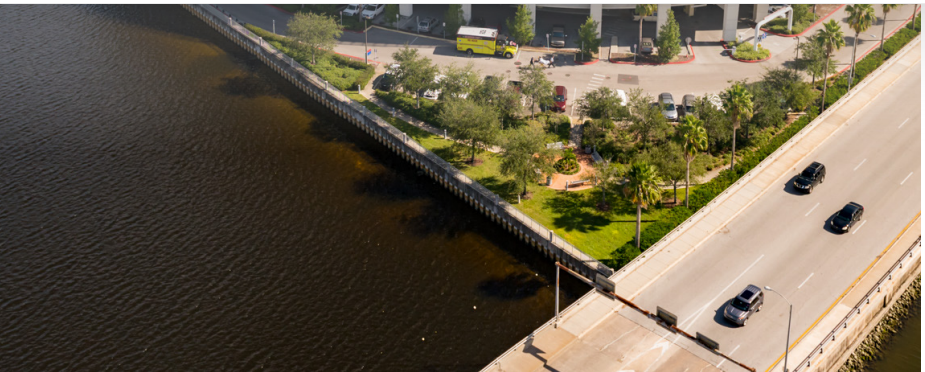
TGH Tampa General Hospital | CANCER INSTITUTE

USF HEALTH MORSANI COLLEGE OF MEDICINE UNIVERSITY OF SOUTH FLORIDA

"Novel Therapeutic Advances in Hodgkin's Disease and DLBCL"



Eduardo M. Sotomayor, MD

Director, TGH Cancer Institute

Professor, USF Health Morsani College of Medicine

University of South Florida

ASCO 2023: S1826 Intergroup Study
Frontline Nivo+AVD vs. BV+AVD in Advanced Stage cHL

Newly diagnosed stage III-IV Hodgkin lymphoma (≥12 y.o.) n=987 pts

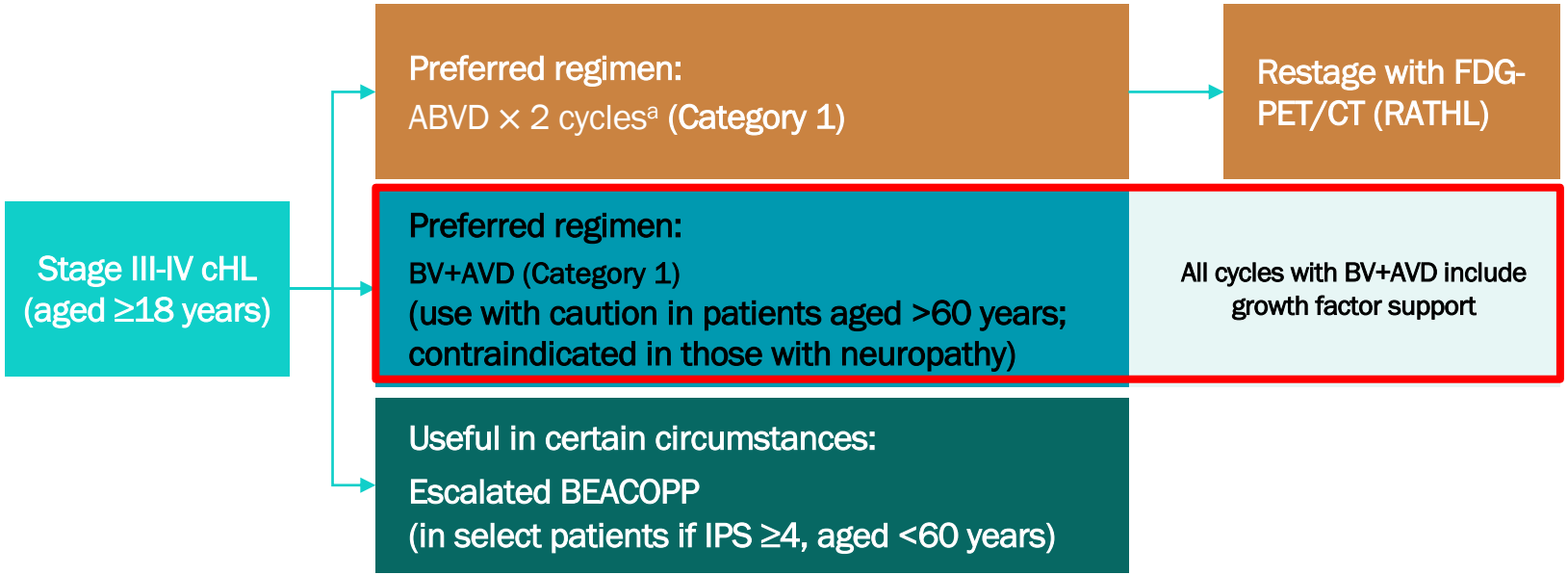
Stratification
- Age
- IPS
- ISRT eligible

At planned 2nd interim analysis (50% of total PFS events), the SWOG Data and Safety Monitoring Committee recommended to report the primary results because the primary PFS endpoint crossed the protocol-specified conservative statistical boundary

k ISRT allowed for
lared ISRT-
prior to
nization with EOT:
5
reduction in max
verse diameter
ual LN ≥2.5 cm
ual extranodal >1

Herrera AF, et al. ASCO 2023, Plenary Session.

NCCN Guidelines in Stage III-IV Classical Hodgkin (Version 2.2023)



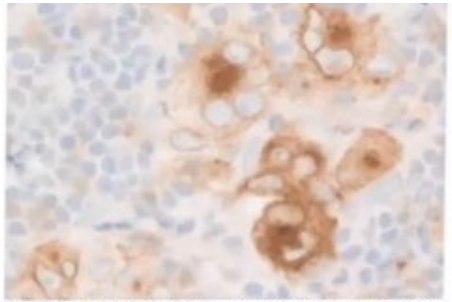
ALL RECOMMENDATIONS CATEGORY 2A UNLESS OTHERWISE INDICATED

[a] *ABVD is preferred based on the toxicity profile and quality of data.*

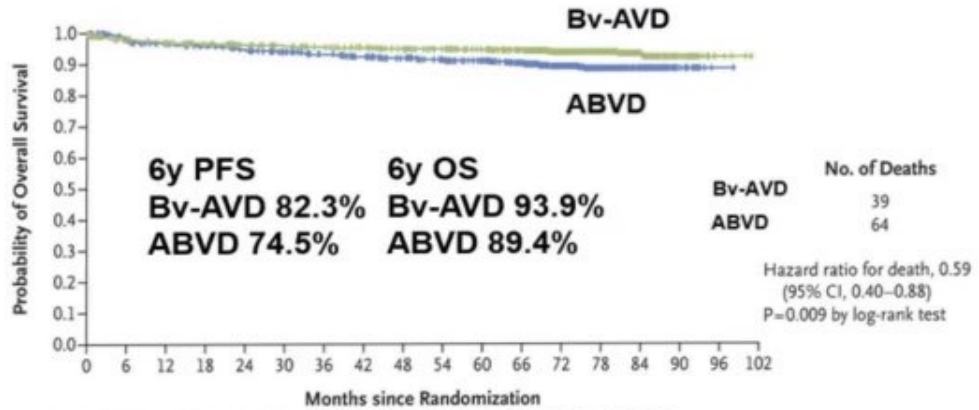
National Comprehensive Cancer Network. Hodgkin Lymphoma (Version 2.2023). Accessed February 2, 2023. https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf

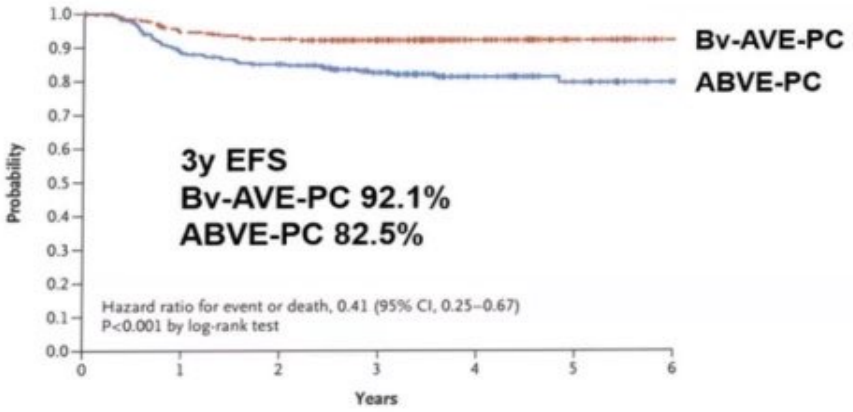
Brentuximab vedotin in advanced stage adult and pediatric Hodgkin Lymphoma

- Brentuximab vedotin (Bv): anti-CD30 antibody drug conjugate
- Bv in frontline treatment of advanced stage cHL improves outcomes in adult (OS) and pediatric (event-free survival) patients[4,5,6]



Source: ASH Image Bank/Girish Venkataraman, MD, MBBS; Megan Parilla, MD





4. Ansell SM et al. NEJM 2022. 5. Castellino SM et al. NEJM 2022. 6. Borchmann P. et al. ISHL, ASH 2022.

Herrera AF, et al. ASCO 2023, Plenary Session.

Can we do better?:
Rationale for Intergroup Study S1826

- Relapses still common (7-20%)[4,5]
- Different chemotherapy backbones still used in peds vs adults & globally[4,5,6]
- Majority of AYA still receive consolidative RT and are vulnerable to late morbidity/mortality[5]
- Bv-AVD adds toxicity vs ABVD in adults[4]
  - ↑ neuropathy, febrile neutropenia/infections/sepsis
  - Requires G-CSF support

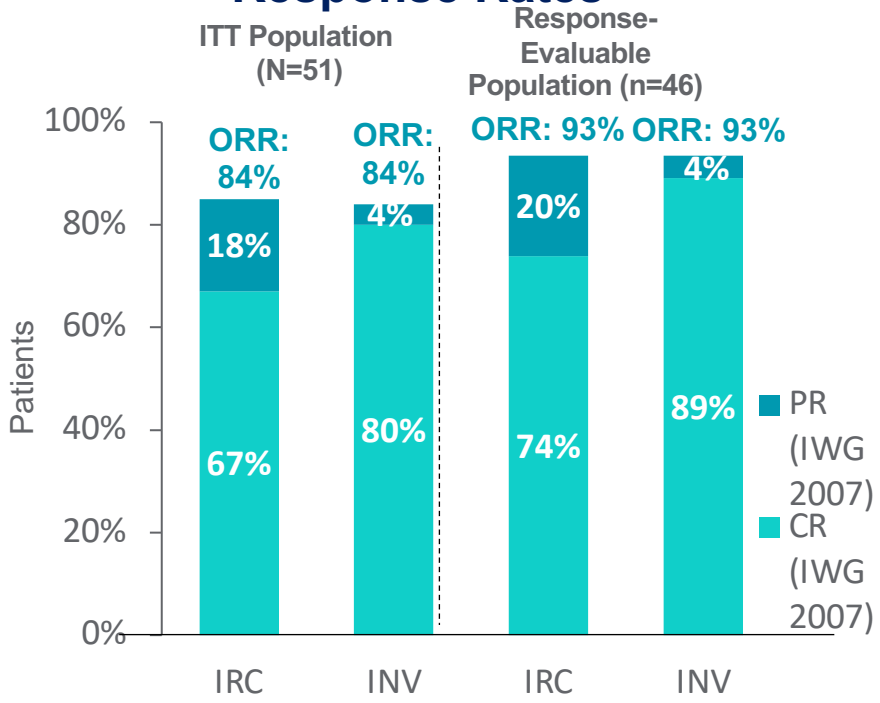
- There remains room to improve outcomes for advanced stage cHL

4. Ansell SM et al. NEJM 2022. 5. Castellino SM et al. NEJM 2022. 6. Borchmann P. et al. ISHL, ASH 2022.

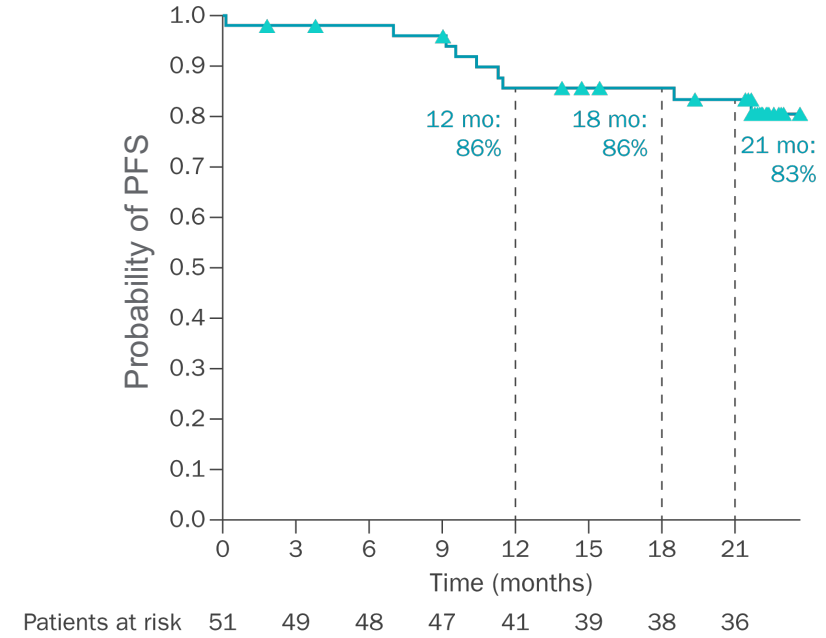
Herrera AF, et al. ASCO 2023, Plenary Session.

Incorporating PD-1 blockade into initial cHL treatment (Nivo + AVD) is highly effective and well tolerated

Response Rates[1]

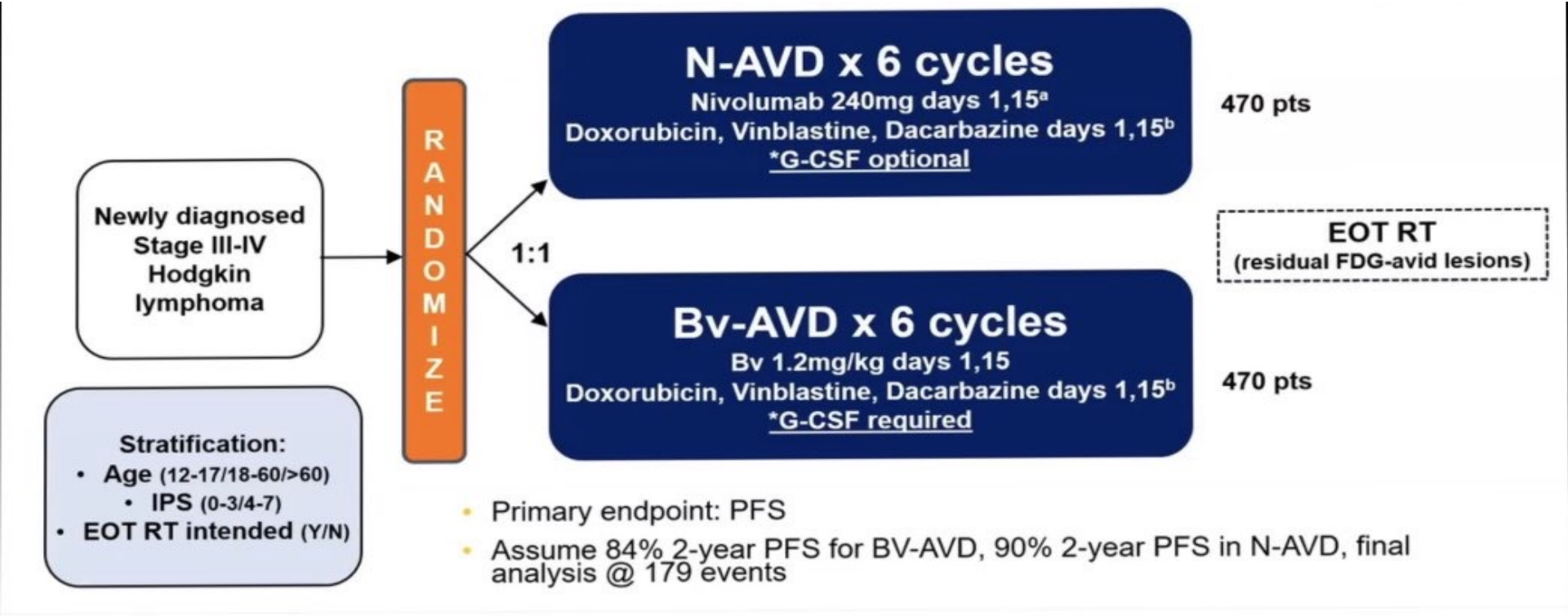


PFS Per Investigator[2]



1. Ramchandren R, et al. J Clin Oncol. 2019;37(23):1997-2007.
2. Ansell S, et al. Hematol Oncol. 2019;37(S2):146-147.

Intergroup Study S1826



Herrera AF, et al. ASCO 2023, Plenary Session.

Intergroup Study S1826: Patient Characteristics

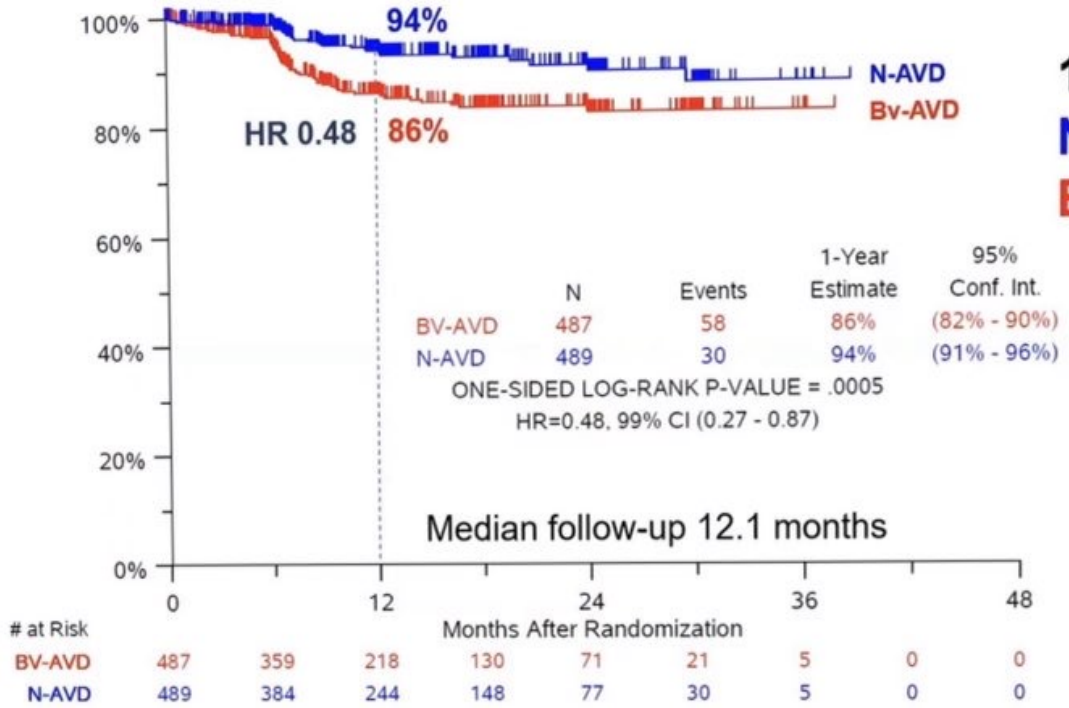
Baseline characteristics	N-AVD n=489 N (%)	Bv-AVD n=487 N (%)
Age, median (range)	27 (12-83)	26 (12-81)
12-17 years	120 (25%)	117 (24%)
18-60 years	323 (66%)	323 (66%)
≥ 61 years	46 (9%)	47 (10%)
Female Sex	218 (45%)	213 (44%)
Race		
White	375 (77%)	364 (75%)
Black	57 (12%)	56 (11%)
Asian	11 (2%)	17 (3%)
Other/Unknown	46 (9%)	50 (10%)
Hispanic	68 (14%)	59 (12%)

Baseline characteristics	N-AVD n=489 N (%)	n=487 N (%)
Stage		
III	187 (38%)	167 (34%)
IV	301 (62%)	317 (65%)
Not reported	1 (0.2%)	3 (1%)
B symptoms present	286 (58%)	274 (56%)
IPS Score		
0-3	331 (68%)	330 (68%)
4-7	158 (32%)	157 (32%)
Bulky disease > 10cm	155 (32%)	131 (27%)
HIV+	10 (2%)	5 (1%)

Representative study, inclusive of high-risk pts

Herrera AF, et al. ASCO 2023, Plenary Session.

Intergroup Study S1826: PFS

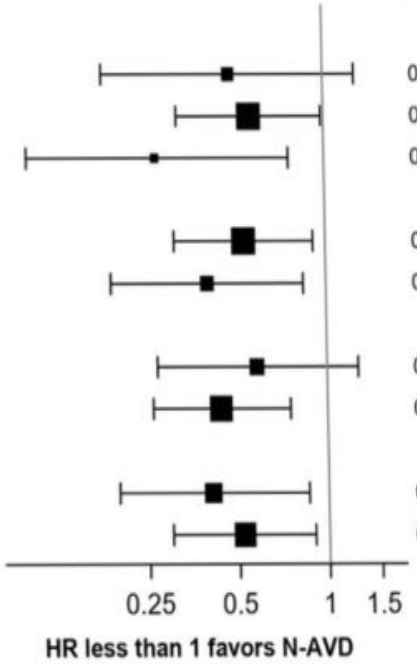


1-year PFS
N-AVD 94%
Bv-AVD 86%

Herrera AF, et al. ASCO 2023, Plenary Session.

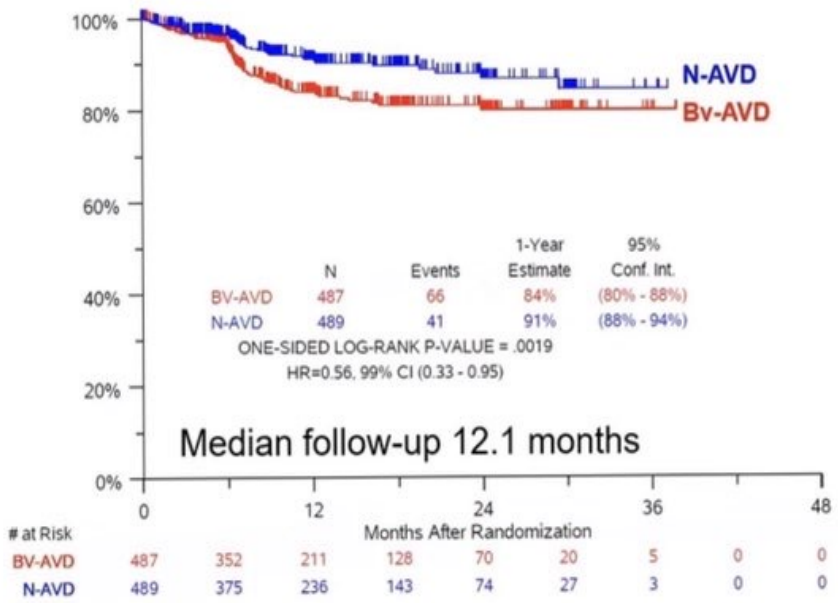
Intergroup Study S1826: PFS benefit across subgroups

Subgroup	N + AVD Events/N (%)	BV + AVD Events/N (%)	HR (95% CI)	P Value
Age				
12 - 17 y	6/120 (5.0)	12/117 (10.3)	0.48 (0.18, 1.27)	0.140
18 - 60 y	19/323 (5.9)	32/323 (9.9)	0.56 (0.32, 0.98)	0.042
> 60 y	5/46 (10.9)	14/47 (29.8)	0.27 (0.10, 0.76)	0.013
IPS				
0 - 3	20/331 (6.0)	36/330 (10.9)	0.53 (0.31, 0.91)	0.023
4 - 7	10/158 (6.3)	22/157 (14.0)	0.40 (0.19, 0.84)	0.015
Stage				
III	11/187 (5.9)	15/167 (9.0)	0.58 (0.27, 1.27)	0.176
IV	19/301 (6.3)	43/317 (13.6)	0.44 (0.26, 0.75)	0.003
Symptoms				
A	10/202 (5.0)	24/210 (11.4)	0.41 (0.20, 0.86)	0.017
B	20/286 (7.0)	34/274 (12.4)	0.52 (0.30, 0.90)	0.020



Herrera AF, et al. ASCO 2023, Plenary Session.

Intergroup Study S1826: EFS



1-year EFS
N-AVD 91%
Bv-AVD 84%

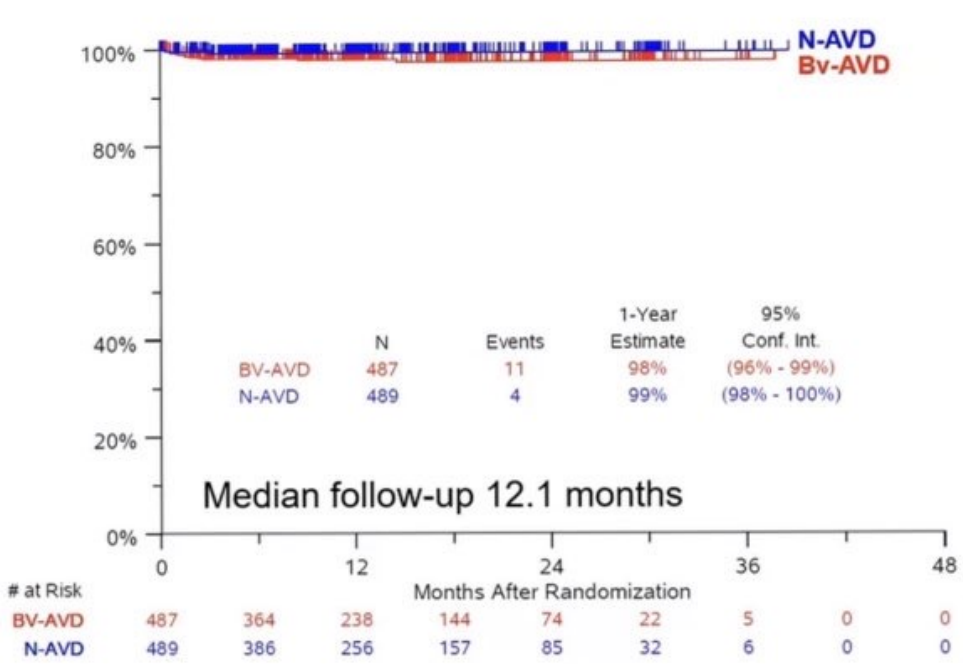
EFS events: death, progression, non-protocol treatment before progression

EFS event	N-AVD	Bv-AVD
Non-protocol chemo before PD	9	6
Non-protocol immunotx before PD	1	0
Non-protocol RT prior to PD	1*	3**
Progression/Relapse	**26**	**47**
Death without progression	**4**	**10**
Total EFS Event	**41**	**66**

* Intended for RT, EOT DS=3, received RT anyways
**1/3 intended for RT, 1 with EOT DS=2 and off tx due to AE then received RT, 2 with EOT DS=3 and received RT anyways

Herrera AF, et al. ASCO 2023, Plenary Session.

Intergroup Study S1826: OS



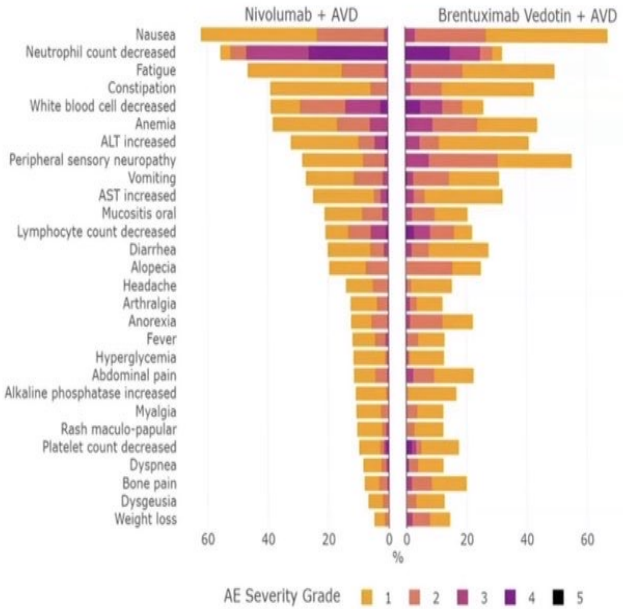
Cause of death	N-AVD	Bv-AVD
Infection	2	4
Sepsis	1	2*
Cardiac arrest	0	1
Pneumonitis	0	1
Dehydration, vomiting, cHL	0	1
cHL	1**	0
Unknown	1	2
Total OS events	**4**	**11**

* 1 death from COVID-19/sepsis
** never received treatment, ineligible on C1D1

Herrera AF, et al. ASCO 2023, Plenary Session.

Intergroup Study S1826: Toxicities

Adverse Events in ≥ 10% patients by Arm



Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Gr N (%)	Gr ≥ 3 N (%)	Any Gr N (%)	Gr ≥ 3 N (%)
Neutropenia	268 (55%)	227 (47%)	152 (32%)	118 (25%)
Anemia	185 (38%)	29 (6%)	207 (44%)	42 (9%)
Thrombocytopenia	48 (10%)	8 (2%)	82 (17%)	15 (3%)
Received G-CSF	265 (54%)		463 (98%)	
Bone pain	39 (8%)		94 (20%)	

More neutropenia after N-AVD
More growth factor use, bone pain in Bv-AVD arm

Toxicity	N-AVD n = 483	Bv-AVD n = 473
Febrile Neutropenia	26 (5%)	32 (7%)
Sepsis	9 (2%)	16 (3%)
Infections/Infestations	22 (5%)	36 (8%)

No increased infectious toxicity in N-AVD arm

Herrera AF, et al. ASCO 2023, Plenary Session.

Intergroup Study S1826: Toxicities

Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Grade No (%)	Grade ≥ 3 No (%)	Any Grade No (%)	Grade ≥ 3 No (%)
ALT increased	**156 (32%)**	**22 (5%)**	**194 (41%)**	**22 (5%)**
AST increased	**120 (25%)**	**12 (2%)**	**153 (32%)**	**13 (3%)**
Rash maculo-papular	51 (11%)	4 (1%)	58 (12%)	0 (0)
Hypothyroidism	**33 (7%)**	**1 (0%)**	**3 (1%)**	**0 (0)**
Rash acneiform	18 (4%)	0 (0)	12 (3%)	0 (0)
Pneumonitis	10 (2%)	2 (0%)	15 (3%)	10 (2%)
Gastritis	10 (2%)	3 (1%)	8 (2%)	0 (0)
Hyperthyroidism	**14 (3%)**	**0 (0)**	**0 (0)**	**0 (0)**
Colitis	5 (1%)	1 (0%)	6 (1%)	4 (1%)

Low rates of immune-related adverse events

Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Gr N (%)	Gr ≥ 3 N (%)	Any Gr N (%)	Gr ≥ 3 N (%)
Peripheral sensory neuropathy	**138 (29%)**	**6 (1%)**	**262 (55%)**	**37 (8%)**
Peripheral motor neuropathy	**20 (4%)**	**1 (0%)**	**35 (7%)**	**6 (1%)**

More neuropathy in Bv-AVD arm

Herrera AF, et al. ASCO 2023, Plenary Session.

Intergroup Study S1826: Treatment Discontinuation

Disposition	N-AVD (n=489) N (%)	Bv-AVD (n=487) N (%)
Treatment ongoing	22	30
Completed treatment	428	400
Discontinued all treatment early	**39 (8%)**	**57 (12%)**
Adverse event	22 (4%)	18 (4%)
Refusal unrelated to AE	10	14
Progression/relapse	**0 (0%)**	**7 (1.4%)**
Death on treatment	**2 (0.4%)**	**8 (1.6%)**
Other – not protocol specified	5	10
Discontinued Bv or Nivolumab	**53 (11%)**	**109 (22%)**
Received radiotherapy	**2 (0.4%)**	**4 (0.8%)**

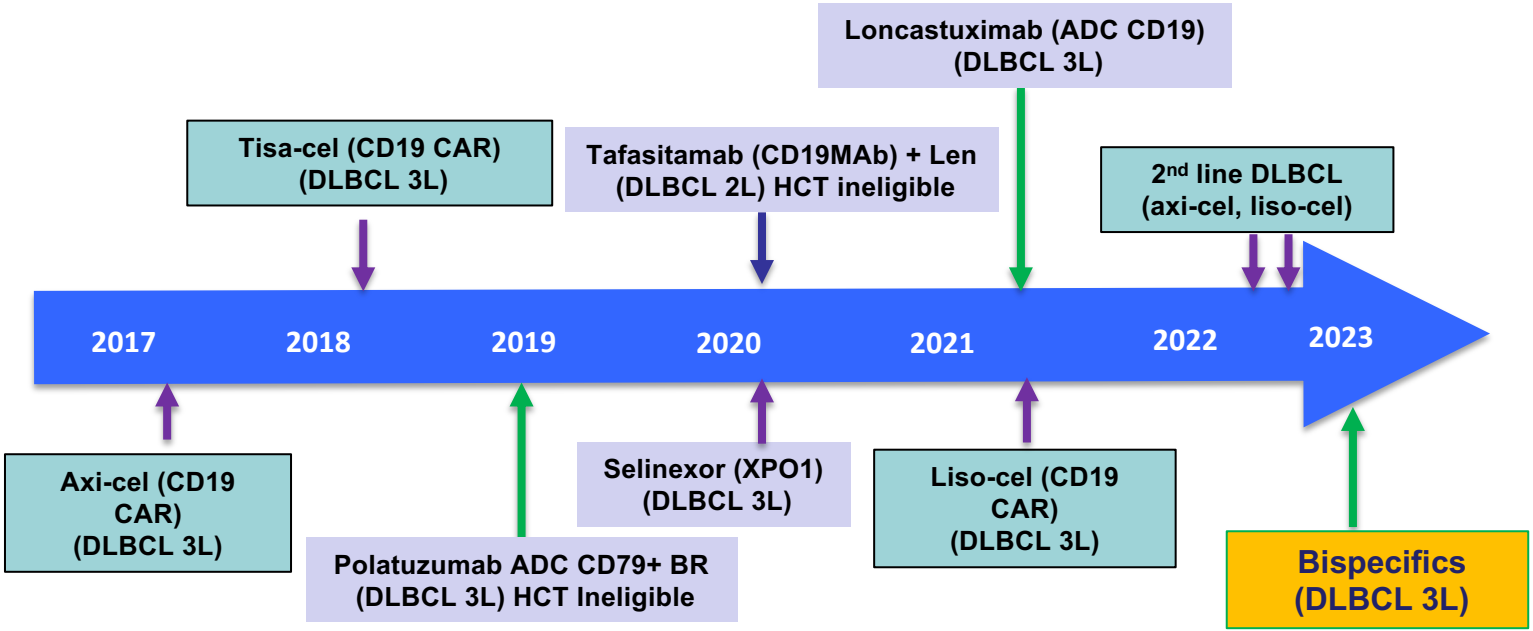
Herrera AF, et al. ASCO 2023, Plenary Session.

Intergroup Study S1826: Conclusions

- N-AVD improved progression-free survival (PFS) compared to Bv-AVD as initial treatment of advanced stage cHL
- N-AVD was well-tolerated
  - Few immune-related adverse events
  - < 1% of patients received radiation therapy (RT)
- Key step towards harmonizing pediatric and adult therapy of cHL
- **N-AVD is poised to be a new standard for treatment of advanced stage cHL**

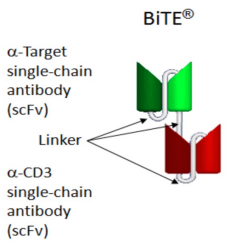
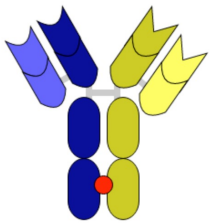
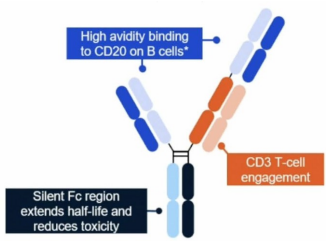
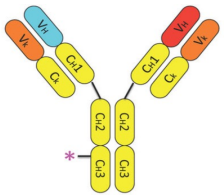
Herrera AF, et al. ASCO 2023, Plenary Session.

FDA Approvals for Relapsed/Refractory DLBCL (2017-2023): Impressive Progress



Chavez, J. et al.

Bispecific Antibodies in B-cell NHL

The Original: Proof of Concept	The New Ones ….and more to come			
Blinatumomab[1]	**Epcoritamab[2]**	**Mosunetuzumab[3]**	**Glofitamab[4]**	**Odronextamab[5]**
				
CD3 (scFV) x CD19 (scFV)	**DuoBody- CD3 x CD20 BsAb**	**CD3 x CD20 Knobs-in-hole Fc BsAb**	**CD3 (Fab) x CD20 (Fab x2) Fc BsAb**	**CD3 x CD20 Common LC Fc BsAb**

- Numerous bispecific antibody structures exist
- **Properties of the BsAbs vary by construct**

- Distinguishing features of BsAbs include:
  - ***"Off-the-shelf"*** *– rapid access, relative ease of delivery* [6,7]
  - ***Adaptable*** *– lack of persistence and ability to modulate dosing may improve tolerability*[6]

1. Queudeville M, et al. Onco Targets Ther. 2017;10:3567-3578. 2. Clausen MR, et al. J Clin Oncol. 2021;39(suppl 15):7518. 3. Budde LE, et al. Blood. 2018;132(suppl 1):399. 4. Hutchings M, et al. Blood. 2020;136(suppl 1):45-46. 5. Bannerji R, et al. Blood. 2020;136(Suppl_1):42-43. Presented at: ASH 2020. Abstract 400. 6. Husain B, et al. BioDrugs. 2018;32(5):441-464. 7. Schuster S. SurvivorNet. Bispecific antibodies: an off-the-shelf approach to treating lymphoma. Accessed June 23, 2022. https://www.survivornet.com/articles/bispecific-antibodies-an-off-the-shelf-approach-to-treating-lymphoma/

Epcoritamab for R/R DLBCL: Phase 2 Pivotal Study EPCORE

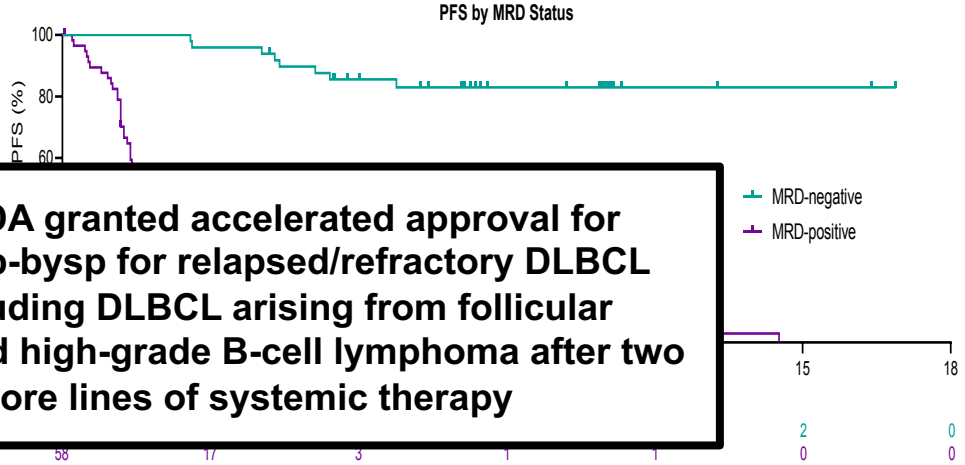
Baseline Characteristics

N= 157 pts
Median lines: 3 (2-11)
Primary refractory: 61%
Prior CAR-T: 39%
Prior auto HCT: 20%
Unlimited treatment (SC)

Results

Median f/u: 10.7 months
ORR= 63%
CR= 39%
PFS in CR pts at EOT: Not reached
Median PFS= 4.4 months**. Not reached in MRD neg.**
CRS all: 49.7% Grade ≥3: 2.5%. Mainly during C1

5/19/23: FDA granted accelerated approval for Epcoritamab-bysp for relapsed/refractory DLBCL NOS, including DLBCL arising from follicular lymphoma and high-grade B-cell lymphoma after two or more lines of systemic therapy



MRD Results per ctDNA Assay	All LBCL n=107
MRD-negative rate, n (%)	49 (45.8) [95% CI: 36.1–55.7]

Thieblemont at Al. EHA Congress 2022

Glofitamab for R/R Large B cell lymphoma (3L): Phase 2 Pivotal Results

Baseline Characteristics

N= 155 pts

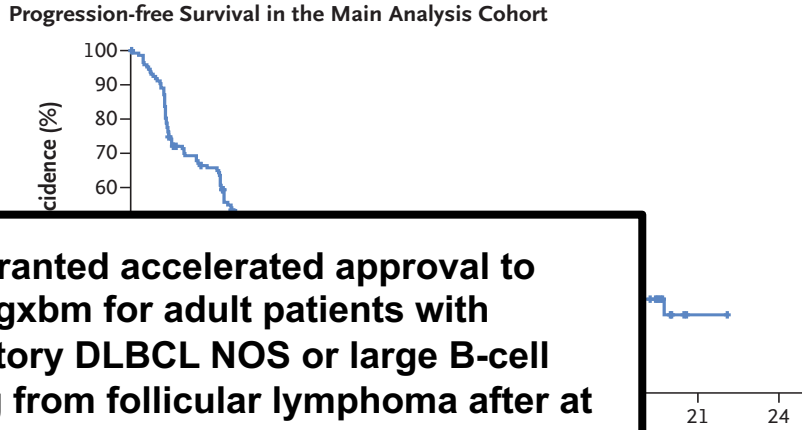
Time limited therapy (12 cycles IV with pretreatment obinutuzumab)

Median lines: 3 (2-7)

Primary refractory: 58%

Prior CAR-T: 38%

Prior auto HCT: 18%



6/15/23: FDA granted accelerated approval to Glofitamab-gxbm for adult patients with relapsed/refractory DLBCL NOS or large B-cell lymphoma arising from follicular lymphoma after at least two lines of systemic therapy

Results

Median f/u: 12.6 months

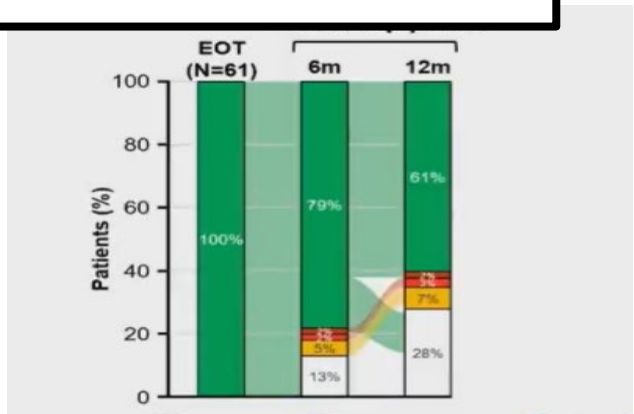
ORR= 52%

CR= 39%

PFS in CR pts at EOT: Not reached

Median PFS= 4.9 months

CRS all: 63%; G≥3= 4% Mainly during C1

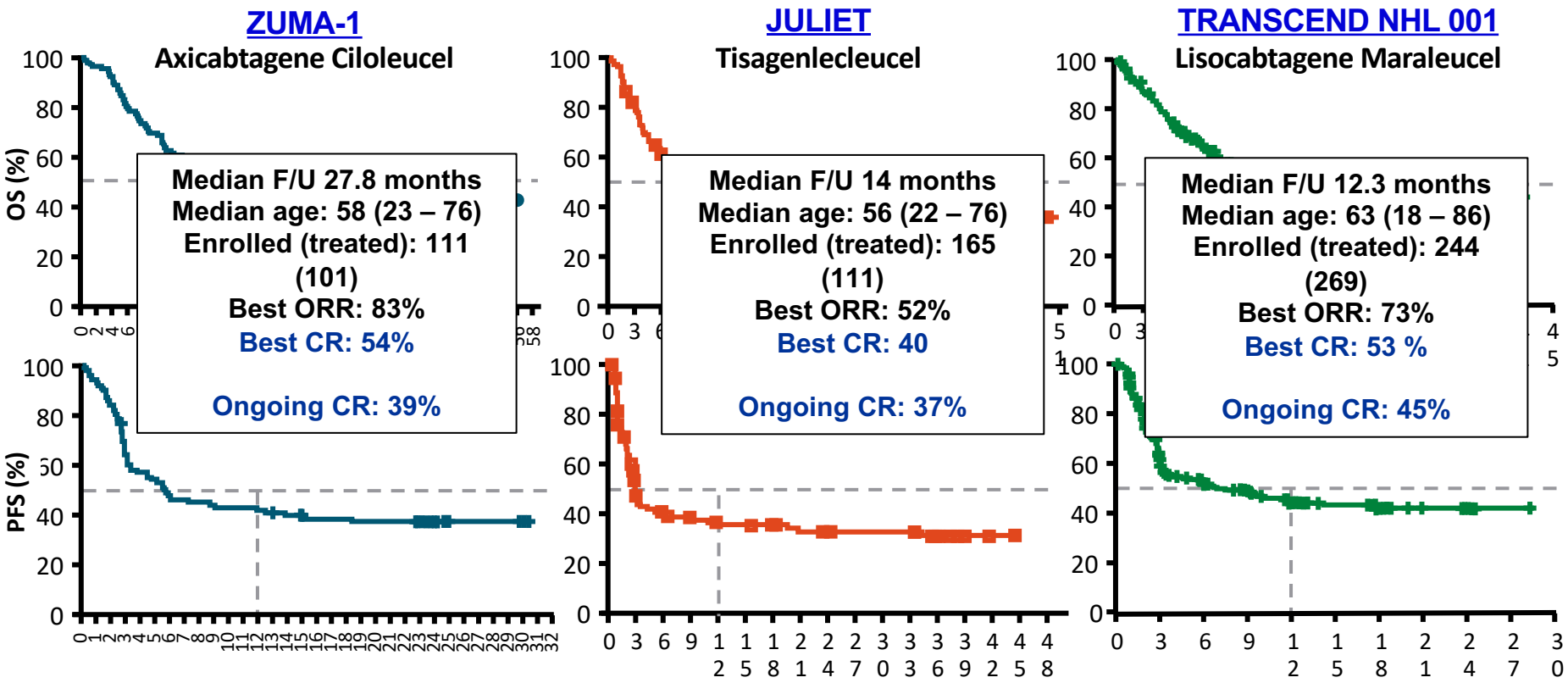


Dickinson M et Al. N Eng J Med 2022.

CAR-T and Bispecific Antibodies in DLBCL: How to use… and sequence them (…a matter of debate)

- ***Let's look at the data:***
  - **"Curative" versus non-curative modality**
- ***Factors that would influence their use and/or sequencing:***
  - **GOAL of Treatment**
  - **Product-related factors**
  - **Patient-related factors**
  - **Tumor-related factors**

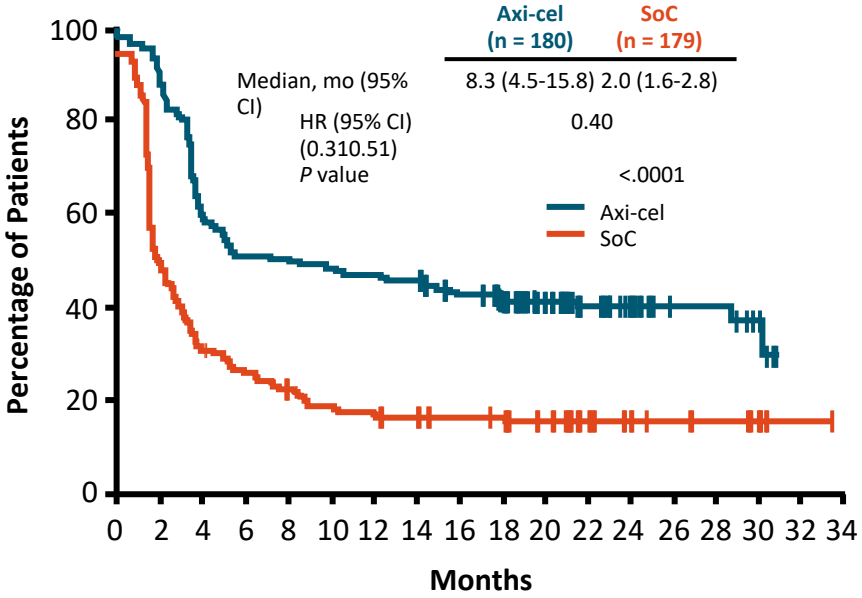
Pivotal Anti-CD19 CAR T Cell Therapy Trials: Third Line DLBCL



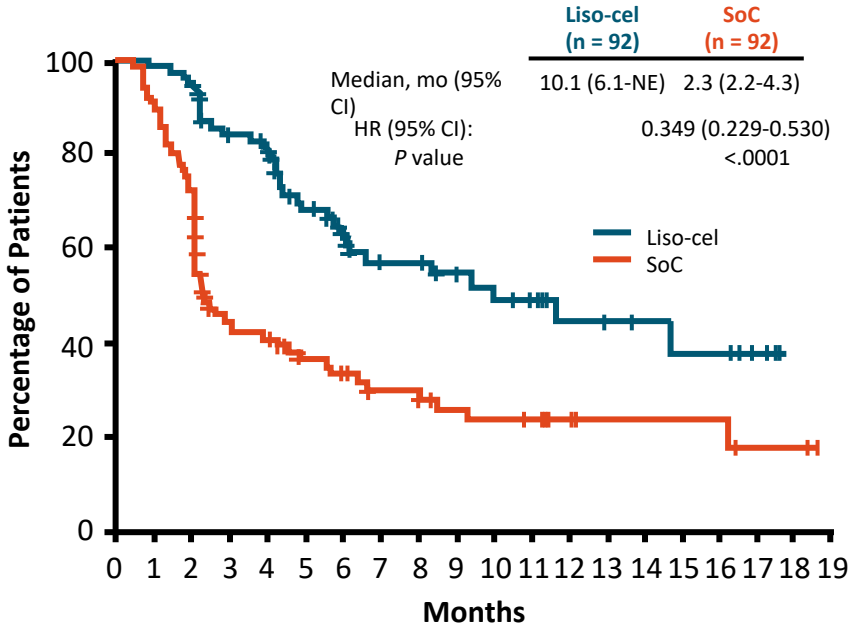
Locke. Lancet Oncol. 2019;20:31. Jacobson. ASH 2020. Abstr 1187. Jaeger. ASH 2020. Abstr 1194. Abramson. Lancet. 2020;396:839.

CD19 CAR T-cell Therapy: A new SOC in Early Relapsed DLBCL (second line)

ZUMA-7: Median EFS[1]



TRANSFORM: Median EFS[2]



1. Locke. NEJM. 2022;386:640. 2. Kamdar.. Lancet. 2022;399:10343.

CD19 CAR T-cells in DLBCL

- **Anti-CD19 CAR T-cells have shown significant efficacy as third line and more recently as second line treatment for patients with relapsed/refractory DLBCL…..**
  - ***It is estimated that 30-40 percent of patients with relapsed/refractory DLBCL might be cured!***
  - **Remaining 60 percent of patients: Unmet need**
- **Cost, manufacture time, side effects, progression while waiting for engineered T cells and mechanisms of resistance remain a significant challenge….**

CAR-T and Bispecific Antibodies in DLBCL: How to use… and sequence them (…a matter of debate)

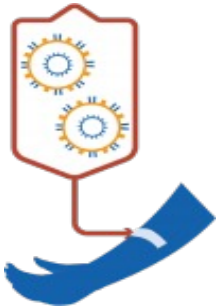
- ***Let's look at the data:***
  - **"Curative" versus non-curative modality**

- ***Factors that would influence their use and/or sequencing:***
  - **GOAL of Treatment**
  - **Product-related factors**
  - **Patient-related factors**
  - **Tumor-related factors**

CAR-T and Bispecific Abs in DLBCL: Factors that would influence their use and/or sequencing

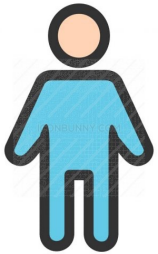
Treatment Goal:

- **Curative** Modality
  - **CAR T-cells: Yes (30-40%)**
  - **Bi-specific : Unknown yet**



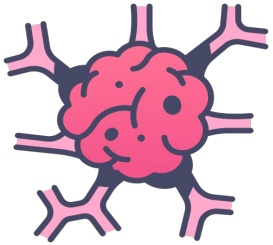
Product Factors:

- Availability (Clinical trials vs. commercial)
- Regulatory entities approval/indications
- **Need for specialized center:**
  - **CAR T: Yes**
  - **Bispecifics: No**
- **Potential administration in outpatient setting**
  - **CAR T: No (yet?)**
  - **Bispecifics: Yes (IV and SC)**



Patient Factors

- **Age,** comorbidities
- Prior treatments
- Patient preference:
  - **One treatment: CAR T**
  - **Multiple treatments: Bispecifics**
- **Cost**



Tumor Factors:

- Rapidly growing tumor
  - **"Off the shelf": Bi-specifics**
  - Need for some therapy for disease control : CAR T-cells
- Tumor antigen density
- Tumor antigen escape
- Tumor Microenvironment

Sequencing of CAR T-cells and Bispecifics in R/R DLBCL

- **CAR T-cells first…then Bispecifics**
  - **Plenty of data….**
  - **Several clinical trials have shown the efficacy and safety of Bispecifics after CAR T failures**

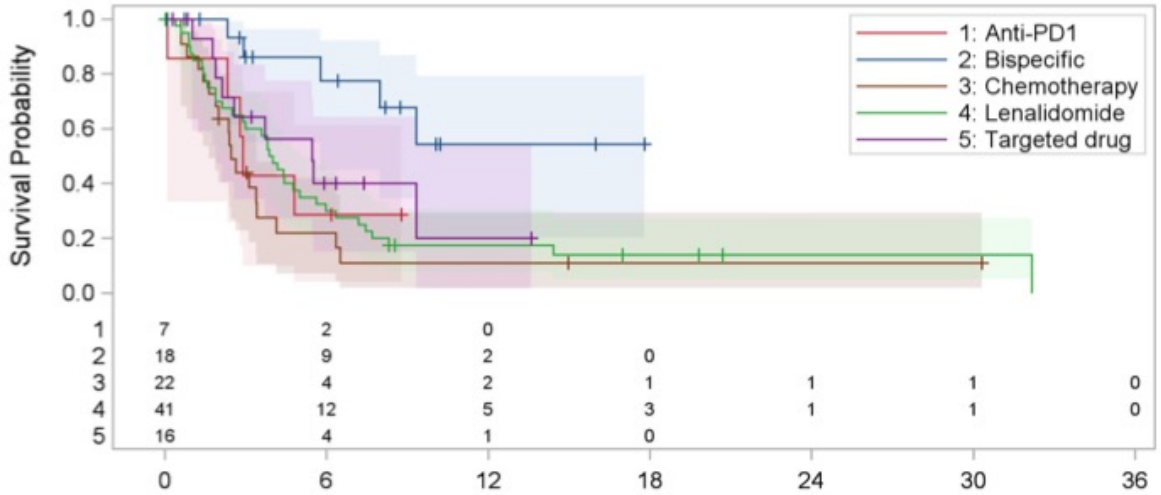


Figure 1: PFS since first progression (months) after CAR T cells therapy according to type of treatment.

Erbella, et al. ASH 2022 Abstract #553

Sequencing of CAR T-cells and Bispecifics in R/R DLBCL

- **Bi-specific first…then CAR T-cells**
  - **Data is emerging….**
  - **ASH 2022: French Descar T Registry: *CAR T-cell therapy remain effective in pts with R/R B-cell NHL after Bispecific antibodies exposure.* *Crochet, G. et.al***
    - **Retrospective study. 28 pts, 23 with DLBCL**
    - **Mainly Glofitamab: ORR:53.6%; CR: 25%. 6mo PFS: 17.4% mDOR: 2.7months. All pts progressed and went to receive bridge therapy**
    - **After CAR T-cells: ORR: 91.6%; CR: 45.8%**
    - **Median follow up 12.3 mo: 1-year PFS:37.2; OS:53.5%**
    - **No new toxicity signals were identified**

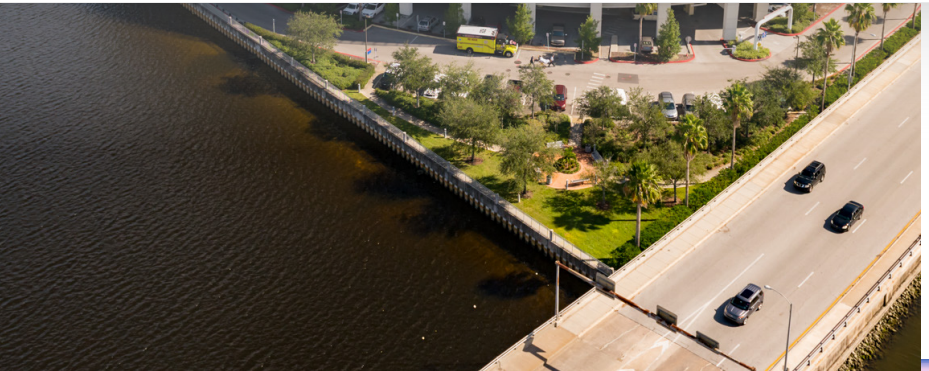
R/R DLBCL: Changing the Treatment Paradigm with CAR T cells and Bispecifics

GOTEL
Grupo Oncológico para el Estudio de los Linfomas

TGH Tampa General Hospital | CANCER INSTITUTE

USF HEALTH MORSANI COLLEGE OF MEDICINE
UNIVERSITY OF SOUTH FLORIDA

THANK YOU !



esotomayor@tgh.org

TGH Tampa General Hospital