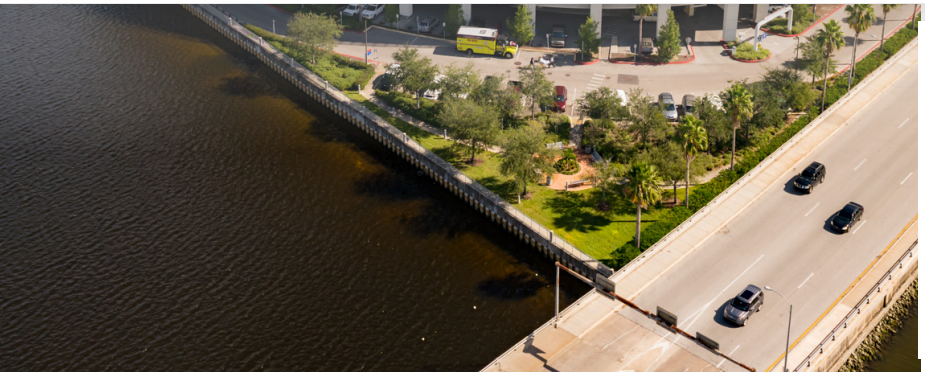
Tampa General Hospital | CANCER INSTITUTE

USF HEALTH MORSANI COLLEGE OF MEDICINE UNIVERSITY OF SOUTH FLORIDA

"Modern Challenges and New Options in Lymphoma Treatment"



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VP and Executive Director, TGH Cancer Institute

Professor, USF Health Morsani College of Medicine

University of South Florida

Modern Challenges and New Options in Lymphoma Treatment

- **In the last 10 years we have witnessed an unprecedent approval of novel targeted therapies and immunotherapies for patients with lymphoma……**

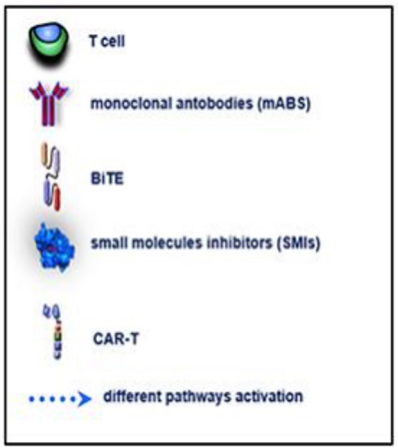
- **While these are great news, they have also brought "modern challenges"**
  - **How to combine them, while optimizing efficacy and minimizing side effects**
  - **How to sequence them…..**
  - **Finite versus continuous treatment**
  - **Emergence of resistance: Double refractory…..CAR T refractory….**

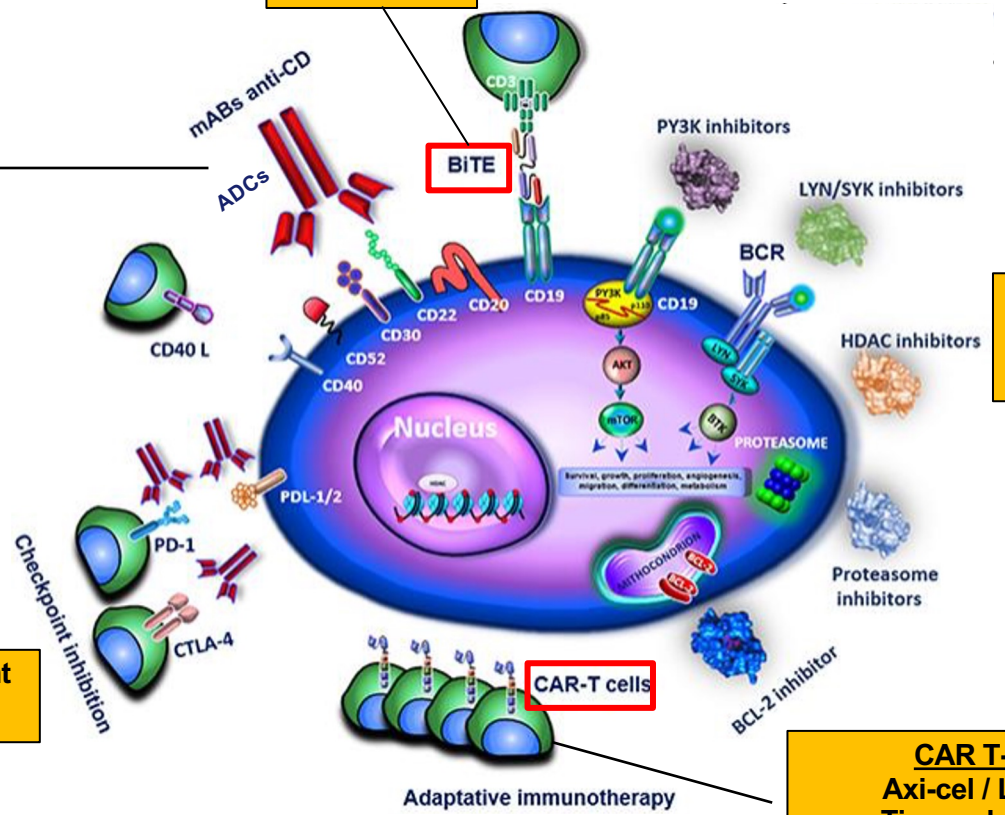
Regardless, these modern challenges are a "good problem" to have!

B-cell Lymphomas: Novel Agents

Bispecific Antibodies

Rituximab
Ofatumumab
Obinotuzumab
Polatuzumab vedotin
Loncastuximab tesirine
Tafasitamab (MOR208)
Ublituximab





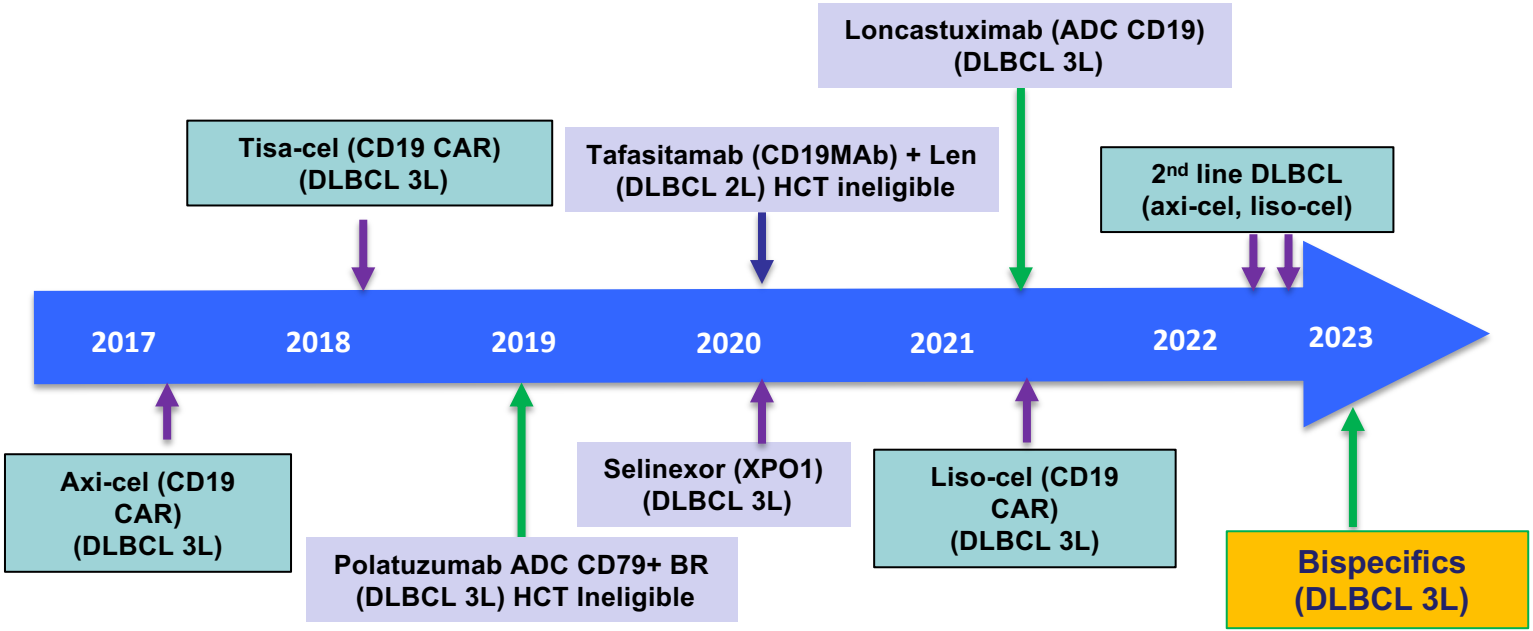
Checkpoint inhibitors

IMIDs:
Lenalidomide
Pomalidomide

CAR T-cells
Axi-cel / Liso-cel
Tisagenlecleucel
Brexucabtagene autoleucel

Figure adapted from Crisci, et al. Front. Oncol. 2019. doi.org/10.3389/fonc.2019.00443

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



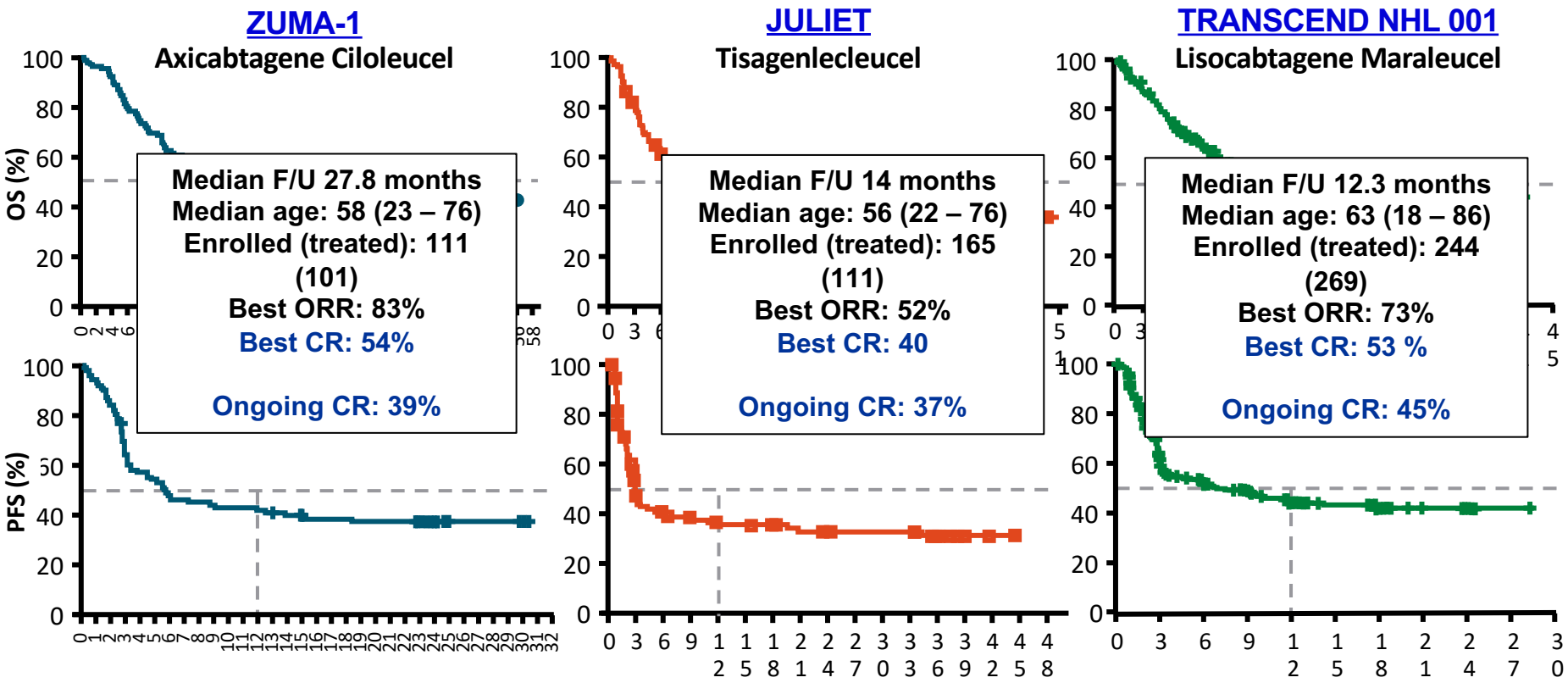
Chavez, J. et al.

First 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**

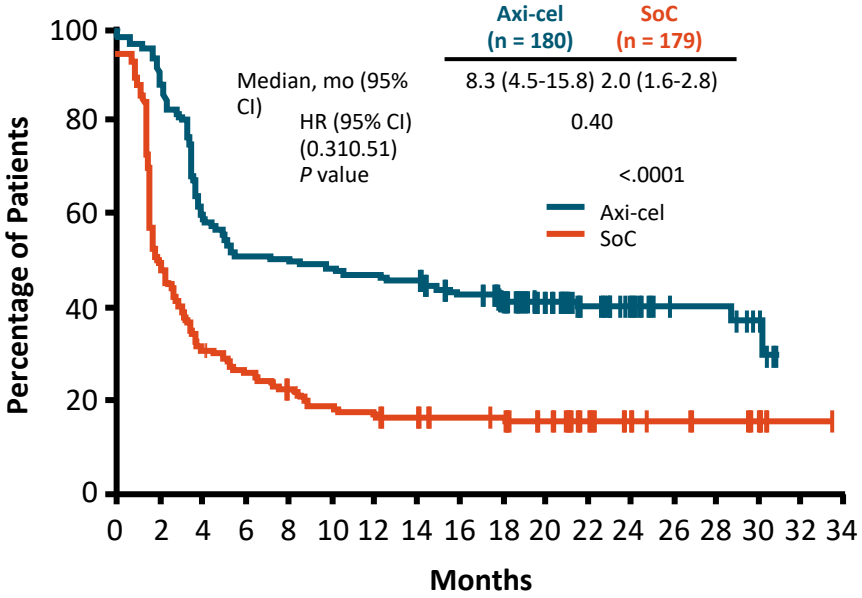
Pivotal Anti-CD19 CAR T Cell Therapy Trials: Third Line DLBCL



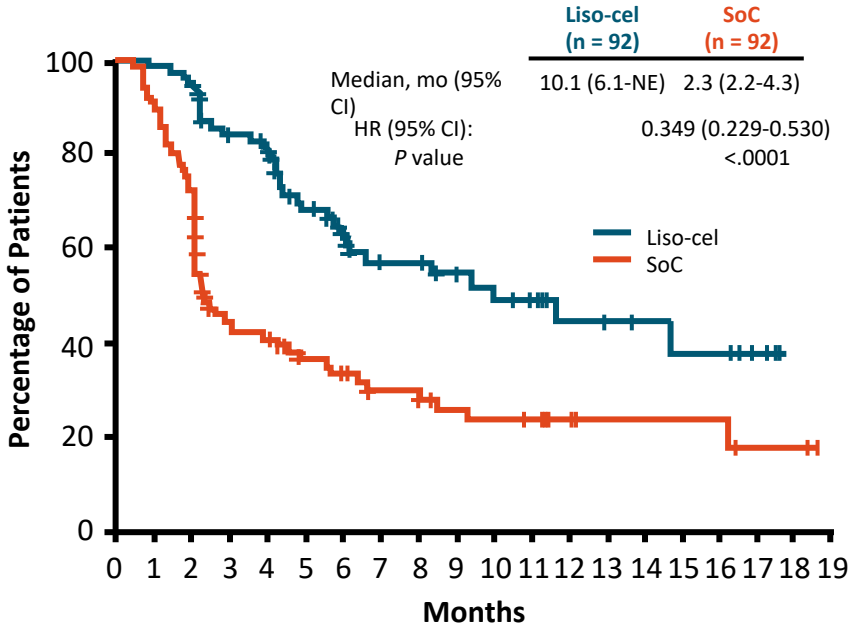
Locke. Lancet Oncol. 2019;20:31. Jacobson. ASH 2020. Abstr 1187. Jaeger. ASH 2020. Abstr 1194. Abramson. Lancet. 2020;396:839.

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

ZUMA-7: Median EFS[1]



TRANSFORM: Median EFS[2]

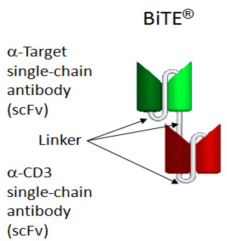
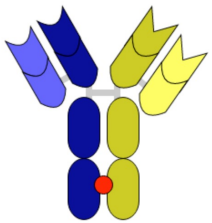
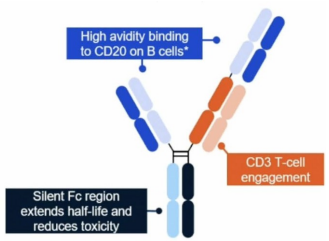
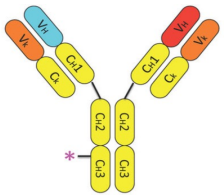


1. Locke. NEJM. 2022;386:640. 2. Kamdar.. Lancet. 2022;399:10343.

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….**

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

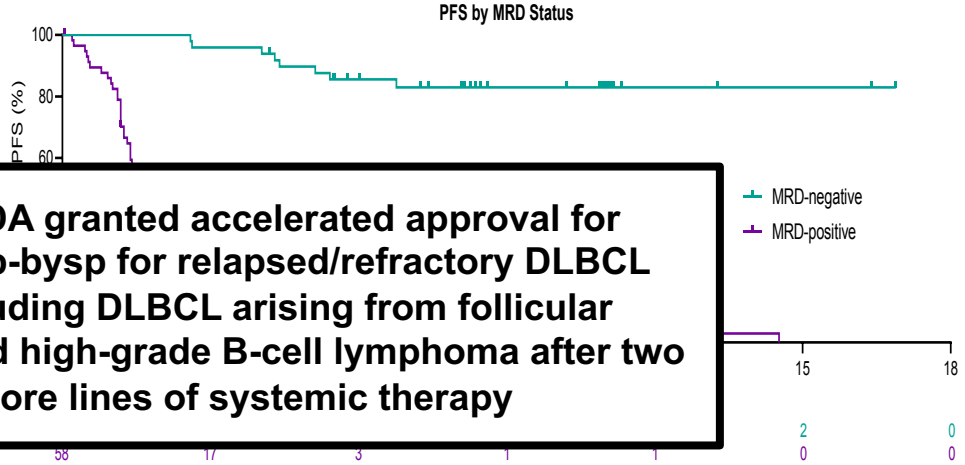
Baseline Characteristics

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

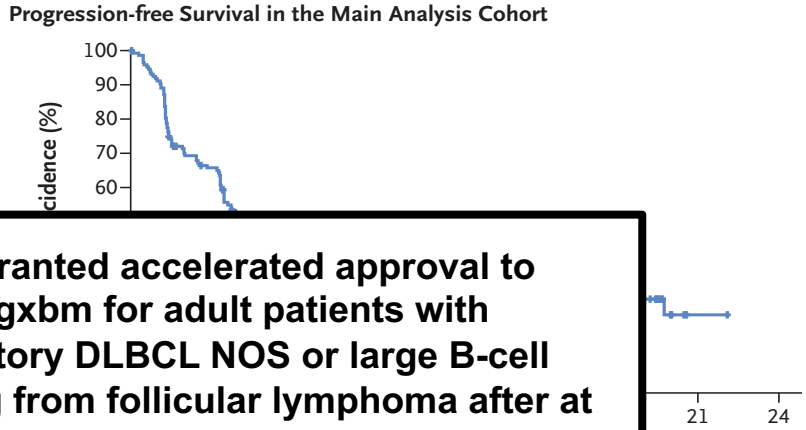
Time limited therapy (12 cycles IV with pretreatment obinutuzumab)

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

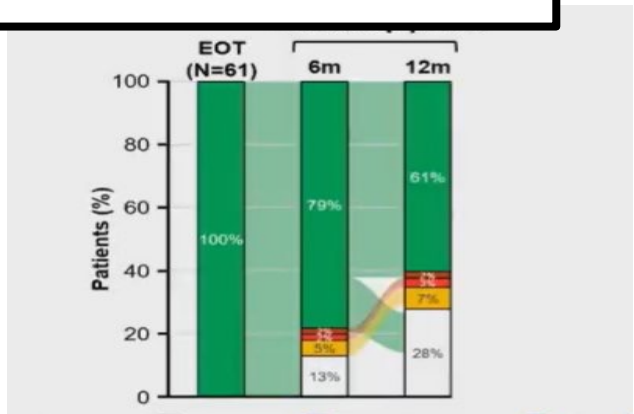
ORR= 52%

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)

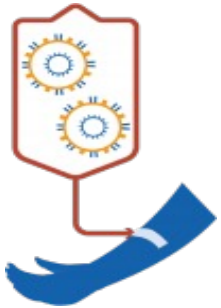
- ***Let's look at the data:***
  - **"Curative" versus non-curative modality**

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

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

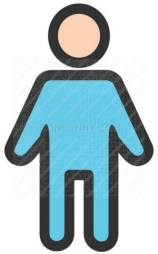
Treatment Goal:

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



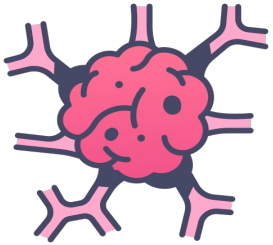
Product Factors:

- 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**

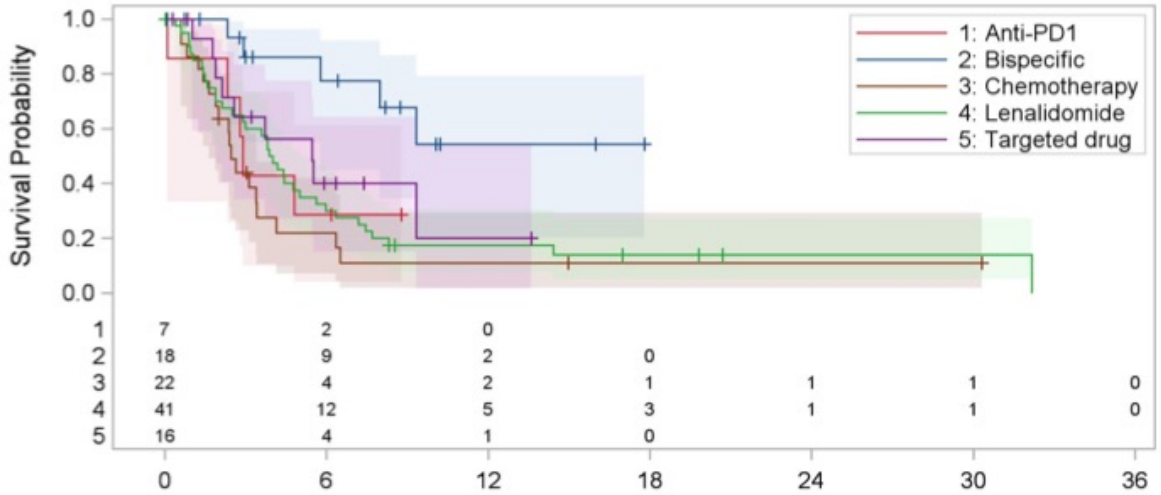


Figure 1: PFS since first progression (months) after CAR T cells therapy according to type of treatment.

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….**
  - **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

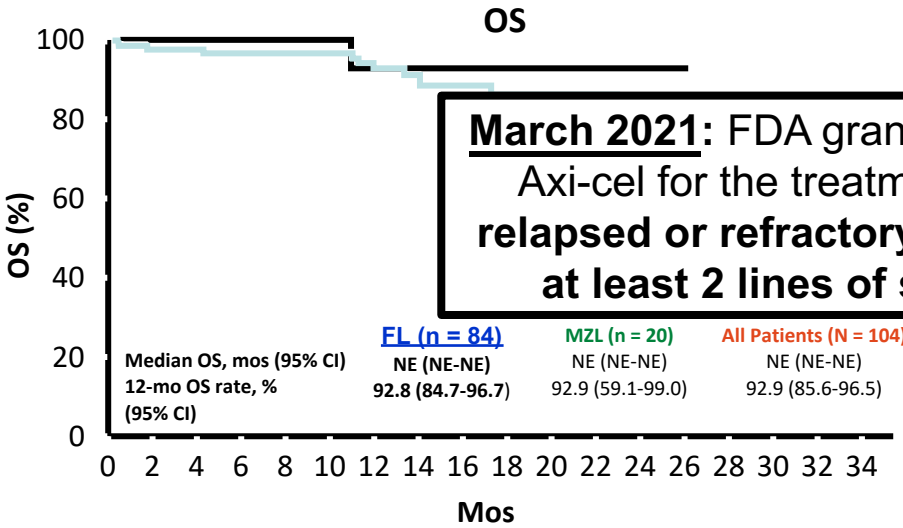
Second Challenge: CAR-T and Bispecific Antibodies in FL: How to use… and sequence them (…a matter of debate)

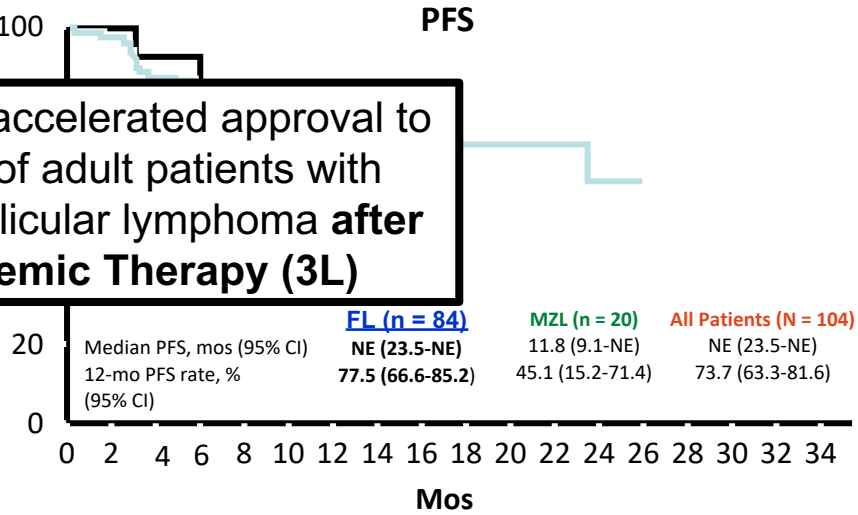
- ***Let's look at the data:***
  - **"Curative" versus non-curative modality**
- ***Factors that would influence their use and/or sequencing:***
  - **GOAL of Treatment**
  - **Product-related factors**
  - **Patient-related factors**
  - **Tumor-related factors**

ZUMA-5: Axi-cel for Patients with Relapsed/Refractory Follicular Lymphoma or MZL

Single-arm phase II study of axicabtagene ciloleucel for patients with R/R indolent B-cell NHL (FL or MZL) with ≥ 2 prior therapies (N = 104)

ORR: 92%; CR rate: 76%





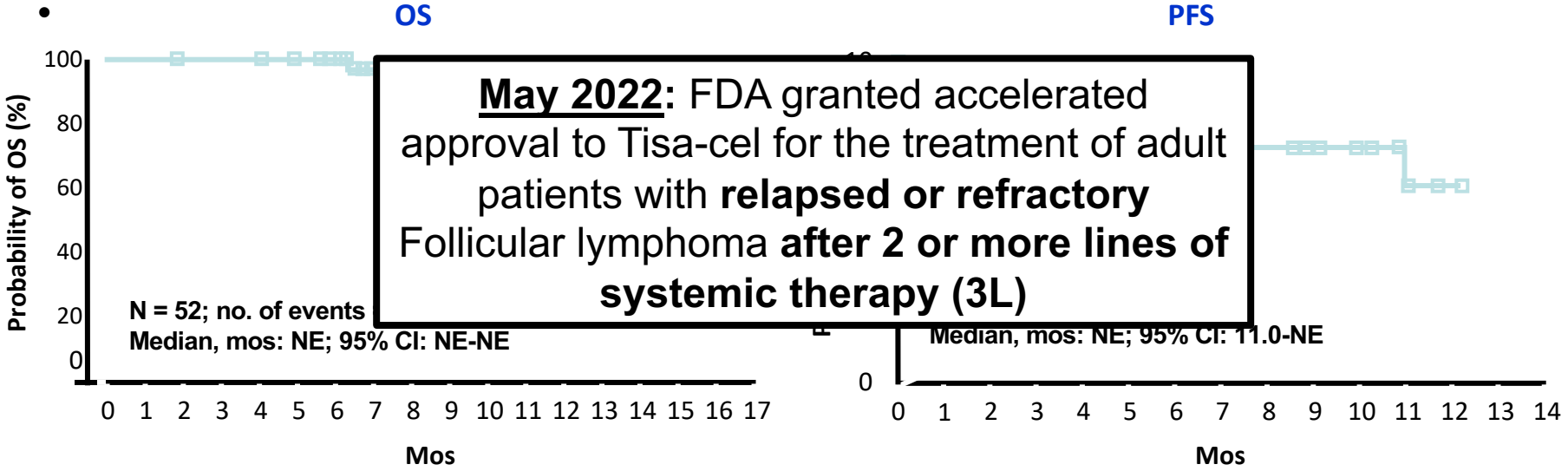
March 2021: FDA granted accelerated approval to Axi-cel for the treatment of adult patients with **relapsed or refractory** Follicular lymphoma **after at least 2 lines of systemic Therapy (3L)**

Jacobson. ASH 2020. Abstr 700.

ELARA: Tisa-cel for Patients with Relapsed/Refractory Folicular Lymphoma

Single-arm phase II study of tisagenlecleucel for patients with R/R FL (N = 97 at interim analysis)

ORR: 83%; CR rate: 65%



May 2022: FDA granted accelerated approval to Tisa-cel for the treatment of adult patients with **relapsed or refractory** Follicular lymphoma **after 2 or more lines of systemic therapy (3L)**

Schuster, Nat. Med December 2021

Bispecific: Mosunetuzumab for R/R Follicular Lymphoma after 2L of Therapy

ORR: 78% CR: 60%

Baseline Characteristics:

N= 90 pts

Time limited therapy (8 cycles IV if CR but up to 17 cycles if Por less)

Median lines: 3 (2-10)

Double refractory: 53%

POD24: 52%

Prior auto HCT: 21%

Results:

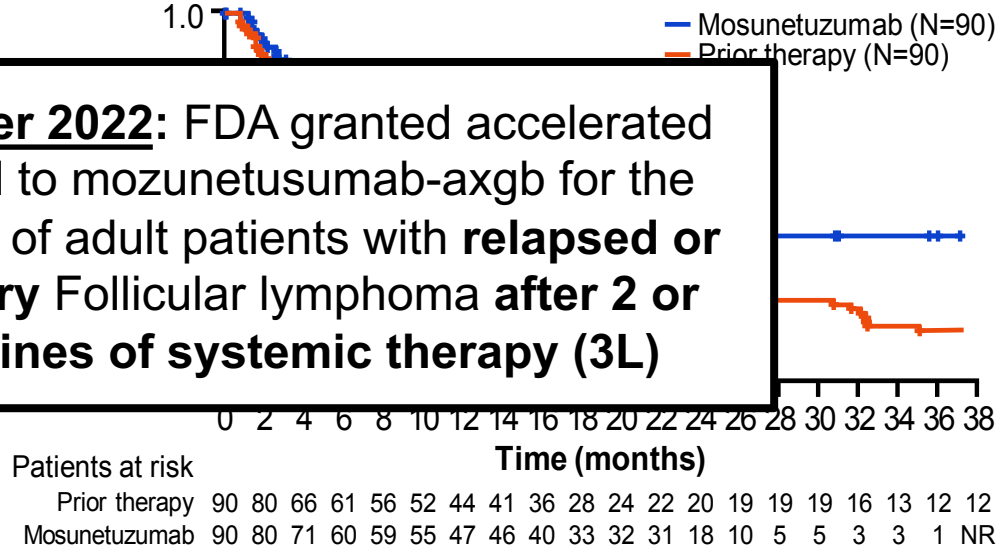
Median f/u: 28.3 months

DoR not reached

Median PFS= 24%

CRS all: 44%; G≥3=2%

December 2022: FDA granted accelerated approval to mozunetusumab-axgb for the treatment of adult patients with **relapsed or refractory** Follicular lymphoma **after 2 or more lines of systemic therapy (3L)**

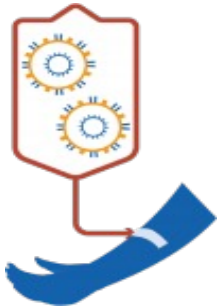


Bartlett N et Al. ASH Meeting 2022.

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

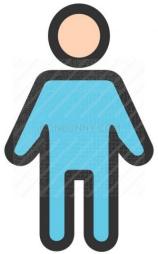
Treatment Goal:

- **Cure**
  - **CAR T-cells: No**
  - **Bi-specific : No**



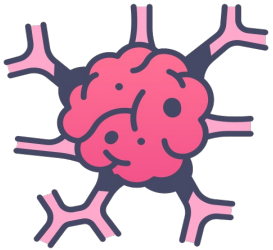
Product Factors:

- Availability (Clinical trials vs. commercial)
- All approved in 3L
- **Need for specialized center:**
  - **CAR T: Yes**
  - **Bispecifics: No**
- **Potential administration in outpatient setting**
  - **CAR T: No**
  - **Bispecifics: Yes (IV and SC)**



Patient Factors

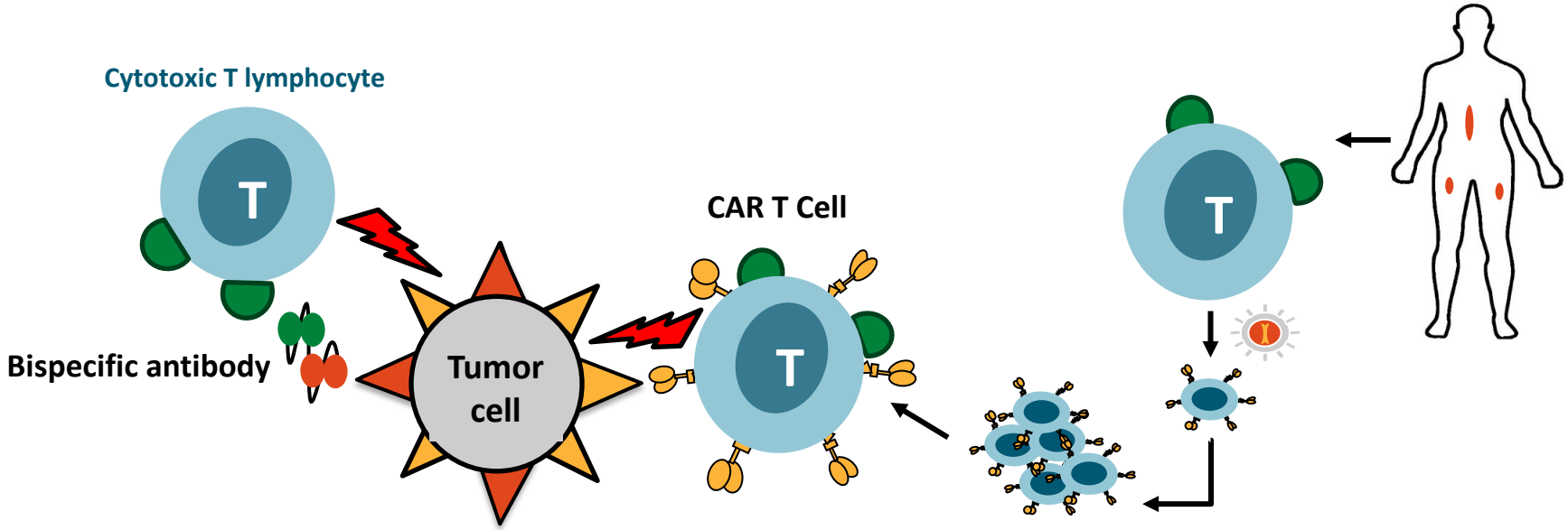
- Age, comorbidities
- Prior treatments
- Patient preference:
  - **One treatment: CAR T**
  - **Multiple treatments: Bispecifics**
- **Cost**



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

Bispecific Antibodies vs CAR T-Cell Therapy

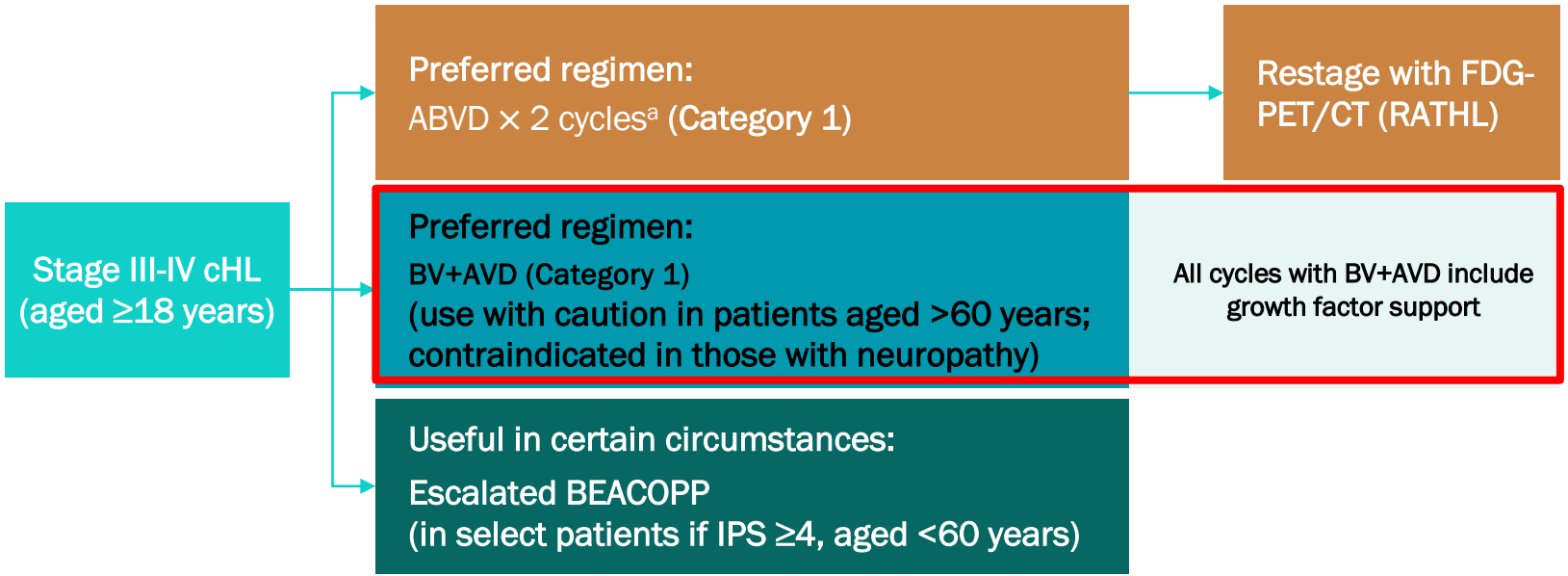


Characteristic	Bispecific Antibodies	CAR T-Cell Therapy
Preparation	"Off the shelf"	*In vitro* manufacturing (3-4 wks)
Dosing	**Repetitive** (Lack of persistence and ability to modulate dosing may improve tolerability)	**Single** (Persistence is associated with some long-lasting side effects)
Side Effects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

Third Challenge: Frontline Treatment of Stage III/IV Hodgkin A+AVD or Nivo+AVD?

- ***Let's look at the data:***
  - **GOAL of frontline treatment in Hodgkin Disease: CURE**
  - **Side effects**

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

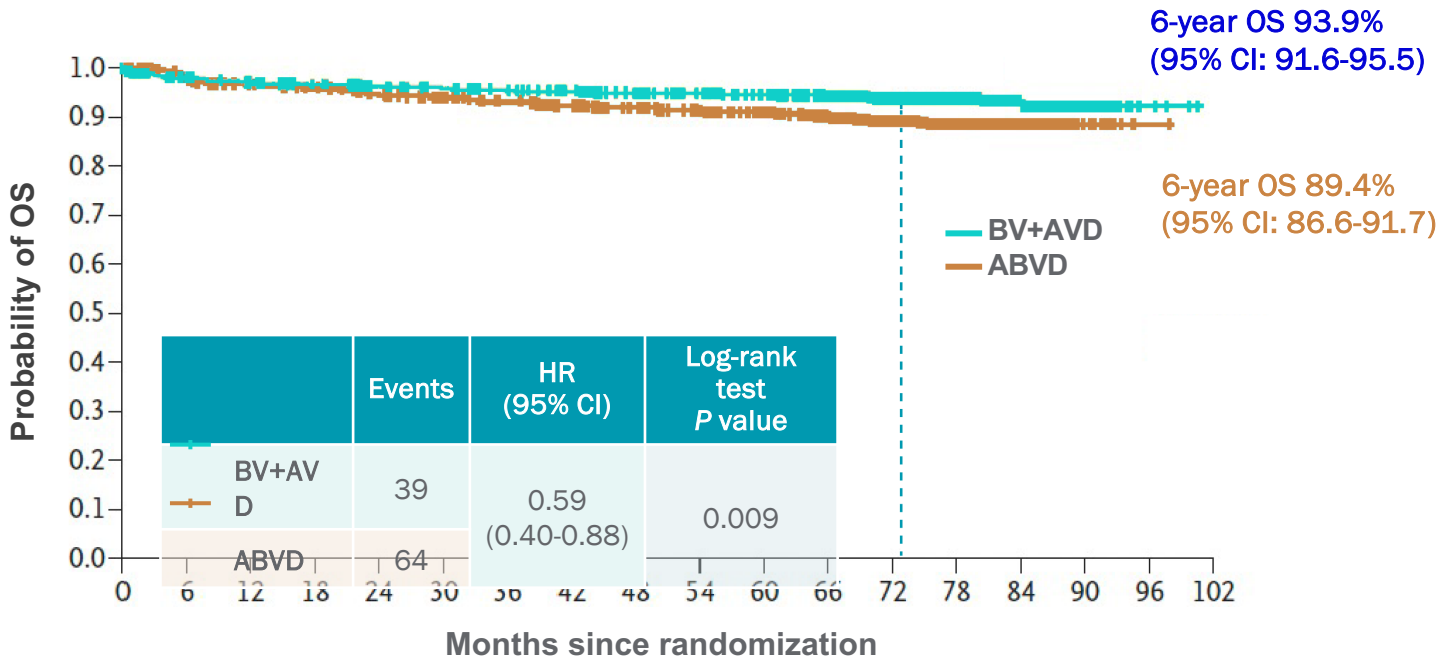


ALL RECOMMENDATIONS CATEGORY 2A UNLESS OTHERWISE INDICATED

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

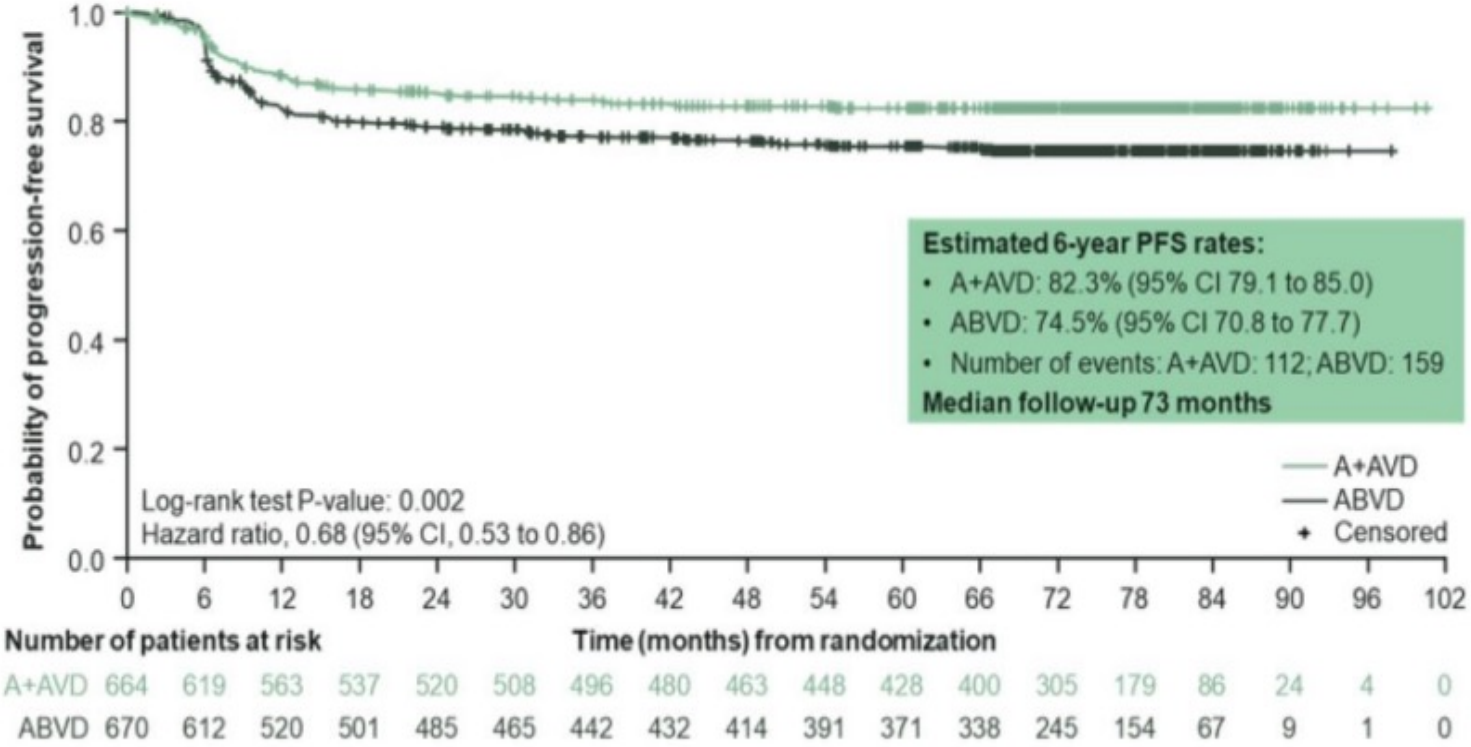
National Comprehensive Cancer Network. Hodgkin Lymphoma (Version 2.2023). Accessed February 2, 2023. https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf

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



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

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

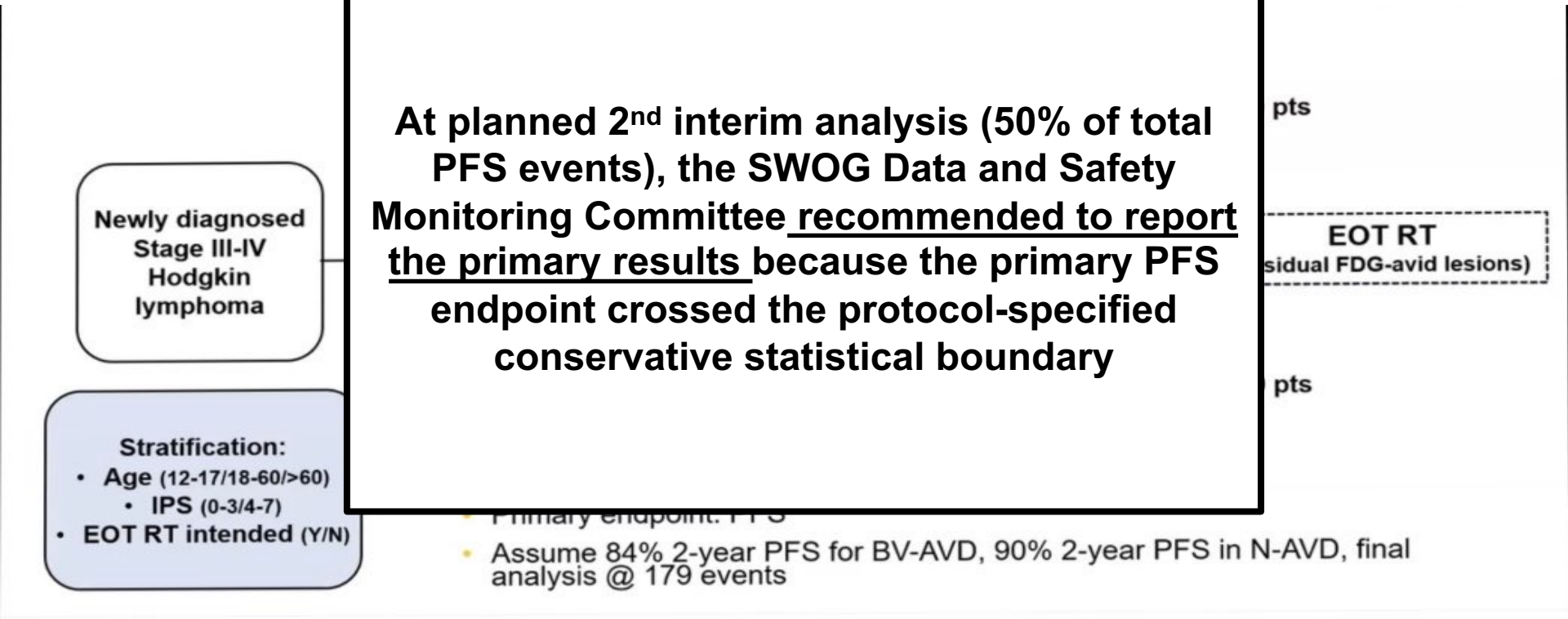
*In 2 patients in the ABVD arm, death was reported to be of indeterminate cause, but the event occurred following investigator-documented disease progression.

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)

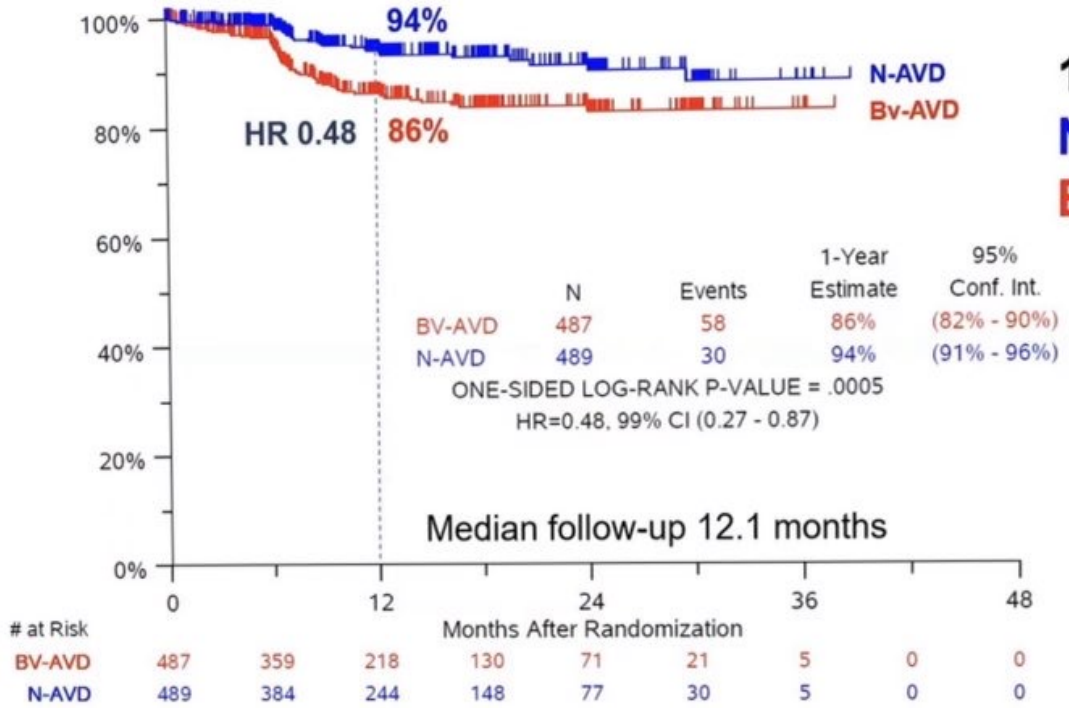
ASCO 2023: S1826 Intergroup Study
Frontline Nivo+AVD vs. BV+AVD in Advanced Stage cHL

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



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

Intergroup Study S1826: PFS



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

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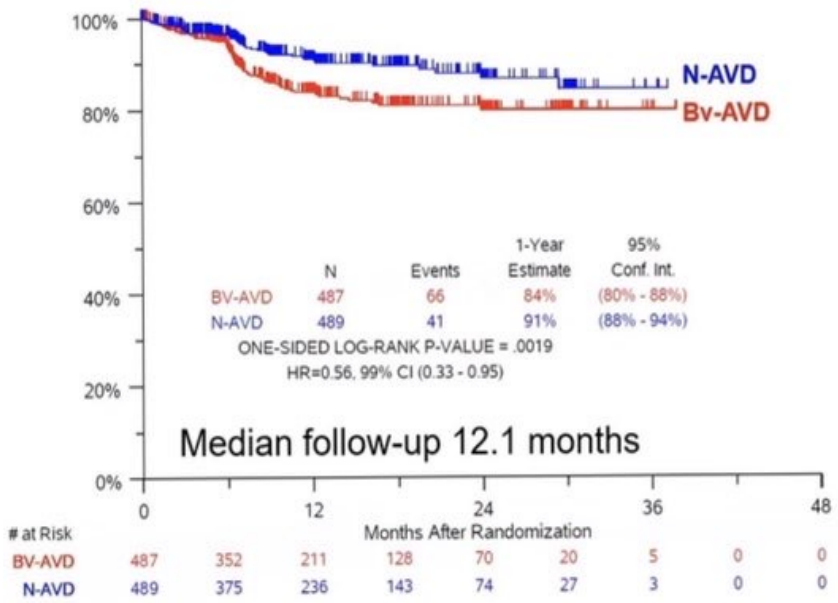
Intergroup Study S1826: EFS



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

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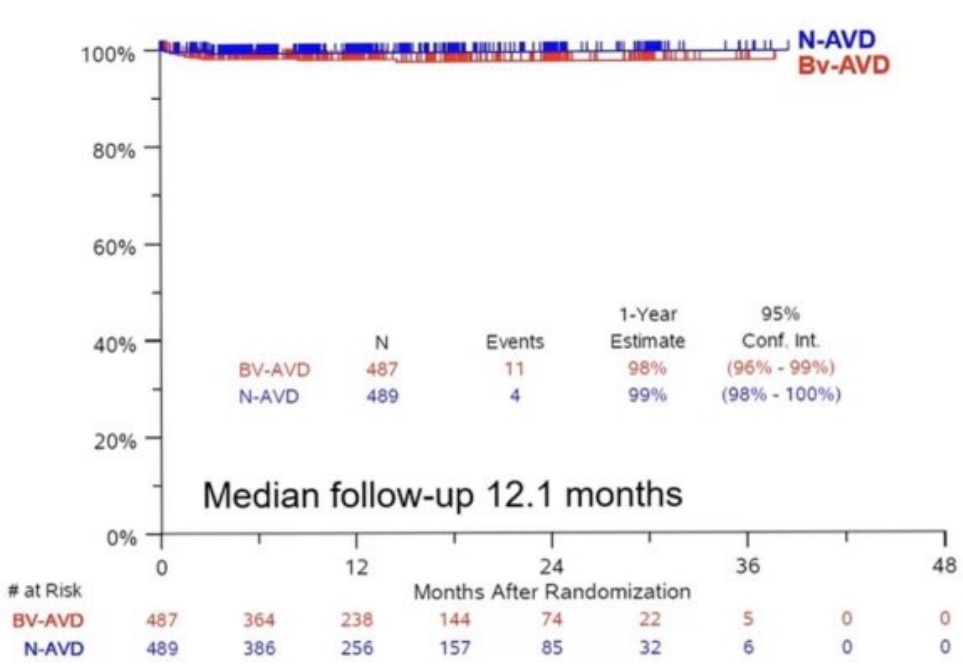
Intergroup Study S1826: OS



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

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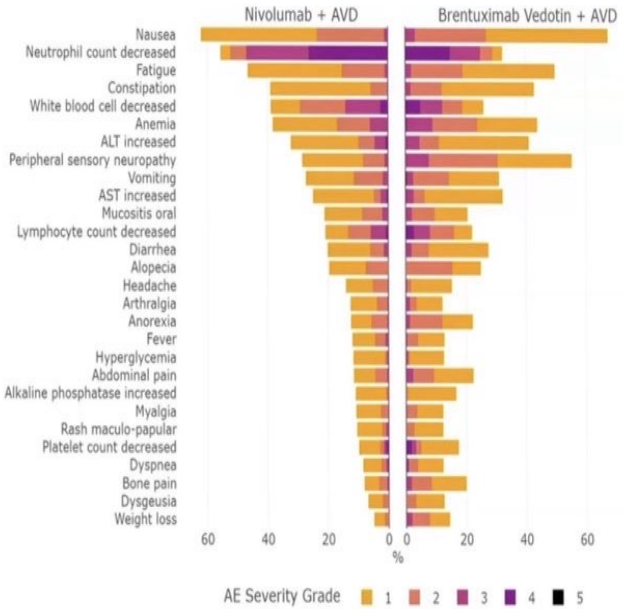
Intergroup Study S1826: Toxicities

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

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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

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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%)**

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Third Challenge: Frontline Treatment of Stage III/IV Hodgkin A+AVD or Nivo+AVD?

- ***Let's look at the data:***
  - **GOAL of treatment in Hodgkin Disease: CURE**
    - **Curative versus non-curative modality**
  - **Side effects**

- ***Longer follow-up with BV + AVD***
  - **Improved OS over ABVD**
- ***Shorter follow-up with Nivo + AVD***
  - **Data from Intergroup Study S1826 is very encouraging, but time will tell whether it will provide (or not) better OS than BV+AVD**
- ***Both are well tolerated regimens with different set of adverse events***

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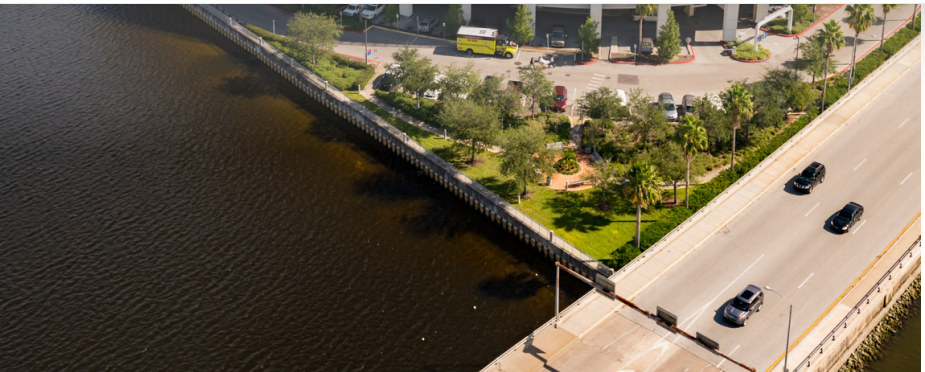
THANK YOU !



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