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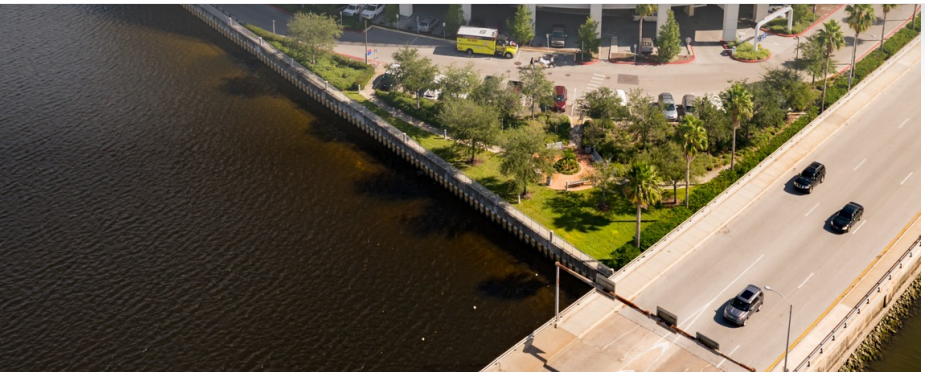
"B cell lymphomas: Updates and Future Directions"



Eduardo M. Sotomayor, MD

Director, TGH Cancer Institute

Professor, Morsani College of Medicine

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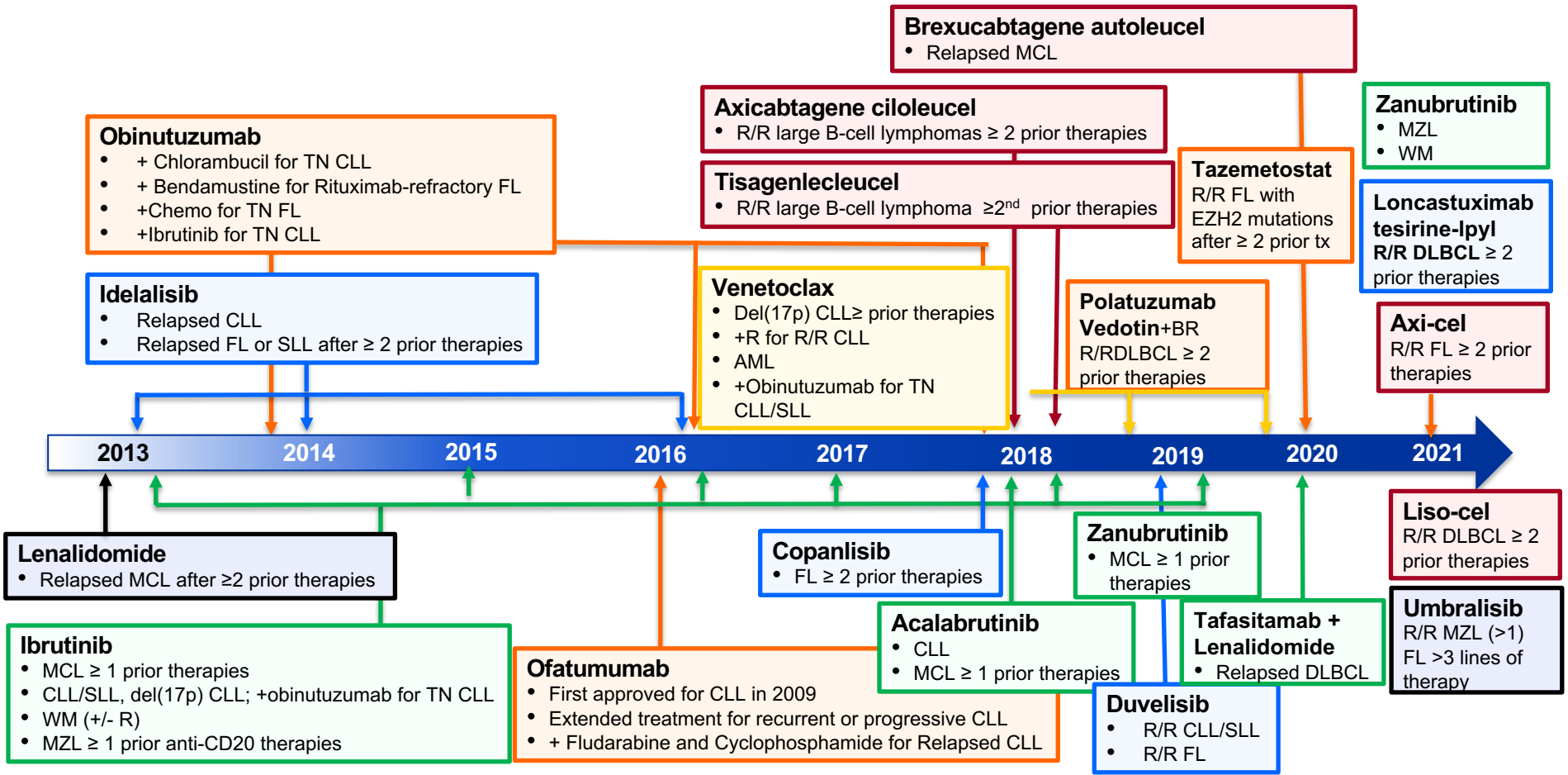
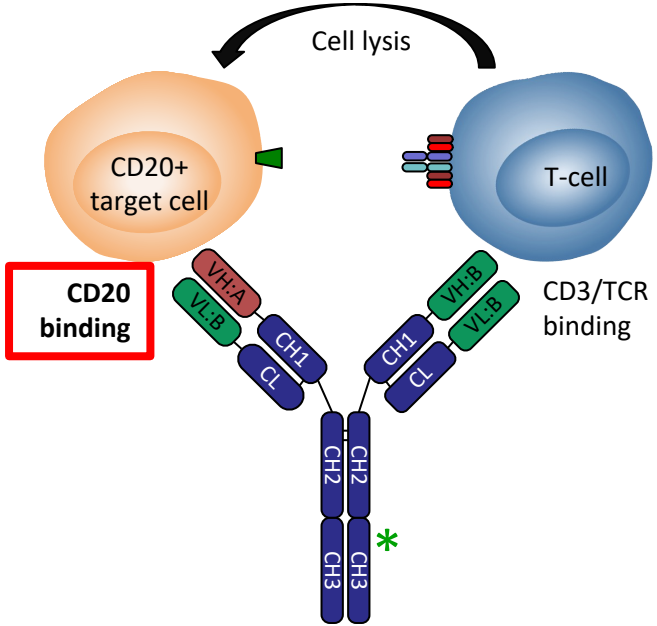
2013-2021: New Agents for B-Cell Malignancies



ASH 2021: Bispecific Antibodies….a game changer?



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

New Options:Targeting CD19, CD79b and CD20 (again..)

- **CD19 is an enticing target for novel approaches:**
  - **CD19 CAR T-cells (Several B-cell malignancies)**
  - **Tafasitamab, anti-CD19 antibody (+/- Lenalidomide) (R/R DLBCL)**
  - **Loncastuximab Tesirine (Anti-CD19 Antibody-Drug Conjugate) (R/R DLBCL)**

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

- **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)….**

Targeting CD19 in B-cell lymphomas: CAR T-cells Successes, Failures and Opportunities

- **Autologous 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) for DLBCL**
    - **One platform approved for MCL (Brexucabtagene autoleucel)**
    - **One platform approved for follicular lymphomas (Axi-cel)**
  - ***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**

- **Moving CD19 CAR T cells into the 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: Will CD19 CAR T-cell Replace 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.

ASH 2021: Real World Data with CAR T-cells

	Author	Study	n	ORR (%)	CR (%)	Toxicities
US Lymphoma CAR T Consortium (Brexu-cel)	Y. Wang	Multicenter, retrospective	107 leuk. 93 infused 46% TP53 7% CNS 82% prior BTK 73% ineligible for ZUMA-2	86% TP53:82%	64% TP53: 50%	CRS: 88% (8% gr≥ 3) ICAN 58% (33% gr ≥ 3) 26% ICU admission Use of toci and steroids more frequent
12 US Academic Centers (Brexu-cel)	J. Romancick	Multicenter, retrospective	55 leuk 52 infused 100% prior BTK (56% failures) 13% CNS	88%	69%	CRS: 84% (10% gr≥ 3) ICAN 57% (31% gr ≥ 3) 4/7 pts with CNS involvement developed NT
European Sites (Brexu-cel)	G. Iacoboni	7 European sites, retrospective	28 leuk 19 infused 32% prior ASCT 15% bridging therapy after apheresis 13% CNS	81	67	CRS: 89% (5% gr> 2) ICAN 63% (26% gr >2) 11% ICU admission

Polatuzumab Vedotin

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

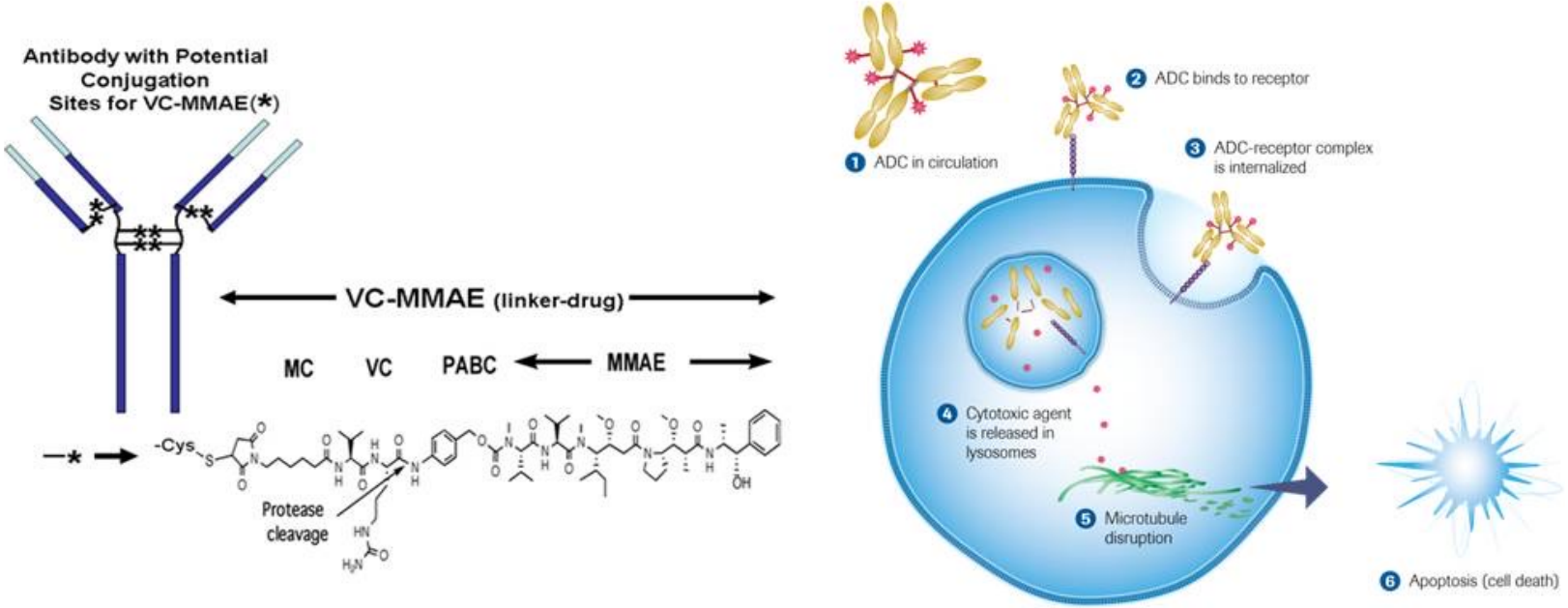


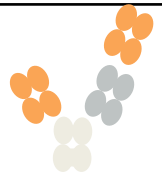
Figure from: Morschhauser, et al. J Clin Oncol. 2014;32(15_suppl):8519.
Doman, et al. Blood. 2009;114:2721-2729. Polson, et al. Blood. 2007;110:616-623. Sehn, et al. ASH 2017;Abstract 2821.

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

- **Polatuzumab vedotin-piiq is a CD79b ADC**
- **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**
- **Similar rates of adverse events/drug dose reductions or drug discontinuation**

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

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**

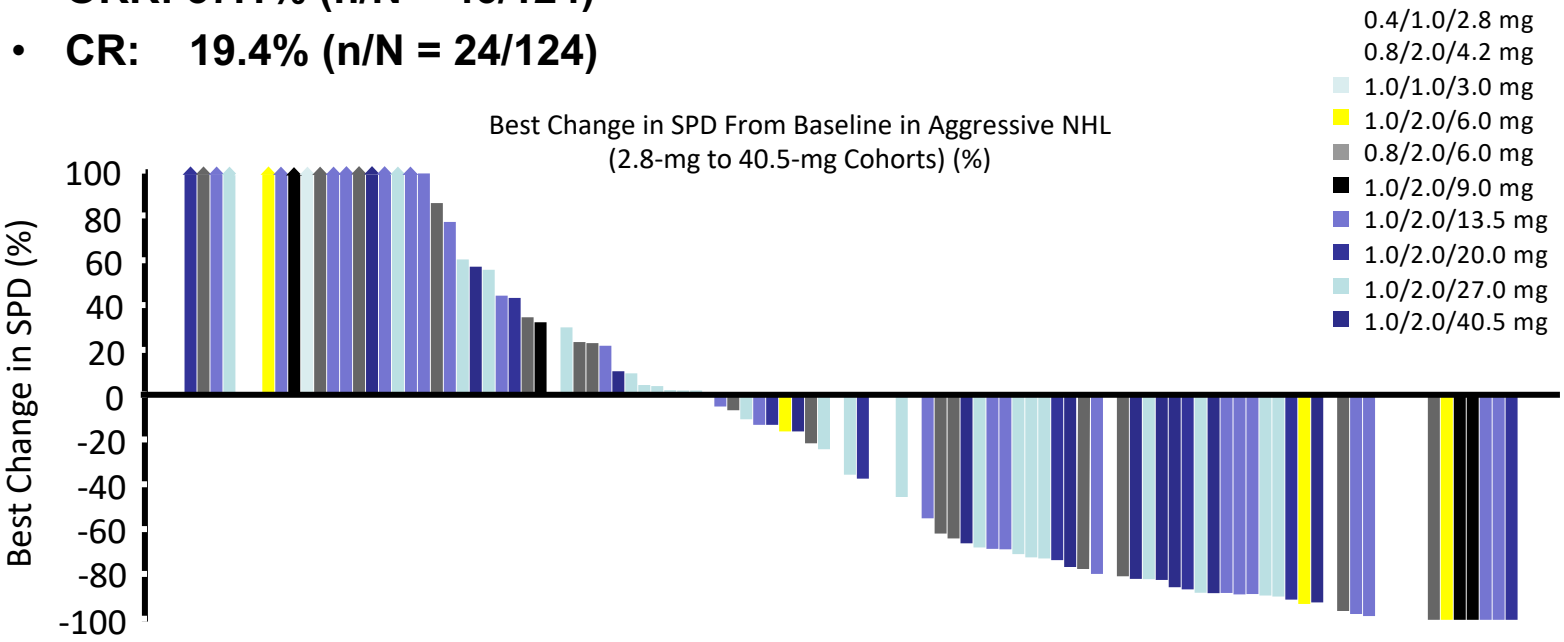
***PR or SD*: treatment continued for ≤ 17 cycles**

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

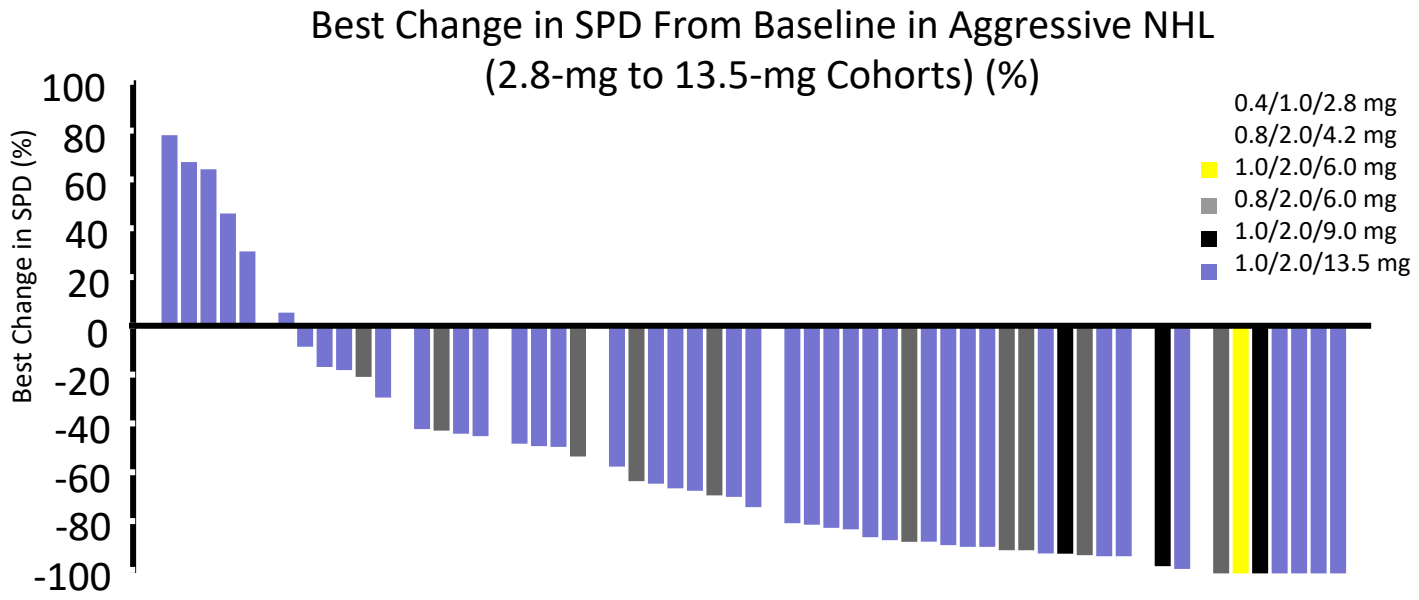
- **ORR: 37.1% (n/N = 46/124)**
- **CR: 19.4% (n/N = 24/124)**



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

Mosunetuzumab-Dose Escalation: Responses in Patients With Indolent NHL

- **ORR: 62.7% (42/67)**
- **CR: 43.3% (29/67)**



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

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

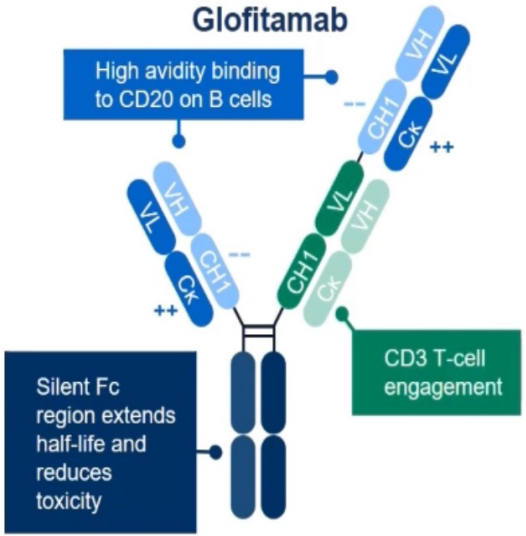
Response, n (%)	Patients With Prior CAR T-Cell Therapy
Total population with prior CAR T-cell therapy (n = 18) ▪ ORR ▪ CR	 7 (38.9) 4 (22.2)
DLBCL (n = 9) ▪ ORR ▪ CR	 2 (22.2) 2 (22.2)
trFL (n = 5) ▪ ORR ▪ CR	 1 (20) 0
FL (n = 4) ▪ ORR ▪ CR	 4 (100) 2 (50)

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.

ASH 2021 “Game changer”: Bispecific antibodies



R/R Mantle Cell Lymphoma

Glofitamab+ Obinutuzumab

-ORR: 81% CMR: 67%

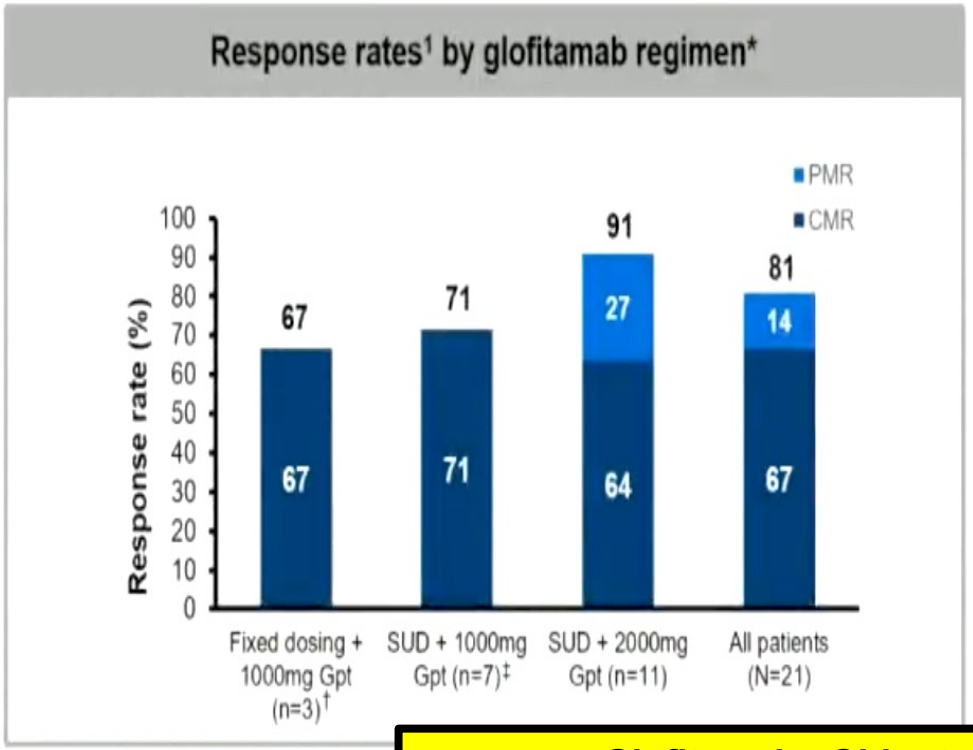
R/R Follicular lymphoma

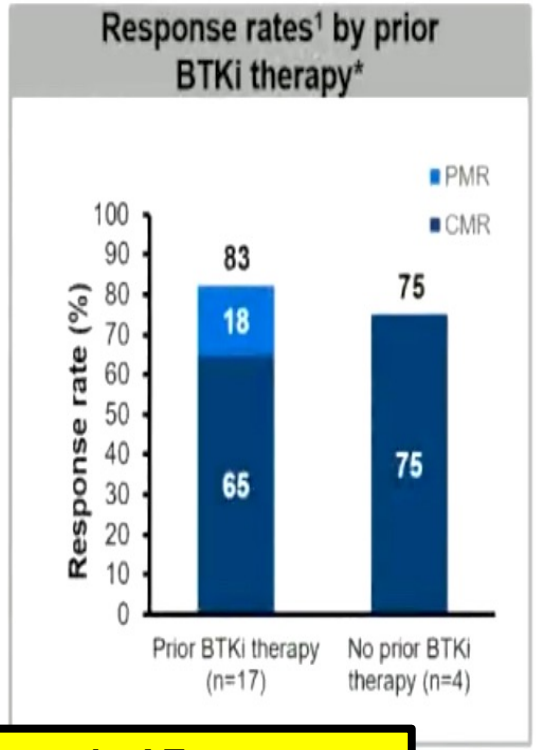
Glofitamab: ORR: 81% CMR: 70%

Glofitamab+Obinutuzumab: ORR:100%,CMR: 74%

- **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**

Glofitamab in R/R MCL: Clinical Activity



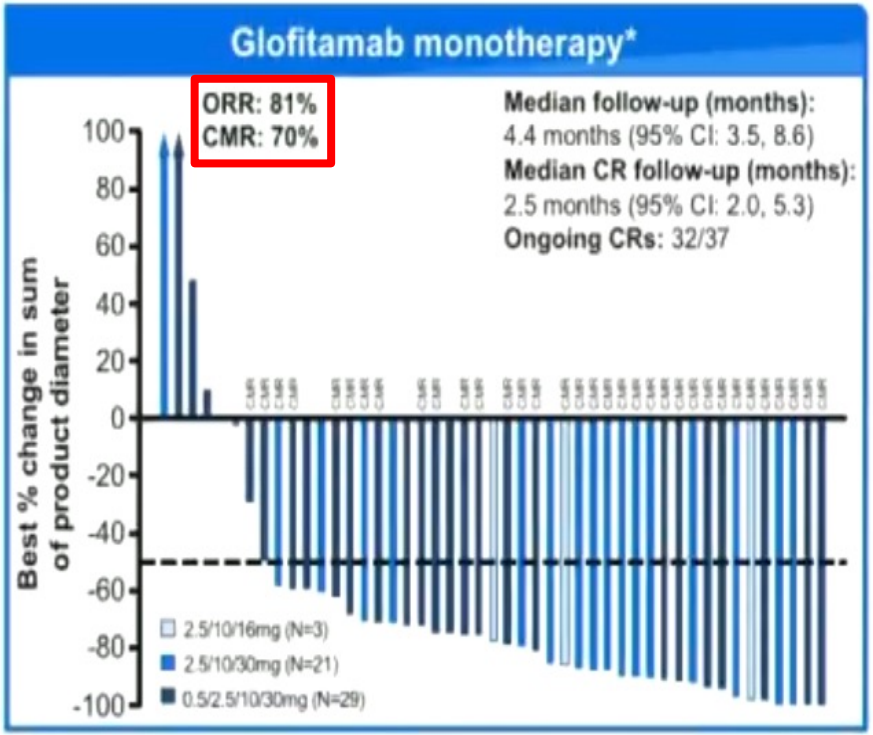


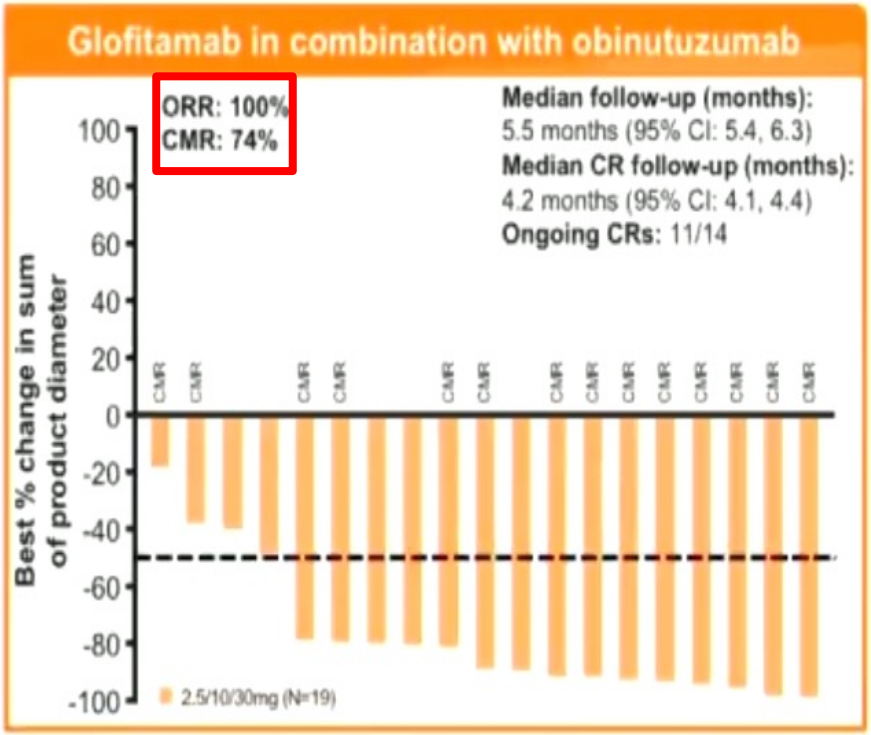
Glofitamab+ Obinutuzumab: AEs

-59% G1-2 CRS.
-1 pt G4 CRS+ rapid PD
-1pt. G2 ICANS

Phillips et al ASH 2021. Abstr 130

Glofitamab monotherapy and w/Obinutuzumab for R/R Follicular Lymphoma





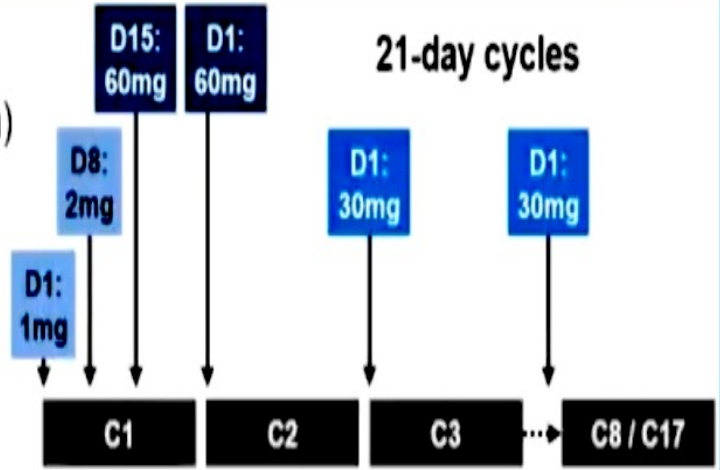
Mosunetuzumab monotherapy for R/R FL with > 2 lines of therapy

Key inclusion criteria

- FL (Grade 1–3a)
- ECOG PS 0–1
- ≥2 prior regimens, including
  - ≥1 anti-CD20 Ab
  - ≥1 alkylating agent

Mosunetuzumab administration

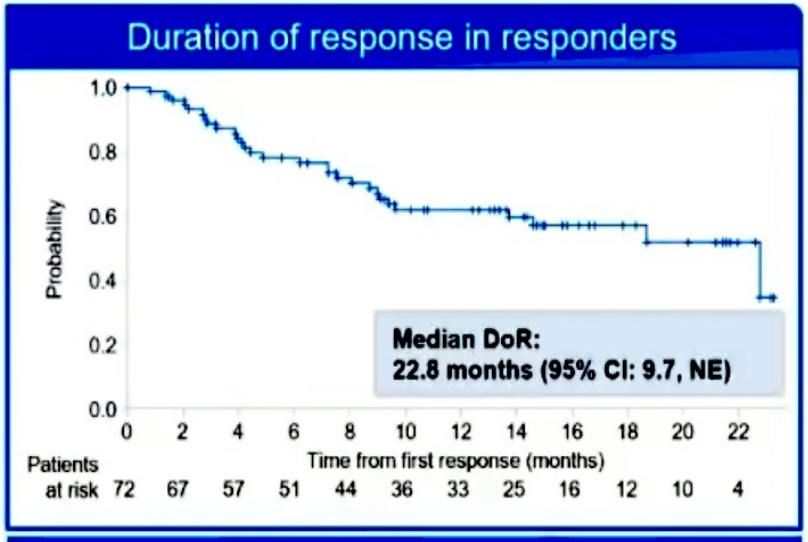
- Q3W intravenous administration
- C1 step-up dosing (CRS mitigation)
- **Fixed-duration treatment**
  - 8 cycles if CR after C8
  - 17 cycles if PR/SD after C8
- **No mandatory hospitalization**



Budde et al ASH 2021. Abstr 127

Mosunetuzumab monotherapy for R/R FL with > 2 lines of therapy

Efficacy endpoint[1]	IRF N (%) [95% CI]	Investigator N (%) [95% CI]
CR	**54 (60%)** [49%, 70%]	54 (60%) [49%, 70%]
ORR	**72 (80%)** [70%, 88%]	70 (78%) [68%, 86%]



Median time to first response, mo (range)	1.4 (1.1, 8.9)
12-month event-free rate, % (95% CI)	62% (50%, 74%)
18-month event-free rate, % (95% CI)	57% (44%, 70%)

DoRC, duration of response in complete responders; mo, month; NE, not estimable

Budde et al ASH 2021. Abstr 127

Future Directions in B-cell NHL Therapy

I. How to better combine these novel therapies

- Duplets versus triplets; safety and “financial toxicity”
- Finite versus infinite treatment (increasing role of MRD assessment)

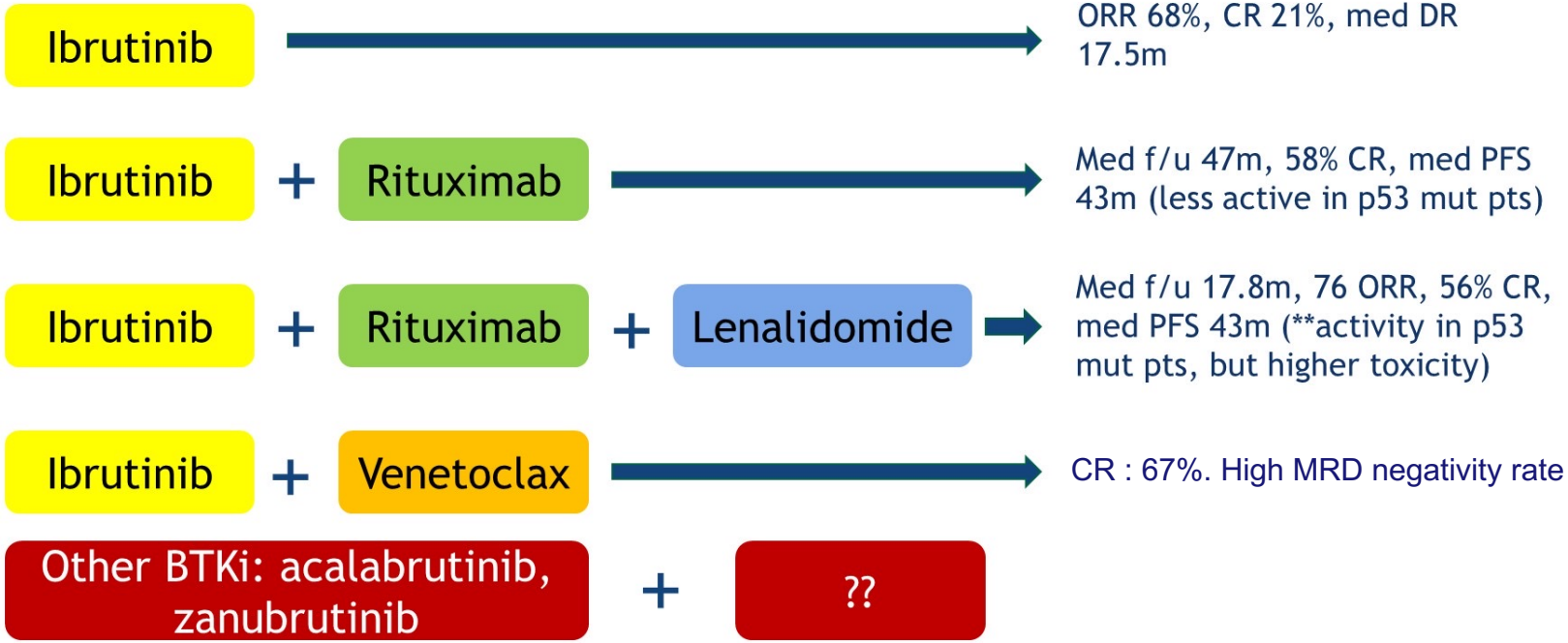
II. Can these novel agents be moved to the frontline setting?

- With chemotherapy: POLARIX Study (DLBCL), SHINE, WINDOW-1 (MCL)
- “Chemo-free” : Targeted agents alone or in combination, Bispecific antibodies

III. Resistance (innate, acquired, TME-mediated) to targeted therapy and/or immunotherapy

-BTK resistance: Pirtobrutinib

Building on Ibrutinib in R/R MCL



Wang New Engl J Med. 2013 Aug 8;369(6):507-16; Jain P Br J Haematol. 2018 Aug;182(3):404-411; Jerkeman Lancet Haematol. 2018 Mar;5(3):e109-e116

Sonali Smith at ASCO 2020 Virtual Education Program

R/R MCL: BTK Plus…

- **Completed trials**
  - AIM: **ibrutinib** + venetoclax (activity in p53 MCL)
  - OAsIs: **ibrutinib** + obinutuzumab + venetoclax (activity in p53 MCL)
  - Venetoclax+ lenalidomide+ rituximab (less active in p53 MCL)

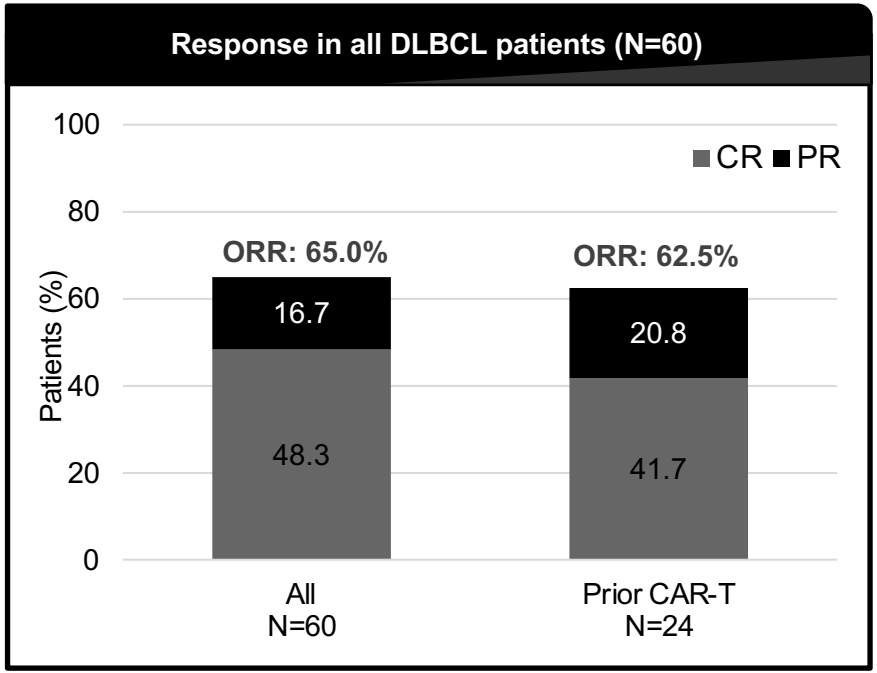
- **Ongoing trials (partial list):**
  - Ibrutinib + ixazomib (phase II)
  - Ibrutinib + copanlisib (phase II)
  - Ibrutinib + palbociclib (phase II)
  - SYMPATICO: Ibrutinib vs ibrutinib + Venetoclax (phase III)

Combinations of Targeted Therapies in Frontline MCL (ASH 2021)

Regimen	Author	Phase	Line of Therapy	ORR (%)	CR (%)	Toxicities
Zanubrutinib, obinutuzumab, venetoclax (in *TP53* mutated)	A. Kumar	II	Frontline	92	80	17% G3 infusion reaction, 8% G3 neutropenia, 33% G1 nausea, 17% G1 LFTs
Acalabrutinib, rituximab, venetoclax	M. Wang	Ib	Frontline	100	90%	62% diarrhea, 52% headache, 48% fatigue. G3-4: 24% neutropenia, 10% pneumonia, 19% COVID-19

Mosunetuzumab + Polatuzumab for R/R DLBCL

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

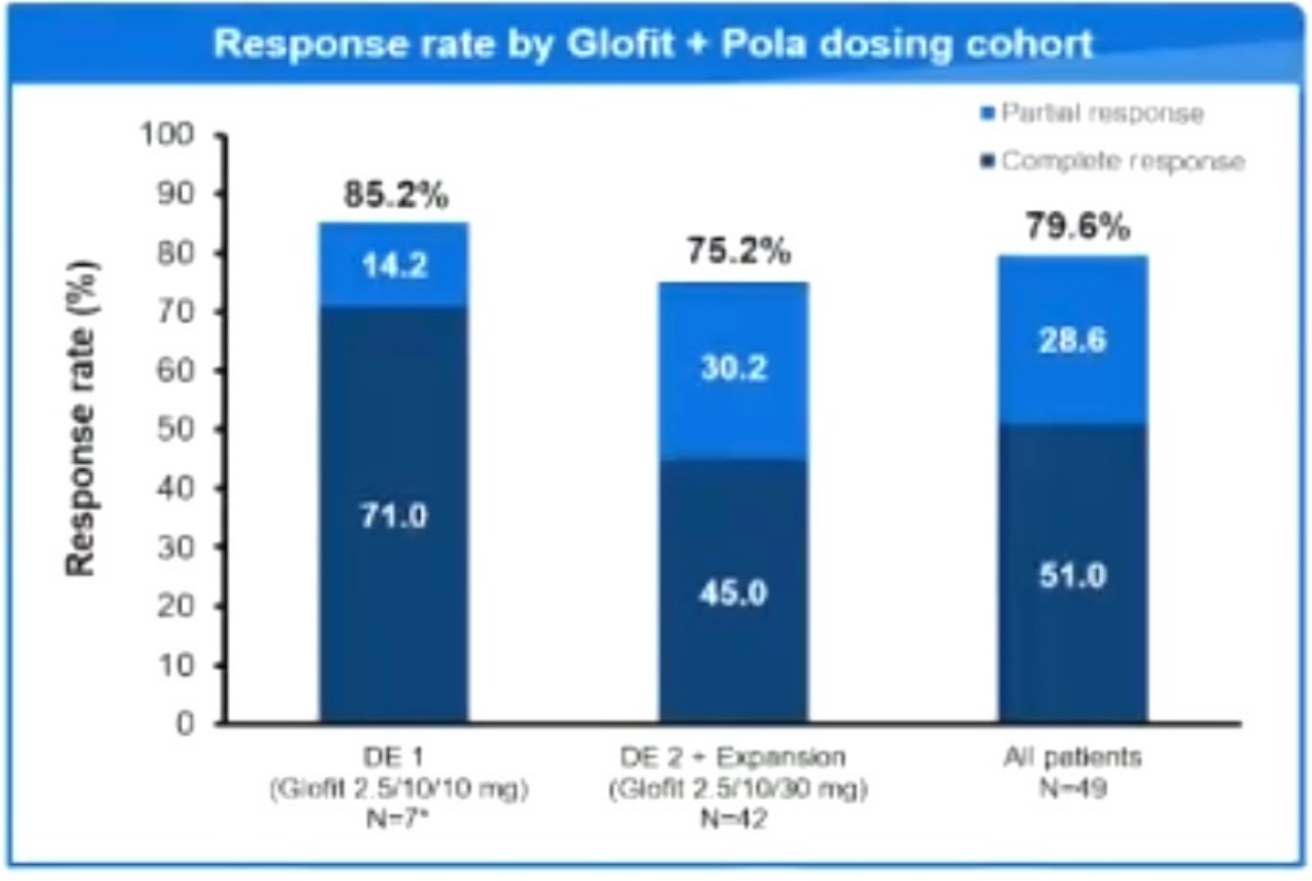


- **Median PFS: 8.9 months (95% CI: 3.5, NE)***

- **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

Glofitamab + Polatuzumab in R/R DLBCL



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?)

Future Directions in B-cell NHL Therapy

I. We are "victims" of our own successes…. A good challenge to have

- How to better combine these novel therapies…duplets versus triplets; safety and "financial toxicity"
- Finite versus infinite treatment (increasing role of MRD assessment)

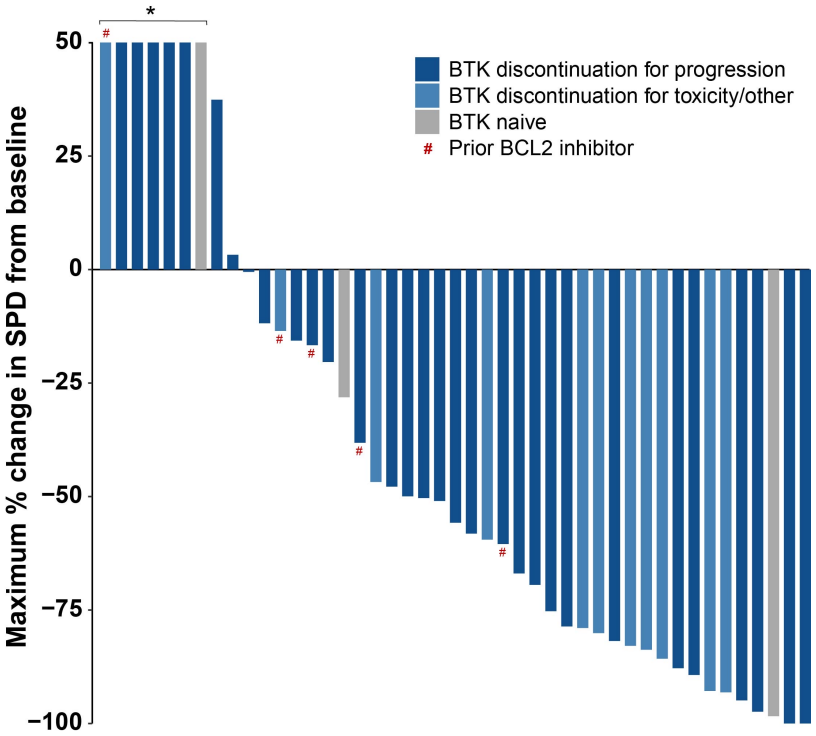
II. Can these novel agents be moved to the frontline setting?

- With chemotherapy: **POLARIX Study (DLBCL),** SHINE, WINDOW-1 (MCL)
- "Chemo-free" : **Bispecific antibodies,** checkpoint blockade antibodies, targeted agents alone or in combination

III. Resistance (innate, acquired, TME-mediated) to targeted therapy and/or immunotherapy

-BTK resistance : Pirtobrutinib (LOXO-305)

Pirtobrutinib in R/R MCL



All MCL Patients	n=56
Overall Response Rate, % (95% CI)	**52% (38-65)**
Best Response	
CR, n (%)	**14 (25)**
PR, n (%)	15 (27)
SD, n (%)	10 (18)
BTK Pre-Treated MCL Patients	**n=52**
Overall Response Rate, % (95% CI)	**52% (38-66)**
Best Response	
CR, n (%)	**13 (25)**
PR, n (%)	14 (27)
SD, n (%)	9 (17)

Opportunities in a "crowded" Therapeutic Landscape: Good Science + Unmet Needs

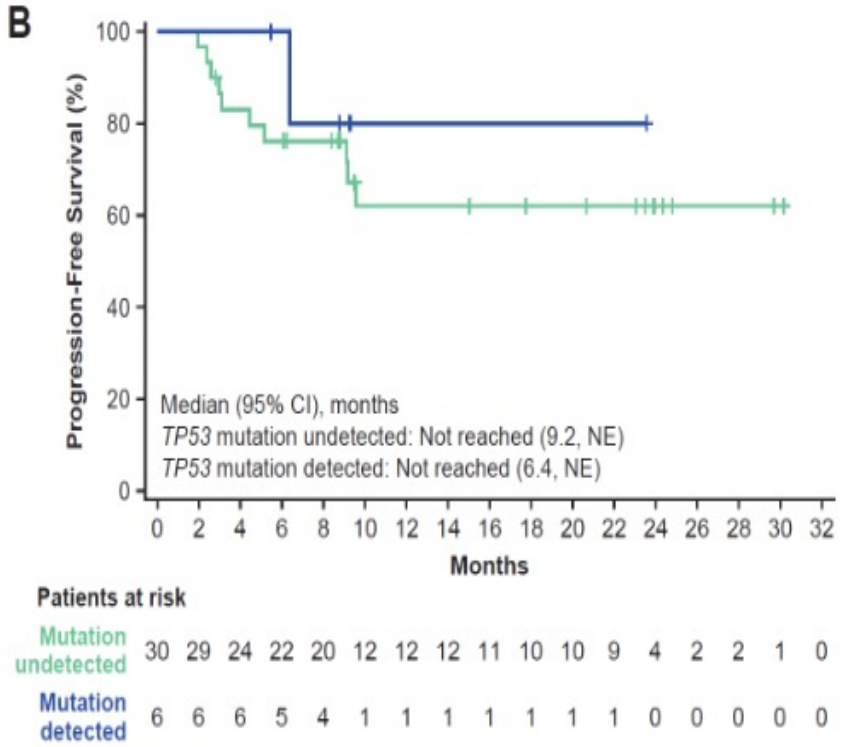
I. **Science**:
- **Allo CAR T-cells**
- Beyond T-cell immunotherapies… **Harnessing Innate Immunity**
  - Genetically engineered NK cells
  - Genetically engineered Macrophages

II. **Unmet Needs in Non-Hodgkin's lymphomas**
- *Difficult to treat lymphomas:*
  - Double/triple hit large B cell lymphomas
  - POD24 low grade lymphomas
  - MCL with p53 abnormalities
  - Transformed lymphomas

Efficacy of CAR T-cells in TP53 altered MCL

- ZUMA-2 two-year PFS for patients with *TP53* mutated MCL: 80%

- **Real world data: 31 pts (46%) with *TP53* alteration.**
- **-ORR 82%, CR 50%**
- -overall 3-month PFS: 80.6%
- -overall 6-month OS: 82.1%



2022: Unmet Needs in NHL

I. Emerging Needs in Non-Hodgkin's lymphomas

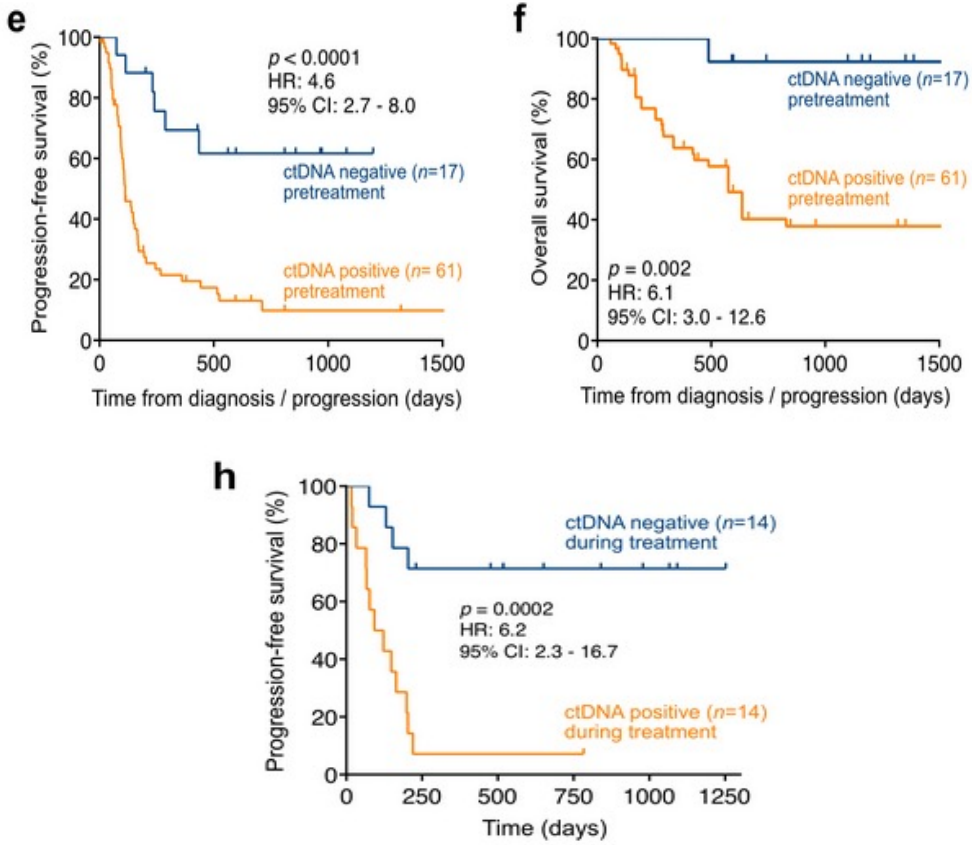
- *Innate or acquired resistance to novel agents*
  - BTK resistance (MCL, CLL, WM, MZL)
  - CD19 CAR T-cells (DLBCL, MCL, FL)
  - Double refractory (FL, MCL)….***triple refractory***

II. "Wide open" lymphomas waiting for scientific discoveries and novel therapies

- T-cell/NK malignancies
- Viral-associated lymphomas
- CNS lymphomas

CNS Lymphomas: Plasma ctDNA levels and clinical outcomes

- **Novel deep sequencing and phased variant enrichment and detection sequencing method applied to samples from patients with CNS lymphoma.**
- **Plasma ctDNA levels correlated with tumor volume. Patients with plasma ctDNA+ at baseline had worse PFS and OS.**
- **-Those with ctDNA+ during treatment had worse PFS.**



Scherer et al. ASH Plenary Session 2021.

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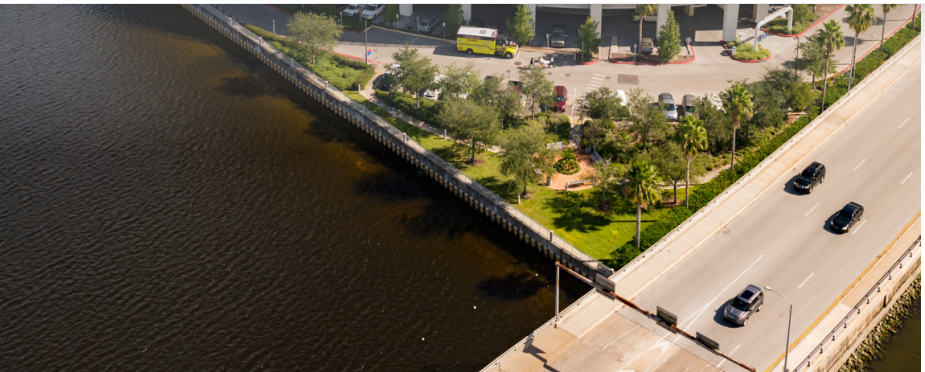
THANK YOU !



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