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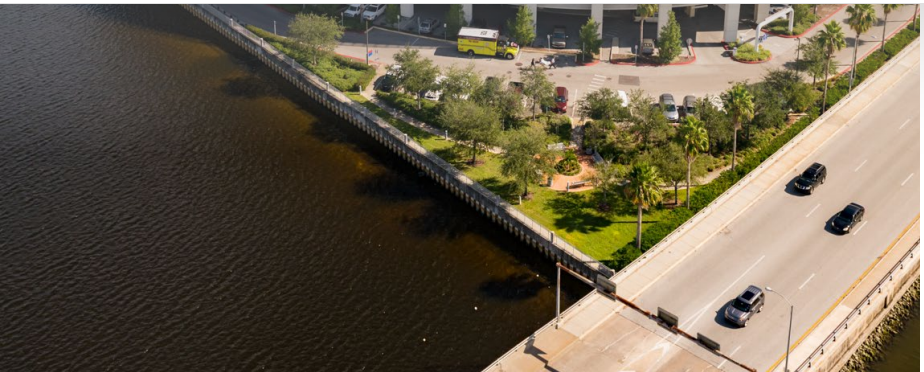
"DLBCL and Hodgkin's Disease: Novel Approaches"



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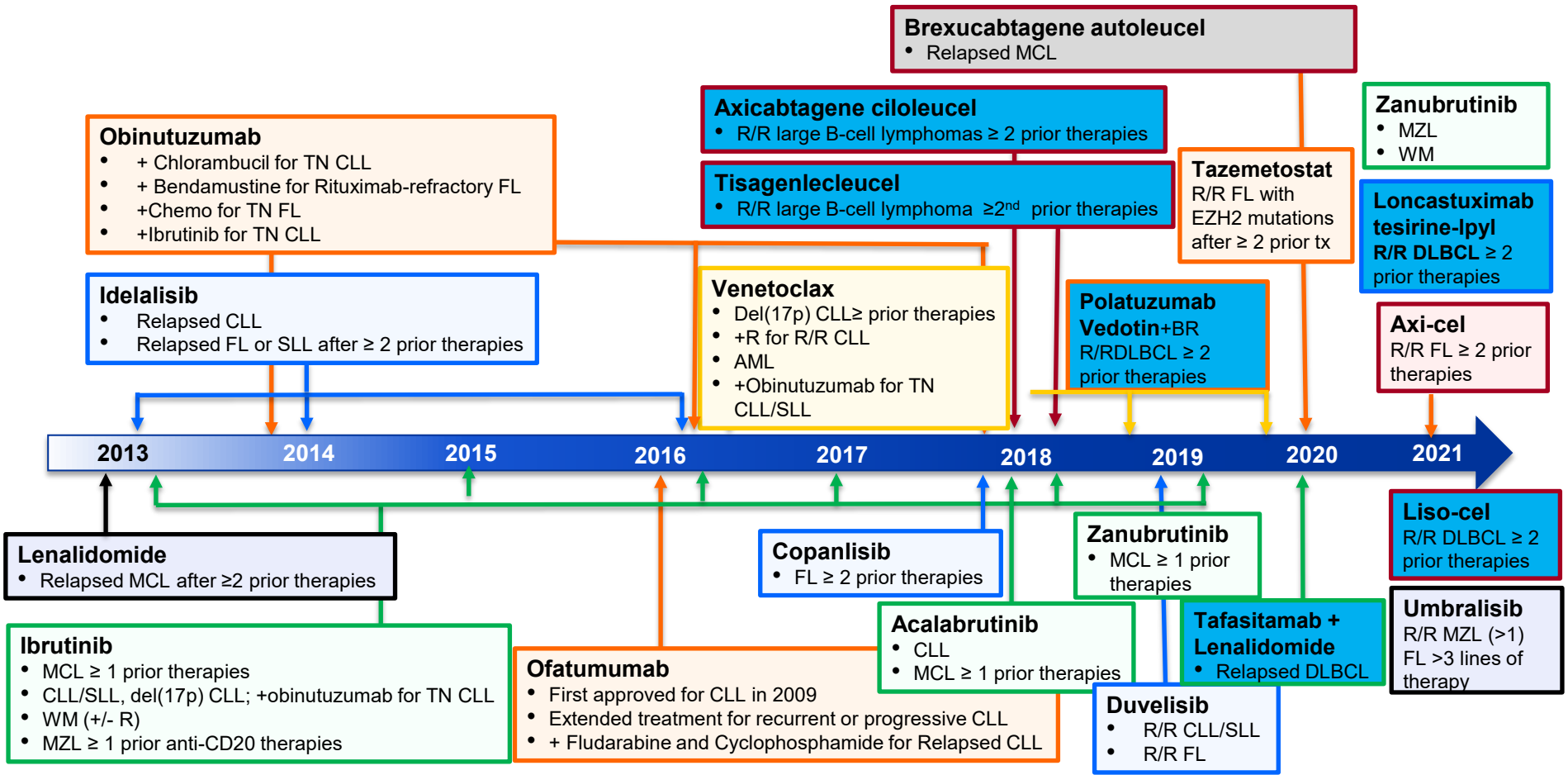
DLBCL: After many years of marginal progress…..a plethora of new treatments

- **2000: Rituximab added to CHOP chemotherapy (RCHOP) 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 used in some subtypes (HIV-associated DLBCL, PMLBC)**
- **Checkpoint blockade: Modest activity in relapsed/refractory DLBCL, but….new encouraging data in frontline setting (Neoadjuvant?)**
- **THE LAST FIVE YEARS:…. CAR T-cells, POLA, TAFA, LONCA**

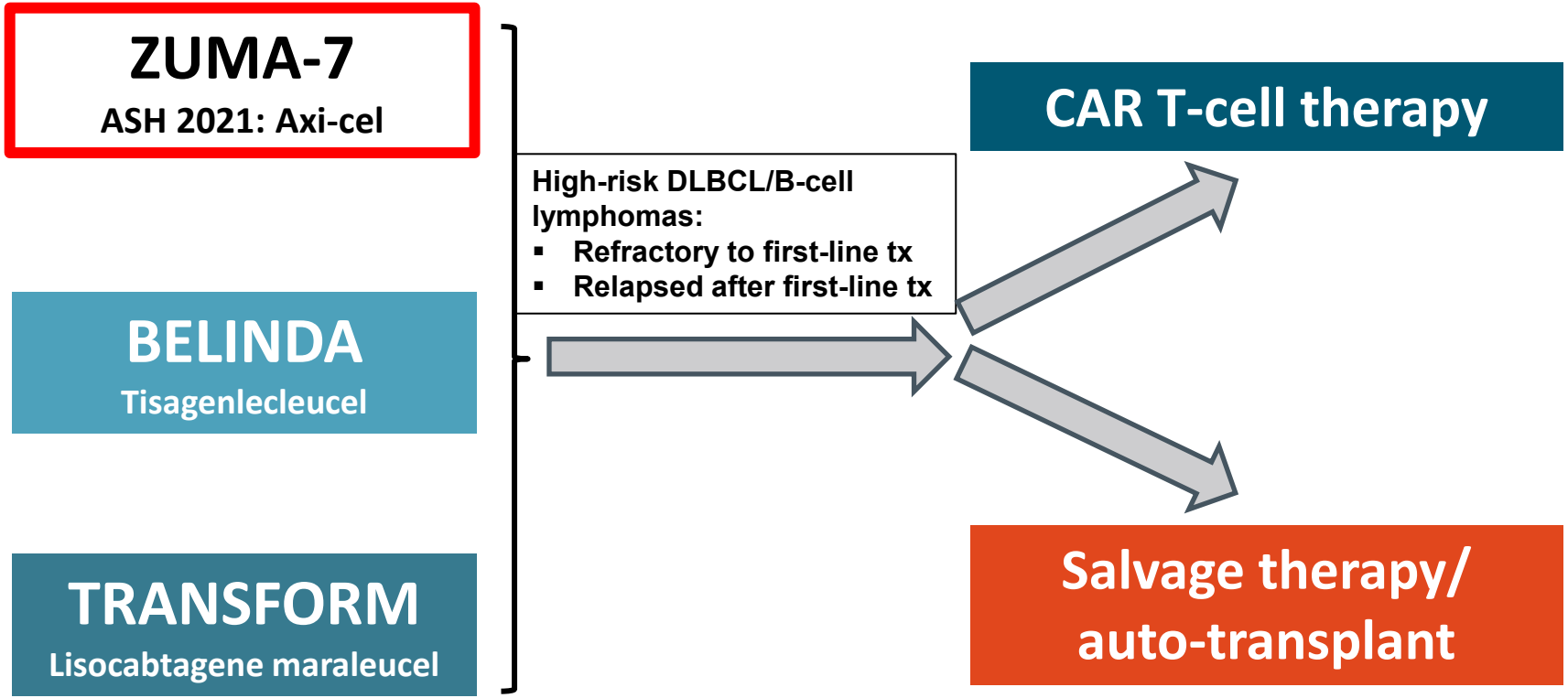
Timeline of Newer Agents for DLBCL



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

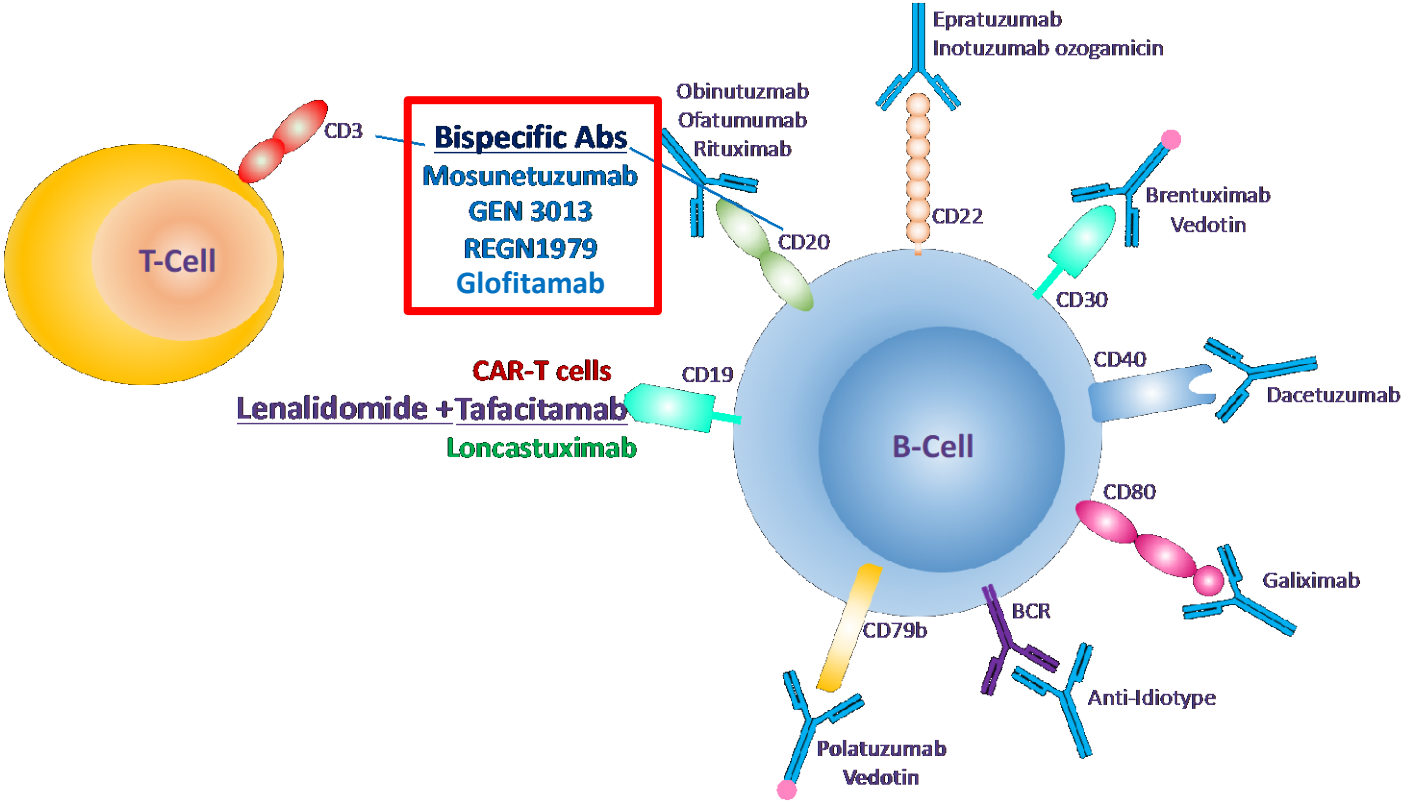
- **CD19 CAR T-cells have shown significant efficacy in patients with relapsed/refractory CD19 positive DLBCL and other B-cell lymphomas.**
  - **Three platforms are FDA-approved (Axi-cel, Tisa-cel and Liso-cel)**
  - **ASH 2021: Challenging ASCT in relapsed DLBCL? Role in frontline therapy for high risk patients?**
- **CD19 is an enticing target for novel approaches:**
  - **Tafasitamab, anti-CD19 antibody (+/- Lenalidomide)**
  - **Loncastuximab Tesirine (Anti-CD19 Antibody-Drug Conjugate)**
- **CD20 is….again an enticing target for bi-specific antibodies:**
  - **Several bi-specific directed T-cell engager (BITE) targeting CD20 and CD3 (CD20 x CD3)….**

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



NCT03391466. NCT03570892. NCT03575351.

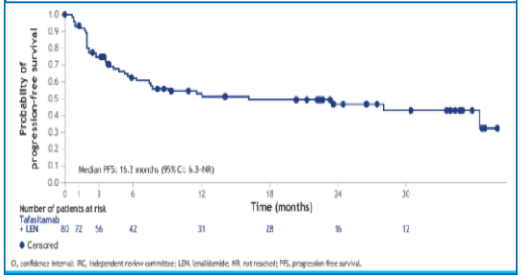
ASH 2021….the saga continues: Bispecific Antibodies



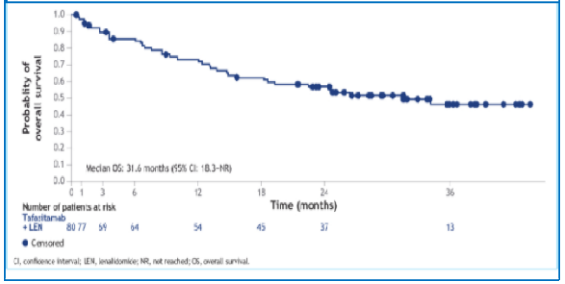
Combination of Tafasitamab and Lenalidomide improves response rates in R/R DLBCL

L-MIND Study – Long-Term Outcomes

IRC-Assessed PFS after > 24 months follow-up



OS after > 24 months follow-up

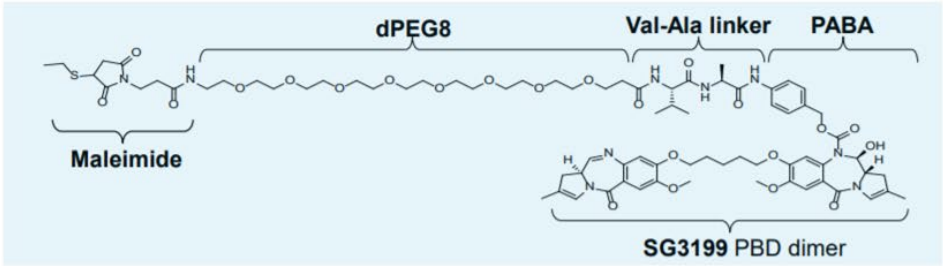


Salles et al. Lancet Oncol 2020

Loncastuximab Tesirine (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**

Figures from Radford, et al. *Hematol Oncol*. 2019;37(52):93-95. doi.org/10.1002/hon.60_2629

Loncastuximab Tesirine Shows Significant Activity in R/R Diffuse Large B-cell Lymphoma

Overall Response Rate: By Clinical Characteristics

Characteristic	Subgroup	All ≥120 µg/kg, % (responders/total)
Age group	<65 Years	33.3 (23/69)
	65–74 Years	52.8 (19/36)
	≥75 Years	59.1 (13/22)
Bulky disease	Absent	46.8 (51/109)
	Present	22.2 (4/18)
Double/Triple hit	Absent	47.6 (50/105)
	Present	22.7 (5/22)
Transformed	No	39.6 (38/96)
	Yes	54.8 (17/31)

Characteristic	Subgroup	All ≥120 µg/kg, % (responders/total)
Number of prior therapies	≤3 lines	43.8 (35/80)
	>3 lines	42.6 (20/47)
Response to first-line therapy	Relapsed	53.1 (43/81)
	Refractory	23.1 (6/26)
Response to most recent therapy	Relapsed	59.1 (26/44)
	Refractory	35.1 (26/74)
Overall		**43.3 (55/127)**

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

Figures from Radford, et al. Hematol Oncol. 2019;37(52):93-95. doi.org/10.1002/hon.60_2629

Polatuzumab Vedotin

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

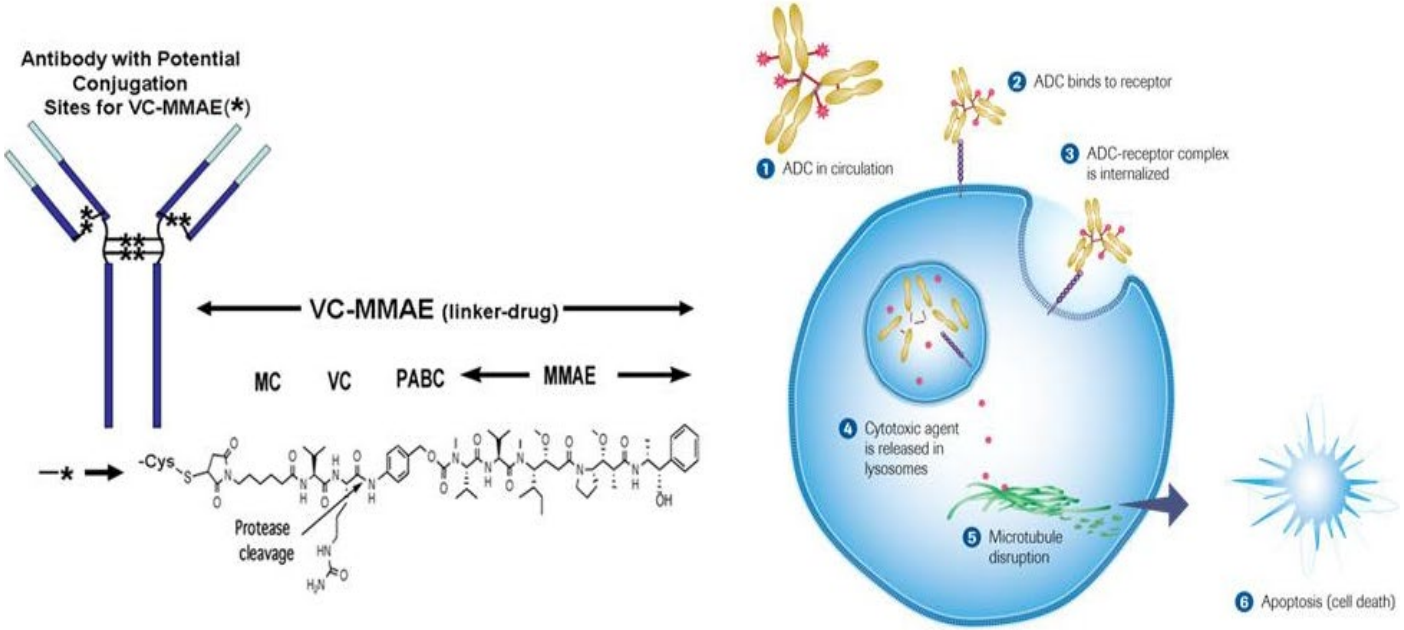


Figure from: Morschhauser, et al. J Clin Oncol. 2014;32(15_suppl):8519.
Doman, et al. Blood. 2009;114:2721-2729. Polson, et al. Blood. 2007;110:616-623. Sehn, et al. ASH 2017;Abstract 2821.

Polatuzumab Vedotin+Bendamustine/Rituximab for R/R DLBCL (Phase II)

R/R DLBCL
- ≥ 1 prior treatment
- ECOG PS 0-2
- Ineligible for SCT
- No grade IIIb FL, no transformed DLBCL, no CNS lymphoma, no prior allo HSCT, no auto HSCT within 100 days

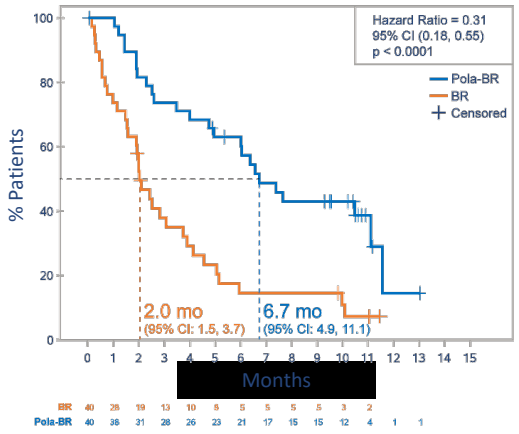
(N = 80)

→ **Polatuzumab Vedotin 1.8 mg/kg Day 1 (each cycle) + Bendamustine 90 mg/m² on Days 2, 3 (cycle 1), then Days 1, 2 (each cycle) + Rituximab 375 mg/m² Day 1 (each cycle)**
(n = 40)

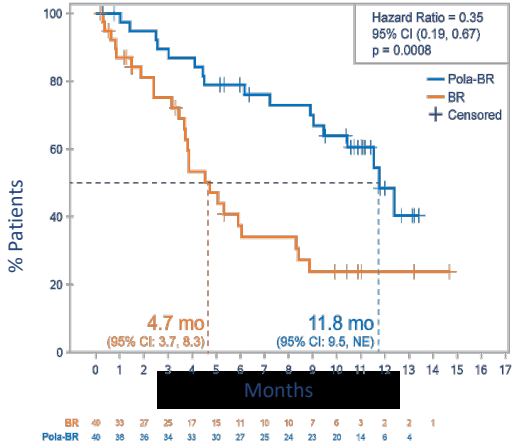
Six 21-day cycles

→ **Bendamustine 90 mg/m² on Days 2, 3 (cycle 1), then Days 1, 2 (each cycle) + Rituximab 375 mg/m² Day 1 (each cycle)**
(n = 40)

PFS



OS



- **CR by IRC 40% vs 15% (*P* = .012)**
- **PV addition associated with improved DoR, EFS, PFS, and OS**
- **OS benefit with PV + BR was consistent across subgroups**

Sehn LH, et al. J Clin Oncol. 2020;38(2):155-165. doi: 10.1200/JCO.19.00172

“Repurposing” checkpoint blockade in DLBCL

Checkpoint Blockade in B-cell NHL

- **Unlike the success in Hodgkin's lymphoma, *clinical trials with checkpoint blockade antibodies in relapsed/refractory B-cell NHL have been disappointed so far*:**
  - Despite malignant B-cells being surrounded by an "army" of T-cells
  - *Role of the immunosuppressive Tumor Microenvironment (TME).* TME is prognostic and potentially predictive of outcomes in DLBCL[1]

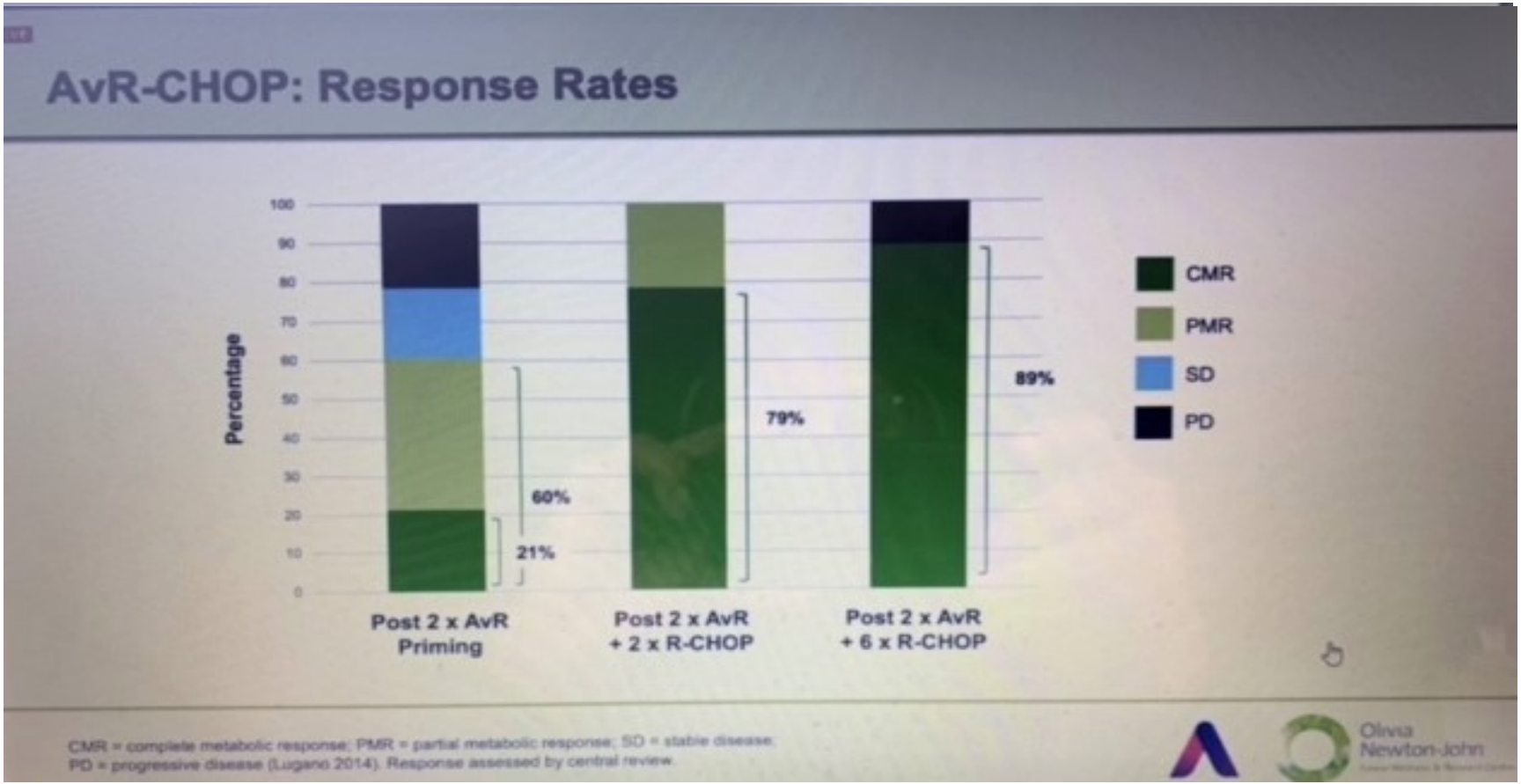
- **Perhaps frontline checkpoint inhibition, given when host immunity is relatively intact, might improve outcomes in DLBCL**
  - Indeed, it has been shown in the neoadjuvant setting for several solid malignancies…including responses in subtypes not known to be sensitive to checkpoint blockade

- **Avelumab (Av) is an anti-PDL1 antibody with ADCC activity & is synergistic with rituximab *in vitro.***

- **<u>Hypothesis</u>: Sequential treatment with Avelumab "priming" followed by R-CHOP might augment chemotherapy efficacy in DLBCL[2]**

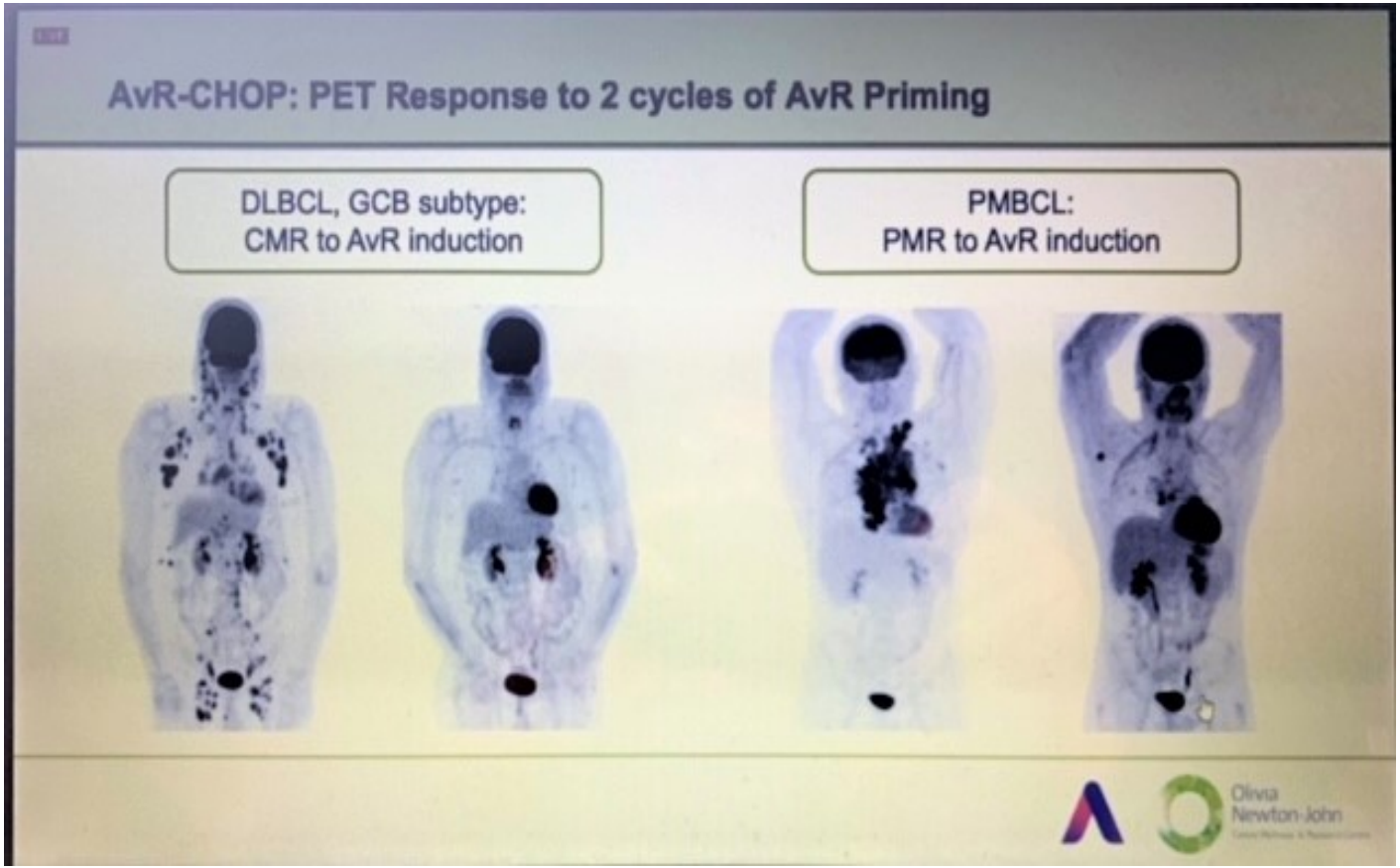
1. Ansell et al. JCO 2019; 2. Hawkes, E. et al, ASH 2020

AvR-CHOP: Single-arm Phase II Study



Hawkes, E. et al, ASH 2020

AvR-CHOP: Single-arm Phase II Study



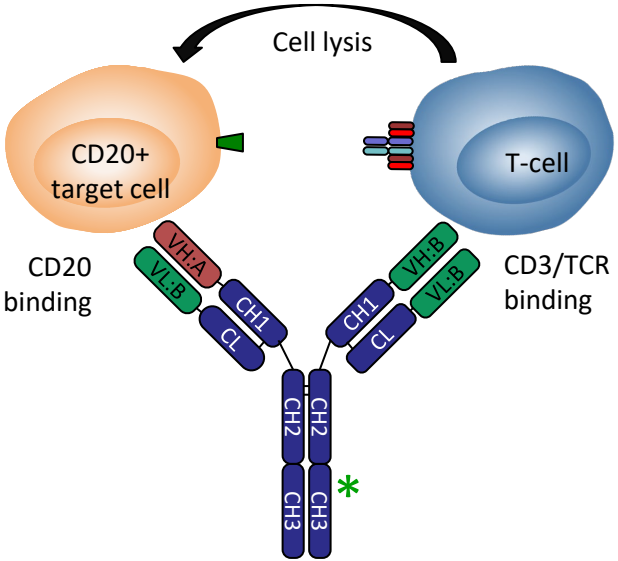
Hawkes, E. et al, ASH 2020

AvR-CHOP: Conclusions

- **ORR of 60% with a CR of 21% to AvR priming suggest potential synergy of avelumab + rituximab and superior efficacy of PDL1 inhibition in the frontline setting as compared to prior studies in the R/R setting**
- **Sequential AvR priming followed by R-CHOP and Av maintenance is feasible with a manageable toxicity profile and a high CR of 89%**
- **Immune-related AE were generally mild to moderate in severity; only one pt. discontinued therapy due to an irAR (gr3 hepatitis). No unexpected toxicity or delays to RCHOP occurred**
- **Further studies of sequential therapy using immune priming strategies prior to R-CHOP in DLBCL should be explored**

Hawkes, E. et al, ASH 2020

Mosunetuzumab (GO297) a Human anti-CD20 x anti-CD3 Monoclonal Bispecific Antibody



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

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.

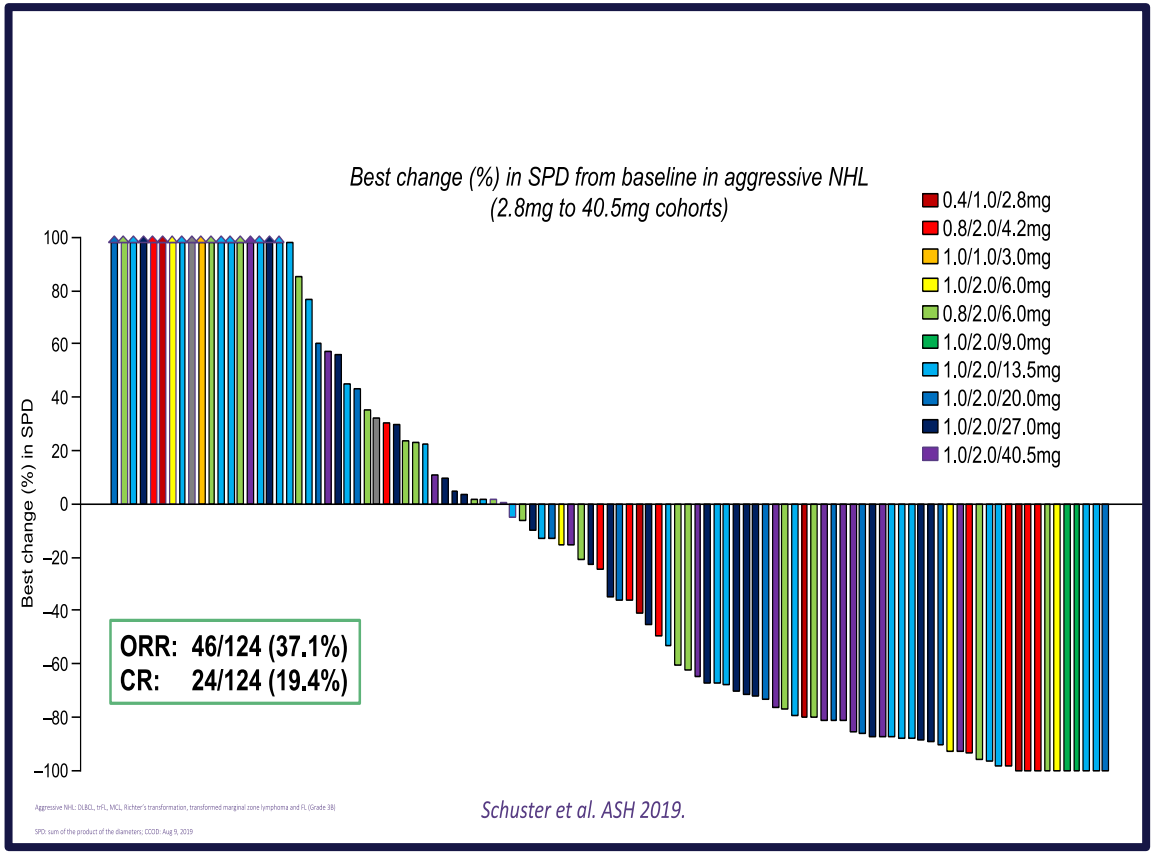
***CR*: discontinuation of treatment**

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



- **Greater efficacy observed with higher exposure to mosunetuzumab**
  - Measured by occupancy of CD20 receptors
- **Patients achieving CR with continuing remission up to 16 m off treatment: n = 17 (70.8%)**
  - ≥ 16 mos after treatment cessation

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

Response Rates Among Patients With Prior CAR T-Cell Therapy and Retreated Patients

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

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

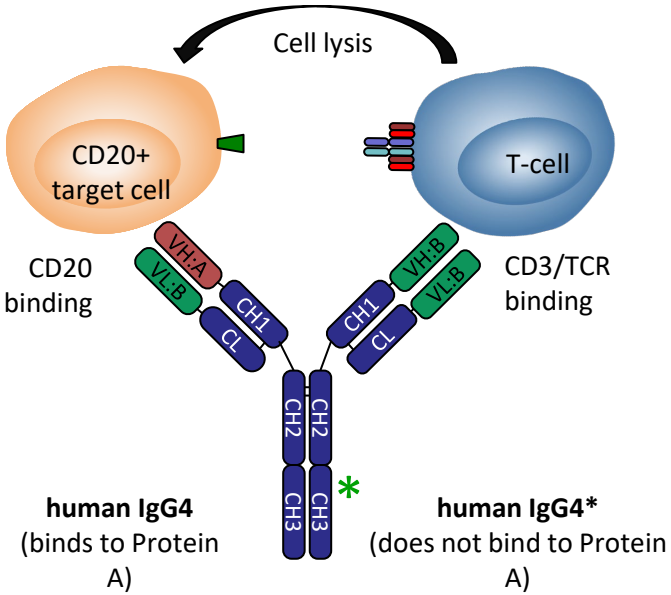
- No CRS events occurred during retreatment

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

Mosunetuzumab in previously untreated elderly patients with DLBCL (ASH 2020)

- 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?)

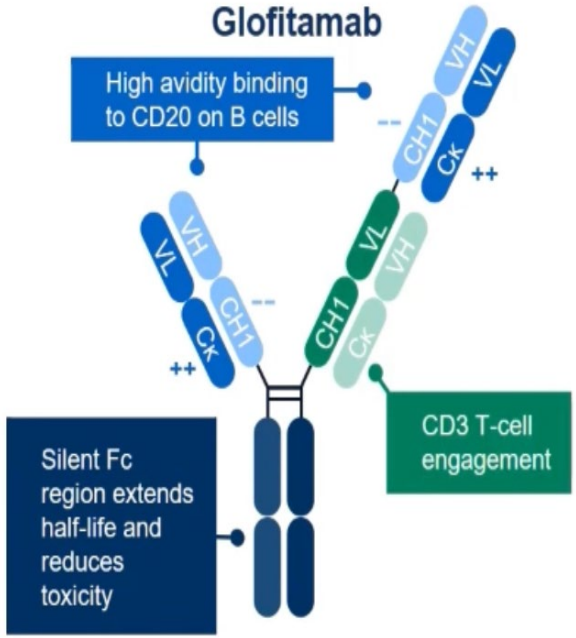
Odronextamab (REGN1979): Human anti-CD20 x anti-CD3 Monoclonal Bispecific Antibody



- **Bispecific, hinge-stabilized mAb based on an IgG4 isotype with reduced effector function**
- **Monovalent for each target**
- **Amino acid substitution introduces asymmetric protein A binding allowing selective isolation and purification**

Bannerji et al. ASH Meeting Abstracts 2017

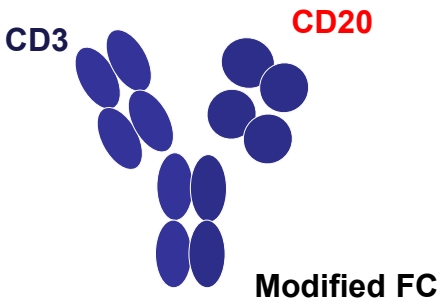
Glofitamab



- **Glofitamab is a 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**

Epcoritamab (formerly GEN3013)

- **Duobody:**
  - Fully humanized IgG1 antibody
  - IgG1 Fc modified to minimize Fc-dependent effector function



- Epcoritamab investigational, **subcutaneously administered** bispecific antibody targeting CD3 x CD20[2]
  - Binds CD3-positive T-cells to malignant CD20-positive B-cells to induce T-cell activation and T-cell–mediated killing of target B-cells

1. Skrabek. Curr Oncol. 2019;26:253. 2. Lugtenburg. ASH 2019. Abstract 758. 3. NCT03625037. 4. Hutchings. ASCO 2020. Abstr 8009.

Bi-Specific Antibodies in B-cell lymphomas: Efficacy

Ab type	CD20/CD3			
	Glofitamab	Mosunetuzumab	Odronextamab	Epcoritamab
N	98	131	136	58
Histology	FL,DLBCL,TFL other	aNHL: 124 iNHL: 67	DLBCL, FL, WM, MCL, MZL	DLBCL, FL, MCL, MZL, SLL
Prior Therapies	3 (1-13)	3 (1-14)	3 (1-11)	3 (1-18)
ORR	aNHL: 60.7% iNHL: 66.7%	aNHL: 37.1% iNHL: 62.7%	DLBCL (> 80 mg): 55% FL (> 5mg): 90%	aNHL > 48 mg sc: 91% iNHL: 90%
	aNHL: 53.6% DLBCL: 54.2%	aNHL: 19% iNHL: 43%	DLBCL: 55% FL: 70%	aNHL: 55% iNHL:n50%

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

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

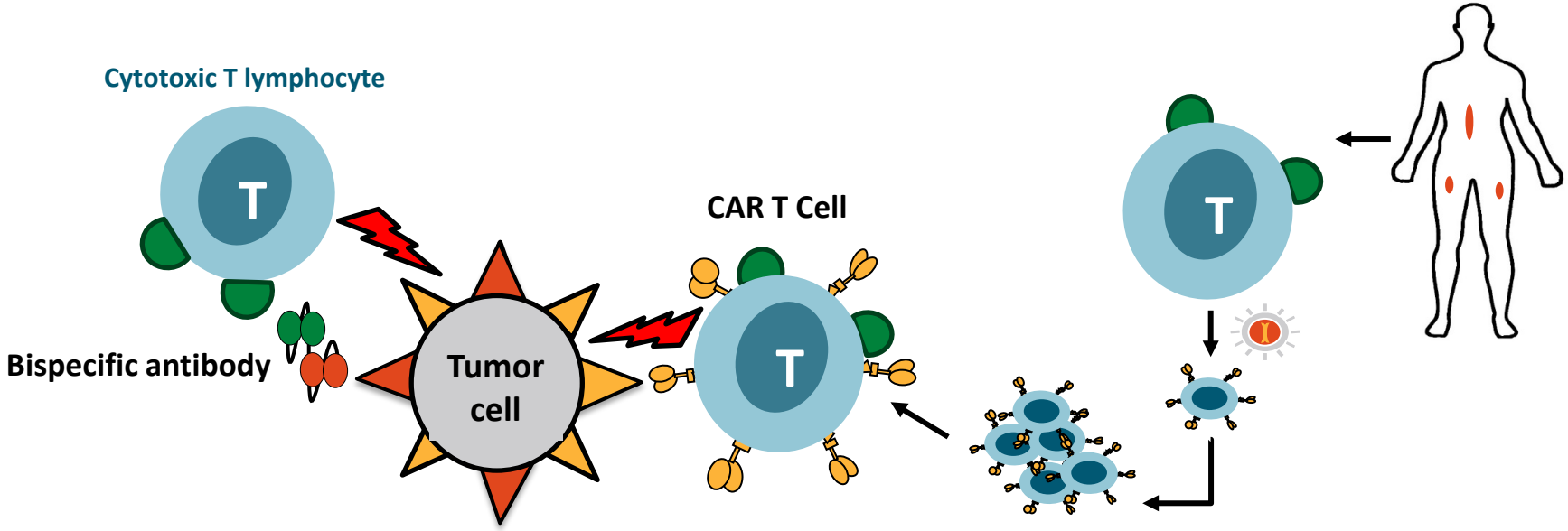
Bi-Specific ABs currently studied in DLBCL: Safety

Antibody	CD20/CD3				CD19/CD3
	Glofitamab	Mosunetuzumab	Odronextamab	Epcoritamab	Blinatumomab
N	64 (> 600 ug)	131	136	58	76
CRS any CRS ≥3	63.5% 3.8%	28.9% 1.1%	61% 7.3%	59% 0	2% 2%
NT any NT ≥3	43.3% NR	49% 1.1%	NR 3.6%%	6.9% 3.4%	56% 24%

CRS, cytokine release syndrome; NT, neurotoxicity;

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

Bispecific Antibodies vs CAR T-Cell Therapy



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

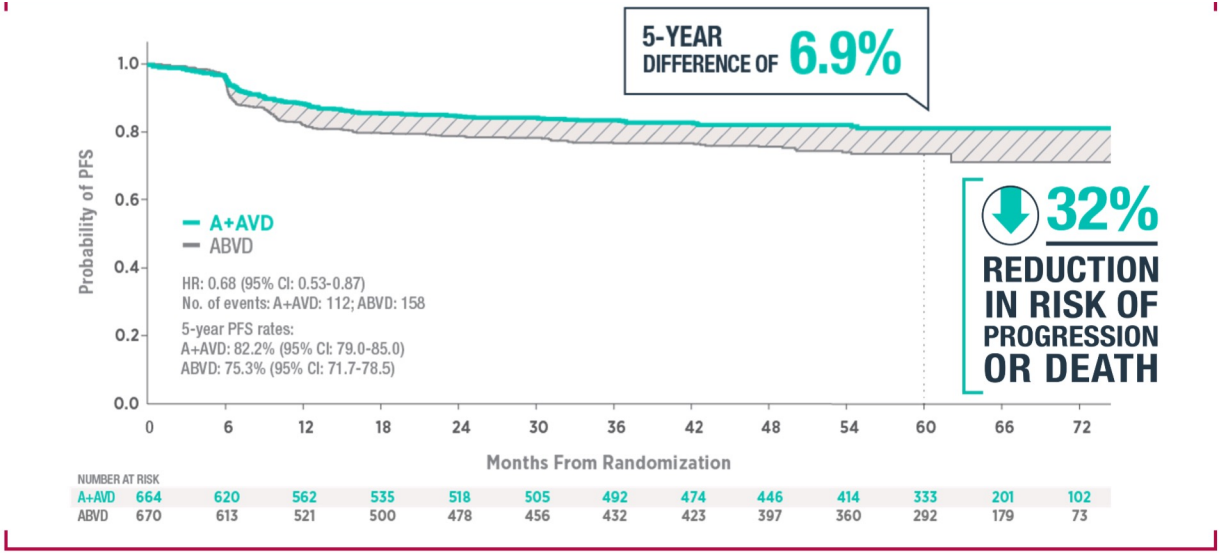
Hodgkin's Disease : Novel Approaches

- The management of classic Hodgkin lymphoma (HL) has changed significantly since the approval of brentuximab vedotin (BV) and the checkpoint inhibitors nivolumab and pembrolizumab.

- **Frontline setting**
  - BV + AVD has been incorporated as frontline treatment for patients with stage III/IV disease (Echelon-1 Trial)

- **First relapse:**
  - Second-line therapy ("salvage") followed by consolidation with autologous stem cell transplant (ASCT) remains the standard of care
  - BV is now routinely incorporated into salvage therapy
  - Studies are evaluating checkpoint inhibitors in the salvage setting as well.

A + AVD: PFS at 5 Years



Hodgkin's Disease: Novel Approaches

- **Second relapse/refractory disease**
  - **Progression after ASCT remains a challenge.**
  - **Checkpoint inhibitors or BV provide prolonged disease control……but patients will eventually progress**

  - **Combinations of BV + checkpoint inhibitors:**
    - **Phase I/II trial of nivolumab plus BV in relapsed or refractory HL: ORR of 82%: CR: 61%[1]**

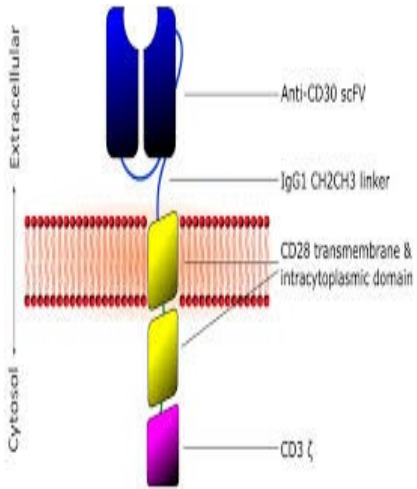
    - **Phase I trial of the triple combination of ipilimumab, nivolumab, and BV: ORR: 95% and CR : 79% in 19 evaluable patients who were treated with at least three cycles[2]**

1. *Herrera AF. et al. Blood. 2018;131:1183-1194*
2. *Diefenbach C. et al. a Blood. 2018;132:679.*

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**

CD30-directed CAR T-cell Therapy for Hodgkin's Disease



- **Grover et al[1]**
  - 18 patients, 16 of whom had HL, with a median of 8 prior therapies.
  - Most patients received lymphodepletion with bendamustine/ fludarabine.
  - Fourteen patients had evidence of disease at the time of CAR–T cell infusion
  - ORR: 50%; CR: 43%.

- **Ramos et al[2]**
  - 37 patients with relapsed/refractory HL
  - Lymphodepletion with fludarabine/cyclophosphamide.
  - ORR: 62, CRR: 51% .
  - 1 year PFS: 36%, longer with Flu lymphodepletion
  - CRS:24%, all grade 1. No neurotoxicity. No Toci/steroids

1. *Grover NS. et al. Blood. 2018;132:681.*
2. *Ramos CA. et al. Blood. 2020.*

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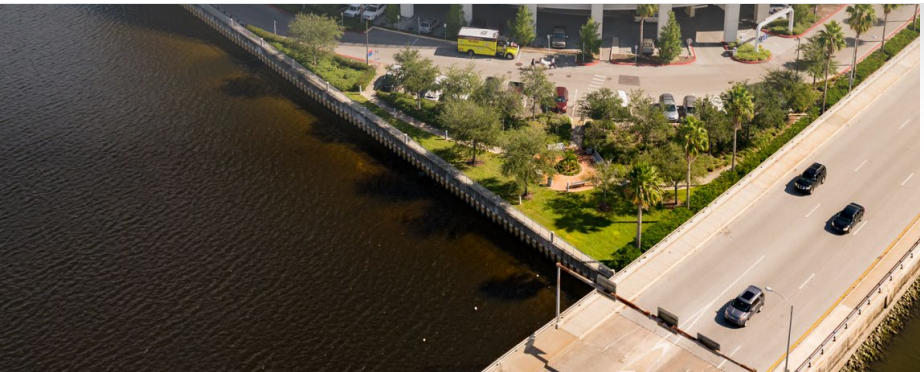
THANK YOU !



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