Memorial Sloan Kettering Cancer Center

# Copanlisib

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# Disclosures

**Consultation or advisory role**

ADC Therapeutics, Arvinas, Astra Zeneca, Bayer, F. Hoffmann-La Roche Ltd, Epizyme, Genentech Inc., ImmunoVaccine, Juno Therapeutics, Karyopharm, Merck, Rocket Medical, Seattle Genetics, TG Therapeutics, Teva

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**Expert Witness**

Bayer

**Stock and other ownership interests**

Merck

Off-label discussions are NOT medical advice

# Copanlisib in ~15 minutes

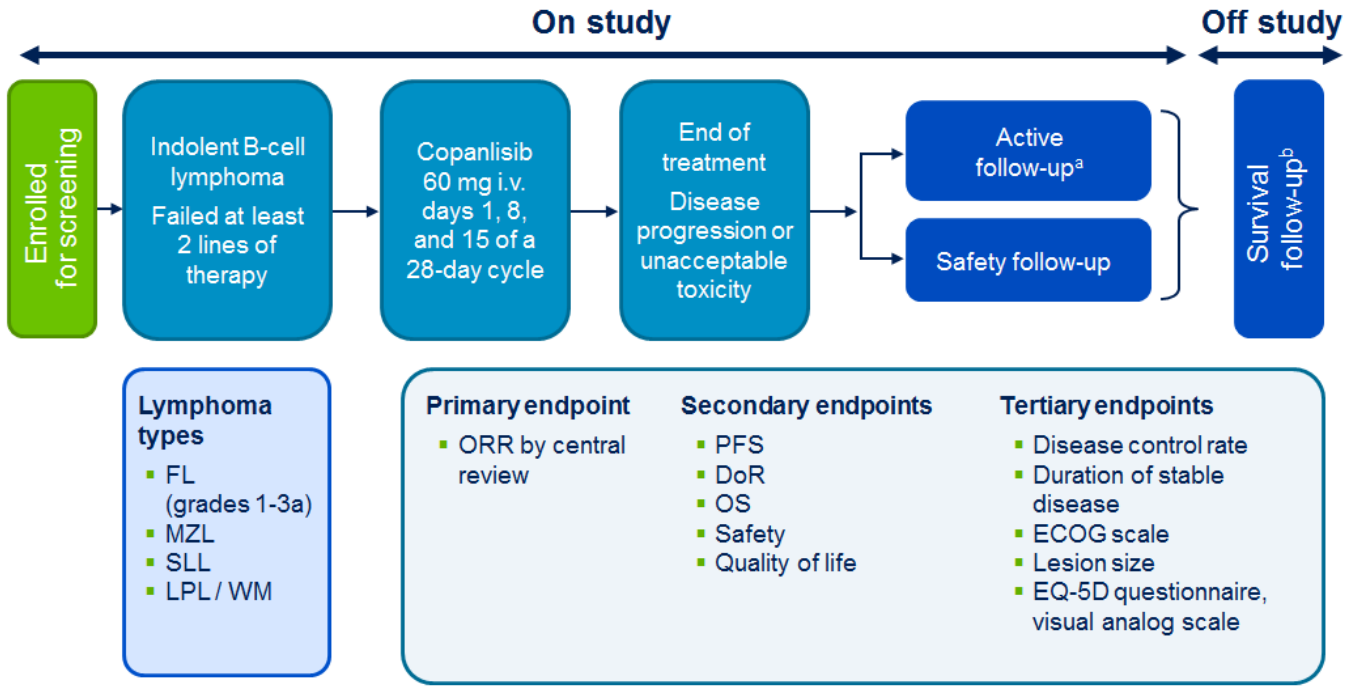
Copanlisib monotherapy – CHRONOS-1 updates

Copanlisib + rituximab – CHRONOS-3

Next steps – CHRONOS-4

# CHRONOS-1: Study Design and Patient Characteristics

- Open-label, multicenter phase 2 study of copanlisib in patients with relapsed/refractory iNHL who have progressed after **≥2 lines of treatment** (patients must have received rituximab and an alkylating agent)[1-4]




| Patient Characteristics | Total (N=142*) |
|---|---|
| Males, n (%) | 71 (50) |
| Median age, years (range) | 63 (25-82) |
| Median time from most recent progression, months (range) | 8.3 (1-73) |
| Median prior anti-cancer therapy lines (range) | 3 (2-9) |
| Prior rituximab, n (%) | 142 (100) |
| Prior alkylating agents, n (%) | 142 (100) |
| Refractory to last regimen, n (%) | 86 (61) |
| Histology, n (%)<br>FL<br>MZL<br>Other | <br>104 (73)<br>23 (16)<br>15 (11) |

[a]Patients who discontinued treatment for any reason other than progressive disease entered active follow-up. [b]Survival follow-up is 3 years. *1/142 patient later confirmed to be DLBCL
**DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **EQ-5D**, Five-Dimension EuroQol questionnaire; **FL**, follicular lymphoma; **iNHL**, indolent non-Hodgkin's lymphoma; **IV**, intravenous; **LPL/WM**, lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia; **MZL**, marginal zone lymphoma; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **SLL**, small lymphocytic lymphoma.

**1**. Dreyling M, *et al. J Clin Oncol.* 2017;35:3898-3905. **2.** Dreyling M, et al. Presented at: International Conference on Malignant Lymphoma; June 14-17, 2017; Lugano, Switzerland. **3**. ClinicalTrials.gov. NCT01660451.
**4**. Dreyling M, et al. *Am J Hematol*. 2020; doi: 10.1002/ajh.25711.

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# CHRONOS-1: 2-Year follow-up in patients with R/R iNHL

| | Total (N=142)[a] | | FL (n=104) | | MZL (n=23) | |
|---|---|---|---|---|---|---|
| | **Primary analysis (June 2016)[1]** | **2-year follow-up (Feb. 2018)[2,3]** | **Primary analysis (June 2016)[1]** | **2-year follow-up (Feb. 2018)[2,3]** | **Primary analysis (June 2016)[1]** | **2-year follow-up (Feb. 2018)[2,3]** |
| Best response, n (%) | | | | | | |
| **ORR, n (%)** | **84 (59)** | **86 (61)** | **61 (59)** | **61 (59)** | **16 (70)** | **18 (78)** |
| Complete response | 17 (12) | 24 (17) | 15 (14) | 21 (20) | 2 (9) | 3 (13) |
| Partial response | 67 (47) | 62 (44) | 46 (44) | 40 (39) | 14 (61) | 15 (65) |
| Stable disease | 43 (30)[b] | 41 (29)[b] | 35 (34)[b] | 35 (34)[b] | 4 (17) | 2 (9) |
| Progressive disease | 3 (2) | 3 (2) | 2 (2) | 2 (2) | 0 | 0 |
| NE/NA | 12 (8) | 12 (9) | 6 (6) | 6 (6) | 3 (13) | 3 (13) |

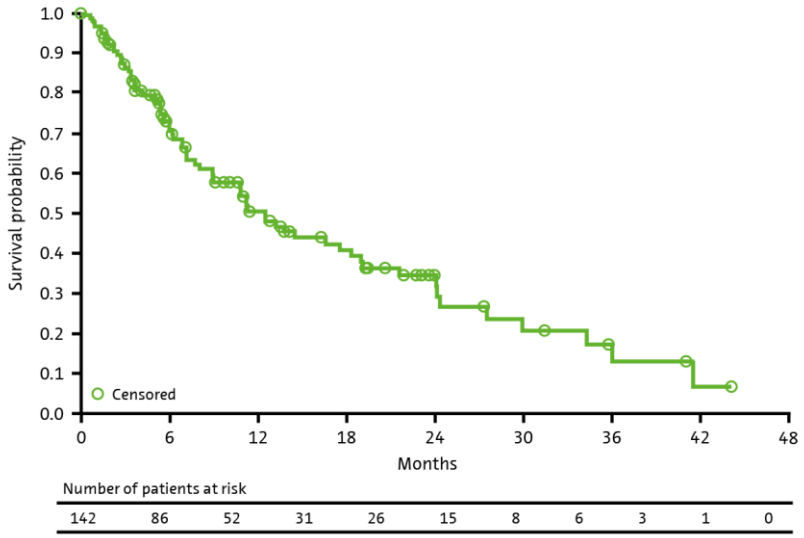
- Clinical activity of copanlisib monotherapy in R/R iNHL:
  - In FL, the ORR was 59% in the 2-year follow up study
  - In MZL, the ORR was 78% in the 2-year follow up study

**CI,** confidence interval; **FL,** follicular lymphoma; **iNHL,** indolent non-Hodgkin's lymphoma; **MZL**: marginal zone lymphoma; **NE/NA,** not evaluable/not available; **ORR,** objective response rate; **R/R,** relapsed/refractory

[a]Full analysis set, includes all treated patients. [b]Includes 1 patient with unconfirmed early stable disease. **1**. Dreyling M, et al. *J Clin Oncol.* 2017;35:3898-3905. **2**. Dreyling M, et al. Presented at: American Society of Hematology Annual Meeting 2018; December 1-4, 2018; San Diego, CA. Abstract 1595. **3**. Dreyling M, et al. *Am J Hematol*. 2020; doi: 10.1002/ajh.25711.

# CHRONOS-1: Outcomes in patients with R/R iNHL

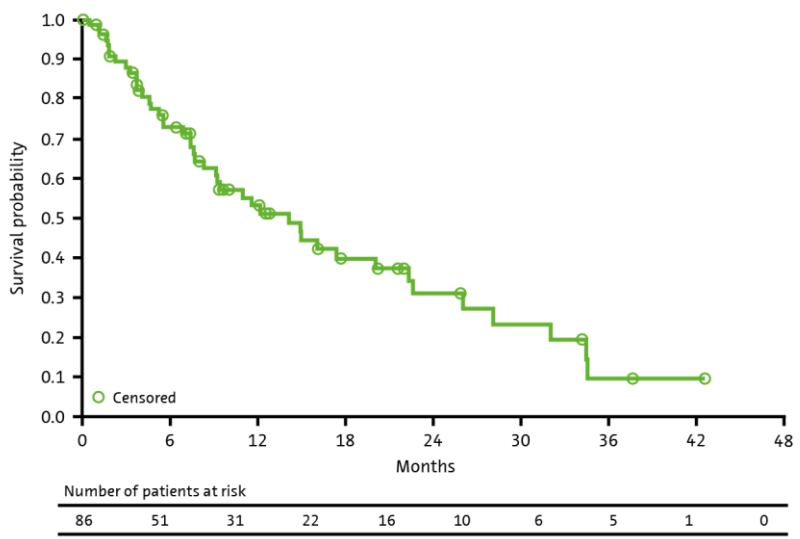
## Progression-free survival[1,2]




**Median progression-free survival:**

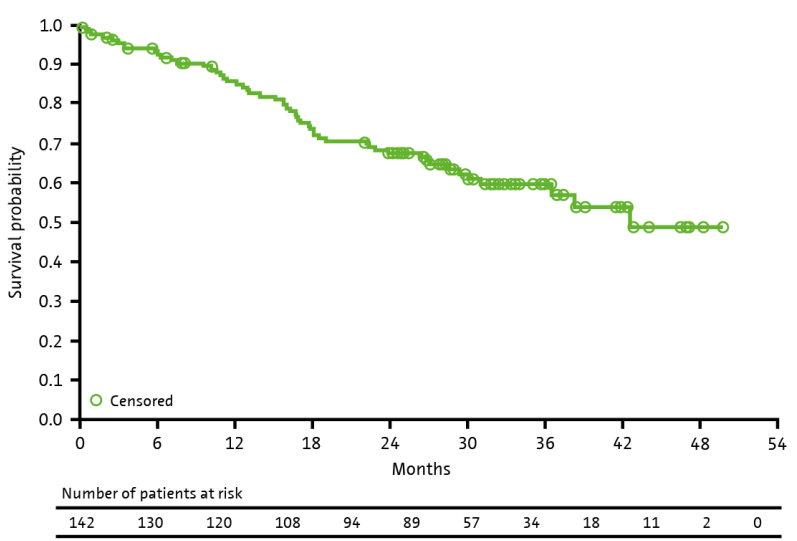
- Overall: **12.5** months (range 0.03-44.2)

## Duration of response[1,2]




- **Median duration of response:**
- Overall: **14.1** months (range 0.03-42.5)

## Overall survival[1,2]




**Median overall survival:**

- Overall: **42.6** months (range 0.2-49.8)

Data reported from February 2018 data cutoff.
**iNHL**, indolent non-Hodgkin's lymphoma; **OS**, overall survival.
**1.** Dreyling M, et al. Presented at: American Society of Hematology Annual Meeting 2018; Abstract 1595. **2**. Dreyling M, et al. *Am J Hematol*. 2020; doi: 10.1002/ajh.25711.

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# CHRONOS-1: Outcomes in POD<24 R/R iNHL

- Patients with follicular lymphoma who have progression of disease (POD) within 24 months (POD <24) of receiving first-line chemo-immunotherapy have worse overall survival than those whose disease progresses after 24 months (POD ≥24), representing a high-risk population[1,2]
- In CHRONOS-1, a total of 93 patients (66.4%) progressed in less than 24 months on first-line treatment and were deemed the POD <24 group for this analysis[3]
- Copanlisib showed efficacy in R/R iNHL, irrespective of POD 24 status[3]

## Patient profile (N=140)[3]

| Median time, months | POD <24 n=93 (66.4%) | POD >24 n=47 (33.6%) |
|---|---|---|
| From 1st line of treatment | 11.0 | 35.3 |
| To progression for most recent prior therapy | 7.0 (65.6% refractory) | 15.7 (48.9% refractory) |

| | All histologies (N=140) | | Follicular lymphoma (n=102) | | Total (N=140) |
|---|---|---|---|---|---|
| | POD <24 (n=93) | POD ≥24 (n=47) | POD <24 (n=68) | POD ≥24 (n=34) | |
| **Best response, n (%)** | | | | | |
| Complete response | 16 (17.2) | 8 (17.0) | 15 (22.1) | 6 (17.6) | 24 (17.1) |
| Partial response | 38 (40.9) | 24 (51.1) | 26 (38.2) | 14 (41.2) | 62 (44.3) |
| Stable disease | 26 (28.0) | 12 (25.5) | 21 (30.9) | 11 (32.4) | 38 (27.1) |
| Unconfirmed early stable disease | 1 (1.1) | 0 | 1 (1.5) | 0 | 1 (0.7) |
| Progressive disease | 1 (1.1) | 2 (4.3) | 0 | 2 (5.9) | 3 (2.1) |
| NE/NA | 11 (11.8) | 1 (2.1) | 5 (7.4) | 1 (2.9) | 12 (8.6) |
| **ORR, n (%)** | 54 (58.1) | 32 (68.1) | 41 (60.3) | 20 (58.8) | 86 (61.4) |
| 95% CI | 47.4, 68.2 | 52.9, 80.9 | 47.7, 72.0 | 40.7, 75.4 | 52.8, 69.5 |

**iNHL,** indolent non-Hodgkin's lymphoma; **NA**, not available; **NE**, not evaluable; **ORR**, objective response rate; **POD**, progression of disease; **R/R**, relapsed/refractory

**1.** Casulo C, et al. *J Clin Oncol.* 2015; 33: 2516-2522. **2.** Jurinovic V, et al. *Blood.* 2016; 128: 1112-1120. **3.** Santoro A, et al. Presented at American Society of Hematology (ASH) 2018 Annual Meeting; San Diego, California Abstract 395.

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# CHRONOS-3: Study design and patient characteristics

– Phase 3, randomized, double-blind, placebo-controlled clinical study of copanlisib in combination with rituximab in patients with iNHL who have relapsed after ≥1 line of treatment, including rituximab

- Patients with relapsed iNHL who have received ≥1 rituximab-containing therapies
- Patients who had a progression-free and treatment-free interval ≥12 months after completion of the last rituximab-containing regimen
- OR patients who are unwilling/unfit or for whom chemotherapy is contraindicated by reason of age, comorbidities and/or residual toxicity

**N=458**

**Randomized 2:1**

**Rituximab + copanlisib**

Rituximab 375 mg/m$^2$ weekly (day 1, 8, 15 and 22 of cycle 1, day 1 of cycles 3, 5, 7 and 9)

Copanlisib 60 mg weekly (days 1, 8 and 15) until PD

**Rituximab + placebo**

Rituximab 375 mg/m$^2$ weekly (day 1, 8, 15 and 22 of cycle 1, day 1 of cycles 3, 5, 7 and 9)

**Primary endpoint:**
PFS by central review

**Secondary endpoints:**
TTP, ORR, CR, DOR, OS, safety

**Exploratory endpoints:**
PK, biomarkers, QoL

**Stratification**: NHL histology (FL vs other (SLL, MZL, LPL/WM); treatment-free ≥12 mo vs unfit/unwilling to receive chemo ≥6 mo from last R-containing therapy; bulky disease; previous treatment with PI3K inhibitor

**Patient population**:
Be considered “rituximab-sensitive” OR unfit/unwilling to receive chemotherapy

**CR**, complete response; **DOR**, duration of response; **FL,** follicular lymphoma; **iNHL**, indolent non-Hodgkin’s lymphoma; **IV**, intravenous; **LPL,** lymphoplasmacytic lymphoma; **MZL,** marginal zone lymphoma; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PI3K**, phosphoinositide 3-kinase; **PK**, pharmacokinetic; **PFS**, progression-free survival; **QoL**, quality of life; **SLL**, small lymphocytic lymphoma; **TTP**, time to progression; **WM,** Waldenström's macroglobulinemia. ClinicalTrials.gov. NCT02367040. Available at: https://clinicaltrials.gov/ct2/show/NCT02367040.

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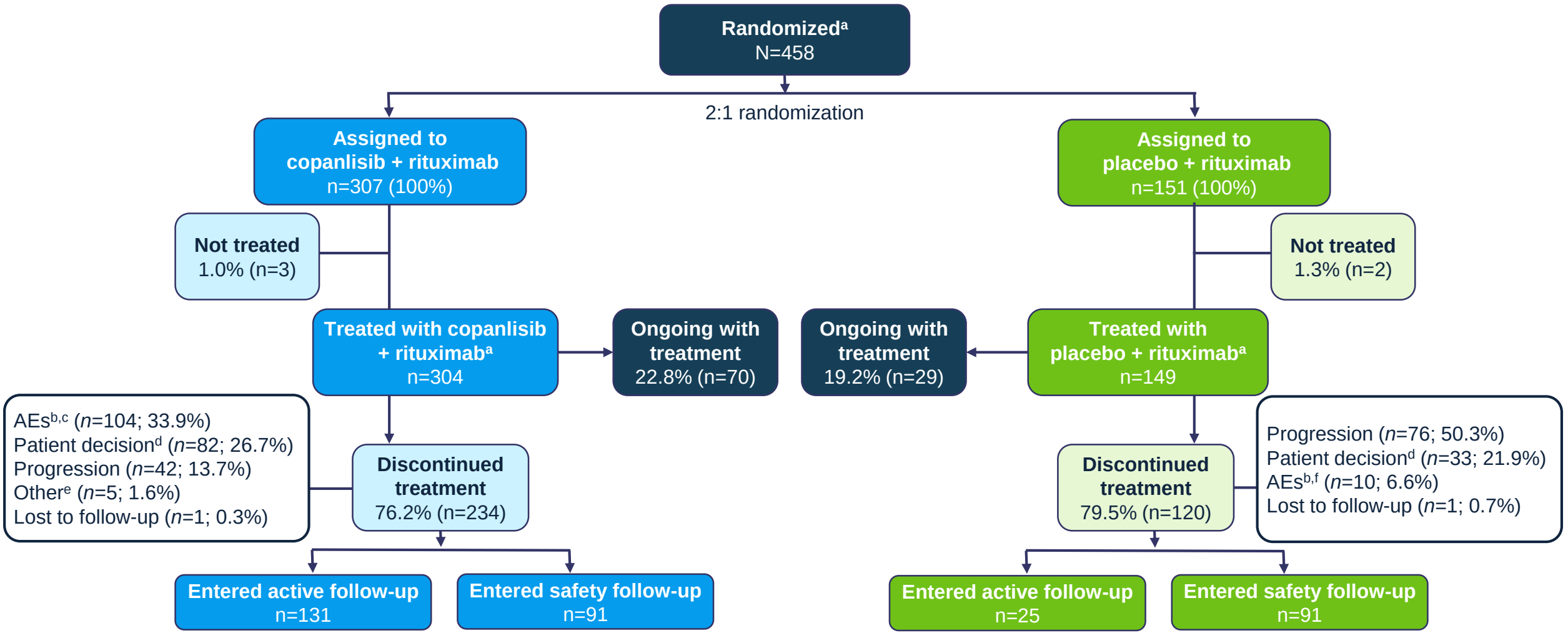
# CHRONOS-3: Patient disposition




**AE**, adverse event.

[a]3 patients assigned to placebo plus rituximab received at least 1 dose of copanlisib. Safety analyses in the copanlisib plus rituximab group therefore included 307 patients (304 in the copanlisib plus rituximab group and 3 in the placebo plus rituximab group) and 146 in the placebo plus rituximab group; [b]Not associated with clinical disease progression; [c]Includes 8 patients with non-treatment-emergent AEs; [d]Includes lack of efficacy, physician or patient decision, switching to other therapy, and withdrawal by patient; [e]Includes failure to meet continuation criteria, non-compliance, protocol violation, randomization mistake, and failed required procedure; [f]Includes 1 case of additional primary malignancy

**1.** Matasar MJ, et al. Presented at: American Association of Cancer Research (AACR) Annual Meeting 2021; April 9-14, 2021. Abstract CT001. **2.** Matasar MJ, et al. *Lancet Oncol.* 2021.

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# CHRONOS-3: Patient demographics

- Patient demographics were balanced between both treatment arms[1,2]
- The median age was 63 years (range, 28 to 91 years)[1,2]
- FL was the most common histology (59.9%) followed by MZL (21.5%)[1,2]
- Approximately 20% of patients were unfit/unwilling to receive chemotherapy[1,2]
- Approximately half the patients had 2 or more prior lines of therapy[1,2]
- **54.8% of patients had stage IV disease, and 25.5% had stage III[1,2]**

| | Copanlisib + rituximab (n=307)[1,2] | Placebo + rituximab (n=151)[1,2] |
|---|---|---|
| **Male, n (%)** | 153 (49.8) | 85 (56.3) |
| **Median age, years (range)** | 63.0 (28-91) | 62.0 (34-85) |
| **Medical history of diabetes, n (%)** | 45 (14.7) | 22 (14.6) |
| **Medical history of hypertension, n (%)** | 114 (37.1) | 53 (35.1) |
| **Histology of lymphoma, n (%)** | | |
| FL | 184 (59.9) | 91 (60.3) |
| 1 | 56 (18.2) | 31 (20.5) |
| 2 | 88 (28.7) | 40 (26.5) |
| 3a | 40 (13.0) | 20 (13.2) |
| MZL | 66 (21.5) | 29 (19.2) |
| SLL | 35 (11.4) | 15 (9.9) |
| LPL/WM | 22 (7.2) | 16 (10.6) |
| **Median time since last systemic therapy, months (range)** | 25.07 (1.0-192.5) | 25.26 (0.8-161.2) |
| **Median time from initial diagnosis, months (range)** | 62.75 (10.3-349.2) | 72.44 (13.3-245.7) |
| **Progression-free and treatment-free interval ≥12 months since last rituximab-containing regimen, n (%)** | 247 (80.5) | 121 (80.1) |
| **Unfit/unwilling to receive chemotherapy, n (%)** | 60 (19.5) | 30 (19.9) |
| **Prior anti-cancer therapy lines, n (%)** | | |
| 1 | 150 (48.9) | 71 (47.0) |
| 2 | 75 (24.4) | 40 (26.5) |
| ≥3 | 82 (26.7) | 40 (26.5) |

**FL**, follicular lymphoma; **LPL**, lymphoplasmacytic lymphoma; **MZL**, marginal zone lymphoma; **SLL**, small lymphocytic lymphoma; **WM**, Waldenström's macroglobulinemia.

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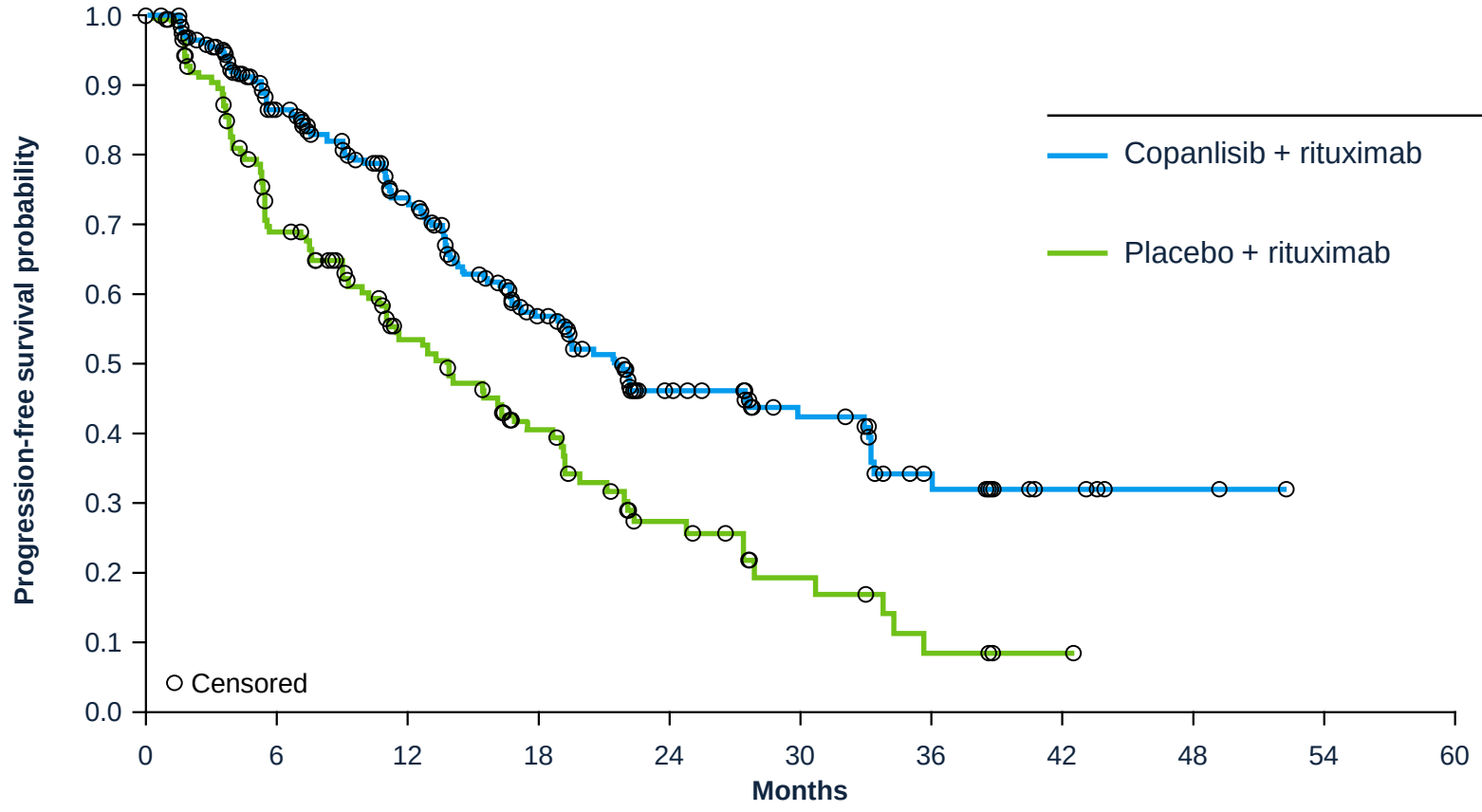
# CHRONOS-3 Primary endpoint: PFS in all iNHL patients

## *(Independent Central Review)*




| | Median PFS (95% CI) | HR (95% CI) | *P* value (1-sided) |
|---|---|---|---|
| Copanlisib + rituximab | **21.5** months (17.8, 33.0) | **0.520 (0.393, 0.688)** | *p*<0.0001 |
| Placebo + rituximab | **13.8** months (10.2, 17.5) | | |

- Median follow-up: 19.2 months[1,2]
- The combination of copanlisib and rituximab demonstrated a superior PFS with a **48%** reduction in the risk of progression or death compared to placebo plus rituximab (HR=0.52)[1,2]

Number of patients at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Copanlisib + rituximab | 307 | 204 | 146 | 88 | 49 | 31 | 15 | 6 | 2 | 0 | 0 |
| Placebo + rituximab | 151 | 85 | 53 | 33 | 16 | 8 | 3 | 1 | 0 | 0 | 0 |

**CI**, confidence interval; **HR**, hazard ratio; **iNHL**, indolent non-Hodgkin's lymphoma; **PFS**, progression-free survival.

**1**. Matasar MJ, et al. Presented at: American Association of Cancer Research (AACR) Annual Meeting 2021; April 9-14, 2021. Abstract CT001. **2**. Matasar MJ, et al. *Lancet Oncol.* 2021

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# CHRONOS-3 Primary endpoint: PFS by histological subtype

## *(Independent Central Review)*

– A reduction in risk of progression or death was also observed across all prespecified histological subtypes including FL (42%; HR=0.58), MZL (53%; HR=0.475), SLL (76%; HR=0.243) and LPL/WM (56%; HR=0.443, NS), showing a global patient benefit irrespective of histology[1,2]

| | FL | | MZL | | SLL | | LPL/WM | |
|---|---|---|---|---|---|---|---|---|
| | C + R | P + R | C + R | P + R | C + R | P + R | C + R | P + R |
| ***N*** | 184 | 91 | 66 | 29 | 35 | 15 | 22 | 16 |
| **Median PFS, months (95% CI)** | **22.2** (17.8, 33.1) | 18.7 (10.2, 21.1) | **22.1** (13.8, NE) | 11.5 (5.6, 16.3) | 14.2 (10.9, 20.5) | 5.7 (3.5, 11.0) | 33.4 (15.5, NE) | 16.6 (4.4, 27.4) |
| **HR (95% CI)** | **0.580** (0.404, 0.833) | | **0.475** (0.245, 0.923) | | **0.243** (0.111, 0.530) | | **0.443** (0.160, 1.231) | |
| **1-sided *P* value** | 0.0014 | | 0.012 | | <0.0001 | | 0.054 | |

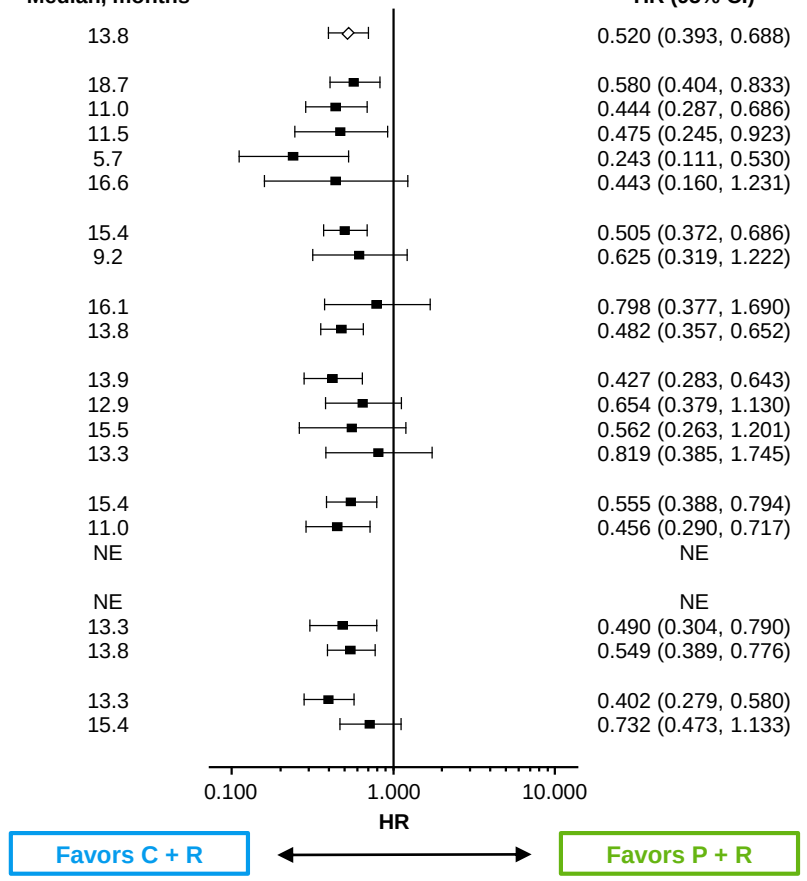
**C**, copanlisib; **CI**, confidence interval; **FL**, follicular lymphoma; **HR**, hazard ratio; **LPL**, lymphoplasmacytic lymphoma; **MZL**, marginal zone lymphoma; **NE**, not evaluable; **PFS**, progression-free survival; **R**, rituximab; **SLL**, small lymphocytic lymphoma; **WM**, Waldenström's macroglobulinemia.

**1.** Matasar MJ, et al. Presented at: American Association of Cancer Research (AACR) Annual Meeting 2021; April 9-14, 2021. Abstract CT001. **2.** Matasar MJ, et al. *Lancet Oncol.* 2021

# CHRONOS-3: PFS subgroup analysis

## *(Independent Central Review)*

| | C + R | | P + R | | | |
|---|---|---|---|---|---|---|
| | Number of events/N | Median, months | Number of events/N | Median, months | HR (95% CI) | 1-sided *p* value |
| Overall | 118/307 | 21.5 | 87/151 | 13.8 | 0.520 (0.393, 0.688) | <0.0001 |
| **iNHL histology** | | | | | | |
| FL | 69/184 | 22.2 | 52/91 | 18.7 | 0.580 (0.404, 0.833) | 0.001 |
| Other iNHL | 49/123 | 21.5 | 35/60 | 11.0 | 0.444 (0.287, 0.686) | <0.0001 |
| MZL | 22/66 | 22.1 | 15/29 | 11.5 | 0.475 (0.245, 0.923) | 0.012 |
| SLL | 20/35 | 14.2 | 12/15 | 5.7 | 0.243 (0.111, 0.530) | <0.0001 |
| LPL / WM | 7/22 | 33.4 | 8/16 | 16.6 | 0.443 (0.160, 1.231) | 0.054 |
| **Entry criterion** | | | | | | |
| Treatment-free for ≥12 months | 94/247 | 22.2 | 73/121 | 15.4 | 0.505 (0.372, 0.686) | <0.0001 |
| Unwilling / unfit for chemotherapy | 24/60 | 16.3 | 14/30 | 9.2 | 0.625 (0.319, 1.222) | 0.082 |
| **Presence of bulky disease** | | | | | | |
| Yes | 22/45 | 16.6 | 10/21 | 16.1 | 0.798 (0.377, 1.690) | 0.277 |
| No | 96/262 | 22.3 | 77/130 | 13.8 | 0.482 (0.357, 0.652) | <0.0001 |
| **Previous lines of systemic anti-cancer therapy** | | | | | | |
| 1 | 53/150 | 22.3 | 41/71 | 13.9 | 0.427 (0.283, 0.643) | <0.0001 |
| 2 | 32/75 | 16.8 | 22/40 | 12.9 | 0.654 (0.379, 1.130) | 0.063 |
| 3 | 14/38 | 27.5 | 13/23 | 15.5 | 0.562 (0.263, 1.201) | 0.066 |
| ≥4 | 19/44 | 19.6 | 11/17 | 13.3 | 0.819 (0.385, 1.745) | 0.302 |
| **ECOG performance status at baseline** | | | | | | |
| 0 | 72/182 | 27.5 | 52/95 | 15.4 | 0.555 (0.388, 0.794) | 0.0005 |
| 1 | 41/113 | 19.4 | 35/55 | 11.0 | 0.456 (0.290, 0.717) | 0.0002 |
| 2 | 5/12 | 12.7 | 0/1 | NE | NE | 0.618 |
| **Geographic region** | | | | | | |
| North America | 4/15 | NE | 0/3 | NE | NE | 0.848 |
| Asia Pacific | 41/125 | 27.7 | 29/50 | 13.3 | 0.490 (0.304, 0.790) | 0.001 |
| Rest of world | 73/167 | 19.4 | 58/98 | 13.8 | 0.549 (0.389, 0.776) | 0.0003 |
| **Age** | | | | | | |
| <65 years | 63/167 | 27.7 | 55/88 | 13.3 | 0.402 (0.279, 0.580) | <0.0001 |
| ≥65 years | 55/140 | 16.6 | 32/63 | 15.4 | 0.732 (0.473, 1.133) | 0.080 |




**C**, copanlisib; **CI,** confidence interval; **FL**, follicular lymphoma; **HR**, hazard ratio; **iNHL**, indolent non-Hodgkin's lymphoma; **LPL**, lymphoplasmacytic lymphoma; **MZL**, marginal zone lymphoma; **P**, placebo; **PFS**, progression-free survival; **R**, rituximab; **SLL**, small lymphocytic lymphoma; **WM**, Waldenström's macroglobulinemia.

**1.** Matasar MJ, et al. Presented at: American Association of Cancer Research (AACR) Annual Meeting 2021; April 9-14, 2021. Abstract CT001. **2.** Matasar MJ, et al. *Lancet Oncol.* 2021

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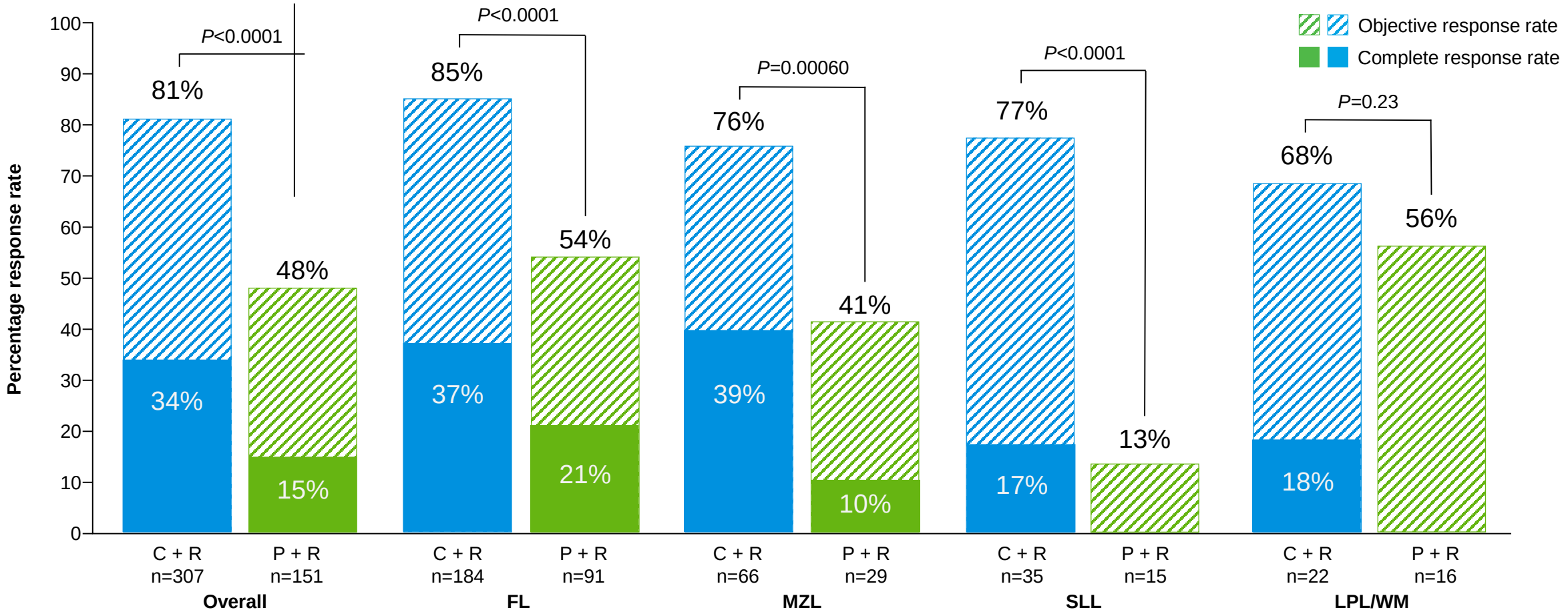
# CHRONOS-3: Objective Response Rate

## *(Independent Central Review)*




**C**, copanlisib; **CRR**, complete response rate; **FL**, follicular lymphoma; **HR**, hazard ratio; **LPL**, lymphoplasmacytic lymphoma; **MZL**, marginal zone lymphoma; **ORR**, objective response rate; **R**, rituximab; **SLL**, small lymphocytic lymphoma; **WM**, Waldenström's macroglobulinemia.

Matasar MJ, et al. *Lancet Oncol*. 2021

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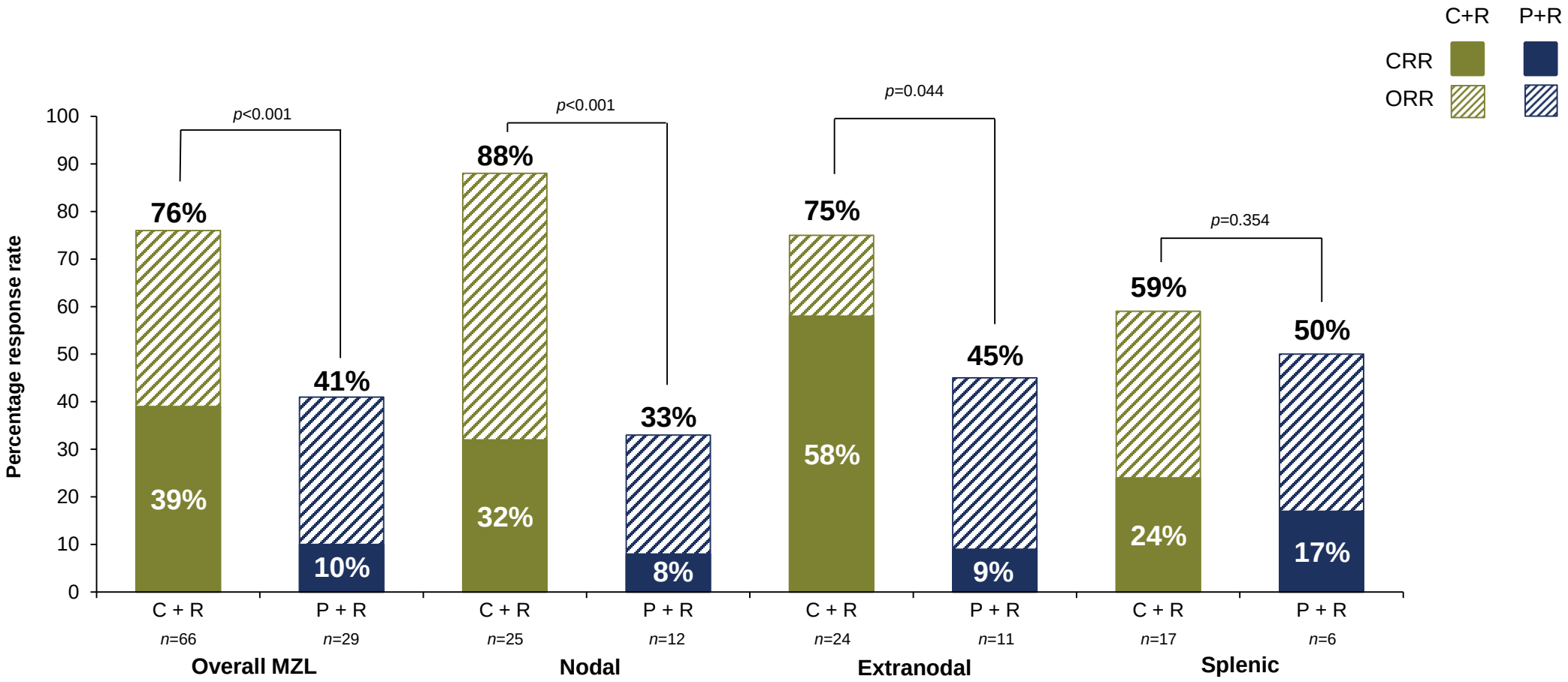
# CHRONOS-3 ORR in MZL

## *(Independent Central Review)*




1-sided *p* values are presented
C + R, copanlisib plus rituximab; P + R, placebo plus rituximab

Ozcan M, et al. Presented at: European Society for Medical Oncology (ESMO) Congress 2021; September 16-21, 2021. Abstract 826O.

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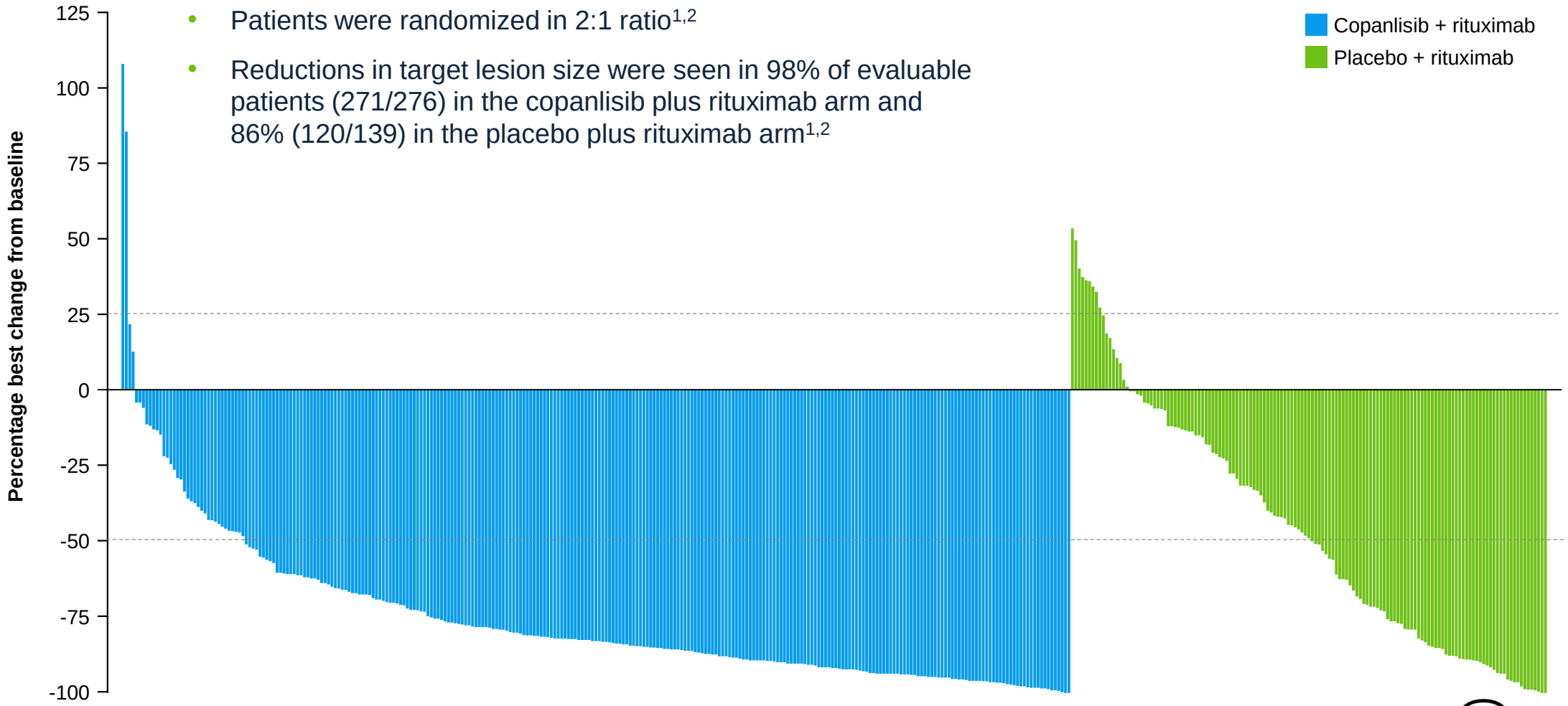
# CHRONOS-3: Reduction in target lesions, all iNHL

## *(Investigator Assessment)*

- Patients were randomized in 2:1 ratio[1,2]
- Reductions in target lesion size were seen in 98% of evaluable patients (271/276) in the copanlisib plus rituximab arm and 86% (120/139) in the placebo plus rituximab arm[1,2]

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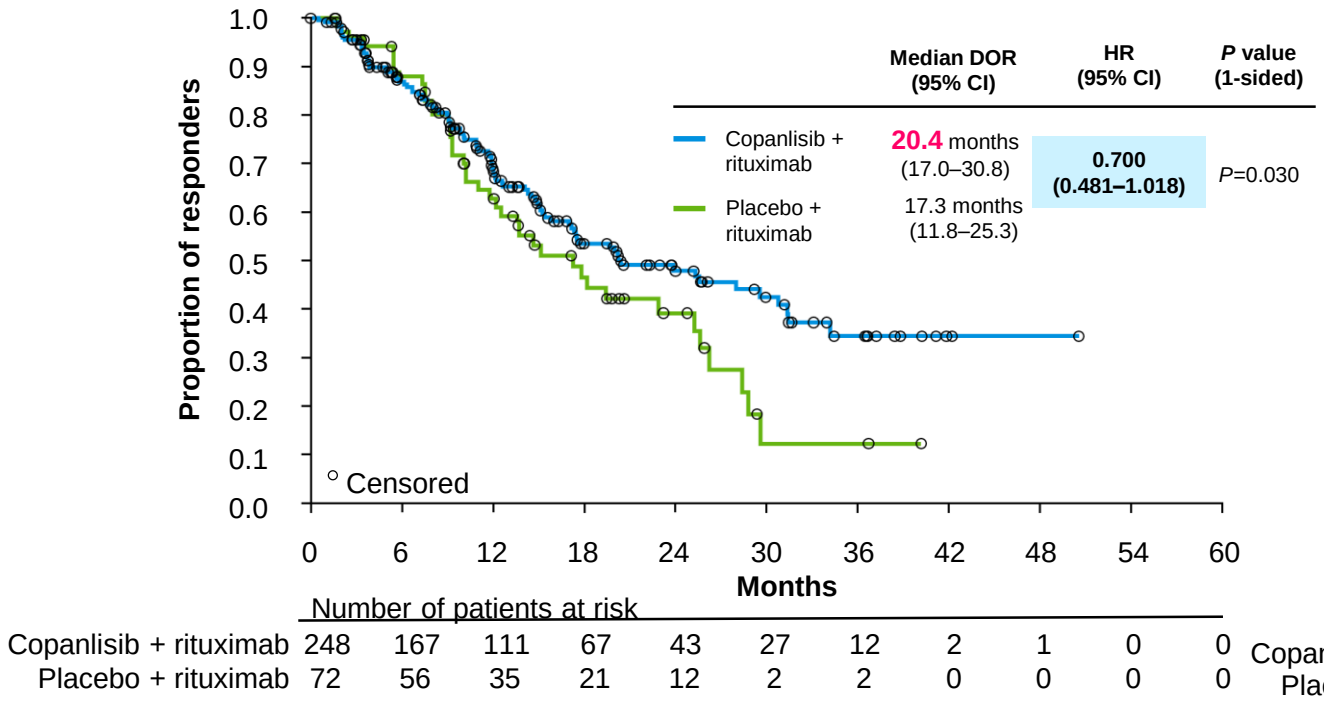
**iNHL**, indolent non-Hodgkin's lymphoma

**1.** Matasar MJ, et al. Presented at: American Association of Cancer Research (AACR) Annual Meeting 2021; April 9-14, 2021. Abstract CT001. **2.** Matasar MJ, et al. *Lancet Oncol.* 2021

# CHRONOS-3: Additional efficacy endpoints

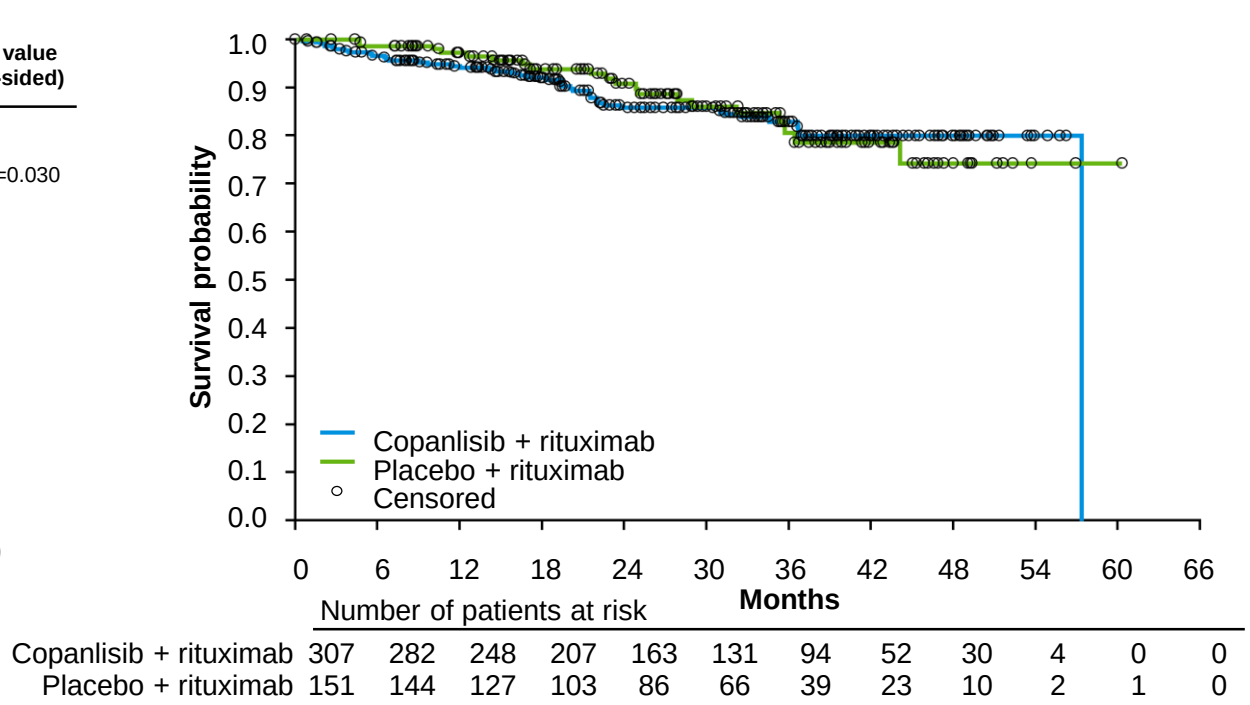
## *(Investigator Assessment)*

### Duration of response




- With a median follow-up of 20.0 months, median DOR was longer for copanlisib plus rituximab vs placebo plus rituximab[1,2]

### Overall survival




- With a median follow-up up 30.1 months, OS was immature[1,2]

**DOR,** duration of response; **iNHL**, indolent non-Hodgkin's lymphoma; **OS**, overall survival.

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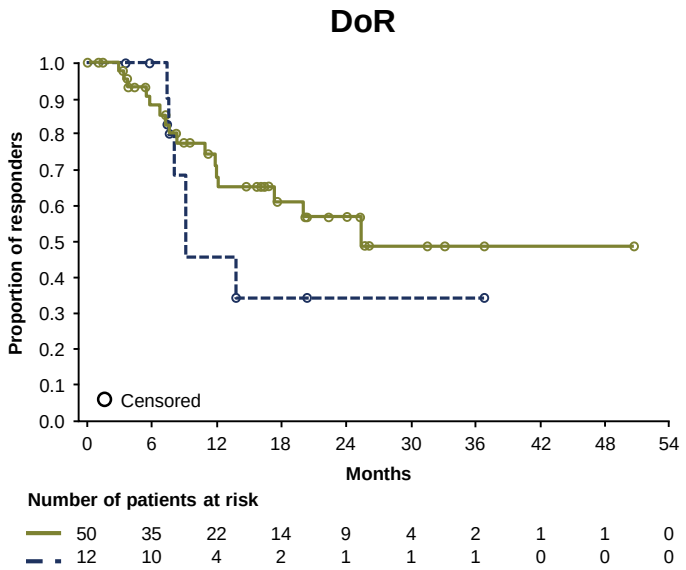
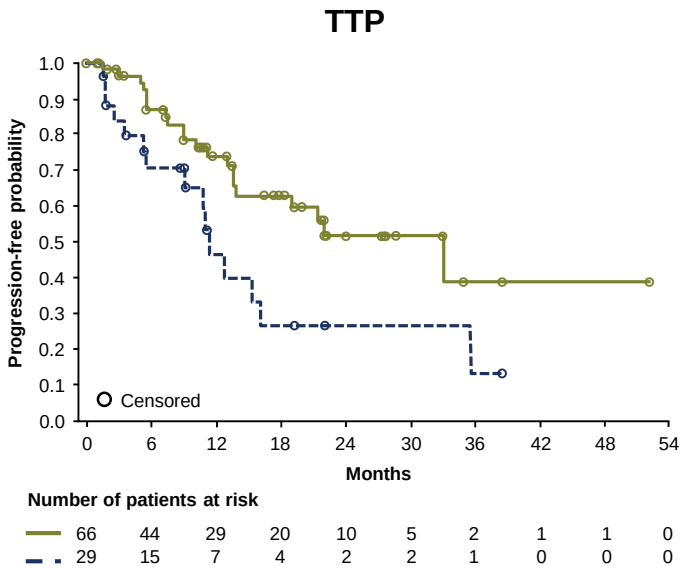
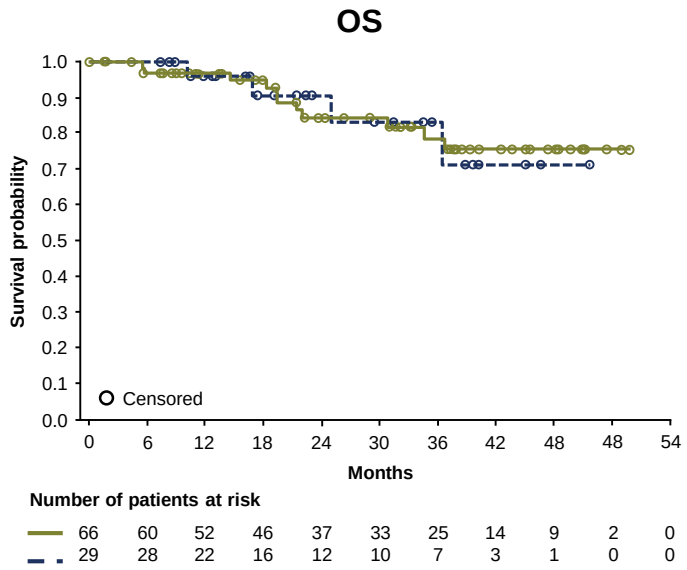
# DoR, TTP, and OS in patients with MZL




| | Median DoR (95% CI) | HR (95% CI) | 1-sided *p* value |
|---|---|---|---|
| Copanlisib+ rituximab | **25.4** months (12.1, NE) | Not reliably estimable | Not reliably estimable |
| Placebo + rituximab | 9.3 months (7.4, NE) | | |

| | Median TTP (95% CI) | HR (95% CI) | 1-sided *p* value |
|---|---|---|---|
| Copanlisib+ rituximab | **33.2** months (13.7, NE) | 0.458 (0.234, 0.895) | 0.010 |
| Placebo + rituximab | 11.5 months (5.6, 16.3) | | |

| | Median OS (95% CI) | HR (95% CI) | 1-sided *p* value |
|---|---|---|---|
| Copanlisib+ rituximab | **NE** | 0.966 (0.307, 3.043) | 0.476 |
| Placebo + rituximab | NE (36.4, NE) | | |

**DOR,** duration of response; **TTP**, time to progression, **MZL**, marginal zone lymphoma **OS**, overall survival.

Ozcan M, et al. Presented at: European Society for Medical Oncology (ESMO) Congress 2021; September 16-21, 2021. Abstract 826O.

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# CHRONOS-3: Overview of safety profile

| TEAEs, n (%) | Copanlisib + rituximab (n=307)[1,2] | | | Placebo + rituximab (n=146)[1,2] | | |
|---|---|---|---|---|---|---|
| | All grades | Grade 3 | Grade 4 | All grades | Grade 3 | Grade 4 |
| **Any TEAE** | 307 (100.0) | 164 (53.4) | 110 (35.8) | 134 (91.8) | 63 (43.2) | 19 (13.0) |
| **Serious TEAEs** | 145 (47.2) | 82 (26.7) | 40 (13.0) | 27 (18.5) | 19 (13.0) | 1 (0.7) |
| **Most common TEAEs (>15%)** | | | | | | |
| Hyperglycemia | 213 (69.4) | 148 (48.2) | 25 (8.1) | 34 (23.3) | 12 (8.2) | 0 |
| Hypertension | 151 (49.2) | 122 (39.7) | 0 | 28 (19.2) | 13 (8.9) | 0 |
| Diarrhea | 103 (33.6) | 15 (4.9) | 0 | 14 (9.6) | 0 | 0 |
| Nausea | 69 (22.5) | 2 (0.7) | 0 | 17 (11.6) | 1 (0.7) | 0 |
| Neutropenia | 64 (20.8) | 21 (6.8) | 27 (8.8) | 24 (16.4) | 9 (6.2) | 9 (6.2) |
| Pyrexia | 63 (20.5) | 5 (1.6) | 0 | 11 (7.5) | 0 | 0 |
| Upper respiratory tract infection | 56 (18.2) | 3 (1.0) | 0 | 24 (16.4) | 0 | 0 |
| **Adverse events of interest** | | | | | | |
| Pneumonitis[a] | 21 (6.8) | 6 (2.0) | 2 (0.7) | 2 (1.4) | 1 (0.7) | 0 |
| Colitis | 4 (1.3) | 1 (0.3) | 0 | 0 | 0 | 0 |
| **Laboratory values** | | | | | | |
| Decreased neutrophil count | 102 (33.2) | 34 (11.1) | 36 (11.7) | 34 (23.3) | 10 (6.8) | 10 (6.8) |
| Decreased white blood cell count | 61 (19.9) | 20 (6.5) | 4 (1.3) | 16 (11.0) | 5 (3.4) | 0 |
| Decreased platelet count | 40 (13.0) | 4 (1.3) | 3 (1.0) | 12 (8.2) | 1 (0.7) | 1 (0.7) |
| Decreased lymphocyte count | 38 (12.4) | 14 (4.6) | 3 (1.0) | 9 (6.2) | 4 (2.7) | 0 |
| Increased alanine aminotransferase | 25 (8.1) | 3 (1.0) | 1 (0.3) | 9 (6.2) | 1 (0.7) | 0 |
| Increased aspartate aminotransferase | 25 (8.1) | 3 (1.0) | 1 (0.3) | 10 (6.8) | 1 (0.7) | 0 |

- The most commonly occurring TEAEs in both arms were hyperglycemia and hypertension[1,2]
  - Copanlisib-related hyperglycemia and hypertension were infusion-related, transient, and did not lead to significant treatment interruptions[1,2]
- The frequency of colitis and pneumonitis events remained low in patients receiving copanlisib plus rituximab[1,2]
- Higher rates of serious TEAEs were seen with copanlisib plus rituximab arm; the incidences of individual serious TEAEs were low in both treatment groups[1,2]

[a]One drug-related death (pneumonitis) occurred in the copanlisib plus rituximab arm.
**TEAE,** treatment-emergent adverse event.
**1.** Matasar MJ, et al. Presented at: American Association of Cancer Research (AACR) Annual Meeting 2021; April 9-14, 2021. Abstract CT001. **2.** Matasar MJ, et al. *Lancet Oncol*. 2021

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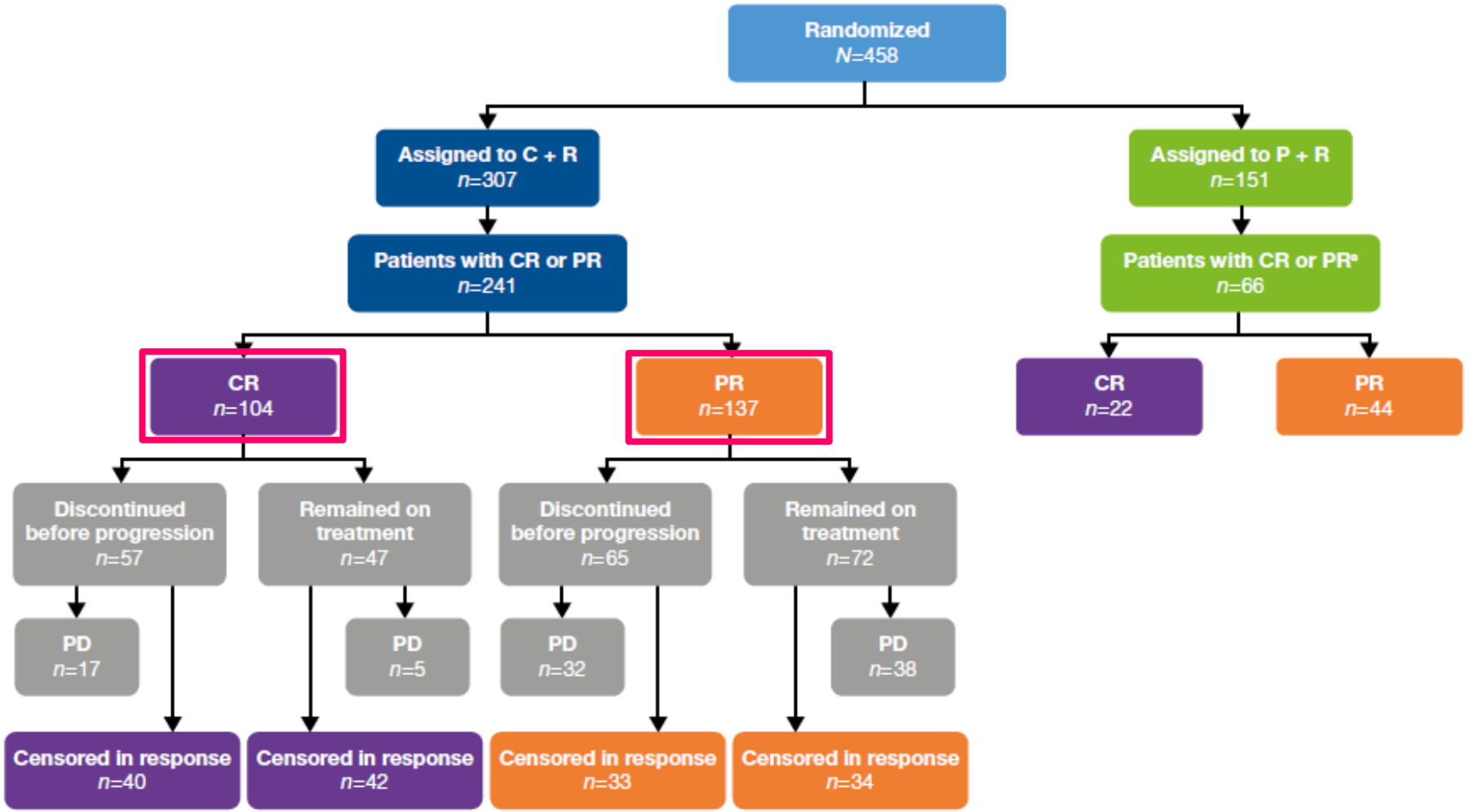
# Summary

- Copanlisib plus rituximab resulted in a 48% reduction in the risk of disease progression or death *vs* placebo plus rituximab in patients with relapsed iNHL
- ORR was significantly increased with copanlisib plus rituximab compared with placebo plus rituximab, with improvements in PFS, ORR, and CRR seen across iNHL subtypes
- Copanlisib plus rituximab demonstrated a safety profile consistent with previous reports of copanlisib and rituximab as monotherapies
- Copanlisib is the first PI3K inhibitor to be safely combined with rituximab and the first to demonstrate broad superior efficacy in combination with rituximab across iNHL histologies

## COPANLISIB COMBINATION THERAPY:

# DURATION OF RESPONSE IN INHL PATIENTS WHO DISCONTINUED TREATMENT PRIOR TO PROGRESSION

# CHRONOS-3: Patient disposition for responders




[a]There were not enough patients within the P + R treatment group to conduct a DoR analysis

**CR,** complete response; **DoR,** duration of response; **PD**, progressive disease; PR, partial response.

1. Matasar MJ, et al. Presented at: American Society of Hematology (ASH) Annual Meeting 2021; December 11-14, 2021, Atlanta, GA. Abstract 3538.

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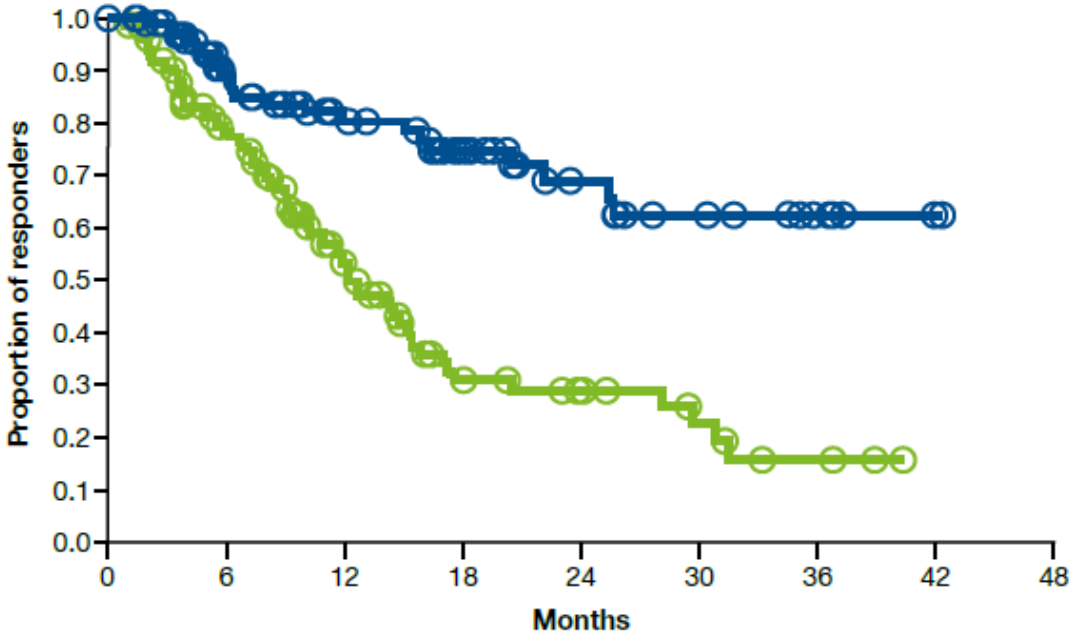
# DoR for CR *vs* PR among patients treated with copanlisib + R




**Number of patients at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Patients with BOR of CR | 104 | 66 | 46 | 33 | 21 | 11 | 5 | 1 | 0 |
| Patients with BOR of PR | 137 | 82 | 44 | 18 | 12 | 7 | 3 | 0 | 0 |

| | Median DoR, months (95% CI) | Response rate at 12 months, % (95% CI) | Response rate at 24 months, % (95% CI) |
|---|---|---|---|
| **CR** | NE (25.7, NE) | 80.3 (71.2, 89.4) | 68.9 (56.6, 81.2) |
| **PR** | 12.3 (10.2, 15.3) | 53.3 (43.5, 63.1) | 28.7 (18.4, 39.1) |

At-risk patient counts were calculated as start of time point. DoR is the time from first CR or PR to disease progression or death from any cause (if no progression is documented), whichever occurs earlier for patients with a BOR of CR (PR).

**BOR**, best overall response; **CI,** confidence interval; **CR,** complete response; **DoR,** duration of response; NE, not evaluable; **PR**, partial response.

**1.** Matasar MJ, et al. Presented at: American Society of Hematology (ASH) Annual Meeting 2021; December 11-14, 2021, Atlanta, GA. Abstract 3538.

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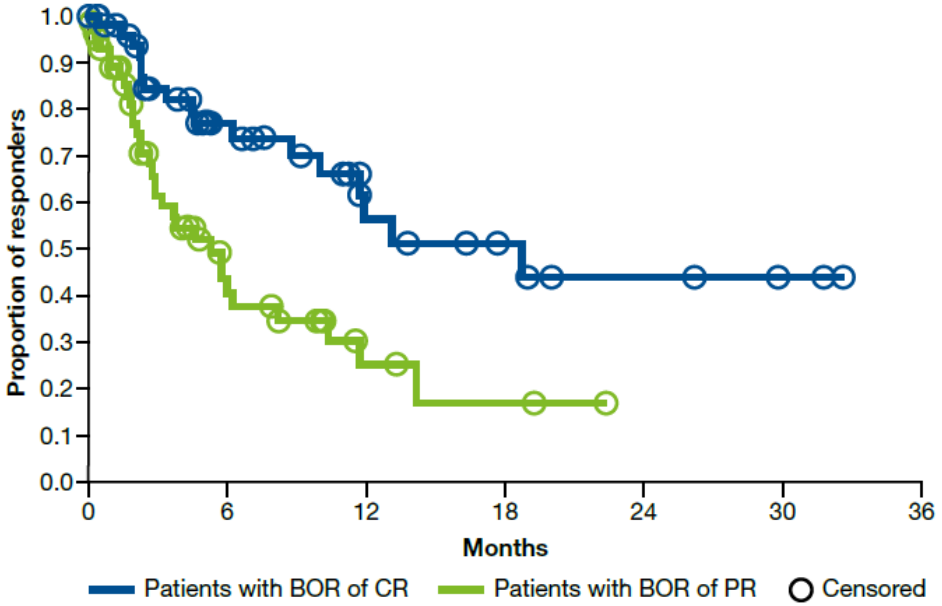
# DoR for patients with CR *vs* PR with copanlisib + R after treatment discontinuation




**Number of patients at risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Patients with BOR of CR | 57 | 24 | 11 | 7 | 4 | 2 | 0 |
| Patients with BOR of PR | 65 | 14 | 5 | 2 | 0 | 0 | 0 |

| | Median DoR, months (95% CI) | Response rate at 12 months, % (95% CI) | Response rate at 24 months, % (95% CI) |
|---|---|---|---|
| **CR** | 18.7 (10.0, NE) | 56.3 (37.9, 74.7) | 43.9 (22.7, 65.0) |
| **PR** | 5.3 (2.9, 8.2) | 25.1 (9.6, 40.7) | NE (NE, NE) |

- Among responding patients who discontinued copanlisib plus rituximab before progression, patients with a CR had a median subsequent DoR of 18.7 months, and 5.3 months for patients with a PR[1]

At-risk patient counts were calculated as start of time point. DoR is the time from last dose date to disease progression or death from any cause (if no progression is documented), whichever occurs earlier for patients with a BOR of CR (PR)

**BOR**, best overall response; **CR,** complete response; **DoR,** duration of response; **iNHL**, indolent non-Hodgkin's lymphoma; **PR**, partial response.

**1.** Matasar MJ, et al. Presented at: American Society of Hematology (ASH) Annual Meeting 2021; December 11-14, 2021, Atlanta, GA. Abstract 3538.

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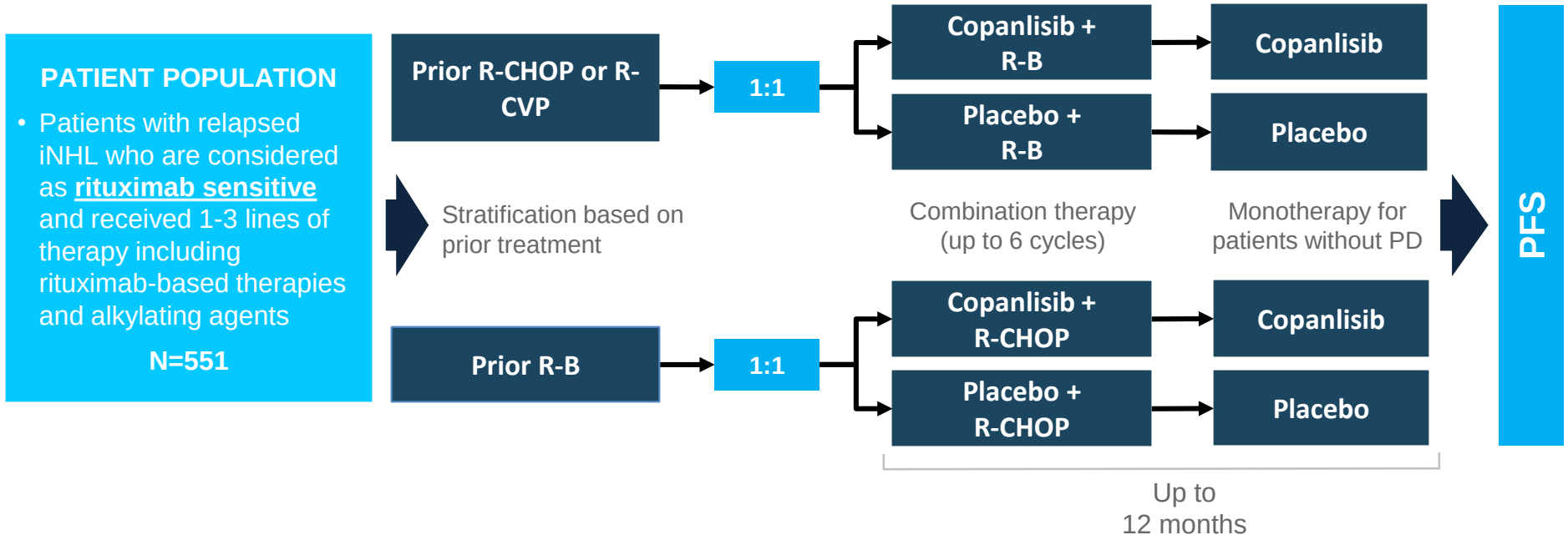
# Ongoing study of copanlisib: CHRONOS-4

- CHRONOS-4 (NCT02626455) is a phase 3 randomized, double blind, placebo-controlled study of copanlisib in combination with either R-CHOP or R-B, in comparison with R-CHOP/R-B and placebo, in patients with iNHL in progression after at least one line of treatment who were pre-exposed to rituximab and alkylating agents




**PRIMARY ENDPOINTS**

- PFS
- Determination of the recommended phase 3 dose of copanlisib (safety run-in phase only)

**SECONDARY ENDPOINTS**

- Objective response rate
- Duration of response
- Time to progression
- Complete response rate
- Overall survival
- Time to deterioration
- Time to improvement in disease-related symptoms
- Safety and tolerability
- Time to next anti-lymphoma treatment

**FL**, follicular lymphoma; **iNHL**, indolent non-Hodgkin's lymphoma; **PD**, progressive disease; **PFS**, progression-free survival; **R-B**, rituximab, bendamustine; **R-CHOP**, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone; **R-CVP**, rituximab plus cyclophosphamide, vincristine, prednisolone. **1**. ClinicalTrials.gov. NCT02626455. Available at: https://clinicaltrials.gov/ct2/show/NCT02626455. Accessed March 2020.

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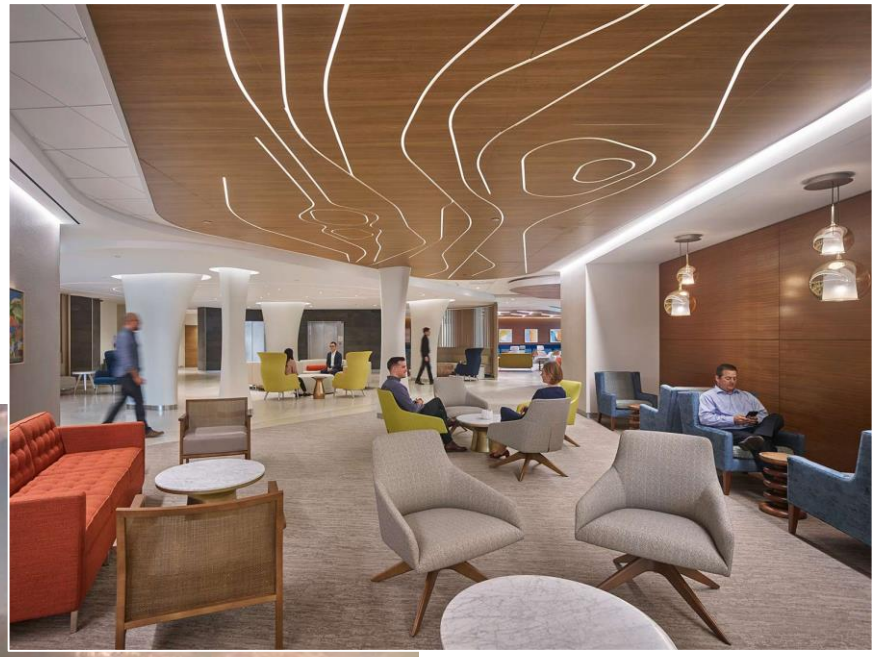
Anita Kumar
Jennifer Lue
Alison Moskowitz
Ariela Noy
Colettte Owens
Lia Palomba
David Straus
Santosh Vardhana
Gottfriend von Keudell
Andy Zelenetz

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# Copanlisib

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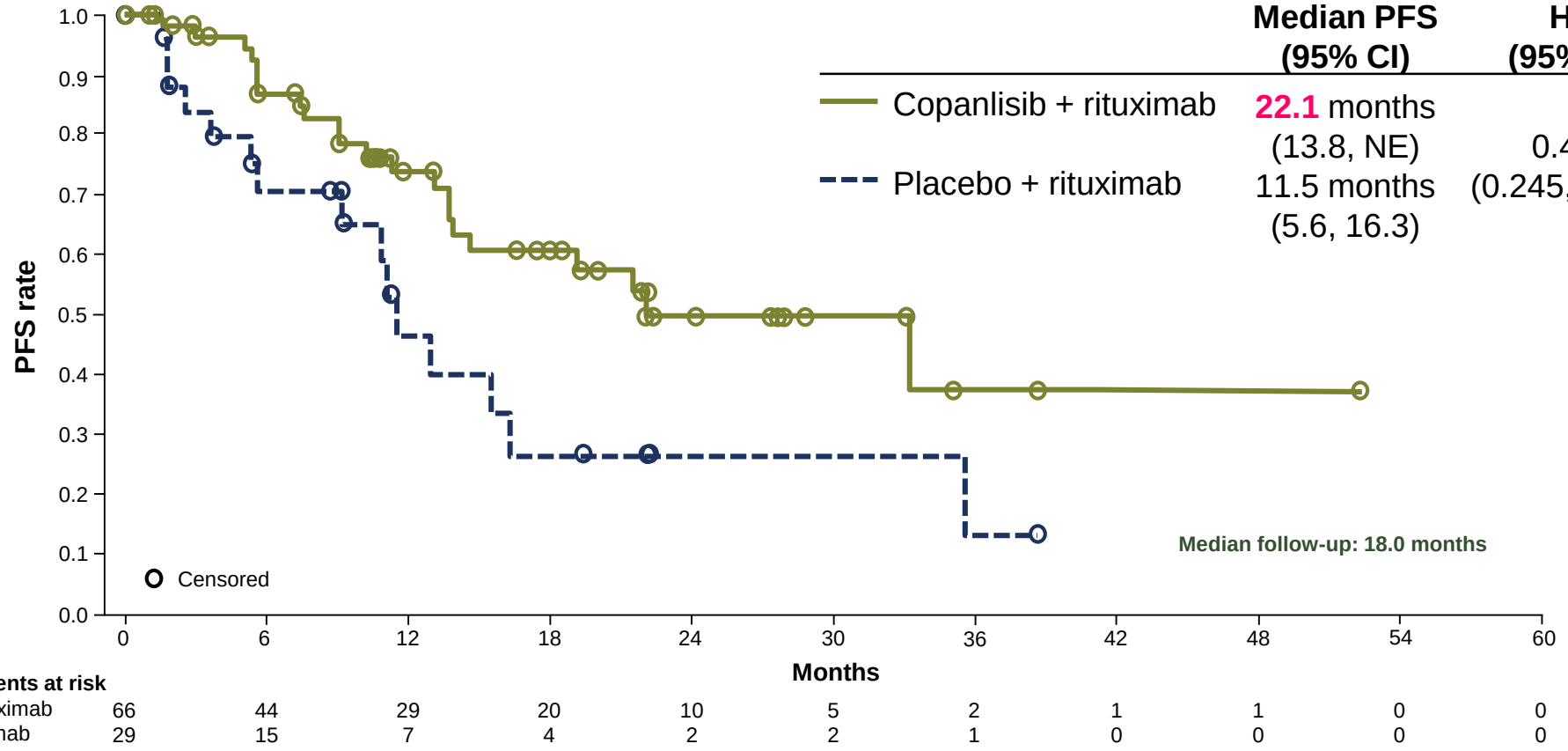
# Backup slides

# Patient characteristics

| | Copanlisib + rituximab *n*=66 | Placebo + rituximab *n*=29 |
|---|---|---|
| **Male, *n* (%)** | 33 (50.0) | 12 (41.4) |
| **Median age, years (range)** | 66 (37-91) | 63 (46-76) |
| **Medical history of diabetes, *n* (%)** | 13 (19.7) | 2 (6.9) |
| **Medical history of hypertension, *n* (%)** | 35 (53.0) | 11 (37.9) |
| **MZL subtype, *n* (%)** | | |
| Nodal | 25 (37.9) | 12 (41.4) |
| Extranodal | 24 (36.4) | 11 (37.9) |
| Splenic | 17 (25.8) | 6 (20.7) |
| **Median time since last systemic therapy, months (range)** | 24.8 (1.6-139.7) | 31.4 (3.9-161.2) |
| **Median time since initial diagnosis, months (range)** | 54.5 (10.3-220.6) | 72.4 (13.3-237.4) |
| **Progression-free and treatment-free for ≥12 months since last rituximab-containing regimen, *n* (%)** | 49 (74.2) | 22 (75.9) |
| **Unwilling or unfit to receive chemotherapy, *n* (%)** | 17 (25.8) | 7 (24.1) |
| **Previous lines of anti-cancer therapy, *n* (%)** | | |
| 1 | 35 (53.0) | 19 (65.5) |
| 2 | 19 (28.8) | 6 (20.7) |
| ≥3 | 12 (18.2) | 4 (13.8) |

Ozcan M, et al. Presented at: European Society for Medical Oncology (ESMO) Congress 2021; September 16-21, 2021. Abstract 826O.

# PFS in patients with MZL




| | Median PFS (95% CI) | HR (95% CI) | 1-sided *p* value |
|---|---|---|---|
| Copanlisib + rituximab | 22.1 months (13.8, NE) | 0.475 (0.245, 0.923) | 0.012 |
| Placebo + rituximab | 11.5 months (5.6, 16.3) | | |

**Number of patients at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Copanlisib + rituximab | 66 | 44 | 29 | 20 | 10 | 5 | 2 | 1 | 1 | 0 | 0 |
| Placebo + rituximab | 29 | 15 | 7 | 4 | 2 | 2 | 1 | 0 | 0 | 0 | 0 |

CI, confidence interval; HR, hazard ratio; NE, not evaluable

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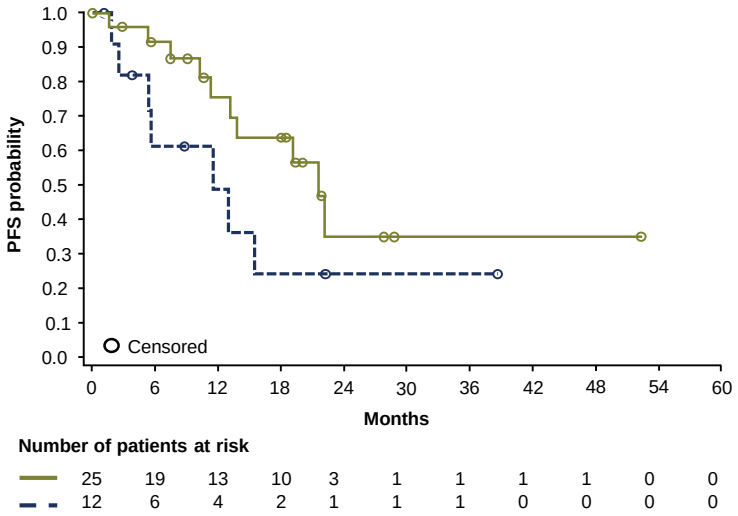
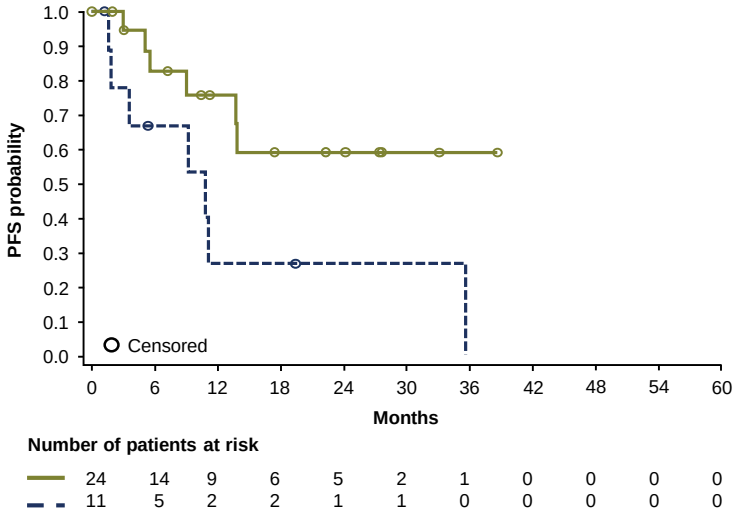
# PFS across MZL subsets

## Nodal



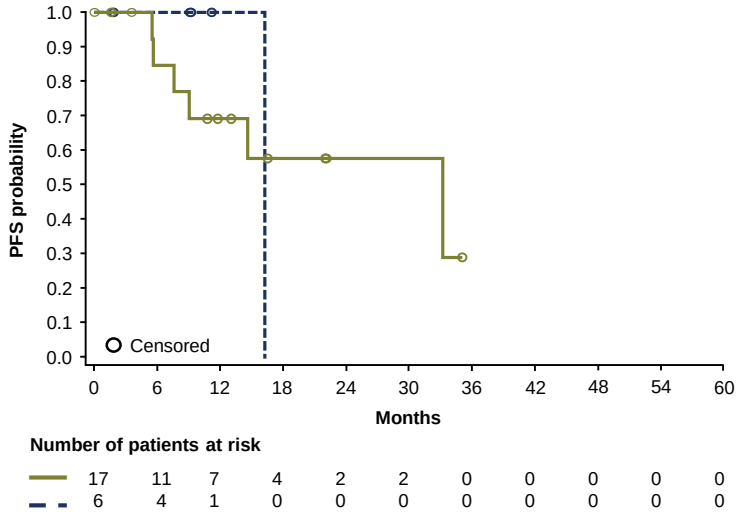

| | Median PFS (95% CI) | HR (95% CI) | 1-sided *p* value |
|---|---|---|---|
| Copanlisib + rituximab | **21.5** months (13.1, NE) | 0.483 (0.183, 1.276) | 0.067 |
| Placebo + rituximab | 11.5 months (2.5, NE) | | |

## Extranodal




| | Median PFS (95% CI) | HR (95% CI) | 1-sided *p* value |
|---|---|---|---|
| Copanlisib + rituximab | **NE** (9.0, NE) | 0.334 (0.111, 1.010) | 0.021 |
| Placebo + rituximab | 10.8 months (1.6, 35.6) | | |

## Splenic




| | Median PFS (95% CI) | HR (95% CI) | 1-sided *p* value |
|---|---|---|---|
| Copanlisib + rituximab | **33.2** months (7.6, NE) | Not reliably estimable | Not reliably estimable |
| Placebo + rituximab | 16.3 months (NE, NE) | | |

Ozcan M, et al. Presented at: European Society for Medical Oncology (ESMO) Congress 2021; September 16-21, 2021. Abstract 826O.

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