2022 Review of Follicular Lymphoma

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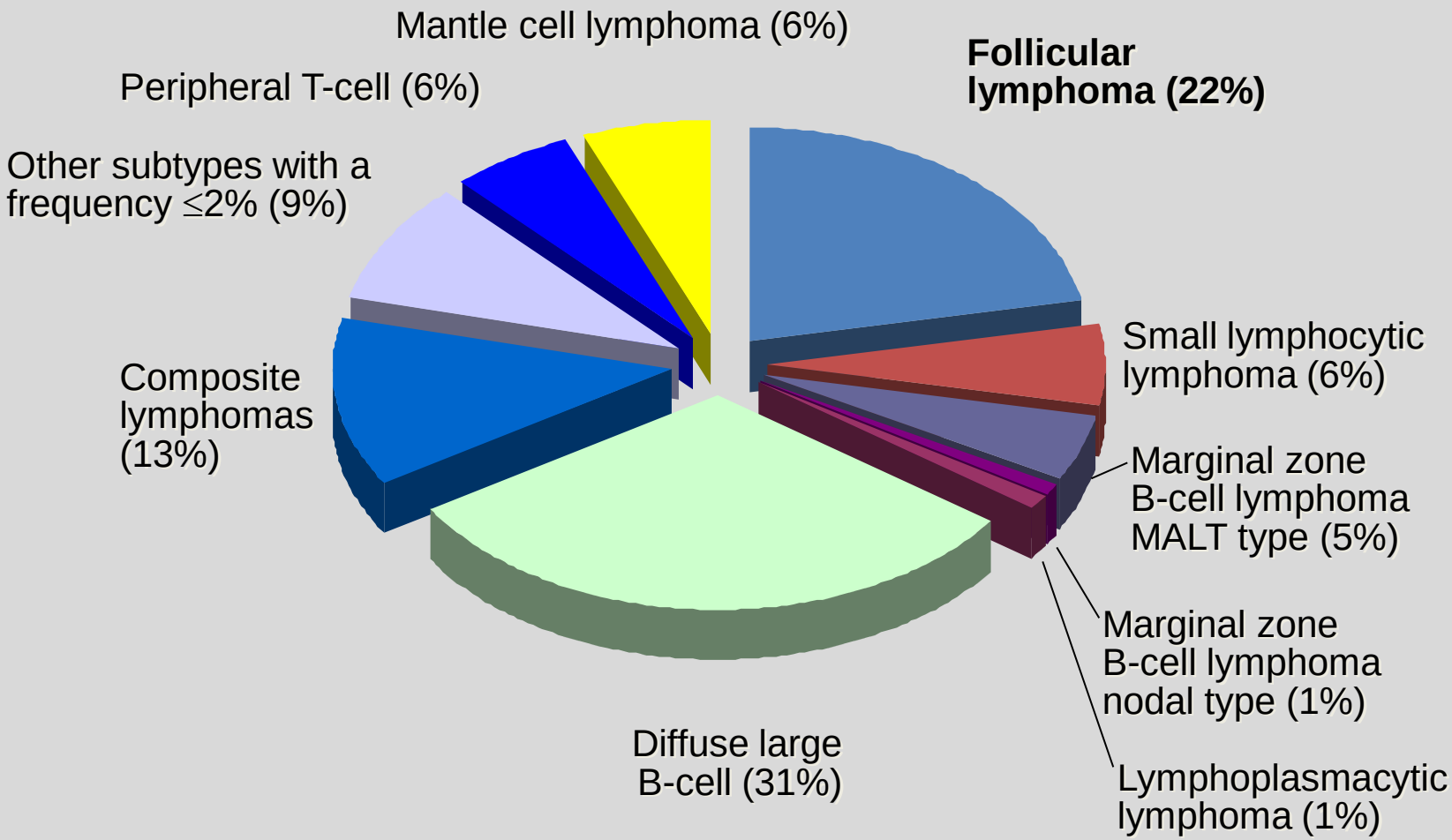
Objectives

- Overview of Follicular Lymphoma
- Frontline options
  - Does initial regimen matter
  - Grade 3a?
  - O vs. R
  - Prognostic Scoring
- POD24
- Transplant?
- R/R Follicular Lymphoma options
  - Lenalidomide
  - Copanlisb
  - Tazemetostat
  - CAR-T
- Future options

Frequency of NHL Subtypes in Adults



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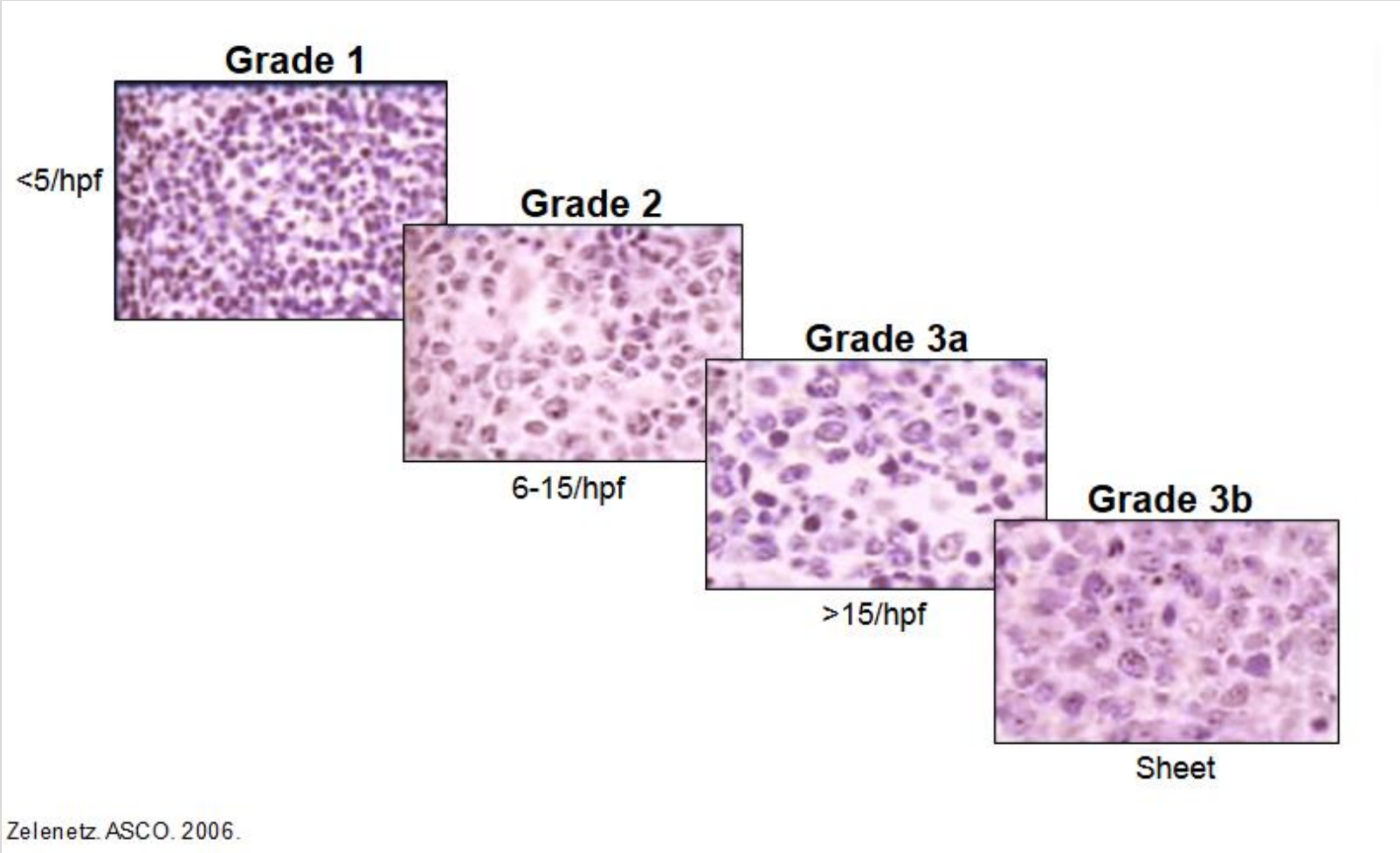
- Follicular lymphoma is the most common indolent lymphoma in US and Western Europe accounting for approximately 22% of all cases of Non-Hodgkin Lymphoma
- Currently the disease is incurable with variable patient disease course and outcomes
- Several viable frontline options but currently no clear standard of care.
  - Diminishing returns with successive cycles of therapy
  - Worse outcomes in patients who relapse within 24 months of chemoimmunotherapy
- Novel agents have moved to the forefront of options in relapsed/refractory (R/R) disease

Background

- Follicular lymphoma is sub-divided into three grades
  - Grade 1-2
    - Difficulty separating 1 and 2. No difference in outcomes between two.
    - Less than 15 centroblasts per HPF
  - Grade 3A
    - Questions exist about the best way to manage Grade 3A given reported differences in outcomes compared to Grade 1-2
    - To date no specific recommendations exist on 1L therapy
    - More than 15 centroblasts per HPF
  - **Grade 3B**
    - **Aggressive and treated like De Novo DLBCL**
    - **Solid sheets of centroblasts**

Classification of FL



Zelenetz. ASCO. 2006.

Transformed lymphoma

- Earliest description of transformation was made in 1942 by Gall and Mallory who noted a “less differentiated appearance” of a repeat biopsy of a patient previously diagnosed with follicular lymphoma.
- The first prospective study was conducted in 1978 by Cullen and Lister[1].
- The incidence of transformation similar in most series. Approximately 3% until cap 30%.
- No clear genetic or microenvironmental driver of the transformative event has been discovered and there is not a clear consensus on the origin of the transformative cell.
- Survival outcomes reported during most early series were poor with the median survival being reported at less than 1 year[1-4].
  - Most studies report a poor prognosis after transformation with median duration of survival ranging from 2.5 months to 2 years.

1. Cullen MH et al. *Cancer.* 1979;44:645–651.
2. Bastion Y et al. *J Clin Oncol.* 1997;15:1587–1594.
3. Armitage JO et al. *Cancer Treat Rep.* 1981;65:413–418.
4. Al-Tourah AJ et al. *J Clin Oncol.* 2008 26(32):5165–5169.

Diagnosis

- In (St. Bartholomew[1]) series of 325 patients with FL transformation was solely defined by histologic diagnosis.
- In two other large series (Bastion[2] and Vancouver series[3]) transformation was defined either by histologic or clinical criteria.
  - Rapidly growing bulky disease
  - Poor performance status
  - B symptoms
  - High LDH
- The incidence of transformation from all three studies was similar
  - Confirmed that in patients who fit the above criteria, transformation is likely even if unable to be confirmed histologically.

1. Montoto S et al. *JCO. 2007*;25(17):2426-33.
2. Bastion Y et al. *J Clin Oncol.* 1997;15:1587–1594.
3. Al-Tourah AJ et al. *J Clin Oncol.* 2008 26(32):5165–5169

Drivers of Transformation

- No clear genetic or microenvironmental driver of the transformative event has been discovered. As well no clear consensus on the origin of the transformative cell.
- Studies have evaluated several biological factors
  - Loss of CD9 expression
  - Mutations in p53
  - Alterations in p16 on chromosome 9p
  - Changes in MYC expression
  - Genetic alterations involving chromosome 1p36.3
  - Tumor microenvironment
    - Decrease in numbers of regulatory T cells as determined by FOXP3 staining
    - Pattern of Treg cells within the follicle.
    - Follicular and/or peri-follicular patterns associated with increased risk of transformation
    - Low PD-1 expression associated with higher risk of transformation.

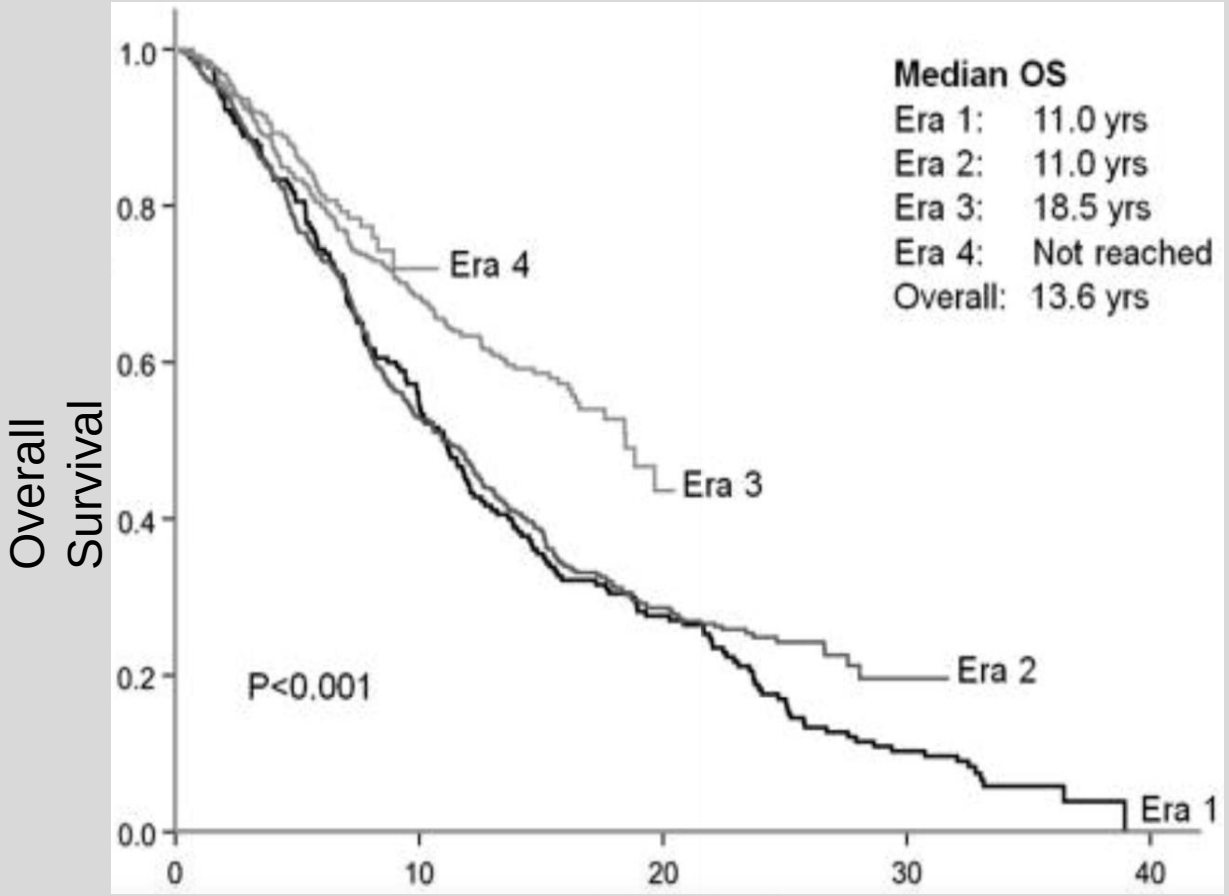
Treatments

- R-CHOP if treatment naïve or previous treatment without the use of an anthracycline
  - Treat and manage similarly to newly diagnosed DLBCL
- Consider alternative salvage regimen if prior R-CHOP or failure to achieve CR with R-CHOP
  - RICE, R-ESHAP, R-DHAP
- Consolidation with autologous stem cell transplantation if eligible
  - Most studies with small numbers with variable follow up and most of studies conducted in pre-rituximab era
  - Largest study from European Bone Marrow Transplant Registry which looked at 50 patients
    - PFS was 13 months
    - OS and PFS was 51% and 30% respectively at 5 years.

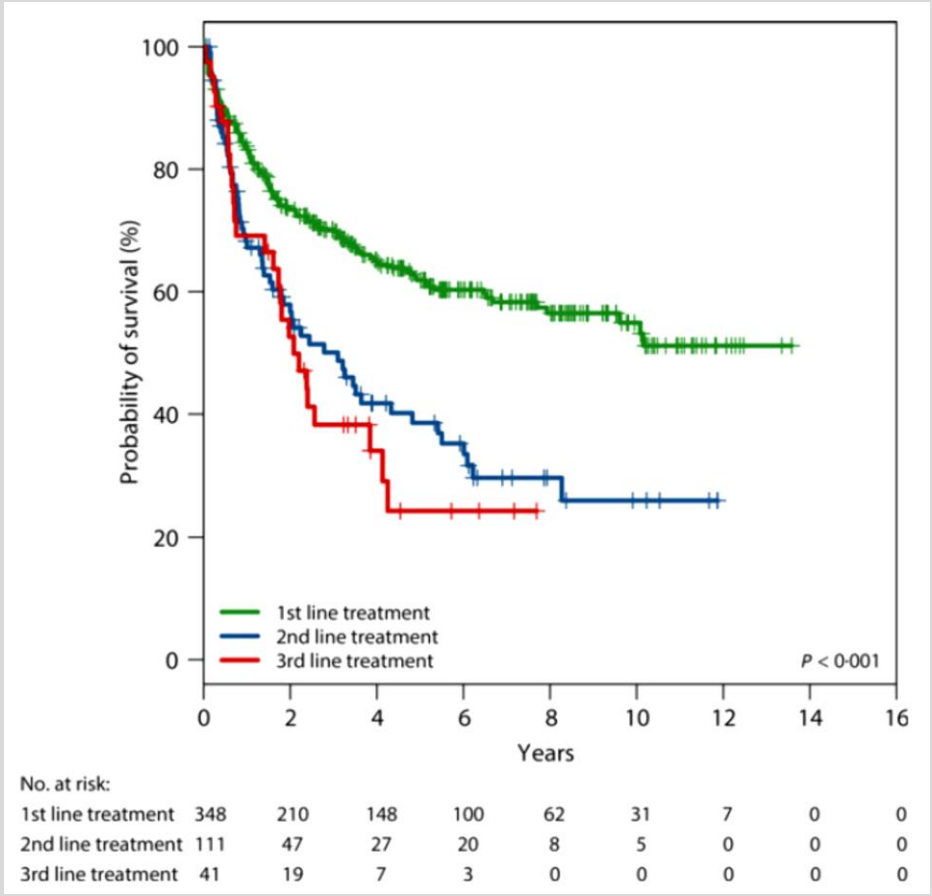
Outcomes

- Most studies report a poor prognosis after transformation with median duration of survival ranging from 2.5 months to 2 years.
  - Patients who achieve a CR after transformation have a more favorable outcome.
  - Other factors associated with improved outcome at time of transformation include
    - Limited disease
    - Good performance status
    - Normal LDH
    - Limited to no prior chemotherapy
    - History of CR to previous therapy

Treatment



Era 1: Pre-Antracycline (1960-1975) **Era 2: Antracycine. (1976-1986)**
Era 3: Agg. Chemo/Purine Analogs (1987-1996) **Era 4: Rituximab (1996-2003)**



Link et al. *BJH,* 2018; 184: 660-63
Rivas-Delgado et al. *BJH* 2018; 184: 753-59

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Frontline Regimens

- No standard frontline regimen
  - Several options including
    - Single Agent Rituximab
    - R-CVP/O-CVP
    - R-CHOP/O-CHOP
    - B-R/B-O
    - R2
  - Grade 3A??
    - Does choice of regimen matter

BR-German Study

- Randomized study comparing BR to R-CHOP
- Enrolled 549 iNHL patients
- Suggested BR should be SOC for iNHL

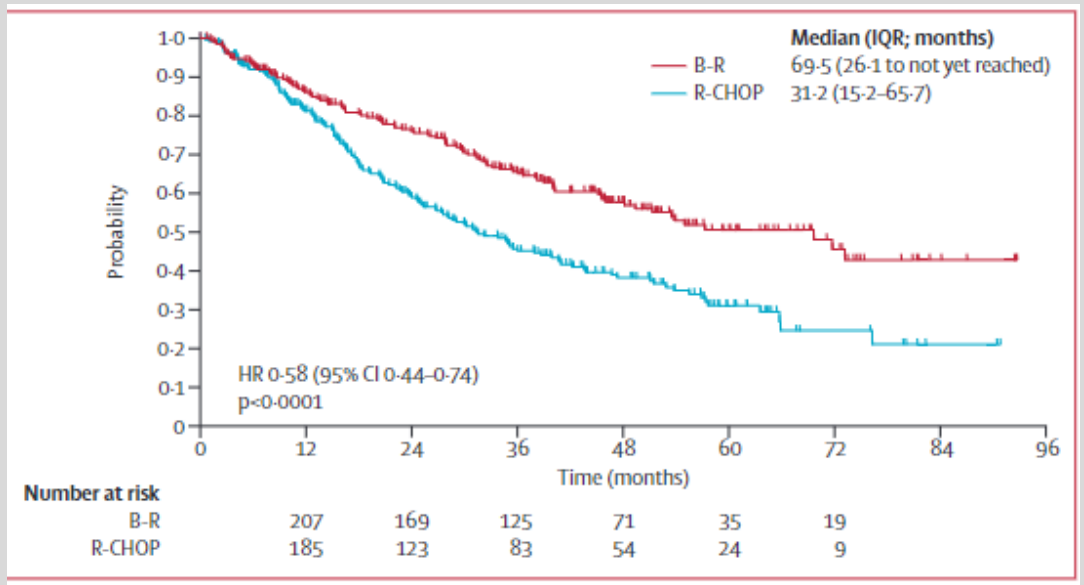

Figure 2: **Progression-free survival**
B-R–bendamustine plus rituximab. R-CHOP–CHOP plus rituximab.

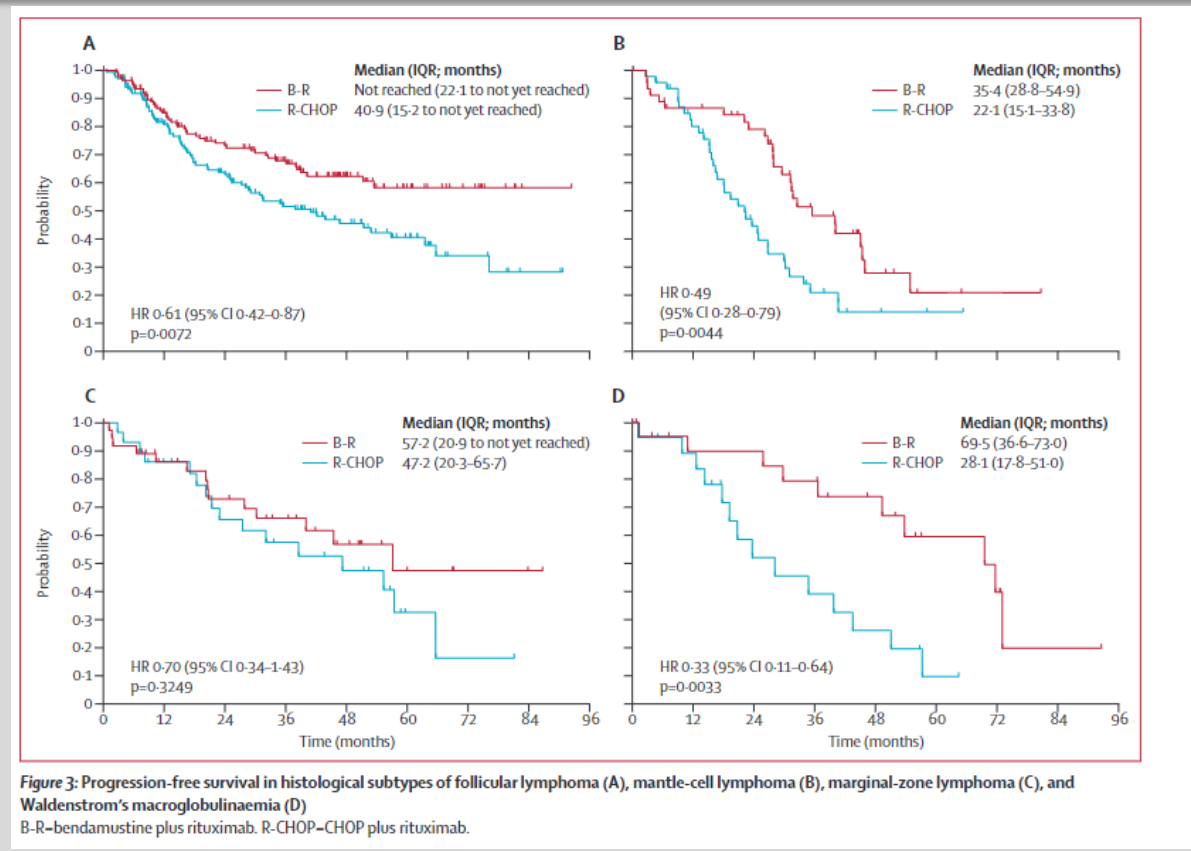

Figure 3: **Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia (D)**
B-R–bendamustine plus rituximab. R-CHOP–CHOP plus rituximab.

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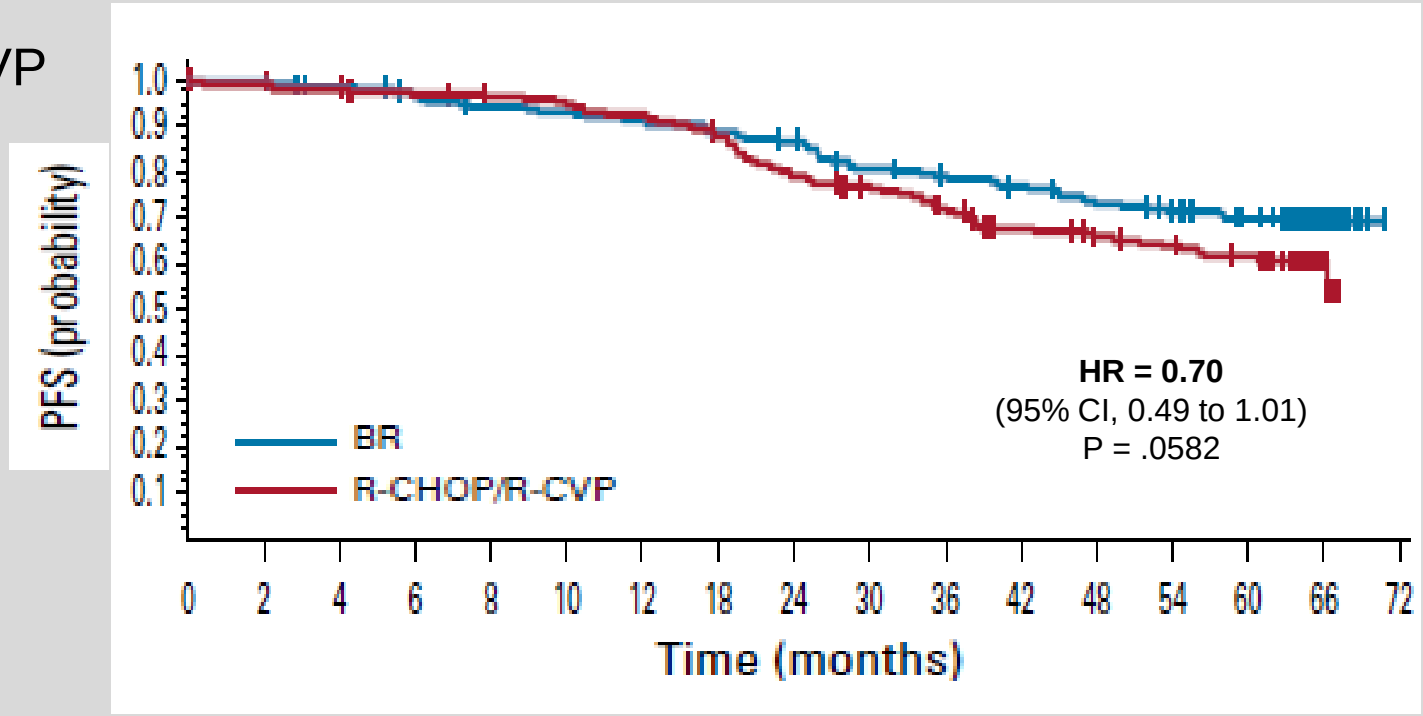
Bright Study

- US equivalent to Rummel study
- 447 iNHL patients
  - R-CVP/R-CHOP vs. BR
- Possible benefit of BR vs. R-CVP but not R-CHOP except MCL

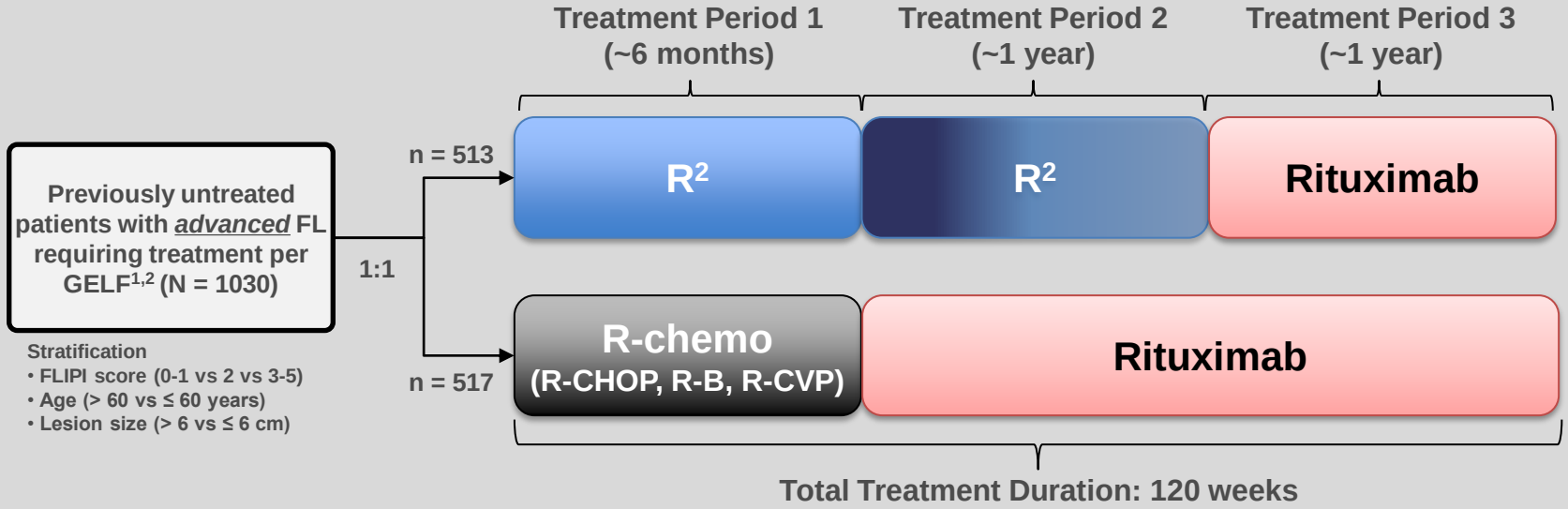
BRIGHT TRIAL:
R-CHOP/R-CVP vs. BR



Flinn et al., JCO. 2019

Relevance: Study Design

- Large Randomized Phase 3 study of R2 (lenalidomide/rituximab) vs. R-Chemo
- Hypothesis (R2 > R-Chemo)

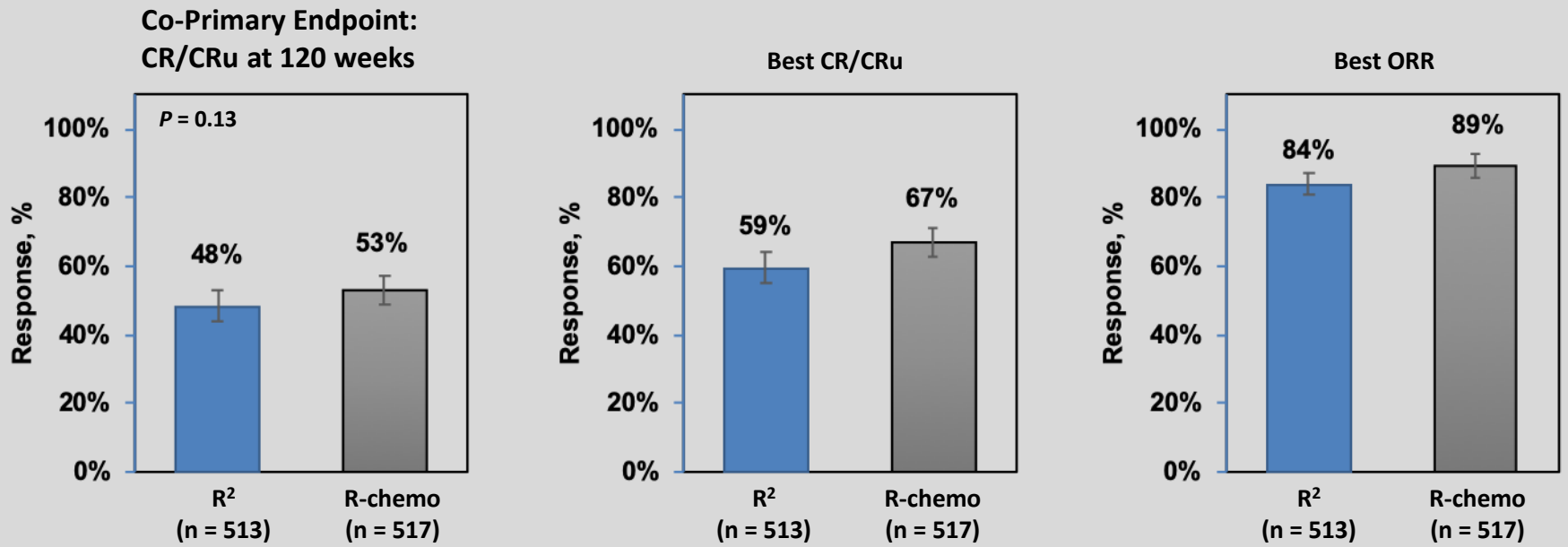


Co-primary endpoints (superiority)*

- CR/CRu at 120 weeks
- PFS

NCT01476787; NCT01650701; EUDRA 2011-002792-42. *Per central (IRC) review by 1999 IWG with CT.
1. Salles et al. *Lancet.* 2011;377:42-51. 2. Brice et al. *J Clin Oncol.* 1997;15:1110-1117.

RELEVANCE: response by IRC (ITT)



- 3-year DOR was 77% for R^2 vs 74% R-chemo (IRC)
- Investigator results were consistent with IRC

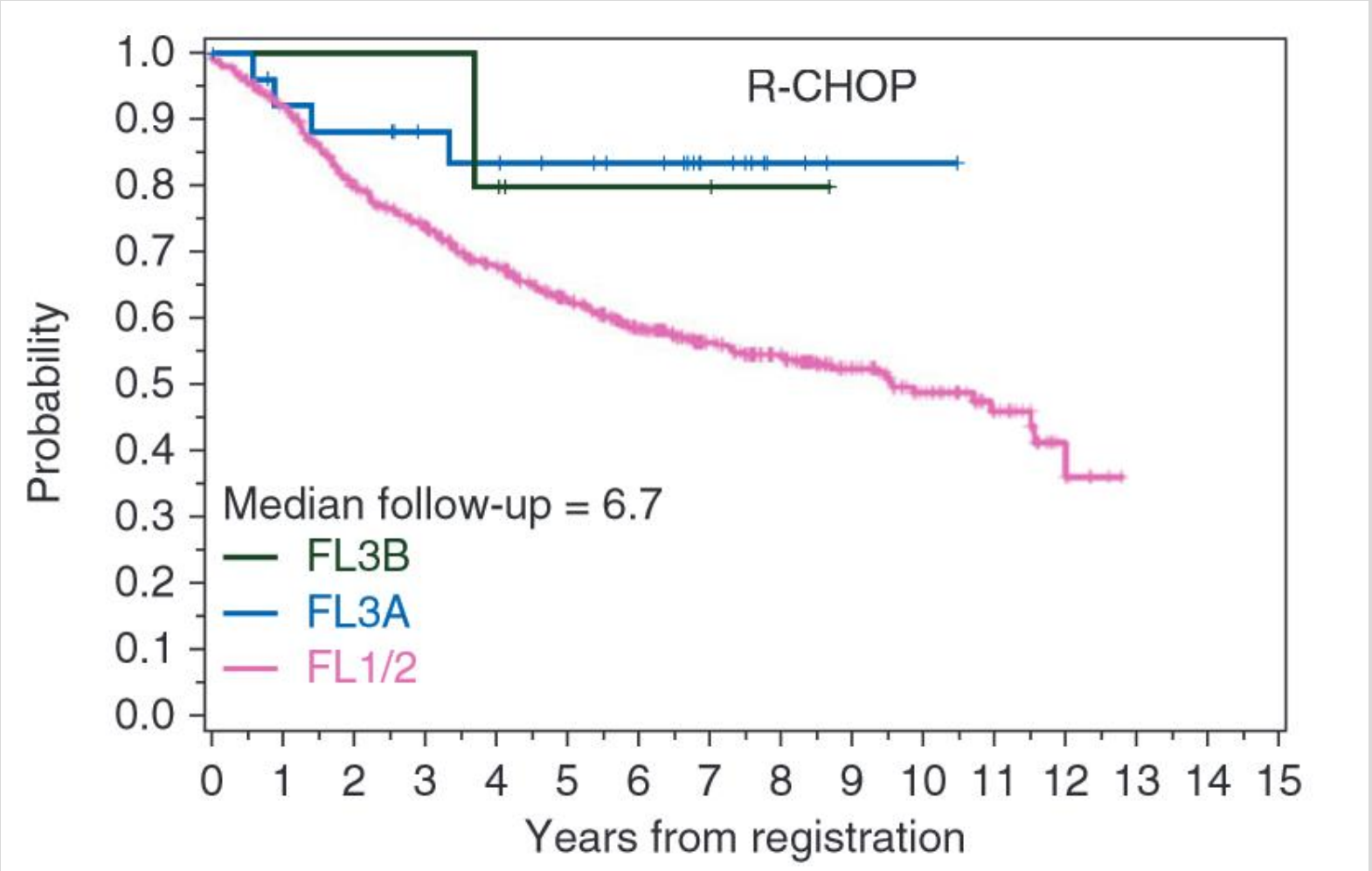
Data cut-off 31May2017.

Grade 3A

- No consensus on how to best treat grade 3A
  - Some argue that CHOP based regimens are best although to date there are no prospective randomized trials to evaluate outcomes between R-CHOP or BR.

Historical Experience with Grade 1-2 versus Grades 3A and 3B

PFS on R-CHOP Treatment by Stage



Koch *et al.*, *Annals of Oncology* 2016; 27(7): p1323

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BR???

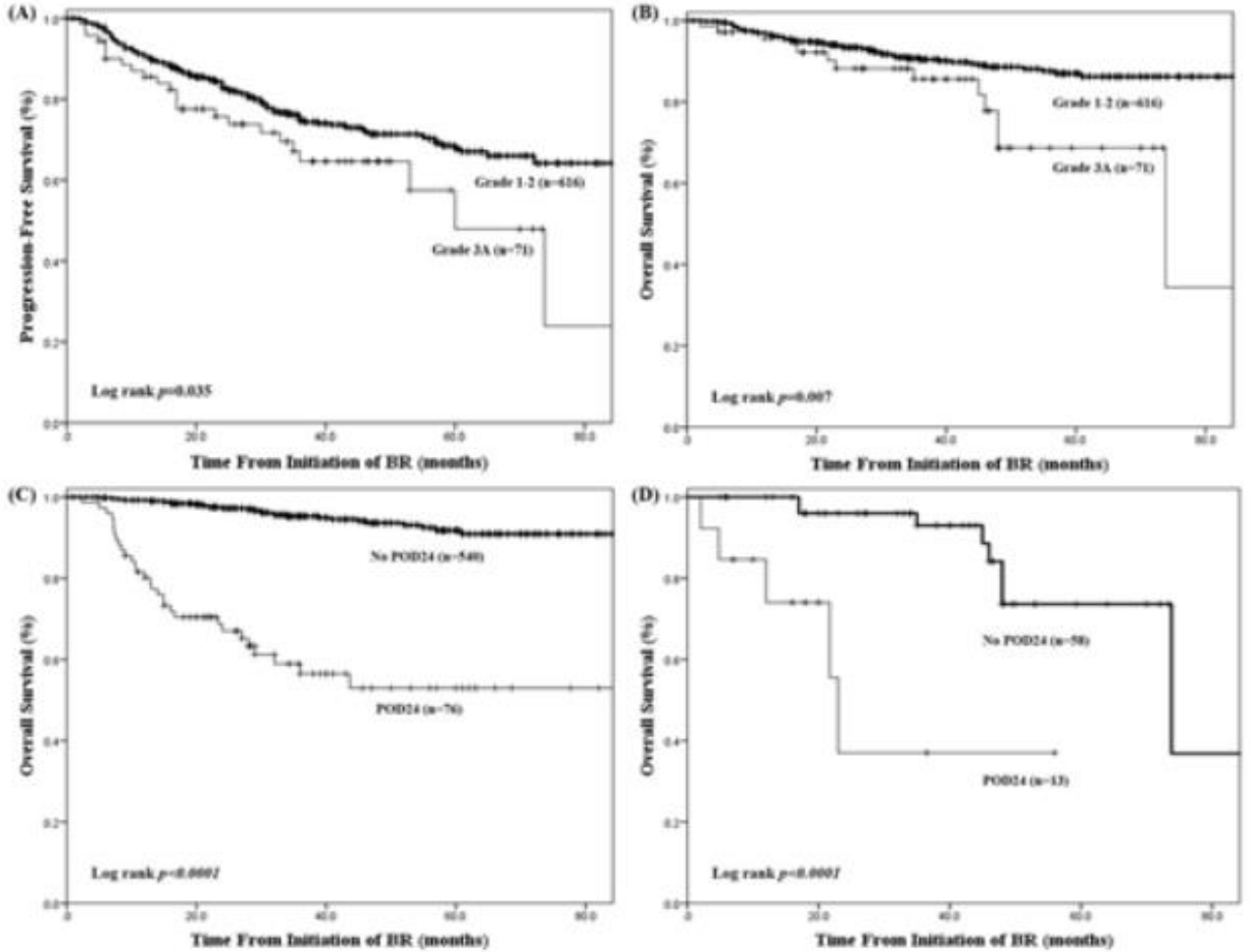
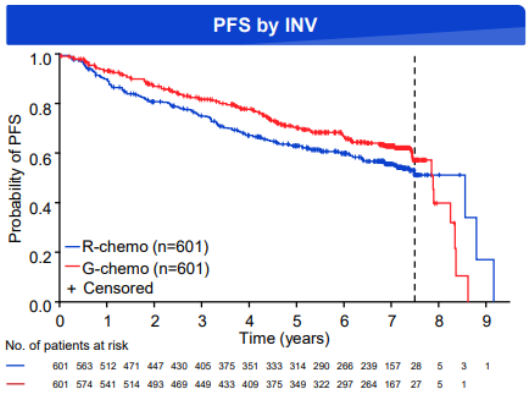


Figure: A) Progression-free survival (PFS) of Grade 1-2 compared to Grade 3A FL. **B)** Overall Survival (OS) of Grade 1-2 compared to 3A FL. **C)** OS from time of initiation of BR for Grade 1-2 FL patients with progression of disease within 24 months (POD24) compared to those without POD24. **D)** OS from time of initiation of BR for Grade 3A FL patients with POD24 compared to those without POD24.

R vs. O

PFS benefit was maintained with G- vs R-chemo after 8 years of follow-up



KM estimates became unreliable beyond 7.5 years, due to low numbers of patients at risk[1]

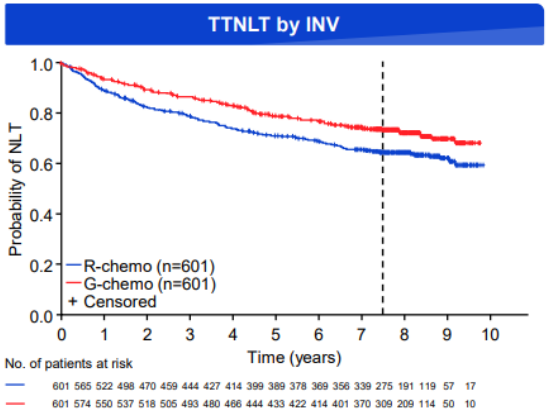
Median observation time: 7.9 (0.0–9.8) years

INV-assessed PFS	G-chemo (n=601)	R-chemo (n=601)
Patients with event, n (%)	206 (34.3)	244 (40.6)
7-year PFS, % (95% CI)	63.4 (59.0–67.4)	55.7 (51.3–59.9)
HR (95% CI)*	0.77 (0.64–0.93)	
P-value	0.006	

*Stratified analysis
KM, Kaplan–Meier

1. Pocock SJ, et al. Lancet 2002;359:1686–1689

Fewer patients had started next lymphoma treatment at 7 years in the G- vs R-chemo arm



TTNLT by INV	G-chemo (n=601)	R-chemo (n=601)
Patients with event, n (%)	160 (26.6)	209 (34.8)
Patients free from NLT at 7 years,* % (95% CI)	74.1 (70.3–77.5)	65.4 (61.4–69.2)
HR (95% CI)†	0.71 (0.58–0.87)	
P-value	0.001	

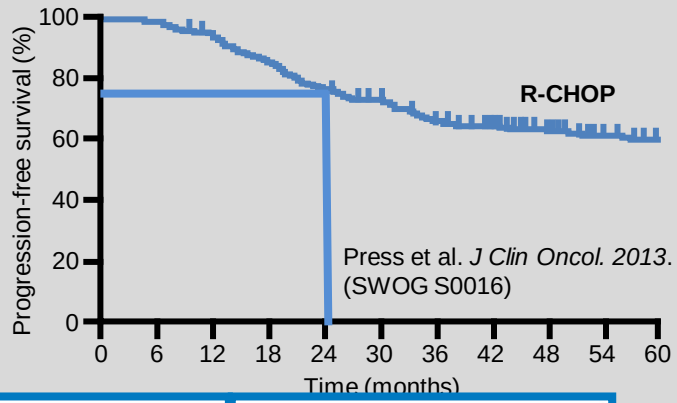
*Patients who were alive and had not started next treatment at 7 years; †Stratified analysis
NLT, next lymphoma treatment

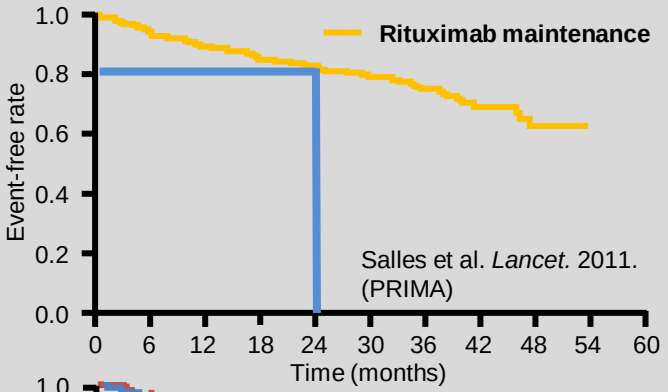
- No OS Benefit

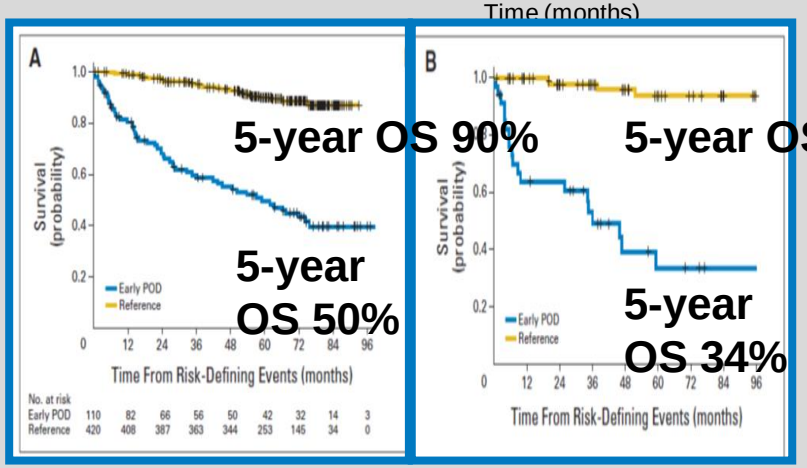
POD24

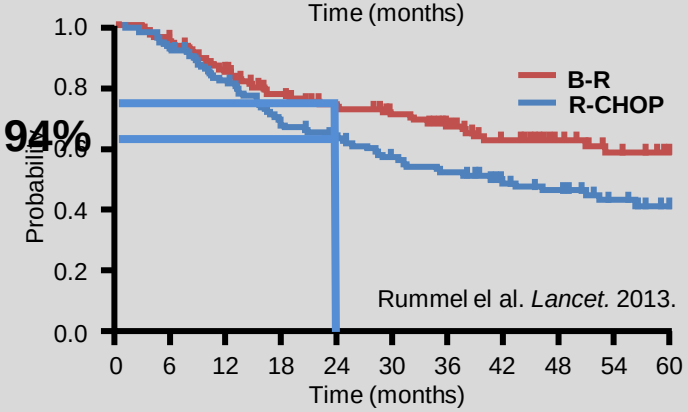
- Truly highest risk patient population in FL
- Outcomes appear poor irrespective of initial therapy
- Identification of these patients in 1L of highest priority

20% of Patients With FL Experience Disease Progression Within 2 years of Chemo-immunotherapy









Original NLCS Cohort Validation Cohort

This suggests a high-risk group of patients who will relapse early despite different treatment approaches; maintenance

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What's in a prediction

- Prognostic scoring systems to date have a questionable role in FL.
  - Initial attempt with FLIPI
    - Has been modified with several updates.
    - FLIPI-2, M7-FLIPI, etc.
  - Can they adequately identify the truly high-risk patients?

M7 FLIPI vs. FLIPI

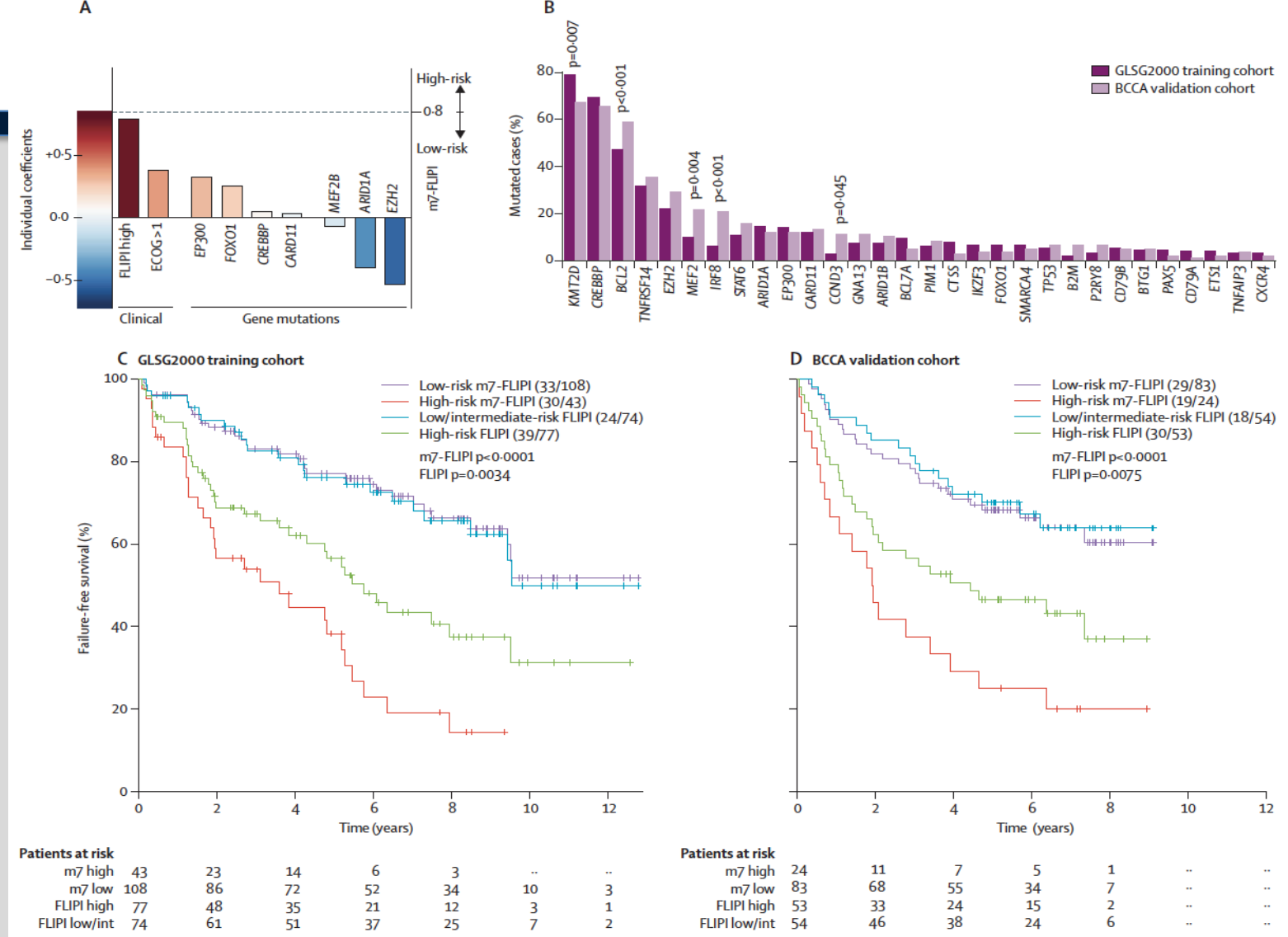
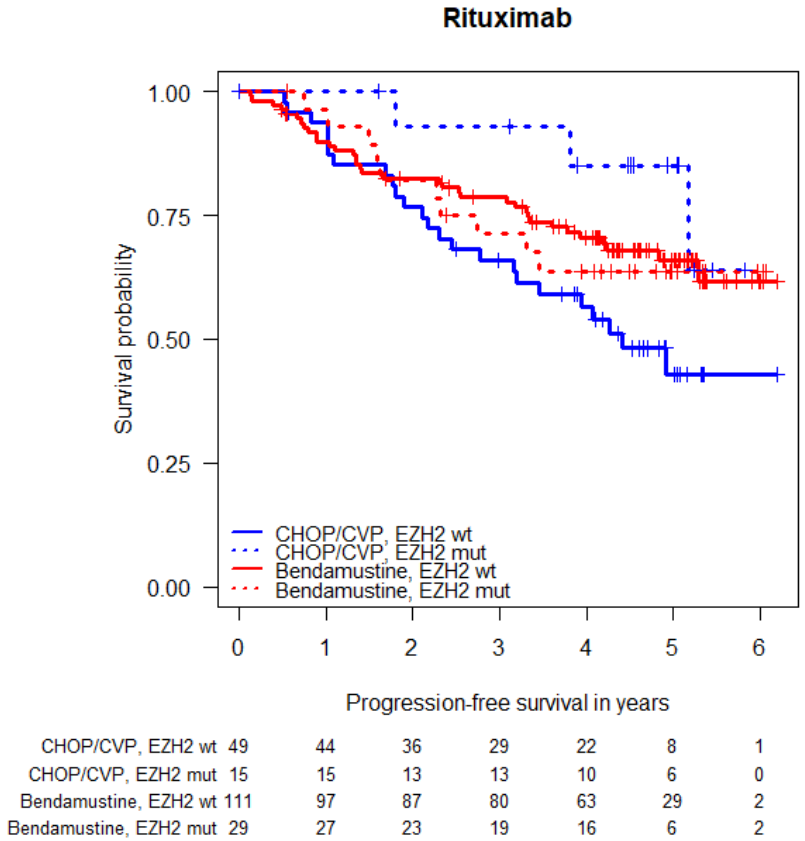
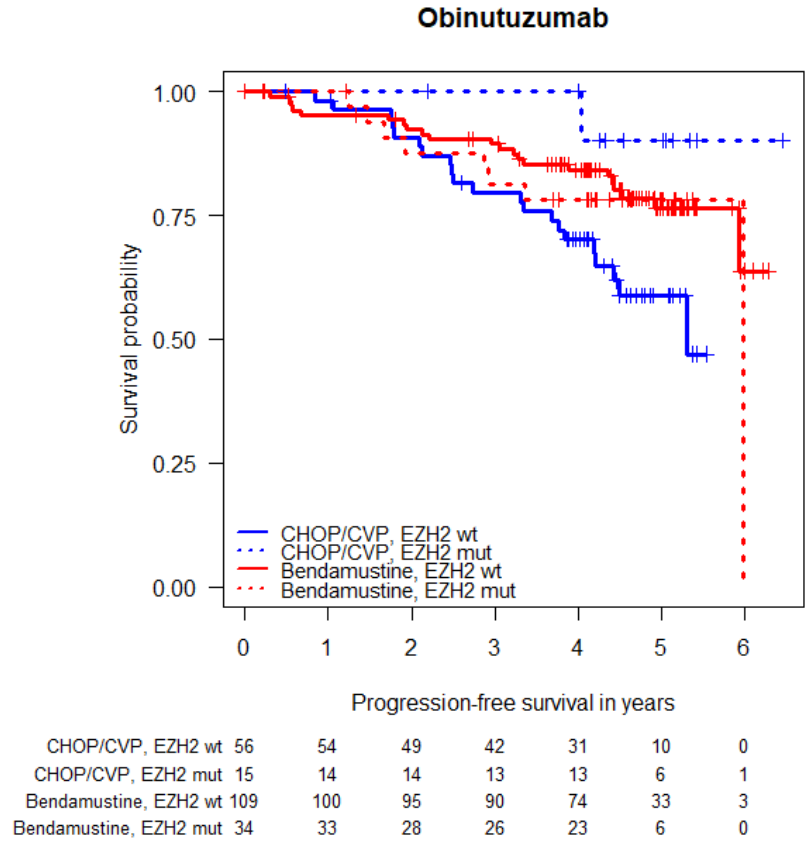


Figure 2: **The clinicogenetic risk model m7-FLIPI**
(A) The m7-FLIPI (m7) is calculated as the sum of individual clinical and gene mutation predictor values weighted by their individual coefficients. (B) Mutation frequencies of the GLSG2000 training and the BCCA validation cohorts. p values by Fisher's exact test, without correction for multiple testing. Depicted are all significantly mutated genes[12] and genes with non-silent mutations in more than 5% of cases from the GLSG2000 training cohort. Detailed mutation plots for both cohorts are shown in the appendix (pp 15, 22). (C) Kaplan-Meier curves for failure-free survival for the GLSG2000 training cohort by FLIPI and by m7-FLIPI. (D) Kaplan-Meier curves for failure-free survival for the BCCA validation cohort by FLIPI and by m7-FLIPI. Numbers in parentheses show number of patients with event/number of patients per cohort. FLIPI low/int=low or intermediate-risk FLIPI.

Pastore A, et al. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. Lancet Oncol. 2015 Sep;16(9):1111-1122. doi: 10.1016/S1470-2045(15)00169-2. Epub 2015 Aug 6. PMID: 26256760.

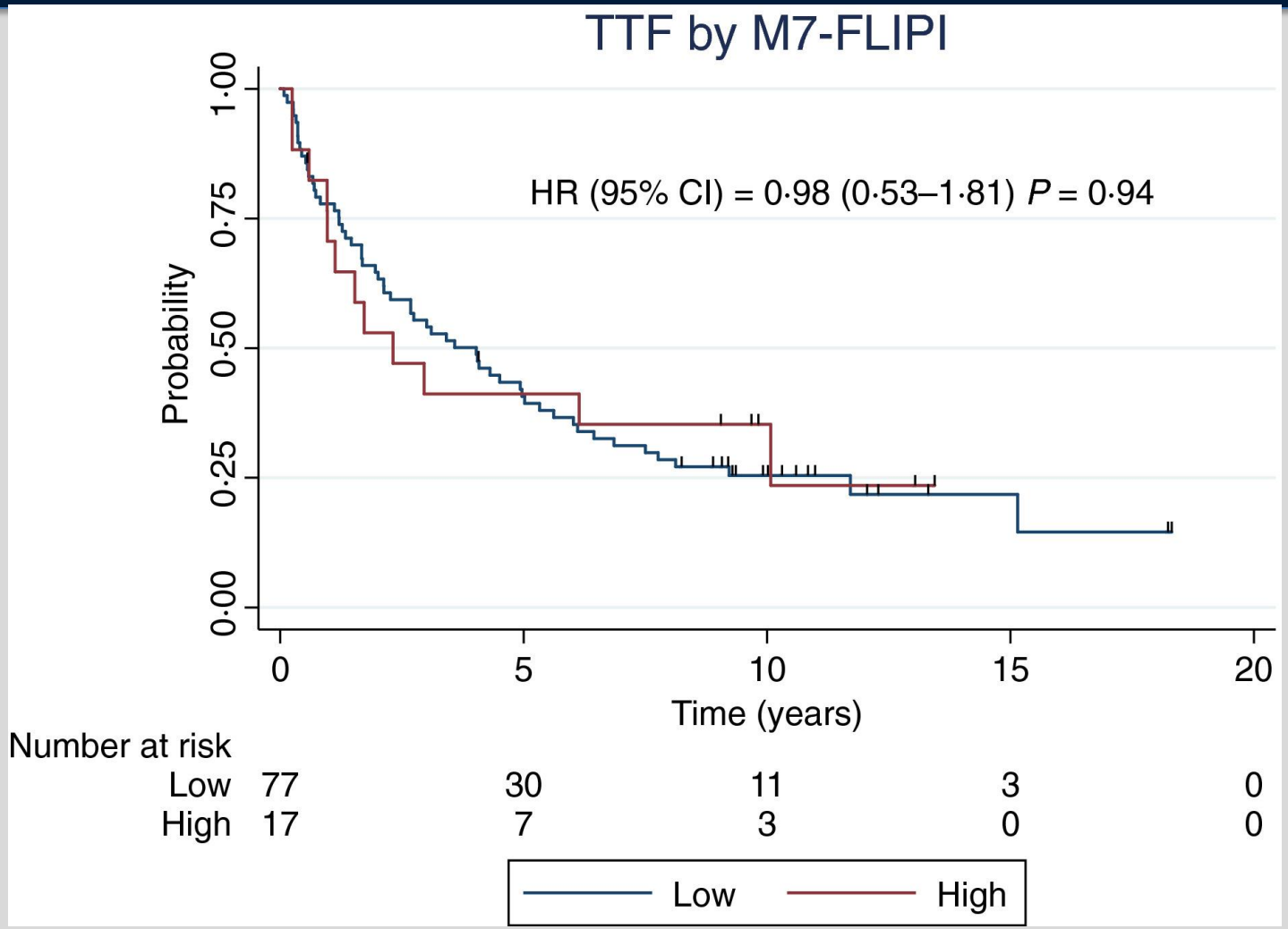
Evaluation of the m7-FLIPI in Patients with Follicular Lymphoma Treated within the Gallium Trial: EZH2 mutation Status May be a Predictive Marker for Differential Efficacy of Chemotherapy





Vindi Jurinovic, PhD et al, Evaluation of the m7-FLIPI in Patients with Follicular Lymphoma Treated within the Gallium Trial: EZH2 mutation Status May be a Predictive Marker for Differential Efficacy of Chemotherapy, Blood, 2019, Figure

M7-FLIPI is not prognostic in follicular lymphoma patients with first-line rituximab chemo-free therapy



Br J Haematol, Volume: 188, Issue: 2, Pages: 259-267, First published: 18 August 2019, DOI: (10.1111/bjh.16159)

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Comparison in POD24

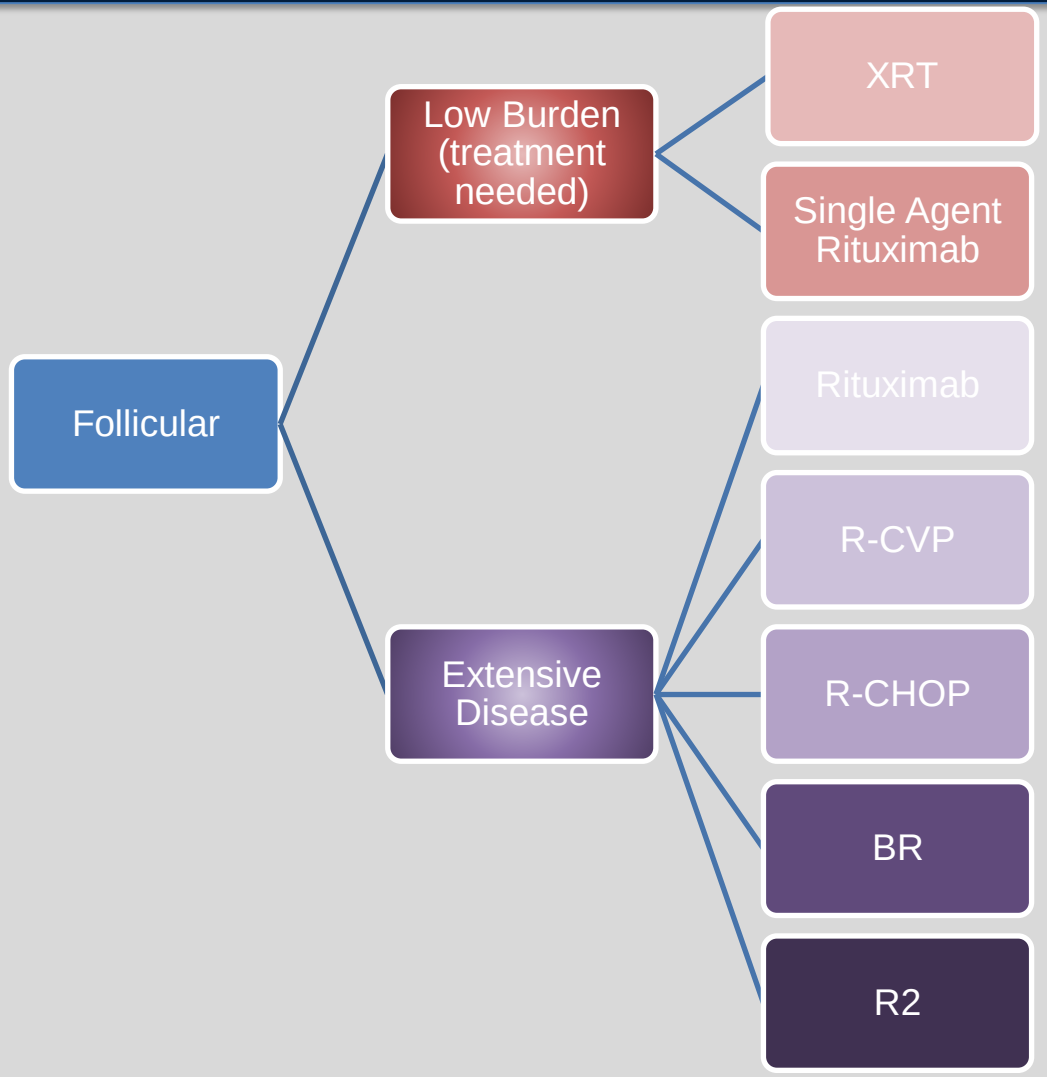
Endpoint	Stratification factor	Sensitivity/TPR	Specificity/TNR	Precision/PPV	NPV	Balanced Accuracy
POD24	FLIPI	22%	87%	64%	50%	54%
	PRIMA-PI	26%	88%	57%	67%	57%
	m7-FLIPI	22%	83%	24%	82%	53%
	POD24-PI	25%	87%	56%	63%	56%
	BCL2	21%	85%	48%	62%	53%
	TNFRSF14	10%	79%	16%	68%	44%
	EZH2	9%	80%	12%	74%	44%
	TP53	25%	83%	12%	92%	54%

What's in a prediction

- Can they adequately identify the truly high-risk patients?
- To date

NO

Treatment Tree

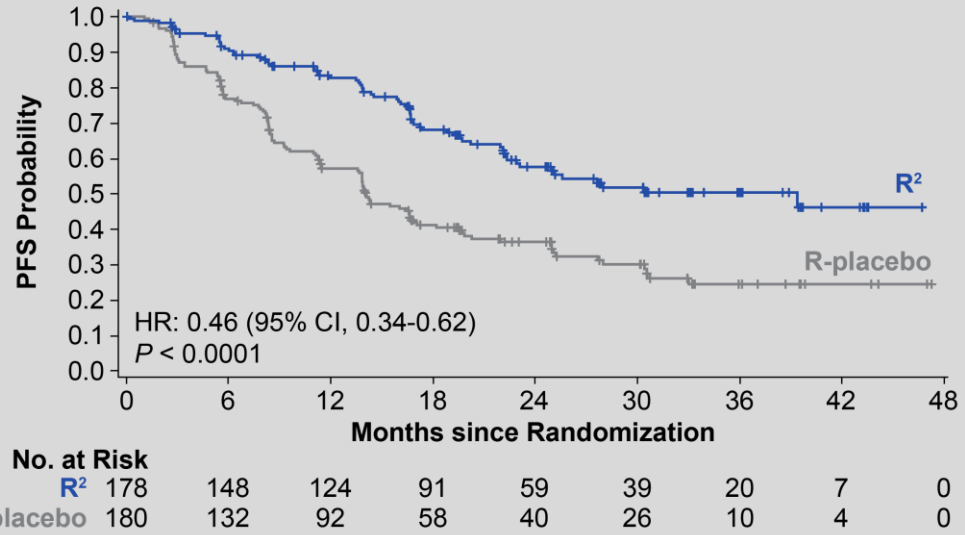


R/R Follicular Lymphoma

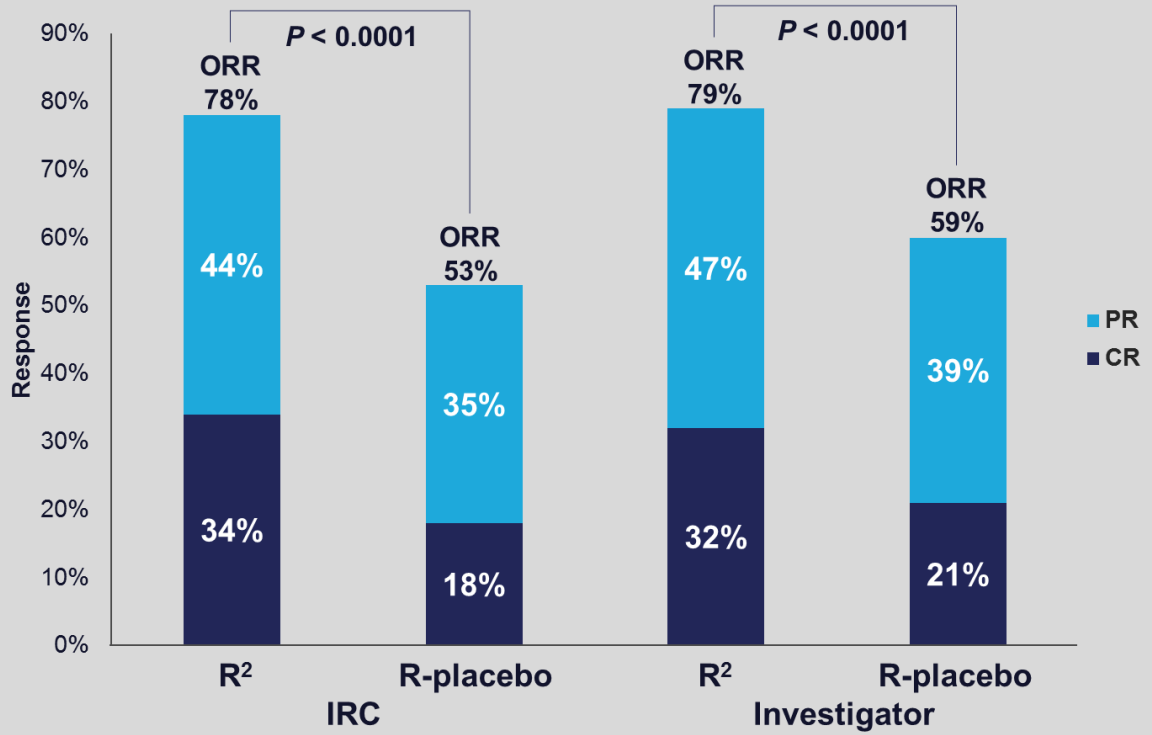
- POD24 worse outcomes
- 2L with two options currents
- 3L and beyond
  - CAR-T with accelerated approval. DOR still maturing and will be key to utilization of this therapy
  - Tazemetostat (those unfit for intensive therapy or 3rd line)
  - PI3K delta inhibitors (idelalisib, duvelisib, copanlisib, umbralisib)



Primary endpoint: progression-free survival (ITT, IRC)



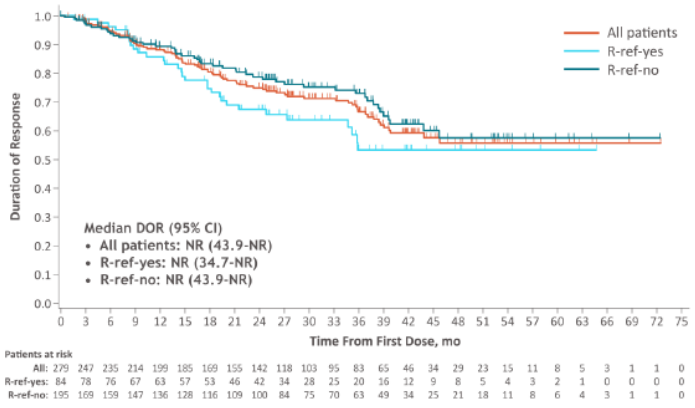
Median PFS	R² (n = 178)	R-placebo (n = 180)	HR (95% CI)	*P* Value
By IRC, mo (95% CI)	39.4 (22.9-NE)	14.1 (11.4-16.7)	0.46 (0.34-0.62)	< 0.0001
By investigator, mo (95% CI)	25.3 (21.2-NE)	14.3 (12.4-17.7)	0.51 (0.38-0.69)	< 0.0001



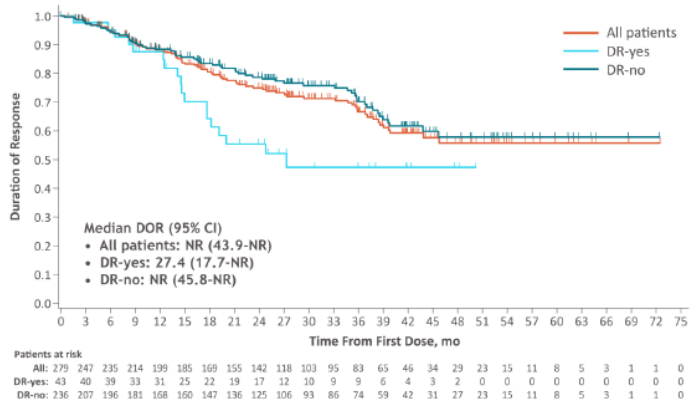
- Median DOR was 36.6 mo (95% CI, 22.9-NR) for R² vs 21.7 mo (95% CI, 12.8-27.6) for R-placebo,
HR 0.53 (95% CI, 0.36-0.79), *P* = 0.0015

Duration of Response[a]

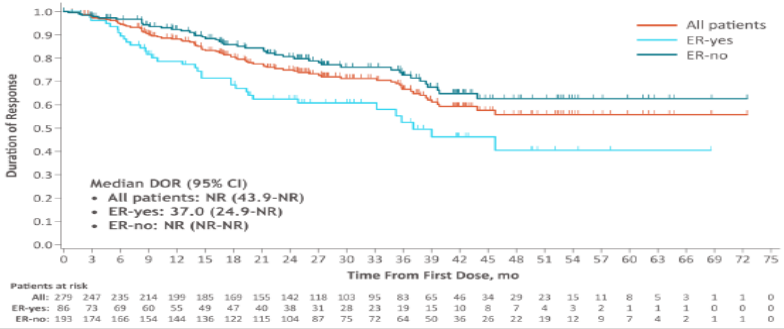
Rituximab Refractory Status



Double Refractory Status

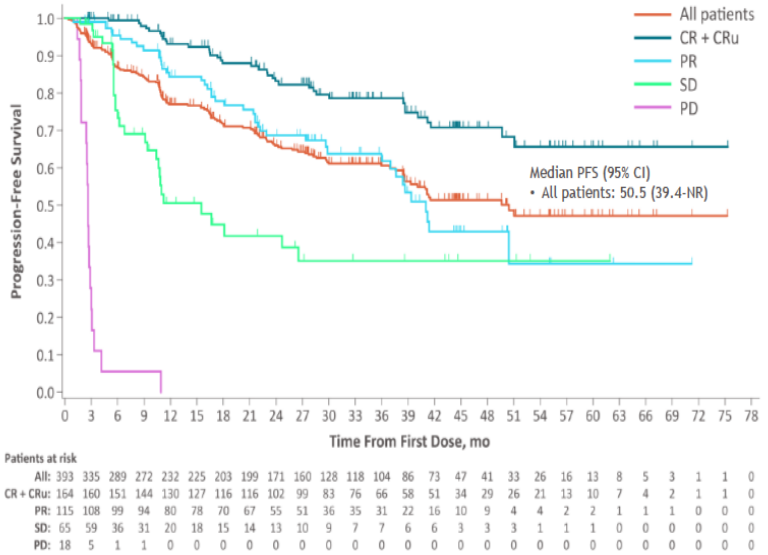


Early Relapse Status



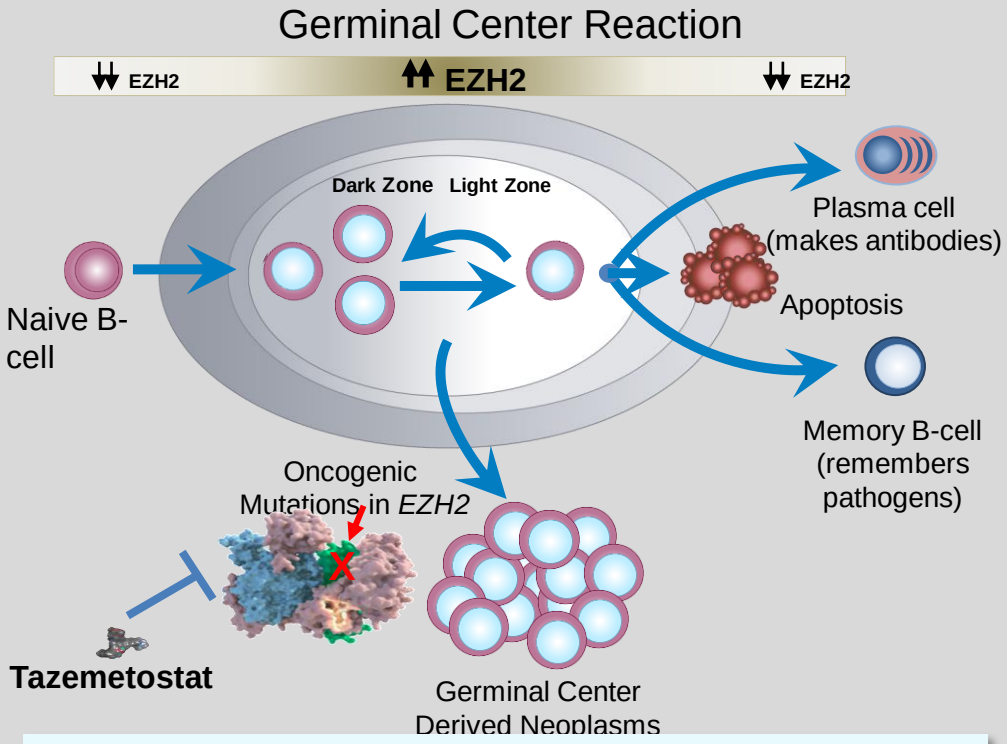
Progression-Free Survival[a]

PFS by Best Overall Response



Tazemetostat, Follicular Lymphoma and *EZH2*

- *EZH2* an epigenetic regulator of gene expression and cell fate decisions[1]
- *EZH2* is required for normal B-cell biology and germinal center formation[2]
  - Oncogenic mutations in *EZH2* suppress exit from germinal state and "lock" B cells in this state thereby transforming into a cancer[2]
- *EZH2* biology relevant in both mutant (MT) and wild-type (WT) *EZH2* FL
  - ~20% of patients with FL also have *EZH2* gain of function mutations[3]



Tazemetostat, an investigational, first-in-class, selective, oral inhibitor of EZH2 has shown antitumor activity in non-Hodgkin's lymphoma patients with either MT or WT EZH2[4,5]

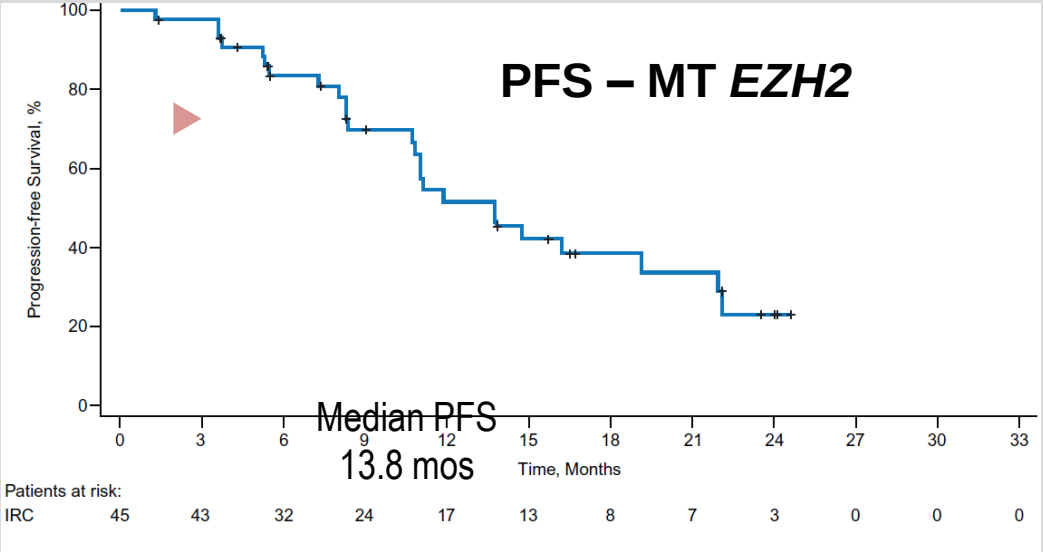
The American Society of Hematology (ASH)
7-10 December 2019
Orlando, FL

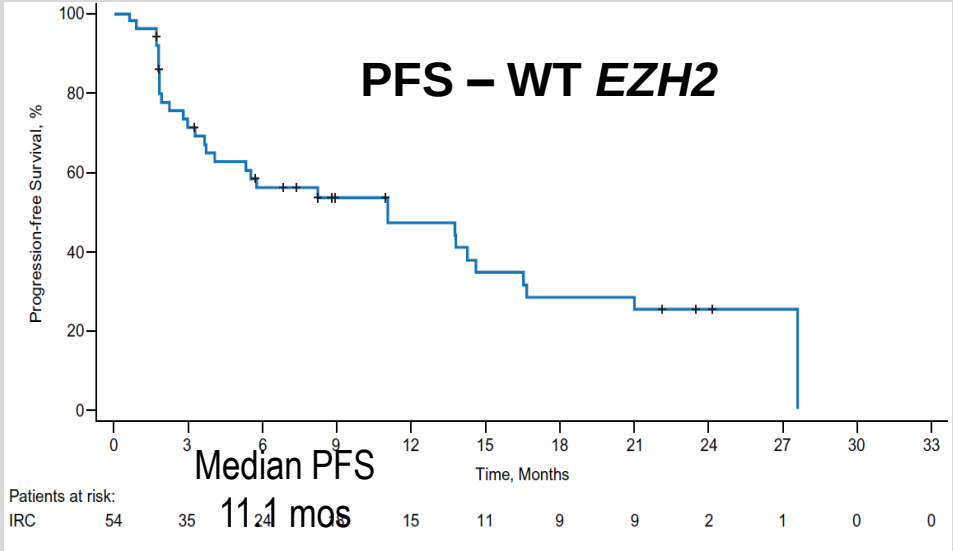
1. Gan L, et al. *Biomark Res*. 2018;6(1):10; 2. Béguelin W, et al. *Cancer Cell*. 2013;23(5)677-692. 3. Bödör C, et al. *Blood*. 2013;122:3165-3168. 4. Italiano A, et al. *Lancet Oncol*. 2018;19(5):649-59; 5. Morschhauser F, et al. *Hematol Oncol*. 2017 Jun;35:24-5.

Tazemetostat ORR in EZH2 Mutant and Wild Type Populations

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

PFS by Investigator and IRC Assessment in the ITT Population





Endpoint by IRC Assessment	ITT Population	
	MT *EZH2* (n=45)	WT *EZH2* (n=54)
PFS, months, median (95% CI)	13.8 (10.7–22.0)	11.1 (3.7–14.6)
PFS at 12 months, median (95% CI)	51.7 (34.4–66.6)	47.1 (31.6–61.1)
PFS at 18 months, median (95% CI)	38.8 (22.7–54.7)	28.3 (14.8–43.4)

- Class of drug recently in press due to withdrawal of indication in FL
  - Idelalisib
  - Duvelisib
  - Umbralisib
- One agent currently still with approval for FL and one additional agent still in clinical studies
  - Copanlisib (IV)
  - Zandelisib (phase III study vs. BR)

Copanlisib

Table 2. Response (Full Analysis Set)

Best Response	Tumor, No. (%)				
	FL (n = 104)	MZL (n = 23)	SLL (n = 8)	LPL/WM (n = 6)	Total (N = 142)*
Complete response	15 (14)	2 (9)	0	0	17 (12)
Partial response	46 (44)	14 (61)	6 (75)	1 (17)	67 (47)
Stable disease	35 (34)†	4 (17)	1 (13)	3 (50)	43 (30)†
Progressive disease	2 (2)	0	1 (13)	0	3 (2)
Not evaluable	0	1 (4)	0	0	1 (< 1)
Not available‡	6 (6)	2 (9)	0	2 (33)	11 (8)
Objective response rate	61 (59)	16 (70)	6 (75)	1 (17)	84 (59)
95% CI§	49 to 68	47 to 87	35 to 97	0.4 to 64	51 to 67
Disease control rate‖	91 (88)	20 (87)	7 (88)	4 (67)	122 (86)‖
95% CI§	80 to 93	66 to 97	47 to 100	22 to 96	79 to 91

Abbreviations: FL, follicular lymphoma; LPL/WM, lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma.

*One patient with diffuse large B-cell lymphoma was included because the initial investigator assessment was indolent non-Hodgkin lymphoma, which was later confirmed by the investigator and central pathology review to be diffuse large B-cell lymphoma.

†Includes one patient with unconfirmed early stable disease (stable disease was assessed < 7 weeks after start of treatment).

‡Of the full analysis set of 142 patients, data for 11 (8%) were not available for the analysis of the primary efficacy variable (objective response rate).

§95% CIs by exact binomial calculation.

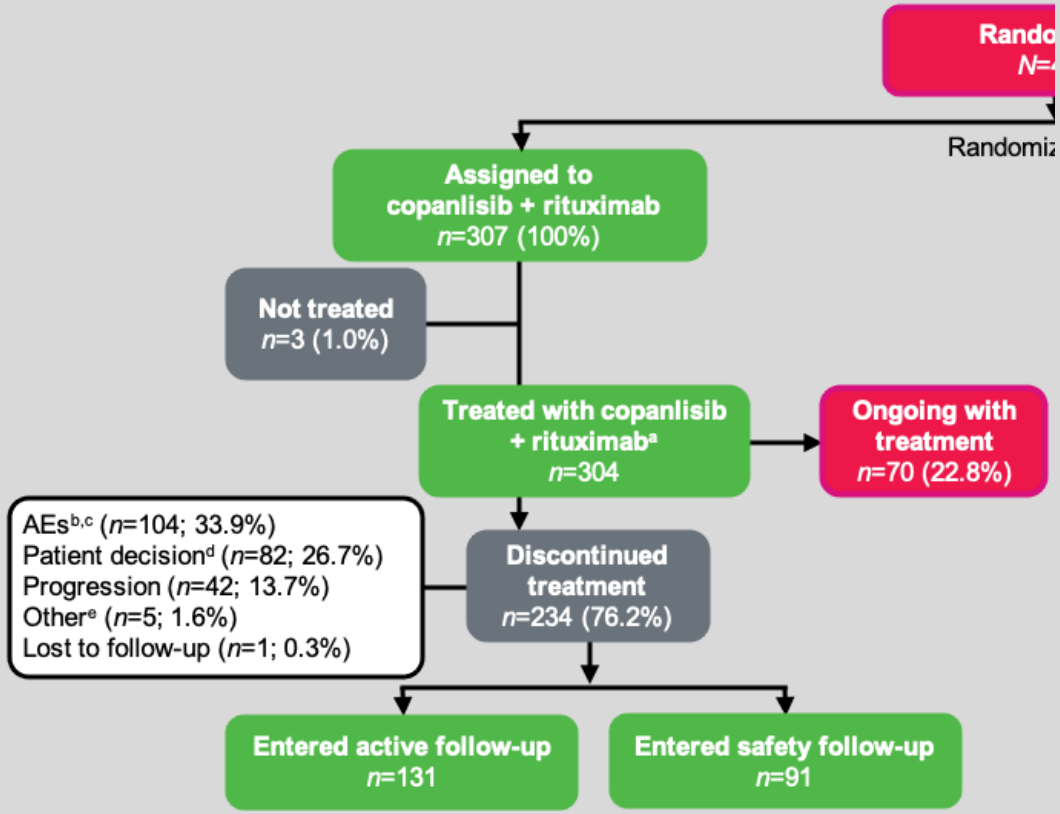
‖One patient with unconfirmed stable disease and four with stable disease or partial response recorded > 35 days from the last treatment were excluded from the calculation.

- The Chronos-1 trial enrolled a total of 142 patients with R/R indolent lymphoma.[1]
- Patients with follicular lymphoma had an ORR of 59%, a CR of 15% and PR of 44%. The median DOR was 12.2 months for patients with follicular lymphoma

Table 2. Response (Full Analysis Set)

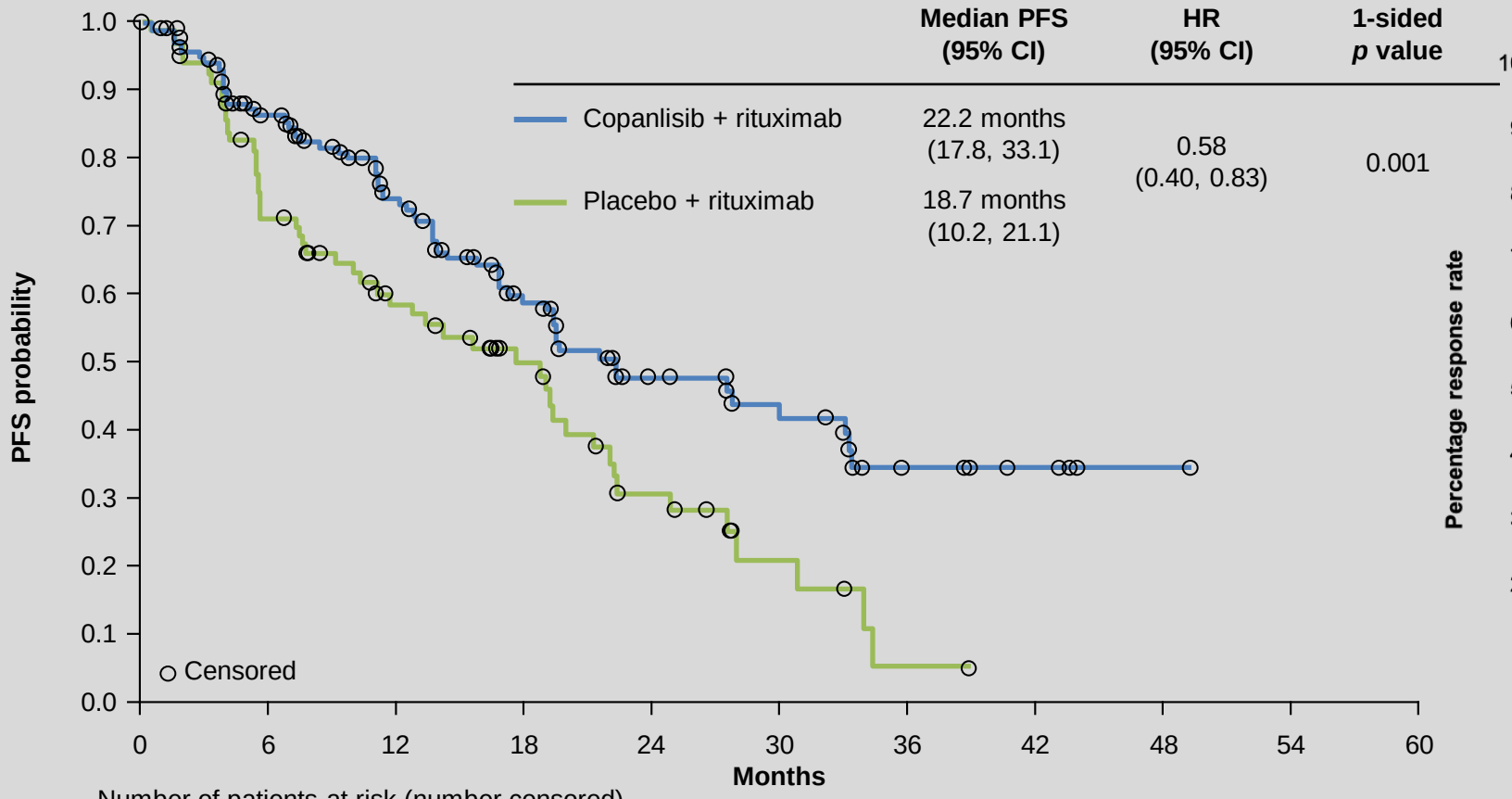
Published in: Martin Dreyling; Armando Santoro; Luigina Mollica; Sirpa Leppä; George A. Follows; Georg Lenz; Won Seog Kim; Arnon Nagler; Panayiotis Panayiotidis; Judit Demeter; Muhit Özcan; Marina Kosinova; Krimo Bouabdallah; Franck Morschhauser; Don A. Stevens; David Trevarthen; Marius Giurescu; Lisa Cupit; Li Liu; Karl Köchert; Henrik Seidel; Carol Peña; Shuxin Yin; Florian Hiemeyer; Jose Garcia-Vargas; Barrett H. Childs; Pier Luigi Zinzani; *Journal of Clinical Oncology* 2017 353898-3905.[1]
DOI: 10.1200/JCO.2017.75.4648

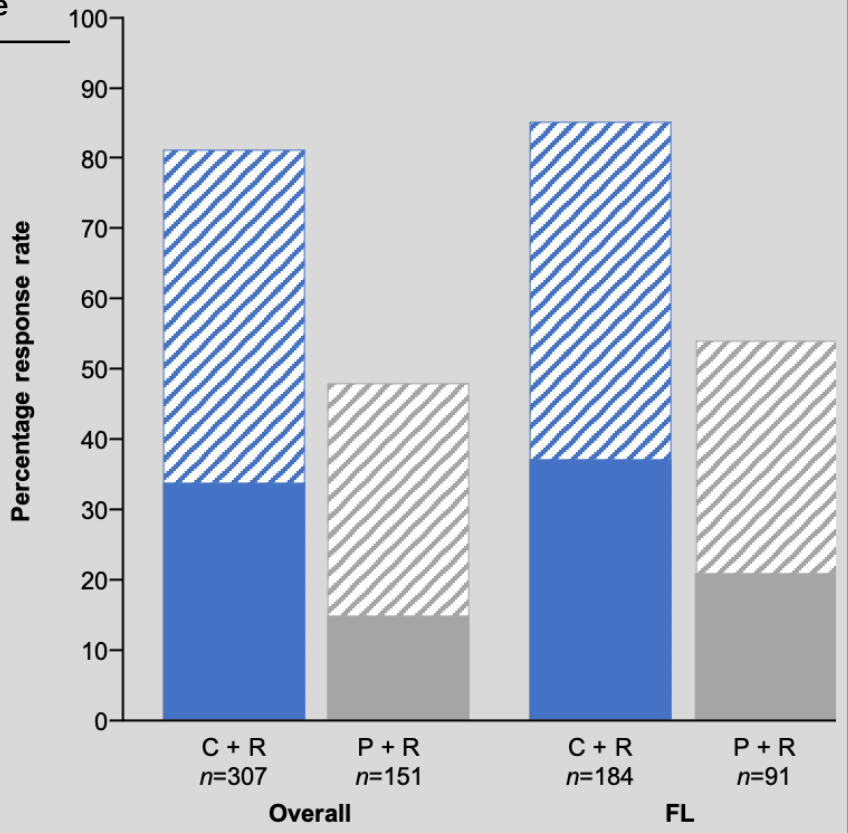
CHRONOS-3: randomized Phase III study of copanlisib plus rituximab vs rituximab / placebo in relapsed indolent non-Hodgkin lymphoma (iNHL):Treatment exposure



	Copanlisib + rituximab *n*=307	Placebo + rituximab *n*=146
Median duration of treatment, months (range)	8.31 (0.2-54.0)	10.78 (0.2-46.6)
Mean duration of treatment, months (standard deviation)	12.0 (11.5)	12.7 (9.9)
Median number of cycles (range)	9 (1-57)	12 (1-51)
Median percentage of planned dose (range)	95.2 (41-106)	100 (67-114)
Dose interruptions or delays, *n* (%)	231 (75.2)	83 (56.8)
Median duration of interruptions or delays, days (range)	7 (1-174)	7 (1-84)
Dose reductions, *n* (%)		
Dose reduction to 45 mg	83 (27.0)	10 (6.8)
Dose reduction to 30 mg	28 (9.1)	0
Discontinuation of any study drug due to AEs, *n* (%)	98 (31.9)	12 (8.2)

PFS/OS in patients with FL





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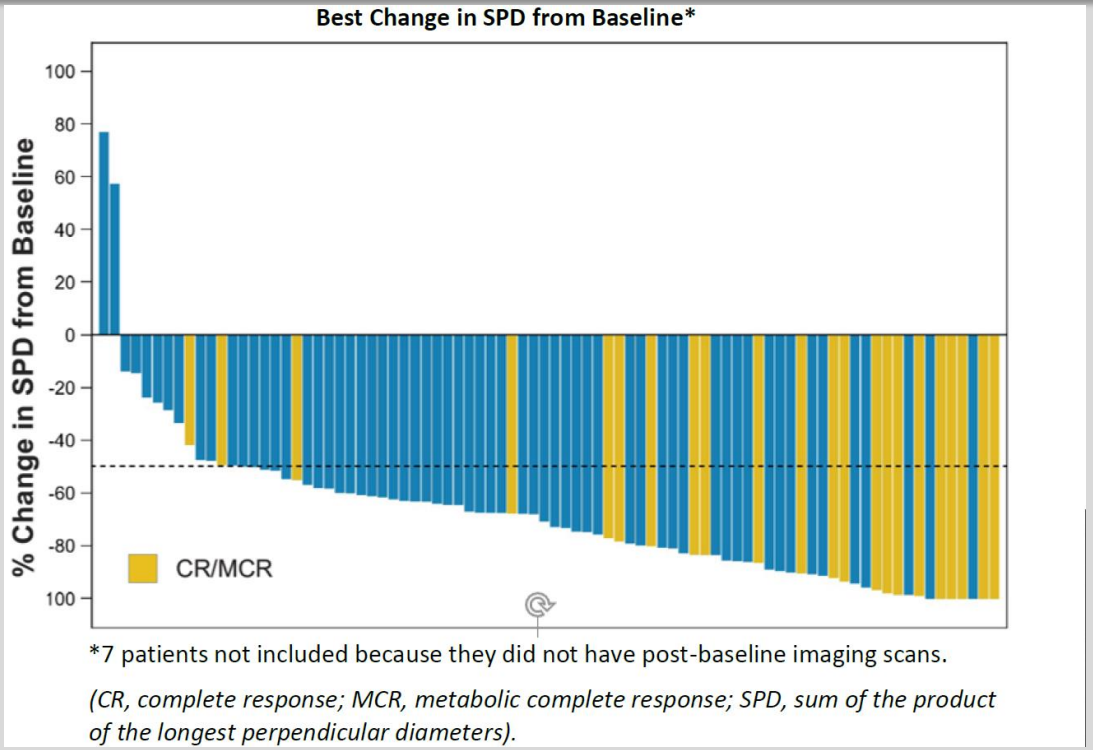
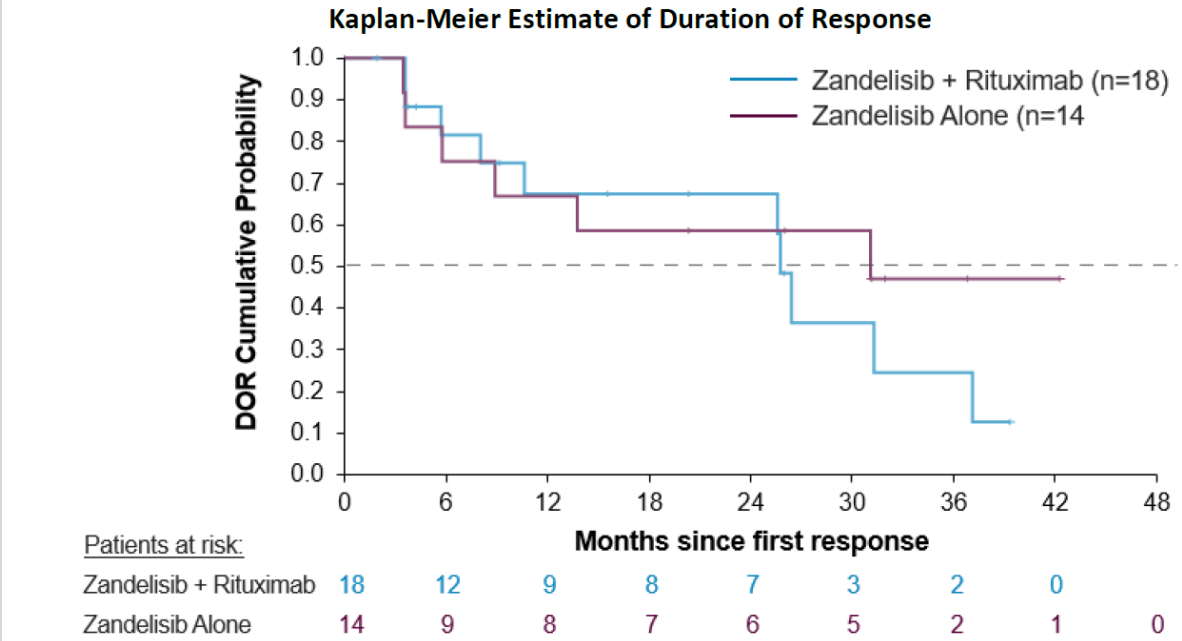
Zandelisib



*7 patients not included because they did not have post-baseline imaging scans.

(CR, complete response; MCR, metabolic complete response; SPD, sum of the product of the longest perpendicular diameters).



- Given at a dose of 60mg daily for two 28-day cycles
- Then days 1-7 thereafter until PD or intolerance.

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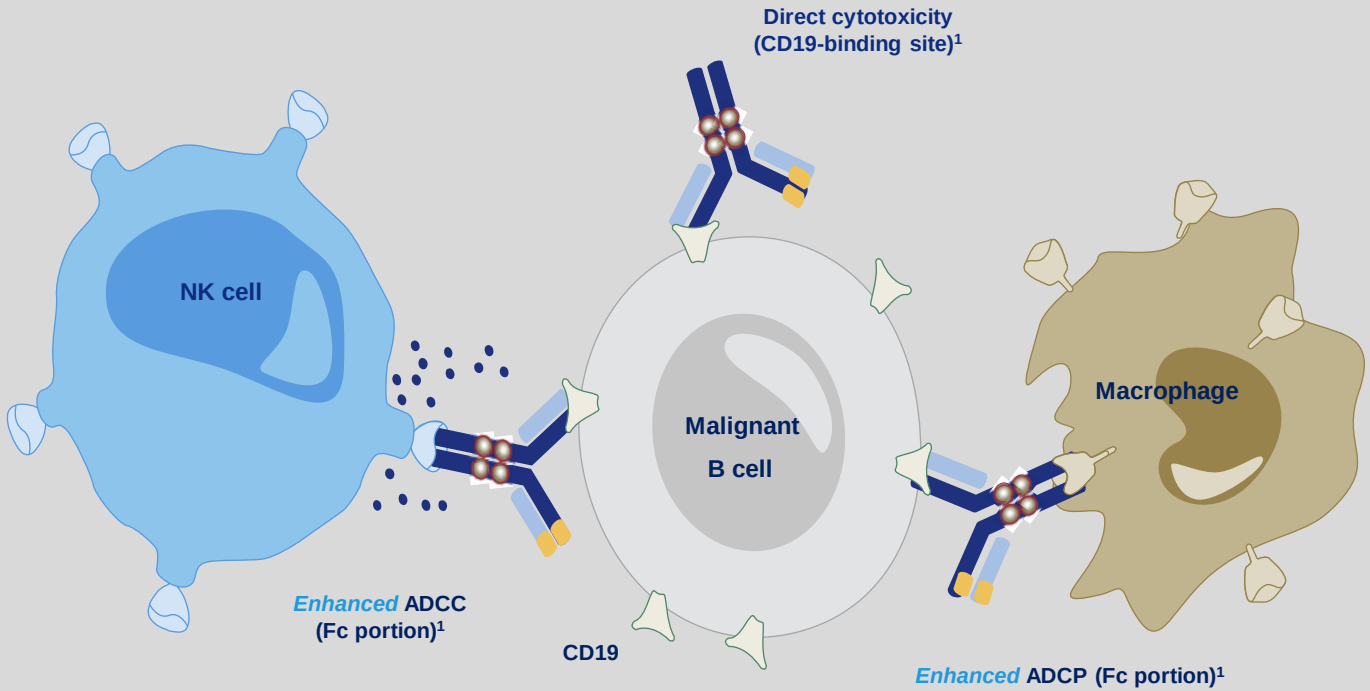
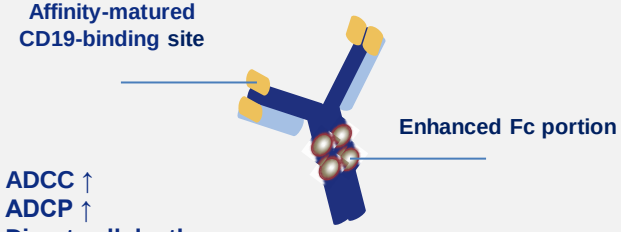


Tafasitamab-cxix (CD19-directed cytolytic mAb)[1-6]



- ADCC ↑
- ADCP ↑
- Direct cell death
- Phase 2a study showed single-agent activity in patients with R/R DLBCL and iNHL

ADCC = antibody-dependent cellular cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; CD19 = cluster of differentiation 19; Fc = fragment crystallizable; iNHL = indolent non-Hodgkin's lymphoma; LEN = lenalidomide; mAb = monoclonal antibody; NK = natural killer.

1. Horton et al. *Cancer Res*. 2008;68:8049; 2. Woyach et al. *Blood*. 2014;124:3553; 3. Jurczak et al. *Ann Oncol*. 2018;29:1266; 4. Witzig et al. *Ann Oncol*. 2015;26:1667; 5. Czuczman et al. *Clin Cancer Res*. 2017;23:4127; 6. MONJUVI (tafasitamab-cxix) Prescribing Information.

Tafasitamab in FL

- Limited data from Phase II study looking at single agent Tafasitamab in multiple subtypes.
- Data suggests that agent has limited efficacy as single agent and likely future in FL is in combination.
  - High rate of stable disease suggesting higher disease control rate vs. true response rate.
  - Questions then arise about partner and sequencing.

Table 1: Overall remission rates

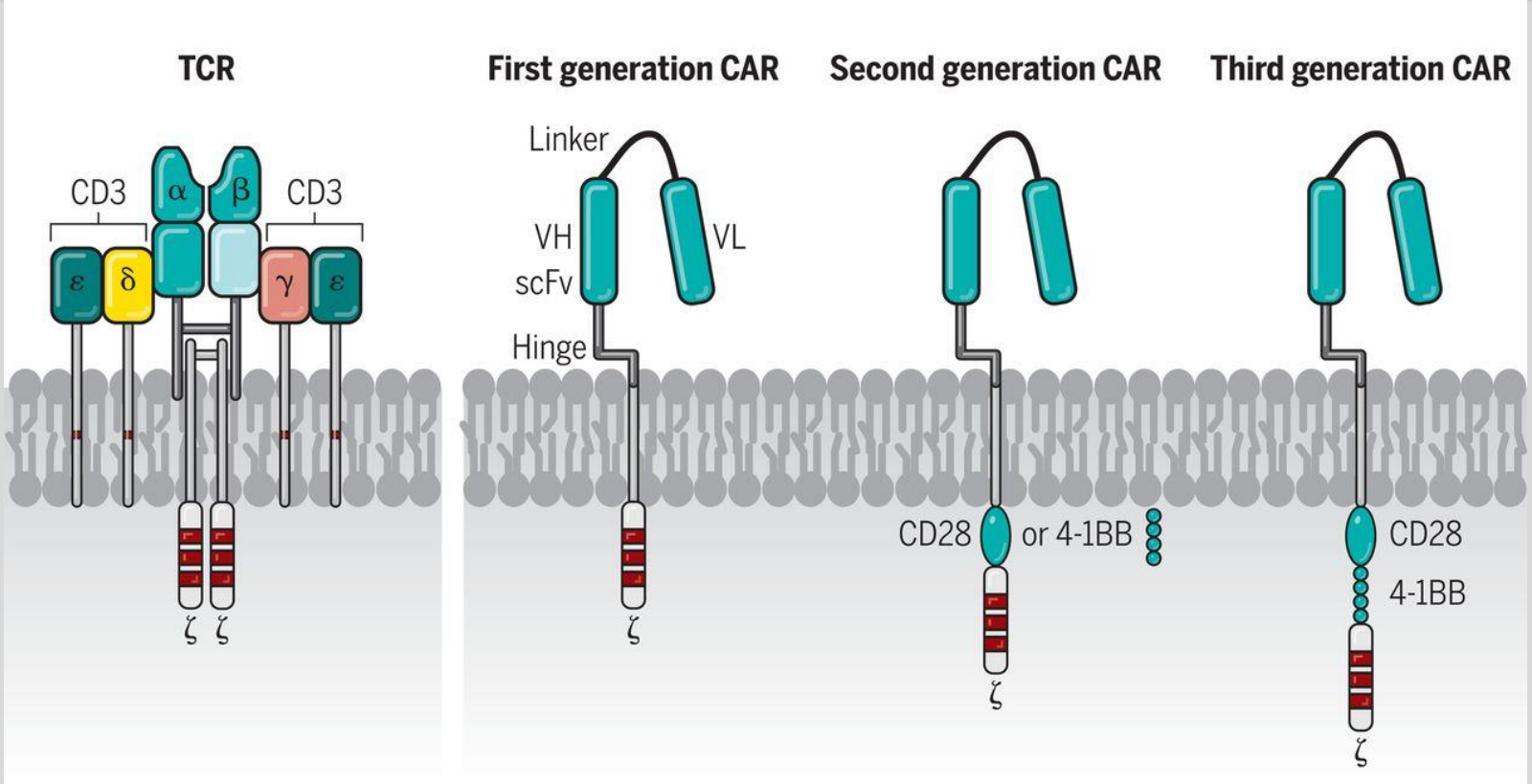
	DLBCL subtype (N=35) n (%)	FL subtype (N=34) n (%)	MCL subtype (N=12) n (%)	Other iNHL (N=11) n (%)	Total (N=92) n (%)
Complete remission (CR)	2 (5.7)	2 (5.9)	0	2 (18.2)	6 (6.5)
Partial remission (PR)	7 (20.0)	8 (23.5)	0	1 (9.1)	16 (17.4)
CR or PR (ORR)	9 (25.7)	10 (29.4)	0	3 (27.3)	22 (23.9)
95% CI	12.5–43.3	15.1–47.5	–	6.0–61.0	15.6–33.9
Stable disease (SD)	5 (14.3)	16 (47.1)	6 (50.0)	4 (36.4)	31 (33.7)
Progressive disease (PD)	11 (31.4)	4 (11.8)	5 (41.7)	3 (27.3)	23 (25.0)
Not evaluable	0	1 (2.9)	0	0	1 (1.1)
No response assessment	10 (28.6)	3 (8.8)	1 (8.3)	1 (9.1)	15 (16.3)

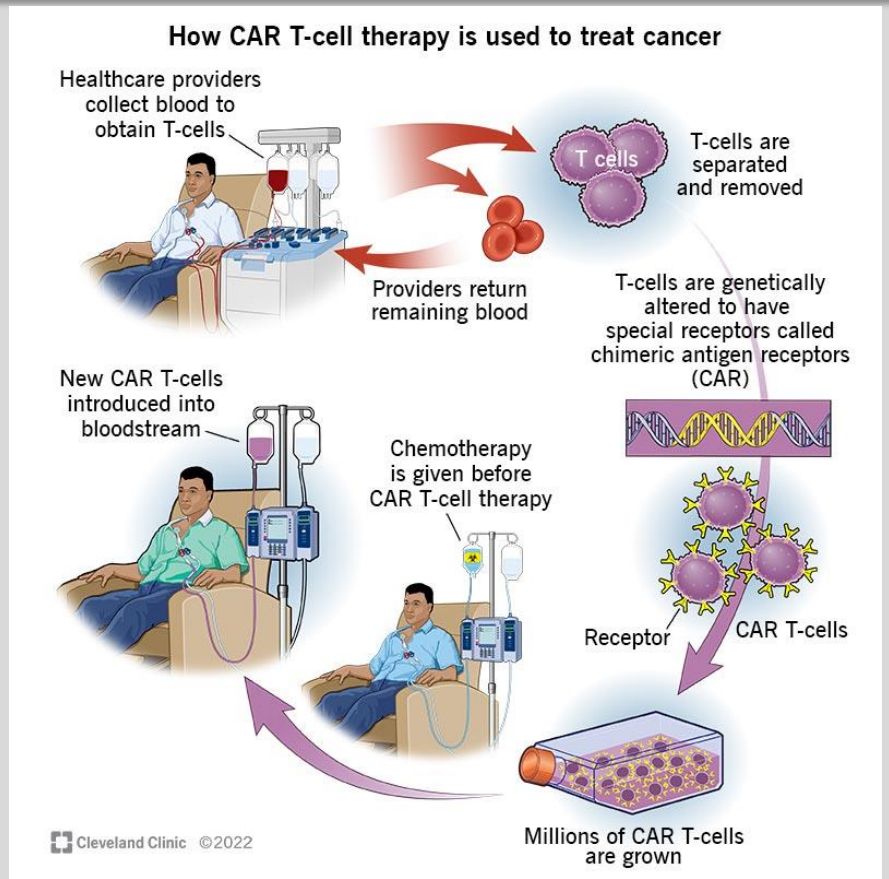
Table 2: Time to event analyses

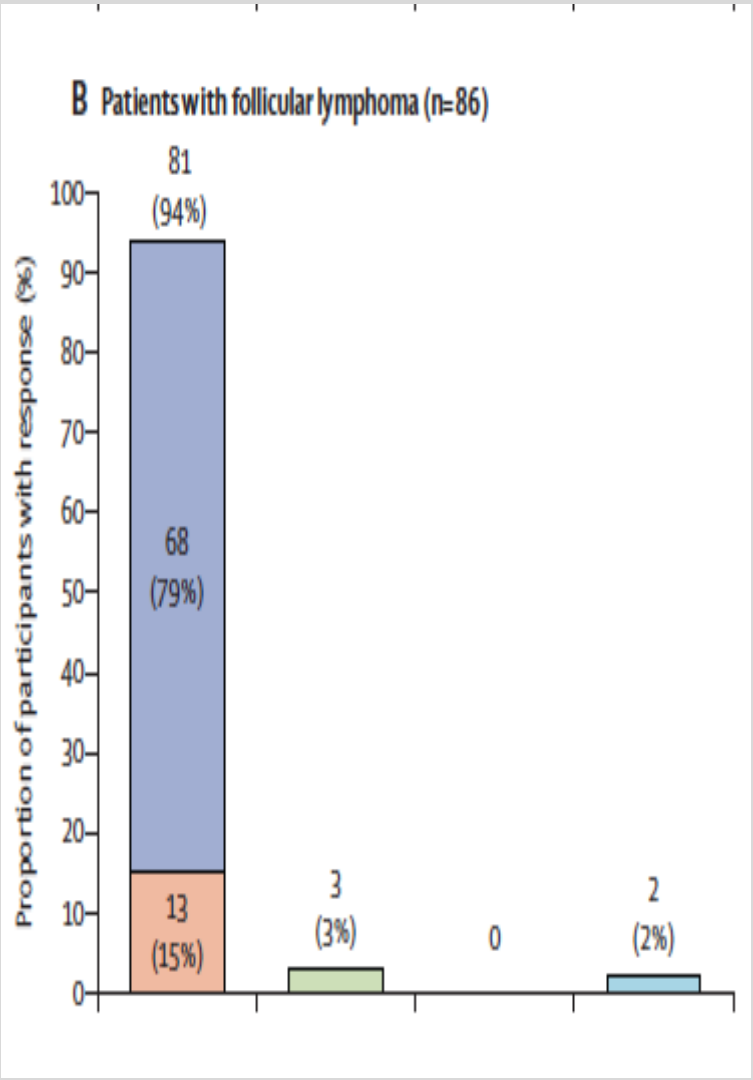
	DLBCL subtype (N=35)	FL subtype (N=34)	MCL subtype (N=12)	Other iNHL (N=11)	Total (N=92)
12-month rate of PFS [%] (95% CI)	34.3 (16.6–52.9)	39.2 (20.8–57.3)	18.7 (1.3–52.2)	53.3 (17.7–79.6)	35.1 (23.6–46.9)
Median DoR [months] (95% CI)	20.1 (1.1–NR)	24.0 (2.6–NR)	No responders	NR (NR–NR)	24.0 (11.1–NR)

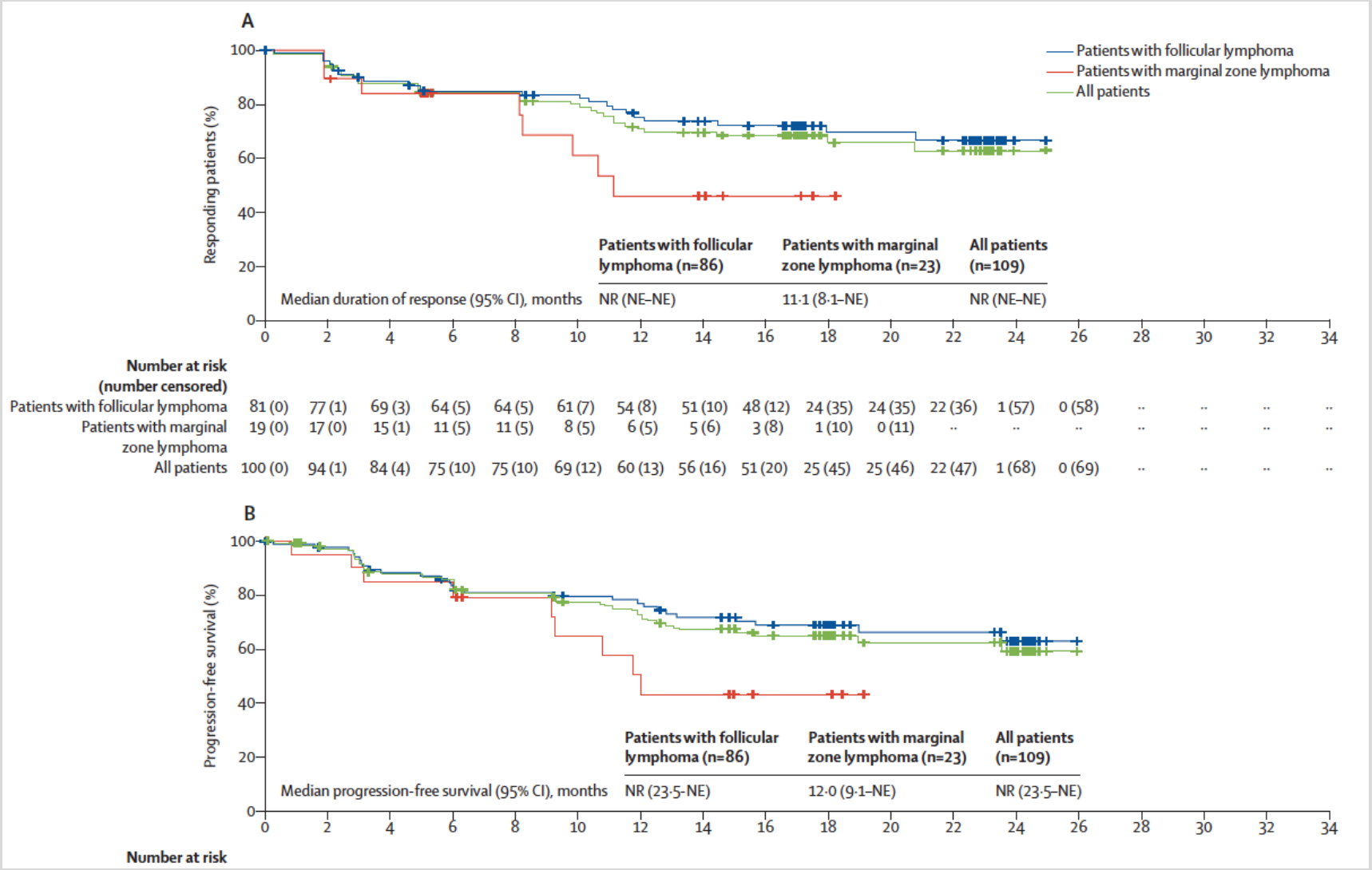
Wojciech Jurczak, MD PhD et al, A Phase IIa, Open-Label, Multicenter Study of Single-Agent Tafasitamab (MOR208), an Fc-Optimized Anti-CD19 Antibody, in Patients with Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma: Long-Term Follow up, Final Analysis, Blood, 2019,

Chimeric Antigen Receptor T-cell Therapy (CAR-T)









Jacobson CA et al.. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022 Jan;23(1):91-103. doi: 10.1016/S1470-2045(21)00591-X. Epub 2021 Dec 8. PMID: 34895487.

Axi-Cel in POD24

- ORR among efficacy-evaluable pts with POD24 (n = 61) and without POD24 (n = 37) was 92% each (complete response rates, 75% and 86%).
- At data cutoff, 52% of pts with POD24 and 70% without POD24 had ongoing responses.
- Median duration of response, progression-free survival, and overall survival were not reached in pts with and without POD24; 18-month estimated rates were 60% and 78%, 55% and 84%, and 85% and 94%

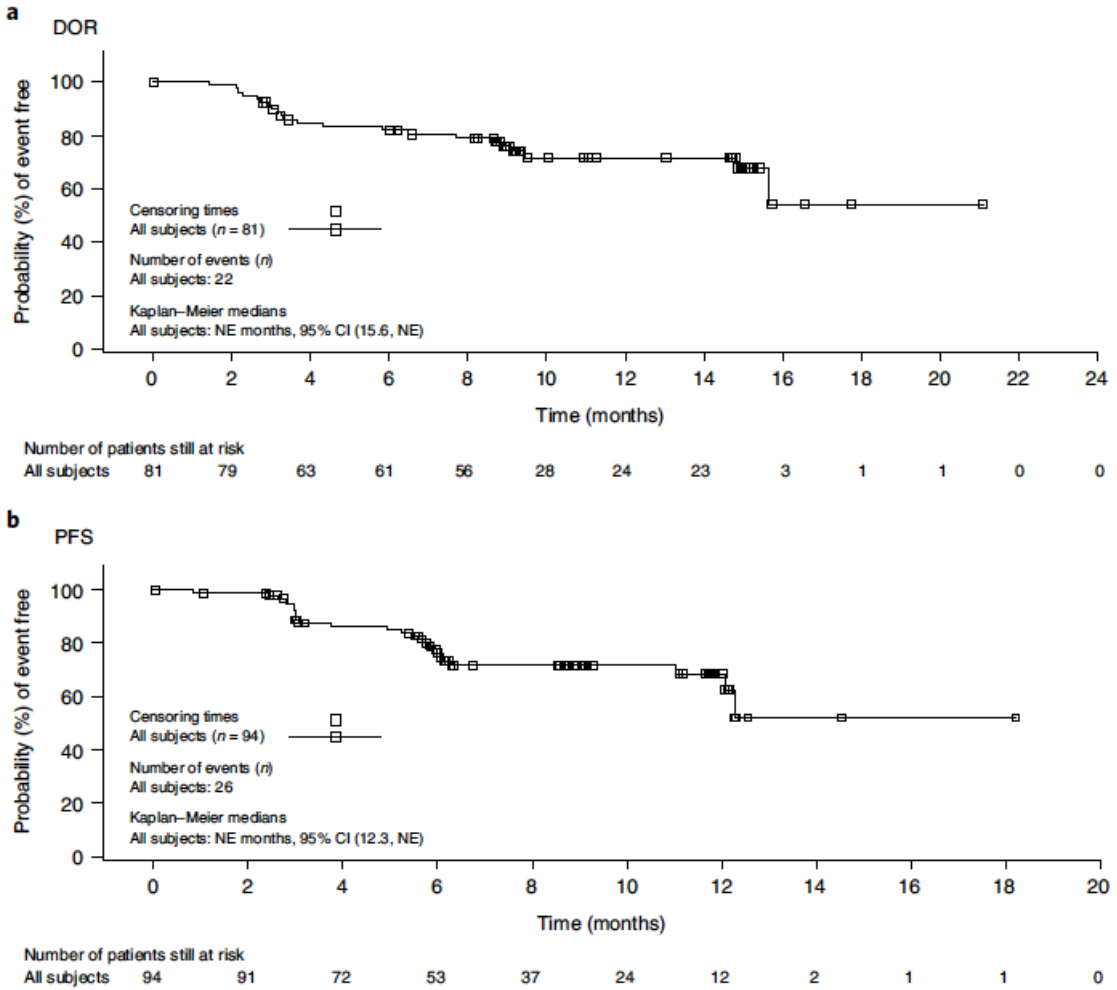
Jacobson et al. Outcomes in ZUMA-5 with axicabtagene ciloleucel (axi-cel) in patients (pts) with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) who had the high-risk feature of progression within 24 months from initiation of first anti-CD20–containing chemoimmunotherapy (POD24).
DOI: 10.1200/JCO.2021.39.15_suppl.7515 *Journal of Clinical Oncology* 39, no. 15_suppl (May 20, 2021) 7515-7515

ELARA Trial

Table 2 | Best overall response in the EAS and per-protocol population[a]

Parameter	Per-protocol set, $n=85$		EAS, $n=94$	
	Local assessment	IRC assessment	Local assessment	IRC assessment
Best overall response, *n* (%)				
CR	64 (75.3); 95% CI, 64.7–84.0	62 (72.9); 95% CI, 62.2–82.0	68 (72.3); 95% CI, 62.2–81.1	65 (69.1); 95% CI, 58.5–78.3
PR	14 (16.5)	12 (14.1)	17 (18.1)	16 (17.0)
SD	2 (2.4)	3 (3.5)	3 (3.2)	3 (3.2)
PD	5 (5.9)	8 (9.4)	6 (6.4)	9 (9.6)
UNK				1 (1.1)
Overall response rate (CR + PR), *n* (%)	78 (91.8); 95% CI, 83.8–96.6	74 (87.1); 95% CI, 78.0–93.4	85 (90.4); 95% CI, 82.6–95.5	81 (86.2); 95% CI, 77.5–92.4

[a]The per-protocol set is a subset of patients in the primary analysis efficacy set with no major protocol deviations. UNK, unknown.



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Tisagenlecleucel in POD24

- Overall data less mature
- Patients with POD24 had lower CRR (59.0%; 95% CI, 45.7–71.4) versus those without (87.9%; 95% CI, 71.8–96.6).

Fowler NH et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med. 2022 Feb;28(2):325-332. doi: 10.1038/s41591-021-01622-0. Epub 2021 Dec 17. PMID: 34921238.

ZUMA-5

- Cytokine release syndrome occurred in 97 [78%] of 124 with FL.
- Most cases were grade 1 or 2 (89 [72%] of 124 with FL
- Grade 3 or worse cytokine release syndrome occurred in eight [6%] of 124 with FL
- Median time to onset of cytokine release syndrome after infusion was 4 days (IQR 2–6) in patients with FL. Median duration was 6 days (IQR 4–8) in patients with FL
- Neurological events occurred in 70 [56%] of 124 with FL, grade 1 or 2 events occurred in 51 [41%] with FL, grade 3 or 4 events occurred in 19 (15%) with FL.
- No grade 5 neurological events occurred.

ELARA

Table 3 | Overall safety profile

Parameter	Treated patients, $n = 97$
Any AE of special interest within 8 weeks post infusion, *n* (%)	88 (90.7)
AESIs occurring in patients 8 weeks post infusion, regardless of study drug relationship, *n* (%)	
CRS	47 (48.5)
Grade ≥3	0
Neurological events	36 (37.1)
Grade ≥3	3 (3.1)
Headache	23 (23.7)
Grade ≥3	1 (1)
Dizziness	6 (6.2)
Grade ≥3	0
Immune effector-cell-associated neurotoxicity syndrome	4 (4.1)
Grade ≥3	1 (1.0)

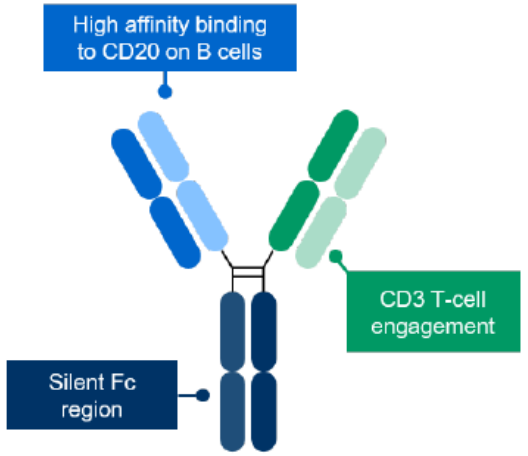
- Offer alternative to CAR-T
  - Several are being explored in various NHL subtypes
    - Most promising are CD20/CD3 bispecfics
    - Longer half-lives compared blinatumomab
    - Differ based on administration
      - IV vs. SQ
      - Duration of administration

Mosunetuzumab

Background

- **FL is characterized by recurrent relapses**
  - response rate and duration decrease with successive treatment lines (conventional agents)[1]
  - POD24 and refractory disease associated with poor prognosis[2,3]
- **Mosunetuzumab**
  - engages and redirects T cells to eliminate malignant B cells[4]
  - off-the-shelf and fixed-duration treatment[4,5]
- **Phase I experience (NCT02500407)[5,6]**
  - encouraging efficacy and manageable safety in patients with R/R FL and ≥2 prior therapies, including POD24 and double refractory[7]
  - effective CRS mitigation with C1 step-up dosing[6,7]

***Mosunetuzumab**:*
CD20xCD3 bispecific antibody[4]



Aim: Share first pivotal Phase II results – mosunetuzumab in R/R FL and ≥2 prior therapies

C, Cycle; CRS, cytokine release syndrome; POD24, progression of disease within 24 months from the start of initial therapy

1. Rivas-Delgado et al. Br J Haematol 2019;184:753–9; 2. Bachy et al. Blood Adv 2021;5:1729–32
3. Seymour et al. Haematologica 2019;104:1202–8; 4. Sun et al. Sci Transl Med 2015;7:287ra70
5. NCT02500407. Available at: https://clinicaltrials.gov; 6. Budde et al. J Clin Oncol 2021 [in press]; 7. Assouline et al. ASH 2020

Planned Therapy/Characteristcs

Study overview

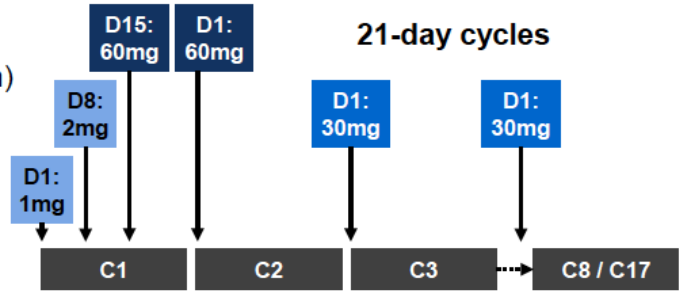
- Single-arm, pivotal Phase II expansion in patients with R/R FL and ≥2 prior therapies

Key inclusion criteria

- FL (Grade 1–3a)
- ECOG PS 0–1
- ≥2 prior regimens, including
  - ≥1 anti-CD20 Ab
  - ≥1 alkylating agent

Mosunetuzumab administration

- Q3W intravenous administration
- C1 step-up dosing (CRS mitigation)
- **Fixed-duration treatment**
  - 8 cycles if CR after C8
  - 17 cycles if PR/SD after C8
- **No mandatory hospitalization**



Endpoints

- Primary: CR (best response) rate by IRF* – assessed vs 14% historical control CR rate[1]
- Secondary: ORR, DoR, PFS, safety and tolerability

*assessed by CT and PET-CT using Cheson 2007 criteria[2]; Ab, antibody; CR, complete response; CT, computed tomography; D, Day; DoR, duration of response; IRF, independent review facility; ORR, objective response rate; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; Q3W, once every 3 weeks; SD, stable disease

1. Dreyling et al. J Clin Oncol 2017;35:3898–905
2. Cheson et al. J Clin Oncol 2007;25:579–86

		N=90
Median number of prior lines, n (range)		3 (2–10)
Prior systemic therapy	Anti-CD20 therapy	90 (100%)
	Alkylator therapy	90 (100%)
	PI3K inhibitor	17 (18.9%)
	IMiD	13 (14.4%)
	CAR-T	3 (3.3%)
Prior ASCT		19 (21.1%)
Refractory to last prior therapy		62 (68.9%)
Refractory to any prior aCD20 therapy		71 (78.9%)
Refractory to any prior aCD20 therapy and alkylator therapy (double refractory)		48 (53.3%)
POD24		47 (52.2%)

Exposure/ORR

	N=90
Number of cycles received*	
<8 cycles	21 (23.3%)
8 cycles	53 (58.9%)
>8 cycles and <17 cycles	5 (5.6%)
17 cycles	11 (12.2%)

*patients receive 8 cycles if in CR after C8, or 17 cycles if in PR/SD after C8

Primary endpoint met: CR rate greater than historical control

Efficacy endpoint[1]	IRF N (%) [95% CI]	Investigator N (%) [95% CI]	Concordance IRF vs investigator
CR	**54 (60%)** [49%, 70%]	54 (60%) [49%, 70%]	93%
ORR	**72 (80%)** [70%, 88%]	70 (78%) [68%, 86%]	96%

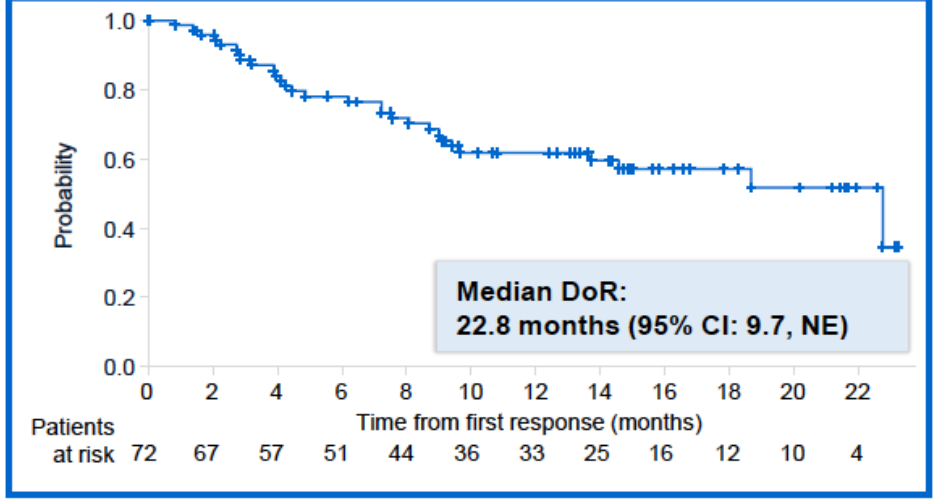
- **60% CR rate significantly greater (p<0.0001)* than 14% historical control CR rate[2]**

*exact binomial test with two-sided alpha level of 5%; CI, confidence interval

1. Cheson et al. J Clin Oncol 2007;25:579–86
2. Dreyling et al. J Clin Oncol 2017;35:3898–905

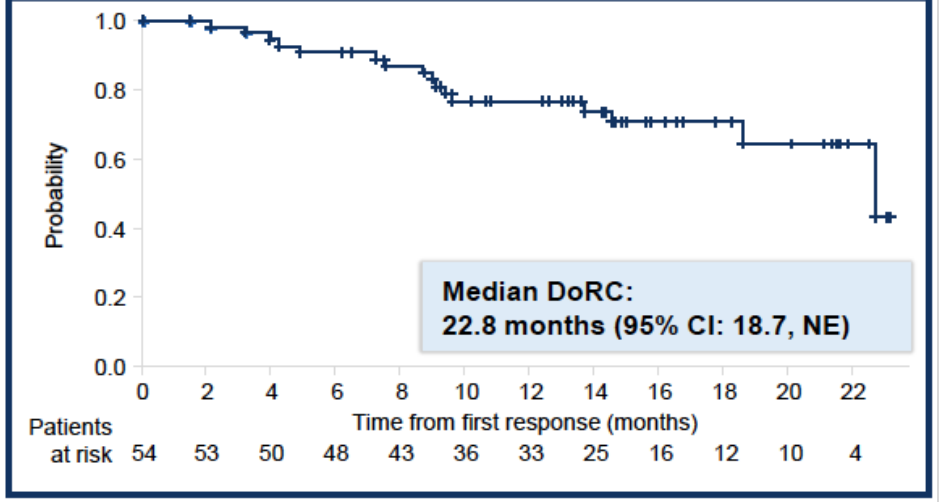
Duration of response

Duration of response in responders



Median time to first response, mo (range)	1.4 (1.1, 8.9)
12-month event-free rate, % (95% CI)	62% (50%, 74%)
18-month event-free rate, % (95% CI)	57% (44%, 70%)

Duration of response in complete responders



Median time to first CR, mo (range)	3.0 (1.1, 18.9)
12-month event-free rate, % (95% CI)	76% (65%, 88%)
18-month event-free rate, % (95% CI)	70% (57%, 84%)

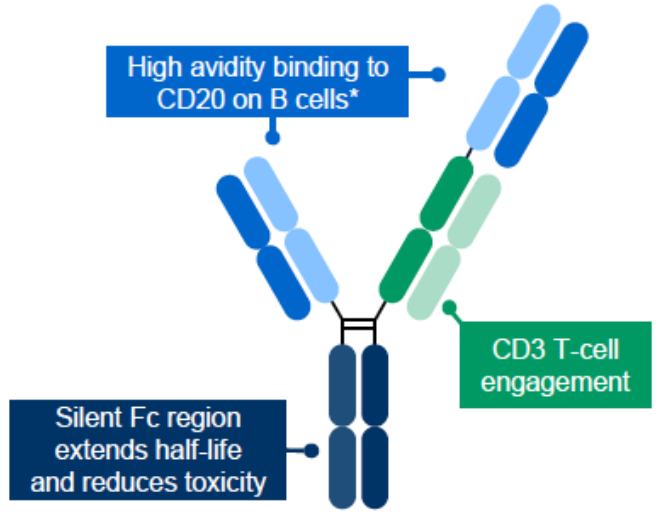
DoRC, duration of response in complete responders; mo, month; NE, not estimable

Glofitamab

Background

- **FL is characterized by recurrent relapses**
  - response rate and duration decrease with successive lines of therapy (conventional agents)[1]
  - POD24 and refractory disease associated with worse prognosis[2,3]
- **Glofitamab**
  - engages and redirects T cells to eliminate malignant B cells[4]
  - off-the-shelf and fixed duration of treatment[4,5]
- **Phase I/II experience (NCT03075696)[5]**
  - promising efficacy and manageable safety as monotherapy and in combination with obinutuzumab in heavily pre-treated R/R B-NHL[6,7]
  - effective CRS mitigation with obinutuzumab pre-treatment and/or C1 step-up dosing[6,7]

Glofitamab: *CD20xCD3 bispecific antibody with 2:1 configuration for increased potency vs 1:1 configuration*[4]

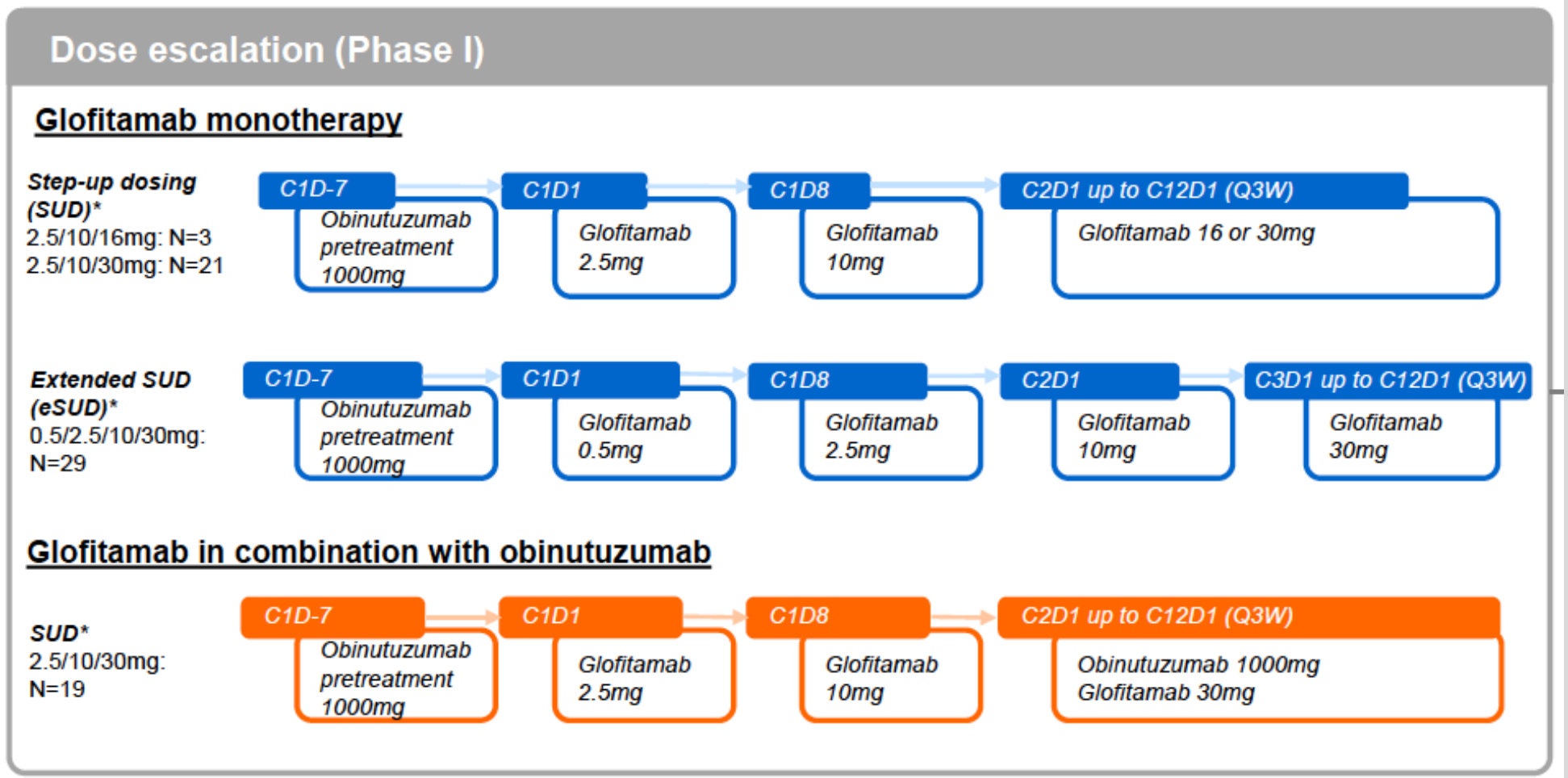


Aim: share updated phase I/II results - glofitamab monotherapy and in combination with obinutuzumab in R/R FL

*Obinutuzumab binds to the same CD20 epitope as glofitamab. B-NHL, B-cell non-Hodgkin lymphoma; C, cycle; CRS, cytokine release syndrome; POD24, progression of disease within 24 months from the start of initial therapy

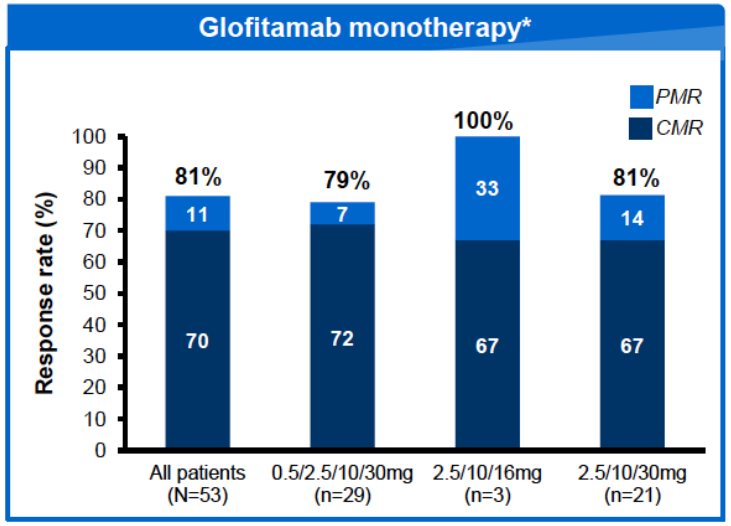
1. Rivas-Delgado et al. Br J Haematol 2019; 2. Bachy et al. Blood Adv 2021; 3. Seymour et al. Haematologica 2019; 4. Bacac, et al. Clin Cancer Res 2018; 5. NCT03075696. Available at: https://clinicaltrials.gov; 6. Hutchings, et al. JCO 2021; 7. Morschhauser, et al. ASH 2019

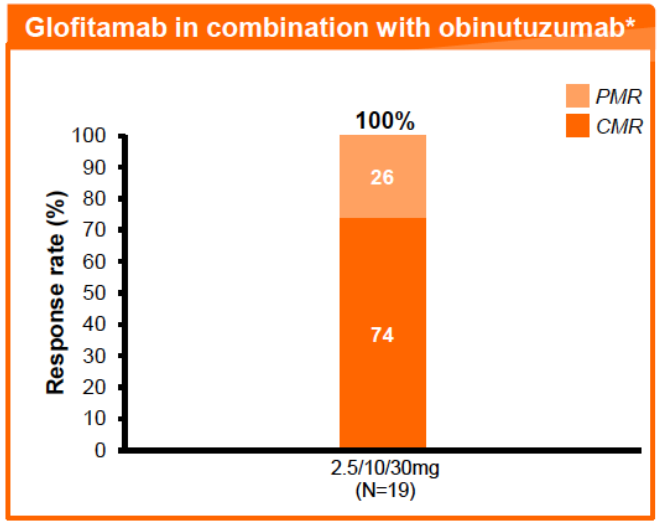
DOSING

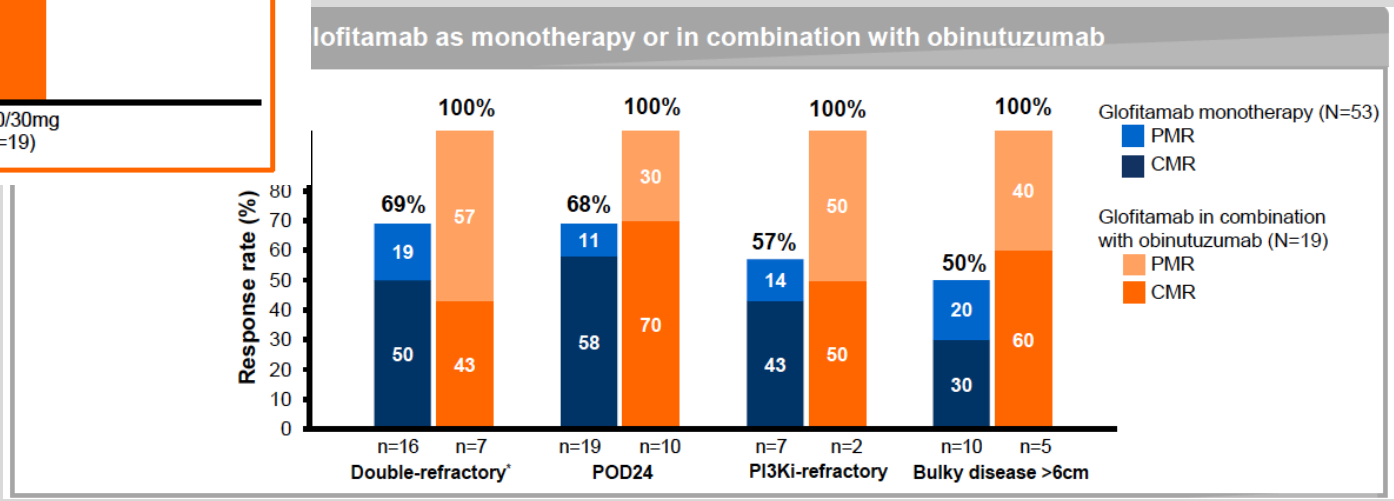

Dose escalation (Phase I)
Glofitamab monotherapy
Step-up dosing (SUD)*
2.5/10/16mg: N=3
2.5/10/30mg: N=21
C1D-7
Obinutuzumab pretreatment 1000mg
C1D1
Glofitamab 2.5mg
C1D8
Glofitamab 10mg
C2D1 up to C12D1 (Q3W)
Glofitamab 16 or 30mg
Extended SUD (eSUD)*
0.5/2.5/10/30mg: N=29
C1D-7
Obinutuzumab pretreatment 1000mg
C1D1
Glofitamab 0.5mg
C1D8
Glofitamab 2.5mg
C2D1
Glofitamab 10mg
C3D1 up to C12D1 (Q3W)
Glofitamab 30mg
Glofitamab in combination with obinutuzumab
SUD*
2.5/10/30mg: N=19
C1D-7
Obinutuzumab pretreatment 1000mg
C1D1
Glofitamab 2.5mg
C1D8
Glofitamab 10mg
C2D1 up to C12D1 (Q3W)
Obinutuzumab 1000mg
Glofitamab 30mg

Patient characteristics/ORR

High-risk subgroups	Double-refractory*	16 (30.2)	7 (36.8)
	POD24	19 (35.8)	10 (52.6)
	PI3K inhibitor-refractory	7 (13.2)	2 (10.5)
	Bulky disease >6cm	10 (18.9)	5 (26.3)







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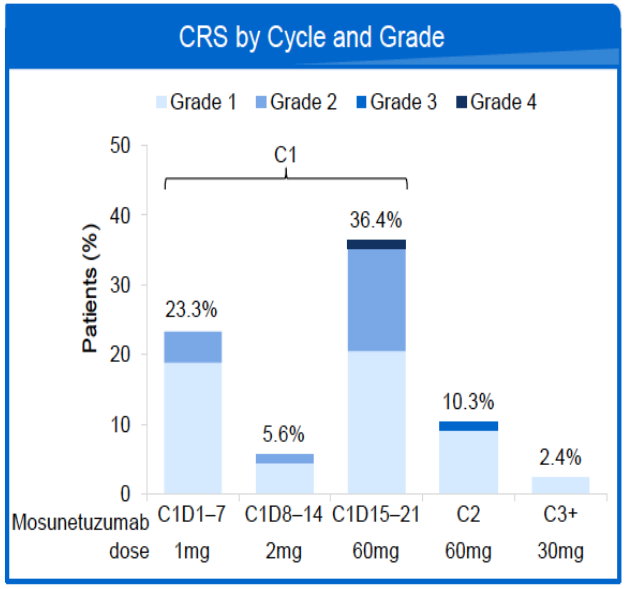
CRS/ICANS

N (%)	N=90
CRS (any Grade)*	40 (44.4%)
Grade 1	23 (25.6%)
Grade 2	15 (16.7%)
Grade 3	1 (1.1%)
Grade 4	1 (1.1%)†
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–23.7)
C1D15	26.6 (0.1–390.9)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	10 (11.1%)
Tocilizumab for CRS management	7 (7.8%)



N (%)	N=90	Additional details
ICANS*	4 (4.4%)	• Confusional state (3.3%; all Grade 1–2†), disturbance in attention and cognitive disorder (1.1% each; all Grade 1†); all resolved
Grade 3	0	• No cases of aphasia, seizures, encephalopathy, or cerebral edema

Mosunetuzumab

N (%) of patients with ≥1 AE unless stated	Glofitamab monotherapy cohorts: Glofitamab SUD cohorts, 2.5/10/16mg and 2.5/10/30mg (N=24)‡	Glofitamab monotherapy cohorts: Glofitamab extended SUD cohort, 0.5/2.5/10/30mg (N=29)	Glofitamab + obinutuzumab cohort (N=19)
Any CRS	19 (79.2)	16 (55.2)	15 (78.9)
Grade 1	15 (62.5)	10 (34.5)	10 (52.6)
Grade 2	3 (12.5)	6 (20.7)	5 (26.3)
Grade 3	1 (4.2)†	0	0
Grade ≥4	0	0	0
Serious AE of CRS (any grade)	12 (50)	9 (31.0)	5 (26.3)
Tocilizumab use in patients with CRS	2 (8.3)	6 (20.7)	5 (26.3)

n (%)	Monotherapy cohorts (N=53)	Glofitamab + obinutuzumab cohort (N=19)
ICANS*	0	0

Glofitamab

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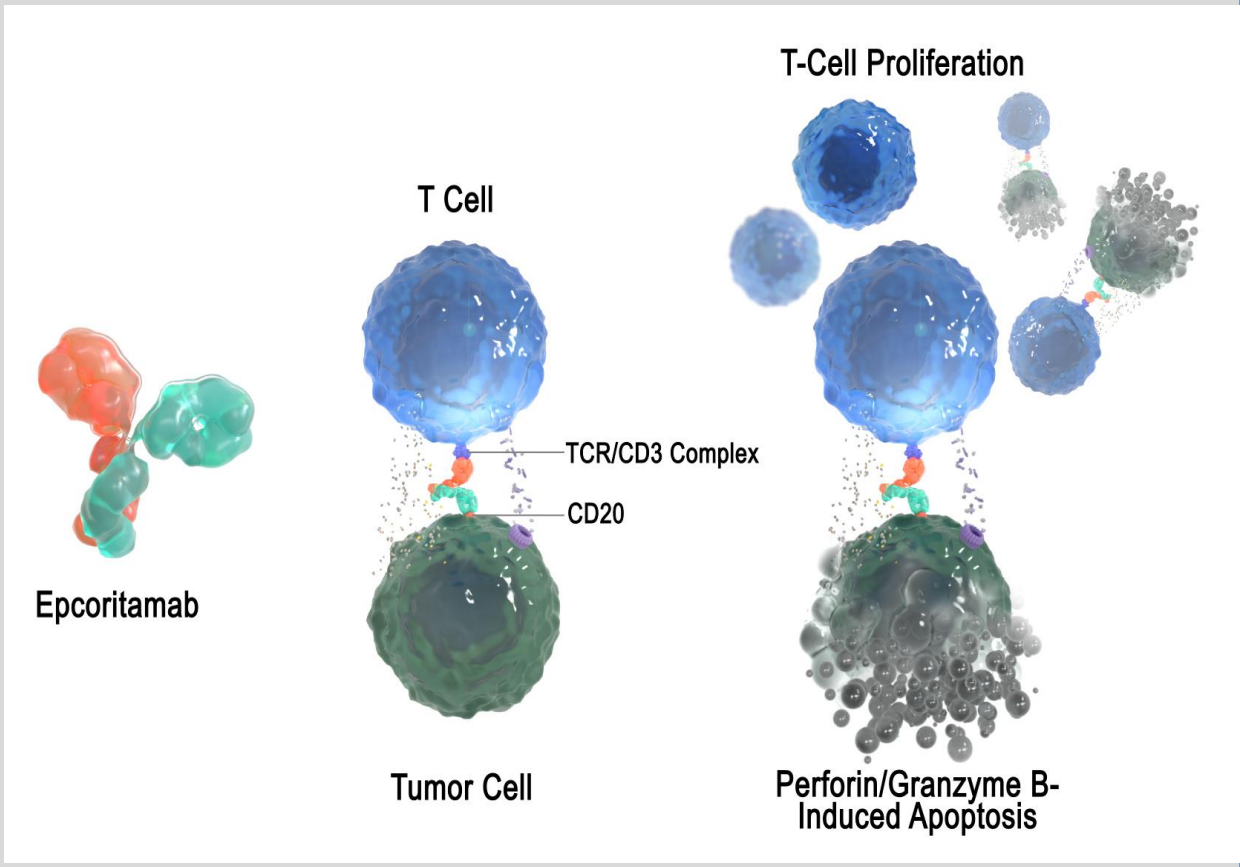
Epcoritamab in B-cell non-Hodgkin Lymphoma

- Epcoritamab is a subcutaneous (SC) IgG1 bispecific antibody (bsAb) that binds CD20 and CD3, which harnesses the patient's immune system to induce T-cell–mediated killing of CD20-positive malignant B-cells[1]
- Epcoritamab key features:
  - SC formulation that allows more gradual increases and lower peaks in plasma cytokine levels as compared to an intravenous formulation, which may help mitigate cytokine release syndrome (CRS)
  - Potent T-cell–mediated killing even when CD20 expression levels are very low
  - Mutations to prevent off-target T-cell killing



1. Engelberts PJ, et al. *EBioMedicine*. 2020;52:102625.

EPCORE NHL-1 Study Design

Dose escalation*

Expansion Cohort

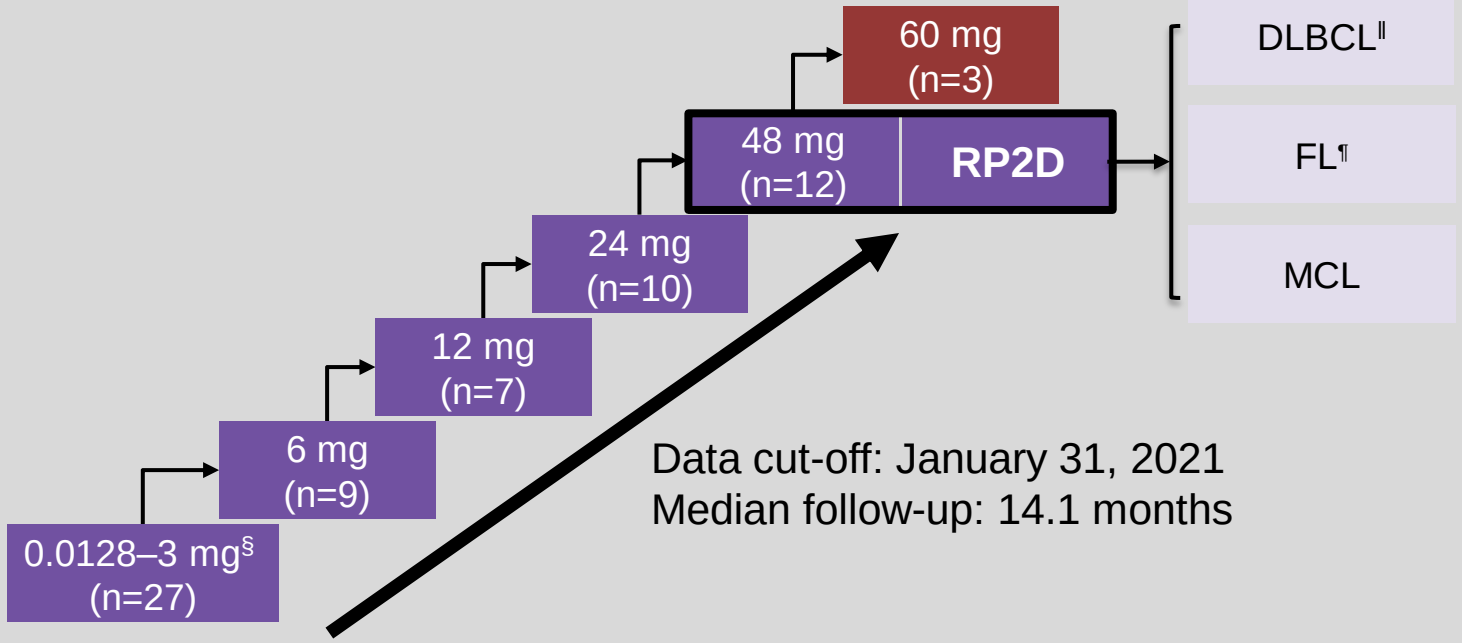
Flat-dose 1 mL SC epcoritamab administered in 28-day cycles
(q1w: Cycles 1–2; q2w: Cycles 3–6; q4w thereafter) until disease progression or unacceptable toxicity

Objectives

Primary
- MTD
- RP2D

Secondary
- Safety
- Anti-tumor activity

Inclusion criteria†
- Adults with R/R CD20+ B-NHL
- Prior treatment with anti-CD20 mAbs
- ECOG PS 0–2
- Measurable disease by CT, MRI, or PET/CT scan**; 6, 12, 18, 24, and every 24 weeks thereafter
- Adequate renal, liver, and hematologic function



To minimize the occurrence and severity of CRS, a priming dose (160 µg, Cycle 1 Day 1) and an intermediate dose (800 µg, Cycle 1 Day 8) of epcoritamab prior to the full dose (beginning on Cycle 1 Day 15), and premedication with corticosteroids, antihistamines, and antipyretics were used (during Cycle 1; as needed in Cycle 2)

*Modified Bayesian optimal interval design consisting of accelerated and standard titration. Accelerated titration includes single-patient cohorts; up to 2 patients may be added (at the currently investigated dose) to obtain additional PK/PD–biomarker data. †Patients previously treated with CAR-T cell therapy were allowed (protocol amended after study start). ‡CT or MRI scans: Weeks 6, 12, 18, 24, and every 12 weeks thereafter. PET scans not required in all patients. §Includes the following priming/final dose levels (mg): 0.004/0.0128, 0.0128/0.04, 0.04/0.12, 0.12/0.38, 0.04/0.76, 0.04/0.25/1.5, 0.04/0.5/3. ‖Includes patients with DLBCL or other aggressive histologies. ¶Includes FL or other indolent histologies

Responses to epcoritamab was seen across B-NHL histologies

Response*	R/R DLBCL†		R/R FL	R/R MCL‡
	12-60 mg	48-60 mg	12-48 mg	0.76-48 mg
Evaluable patients	22§	11§	5‖	4**
ORR, n (%) ¶	15 (68)	10 (91)	4 (80)††	2 (50)
CR	10 (46)	6 (55)	3 (60)	1 (25)
PR	5 (23)	4 (36)	1 (20)	1 (25)
SD, n (%)	1 (5)	0	0	1 (25)
PD, n (%)	5 (23)	0	1 (20)	0

Represents the modified response-evaluable set. *Data are not shown for 23 patients with R/R DLBCL and 6 patients with FL who received <12 mg doses and for 6 additional patients with other R/R B-NHL histologies. †Includes 3 patients who received 60-mg dose before RP2D was determined. ‡3 patients had blastoid/pleomorphic MCL; 1 had unknown histology. §Excludes 1 patient who discontinued before first assessment due to COVID-19. ‖Excludes 1 patient who discontinued before first assessment due to cardiac bypass surgery. ¶Response rates are based on number of evaluable patients (defined as patients with ≥1 post-baseline disease assessment or who died without a post-baseline disease assessment). **Includes 1 patient who died before assessment. ††6/10 patients had response evaluation by PET scans (not mandatory until recent protocol amendment).

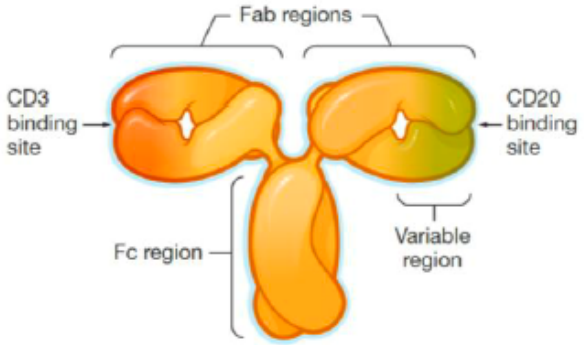
Treatment-emergent AEs, n (%)	Epcoritamab Dose			Total (N=68)
	≥24 mg (n=53)	48 mg (N=12)	60 mg (n=3)	
Cytokine release syndrome				
Grade 1	15 (28)	4 (33)	1 (33)	20 (29)
Grade 2	15 (28)	4 (33)	1 (33)	20 (29)
Grade 3	0	0	0	0
Neurological symptoms				
Grade 1	2 (4)	0	0	2 (3)
Grade 2	0	0	0	0
Grade 3	2 (4)	0	0	2 (3)
Tumor lysis syndrome				
Grade 3	0	1 (8)	0	1 (1)

- Majority of CRS events occurred in Cycle 1
- Neurotoxicity was limited and transient (median [range] 1.5 [<1–3] days) and manageable with standard therapy

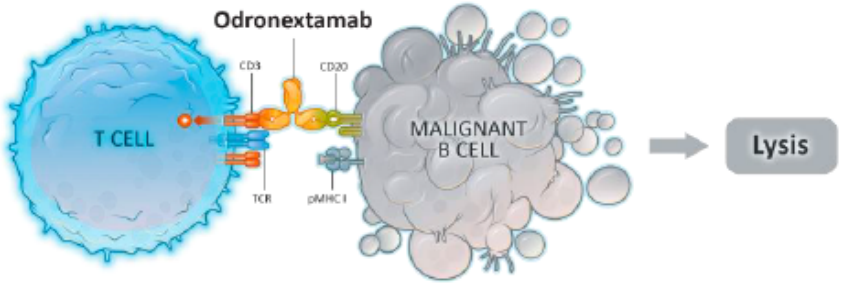
Odronextamab

Introduction

Odronextamab bispecific antibody structure



Odronextamab mechanism of action



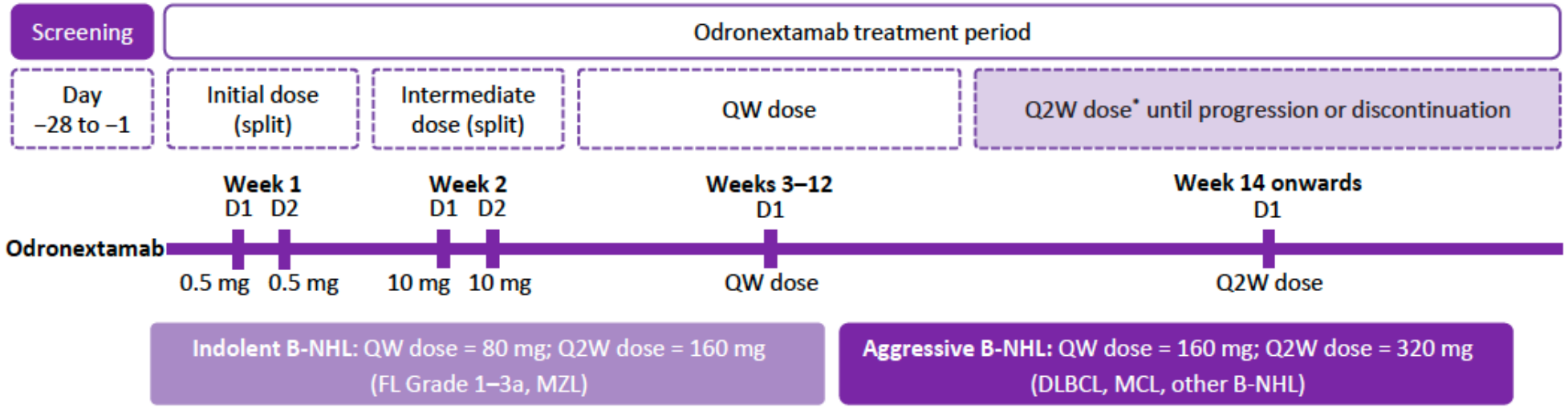
- Odronextamab (REGN1979) is a CD20 x CD3 bispecific antibody:
  - Binds to CD3 on T cells and CD20 on malignant B cells, triggering T-cell-mediated cytotoxicity independent of T-cell-receptor recognition[1,2]
- Off-the-shelf treatment for IV infusion
- Results from a first-in-human, Phase 1 study (NCT02290951; R1979-HM-1333) investigating odronextamab in patients with R/R B-NHL have been reported previously, and at ASH this year[3,4]
- Here, we report the study design of a potentially pivotal Phase 2, open-label, multi-cohort study designed to assess the antitumor activity and safety of odronextamab monotherapy in patients with R/R B-NHL (NCT03888105; R1979-ONC-1625)

B-NHL, B-cell non-Hodgkin lymphoma; IV, intravenous; R/R, relapsed/refractory.

1. Smith EJ, et al. *Sci Rep*. 2015;5:17943;
2. Choi BD, et al. *Expert Opin Biol Ther*. 2011;11:843–53;
3. Bannerji R, et al. *Blood*. 2019;134(Supplement_1):762;
4. Bannerji R, et al. ASH Annual Meeting 2020. Abstract #400.

Dosing

Odronextamab dose schedule



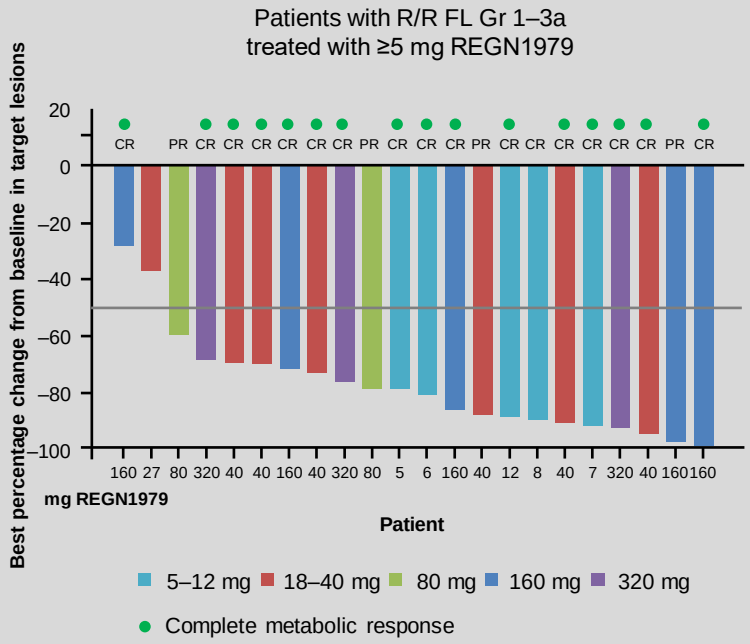
- Odronextamab is administered IV in the outpatient setting†
- Dexamethasone premedication‡ and split, step-up doses are used to mitigate the risk for CRS
- Response is assessed according to Lugano criteria: Q8W in first year, Q12W in second year, and Q24W thereafter

*If a patient has demonstrated a CR that is durable for at least 9 months, then study treatment will be administered Q4W at the same dose.
†Patients are hospitalized for observation during step-up dosing and for the first full QW dose.
‡Dexamethasone is administered IV prior to each odronextamab infusion during weeks 1–4, before being tapered or discontinued, or substituted with a different corticosteroid, from week 5.
B-NHL, B-cell non-Hodgkin lymphoma; CR, complete response; CRS, cytokine release syndrome; D, day; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IV, intravenous; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; QW, once weekly; QXW, once every X weeks.

Efficacy Follicular

ORR/CR rate in patients treated with REGN1979 ≥5 mg was 95%/77%

BOR by Lugano Criteria[1]	REGN1979 dose groups						
	<5 mg (N=7)	5–12 mg (N=5)	18–40 mg (N=7)	80 mg (N=2)	160 mg (N=5)	320 mg (N=3)	Total for ≥5 mg (N=22)
ORR (CR/PR), **n** (%)	**1** (14.3)	**5** (100)	**6**(85.7)	**2** (100)	**5** (100)	**3** (100)	**21** (95.5)
Complete response	**1** (14.3)	**5** (100)	**5**(71.4)	0	**4** (80.0)	**3** (100)	**17** (77.3)
Partial response	0	0	**1** (14.3)	**2** (100)	**1** (20.0)	0	**4** (18.2)
Stable disease	**4** (57.1)	0	**1** (14.3)	0	0	0	**1** (4.5)
Progressive disease	**2** (28.6)	0	0	0	0	0	0

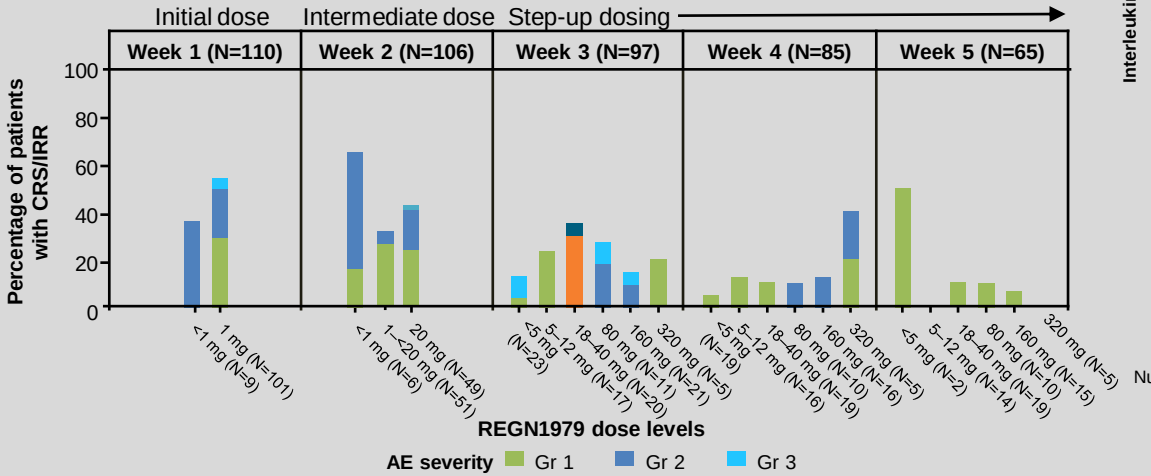


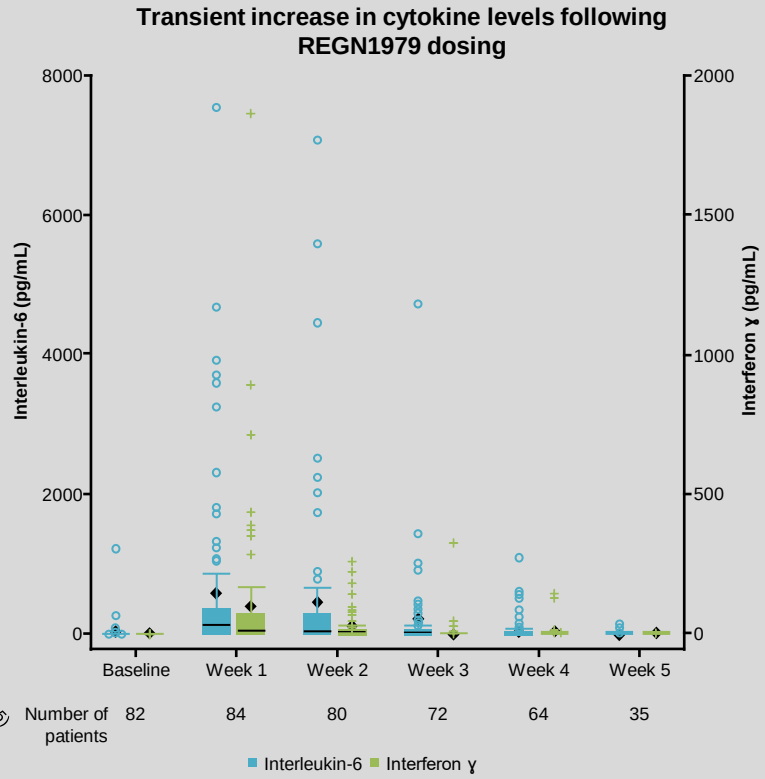
*First dose at least 12 weeks before data cut-off. BOR, best overall response; CR, complete response; FL, follicular lymphoma; Gr, grade; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory. 1. Cheson BD et al. *J Clin Oncol.* 2014;32:3059–3067.

Data cut-off date: September 03, 2019

AEs with step up dosing

- IRR/CRS events occurred predominantly during Weeks 1–3 and declined thereafter, without dose-dependent increase in incidence or severity
- At data cut-off, eight patients experienced Gr 3 IRR/CRS*, without reported Gr 4 or 5 IRR/CRS events†
  - After data cut-off, one patient with aggressive MCL blastoid variant, with bone marrow involvement and bulky disease, experienced Gr 4 CRS (and TLS)
- No patient discontinued due to IRR/CRS





*IRR, infusion-related reaction according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03; CRS, cytokine release syndrome according to adapted Lee DW et al. *Blood* 2014;124:188–195.; †For patients who experienced both IRR and CRS during the same week, the maximum Gr of either was used. AE, adverse event; Gr, grade; MCL, mantle cell lymphoma; TLS, tumor lysis syndrome.

Data cut-off date: September 03, 2019

Conclusion

- 1L Follicular remains without a SOC with several options available
- Unfortunately, no prognostic score can identify highest risk patients (POD24)
- R2 currently best option in 2L for those who receive CIT with 1L treatment
- 3L and beyond have several options
  - Tazemetostat
  - Copanlisib
  - CAR-T
- Bispecifics likely to get approval soon
  - Will compete with CAR-T as most effective 3L option until combination studies complete which would move bispecifics to 1L or 2L therapy.