Novel and Emerging Therapeutic Strategies in the Management of Select B-Cell Lymphomas
An Interactive Grand Rounds Series

John P Leonard, MD
Richard T Silver Distinguished Professor of Hematology and
Medical Oncology
Associate Dean for Clinical Research
Executive Vice Chair, Joan and Sanford I Weill Department of Medicine
Weill Cornell Medicine
New York, New York

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Contracted Research	Agios Pharmaceuticals Inc, Celgene Corporation
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Medical Director
Medical Informatics
Department of Medicine
Memorial Sloan Kettering
Cancer Center
New York, New York

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Neumann M and Mildred
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Chief, Division of
Hematology/Oncology
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Project Chair
Neil Love, MD
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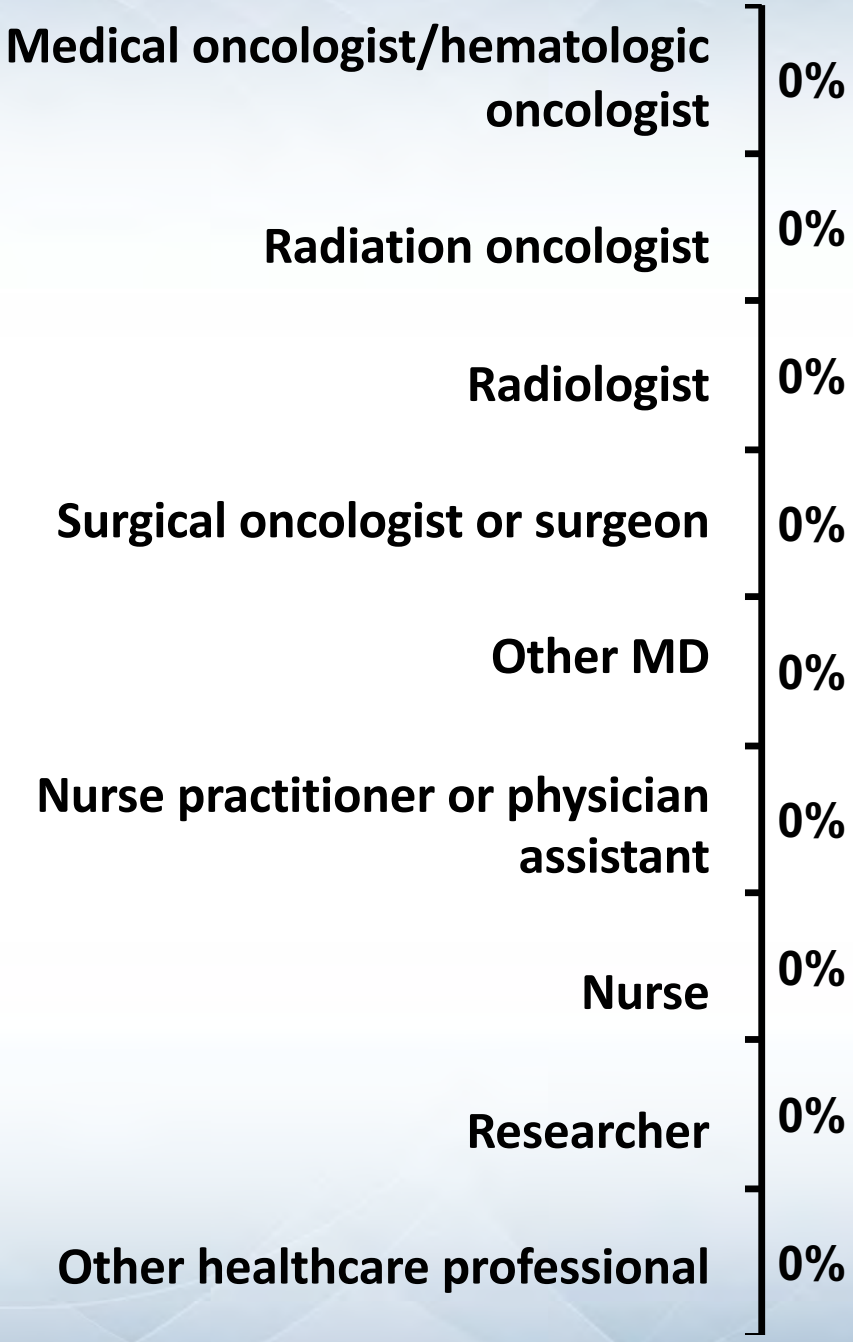
Which of the following best represents your clinical background?

1. Medical oncologist/hematologic oncologist
2. Radiation oncologist
3. Radiologist
4. Surgical oncologist or surgeon
5. Other MD
6. Nurse practitioner or physician assistant
7. Nurse
8. Researcher
9. Other healthcare professional



Management of Select B-Cell Lymphomas

Module 1: Chronic Lymphocytic Leukemia (CLL)

- First-line ibrutinib-based regimens for younger (E1912) and older patients (A041202)
- Ibrutinib/obinutuzumab in treatment-naïve CLL (iLLUMINATE)
- CLL14 trial: Venetoclax/obinutuzumab in the first-line setting
- Venetoclax/rituximab for relapsed/refractory CLL (MURANO)
- Breakthrough therapy designation for acalabrutinib (ELEVATE-TN, ASCEND)

Module 2: Mantle Cell Lymphoma (MCL)

- BTK inhibitors (ibrutinib, acalabrutinib)
- Venetoclax

Module 3: CAR T-Cell Therapy

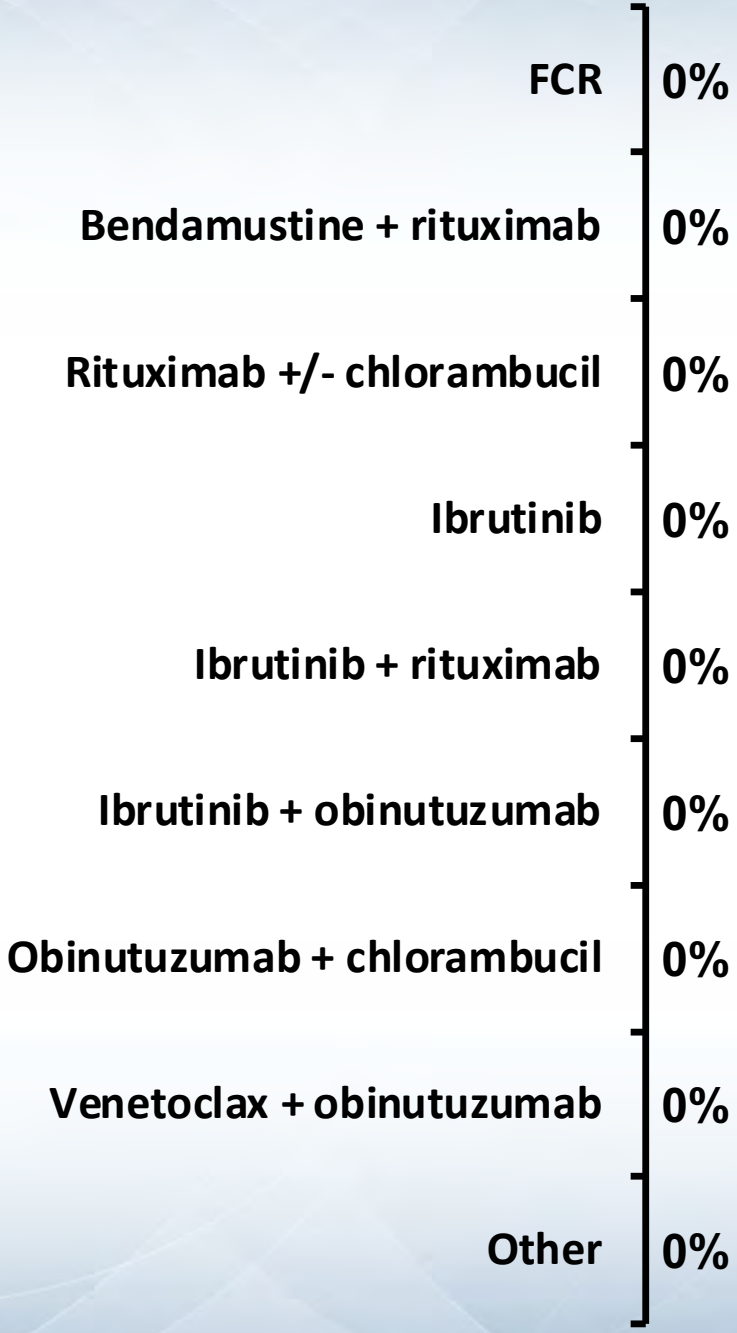
- JULIET (tisagenlecleucel), TRANSCEND NHL 001 (lisocabtagene maraleucel) and ZUMA-1 (axicabtagene ciloleucel) trials in DLBCL

Module 4: Advanced Hodgkin Lymphoma (HL)

- ECHELON-1 trial: Brentuximab vedotin/AVD vs ABVD as front-line therapy
- Checkpoint inhibitors in relapsed/refractory disease and trials in earlier settings

What is your usual preferred initial regimen for a 60-year-old patient with CLL with IGHV unmutated and no del(17p) or TP53 mutation who requires treatment?

1. FCR
2. Bendamustine + rituximab
3. Rituximab +/- chlorambucil
4. Ibrutinib
5. Ibrutinib + rituximab
6. Ibrutinib + obinutuzumab
7. Obinutuzumab + chlorambucil
8. Venetoclax + obinutuzumab
9. Other



What is your usual preferred initial regimen for a 60-year-old patient with CLL and no del(17p) or TP53 mutation who requires treatment?

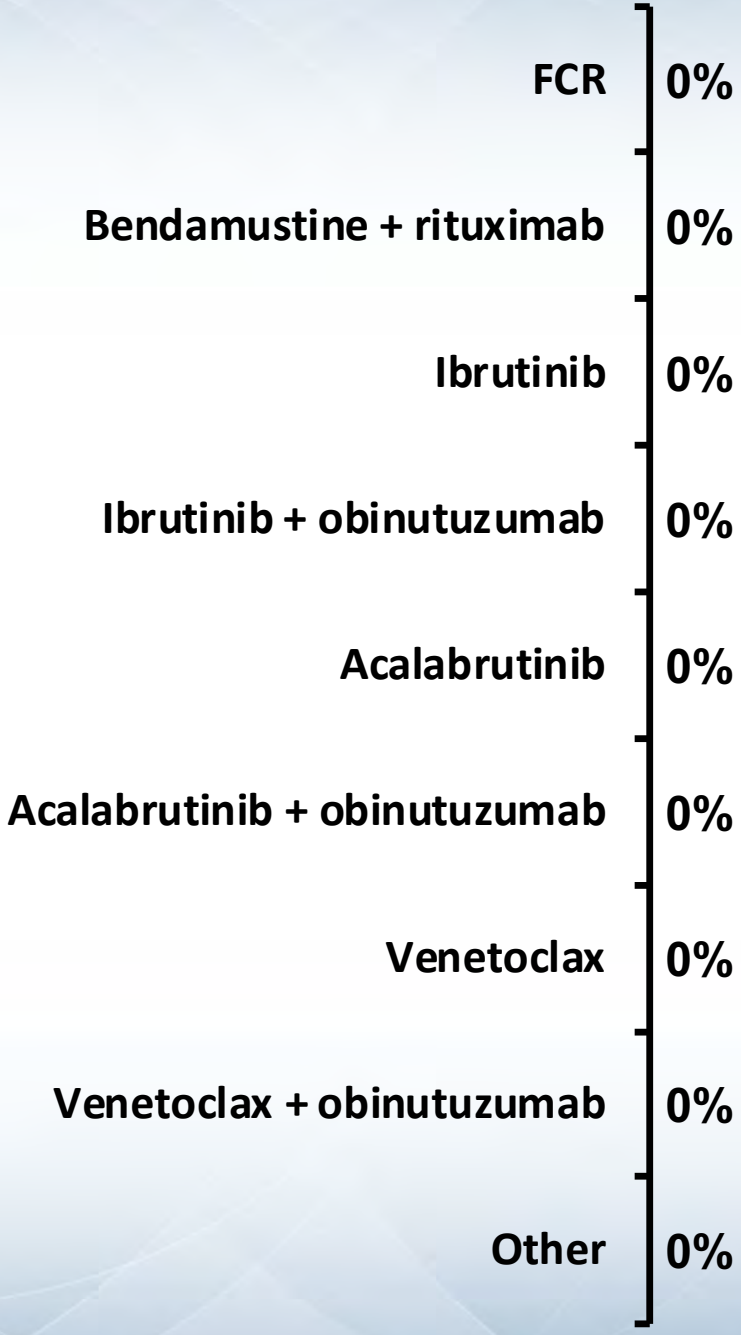
	IGHV mutation	No IGHV mutation
 BRUCE D CHESON, MD	Venetoclax/obinutuzumab	Venetoclax/obinutuzumab
 ANDREW M EVENS, DO, MSC	FCR or Ibrutinib	Ibrutinib
 ANN S LACASCE, MD, MMSC	FCR	Ibrutinib
 JOHN P LEONARD, MD	Ibrutinib	Ibrutinib
 JULIE M VOSE, MD, MBA	FCR	Ibrutinib

What is your usual preferred initial regimen for a 75-year-old patient with CLL and no del(17p) or TP53 mutation who requires treatment?

	IGHV mutation	No IGHV mutation
 BRUCE D CHESON, MD	Venetoclax/obinutuzumab	Venetoclax/obinutuzumab
 ANDREW M EVENS, DO, MSC	Ibrutinib	Ibrutinib
 ANN S LACASCE, MD, MMSC	Venetoclax/obinutuzumab	Venetoclax/obinutuzumab
 JOHN P LEONARD, MD	Ibrutinib	Ibrutinib
 JULIE M VOSE, MD, MBA	Ibrutinib	Ibrutinib

What is your usual preferred initial regimen for a 60-year-old patient with del(17p) CLL who requires treatment?

1. FCR
2. Bendamustine + rituximab
3. Ibrutinib
4. Ibrutinib + obinutuzumab
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax
8. Venetoclax + obinutuzumab
9. Other



What is your usual preferred initial regimen for a 60-year-old patient with del(17p) CLL who requires treatment?

 BRUCE D CHESON, MD	Acalabrutinib
 ANDREW M EVENS, DO, MSC	Ibrutinib/obinutuzumab
 ANN S LACASCE, MD, MMSC	Ibrutinib
 JOHN P LEONARD, MD	Ibrutinib
 JULIE M VOSE, MD, MBA	Ibrutinib

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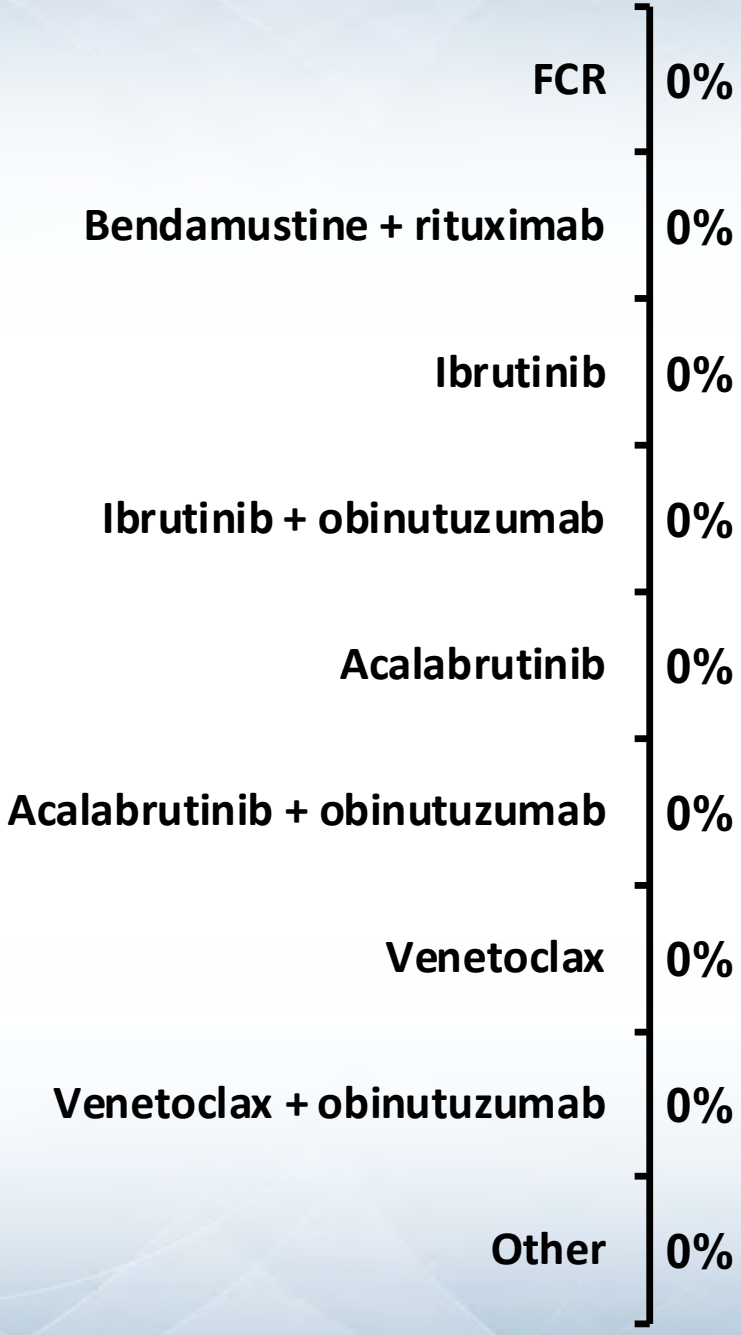
What is your usual preferred initial regimen for a 60-year-old patient with del(17p) CLL who requires treatment, has a history of atrial fibrillation and is receiving anticoagulation therapy?

1. FCR
2. Bendamustine + rituximab
3. Ibrutinib
4. Ibrutinib + obinutuzumab
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax
8. Venetoclax + obinutuzumab
9. Other



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 ANDREW M EVENS, DO, MSC	Venetoclax/obinutuzumab
 ANN S LACASCE, MD, MMSC	Acalabrutinib
 JOHN P LEONARD, MD	Venetoclax/obinutuzumab
 JULIE M VOSE, MD, MBA	Venetoclax/obinutuzumab

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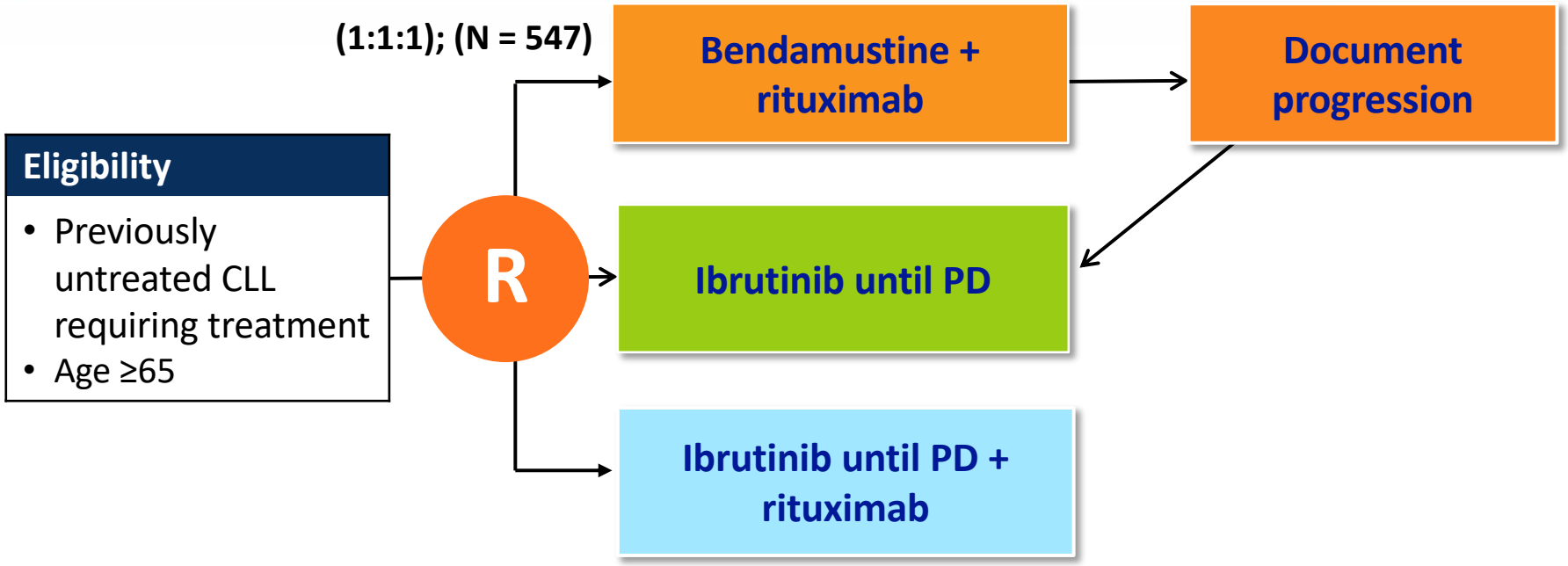
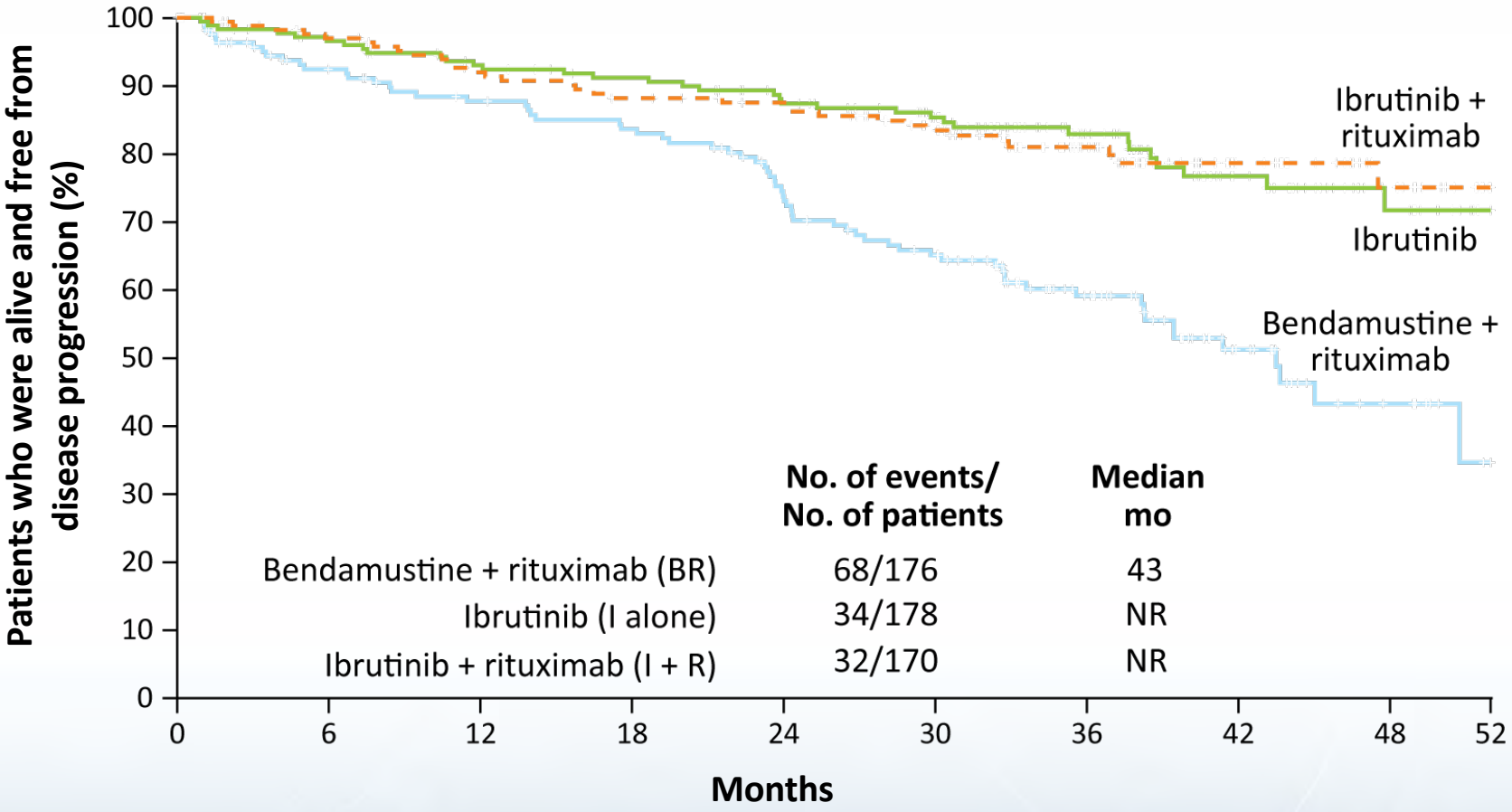
Phase III ALLIANCE A041202 Study Design



Primary endpoint: PFS
Secondary endpoints: OS, ORR, Impact of MRD on PFS and OS, Duration of response, Toxicity and Tolerability

Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.
Woyach J et al. Alliance Fall Group Meeting, November 5, 2015.

ALLIANCE A041202: Efficacy with Ibrutinib Alone or in Combination with Rituximab Compared to Bendamustine/Rituximab (BR)



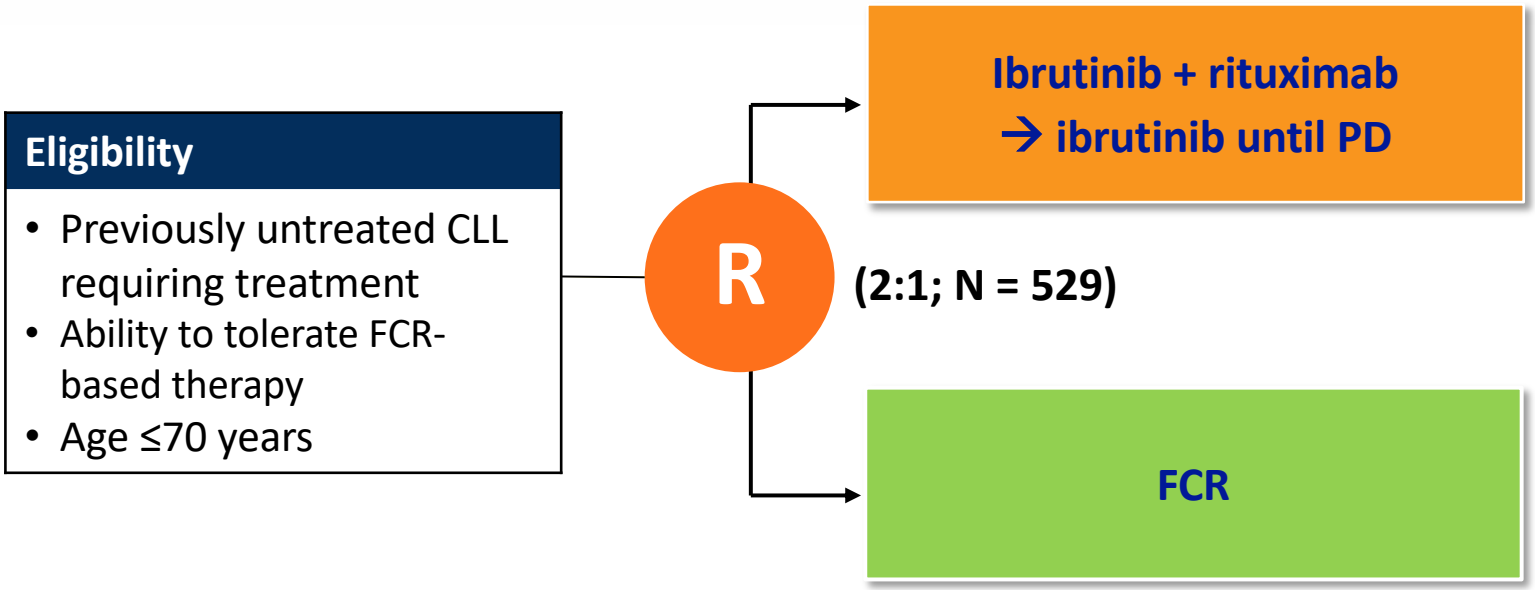
Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.

ALLIANCE A041202: Grade 3-5 Adverse Events of Special Interest

Adverse event	Bendamustine + rituximab (N = 176)	Ibrutinib (N = 180)	Ibrutinib + rituximab (N = 181)	*p*-value
Hematologic – Any grade 3-4	61%	41%	39%	<0.001
Anemia	12%	12%	6%	0.09
Decreased neutrophil count	40%	15%	21%	<0.001
Decreased platelet count	15%	7%	5%	0.008
Non-hematologic – Any grade 3-5	63%	74%	74%	0.04
Bleeding	0	2%	3%	0.46
Infections	15%	20%	21%	0.62
Febrile neutropenia	7%	2%	1%	<0.001
Atrial fibrillation	3%	9%	6%	0.05
Hypertension	15%	29%	34%	<0.001

Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.

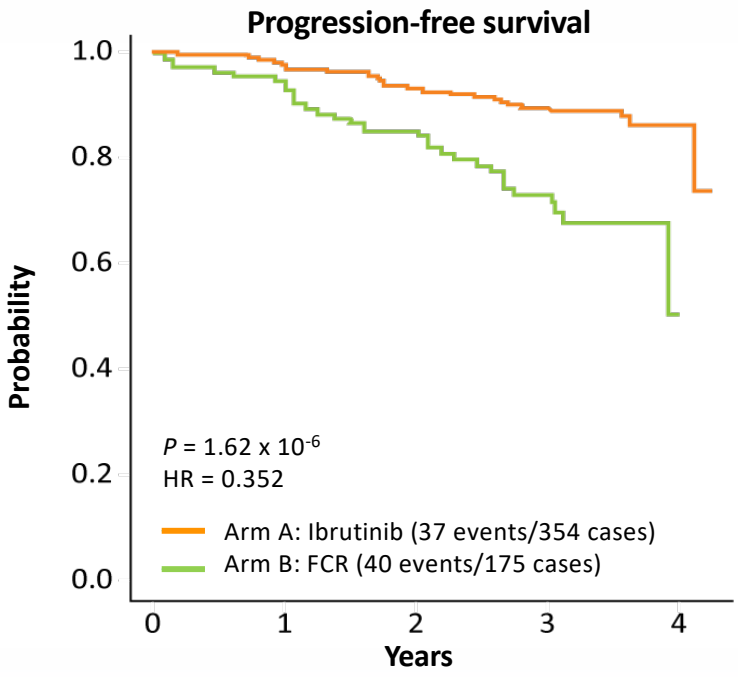
Phase III ECOG-ACRIN E1912 Study Design

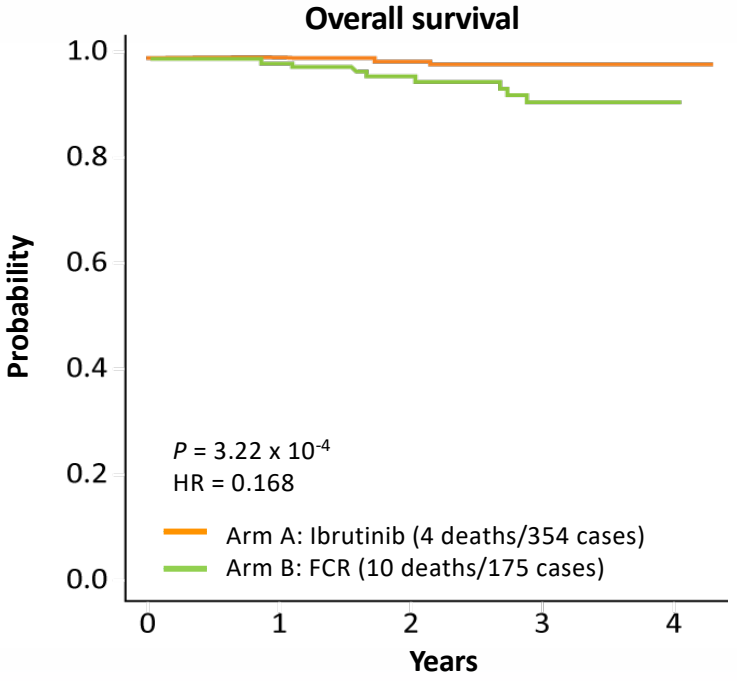


Primary endpoint: PFS
Secondary endpoints: OS, ORR, Toxicity and Tolerability

ECOG-ACRIN E1912 Physician Fact Sheet, version 01/15/16; Clinicaltrials.gov (NCT02048813); Shanafelt TD et al. *Proc ASH* 2018;Abstract LBA-4.

ECOG-ACRIN E1912: Up-Front Ibrutinib and Rituximab (IR) Compared to FCR in Younger Patients with CLL



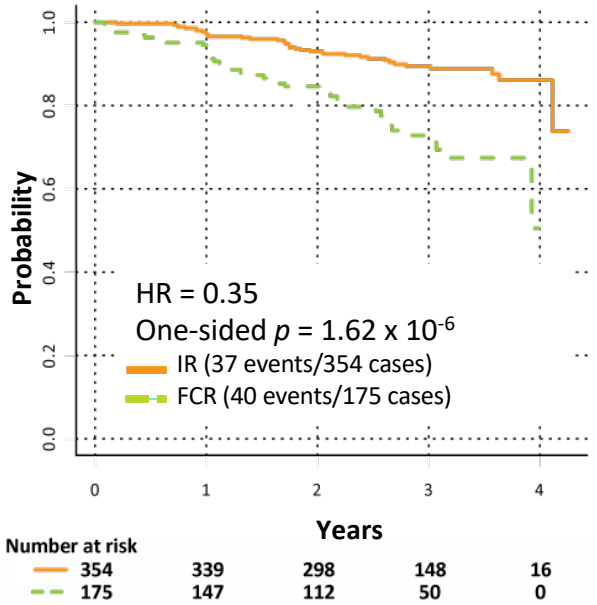


- IR was also superior to FCR for patients without IGHV mutations (HR = 0.262; $p < 0.0001$) but not for those with IGHV mutations (HR = 0.435; $p = 0.07$).
- FCR was more frequently associated with Grade 3/4 neutropenia (FCR: 44% vs IR: 23%; $p < 0.0001$) and infectious complications (FCR: 17.7% vs IR: 7.1%; $p < 0.0001$).

Shanafelt TD et al. *Proc ASH* 2018;Abstract LBA-4.

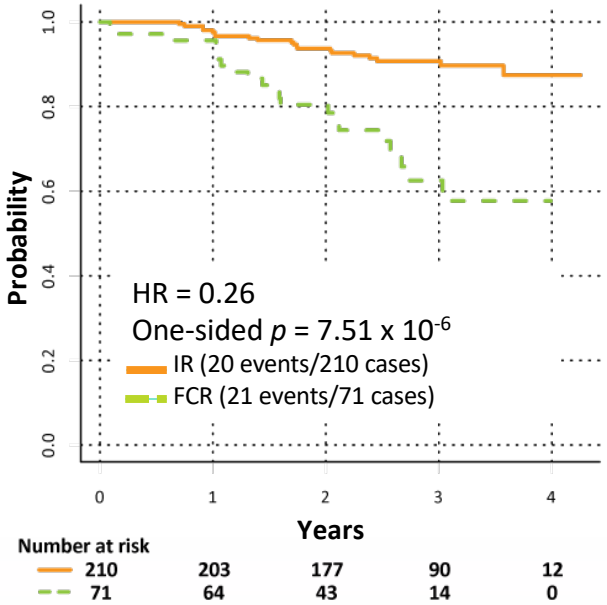
ECOG-E1912: Progression-Free Survival

All comers (ITT analysis)



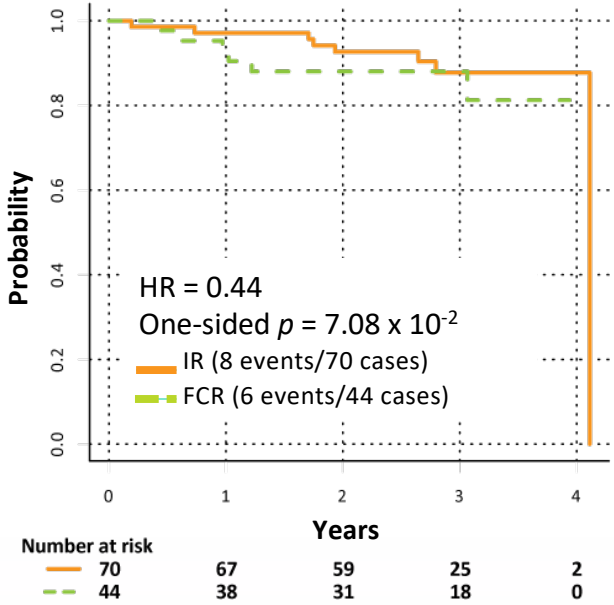
HR = 0.35
One-sided $p < 0.00001$

No IGHV mutation



HR = 0.26
One-sided $p < 0.00001$

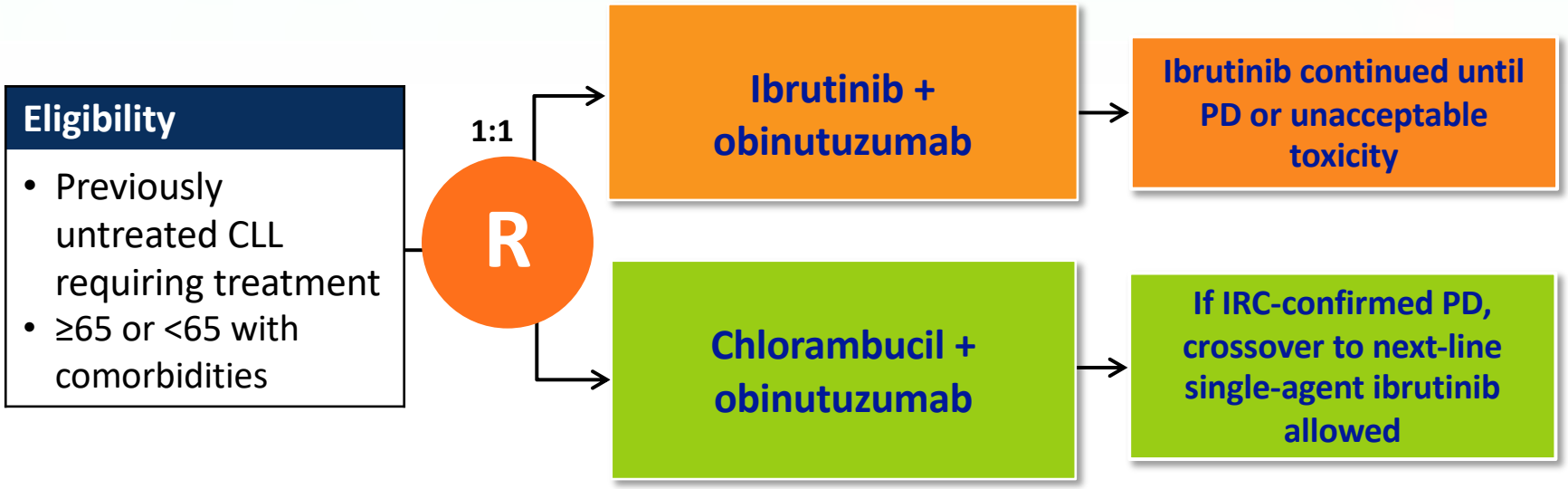
IGHV mutation



HR = 0.44
One-sided $p = 0.07$

Shanafelt TD et al. *Proc ASH* 2018;Abstract LBA-4.

Phase III iLLUMINATE Study Design



Stratification

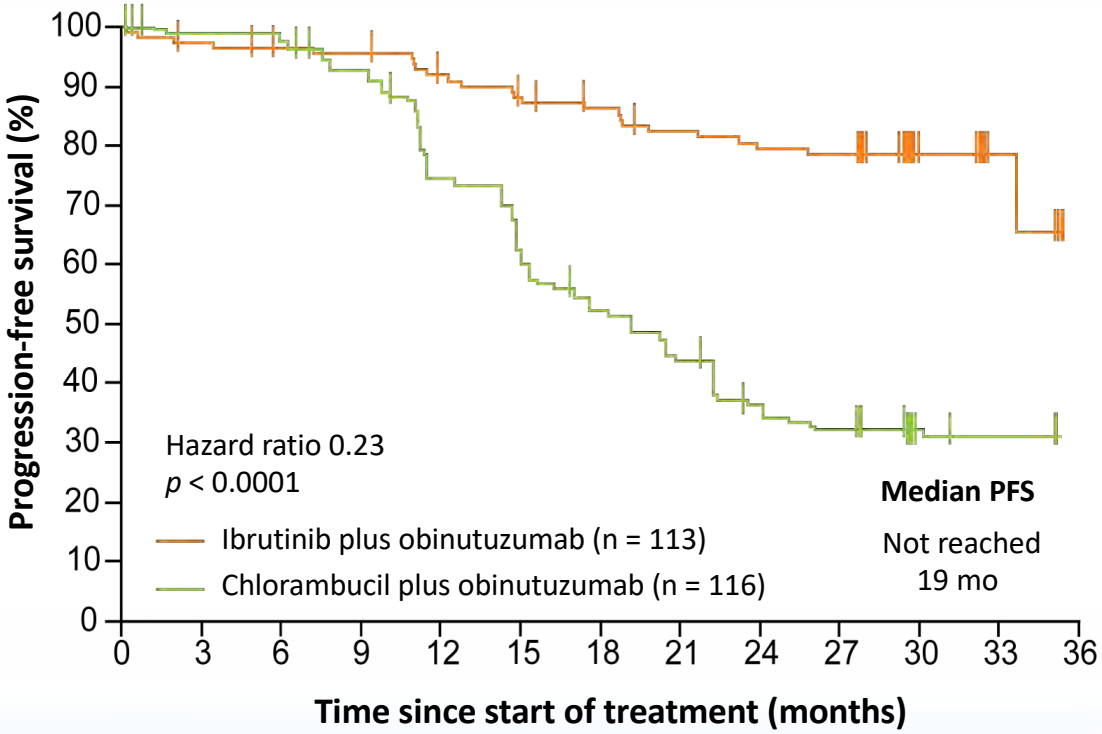
- ECOG PS (0-1 vs 2)
- Del(17p)/del(11q) (+/+ vs +/- vs -/+ vs -/-)

Primary endpoint: PFS by IRC in ITT

Secondary endpoints: PFS in high-risk patients (positive for del(17p) or *TP53* mutation, del(11q), or unmutated *IGHV*), MRD, ORR, OS, IRRs, safety

Moreno C et al. *Lancet Oncol* 2019;20(1):43-56.

iLLUMINATE: A Phase III Trial of Ibrutinib and Obinutuzumab as First-Line Therapy for CLL



Most common Grade 3/4 AEs

- Neutropenia
- Thrombocytopenia

Serious AEs

- Ibrutinib/obinutuzumab: 58%
- Chlorambucil/obinutuzumab: 35%

Moreno C et al. *Lancet Oncol* 2019;20(1):43-56.

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For a patient with newly diagnosed CLL that you decide to treat with up-front venetoclax/obinutuzumab how long do you generally continue treatment?

Do you conduct MRD assessment at the end of treatment, and if so, how do you approach if MRD is present?

	How long continue treatment?	MRD assessment?
 BRUCE D CHESON, MD	1 year	Yes, follow patient
 ANDREW M EVENS, DO, MSC	1 year	No
 ANN S LACASCE, MD, MMSC	1 year	Yes, discuss continuing venetoclax
 JOHN P LEONARD, MD	1 year	No
 JULIE M VOSE, MD, MBA	1 year	No

FDA Approves Venetoclax for First-Line CLL or SLL

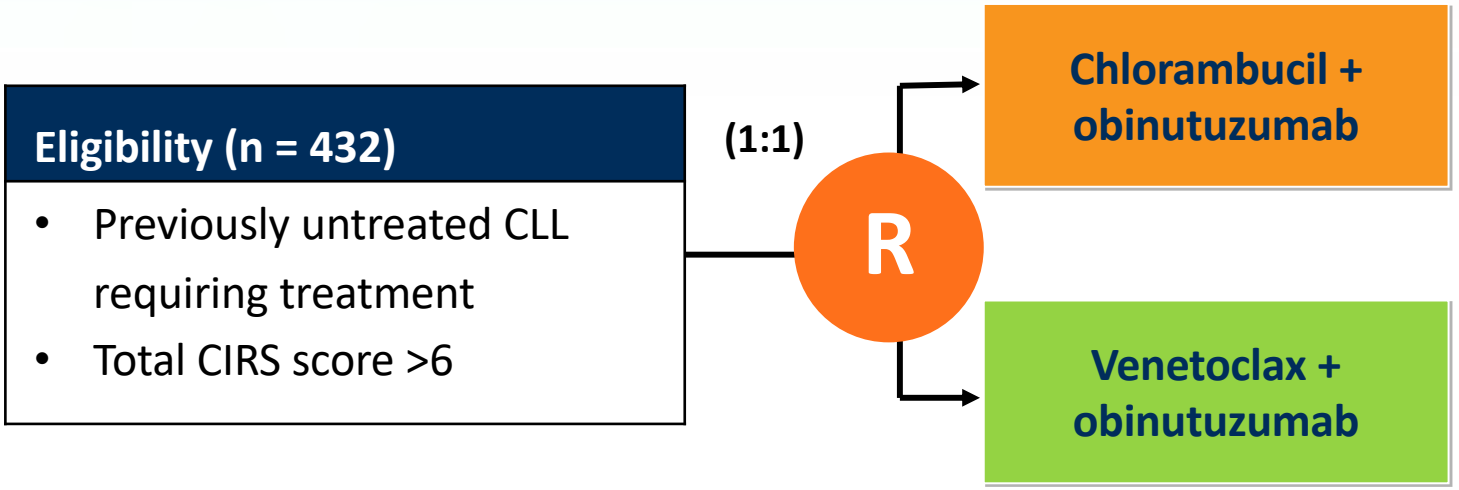
Press Release – May 15, 2019

"On May 15, 2019, the Food and Drug Administration approved venetoclax for adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Approval was based on CLL14 (NCT02242942), a randomized (1:1), multicenter, open label, actively controlled trial of venetoclax in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb) in 432 patients with previously untreated CLL with coexisting medical conditions."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-venetoclax-cll-and-sll

CLL14 Phase III Study Schema

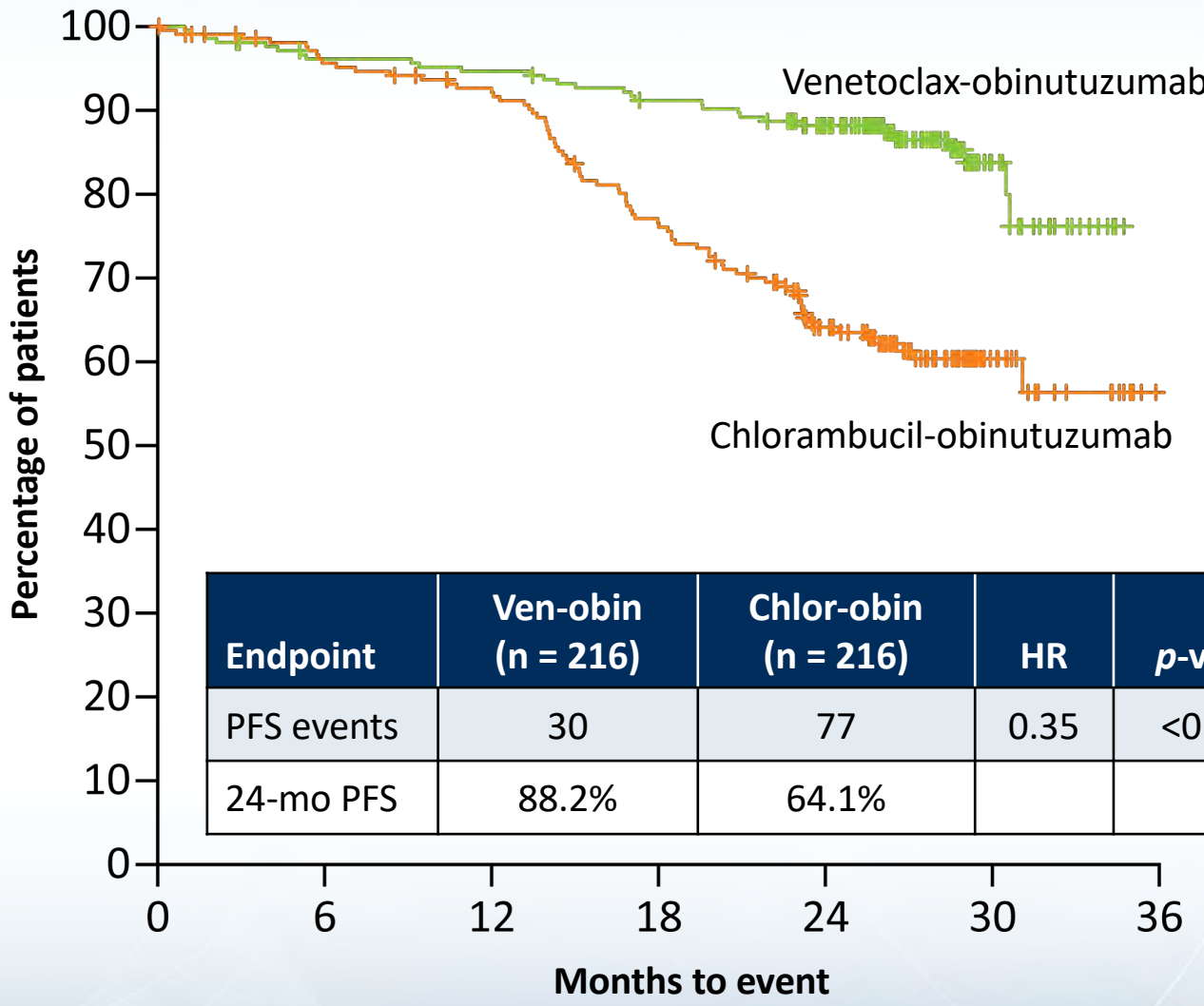


Primary endpoint: Progression-free survival

- Treatment duration in both groups: 12 cycles, 28 days each
- No crossover was allowed
- Daily oral venetoclax regimen
  - Initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week)
  - Thereafter continuing at 400 mg daily until completion of cycle 12

www.clinicaltrials.gov. Accessed October 2019 (NCT02242942).
Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

CLL14: Investigator-Assessed Progression-Free Survival

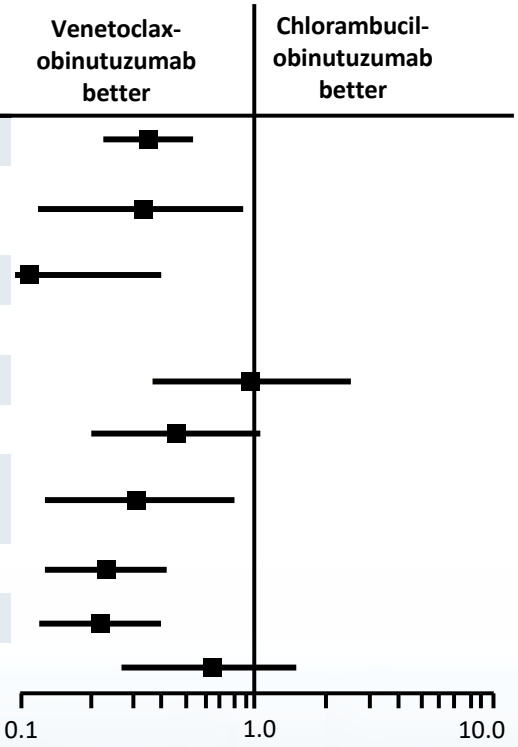


Endpoint	Ven-obin (n = 216)	Chlor-obin (n = 216)	HR	*p*-value
PFS events	30	77	0.35	<0.001
24-mo PFS	88.2%	64.1%		

Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

CLL14: Investigator-Assessed Progression-Free Survival by Prognostic Subgroups

Category	Subgroup	Total n	Chlorambucil-obinutuzumab n	Chlorambucil-obinutuzumab PFS rate month 24 (%)	Venetoclax-obinutuzumab n	Venetoclax-obinutuzumab PFS rate month 24 (%)	Hazard ratio
All		432	216	64.1	216	88.1	0.34
Cytogenetic subgroups as per hierarchy	del(17p)	31	14	23.1	17	64.7	0.33
	del(11q)	74	38	41.3	36	91.2	0.11
	Trisomy 12	76	40	55.6	36	100.0	NE
	No abnormalities	92	42	82.1	50	87.2	0.93
	del(13q)	120	59	78.3	61	88.1	0.45
TP53 deletion and/or mutation	Present	46	22	32.7	24	73.9	0.31
	Not present	287	139	65.0	148	92.1	0.23
IGHV mutation status	Unmutated	244	123	51.0	121	89.4	0.22
	Mutated	159	83	85.6	76	90.3	0.64



Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

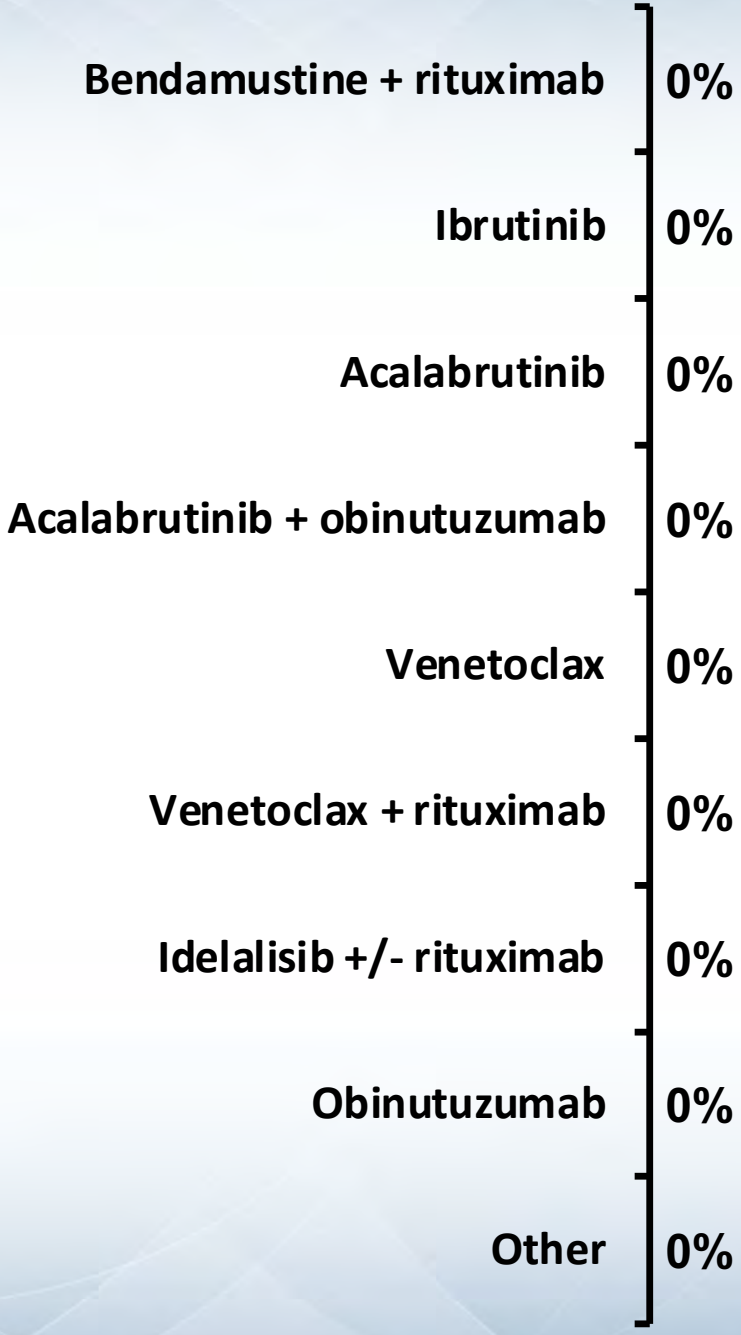
CLL14: Minimal Residual Disease 3 Months After Treatment

	MRD-negative patients		MRD responders	
Minimal residual disease 3 months after treatment	**Veneto-obin (N = 216)**	**Chloram-obin (N = 216)**	**Veneto-obin (N = 216)**	**Chloram-obin (N = 216)**
MRD in bone marrow	56.9%	17.1%	33.8%	10.6%
Odds ratio, *p*-value	OR: 6.4, $p < 0.0001$		OR: 4.3, $p < 0.0001$	
MRD in peripheral blood	75.7%	35.2%	42.1%	14.4%
Odds ratio, *p*-value	OR: 5.7, $p < 0.0001$		OR: 4.3, $p < 0.0001$	

Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

Reimbursement and regulatory issues aside, which second-line therapy would you recommend for a 60-year-old patient with CLL with an IGHV mutation but no del(17p) or TP53 mutation who responded to FCR and then experienced disease progression 3 years later?

1. Bendamustine + rituximab
2. Ibrutinib
3. Acalabrutinib
4. Acalabrutinib + obinutuzumab
5. Venetoclax
6. Venetoclax + rituximab
7. Idelalisib +/- rituximab
8. Obinutuzumab
9. Other



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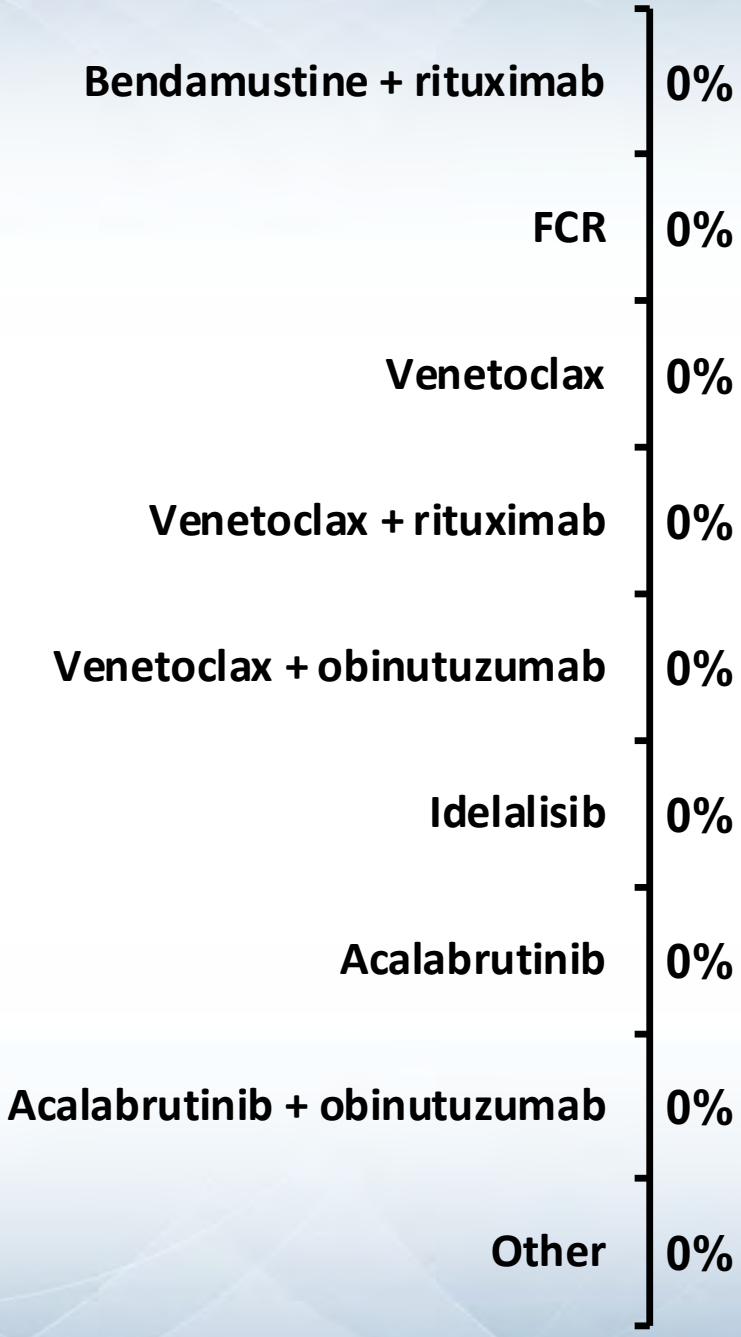
 BRUCE D CHESON, MD	Venetoclax/rituximab
 ANDREW M EVENS, DO, MSC	Ibrutinib
 ANN S LACASCE, MD, MMSC	Ibrutinib
 JOHN P LEONARD, MD	Ibrutinib
 JULIE M VOSE, MD, MBA	Venetoclax/obinutuzumab

Reimbursement and regulatory issues aside, which second-line systemic therapy would you recommend for a 75-year-old patient with CLL with an IGHV mutation but no del(17p) or TP53 mutation who responded to ibrutinib and then experienced disease progression 3 years later?

1. Bendamustine + rituximab
2. FCR
3. Venetoclax
4. Venetoclax + rituximab
5. Venetoclax + obinutuzumab
6. Idelalisib
7. Acalabrutinib
8. Acalabrutinib + obinutuzumab
9. Other



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 JOHN P LEONARD, MD	Venetoclax/obinutuzumab
 JULIE M VOSE, MD, MBA	Venetoclax/obinutuzumab

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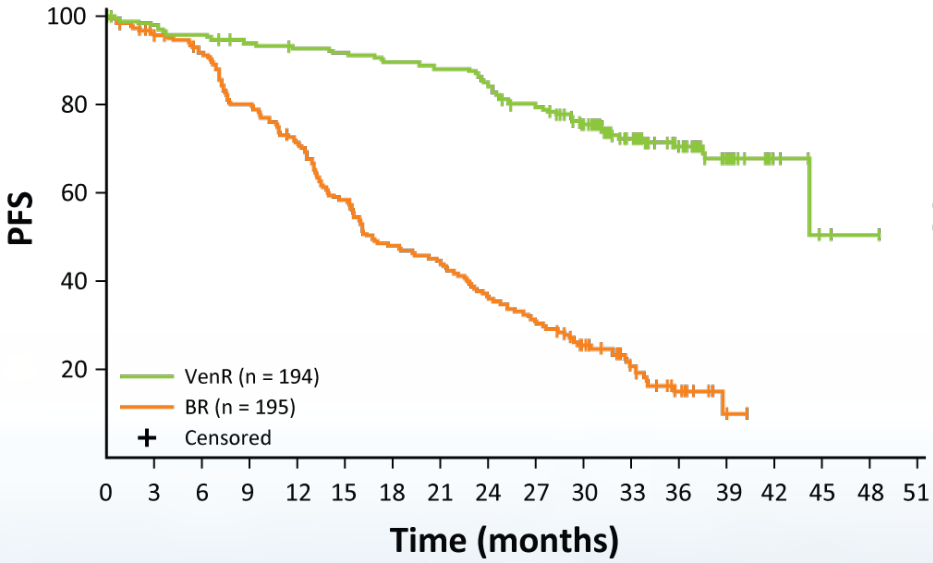
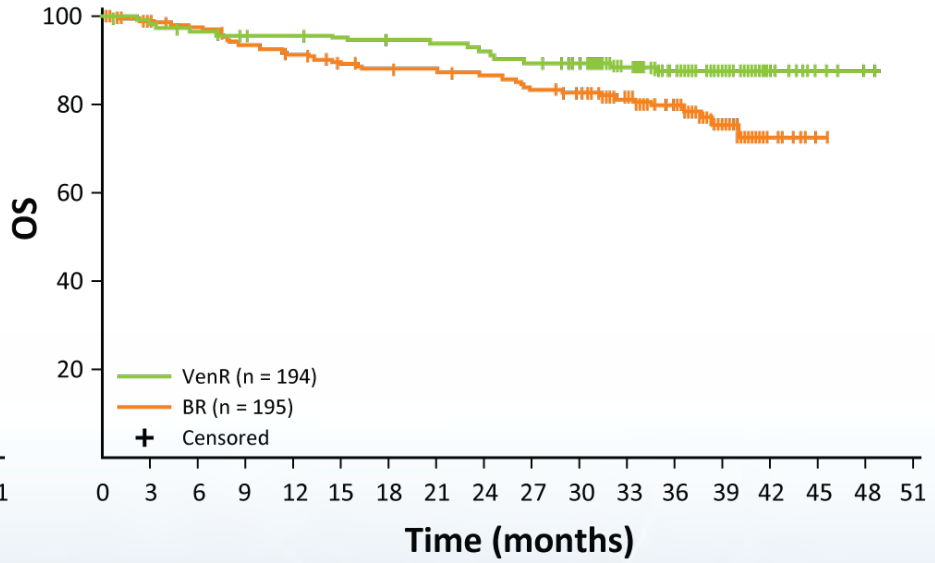
MURANO: Survival Analyses of Venetoclax/ Rituximab in R/R CLL (36-month median follow-up)

	VenR (n = 194)	BR (n = 195)	Hazard ratio	*p*-value
3-yrs PFS	71.4%	15.2%	0.16	<0.001
3-yrs OS	87.9%	79.5%	0.50	0.0093





Kater AP et al. *J Clin Oncol* 2019;37(4):269-77.

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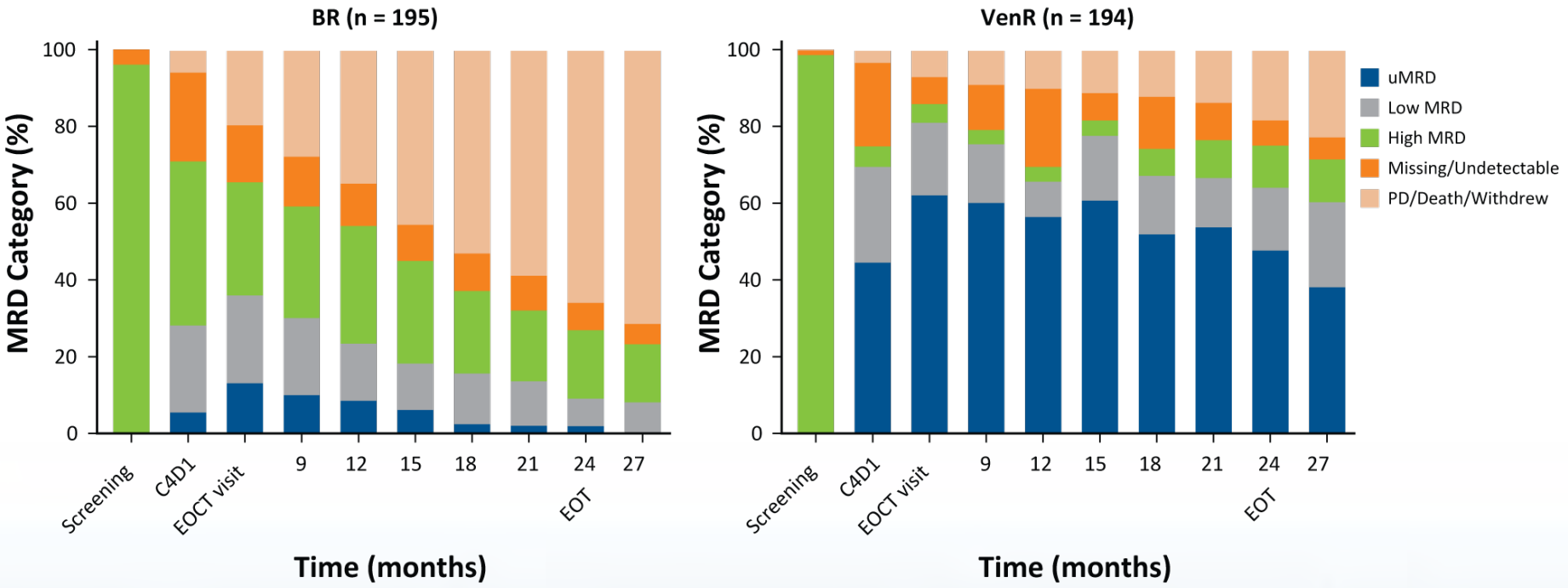
MURANO: Peripheral Blood MRD Status for Venetoclax + Rituximab (VenR) Compared to BR at Various Timepoints



Kater AP et al. *J Clin Oncol* 2019;37(4):269-77.

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Acalabrutinib Granted US Breakthrough Therapy Designation for Chronic Lymphocytic Leukemia

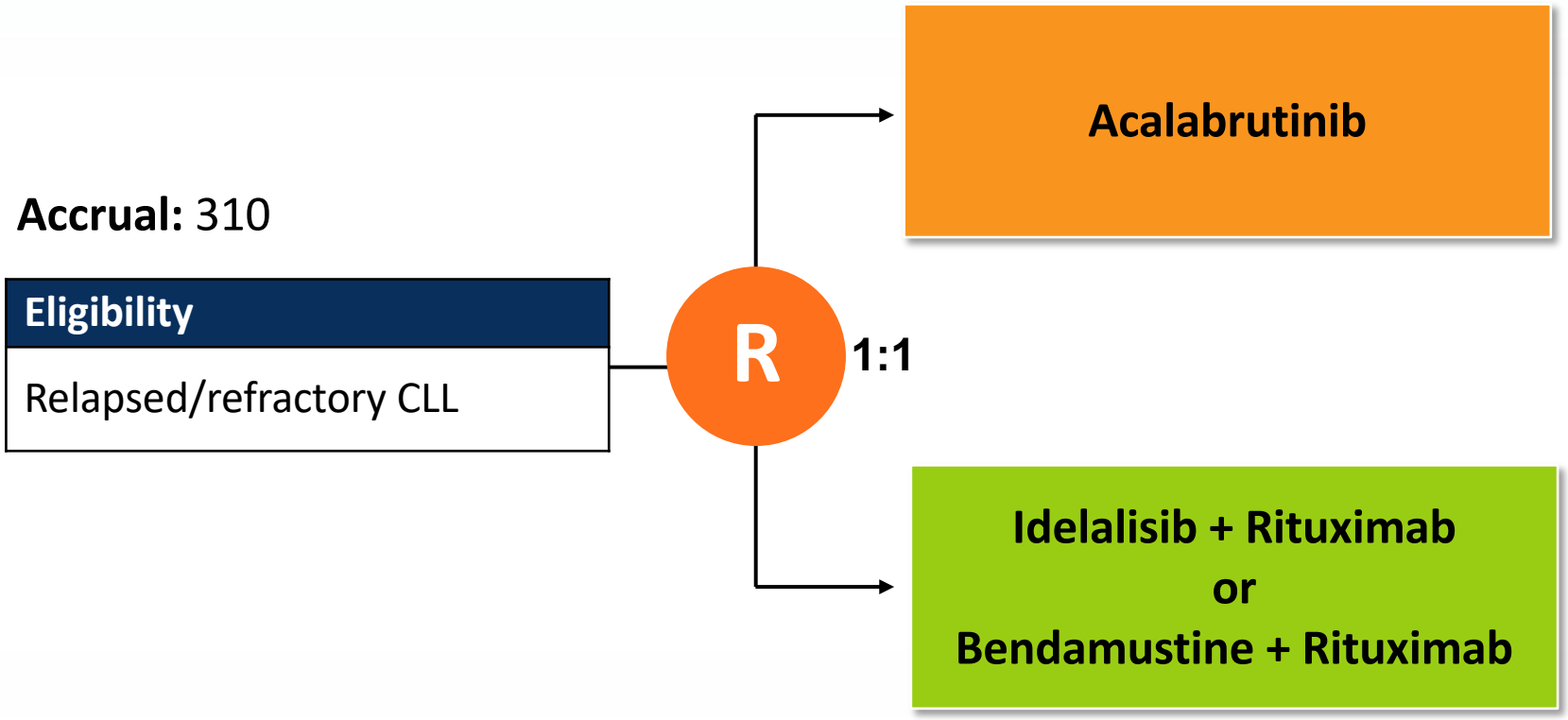
Press Release – August 14, 2019

"The US FDA has granted Breakthrough Therapy Designation (BTD) for acalabrutinib as a monotherapy treatment for adult patients with CLL, one of the most common types of leukaemia in adults.

The FDA granted the BTD based on positive results from the interim analyses of the ELEVATE-TN and ASCEND Phase III clinical trials. Together the trials showed that acalabrutinib alone or in combination significantly increased the time patients lived without disease progression or death, with safety and tolerability that was consistent with its established profile."

https://www.astrazeneca.com/media-centre/press-releases/2019/calquence-granted-us-breakthrough-therapy-designation-for-chronic-lymphocytic-leukaemia-14082019.html

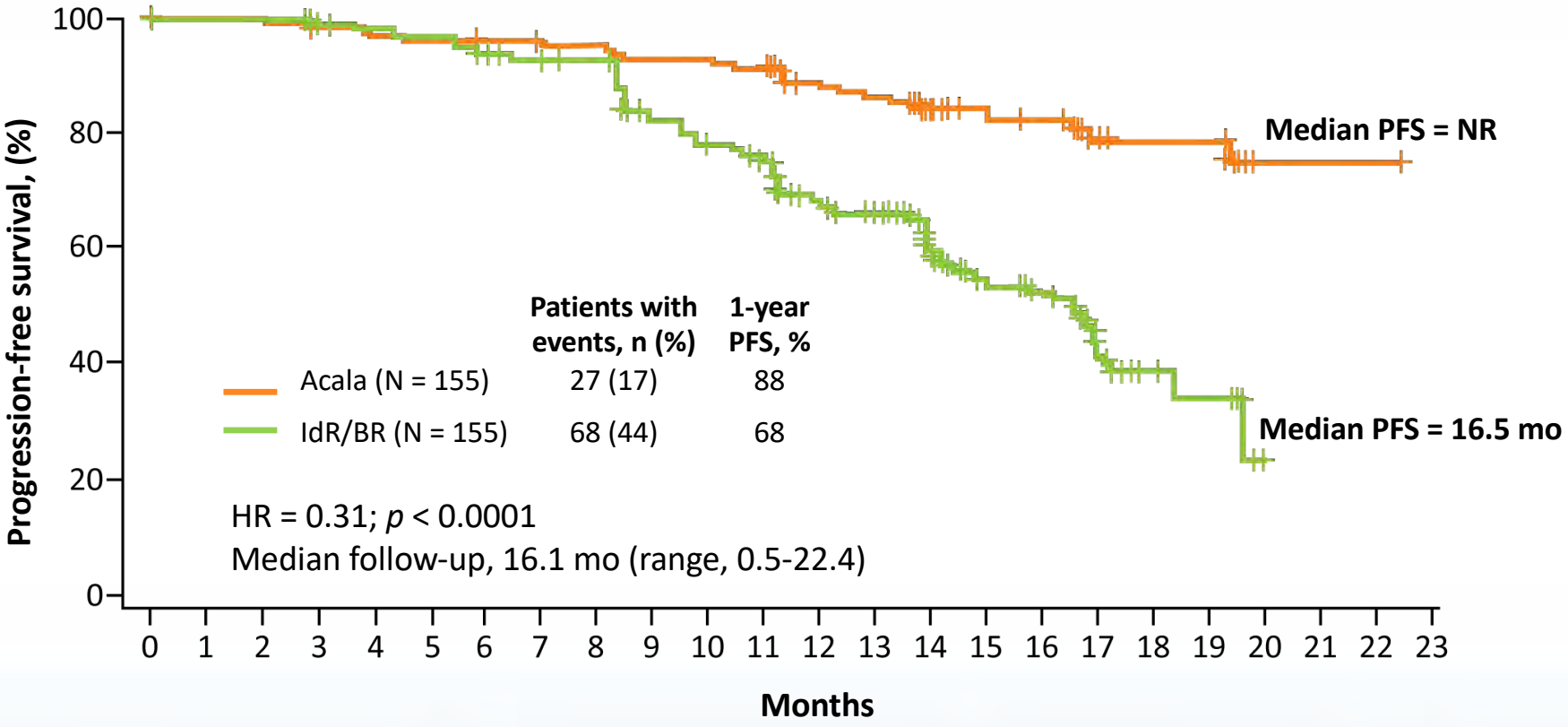
ASCEND Phase III Trial Schema



Primary endpoint: Progression-free survival by IRC

Ghia P et al. *Proc EHA* 2019;Abstract LBA 2606.
www.clinicaltrials.gov. Accessed October 2019.

ASCEND: Progression-Free Survival (IRC)



Ghia P et al. *Proc EHA* 2019;Abstract LBA 2606.

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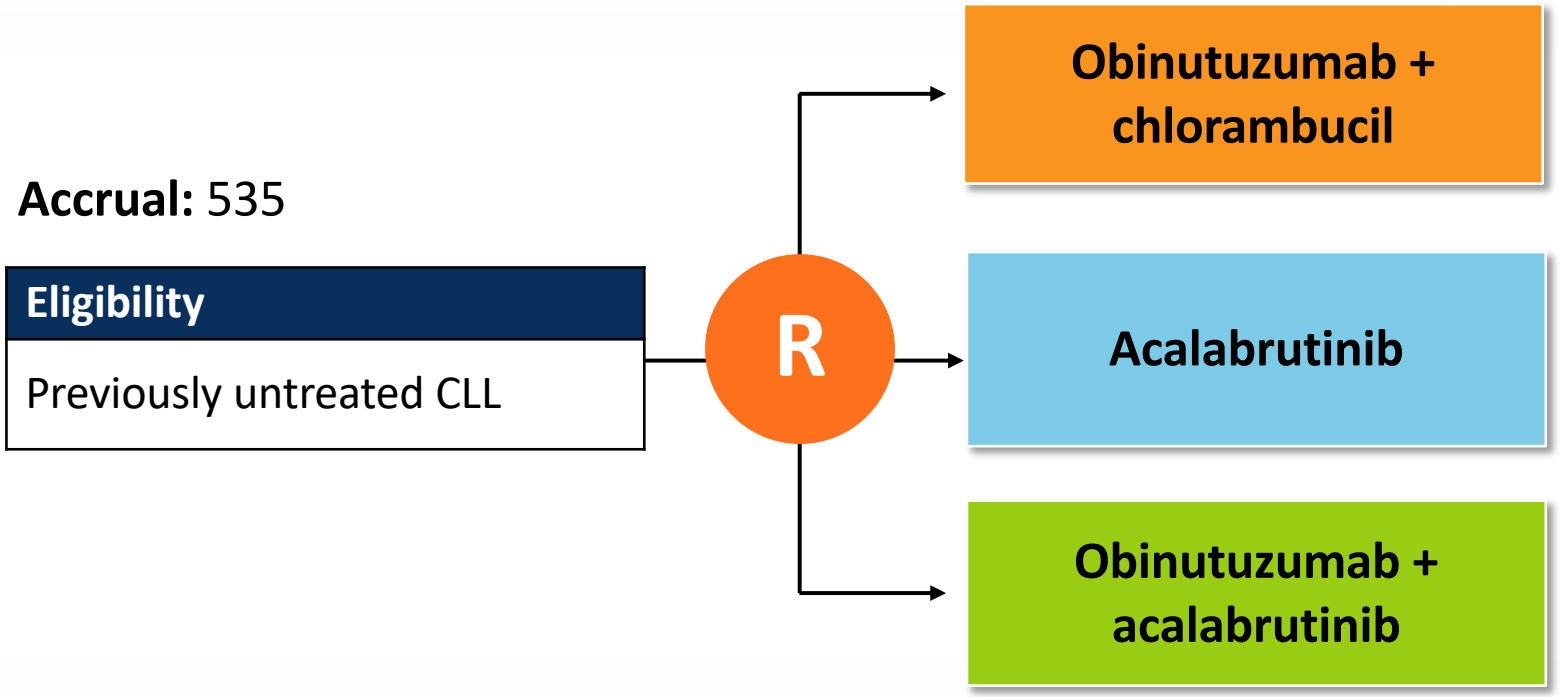
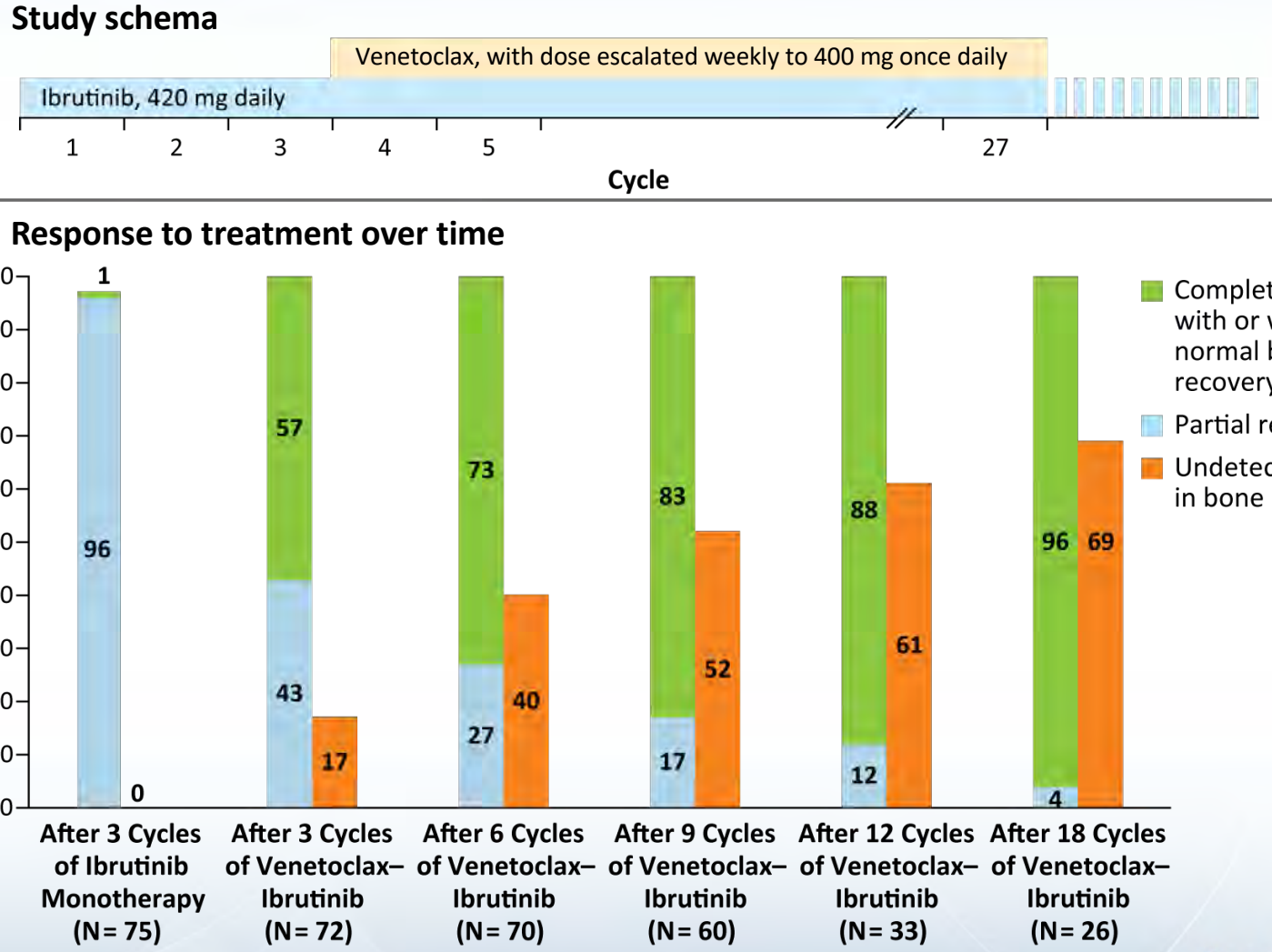
ELEVATE-TN CLL: Phase III Trial Schema



Primary endpoint: Progression-free survival

www.clinicaltrials.gov. (NCT02475681) Accessed October 2019.

Phase II Study of Ibrutinib and Venetoclax for Untreated, High-Risk and Older Patients with CLL



Jain N et al. *N Engl J Med* 2019;380(22):2095-103.

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Selected Ongoing Phase III Studies of First-Line Therapy in CLL

Study	Target N	Randomization	Primary endpoint(s)
FLAIR (ISRCTN01844152)	754	• Ibrutinib • Ibrutinib + rituximab • Ibrutinib + venetoclax • FCR	PFS
GLOW/CLL3011 (NCT03462719)	211	• Ibrutinib + venetoclax • Chlorambucil + obinutuzumab	PFS
GAIA/CLL13 (NCT02950051)	920	• Standard chemo (FCR/BR) • Venetoclax + rituximab • Venetoclax + obinutuzumab • Ibrutinib + venetoclax + obinutuzumab	PFS MRD negativity rate

Clinicaltrials.gov, Accessed October 2019
www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-ibrutinib-rituximab-chronic-lymphocytic-leukaemia-flair#undefined

Management of Select B-Cell Lymphomas

Module 1: Chronic Lymphocytic Leukemia (CLL)

- Ibrutinib/obinutuzumab in treatment-naïve CLL (iLLUMINATE)
- First-line ibrutinib-based regimens for younger (E1912) and older patients (A041202)
- CLL14 trial: Venetoclax/obinutuzumab in the first-line setting
- Venetoclax/rituximab for relapsed/refractory CLL (MURANO)
- Breakthrough therapy designation for acalabrutinib (ELEVATE-TN, ASCEND)

Module 2: Mantle Cell Lymphoma (MCL)

- BTK inhibitors (ibrutinib, acalabrutinib)
- Venetoclax

Module 3: CAR T-Cell Therapy

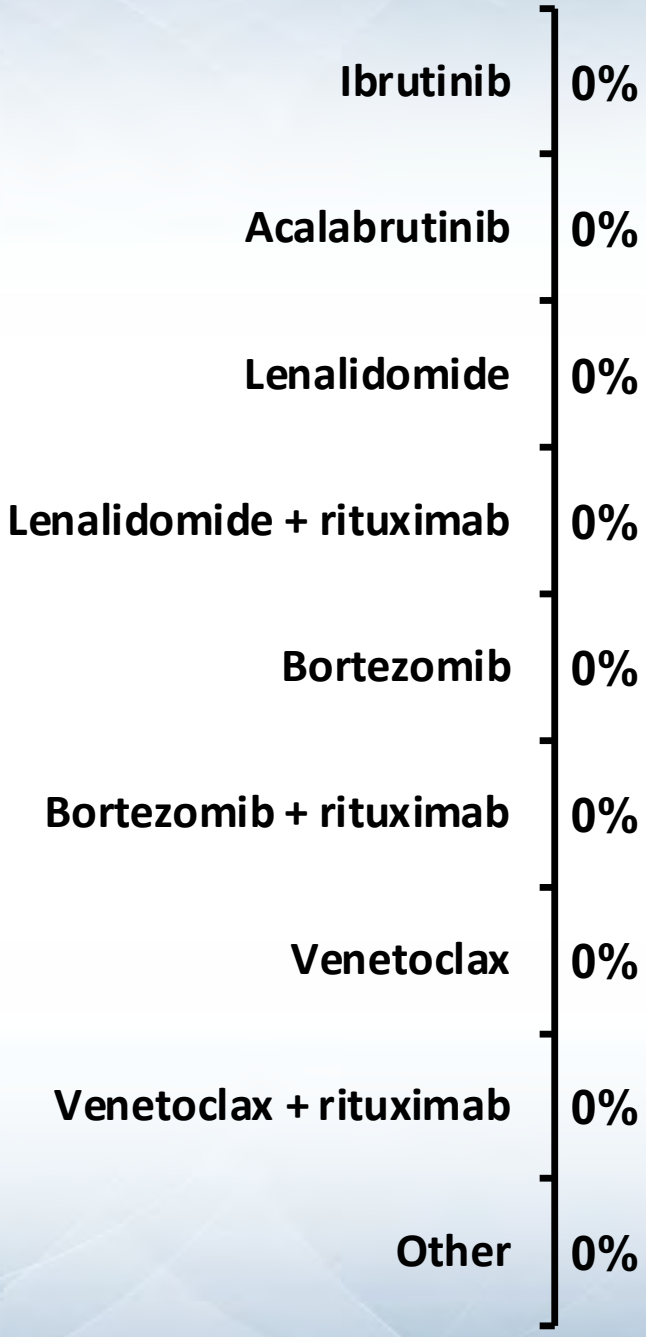
- JULIET (tisagenlecleucel), TRANSCEND NHL 001 (lisocabtagene maraleucel) and ZUMA-1 (axicabtagene ciloleucel) trials in DLBCL

Module 4: Advanced Hodgkin Lymphoma (HL)

- ECHELON-1 trial: Brentuximab vedotin/AVD vs ABVD as front-line therapy
- Checkpoint inhibitors in relapsed/refractory disease and trials in earlier settings

What would you generally recommend for a 65-year-old patient with mantle cell lymphoma (MCL) who is initially treated with BR followed by 2 years of maintenance rituximab and experiences disease relapse 3 years later?

1. Ibrutinib
2. Acalabrutinib
3. Lenalidomide
4. Lenalidomide + rituximab
5. Bortezomib
6. Bortezomib + rituximab
7. Venetoclax
8. Venetoclax + rituximab
9. Other



What would you generally recommend for a 65-year-old patient with MCL who is initially treated with BR followed by 2 years of maintenance rituximab and experiences disease relapse 3 years later? What if the same patient has a history of atrial fibrillation and is receiving anticoagulation therapy?

	2nd-line therapy	2nd-line therapy; atrial fibrillation and anticoagulation therapy
 BRUCE D CHESON, MD	Acalabrutinib	Acalabrutinib
 ANDREW M EVENS, DO, MSC	Ibrutinib	Acalabrutinib
 ANN S LACASCE, MD, MMSC	Acalabrutinib	Acalabrutinib
 JOHN P LEONARD, MD	Ibrutinib	Lenalidomide/rituximab
 JULIE M VOSE, MD, MBA	Acalabrutinib	Acalabrutinib

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Pooled Analysis of Ibrutinib in R/R MCL: Extended 3.5-Year Follow-Up

(Phase II PCYC-1104 and SPARK and Phase III RAY Studies)

Endpoint	Overall (N = 370)	Prior Lines of Therapy	
		1 (n = 99)	2 (n = 271)
Median PFS	**12.5 mo**	**25.4 mo**	**10.3 mo**
Median PFS by best response			
CR (n = 100)	Not reached	57.5 mo	Not reached
PR (n = 158)	12.8 mo	24.2 mo	10.6 mo
Median OS	**26.7 mo**	**Not reached**	**22.5 mo**
Median OS by best response			
CR (n = 100)	Not reached	Not reached	Not reached
PR (n = 158)	25.4 mo	36.0 mo	22.7 mo
ORR / CR	**70% / 27%**	**78% / 37%**	**67% / 23%**

Rule S et al. *Hematol* 2019;[Epub ahead of print].

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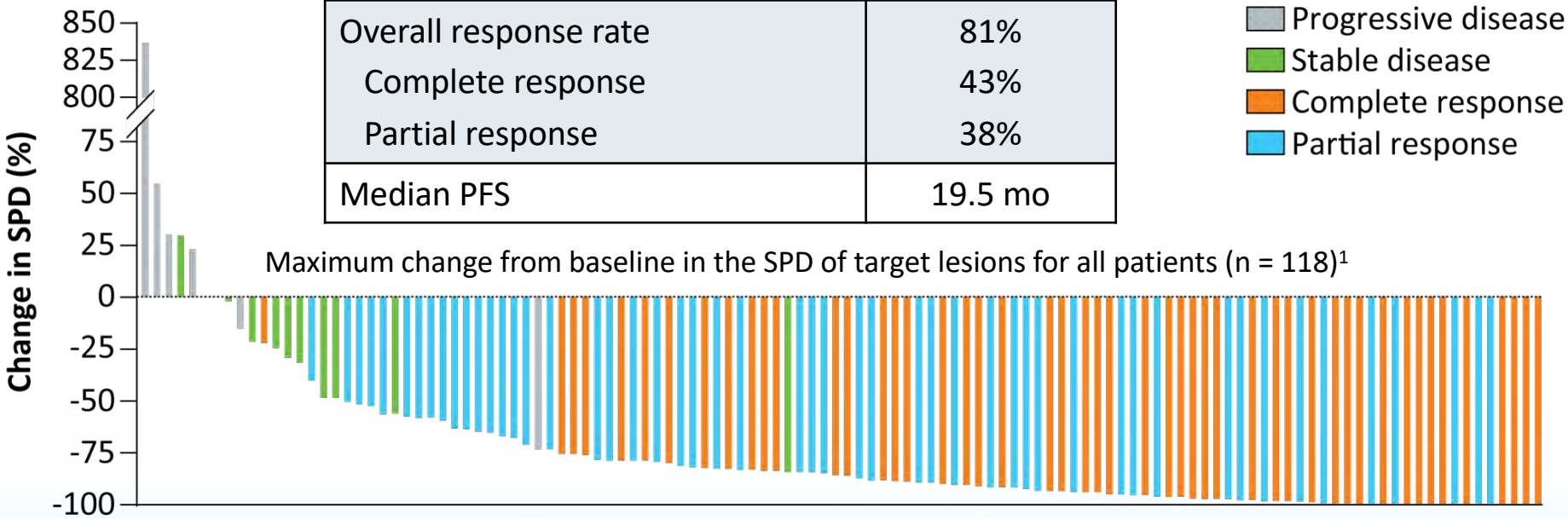
ACE-LY-004 Phase II Trial of Acalabrutinib in Relapsed/Refractory MCL: Response and Long-Term Follow-Up Results

Long-term follow-up >24 mo[2]	N = 124
Overall response rate	81%
Complete response	43%
Partial response	38%
Median PFS	19.5 mo



Maximum change from baseline in the SPD of target lesions for all patients (n = 118)[1]

[1] Wang M et al. *Lancet* 2018;391(10121):659-67; [2] Wang M et al. *Proc ASH* 2018;Abstract 2876.

FDA Grants Priority Review of Zanubrutinib NDA for Relapsed/Refractory MCL

Press Release – August 21, 2019

"The US Food and Drug Administration (FDA) has accepted the company's New Drug Application (NDA) for zanubrutinib for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. The FDA granted Priority Review for the NDA and has set a Prescription Drug User Fee Act (PDUFA) target action date of February 27, 2020. This follows the FDA's Breakthrough Therapy designation for zanubrutinib in this setting earlier this year.

The NDA data package includes data from the global Phase 1/2 trial (NCT02343120) in patients with B-cell lymphomas and an aggregate of 123 patients in the multicenter Phase 2 trial of zanubrutinib in patients with relapsed or refractory (R/R) MCL in China (NCT03206970), as well as safety data on 641 patients from five clinical trials, and non-clinical data."

https://www.globenewswire.com/news-release/2019/08/21/1905119/0/en/BeiGene-Announces-U-S-FDA-Acceptance-and-Grant-of-Priority-Review-for-its-New-Drug-Application-of-Zanubrutinib-in-Patients-with-Relapsed-Refractory-Mantle-Cell-Lymphoma.html

Efficacy of Zanubrutinib in MCL

Study	Evaluable patients	ORR / CR	Median DoR	Median PFS
Ph 1/2 (NCT02343120)	N = 48 R/R = 37 TN = 11	87%/31% 87%/30% 88%/38%	16.2 mo (all) 14.7 mo 14.7 mo	15.4 mo
Ph 2 (NCT03206970)	N = 86 R/R	85%/77%	14.0 mo	16.7 mo

Song Y et al. *Proc ICML* 2019;Abstract 015.
Tam CS et al. *Proc ICML* 2019;Abstract 191.

Based on available data and regulatory and reimbursement issues aside, would you attempt to access venetoclax for select patients with relapsed/refractory MCL?

 BRUCE D CHESON, MD	Yes, after a BTK inhibitor
 ANDREW M EVENS, DO, MSC	Yes, after a BTK inhibitor followed by lenalidomide
 ANN S LACASCE, MD, MMSC	Yes, after a BTK inhibitor
 JOHN P LEONARD, MD	Yes, after a BTK inhibitor followed by lenalidomide
 JULIE M VOSE, MD, MBA	Yes, after a BTK inhibitor

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Venetoclax Monotherapy in BTK Inhibitor-Resistant MCL: Results Summary

Clinical endpoint	Venetoclax (N = 20)
Overall response rate (ORR) Complete response rate	60% 20%
ORR (prior response to BTKi) ORR (primary resistance to BTKi)	72.7% 44.4%
Median PFS	2.6 mo
Median OS	4.3 mo

No cases of clinical TLS were observed

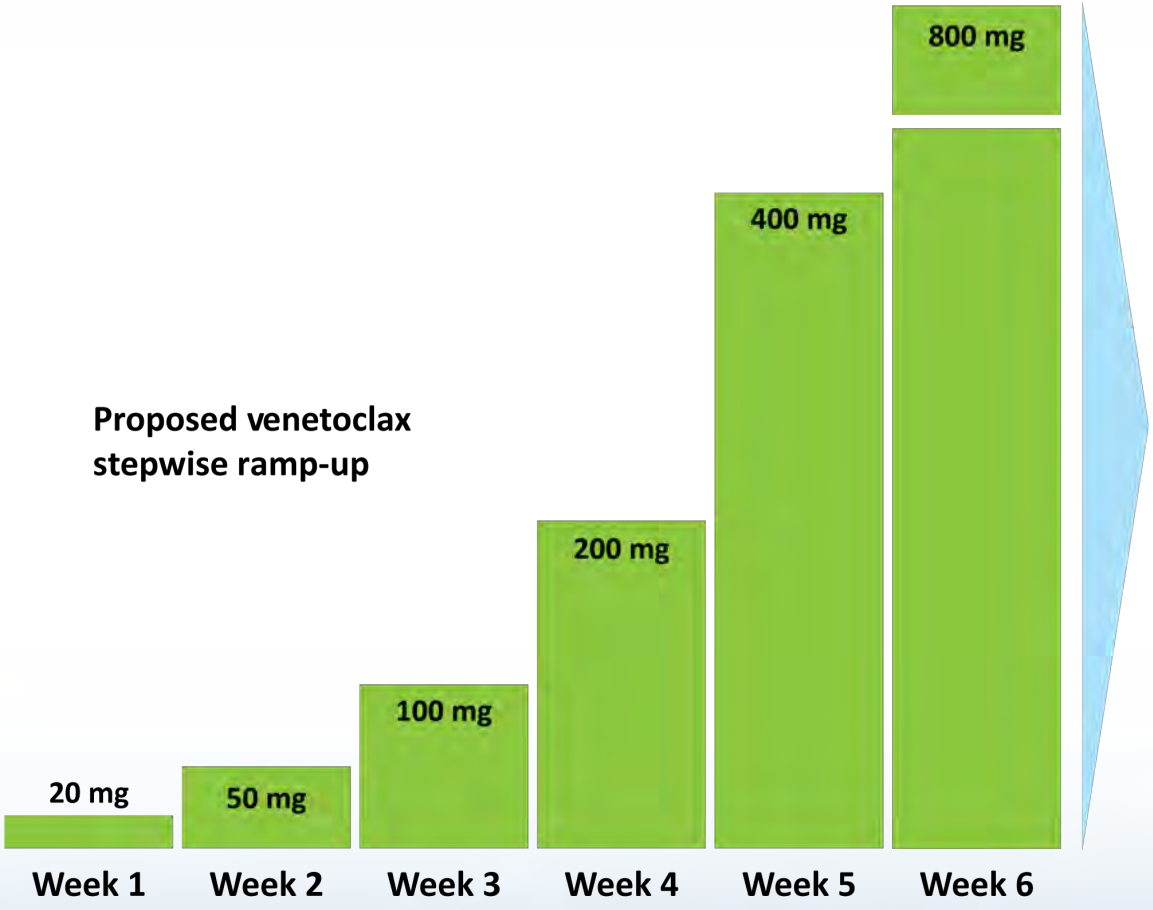
Eyre T et al. *Proc EHA* 2018;Abstract S855.

AIM: Phase II Trial of Ibrutinib/Venetoclax in R/R MCL
(median 2 prior therapies)

Primary endpoint	Without PET (n = 24)	With PET (n = 24)
CR at 16 weeks	10 (42%)	15 (62%)
Best response		
CR	16 (67%)	17 (71%)
Best response, total population, according to MRD response		
MRD negative	16 (67%)	9 (38%)
MRD not negative	8 (33%)	15 (62%)

Tam CS et al. *N Engl J Med* 2018;378(13):1211-23.

Proposed Stepwise Ramp-up Dosing of Venetoclax to Mitigate Risk of Tumor Lysis Syndrome (TLS)



- To minimize TLS risk, the venetoclax starting dose is 20 mg once daily for 7 days followed by a gradual stepwise weekly ramp-up to reach a dose of 400 mg daily by 5 weeks.
- For patients with MCL who receive venetoclax monotherapy, 1 additional ramp-up to 800 mg by 6 weeks is suggested, given the possibility of deeper responses observed at this dose compared to lower doses in the Phase I study.

Davids MS et al. *J Clin Oncol* 2018;36(35):3525-7.

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- ECHELON-1 trial: Brentuximab vedotin/AVD vs ABVD as front-line therapy
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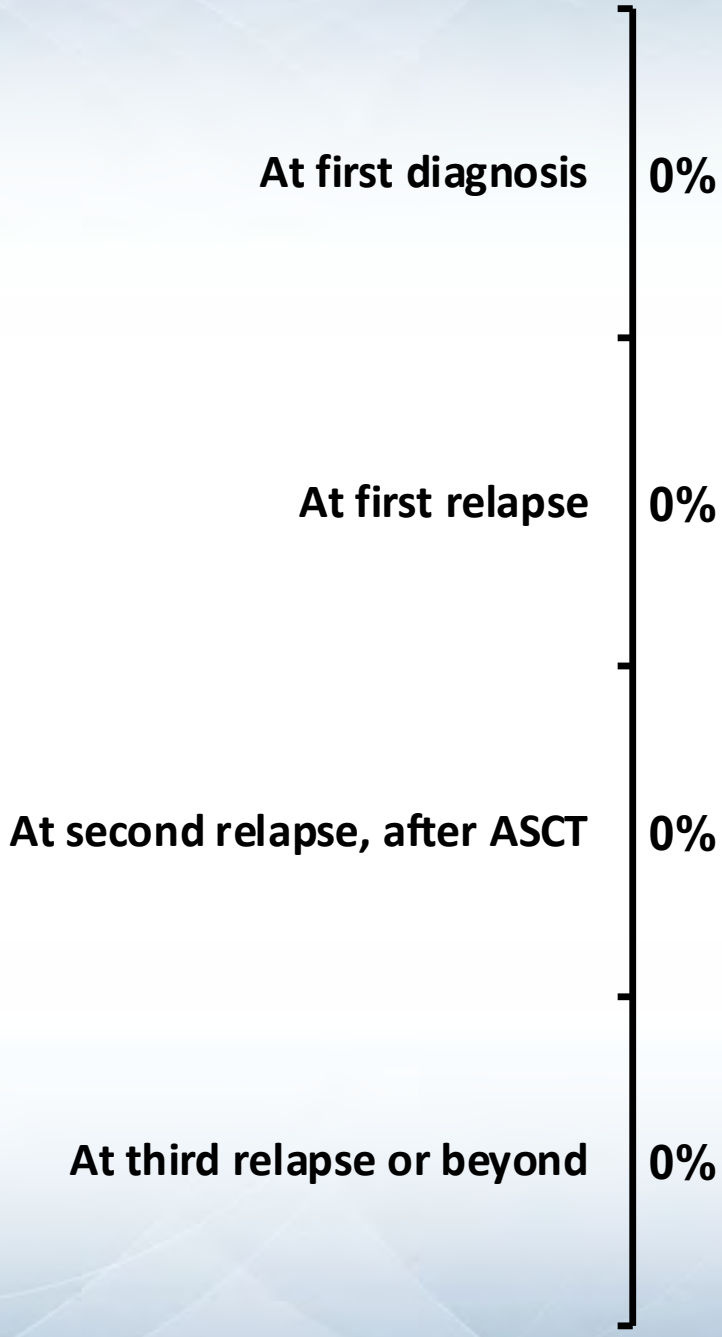
For most cases of DLBCL, when is the optimal time to refer a patient for a consultation regarding anti-CD19 CAR T-cell therapy?

1. At first diagnosis
2. At first relapse
3. At second relapse, after ASCT
4. At third relapse or beyond



For most cases of DLBCL, when is the optimal time to refer a patient for a consultation regarding anti-CD19 CAR T-cell therapy? What about double-hit DLBCL?

	Refer DLBCL for CAR-T consultation?	Refer double-hit DLBCL for consultation?
 BRUCE D CHESON, MD	At first relapse	At first diagnosis
 ANDREW M EVENS, DO, MSC	At first relapse	At first relapse
 ANN S LACASCE, MD, MMSC	At first relapse	At first relapse
 JOHN P LEONARD, MD	At second relapse, after ASCT	At first relapse
 JULIE M VOSE, MD, MBA	At first relapse	At second relapse, after ASCT

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Regulatory and reimbursement issues aside, what is the optimal treatment approach for a patient with relapsed/refractory DLBCL after primary treatment with R-CHOP?

 BRUCE D CHESON, MD	CAR T-cell therapy
 ANDREW M EVENS, DO, MSC	Salvage chemo followed by ASCT if in CR with salvage chemo
 ANN S LACASCE, MD, MMSC	Likely CAR T-cell therapy
 JOHN P LEONARD, MD	Salvage chemo followed by ASCT
 JULIE M VOSE, MD, MBA	Salvage chemo followed by ASCT

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What is the optimal treatment approach for a 65-year-old patient with DLBCL who responds to R-CHOP and then R-DHAP followed by transplant on relapse but subsequently develops disease progression?

 BRUCE D CHESON, MD	CAR T-cell therapy
 ANDREW M EVENS, DO, MSC	CAR T-cell therapy
 ANN S LACASCE, MD, MMSC	Depends on disease burden — whether polatuzumab vedotin/BR needed prior to CAR-T
 JOHN P LEONARD, MD	CAR T-cell therapy
 JULIE M VOSE, MD, MBA	Polatuzumab vedotin/BR followed by CAR-T

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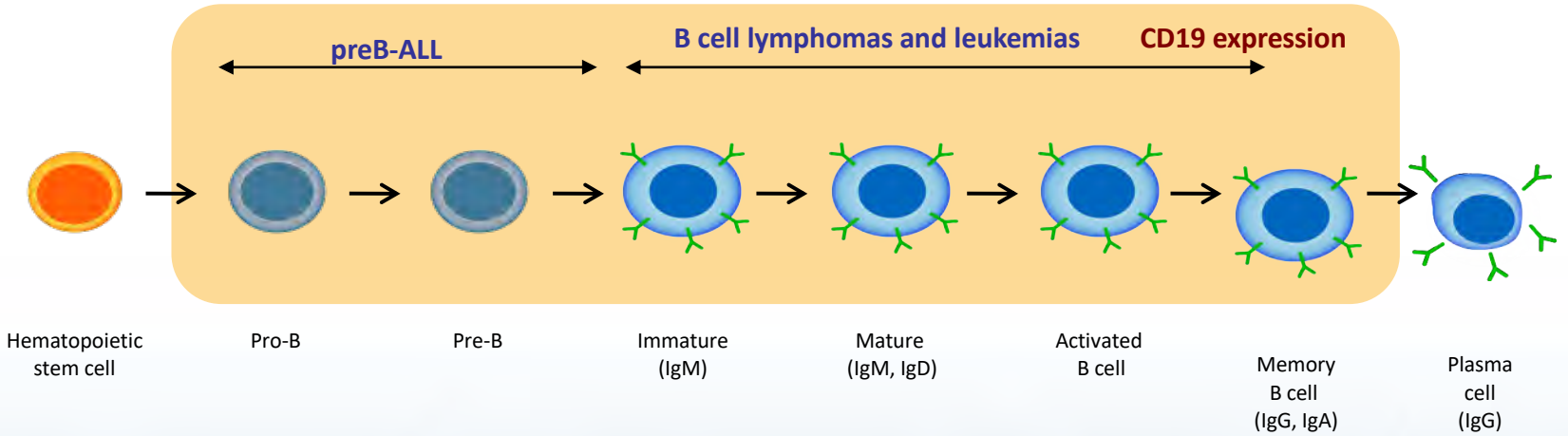
CD19: An Ideal Tumor Target in B-Cell Lymphomas

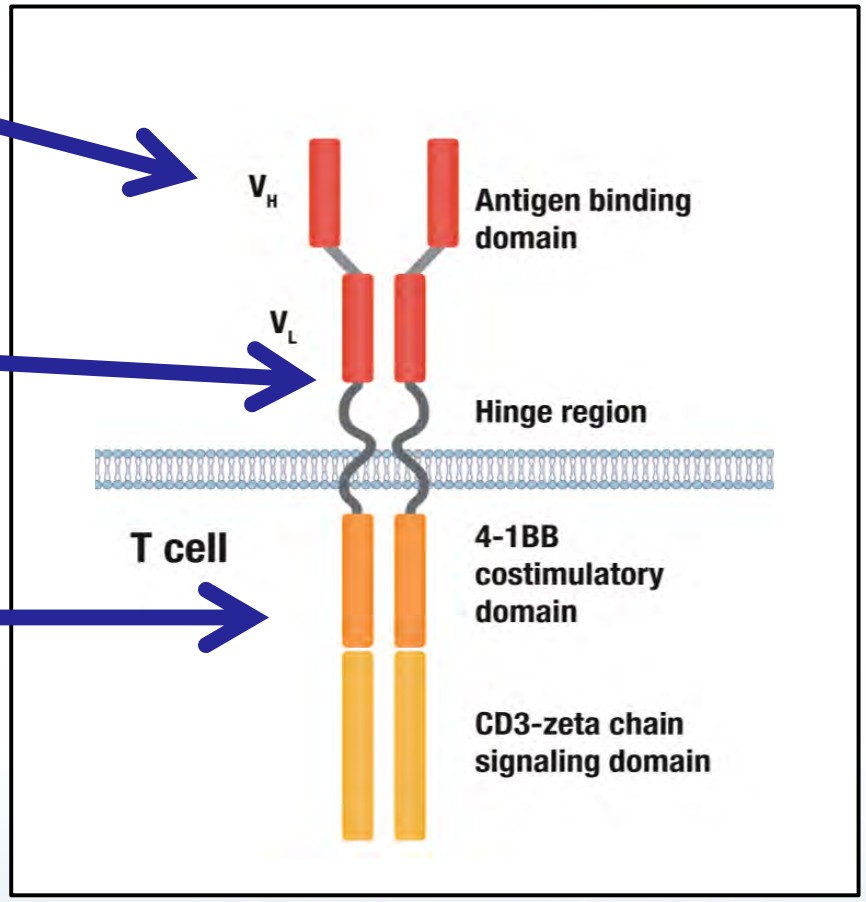
- CD19 expression is generally restricted to B cells and B-cell precursors[1]
  - CD19 is not expressed on hematopoietic stem cells[1]
- CD19 is expressed by most B-cell lymphomas[1]
  - CLL, B-ALL, DLBCL, FL, MCL[1]
- Antibodies against CD19 inhibit tumor cell growth



1. Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397. Image adapted from Janeway CA, Travers P, Walport M, et al. *Immunobiology*. 5th ed. NY, NY: Garland Science; 2001:221-293; Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397; and Feldman M, Marini JC. Cell cooperation in the antibody response. In: Roitt I, Brostoff J, Male D, eds. *Immunology*. 6th ed. Maryland Heights, Missouri: Mosby;2001:131-146.

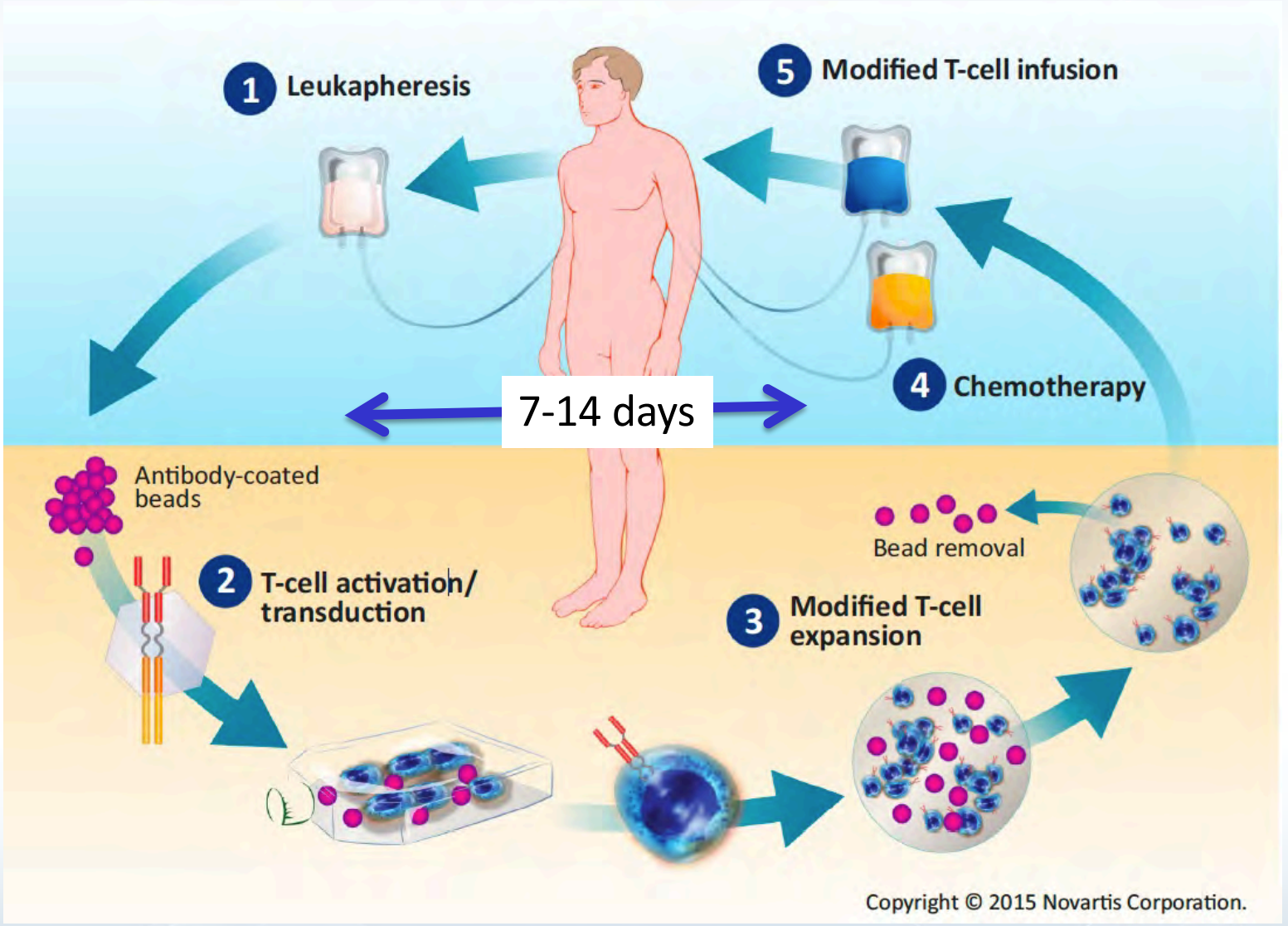
Targeting with Chimeric Antigen Receptors

- Antibody to target a specific protein on cancer cell.
- Sequences bring and keep protein on the surface of T cell
- Signals for T cell activation (killing), growth, and survival



Courtesy, David Porter, MD, February 2019

Overview of CAR-T Cell Therapy



Modification, Courtesy, David Porter, MD

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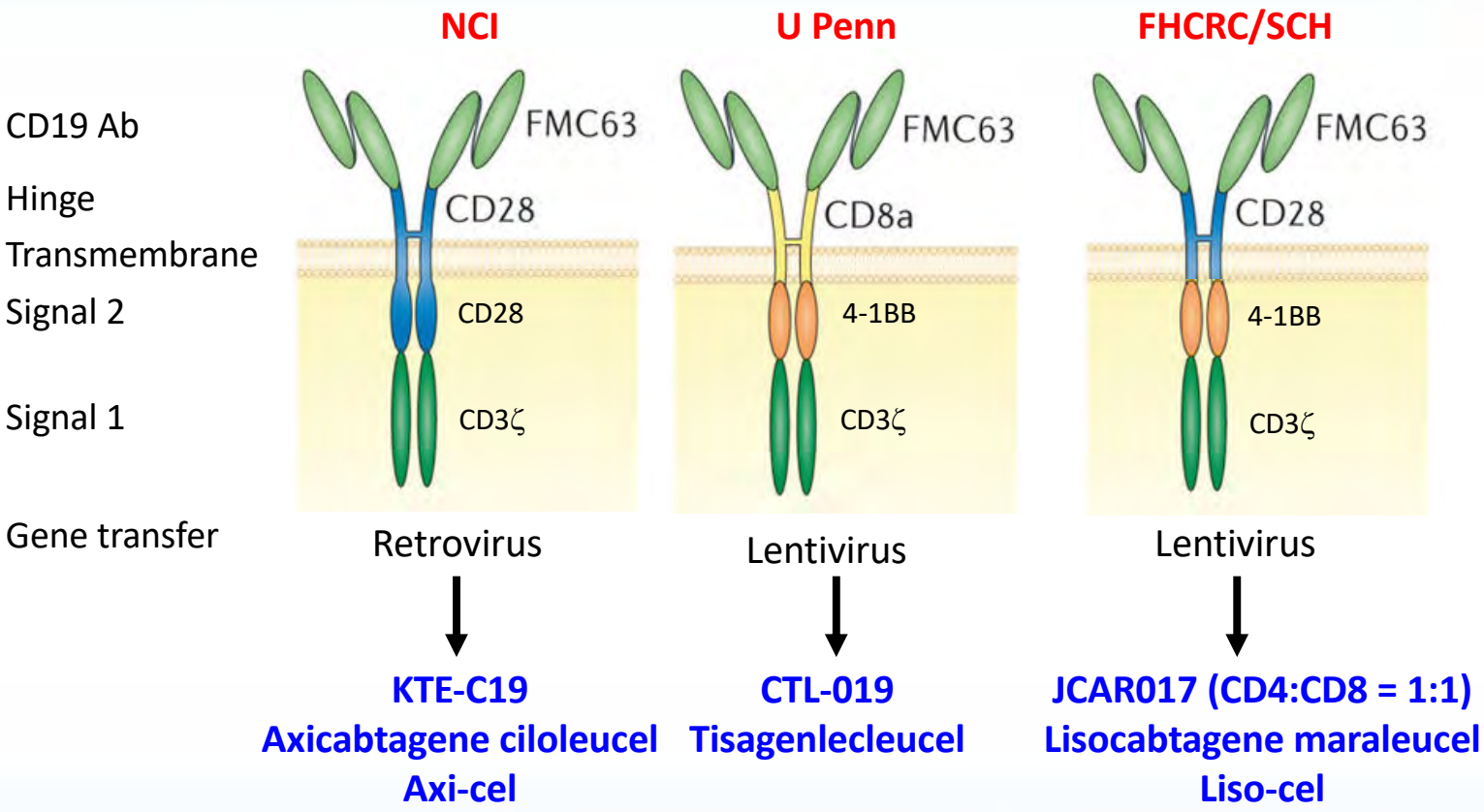
CD19 CAR-T Constructs in Pivotal Trials in NHL



Adapted: van der Steegen et al. *Nat Rev Drug Discov* 2015

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

	ZUMA-1 Axicabtagene ciloleucel	JULIET Tisagenlecleucel	TRANSCEND NHL 001 Lisocabtagene maraleucel
Evaluable pts	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.

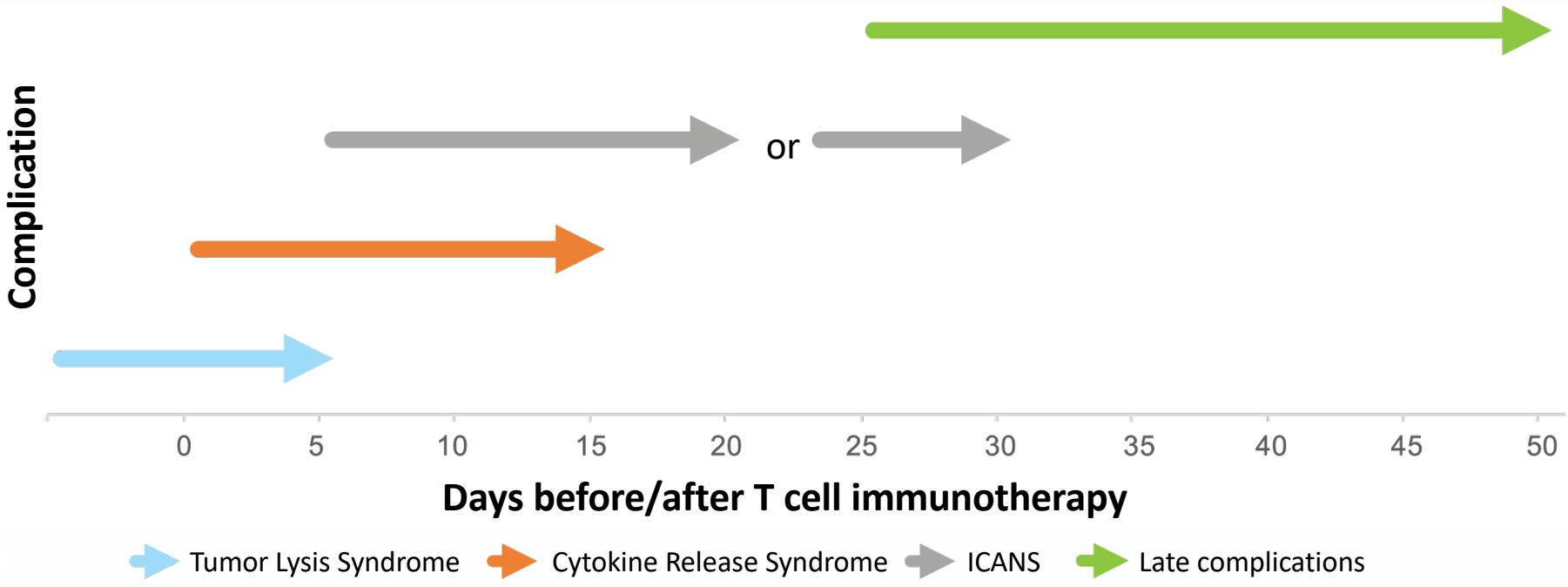
Pivotal CAR-T Studies in DLBCL: Summary of Efficacy

	ZUMA-1 Axicabtagene ciloleucel	JULIET Tisagenlecleucel	TRANSCEND NHL 001 Lisocabtagene maraleucel
Evaluable pts	101	93	102 (Core: 73)
Median f/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.

Timing of T-Cell Immunotherapy Complications

No significant acute infusional toxicity



ICANS = immune effector cell–associated neurotoxicity syndrome

Varadarajan I, Lee DW. *Cancer J* 2019;25(3):223-30.

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 3-10%

Neurologic toxicity – may be mild or life-threatening

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

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

Pivotal CAR-T Studies in DLBCL: Select Toxicity

	ZUMA-1 Axicabtagene ciloleucel	JULIET Tisagenlecleucel	TRANSCEND NHL 001 Lisocabtagene maraleucel
All grade CRS	93%	58%	37%
Grade ≥3 CRS	13%	23%	1%
All grade neurotoxicity	64%	21%	23%
Grade ≥3 neurotoxicity	28%	12%	13%
Tocilizumab use	43%	15%	17%
Steroid treatment	27%	11%	21%

Locke F et al; ZUMA-1 Investigators. *Lancet Oncol* 2019;20(1):31-42. Neelapu SS et al. *N Engl J Med* 2017;377:2531-44. 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. Abramson JS et al. ASCO 2019 Education Book.

Generally Accepted Management Approaches for CRS and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Cytokine Release Syndrome

- Detailed, immediate evaluation for infection; empiric broad-spectrum antibiotics for first fever
- Repeated IV fluid boluses avoided where possible; may exacerbate complications of capillary leak
- Tocilizumab only FDA-approved agent and is the first line of treatment for CRS
  - Can mitigate CRS severity likely without decreasing efficacy of immunotherapy
  - Usually indicated for any patient with recurrent or refractory hypotension related to CRS; should be used before grade 3 CRS or worse develops
  - Multiple doses may be required but generally do not exceed 2 doses without addition of steroids
- Corticosteroids should be added if there is no response to tocilizumab

Immune Effector Cell-Associated Neurotoxicity Syndrome

- Detailed, immediate evaluation for any suspected neurologic dysfunction; admission to hospital if ICANS suspected
- Tocilizumab should be avoided if patient has ICANS without any ongoing evidence of CRS
- Corticosteroids should be given for grade ≥2 ICANS

Varadarajan I, Lee DW. *Cancer J* 2019;25(3), pp.223-230.

Comparison of Axicabtagene Ciloleucel in ZUMA-1 and Treatment in the "Real World" at 17 US Centers

	ZUMA-1	This study
N infused patients	108	165
Patients meeting ZUMA-1 eligibility criteria	100%	51%
Age, median (range)	58 (23-76)	59 (21-82)
ECOG 0 or 1	100%	84%
Prior autologous transplant	23%	31%
DLBCL including HGBCL, not tFL or PMBCL	78%	61%
ORR/CR	82%/58% (best)	79%/50% (day 30)
Grade 3 or higher toxicity	CRS 13%/NEs 31%	CRS 7%/NEs 31%

CRS = cytokine release syndrome; NE = neurologic toxicity

Nastoupil LJ et al. *Proc ASH* 2018;Abstract 91.

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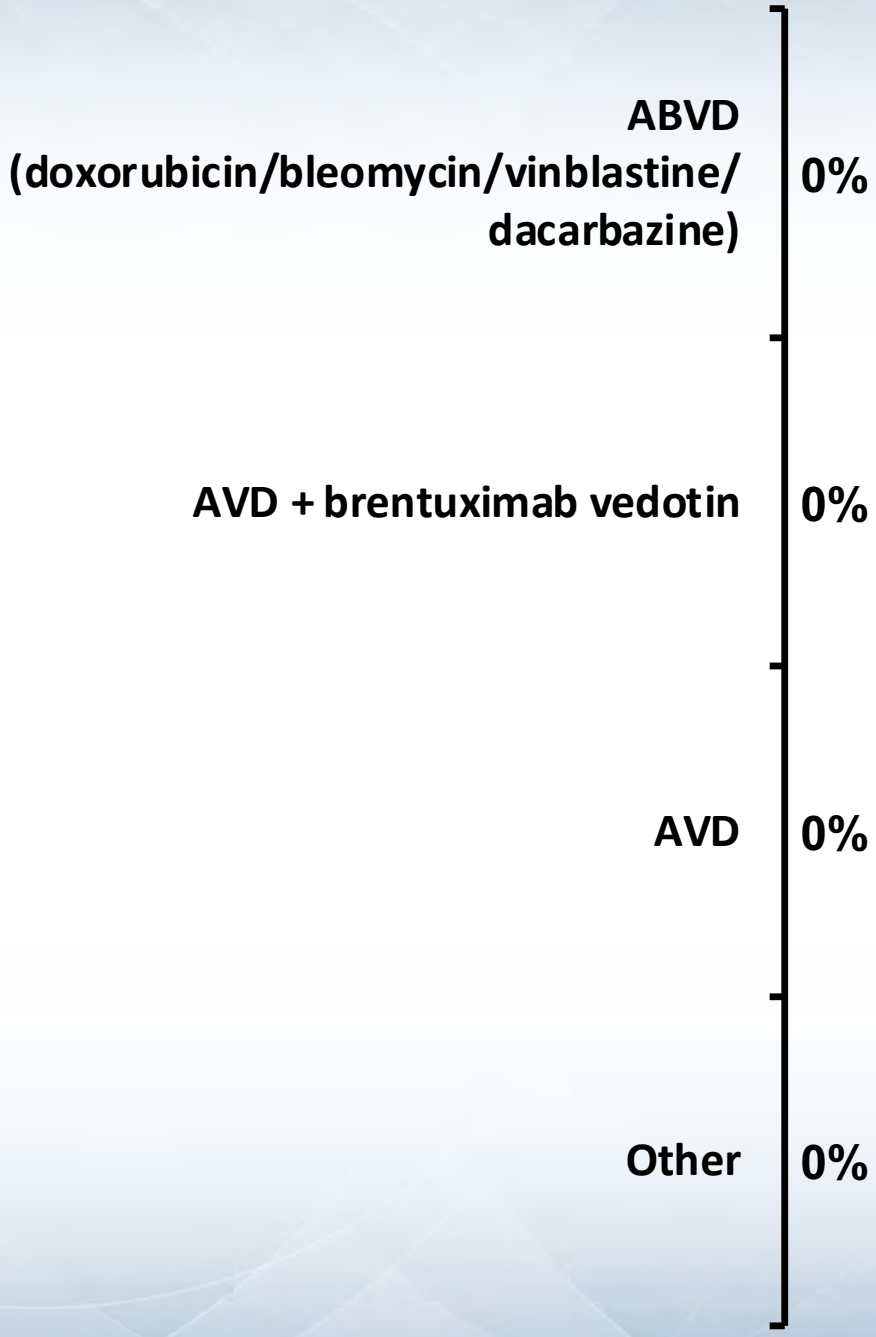
In general, what is your usual first-line systemic therapy for a 65-year-old patient with Stage IV HL?

1. ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine)
2. AVD + brentuximab vedotin
3. AVD
4. Other



In general, what is your usual first-line systemic therapy for a 65-year-old patient with Stage IV HL?

Regulatory and reimbursement issues aside, what in general would be your preferred bridge to transplant for a patient with HL who is experiencing relapse after up-front ABVD?

	First-line?	Bridge to transplant?
 BRUCE D CHESON, MD	AVD	BV/bendamustine
 ANDREW M EVENS, DO, MSC	AVD + BV (sequential)	ICE
 ANN S LACASCE, MD, MMSC	ABVD	BV/nivolumab
 JOHN P LEONARD, MD	AVD or PVAG	BV/bendamustine
 JULIE M VOSE, MD, MBA	ABVD	ICE

BV = brentuximab vedotin; ICE = ifosfamide/carboplatin/etoposide;
PVAG = prednisone/vinblastine/doxorubicin/gemcitabine

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A 27-year-old man is diagnosed with Stage IVB classical Hodgkin lymphoma (HL) with nodal, spleen and bone involvement. Albumin is 3.1 g/dL, hemoglobin (Hgb) is 8.6 g/dL and white blood cell (WBC) count is 17,500. International Prognostic Score (IPS) = 5. What initial treatment would you recommend?

 BRUCE D CHESON, MD	PET-adapted ABVD
 ANDREW M EVENS, DO, MSC	Brentuximab vedotin + AVD
 ANN S LACASCE, MD, MMSC	Brentuximab vedotin + AVD
 JOHN P LEONARD, MD	Brentuximab vedotin + AVD
 JULIE M VOSE, MD, MBA	Brentuximab vedotin + AVD

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Regulatory and reimbursement issues aside, what would you recommend for an 85-year-old frail patient with symptomatic advanced-stage HL who is not a candidate for aggressive chemotherapy but is seeking active treatment?

 BRUCE D CHESON, MD	Brentuximab vedotin + nivolumab
 ANDREW M EVENS, DO, MSC	Brentuximab vedotin/dacarbazine
 ANN S LACASCE, MD, MMSC	Brentuximab vedotin/dacarbazine
 JOHN P LEONARD, MD	Brentuximab vedotin/dacarbazine
 JULIE M VOSE, MD, MBA	Brentuximab vedotin/dacarbazine

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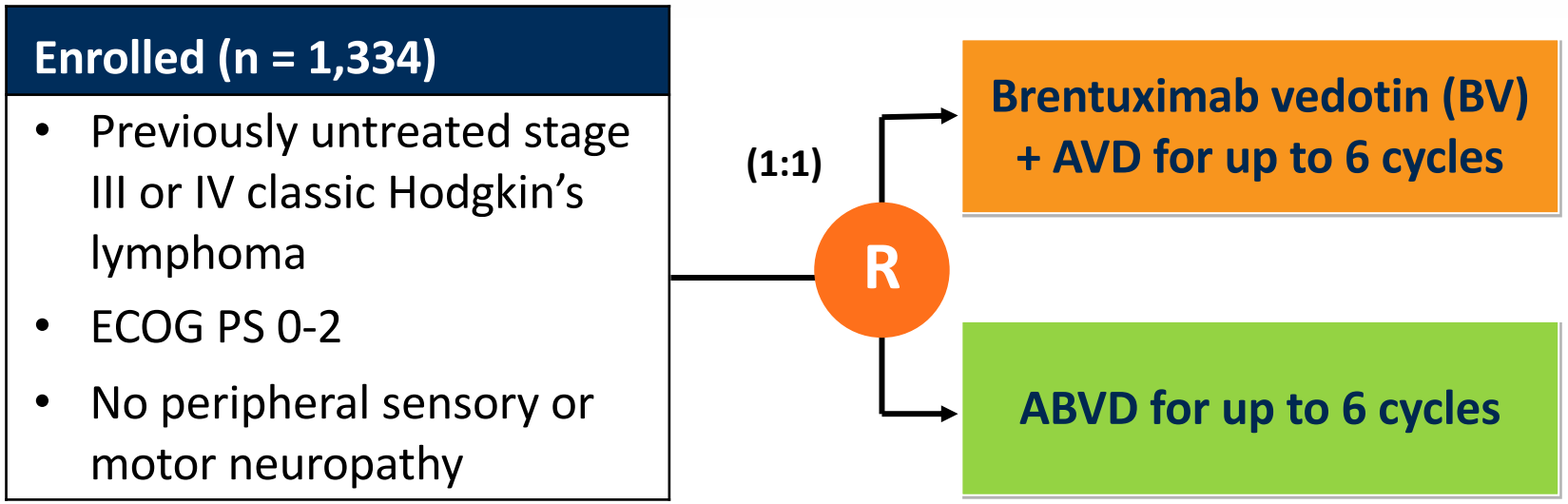
ECHELON-1 Phase III Study Schema



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 3 Years

Group	BV + AVD	ABVD	Hazard ratio	*p*-value
All pts (ITT) (n = 664, 670)	83%	76%	0.70	0.005
PET2-negative (n = 577, 573)	86%	80%	0.69	0.009
PET2-positive (n = 58, 63)	68%	52%	0.59	0.077
Patients <60 years				
PET2-negative (n = 512, 489)	87%	81%	0.71	0.034
PET2-positive (n = 51, 54)	69%	55%	0.60	0.117

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

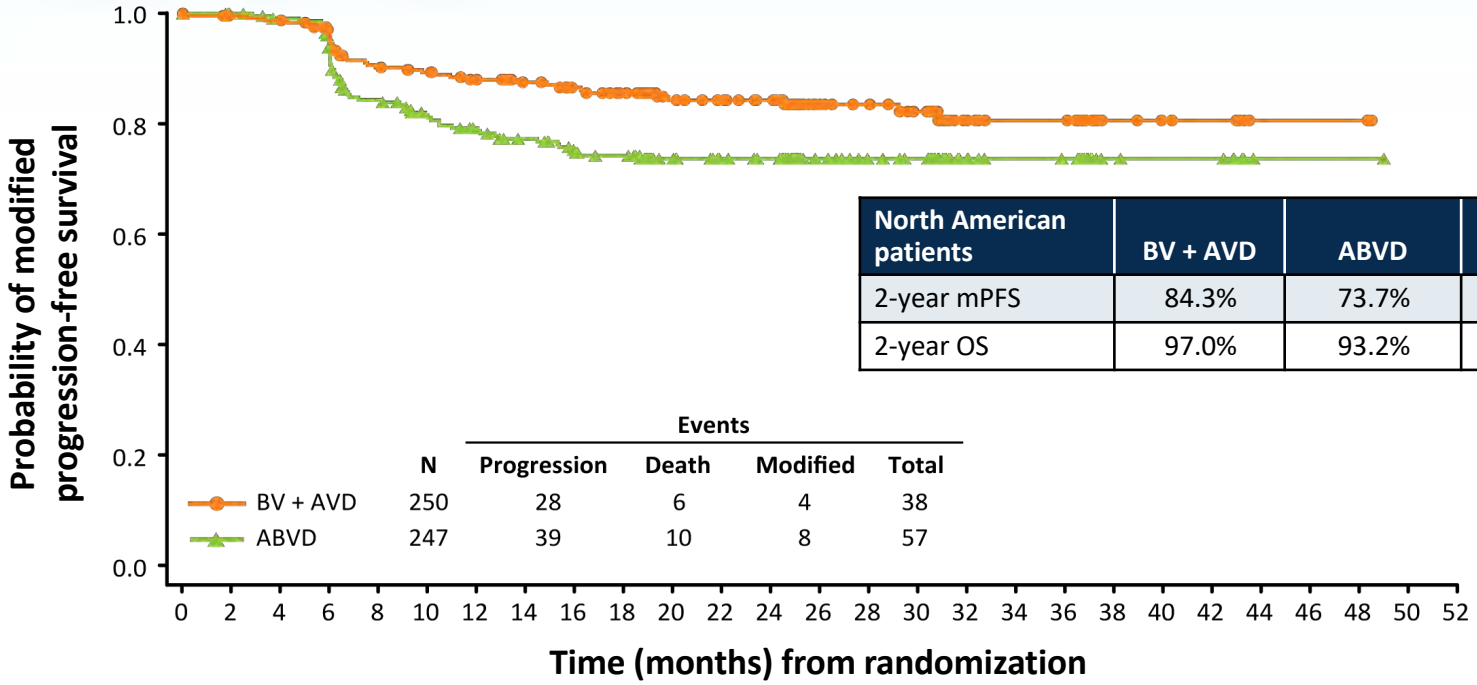
Straus DJ et al. *Proc ASCO* 2019;Abstract 7532.

ECHELON-1: Efficacy and Safety of Brentuximab Vedotin + AVD versus ABVD in Older Patients

	Pts aged ≥60 yrs		Pts aged <60 yrs	
	BV + AVD (n = 84)	ABVD (n = 102)	BV + AVD (n = 580)	ABVD (n = 568)
2-yr mPFS (IRF)	70%	71%	84%	78%
	HR = 1.0, *p* = 0.993		HR = 0.73, *p* = 0.025	
Grade 3/4 AEs	88%	80%	82%	63%
Fatal AEs	4%	5%	1%	1%
Any grade neutropenia	73%	66%	68%	53%
Any grade febrile neutropenia	37%	17%	17%	6%
Any grade peripheral neuropathy	65%	43%	67%	43%
Any grade pulmonary AEs	2%	13%	2%	6%

Evens AM et al. *Proc ASH* 2018;Abstract 1618.

ECHELON-1: Efficacy of Brentuximab Vedotin (BV) with Chemotherapy in North American Patients with Newly Diagnosed Stage III or IV Hodgkin Lymphoma



North American patients	BV + AVD	ABVD	HR, *p*-value
2-year mPFS	84.3%	73.7%	0.60, $p = 0.012$
2-year OS	97.0%	93.2%	0.51, $p = 0.094$

mPFS by regional patient population	HR	*p*-value
North America	0.60	0.012
Europe	0.83	0.281
Asia	0.91	0.810

Ramchandren R et al. *Clin Cancer Res* 2019;25(6):1718-26.

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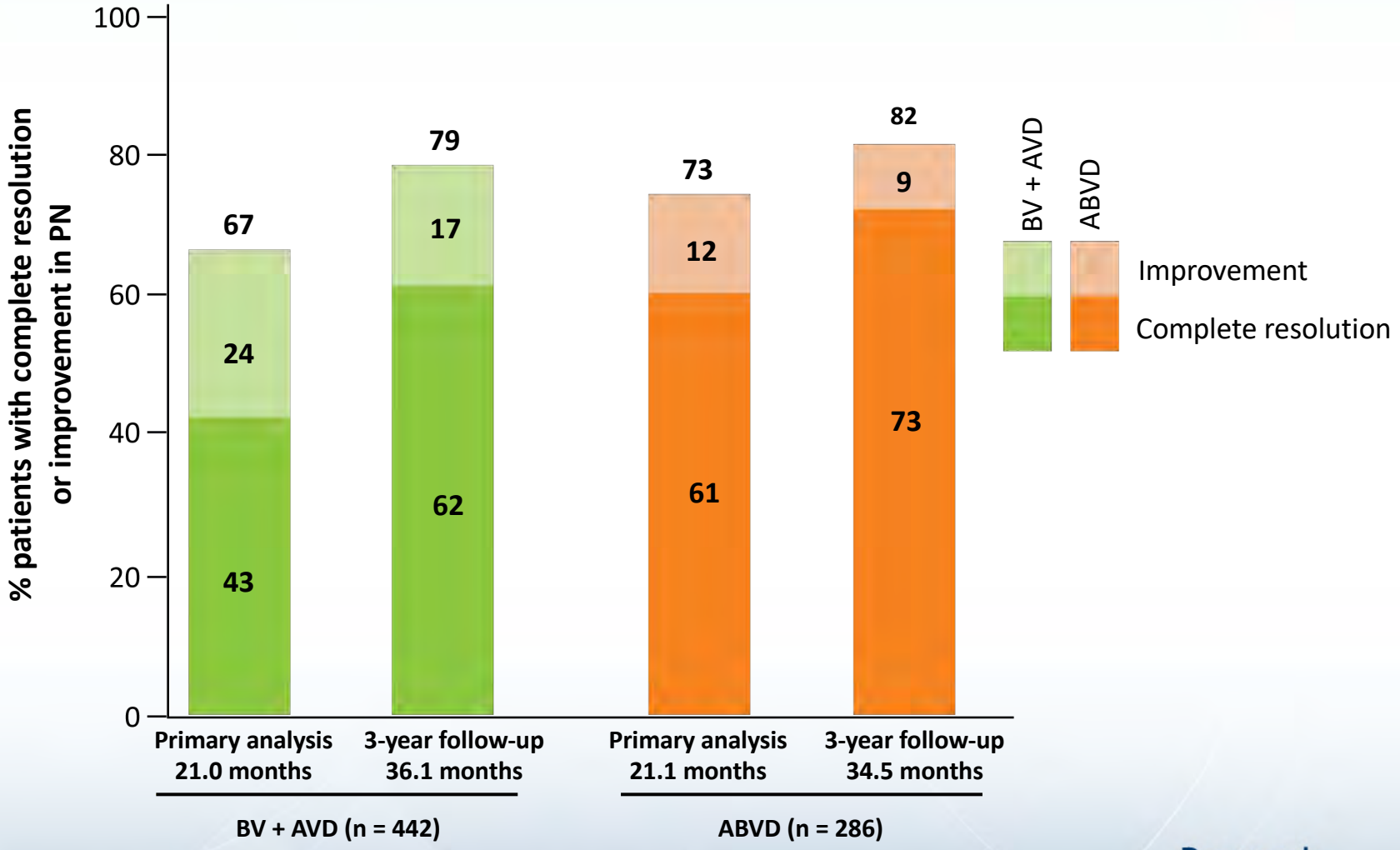
ECHELON-1: Complete Resolution and Improvement of Peripheral Neuropathy at 3 Years



Straus DJ et al. *Proc ASCO* 2019;Abstract 7532.

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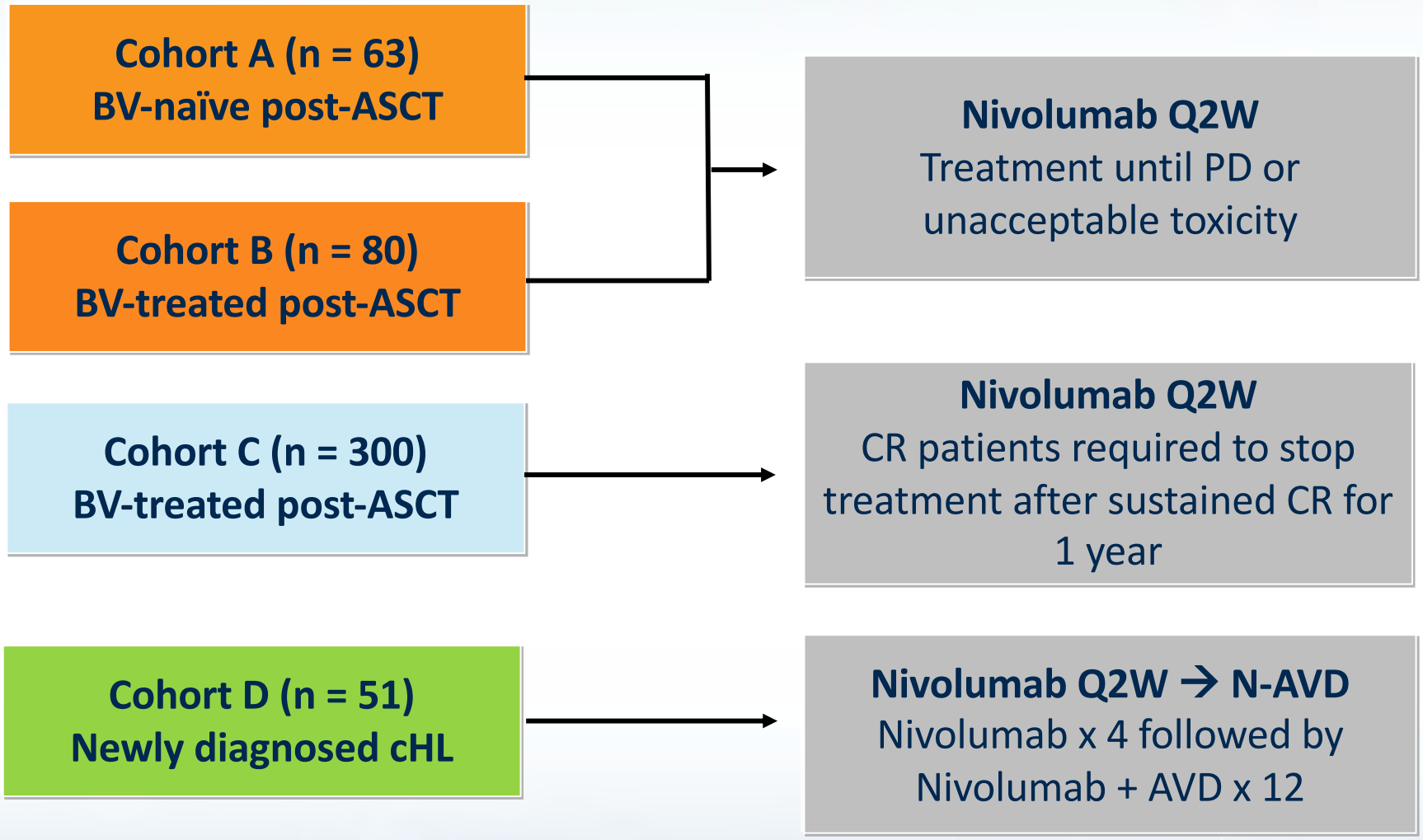
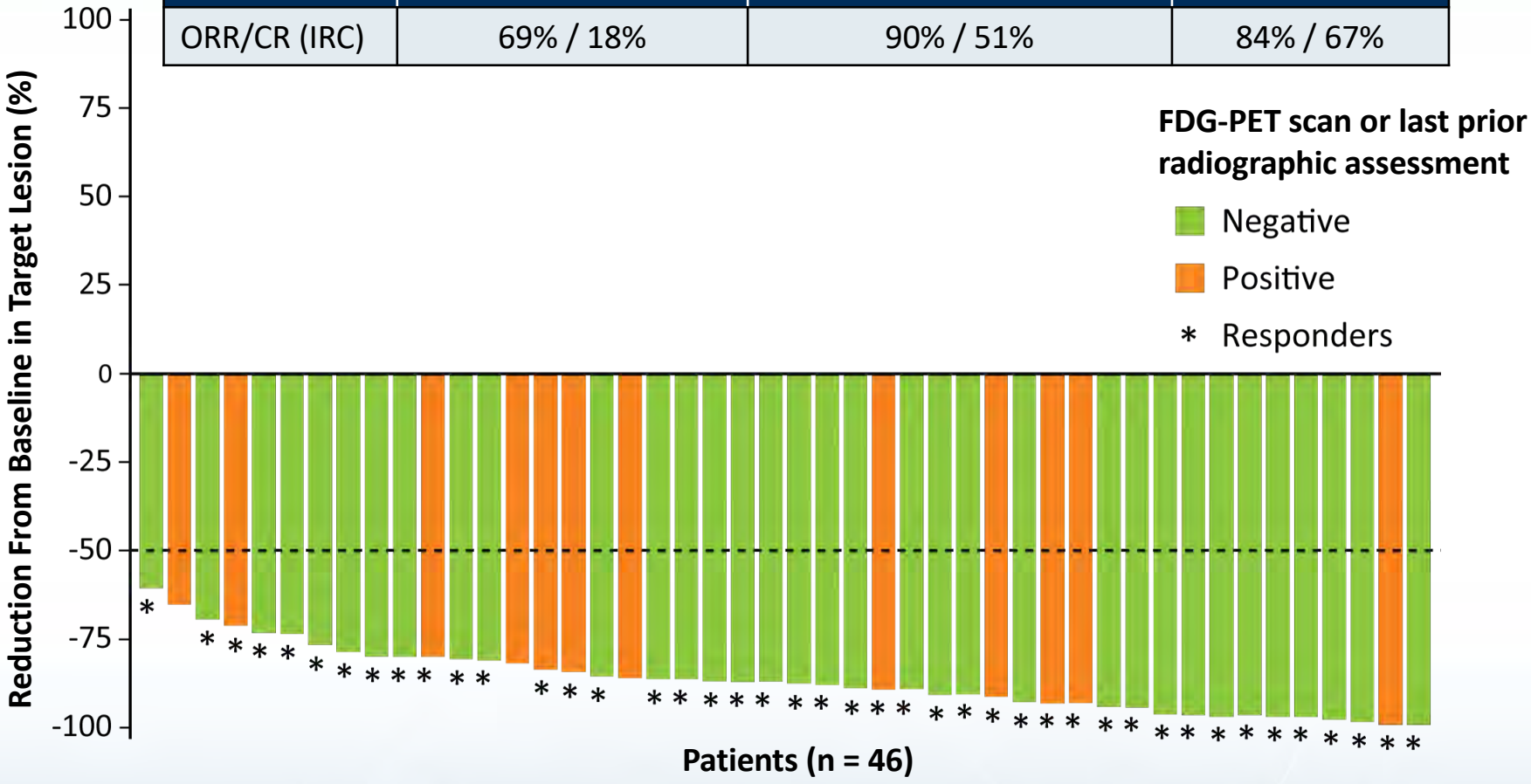
CheckMate 205 Phase II Study Schema



Clinicaltrials.gov. Accessed Sept 20, 2019 (NCT02181738).
Younes A et al. *Lancet Oncol* 2016;17:1283-94.
Ramchandren R et al. *J Clin Oncol* 2019;37(23):1997-2007.

CheckMate 205 (Cohort D): Nivolumab for Newly Diagnosed Advanced-Stage Classic HL

	End of monotherapy	After 2 combination cycles	End of therapy
ORR/CR (IRC)	69% / 18%	90% / 51%	84% / 67%



Ramchandren R et al. *J Clin Oncol* 2019;37(23):1997-2007.

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CheckMate 205: Select Safety Outcomes with Nivolumab → Nivolumab/AVD

Treatment-related AE	N = 51	
	Any grade	Grade 3-4
Total pts with TRAE	**49 (96%)**	**30 (59%)**
Neutropenia	28 (55%)	25 (49%)
Febrile neutropenia	5 (10%)	5 (10%)
ALT increase	4 (8%)	2 (4%)
Peripheral neuropathy	4 (8%)	0 (0%)
Nonendocrine IMAEs		
Rash	3 (6%)	0 (0%)
Endocrine IMAEs		
Hypothyroidism/thyroiditis	9 (18%)	0 (0%)
Hyperthyroidism	4 (8%)	0 (0%)

31% (n = 16) of patients experienced infusion-related reaction, all Grade 1-2
IMAEs = immune-mediated AEs

Ramchandren R et al. *J Clin Oncol* 2019;37(23):1997-2007.

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