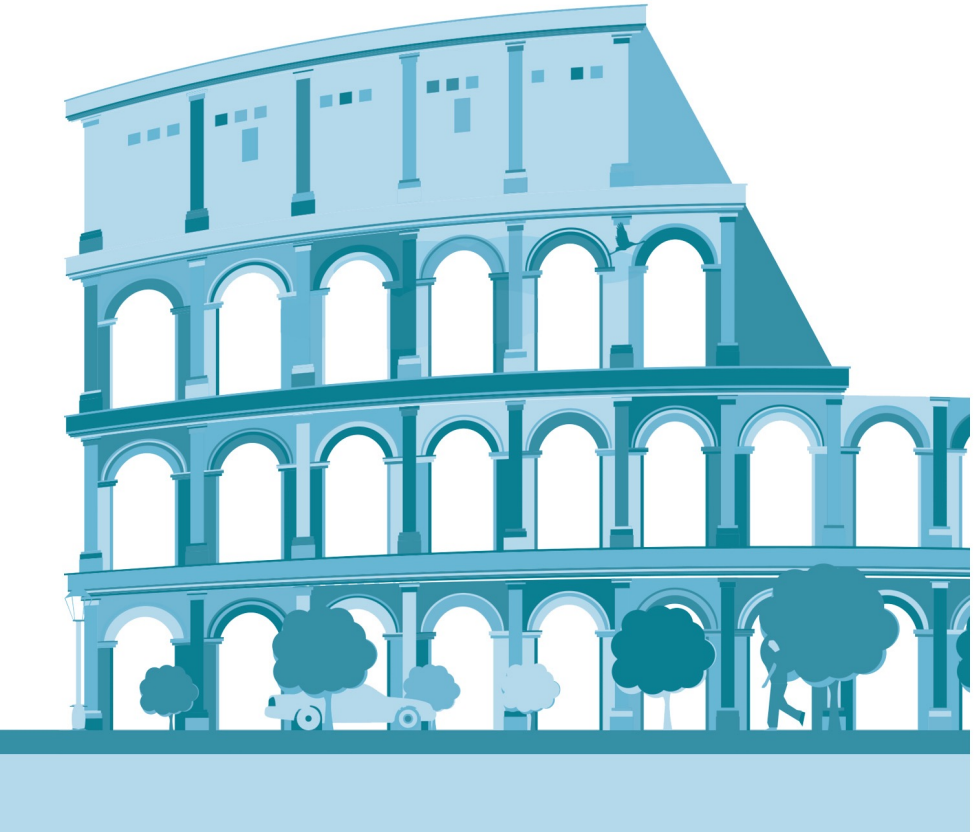


CAR-TALKING

News dal mondo CAR-T

Roma, Starhotels Metropole
19 aprile 2023

Altri approcci terapeutici di salvataggio nel linfoma follicolare

Luigi Rigacci
UOC Ematologia e Centro Trapianti
Policlinico Universitario Campus Bio-Medico
Roma

Disclosure: Luigi Rigacci

Company name	Research support	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Gilead				X	X	
Novartis				X	X	
Sandoz				X	X	
Abbvie				X	X	
Servier				X		
Celgene				X		
Janssen				X	X	
Incyte				X	X	
Menarini		X				
Takeda					X	

Recurrent Follicular Lymphoma

Factors to be considered:

- What are the previous therapies and how well did they work?
- What is the current situation?
  - Patient age/comorbidities
  - Disease-related symptoms
  - Tumor burden
  - Prognostic factors (eg, LDH)
- Patient's goals

Recurrent Follicular Lymphoma

Conventional strategies

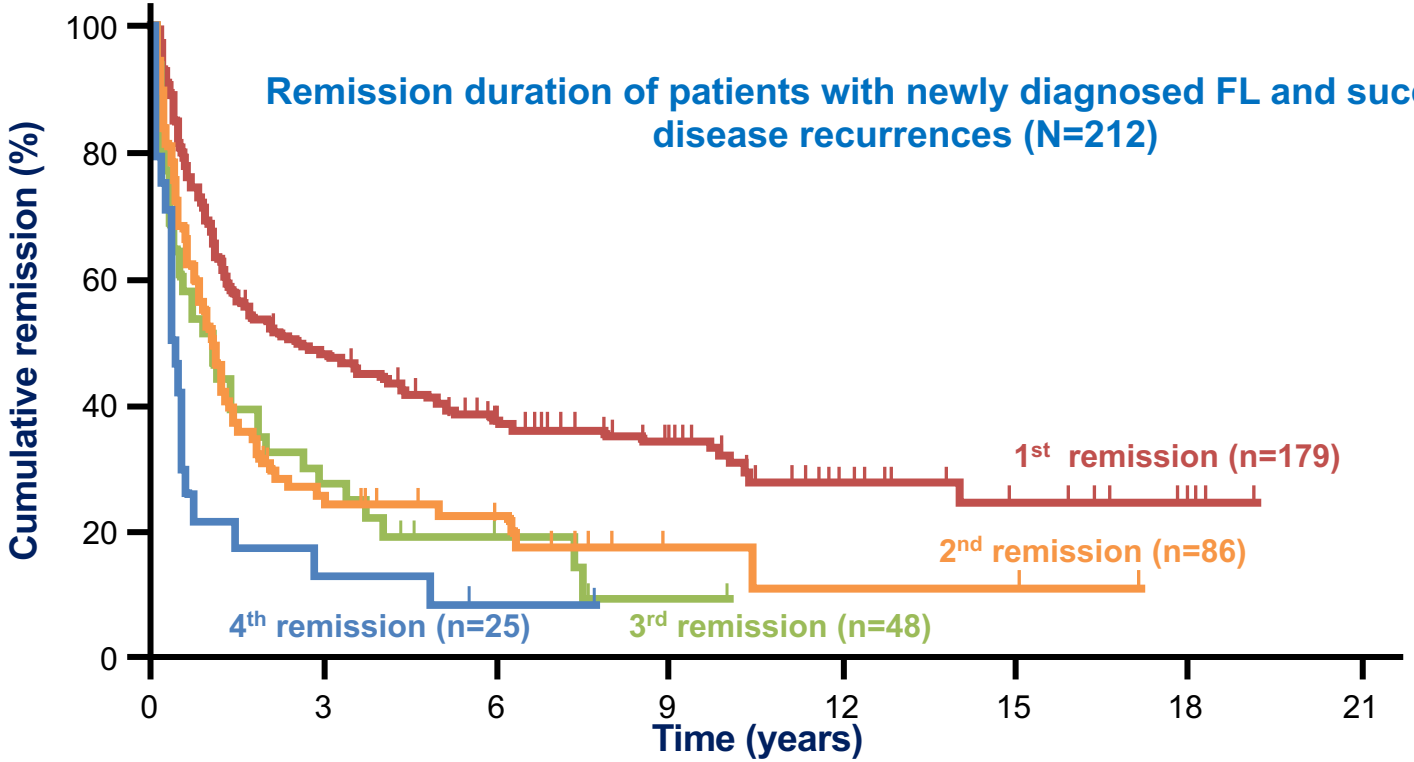
- Rituximab ± maintenance
- Chemoimmunotherapy ± maintenance
- Rituximab Lenalidomide
- Radioimmunotherapy
- Radiotherapy
- Autologous transplantation
- Allogeneic transplantation

Novel strategies

–Novel monoclonal antibodies
–Pi3K inhibitors
–BTK inhibitors
–Others

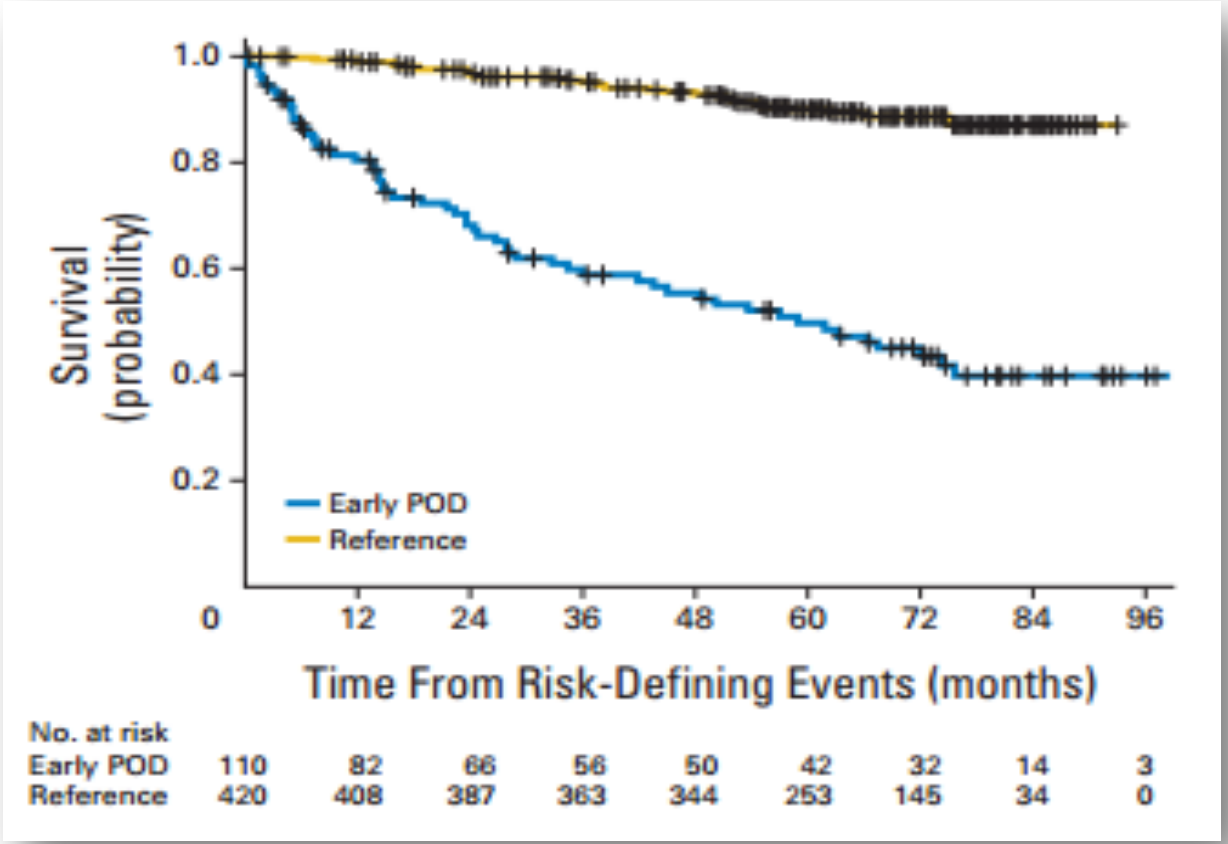
CONVENTIONAL STRATEGIES

Treatment response progressively shortens with each relapse



Study conducted in pre-rituximab era: most common first-line treatments were single-agent chemotherapy, combination chemotherapy and radiotherapy; most common treatments for first remission were chlorambucil (65%), CHOP (10%) and radiotherapy (9%)
CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone

Johnson PWM, *et al. J Clin Oncol* 1995; 13:140–147.



POD within 2 ys after RCHOP is associated with poor outcome (OS@5ys: 50%)

Casulo et al, JCO 2015

Paradigm of relapsed/refractory Follicular Lymphoma

Age >65 years		Age <65 years	
Early relapse (POD24)	**Late relapse (no POD24)**	**Early relapse (POD24)**	**Late relapse (no POD24)**
R^2/R-chemotherapy +/– R maintenance	Watch and Wait	ASCT	Watch and Wait
R^2	R^2/R-chemotherapy +/– R maintenance	R-chemotherapy +/– R maintenance	R^2/R-chemotherapy +/– R maintenance
Radioimmunotherapy	R^2	R^2	Radioimmunotherapy
R monotherapy	R monotherapy	Radioimmunotherapy	R monotherapy
	Radioimmunotherapy	Allo-transplant	

Is watch and wait still acceptable for patients with low-grade follicular lymphoma?

James O. Armitage[1] and Dan L. Longo[2]

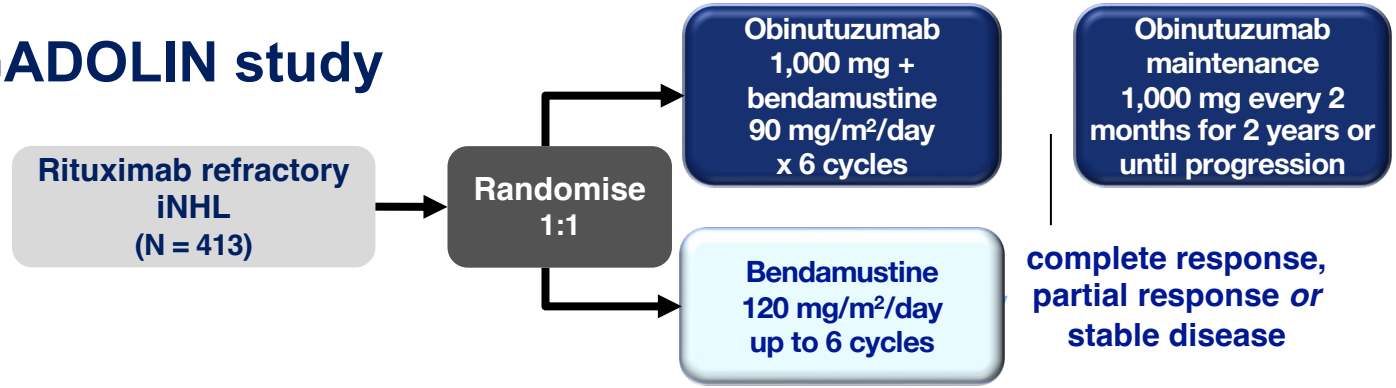
[1]University of Nebraska Medical Center, Omaha, NE; and [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

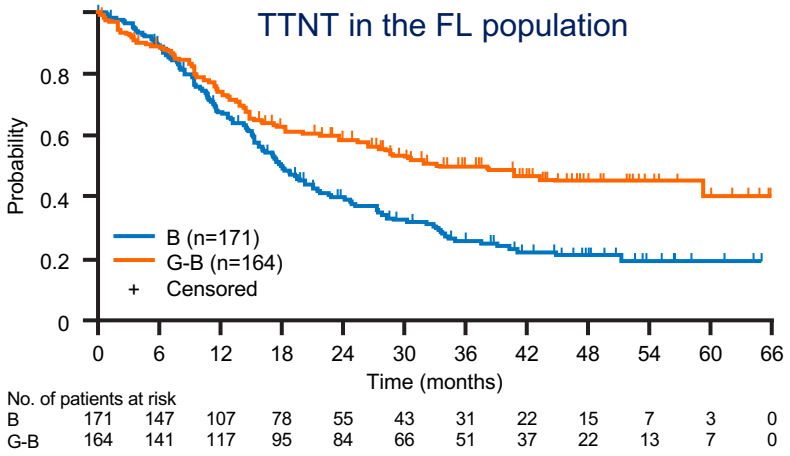
BLOOD, 9 JUNE 2016 • VOLUME 127, NUMBER 23

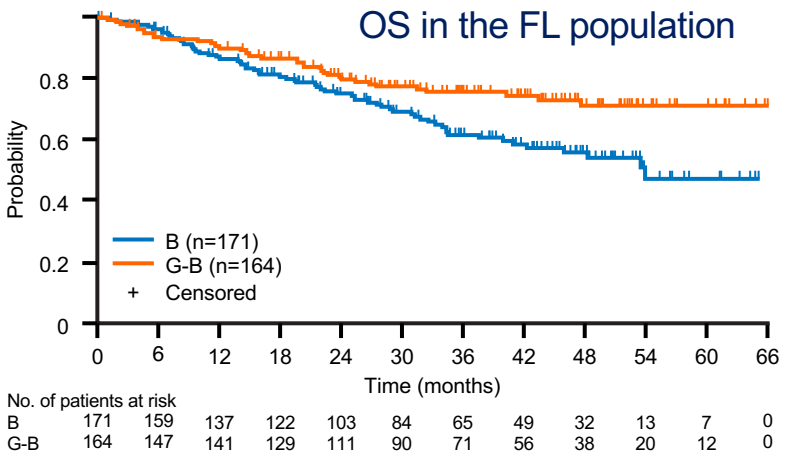
Table 1. Caveats for using watch and wait for patients with low-grade FL

• The patient should be asymptomatic
• The patient should not want therapy (after learning the data regarding watch and wait)
• The physician should be willing to observe the patient closely (ie, FL is cancer and occasionally progresses rapidly)
• Although not proven, the patient understands that delaying therapy might possibly adversely impact survival

the GADOLIN study

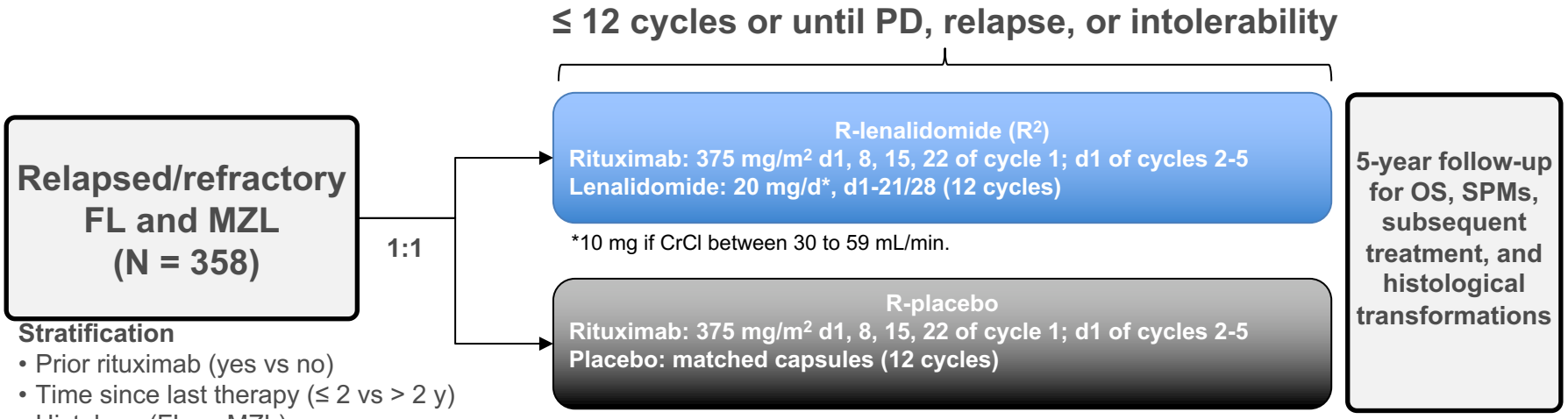






The GADOLIN study demonstrates a significant improvement in OS in the G-B arm

AUGMENT: R2 vs rituximab monotherapy in R/R iNHL



Stratification
- Prior rituximab (yes vs no)
- Time since last therapy (≤ 2 vs > 2 y)
- Histology (FL vs MZL)

Key eligibility criteria
- MZL or FL (grades 1-3a) in need of treatment
- ≥ 1 prior chemotherapy, immunotherapy or chemoimmunotherapy
- Not rituximab refractory

- Prophylactic anticoagulation / antiplatelet Rx recommended for at risk patients
- Growth factor use was allowed per ASCO/ESMO guidelines[2,3]

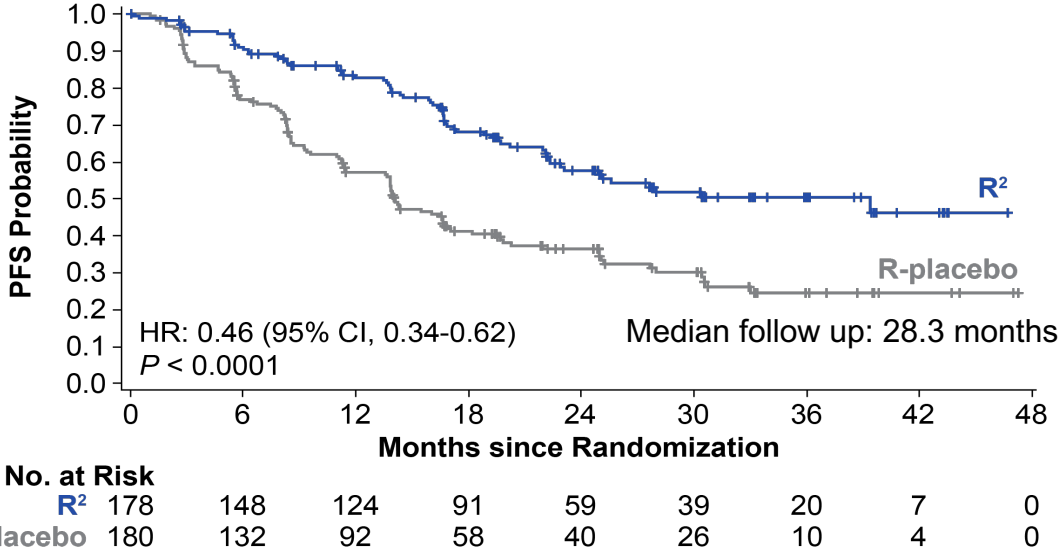
» Primary endpoint: PFS by IRC (2007 IWG criteria w/o PET)

NCT01938001

1. Leonard JP, et al. *J Clin Oncol.* 2019;37:1188-99. 2. Crawford et al. *Ann Oncol.* 2010;21 Suppl 5:248-251.
3. Smith et al. *J Clin Oncol.* 2015;33:3199-3212.

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

AUGMENT: primary endpoint - PFS



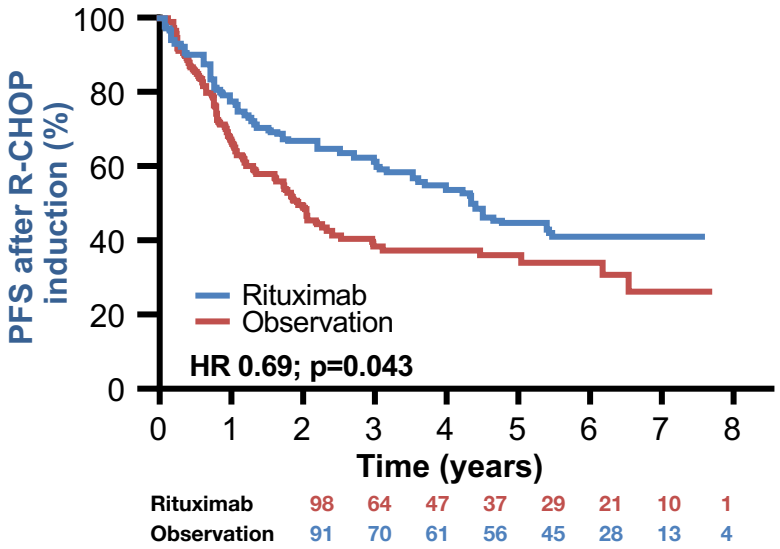
Median PFS	R² (n = 178)	R-placebo (n = 180)	HR (95% CI)	*P* Value
By IRC, mo (95% CI)	39.4 (22.9-NE)	14.1 (11.4-16.7)	0.46 (0.34-0.62)	< 0.0001
By investigator, mo (95% CI)	25.3 (21.2-NE)	14.3 (12.4-17.7)	0.51 (0.38-0.69)	< 0.0001

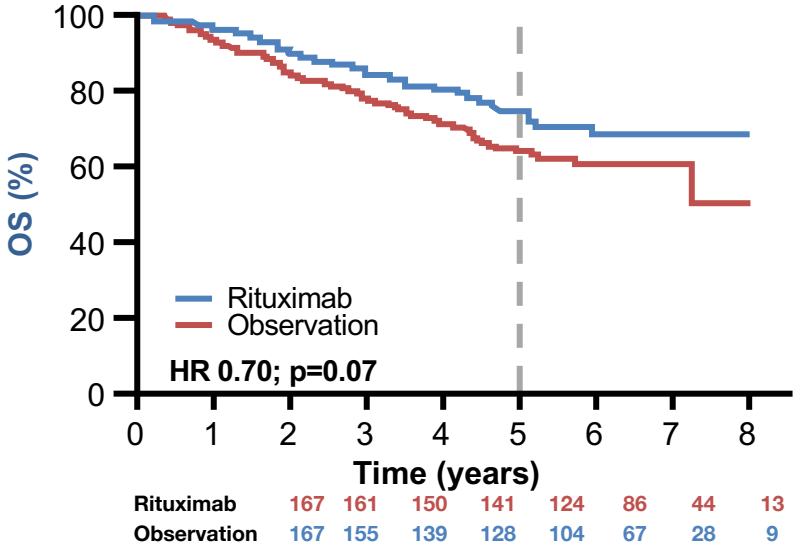
*Censoring rules based on FDA guidance.
Data cutoff June 22, 2018.

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

Rituximab maintenance in relapsed FL setting studied in rituximab-naive population

High tumour burden, Stage III/IV





- Grade 3/4 neutropenia was observed in 11.5% of patients in rituximab maintenance arm vs. 6.0% in the observation arm
- Increased Grade 3/4 infection rates were also observed in in the maintenance group (9.7%) vs. the observation group (2.4%) (p=0.01)

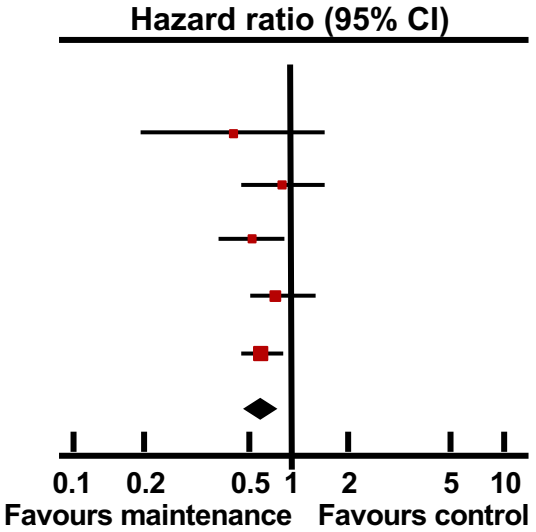
van Oers MHJ, *et al. J Clin Oncol* 2010; 28:2853–2858.

Rituximab maintenance improves OS in relapsed/refractory FL

High tumour burden, Stage III/IV

Systematic review and meta-analysis of rituximab maintenance for relapsed/refractory FL (N=2,586)

Study	Hazard ratio
Forstpointner 2006	0.49 (0.18, 1.30)
Hainsworth 2005	0.86 (0.49, 1.49)
Martinelli 2010	0.54 (0.30, 0.97)
Pettengell 2010	0.88 (0.54, 1.43)
van Oers 2010	0.70 (0.48, 1.01)
Pooled analysis (95% CI)	**0.72 (0.57, 0.91)**
Test for overall effect: p=0.005	



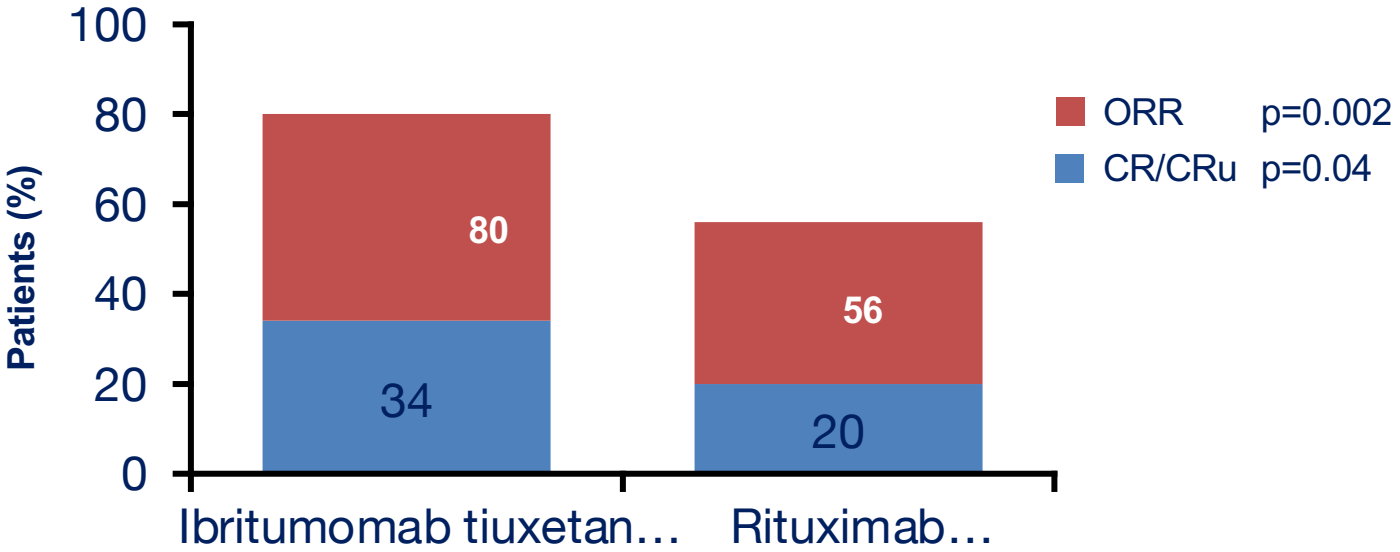
- Rituximab maintenance was associated with a higher rate of Grade 3/4 adverse events (pooled risk ratio 1.60; 95% CI=1.29, 1.99) and all-grade infections (pooled risk ratio 1.67; 95% CI=1.40, 2.00) vs. no maintenance

Vidal L, *et al. J Natl Cancer Inst* 2011; 103:1799–1806.

Radioimmunotherapy leads to high response rates and durable remissions in relapsed FL

High tumour burden, Stage III/IV

Ibritumomab tiuxetan: Randomised Phase III trial in relapsed low-grade NHL (N=143)



- One patient developed myelodysplastic syndrome during the study; during follow-up, an additional patient developed acute myeloid lymphoma

Gordon L, *et al. Clin Lymphoma* 2004; 5:98–101.

Autologous and Allogeneic SCT: a cure for relapsed Follicular Lymphoma in the Rituximab era ?

Autologous Stem Cell Transplantation (SCT)

Advantages

- increase "dose intensity": improves CR rates and disease free-survival
- elimination of residual lymphoma cells
- NRM below 5%

Disadvantages

- graft contamination
- therapy-related MDS, acute leukemias and solid tumors

Phase II studies investigating autologous SCT in *relapsed* FL

	Number of Patients	R included in salvage CT	PFS	OS
Schouten et al, 2000	65	0	55-58% at 2 year	71-77% at 4 year
Rohatiner et al, 2007	121	0	55% at 5 year	71% at 5 years
Sebban, et al, 2008	98	33%	51% at 5 year	70% at 5 year
Vose, et al, 2008	248	Few (not reported)	44% at 5 year	63% at 5 year
Tarella et al, 2008	61+	100%	57 at 5 year	75% at 5 year
Le Gouill et al, 2011	112*	100%	52 at 3 year	92% at 3 year
Le Gouill et al, 2011	53*	0	40 at 3 year	63% at 3 year
Evens et al, 2013	135	100%	57% at 3 year	87% at 3 year
Pettengell et al, 2013	280	0	48-42% at 10 years	66.1-74.5% at 10 year
Klyuchnikov et al[#], 2015	250	100%	41% at 5 year	74% at 5 year
Klyuchnikov et al[$], 2015	136	100%	36% at 5 year	59 at 5 year

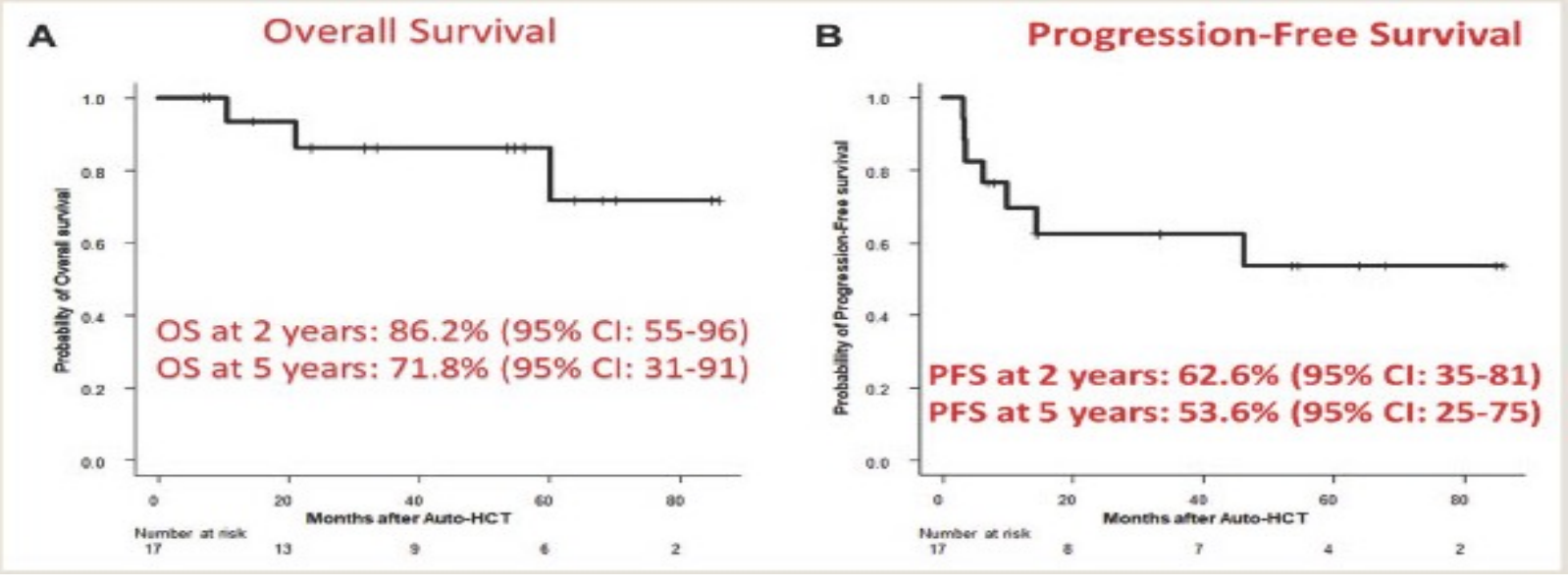
Does Up-front Autologous Stem-Cell Transplantation at First Relapse Improve Outcome in Transplant-Eligible Follicular Lymphoma Patients Whose Disease Relapses Within 24 Months?

Ayel Yahya,[1] Osman Radhwi,[2] Mohamad Sobh,[1] Lothar Huebsch,[1]

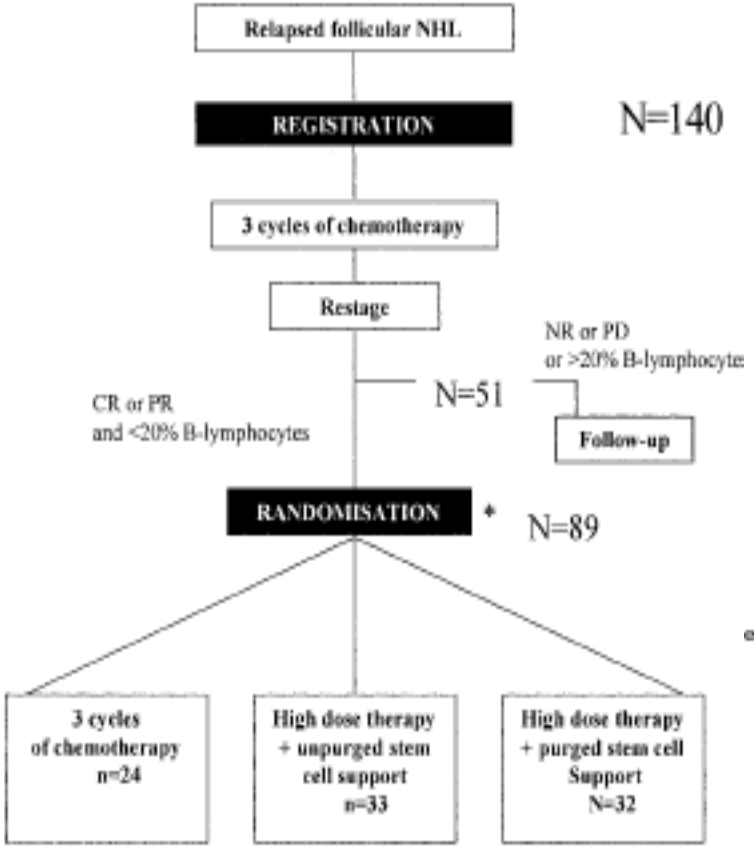
Clinical Lymphoma, Myeloma & Leukemia April 2021

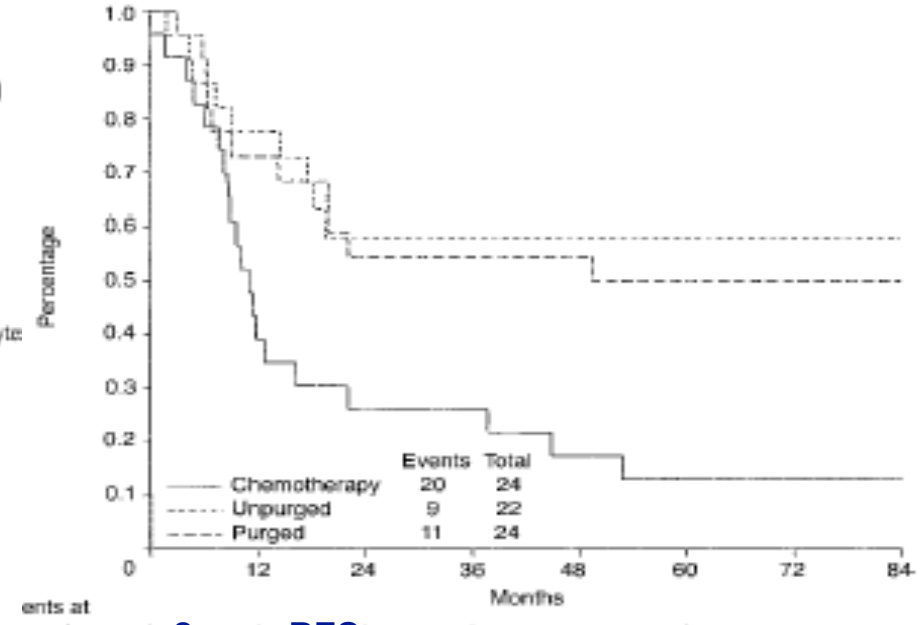
Table 2 Treatment Response

Characteristic	Value
Time to progression after first-line therapy (months), median (range)	12.2 (3-21)
Time from first relapse to ASCT (months), median (range)	6.8 (2-23)
Status 2-3 months after ASCT, n (%)	
ORR	15 (88)
CR2	5 (29)
PR2	10 (59)
No response	2 (12)



Phase III CUP trial in relapsed FL





2-year PFS curves:
Chemotherapy arm: 26%
Unpurged arm: 58%
Purged arm: 55%

Schouten et al, JCO 2003

Allogeneic transplantation in follicular lymphomas

Pros

- *Long-term outcome is still largely unsatisfactory in patients relapsing after auto-HSCT or more than two lines*
- *The postulated "Graft-Versus-Lymphoma" effect*
- *Allogeneic stem cells are free from tumor contamination*

Cons

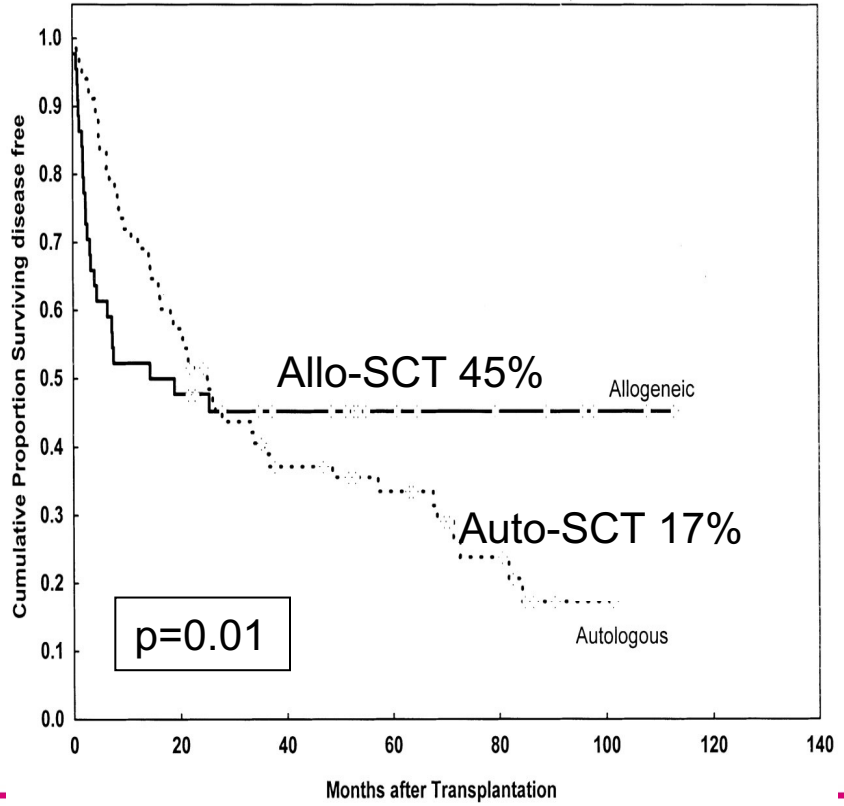
- *Morbidity and mortality still not negligible and in some cases relevant*
- *Proper patient selection and transplant timing are sometimes lacking*
- *Cooperation with lymphoma groups has to be improved*
- *Competition with new drugs in the setting of refractory/relapsed patients*
- *PROPER GRAFT SOURCE (MUD, UCD, Sib, haplo)*
- *Late complications of alloSCT*

Allo-SCT for relapsed or refractory FL

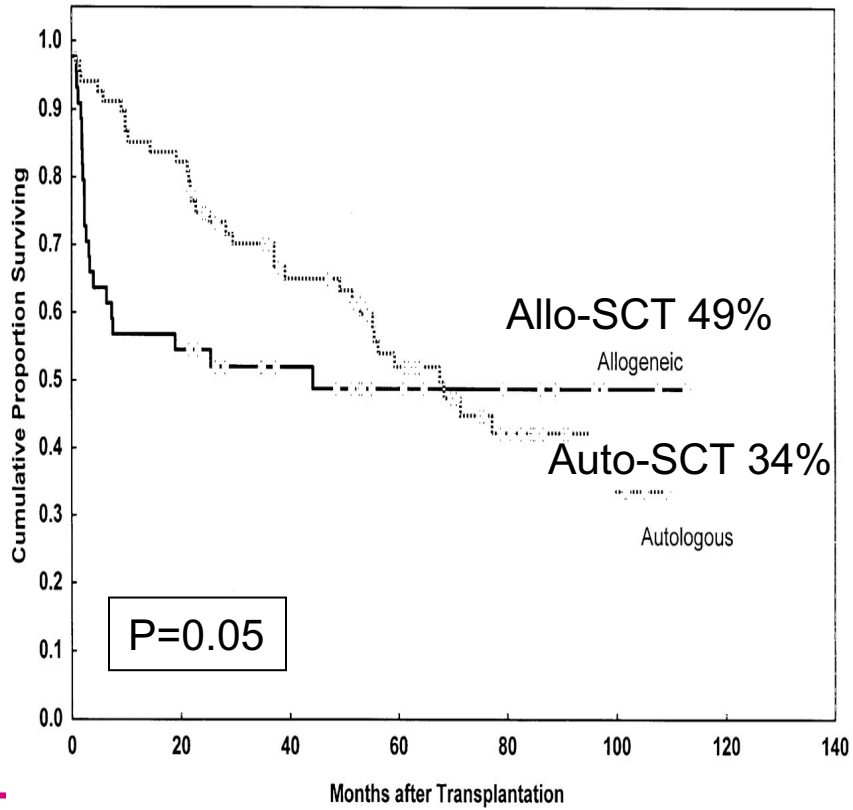
Reference	n°pts	Conditioning regimen	TRM	EFS/PFS	OS
Khouri, et al. 2001[#]	20	Flu/Cy - Flu/Cy/Ritux	10% at 2 year	84% at 2 year	84% at 2 year
Robinson et al. 2002	52	Fludarabine-based	22%	61% at 1 year	73% at 1 year
Morris et al. 2004[%]	41	Flu/Mel/Campath-1H	11% at 3 year	65% at 3 year	55% at 3 year
Faulkner et al. 2004[&]	28	BEAM/Campath-1H	13.3%	69% at 2 year	63.1% at 3 year
Corradini et al, 2007*	27	Flu/Cy/Thiotepa	14% at 3 year*	86%at 3 year	88% at 3 year
Khouri et al, 2008	47	Flu/Cy/Ritux	15% at 5 year	85% at 5 year	83% at 5 year
Hari et al, 2008	88	RIC	27% at 3 year	55% at 3 year	62% at 3 year
Hari et al, 2008	120	MAC	25% at 3 year	67% at 3 year	71% at 3 year
Thomson et al, 2010	82	Flu/Mel/Alemtuzumab	15% at 4 year	74% at 4 year	76% at 4 year
Pinana et al. 2010	37	Flu/Mel	41% at 4 year	57% at 4 year	54% at 4 year
Delgado et al. 2011	164	RIC	17% at 3 year	58% at 5 year	72% at 5 year
Robinson et al. 2013	149	RIC	22% at 3 year	57% at 5 year	67% at 5 year
Evens et al. 2013	48	RIC	24% at 3 year	52% at 3 year	61% at 3 year
Klyuchnikov et al. 2015	268	RIC	26% at 5 year	58% at 5 year	66% at 5 year
Klyuchnikov et al, 2016	61	RIC	27% at 5 year	51% at 5 year	54% at 5 year
Robinson 2016[+]	183	RIC	27% at 2 years	48% at 5 year	51% at 5 year

Auto versus allo-SCT in relapsed FCL

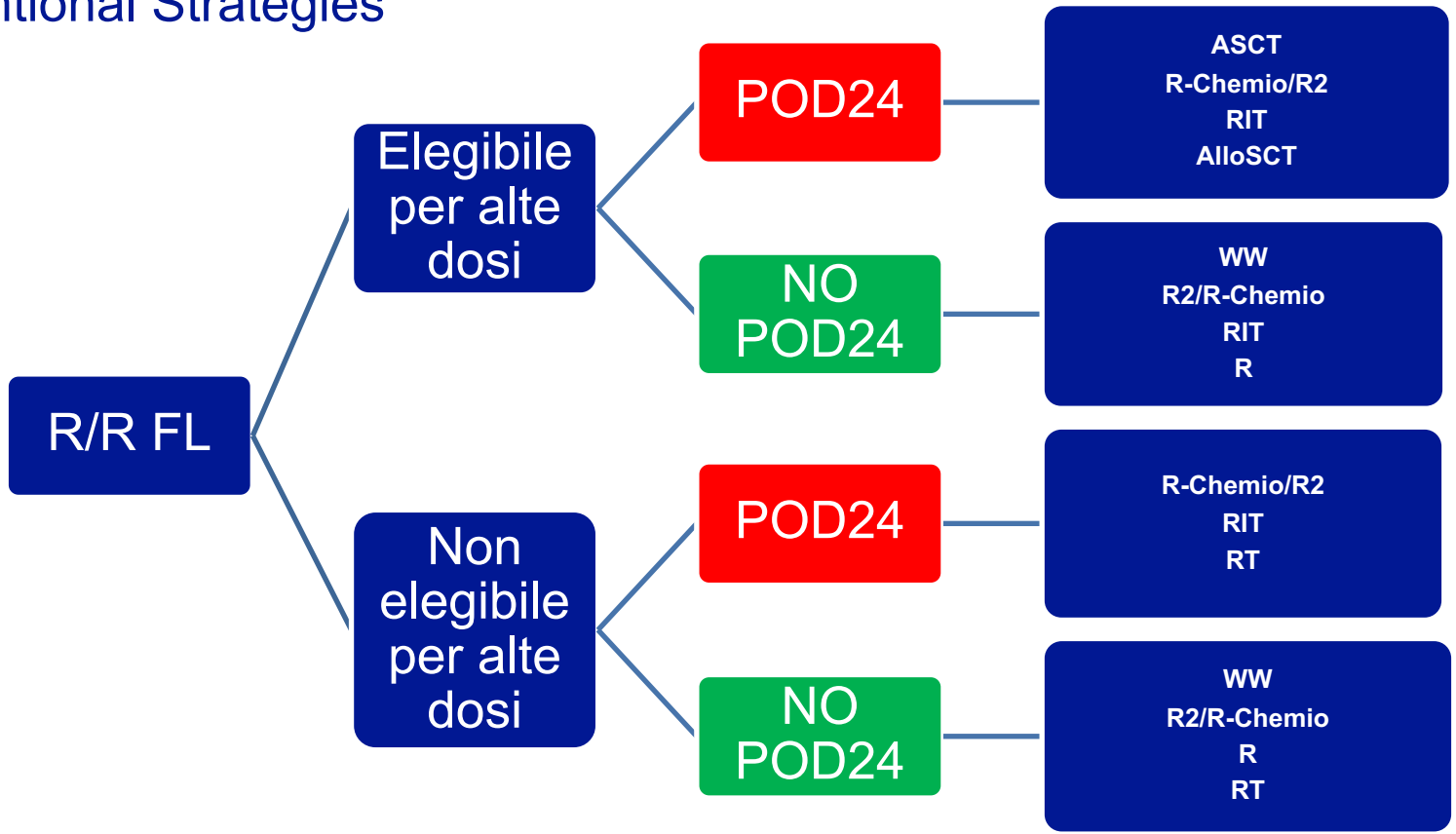
Disease Free Survival



Overall Survival

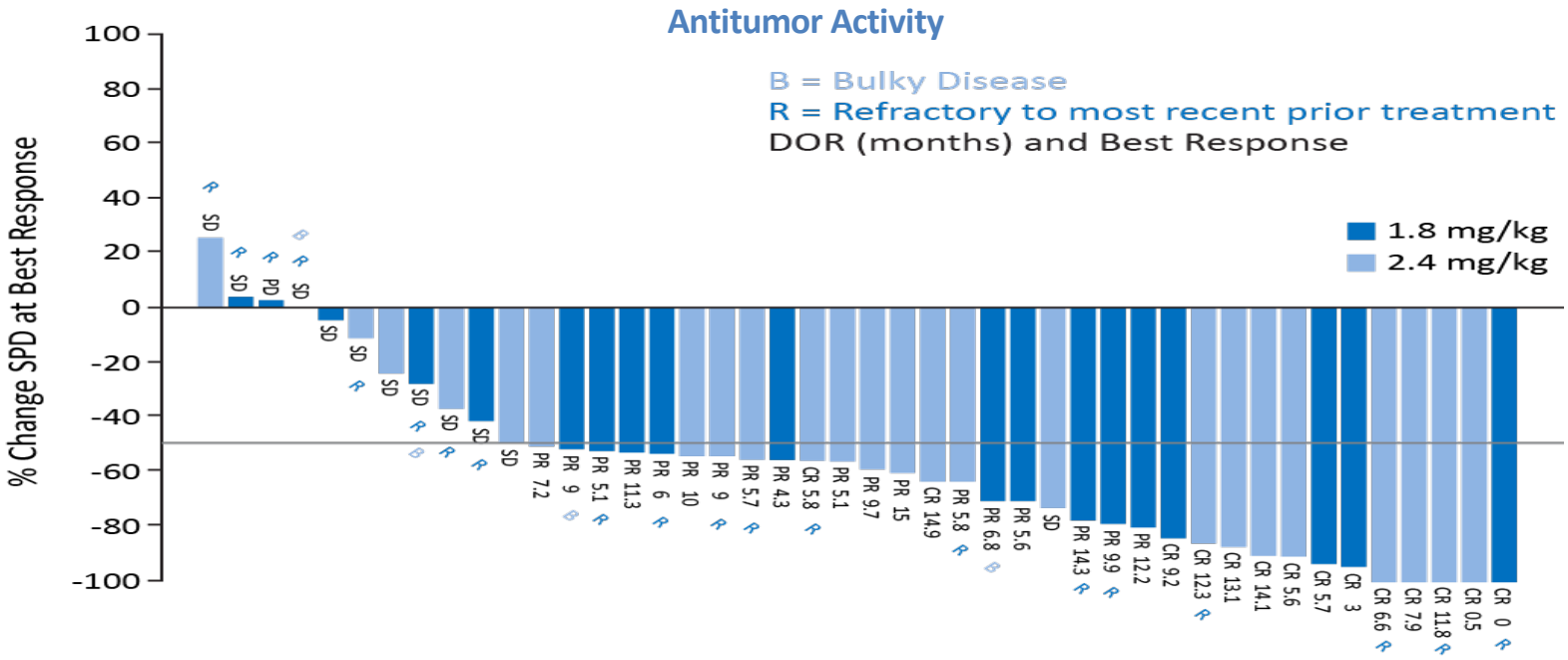


Conventional Strategies



NOVEL STRATEGIES

Polatuzumab vedotin: Phase II ROMULUS efficacy
FL (relapsed/refractory) cohort



» 70% ORR (20% CR) at 1.8 mg/kg
» 76% ORR (44% CR) at 2.4 mg/kg

ClinicalTrials.gov: NCT01691898.
Reference: Advani R, et al. ASCO. 2015 [abstract 8503].
Note: Polatuzumab vedotin is being developed in collaboration with Seattle Genetics.

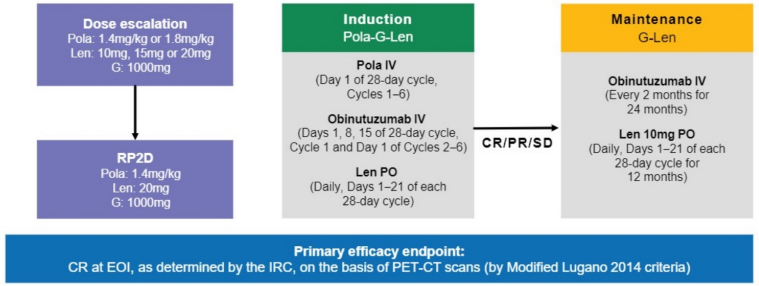
Polatuzumab vedotin plus obinutuzumab and lenalidomide in patients with relapsed/refractory follicular lymphoma: primary analysis of the full efficacy population in a Phase Ib/II trial

Catherine Diefenbach,[1] Brad Kahl,[2] Lalita Banerjee,[3] Andrew McMillan,[4] Fiona Miall,[5] Javier Briones,[6] Raul Cordoba,[7] Jamie Hirata,[8] YiMeng Chang,[9] Lisa Musick,[8] Pau Abrisqueta[10]

[1]Perlmutter Cancer Center at NYU Langone Health, New York, NY, USA; [2]Division of Oncology, Washington University, St Louis, MO, USA; [3]Oncology Centre, Maidstone and Tunbridge Wells NHS Trust, Kent, United Kingdom; [4]Centre for Clinical Haematology, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom; [5]Department of Haematology, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [6]Department of Hematology, Hospital Santa Creu i Sant Pau, Barcelona, Spain; [7]Fundacion Jimenez Diaz University Hospital, Madrid, Spain; [8]Genentech, Inc., South San Francisco, CA, USA; [9]F. Hoffmann-La Roche Ltd, Mississauga, Canada; [10]Hospital Vall Hebron, Barcelona, Spain

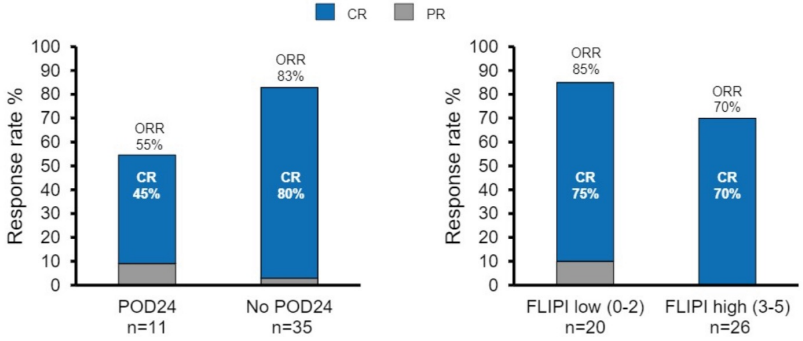
Study design

Open-label, single-arm, Phase Ib/II study in patients with R/R FL

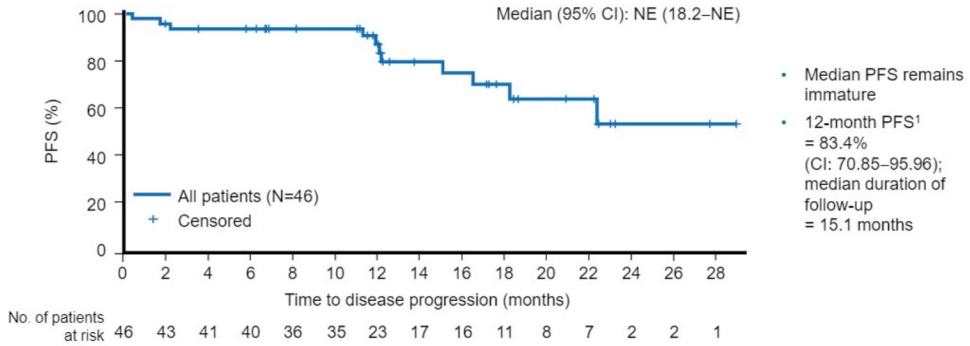


Subgroup analysis

POD24 and FLIPI high



Kaplan-Meier curve of PFS



- Median PFS remains immature
- 12-month PFS[1] = 83.4% (CI: 70.85–95.96); median duration of follow-up = 15.1 months

Diefenbach C. ASH 2019

EZH2 Inhibitor

EZH2 inhibition by tazemetostat: mechanisms of action, safety and efficacy in relapsed/refractory follicular lymphc

Edith Julia[1,2] & Gilles Salles*[,2,3]

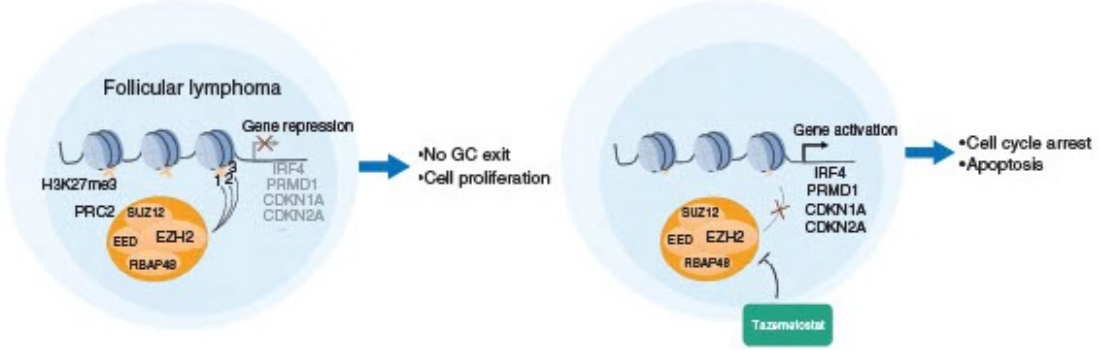


Table 3. Results of clinical trials of tazemetostat in follicular lymphomas. Medians reported with interquartile ranges.

Clinical trial	Phase	Trial design	Inclusion criteria		Patients (n)	Prior lines (n)	Dosing	ORR	CR	Median duration of response	Median PFS	Ref.
E7438-G000-101 NCT01897571	I	Open-label, multicenter, 3 + 3 dose-escalation followed by expansion phase	R/R B-cell NHL†		21	3	100–1600 mg BID	8/21‡ (38%)	3/21§	12.4 months		[51]
E7438-G000-101 NCT01897571	II	Open-label, multicenter	R/R FL including grade 3b and transformed	*EZH2* mutant	45	2 (1–11)	800 mg BID	69% (53.4–81.1)	6/45 (13%)	10.9 months (7.2–NE)	13.8 months (10.7–22.0)	[55]
				EZH2 WT	54	3 (1–8)		35% (22.7–49.4)	2/54 (4%)	13 months (5/6–NE)	11.1 months (3.7–14.6)	

EZH2-inhibitor	ClinicalTrials.gov identifier	Clinical phase	Histology	Comments
Tazemetostat	NCT01897571	Phase I/II	Advanced Solid and B-cell NHL (phase I) FL and DLBCL (phase II)	FDA approved for RR EZH2m FL and epithelioid sarcoma
GSK2816126	NCT02082977	Phase I	FL, DLBCL, and other advanced malignancies	Terminated due to lack of efficacy[47]
Valemetostat	NCT02732275 NCT04102150	Phase I Phase II	Different NHL in phase I; adult T-cell leukemia/ lymphoma in phase II	EZH1/2 inhibitor; active in B- and T-cell lymphoma
CPI-1205	NCT02395601	Phase I	RR B-cell Lymphoma	Pending results
CPI-0209	NCT04104776	Phase I/II	Advanced malignancies including lymphoma	Monotherapy and with irinotecan; results pending
SHR2554	NCT03603951	Phase I	RR B-cell lymphoma	Results pending
PF-06821497	NCT03460977	Phase I/II	FL, DLBCL, and solid tumors	Results pending

The role of tazemetostat in relapsed/ refractory follicular lymphoma

Gottfried von Keudell and Gilles Salles

Ther Adv Hematol

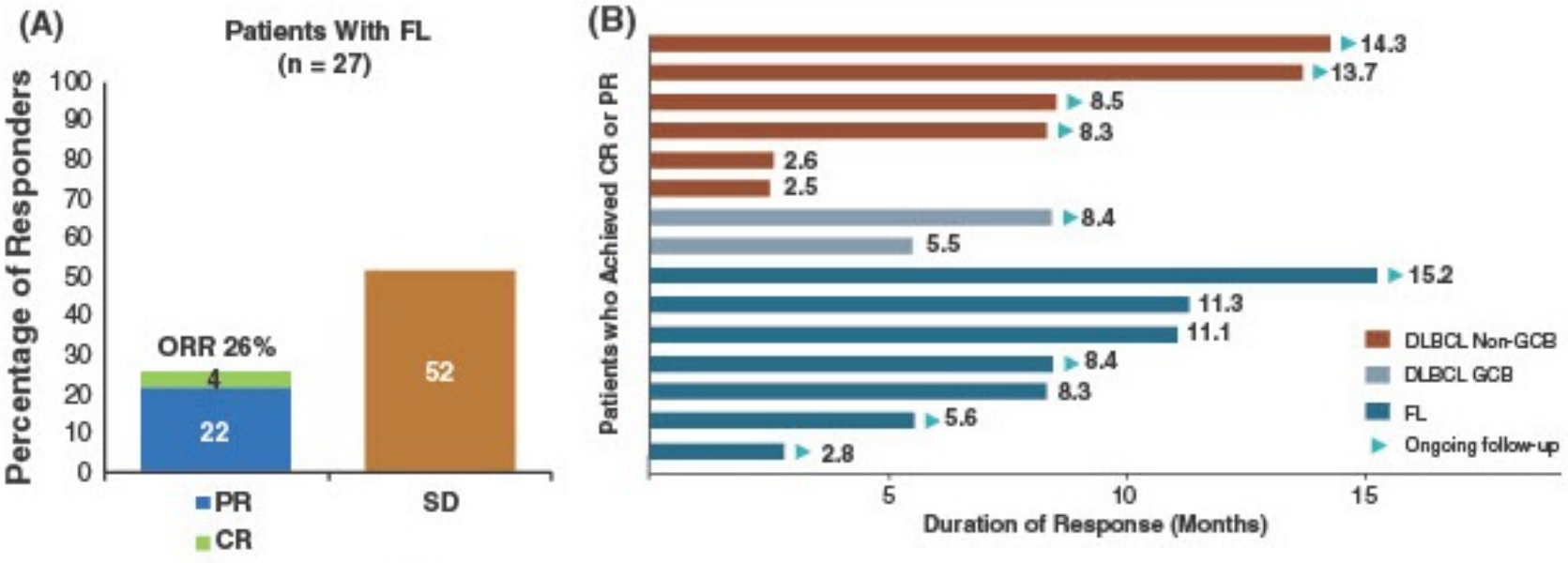
2021, Vol. 12: 1–8

EZH2-inhibitor combinations	ClinicalTrials.gov identifier	Clinical phase	Enrolled patients	Histology	Comments
T-RCHOP	NCT02889523	Phase I/II	172	Newly diagnosed FL and DLBCL	The only current upfront study[49]
Tazemetostat + rituximab + lenalidomide/placebo	NCT04224493	Phase I–III	518	RR FL	Ongoing, randomized, double-blind, placebo controlled multicenter, international
Tazemetostat + rituximab	NCT04590820	Phase II	44	RR FL	Ongoing, multicenter
Atezolizumab + obinutuzumab or tazemetostat	NCT02220842	Phase Ib	96	RR DLBCL	Terminated due to lack of efficacy

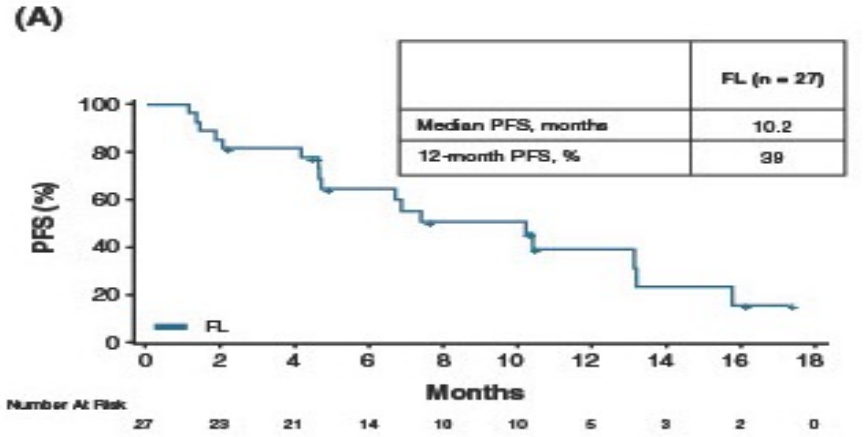
Safety and activity of ibrutinib in combination with durvalumab in patients with relapsed or refractory follicular lymphoma or diffuse large B-cell lymphoma

IBRUTINIB DURVALUMAB

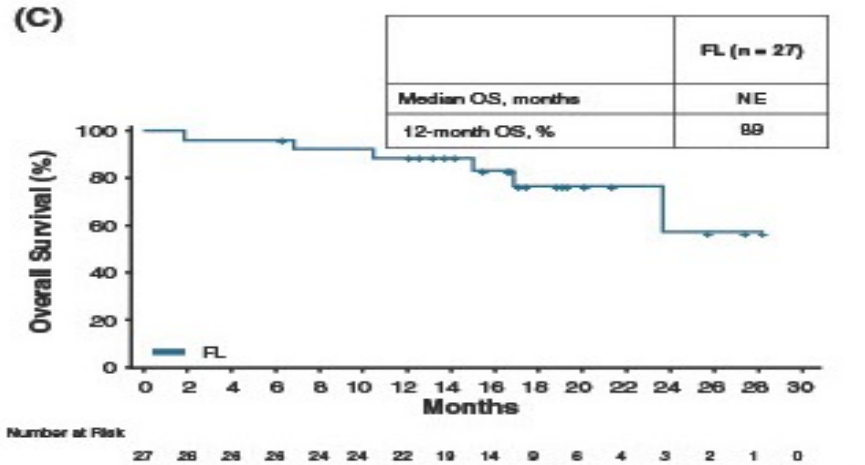
Alex F. Herrera[1] | Andre Goy[2] | Amitkumar Mehta[3] | Radhakrishnan Ramchandren[4] | John M. Pagel[5] | Jakub Svoboda[6] | Shanhong Guan[7] | John S. Hill[8] | Kevin Kwei[8] | Emily A. Liu[9] | Tycel Phillips[10]



Progression free survival in patients with FL



Overall survival in patients with FL

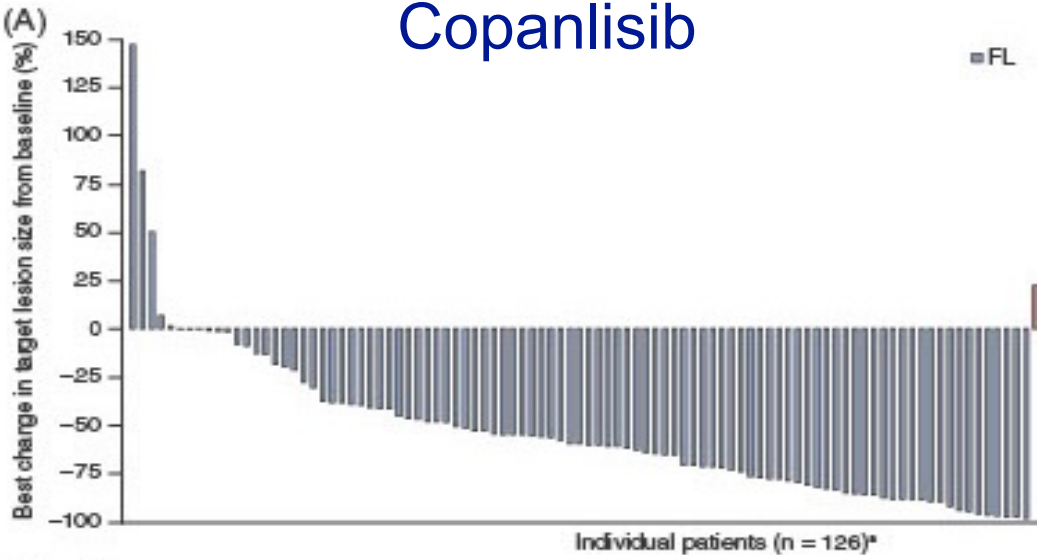


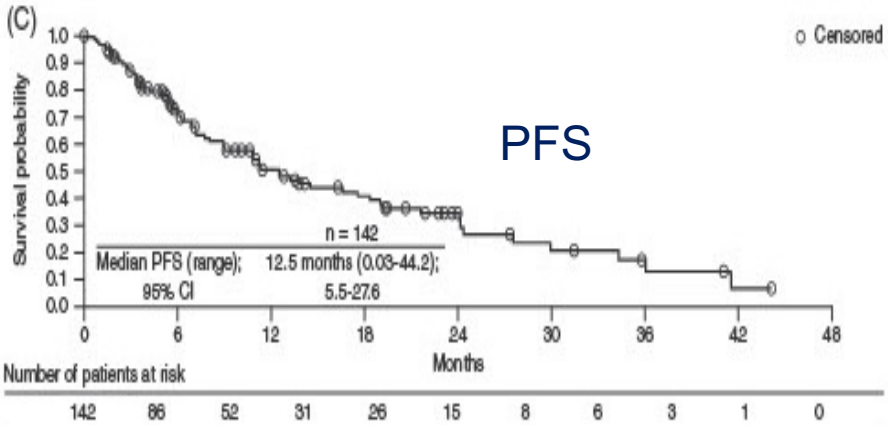
Copanlisib

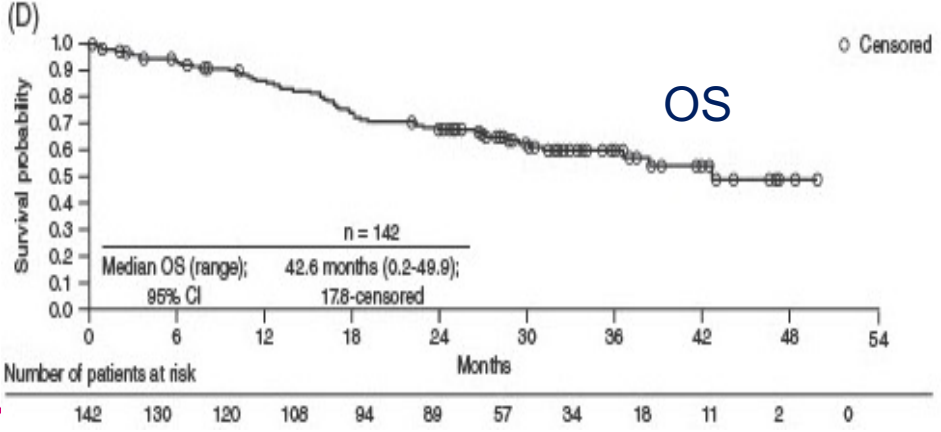
Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study

Martin Dreyling[1] | Armando Santoro[2] | Luigina Mollica[3] | Sirpa Leppä[4] | George Follows[5] | Georg Lenz[6] | Won Seog Kim[7] | Arnon Nagler[8] | Maria Dimou[9] | Judit Demeter[10] | Muhit Özcan[11] | Marina Kosinova[12] | Krimo Bouabdallah[13] | Franck Morschhauser[14] | Don A. Stevens[15] | David Trevarthen[16] | Javier Munoz[17] | Liana Rodrigues[18] | Florian Hiemeyer[19] | Ashok Miriyala[20] | Jose Garcia-Vargas[20] | Barrett H. Childs[20] | Pier Luigi Zinzani[21]

Am J Hematol. 2020;95:362–371.

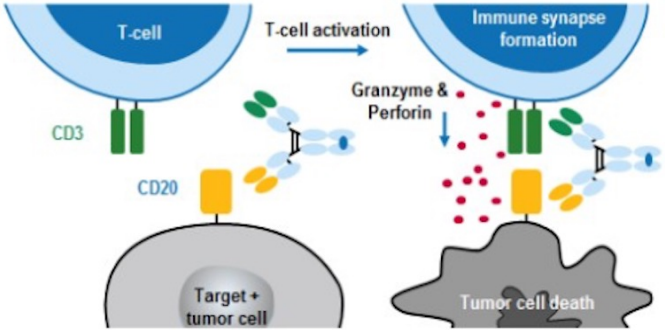






Mosunetuzumab Induces Complete Remissions in Poor Prognosis Non-Hodgkin Lymphoma patients including those who are resistant to or relapsing after CAR-T therapies and is active in treatment through multiple lines.
Shuster SJ, et al. ASH 2019, Plenary session.

- Mosunetuzumab (RG7828; BTCT4465A)
  - Full-length, fully humanized IgG1 bispecific antibody[1]
  - Redirects T cells to engage and eliminate B cells; T-cell activation, cytokine elevation and increase in TILs observed (**Hernandez et al. ASH 2019 P-1585**)
  - No ex-vivo T cell manipulation required ('off-the-shelf' and no delay in treatment)



- GO29781
  - Phase I/Ib dose-escalation and expansion study in heavily pre-treated R/R B-cell NHL
  - Cycle 1 step-up dosing: mitigates CRS, allowing dose escalation to maximize therapeutic potential[2,3]
- We report data for 270 R/R B-cell NHL pts, including 30 pts with prior CAR-T

Registry number: NCT02500407

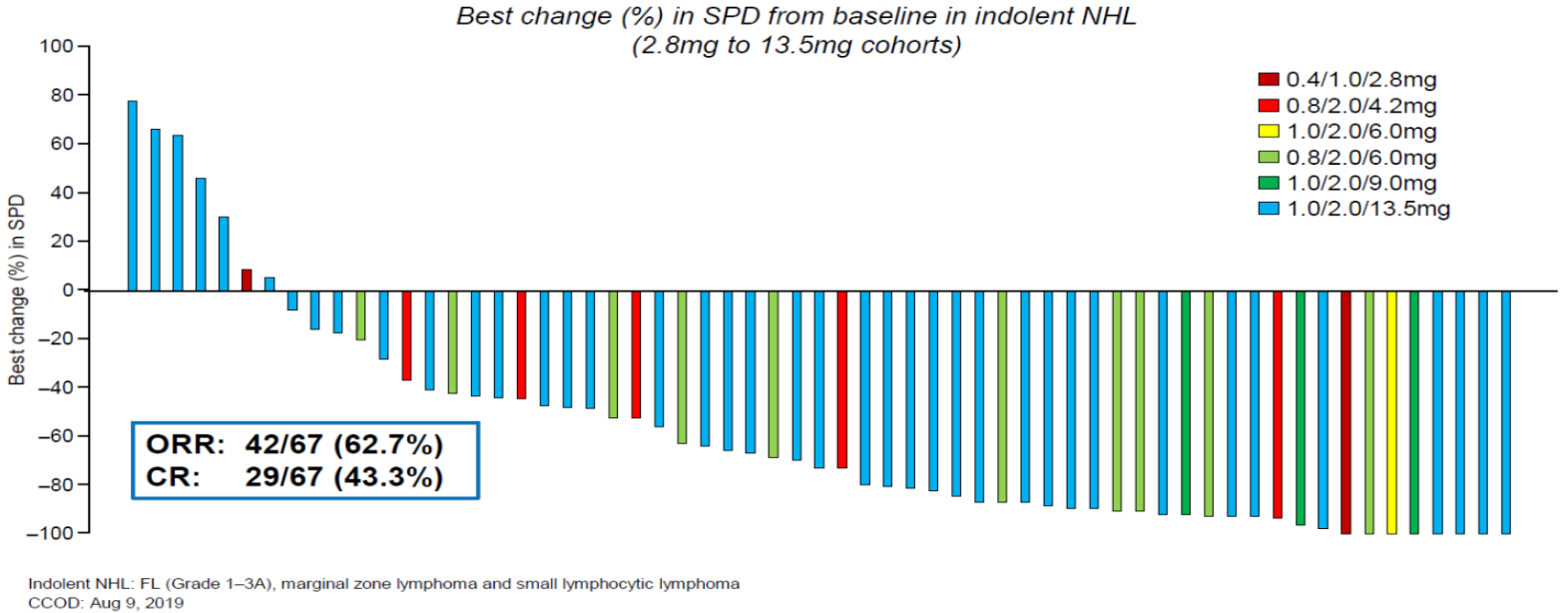
CRS, cytokine release syndrome; NHL, non-Hodgkin lymphoma; pts, patients; R/R, relapsed or refractory; TILs, tumor-infiltrating lymphocytes

1. Sun et al. Sci Transl Med 2015
2. Budde et al. ASH 2018; 3 Bartlett et al. ASCO 2019

Mosunetuzumab: Responses seen in heavily pretreated patients with R/R non-Hodgkin lymphoma (NHL)

270 patients included prior to this presentation (2/3 aNHL, 1/3 iNHL)

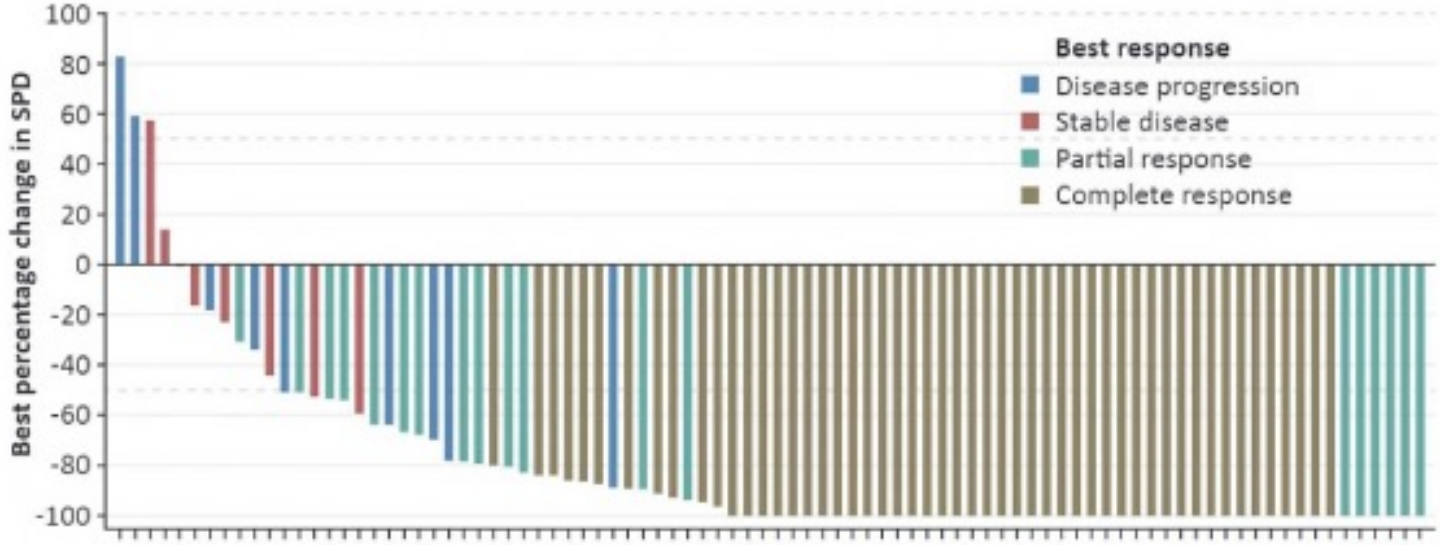
Objective response rate in indolent NHL



Indolent NHL: FL (Grade 1–3A), marginal zone lymphoma and small lymphocytic lymphoma
CCOD: Aug 9, 2019

127 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

Figure. Waterfall plot of best percentage change in SPD as assessed by PET/CT and independent review facility in all 3L+ R/R FL pts



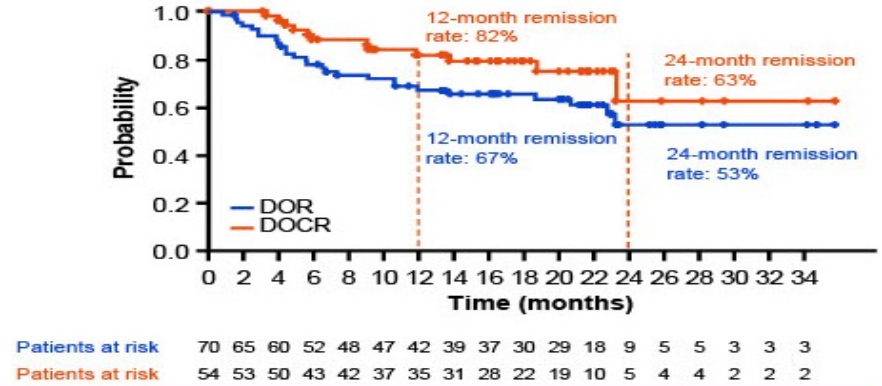
L. Elizabeth Budde[1] ASH 2021

Mosunetuzumab Monotherapy Demonstrates Durable Efficacy with a Manageable Safety Profile in Patients with Relapsed/Refractory Follicular Lymphoma who Received ≥2 Prior Therapies: Updated Results from a Pivotal Phase II Study

Durability of responses

Efficacy endpoint by investigator assessment	N=90
Median DOR, months (range), n=70 24-month DOR (95% CI)	NR (21–NR) 53% (38–68)
Median DOCR, months (range), n=54 24-month DOCR (95% CI)	NR (23–NR) 63% (38–88)
Median PFS, months (range) 24-month PFS (95% CI)	24 (12–NR) 48% (36–60)
Median TTNT, months (range) 24-month TTNT (95% CI)	NR (18–NR) 56% (45–67)
Median OS, months (range) 24-month OS (95% CI)	NR (NR–NR) 87% (80–94)

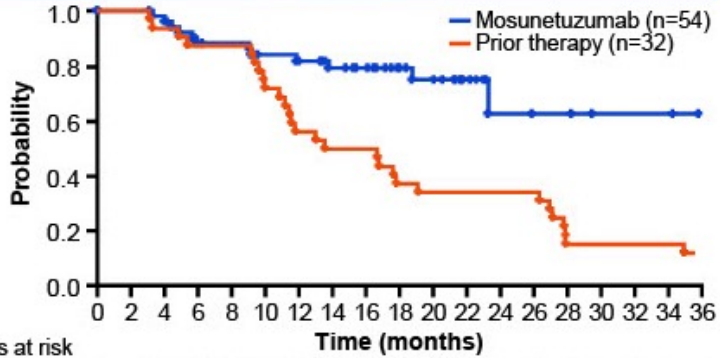
DOR and DOCR



Durable responses: majority of patients in remission after 2 years

DOCR and PFS with mosunetuzumab versus last prior therapy

DOCR

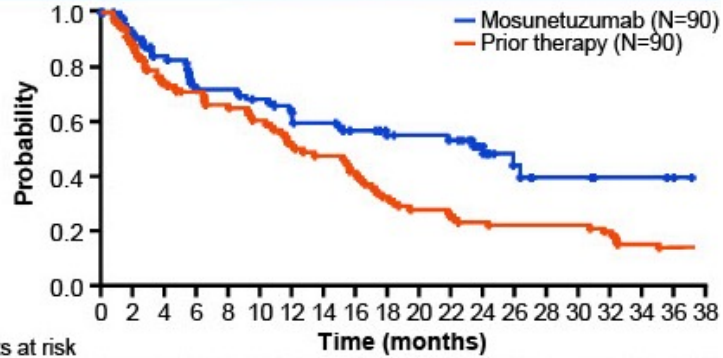


Patients at risk

Prior therapy	32	32	30	28	28	23	18	16	16	12	11	11	11	5	5	5	5	4
Mosunetuzumab	54	53	50	43	42	37	35	31	28	22	19	10	5	4	4	2	2	2	NR

	Mosunetuzumab (n=54)	Last prior therapy (n=32)
Median DOCR, months (95% CI)	NR (23–NR)	15 (11–26)

PFS



Patients at risk

Prior therapy	90	80	66	61	56	52	44	41	36	28	24	22	20	19	19	19	16	13	12	12
Mosunetuzumab	90	80	71	60	59	55	47	46	40	33	32	31	18	10	5	5	3	3	1	NR

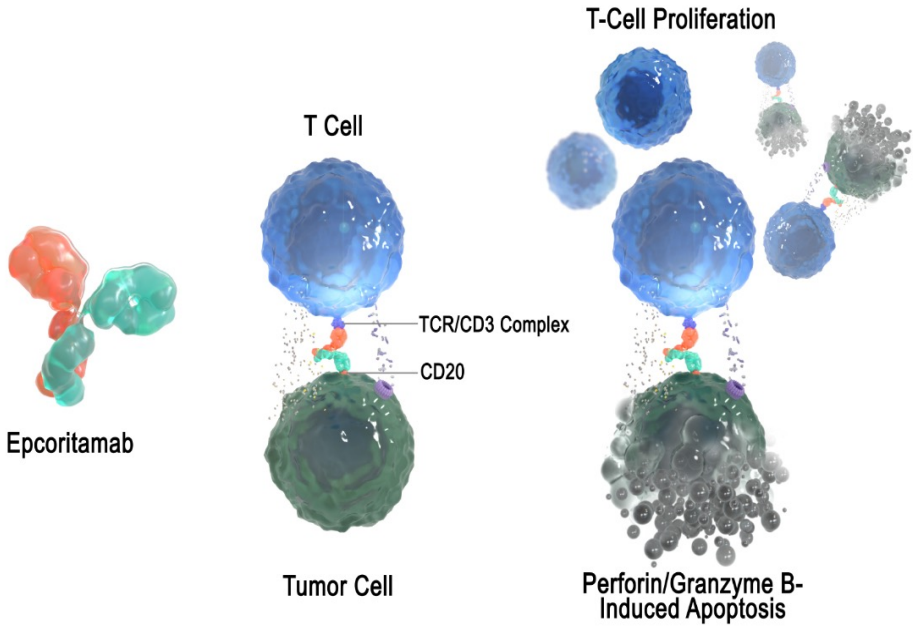
	Mosunetuzumab (N=90)	Last prior therapy (N=90)
Median PFS, months (95% CI)	24 (12–NR)	12 (10–16)

Extended DOCR and 12-month improvement in median PFS with mosunetuzumab compared with last prior therapy

Epcoritamab (DuoBody®-CD3xCD20)

Epcoritamab (DuoBody®-CD3×CD20) is a subcutaneously administered bispecific antibody that induces T-cell–mediated killing of CD20-expressing tumors[1,2]

- **Induces T-cell activation** by binding to CD3 on T cells and CD20 on malignant B cells
- **Promotes immunological synapse** between bound cells, resulting in apoptosis of B cells
- **Binds to a distinct epitope on CD20**, different from the epitopes of rituximab and obinutuzumab
- **Retains activity** in the presence of CD20 mAbs



1. Engelberts PJ, et al. EBioMedicine. 2020;52:102625. 2. Chiu C, et al. Presented at EHA 2020. [Abstract #EP1330].

EPCORE™ NHL-1 Study Design

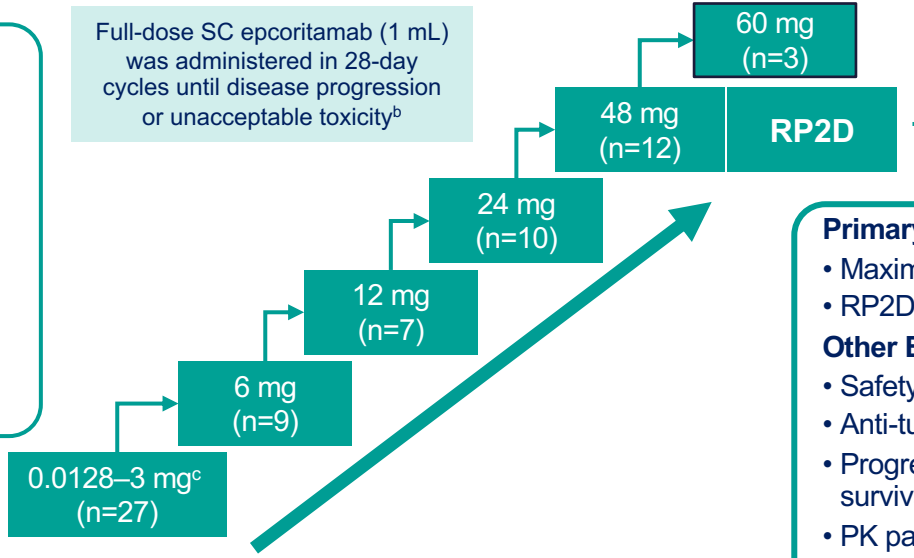
EPCORE™ NHL-1 (NCT03625037) is an international, multicenter, open-label, single-arm, phase 1/2 trial of epcoritamab in patients with relapsed or refractory CD20+ B-NHL

Key Inclusion Criteria

- Adults with documented R/R CD20+ mature B-cell neoplasm
- ECOG PS 0-2
- Prior treatment with anti-CD20 mAbs
- Measurable disease based on CT, MRI, or FDG PET CT scans[a]

Dose escalation

Full-dose SC epcoritamab (1 mL) was administered in 28-day cycles until disease progression or unacceptable toxicity[b]



Dose expansion[d]

- DLBCL[e]
- FL[f]
- MCL

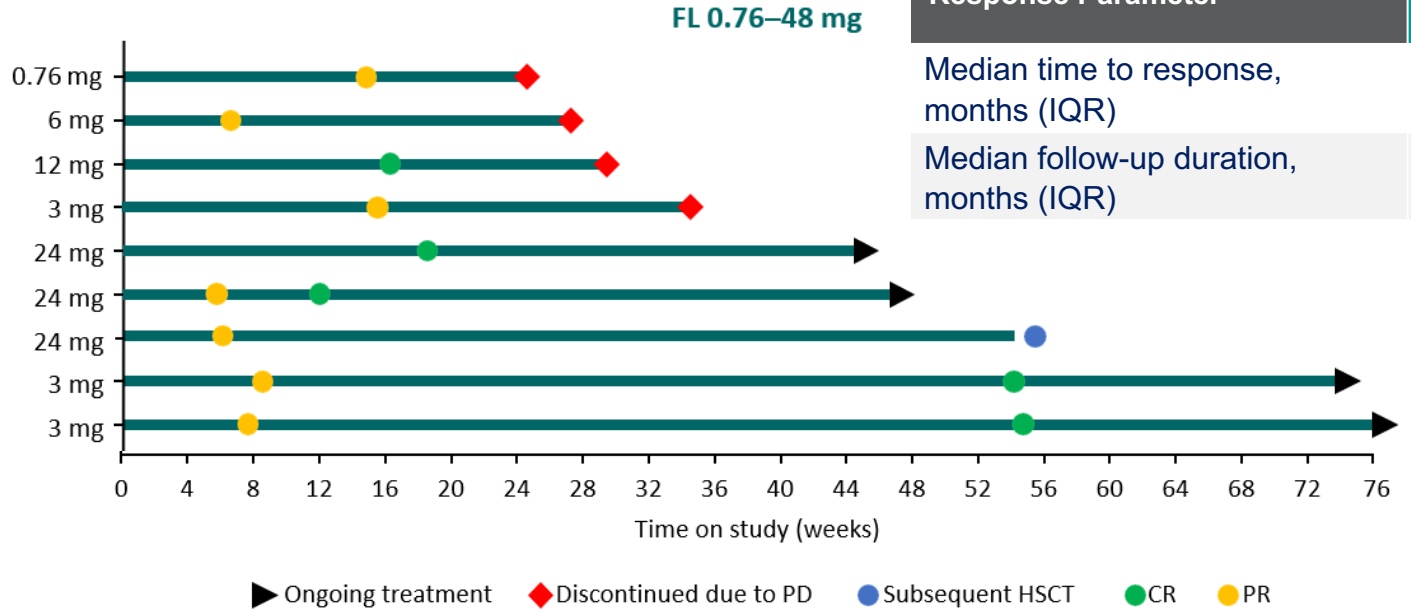
Primary Endpoints
- Maximum tolerated dose
- RP2D

Other Endpoints
- Safety and tolerability
- Anti-tumor activity[g]
- Progression-free survival
- PK parameters
- PD biomarkers of response

Treatment Response by Diagnosis (N=66)

Response Parameter[b], n (%)	R/R DLBCL[c]			R/R FL[d]		R/R MCL[e]	
	12–60 mg (n=22)	48 mg (n=8)	60 mg (n=3)	0.76–48 mg (n=10)	48 mg (n=1)	0.76–48 mg (n=4)[f]	48 mg (n=1)
ORR, n (%) (95% CI)	15 (68) (45–86)	7 (88) (47–100)	3 (100) (29–100)	9 (90) (55–100)	0 (0–98)	2 (50) (7–93)	1 (100) (3–100)
CR, n (%)	10 (45)	3 (38)	3 (100)	5 (50)	0	1 (25)	0
PR, n (%)	5 (23)	4 (50)	0	4 (40)	0	1 (25)	1 (100)
SD, n (%)	1 (5)	0	0	0	0	1 (25)	0
PD, n (%)	5 (23)	0	0	1 (10)	1 (100)	0	0

Response Profile for R/R FL



Response Parameter	0.76–48 mg (n=10)	48 mg (n=1)
Median time to response, months (IQR)	1.9 (1.5–3.5)	NA
Median follow-up duration, months (IQR)	13.6 (10.4–16.5)	6.6 (6.6–6.6)

- **Responses deepened over time in three patients who had PR that converted to CR over 6 to 45 weeks**
- **Four patients experienced ongoing response at the time of data cutoff**

EPCORE™ NHL-2: Epcoritamab in Combination with Other Agents

Phase Ib/II B-cell NHL (N=130)

Dose Escalation → **Dose Expansion**

Epcoritamab +

- R-CHOP (IV) (in previously untreated DLBCL)
- R^2 (in R/R FL)
- BR (in previously untreated FL)
- R-DHAX/C (in R/R DLBCL eligible for ASCT)
- GemOx (in R/R DLBCL ineligible for ASCT)

→ **Epcoritamab +**

- R-CHOP (in previously untreated DLBCL)
- R^2 (in R/R FL)
- BR (in previously untreated FL)
- R-DHAX/C (in R/R DLBCL eligible for ASCT)
- GemOx (in R/R DLBCL ineligible for ASCT)

Key Inclusion Criteria

- ≥1 measurable nodal lesion or ≥1 measurable extra-nodal lesion on CT or MRI
- ECOG PS of 0, 1 or 2

Objectives

Primary

Dose Escalation
- DLTs
- AEs/safety

Dose Expansion
- ORR

Secondary

Dose Escalation/Expansion
- PK
- ADAs
- DOR, TTR, PFS, OS, TTNT
- MRD negativity

Dose Expansion only
- AEs, lab values, dose interruptions

Safety run-in
- ORR

www.ClinicalTrials.gov – NCT04663347.

Subcutaneous Epcoritamab with Rituximab + Lenalidomide in Patients with Relapsed or Refractory Follicular Lymphoma: Phase 1/2 Trial Update

Study Design: EPCORE NHL-2, Arm 2b

A phase 1b/2, open-label trial evaluating the safety and antitumor activity of epcoritamab + R² in adults with R/R FL[a]

Key inclusion criteria

- R/R CD20⁺ FL
  - Grade 1, 2, or 3A
  - Stage II–IV
- Need for treatment based on symptoms or disease burden, as determined by GELF criteria[1]
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

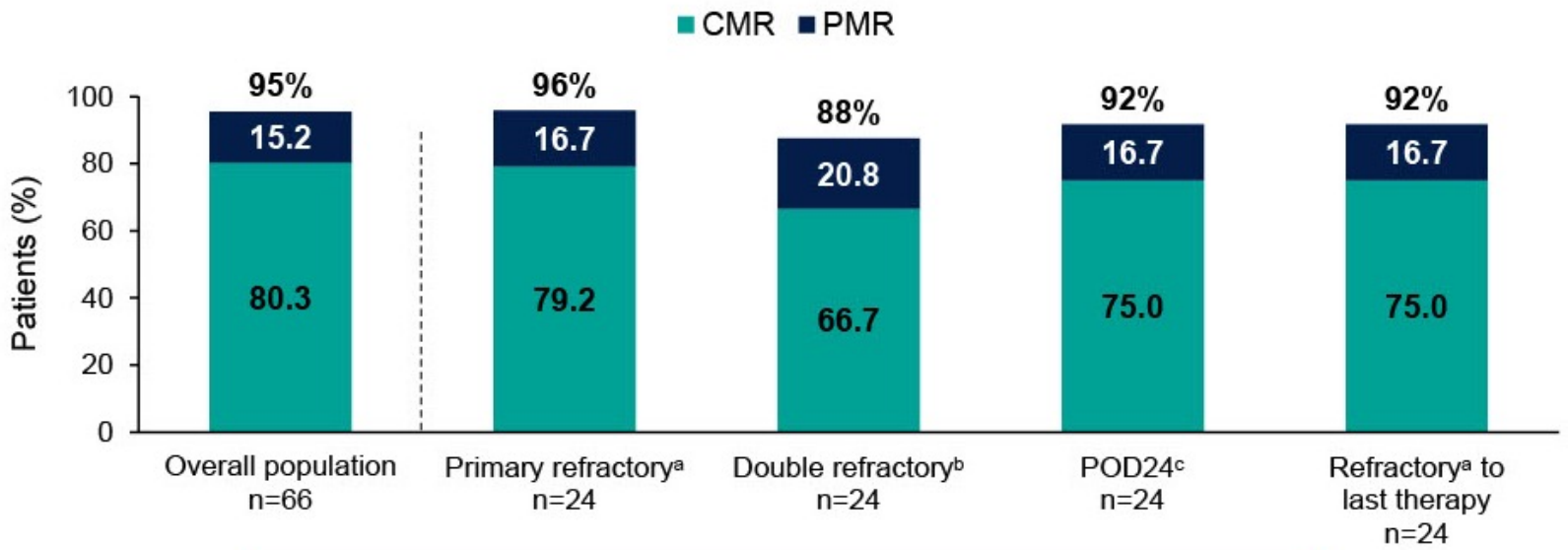
		Treatment Regimen Epcoritamab SC 48 mg + R²						
	Agent	C1	C2	C3	C4	C5	C6–C12	C13+
	Epcoritamab SC 48 mg	QW	QW	Q4W	Q4W	Q4W	Q4W	Q4W Up to 2 years
R²	Rituximab IV 375 mg/m²	QW	Q4W	Q4W	Q4W	Q4W		
R²	Lenalidomide oral 20 mg	Daily for 21 d (for 12 cycles)						

Data cutoff: September 16, 2022
Median follow-up: 6.4 mo

Primary objective: Safety and antitumor activity[b]

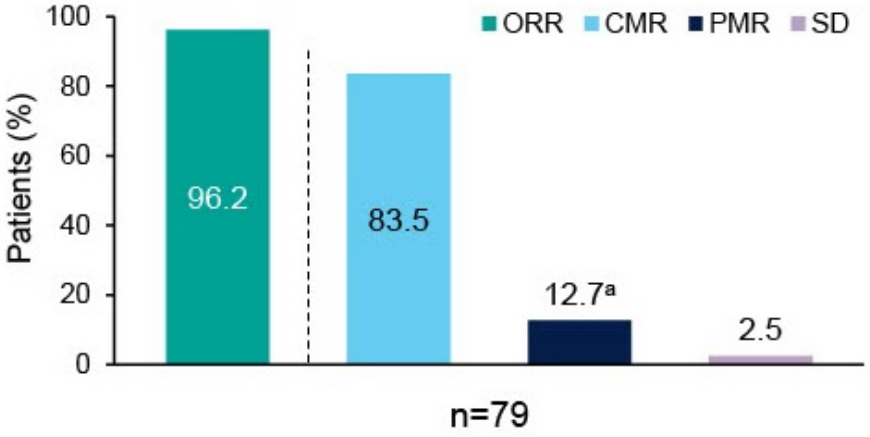
Overall response rate 95%
Complete metabolic response 80%

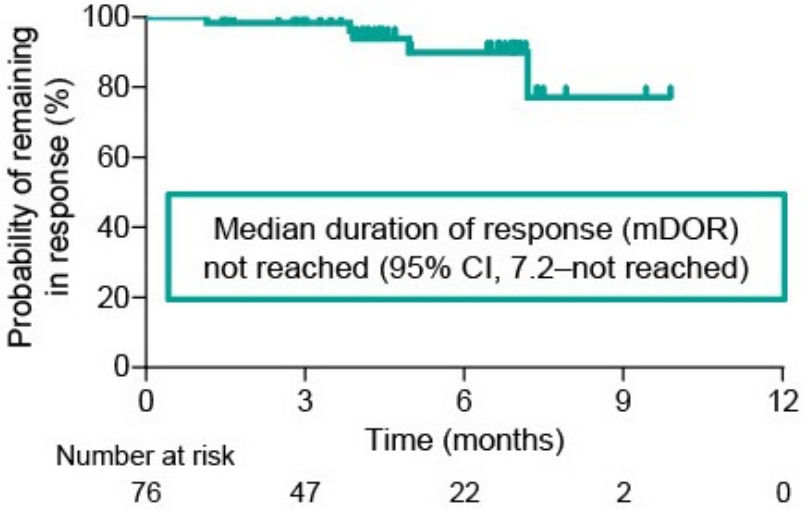
Responses Across High-risk Subgroups



Deep responses consistent across high-risk R/R FL subgroups

Updated Response Data





Data cutoff: October 31, 2022

Median follow-up: 5.6 mo (range, 1.2+ to 11.5+)

- **Epcoritamab + R² showed potent antitumor activity**
  - High response rates: ORR 96.2%, CMR 83.5%; majority achieved at first assessment
  - Deep responses observed across high-risk subgroups
  - Durable responses have been observed
- **Safety remained consistent with previous reports**
  - No grade ≥3 CRS observed; CRS events mostly occurred after the first full dose

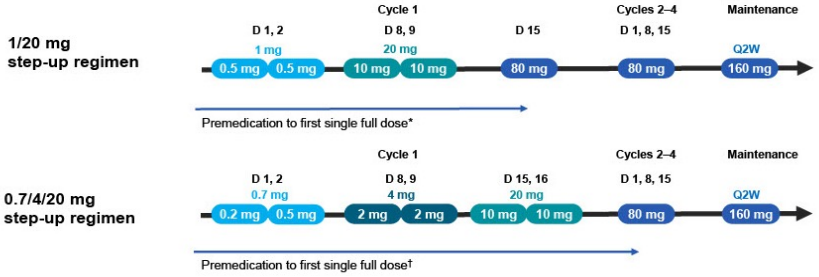
Odronextamab in Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) Grade 1–3a: Results from a Prespecified Analysis of the Phase 2 Study ELM-2

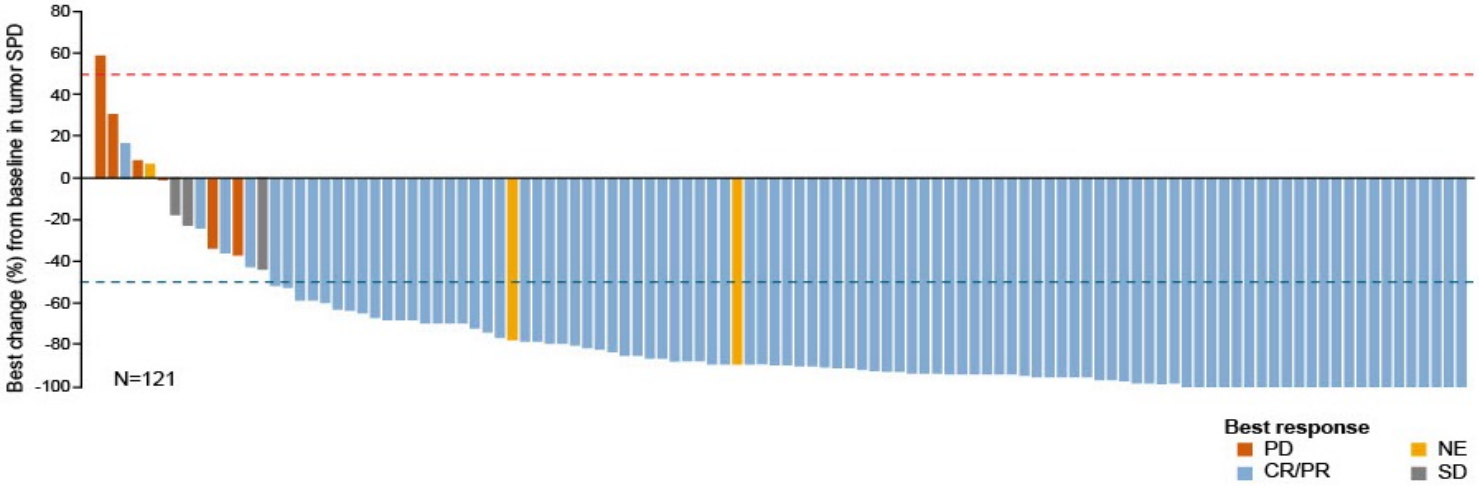
Tae Min Kim[1], Michal Taszner[2], Seok-Goo Cho[3], Silvana Novelli[4], Steven Le Gouill[5], Michelle Poon[6], Jose C. Villasboas[7], Rebecca Champion[8], Emmanuel Bachy[9], Stephanie Guidez[10], Aranzazu Alonso[11], Deepa Jagadeesh[12], Michele Merli[13], David Tucker[14], Jingxian Cai[15], Carolina Leite de Oliveira[15], Min Zhu[15], Aafia Chaudhry[15], Hesham Mohamed[15], Srikanth Ambati[15], Stefano Luminari[16], on behalf of ELM-2 Investigators

[1]Seoul National University Hospital, Seoul, South Korea; [2]Department of Haematology and Transplantology, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland; [3]The Catholic University of Korea, Seoul St. Mary's Hospital Hematology, Seoul, South Korea; [4]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [5]Service d'Hématologie Clinique, Centre Hospitalier Universitaire de Nantes, Nantes, France (currently at Institut Curie, Paris, France and Université UVSQ, France); [6]Hematology Oncology National University Hospital, Singapore; [7]Mayo Clinic Rochester, Rochester, MN, USA; [8]Norton Cancer Institute, Louisville, KY, USA; [9]Hospices Civils de Lyon and Université Claude Bernard Lyon 1, Lyon, France;[10]Centre Hospitalier Universitaire (CHU) de Poitiers, Poitiers, France; [11]Hospital Universitario Quiron Salud Madrid, Madrid, Spain; [12]Cleveland Clinic Main Campus, Cleveland, OH, USA; [13]Ospedale di Circolo e Fondazione Macchi, Varese, Italy; [14]Royal Cornwall Hospital, Cornwall, United Kingdom; [15]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [16]Division of Hematology, Azienda Unità Sanitaria Locale-IRCCS, Reggio Emilia, Italy

Cycle 1 step-up regimen optimized during the course of the study to further mitigate the risk for cytokine release syndrome

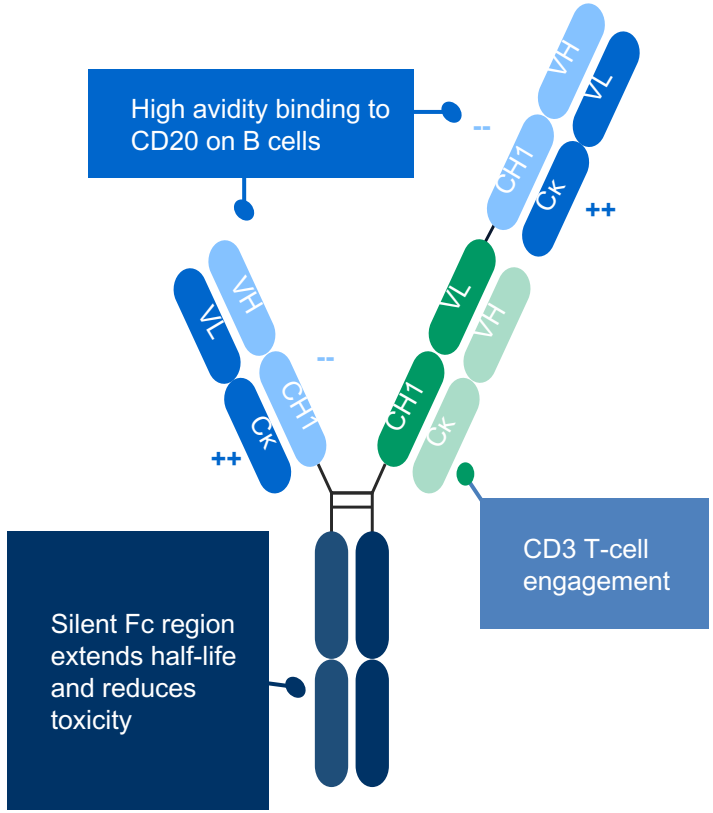
- The study initiated with a Cycle 1 step-up regimen of 1/20/80 mg
- This was modified to 0.7/4/20 mg during Cycle 1 to further mitigate the risk of CRS





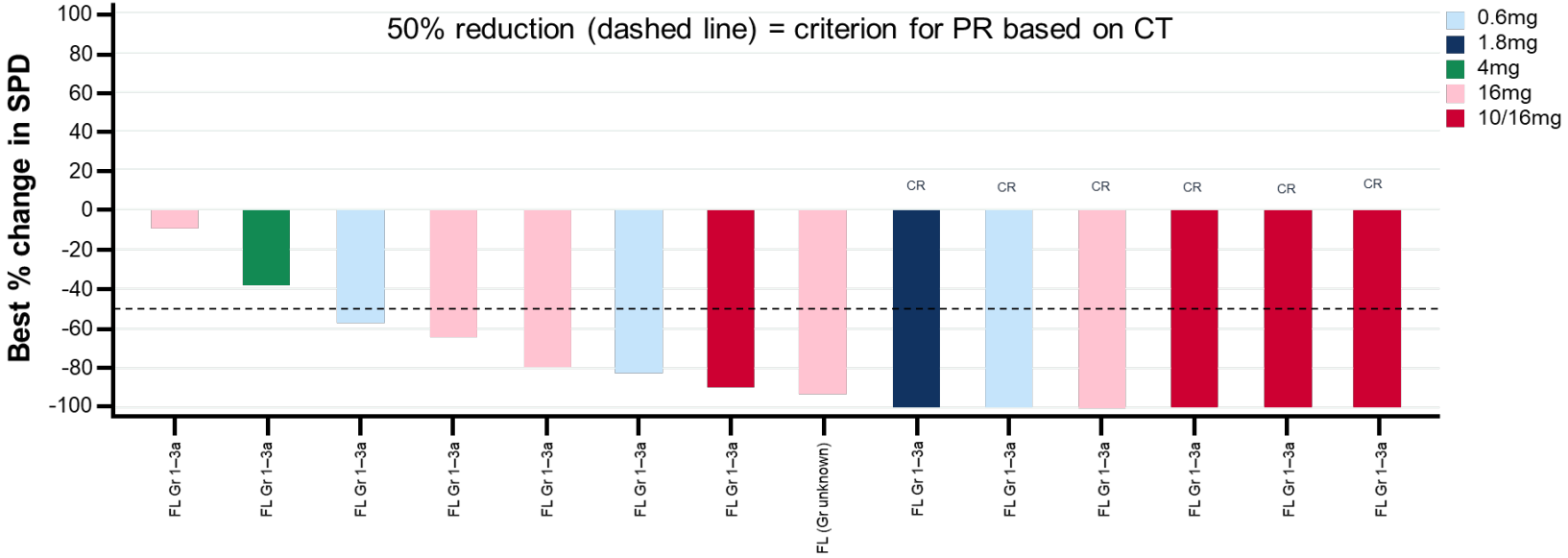
Glofitamab

- **Glofitamab** is a T-cell-engaging bispecific full-length antibody with a unique 2:1 molecular configuration
  - Glofitamab's molecular configuration associated with superior potency under experimental conditions vs CD20-CD3 bispecific antibodies with a 1:1 format[1,2]
  - 'Off-the shelf' availability
- Obinutuzumab pretreatment (Gpt) is used to mitigate cytokine release syndrome (CRS),* and allow for rapid escalation of glofitamab to clinically active doses[3]
  - PK modelling showed that step-up dosing in addition to Gpt can further reduce CRS[4]



1. Bacac M, et al. Clin Cancer Res 2018;24:4785–97; 2. Morschhauser F, et al. 61st ASH Annual Meeting & Exposition, December 7–10, 2019 (P-1584); 3. Dickinson M, et al. 25th EHA Congress, June 11–14, 2020 (Presentation S241); 4. Djebli N, et al. ASH 62nd Annual Meeting Meeting & Exposition, December 5–8, 2020 (P-1198).

Glofitamab – anti-tumor activity across doses 0.6-25 mg



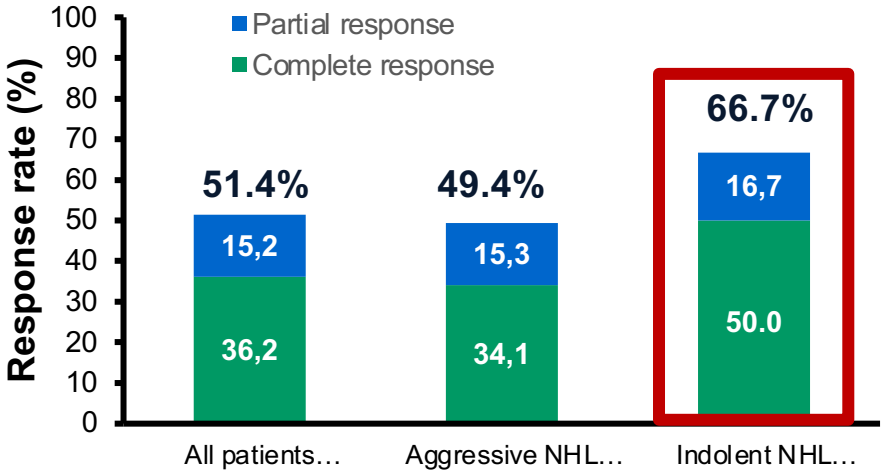
Efficacy in indolent lymphoma

Glofitamab Step-Up Dosing Induces High Response Rates in Patients with Hard-to-treat Refractory or Relapsed (R/R) Non-Hodgkin Lymphoma (NHL)

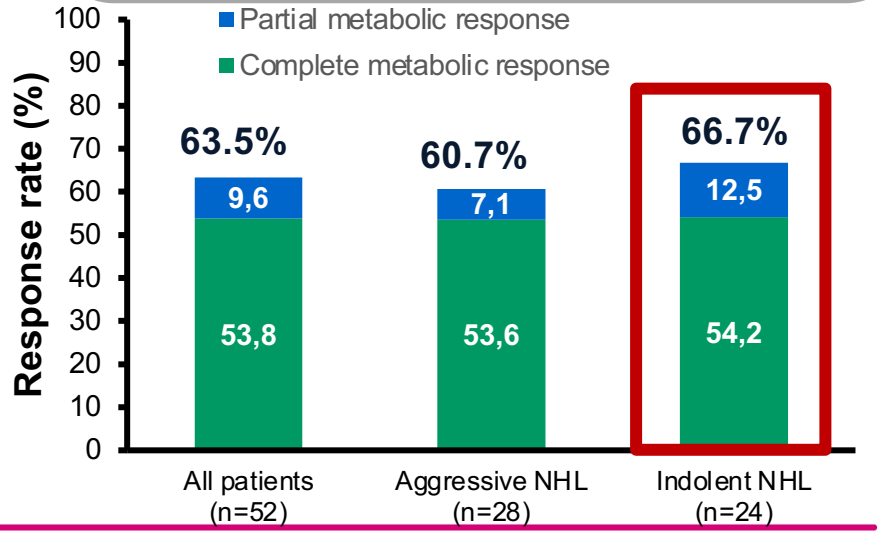
Martin Hutchings,[1] Carmelo Carlo-Stella,[2] Emmanuel Bachy,[3] Fritz C Offner,[4] Franck Morschhauser,[5] Michael Crump,[6] Gloria Iacoboni,[7] Anna Sureda,[8] Joaquin Martinez-Lopez,[9] Linda Lundberg,[10] Anesh Panchal,[11] David Perez-Callejo,[10] James Relf,[11] David Carlile,[11] Emily Piccione,[12] Kathryn Humphrey,[11] Michael J Dickinson[13]

High response to glofitamab was maintained with step-up dosing

Glofitamab ≥10mg fixed dosing (10, 16, 25, 10/16mg)[1]



Glofitamab step-up dosing 2.5/10/16mg or 2.5/10/30mg



Riflessioni sulle nuove terapie

In generale in una malattia dove la chemioterapia ha un ruolo non determinante l'utilizzo di farmaci target dovrebbe essere estremamente vantaggioso

In una malattia dove il sistema immunitario dell'ospite gioca evidentemente un ruolo fondamentale nel controllo della malattia (vedi WW) l'utilizzo di anticorpi bispecifici che 'facilitano' l'attivazione del sistema immunitario stesso dovrebbe essere teoricamente molto valida.

Più precocemente si utilizzano e, teoricamente, migliori dovrebbero essere i risultati.

L'immunoterapia sicuramente sostituirà, almeno in alcuni tipi di linfoma, la chemioterapia oppure rappresenterà la terapia di salvataggio

GRAZIE