# Optimal management of newly diagnosed and relapsed/refractory follicular lymphoma

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# Considerations in the choice of therapy for FL patients at diagnosis or relapse

- Indications for therapy
- Bulk of disease
- Comorbidities
- Toxicity concerns
- Interest in and availability of clinical trials
- Risk of transformation
- Grade (typically I treat FL grade 1, 2 and 3A similarly)

Courtesy of John P Leonard, MD

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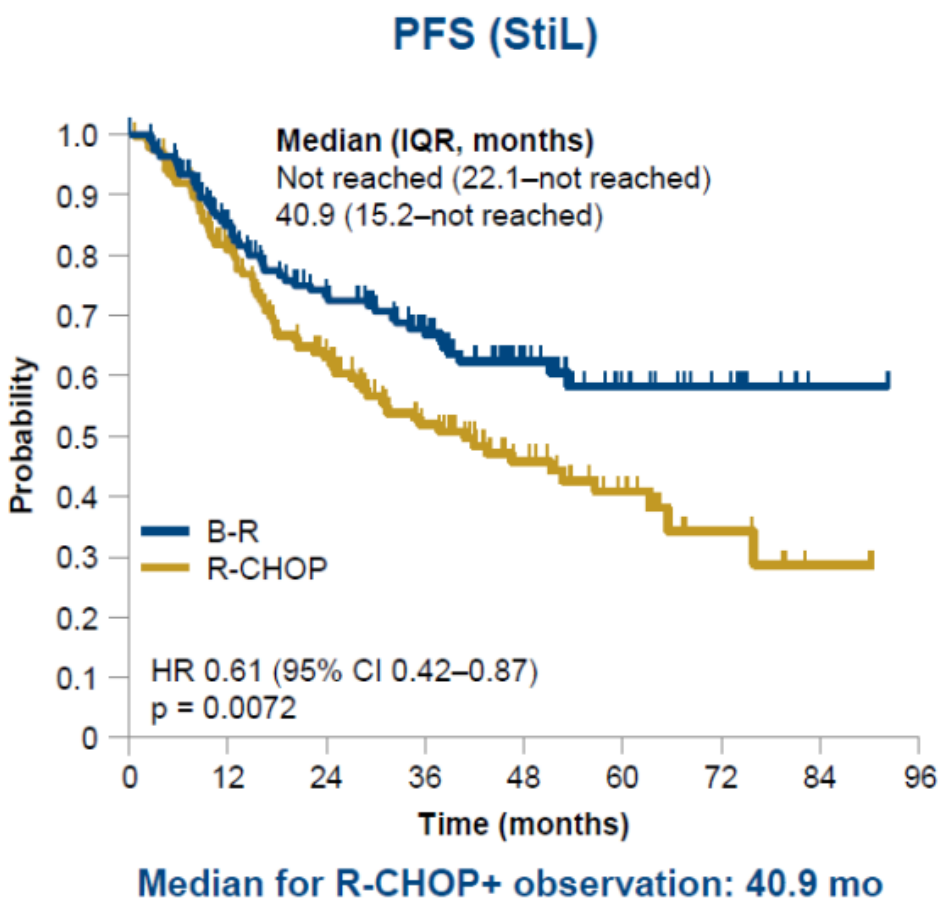
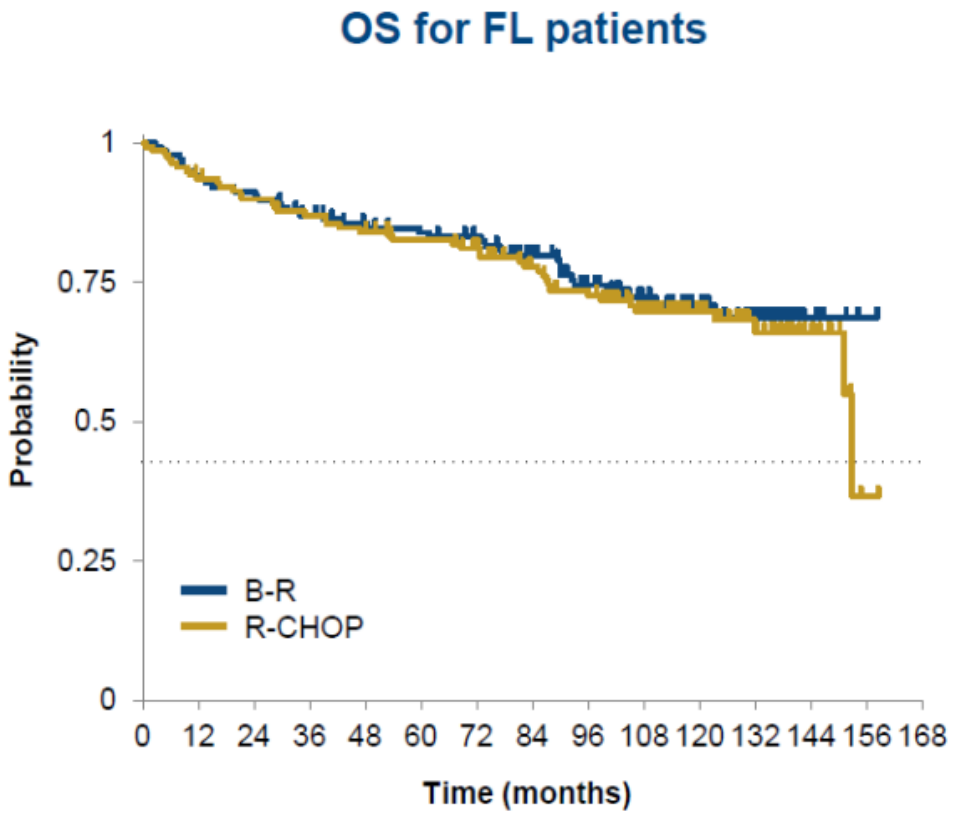
# Bendamustine-Rituximab vs R-CHOP for advanced stage FL




**Median for R-CHOP+ observation: 40.9 mo**




Rummel MJ, et al. Lancet. 2013:381:1203-10. and updated ASCO 2017

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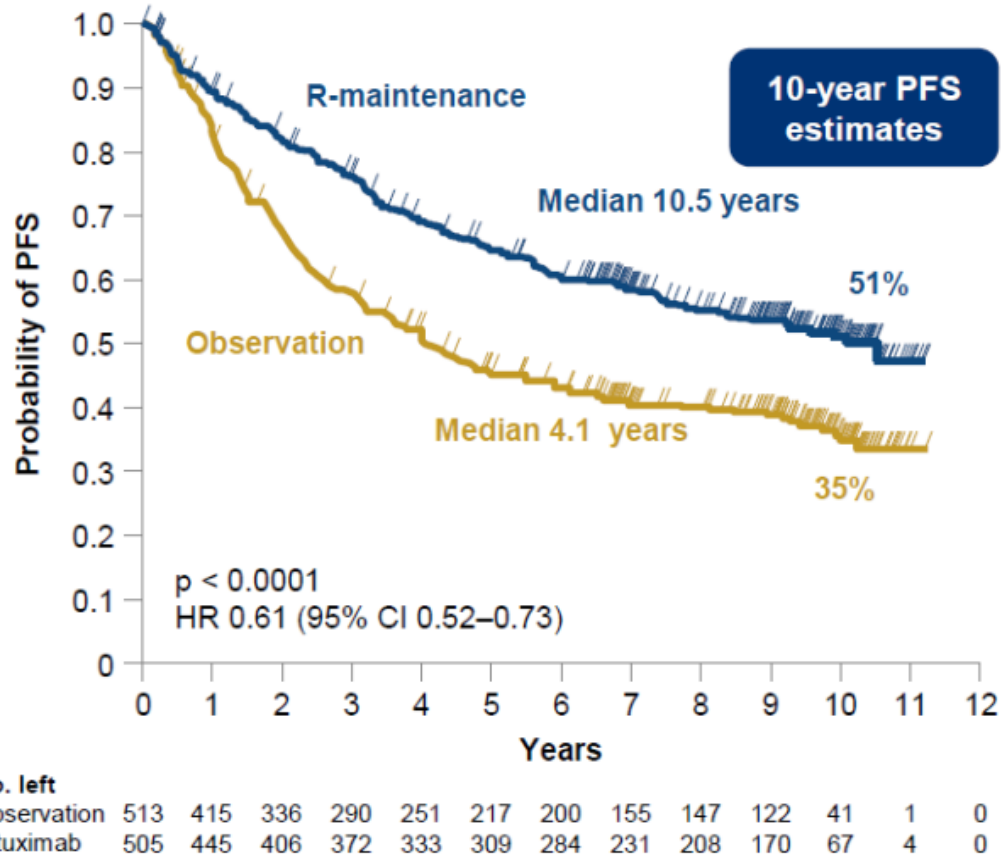
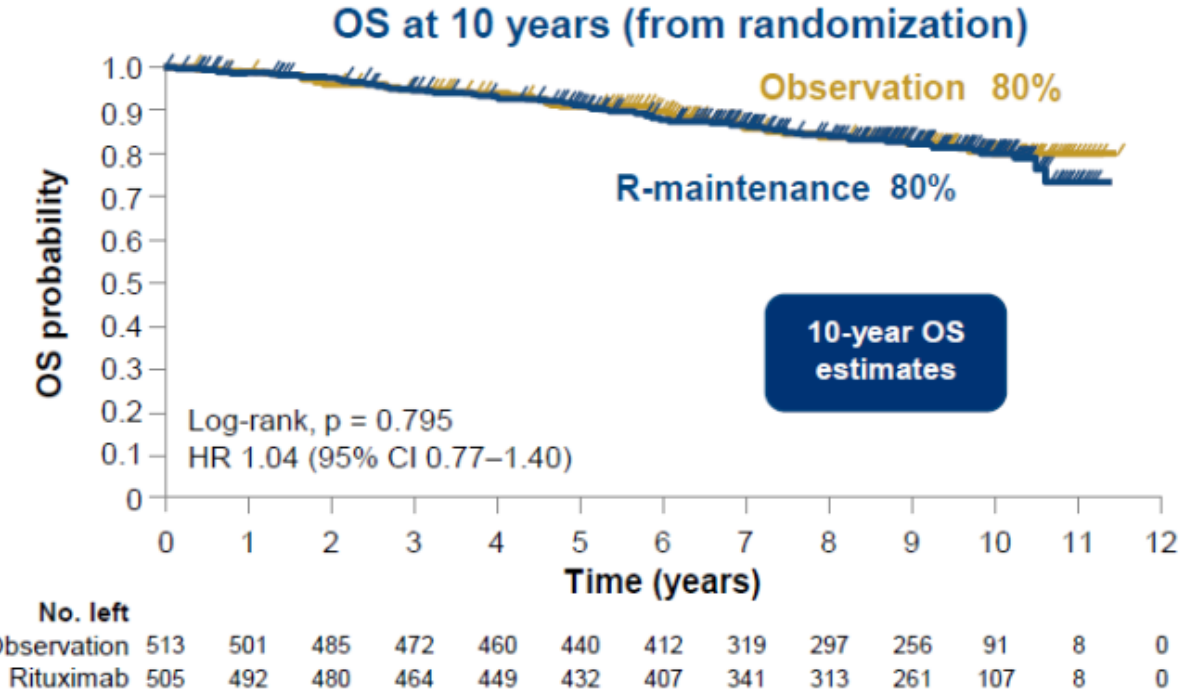
# PRIMA: Maintenance R after R-CHOP/R-CVP improves PFS but not OS




Salles G, et al, ASH 2017

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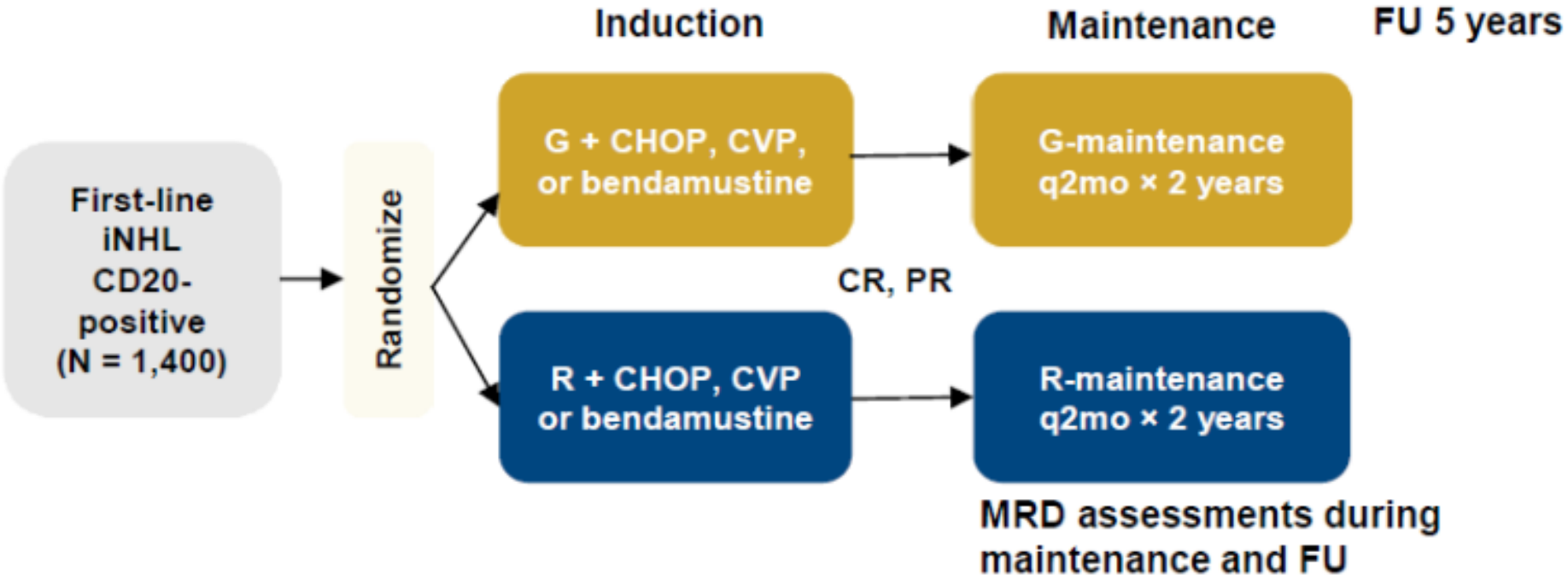
# GALLIUM: Obinutuzumab (G) vs Rituximab with chemotherapy (and as maintenance)




Marcus R, et al. N Engl J Med. 2017; 377:1331-44.

Courtesy of John P Leonard, MD

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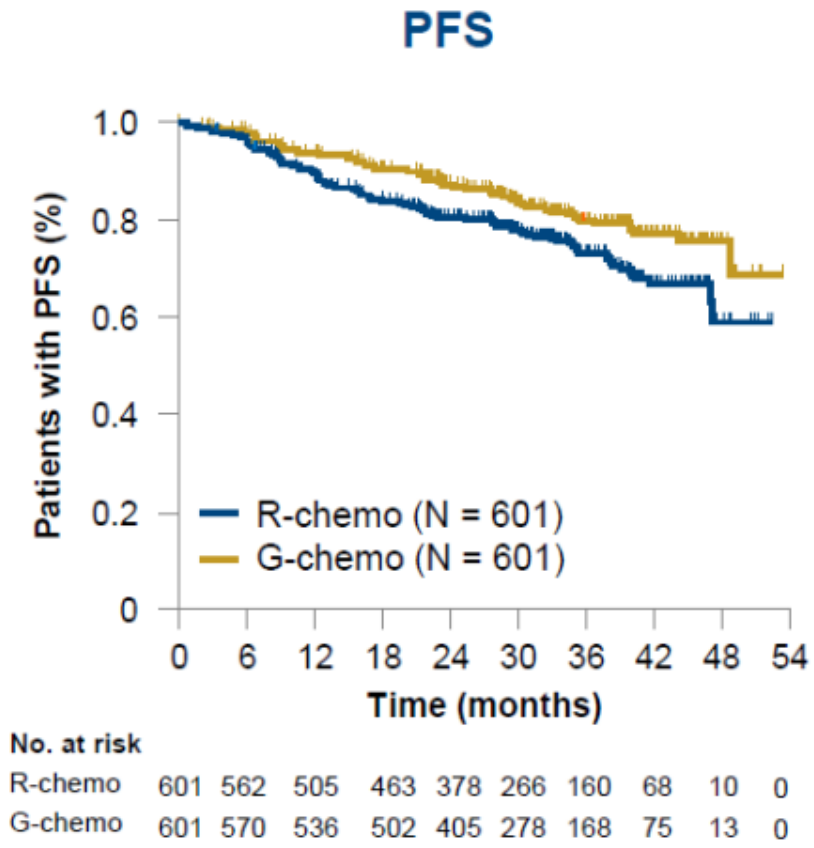
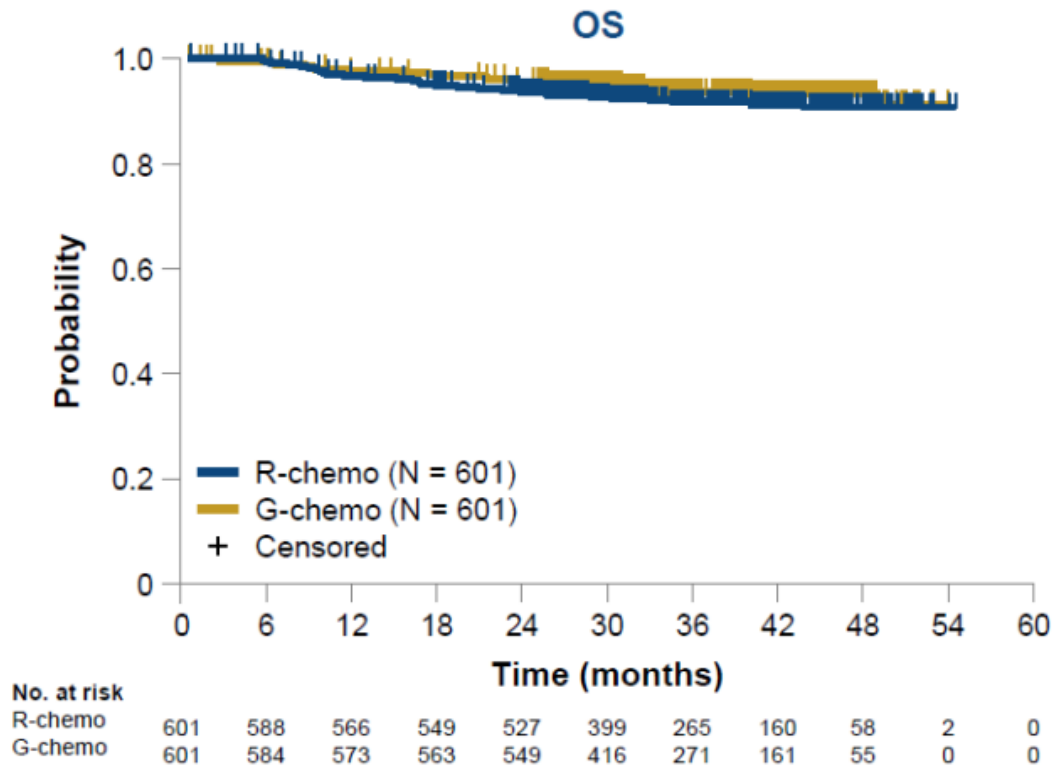
# GALLIUM: Obinutuzumab vs Rituximab with chemotherapy (and as maintenance) improves PFS but not OS




Marcus R, et al. N Engl J Med. 2017; 377:1331-44.

Courtesy of John P Leonard, MD

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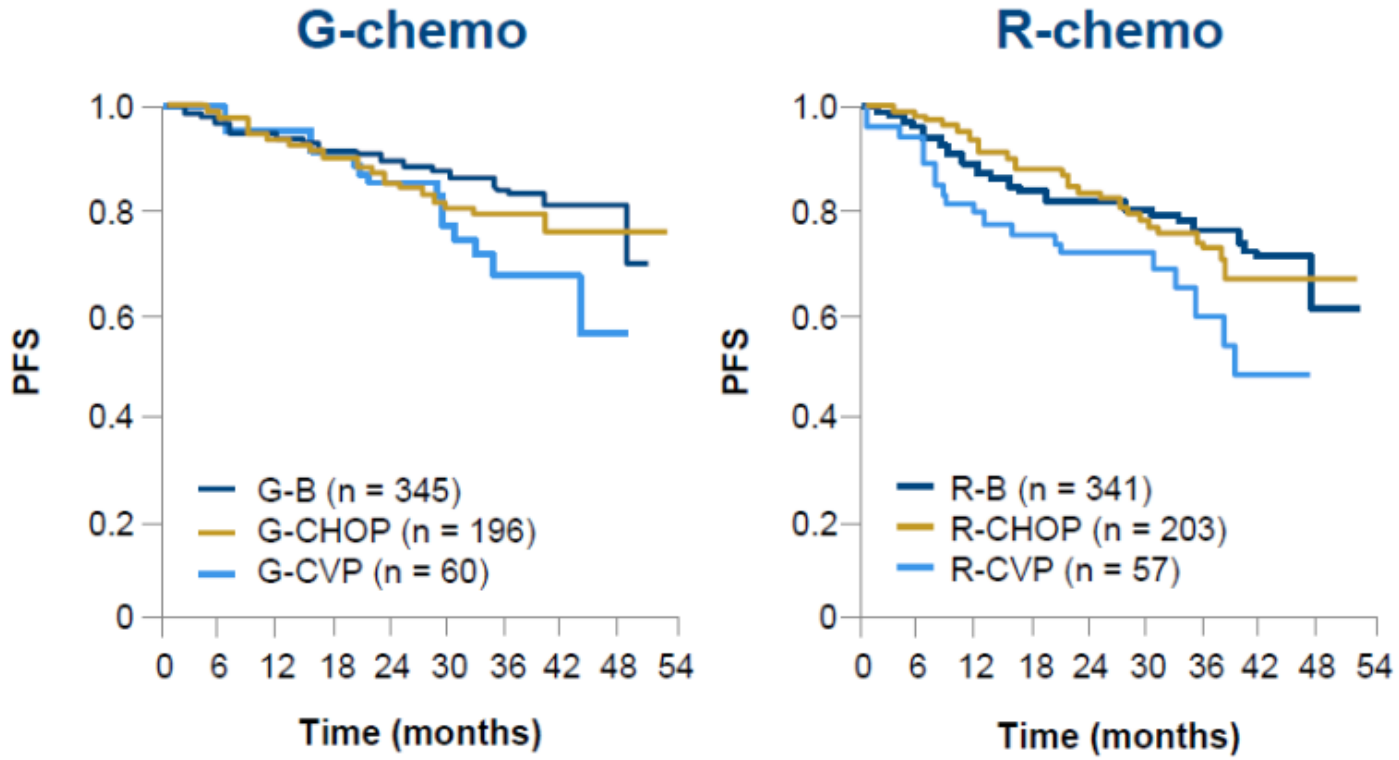
# GALLIUM: Obinutuzumab vs Rituximab with chemotherapy (and as maintenance): Effects across regimens




| | HR (95% CI) |
|---|---|
| G-B vs R-B | 0.61 (0.43–0.86) |
| G-CHOP vs R-CHOP | 0.77 (0.50–1.20) |
| G-CVP vs R-CVP | 0.63 (0.32–1.21) |

Hiddemann, et al. J. Clin Oncol 2018

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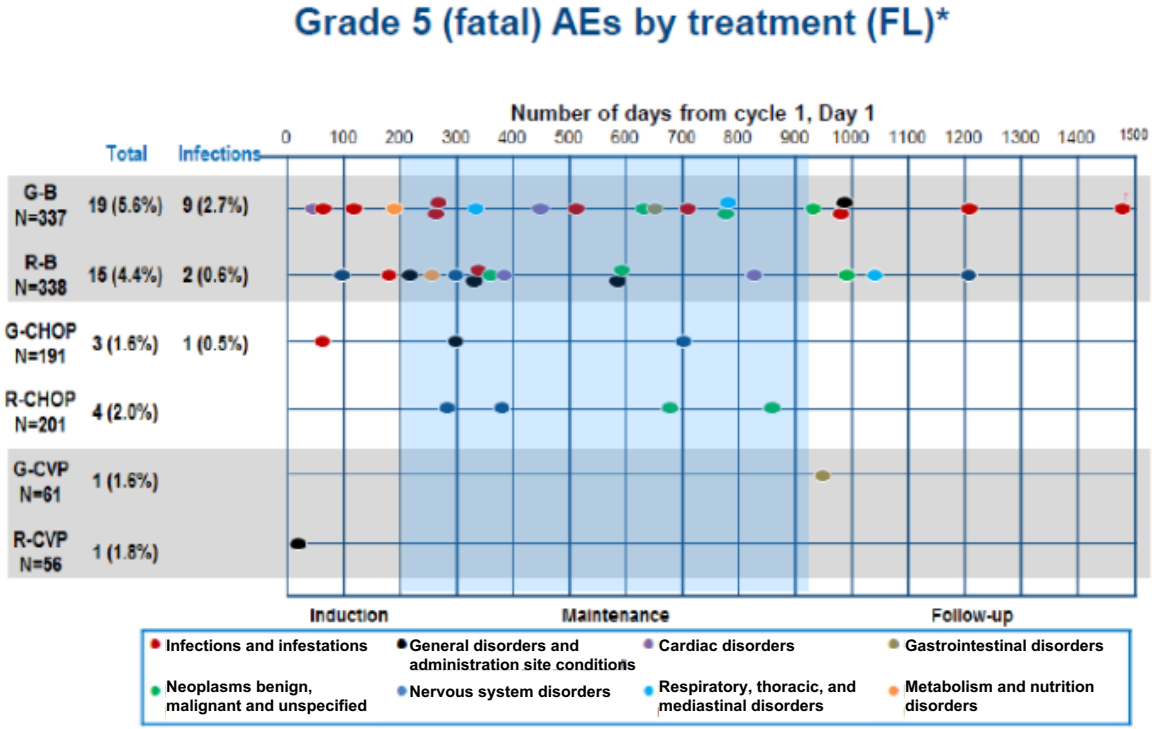
# GALLIUM: Obinutuzumab vs Rituximab with chemotherapy (and as maintenance): High-grade adverse events

| % (n) | R-chemo (N = 597) | G-chemo (N = 595) |
|---|---|---|
| Any AE, % | 98.3 | 99.5 |
| Grade ≥ 3 AEs (> 5% in either arm) | 67.8 | 74.6 |
| Neutropenia | 37.9 | 43.9 |
| Leucopenia | 8.4 | 8.6 |
| Febrile neutropenia | 4.9 | 6.9 |
| IRRs | 3.7 | 6.7 |
| Throm | | 6.1 |
| Grade ≥ by cate | | |
| Infecti | | 20.0 |
| IRRs | | 12.4 |
| Secon | | 4.7 |
| SAEs, | | 46.1 |
| AEs ca disconti | | 16.3 |
| Grade 5 | | 4.0 |
| Median baseli induct | | −1.50 (−22.3; −6.5) |

| | Total (%) | Infections (%) |
|---|---|---|
| G-B N = 337 | 19 (5.6) | 9 (2.7) |
| R-B N = 338 | 15 (4.4) | 2 (0.6) |
| G-CHOP N = 191 | 3 (1.6) | 1 (0.5) |
| R-CHOP N = 201 | 4 (2.0) | |
| G-CVP N = 61 | 1 (1.6) | |
| R-CVP N = 56 | 1 (1.8) | |

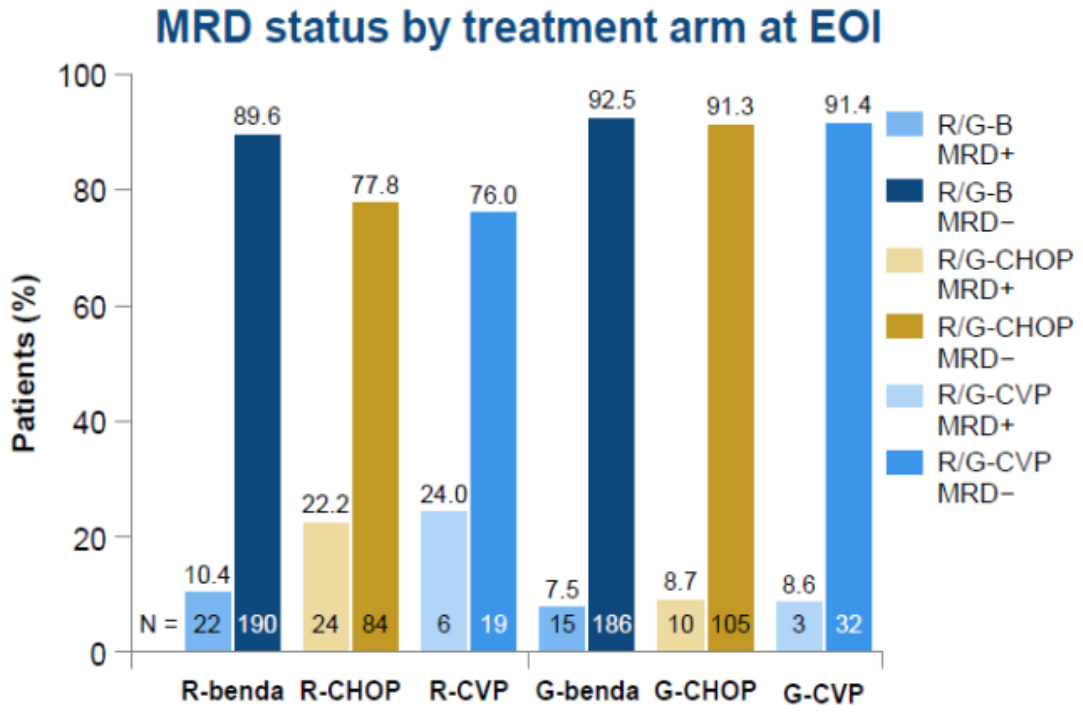


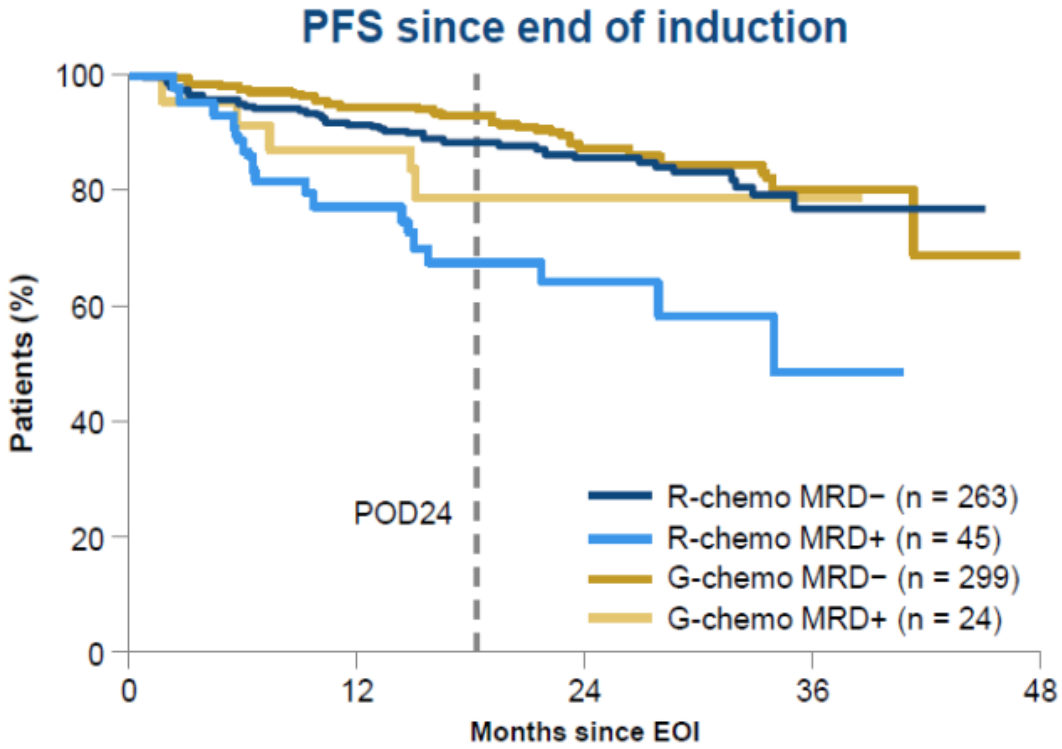

Marcus R, et al. N Engl J Med. 2017; 377:1331-44.

Courtesy of John P Leonard, MD

Weill Cornell Medicine NewYork-Presbyterian

# GALLIUM: Obinutuzumab vs Rituximab with chemotherapy (and as maintenance): MRD negativity



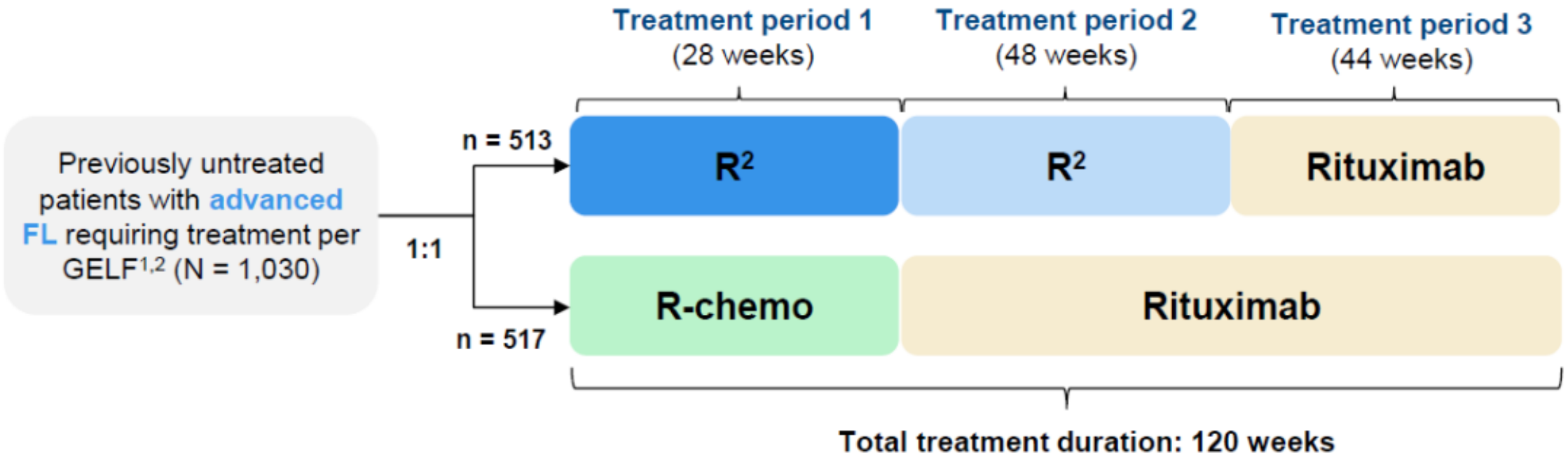




- PD or death due to PD at 24-mos post randomization events occurred in less pts on the G-chemo arm (9.5% vs 16.3%)
  - The cumulative incidence rates were lower on the G-chemo arm (10.1% vs 17.4%)
- The average HR-based reduction in the risk of a POD24 event with G-chemo relative to R-chemo was 46.0%
- The risk of a PFS event in the 24 mos after randomization was lower on the G-chemo arm (12.5% vs 18.9%)
- The relative risk reduction for PFS events was 33.9%

Courtesy of John P Leonard, MD

Pott C, et al. ASH 2016 ; Seymour et al. Haematologica 2019;104(6):1202-1208.

# RELEVANCE: Lenalidomide-Rituximab ($R^2$) vs Chemo-R




Morschhauser F, et al, NEJM 2018

Courtesy of John P Leonard, MD

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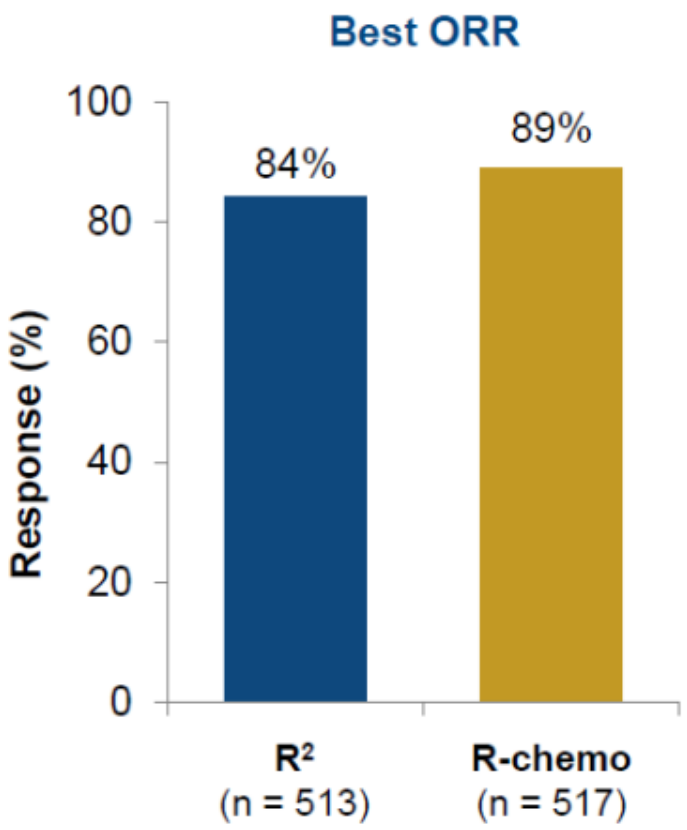
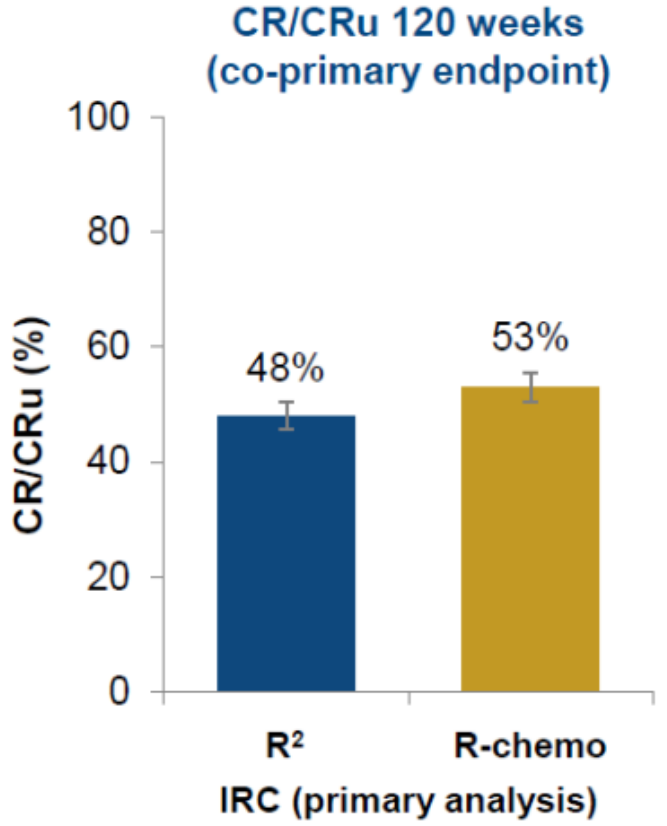
# RELEVANCE: Lenalidomide-Rituximab ($R^2$) vs Chemo-R
# Similar ORR and CR as initial therapy for FL




Morschhauser F, et al, NEJM 2018

Courtesy of John P Leonard, MD

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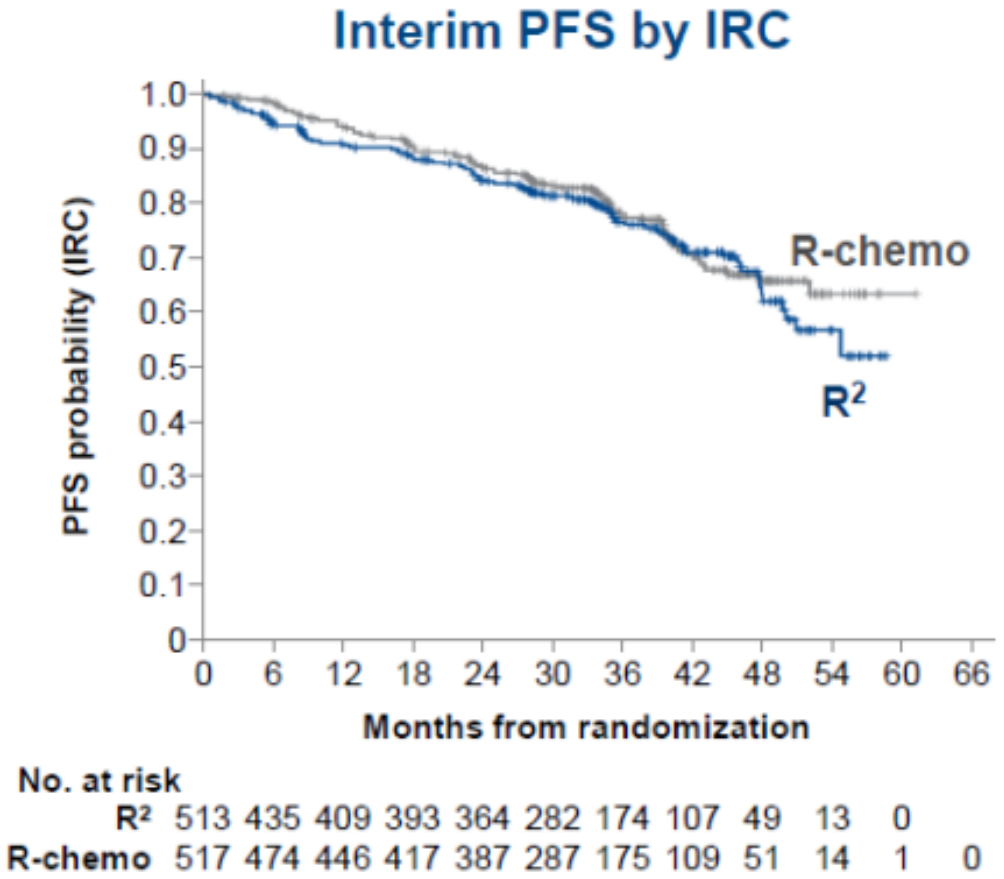
# RELEVANCE: Lenalidomide-Rituximab ($R^2$) vs Chemo-R
# Similar PFS and OS as initial therapy for FL




Morschhauser F, et al, NEJM 2018

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# RELEVANCE: Lenalidomide-Rituximab ($R^2$) vs Chemo-R
# Safety comparisons

| | $R^2$ | R-chemo |
|---|---|---|
| Grade 4 neutropenia, % | 32 | 50 |
| Time to grade 3/4 neutropenia, months | 3.7 | 0.6 |
| Febrile neutropenia, % | 2 | 7 |
| Range of grade ≥ 3 TEAEs, % | ~ 60 | ~ 70 |
| Grade 3/4 infections, % | 2 | 4 |
| Grade ≥ 3 rash, % | 7 | 1 |

- R-chemo was associated with more febrile neutropenia, growth factor usage, nausea, vomiting, neuropathy, and alopecia
- $R^2$ was associated with more frequent cutaneous reaction, tumour flare, and diarrhea

Morschhauser F, et al, NEJM 2018

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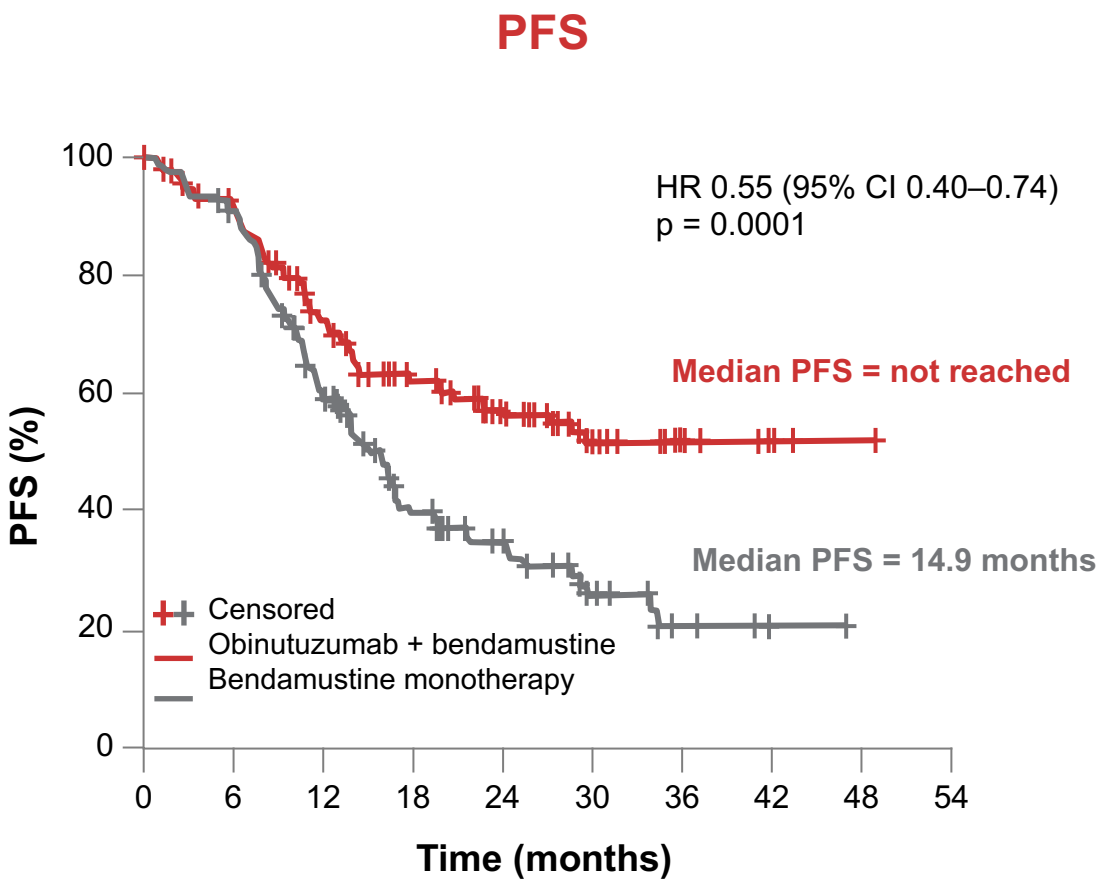
# What are considerations in approaching a patient with recurrent FL?

- Do they have transformation?
- Do they need treatment (vs observation)?
- Duration of prior response
- Age and comorbidities
- Prior therapies

Courtesy of John P Leonard, MD

# GADOLIN study: obinutuzumab improves PFS and OS in recurrent iNHL when added to bendamustine




The addition of obinutuzumab also improved PFS in patients who were refractory to both alkylators and rituximab

- HR 0.56 (0.40-0.78)

Sehn LH, et al. Lancet Oncol. 2016;17:1081-93.

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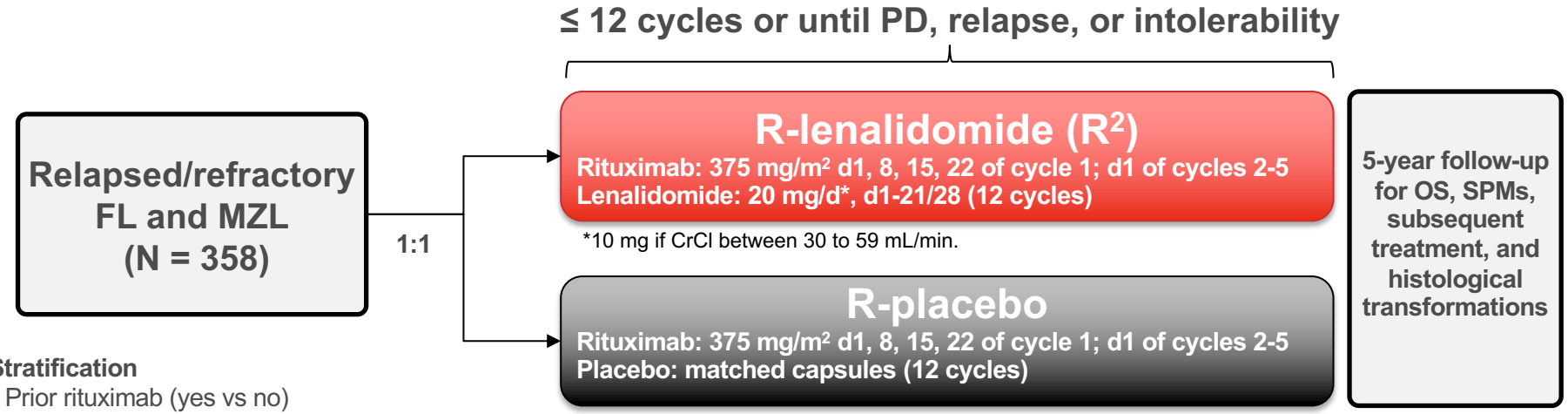
# AUGMENT: $R^2$ vs rituximab monotherapy in R/R iNHL




**Stratification**
- Prior rituximab (yes vs no)
- Time since last therapy (≤ 2 vs > 2 y)
- Histology (FL vs MZL)

**Key eligibility criteria**
- MZL or FL (grades 1-3a) in need of treatment
- ≥ 1 prior chemotherapy, immunotherapy or chemoimmunotherapy
- Not rituximab refractory

- Primary endpoint: PFS by IRC (2007 IWG criteria w/o PET)

$R^2$ is FDA approved for previously treated FL and MZL.

NCT01938001
1. Crawford et al. *Ann Oncol.* 2010;21 Suppl 5:248-251. 2. Smith et al. *J Clin Oncol.* 2015;33:3199-3212.

Leonard et al. JCO 2019

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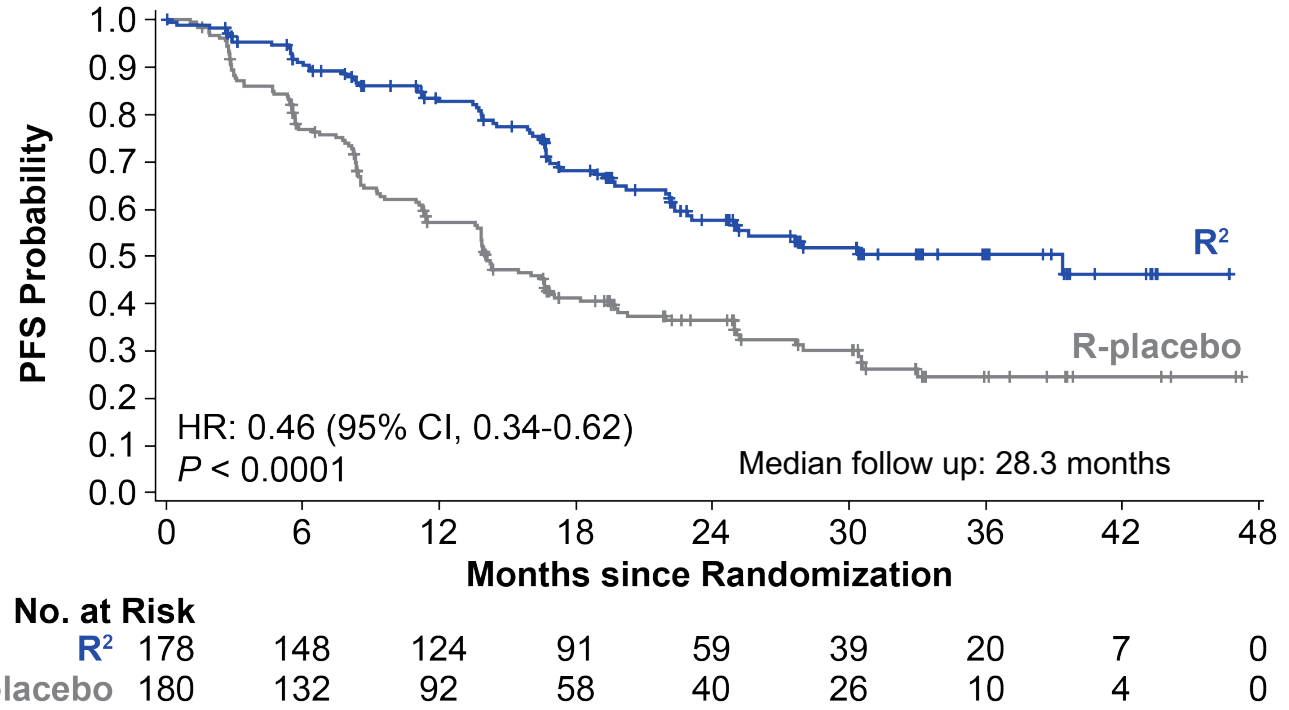
# AUGMENT primary endpoint: Progression-free survival (ITT, IRC)




| 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 |

Leonard et al. JCO 2019

*Censoring rules based on FDA guidance.
Data cutoff June 22, 2018.

Courtesy of John P Leonard, MD

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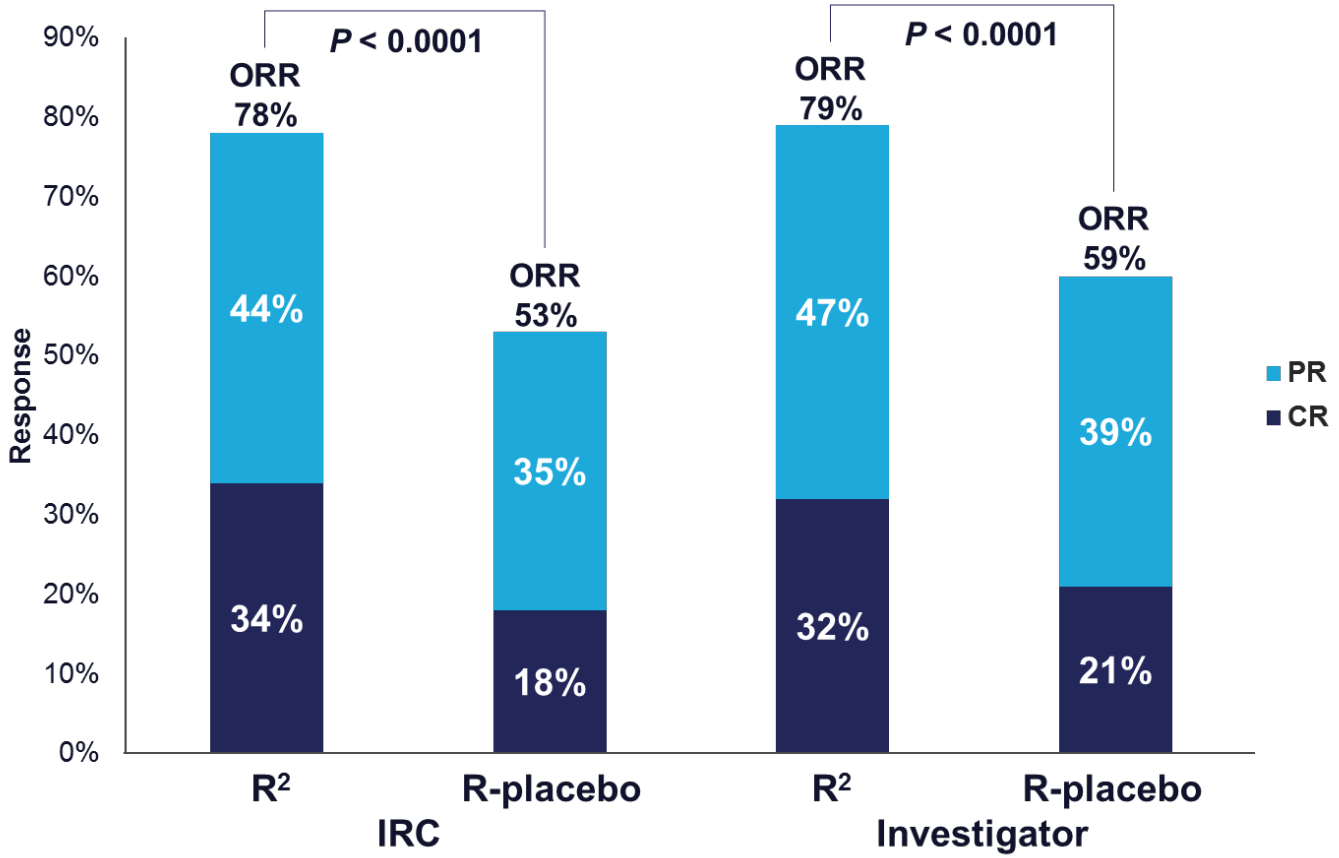
# AUGMENT response data (ITT)




- Median DOR was 36.6 mo (95% CI, 22.9-NR) for $R^2$ 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

Leonard et al. JCO 2019

Response and progression outcomes were assessed by a blinded, independent central review using 2007 IWG criteria based on computed axial tomography/magnetic resonance imaging (CT/MRI) scans. Patients with gastric mucosa-associated lymphoid tissue lymphoma underwent endoscopy for response evaluation. Bone marrow biopsy was required to confirm CR.

Data cutoff June 22, 2018.

Courtesy of John P Leonard, MD

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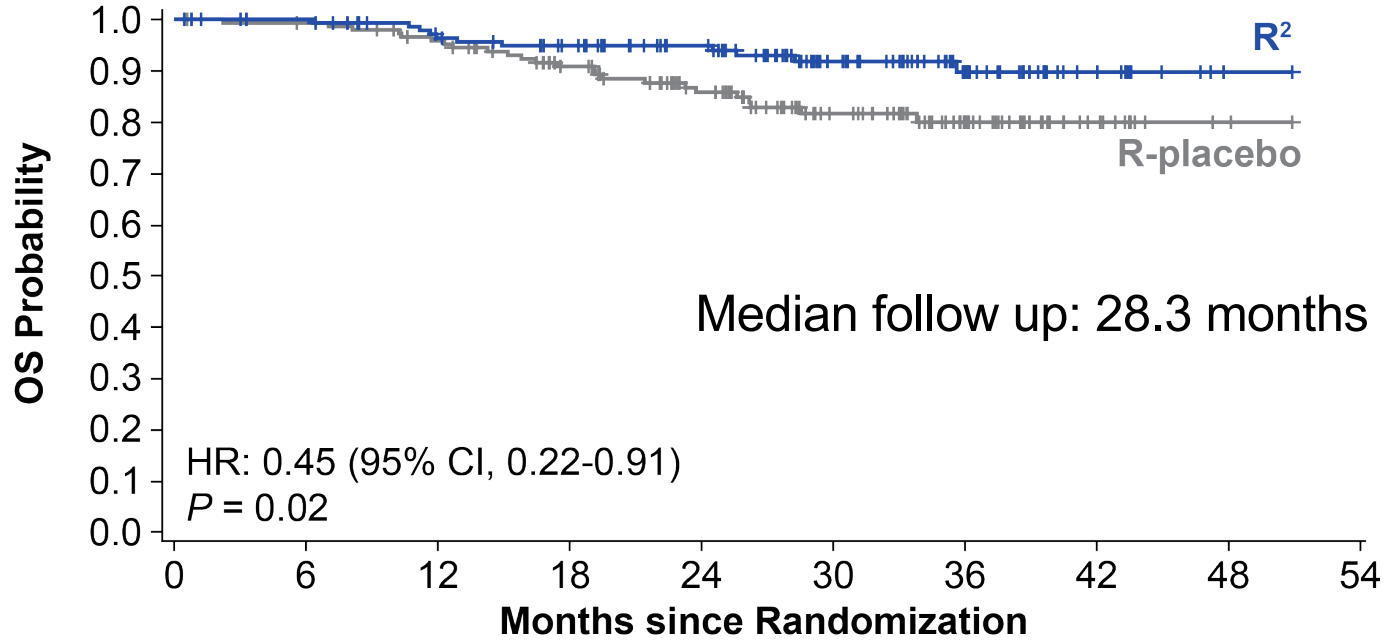
# AUGMENT: Overall survival in FL patients (prespecified subgroup analysis)




| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $R^2$ | 147 | 142 | 130 | 121 | 105 | 70 | 39 | 13 | 1 | 0 |
| R-placebo | 148 | 145 | 137 | 117 | 94 | 64 | 35 | 12 | 2 | 0 |

- 35 total deaths (11 $R^2$, 24 R-placebo)
- 2-year OS was 95% (95% CI, 90%-98%) for $R^2$ and 86% (95% CI, 79%-91%) for R-placebo

Leonard et al. JCO 2019

Data cutoff June 22, 2018.

Courtesy of John P Leonard, MD

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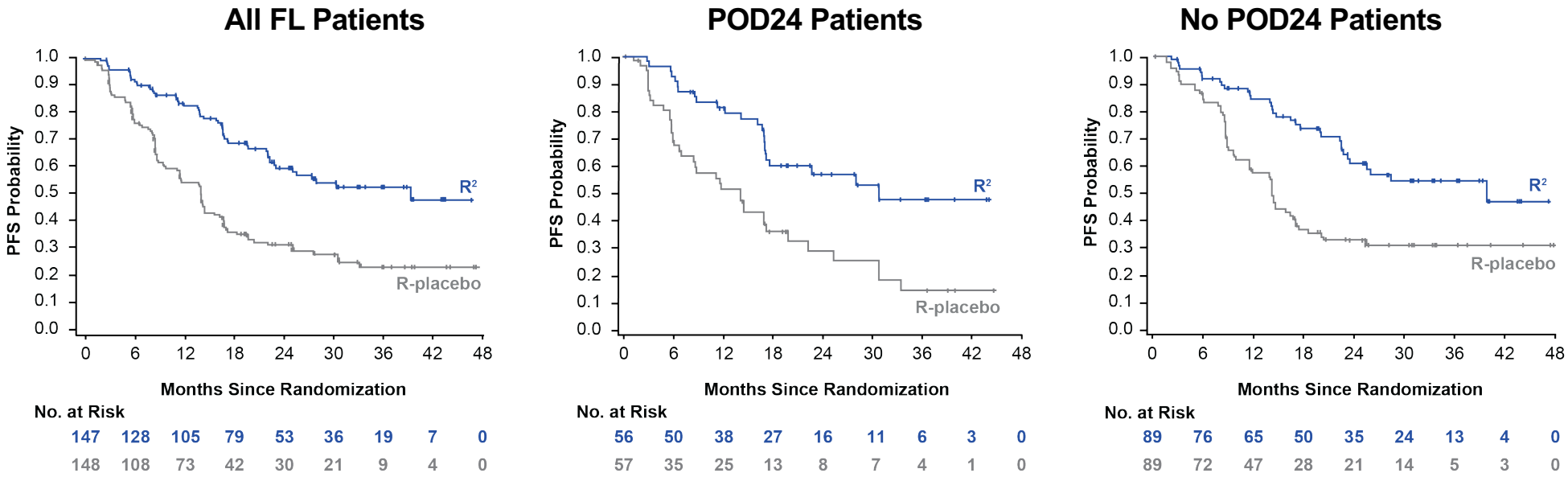
# AUGMENT: PFS for All FL patients and by POD24 status




| Median PFS, mo (95% CI) *(n $R^2$/n R-placebo)* | All FL Patients *(n = 147/148)* | POD24 *(n = 56/57)* | No POD24 *(n = 89/89)* |
|---|---|---|---|
| **$R^2$** | 39.4 (23.1-NR) | 30.4 (16.8-NR) | 39.4 (22.9-NR) |
| **R-placebo** | 13.9 (11.2-16.0) | 13.8 (6.7-16.9) | 13.9 (11.2-16.6) |
| **HR (95% CI)** | 0.40 (0.29-0.56) | 0.41 (0.24-0.68) | 0.43 (0.28-0.65) |
| ***P* value** | < 0.0001 | 0.0004 | < 0.0001 |

Data cutoff June 22, 2018. *Censoring rules were based on FDA guidance.

POD24 was defined post-hoc as progression or relapse within 2 years of initial antilymphoma treatment, which included immunotherapy and/or chemotherapy

Courtesy of John P Leonard, MD

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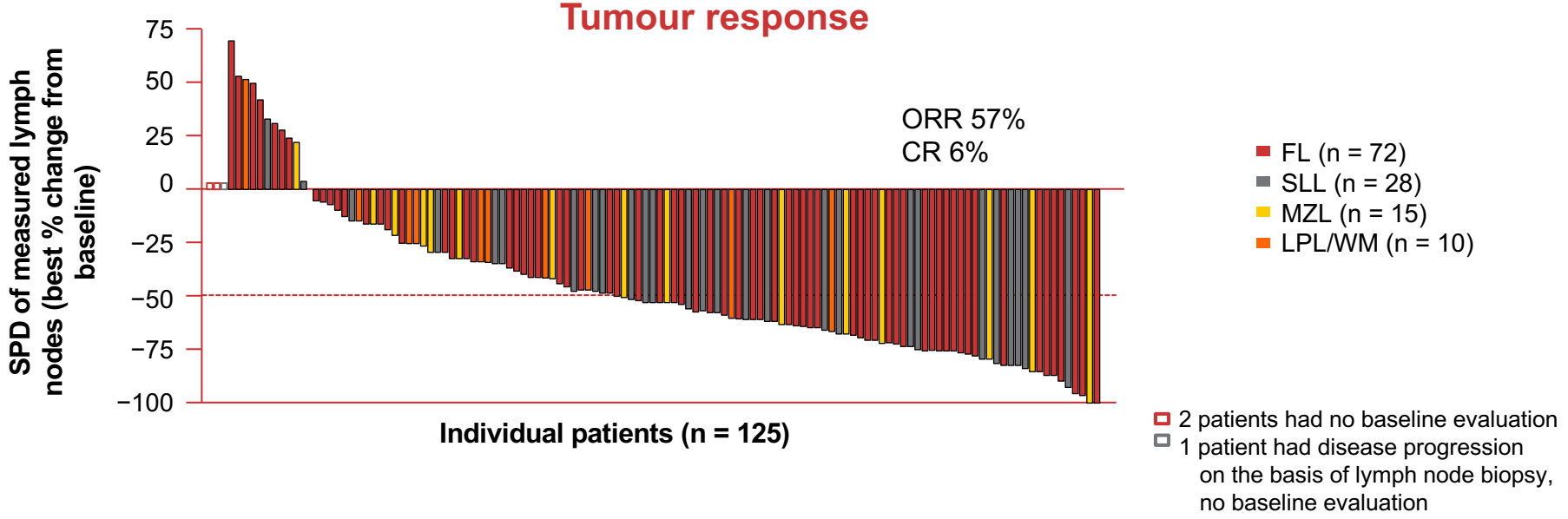
# Idelalisib: selective PI3K inhibitor in double refractory iNHL

Single-arm phase 2 study (n = 125)

**Rituximab + alkylator-refractory iNHL** → **Idelalisib 150 mg b.i.d. continuously** → **Therapy maintained until progression** → **Long-term follow-up**

## Tumour response




Gopal AJ, et al. N Engl J Med. 2014;370:1008-18.

Courtesy of John P Leonard, MD

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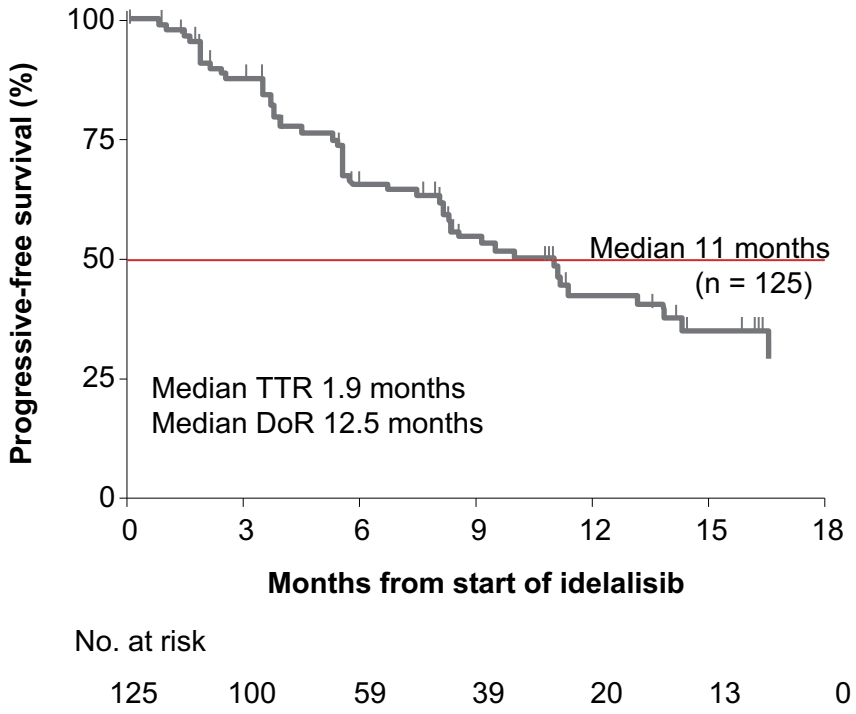
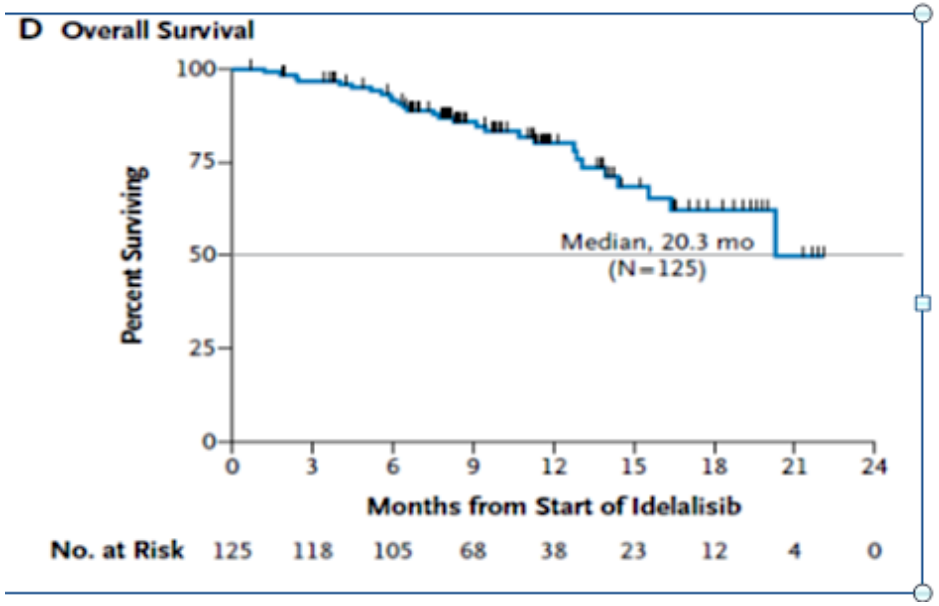
# PFS and OS in patients with recurrent iNHL treated with idelalisib

## PFS




## OS




Gopal AJ, et al. N Engl J Med. 2014;370:1008-18.

Courtesy of John P Leonard, MD

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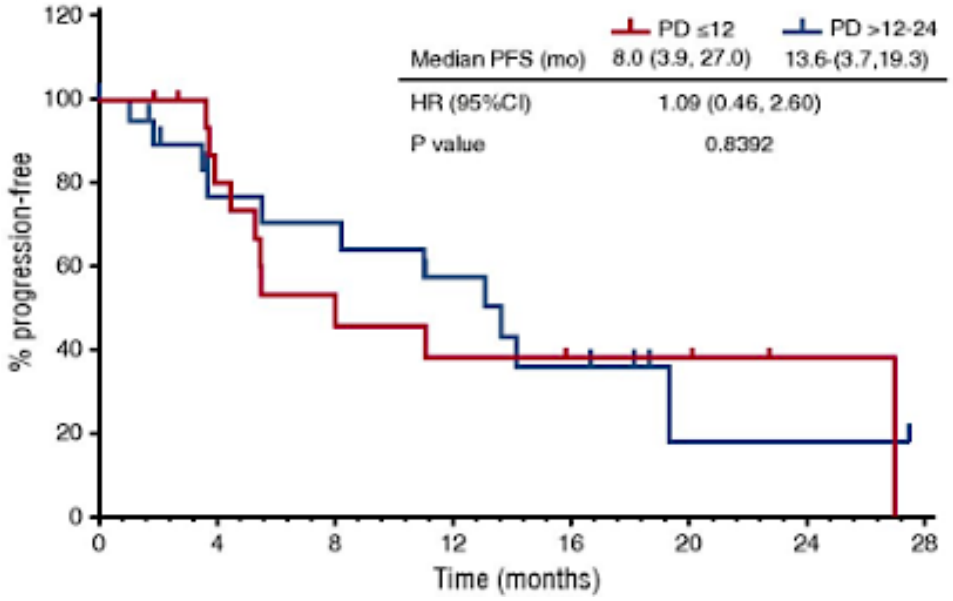
# Idelalisib in “early progressor” FL

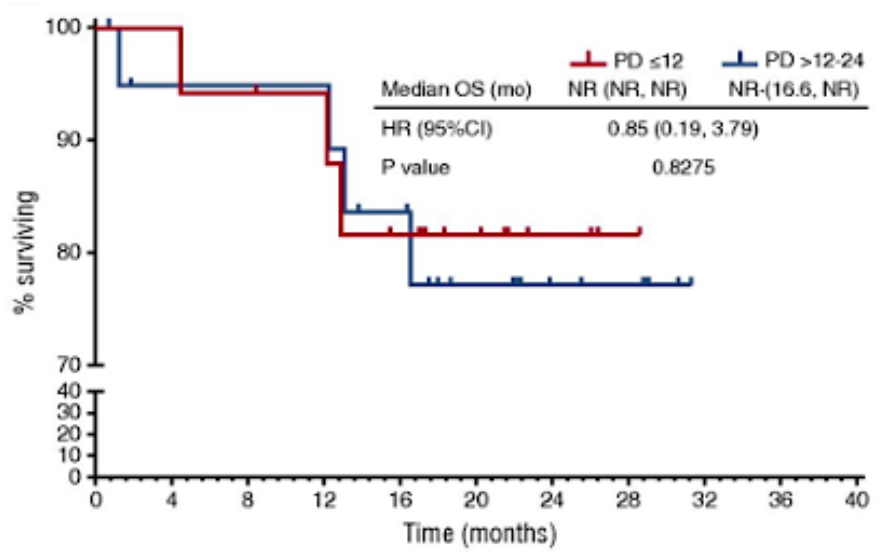
## Retrospective analysis of 37 FL patients with progression within 24 months of initial chemoimmunotherapy

ORR 57%, CR 13%

**PFS**




**OS**




Gopal AK, et al Blood. 2017;129:3037-9.

Courtesy of John P Leonard, MD

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# CHRONOS-1: Copanlisib in Patients With Relapsed, Indolent or Aggressive NHL

**Phase 2 study**
- **142 patients with relapsed or refractory indolent lymphoma after ≥2 lines of therapy**

**Copanlisib 60 mg intravenously on days 1, 8, and 15 of a 28-day cycle.**

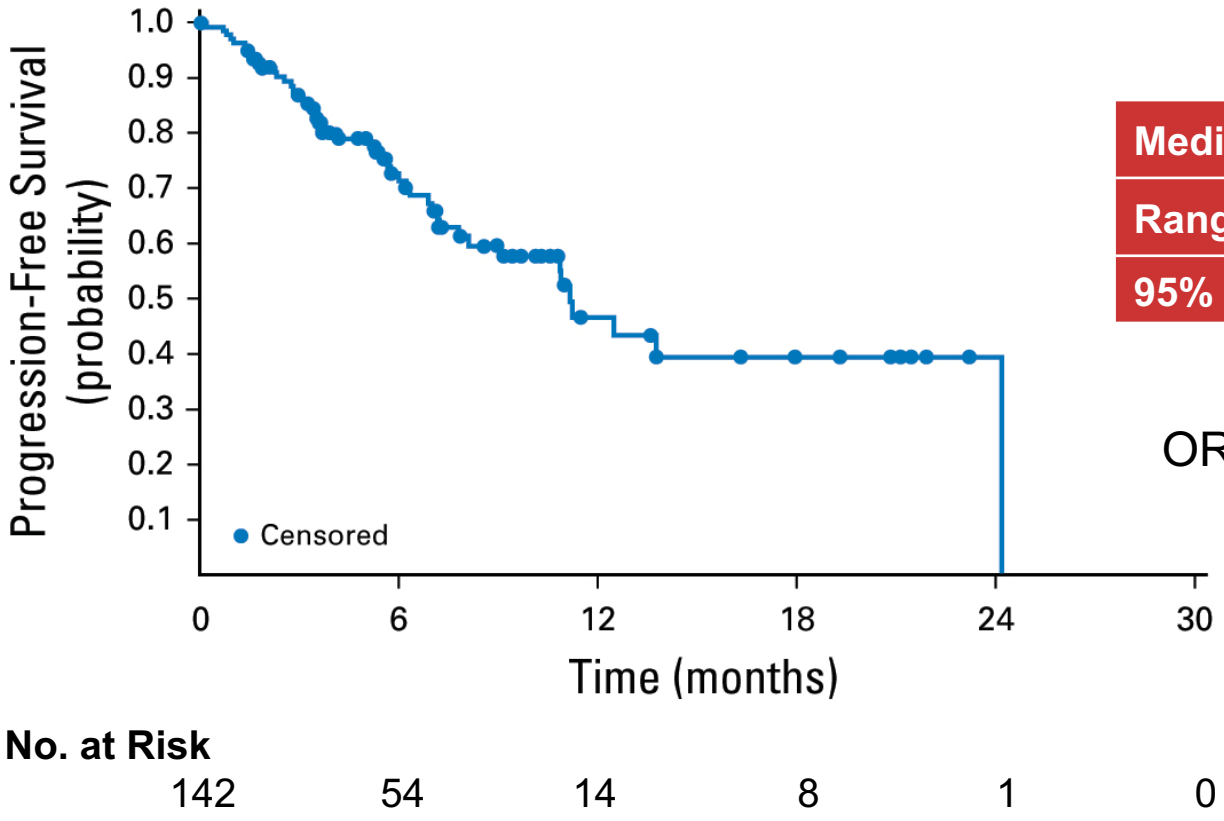
Primary end point was ORR; secondary end points included duration of response, PFS, OS. In addition, safety and gene expression were evaluated

**Dreyling M, et al. J Clin Oncol. 2017;35:3898-3905.**

Courtesy of John P Leonard, MD

Weill Cornell Medicine NewYork-Presbyterian

# PFS of Copanlisib in R/R Indolent Lymphoma




| | |
|---|---|
| **Median, mo** | 11.2 |
| **Range** | 0.2-24.0 |
| **95% CI** | 8.1-24.0 |

ORR 59% (12% CR)

**Dreyling M et al. J Clin Oncol. 2017;35:3898-3905.**

Courtesy of John P Leonard, MD

Weill Cornell Medicine NewYork-Presbyterian

# Duvelisib in recurrent indolent NHL (Oral PI3K delta/gamma inhibitor)

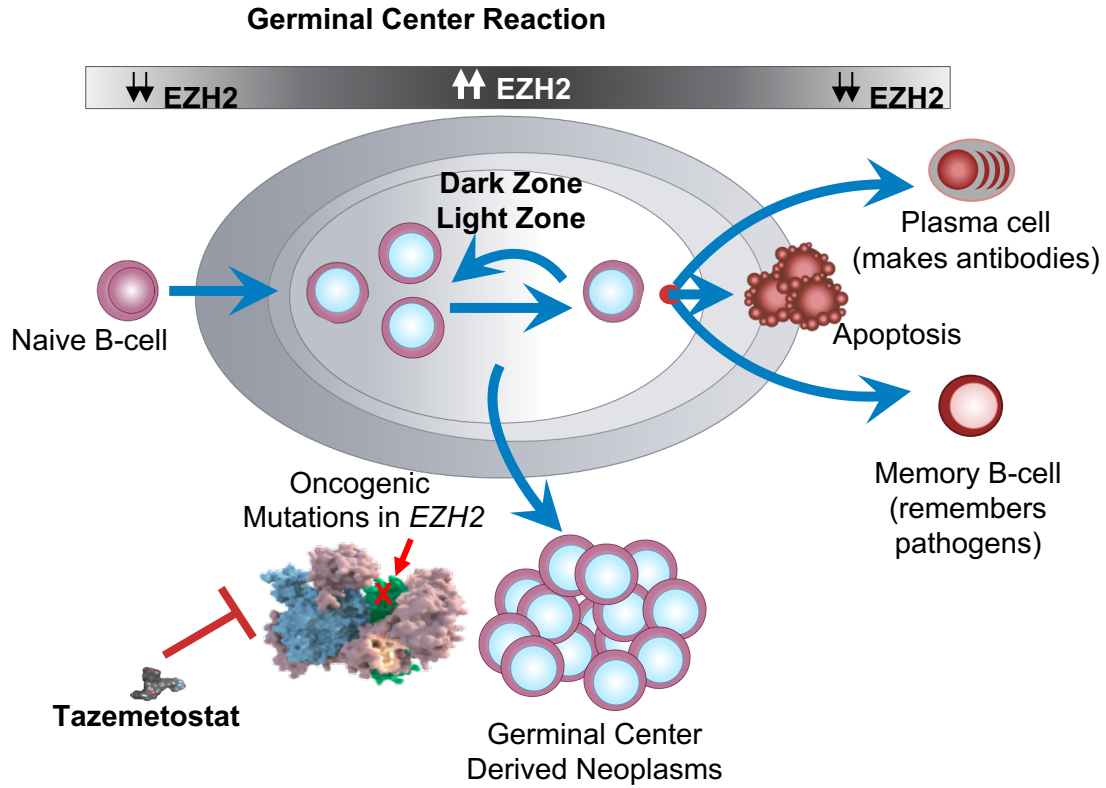
- Indolent lymphoma patients “double refractory” to rituximab and chemotherapy/radioimmunotherapy
- 25 mg po BID continuous dosing (w/PCP prophylaxis)
- 129 subjects, 83 with FL, median age 65, median 3 prior rx
- ORR 46%, median duration 9.9 months
- Principal toxicities cytopenias, diarrhea
- Led to FDA approval

Zinzani et al, ICML 2017

Courtesy of John P Leonard, MD

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

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*

**On June 18, 2020, Tazemetostat was granted accelerated FDA approval for R/R FL with EZH2 mutations after at least 2 prior systemic therapies and for R/R FL with no satisfactory alternative treatment options**

Courtesy of John P Leonard, MD

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# Tazemetostat ORR in EZH2 mutant and wild type populations (recurrent FL)

| | *EZH2* Mutant Cohort (n=45) | | *EZH2* WT Cohort (n=54) | |
|---|---|---|---|---|
| **Parameter** | **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) |

Morschhauser, ICML 2019

Courtesy of John P Leonard, MD

Weill Cornell Medicine NewYork-Presbyterian

# Case 1

A 67-year-old woman is diagnosed with follicular lymphoma grade 1 with diffuse lymphadenopathy, 2 cm in multiple sites. Due to cosmetic issues, she decides to pursue treatment with rituximab single agent x 4 doses with a clinical response. 11 months later she develops progression of disease and mild leg swelling. Physical examination shows 2-cm bilateral cervical adenopathy and 3-4 cm unilateral inguinal adenopathy. PET/CT scan confirms the enlarged lymph nodes noted on physical exam, mild splenomegaly, and in addition 2 cm mediastinal and 2.5 cm abdominal lymph nodes are also demonstrated. Maximum SUV is 7.3. Laboratory studies are normal except for mild anemia. Biopsy of inguinal LN shows follicular lymphoma, grade 1. How to treat her?

- This patient opted for Bendamustine/Rituximab. Other options include R retreatment with maintenance, Benda/Obinutuzumab, $R^2$, R-Obinutuzumab.

Courtesy of John P Leonard, MD

# Case 2

A 59 year old male (surgeon) develops diffuse LAN (4-5 cm) in the abdomen and pelvis with symptoms of discomfort. SUV in 10 range. Labs and LDH normal. Biopsy shows FL, Grade 1. Receives Bendamustine and Rituximab without maintenance, with end of treatment PET negative. No maintenance given

One year later he develops palpable inguinal LAN. Labs normal except platelets 130K. PET shows inguinal and pelvic LAN in 2-3 cm range and SUV 11. Biopsy showed FL grade 2. Anxious to start treatment and concerned about his “early progression”.

He opted for lenalidomide/obinutuzumab. Other options include CHOP-O (neuropathy a concern), $R^2$, PI3Ki, stem cell transplant? EZH2i at some point.

Courtesy of John P Leonard, MD