Oncology Grand Rounds

New Agents and Strategies in Hodgkin and Non-Hodgkin Lymphomas

Tuesday, June 2, 2020

5:00 PM – 6:30 PM ET

Faculty

Kim Leake, MSN, FNP-C
Mollie Moran, APRN-CNP, AOCNP
Craig Moskowitz, MD
Michael E Williams, MD, ScM

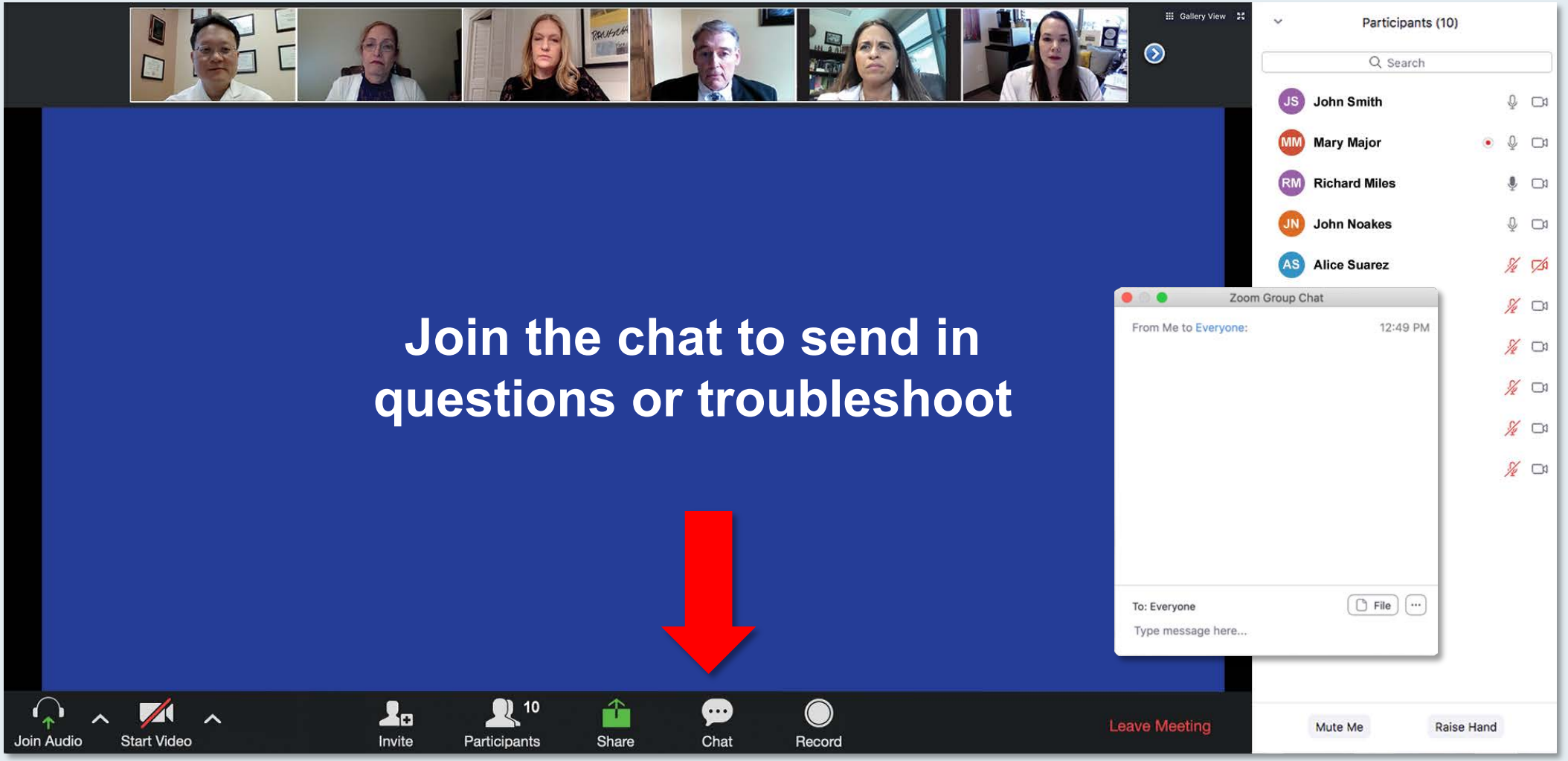
Moderator

Neil Love, MD

Research To Practice®

Familiarizing yourself with the Zoom interface

How to participate in the chat



RTP Live Webinar Nursing Series

Monday	Tuesday	Wednesday	Thursday	Friday
25	26 **Breast Ca** **5:00 PM**	27	28 **GI Ca** **5:00 PM**	29
Jun 1	2 **Lymphoma** **5:00 PM**	3	4 **CLL** **5:00 PM**	5
8	9 **GYN** **5:00 PM**	10	11 **Metastatic Lung Ca** **5:00 PM**	12
15	16 **Locally Advanced Lung Ca** **5:00 PM**	17	18 **Bladder Ca** **5:00 PM**	19
22	23 **CAR-T** **5:00 PM**	24	25 **PARP** **5:00 PM**	26
29	30 **Prostate Ca** **5:00 PM**	Jul 1 9 AM	2	3
6	7	8	9	10

Oncology Grand Rounds

New Agents and Strategies in Chronic Lymphocytic Leukemia

Thursday, June 4, 2020

5:00 PM – 6:30 PM ET

Faculty

Amy Goodrich, CRNP
Brad S Kahl, MD
Robin Klebig, APRN, CNP, AOCNP
Jeff Sharman, MD

Moderator

Neil Love, MD

Research To Practice®

Oncology Grand Rounds

New Agents and Strategies in Hodgkin and Non-Hodgkin Lymphomas

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Research To Practice®

Beyond chemotherapy:
Novel agents and regimens in the management of lymphomas

- Polatuzumab vedotin (DLBCL)
- CAR T-cell therapy (DLBCL)
- Brentuximab vedotin (HL, PTCL)
- Immune checkpoint inhibitors (HL)
- “R-squared” (R^2) lenalidomide/rituximab (FL, MCL)
- BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib) (MCL)
- Venetoclax (MCL)

Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL)

- Polatuzumab vedotin, CAR T-cell therapy

Module 2: Hodgkin Lymphoma (HL) and Peripheral T-Cell Lymphoma (PTCL)

- Brentuximab vedotin, immune checkpoint inhibitors

Module 3: Follicular Lymphoma (FL)

- Lenalidomide/rituximab (R^2), PI3K inhibitors

Module 4: Mantle Cell Lymphoma (MCL)

- BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib), venetoclax, lenalidomide

Module 5: Management of Lymphomas in the Era of COVID-19

- Telemedicine, minimization of surgeries, reduced infusions and clinic visits

About the Enduring Program

- This webinar is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs visit our website, www.ResearchToPractice.com

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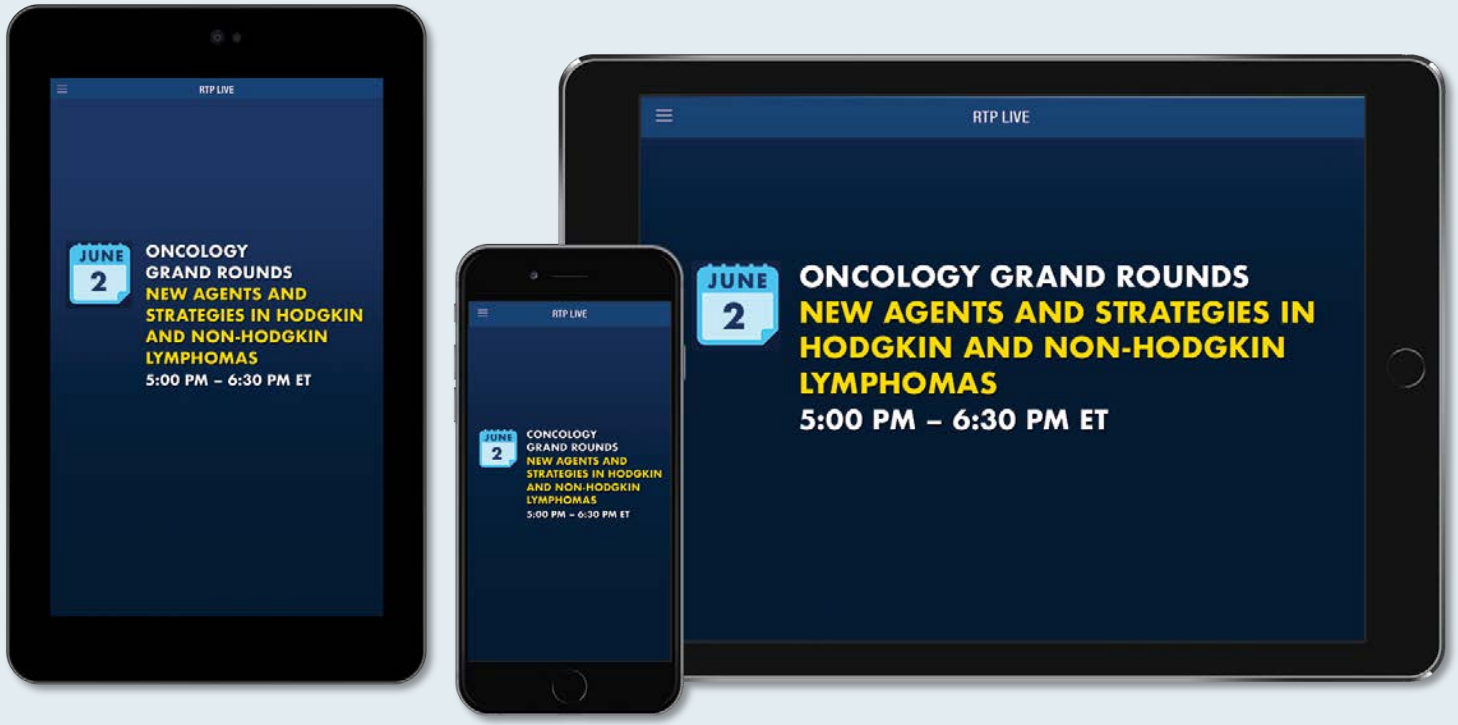
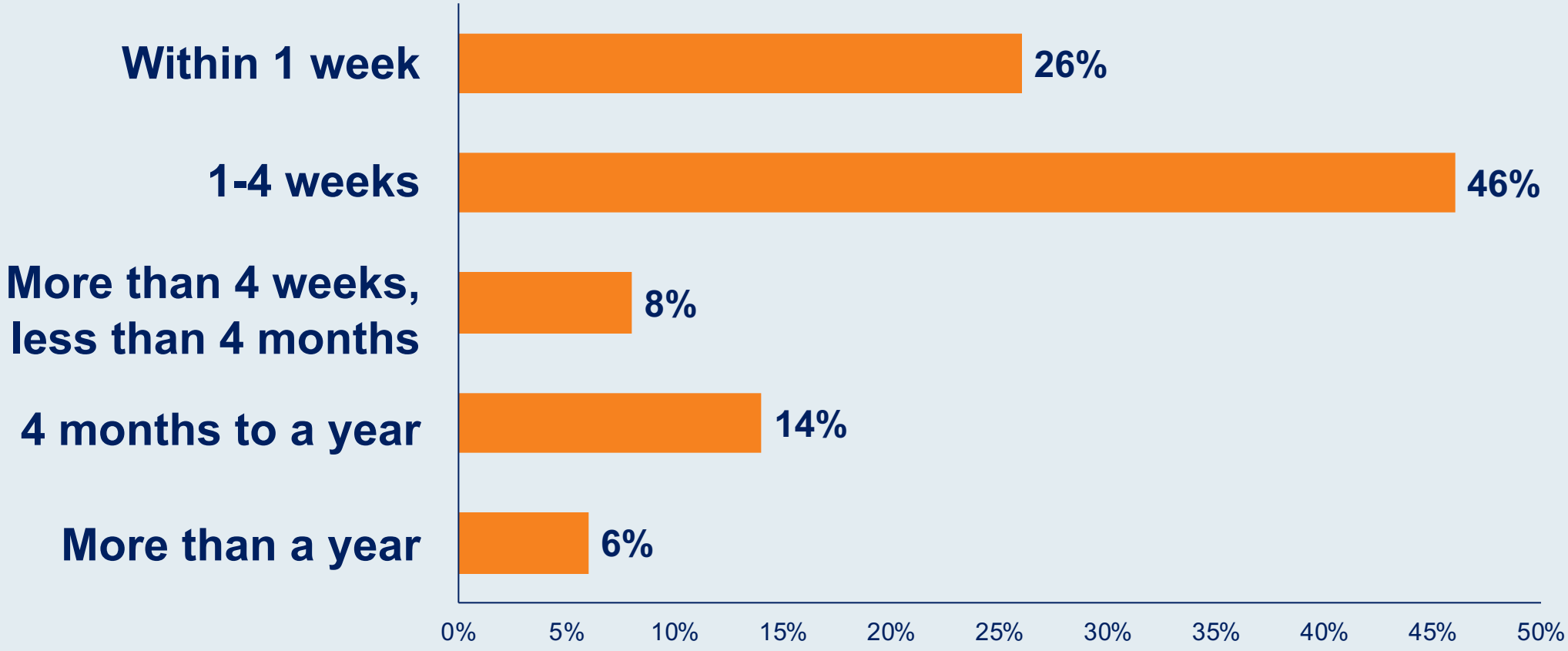
Download the RTP Live app on your smartphone or tablet to access program information, including slides being presented during the program:

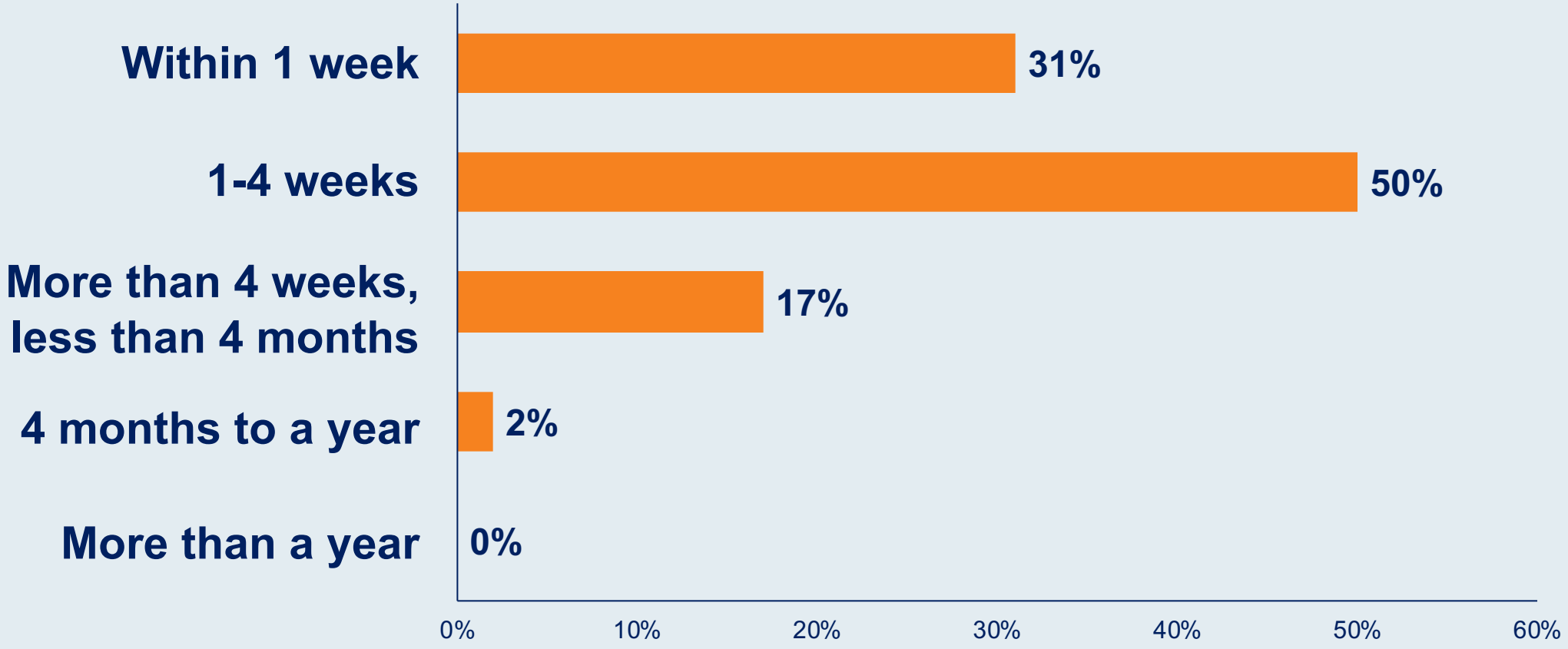
www.ResearchToPractice.com/RTPLiveApp



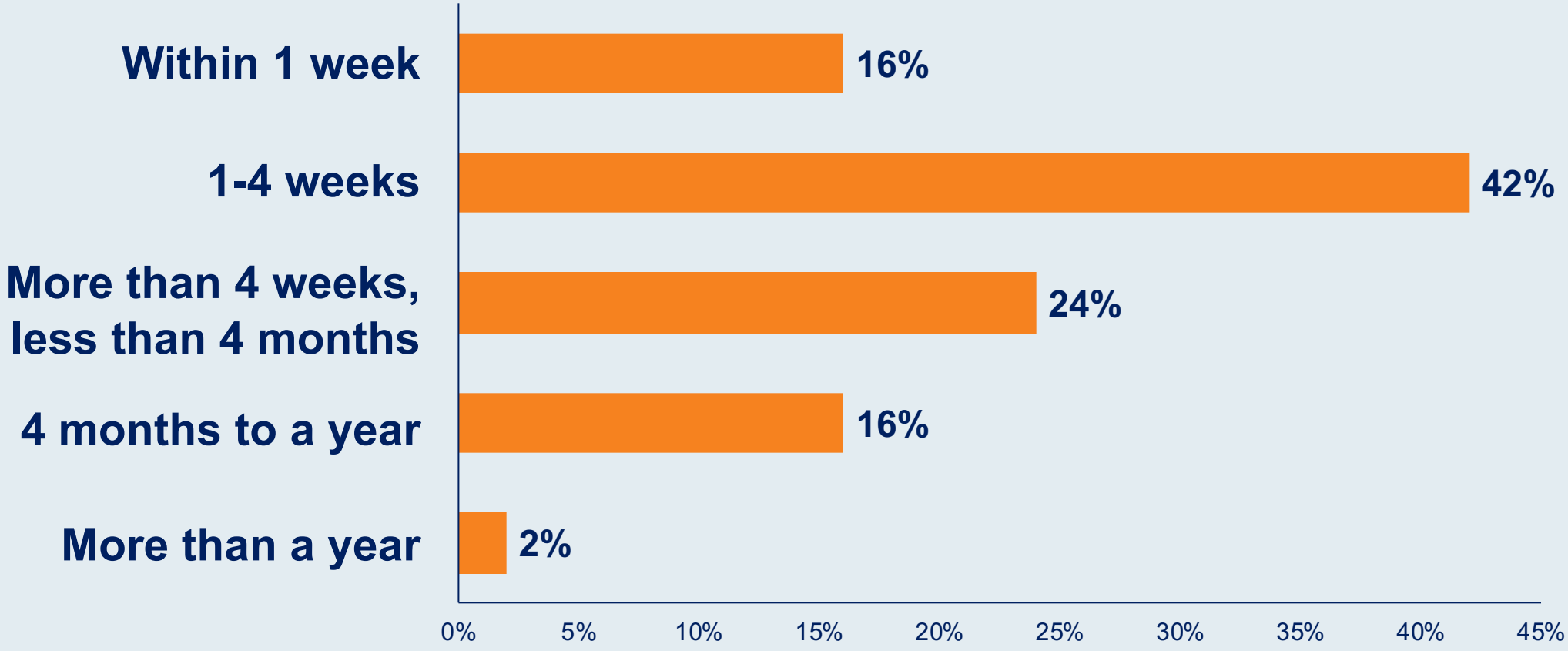
When was the last time you encountered a patient with Hodgkin lymphoma (HL)?



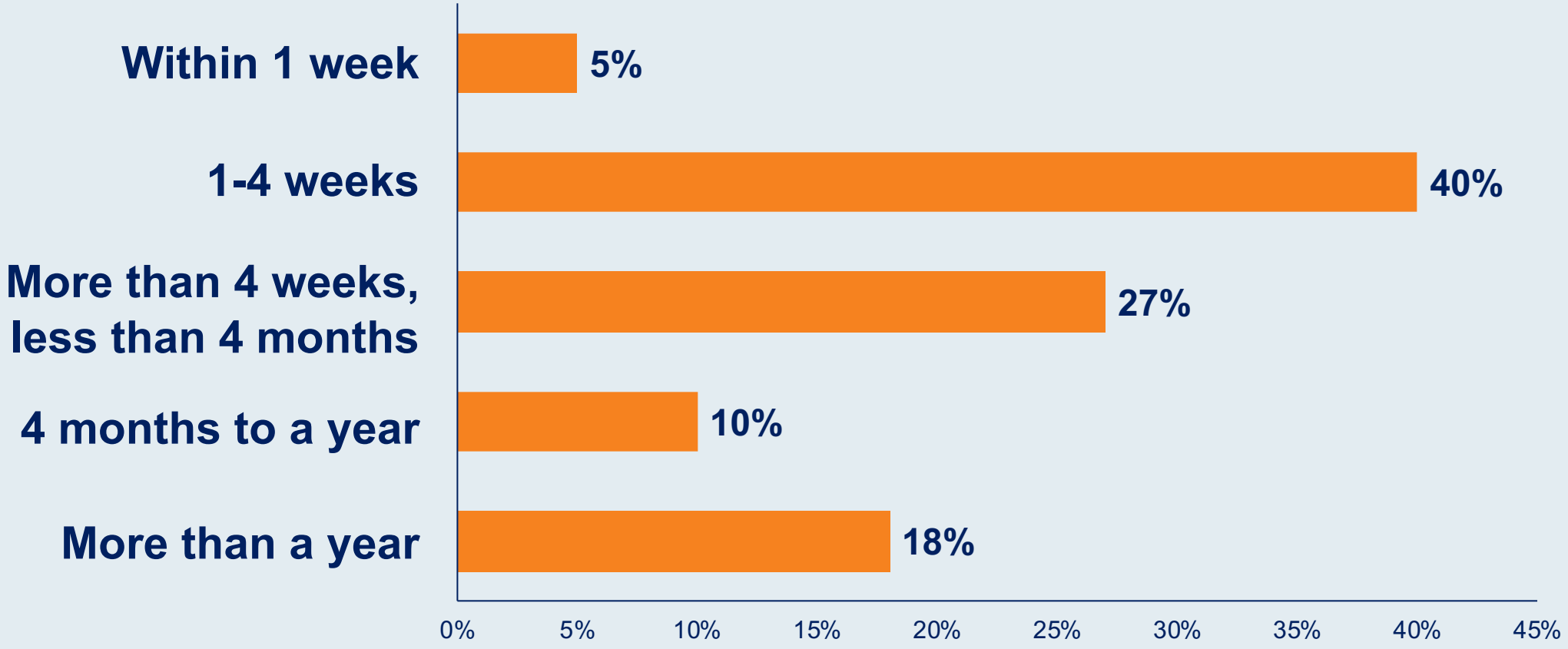
When was the last time you encountered a patient with diffuse large B-cell lymphoma (DLBCL)?



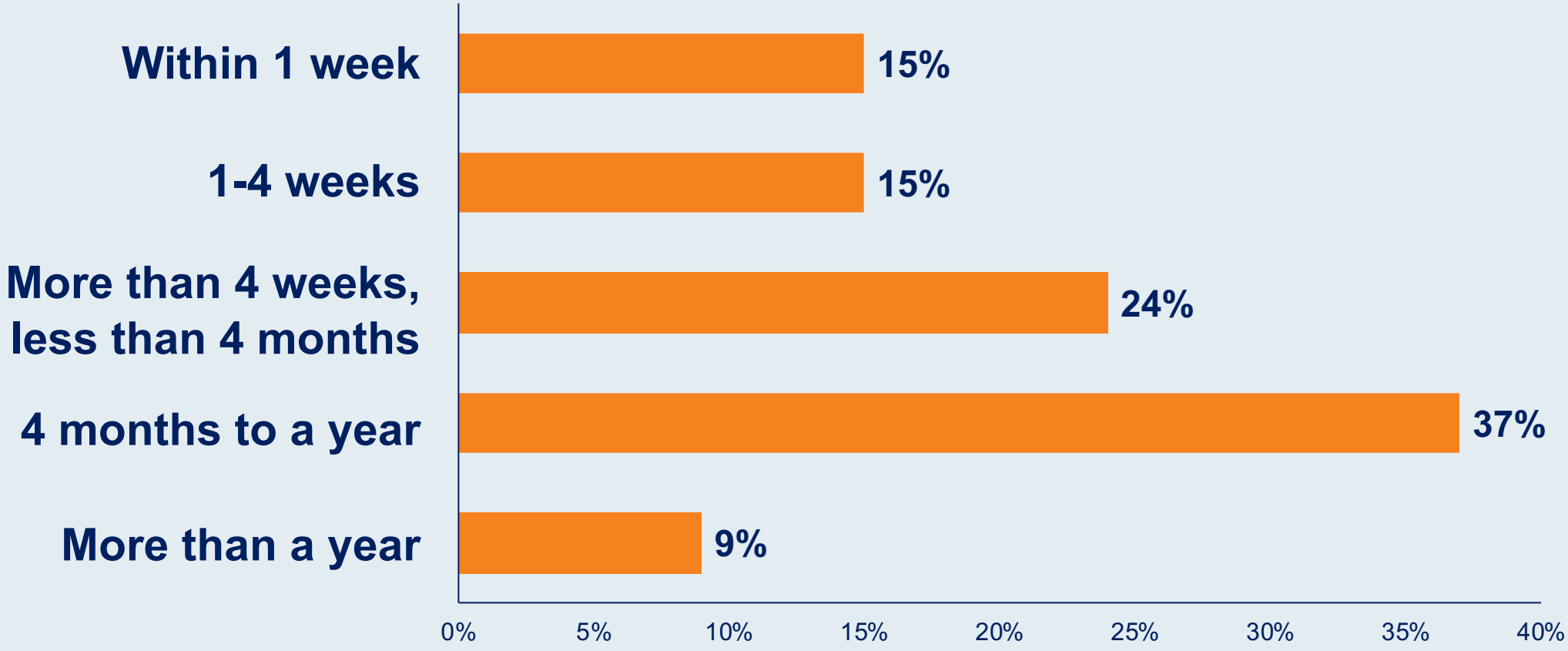
When was the last time you encountered a patient with follicular lymphoma (FL)?



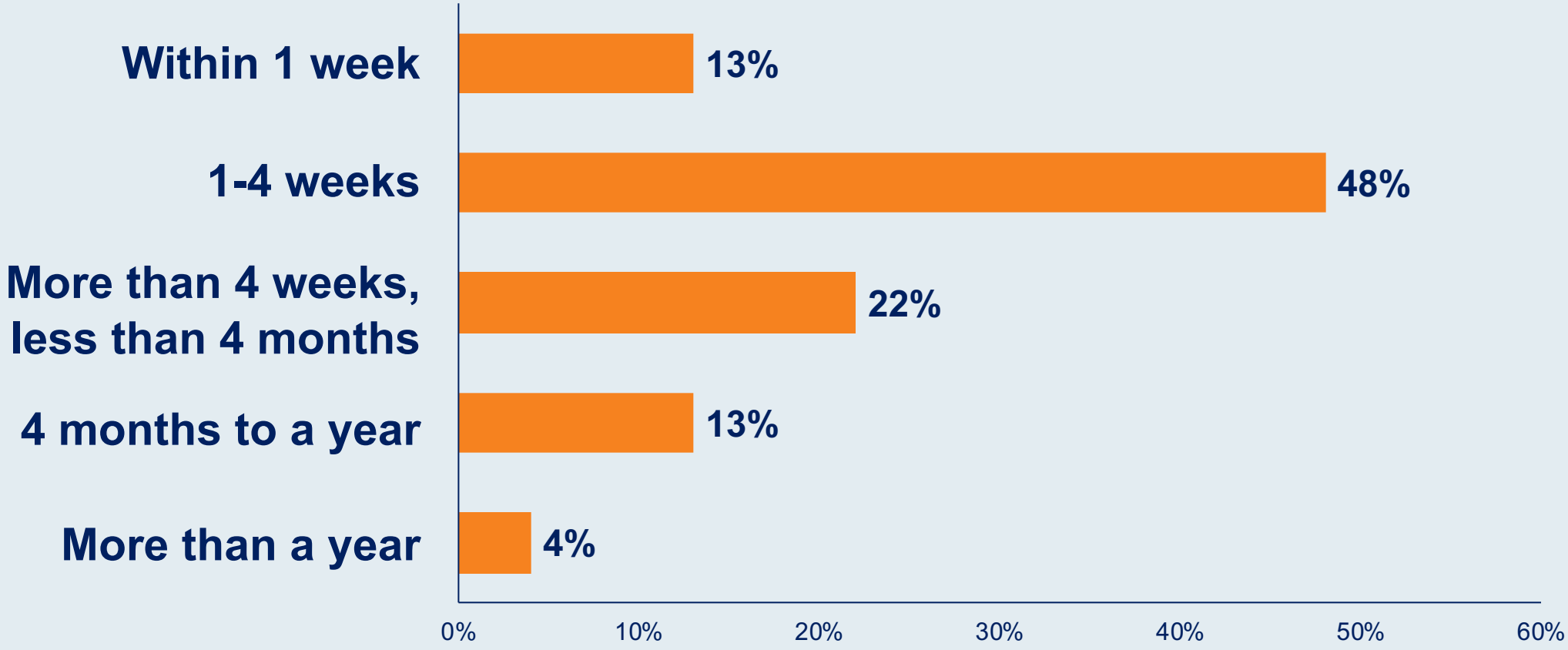
When was the last time you encountered a patient with mantle cell lymphoma (MCL)?



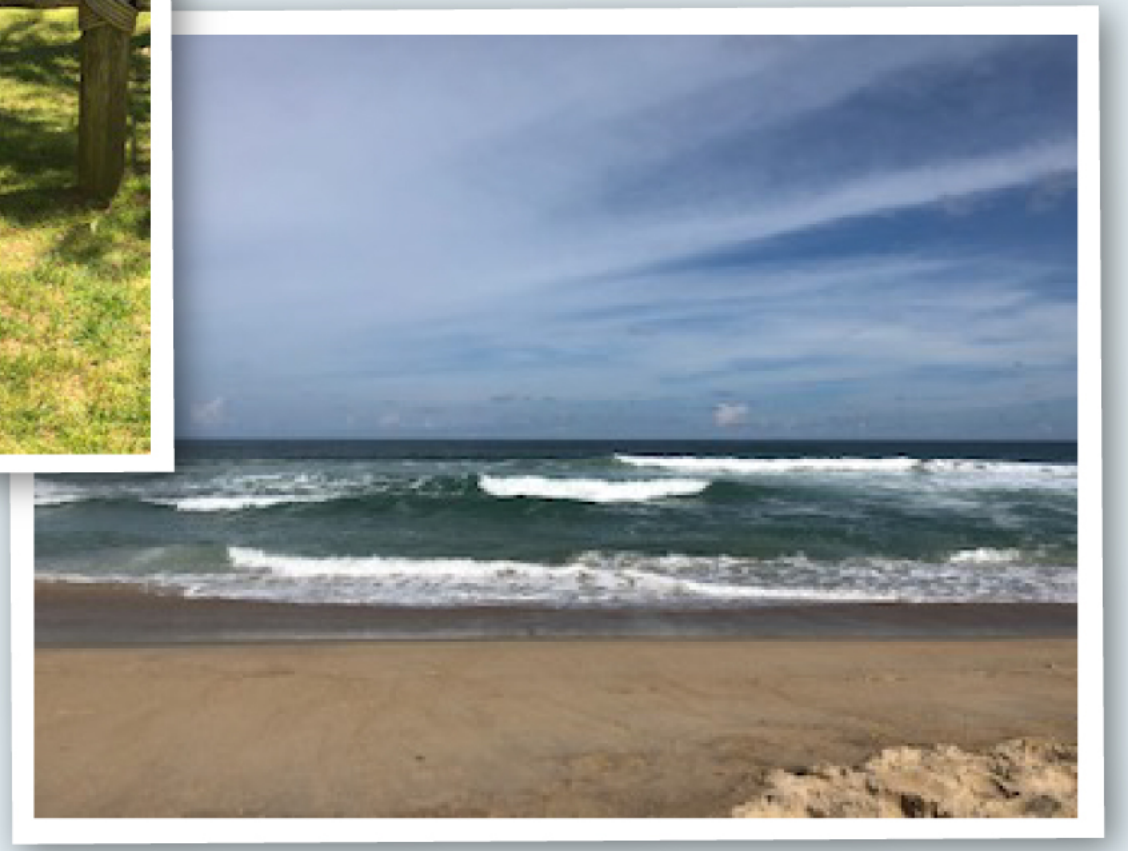
When was the last time you encountered a patient with T-cell lymphoma (TCL)?



When was the last time you encountered a patient with chronic lymphocytic leukemia (CLL)?



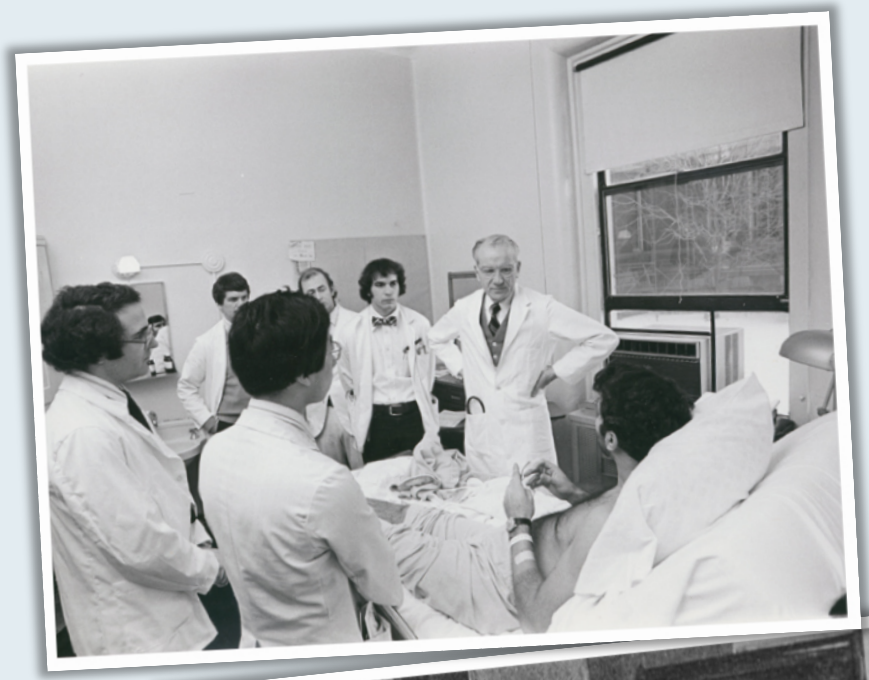
Kim Leake, MSN, FNP-C
Emily Couric Clinical Cancer Center
Charlottesville, Virginia

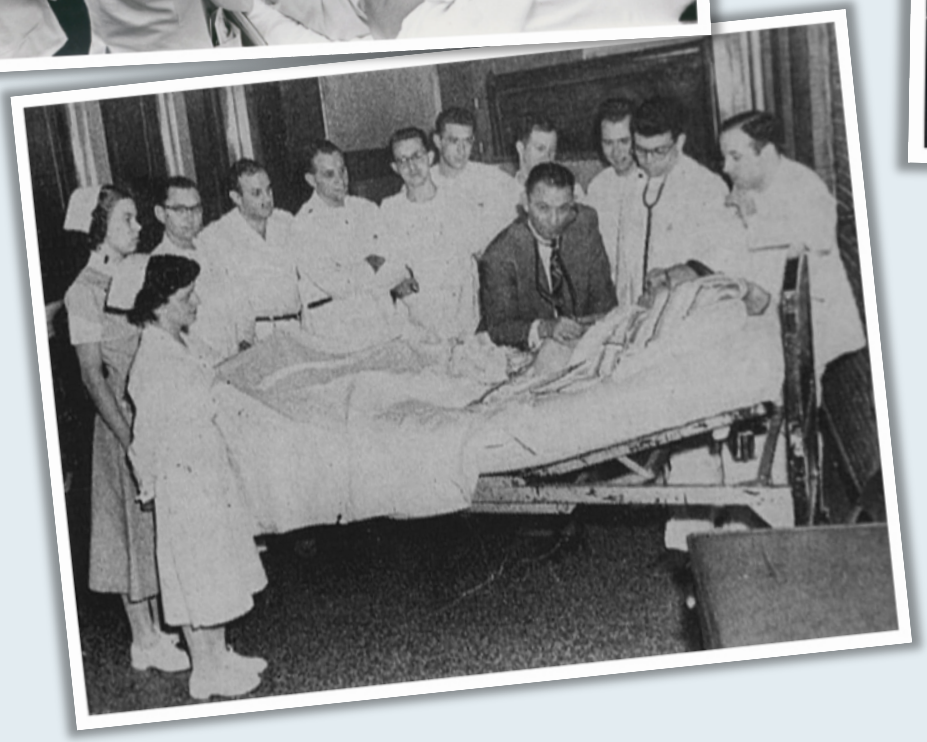


Mollie Moran, APRN-CNP, AOCNP
The James Cancer Hospital at
The Ohio State University
Columbus, Ohio

Craig Moskowitz, MD
Sylvester Comprehensive Cancer Center
University of Miami Health System
Miami, Florida

Michael E Williams, MD, ScM
University of Virginia School of Medicine
Charlottesville, Virginia

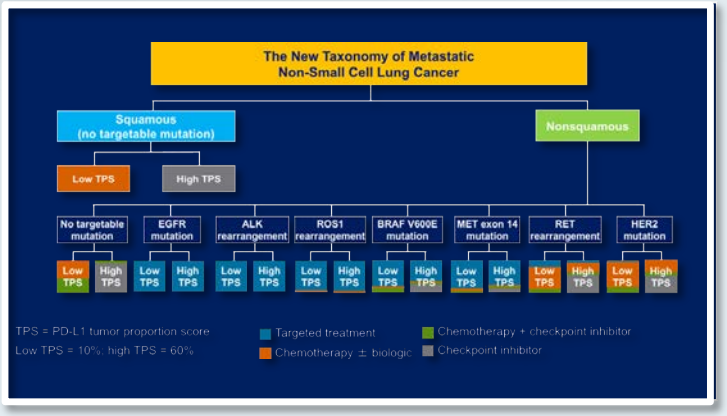


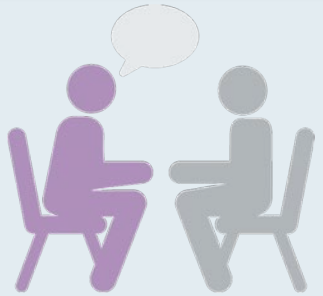



The Birmingham News

Oncology Grand Rounds: Format

- **Personalized oncology strategy**
  - New markers and agents
- **Patient counseling and education as a component of that strategy**
  - Symptom management
- **Discussion of actual cases from nurse faculty**
  - The bond that heals; trust and integrity
  - Supporting family and loved ones





The Core Oncology Triad
Developing an Individualized Oncology Strategy

Day in the Life: NURSE 8

- 72 M, Lung cancer, Pemetrexed, carboplatin, Socioeconomic status
- 31 F, Benign hematology, transfusion exchange, Depression
- 72 F, AML and HCC, Pembrolizumab, Acceptance of disease
- 73 F, Mantle Cell Lymphoma, Study drug, Acceptance of disease
- 30 F, Breast cancer, AC, Young age
- 61 F, Colorectal cancer, completed FOLFOX, Language barrier
- 63 F, Multiple myeloma, Daratumumab, Language barrier
- 56 F, Head and neck cancer, Pembrolizumab, Socioeconomic status
- 79 F, Multiple myeloma, Surveillance, Culture
- 58 M, Multiple myeloma, Zoledronic acid, poor attitude
- 85 F, Ovarian cancer, will receive study drug, had multiple lines of therapy

Day in the Life: NURSE 8

- 80 F, AML and Lung cancer, Pembrolizumab, venetoclax, azacitidine, family support
- 70 F, Lung cancer, Pemetrexed/carbo/pembrolizumab, Acceptance of disease
- 37 F, Benign hematology, Opioid addiction
- 26 F, Hodgkin lymphoma, Nivolumab, Family support
- 63 M, Colorectal cancer, Surveillance, Socioeconomic status
- 91 M, Myeloproliferative neoplasm, Surveillance, ETOH use
- 31 M, Testicular cancer, Surveillance, Anxiety/depression
- 67 F, Multiple myeloma, Bortezomib, Positive outlook
- 50 F, Breast cancer, AC, Family support

Agenda

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- Polatuzumab vedotin, CAR T-cell therapy

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Module 1: Diffuse Large B-Cell Lymphoma (DLBCL)

- Polatuzumab vedotin, CAR T-cell therapy

Polatuzumab vedotin is currently approved for the treatment of recurrent diffuse large B-cell lymphoma…

a. As monotherapy

b. In combination with BR

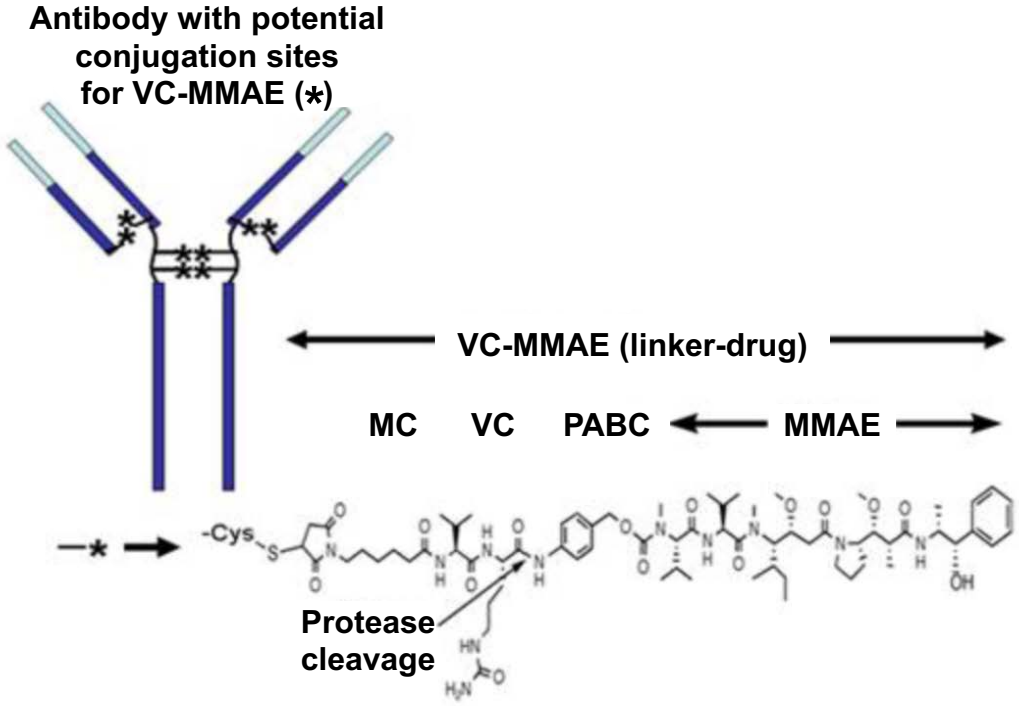
c. In combination with rituximab

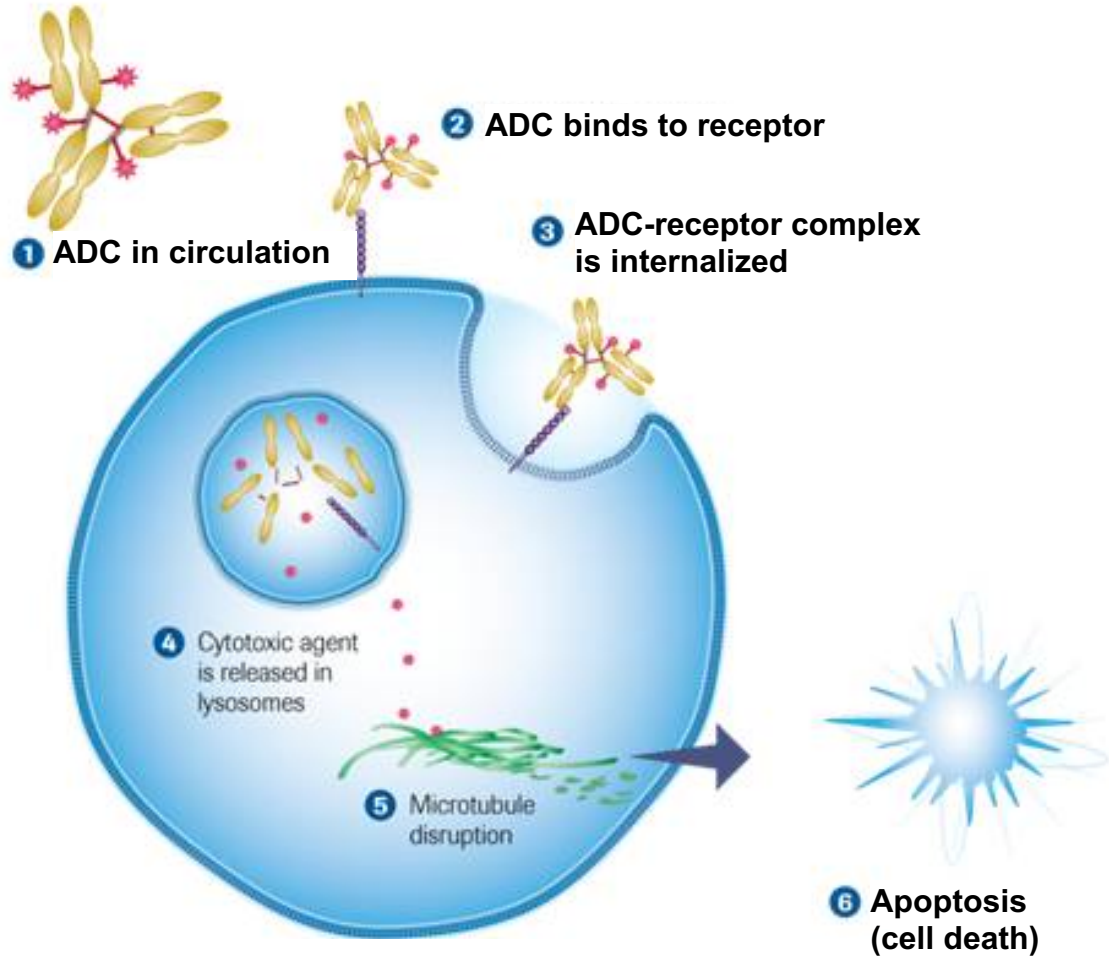
d. In combination with obinutuzumab

e. I don’t know

Mechanism of Action of Polatuzumab Vedotin

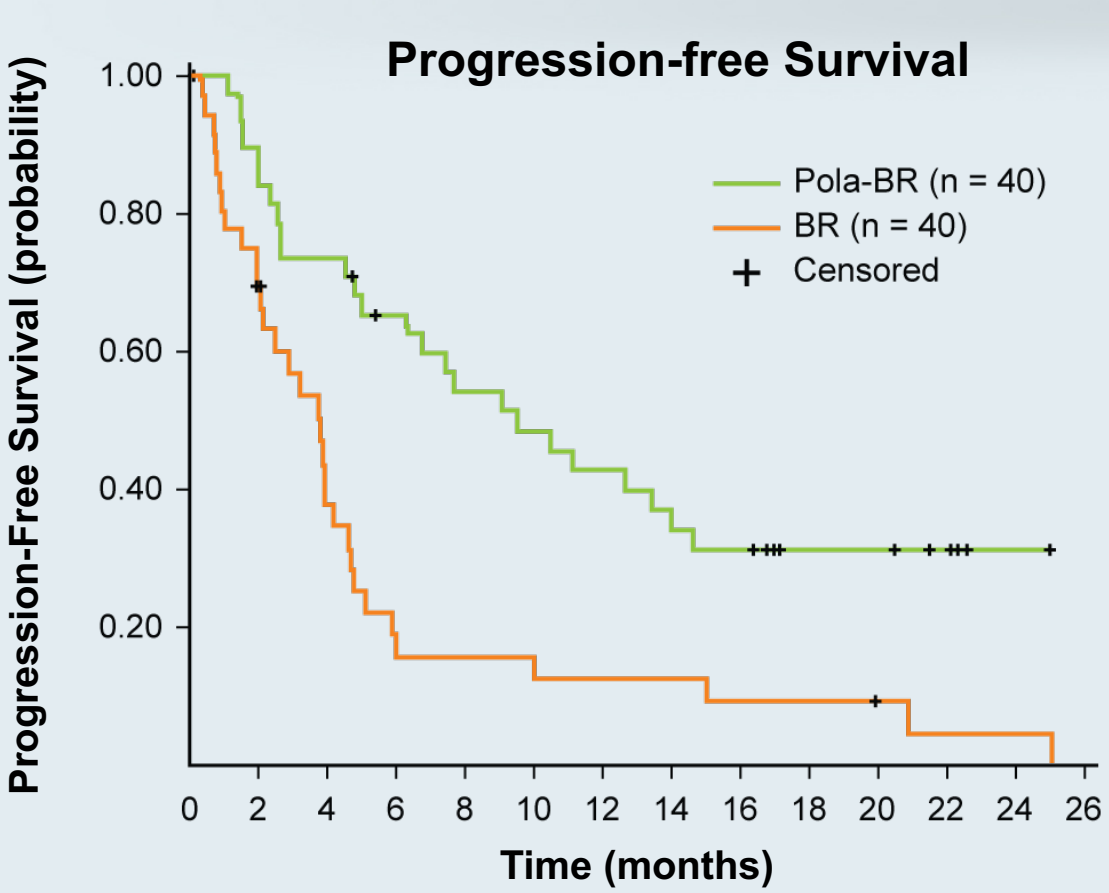
Polatuzumab vedotin is an antibody-drug conjugate (ADC) consisting of monomethyl auristatin E (MMAE) conjugated to anti-CD22 and CD79b monoclonal antibodies via a cleavable linker molecule

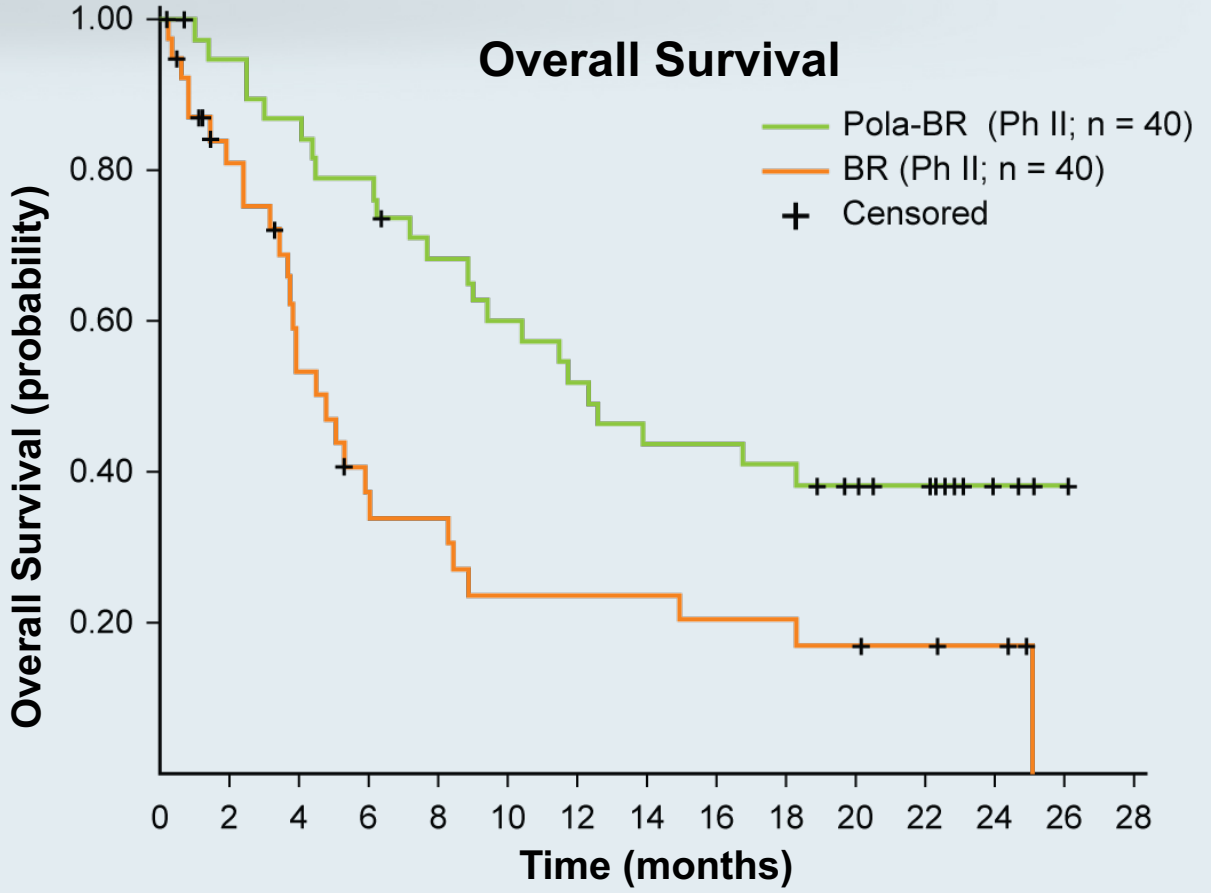




Morschhauser F et al. *Proc ASCO* 2014;Abstract 8519.

Randomized Phase II Survival Analyses: Polatuzumab Vedotin/BR vs BR in R/R DLBCL





	Pola-BR	BR	HR	*P*-value
mPFS (IRC)	9.5 mo	3.7 mo	0.36	<0.001

	Pola-BR	BR	HR	*P*-value
mOSS (IRC)	12.4 mo	4.7 mo	0.42	0.002

Sehn LH et al. *J Clin Oncol* 2020;38(2):155-65.

Select Adverse Events: Polatuzumab Vedotin/BR vs BR in R/R DLBCL

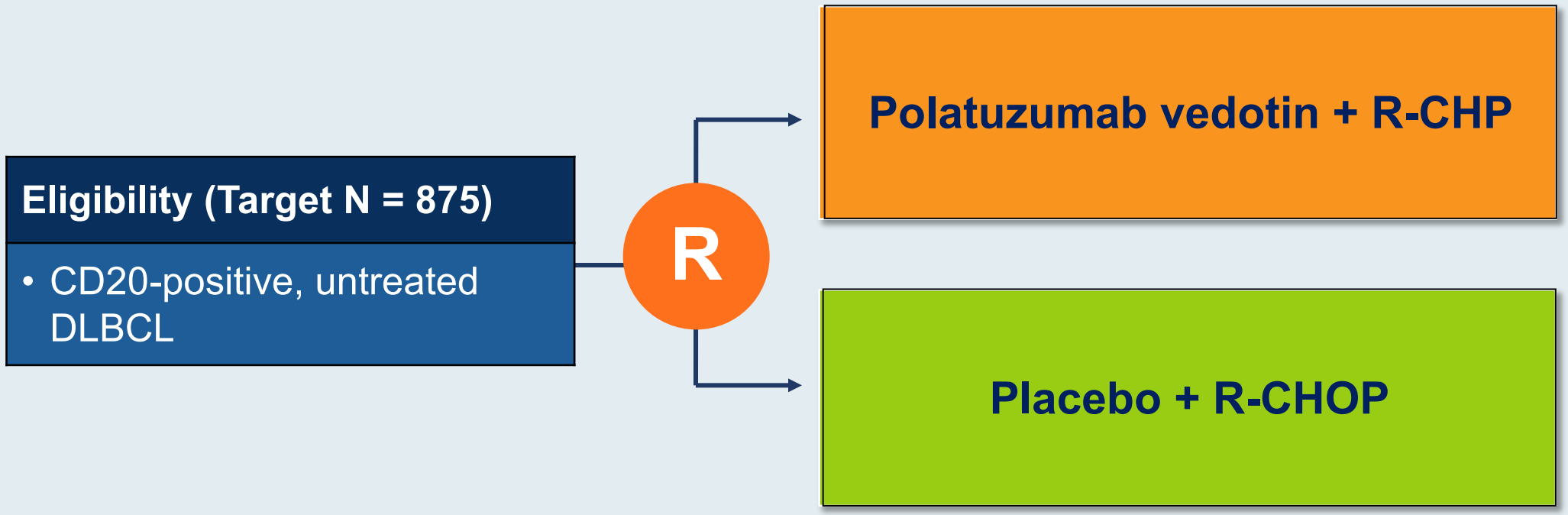
	Pola-BR (n = 39)		BR (n = 39)	
Adverse Event	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Anemia	54%	28%	26%	18%
Neutropenia	54%	46%	39%	33%
Thrombocytopenia	49%	41%	28%	23%
Lymphopenia	13%	13%	0	0
Peripheral neuropathy*	44%	0	8%	0

* Peripheral neuropathy was Grade 1-2 and resolved in most patients

Sehn LH et al. *J Clin Oncol* 2020;38(2):155-65.

POLARIX: An Ongoing Phase III Trial of Polatuzumab Vedotin with R-CHP versus R-CHOP for Patients with Untreated DLBCL

Trial identifier: NCT03274492 **(Open)**



<u>Primary endpoint</u>: Progression-free survival

www.clinicaltrials.gov. Accessed April 2019.

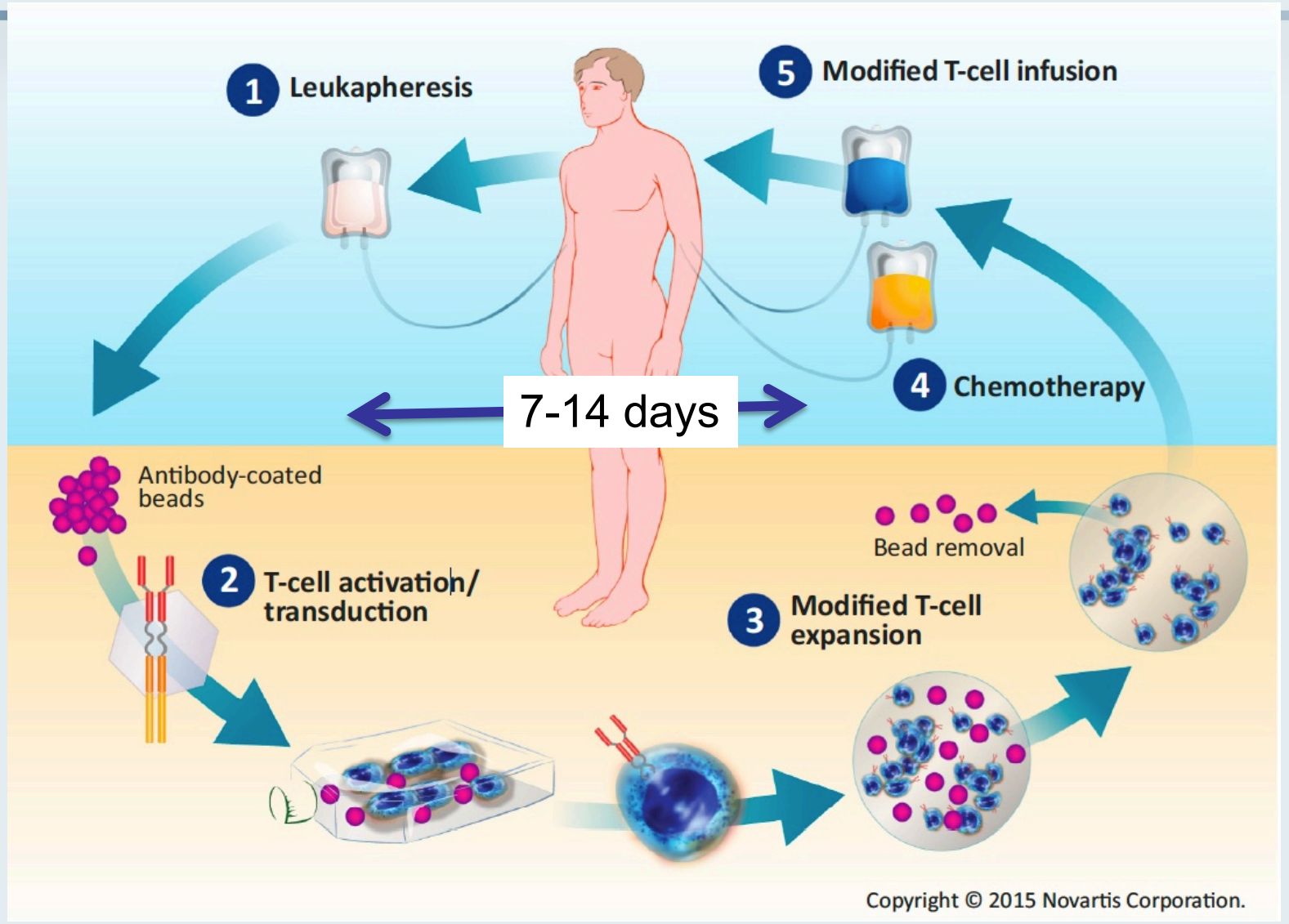
A patient with DLBCL should be in adequate physical condition to undergo autologous stem cell transplant in order to be a suitable candidate for CAR T-cell therapy.

a. Agree

b. Disagree

c. I don’t know

Overview of CAR T-Cell Therapy



Modification, Courtesy, David Porter, MD

Pivotal CAR-T Studies in DLBCL: Study and Patient Characteristics

	ZUMA-1 Axicabtagene ciloleucel	JULIET Tisagenlecleucel	TRANSCEND NHL 001 Lisocabtagene maraleucel
Evaluable patients	101	93	102 (core: 73)
Lymphoma subtypes	DLBCL, transformed lymphoma, PMBCL	DLBCL, transformed lymphoma	DLBCL, transformed lymphoma (core)
≥3 lines of therapy	69%	51%	50%
Refractory to last therapy	77%	54%	67%
Prior auto HCT	21%	49%	38%

Locke F et al; ZUMA-1 Investigators. *Lancet Oncol* 2019;20(1):31-42.
Schuster SJ et al; JULIET Investigators. *N Engl J Med* 2019;380(1):45-56.
Abramson JS et al; TRANSCEND NHL 001 Investigators. *Proc ASCO* 2018;Abstract 7505.

Pivotal CAR-T Studies in DLBCL: Summary of Efficacy

	ZUMA-1 Axicabtagene ciloleucel	JULIET Tisagenlecleucel	TRANSCEND NHL 001 Lisocabtagene maraleucel
Evaluable patients	101	93	102 (core: 73)
Median follow-up	15.4 mo	19.3 mo	12 mo
Best ORR	83%	52%	75%
CR	58%	40%	55%
6-mo ORR	41%	33%	47%
12-mo OS	59%	49%	63%

Locke F et al; ZUMA-1 Investigators. *Lancet Oncol* 2019;20(1):31-42.
Schuster SJ et al; JULIET Investigators. *N Engl J Med* 2019;380(1):45-56.
Abramson JS et al; TRANSCEND NHL 001 Investigators. *Proc ASCO* 2018;Abstract 7505.

Chimeric antigen receptor (CAR) T-cell therapy is commonly associated with…

a. Prolonged cytopenias

b. Rash and skin sensitivity

c. Differentiation syndrome

d. Fever and hypotension requiring care in the ICU

e. Peripheral neuropathy

f. I don’t know

CAR-T-Associated Cytokine Release Syndrome (CRS) and Neurologic Toxicity

CRS — May be mild or life-threatening

- Occurs with CART19 activation and expansion
- Dramatic cytokine elevations (IL-6, IL10, IFNɣ, CRP, ferritin)
- Fevers initially (can be quite high: 105˚F)
- Myalgias, fatigue, nausea/anorexia
- Capillary leak, headache, hypoxia and hypotension
- CRS-related mortality 3% to 10%

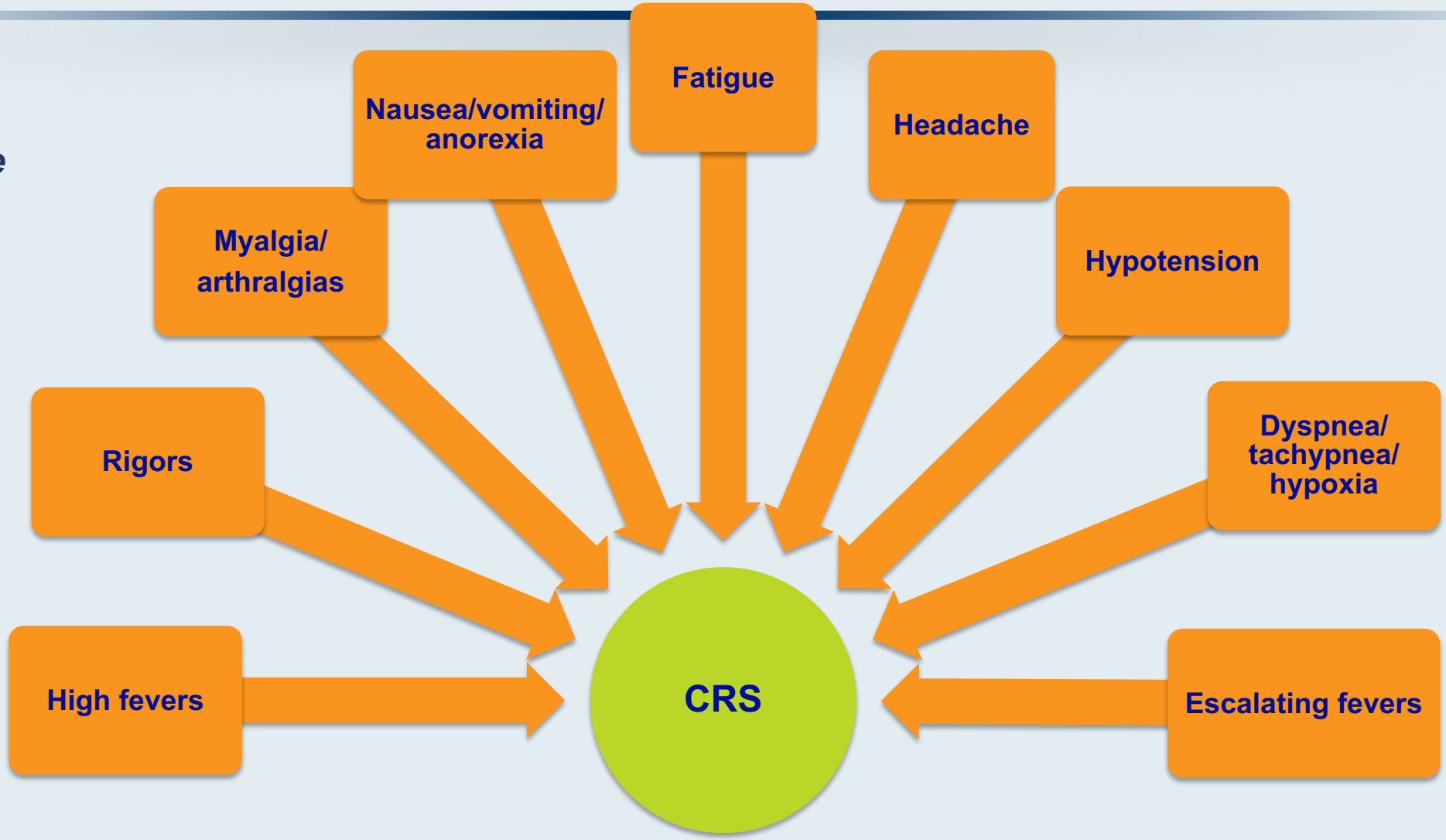
Neurologic toxicity — May be mild or life-threatening

- Mechanism unclear, referred to as immune effector cell-associated neurotoxicity syndrome (ICANS)
- Encephalopathy
- Seizures
- Delirium, confusion, aphasia, agitation, sedation, coma

Varadarajan I, Lee DW. *Cancer J* 2019;25(3):223-30.
Abramson JS et al. ASCO 2019 Education Book.

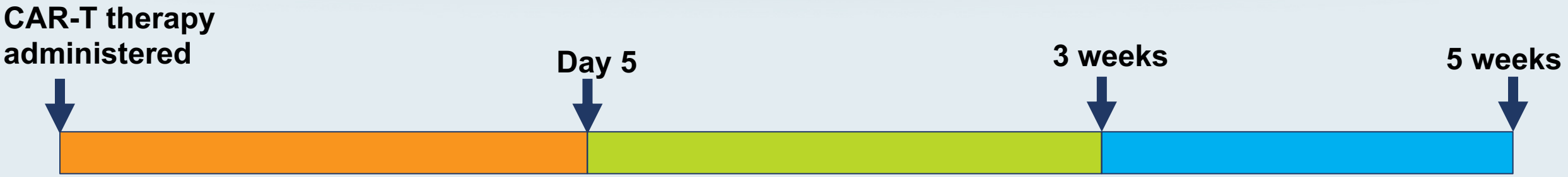
Cytokine Release Syndrome (CRS): Common Symptoms

Based on CAR T-cell experience



Diagnosis based on clinical symptoms and events

CRES: Timeline of Events



Phase 1 (Days 0-5)

- Concurrent with high fever and other CRS symptoms
- Typically shorter duration and lower grade (Grade 1-2)
- Anti-IL-6 therapy is effective

Phase 2 (Day 5 onward)

- CRS and fever have subsided
- Typically longer duration and higher grade (Grade 3+)
- Anti-IL-6 therapy is not effective; corticosteroids recommended

Delayed events

- 10% of patients experienced delayed neurotoxic events, including seizures and episodes of confusion, during the 3rd or 4th week after treatment

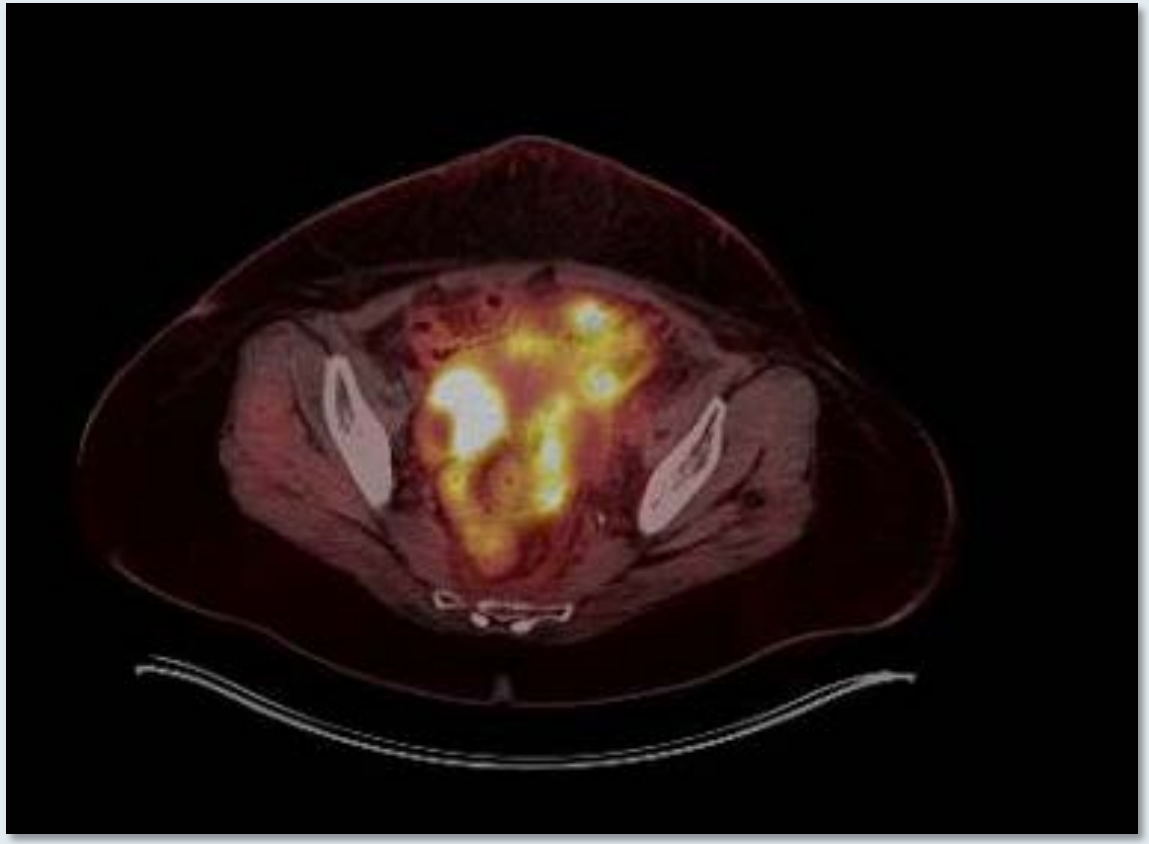
Neelapu SS et al. *Nat Rev Clin Oncol* 2018;15(1):47-62.

59-year-old woman with PMH of CAD, T2DM, and tobacco use (from the practice of Ms Leake)

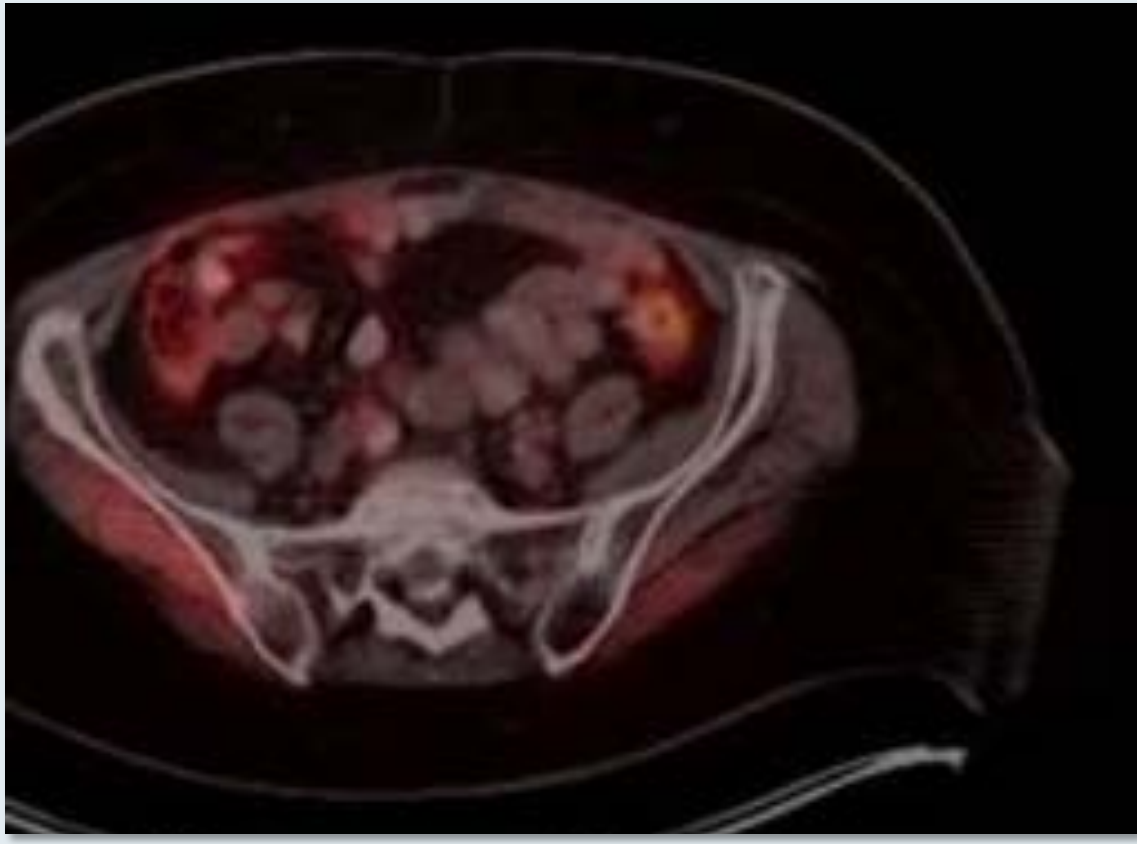
- **3/2018: Stage IV DLBCL,** GCB subtype, t(14;18), extranodal L **ovarian involvement**
- R-CHOP x 6 with prophylactic intrathecal methotrexate and Ara-C
- **3/2019: PD in left ovary**
- R-ICE x 3
- **7/2019:** R-BEAM / **autoSCT** with consolidative XRT
- 10/2019: PD (peritoneal lymphomatosis)
- **11/2019: BR-polatuzumab vedotin** x 2 prior to cell collection for CAR T
- **02/2020: CAR T-cell therapy** (cyclophosphamide/fludarabine lymphodepletion)
  - Tolerated fairly well, with some CRS, neurotoxicity
- Currently, in remission and doing well

59-year-old woman (from the practice of Ms Leake)

Relapse – prior to polatuzumab vedotin



After 2 cycles of polatuzumab vedotin



59-year-old woman (from the practice of Ms Leake)

Patient Education

- Infection risk: Instruct on fever, neutropenia and s/s of infection to include cough, mouth sores
- Peripheral neuropathy: Burning, numbness, or tingling that is new or worse, or balance changes.
- Tumor lysis: Mood changes, confusion, muscle pain/cramps, heartbeat that does not feel right, seizures, decreased appetite, vomiting or upset stomach
- Fatigue: Weakness
- PML
- Hepatotoxicity: Dark urine, fatigue, stomach pain, light-colored stools, emesis, yellow eyes or skin
- Infusion reactions
- Constipation/diarrhea
- PPX with PJP/HSV prevention.
- Bleeding: Coughing up blood, blood in urine, stools (black, red or tarry stools).
- Vomiting/nausea
- Smoking cessation: Tobacco treatment program through UVA

59-year-old woman (from the practice of Ms Leake)

Symptom Management

- Bowel regimen: Constipation (stool softeners, laxatives) or diarrhea (loperamide, probiotics, etc)
- Hydration (encourage fluids)
- Anti-nausea medication
- Mouth care
- Chronic pain: Pain regimen prescribed and managed by palliative

Psychosocial Support

- Integrate and collaborative SW care into plan of care-financial support, lodging, etc. Patient does not live local and family members not readily available to assist with care
- Collaborative care with palliative for chronic pain
- Possible antidepressant: Assess need
- Mindfulness–based stress

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Module 2: Hodgkin Lymphoma (HL) and Peripheral T-Cell Lymphoma (PTCL)

- Brentuximab vedotin, immune checkpoint inhibitors

Based on the results of the Phase III ECHELON-1 trial, which of the following regimens resulted in a progression-free survival advantage over standard ABVD as first-line therapy for patients with Stage III or IV classical Hodgkin lymphoma (HL)?

a. ABVD + bendamustine

b. ABVD + nivolumab

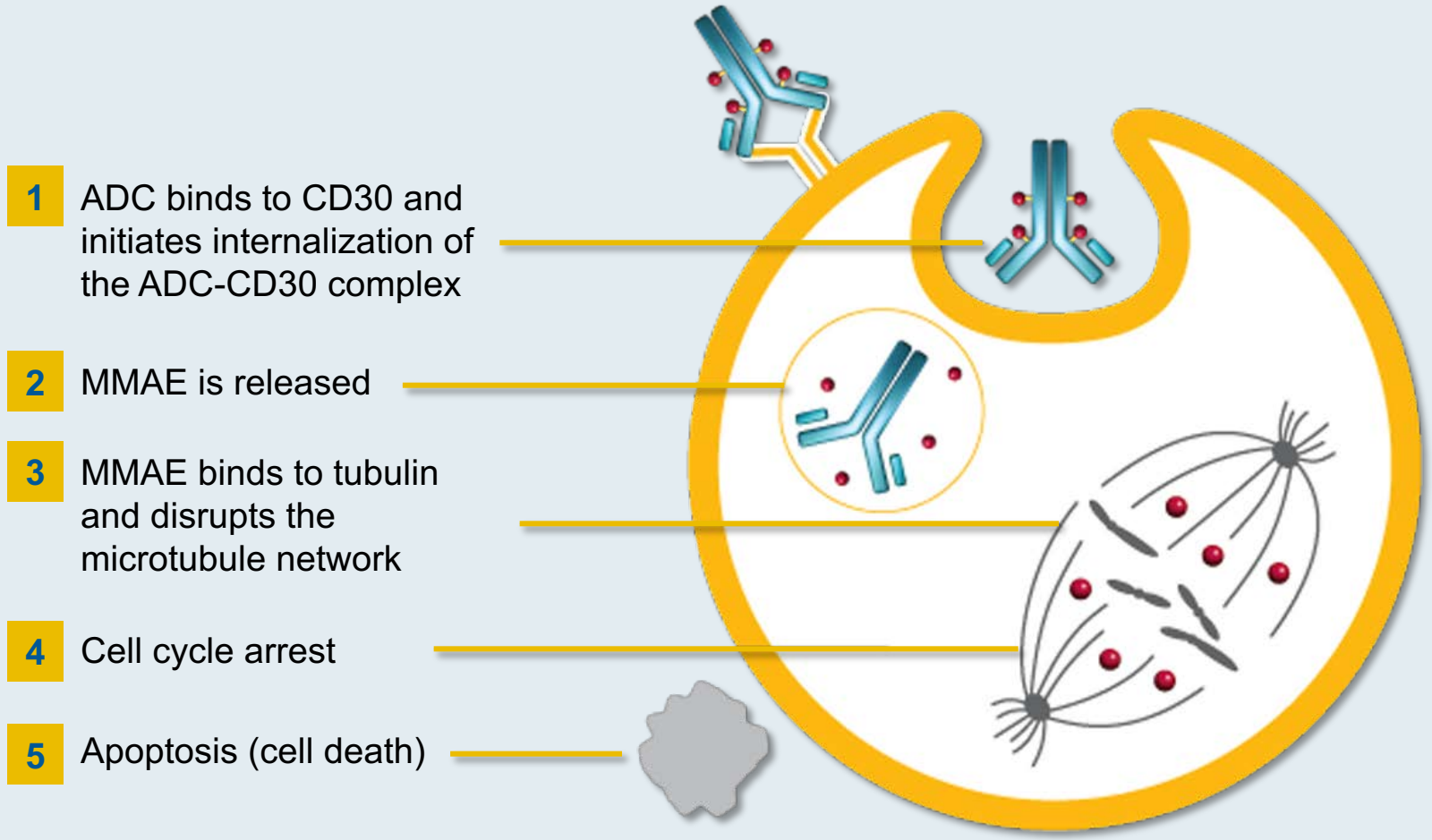
c. AVD + brentuximab vedotin

d. Brentuximab vedotin + nivolumab

e. I don’t know

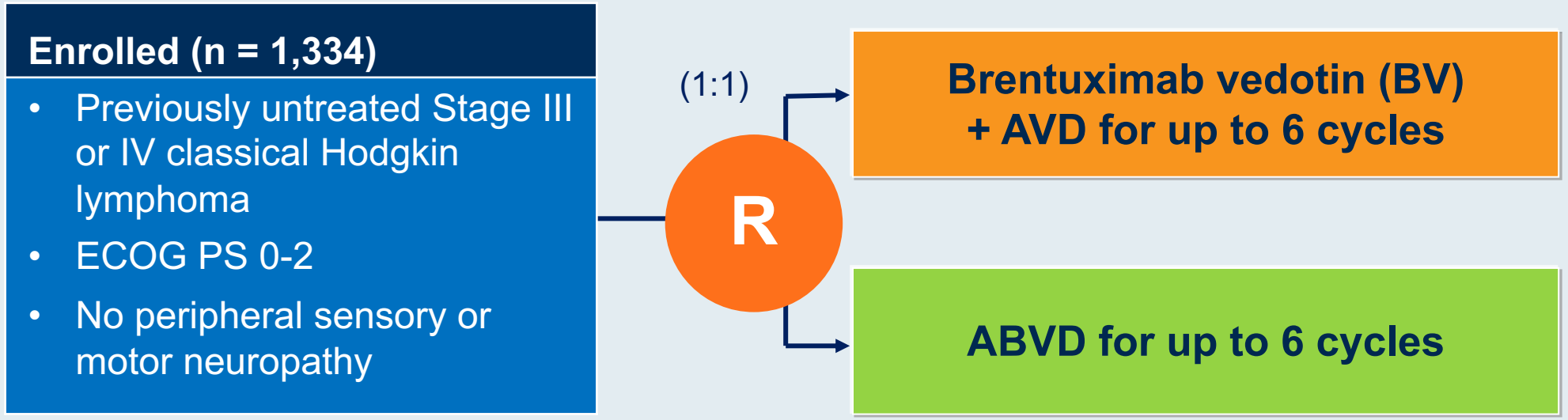
Mechanism of Action of Brentuximab Vedotin

Brentuximab vedotin is an antibody-drug conjugate (ADC) targeted to cells expressing CD30 on their surface



Courtesy of Julie M Vose, MD, MBA.

ECHELON-1 Phase III Study Schema



Primary endpoint: Modified progression-free survival
Key secondary endpoint: Overall survival

Straus DJ et al. *Proc ASCO* 2019;Abstract 7532.
Connors JM et al. *N Engl J Med* 2018;378:331-44.

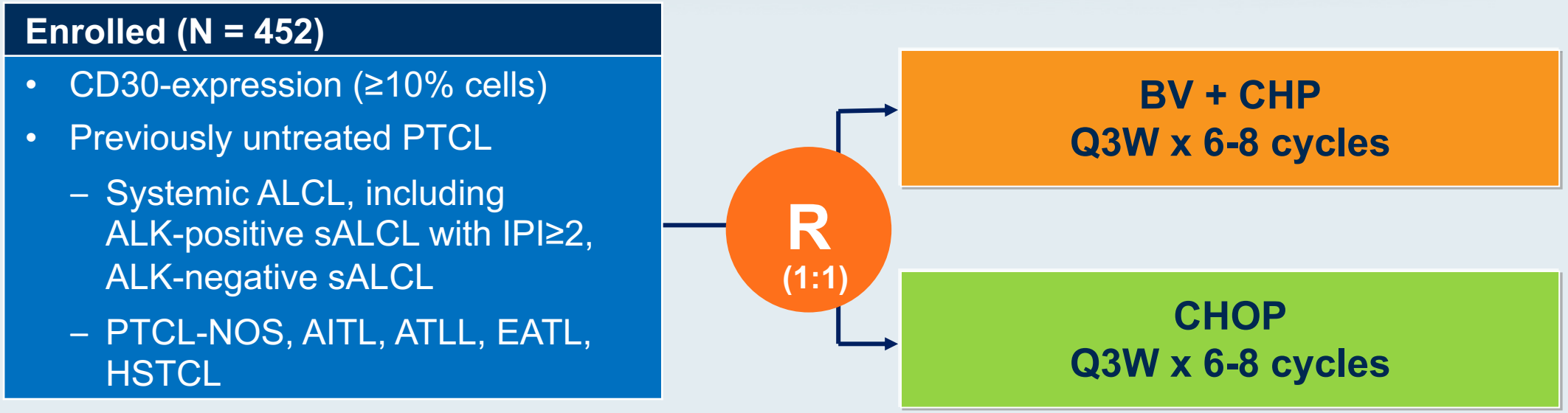
Update of ECHELON-1: PFS at 42 Months

Group	BV + AVD	ABVD	Hazard ratio
All patients (ITT) (n = 664, 670)	82.4%	76.2%	0.697
PET2-negative	85.0%	79.6%	0.695
PET2-positive	68.3%	51.5%	0.552

PET2, PET conducted at the end of the second 28-day cycle of treatment

Bartlett NL et al. ASH 2019;Abstract 4026.

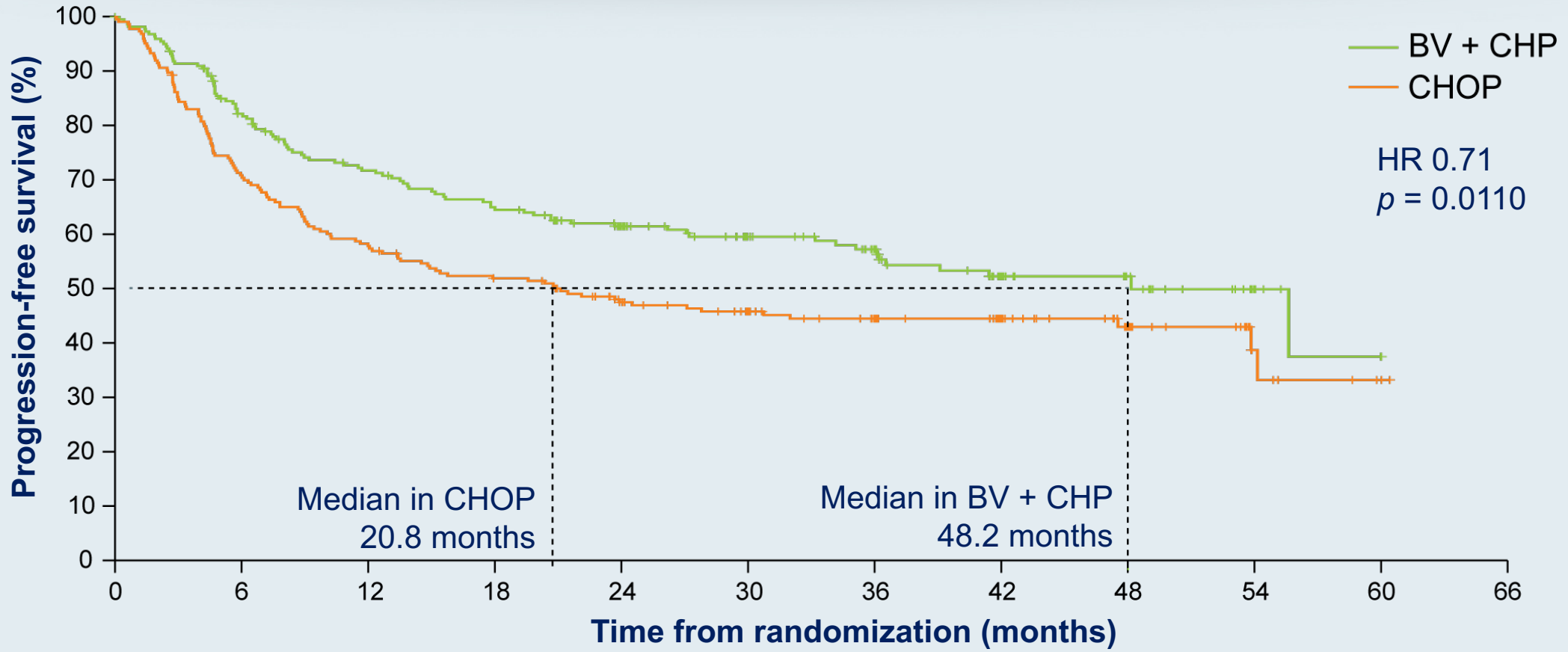
ECHELON-2 Phase III Study Schema



Primary endpoint: Modified progression-free survival
Key secondary endpoint: Overall survival

Illidge T et al. EHA 2019;Ab PS1070.

ECHELON-2: Efficacy of Brentuximab Vedotin + CHP versus CHOP in CD30-Positive PTCL



- Median OS was not reached in either subgroup ($p = 0.0244$, HR 0.66), though it was numerically in favor of BV + CHP for key patient subgroups analyzed.

Horwitz S et al. *Lancet* 2019;393(10168):229-40.

Patients at high risk for disease progression after undergoing transplant for relapsed HL may receive 1 year of consolidation treatment with…

a. Nivolumab

b. Brentuximab vedotin

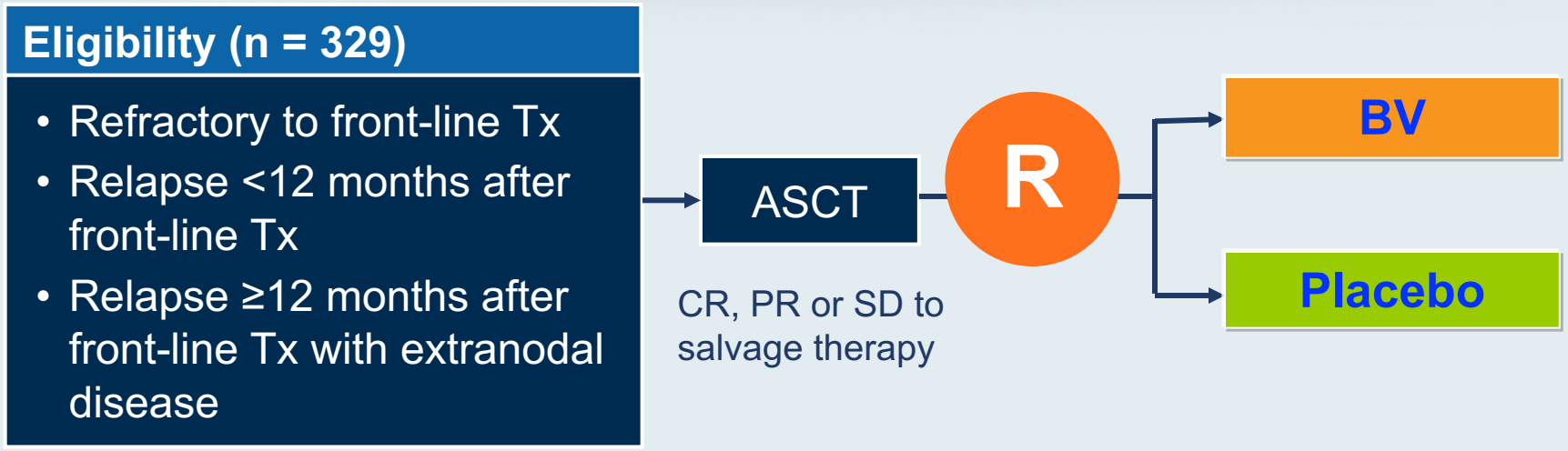
c. Nivolumab + brentuximab vedotin

d. Chemotherapy

e. Other

f. I don’t know

AETHERA Phase III Trial: BV Consolidation After Transplant



- Median PFS update (median 5 years follow-up):
  - BV: not reached
  - Placebo: 15.8 mo
- No OS benefit at interim analysis (analysis planned for 2020)

Moskowitz CH et al. *Lancet* 2015;385(9980):1853-62; Sweetenham J et al. *Proc ASH* 2015;Abstract 3172; Moskowitz CH et al. *Blood* 2018;132(25):2639-42.

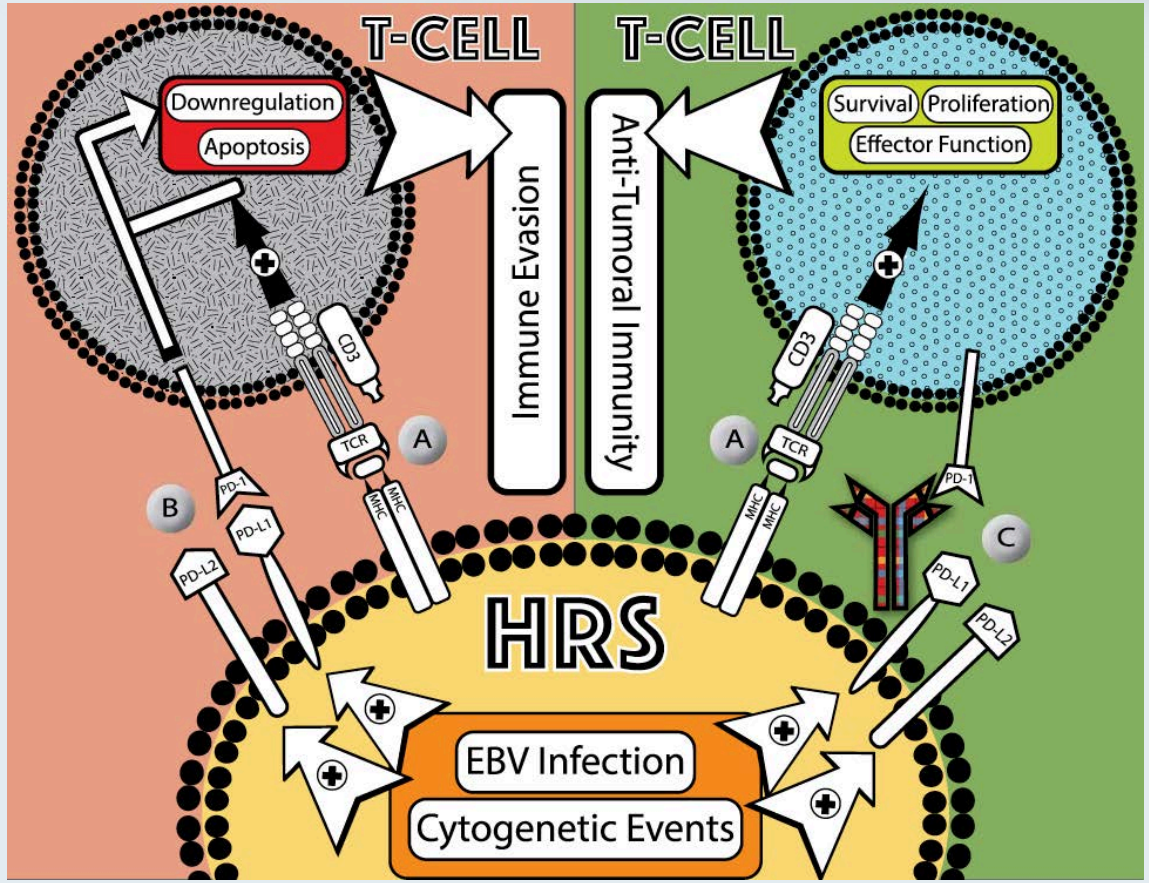
Relapsed HL can be effectively palliated with systemic therapy but cannot be cured.

a. Agree

b. Disagree

c. I don’t know

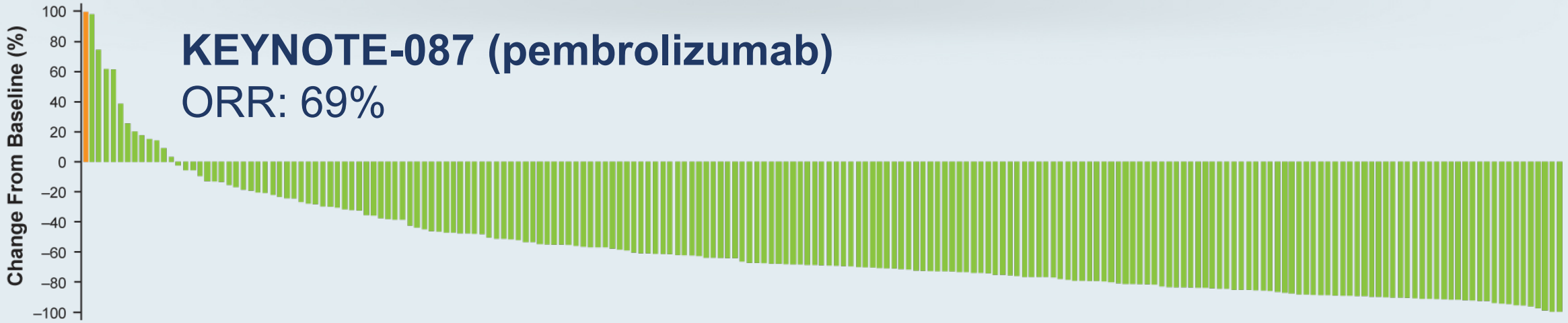
Targeting the PD-1/PD-L1 Axis in HL

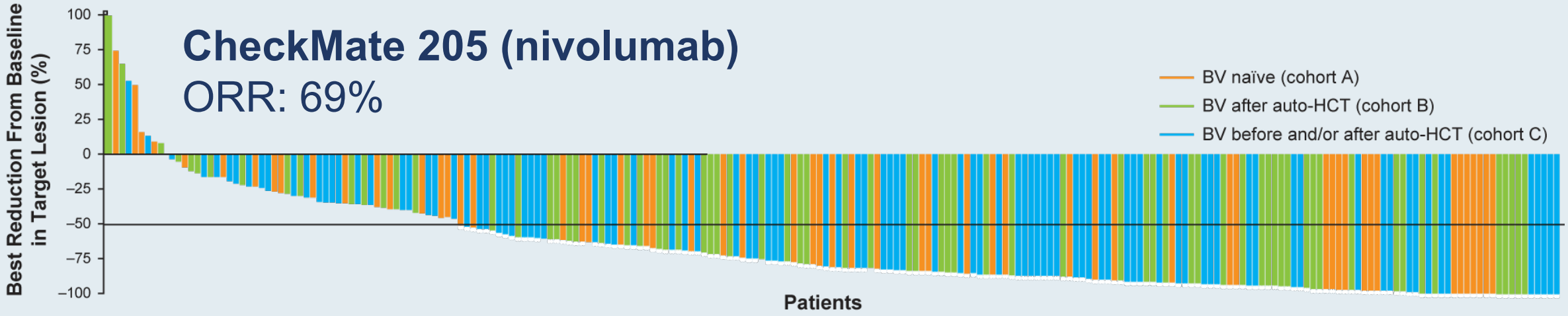


- **HL characterized by small number of malignant Hodgkin Reed-Sternberg cells (HRS) surrounded by normal immune cells**
- 9p24.1 chromosomal abnormalities frequently observed in HRS
- **More than 90% of HRS have alterations in PD-L1 and PD-L2 loci**
- Malignant Hodgkin and RS cells overexpress PD-L1/L2 ligands (due to cytogenetic events, infection with EBV)

Villasboas JC, Ansell SA. *Cancer J* 2016;22(1):17-22; Roemer MGM et al. *J Clin Oncol* 2016;34(23):2690-7.

Immune Checkpoint Inhibitors in R/R HL





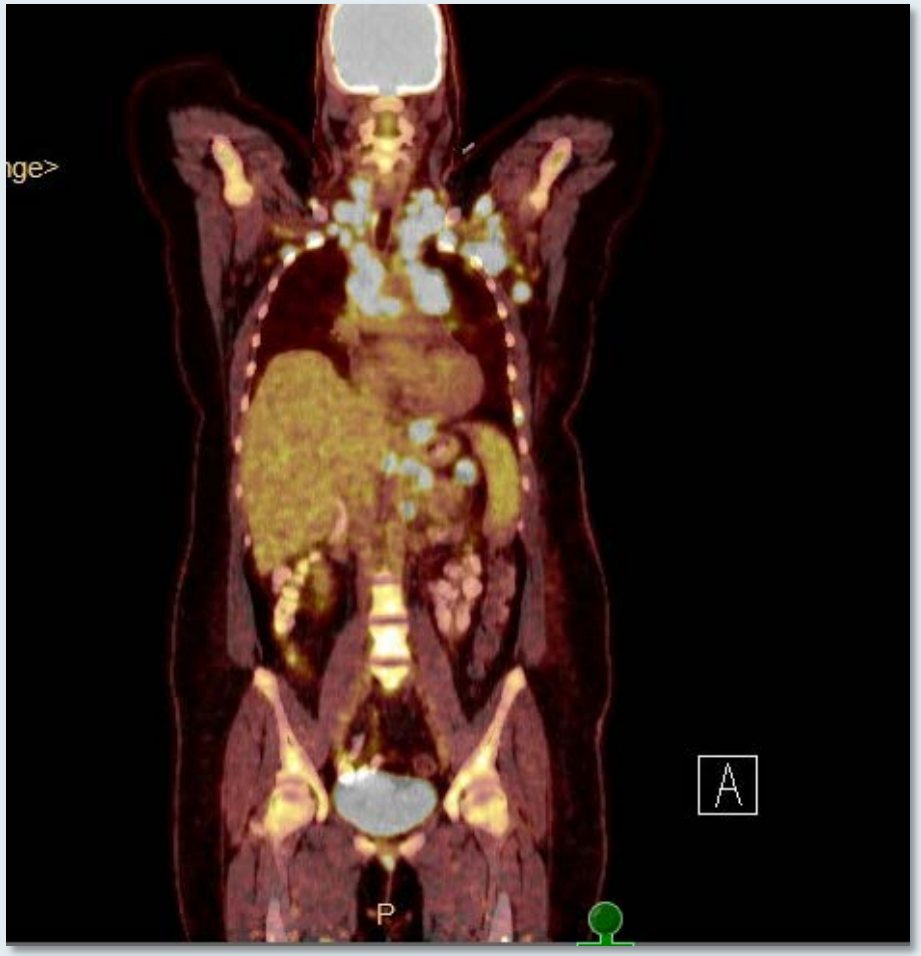
Chen R et al. *J Clin Oncol* 2017;35(19):2125-32; Armand P et al. *J Clin Oncol* 2018;36(14):1428-39.

31-year-old woman (from the practice of Ms Moran)

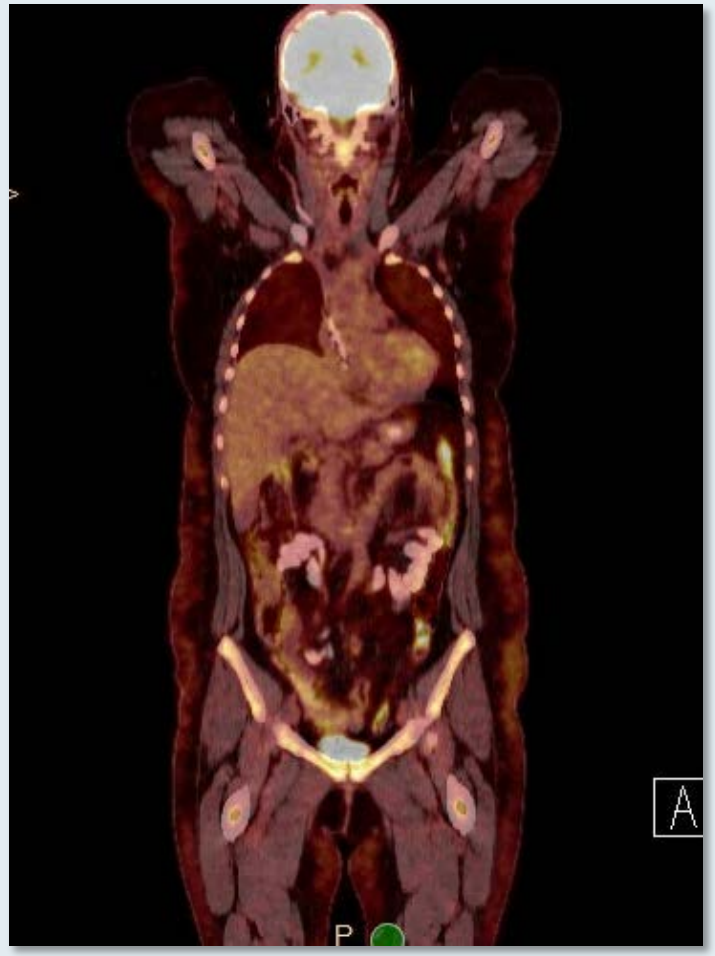
- 2018: Presented to PCP with acute onset of cough – No relief from antibiotics and steroids
- ER with palpitations, believed to be due to pseudoephedrine
  - CTPE: Perivascular LNs 2.6 x 2.3 cm, Hilar LN 2.6 cm, FNA: Negative for malignancy
- 12/2018 repeat of CT: No change to LNs
- 4/2019 skin rash biopsy: Positive for erythema nodosum
  - WBC 12.1, Hgb 10.4, Albumin 3.5, ESR 51
- 5/2019 repeat CT scan: Increased chest LNs, splenic mass
- 6/2019 LN Biopsy: Stage IV nodular sclerosing Hodgkin lymphoma (EBER-negative)
  - IPS 3, Hgb <10.5, Albumin <4
- ABVD + BV x 6 → PET-negative after 2 cycles, EOT PET: Negative
  - BV dose reduced C2 due to peripheral neuropathy
  - Vinblastine decreased by 25% then 50% then discontinued due to peripheral neuropathy

31-year-old woman (from the practice of Ms Moran)

Before ABVD + BV



After ABVD + BV



Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL)

- Polatuzumab vedotin, CAR T-cell therapy

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Module 3: Follicular Lymphoma (FL)

- Lenalidomide/rituximab (R^2), PI3K inhibitors

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- BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib), venetoclax, lenalidomide

Module 5: Management of Lymphomas in the Era of COVID-19

- Telemedicine, minimization of surgeries, reduced infusions and clinic visits

Module 3: Follicular Lymphoma (FL)

- Lenalidomide/rituximab (R^2), PI3K inhibitors

Patients with advanced-stage follicular lymphoma (FL) who are not experiencing symptoms from their disease may receive treatment with…

a. Observation

b. Rituximab

c. Chemotherapy + anti-CD20 antibody

d. All of the above

e. a and b only

f. I don’t know

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

RITUXIMAB PROVIDES LONG REMISSIONS IN LOW TUMOR BURDEN FOLLICULAR LYMPHOMA

In patients who responded to Rituximab weekly x 4 doses, a clinical trial compared:

- Maintenance R (MR): continue R one dose q3 months until relapse, vs
- Retreatment R (RR): at relapse, repeat weekly R x4 doses

Results:

- Median time to R failure: 3.9 y (RR) vs 4.3 y (MR)
- Few patients at 3 y required chemo: 84% vs 95%
- Much less rituximab with RR strategy: 4 vs 18 doses
- About 30% remain in remission 5y after R x 4 weekly doses

- **Conclusion:** Favors Rituximab retreatment at time of relapse rather than ongoing maintenance therapy

Rituximab extended schedule or re-treatment trial for low-tumor burden follicular lymphoma: eastern cooperative oncology group protocol e4402. Kahl, Wong, Williams et al. JCO 2014

Comparison of Cell Death Induced by Obinutuzumab and Rituximab

Type II anti-CD20 antibody[1]

Enhanced DCD vs rituximab[2]

Glycoengineered Fc region[3]

Up to 100-fold increase in ADCC vs rituximab[3,4]

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).

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

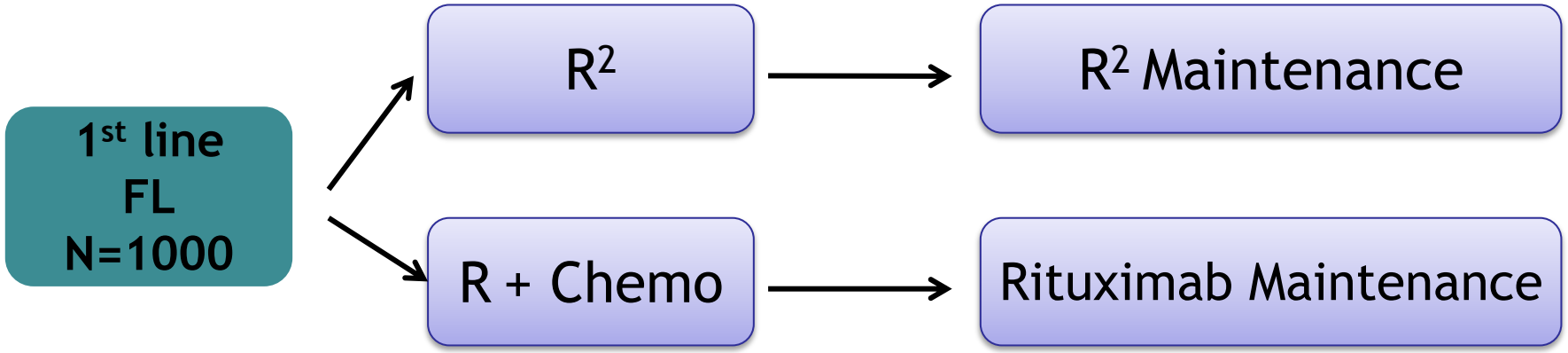
b. Lenalidomide/rituximab has less toxicity

c. BR has less toxicity

d. I don’t know

Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma: RELEVANCE Study

Rituximab and Lenalidomide vs. R-Chemotherapy



- R + chemo: Investigator's choice of R-CHOP, R-CVP, BR
- R + Oral Len 20 mg d 1-21 for 6 cycles, then Len10 mg

N Engl J Med 379:934-947, September 6, 2018
El J Med
Volume 379(10):934-947
September 6, 2018

RELEVANCE TRIAL: Summary
Untreated, advanced-stage FL (n=1030)

- Phase 3 trial of Len/R vs R-Chemo
- After a median follow-up of 39 months:

- **Complete Remission**: Len/R 48% vs R-Chemo 53%
- **Progression-free survival**: 77% vs 78%
- **Overall Survival**: 94% in each arm

- **Conclusion:** Len/R provided similar benefit to R-chemo, with generally fewer toxicities aside from rash

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What is the usual second-line therapy for a patient with FL who experiences disease progression on first-line BR?

a. Re-treatment with BR

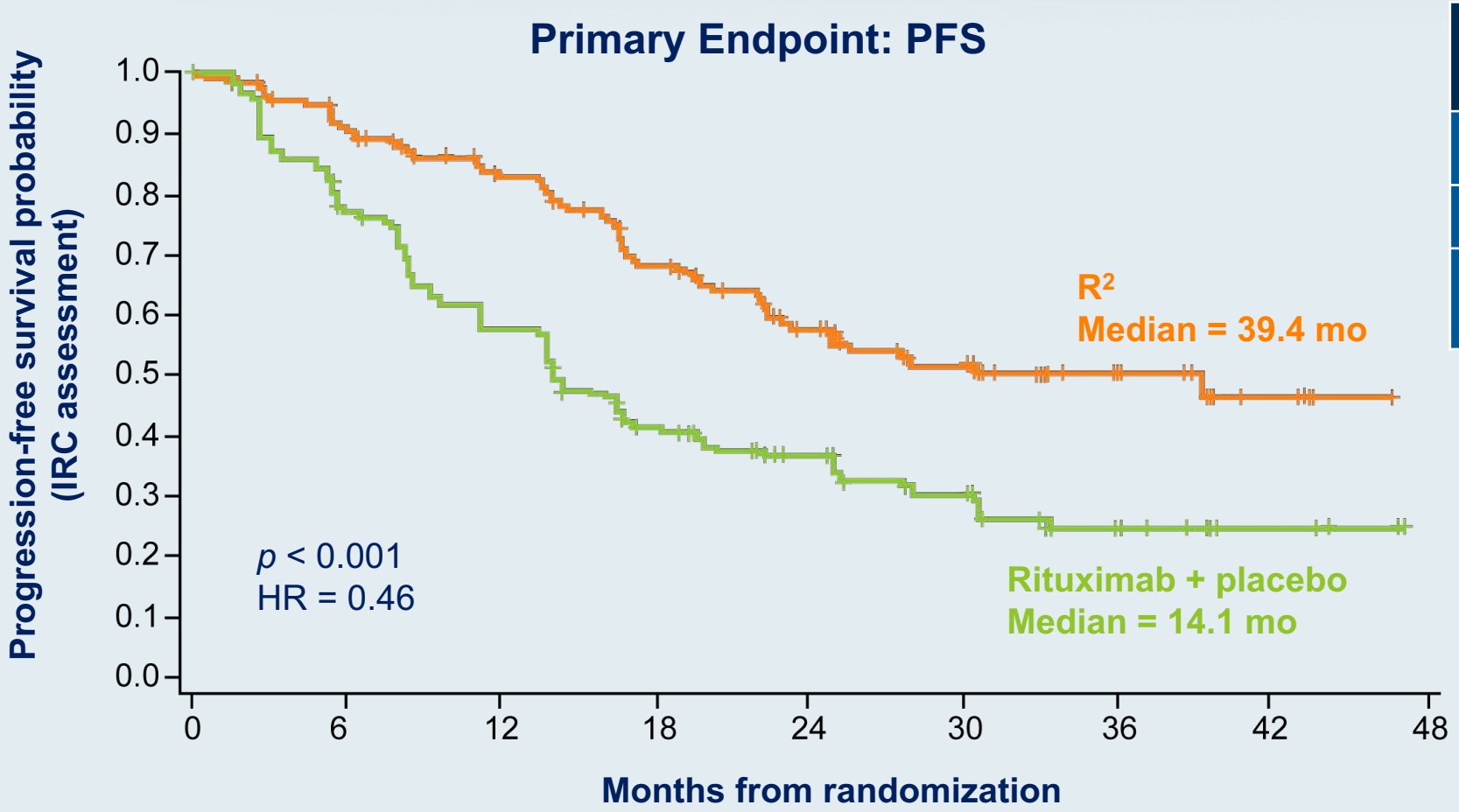
b. Obinutuzumab/bendamustine

c. Rituximab/lenalidomide

d. A PI3K inhibitor (eg, idelalisib, copanlisib, duvelisib)

e. I don’t know

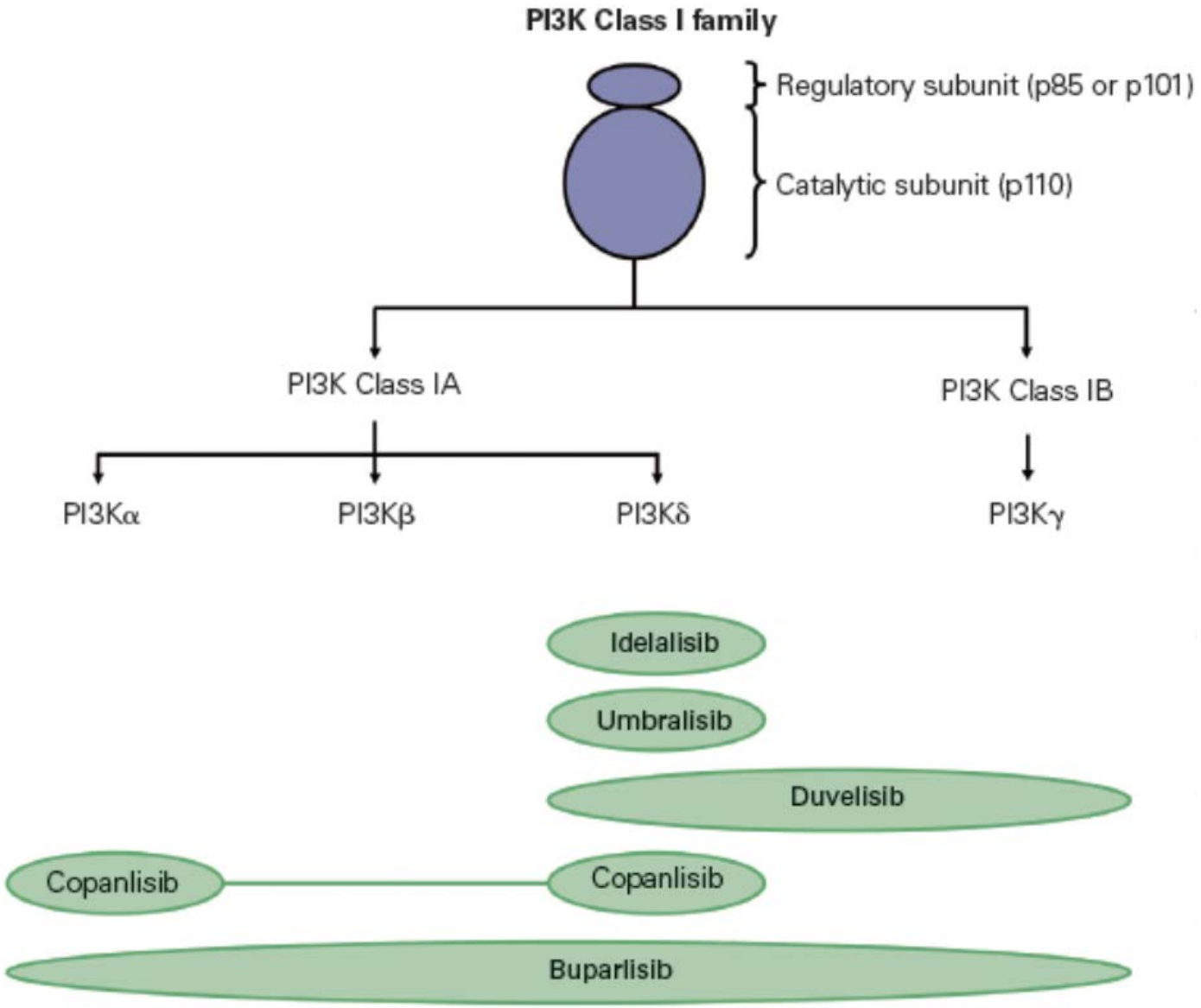
AUGMENT Trial: R^2 versus Rituximab/Placebo in R/R FL or Marginal Zone Lymphoma



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

Leonard JP et al. *J Clin Oncol* 2019;37(14):1188-99.

PI3Ki (Phosphatidylinositol 3-kinase inhibitors) in FL



(Greenwell IB et al. Oncology Journal 2017; 31)

Approved PI3K inhibitors in R/R Follicular Lymphoma

	Idelalisib	Copanlisib	Duvelisib
FDA approval	Jul 29, 2014	Sep 14, 2017	Sep 24, 2018
Isoforms	PI3K delta	Pan-PI3K	PI3K delta/gamma
Formulation	150 mg **PO** BID	60 mg **IV** Q weekly 3 wks on, 1 wk off	25 mg **PO** BID
Indication in FL	Relapsed after at least two prior systemic therapies	Relapsed after at least two prior systemic therapies	Relapsed after at least two prior systemic therapies
Pivotal trial	iNHL, no response to rituximab and an alkylating agent or relapse within 6 mo	Rel/refr FL	Rel/refr FL
Results	iNHL, n=125 **ORR 57%, CR 6%**	FL, n=104 **ORR 59%, CR 14%**	FL, n=83 **ORR 42%, 1 CR**
	mDOR 12.5 mo	**mDOR 12.2 mo**	**43% maintained responses for ≥6mo, 17% maintained responses for ≥12mo**
Side effects	**Pneumonitis, transaminitis, colitis**	**Hyperglycemia, hypertension**, infections, neutropenia	**Infection, diarrhea or colitis, and pneumonia**

S deVos Sep 2019 (Gopal A, et al. NEJM 2014; 370:1008-18)

(https://www.fda.gov/Drugs/Information)

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

a. Thrombocytopenia

b. Rash

c. Hyperglycemia

d. I don’t know

Patients receiving idelalisib and duvelisib may develop delayed-onset…

a. Renal dysfunction

b. Immune-related pneumonitis

c. Hypothyroidism

d. All of the above

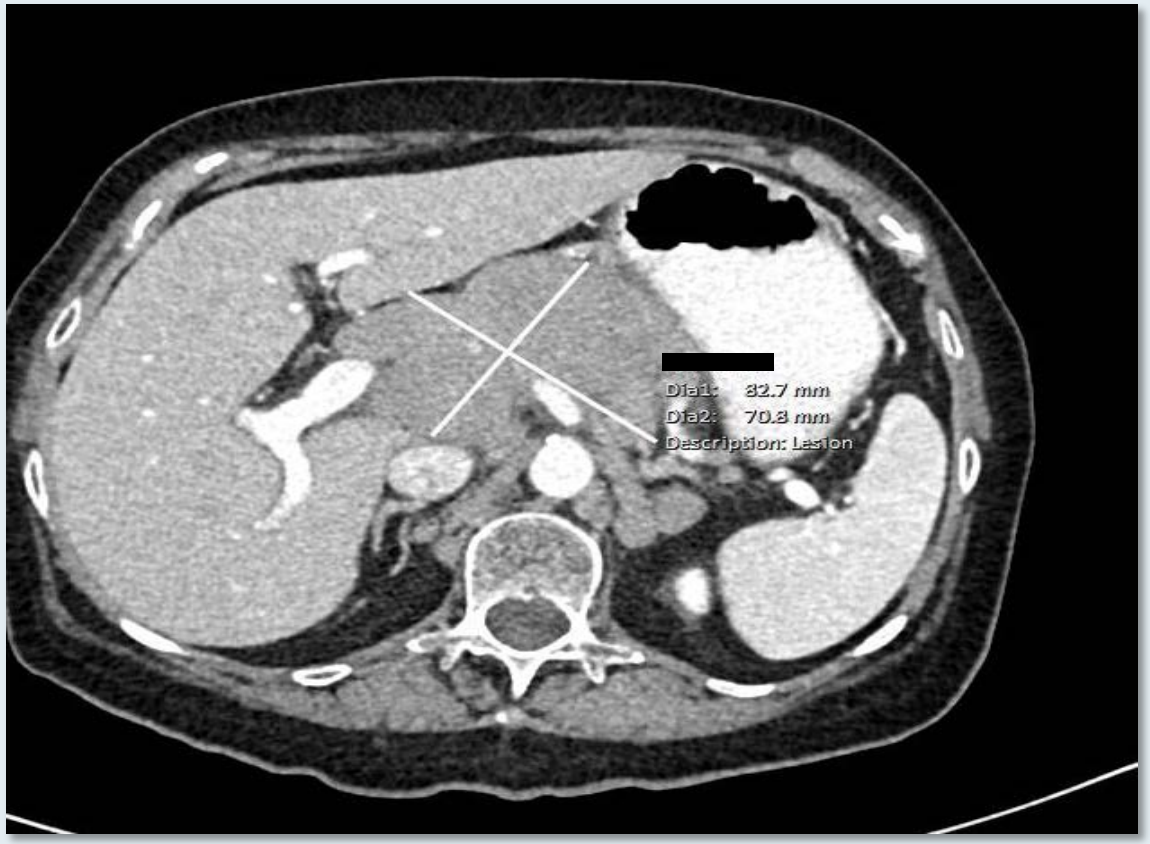
e. I don’t know

Very active 75-year-old woman and business owner (from the practice of Ms Leake)

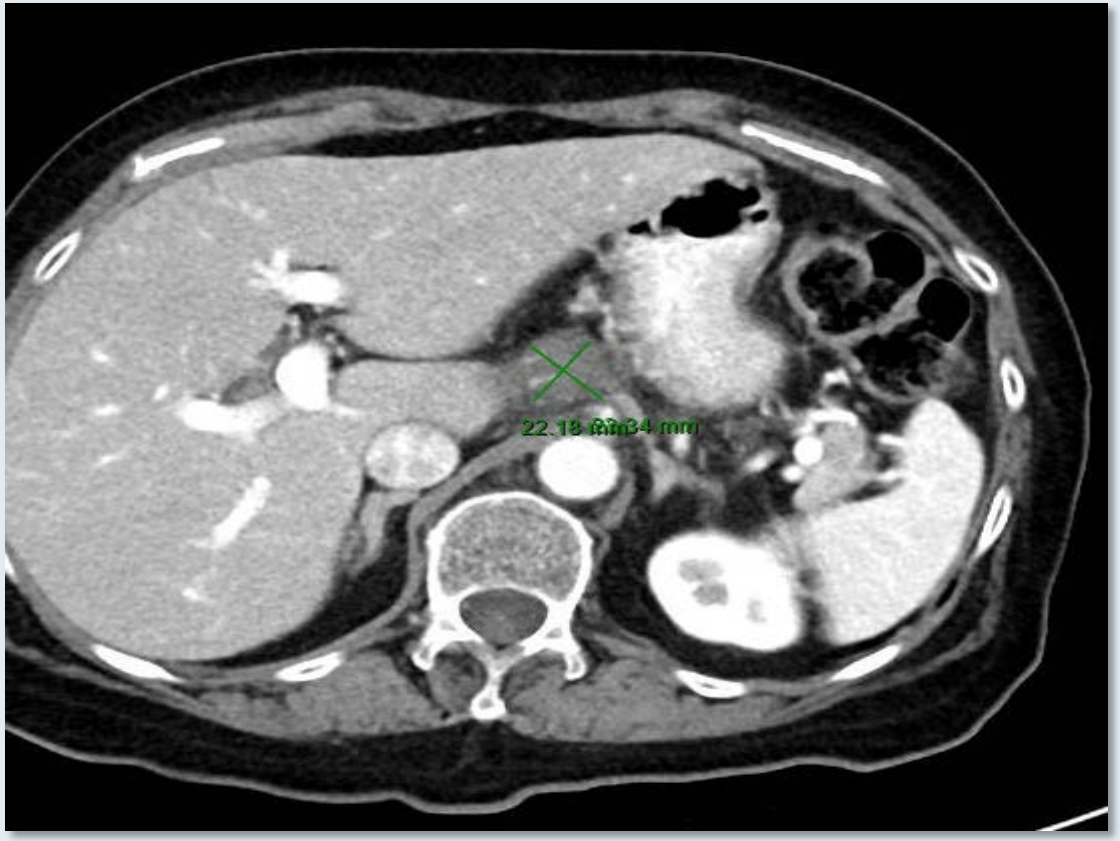
- 2004: Diagnosed with follicular lymphoma
  - Spontaneous regression w/o treatment
- 2013: Recurrent lymphoma
  - RCHOP x 6
  - 9/2013 Post-treatment PET/CT: Consistent with CR
- 6/2019: Recurrence, consistent with prior FL transformed to Grade 3b
- Rituximab weekly x 4 doses + lenalidomide 20 mg daily x 12
- 9/2019: Maintenance monthly rituximab x 1 year, continue lenalidomide 20 mg
  - Changed rituximab to every 2 months due to COVID-19 pandemic
  - Lenalidomide reduced to 10 mg due to GI cramping

Very active 75-year-old woman (from the practice of Ms Leake)

6/5 – Pre-treatment with R^2



11/26/19 – Restage



Very active 75-year-old woman (from the practice of Ms Leake)

Plan of Care

- Frequency of rituximab changed to every 2 months due to COVID
- Decreased lenalidomide to 10 mg po due to intolerance r/t abdominal cramping and nausea; Improved symptoms since dose change
- Reimage for response
- Reinforced with each visit- counseling re Rx regimen, symptom management and precautions during COVID epidemic; understands the increased risk for severe infection due to age, lymphoma and current treatment regimen

Very active 75-year-old woman (from the practice of Ms Leake)

Patient Education

- Controlled drug: Discussed patient survey and patient/physician agreement with compliance
- Hazardous handling of medication; Timing of drug, frequency and storing of medication
- Rash and fatigue
- GI upset: Constipation, diarrhea, nausea, vomiting and cramping
- Peripheral neuropathy
- Low blood counts (anemia, thrombocytopenia, neutropenia)
- Dosing with frequency and storing.
- Monitor for SOB, CP, cough or extremity swelling (PE/DVT): Anticoagulant-aspirin-prophylaxis
- May cause dizziness (lenalidomide)
- Hepatitis reactivation: Monitor Hep B (rituximab)
- PML: Neuro changes
- Infection risk: Due to low blood counts and impaired immune system.
- Immunization: Low response to vaccines-no live vaccines.

Very active 75-year-old woman (from the practice of Ms Leake)

Symptom management

- Fatigue: Encourage exercise, rest and well-balanced meals
- Low blood counts: Growth factor for neutropenia or blood products
- Neuropathy: Measures to minimize discomfort if present and safety
- GI upset: Antiemetic, stool softener/laxative, loperamide
- Rash: Topical steroid or antihistamine
- Monitor chemistries: Adjust meds prn

Psychosocial support

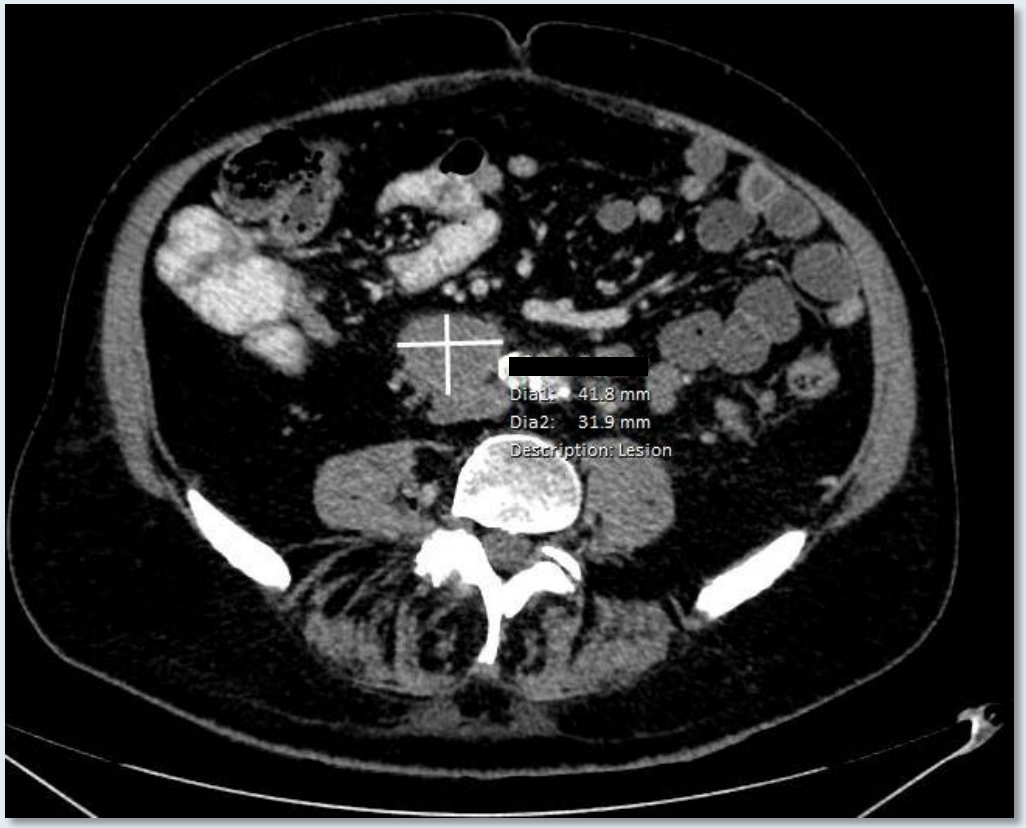
- Continue to support lifestyle changes: Encourage healthy living, exercise, well rounded diet and pursue outside interests
- Working is very important for patient: Encourage to continue working but with limitations based on fatigue and ability to perform tasks any given day
- Lifestyle: Plays golf, travel and family

85-year-old man with PMH of CAD, HFprEF, HTN, MDD, BPH, osteoarthritis and chronic pain (from the practice of Ms Leake)

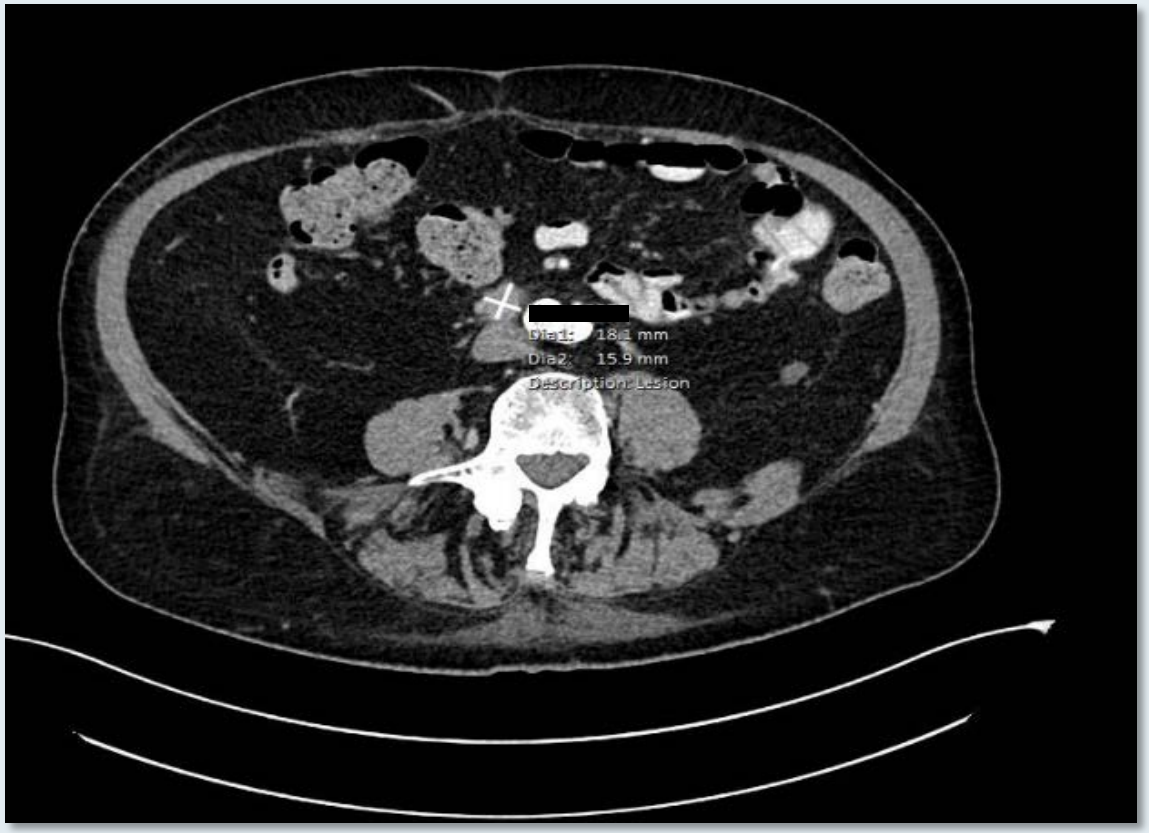
- 12/2016: Low-grade small B-cell Lymphoma with high IgM level, bladder wall involvement and right axilla
- BR x 6 (dose reduced due to age, PS)
  - 6/2018: Post-treatment PET/CT: CR
- 1/2019: Cervical lymph node B cell lymphoma
- R-CVP x 1 → mini-R-CHOP x 2 → PD one month later
- 4/2019: Palliative copanlisib, with dramatic response
- 7/2019 MRI: Lymphomatous mass T11 vertebral body treated with RT
- 8/2019: Rapid decline, hospice, patient dies

85-year-old man (from the practice of Ms Leake)

Pre-Copanlisib (3/27/2019)



Post-Copanlisib (7/2019)



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Module 4: Mantle Cell Lymphoma (MCL)

- BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib), venetoclax, lenalidomide

In general, patients with mantle cell lymphoma (MCL) have a poor short-term prognosis and require treatment even if they are asymptomatic.

a. Agree

b. Disagree

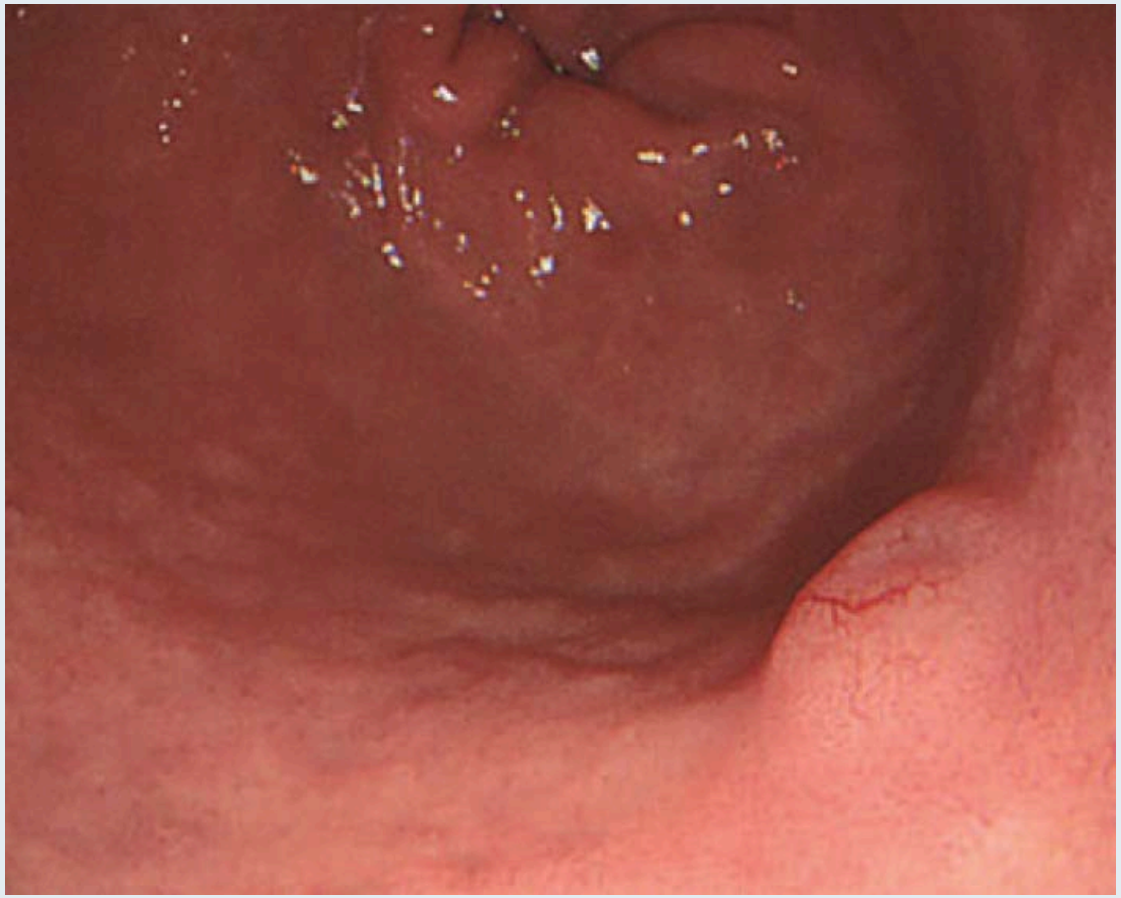
c. I don’t know

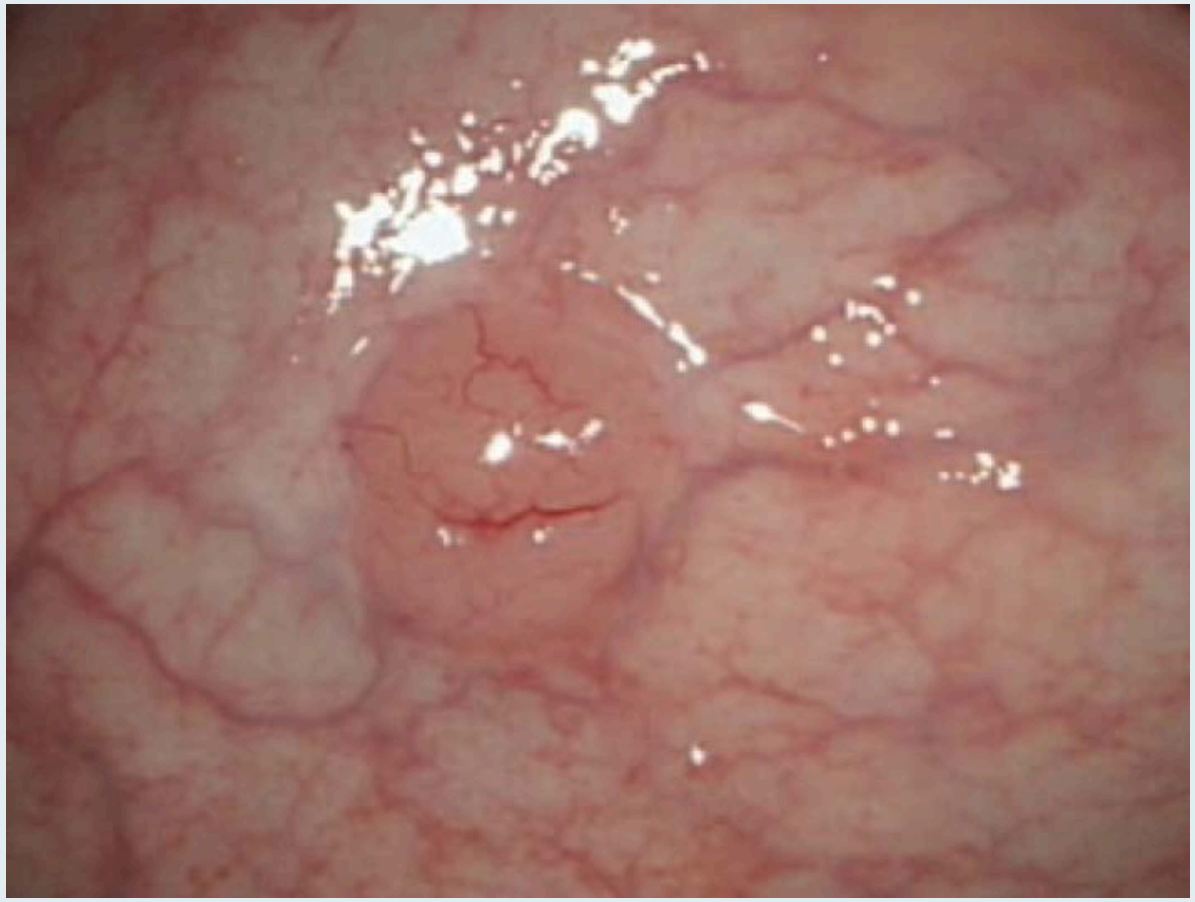
Mantle cell lymphoma: Typical Presentation

- 74% male, average age 63 years
  - **Usually advanced stage at diagnosis**
- Diffuse adenopathy and splenomegaly
- GI tract and other sites of extranodal involvement are common
- Clinical spectrum ranges from indolent to very aggressive disease

Gastrointestinal Involvement in MCL

Case report: Submucosal lesions in the gastric antrum, duodenal bulb and rectum by endoscopy





Li D et al. *Medicine* 2017;96:11(e6321).

What is generally the most common second-line therapy for patients with mantle cell lymphoma who experience disease progression on first-line BR?

a. A BTK inhibitor (eg, ibrutinib, acalabrutinib)

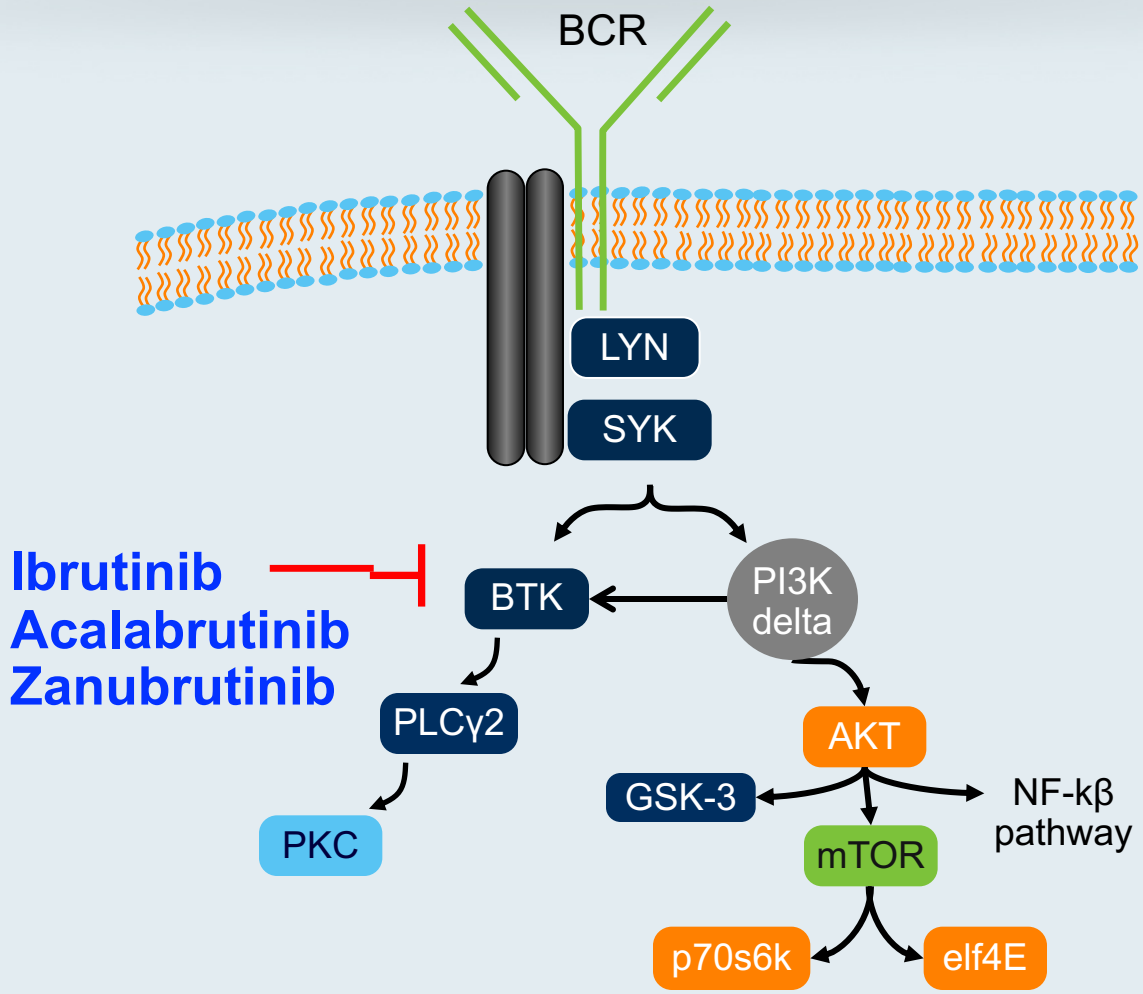
b. Lenalidomide/rituximab

c. Bortezomib

d. Venetoclax

e. I don’t know

Mechanism of Action of BTK Inhibitors

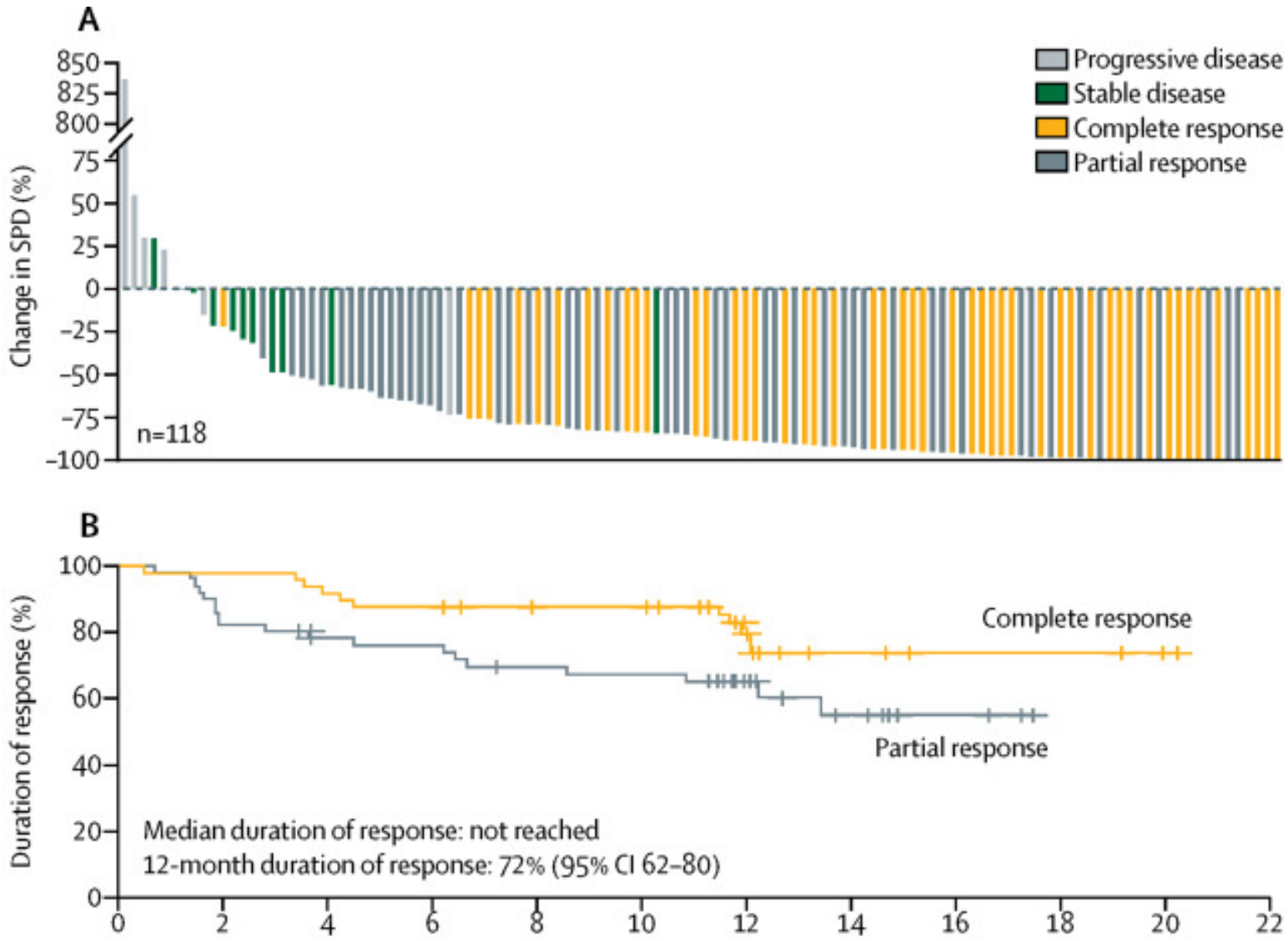


Woyach JA et al. *Blood* 2012;120(6):1175-84.

Targeted, non-Chemotherapy Approaches for Relapsed/Refractory MCL

Agent	N	Response Rate	mDOR (mo.)
Bortezomib	155	33%	9.2 m
Temsirolimus	54	22%	7.1 m
Lenalidomide	134	28%	16.6 m
Lenalidomide-rituximab	52	57%	18.9 m
Idelalisib	40	40%	4 m
Ibrutinib	111	68%	17.5 m
Acalabrutinib	124	81%	72% at 12 m
Zanubrutinib	86	84%	16.7 m
Venetoclax	28	75%	12 m
Ibrutinib-Venetoclax	24	71% (all CR)	80% at 12 m

Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, phase 2 trial



Wang M, et al. Lancet 2018

Acalabrutinib may result in fewer of the toxicities commonly associated with ibrutinib, but it is noteworthy for the occurrence of _____ during the first month of treatment.

a. Hair loss

b. Headache

c. Constipation

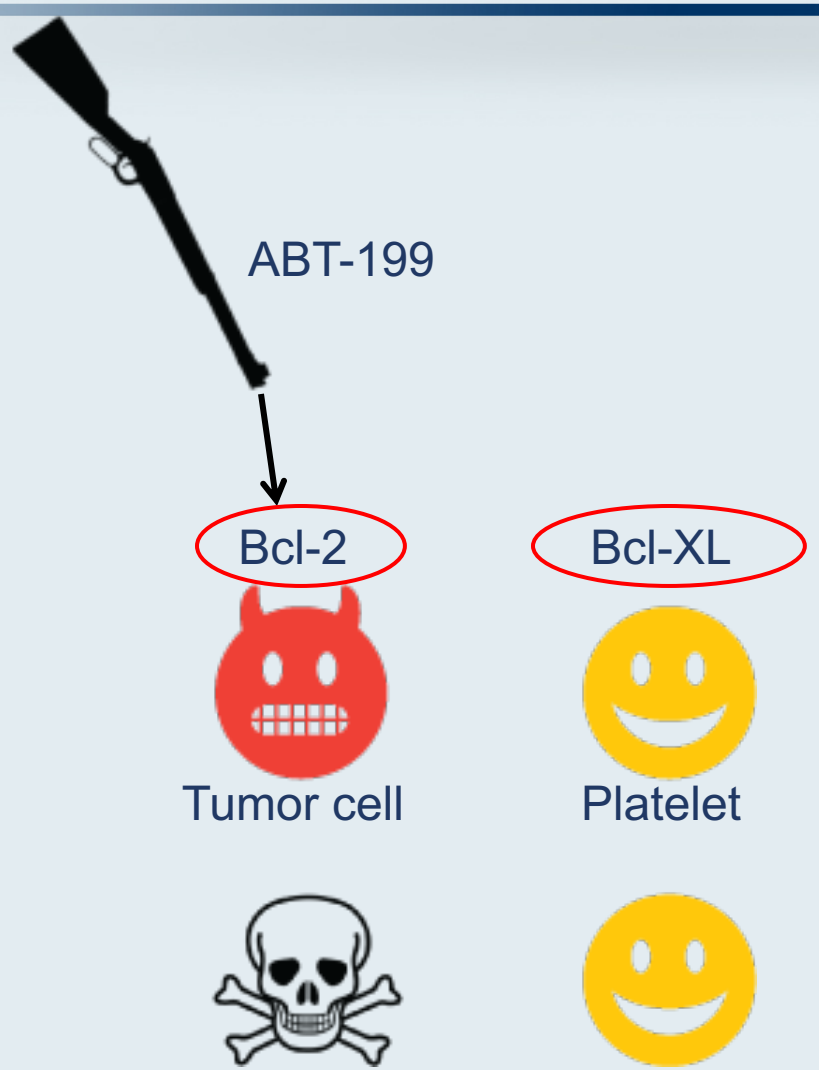
d. Visual disturbances

e. I don’t know

Acalabrutinib vs. Ibrutinib in MCL

- Acalabrutinib appears to have better safety profile
  - Very infrequent atrial fibrillation and bleeding events
  - More headache with acalabrutinib, especially in first weeks of Rx – responds to caffeine
- Both are oral agents that have similar efficacy, so choose based on patient factors (e.g., bleeding risk, Afib history)
- Acala and Ibrutinib are being tested in combinations with chemotherapy, rituximab or venetoclax in current clinical trials
- Zanubrutinib is a newly-approved BTKi that appears to be similar to Acala in response and toxicities

Mechanism of Action of Venetoclax (ABT-199)



Bcl-2 functions to prevent cell death by apoptosis

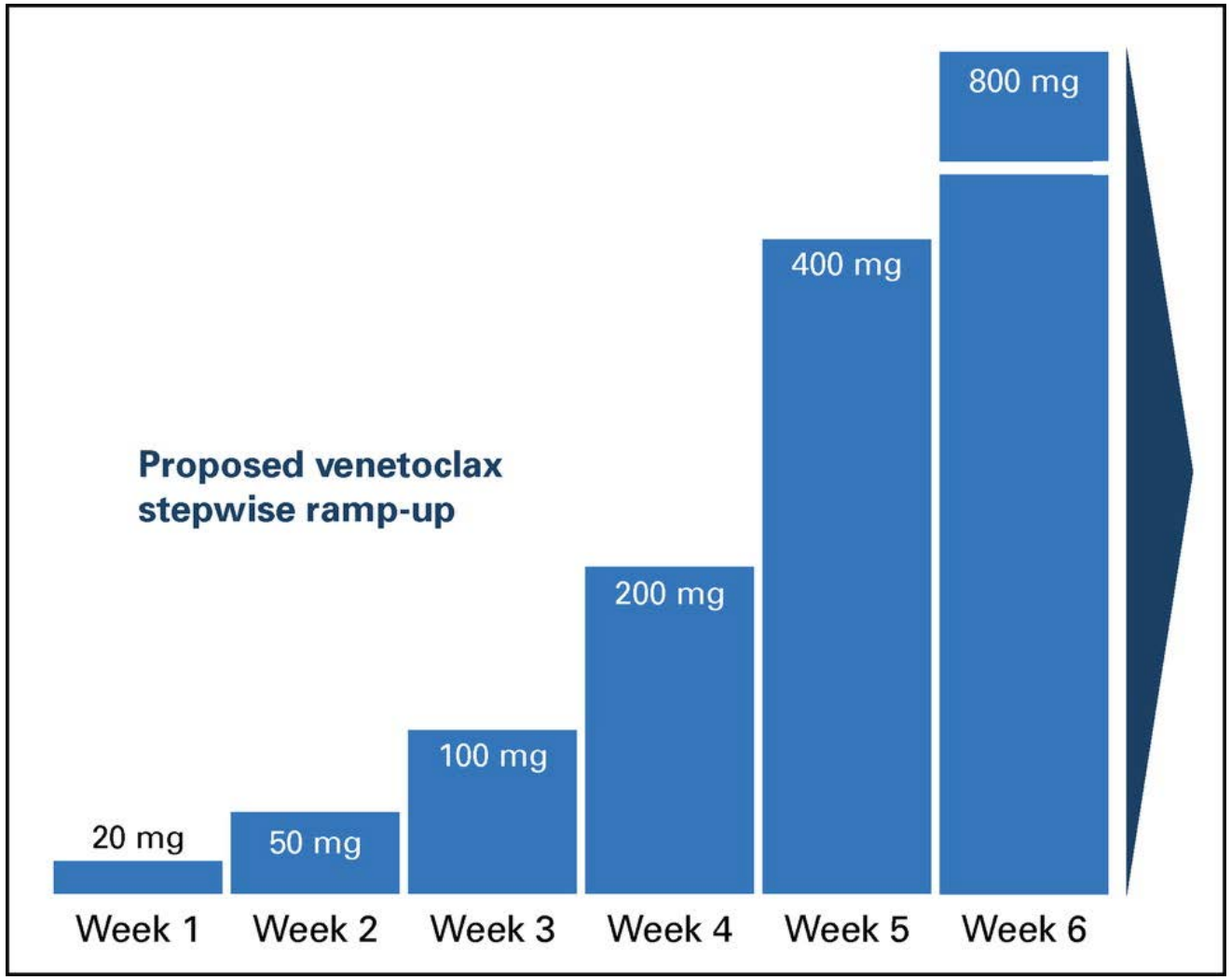
Venetoclax is specific for Bcl-2 and inhibits its function, thereby removing the block on apoptosis

Adapted from Davids MS, Letai A. *Cancer Cell* 2013;23(2):139-41.

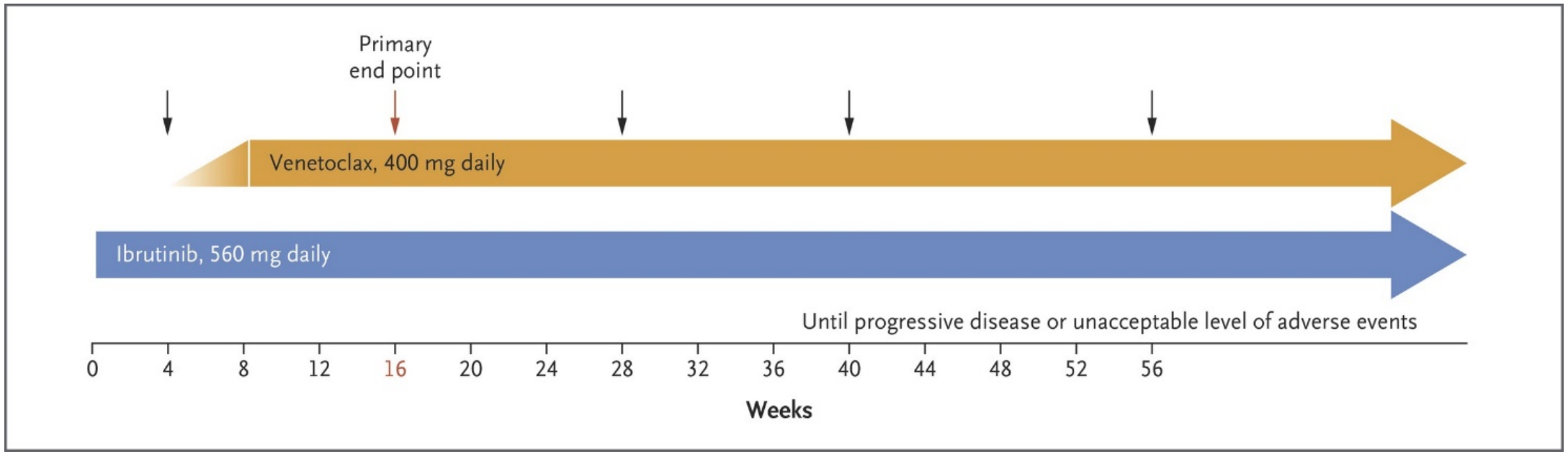
Revised Dose Ramp-Up to Mitigate the Risk of Tumor Lysis Syndrome When Initiating Venetoclax in Patients With Mantle Cell Lymphoma

MS Davids, G von Keudell, CA Portell, JB Cohen, et al

J Clin Oncol 2018; 36: 3525-7



Ibrutinib plus venetoclax in MCL: Study Schema



24 MCL patients; 23 relapsed or refractory
Most had very poor risk features

Tam CS et al. N Engl J Med 2018;378:1211-1223

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72-year-old man (from the practice of Ms Moran)

- 9/2016: Presented to PCP with increased fatigue, DOE and palpable nodes in his neck
  - Right cervical node biopsy: MCL, BM biopsy: Positive, FISH: t(11;14)
  - PET scan: Positive above and below diaphram
  - Endoscopy biopsy: Negative
  - IPI 2, Hgb 14, WBC 7.2, ECOG 1, LDH 182
- 10/2016: Ibrutinib 560 mg po daily
  - 11/2016: Hospital admission for neutropenic fevers and pneumonia
- 10/2017: Sinus surgery for recurrent sinus infections negative aspergillus
  - Ibrutinib held 7 days prior and 7 days after surgery
- 12/2019: Patient retired from farming
- Patient currently faring well on ibrutinib

Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL)

- Polatuzumab vedotin, CAR T-cell therapy

Module 2: Hodgkin Lymphoma (HL) and Peripheral T-Cell Lymphoma (PTCL)

- Brentuximab vedotin, immune checkpoint inhibitors

Module 3: Follicular Lymphoma (FL)

- Lenalidomide/rituximab (R^2), PI3K inhibitors

Module 4: Mantle Cell Lymphoma (MCL)

- BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib), venetoclax, lenalidomide

Module 5: Management of Lymphomas in the Era of COVID-19

- Telemedicine, minimization of surgeries, reduced infusions and clinic visits

Module 5: Management of Lymphomas in the Era of COVID-19

- Telemedicine, minimization of surgeries, reduced infusions and clinic visits

Guidance on Lymphomas During the Era of COVID-19

American Society of Hematology (ASH) Resources

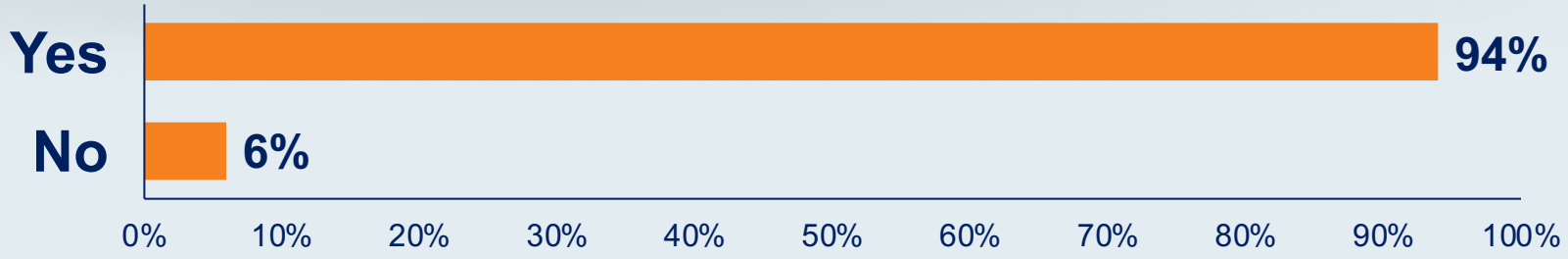
- **COVID-19 and Aggressive Lymphoma: Frequently Asked Questions (v2.1; last updated 5/4/2020)**
- **COVID-19 and Indolent Lymphomas: Frequently Asked Questions (v2.1; last updated 5/4/2020)**
- **COVID-19 and Hodgkin Lymphoma: Frequently Asked Questions (v2.2; last updated 5/4/2020)**

European Society of Medical Oncology (ESMO) Resources

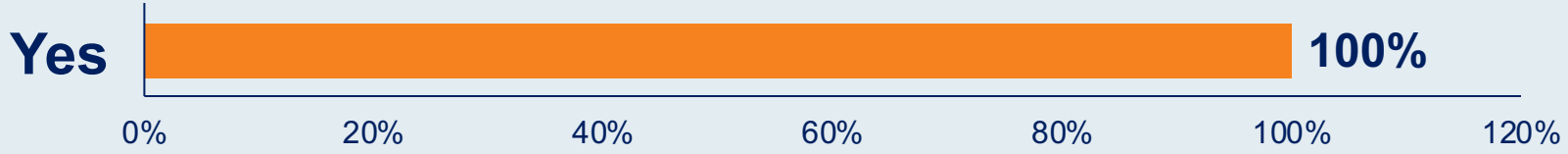
- **ESMO management and treatment adapted recommendations in the COVID-19 era: Diffuse large B-cell lymphoma, Mantle cell lymphoma and Aggressive T-cell lymphomas**
- **ESMO management and treatment adapted recommendations in the COVID-19 era: Indolent B-NHL (Follicular Lymphoma, Marginal Zone Lymphoma, Waldenström's Macroglobulinaemia)**
- **ESMO management and treatment adapted recommendations in the COVID-19 era: Hodgkin lymphoma**

https://www.hematology.org/covid-19/; https://www.esmo.org/guidelines/

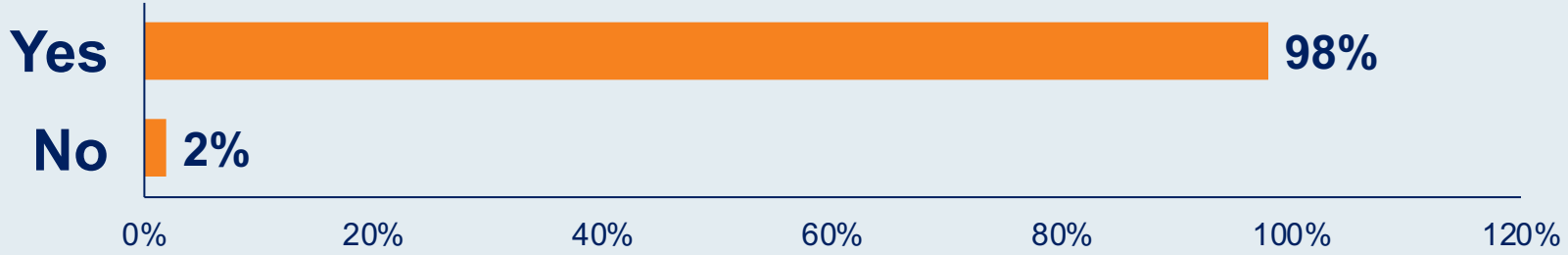
Are you restricting the number of visitors allowed in your clinic during the COVID-19 pandemic?



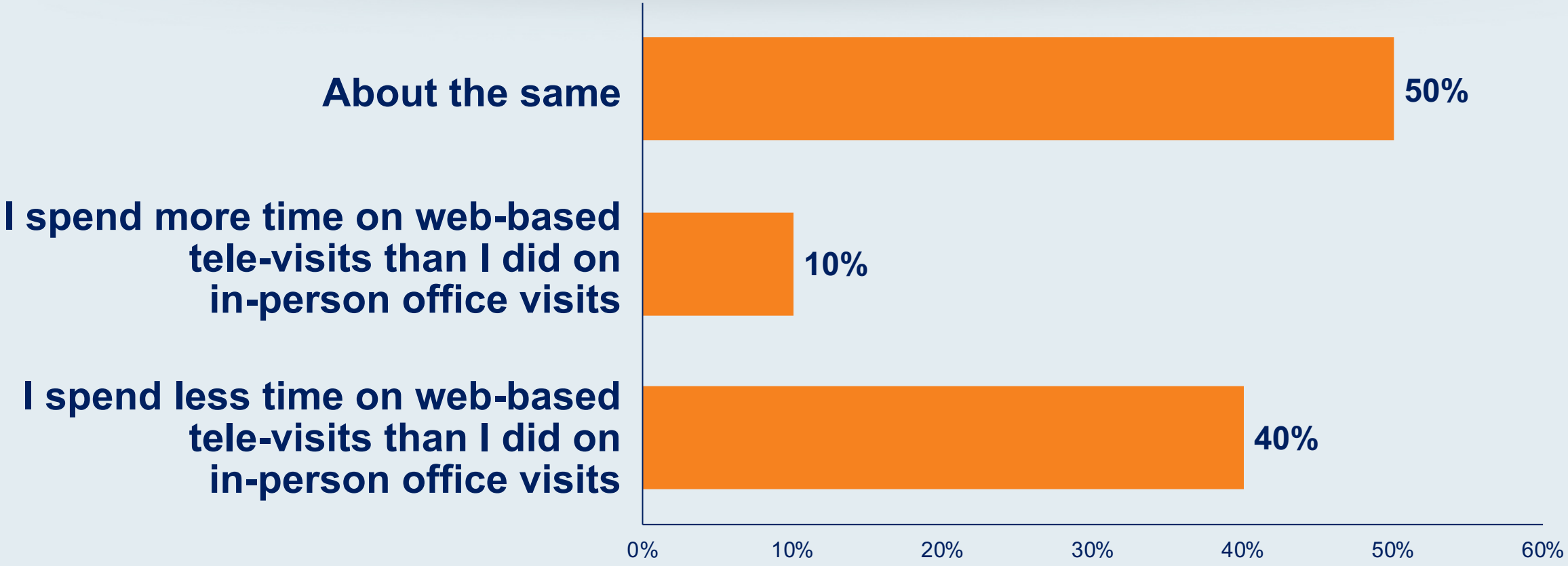
Are the healthcare workers in your clinic required to wear masks or other personal protective equipment (PPE) during the COVID-19 pandemic?



Are the patients who visit your clinic required to wear masks or other PPE during the COVID-19 pandemic?



How does the amount of time you spend on web-based tele-visits compare to the amount of time you would have spent conducting in-person office visits before the COVID-19 pandemic?



Duration of time spent for each web-based tele-visit (median): 20 minutes

Thank you for joining us!

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