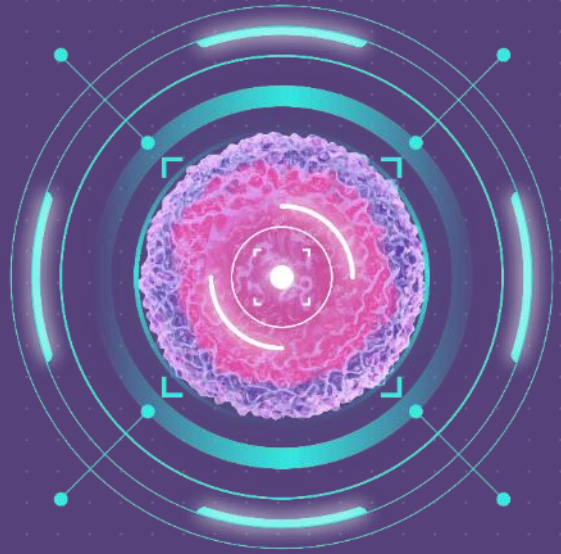
LymphomaHub

# NEW CHEMOTHERAPY-FREE APPROACHES FOR THE TREATMENT OF LYMPHOID MALIGNANCIES



Scientific Education Support

Lymphoma Hub is delivered by Scientific Education Support (SES)

# FL – chemotherapy-free regimens: pros and cons

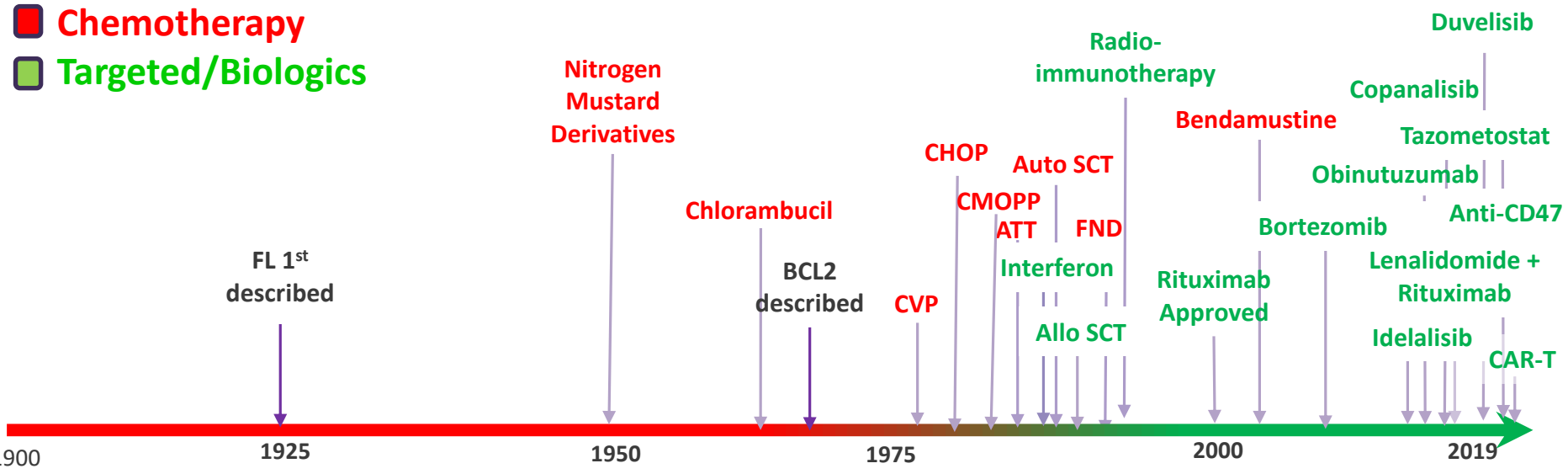
Nathan Fowler
University of Texas MD Anderson Cancer Centre
Houston, TX, USA

LymphomaHub

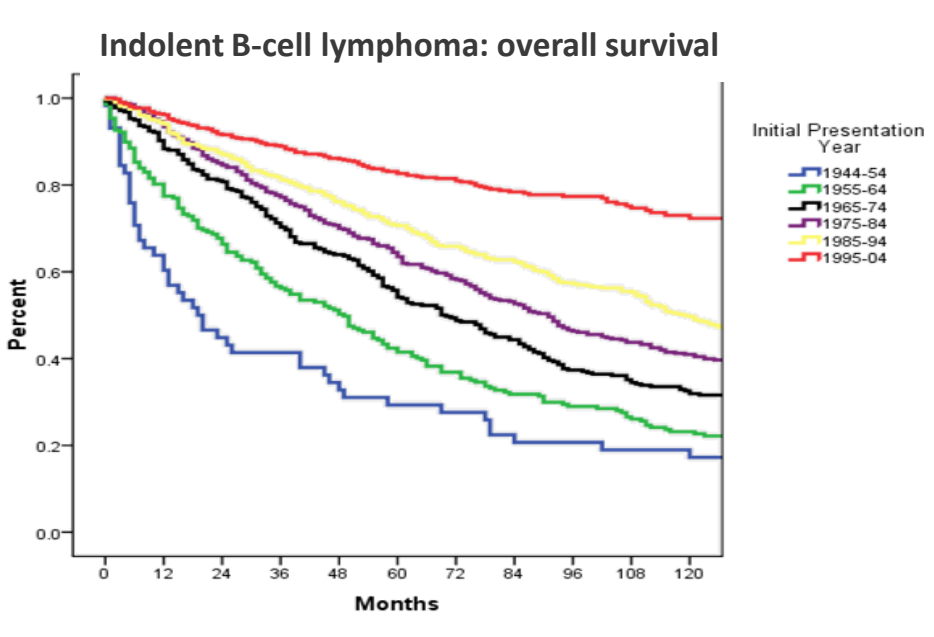
## Disclosures – Nathan Fowler

| | |
|---|---|
| Research funding | Roche, Verastem, TG Therapeutics, Abbvie, Celgene, Jannsen, Gilead |
| Honoraria/Advisory Board | Roche, Verastem, TG Therapeutics, Abbvie, Celgene, Jannsen, Gilead |

# Short(ish) history of selected therapy development of follicular lymphoma



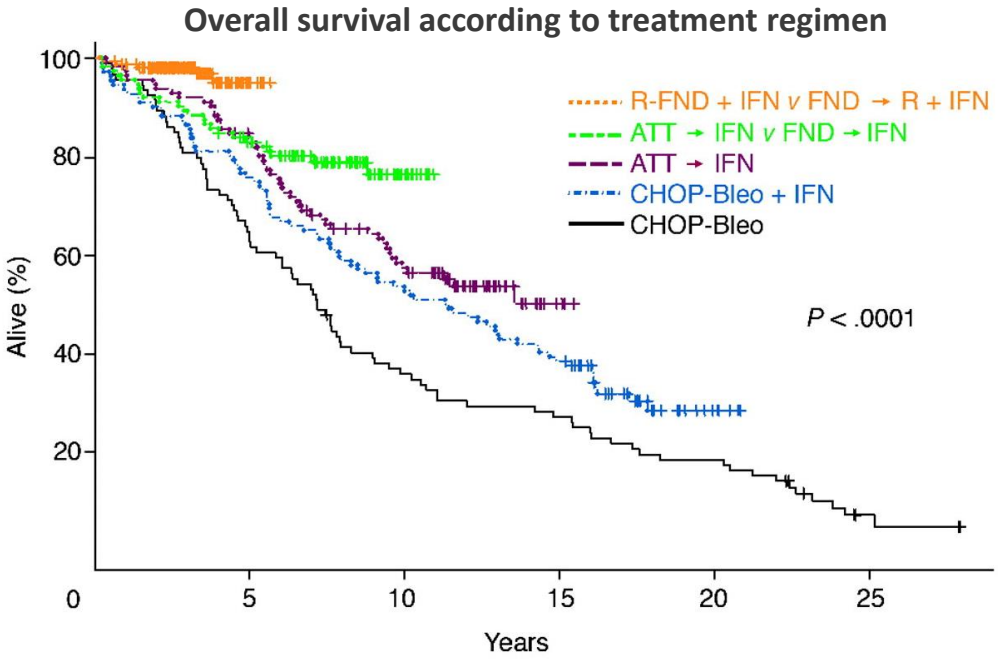
# Indolent lymphoma: improving survival




| Percent survival | | |
|---|---|---|
| **Year** | **60 months** | **120 months** |
| 1944–54 | 29.3 | 17.2 |
| 1955–64 | 41.5 | 23.2 |
| 1965–74 | 54.1 | 31.9 |
| 1975–84 | 63.5 | 41.0 |
| 1985–94 | 70.6 | 49.6 |
| 1995–04 | 82.7 | 72.3 |

Neelapu S. 60 Years of Survival Outcomes at the MD Anderson Cancer Center. Springer. 2013. pp. 241–250.

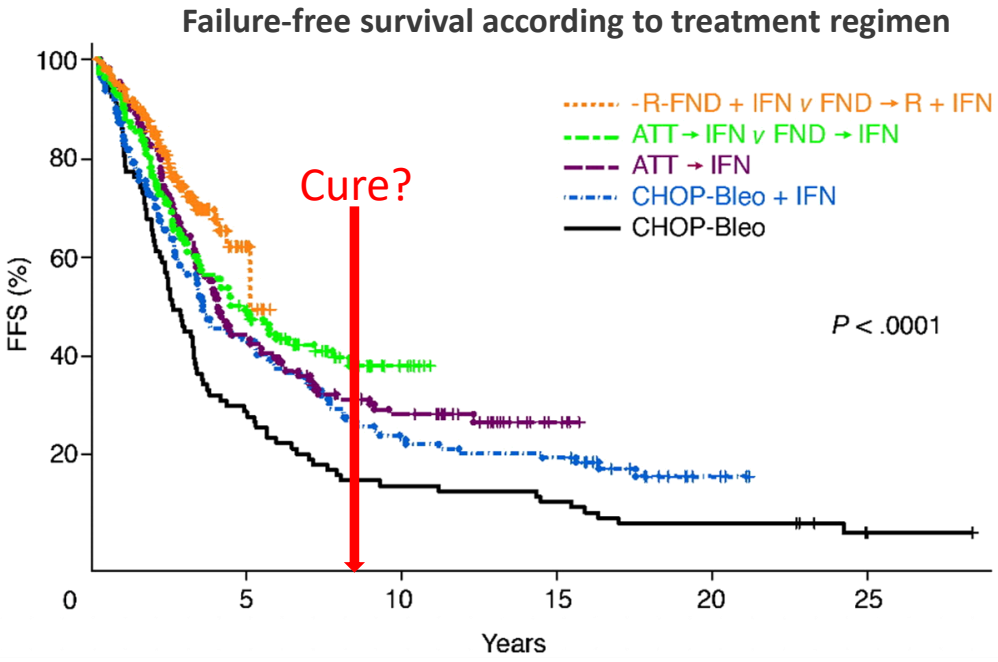
# Historical studies at MD Anderson with chemo overall survival




R, rituximab; FND, fludarabine, mitoxantrone, and dexamethasone; IFN, interferon alfa; ATT, alternating triple therapy with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin, with etoposide, methylprednisolone, cytarabine, and cisplatin, with mitoxantrone, vincristine, prednisone, and procarbazine with IFN maintenance; CHOP-Bleo, cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin.

Liu Q, *et al. J Clin Oncol.* 2006;24:1582–9

# Historical studies at MD Anderson with failure-free survival (FFS)




R, rituximab; FND, fludarabine, mitoxantrone, and dexamethasone; IFN, interferon alfa; ATT, alternating triple therapy with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin, with etoposide, methylprednisolone, cytarabine, and cisplatin, with mitoxantrone, vincristine, prednisone, and procarbazine with IFN maintenance; CHOP-Bleo, cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin.

Liu Q, *et al. J Clin Oncol.* 2006;24:1582–9

# Why do we need more (*better?*) options?

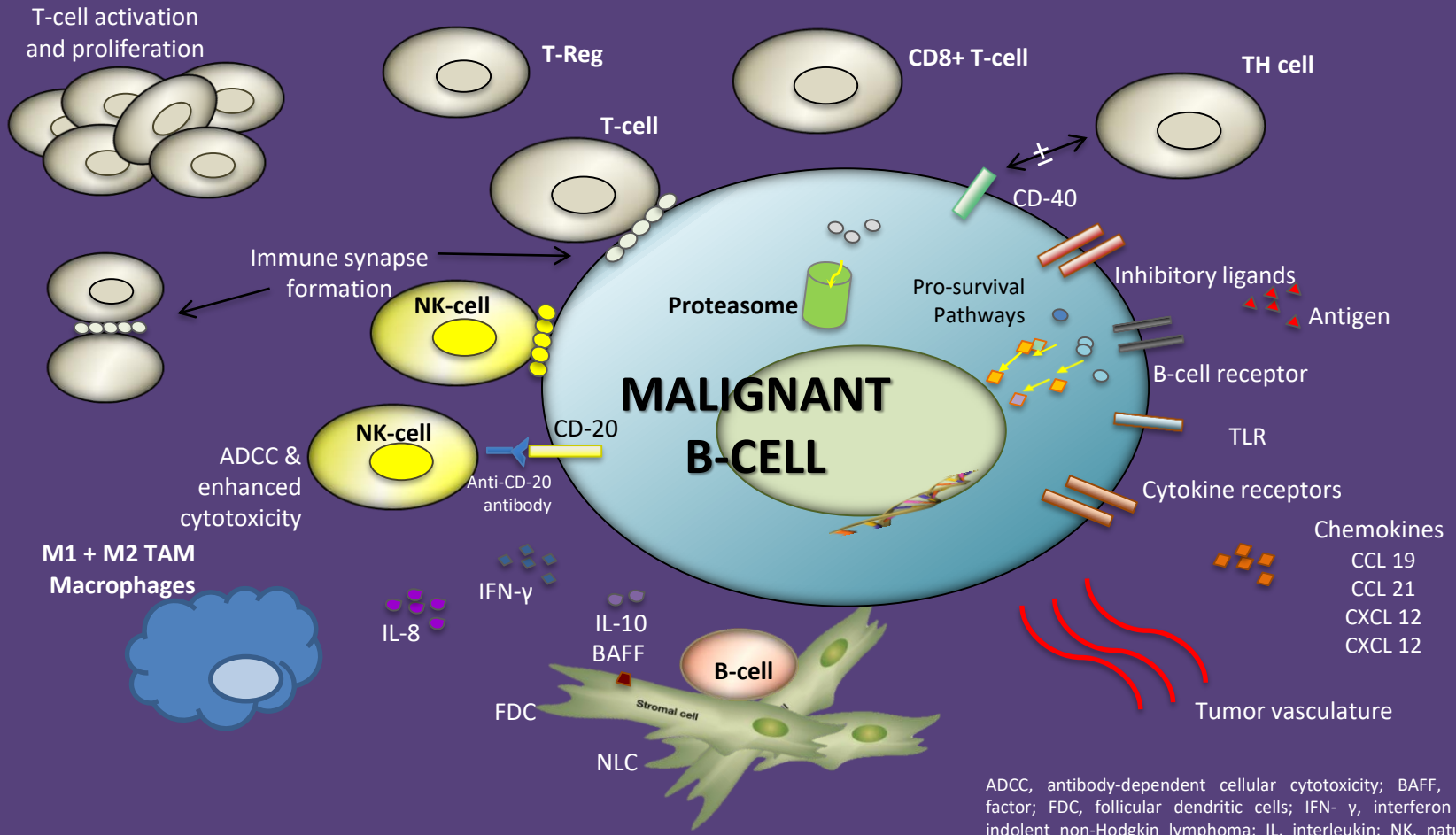
- Chemotherapy is associated with short- and long-term toxicity[1–5]
  - Infection
  - Fatigue
  - Nausea
  - Cytopenias
  - Secondary malignancies

- Most patients are still not cured with traditional regimens[5–8]

- Unselected therapy does not benefit all populations

1. Green MR, et al. *Blood*. 2013;121(9):1604-1611; **2.** Hiddemann W, et al. At: ICML; 2017. Abstract 107; 3. National Cancer Institute. updated August 2018, www.cancer.gov/about cancer/treatment/side effects; 4. Federico M, et al. *J Clin Oncol* . 2013;31(12):1506 1513; 5. Marcus R, et al. N Engl J Med . 2017;377(14):1331 1344; 6. Fowler N. Hematology Am Soc Hematol Educ Program. 2016;2016(1):277 283; 7. Cabanillas F. J Clin Oncol . 2013; 31(1):14; 8. Alperovich A, *et al*. In: ASH Annual Meeting & Exposition; 2016. Abstract 2955.

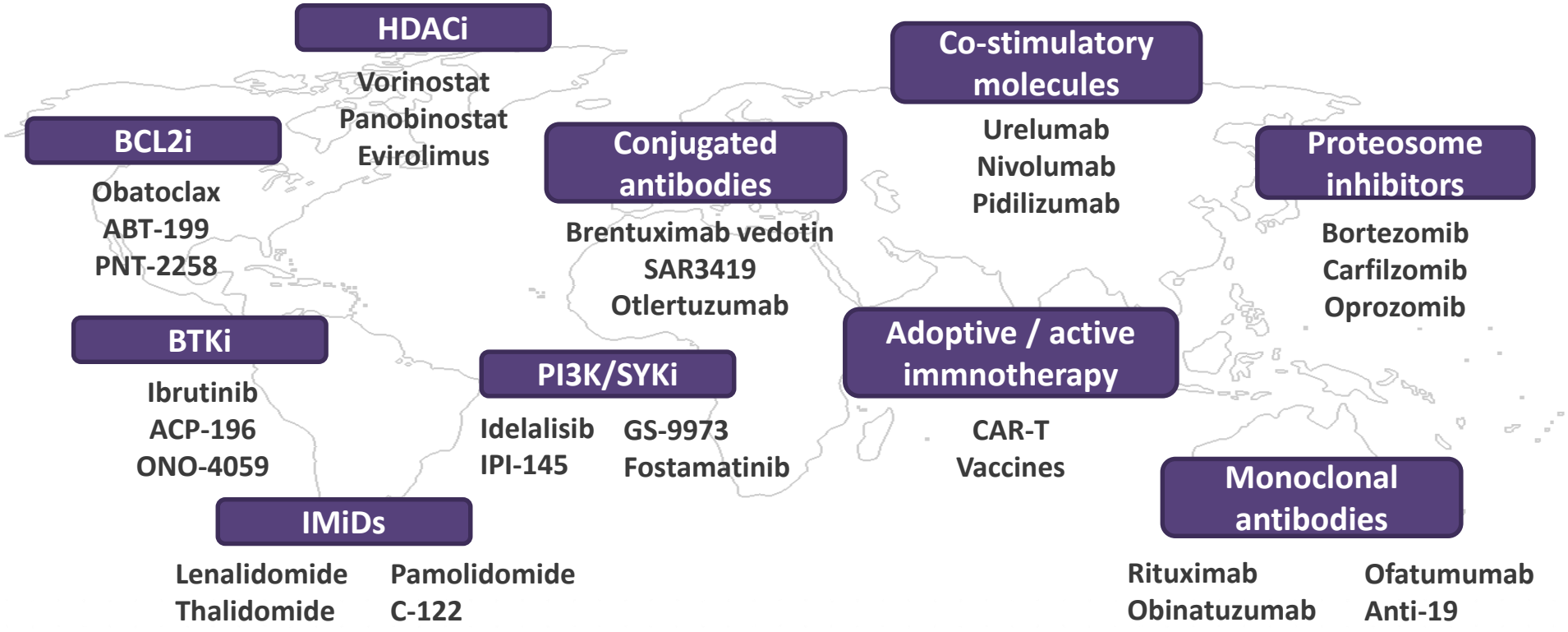
# Survival advantage in iNHL




ADCC, antibody-dependent cellular cytotoxicity; BAFF, B-cell-activating factor; FDC, follicular dendritic cells; IFN- γ, interferon gamma; iNHL, indolent non-Hodgkin lymphoma; IL, interleukin; NK, natural killer; NLC, nurse-like cell; TAM, tumour-associated; TH, T helper; TLR, toll-like receptors

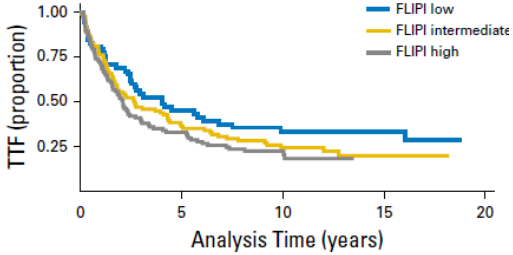
Fowler & Dunleavy; 2013 Dublin Summit on Immune Microenvironment

# The world of ‘Biologics’ in indolent lymphoma

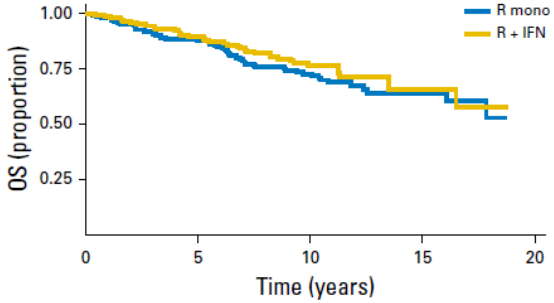



BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell therapy; ImiDs, immunomodulatory drugs; HDACi, histone deacetylase inhibitor; PI3K, phosphoinositide 3-kinase; SYK, spleen tyrosine kinase inhibitor

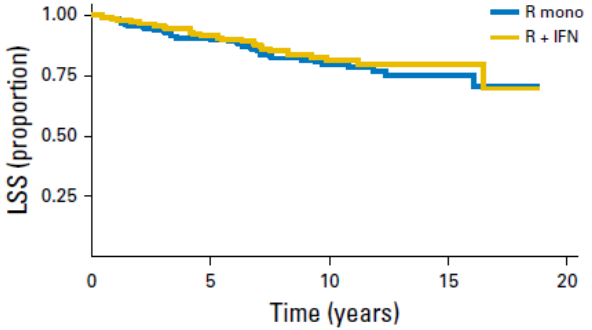
# Long-term outcomes of symptomatic patients treated without initial chemotherapy




| No. at risk: | | | | | |
|---|---|---|---|---|---|
| FLIPI low | 58 | 24 | 13 | 8 | 0 |
| FLIPI intermediate | 101 | 33 | 17 | 2 | 0 |
| FLIPI high | 108 | 32 | 11 | 0 | 0 |




| No. at risk: | | | | | |
|---|---|---|---|---|---|
| R mono | 173 | 138 | 82 | 20 | 0 |
| R + IFN | 148 | 124 | 67 | 8 | 0 |

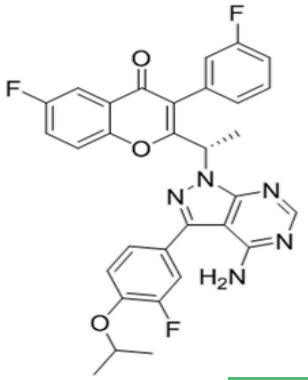



| No. at risk: | | | | | |
|---|---|---|---|---|---|
| R mono | 173 | 138 | 82 | 20 | 0 |
| R + IFN | 148 | 124 | 67 | 8 | 0 |

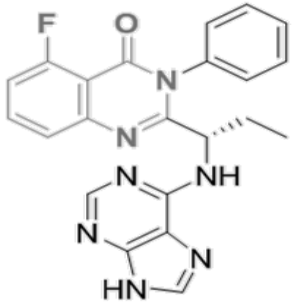
Adapted from Lockmer S, *et al. J Clin Oncol*. 2018 DOI: 10.1200/JCO.18.00262

# Selected PI3K inhibitors

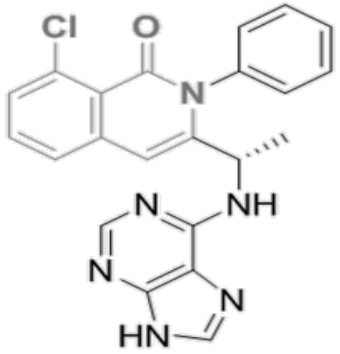
**Umbralisib** (TGR-1202)



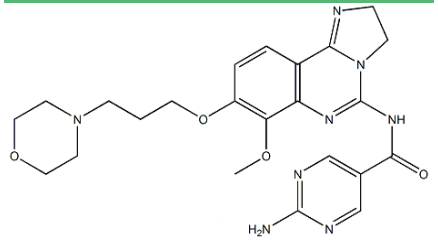
**Idelalisib (GS-1101)**



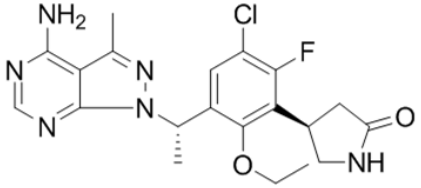
**Duvelisib (IPI-145)**



**Copanlisib** (BAY80-6946)

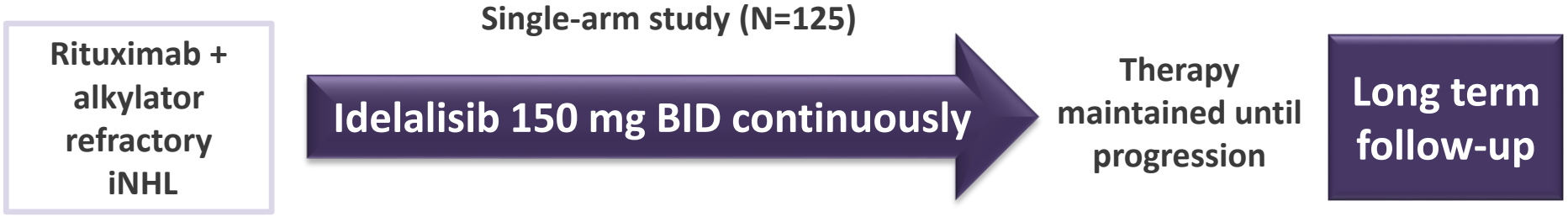


**Parsaclisib** (INCB050465)



PI3K, Phosphoinositide 3-kinases

# Idelalisib: Phase II trial in refractory iNHL

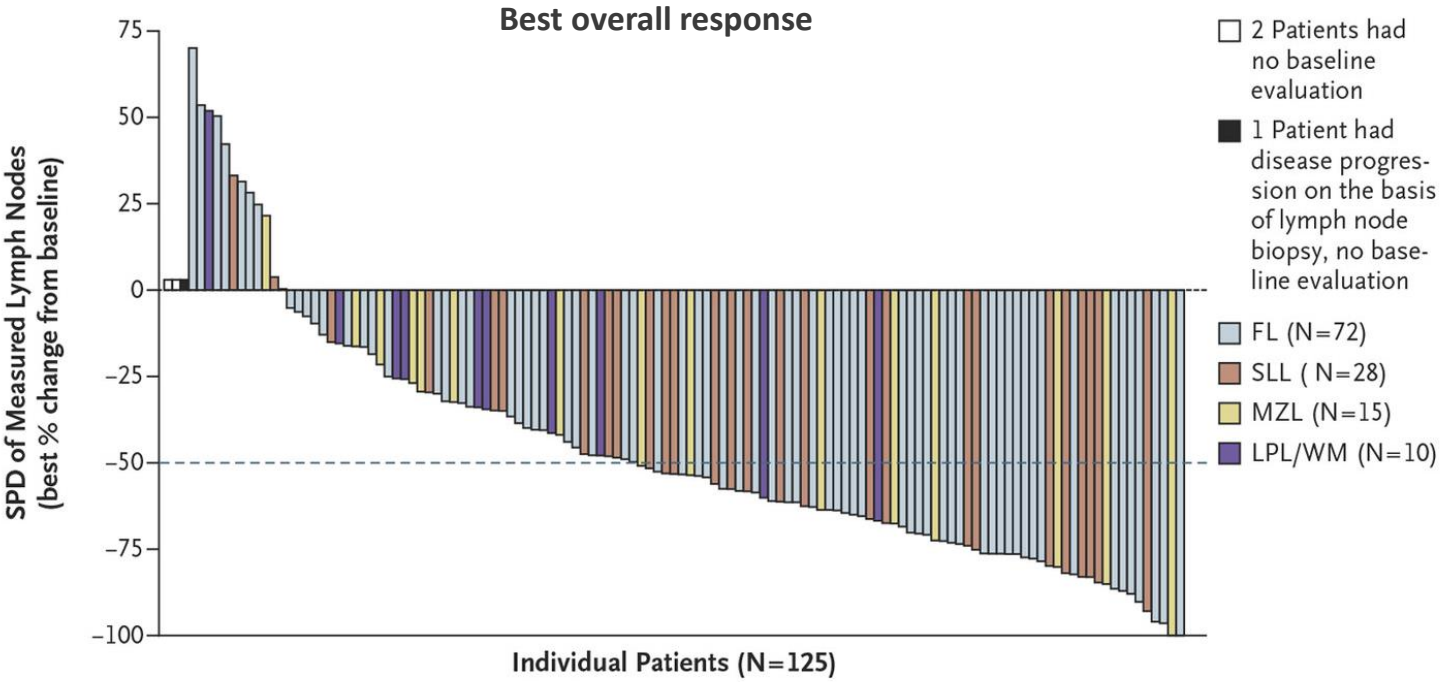



- Tumor assessments:
  - Weeks 0, 8, 16, 24, 36, 48
  - Every 12 weeks thereafter
  - Evaluated by IRC
    - Two radiologists with adjudication if needed
    - clinical review
- Primary endpoint:
  - Overall response rate
- Secondary endpoints:
  - Duration of response
  - Progression-free survival
  - Overall survival
  - Safety

BID, twice a day; iNHL, indolent non-Hodgkin lymphoma; IRC, independent review committee

Gopal A, *et al. N Engl J Med*. 2014;370:1008–18

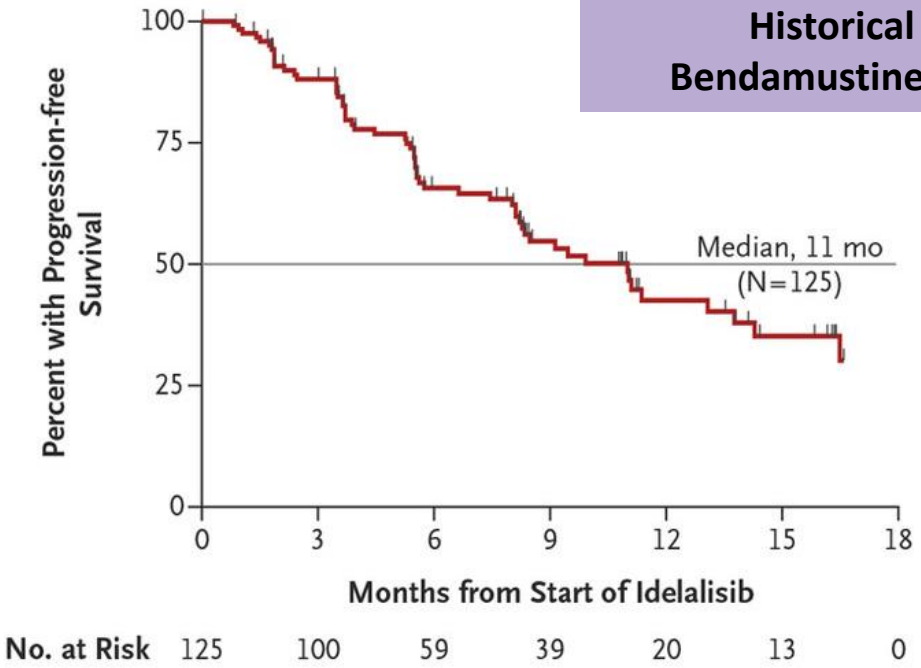
# Tumour response




FL, follicular lymphoma; LPL/WM, lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia; MZL, marginal-zone lymphoma; SLL, small lymphocytic lymphoma; SPD, sums of the products of the perpendicular dimensions

Gopal A, *et al. N Engl J Med*. 2014;370:1008–18

# Progression-free survival




**Historical control:**
**Bendamustine: DoR 10 mo**

DoR, duration of response; mo, months

Gopal A, *et al. N Engl J Med*. 2014;370:1008–18

# Adverse events

| Event or abnormality, n (%) | Any | Grade ≥3 |
|---|---|---|
| **Adverse event** | 103 (82) | 68 (54) |
| Diarrhoea | 54 (43) | 16 (13) |
| Nausea | 37 (30) | 2 (2) |
| Fatigue | 37 (30) | 2 (2) |
| Cough | 36 (29) | 0 |
| Pyrexia | 35 (28) | 2 (2) |
| Decrease appetite | 22 (18) | 1 (1) |
| Dyspnea | 22 (18) | 4 (3) |
| Abdominal pain | 20 (16) | 3 (2) |
| Vomiting | 19 (15) | 3 (2) |
| Upper respiratory tract infection | 18 (14) | 0 |
| Weigh decreased | 17 (14) | 0 |
| Rash | 16 (13) | 2 (2) |
| Asthenia | 14 (11) | 3 (2) |
| Night sweats | 14 (11) | 0 |
| Pneumonia | 14 (11) | 9 (7) |
| Peripheral oedema | 13 (10) | 3 (2) |
| Headache | 13 (10) | 1 (1) |

| Event or abnormality, n (%) | Any | Grade ≥3 |
|---|---|---|
| **Hematopoietic laboratory abnormality** | 70 (56) | 34 (27) |
| Decreased neutrophils | 35 (28) | 2 (2) |
| Decreased hemoglobin | 32 (26) | 8 (6) |
| Decreased platelets | | |
| **Chemical laboratory abnormality** | | |
| Increased ALT | 59 (47) | 16 (13) |
| Increased AST | 44 (35) | 10 (8) |
| Increased alkaline phosphatase | 28 (22) | 0 |
| Increased bilirubin | 13 (10) | 0 |

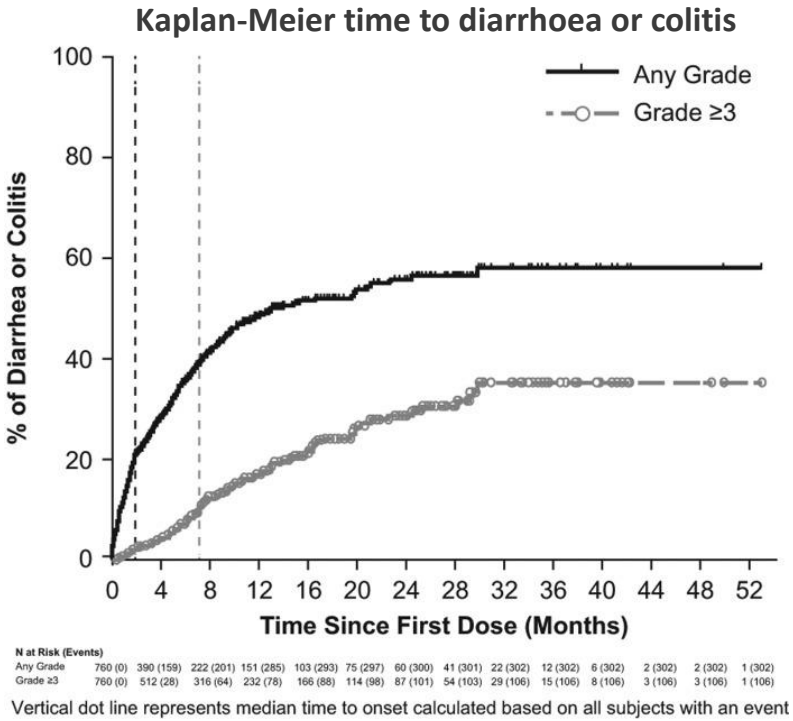
ALT, alanine aminotransferase; AST, aspartate aminotransferase

Gopal A, *et al. N Engl J Med*. 2014;370:1008–18

# Diarrhoea incidence with idelalisib

Bimodal appearance of GI side effects

- Early diarrhoea
  - Usually self-limited
  - Responds to anti-diarrhoeals
- Late diarrhoea/colitis
  - Occurs randomly
  - Can be unresponsive to therapy




Coutré S, *et al. Leuk Lymphoma.* 2015;56:2779–86

# PI3Ki: copanalisib (BAY 80-6946)

- Inhibitor of PI3K- alpha and beta isoforms
- Phase II study (CHRONOS-1):
  - 142 patients with indolent B-cell lymphoma, relapsed or refractory to ≥2 lines of therapy
  - IV administration on Days 1, 8, and 15 of a 28-day cycle
  - Primary endpoint: Overall response rate (ORR)
  - Results:
    - ORR 61%, CR 17% (n=104 FL pts)
    - Median PFS: 12.5 months

Response evaluation by independent assessment

| | All patients (n=142) N (%) | FL (n=104) N (%) | MZL (n=23) N (%) |
|---|---|---|---|
| Complete response (CR) | 24 (16.9) | 21 (20.2) | 3 (13.0) |
| Partial response (PR) | 62 (43.7) | 40 (38.5) | 15 (65.2) |
| Objective response (ORR) | 86 (60.6) | 61 (58.7) | 18 (78.3) |
| Stable disease (SD) | 40 (28.1) | 34 (32.7) | 2 (8.7) |
| Progressive disease (PD) | 3 (2.1) | 2 (1.9) | 0 |
| Unconfirmed early SD | 1 (0.7) | 1 (0.96) | 0 |
| NA/NE | 12 (8.5) | 6 (5.8) | 3 (13.0) |

NA, not available, NE, not evaluable

CR, complete response; ORR, overall response rate; PR, partial response; PD, progressive disease; PI3K, phosphoinositide 3-kinases; SD, stable disease

Dreyling et al. Blood 2018; 132:1595

# Duvelisib (IPI-145)
# Phase II Dynamo study

Refractory iNHL patients
N = 129

**Duvelisib 25 mg BID**

**Study end points**

**Primary:**
- Overall response rate (ORR)

**Secondary:**
- Safety
- Duration of response (DoR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Time to response (TTR)
- Pharmacokinetics (PK)

**Selected inclusion criteria**
- iNHL defined as:
  - Follicular lymphoma (FL)
  - Small lymphocytic lymphoma (SLL)
  - Marginal zone lymphoma (MZL)
- Refractory to rituximab
- Refractory to a chemotherapy regimen or radioimmunotherapy

| Primary endpoint | ORR by IRC |
|---|---|
| **All patients (N=129)** | **47%** |
| FL (n=83) | 42% |
| SLL (n=28) | 68% |
| MZL (n=18) | 39% |

| Secondary efficacy endpoints | All patients (N=129) |
|---|---|
| mDoR, months | 10.0 |
| mPFS, months | 9.5 |
| mOS, months | 28.9 |
| mTTR, months | 1.87 |

BID, twice a day; DoR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IRC, independent review committee; m, median; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall response; PFS, progression-free survival; PK, pharmacokinetics; SLL, small lymphocytic lymphoma; TTR, time to response

Flinn IW, *et al. J Clin Oncol.* 2019;11:912–22

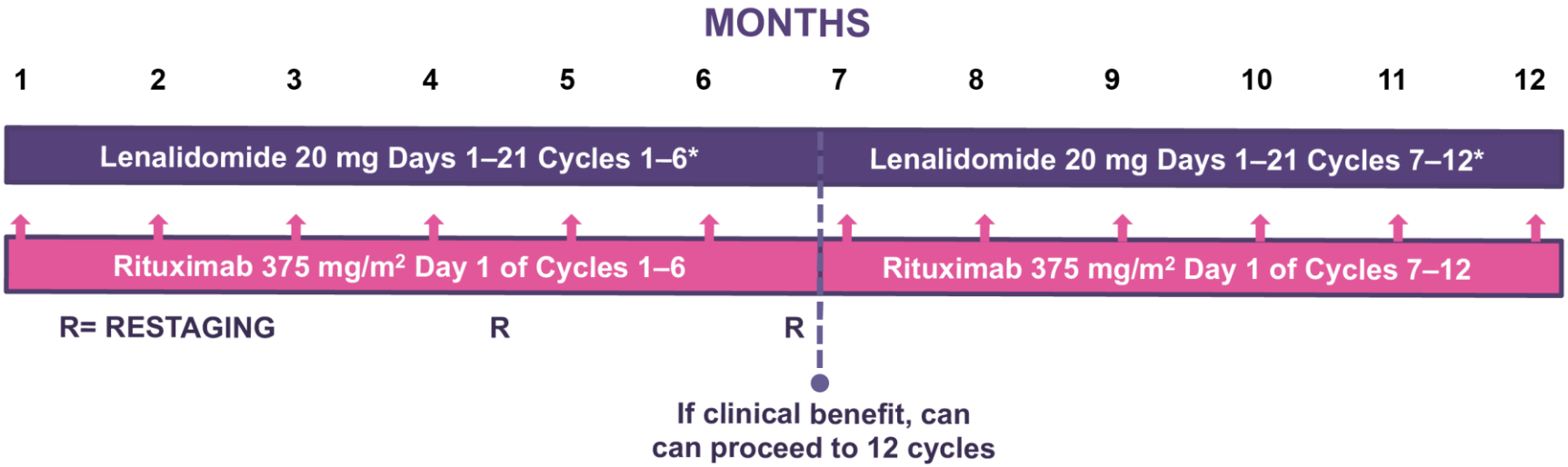
# Selected single-agent PI3K inhibitor trials

| Agent | | Route | Efficacy | Notes |
|---|---|---|---|---|
| Idelalisib[1] | PI3K delta | Oral | Ph 2 double refractory iNHL<br>ORR: 57% CR: 6%<br>PFS: 11 mo | • Double refractory population<br>• Transaminitis<br>• Diarrhoea/colitis |
| Duvelisib[2] | PI3K delta gamma | Oral | Ph 2 double refractory iNHL<br>ORR: 47% CR: 2%<br>PFS: 9.5 mo | • Highly refractory population<br>• ≥ Grade 3 neutropenia: 25%<br>• ≥ Grade 3 diarrhoea: 15%<br>• 5 deaths (n=129) treatment related |
| Umbralisib[3] (TGR-1202) | PI3K delta | Oral | Ph 1/2 relapsed CLL/NHL<br>ORR (iNHL): 49% CR: 11%<br>ORR (aNHL): 24% CR: 8%<br>PFS (NHL/CLL): 27 mo | • Gr 3 neutropenia 16%<br>• Gr 3 diarrhoea 3%<br>• AST/ALT ↑6% (3% Gr 3/4) |
| Copanlisib[4] | PI3K alpha delta | IV | Ph 2 relapsed iNHL:<br>ORR: 59%, CR:12%<br>PFS: 11.2 mo<br>Ph 2 relapsed aggressive NHL:[5]<br>ORR: 27% | • ≥ Grade 3 hypertension: 23%<br>• ≥ Grade 3 hyperglycaemia: 40%<br>• Any grade diarrhoea/colitis: 18%/1%<br>• 3 deaths (n=142) treatment related |
| INCB050465[6] | PI3K delta | Oral | Ph 1/2 relapsed NHL<br>FL: ORR 78% (7/9 patients)<br>DLBCL: ORR 36% (5/14 patients)<br>MCL: ORR 75% (3/4 patients) | • ≥ Grade 3 diarrhea/colitis 31%/6%<br>• ≥ Grade 3 neutropenia: 21%<br>• No ≥ Grade 2 transaminitis<br>• Exploring weekly dosing beyond Week 9 |

CLL, chronic lymphocytic leukaemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IV, intravenous; MCL, mantle cell lymphoma; ORR, overall response rate; PFS, progression-free survival; ph, phase; PI3K, phosphoinositide 3-kinase

1. Gopal A, *et al. N Engl J Med*. 2014;370:1008–18; 2. Flinn IW, *et al. J Clin Oncol.* 2019;11:912–22; 3. reference TBC; 4. Dreyling M, *et al.* AACR 2017. Abstract #CT149; 5. Dreyling M, *et al. Annals Oncol.* 2017;28:2169–78; 6. Ramchandren R, *et al.* ASCO 2017. Abstract #7530

# Phase II study of R2 in untreated indolent lymphoma: study design




- Planned enrollment
  - N = 50 follicular lymphoma (Grade I/II)
  - N = 30 small lymphocytic lymphoma (SLL)
  - N = 30 marginal zone lymphoma
- Groups analysed independently for response and toxicity

*SLL patients: dose escalation of lenalidomide starting with Cycle 1: (10 mg, 15 mg, 20 mg)
R, restaging; SLL, small lymphocytic lymphoma ; R2, lenalidomide + rituximab
Fowler NH, *et al.* ASH 2012. Abstract 901

# Response rates

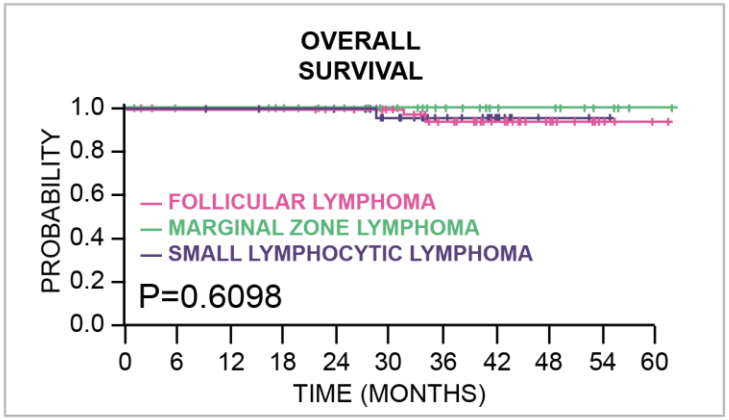
| | SLL (N=30) | MZL (N=27) | FL (N=46) | All Patients Eval* (N=103) | All Patients ITT (N=110) |
|---|---|---|---|---|---|
| ORR, n (%)[1] | 24 (80) | 24 (89) | 45 (98) | 93 (90) | 93 (85) |
| CR/CRu[1] | 7 (23) | 18 (67) | 40 (87) | 65 (63) | 66 (59) |
| PR[1] | 17 (57) | 6 (22) | 5 (11) | 28 (27) | 27 (25) |
| SD, n (%) [2] | 4(13) | 3(11) | 1(2) | 8(8) | 8(7) |
| PD, n (%) [2] | 2(7) | 0 | 0 | 2(2) | 2(2) |

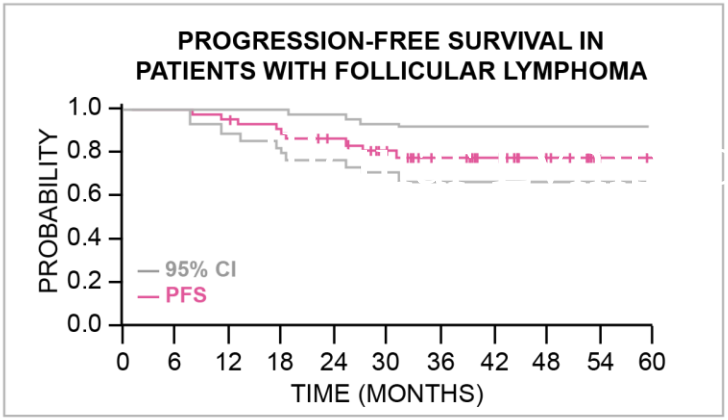
* 7/110 patients were not evaluable for response: n=5 due to adverse events in Cycle 1 without response assessment, n=1 non-compliance and n=1 withdrawal of consent

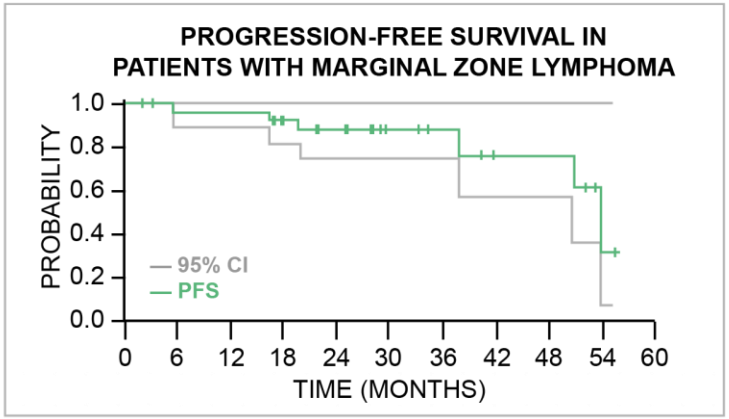
CR(u), complete response (unconfirmed); Eval, evaluable; FL, follicular lymphoma; ITT, intent to treat; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma

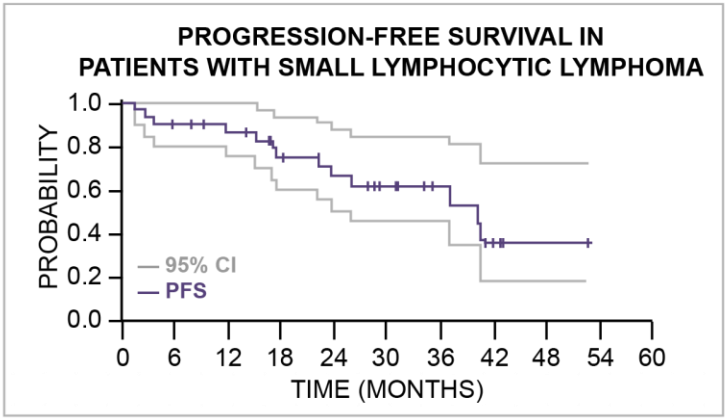
1. Fowler N, *et al. Lancet Oncol.* 2014;15:1311–8; 2. Fowler NH, *et al.* ASH 2012. Abstract 901

# Progression-free survival



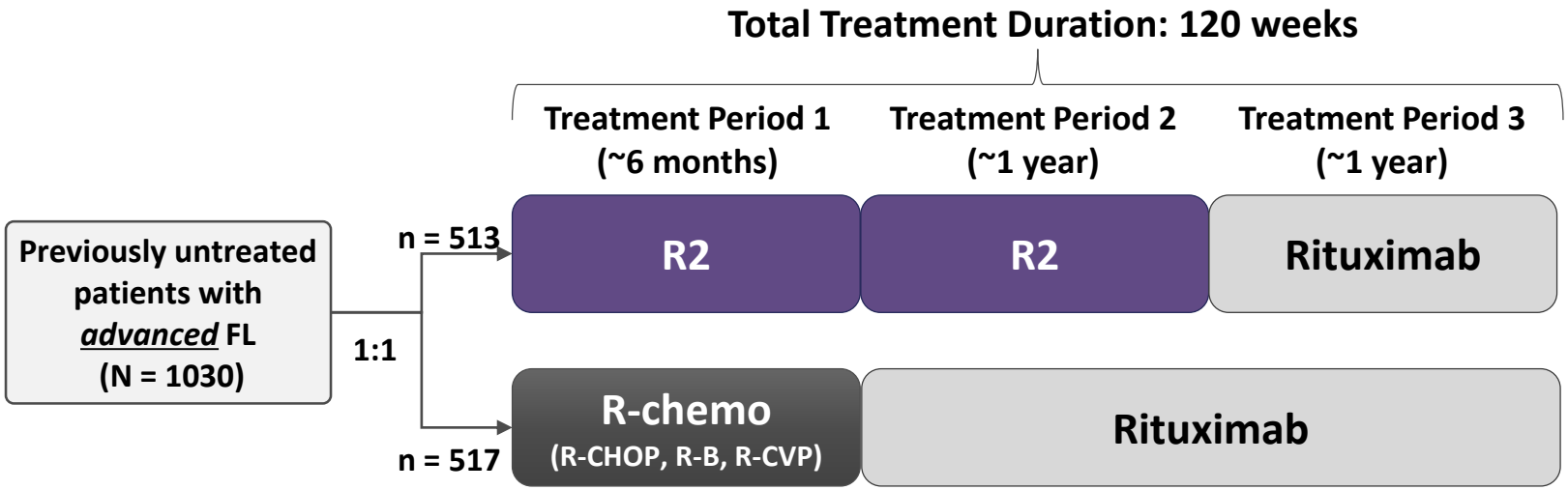




CI, confidence interval; PFS, progression-free survival

Fowler N, *et al. Lancet Oncol.* 2014;15:1311–8

# RELEVANCE - phase III study in untreated follicular lymphoma




**Stratification**

- FLIPI score (0-1 vs 2 vs 3-5)
- Age (> 60 vs ≤ 60 years)
- Lesion size (> 6 vs ≤ 6 cm)

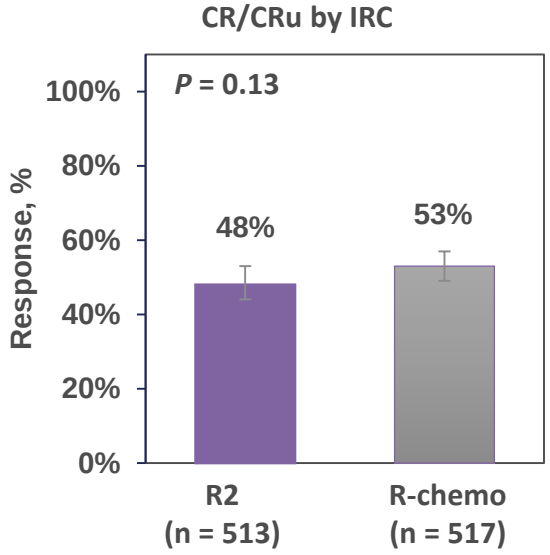
**Co-primary endpoints**

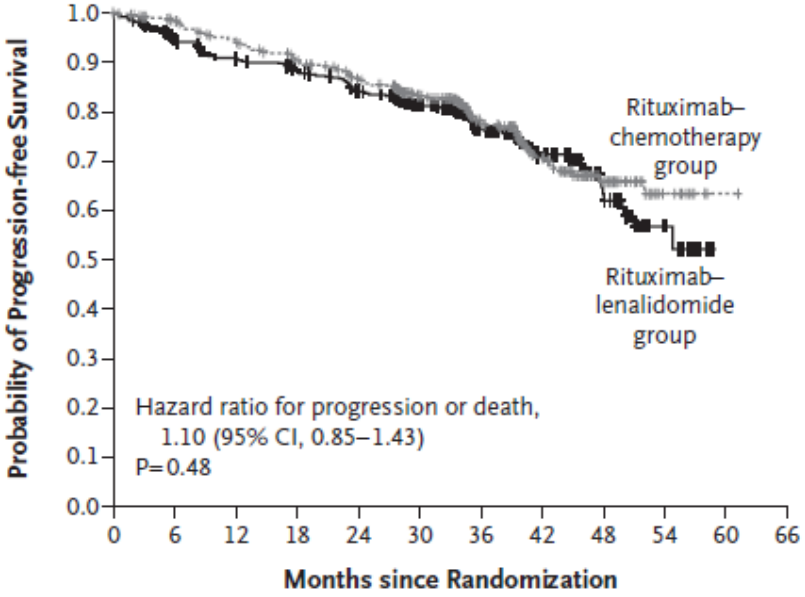
- CR/CRu at 120 weeks
- PFS

CR, complete response; CR30, complete response at 30 months; CRu, complete response unconfirmed; FLIPI, follicular lymphoma international prognostic index; GELF, Groupe d'Etude des Lymphomes Folliculaires; R-B, rituximab, bendamustine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone; R », lenalidomide + rituximab

Morschhauser F, Fowler N, *et al. N Engl J Med* 2018;379:934–47

# RELEVANCE -primary endpoints



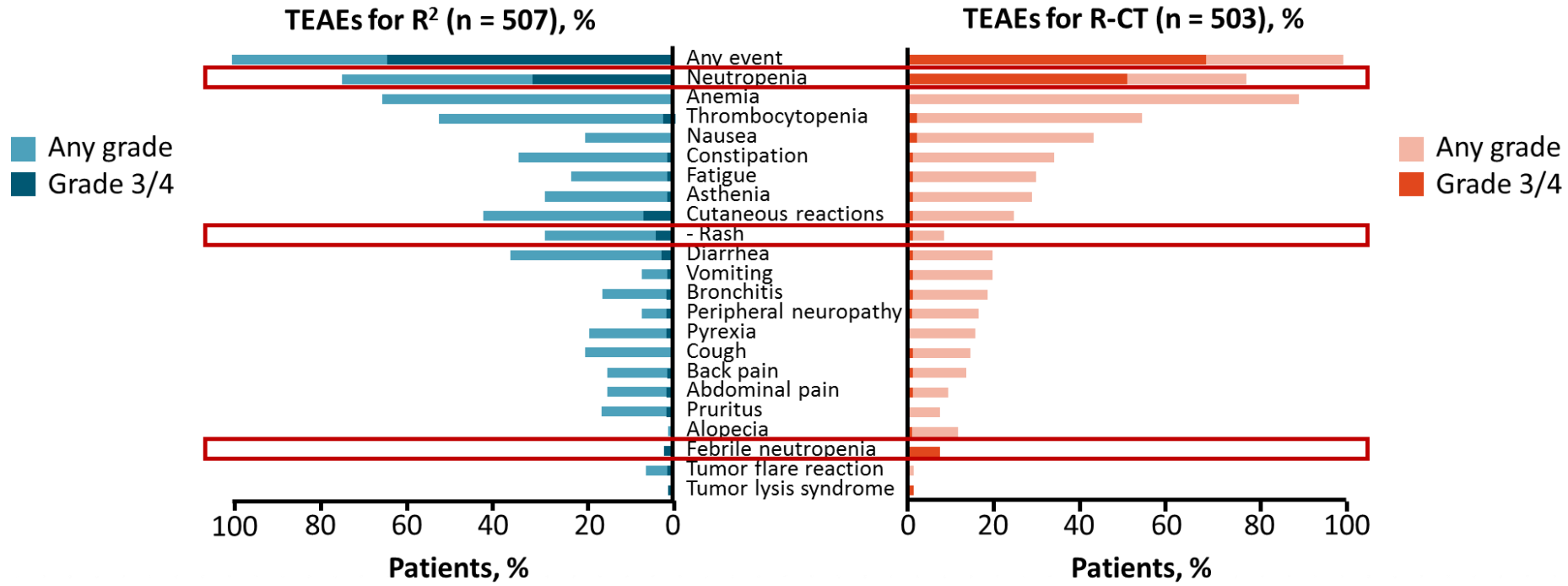




**No. at Risk**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rituximab–lenalidomide group | 513 | 435 | 409 | 393 | 364 | 282 | 174 | 107 | 49 | 13 | 0 | |
| Rituximab–chemotherapy group | 517 | 474 | 446 | 417 | 387 | 287 | 175 | 109 | 51 | 14 | 1 | 0 |

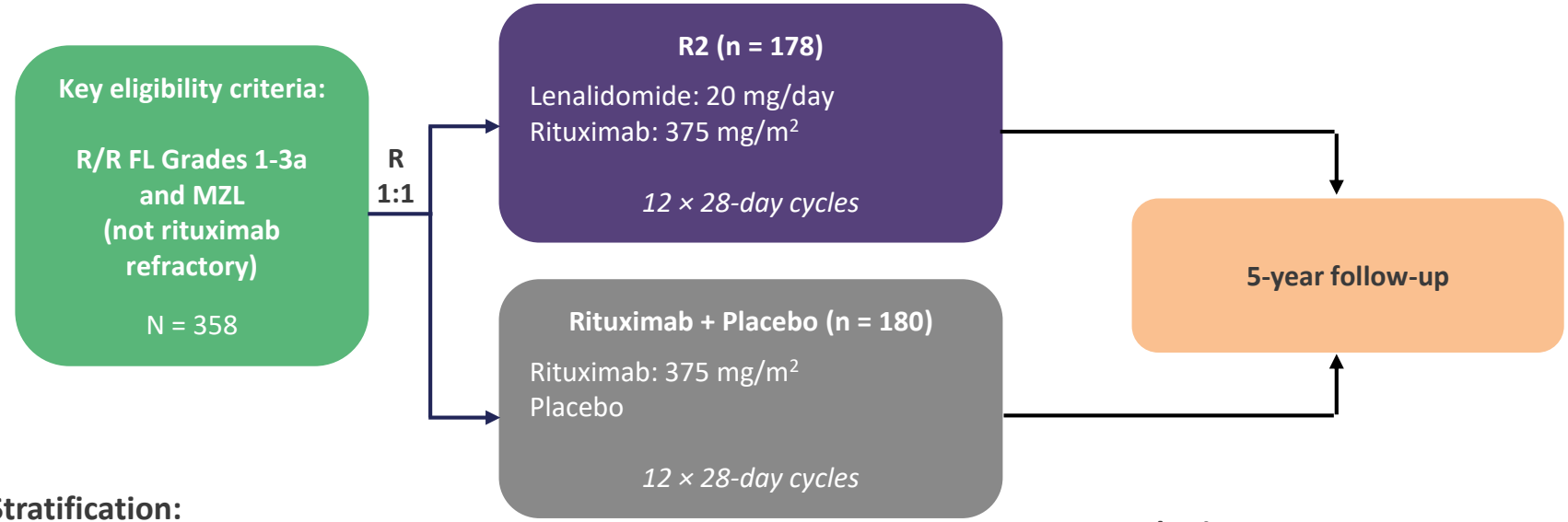
CR, complete response; CRu, complete response unconfirmed, R2 ,lenalidomide + rituximab;
Morschhauser F, Fowler N, *et al. N Engl J Med* 2018;379:934–47

# RELEVANCE: adverse events




Morschhauser F, Fowler N, *et al. N Engl J Med* 2018;379:934–47

# AUGMENT - Phase III study of R2 in relapsed or refractory NHL




**Stratification:**

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

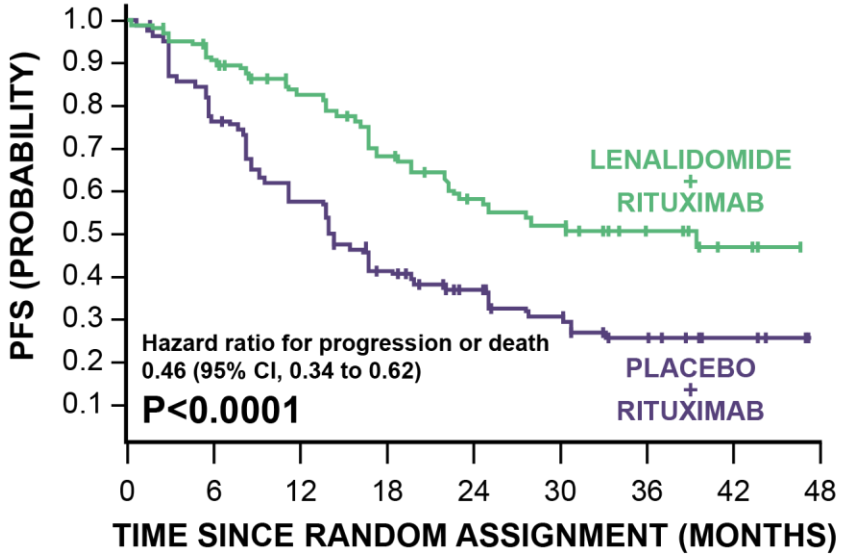
**Endpoints:**

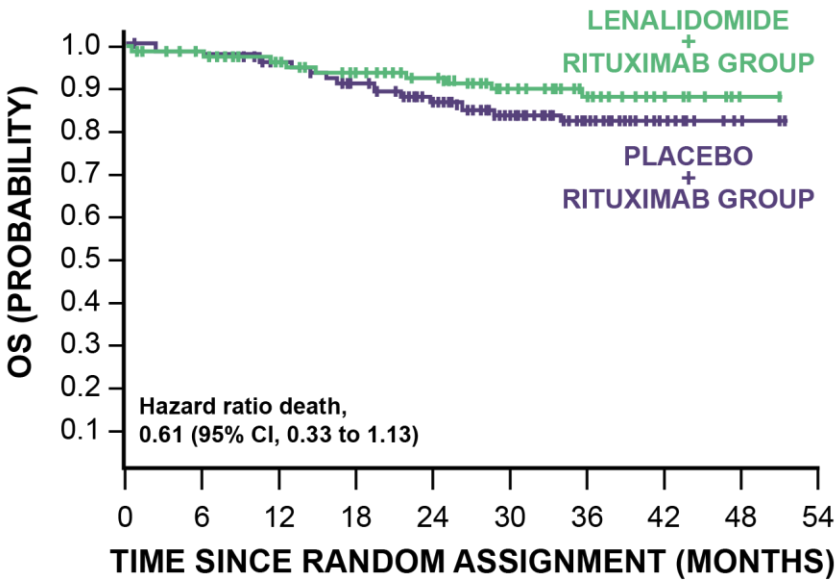
- Primary: PFS
- Secondary: ORR, OS, TTNLT

FL, follicular lymphoma; ITT, intent to treat; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival ; TTNLT, time to next anti-lymphoma therapy; R2, lenalidomide + rituximab.

Leonard J, *et al. J Clin Oncol*. 2019;37:1188–99

# AUGMENT – efficacy in ITT patients with relapsed or refractory NHL




| NO. AT RISK | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| LENALIDOMIDE +RITUXIMAB | 178 | 148 | 124 | 91 | 59 | 39 | 20 | 7 | 0 |
| PLACEBO +RITUXIMAB | 180 | 132 | 92 | 58 | 40 | 26 | 10 | 4 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 178 | 167 | 155 | 143 | 122 | 80 | 44 | 15 | 1 | 0 |
| 180 | 176 | 167 | 145 | 116 | 79 | 40 | 14 | 3 | 0 |

ITT – intended to treat ;OS, overall survival; PFs, progression-free survival.

Leonard J, *et al. J Clin Oncol*. 2019;37:1188–99

# AUGMENT – side effects

| | Any grade AEs | | Grade 3/4 AEs | |
|---|---|---|---|---|
| | R2 (n=176) | Rituximab + placebo (n=180) | R2 (n=176) | Rituximab + placebo (n=180) |
| **Haematological AEs** | | | | |
| Neutropenia*, n (%) | 102 (58) | 40 (22) | 88 (50) | 23 (13) |
| Leukopenia, n (%) | 36 (20) | 17 (9) | 12 (7) | 3 (2) |
| **Non-haematological AEs** | | | | |
| Diarrhoea, n (%) | 55 (31) | 41 (23) | 5 (3) | 0 |
| Constipation, n (%) | 46 (26) | 25 (14) | 0 | 0 |
| Cough, n (%) | 40 (23) | 31 (17) | 1 (1) | 0 |
| Fatigue, n (%) | 38 (22) | 33 (18) | 2 (1) | 1 (1) |
| Pyrexia, n (%) | 37 (21) | 27 (15) | 1 (1) | 3 (2) |

*Febrile neutropenia occurred in 5 patients (3%) and 1 patient (1%) in R2 and placebo plus rituximab groups, respectively; all occurrences were Grade 3 or 4.
AE, adverse event; R2, lenalidomide + rituximab
Leonard J, *et al. J Clin Oncol*. 2019;37:1188–99

# Tazemetostat Phase II study

- Tazemetostat: first-in-class, oral inhibitor of EZH2
- Phase II, multi-center, open-label study in 6 cohorts of patients with R/R DLBCL or FL

| Patients (N=210) | TEAEs | Treatment-related TEAEs |
|---|---|---|
| Adverse event (any), n(%) | 190 (90) | 123 (59) |
| Grade ≥3 | 91 (43) | 38 (18) |
| SAE | 81 (39) | 20 (10) |
| AE leading to dose interruption | 50 (24) | 31 (15) |
| AE leading to dose reduction | 8 (4) | 7 (3) |
| AE leading to drug discontinuation or study withdrawal | 26 (12) | 5 (2) |

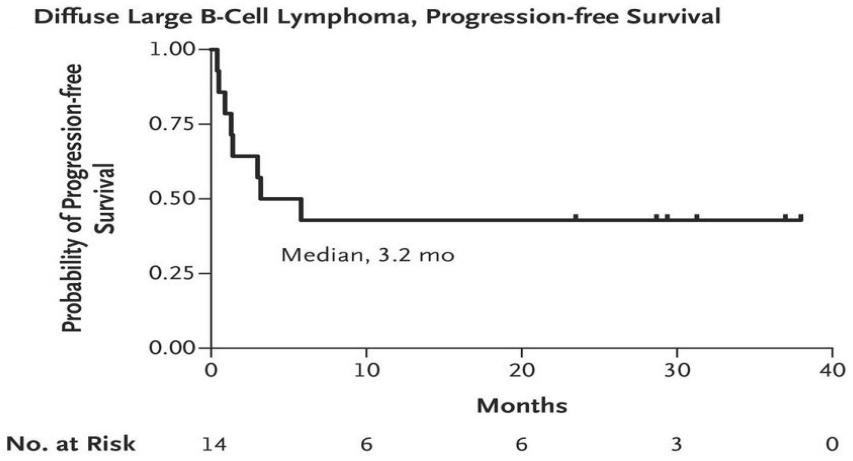
| Best response | FL EZH2 MT (n=13) | FL EZH2 WT (n=54) | DLBCL EZH2 MT (n=17) | DLBCL EZH2 WT (n=119) |
|---|---|---|---|---|
| **Objective response rate, n(%)** | **12 (92)** | **14 (26)** | **5 (29)`** | **18 (15)** |
| Complete response | 1 (8) | 3 (6) | 0 | 10 (8) |
| Partial response | 11 (85) | 11 (20) | 5 (29) | 8 (7) |
| Stable disease (SD) | 1 (8) | 23 (43) | 6 (35) | 22 (18) |
| SD study drug ongoing | 1 (8) | 12 (22) | 1 (6) | 4 (3) |
| Progressive disease | 0 | 13 (24) | 6 (35) | 60 (50) |

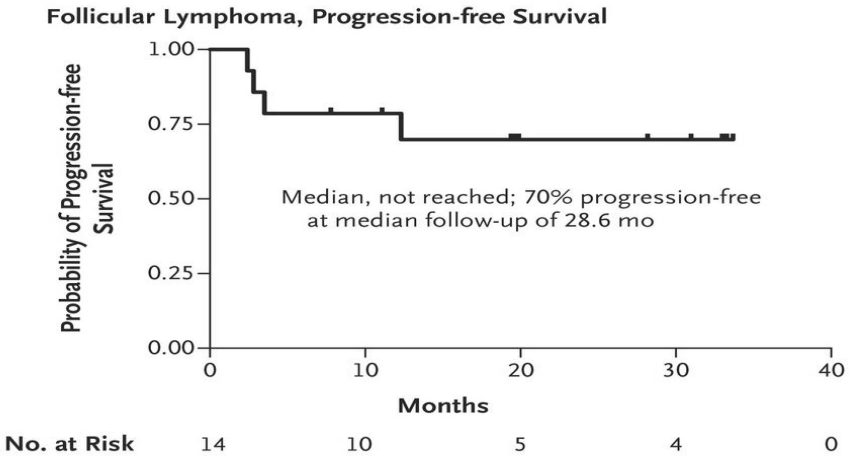
AE, adverse event; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MT, mutated; R/R, relapsed/refractory; SAE, serious adverse event; SD, stable diease; TEAE, treatment-emergent adverse event; WT, wild-type

Morschhauser F, *et al* ICML 2017. Abstract #004

# CAR-T cells for FL

- CD19-directed CAR (CTL019)
- Patients with R/R DLBCL or FL
- Complete response rate: 10/14 patients with FL (71%; 95% CI, 42–92)




CAR, chimeric antigen receptor; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; mo, months

Schuster S, *et al. New Engl J Med.* 2017;377:2545–54

# Should we switch to ‘chemo-free’ regimens in follicular lymphoma?

**Chemotherapy Backbones**
**PROS and CONS**

+ Long term data available
+ High efficacy rate
+ Known toxicities
+ Inexpensive*
+Limited duration

- Mostly intravenous
- Associated with acute/late toxicity
- High Infection rate
- Unselected
- Genotoxic
- Rarely curative

**Biologic Backbones**
**PROS and CONS**

+ Improved QOL?
+ Selected
+ Mostly Oral

- Expensive**
- Prolonged duration of therapy
- Unknown long term AEs
- Unpredictable toxicity
- No biomarkers
- Single-agent modest activity

**Costs less than a Ferrari.*

***Costs more than a Ferrari. (>1)*


Round table
discussion

# Thank you