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EXPERTS KNOWLEDGE SHARE

SELECTING THE APPROPRIATE TREATMENT FOR INDOLENT NHL: THE NOW AND THE NEXT

Prof. Alexey Danilov, MD, PhD
Assoc. Prof. Stefan K. Barta, MD, MRCP
Dr. Jessica Okosun, MD, PhD

Monday May 3rd, 2021

EXPERTS KNOWLEDGE SHARE

THE OBJECTIVE OF THIS MEETING IS TO DISCUSS SELECTING THE APPROPRIATE TREATMENT FOR INDOLENT NHL: THE NOW AND THE NEXT

A CHANCE TO **HEAR THE VIEWS OF EXPERTS** AND ALLOW THEM TO ANSWER THE QUESTIONS THAT ARE IMPORTANT TO YOU

YOUR OPPORTUNITY TO **DISCUSS AND SHARE LEARNINGS**

REVIEW AND DISCUSS **PATIENT CASE STUDIES** USING THE QUESTIONS THAT YOU HAVE SENT IN ADVANCE OF THIS EVENT

EXPERTS KNOWLEDGE SHARE EDUCATIONAL OBJECTIVES

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YOU WILL LEARN MORE ABOUT AND DISCUSS:

The current and future treatment landscape in indolent non-Hodgkin lymphoma (NHL)

Considerations regarding treatment selection for patients with indolent NHL

- Including the future use of targeted therapies, chimeric antigen receptor (CAR)-T cell therapy and bispecifics

INTRODUCING THE SCIENTIFIC COMMITTEE

Prof. Alexey Danilov, MD, PhD

City of Hope National Medical Centre, Duarte, CA, USA

Assoc. Prof. Stefan K. Barta, MD, MRCP

University of Pennsylvania, Philadelphia, PA, USA

Dr. Jessica Okosun, MD, PhD

Barts Cancer Institute and St Bartholomew's Hospital, London, UK

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EXPERTS KNOWLEDGE SHARE AGENDA

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SELECTING THE APPROPRIATE TREATMENT FOR INDOLENT NHL: THE NOW AND THE NEXT

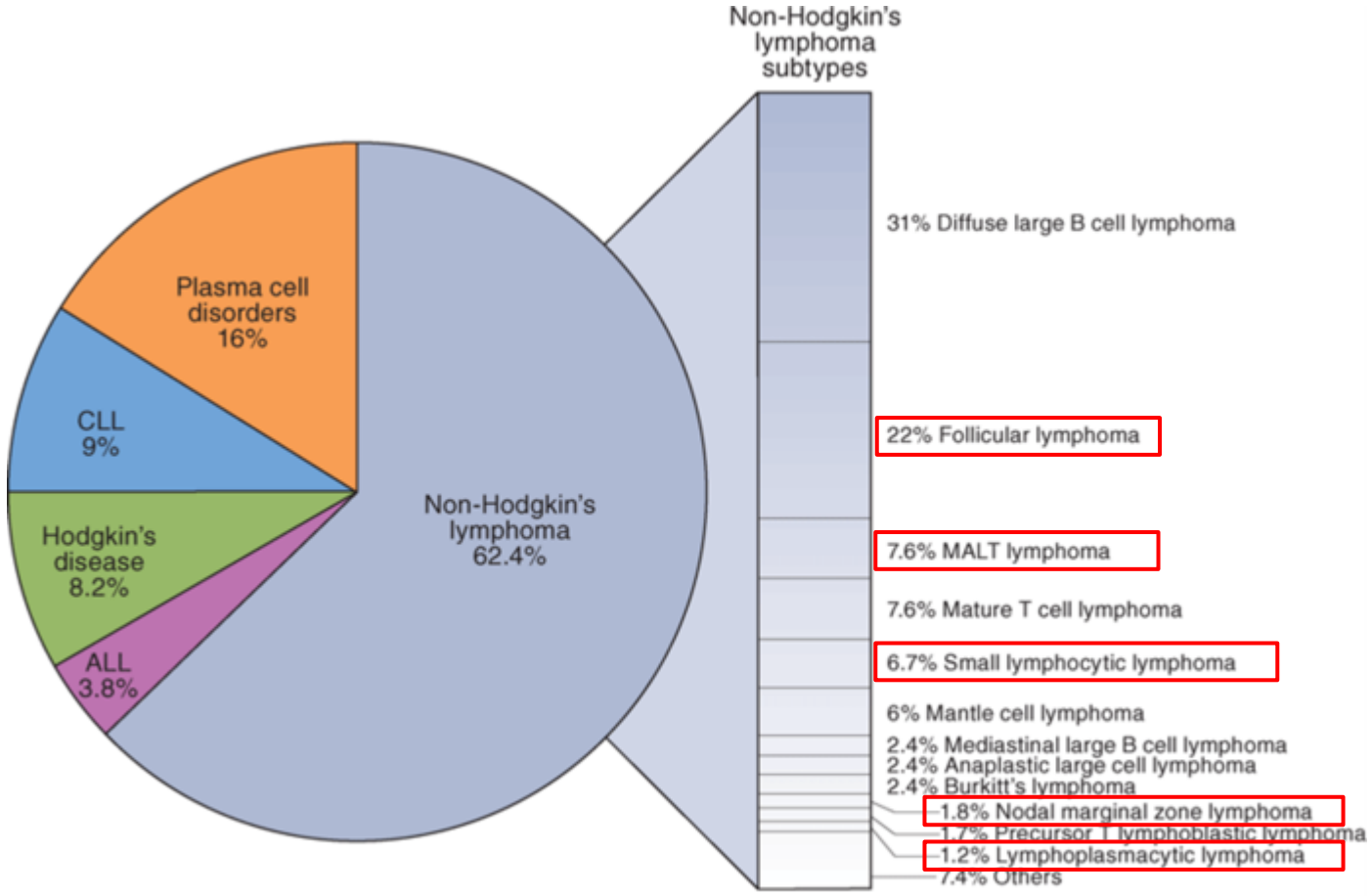
Time	Topic	Facilitator
5 minutes	Welcome and introductions	COR2ED
5 minutes	Overview and scene setting	Alexey Danilov
15 minutes	**First-line treatment** selection for indolent NHL	Stefan Barta
15 minutes	Treatment selection for **relapsed/refractory indolent NHL**	Jessica Okosun
5 minutes	Lead-in to breakout sessions	COR2ED
25 minutes	Three breakout groups Groups discussing questions and case studies and sharing experience	All (moderated by Faculty)
15 minutes	The **future treatment landscape** in indolent NHL	Alexey Danilov
5 minutes	Closing remarks	COR2ED

FIRST-LINE TREATMENT SELECTION FOR INDOLENT NHL

Stefan K. Barta, MD, MS, MRCP (UK)

Associate Professor of Medicine
University of Pennsylvania, Philadelphia, PA, USA

INDOLENT B-CELL LYMPHOMAS – OVERVIEW



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

- Indolent lymphomas are generally considered **incurable, but treatable** lymphomas, with survival usually measured in the current era in "decades"
- **Most common indolent B-cell lymphomas** are follicular lymphoma (**FL**) >> marginal zone lymphoma (**MZL**) (MALT [mucosa-associated lymphoid tissue], nodal, splenic) > small lymphocytic lymphoma (**SLL**)> lymphoplasmacytic lymphoma (**LPL**)
- Median age of diagnosis 65, but can occur at much younger ages
- Risk of **transformation** to an aggressive B-cell malignancy varies by histology (FL [2-3%/year] > SLL > MZL)

ALL, acute lymphocytic leukaemia.

Teras LR, et al. CA Cancer J Clin. 2016;66:443-59; Smith A, et al. Br J Cancer. 2015;112:1575-84

INITIAL ASSESSMENT

- Treatment depends largely on stage, disease “bulk”, and symptoms, therefore **adequate staging is paramount**
  - Staging with positron emission tomography/computed tomography (PET/CT) or computed tomography of chest, abdomen, pelvis (CT CAP) +/- neck
  - Bone marrow biopsy in certain circumstances

- **Prognostic tools** take into account mainly clinical factors, such as age, stage, lactate dehydrogenase (LDH), number of involved sites, bone marrow involvement +/- molecular information and response to initial therapy:
  - Follicular Lymphoma International Prognostic Index (FLIPI); FLIPI2; PRIMA-PI; M7-FLIPI[1-4]
  - MALT Lymphoma prognosis index (MALT-IPI)[5]
  - CLL-IPI[6]
  - Positive PET after induction chemoimmunotherapy (CIT)[7]
  - Early relapse after completion of initial CIT[8]

CLL, chronic lymphocytic leukaemia; IPI, International Prognostic Index; MALT, mucosa-associated lymphoid tissue

1. Solal-Celigny P, et al. Blood. 2004;104:1258-65; 2. Federico M, et al. J Clin Oncol. 2009;27:4555-62; 3. Bachy E, et al. Blood. 2018;132:49-58; 4. Huet S, et al. Lancet Oncol. 2018;19:549-61; 5. Thieblemont C, et al. Blood. 2017;130:1409-17; 6. International CLL-IPI working group. Lancet Oncol. 2016;17:779-90; 7. Trotman J. Lancet Oncol. 2018; 19: 1530-42; 8. Casulo C, et al. J Clin Oncol. 2015;33:2516-22; 9. Launonen A, et al. Blood. 2017;130 (suppl 1):1490

FOCUS ON FL AND NODAL MZL – WHEN TO TREAT?

Early stage:

- Select patients may be treated with local therapy with “curative intent”

Advanced disease:

- ***Candidates for “watchful waiting”***
  - Asymptomatic; low bulk, slowly progressive disease; no impending organ compromise
- ***Indicators to initiate treatment***
- ***Groupe d'Etude des Lymphomes Folliculaires*** **(GELF) criteria:**
  - Tumour size: any site >7 cm or ≥3 sites >3 cm
  - B symptoms
  - Spleen: below umbilical line
  - Compressive symptoms
  - Pleural or peritoneal effusion
- Other criteria:
  - Cytopenias
  - Impairment of major organ function
  - Marked blood lymphocytosis
  - Steady or rapid progression

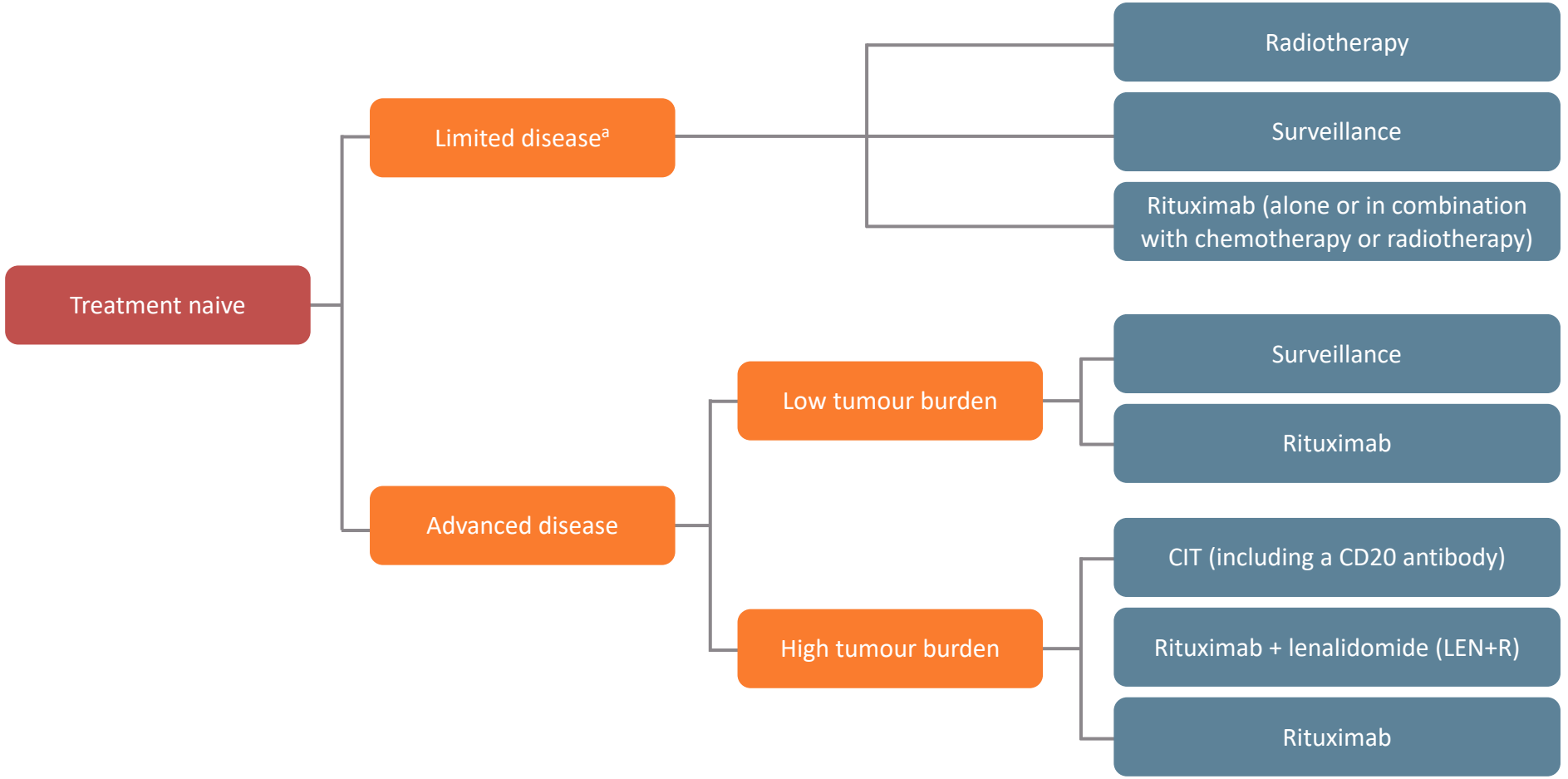
Watch and wait:

- No overall survival (OS) benefit of initiation of CIT at diagnosis over delayed initiation has been shown
- Assumes that delay in exposure to therapy and its attendant side-effects results in an improved quality of life (QoL)
- Average time from diagnosis to treatment: 30 months
- At 10 years, ca. 20% still do not require therapy

CIT, chemoimmunotherapy; FL, follicular lymphoma, MZL, marginal zone lymphoma

Press OW, Palanca-Wessels MC. J Clin Oncol. 2013;31:1496-8; NCCN Guidelines V3.2021; Brice P, et al. J Clin Oncol. 1997;15:1110-7; Portlock CS, Rosenberg SA. Ann Intern Med. 1979;90:10-3; Horning SJ, Rosenberg SA. N Engl J Med. 1984;311:1471-5; Ardeshna KM, et al. Lancet. 2003;362:516-22

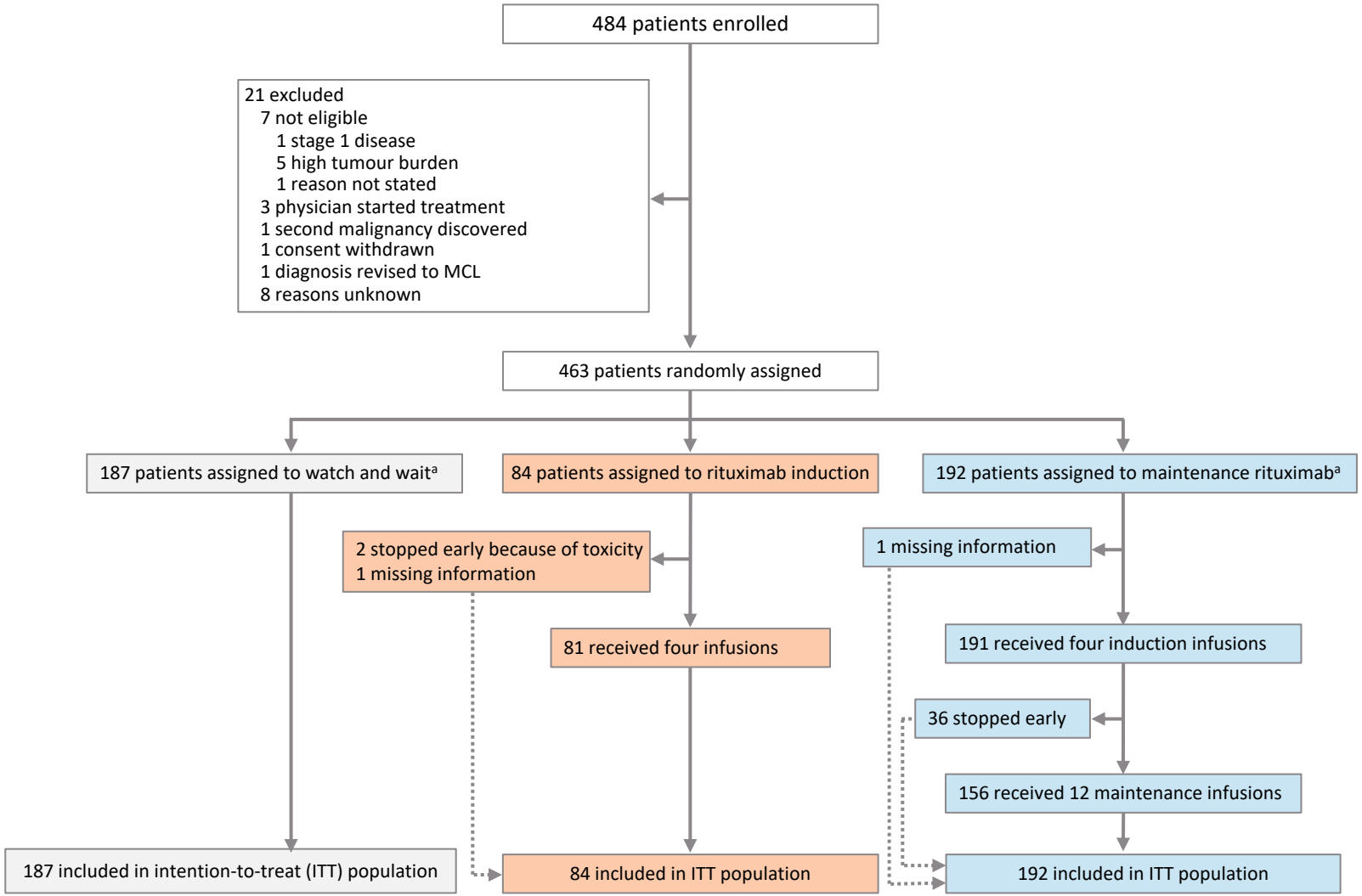
PROPOSED TREATMENT ALGORITHM FOR NEWLY DIAGNOSED FOLLICULAR OR NODAL MZL REQUIRING TREATMENT



[a] Patients with limited disease but high tumour burden should be treated as per patients with advanced disease and high tumour burden
CD20, cluster of differentiation 20; CIT, chemoimmunotherapy; MZL, marginal one lymphoma
Modified from Matasar MJ, et al. Oncologist. 2019;24:e1236-50

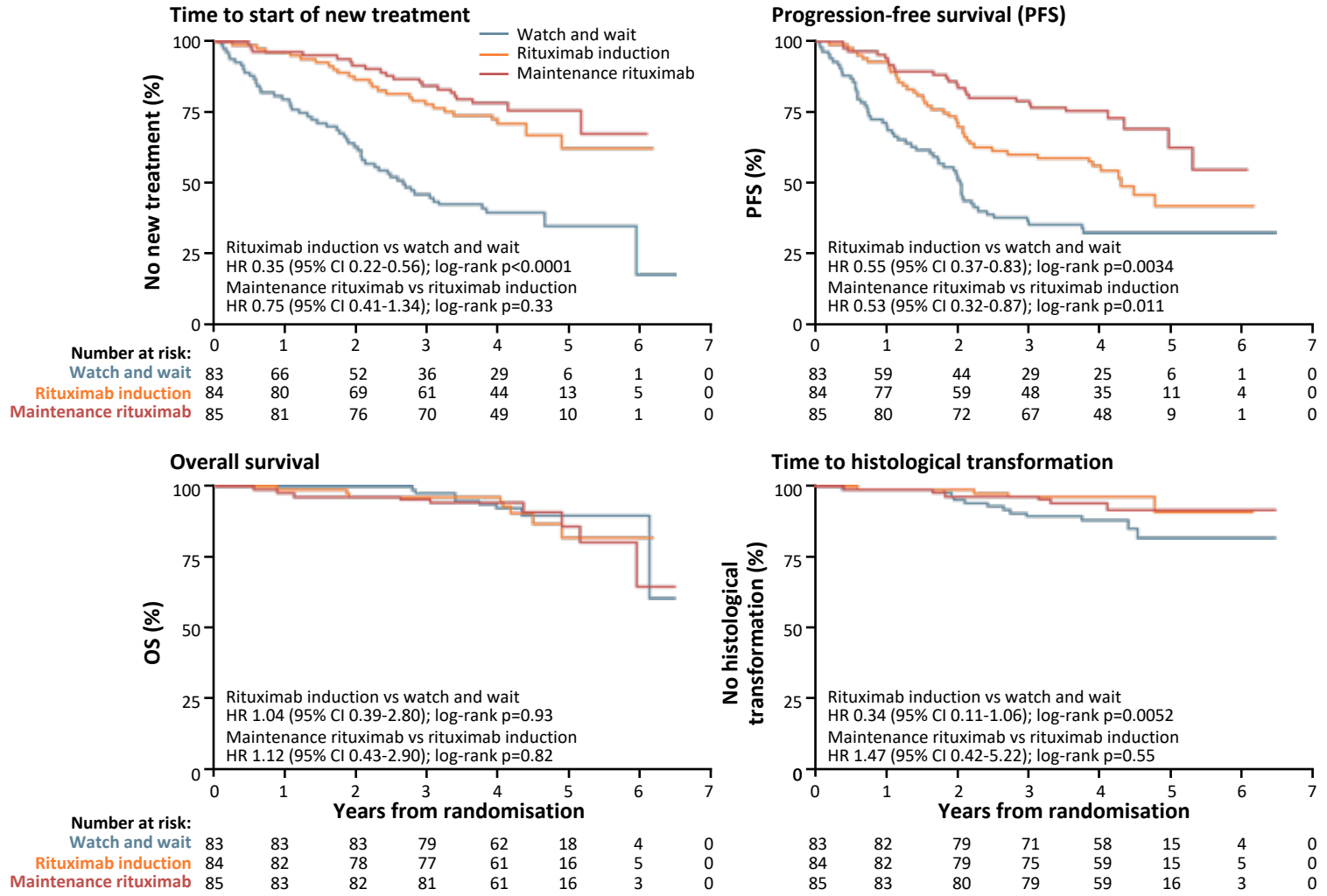
“WATCH AND WAIT” VS RITUXIMAB IN LOW TUMOUR BURDEN FL

RITUXIMAB FOR LOW TUMOUR BURDEN FL



[a] Inclusive of the patients enrolled in the three-arm study (83 in the watch and wait group and 85 in the maintenance rituximab group)
FL, follicular lymphoma; MCL, mantle-cell lymphoma
Ardeshna KM, et al. Lancet Oncol. 2014;15:424-35

RITUXIMAB FOR LOW TUMOUR BURDEN FL



- **Overall response rate (ORR) improved** for rituximab maintenance vs rituximab induction:
  - 6 months 91% vs 77% (p=0.043)
  - 2 years 84% vs 57% (p=0.001)

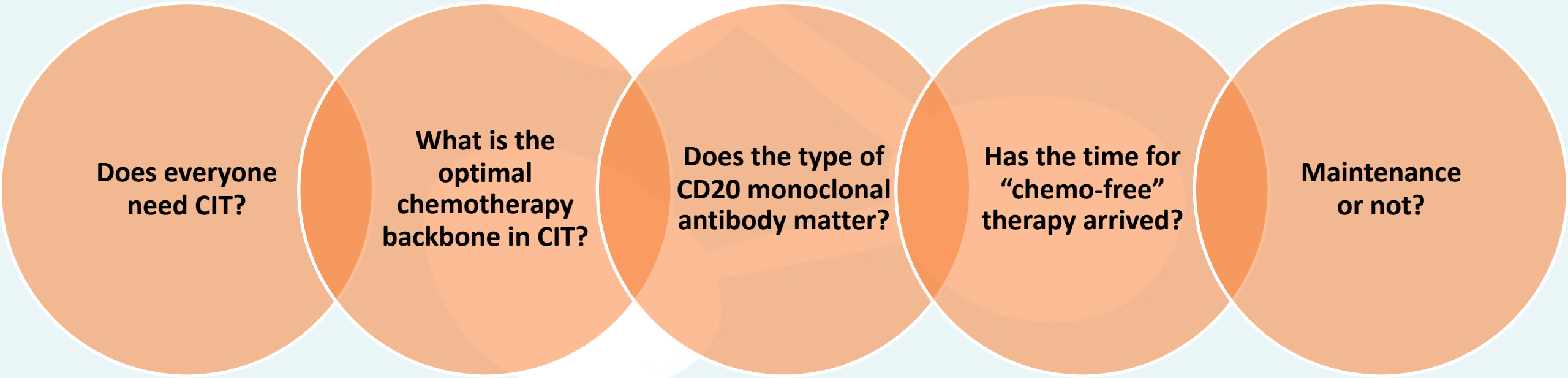
- **QoL showed significant improvement** in the Mental Adjustment to Cancer scale & Illness Coping Style scores for rituximab maintenance over "watch and wait"
  - Only Mental Adjustment to Cancer scores better in rituximab maintenance vs rituximab induction

CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; OS, overall survival; QoL, quality of life

Ardeshna KM, et al. Lancet Oncol. 2014;15:424-35

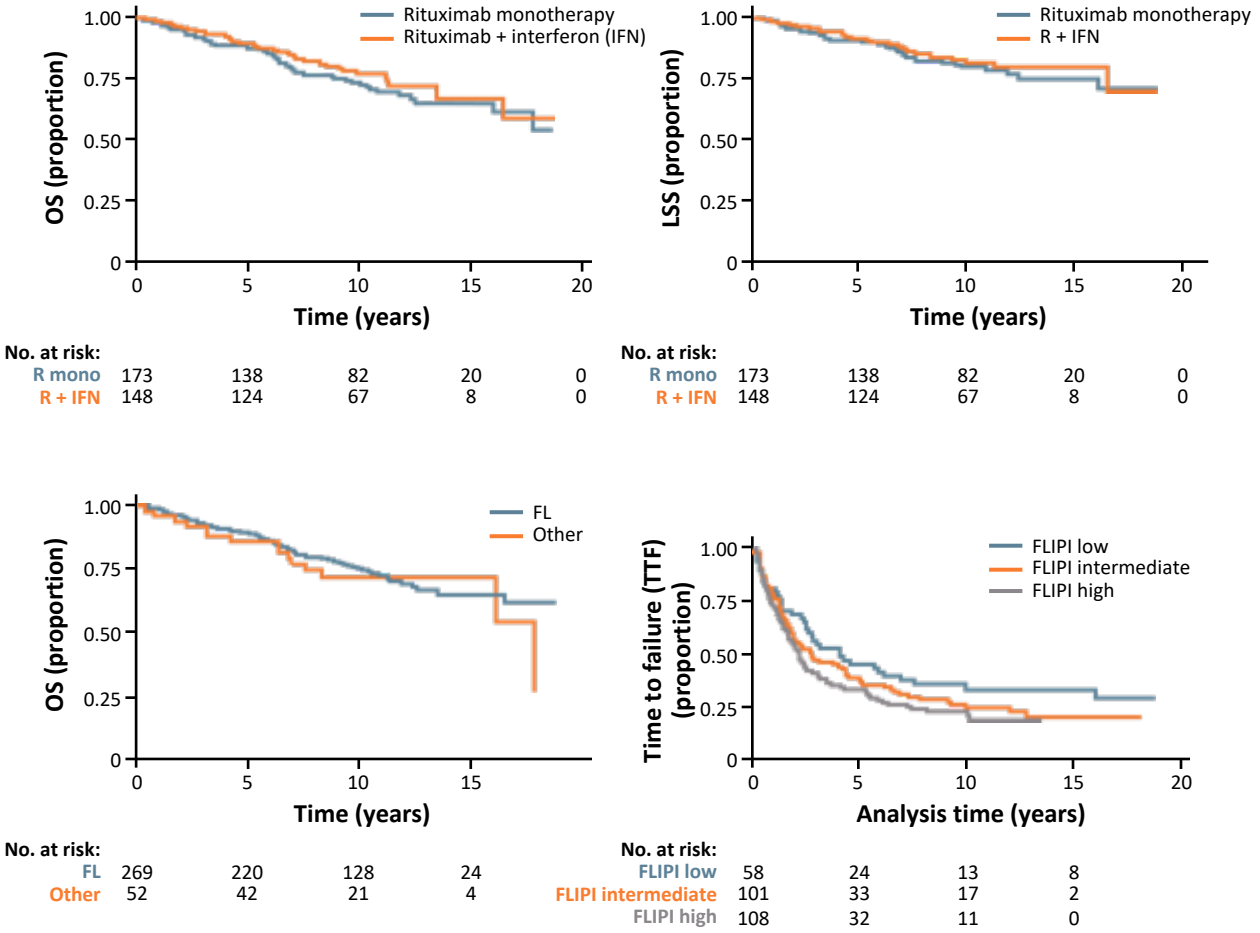
TREATMENT OPTIONS FOR ADVANCED INDOLENT B-CELL LYMPHOMAS

FOCUS ON FL AND NODAL MZL



CD20, cluster of differentiation 20; CIT, chemoimmunotherapy; FL, follicular lymphoma; MZL, marginal zone lymphoma

RITUXIMAB ALONE FOR ADVANCED INDOLENT B-CELL NHL



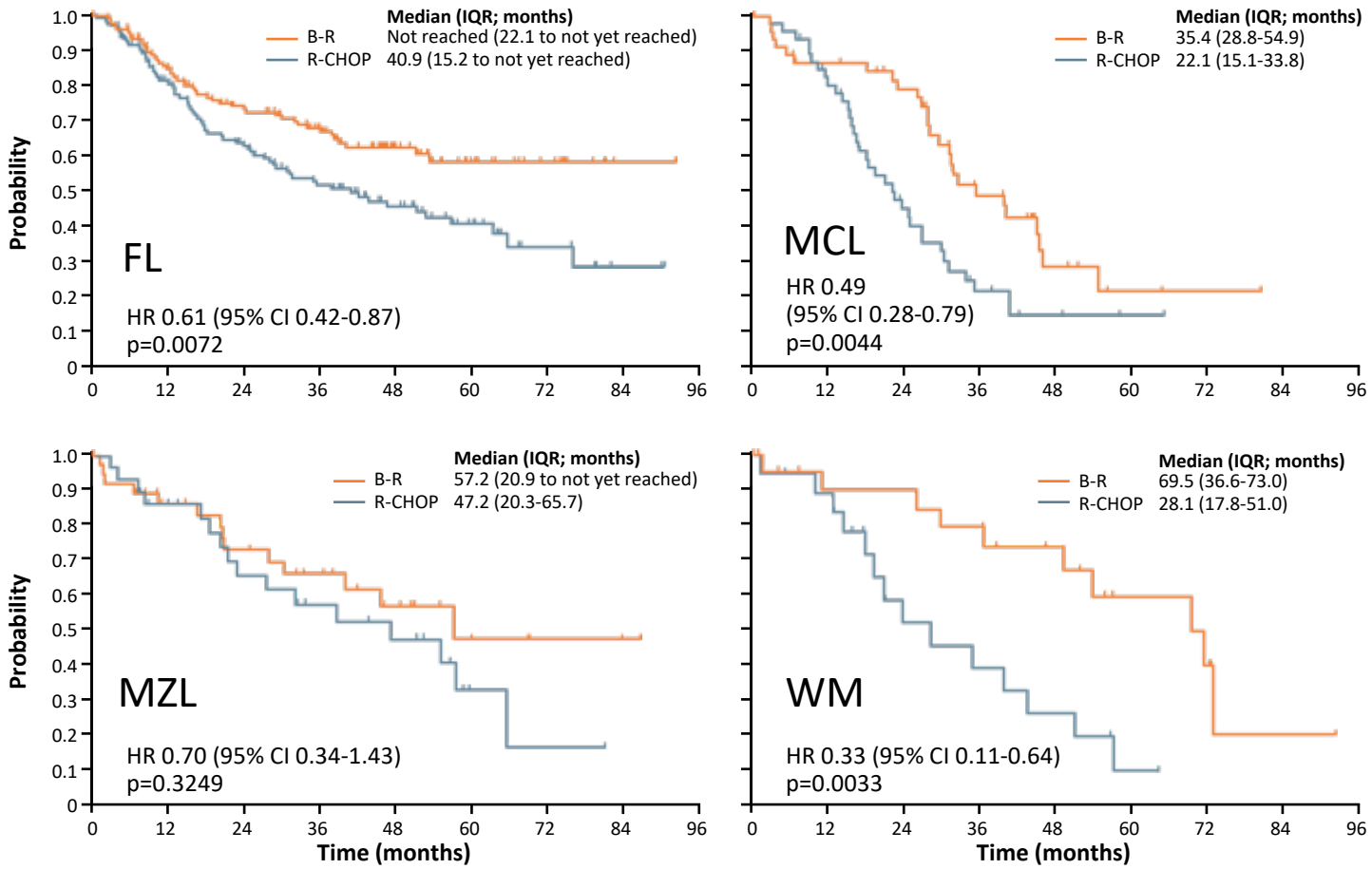
- **Retrospective analysis** of 439 patients treated on two prospective Nordic Lymphoma Group (NLG) trials with rituximab monotherapy or rituximab + IFNα-2a
  - FL (Grade 1-3a): 84%; MZL 8%
  - Median follow-up: 10.6 years (range 0.1-18.8)
- **OS rate since randomisation**
  - 10-year OS rate 75% (LSS: 82%)
  - 15-year OS rate 65% (LSS: 77%)
- 36% never required chemotherapy during follow-up
- **Early progression of disease (POD)** (≤2 years) associated with worse OS:
  - 10-year OS rates 62% vs 89%
  - 15-year OS rates 53% vs 78%
- At 10 and 15 years after random assignment, the cumulative **risk of transformation** was 20% and 24% (slightly higher in non-FL group)

FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; LSS, lymphoma-specific survival; NHL, non-Hodgkin's lymphoma; OS, overall survival

Lockmer S, et al. J Clin Oncol. 2018;36:3315-23

STiL STUDY: B-R VS R-CHOP AS FIRST-LINE TREATMENT IN INDOLENT AND MANTLE-CELL LYMPHOMAS

PFS by subtype



	B-R (N=261)	R-CHOP (N=253)
Age (years)	64 (34-83)	63 (31-82)
<60	94 (36%)	90 (36%)
61-70	107 (41%)	105 (42%)
>70	60 (23%)	58 (23%)
Stage		
II	9 (3%)	9 (4%)
III	50 (19%)	47 (19%)
IV	202 (77%)	197 (78%)
Histology		
Follicular	139 (53%)	140 (55%)
Mantle cell	46 (18%)	48 (19%)
Marginal zone	37 (14%)	30 (12%)
Lymphoplasmacytic[a]	22 (8%)	19 (8%)
Small lymphocytic	10 (4%)	11 (4%)
Low grade, unclassifiable	7 (3%)	5 (2%)

[a] WM

Responses B-R vs R-CHOP:

ORR 93% vs 91% (not significant)

Complete response (CR) rate 76% vs 40% (p=0.02)

B-R, bendamustine plus rituximab; CI, confidence interval; FL, follicular lymphoma; IQR, interquartile range; HR, hazard ratio; MCL, mantle-cell lymphoma; MZL, marginal zone lymphoma; PFS, progression-free survival; R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab; WM, Waldenstrom's macroglobulinaemia

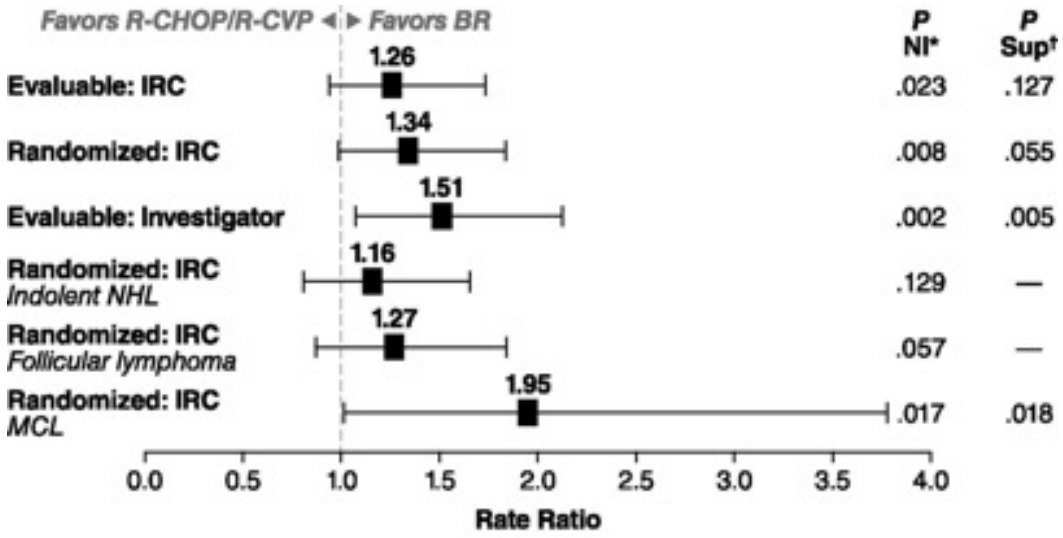
Rummel MJ, et al. Lancet. 2013;381:1203-10

BRIGHT STUDY: B-R OR R-CHOP/R-CVP IN FIRST-LINE TREATMENT OF INDOLENT NHL OR MCL

Patient characteristics at baseline

Characteristic	BR (N=224)	R-CHOP/R-CVP (N=223)
Age, median, years (range)	60 (28-84)	58 (25-86)
Sex (male/female, %)	61/39	59/41
Baseline ECOG PS, n (%)		
0	144 (64)	143 (64)
1	70 (31)	69 (31)
≥2	10 (4)	10 (4)
Histologic classification		
Lymphoplasmacytic	5 (2)	6 (3)
Marginal zone	28 (12)	18 (8)
Mantle cell	36 (16)	38 (17)
Follicular, Grade 1	84 (38)	70 (31)
Follicular, Grade 2	70 (31)	90 (40)
Missing	1 (<1)	1 (<1)

Complete response rate (IRC) ratios as per treatment arm



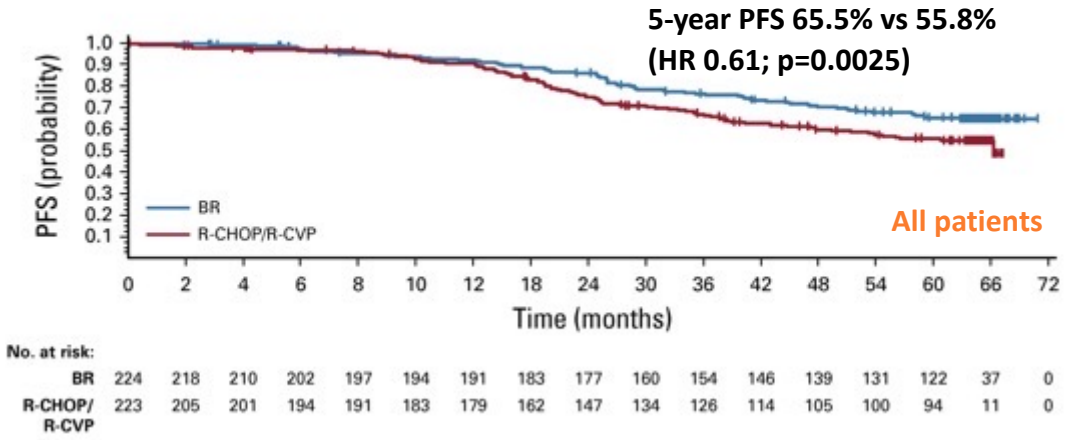
Independent review committee (IRC) assessment or response

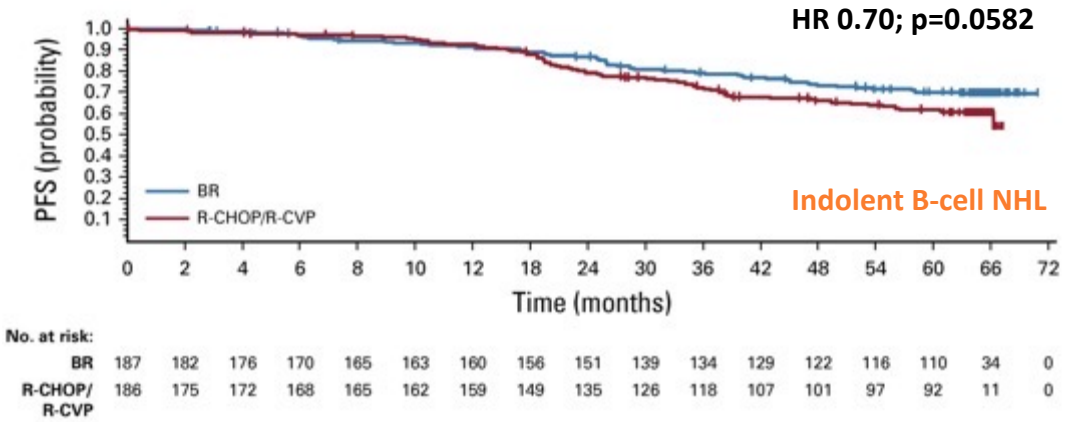
Response category, n (%)	B-R (N=213)	R-CHOP/R-CVP (N=206)	CR-rate ratio	p (NI)	p (Sup)
CR	67 (31)	52 (25)	1.26	0.0225	0.1269
95% CI	(25.3-38.2)	(19-31.7)	(0.93-1.73)		
Partial response (PR)	139 (65)	135 (66)	NA	NA	NA
Stable disease (SD)	6 (3)	18 (9)	NA	NA	NA
Progressive disease (PD)	1 (<1)	0	NA	NA	NA
Unknown	0	1 (<1)	NA	NA	NA
Overall response (CR + PR)	206 (97)	187 (91)	NA	NA	NA
95% CI	(93.3-98.7)	(86.0-94.4)	NA	NA	NA

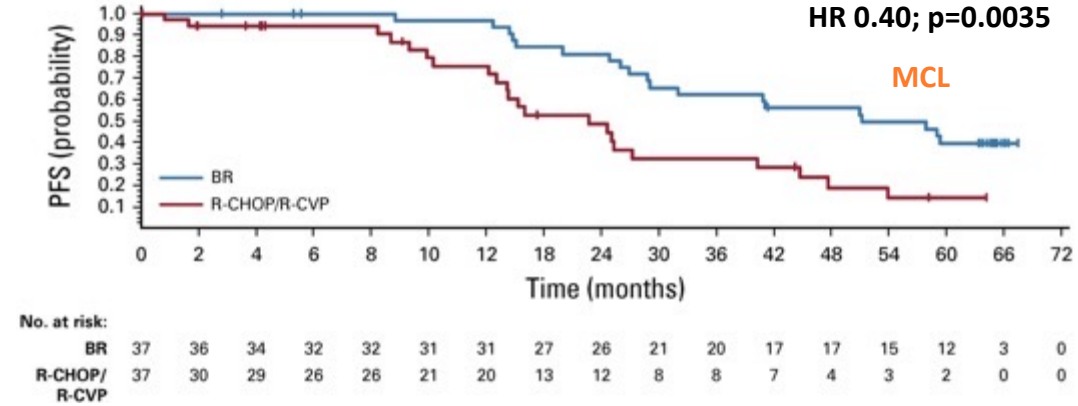
B-R, bendamustine plus rituximab; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MCL, mantle-cell lymphoma; NA, not applicable; NHL, non-Hodgkin's lymphoma; NI, noninferiority; Sup, superiority; R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab; R-CVP, rituximab plus cyclophosphamide, vincristine, prednisone

Flinn IW, et al. Blood. 2014;123:2944-52; Flinn IW, et al. J Clin Oncol. 2019;37:984-91

BRIGHT STUDY: B-R OR R-CHOP/R-CVP IN FIRST-LINE TREATMENT OF INDOLENT NHL OR MCL







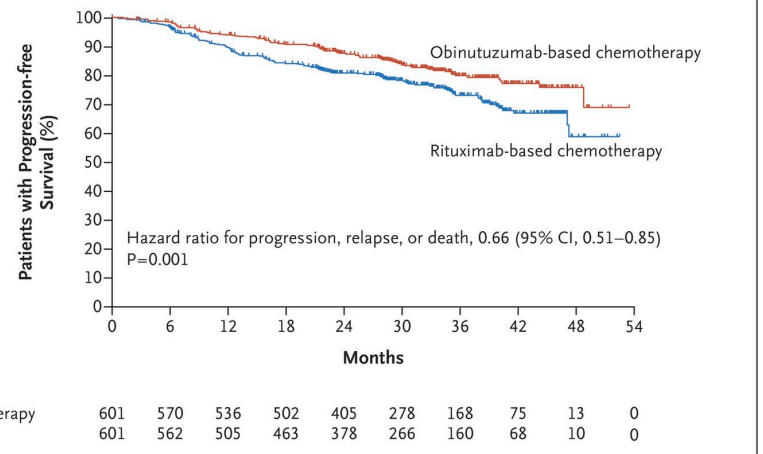
B-R vs R-CHOP: HR 0.65 (95% CI 0.4-1.06)
B-R vs R-CVP: HR 0.59 (95% CI 0.38-0.90)

B-R, bendamustine plus rituximab; HR, hazard ratio; MCL, mantle-cell lymphoma; NHL, non-Hodgkin's lymphoma; PFS, progression-free survival; R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab; R-CVP, rituximab plus cyclophosphamide, vincristine, prednisone

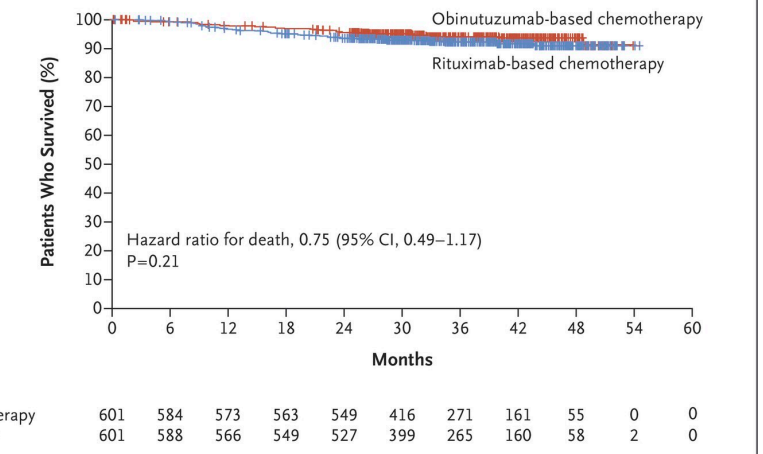
Flinn IW, et al. Blood. 2014;123:2944-52; Flinn IW, et al. J Clin Oncol. 2019;37:984-91

GALLIUM: OBINUTUZUMAB- VS RITUXIMAB-BASED CIT IN FL

PFS



OS



	Obinutuzumab group	Rituximab group
IRC-assessed PFS		
Patients with progression, relapse, or death, n (%)	93 (15.5)	125 (20.8)
Rate of estimated 3-year PFS (95% CI), %	81 (77.9-85.2)	77.9 (73.8-81.4)
HR for progression, relapse, or death (95% CI)	0.71 (0.54-0.93)	
p value by log-rank test	0.01	
Treatment response at end of induction phase		
CR or PR	532 (88.5)	522 (86.9)
Difference (95% CI) – percentage points	1.6 (−2.1 -5.5)	
p value by Cochran–Mantel–Haenszel test	0.33	
CR	117 (19.5)	143 (23.8)
Difference (95% CI) – percentage points	−4.3 (−9.1 to 0.4)	
p value by Cochran–Mantel–Haenszel test	0.07	

CI, confidence interval; CIT, chemoimmunotherapy; CR, complete response; FL, follicular lymphoma; IRC, independent review committee; OS, overall survival; PFS, progression-free survival; PR, partial response

Marcus R, et al. N Engl Med. 2017;377:1331-44

GALLIUM: OBINUTUZUMAB- VS RITUXIMAB-BASED CIT IN FL

Event	Induction phase		Maintenance and observation phases		Follow-up	
	Obinutuzumab	Rituximab	Obinutuzumab	Rituximab	Obinutuzumab	Rituximab
Infection						
Bendamustine	27/338 (8.0)	26/338 (7.7)	52/312 (16.7)	39/305 (12.8)	25/270 (9.3)	6/263 (2.3)
CHOP	14/193 (7.3)	13/203 (6.4)	7/179 (3.9)	11/187 (5.9)	2/128 (1.6)	2/143 (1.4)
CVP	3/61 (4.9)	4/56 (7.1)	5/57 (8.8)	1/43 (2.3)	1/44 (2.3)	2/45 (4.4)
Second neoplasm						
Bendamustine	0	0	21/312 (6.7)	18/305 (5.9)	14/270 (5.2)	2/263 (0.8)
CHOP	0	0	8/179 (4.5)	8/187 (4.3)	1/128 (0.8)	1/143 (0.7)
CVP	0	0	0	1/43 (2.3)	0	0

CIT, chemoimmunotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; FL, follicular lymphoma

Marcus R, et al. N Engl Med. 2017;377:1331-44

RELEVANCE TRIAL: RITUXIMAB + LENALIDOMIDE (LEN+R) VS R-CHEMO

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Baseline demographic and disease characteristics (ITT population)

Characteristic	LEN+R group (N=513)	R-chemo group (N=517)	Total (N=1,030)
Median age (range), years	59 (30-89)	59 (23-83)	59 (23-89)
Age >70 years, n (%)	80 (16)	78 (15)	158 (15)
Male sex, n (%)	251 (49)	251 (49)	502 (49)
Ann Arbor stage, n (%)			
I or II	30 (6)	40 (8)	70 (7)
III or IV	483 (94)	477 (92)	960 (93)
Bulky disease, n (%)	218 (42)	199 (38)	417 (40)
FL, Grade, n (%)			
1 or 2	437 (85)	443 (86)	880 (85)
3a	65 (13)	63 (12)	128 (12)
Unspecified or grade other than 1, 2 or 3a	11 (2)	11 (2)	22 (2)
LDH >ULN, n (%)	156 (30)	137 (26)	293 (28)
B symptoms, n (%)	141 (27)	134 (26)	275 (27)
FLIPI score, n (%)			
0 or 1	77 (15)	76 (15)	153 (15)
2	183 (36)	191 (37)	374 (36)
3 to 5	253 (49)	250 (48)	503 (49)

Efficacy (ITT population)

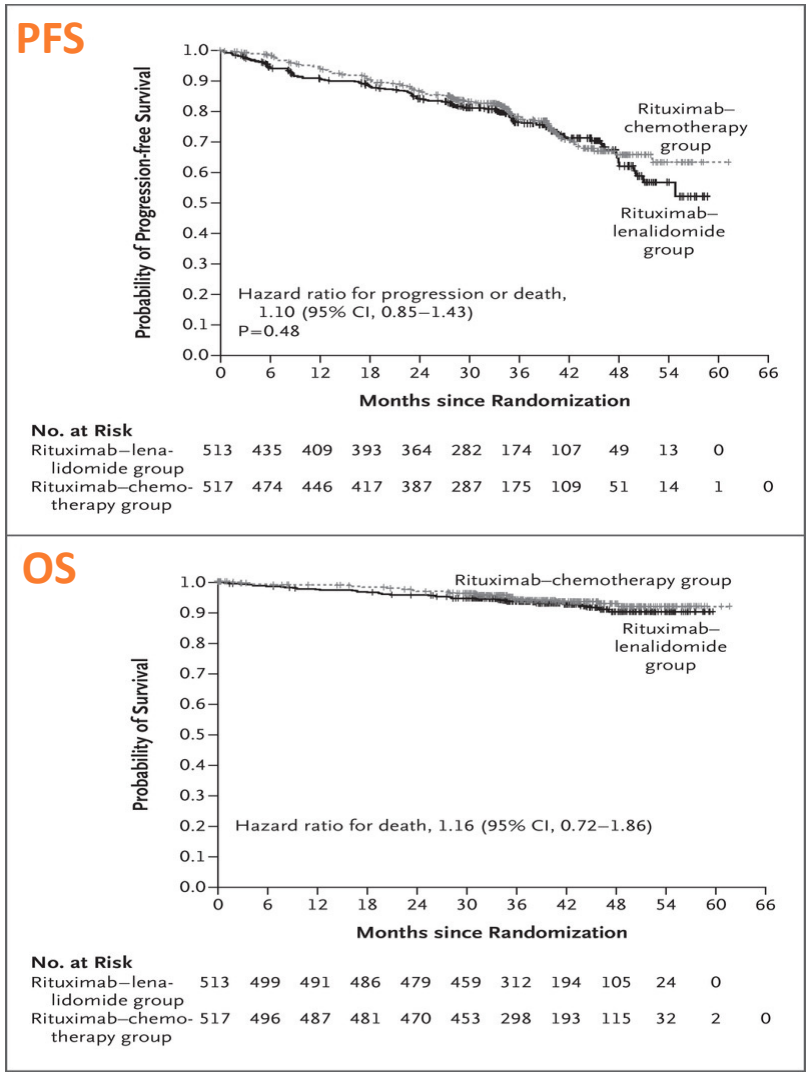
Variable	LEN+R group (N=513)	R-chemo group (N=517)	HR (95% CI)	p value
Response status at 120 weeks, as assessed by IRC				
Overall response, n (% [95% CI])	312 (61 [56-65])	336 (65 [61-69])		
Confirmed or unconfirmed CR, n (% [95% CI])	247 (48 [44-53])	274 (53 [49-57])		0.13
PR, n (%)	65 (13)	62 (12)		
SD, n (%)	2 (<1)	0		
PD or death, n (%)	87 (17)	79 (15)		
Not evaluated or data missing, n (%)	112 (22)	102 (20)		
PFS at 3 years				
Rate, per IRC, % (95% CI)	77 (72-80)	78 (74-82)	1.0 (0.85-1.43)	0.48
Rate, per investigator, % (95% CI)	77 (72-80)	78 (74-81)	0.94 (0.73-1.22)	0.63
OS rate at 3 years, % (95% CI)	94 (91-96)	94 (91-96)	1.16 (0.72-1.86)	

R-chemo: 372 (72%) R-CHOP; 117 (23%) B-R; 28 (5%) R-CVP

B-R, bendamustine plus rituximab; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; LEN+R, rituximab plus lenalidomide; R-chemo, rituximab plus chemotherapy; R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab; R-CVP, rituximab plus cyclophosphamide, vincristine, prednisone; SD, stable disease; ULN, upper limit of normal

Morschhauser F, et al. N Engl J Med. 2018;379:934-47

RELEVANCE: PFS AND OS SIMILAR, BUT DIFFERENT TOXICITY PROFILE



Adverse events (AEs) during the treatment period in the safety population

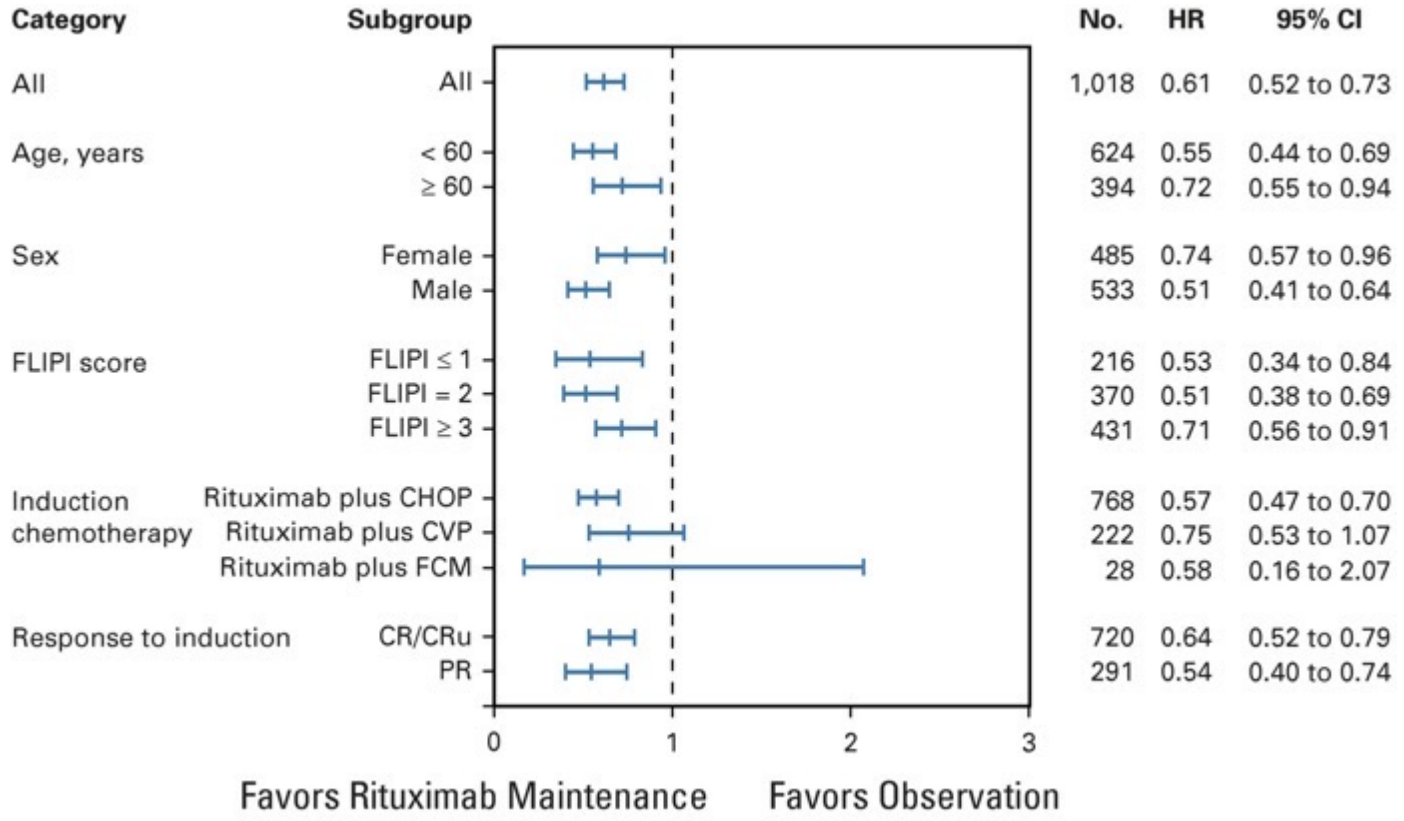
AE, n (%)	LEN+R group (N=507)		R-chemo group (N=503)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Neutropenia	381 (75)	160 (32)	386 (77)	252 (50)
Anaemia	333 (66)	0	446 (89)	0
Thrombocytopenia	268 (53)	11 (2)	266 (53)	8 (2)
Cutaneous reactions	220 (43)	36 (7)	120 (24)	5 (1)
Diarrhoea	187 (37)	10 (2)	95 (19)	6 (1)
Constipation	178 (35)	1 (<1)	167 (33)	5 (1)
Rash	146 (29)	20 (4)	39 (8)	1 (<1)
Fatigue	115 (23)	1 (<1)	147 (29)	4 (<1)
Nausea	100 (20)	0	209 (42)	8 (2)
Abdominal pain	78 (15)	4 (<1)	46 (9)	4 (<1)
Myalgia	73 (14)	0	29 (6)	1 (<1)
Arthralgia	71 (14)	3 (<1)	70 (14)	1 (<1)
Peripheral oedema	69 (14)	0	47 (9)	1 (<1)
Muscle spasms	68 (13)	0	21 (4)	0
Infusion-related reaction	66 (13)	7 (1)	56 (11)	1 (<1)
Upper respiratory tract infection	47 (9)	0	55 (11)	0
Vomiting	34 (7)	2 (<1)	94 (19)	7 (1)
Peripheral neuropathy	35 (7)	1 (<1)	79 (16)	3 (<1)
Tumour flare reaction	30 (6)	7 (1)	1 (<1)	0
Leucopenia	21 (4)	8 (2)	48 (10)	30 (6)
Febrile neutropenia	11 (2)	11 (2)	34 (7)	33 (7)
Tumour lysis syndrome	7 (1)	6 (1)	5 (1)	3 (<1)
Alopecia	5 (1)	0	45 (9)	3 (<1)

OS, overall survival; PFS, progression-free survival; LEN+R, rituximab plus lenalidomide; R-chemo, rituximab plus chemotherapy

Morschhauser F, et al. N Engl J Med. 2018;379:934-47

PRIMA STUDY – 10 YEAR FOLLOW UP
N=1,018

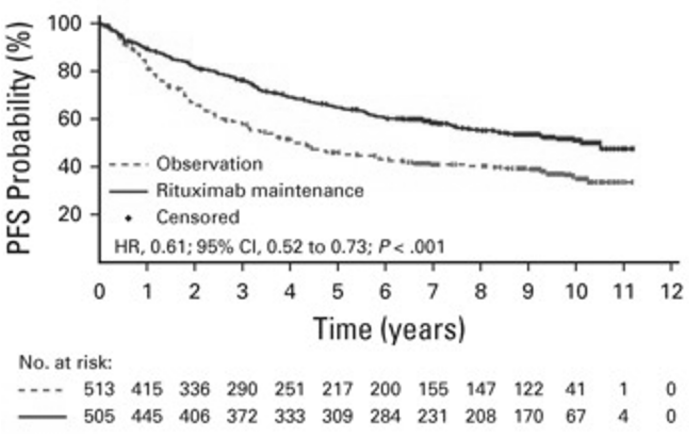
- **Observation vs rituximab maintenance**
  (every 8 weeks × 12)
- **Median duration of follow-up:**
  9.0 years (range 0.0-11.5)
- **Median PFS:**
  - Observation: 4.1 years
  - Rituximab maintenance 10.5 years
  - HR 0.61; 95% CI, 0.52-0.73; p<0.001
- **10-year OS rate** estimates:
  - Observation: 79.9%
  - Rituximab maintenance: 80.1%
  - HR 1.04; 95% CI 0.77-1.40; p=0.7948

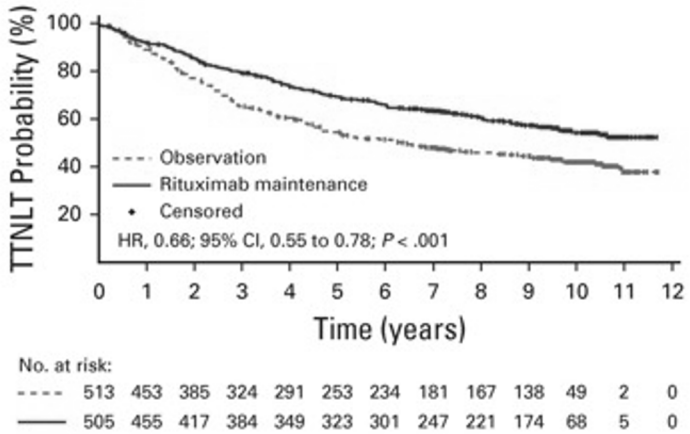


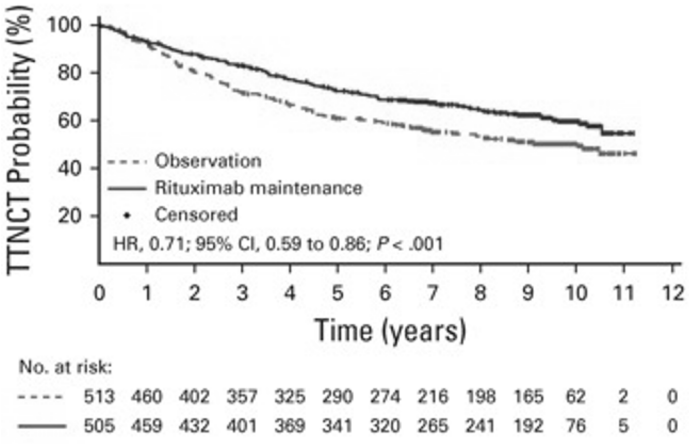
CI, confidence interval; CR(u), (unconfirmed) complete response; FCM, fludarabine, cyclophosphamide, mitoxantrone; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; OS, overall survival; PR, partial response

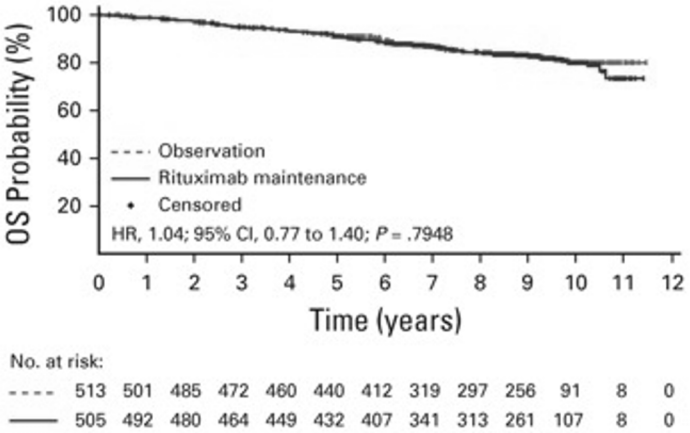
Bachy E, et al. J Clin Oncol. 2019;37:2815-24.

PRIMA STUDY – 10 YEAR FOLLOW UP[1]









How about MZL?

- **StiL NHL7-2008 MAINTAIN[2]**
  - 2-year PFS superior with rituximab maintenance vs observation
    - Median PFS NR vs 92.2 months (HR 0.35; p=0.008)
  - OS rate at 6 years 92% with rituximab maintenance vs 86% with observation
    - HR 0.52 (95% CI 0.20-1.39)

Extended maintenance?

- PFS numerically superior with 4 vs 2 years of rituximab maintenance[3]
  - HR 0.75 (95% CI 0.45-1.24)

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; MZL, marginal zone lymphoma; NR, not reached; TTNCT, time to next chemotherapy treatment; TTNLT, time to next antilymphoma treatment

1. Bachy E, et al. J Clin Oncol. 2019;37:2815-24; 2. Rummel MJ, et al. J Clin Oncol 2018 36:15_suppl, 7515-7515; 3. Rummel MJ, et al. Clin Lym Myel Leuk 2018 18 (Sup1):S101-103.

WHAT DO THE GUIDELINES SAY?

NCCN

ESMO

NCCN GUIDELINES FOR ADVANCED FL

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2021
Follicular Lymphoma (grade 1-2)

NCCN Guidelines Index
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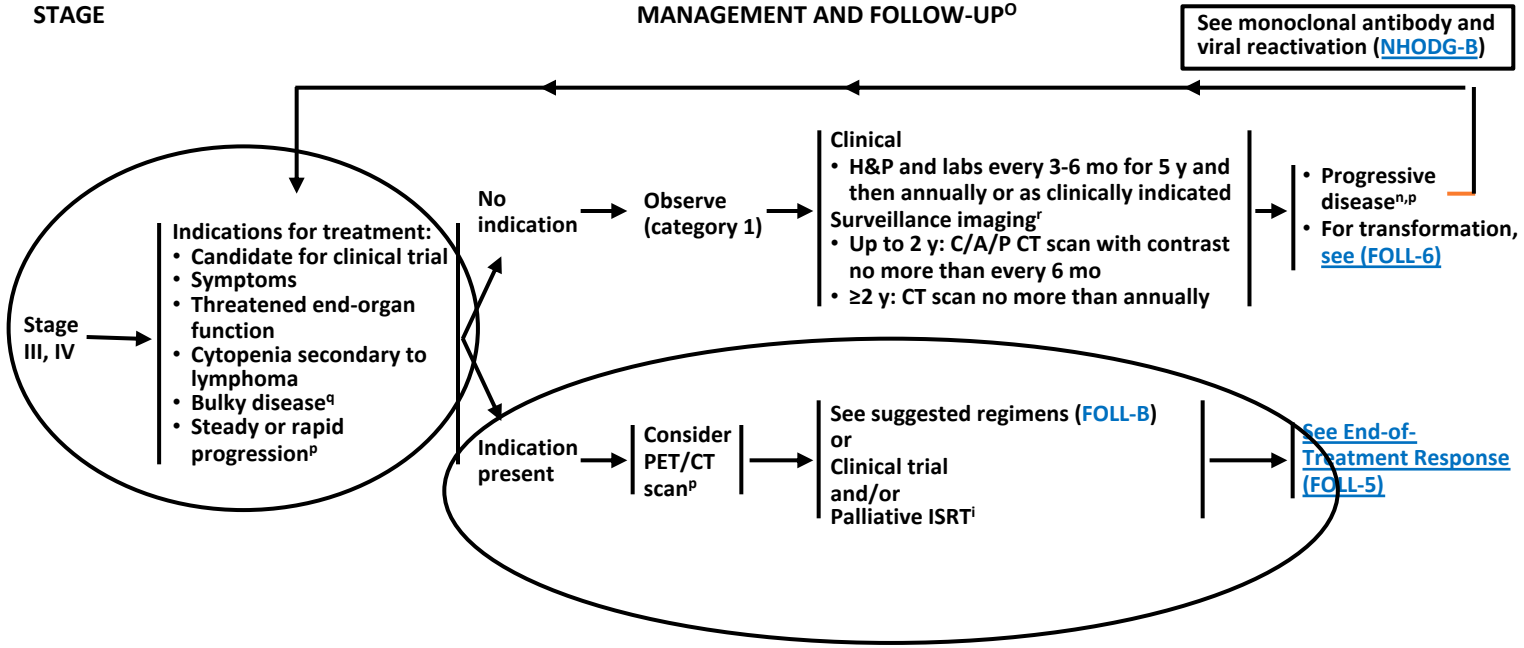
Discussion



FIRST-LINE THERAPY

Preferred regimens (in alphabetical order)
- Bendamustine + obinutuzumab or rituximab
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab or rituximab
- CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab or rituximab
- Lenalidomide + rituximab

Other recommended regimens
- Lenalidomide + obinutuzumab (category 2B)
- Rituximab (375 mg/m^2 weekly for 4 doses) (consider for low tumour burden)

FIRST-LINE THERAPY FOR ELDERLY OR INFIRM
(if none of the above are expected to be tolerable in the opinion of the treating physician)

Preferred regimens
- Rituximab (375 mg/m^2 weekly for 4 doses)

Other recommended regimens
- Chlorambucil ± rituximab
- Cyclophosphamide ± rituximab
- Ibritumomab tiuxetan (category 2B)

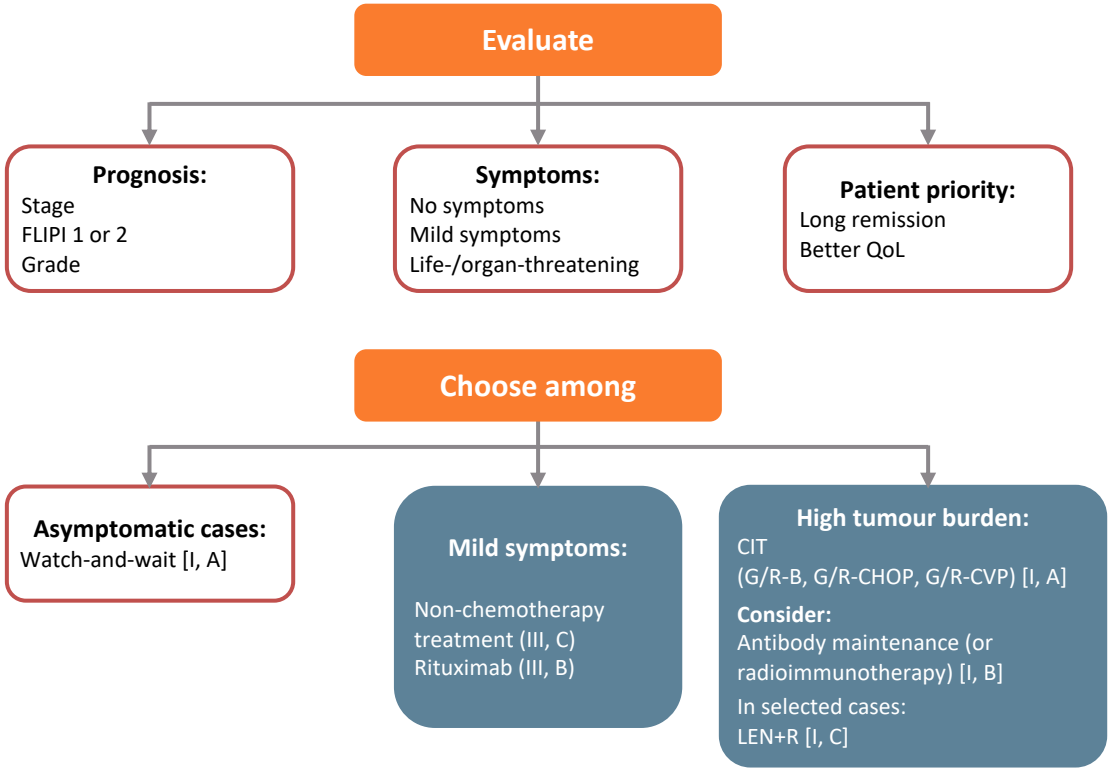
FIRST-LINE CONSOLIDATION OR EXTENDED DOSING (optional)

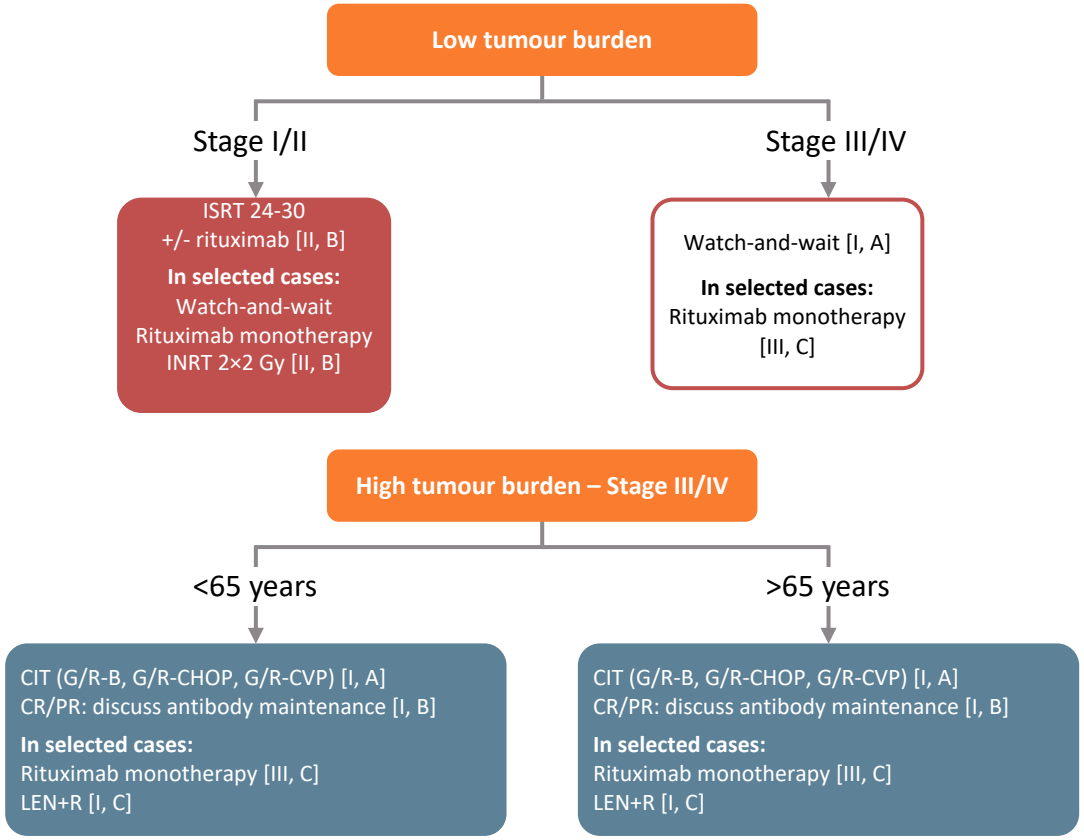
Preferred regimens following chemoimmunotherapy
- Rituximab maintenance 375 mg/m^2 one dose every 8-12 weeks for 2 years for patients initially presenting with high tumour burden (category 1)
- Obinutuzumab maintenance (1,000 mg every 8 weeks for 12 doses

Other recommended regimens
- If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m^2 one dose every 8 weeks for 4 doses
- Ibritumomab tiuxetan (category 2B)

A/AP CT, computed tomographic chest abdomen pelvis; mo, months; PET/CT, positron emission tomography/computerized tomography; y, years

ESMO CLINICAL PRACTICE GUIDELINES





B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CIT, chemoimmunotherapy; FLIPI, Follicular Lymphoma International Prognostic Index; G/R, obinutuzumab/rituximab; INRT, involved node radiotherapy; ISRT, involved-site radiation therapy; QoL, quality of life; LEN+R, rituximab plus lenalidomide; R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab; R-CVP, rituximab plus cyclophosphamide, vincristine, prednisone

Dreyling M, et al. Ann Oncol. 2021;32:298-308

HOW DO YOU CHOOSE THE RIGHT TREATMENT FOR YOUR PATIENT?

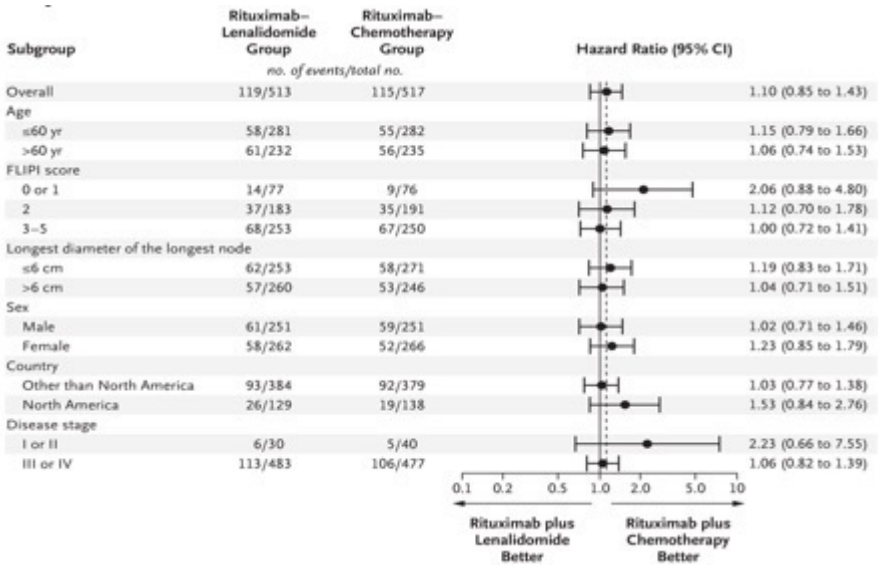
CAN CLINICAL FACTORS GUIDE US?

StiL study: B-R vs R-CHOP/R-CVP

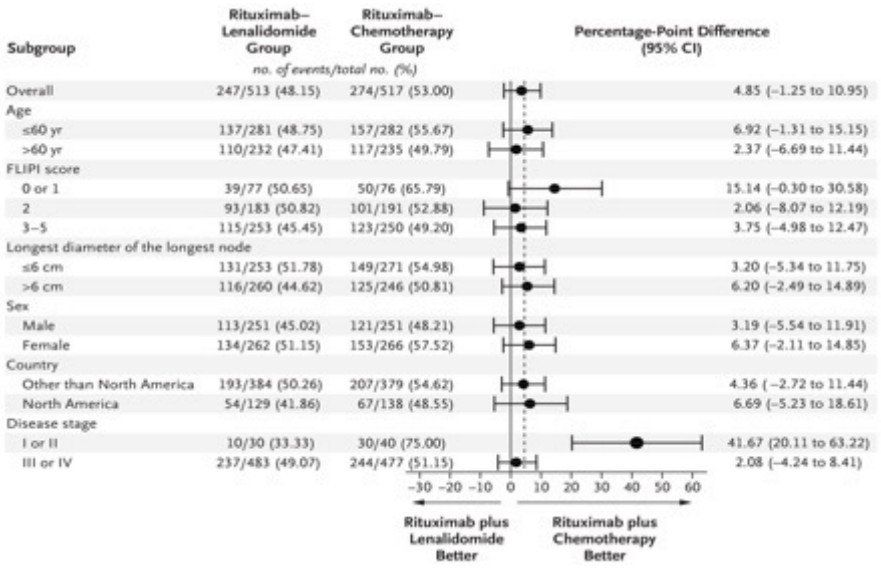
	HR (95% CI)	p value
Age (years)		
≤60 (n=199)	0.52 (0.33-0.79)	0.002
>60 (n=315)	0.62 (0.45-0.84)	0.002
LDH concentration		
Normal (n=319)	0.48 (0.34-0.67)	<0.0001
Elevated (n=184)	0.74 (0.50-1.08)	0.118
FLIPI subgroup		
Favourable (0-2 risk factors; n=143)	0.56 (0.31-0.98)	0.043
Unfavourable (3-5 risk factors; n=127)	0.63 (0.38-1.04)	0.068

RELEVANCE study: LEN+R vs R-chemo

PFS



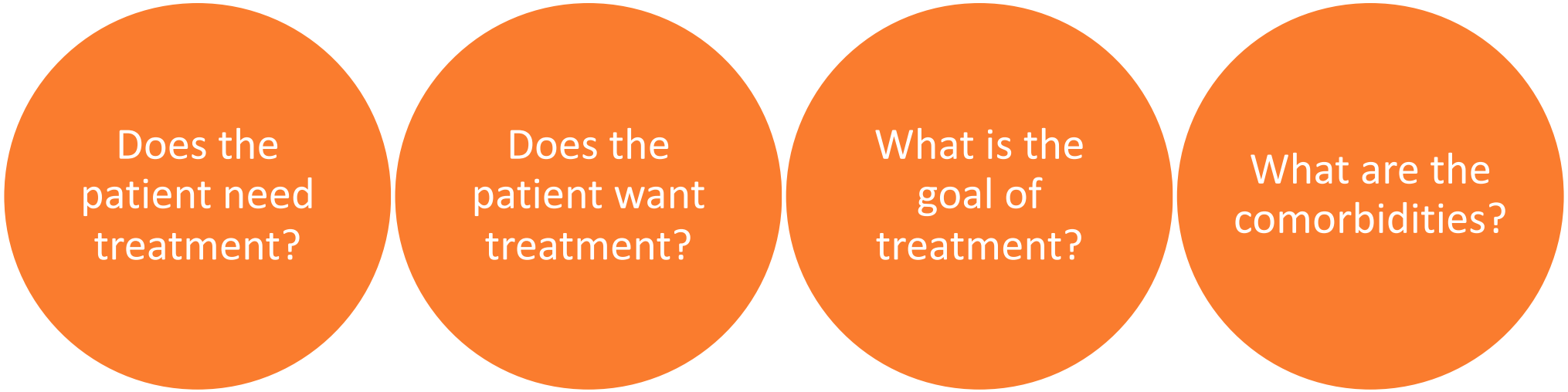
Confirmed or unconfirmed CR at 120 weeks



B-R, bendamustine plus rituximab; CI, confidence interval; CR, complete response; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; LDH, lactate dehydrogenase; PFS, progression-free survival; LEN+R, rituximab plus lenalidomide; R-chemo, rituximab plus chemotherapy; R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab; R-CVP, rituximab plus cyclophosphamide, vincristine, prednisone; yr, years

Rummel MJ, et al. Lancet. 2013;381:1203-10; Morschhauser F, et al. N Engl J Med. 2018;379:934-47

QUESTIONS TO CONSIDER WHEN CHOOSING INITIAL TREATMENT



→ In the upfront setting, we have multiple prognostic markers, but unfortunately there is a lack of predictive biomarkers

*"As **various therapeutic approaches may achieve durable responses in the vast majority** of patients, the **selection of optimal treatment is mainly based on clinical risk factors, symptoms and individual patient priorities.** PET- and MRD-based tailored treatments are currently being evaluated in ongoing studies but are not yet routine clinical practice." **ESMO Guidelines,*** **Dreyling M, et al. Ann Oncol. 2021;32:298-308**

MRD, minimal residual disease; PET, positron emission tomography

TREATMENT SELECTION FOR RELAPSED/REFRACTORY INDOLENT NHL

Dr. Jessica Okosun, MD, PhD

DISCLOSURES JESSICA OKOSUN

- Gilead Sciences
- BeiGene

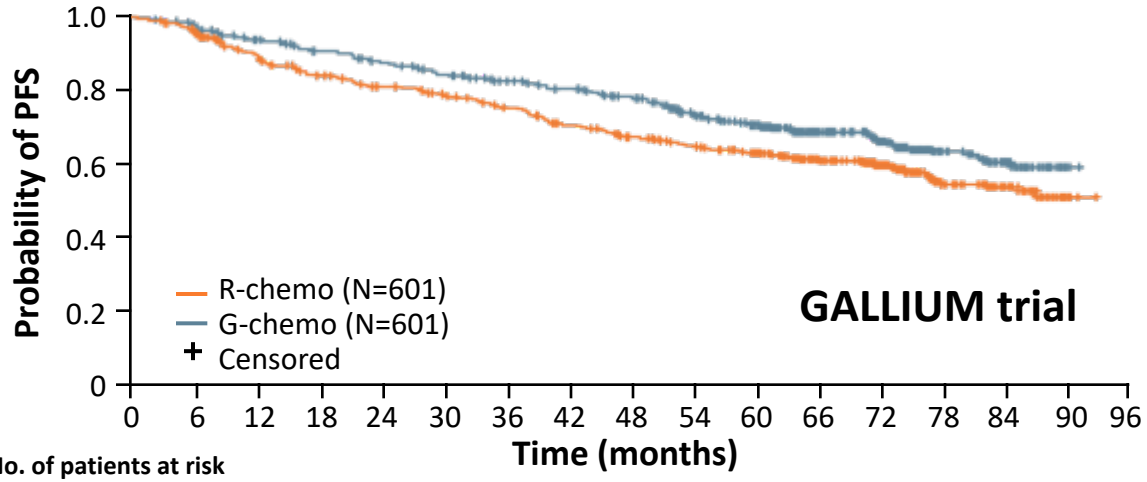
MOST PATIENTS WITH INDOLENT NHL WILL RELAPSE

Despite the favourable outcomes for indolent NHL (FL and MZL)…

FL[1,2]

PFS: G-chemo vs R-chemo

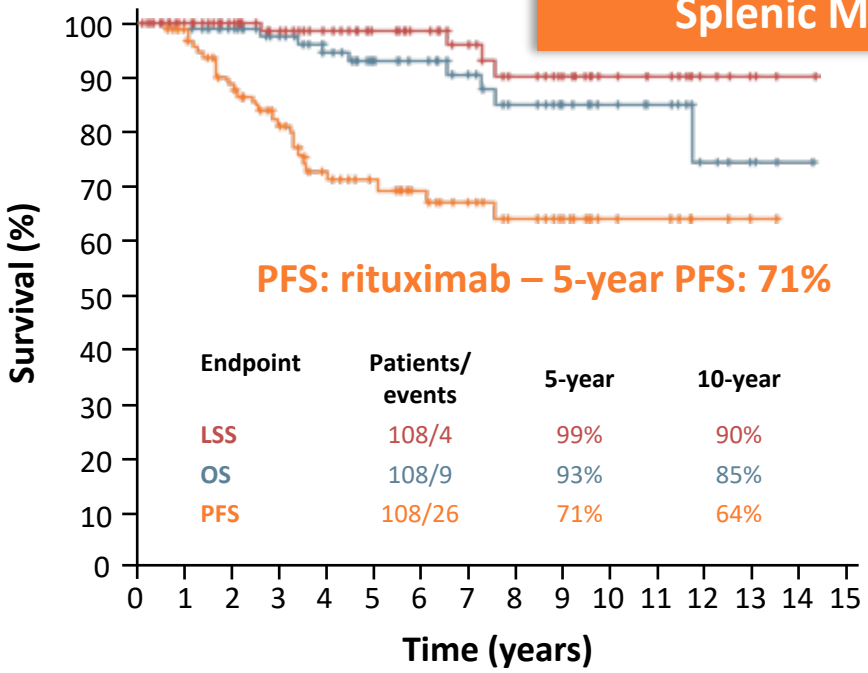
5-year PFS: **70.5%** vs **63.2%** (**G** vs **R**) HR 0.76; p=0.0043



No. of patients at risk

R-chemo	601	563	512	471	447	429	404	373	349	328	304	247	176	88	52	3
G-chemo	601	574	539	512	491	467	446	430	406	368	334	269	182	98	53	4

Splenic MZL[3]



PFS: rituximab – 5-year PFS: 71%

Endpoint	Patients/ events	5-year	10-year
LSS	108/4	99%	90%
OS	108/9	93%	85%
PFS	108/26	71%	64%

FL, follicular lymphoma; G-chemo, obinutuzumab plus chemotherapy; HR, hazard ratio; LSS, lymphoma-specific survival; MZL, marginal zone lymphoma; NHL, non-Hodgkin's lymphoma; OS, overall survival; PFS, progression-free survival; R-chemo, rituximab plus chemotherapy

1. Marcus R, et al. N Engl J Med. 2017;377:1331-44; 2. Townsend W, et al. ASCO 2020. Abstract #8023; 3. Kalpadakis C, et al. Blood. 2018;132:666-70

CONSIDERATIONS AND APPROACH TO RELAPSED FL (AND INDOLENT NHL)

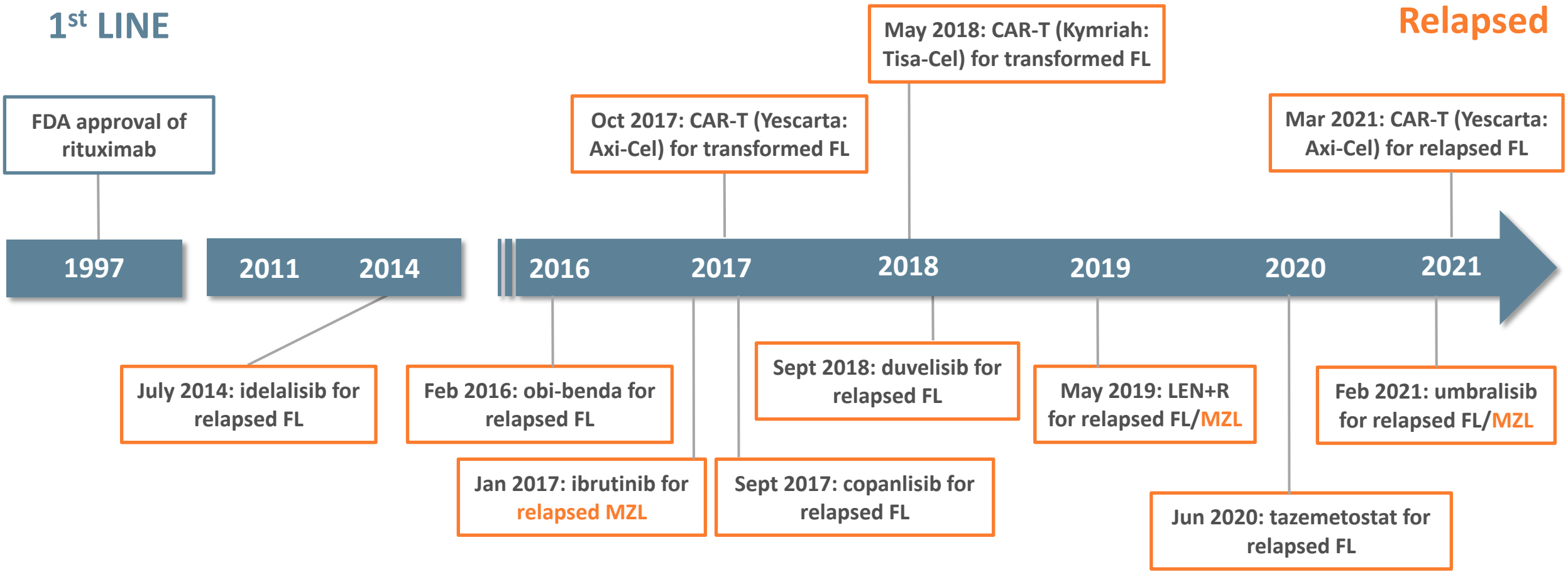
TAKE A BIOPSY! to exclude transformation (especially for FL)

Depends on:

- Is treatment actually required?
- Prior therapies (immunotherapy, chemotherapy)
- **Duration and quality of response – how well did they work?**
- Current clinical situation and risk factors at relapse
  - Patient's age, performance status, comorbidities
  - Disease burden
- Is the patient fit for a transplant? Auto/allo?
- Patient's goals

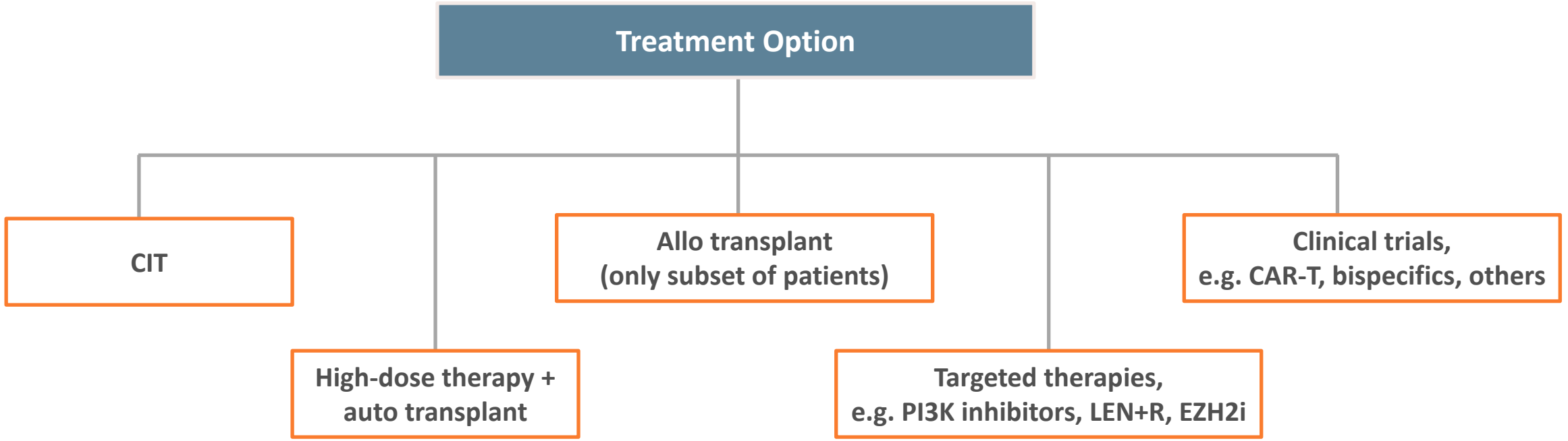
FL, follicular lymphoma; NHL, non-Hodgkin's lymphoma

TIMELINES AND KEY FDA DRUG APPROVALS IN FL/MZL



Axi-Cel, axicabtagene lisoleucel; CAR-T, chimeric antigen receptor T cell; FL, follicular lymphoma; MZL, marginal zone lymphoma; Obi-benda, obinutuzumab + bendamustine; Tisa-Cel, tisagenlecleucel

MULTIPLE TREATMENT OPTIONS FOR R/R FL (STANDARD AND NOVEL)

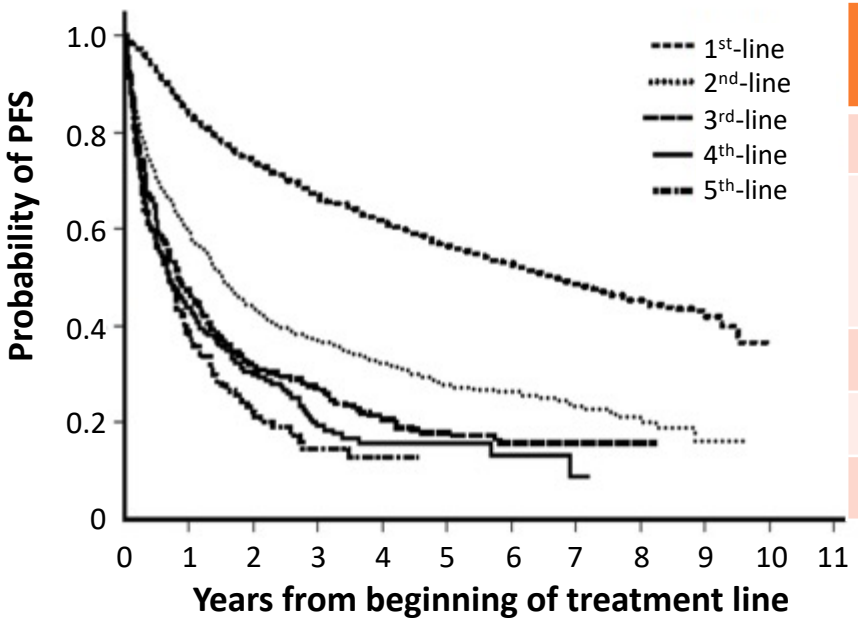


- A standard approach for relapsed/refractory (R/R) FL remains challenging
- Sequencing therapies is particularly important

CAR-T, chimeric antigen receptor T cell; CIT, chemoimmunotherapy; EZH2i, enhancer of zeste homologue 2 inhibitor; FL, follicular lymphoma; PI3K, phosphoinositide 3-kinase; LEN+R, rituximab plus lenalidomide

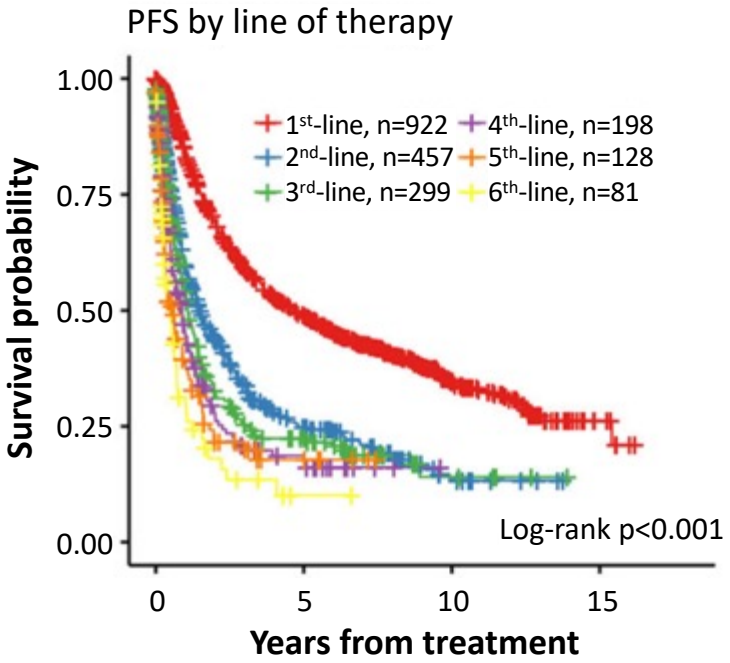
OUTCOMES FOR 2L+ OF THERAPY NEEDS IMPROVING

Data from National LymphoCare Study[1]



Treatment line	Median PFS years (95% CI)
First	6.62 (6.10-7.20)
Second Rituximab R-chemo	1.50 (1.35-1.70) 1.50 (1.26-2.11) 1.48 (1.08-1.77)
Third	0.83 (0.68-1.09)
Fourth	0.69 (0.50-0.97)
Fifth	0.68 (0.43-0.88)

Data from Memorial Sloan Kettering Cancer Center[2]



After 2nd lines of treatment:

- Median disease-free or progression-free period is 1 year or less (excl. transplants)

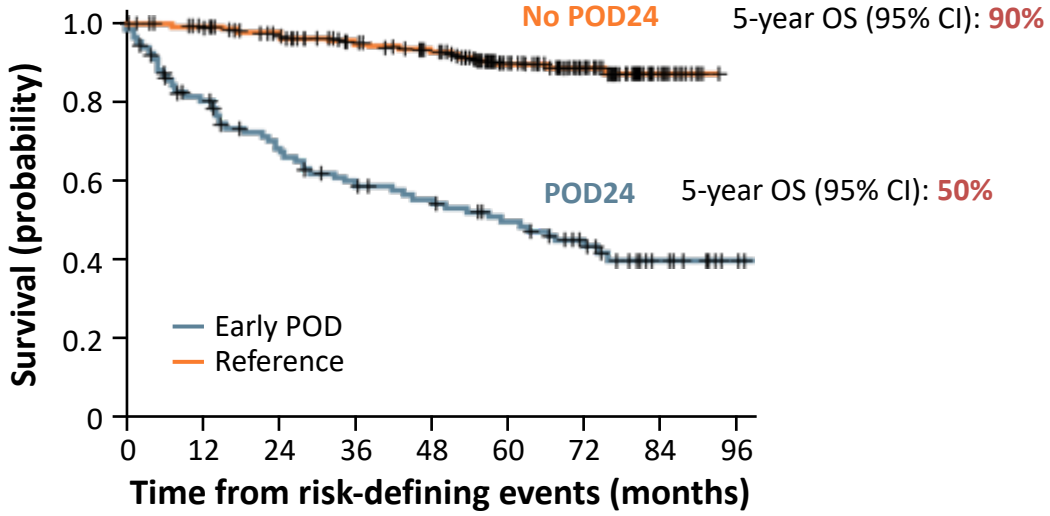
CI, confidence interval; PFS, progression-free survival; R-chemo, rituximab plus chemotherapy

1. Link BK, et al. Br J Haematol. 2019;184:660-3; 2. Batlevi CL, et al. Blood Cancer J. 2020;10:74

NOT ALL FL RELAPSES ARE THE SAME: WHO ARE HIGH-RISK FL PATIENTS?

Early progression of disease (POD 24)[1]

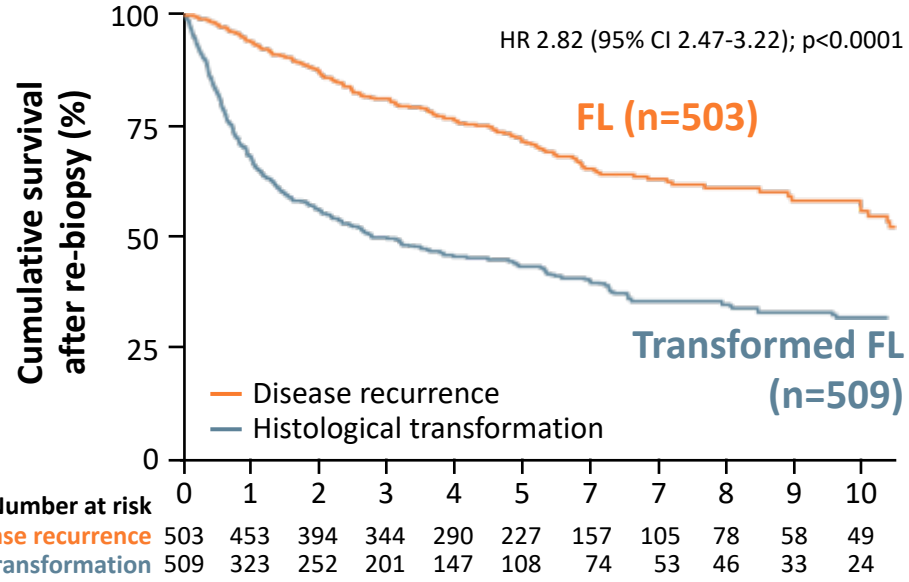
LymphoCare: 530 R-CHOP-treated patients



Applies to EFS12 and EFS24

Transformation to aggressive lymphoma[2]

5-year OS post-transformed FL: 43%
(34% with early [≤1 year] transformation)



Survival poor after transformation

CI, confidence interval; EFS 12/24, event-free survival at 12/24 months; FL, follicular lymphoma; HR, hazard ratio; OS, overall survival; POD(24), progression of disease (within 2 years); R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab

1. Casulo C, et al. J Clin Oncol. 2015;33:2516-22; 2. Federico M, et al. Lancet Haematol. 2018;5:e359-67

WHAT ARE THE OPTIONS FOR EARLY PROGRESSED FL PATIENTS?

1. HOW DO WE IDENTIFY EARLY PROGRESSORS?

- **Clinical tools:**
  - PRIMA-PI[1]
  - FLEX (FL Evaluation Index)[2]
- **Molecular tools:**
  - M7-FLIPI (mutations)[3]
  - Gene expression[4]

Is it **ACTIONABLE**?
Low prognostic **ACCURACY**
Is it widely **ACCESSIBLE/AFFORDABLE**?

2. HOW TO TREAT EARLY PROGRESSORS?

- No treatment shown to be superior to another in this setting
- Options:
  - High-dose therapy/stem cell transplantation for those who are fit
  - CIT options
  - Targeted therapies (lenalidomide, PI3K inhibitors)
  - Clinical trials

Future approaches: auto vs bispecifics vs CAR-T?

CAR-T, chimeric antigen receptor T cell; CIT, chemoimmunotherapy FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; PI3K, phosphoinositide 3-kinase

1. Bachy E, et al. Blood. 2018;132:49-58; 2. Mir F, et al. Am J Hematol. 2020;95:1503-10; 3. Pastore A, et al. Lancet Oncol. 2015;16:1111-22;
4. Huet S, et al. Lancet Oncol. 2018;19:549-56

COMPARISON OF EFFICACY IN PATIENTS WITH POD24 FL

Agent	ORR, %	PFS	OS
LEN+R (n=43)	48	50% at 1 year	NA
Lenalidomide-obinutuzumab (n=24)	67	75% at 1 year	87% at 1 year
Idelalisib (n=37)	57	11 months (median)	NA
Copanlisib (n=93)	58	11 months (median)	43 months (median)

FL, follicular lymphoma; NA, not applicable; OS, overall survival; PFS, progression-free survival; POD24, progression of disease within 2 years; LEN+R, rituximab plus lenalidomide

Casulo C, Barr PM. Blood. 2019;133:1540-47

VALUE OF HIGH-DOSE THERAPY AND ASCT FOR EARLY PROGRESSORS

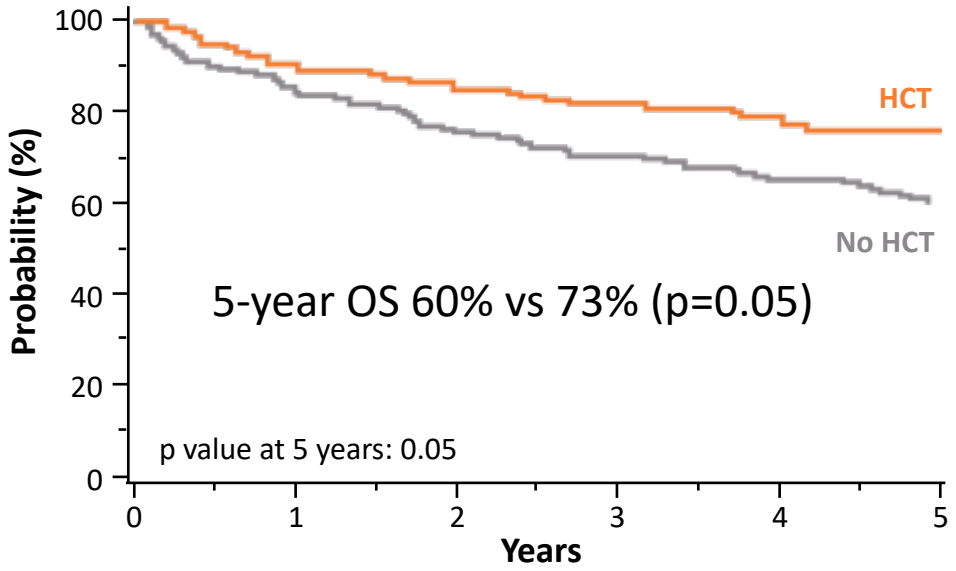
Retrospective study (Center for International Blood and Marrow Transplant Research and National LymphoCare Study)[1]

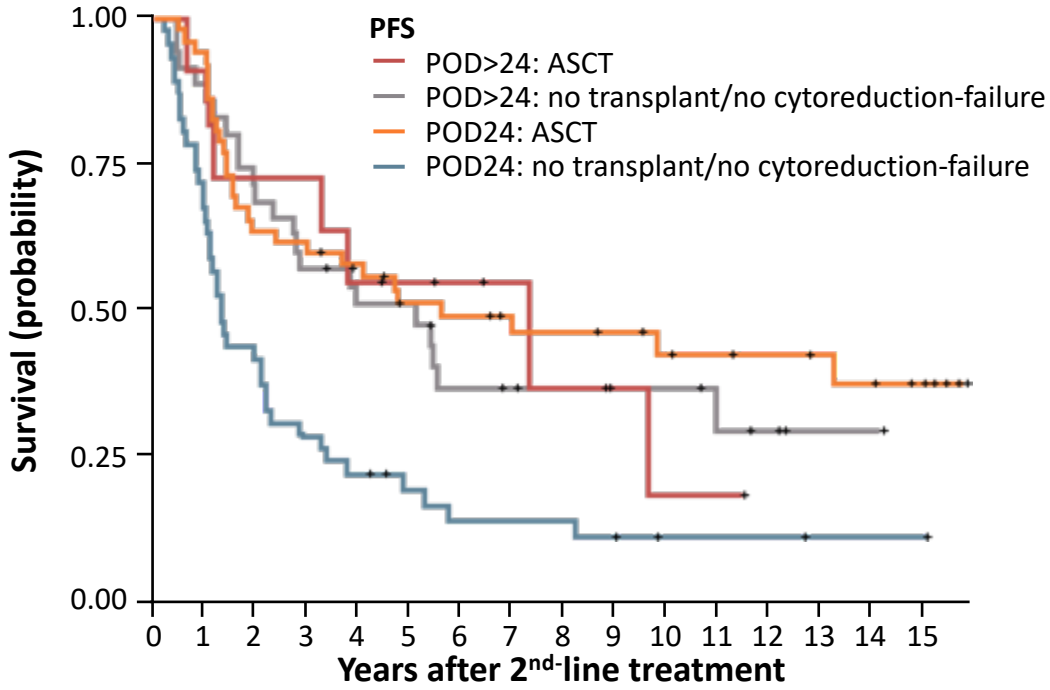
- Failed to achieve PR or early relapse (≤2 years)
- N=349 (175 ASCT and 174 non-ASCT)

Retrospective study (GLSG1996 and GLSG2000)[2]

- 162 patients with progression, in need of treatment
  - POD24: n=113; POD>24: n=49

OS of patients receiving HCT <1 year of therapy failure vs no HCT

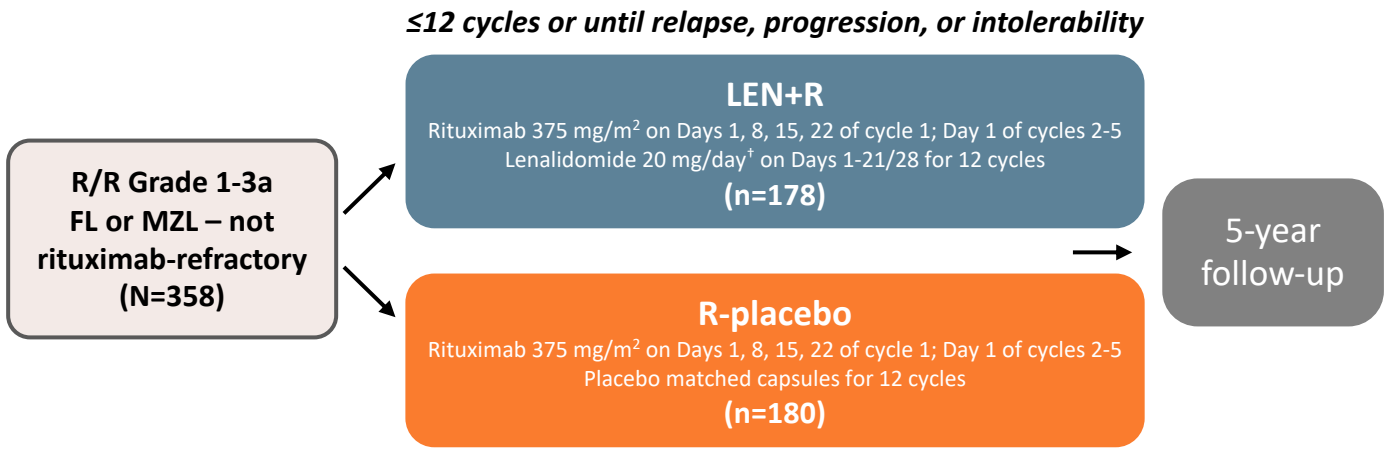




ASCT, autologous stem cell transplant; HCT, haematopoietic stem cell transplantation; OS, overall survival; PFS, progression-free survival; PR, partial response; POD(24), progression of disease (within 2 years)

1. Casulo C, et al. Biol Blood Marrow Transplant. 2018;24:1163-71; 2. Jurinovic V, et al. Biol Blood Marrow Transplant. 2018;24:1172-9

AUGMENT: PHASE 3 STUDY FOR R/R FL: LEN+R VS R-PLACEBO

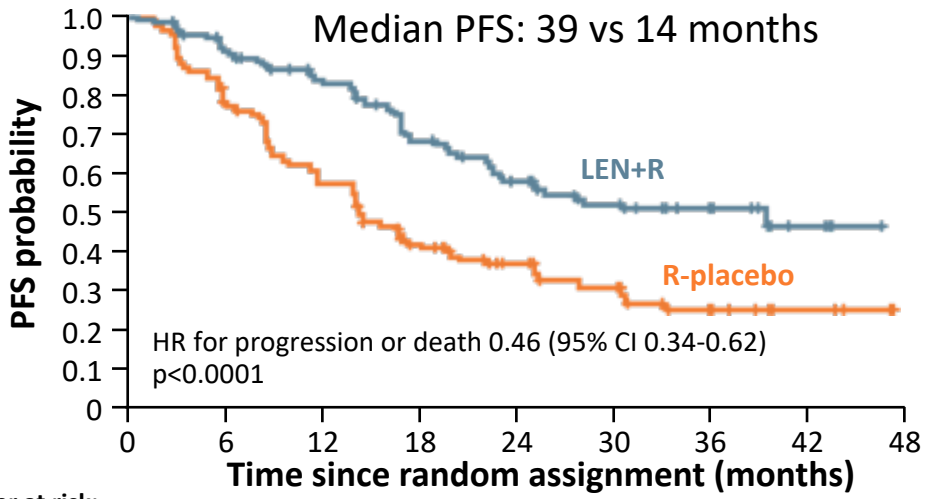


Primary endpoint:
- IRC-assessed PFS (2007 IWG criteria without PET)

Secondary endpoint:
- ORR, CR, OS

PFS in R/R FL

2-year PFS 58% (LEN+R) vs 36% (R-placebo)



Number at risk:

LEN+R	178	148	124	91	59	39	20	7	0
Placebo + rituximab	180	132	92	58	40	26	10	4	0

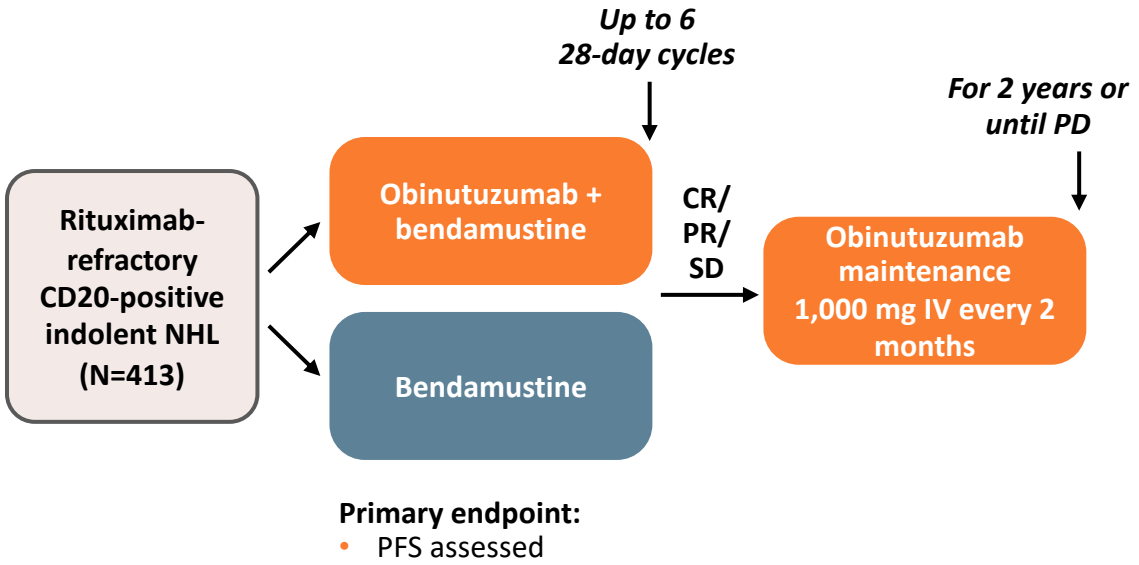
LEN+R is FDA-approved for previously treated FL

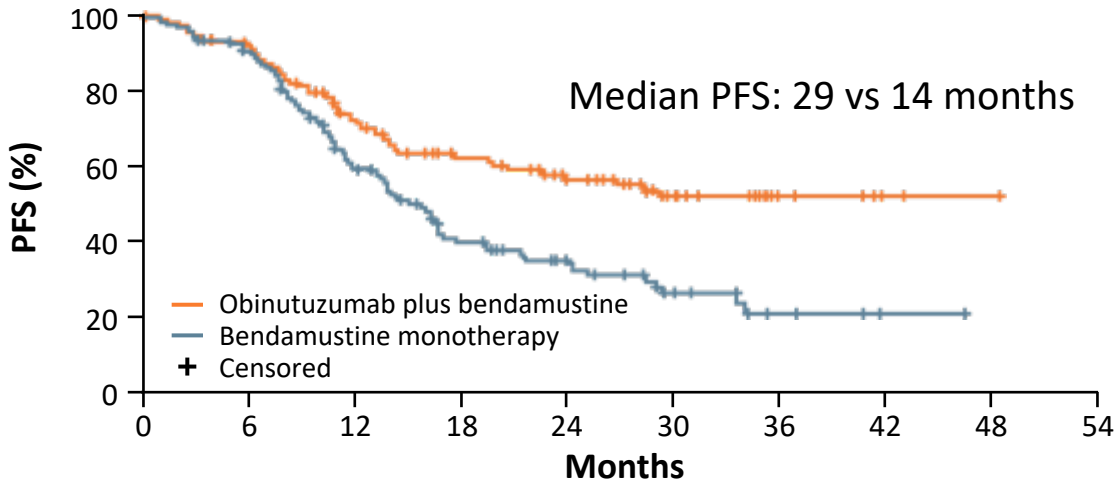
CI, confidence interval; CR, complete response; FL, follicular lymphoma; HR, hazard ratio IRC, independent review committee; IWG, International Working Group; MZL, marginal zone lymphoma; OS, overall survival; ORR, overall response rate; PET, positron emission tomography; PFS, progression-free survival; LEN+R, rituximab plus lenalidomide; R-placebo, rituximab plus placebo; R/R, relapsed/refractory

Leonard JP, et al. J Clin Oncol. 2019;37:1188-99

BENDAMUSTINE +/- OBINUTUZUMAB IN RITUXIMAB-REFRACTORY FL

GADOLIN – RANDOMIZED, INTERNATIONAL PHASE 3 TRIAL





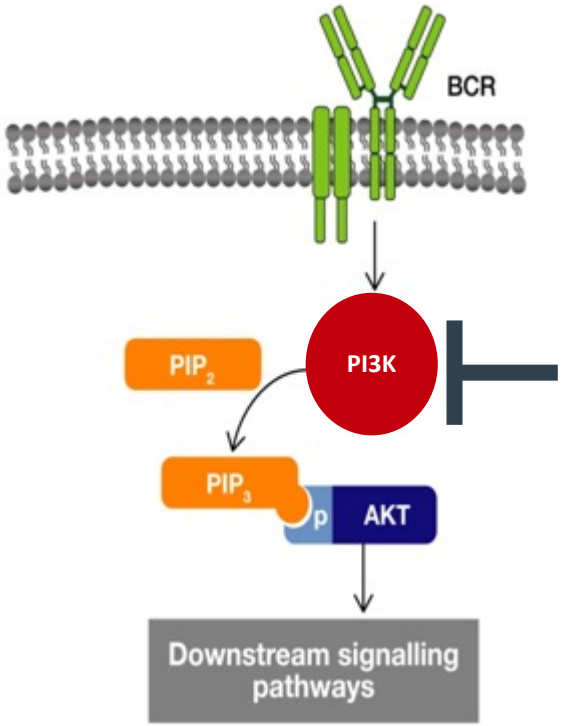
Obinutuzumab + bendamustine followed by obinutuzumab:

FDA-approved for patients with FL who have relapsed after or are refractory to a rituximab-containing regimen

CD20, cluster of differentiation 20; CR, complete response; FL, follicular lymphoma; IV, intravenous; NHL, non-Hodgkin's lymphoma; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease

Sehn LH, et al. Lancet Oncol. 2016;17:1081-93; Cheson BD, et al. J Clin Oncol. 2018;36:2259-66

B-CELL RECEPTOR SIGNALLING AND PI3K INHIBITORS



Idelalisib (δ)
Duvelisib (γδ)
Copanlisib (αδ)
Umbralisib (δ)
ME-401 (δ)

4 FDA-approved PI3K inhibitors in relapsed FL; 1 in relapsed MZL

	Idelalisib[1]	Copanlisib[2]	Duvelisib[3]	Umbralisib[4]
Mechanism of action	Selective PI3Kδ	Pan-class I PI3K inhibitor	Dual inhibitor of PI3Kγδ	PI3Kδ and CK1-ε
Indication	Relapsed FL after ≥2 prior systemic therapies	Relapsed FL after ≥2 prior systemic therapies	R/R FL after ≥2 prior therapies	R/R FL after ≥3 prior therapies
Dosing	150 mg orally (PO) twice daily (BID)	IV 60 mg on days 1, 8, and 15 of a 28-day cycle	25 mg PO BID	Oral 800 mg once daily (QD)

BCR, B-cell receptor; PI3K, phosphoinositide 3-kinase; FL, follicular lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory

1. Gopal AK, et al. N Engl J Med. 2014;370:1008-18; 2. Dreyling M, et al. J Clin Oncol. 2017;35:3898-905; 3. Flinn IW, et al. J Clin Oncol. 2019;37:984-91; 4. Fowler NH, et al. J Clin Oncol. 2021. DOI: 10.1200/JCO.20.03433

CLINICAL EFFICACY AND SAFETY OF PI3K INHIBITORS IN R/R INDOLENT NHL

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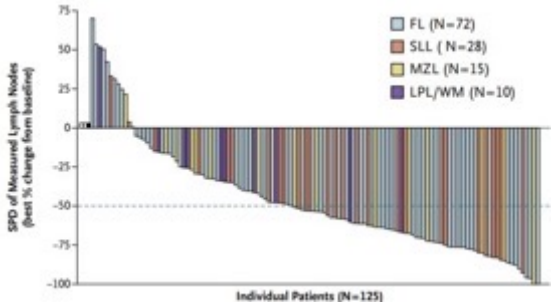
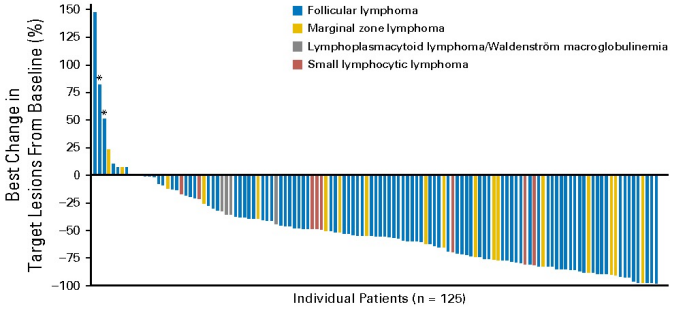
Idelalisib



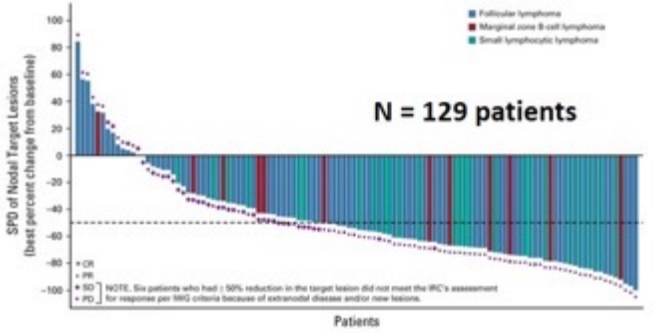
Transaminitis, colitis, pneumonitis, infections

Copanlisib



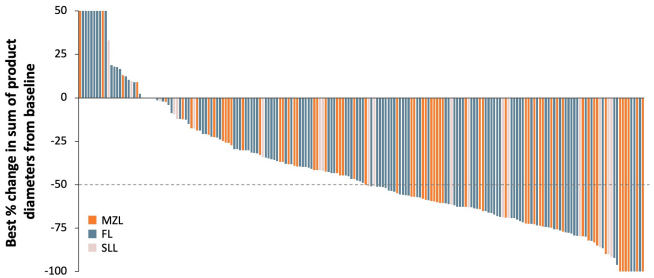
Hyperglycaemia, hypertension, pneumonitis, diarrhoea

Duvelisib



Colitis, pneumonitis, cutaneous reactions

Umbralisib



Colitis, hepatotoxicity, cutaneous reactions

TAKE-HOME:

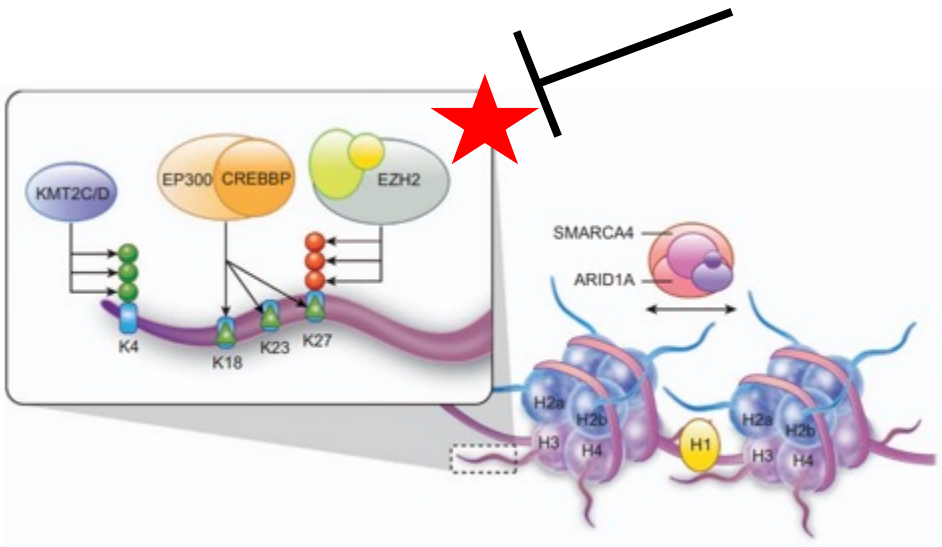
ORR:	40-60%
Median DoR:	10-14 months
Median PFS:	9-12 months
Grade 3 or 4 AEs:	55-88%

AE, adverse event; CR, complete response; DoR, duration of response; FL, follicular lymphoma; LPL/WM, lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia; MZL, marginal zone lymphoma; NHL, non-Hodgkin's lymphoma; ORR, objective/overall response rate; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; SD, stable disease; SLL, small lymphocytic lymphoma

1. Gopal AK, et al. N Engl J Med. 2014;370:1008-18; 2. Dreyling M, et al. J Clin Oncol. 2017;35:3898-905; 3. Flinn IW, et al. J Clin Oncol. 2019;37:984-91; 4. Fowler NH, et al. J Clin Oncol. 2021. DOI: 10.1200/JCO.20.03433

EZH2 MUTATIONS IN FL

- EZH2 is a histone methyltransferase, an epigenetic regulator
- Oncogenic gain of function mutations in approx. 20% of FL and GCB-DLBCL



Tazemetostat, first-in-class, selective, oral inhibitor of EZH2 – FDA approval

Screening

Archival tissue analysed for *EZH2* hot spot activating mutations

Eligibility, enrollment

- FL, *EZH2* MT (N=45)
- FL, *EZH2* WT (N=54)

Cohort assignment

Tazemetostat 800 mg BID

KEY OBJECTIVES

Primary endpoint:
- **ORR**

Secondary endpoint:
- DoR
- PFS
- Safety
- Pharmacokinetics

End of trial follow-up

Response assessed every 8 weeks using 2007 IWG-NHL criteria

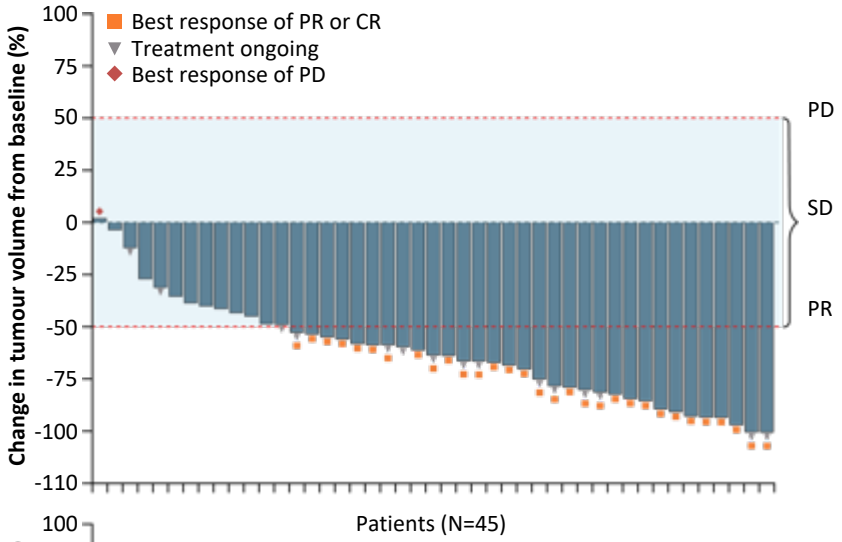
Treatment continues until progressive disease or withdrawal

DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; EZH2, enhancer of zeste homologue 2; FL, follicular lymphoma; MT, mutated; ORR, objective response rate; WT, wild type

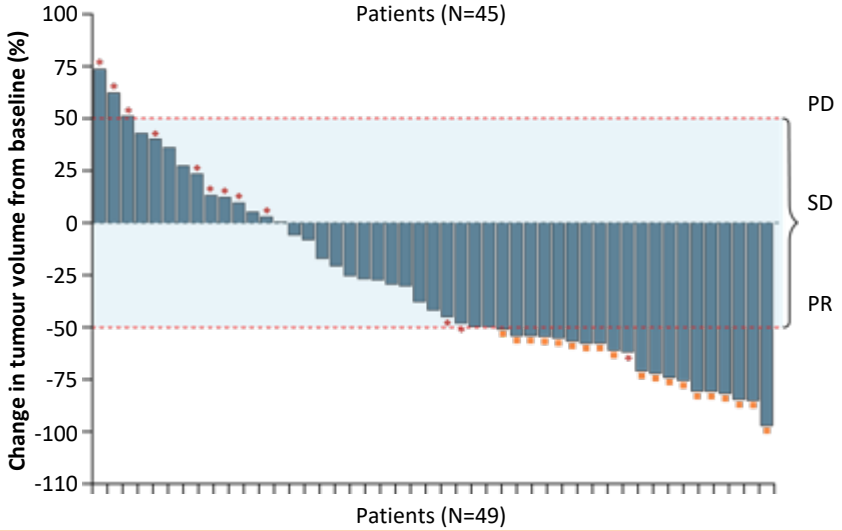
Morschhauser F, et al. Lancet Oncol. 2020;21:1433-42; Bödör C, et al. Blood. 2013;122:3165-8; Morin RD, et al. Nat Genet. 2010;42:181-5

TAZEMETOSTAT (EZH2i)
FIRST TREATMENT TARGETING GENETIC MUTATIONS

EZH2 MT



EZH2 WT



	EZH2^{mut} (N=45)	
	IRC-assessed	**Investigator-assessed**
Objective response rate[a]	31 (69%; 53-82)	35 (78%; 63-89)
Overall disease control rate[b]	44 (98%)	45 (100%)
Best overall response		
CR	6 (13%)	4 (9%)
PR	25 (56%)	31 (69%)
SD	13 (29%)	10 (22%)
PD	1 (2%)	0
Not estimable or unknown	0	0

	EZH2^{wt} (N=54)	
	IRC-assessed	**Investigator-assessed**
Objective response rate[a]	19 (35%; 23-49)	18 (33%; 21-48)
Overall disease control rate[b]	37 (69%)	34 (63%)
Best overall response		
CR	2 (4%)	3 (6%)
PR	17 (31%)	15 (28%)
SD	18 (33%)	16 (30%)
PD	12 (22%)	16 (30%)
Not estimable or unknown	5 (9%)	4 (7%)

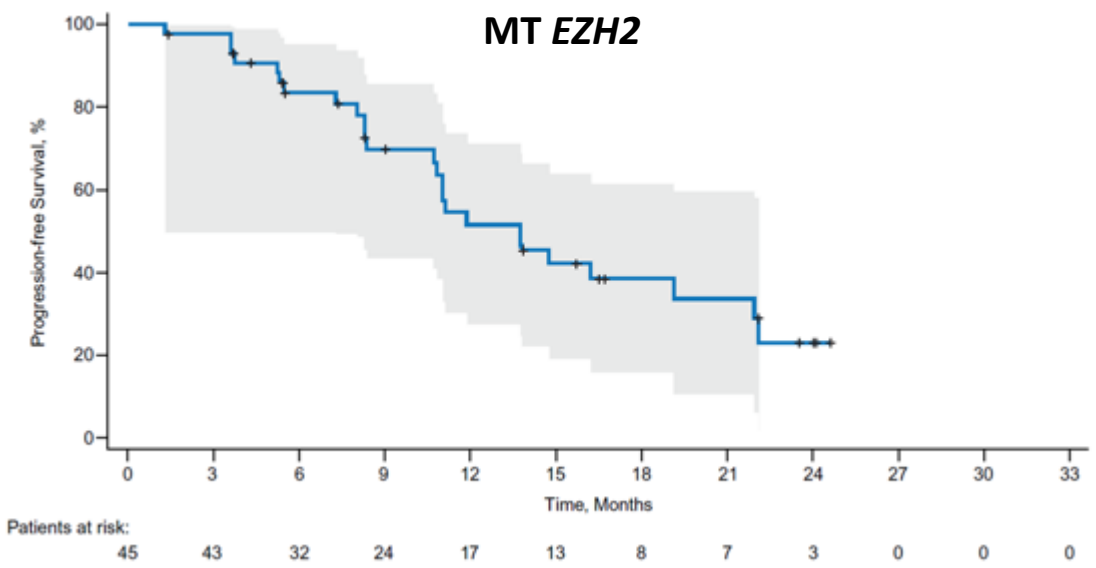
Safety: Very well tolerated

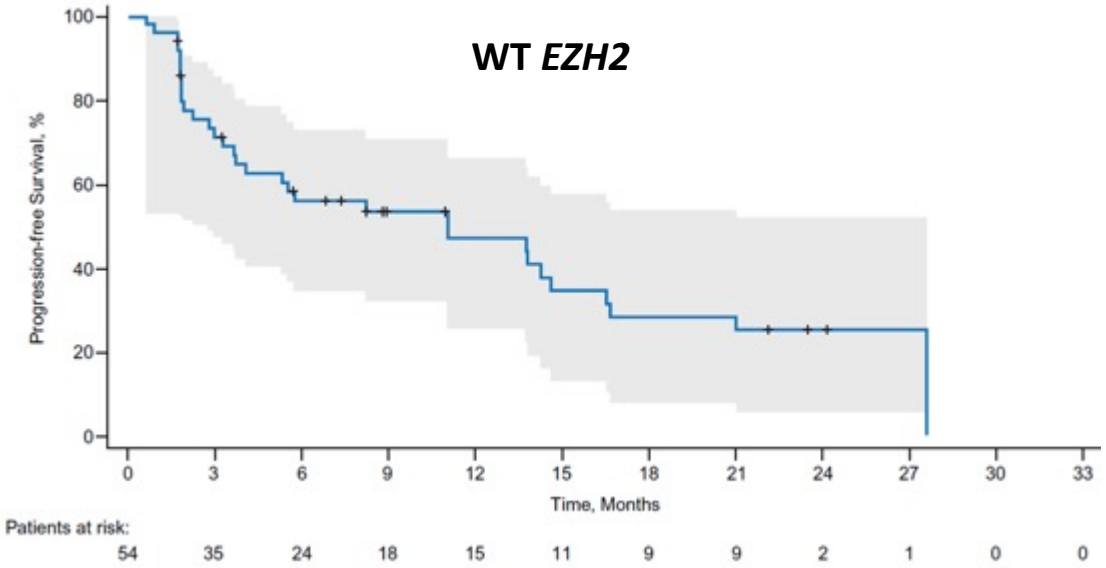
[a] Objective response rate includes patients with CR or PR; [b] Overall disease control rate includes patients with a CR, PR, or SD

CR, complete response; EZH2i, enhancer of zeste homologue 2 inhibitor; IRC, independent review committee; PD, progressive disease; PR, partial response; SD, stable disease

Morschhauser F, et al. Lancet Oncol. 2020;21:1433-42

PFS, BY IRC ASSESSMENT, IN MT AND WT *EZH2* COHORTS





Endpoint	MT *EZH2* INV (n=45)	MT *EZH2* IRC (n=45)	WT *EZH2* INV (n=54)	WT *EZH2* IRC (n=54)
Median (95% CI) PFS, months	13.8 (8.4, 16.4)	13.8 (10.7, 22.0)	5.6 (3.3, 11.1)	11.1 (3.7, 14.6)
KM estimate of PFS (95% CI) at 6 months, %	83.3 (68.0, 91.7)	83.6 (68.6, 91.8)	46.4 (32.2, 59.4)	55.9 (40.7, 68.7)
KM estimate of PFS (95% CI) at 12 months, %	53.2 (36.2, 67.6)	51.7 (34.4, 66.6)	35.8 (22.8, 49.0)	47.1 (31.6, 61.1)
KM estimate of PFS (95% CI) at 18 months, %	31.0 (16.4, 46.8)	38.8 (22.7, 54.7)	22.5 (11.8, 35.)	28.3 (14.8, 43.4)

CI, confidence interval; IRC, independent review committee; INV, investigator-assessed; KM, Kaplan–Meier; MT, mutated; PFS, progression-free survival; WT, wild type

Morschhauser F, et al. Blood. 2019;134(suppl 1):123

WHAT DO THE GUIDELINES SUGGEST FOR R/R FL?

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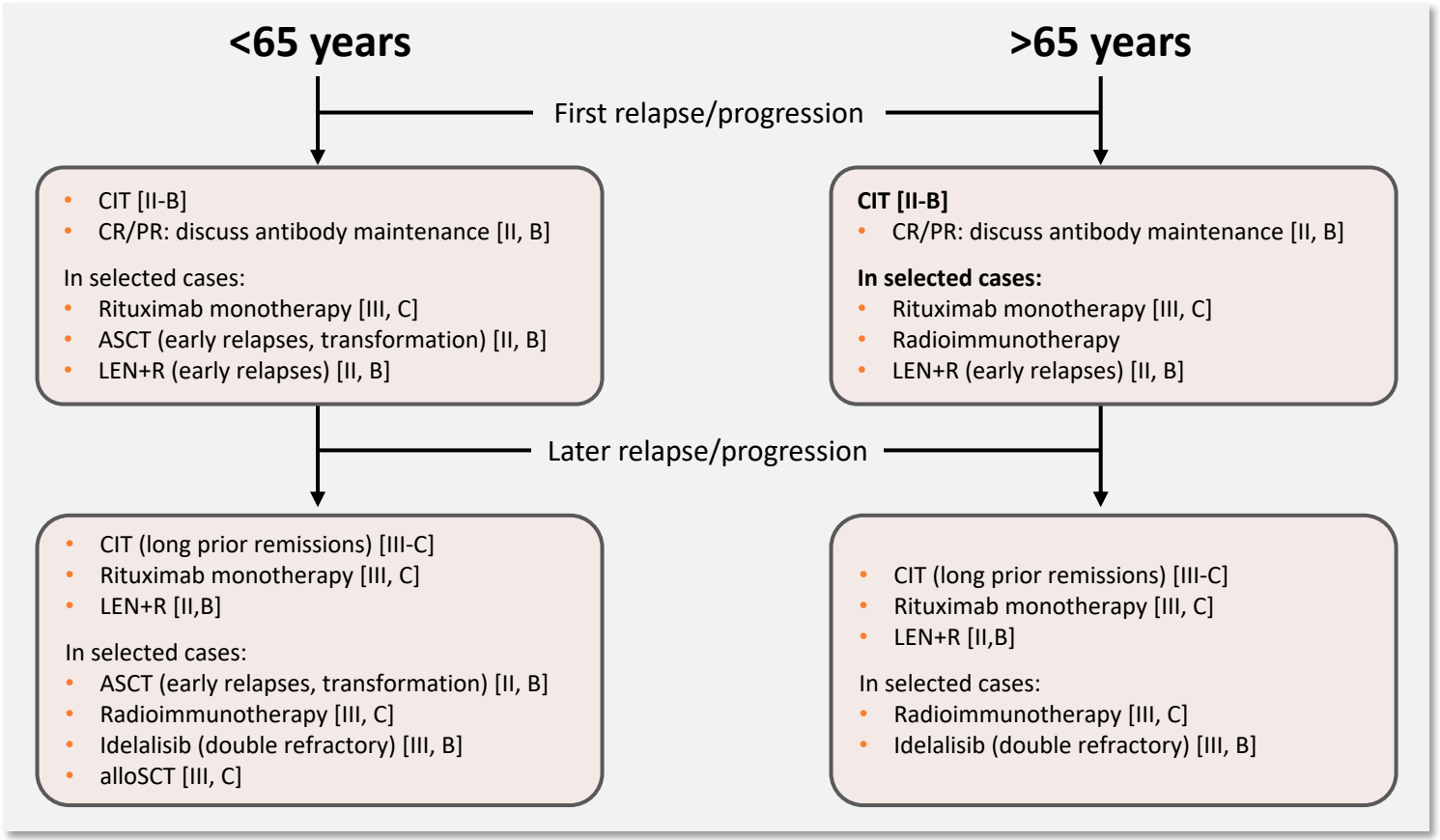
NCCN National Comprehensive Cancer Network®

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Second-line and subsequent therapy

- Preferred regimens (alphabetical order)
  - Bendamustine + obinutuzumab or rituximab
  - CHOP + obinutuzumab or rituximab
  - CVP + obinutuzumab or rituximab
  - LEN+R
- Other recommended regimens (alphabetical order)
  - Ibritumomab tiuxetan
  - Lenalidomide (if not a candidate for anti-CD20 monoclonal antibody therapy)
  - Lenalidomide + obinutuzumab
  - Obinutuzumab
  - PI3K inhibitors (R/R after 2 prior therapies)
    - Copanlisib
    - Duvelisib
    - Idelalisib
  - Rituximab
  - Tazemetostat
    - *EZH2* mutation positive R/R disease after 2 prior therapies
    - *EZH2* wild type R/R disease in patients who have no satisfactory alternative treatment



ASCT, autologous stem cell transplant; CD20, cluster of differentiation 20; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CIT, chemoimmunotherapy; CR, complete response; CVP, cyclophosphamide, vincristine, prednisone; FL, follicular lymphoma; PI3K, phosphoinositide 3-kinase; PR, partial response; LEN+R, rituximab plus lenalidomide; R/R, relapsed/refractory

Rummel MJ, et al. Lancet. 2013;381:1203-10

APPROACH TO TREATMENT SELECTION FOR R/R INDOLENT NHL

For FL

- Consider a **clinical trial** as a first option
- **Early progressors** (POD24) – **younger patients** – *consider* high-dose therapy and ASCT
- In **rituximab-refractory patients** – *Obinutuzumab-chemotherapy (obinutuzumab-bendamustine, obinutuzumab-CHOP)*
- In **older patients** – *consider LEN+R, tazemetostat (in EZH2-mutated patients)*
- **Double-refractory patients**: *consider PI3K inhibitors (BUT mindful of toxicities, comorbidities, QoL)*

For MZL

- **Clinical trial** as above
- **LEN+R, ibrutinib, umbralisib**

ASCT, autologous stem cell transplant; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; FL, follicular lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin's lymphoma; POD24, progression of disease within 24 months; PI3K, phosphoinositide 3-kinase; LEN+R, rituximab plus lenalidomide; R/R, relapsed/refractory; QoL, quality of life

THE FUTURE TREATMENT LANDSCAPE IN INDOLENT NHL

Prof. Alexey Danilov, MD, PhD

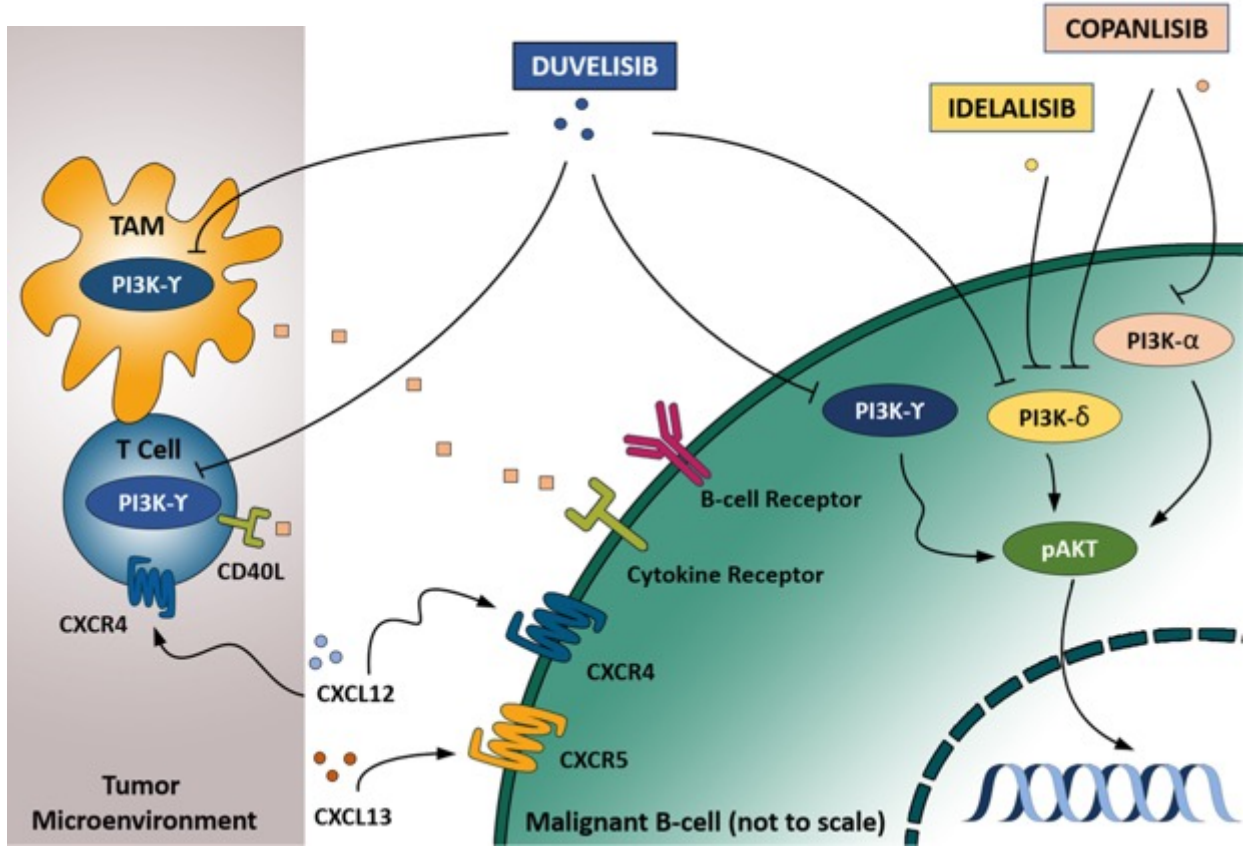
DISCLOSURES ALEXEY DANILOV

- AstraZeneca
- Gilead Sciences
- Takeda Oncology
- Genentech
- TG Therapeutics
- Bayer Oncology
- Bristol-Myers Squib
- BeiGene
- SecuraBio
- Pharmacyclics

PI3K INHIBITION: RATIONALE

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

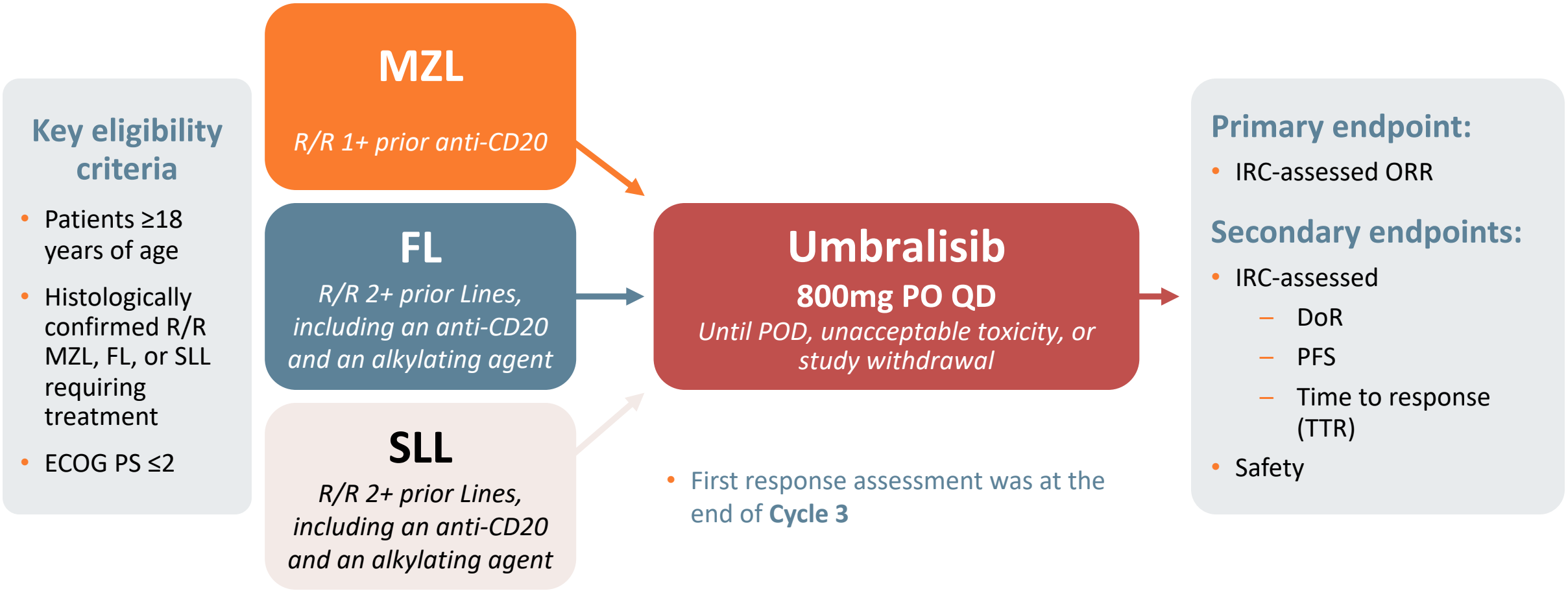
Targeting PI3K isoforms



FL, follicular lymphoma; NHL, non-Hodgkin's lymphoma; PI3K, phosphoinositide 3-kinase; R/R, relapsed/refractory

Westin JR. Clin Lymphoma Myeloma Leuk. 2014;14:335-42; von Keudell G, Moskowitz AJ. Curr Hematol Malig Rep. 2019;14:405-13; Patel K, et al. Blood. 2019;134:1573-77

UNITY-NHL STUDY DESIGN



CD20, cluster of differentiation 20; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; PFS, progression-free survival; PO, orally; POD, progression of disease; QD, once daily; SLL, small lymphocytic lymphoma; R/R, relapsed/refractory

Zinzani PL, et al. ASH 2020. Abstract #2934

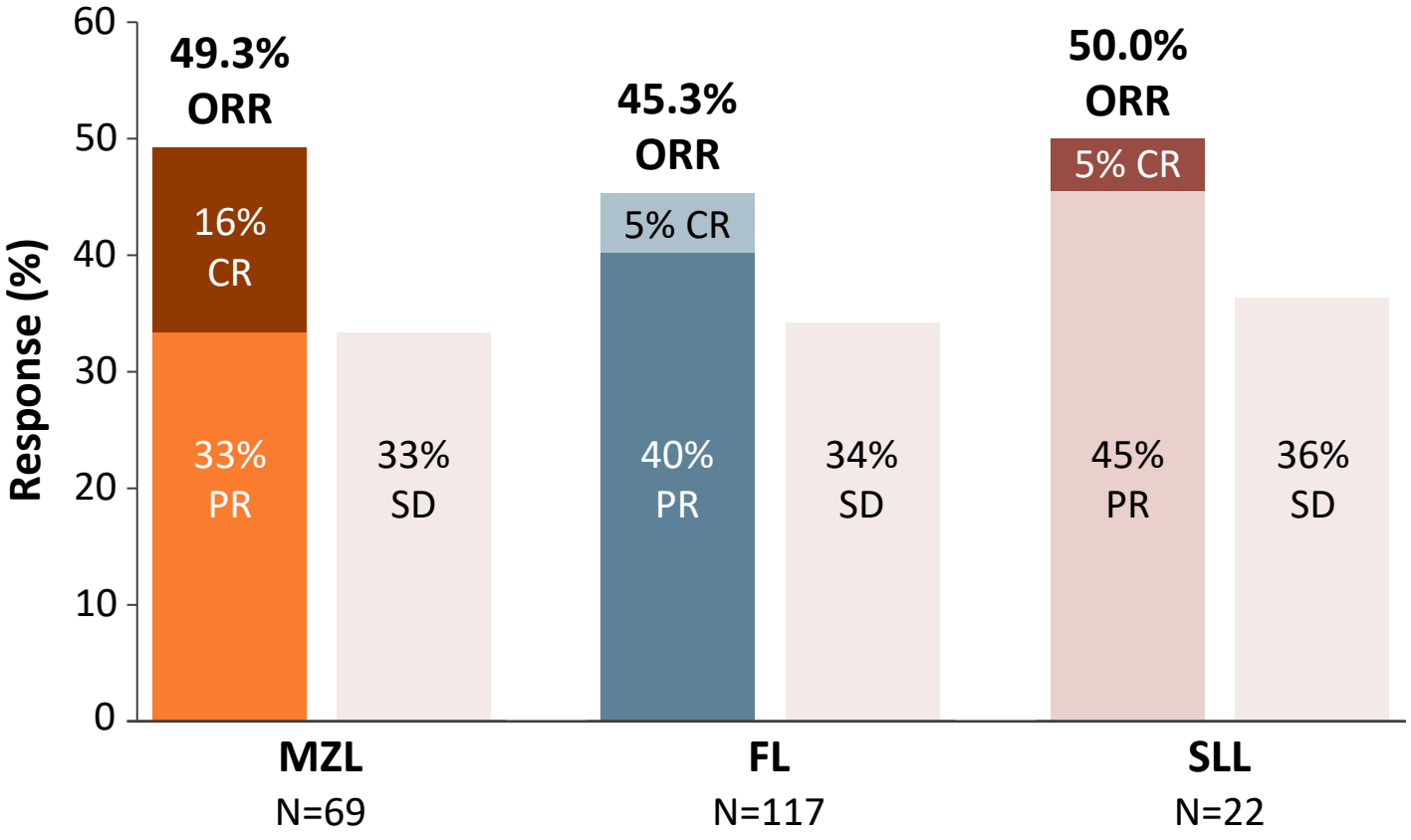
ALL CAUSALITY ADVERSE EVENTS (>15%)

AE, n (%) (N=208)	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhoea	**123 (59.1)**	64 (30.8)	38 (18.3)	21 (10.1)	0	0
Nausea	**82 (39.4)**	52 (25.0)	29 (13.9)	1 (0.5)	0	0
Fatigue	**64 (30.8)**	38 (18.3)	19 (9.1)	7 (3.4)	0	0
Vomiting	**49 (23.6)**	29 (13.9)	19 (9.1)	1 (0.5)	0	0
Cough	**43 (20.7)**	35 (16.8)	8 (3.8)	0	0	0
ALT increased	**42 (20.2)**	13 (6.3)	15 (7.2)	11 (5.3)	3 (1.4)	0
AST increased	**39 (18.8)**	19 (9.1)	5 (2.4)	15 (7.2)	0	0
Decreased appetite	**39 (18.8)**	23 (11.1)	12 (5.8)	4 (1.9)	0	0
Dizziness	**38 (18.3)**	29 (13.9)	8 (3.8)	1 (0.5)	0	0
Neutropenia	**33 (15.9)**	5 (2.4)	4 (1.9)	10 (4.8)	14 (6.7)	0
Headache	**33 (15.9)**	22 (10.6)	9 (4.3)	2 (1.0)	0	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Zinzani PL, et al. ASH 2020. Abstract #2934

IRC-ASSESSED OVERALL RESPONSE PRIMARY ENDPOINT



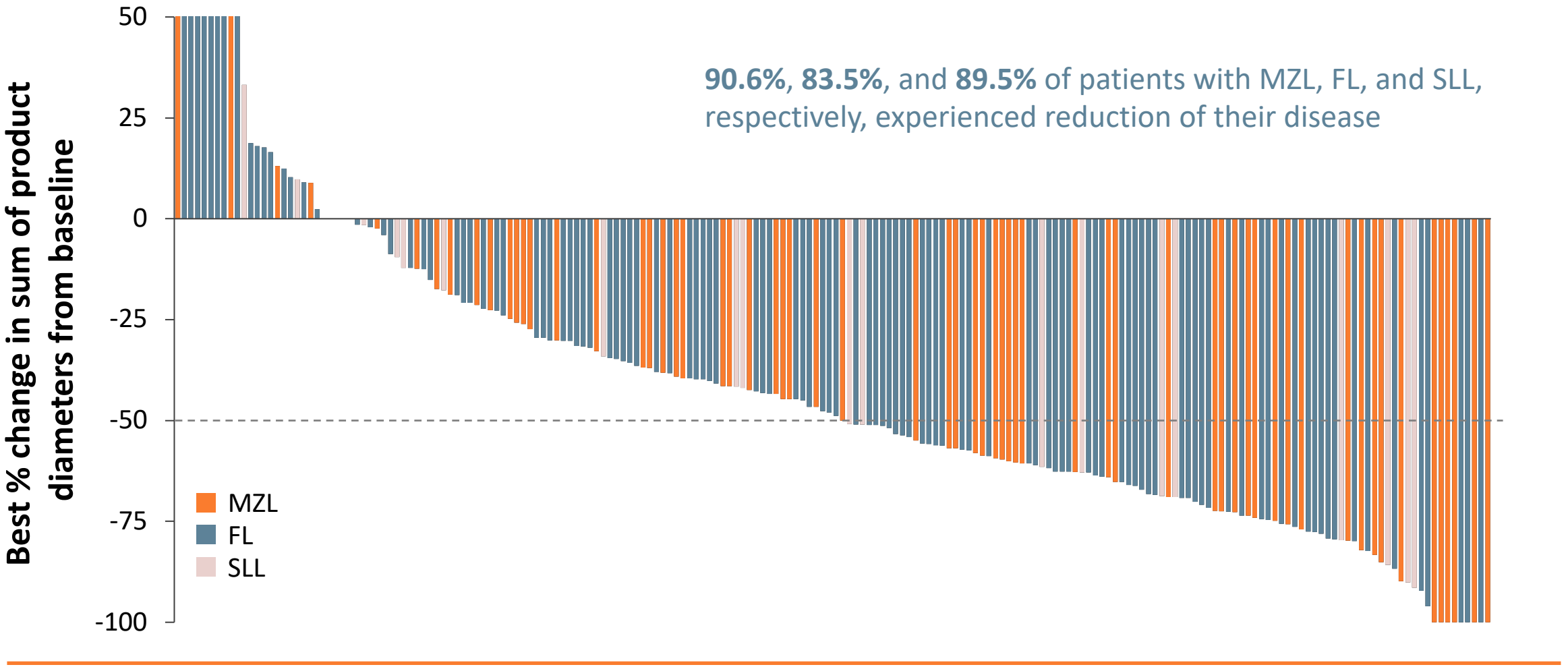
Cohort	DCR, %	Median TTR, months	Median follow-up, months
MZL	82.6	2.8	27.8
FL	79.5	4.6	27.5
SLL	86.4	2.7	29.3

Across entire indolent NHL population (n=208) umbralisib produced a **47.1%** ORR and **81.3%** DCR

CR, complete response; DCR, disease control rate (CR + PR + SD); FL, follicular lymphoma; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; PR, partial response; SD, stable disease; SLL, small lymphocytic lymphoma; TRR, time to response

Zinzani PL, et al. ASH 2020. Abstract #2934

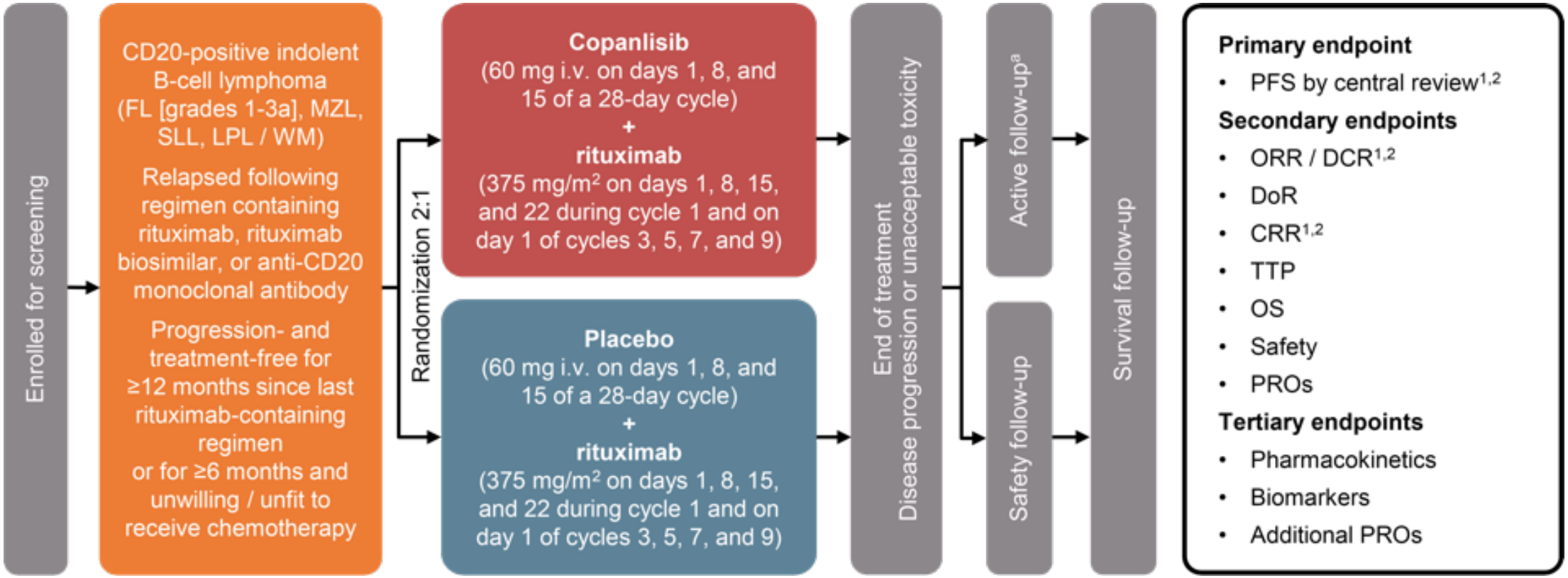
IRC-ASSESSED RESPONSE IN INDEX LESION SIZE



90.6%, **83.5%**, and **89.5%** of patients with MZL, FL, and SLL, respectively, experienced reduction of their disease

Note: Waterfall plot includes all patients with an evaluable post-baseline scan (N=198)
FL, follicular lymphoma; IRC, independent review committee; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma
Zinzani PL, et al. ASH 2020. Abstract #2934

CHRONOS-3 STUDY DESIGN



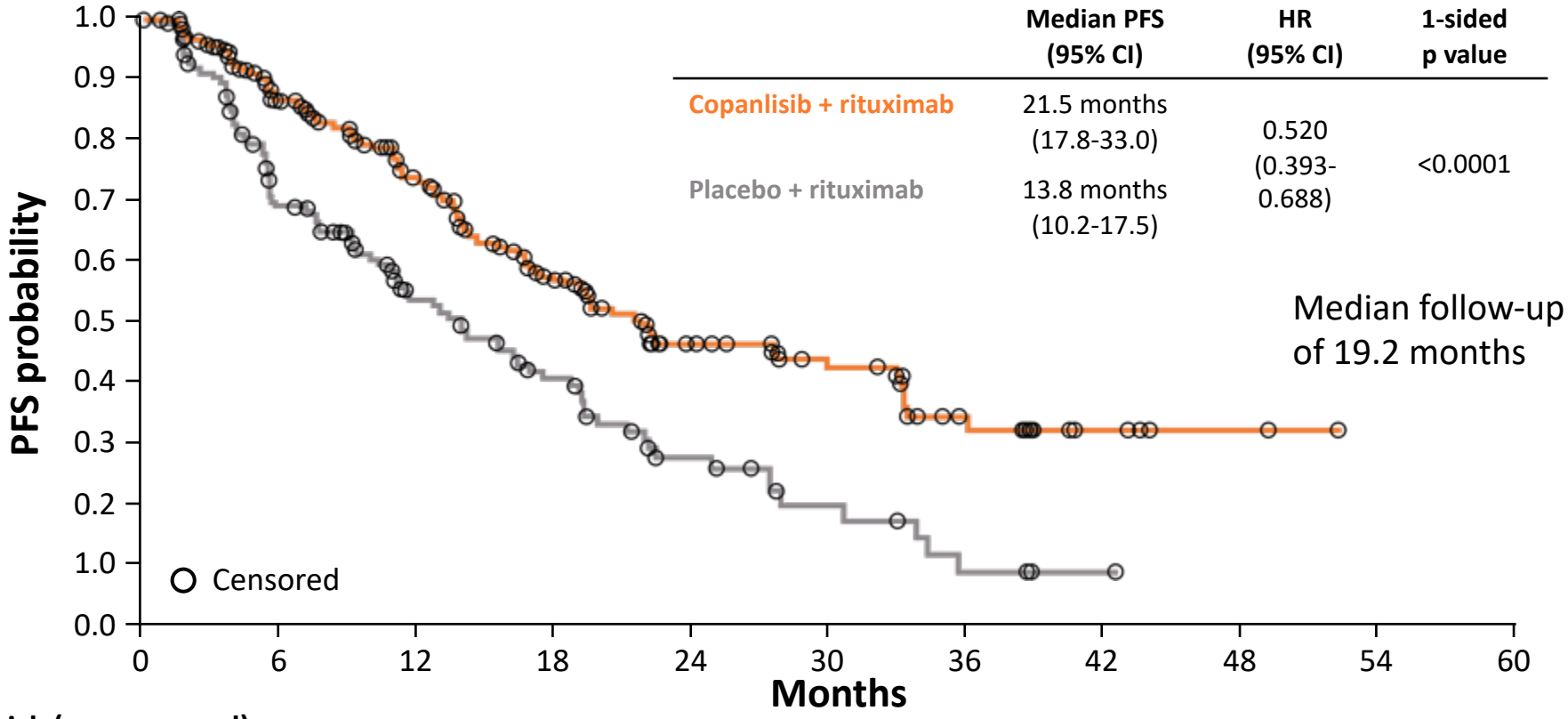
Median no. of prior treatments:[3]
1: ~50% | 2: ~25% | ≥3: ~25%

[a] Patients who discontinued treatment for any reason other than progressive disease entered active follow-up

CRR, complete response rate; DCR, disease control rate; DoR, duration of response; LPL/WM, lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia; MZL, marginal zone lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; SLL, small lymphoplasmacytic lymphoma; TTP, time to progression

1. Cheson BD, et al. J Clin Oncol. 2007;25:579-86; 2. Owen RG, et al. Br J Haematol; 2013;160:171-6; 3. Matasar MJ, et al. Lancet Oncol. 2021:S1470-2045(21)00145-5

CHRONOS-3 PRIMARY ENDPOINT: PFS IN ALL PATIENTS WITH INDOLENT NHL



	Median PFS (95% CI)	HR (95% CI)	1-sided p value
Copanlisib + rituximab	21.5 months (17.8-33.0)	0.520 (0.393-0.688)	<0.0001
Placebo + rituximab	13.8 months (10.2-17.5)		

Median follow-up of 19.2 months

No. of patients at risk (no. censored)

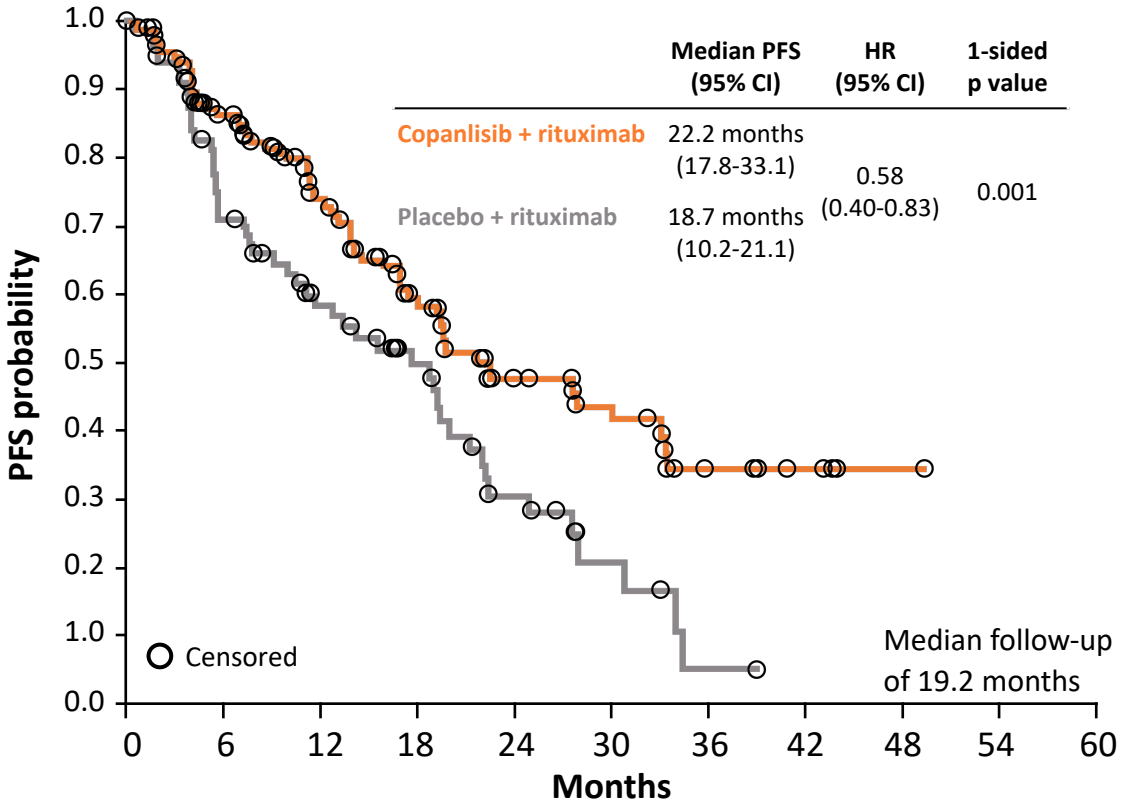
Copanlisib + rituximab	307 (0)	204 (67)	146 (97)	88 (125)	49 (149)	31 (164)	15 (175)	6 (183)	2 (187)	0 (189)	0 (189)
Placebo + rituximab	151 (0)	85 (25)	53 (41)	33 (49)	16 (56)	8 (60)	3 (61)	1 (63)	0 (64)	0 (64)	0 (64)

CI, confidence interval; HR, hazard ratio; NHL, non-Hodgkin's lymphoma; PFS, progression-free survival

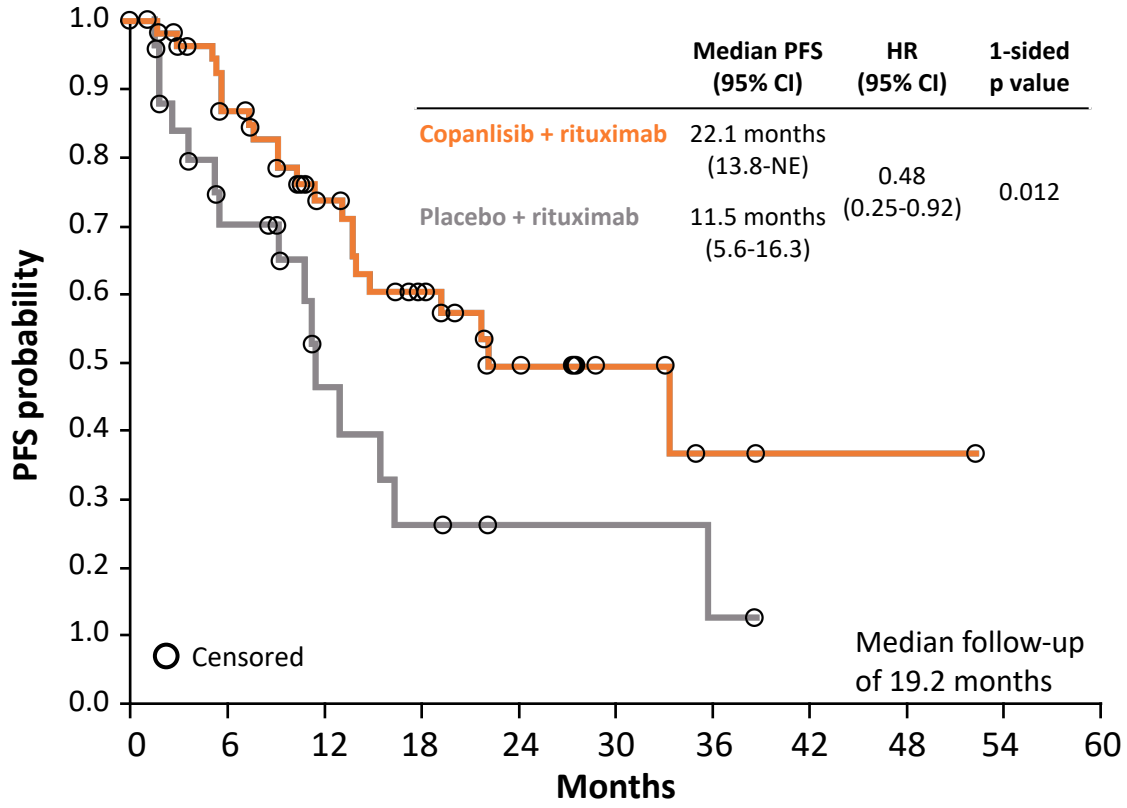
Matasar MJ, et al. Lancet Oncol. 2021:S1470-2045(21)00145-5

CHRONOS-3
PFS IN SUBGROUPS

PFS in patients with FL



PFS in patients with MZL



No. of patients at risk (no. censored)

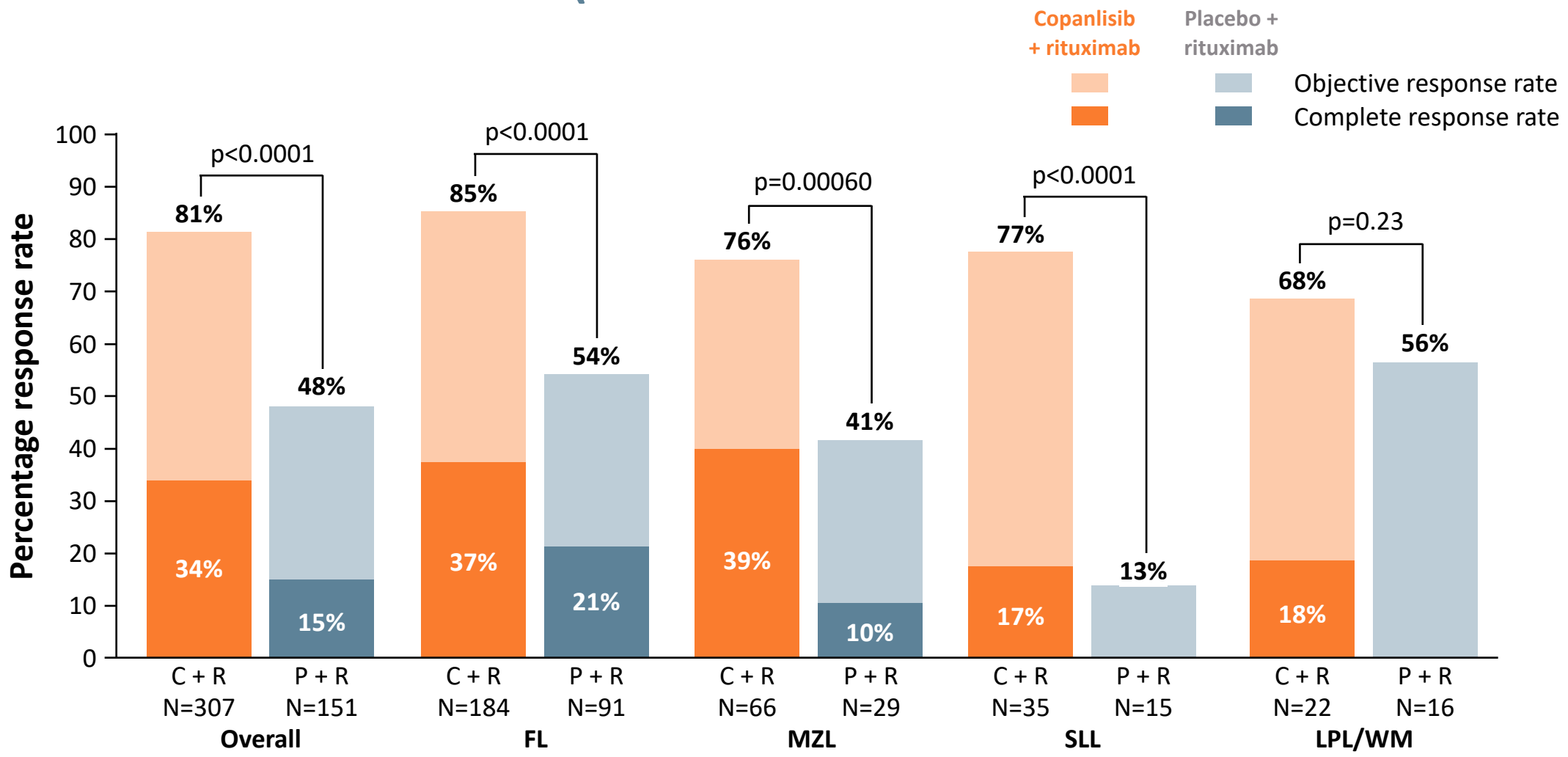
Copanlisib + rituximab	184 (0)	121 (40)	87 (59)	53 (77)	30 (91)	20 (98)	9 (106)	4 (111)	1 (114)	0 (115)	0 (115)
Placebo + rituximab	91 (0)	56 (12)	37 (22)	25 (29)	12 (33)	5 (37)	1 (38)	0 (39)	0 (39)	0 (39)	0 (39)

Copanlisib + rituximab	66 (0)	44 (15)	29 (24)	20 (28)	10 (35)	5 (40)	2 (42)	1 (43)	1 (43)	0 (44)	0 (44)
Placebo + rituximab	29 (0)	15 (7)	7 (11)	4 (11)	2 (13)	2 (13)	1 (13)	0 (14)	0 (14)	0 (14)	0 (14)

CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; PFS, progression-free survival

Matasar MJ, et al. Lancet Oncol. 2021:S1470-2045(21)00145-5

CHRONOS-3
OBJECTIVE RESPONSE RATE (INDEPENDENT REVIEW)



C, copanlisib; FL, follicular lymphoma; LPL/WM, lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia; MZL, marginal zone lymphoma; P, placebo; R, rituximab; SLL, small lymphocytic lymphoma

Matasar MJ, et al. Lancet Oncol. 2021:S1470-2045(21)00145-5

CHRONOS-3 - TREATMENT-EMERGENT AEs LEADING TO DISCONTINUATION

Treatment-emergent adverse event (TEAEs) leading to discontinuation, n (%) [a]	Copanlisib + rituximab (N=307)			Placebo + rituximab (N=146)		
	All grades	Grades 1 or 2	Grades 3 or 4	All grades	Grades 1 or 2	Grades 3 or 4
Any TEAE leading to discontinuation	96 (31.3)	37 (12.1)	56 (18.2)	12 (8.2)	3 (2.1)	8 (5.5)
MedDRA preferred term						
Pneumonitis	19 (6.2)	11. (3.6)	8 (2.6)	0	0	0
Hyperglycaemia	8 (2.6)	1 (0.3)	7 (2.3)	0	0	0
Interstitial lung disease	4 (1.3)	1 (0.3)	3 (1.0)	0	0	0
Pneumocystis jirovecii pneumonia	4 (1.3)	2 (0.7)	2 (0.7)	0	0	0
Pneumonia	4 (1.3)	0	3 (1.0)	1 (0.7)	0	1 (0.7)
Bronchitis	3 (1.0)	3 (1.0)	0	0	0	0
Cough	2 (0.7)	2 (0.7)	0	0	0	0
Hypertension	2 (0.7)	0	2 (0.7)	1 (0.7)	0	1 (0.7)
Mucosal inflammation	2 (0.7)	0	2 (0.7)	0	0	0
Pruritus	2 (0.7)	2 (0.7)	0	0	0	0
Respiratory failure	2 (0.7)	0	2 (0.7)	0	0	0
Dyspnoea	0	0	0	2 (1.4)	1 (0.7)	1 (0.7)
Investigations	13 (4.2)	8 (2.6)	5 (1.6)	2 (1.4)	0	2 (1.4)
Hyponatraemia	3 (1.0)	1 (0.3)	2 (0.7)	0	0	0
Increased amylase	3 (1.0)	1 (0.3)	2 (0.7)	0	0	0
Increased lipase	3 (1.0)	0	3 (1.0)	0	0	0
Increased hepatitis B DNA	2 (0.7)	2 (0.7)	0	0	0	0
Increased ALT	2 (0.7)	0	2 (0.7)	0	0	0
Increased AST	2 (0.7)	0	2 (0.7)	0	0	0
Decreased weight	2 (0.7)	2 (0.7)	0	0	0	0
Increased blood creatinine phosphokinase	0	0	0	2 (1.4)	0	2 (1.4)

[a] Includes events occurring in ≥2 patients in either treatment arm

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities

Matasar MJ, et al. Lancet Oncol. 2021:S1470-2045(21)00145-5

ZUMA-5
STUDY DESIGN

Multicentre, single-arm phase 2 trial

Patients with R/R FL (Grade 1-3a) or MZL (nodal or extranodal), ≥2 prior lines of therapy including anti-CD20 monoclonal antibody (mAb) + alkylating agent (N=146)

Conditioning chemotherapy

Fludarabine 30 mg/m^2 + **Cyclophosphamide** 500 mg/m^2 Days -5, -4, -3

CAR-T Cells

Axi-Cel 2 × 10^6 cells/kg Day 0

Followed for safety up to 15 years

Patients with SD but no relapse >1 year from completion of last therapy ineligible. Single-agent anti-CD20 mAb not counted as line of therapy for eligibility. Median time to delivery of axi-cel: 17 days following leukapheresis.

- **Primary endpoint:** Objective response rate (IRRC-assessed per Lugano classification)
- **Key secondary endpoints:** CR rate (IRRC-assessed), DoR, PFS, OS, AEs, CAR T cell, and cytokine levels

AE, adverse event; Axi-Cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T cell; CR, complete response; DoR, duration of response; FL, follicular lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; OS, overall survival; R/R, relapsed/refractory; SD, stable disease

Jacobson C. ASH 2020. Abstract #700. NCT03105336

ZUMA-5
BASELINE PATIENT CHARACTERISTICS

Characteristic	Axi-Cel		
	FL (n=124)	MZL (n=22)	Overall (N=146)
Median age, years (range)	60 (34-79)	66 (48-77)	61 (34-79)
• ≥ 65 years, n (%)	38 (31)	13 (59)	51 (35)
Male, n (%)	73 (59)	10 (45)	83 (57)
ECOG PS 1, n (%)	46 (37)	9 (41)	55 (38)
Stage III/IV disease, n (%)	106 (85)	20 (91)	126 (86)
≥3 FLIPI, n (%)	54 (44)	14 (64)	68 (47)
High tumour bulk by GELF, n (%)[a]	64 (52)	8 (36)	72 (49)

* Involvement of ≥3 nodal sites (≥3 cm each); any nodal or extranodal tumour mass ≥7 cm; B symptoms; splenomegaly; pleural effusions or peritoneal ascites; cytopenias; or leukaemia

Characteristic	Axi-Cel		
	FL (n=124)	MZL (n=22)	Overall (N=146)
Median prior tx, n (range)	3 (1-10)[a]	3 (2-8)	3 (1-10)
• ≥3	78 (63)	15 (68)	93 (64)
• PI3K inhibitor	34 (27)	9 (41)	43 (29)
Refractory disease, n (%)[b]	84 (68)	16 (73)	100 (68)
POD24 from first anti-CD20 mAb tx, n (%)[c]	68 (55)	11 (52)	79 (55)
Prior ASCT, n (%)	30 (24)	3 (14)	33 (23)

[a] n=3 with 1 prior line of therapy before protocol amendment requiring ≥2. [b] PD within 6 months of most recent prior tx. [c] 24 months from start of first anti-CD20–containing immunochemotherapy to progression; % based on patients ever receiving this therapy.

ASCT, autologous stem cell transplantation; Axi-Cel, axicabtagene ciloleucel; CD20, cluster of differentiation 20; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, *Groupe d'Etude des Lymphomes Folliculaires*; mAb, monoclonal antibody; MZL; marginal zone lymphoma; PD, progressive disease; PI3K, phosphoinositide 3-kinase; POD24, progression of disease within 24 months; tx, treatment

Jacobson C. ASH 2020. Abstract #700

ZUMA-5
IRRC-ASSESSED OBJECTIVE RESPONSE RATE

IRRC-assessed response, n (%) [a,b]	Axi-Cel		
	FL (n=84)	MZL (n=20)	Overall (N=104)
ORR	79 (94)	17 (85)	96 (92)
CR	67 (80)	12 (60)	79 (76)
PR	12 (14)	5 (25)	17 (16)
SD	3 (4)	0	3 (3)
ND	2 (2)	3 (15)	5 (5)

[a] For investigator-assessed response (N=104): ORR, 95%; CR rate, 77%.
[b] n=4 (1 FL, 3 MZL) had no disease at or post baseline per IRRC but were considered to have disease by investigator; n=1 FL patient died before initial disease assessment

- Median **time to first response:** 1.0 months (range: 0.8-3.1)
- 13/25 (52%) FL patients with **initial PR converted to CR** after median 2.2 months (range: 1.9-11.2)
- **ORR was consistent across all subgroups** analysed including by FLIPI score, high tumour burden, and previous treatment

Axi-Cel, axicabtagene ciloleucel; BL, baseline; CR, complete response; FL, follicular lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; ND, undefined/not done; ORR, objective response rate; PR, partial response; SD, stable disease
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ZUMA-5
DURATION OF RESPONSE

DoR	FL (n=84)	MZL (n=20)	Overall (N=104)
Median follow-up, months (range)	18.5 (12.2-31.6)	12.1 (1.4-26.8)	17.5 (1.4-31.6)
Median DoR, months (95% CI)	NE (20.8-NE)	10.6 (8.1-NE)	NE (20.8-NE)
12-month DoR rate, % (95% CI)	77.0 (65.6-85.1)	NE (NE-NE)	71.7 (60.7-80.1)
Ongoing response at cut-off, %	64[a]	50	NR

[a] 78% in subset with CR; 17% in subset with PR

DoR by best response (95% CI)	FL		MZL	
	CR (n=67)	PR (n=12)	CR (n=12)	PR (n=5)
Median DoR, months	NE (20.8-NE)	2.8 (2.1-8.2)	10.6 (3.1-NE)	8.1 (NE-NE)
12-month DoR rate, %	87.0 (75.6-93.3)	13.6 (1.0-42.6)	NE (NE-NE)	0 (NE-NE)

CI, confidence interval; CR, complete response; DoR, duration of response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; PR, partial response

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ZUMA-5 SURVIVAL

Outcome (95% CI)	FL (n=84)	MZL (n=20)	Overall (N=104)
Median PFS, months	NE (23.5-NE)	11.8 (9.1-NE)	NE (23.5-NE)
12-month PFS rate, %	77.5 (66.6-85.2)	45.1 (15.2-71.4)	73.7 (63.3-81.6)
Median OS, months	NE (NE-NE)	NE (NE-NE)	NE (NE-NE)
12-month OS rate, %	92.8 (84.7-96.7)	92.9 (59.1-99.0)	92.9 (85.6-96.5)

CI, confidence interval; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; OS, overall survival; PFS, progression-free survival

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ZUMA-5
CYTOKINE-RELEASE SYNDROME

Parameter	FL (n=124)	MZL (n=22)	Overall (N=146)
Cytokine-release syndrome (CRS), n (%)			
• Any grade	97 (78)	22 (100)	119 (82)
• Grade ≥3	8 (6)	2 (9)	10 (7)a
Most common any-grade symptoms, n/N (%)			
• Pyrexia	94/97 (97)	20/22 (91)	114/119 (96)
• Hypotension	39/97 (40)	10/22 (45)	49/119 (41)
AE management, n (%)			
• Tocilizumab	56 (45)	15 (68)	71 (49)
• Corticosteroids	19 (15)	6 (27)	25 (17)
Median time to onset, days (range)	4 (1-15)	4 (1-9)	4 (1-15)
Median duration of events, days (range)	6 (1-27)	6 (2-14)	6 (1-27)
Patients with resolved events, n/N (%)	96/97 (99)[b]	22/22 (100)	118/119 (99)

No ongoing events at data cut-off.
[a] Grade 4/5, n=1 each. [b] n=1 death on Day 7 due to multisystem organ failure with CRS before CRS resolution

AE, adverse event; FL, follicular lymphoma; MZL, marginal zone lymphoma
Jacobson C. ASH 2020. Abstract #700

ZUMA-5
NEUROLOGIC EVENTS

Parameter	FL (n=124)	MZL (n=22)	Overall (N=146)
Neurologic events, n (%)			
• Any grade	70 (56)	17 (77)	87 (60)
• Grade ≥3	19 (15)	9 (41)	28 (19)[a]
Most common any-grade symptoms, n/N (%)			
• Tremor	36/70 (51)	9/17 (53)	45/87 (52)
• Confusional state	28/70 (40)	7/17 (41)	35/87 (40)
AE management, n (%)			
• Corticosteroids	38 (31)	14 (64)	52 (36)
• Tocilizumab	7 (6)	2 (9)	9 (6)
Median time to onset, days (range)	7 (1-177)	7 (3-19)	7 (1-177)
Median duration of events, days (range)	14 (1-452)	10 (2-81)	14 (1-452)
Patients with resolved events, n/N (%)	67/70 (96)	14/17 (82)	81/87 (93)

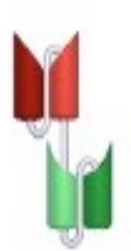
Ongoing events at data cut-off: Grade 1 memory impairment (n=2) and attention disturbance, intermittent paresthesia, and tremor (n=1 each); Grade 2 facial paresthesia (n=1).
[a] Grade 4, n=3; no Grade 5 events

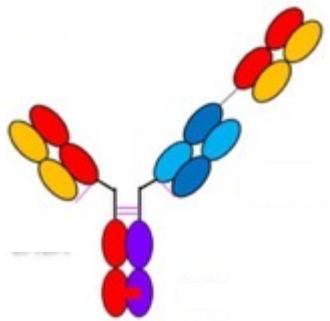
FL, follicular lymphoma; MZL, marginal zone lymphoma
Jacobson C. ASH 2020. Abstract #700

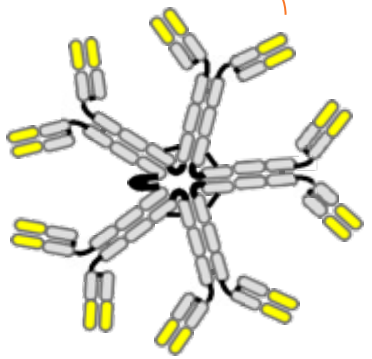
BISPECIFIC ANTIBODIES IN B-NHL UNDER DEVELOPMENT

CD19

CD20







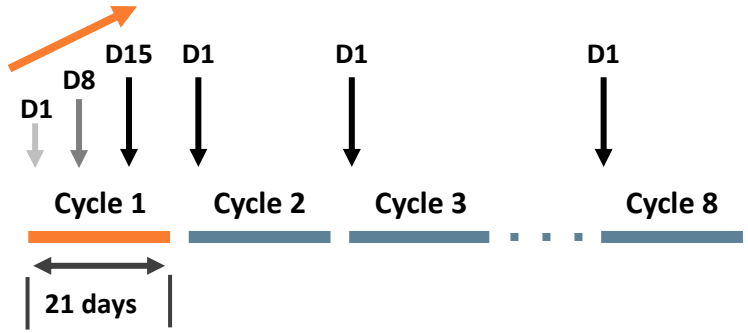
BITE® (1:1)	Full-length IgG (1:1)	Full-length IgG (2:1)	IgM (10:1)
Blinatumomab	Mosunetuzumab Odronextamab Epcoritamab	Glofitamab	IgM2323

CD, cluster of differentiation; Ig, immunoglobulin; NHL, non-Hodgkin's lymphoma

MOSUNETUZUMAB SHOWS PROMISING EFFICACY IN PATIENTS WITH MULTIPLY RELAPSED FL

UPDATED CLINICAL EXPERIENCE FROM A PHASE 1 DOSE-ESCALATION TRIAL

Cycle 1 D1/D8/D15 dose:
0.4/1.0/2.8–1/2/13.5 mg



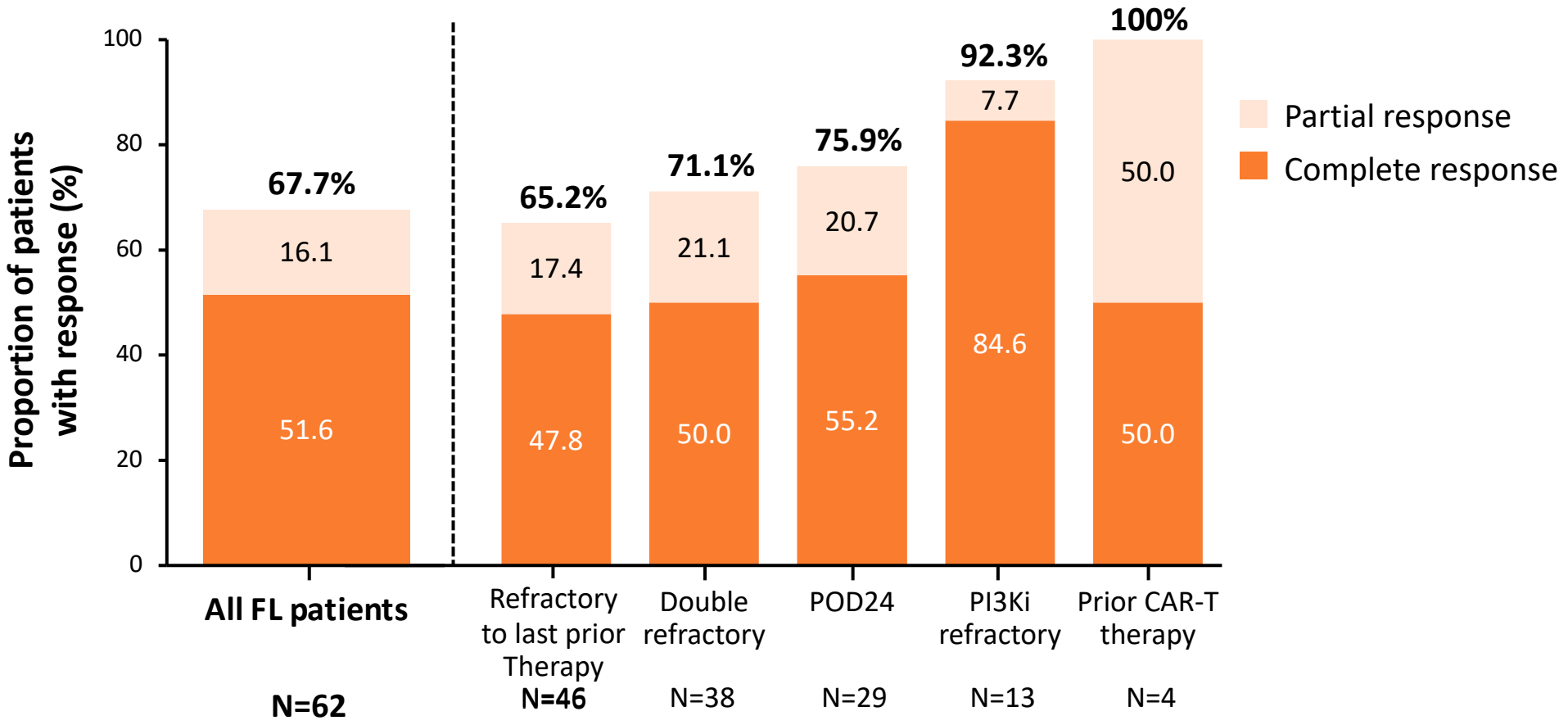
Key inclusion criteria (FL cohort)

- R/R FL (Grades 1-3a; expected to express CD20)
- ≥2 prior systemic therapies
- Age ≥18 years
- ECOG PS ≤1

CD20, cluster of differentiation 20; D, Day; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; R/R, relapsed/refractory

Assouline S, et al. ASH 2020. Abstract #702

MOSUNETUZUMAB RESPONSE RATES (INVESTIGATOR-ASSESSED) IN PATIENTS WITH R/R FL



High and consistent complete response rates were observed in high-risk populations, including those with double-refractory disease, POD24, PI3Ki refractory, and those who received prior CAR-T therapy

CAR-T, chimeric antigen receptor T cell; FL, follicular lymphoma; PI3Ki, phosphoinositide 3-kinase inhibitor; POD24, progression of disease within 2 years; R/R, relapsed/refractory

Assouline S, et al. ASH 2020. Abstract #702

ANTI-CD20 BISPECIFIC ANTIBODIES SHOW ENCOURAGING RESULTS IN R/R FL

Study	Route	ORR	CR	Follow-up & DoR	Toxicities
Mosunetuzumab 0.4/1/2.8 -1/2/13.5 mg *Assouline et al*[1]	IV; Q21 days (C1: D1,8,15) If CR: up to 8 cycles If SD/PR: 17 cycles (N=62)	67.7%	51.6%	Follow-up 18.4 months, DoR 20.4 months (9.4-22.7)	CRS: 17.7 % (0 grade ≥3) ICANS: 0
Odronextamab 80-320mg *Bannerji et al*[2]	IV; Q7 days x 12 ➔ Q14 days (N=38)	90%[a]	70%	Follow-up 21 months, 81% of CR ongoing	CRS: 65.8 % (2.6% grade ≥3) ICANS: 0
Glofitamab 2.5/10/16-30 mg *Hutchings et al*[3]	Obinutuzumab x1 on day -7 IV; Q21 days x 12 (C1: D1,8) (N=24)	66.7%	54.2%	PFS: 11.8 months	CRS: 63.5% (3.8% grade ≥3) ICANS: 3.5% (1.2% grade ≥3)
Epcoritamab 0.76-48 mg *Hutchings et al*[4]	SC; C1-2: Q1W ➔ C3-6: Q2W ➔ Q4W (N=12)	80-90%	50-60%	CR (5): 1 PD PR (4): 3 PD at 28 weeks	CRS: 58% (0 grade ≥3) ICANS: 0

[a] Objective response rate

Ab, antibody; C, cycle; CD20, cluster of differentiation 20; CR, complete response; D, day; DoR, duration of response; CRS, cytokine release syndrome; FL, follicular lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; Q, every; R/R, relapsed/refractory; SC, subcutaneous; W, week

Assouline S, et al. ASH 2020. Abstract #702; Bannerji R, et al. ASH 2020. Abstract #400; Hutchings M, et al. ASH 2020. Abstract #403; Hutchings M, et al. ASH 2020. Abstract #402

TAKE-HOME MESSAGES FOR FL

Non-chemotherapy options increasing!

- Lenalidomide-obinutuzumab promising in 1st line; needs broader study
- Multiple novel therapies coming in R/R FL

Non-chemotherapy options should be considered for early progressing (POD24) patients with FL early on

Newly approved therapies include EZH2 (tazametostat) and dual PI3K/CK inhibitors (umbralisib)

Copanlisib + rituximab leads to improved PFS vs rituximab alone

CAR-T cells are a highly active modality that recently received approval in the US

Bispecific antibodies show promising activity in FL

CAR, chimeric antigen receptor; EZH2, enhancer of zeste homologue 2; FL, follicular lymphoma; PI3K, phosphoinositide 3-kinase; POD24, progression of disease within 2 years; PFS, progression-free survival; R/R, relapsed/refractory

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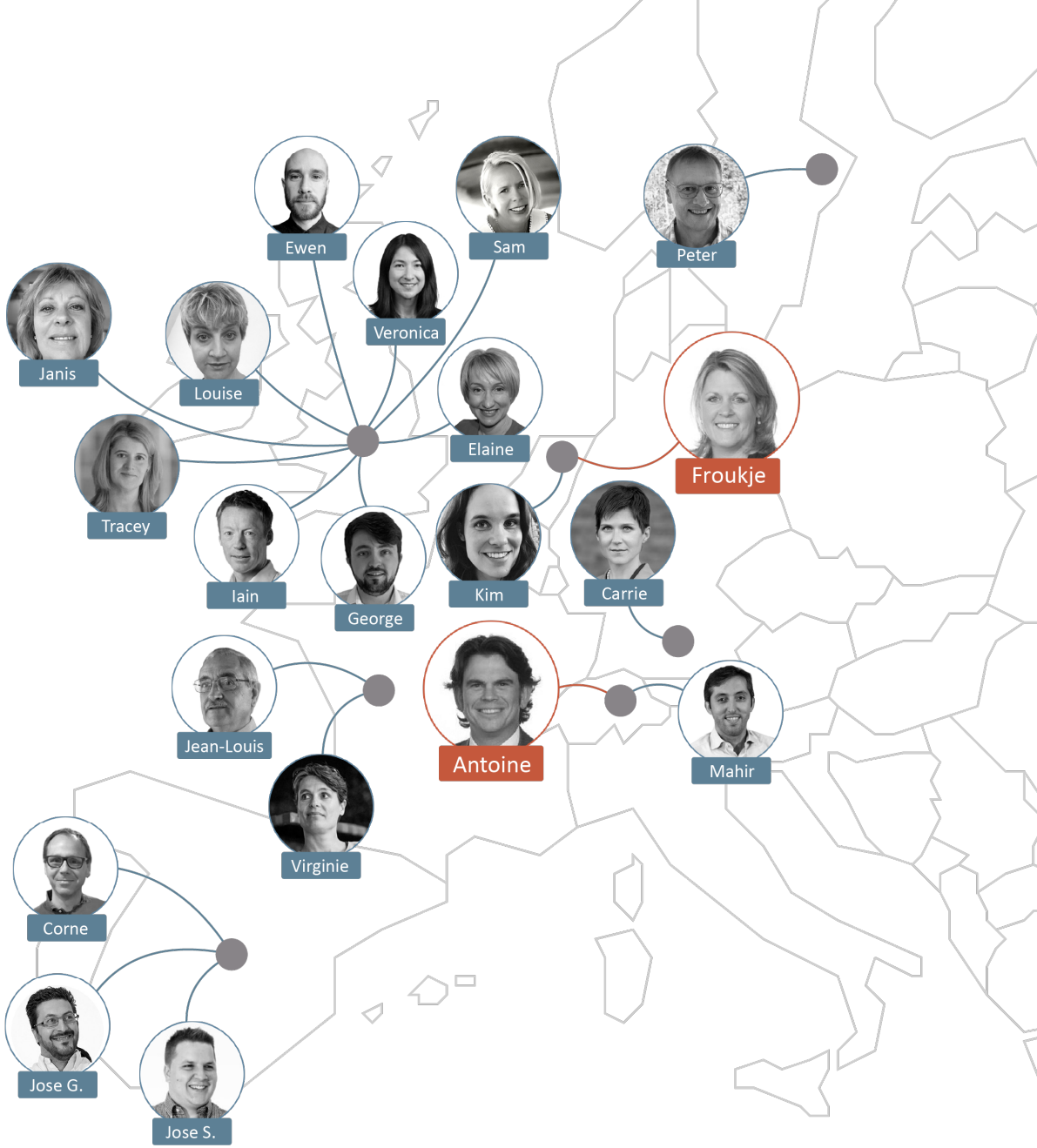

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