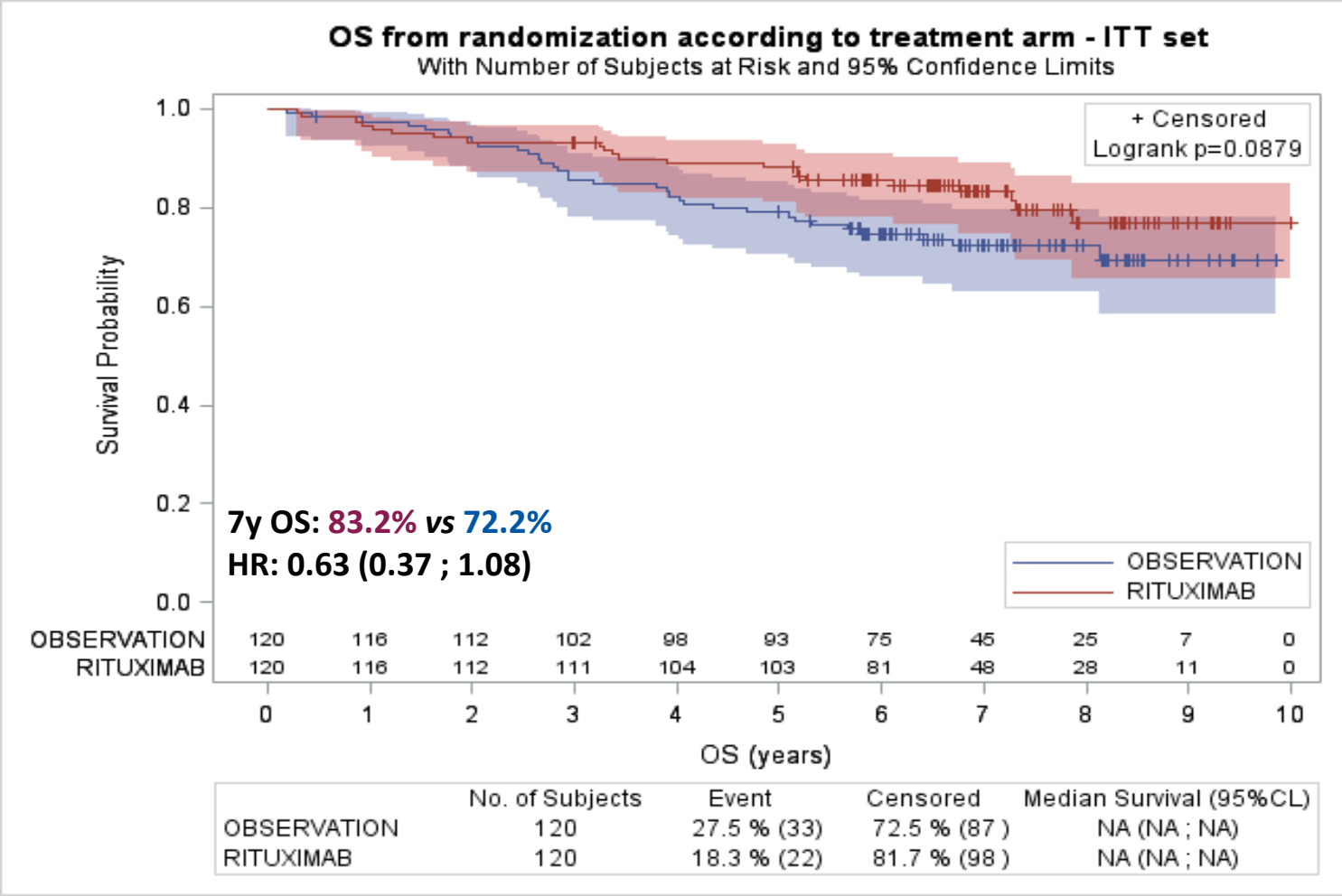
# Relapses during *versus* after 3 years of theorical RM

**The end of RM was not associated with an increase of the relapses**




ICML, Abstract 100, June 14th 2023

# Overall Survival from randomization



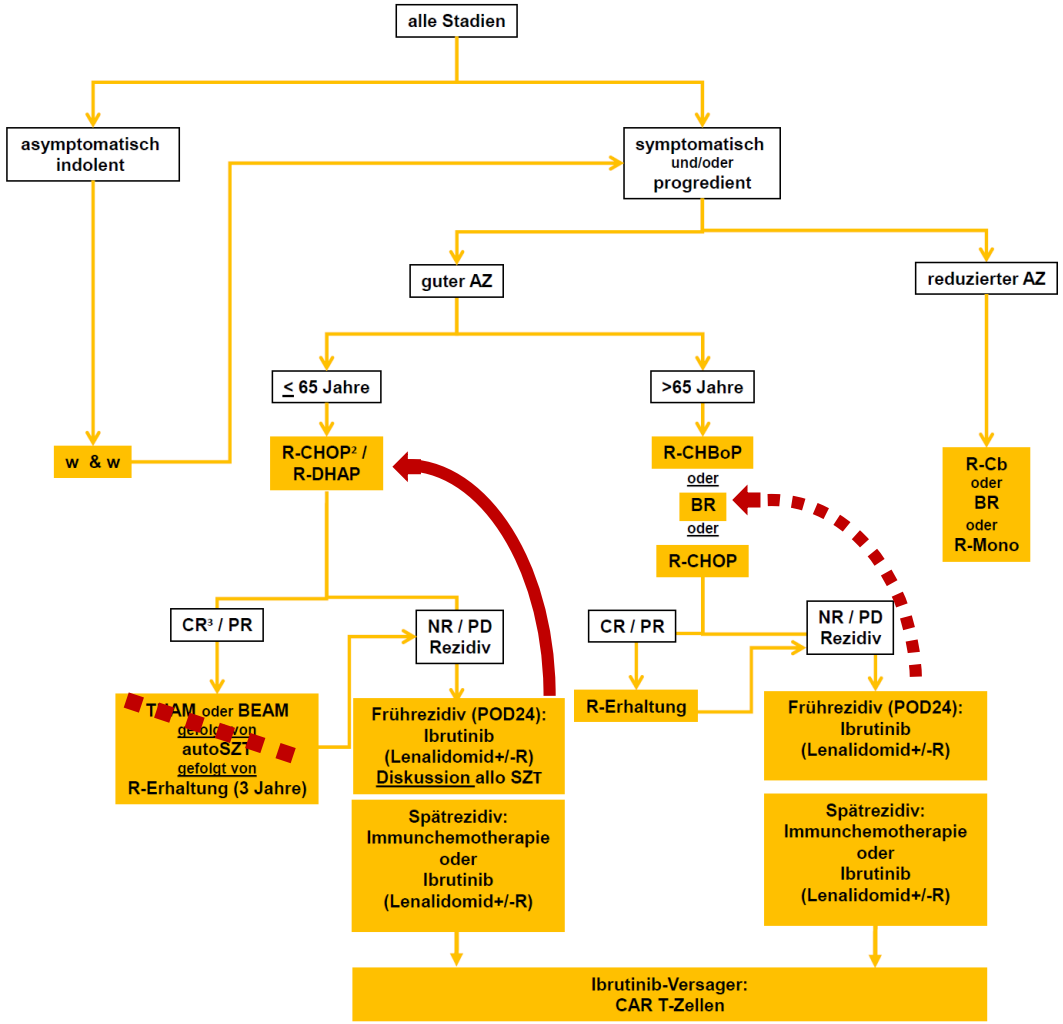

| Cause of death | Observation, N=33/120 (27.5%) | Rituximab, N=22/120 (18%) |
|---|---|---|
| Lymphoma | 16 (48.5%) | 11 (50%) |
| Secondary Malignancies | 6 (18%) | 7 (32%) |
| Treatment related: infectious | 3 (9%) | 1 (5%) |
| Vascular event | 2 (6%) | 0 (0%) |
| Treatment related during allotransplant | 2 (6%) | 2 (9%) |
| Other | 2 (6%)** | 1 (4%)* |
| Unknown | 2 (6%) | 0 |

*Suicide, **acute respiratory destress, car accident,


ICML, Abstract 100, June 14th 2023

# Mantle cell Lymphoma

## Onkopedia 2023



# Kapitel 2

First line MCL (targeted therapy)

# Five-year update of the first-line IMCL-2015 GELTAMO study. Prolonged molecular and clinical responses were observed after MRD-driven ibrutinib discontinuation

**Eva Giné,** Alejandro Medina Herrera, Fátima de la Cruz, Ana Jiménez Ubieto, Javier López Jimenez, Alejandro Martín, M José Terol, Eva Gonzalez Barca, María Casanova, Adolfo de la Fuente, Ana Marín Niebla, Ana Muntañola, Tomás José González-López, Marta Aymerich, Xavier Setoain, Montserrat Cortés-Romera, Amanda Rotger, Sonia Rodríguez, Ferran Nadeu, Cristina López, Sílvia Beà, Ramon García Sanz, Elias Campo, Armando López-Guillermo.

*H. Clínic de Barcelona, IDIBAPS, CIBERONC; H. Clínico de Salamanca, IBMCC, IBSAL, CIBERONC ; H. Virgen del Rocío, Sevilla; H. U 12 de Octubre, Madrid; H. U. Ramón y Cajal, Madrid; H. Clínico de Salamanca, IBMCC, IBSAL, CIBERONC ; H. Clínico de Valencia, INCLIVA; H. Duran i Reynals, ICO, Hospitalet Llobregat; H. Costa del Sol, Marbella; H. MD Anderson Cancer Center, Madrid; H. U. Vall d'Hebrón, VHIO; H. U. Mutua de Terrassa ; H. U. Burgos; H. Clínic de Barcelona, CIBERBBN; H. U. Bellvitge, Hospitalet de Llobregat; H. Gregorio Marañon, Madrid; H. Clínic de Barcelona, IDIBAPS, CIBERONC; H. Clínico de Salamanca, IBMCC, IBSAL, CIBERONC ; H. Clínic de Barcelona, IDIBAPS, CIBERONC, University of Barcelona.*

**NCT 02682641, EudraCT: 2015-004158-17**

***Sponsor: Grupo Español de Linfomas y Trasplante de Médula Ósea***

***Janssen Clinical Investigator-Initiated Study (IIS) Research Support***

***egine@clinic.cat***

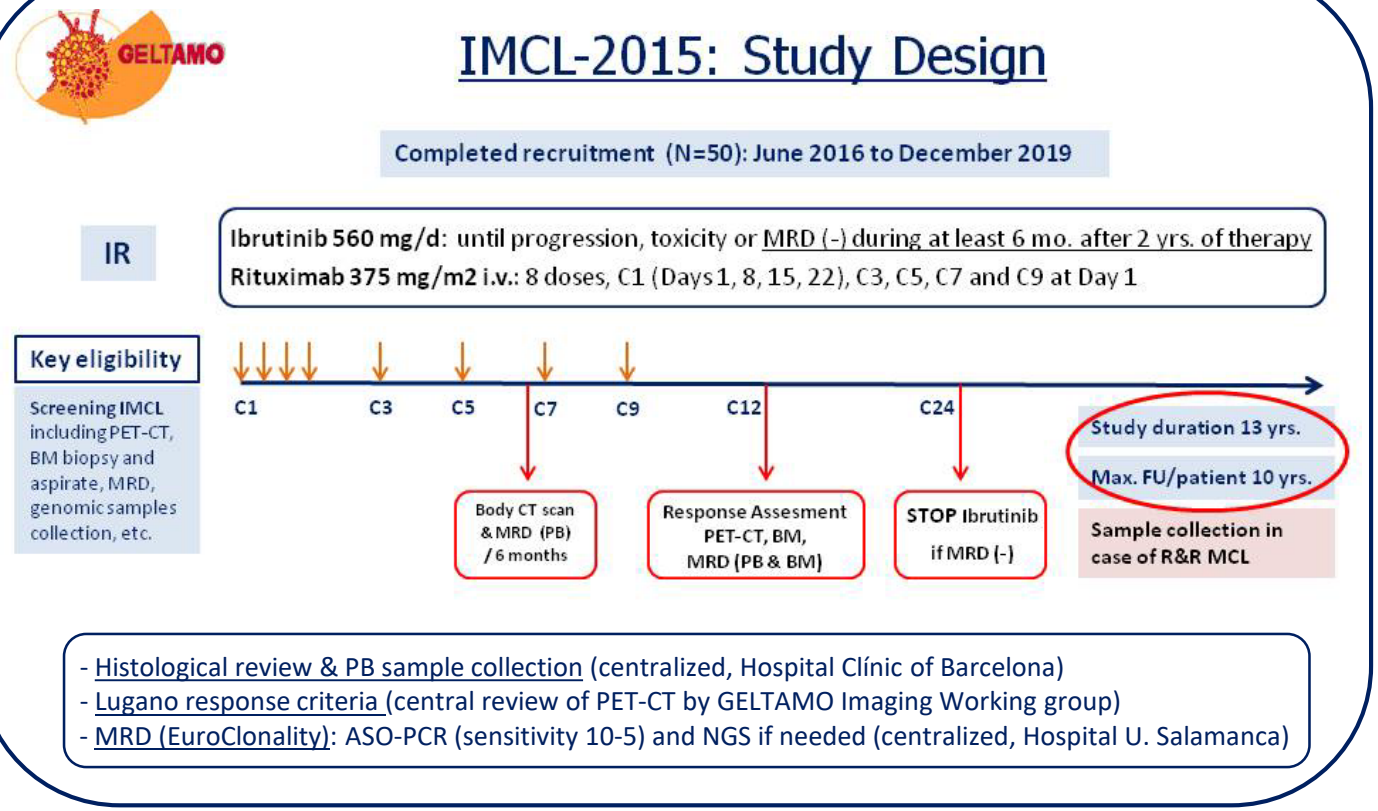
# IMCL-2015

**"Multicentric phase II trial to evaluate the efficacy and safety of Ibrutinib in combination with rituximab in patients with indolent clinical forms of Mantle Cell Lymphoma"**

**Phase II (N= 50 patients, 14 GELTAMO sites)**

- Upfront Ibrutinib + Rituximab combination in IMCL
- Biological studies: IGHV mutational study, DNA copy number, *WGS/WES* and epigenetic studies in PB samples (and tissue when possible) before treatment and in case of relapse

## IMCL-2015: Study Design

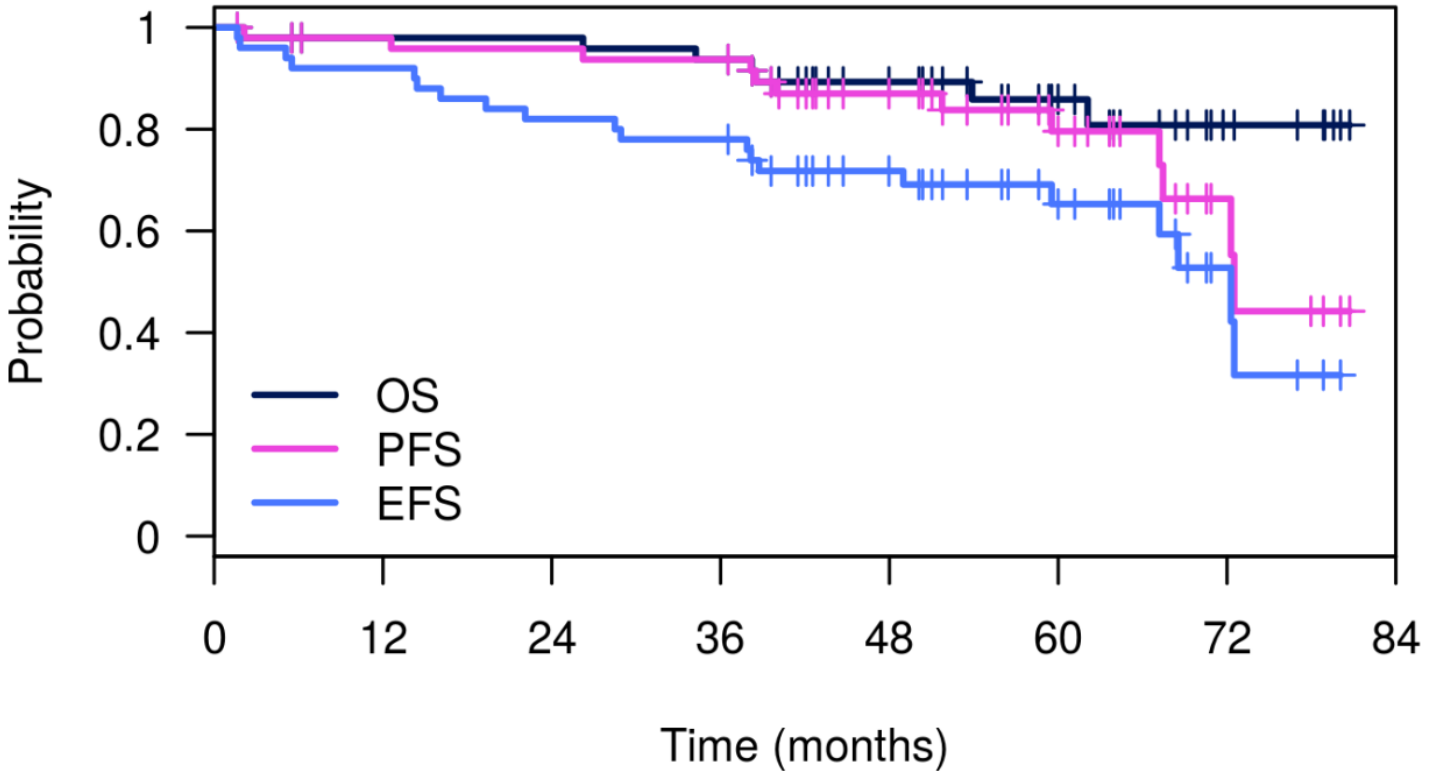



## Key inclusion and exclusion criteria:

- Asymptomatic MCL patients, no prior treatments, observation for at least 3 months
- Eligible both leukemic non nodal presentations and cases with lymph nodes < 3 cm and Ki67 < 30%
- Blastoid variants excluded

*E Giné et al, JCO 2022;40(11):1196-1205*

# IMCL-2015: SURVIVAL




**No. at risk:**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| OS | 50 | 46 | 46 | 44 | 31 | 19 | 7 | 0 |
| PFS | 50 | 46 | 45 | 44 | 30 | 18 | 6 | 0 |
| EFS | 50 | 46 | 41 | 39 | 27 | 16 | 5 | 0 |

5-yr OS: 86% (CI95%: 75-97)

5-yr PFS: 80% (CI95%: 66-93)

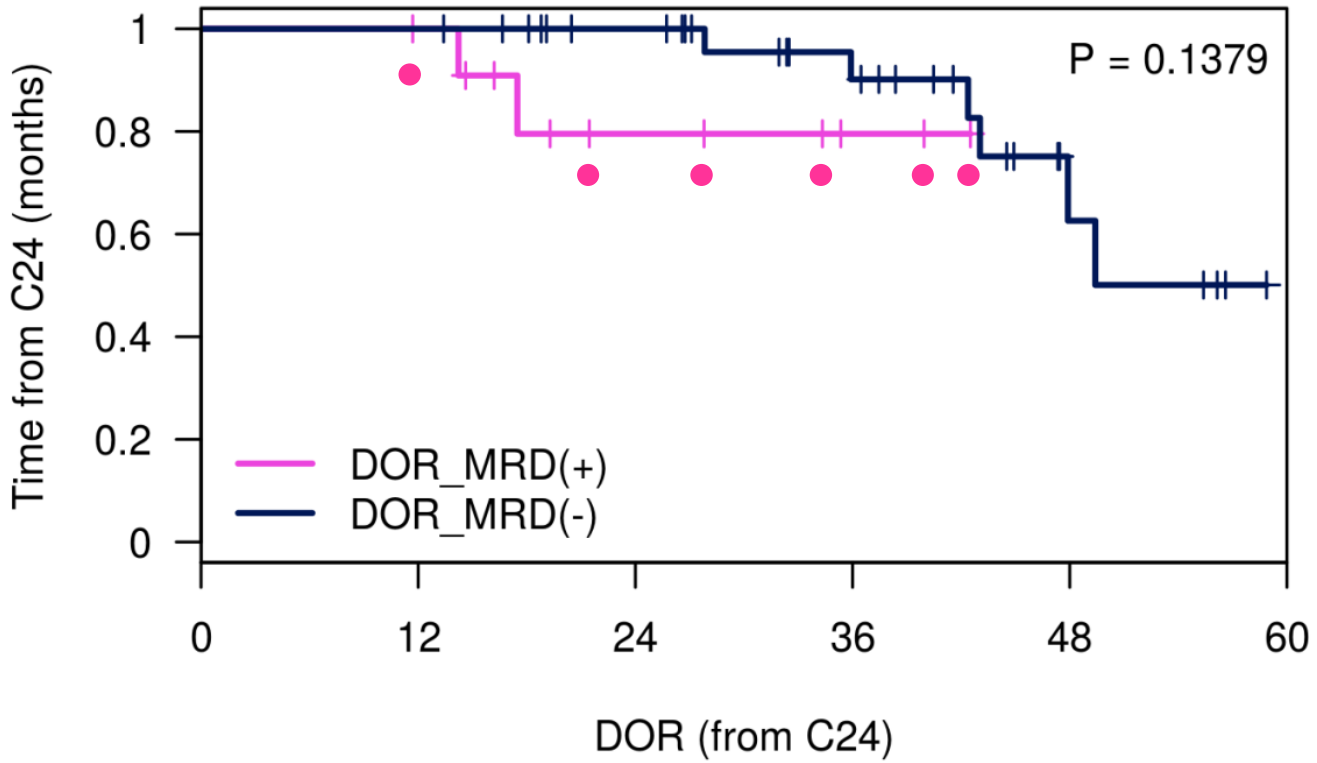
5-yr EFS: 65% (CI95%: 50-79)

**Median PFS: 72 months (CI 95%: 66-79)**

*(Data cut-off 15 March 2023)*

# IMCL-2015: DOR from C24 According to MRD Status and Ibrutinib Discontinuation

## DOR from C24 evaluation (n=44)




**No. at risk:**

| | | | | | | |
|---|---|---|---|---|---|---|
| DOR_MRD(+) | 12 | 11 | 5 | 2 | 0 | 0 |
| DOR_MRD(-) | 32 | 32 | 26 | 17 | 5 | 0 |

- **MRD (-) / Ibrutinib discontinuation (n=32)**
  - **Progression (n=6)**
- **MRD (+) / Ibrutinib ongoing (n=12)**
  - **Progression (n=2)**

- MRD (-): 20 /32 (63%) patients continue MRD (-) at last control

- MRD(+): 6/12 (50%) patients continue on Ibrutinib

● Ibrutinib ongoing

*Medians DOR: not reached*

***(Data cut-off 20 March 2023)***

# Kapitel 3

Relapsed high risk MCL (p53)

# Outcomes of autologous transplant, allogeneic transplant, and CAR T cell therapy in *TP53* altered mantle cell lymphoma: a multi-institution retrospective analysis

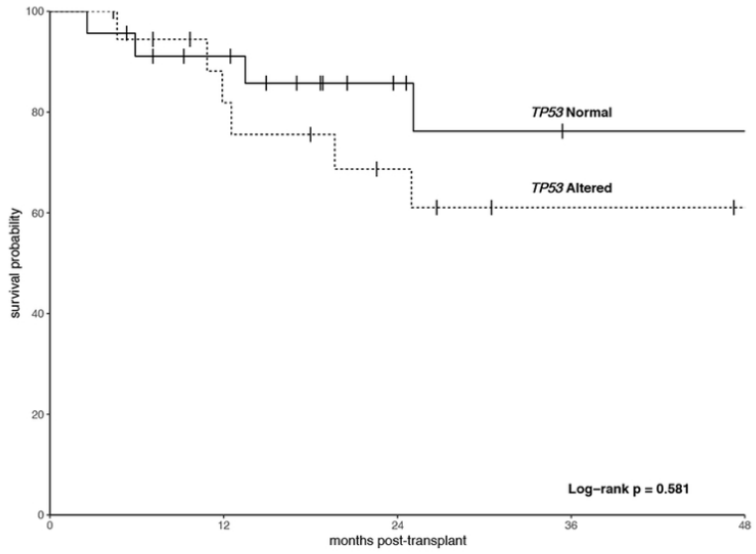
M. Messmer [1], A. Stack [1], M. Deng [2], E. Handorf [2], N. Kapoor [3], Y. Sawalha [3], A. M. Bock [4], Y. Wang [4], K. Graf [5], B. Greenwell [5], J. Cleveland [6], R. Advani [6], D. Adrianzen Herrera [7], E. Cai [8], M. Spinner [8], A. Hassan [9], S. Rajguru [9], M. S. Phillips [10], S. D. Smith [10], T. Brooks [11], D. Bond [3], B. Hill [11], J. Murphy [12], N. Wagner-Johnston [12], M. Zahid [13], F. T. Awan [13], P. Ramakrishnan Geethakumari [13], W. Tompkins [14], S. Deshpande [14], J. Svoboda [14], C. Ryu [15], J. Amengual [15], J. Anna [16], M. Kamdar [16], K. Goparaju [17], J. Martin [17], M. Burkart [18], R. Karmali [18], A. Khan [19], D. Modi [19], M. Nickel [20], B. Hambley [20], K. Baron [21], H. Shah [21], D. Wallace [22], J. W. Friedberg [22], C. Hannah [23], V. Bachanova [23], N. Ghosh [24], S. Park [24], K. David [25], J. Darrah [26], R. I. Fisher [27], N. Khan [28]

[1] Fox Chase Cancer Center, Hematology/Oncology, Philadelphia, PA, United States of America, [2] Fox Chase Cancer Center, Biostatistics, Philadelphia, PA, United States of America, [3] Ohio State University, Columbus, OH, United States of America, [4] Mayo Clinic, Rochester, MN, United States of America, [5] Medical University of South Carolina, Charleston, SC, United States of America, [6] Stanford University, Palo Alto, CA, United States of America, [7] University of Vermont, Burlington, VT, United States of America, [8] University of California, San Francisco, San Francisco, CA, United States of America, [9] University of Wisconsin, Madison, WI, United States of America, [0] Fred Hutchinson Cancer Center, Seattle, WA, United States of America, [11] Cleveland Clinic, Cleveland, OH, United States of America, [12] Johns Hopkins University, Baltimore, MD, United States of America, [13] Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, United States of America, [14] University of Pennsylvania, Philadelphia, PA, United States of America, [15] Columbia University, New York, NY, United States of America, [16] University of Colorado, Aurora, CO, United States of America, [17] University Hospitals, Cleveland, OH, United States of America, [18] Northwestern University, Chicago, IL, United States of America, [19] Karmanos Cancer Center, Detroit, MI, United States of America, [20] University of Cincinnati, Cincinnati, OH, United States of America, [21] University of Utah, Salt Lake City, UT, United States of America, [22] Wilmot Cancer Institute, University of Rochester, Rochester, NY, United States of America, [23] University of Minnesota, Minneapolis, MN, United States of America, [24] Levine Cancer Institute, Charlotte, NC, United States of America, [25] Rutgers University, New Brunswick, NJ, United States of America, [26] Cedars-Sinai Cancer Center, Los Angeles, CA, United States of America, [27] Independent Consultant, Chicago, IL, United States of America, [28] Swedish Cancer Institute, Seattle, WA, United States of America

# Alternative Approaches

## Allo-HCT

- *TP53* alteration did not affect PFS or OS after allo-HCT in small single-institution study (Lin et al. Br J Haematol 2019)
- High morbidity and mortality – 20% 2-year non-relapse mortality

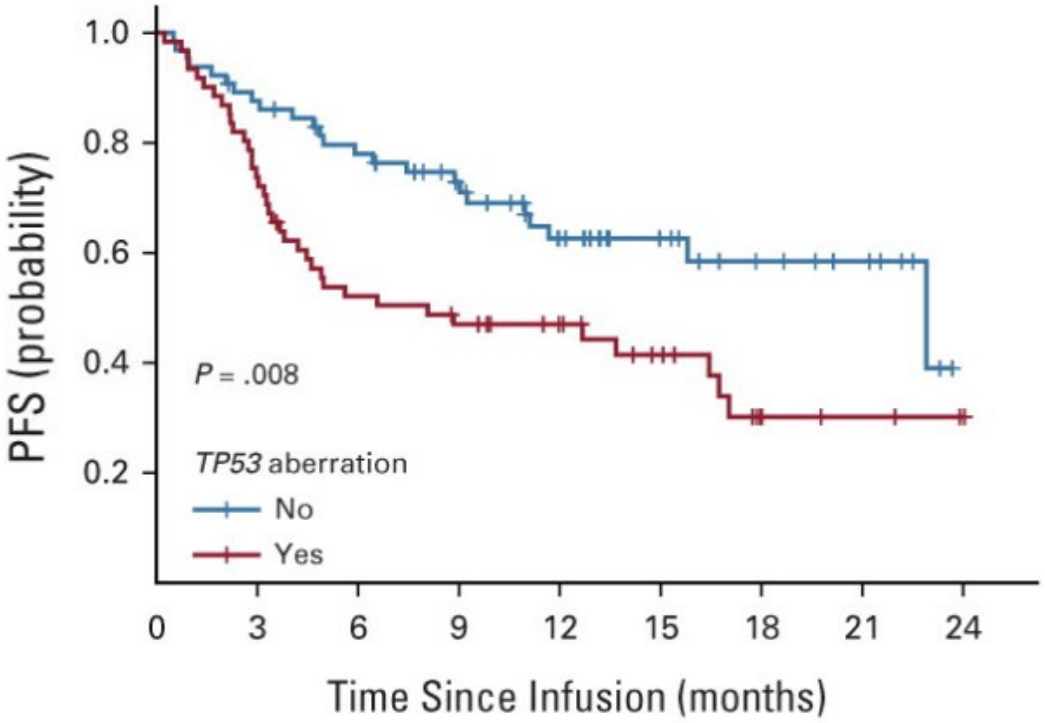



**Risk Table**

| *TP53* Status | 0-month | 12-month | 24-month | 36-month | 48-month |
|---|---|---|---|---|---|
| Negative | 23 | 18 | 10 | 7 | 7 |
| Positive | 19 | 13 | 9 | 6 | 5 |

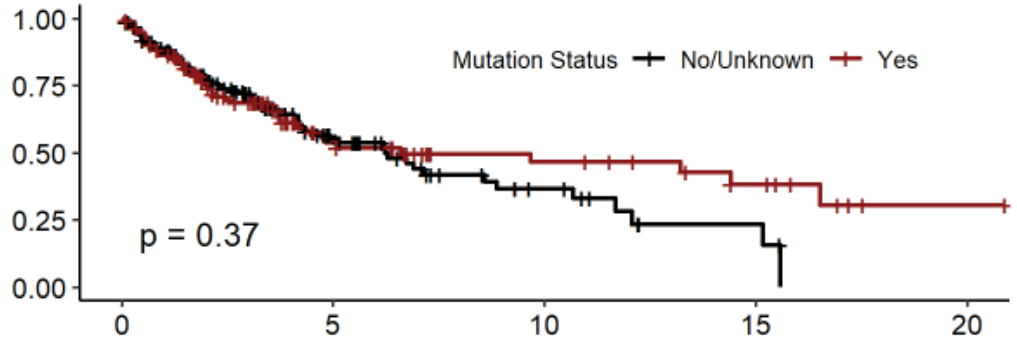
## CAR-T

- In Zuma-2, 2/6 patients with *TP53* mutation with ongoing response at updated analysis (Wang M et al. JCO 2023)
- *TP53* aberration (n = 61) associated with inferior PFS after Brexucabtagene Autoleucel in standard of care practice (Wang Y et al. JCO 2023)



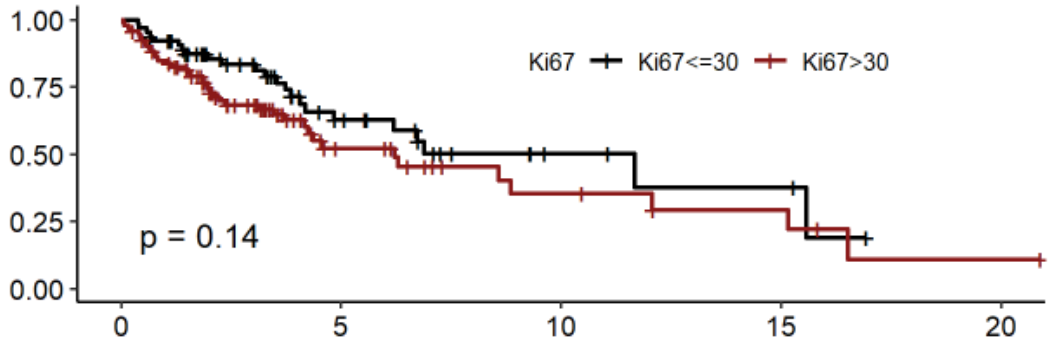
# Overall Survival – By Subgroup (n=254)

## *TP53* Mutated vs Other Alteration



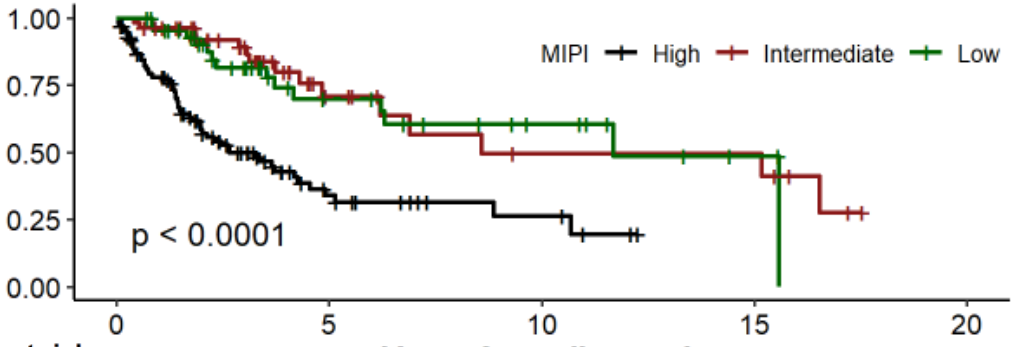

| Number at risk | | | | | |
|---|---|---|---|---|---|
| No/Unknown | 138 | 37 | 11 | 3 | 0 |
| Yes | 113 | 28 | 15 | 8 | 1 |

## Ki67



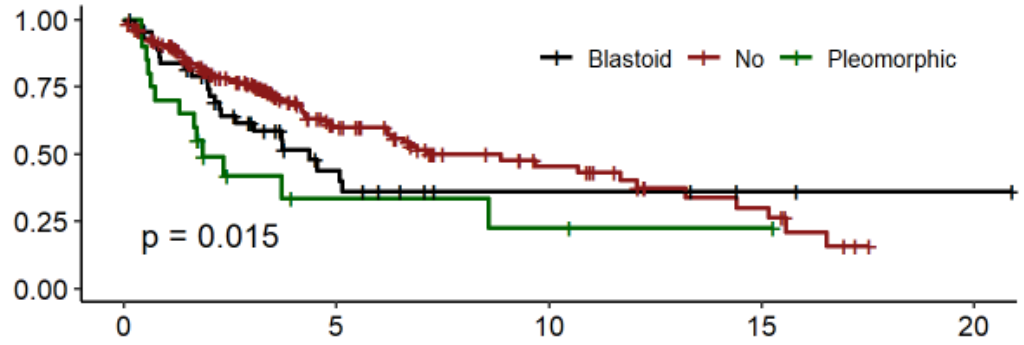

| Number at risk | | | | | |
|---|---|---|---|---|---|
| Ki67<=30 | 65 | 20 | 5 | 3 | 0 |
| Ki67>30 | 94 | 17 | 7 | 4 | 1 |

## MIPI Category




| Number at risk | | | | | |
|---|---|---|---|---|---|
| High | 100 | 14 | 5 | 0 | 0 |
| Intermediate | 54 | 13 | 6 | 6 | 0 |
| Low | 45 | 16 | 8 | 2 | 0 |

## Blastoid or Pleomorphic



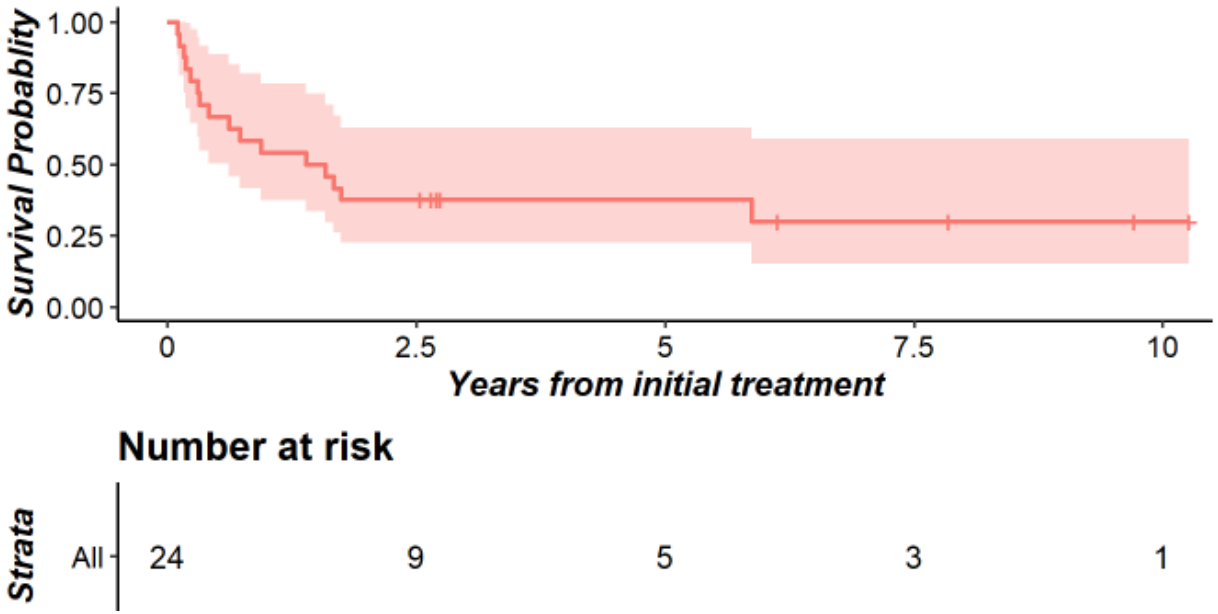

| Number at risk | | | | | |
|---|---|---|---|---|---|
| Blastoid | 45 | 11 | 4 | 2 | 1 |
| No | 186 | 51 | 20 | 8 | 0 |
| Pleomorphic | 20 | 3 | 2 | 1 | 0 |

# Allo-HCT

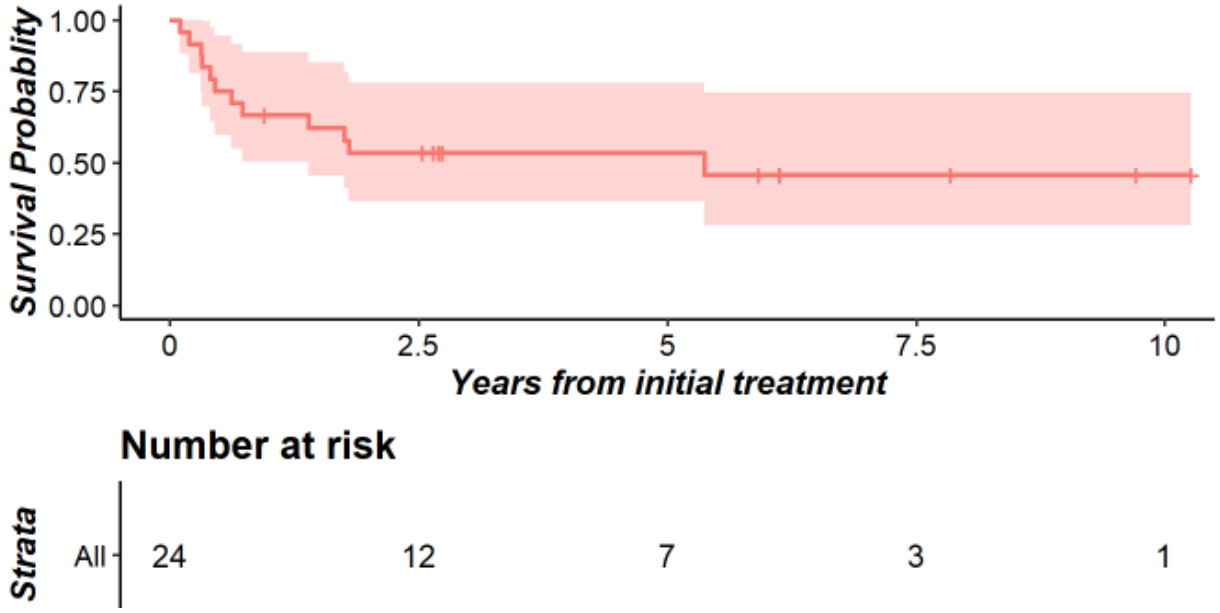
- 26 of 254 underwent allo-HCT
- 24 had confirmed *TP53* alteration prior to allo-HCT
- Median EFS 1.5 years (95% CI, 0.6 to NE)
- Median OS 5.4 years (95% CI, 1.4 to NE)
- 12 month non-relapse mortality – 17%

| | |
|---|---|
| Lines of prior therapy, median (range) | 2 (1-5) |
| Prior BTK inhibitor, No. (%) | 11 (46) |
| Prior CAR-T | 4 (17) |
| Matched | 17 (74) |
| Related | 12 (50) |
| Peripheral collection | 16 (70) |
| Myeloablative conditioning | 6 (25) |
| Post-transplant cyclophosphamide | 11 (46) |
| Antithymocyte globulin | 3 (13) |

## Event Free Survival




## Overall Survival

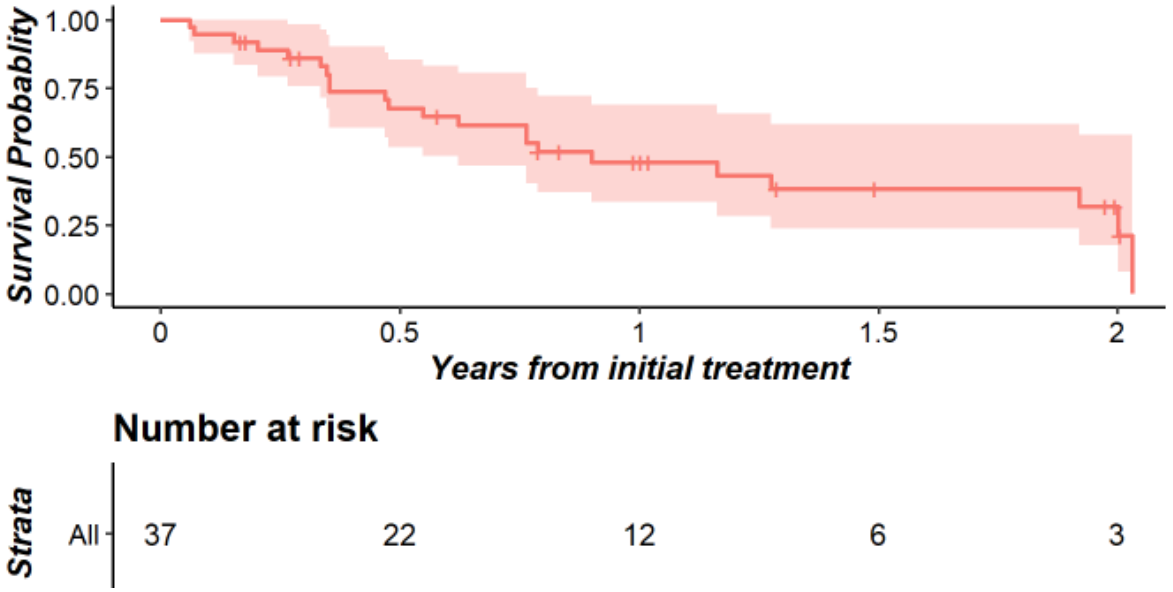


# CAR-T

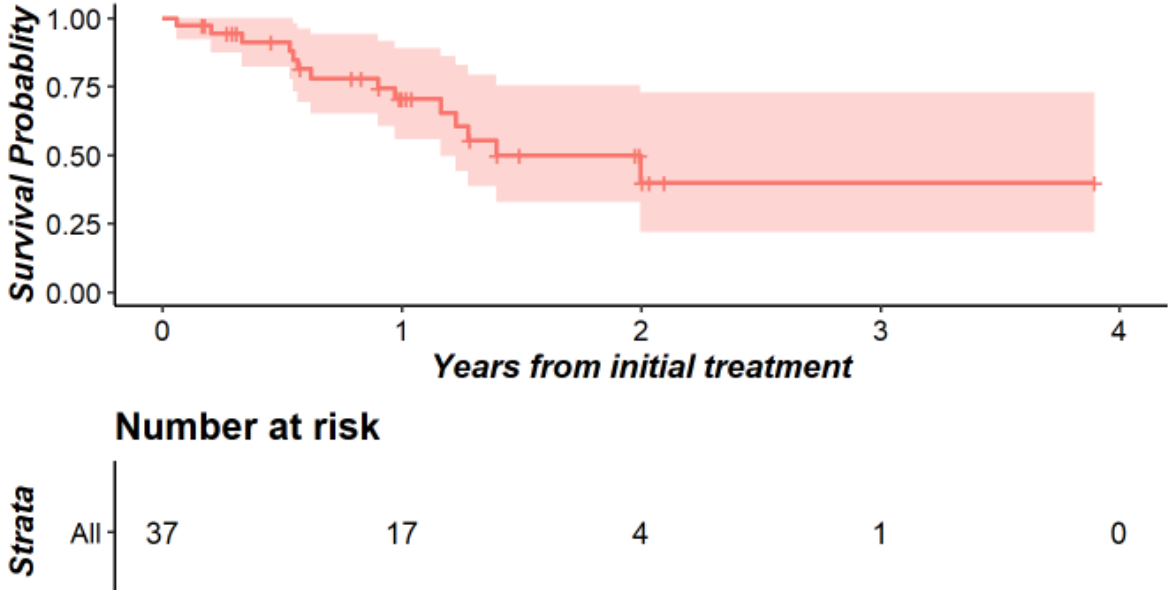
- 43 of 254 underwent CAR-T therapy
- 37 had confirmed *TP53* alteration prior to CAR-T
- Overall response 97%, Complete response 83%
- Median EFS 0.9 years (95% CI, 0.6 to NE)
- Median OS 1.4 years (95% CI, 1.4 to NE)
- 12 month non-relapse mortality – 8%

| | |
|---|---|
| Lines of prior therapy, median (range) | 3 (1-6) |
| Prior BTK inhibitor, No. (%) | 34 (92) |
| Prior bendamustine, No. (%) | 18 (49) |
| Prior allo-HCT | 1 (3) |
| Bridging therapy | 31 (84) |

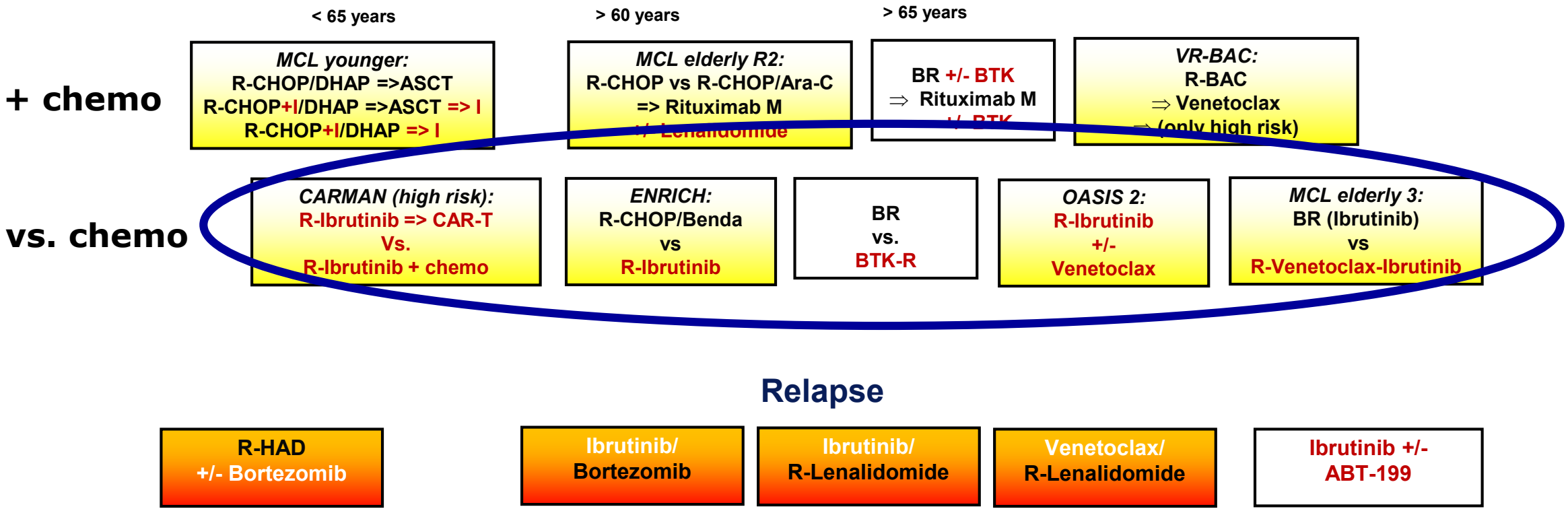
## Event Free Survival




## Overall Survival



# European MCL Network
## Study generation 2023




## Relapse

# TRIANGLE: 23rd annual meeting in Sevilla 2022

Die Kurzpräsentationen sind online unter

**www.lymphome.de/icml2023**

Für den Inhalt verantwortlich:

Prof. Dr. med. Martin Dreyling

Klinikum der Universität München

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