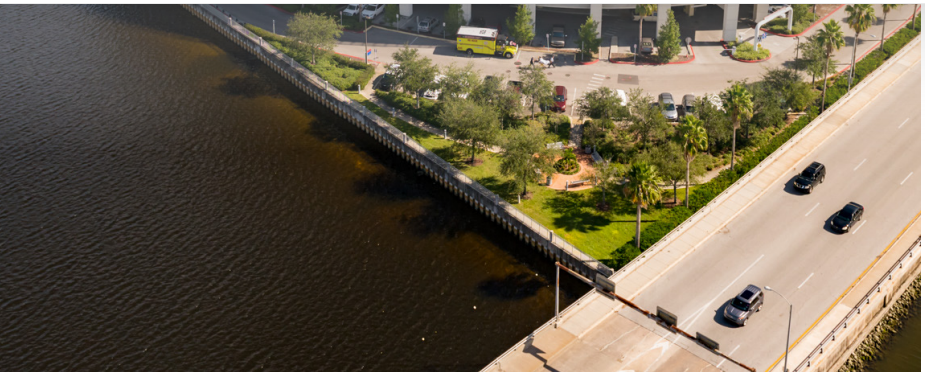
Tampa General Hospital | CANCER INSTITUTE

USF HEALTH MORSANI COLLEGE OF MEDICINE UNIVERSITY OF SOUTH FLORIDA

"DLBCL and Hodgkin's Disease: Novel Approaches"



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Director, TGH Cancer Institute

Professor, Morsani College of Medicine

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DLBCL: After many years of marginal progress…..a plethora of new effective treatments

- **2000: Rituximab added to CHOP chemotherapy (R-CHOP) for frontline treatment of DLBCL …new standard of care**
- **Several attempts to improve frontline treatment of DLBCL beyond R-CHOP (novel anti-CD20 antibodies or targeted therapy in combination with CHOP)…..Failed**
- **DA-EPOCH-R used in some subtypes (HIV-associated DLBCL, PMLBC)**
- **Checkpoint blockade: Modest activity in relapsed/refractory DLBCL, but….new encouraging data in frontline setting.**
- **THE LAST FIVE YEARS:…. CAR T-cells, POLA, TAFA, LONCA, BI-SPECIFICS Abs, single agent or combinations**

Targeting CD19, CD79b and CD20 (again..) in DLBCL

- CD19 is a proven target in DLBCL:
  - CAR T-cells
  - Tafasitamab, anti-CD19 antibody (+/- Lenalidomide) (R/R DLBCL)
  - Loncastuximab Tesirine (Anti-CD19 Antibody-Drug Conjugate) (R/R DLBCL)

- CD79b
  - Polatuzumab vedotin-R-CHP in frontline DLBCL (POLARIX Study)

- CD20 is….again an enticing target…bi-specific antibodies:
  - Several bi-specific directed T-cell engager (BITE) targeting CD20 and CD3 (CD20 x CD3)….

CD19 CAR T-cells in DLBCL
Successes, Failures and Opportunities

- **Autologous CD19 CAR T-cells have shown significant efficacy in patients with relapsed/refractory CD19 positive DLBCL**
  - **Three platforms are FDA-approved (Axi-cel, Tisa-cel and Liso-cel) for DLBCL**
    - ***Cost, manufacture time, toxicity, progression while waiting for engineered T cells. Mechanisms of resistance***
  - **It is estimated that 30-40 percent of patients with large B-cell lymphoma might be cured with CD19 CAR T-cells….**
  - **Remaining 60 percent: Unmet need**
- **Role of CD19 CAR T cells in first relapse setting:**
  - **Is it better than autologous stem cell transplant for patients with DLBCL that relapsed within 12 months of frontline chemoimmunotherapy?**
  - **ASH 2021: ZUMA-7, TRANSFORM and BELINDA Trials**

ASH 2021: CD19 CAR T-cell versus Autologous transplant for DLBCL?

ZUMA-7
ASH 2021: Axi-cel

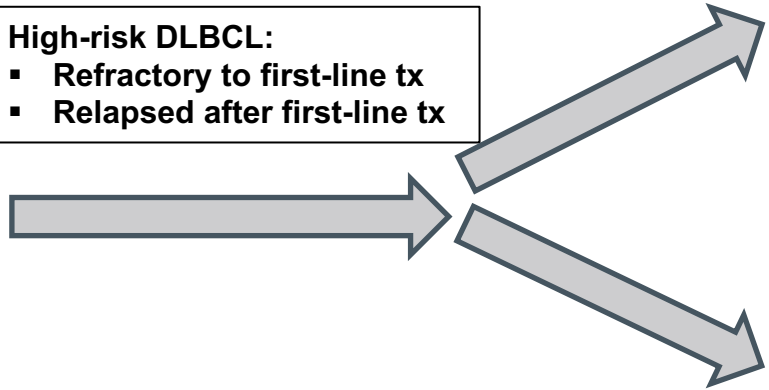
TRANSFORM
ASH 2021: Liso-cel

Positive: CAR T-cells better than ASCT

BELINDA
Tisagenlecleucel

No differences

High-risk DLBCL:
- Refractory to first-line tx
- Relapsed after first-line tx

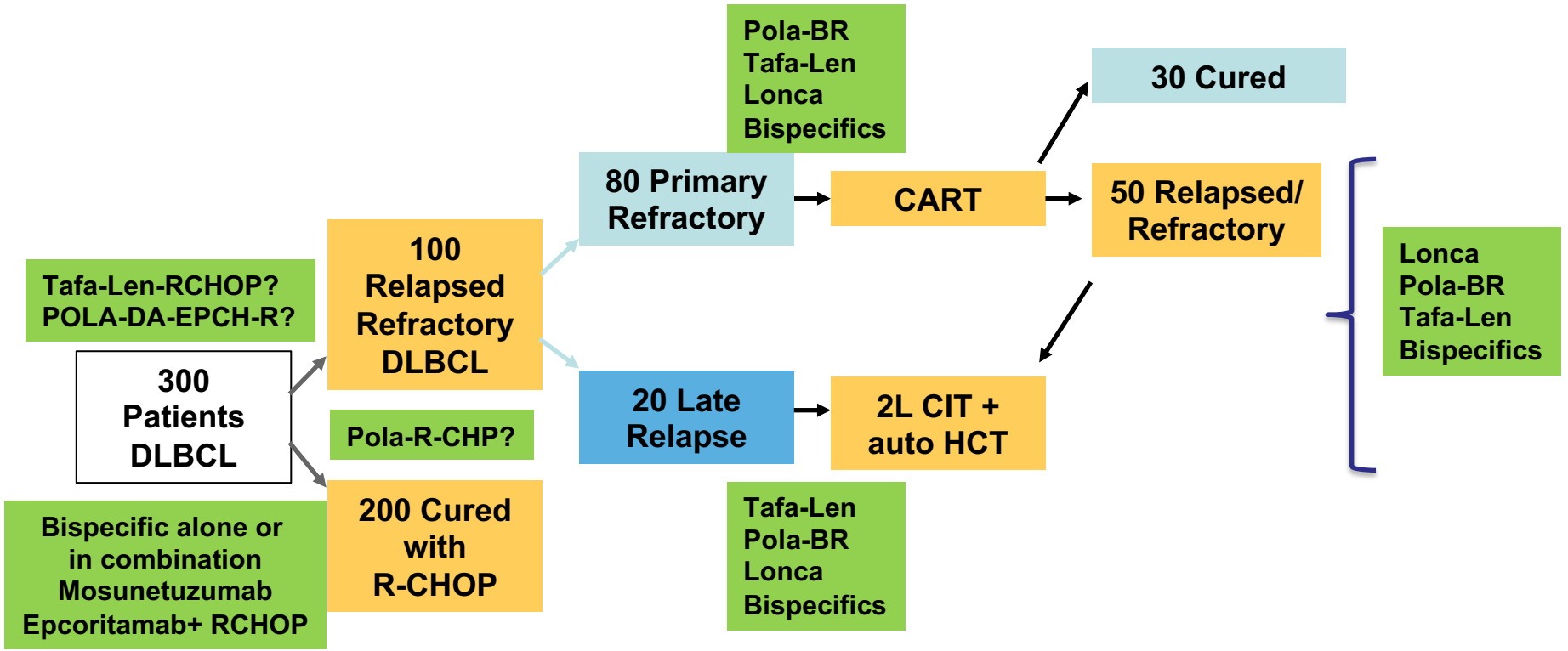


CAR T-cell therapy

Salvage therapy/ auto-transplant

NCT03391466. NCT03570892. NCT03575351.

DLBCL: Changing the Treatment Paradigm



Flow chart adapted from Friedberg. Hematology Am Soc Hematol Educ Program 2011

Polatuzumab Vedotin

- **Humanized anti-CD79b mAb conjugated to MMAE**
  - **CD79b is a B-cell-specific surface antigen expressed in NHL**

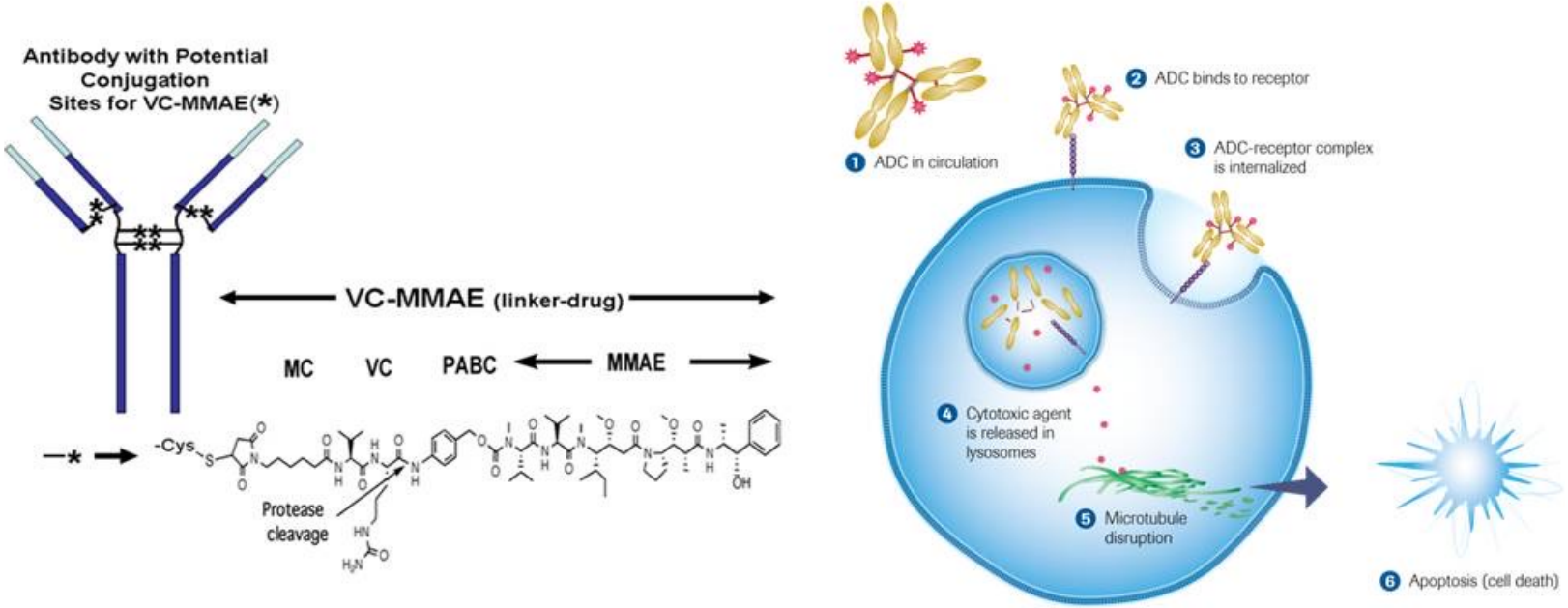


Figure from: Morschhauser, et al. J Clin Oncol. 2014;32(15_suppl):8519.
Doman, et al. Blood. 2009;114:2721-2729. Polson, et al. Blood. 2007;110:616-623. Sehn, et al. ASH 2017;Abstract 2821.

POLARIX: Pola-R-CHP vs. R-CHOP for previously untreated patients with DLBCL (ASH 2021)

- **789 pts in 23 countries**
  - **No differences in CR rate (78% Pola-R-CHP vs 74% R-CHOP)**
  - **No differences in OS at 2 years (88.7 % vs 88.6%)**

- ***Study meet its primary endpoint with a 27% reduction in the relative risk of disease progression, relapse or death associated with Pola-R-CHP***
  - **At 2 years, 76.7% of those receiving pola-R-CHP and 70.2% of those receiving R-CHOP survived without disease progression or relapse**

  - **Double expressors or double/triple hit DLBCL treated with Pola-R-CHP seems to have better outcomes (PFS) than those treated with R-CHOP**

- **Similar rates of adverse events/drug dose reductions or drug discontinuation**

Tilly et al. ASH 2021, LBA-1; NEJM 2022

Outcomes by BCL2 and MYC expression and rearrangements in the POLARIX Trial (ASCO 2022)

- **Pre-specified exploratory analysis: IHC for double expressors and rearrangements (R) by FISH for double/triple hit DLBCL as independent prognostic markers**

- ***Multivariate analysis support the benefit of Pola-R-CHP in patients with BCL2+ and MYC+ DLBCL***

- **The poor prognostic impact associated with double expressors appears reduced in POLA-R-CHP vs. R-CHOP treated pts**

Morschhauser, F. et al. ASCO 2022-Abst. 7517

ASCO 2022: POLA+Others in frontline and R/R DLBCL

- **POLA-DA-EPCH-R for upfront treatment[1]**
  - Can POLA be safely incorporated into other intensified regimens?
  - Single center, open label trial: 6 cycles of POLA-D-EPCH-R in aggressive B-cell lymphomas (HGBCL, PMBCL and selected DLBCL-NOS)
  - 18 pts. Pola at 1.8 mg/kg on day 1.
  - Only 3 DLT. Five SAES: Grade 5 sepsis/typhlitis, 3 episodes of febrile neutropenia and a grade 3 perforation of colonic diverticula. Grade 1 peripheral sensory neuropathy
  - **ORR: 93%; CR: 71% with one PD**

- **Phase III POLARGO trial: Initial safety results from the run-in stage[2]**
  - Phase III trial, multicenter, open label , POLA-R-GemOx vs. R-GmOX
  - 15 pts. No grade 5 AES or AEs leading to drug discontinuation.
  - Peripheral neuropathy was manageable. No cases of Grade $\geq$3 PN
  - **EOT ORR: 40%; CR: 27%.** 7 patients had PD. 10 pts went to receive subsequent therapy including CAR T-cells and SCT.

1. Lynch, R. et.al. Abst. 7546 ; 2. Matasar, M. Abst. 7551

Tafasitamab (Anti-CD19 MAb) in R/R DLBCL

- **L-MIND STUDY:** FDA granted approval for tafasitamab (anti-CD19 MAb) + lenalidomide (25 mg PO QD) for adult patients with R/R DLBCL who are not eligible for ASCT

- **RE-MIND** (retrospective observational matched control study): Tafa + Len had a statistically significant improved ORR compared with lenalidomide monotherapy for patients with R/R DLBCL who are ineligible for ASCT

- **ASCO 2022: Subgroup Analysis in REMIND2:**
- Tafa + Len versus systemic therapies pooled (STP), Pola-BR, R2, and CD19 CAR T-cells.
  - —3,454 pts enrolled received STP, Pola-BR, R2 and CAR T
  - —Matched pairs for patients received Tafa + Len
  - —*Tafa+ Len may be associated with improved OS versus selected systemic therapies for certain pts with high-risk disease*
- *Nowakoswki et al. ASCO 2022 Abst 7560*

	L-MIND (N= 81)
Median follow-up	17.3 months
ORR	60%
CR	42.5%
mDOR	21.7 months
12-month DOR	71.6%
mOS	NR
12-month OS	73.7%
mPFS	12.1 months

Tafasitamab in DLBCL

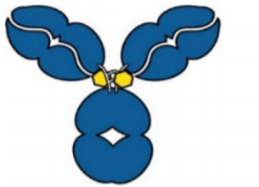
Ongoing Studies:

- **First-MIND (Phase 1b):** R-CHOP +Tafa +/- LEN + for newly diagnosed, previously untreated DLBCL
  - Primary analysis (ASH 2021), demonstrated that adding Tafa + Len does not impair dosing and scheduling of R-CHOP
  - Toxicities were similar to those expected with R-CHOP alone

- **frontMIND:** Phase III, randomized, double blind study of R-CHOP+ Tafa+LEN versus R-CHOP alone for newly diagnosed high intermediate and high risk DLBCL
  - Approx. 880 patients will be randomized in 350 centers worldwide
  - 6 cycles every 21 days of R-CHOP+ Tafa (12 mg/kg IV, D 1,8 and 15) + LEN (25 mg PO D1-10) vs R-CHOP and placebos

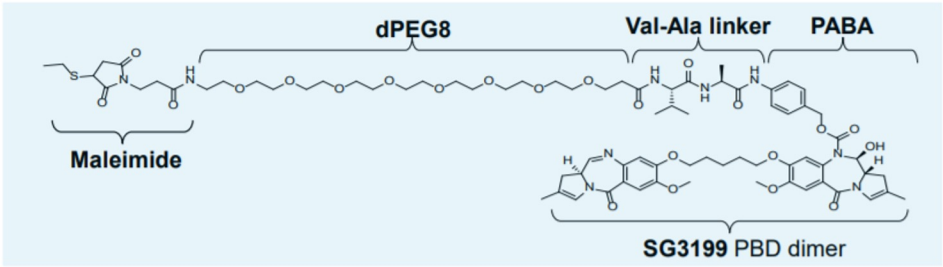
- **B-MIND (Phase II/III):** Tafa + Benda vs rituximab + Benda for R/R DLBCL

Loncastuximab Tesirine-lpyl (ADCT-402)



Anti-CD19 Ab

Tesirine/
SG3249



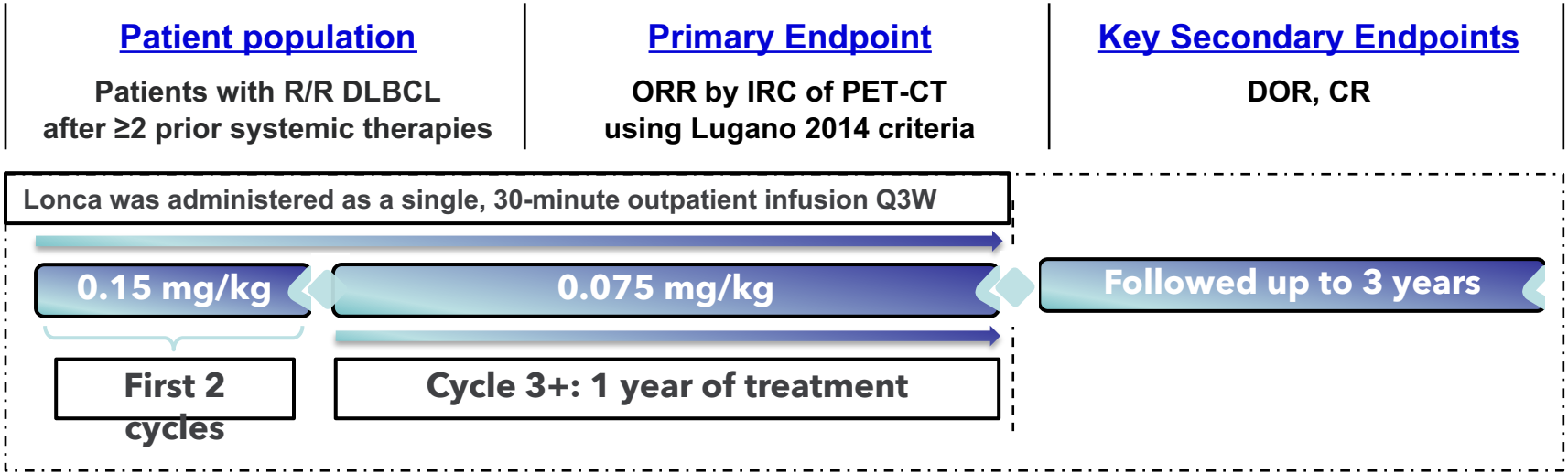
Loncastuximab tesirine comprises a humanized anti-CD19 Ab stochastically conjugated to a potent PBD dimer toxin[1]

The majority of B-cell malignancies express CD19 at normal to high levels[2]

1. Loncastuximab tesirine binds to CD19 antigen on the tumour cell surface
2. ADC is internalized, the linker is cleaved, and PBD dimers are released
3. Cytotoxic DNA cross-link formation
4. Stalled DNA replication fork
5. Cell goes into apoptosis

From Radford, et al. Hematol Oncol. 2019;37(52):93-95

LOTIS-2: Phase II, Open-Label, Single-Arm Study



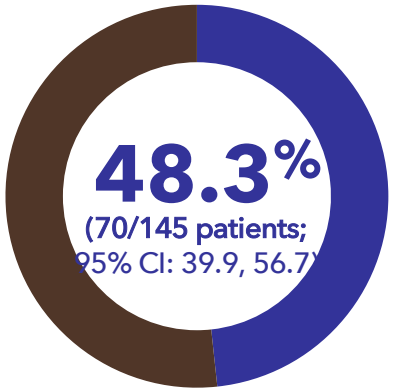
Patients continued treatment until progressive disease or unacceptable toxicity, up to 1 year.

Key inclusion criteria: Transplant-eligible and -ineligible patients; DLBCL NOS; DLBCL arising from low-grade lymphoma; HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements; ECOG PS 0-2.

Key exclusion criteria: Patients with bulky disease (tumors ≥10 cm) and active CNS lymphoma.
Among the 145 patients, the median number of cycles received was 3, with 34% receiving 5 or more cycles.

Lonca Showed Significant Activity in R/R DLBCL

ORR[1,a-c]
(Primary Endpoint)



CR: 24.1% (95% CI: 17.4, 31.9)

PR: 24.1% (95% CI: 17.4, 31.9)

Median TTR[b]

1.3 months
(Range: 1.1-8.1)

Median DOR[b,c] (n=70)

10.3 months
(95% CI: 6.9, NE)

- **The most common grade ≥3 TEAEs (≥10%):**
  - **Gamma-glutamyltransferase increase (20.2%)**
  - **Decreased neutrophils (38%)**
  - **Decreased platelets (27.1%)**
  - **Anemia (11.6%)**

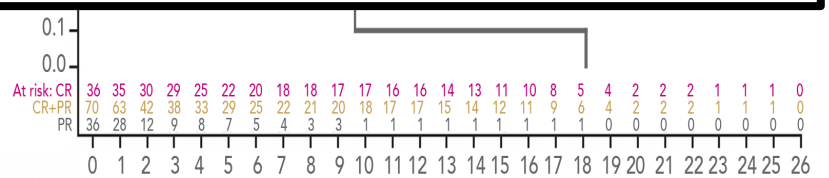
Caimi, PF, et al. Lancet Oncol. 2021;22(6):790-800. 2. Data on file. ADC Therapeutics SA.

Lonca Showed Activity in R/R DLBCL, including difficult-to-treat disease

- **LOTIS-5: Phase III Lonca-R vs R-GemOx**
  - **Safety run-in comparing the safety of Lonca-R to previous Lonca safety data was completed in January 2022 without significant differences in toxicities**
  - **330 patients. Primary endpoint is PFS by ICR.**
  - **Lonca-R: Lonca at 0.15 mg/kg + R every 3 weeks x 2 cycles. Then Lonca at 0.075 mg/kg + R every 3 cycles up to 6 cycles.**

	Present	22.7 (5/22)
Transformed	No	39.6 (38/96)
	Yes	54.8 (17/31)

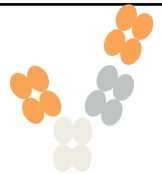
recent therapy	Refractory	35.1 (26/74)
Overall		43.3 (55/127)



FDA Approval for Treatment of Adults with R/R DLBCL after two or more lines of systemic therapy

1. Caimi, PF, et al. Lancet Oncol. 2021;22(6):790-800. 2. Zinzani PL et al. (ICML) Virtual Congress, 2021. 3. Data on file. ADC Therapeutics SA.

Structure of Selected BITE/Bispecific Antibodies

Bispecific Ab	Targets	Design	Ig Fragment Formats
Blinatumomab	CD19 x CD3		• 2 murine scFv joined by glycine-serine linker • Monovalent CD19 and monovalent CD3 binding • Cloned from murine Abs
Mosunetuzumab	CD20 x CD3		• Humanized mouse IgG1-based Ab • Bivalent CD20 and monovalent CD3ε binding • Modified Fc devoid of FcγR and complement binding
Glofitamab	**$CD20_2$** x CD3		• Immunized mouse IgG1-based Ab • **Bivalent CD20** and monovalent CD3ε binding • Modified Fc devoid of FcγR and complement binding
Odronextamab	**CD20** x CD3		• Fully human IgG4-based heterodimeric Ab • Monovalent CD19 and monovalent CD3ε binding • Fc-dependent effector function-minimized Ab with Fc of the antiCD3ε heavy chain modified to reduce Protein A binding • Common κ light chain from antiCD3ε mAb
Epcoritamab	**CD20** x CD3		• Humanized mouse IgG1-based Ab • Monovalent CD20 and monovalent CD3ε binding • IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield

Schuster. ICML 2021. Abstr EB16

Mosunetuzumab in R/R B-cell NHL: Study Design

- **Open-label phase I/Ib study**

Patients with R/R B-cell NHL after ≥ 1 prior regimen; ECOG PS ≤ 1; no available treatment options; no CAR T-cell therapy in past 30 days; no prior allogeneic SCT (N = 270)

Cycle 1 Step-up Dosing

Mosunetuzumab IV*
Days 1, 8, 15 for 21 days

Cycles 2-8 Fixed Dosing

Mosunetuzumab IV
Day 1 for 21 Days

*Safety doses (cycle 1): Day 1/8/15: 0.4/1.0/2.8 to 1.0/2.0/60.0 mg; efficacy doses (cycle 1): Day 1/8/15: 0.4/1.0/2.8 to 1.0/2.0/40.5 mg.

***CR*: discontinuation of treatment**

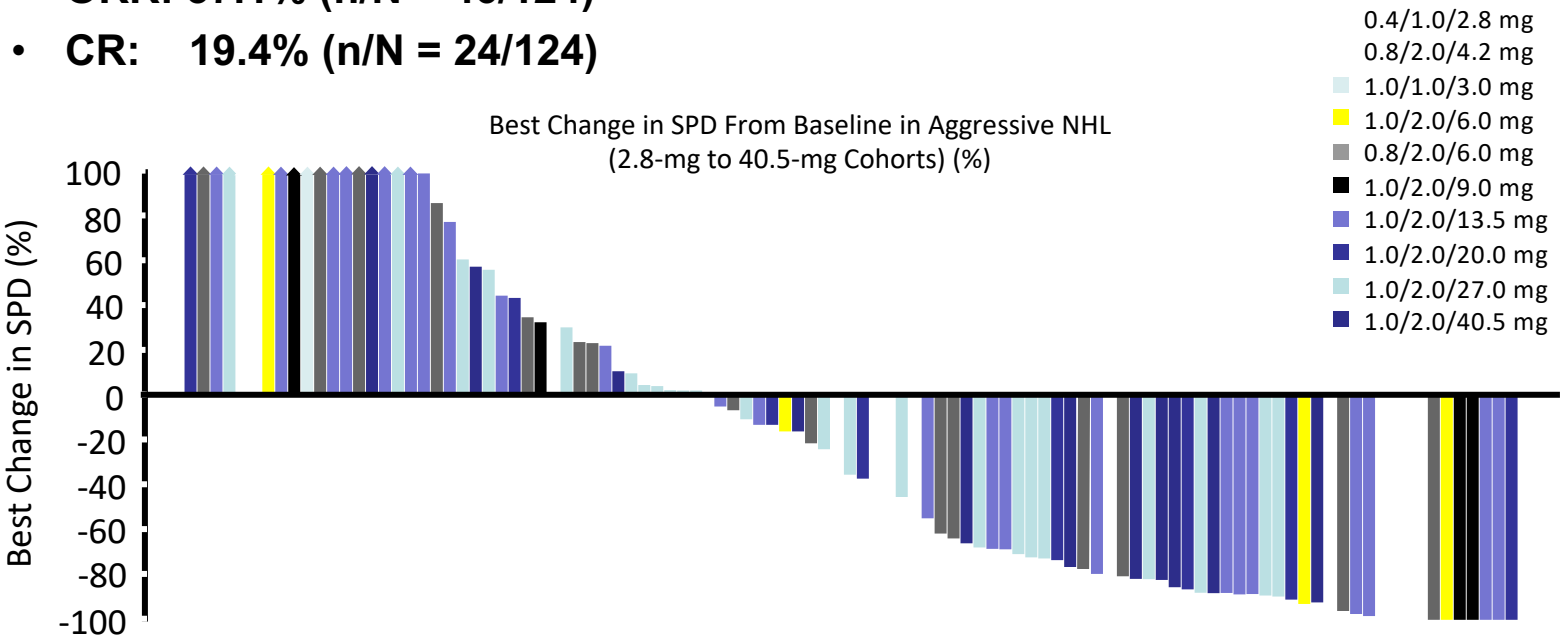
***PR or SD*: treatment continued for ≤ 17 cycles**

Primary objectives: safety, tolerability, maximum tolerated dose, best objective response

S. Schuster et al. ASH 2019. Abstr 6.

Mosunetuzumab-Dose Escalation: Responses in Patients With Aggressive NHL

- **ORR: 37.1% (n/N = 46/124)**
- **CR: 19.4% (n/N = 24/124)**



S. Schuster et al. ASH 2019. Abstr 6.

Efficacy in Patients With Prior CAR T-Cell Therapy and in Retreated Patients

Response, n (%)	Patients With Prior CAR T-Cell Therapy
Total population with prior CAR T-cell therapy (n = 18) ▪ ORR ▪ CR	 7 (38.9) 4 (22.2)
DLBCL (n = 9) ▪ ORR ▪ CR	 2 (22.2) 2 (22.2)
trFL (n = 5) ▪ ORR ▪ CR	 1 (20) 0
FL (n = 4) ▪ ORR ▪ CR	 4 (100) 2 (50)

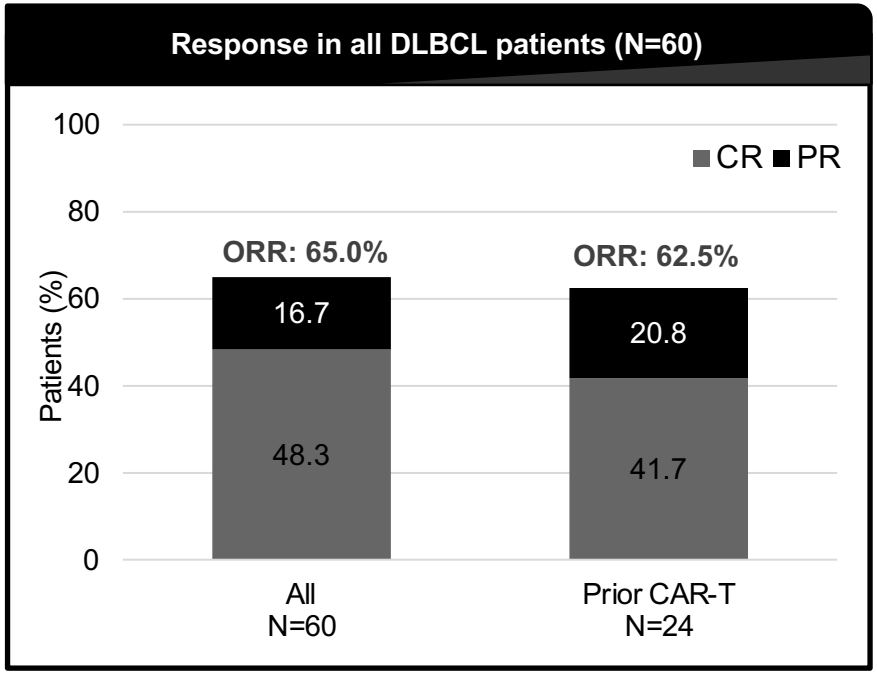
Response, n (%)	Retreated Patients (n = 4)
▪ ORR ▪ CR	3 (75) 1 (25)

- No CRS events occurred during retreatment

S. Schuster et al. ASH 2019. Abstr 6.

Mosunetuzumab + Polatuzumab for R/R DLBCL

- **Median duration of response: NE (0.03–17.8 months)***



- **Median PFS: 8.9 months (95% CI: 3.5, NE)***

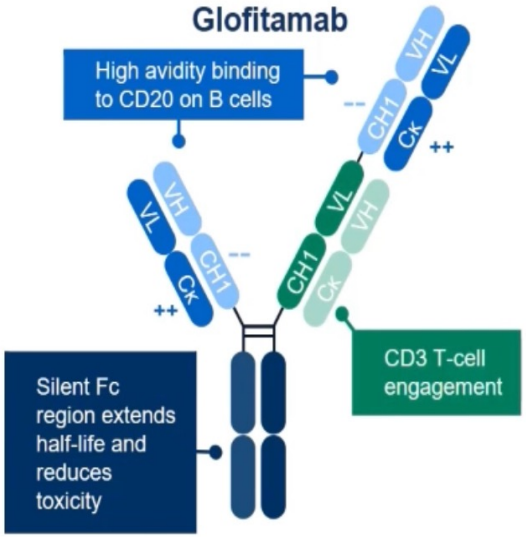
- **Of 29 patients achieving CR, 28 (96.6%) remained in CR and 1 (3.4%) had PD at data cut-off**

Budde et al ASH 2021. Abstr 533

Frontline: Mosunetuzumab in Previously Untreated Elderly Patients with DLBCL

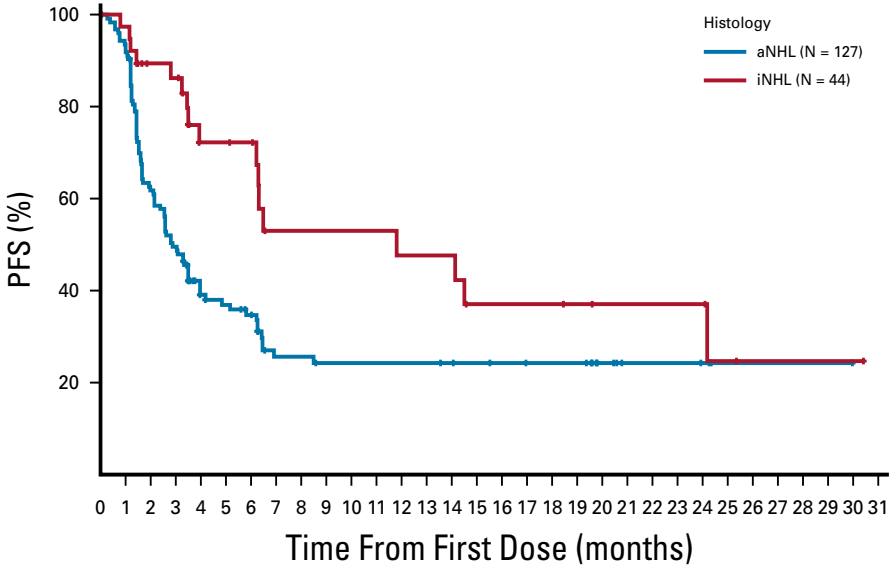
- Elderly patients with DLBCL unfit for conventional treatment (>80 y/o)
- Stepping up dose (D1/D8/D15)
- Optional pretreatment with prednisone+ vincristine
- ORR: 63%; CR: 45%. Durable responses
- CRS mostly grade 1 and limited to first administration
- Might represent a “Chemo-free” option for elderly patients (versus mini-R-CHOP?)

Glofitamab



PFS in Indolent and Aggressive NHL

Hutchings et.al. JCO 2021



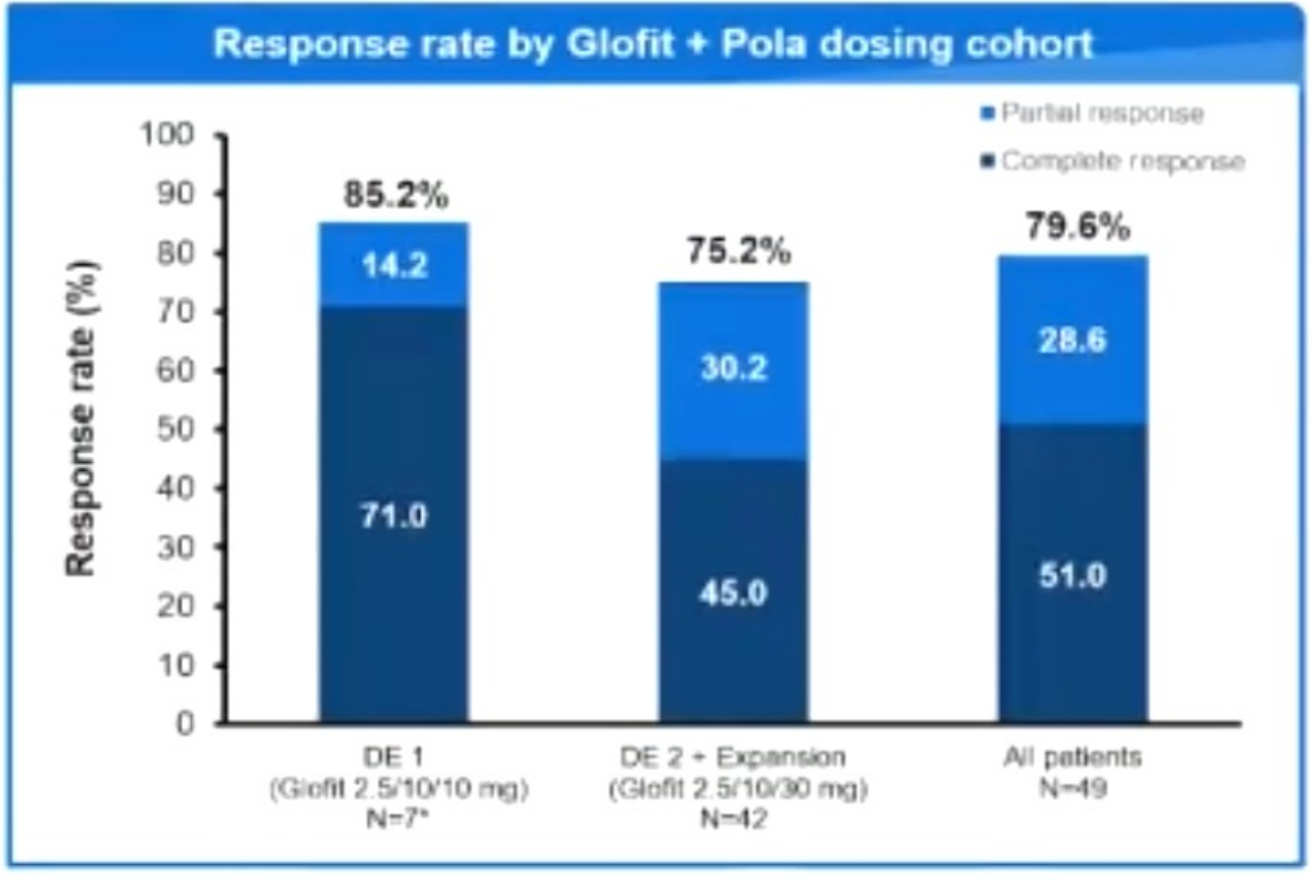
- **Glofitamab is BiAbs with unique IgG full length antibody with 2:1 configuration.**
- **Superior pre-clinical activity over classical 1:1 BiAbs**
- **Obinutuzumab pretreatment allowed for rapid escalation and mitigating the risk of CRS**

ASCO 2022: Pivotal Phase II expansion: Glofitamab in pts with R/R DLBCL >2 prior therapies (M.Dickison et al)

ORR: 50% and CR: 35.2 . Projected 12m OS:48%

Median time to CR: 42 days

Glofitamab + Polatuzumab in R/R DLBCL



Epcoritamab (SC) – ASCO 2022

	Author	Setting	n	ORR (%)	CR (%)	Toxicities
Epco + R-CHOP	L. Falchi (MSKCC)	Frontline High risk (IPI 3-5) Epco weekly (C1-4) Epco every 3 w (C5-6) Epco every 4 weeks x 1 year	33 pts 24% double or triple hit	96%	68%	CRS: 45%(3% gr≥ 3) C1 ICANS: 3% gr 2 Safety profile is manageable CRS mostly low grade No Tx discontinuation
Epco + GemOx	J. Brody (Mt. Sinai)	R/R ineligible for ASCT Epco weekly (C1-3) Epco every 2w (C4-9) Epco every 4 weeks x 1 year	27 pts Mostly primary refractory	92%	60%	CRS: 70% (all gr1-2) C1 ICANS: 1pt (Gr3)
Epco + R-DHAX/C	P. Abrisqueta (Vall d'Hebron)	R/R eligible for ASCT Standard R-DHAX/C Epco weekly 21 day cycle (C1-3)	27 pts 23 evaluable patients, 11 pts underwent ASCT	100%	82%	CRS: 30% (all gr1-2) ICANs: 1 pt (gr2)

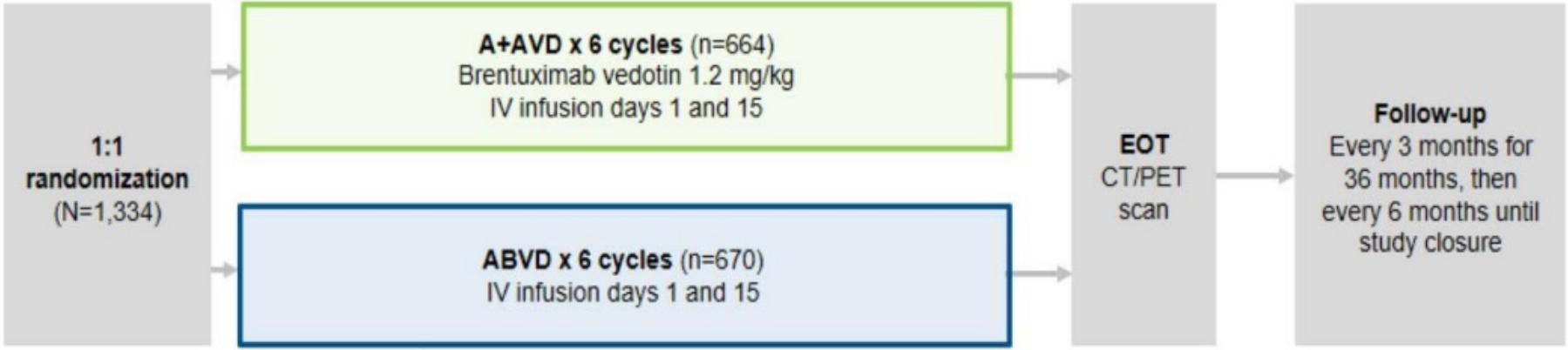
Hodgkin's Disease: Frontline Setting

FIRST-LINE BRENTUXIMAB VEDOTIN PLUS CHEMOTHERAPY IMPROVES OVERALL SURVIVAL IN PATIENTS WITH STAGE III/IV CLASSICAL HODGKIN LYMPHOMA: AN UPDATED ANALYSIS OF ECHELON-1

Stephen M. Ansell, John Radford, Joseph M. Connors, Won-Seog Kim, Andrea Gallamini, Radhakrishnan Ramchandren, Jonathan W. Friedberg, Ranjana Advani, Martin Hutchings, Andrew M. Evens, Piotr Smolewski, Kerry J. Savage, Nancy L. Bartlett, Hyeon-Seok Eom, Jeremy S. Abramson, Cassie Dong, Frank Campana, Keenan Fenton, Markus Puhlmann, and David J. Straus, for the ECHELON-1 Study Group

American Society of Clinical Oncology (ASCO) Annual Meeting 2022. Chicago, IL. June 3–7, 2022. Abstract No. 7503

Phase 3 ECHELON-1 study design



Primary endpoint: modified PFS per IRF (previously reported[1])

Key secondary endpoint: alpha-controlled, event-driven analysis of OS

Long-term follow-up assessments:

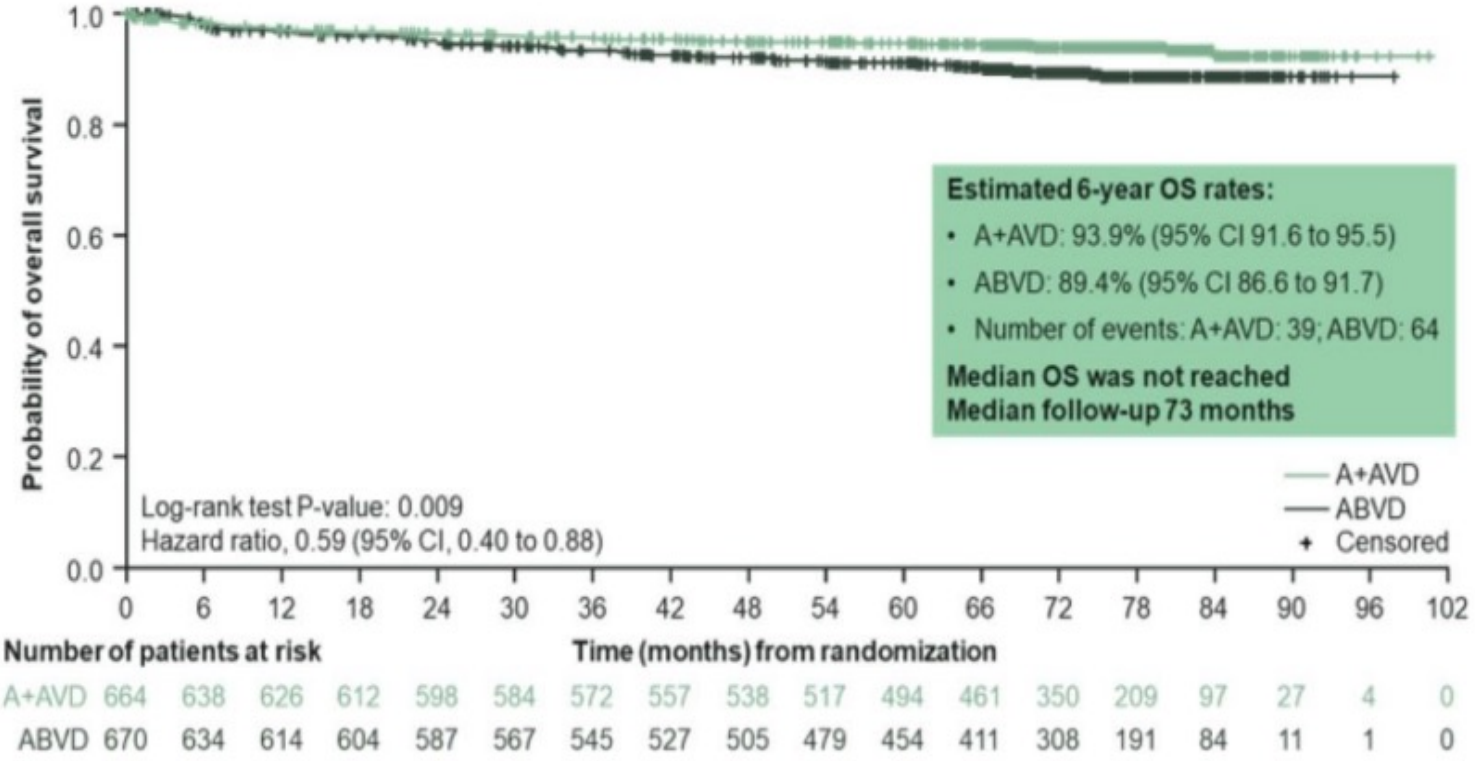
- Exploratory analysis of OS among patients who were PET2-positive and PET2-negative
- PFS per investigator
- Subsequent treatment use
- Safety outcomes including:
  - PN resolution and improvement rates
  - Second malignancies
  - Outcomes of pregnancy among patients and their partners

Data cut-off for current analysis, June 1, 2021.

CT, computerized tomography; EOT, end of treatment; IRF, independent review facility; ITT, intention to treat; IV, intravenous; PET2, PET status at the end of cycle 2.

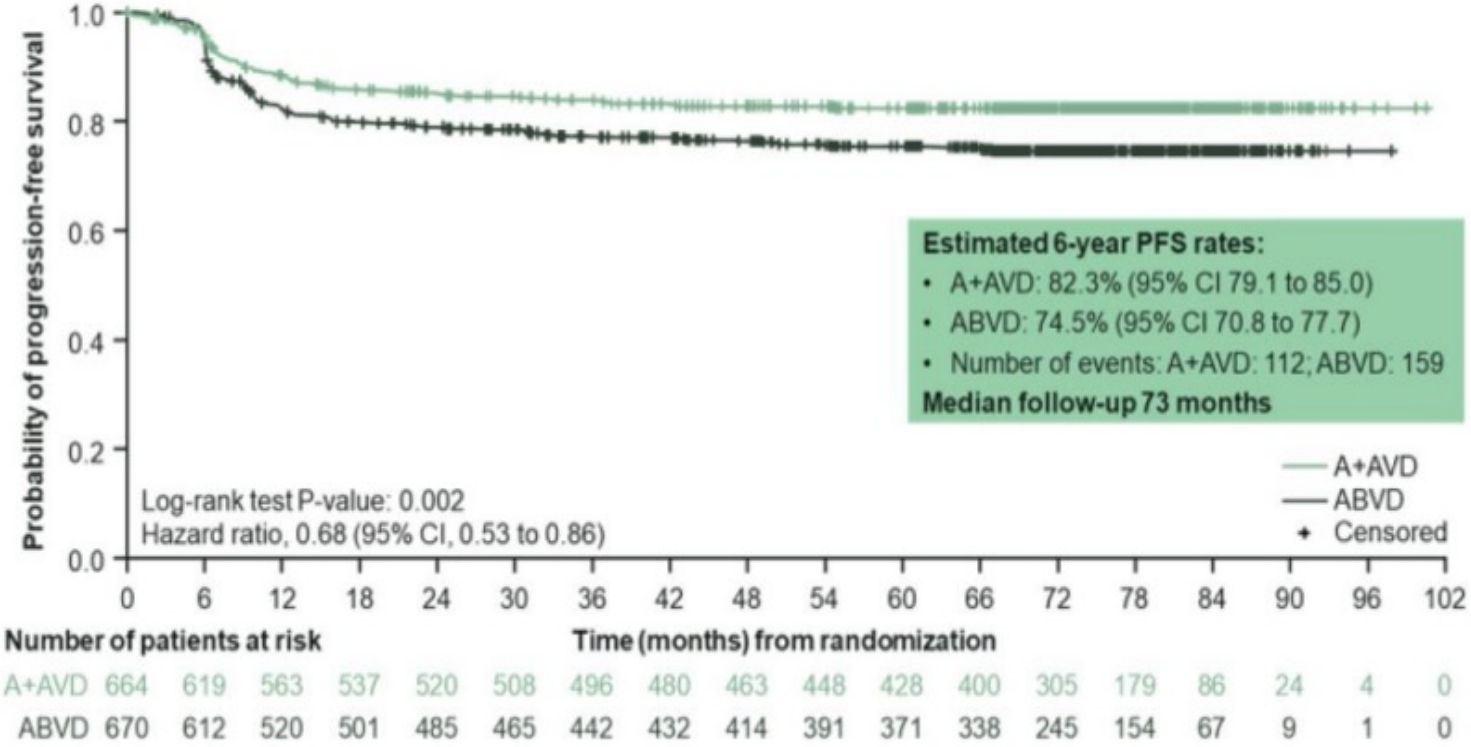
1. Connors JM, et al. N Engl J Med 2018;378:331–44.

A+AVD significantly improved OS with a 41% reduction in risk of death compared with ABVD



CI, confidence interval.

A+AVD reduced the risk of progression or death by 32% when compared with ABVD



Fewer patients died from HL and disease- or treatment-related complications with A+AVD vs ABVD

Cause of death per investigator	A+AVD (n=662)	ABVD (n=659)
Total Deaths	**39 (5.9%)**	**64 (9.7%)**
Hodgkin lymphoma or complications	32	45
Second malignancies	1	11
Other causes	**6**	**8**
Unknown cause	1	5*
Accident or suicide	3	0
COVID-19	0	1
Heart failure	1	1
Intracranial hemorrhage	1	0
Lower respiratory tract infection	0	1

*In 2 patients in the ABVD arm, death was reported to be of indeterminate cause, but the event occurred following investigator-documented disease progression.

Among those who died:

- A+AVD: 19 patients had prior disease progression (not always the cause of death); 18 received subsequent therapy
- ABVD: 28 patients had prior disease progression, 25 received a subsequent therapy (13 received brentuximab vedotin)

Hodgkin's Disease : Relapsed/refractory

- **First relapse:**
  - Second-line therapy ("salvage") followed by consolidation with autologous stem cell transplant (ASCT) remains the standard of care
  - Primary refractory disease (PRD) and early relapse (ER, < 12 months) are predictors of poorer prognosis as compared with late relapse (>12 months)
  - **ASCO 2022 (S. Desai et al. Abstract 7515)**
    - In pts wit PRD and ER, BV/Nivo has higher ORR and CR
    - Combination leads to significantly higher PFS comparable to patients with late relapse
    - BV/Nivo may be the preferable salvage treatment in early as well as late relapse.

Hodgkin's Disease: Novel Approaches

- **Second relapse/refractory disease**
  - **Allogeneic stem cell transplant remains a consideration.**
  - **Other Options: Single-agent chemotherapy or noncytotoxic agents (panobinostat, everolimus and lenalidomide)**
  - **CD30-directed CAR T-cell therapy is promising.**
  - **Bi-specifics are being evaluated in clinical trials**

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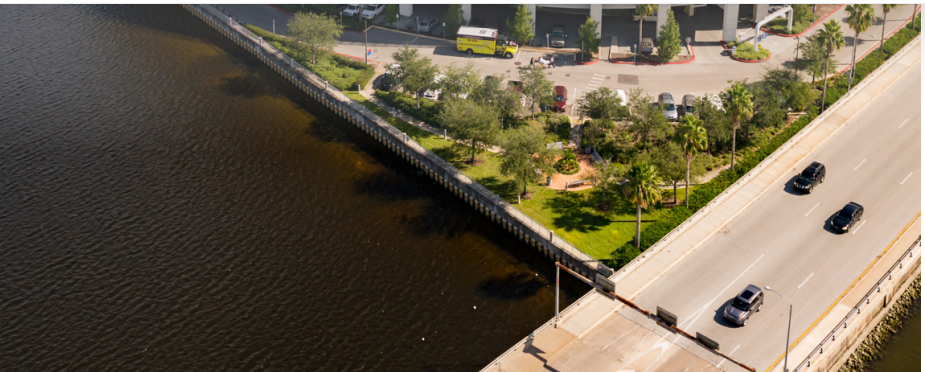
THANK YOU !



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