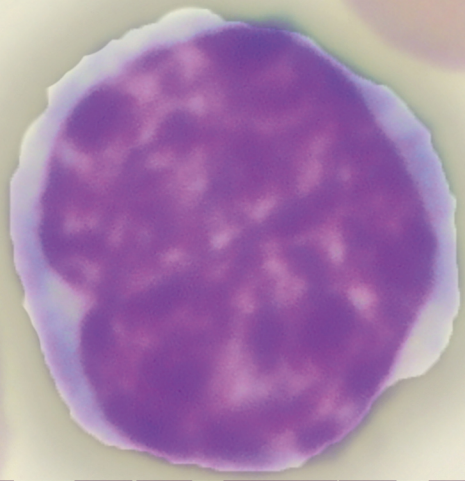
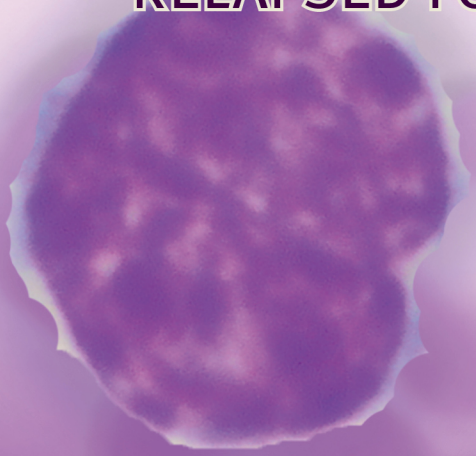


A 3D VIEW-

Going Beyond the Practice Guidelines to Leverage Mutations in the Pursuit of Unique Treatment Approaches:

RELAPSED FOLLICULAR LYMPHOMA



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

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

FACULTY CHAIR

John M. Pagel, MD, PhD
Affiliate Associate Member
Division of Oncology
University of Washington School of Medicine
Chief of Hematologic Malignancies Program
Swedish Cancer Institute
Seattle, WA

FACULTY PRESENTERS

Utkarsh Acharya, DO, FACP
Attending Physician, Hematologic Malignancies & Cellular Therapy
Dana-Farber Cancer Institute
Instructor in Medicine
Harvard Medical School
Boston, MA

John Burke, MD
Associate Chair
US Oncology Hematology Research Program
Rocky Mountain Cancer Centers
Aurora, CO

Nathan H. Fowler, MD
Professor
The University of Texas MD Anderson Cancer Center
Houston, TX

Ryan W. Jacobs, MD
Department of Hematology, Lymphoma Division
Assistant Professor of Medicine
Levine Cancer Institute/Atrium Health
Charlotte, NC

Amitkumar Mehta, MD
Associate Professor
Director, Lymphoma Program
O'Neal Comprehensive Cancer Center at UAB
Birmingham, AL

Loretta J. Nastoupil, MD
Associate Professor
Section Chief, Indolent Lymphoma
Department of Lymphoma/Myeloma
UT MD Anderson Cancer Center
Houston, TX

Nishitha Reddy, MD, MSCI
Associate Professor of Medicine
Vanderbilt University Medical Center
Nashville, TN

Nirav N. Shah, MD
Associate Professor of Medicine
Division of Hematology/Oncology
Medical College of Wisconsin
Milwaukee, WI

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. John M. Pagel has received consulting fees from Gilead, AstraZeneca, Loxo Oncology, and BeiGene.

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 nothing to disclose.

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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2. Participate in the live virtual activity.
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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

Chief of Hematologic Malignancies

Swedish Cancer Institute

Seattle, WA

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.

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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	$<1 \times 10^{9}$/L	0.008	1.27	1.06–1.52
LDH	>ULN	$<10^{-3}$	1.50	1.26–1.77

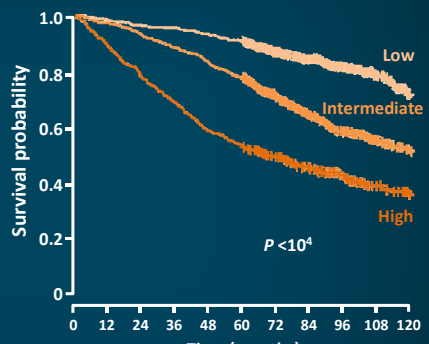
Outcome and relative risk of death according to risk group as defined by FLIPI (N = 1795)

Risk Group	No. of factors	Patients	OS, % (SE) 5-yr	OS, % (SE) 10-yr	RR	95% CI
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.

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

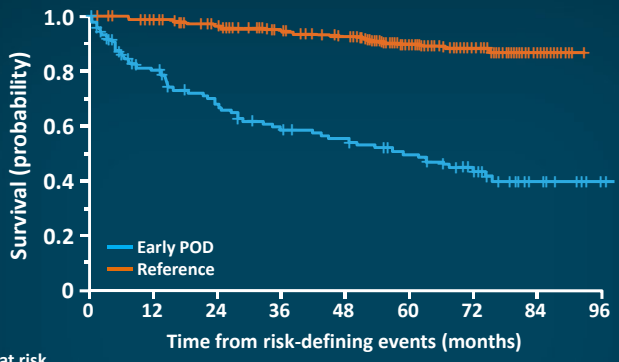
Survival of the 1795 patients according to risk group as defined by the FLIPI



No. of events											
Low	–	12	25	29	46	60	83	95	106	113	125
INTMD	–	19	49	79	118	150	192	225	247	255	261
High	–	54	109	152	202	229	245	260	268	274	278

No. at risk											
Low	641	629	616	612	595	581	450	337	241	157	93
INTMD	670	651	621	591	552	519	385	263	178	108	68
High	484	430	375	332	282	255	193	139	98	56	33

Follicular Lymphoma: POD24



No. at risk									
Early POD	110	82	66	56	50	42	32	14	3
Reference	420	408	387	363	344	253	145	34	0

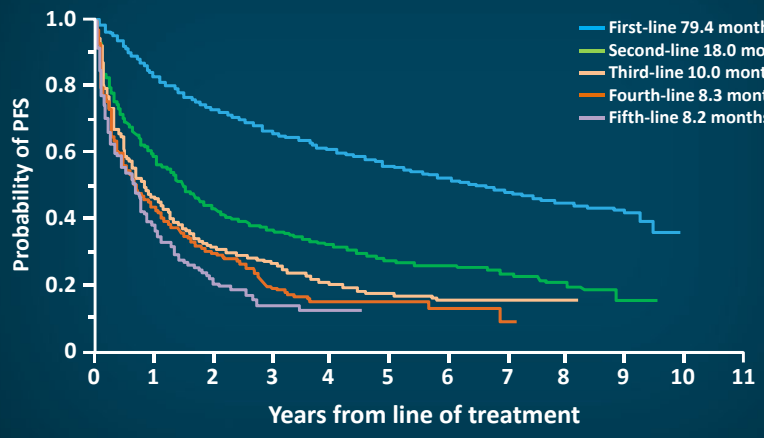
- Early progression: <24 months after R-chemoimmunotherapy, or POD24; poor prognostic marker
- Many of these patients have occult transformation to DLBCL

POD = progression of disease; POD24 = POD within 24 months; DLBCL = diffuse large B-cell lymphoma; R = rituximab.

Casulo C, et al. *J Clin Oncol*. 2015;33:2516-2522.

Defining Unmet Needs: PFS by Treatment Line

National LymphoCare Study



PFS = progression-free survival.

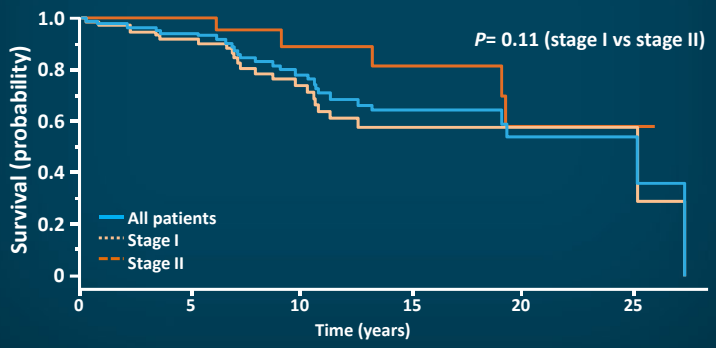
Link BK, et al. *Br J Haematol*. 2019;184:660-663.

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 fractions[3]



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 trial[1] Phase 3 BR vs R-CHOP	**BRIGHT trial[2] Phase 3 BR vs R-CHOP/R-CVP**	**Gallium trial[3] Phase 3 G- vs R- chemo**	**RELEVANCE trial[4] Phase 3 R^2 (lenalidomide + R) vs R-chemo**	**PRIMA[5,6] Phase 3 Rituximab maintenance**
• BR superior to R-CHOP	• Trend toward PFS benefit with BR vs R-CHOP/ R-CVP	• Superior PFS with G- vs R-chemo, but no difference in OS • More grade 3-5 AEs with G (75% vs 68%) • Approval in 2017 for initial chemotherapy and maintenance G	• Similar efficacy with R^2 compared with R-chemotherapy • Less hematologic toxicity with R^2, but more grade 3/4 cutaneous toxicity (7% vs 1%)	• Superior PFS (and TTNT), but not OS, 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
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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?

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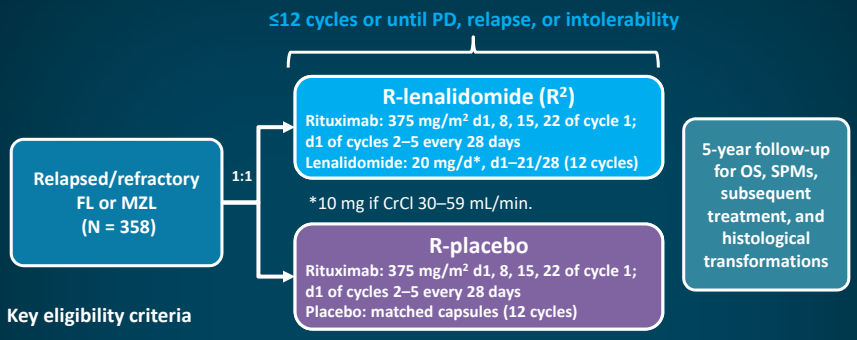
C. Begin ibritumomab tiuxetan
D. Begin tazometostat
E. A, B and D
F. All of the above

AUGMENT: Double-Blind, Phase 3, R^2 vs R



Key eligibility criteria

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

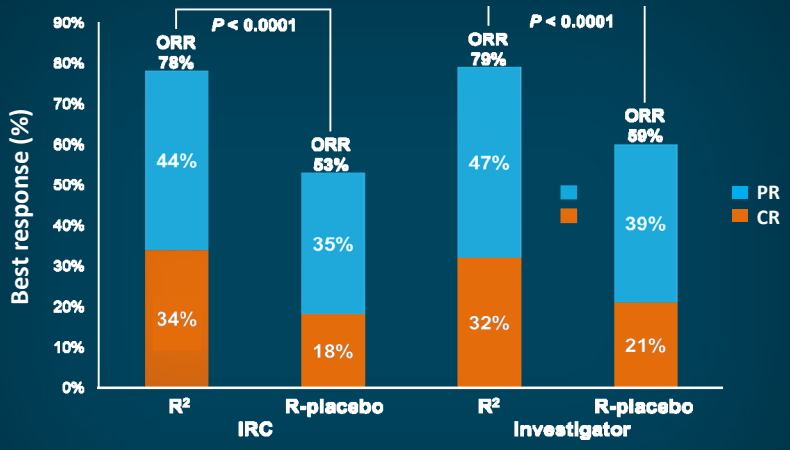
Prophylactic anticoagulation/antiplatelet treatment recommended for at-risk patients

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.

R^2 vs R: Response

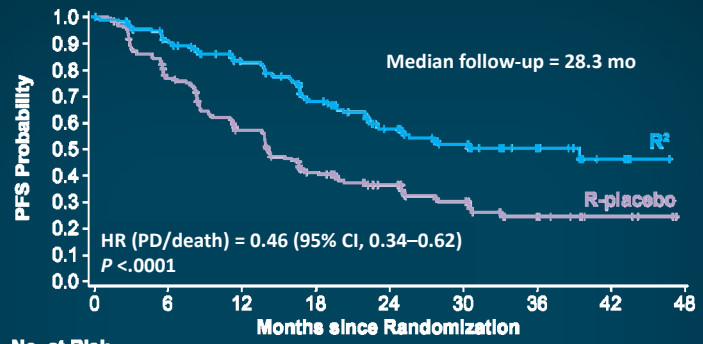


Median DoR was 36.6 mo (95% CI, 22.9–NR) for R2 vs 21.7 mo (95% CI, 12.8–27.6) for R-placebo, HR = 0.53 (95% CI, 0.36–0.79), *P*= .0015

PR = partial response; CR = complete response; DoR = duration of response; mo = month(s); NR = not reached; HR = hazard ratio.

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

Primary Endpoint: PFS (ITT, IRC)



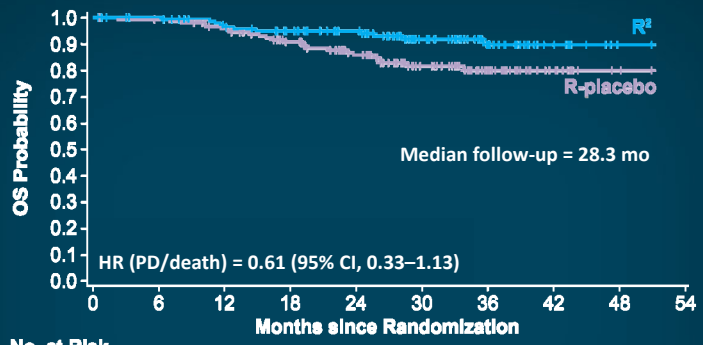
No. at Risk									
R²	178	148	124	91	59	39	20	7	0
R-placebo	180	132	92	58	40	26	10	4	0

Median PFS	R² (n = 178)	R-PBO (n = 180)	HR (95% CI)	*P* Value
By IRC, mo (95% CI)	39.4 (22.9–NR)	14.1 (11.4–16.7)	0.46 (0.34–0.62)	<.0001
By investigator, mo (95% CI)	25.3 (21.2–NR)	14.3 (12.4–17.7)	0.51 (0.38–0.69)	<.0001

ITT = intention to treat; PBO = placebo.

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

Overall Survival In Patients With FL

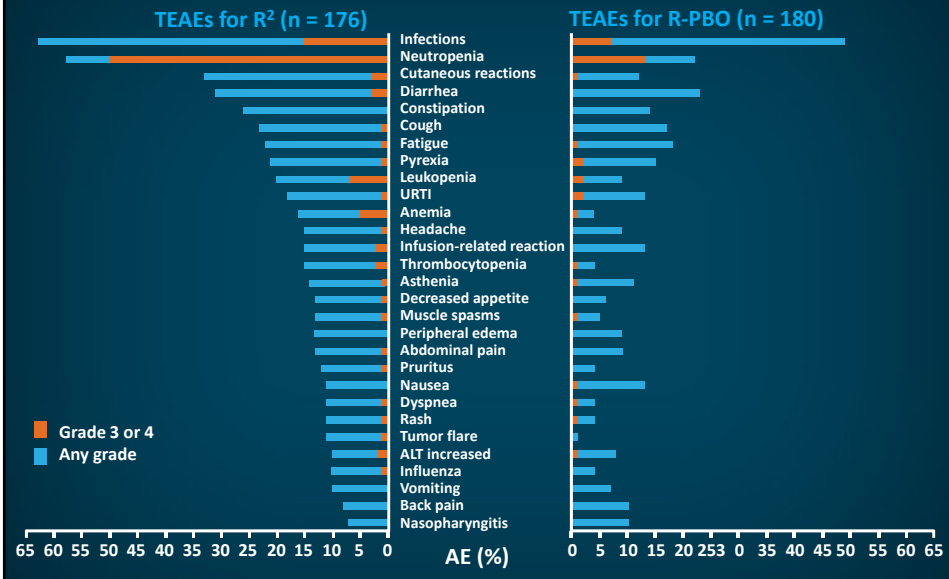


No. at Risk										
R²	147	142	130	121	105	70	39	13	1	0
R-placebo	148	145	137	117	94	64	35	12	2	0

- 41 total deaths (15 R^2, 26 R-placebo)
- 2-year OS was 93% for R^2 and 87% for R-placebo

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

R^2 vs R Treatment-Emergent AEs (TEAEs)



AE = adverse event; URTI = upper respiratory tract infection; ALT = alanine aminotransferase.

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

R^2 vs R: Other Data of Interest

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

AEs of interest (safety), n (%)	R^2 (n = 176)	R-PBO (n = 180)
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.

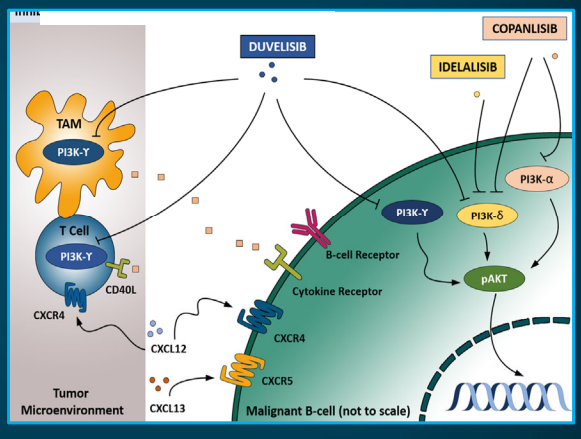
AUGMENT (R^2 vs R)
Conclusions

- Higher response rates and longer PFS with R^2 compared with R-alone
- Benefit seen across all groups except for marginal-zone lymphoma
- Survival advantage observed for follicular lymphoma group treated with R^2
- R^2 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

Targeting PI3Ki Isoforms



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

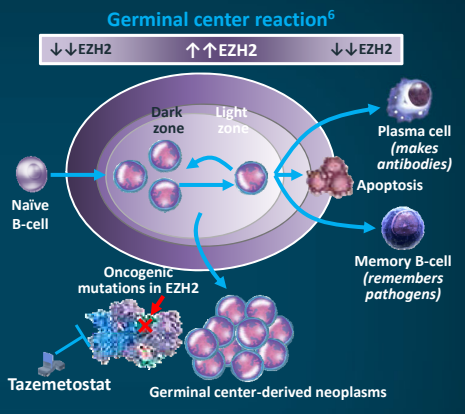
2D

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 decisions[1]
- EH2 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, transforming into cancer[2]
- EZH2 biology is relevant in MT and wild-type WT EZH2 FL[2]
- ~20% of patients with FL have EZH2 gain-of-function mutations[3,4]



Tazemetostat is first-in-class, selective, oral inhibitor of EZH2 has shown antitumor activity in patients with either MT or WT EZH2[4,5]

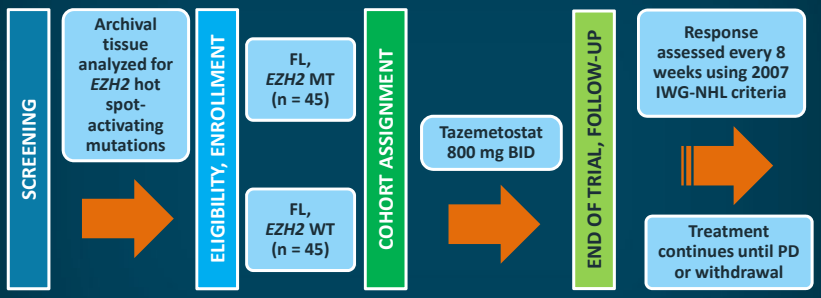
EZH2 = enhancer of zeste homolog 2; MT = mutant type; WT = wild-type.

1. Gan L, et al. *Biomark Res.* 2018:6:10. 2. Béguelin W, et al. *Cancer Cell.* 2013;23:677-692. 3. Bödör 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)°	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)

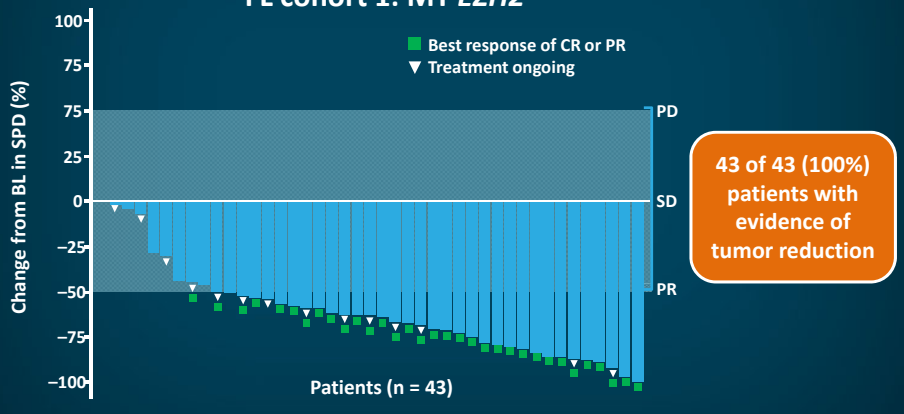
SD = stable disease.

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

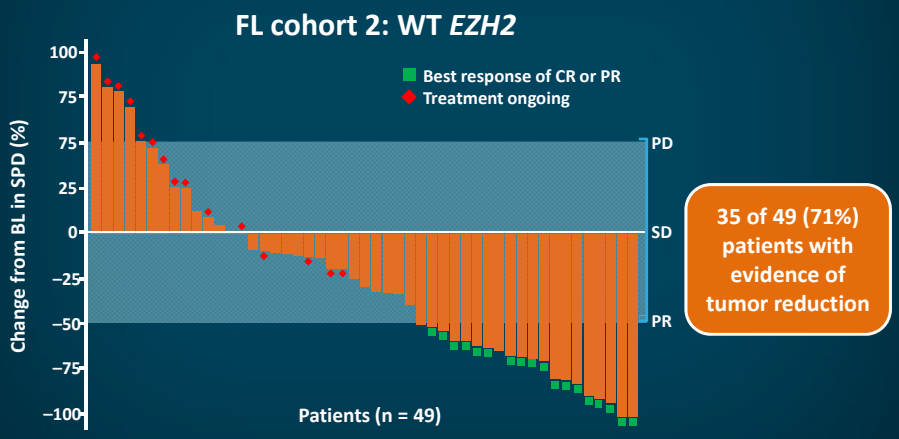


SPD = sum of the product of diameters.

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

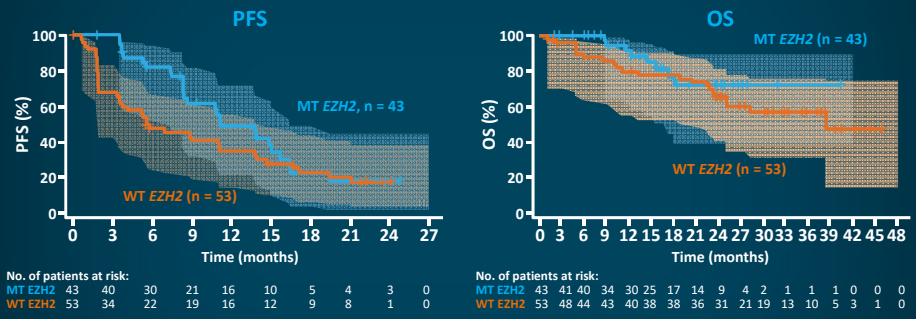
NE = not estimable.

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

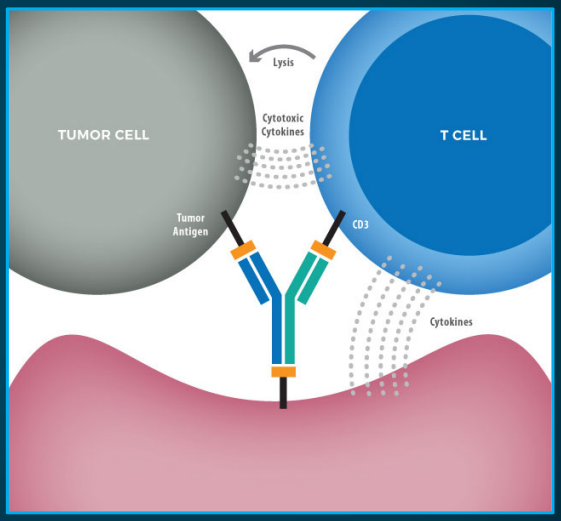
2D

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

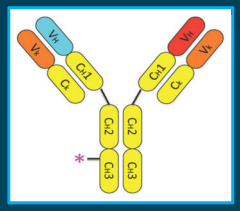


Next Generation B-Cell BsAbs

Mosunetuzumab[1]

CD3 x CD20 knobs-in-hole IgG1 Fc BsAb

REGN1979[2]

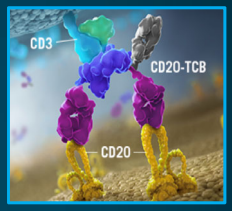


CD3 x CD20 common LC IgG4 Fc BsAb

Xmab13676[3]

CD3 (scFv) x CD20 (Fab) Fc BsAb

RG6026 (CD20-Tcb)[4]



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

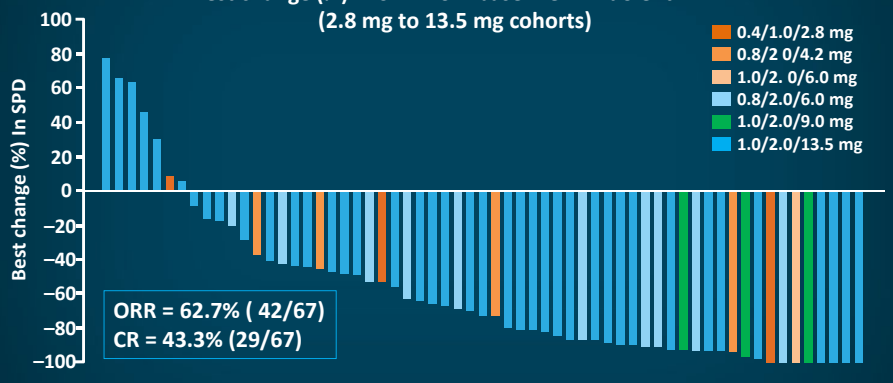
Recent studies presented efficacy data for BsAbs in indolent NHL (mostly FL)

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%)

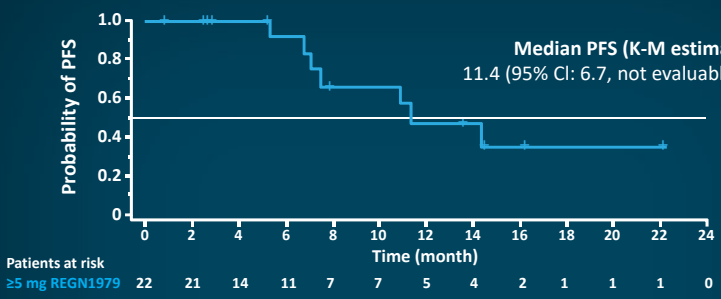
Cytokine-release syndrome was most common AE

- **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 inhibitor[1]
  - 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 trial[2]
  - 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) therapy[3]
  - 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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Thank you!

Going Beyond the Practice Guidelines: Relapsed/Refractory Follicular Lymphoma

Resource	Address
Solal-Céligny P, et al. Follicular lymphoma international prognostic index. *Blood*. 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. *J Clin Oncol*. 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. *Br J Haematol*. 2019;184:660-663.	https://pubmed.ncbi.nlm.nih.gov/29611177/
Freedman A, Jacobsen E. Follicular lymphoma: 2020 update on diagnosis and management. *Am J Hematol*. 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. *J Clin Oncol*. 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. *Lancet*. 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 *J Clin Oncol*. 2019;37:2815-2824.	https://pubmed.ncbi.nlm.nih.gov/31339826/
Morschhauser F, et al. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. *N Engl J Med*. 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. *J Clin Oncol.* 2019;37:1188-1199.	https://pubmed.ncbi.nlm.nih.gov/30897038/
Patel K, et al. Duvelisib for CLL/SLL and follicular non-Hodgkin lymphoma. *Blood.* 2019;134:1573-1577.	https://pubmed.ncbi.nlm.nih.gov/31554637/

von Keudell G, Moskowitz AJ. The Role of PI3K inhibition in lymphoid malignancies. *Curr Hematol Malig Rep*. 2019;14:405-413.	https://pubmed.ncbi.nlm.nih.gov/31359259/
Gopal AK, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 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. *J Clin Oncol*. 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. *J Clin Oncol*. 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. *Biomark Res.* 2018:6:10.	https://pubmed.ncbi.nlm.nih.gov/29556394/
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