Foliküler Lenfoma İLEG ASH Sonrası Lenfoproliferatif Hastalıklar Güncellemesi

Dr. O. Meltem Akay

Koç Üniversitesi Tıp Fakültesi Hematoloji BD

Foliküler Lenfoma

Birinci basamak FL tedavisi

- İmmünokemoterapi: FOLL12 çalışması alt grup analizi
- OB-VEN: PrECOG 0403 çalışması
- R2: Relevance çalışması 6-yıl takip

Relaps refrakter FL tedavisi

- R2: Magnify çalışması
- Bispesifik antikorlar: Mosunetuzumab, Glofitamab
- CAR-T hücre tedavisi: Elara çalışması altgrup analizi, Standart tedaviler ile karşılaştırma

İdame tedavisi

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FONDAZIONE ITALIANA LINFOMI

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Impact of Immunochemotherapy with R-Bendamustine or R-CHOP in the Post-Induction Management of Treatment Naïve Advanced Stage Follicular Lymphoma Patients: A Subset Analysis of the FOLL12 Trial By the Fondazione Italiana Linfomi (FIL)

S. Luminari*, M.E. Nizzoli, A. Chiarenza, D. Mannina, A. Tucci, C. Boccomini, L. Farina, J. Olivieri, L. Marcheselli, S. Ferrero, L. Arcaini, A. Pulsoni, G. Musuraca, C. Califano, M. Merli, A. Bari, A. Conconi, F. Re, M. Balzarotti, M. Ladetto, C. Patti, A. Pinto, M.G. Cabras, P. Musto, G. Gini, A. Arcari, M. Manni, A. Versari, M. Federico

UNIMORE

* Azienda USL IRCCS Reggio Emilia and University of Modena and Reggio Emilia, Modena, Italy

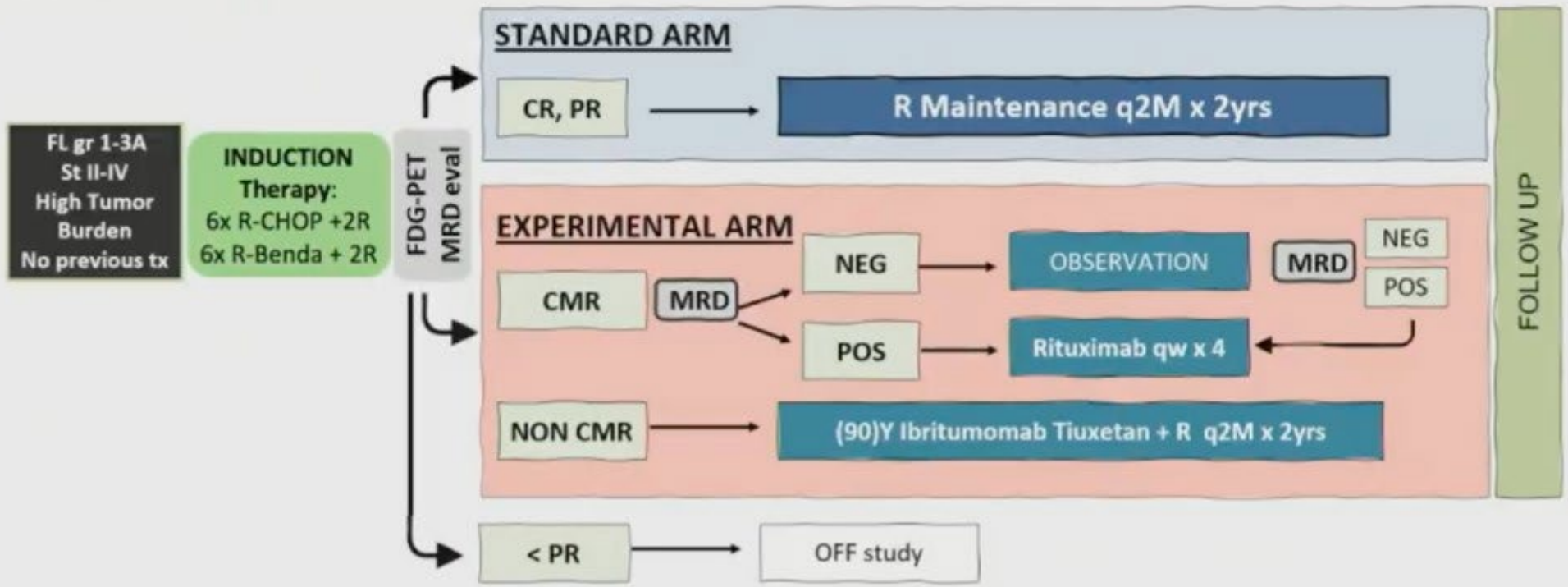
CORE

Study Background and hypothesis

- Standard approach for Advanced stage high tumor-burden FL requires induction immunochemotherapy followed by antiCD20 maintenance for all responding patients.
- CHOP and bendamustine are identified as the main alternative options with discordant data about their relative efficacy (Stil and Bright trial)
- Rituximab maintenance improves PFS after R-CHOP (PRIMA trial) but no prospective data are available for R-Bendamustine

Response-Adapted Postinduction Strategy in Patients With Advanced-Stage Follicular Lymphoma: The FOLL12 Study

EUDRACT N° : 2012-003170-60



Luminari et al JCO 2021.

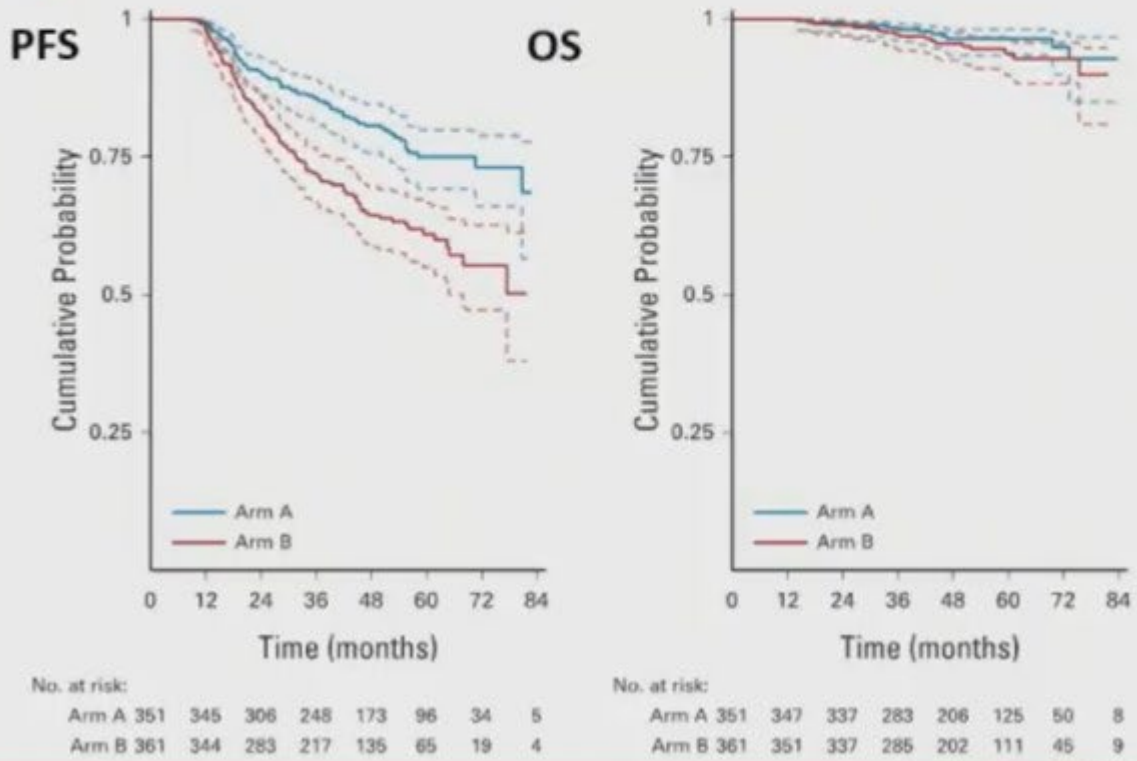
Response-Adapted Postinduction Strategy in Patients With Advanced-Stage Follicular Lymphoma: The FOLL12 Study

N= 722
Median F-up 56 months (1-97),
Events 183/342 (53%)

Non Inferiority design (7% NI margin)

Arm A: standard maintenance

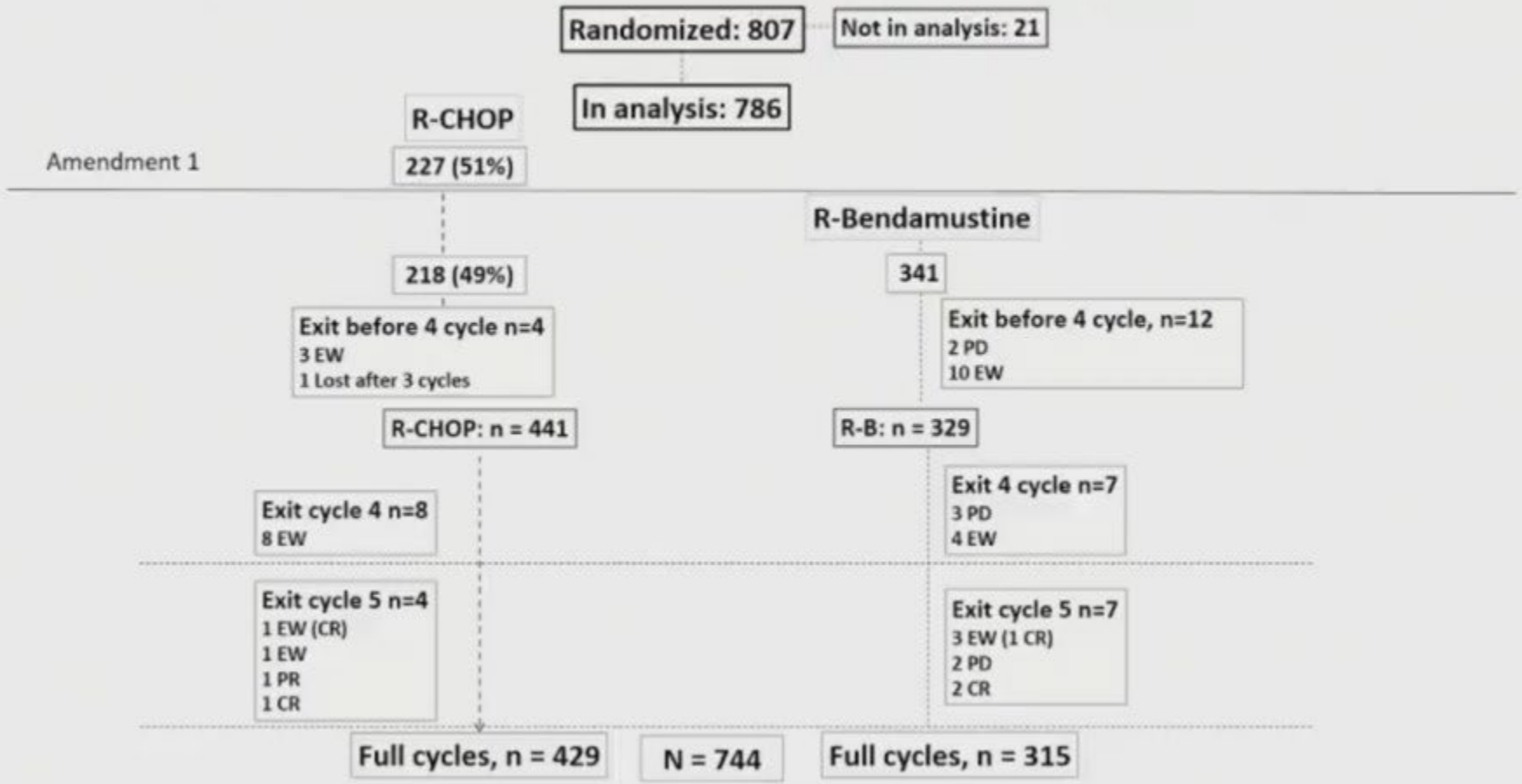
Arm B: response adapted therapy
CMR: 90% No treatment
noCMR: 10% RIT + R maint



Luminari et al JCO 2021.

Patients disposition in the FOLL12 trial

Treatment choice was allowed after amend#1 (N> 227) and was done on a patient basis



Current analysis (unplanned)

To assess the role of induction therapy (R-CHOP or R-Bendamustine) in terms of:

- **Response rates**
- **PFS**
- **OS**
- **Safety**

Patients Characteristic (n=786)

Treatment choice was allowed after amend#1 (N> 227) and was done on a patient basis

Factor	R-CHOP (N=445)	RB (N=341)	Total (N=786)			
	n (%)	n (%)	n (%)	P-value *	OR (95%CI)	Missing
Age >60	189 (42)	202 (59)	391 (50)	<0.001	1.97 (1.48-2.62)	-
Female sex	212 (48)	202 (59)	414 (53)	0.002	1.60 (1.20-2.12)	-
Grade 3a	123 (28)	68 (20)	191 (24)	0.015	0.65 (0.46-0.91)	-
B-symptoms	116 (26)	41 (12)	157 (20)	<0.001	0.39 (0.27-0.58)	6
Bone Marrow+	256 (58)	181 (53)	437 (56)	0.219	0.84 (0.63-1.11)	-
Stage III-IV	402 (91)	295 (87)	697 (89)	0.134	0.70 (0.45-1.10)	3
Hb <12 g/dL	69 (16)	58 (17)	127 (16)	0.625	1.12 (0.76-1.64)	-
LodLIN >6 cm	266 (60)	169 (50)	435 (55)	0.005	0.66 (0.50-0.88)	-
B2M >ULN	240 (54)	187 (55)	427 (54)	0.829	1.04 (0.78-1.38)	-
Nodal sites >4	190 (43)	129 (39)	319 (41)	0.239	0.83 (0.62-1.12)	10
LDH >ULN	106 (24)	67 (20)	173 (23)	0.256	0.81 (0.57-1.14)	20
FLIPI-2 3/5	172 (39)	144 (42)	316 (40)	0.340	1.16 (0.87-1.55)	-
Experim. arm	232 (52)	161 (47)	393 (50)	0.195	0.82 (0.62-1.09)	-

* Fisher's exact test

OR:odds ratio, association with RB vs RCHOP

Response to Treatment

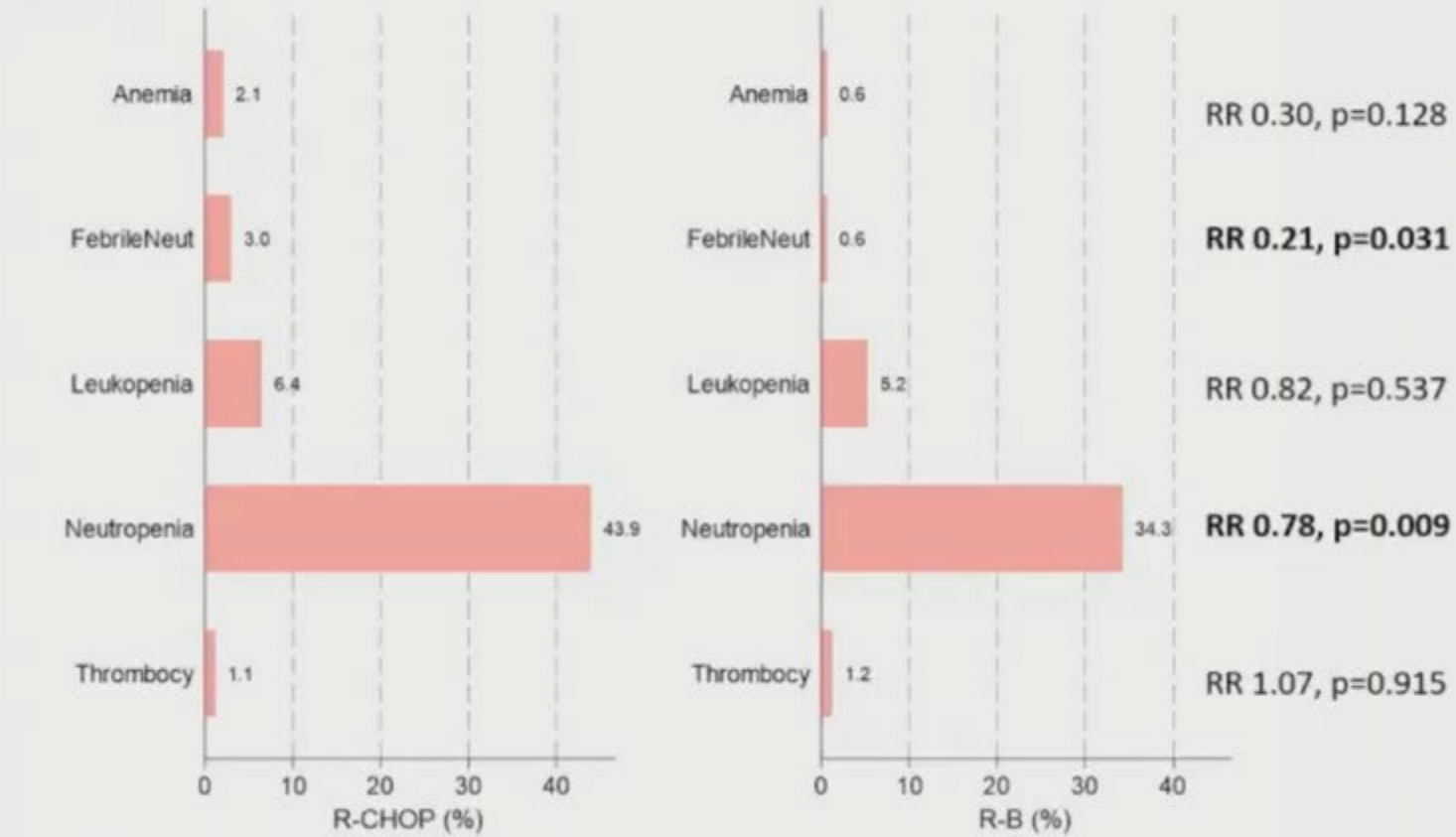
Factor (n=786)	R-CHOP	RB	Total	P-value *	OR (95%CI)
	n (%)	n (%)	n (%)		
Full Cycles	413 (93)	299 (88)	712 (91)	0.019	0.55 (0.34-0.89)
CR EoI	341 (77)	265 (78)	606 (77)	0.733	1.06 (0.76-1.49)
ORR EoI	416 (93)	302 (89)	718 (91)	0.021	0.54 (0.33-0.89)
With full therapy and CR/PR (n=712)					
MRD + with marker at BS (n=393)	37 (16)	21 (13)	58 (15)	0.564	0.83 (0.47-1.48)
Revised PET+ at EoI	42 (10)	23 (8)	65 (9)	0.294	0.74 (0.44-1.27)
Maintenance, yes	212 (51)	163 (55)	375 (53)	0.404	1.14 (0.84-1.53)

* Fisher's exact test

BS baseline; EoI: end of induction; CR: Complete Response; ORR: overall response rate (CR+PR);
OR:odds ratio, association with factor (outcome) RB vs RCHOP, univariable

Hematological Adverse Events during Induction

CTCAE >2

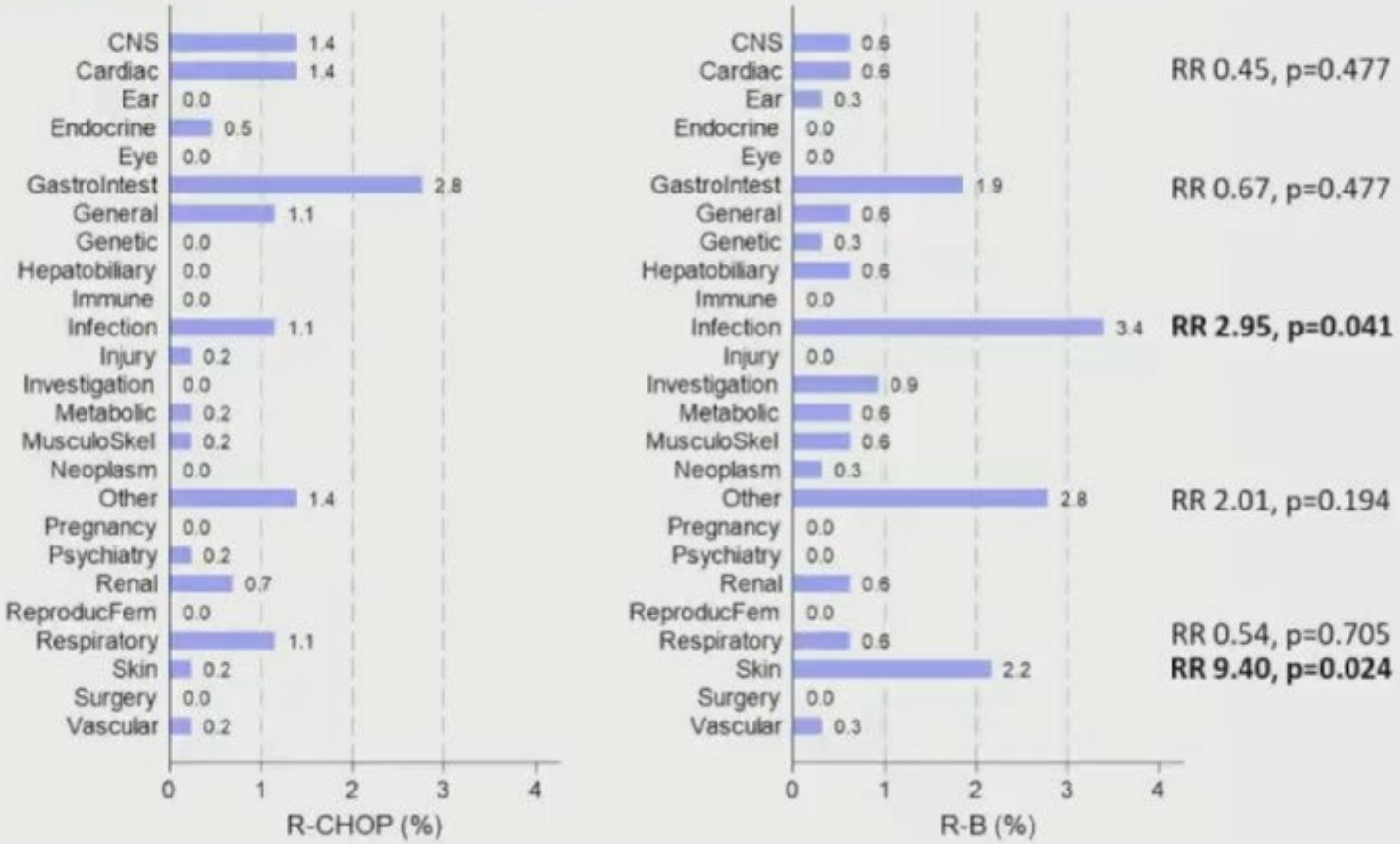


RR: risk ratio R-B vs R-CHOP; p: Fisher's exact test.

Extra-hematological Adverse Events during Induction

CTCAE >2

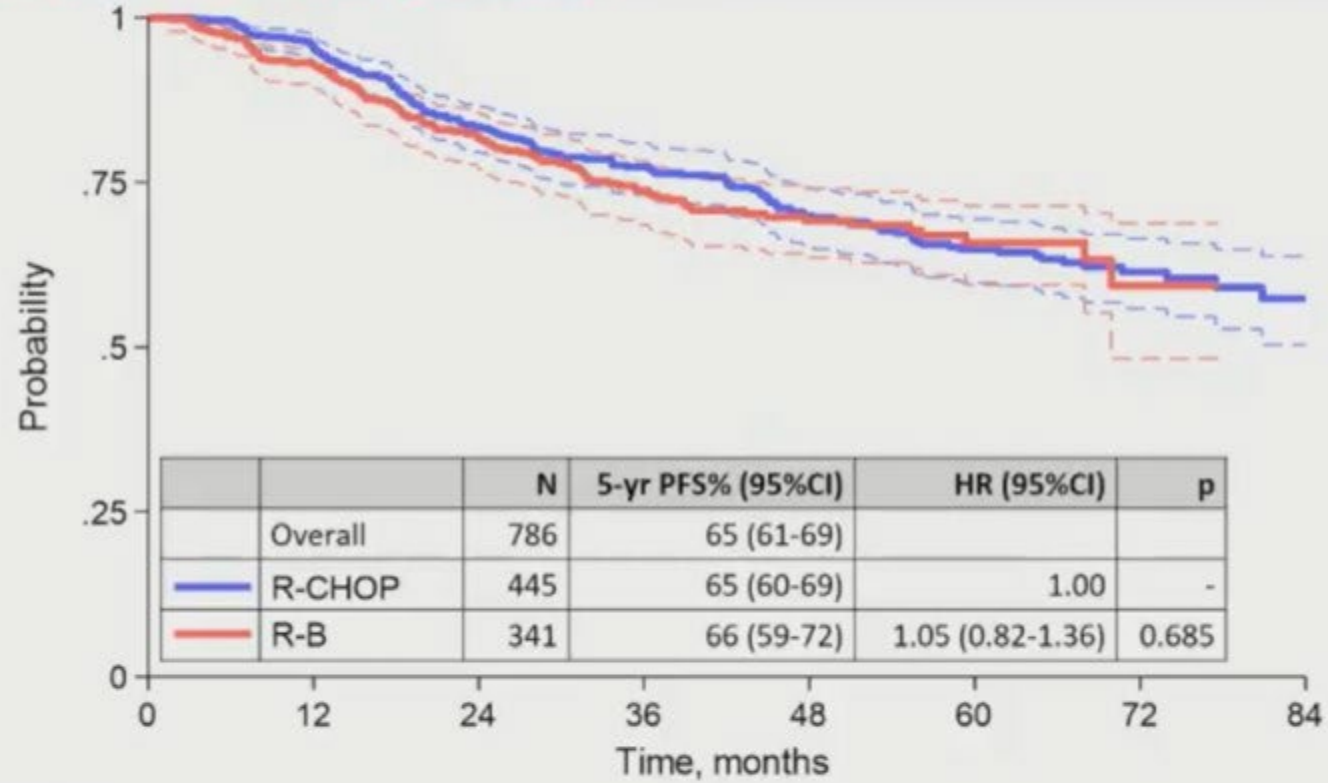
Patients with SAE's by treatment: R-CHOP 29 (6.5%) vs R-B 42 (12.3%)p=0.006



RR: risk ratio R-B vs R-CHOP; p: Fisher's exact test.

Progression Free Survival (n=786)

Non randomized comparison

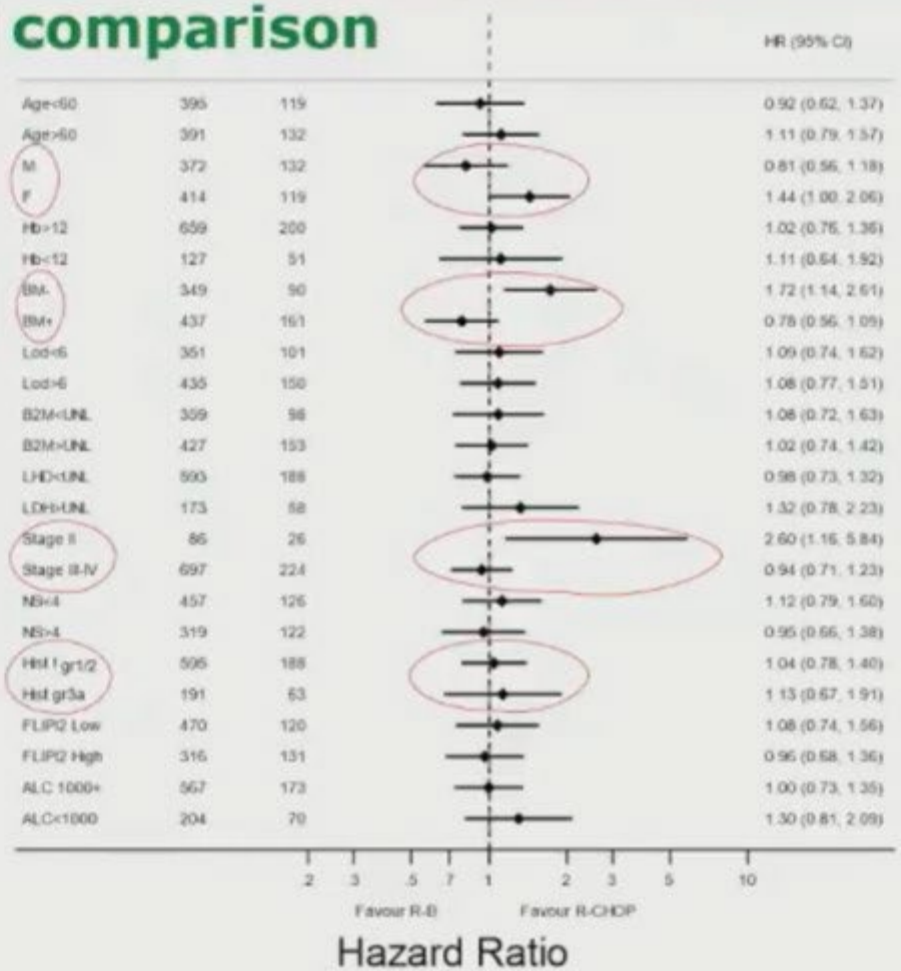


		N	5-yr PFS% (95%CI)	HR (95%CI)	p
	Overall	786	65 (61-69)		
R-CHOP	R-CHOP	445	65 (60-69)	1.00	-
R-B	R-B	341	66 (59-72)	1.05 (0.82-1.36)	0.685

At risk								
RCHOP	445	417	360	316	235	159	76	21
RB	341	306	257	203	119	57	10	0

PFS – Forest Plot

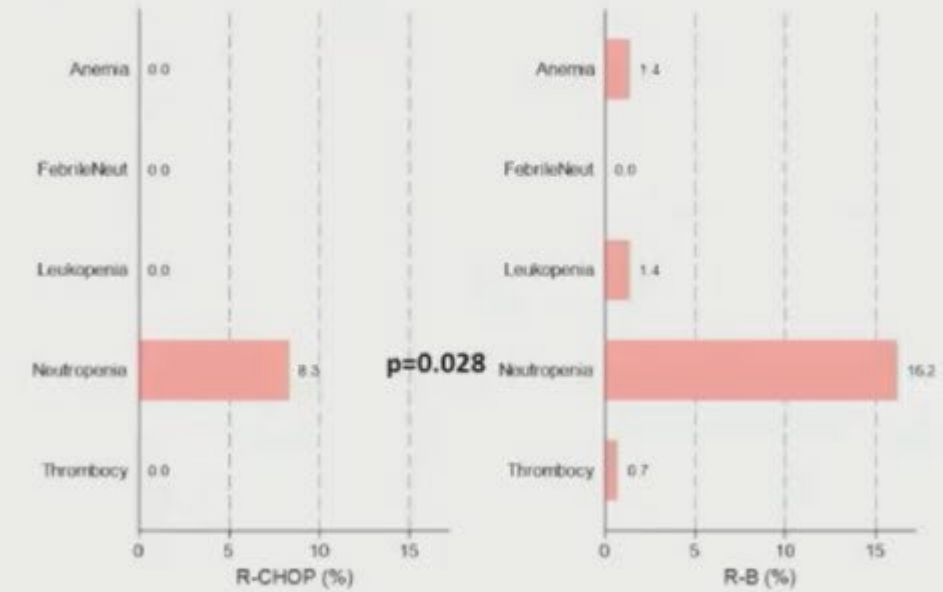
Non randomized comparison



Adverse Events Post-induction. Full doses

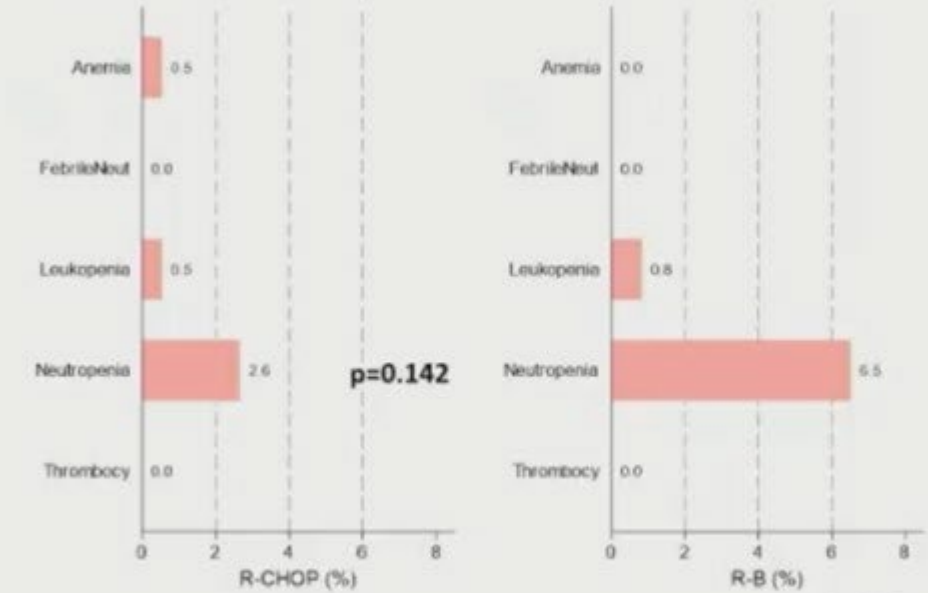
Hematological CTCAE >2

Maintenance (Excluded zevalin)



N=340
N=353

Observational

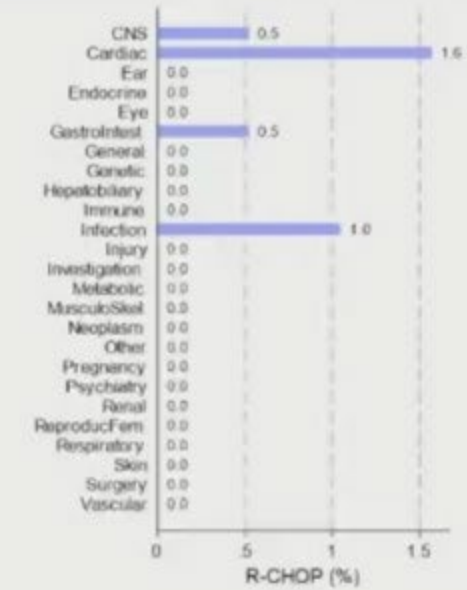


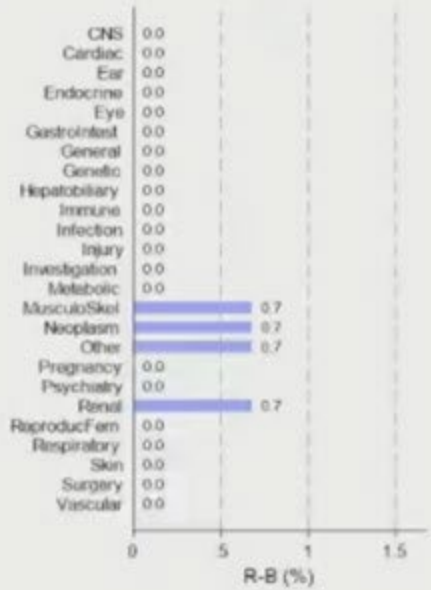
N=312
M=331

Adverse Events Post-induction. Full doses

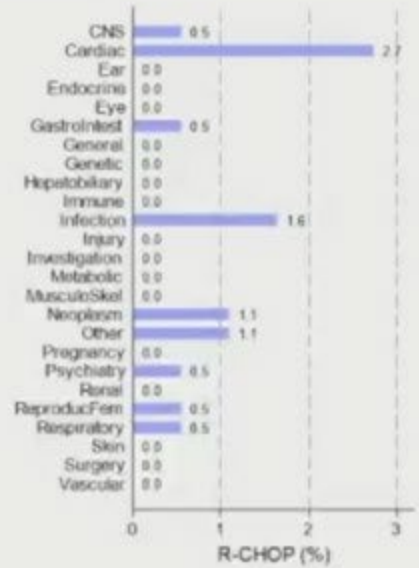
Extra-hematological CTCAE >2

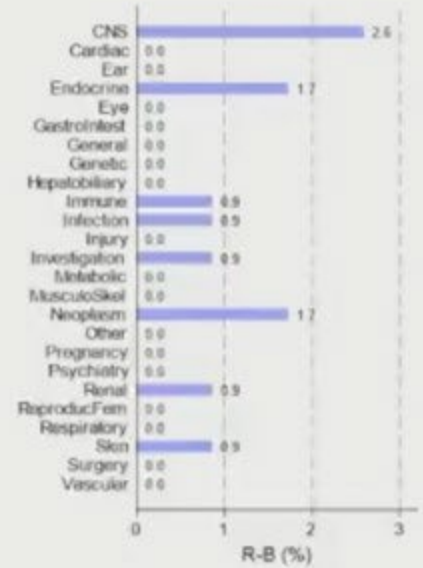
Maintenance (Exluded zevalin)



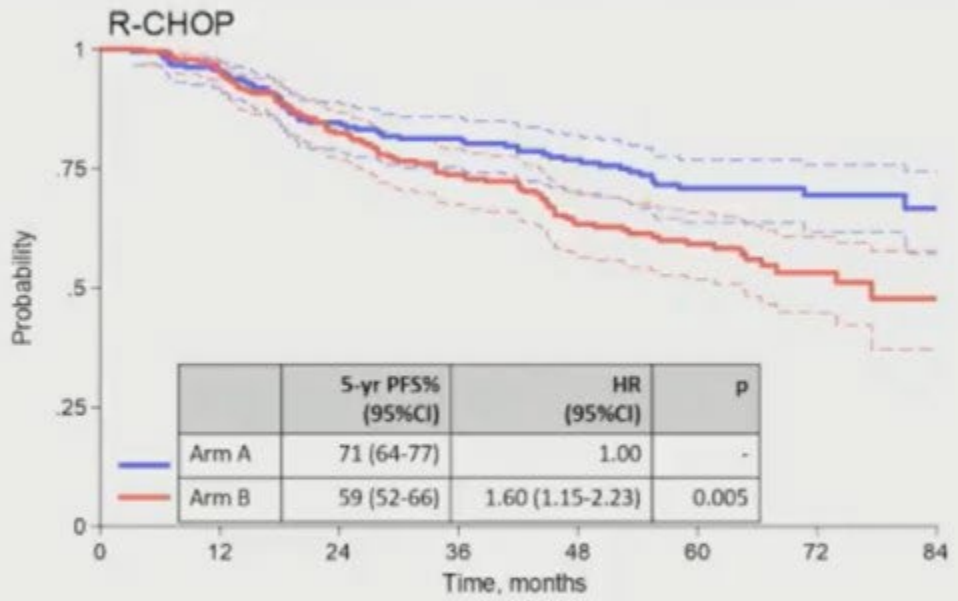


Observational)

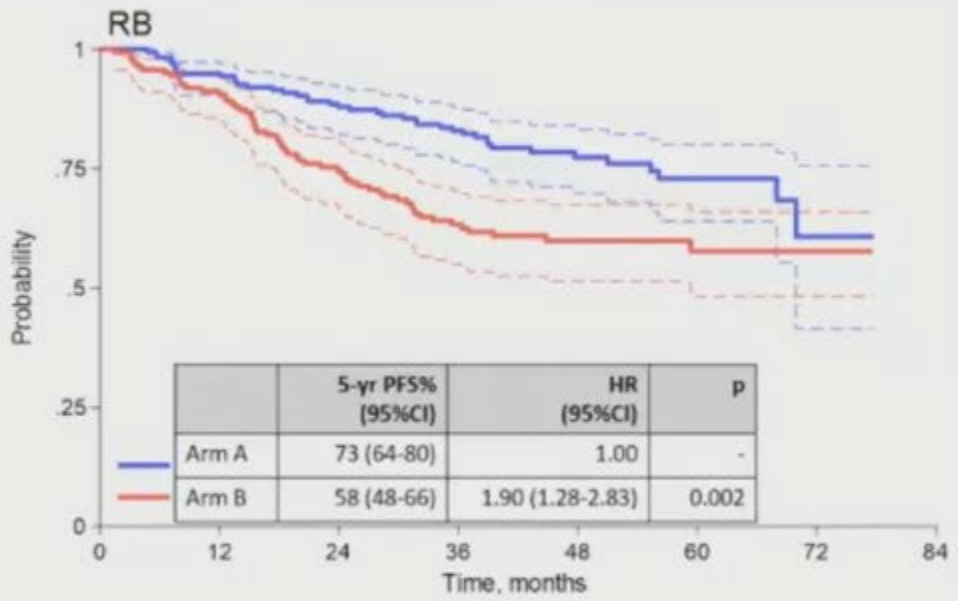




PFS – by randomization arm (n=786)



	5-yr PFS% (95%CI)	HR (95%CI)	p
Arm A	71 (64-77)	1.00	-
Arm B	59 (52-66)	1.60 (1.15-2.23)	0.005



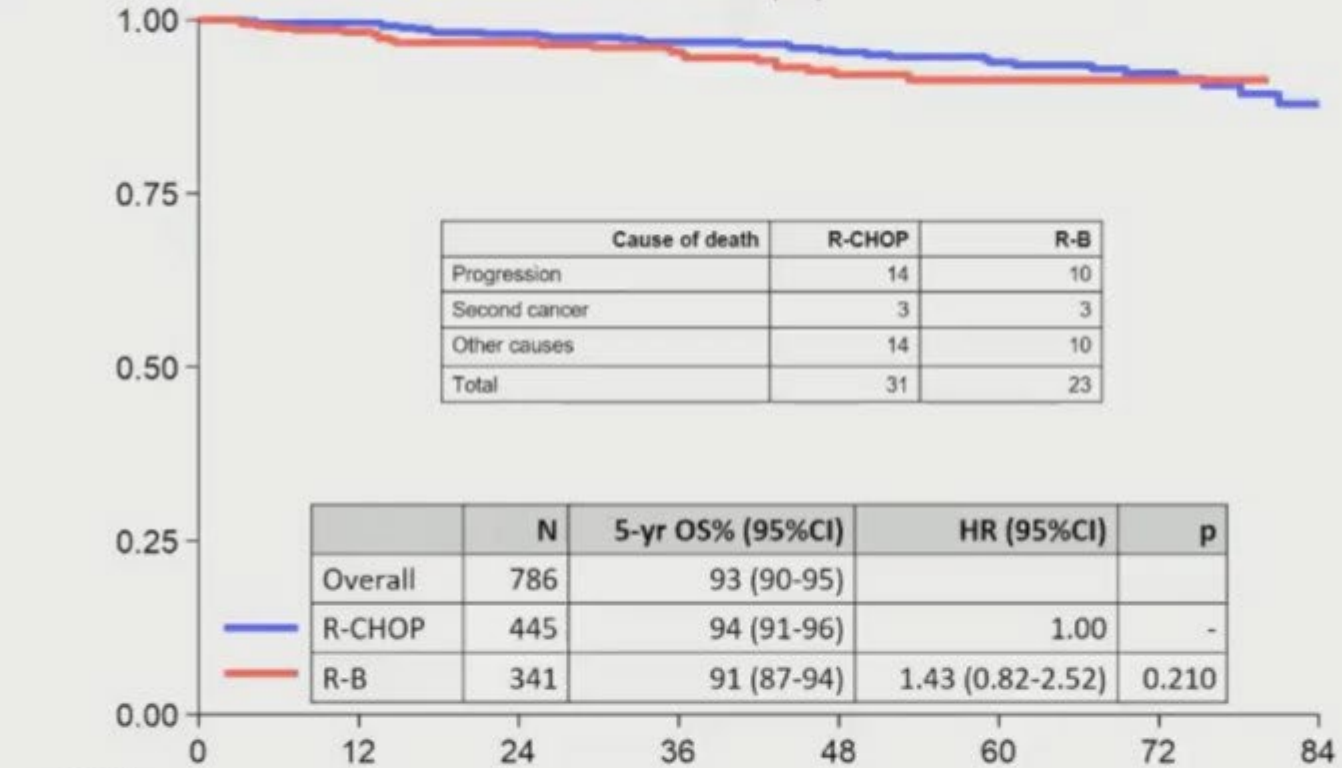
	5-yr PFS% (95%CI)	HR (95%CI)	p
Arm A	73 (64-80)	1.00	-
Arm B	58 (48-66)	1.90 (1.28-2.83)	0.002

Arm A: standard maintenance

Arm B: response adapted therapy

Overall Survival (n=786)

Median follow-up: 56 months (95%CI 54-58) range 1-97 months
Deaths n= 54 (7%)



Cause of death	R-CHOP	R-B
Progression	14	10
Second cancer	3	3
Other causes	14	10
Total	31	23

	N	5-yr OS% (95%CI)	HR (95%CI)	p
Overall	786	93 (90-95)		
R-CHOP	445	94 (91-96)	1.00	-
R-B	341	91 (87-94)	1.43 (0.82-2.52)	0.210

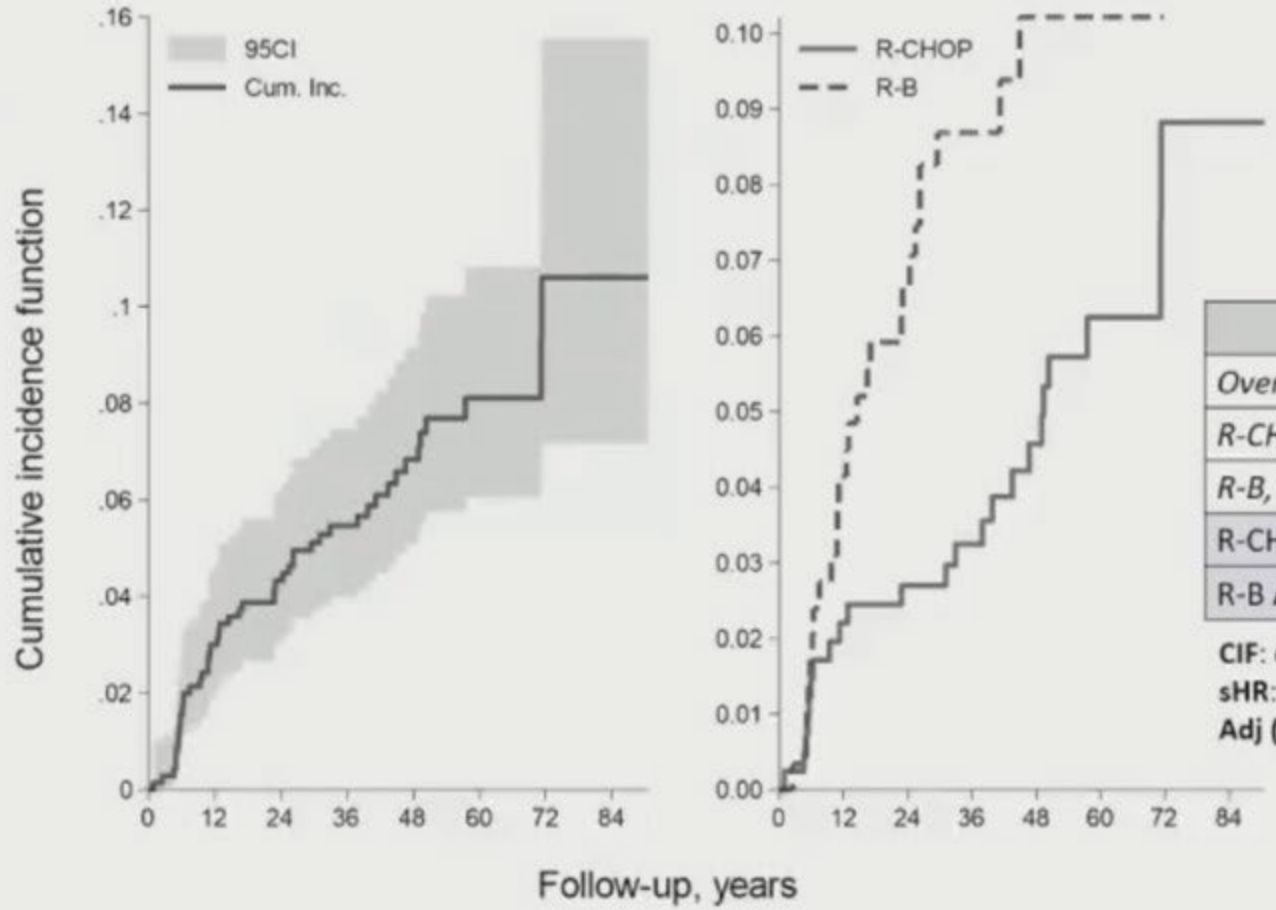
At risk								
RCHOP	445	434	423	391	318	231	129	44
RB	341	322	302	255	159	78	13	0

Second malignancies after EoI (n=712)

Type	R-CHOP	R-B	Total
Hematological	**11**	**12**	**23**
MDS	-	*2*	*2*
DLBCL (tFL)	*9*	*9*	*18*
HL	-	*1*	*1*
CLL	*1*	-	*1*
MZL	*1*	-	*1*
Solid	**12**	**14**	**26**
Lung	-	*2*	*2*
Neuroendocrine	*2*	-	*2*
Gastrointestinal	*2*	*3*	*5*
Prostate	*1*	*1*	*2*
Bladder	*4*	*1*	*5*
Mesenchymal	*1*	-	*1*
Breast	-	*3*	*3*
Thyroid	-	*1*	*1*
Pancreas	*2*	-	*2*
Kidney	-	*1*	*1*
Parotid	-	*1*	*1*
NA	-	*1*	*1*
Total	**23**	**26**	**49**

Excluded 6 basal cell epithelioma

Second malignancies after EoI (n=712)



	5-yr CIF% (95%CI)	sHR (95%CI)	p
Overall	8.1 (6.0-10.6		
R-CHOP, raw	*6.2 (3.9-9.3)*	*1.00*	-
R-B, raw	*10.2 (6.7-14.5)*	*2.06 (1.18-3.60)*	*0.011*
R-CHOP	6.7 (4.5-10.0)	1.00	-
R-B **Adj. (1)**	10.6 (7.2-15.7)	1.83 (1.03-3.24)	0.039

CIF: cumulative incidence function by Gooley
sHR: subdistributional HR, Fine-Gray
Adj (1): sex, Age>60 binary covariate

Conclusions.

- The FOLL12 trial allowed a non randomized comparison between R-CHOP and R-Bendamustine for TN High tumor burden FL
- Bendamustine is favourite option for females and old patients, CHOP is preferred in young high risk subjects
- CHOP and bendamustine showed similar activity and efficacy with different safety profile during induction and maintenance therapy
- Proven efficacy of rituximab maintenance after CHOP and Bendamustine
- Slight increase of non lethal second malignancies after Bendamustine (vs CHOP)

American Society *of* Hematology

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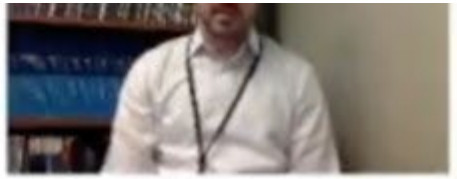
Phase II study of Venetoclax in Combination with Obinutuzumab and Bendamustine in Patients with High Tumor Burden Follicular Lymphoma as Front Line Therapy

PrE0403

Craig A. Portell, MD
University of Virginia
on behalf of all authors

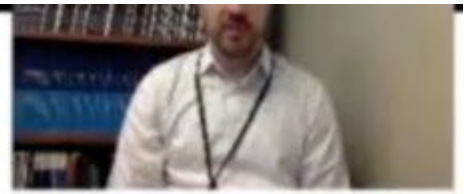
NCT03113422



Background

- Standard treatment for High Tumor Burden (HTB) Follicular lymphoma (FL) includes obinutuzumab and bendamustine (OB)[1]
- Venetoclax (VEN) an oral, BCL-2 inhibitor, is an attractive drug in FL.
  - BCL-2 upregulation through translocation with IGH is pathognomonic for FL
  - Single agent VEN had an ORR of 38% (11/29) with median PFS of 10.8 mo in a phase I study[2].
  - Pre-clinical studies have suggested VEN may be synergistic with chemotherapy
- We evaluated the combination of OB-VEN in frontline HTB-FL
  - Patients accrued between 12/2017 to 11/2020 at 10 US Sites
- Presenting End of Induction response and safety

[1]Marcus R, Davies A, Ando K et al. N Engl J Med 2017;
[2] Davids MS et al, CCR 2021



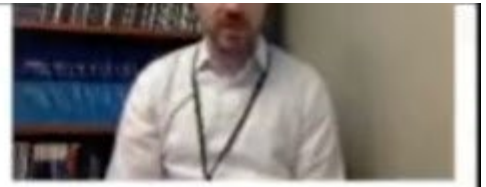
Study Objectives

Primary Objective

- To estimate the proportion of patients given the combination OB-VEN achieving a complete remission (CR) at the end of induction

Secondary Objectives

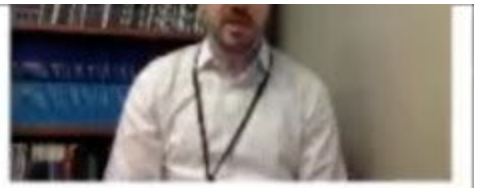
- To determine the ORR of treated patients
- To determine the proportion of patients who achieve a PR with induction therapy and later convert to CR with maintenance
- To evaluate PFS and OS in the intent to treat (ITT) population
- To evaluate the compliance and toxicities of patients receiving induction and maintenance therapy



Key Eligibility

- Age ≥18 years with biopsy-proven follicular B-cell NHL
  - WHO classification: grades 1, 2, and 3a
  - No evidence of transformation to large cell histology
- Meet criteria for High Tumor Burden as defined by:
  - One GELF criteria **OR**
  - FLIPI-1 score ≥3
- Stage II, III or IV disease (Modified Ann Arbor Staging)
- At least one parameter of measurable disease by PET/CT
- Adequate organ and hematologic function
- ECOG PS 0-2

Study Schema



N=56

REGISTRATION

Induction[3]

Cycle 1-6:
Obinutuzumab[1] 1000 mg IV d1 +
Bendamustine 90 mg/m^2 IV d1, 2
every 28 days

Cycle 1-6:
Venetoclax[2] 800 mg PO daily
days 1-10 of each
28 day cycle

PR or SD

Complete Response

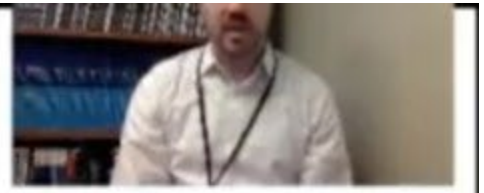
Maintenance[4]

Obinutuzumab 1000 mg IV
every 2 months x 12 cycles

Venetoclax 800 mg PO daily
days 1-28
every 28 days x 24 cycles

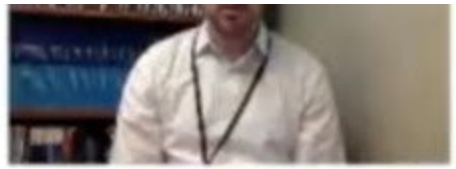
Obinutuzumab 1000 mg IV
every 2 months x 12 cycles

[1] Cycle 1 only: obinutuzumab 100 mg IV day 1 and 900 mg on day 2 followed by day 8 and day 15, 1000 mg IV.
[2] Due to high rate of laboratory TLS in first 21 patients, study was amended to start venetoclax at Cycle 2 through 6 only
[3] Growth Factor was required during induction cycles
[4] Patients move on to the maintenance phase begins 8-12 weeks after induction. Maintenance for 2 years after induction.



N=56		
Age median years (range)	62 (33-79)	
	N	(%)
Male	35	(63%)
Female	21	(38%)
Grade		
I/II	42	(75%)
IIIa	9	(16%)
Missing	5	(9%)
Stage		
II	2	(4%)
III	16	(29%)
IV	38	(68%)
Risk Profile		
High Tumor Burden by GELF	54	(96%)
High Risk FLIPI-1	32	(57%)
*HTB GELF AND High risk FLIPI-1	30	(54%)

Baseline Characteristics



Patient Flow

Eligible & Enrolled (n=57)

→ **Withdrew after registration (n=1)**

Started Induction Therapy (n=56)

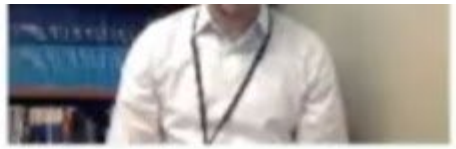
→ **Discontinued induction treatment before 6 cycles (n=11)**
- Adverse events (8)
- Investigator discretion (2)
- Patient withdrawal (1)

Completed 6 cycles induction (n=45)

→ **Completed induction and no maintenance (n=11)**
- Adverse events (4)
- Death (1)
- Investigator discretion (3)
- Patient withdrawal (1)
- Disease progression (1)
- Treatment interruption >28 days (1)

Completed induction and started maintenance (n=34)

Response



End of Induction Response*		
Complete Response	73.2%	41/56
Overall Response	92.9%	52/56

*3 pts unevaluable due to no post-baseline scans (considered non-responders)

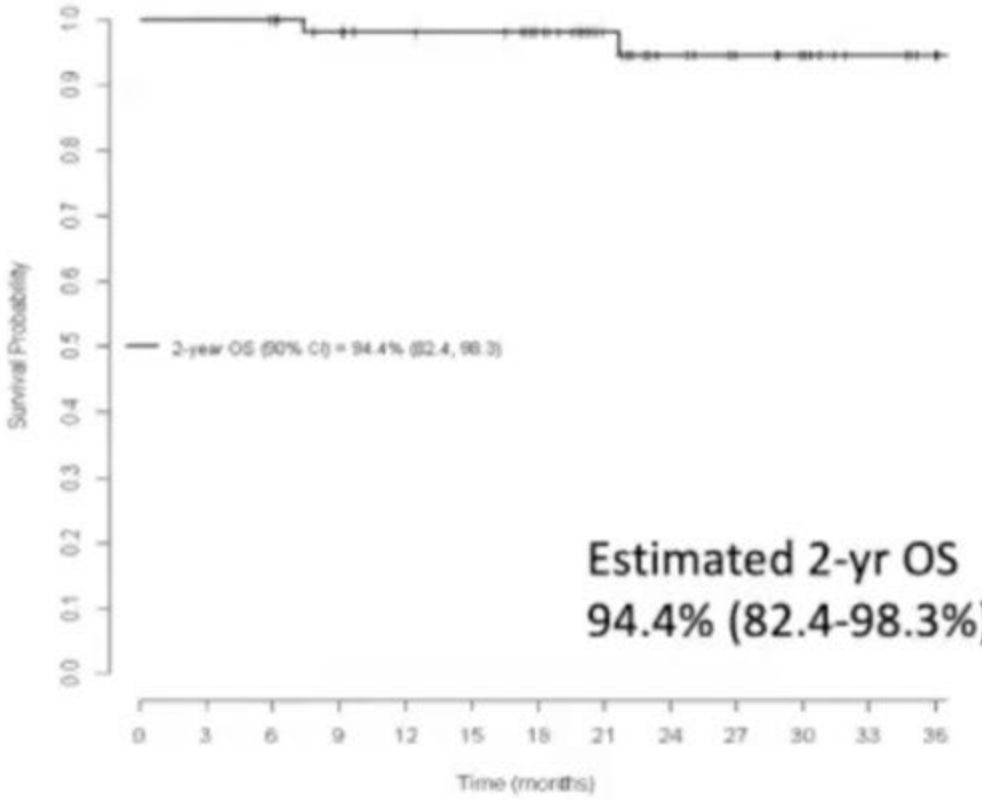
Pre-Planned Primary endpoint of ≥30 CRs was met, thus study positive

*Response based on Lugano Criteria with PET/CT and BM assessment

Response

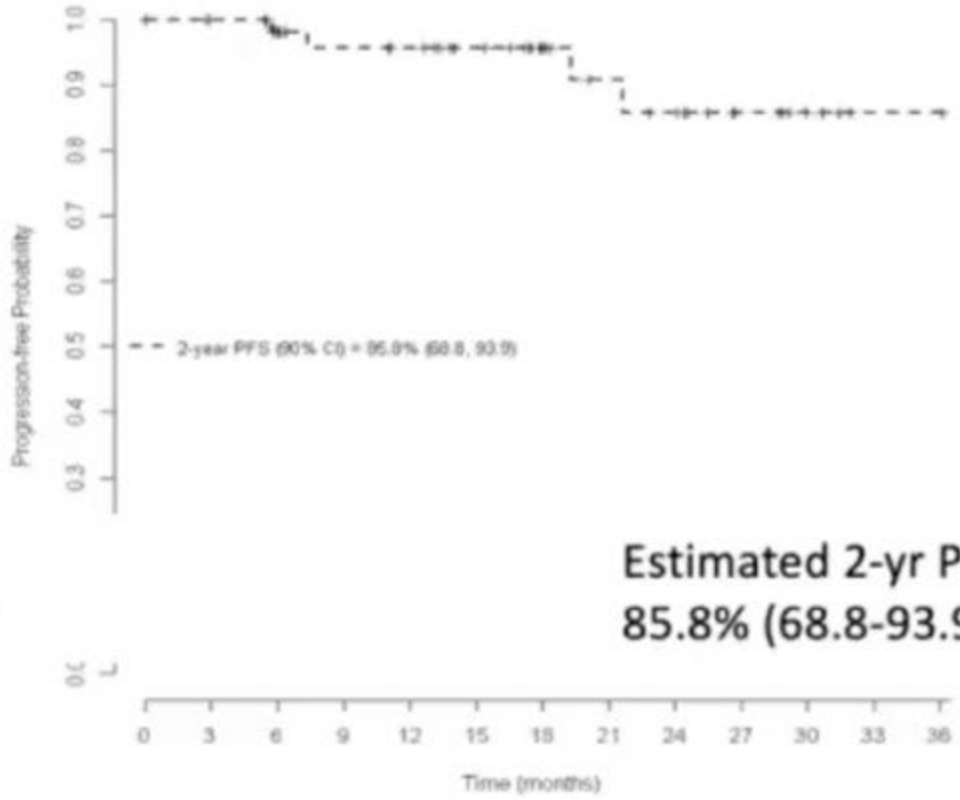
Median Follow up 20.9 months*

Overall Survival



Estimated 2-yr OS
94.4% (82.4-98.3%)

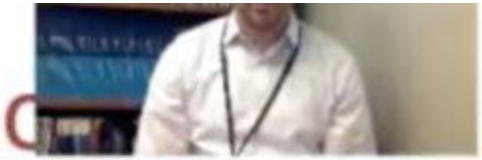
Progression Free Survival



Estimated 2-yr PFS
85.8% (68.8-93.9%)

*At time of data cut-off

Adverse Events[1] (>10%) During Induc



Event	All Grades	Grade ≥ 3	
Nausea	46 (82.1%)	3	(5.4%)
Fatigue	34 (60.7%)	3	(5.4%)
Vomiting	26 (46.4%)	2	(3.6%)
Diarrhea	24 (42.9%)	2	(3.6%)
Thrombocytopenia	23 (41.1%)	8	(14.3%)
Neutropenia	21 (37.5%)	9	(16.1%)
Headache	16 (28.6%)	0	(0%)
Decreased Appetite	15 (26.8%)	1	(1.8%)
Anemia	12 (21.4%)	1	(1.8%)
Infusion related reaction	11 (19.6%)	3	(5.4%)
Hyperuricemia	10 (17.9%)	3	(5.4%)
AST/ALT increase	10 (17.9%)	0	(0%)
Constipation	10 (17.9%)	0	(0%)

[1] Adverse Events collected using CTCAE V5.0

Adverse Events (>10%) During Induct

Event	All Grades	Grade ≥ 3	
Upper respiratory infection	9 (16.1%)	0	(0%)
Tumor lysis syndrome[2]	8 (14.3%)	8	(14.3%)
Abdominal Pain	8 (14.3%)	1	(1.8%)
Alkaline Phosphatase increase	7 (12.5%)	0	(0%)
Dysgeusia	7 (12.5%)	0	(0%)
Dyspepsia	7 (12.5%)	0	(0%)
Pyrexia	7 (12.5%)	0	(0%)
Overall Adverse Events Gr ≥ 3		47	(83.9%)
Serious Adverse Events		31	(55.4%)

[2] TLS was closely monitored in C1: 8/21 participants developed [laboratory] TLS when VEN was administered in C1; no clinical TLS was seen; 0/35 when VEN began in C2, although reporting criteria were also revised

Adverse Events (>10%) During Induct

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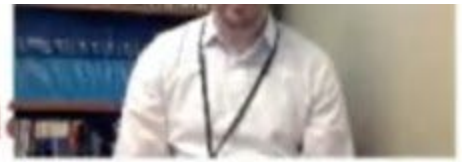
Treatment Emergent AEs of Interest (Induction Pha



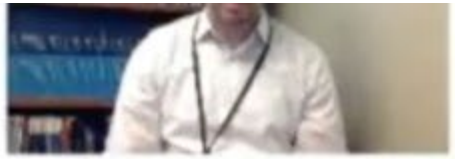
Grade 5 CMV encephalitis as well as PJP pneumonia after C6 of induction

- Study amended as a result
  - Prophylaxis for PJP within 2 weeks of OB and continued through induction
  - Anti-viral prophylaxis for simple viral infections and continued for at least 6 months after induction
  - Monitored for CMV reactivation using Quantitative PCR assay for CMV DNA
    - **Induction Phase:** once a month
    - **Maintenance Phase:** once every 2 months
- No additional cases of CMV reactivation to date

Treatment Emergent AEs of Interest (Maintenance

- Grade 3 PJP pneumonia
  - PJP pneumonia: post 3rd dose of obinutuzumab
  - On Bactrim prophylaxis for 6 months
- Grade 4 BK virus nephropathy leading to ESRD and chronic hemodialysis
  - Post 6 doses of obinutuzumab
- Grade 5 myocarditis
  - Suspected—not proven—to be viral in etiology
  - Post 8 doses of obinutuzumab and 18 months of venetoclax

Treatment modifications



- At the time of the 4th AE of interest (myocarditis):
  - All patients had finished induction
  - Only 7 patients remained on maintenance
  - All other patients had either completed maintenance or discontinued early due to COVID considerations

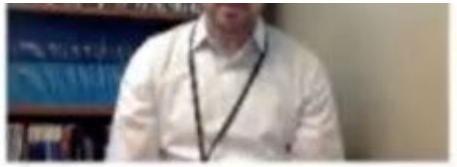
- After discussion with investigators of those 7 patients, it was decided to stop additional maintenance therapy

Conclusions

- This single arm, multi-center Phase II study of OB-VEN in untreated HTB FL showed high CR rate (73%) and met its primary endpoint
- Estimated 2-year PFS of 86% appears promising
- No clinical TLS observed but laboratory TLS was identified. Unclear if attributed solely to VEN 800, as baseline laboratory TLS rate for OB is unknown.
- The rate of Grade ≥3 AE of 83.9% (when viewed with 69% for OB in GALLIUM[1]), and emerging opportunistic infections suggests this combination may be too toxic for this patient population

[1]Hiddeman, JCO 2018

Conclusions cont.



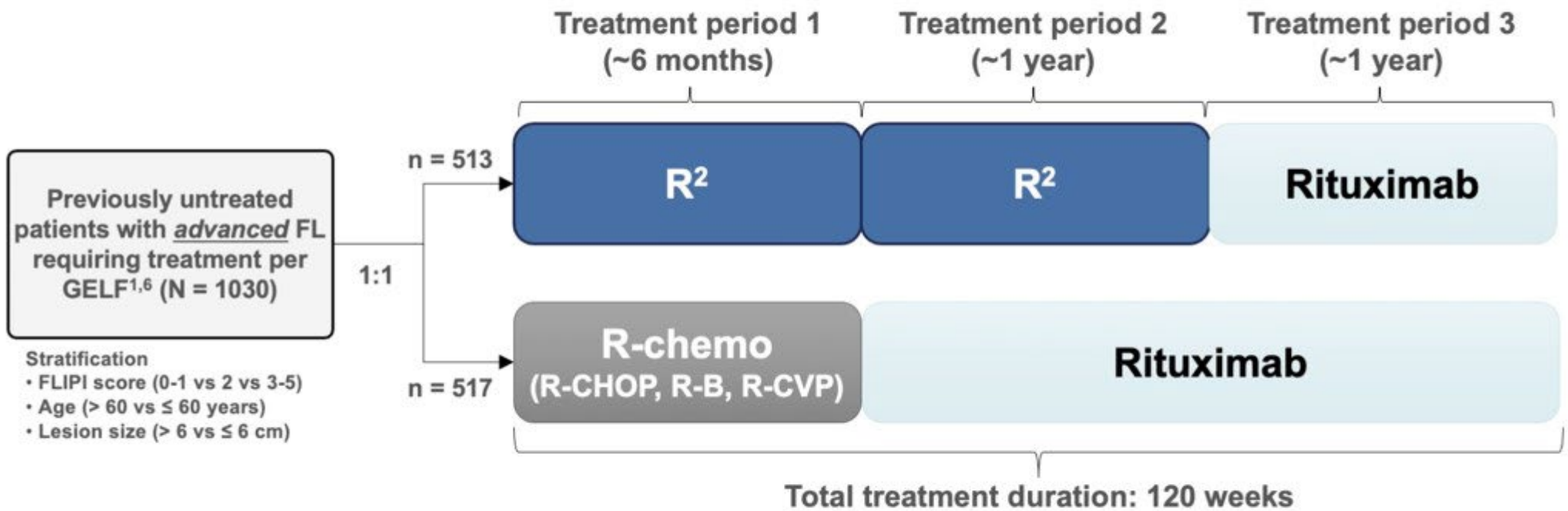
- While study *met the primary endpoint*, and the combination appears highly efficacious, we believe the risk/benefit profile of the combination of OB-VEN with maintenance O *is not appropriate for a frontline FL population*
  - Study design attempted to protect against hypogammaglobulinmia related complications with careful monitoring prior to and during maintenance obinutuzumab and strict rules for discontinuation
  - CMV reactivation/PJP/BK virus nephropathy suggest T-cell defects from the OB plus Ven combination
- T-cell populations were not measured during the trial. Plans to evaluate exploratory objectives are also ongoing
- Participants will continue to be followed for safety, progression, and survival

Six-Year Results from the Phase 3 Randomized Study RELEVANCE Show Similar Outcomes for Previously Untreated Follicular Lymphoma Patients Receiving Lenalidomide Plus Rituximab (R^2) versus Rituximab-Chemotherapy Followed by Rituximab Maintenance

Franck Morschhauser, MD, PhD;[1] Loretta Nastoupil, MD;[2] Pierre Feugier, MD, PhD;[3] Jean-Marc Schiano de Colella, MD;[4] Hervé Tilly, MD;[5] Maria Lia Palomba, MD;[6] Emmanuel Bachy, MD, PhD;[7] Christophe Fruchart, MD;[8] Edward N Libby, MD;[9] Rene-Olivier Casasnovas, MD;[10] Ian W Flinn, MD, PhD;[11] Corinne Haioun, MD;[12] Hervé Maisonneuve, MD;[13] Loic Ysebaert, MD, PhD;[14] Nancy L Bartlett, MD;[15] Kamal Bouabdallah, MD[16] Pauline Brice, MD;[17] Vincent Ribrag, MD;[18] Steven Le Gouill, MD, PhD;[19] Nicolas Daguindau, MD;[20] Vincet Delwail, MD;[21] Gian Matteo Pica, MD;[22] Alejandro Martín García-Sancho, MD, PhD;[23] Armando López-Guillermo, MD;[24] Jean-François Larouche, MD;[25] Kiyoshi Ando, MD;[26] Maria Gomes da Silva, MD, PhD;[27] Marc André, MD;[28] Wu Kalung, MD;[29] Laurie H Sehn, MD, MPH;[30] Koji Izutsu, MD, PhD;[31] Guillaume Cartron, MD, PhD;[32] Argyrios Gkasiamis, MD;[33] Russell Crowe,[33] Luc Xerri, MD, PhD;[34] Nathan H Fowler, MD;[35] and Gilles Salles, MD;[6] on behalf of the RELEVANCE trial investigators

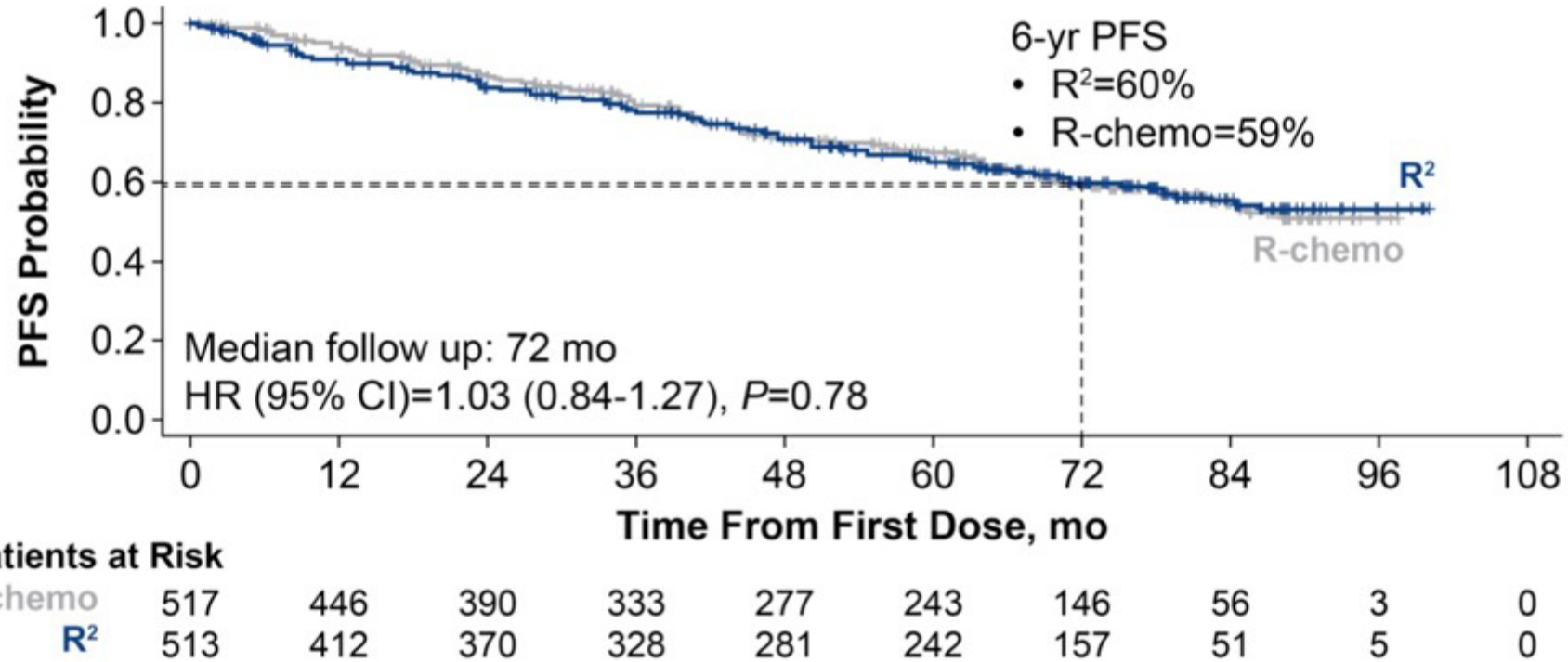
[1]University of Lille, CHU Lille, France; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Nancy University Hospital, Vandoeuvre-lès-Nancy, France; [4]Institut Paoli-Calmettes, Marseille, France; [5]Centre Henri Becquerel, Rouen, France; [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]Hospices Civils De Lyon, Lyon, France; [8]CH de Dunkerque, France; [9]University of Washington, Seattle, WA, USA; [10]CHU Dijon-Bourgogne, Dijon, France; [11]Sarah Cannon Research Institute, Nashville, TN, USA; [12]Henri Mondor University Hospital, UPEC, Créteil, France; [13]Centre Hospitalier Départemental Vendée, La Roche-sur-Yon, France; [14]Institut Universitaire du Cancer Toulouse-Oncopole, Toulouse, France; [15]Washington University School of Medicine, St. Louis, MO, USA; [16]Hôpital Haut-Lévêque, Pessac, France; [17]Hôpital Saint-Louis, Paris, France; [18]Institut Gustave Roussy, Villejuif, France; [19]Nantes Medical University, Nantes, France; [20]Annecy Hospital, Annecy, France; [21]CHU de Poitiers, Poitiers, France; [22]Centre Hospitalier Métropole Savoie Chambéry, Chambéry, France; [23]Hospital Universitario de Salamanca, Salamanca, Spain; [24]Hospital Clínic de Barcelona, Barcelona, Spain; [25]CHU de Québec, Québec, Canada: [26]Tokai University School of Medicine, Kanagawa, Japan; [27]Instituto Português de Oncologia de Lisboa, Lisboa, Portugal; [28]CHU UCL Namur, Yvoir, Belguim; [29]ZNA Stuivenberg, Antwerp, Belguim; [30]BC Cancer Centre for Lymphoid Cancer, Vancouver, Canada; [31]National Cancer Center Hospital, Tokyo, Japan; [32]CHU Montpellier, Montpellier, France; [33]Bristol Myers Squibb, Princeton, NJ, USA; [34]Institut Paoli-Calmettes, Marseille, France; [35]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

RELEVANCE study design



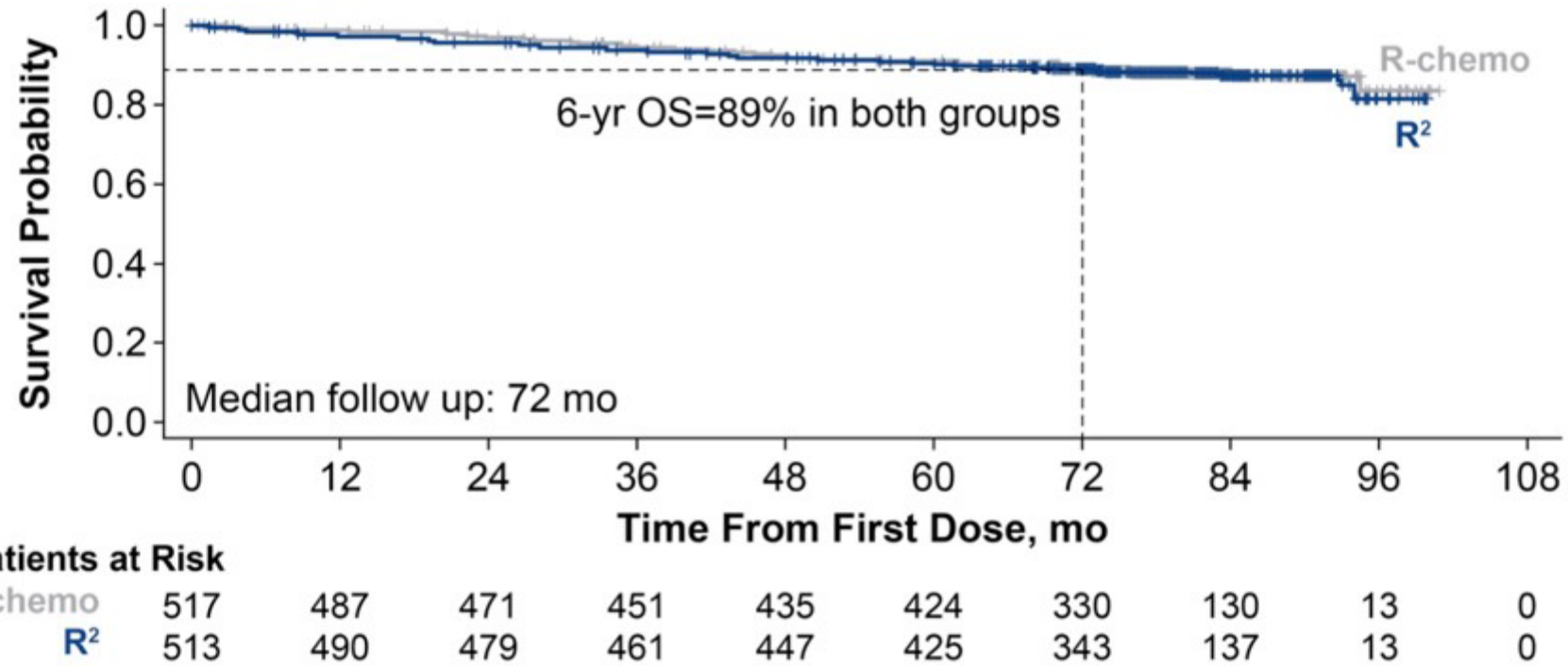
- Co-primary endpoints: CR/CRu at 120 weeks and PFS by IRC based on 1999 IWG criteria
- The prespecified second interim analysis was done after 75% of total PFS events were reached

Progression-free survival by IRC, FDA censoring rules



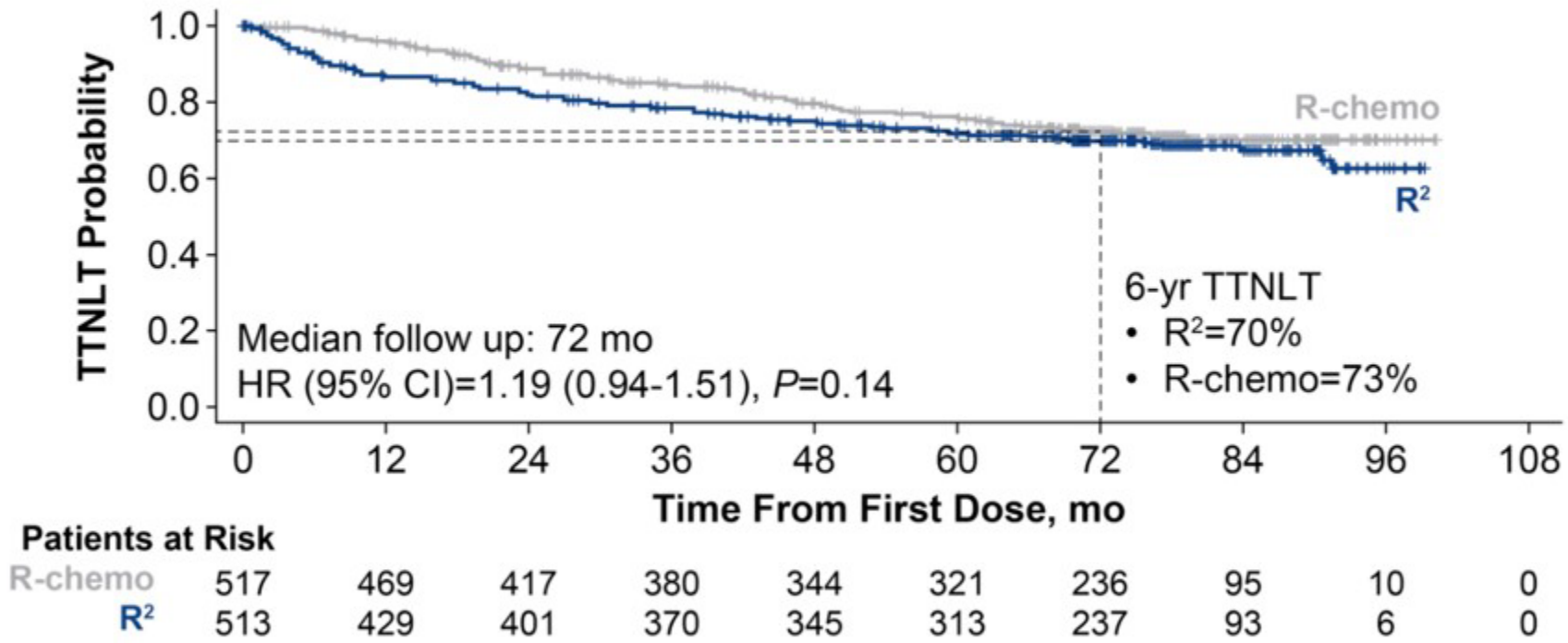
- Median PFS by IRC assessment (co-primary endpoint) was not reached in either group (hazard ratio [HR]=1.03, *P* = 0.78)
  - 6-year PFS rates in the R² and R-chemo groups were 60% (95% CI, 55%-64%) and 59% (95% CI, 54%-64%), respectively
  - Similar 6-year PFS rates in the R² vs R-chemo groups were observed by investigator analysis (64% vs 63%), and by IRC using EMA

Overall survival



- Median OS was not reached in either group (HR=1.00)
  - 6-year OS was the same in both groups at 89%

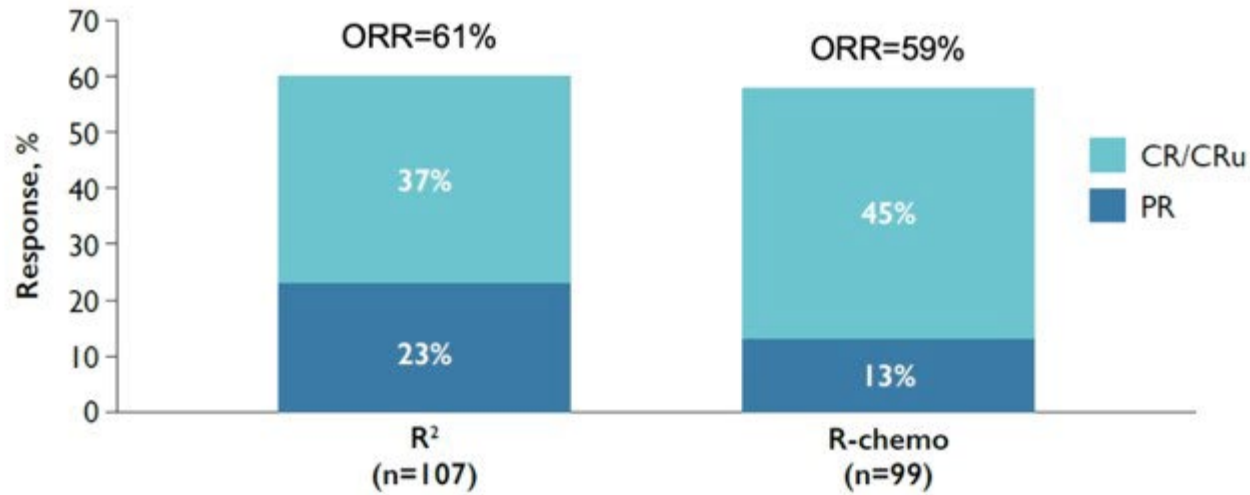
Time to next lymphoma treatment



- Median time to next antilymphoma treatment (TTNLT) was not reached in either group (HR=1.19, *P*=0.14)
  - 6-year TTNLT in the R² and R-chemo groups were 70% (95% CI, 65%-73%) and 73% (95% CI, 68%-76%), respectively

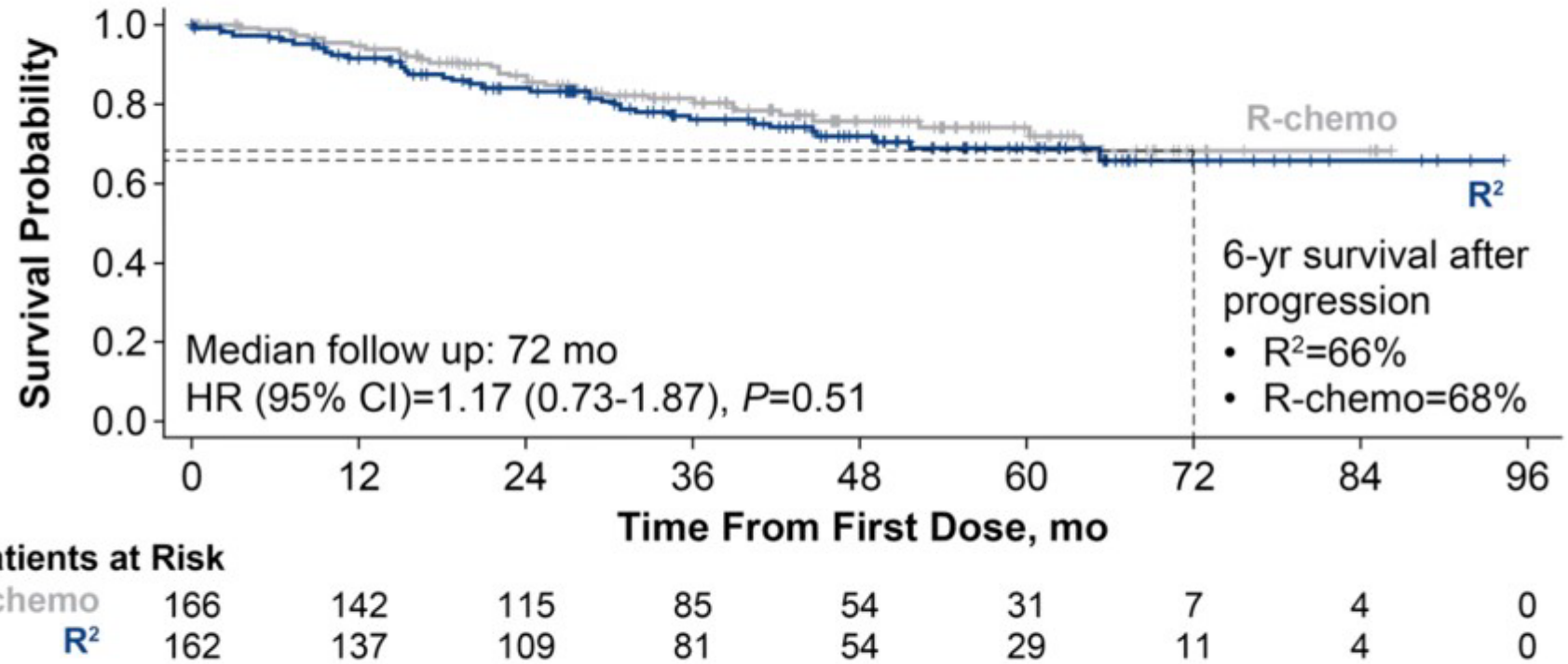
Response after progression

Treatment after progression/relapse, n (%)	R^2 (n=107)	R-chemo (n=99)
Immunotherapy and chemotherapy	86 (80)	62 (63)
Chemotherapy	14 (13)	12 (12)
Immunotherapy alone	4 (4)	18 (18)
Conditioning regimen[a]	12 (11)	19 (19)
Radiotherapy	2 (2)	14 (14)
Radio-immunotherapy	1 (1)	1 (1)
Other treatment	9 (8)	14 (14)



- A similar number of patients went on to receive additional treatment after progression in the R^2 (n=107) and R-chemo (n=99) groups
- Overall response rate (ORR) to subsequent treatment was similar in both groups, 61% and 59%, respectively

Survival after progression



Patients at Risk

R-chemo	166	142	115	85	54	31	7	4	0
R²	162	137	109	81	54	29	11	4	0

- Survival after progression was similar in both groups (HR=1.17, *P*=0.51)
  - 6-year survival after progression in the R² and R-chemo groups were 66% (95% CI, 55%-75%) and 68% (95% CI, 56%-78%), respectively

Safety

- The overall safety profile in both groups was consistent with the first interim analysis in 2017, and no new safety signals were detected
- The similar incidence of histologic transformation in R^2 group vs R-chemo groups was maintained after longer follow-up reported here (R^2=13, R-chemo=11)
- The total number of patients with a second primary malignancy (SPM) was 57 (11%) in the R^2 group and 67 (13%) in the R-chemo group

Conclusions

- With a median follow-up time of 72 months:
  - 6-year PFS rate was similar in both groups (60% R^2 vs 59% R-chemo).
  - Both groups had similar, excellent 6-year OS rates of 89%
- ORR to subsequent treatment and survival after progression were similar in both groups, indicating that chances of responding to subsequent therapy are not compromised by either treatment
- Rate of transformation over the course of 72 months was less than 1% per year in both groups, which is well within the historical rate of 2%-3%,[1] demonstrating that R^2 does not increase risk for histologic transformation compared with R-chemo
- No new safety signals were detected
- R^2 continues to demonstrate comparable efficacy and safety vs R-chemo and provides an acceptable chemo-free alternative to R-chemo based on immunotherapy/immunomodulation

Foliküler Lenfoma

- Birinci basamak FL tedavisi
  - İmmünokemoterapi: FOLL12 çalışması alt grup analizi
  - OB-VEN: PrECOG 0403 çalışması
  - R2: Relevance çalışması 6-yıl takip

- Relaps refrakter FL tedavisi
  - R2: Magnify çalışması
  - Bispesifik antikorlar: Mosunetuzumab, Glofitamab
  - CAR-T hücre tedavisi: Elara çalışması altgrup analizi, Standart tedaviler ile karşılaştırma

- İdame tedavisi

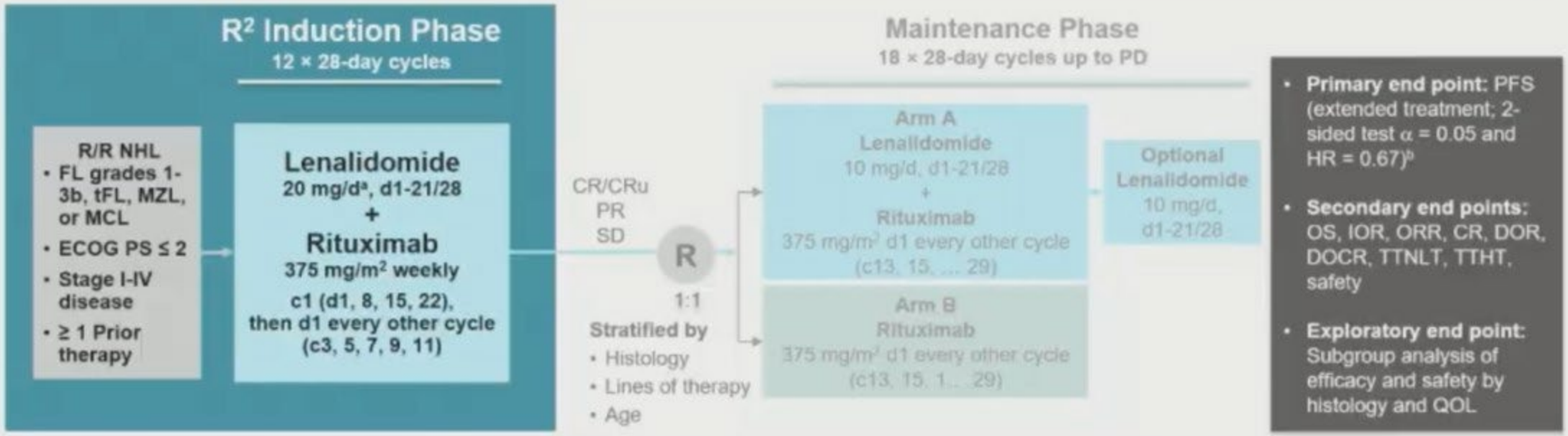
Completed Induction Phase Analysis of MAGNIFY: Phase 3b Study of Lenalidomide + Rituximab (R^2) Followed By Maintenance in Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

Frederick Lansigan, MD;[1] David Jacob Andorsky, MD;[2] Morton Coleman, MD, FACP;[3] Abdulraheem Yacoub, MD;[4] Jason M. Melear, MD;[5] Suzanne R. Fanning, DO;[6] Kathryn S. Kolibaba, MD;[7] Chris Reynolds, MD;[8] Grzegorz S. Nowakowski, MD;[9] Mecide Gharibo, MD;[10] Jung Ryun Ahn, MD;[10] Ju Li, PhD;[10] Mathias J. Rummel, MD, PhD;[11] and Jeff P. Sharman, MD;[12] on behalf of the MAGNIFY Trial Investigators

[1]Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; [2]Rocky Mountain Cancer Centers, US Oncology Research, Boulder, CO, USA; [3]Clinical Research Alliance Inc, Weill Cornell Medicine, New York, NY, USA; [4]University of Kansas Cancer Center, Westwood, KS, USA; [5]Texas Oncology – Austin, US Oncology Research, Austin, TX, USA; [6]Prisma Health, US Oncology Research, Greenville, SC, USA; [7]US Oncology Research, Vancouver, WA, USA; [8]IHA Hematology Oncology Consultants – Ann Arbor, Ypsilanti, MI, USA; [9]Mayo Clinic, Rochester, MN, USA; [10]Bristol Myers Squibb, Princeton, NJ, USA; [11]Justus-Liebig Universität, Giessen, Germany; [12]Willamette Valley Cancer Institute and Research Center, US Oncology Research, Eugene, OR, USA

ASH 2021, Presentation 812

MAGNIFY Study Design



- **Primary end point:** PFS (extended treatment; 2-sided test $\alpha = 0.05$ and HR = 0.67)[b]
- **Secondary end points:** OS, IOR, ORR, CR, DOR, DOCR, TTNLT, TTHT, safety
- **Exploratory end point:** Subgroup analysis of efficacy and safety by histology and QOL

- Data presented here are the complete analysis from the induction phase in patients with FL grades 1-3a or MZL (FL grade 3b, tFL, and MCL not included)[c]
- The focus of this current interim analysis was ORR, DOR, PFS, and safety
  - Response was assessed by 1999 IWG criteria

NCT01996865.
ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; tFL, transformed FL.
[a]Lenalidomide is administered at 10 mg if creatinine clearance is ≥ 30 to < 60 mL/min. [b]Assessed per computed tomography/magnetic resonance imaging and 1999 International Working Group criteria with modifications to include extranodal disease. [c]Data cutoff 05Mar2021.

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Baseline Characteristics and Treatment History

Characteristic, n (%)	Total (n = 394)
Age, median (range), y	66 (35-91)
≥ 65 y	221 (56)
Male	210 (53)
ECOG PS at enrolment	
0	193 (49)
1	192 (49)
2	9 (2)
Positive bone marrow involvement	123 (31)
Ann Arbor disease stage at enrollment	
I/II	66 (17)
III	99 (25)
IV	229 (58)
Bulky disease (> 7 cm or > 3 cm x 3)	161 (41)

Characteristic, n (%)	Total (n = 394)
FL	318 (81)
Grade 1	116 (29)
Grade 2	147 (37)
Grade 3a	55 (14)
MZL	76 (19)
MALT[a]	15 (4)
Nodal	44 (11)
Splenic	17 (4)
Prior lines of antilymphoma treatment, median (range)	2 (1-8)
Prior therapies	
Rituximab containing	372 (94)
Rituximab + chemotherapy	289 (73)
Rituximab monotherapy	159 (40)
Rituximab refractory[b]	140 (36)
Double refractory[c]	85 (22)
Early relapse[d]	133 (34)

MALT, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue.
[a]Three patients had gastric MALT. [b]Defined as experiencing a best response of PD or SD to rituximab or rituximab-containing regimen or a response lasting < 6 months after last rituximab dose.
[c]Defined as being refractory to both rituximab and an alkylating agent. [d]Defined as progressing or relapsing within 2 years of initial diagnosis.

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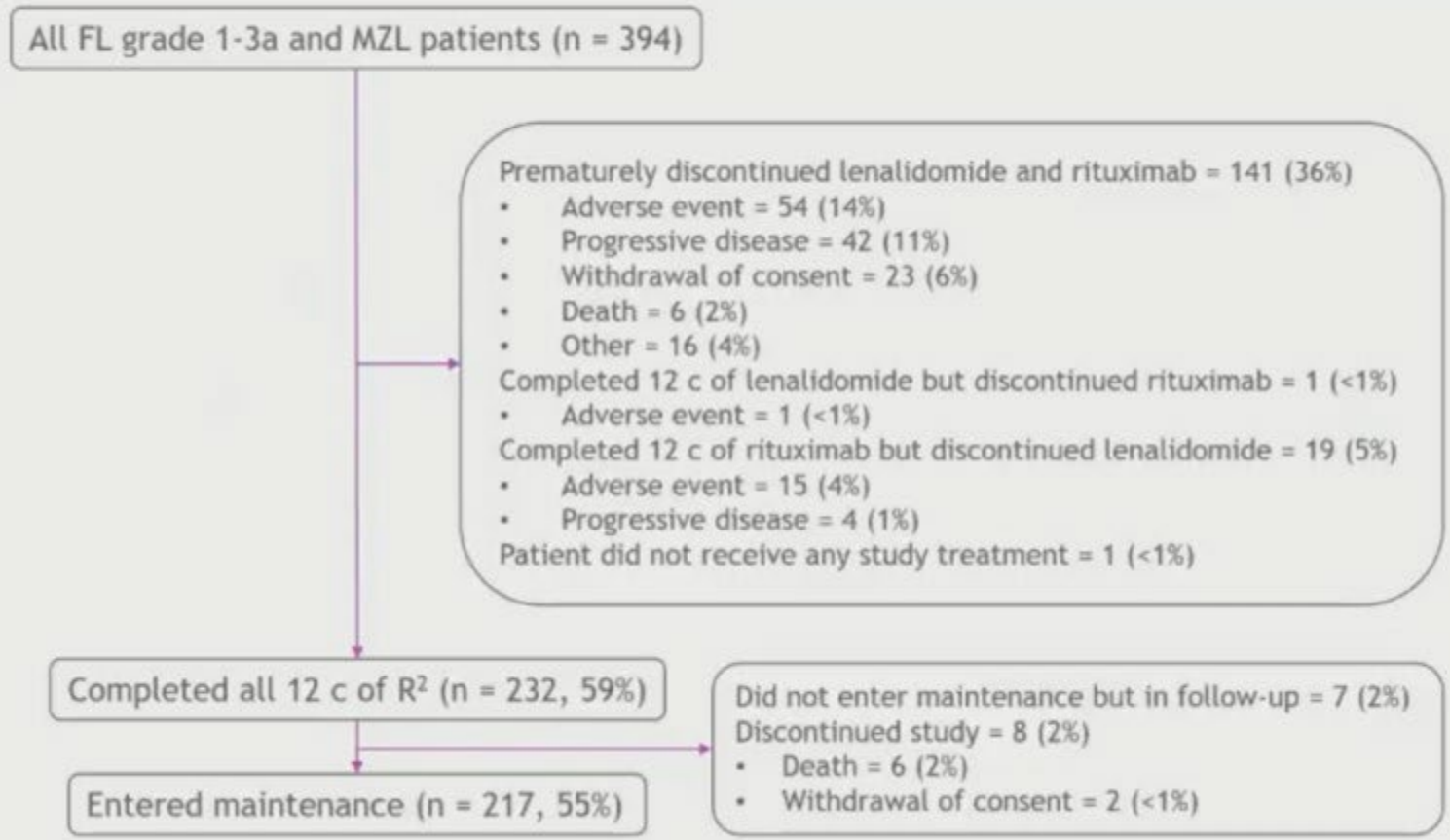
Patient Disposition



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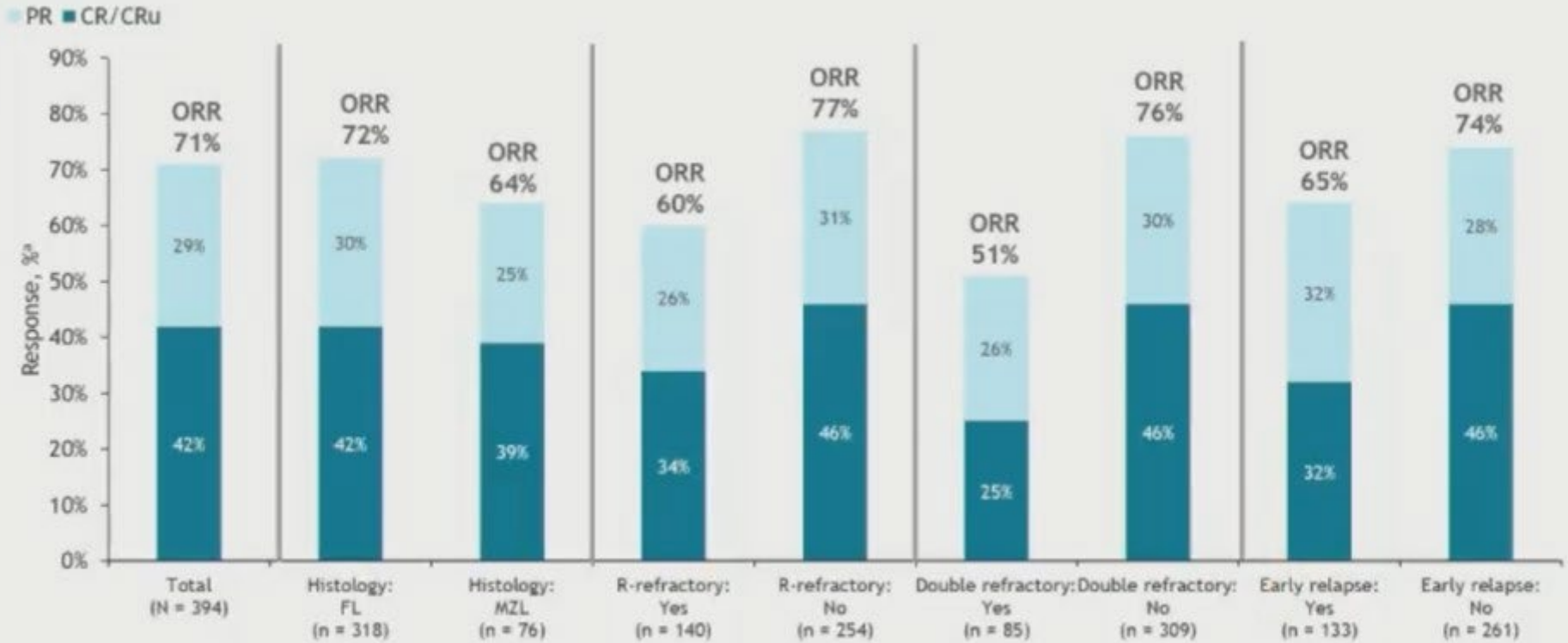
Best Overall Response in R^2 Induction Treatment Phase



- R^2 showed clinical activity in patients with R/R iNHL, including those with FL or MZL histology and those refractory to rituximab, double refractory, or early relapse

[a]ORR may not equal PR + CR due to rounding

CR, complete response; CRu, CR unconfirmed; ORR, overall response rate; PR, partial response.

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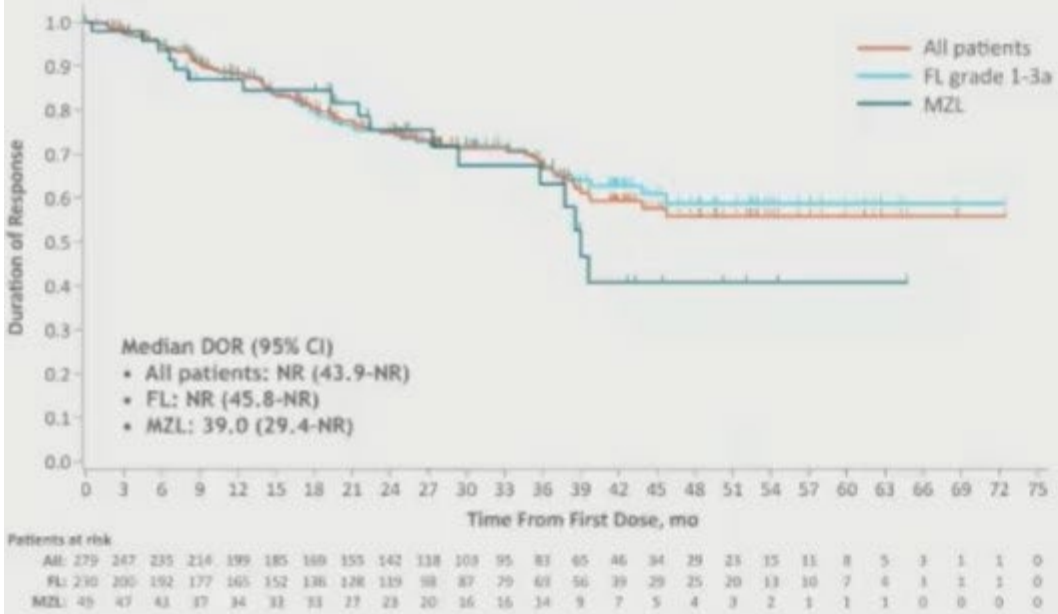
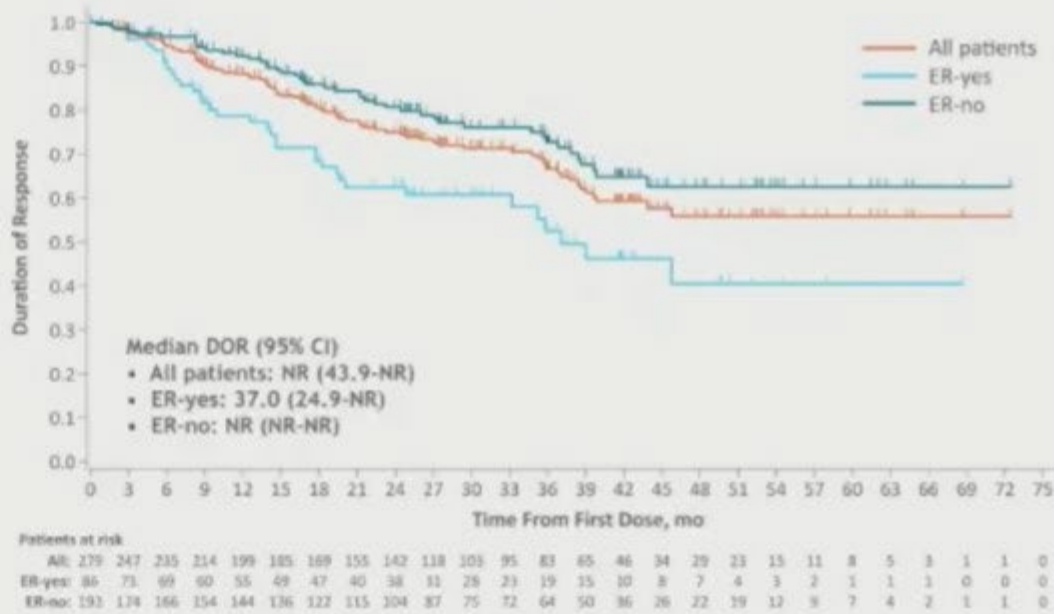
Duration of Response[a]

Histology



Early Relapse Status



- Median duration of follow-up: 40.6 months (range, 0.6-79.6)
- Median time to response in all patients was 2.8 mo (range, 0.5-17.2)

DOR, duration of response; NR, not reached.
[a]Induction treatment ITT population. If patients were already in maintenance at data cutoff, then response assessments also contributed to DOR.

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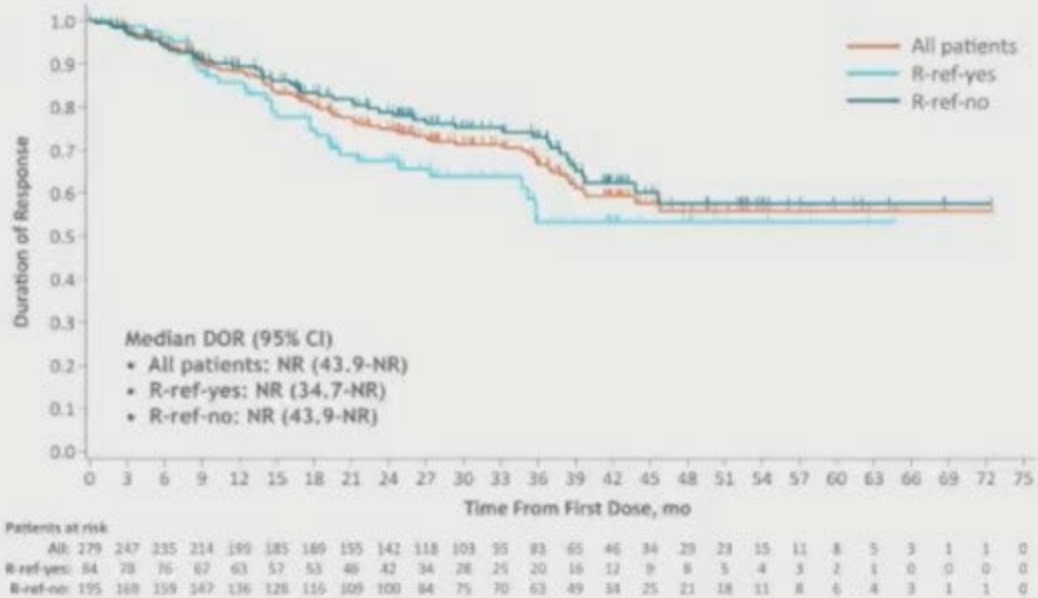
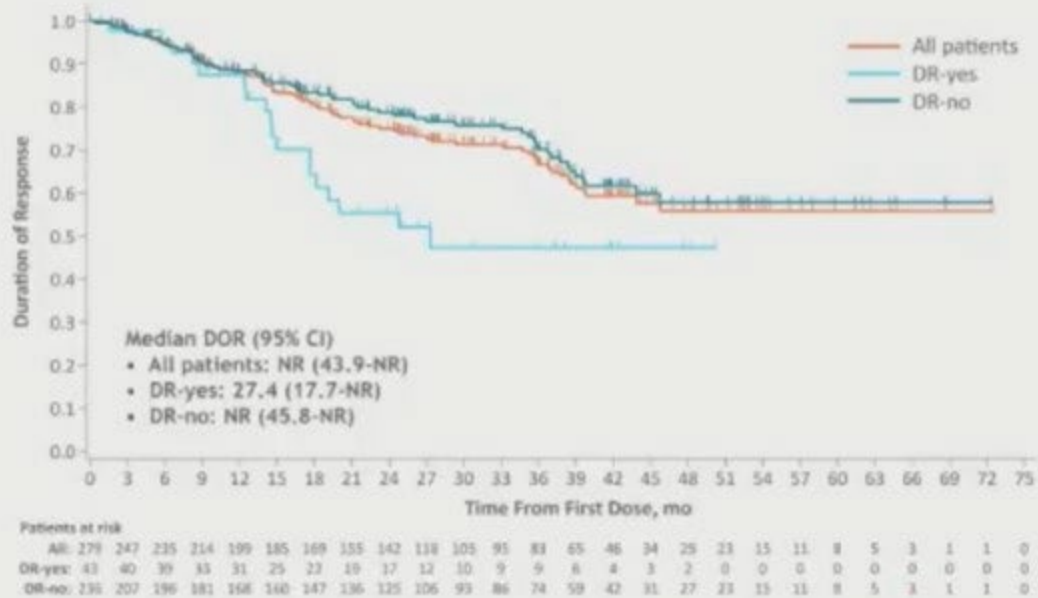
Duration of Response[a]

Rituximab Refractory Status



Double Refractory Status



[a]Induction treatment ITT population. If patients were already in maintenance at data cutoff, then response assessments also contributed to DOR.

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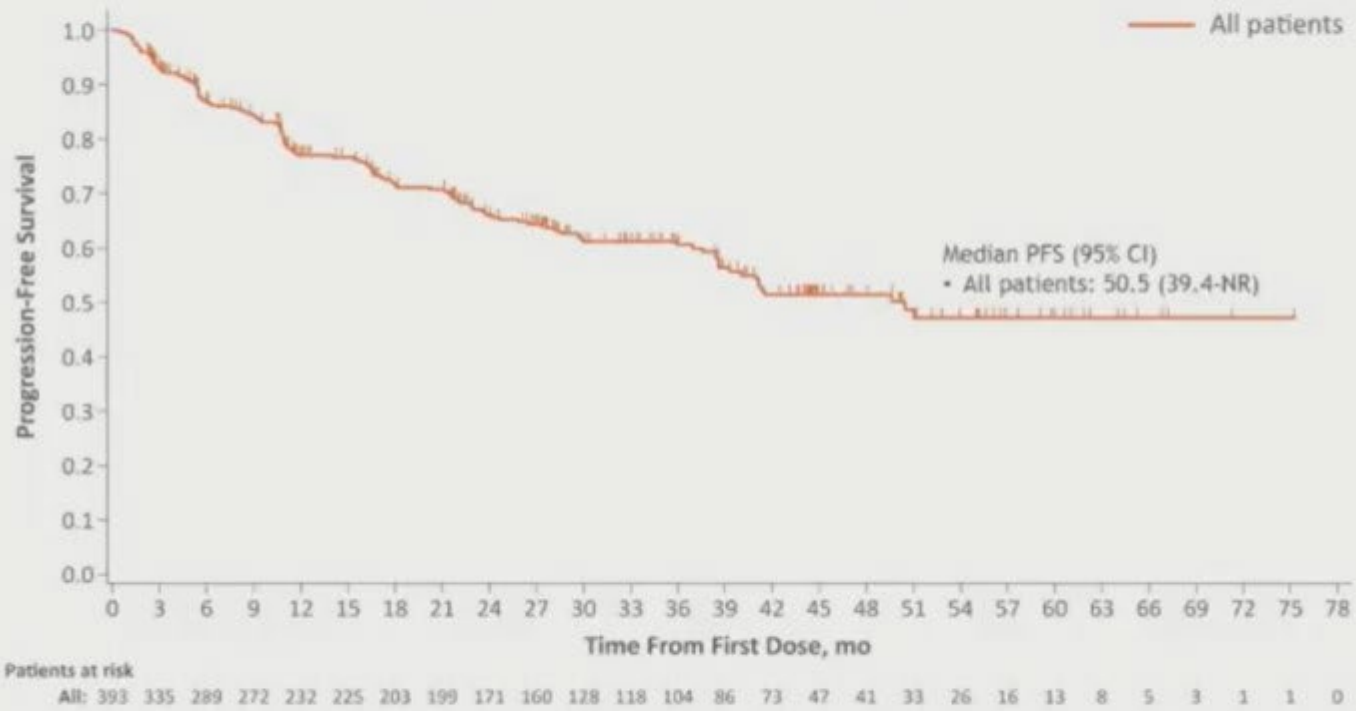
Progression-Free Survival[a]

PFS by Best Overall Response



[a]Induction treatment ITT population. If patients were already in maintenance at data cutoff, then response assessments also contributed to PFS.

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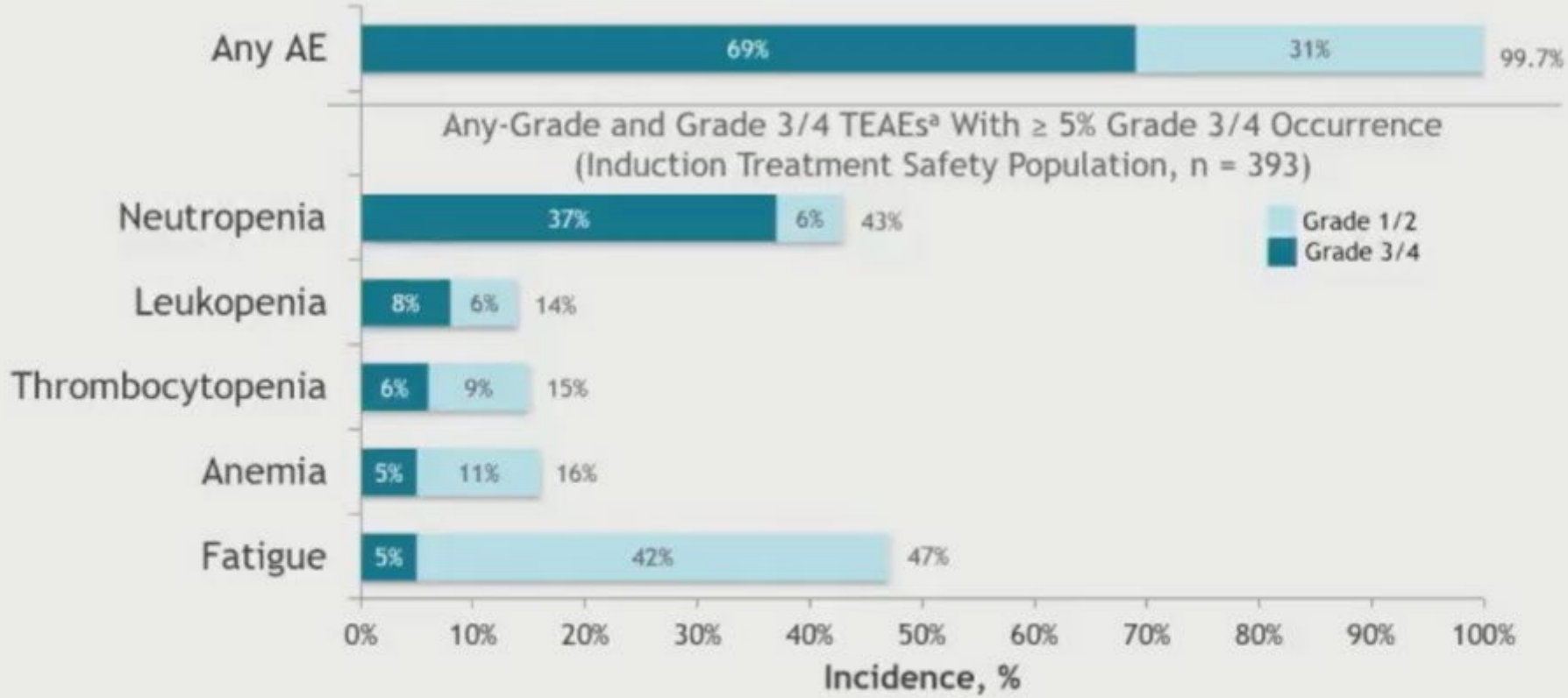
Treatment Emergent Adverse Events



- Other any-grade and grade 3/4 TEAEs of interest included rash maculopapular (17% and 1%), infusion-related reaction (12% and 1%), tumor flare reaction (4% and 1%), febrile neutropenia (3% and 3%), and tumor lysis syndrome (1% and < 1%)
- Concomitant growth factors (G-CSF/GM-CSF) were administered in 63 patients (16%)

[a]Assessed per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. TEAEs include any AEs occurring on or after first dose date of induction treatment through 28 days after the last dosing date of study treatment.

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Dose Modifications Due to TEAEs

Patients with ≥ 1 TEAE leading to dose modification in induction period, n (%)	Total (n = 393)
Early lenalidomide discontinuation	75 (19)
Early rituximab discontinuation	46 (12)
Lenalidomide dose reduction/interruption	252 (64)
Rituximab dose interruption	116 (30)

- Neutropenia was the most common TEAE leading to lenalidomide discontinuation (n = 22, 6%) and reduction/interruption (n = 125, 32%), and rituximab discontinuation (n = 10, 3%)
- Infusion-related reaction was the most common TEAE leading to rituximab interruption (n = 32, 8%)

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Conclusions

- These data represent complete analysis of patients with FL grade 1-3a and MZL in the induction phase of MAGNIFY
- R^2 is active with deep and durable responses in patients with R/R FL grade 1-3a and MZL, including rituximab-refractory, double-refractory, and early relapse patients
- R^2 has a tolerable safety profile in patients with R/R FL grade 1-3a and MZL
- The MAGNIFY trial is ongoing to compare R^2 vs rituximab maintenance treatment in patients with R/R FL and MZL
  - 232 Patients have completed 12 cycles of induction treatment, and 217 have proceeded to maintenance treatment
- Results shown here from MAGNIFY align with those previously shown in AUGMENT of R^2 activity in R/R patients with iNHL

Lansigan F, et al. ASH 2021 [Abstract #812]

Mosunetuzumab Monotherapy is an Effective and Well-Tolerated Treatment Option for Patients with Relapsed/ Refractory (R/R) Follicular Lymphoma (FL) who have Received ≥2 Prior Lines of Therapy: Pivotal Results from a Phase I/II Study

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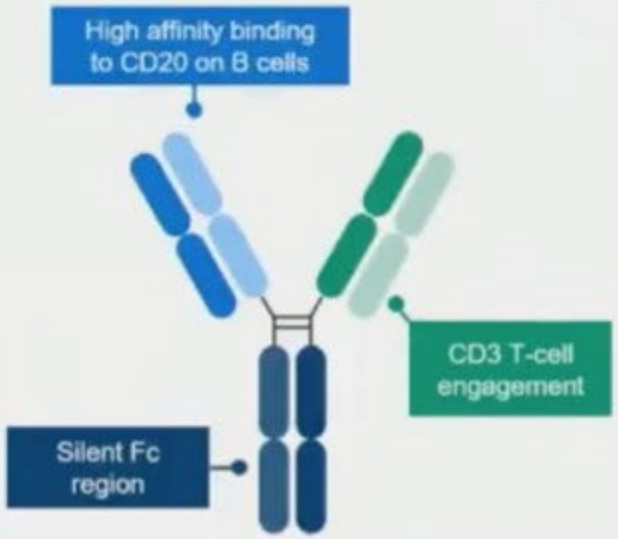
Accepted as an Oral Presentation at the 63rd ASH Annual Meeting and Exposition

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

Study overview

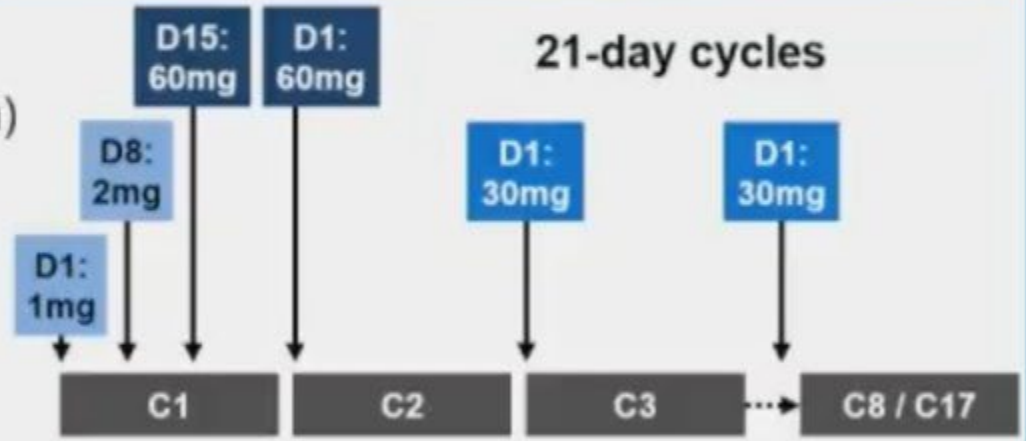
- Single-arm, pivotal Phase II expansion in patients with R/R FL and ≥2 prior therapies

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

Baseline characteristics

		N=90
Median age, years (range)		60 (29–90)
Male		55 (61.1%)
ECOG PS	0	53 (58.9%)
	1	37 (41.1%)
Ann Arbor stage	I–II	21 (23.3%)
	III–IV	69 (76.7%)

		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%)

Cut-off date: August 27, 2021; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell; IMiD, immunomodulatory drug; PI3K, phosphoinositide 3-kinase

Exposure and patient disposition

	N=90
Median duration of follow-up, months (range)	18.3 (2.0–27.5)
Patient disposition	
Completed treatment	54 (60.0%)
Discontinued treatment	36 (40.0%)
Active on retreatment	2 (2.2%)
In follow-up	76 (84.4%)
Discontinued study	12 (13.3%)

	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

Cut-off date: August 27, 2021

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%

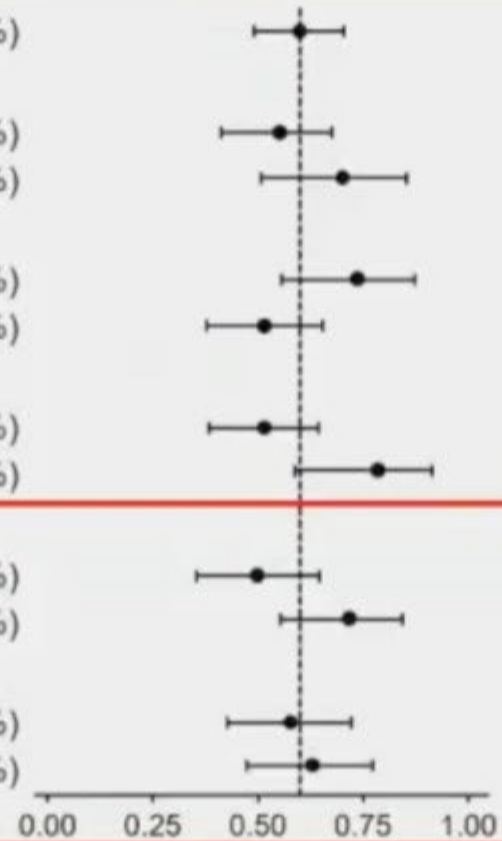
- **60% CR rate significantly greater ($p<0.0001$)* than 14% historical control CR rate[2]**

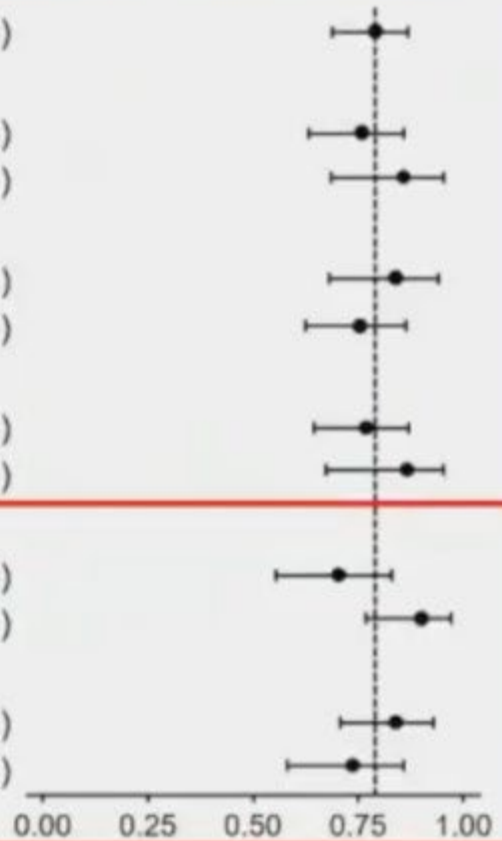
*exact binomial test with two-sided alpha level of 5%; CI, confidence interval

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

Comparable response rates in high-risk subgroups

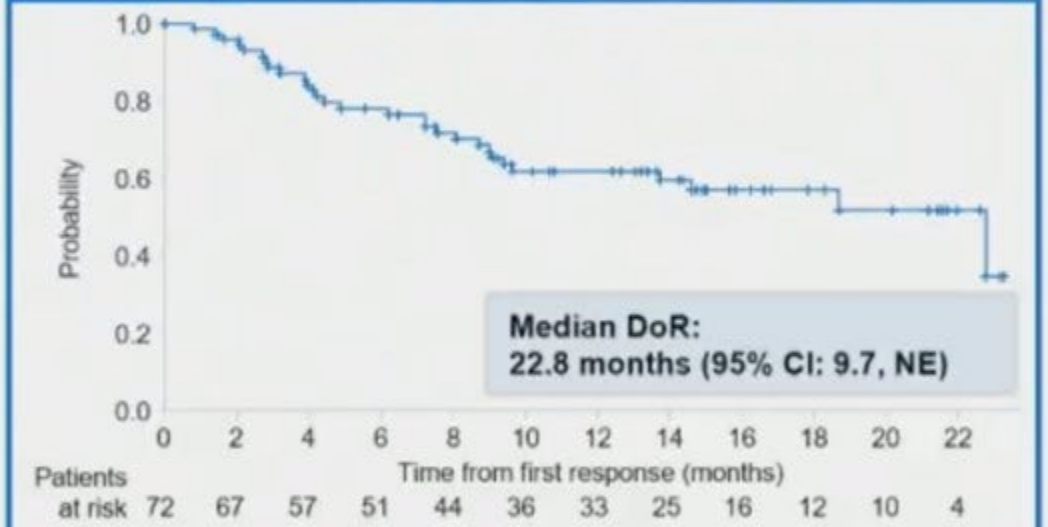
	CR rate (95% CI) by IRF	ORR (95% CI) by IRF
All patients	60% (49%, 70%)	80% (70%, 88%)
Age		
<65 years (n=60)	55% (42%, 68%)	77% (64%, 87%)
≥65 years (n=30)	70% (51%, 85%)	87% (69%, 96%)
Number of prior therapies		
2 (n=34)	74% (56%, 87%)	85% (69%, 95%)
≥3 (n=56)	52% (38%, 65%)	77% (64%, 87%)
R/R to last prior therapy		
Yes (n=62)	52% (39%, 65%)	77% (65%, 87%)
No (n=28)	79% (59%, 92%)	86% (67%, 96%)
Double refractory		
Yes (n=48)	50% (35%, 65%)	71% (56%, 83%)
No (n=42)	71% (55%, 84%)	90% (77%, 97%)
POD24		
Yes (n=47)	57% (42%, 72%)	85% (72%, 94%)
No (n=43)	63% (47%, 77%)	74% (59%, 86%)





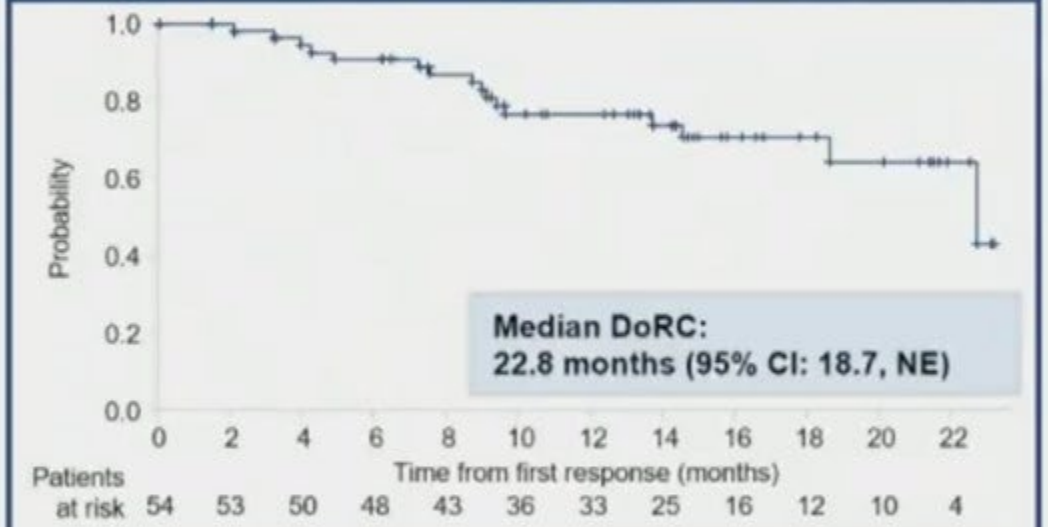
Duration of response

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

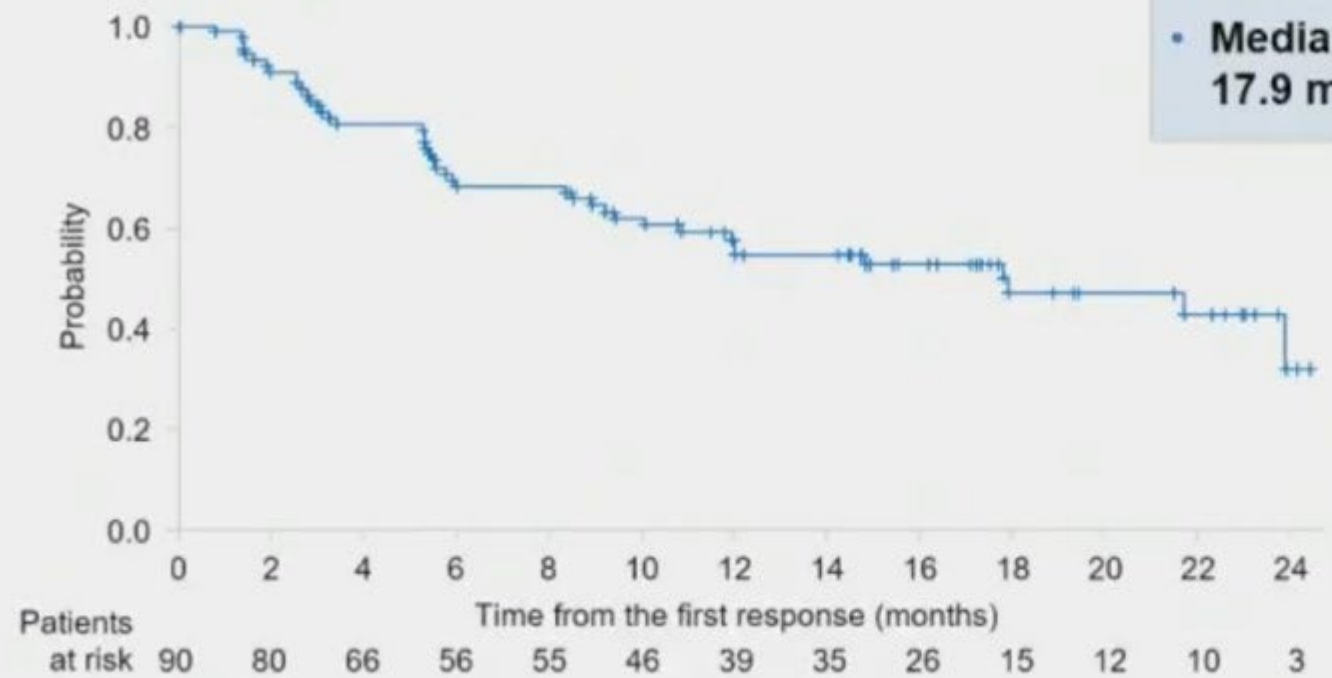


Median time to first CR, mo (range)	3.0 (1.1, 18.9)
12-month event-free rate, % (95% CI)	76% (65%, 88%)
18-month event-free rate, % (95% CI)	70% (57%, 84%)

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

Progression-free survival

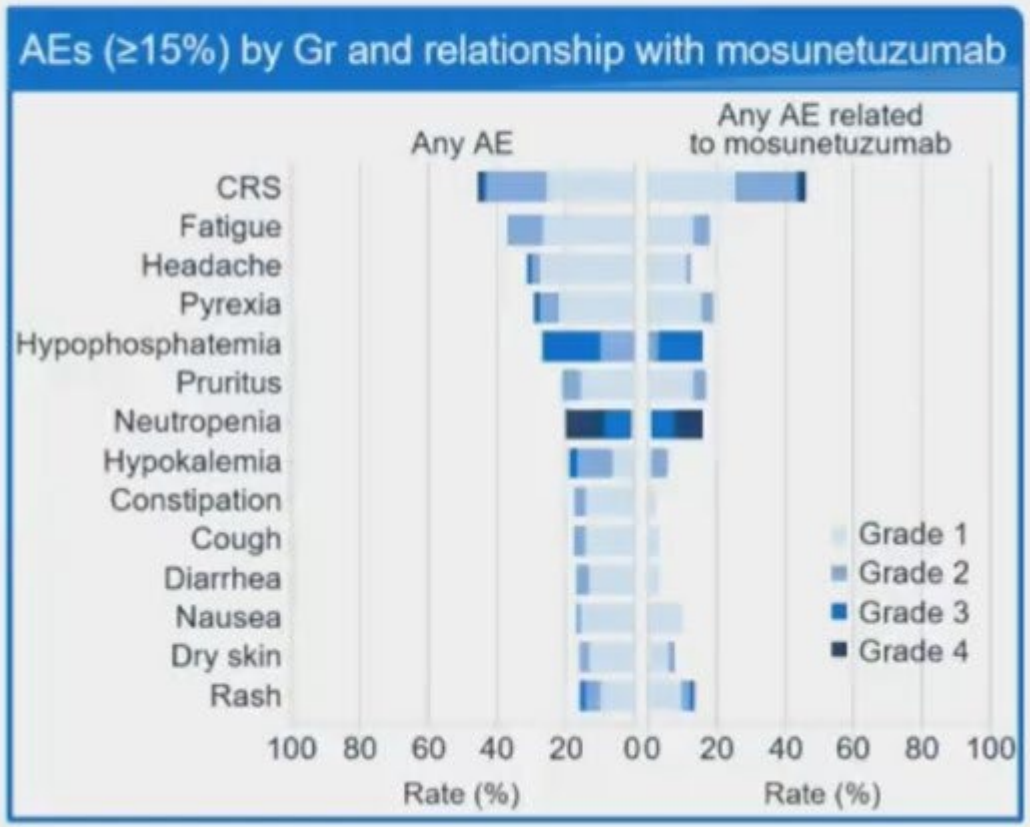
Progression-free survival (N=90)



- **Median PFS: 17.9 months (95% CI: 10.1, NE)**

Mosunetuzumab has a manageable safety profile

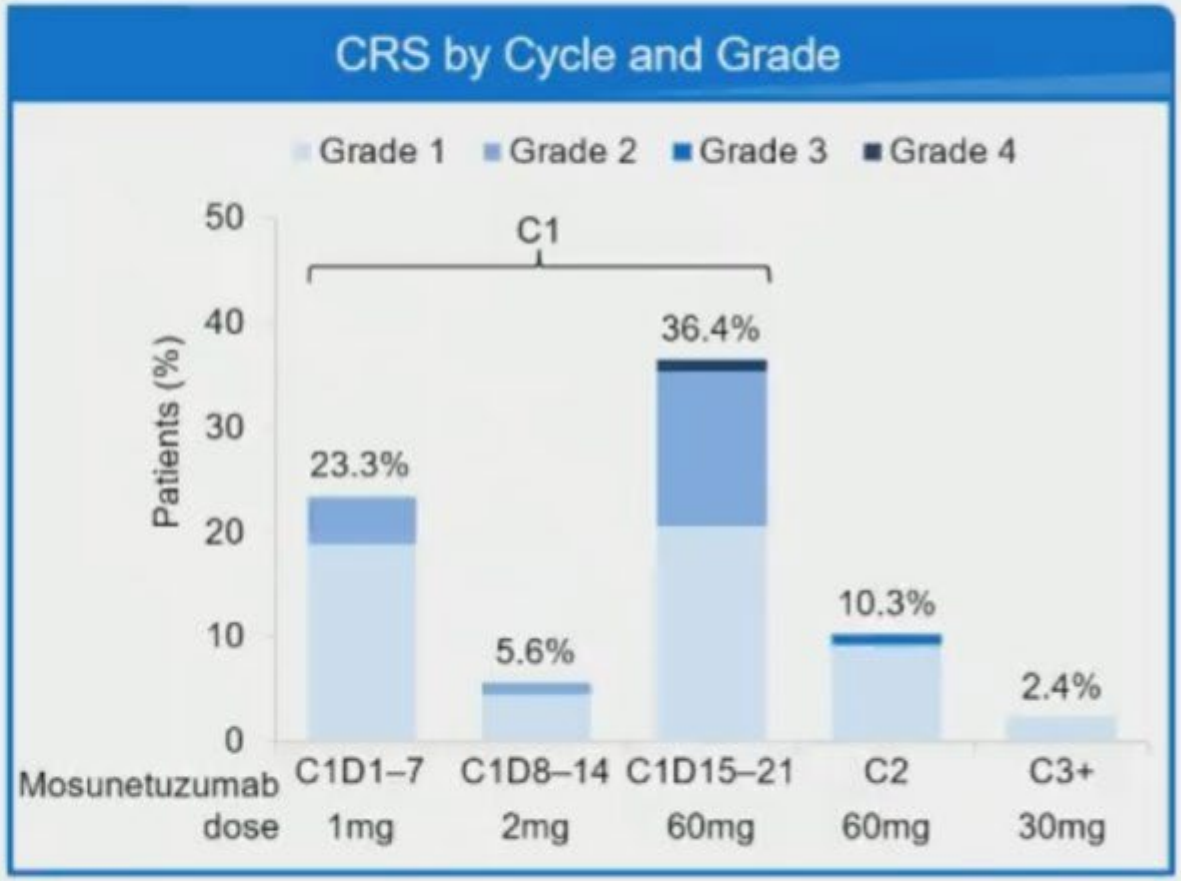
N (%)	N=90
AE	90 (100%)
Mosunetuzumab related*	83 (92.2%)
Grade 3–4 AE	63 (70.0%)
Mosunetuzumab related*	46 (51.1%)
Serious AE	42 (46.7%)
Mosunetuzumab related*	30 (33.3%)
Grade 5 (fatal) AE	2 (2.2%)†
Mosunetuzumab related*	0
AE leading to discontinuation of treatment	4 (4.4%)‡
Mosunetuzumab related*	2 (2.2%)‡



*AE considered related to treatment by the investigator; †mosunetuzumab unrelated: malignant neoplasm progression and unexplained death (1 patient each); ‡mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Esptein-Barr viremia and Hodgkin's disease (1 patient each); AE, adverse event; Gr, Grade

Cytokine release syndrome

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%)



- **CRS was predominately low Grade and in Cycle 1. All events resolved.**

*assessed using ASTCT criteria[1]; †patient with leukemic phase FL

1. Lee et al. Biol Blood Marrow Transplant 20192019;25:625–38

Other adverse events of interest

N (%)	N=90	Additional details
ICANS* Grade 3	4 (4.4%) 0	• Confusional state (3.3%; all Grade 1–2†), disturbance in attention and cognitive disorder (1.1% each; all Grade 1†); all resolved • No cases of aphasia, seizures, encephalopathy, or cerebral edema
Neutropenia‡ Grade 3–4 Febrile neutropenia	26 (28.9%) 24 (26.7%) 0	• 98.1% resolved • Serious AE of infection concurrent with Grade 3–4 neutropenia in 2 patients
Serious AE of infection (any Grade)§ Grade 3–4	18 (20.0%) 13 (14.4%)	• UTI (3.3%), pneumonia, COVID-19, Epstein-Barr viremia, septic shock (2.2% each)

- **ICANS events were infrequent and all Grade 1–2**

*mosunetuzumab-related neurological AEs potentially consistent with ICANS; †graded per CTCAE V4; ‡grouped term including Preferred Term 'neutropenia' and 'neutrophil count decreased'; §System Organ Class 'infections and infestations'; ICANS, immune effector cell-associated neurotoxicity syndrome; UTI, urinary tract infection;

Conclusions

- Pivotal Phase II study of mosunetuzumab, a CD20xCD3 T-cell-engaging bispecific antibody, met primary efficacy endpoint (CR rate: 60%, $p<0.0001$; ORR: 80%)
- Deep and durable responses achieved in heavily pre-treated/high-risk R/R FL with fixed-duration treatment
- Favorable tolerability profile, with most CRS confined to Cycle 1 and low Grade; treatment administration without mandatory hospitalization
- First T-cell-engaging bispecific antibody to demonstrate clinically meaningful outcomes for patients with R/R FL in pivotal Phase II setting
  - potentially promising off-the-shelf, outpatient therapy

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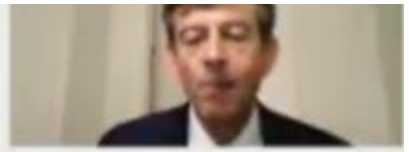


Glofitamab as Monotherapy and in Combination with Obinutuzumab Induces High Complete Response Rates in Patients with Multiple Relapsed or Refractory (R/R) Follicular Lymphoma (FL)

Franck Morschhauser,[1] Carmelo Carlo-Stella,[2] Michael Dickinson,[3] Tycel Phillips,[4] Roch Houot,[5] Fritz Offner,[6] Corinne Haioun,[7] Paolo Corradini,[8] Martin Hutchings,[9] Anna Sureda,[10] Joaquin Martinez-Lopez,[11] Tomasz Wróbel,[12] Shang-Ju Wu,[13] Linda Lundberg,[14] Estefania Mulvihill,[14] David Perez-Callejo,[14] James Relf,[15] Anesh Panchal,[15] Kathryn Humphrey,[15] Emmanuel Bachy[16]

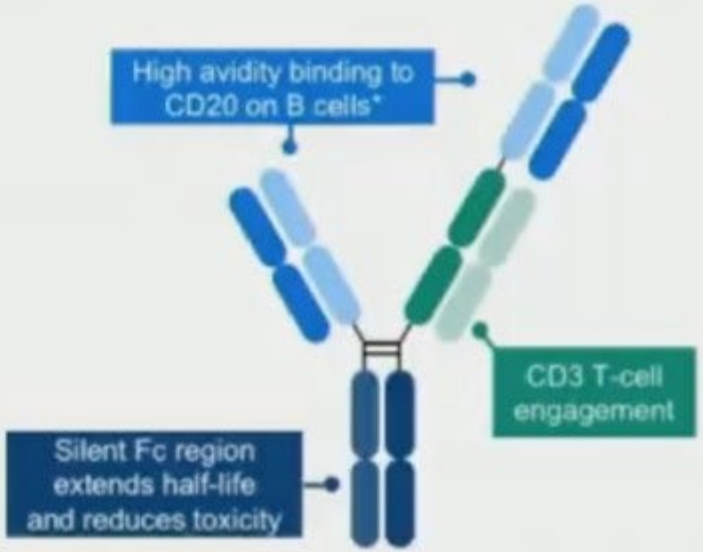
[1]CHU Lille, Service des Maladies du Sang, F-59000 Lille, France; [2]Humanitas University and Humanitas Research Hospital, Milan, Italy; [3]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Australia; [4]University of Michigan Medical School, Ann Arbor, Michigan, USA; [5]CHU de Rennes, Université de Rennes, INSERM U1236, EFS, Rennes, France; [6]Universitair Ziekenhuis Gent, Ghent, Belgium; [7]Hôpital Henri Mondor, AP-HP, Créteil, France; [8]University of Milan; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [9]Rigshospitalet, Copenhagen, Denmark; [10]Institut Català d'Oncologia Hospitalet, IDIBELL, Universitat de Barcelona, Barcelona, Spain; [11]Hospital Universitario 12 de Octubre (H12O), Centro Nacional de Investigaciones Oncológicas (CNIO)-H12O and Universidad Complutense de Madrid, Madrid, Spain; [12]Wroclaw Medical University, Wroclaw, Poland; [13]National Taiwan University Hospital, Taipei, Taiwan; [14]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [15]Roche Products Ltd, Welwyn Garden City, United Kingdom; [16]Hospices Civils de Lyon and Université Claude Bernard, Pierre-Bénite, France.

Accepted as an Oral Presentation at the 63rd ASH Annual Meeting and Exposition

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]

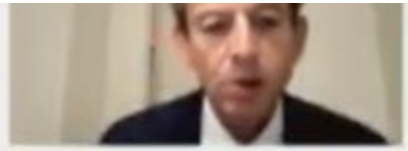


Aim: share updated phase I/II results - glofitamab monotherapy and in combination with obinutuzumab in R/R FL

*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

Glofitamab regimens investigated in R/R FL



Dose escalation (Phase I)

Glofitamab monotherapy

Step-up dosing (SUD)*
2.5/10/16mg: N=3
2.5/10/30mg: N=21

C1D-7	C1D1	C1D8	C2D1 up to C12D1 (Q3W)
Obinutuzumab pretreatment 1000mg	Glofitamab 2.5mg	Glofitamab 10mg	Glofitamab 16 or 30mg

Extended SUD (eSUD)*
0.5/2.5/10/30mg: N=29

C1D-7	C1D1	C1D8	C2D1	C3D1 up to C12D1 (Q3W)
Obinutuzumab pretreatment 1000mg	Glofitamab 0.5mg	Glofitamab 2.5mg	Glofitamab 10mg	Glofitamab 30mg

Glofitamab in combination with obinutuzumab

SUD*
2.5/10/30mg: N=19

C1D-7	C1D1	C1D8	C2D1 up to C12D1 (Q3W)
Obinutuzumab pretreatment 1000mg	Glofitamab 2.5mg	Glofitamab 10mg	Obinutuzumab 1000mg Glofitamab 30mg

Dose expansion (Phase II)

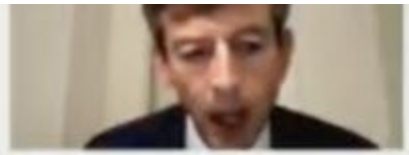
(Currently enrolling)

Glofitamab monotherapy (SUD)

2.5/10/30mg

Population characteristics: *R/R FL Gr 1–3A; ≥1 prior systemic therapy; age ≥18 years; ECOG PS ≤1*

Clinical cut-off date: May 18, 2021; *Glofitamab IV. Gr, Grade; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; Q3W, every three weeks



Baseline characteristics

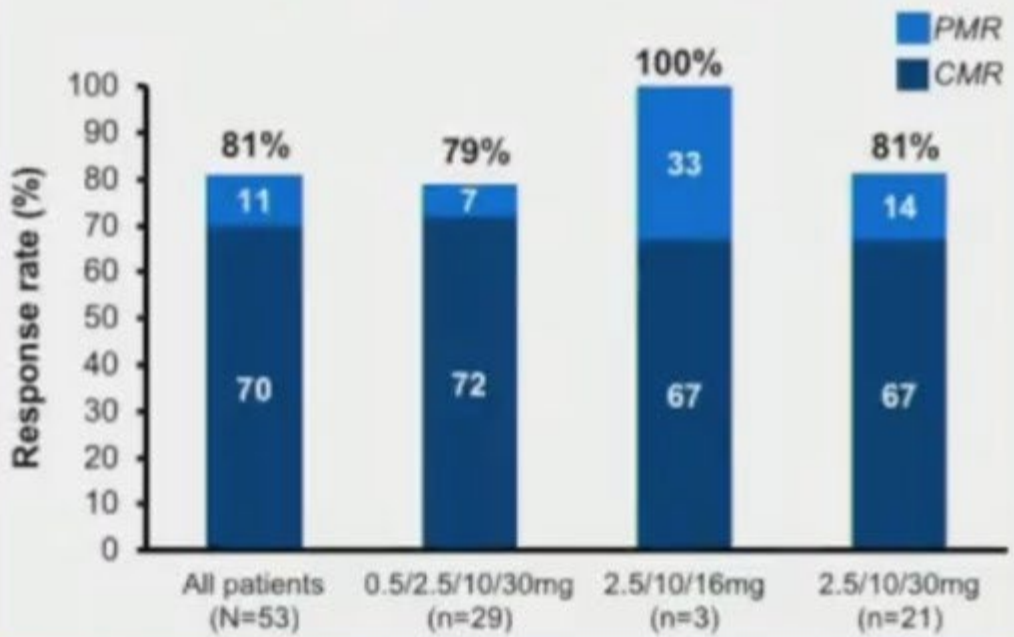
N (%) of patients unless stated		Glofitamab monotherapy cohorts (N=53)	Glofitamab + obinutuzumab cohort (N=19)
Median age, years (range)		64 (33–83)	61 (41–78)
Male		29 (54.7)	11 (57.9)
FLIPI 1 score 3–5		28 (52.8)	11 (57.9)
Median number of prior lines, n (range)		3 (1–12)	2 (1–5)
Prior systemic therapy	Chemotherapy	51 (96.2)	19 (100)
	Anti-CD20 monoclonal antibody	52 (98.1)	19 (100)
	Autologous stem-cell transplant	7 (13.2)	3 (15.8)
	PI3K inhibitor	9 (17.0)	3 (15.8)
	CAR-T	1 (1.9)	0
Refractory status	Refractory to any prior therapy	36 (67.9)	13 (68.4)
	Refractory to most recent therapy line	28 (52.8)	8 (42.1)
	Refractory to any prior anti-CD20	31 (58.5)	10 (52.6)
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)

- **Most patients had heavily pretreated R/R FL and/or characteristics commonly associated with a poor prognosis**

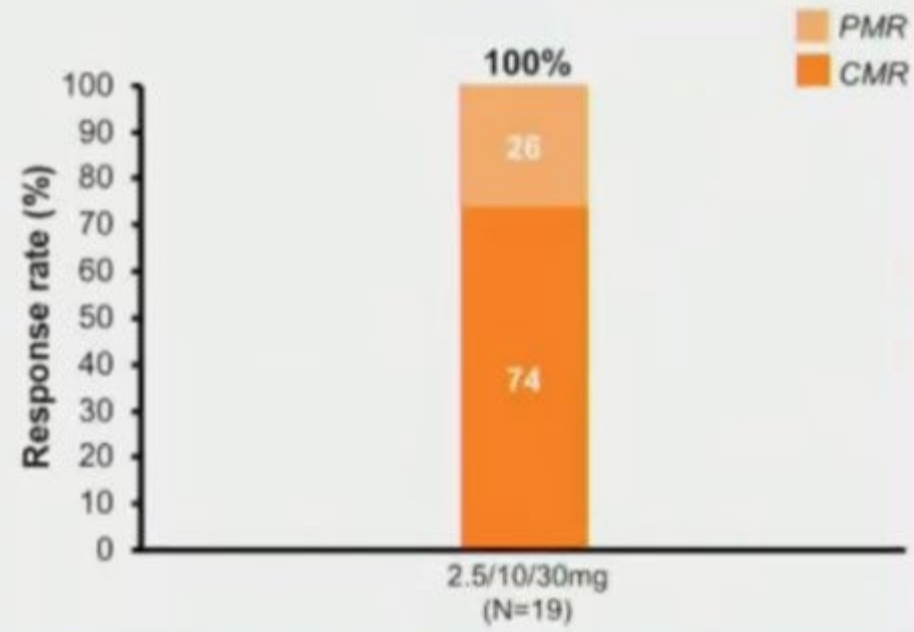
*Refractory to prior anti-CD20 antibodies and alkylating agents; CAR-T, chimeric antigen receptor T cell; FLIPI, Follicular Lymphoma International Prognostic Index; Mono, monotherapy; PI3K, phosphoinositide 3-kinase; POD24, progression of disease within 24 months of frontline treatment; SPD, sum of the product of the diameters

Response rates in R/R FL

Glofitamab monotherapy*



Glofitamab in combination with obinutuzumab*

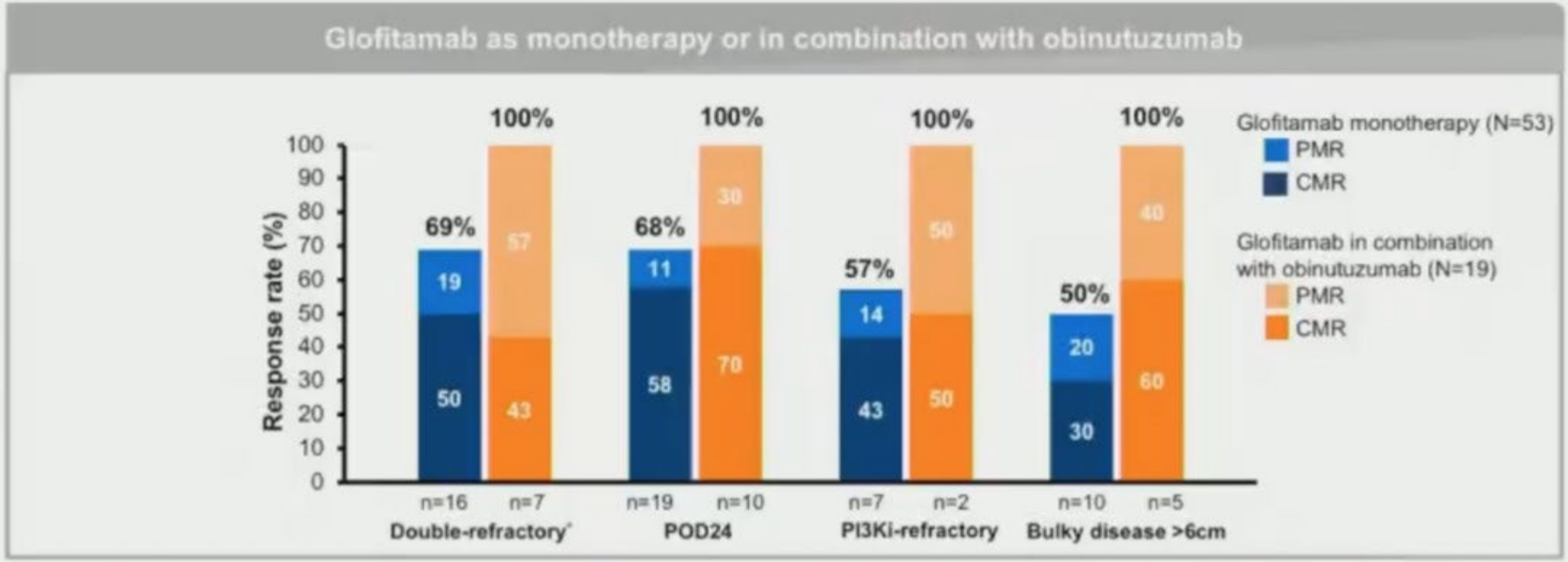


- **Glofitamab as monotherapy and in combination with obinutuzumab resulted in high response rates**

*Data cut-off: May 18, 2021. Best overall response. Secondary efficacy population includes all patients who had a response assessment performed (investigator assessed), or who were still on treatment at the time of their first scheduled response assessment (Lugano 2014 criteria[1]).
CMR, complete metabolic response; PMR, partial metabolic response

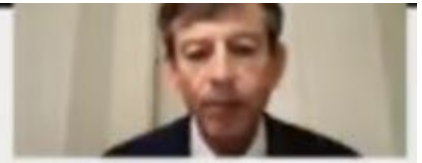
1. Cheson, et al. J Clin Oncol 2014.

Response rates in high-risk subgroups



- **High and consistent response rates in high-risk patient population**

*Patients refractory to anti-CD20 antibodies and alkylating agents



Adverse event overview

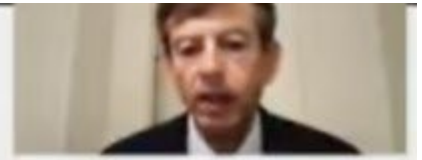
Adverse events, n (%)*	Glofitamab monotherapy cohorts (N=53)	Glofitamab + obinutuzumab cohort (N=19)
Any AE	50 (94.3)	19 (100)
Glofitamab related	47 (88.7)	18 (94.7)
Serious AE	26 (49.1)	8 (42.1)
Glofitamab related	23 (43.4)	6 (31.6)
Grade 3–4 AE	20 (37.7)	8 (42.1)*
Glofitamab related	17 (32.1)	9 (47.4)*
Grade 5 (fatal) AE	2 (3.8)	1 (5.3)
Glofitamab related	0 (0.0)	0 (0.0)
AE leading to treatment discontinuation	0	1 (5.3)
Glofitamab related	0	0

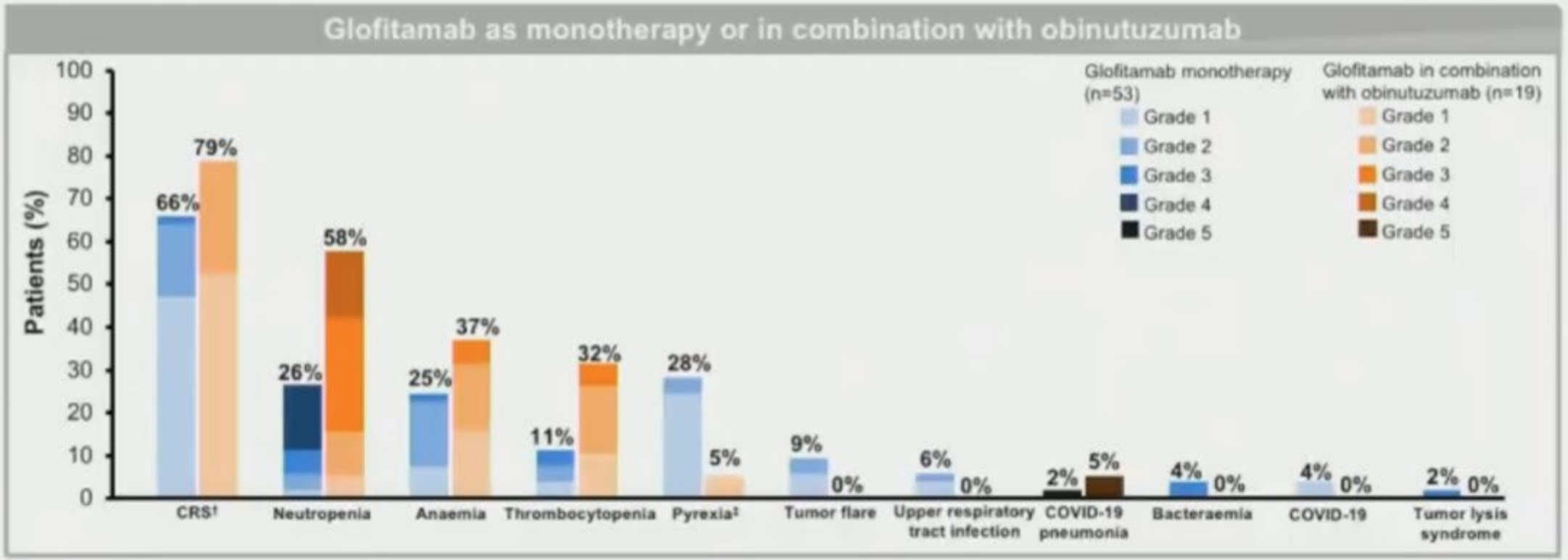
- Grade 5 (fatal) AEs monotherapy:
  - Cardio-respiratory arrest
  - COVID-19 pneumonia
- Grade 5 (fatal) AEs glofitamab + obinutuzumab:
  - COVID-19 pneumonia
- AE leading to glofitamab discontinuation in glofitamab + obinutuzumab:
  - COVID-19 pneumonia

- **No glofitamab-related AEs leading to treatment discontinuation were observed**

*One patient had a Grade 5 AE that was not related to glofitamab, however they had a Grade 3 AE (neutropenia) that was related to glofitamab; most extreme grade is shown. AE, adverse event

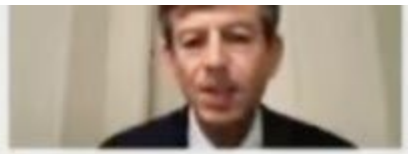
Common adverse events of clinical interest*





- **Myelosuppression was more common in patients who received glofitamab in combination with obinutuzumab**

*No febrile neutropenia AEs were observed. †By ASTCT criteria. ‡Pyrexia events separate from CRS.
CRS, cytokine release syndrome



Cytokine release syndrome*

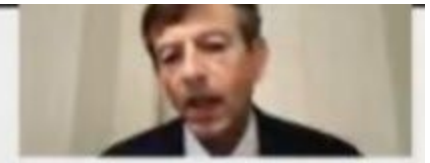
N (%) of patients with ≥1 AE unless stated	Glofitamab monotherapy cohorts		Glofitamab + obinutuzumab cohort (N=19)
	Glofitamab SUD cohorts, 2.5/10/16mg and 2.5/10/30mg (N=24)‡	Glofitamab extended SUD cohort, 0.5/2.5/10/30mg (N=29)	
Any CRS	19 (79.2)	16 (55.2)	15 (78.9)
Grade 1	15 (62.5)	10 (34.5)	10 (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)

- **Most CRS events were low grade and no meaningful difference in CRS was observed across glofitamab dosing regimens**

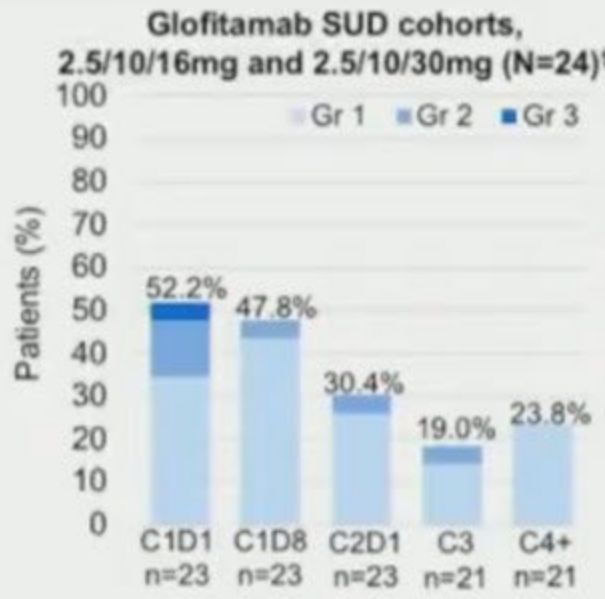
*By ASTCT criteria[1]; †One patient in the 2.5/10/16 mg cohort had a Grade 3 CRS event; ‡One pt had not received glofitamab 2.5mg at CCOD.
SUD, step-up dosing

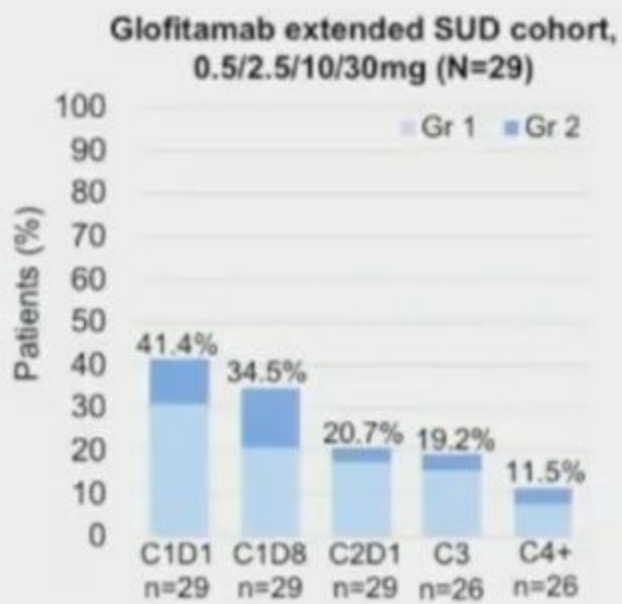
1. Lee et al. Biol Blood Marrow Transplant 2019

CRS onset by glofitamab dose



CRS by cycle and grade in glofitamab monotherapy cohorts*

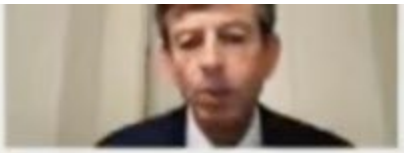




- **No clear benefit in CRS mitigation was observed with extended step-up dosing**

*By ASTCT criteria[1]; †One patient had not received glofitamab 2.5mg at CCOD

1. Lee et al. Biol Blood Marrow Transplant 2019



Other adverse events of interest

n (%)	Monotherapy cohorts (N=53)	Glofitamab + obinutuzumab cohort (N=19)
ICANS*	0	0
Tumor flare	5 (9.4)	0
Grade ≥3	0	0
Serious	1 (1.9)	0
Neutropenia	14 (26.4)	11 (57.9)
Grade ≥3	11 (20.8)	8 (42.1)
Serious	0	1 (5.3)
Febrile neutropenia	0	0
Infections	19 (35.8)	2 (10.3)
Grade ≥3	7 (13.2)	1 (5.3)
Serious	8 (15.1)	1 (5.3)

- **No ICANS or febrile neutropenia AEs were observed. Tumor flare occurred infrequently**

*Glofitamab-related neurologic AEs potentially consistent with immune effector cell-associated neurotoxicity syndrome (ICANS)

Conclusions

- Glofitamab demonstrated high response rates as monotherapy or in combination with obinutuzumab in patients with heavily pre-treated R/R FL, including in high-risk subgroups (dose-escalation data)
- Glofitamab monotherapy and in combination with obinutuzumab
  - CR rates were high and comparable, conclusions on durability are limited by short follow-up
  - Increased myelosuppression in glofitamab in combination with obinutuzumab cohort, although clinical consequences were not different
- No clear benefit in CRS mitigation was observed with extended versus standard step-up dosing of glofitamab
- Phase II expansion cohort with glofitamab monotherapy (2.5mg/10mg/30mg) is being prioritised based on these data

Oral 131

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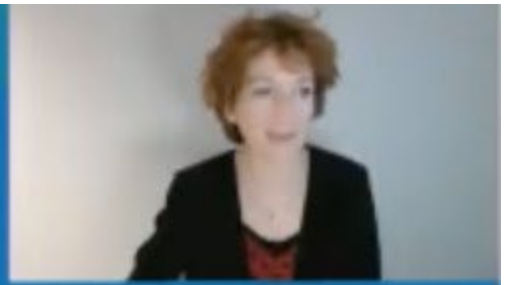

Efficacy of Tisagenlecleucel in Adult Patients with High-Risk Relapsed/Refractory Follicular Lymphoma: Subgroup Analysis of the Phase II ELARA Study

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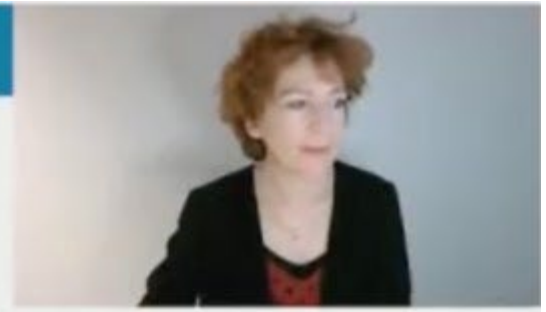
Introduction



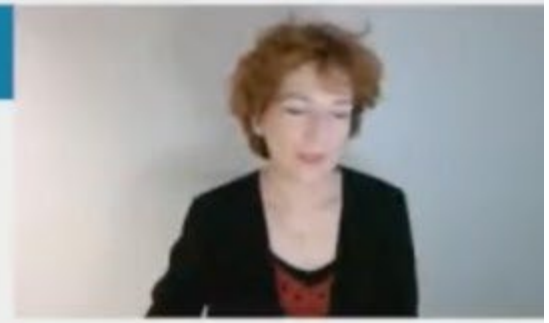
- FL is an indolent disease with a continuous relapsing pattern[1]
  - Patients with high-risk disease such as POD24, high tumor burden, and high Ann Arbor stage, have poor prognosis with current treatment options[1,2]
  - Novel therapies such as tisagenlecleucel are being investigated to improve outcomes
    - Tisagenlecleucel is an autologous anti-CD19 CAR-T cell therapy[3,4]

- Primary analysis of the ELARA trial in patients with r/r FL with a median follow-up of 11 months for efficacy reported high rates of durable response[5]
  - High ORR (86.2%) and CRR (66.0%)
  - 6-month PFS rate was 76%

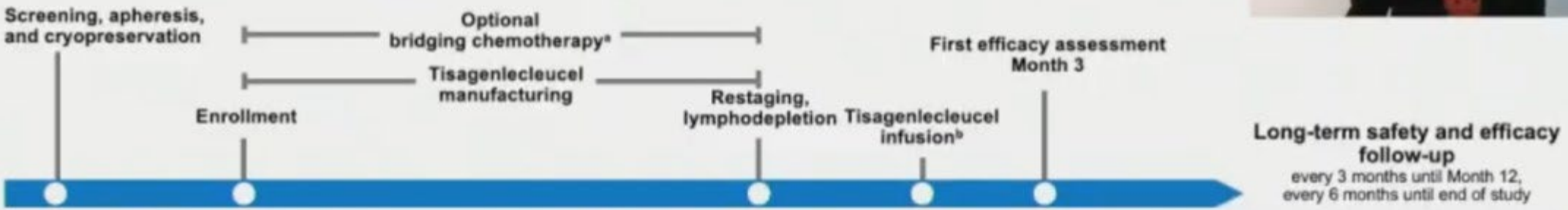
- **Here, we report**:
  - **Updated efficacy results from the overall population in the extended follow-up analysis (N=97 for safety; N=94 for efficacy)**
    - Data cutoff: When 90 patients received tisagenlecleucel and completed at least 12 months of follow-up post infusion
  - **Subgroup analysis of patients with high-risk disease including high TMTV**

CAR, chimeric antigen receptor; CD, cluster of differentiation; CRR, complete response rate; FL, follicular lymphoma; ORR, overall response rate; PFS, progression-free survival; POD24, progression of disease within 24 months from first immunochemotherapy; r/r, relapsed or refractory; TMTV, total metabolic tumor volume.

1. Casulo C, Barr PM. *Blood*. 2019;133(14):1540-1547; 2. Leonard JP, et al. *J Clin Oncol*. 2019;37(14):1188-1199; 3. Maude SL, et al. *N Engl J Med*. 2018;378(5):439-448; 4. Schuster SJ, et al. *N Engl J Med*. 2019;380(1):45-56; 5. Schuster SJ, et al. Presented at ASCO 2021. Oral presentation 7508.



ELARA Study Design



Key eligibility criteria	Study treatment	End points

• ≥18 years of age
• FL grade 1, 2, or 3A
• Relapsed/refractory disease[c]
• No evidence of histological transformation/FL3B
• No prior anti-CD19 therapy or allogeneic HSCT
	• Lymphodepleting chemotherapy options:
	  • Fludarabine (25 mg/m^2 IV daily for 3 days) + cyclophosphamide (250 mg/m^2 IV daily for 3 days)
	  • Bendamustine 90 mg/m^2 IV daily for 2 days
	• Tisagenlecleucel dose range (single IV infusion) was 0.6-6×10^8 CAR-positive viable T cells
		Primary: CRR by IRC
		
		Secondary: ORR, DOR, PFS, OS, safety, cellular kinetics

- Bridging therapy was allowed and was followed by disease re-evaluation before tisagenlecleucel infusion
- Timing of planned analyses

Planned analyses	Minimum follow-up from infusion	Median follow-up
Interim analysis	≈50 patients with ≥6 months follow-up	10 months
Primary analysis	90 patients with ≥6 months follow-up	11 months
Extended follow-up analysis	**90 patients with ≥12 months follow-up**	**17 months**

[a]Disease was reassessed prior to infusion for all patients requiring bridging therapy. [b]Infusion was conducted on an in- or outpatient basis at investigator discretion. [c]Refractory to ≥2nd line of systemic therapy (including an anti-CD20 antibody and alkylating agent) or relapsed within 6 months after ≥2nd line of therapy or after an autologous HSCT.

CAR, chimeric antigen receptor; CD, cluster of differentiation; CRR, complete response rate; DOR, duration of response; EAS, efficacy analysis set; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplant; IRC, independent review committee; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

ELARA: Extended Follow-up Analysis

Consistent Tisagenlecleucel Safety Profile

- **Median follow-up was 17 months** (range, 10-26 months)
- 17 patients (18%) were treated in the outpatient setting

Adverse Events of Special Interest within 8 Weeks[a]	Patients (N=97)	
	All Grades n (%)	Grade ≥3 n (%)
All adverse events	94 (96.9)	69 (71.1)
CRS[b,c]	47 (48.5)	0
All nervous system disorders[d]	36 (37.1)	3 (3.1)
ICANS	4 (4.1)	1 (1.0)
Infections	18 (18.6)	5 (5.2)
Tumor lysis syndrome	1 (1.0)	1 (1.0)
Hypogammaglobulinemia	9 (9.3)	0
Hematologic disorders including cytopenias		
Neutropenia[e,f]	32 (33.0)	31 (32.0)
Anemia[e]	24 (24.7)	13 (13.4)
Thrombocytopenia[e]	16 (16.5)	9 (9.3)

[a]AESIs within 8 weeks post-infusion. [b]CRS was graded using Lee scale 2014. [c]Refers to first CRS episode only. [d]Nervous system disorders include headache, dizziness, ICANS, encephalopathy, paraesthesia, tremor, dysgeusia, dyskinesia, migraine, peripheral sensory neuropathy, syncope. [e]One of multiple preferred terms evaluated under the AESI "Hematologic disorders including cytopenias." [f]Median duration of grade 3/4 neutropenia was 52 days (based on laboratory data).

AESI, adverse event of special interest; CRS, cytokine release syndrome; ICANS, immune effector cell associated neurotoxicity syndrome.

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ELARA: Extended Follow-up Analysis

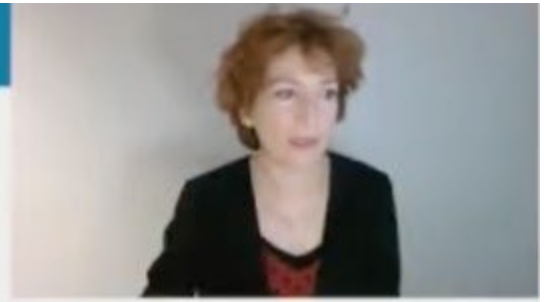
CRS Events within 8 Weeks Were Grade 1/2

Events Within 8 Weeks of Infusion,[a] %	All Patients (N=97)
Patients with CRS (Lee scale)[1]	48.5
Maximum CRS grade	
Grade 1	27.8
Grade 2	20.6
Grade 3/4	0
Median onset of CRS, days	4.0
Min-Max	1-14
Median duration of CRS, days	4.0
Min-Max	1-24

Only the first CRS episode is summarized for each patient.

[a]Occurring within 8 weeks of tisagenlecleucel infusion.
CRS, cytokine release syndrome.
1. Lee DW, et al. *Blood*. 2014;124(2):188-195.

ELARA: Extended Follow-up Analysis Shows Compelling Efficacy Outcomes



- As of March 29, 2021, 97 patients received tisagenlecleucel and 94 were evaluable for efficacy
- CR rates are consistent and durable for the interim, primary analyses, and this extended follow-up analysis
- Complete response correlated with durability and prolonged PFS
  - **Among patients who achieved CR, 12-month PFS was 85.5% (95% CI, 74-92) and estimated DOR rate at 9 months was 86.5% (95% CI, 75-93)**

Efficacy Results of Extended Follow-up Analysis

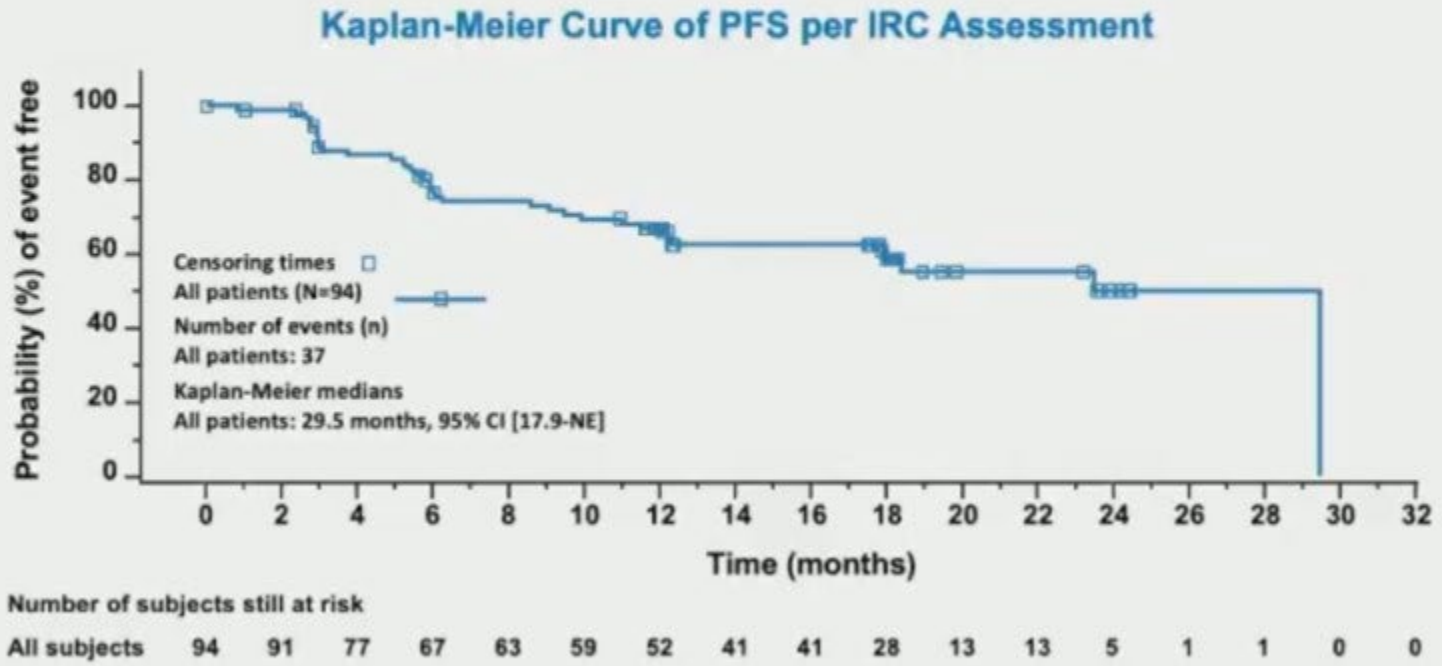
Endpoint	% (95% CI)
ORR[a]	**86.2** (77.5-92.4)
CRR[a]	**69.1** (58.8-78.3)
12-mo PFS	**67.0** (56.0-75.8)
9-mo DOR	**76.0** (64.6-84.2)

[a]ORR and CRR were comparable with the primary efficacy analysis (ORR 86.2% and CRR 66.0%).

BOR, best overall response; CI, confidence interval; CR, complete response; CRR, complete response rate; DOR, duration of response; ORR, overall response rate; PFS, progression-free survival.

ELARA: Durable Response and Promising 12-mo PFS Confirmed with Longer Follow-up

- With a longer median follow-up of 21 months (August 3, 2021 data cutoff)
  - **Median PFS was 29.5 months** (95% CI, 17.9-NE)[a]



[a]Median PFS should be interpreted with caution due to the low number of patients at risk after Month 24.
CI, confidence interval; IRC, independent review committee; NE, not estimable; PFS, progression-free survival.

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ELARA: High-Risk Subgroups

- Descriptive efficacy subanalyses were performed for 9 high-risk subgroups
- Multivariate analysis was performed to identify factors predictive of worse PFS

High-Risk Group	Patients (N=94), %
≥5 lines of prior therapy	28.7
High FLIPI score at study entry	60.6
Prior HSCT therapy	37.2
POD24	64.9
Bulky disease at baseline (GELF criteria)[1]	64.9
LDH prior to infusion > ULN	32.2
CRP prior to infusion > ULN	52.2
Double refractory[a]	69.1
High TMTV >510 ml at baseline[b,2]	21.3

[a]Double refractory is defined as failure to respond or relapsed within 6 months following therapy with anti-CD20 and alkylating agents, any regimen. [b]Quantitative tumor burden is assessed by FDG-PET/CT. TMTV was measured using the 41% thresholding method, and the 510 ml cut point, determined by X tile and receiver operating characteristic analysis.

CRP, C-reactive protein; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; HSCT, hematopoietic stem cell transplant; LDH, lactate dehydrogenase; POD24, progression of disease within 24 months from first immunochemotherapy; TMTV, total metabolic tumor volume; ULN, upper limit of normal.

1. Brice P, Bastion Y, Lepage E, et al. *J Clin Oncol.* 1997;15(3):1110-1117; 2. Cottereau AS, Versari A, Luminari S, et al. *Blood.* 2018;131(22):2449-2453.

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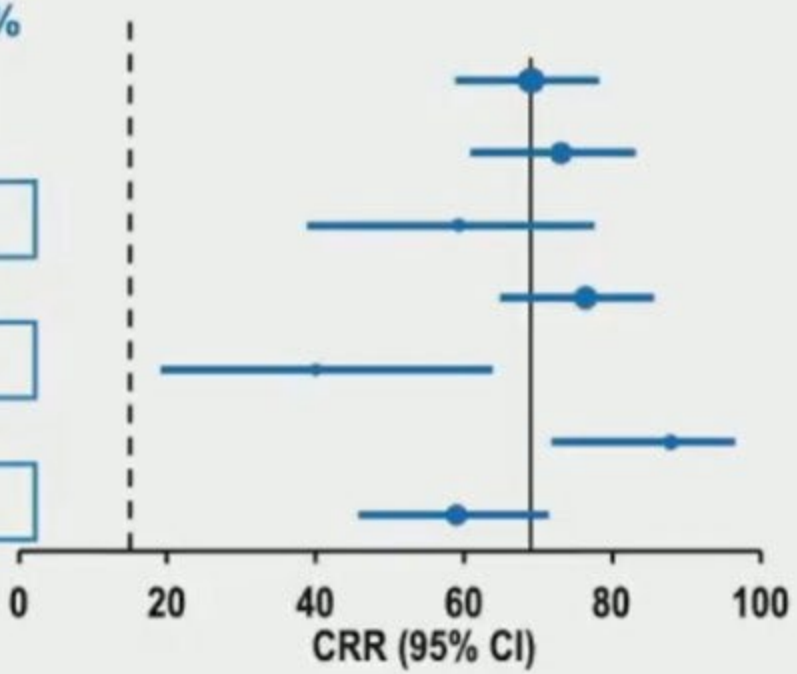
ELARA: High-Risk Subgroups

High Rates of Durable Responses in High-Risk Subgroups

Descriptive Subgroup Analysis

- There was a decrease in **CRR (%)** for these high-risk subgroups compared with corresponding low-risk subgroups

		n	CRR %
Overall		94	69.1
Prior therapy	<5 lines	67	73.1
	≥5 lines	27	59.3
High TMTV (>510 ml)[a,b]	No	72	76.4
	Yes	20	40.0
POD24	No	33	87.9
	Yes	61	59.0



[a]Analysis for the high TMTV subgroup was limited by small sample size. [b]At baseline.
Median TMTV 155.32 cm^3; range, 0.1-2470.4 cm^3. Vertical dashed line represents the null hypothesis of CRR 15% or less. Vertical solid line represents the CRR% in the overall population.
CI, confidence interval; CRR, complete response rate; POD24, progression of disease within 24 months from first immunochemotherapy; TMTV, total metabolic tumor volume.

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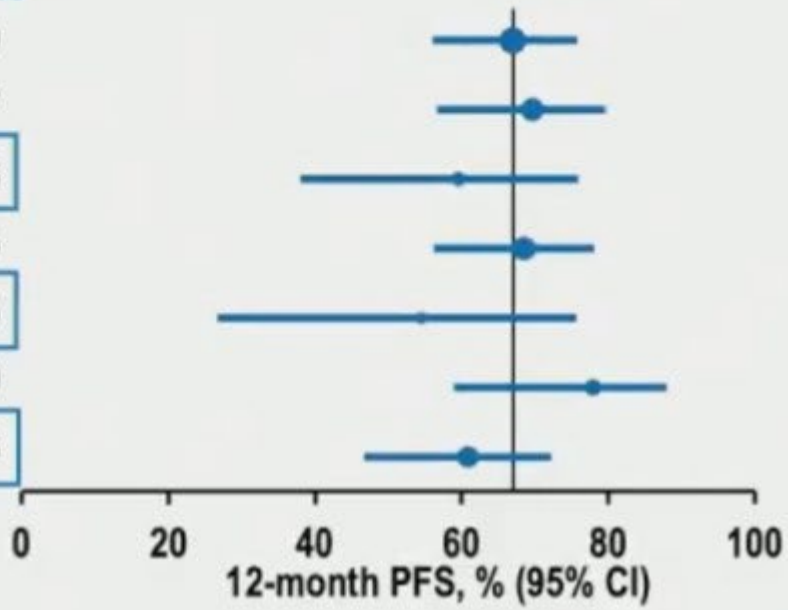
ELARA: High-Risk Subgroups

High Rates of Durable Responses in High-Risk Subgroups (cont)

Descriptive Subgroup Analysis

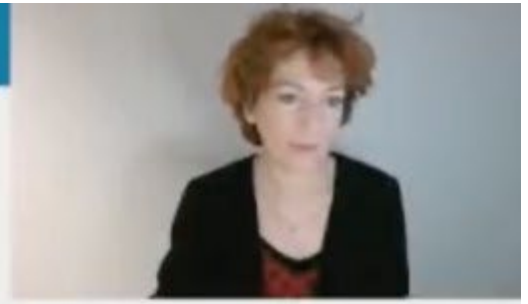
- There was a decrease in **12-month PFS (%)** for these high-risk subgroups compared with corresponding low-risk subgroups

		n	PFS %
Overall		94	67.0
Prior therapy	<5 lines	67	69.7
	≥5 lines	27	59.6
High TMTV (>510 ml)[a,b]	No	72	68.5
	Yes	20	54.5
POD24	No	33	77.9
	Yes	61	60.8



[a]Analysis for the high TMTV subgroup was limited by small sample size. [b]At baseline.
Median TMTV 155.32 cm^3; range, 0.1-2470.4 cm^3.Vertical solid line represents the median 12-month PFS in the overall population.
CI, confidence interval; PFS, progression-free survival; POD24, progression of disease within 24 months from first immunochemotherapy; TMTV, total metabolic tumor volume.

Presented at the 2021 ASH Annual Meeting and Exposition; December 11-14, 2021; Atlanta, GA, and Virtual



ELARA: High-Risk Subgroups
POD24 and High TMTV Demonstrated Efficacy

- Although POD24 and high TMTV (>510 ml) were associated with less favorable PFS in the multivariate analysis of high-risk factors, efficacy in these high-risk subgroups was still superior to the current non-CAR-T standards of care[1-6]

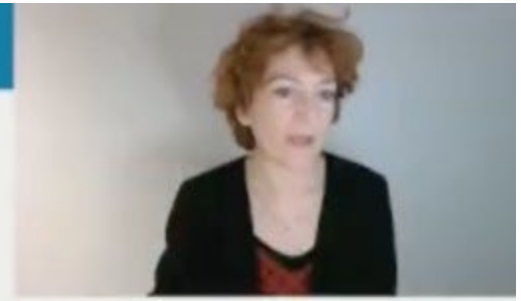
Disease Characteristic	Descriptive Analysis		Multivariate Analysis
	High-Risk 12-Month PFS (%)	Low-Risk 12-Month PFS (%)	Hazard Ratio (95% CI)
POD24	60.8	77.9	2.3 (1.0-5.3)
TMTV[a]	54.5	68.5	2.5 (1.3-5.6)

[a]TMTV median 155.32 cm^3; range, 0.1-2470.4 cm^3.

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; POD24, progression of disease within 24 months from first immunochemotherapy; TMTV, total metabolic tumor volume.

1. Leonard JP, et al. *J Clin Oncol.* 2019;37(14):1188-1199. 2. Gopal AK, et al. *N Engl J Med.* 2014;37(14):1188-1199; 3. Dreyling M, et al. *Am J Hematol.* 2020;95(4):362-371; 4. Flinn IW, et al. *J Clin Oncol.* 2019;37(11):912-922; 5. Fowler NH, et al. *J Clin Oncol.* 2021;39(15):1609-1618; 6. Morschhauser F, et al. *Lancet Oncol.* 2020;21(11):1433-1442.

Presented at the 2021 ASH Annual Meeting and Exposition; December 11-14, 2021; Atlanta, GA, and Virtual



Conclusions

Overall patient population

- At a median follow-up of 17 months in patients with r/r FL and ≥2 prior lines of therapy, tisagenlecleucel demonstrated
  - High ORR (86.2%) and CRR (69.1%)
  - Durable responses and promising 12-month PFS (67.0%)
- Safety data are consistent with the established favorable tisagenlecleucel safety profile

High-risk subgroups

- Tisagenlecleucel induced high rates of durable responses among patients with high-risk disease
- In multivariate analyses, POD24 and TMTV appeared to impact PFS vs the low-risk group, but is still superior to the current non-CAR-T cell therapy standards of care for patients with r/r FL[1-11]
  - POD24: 12-month PFS 60.8%
  - High TMTV: 12-month PFS 54.5%
- Further exploration of the prognostic value of high TMTV in the CAR-T cell therapy setting is warranted

ELARA and FL-related presentations also at ASH 2021:

- Fowler NH, et al. Poster 3533.
- Salles G, et al. Posters 3528 and 1349.
- Hao Y, et al. Poster 2419.
- Bollu V, et al. Poster 1360.

CAR, chimeric antigen receptor; CRR, complete response rate; FL, follicular lymphoma; ORR, overall response rate; PFS, progression-free survival; POD24, progression of disease within 24 months from first immunochemotherapy; r/r, relapsed or refractory; TMTV, total metabolic tumor volume.

1. Leonard JP, et al. *J Clin Oncol*. 2019;37(14):1188-1199; 2. Witzig et al. *J Clin Oncol*. 2002;20(15):3262-9; 3. Multi-disciplinary Review and Evaluation for Tazverik® (tazemetostat) FDA 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/211723Orig1s000MultidisciplineR.pdf; 4. Salles G, et al. *Haematologica*. 2017;102(4):e156-e159; 5. Zydelig® FDA Clinical Review (2014) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205858Orig1s000MedR.pdf; 6. Dreyling M, *et al. Am J Hematol*. 2020;95(4):362-371; 7. Dreyling M, et al. *Ann Oncol*. 2017;28(9):2169-2178; 8. Flinn IW, et al. *J Clin Oncol*. 2019;37(11):912-922; 9. Morschhauser F, et al. *Lancet Oncol*. 2020;21(11):1433-1442; 10. Fowler NH, et al. *J Clin Oncol*. 2021;39(15):1609-1618; 11. Andorsky DJ, et al. *Br J Haematol*. 2019;184(2):215-222.

Presented at the 2021 ASH Annual Meeting and Exposition; December 11-14, 2021; Atlanta, GA, and Virtual

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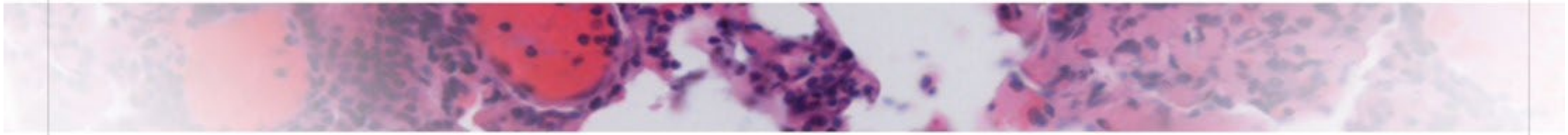
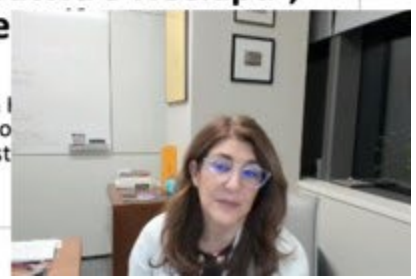


A Comparison of Clinical Outcomes from Updated ZUMA-5 (Axicabtagene Ciloleucel) and the International SCHOLAR-5 External Control Cohort in Relapsed/Refractory Follicular Lymphoma (r/r FL)

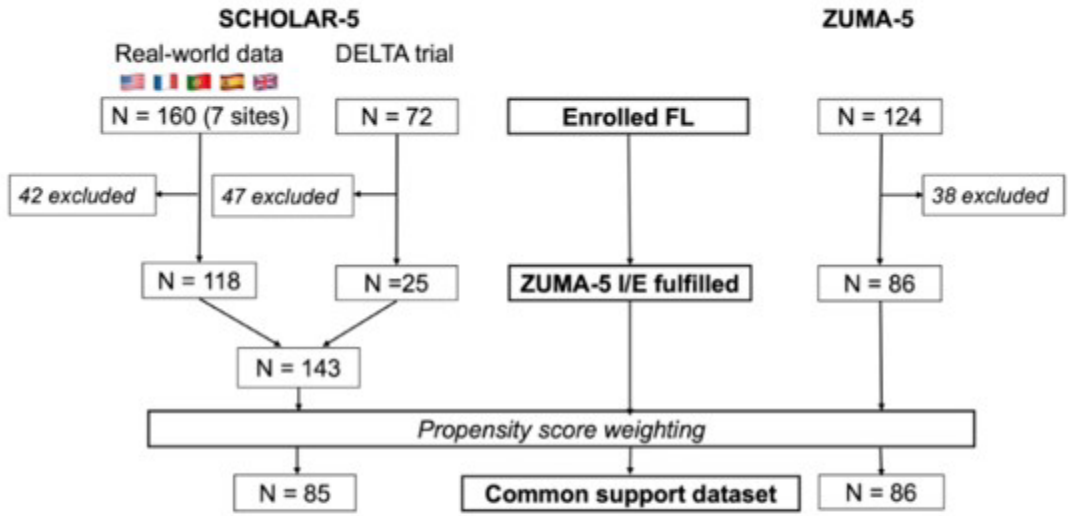
M. Lia Palomba[1]; Paola Ghione[1, 2]; Anik R Patel[3]; Kevin Deighton[4]; Caron A Jacobson[5]; Myrna Nahas[3]; A Scott Jung[3]; Anthony J Hatswell[4]; Steve Kanters[6]; Eve Limbrick-Oldfield[6]; Sally W Wade[7]; Julia Thornton Snider[3]; Sattva S Neelapu[8]; Maria Teresa Ribeiro[9]; John Gribben[10]; John Radford[11]; Sabela Bobillo[12]; Herve Ghesquie

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [3]Kite, A Gilead Company, Santa Monica, CA; [4]Delta
Farber Cancer Institute, Boston, MA, USA; [6]RainCity Analytics, Vancouver, BC, Canada; [7]Wade Outcomes Research and Consulting, Salt Lake City, UT; [8]The University o
Center, Houston, TX, USA; [9]Portuguese Oncology Institute of Porto, Porto, Portugal; [10]Cancer Research UK Barts Centre, London, UK. [11]The Christie NHS Foundation Trust
Manchester, UK; [12]Vall D'Hebron Insitute of Oncology, Barcelona, Spain; [13]Centre Hospitalier Lyon Sud, Lyon, France

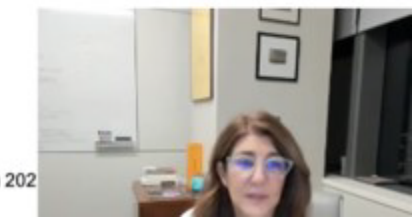


Introduction

- In the pivotal ZUMA-5 single-arm trial,[1] axi-cel demonstrated high rates of durable response in r/r FL patients, including those with high-risk disease.
- The international SCHOLAR-5 external cohort was constructed to allow the comparison of ZUMA-5 to alternative available therapies for r/r FL.



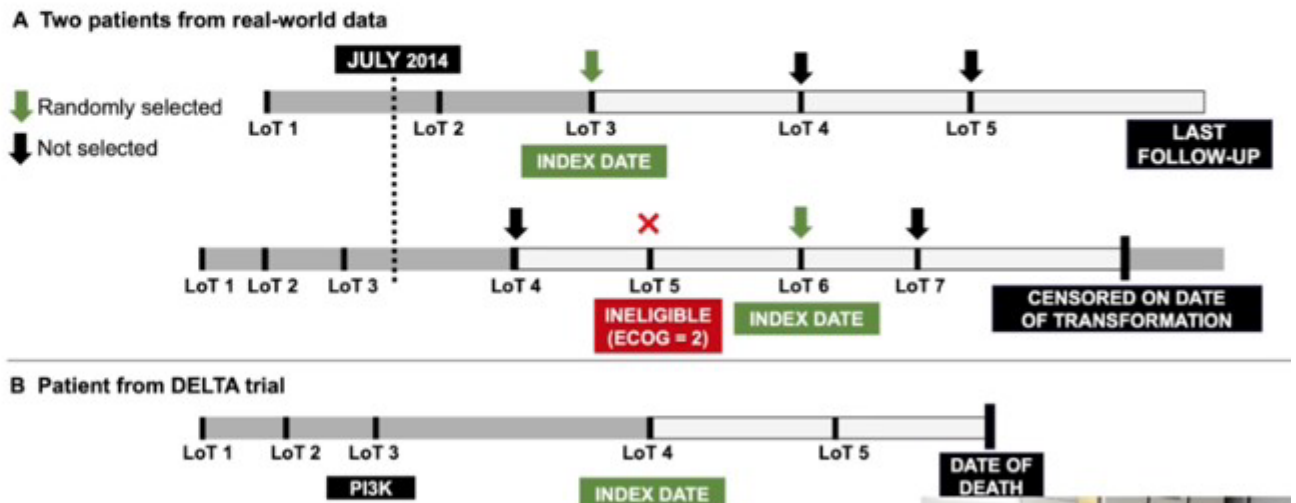
- A previous weighted analysis including 18 -month ZUMA-5 data, compared to SCHOLAR-5 data, showed a substantial clinical benefit of axi-cel in overall response rate (ORR), complete response (CR), progression-free survival (PFS), and overall survival (OS).[2]
- Here, we present an updated comparative analysis using 24-month ZUMA-5.



[1]Jacobson C et al. Lancet Oncology 2021, accepted.
[2]Ghione, P. Et al. A comparison of clinical outcomes from ZUMA-5 (axicabtagene ciloleucel) and the international SCHOLAR-5 external control cohort in relapsed/refractory follicular lymphoma (r/r FL) 202

Methods

- The international SCHOLAR-5 cohort data were extracted for patients who initiated a ≥3rd line of therapy (LoT) on or after July 2014. Lines that were eligible for inclusion in the analysis were entered into a random selection. A single LoT for each patient was included.
- The SCHOLAR-5 and ZUMA-5 cohorts were balanced for patient characteristics through propensity scoring on prespecified prognostic factors and standardized mortality ratio weighting[3].
- ORR and CR were compared using odds ratios. OS, PFS and next treatment-free survival (NTFS) were evaluated using Kaplan-Meier analysis.



[3]Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. Am J Epidemiol 2006; 163(12): 1149-56.

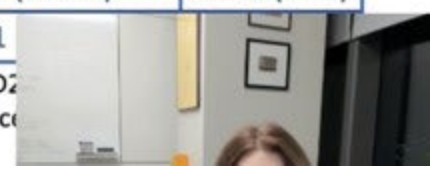
Results: Patient characteristics

- 143 patients were identified in SCHOLAR-5, reducing to a weighted sum of 85 after applying propensity score weights, versus 86 patients in ZUMA-5
- Median follow-up time for ZUMA-5 and SCHOLAR-5 were 29.4 and 26.2 months respectively.

Patient characteristics before and after propensity weighting

		SCHOLAR-5 before weighting (n = 143)	ZUMA-5 (n = 86)	SCHOLAR-5 after weighting (n = 85)	SMD (p-value)
Median age (range), years		64 (36 – 89)	62 (34 – 79)	61 (36 – 89)	0.036 (.85)
Male, n (%)		81 (56.6%)	48 (55.8%)	53 (61.9%)	0.123 (.46)
POD24, n (%)		51 (35.7%)	49 (57.0%)	47 (55.9%)	0.022 (.90)
Prior lines of therapy, median (range)		2 (2-8)	3 (2-9)	3 (2-8)	0.047 (.81)
Refractory to prior line, n (%)		87 (60.6%)	63 (73.3%)	65 (76.6%)	0.077 (.61)
Prior SCT, n (%)		31 (21.7%)	21 (24.4%)	24 (28.0%)	0.080 (.64)
Size of largest nodal mass (cm)*		4.16 (2.75 – 6.50)	4.35 (3.27 – 6.43)	4.02 (2.90 – 6.25)	0.094 (.59)
Time since last therapy (months)*		6.76 (1.16 – 22.66)	3.53 (1.77 – 9.01)	2.30 (0.69-7.99)	0.056 (.67)
Time since diagnosis (months)*		84.79 (52.99 – 130.47)	59.86 (35.10– 96.62)	64.55 (40.96 – 115.79)	0.100 (.52)
ECOG, n (%):	0	39 (33.1%)	51 (59.3%)	21 (29.0%)	0.640 (.002)
	1	79 (66.9%)	35 (40.7%)	51	

* Median and inter-quartile range ; ECOG, Eastern Co-operative Oncology Group performance; POD2
24 months of first-line anti-CD20 monoclonal antibody and chemotherapy combination; SCT, stem-c



Results: Response outcomes

- ORR and CR were higher in ZUMA-5 compared to SCHOLAR-5.
- In the sub-group analysis of ≥4th LoT patients, which compared 60 patients from ZUMA-5 to 59 patients from SCHOLAR-5, these differences were more pronounced

Response outcomes

		SCHOLAR-5	ZUMA-5	Odds ratio	P value
Primary analysis: ≥ 3rd LoT	**ORR**	42/85 (**49.9%**)	81/86 (**94.2%**)	16.2 (5.6, 46.9)	< .001
	CR	25/85 (**29.9%**)*	68/86 (**79.1%**)**	8.85 (4.3, 18.25)	< .001
Sub-group analysis: ≥ 4th LoT	**ORR**	24/59 (**40.3%**)	57/60 (**95%**)	28.14 (7.38, 107.33)	< .001
	CR	12/59 (**20.6%**)*	48/60 (**80%**)	15.42 (5.82, 40.83)	< .001

* Response assessment includes CT-based and PET-Based scans with limited confirmatory bone marrow biopsy;
**13 patients with imaging CRs did not receive confirmatory bone marrow biopsy
CR, complete response; LoT, line of treatment; ORR, overall response rate.

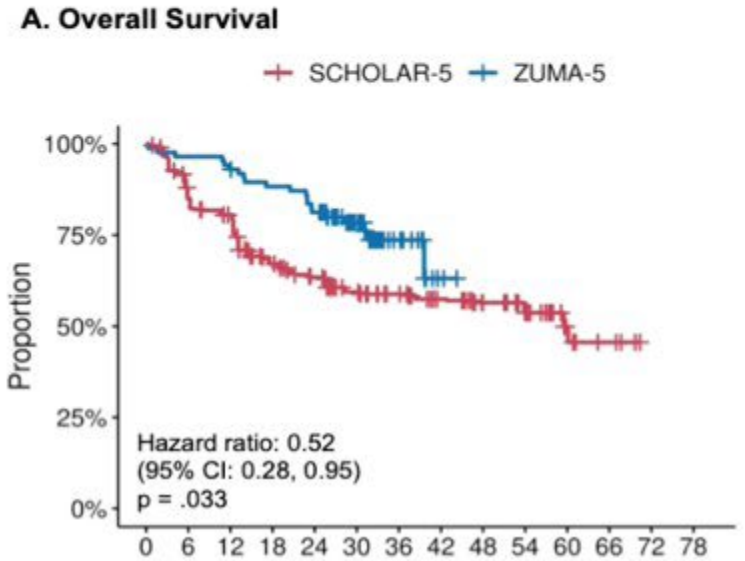
Results: Time-to-event outcomes

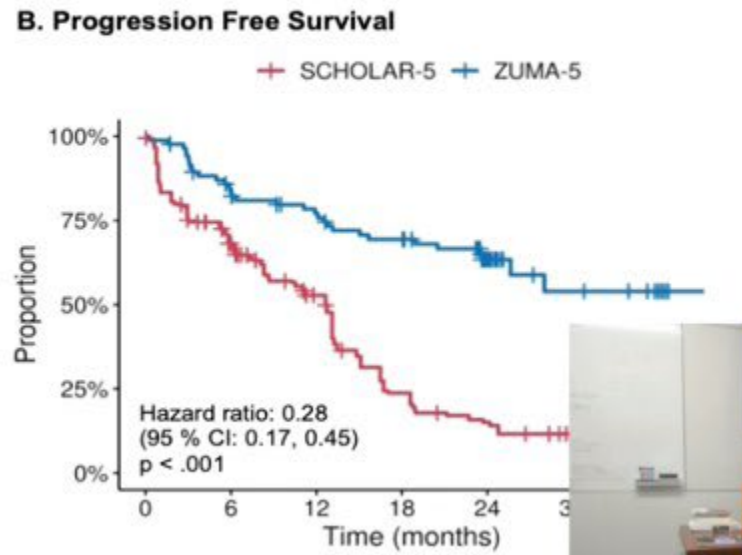
- The hazard ratios for OS and PFS were both clinically and statistically significant

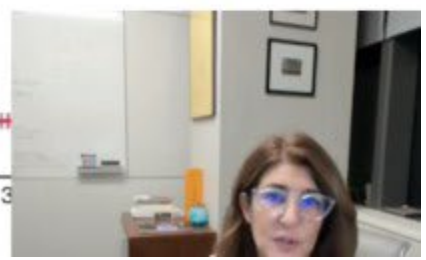
Time-to-event outcomes

		24 months % (95% CI)		Median months (95% CI)		Hazard ratio (95% CI)	p-value
		SCHOLAR-5	ZUMA-5	SCHOLAR-5	ZUMA-5		
Primary analysis: ≥ 3rd LoT	OS	63.4 (50.3, 76.4)	81.2 (71.2, 88.1)	59.8 (21.9, -)	NR (39.6, -)	0.52 (0.28, 0.95)	.033
	PFS	15.0 (4.8, 25.2)	63.4 (51.6, 73.0)	12.7 (6.2, 14.7)	39.6 (25.7, -)	0.28 (0.17, 0.45)	<0.001
	NTFS	49.5 (36.3, 62.7)	63.8 (52.7, 73.0)	14.4 (6.2, 25.8)	39.6 (28.0, -)	0.58 (0.36, 0.95)	.031
Sub-group analysis: ≥ 4th LoT	OS	51.5 (36.2, 66.8)	79.8 (67.1, 88.0)	28.4 (12.3, -)	NR (39.6, -)	0.43 (0.23, 0.81)	.010
	PFS	5.7 (0, 12.2)	59.0 (44.5, 71.0)	3.5 (1.8, 12.9)	28.0 (20.5, -)	0.20 (0.12, 0.33)	<.001
	NTFS	43.3 (28.0, 58.6)	59.8 (46.2, 70.9)	14.2 (5.8, -)	39.6 (22.8, -)	0.58 (0.33, 1.00)	.051

LoT, line of treatment; NTFS, next treatment-free survival; OS, overall survival; PFS, progression-free survival.





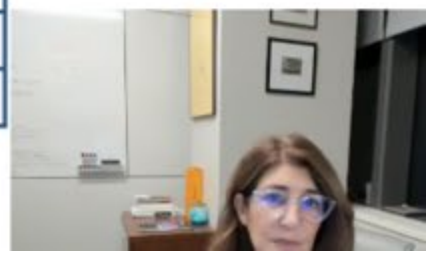


SCHOLAR-5 Outcomes by LoT

- Quality and duration of clinical response decreased with increasing LoTs.

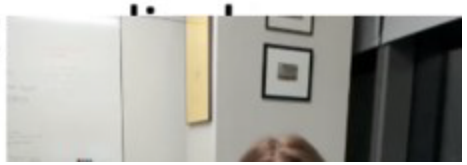
		3rd LoT	4th LoT	≥ 5th LoT
Response outcomes				
ORR	N responders % (95% CI)	59/89 66.3% (55.5, 76.0)	26/49 53.1% (38.3, 67.5)	13/35 37.4% (22.1, 55.7)
CR	N responders % (95% CI)	38/89 42.7% (32.3, 53.6)	16/49 32.7% (19.9, 47.5)	6/35 17.1% (7.9, 33.3)
Time-to-event outcomes				
		N = 98	N = 52	N = 27
OS	Median months (95% CI)	NR (53.2 – NE)	30.4 (22.3 – NE)	13.1 (12.0 – NE)
	24 months % (95% CI)	79.6 (71.5 – 88.5)	57.3 (44.4 – 73.8)	36.1 (21.7, 60.1)
PFS	Median months (95% CI)	11.0 (8.6, 17.1)	7.4 (5.3, 15.1)	4.0 (3.1, 11.4)
	24 months % (95% CI)	20.4 (11.9 – 35.2)	11.5 (4.6 – 28.5)	3.5 (0.6, 22.6)
NTFS	Median months (95% CI)	21.2 (16.3 – 41.9)	22.9 (9.1 – NE)	8.7 (4.3 – 16.7)
	24 months % (95% CI)	48.3 (38.7 – 60.3)	46.2 (33.7 – 63.3)	22.38 (12.6 – 39.8)

CR, complete response; LoT, line of treatment; NTFS, next treatment-free survival; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.



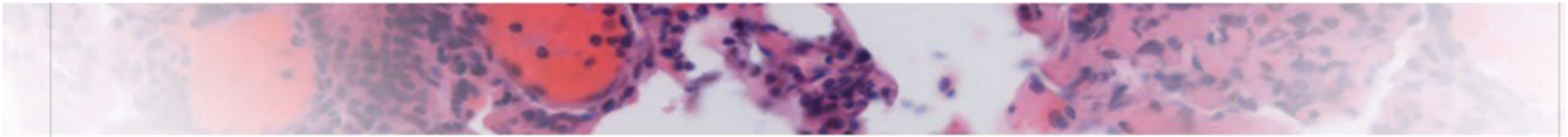
Conclusions

- Compared to currently available therapies in r/r FL patients, axi-cel demonstrated a clinically and statistically significant improvement in overall response rate and complete response.
- Similarly, axi-cel demonstrated a clinically and statistically significant improvement PFS, NTFS and OS, highlighting the durable treatment effect of axi-cel.
- Analysis of real-world outcomes show poor clinical outcomes that worsen with increasing LoT.
- These findings suggest that axi-cel addresses an important unmet need for r/r FL patients.



Foliküler Lenfoma

- Birinci basamak FL tedavisi
  - İmmünokemoterapi: FOLL12 çalışması alt grup analizi
  - OB-VEN: PrECOG 0403 çalışması
  - R2: Relevance çalışması 6-yıl takip
- Relaps refrakter FL tedavisi
  - R2: Magnify çalışması
  - Bispesifik antikorlar: Mosunetuzumab, Glofitamab
  - CAR-T hücre tedavisi: Elara çalışması altgrup analizi, Standart tedaviler ile karşılaştırma
- İdame tedavisi



Rituximab Maintenance Benefits Less for Follicular Lymphoma Patients with Low Risk of the FLIPI

Tingyu Wang, Ru Li, Rui Lv, Yi Wang, Ying Yu, Jiawen Chen, Wenjie Xiong, Qi Wang, Wei Liu, Wenyang Huang, Weiwei Sui, Gang An, Yan Xu, Dehui Zou, Jianxiang Wang, Lugui Qiu, and Shuhua Yi

State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Blood Diseases Hospital & Institute of Hematology, Chinese Academy of Medical Sciences & Peking Union Medical College

Background

- Follicular lymphoma (FL) is an incurable indolent disease with a heterogeneous course.
- Rituximab-based immunochemotherapy is now the standard choice for the first-line therapy of FL.
- Rituximab maintenance (RM) in patients with response prolongs PFS.
- The Follicular Lymphoma International Prognostic Index (FLIPI) is the most commonly used prognostic system to predict survival.
- The impact of RM on patients in different FLIPI risks remains not clear.

Baseline characteristics

	Total (n=192)	Control (n=96)	RM (n=96)	P value
Age≥ 65 y	5.2 (10/192)	6.3 (6/96)	4.2 (4/96)	0.747
Gender (Male)	45.8 (88/192)	48.9 (47/96)	42.7 (41/96)	0.385
B symptoms	21.7 (44/203)	26.0 (25/96)	19.8 (19/96)	0.303
Ann Arbor stage III-IV	84.7 (161/190)	78.7 (74/94)	90.6 (87/96)	0.027
B2-MG > UNL	40.5 (62/153)	40.0 (30/75)	41.0 (32/78)	0.897
LDH > UNL	15.8 (30/190)	17.7 (17/96)	13.8 (13/94)	0.552
Bulk	20.9 (24/115)	20.4 (11/54)	21.3 (13/61)	1
SUVmax≥10	60.0 (45/75)	60.0 (24/40)	60.0 (21/35)	1
FLIPI low risk	27.8 (47/169)	30.1 (25/83)	25.6 (22/86)	0.766
FLIPI intermediate risk	47.3 (80/169)	47.0 (39/83)	47.7 (41/86)	
FLIPI high risk	24.9 (42/169)	22.9 (19/83)	26.7 (23/86)	
Grade 1-2	63.5 (106/167)	54.9 (45/82)	71.8 (61/85)	0.042
Grade 3A	25.7 (43/167)	29.3 (24/82)	22.4 (19/85)	
Grade 3B	10.8 (18/167)	15.9 (13/82)	5.9 (5/85)	
Ki67≥30%	63.0 (102/162)	69.5 (57/82)	56.3 (45/80)	0.081
Leukemic phase	23.4 (26/111)	24.1 (14/58)	22.6 (12/53)	0.736
Intensive induction	19.8 (38/192)	20.8 (20/96)	18.8 (18/96)	0.422

Patients in the RM group were characterized by advanced stage and low degree of histological grade compared to those in the control group.

Outcomes of patients with FL at our center

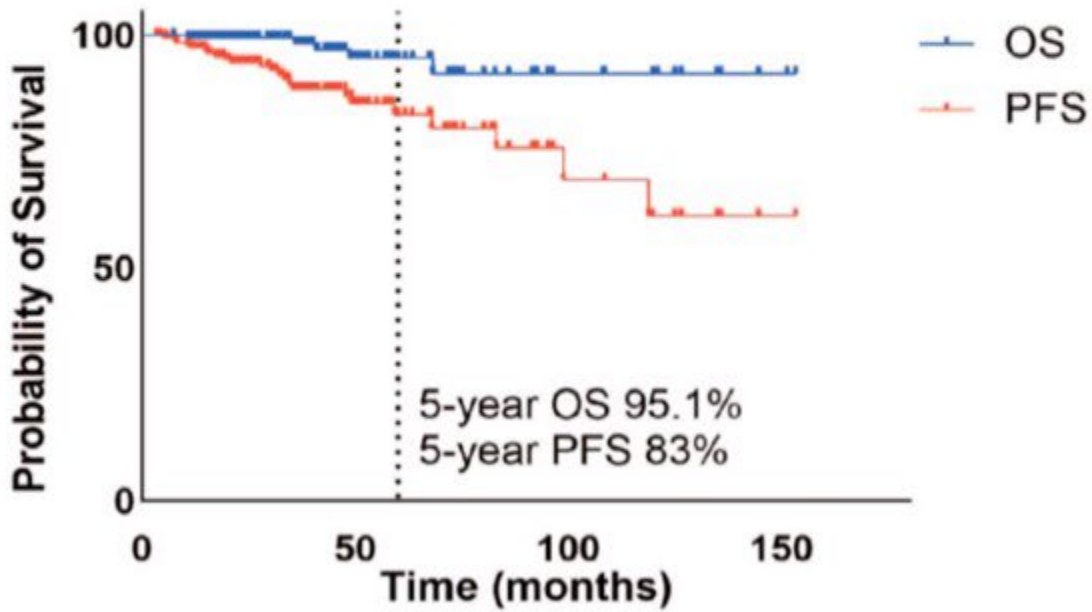


Figure 1. Overall survival and Progression-free survival

- Median follow-up was 36.4 months.
- Median overall survival (OS) and progression-free survival (PFS) were not reached.
- The 5-year OS rate was 95%.
- The 5-year PFS rate was 83%.

PFS of patients responding to induction

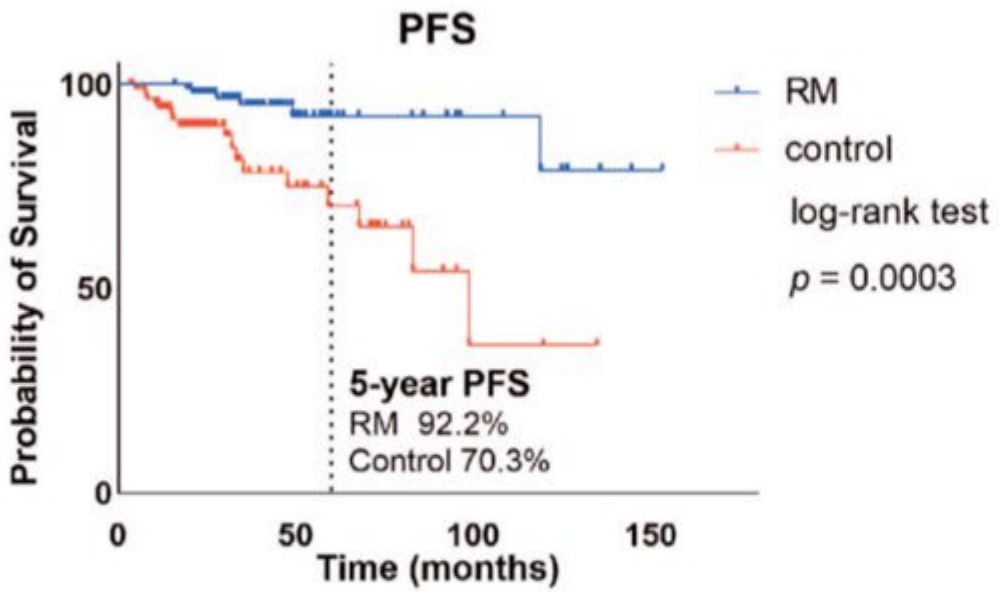


Figure 2. Progression-free survival by RM

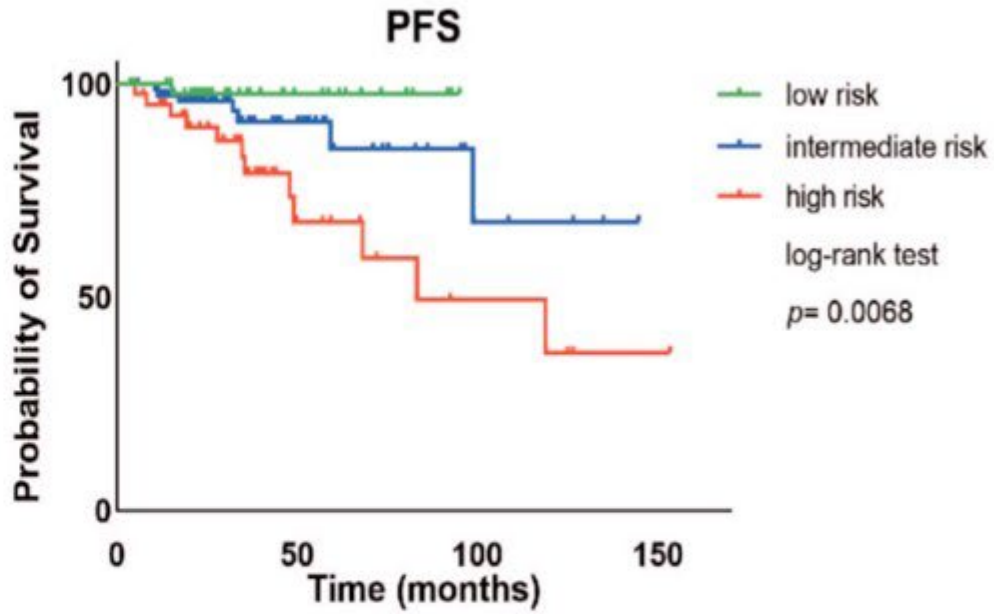


Figure 3. Progression-free survival by FLIPI

Regular RM treatment prolonged PFS of patients who responded to induction therapy.

The FLIPI was still a significant predictor for PFS in the Rituximab era.

FL patients with low risk of the FLIPI benefited less from RM treatment

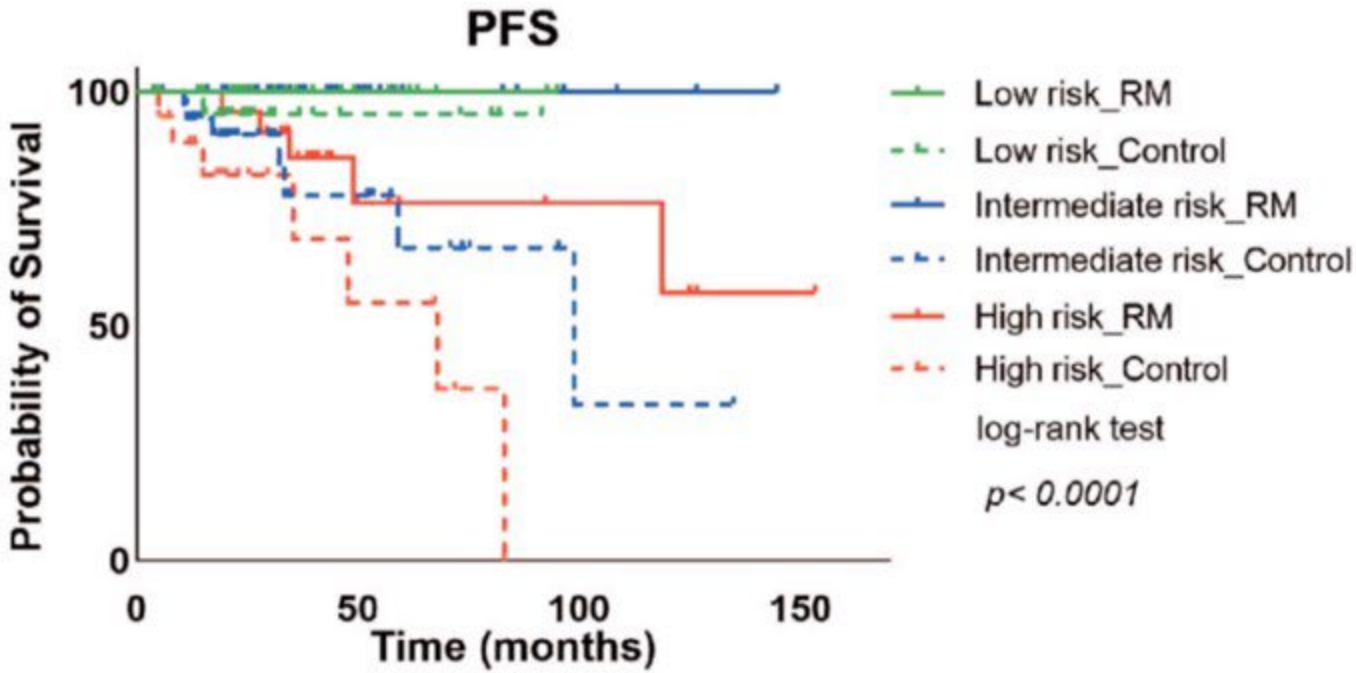


Figure 4. Progression-free survival by FLIPI and RM

- Patients with low risk of the FLIPI had long PFS regardless of RM treatment.
- Patients with intermediate risk and high risk of the FLIPI had longer PFS in the RM group than those in the control group.

Conclusion

- Standard rituximab maintenance significantly prolonged PFS in the FLIPI intermediate-risk and high-risk patients with FL.
- Patients in the low risk of the FLIPI did not benefit from RM treatment.

Teşekkürler