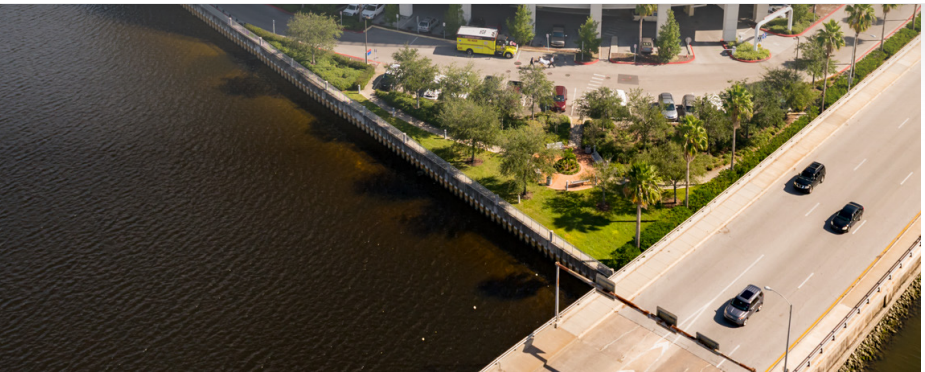
TGH Tampa General Hospital | CANCER INSTITUTE

USF HEALTH MORSANI COLLEGE OF MEDICINE UNIVERSITY OF SOUTH FLORIDA

"DLBCL and Hodgkin Lymphoma"



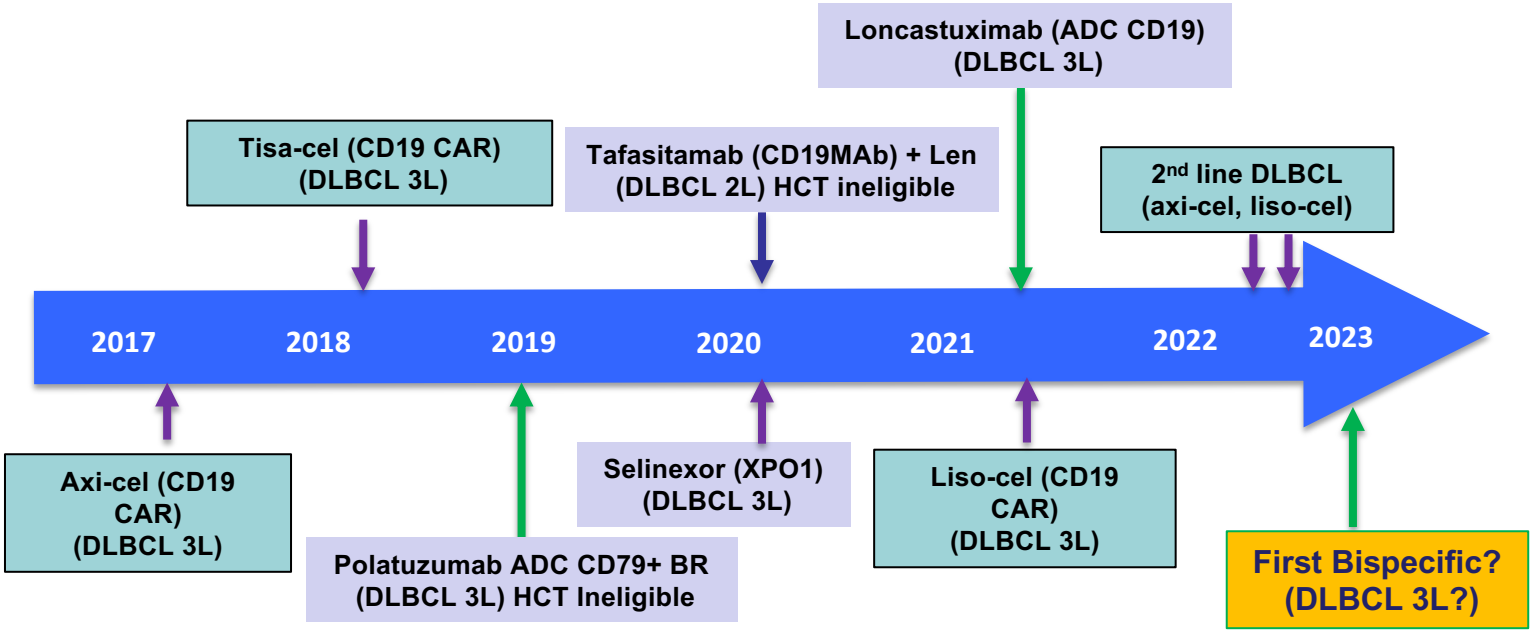
Eduardo M. Sotomayor, MD

Director, TGH Cancer Institute

Professor, USF Morsani College of Medicine

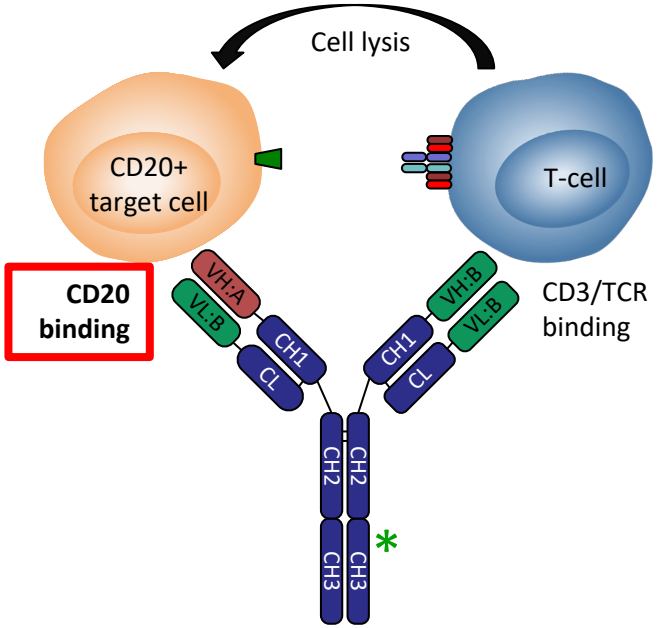
University of South Florida

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



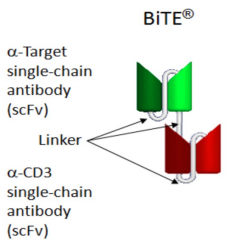
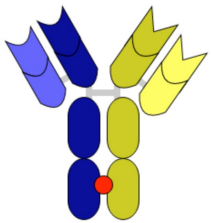
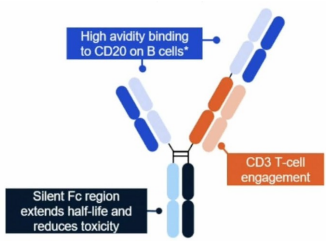
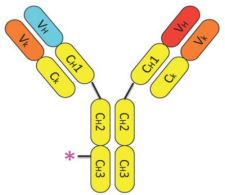
Chavez, J. et al.

Bispecific Antibodies….a game changer in DLBCL



Cross-linking results in targeted activation of local T-cells and T-cell-mediated killing of CD20+ B-cells (independently of TCR-mediated recognition)

Bispecific Antibodies in B-cell NHL

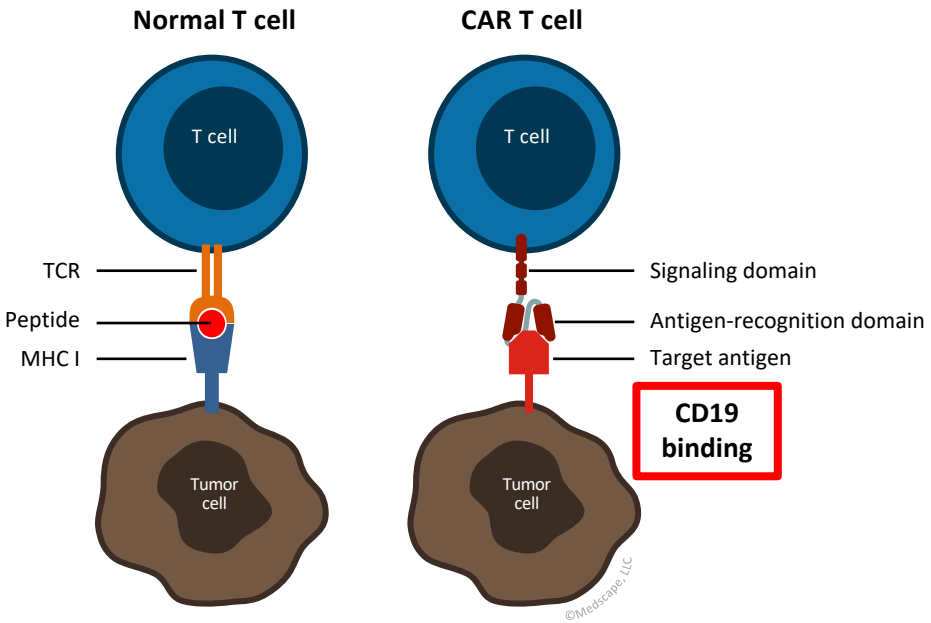
The Original: Proof of Concept	The New Ones ….and more to come			
Blinatumomab[1]	**Epcoritamab[2]**	**Mosunetuzumab[3]**	**Glofitamab[4]**	**Odronextamab[5]**
				
CD3 (scFV) x CD19 (scFV)	**DuoBody- CD3 x CD20 BsAb**	**CD3 x CD20 Knobs-in-hole Fc BsAb**	**CD3 (Fab) x CD20 (Fab x2) Fc BsAb**	**CD3 x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

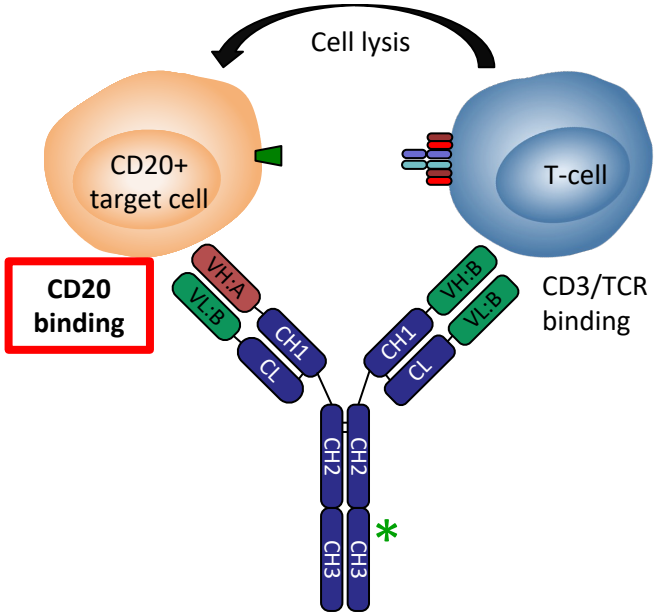
- Numerous bispecific antibody structures exist
- **Properties of the BsAbs vary by construct**

- 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/

CAR-T and Bispecific Abs: Activation of Endogenous T-cells

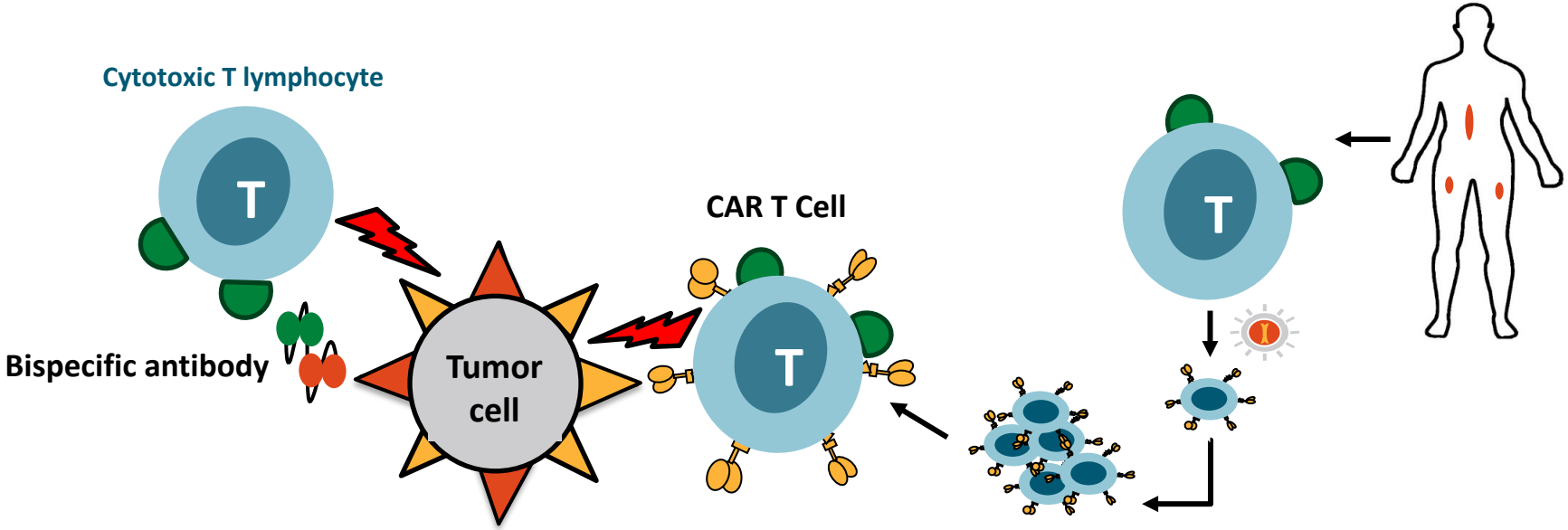




Ex vivo **modification/activation of endogenous T-cells by "engineering" to unleash their full potential: "Tour de force"**

In vivo activation **of endogenous T-cells by monoclonal antibodies that also create a "bridge" to target cells, unleashing their full potential**

Bispecific Abs and CAR T-Cells: Differences

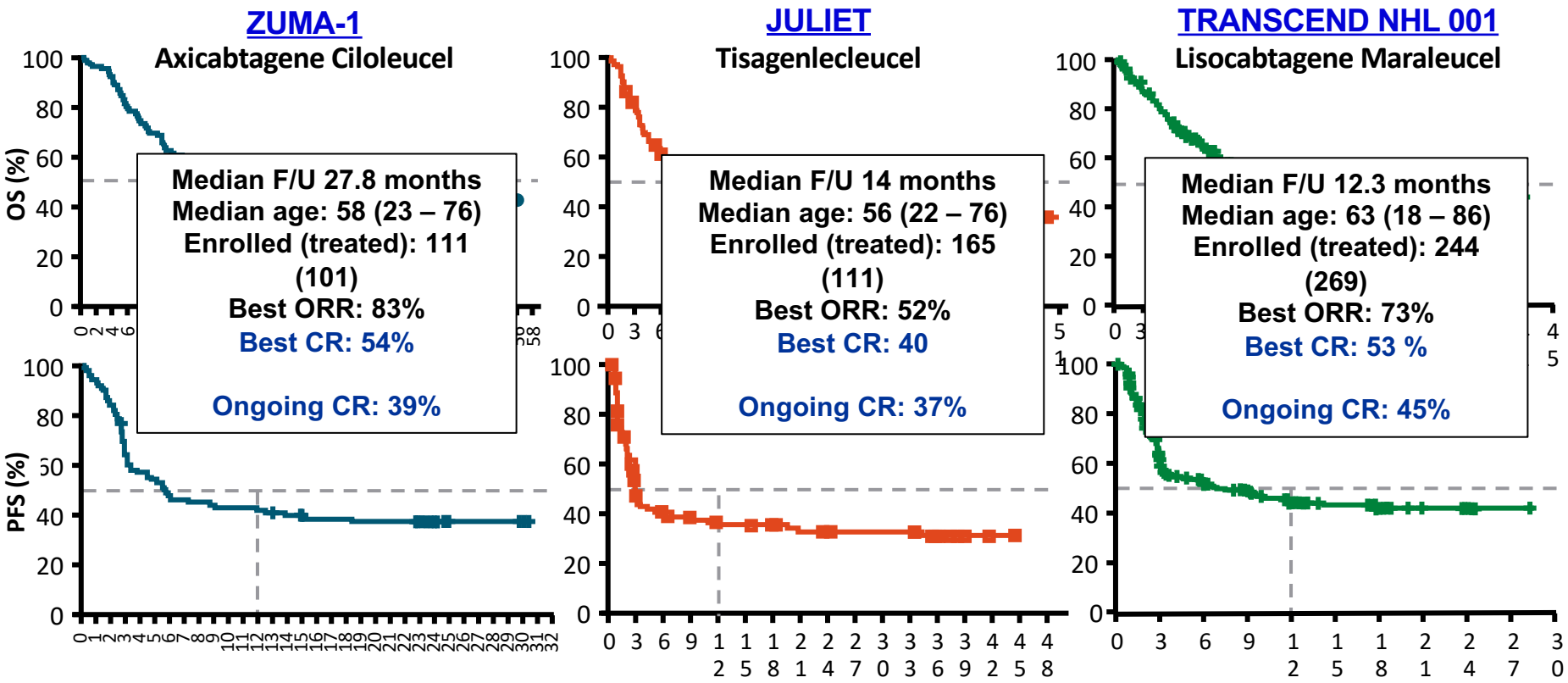


Characteristic	Bispecific Antibodies	CAR T-Cell Therapy
Preparation	"Off the shelf"	*In vitro* manufacturing (3-4 wks)
Dosing	**Repetitive** (Lack of persistence and ability to modulate dosing may improve tolerability)	**Single** (Persistence is associated with some long-lasting side effects)
Side Effects incidence and Grade	Less	Greater

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

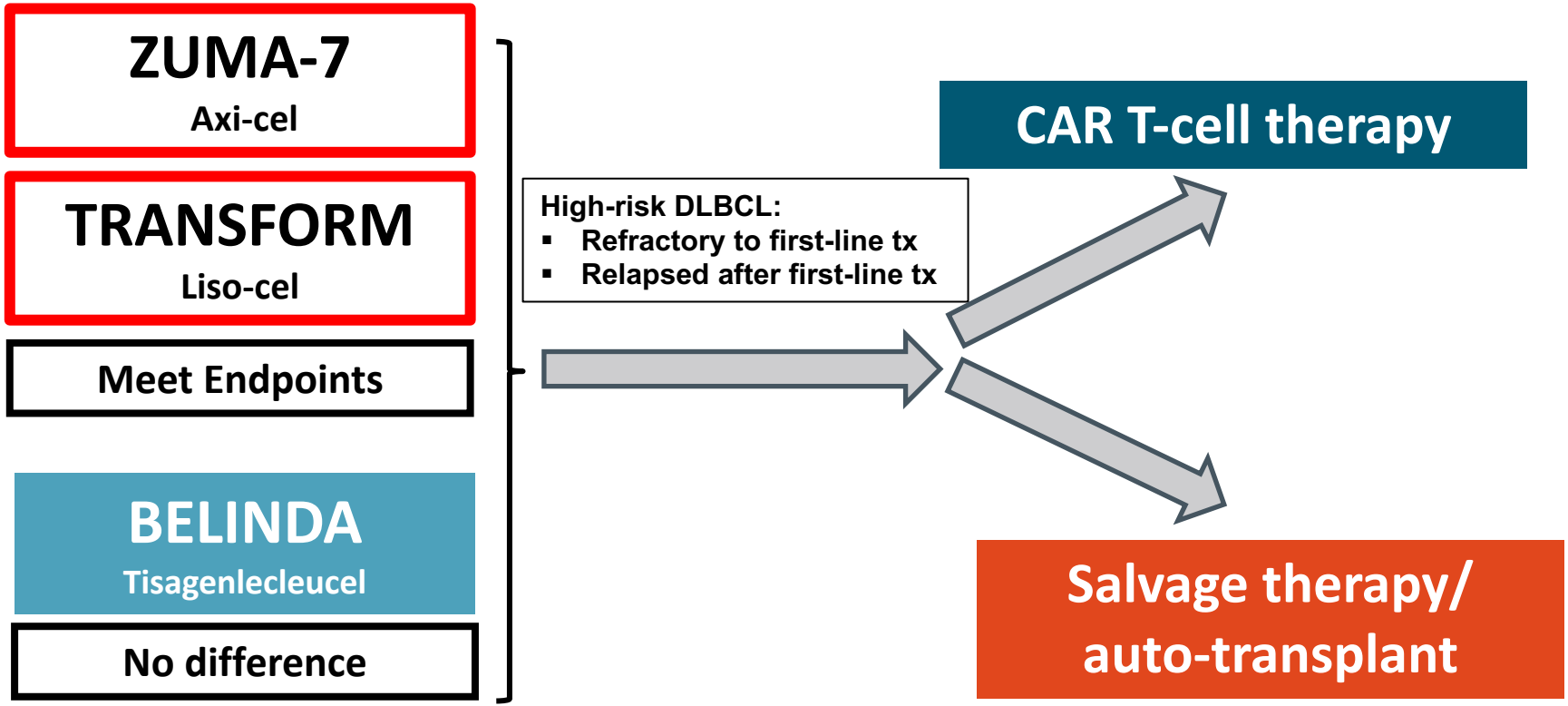
- ***Let's look at the data:***
  - **"Curative" versus non-curative modality**
- ***Factors that would influence their use and/or sequencing:***
  - **GOAL of Treatment**
  - **Product-related factors**
  - **Patient-related factors**
  - **Tumor-related factors**

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.

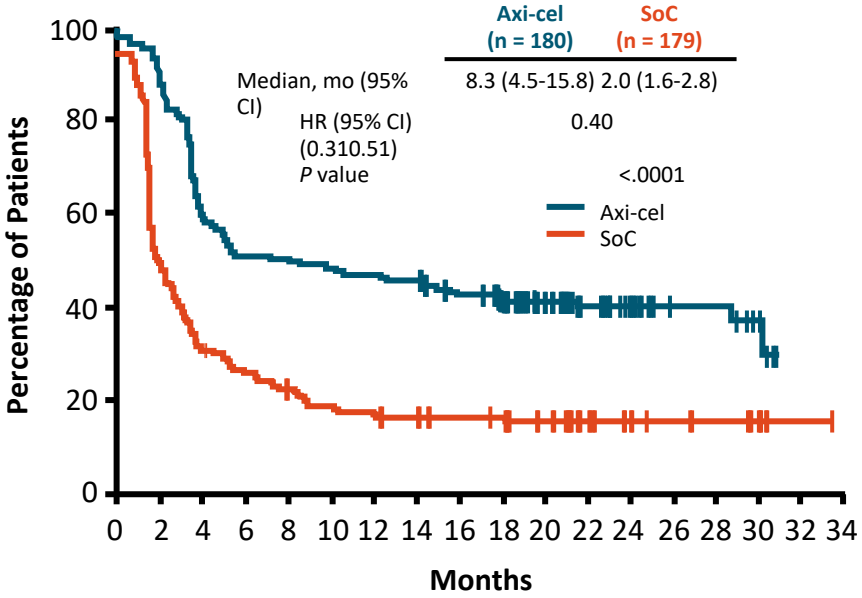
Anti-CD19 CAR T-cell Therapy Trials: Second Line CAR T versus ASCT for high risk relapsed DLBCL



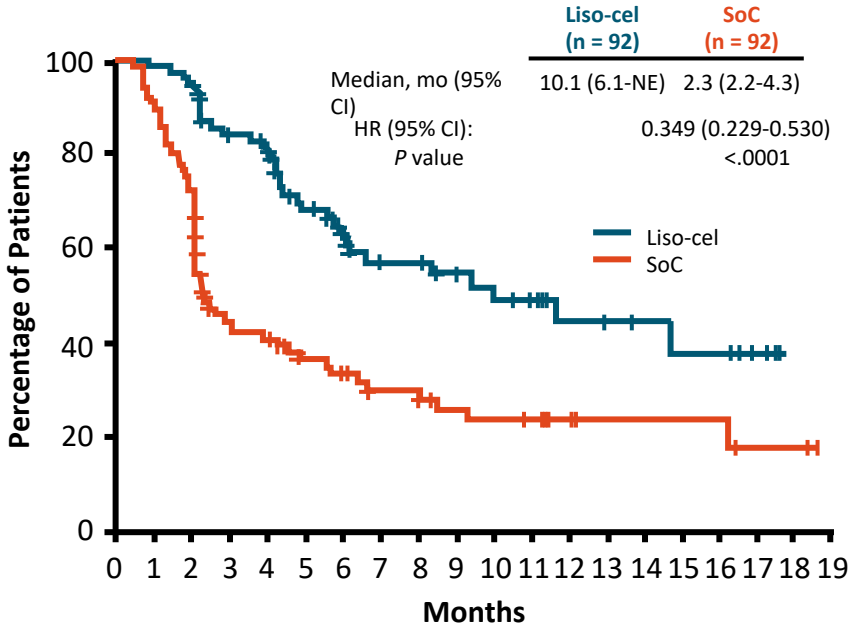
NCT03391466. NCT03570892. NCT03575351.

CD19 CAR T-cell Therapy: A new SOC in Early Relapsed DLBCL

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….**

Bispecifics Antibodies in Diffuse large B-cell lymphoma

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

Baseline Characteristics

N= 155 pts

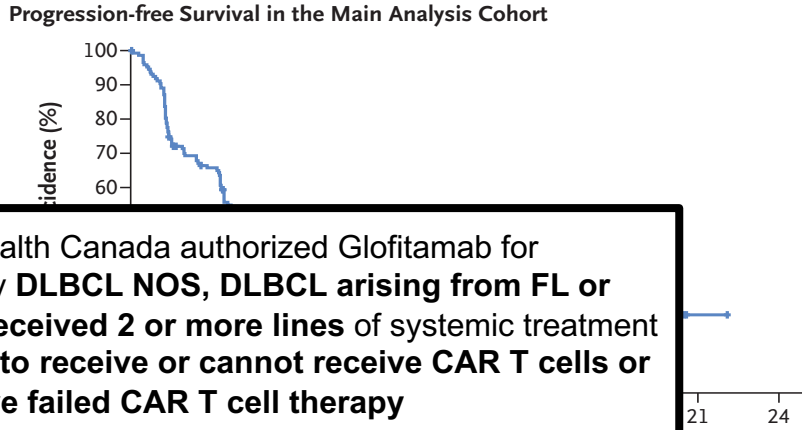
Time limited therapy (12 cycles IV with pretreatment obinutuzumab)

Median lines: 3 (2-7)

Primary refractory: 58%

Prior CAR-T: 38%

Prior auto HCT: 18%



3/24/23: Health Canada authorized Glofitamab for relapsed/refractory **DLBCL NOS, DLBCL arising from FL or PMBCL**, **who have received 2 or more lines** of systemic treatment **and** are **not eligible to receive or cannot receive CAR T cells or have failed CAR T cell therapy**

-US: Awaiting FDA decision

Results

Median f/u: 12.6 months

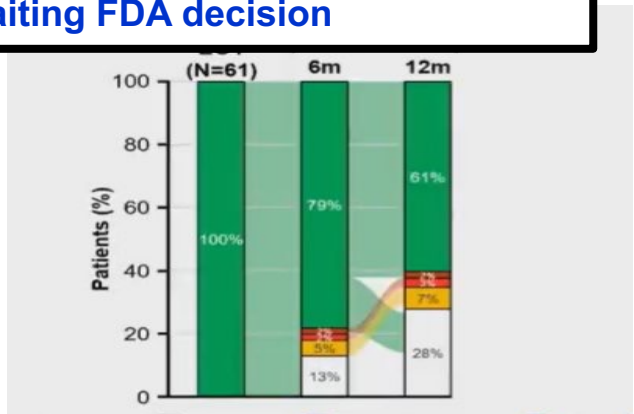
ORR= 52%

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.

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

Baseline Characteristics

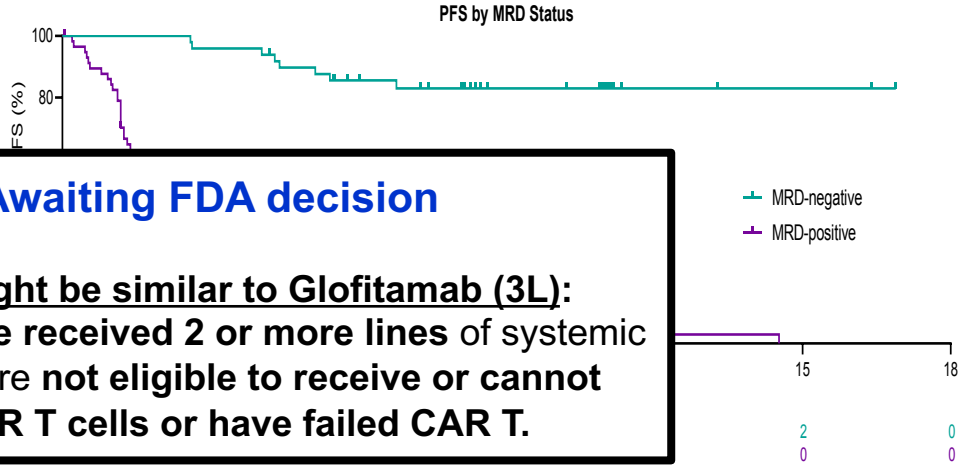
N= 157 pts
Median lines: 3 (2-11)
Primary refractory: 61%
Prior CAR-T: 39%
Prior auto HCT: 20%
Unlimited treatment (SC)

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

US: Awaiting FDA decision

Indication might be similar to Glofitamab (3L):
Patients who have received 2 or more lines of systemic treatment **and** are **not eligible to receive or cannot receive CAR T cells or have failed CAR T.**



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

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

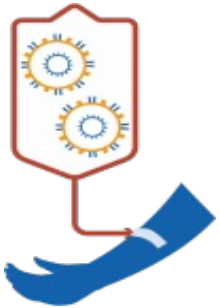
- ***Let's look at the data:***
  - **"Curative" versus non-curative modality**

- ***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

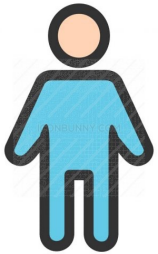
Treatment Goal:

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



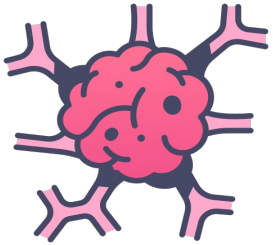
Product Factors:

- 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

Mosunetuzumab for Untreated Elderly DLBCL ineligible for anthracycline based CIT

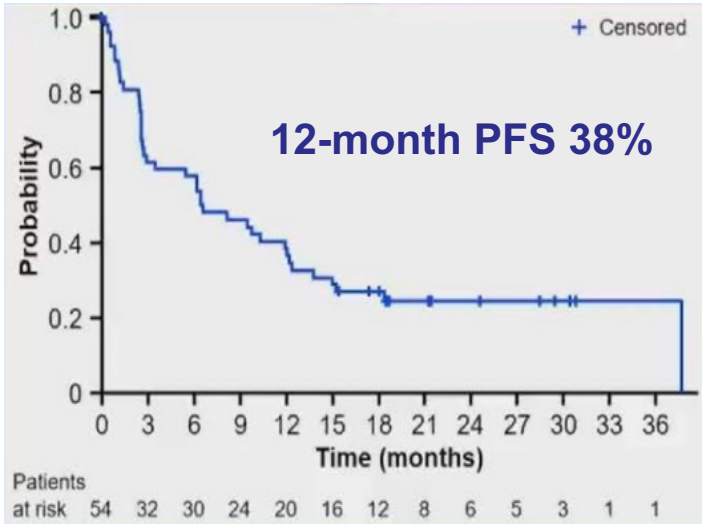
Baseline Characteristics

Untreated DLBCL (n=54)
Eligible if:

- **Age > 80**
- **Age 60-79 if: impairment > 1 ADL, instrumental ADL, inability to tolerate full dose CHOP**

Results

Best response, n (%) [95% CI]	N=54
ORR	30 (**56**) [41–69]
CR	23 (**43**) [29–57]
Response at EOT, n (%) [95% CI]	**N=54**
ORR	24 (**44**) [31–59]
CR	19 (**35**) [23–49]



CRS grade1-2: 26%, No G≥3 GRS, tocilizumab use 0%

Olszewski et Al. ASH 2022

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**

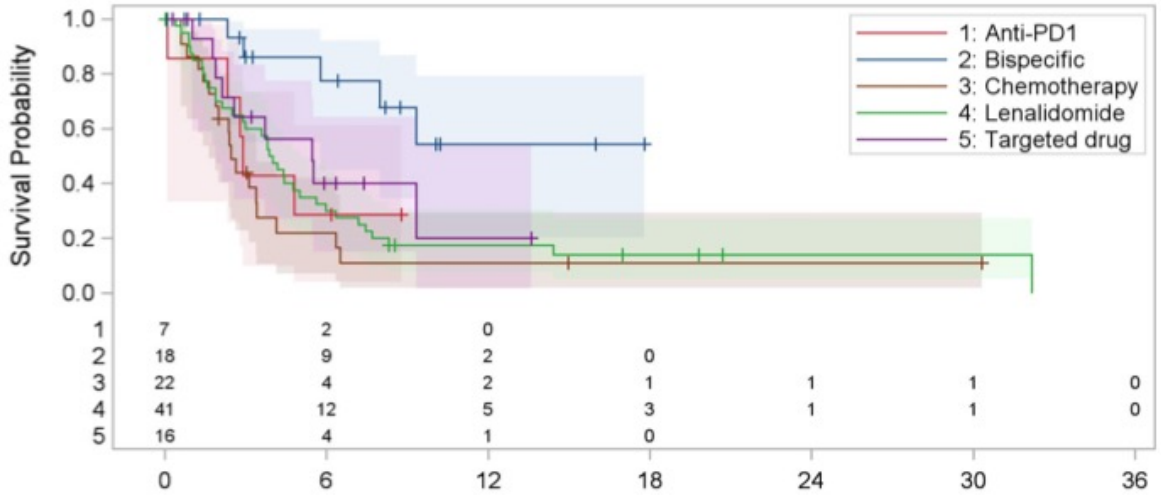


Figure 1: PFS since first progression (months) after CAR T cells therapy according to type of treatment.

Erbella, et al. ASH 2022 Abstract #553

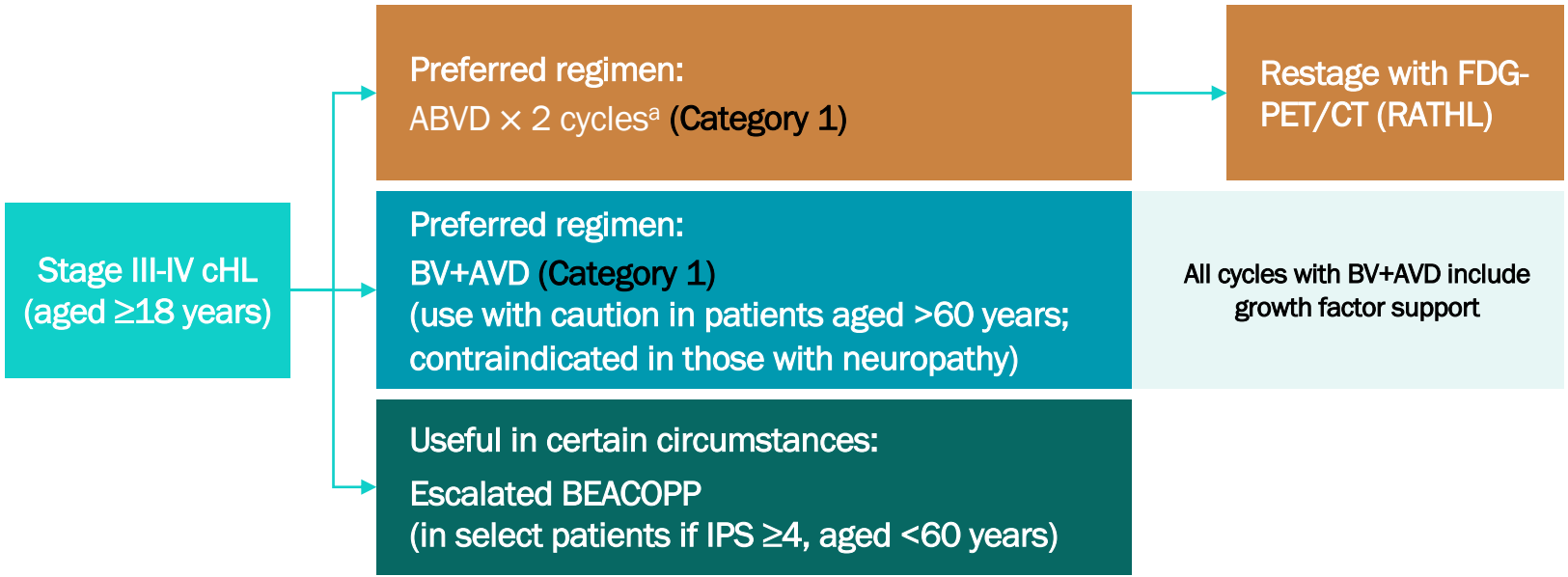
Sequencing of CAR T-cells and Bispecifics in R/R DLBCL

- **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

Advanced Hodgkin Lymphoma: Frontline Treatment

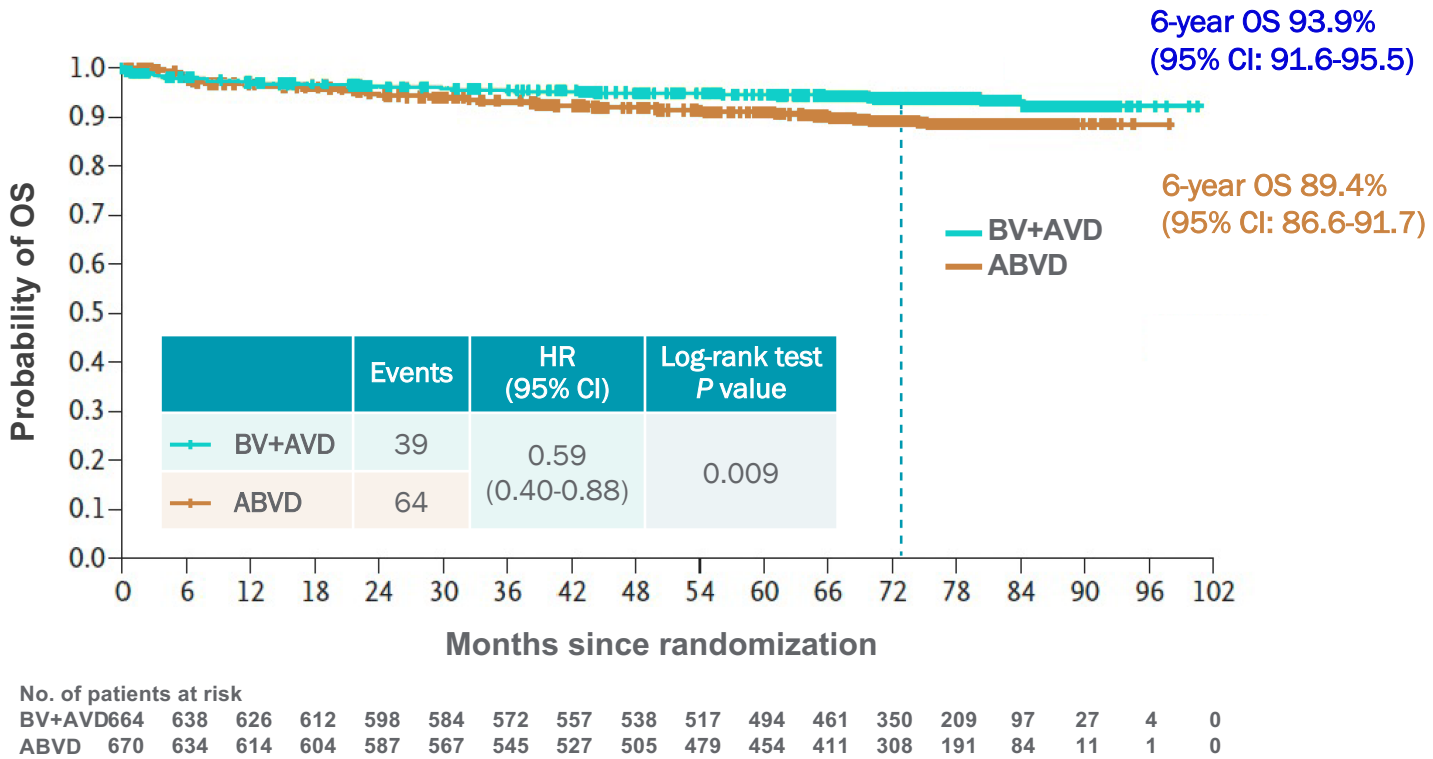
NCCN Guidelines in Stage III-IV Classical Hodgkin (Version 2.2023)



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

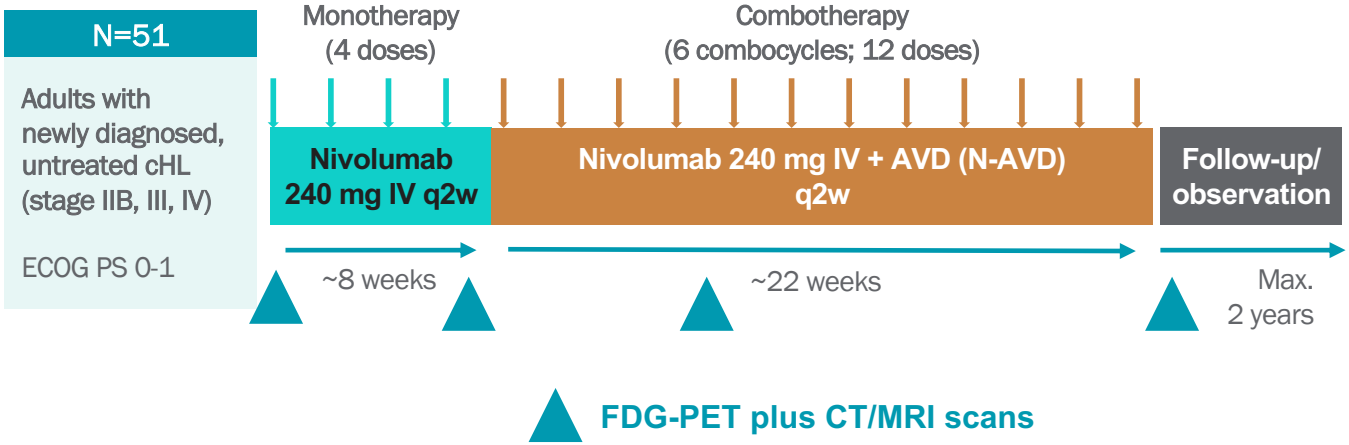
National Comprehensive Cancer Network. Hodgkin Lymphoma (Version 2.2023). Accessed February 2, 2023. https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf

Echelon-1: OS per Investigator at 6-Year Follow-up



Ansell SM, et al. N Engl J Med. 2022;387(4):310-320

Checkpoint blockade Abs in Frontline HL
Phase 2 CheckMate 295: Nivo + AVD



Primary Endpoint

- Safety and tolerability (grade 3-5 treatment-related AEs)

Additional Endpoints

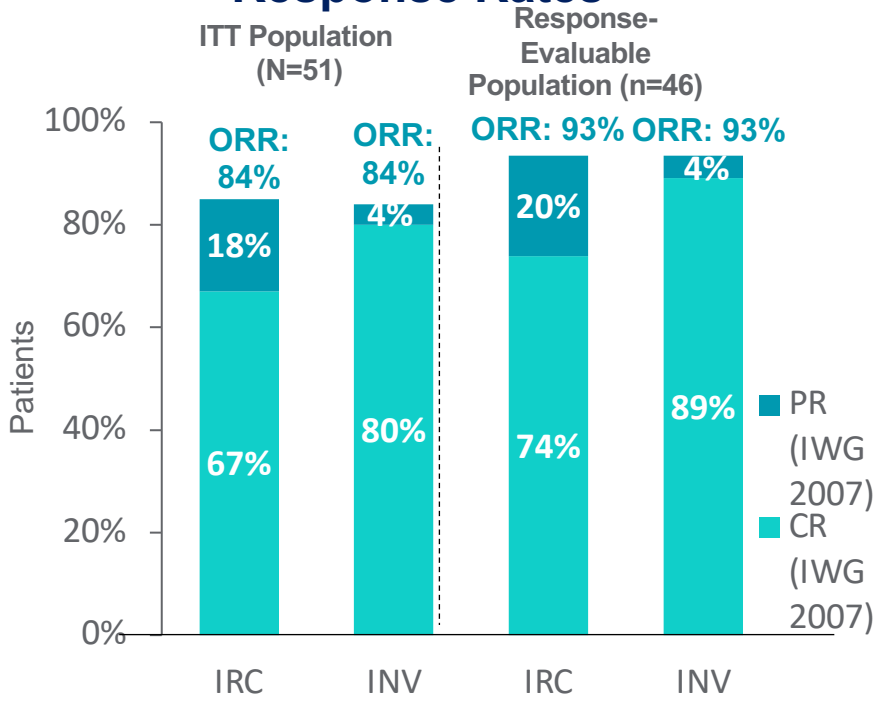
- Discontinuation rate
- CR and ORR by IRC
- CR and ORR by investigator
- mPFS
- OS

- **Responses were assessed using the IWG 2007 criteria**
- **Median duration of follow-up: 11.1 months (clinical cutoff: August 31, 2017)**
- **Bleomycin was excluded due to potential overlapping pulmonary toxicity**

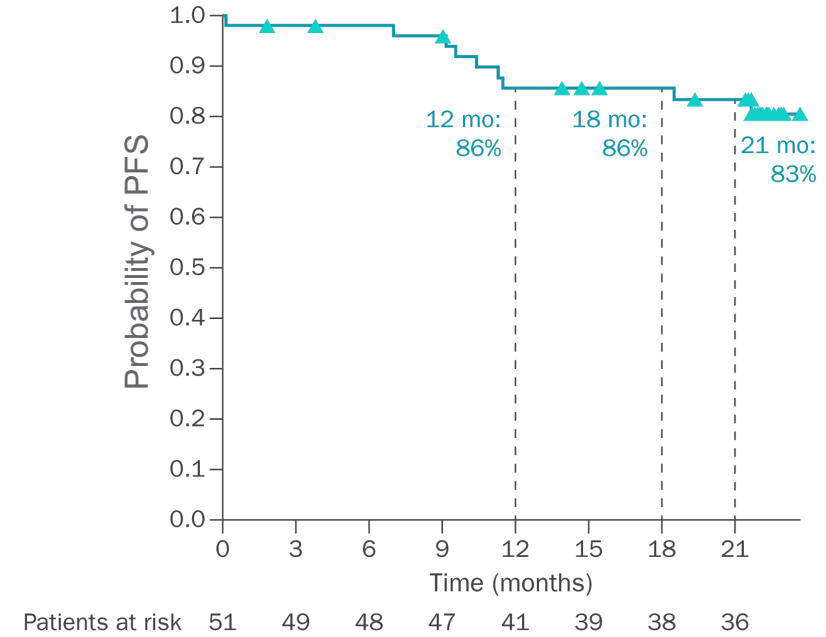
Ramchandren R, et al. J Clin Oncol. 2019;37(23):1997-2007.

Phase 2 CheckMate 295: Nivo + AVD
End of Treatment Response and PFS

Response Rates[1]

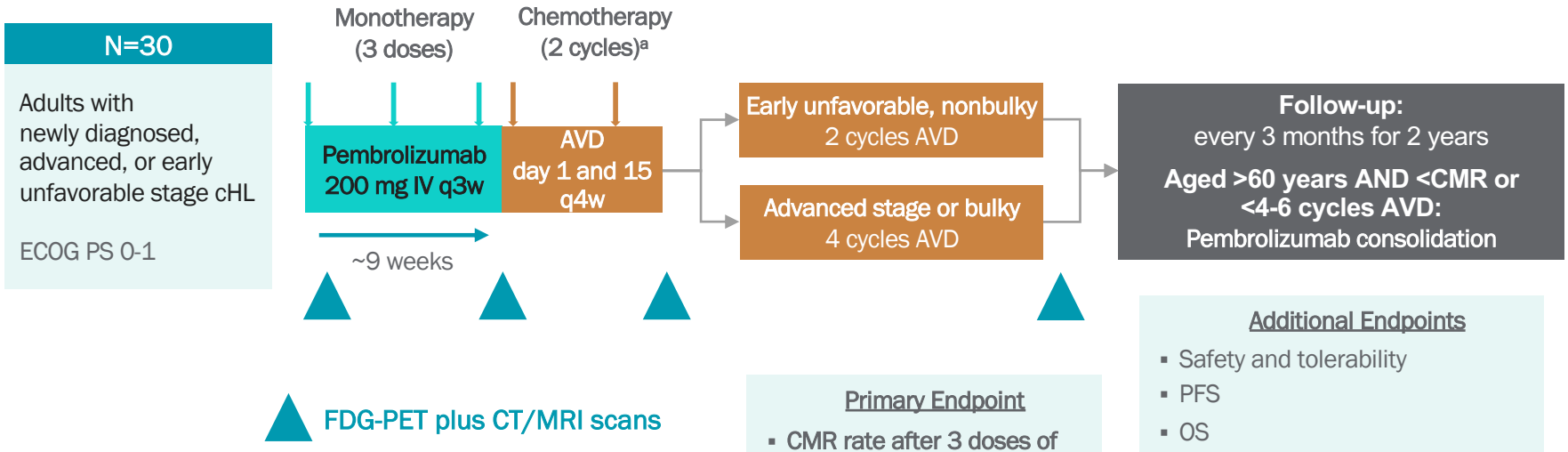


PFS Per Investigator[2]



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.

Checkpoint blockade Abs in Frontline HL: Phase 2 Pembro → AVD



Primary Endpoint

- CMR rate after 3 doses of pembrolizumab monotherapy by IRR per Lugano 2014 response criteria

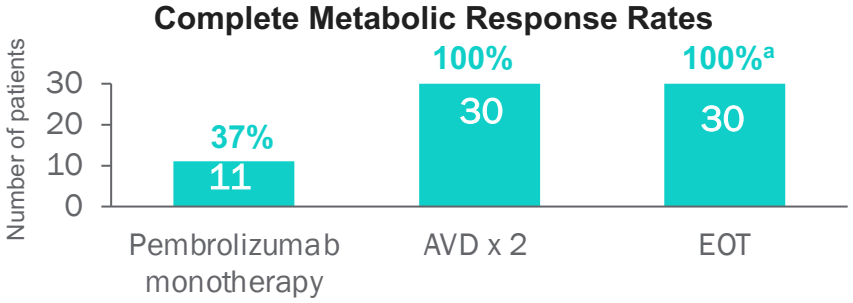
Additional Endpoints

- Safety and tolerability
- PFS
- OS
- CMR after 2 cycles of AVD and EOT
- Decline in MTV after pembrolizumab monotherapy

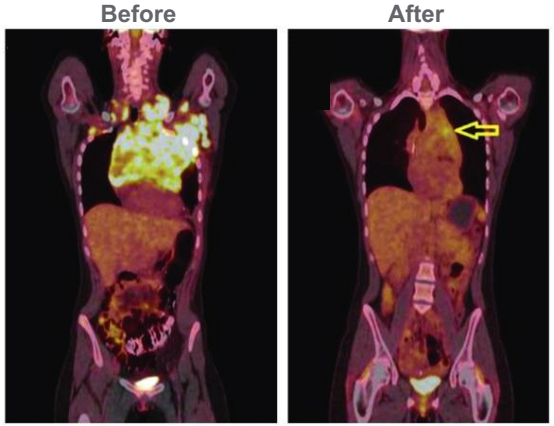
[a] **The protocol recommended but did not require that patients with positive interim PET-CTs after 2 cycles of AVD chemotherapy transition to escalated BEACOPP**

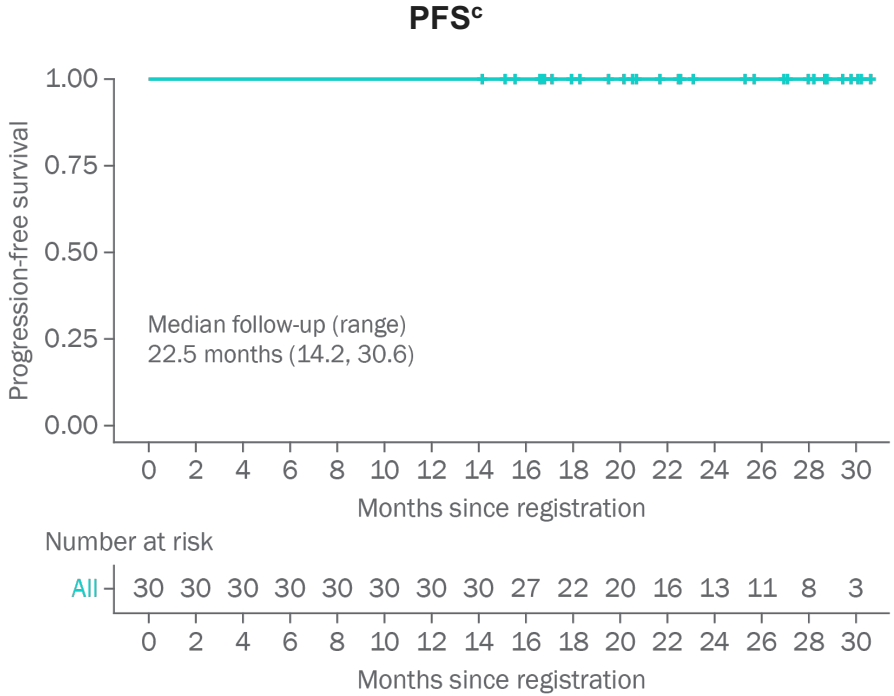
Allen PB, et al. Blood. 2021;137(10):1318-1326.

Phase 2 Pembro → AVD: Response and PFS



PET-CT Before and After Pembrolizumab Monotherapy[b]





[a] In 2 patients with early unfavorable stage cHL who received 4 cycles of AVD, diagnostic CT scans substituted for PET4, as permitted by protocol at EOT. [b] Coronal fused PET-CT images of a 23-year-old woman with cHL. [c] OS is identical and not shown.

Allen PB, et al. Blood. 2021;137(10):1318-1326.

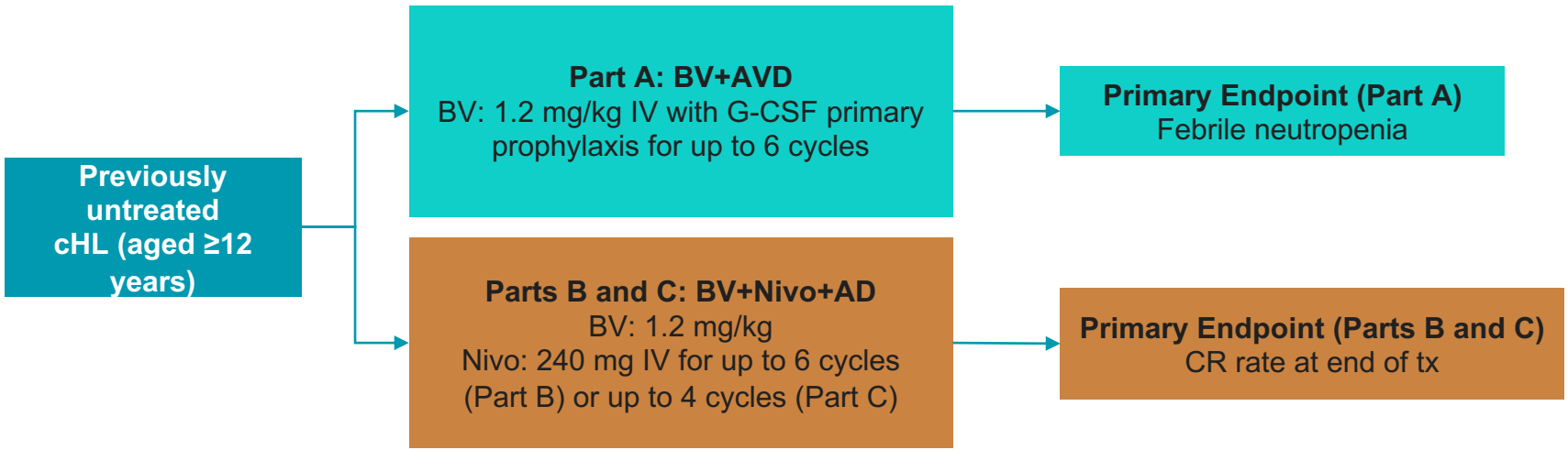
Checkpoint blockade Trials in Frontline HL: Safety

TRAEs, n (%)	Nivolumab-AVD (n=51)[1,a]		Pembrolizumab-AVD (n=30)[2,b]	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Hematologic				
Neutropenia	28 (55)	25 (49)	4 (13)	3 (10)
WBC count decreased	7 (14)	1 (2)	-	-
Leukopenia	-	-	6 (20)	0
Lymphopenia	-	-	4 (13)	1 (3)
Febrile neutropenia	5 (10)	5 (10)	-	-
Anemia	5 (10)	2 (4)	9 (30)	0
Immune-related AEs				
Rash	3 (6)	0	6 (20)	0
IRR	1 (2)	0	5 (17)	0
Hypothyroidism/thyroiditis	9 (18)	0	3 (10)[c]	0
Hyperthyroidism	4(8)	0		
ALT increased	2 (4)	2 (4)	1 (3)	1 (3)
AST increased	1 (2)	1 (2)	1 (3)	1 (3)
Other[a]				
Nausea	18 (35)	1(2)	5 (17)	0
ALT increased	4 (8)	2 (4)	6 (20)	0
AST increased	-	-	5 (17)	0
Hypertension	-	-	8 (27)	0
IRR	16 (31)	0	-	-
Fatigue	13 (25)	0	4 (13)	0

[a] TRAEs in ≥5% of patients. [b] Hematologic and other TRAES in >1 patient. [c] Reported as thyroid disorders. [d] Nonimmune related.

1. Ramchandren R, et al. J Clin Oncol. 2019;37(23):1997-2007. 2. Allen PB, et al. Blood. 2021;137(10):1318-1326.

Frontline BV+ AVD or BV+Nivo+AD in cHL

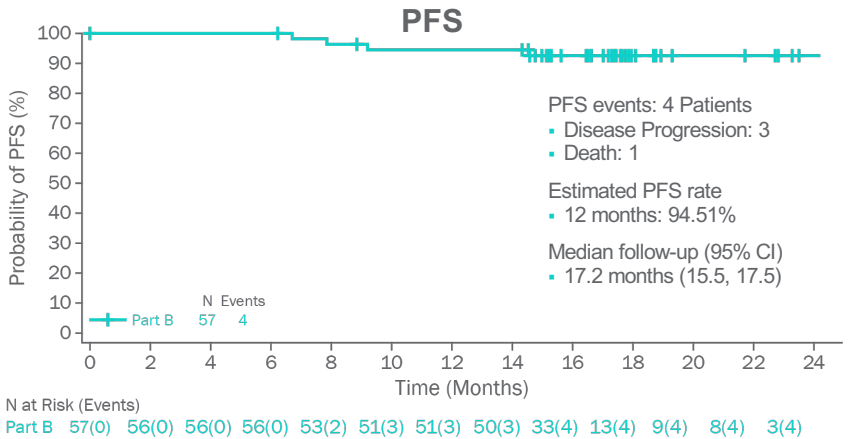


- **Part A: TN stage III/IV cHL**
- **Part B: TN stage IIA (bulky)/IIB/III/IV cHL**
- **Part C: TN stage I/II nonmediastinal cHL**

Clinicaltrials.gov. Accessed January 31, 2023. https://clinicaltrials.gov/ct2/show/NCT036

Frontline BV+ AVD or BV+Nivo+AD in cHL: Efficacy and Safety

Responses	Part B (N=57)
ORR, % (95% CI)[a]	93 (83.0-98.1)
CR	88 (76.3-94.9)
PR	5 (1.1-14.6)
Patients with DOR of ≥12 mo, %	93
95% CI	(81.7-97.2)
Patients with DOCR of ≥12 mo, %	92
95% CI	(80.0-96.9)



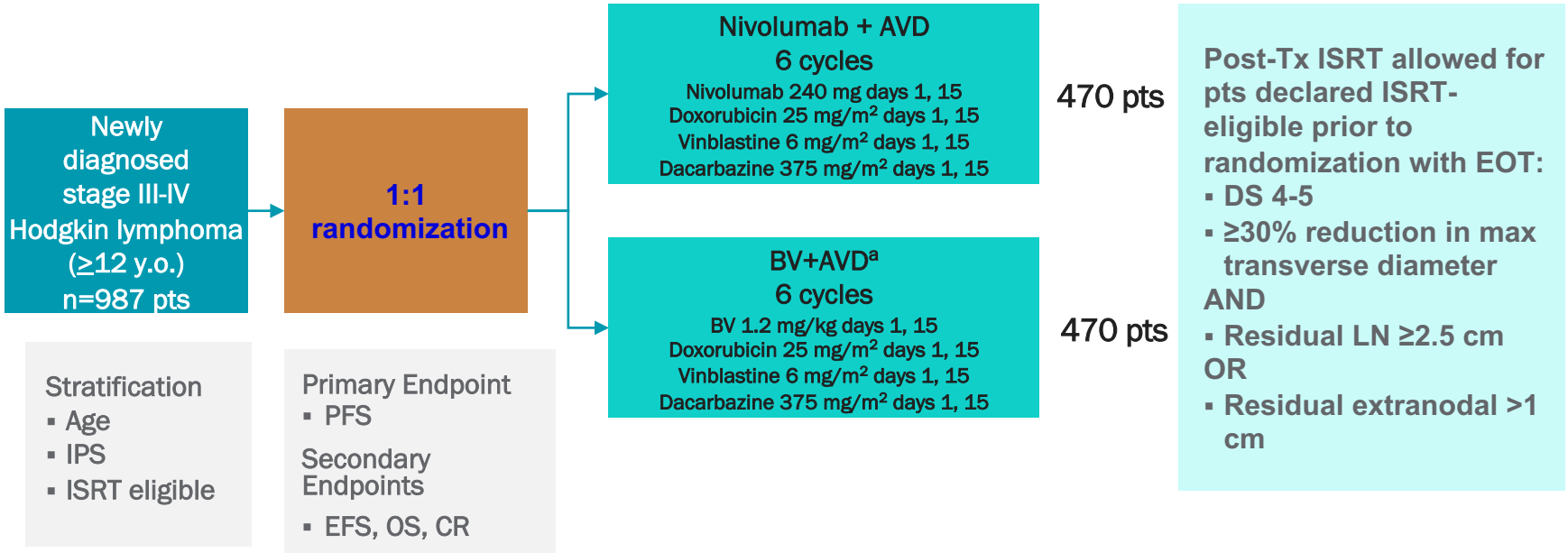
Safety, n (%)	Part B (N=57)
Grade ≥3 TEAEs	29 (51)
Any SAE	8 (14)
Any immune-mediated AE	20 (35)
Dose modifications	42 (74)
Delay	16 (28)
Reduction	14 (25)
Elimination	22 (39)

- **Nausea (65%), fatigue (47%), and peripheral sensory neuropathy (42%) were the most frequently reported TEAEs**
  - **Peripheral sensory neuropathy** was primarily low grade **(4% grade ≥3)**
- **No TEAEs led to death, and no cases of febrile neutropenia were reported**
- Most common SAEs were pneumonitis (5%) and pyrexia (5%), and all cases resolved fully
- Most common immune-mediated AEs were hypothyroidism (9%), pneumonitis (5%), and maculo-papular rash (5%)

[a] Per LYRIC per investigator assessment.

Lee H, et al. ASH 2022. Abstract 314.

S1826 Intergroup Study: Frontline Nivo+AVD or BV+AVD in advanced stage cHL (closed to accrual 12/1/2022)



[a] **G-CSF is mandatory in BV+AVD arm**, optional in N+AVD arm

Herrera AF, et al. ASH 2020. Abstract 2969.

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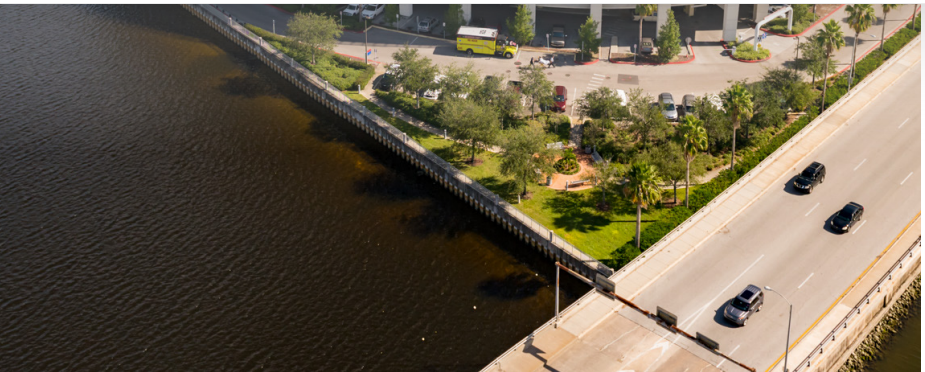
THANK YOU !



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