CAR-TALKING

News dal mondo CAR-T

Bari, Hotel Excelsior
22 maggio 2023

Altri Approcci terapeutici di salvataggio nel Linfoma Follicolare

Vincenzo Pavone

AO Cardinale G.Panico U.O Ematologia e TMO –Tricase(LE)

UNMET CLINICAL NEED

.

Results of new MoAb, bi-specific, drug conjugated MoAb and checkpoint inhibitors

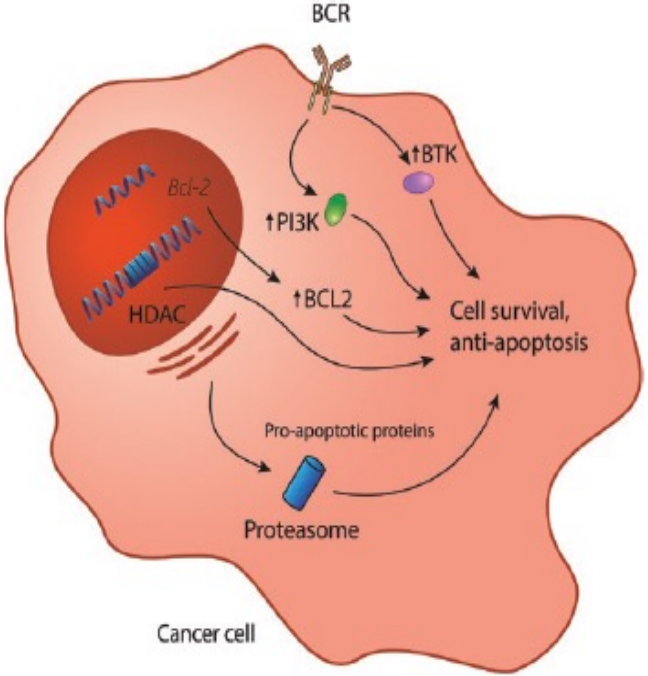

Figure 2 Schematic representation of key pathways that may promote cell survival in B-cell lymphoma. Several pathways that promote cell survival in B-cell lymphoma have been identified: increased expression of kinases PI3K and BTK, downstream of the B-cell receptor and increased BCL-2 expression after chromosomal mutations. HDAC influences gene expression, and dysregulation may promote tumor survival. How HDAC inhibitors work exactly has not been fully elucidated. Chromosomal translocations or mutation may lead to increased expression of BCL-2, which inhibits apoptosis. The proteasome is responsible for the degradation of various proteins, including factors regulating the progression of the cell cycle and pro-apoptotic proteins. Proteasome inhibition leads to apoptosis, possibly due to the increased presence of pro-apoptotic proteins or by toxic stress caused by protein accumulation. HDAC: histone deacetylase; BCR: B-cell receptor; BTK: Bruton's tyrosine kinase; PI3K: phosphoinositide 3-kinase.

Upcoming immunotherapeutic combinations for B-cell lymphoma

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Summary

After initial introduction for B-cell lymphomas as adjuvant therapies to established cancer treatments, immune checkpoint inhibitors and other immunotherapies are now integrated in mainstream regimens, both in adult and pediatric patients. We here provide an overview of the current status of combination therapies for B-cell lymphoma, by in-depth analysis of combination therapy trials registered between 2015–2020. Our analysis provides new insight into the rapid evolution in lymphoma treatment, as propelled by new additions to the treatment arsenal. We conclude with prospects on upcoming clinical trials which will likely use systematic testing approaches of more combinations of established chemotherapy regimens with new agents, as well as new combinations of immunotherapy and targeted therapy. Future trials will be set up as basket or umbrella-type trials to facilitate the evaluation of new drugs targeting specific genetic changes in the tumor or associated immune microenvironment. As such, lymphoma patients will benefit by receiving more tailored treatment that is based on synergistic effects of chemotherapy combined with new agents targeting specific aspects of tumor biology and the immune system.

The Challenge of Follicular NHL

- Indolent behavior and is responsive to many treatments, but remains incurable
- Most patients have a prolonged survival, but a subset exhibit treatment-resistant disease that will affect their longevity
- Wide range of treatment options of varying intensity
- Goal is to control the disease, while maintaining quality of life

Key aspects in the management of r/r FL

- Risk is heterogeneous but prognostic indexes are missing in the r/r setting
- Current recommendations based on weak evidence (i.e., ASCT)
- Key decisional factors
  - duration of response, tumor burden, prior therapy
  - patients' age and comorbid conditions
  - availability of active drugs/therapies
- Few registered agents

- BR, bendamustine and rituximab; r/r relapsed/refractory.

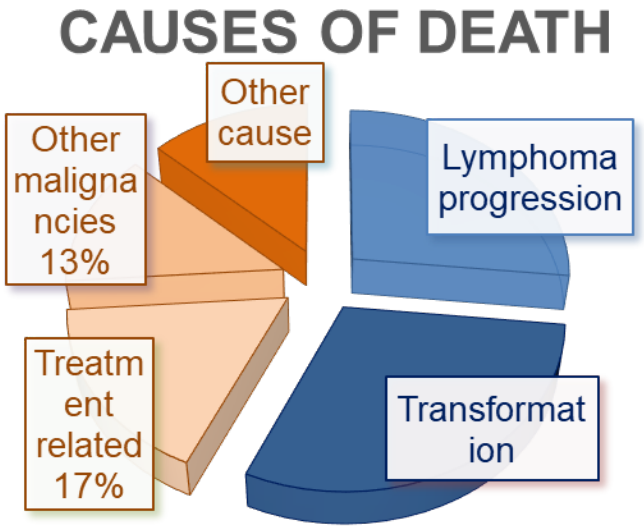
- Luminari S, personal communication. Dreyling M, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021:32;298-308. Gopal AK, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014;370:1008-18. Puvvada SD, et al. Yttrium-90-ibritumomab tiuxetan (Zevalin®) radioimmunotherapy after cytoreduction with ESHAP chemotherapy in patients with relapsed follicular non-Hodgkin lymphoma: final results of a phase II study. Oncology. 2018; 94:274-80. Karmali R, et al. Rituximab: a benchmark in the development of chemotherapy-free treatment strategies for follicular lymphomas. Ann Oncol. 2018;29:332-40. Zinzani PL, et al. Venetoclax-rituximab with or without bendamustine vs bendamustine-rituximab in relapsed/refractory follicular lymphoma. Blood. 2020;136:2628-37. Cheson BD, et al. Overall survival benefit in patients with rituximab refractory indolent non-Hodgkin lymphoma who received obinutuzumab plus bendamustine induction and obinutuzumab maintenance in the GADOLIN study. J Clin Oncol. 2018;36:2259-66.

Common features of FL

Can be asymptomatic	*W&W is an option*
Can be localized	*RT is an option*
Relapsing remitting course	*Strategy matters*
Survival is improving	*Late effects matter*
Can transform into aggressive-subtypes	*Suspect TFL at each relapse*

Cause of Death in Follicular Lymphoma in the First Decade of the Rituximab Era: A Pooled Analysis of French and US Cohorts

Clémentine Sarkozy, MD[1]; Matthew J. Maurer, MS[2]; Brian K. Link, MD[3]; Hervé Ghesquieres, MD, PhD[1]; Emmanuelle Nicolas, MD[4]; Carrie A. Thompson, MD[2]; Alexandra Traverse-Glehen[1]; Andrew L. Feldman, MD[2]; Cristine Allmer[2]; Susan L. Slager[2]; Stephen M. Ansell, MD, PhD[2]; Thomas M. Habermann, MD[2]; Emmanuel Bachy[1]; James R. Cerhan, MD, PhD[2]; and Gilles Salles, MD, PhD[1]

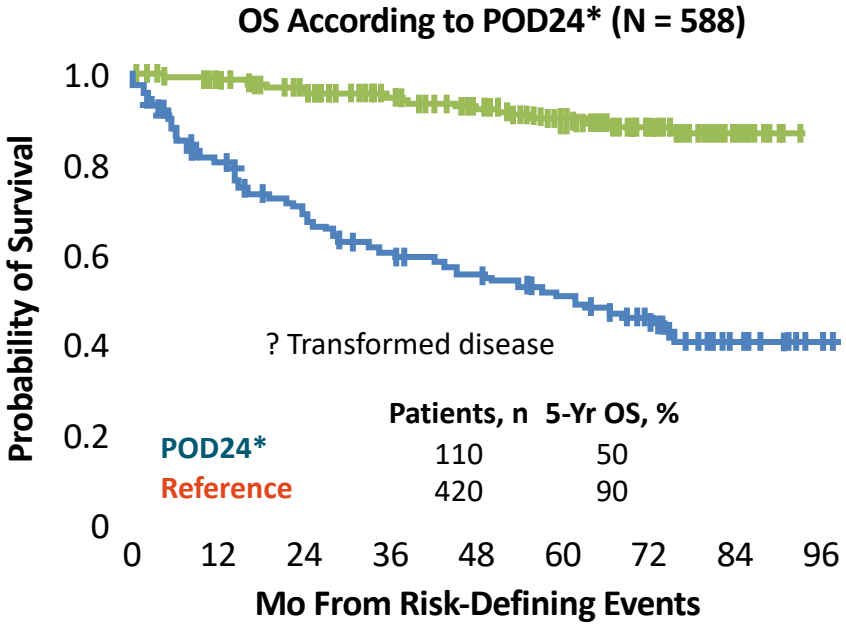


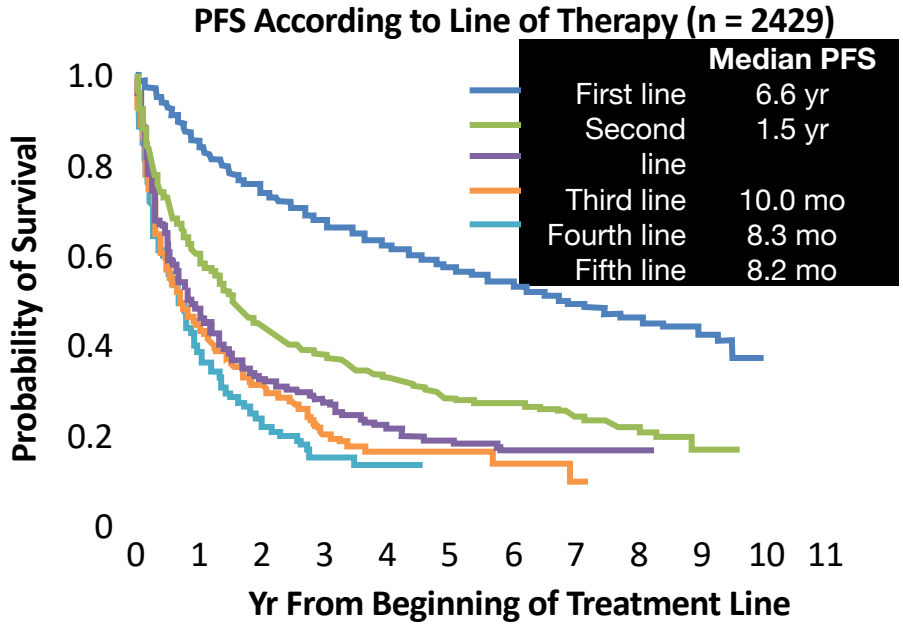
10-year incidence (%) of FL deaths

		FL related	FL unrelated
Age			
	< 60 yrs	9.4	1.5
	61 – 70 yrs	14.2	5.8
	>70 years	25.4	16.6
FLIPI			
	0-1	4.0	3.7
	2	10.0	6.4
	3-5	**27.4**	5.2
EFS24			
	Achieved	6.7	5.7
	Not achieved	**36.1**	7.0
tFL			
	no	8.1	6.2
	yes	**45.9**	4.7

Sarkozy C et al. Cause of Death in Follicular Lymphoma in the First Decade of the Rituximab Era: A Pooled Analysis of French and US Cohorts. J Clin Oncol. 2019;37:144-52.

National LymphoCare Study: Outcomes According to POD24 and Line of Therapy



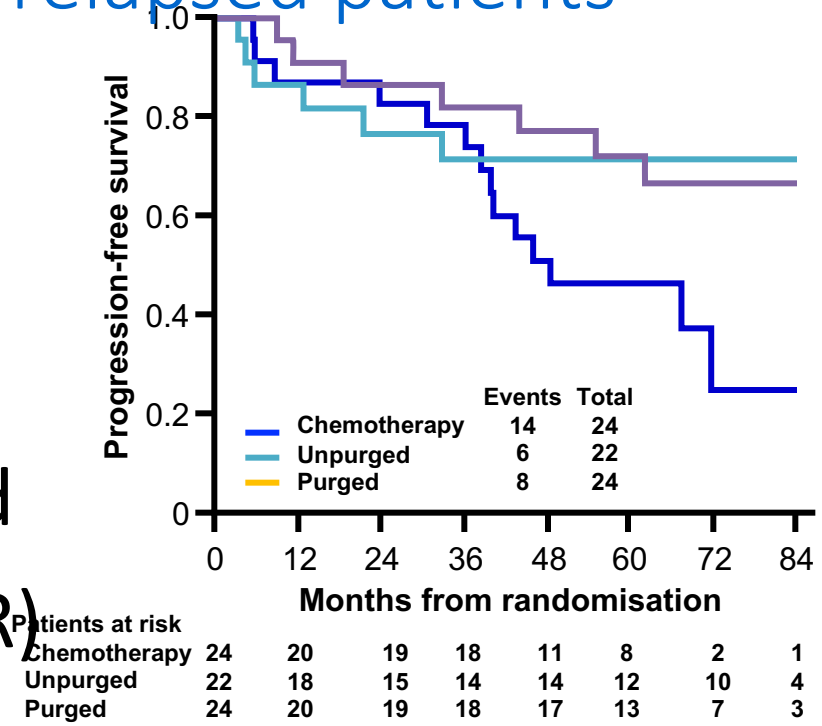


*POD24: relapse within 24 mo after initial therapy. Given figure is of patients treated with 1L R-CHOP. Similar results found for independent validation set and for 1L R-CVP/R-fludarabine in exploratory analyses.

Casulo C, JCO 2015; Br J Haematol. 2019;184:660.

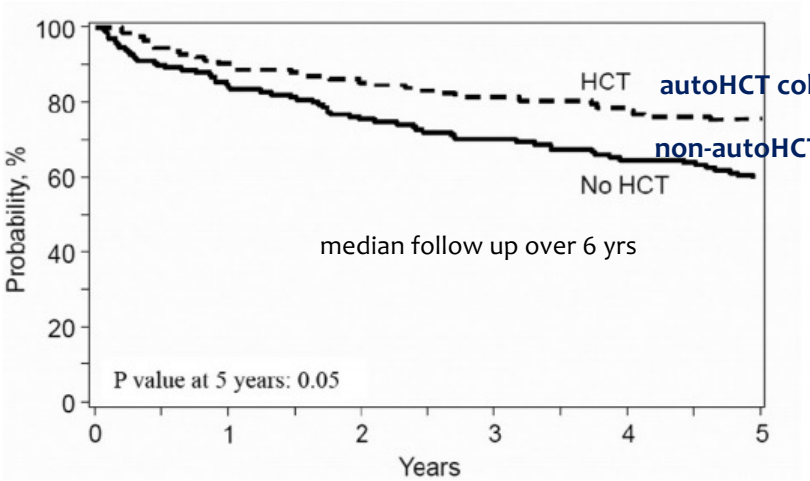
High-dose chemotherapy and ASCT prolongs survival in relapsed patients

- The CUP trial
  - –Relapsed follicular lymphoma
  - –24 chemotherapy
  - –33 HDCT unpurged
  - –32 HDCT purged (R)
- p=0.037
- Early interrupted (Actual pts 70 vs 250)



Schouten HC, *et al. J Clin Oncol* 2003; 21:3918–3927

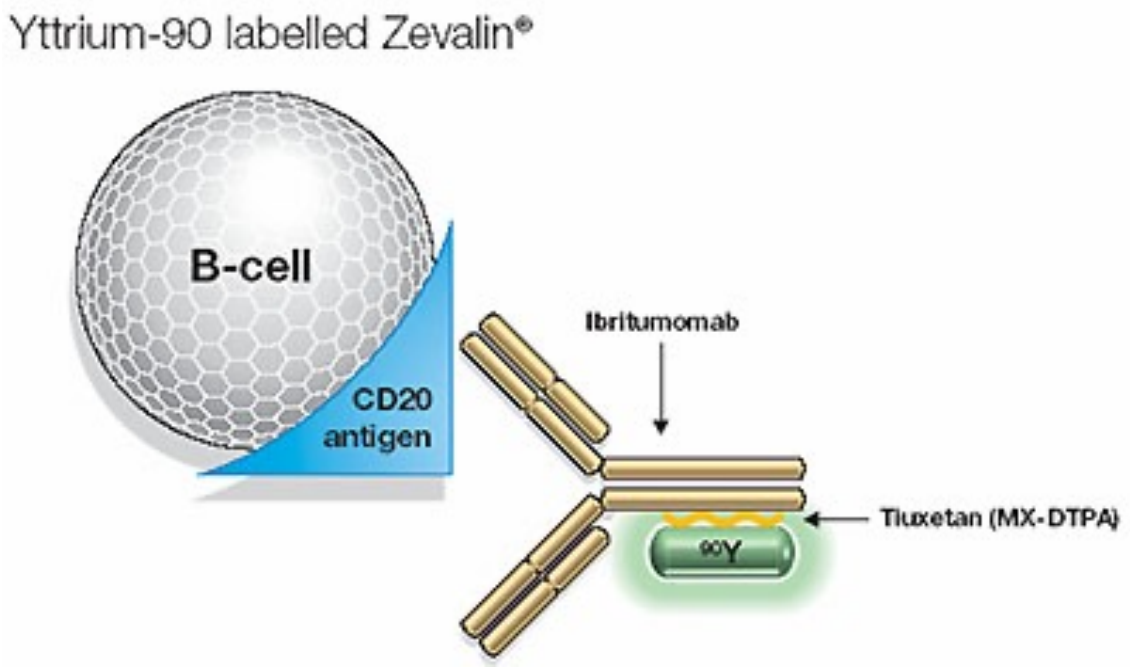
Overall Survival of patients receiving **HCT within 1 yrs of therapy failure** compared to no HCT

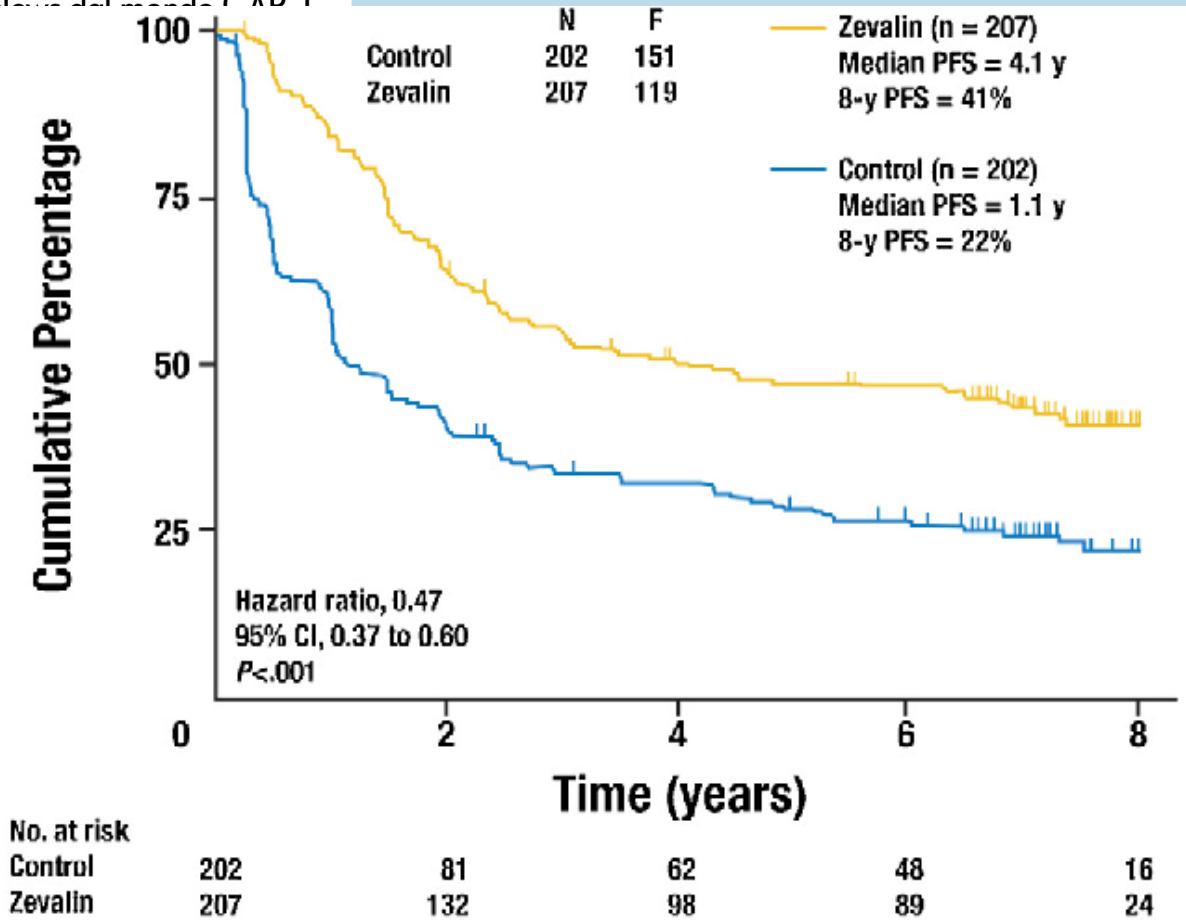


improved OS for pts receiving autoHCT within 1 year of treatment failure (5-yrs OS 73% vs 60%)

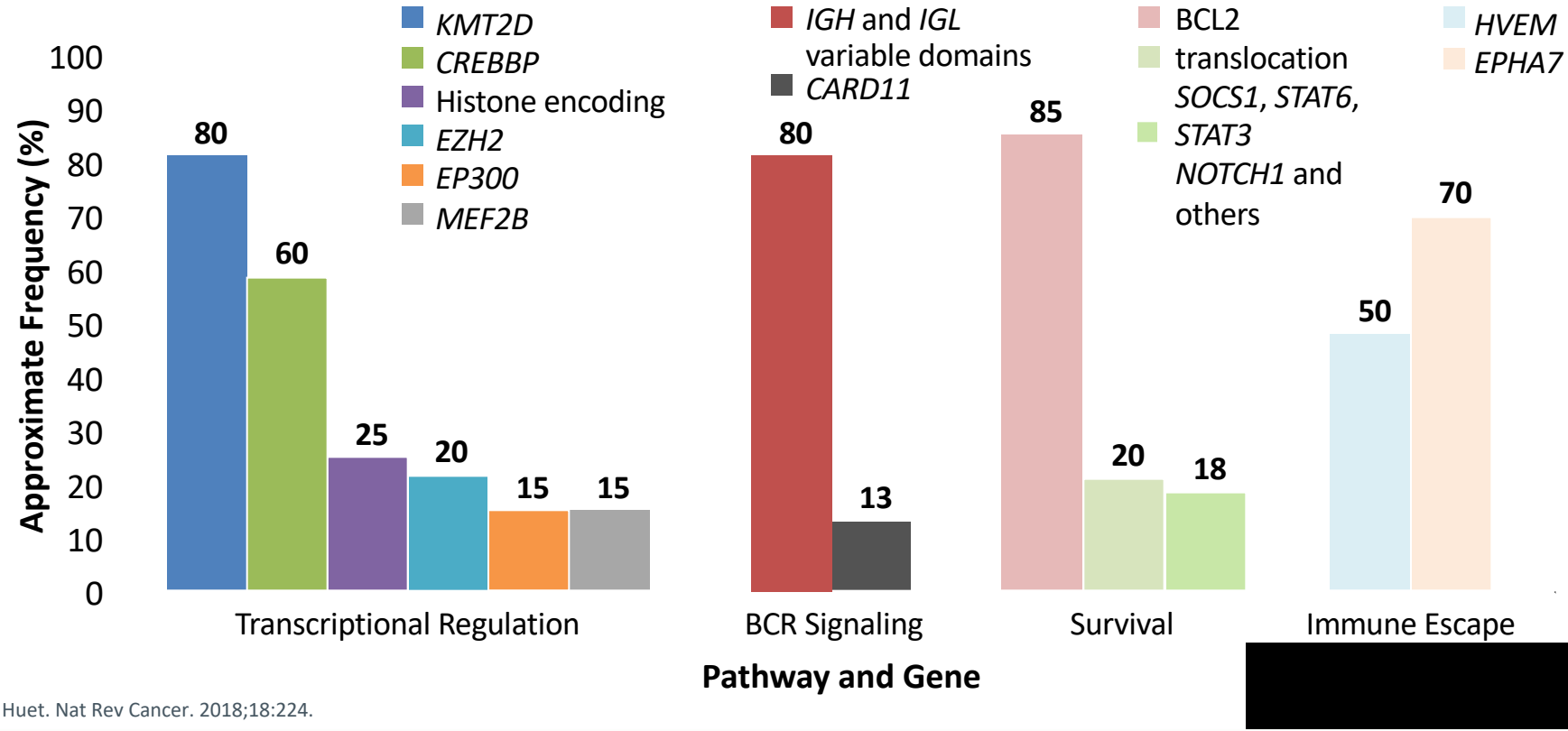
- this support consideration of **early consolidation** with autoHCT in select FL patients experiencing ETF
- With refined understanding of high-risk FL biology and identification of predictive biomarkers at diagnosis of FL, autoHCT could be considered as a component of precision medicine trials with a goal of changing the natural history of high-risk FL

Casulo C et al, Biol Blood Marrow Transplant, 2018


Yttrium-90 labelled Zevalin®
B-cell
CD20 antigen
Ibritumomab
Tiuxetan (MX-DTPA)
90Y

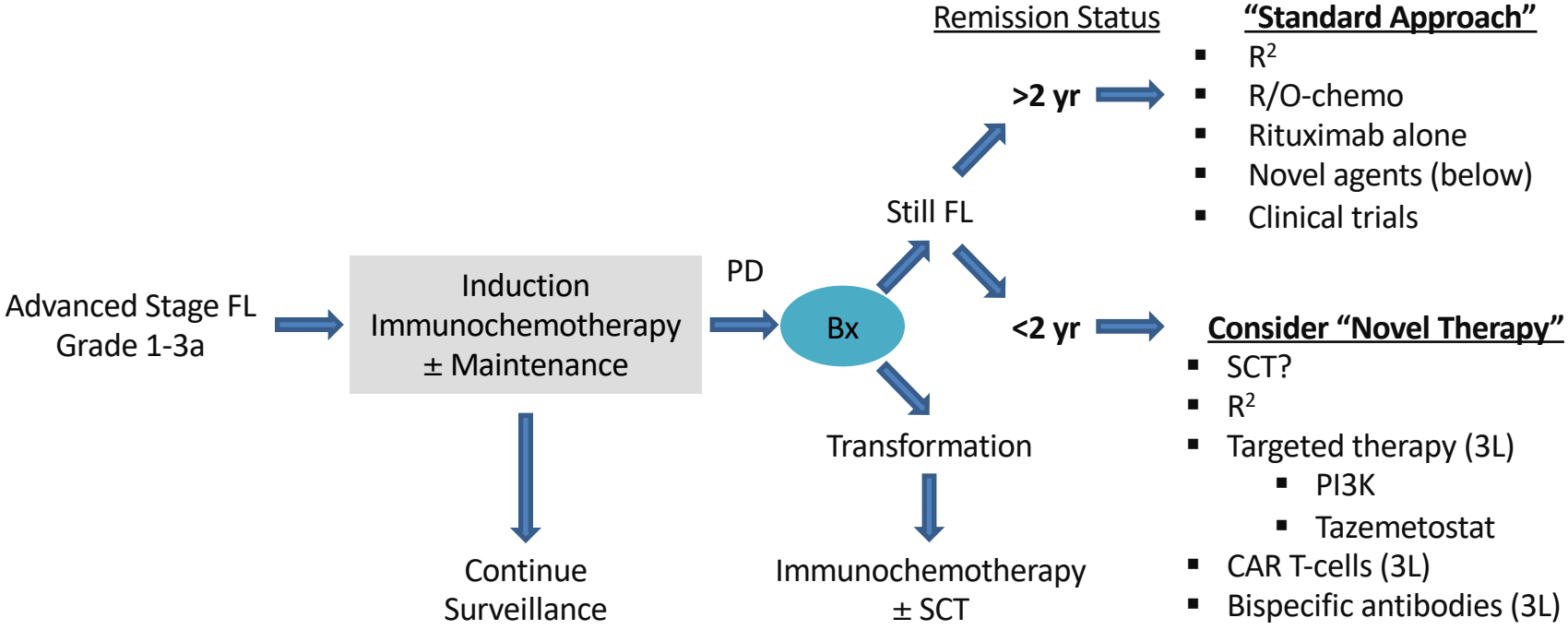

N F
Control 202 151
Zevalin 207 119
Zevalin (n = 207)
Median PFS = 4.1 y
8-y PFS = 41%
Control (n = 202)
Median PFS = 1.1 y
8-y PFS = 22%
Hazard ratio, 0.47
95% CI, 0.37 to 0.60
P<.001
Cumulative Percentage
100
75
50
25
0
2
4
6
8
Time (years)
No. at risk
Control 202 81 62 48 16
Zevalin 207 132 98 89 24

Common Genetic Alterations in Follicular Lymphoma



Huet. Nat Rev Cancer. 2018;18:224.

Treatment of Follicular Lymphoma



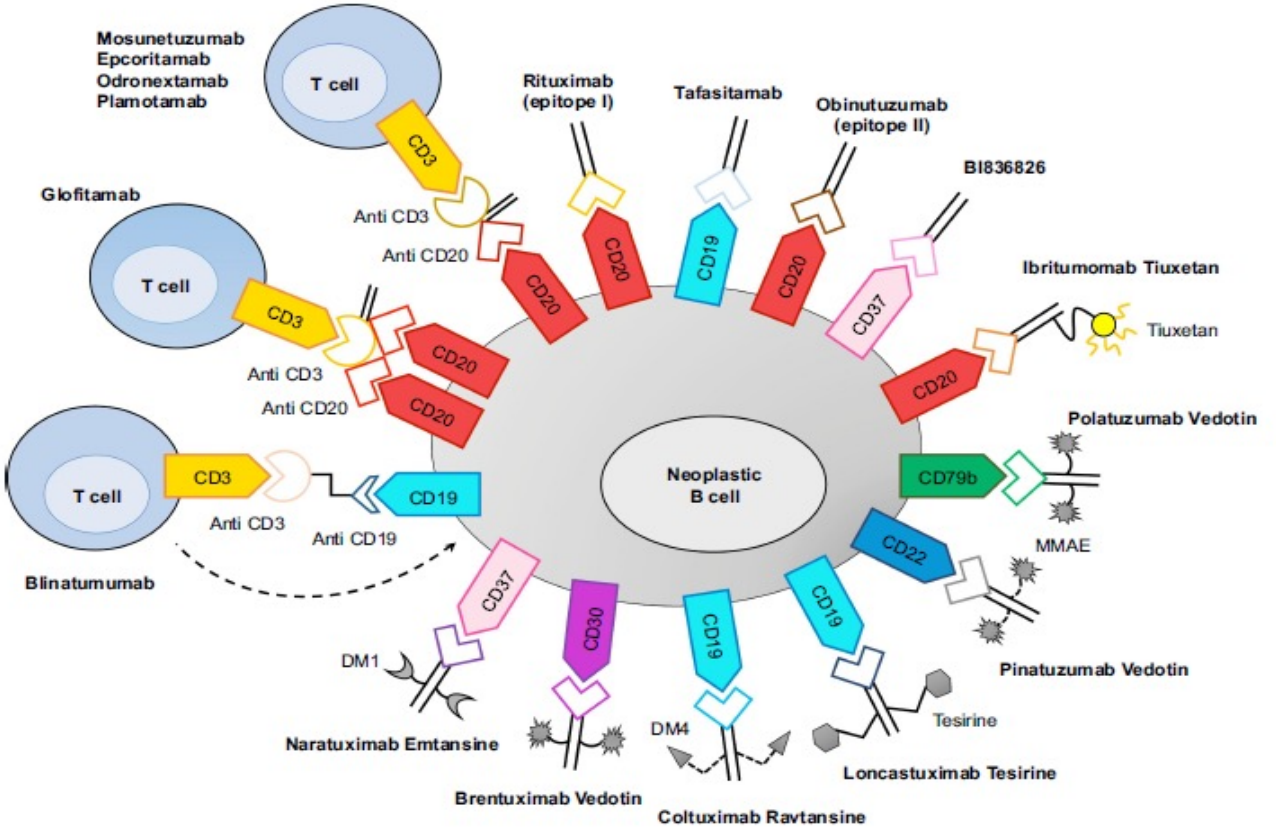


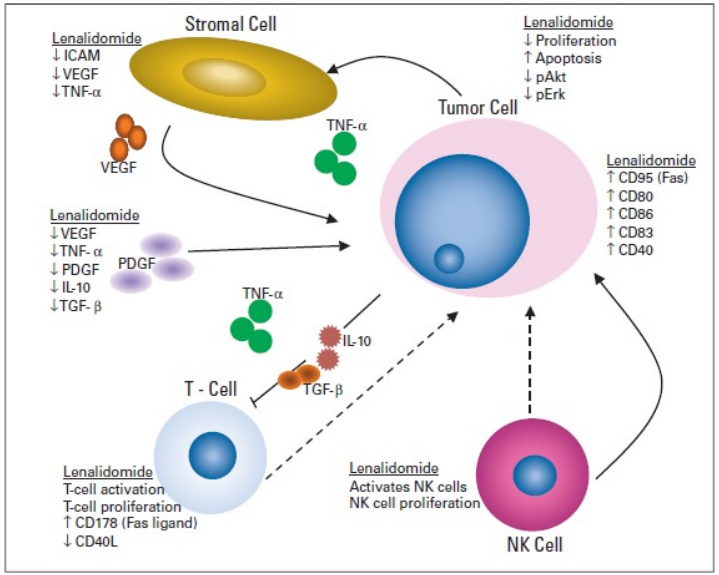
Figure 1 Monoclonal antibodies, including naked antibodies, antibody–drug conjugates, radioimmunoconjugates, and bispecific antibodies, are able to target Bcells on different surface antigens and with a number of cytotoxic mechanisms of action.

Immunomodulatory drug

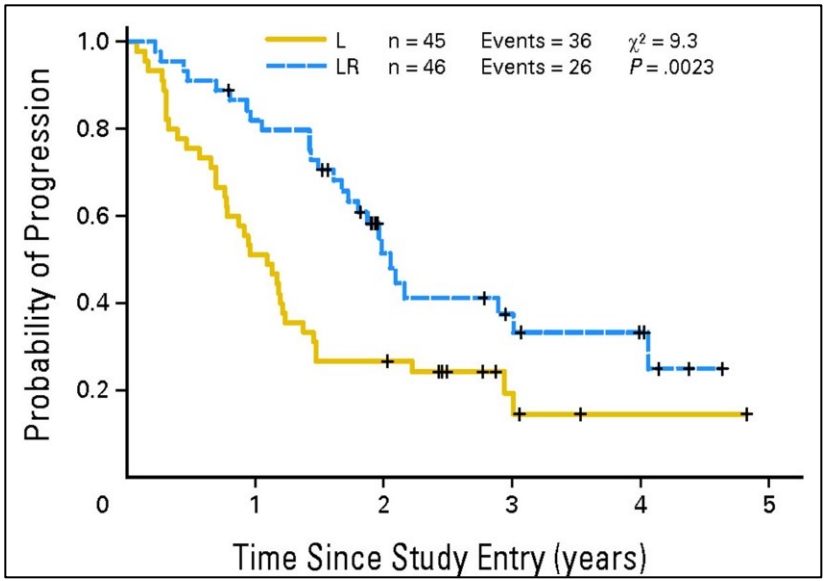
- lenalidomide

Lenalidomide is a member of the IMiD class of agents, has a pleiotropic mechanism of action, and works in synergy with rituximab in follicular lymphoma (R^2)

Action of lenalidomide[1]



Time to progression[2]



Erk, extracellular signal regulated kinase; L, lenalidomide; LR, lenalidomide and rituximab; NK, natural killer; pAkt, phosphorylated pErk, phosphorylated Erk.

1. Chiappella A, Vitolo U. Adv Hemat. 2012;12:498342. 2. Leonard JP, et al. J Clin Oncol. 2015;33:3635-40.

AUGMENT: R^2 vs Rituximab Monotherapy in R/R iNHL

» Multicenter, placebo-controlled, randomized phase III trial

Stratified by prior rituximab (yes vs no), time since last therapy (≤ vs >2 yr), histology (FL vs MZL)

Adult patients with R/R grade 1-3a FL or MZL; ≥1 prior chemo/immunotherapy; not rituximab refractory (N = 358)

Rituximab 375 mg/m^2 + **Lenalidomide** 20 mg/day* (n = 178[†])

Rituximab 375 mg/m^2 + **Placebo (PBO)** (n = 180[‡])

R- Lena:
[†]FL, n = 147
MZL, n = 31

R-PBO:
[‡]FL, n = 148
MZL, n = 32

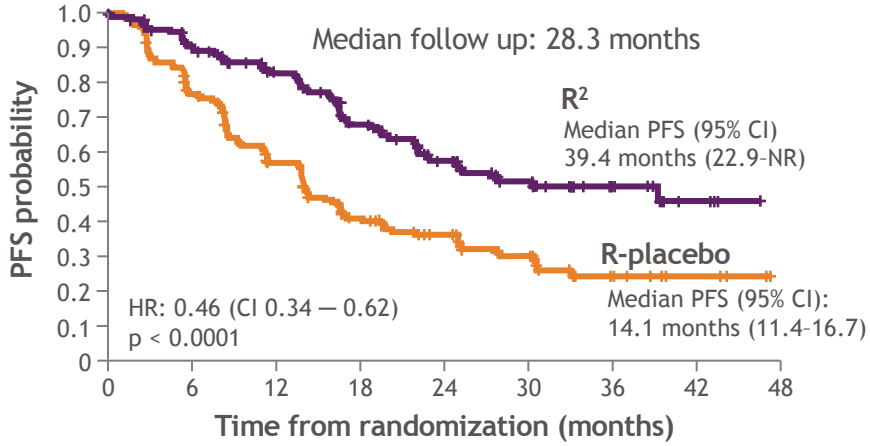
≤12 cycles or until PD, relapse, or intolerability; 5-yr follow-up for OS, SPMs, subsequent treatment, and histologic transformations

Rituximab: Days 1, 8, 15, 22 of cycle 1; Day 1 of cycles 2-5. Lenalidomide: Days 1-21 of 28.
*10 mg/day if CrCl 30-59 mL/min.

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

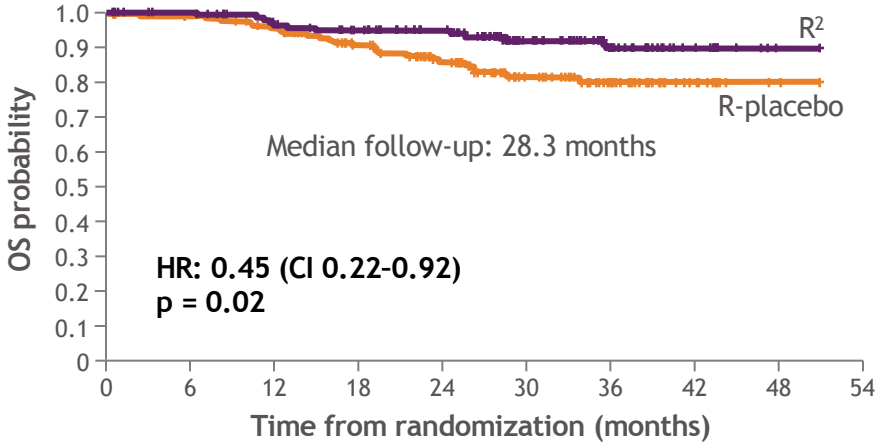
AUGMENT: PFS and OS advantage for R² in relapsed/refractory follicular lymphoma

PFS (ITT, IRC)



Number at risk									
R²	178	148	124	91	59	39	20	7	0
R-placebo	180	132	92	58	40	26	10	4	0

OS (patients with FL)



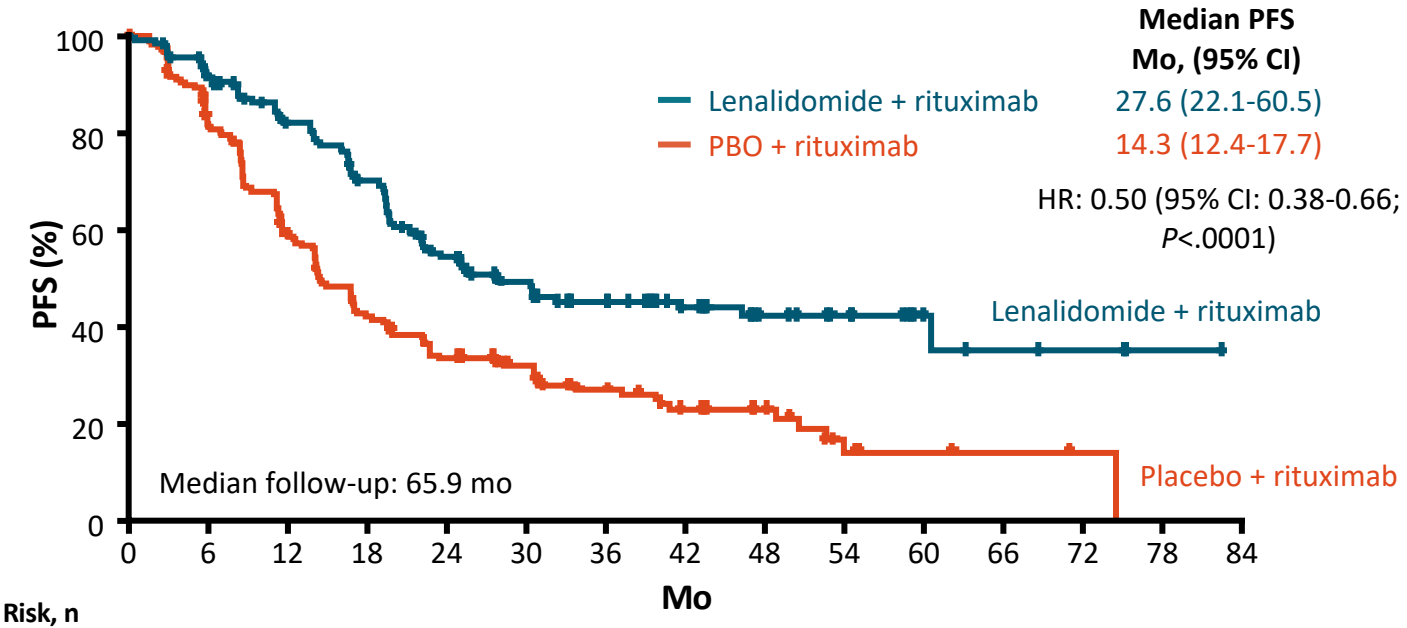
Number at risk										
R²	147	142	130	121	105	70	39	13	1	0
R-placebo	148	145	137	117	94	64	35	12	2	0

- 41 total deaths (15 with R²; 26 with R-placebo) in treated patients
- 2-year OS (95% CI) was 95% (90-98) for R² and 86% (79-91) for R-placebo

Data cutoff June 22, 2018. ITT, intention to treat; NR, not reached; R-placebo, R plus placebo.

Leonard JP, et al. J Clin Oncol. 2019

AUGMENT: 5-Yr PFS (ASH 2022)



Patients at Risk, n														
Lenalidomide + rituximab	178	151	128	107	79	62	49	34	18	13	6	4	3	1	0
PBO + rituximab	180	141	98	69	53	41	29	21	13	5	3	2	1	0	0

Leonard. ASH 2022. Abstr 230.

AUGMENT: 5-Yr Safety (ASH 2022)

TEAE, n (%)	Lenalidomide + Rituximab (n = 176)	PBO + Rituximab (n = 180)
Any grade	174 (99)	173 (96)
▪Related to lenalidomide or PBO	159 (90)	118 (66)
▪Related to rituximab	134 (76)	105 (58)
Grade 3/4	121 (69)	58 (32)
▪Related to lenalidomide or PBO	101 (57)	38 (21)
▪Related to rituximab	57 (32)	20 (11)

- Most common grade 3/4 TEAE was neutropenia:

  50% with lenalidomide + rituximab vs 13% with PBO + rituximab

- No new safety signals detected in updated safety analysis as compared to primary analysis including no increase in secondary malignancies

Leonard. ASH 2022. Abstr 230.

BTK Inhibitor

- zanubrutinib

ROSEWOOD: Next-Generation BTK Inhibitor Zanubrutinib With Obinutuzumab in R/R FL

» Global, randomized, open-label phase II trial

Stratification by geographic region, number of prior lines, rituximab refractory status

Adults with grade 1-3a R/R FL **previously treated with ≥2 prior regimens,** including an anti-CD20 antibody and appropriate alkylator-based combination therapy; no prior BTK inhibitor; ECOG PS 0-2
(N = 217)

2:1

Zanubrutinib + Obinutuzumab*
(n = 145)

Obinutuzumab*
(n = 72)

Treated until disease progression or unacceptable toxicity†

*Zanubrutinib dosed at 160 mg PO BID. Obinutuzumab dosed at 1000 mg IV on Days 1,8,15 of cycle 1 and Day 1 of cycles 2-6, then Q8W to ≥20 doses.
†Patients assigned to obinutuzumab with centrally confirmed PD or no response at 12 mo could crossover to receive combination therapy.

- **Primary endpoint:** IRC-assessed ORR according to Lugano classification
- **Key secondary endpoints:** investigator-assessed ORR, CR, DoR, PFS, OS, safety

Zinzani. ASCO 2022. Abstr 7510.

ROSEWOOD: Response

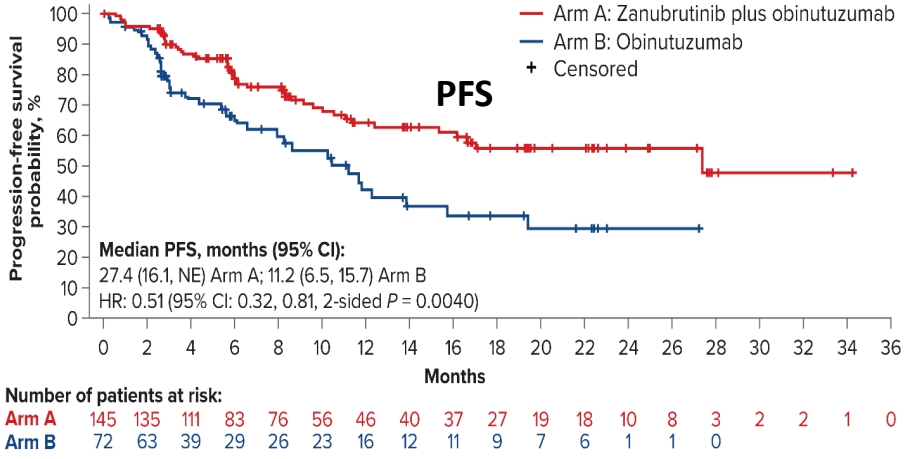
Response by ICR	Zanubrutinib + Obinutuzumab (n = 145)	Obinutuzumab (n = 72)	*P* Value
ORR, %	68.3	45.8	.0017
Best overall response, n (%)			
CR	54 (37.2)	14 (19.4)	.0083
PR	45 (31.0)	19 (26.4)	--
SD	25 (17.2)	14 (19.4)	--
Nonprogressive disease	3 (2.1)	4 (5.6)	--
PD	13 (9.0)	15 (20.8)	--
D/c prior to first assessment	4 (2.8)	6 (8.3)	--
NE	1 (0.7)	0 (0)	--

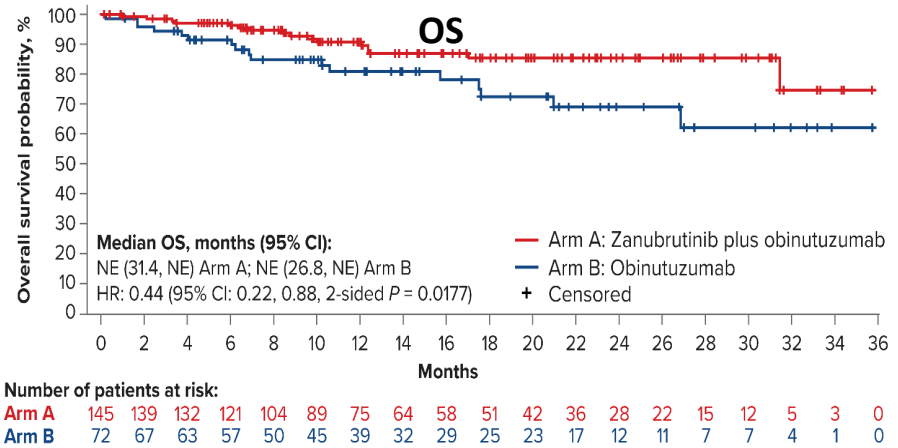
Median follow-up: 12.5 mo.

- Combination with improved ORR vs obinutuzumab across most patient subgroups, except in patients with bulky disease
- **29 patients in the obinutuzumab arm crossed over** to receive zanubrutinib and obinutuzumab, with 7 patients (24.1%) achieving an objective response, including 2 patients with CR

Zinzani. ASCO 2022. Abstr 7510.

ROSEWOOD: PFS and OS





Ongoing phase III MAHOGANY trial is evaluating
zanubrutinib + obinutuzumab vs R^2 in patients with R/R FL
after ≥1 line of systemic therapy including an anti-CD20 mAb (NCT

Zinzani. ASCO 2022. Abstr 7510.

Anti CD19

- tafasitamab

InMIND: Tafasitamab + R^2 vs R^2 Alone in R/R FL or MZL

» Global, double-blind, placebo-controlled, randomized phase III trial

– Tafasitamab: Fc-engineered humanized **anti-CD19 mAb**

FL: POD24 (yes vs no), refractory to anti-CD20 tx (yes vs no), prior lines tx (<2 vs ≥2)
MZL: prior lines tx (<2 vs ≥2)

Adults with R/R
FL (grade 1-3a)
or MZL
previously treated with
≥1 anti-CD20 mAb;
no prior R^2;
ECOG PS 0-2
(Planned N = 618;
FL, 528; MZL, 60-90)

Tafasitamab 12 mg/kg IV* +
Rituximab†/Lenalidomide‡

Placebo IV§ +
Rituximab†/Lenalidomide‡

12 cycles

5-yr follow-up

***Tafasitamab given Days 1, 8, 15, 22 of cycles 1-3 and Days 1, 15 of cycles 4-12 on 28-day cycle.**

†Rituximab dosed at 375 mg/m^2 IV; given on Days 1, 8, 15, 22 of cycle 1, then Day 1 of cycles 2-5.

‡**Lenalidomide dosed at 20 mg PO QD given on Days 1-21 for 12 cycles**. §Placebo given as 0.9% saline solution IV.

- **Primary endpoint:** PFS by investigator per Lugano 2014 criteria in FL population
- **Key secondary endpoints:** PFS in overall population, PET/CR at EOT and OS in FL popu[redacted]

Sehn. ASCO 2022. Abstr TPS7583. NCT04680052.

Epigenetic Modifiers

- Tazemetostat

Phase II Study: Tazemetostat in R/R FL

- Open label, multicohort, **single-arm phase II study**

SCREENING: *Central testing of archival tissue for* EZH2 *hot spot activating mutations*

Adults with **R/R FL (grade 1-3b)**
with measurable disease per IWG-NHL
following ≥2 prior systemic treatments
(including ≥1 anti-CD20–based regimen);
transformed FL allowed;
tumor tissue for *EZH2* mutation testing;
life expectancy ≥3 mo; ECOG PS 0-2
(N = 99)

Cohorts

Mutant *EZH2*
(n = 45)

Wild-type *EZH2*
(n = 54)

Tazemetostat 800 mg BID

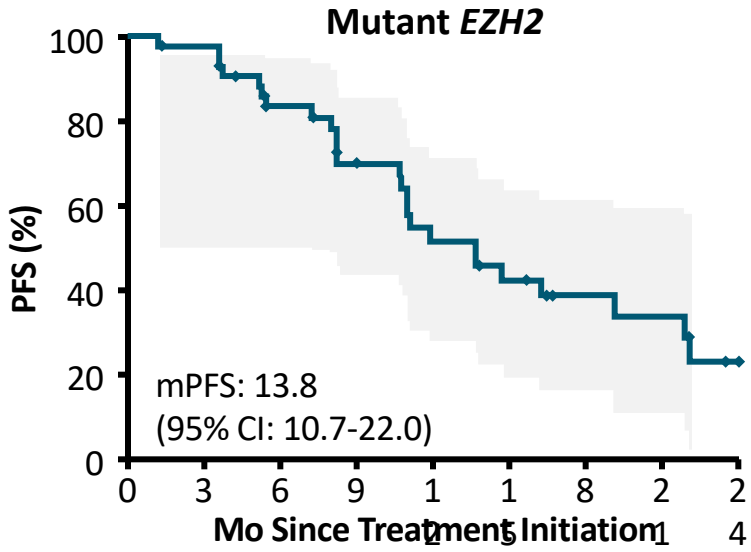
Response assessment by 2007 IWG-NHL criteria Q8W.

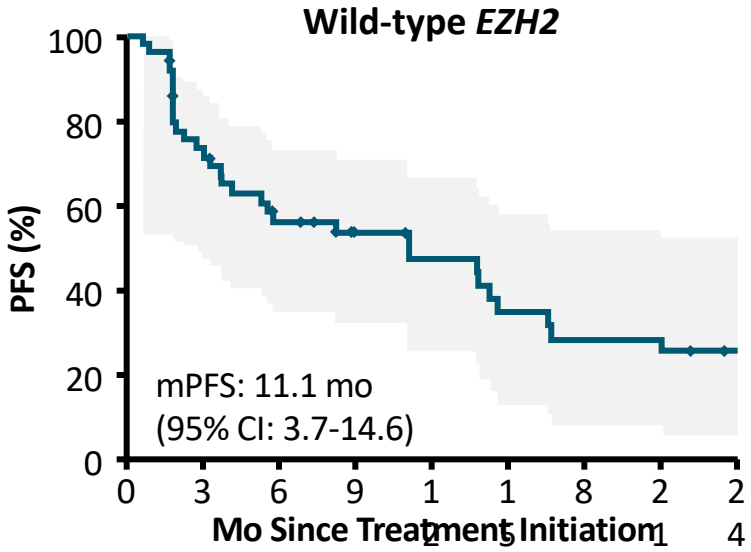
Treatment continues until PD or withdrawal

- **Primary endpoint:** ORR; Results: **69% (EZH2 mut); 35% (EZH2 W-T)**
- **Secondary endpoints:** DoR, PFS, safety/tolerability

Morschhauser. Lancet Oncol. 2020;21:1433

Phase II Study: PFS by IRC





- Approved by FDA for adults with *EZH2*mut+ R/R FL after ≥2 prior systemic therapies or any adult with R/R FL without alternative treatment options

Morschhauser. Lancet Oncol. 2020;21:1433. Tazemetostat PI.

SYMPHONY-1 Phase Ib: Tazemetostat + R^2 in R/R FL

- Phase Ib safety run-in analysis (stage 1) of international, randomized, double-blind phase Ib/III trial (median follow-up: 11.2 mo)
  - Stage 2: phase III design comparing tazemetostat at RP3D + R^2 vs placebo + R^2 in patients with R/R FL
  - Stage 3 (to be executed if stage 2 futility analysis finds that efficacy fails in overall population but is promising for *EZH2*-mutated subpopulation): in patients with *EZH2*-mutated R/R FL

Adults with **R/R FL grades 1-3A**; tumor tissue for *EZH2* mut testing; ≥1 prior systemic CT, IO, or CIT; prior HSCT, CAR T-cell tx permitted; no prior lenalidomide, tazemetostat, or other EZH2 inhibitor; measurable disease per Lugano; ECOG PS 0-2
(N = 44)

→

Phase Ib: Dose Escalation (3 + 3 Design)

Tazemetostat 400/600/800 mg BID x 28-d cycles +
Rituximab 375 mg/m^2 IV on D1,8,15,22 of cycle 1, then D1 of cycles 2-5 +
Lenalidomide 20 mg* PO QD on D1-21 of 28-d cycles x 12

*10 mg if CrCl <60 mL/min.

- **Primary endpoints:** safety/tolerability, tazemetostat RP3D
- **Secondary endpoint:** safety PK parameters

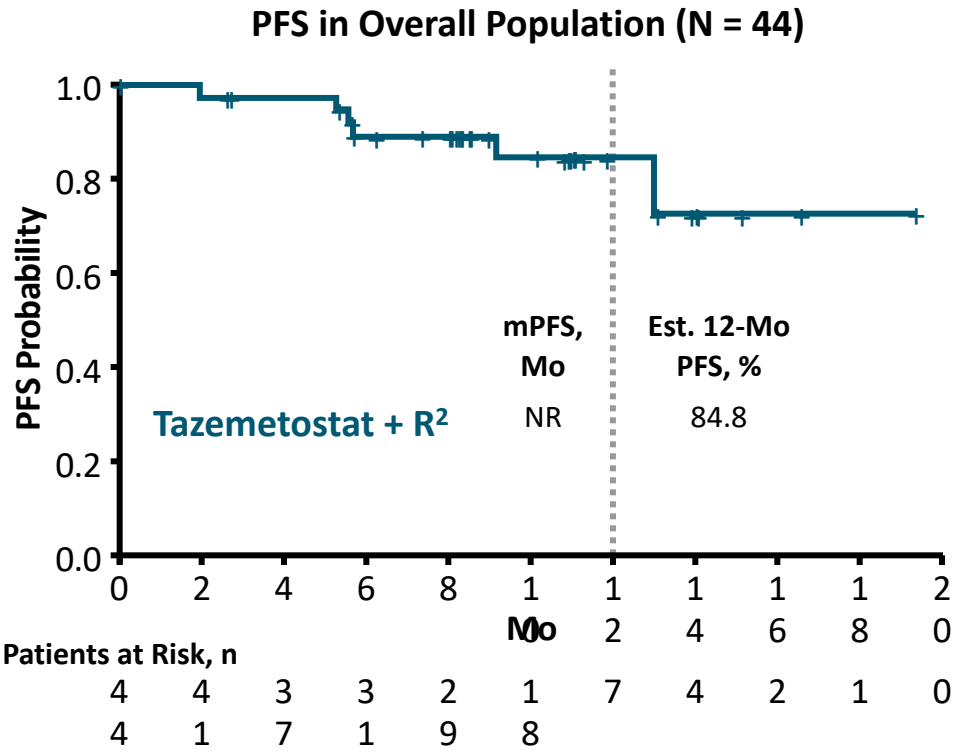
Batlevi. ASH 2022. Abstr 954. NCT04224493.

SYMPHONY-1 Phase Ib: Efficacy in Overall Population

Response	Tazemetostat + R² (n = 41)
ORR, n (%)	40 (97.6)
▪ CR	21 (51.2)
▪ PR	19 (46.3)
▪ SD	1 (2.4)
Median DoR, mo	NR

At data cutoff (June 14, 2022):

- 56.8% (25/44): treatment ongoing
- 6.8% (3/44): PD



Batlevi. ASH 2022. Abstr 954.

Conclusions: Tazemetostat

- Single-agent tazemetostat active in patients with R/R FL
  - ORR greater in patients with *EZH2* mutation
- Combination of tazemetostat with R^2 was generally well tolerated and demonstrated preliminary antitumor activity in patients with R/R FL
  - RP3D identified as 800 mg BID
  - **ORR in overall population was 97.6%** and ranged from 96.2% to 100% across subgroups (including *EZH2* mutation status, rituximab sensitivity, POD24)
  - Median DoR not reached
- Randomized phase III portion of SYMPHONY-1 will compare tazemetostat 800 mg BID + R^2 vs PBO + R^2 in pts with R/R FL after ≥1 prior therapy

PI3K Inhibitors

PI3K Inhibitors: Established Agents

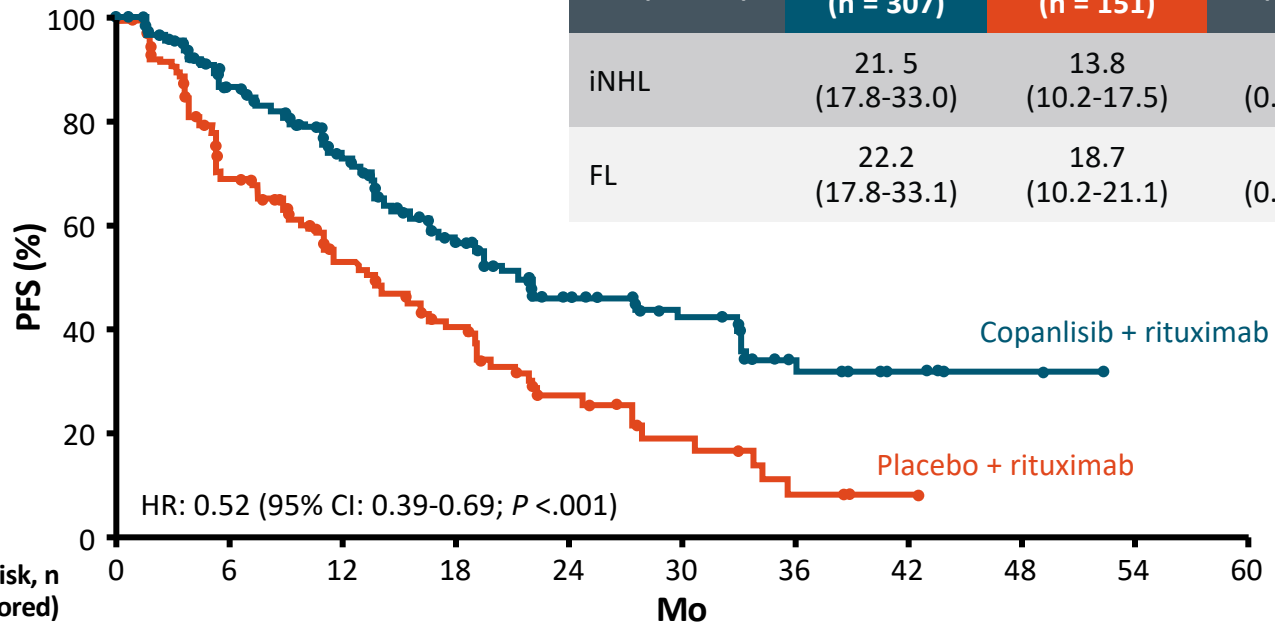
Agent	~~Idelalisib~~[1]	~~Duvelisib~~[2]	Copanlisib[3,4]
Isoform target	Delta	Delta, gamma	Alpha, delta
Trial	Phase II DELTA	Phase II DYNAMO	Phase II CHRONOS-1
Population (N)	iNHL with relapse ≤6 mo or refractory to R and alkylating agent (125 iNHL*)	iNHL with relapse ≤6 mo or refractory to R and either CT or RIT (129 iNHL‡/83 FL)	iNHL with relapse after or refractory to R and alkylating agent (142 iNHL†/104 FL)
Approval (yr)	≥2 prior therapies (2014)	≥2 prior therapies (2018)	≥2 prior therapies (2017)
ORR, n (%) ▪CR, n (%)	71 (57) 7 (6)	61 (47)/35 (42) 2 (2)/1 (1)	86 (61)/61 (59) 24 (17)/21 (20)
Median PFS, mo	11	9.5	12.5
Median OS, mo	20.3	28.9	42.6
Grade ≥3 AEs	Diarrhea (13%), elevated ALT (13%), elevated AST (8%)	Diarrhea (15%), pneumonia (5%), fatigue (5%), elevated ALT (5.4%), elevated AST (3.1%)	Hyperglycemia (40%), pneumonia (11%), diarrhea (8.5%), elevated ALT (0.7%) **31% discontinuation**

*Including FL, n = 72; SLL, n = 28; MZL, n = 15; LPL/WM, n = 10. †Including FL, n = 104; MZL, n = 23; SLL, n = 8; LPL/WM, n = 6; DLBCL, n = 1 (originally assessed as iNHL).
‡Including FL, n = 83, SLL, n = 28; MZL, n = 18.

1. Gopal. NEJM. 2014;370:1008. 2. Flinn. JCO. 2019;37:912. 3. Dreyling. JCO. 2017;35:3898. 4. Dreyling. Am J Hematol. 2020;95:362.

CHRONOS-3: PFS

Median PFS, Mo (95% CI)	Copanlisib + Rituximab (n = 307)	Placebo + Rituximab (n = 151)	HR (95% CI)	1-Sided *P* Value
iNHL	21. 5 (17.8-33.0)	13.8 (10.2-17.5)	0.52 (0.39-0.69)	<.0001
FL	22.2 (17.8-33.1)	18.7 (10.2-21.1)	0.58 (0.40-0.83)	.001

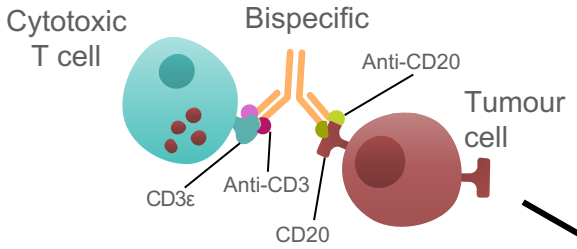


Patients at Risk, n (number censored)											
Copanlisib + rituximab	307 (0)	204 (67)	146 (97)	88 (125)	49 (149)	31 (164)	15 (175)	6 (183)	2 (187)	0 (189)	0 (189)
Placebo + rituximab	151 (0)	85 (26)	53 (41)	33 (49)	16 (56)	8 (60)	3 (61)	1 (63)	0 (64)	0 (64)	0 (64)

Matasar. Lancet Oncol. 2021;22:678.

Bispecific Antibodies

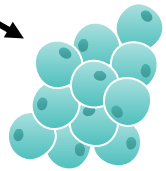
Mode of action of anti-CD20/CD3 bispecific antibodies



1. Local secretion of chemokines leading to the recruitment of T cells from the periphery

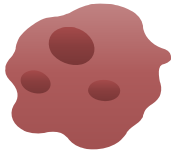
Anti-CD20/CD3 bispecifics redirect endogenous non-specific T cells to engage and eliminate malignant B cells in NHL[1–3]

2. T cells undergo proliferation and expansion at the tumour site



3. T-cell activation occurs via downstream signalling events leading to the secretion of cytotoxic granules

5. Apoptosis



4. Potent lysis of tumour cells

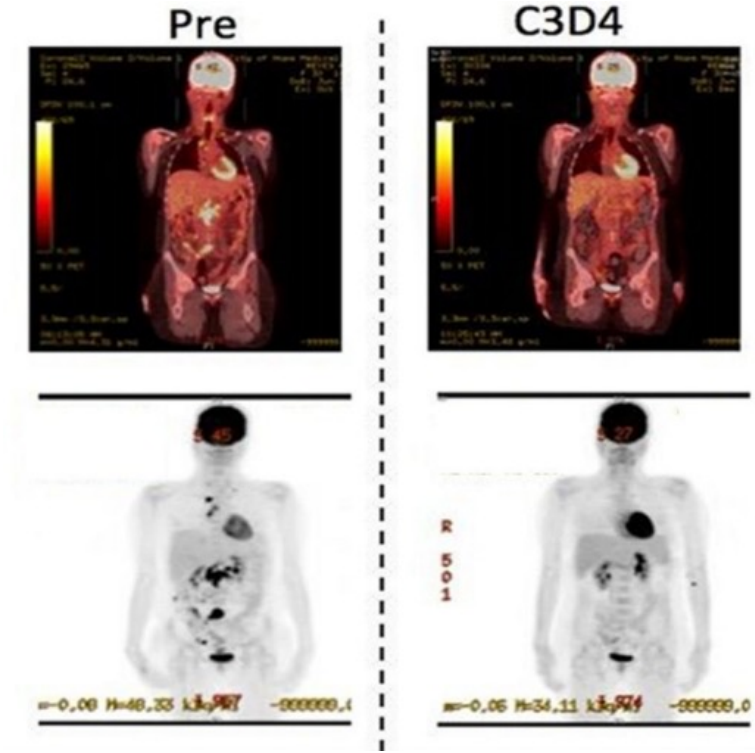
6. T cell–mediated tumour killing

» NHL, non-Hodgkin lymphoma

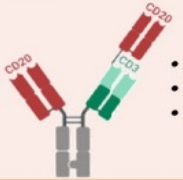
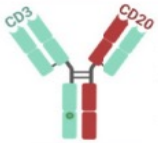
» 1. Sun LL, et al. Sci Transl Med 2015;7:287ra70;
2. Dieckmann NM, et al. J Cell Science 2016;129:2:2881–6
3. Bacac M, et al. Clin Cancer Res 2018;24:4785–97 Adapted from Aldoss I, et al. Leukemia 2017;31:777–87

Novel Agents for DLBCL: Bispecific Antibodies

CR in a CAR-T-refractory patient with DLBCL



The bispecific antibody panorama

Bi-Specific Antibody	Targets	Design	Ig Fragment Formats
blinatumomab	CD19 x CD3		• two murine scFv joined by a glycine-serine linker • monovalent CD19 and monovalent CD3 binding • cloned from anti-CD19 (clone HD37) and anti-CD3 (clone L2K-07) murine mAbs
mosunetuzumab	CD20 x CD3		• humanized mouse heterodimeric IgG1-based antibody • monovalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding
glofitamab	$(CD20)_2$ x CD3		• humanized mouse IgG1-based antibody • bivalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding
odronextamab	CD20 x CD3		• fully human IgG4-based heterodimeric antibody • monovalent CD20 and monovalent CD3ε binding • Fc-dependent effector function-minimized antibody with Fc of the anti-CD3ε heavy chain modified to reduce Protein A binding • common κ light chain from anti-CD3ε mAb
epcoritamab	CD20 x CD3		• humanized mouse IgG1-based heterodimeric antibody • monovalent CD20 and monovalent CD3 binding • IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield

Bispecific Antibodies

- mosunetuzumab

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

Pivotal, single-arm, multicenter, phase II expansion in patients with R/R FL and ≥2 prior therapies[1]

Key inclusion criteria

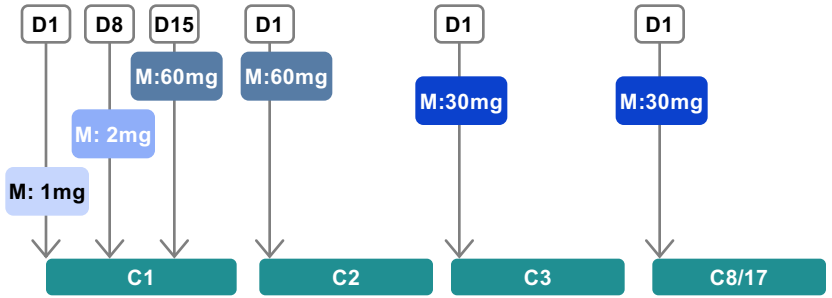
- FL grade 1–3A
- ECOG PS 0–1
- **≥2 prior therapies including an anti-CD20 antibody and an alkylator**

Data analysis

- Study met its primary endpoint: **60% CR rate versus 14% historical control** (p <0.0001) [2,3]
- Updated efficacy and safety analysis with median **28.3 months of follow-up** (10 months after the previous report)

Mosunetuzumab administration

- IV mosunetuzumab administered in 21-day cycles with step-up dosing in C1
- Fixed-duration treatment:
  - **8 cycles if CR after C8;**
  - **17 cycles if PR/SD after C8**
- Re-treatment with mosunetuzumab permitted at relapse for patients who achieved CR
- No mandatory hospitalization



1. Bartlett NL, et al. ASH 2022. Abstract 610;
2. Dreyling M, et al. J Clin Oncol 2017;35:3898–3905;
3. Budde LE, et al. Lancet Oncol 2022;23:1055–1065

Baseline characteristics and response

	N=90
Median age, years (range)	60 (29–90)
Male	61%
Ann Arbor stage I/II III/IV	 23% 77%
Median lines of prior therapy, n (range)	3 (2–10)
Refractory to last prior therapy	69%
Refractory to any prior anti-CD20 therapy	79%
Progression of disease within 24 months from start of first-line therapy (POD24)	52%
Double refractory to prior anti-CD20 and alkylator therapy	53%
Prior autologous stem cell transplant	21%

Efficacy endpoint in the overall population by investigator assessment	% (95% CI)
ORR	**78%** (68–86)
CR	**60%** (49–70)

Time to first response (median [range]): **1.4 months**

(1.0–11)

Time to first CR (median [range]): **3.0 months**

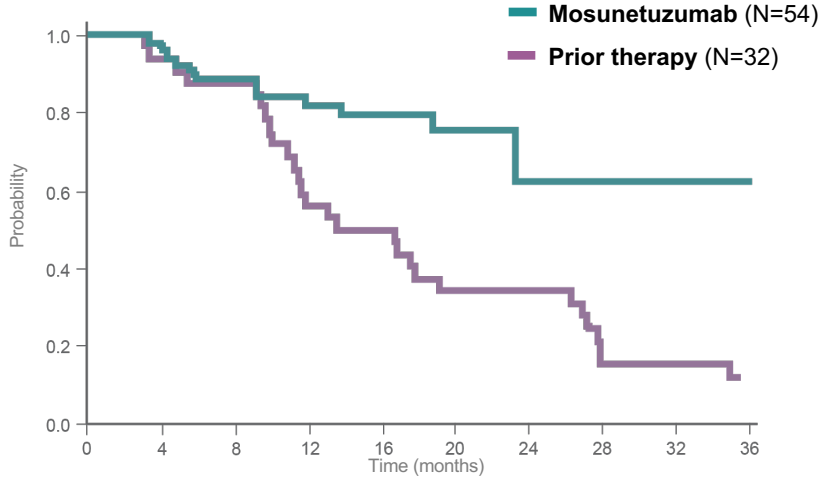
ORR: objective response rate

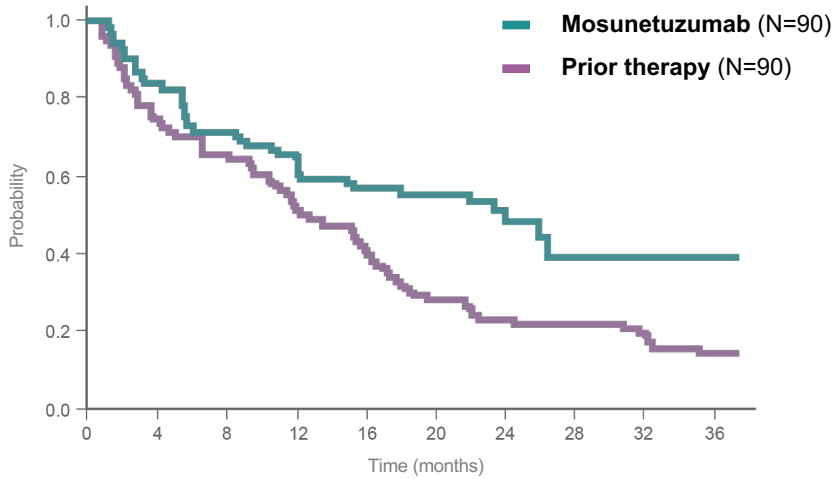
Mod. da: Bartlett NL, et al. ASH 2022. Abstract 610

DOCR

PFS

DOCR and PFS with mosunetuzumab versus last prior therapy





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

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

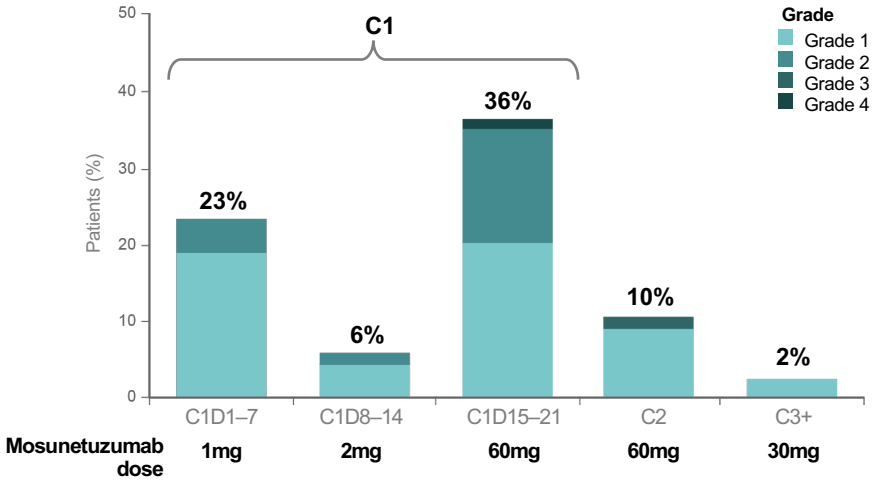
Extended DOCR and 12-month improvement in median PFS with mosunetuzumab compared with last prior therapy

Mod. da: Bartlett NL, et al. ASH 2022. Abstract 610

CRS summary

CRS by ASTCT criteria[1]	N=90
CRS (any grade)	44%
Grade 1	26%
Grade 2	17%
Grade 3	1%
Grade 4	1%
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–24)
C1D15	27 (0.1–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	11%
Tocilizumab for CRS management	8%
Events resolved	100%

CRS BY CYCLE AND GRADE



All CRS events resolved; no new events were reported with 10 months of additional follow-up
No correlation observed between the occurrence of CRS and tumor

[1]*As per Lee DW, et al. Biol Blood Marrow Transplant 2019; 25: 625–638*
ASTCT: American Society for Transplantation and Cellular Therapy

Mod. da: Bartlett NL, et al. ASH 2022. Abstract 610

Anticorpi BISPECIFICI

- epcoritamab

EPCORE NHL-2: study design

- Multicenter, open-label phase Ib/II trial (current analysis reported data from arm 6 and arm 2b)

Median follow-up: 8.1 months (1.4+ to 10.7)[1]

Patients with untreated CD20+ FL; grade 1–3A; treatment needed based on symptoms or disease burden per GELF criteria; measurable disease by CT/MRI; adequate organ function; ECOG PS 0–2 (N=41)

→

Arm 6:
Epcoritamab 48 mg SC* QW for C1-2, Q4W for C3+ up to 2 years
+
R² for C1–12†

→

- **Primary endpoints:** antitumor activity (ORR), safety
- **Key secondary endpoint:** DOR

Median follow-up: 6.4 months[2]

Patients with R/R CD20+ FL; grade 1–3A; stage II–IV; treatment needed based on symptoms or disease burden per GELF criteria; measurable disease by CT/MRI; adequate organ function; ECOG PS 0–2 (N=76)

→

Arm 2b
Epcoritamab 48 mg SC* QW for C1-2, Q4W for C3+ up to 2 years
+
R² for C1–12†

→

- **Primary endpoints:** safety, antitumor activity

**Epcoritamab administered in 28-day cycles, with step-up dosing comprising priming and intermediate doses prior to first full dose, along with corticosteroid as CRS prophylaxis. †Rituximab 375 mg/m² IV QW for C1, Q4W for C2–6 (arm 6) or C2–5 (arm 2b); lenalidomide 20 mg PO QD x 21 days for C1–12.*
GELF: Groupe d'Etude des Lymphomes Folliculaires

Mod. da: 1. Falchi L, et al. ASH 2022. Abstract n. 611; 2. Falchi L, et al. ASH 2022. Abstract n. 609.

EPCORE NHL-2: baseline characteristics

Characteristic		1L FL[1] (N=41)	R/R FL[2] (N=76)
Median age, yr (range)		57 (39–78)	64 (30–79)
Female, N (%)		20 (49)	37 (49)
Median time from dx to first dose, weeks (range)		12 (2–352)	--
Ann Arbor stage, N (%)	I-II*	3 (7)	12 (16)
	III	16 (39)	19 (25)
	IV	22 (54)	45 (59)
Histologic grade, N (%)	1	5 (12)	6 (8)
	2	29 (71)	37 (49)
	3A	7 (17)	24 (32)
FLIPI, N (%)†	0-1	10 (24)	7 (9)
	2	14 (34)	24 (32)
	3–5	14 (34)	39 (51)
ECOG PS, N (%)	0	34 (83)	48 (63)
	1	6 (15)	25 (33)
	2	1 (2)	3 (4)

Characteristic	R/R FL[2] (N=76)
Median time from dx to first dose, months (range)	59 (4–331)
Median time from end of last line of tx to first dose, months (range)	16 (0.2–198)
Median no. prior lines of tx, n (range)	1 (1–9)
• 1 prior line, N (%)	41 (54)
• 2 prior lines, N (%)	21 (28)
• ≥3 prior lines, N (%)	14 (18)
Primary refractory‡ disease, N (%)	29 (38)
Double refractory§ disease, N (%)	30 (39)
POD24,‖ N (%)	32 (42)
Refractory‡ to last line of tx, N (%)	29 (38)
Prior ASCT, N (%)	8 (11)
Prior CAR-T-cell therapy, N (%)	2 (3)

*For R/R arm 2b, all patients stage II. †Unknown for 3 and 6 patients in 1L and R/R FL arms, respectively. ‡No response or relapse within 6 months after prior therapy. §Refractory to both anti-CD20 and an alkylating agent ‖Progression within 2 years of initiating first-line treatment including immunochemotherapy. Dx: diagnosis; tx: treatment

Mod. da: 1. Falchi L, et al. ASH 2022. Abstract n. 611; 2. Falchi L, et al. ASH 2022. Abstract n. 609.

EPCORE NHL-2: CRS events

CRS outcome, N (%)	1L FL[1] (N=41)	R/R FL[2] (N=76)
CRS • Grade 1 • Grade 2	22 (54) 16 (39) 6 (15)	33 (43) 25 (33) 8 (11)
Median time to onset after first full dose, days (range)	3 (1–6)	2 (1–9)
CRS resolution	22 (100)	33 (100)
Median time to resolution, days (range)	4 (1–10)	2 (1–23)
CRS leading to tx d/c	0	0
Tocilizumab use	4 (10)	8 (11)

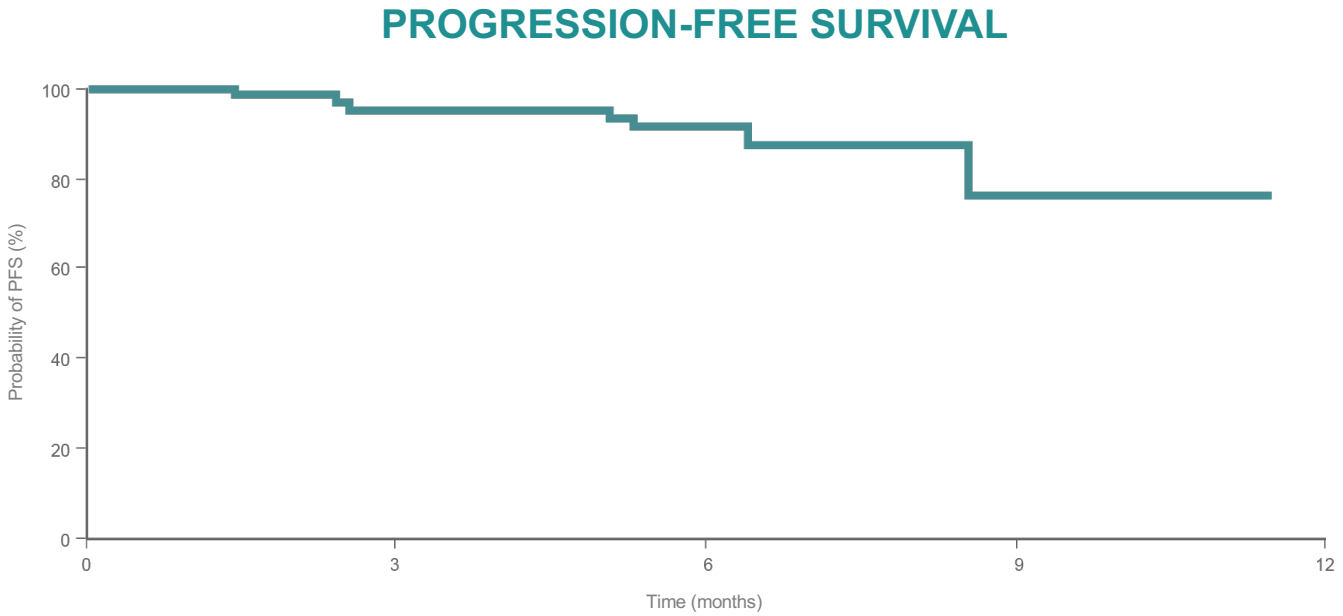
CRS events by dosing period, %	1L FL[1] (N=41)		R/R FL[2] (N=76)	
	Gr 1	Gr 2	Gr 1	Gr 2
Priming C1D1	5	0	3	3
Intermediate C1D8	2	0	0	0
First full C1D15	32	15	32	9
Second full C1D22	3	0	1	0
Third full+ C2D1+	10	0	3	0

- No grade ≥3 CRS events were observed
- CRS timing was predictable; most cases occurred following first full dose

Tx d/c: treatment discontinuation

Mod. da: 1. Falchi L, et al. ASH 2022. Abstract n. 611; 2. Falchi L, et al. ASH 2022. Abstract n. 609.

EPCORE NHL-2: PFS in R/R FL



Median PFS not reached (95% CI, 8.5–not reached)

Data cutoff: October 31, 2022.
Median follow-up: 5.6 months (range, 1.2+ to 11.5+)

Mod. da: Falchi L. et al. ASH 2022. Abstract n. 609.

rapid communications

Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell–Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial

Martin Hutchings, PhD[1]; Franck Morschhauser, MD, PhD[2]; Gloria Iacoboni, MD[3,4]; Carmelo Carlo-Stella, MD[5]; Fritz C. Offner, MD, PhD[6]; Anna Sureda, MD, PhD[7]; Gilles Salles, MD[8]; Joaquín Martínez-Lopez, MD, PhD, MBA[9]; Michael Crump, MD[10]; Denise N. Thomas, MSc[11]; Peter N. Morcos, PharmD[11]; Cristiano Ferlini, MD[11]; Ann-Marie E. Bröske, PhD[12]; Anton Belousov, PhD[13]; Marina Bacac, PhD[13]; Natalie Dimier, PhD[14]; David J. Carlile, PhD[14]; Linda Lundberg, PhD[15]; David Perez-Callejo, MD, PhD[15]; Pablo Umaña, PhD[13]; Tom Moore, MD[12]; Martin Weisser, MD[12]; and Michael J. Dickinson, MBBS, DMedSci[16]

abstract

PURPOSE Glofitamab is a T-cell–engaging bispecific antibody possessing a novel 2:1 structure with bivalency for CD20 on B cells and monovalency for CD3 on T cells. This phase I study evaluated glofitamab in relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL). Data for single-agent glofitamab, with obinutuzumab pretreatment (*Gpt*) to reduce toxicity, are presented.

METHODS Seven days before the first dose of glofitamab (0.005-30 mg), all patients received 1,000 mg *Gpt*. Dose-escalation steps were determined using a Bayesian continuous reassessment method with overdose control. Primary end points were safety, pharmacokinetics, and the maximum tolerated dose of glofitamab.

RESULTS Following initial single-patient cohorts, 171 patients were treated within conventional multipatient cohorts and received at least one dose of glofitamab. This trial included heavily pretreated patients with R/R B-NHL; most were refractory to prior therapy (155; 90.6%) and had received a median of three prior therapies. One hundred and twenty-seven patients (74.3%) had diffuse large B-cell lymphoma, transformed follicular lymphoma, or other aggressive histology, and the remainder had indolent lymphoma subtypes. Five (2.9%) patients withdrew from treatment because of adverse events. Cytokine release syndrome occurred in 86 of 171 (50.3%) patients (grade 3 or 4: 3.5%); two (1.2%) patients experienced grade 3, transient immune effector cell–associated neurotoxicity syndrome-like symptoms. The overall response rate was 53.8% (complete response [CR], 36.8%) among all doses and 65.7% (CR, 57.1%) in those dosed at the recommended phase II dose. Of 63 patients with CR, 53 (84.1%) have ongoing CR with a maximum of 27.4 months observation.

CONCLUSION In patients with predominantly refractory, aggressive B-NHL, glofitamab showed favorable activity with frequent and durable CRs and a predictable and manageable safety profile.

J Clin Oncol 39:1959-1970. © 2021 by American Society of Clinical Oncology

TABLE 3. Summary of Efficacy Data in Patients Receiving Glofitamab by Dose Level and Histology as of August 3, 2020 (Primary Efficacy Population)

Response	All Histologies	aNHL[a]	DLBCL	trFL	FL (Gr 1-3A)
All cohorts, No.	171	127	73	29	44
Overall response rate[b]					
No. (%)	92 (53.8)	61 (48.0)	30 (41.4)	16 (55.2)	31 (70.5)
95% CI	46.0 to 61.4	39.1 to 57.1	29.7 to 53.2	35.7 to 73.6	54.8 to 83.2
CR					
No. (%)	63 (36.8)	42 (33.1)	21 (28.8)	10 (34.5)	21 (47.7)
95% CI	29.6 to 44.5	25.0 to 42.0	18.8 to 40.6	17.9 to 54.3	32.5 to 63.3
PR					
No. (%)	29 (17.0)	19 (15.0)	9 (12.3)	6 (20.7)	10 (22.7)
95% CI	11.7 to 23.4	9.3 to 22.4	5.8 to 22.1	8.0 to 39.7	11.5 to 37.8
≥ 10 mg cohorts, No.	98	69	38	14	29
Overall response rate[b]					
No. (%)	62 (63.3)	42 (60.9)	21 (55.3)	9 (64.3)	20 (69.0)
95% CI	52.9 to 72.8	48.4 to 72.4	38.3 to 71.4	35.1 to 87.2	49.2 to 84.7
CR					
No. (%)	51 (52.0)	34 (49.3)	16 (42.1)	9 (64.3)	17 (58.6)
95% CI	41.7 to 62.2	37.0 to 61.6	26.3 to 59.2	35.1 to 87.2	38.9 to 76.5
PR					
No. (%)	11 (11.2)	8 (11.6)	5 (13.2)	0	3 (10.3)
95% CI	5.7 to 19.2	5.1 to 21.6	4.4 to 28.1	—	—
RP2D 2.5/10/30 mg, No.	35	14	5	3	21
Objective response rate[b]					
No. (%)	23 (65.7)	10 (71.4)	3 (60.0)	3 (100.0)	13 (61.9)
95% CI	47.8 to 80.9	41.9 to 91.6	—	—	38.4 to 81.9
CR					
No. (%)	20 (57.1)	9 (64.3)	2 (40.0)	3 (100.0)	11 (52.4)
95% CI	39.4 to 73.7	35.1 to 87.2	—	—	29.8 to 74.3
PR					
No. (%)	3 (8.6)	1 (7.1)	1 (20.0)	0	2 (9.5)
95% CI	1.8 to 23.1	0.2 to 33.9	—	—	1.2 to 30.4

Abbreviations: aNHL, aggressive non-Hodgkin lymphoma; CR, complete response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; Gr, grade; MCL, mantle cell lymphoma; PET, positron emission tomography; PMBCL, primary mediastinal B-cell lymphoma; PR, partial response; RP2D, recommended phase II dose; trFL, transformed follicular lymphoma; trMZL, transformed marginal zone lymphoma.

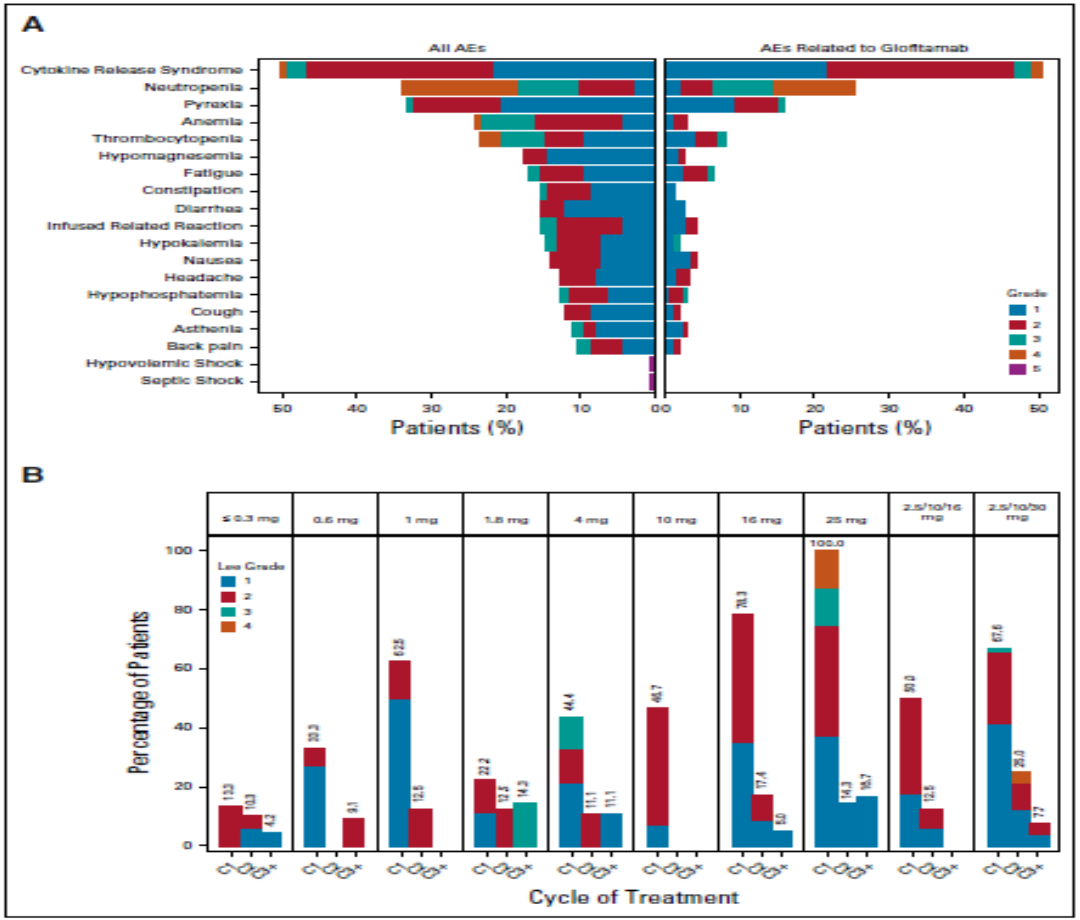


FIG 1. (A) Shows adverse events with an incidence of ≥ 10% or an NCI-CTCAE grade of 5 as of August 3, 2020. (B) Shows the incidence of CRS by cycle and dose (Lee grade).[10] CRS events were predominantly confined to cycles 1 and 2. Step-up

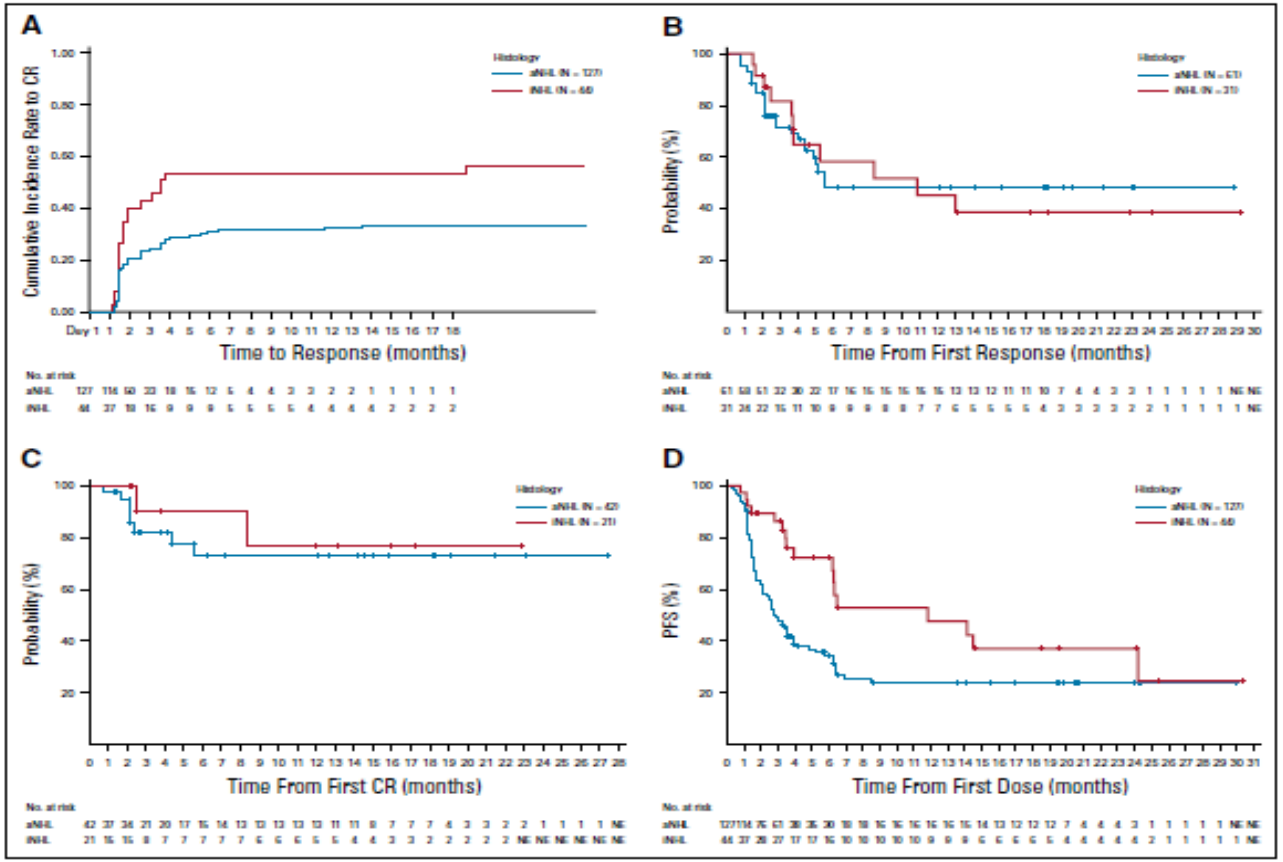
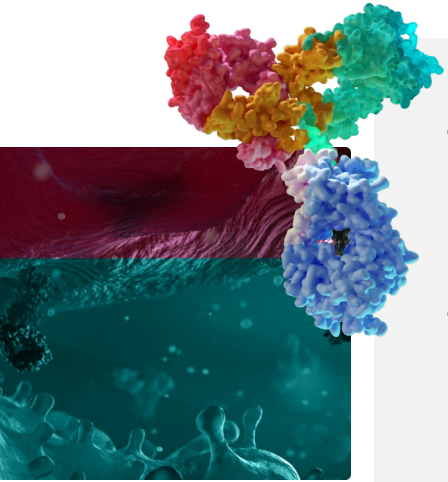


FIG 3. (A) Represents the cumulative incidence of time to CR. Kaplan-Meier curves for (B) DOR (PR and CR), (C) duration of CR, and (D) PFS. aNHL, aggressive non-Hodgkin lymphoma; CR, complete response; DOR, duration of response; iNHL, indolent non-Hodgkin lymphoma; NE, not estimable; PFS, progression-free survival; PR, partial response.

Conclusioni



- **Mosunetuzumab:** conferma dati di attività, efficacia e sicurezza
  - Utilizzo in combinazione (*ongoing phase III*), possibilità di uso sottocute
- **Odronextamab:** dati molto promettenti di attività e sicurezza*, step-up dosing* più lungo
  - Ambizioso programma di sviluppo per FL 1ª linea, R/R in combinazione
- **Epcoritamab:** conferma dati di attività in combinazione con R^2, elevata maneggevolezza


BISPECIFIC
T ASC
CAR-T
ALLOSCT
IMIDS
CHECK-IN
DRUG-CON-
MoAB
NEW MoAB

BISPECIFIC

CAR-T

IMIDS

NEW MoAB

MULTITARGET

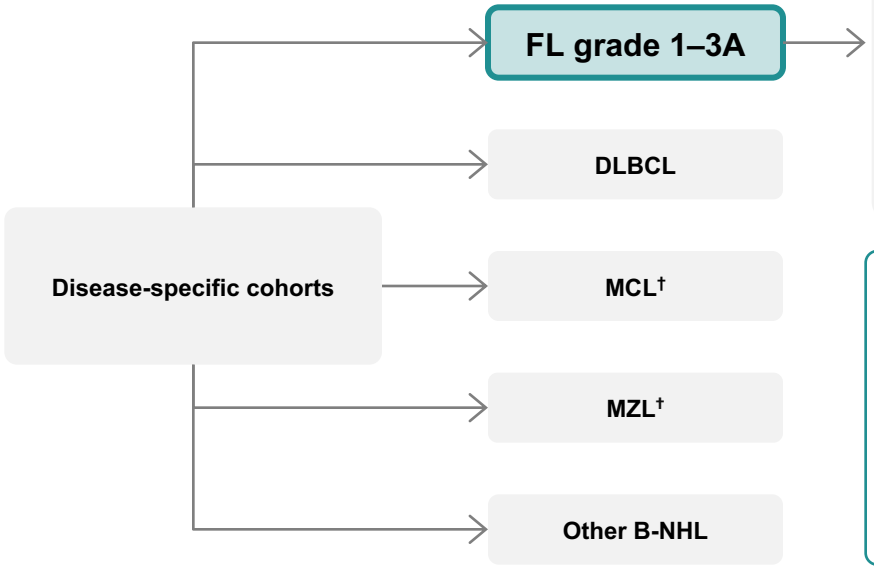
Anticorpi BISPECIFICI

- odronextamab

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

ELM-2 phase 2, open-label, multi-cohort, multicenter study of odronextamab monotherapy for patients with R/R B-NHL (NCT03888105)[1]

- R/R DLBCL cohort results also presented at ASH 2022[2]



Key eligibility criteria

- FL grades 1–3A
- ECOG PS 0 or 1
- Refractory to or relapsed after ≥2 prior lines of therapy, including an anti-CD20 antibody and an alkylator

Primary endpoint

- ORR* by ICR

Key secondary endpoints

- ORR* by local investigator
- CR, DOR, PFS, and OS
- Safety and tolerability

Odronextamab administration:
IV, 21-day cycles

- Cycle 1 step-up
- Cycles 2–4 80mg days 1, 8,15
- Cycle 5 onwards 160mg Q2W
- Treatment until disease progression

**According to Lugano criteria. †New enrolment is currently paused.*
CD, cluster of differentiation; ICR, independent central review; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; Q2W, every 2 weeks

Mod. da: 1. Kim TM, et al. ASH 2022. Abstract n. 949;
2. Kim WS, et al. ASH 2022. Abstract n. 444

Baseline characteristics

- Heavily pretreated, highly refractory patient population

Patient and disease characteristics	N=131
Median age, years (range)	61 (22–84)
Age ≥65	38.9%
Male	53.4%
Ann Arbor stage (I-II, III-IV)	15.3%/84.7%
FLIPI risk score 0–1, 2, 3–5	14.5%/26.7%/58.8%
Bulky disease (investigator assessment)	13.7%
Median no. of prior lines, n (range)	3.0 (2–13)
Prior ASCT	30.5%
Prior PI3K inhibitor	13.7%
Prior R^2 (lenalidomide + rituximab)	13.7%
Refractory to last line of therapy	71.0%
Refractory to anti-CD20 antibody	74.8%
Double refractory to alkylator/anti-CD20 Ab	43.5%
POD24	48.1%

	N=131
Cycle 1 step-up regimen (1/20 mg)/(0.7/4/20 mg)	51.9%/48.1%
Median duration of exposure, weeks (range)	22.1 (0.4–137.0)
Median number of doses (range)	19 (1–61)
Median number of cycles (range)	9.1 (0.1–66.5)
Completed cycle 1	95.4%
Completed ≥4 cycles	80.9%
Treatment ongoing	42.7%
Treatment discontinued	57.3%
Disease progression	19.8%
Patient or physician decision/withdrawal of consent	17.6%
Adverse event	9.9%
Death	9.9%

Data cut of date: Sep 15, 2022.
Ab, antibody; ASCT, autologous stem cell transplant; FLIPI, Follicular Lymphoma International Prognostic Index

Mod. da: Kim TM, et al. ASH 2022. Abstract n. 949

Odronextamab efficacy: objective response rate

Best overall response	Independent central review N=121*	Investigator evaluation N=121*
Objective response rate (ORR)†	**81.8%** [95% CI: 73.8–88.2%]	81.8% [95% CI: 73.8–88.2%]
Complete response	**75.2%**	70.2%
Partial response	6.6%	11.6%
Stable disease	5.8%	2.5%
Progressive disease	4.1%	5.8%

Week 12 response assessment by independent central review		1/20 step-up regimen N=68	0.7/4/20 step-up regimen N=53
	ORR	72.1% [95% CI: 59.9–82.3%]	75.5% [95% CI: 61.7–86.2%]
Complete response		61.8%	71.7%

- **Majority of R/R FL patients achieved a complete response**
- **92% of responders were complete responders**
- **Consistent efficacy observed at week 12 regardless of cycle 1 step-up regimen**

- Median opportunity of follow-up: 22.4 months (range, 2.6–33.0)

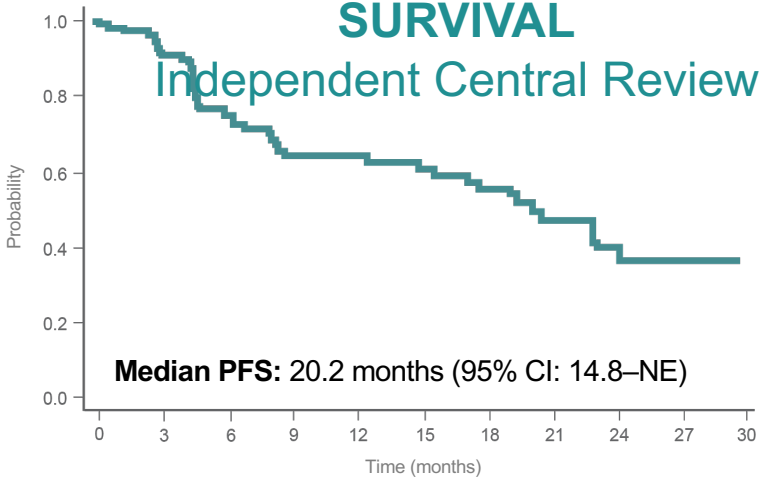
Data cut of date: Sep 15, 2022.
**Efficacy evaluable (with an opportunity for assessment at 12 weeks); †ORR = complete responses + partial responses*

Mod. da: Kim TM, et al. ASH 2022. Abstract n. 949

Progression-free survival and overall survival

PROGRESSION-FREE SURVIVAL

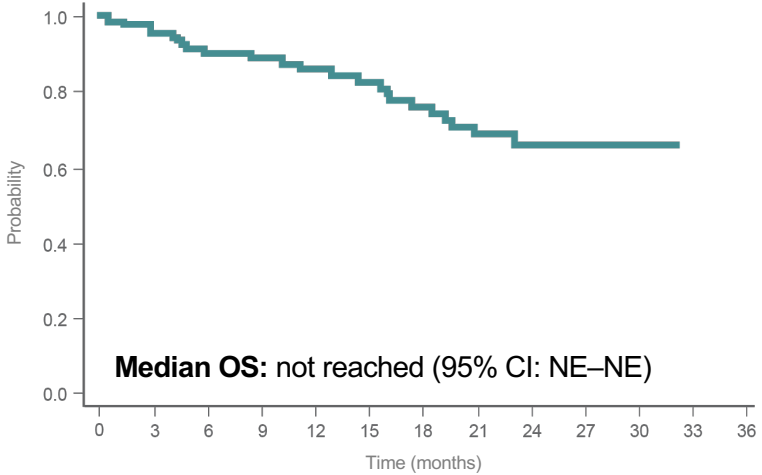
Independent Central Review



12-month PFS rate: 64.0% (95% CI: 52.7–73.3)

18-month PFS rate: 55.3% (95% CI: 43.1–65.8)

OVERALL SURVIVAL



12-month OS rate: 86.1% (95% CI: 77.0–91.9)

18-month OS rate: 76.3% (95% CI: 64.8–84.5)

Data cut of date: Sep 15, 2022.
NE: not estimable

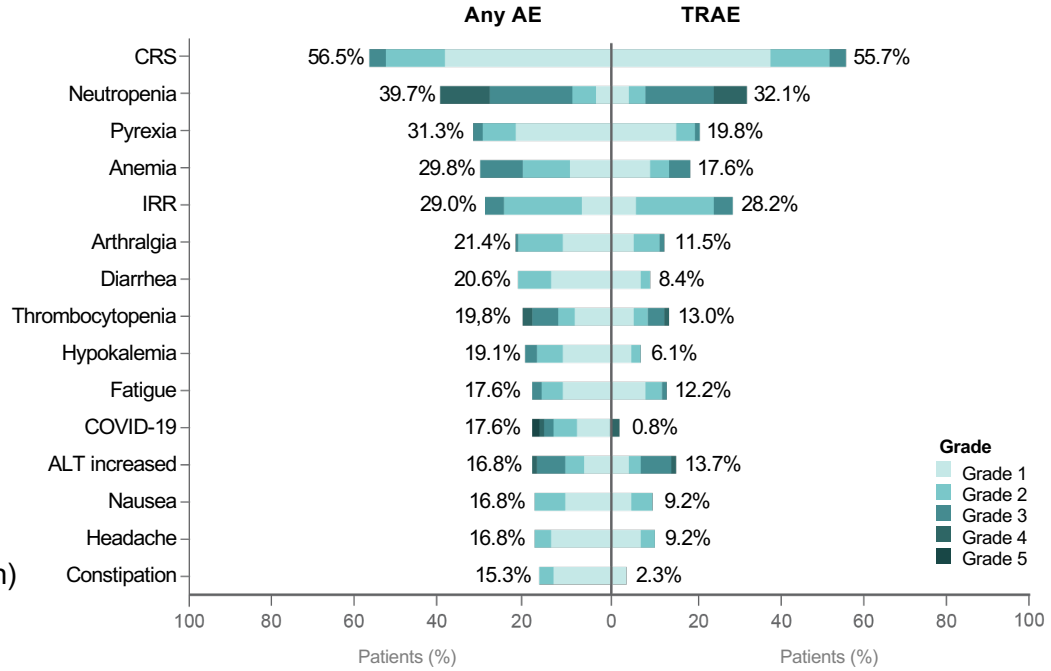
Mod. da: Kim TM. et al. ASH 2022. Abstract n. 949

Odronextamab safety profile

Treatment-emergent adverse events, N (%)	Patients, N=131	
	All events	TRAEs
Any TEAE	131 (100%)	118 (90.1%)
Grade ≥3 TEAE	102 (77.9%)	73 (55.7%)
Serious AE	81 (61.8%)	53 (40.5%)
Grade 5 TEAE	17 (13.0%)	3 (2.3%)
Related to COVID-19	7 (5.3%)	0
Other grade 5 events	10 (7.6%)	3 (2.3%)
TEAE leading to treatment discontinuation	15 (11.5%)	10 (7.6%)

- Grade 5 TRAEs: pneumonia, PML, systemic mycosis (N=1 each)
- TRAEs leading to treatment discontinuation: IRR (N=2); IRR and tremor (N=1); ALT increase; arthralgia; CRS; epilepsy; PML; viral bronchitis; weight decrease (N=1 each)

AEs (≥15% any grade) and TRAEs



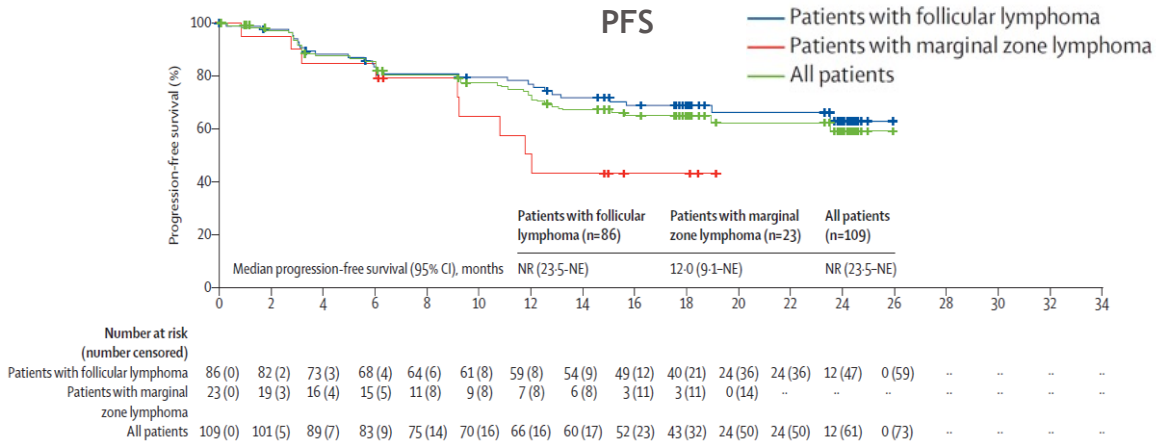
Data cut of date: Sep 15, 2022.
AEs per NCI-CTCAE v5.0. CRS per Lee DW, et al. Biol Blood Marrow Transplant 2019; 25: 625–638
ALT, alanine aminotransferase; IRR, infusion-related reaction; PML, progressive multifocal leukoencephalopathy; TEAE, treatment-emergent AE; TRAE, treatment-related AE.

Mod. da: Kim TM, et al. ASH 2022. Abstract n. 949

CAR-T

ZUMA-5: efficacy and safety of patients with relapsed/refractory follicular lymphoma receiving axicabtagene ciloleucel

Patient characteristics	Patients (N = 148)
Median age, years (range)	60 (53-67)
Tumor type, n (%) FL MZL	124 (83.8) 24 (16.2)
Stage III-IV disease, n (%)	106 (85)
Median prior lines, n (range)	3 (2–4)
Refractory disease, n (%)	84 (68)
Prior HSCT, n (%)	33 (22)
TEAEs of interest	**Axi-cel**
Grade ≥ 3 CRS, n (%)[a]	8 (6)
Grade ≥ 3 neurological toxicity, n (%)	19 (15)



- Out of 86 patients, 95% achieved best ORR and 79% achieved best CR
- 12-month DOR was achieved by 72% of patients
- 18-month OS was 87.4% (median OS was not achieved)

Axicabtagene ciloleucel has not yet obtained approved outside the USA for r/r FL. The safety and efficac
systemic therapy. In the EU, axicabtagene ciloleucel has received positive CHMP opinion for the treatm
April 2022. Accessed May 2022.

[a] CRS was graded using Lee criteria, 2014.

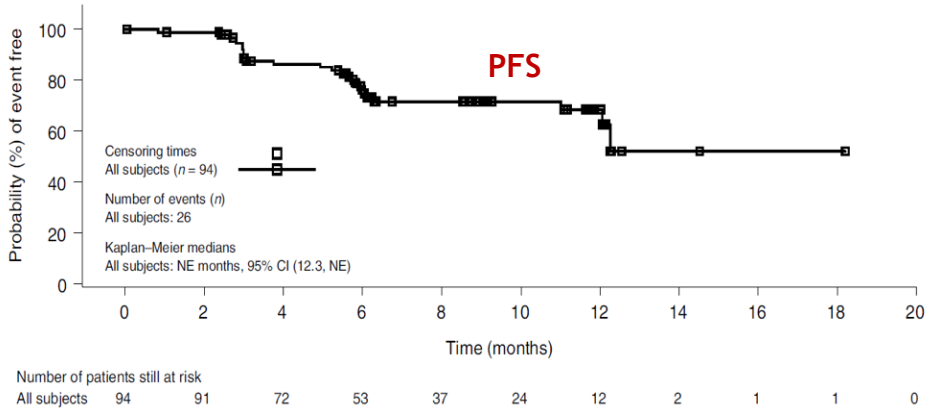
Axi-cel, axicabtagene ciloleucel; CHMP, Committee for Medicinal Products for Human Use; HSCT, haematopoietic SCT.

Jacobson CA, et al. Lancet Oncol.2022;23:91-103.

ELARA: efficacy and safety of patients with relapsed/refractory follicular lymphoma receiving tisagenlecleucel

Characteristics	Patients (N = 97)
Median age, years, (range)	57 (49-64)
Stage III-IV disease, n (%)	83 (85.6)
Median prior lines, n (range)	4 (2-13)
Refractory to last line of therapy, n (%)	76 (78.4)
Prior HSCT, n (%)	35 (36.1)

TEAEs of interest	Tisa-cel
Grade ≥ 3 CRS, %[a]	0
Grade ≥ 3 neurological toxicity, n (%)	3 (3.1)



- Out of 94 patients, 86.2% achieved best ORR and 69.1% achieved best CRR
- Median DOR, PFS, and OS were not reached
- 9-months DOR was 86.5%
- 12-month PFS was 85.5%

In the EU, tisagenlecleucel is indicated for adult patients with r/r FL after two or more lines of systemic therapy. In the USA, Novartis has been granted accelerated approval for tisagenlecleucel for the treatment of adult patients with r/r FL after 2 or more lines of systemic therapy. Available from: https://www.novartis.com/news/media-releases/fda-approves-novartis-kymriah-car-t-cell-therapy-adult-patients-relapsed-or-refractory-follicular-lymphoma. Last updated May 2022. Accessed May 2022.

[a] CRS was graded using Lee criteria, 2014.

NE, neurological event; tisa-cel, tisagenlecleucel.

Fowler NH, et al. Nat Med. 2022;28:325-32.

Terapia di seconda linea del Linfoma follicolare. Esiste una sequenza ottimale?

- Il LF rec/refr ha un andamento clinico eterogeneo; numerose opzioni oltre immunoct
- Il tempo alla recidiva rappresenta un fattore prognostico rilevante (POD24)
- Considerare anche: caratteristiche paziente; rischio di trasformazione; obiettivo della terapia; rapporto beneficio/tossicità; preferenze del paziente;
- **Recidiva ultrapreoce**
  - **Ora ASCT, in futuro CART (bispec combo?)**
- **Recidiva intermedia**
  - **Ora immunoct/R2, in futuro bispecifici (combo), CART?**
- **Recidiva tardiva**
  - **R2, in futuro bispec (mono or combo + Len), BTK-inh? CART?**

Eppur si muove...

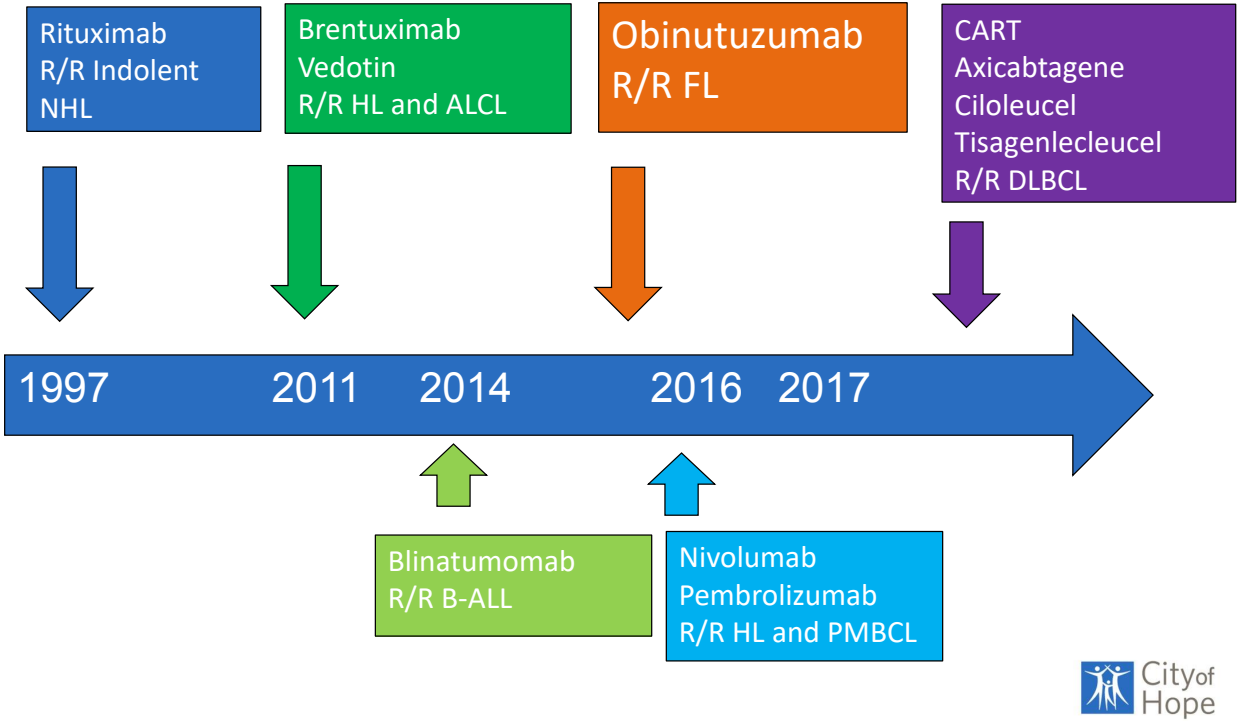
La terapia nel MONDO LINFOMI

Il razionale biologico delle combinazioni nei linfomi non Hodgkin

Dr Vincenzo Pavone

BARI, 28 GIUGNO 2022

Immunotherapy Landscape



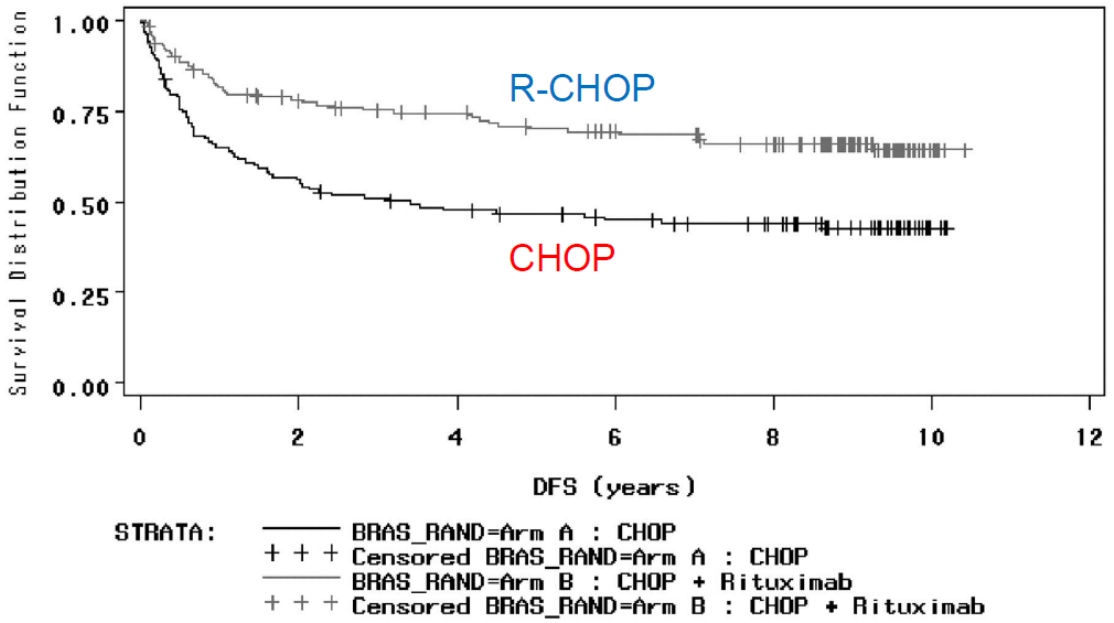
City of Hope

Table 10. Selected immunotherapy approaches clinically approved for treatment of NHL.

Class of Agents/Agent	Targeted Structure	Effective in NHL Subtypes
Monospecific monoclonal antibodies		
Rituximab	CD20	All B-NHL [11,12]
Obinutuzumab	CD20	CLL/SLL [13], FL frontline [14], R/R FL [15]
Tafasitamab	CD19	R/R B-NHL [26], R/R DLBCL [27]
Alemtuzumab	CD52	Mycosis fungoides [33], T-PLL [34]
Mogamulizumab	CCR4	Adult T-cel leukemia/lymphoma [37,38]
Bispecific monoclonal antibodies		
Blinatumomab	CD3-CD19	R/R B-NHL [48] R/R DLBCL [49,50]
Mosunetuzumab	CD3-CD20	R/R B-NHL [52]
Glofitamab	CD3-CD20	R/R B-NHL [56,57]
Checkpoint inhibitors		
Pembrolizumab	PD-1	R/R PMBCL [80,81], Richter's syndrome [93], mycosis fungoides [95]
Nivolumab	PD-1	R/R PMBCL [83], PCNSL and PTL [77]
Pidilizumab	PD-1	DLBCL after autologous SCT [75]
CAR-T cells		
Tisagenlecleucel	CD19	R/R aggressive NHL [141]
Axicabtagene ciloleucel	CD19	R/R aggressive NHL [142,143]
Lisocabtagene maraleucel	CD19	R/R aggressive NHL [144]
Brexucabtagene autoleucel	CD19	R/R MCL [150]
Immunomodulatory agents		
Lenalidomide	Cereblon	R/R FL and MZL [180] MCL frontline [182,183], R/R PCNSL [184], R/R DLBCL [185]
Avadomide	Cereblon	R/R DLBCL [194]

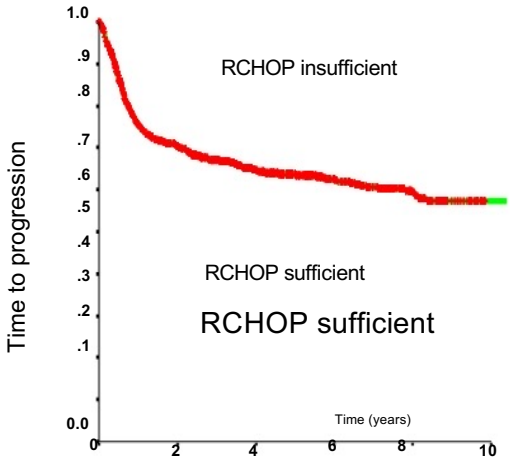
Abbreviations: B-NHL = B-non Hodgkin's lymphoma, CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma, FL = follicular lymphoma, R/R = relapsed/refractory, DLBCL = diffuse large B-cell lymphoma, T-PLL = T-prolymphocytic leukemia, PMBCL = primary mediastinal B-cell lymphoma, PCNSL = primary central nervous system lymphoma, PTL = primary testicular lymphoma, SCT = stem cell transplantation, MCL = mantle cell lymphoma, MZL = marginal zone lymphoma.

Disease-free survival in patients treated with CHOP and R-CHOP -10 yrs F/U



Bertrand Coiffier et al. Blood 2010;116:2040-2045

Heterogeneity of outcomes in DLBCL



RCHOP insufficient

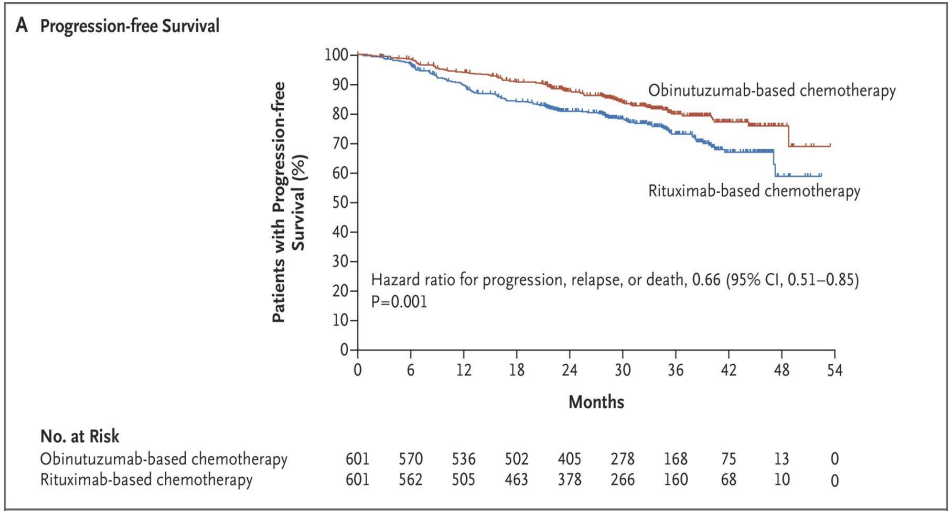
- Clinical factors
  - IPI (R-IPI)
- Interim PET scan
- GEP
  - ACB vs GCB
- Protein expression
  - MYC and BCL2
- Chromosomal alterations
  - MYC, BCL2, BCL6
- Deep sequencing analysis

Two broad strategies:

- Target both subgroups
  - possibly overtreating RCHOP “sufficient group”
- Target RCHOP “insufficient” group provided
  - it can be identified
  - It cab be targeted

Obinutuzumab (Gallium)

- Randomized Phase III in untreated FL
- R-bendamustine vs O-bendamustine plus O maintenance
- PFS benefit with O vs. R (3 yr PFS 80% vs. 73.3%, p=0.01)



Marcus R et al. NEJM 2017

City of Hope

Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data

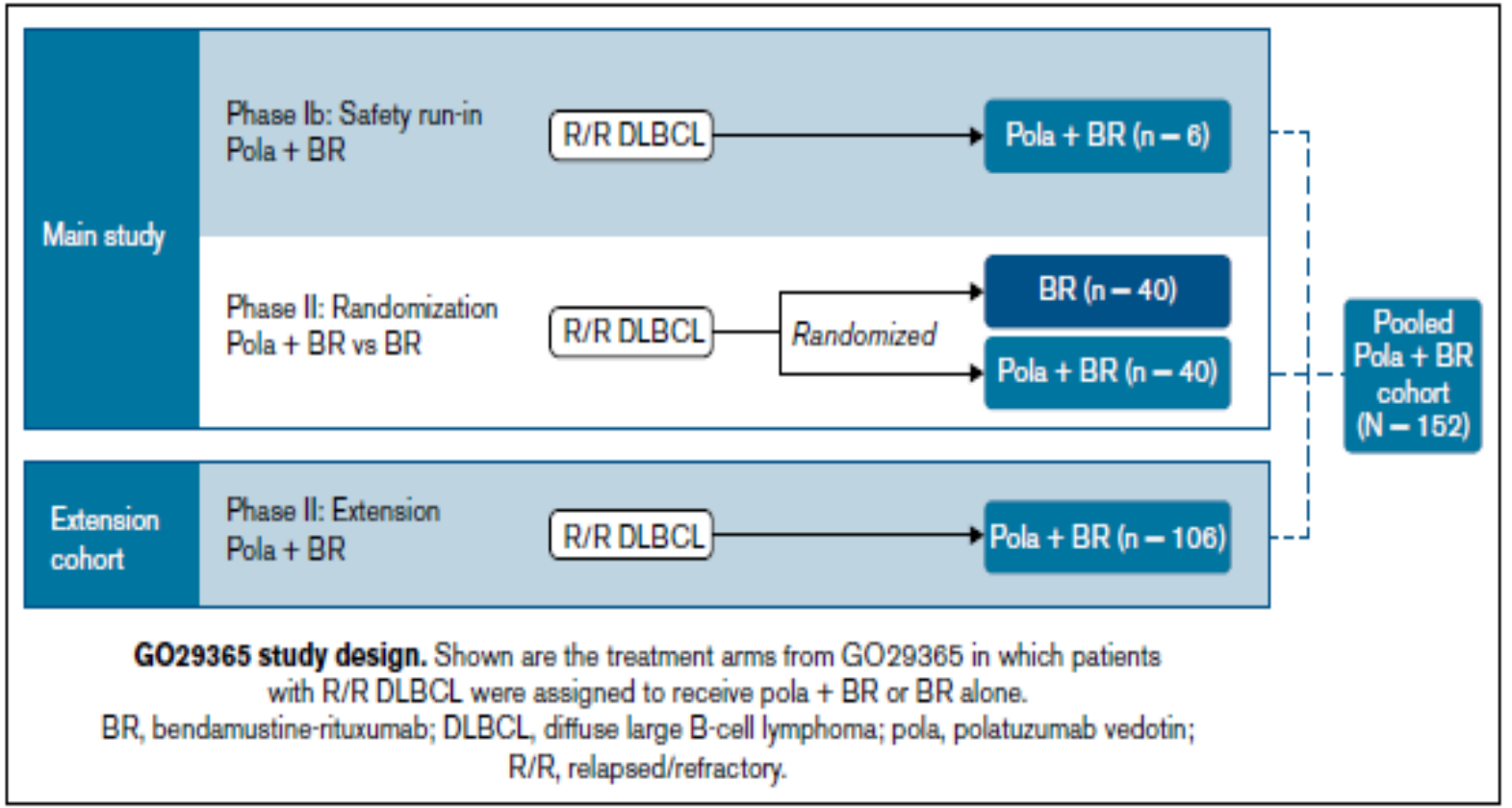
Laurie H. Sehn,[1] Mark Hertzberg,[2] Stephen Opat,[3] Alex F. Herrera,[4] Sarit Assouline,[5] Christopher R. Flowers,[6] Tae Min Kim,[7] Andrew McMillan,[8] Muhit Ozcan,[9] Violaine Safar,[10] Gilles Salles,[10] Grace Ku,[11] Jamie Hirata,[11] Yi Meng Chang,[12] Lisa Musick,[11] and Matthew J. Matasar[13]

[1]BC Cancer Centre for Lymphoid Cancer and The University of British Columbia, Vancouver, BC, Canada; [2]Prince of Wales Hospital and University of New South Wales, Sydney, NSW, Australia; [3]Clinical Haematology, Monash Health and Monash University, Clayton, VIC, Australia; [4]City of Hope Medical Centre, Duarte, CA; [5]Jewish General Hospital, Montreal, QC, Canada; [6]Winship Cancer Institute of Emory University, Atlanta, GA; [7]Seoul National University Hospital, Seoul, South Korea; [8]Center for Clinical Haematology, Nottingham University Hospitals NHS Trust, Nottingham, UK; [9]Ankara University, Ankara, Turkey; [10]Centre Hospitalier Lyon-Sud, Lyon, France; [11]Genentech, Inc., South San Francisco, CA; [12]F. Hoffmann–La Roche Ltd., Mississauga, ON, Canada; and [13]Memorial Sloan-Kettering Cancer Center, New York, NY

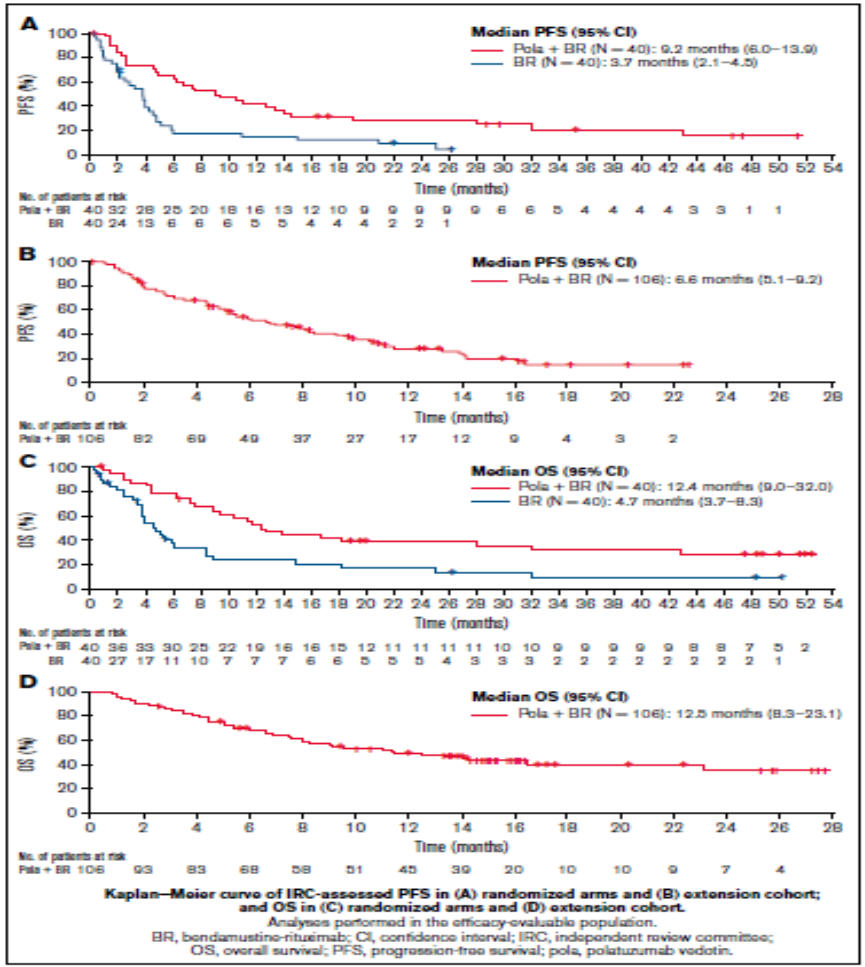
Key Points

- Consistent with previous results, pola + BR has a tolerable safety profile.
- The survival benefit of pola + BR vs BR persists with longer follow-up; efficacy in the pola + BR extension and randomized arms was similar.

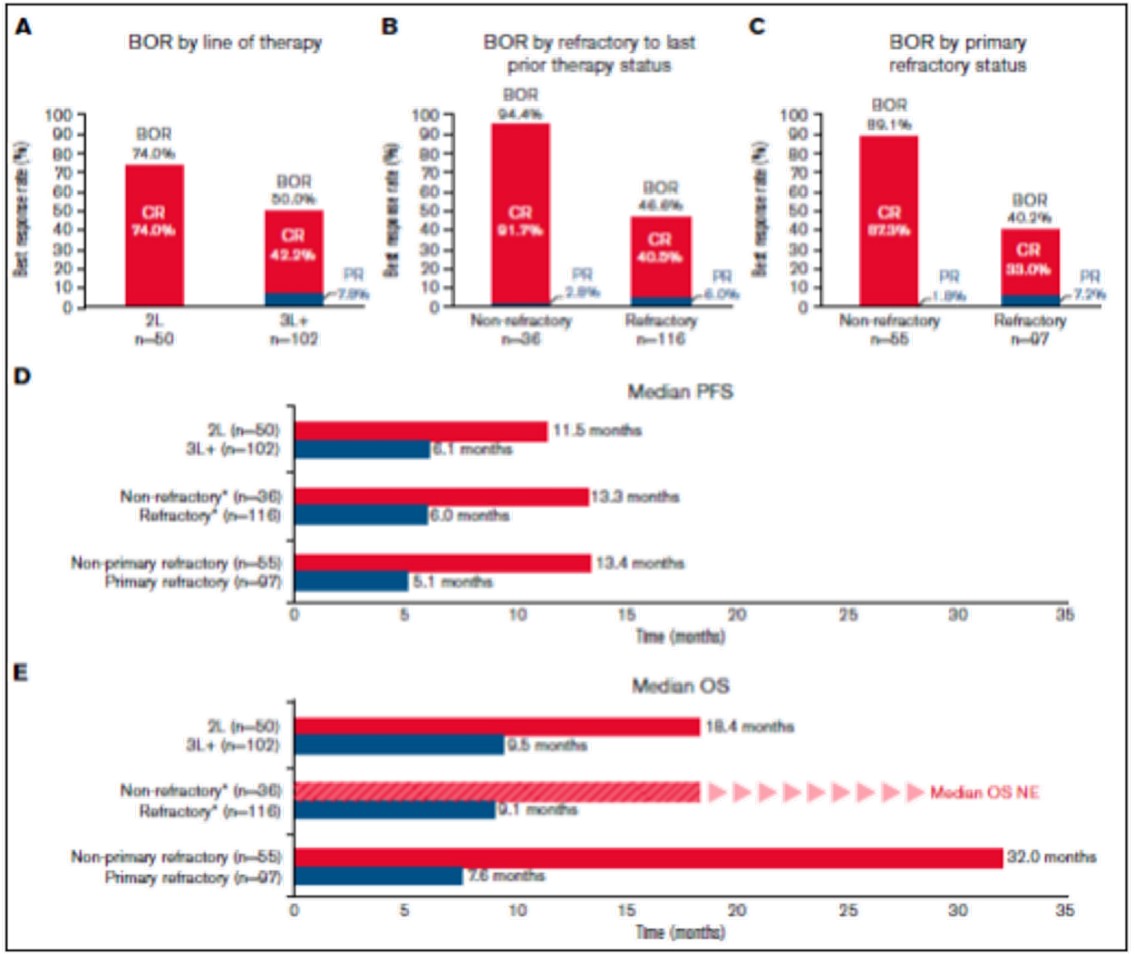
Polatuzumab vedotin plus bendamustine and rituximab (pola + BR) received regulatory approvals for relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) based on primary results from the randomized arms of the GO29365 study. After the randomized phase, 106 additional patients received pola + BR in a single-arm extension cohort. We report updated results from the randomized arms and results of the extension cohort. In this phase 1b/2 study, patients with R/R DLBCL who were transplant ineligible received up to six 21-day cycles of pola + BR or BR. The primary end point of the randomized arms was the complete response (CR) rate at end of treatment. Primary objectives of the extension cohort were safety, pharmacokinetic profile, and efficacy of pola + BR. As of 7 July 2020, a total of 192 patients with R/R DLBCL were enrolled in the pola + BR cohort (n = 152 [safety run-in, n = 6; randomized, n = 40; extension cohort, n = 106]) or the BR cohort (n = 40). Significant survival benefit with pola + BR vs BR persisted in the randomized arms (median progression-free survival, 9.2 vs 3.7 months [hazard ratio, 0.39; 95% confidence interval, 0.23-0.66]; median overall survival, 12.4 vs 4.7 months [hazard ratio, 0.42; 95% confidence interval, 0.24-0.72]). In the extension cohort, the independent review committee–assessed objective response rate was 41.5%, and the CR rate was 38.7%; median independent review committee–assessed progression-free survival and overall survival were 6.6 months and 12.5 months, respectively. No new safety signals with pola + BR were identified. Pola + BR is an effective treatment option for patients with R/R DLBCL, with a well-characterized and manageable safety profile. This trial was registered at www.clinicaltrials.gov as #NCT02257567.



GO29365 study design. Shown are the treatment arms from GO29365 in which patients with R/R DLBCL were assigned to receive pola + BR or BR alone.
BR, bendamustine-rituximab; DLBCL, diffuse large B-cell lymphoma; pola, polatuzumab vedotin; R/R, relapsed/refractory.



Kaplan–Meier curve of IRC-assessed PFS in (A) randomized arms and (B) extension cohort; and OS in (C) randomized arms and (D) extension cohort.
Analyses performed in the efficacy-evaluable population.
BR, bendamustine-rituximab; CI, confidence interval; IRC, independent review committee; OS, overall survival; PFS, progression-free survival; pola, polatuzumab vedotin.


A
BOR by line of therapy
Best response rate (%)
BOR 74.0%
CR 74.0%
BOR 50.0%
CR 42.2%
PR 7.8%
2L n=50
3L+ n=102
B
BOR by refractory to last prior therapy status
BOR 94.4%
CR 91.7%
PR 2.8%
BOR 46.6%
CR 40.5%
PR 6.0%
Non-refractory n=36
Refractory n=116
C
BOR by primary refractory status
BOR 89.1%
CR 87.3%
PR 1.8%
BOR 40.2%
CR 33.0%
PR 7.2%
Non-refractory n=55
Refractory n=97
D
Median PFS
2L (n=50)
3L+ (n=102)
11.5 months
6.1 months
Non-refractory* (n=36)
Refractory* (n=116)
13.3 months
6.0 months
Non-primary refractory (n=55)
Primary refractory (n=97)
13.4 months
5.1 months
Time (months)
E
Median OS
2L (n=50)
3L+ (n=102)
18.4 months
9.5 months
Non-refractory* (n=36)
Refractory* (n=116)
Median OS NE
9.1 months
Non-primary refractory (n=55)
Primary refractory (n=97)
32.0 months
7.6 months
Time (months)

TPS8070

POLARGO: Randomized phase III study of polatuzumab vedotin plus rituximab, gemcitabine, and oxaliplatin (R-GemOx) in relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL)

Corinne Haioun,[1] Matthew Matasar,[2] Juan-Manuel Sancho,[3] Andreas Viardot,[4] Juana Hernandez,[5] Thomas Perretti,[5] Andrew McMillan[6]

Summary

Pola plus BR is approved for use in R/R DLBCL in several countries

R-GemOx is a recommended treatment option in R/R DLBCL

The POLARGO study is currently open and enrolling patients

POLARGO is a phase III study of pola-R-GemOx vs R-GemOx in R/R DLBCL

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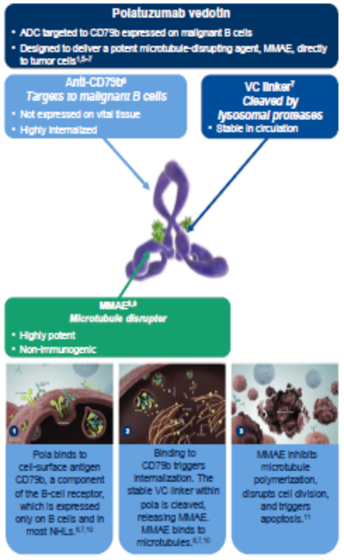
Background

- The antibody-drug conjugate (ADC) polatuzumab vedotin (pola) targets CD79b on B-cell malignancies (Figure 1).
- In the phase II GO29365 study (NCT02257567) pola plus bendamustine and rituximab (BR) improved complete response (CR; by positron emission tomography-computed tomography [PET-CT] at end of treatment) rate and overall survival (OS) in patients with R/R DLBCL, compared with BR alone (CR rate: 40% vs 18%, respectively, p=0.026; median OS: 12.4 vs 4.7 months, respectively, p=0.0023).[1]
- As a result, pola-BR was approved by the U.S. Food and Drug Administration for patients with R/R DLBCL after ≥2 prior therapies.[2] In January 2020, pola-BR was granted conditional European marketing authorization in patients with transplant-ineligible R/R DLBCL.[3]
- A range of therapies are used for R/R DLBCL and one recommended option is R-GemOx;[4] addition of pola to this regimen may further improve outcomes.
- In the POLARGO study (MO40598; NCT04182204), the safety and efficacy of pola-R-GemOx vs R-GemOx alone will be assessed in patients with R/R DLBCL.

Figure 1: Pola mode of action[1,5–11]

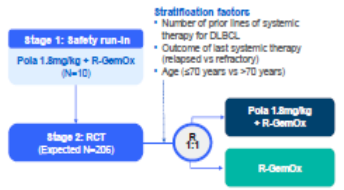

Polatuzumab vedotin
ADC targeted to CD79b expressed on malignant B cells
Designed to deliver a potent microtubule-disrupting agent, MMAE, directly to tumor cells[1,5–7]
Anti-CD79b[6]
Targets to malignant B cells
Not expressed on vital tissue
Highly internalized
VC linker[7]
Cleaved by lysosomal proteases
Stable in circulation
MMAE[8,9]
Microtubule disrupter
Highly potent
Non-immunogenic
1
2
3
Pola binds to cell-surface antigen CD79b, a component of the B-cell receptor, which is expressed only on B cells and in most NHLs.[6,7,10]
Binding to CD79b triggers internalization. The stable VC linker within pola is cleaved, releasing MMAE. MMAE binds to microtubules.[6,7,10]
MMAE inhibits microtubule polymerization, disrupts cell division, and triggers apoptosis.[11]

MMAE, monomethyl auristatin E; NHL, Non-Hodgkin lymphoma; VC, valine citrulline.

POLARGO is a global, multi-center, randomized, phase III study of pola-R-GemOx vs R-GemOx alone in patients with R/R DLBCL

- The study comprises a safety run-in stage and a randomized controlled trial (RCT) stage (Figure 2).
- Planned enrollment is 216 patients from 80–90 sites globally.

Figure 2: Study design


Stratification factors
Number of prior lines of systemic therapy for DLBCL
Outcome of last systemic therapy (relapsed vs refractory)
Age (≤70 years vs >70 years)
Stage 1: Safety run-in
Pola 1.8mg/kg + R-GemOx (N=10)
Stage 2: RCT (Expected N=206)
R 1:1
Pola 1.8mg/kg + R-GemOx
R-GemOx

Patients must have histologically confirmed R/R DLBCL

Key inclusion criteria:

- Confirmed availability of archival or freshly collected tumor tissue prior to enrollment
  - Relapse defined as disease that recurs following a response lasting ≥6 months from completion of the last line of therapy
  - Refractory defined as disease that progressed during previous therapy or stable disease for up to 6 months from completion of the last line of therapy.
- Eastern Cooperative Oncology Group performance status 0–2.
- Adequate hematologic function.

Key exclusion criteria:

- Previous allogeneic stem-cell transplantation (SCT) and/or planned autologous/allogeneic SCT.
- Baseline peripheral neuropathy (PN) grade >1 (as assessed by National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 [NCI CTCAE v5.0]).

The RCT stage primary endpoint is overall survival

- Safety run-in stage primary endpoint: safety and tolerability of pola-R-GemOx, with a focus on PN.
- RCT stage primary endpoint: OS.
- Secondary endpoints: investigator- and independent review committee-assessed best overall response, progression-free survival, duration of objective response, event-free survival, CR rate and objective response rate (Lugano 2014 criteria); safety with a focus on PN.

Patients will receive up to eight cycles of pola-R-GemOx or R-GemOx (Table 1)

- Patients in the safety run-in stage will receive pola (1.8mg/kg) + R-GemOx (R, 375mg/m²; Gem, 1000mg/m²; Ox, 100mg/m²) administered in 21-day cycles.
- If pola + R-GemOx is tolerable in the safety run-in stage, patients will be randomized 1:1 to receive up to eight 21-day cycles of either pola + R-GemOx or R-GemOx alone.

Table 1: Treatment schedule

Cycles 1–8				
Drug order	Dose	D1	D2	D3–21
Rituximab	375mg/m²	■		
Pola	1.8mg/kg	■		
Gemcitabine	1000mg/m²		■	
Oxaliplatin	100mg/m²		■	

Safety and efficacy will be assessed with up to 2 years of follow-up

- Safety will be assessed by recording the incidence, nature, and severity of AEs (NCI CTCAE v5.0).
- Dose interruptions, reductions, and intensity will be used to determine tolerability.
- Health-related quality of life will be assessed.
- PET-CT and CT scans will be obtained at screening, during, and after the treatment period; 28 days after the last dose of study drug; and then every 2 months (PET-CT), and 6 (CT) months during follow-up for up to 2 years.

Enrollment began in February 2020 and this trial is currently recruiting.

Presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting | 29 May – 2 June 2020

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Trial in Progress: A Multicentre, Parallel Arm, Open-Label Trial of Frontline R-CHOP/Polatuzumab Vedotin-RCHP and Glofitamab in Younger Patients with Higher Risk Diffuse Large B Cell Lymphoma (COALITION)

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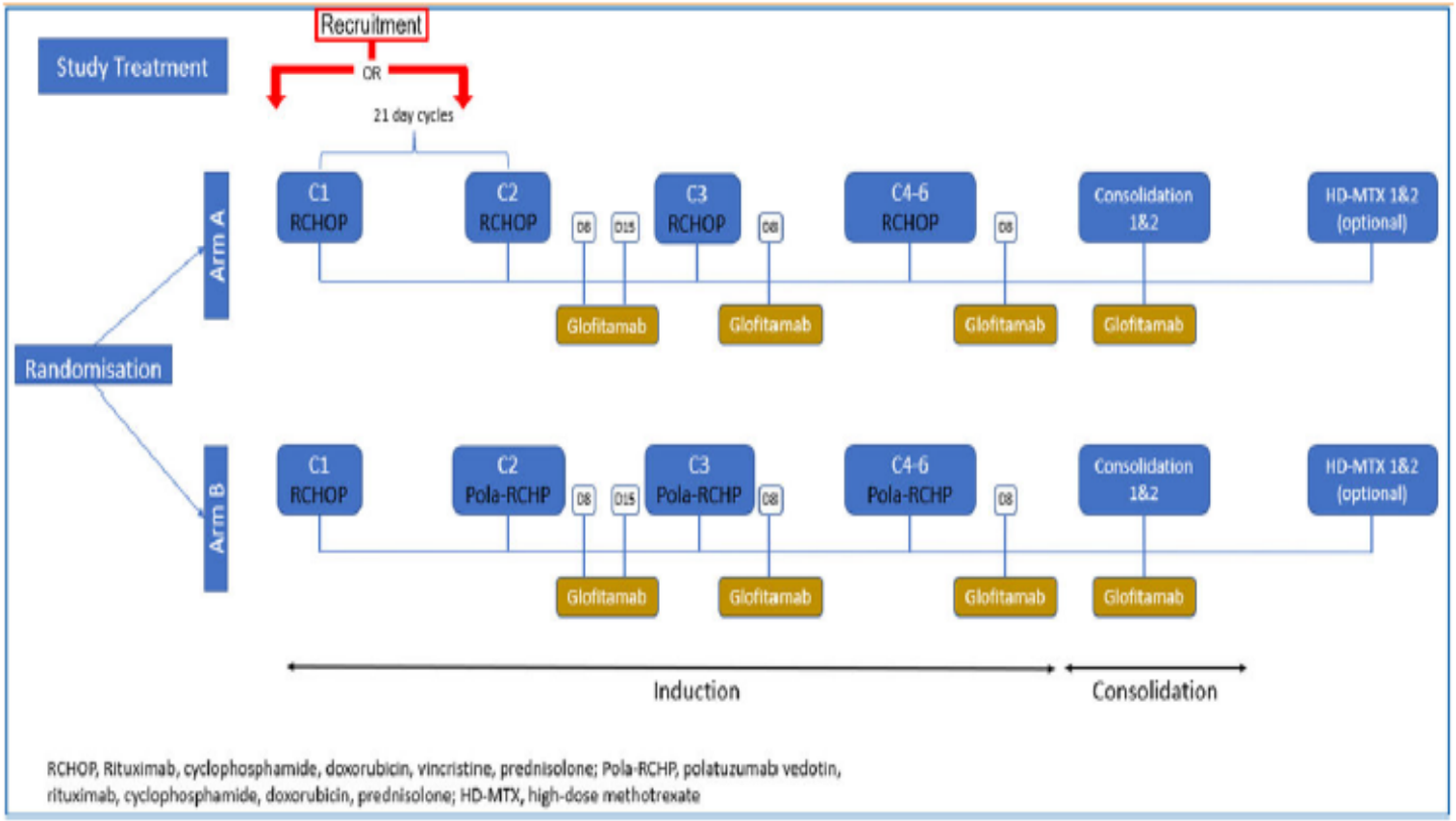
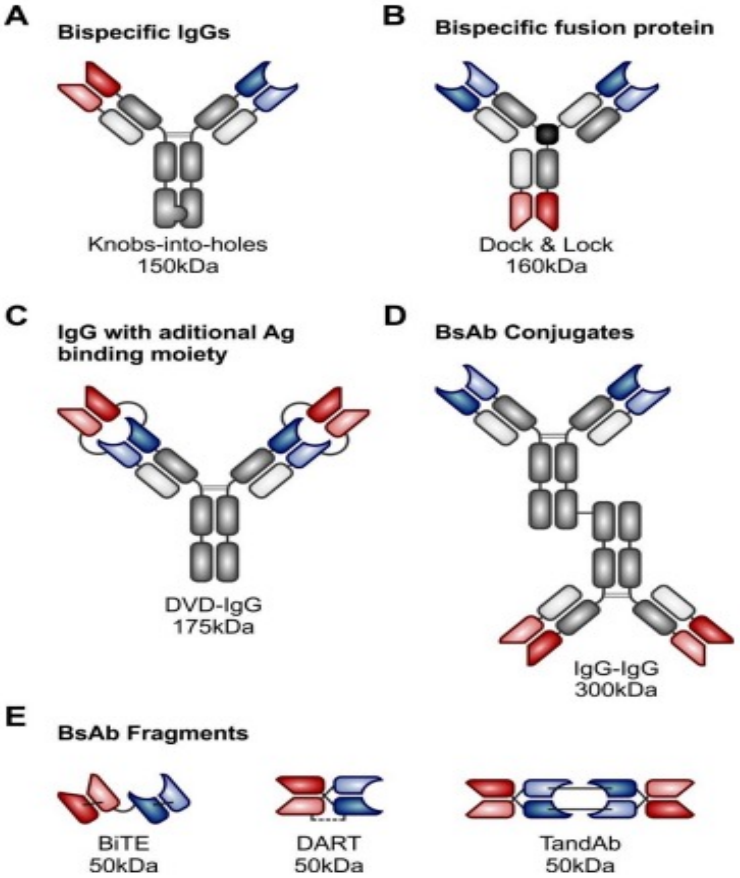
Abstract Background:
R-CHOP remains a standard frontline treatment for patients with DLBCL and high-grade B-cell lymphoma (HGBL). A significant proportion of patients will have refractory disease or subsequently relapse, particularly those with high-risk features such as an elevated IPI score or rearrangements of MYC and BCL2 and/or BCL6 (double/triple hit (DH/TH)). This population remains in need of improved induction treatments that can reduce the requirement for subsequent therapies which are associated with significant toxicities and diminishing response rates.
Rationale:
Glofitamab is a novel full-length bispecific antibody with a unique 2:1 configuration (two CD20 binding domains and one CD3 binding domain). In combination with a single pre-dose of obinutuzumab, glofitamab has demonstrated >70% complete remission in aggressive B-cell lymphoma at the recommended target dose in a phase 1 trial (Carlo-Stella, EHA 2021). Pre-clinical studies suggest that glofitamab's activity is retained in the presence of concomitant cytotoxic and CD20 antibody therapies, making it an attractive agent for combination with R-CHOP-like induction. Polatuzumab vedotin (pola) is an antibody-drug conjugate approved for R/R DLBCL in combination with BR, and is currently in evaluation for the front-line treatment of DLBCL in combination with RCHP in a randomised trial.
The safety and preliminary efficacy of glofitamab in combination with R-CHOP, or pola-RCHP as a front-line treatment for high risk DLBCL is being evaluated.
Study Design and Methods:
This is a parallel-arm phase Ib/II trial. Treatment consists of an initial cycle of R-CHOP, followed by 5 cycles of combination induction treatment and 2 cycles of consolidation glofitamab monotherapy. Key inclusion criteria are: age 18-65 years, a diagnosis of DLBCL or HBGL, high-risk features (IPI >3 or NCCN-IPI >4 or presence of DH/TH), treatment naïve or after 1 cycle of R-CHOP, ECOG 0-3. The primary endpoint is the safety of the combination and secondary endpoints include complete response rates at interim and end of treatment FDG-PET assessments by Lugano criteria, progression free survival and overall survival. Correlative studies assessing baseline immunologic profiles, tumour phenotype and potential resistance mechanisms are planned.
Approximately 40 patients will be treated in each arm across 12-14 Australian sites. The trial commenced recruitment in July 2021 (NCT04914741). The ability to recruit prior to either cycle 1 or cycle 2 allows seamless cross-referral from non-trial sites.

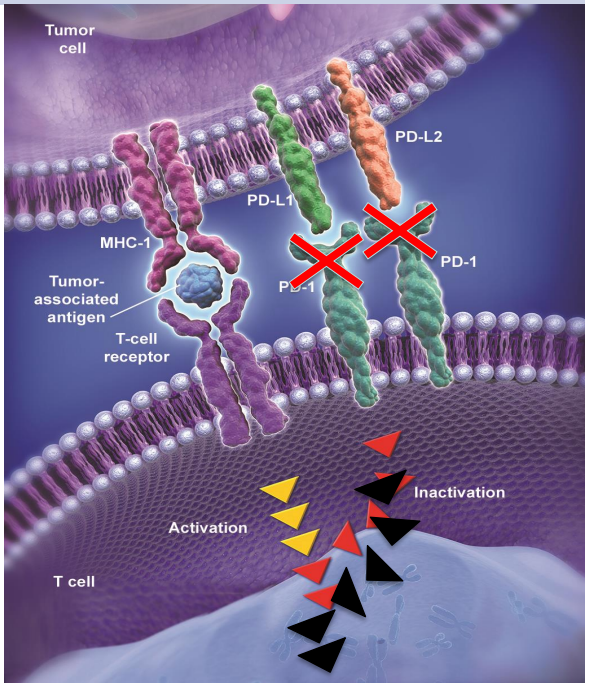

Study Treatment
Recruitment
OR
21 day cycles
Randomisation
Arm A
Arm B
C1 RCHOP
C2 RCHOP
C3 RCHOP
C4-6 RCHOP
Consolidation 1&2
HD-MTX 1&2 (optional)
D8
D15
Glofitamab
C1 RCHOP
C2 Pola-RCHP
C3 Pola-RCHP
C4-6 Pola-RCHP
Induction
Consolidation
RCHOP, Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; Pola-RCHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisolone; HD-MTX, high-dose methotrexate

Vaccines **2020**, *8*, 708



The PD-1 and PD-L1/L2 Pathway

- PD-1 is an immune checkpoint receptor
- Binding of PD-1 by its ligands PD-L1 or PD-L2 leads to downregulation of T-cell function
- This mechanism is usurped by many tumors
- PD-1 blockade through mAb therapy can restore effective anti-tumor immunity



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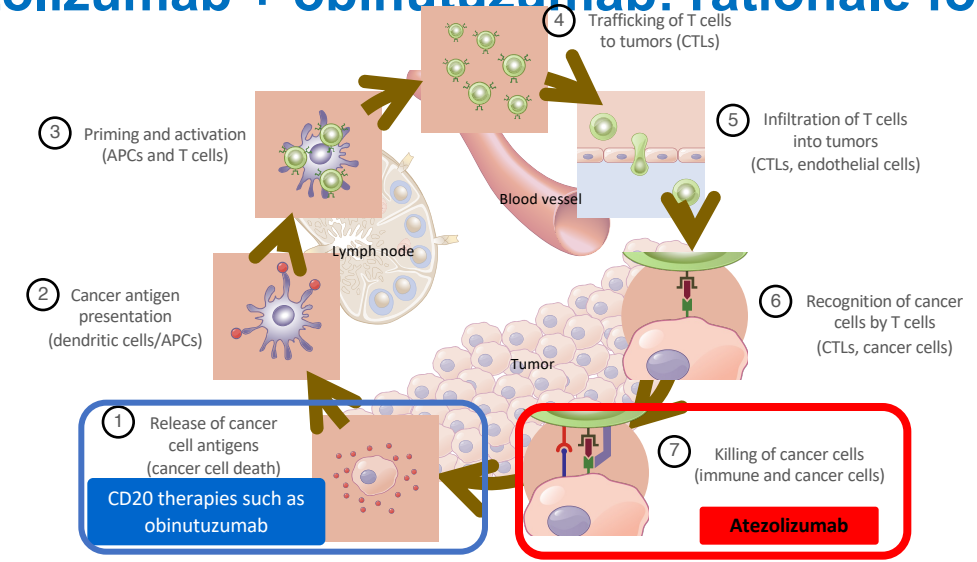
City of Hope

Atezolizumab + obinutuzumab: rationale for combination



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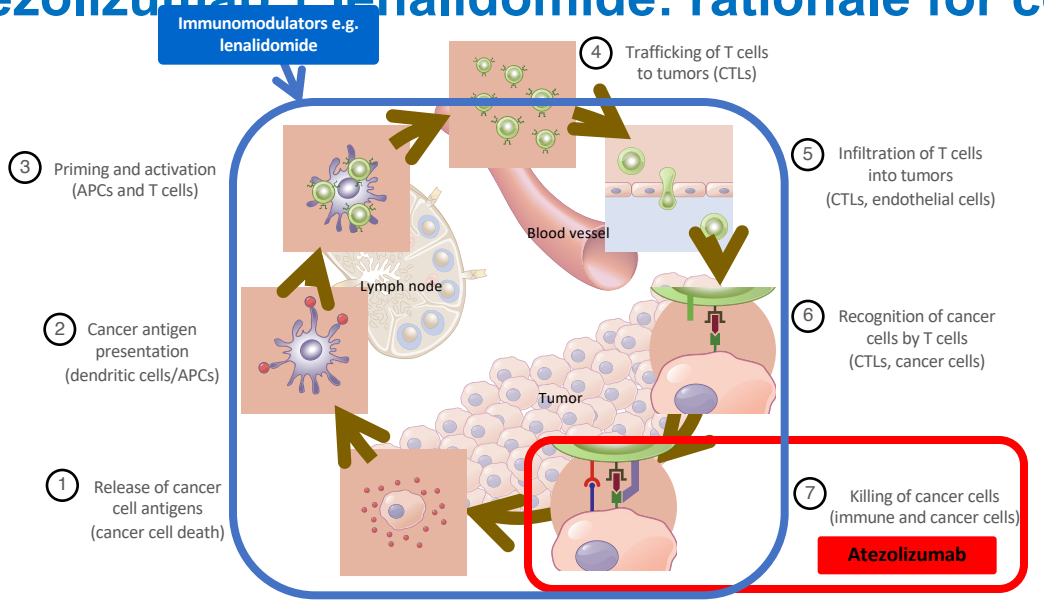
Chen DS & Mellman I. Immunity 2013;39:1–10, Images adapted from reference.

Atezolizumab + lenalidomide: rationale for combination



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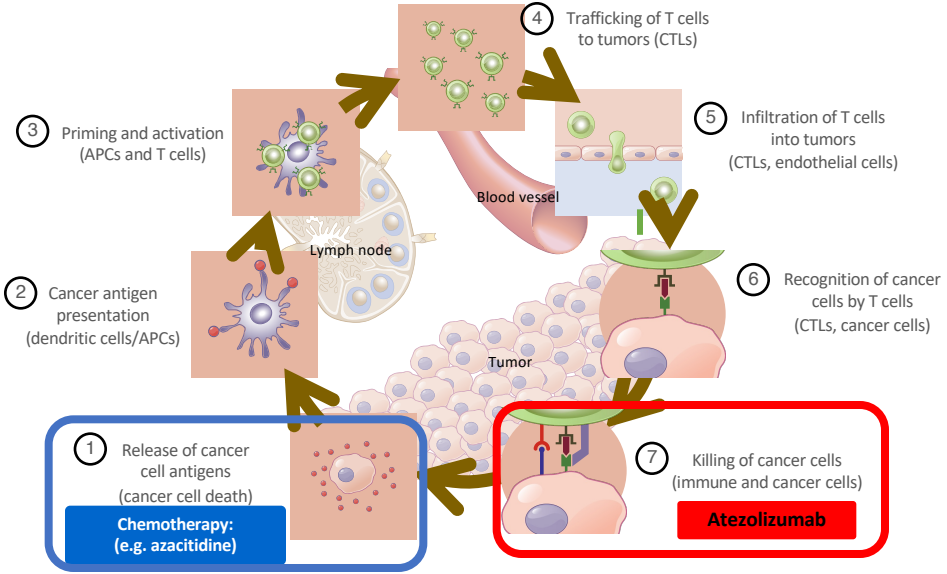
Chen DS & Mellman I. Immunity 2013;39:1–10, Images adapted from reference.

Atezolizumab + azacitidine: rationale for combination



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Chen DS & Mellman I. Immunity 2013;39:1–10, Images adapted from reference.

CHECKPOINT INHIBITORS

Table 6. Selected clinical trials that incorporate immune checkpoint inhibitors in experimental therapy of NHL.

Drug Combination	Mode of Action of the Combination Agent(s) Other Than Immune Checkpoint Inhibitors	Study Phase	Disease Status	Estimated Study Completion Date	ClinicalTrials.gov Identifier (Other Identifier)
Nivolumab + R(ituximab)-GemOx compared to R-GemOx	immunochemotherapy gemcitabine + oxaliplatin (GemOx)	2/3	R/R elderly B-NHL	November 2024	NCT03366272 (NIVEAU)
Avelumab +/− Utomilumab +/− Rituximab +/− Azacitidine +/− bendamustin +/− Gemcitabine +/− Oxaliplatine	CD137 (4-1BB) antigen agonist antibody utomilumab, anti-CD20 antibody rituximab, epigenetic modulator azacitidine, conventinal chemotherapy GemOx	1/3	R/R DLBCL	December 2019	NCT02951156 (JAVELIN DLBCL)
Nivolumab + DA-EPOCH-R + Nivolumab as a consolidation	immunochemotherapy regimen (dose-adjusted EPOCH-R)	2	B-NHL	December 2021	NCT03749018
Nivolumab + Copanlisib	pan-PI3K inhibitor copanlisib	2	R/R DLBCL, PMBCL	October 2021	NCT03484819
Pembrolizumab		2	untreated B-NHL	September 2024	NCT03498612
Pembrolizumab		2	R/R grey-zone lymphoma, R/R PCNSL, R/R DLBCL	July 2022	NCT03255018
Pembrolizumab + R-CHOP	R-CHOP immunochemotherapy regimen	2	DLBCL, high-grade B-NHL	August 2024	NCT03995147
Pembrolizumab + Rituximab +/− Lenalidomide	anti-CD20 antibody, immunomodulatory agent lenalidomide	2	R/R FL, R/R DLBCL	November 2021	NCT02446457

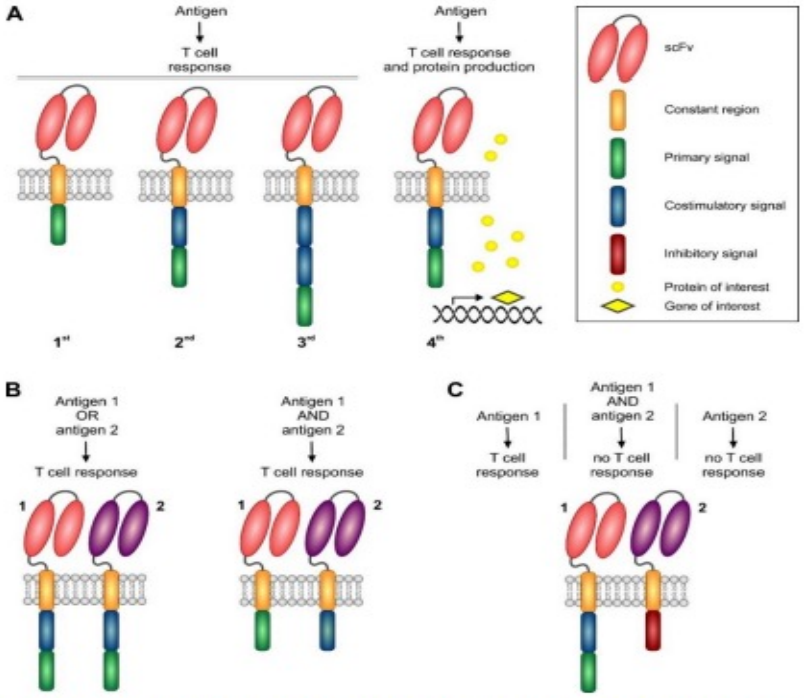


Figure 4. Schematic representation of design of four generations of CAR. **Legend: Conventional CARs:** (**A**) 1st to 3rd generation are defined by their signaling domains: a primary signaling domain only (1st generation); signaling and co-stimulatory domains (2nd generation); combined co-stimulatory domains (3rd generation); a release of activating cytokine upon CAR engagement (4th generation). **Co-expression of two different CARs:** (**B**) engagement of either CAR triggers downstream activation (left); engagement of both CARs triggers downstream activation (right); (**C**) engagement of inhibitory CAR prevents T-cell activation in the presence of cells that express the target antigen 2.

Table 8. Selected clinical trials that incorporate CAR T-cell products in experimental therapy of NHL.

Drug Combination	Mode of Action	Study Phase	Disease Status	Estimated Study Completion Date	ClinicalTrials.gov Identifier (Other Identifier)
Axi-cel	Anti-CD19 CAR T-cells versus ASCT (2nd line therapy)	3	R/R hgB-NHL	January 2022	NCT03391466 (ZUMA-7)
Liso-cel	Anti-CD19 CAR T-cells versus ASCT (2nd line therapy)	3	R/R hgB-NHL	January 2024	NCT03575351 (TRANSFORM)
Tisa-cel	Anti-CD19 CAR T-cells versus ASCT (2nd line therapy)	3	R/R hgB-NHL	December 2025	NCT03570892 (BELINDA)
Axi-cel	Anti-CD19 CAR T-cells	2	R/R FL, R/R MZL	February 2022	NCT03105336 (ZUMA-5)
Liso-cel	Anti-CD19 CAR T-cells	2	R/R B-NHL ineligible for ASCT	April 2021	NCT03483103 (TRANSCEND-PILOT-017006)
KTE-X19	Anti-CD19 CAR T-cells	1	R/R SLL/CLL	August 2021	NCT03624036
Liso-cel + ibrutinib	Anti-CD19 CAR T-cells + BTK inhibitor ibrutinib	1/2	R/R CLL/SLL	October 2021	NCT03331198
Axi-cel + acalabrutinib	BTK inhibitor acalabrutinib administered before leukapheresis	1/2	R/R hgB-NHL	March 2024	NCT04257578
CD30.CAR T cells	Anti-CD30 CAR T-cells	1	R/R HL, CD30+ NHL	April 2021	NCT02917083 (RELY-30)
AUTO4	Anti-TRBC1 CAR T-cells	1/2	R/R T-NHL	July 2021	NCT03590574
CD4CAR	Anti-CD4 CAR T-cells	1	R/R T-NHL	December 2022	NCT03829540
Axi-cel	Anti-CD19 CAR T-cells	1	DLBCL (PET+ after 2 cycles of therapy)	June 2021	NCT03761056 (ZUMA-12)
ALTCAR.CD30	ASCT followed by anti-CD30 CAR T-cells	1	R/R HL, CD30+ NHL	September 2021	NCT02663297
AlloSCT + CAR-T	T-cell depleted alloSCT + donor anti-CD19 CAR T-cell-based consolidation	1	B-ALL, CLL, NHL	September 2023	NCT04556266
CAR 20/19	Bispecific anti-CD20/anti-CD19 CAR T-cells	1/2	R/R B-NHL	May 2023	NCT04186520
Liso-cel + avadomide, iberdomide, ibrutinib, or durvalumab	Anti-CD19 CAR T-cells in combination with immunomodulatory drugs avadomide/iberdomide, BTK inhibitor ibrutinib or anti PD-L1 checkpoint durvalumab	1/2	R/R hgB-NHL	August 2023	NCT03310619 (PLATFORM)
AUTO3 + pembrolizumab	Dual anti-CD19/anti-CD22 CAR T-cells + anti PD-1 immune checkpoint inhibitor	1/2	R/R hgB-NHL	March 2021	NCT03287817 (ALEXANDER)

CD19

Optimal TARGET in DLBCL nHL

Broadly expressed than CD20

Is expressed in CD20 down regulation following Rituximab exposure

CD19: Role in Lymphomagenesis

Modulating BCR

B cell activation both antigen indipendent and immunoglobulin induced via protein kinase (BTK, RAS)

Essential to the chronic activated of BCR → Lymphomagenesis

↑ C-MYC levels and function

The use of tafasitamab in diffuse large B-cell lymphoma

Ther Adv Hematol

2021, Vol. 12: 1–13

DOI: 10.1177/20406207211027458

Johannes Düll, Max Topp and Gilles Salles

Abstract: Patients who relapse or are refractory after first-line therapy for diffuse large B-cell lymphoma (DLBCL) frequently have poor prognoses, especially when they are not candidates for autologous stem cell transplant (ASCT). Tafasitamab is a humanized monoclonal anti-CD19 antibody that has recently been approved by the FDA in combination with lenalidomide for the treatment of relapsed/refractory (R/R) DLBCL in patients who are not eligible for ASCT. Tafasitamab has an Fc region which has been modified to have an increased affinity for Fcγ receptors, to potentiate antibody-dependent cellular cytotoxicity and antibody-dependent cell-mediated phagocytosis. Here, we review the development, mode of action and clinical data for tafasitamab in combination with lenalidomide in R/R DLBCL, and discuss the various ways in which this novel antibody could be utilized in the treatment sequence to improve clinical outcomes for patients with DLBCL.

TAFASITAMAB

Second generation of CD-19-targeting MoAb
with specific engeniered Fc variant region

↑ ADCC via interaction of CD19 – MoAbFc
with effector cell FCYRs

↓

Immuno response by NK activeted cytotoxic attack

↑ ADCC

LENALIDOMIDE IN DLBCL nHL

Altere the balance of pro and antinflammatory cytokines in microenvironment

↓ Angiogenesis

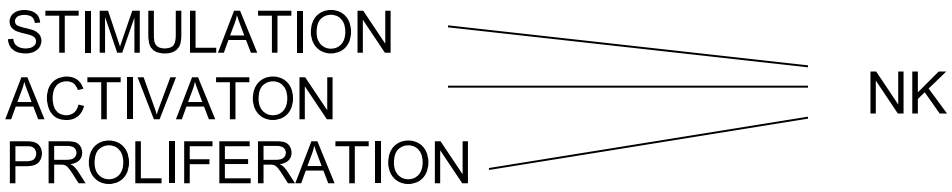
↑ Cell Cycle arrest and Apoptosis

↓ Down regulate expression of checkpoint inhibitors

↑ proliferation of NK and NK cytotoxicity and of CD8 and CD4

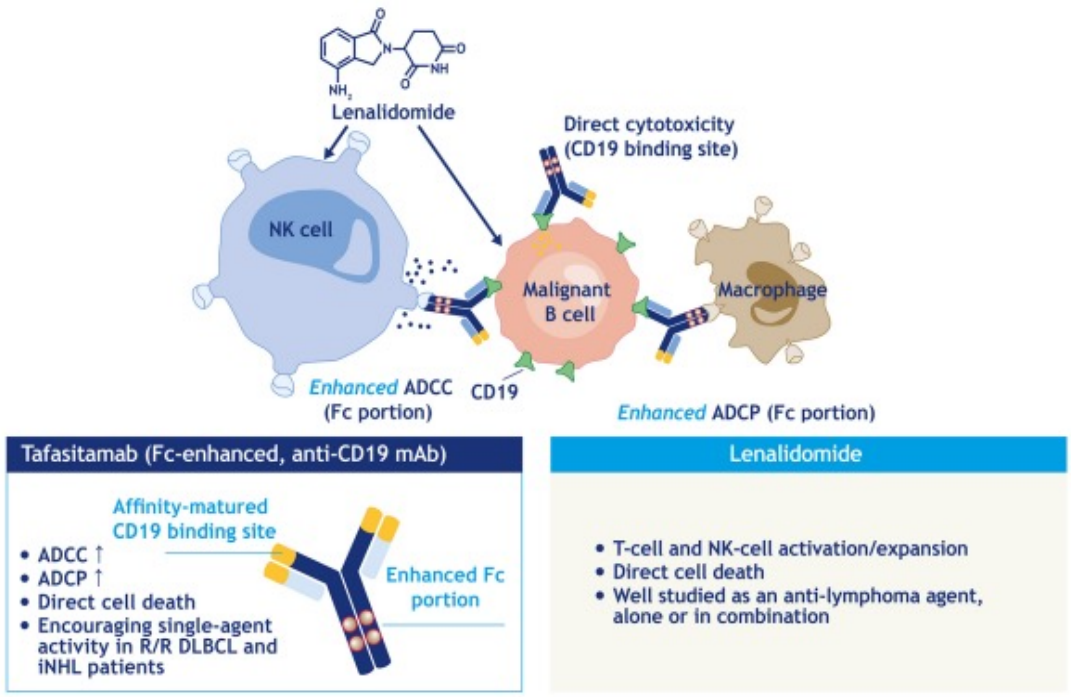
↑ ADCC

TAFASITAMAB plus LENALIDOMIDE



AMPLIFICATION of NK Cell Mediated ADCC

Ps Baseline peripheral NK-Cell count <100 µl: PFS in 6 -CHOP



ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; DLBCL, diffuse large B-cell lymphoma; INHL, indolent non-Hodgkin's lymphoma; mAb, monoclonal antibody; NK, natural killer; R/R, relapsed/refractory.

Figure 1. Combination mechanism of action of tafasitamab and lenalidomide.[41]

J Düll, M Topp *et al.*

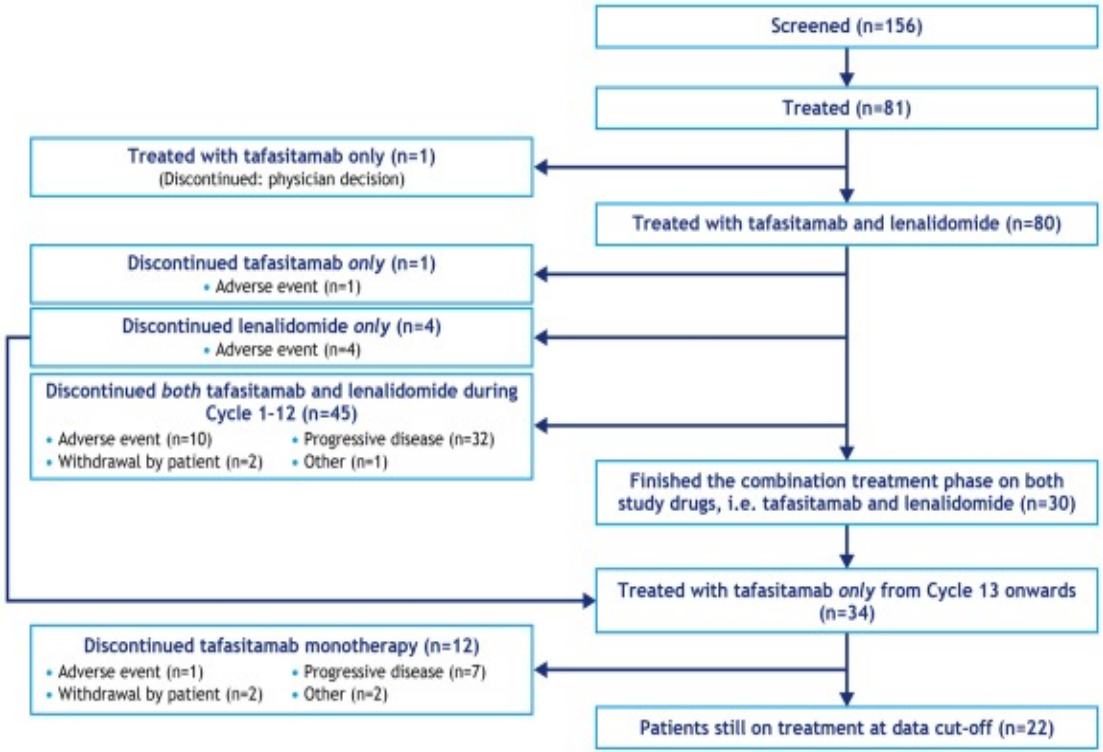
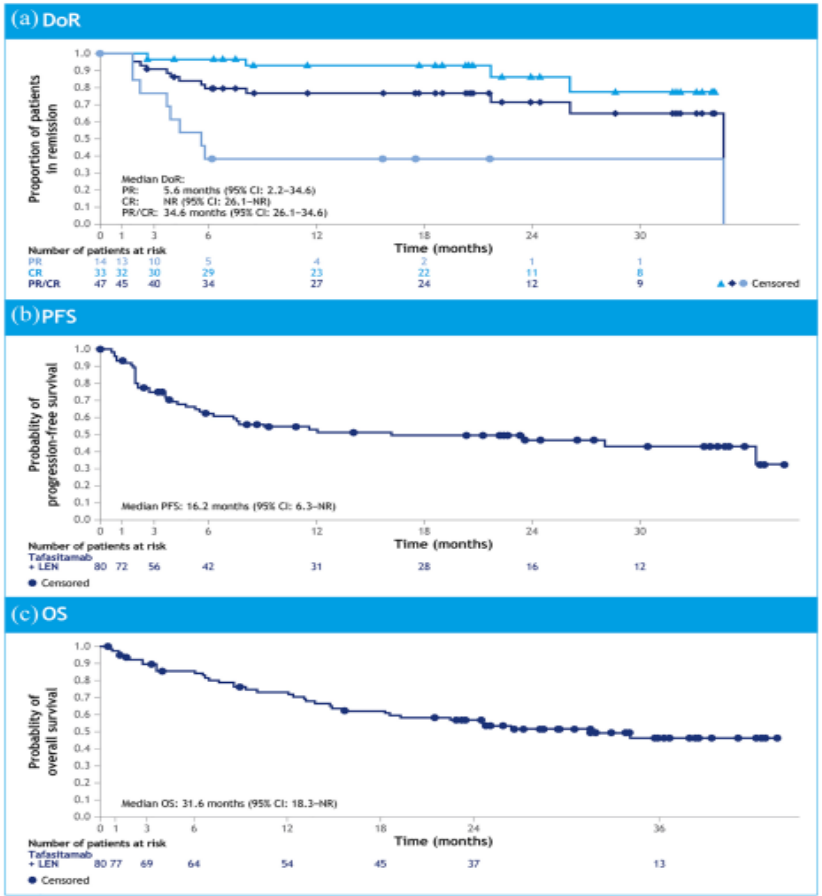


Figure 2. L-MIND schema.[43]

Table 1. ORR and CRR in the primary and long-term analyses of L-MIND.

	Tafasitamab plus lenalidomide N = 80[b]	
	Primary analysis Data cut-off: 30 November 2018[33]	Follow-up analysis Data cut-off: 30 November 2019[42]
Best objective response, *n* (%)		
CR	34 (43)	32 (40)
PR	14 (18)	14 (18)
ORR – CR + PR; *n* (%) (95% CI)[a]	48 (60) (48–71)	46 (58) (45.9–68.5)
Median DoR – IRC; months (95% CI)	21.7 (21.7–NR)	34.6 (26.1–34.6)
Median PFS – IRC; months (95% CI)	12.1 (5.7–NR)	12.1 (6.3–NR)
Median OS, months (95% CI)	NR (18.3–NR)	31.6 (18.3–NR)

[a]Using the two-sided 95% Clopper–Pearson exact method based on a binomial distribution.
[b]One patient received tafasitamab only and was excluded from 81 enrolled patients.
CI, confidence interval; CR, complete response; CRR, complete response rate; DoR, duration of response; IRC, independent review committee; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.



CI, confidence interval; CR, complete response; DoR, duration of response; LEN, lenalidomide; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response.

Therapeutic Advances in Hematology 12

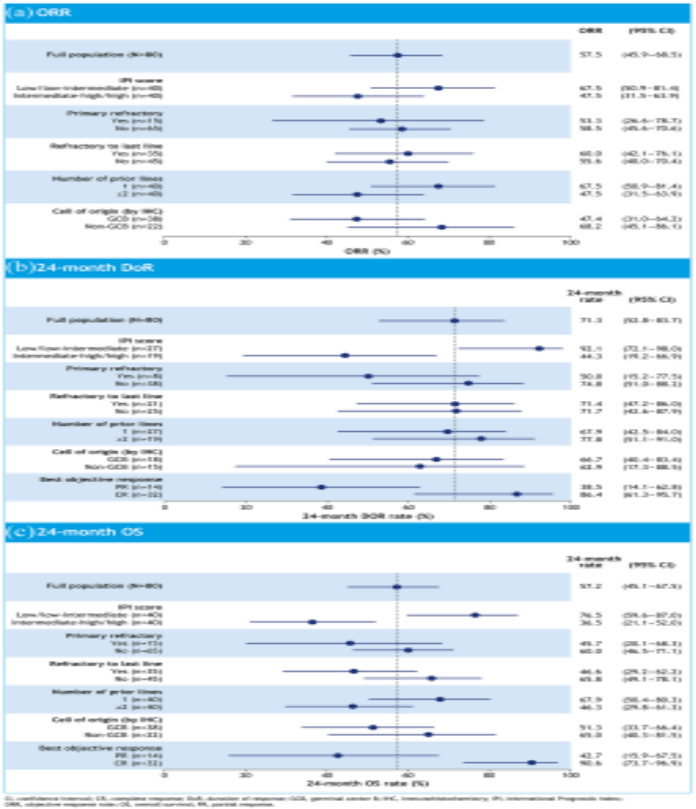


Figure 4. Forest plots for (a) ORR, (b) 24-month duration of response and (c) 24-month OS.[42]

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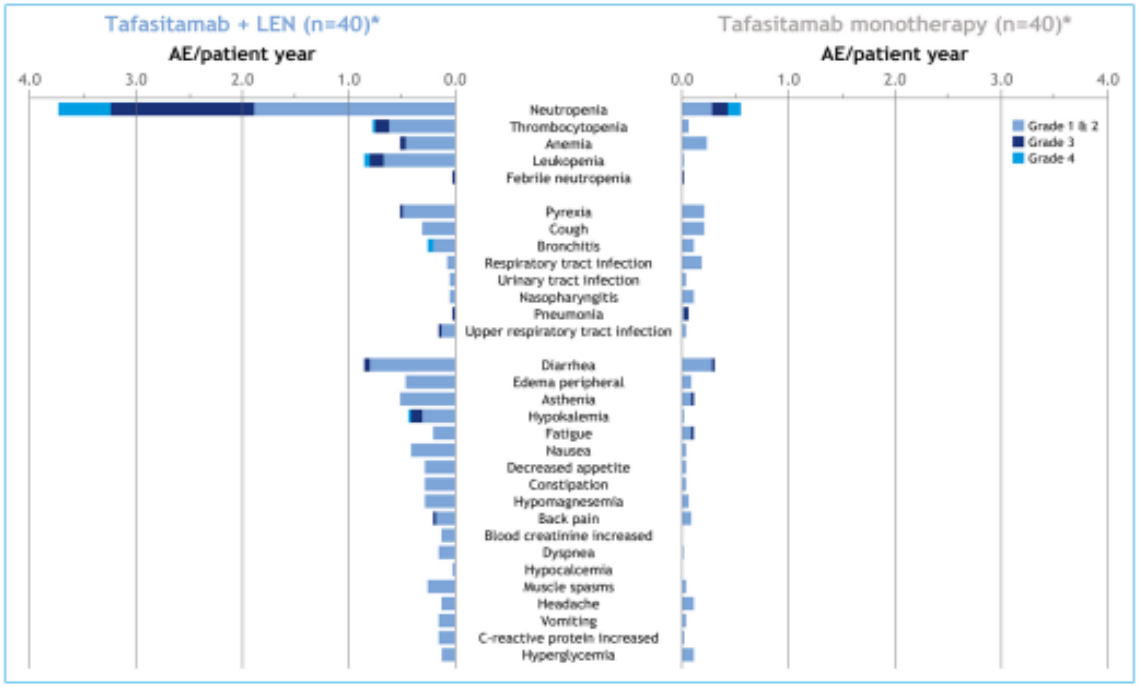

AE, adverse event; LEN, lenalidomide. *n = 40 includes 30 patients who completed 12 cycles of tafasitamab plus lenalidomide and continued tafasitamab monotherapy, and 10 patients who discontinued lenalidomide but continued tafasitamab monotherapy.

Figure 5. AEs per patient-year during combination and monotherapy phases.[43]
*n = 40 includes 30 patients who completed 12 cycles of tafasitamab plus lenalidomide and continued tafasitamab monotherapy and 10 patients who discontinued lenalidomide but continued tafasitamab monotherapy.
AE, adverse event; LEN, lenalidomide.

Tafasitamab Plus Lenalidomide Versus Pola-BR, R2 e CAR T: confronto dei risultati di RE-MIND2, uno studio di coorte osservazionale e retrospettivo nel linfoma diffuso a grandi cellule B recidivante/refrattario

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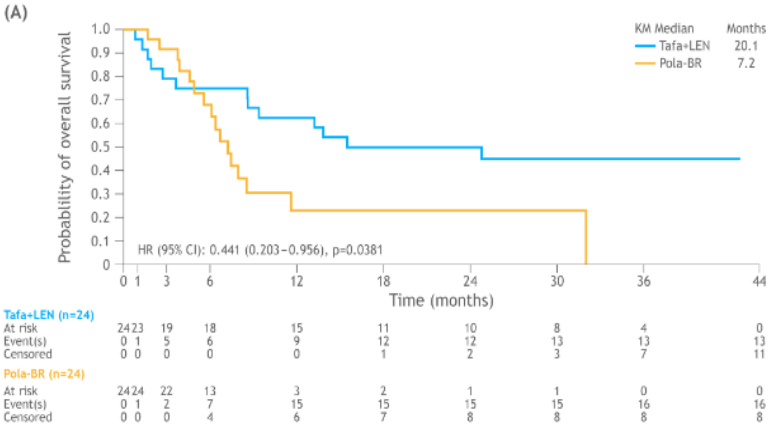
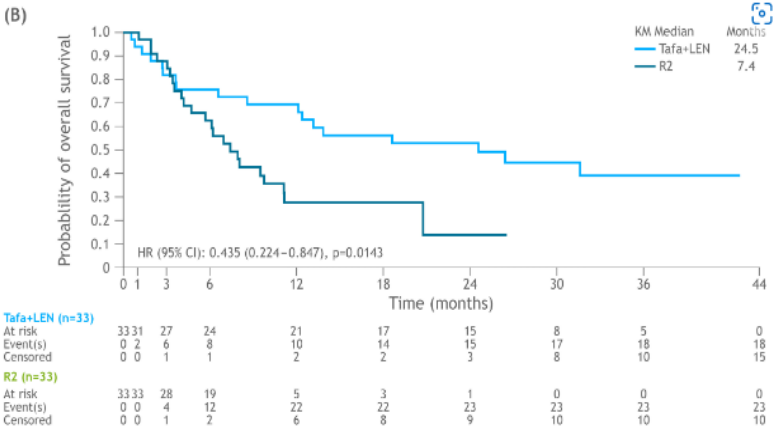
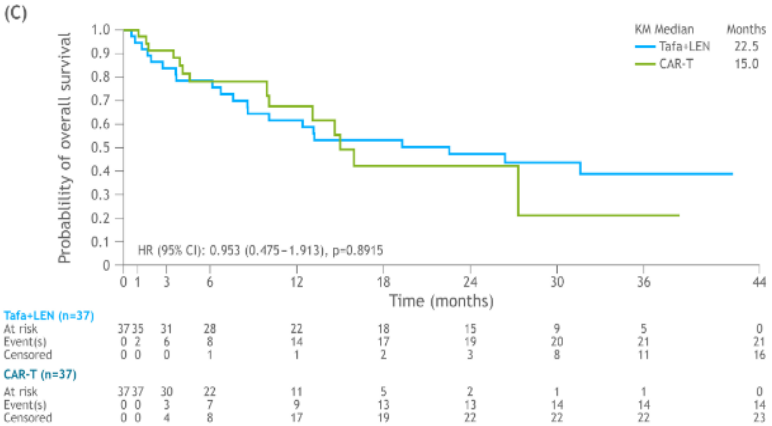
Abstract

Background

Several therapies are recommended by NCCN/ESMO guidelines for autologous stem cell transplant (ASCT)-ineligible patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). In the single-arm, Phase II L-MIND study (NCT02399085), the chemotherapy-free regimen tafasitamab + lenalidomide (LEN) demonstrated efficacy for this patient population. In the absence of randomized clinical trial data, RE-MIND2 (NCT04697160), an observational, retrospective cohort study, compared patient outcomes from L-MIND with matched patient populations treated with NCCN/ESMO recommended therapies for ASCT-ineligible patients with R/R DLBCL.







	Tafasitamab+LEN vs Pola-BR		Tafasitamab+LEN vs R2		Tafasitamab+LEN vs CAR-T	
	Tafasitamab + LEN (n=24)	Pola-BR (n=24)	Tafasitamab + LEN (n=33)	R2 (n=33)	Tafasitamab + LEN (n=37)	CAR-T (n=37)
ORR, n (%) (95% CI)	15 (62.5) (40.6–81.2)	14 (58.3) (36.6–77.9)	21 (63.6) (45.1–79.6)	10 (30.3) (15.6–48.7)	22 (59.5) (42.1–75.2)	28 (75.7) (58.8–88.2)
Fisher's exact test p-value of ORR	1.0000		0.0130		0.2140	
CRR as best response, n (%) (95% CI),	7 (29.2) (12.6–51.1)	5 (20.8) (7.1–42.2)	13 (39.4) (22.9–57.9)	5 (15.2) (5.1–31.9)	14 (37.8) (22.5–55.2)	16 (43.2) (27.1–60.5)
Fisher's exact test p-value of CRR	0.7400		0.0514		0.8131	
PFS (months), median (95% CI)	8.0 (1.9–19.9)	5.0 (2.5–5.6)	5.9 (3.6–36.7)	2.8 (2.0–5.8)	6.3 (3.6–22.5)	4.0 (3.1–12.8)
HR* (95% CI), p-value*	0.482 (0.217–1.073) 0.0740 Time dependent HR** <4 months of FU: 0.819 (0.339–1.978); 0.6572 ≥4 months of FU: 0.119 (0.027–0.529); 0.0052		0.511 (0.281–0.927) 0.0272		0.612 (0.302–1.240) 0.1731	
DoR, median (95% CI)	17.7 (3.6–34.8)	2.3 (0.3–6.1)	34.8 (3.6–34.8)	12.4 (2.7–19.3)	26.1 (4.4–NR)	5.9 (2.0–10.0)

Abbreviations: CAR-T, CD19 chimeric antigen receptor T-cell therapies; CI, confidence interval; CRR, complete response rate; DoR, duration of response; EFS, event-free survival; FU, Follow-up; LEN, lenalidomide; ORR, objective response rate; PFS, progression-free survival; pola-BR, polatuzumab vedotin + bendamustine + rituximab; HR, hazard ratio; R2, rituximab + lenalidomide. *Cox proportional hazard model. **Time dependent HRs are also used because hazards are not proportional. †Calculated using Wald Test.

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RESEARCH REPORT

Tafasitamab mediates killing of B-cell non-Hodgkin's lymphoma in combination with γδ T cell or allogeneic NK cell therapy

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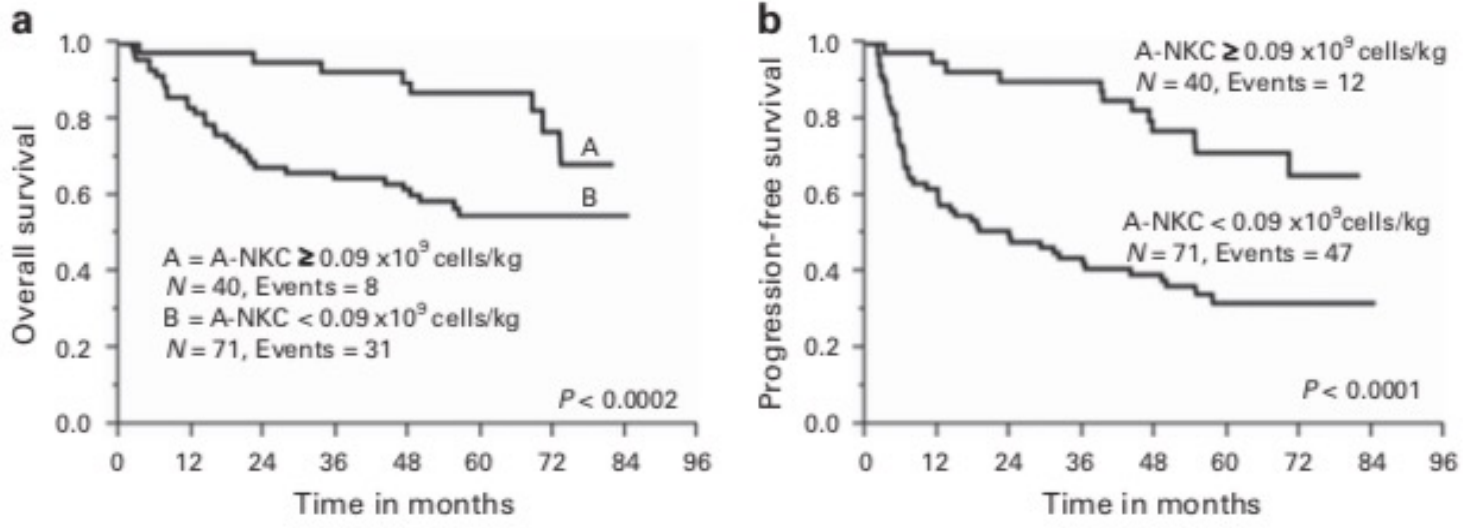
Abstract

Tafasitamab is an Fc-modified monoclonal antibody that binds to CD19, a cell-surface antigen that is broadly expressed on various types of B-cell non-Hodgkin's lymphoma (NHL). Antibody-dependent cellular cytotoxicity (ADCC), a key mode of action of tafasitamab, is mediated through the binding of tafasitamab's Fc region to FcγRIIIa receptors on immune effector cells and results in antitumor activity. Despite the proven clinical activity of tafasitamab in combination with lenalidomide in the treatment of diffuse large B-cell lymphoma (DLBCL), a higher number of immune cells in cancer patients may improve the activity of tafasitamab. Here, we characterized two ex vivo-expanded FcγRIIIa receptor—expressing cell types—γδ T and MG4101 natural killer (NK) cells—as effector cells for tafasitamab in vitro, and found that in the presence of these cells tafasitamab was able to induce ADCC against a range of NHL cell lines and patient-derived cells. We also explored the concept of effector cell supplementation during tafasitamab treatment in vivo by coadministering MG4101 NK cells in Raji and Ramos xenograft models of NHL. Combination treatment of tafasitamab and allogeneic MG4101 NK cells in these models demonstrated a survival benefit compared with tafasitamab or MG4101 monotherapy (Raji: 1.7- to 1.9-fold increase in lifespan; Ramos: 2.0- to 4.1-fold increase in lifespan). In conclusion, adoptive cell transfer of ex vivo-expanded allogeneic NK or autologous γδ T cells in combination with tafasitamab treatment may potentially be a promising novel approach to increase the number of immune effector cells and enhance the antitumor effect of tafasitamab.


a
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
A
B
A = A-NKC ≥ 0.09 x10^9 cells/kg
N = 40, Events = 8
B = A-NKC < 0.09 x10^9 cells/kg
N = 71, Events = 31
P < 0.0002
0 12 24 36 48 60 72 84 96
Time in months
b
Progression-free survival
A-NKC ≥ 0.09 x10^9 cells/kg
N = 40, Events = 12
A-NKC < 0.09 x10^9 cells/kg
N = 71, Events = 47
P < 0.0001
Time in months

Venetoclax and Navitoclax in Combination with Chemotherapy in Patients with Relapsed or Refractory Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma

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ABSTRACT Combining venetoclax, a selective BCL2 inhibitor, with low-dose navitoclax, a BCL-X_L/BCL2 inhibitor, may allow targeting of both BCL2 and BCL-X_L without dose-limiting thrombocytopenia associated with navitoclax monotherapy. The safety and preliminary efficacy of venetoclax with low-dose navitoclax and chemotherapy was assessed in this phase I dose-escalation study (NCT03181126) in pediatric and adult patients with relapsed/refractory (R/R) acute lymphoblastic leukemia or lymphoblastic lymphoma. Forty-seven patients received treatment. A recommended phase II dose of 50 mg navitoclax for adults and 25 mg for patients <45 kg with 400 mg adult-equivalent venetoclax was identified. Delayed hematopoietic recovery was the primary safety finding. The complete remission rate was 60%, including responses in patients who had previously received hematopoietic cell transplantation or immunotherapy. Thirteen patients (28%) proceeded to transplantation or CAR T-cell therapy on study. Venetoclax with navitoclax and chemotherapy was well tolerated and had promising efficacy in this heavily pretreated patient population.

SIGNIFICANCE: In this phase I study, venetoclax with low-dose navitoclax and chemotherapy was well tolerated and had promising efficacy in patients with relapsed/refractory acute lymphoblastic leukemia or lymphoblastic lymphoma. Responses were observed in patients across histologic and genomic subtypes and in those who failed available therapies including stem cell transplant.

See related commentary by Larkin and Burd, p. 1324.

Combinations

- ADC + Checkpoint inhibitors
  - BV + nivolumab
  - BV + nivolumab + ipilimumab
- ADC + BITE
  - Polatuzumab plus CD20/CD3 Ab
- BITE + PD1 inhibitors
  - Blinatumomab plus pembrolizumab
  - CD20/CD3 Ab + atezolimumab
- CART + PD1 inhibitors

City of Hope

Grazie per l'attenzione