Eppur si muove...

La terapia nel MONDO LINFOMI

Il razionale biologico delle combinazioni nei linfomi non Hodgkin

Dr Vincenzo Pavone

BARI, 28 GIUGNO 2022

R/R DLBCL

UNMET CLINICAL NEED

- Results of ASCT mainly in chemiosensitive patients
- median age for DLBCL nHL 65years
- CAR-T not for all pts

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

Immunotherapy Landscape

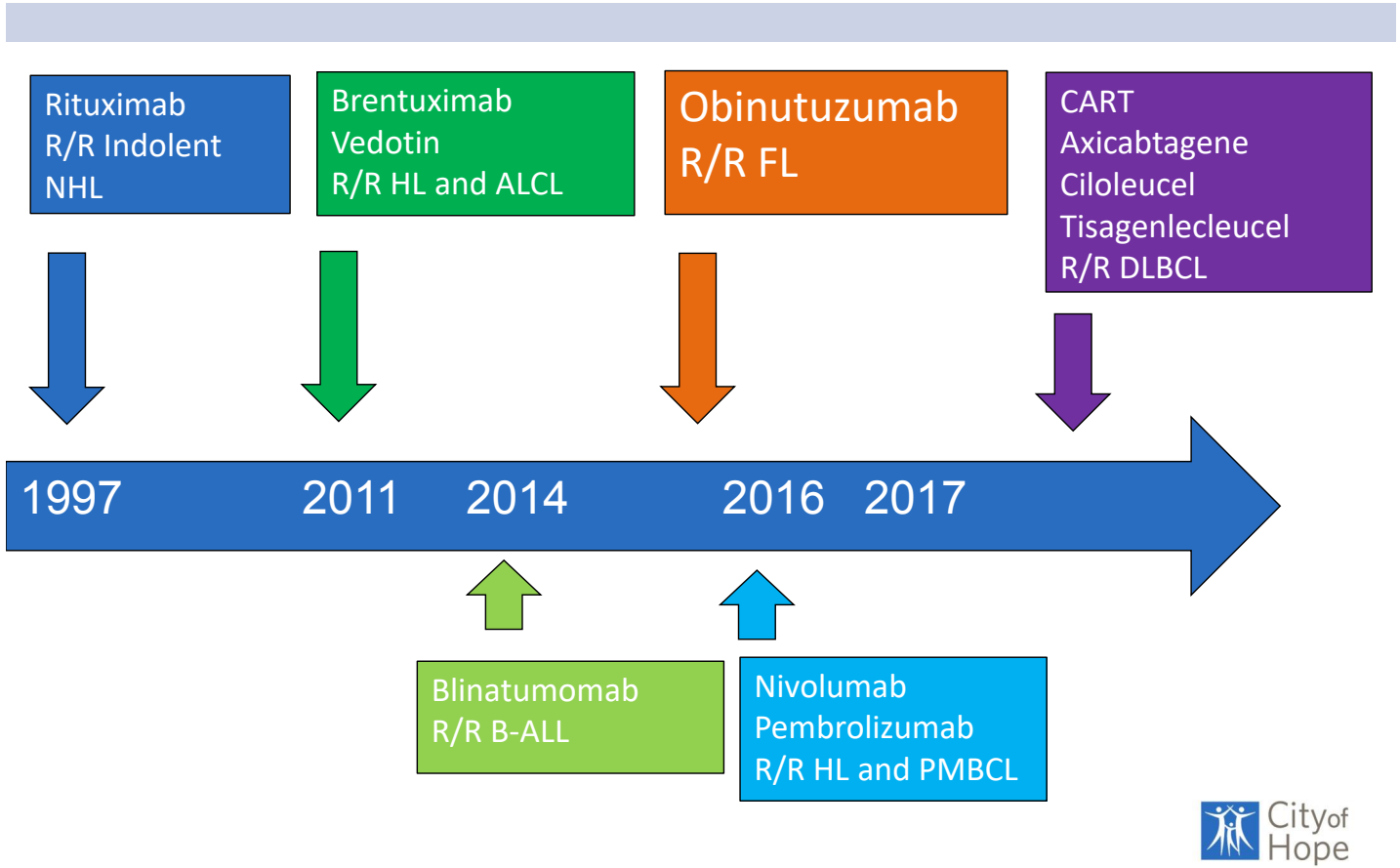

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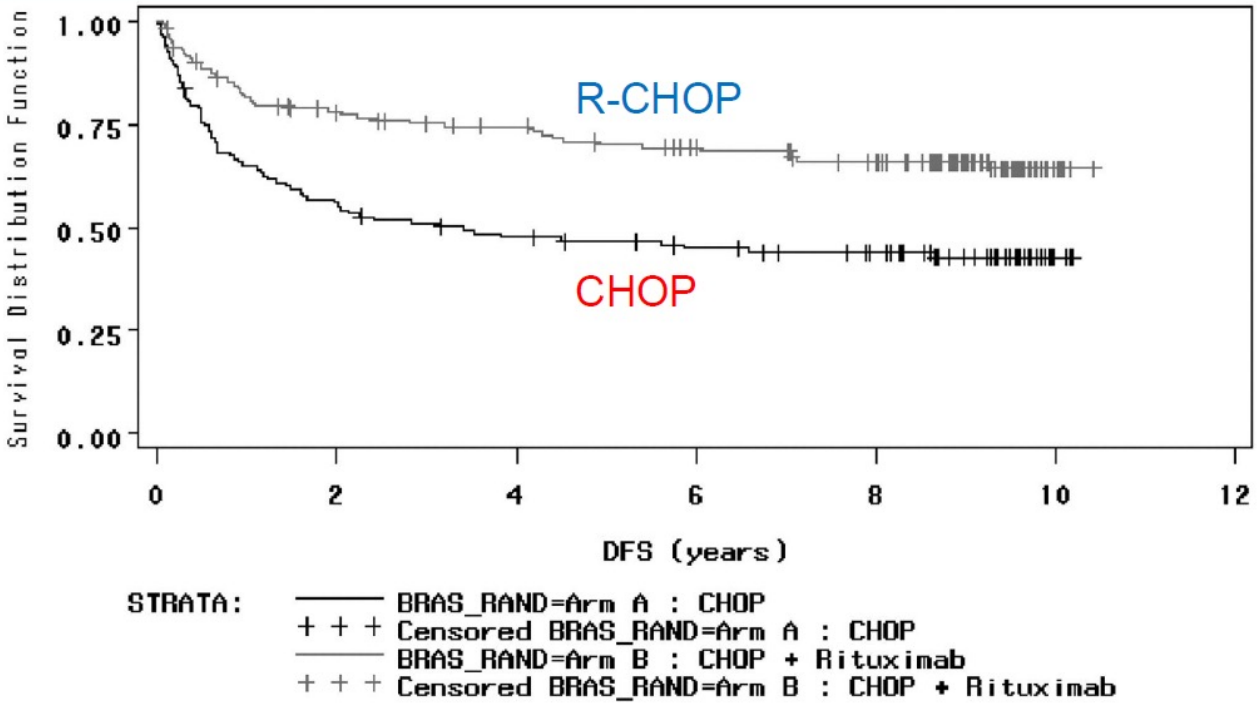
Table 10. Selected immunotherapy approaches clinically approved for treatment of NHL.

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]

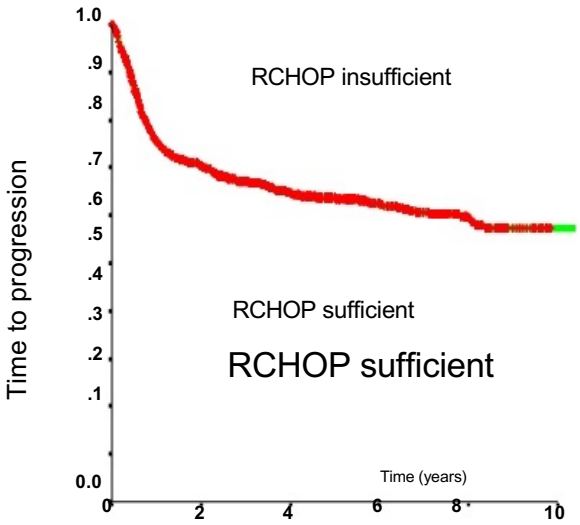
Abbreviations: B-NHL = B-non Hodgkin's lymphoma, CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma, FL = follicular lymphoma, R/R = relapsed/refractory, DLBCL = diffuse large B-cell lymphoma, T-PLL = T-prolymphocytic leukemia, PMBCL = primary mediastinal B-cell lymphoma, PCNSL = primary 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

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.

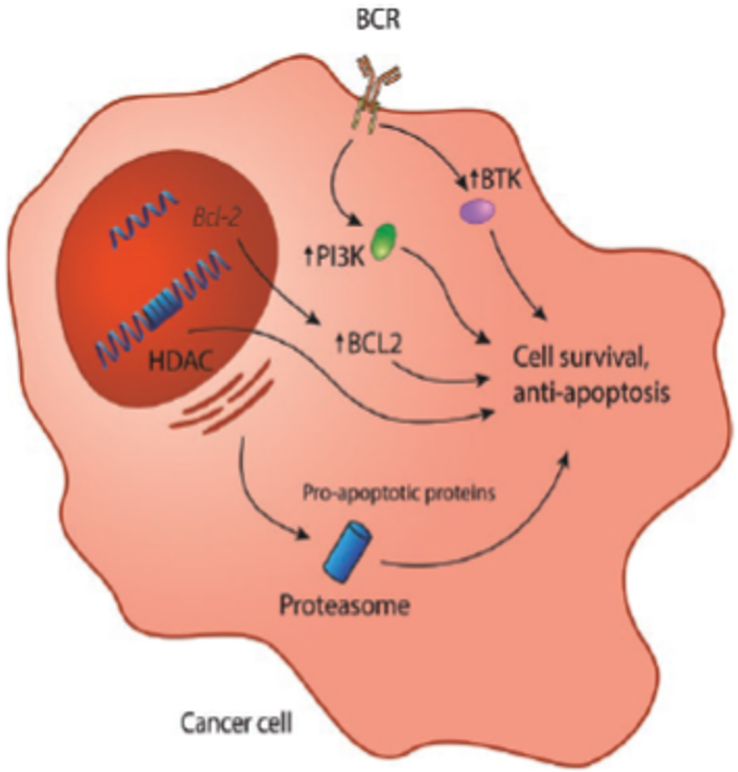


Figure 2 Schematic representation of key pathways that may promote cell survival in B-cell lymphoma. Several pathways that promote cell survival in B-cell lymphoma have been identified: increased expression of kinases PI3K and BTK, downstream of the B-cell receptor and increased BCL-2 expression after 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.

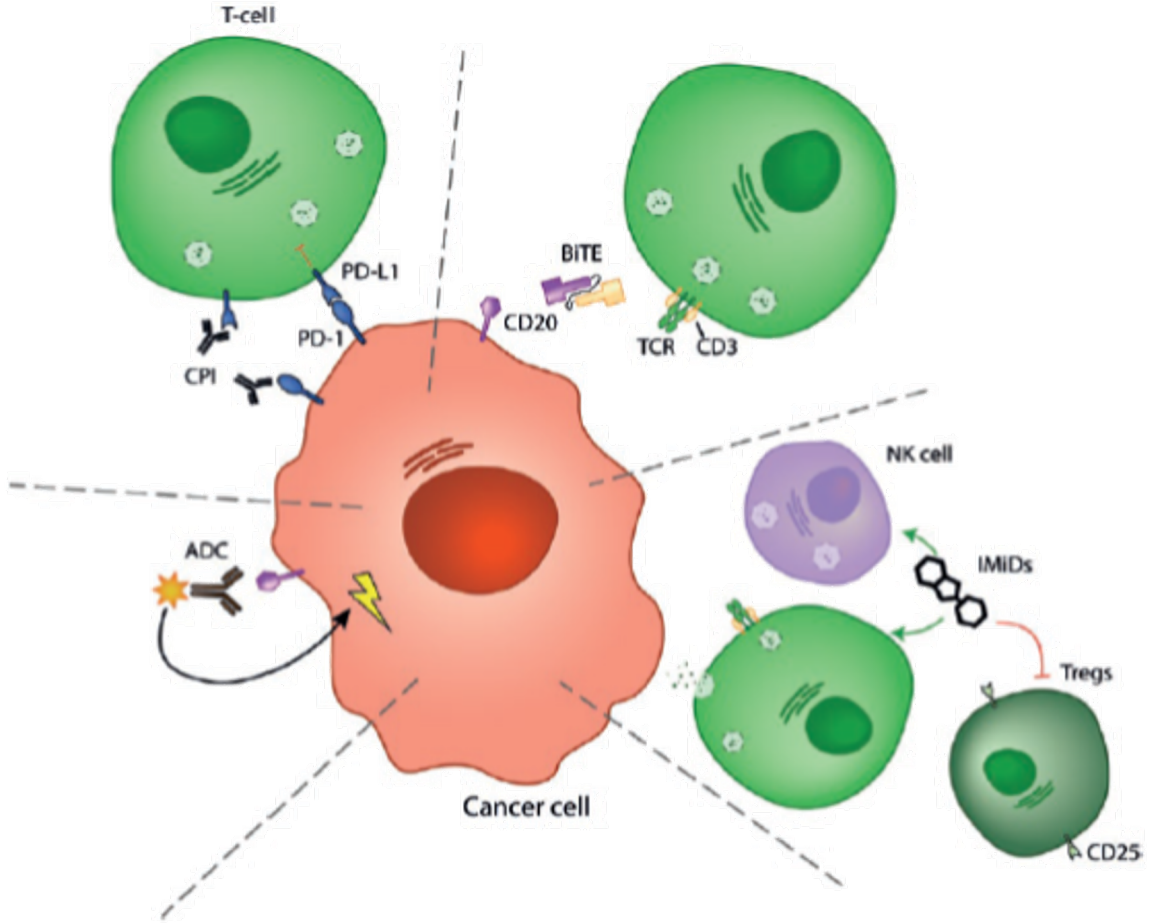


Figure 1 Schematic representation of immunotherapeutic options. Checkpoint inhibitors such as anti-PD-L1 can prevent cancer cells from suppressing T cell reactivity, thereby enhancing the immune response. Bispecific T cell engagers can keep T cells close to cancer cells to allow them to better exert their function. Immunomodulatory drugs stimulate the immune response through various approaches, such a s stimulating NK- and T-cells and inhibiting Tregs, Antibody-drug conjugates can carry toxic agents to the proximity of tumor cells. CPI: checkpoint inhibitor; ADC: antibody-drug conjugate; BiTE: bispecific T-cell engagers; TCR: T-cell receptor; NK: natural killer; Treg: T regulatory cell.

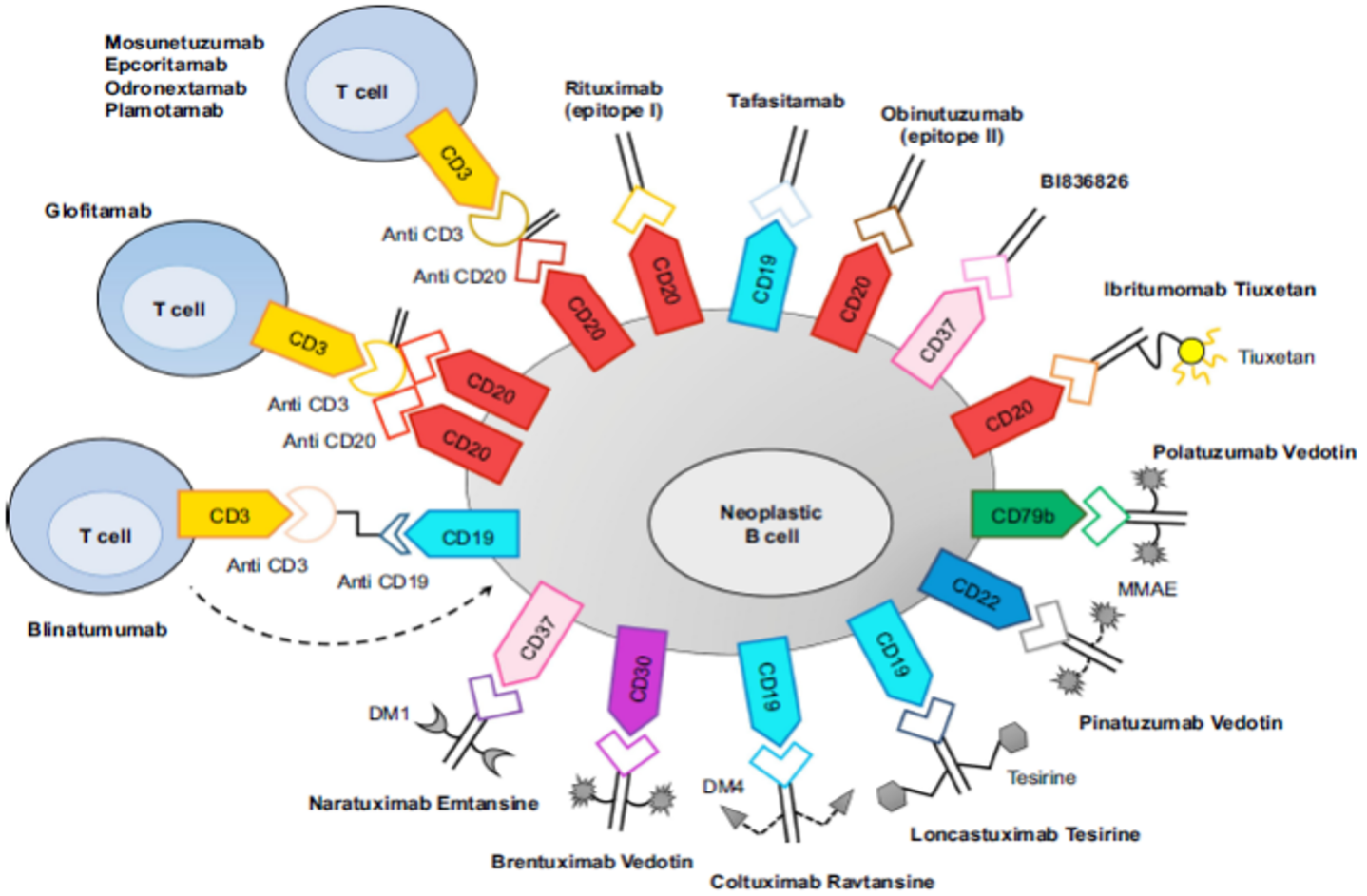
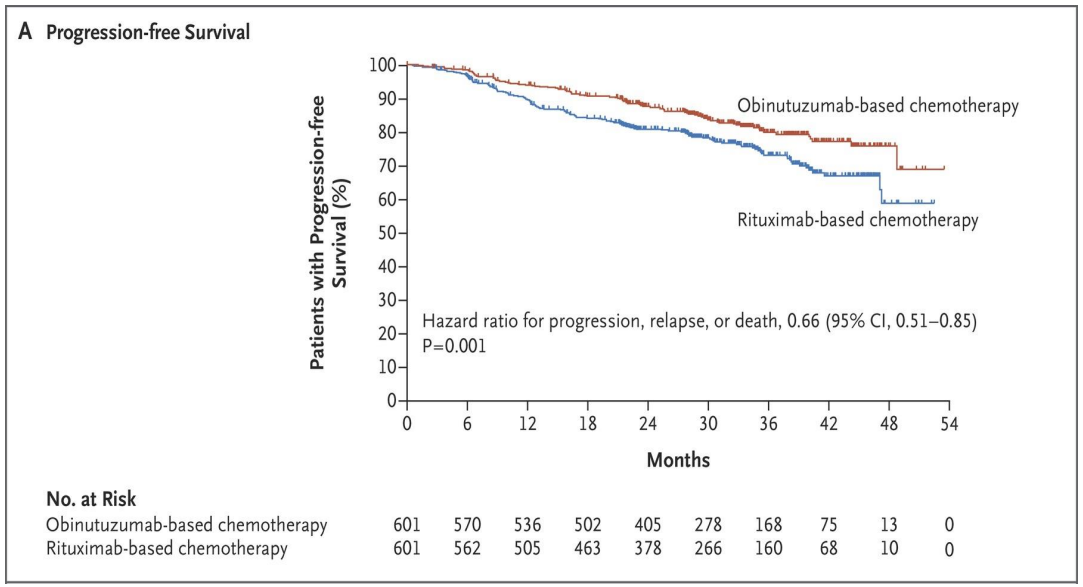


Figure 1 Monoclonal antibodies, including naked antibodies, antibody–drug conjugates, radioimmunoconjugates, and bispecific antibodies, are able to target Bcells on different surface antigens and with a number of cytotoxic mechanisms of action.

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

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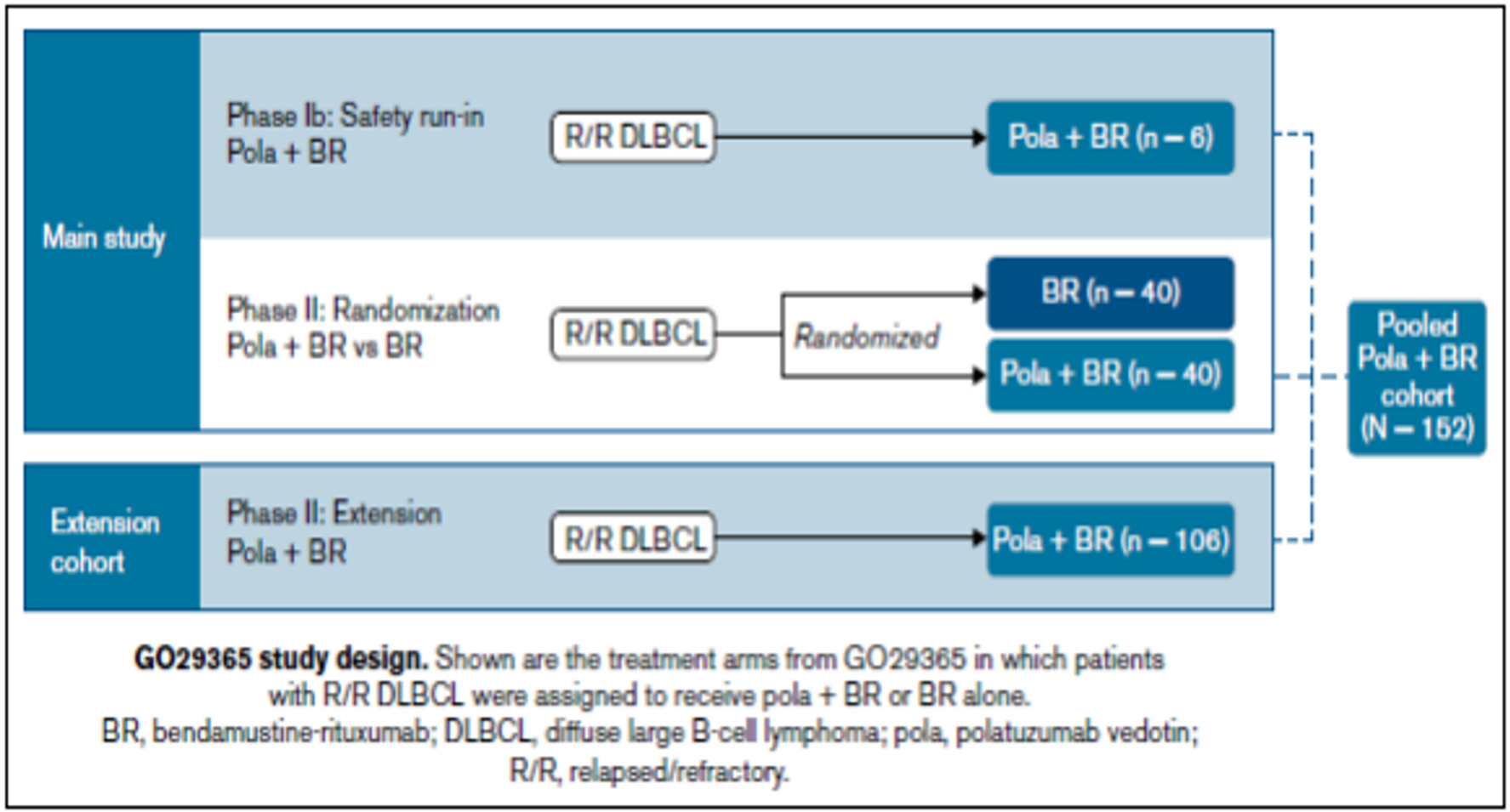
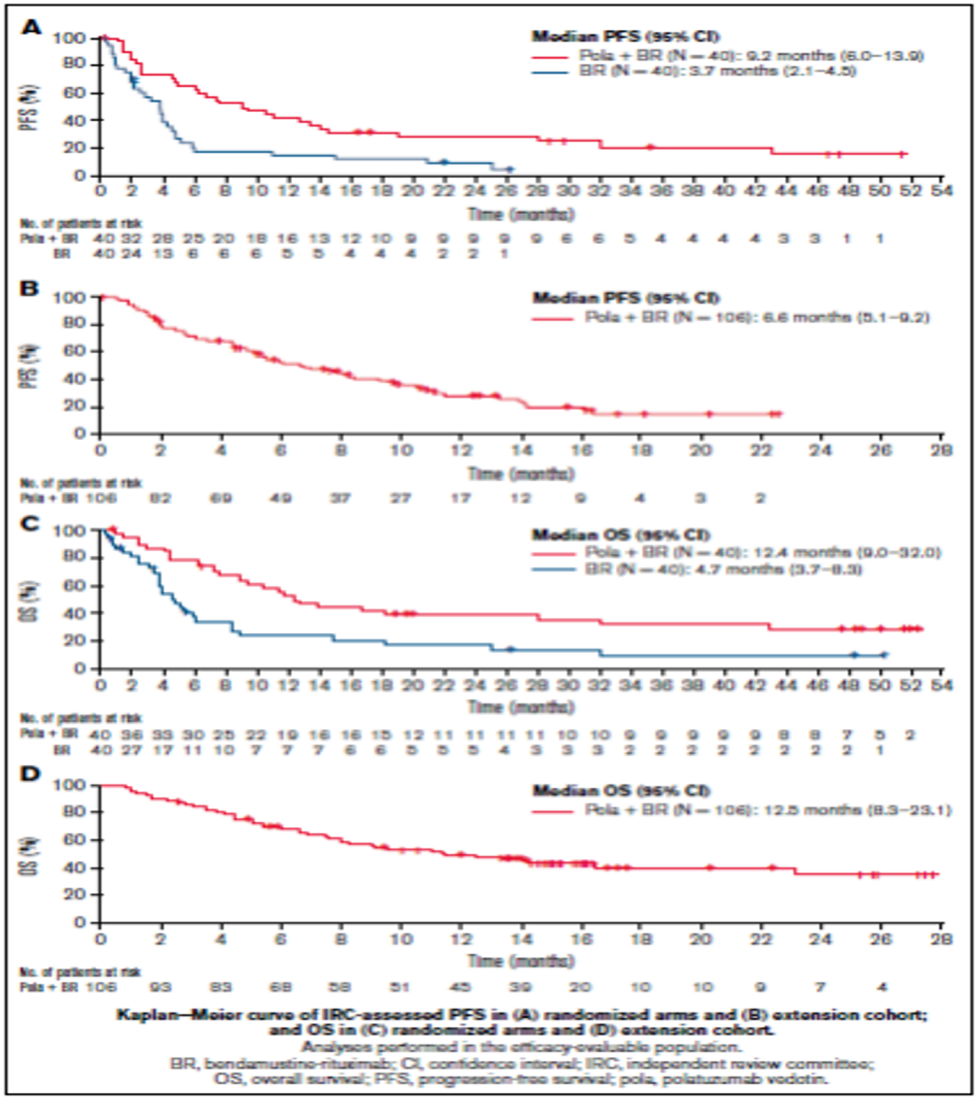
Key Points

- 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.

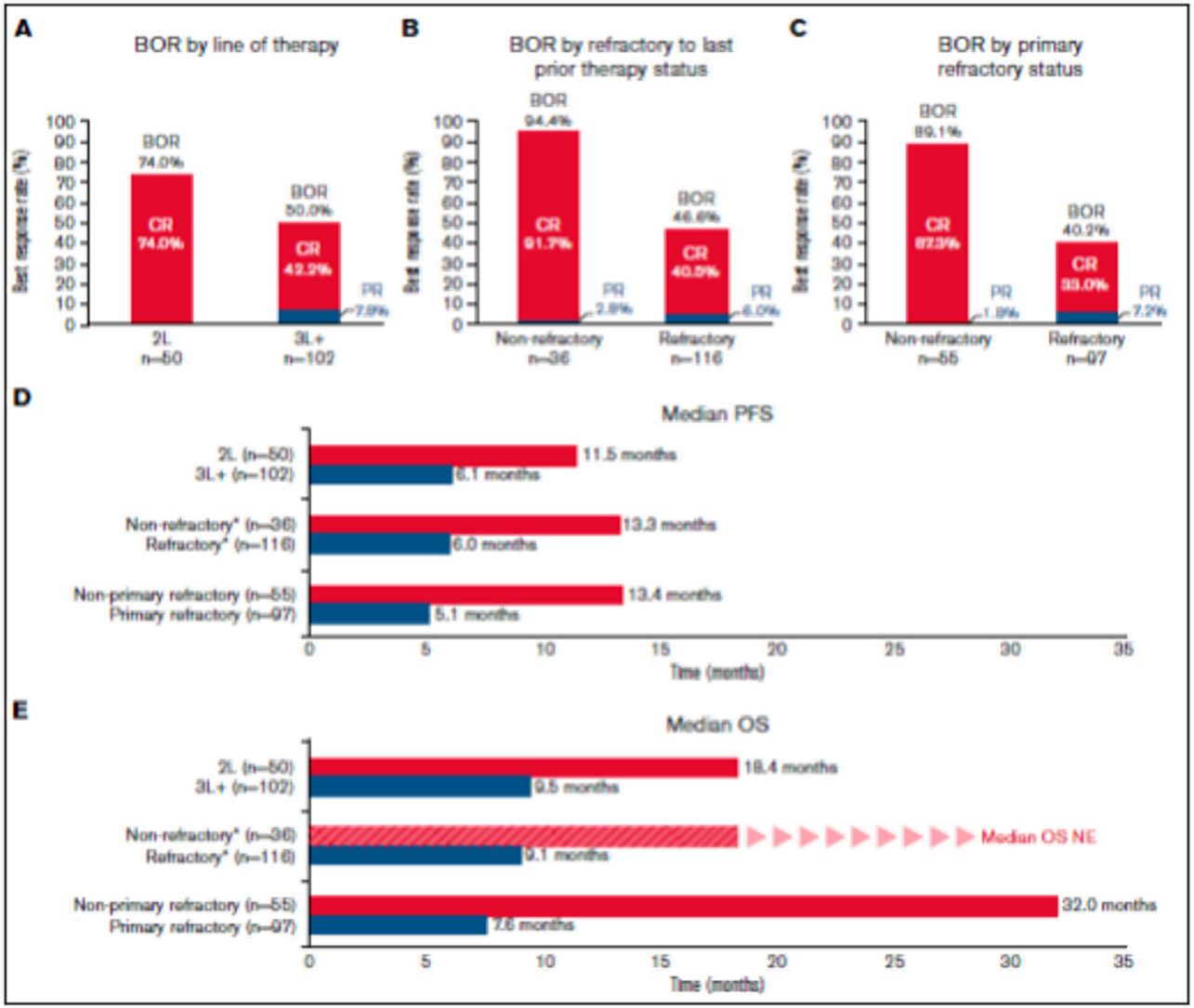
Polatuzumab vedotin plus bendamustine and rituximab (pola + BR) received regulatory approvals for relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) based on primary results from the randomized arms of the GO29365 study. After the randomized phase, 106 additional patients received pola + BR 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
18.4 months
9.5 months
Median OS NE
9.1 months
32.0 months
7.6 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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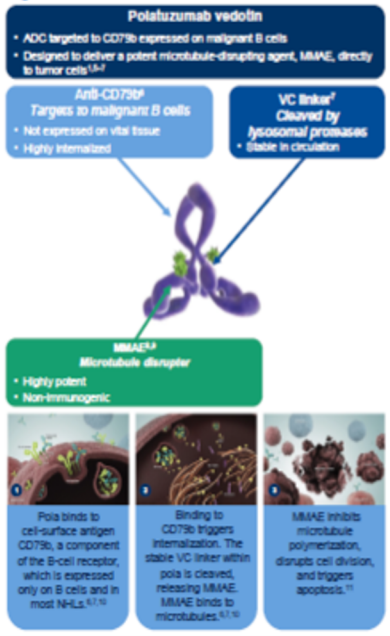
Background

- 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]

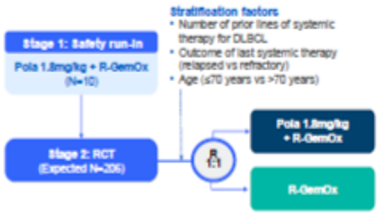


MMAE, monomethyl auristatin E; NHL, Non-Hodgkin lymphoma; VC, valine-citrulline.

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



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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Disclosures

Dr Haioun (Roche, Novartis, Servier/Pfizer, Gilead Sciences): consulting or advisory role; F. Hoffmann-La Roche Ltd, Celgene, Janssen-Cilag, Gilead Sciences, Takeda, Mitenyi Biotec): travel, accommodations or expenses; F. Hoffmann-La Roche Ltd, Celgene, Amgen): BMS: stock or other ownership interests; Genentech, Inc., Servier, Janssen, Takeda, Gilead Sciences): research funding; Genentech, Inc., F. Hoffmann-La Roche Ltd, AbbVie/Genmab, Servier, Pharmacyclics, Janssen, Takeda, Celgene, Roche Medical, Gilead Sciences): travel, accommodations or expenses; Genentech, Inc., F. Hoffmann-La Roche Ltd, Takeda, Celgene, Janssen, Gilead Sciences): patents, royalties, or licensing arrangements; F. Hoffmann-La Roche Ltd, Janssen, Gilead Sciences): patents, royalties, or licensing arrangements; F. Hoffmann-La Roche Ltd, Takeda, Celgene, Janssen, Gilead Sciences): consulting or advisory role; F. Hoffmann-La Roche Ltd, Janssen, Gilead Sciences): travel, accommodations or expenses; F. Hoffmann-La Roche Ltd, Janssen, Gilead Sciences): consulting or advisory role; F. Hoffmann-La Roche Ltd, Abbvie/Genmab, Novartis, Celgene): travel, accommodations or expenses; F. Hoffmann-La Roche Ltd, Abbvie/Genmab, Novartis, Celgene): consulting or advisory role; F. Hoffmann-La Roche Ltd, Abbvie/Genmab, Novartis, Celgene): travel, accommodations or expenses; F. Hoffmann-La Roche Ltd, Abbvie/Genmab, Janssen): employment; F. Hoffmann-La Roche Ltd): TP: employment; F. Hoffmann-La Roche

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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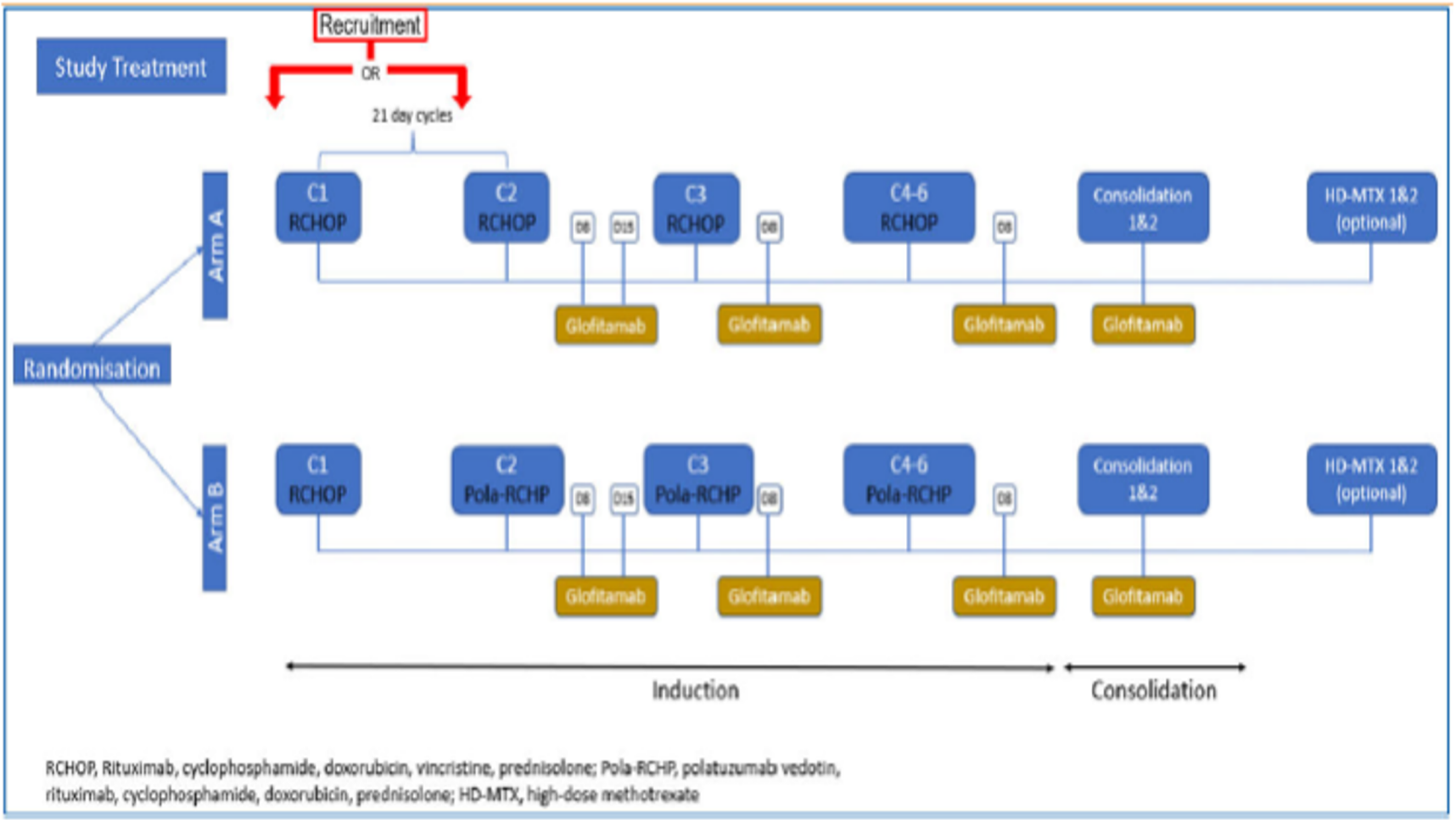
Abstract Background:
R-CHOP remains a standard frontline treatment for patients with DLBCL and high-grade B-cell lymphoma (HGBL). A significant proportion of patients will have refractory disease or subsequently relapse, particularly those with high-risk features such as an elevated IPI score or rearrangements 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)
C1 RCHOP
C2 Pola-RCHP
C3 Pola-RCHP
C4-6 Pola-RCHP
Consolidation 1&2
HD-MTX 1&2 (optional)
D8
D15
Glofitamab
Induction
Consolidation
RCHOP, Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; Pola-RCHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisolone; HD-MTX, high-dose methotrexate

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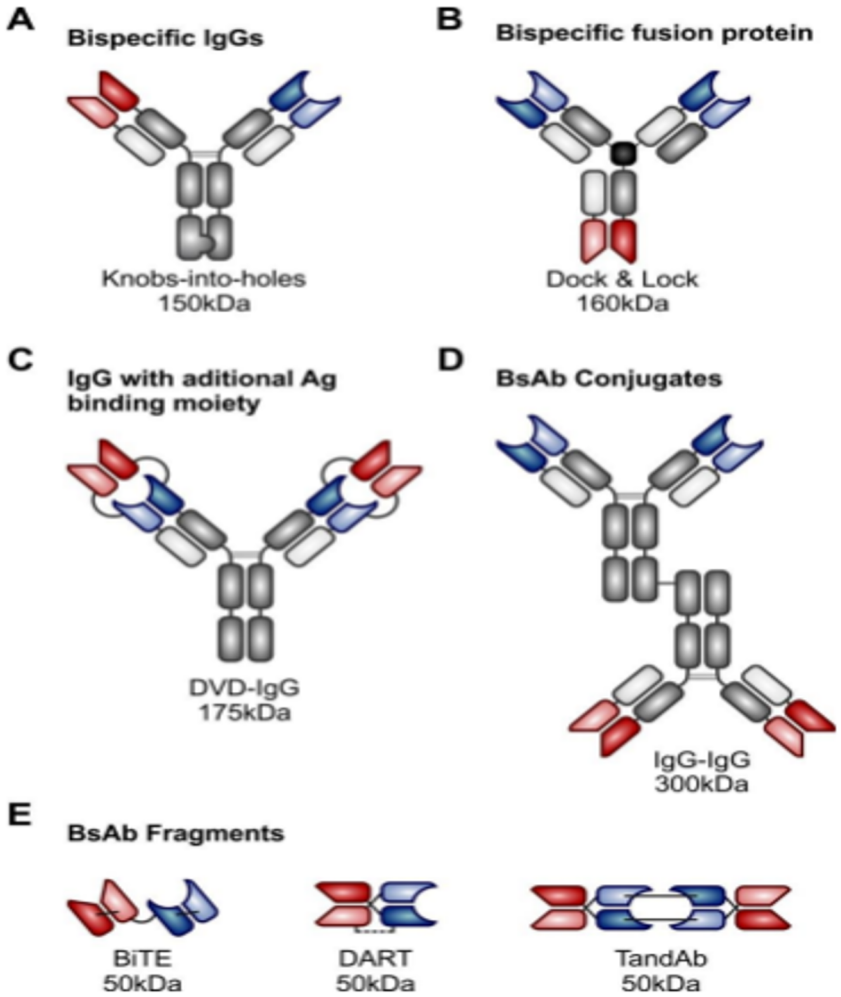
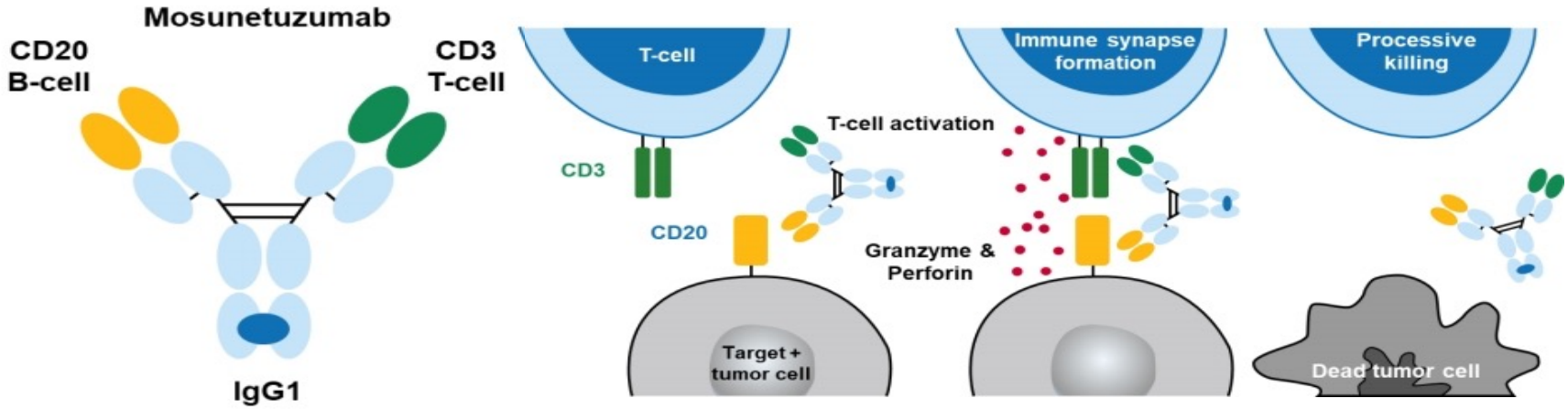


Novel Agents for DLBCL: Bispecific Antibodies

Mosunetuzumab: a bispecific antibody targeting CD3 and CD20

- **Full-length humanized IgG1 antibody**
  - Longer half-life than fragment-based drug formats
  - PK properties enable once weekly to q3w dosing
  - Does not require *ex-vivo* T-cell manipulation
  - Off the shelf, readily available treatment

- **Mechanism of action**
  - Redirects T-cells to engage and eliminate malignant B-cells
  - Conditional agonist: T-cell activation dependent on B-cell engagement
  - Amino-acid substitution (N297G) to inactivate ADCC and avoid destruction of engaged T cells



ADCC, antibody-dependent cell-mediated cytotoxicity

Sun et al. Sci Transl Med 2015

AEs of special interest

n, (%)	All safety-evaluable (N=131)	Description
CRS (Lee criteria) [1]	30 (22.9%)	• Majority during cycle 1; median duration 2 days (range 0–19) • Two patients treated with tocilizumab • 40/41 (98%) events resolved
Grade 1–2	30 (22.9%)	
Grade ≥3	0	
Neurologic AEs †	64 (48.9%)	• Most common: headache (15.3%), dizziness (9.9%), insomnia (9.2%) • Grade 3: seizure (HLH); confusion and hepatic encephalopathy; post-herpetic neuralgia (n=1 each)
Grade 1–2	61 (46.6%)	
Grade ≥3	3 (2.3%)	
Treatment-related (any grade) ‡	27 (20.6%)	
Treatment-related (Grade ≥3) ‡	1 (0.8%)	
Neutropenia*	25 (19.1%)	• Responsive to G-CSF; 37/41 (90%) events resolved • No concurrent Grade ≥3 infections reported
Grade 1–2	3 (2.3%)	
Grade ≥3	22 (16.8%)	
Febrile neutropenia	4 (3.1%)	

- *Includes AE terms 'neutropenia' and 'neutrophil count decreased'. Febrile neutropenia events were deemed unrelated to mosunetuzumab by investigator; Defined as all AEs occurring in either the SOC nervous system disorders or SOC psychiatric disorders. Per investigator assessment; Data cut-off date: 17 August 2018

- 1. Lee DW, et al. Blood 2014;124:188–195

MOSUNETUZUMAB

218 R/R BnHL: 44% CR

grade 2 CRS, and neurotoxicity

DLBCL nHL 85% CR ORR 98%

future direction:

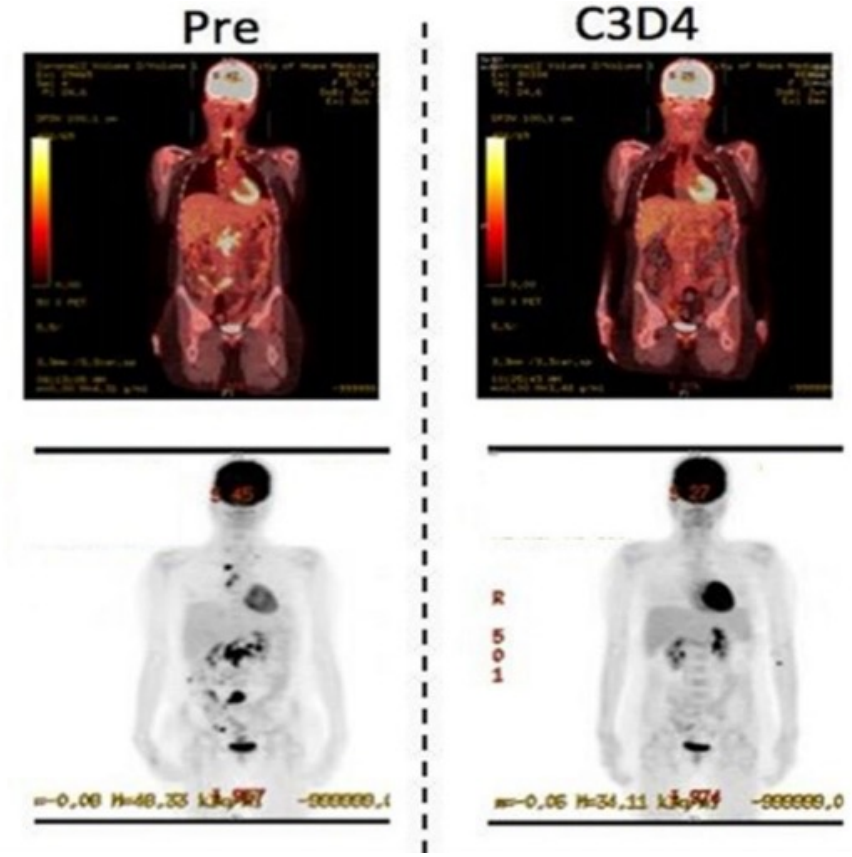
1st Line MOSU+/- POLATUZUMAB

MOSU as consolidation after PR

Bridge to transplant and/or CAR-T

Novel Agents for DLBCL: Bispecific Antibodies

CR in a CAR-T-refractory patient with DLBCL



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.

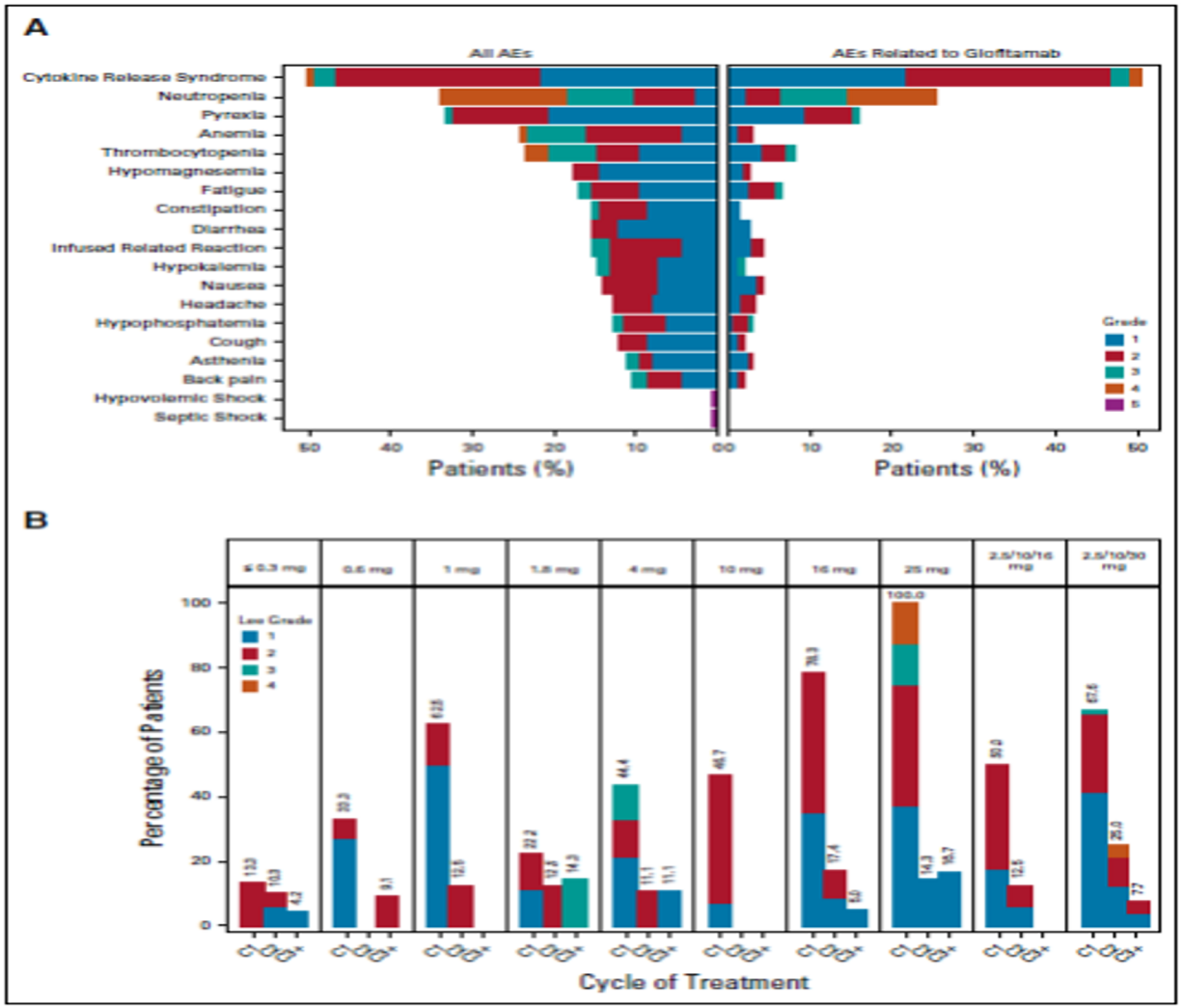
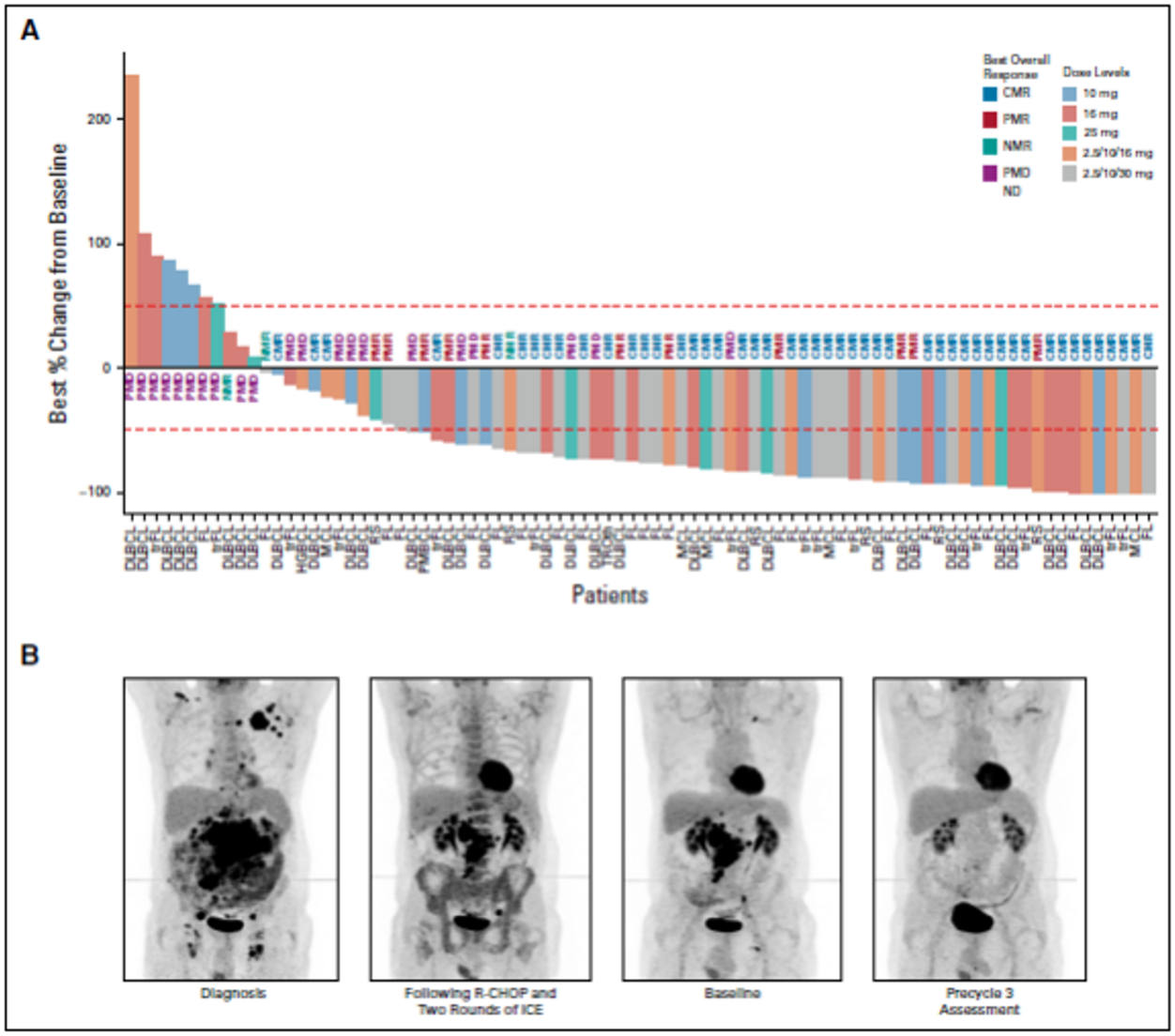


FIG 1. (A) Shows adverse events with an incidence of ≥ 10% or an NCI-CTCAE grade of 5 as of August 3, 2020. (B) Shows the incidence of CRS by cycle and dose (Lee grade).[28] CRS events were predominantly confined to cycles 1 and 2. Step-up


A
Best Overall Response
CMR
PMR
NMR
PMD
ND
Dose Levels
10 mg
16 mg
25 mg
2.5/10/16 mg
2.5/10/30 mg
Best % Change from Baseline
200
100
0
−100
Patients
B
Diagnosis
Following R-CHOP and Two Rounds of ICE
Baseline
Precycle 3 Assessment

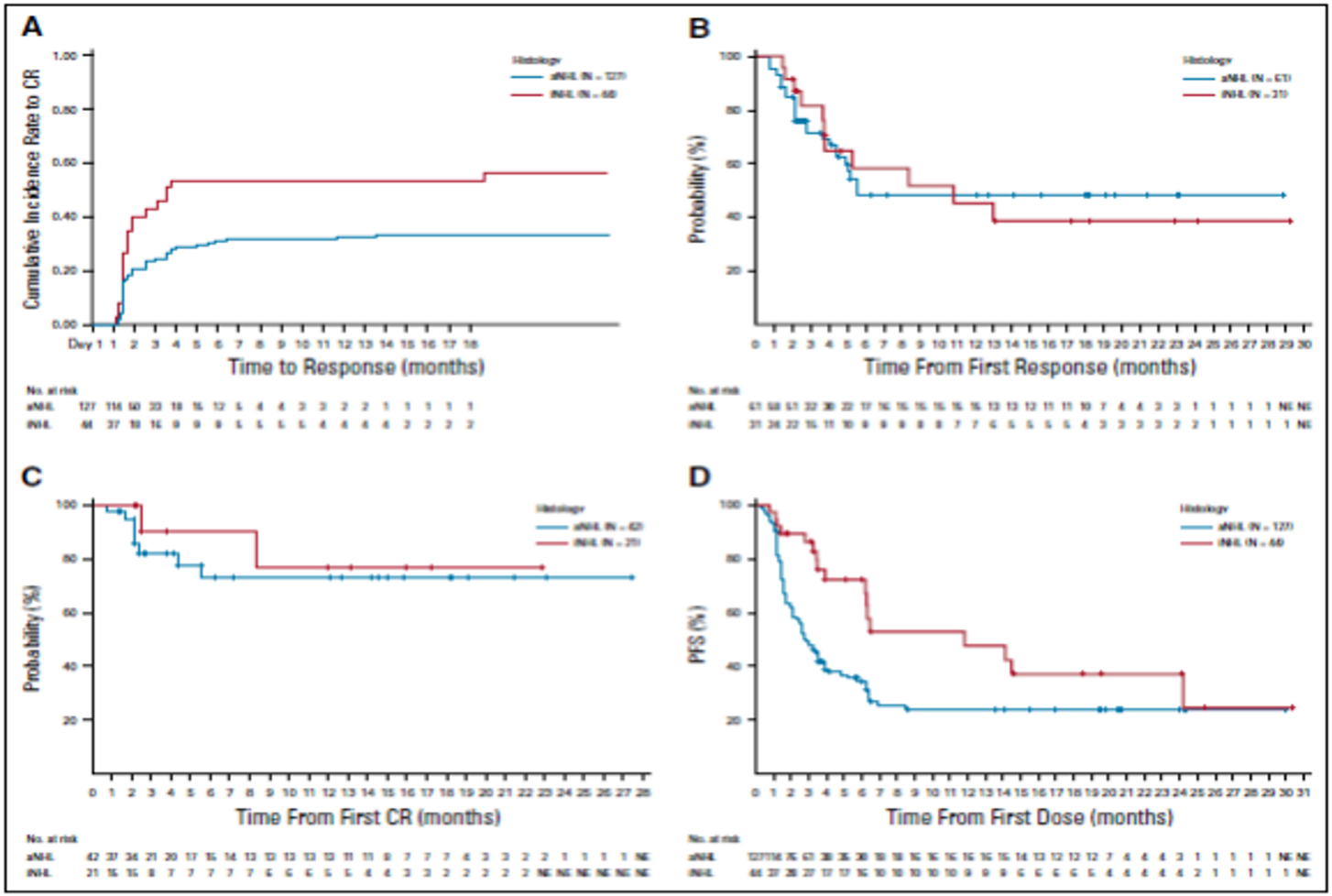


FIG 3. (A) Represents the cumulative incidence of time to CR. Kaplan-Meier curves for (B) DOR (PR and CR), (C) duration of CR, and (D) PFS. aNHL, aggressive non-Hodgkin lymphoma; CR, complete response; DOR, duration of response; iNHL, indolent non-Hodgkin lymphoma; NE, not estimable; PFS, progression-free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

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GLOFITAMAB

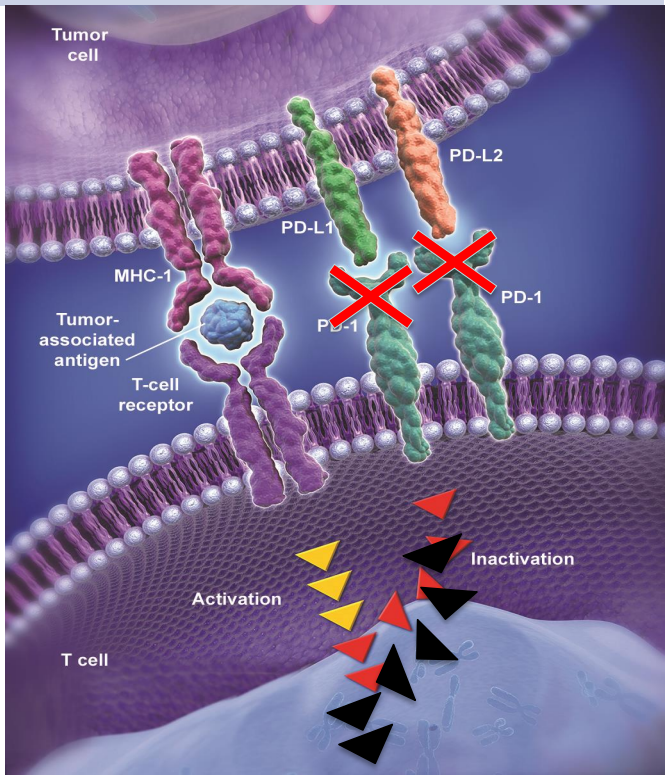
Table 3. Selected clinical trials that incorporate glofitamab in experimental therapy of B-NHL.

Drug Combination	Target Antigens	Mode of Action of the Combination Agent(s) Other Than Bispecific Antibody	Study Phase	Disease Status	Estimated Study Completion Date	ClinicalTrials.gov Identifier (Other Identifier)
Glofitamab + GemOx compared to rituximab + GemOx	CD20/CD3	cytostatics gemcitabine and oxaliplatin (GemOx), anti-CD20 rituximab	3	R/R DLBCL	March 2022	NCT04408638
Glofitamab + obintuzumab with obinutuzumab pretreatment	CD20/CD3	glycoengeneered anti-CD20 obinutuzumab	1	R/R B-NHL	June 2022	NCT03075696
Glofitamab + obintuzumab or rituximab + CHOP with obinutuzumab pretreatment	CD20/CD3	chemotherapy CHOP, anti-CD20 obintuzumab, anti-CD20 rituximab	1	newly dg and R/R B-NHL	December 2023	NCT03467373
Glofitamab + atezolizumab or polatuzumab-vedotin with obinutuzumab pretreatment	CD20/CD3	PD-L1 inhibitor atezolizumab, anti-CD79B antibody-drug conjugate polatuzumab-vedotin	1	R/R B-NHL	August 2021	NCT03533283
Glofitamab + RO7227166 with obinutuzumab pretreatment	CD20/CD3	CD19 Targeted 4-1BB Ligand RO7227166	1	R/R B-NHL	January 2023	NCT04077723
Glofitamab + lenalidomide +/− obinutuzumab	CD20/CD3	Immunomodulatory agent lenalidomide	1	R/R FL	August 2022	NCT04246086

Abbreviations: CHOP= cyclophosphamide + doxorubicin + vincristine + prednisone; DLBCL= diffuse large B-cell lymphoma; FL= follicular lymphoma; PD-L1= programmed death ligand 1; R/R= relapsed/refractory; B-NHL= B cell non-Hodgkin lymphomas.

The PD-1 and PD-L1/L2 Pathway

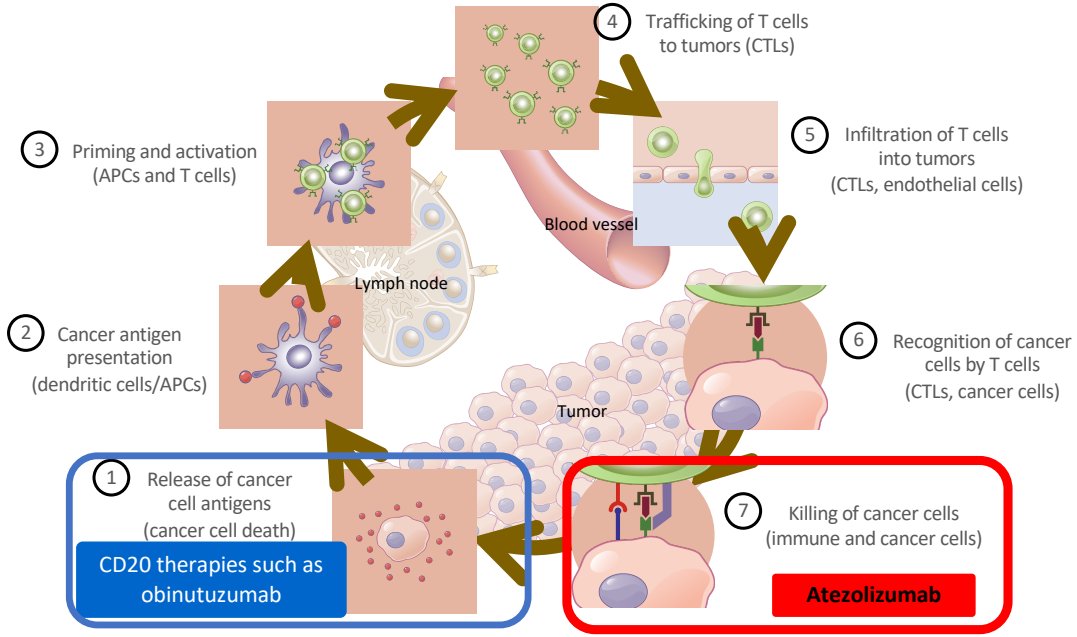
- PD-1 is an immune checkpoint receptor
- Binding of PD-1 by its ligands PD-L1 or PD-L2 leads to downregulation of T-cell function
- This mechanism is usurped by many tumors
- PD-1 blockade through mAb therapy can restore effective anti-tumor immunity



Topalian et al. *N Engl J Med*. 2012.
Garon et al. *N Engl J Med*. 2015.
Robert et al. *Lancet*. 2014.

City of Hope

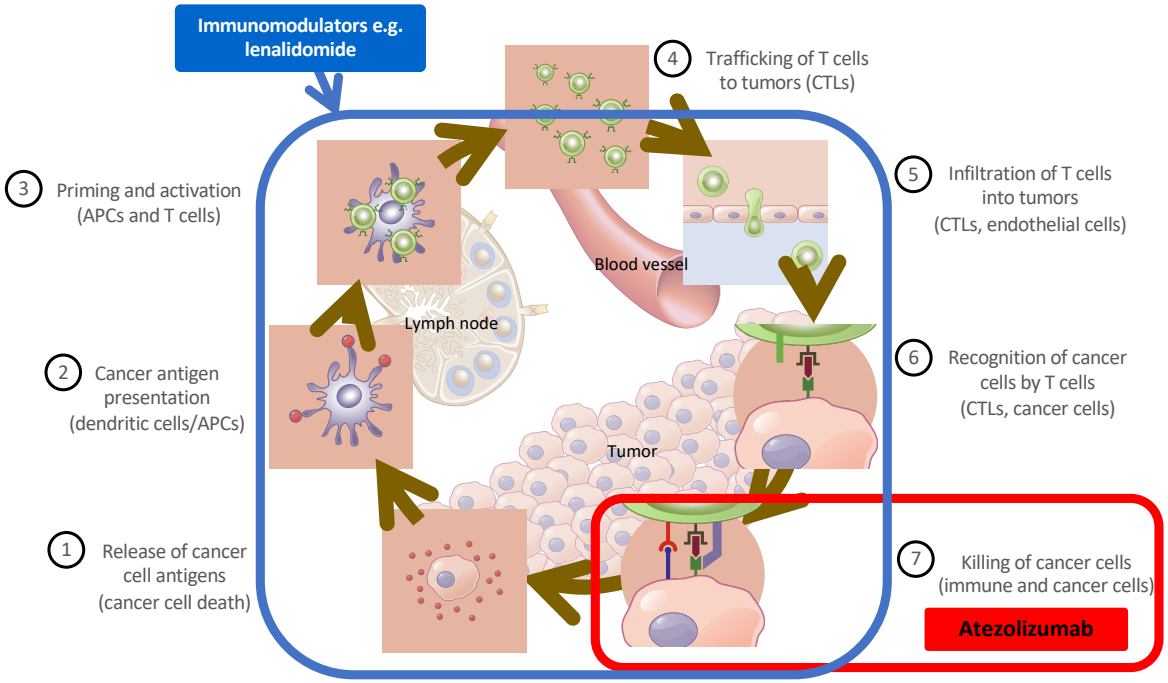
Atezolizumab + obinutuzumab: rationale for combination



References: 1. Anderson KC, et al. *Blood*. 1984;63:1424-1433. **2.** Mössner E, et al. *Blood.* 2010;115:4393-4402. **3.** Merelli B, et al. *Crit Rev Oncol Hematol.* 2014;89:140-165.

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

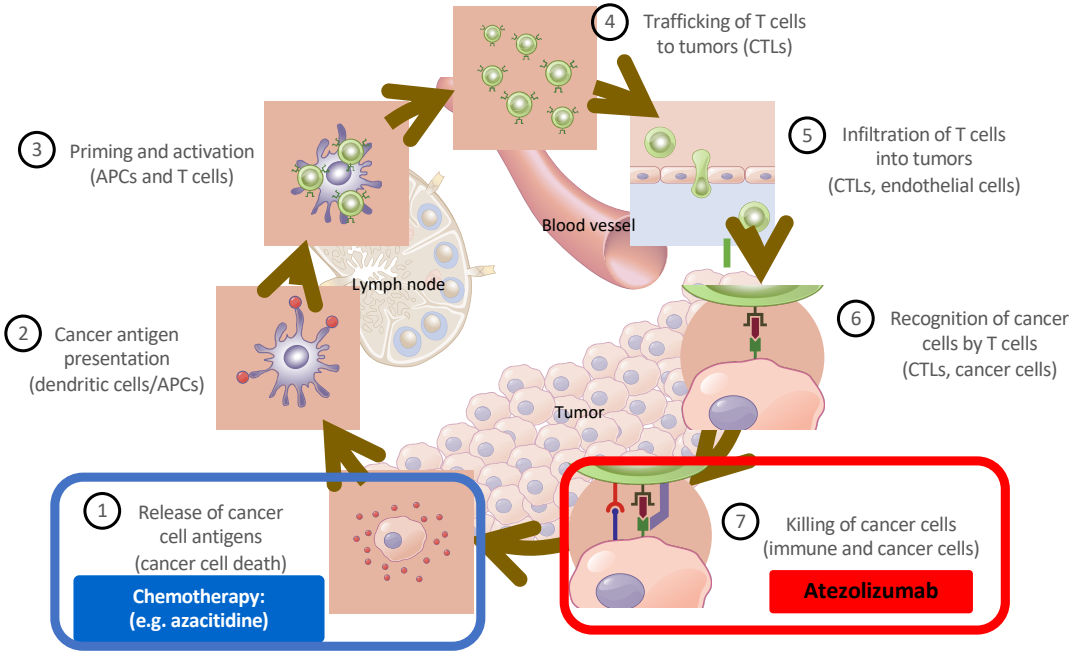
Atezolizumab + lenalidomide: rationale for combination



References: 1. Kotla V, et al. *J Hematol Oncol.* 2009;2:36. **2.** Dimopoulos MA, et al. *Crit Rev Oncol Hematol.* 2013;88(suppl 1):S23-35.

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

Atezolizumab + azacitidine: rationale for combination



References: 1. Zitvogel L, et al. *Nat Rev Immunol*, 2008. 8, 59-73. **2.** Chen DS, Mellman I. *Immunity*. 2013;39:1-10. **3.** Giaccone G, et al. ECC. 2015 [abstract P247]. **4.** Liu SV, et al. ASCO. 2015 [abstract 8030]

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

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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

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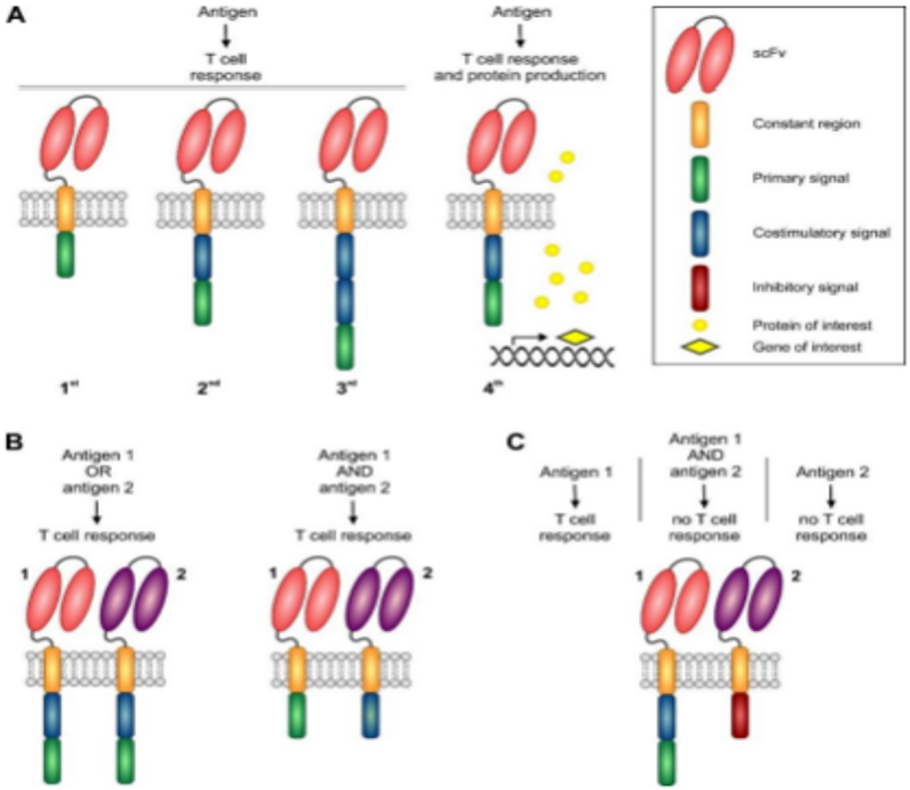


Figure 4. Schematic representation of design of four generations of CAR. **Legend: Conventional CARs:** (**A**) 1st to 3rd generation are defined by their signaling domains: a primary signaling domain only (1st generation); signaling and co-stimulatory domains (2nd generation); combined co-stimulatory 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

Johannes Düll, Max Topp and Gilles Salles

Ther Adv Hematol

2021, Vol. 12: 1–13

DOI: 10.1177/20406207211027458

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

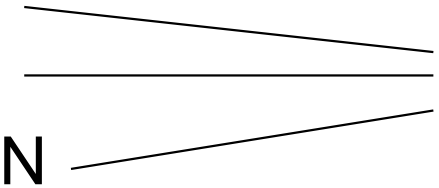
↓ Down regulate expression of checkpoint inhibitors

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

↑ ADCC

TAFASITAMAB plus LENALIDOMIDE

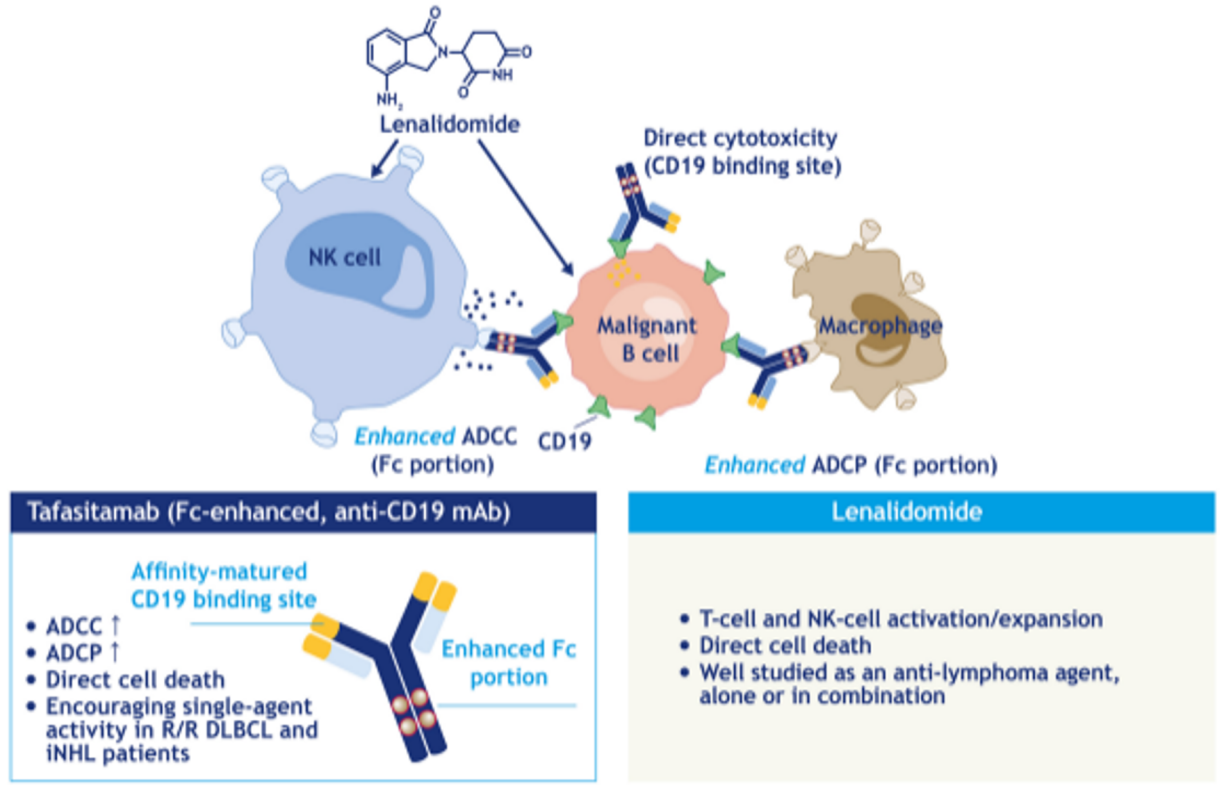
STIMULATION
ACTIVATON
PROLIFERATION



NK

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]

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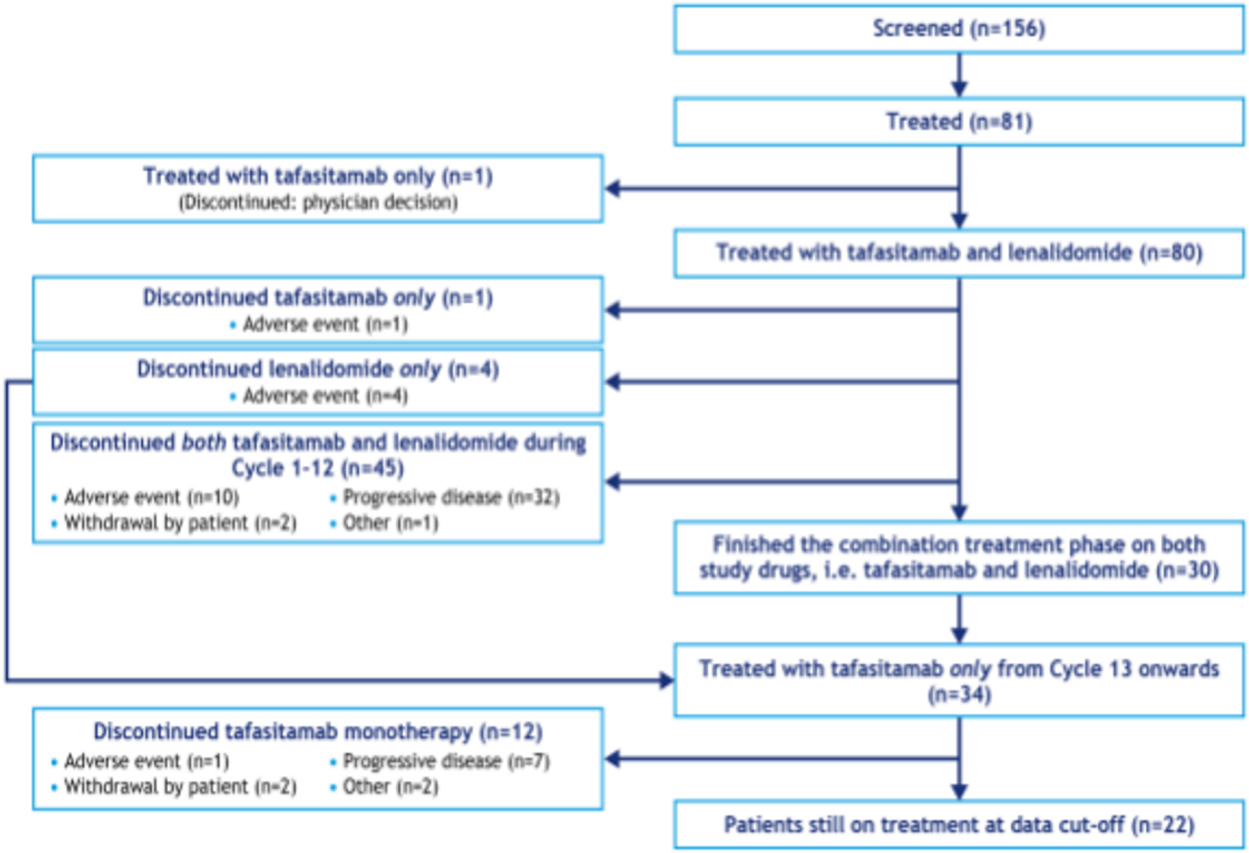

Figure 2. L-MIND schema.[43]

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.

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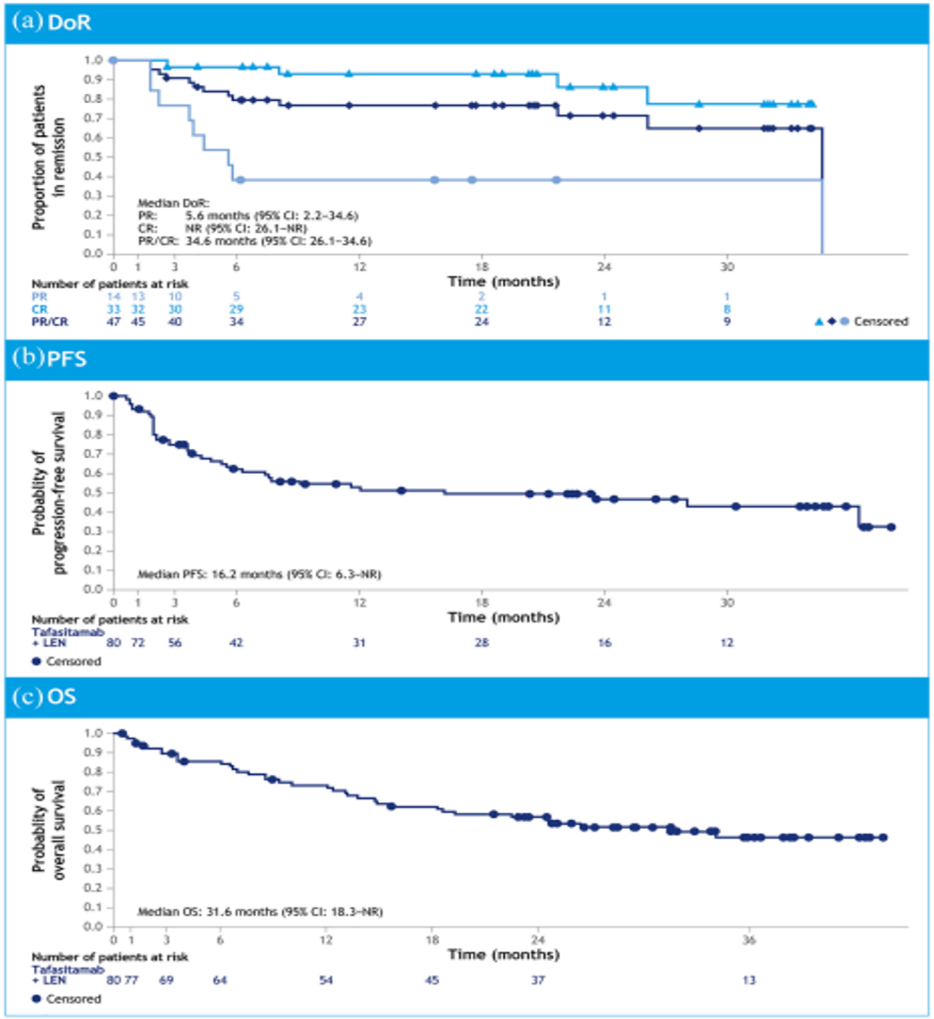

CI, confidence interval; CR, complete response; DoR, duration of response; LEN, lenalidomide; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response.

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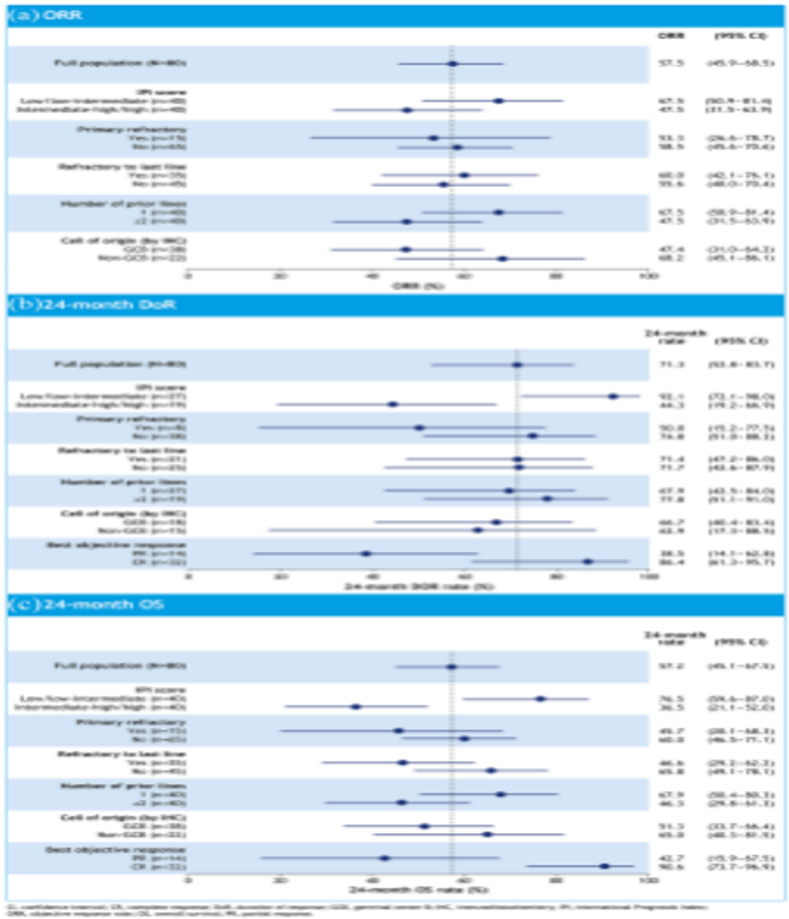

Figure 4. Forest plots for (a) ORR, (b) 24-month duration of response and (c) 24-month OS.[42]

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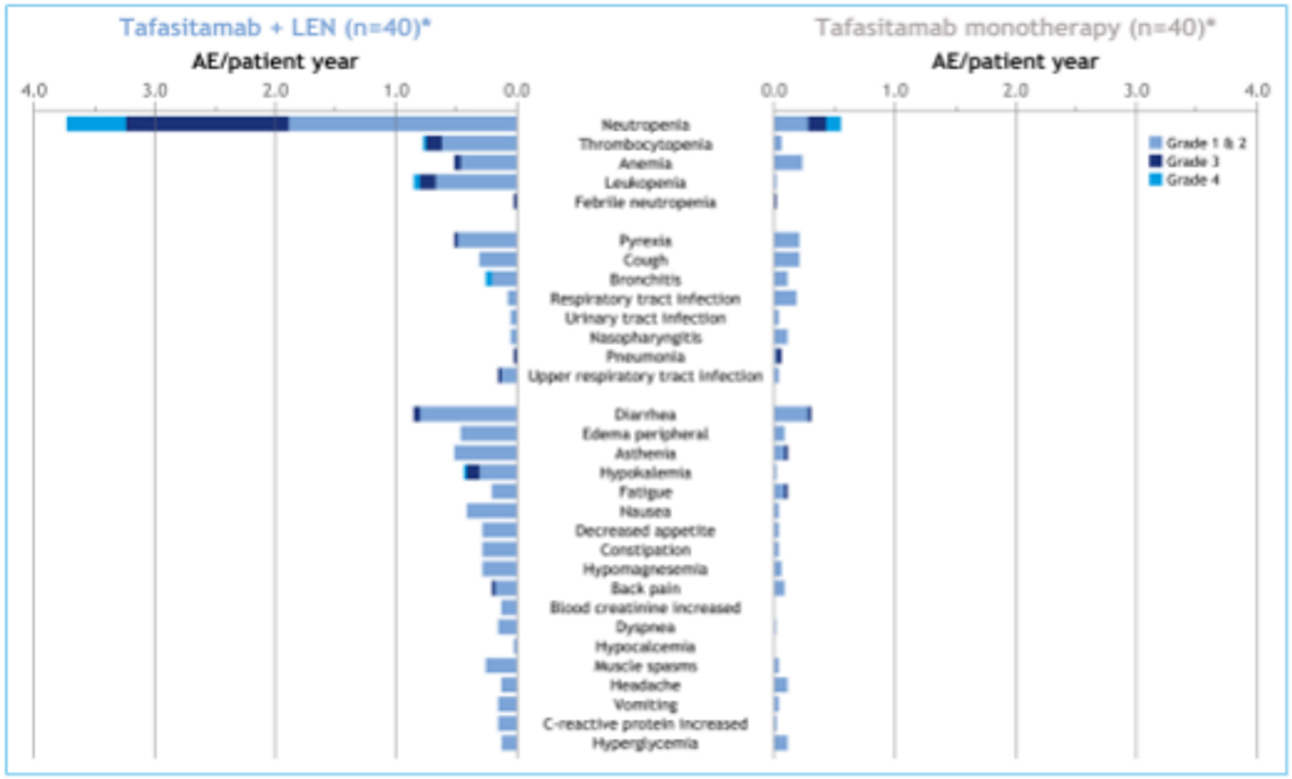


AE, adverse event; LEN, lenalidomide. *n = 40 includes 30 patients who completed 12 cycles of tafasitamab plus lenalidomide and continued tafasitamab monotherapy, and 10 patients who discontinued lenalidomide but continued tafasitamab monotherapy.

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

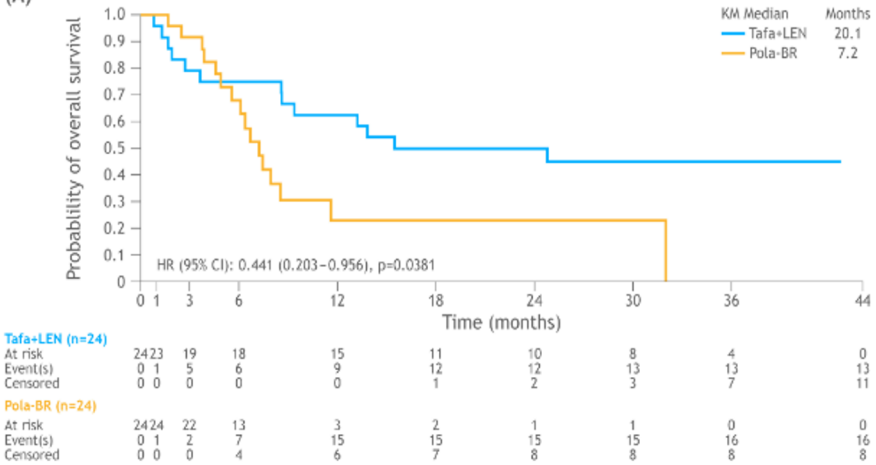
Grzegorz S. Nowakowski, Dok Hyun Yoon, Patrizia Mondello, Erel Joffe, Isabelle Fleury, Anthea Peters, Richard Greil, Matteo Ku, Reinhard Marchi, Kibum Kim, Pier Luigi Luigi Zinzani, Judith Trotman, Lorenzo Sabatelli, Dan Huang, Eva E. Waltl, Marco Winderlich, Sumeet Ambarkhane, Nuwan C. Kurukulasuriya, Raul Cordova, Georg Hess, Gilles Salles

Abstract

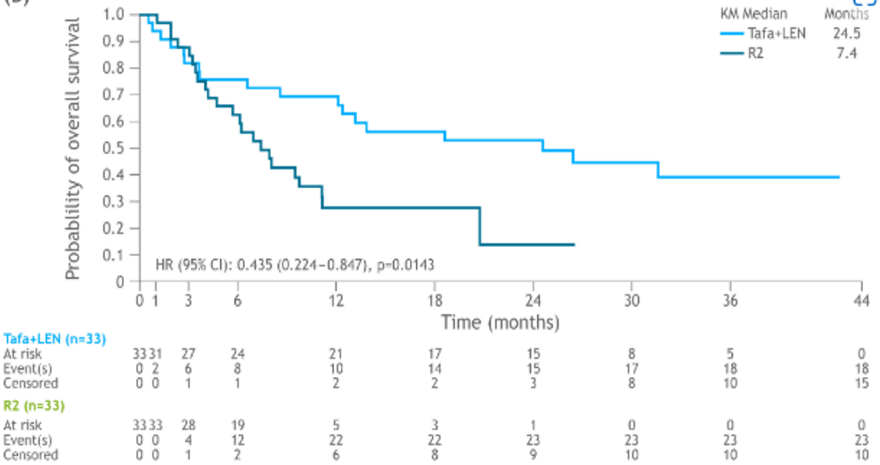
Background

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.

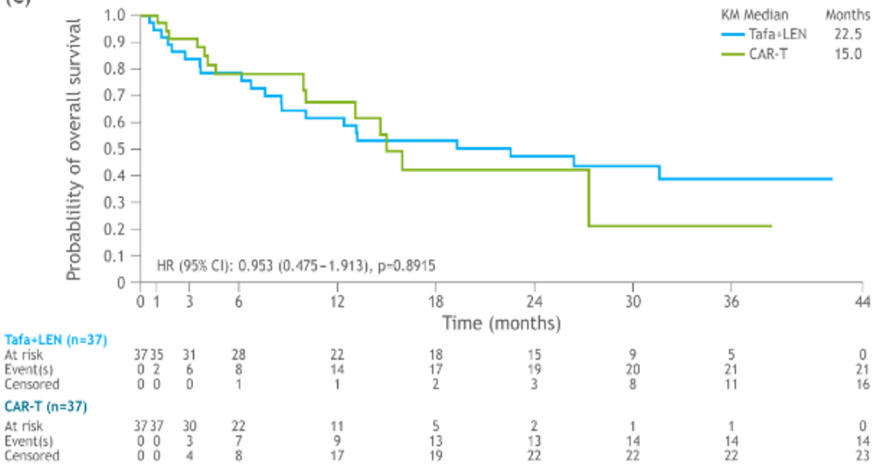
(A)



(B)



(C)



	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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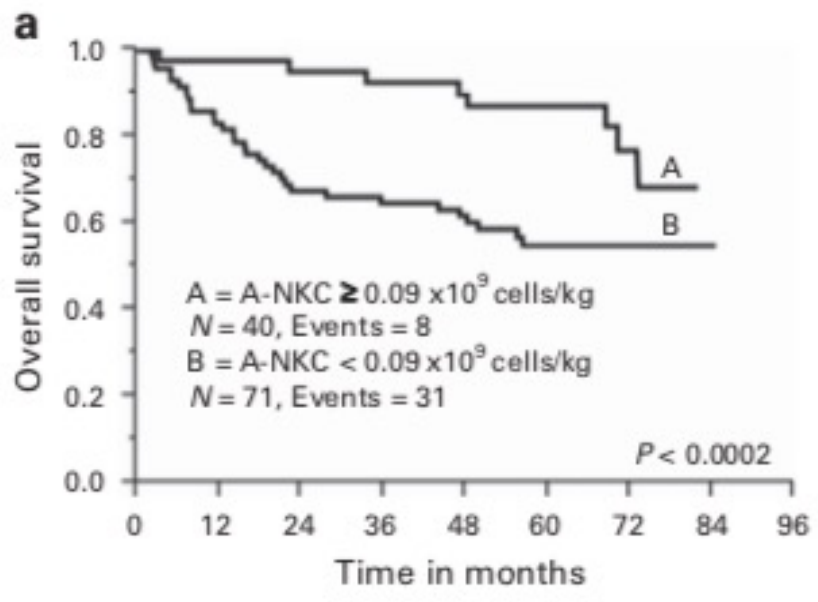
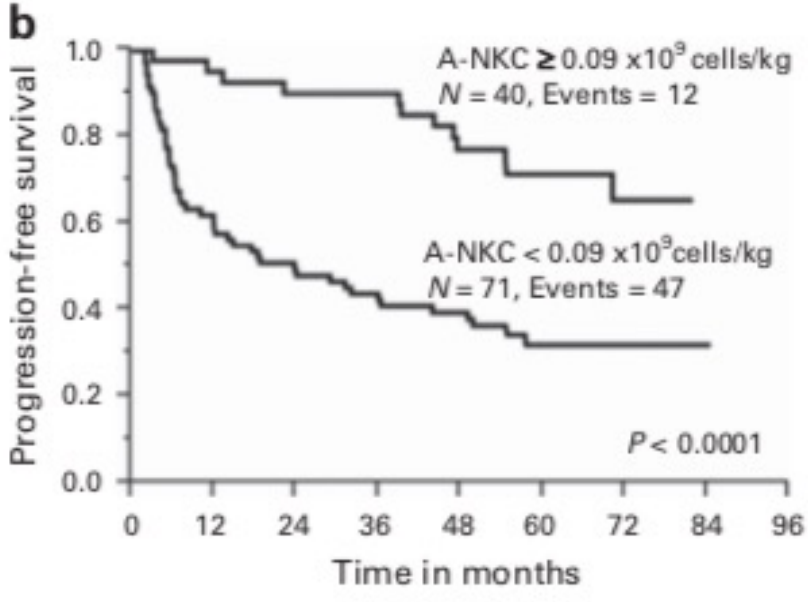
Received: 30 June 2021 / Accepted: 28 January 2022

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
1.0
0.8
0.6
0.4
0.2
0.0
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
0 12 24 36 48 60 72 84 96
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


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

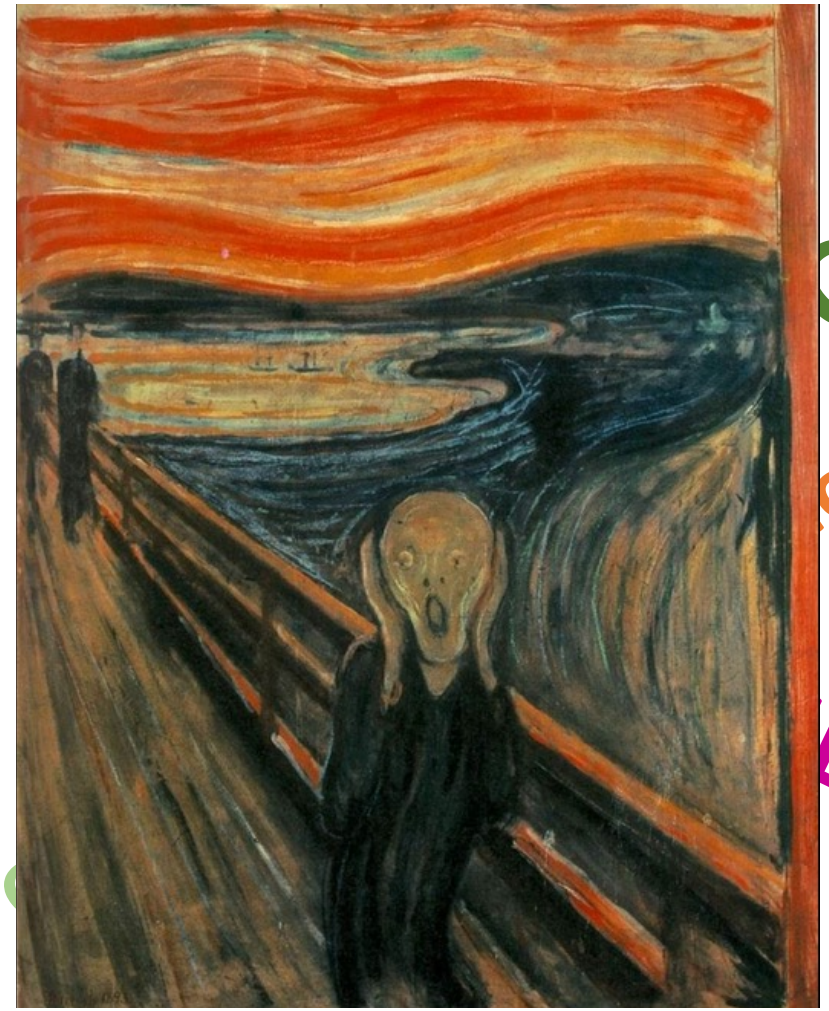
BISPECIFIC

CAR-T

oAB

IMIDS

EW MoAB



MULTITARGET COMBINATION

Grazie per l'attenzione