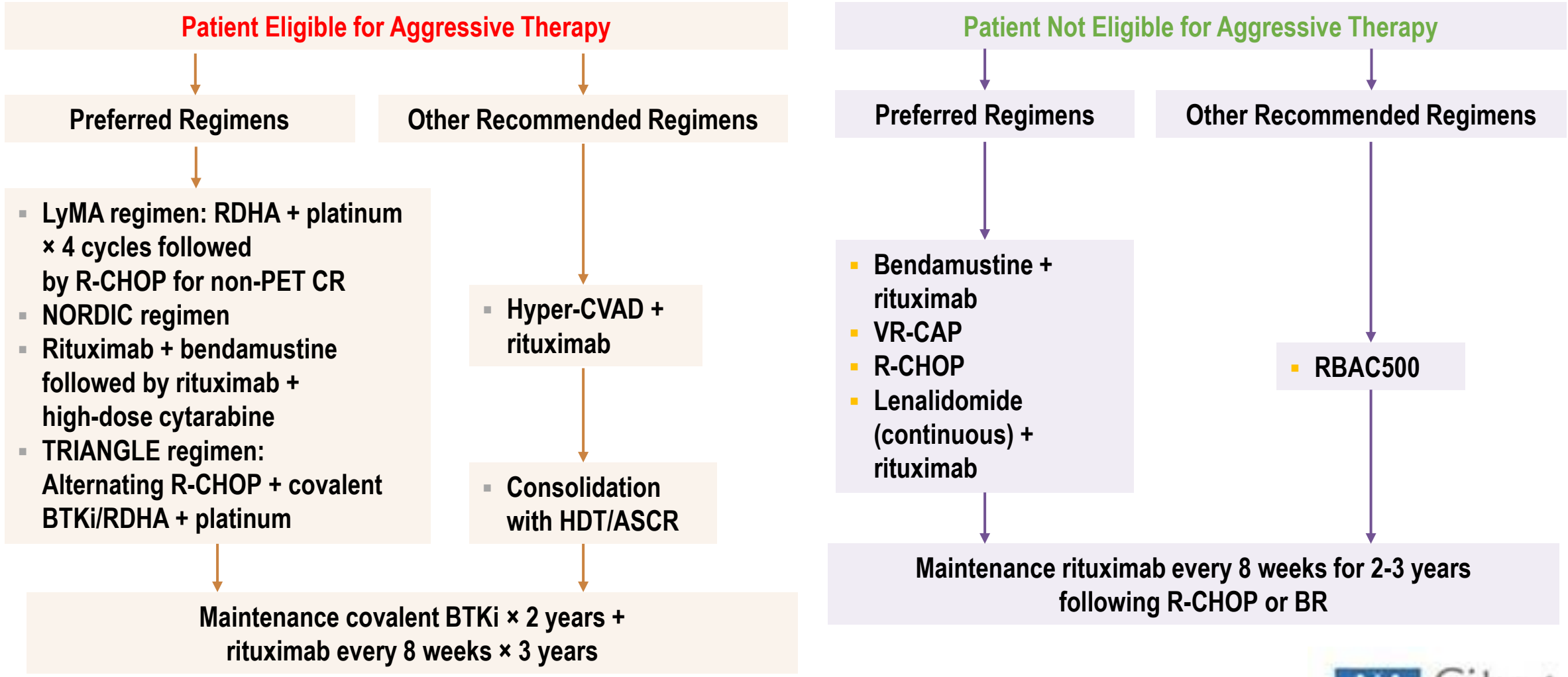
# Transplant-Free First-Line MCL: Opportunities and Challenges in the New Treatment Era

**Alexey V. Danilov, M.D., Ph.D.**
**Marianne and Gerhard Pinkus Professor in Early Clinical Therapeutics**
**Director, Early Phase Therapeutics Program**
**Co-Director, Toni Stephenson Lymphoma Center**
**City of Hope National Medical Center**


# Disclosures

- Consulting fees: Abbvie, AstraZeneca, BeiGene, Bristol Meyers Squibb, Genentech, GenMab, Incyte, Janssen, Lilly Oncology, MEI Pharma, Merck, Nurix and Prelude
- Research funding: Abbvie, AstraZeneca, Bayer Oncology, Beigene, Bristol Meyers Squibb, Cyclacel, GenMab, Lilly Oncology, MEI Pharma, Morphosys and Nurix.

# “Classical” approach to treatment of MCL – before TRIANGLE



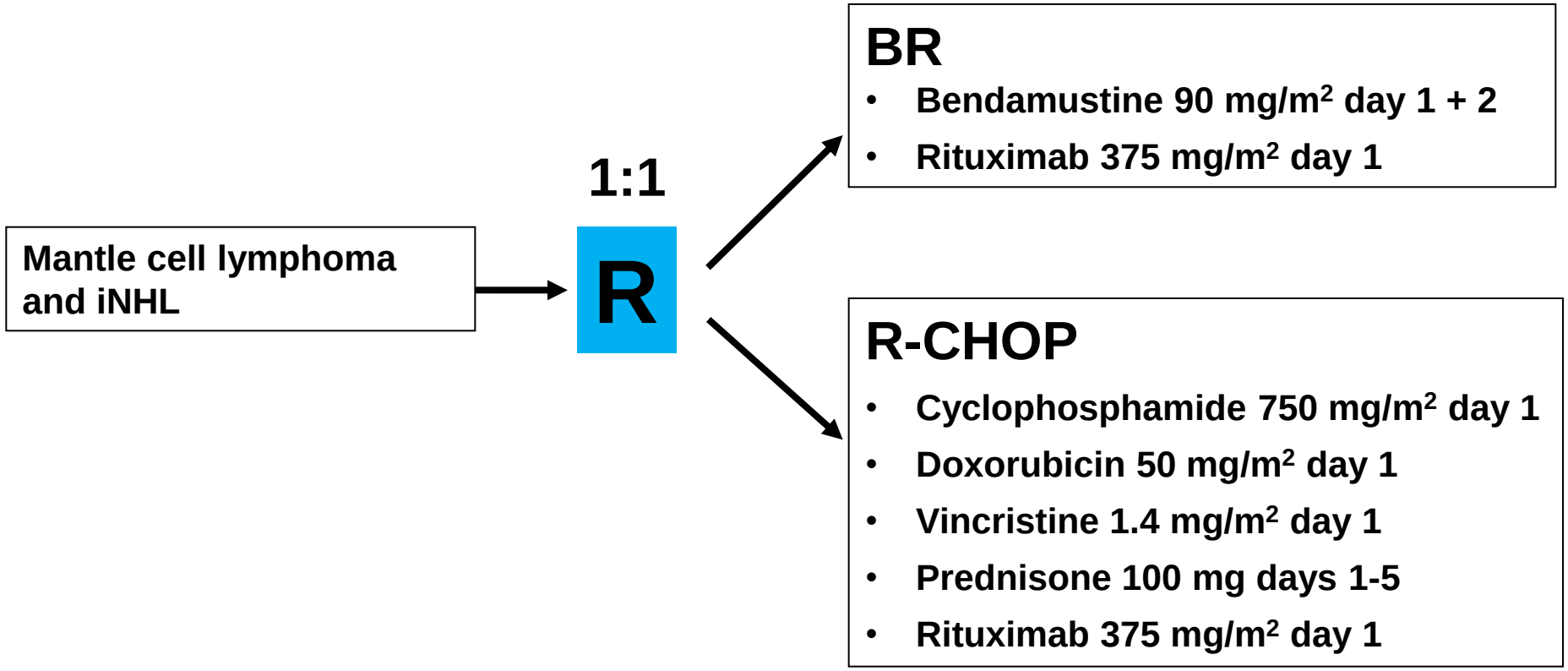

City of Hope.

# Older patients: not eligible for aggressive induction

# StiL Trial: BR vs R-CHOP

## Phase III noninferiority trial

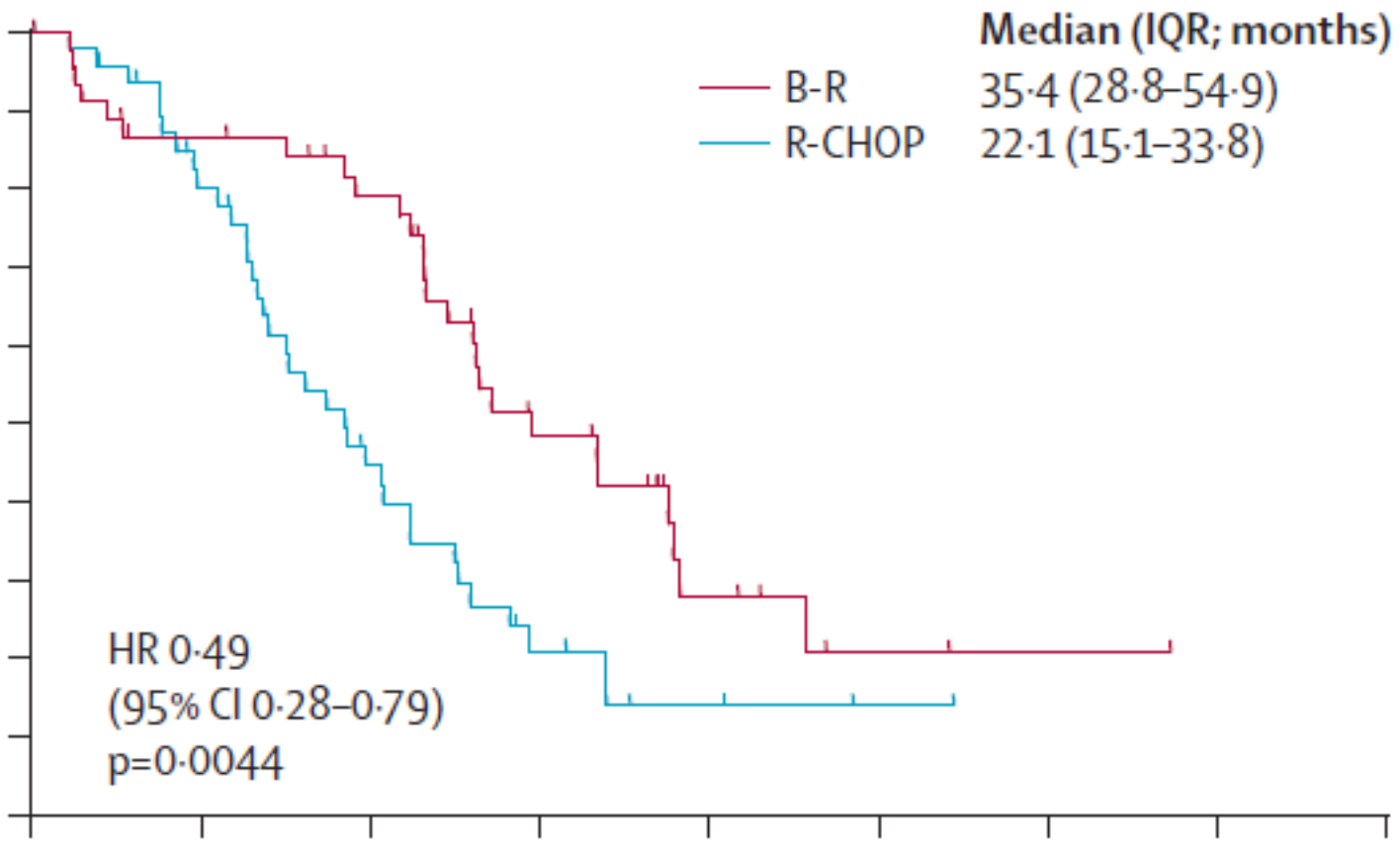
## N = 549 (94 patients with MCL)




StiL, Study group indolent Lymphomas

Rummel MJ, et al. *Lancet.* 2013;381(9873):1203-1210.

# StiL Trial: Progression-Free Survival (PFS)




HR, hazard ratio; IQR, interquartile range

Rummel MJ, et al. *Lancet.* 2013;381(9873):1203-1210.

LB3439

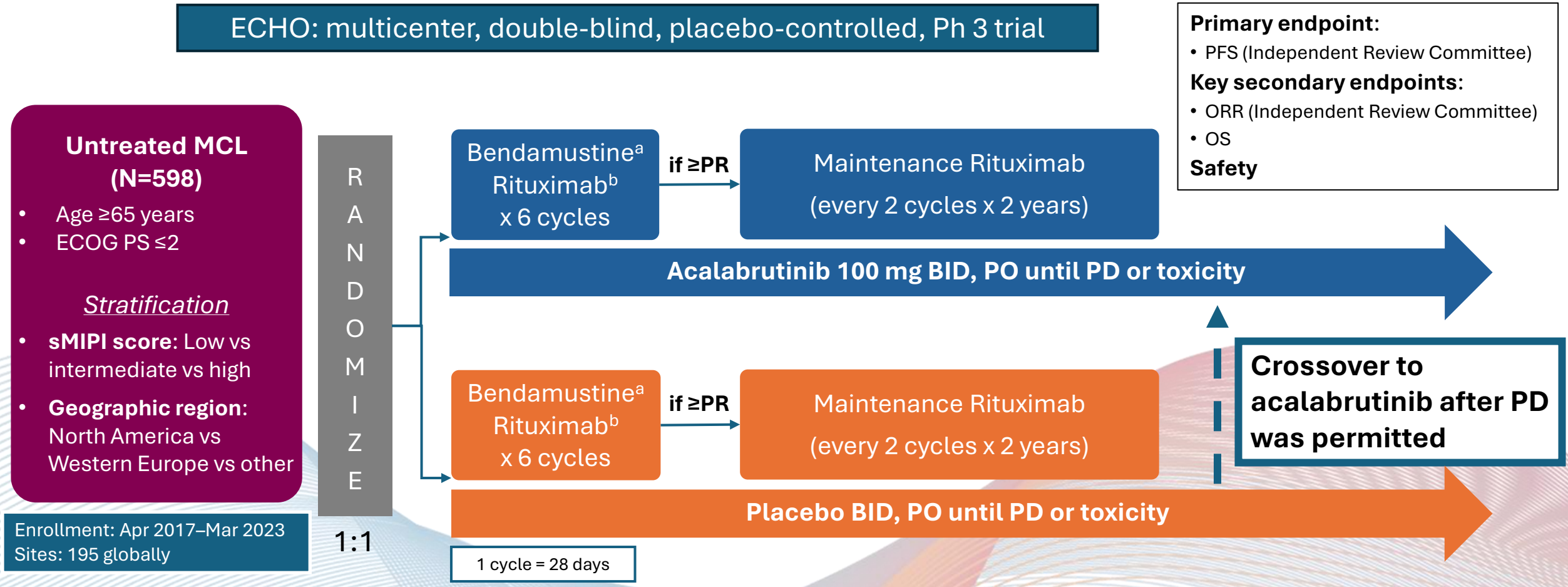
# Acalabrutinib plus bendamustine and rituximab in untreated mantle cell lymphoma (MCL): Results from the phase 3, double-blind, placebo-controlled ECHO trial

Michael Wang[1], Jiri Mayer[2], David Belada[3], Yuqin Song[4], Wojciech Jurczak[5], Jonas Paludo[6], Michael P. Chu[7], Iryna Kryachok[8], Laura Fogliatto[9], Chan Cheah[10], Marta Morawska[11,12], Juan-Manuel Sancho[13], Yufu Li[14], Caterina Patti[15], Cecily Forsyth[16], Jingyang Zhang[17], Robin Lesley[17], Safaa Ramadan[18], Simon Rule[18], Martin Dreyling[19]

[1]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [2]University Hospital Brno, Brno, Czech Republic; [3]4th Department of Internal Medicine – Haematology, Charles University, Hospital and Faculty of Medicine, Hradec Králové, Czech Republic; [4]Peking University Cancer Hospital & Institute, Beijing, China; [5]Malopolskie Centrum Medyczne S.C, Krakow, Poland; [6]Mayo Clinic, Rochester, MN, USA; [7]Cross Cancer Institute, University of Alberta, Edmonton, Canada; [8]National Cancer Institute, Kyiv, Ukraine; [9]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; [10]Sir Charles Gairdner Hospital, Nedlands, Australia; [11]Experimental Hematooncology Department, Medical University of Lublin, Lublin, Poland; [12]Hematology Department, St. John's Cancer Center, Lublin, Poland; [13]ICO-IJC-Hospital Germans Trias i Pujol, Badalona, Spain; [14]Henan Cancer Hospital, Zheng Zhou, China; [15]A.O.O.R. Villa Sofia Cervello, Palermo, Italy; [16]Central Coast Haematology, North Gosford, Australia; [17]AstraZeneca, South San Francisco, CA, USA; [18]AstraZeneca, Cambridge, UK; [19]Klinikum der Universitaet Munchen, Muenchen, Germany

**Presented at the European Hematology Association (EHA) Annual Meeting; June 13–16, 2024; Madrid, Spain**

# Study Design




[a]Bendamustine 90 mg/m$^2$ on days 1 and 2. [b]Rituximab 375 mg/m$^2$ on day 1.
BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, orally; PR, partial response.

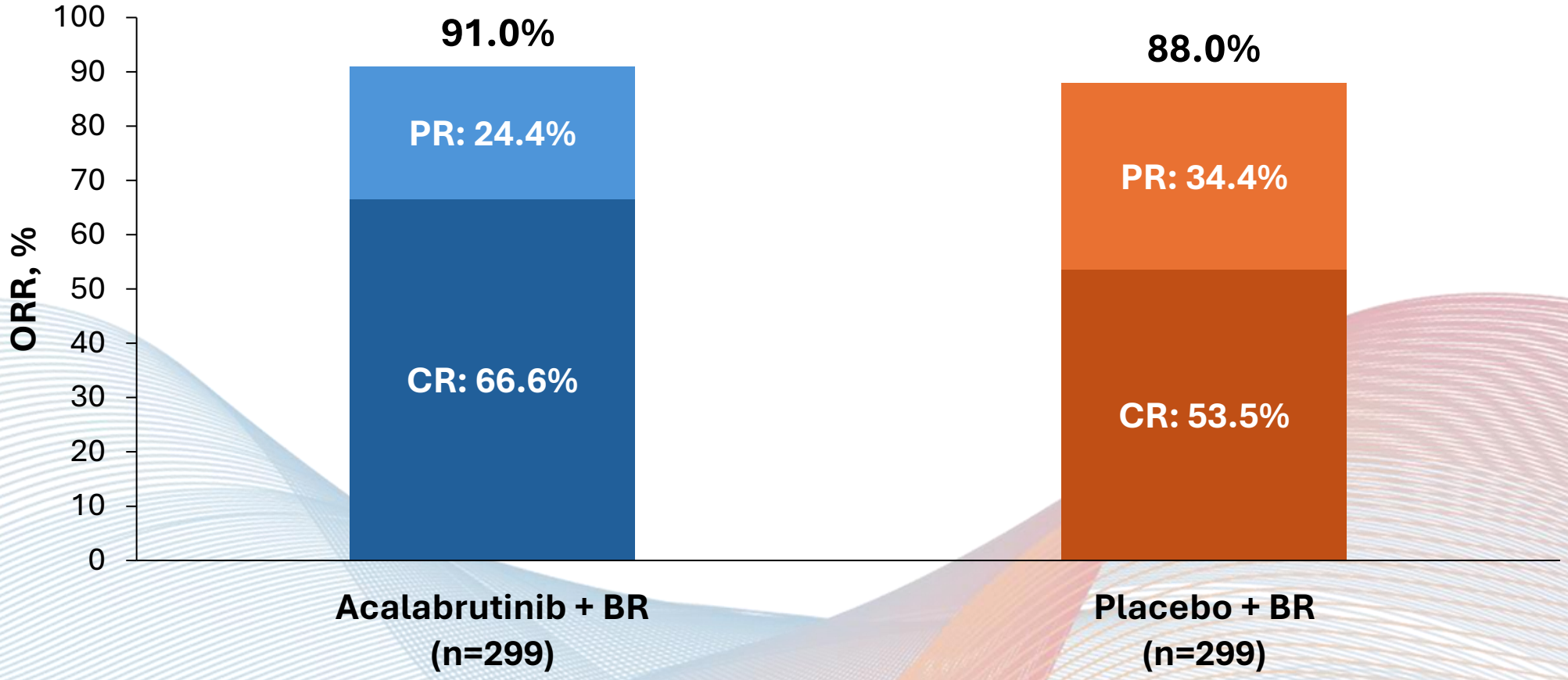
# Demographics and Baseline Characteristics

| | Acalabrutinib + BR (n=299) | Placebo + BR (n=299) |
|---|---|---|
| Age, median (range), y | 71 (65–85) | 71 (65–86) |
| ≥75 y, n (%) | 84 (28.1) | 77 (25.8) |
| Male, n (%) | 214 (71.6) | 209 (69.9) |
| ECOG PS, n (%) | | |
| 1 | 129 (43.1) | 132 (44.1) |
| 2 | 12 (4.0) | 23 (7.7) |
| Tumor bulk ≥5 cm, n (%) | 112 (37.5) | 113 (37.8) |
| Blastoid/pleomorphic histology, n (%) | 41 (13.7) | 38 (12.7) |
| Simplified MIPI score, n (%) | | |
| Low risk | 99 (33.1) | 101 (33.8) |
| Intermediate risk | 128 (42.8) | 125 (41.8) |
| High risk | 72 (24.1) | 73 (24.4) |
| Extranodal disease, n (%) | 264 (88.3) | 277 (92.6) |
| *TP53* status, n (%)[a] | | |
| Mutated | 22 (7.4) | 29 (9.7) |
| Unmutated | 97 (32.4) | 83 (27.8) |
| Ki-67, n (%) | | |
| <30% | 133 (44.5) | 126 (42.1) |
| ≥30% | 139 (46.5) | 147 (49.2) |

[a]All other patients in the acalabrutinib (n=180) and placebo (n=187) groups had unknown *TP53* mutation status.
BR, bendamustine + rituximab; ECOG PS, Eastern Cooperative Oncology Group performance status; MIPI, Mantle Cell Lymphoma International Prognostic Index.

# Best Overall Response and Complete Response Rates

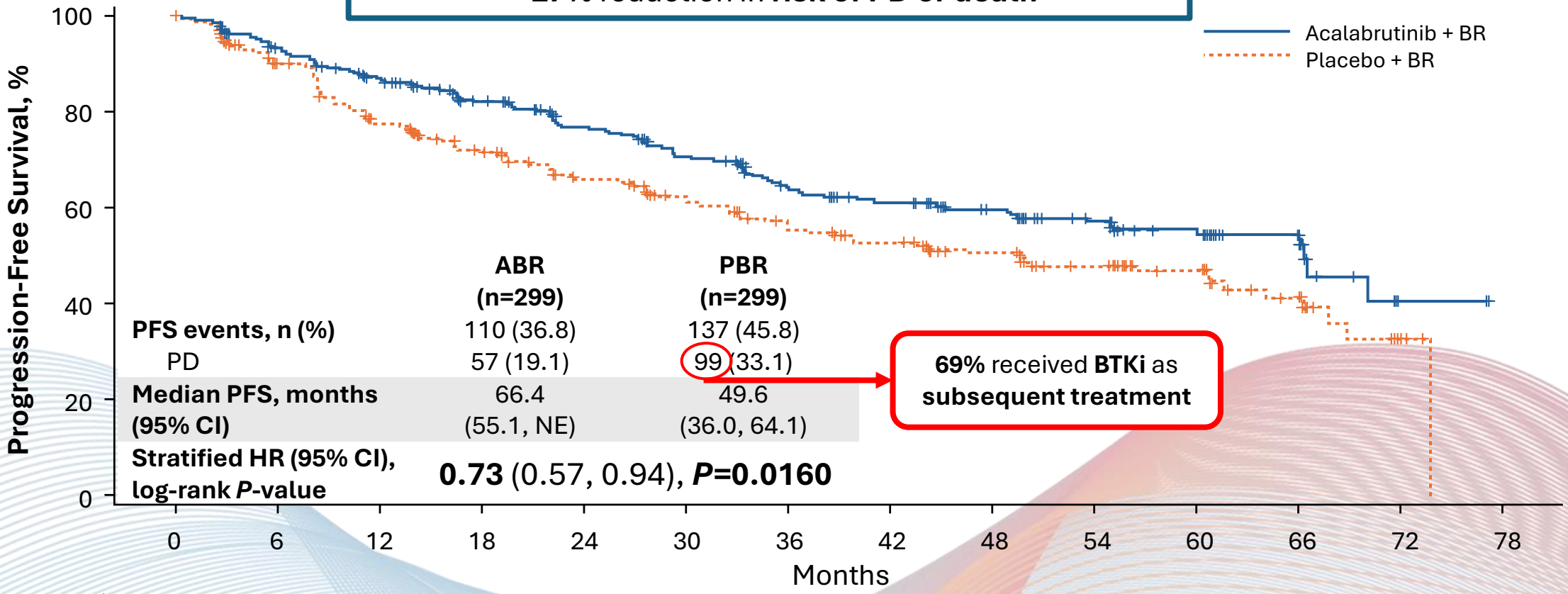
- An additional 13% of patients achieved CR with acalabrutinib + BR




BR, bendamustine + rituximab; CI, confidence interval; CR, complete response; ORR, overall response rate; PR, partial response.

# PFS (primary endpoint) Was Significantly Improved With Acalabrutinib + BR

- **Significant improvement in median PFS by ~17 mo**
  - **27%** reduction in **risk of PD or death**[a]




| | ABR (n=299) | PBR (n=299) |
|---|---|---|
| **PFS events, n (%)** | 110 (36.8) | 137 (45.8) |
| PD | 57 (19.1) | 99 (33.1) |
| **Median PFS, months (95% CI)** | 66.4 (55.1, NE) | 49.6 (36.0, 64.1) |
| **Stratified HR (95% CI), log-rank *P*-value** | **0.73** (0.57, 0.94), ***P*=0.0160** | |

**69%** received **BTKi** as **subsequent treatment**

Number at risk

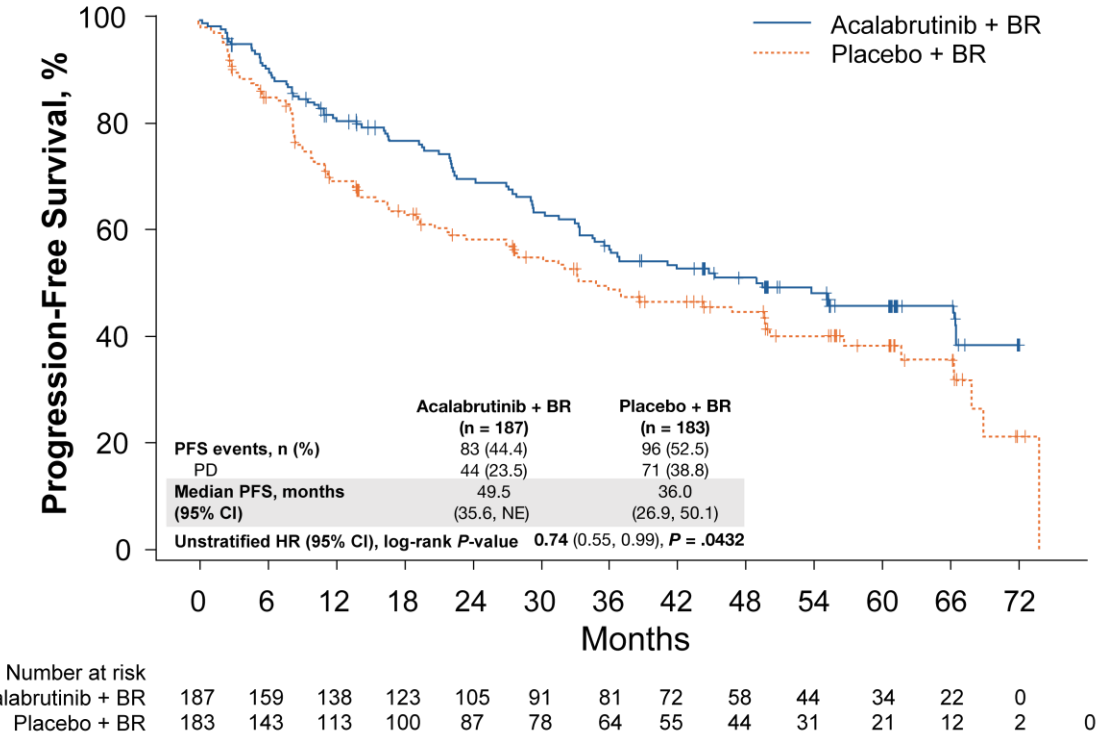
| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acala + BR | 299 | 258 | 232 | 205 | 182 | 156 | 136 | 122 | 98 | 73 | 53 | 34 | 2 | 0 |
| Placebo + BR | 299 | 243 | 204 | 181 | 159 | 142 | 118 | 102 | 84 | 63 | 44 | 25 | 4 | 0 |

[a]At a median follow-up of 45 months.

ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; NE, not estimable; PBR, placebo + bendamustine + rituximab; PD, progressive disease; PFS, progression-free survival.

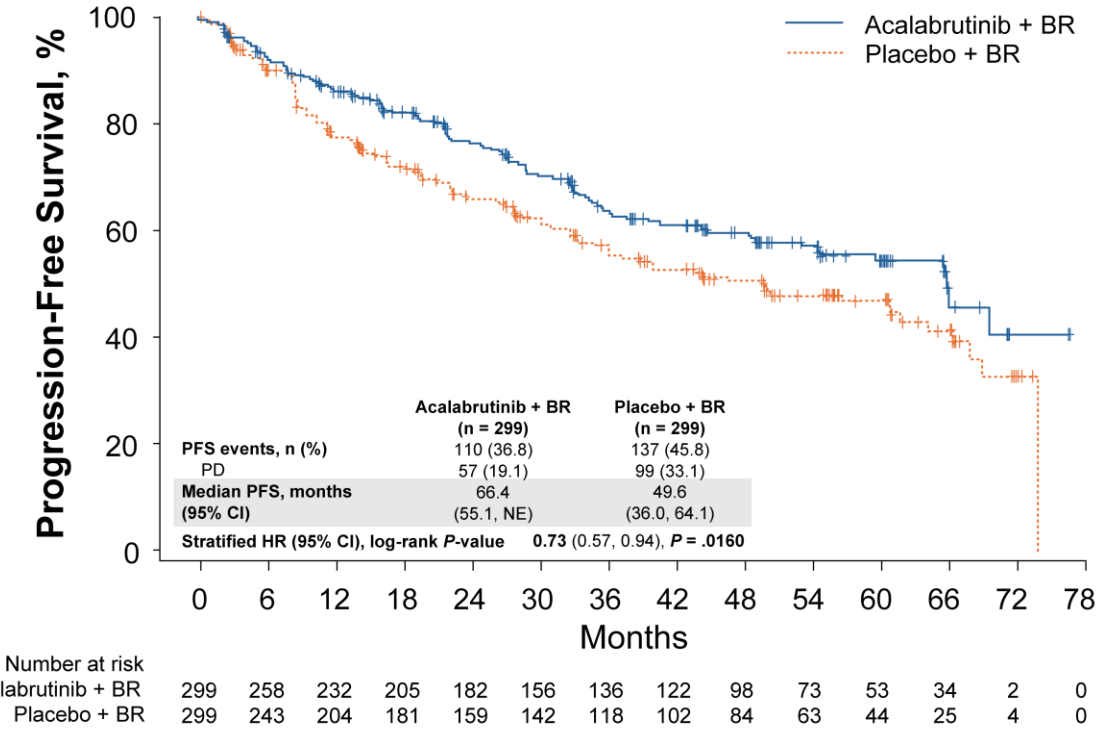
# Significantly Longer PFS With ABR in Patients With High-risk MCL

## PFS in High-risk Population[1]




- After PD, 38 (53.5%) of 71 patients with high-risk disease who progressed on placebo crossed over to acalabrutinib

## PFS in Full Analysis Population[2]

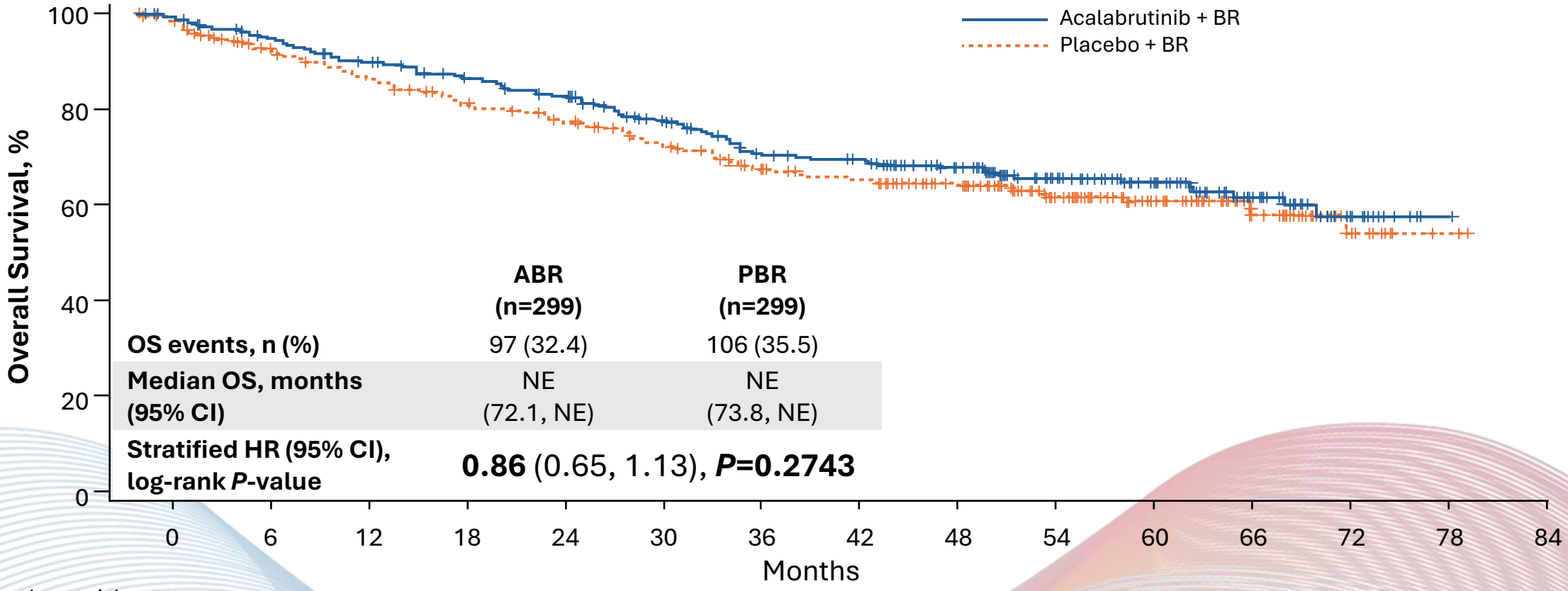



- Of the 99 patients who progressed on placebo, 75 (75.8%) received at least 1 subsequent anticancer therapy, and among these 75, 68 (90.7%) received BTKis, including 51 patients who crossed over to acalabrutinib within the trial[1]

BR, bendamustine-rituximab; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; MCL, mantle cell lymphoma; NE, not estimable; PD, progressive disease; PFS, progression-free survival.


1. Presented at the European Hematology Association (EHA) Annual Meeting; June 12–15, 2025; Milan, Italy. S233
2, Wang M, et al. *J Clin Oncol.* 2025:101200JCO2500690. doi: 10.1200/JCO-25-00690. Online ahead of print.

# Overall Survival Including Crossover




| | ABR (n=299) | PBR (n=299) |
|---|---|---|
| **OS events, n (%)** | 97 (32.4) | 106 (35.5) |
| **Median OS, months (95% CI)** | NE (72.1, NE) | NE (73.8, NE) |
| **Stratified HR (95% CI), log-rank *P*-value** | **0.86** (0.65, 1.13), ***P*=0.2743** | |

Number at risk

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acala + BR | 299 | 280 | 259 | 243 | 230 | 207 | 181 | 163 | 146 | 110 | 86 | 58 | 25 | 3 | 0 |
| Placebo + BR | 299 | 268 | 247 | 229 | 215 | 193 | 175 | 157 | 141 | 108 | 78 | 51 | 21 | 3 | 0 |

Median follow-up of 45 months.

ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PBR, placebo + bendamustine + rituximab.

# Adverse Events of Interest

| | Acalabrutinib + BR (n=297) | | Placebo + BR (n=297) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| **Event, n (%)** | | | | |
| Atrial fibrillation | 18 (6.1) | 11 (3.7) | 13 (4.4) | 5 (1.7) |
| Hypertension | 36 (12.1) | 16 (5.4) | 47 (15.8) | 25 (8.4) |
| Major bleeding[a] | 7 (2.4) | 6 (2.0) | 16 (5.4) | 10 (3.4) |
| Infections[b] | 232 (78.1) | 122 (41.1) | 211 (71.0) | 101 (34.0) |
| Second primary malignancies (excluding non-melanoma skin)[b] | 29 (9.8) | 16 (5.4) | 32 (10.8) | 20 (6.7) |
| **Median treatment exposure (range), months** | 29 (0.1, 80.1) | | 25 (0.03, 76.4) | |

[a]Grouping of preferred terms; defined as a hemorrhagic event that is serious, or grade ≥3 in severity, or that is a CNS hemorrhage (any severity grade). [b]Grouping of preferred terms.
BR, bendamustine + rituximab; CNS, central nervous system.

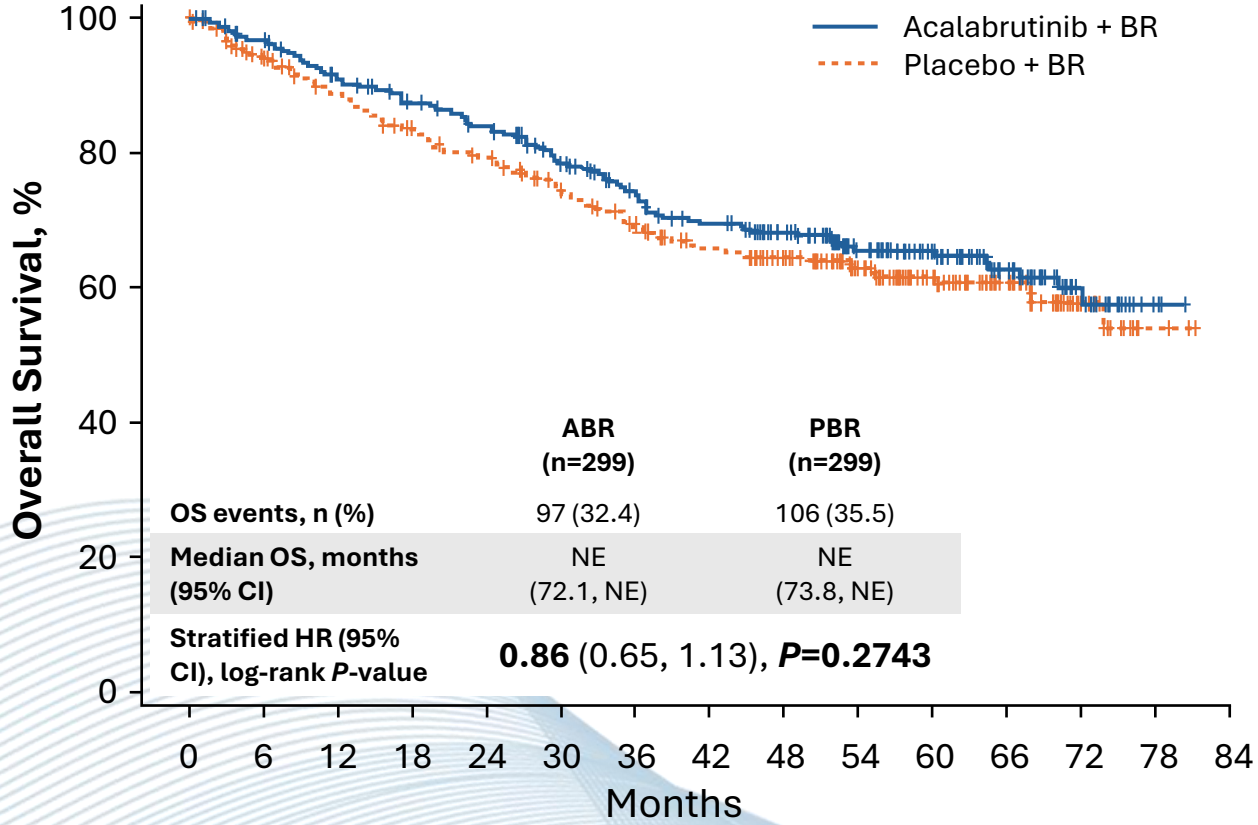
# Deaths

| n (%) | Acalabrutinib + BR (n=299) | Placebo + BR including crossover (N=299) |
|---|---|---|
| **Total deaths** | 97 (32.4) | 106 (35.5) |
| Due to disease progression | 30 (10.0) | 43 (14.4) |
| Due to AEs ≤30 days of last dose of study drug (TEAEs) | 27 (9.0) | 27 (9.0) |
| Due to AEs >30 days after last dose of study drug | 19 (6.4) | 14 (4.7) |
| Other[a] | 14 (4.7) | 16 (5.4) |
| Unknown | 7 (2.3) | 6 (2.0) |

[a]"Other" includes fatal adverse events occurring >30 days after last study drug dose AND not considered treatment-related.
AE, adverse event; BR, bendamustine + rituximab; TEAE, treatment-emergent adverse event.

# OS With and Without COVID-19 Deaths: Prespecified Sensitivity Analysis

## Full analysis population (including crossover)

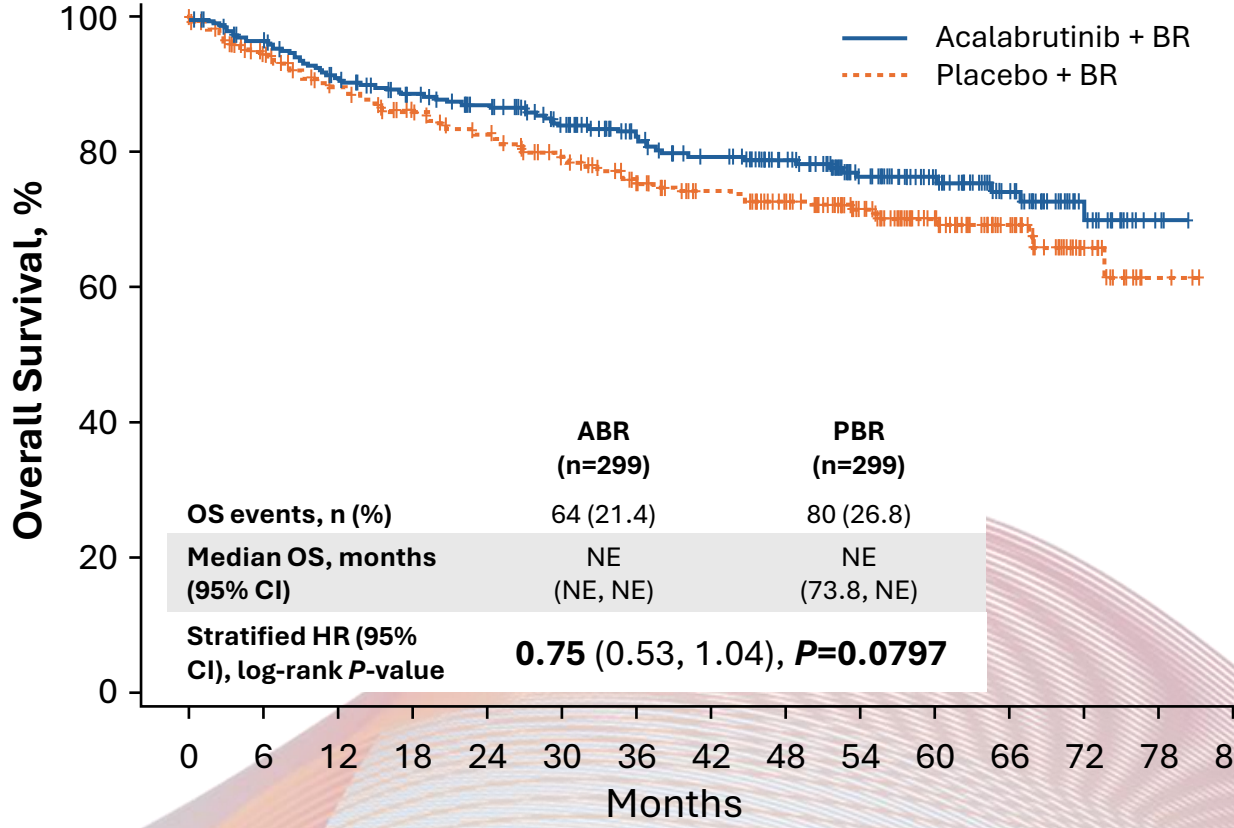



| | ABR (n=299) | PBR (n=299) |
|---|---|---|
| **OS events, n (%)** | 97 (32.4) | 106 (35.5) |
| **Median OS, months (95% CI)** | NE (72.1, NE) | NE (73.8, NE) |
| **Stratified HR (95% CI), log-rank *P*-value** | **0.86** (0.65, 1.13), ***P*=0.2743** | |

Number at risk

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acala + BR | 299 | 280 | 259 | 243 | 230 | 207 | 181 | 163 | 146 | 110 | 86 | 58 | 25 | 3 | 0 |
| Placebo + BR | 299 | 268 | 247 | 229 | 215 | 193 | 175 | 157 | 141 | 108 | 78 | 51 | 21 | 3 | 0 |

## COVID-19 deaths censored




| | ABR (n=299) | PBR (n=299) |
|---|---|---|
| **OS events, n (%)** | 64 (21.4) | 80 (26.8) |
| **Median OS, months (95% CI)** | NE (NE, NE) | NE (73.8, NE) |
| **Stratified HR (95% CI), log-rank *P*-value** | **0.75** (0.53, 1.04), ***P*=0.0797** | |

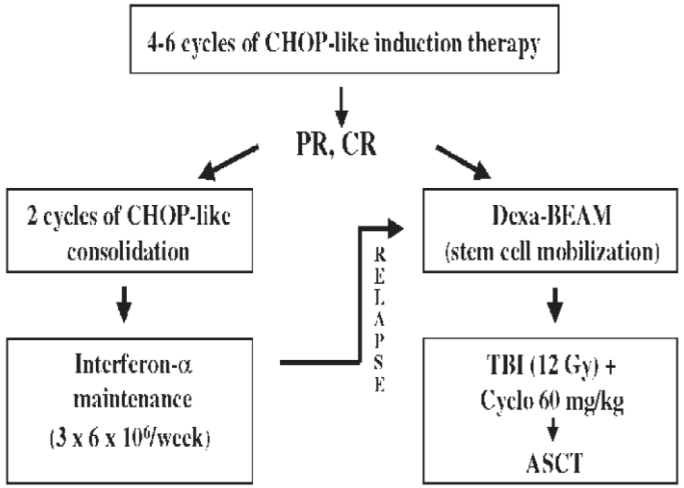
Number at risk

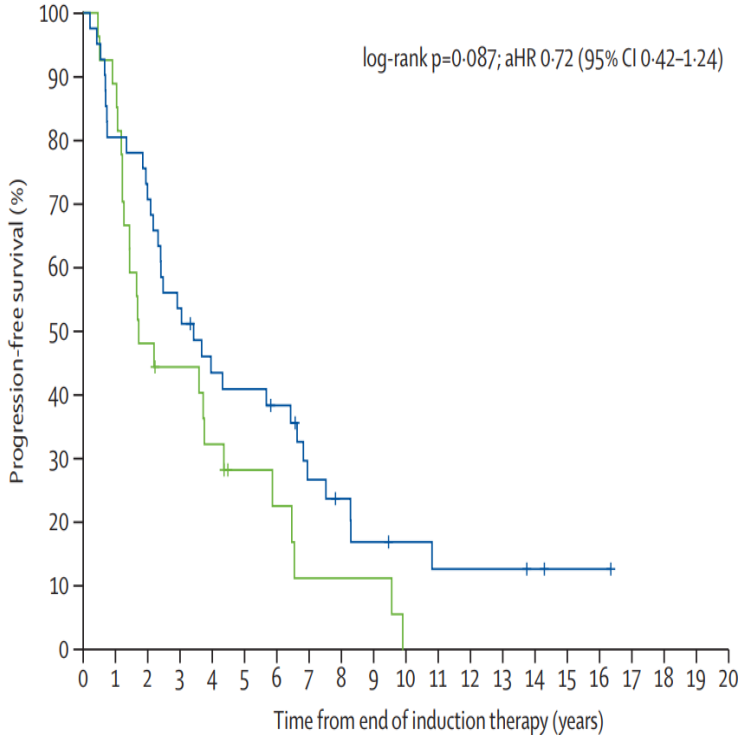
| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acala + BR | 299 | 280 | 259 | 243 | 230 | 207 | 181 | 163 | 146 | 110 | 86 | 58 | 25 | 3 | 0 |
| Placebo + BR | 299 | 268 | 247 | 229 | 215 | 193 | 175 | 157 | 141 | 108 | 78 | 51 | 21 | 3 | 0 |

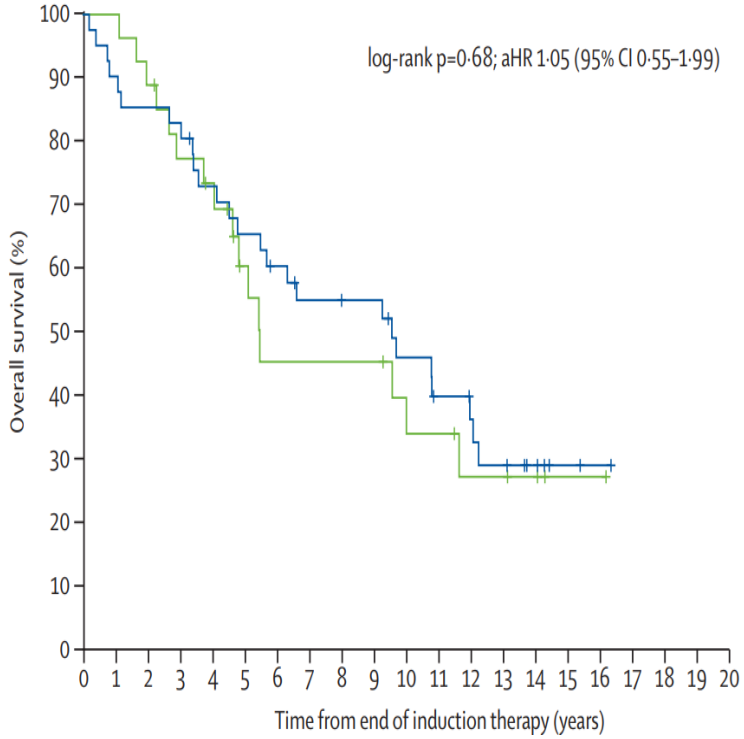
ABR, acalabrutinib + bendamustine + rituximab; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; NE, not estimable; OS, overall survival; PBR, placebo + bendamustine + rituximab.

# …and now to younger patients eligible for aggressive induction…

# There are no randomized trials which confirm benefit of ASCT in MCL

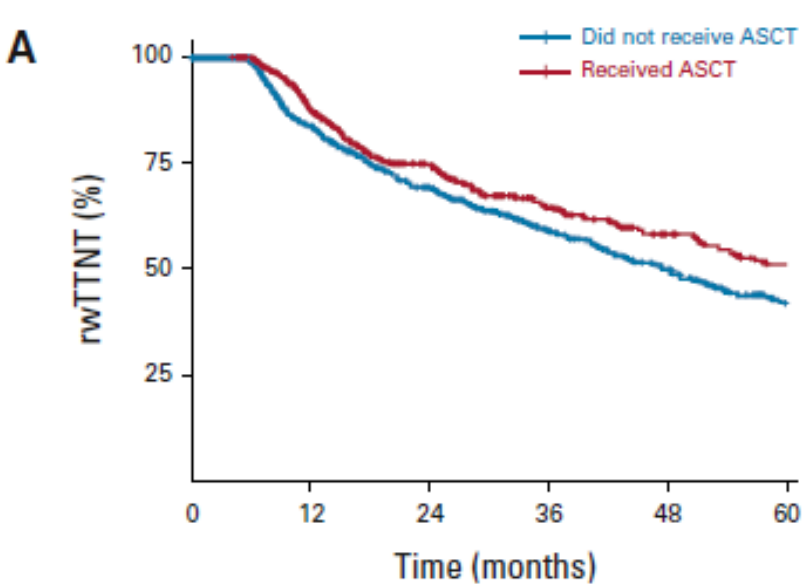



Dreyling M, et al. *Blood.* 2005 Apr 1;105(7):2677-84.
Lancet Haematol 2021; 8: e648–57

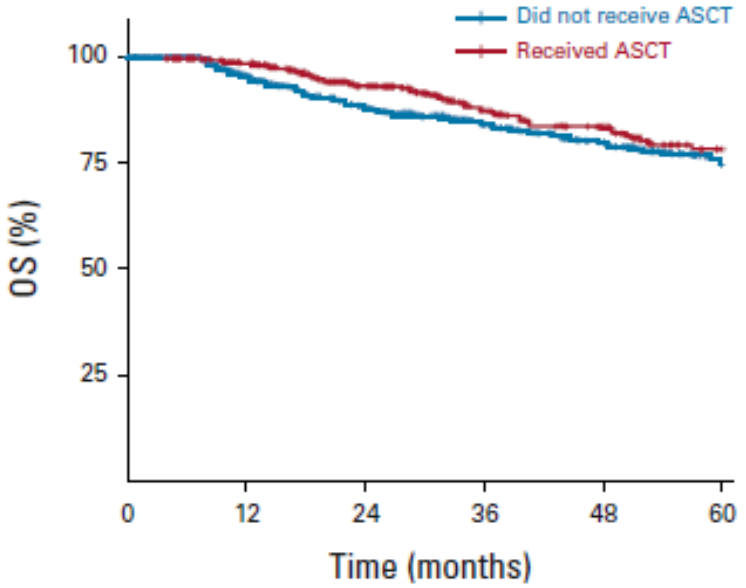
# ASCT in MCL: retrospective analysis – Flatiron cohort




No. at risk:

| | | | | | | |
|---|---|---|---|---|---|---|
| Did not receive ASCT | 680 | 451 | 331 | 228 | 164 | 106 |
| Received ASCT | 282 | 222 | 160 | 112 | 81 | 59 |

| | Age < 65 Years and ASCT-Eligible n = 962 | |
|---|---|---|
| | Received ASCT n = 282 | Did Not Receive ASCT n = 680 |
| Median rwTTNT (95% CI), months | 59.9 (51.3 to 75.6) | 48.3 (41.9 to 53.6) |
| rwTTNT rate at 3 years, % (95% CI) | 65 (59 to 71) | 59 (55 to 64) |
| HR (95% CI) | 0.84 (0.68 to 1.03) | |
| Log-rank test *P* | .10 | |




No. at risk:

| | | | | | | |
|---|---|---|---|---|---|---|
| Did not receive ASCT | 680 | 616 | 418 | 319 | 251 | 186 |
| Received ASCT | 282 | 251 | 194 | 144 | 112 | 86 |

| | Age < 65 Years and ASCT-Eligible n = 962 | |
|---|---|---|
| | Received ASCT n = 282 | Did Not Receive ASCT n = 680 |
| Median OS (95% CI), months | 109 (96.1 to NE) | 113 (102.9 to NE) |
| OS rate at 3 years, % (95% CI) | 88 (83 to 92) | 84 (81 to 88) |
| HR (95% CI) | 0.86 (0.63 to 1.18) | |
| Log-rank test *P* | .4 | |

*Martin et al, JCO 2022*

City of Hope

# Has transplant-free future arrived in MCL?

# YES!..

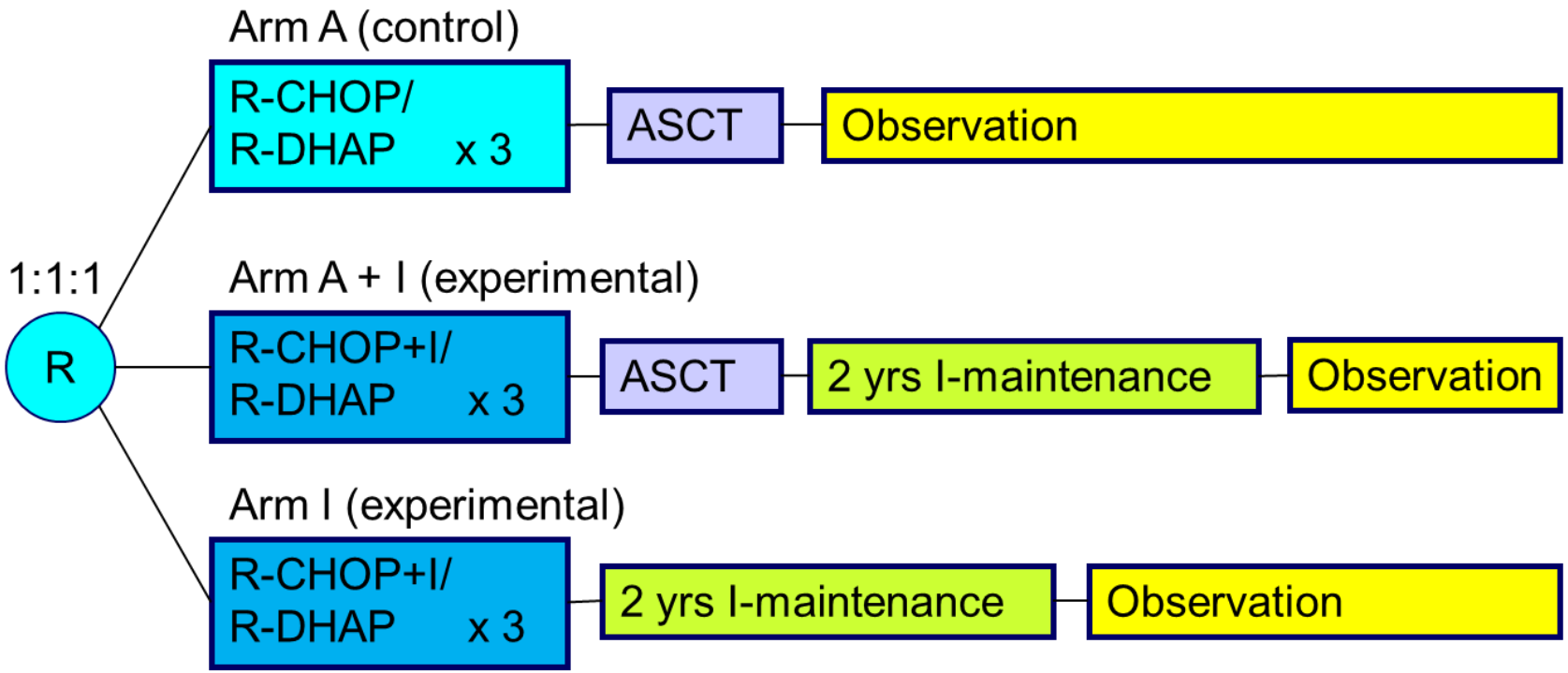
# Abstract #240: Role of Autologous Stem Cell Transplantation in the Context of Ibrutinib-Containing First-Line Treatment in Younger Patients with Mantle Cell Lymphoma: Results from the Randomized Triangle Trial By the European MCL Network

**Martin Dreyling, MD**1, Jeanette K Doorduijn, MD, PhD2, Eva Gine, MD3, Mats Jerkeman, MD, PhD4, Jan Walewski, MD, Prof.5, Martin Hutchings, MD, PhD6,7, Ulrich Mey, MD, Prof.8,9, Jon Riise, MD, PhD10*, Marek Trneny, Prof., MD, CSc.11, Vibeke KJ Vergote, MD12*, Daniela Donnarumma13*, Ofer Shpilberg, MD, MPH14*, Maria Gomes da Silva, MD, PhD15*, Sirpa Leppä, MD, PhD16, Linmiao Jiang, MSc17*, Christiane Pott, MD18*, Wolfram Klapper, MD, Prof19*, Christian Schmidt, MD20*, Michael Unterhalt, MD21*, Marco Ladetto, MD22 and Eva Hoster, PhD, Prof.23,24*

1 University Hospitals Plymouth NHS Trust, Plymouth, United Kingdom, 2 Lund University Hospital, Lund, Sweden, 3 Plymouth University, Faculty of Health, Plymouth, United Kingdom, 4 Institute of Health Research, Exeter University, Exeter, United Kingdom, 5 Department of Immunology, Genetics and Pathology, Cancer Precision Medicine Unit, Uppsala University, Uppsala, Sweden, 6 Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland, 7 Dept. of Hematology, Odense University Hospital, Odense, Denmark, 8 St. Olav University Hospital, Department of Oncology, Trondheim, Norway, 9 Southampton Experimental Cancer Medicine Centre, University of Southampton, Southampton, United Kingdom, 10 Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, 11 University College London Hospitals NHS Foundation Trust, London, United Kingdom, 12 Department of Hematology, Zealand University Hospital, Roskilde, Denmark, 13 Department of Oncology, Oslo University Hospital, Oslo, Norway, 14 Karolinska University Hospital, Department of Haematology, Stockholm, Sweden, 15 Linkoping University Hospital, Linkoping, Sweden, 16 Haematology, Leeds Cancer Centre, Leeds, United Kingdom, 17 HMDS, Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, 18 Haematological Malignancy Diagnostic Service, Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, 19 Plymouth University, Peninsula Clinical Trials Unit, Plymouth, United Kingdom, 20 Department of Hematology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, 21 Aarhus University Hospital, Aarhus C, Denmark, 22 Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom, 23 Department of Clinical Haematology, Oxford University Hospitals NHS Trust, Old Road, United Kingdom, 24 Executive Director, Haematology R&D, AstraZeneca, Cambridge, United Kingdom.

# *TRIANGLE*: Trial Design

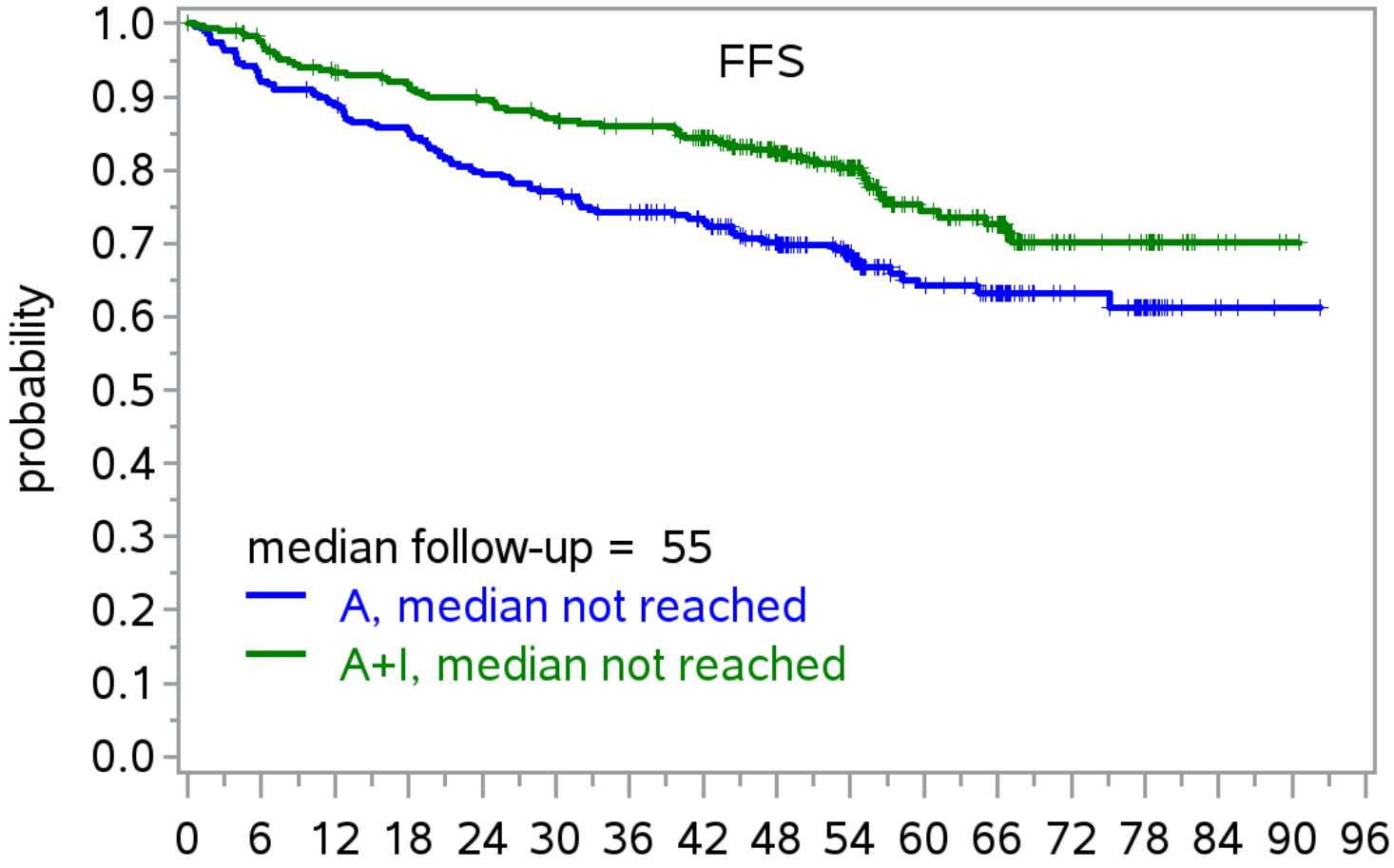
- Patients with MCL
- Previously untreated
- Stage II-IV
- <66 years
- Suitable for HA and ASCT
- ECOG 0-2




- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.
- **Follow-up = 55 months**

Abstract #240

# *TRIANGLE:* FFS Superiority of A+I vs. A

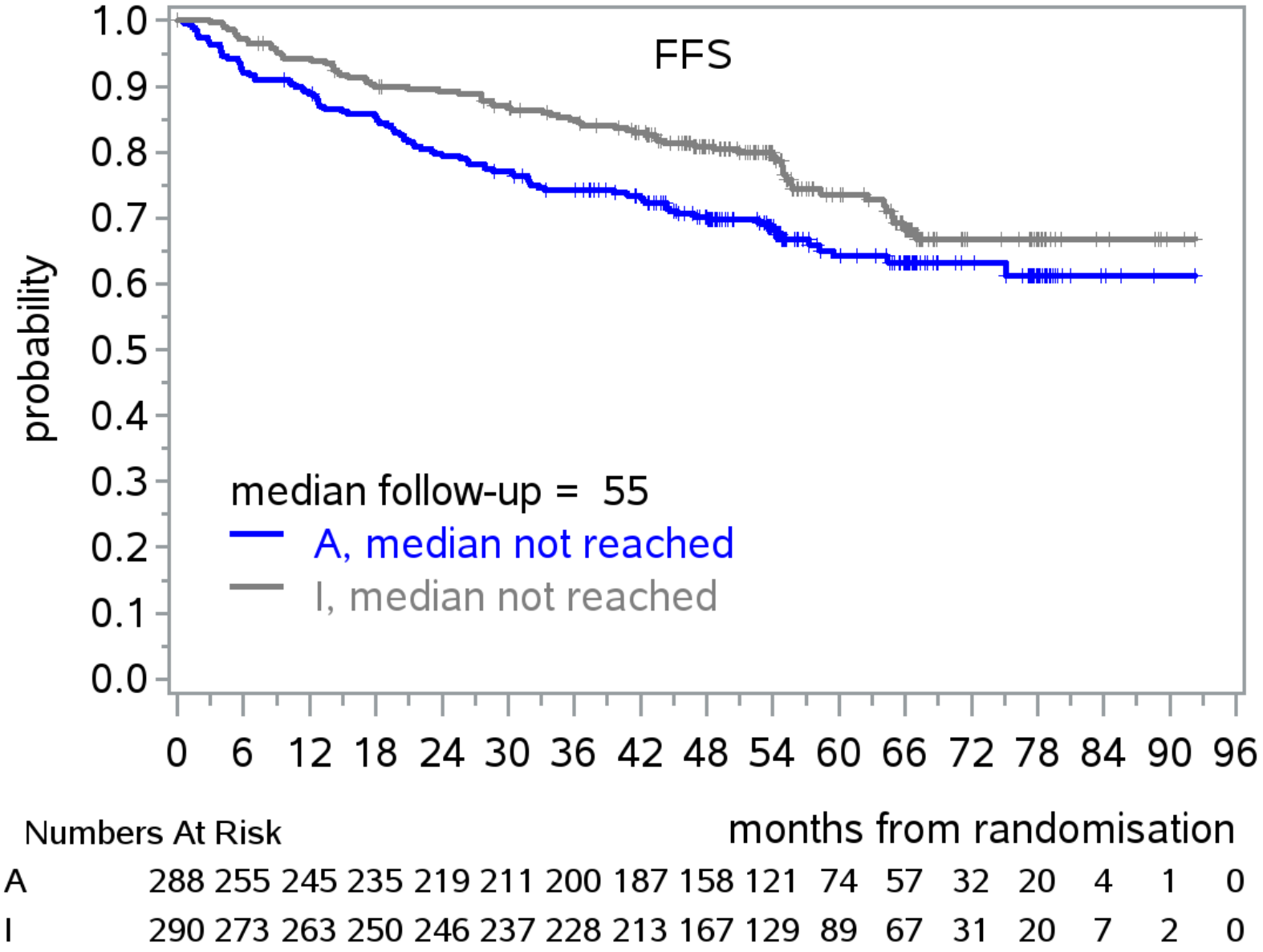



Numbers At Risk

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | 288 | 255 | 245 | 235 | 219 | 211 | 200 | 187 | 158 | 121 | 74 | 57 | 32 | 20 | 4 | 1 | 0 |
| A+I | 292 | 274 | 259 | 252 | 245 | 236 | 230 | 217 | 180 | 141 | 89 | 70 | 28 | 24 | 6 | 2 | 0 |

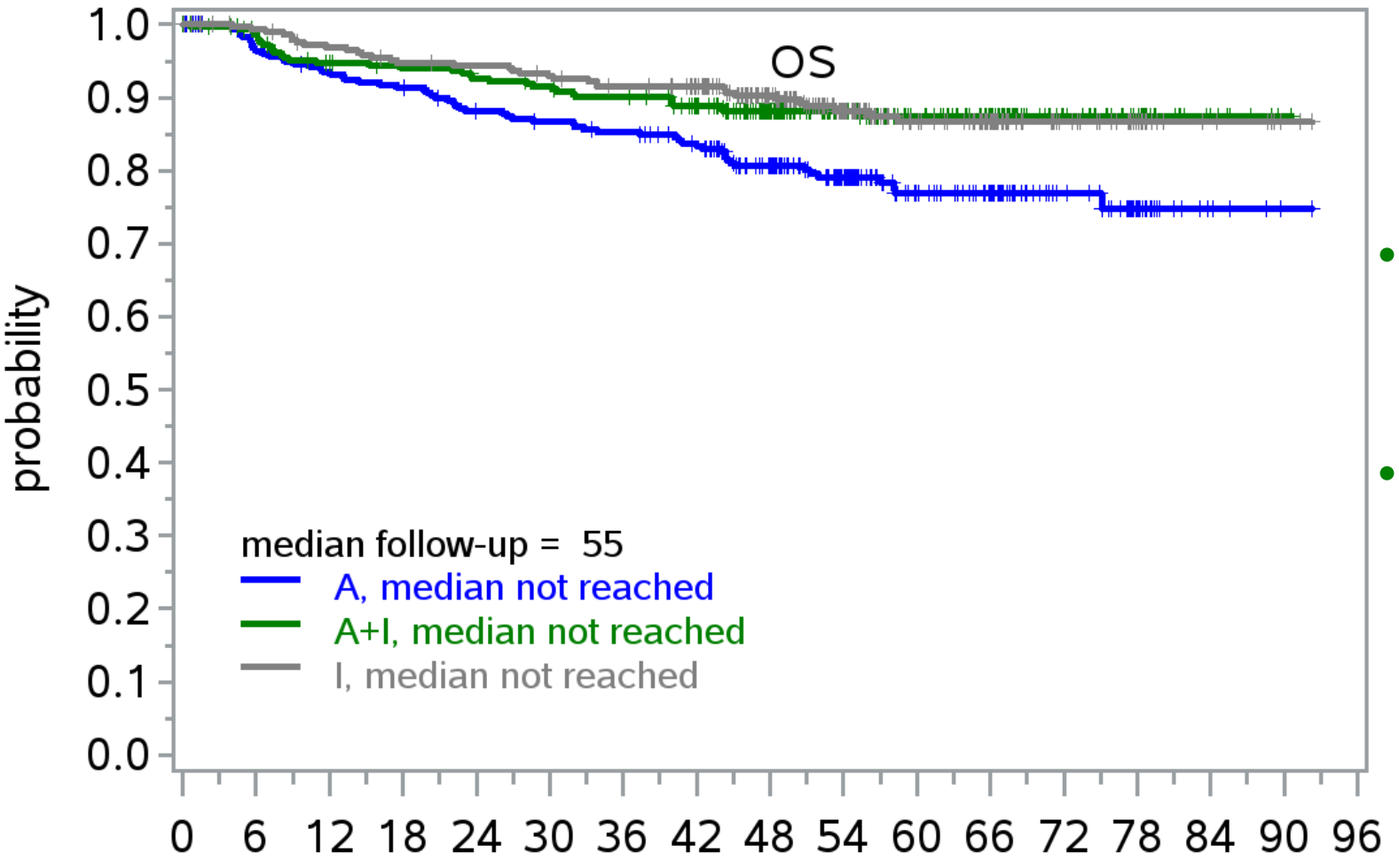
- Superiority of A+I vs. A
  - 4-year FFS A+I: 82%
  - 4-year FFS A: 70%
- p-value (overrunning, one-sided): p=0.0026
- HR (A+I vs. A): HR=0.64

# *TRIANGLE:* No FFS Superiority of A vs. I




- Superiority of A vs. I rejected
  - 4-year FFS A: 70% (MCL Younger: 70%)
  - 4-year FFS I: 81%
- p-value (overrunning, one-sided): p=0.9890
- HR (A vs. I): HR=1.29
- **Superiority of I (two-sided, retrospective) p=0.0208**

# *TRIANGLE:* Overall survival



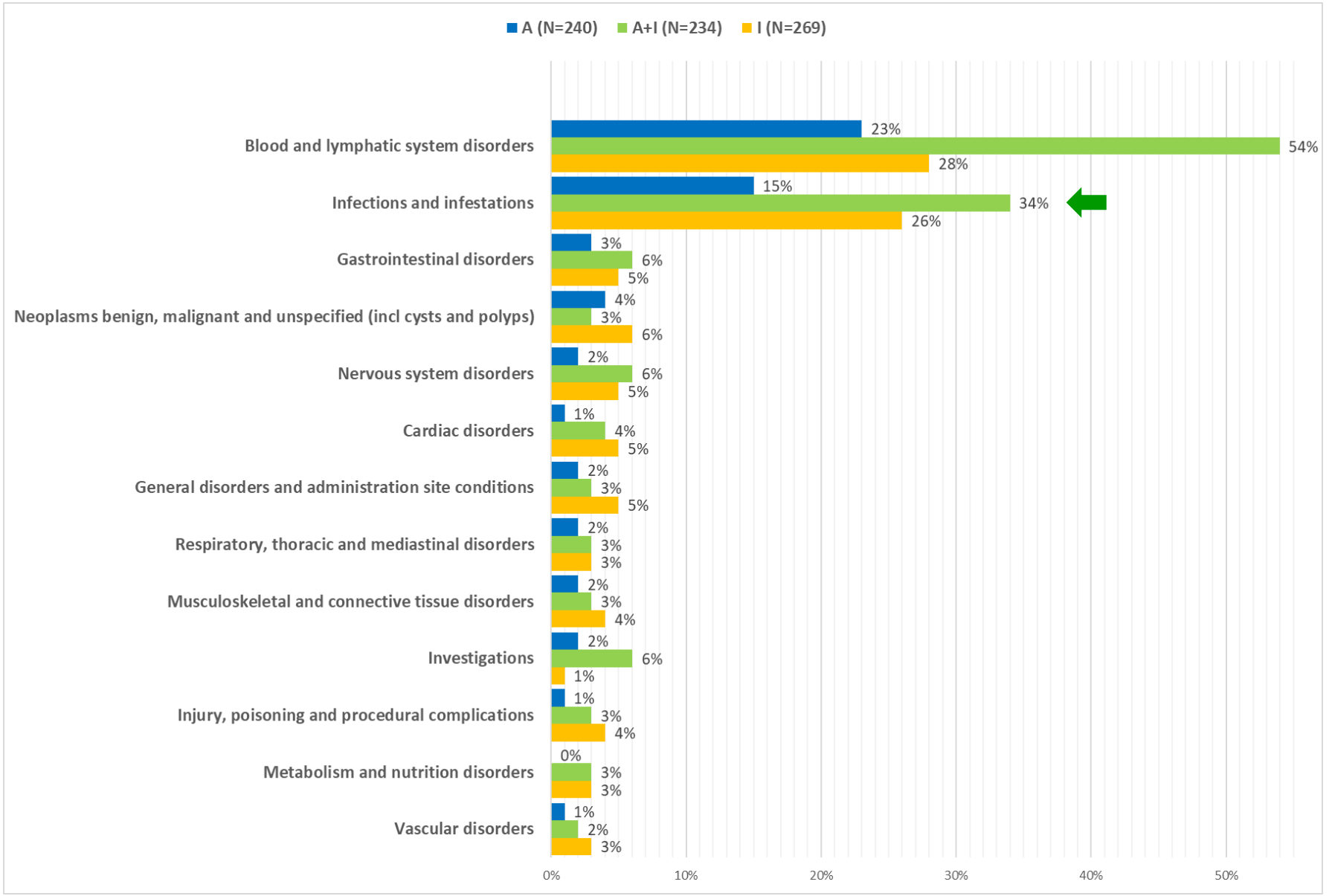

Numbers At Risk

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | 288 | 270 | 260 | 255 | 243 | 238 | 233 | 222 | 186 | 145 | 92 | 73 | 41 | 23 | 5 | 1 |
| A+I | 292 | 281 | 267 | 262 | 257 | 253 | 248 | 235 | 201 | 160 | 107 | 83 | 39 | 26 | 8 | 2 |
| I | 290 | 282 | 273 | 266 | 264 | 259 | 253 | 243 | 194 | 147 | 101 | 78 | 41 | 21 | 7 | 2 |

- **ASCT + I OR I vs ASCT**: Ibrutinib containing arms were superior
- **ASCT + I vs I:** Analysis Ongoing

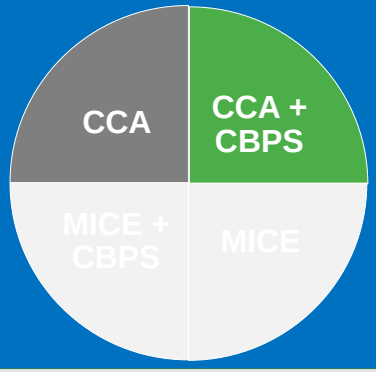
Abstract #240

# *TRIANGLE:* Grade ≥3 AEs (maintenance/follow-up)

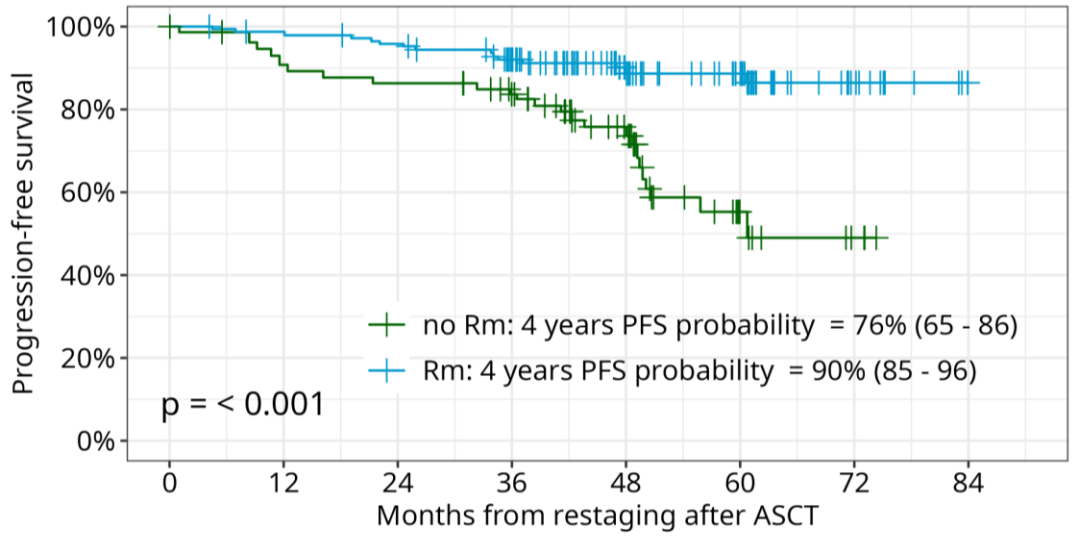



Abstract #240

# PFS based on Rituximab maintenance

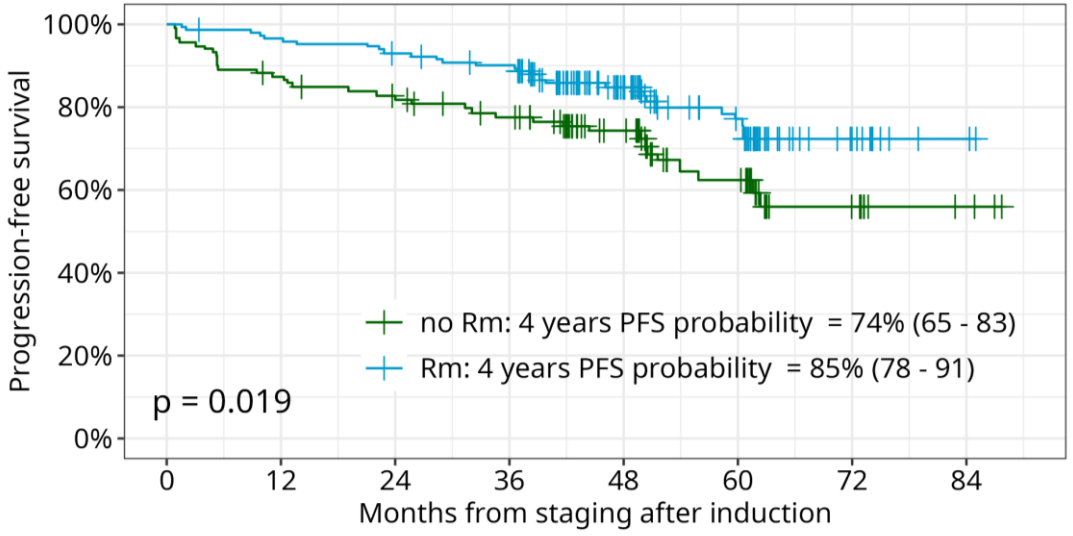



## Arm A+I: PFS




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| noRm group | | | | | | | | |
| At risk | 85.3 | 75.1 | 71.6 | 63.8 | 41 | 12.9 | 6 | 0 |
| Event | 0 | 8.1 | 11.5 | 13.5 | 19.5 | 28.7 | 29.7 | 29.7 |
| Rm group | | | | | | | | |
| At risk | 151.8 | 146.9 | 142.1 | 125.8 | 85.7 | 63 | 24.5 | 0 |
| Event | 0 | 3.1 | 6.9 | 12.8 | 14.6 | 15.5 | 16.6 | 16.6 |

## Arm I: PFS




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| noRm group | | | | | | | | |
| At risk | 116.7 | 100.7 | 92.5 | 82.6 | 59.8 | 38.2 | 19.3 | 6 |
| Event | 0 | 14.1 | 20.2 | 26.2 | 29.2 | 35.8 | 37.7 | 37.7 |
| Rm group | | | | | | | | |
| At risk | 157.2 | 148.3 | 141.5 | 135.3 | 87.3 | 57.9 | 23 | 3.9 |
| Event | 0 | 7 | 12.8 | 16.9 | 22.8 | 28.7 | 30.6 | 30.6 |

*Propensity Score including MIPI single variables, response after induction (arm I) after ASCT (arm A, A+I), Ki67, cytology

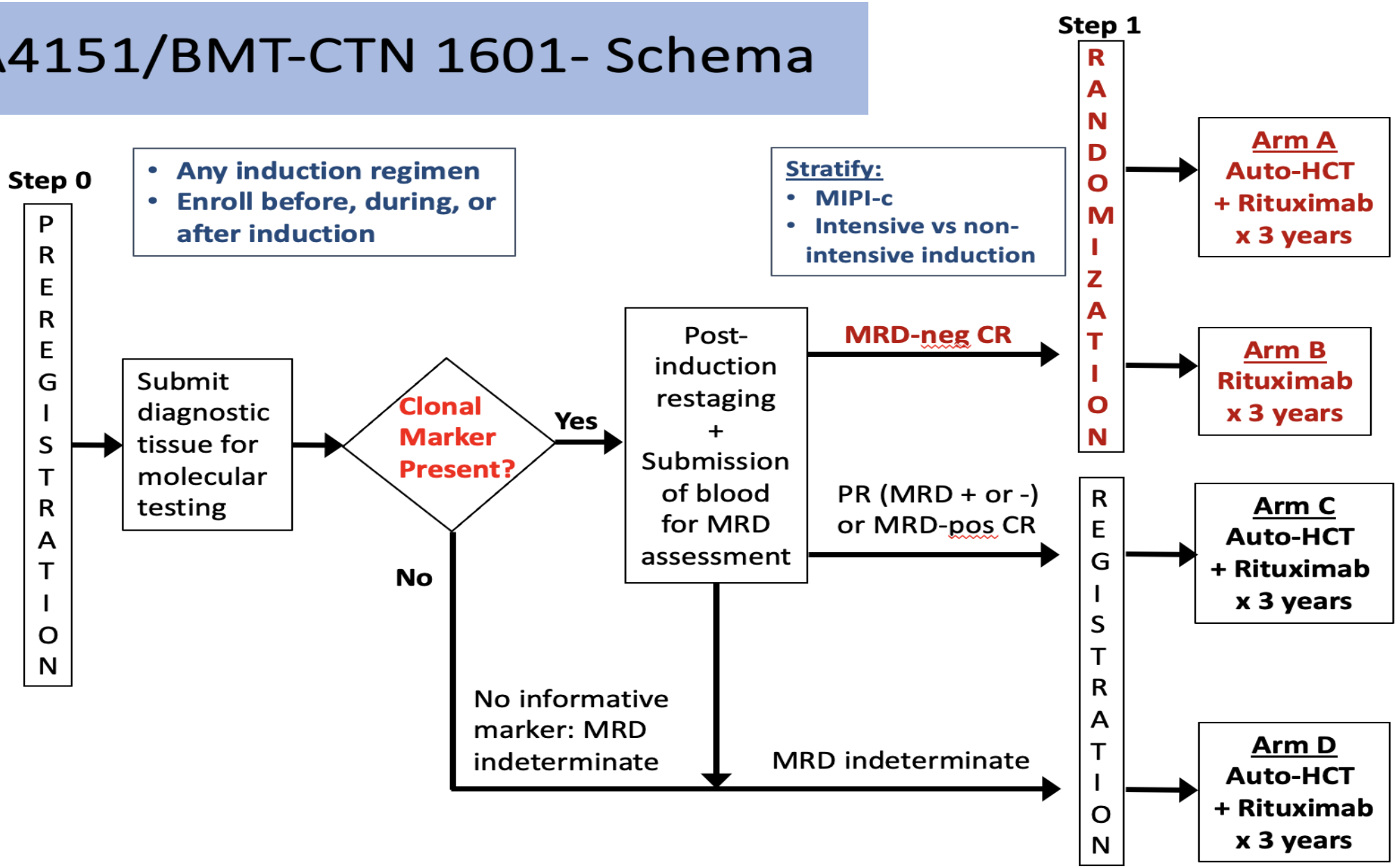
Abstract #237

# LBA-6: Lack of Benefit of Autologous Hematopoietic Cell Transplantation (auto-HCT) in Mantle Cell Lymphoma (MCL) Patients (pts) in First Complete Remission (CR) with Undetectable Minimal Residual Disease (uMRD): Initial Report from the ECOG-ACRIN EA4151 Phase 3 Randomized Trial

**Timothy S. Fenske, MD**1, Xin Victoria Wang, PhD2*, Brian G. Till, MD3, Kristie A. Blum, MD4, Matthew Lunning, DO5, Hillard M. Lazarus, MD6, Paul A.S. Fishkin, MD7, Lale Kostakoglu Shields, MD, MPH8*, David W. Scott, MBChB, PhD9, Ann S. LaCasce, MD10, Patrick B. Johnston, MD, PhD11*, Amanda F. Cashen, MD12, Leslie L. Popplewell, MD, MPH13, Robert M. Dean, MD14, Nausheen Ahmed, MD15, Nirav N. Shah, MD16, Nina D. Wagner-Johnston, MD17, Boyu Hu, MD18, Bhagirathbhai R. Dholaria, MBBS19, Richard F. Little, MD, MPH20, Jonathan W. Friedberg, MD21, John P. Leonard, MD22 and Brad S. Kahl, MD12

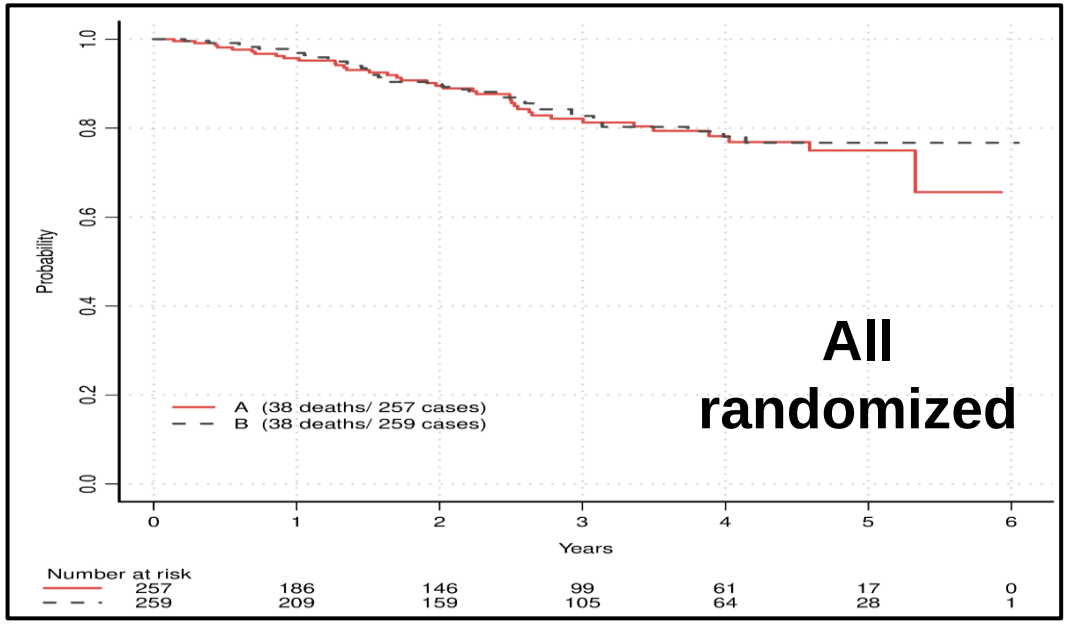
1 Medical College of Wisconsin, Milwaukee, WI, 2 Dana-Farber Cancer Institute / ECOG-ACRIN Biostatistics, Boston, MA, 3 Fred Hutchinson Cancer Center, University of Washington, Seattle, WA, 4 Emory University / Winship Cancer Institute, Atlanta, GA, 5 University of Nebraska Medical Center, Omaha, NE, 6 Case Western Reserve University, Cleveland, OH, 7 Illinois CancerCare, P.C., Peoria, IL, 8 NYU Langone Health, New York, NY, 9 Centre for Lymphoid Cancer, British Columbia Cancer, Vancouver, BC, Canada, 10 Dana-Farber Cancer Institute, Boston, MA, 11 Mayo Clinic, Rochester, MN, 12 Washington University School of Medicine, Saint Louis, MO, 13 City of Hope Cancer Treatment Center, Atlanta, GA, 14 Case Comprehensive Cancer Center, Cleveland Clinic Taussig Cancer Institute and Case Western Reserve University, Cleveland, OH, 15 University of Kansas Cancer Center, Kansas City, KS, 16 Medical College of Wisconsin, Brookfield, WI, 17 Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, Baltimore, MD, 18 Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, 19 Vanderbilt University Medical Center, Nashville, TN, 20 National Cancer Institute, National Institutes of Health, Washington, DC, 21 Wilmot Cancer Institute, University of Rochester, Rochester, NY, 22 Weill Cornell Medicine, New York, NY.

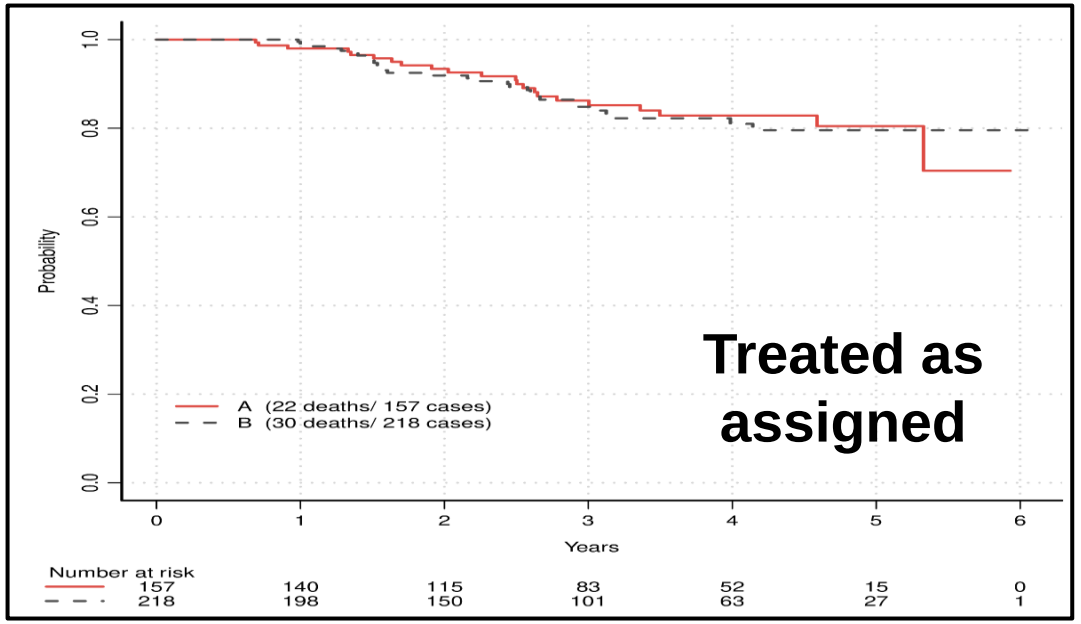
# EA4151/BMT-CTN 1601- Schema



# OS – Arms A & B

- With median follow up of 2.7 years, the futility boundary was an OS hazard ratio (HR) of 0.984 for Arm A vs B.
- The estimated OS HR for Arm A vs B in all randomized (n=516) and pts treated as assigned (n=375) were 1.11 (CI 0.71-1.74, p=0.66) and 1.00 (CI 0.58-1.74, p=0.99), respectively **and crossed the futility boundary**.
- The 3 year OS for Arms A and B were 82.1% and 82.7% in all randomized pts, and 86.2% and 84.8% in pts treated as assigned.



# Chemo-free induction?

# Abstract #235: Ibrutinib-Rituximab Is Superior to Rituximab-Chemotherapy in Previously Untreated Older Mantle Cell Lymphoma Patients: Results from the International Randomized Controlled Trial, Enrich

***David John Lewis, MD**1*, Mats Jerkeman, MD, PhD2, Lexy Sorrell3*, David Wright4*, Ingrid Glimelius, MD, PhD5, Annika Pasanen, MD, PhD6*, Jacob Haaber Christensen, MD, PhD7*, Karin Fahl Wader, MD, PhD8*, Andrew J. Davies, MD, PhD9*, Nick Morley10*, Christopher McNamara, MD11*, Christian Bjørn Poulsen, MD, PhD12*, Jon Riise, MD, PhD13*, Kristina Sonnevi, MD PhD14*, Ingemar Lagerlöf, PhD15*, Cathy Burton16*, Surita Dalal, PhD17*, Andrew Rawstron, PhD18*, Ruth M de Tute, MSc, PhD, FRCPath17*, Victoria Allgar19*, Sree Aroori19*, Mark Warner19*, Brian Wainman19*, Claire Scully19*, Jeanette Sanders19*, Carsten Utoft Niemann, MD, PhD20*, Helle Toldbod, PhD, MS21*, Nicola Crosbie1*, Mark J , PhD, MBChB22, Toby A. Eyre23* and Simon Rule, MD1,24**

1 University Hospitals Plymouth NHS Trust, Plymouth, United Kingdom, 2 Lund University Hospital, Lund, Sweden, 3 Plymouth University, Faculty of Health, Plymouth, United Kingdom, 4 Institute of Health Research, Exeter University, Exeter, United Kingdom, 5 Department of Immunology, Genetics and Pathology, Cancer Precision Medicine Unit, Uppsala University, Uppsala, Sweden, 6 Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland, 7 Dept. of Hematology, Odense University Hospital, Odense, Denmark, 8 St. Olav University Hospital, Department of Oncology, Trondheim, Norway, 9 Southampton Experimental Cancer Medicine Centre, University of Southampton, Southampton, United Kingdom, 10 Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, 11 University College London Hospitals NHS Foundation Trust, London, United Kingdom, 12 Department of Hematology, Zealand University Hospital, Roskilde, Denmark, 13 Department of Oncology, Oslo University Hospital, Oslo, Norway, 14 Karolinska University Hospital, Department of Haematology, Stockholm, Sweden, 15 Linkoping University Hospital, Linkoping, Sweden, 16 Haematology, Leeds Cancer Centre, Leeds, United Kingdom, 17 HMDS, Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, 18 Haematological Malignancy Diagnostic Service, Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, 19 Plymouth University, Peninsula Clinical Trials Unit, Plymouth, United Kingdom, 20 Department of Hematology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, 21 Aarhus University Hospital, Aarhus C, Denmark, 22 Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom, 23 Department of Clinical Haematology, Oxford University Hospitals NHS Trust, Old Road, United Kingdom, 24 Executive Director, Haematology R&D, AstraZeneca, Cambridge, United Kingdom.

# Trial design

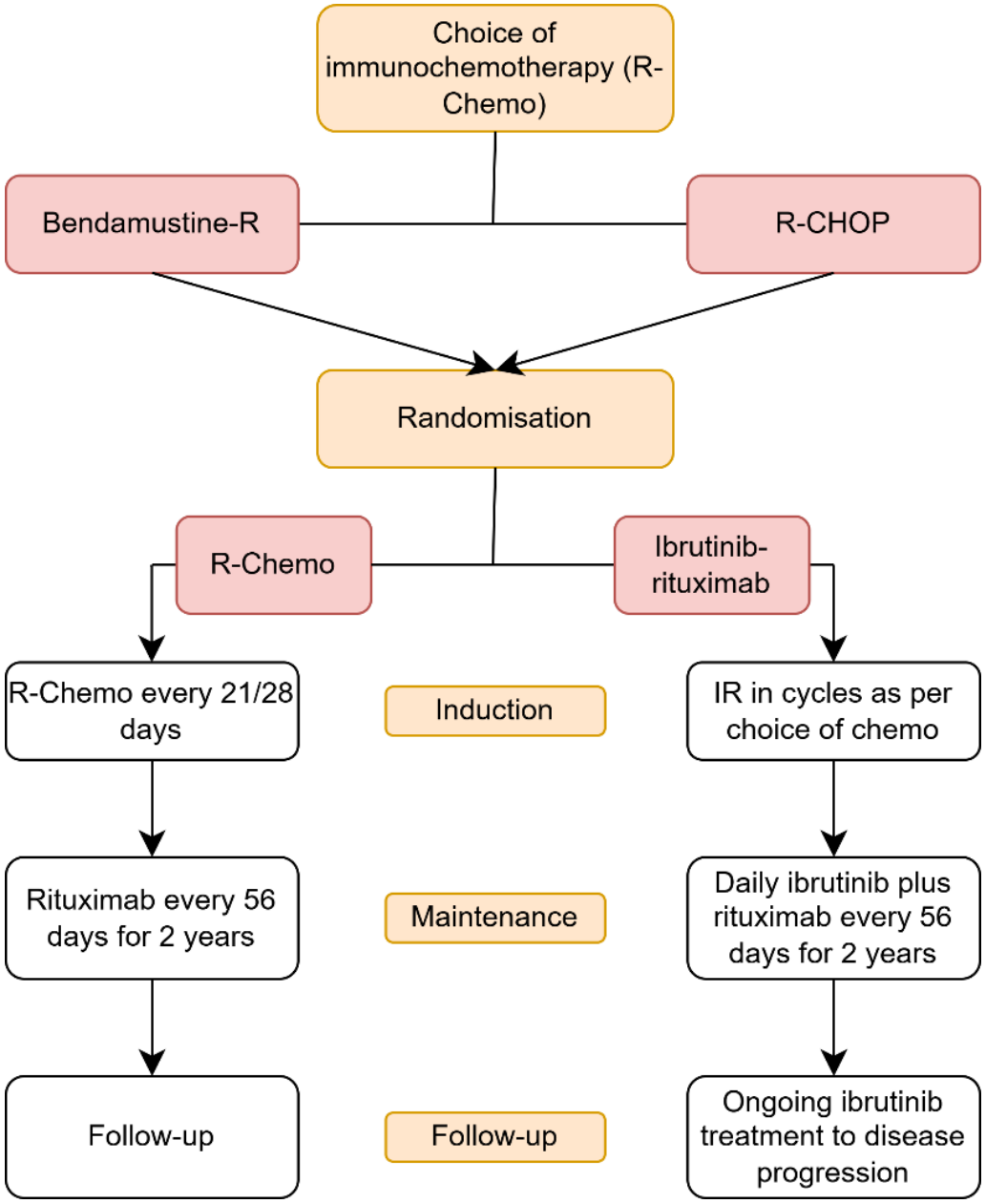
- Inclusion criteria

•60 years or older
•Pathologically confirmed MCL
•Previously untreated, measurable (>1.5cm), stage II-IV MCL in need of treatment
•ECOG 0-2

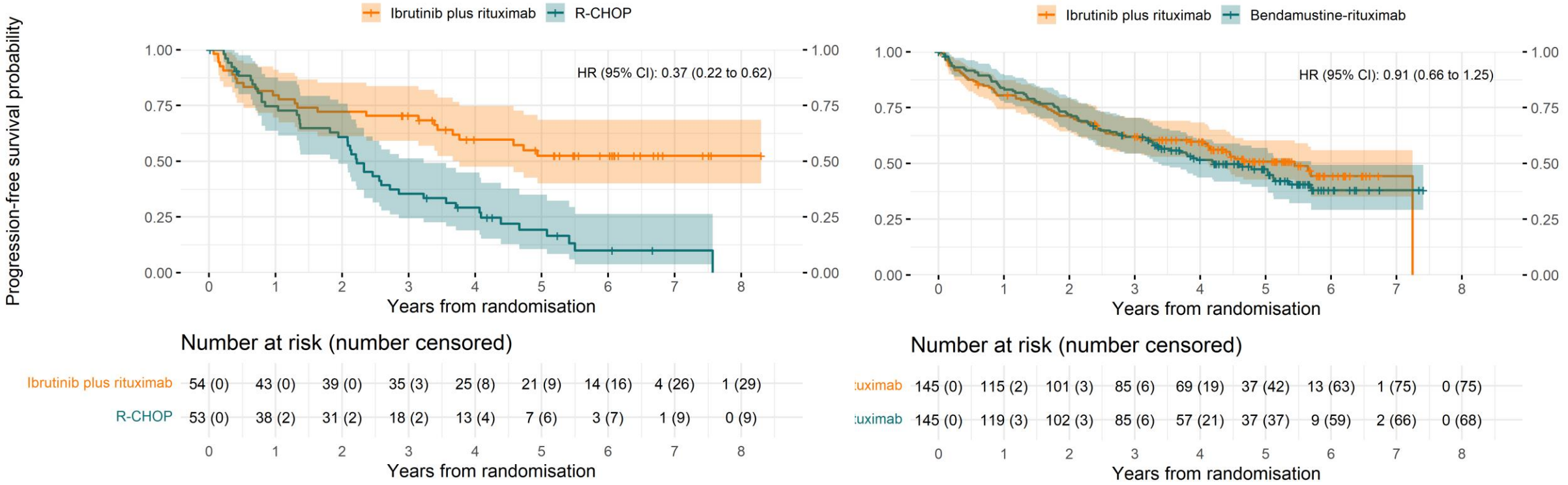
- Exclusion criteria

•Considered fit for stem cell transplantation
•CNS involvement

**Rituximab** 375mg/m$^2$
**Ibrutinib** - 560mg od
**Bendamustine** 90mg/m$^2$ D1+D2 of 28 day cycle
**CHOP** - (Cyclophosphamide 750mg/m$^2$, Doxorubicin 50mg/m$^2$, Vincristine 1.4mg/m$^2$, Prednisolone 100mg *5 days) 21 day cycle
Maintenance rituximab - 1400mg sc every 56 days



# PFS for R-CHOP or BR vs IR




**PFS difference is mainly driven by lack of benefit with R-CHOP**

- **Similar findings with OS**

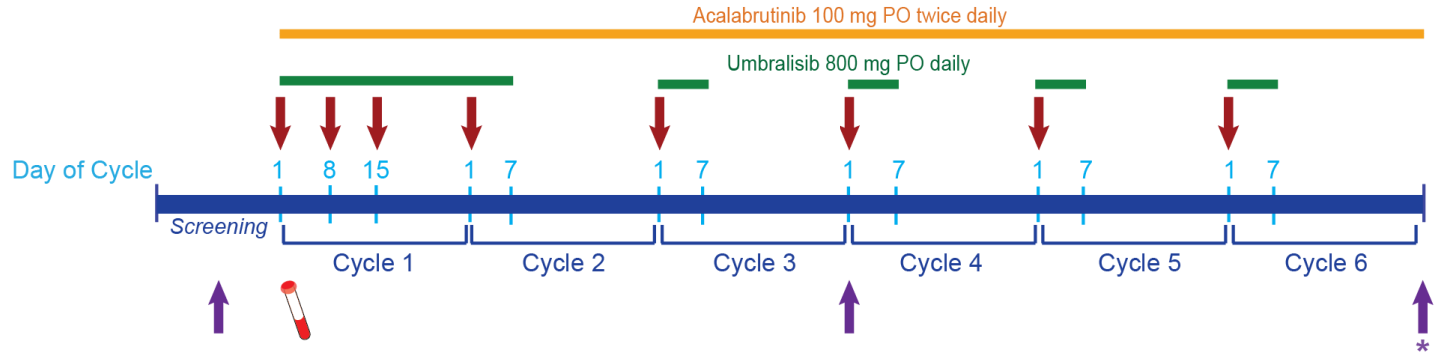
**Subgroup analysis:**

- **Blastoid (n=25) – Shorter PFS with IR**
- **TP53 Mutation (n=40) – Longer PFS with IR**

Abstract #235

# Acalabrutinib-umbralisib-ublituximab (AU2) in MCL: Dosing Schema

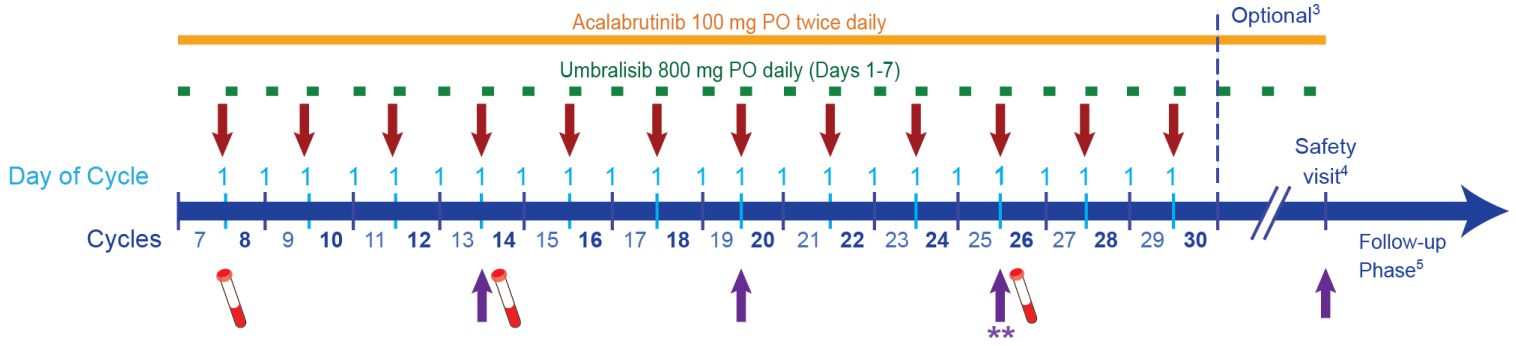

**Induction Phase (6 cycles)**




12 patients
6/12 had *TP53* mutation

**Maintenance Phase (24 cycles)**

***Ublituximab* <u>every 2 cycles</u>**

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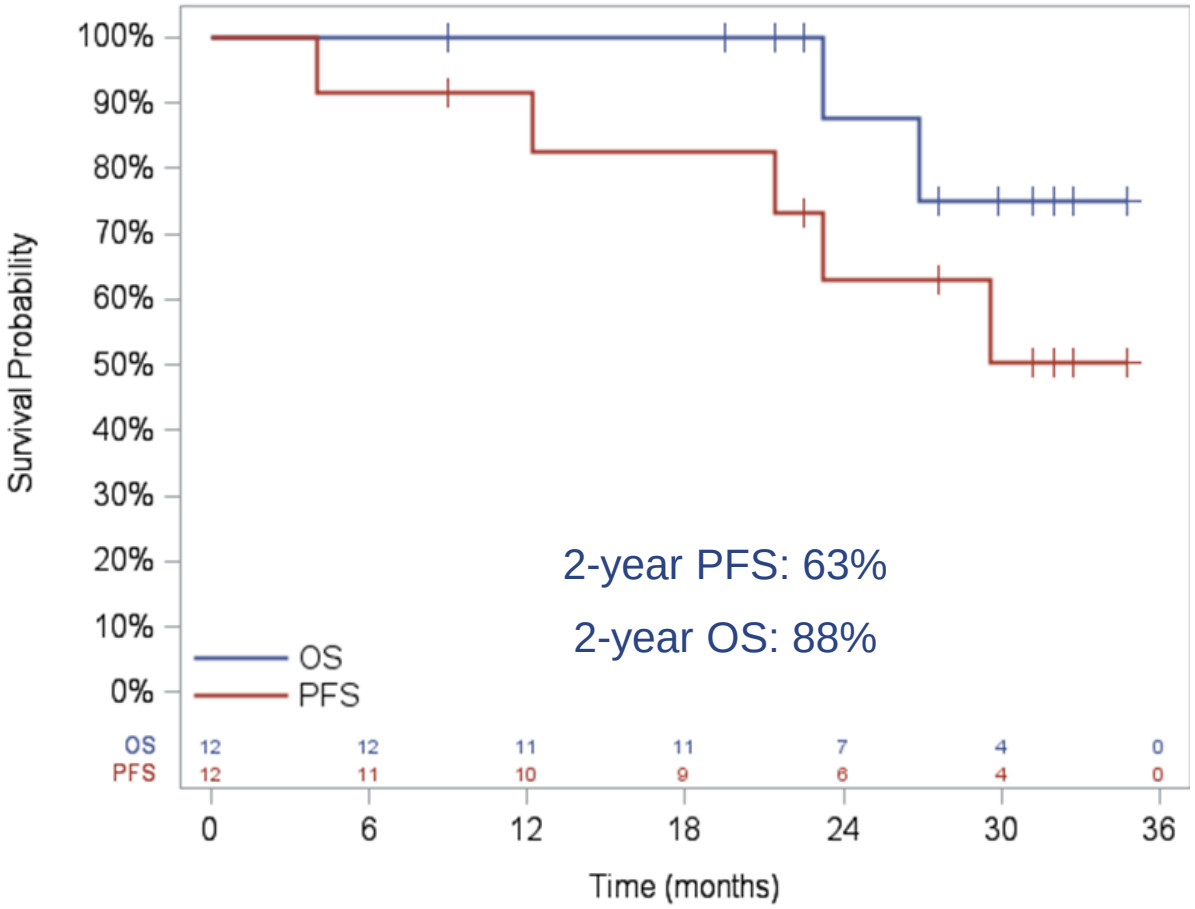
# AU2 efficacy after median follow up 2.5 years

## All patients

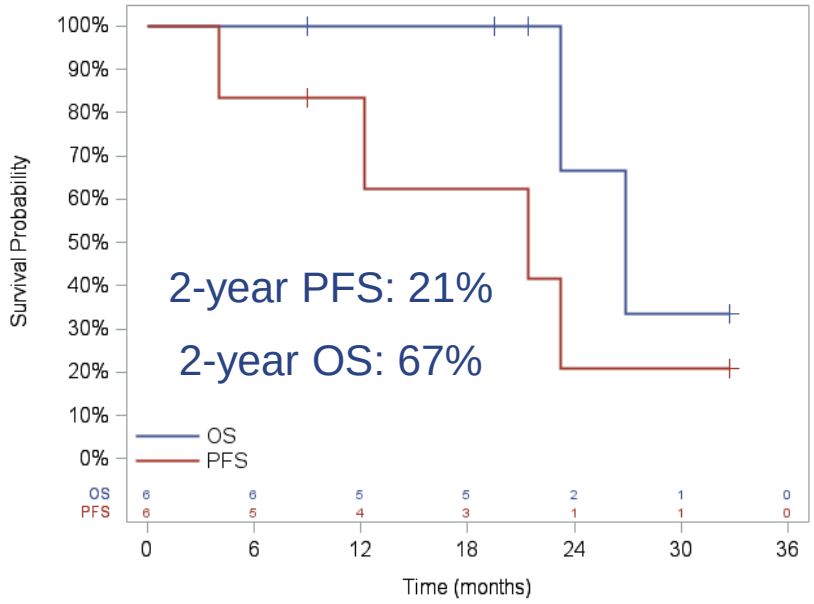



**ORR 100%**

**CR 100%**

**uMRD ($10^{-6}$) 73%**

## *TP53*$^{mut}$

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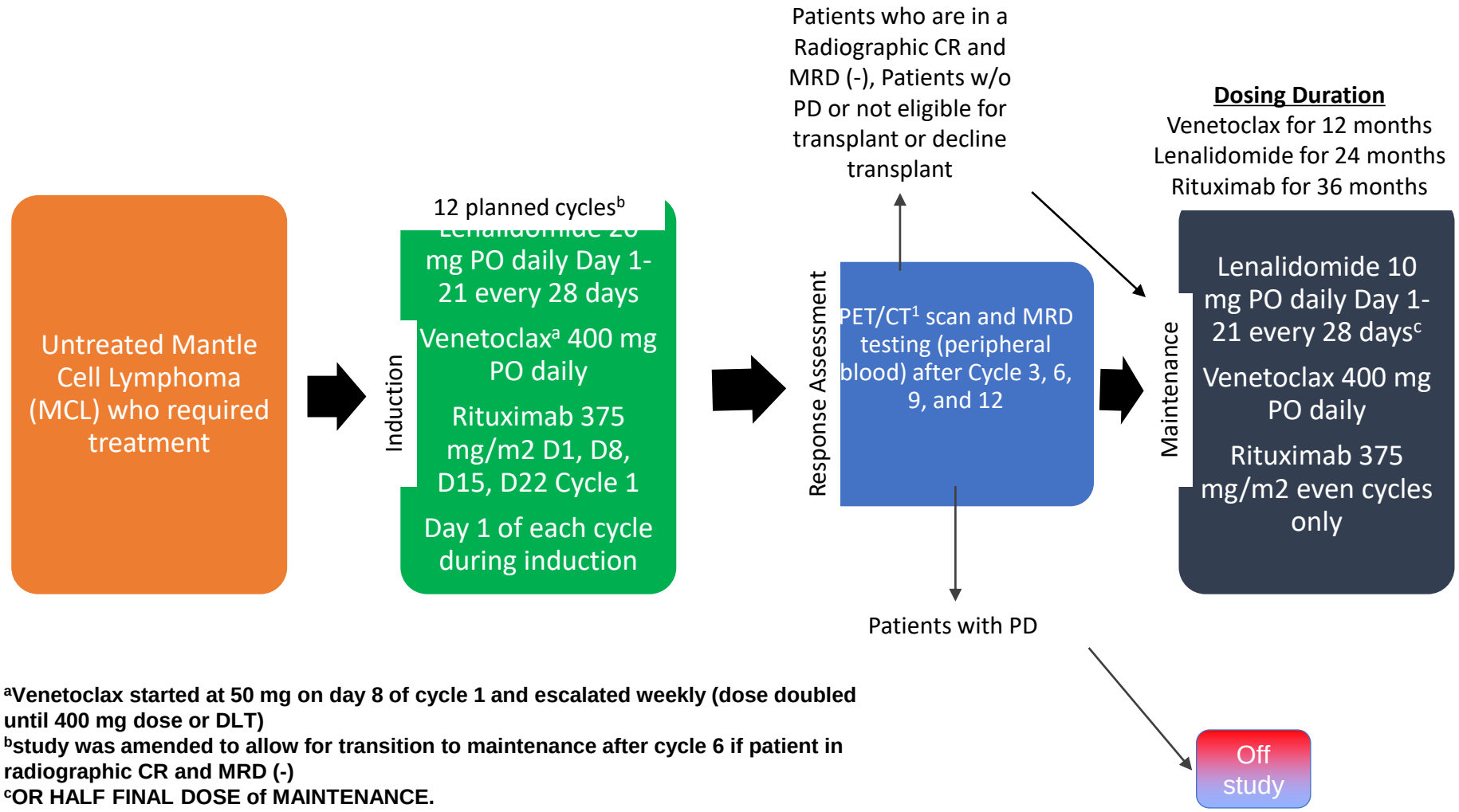
# Venetoclax+Lenalidomide+Rituximab (VALOR) in de novo MCL




**[a]Venetoclax started at 50 mg on day 8 of cycle 1 and escalated weekly (dose doubled until 400 mg dose or DLT)**
**[b]study was amended to allow for transition to maintenance after cycle 6 if patient in radiographic CR and MRD (-)**
**[c]OR HALF FINAL DOSE of MAINTENANCE.**

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# Patient characteristics

| Characteristic | Patients (N =28) |
|---|---|
| Variant<br>• Blastoid/Blastic<br>• Pleomorphic | <br>• 4 (14%)<br>• 2 (7%) |
| Ki-67<br>• <30%<br>• ≥30% | <br>• 8 (one not reported at COH)<br>• 19 |
| P53 status<br>• Deleted<br>• Mutated | <br>• 1 (had concurrent mutation)<br>• 4* |
| Cytogenetics at diagnosis<br>• 25<br>• 3 | <br>• Normal<br>• Abnormal |
| Unfit for or ineligible for high dose chemotherapy | • 3 patients<br>  • Two patients for age/fitness<br>  • One patient concurrent medical condition |

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# Toxicities

| AE Name | Any Grade | Grade >= 3 |
|---|---|---|
| Neutrophil count decreased | 85.7%(24) | 75%(21) |
| Platelet count decreased | 60.7%(17) | 60.7%(17) |
| Anemia | 50%(14) | 32.1%(9) |
| Febrile neutropenia | 14.3%(4) | 14.3%(4) |
| Tumor lysis syndrome | 14.3%(4) | 14.3%(4) |
| Hypokalemia | 28.6%(8) | 10.7%(3) |
| White blood cell decreased | 21.4%(6) | 10.7%(3) |
| Lymphocyte count decreased | 14.3%(4) | 10.7%(3) |
| Diarrhea | 75%(21) | 7.1%(2) |
| Fatigue | 71.4%(20) | 7.1%(2) |
| Upper respiratory infection | 25%(7) | 3.6%(1) |
| Dysgeusia | 42.9%(12) | 0%(0) |
| Nausea | 42.9%(12) | 0%(0) |
| Headache | 39.3%(11) | 0%(0) |
| Bruising | 28.6%(8) | 0%(0) |
| Constipation | 28.6%(8) | 0%(0) |
| Pruritus | 28.6%(8) | 0%(0) |
| Abdominal pain | 25%(7) | 0%(0) |
| Rash maculo-papular | 25%(7) | 0%(0) |

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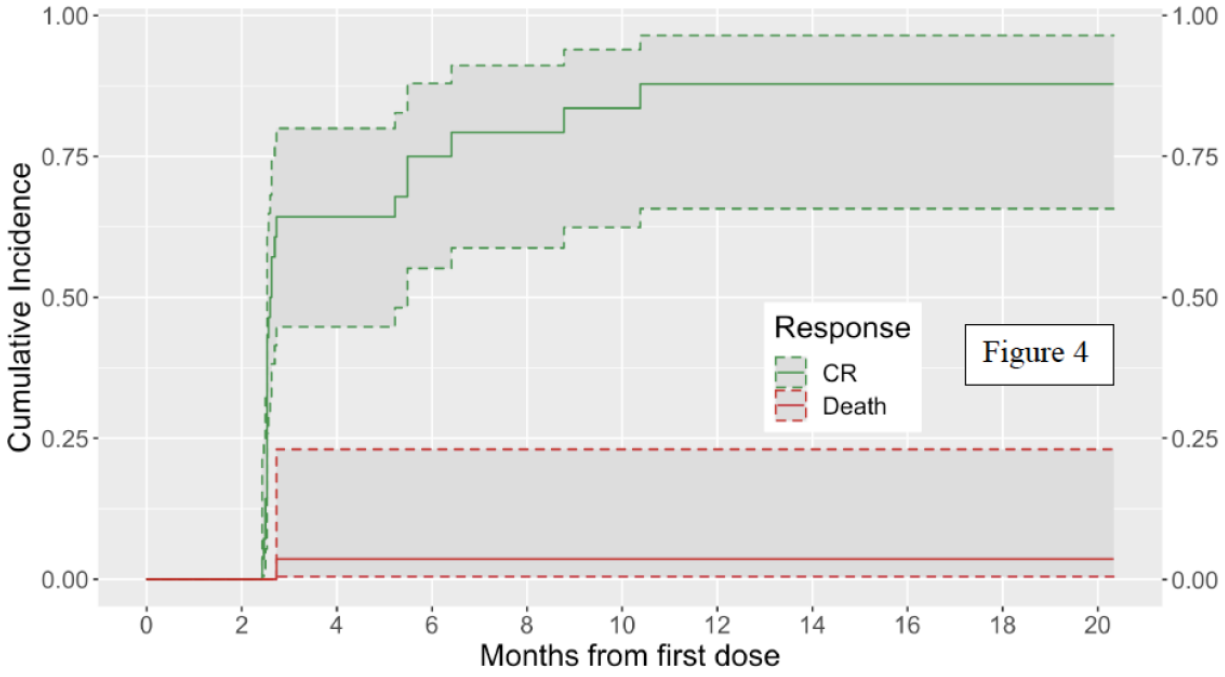
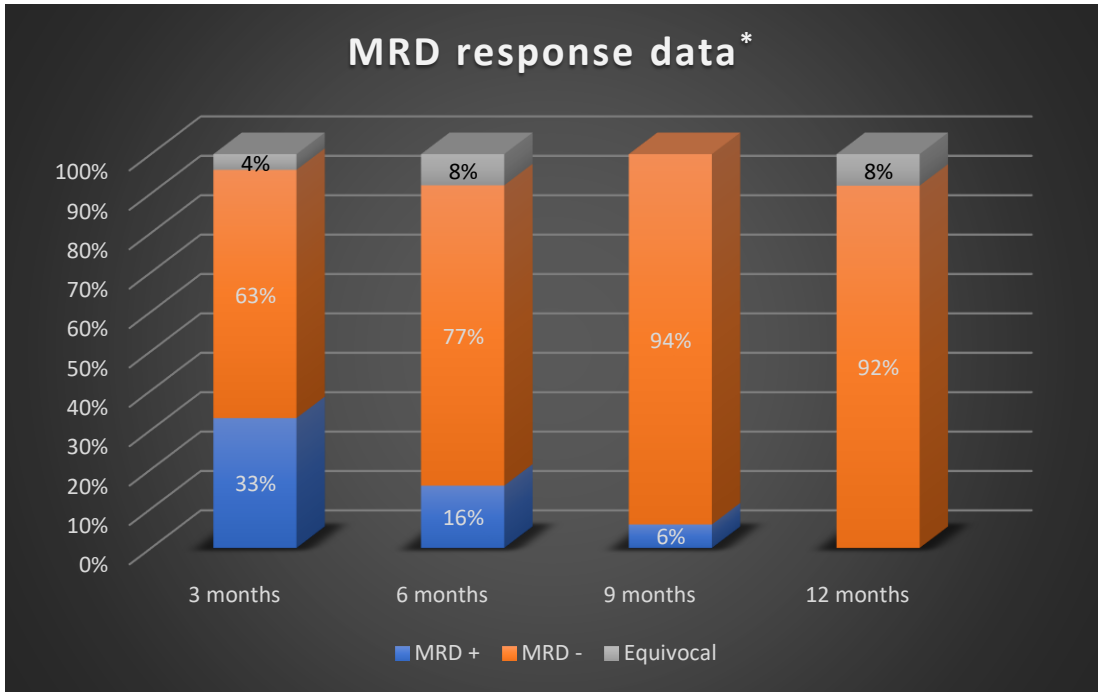
# Response and MRD

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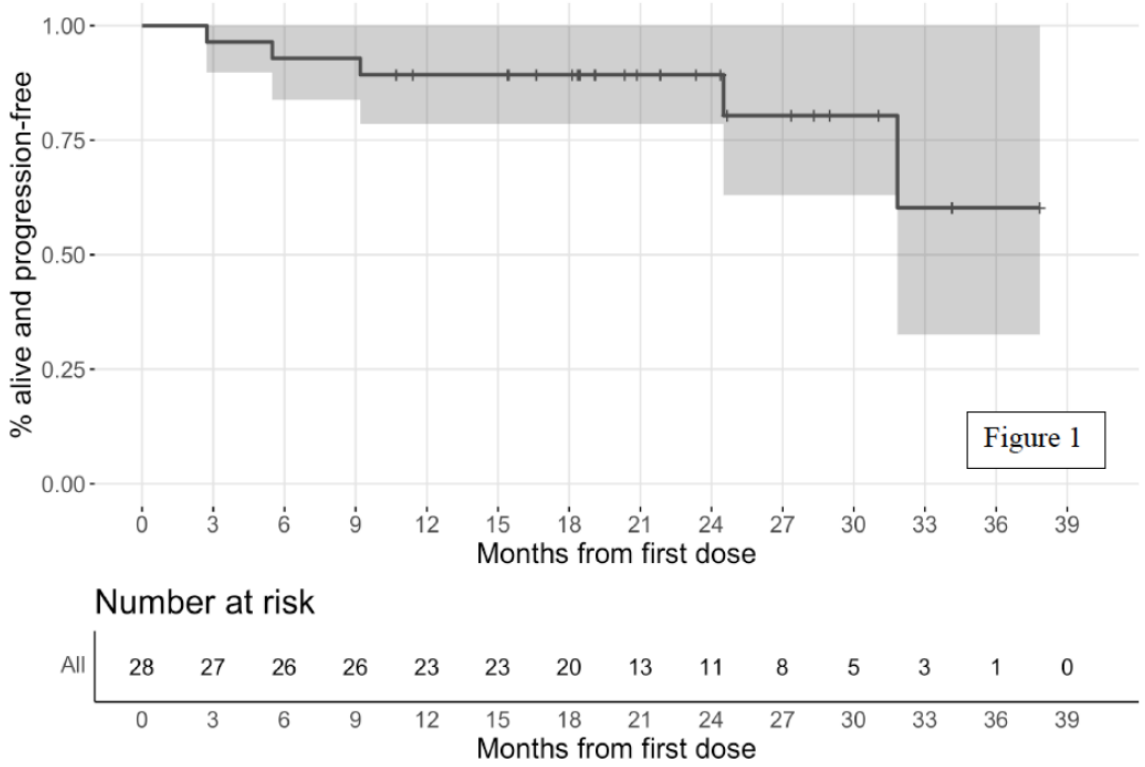
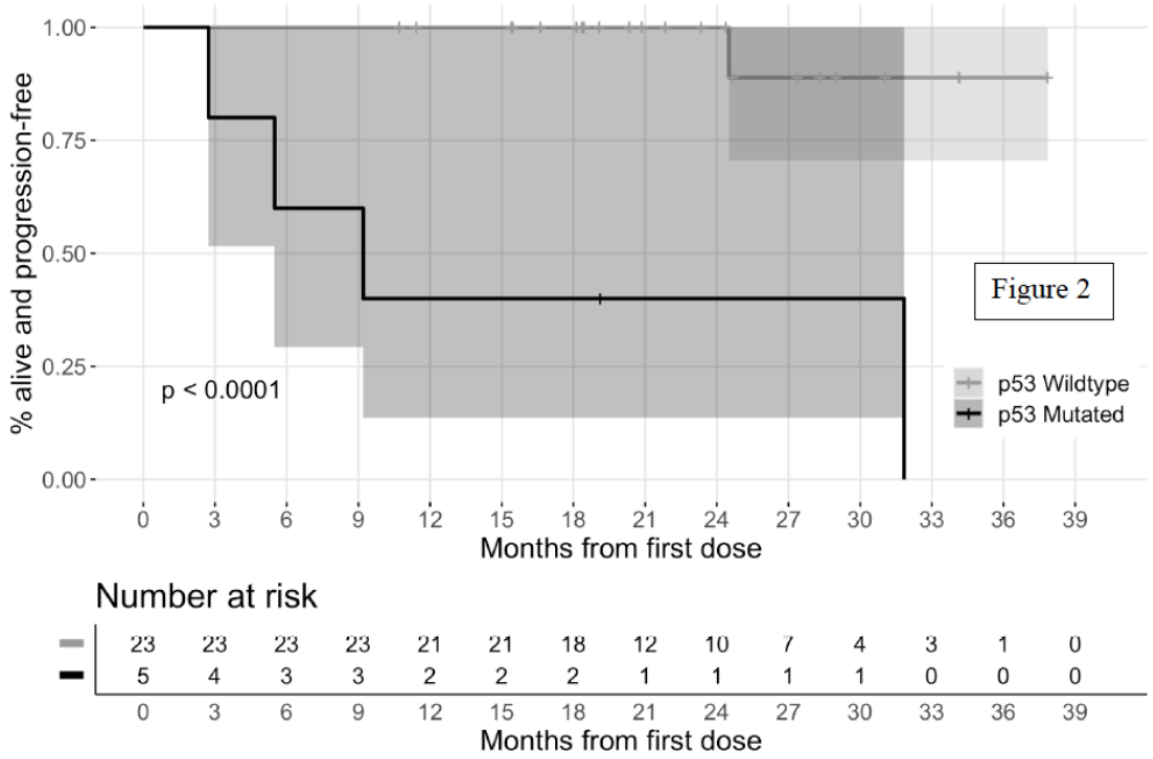
# Progression-free survival




2-year PFS = 89%

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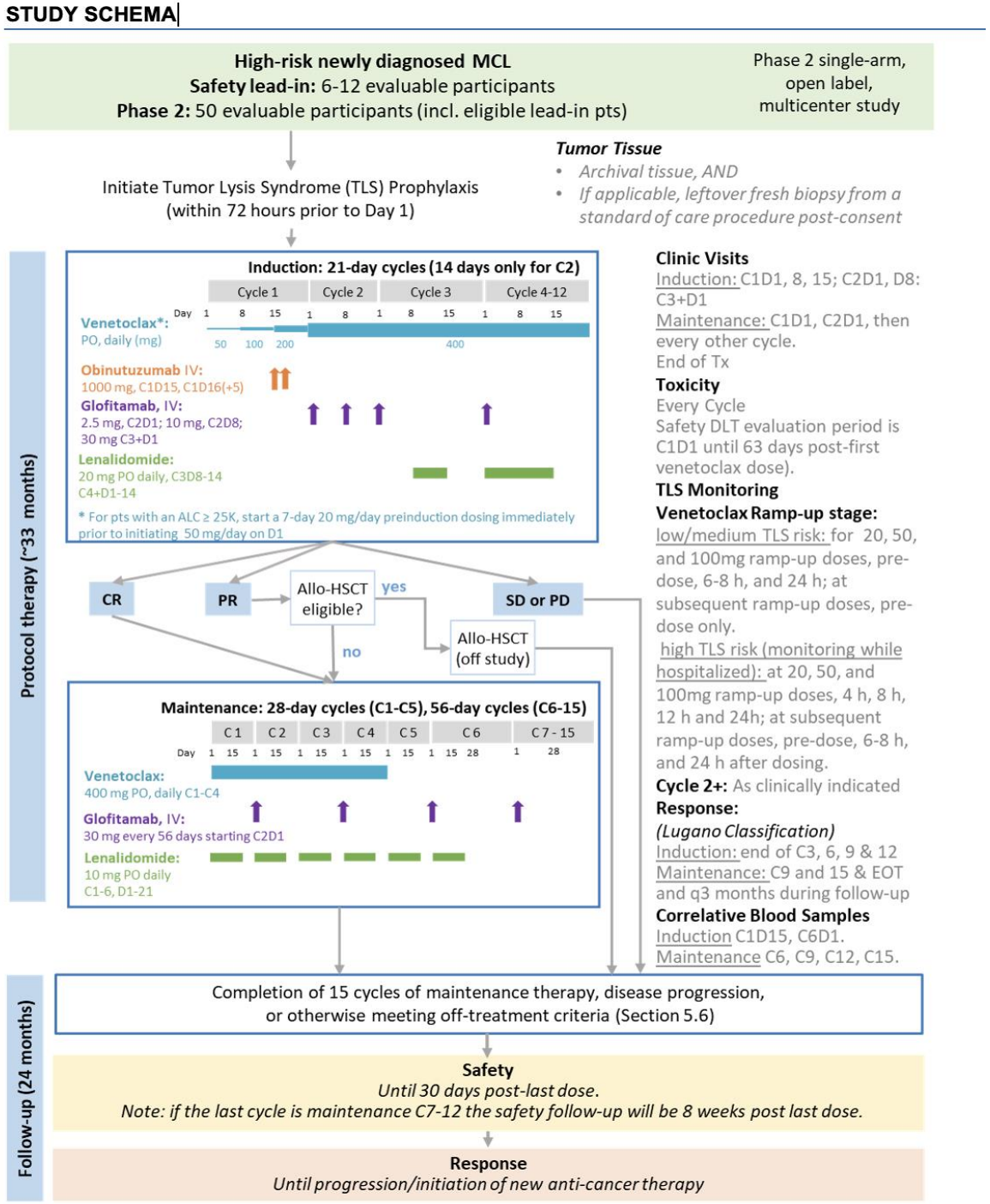
# GLOVe in 1L high-risk MCL

- **Inclusion**
  - High risk features as classified by Jain et al. JCO 2020
    - Blastoid/Pleomorphic variants
    - Ki67≥50%
    - Presence of a TP53 mutation defined by either molecular testing or IHC
    - del (17p) by FISH
    - complex karyotype
      - 3 or more cytogenetic abnormalities in addition to t(11:14)
    - High-risk MIPI score (≥6.2)
    - Bulky disease
- **Exclusion**
  - Prior systemic therapy excluding corticosteroids.

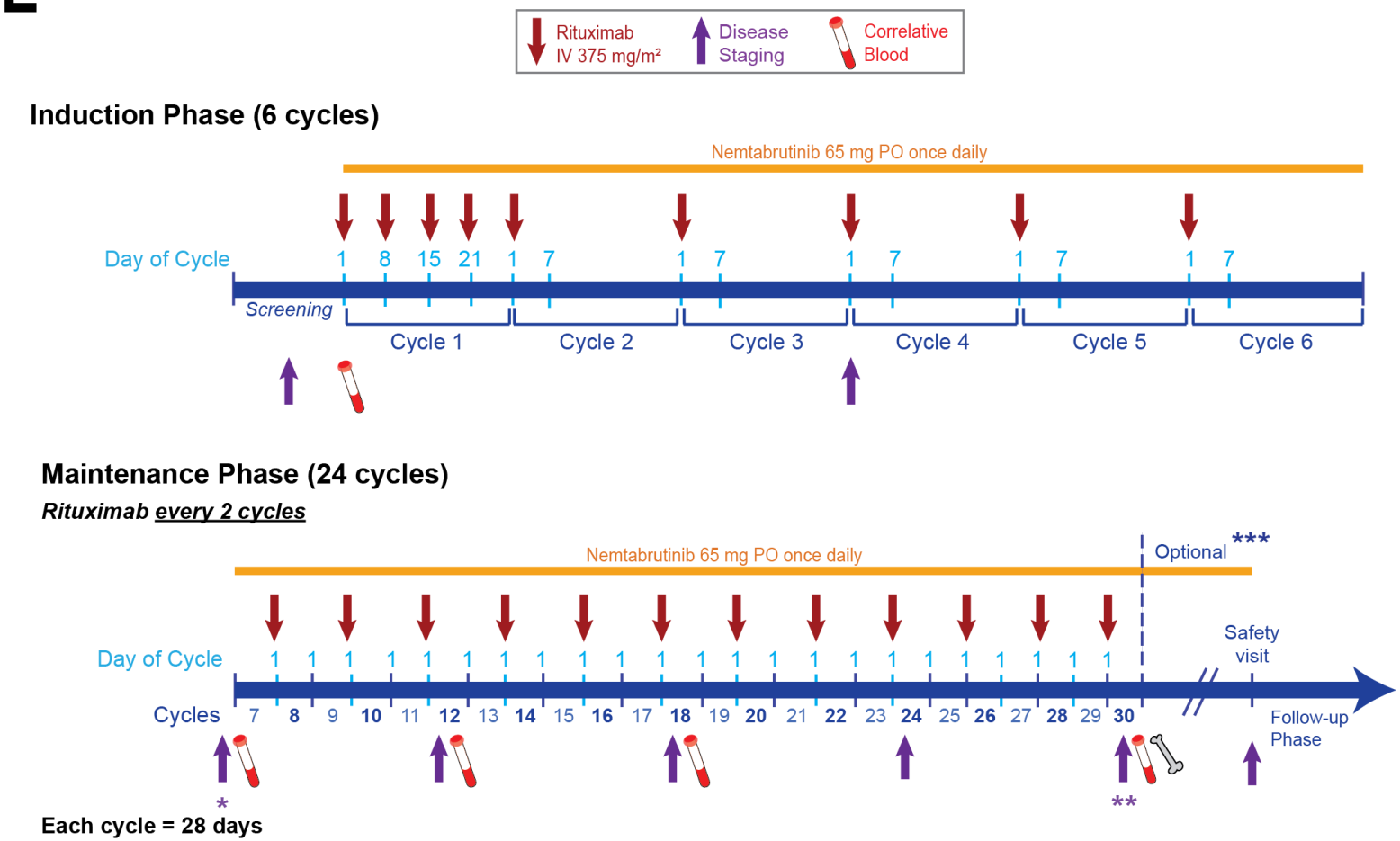


# R-nemta in *de novo* MCL

- **Inclusion**
  - Pretty much any patients with previously untreated MCL

**Participating sites:**

- COH Duarte
- COH Atlanta
- Northwestern University
- Cleveland Clinic




*Participants with PR or CR at the end of Induction will be eligible to proceed to Maintenance

Participants may continue therapy with nemtabrutinib beyond 30 cycles if they have not achieved or maintained CR state at the end of 30 cycles of therapy

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# Summary: MCL

Targeted therapy with BTKi secured its role in frontline therapy for MCL
ECHO is the preferred regimen for older patients
Most patients with MCL do not need consolidation with ASCT in first remission.
*It is entirely unclear which patients, if any, need ASCT*
Rituximab maintenance can prolong PFS in targeted era
In this context, ECHO regimen is a reasonable approach to use in the initial treatment of younger patients
Chemo-free regimens are coming fast and furious

ECHO – BR+acala improves PFS over BR
Triangle – No benefit to ASCT in era of BTKi. Rituximab maintenance improves PFS
Enrich – IR improves PFS & OS over RCHOP and less toxicity than BR in frontline
EA4151 – Minimal (if any) benefit to ASCT in era of BTKi