

Dissecting the Decision: Clinical and Nursing Investigators Provide Practical Perspectives on Key Issues in the Management of Follicular Lymphoma

**Wednesday, November 18, 2020
5:00 PM – 6:00 PM ET**

Faculty

**Robin Klebig, APRN, CNP, AOCNP
Ann S LaCasce, MD, MMSc**

Moderator

Neil Love, MD

Commercial Support

This activity is supported by an educational grant from Bristol-Myers Squibb Company.

Dr Love — Disclosures

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Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Klebig — Disclosures

No financial interests or affiliations to disclose.

Dr LaCasce — Disclosures

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We Encourage Clinicians in Practice to Submit Questions

The image shows a Zoom meeting interface. At the top, there is a gallery view of six participants. The main area is a white slide with the text: "You may submit questions using the Zoom Chat option below". A large red arrow points downwards from this text. On the right side, there is a "Participants (10)" list with names and icons for audio and video. Below the list is a "Zoom Group Chat" window showing a message from "Me to Everyone" at 12:49 PM. At the bottom, there is a toolbar with icons for "Join Audio", "Start Video", "Invite", "Participants", "Share", "Chat", "Record", "Leave Meeting", "Mute Me", and "Raise Hand".

Feel free to submit questions now before the program begins and throughout the program.

Familiarizing Yourself with the Zoom Interface

How to answer poll questions

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Search

JS John Smith

MM Mary Major

RM Richard Miles

JN John Noakes

AS Alice Suarez

JP Jane Perez

RS Robert Stiles

JF Juan Fernandez

AK Ashok Kumar

JS Jeremy Smith

Quick Poll

Carfilzomib +/- dexamethasone

Pomalidomide +/- dexamethasone

Carfilzomib + pomalidomide +/- dexamethasone

Elotuzumab + lenalidomide +/- dexamethasone

Elotuzumab + pomalidomide +/- dexamethasone

Daratumumab + lenalidomide +/- dexamethasone

Daratumumab + pomalidomide +/- dexamethasone

Daratumumab + bortezomib +/- dexamethasone

Ixazomib + Rd

Other

Submit

1. Carfilzomib +/- dexamethasone

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3. Carfilzomib + pomalidomide +/- dexamethasone

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9. Ixazomib + Rd

10. Other

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Upcoming Webinars

**Thursday, November 19, 2020
12:00 PM – 1:00 PM ET**

**Meet The Professor: Management
of Multiple Myeloma**

Faculty

Kenneth C Anderson, MD

Moderator

Neil Love, MD

**Friday, November 20, 2020
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**Meet The Professor: Management
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Prof John G Gribben, MD, DSc, FMedSci

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**Meet The Professor:
Management of Ovarian
Cancer**

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**Tuesday, December 1, 2020
5:00 PM – 6:00 PM ET**

**Year in Review: Clinical Investigators
Provide Perspectives on the Most
Relevant New Publications, Data Sets
and Advances in Oncology
Prostate Cancer**

Faculty

Emmanuel S Antonarakis, MD
Andrew J Armstrong, MD, ScM

Moderator

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Upcoming Webinars

Friday, December 4, 2020

**Consensus or Controversy?
Investigators Discuss Clinical
Practice Patterns and Available
Research Data Guiding the
Management of Hematologic Cancers**

A 4-Part Friday Satellite Symposia Live Webinar
Series Preceding the 62nd ASH Annual Meeting

Moderator

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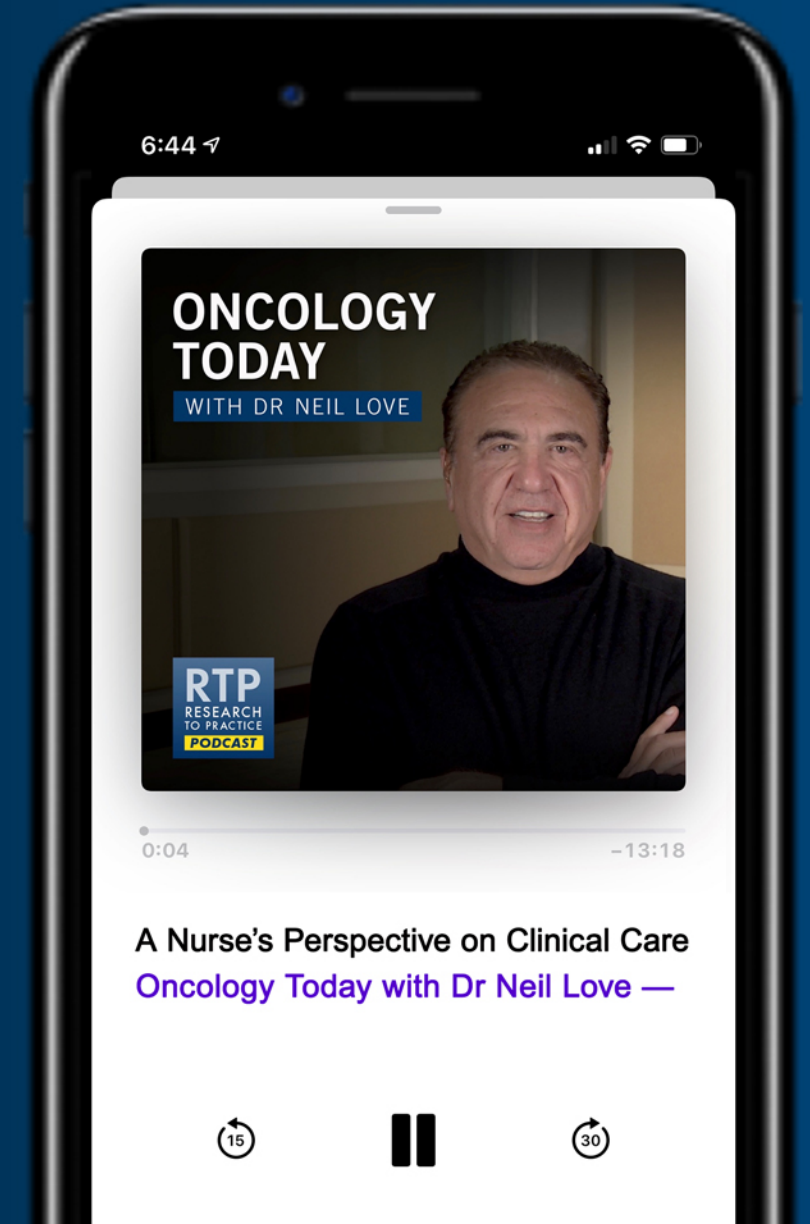
ONCOLOGY TODAY

WITH DR NEIL LOVE

A Nurse's Perspective on Clinical Care for Patients with Lung Cancer at Massachusetts General Hospital During COVID-19



MS KELLY GOODWIN
ONCOLOGY NURSE
MASSACHUSETTS GENERAL HOSPITAL



Thank you for joining us!

**CNE (NCPD) credit information will be
emailed to each participant tomorrow morning.**

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Robin Klebig, APRN, CNP, AOCNP

Nurse Practitioner

Assistant Professor of Medicine

Division of Hematology

Mayo Clinic

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Ann S LaCasce, MD, MMSc

Director, Dana-Farber/Mass General Brigham Fellowship in Hematology/Oncology

Associate Professor of Medicine, Harvard Medical School

Lymphoma Program

Dana-Farber Cancer Institute

Boston, Massachusetts

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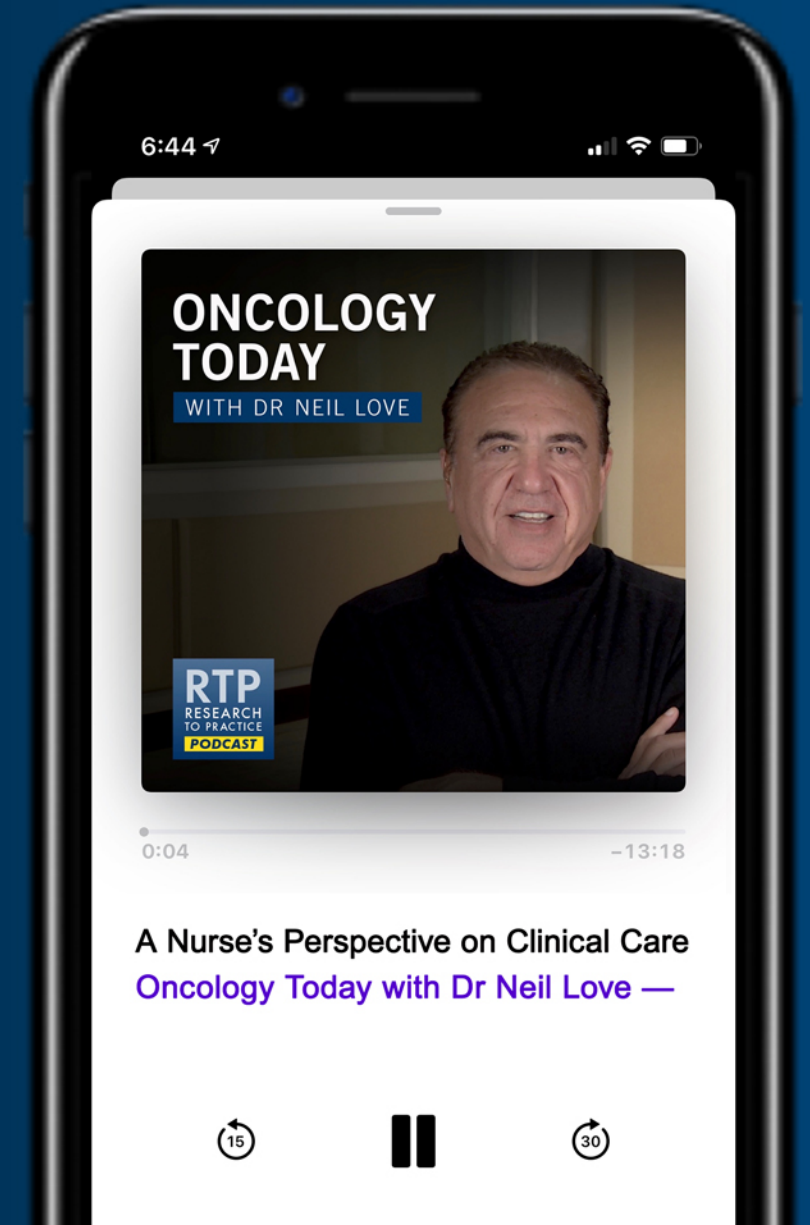
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Consensus or Controversy? Investigators Discuss Clinical Practice Patterns and Available Research Data Guiding the Management of Hematologic Cancers

A 4-Part Friday Satellite Symposia Live Webinar Series Preceding the 62nd ASH Annual Meeting

Friday, December 4, 2020

Multiple Myeloma

8:30 AM – 10:00 AM Pacific Time
(11:30 AM – 1:00 PM ET)

Chronic Lymphocytic Leukemia

12:00 PM – 1:30 PM Pacific Time
(3:00 PM – 4:30 PM ET)

Acute Myeloid Leukemia

3:00 PM – 4:30 PM Pacific Time
(6:00 PM – 7:30 PM ET)

Hodgkin and Non-Hodgkin Lymphoma

7:00 PM – 8:30 PM Pacific Time
(10:00 PM – 11:30 PM ET)

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Management of Follicular Lymphoma

Module 1: Newly Diagnosed Follicular Lymphoma (FL)

- Initiation of active therapy versus watchful waiting; indications for rituximab monotherapy
- Choice of systemic therapy for patients requiring treatment; importance of age, tumor bulk and symptomatology
- Amelioration of treatment-related side effects

Module 2: Management of Relapsed/Refractory (R/R) FL

- Factors affecting the sequencing of systemic therapy for R/R disease (eg, previous treatment, remission duration, symptomatology)
- Role of lenalidomide/rituximab in the management of R/R FL
- Available clinical research data with the FDA-approved PI3K inhibitors
- Recent FDA approval and current clinical role of tazemetostat
- Data with the use of CD19-directed CAR T-cell therapy for patients with R/R FL

Overview of Follicular Lymphoma

- 5-year relative survival rate: 89.0%
- Median age at diagnosis: 63 years
- Stage at diagnosis (percent of patients who present with):
 - Stage I disease = 25%
 - Stage II disease = 15%
 - Stage III disease = 26%
 - Stage IV disease = 27%

Considerations in the Choice of Therapy at Diagnosis or Relapse for Patients with FL

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

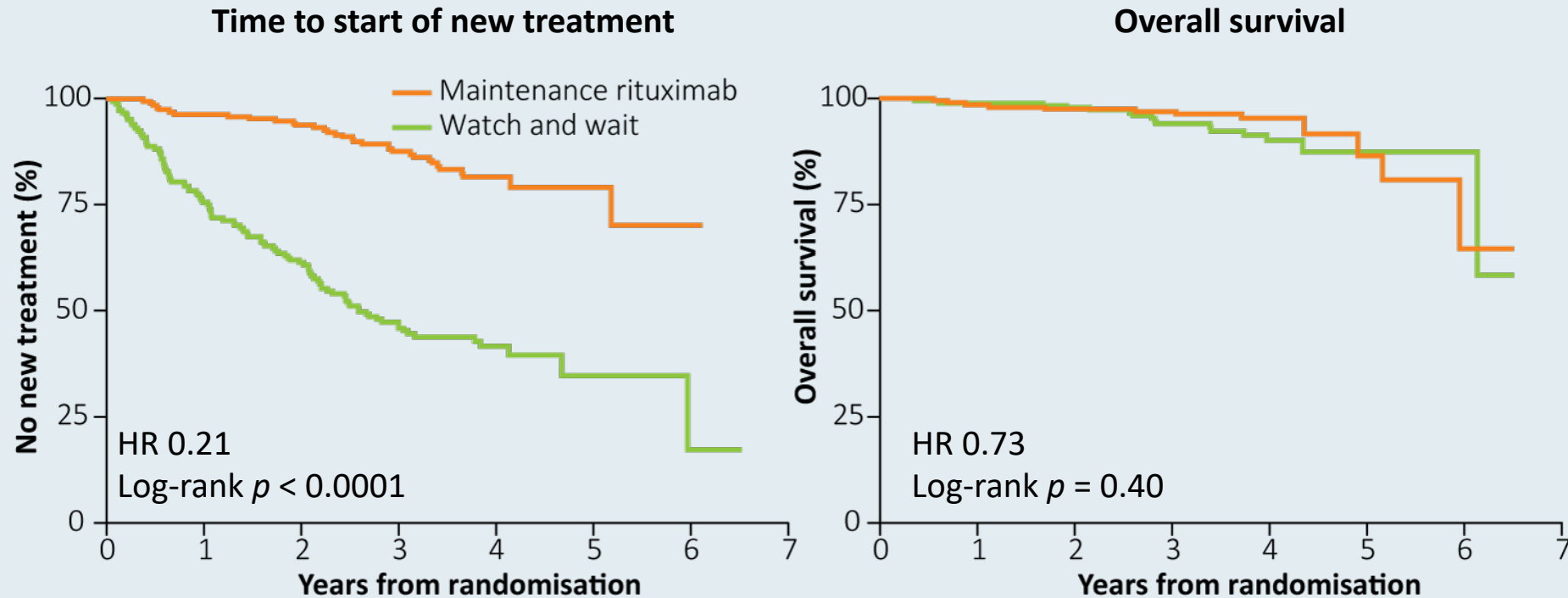
What is the most likely initial management approach for a 59-year-old patient with asymptomatic follicular lymphoma (FL)?

- a. Observation
- b. Rituximab
- c. Chemotherapy + anti-CD20 antibody
- d. Lenalidomide + anti-CD20 antibody
- e. I don't know

Select Management Approaches — Newly Diagnosed FL

- Observation off treatment
- Anti-CD20 antibody (Ab) monotherapy – rituximab; obinutuzumab
- Chemotherapy/anti-CD20 Ab (bendamustine with rituximab/obinutuzumab)
- Rituximab/lenalidomide (R²)

Rituximab Monotherapy Compared to Active Surveillance (Watch and Wait)



- Indication: Comorbidities not conducive to chemoimmunotherapy, low tumor burden and/or slowly progressing disease
- Schedule: Induction rituximab 375 mg/m² weekly for 4 weeks +/- maintenance rituximab q2m for 2 years

Do you use subcutaneous rituximab in select patients with lymphoma?

- a. Yes
- b. No
- c. No, but I would like to
- d. I am not familiar with this agent

Subcutaneous (SubQ) Rituximab

Indication

- Previously approved indications for rituximab in FL, DLBCL and CLL

Administration

- Shortens administration time to 5 to 7 minutes compared to IV (up to several hours)
- Flat dosing

Efficacy

- No significant difference in ORR, PFS, OS between IV and subQ

Toxicity

- No significant difference in AEs, including serious AEs, between IV and subQ

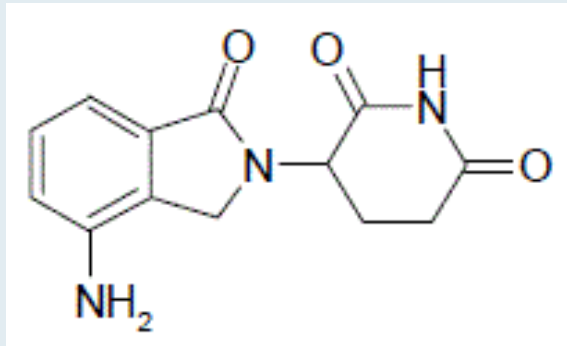
Which of the following regimens appears to have the same efficacy as bendamustine/rituximab (BR) as first-line treatment for symptomatic FL?

- a. Rituximab alone
- b. Lenalidomide/rituximab
- c. Obinutuzumab
- d. R-CHOP
- e. None of the above
- f. I don't know

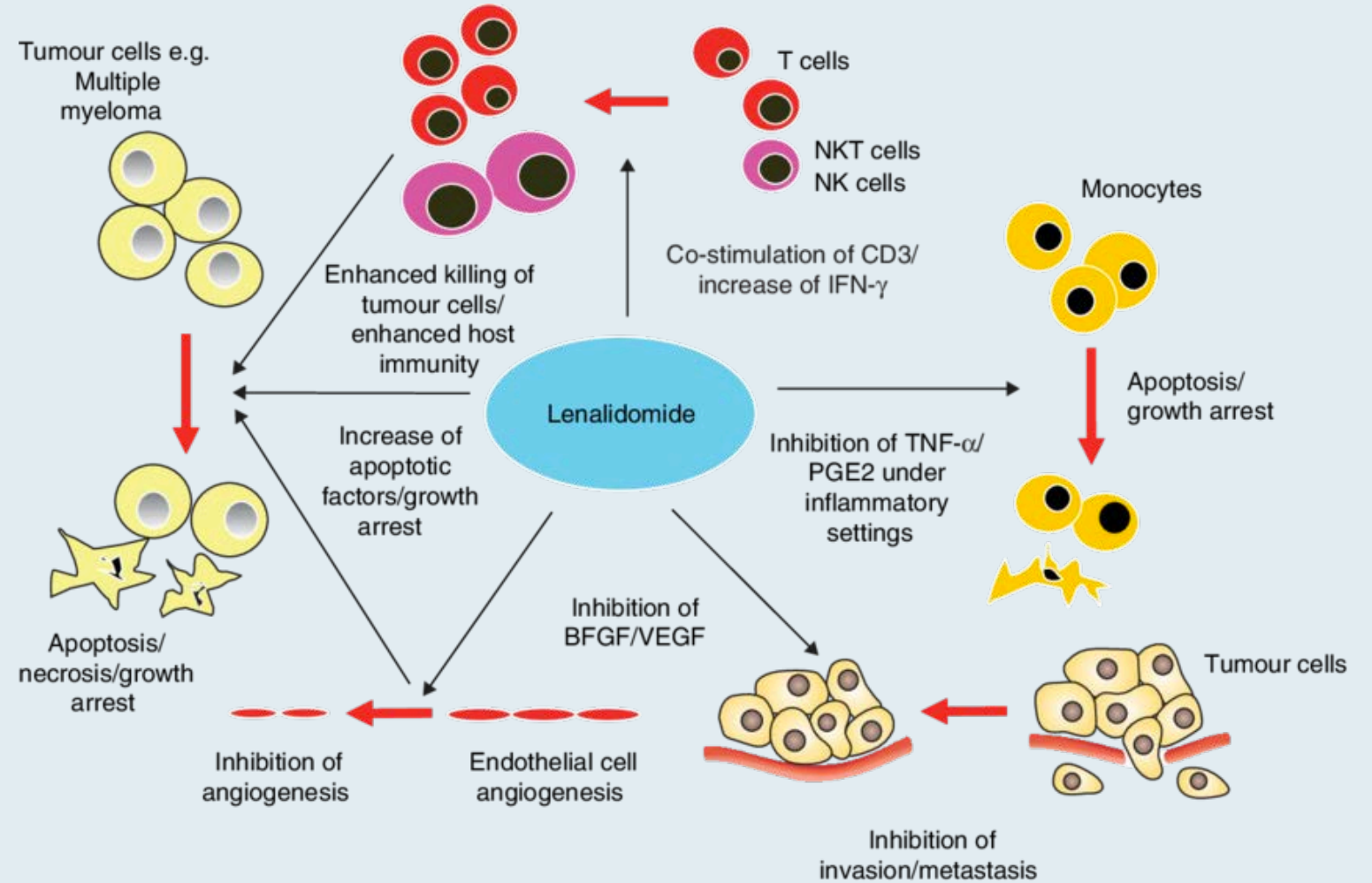
From a quality-of-life perspective, how would you compare the global tolerability/toxicity of lenalidomide/rituximab to that of BR when used as up-front therapy for FL?

- a. About the same
- b. Lenalidomide/rituximab has less toxicity
- c. BR has less toxicity
- d. I don't know

Lenalidomide Mechanism of Action



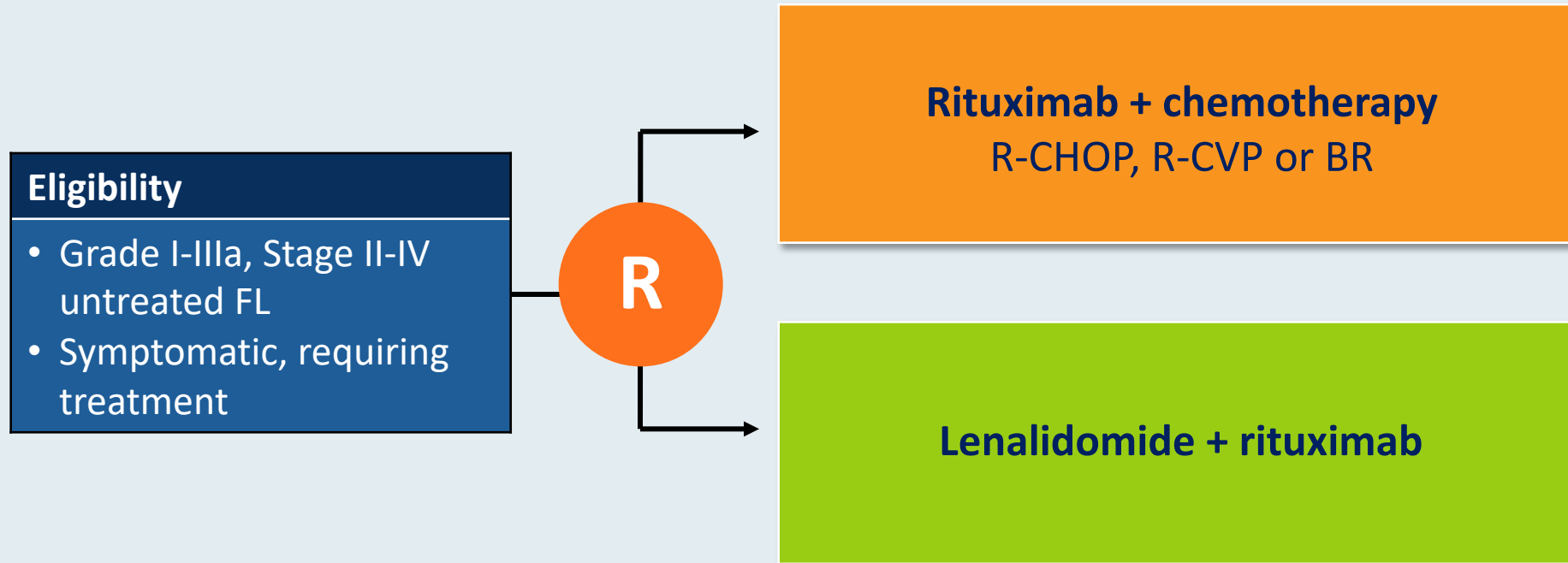
- Rash
- Cytopenias
- Diarrhea
- Thrombosis
- Muscle cramping



Galustian et al. Exp Opin Pharm 2016

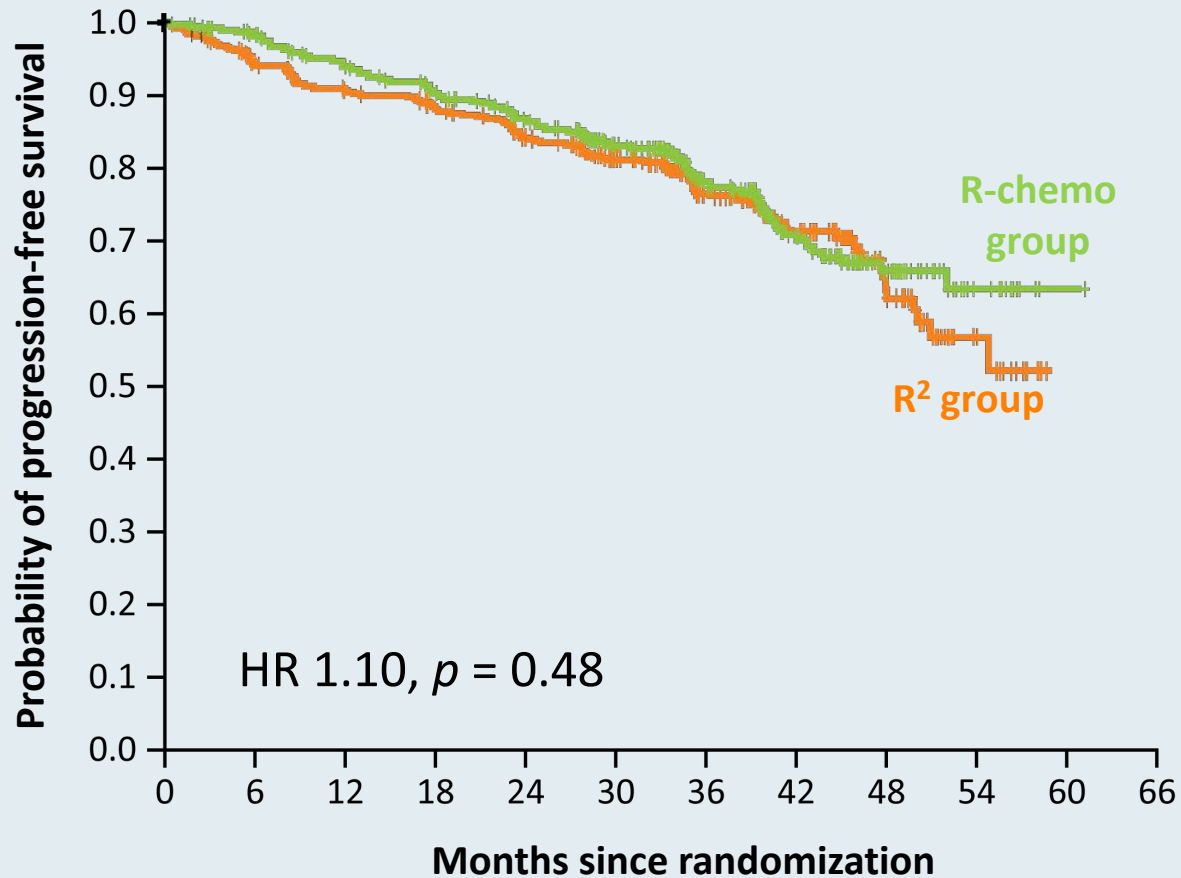
RELEVANCE: A Phase III Trial of Rituximab with Lenalidomide versus Rituximab with Chemotherapy for Patients with Untreated FL

Trial identifier: NCT01476787 (Closed)



Primary endpoints: Complete response rate at 120 weeks and PFS

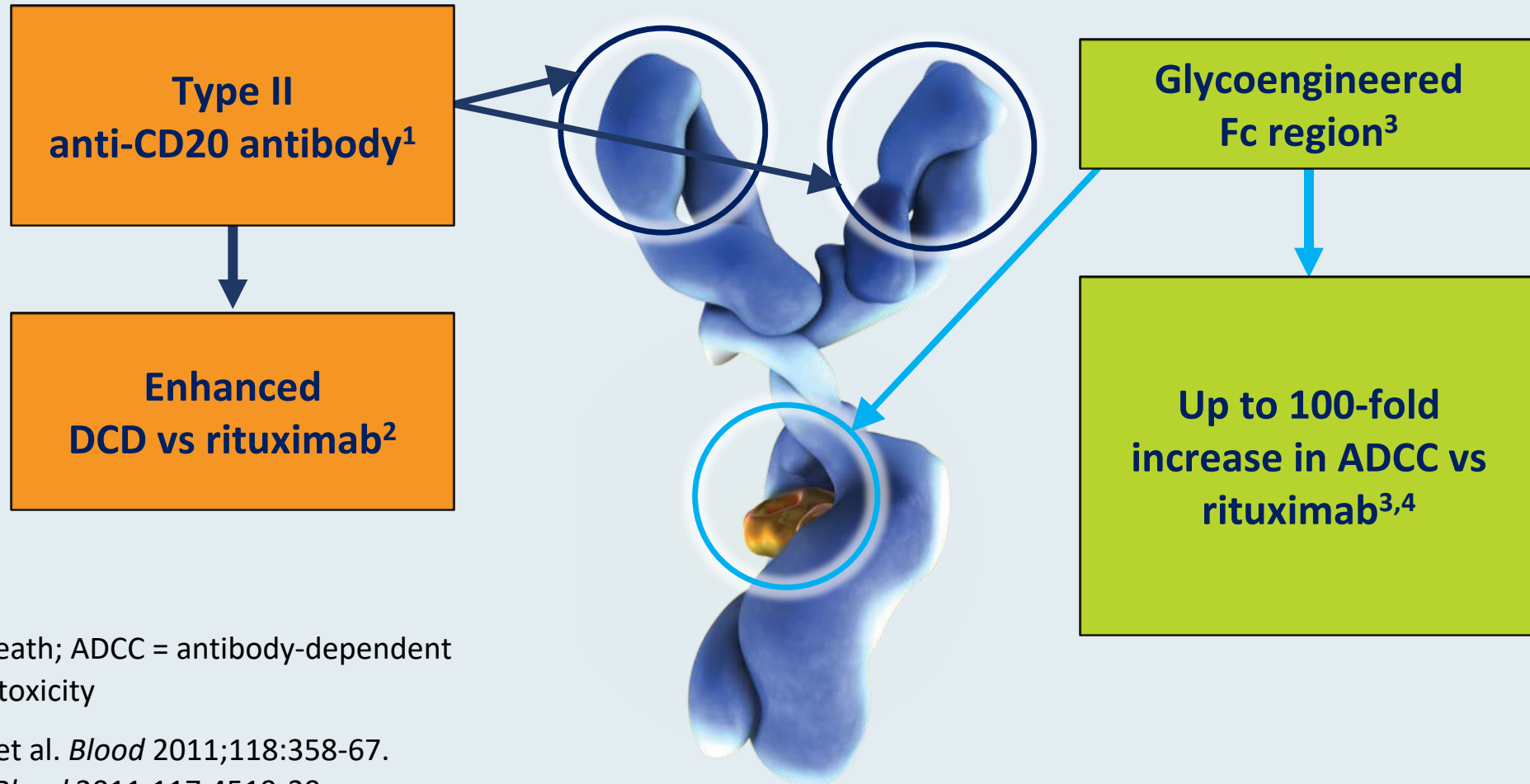
RELEVANCE: Rituximab + Lenalidomide (R²) versus Rituximab + Chemotherapy (R-chemo) in Untreated, Advanced FL



Grade 3-4 adverse events	R ² (n = 507)	R-chemo (n = 503)
Neutropenia	32%	50%
Febrile neutropenia	2%	7%
Cutaneous reactions	7%	1%
Diarrhea	2%	1%
Tumor lysis syndrome	1%	<1%

- Efficacy results were similar between R² and R-chemo in advanced, untreated follicular lymphoma.
- The safety profile differed between the 2 groups.

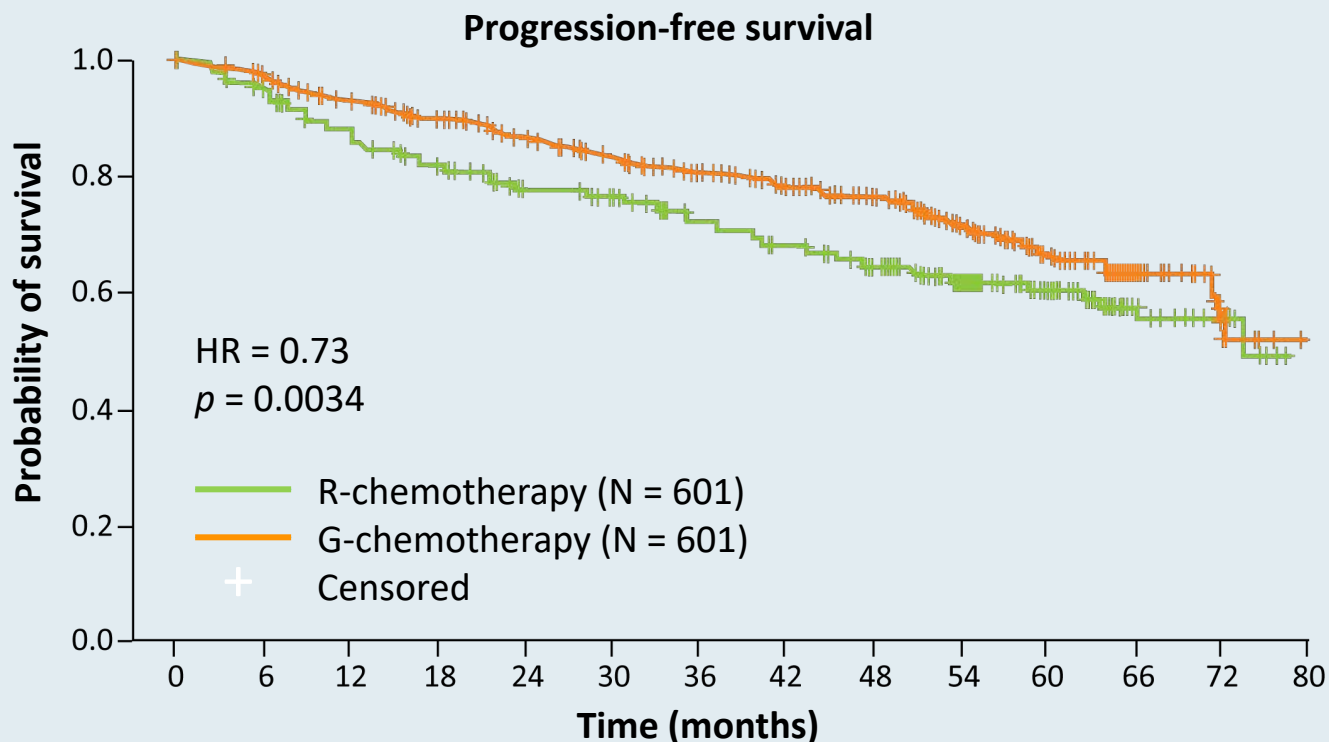
Comparison of Cell Death Induced by Obinutuzumab and Rituximab



DCD = direct cell death; ADCC = antibody-dependent cell-mediated cytotoxicity

1. Niederfellner G et al. *Blood* 2011;118:358-67.
2. Alduaij W et al. *Blood* 2011;117:4519-29.
3. Mössner E et al. *Blood* 2010;115:4393-402.
4. Herter S et al. Poster presentation at ASH 2010 (Abstract 3925).

GALLIUM: Four-Year Results with Obinutuzumab-Based Immunochemotherapy for Previously Untreated FL



	G-chemo (n = 601)	R-chemo (n = 601)
Any adverse event (AE)	99.8%	99.5%
Grade 3-5 AEs	79.2%	71.2%
Infections	22.2%	18.6%
Neutropenia	48.4%	41.4%
Second cancer	6.9%	4.4%

G = obinutuzumab; R = rituximab

- G-chemo continues to demonstrate clinically meaningful improvements in outcomes relative to R-chemo for patients with previously untreated FL
- OS data remain immature, with additional follow-up needed to draw conclusions

GALLIUM: Safety Summary

	R-chemo (n = 597)	G-chemo (n = 595)
Any AE	98%	100%
Grade ≥3 AEs (≥5% in either arm)	68%	75%
Neutropenia	40%	46%
Thrombocytopenia	3%	6%
Grade ≥3 AEs of special interest		
Infections	16%	20%
Infusion-related reactions	7%	12%
Second neoplasms	3%	5%
Grade 5 AEs	3%	4%

Case Presentation: A patient with newly diagnosed FL

- **Presentation: Worsening fatigue over the past month**
- **Physical exam: Palpable spleen and multiple enlarged cervical nodes**
- **Biopsy: Stage III, Grade II FL**



Patient 1: An otherwise healthy 82-year-old woman whose husband recently died of COVID-19 and who tested positive herself but never developed any symptoms. Receives rituximab monotherapy.



Patient 2: A 59-year-old carpenter with no significant past medical history. He is divorced and enjoys visiting his lakefront cabin on weekends. He is concerned about the impact of treatment on his quality of life and ability to travel. Receives BR as initial treatment.



Patient 3: A 72-year-old retired schoolteacher with a 10-year history of diabetes requiring insulin, hypertension and hyperlipidemia (PS = 1). She is quite reticent about receiving chemotherapy. Receives R² as initial therapy.

What is the current accessibility for your patients to undergo cancer-related elective surgery compared to before the COVID-19 pandemic?

- a. About the same
- b. Somewhat less
- c. Very much less

Approximately what proportion of your current patient interactions are telemedicine or virtual visits?

- a. None
- b. 5% or less
- c. 6%-10%
- d. 11%-20%
- e. 21%-30%
- f. 31%-40%
- g. 41%-50%
- h. Greater than 50%

Approximately what proportion of your patients do not have access to virtual visits due to limitations in their personal technology (eg, only has landline or flip phone)?

- a. None
- b. 5% or less
- c. 6%-10%
- d. 11%-20%
- e. 21%-30%
- f. 31%-40%
- g. 41%-50%
- h. Greater than 50%

Patient 1: An 82-year-old woman with FL

Treatment plan: Rituximab for 4 cycles



Special Considerations

- Retired insurance office assistant
- Provides care to 3 grandchildren
- Husband recently died of COVID-19
- Patient tested positive for COVID-19 but never developed symptoms
- Currently on antidepressants

Questions from the patient

- How often will she need to go to the clinic? What will happen while she is there?
- What can she expect for the future as it relates to her FL?
- She takes multiple health-enhancing supplements — is that OK? Are there any specific dietary nutrition recommendations?
- She has been sedentary for years — are there any specific suggestions for exercise?
- Should she get a flu shot? Will it be effective with her treatment?

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Patient 2: A 59-year-old man with FL

Treatment plan: Bendamustine/rituximab for 6 cycles



Special Considerations

- **Carpenter with no significant past medical history**
- **Divorced with 2 adult children who work and attend college**
- **Enjoys visiting his lakefront cabin on weekends**
- **Is concerned about the impact of treatment on his quality of life and ability to travel**

Questions from the patient

- **How often will he need to go to the clinic? What will happen while he is there?**
- **Will his treatment make him more susceptible to COVID-19, or to COVID-19-related complications if he were to contract the virus?**
- **Will he be able to continue working?**
- **Will he lose his hair? Will his sexual function be affected?**

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Patient 3: A 72-year-old woman with FL

Treatment plan: Rituximab/lenalidomide



Special Considerations

- **Retired schoolteacher**
- **Husband died 3 years ago of lung cancer and experienced significant chemotherapy-associated toxicity — she is reticent about receiving chemotherapy**
- **10-year history of diabetes requiring insulin, hypertension and hyperlipidemia (PS = 1)**

Questions from the patient

- **How often will she need to go to the clinic? What will happen while she is there?**
- **She has a history of chronic constipation — how, if at all, will this be impacted by the treatment?**
- **She takes multiple supplements and wants to know about diet and nutrition.**

Management of Follicular Lymphoma

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Case Presentation – Dr LaCasce: A 79-year-old man with relapsed follicular lymphoma

- 79 M with atrial fibrillation, sleep apnea and heart failure with a normal ejection fraction in second opinion. He initially presented in late 2015 with fatigue and night sweats.
- He was found have extensive adenopathy and splenomegaly. Biopsy revealed follicular lymphoma with elevated ki67 of 50%. FLIPI 4. He was treated with **dose reduced BR** with PR on CT (no PET performed) and initiated **rituximab maintenance**. His course was c/b febrile neutropenia, and **rituximab was discontinued** in late 2016.
- By late 2017, he had progressive disease and was started on **RCVP** with minimal residual disease on end-of-chemo PET. He then received **maintenance rituximab** through October 2019.
- By January 2020, he had extensive progression and received **obinutuzumab single agent x 6** with **addition of lenalidomide** in July which was d/c after dose reduction due to thrombocytopenia. His course was complicated by pneumonia.
- In September, he was started on **copanlisib** and is tolerating very well with improvement in his fatigue and performance status.

Select Management Approaches — Relapsed/Refractory FL

- Anti-CD20 antibody (Ab) monotherapy – rituximab; obinutuzumab
- Chemotherapy/anti-CD20 Ab (bendamustine with rituximab/obinutuzumab)
- Rituximab/lenalidomide (R²)
- PI3 kinase inhibitors
 - Idelalisib
 - Copanlisib
 - Duvelisib
- EZH2 inhibitor (tazemetostat)
- CAR T-cell therapy

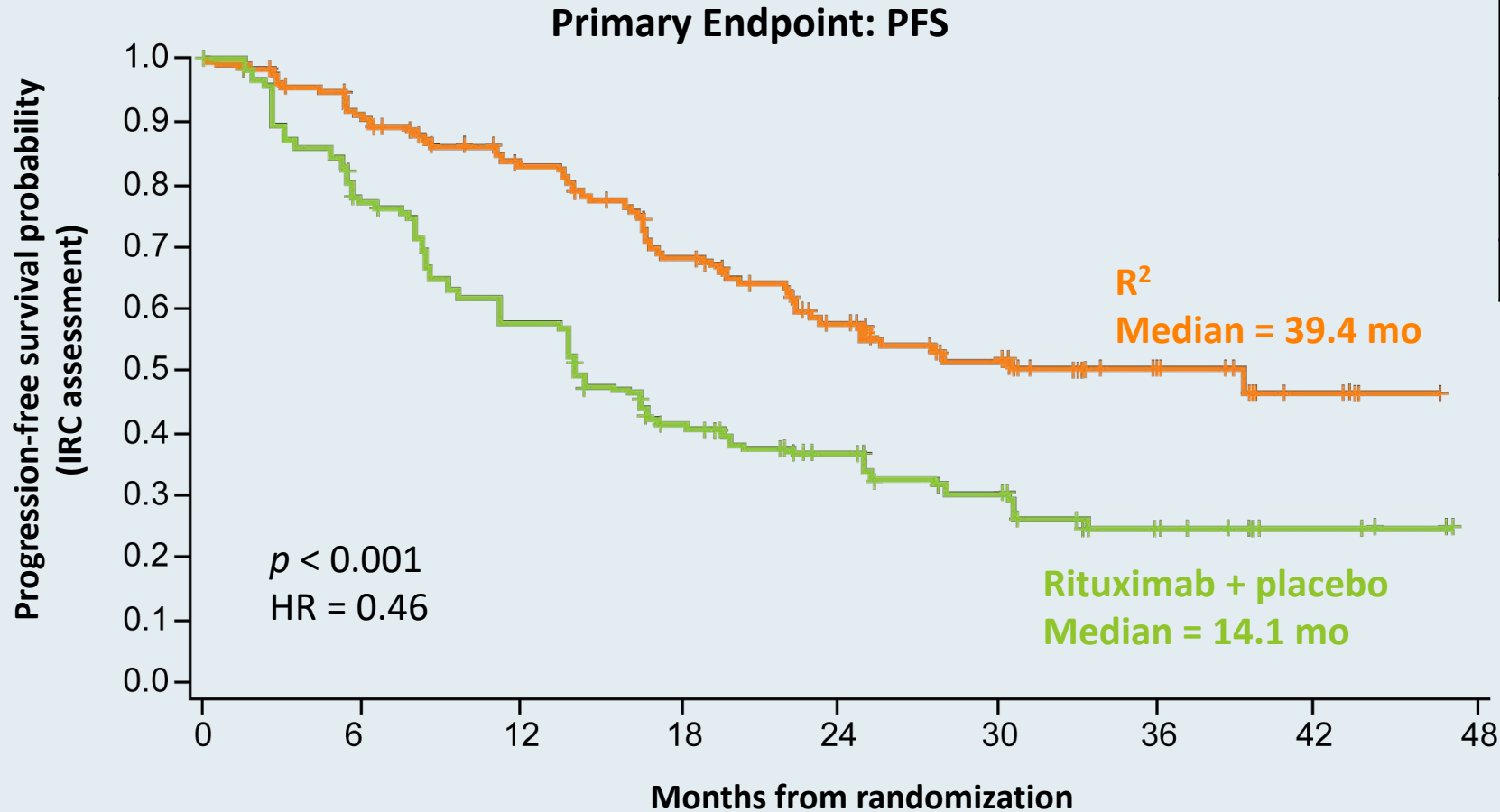
What are considerations in approaching a patient with recurrent FL?

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

What is the most common second-line therapy for a patient with FL who experiences disease progression 2.5 years after receiving 6 cycles of first-line BR?

- a. Re-treatment with BR
- b. Obinutuzumab/bendamustine
- c. Rituximab/lenalidomide
- d. A PI3K inhibitor (eg, idelalisib, copanlisib, duvelisib)
- e. Tazemetostat
- f. I don't know

AUGMENT Trial: R² versus Rituximab/Placebo in R/R FL or Marginal Zone Lymphoma



	R ² (n = 178)	R/placebo (n = 180)
ORR	78%	53%
CR	34%	18%
Median DOR	36.6 mo	21.7 mo

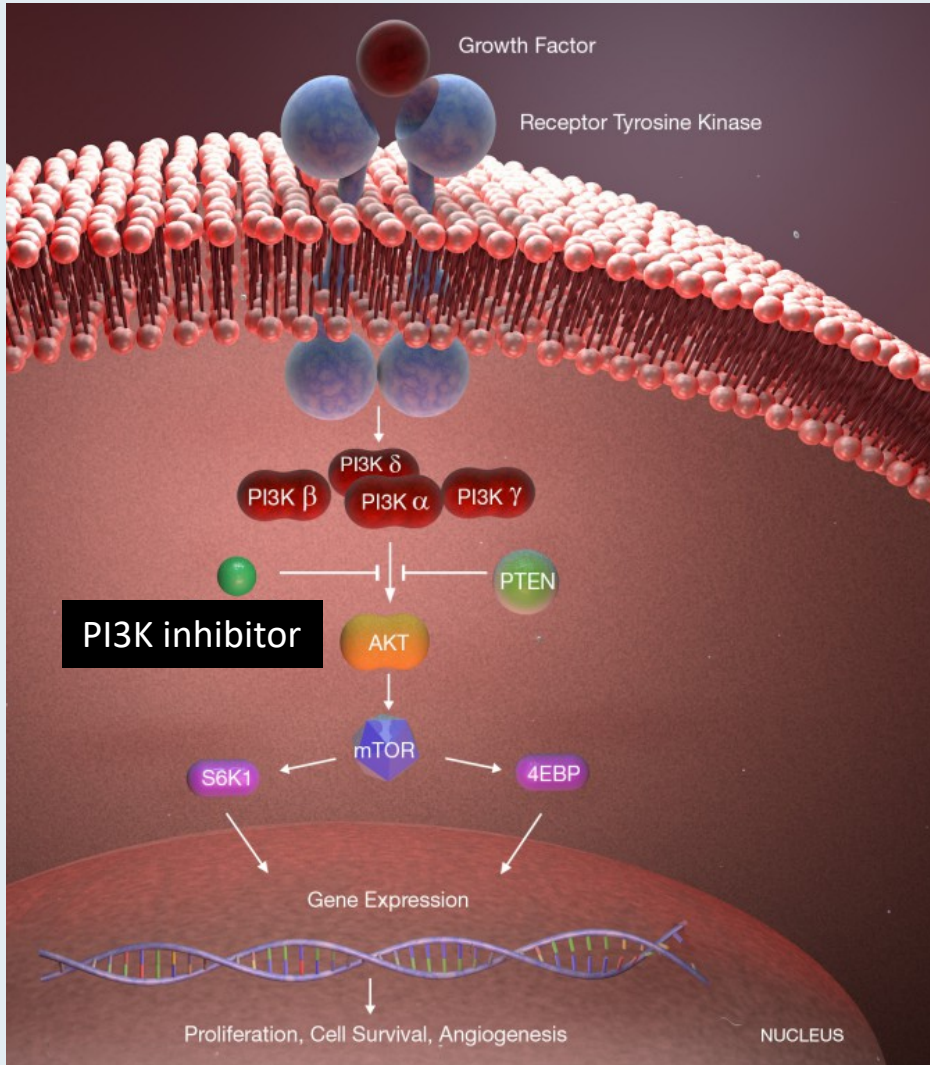
Patients receiving idelalisib and duvelisib may develop delayed-onset...

- a. Renal dysfunction
- b. Immune-related pneumonitis
- c. Hypothyroidism
- d. All of the above
- e. I don't know

A common side effect among patients receiving copanlisib for relapsed FL is...

- a. Thrombocytopenia
- b. Rash
- c. Hyperglycemia
- d. I don't know

PI3K Activation in B-Cell Lymphomas



- PI3K/AKT/mTOR pathway is frequently activated in human cancer
- Constitutive activation of the PI3K pathway in B-cell lymphomas allows for increased growth and survival of malignant cells
- PI3K inhibitors idelalisib and copanlisib block PI3K activity

PI3K Inhibitors for FL: Indication and Dosing

	Idelalisib¹	Copanlisib²	Duvelisib³
Mechanism of action	Selective PI3K δ inhibitor	Pan-PI3K inhibitor	Dual inhibitor of PI3K δ,γ
Indication	Relapsed FL after at least 2 prior systemic therapies	Relapsed FL after at least 2 prior systemic therapies	R/R FL after at least 2 prior systemic therapies
Dosing	150 mg orally, twice daily	1 hour IV infusion weekly (3 weeks on, 1 week off)	25 mg orally, twice daily

¹ Gopal AK et al. *N Engl J Med* 2014;370(11):1008-18; Idelalisib package insert, October 2018.

² Dreyling M et al. *J Clin Oncol* 2017;35(35):3898-905; Copanlisib package insert, September 2017.

³ Flinn IW et al. *J Clin Oncol* 2019;[Epub ahead of print]; Duvelisib package insert, September 2018.

PI3K Inhibitors for FL: Activity and Tolerability

	Idelalisib ¹	Copanlisib ²	Duvelisib ³
Activity	<ul style="list-style-type: none"> • ORR: 57% (6% CR) • Median time to response: 1.9 mo • Median DoR: 12.5 mo 	<ul style="list-style-type: none"> • ORR: 59% (12% CR) • Median time to response: 1.7 mo • Median DoR: 22.6 mo 	<ul style="list-style-type: none"> • ORR: 42.2% (1.2% CR) • Median time to response: 1.9 mo* • Median DoR: 10 mo*
Tolerability	Grade ≥3 AEs: 54% <ul style="list-style-type: none"> • Neutropenia: 27% • Diarrhea: 13% • Increased ALT: 13% 	Grade ≥3 TRAEs: 84% <ul style="list-style-type: none"> • Hyperglycemia: 41% • Hypertension: 24% • Neutropenia: 24% 	Grade ≥3 AEs: 88%* <ul style="list-style-type: none"> • Neutropenia: 25%* • Diarrhea: 15%* • Increased AST: 3.1%*

* All patients on study (FL, SLL, marginal zone-B lymphoma)

¹ Gopal AK et al. *N Engl J Med* 2014;370(11):1008-18; Idelalisib package insert, October 2018.

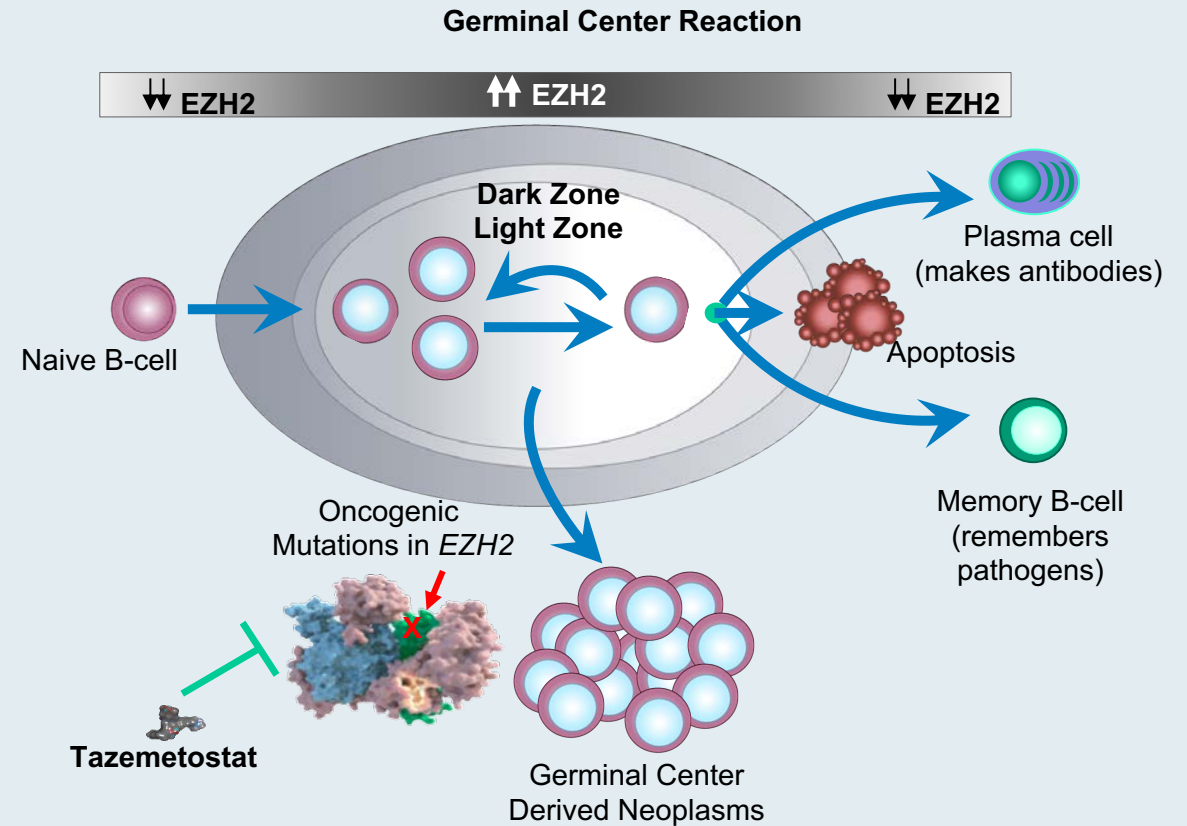
² Dreyling M et al. *J Clin Oncol* 2017;35(35):3898-905; Copanlisib package insert, September 2017.

³ Flinn IW et al. *J Clin Oncol* 2019;37(11):912-22; Zinzani PL et al. *Proc EHA* 2017;Abstract S777; Duvelisib package insert, September 2018.

Follicular Lymphoma and EZH2

- *EZH2* an 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 thereby transforming into a cancer²
- *EZH2* biology relevant in both mutant (MT) and wild-type (WT) *EZH2* FL
 - ~20% of patients with FL also have *EZH2* gain of function mutations³

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



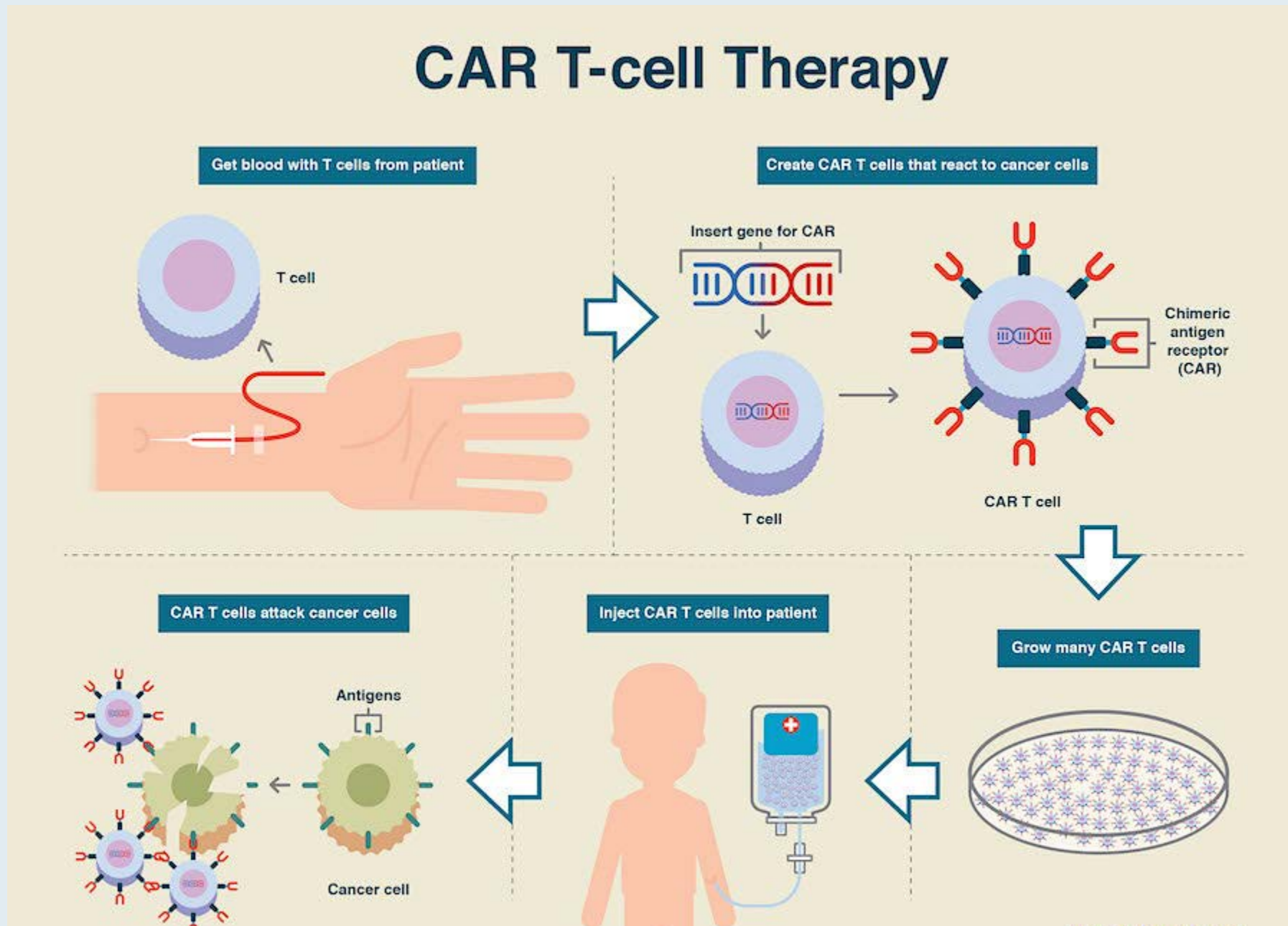
Tazemetostat, a selective, oral inhibitor of EZH2 has shown antitumor activity in non-Hodgkin's lymphoma patients with either MT or WT EZH2^{4,5}

Tazemetostat ORR in EZH2-Mutant and Wild-Type Populations (Recurrent FL)

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

Morschhauser, ICML 2019

CAR T-cell Therapy



Phase II ZUMA-5 Trial Design

Estimated Enrollment (N = 160)

- Follicular lymphoma (FL) or marginal zone lymphoma (MZL)
- Disease progression after 2 or more lines of treatment with combination chemoimmunotherapy
- ECOG PS 0-1
- No transformed FL or MZL
- No SLL or Grade IIIB FL



**Axicabtagene Ciloleucel
(Axi-Cel)**

Primary endpoint: Objective Response Rate

FDA to Review sBLA for Axi-Cel in R/R FL and MZL

Press Release – September 4, 2020

The FDA has accepted a supplemental Biologics License Application (sBLA) for Axi-Cel for the treatment of patients with R/R FL or MZL after 2 or more prior lines of systemic therapy.

This would be the first potential CAR T-cell therapy for patients with relapsed/refractory FL and MZL.

Data supporting the sBLA come from the primary analysis of the Phase 2 ZUMA-5 trial.

Phase II ELARA Trial Design

Eligibility (N = 97)

- Relapsed or Refractory Follicular Lymphoma (Grade I, II, IIIA)
- No evidence of disease transformation
- No prior anti-CD19 therapy, gene therapy. Adoptive T-cell therapy
- No prior allogeneic hematopoietic SCT



**Tisagenlecleucel
(single infusion)**

Primary endpoint: Complete Response Rate

ELARA Meets Primary Endpoint at Interim Analysis in Follicular Lymphoma

Press Release – August 4, 2020

Positive results announced from the Phase II ELARA trial of tisagenlecleucel in patients with R/R FL. At the interim analysis, the global study met its primary endpoint of complete response rate (CRR), as assessed by independent review committee.

No new safety signals were observed. Results from the ELARA trial will be presented at an upcoming medical meeting and included in US and EU regulatory submissions.

Tisagenlecleucel was the first-ever FDA-approved CAR-T cell therapy, and the first-ever CAR-T to be approved in two distinct indications. It is a one-time treatment designed to empower patients' immune systems to fight their cancer. Tisagenlecleucel is currently approved for the treatment of R/R pediatric and young adult (up to 25 years of age) ALL and R/R adult DLBCL

Meet The Professor
Management of Multiple Myeloma

Thursday, November 19, 2020
12:00 PM – 1:00 PM ET

Faculty

Kenneth C Anderson, MD

Moderator

Neil Love, MD

Thank you for joining us!

**CNE (NCPD) credit information will be
emailed to each participant tomorrow morning.**