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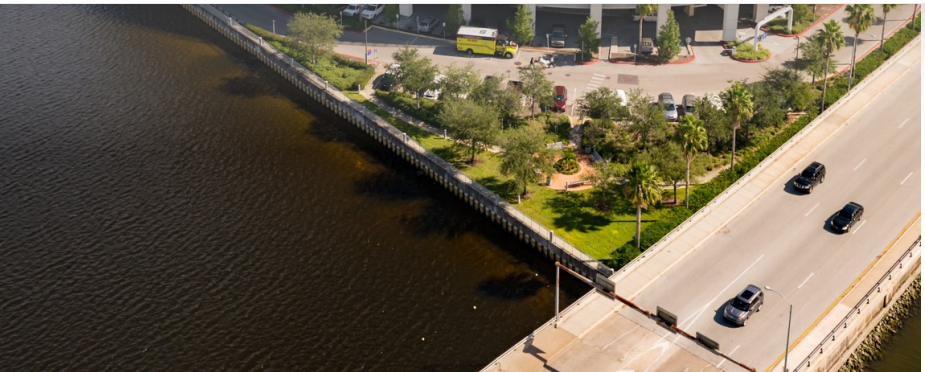
"Modern Challenges and New Options for B-cell NHL"



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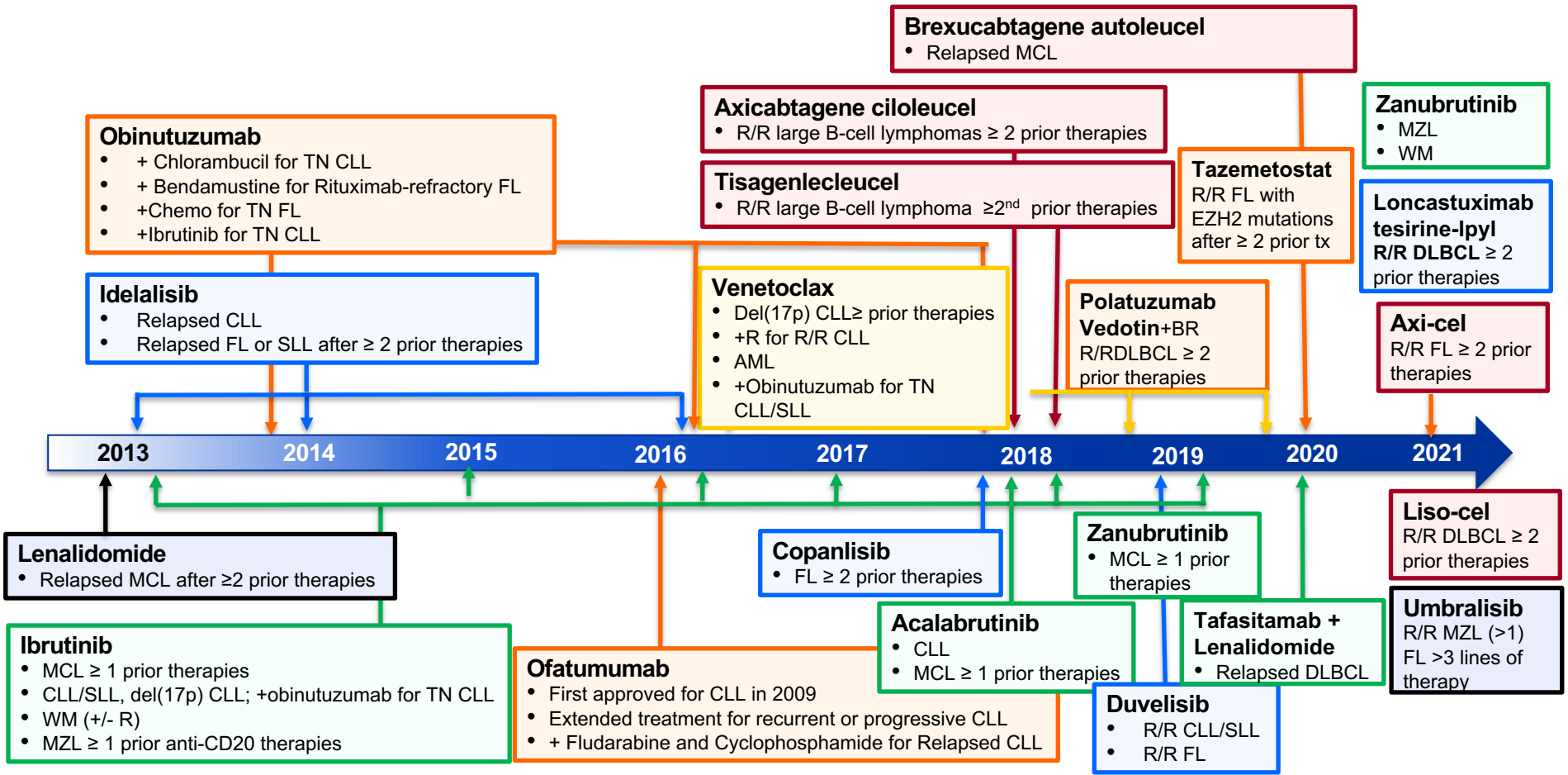
B-cell NHL in the Modern Era:
A rapidly changing and….challenging Landscape

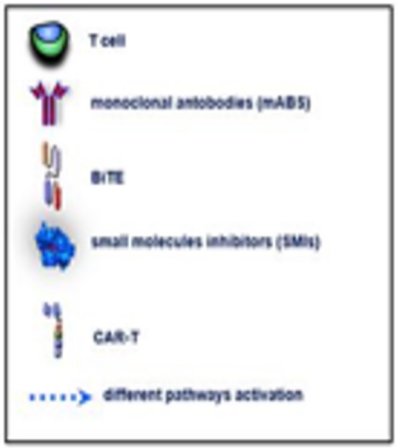
Targeted Therapy

Immunotherapy

Timeline of Newer Agents for B-Cell Malignancies



B-cell NHL: Targeted therapy and Immunotherapy



Rituximab
Ofatumumab
Obinutuzumab
Polatuzumab vedotin
Loncastuximab tesirine
Tafasitamab
Ublituximab

Tazemetostat

Copanlisib
Duvelisib
Idelalisib
Umbralisib

Lenalidomide
Pomalidomide

Ibrutinib
Acalabrutinib
Zanubrutinib
Pirtobrutinib

Venetoclax

Axi-cel / Liso-cel
Tisagenlecleucel
Brexucabtagene autoleucel

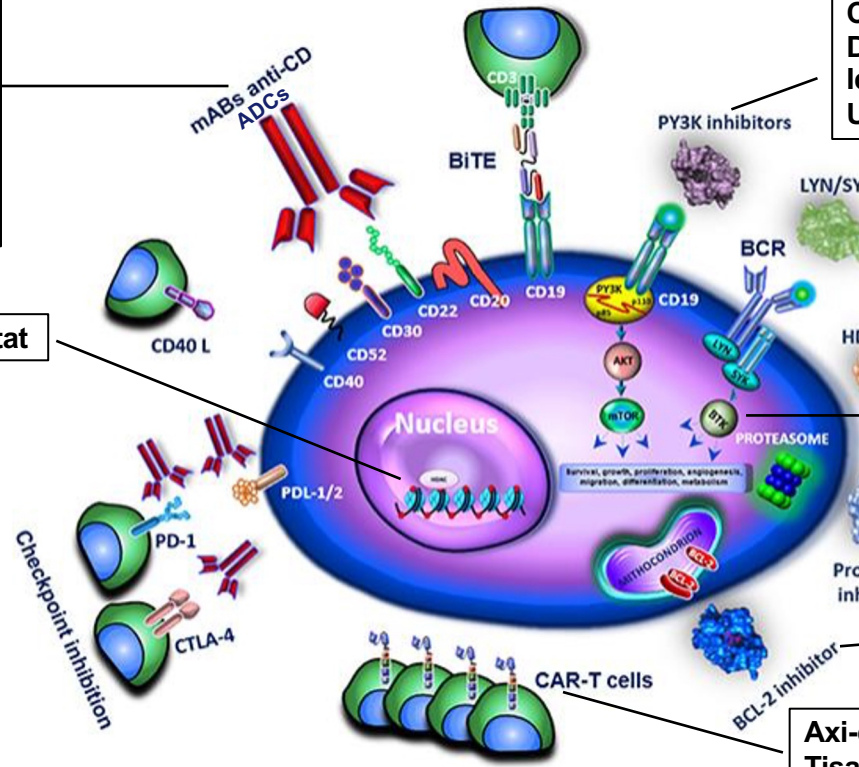
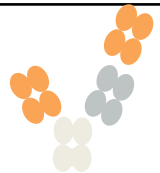


Figure adapted from Crisci, et al. Front. Oncol. 2019. doi.org/10.3389/fonc.2019.00443

The saga continues…..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

Modern Challenges and New Options in B-cell NHL Therapy

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

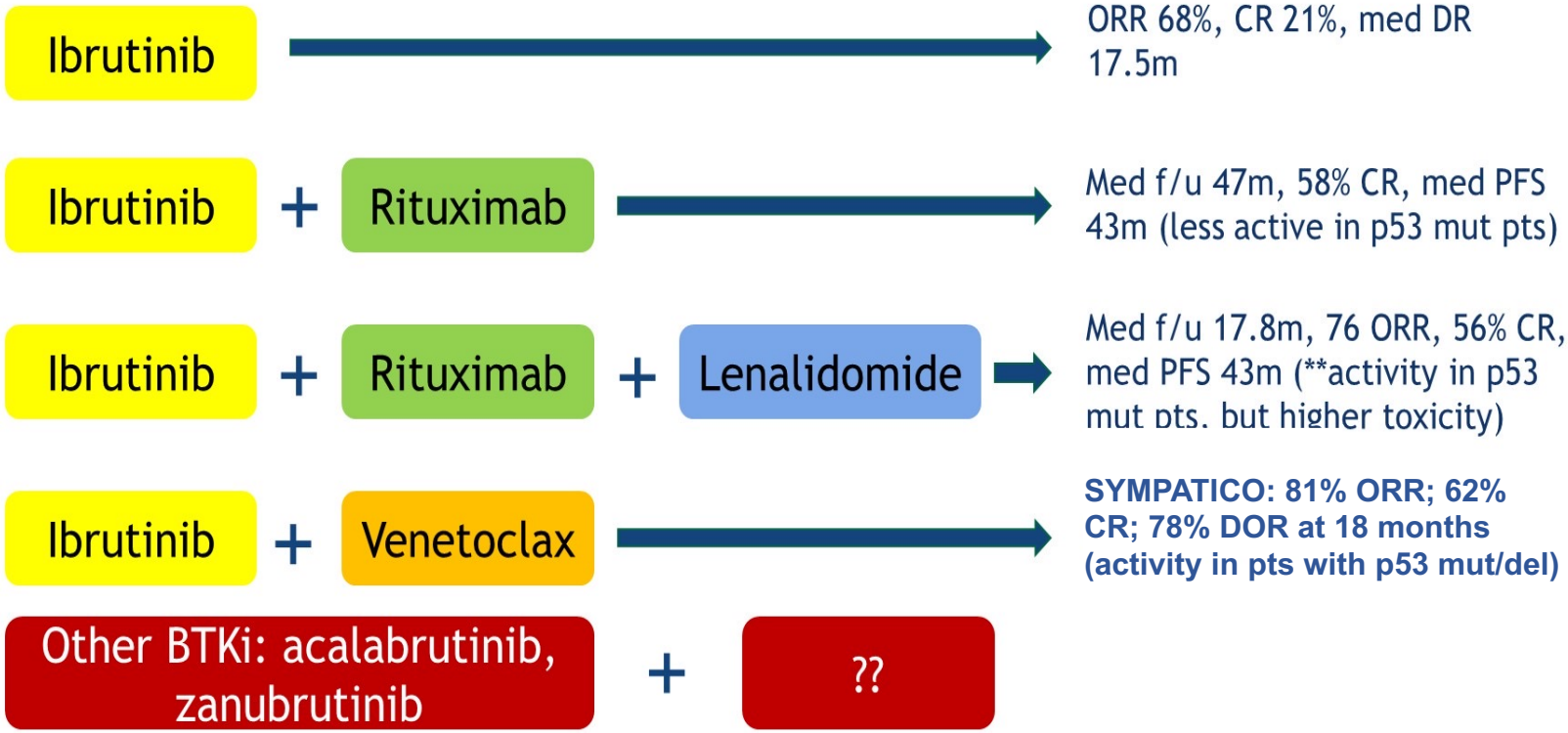
- How to better combine these novel therapies…"duplets/triplets" in the **relapsed/refractory and frontline setting**

- 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 and/or other targeted therapies:
  - **POLARIX Study (DLBCL)**
  - **SHINE Study (MCL)**
  - **"WINDOW" -1/2 trials (MCL)**

Building on BTKs in R/R MCL

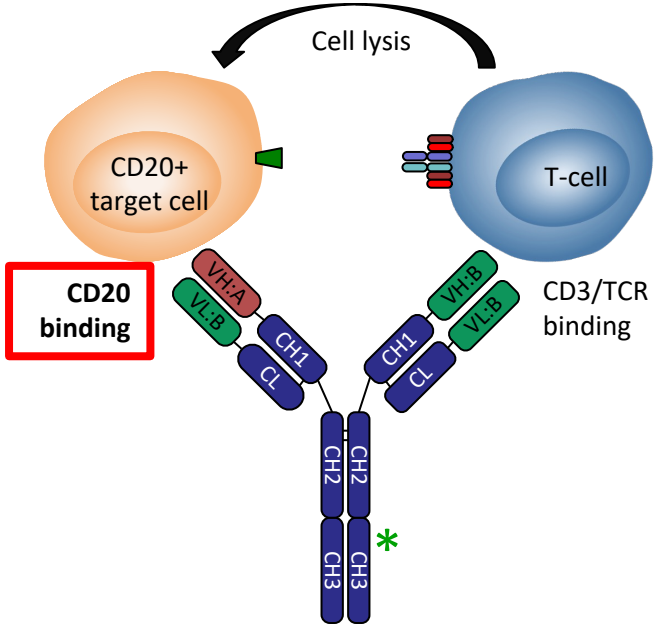


Wang New Engl J Med. 2013 Aug 8;369(6):507-16; Jain P Br J Haematol. 2018 Aug;182(3):404-411; Jerkeman Lancet Haematol. 2018 Mar;5(3):e109-e116

BTK's combinations in Frontline MCL

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

Bispecific Antibodies: Game changer in NHL?



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.

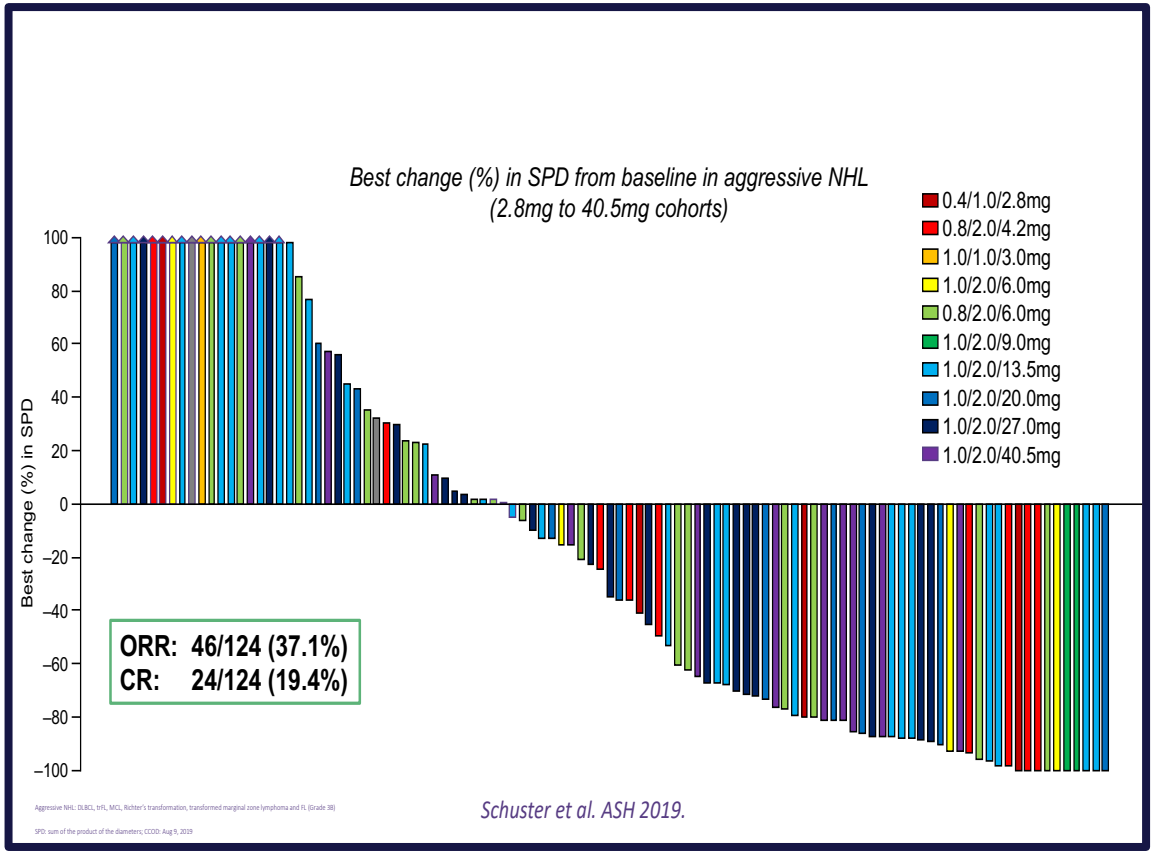
***CR*: discontinuation of treatment**

***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.

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)

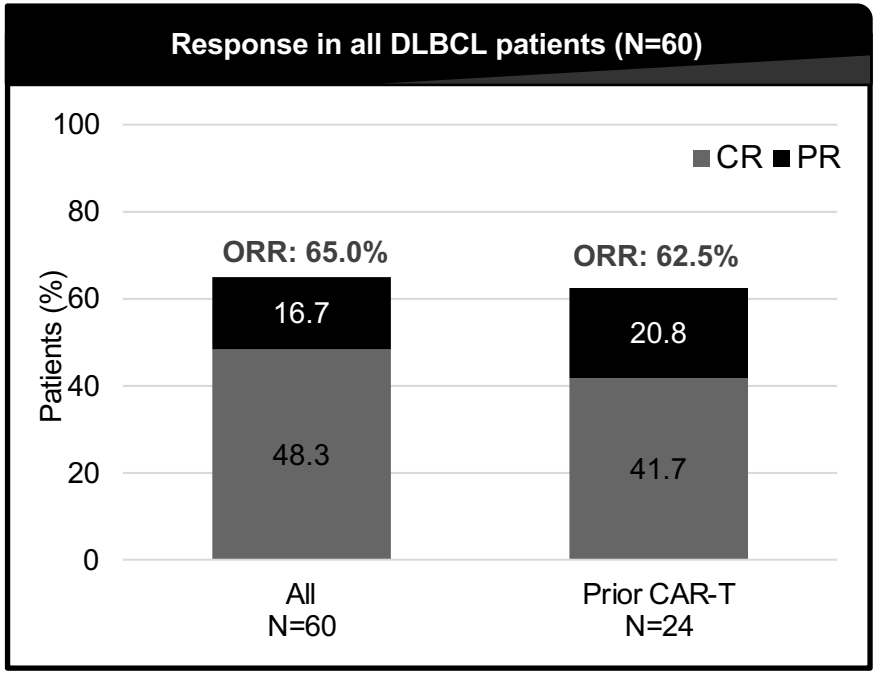
Response, n (%)	Retreated Patients (n = 4)
▪ ORR ▪ CR	3 (75) 1 (25)

- No CRS events occurred during retreatment

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

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)***

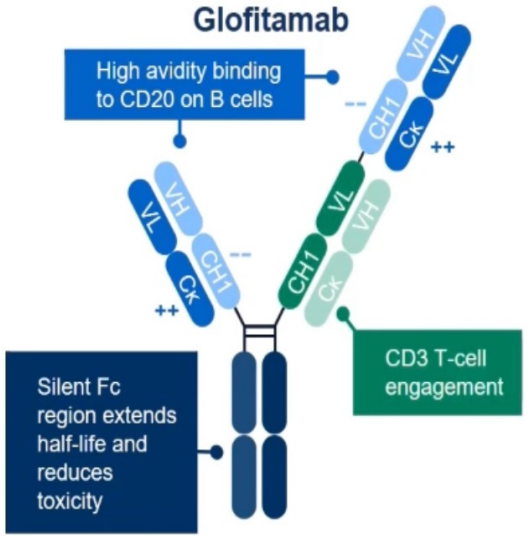
- **Of 29 patients achieving CR, 28 (96.6%) remained in CR and 1 (3.4%) had PD at data cut-off**

Budde et al ASH 2021. Abstr 533

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?)

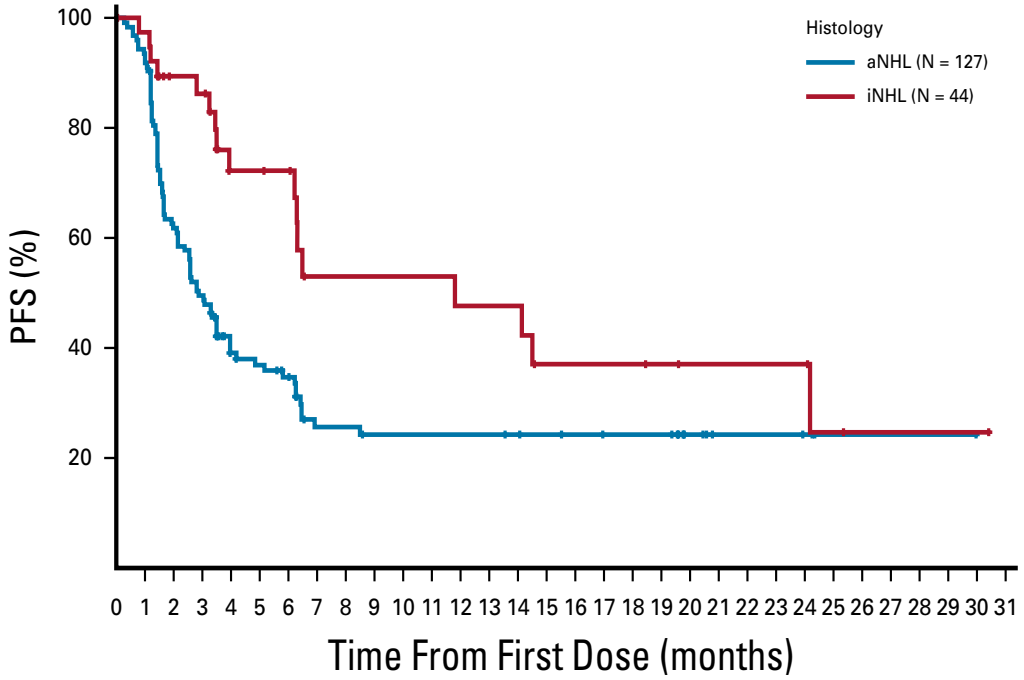
Glofitamab



- **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**

PFS in Indolent and Aggressive NHL

Hutchings et.al. JCO 2021



Glofitamab

R/R Follicular lymphoma

Glofitamab: ORR: 81% CMR: 70%
Glofitamab+ Obinutuzumab ORR:100%,CMR: 74%

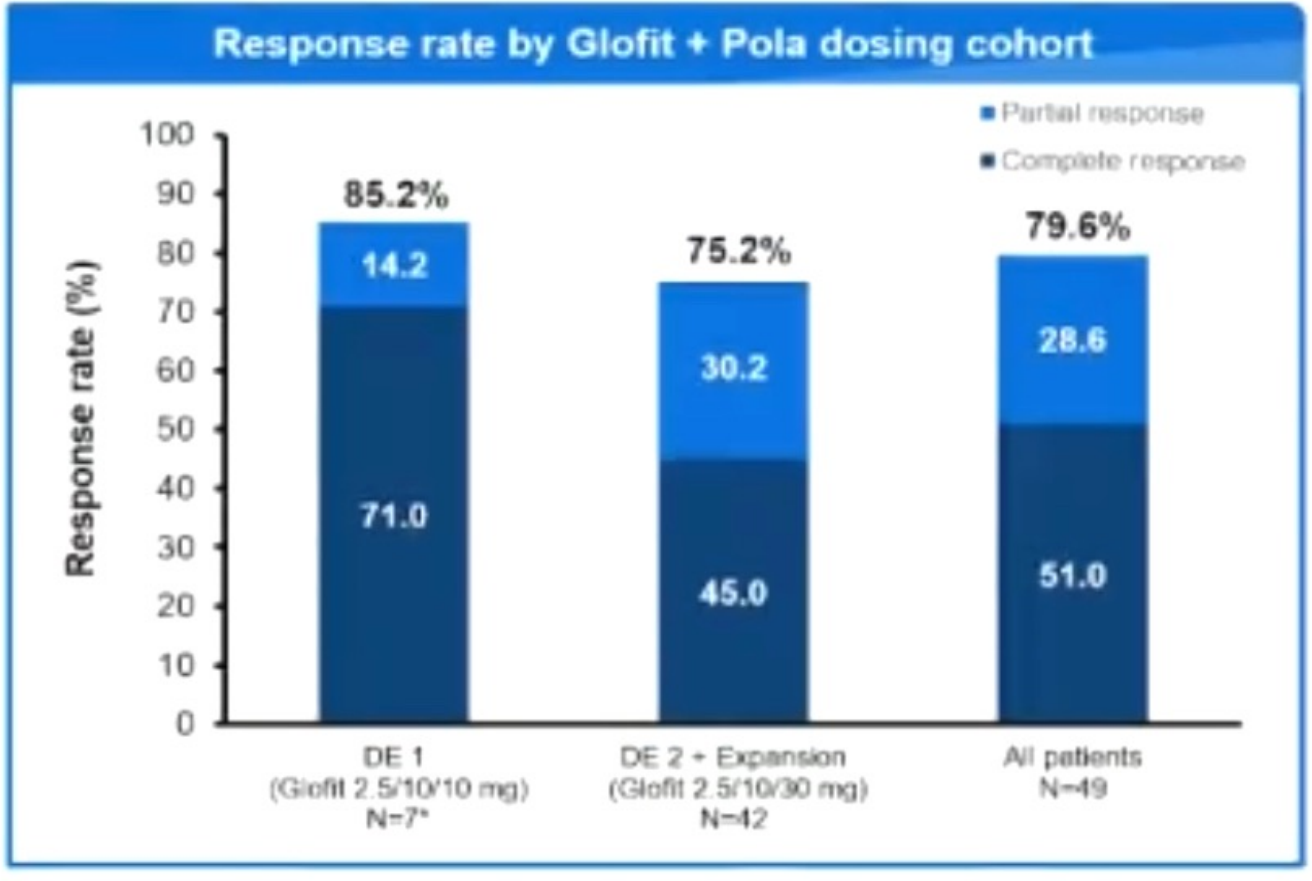
R/R Mantle Cell Lymphoma

Glofitamab + Obinutuzumab
-**ORR: 81% CMR: 67%**
-59% G1-2 CRS.
-1 pt G4 CRS+ rapid PD
-1pt. G2 ICANS

ASCO 2022: R/R DLBCL

Pivotal Phase II expansion: R/R DLBCL >2 prior therapies (M.Dickison et al)
ORR: 50%; CR: 35.2 . Projected 12m OS:48%
Median time to CR: 42 days

Glofitamab + Polatuzumab in R/R DLBCL



Epcoritamab (SC) – ASCO 2022

	Author	Setting	n	ORR (%)	CR (%)	Toxicities
Epco + R-DHAX/C	P. Abrisqueta (Vall d'Hebron)	R/R DLBCL eligible for ASCT Standard R-DHAX/C Epco weekly 21 day cycle (C1-3)	27 pts 23 evaluable patients, 11 pts underwent ASCT	100%	82%	CRS: 30% (all gr1-2) ICANs: 1 pt (gr2)
Epco + R2	L. Falchi (MSKCC)	R/R follicular lymphoma Epco + R2 x 12 cycles of 28 Epco weekly (C1-3) Epco every 2w (C4-9) Epco every 4w C>10 up to 2 years	30 pts	100%	CMR: 93%	CRS: 50% (gr1-2;43%, gr3: 7%) most in C1 ICANS: 1pt (Gr2)

Epcoritamab (SC) – ASCO 2022

	Author	Setting	n	ORR (%)	CR (%)	Toxicities
Epco + R-CHOP	L. Falchi (MSKCC)	Frontline DLBCL High risk (IPI 3-5) Epco weekly (C1-4) Epco every 3 w (C5-6) Epco every 4 weeks x 1 year	33 pts 24% double or triple hit	96%	68%	CRS: 45%(3% gr≥ 3) C1 ICANS: 3% gr 2 Safety profile is manageable CRS mostly low grade No Tx discontinuation
Epco + GemOx	J. Brody (Mt. Sinai)	R/R DLBCL ineligible for ASCT Epco weekly (C1-3) Epco every 2w (C4-9) Epco every 4 weeks x 1 year	27 pts Mostly primary refractory	92%	60%	CRS: 70% (all gr1-2) C1 ICANS: 1pt (Gr3)

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Polatuzumab Vedotin

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

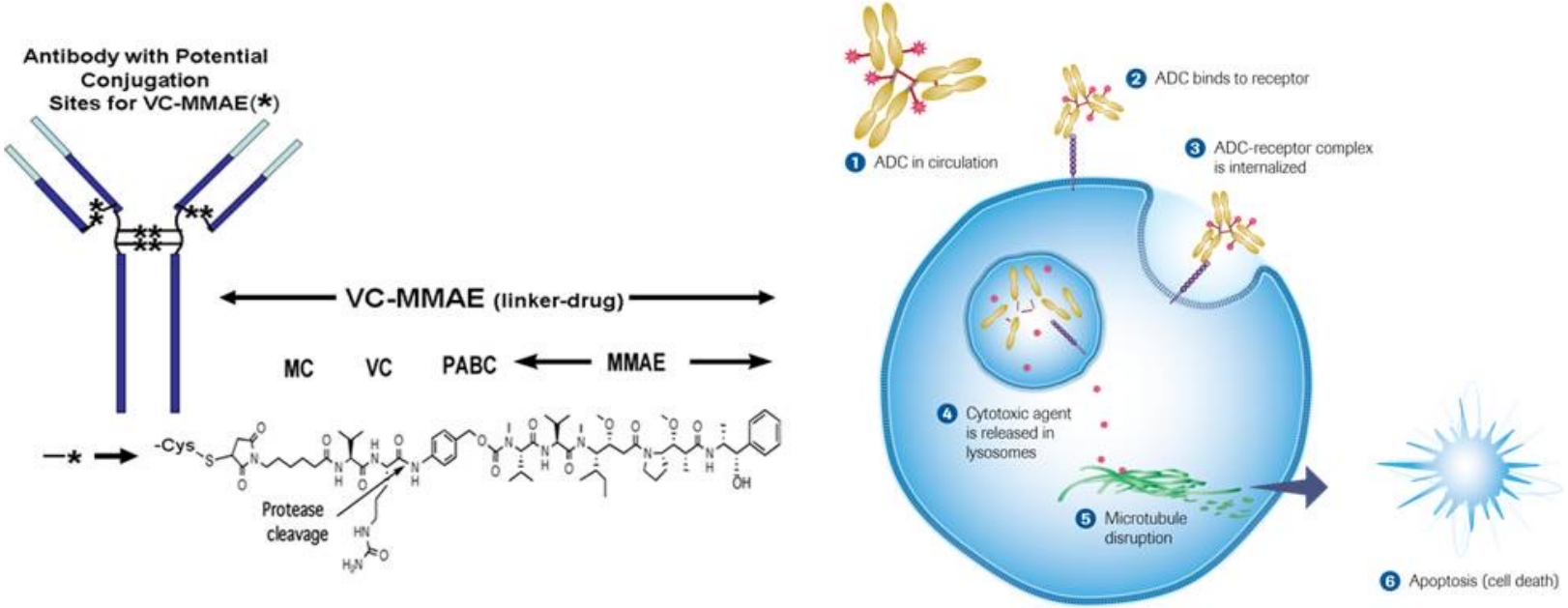


Figure from: Morschhauser, et al. J Clin Oncol. 2014;32(15_suppl):8519.
Doman, et al. Blood. 2009;114:2721-2729. Polson, et al. Blood. 2007;110:616-623. Sehn, et al. ASH 2017;Abstract 2821.

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

- **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**

  - **Double expressors or double/triple hit DLBCL treated with Pola-R-CHP seems to have better outcomes (PFS) than those treated with R-CHOP**

- **Similar rates of adverse events/drug dose reductions or drug discontinuation**

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

ASCO 2022: Outcomes by BCL2 and MYC expression and rearrangements in the POLARIX Trial

- **Pre-specified exploratory analysis: IHC for double expressors and rearrangements (R) by FISH for double/triple hit DLBCL as independent prognostic markers**

- ***Multivariate analysis support the benefit of Pola-R-CHP in patients with BCL2+ and MYC+ DLBCL***

- **The poor prognostic impact associated with double expressors appears reduced in POLA-R-CHP vs. R-CHOP treated pts**

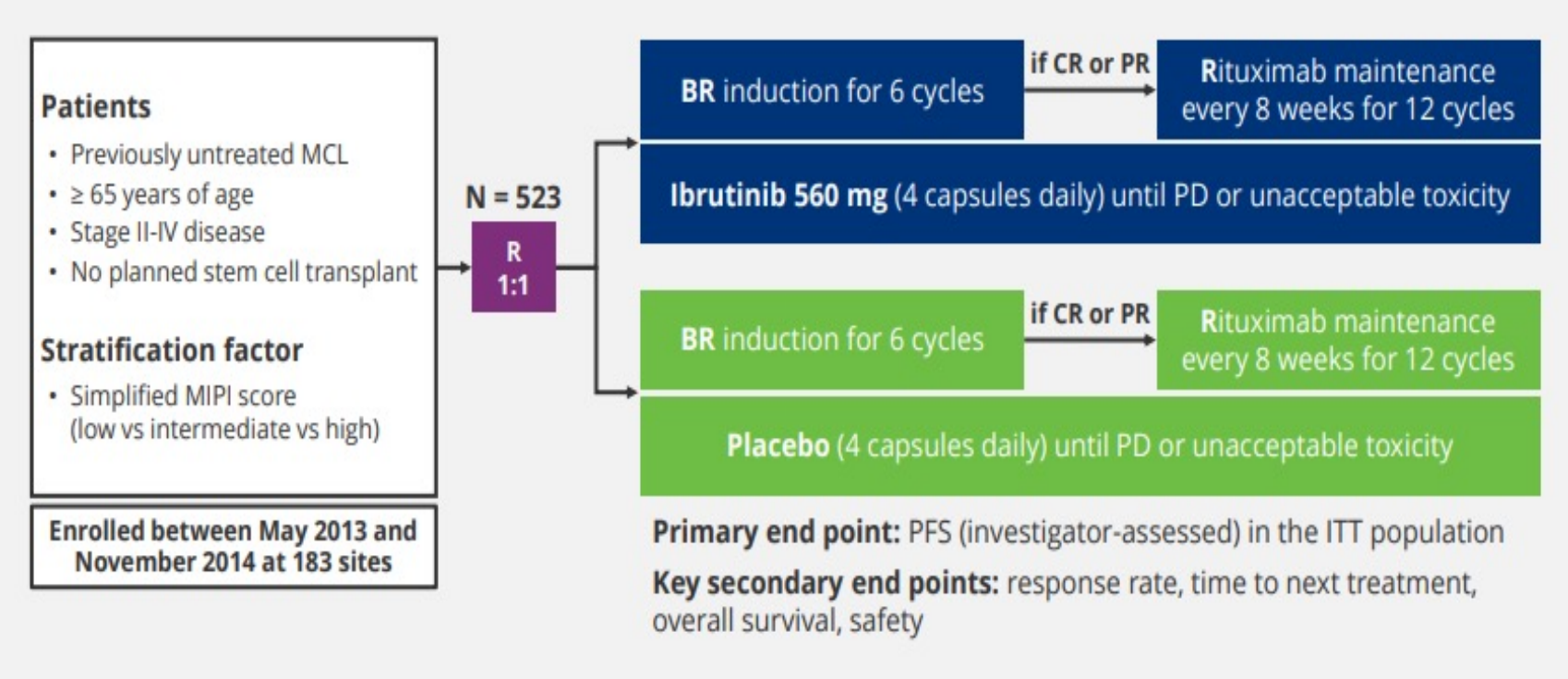
Morschhauser, F. et al. ASCO 2022-Abst. 7517

ASCO 2022: POLA+Others in frontline DLBCL

- **POLA-DA-EPCH-R for upfront treatment[1]**
  - **Can POLA be safely incorporated into other intensified regimens?**
  - **Single center, open label trial: 6 cycles of POLA-D-EPCH-R in aggressive B-cell lymphomas (HGBCL, PMBCL and selected DLBCL-NOS)**
  - **18 pts. Pola at 1.8 mg/kg on day 1.**
  - **3 DLT. Five SAES: Grade 5 sepsis/typhlitis, 3 episodes of febrile neutropenia and a grade 3 perforation of colonic diverticula. Grade 1 peripheral sensory neuropathy**
  - **ORR: 93%; CR: 71% with one PD**

1. Lynch, R. et.al. Abst. 7546 ; 2. Matasar, M. Abst. 7551

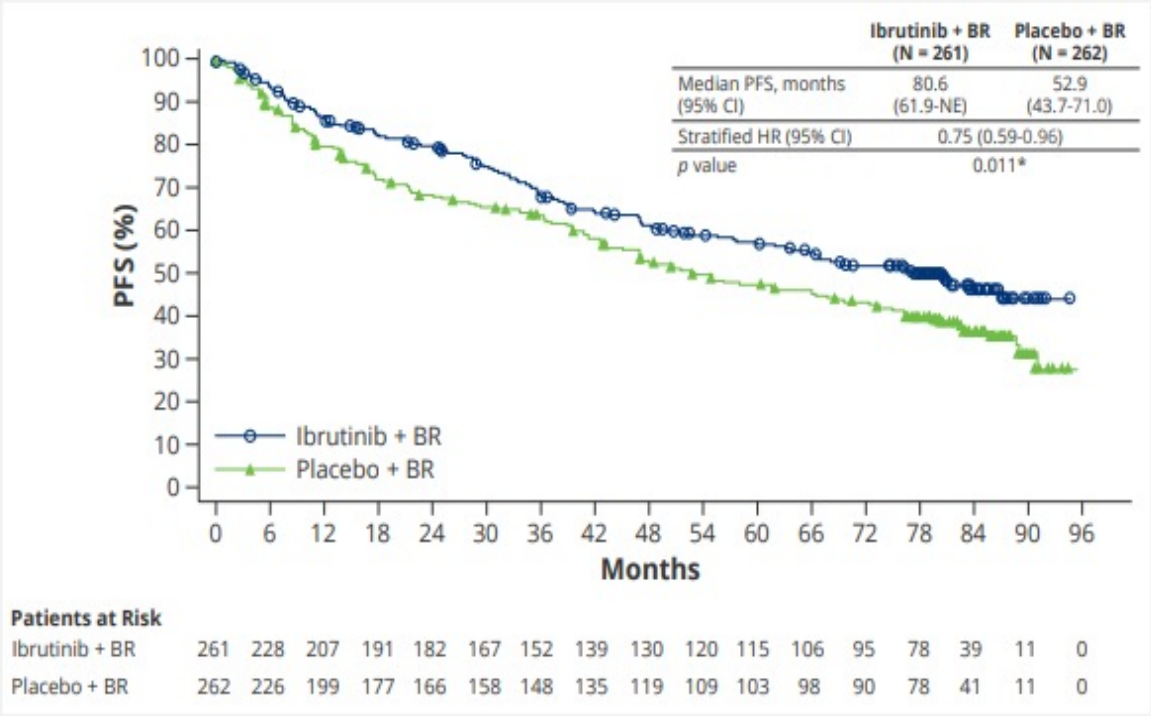
Phase III SHINE Study - Frontline MCL



Median age was 71 years (range, 65–87), 65.6% of pts had low/intermediate simplified MIPI, and 8.6% had blastoid/pleiomorphic histology.

Wang, M. et al. LBA 7502, ASCO 2022; NEJM June 2022

Primary Endpoint of Improved PFS was met



	Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median PFS, months (95% CI)	80.6 (61.9-NE)	52.9 (43.7-71.0)
Stratified HR (95% CI)	0.75 (0.59-0.96)	
p value	0.011*	

Patients at Risk

Ibrutinib + BR	261	228	207	191	182	167	152	139	130	120	115	106	95	78	39	11	0
Placebo + BR	262	226	199	177	166	158	148	135	119	109	103	98	90	78	41	11	0

Ibrutinib + BR and R maintenance achieved:

- **Significant improvement in median PFS by 2.3 years** (6.7 vs 4.4 years)
- **25% reduction** in risk of PD or death

Wang, M. et al. LBA 7502, ASCO 2022, NEJM June 2022

MCL Frontline Setting: Phase III SHINE Study

Results:

- Median PFS was 80.6 months (Ibr +BR and R maintenance) versus 52.9 months (Pbo +BR and R maintenance), a 50% improvement. (hazard ratio, 0.75; one-sided P = 0.011).

- **CR rate was 65.5% in the Ibr arm and 57.6% in the Pbo arm (P = 0.0567). No difference in OS between treatment arms (P = 0.648).**

- **Time to next treatment was longer in the Ibr arm compared with the Pbo arm (P < 0.001).**

- **Atrial fibrillation was reported in 13.9% and 6.5% of pts in the Ibr and Pbo arms, respectively.** Rates of major hemorrhage, hypertension, arthralgia, and secondary primary malignancies were similar in both arms.

Conclusions: Ibr combined with BR and R maintenance significantly improved PFS compared with standard chemoimmunotherapy, with a median PFS of 6.7 years. The safety profile was consistent with the known profiles of the individual drugs.

Wang, M. et al. LBA 7502, ASCO 2022

“Window” Approach in Frontline Treatment?

A Window of Opportunity – Ibrutinib with Rituximab Induction

PART A: Chemo-free Window with Rituximab-Ibrutinib

Current Standard is Chemo-immunotherapy
R-HyperCVAD
R-MTX/Ara C
8 Cycles

Toxicity ↓

Survival ↑

PART B: Less chemotherapy (only 4 cycles HyperCVAD)

Wang, et al. MD Anderson Cancer Center

Window-1 Trial in Frontline MCL

Response and Outcomes from Window-1 Trial[1]	All pts	Low risk (n= 61)	High risk (n = 70)
Chemo-free (IR) induction, ORR/CR	100%/ 88%	100%/ 90%	98%/ 84%
R-HCVAD consolidation, ORR/CR *(10 pts did not take part B)*	100%/ 98%	100%/ 98%	100%/ 97%
MRD negative at best response *(n=114 pts)*	74%	69%	79%
Median PFS	NR	NR	NR
Median OS	NR	NR	NR

1. Wang, et al. Blood. 2020;136 (Supplement 1):35–36. 2. Greenwell,et al. Blood. 2020;136 (Supplement 1): 33–34.

Phase-II WINDOW-2 trial:
Ibrutinib plus rituximab and venetoclax (IRV) followed by risk-stratified observation or short course R HyperCVAD/MTX in young patients with previously untreated mantle cell lymphoma

Michael L. Wang et al.

MD Anderson Cancer Center, Houston, Texas

IRV in Frontline Mantle Cell Lymphoma

- **"Chemo-free" IRV induced an unprecedented efficacy before chemo consolidation.**
  - 48 patients received IRV. **Best response was 96% and CR of 92%.**
  - After part 2, the best ORR remained unaltered, 96% (92% CR and 4% PR).
  - The median number of cycles of triplet IRV to reach best response was 8 cycles (range 2- 12).

- **Thirteen patients (26%) came off study –5 for adverse events, 3 for on study deaths, and 2 for patient choice, 2 patients lost to follow up and one for disease progression**

- **Overall, 5 patients died (3 on trial and 2 patients died off study, one due to progressive disease and another due to COVID pneumonia).**

- ***WINDOW-2 approach suggests that patients with low risk MCL, may not need chemotherapy but further follow up is warranted***

ESMO 2022: Highlights in B-cell NHL

- Phase I trial of **PF-06821497**, a potent and selective **inhibitor of EZH2**, in patient s with R/R follicular lymphoma ***(M. T. Cheweizer et.al)***
  - **N=15 pts. 4 PR, 6 minor responses, 1 stable disease and 1 progressive disease.**

- A phase I study of **TRS005:** An **anti-CD20-MMAE antibody-drug conjugate** in R/R B-cell NHL ***(Y-K Shi et al)***
  - **N= 40 pts. ORR: 37%. Disease control rate: 60% Seems to have activity in DLNCL, FL, MCL and MZL. Liver toxicity**

- **Orelabrutinib (covalent BTK inh.)** plus R-CHOP for untreated non-germinal center b-cell like (GCB) DLBCL patients with extranodal disease ***(M. Wang et al)***
  - **N= 22 pts. ORR: 90.9%. CR: 75%. Median follow up: 11months. Serious AEs included febrile neutropenia (3 pts) and atrial flutter (1 pt)**

- **VITALIZE:** A phase 2b, open label, multicenter, randomized parallel-group, two-stage study of **Maveropepimut-S (Survivin),** pembrolizumab with or without intermittent low dose cyclophosphamide in patients with R/R DLBCLM. ***(M. Matasar et al)***
  - **Durable CR and PR and, persistent surviving-specific T cells in particular in pts. with PDL1+ disease.**

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

I. Science:

- Understanding efficacy and mechanism(s) of resistance ("Window" trials) in the frontline setting

- 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
  - Primary CNS lymphomas
  - Viral-associated lymphomas

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)… **non-covalent BTK**
  - CD19 CAR T-cells (DLBCL, MCL, FL)…. **CLL/SLL**
  - Double refractory (FL, MCL)

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

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

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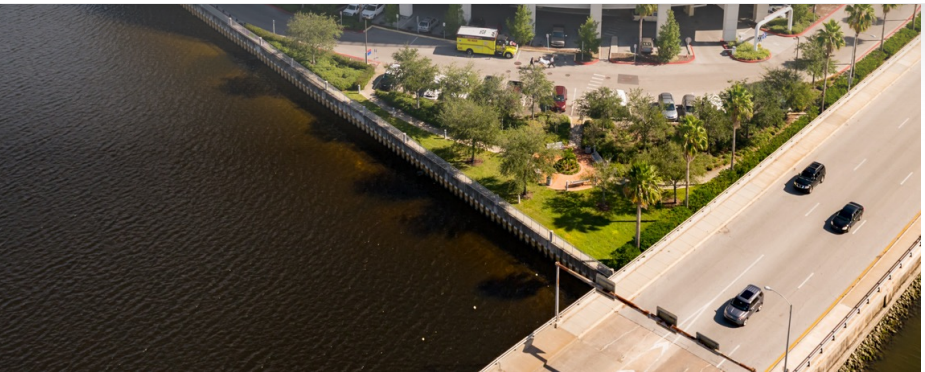
THANK YOU !



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