Updates in Diffuse Large B-cel Lymphoma

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Outline

1. Updates in Stratification and Prognostication
2. Updates in Frontline Treatment
3. Updates in CNS relapse prevention
4. Updates in R/R Setting

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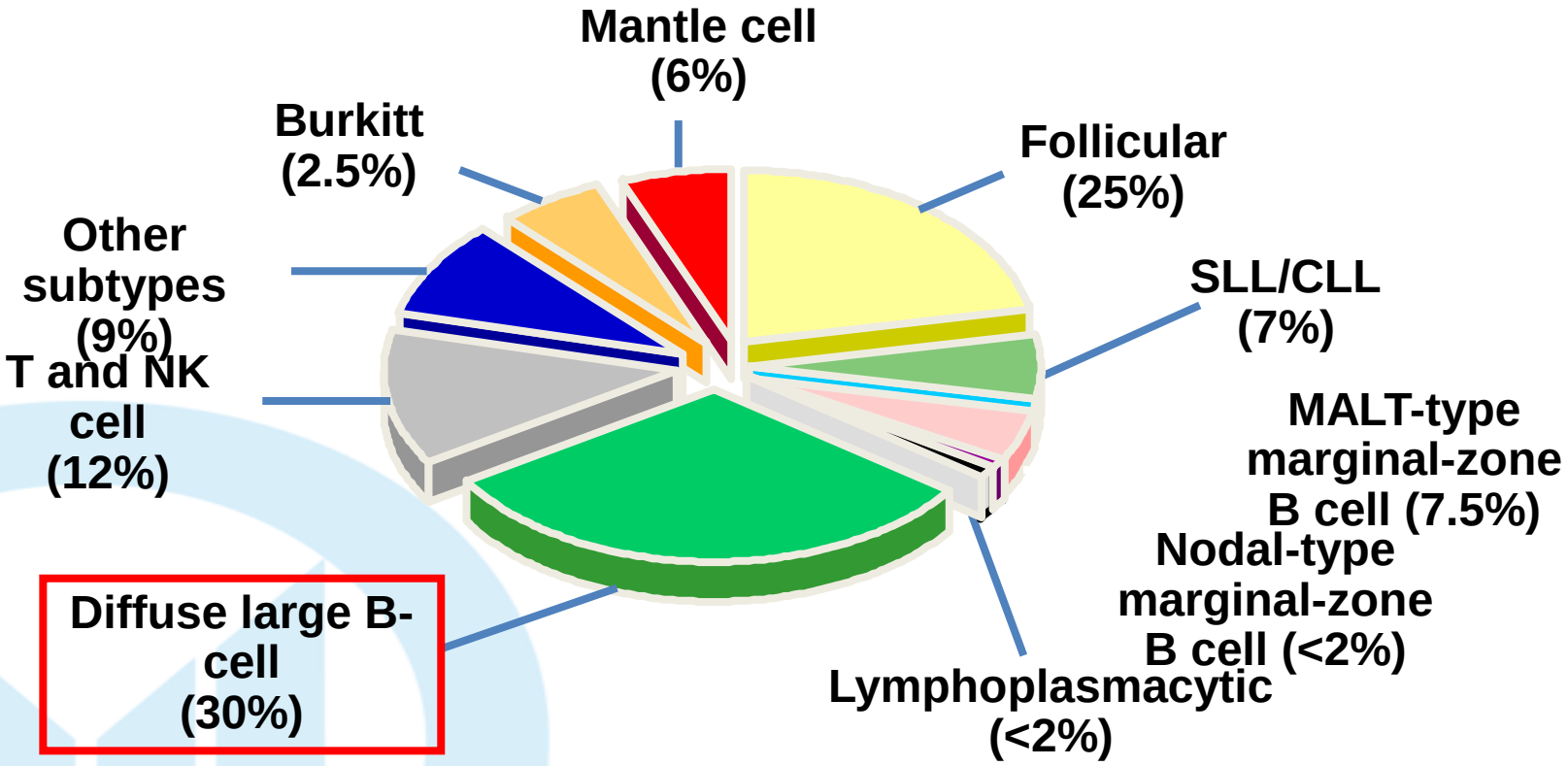
Most Common Subtypes of NHL



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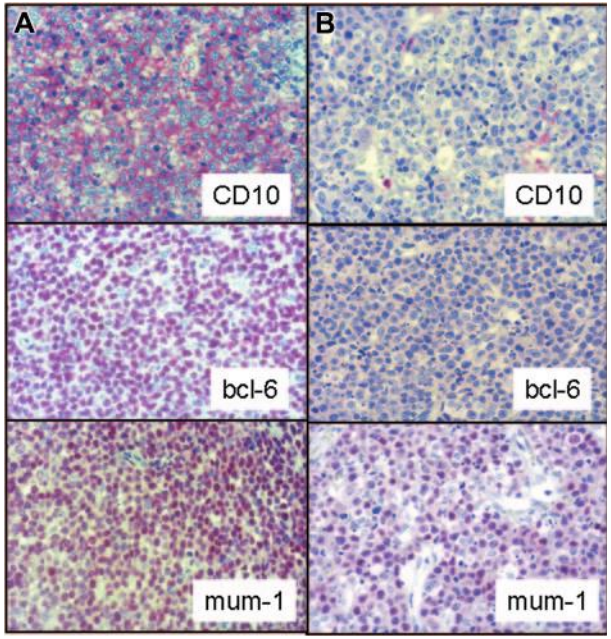
Lichtman MA. Williams Hematology. 7th ed. New York, NY: McGraw Hill. 2006;1408.

WHO 2016: Refinements of aggressive B-cell lymphomas classification

- DLBCL: Distinction between ABC and GCB subtypes (IHC algorithms acceptable)
- DLBCL double expressor (MYC and BCL2)
- High grade B-cell lymphomas with *MYC-R*, *BCL2-R* and/or *BCL6-R*
- High grade B-cell lymphomas NOS (replaces BCLU)



Oschiles et al. Blood 2006 (107):10.
Swerdlow et al. Blood 2017 (127): 20

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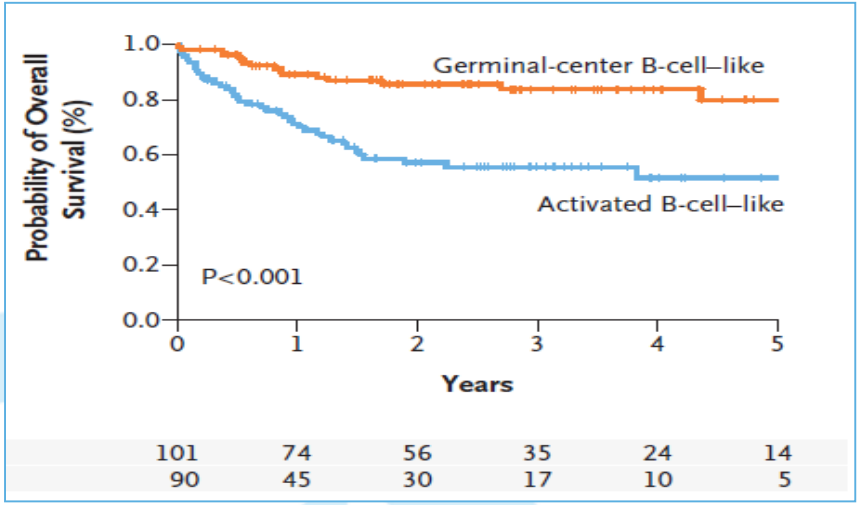
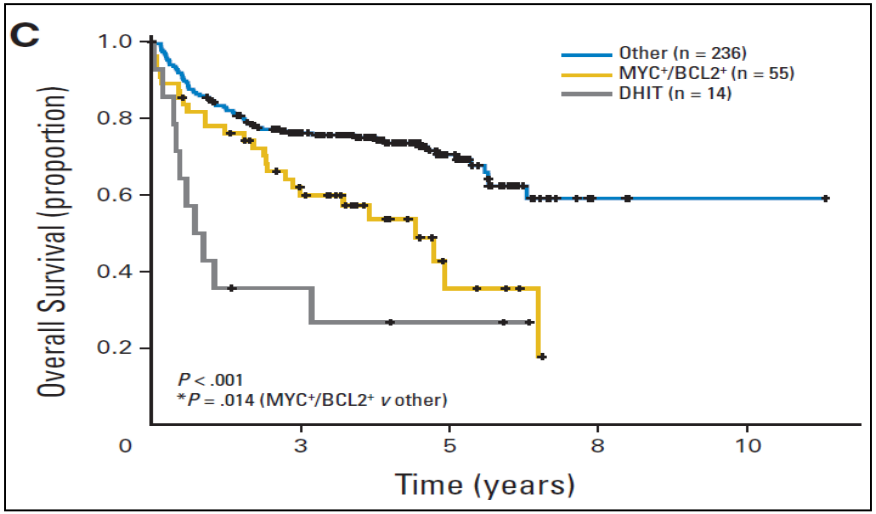
DLBCL is a molecularly heterogeneous disease; certain patient subsets do worse

Patients with ABC DLBCL are less likely to be cured by R-CHOP



N Engl J Med. 2008 Nov 27;359(22):2313-23

"Double-Hit" (Myc + Bcl-2) carries worst prognosis



J Clin Oncol 2012 30:3452-3459.

Additional Unmet Need

- Primary refractory or first relapse within 12 months
- High IPI score at relapse
- Transformed lymphoma
- Relapse post ASCT or not ASCT eligible

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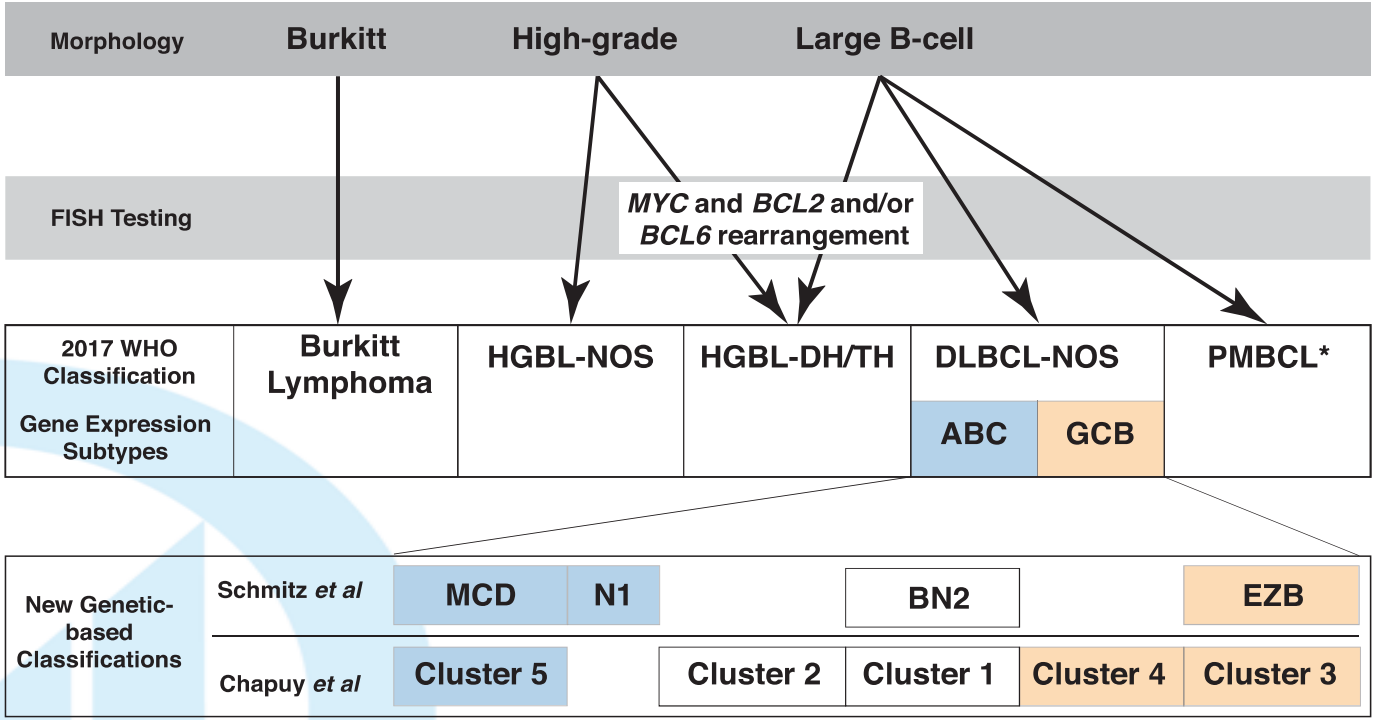
Evolving role of NGS in aggressive B-cell lymphomas classification



Pasqualucci. Blood 2018

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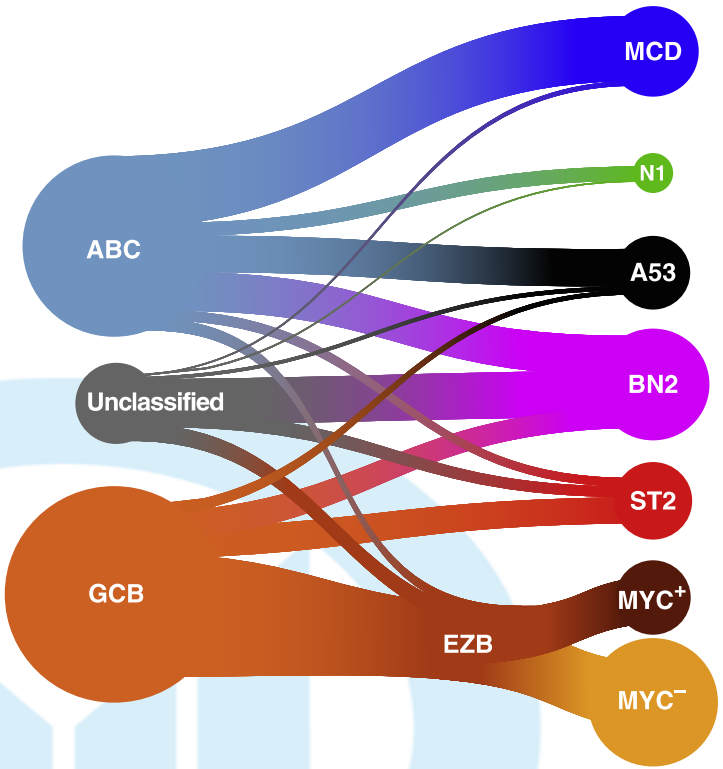
Implications of DLBCL subtypes and potential therapies

A



	Prevalence	5-yr overall survival	Genetic themes	Genetically related lymphomas	Gene expression signatures	Potential therapeutic targets
MCD	8.7%	40% (All) 37% (ABC)	My-T-BCR-dependent NF-κB Immune evasion-MHC class I Cell survival - *BCL2* expression Altered B cell differentiation G1-S cell cycle/p53 checkpoint BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	Primary extranodal DLBCL Transformed WM	B cell activation NF-κB IRF4 Myc Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 $BCL2\text{-}BCLX_L\text{-}MCL1$ JAK1 IRAK4 IRF4
N1	1.7%	27% (All) 22% (ABC)	NOTCH1 signaling Altered B cell differentiation BCR: IgM > IgG	NOTCH1-mutant CLL	NOTCH Quiescence Plasma cell T cell-myeloid-FDC	NOTCH1 Immune checkpoints
A53	5.8%	63% (All) 33% (ABC) 100% (GCB)	*TP53* inactivation/DNA damage Aneuploidy Immune evasion - *B2M* loss BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	–	p53 Immune low	BCR-dep. NF-κB
BN2	13.3%	67% (All) 76% (ABC) 100% (GCB) 38% (UC)	NOTCH2 signaling Altered B cell differentiation BCR-dependent NF-κB Immune evasion - *CD70* loss Proliferation - Cyclin D3 BCR: IgM >> IgG; $IgV_H4\text{-}34^{++}$	MZL Transformed MZL	B cell activation NF-κB NOTCH Proliferation	BCR-dep. NF-κB PI3 kinase mTORC1 BCL2 NOTCH2
ST2	6.4%	84% (All) 81% (GCB)	JAK/STAT3 signaling NF-κB activation *P2RY8* – *GNA13* inactivation Altered B cell differentiation BCR: IgG >> IgM	NLPHD THRLBCL	GC B cell PI3K signaling JAK2 signaling Glycolysis Stromal	PI3 kinase JAK2
EZB	5.9% (MYC^+) 17.6% (MYC^-)	48% (MYC^+) 82% (MYC^-)	Chromatin modification Anti-apoptosis PI3 kinase signaling *S1PR2* – *GNA13* inactivation Altered T_{FH} interactions MYC (EZB-MYC^+) BCR: IgG > IgM	FL Transformed FL BL (EZB-MYC^+)	GC LZ (MYC^-) GC IZ (MYC^+) BCL6 (MYC^+) TCF3 (both) T_{FH} cells (MYC^-) Stromal (MYC^-) Immune low (MYC^+)	PI3 kinase mTORC1 EZH2 BCL2-MCL1

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Double-Hit Signature With TP53 Abnormalities Predicts Poor Survival in Patients With Germinal Center B-Cell Like (GCB) DLBCL Treated With R-CHOP

Background

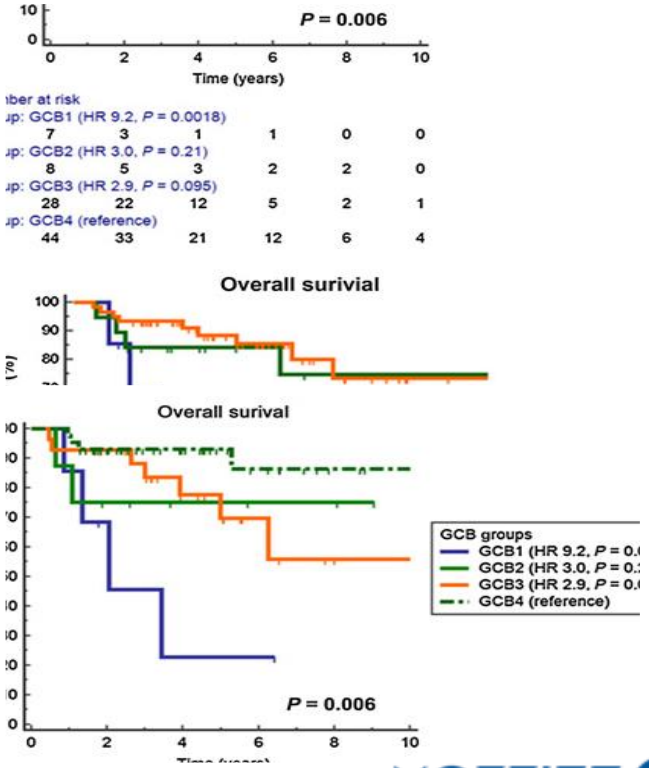
Genomic analysis of cases of de novo GCB DLBCL, including those patients with DH lymphoma (presence of *MYC* and *BCL2* and/or *BCL6* translocations)

The objective was to develop a molecular subtyping schema to risk-stratify patients with GCB DLBCL treated with R-CHOP

Results

87 non GCB DLBCL cases divided into 4 groups:

- GCB1 (DH positive, *TP53* inactivation): poor survival
- GCB2 (DH positive, *TP53* wildtype): good survival
- GCB3 (DH negative, *EZH2* mutation and/or *BCL2* translocation): intermediate survival
- GCB4 (DH negative, without *EZH2* mutation or *BCL2* translocation): excellent survival



Song et A. ASH Meeting Abstracts 2020: 533

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Updates in Frontline DLBCL Treatment

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Outcomes adding novel agents and DA-EPOCH

Clinical trial	ORR (CR) %	PFS	OS
PYRAMID (bortezomib- non GCB)[1] VR-CHOP (n=92) R-CHOP (n=91)	96 (56) 98 (49)	2-yr: 82% 2-yr: 78% p=0.611	2-yr: 93% 2-yr: 88%; p= 0.763
CALGB/Alliance 50303[2] R-CHOP (n= 233) DA-EPOCH-R (n= 232)	89.3 (62.3) 88.8 (61.1)	3-yr: 81% 3-yr: 79%; p= 0.438	3-yr: 85% 3-yr: 85%; p= 0.420
GOYA (obinutuzumab)[3] R-CHOP (n=712) G-CHOP (n=706)	77.9 (59.5) 77.4 (56.7)	3-yr: 66.5% 3-yr: 69.9%; p= 0.92	3-yr: 81.4% 3-yr: 81.2%; p= 1.0
PHOENIX (Ibrutinib)[4] IR-CHOP (n=419) R-CHOP (n=419)	89.3 (67.3) 93.1 (68.0)	HR: 0949 (0.704– 1.279) (p= 0.731)	HR: 0.991 (0.712-1.183) (p= 0.959)
ROBUST (lenalidomide)[5] R2-CHOP (n=285) R-CHOP (n= 285)	91 (65) 91 (64)	HR: 0.85 (0.63-1.14) (*p* = 0.29)	2-yr: 79% 2-yr: 80%; p= NS
REMARC (lenalidomide maintenance)[6] R-CHOP → Len (n= 323) R-CHOP → Px (n= 327)		2-yr: 80% 2-yr: 75%, p= 0.0135)	2-yr: 89% 2-yr: 87%, p= NS

[1]Leonard JP et al JCO 2017, [2]Bartlett NL et al JCO 2019, [3]Vitolo U et al JCO 2017, [4]Younes A et al JCO 2019, [5]Nowakowski et al JCO 2021, [6]Thieblemont C, et al. JCO 2017

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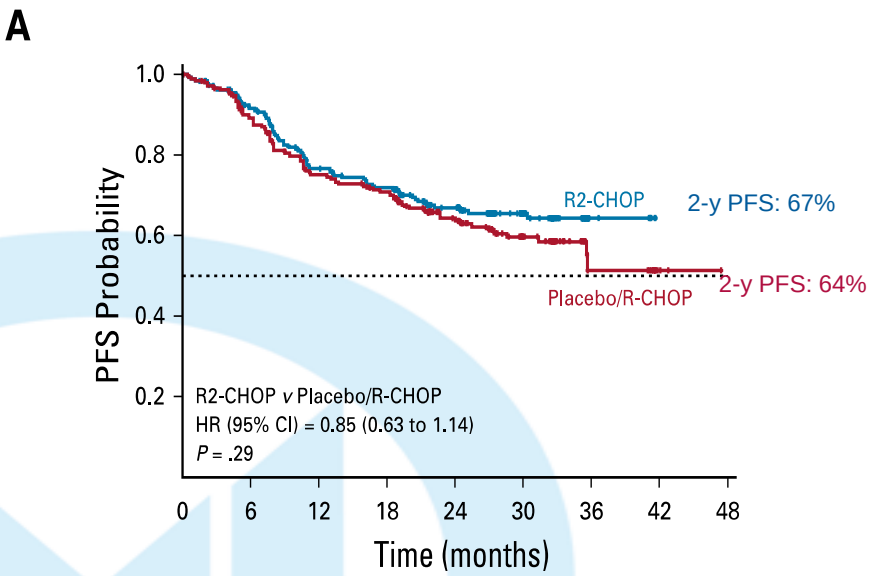
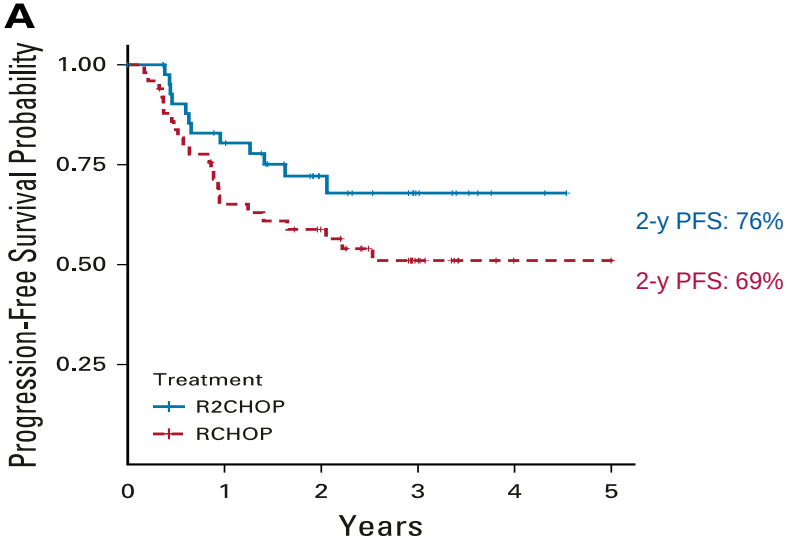
Does lenalidomide + R-CHOP improve outcomes in DLBCL?

ROBUST: R2-CHOP vs R-CHOP



ECOG E1412: R2-CHOP vs R-CHOP



Nowakowski et al JCO 2021/doi10.1200/jco.20.01366, Nowakowski et al JCO 2021/doi10.12100/jco.20.01375

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Does lenalidomide + R-CHOP improve outcomes in DLBCL?

ROBUST: R2-CHOP vs R-CHOP	ECOG E1412: R2-CHOP vs R-CHOP
✓ Phase III (Only ABC by GEP (NanosTring) ✓ N= 570 (R-CHOP: 285, R2-CHOP= 285). Primary endpoint: PFS ✓ Median age 65 (21 – 83) ✓ IPI 3 – 5: 58%, Stage III/IV: 87% ✓ Median time from Dx to treatment: 31 days ✓ Lenalidomide dose: 15 mg d1-d14 every three weeks	✓ Phase II (all DLBCL but stratified by COO [also using GEP-NanosTring]) ✓ N= 280 (R-CHOP: 145, R2-CHOP: 135). Primary endpoint: PFS ✓ Median age 66 (24 – 92) ✓ IPI 3-5: 66%, Stage III/IV: 97% ✓ Median time from Dx to treatment: 21 days ✓ Lenalidomide dose: 25 mg d1-d10 every three weeks

Nowakowski et al JCO 2021/doi10.1200/jco.20.01366, Nowakowski et al JCO 2021/doi10.12100/jco.20.01375

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SENIOR trial: SQ rituximab-mini CHOP +/- lenalidomide in DLBCL in older than 80

- Multicenter, randomized, double-blind, placebo-controlled phase III study

Stratified by COO, age ≥ 85, IADL, CIRSG, Albumin

Pts aged ≥ 80 yrs with untreated CD20+ DLBCL, stages II-IV, IPI ≥ , CrCl ≥ 40

R2-mini CHOP* (n = 122)

R-mini CHOP (n = 127)

Follow up End points: PFS, OS, AEs

*Lenalidomide given 10 mg days 1- 14

- *Primary endpoint*: PFS, defined as first documented relapse or progression assessed by blinded independent review, or all-cause death
- *Secondary endpoints*: safety, OS, efficacy by R-CHOP response

Oberic L et al *J Clin Oncol* 2021

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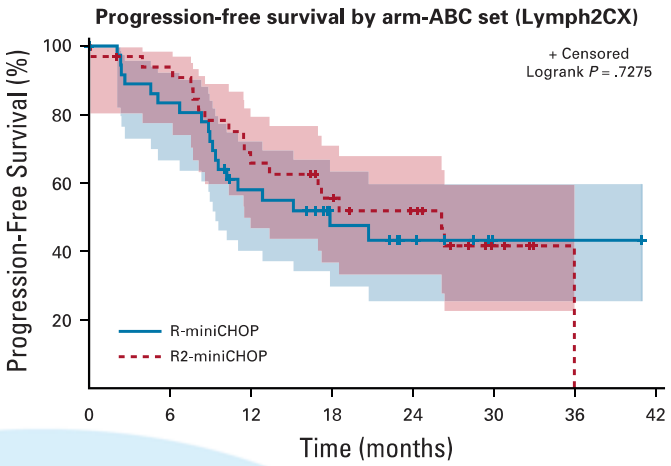
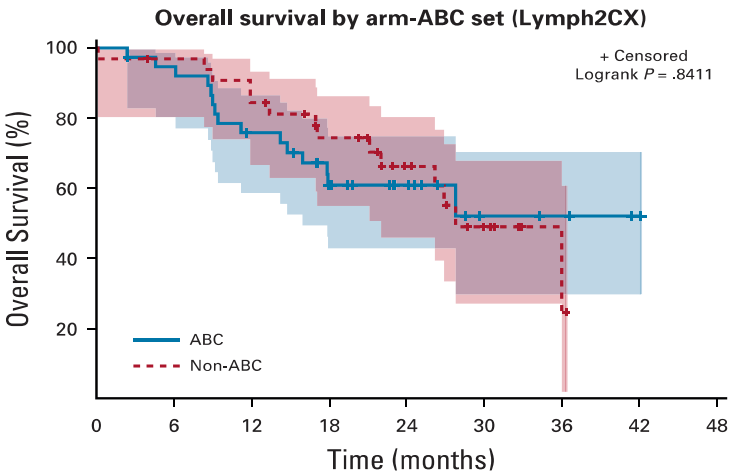
SENIOR trial: Outcomes and Prognostic Factors





Variable	HR (95% CI)	*P*
IPI (0-2 *v* 3-5)	0.94 (0.43 to 2.04)	.871
Non-ABC *v* ABC (Lymph2CX)	1.14 (0.68 to 1.92)	.614
IADL scale	0.72 (0.44 to 1.18)	.193
MNA (normal *v* malnourished)	1.16 (0.67 to 2.03)	.596
Ann Arbor stage (II-III *v* IV)	2.01 (0.94 to 4.32)	.073
Lymphocyte count (< 1 *v* ≥1 G/L)	0.80 (0.50 to 1.30)	.373
Albumin (≤35 *v* > 35 g/L)	2.08 (1.25 to 3.57)	**.005**

Oberic L et al *J Clin Oncol* 2021

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SENIOR trial: Outcomes and Safety

Adverse events	R-miniCHOP (n= 124)	R2-miniCHOP (n= 117)
Grade 3-4 (%patients)	71 (74%)	95 (81%)
Neutropenia	22 (18%)	38 (35%)
Thrombocytopenia	1 (0.8%)	9 (7.6%)
Febrile neutropenia	1 (0.8%)	3 (3.4%)
Infections	10 (8%)	16 (13.5%)
DVT/PE	1 (0.8%)	13 (11%)
Grade 5 (fatal)	7 (5.6%)	8 (6.8%)

- ✓ Lenalidomide did not improve outcomes in > 80 DLBCL
- ✓ Lenalidomide was associated with higher toxicity
- ✓ Low dosing (10mg) might have prevented efficacy
- ✓ Mini-RCHOP is well tolerated in older patients but with good PS, nutritional status and functionality.

Oberic L et al *J Clin Oncol* 2021

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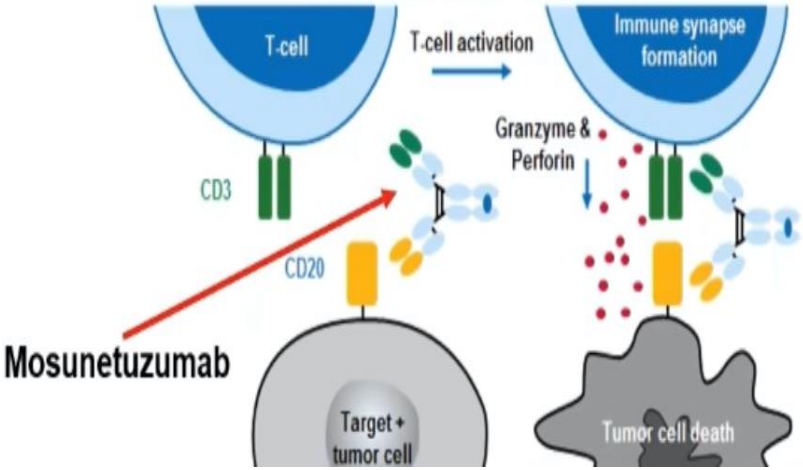
Single agent Mosunetuzumab (bi-specific antibody) for elderly/unfit patients with untreated DLBCL

- ✓ Mini R-CHOP is SOC with PFS and OS 47 and 69%, respectively
- ✓ About 30% of DLBCL pts older than 75 are unable to receive standard R-CHOP
- ✓ Frailty and comorbidities affects outcomes
- ✓ Other regimens such as BR or R-CVP, while better tolerated, have suboptimal outcomes



Olzewski A et al. ASH Meeting Abstracts 2020

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GO40554: Phase I/II of mosunetuzumab for elderly/unfit 1L DLBCL

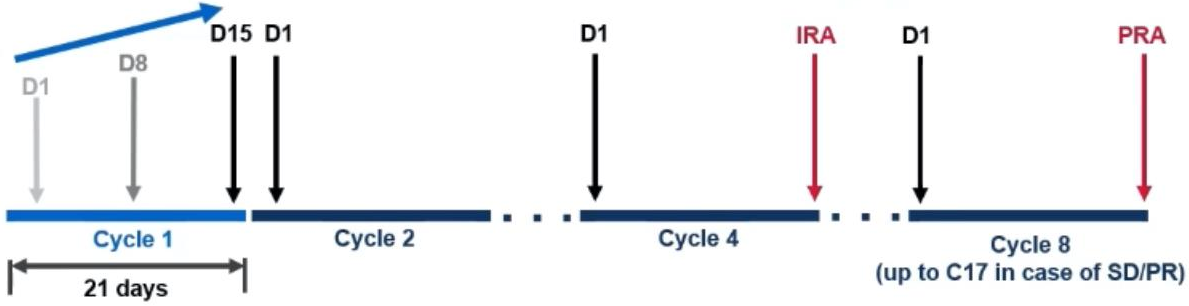
Key inclusion criteria

- Treatment naïve DLBCL or HGBL
- Age ≥80 years or 60–79 years with impairment in:
  - ≥1 ADL or
  - instrumental ADL or
  - inability to tolerate full dose CIT

Study design (1L DLBCL elderly/unfit)

- Optional pre-phase treatment with prednisone ± vincristine
- Step-up dosing of mosunetuzumab during Cycle (C) 1 D1/D8/D15
- Response assessments: at interim (C4; IRA) primary (C8; PRA), and every 6 months

Dosing schedule



First safety cohort dose:
C1D1: 1mg; C1D8: 2mg; C2–C8D1: 13.5mg

Second safety cohort dose:
C1D1: 1mg; C1D8: 2mg; C2–C8D1: 30mg

Expansion cohort dose:
C1D1: 1mg; C1D8: 2mg; C2–C8D1: 30mg

Olzewski A et al. ASH Meeting Abstracts 2020

GO40554: Phase I/II of mosunetuzumab for elderly/unfit 1L DLBCL

Characreristics	DLBCL (n= 29)
Median age Age ≥ 80	82 (67 – 100) 21 (72)
IPI score ≥ 3	15 (52%)
ECOG/PS ≥ 2	9 (31%)
Stage III/IV	18 (62%)
DLBCL subtype non GCB GCB	 16 (55%) 13 (45%)
Elevated LDH	15 (52%)

- ✓ 29 patients with DLBCL enrolled (8 pts younger than 80)
- ✓ DL 1 mg→ 2 mg→ 13mg (n=8 pts)
- ✓ DL 1 mg→ 2 mg→ 30mg (n= 21 pts)
- ✓ N=7 safety cohort, N=14 expansion cohort
- ✓ 16 pts had a median of 6 cycles
- ✓ CRS: 47% (all grade 1)

Oberic L et al *J Clin Oncol* 2021

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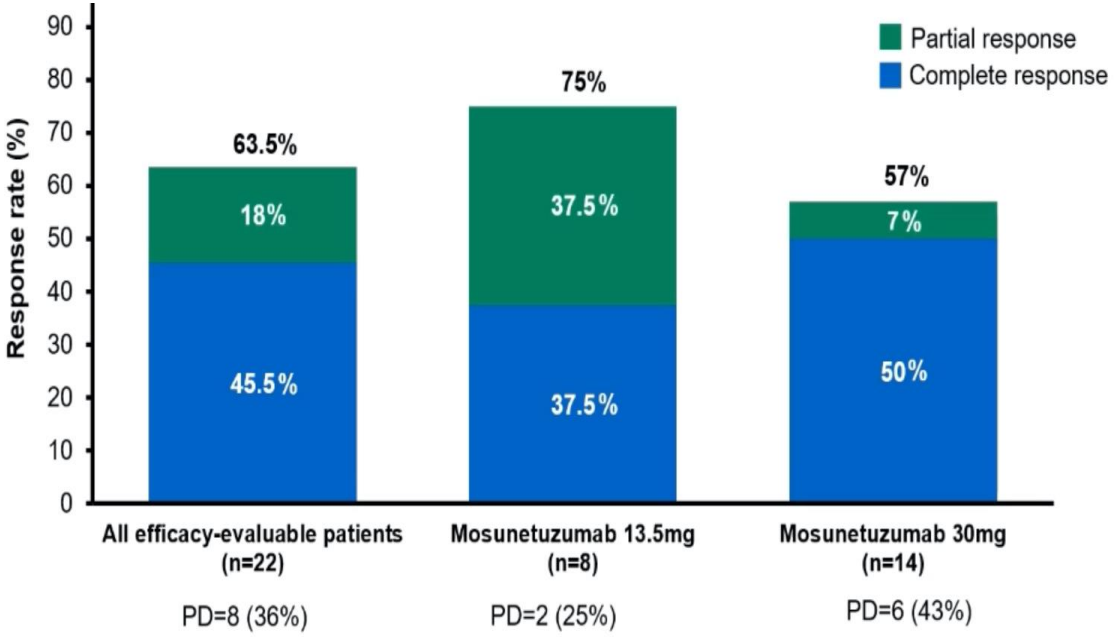
GO40554: Phase I/II of mosunetuzumab for elderly/unfit 1L DLBCL



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Mosunetuzumab + CHOP (M-CHOP) for untreated DLBCL

- ✓ N= 43
  - R/R NHL: 7 pts
  - DLBCL: 43 pts
- ✓ Schedule:
  - C1 Mosun step up C1D1(1mg), D8(2mg), D15(30mg). Mosun 30 mg on D1 C2-C6
  - PR/SD were allowed Mosun for additional 11 cycles
- ✓ General characteristics
  - Stage II-IV, median IPI 3 (2-4), median age 66
- ✓ Adverse events:
  - CRS grade 1-2 53%. 1 pt received tocilizumab. No vasopressor
  - No ICANS

	M-CHOP	
Best objective response* – No. (%)	R/R NHL (n=7)	1L DLBCL (n=27)
Overall response	6 (85.7)	26 (96.3)
Complete response	5 (71.4)	23 (85.2)
Partial response	1 (14.3)	3 (11.1)
Stable disease	-	-
Progressive disease	1 (14.3)	-
Data not available (discontinued)	-	1 (3.7)

Phillips T et al. ASH Meeting Abstracts 2020

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PD-1 inhibition in NHL: Potential effect on priming

- PD-1/PD-L1 inhibition appears to sensitize R/R NHL to subsequent chemotherapy
- Prior PD-1/PD-L1 inhibitor therapy induces higher responses to chemotherapy in treatment naïve solid tumors (many who arte not known to be sensitive to PD-1/PD-L1 inhibition
- There is evidence of PD-1/PD-L1 inbibition syngergy with rituximab

Carreau N et al. Br J Haematol 2020, Forde et al, NEJM 2018, Nastoupil L et al. ASCO Meeting Abstracts 2017

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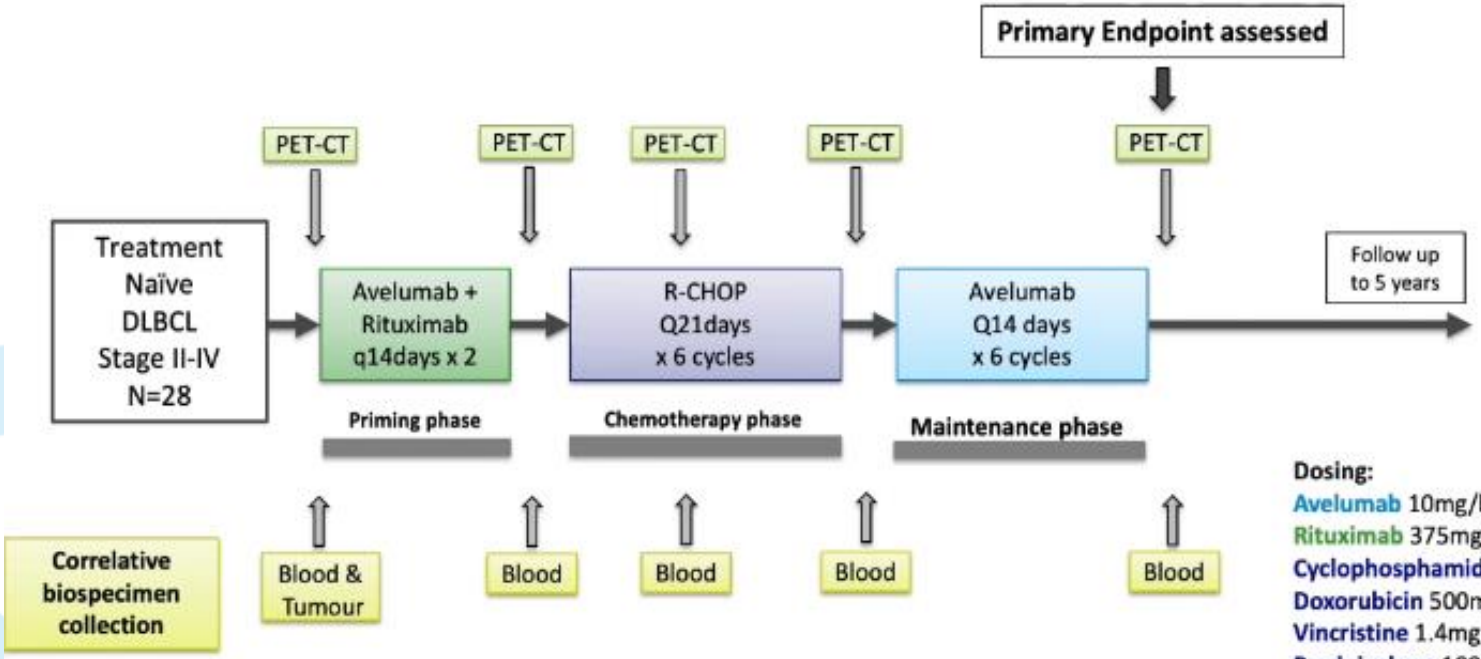
Induction and Maintenance Avelumab Plus R-CHOP in Patients with Diffuse Large B-Cell Lymphoma (DLBCL): Phase II Avr-CHOP Study



Dosing:
Avelumab 10mg/kg IV Day 1
Rituximab 375mg/m2 IV D1
Cyclophosphamide 1400mg/m2 IV D1
Doxorubicin 500mg/m2 IV D1
Vincristine 1.4mg/m2 (max 2mg) IV D1
Prednisolone 100mg po Days1-5

Hawkes E et al. ASH Meeting Abstracts 2020

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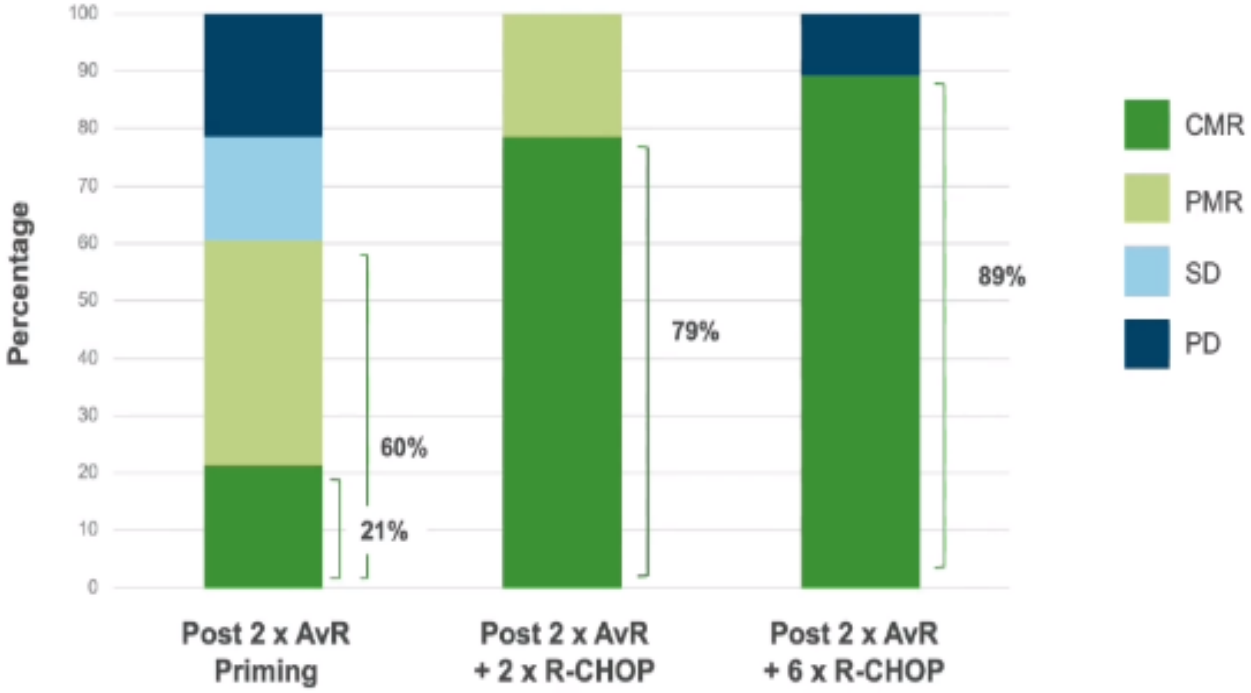
Avelumab Plus R-CHOP in Newly Diagnosed DLBCL (Avr-CHOP): Efficacy of priming and combination



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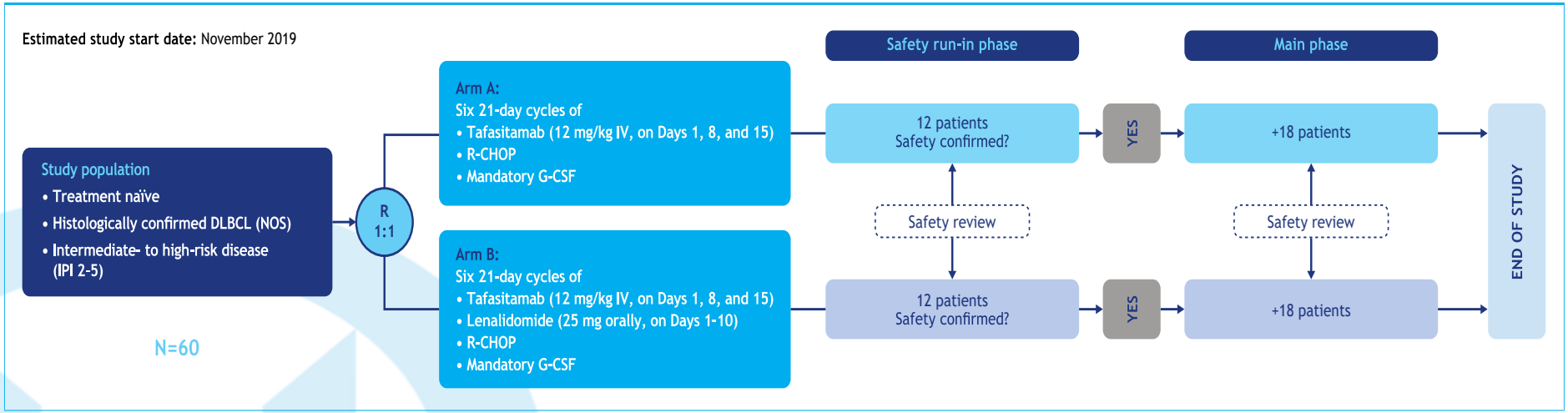
Phase Ib Randomized Study to Assess Safety and Preliminary Efficacy of Tafasitamab or Tafasitamab + Lenalidomide with R-CHOP in Patients with Newly DLBCL: The First-Mind Trial



Burke J et al. ASH Meeting Abstracts 2019

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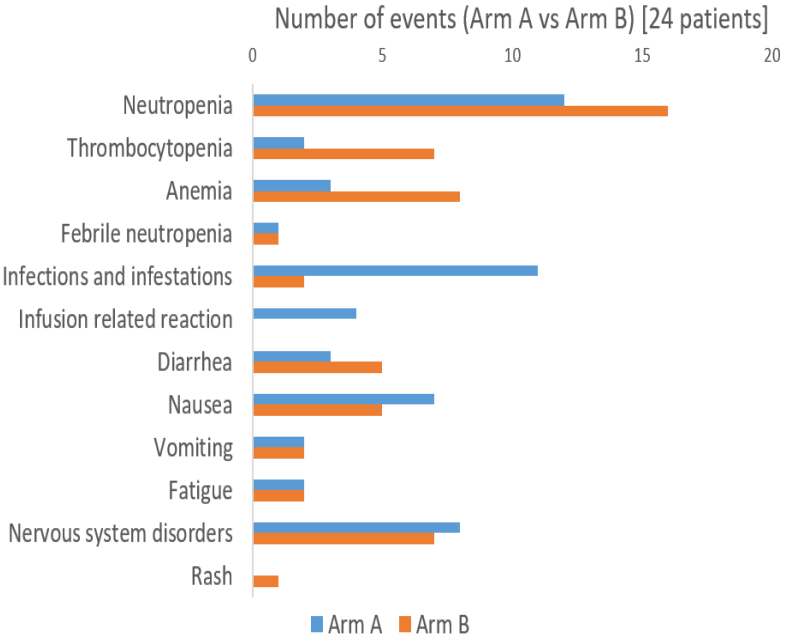
Phase Ib Randomized Study to Assess Safety and Preliminary Efficacy of Tafasitamab or Tafasitamab + Lenalidomide with R-CHOP in Patients with Newly DLBCL: The First-Mind Trial

- ✓ 36 patients randomized; results presented for 24 patients (Arm A, n = 13; Arm B, n = 11)
- ✓ AEs:
- ✓ Any-grade AEs: 111 in Arm A; 137 in Arm B
- ✓ G≥3 neutropenia: 54% in Arm A; 46% in Arm B
- ✓ G≥3 thrombocytopenia: 8% in Arm A; 18% in Arm B
- ✓ 23 SAEs were observed: 11 in Arm A; 12 in Arm B
- ✓ 1 SUSAR, *Pneumocystis jirovecii* pneumonia, was reported in Arm B
- ✓ No treatment-associated deaths occurred



Belada D et al ASH Meeting Abstracts 2020

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CNS Relapse Prevention in Aggressive Lymphomas

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Background- CNS relapse in DLBCL

- Occurs in 5% overall. It is > 10% in high risk groups (High NCCN-IPI score, high CNS IPI score, double hit lymphoma, double expressor)
- More parenchymal relapses than leptomeningeal relapses
- Current types of CNS prophylaxis:
  - *Intrathecal*: Less toxic, more accessible. CONS: invasive, minimal parenchymal penetration
  - *Intravenous*: usually HD MTX. Potentially better parenchymal penetration but requires hospitalization, could be toxic in older patients or with comorbidities.
- 15-20% of patients will receive either IT or IV CNS prophylaxis

Villa et al Ann Oncol 2010; Schmitz et al JCO 2016

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CNS Prophylaxis in Aggressive Non-Hodgkin Lymphoma: A US Multicenter Retrospective Analysis

Orellana-Noia VM, Reed DR, Sen JM, Barlow CB, Malecek M-K, Kahl BS, Spinner MA, Advani R, Voorhees TJ, Snow A, Grover NS, Ayers A, Romancik J, Liu Y, Huntington SF, Chavez JC, Saeed H, Lazaryan A, Raghunathan V, Spurgeon SE, Ollila TA, Del Prete C, Olszewski AJ, Ayers EC, Landsburg DJ, Echalier B, Lee J, Kamdar M, Caimi PF, Fu T, Liu J, David KA, Alharthy H, Law J, Karmali R, Shah H, Stephens DM, Major A, Rojek AE, Smith SM, Yellala A, Kallam A, Nakhoda S, Khan N, Cohen JB, Portell CA

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CNS relapse by prophylaxis route

5.5%

Overall CNS relapse rate

N=1024

N=808 → **5.3%** CNS relapse after **INTRATHECAL** prophylaxis

N=216 → **7.1%** CNS relapse after **INTRAVENOUS** prophylaxis

P=0.18

No significant difference between routes

- Age
- Stage
- Histology
- Cell of origin (Hans)
- Serum LDH
- Double-hit status
- HIV status
- CNS-IPI
- Number of EN sites
- Individual EN site(s)
- No. prophylaxis doses
- Frontline regimen

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CNS relapse by route: Propensity score matched analysis

Aim: retrospectively assess impact of prophylaxis route in those who are **eligible for either route**

Propensity Score Matching Covariates:

- Age >70
- renal function
- chemotherapy regimen (RCHOP v REPOCH)

Selected to reflect hypothetical eligibility for HD-MTX

5.5%

Overall CNS relapse rate

N=1024

N=186 → **5.4%** CNS relapse after **INTRATHECAL** prophylaxis (N=10)

N=186 → **8.0%** CNS relapse after **INTRAVENOUS** prophylaxis (N=15)

P=0.25

NO significant difference seen across routes

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Ineffectiveness of IV High-Dose Methotrexate for Prevention of CNS Relapse in Patients with High-Risk DLBCL

Robert Puckrin, Haidar El Darsa, Sunita Ghosh, Anthea Peters, Douglas A. Stewart
University of Calgary & University of Alberta
Alberta, Canada

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Alberta Lymphoma Guidelines

Prophylactic HD-MTX
3.5g/m^2 IV x 3 doses

- CNS-IPI score 4-6 *
- Double hit lymphoma
- Testicular lymphoma

* From 2012-15, HD-MTX recommended if elevated LDH, ECOG >1, and >1 extranodal site

Intensive chemoimmunotherapy
or consolidative autotransplant

- High IPI score
- Double hit lymphoma

Puckrin et al ASH Meeting Abstracts 2020

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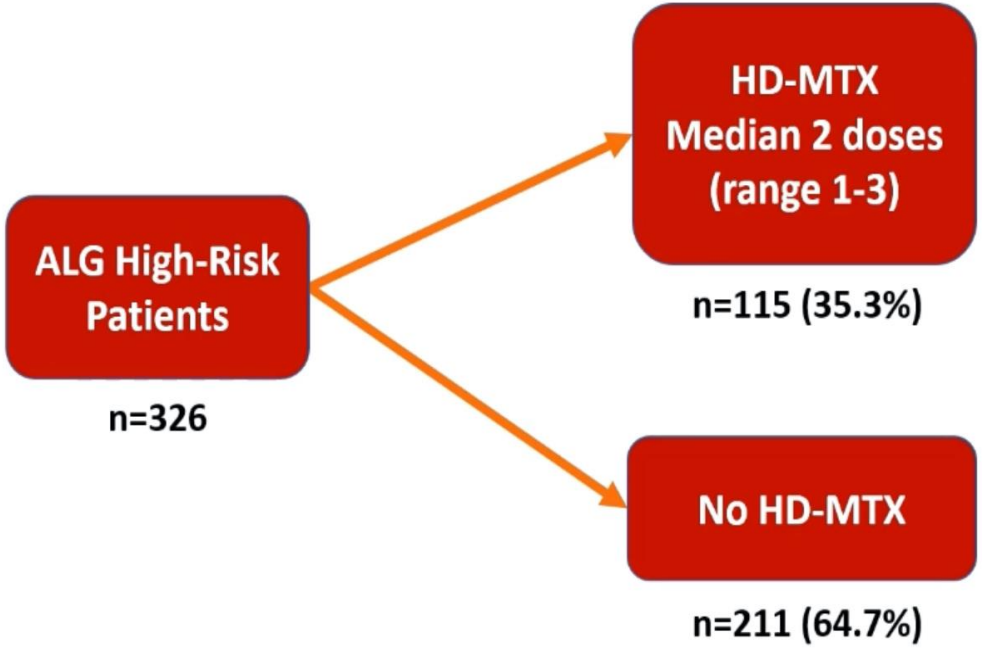
Utilization of prophylactic HD MTX



HD-MTX use associated with:

- Younger age (median 60 vs. 64 y)
- >1 extranodal site (85% vs. 76%)
- Kidney/adrenals involved (29% vs. 15%)
- Double hit lymphoma (39% vs. 10%)

Reason for no HD-MTX:

- Not documented (n=151)
- Toxicity concerns (n=29)
- Other (n=31)

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CNS Relapse Risk By Treatment

Treatment	CNS relapse risk	Hazard Ratio and P value	
Prophylactic HD-MTX (n=115)	11.2% vs. 12.2%	0.92 (95% C.I. 0.44-1.9)	0.82
Intensive chemoimmunotherapy (n=35)	5.7% vs. 12.6%	0.64 (95% C.I. 0.20-2.0)	0.43
Consolidative autotransplant (n=68)	6.0% vs. 13.7%	0.55 (95% C.I. 0.24-1.3)	0.15
Intensive chemo or autotransplant (n=102)	6.0% vs. 14.6%	0.47 (95% C.I. 0.19-1.1)	0.09

Puckrin et al ASH Meeting Abstracts 2020

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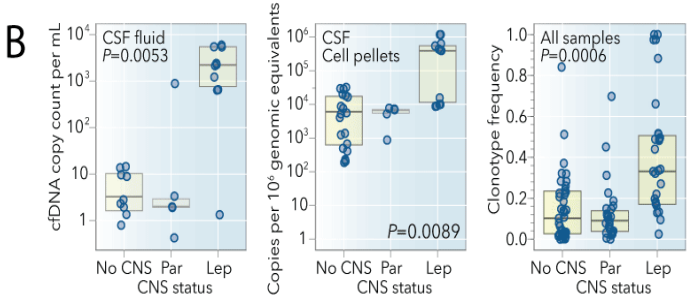
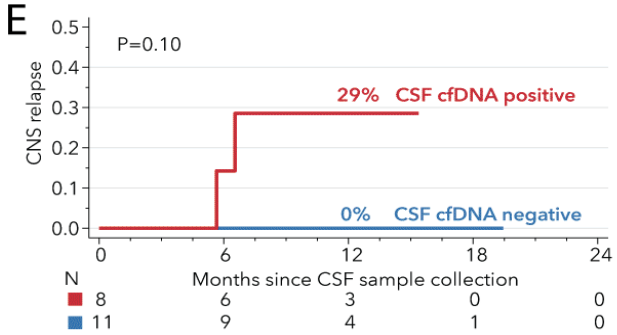
Role of cell free cfDNA as prognostic tool for CNS lymphomas

- Two-part study:
  - N= 6 patients with known CNS involvement by DLBCL
  - N= 19 patients newly diagnosed DLBCL. Underwent NGS MRD assessment
- High risk disease: high CNS-IPI score, epidural mass, histology (DHL, BL, HIV plasmablastic lymphoma)
- NGS-MRD in CSF + in all 6 patients with intraparenchymal disease
- Median follow up 11 months
  - NGS-MRD- → no CNS relapse
  - NGS-MRD+ → 2/10 CNS relapse (12-month incidence of relapse was 29%)





Olszewski et al ASH Meeting 2020

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Updates in R/R DLBCL

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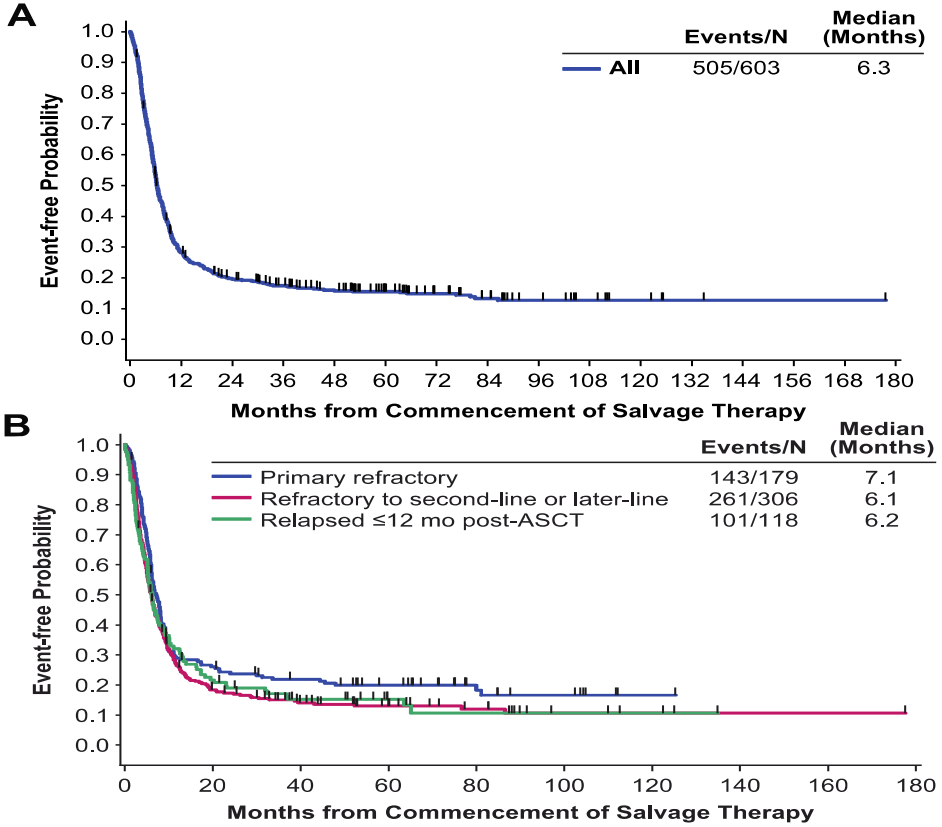
SCHOLAR-1: Outcomes of patients with refractory DLBCL

- **SCHOLAR-1**: Poor outcomes in patients:
  - Progressive disease to R-CHOP
  - Relapse post autologous HCT < 12 months-
  - Refractory to second or later line (N = 636)
- **Outcomes**(N = 636)
  - ORR = 26%
  - CR rate = 7%
  - Median OS = 6.3 mo



1. Crump M, et al. *Blood.* 2017;130:1800-1808. 2. Neelapu SS, et al. *Ann Oncol.* 2017;28(suppl 5):v403-v427 (abst1161P). Neelapu SS, et al. ASH 2017. Abstract #579.

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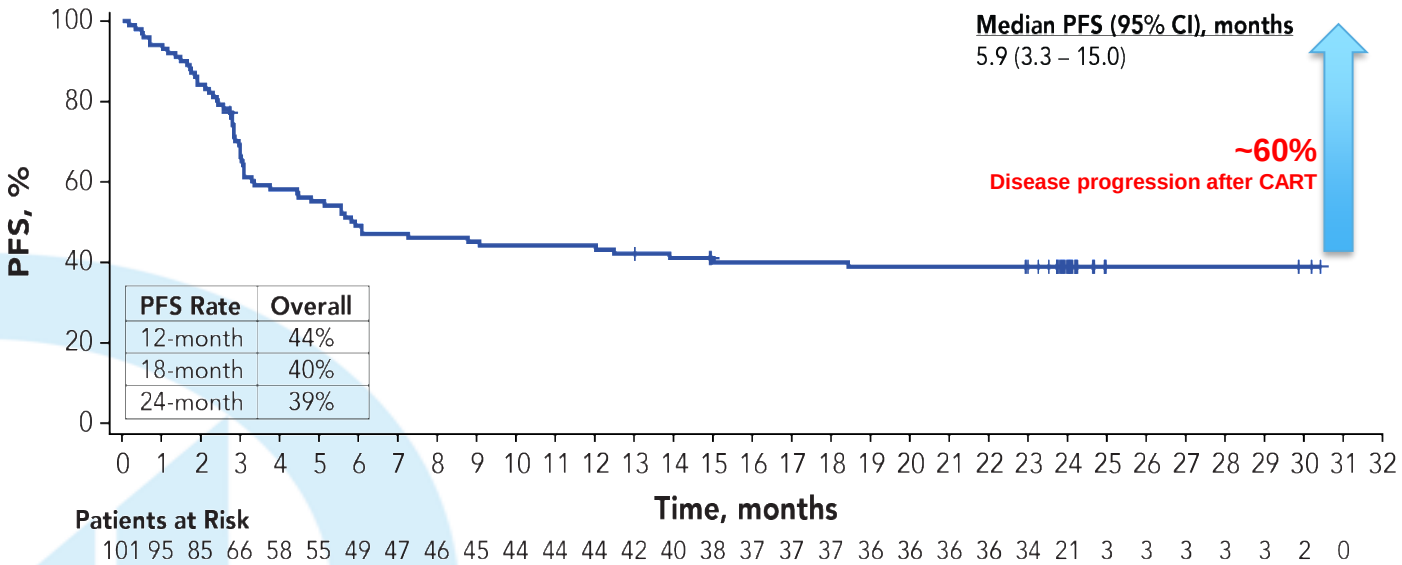
ZUMA-1: Axi-Cel for R/R DLBCL- PFS at 27.5 months follow up



Locke et al. Lancet Oncol 2018

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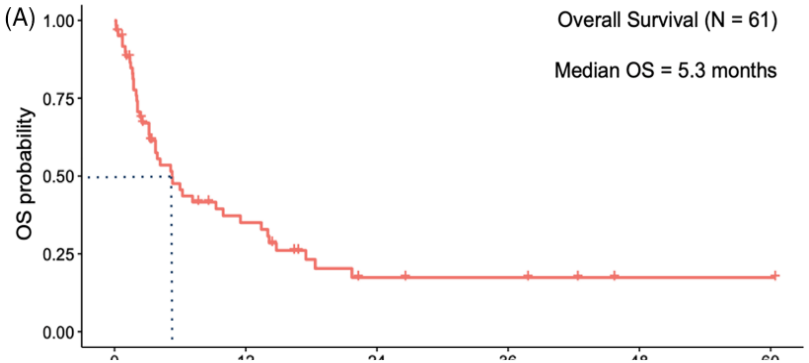
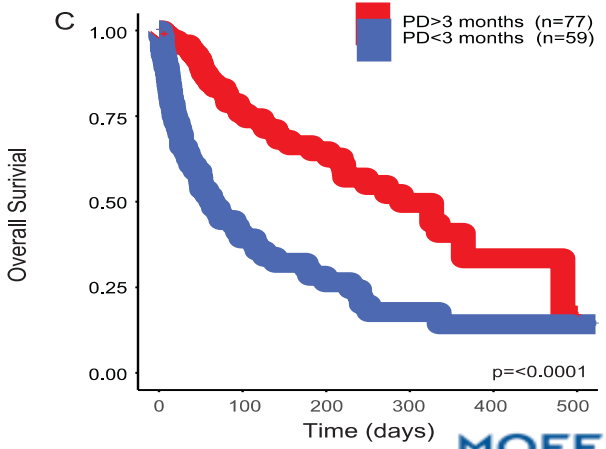
Post CART relapse: Poor Outcomes

- **FHCRC** (n=61)
- Early PD vs Late PD (≤ 30 days)
- **OS from PD= 5.3 months**
- Treatment post CART relapse
  - 2nd CART (14), targeted therapy (14), chemotherapy (5), XRT (4), allo HCT (1), IT therapy (1)
  - No differences in OS for an specific approach



- **US CART Consortium** (n= 136)
- Early PD vs Late PD (≤ 3 months)
- **OS from PD= 6 months**
- Treatment post CART relapse
  - Lenalidomide (30%), CBI (30%), chemotherapy (20%), XRT (10%)
  - ORR: CBI= 24%, Len= 20%, chemotherapy= 11%



Chow et al *Am J Hematol* 2019; Spiegel et al *ASCO Meeting Abstracts* 2019

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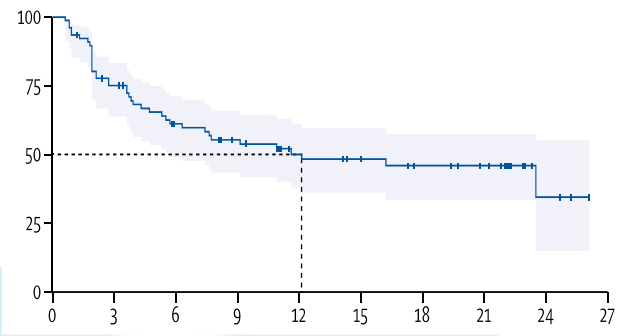
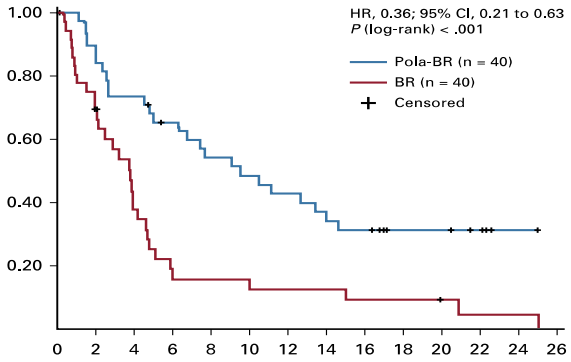
Current non-CART approved therapies for R/R DLBCL

Lenalidomide + Tafasitamab



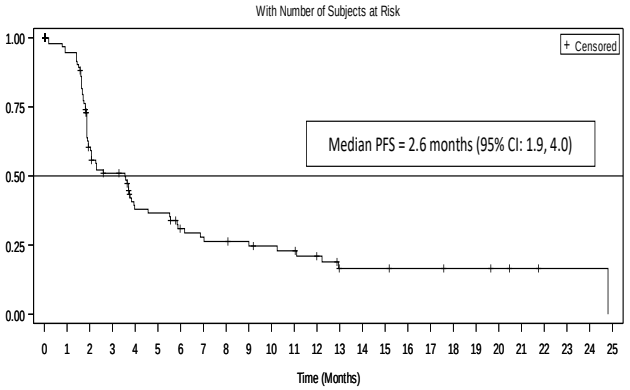
Median follow up: 17.3 months
Median PFS: 12.1 months

Polatuzumab + BR



Median follow up: 22.3 months
Median PFS: 9.5 months

Selinexor



Median follow up: 14.7 months
Median PFS: 2.6 months

Gilles et al *Lancet* 2020, Sehn et al *J Clin Oncol* 2019, Kalakonda et al *Lancet Haematol* 2020

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Summary of novel approaches for DLBCL

	Selinexor	Polatuzumab + BR	Tafasitamab + Lenalidomide	Mosunetuzumab	REGN1979 (> 80 mg)
	(N=134)	(N=40)	(N=81)	(N=274)	(N= 110)
Median Age, years (range)	67 (35, 91)	67 (33, 86)	72 (62, 76)	62 (19-96)	67 (30 – 38)
Study Phase	II	II	II	I/II	I/II
Prior regimens, median (range)	2 (1 - 5)	2 (1 - 7)	2 (1-4)	3 (1– 14)	3 (1 – 11)
1, n (%)	0	11 (28)	40 (50)	NR	NR
2, n (%)	84 (63)	11 (28)	35 (43)	NR	NR
≥3, n (%)	46 (34)	18 (45)	6 (7)	NR	NR
Type of DLBCL					
De novo DLBCL, n (%)	101 (75)	38 (95)	74 (91)	117 (65)	61 (87.1)
Transformed DLBCL, n (%)	31 (23)	0	7 (9)	32 (17.8)	NR
Missing/Other, n (%)	2 (2)	2 (5)	NR	21 (11.7)	9 (8.2)
Prior CART therapy	0	0	0	30 (11.1)	19 (10.9)
Responses					
Best ORR (%)	29	45	60*	37.1	57.9
Complete Response (%)	13	40	43	19.4	42.1
Partial Response (%)	16	5	18	17.7	15.8
Duration of Response (median, months)	9.3	12.6	21.7	NR	NR
DOR >6 months (%)	38	64	93	NR	100 (4 mo)
Median Overall Survival, months	9.0	12.4	Not reached	NR	NR

*LMIND ORR ≥2 prior regimens 50%

GO29365 – Sehn et al JCO Nov 2019; SADAL United States Package Insert 2020; LMIND Salles, Duelles et al Lancet Oncol June; 2020; Schuster et al ASH 2019; Bannerji et al ASH 2019

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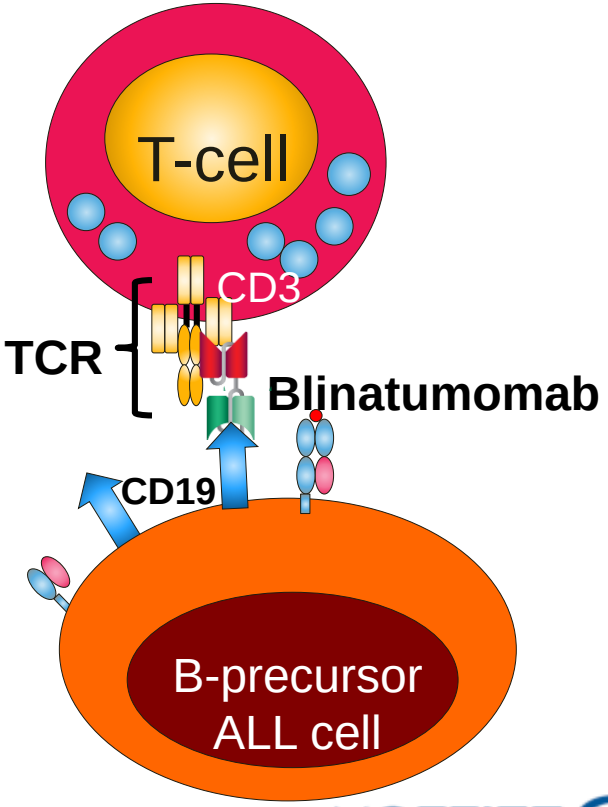
Bi-Specific Antibodies

Blinatumomab: T-Cell–Engaging BiTE Antibody

- Blinatumumab is a BiTE antibody designed to direct cytotoxic T-cells to CD19-expressing cancer cells[1]
- Currently indicated for treating Ph-negative relapsed/refractory B-cell precursor ALL (approved December 2014)[2]
  - Administration: 28 µg/day continuous IV infusion over 28 days
- Boxed warnings: **CRS** and neurological toxicities



1. Bargou R, et al. Science. 2008;321:974-977.
2. Blinatumomab [package insert]. December 2014.

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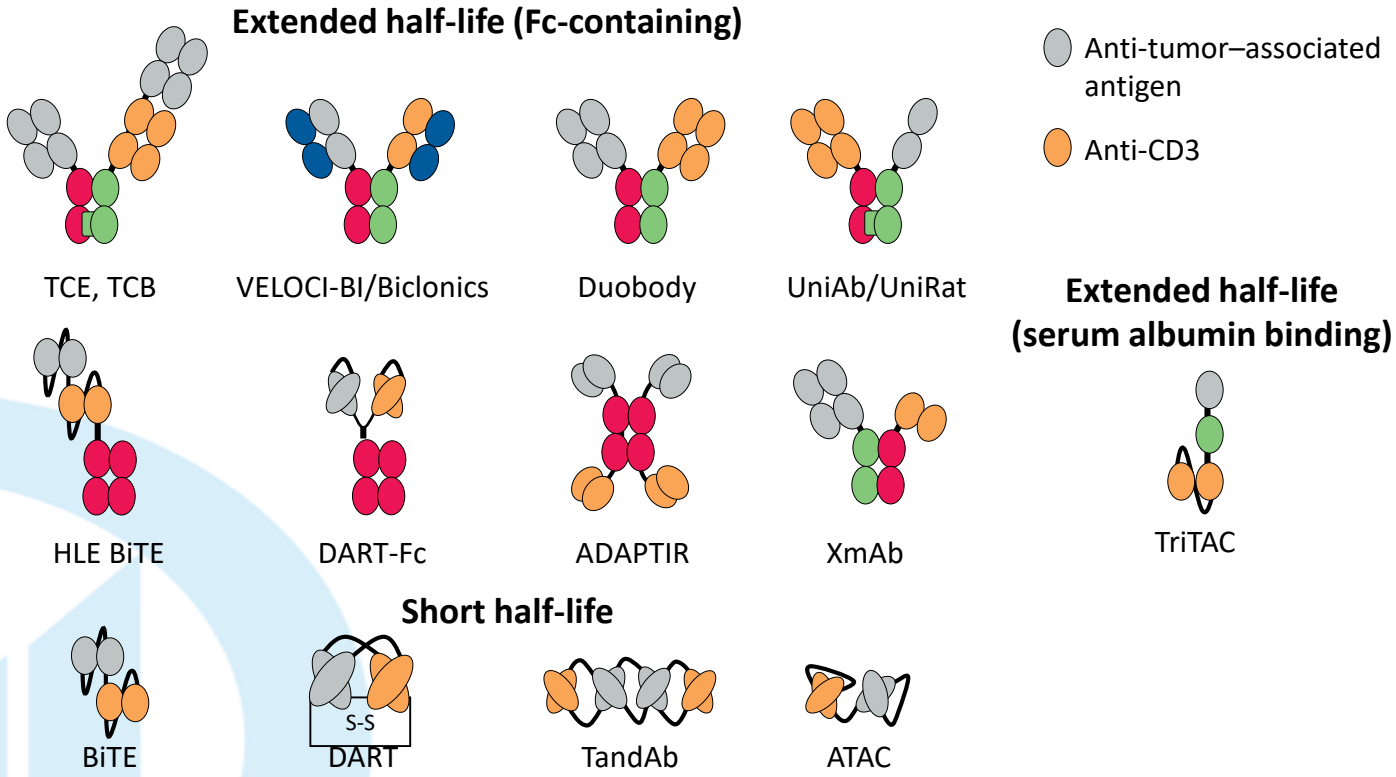
T-Cell Engager Antibody Constructs in Clinical Evaluation



Kontermann. Drug Discov Today. 2015;20:838. Ellergman. Methods. 2019;154:102. Strohl. Antibodies (Basel). 2019;8:41. Suurs. Pharmacol Ther. 2019;201:103. Costa. ASH 2019. Abstr 143.

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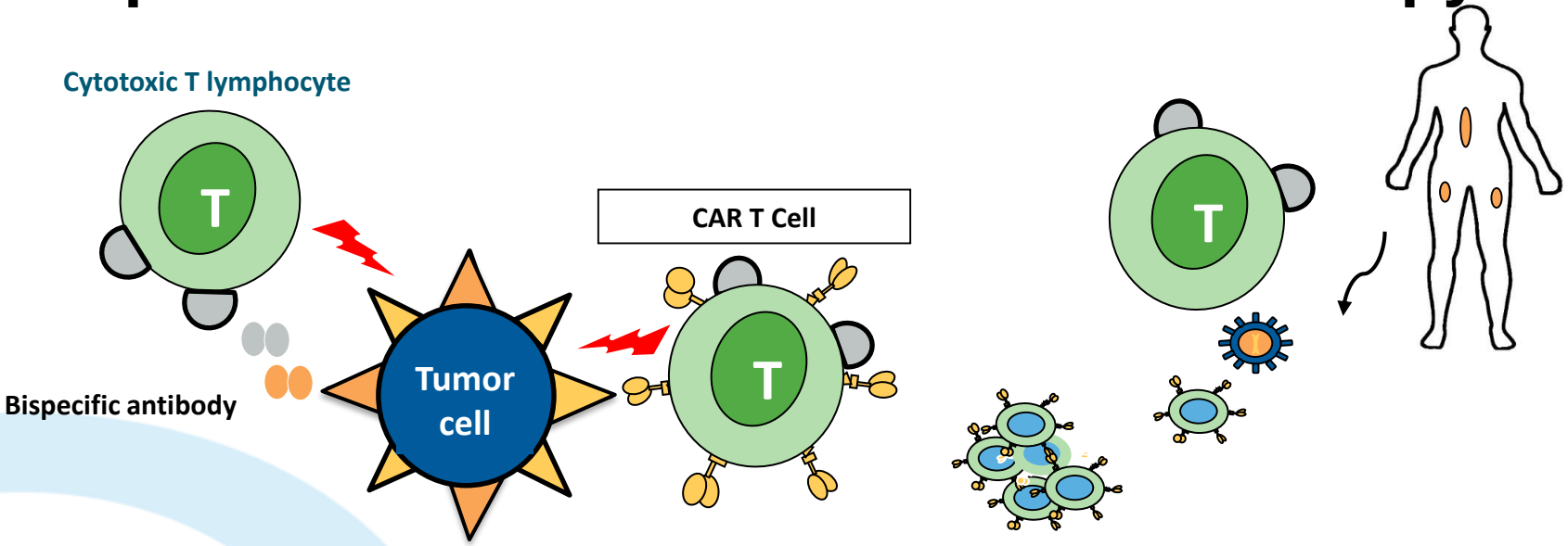
Bispecific Antibodies vs CAR T-Cell Therapy



Characteristic	Bispecific Antibodies	CAR T-Cell Therapy
Preparation	“Off the shelf”	In vitro manufacturing (3-4 wks)
Dosing	Repetitive	Single (following lymphodepleting CT)
CRS incidence	Less	Greater

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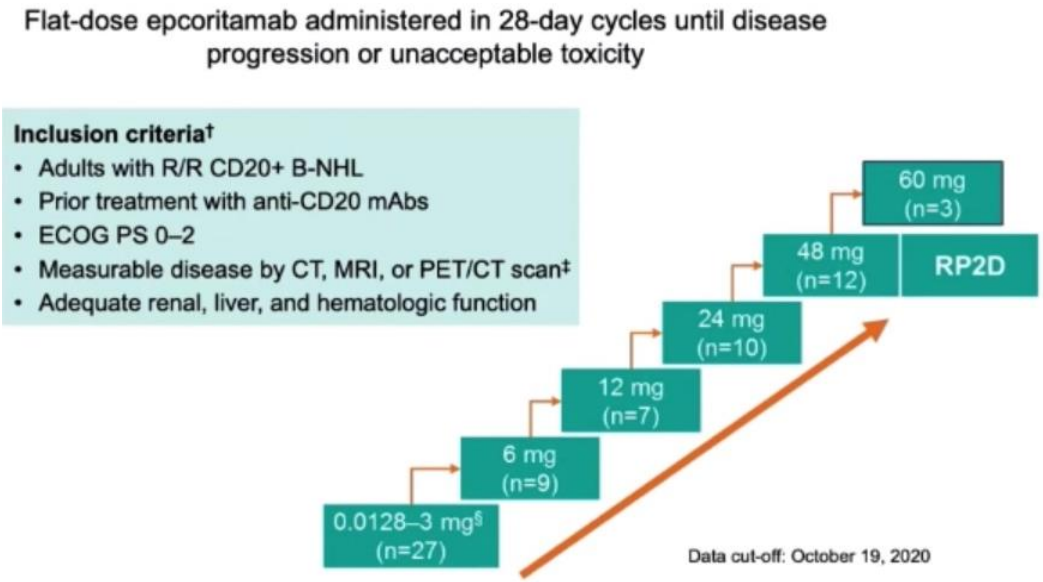
GCT3013-01: Epcoritamab (subcutaneous CD20/CD3 bi-specific antibody) for refractory NHL

- Epocoritamab: (DuoBody) BiAbs SQ administration
- Low volume (1 ml)
- Long plasma half life
- T-cell killing occurs at low CD20 expression levels
- RP2D was recommended at 48 mg



Hutchings M, et al. ASH Meeting Abstracts 2020.

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Epcoritamab in R/R B-Cell NHL: Baseline Characteristics

Characteristic	All Patients* (N = 68)	DLBCL/HGBCL (n = 46)	FL (n = 12)
Median age, yrs (range)	68 (21-84)	68 (21-82)	73 (35-84)
Male, n (%)	45 (66)	30 (65)	8 (67)
Median time since diagnosis, mos (range)	26.7 (6-330)	22.5 (6-288)	65.6 (14-330)
Median no. prior therapies (range)	3 (1-18)	3 (1-6)	5 (1-18)
Prior therapies, n (%)			
▪ Anti-CD20 mAb	68 (100)	46 (100)	12 (100)
▪ Anthracyclines	62 (89.7)	46 (100)	9 (75)
▪ Alkylating agents	67 (98.3)	42 (100)	12 (100)
▪ ASCT	7 (10)	5 (11)	1 (8)
▪ CAR T-cell	6 (9)	5 (11)	1 (8)
Refractory to, n (%):			
▪ Most recent systemic therapy	59 (86)	42 (91)	10 (83)
▪ Most recent anti-CD20 mAb (last line)	60 (88)	40 (87)	10 (83)
▪ Alkylating agents	56 (82)	42 (91)	9 (75)

*Histology: DLBCL, 67.2% (de novo, 34.5%; transformed, 29.3%; unknown, n = 2); HGBCL, 5.2%; FL, 19.0%; MCL, 5.2%; MZL, 1.7%; SLL, 1.7%.

Hutchings. ASH Meeting Abstracts 2020.

Epcoritamab in R/R B-Cell NHL: Baseline Characteristics

Characreristics	DLBCL (N= 46)	
	12 – 60 mg (n= 23)	48 – 60mg (n= 12)
Evaluable pts	22	11
ORR	15 (68%)	10 (91%)
CR	10 (46%)	6 (55%)
PR	5 (23%)	4 (36%)
SD	1 (5%)	0
Progressive disease	5 (23%)	0

- ✓ Median follow up (DLBCL): 7 months
- ✓ 4 pts post CART relapse: 2 CR and 2 PR
- ✓ Safety
  - ✓ **CRS G1-2 59%. No G ≥ 3 CRS**
  - ✓ **No ICANS**
- ✓ The RP2D was determined at 48 mg

Hutchings. ASH Meeting Abstracts 2020.

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Odronextamab CD20/CD3 BiAbs in B-NHL: Baseline Characteristics

Characteristic	Odronextamab (N = 136)
Median age, yrs (range)	67 (27-89)
Male, n (%)	96 (70.6)
ECOG PS 0/1, n (%)	57 (41.9)/79 (58.1)
Ann Arbor stage, n (%) ▪ I-II ▪ III-IV	 18 (13.2) 118 (86.8)
Bulky disease, n (%)	46 (33.8)
B-NHL, n (%) ▪ DLBCL ▪ FL grade 1-3a ▪ MCL ▪ MZL ▪ Other*	 78 (57.4) 38 (27.9) 12 (8.8) 6 (4.4) 2 (1.5)

Characteristic	Odronextamab (N = 136)
Median prior lines of therapy, n (range)	3 (1-11)
Prior ASCT, n (%)	10 (7.4)
Prior CAR T-cell therapy,† n (%)	**35 (25.7)**
Refractory to last line of therapy, n (%)	109 (80.1)
Refractory to anti-CD20 antibody, n (%)	113 (83.1)
Refractory to alkylator therapy, n (%)	92 (67.6)
Double refractory to alkylator therapy and anti-DC20 antibody, n (%)	91 (66.9)

DLBCL, n = 30; FL, n = 2; MCL, n = 3. No response or relapse within ≤ 6 mos.

Bannerji. ASH 2020. Abstr 400.

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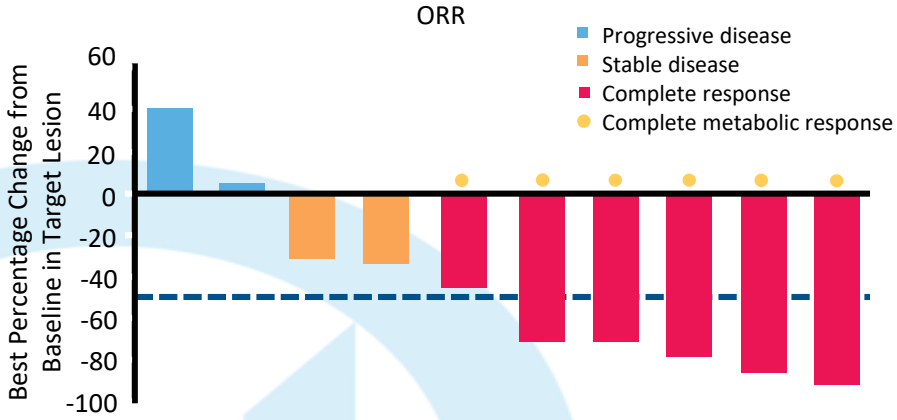
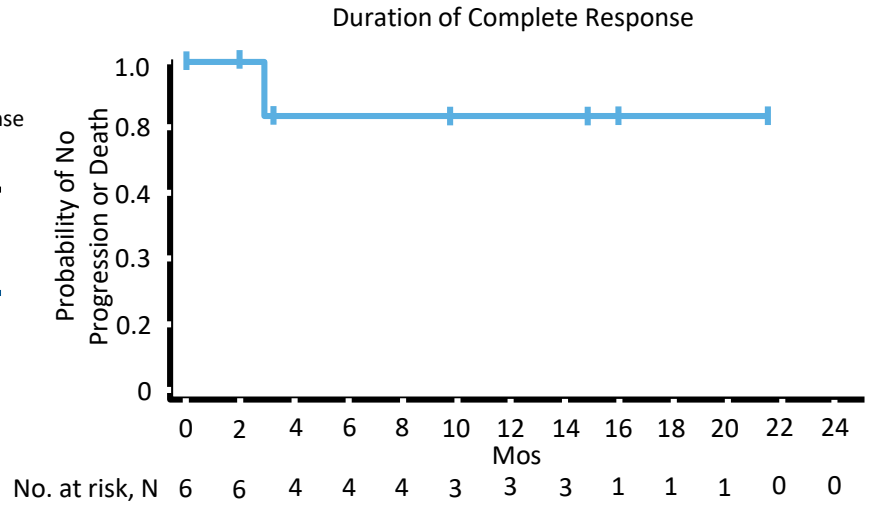
Odronextamab in B-NHL: Antitumor Activity in R/R DLBCL With Doses 80-320 mg (No Prior CAR T-Cells)

- ORR: 55% (6/11); CR rate: 55% (6/11); median duration of CR: not reached
  - 83% of CRs durable (ie, lasting ≥ 3 mos), ongoing up to 21 mos





Median duration follow-up: 6 mos (range: 1-24).

Bannerji. ASH 2020. Abstr 400.

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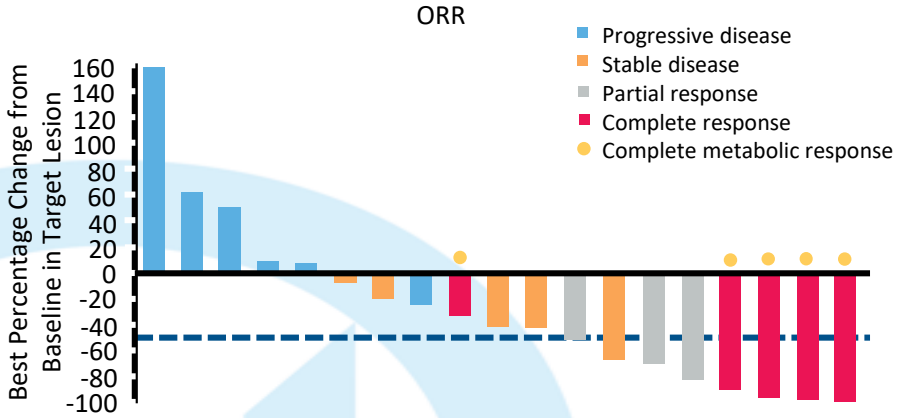
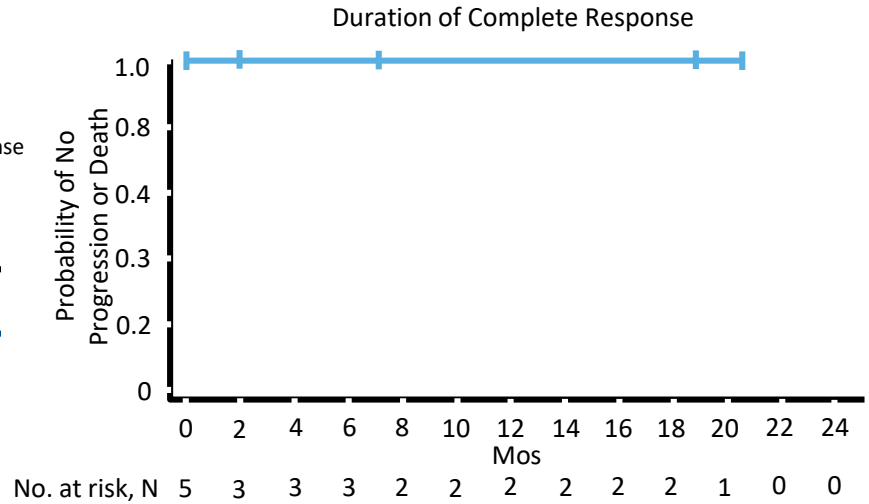
Odronextamab in B-NHL: Antitumor Activity in R/R DLBCL (relapse post CART) Doses 80-320 mg

- ORR: 33% (8/24); CR rate: 21% (5/24); median duration of CR: not reached
  - 100% of CRs ongoing at last tumor assessment, up to 20 mos





Median duration follow-up: 3 mos (range: 0-22).

Bannerji. ASH 2020. Abstr 400.

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Odronextamab in B-NHL: Cytokine-Release Syndrome

CRS, n (%)	DLBCL (n = 78)	FL Grade 1-3a (n = 38)	Other B-NHL‡ (n = 20)	All Patients (N = 136)
Grade 1	31 (39.7)	13 (34.2)	4 (20.0)	48 (35.3)
Grade 2	14 (17.9)	11 (28.9)	0	25 (18.4)
Grade 3	**4 (5.1)***	**1 (2.6)†**	**4 (20.0)**	**9 (6.6)**
Grade 4	**0**	**0**	**1 (5.0)**	**1 (0.7)**
All cases	49 (62.8)	25 (65.8)	9 (45.0)	83 (61.0)

*Occurred during step-up dosing, n = 2 in Wk 1 (including after 1-mg initial dose), n = 2 in Wk 2. †Occurred during full-dose period (ie, Wk 3 onwards). Includes MCL, MZL, FL grade 3b, and Waldenström macroglobulinemia.

- Most CRS events mild or moderate, resolved within median 2 days (range: 1-41) with supportive care

Bannerji. ASH 2020. Abstr 400.

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Bi-Specific Antibodies currently studied in DLBCL: Efficacy

Ab type	CD20/CD3			CD20/CD3 sq	CD19/CD3
	Glofitamab	Mosunetuzumab	Odronextamab	Epcoritamab	Blinatumomab
Phase	1	1/1b	1	1	2
N	98	131	68	58	110
Histology	FL,DLBCL,TFL other	DLBCL, TFL, FL, other	DLBCL, FL, WM, MCL, MZL	DLBCL, FL, MCL, MZL, SLL	Aggressive NHL
Prior Therapies	3 (1-13)	3 (1-14)	3 (1-11)	3 (1-18)	Second salvage
ORR	aNHL: 60.9% DLBCL: 55%	DLBCL/TFL: 34%	DLBCL: 60%	91% (> 48mg)	37%
CR	aNHL: 49.3% DLBCL: 42%	DLBCL/TFL: 19%	DLBCL: 60% (> 80 mg)	55% (> 48 mg)	22%

ORR, overall response rate; CR, complete response; TFL, transformed follicular lymphoma

1. Hutchings M, et al. ASH 2018. Abstract #226. 2. Budde LE, et al. ASH 2018. Abstract #399. 3. Banerji R, et al. ASH 2018. Abstract #1690. 4. Coyle L, et al. ASH 2018. Abstract #400.

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Bi-Specific Antibodies currently studied in DLBCL: Safety

Antibody	CD20/CD3				CD19/CD3
	CD20-TCB	Mosunetuzumab	REGN1979	GEN3013	Blinatumomab
N	64 (> 600 ug)	131	68	58	41
DLTs	1 at 220 ug (MI)	Not reported	None	None	N/A
MTD	Not reached	Not reached	Not reached	Not reached	N/A
Grade ≥ 3AEs Grade 5	56% (27% related) 0	55% (26% related) 2%	75% 4% (1% related)		71% 22%
CRS any CRS ≥3	39% 0%	23% 0%	47% 6%	56.9% 0	2% 2%
NT any NT ≥3	30% (6% related) 5%	49% 2%	41% 3%	6.9% 3.4%	56% 24%

CRS, cytokine release syndrome; NT, neurotoxicity; MTD, maximum tolerated dose; DLT, dose limiting toxicity Hutchings M, et al. ASH 2018. Abstract #226. 2. Budde LE, et al. ASH 2018. Abstract #399. 3. Banerji R, et al. ASH 2018. Abstract #1690. 4. Coyle L, et al. ASH 2018. Abstract #400.

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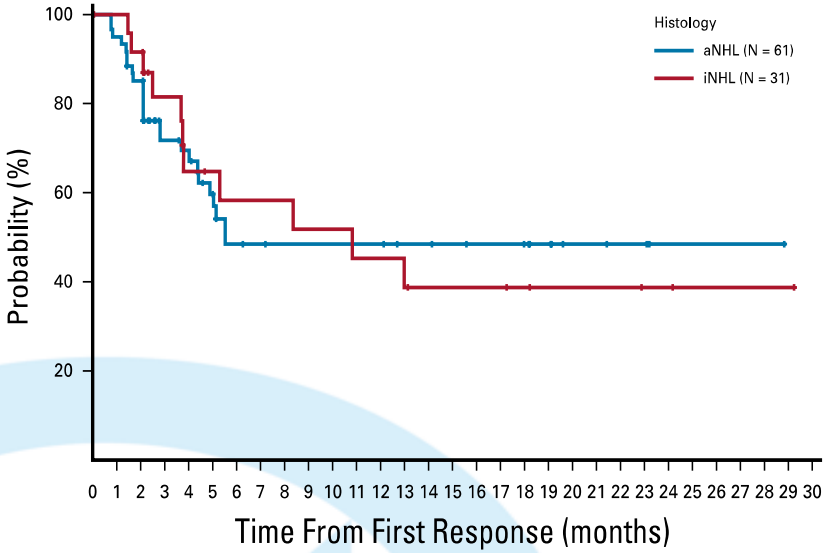
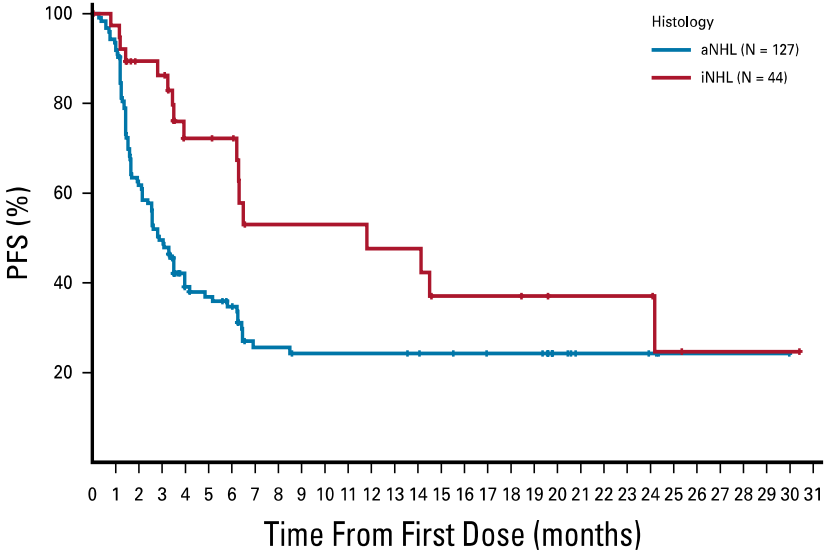
Glofitamab CD20/CD3 TCD BiAbs: Duration of response and PFS in aggressive and indolent R/R NHL





Median DOR aNHL: 5.5 months
Median DOR iNHL: 10.8 months
Median duration of CR: Not reached

Median PFS aNHL: 2.9 months
Median PFS iNHL: 11.8 months

Hutchings. J Clin Oncol 2021.

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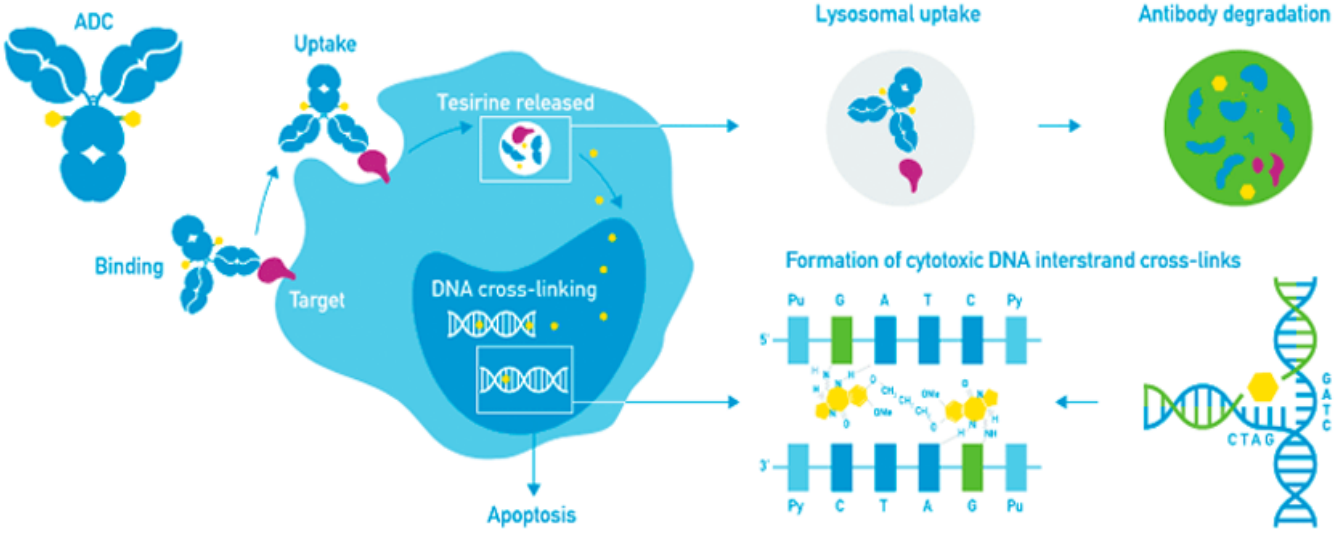
Phase II: Loncastuximab tesirine anti-CD19 ADC in R/R DLBCL



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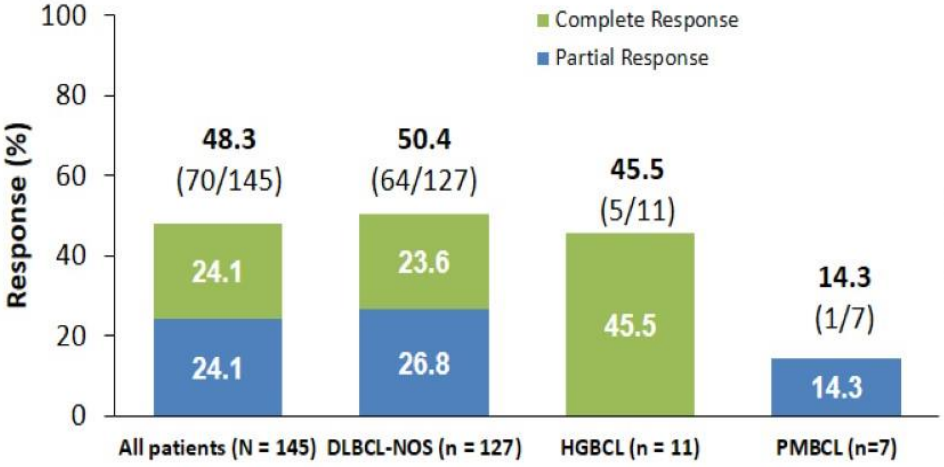
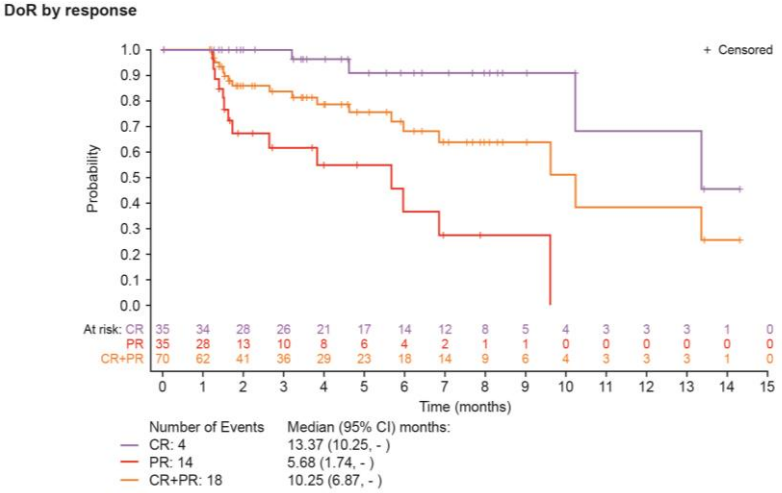
Loncastuximab for R/R DLBCL: responses by histology and DoR





- *ORRs in high-risk subgroups*: transformed disease (44.8%), aged 65–74 (45.8%), aged ≥75 (52.4%), double- or triple-hit DLBCL (33.3% [all CRs]), and prior **CAR T therapy (46.2%)**
- Any-grade TEAEs: GGT increased (40.7%), neutropenia (39.3%), thrombocytopenia (33.1%), and fatigue (27.6%)
- G≥3 TEAEs: neutropenia (25.5%), thrombocytopenia (17.9%), GGT increased (16.6%), and anemia (10.3%)

Carlo-Stella. EHA 2020 Abstract S233; Caimi et Al. ASH Meeting Abstracts 2020

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Combination studies in R/R DLBCL

- [1]**ViPOR (NCI study):** Phase Ib/II of venetoclax, ibrutinib, prednisone, lenalidomide and obinutuzumab. Limited duration therapy- 6 months. (n= 53 pts; 23% prior CART):
  - Non GCB→ ORR: 64%, CR: 57%
  - GCB→ ORR: 47%, CR: 18%
- [2]Ph Ib/II Polatuzumab, venetoclax and rituximab (n= 48 pts):
  - ORR: 65%, CR: 31%
- [3]LOTIS: Loncastuximab + ibrutinib (n= 28 pts)
  - ORR: 73.7%, CR: 45.5 %.

[1]Melani et Al. ASH Meeting Abstracts 2020: 598; [2]Gritti et Al. ASH Meeting Abstracts 2020: 599; [3]Depaus et Al. ASH Meeting Abstracts 2020: 2099

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Conclusions

- Better knowledge on the molecular and genetic aspects of DLBCL. Therapeutic implications?
- R-CHOP remains as standard of care in the DLBCL frontline setting. Future studies ongoing: POLARIX, First-MIND. ZUMA-12
- DLBCL CNS relapses represent an unmet need. The best preventive strategy remains unknown. RoI of cfDNA in prognostication and treatment?
- DLBCL post CART failure has a very poor prognosis. Improving CAR-T efficacy and/or best treatment at relapse. Bi-specific antibodies and combinatorial targeted agents seem active

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