# 19th International Ultmann Chicago Lymphoma Symposium

**LIVE Symposium**

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19TH ULTMANN

THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

# Targeted Agents in Follicular Lymphoma (Small Molecules)

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# Disclosures

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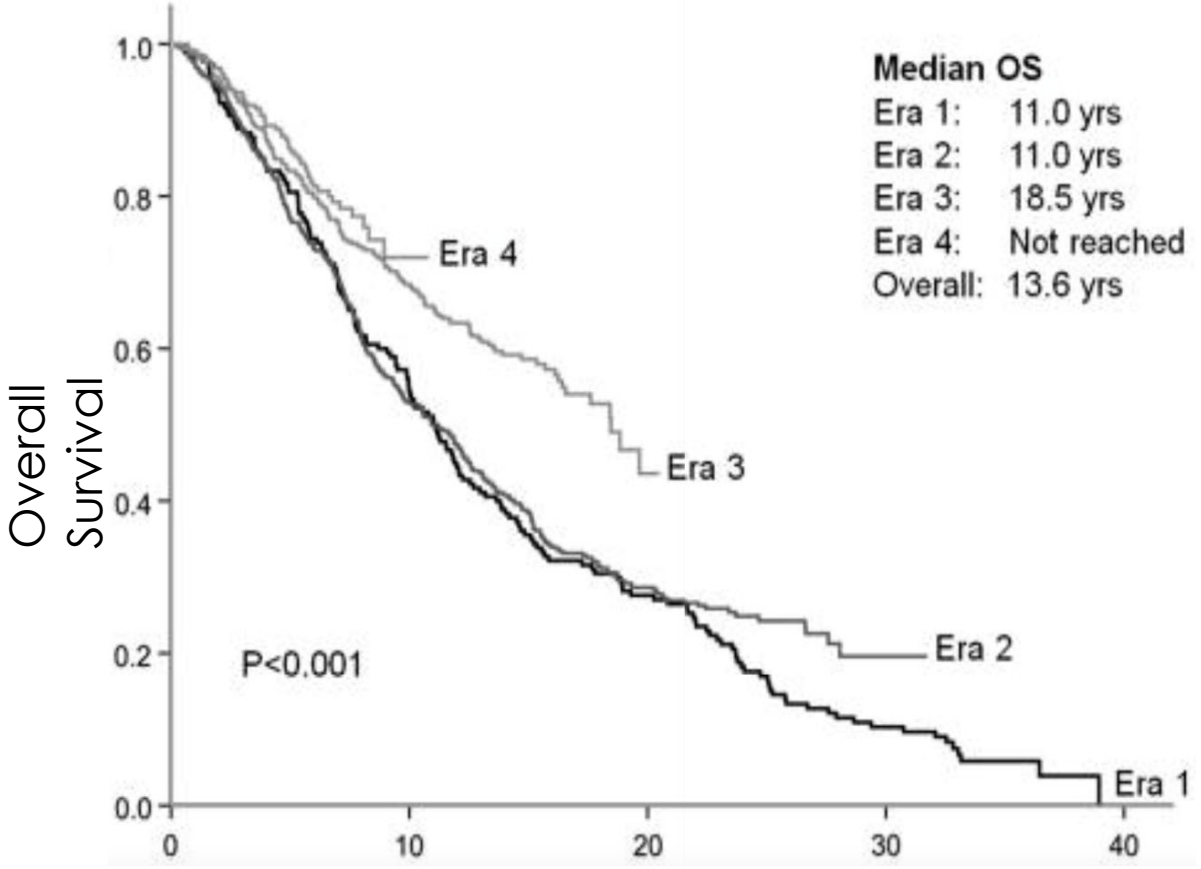
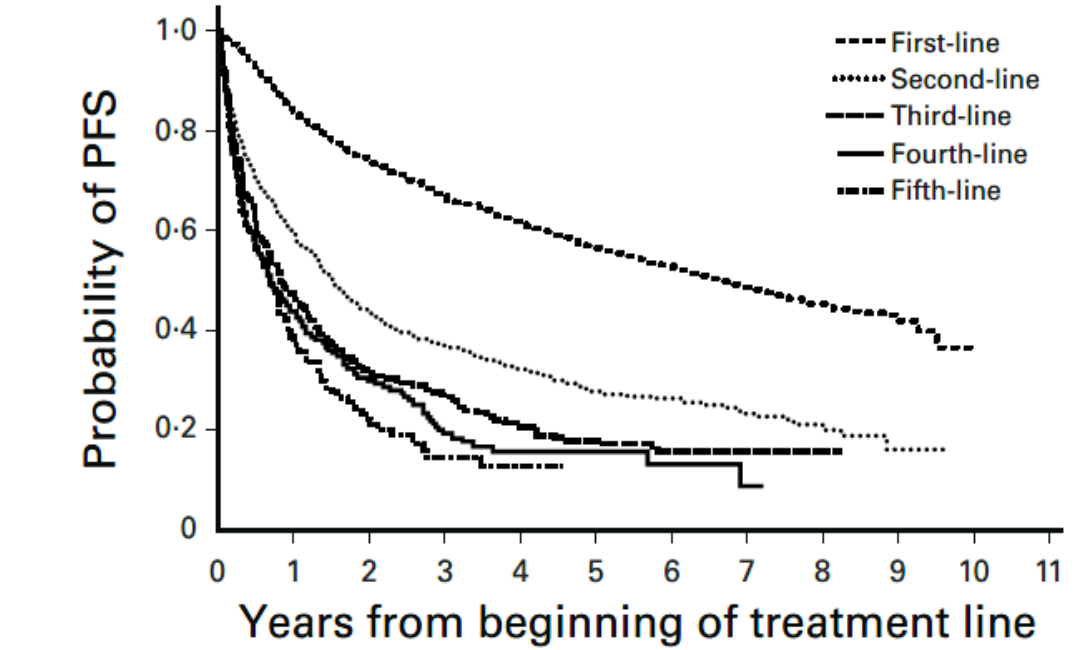
# Follicular Lymphoma

- Follicular lymphoma is the most common indolent lymphoma in US and Western Europe accounting for approximately 22% of all cases of Non-Hodgkin Lymphoma
- Currently the disease is incurable with variable patient disease course and outcomes
- Several viable frontline options but currently no clear standard of care.
  - Diminishing returns with successive cycles of therapy
  - Worse outcomes in patients who relapse within 24 months of chemoimmunotherapy
- Novel agents have moved to the forefront of options in relapsed/refractory (R/R) disease

# Treatment Outcomes in Follicular Lymphoma




**Era 1: Pre-Antracycline (1960-1975)** **Era 2: Antracycine. (1976-1986)**
**Era 3: Agg. Chemo/Purine Analogs (1987-1996)** **Era 4: Rituximab (1996-2003)**



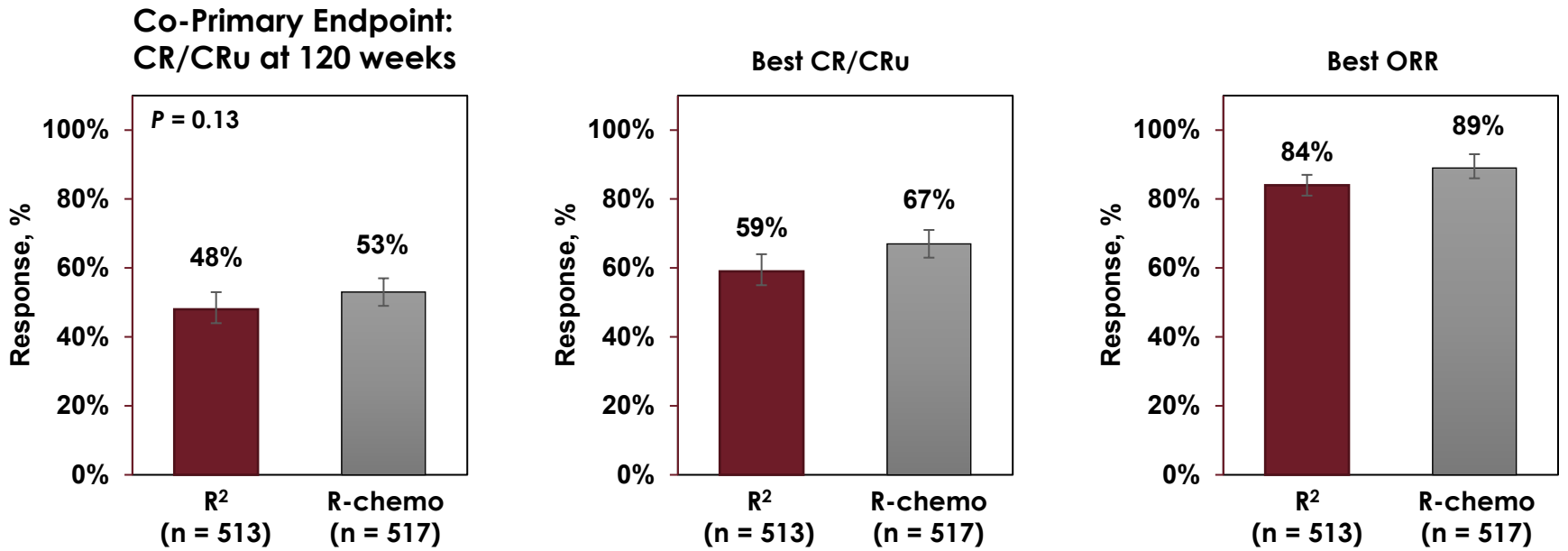

| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| First-line | 2429 | 1916 | 1602 | 1381 | 1202 | 1035 | 869 | 635 | 329 | 96 | 1 | 0 |
| Second-line | 889 | 489 | 331 | 256 | 199 | 137 | 104 | 57 | 24 | 5 | 0 | |
| Third-line | 438 | 181 | 109 | 78 | 50 | 30 | 18 | 5 | 1 | 0 | | |
| Fourth-line | 229 | 91 | 49 | 24 | 14 | 8 | 3 | 1 | 0 | | | |
| Fifth-line | 123 | 42 | 19 | 9 | 5 | 0 | | | | | | |

Tan et al. Blood 2013
Link et al. *BJH,* 2018; 184: 660-63
Rivas-Delgado et al. *BJH* 2018; 184: 753-59

# Frontline Follicular Lymphoma

- Only option for frontline FL is lenalidomide-rituximab (R2) based on Relevance Study.
- Study designed as a superiority study but results indicated that R2 is non-inferior to chemo-immunotherapy in frontline FL.

# RELEVANCE: Response by IRC (ITT)

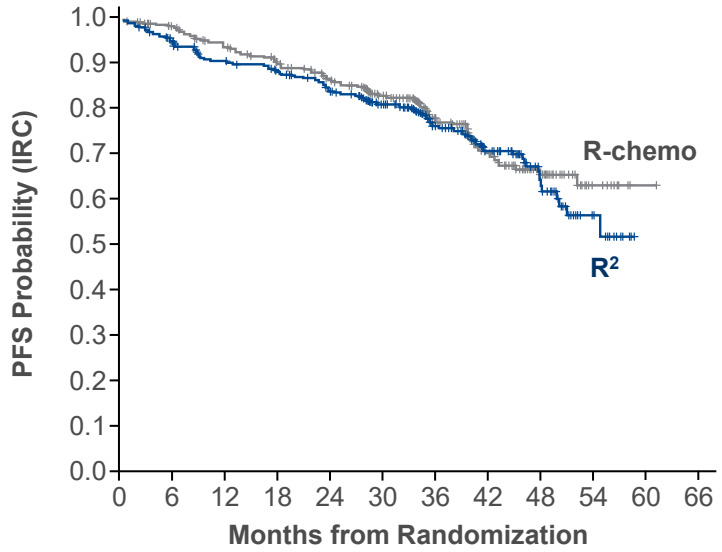



- 3-year DOR was 77% for $R^2$ vs 74% R-chemo (IRC)
- Investigator results were consistent with IRC

Data cut-off
31May2017.

# Relevance: Interim PFS By IRC

**Co-Primary Endpoint: Interim PFS (~50% events)**




Number of Patients at Risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| R² | 513 | 435 | 409 | 393 | 364 | 282 | 174 | 107 | 49 | 13 | 0 |
| R-chemo | 517 | 474 | 446 | 417 | 387 | 287 | 175 | 109 | 51 | 14 | 1 | 0 |

| | R² (n = 513) | R-chemo (n = 517) |
|---|---|---|
| Events, n (%) | 119 (23) | 111 (21) |
| 3-year PFS (95% CI) | 77% (72%-80%) | 78% (74%-82%) |
| HR (95% CI) | 1.10 (0.85-1.43) | |
| *P* value | 0.48 | |

- At a median follow-up of 37.9 months, interim PFS was similar in both arms

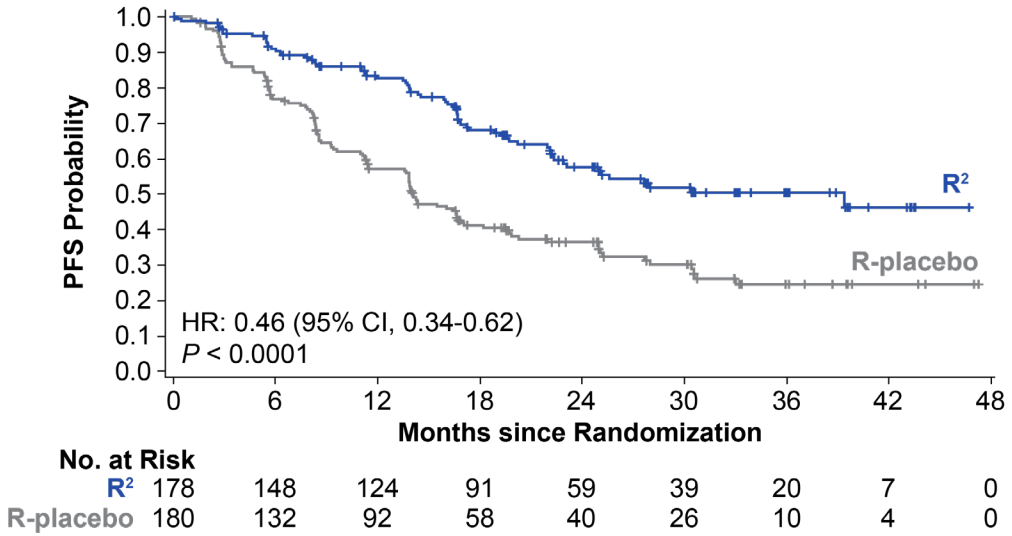
Data cut-off 31May2017.

# Relapsed/Refractory (R/R) Follicular Lymphoma

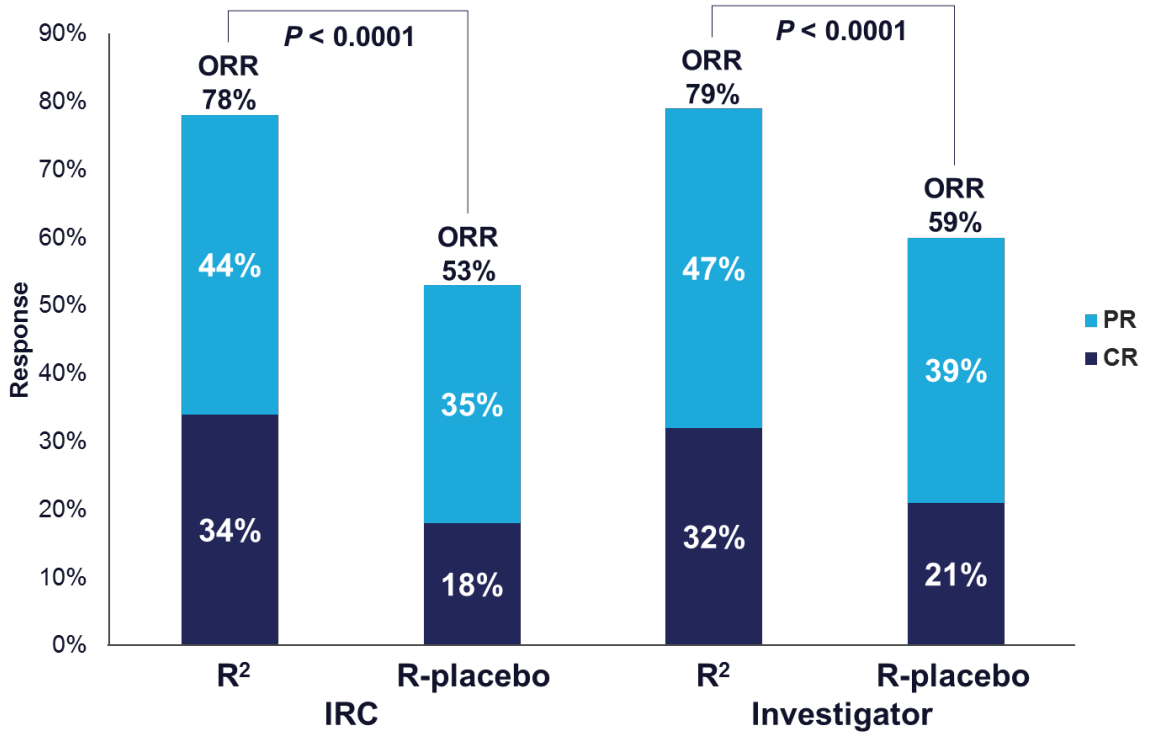
- Several small molecules approved for R/R FL including R2
  - Approved for 2L treatment
  - Additional option for 2L FL is Tazemetostat (those intolerant of other treatments).
- 3L FL had several options but the total has decreased in last several months
  - Currently one PI3K delta inhibitors and Tazemetostat are currently approved small molecule inhibitors.
- Several agents with rationale mechanism of actions have been explored but have not demonstrated any significant efficacy in R/R FL.
  - Ibrutinib
  - Venetoclax

# R2 –Augment Study (R2 vs. Rituximab)

Primary endpoint: progression-free survival (ITT, IRC)




| Median PFS | R² (n = 178) | R-placebo (n = 180) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| **By IRC, mo (95% CI)** | 39.4 (22.9-NE) | 14.1 (11.4-16.7) | 0.46 (0.34-0.62) | < 0.0001 |
| **By investigator, mo (95% CI)** | 25.3 (21.2-NE) | 14.3 (12.4-17.7) | 0.51 (0.38-0.69) | < 0.0001 |

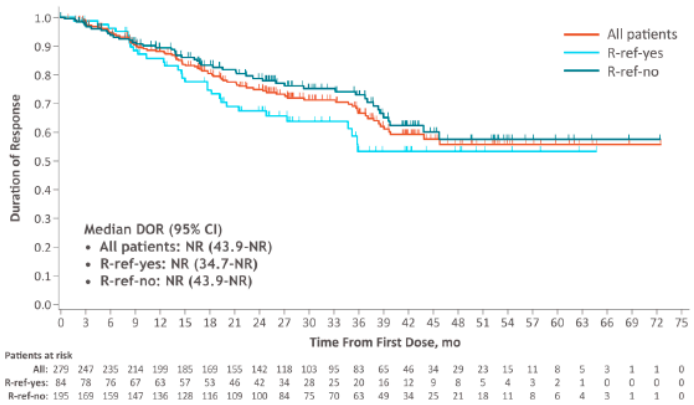



- Median DOR was 36.6 mo (95% CI, 22.9-NR) for R² vs 21.7 mo (95% CI, 12.8-27.6) for R-placebo,
HR 0.53 (95% CI, 0.36-0.79), *P* = 0.0015

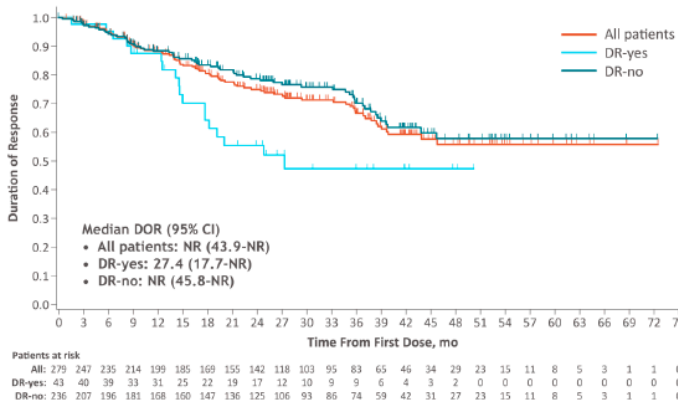
# R2 - Magnify

## Duration of Response[a]

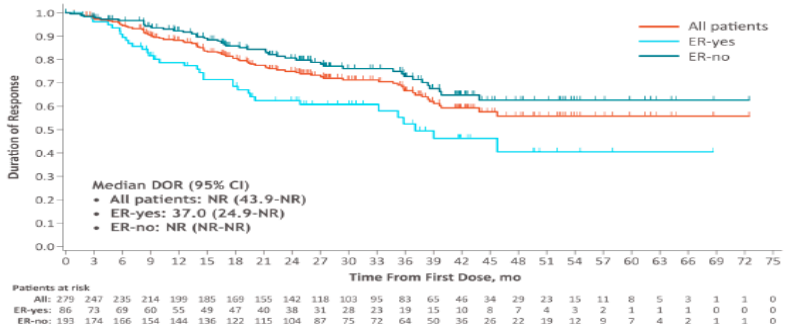
### Rituximab Refractory Status




### Double Refractory Status

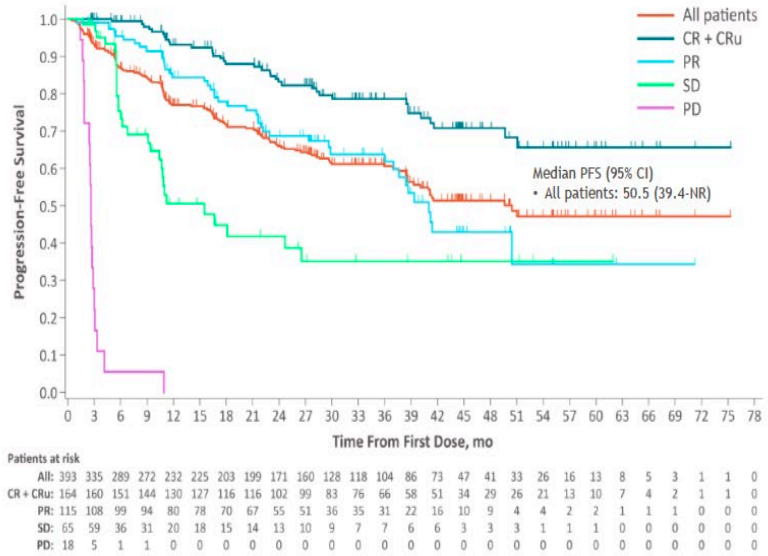



### Early Relapse Status



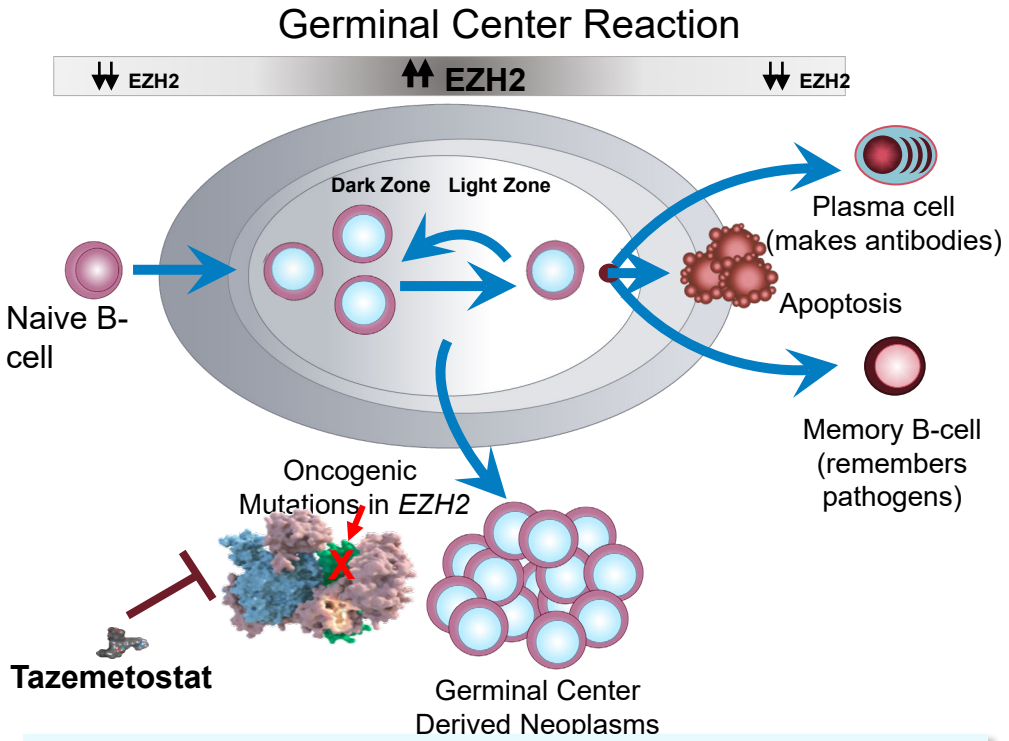

## Progression-Free Survival[a]

### PFS by Best Overall Response



# Tazemetostat, Follicular Lymphoma and *EZH2*

- *EZH2* an epigenetic regulator of gene expression and cell fate decisions[1]
- *EZH2* is required for normal B-cell biology and germinal center formation[2]
  - Oncogenic mutations in *EZH2* suppress exit from germinal state and "lock" B cells in this state thereby transforming into a cancer[2]
- *EZH2* biology relevant in both mutant (MT) and wild-type (WT) *EZH2* FL
  - ~20% of patients with FL also have *EZH2* gain of function mutations[3]




**Tazemetostat, an investigational, first-in-class, selective, oral inhibitor of EZH2 has shown antitumor activity in non-Hodgkin's lymphoma patients with either MT or WT EZH2[4,5]**

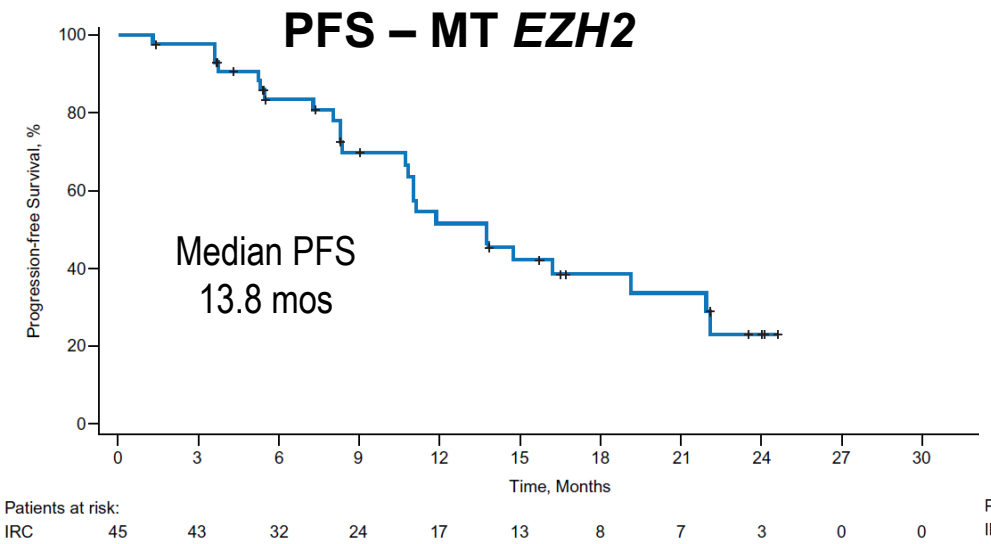
The American Society of Hematology (ASH)
7-10 December 2019
Orlando, FL

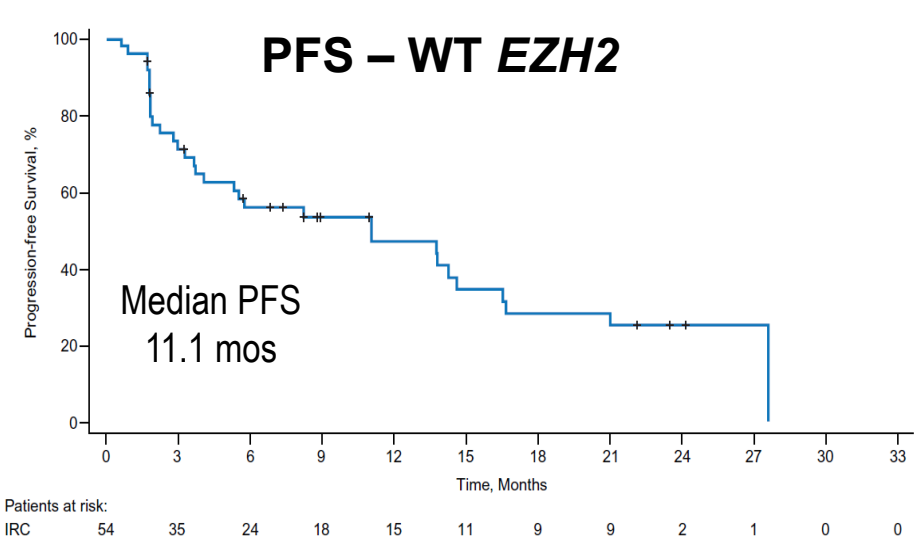
1. Gan L, et al. *Biomark Res*. 2018;6(1):10; 2. Béguelin W, et al. *Cancer Cell*. 2013;23(5)677-692. 3. Bödör C, et al. *Blood*. 2013;122:3165-3168. 4. Italiano A, et al. *Lancet Oncol*. 2018;19(5):649-59; 5. Morschhauser F, et al. *Hematol Oncol*. 2017 Jun;35:24-5.

# Tazemetostat ORR in EZH2 Mutant and Wild Type Populations

| Parameter | *EZH2* Mutant cohort (n=45) | | *EZH2* WT cohort (n=54) | |
|---|---|---|---|---|
| | Investigator | IRC | Investigator | IRC |
| **ORR, n (%)** | **35 (78)** | **31 (69)** | **18 (33)** | **19 (35)** |
| CR, n (%) | 4 (9) | 6 (13) | 3 (6) | 2 (4) |
| PR, n (%) | 31 (69) | 25 (56) | 15 (28) | 17 (31) |
| SD, n (%) | 10 (22) | 13 (29) | 16 (30) | 18 (33) |
| PD, n (%) | 0 | 1 (2)[c] | 16 (30) | 12 (22) |
| DOR, months, median (95% CI) | 8.3 (5.5–13.8) | 10.9 (7.2–NE) | 14.7 (7.6–NE) | 13.0 (5.6–NE) |

# PFS by Investigator and IRC Assessment in the ITT Population




| Endpoint by IRC Assessment | ITT Population | |
|---|---|---|
| | MT *EZH2* (n=45) | WT *EZH2* (n=54) |
| PFS, months, median (95% CI) | 13.8 (10.7–22.0) | 11.1 (3.7–14.6) |
| PFS at 12 months, median (95% CI) | 51.7 (34.4–66.6) | 47.1 (31.6–61.1) |
| PFS at 18 months, median (95% CI) | 38.8 (22.7–54.7) | 28.3 (14.8–43.4) |

# PI3Ki

- Class of drug recently in press due to withdrawal of indication in FL
  - Idelalisib
  - Duvelisib
  - Umbralisib
- One agent currently still with approval for FL and one additional agent still in clinical studies
  - Copanlisib (IV)
  - Zandelisib

# Copanlisib

**Table 2.** Response (Full Analysis Set)

| Best Response | Tumor, No. (%) | | | | |
|---|---|---|---|---|---|
| | FL (n = 104) | MZL (n = 23) | SLL (n = 8) | LPL/WM (n = 6) | Total (N = 142)* |
| Complete response | 15 (14) | 2 (9) | 0 | 0 | 17 (12) |
| Partial response | 46 (44) | 14 (61) | 6 (75) | 1 (17) | 67 (47) |
| Stable disease | 35 (34)† | 4 (17) | 1 (13) | 3 (50) | 43 (30)† |
| Progressive disease | 2 (2) | 0 | 1 (13) | 0 | 3 (2) |
| Not evaluable | 0 | 1 (4) | 0 | 0 | 1 (< 1) |
| Not available‡ | 6 (6) | 2 (9) | 0 | 2 (33) | 11 (8) |
| Objective response rate | 61 (59) | 16 (70) | 6 (75) | 1 (17) | 84 (59) |
| 95% CI§ | 49 to 68 | 47 to 87 | 35 to 97 | 0.4 to 64 | 51 to 67 |
| Disease control rate‖ | 91 (88) | 20 (87) | 7 (88) | 4 (67) | 122 (86)‖ |
| 95% CI§ | 80 to 93 | 66 to 97 | 47 to 100 | 22 to 96 | 79 to 91 |

Abbreviations: FL, follicular lymphoma; LPL/WM, lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma.

*One patient with diffuse large B-cell lymphoma was included because the initial investigator assessment was indolent non-Hodgkin lymphoma, which was later confirmed by the investigator and central pathology review to be diffuse large B-cell lymphoma.

†Includes one patient with unconfirmed early stable disease (stable disease was assessed < 7 weeks after start of treatment).

‡Of the full analysis set of 142 patients, data for 11 (8%) were not available for the analysis of the primary efficacy variable (objective response rate).

§95% CIs by exact binomial calculation.

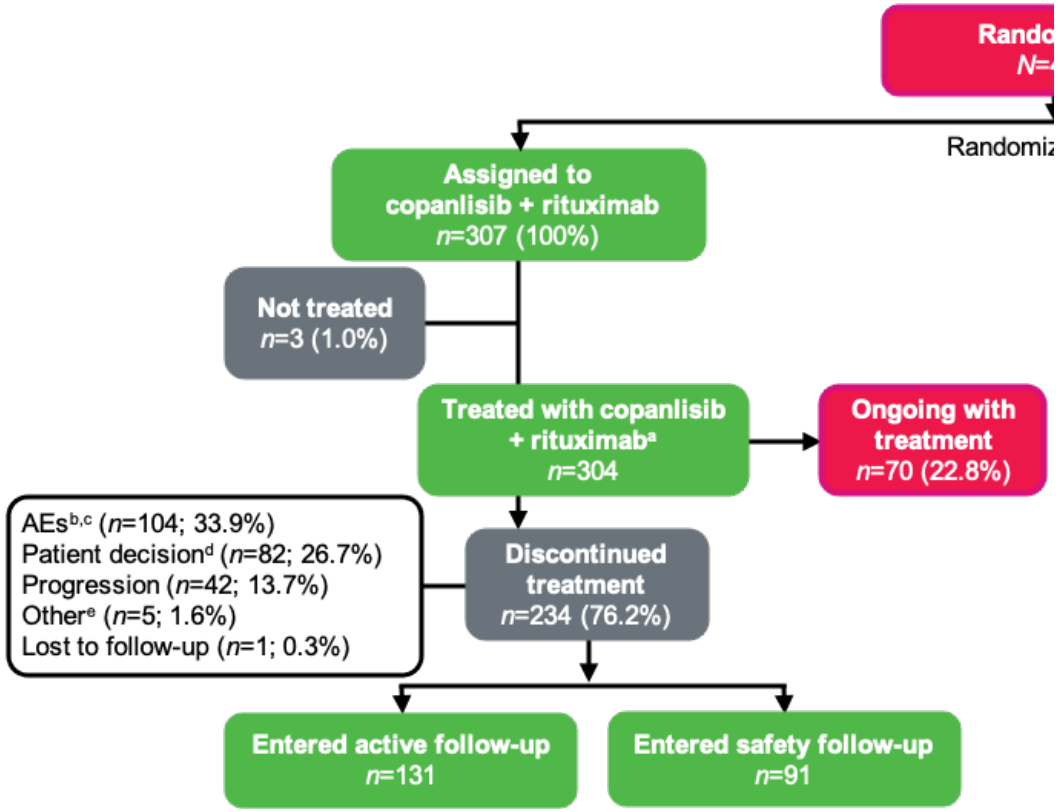
‖One patient with unconfirmed stable disease and four with stable disease or partial response recorded > 35 days from the last treatment were excluded from the calculation.

*Table 2. Response (Full Analysis Set)*

- The Chronos-1 trial enrolled a total of 142 patients with R/R indolent lymphoma.[1]
- Patients with follicular lymphoma had an ORR of 59%, a CR of 15% and PR of 44%. The median DOR was 12.2 months for patients with follicular lymphoma

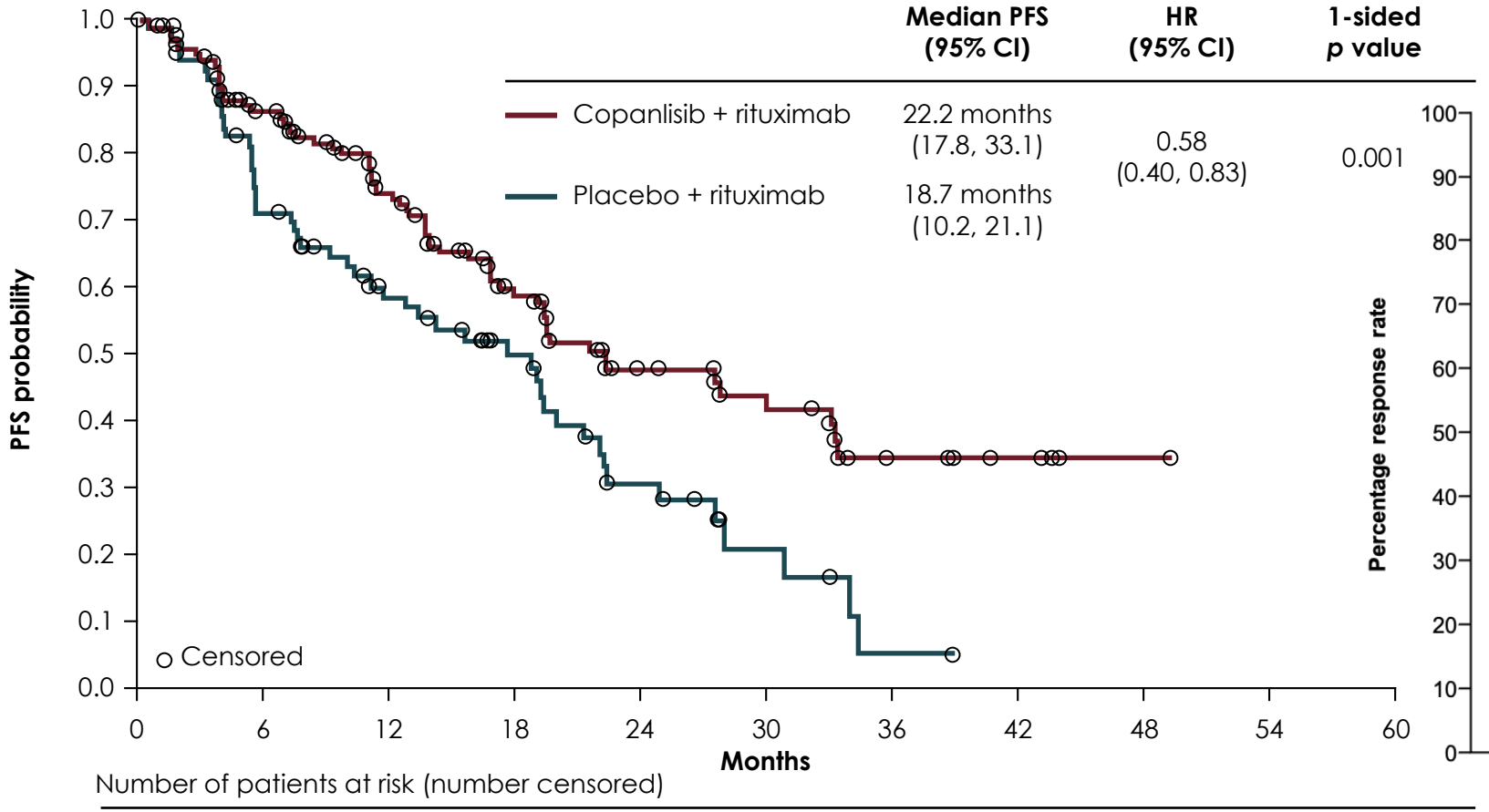
Published in: Martin Dreyling; Armando Santoro; Luigina Mollica; Sirpa Leppä; George A. Follows; Georg Lenz; Won Seog Kim; Arnon Nagler Panayiotis Panayiotidis; Judit Demeter; Muhit Özcan; Marina Kosinova; Krimo Bouabdallah; Franck Morschhauser; Don A. Stevens; David Trevarthen; Marius Giurescu; Lisa Cupit; Li Liu; Karl Köchert; Henrik Seidel; Carol Peña; Shuxin Yin; Florian Hiemeyer; Jose Garcia-Vargas; Barrett H. Childs; Pier Luigi Zinzani; *Journal of Clinical Oncology* 2017 353898-3905.[1]
DOI: 10.1200/JCO.2017.75.4648

# CHRONOS-3: randomized Phase III study of copanlisib plus rituximab vs rituximab / placebo in relapsed indolent non-Hodgkin lymphoma (iNHL):Treatment exposure



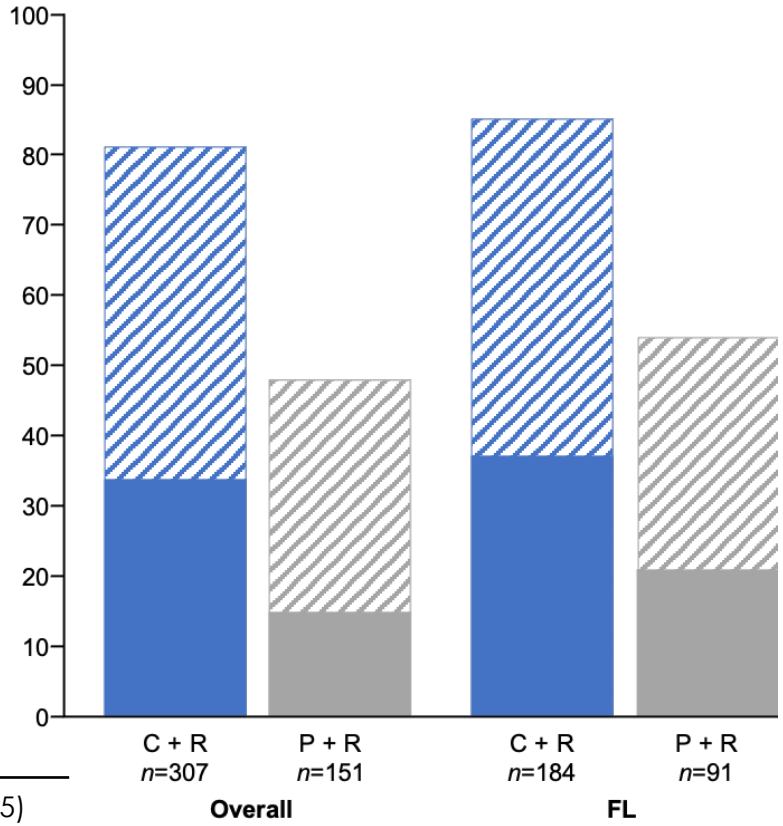

| | Copanlisib + rituximab *n*=307 | Placebo + rituximab *n*=146 |
|---|---|---|
| **Median duration of treatment, months (range)** | 8.31 (0.2-54.0) | 10.78 (0.2-46.6) |
| **Mean duration of treatment, months (standard deviation)** | 12.0 (11.5) | 12.7 (9.9) |
| **Median number of cycles (range)** | 9 (1-57) | 12 (1-51) |
| **Median percentage of planned dose (range)** | 95.2 (41-106) | 100 (67-114) |
| **Dose interruptions or delays, *n* (%)** | 231 (75.2) | 83 (56.8) |
| **Median duration of interruptions or delays, days (range)** | 7 (1-174) | 7 (1-84) |
| **Dose reductions, *n* (%)** | | |
| **Dose reduction to 45 mg** | 83 (27.0) | 10 (6.8) |
| **Dose reduction to 30 mg** | 28 (9.1) | 0 |
| **Discontinuation of any study drug due to AEs, *n* (%)** | 98 (31.9) | 12 (8.2) |

# PFS/OS in patients with FL




Number of patients at risk (number censored)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Copanlisib + rituximab | 184 (0) | 121 (40) | 87 (59) | 53 (77) | 30 (91) | 20 (98) | 9 (106) | 4 (111) | 1 (114) | 0 (115) | 0 (115) |
| Placebo + rituximab | 91 (0) | 56 (12) | 37 (22) | 25 (29) | 12 (33) | 5 (37) | 1 (38) | 0 (39) | 0 (39) | 0 (39) | 0 (39) |



# Disposition & Exposure

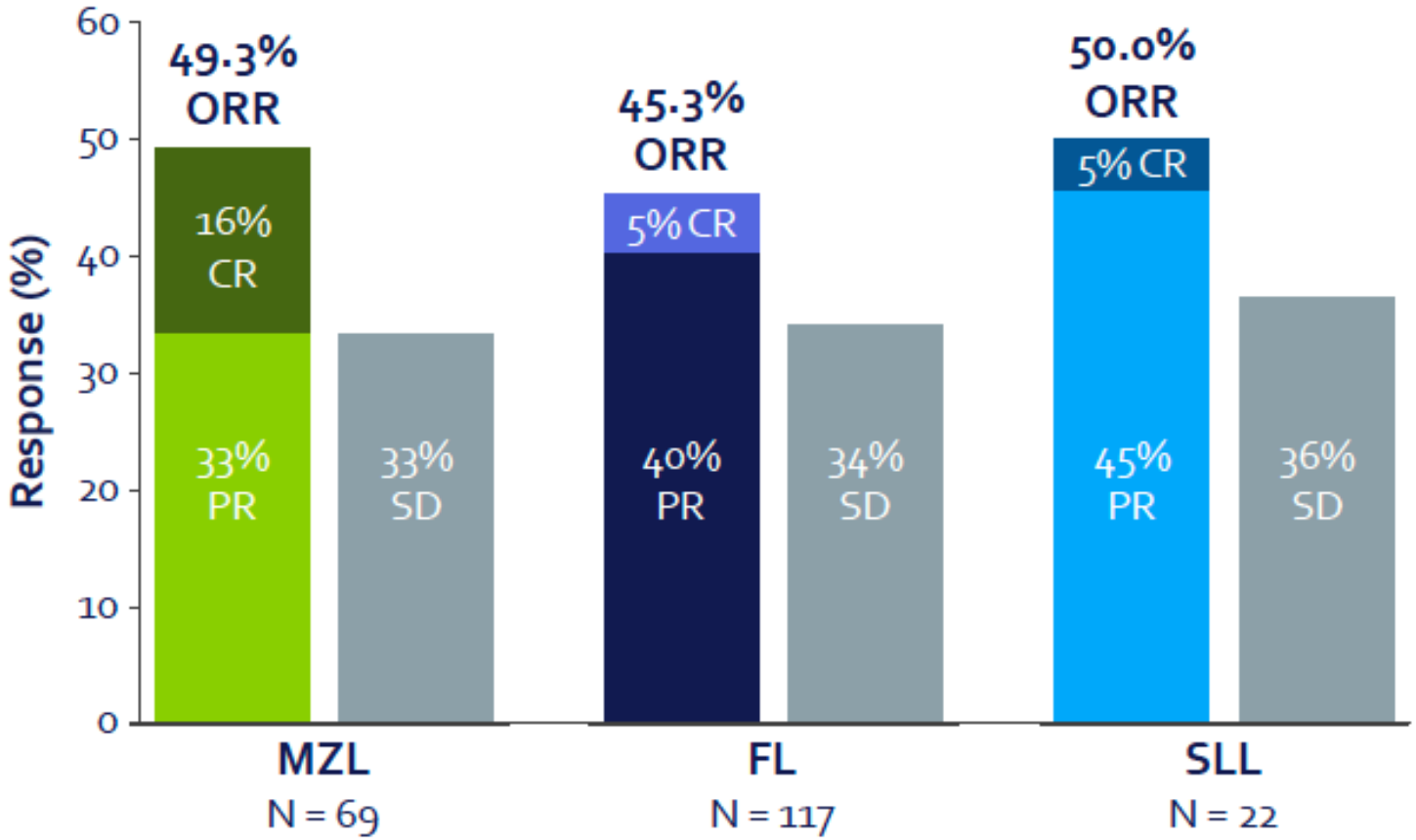
## Unity-NHL Study (UTX-TGR-205: Umbraslisib

| | MZL N=69 | FL N=117 | SLL N=22 | Total N=208 |
|---|---|---|---|---|
| **Treated with at least one dose, n (%)** | 69 (100) | 117 (100) | 22 (100) | 208 (100) |
| **Exposure, median (range), months** | 9.8 (0.2 – 27) | 7.6 (1.0 – 27) | 10.9 (0.7 – 25) | 8.4 (0.2 – 27) |
| **Median follow up, months** | 27.8 | 27.5 | 29.3 | 27.7 |
| **Treatment status, n (%)** | | | | |
| Ongoing | 26 (38) | 27 (23) | 7 (32) | 60 (29) |
| Discontinued | 43 (62) | 90 (77) | 15 (68) | 148 (71) |
| Adverse event | 16 (23) | 14 (12) | 2 (9) | 32 (15) |
| Death | 0 | 0 | 1 (5)[a] | 1 (0.5) |
| Non-compliance | 0 | 1 (1) | 0 | 1 (0.5) |
| Investigator decision | 5 (7) | 8 (7) | 3 (14) | 16 (8) |
| Progressive disease | 19 (28) | 62 (53) | 7 (32) | 88 (42) |
| Withdrew consent | 3 (4) | 2 (2) | 1 (5) | 6 (3) |
| Other | 0 | 3 (3) | 1 (5) | 4 (2) |



FL: follicular lymphoma; MZL: marginal zone lymphoma; SLL: small lymphocytic lymphoma. [a]One SLL patient had a fatal myocardial infarction unrelated to umbralisib; there were no other fatalities

# IRC-Assessed Overall Response Primary Endpoint




| Cohort | DCR | Median TTR | Median FU |
|---|---|---|---|
| MZL | 82.6 % | 2.8 mo | 27.8 mo |
| FL | 79.5% | 4.6 mo | 27.5 mo |
| SLL | 86.4% | 2.7 mo | 29.3 mo |

Across entire indolent NHL population (n=208) umbralisib produced a **47.1%** ORR and **81.3%** DCR

CR: complete response; DCR: disease control rate (CR + PR + SD); FL: follicular lymphoma; FU: follow up; IRC: independent review committee; mo: months; MZL: marginal zone lymphoma; ORR: overall response rate; PR: partial response; SD: stable disease; TTR: time to response.

# Future Directions/Conclusions

- R2 is the only agent currently with a role in frontline FL. While a range of small molecules have become the staple for the management of R/R FL
- Several agents are in development that might impact current landscape
  - Zandelisib
    - 2nd generation PI3Ki being explored in phase 2 (TIDAL) and phase 3 (COASTAL) study
  - CC-99282
    - a novel, small molecule CELMoD® agent that co-opts cereblon to induce targeted degradation of Ikaros/Aiolos currently in early phase studies
  - Capivasertib
    - AKT inhibitor being developed by AstraZeneca currently in early phase studies

# ARS

What agents are approved in the 2L for the management of patients with R/R follicular lymphoma.

A. Lenalidomide
B. Copanlisib
C. Axi-cel
D. Tazemetostat
E. A and D
F. All of the above