



A 3D VIEW-

**Going Beyond the Practice Guidelines to Leverage Mutations
in the Pursuit of Unique Treatment Approaches:
RELAPSED FOLLICULAR LYMPHOMA**

***A 3D View - Going Beyond the Practice Guidelines to Leverage
Mutations in the Pursuit of Unique Treatment Approaches: Relapsed
Follicular Lymphoma***

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PROGRAM OVERVIEW

This activity will cover the treatment and management of patients with relapsed follicular lymphoma.

EDUCATIONAL AUDIENCE

This CME initiative is designed to meet the educational needs of hematologist-oncologists and other healthcare professionals involved in the treatment of adults with follicular lymphoma.

LEARNING OBJECTIVES

Upon completion of the program, attendees should be able to:

- Review diagnostics and prognostic biomarkers to advance the timely identification and risk assessment of patients with FL for prompt treatment and or referral
- Describe current treatment options for patients with multiple relapses in the management of follicular lymphoma
- Discuss the efficacy and safety data for agents in late stage of development and their unique mechanism of action in patients with FL who have experienced multiple relapses

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Dr. Utkarsh Acharya has nothing to disclose.

Dr. John Burke has served on the speaker's bureau for Seattle Genetics and Beigene; he has received consulting fees from Morphosys, Adaptive Biotechnologies, Genentech/Roche, AbbVie, Kura, and Epizyme. He has been contracted for research with Seattle Genetics.

Dr. Nathan H. Fowler has received consulting fees from Roche, Celgene, Gilead, Novartis, and BMS; he has been contracted for research with Roche, Gilead, and Novartis.

Dr. Ryan W. Jacobs has served on the speakers' bureau for Pharmacyclics, Genentech, Janssen, AbbVie, Sanofi Genzyme, and AstraZeneca. He has received consulting fees from AbbVie, AstraZeneca, Seattle Genetics, Verastem, and Janssen. He has received research funding from Pharmacyclics and TG Therapeutics.

Dr. Amitkumar Mehta has served on the speakers' bureau for Gilead, AstraZeneca, Pharmacyclics, Seattle Genetics, Incyte, Morphosys/Incyte, TG Therapeutics, Carevive, Kyowa Kirin, and Rigel Pharmaceuticals and he has received consulting fees from Astra Zeneca, Pharmacyclics, Seattle Genetics, Incyte, Morphosys/Incyte, TG Therapeutics, Carevive, Kyowa Kirin, and Rigel Pharmaceuticals; he also reports other research funding received from Incyte, Takeda, fortyseven inc/Gilead, Juno Pharmaceuticals/BMS, Celgene/BMS, Oncotartis, Innate Pharmaceuticals, Seattle Genetics, TG Therapeutics, Affimed, Merck, Kite/Gilead, Roche-Genentech, ADC therapeutics, Miragen, and Rhizen Pharmaceuticals.

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Dr. Nishitha Reddy has served on the speakers' bureau for Seagen and Celgene.

Dr. Nirav N. Shah has received consulting fees from Lilly, Legend, TG Therapeutics, Celgene, and Kite; and he has been contracted for research with Miltenyi.

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in the Pursuit of Unique Treatment Approaches:
RELAPSED FOLLICULAR LYMPHOMA

Program Agenda

I. Initial Diagnosis and Prognostic Indices to Assess Patient Risk - Follicular Lymphoma

- A. Work up for follicular lymphoma
 - i. Immunophenotyping using immunohistochemistry
- B. Prognostic biomarkers and their predicated outcomes
 - i. Prognostic tools and clinical practice
 - FLIPI: 5-yr and 10-yr OS
 - POD24: 5-yr OS
 - ii. Ready for prime time or research only?

II. Available Treatment Options in the Patient After Multiple Relapses

- A. National Comprehensive Cancer Network practice guidelines
 - i. Preferred options – 2L and beyond
 - Chemoimmunotherapy with anti-CD20 mAB
 - Lenalidomide with/without rituximab
 - ii. Other recommended options
 - PI3K inhibitors – Efficacy and safety review

III. Emerging Compound in Late Stage of Development in the Third Line

- A. EZH2 inhibitor
 - i. EZH2's role in tumorigenesis
 - ii. **3D Theme:** depiction of the tumorigenic effects of activated EZH2 mutation including immune suppression
 - iii. Anti-tumor effects of tazometostat
 - **3D Theme:** anti-tumor mechanism of action of tazometostat
 - iv. Clinical trials findings
 - Relapsing follicular lymphoma
 - Activating mutation and wild type EZH2 tumors
 - Tolerability and adverse event profile
- B. Bi-specific antibodies

IV. Conclusions

V. Questions and Answers

***Going Beyond the Practice Guidelines
to Leverage Mutations in the Pursuit
of Unique Treatment Approaches:
Relapsed Follicular Lymphoma***

Program Chair

John M. Pagel, MD, PhD

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Disclosures

- Please see the program overview for specific speaker disclosure information.
- During the course of this lecture, the faculty may mention the use of medications for both FDA-approved and non-approved indications.

This activity is supported by an educational grant from Epizyme Inc.

Learning Objectives

- Review diagnostics and prognostic biomarkers to advance the timely identification and risk assessment of patients with follicular lymphoma (FL) for prompt treatment and or referral
- Describe current treatment options for patients with multiple relapses in the management of FL
- Discuss the efficacy and safety data for agents in late stage of development and their unique mechanism of action in patients with FL who have experienced multiple relapses

Follicular Lymphoma International Prognostic Index (FLIPI) Scoring System

Cox regression analysis in 1795 patients exhibiting 8 parameters with significant influence on OS

Variable	Adverse Factor	P-value	RR	95% CI
Sex	Male	0.001	1.33	1.14–1.56
Age	>60 years	<10 ⁻³	2.40	2.05–2.81
Ann Arbor stage	III-IV	<10 ⁻³	1.66	1.26–2.19
Bone marrow	Involved	0.001	1.37	1.14–1.64
Number of nodal sites	>4	0.001	1.32	1.11–1.56
Hemoglobin level	<120 g/L	<10 ⁻³	1.59	1.31–1.92
PB lymphocyte count	<1 x 10 ⁹ /L	0.008	1.27	1.06–1.52
LDH	>ULN	<10 ⁻³	1.50	1.26–1.77

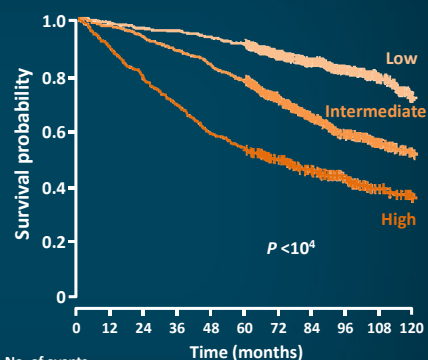
Outcome and relative risk of death according to risk group as defined by FLIPI (N = 1795)

Risk Group	No. of factors	Patients	OS, % (SE)		RR	95% CI
			5-yr	10-yr		
Low	0–1	36%	90.6 (1.2)	70.7 (2.7)	1.0	NA
INTMD	2	37%	77.6 (1.6)	50.9 (2.7)	2.3	1.9–2.8
High	≥3	27%	52.5 (2.3)	35.5 (2.8)	4.3	3.5–5.3

OS = overall survival; RR = relative risk (death); CI = confidence interval; PB = peripheral blood; LOH = lactate dehydrogenase; ULN = upper limit of normal; INTMD = intermediate; yr = year(s); NA = not applicable.

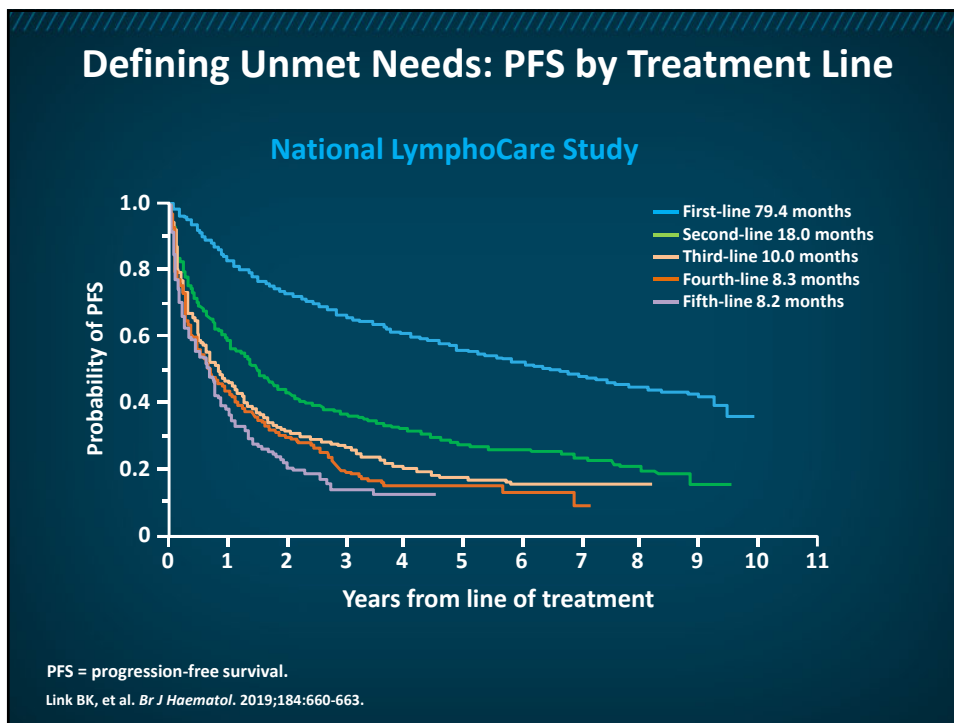
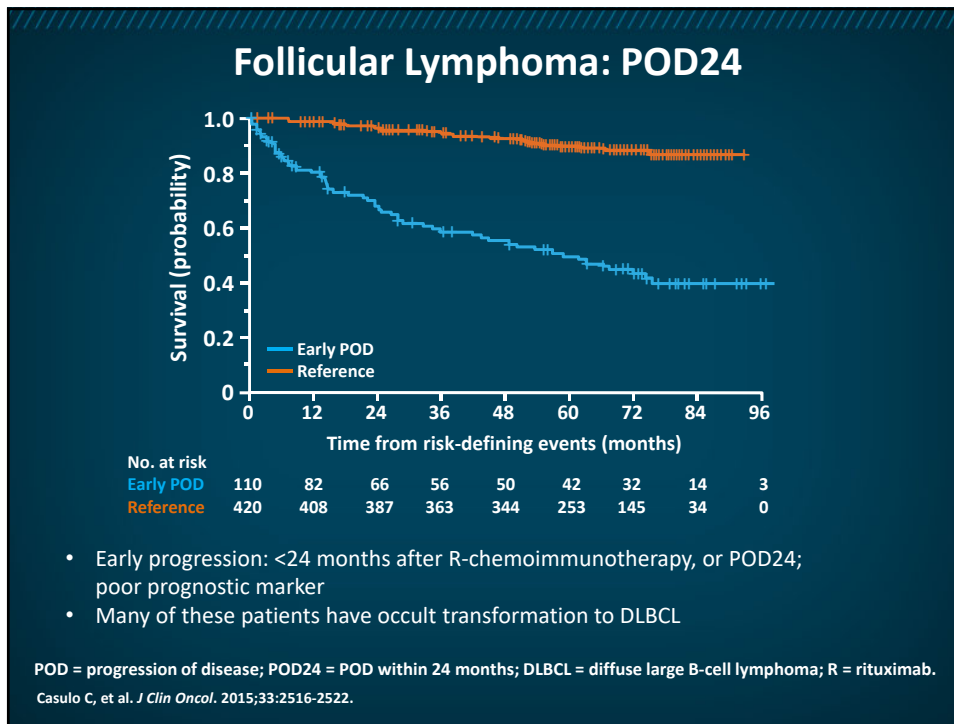
Sokal-Céligny P et al. *Blood*. 2004;104:1258-1265.

Survival of the 1795 patients according to risk group as defined by the FLIPI



No. of events	Low	INTMD	High
12	25	29	46
60	83	95	106
120	113	125	152
180	143	152	192
240	163	178	245
300	178	198	268
360	183	208	274
420	188	213	278

No. at risk	Low	INTMD	High
0	641	629	616
12	629	612	595
24	616	581	450
36	595	337	241
48	581	217	157
60	450	178	108
72	337	178	68
84	241	178	68
96	157	178	68
108	93	178	68
120	68	178	68

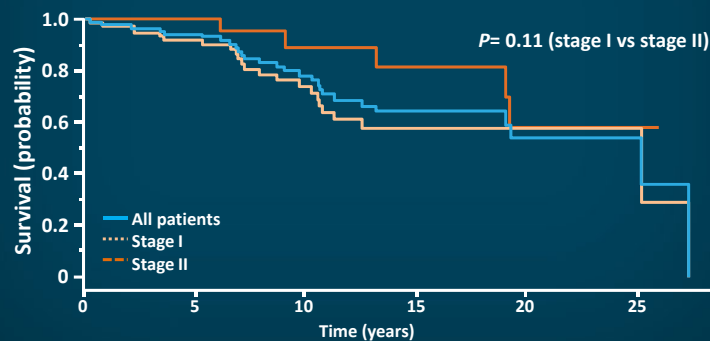


Follicular Lymphoma: Unmet Needs

- Excellent OS is largely driven largely by response to 1st-line (1L) therapy
- 20–25% of patients will experience rapid progression (POD24) after 1L treatment; associated with poorer OS
 - Unmet need #1: 1st-line therapies that may reduce POD24
- Around 35–40% of patients will experience relapse after 1L treatment, requiring subsequent therapy
 - Unmet need #2: 1st-line therapies that reduce risk of any relapse
- PFS drastically shortens with 2nd-line (2L) and beyond therapy
 - Unmet need #3: better therapies in 2L+ FL

FL: Initial Treatment for Stage I/II Disease

- Approximately 10–30% of patients will have stage I/II disease^{1,2}
- The main therapeutic approach is RT, yielding 10-year OS rates of 60–80%²
- Recommended dosage: 24–30 Gy in 12–15 fractions³



RT = radiotherapy; Gy = gray (unit of absorbed dose of ionizing radiation).

1. Carbone A, et al. *Nat Rev Dis Primers*. 2019;5:83. 2. Freedman A, Jacobsen E. *Am J Hematol*. 2020;95:316-327. 3. Illidge T, et al. *Int J Radiat Oncol Biol Phys*. 2014;89:49-58.

FL: Initial Treatment for Advanced Disease

- Advanced FL is not curable, but treatment can prolong OS

CIT is generally recommended for active therapy			R ² considered in certain patients (eg, desiring chemotherapy-free regimens)	R maintenance for patients who respond to induction therapy
StiL trial¹ Phase 3 BR vs R-CHOP	BRIGHT trial² Phase 3 BR vs R-CHOP/R-CVP	Gallium trial³ Phase 3 G- vs R- chemo	RELEVANCE trial⁴ Phase 3 R ² (lenalidomide + R) vs R-chemo	PRIMA^{5,6} Phase 3 Rituximab maintenance
<ul style="list-style-type: none"> BR superior to R-CHOP 	<ul style="list-style-type: none"> Trend toward PFS benefit with BR vs R-CHOP/R-CVP 	<ul style="list-style-type: none"> Superior PFS with G- vs R-chemo, but <u>no difference in OS</u> More grade 3-5 AEs with G (75% vs 68%) Approval in 2017 for initial chemotherapy and maintenance G 	<ul style="list-style-type: none"> Similar efficacy with R² compared with R-chemotherapy Less hematologic toxicity with R², but more grade 3/4 cutaneous toxicity (7% vs 1%) 	<ul style="list-style-type: none"> Superior PFS (and TTNT), but <u>not OS</u>, with R maintenance FDA approved in 2011 as maintenance therapy in patients with FL who respond to induction therapy

*No head-to-head studies have been conducted and direct comparisons cannot be made between these studies.

1. Rummel MJ, et al. *Lancet*. 2013;381:1203. 2. Flinn IW, et al. *J Clin Oncol*. 2019;37:984. 3. Marcus R, et al. *N Engl J Med*. 2017;377:1331. 4. Morschhauser F, et al. *N Engl J Med*. 2018;379:934. 5. Salles G, et al. *Lancet*. 2011;377:42. 6. Bachy E, et al. *J Clin Oncol*. 2019;37:2815

POD24—Strategies and Population at Risk

- No clear predictors at diagnosis of which patients are at risk for POD24
 - Does not correlate with stage of disease; there is some correlation with high-risk FLIPI
 - PET/CT staging and biopsy of hottest node at diagnosis to assess for occult DLBCL transformation
- Possible strategies for reduction in POD24
 - Lenalidomide-rituximab/obinutuzumab
 - Bendamustine-obinutuzumab (compared with BR)
 - R-CHOP (if concern for concomitant DLBCL transformation)

PET = positron-emission tomography; CT = computed tomography.

Treating Relapsed or Refractory Disease

Patient Case: Relapsed FL After 2 Prior Therapies

- 73-yr-old female diagnosed 6 years ago with grade 1/2 FL
- She was treated with BR followed by maintenance rituximab
- 4 yrs later, she experienced asymptomatic relapse of grade 1/2 FL (max size 6 cm, max SUV 7)
- She was then treated with lenalidomide plus rituximab for 12 mos and achieved a PR
- Now 33 mos later, she has asymptomatic inguinal adenopathy
- PET/CT: diffuse adenopathy (max size 4 cm, max SUV 7)

SUV=standardized uptake values.

Patient Case: Relapsed FL After 2 Prior Therapies

Given this patient's history and current findings, what are your next options?

- A. Begin tazometostat
- B. Begin PI3K inhibitor therapy
- C. Begin obinutuzumab
- D. Begin ibritumomab tiuxetan
- E. All of the above

Patient Case: Relapsed FL After 2 Prior Therapies

Given this patient's history and current findings, what are your next options?

- A. Begin tazometostat
- B. Begin PI3K inhibitor therapy
- C. Begin obinutuzumab
- D. Begin ibritumomab tiuxetan
- E. All of the above**

**Patient Case:
Relapsed FL After 2 Prior Therapies**

Genetic test results are positive for a EZH2 mutation and platelet count of 75,000. Does this information change your choice of treatment?

- A. Begin PI3K inhibitor therapy
- B. Begin obinutuzumab
- C. Begin ibritumomab tiuxetan
- D. Begin tazometostat
- E. A, B and D
- F. All of the above

**Patient Case:
Relapsed FL After 2 Prior Therapies**

Genetic test results are positive for a EZH2 mutation and platelet count of 75,000. Does this information change your choice of treatment?

- A. Begin PI3K inhibitor therapy
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- D. Begin tazometostat
- E. A, B and D
- F. All of the above**

AUGMENT: Double-Blind, Phase 3, R² vs R

≤12 cycles or until PD, relapse, or intolerance

Relapsed/refractory
FL or MZL
(N = 358)

1:1

R-lenalidomide (R²)
Rituximab: 375 mg/m² d1, 8, 15, 22 of cycle 1;
d1 of cycles 2–5 every 28 days
Lenalidomide: 20 mg/d*, d1–21/28 (12 cycles)

*10 mg if CrCl 30–59 mL/min.

R-placebo
Rituximab: 375 mg/m² d1, 8, 15, 22 of cycle 1;
d1 of cycles 2–5 every 28 days
Placebo: matched capsules (12 cycles)

5-year follow-up
for OS, SPMs,
subsequent
treatment, and
histological
transformations

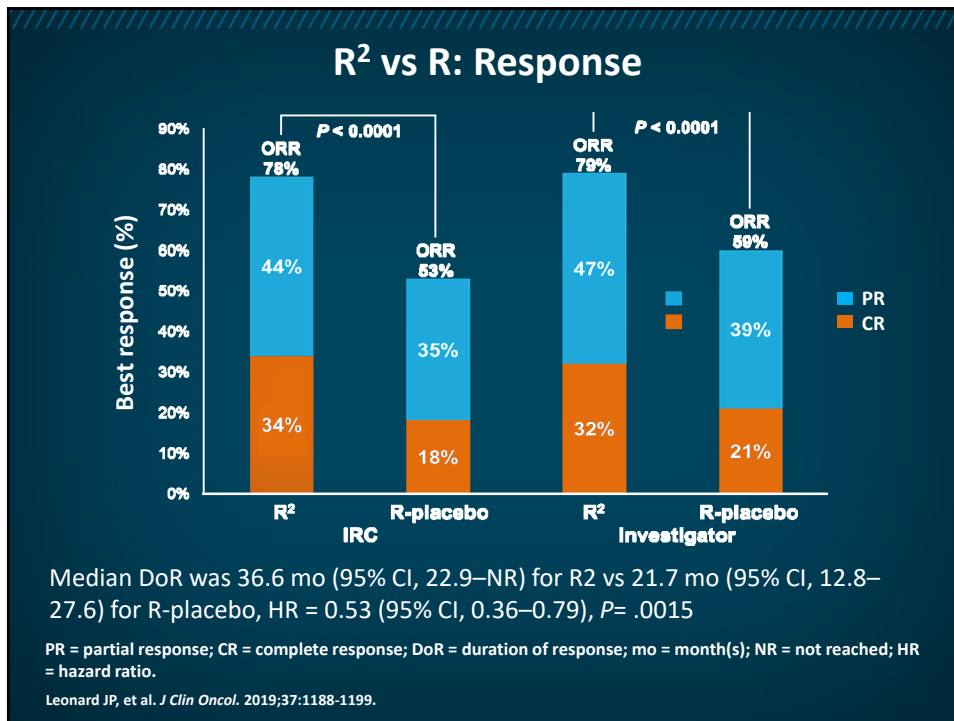
Key eligibility criteria

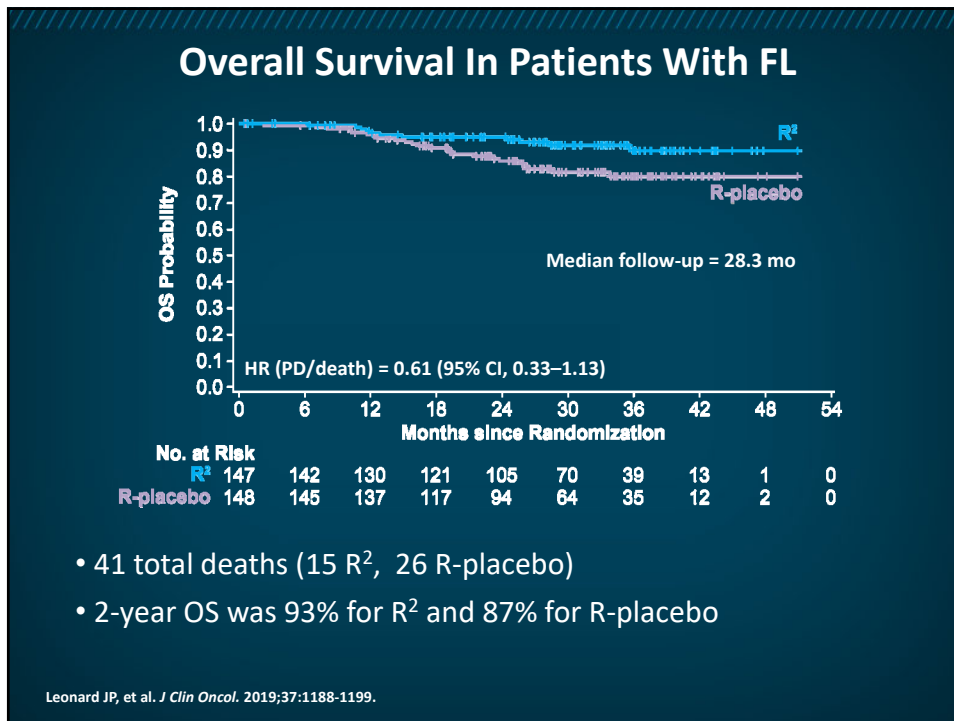
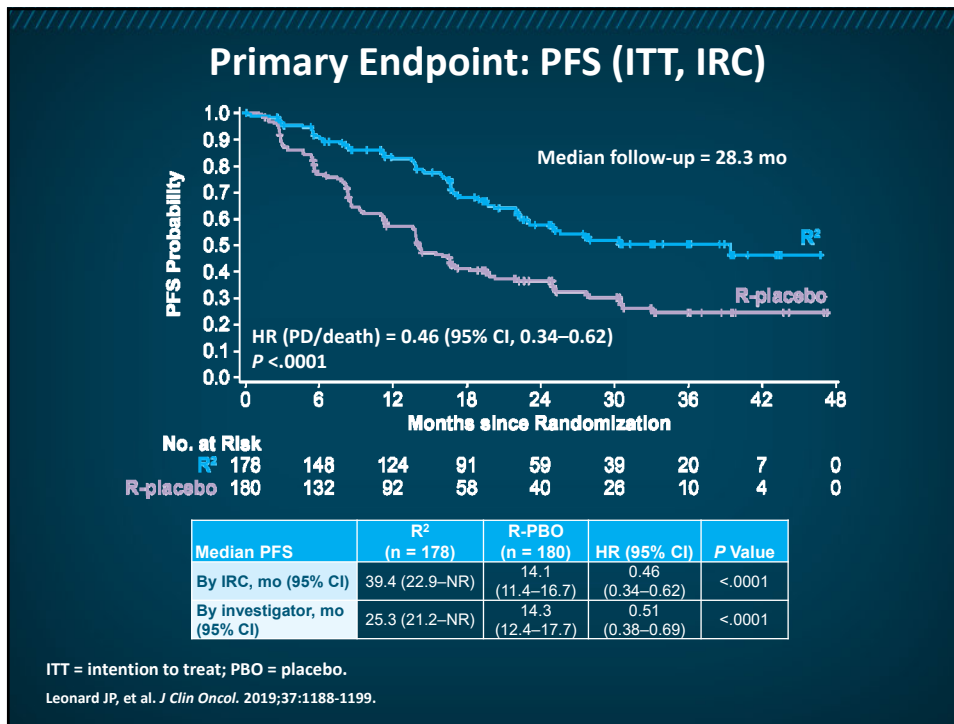
- MZL or FL (grades 1–3a) in need of treatment
- ≥1 prior chemotherapy, immunotherapy, or chemoimmunotherapy
- Not rituximab refractory

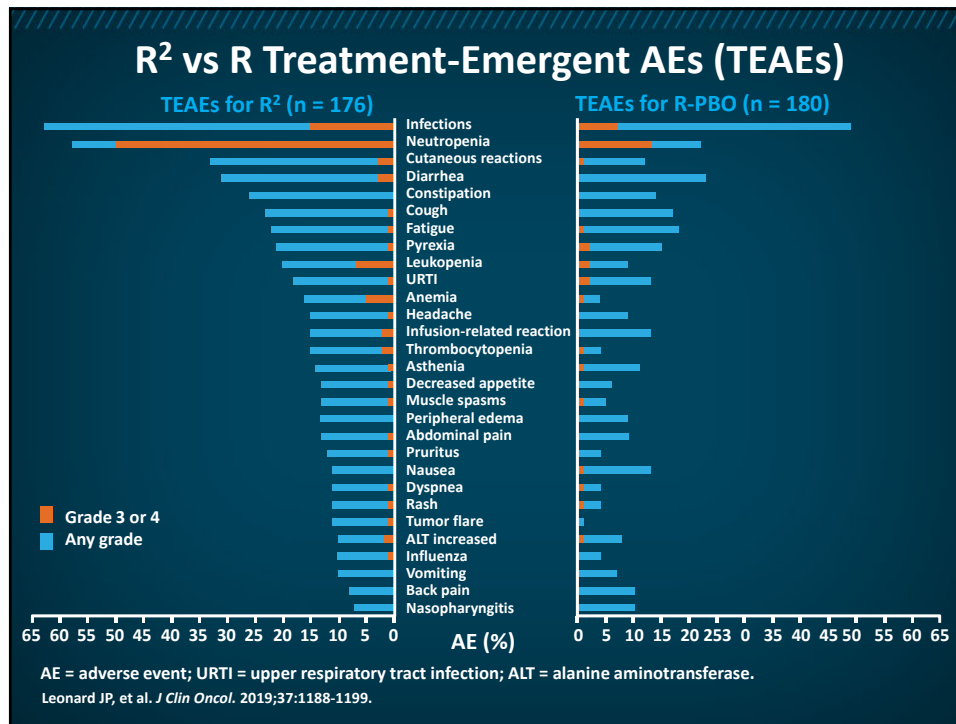
Prophylactic anticoagulation/antiplatelet treatment recommended for at-risk patients

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

PD = progressive disease; MZL = marginal-zone lymphoma; CrCl = creatinine clearance; IRC = independent radiology review; IWG = International Working Group; w/o = without; SPM = secondary primary malignancy.
Leonard JP, et al. *J Clin Oncol.* 2019;37:1188-1199.







R² vs R: Other Data of Interest

	R ² (n = 178)	R-PBO (n = 180)
Histological transformation (ITT)		
Patients with histological transformation, n (%)	2 (1)	10 (6)
Incidence rate per 100 person-years	0.5%	2.5%

	R ² (n = 176)	R-PBO (n = 180)
AEs of interest (safety), n (%)		
All second primary malignancies	6 (3)	10 (6)
Hematologic malignancies	1 (1)	2 (1)
Solid tumor	2 (1)	6 (3)
Noninvasive	3 (2)	3 (2)
Venous thromboembolism AEs	6 (3)	3 (2)
Arterial thromboembolism AEs	1 (1)	4 (2)
Mixed thromboembolism AEs	3 (2)	1 (1)

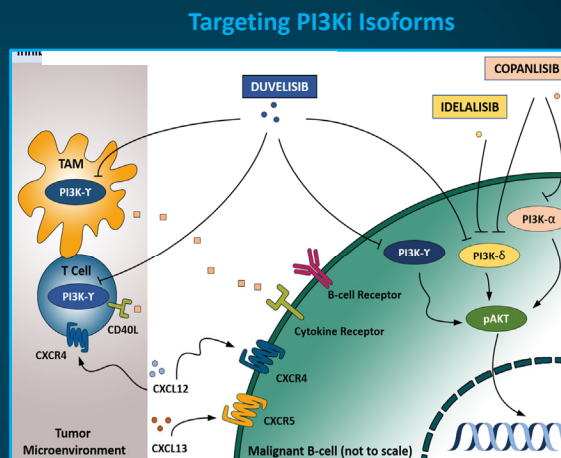
Leonard JP, et al. *J Clin Oncol.* 2019;37:1188-1199.

AUGMENT (R² vs R) Conclusions

- Higher response rates and longer PFS with R² compared with R-alone
- Benefit seen across all groups except for marginal-zone lymphoma
- Survival advantage observed for follicular lymphoma group treated with R²
- R² represents a good treatment option for previously treated indolent B-cell lymphoma

PI3K Inhibition: Rationale

- The phosphatidylinositol-3-kinase (PI3K) pathway is aberrantly activated in many cancers, including NHL, contributing to proliferation and resistance to therapy
- The delta isoform of p110 catalytic subunit is of particular interest in lymphoma
- Several PI3Ki approved for R/R FL and ≥ 2 prior therapies



NHL = non-Hodgkin lymphoma; PI3Ki = PI3K inhibitor; TAM = tumor-associated macrophage; R/R = relapsed/refractory.

Westin JR. *Clin Lymphoma Myeloma Leuk.* 2014;14:335-342. von Keudell G, Moskowitz AJ. *Curr Hematol Malig Rep.* 2019;14:405-413. Patel K, et al. *Blood.* 2019;134:1573-1577.

PI3Ki: Idelalisib

- Idelalisib primarily targets the delta isoform of PI3K
- Idelalisib evaluated in a phase 2 trial enrolling 125 patients with indolent B-NHL (FL, SLL, MZL) who were refractory to rituximab and an alkylator
- ORR for 72 patients with FL was 54%
 - In the overall patient cohort, the ORR was 57%, with a CR in 6%
- Median PFS was 11 months; median OS was 20.3 months
- Grade ≥ 3 diarrhea reported in 13%
- Accelerated FDA approval granted in 2014 for patients with ≥ 2 prior therapies

B-NHL = B-cell NHL; SLL = small lymphocytic leukemia; ORR = overall/objective response rate.

Gopal AK, et al. *N Engl J Med.* 2014;370:1008-1018. von Keudell G, Moskowitz AJ. *Curr Hematol Malig Rep.* 2019;14:405-413.

PI3Ki: Copanlisib

- Copanlisib targets alpha and delta isoforms of PI3K
- Copanlisib evaluated in a phase 2 trial enrolling 142 patients with R/R indolent B-NHL and prior rituximab and alkylating agents
- Updated ORR for 104 patients with FL was 59% (CR, 20%)
- Median PFS was 12.5 months
- Grade 3/4 hyperglycemia in 40%, grade 3/4 pneumonia in 11%, grade 3 diarrhea in 8.5%
- Accelerated FDA approval in 2017 for patients with ≥ 2 prior therapies

Dreyling M, et al. *J Clin Oncol.* 2017;35:3898-3905. Dreyling M, et al. *Am J Hematol.* 2019;Dec 23: Epub ahead of print. Copanlisib (Aliqopa™) prescribing information (PI) 2020 (http://labeling.bayerhealthcare.com/html/products/pi/Aliqopa_PI.pdf). Accessed 10/15/2020.

PI3Ki: Duvelisib

- Duvelisib targets delta and gamma isoforms of PI3K
- Evaluated in a phase 2 study enrolling 129 patients with relapsed/refractory indolent NHL refractory to both rituximab and chemotherapy or radioimmunotherapy
- ORR for 83 patients with FL was 42% (CR, 1%)
- Median PFS was 9.5 months
- Grade ≥ 3 AEs: diarrhea (15%), pneumonia (5%), fatigue (5%)
- Accelerated FDA approval in 2018 for patients with ≥ 2 prior therapies

Flinn IW, et al. *J Clin Oncol*. 2019;37:912-922.

Emerging Data in Follicular Lymphoma

Please scan the QR codes below to watch an animation depicting the tumorigenic effects of activated EZH2 mutation, including immune suppression

2D



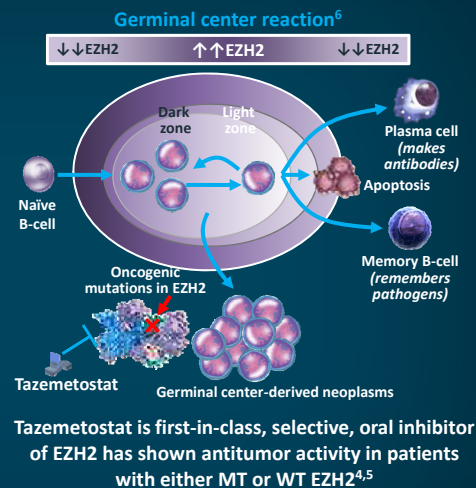
3D



To request a pair of glasses to view the 3D animations, please email jmcmullen@medlearninggroup.com

Follicular Lymphoma and EZH2

- EZH2 is epigenetic regulator of gene expression and cell-fate decisions¹
- EZH2 is required for normal B-cell biology and germinal-center formation²
- Oncogenic mutations in EZH2 suppress exit from germinal state and “lock” B cells in this state, transforming into cancer²
- EZH2 biology is relevant in MT and wild-type WT EZH2 FL²
- ~20% of patients with FL have EZH2 gain-of-function mutations^{3,4}

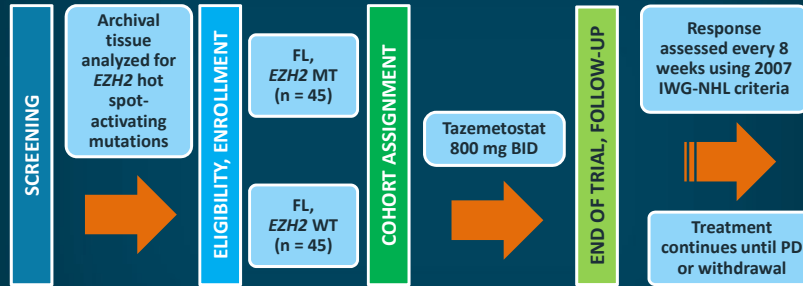


EZH2 = enhancer of zeste homolog 2; MT = mutant type; WT = wild-type.

1. Gan L, et al. *Biomark Res.* 2018;6:10. 2. Béguelin W, et al. *Cancer Cell.* 2013;23:677-692. 3. Böttcher C, et al. *Blood.* 2013;122:3165-3168. 4. Italiano A, et al. *Lancet Oncol.* 2018;19:649-659. 5. Morschhauser F, et al. *Hematol Oncol.* 2017;35:24-25 (abstract 4). 6. Morschhauser F, et al. International Conference on Malignant Lymphoma (ICML). 2019

Phase 2 Study of Tazemetostat in R/R FL Patients Trial Design

- Enrollment initiated July 2015 ; last data cut June 7, 2019
- Conducted at 56 sites across North America, Europe, Asia, and Australia



- **Inclusion criteria**
 - Age ≥18 years
 - ECOG PS: 0–2
 - Life expectancy ≥3 months
 - R/R FL after ≥2 prior therapies, including anti-CD20
- **Key objectives**
 - Primary endpoint = ORR
 - Secondary endpoints = DoR, PFS, safety, and pharmacokinetics

BID = twice daily; ECOG = Eastern Cooperative Oncology Group; PS = performance status.
Morschhauser F, et al. International Conference on Malignant Lymphoma (ICML). 2019

Phase 2 Study of Tazemetostat in R/R FL Patients Baseline Demographics (ITT Population)

Characteristic	MT EZH2 (n = 45)	WT EZH2 (n = 54)
Median age, years (range)	62 (38–80)	61 (36–87)
Males, n (%)	19 (42)	34 (63)
ECOG PS 0–1, n (%)	45 (100)	49 (91)
Prior lines of anticancer therapy, n (%)		
1	2 (4)	0 (0)
2	22 (49)	18 (33)
3	10 (22)	11 (20)
4	5 (11)	9 (17)
≥5	6 (13)	16 (30)
Median (range)	2 (1–11)	3 (2–8)

Characteristic	MT EZH2 (n = 45)	WT EZH2 (n = 54)
Transformed FL or Grade 3 B, n (%)	3 (7)	8 (15)
Refractory to rituximab-containing regimen, n (%)	18 (40)	33 (61)
Refractory to last regimen, n (%)	18 (40)	20 (37)
Prior HSCT, n (%)	4 (9)	21 (39)
Double refractory, n (%)	10 (22)	21 (39)
Median time from initial diagnosis, years	4.7	6.5
Median time from last exposure to last prior therapy, months	4.2	6.8

HSCT = hematopoietic stem-cell transplantation.

Morschhauser F, et al. International Conference on Malignant Lymphoma (ICML). 2019.

Phase 2 Study of Tazemetostat in R/R FL Patients Results: Best Response

Clinically meaningful response for both MT and WT EZH2
FL patients

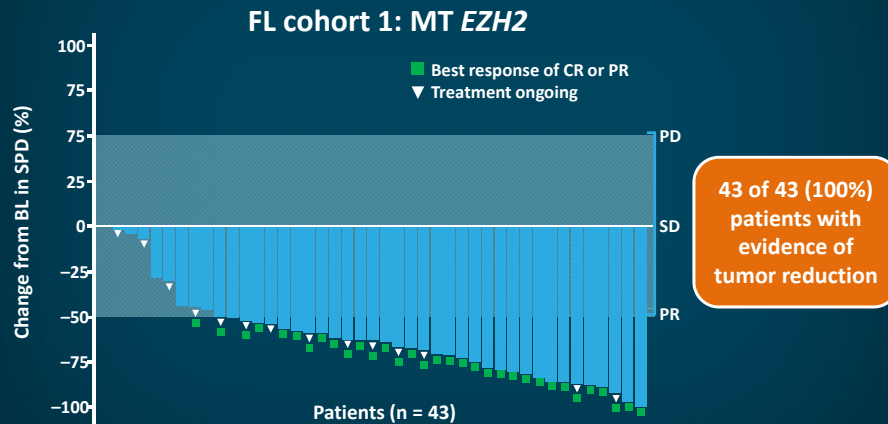
Best Response	FL with EZH2 MT (n = 45)		FL with EZH2 WT (n = 54)	
	Investigator	IRC	Investigator ¹	IRC ²
ORR, % (n) (95% CI)	78% (35) (62.9–88.8)	69% (31) (53.4–81.8)	33% (18) (21.1–47.5)	35% (19) (22.7–49.4)
CR, % (n)	9% (4)	13% (6)	6% (3)	4% (2)
PR, % (n)	69% (31)	56% (25)	28% (15)	31% (17)
SD, % (n)	22% (10)	29% (13)	30% (16)	33% (18)
PD, % (n)	0%, (0)	2% (1) ^c	30% (16)	22% (12)
Patients ongoing, % (n)	25.7% (9)	29% (13)	5.6% (1)	0% (0)
DoR, median mo, (95% CI)	8.3 (5.5–13.8)	10.9 (7.2–NR)	14.7 (7.6–NR)	13 (5.6–NR)
PFS, median mo (95% CI)	13.8 (8.4–16.4)	13.8 (10.7–22.0)	5.6 (3.3–11.1)	11.1 (3.7–14.6)

SD = stable disease.

Morschhauser F, et al. International Conference on Malignant Lymphoma (ICML). 2019.

Phase 2 Study of Tazemetostat in R/R FL Patients Results: Tumor Change for MT EZH2

Tumor change from baseline for MT EZH2 FL patients

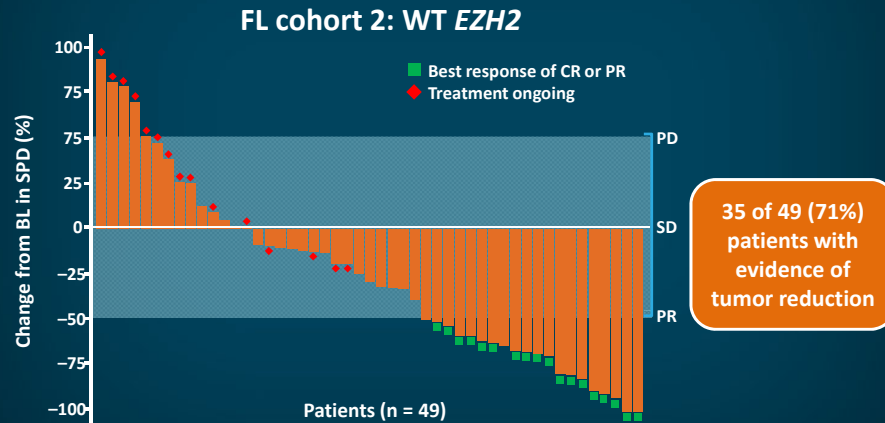


SPD = sum of the product of diameters.

Morschhauser F, et al. International Conference on Malignant Lymphoma (ICML). 2019.

Phase 2 Study of Tazemetostat in R/R FL Patients Results: Tumor Change for WT EZH2

Tumor change from baseline for WT EZH2 FL patients



Morschhauser F, et al. International Conference on Malignant Lymphoma (ICML). 2019.

Phase 2 Study of Tazemetostat in R/R FL Patients Results: Activity and DoR

Activity and durability observed across both cohorts

Endpoint	Response Evaluable Population	
	MT EZH2 (n = 43)	WT EZH2 (n = 53)
Median time to first response, mo (range)	4.2 (3.5–5.4)	3.7 (2.1–3.8)
Median DoR, mo (95% CI)	8.3 (4.0–12.7)	13.0 (7.3–NE)
Median PFS, mo (95% CI)	11.1 (8.4–15.7)	5.7 (3.5–11.1)
Median OS, mo (95% CI)	NR (NE–NE)	38.4 (25.0–NE)
Median follow-up, mo (range)	15.9 (0.4–40.3)	24.9 (0.3–46.0)

Maximum DoR MT EZH2 = 22.2 months; WT EZH2 = 22.6 months

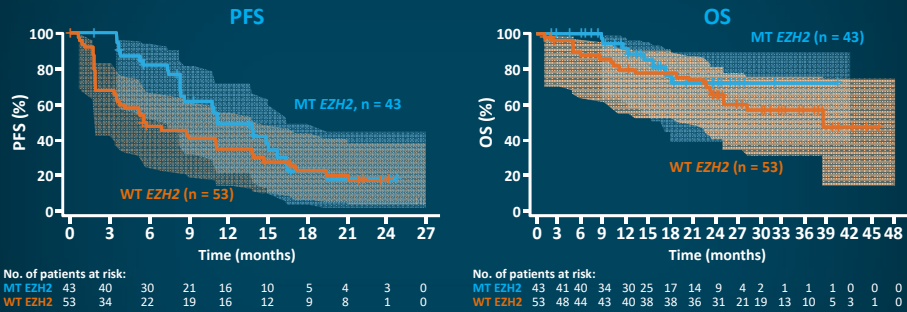
- 11 (24%) patients enrolled in past 12 months
- 17 (38%) patients ongoing

NE = not estimable.

Morschhauser F, et al. International Conference on Malignant Lymphoma (ICML). 2019.

Phase 2 Study of Tazemetostat R/R FL Patients Results: PFS and OS

Landmark analysis for responders in WT EZH2



Endpoint	Response-Evaluable Population	
	MT EZH2 (n = 43)	WT EZH2 (n = 53)
Median PFS, mo (95% CI)	11.1 (8.4–15.7)	5.7 (3.5–11.1)
Median OS, mo (95% CI)	NR (NE–NE)	38.4 (25.0–NE)

Morschhauser F, et al. International Conference on Malignant Lymphoma (ICML). 2019.

Phase 2 Study of Tazemetostat in R/R FL Patients Safety and AEs in ≥10% Patients

Category, n (%)	All TEAEs (N = 99)		TRAEs (N = 99)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Nausea	24 (24)	0 (0)	20 (20)	0 (0)
Asthenia	19 (19)	4 (4)	15 (15)	2 (2)
Diarrhea	18 (18)	0 (0)	12 (12)	0 (0)
Fatigue	17 (17)	2 (2)	12 (12)	1 (1)
Alopecia	17 (17)	0 (0)	14 (14)	0 (0)
Cough	16 (16)	0 (0)	2 (2)	0 (0)
URTI	15 (15)	0 (0)	1 (1)	0 (0)
Bronchitis	15 (15)	0 (0)	3 (3)	0 (0)
Anemia	14 (14)	5 (5)	9 (9)	2 (2)
Abdominal pain	12 (12)	1 (1)	2 (2)	0 (0)
Headache	12 (12)	0 (0)	5 (5)	0 (0)
Vomiting	12 (12)	2 (2)	6 (6)	1 (1)
Back pain	11 (11)	0 (0)	0 (0)	0 (0)
Pyrexia	10 (10)	0 (0)	2 (2)	0 (0)
Thrombocytopenia	10 (10)	5 (5)	8 (8)	3 (3)

- Treatment with tazemetostat was generally well tolerated
 - 5% patients discontinued treatment due to a treatment-related AE (TRAE)
 - 9% patients had a dose reduction due to a TRAE
 - Low rate of grade ≥3 TRAEs
- No treatment-related deaths

Morschhauser F, et al. International Conference on Malignant Lymphoma (ICML). 2019.

Phase 2 Study of Tazemetostat in R/R FL Patients Conclusion

- Tazemetostat, a first-in-class EZH2 inhibitor, demonstrates durable, single-agent antitumor activity in difficult-to-treat patients with relapsed/refractory FL
 - ORR of 77% and 34% in MT and WT EZH2, respectively
 - All patients in MT cohort and majority of patients in WT cohort demonstrated a reduction in tumor volume
 - Durable clinical activity across both MT and WT cohorts, with patients on therapy up to 23 months and responses continuing to deepen over time.
 - PFS of 11.1 and 5.7 months in MT and WT EZH2, respectively
- Tazemetostat is well tolerated in FL patients
 - Associated with a low frequency of drug-related AEs, including grade ≥ 3 TEAEs, and low frequency of dose reduction or discontinuation due to AEs

Morschhauser F, et al. International Conference on Malignant Lymphoma (ICML). 2019.

Please scan the QR codes below to watch the
anti-tumor mechanism of action of Tazemetostat

2D



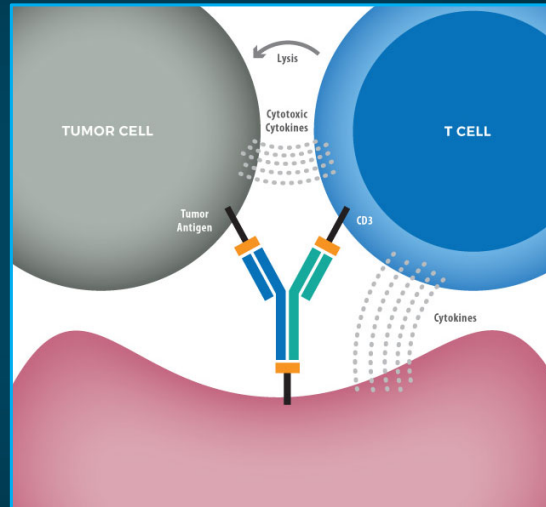
3D



To request a pair of glasses to view the 3D animations,
please email jmcmullen@medlearninggroup.com

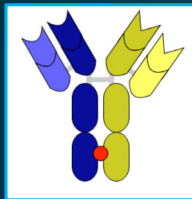
Bispecific Antibodies (BsAbs)

- **Off shelf**—rapid access, relative ease of delivery
- **Adaptable**—lack of persistence and ability to modulate dosing may improve tolerability



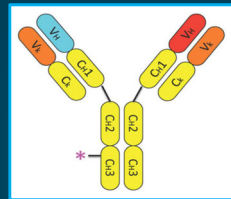
Next Generation B-Cell BsAbs

Mosunetuzumab¹



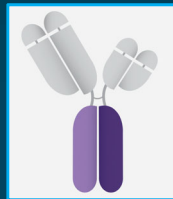
CD3 x CD20 knobs-in-hole
IgG1 Fc BsAb

REGN1979²



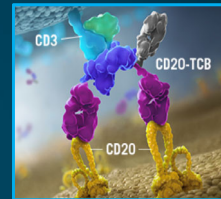
CD3 x CD20 common LC
IgG4 Fc BsAb

Xmab13676³



CD3 (scFv) x CD20 (Fab)
Fc BsAb

RG6026 (CD20-Tcb)⁴



CD3 (Fab) x CD20 (Fab x2)
Fc BsAb

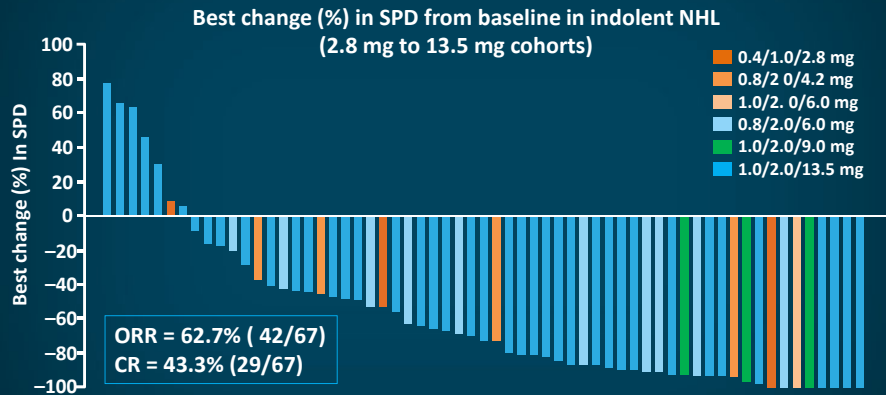
Recent studies presented efficacy data for BsAbs in indolent NHL (mostly FL)

CD = cluster of differentiation; IgG = immunoglobulin G; Fc = fragment crystallizable (region); LC = light chain; sc = single-chain; Fab = antigen-binding fragment.

1. Schuster SJ, et al. *Blood*. 2019;134(suppl 1): abstract 6. 2. Bannerji R, et al. *Blood*. 2019;134(suppl 1): abstract 762. 3. Patel K, et al. *Blood*. 2019;134(suppl 1): abstract 4079. 4. Dickinson MJ, et al. *Hematol Oncol*. 2019;37 (2 suppl):92-93 (abstract 053).

Phase 1 Mosunetuzumab in R/R NHL

Objective response rate in indolent NHL



Indolent NHL FL (Grade 1–3), marginal zone lymphoma, and small lymphocytic lymphoma

Schuster SJ, et al. *Blood*. 2019;134(suppl 1): abstract 6.

Phase 1 Mosunetuzumab in R/R NHL: AEs

AEs with Mosunetuzumab (N = 270)	
All grade AEs in >15% pts	
Cytokine-release syndrome	78 (28.9%)
Neutropenia	65 (24.1%)
Fatigue	55 (20.4%)
Hypophosphatemia	52 (19.3%)
Diarrhea	45 (16.7%)
Pyrexia	44 (16.3%)
Headache	42 (15.6%)
Nausea	41 (15.2%)
Grade 3/4 AEs in >5% pts	
Neutropenia	59 (21.8%)
Hypophosphatemia	36 (13.3%)
Anemia	24 (8.9%)

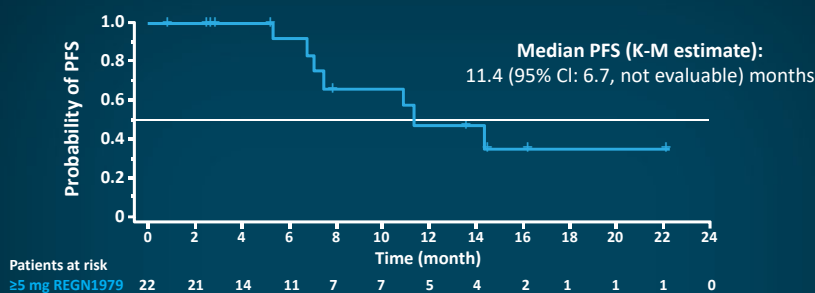
Cytokine-release syndrome was most common AE

- Mostly Gr 1 = 20%
- Gr 2 = 7.8%
- Gr 3 = 1.1% (uncommon)

Gr = grade.

Schuster SJ, et al. *Blood*. 2019;134(suppl 1): abstract 6.

Phase 1 REGN1979 in R/R NHL (2L+)



Censored patients for current K-M estimates are mostly due to relatively short follow-up

Patients with FL Gr 1–3a Treated with 25 mg REGN1979	n = 22
Median duration of follow-up (range), months	6.8 (1.0–22.1)
Number of patients with ongoing responses at the last tumor assessment	14 of 21
Number of patients with ongoing CRs at the last tumor assessment	12 of 17

K-M, Kaplan-Meier.

Bannerji R, et al. *Blood*. 2019;134(suppl 1): abstract 762.

Bispecific Antibodies—Conclusions

- High ORR and CR rates at active dosing in phase 1 studies are encouraging
- Potential ability to dose more broadly than with CAR-T
- Potential to help meet several unmet needs in further investigation
 - Unmet need #1 (reduce POD24) and #2 (reduce relapse)
 - Lenalidomide + anti-CD20 + BsAb?
 - Chemoimmunotherapy + BsAb?
 - BsAb alone?
 - Unmet need #3 (improve therapy for R/R FL)
 - BsAb alone?
 - BsAb + CAR-T?

CAR-T = chimeric antigen receptor T cell (therapy).

ASH 2020 Update

- BRUIN—global, phase 1/2 trial: BTK inhibitor¹
 - Second line and beyond, LOXO-305 monotherapy in CLL/SLL or NHL
 - Phase 2 endpoints: primary = ORR; secondary = DoR, OS, safety
 - AEs: fatigue (20%), diarrhea (17%), contusion (13%)
 - FL efficacy was evaluable in 8 pts, responses observed in 4 pts
- ROR1-targeting antibody-drug conjugate (VLS-101), phase 1 trial²
 - Heavily pre-treated CLL, DLBCL, FL, MCL, MZL, or RTL
 - Neuropathy and neutropenia were reversible
 - Durable objective responses in advanced MCL or DLBCL, not other tumors
- Zuma-5—multicenter, phase 2 trial: axicabtagene ciloleucel (Axi-Cel autologous anti-CD19 (CAR-T) therapy³
 - R/R FL or MZL after ≥2 lines of therapy
 - At median f/u of 17.5 months, ORR/CR = 94%/80% with FL and 85%/60% with MZL
 - Grade ≥3 AEs in 86% iNHL; neutropenia, anemia. Grade ≥3 CRS 7% and neurologic events 19% of pts with iNHL; most resolved by data cutoff.

BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; ROR = receptor tyrosine kinase-like orphan receptor; DLBCL = diffuse large B-cell lymphoma; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; RTL = Richter transformation lymphoma; iNHL = indolent NHL.

1. Mato AR, et al. ASH 2020:abstract 542. 2. Wang M, et al. ASH 2020:abstract 121. 3. Jacobson C, et al. ASH 2020:abstract 700.

Take Home for FL

- Non-chemotherapy options are increasing!
 - Multiple novel therapies are coming in R/R FL
 - CD3-CD20 BsAbs and tazemetostat promising single-agent therapies
 - Both agents should be studied in rational combination therapies
- Early progressing (POD24) FL patients have high-risk disease
- Non-chemotherapy-based treatments are emerging as preferred options in 2nd-line+ FL
- Cellular/immunotherapies are blossoming in lymphoma
 - CAR T-cell therapy may offer durable remission, but timing is sometime challenging; need to plan for high risk patients early!


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Going Beyond the Practice Guidelines: Relapsed/Refractory Follicular Lymphoma

Resource	Address
Solal-Céligny P, et al. Follicular lymphoma international prognostic index. <i>Blood</i> . 2004;104:1258-1265.	https://pubmed.ncbi.nlm.nih.gov/15126323/
Casulo C, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: An analysis from the National LymphoCare Study. <i>J Clin Oncol</i> . 2015;33:2516-2522.	https://pubmed.ncbi.nlm.nih.gov/26124482/
Link BK, et al. Second-line and subsequent therapy and outcomes for follicular lymphoma in the United States: Data from the observational National LymphoCare Study. <i>Br J Haematol</i> . 2019;184:660-663.	https://pubmed.ncbi.nlm.nih.gov/29611177/
Freedman A, Jacobsen E. Follicular lymphoma: 2020 update on diagnosis and management. <i>Am J Hematol</i> . 2020;95:316-327.	https://pubmed.ncbi.nlm.nih.gov/31814159/

Treatment of Relapsed/Refractory Follicular Lymphoma

Resource	Address
Flinn IW, et al. First-line treatment of patients with indolent non-Hodgkin lymphoma or mantle-cell lymphoma with bendamustine plus rituximab versus R-CHOP or R-CVP: Results of the BRIGHT 5-year follow-up study. <i>J Clin Oncol</i> . 2019;37:984-991.	https://pubmed.ncbi.nlm.nih.gov/30811293/
Rummel MJ, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: An open-label, multicentre, randomised, phase 3 non-inferiority trial. <i>Lancet</i> . 2013;381:1203-1210.	https://pubmed.ncbi.nlm.nih.gov/23433739/
Bachy E, et al. Sustained progression-free survival benefit of rituximab maintenance in patients with follicular lymphoma: Long-term results of the PRIMA Study <i>J Clin Oncol</i> . 2019;37:2815-2824.	https://pubmed.ncbi.nlm.nih.gov/31339826/
Morschhauser F, et al. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. <i>N Engl J Med</i> . 2018;379:934-947.	https://pubmed.ncbi.nlm.nih.gov/30184451/
Leonard JP, et al. AUGMENT: A Phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. <i>J Clin Oncol</i> . 2019;37:1188-1199.	https://pubmed.ncbi.nlm.nih.gov/30897038/
Patel K, et al. Duvelisib for CLL/SLL and follicular non-Hodgkin lymphoma. <i>Blood</i> . 2019;134:1573-1577.	https://pubmed.ncbi.nlm.nih.gov/31554637/

von Keudell G, Moskowitz AJ. The Role of PI3K inhibition in lymphoid malignancies. <i>Curr Hematol Malig Rep</i> . 2019;14:405-413.	https://pubmed.ncbi.nlm.nih.gov/31359259/
Gopal AK, et al. PI3K δ inhibition by idelalisib in patients with relapsed indolent lymphoma. <i>N Engl J Med</i> . 2014;370:1008-1018.	https://pubmed.ncbi.nlm.nih.gov/24450858/
Dreyling M, et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. <i>J Clin Oncol</i> . 2017;35:3898-3905.	https://pubmed.ncbi.nlm.nih.gov/28976790/
Flinn IW, et al. DYNAMO: A phase II study of duvelisib (IPI-145) in patients with refractory indolent non-Hodgkin lymphoma. <i>J Clin Oncol</i> . 2019;37:912-922.	https://pubmed.ncbi.nlm.nih.gov/30742566/

Treatment of EZH2 Mutations in Follicular Lymphoma

Resource	Address
Gan L, et al. Epigenetic regulation of cancer progression by EZH2: From biological insights to therapeutic potential. <i>Biomark Res</i> . 2018;6:10.	https://pubmed.ncbi.nlm.nih.gov/29556394/
Béguelin W, et al. EZH2 is required for germinal center formation and somatic EZH2 mutations promote lymphoid transformation. <i>Cancer Cell</i> . 2013;23:677-692.	https://pubmed.ncbi.nlm.nih.gov/23680150/
Italiano A, et al. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: A first-in-human, open-label, phase 1 study. <i>Lancet Oncol</i> . 2018;19:649-659.	https://pubmed.ncbi.nlm.nih.gov/29650362/
Bödör C, et al. EZH2 mutations are frequent and represent an early event in follicular lymphoma. <i>Blood</i> . 2013;122:3165-3168.	https://pubmed.ncbi.nlm.nih.gov/24052547/
Morschhauser F, et al. Interim update from a phase 2 multicenter study of tazemetostat, an EZH2 inhibitor, in patients with relapsed or refractory follicular lymphoma. <i>Hematol Oncol</i> . 2019;37: 154-156.	https://www.epizyme.com/wp-content/uploads/2019/11/ICML_2019_FL_Morschhauser_105_oral-presentation_FINAL06212019.pdf
Schuster SJ, et al. Mosunetuzumab induces complete remissions in poor prognosis non-Hodgkin lymphoma patients, including those who are resistant to or relapsing after chimeric antigen receptor T-cell (CAR-T) therapies, and is active in treatment through multiple lines. <i>Blood</i> . 2019;134(suppl 1):6.	https://ashpublications.org/blood/article/134/Supplement_1/6/427814/Mosunetuzumab-Induces-Complete-Remissions-in-Poor
Bannerji R, et al. Clinical activity of REGN1979, a bispecific human, anti-CD20 x anti-CD3 antibody, in patients with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL). <i>Blood</i> . 2019;134(suppl 1):762.	https://ashpublications.org/blood/article/134/Supplement_1/762/426951/Clinical-Activity-of-REGN1979-a-Bispecific-Human