Fred Hutch
Cancer Center

Updates on CLL and Lymphoma

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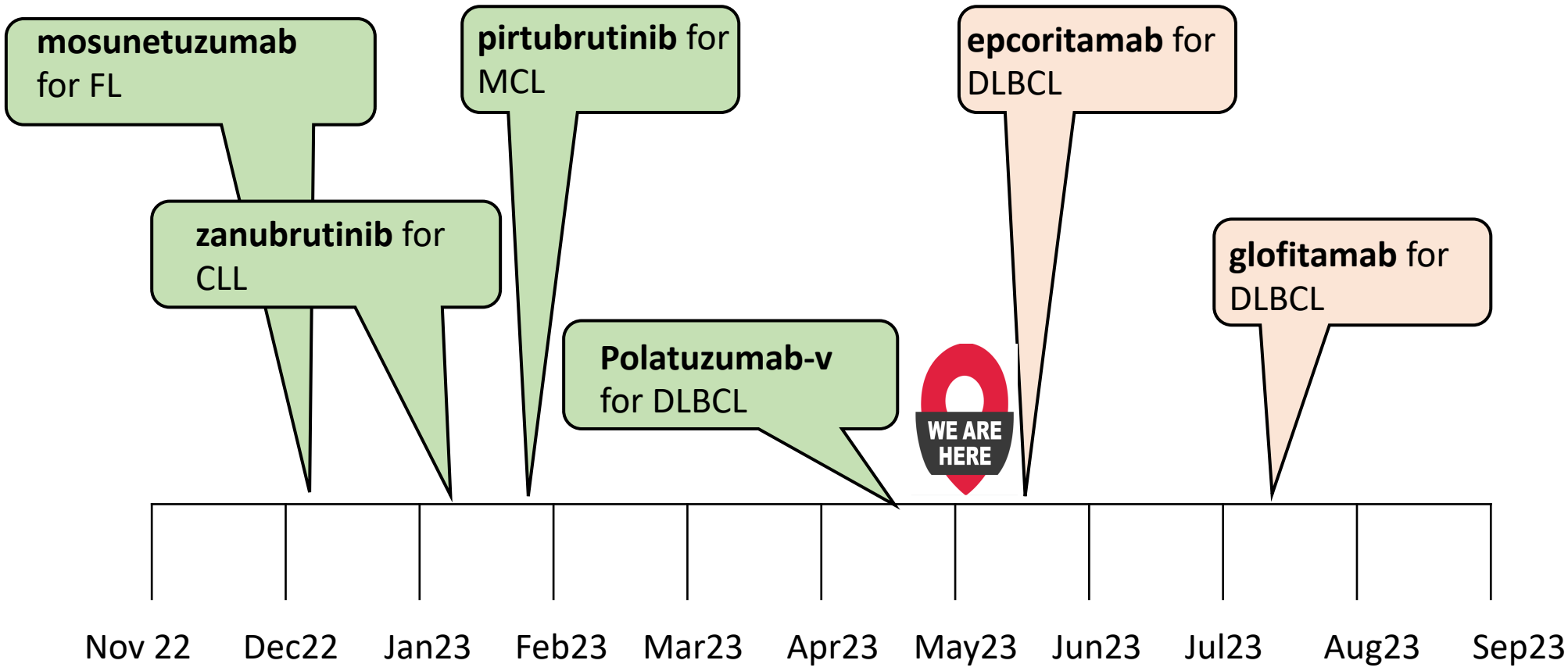
Big news in Lymphoma and CLL



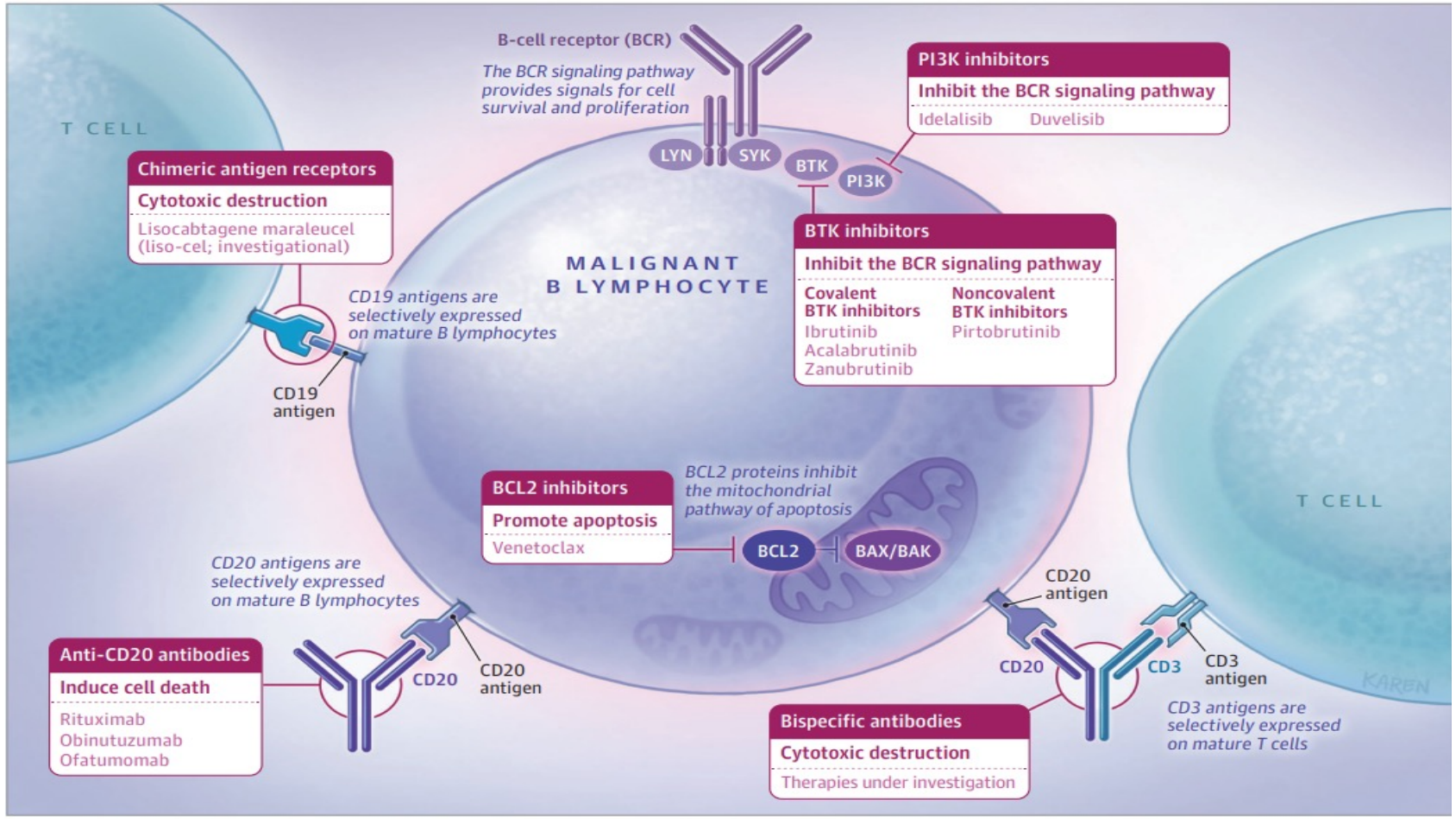
FDA approved

PDUFA date

Big news in Lymphoma and CLL

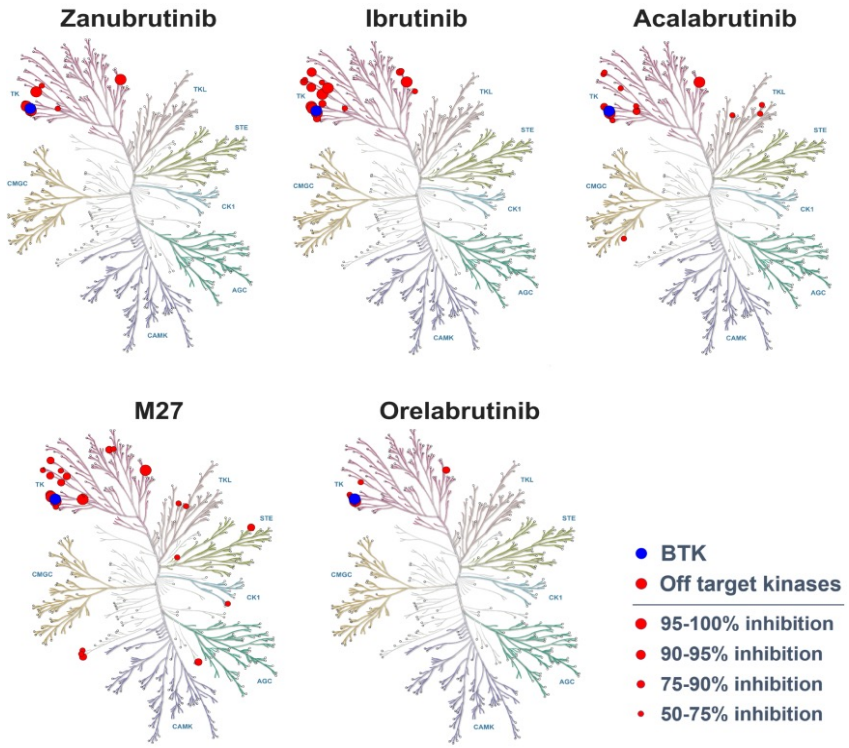
- CLL
  - **Zanubrutinib** for first-line and relapsed CLL **(FDA approved)**
- MCL
  - **Pirtobrutinib** for 3rd line MCL (after cBTKi) **(FDA approved)**
- FL
  - **Mosunetuzumab** for 3rd line FL **(FDA approved)**
- DLBCL
  - **Polatuzumab Vedotin** for 1st line DLBCL **(FDA approved)**
  - **Epcoritamab** for 3rd line DLBCL **(Approval is expected)**
  - **Glofitamab** for 3rd line DLBCL **(Approval is expected)**

Treatment options for CLL



Shadman, JAMA, 2023

Zanubrutinib vs. Ibrutinib in r/r CLL (ALPINE study)



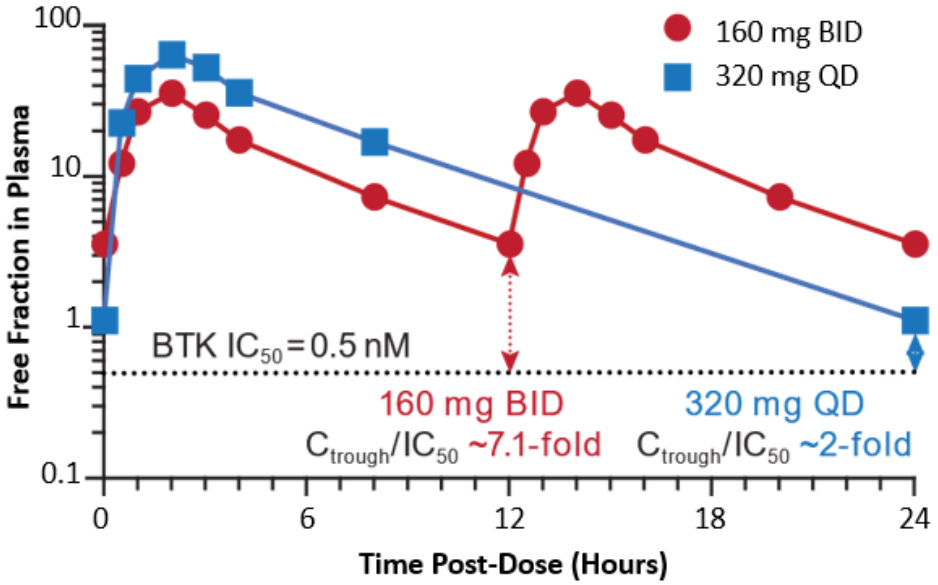
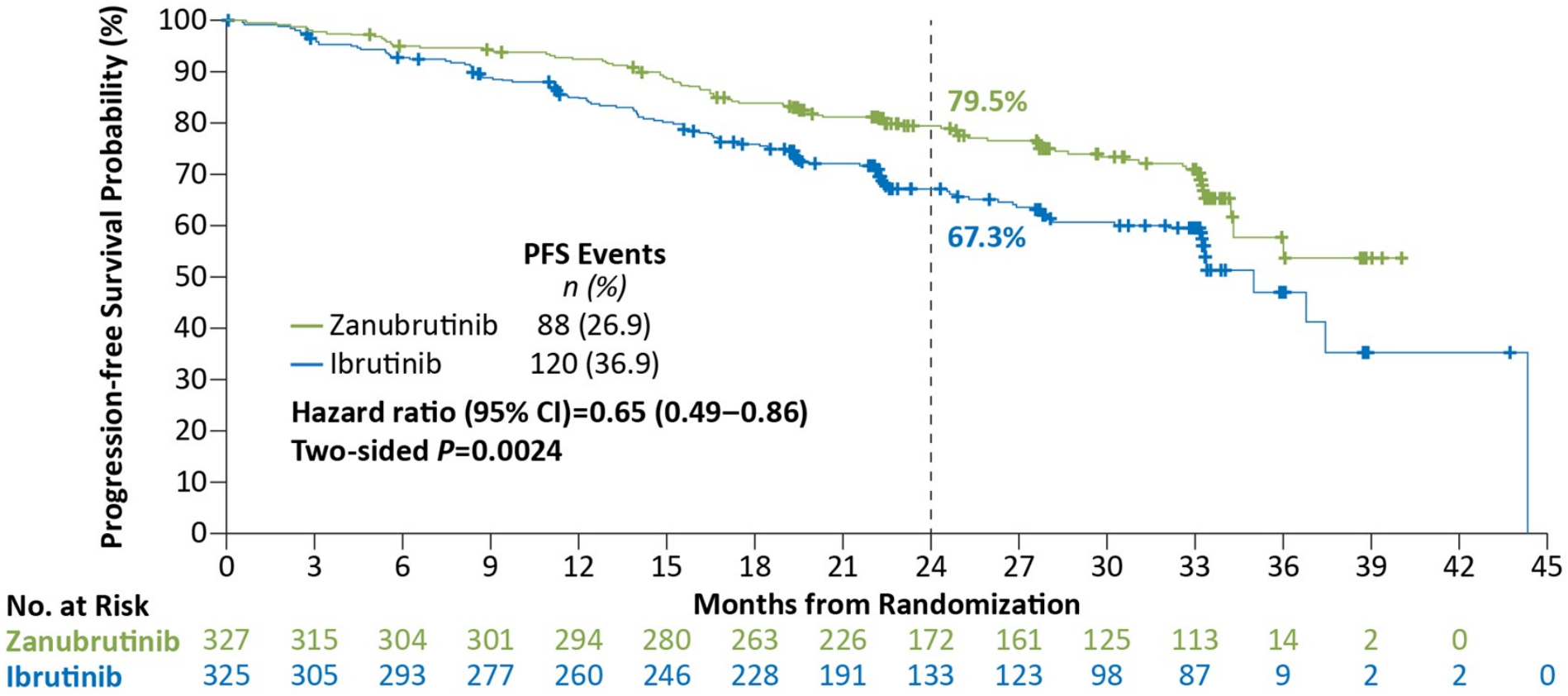


Figure modified from Ou YC, Tang Z, Novotny W, et al *Leukemia & Lymphoma.* 2021; 62(11):2612-2624.

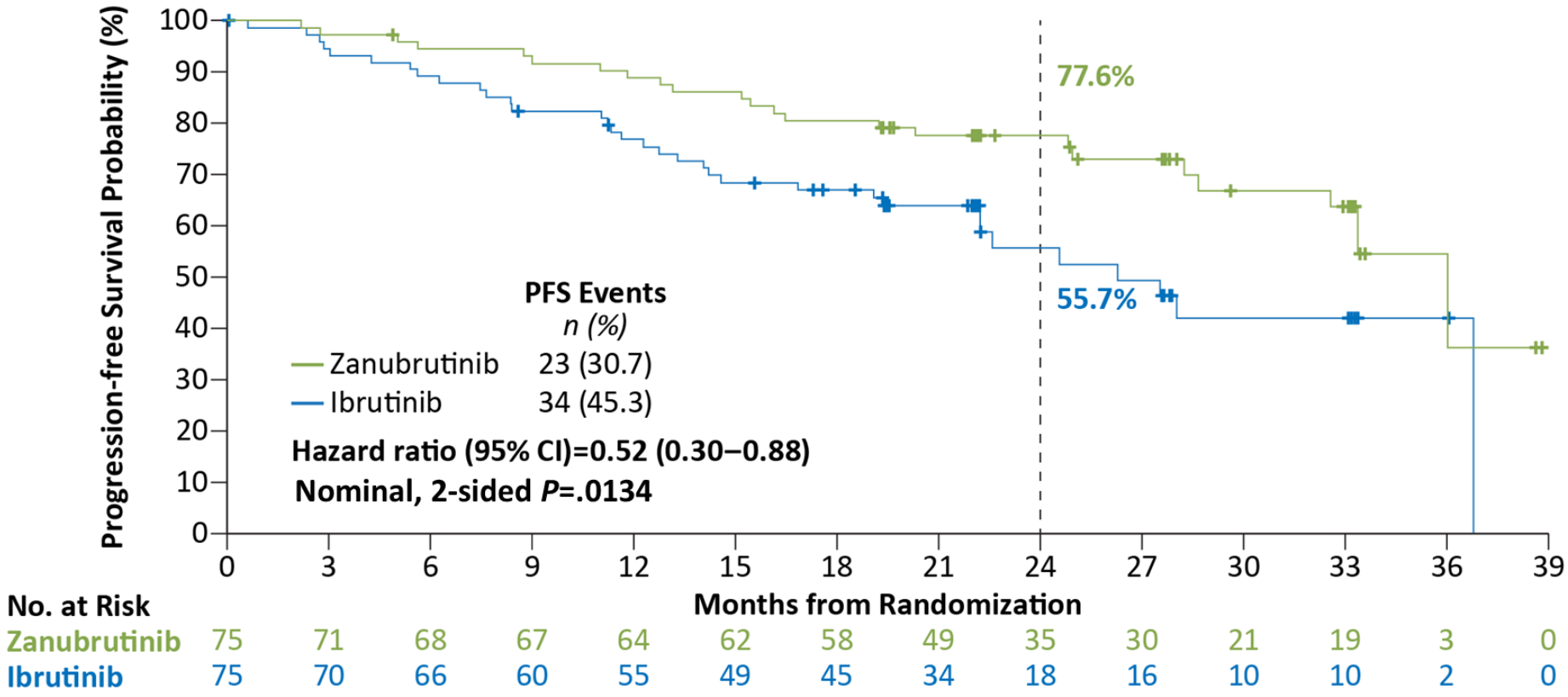
Assayed by Reaction Biology Corp. at 100X of IC_{50} (against BTK) concentration with IC_{50} (BTK)s of 0.71±0.09, 0.32±0.09, 24±9.2, 63±28 and 15±5.5 nM (n=3), for zanubrutinib, ibrutinib, acalabrutinib, M27, and orelabrutinib, respectively.

Zanubrutinib vs. Ibrutinib in r/r CLL
PFS in all patients



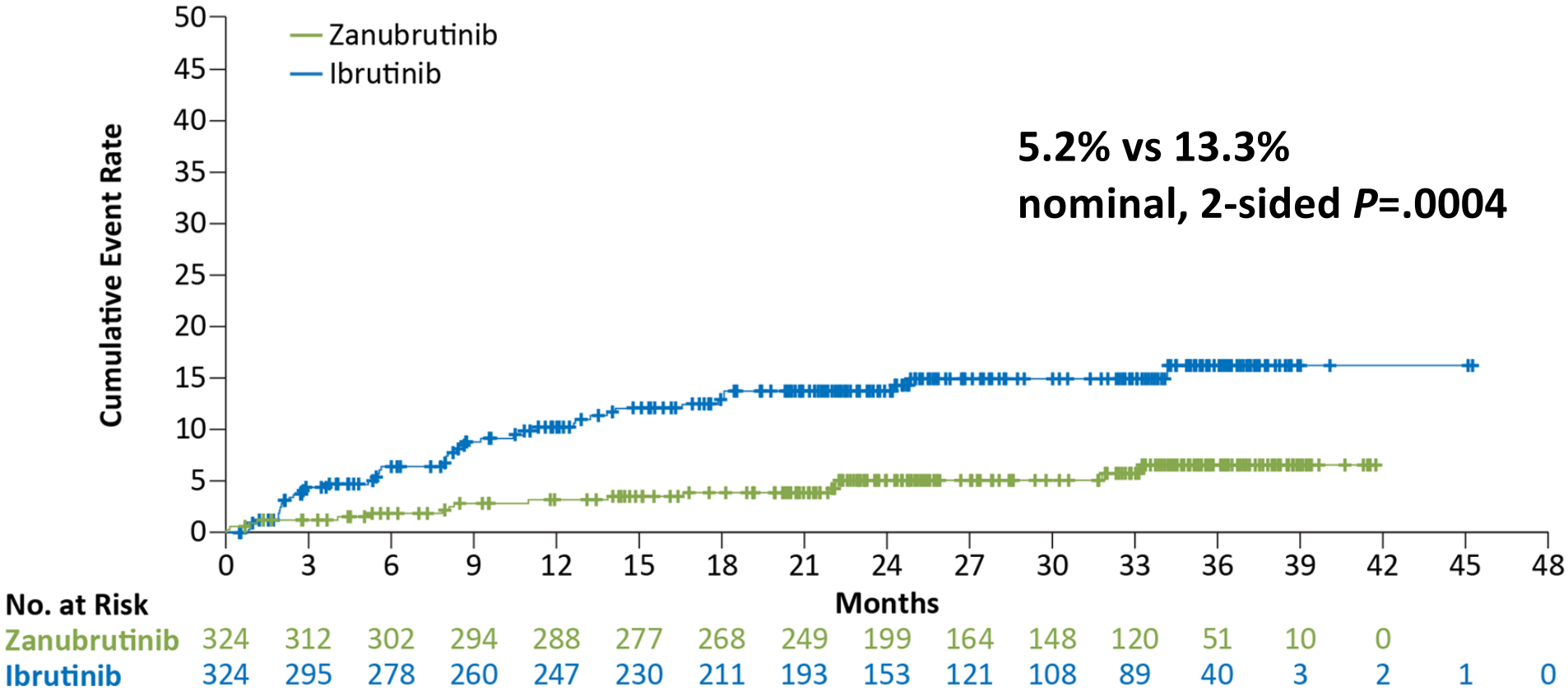
Brown, NEJM, 2023

Zanubrutinib vs. Ibrutinib in r/r CLL
PFS in del17p/mTP53



Brown, NEJM, 2023

Zanubrutinib vs. Ibrutinib in r/r CLL
Incidence of AFib/AFlutter



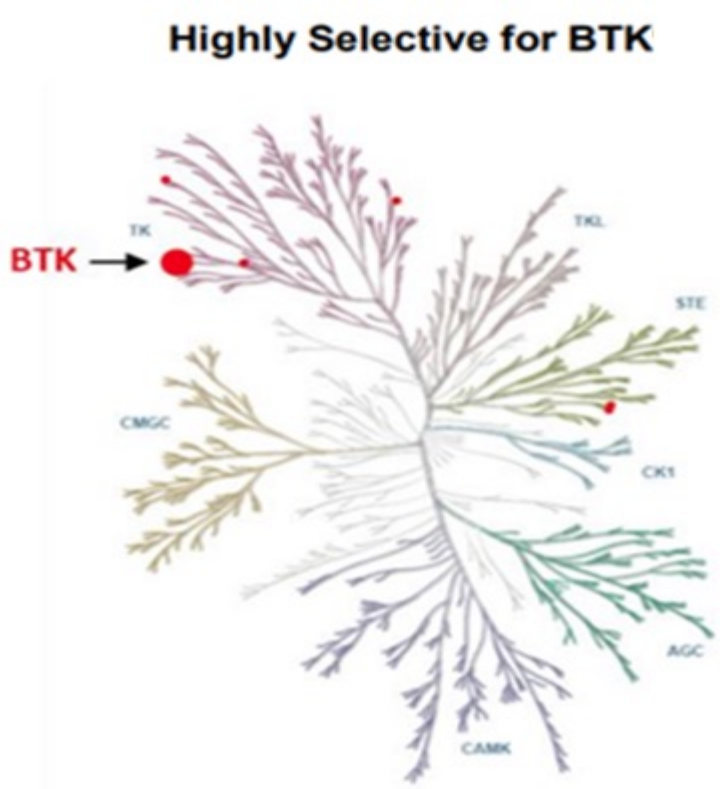
5.2% vs 13.3%
nominal, 2-sided *P*=.0004

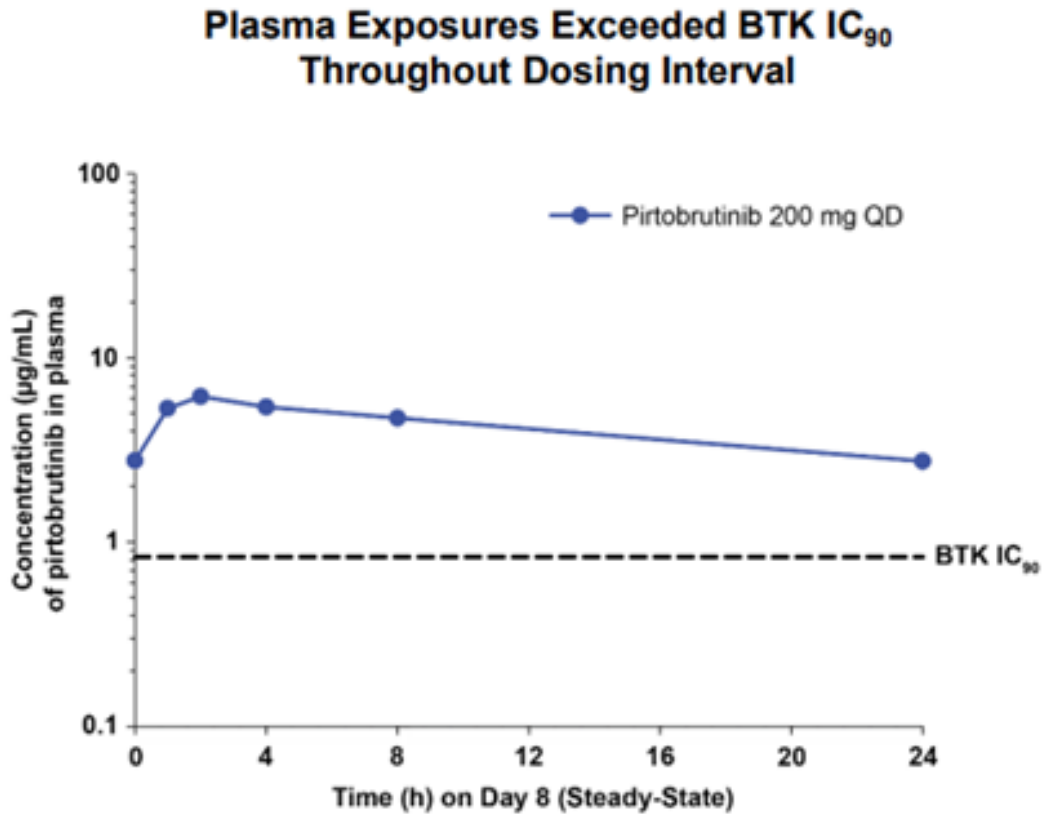
Brown, NEJM, 2023

ALPINE study: Take home points

- Zanubrutinib has higher efficacy than ibrutinib in r/r CLL/SLL
- Zanubrutinib is better tolerated and has lower rate of Afib
- First study showing improved efficacy of any BTKi over ibrutinib
- Based on this study and SEQUOIA (first line), zanubrutinib was approved for treatment of CLL/SLL in all lines of treatment

Pirtobrutinib for MCL (BRUIN study)





Wang, ASH, 2022

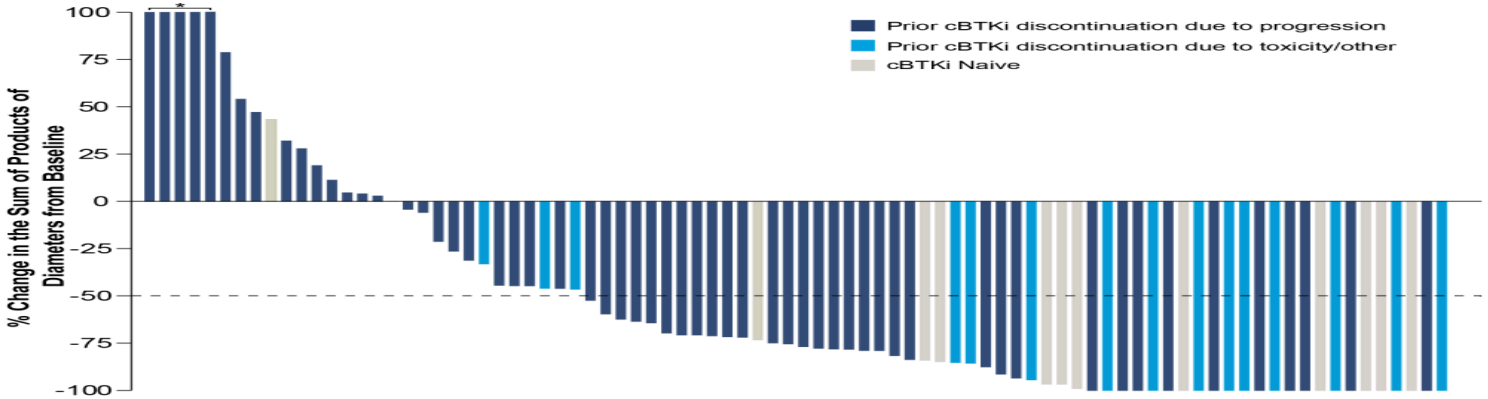
Pirtobrutinib for MCL (BRUIN study)

Characteristics	Prior cBTKi (n=90)	cBTKi Naïve (n=14)
Median age, years (range)	70 (46-87)	67 (60-86)
Male, n (%)	72 (80)	10 (71)
Histology, n (%)		
Classic	70 (78)	11 (79)
Pleomorphic/Blastoid	20 (22)	3 (21)
ECOG PS, n (%)		
0	61 (68)	5 (36)
1	28 (31)	8 (57)
2	1 (1)	1 (7)
sMIPI Score, n (%)		
Low risk (0-3)	20 (22)	3 (21)
Intermediate risk (4-5)	50 (56)	5 (36)
High risk (6-11)	20 (22)	6 (43)
Tumor Bulk (cm), n (%)		
<5 / ≥5	66 (73) / 24 (27)	9 (64) / 5 (36)
<10 / ≥10	87 (97) / 3 (3)	12 (86) / 2 (14)
Bone Marrow Involvement, n (%)		
Yes	46 (51)	4 (29)
No	44 (49)	10 (71)
Reason discontinued any prior cBTKi[a], n (%)		
Progressive disease	74 (82)	-
Toxicity/Other	16 (18)	-
Median number prior lines of systemic therapy (range)	3 (1-8)	2 (1-3)
Prior therapy, n (%)		
BTK inhibitor	90 (100)	0 (0)
Anti-CD20 antibody	86 (96)	14 (100)
Chemotherapy	79 (88)	14 (100)
Immunomodulator	19 (21)	1 (7)
Stem cell transplant	19 (21)	7 (50)
Autologous	17 (19)	7 (50)
Allogeneic	4 (4)	0 (0)
BCL2 inhibitor	14 (16)	0 (0)
CAR-T	4 (4)	0 (0)
PI3K inhibitor	3 (3)	1 (7)

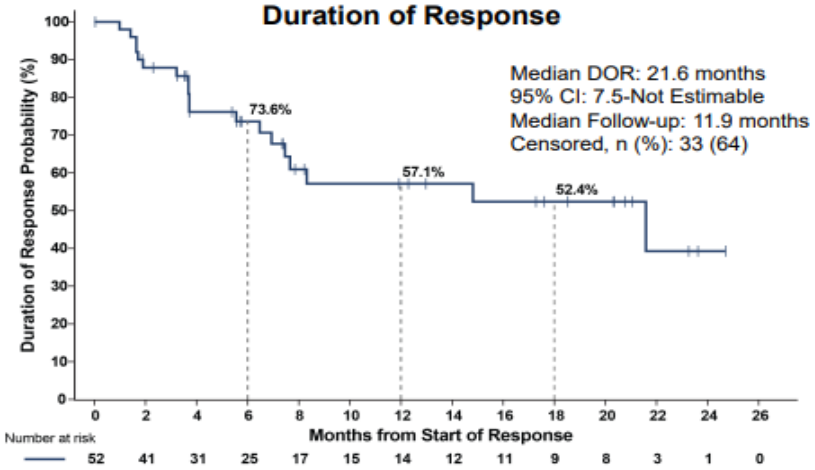
Data cutoff date of 31 January 2022. [a]Calculated as percent of patients who received prior cBTKi.

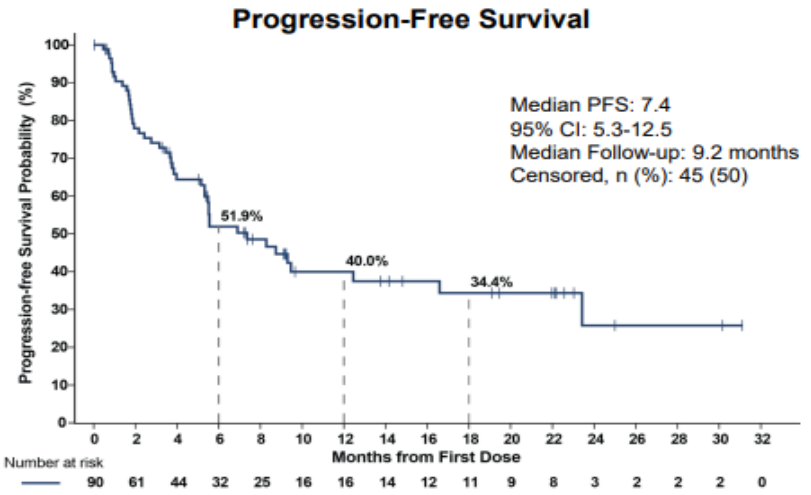
Wang, ASH, 2022

Pirtobrutinib for MCL (BRUIN study)



Data cutoff date of 31 January 2022. Data for 18 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. *Indicates patients with >100% increase in SPD..





Data cutoff date of 31 January 2022. Response status per Lugano 2014 criteria based on IRC assessment.

Prior cBTKi MCL Patients	n=90
Overall Response Rate[a], % (95% CI)	**57.8% (46.9-68.1)**
Best Response[b]	
CR, n (%)	18 (20.0)
PR, n (%)	34 (37.8)
SD, n (%)	14 (15.6)
PD, n (%)	15 (16.7)

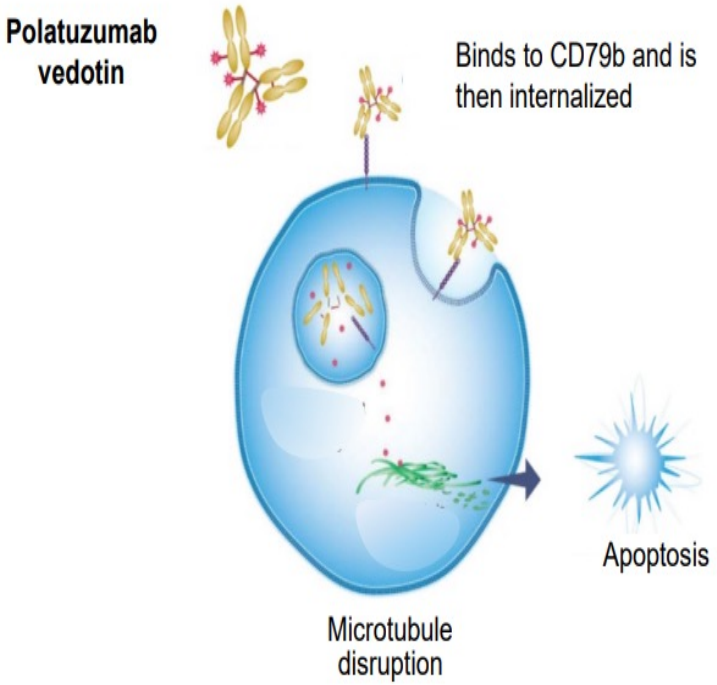
cBTKi Naïve MCL Patients	n=14
Overall Response Rate[a], % (95% CI)	**85.7% (57.2-98.2)**
Best Response[c]	
CR, n (%)	5 (35.7)
PR, n (%)	7 (50.0)
SD, n (%)	0 (0.0)
PD, n (%)	1 (7.1)

Wang, ASH, 2022

BRUIN study: Take home points

- Pirtobrutinib is safe and effective in patients with high-risk relapsed MCL
- Efficacy after covalent BTK inhibitors ((ibrutinib, acalabrutinib or zanubrutinib)
- is important and serves an unmet need
- Based on the BRUIN study, the drug received accelerated approval in patients with relapsed MCL after 2 prior lines of treatment that included a cBTKi
- A randomized trial comparing pirtobrutinib vs. BTKi of choice is currently ongoing

Polatuzumab Vedotin for 1st line DLBLC (Polarix Study)



Patients

- Previously untreated DLBCL
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

Stratification factors

- IPI score (2 vs 3–5)
- Bulky disease (<7.5 vs ≥7.5cm)
- Geographic region (Western Europe, US, Canada, & Australia vs Asia vs rest of world)

R 1:1

Pola-R-CHP

Polatuzumab vedotin (1.8mg/kg)*
R-CHP + vincristine placebo

Cycles 1–6
(1 cycle=21 days)

R-CHOP

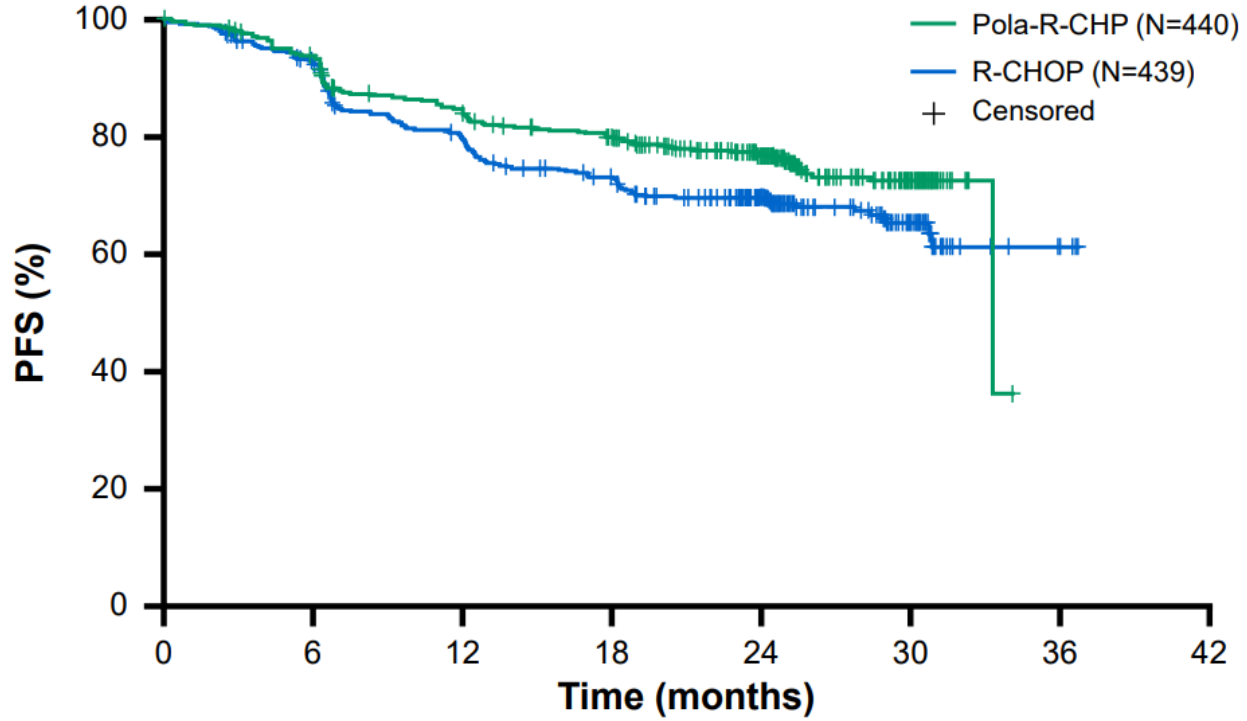
R-CHOP† + polatuzumab vedotin placebo

Rituximab
375mg/m²

Cycles 7 & 8

Tilly, NEJM, 2022

Polatuzumab Vedotin for 1st line DLBLC (Polarix Study)



No. of patients at risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
NE, not evaluable.

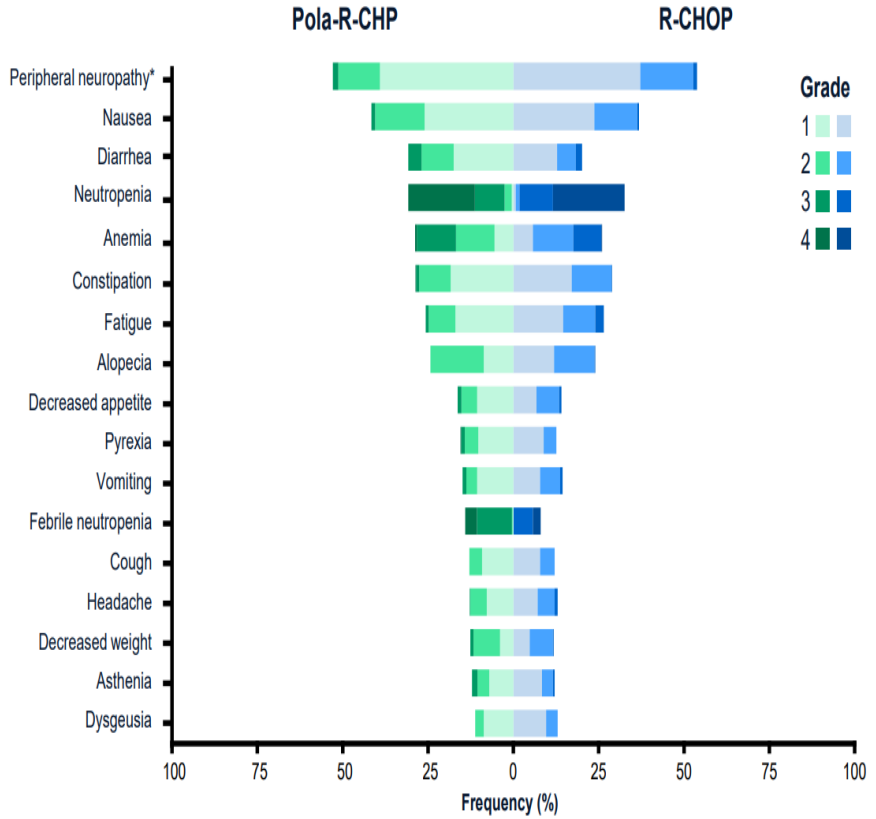
HR 0.73 (P<0.02)
95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP
- **24-month PFS:**
  76.7% with Pola-R-CHP versus
  70.2% with R-CHOP (**Δ=6.5%**)

Tilly, NEJM, 2022

Polatuzumab Vedotin for 1st line DLBLC (Polarix Study)

n (%)	Pola-R-CHP (N=435)	R-CHOP (N=438)
Any-grade adverse events	426 (97.9)	431 (98.4)
Grade 3–4	251 (57.7)	252 (57.5)
Grade 5	13 (3.0)	10 (2.3)
Serious adverse events	148 (34.0)	134 (30.6)
Adverse events leading to:		
Discontinuation of any study drug	27 (6.2)	29 (6.6)
Polatuzumab vedotin / vincristine	19 (4.4)	22 (5.0)
Dose reduction of any study drug	40 (9.2)	57 (13.0)

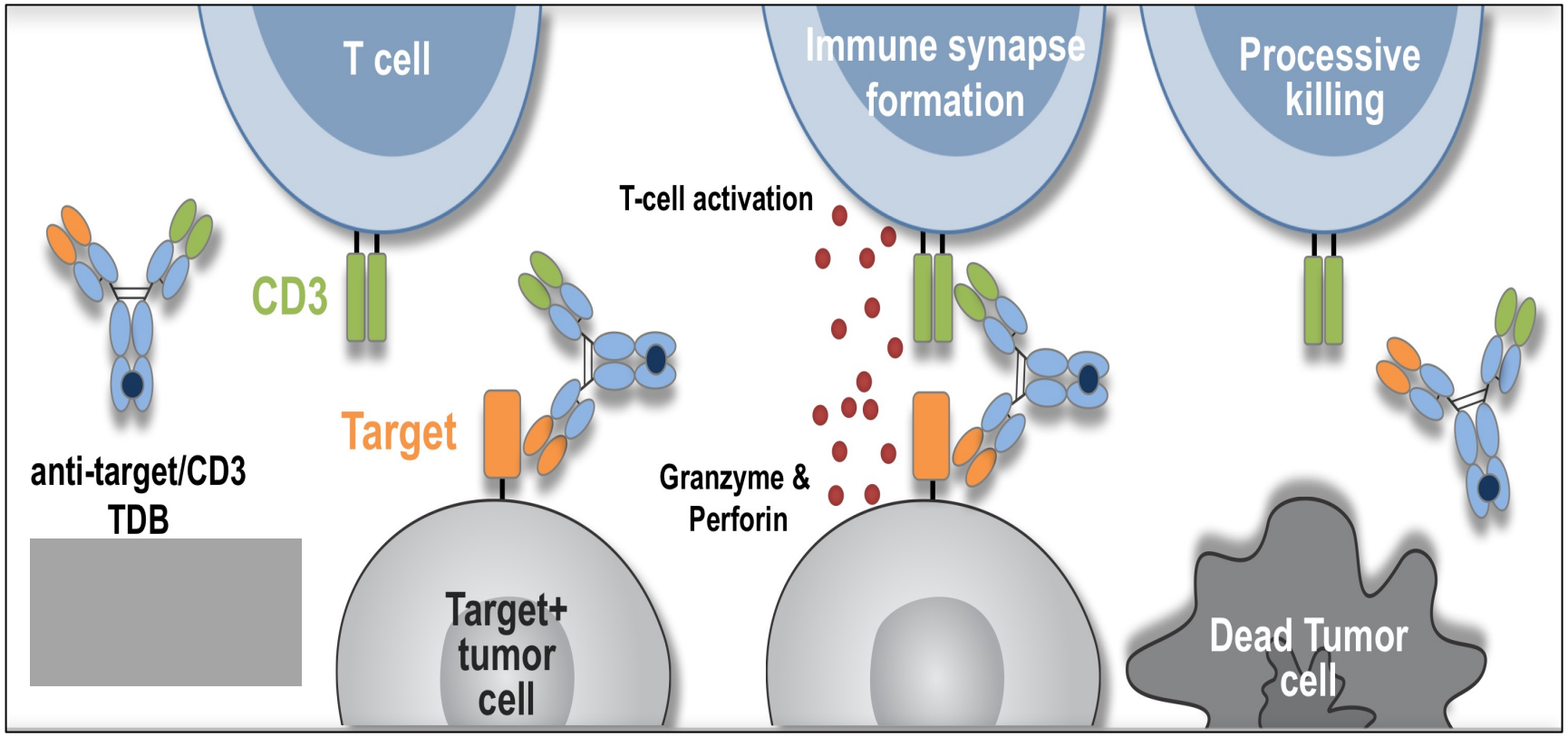


Tilly, NEJM, 2022

POLARIX study: Take home points

- Polarix met the primary efficacy end point of PFS and Pola-R-CHP was superior to R-CHOP
- No added toxicity in a double blind trial
- New standard of care for 1st line DLBCL
- Based on this study, Pola-R-CHP was approved in first-line for patients with DLBCL (IPI >1)

Bispecific antibodies

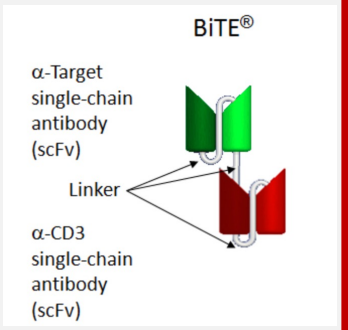


Bispecific antibodies

The Original: Proof of Concept

The Emerging: Viable Future Therapies?

Blinatumomab

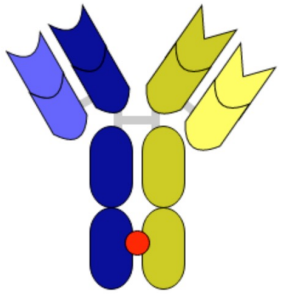


CD3 (scFV) x CD19 (scFV)

Epcoritamab

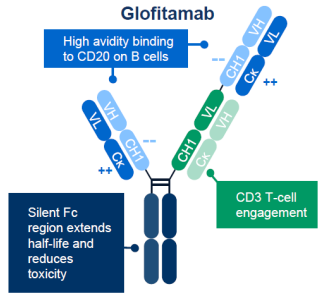
DuoBody- CD3 x CD20 BsAb

Mosunetuzumab



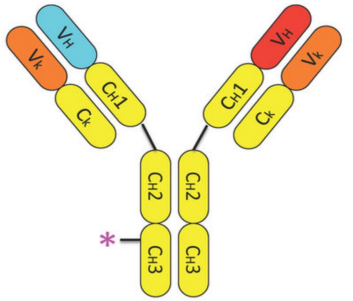
CD3 x CD20 Knobs-in-hole Fc BsAb

Glofitamab



3 (Fab) x CD20 (Fab x2) Fc BsAb

Odronextamab



CD3 x CD20 Common LC Fc BsAb

PDUFA: 5/21/23
For DLBCL

Approved: 12/22/22
For FL

PDUFA: 7/1/23
For DLBCL

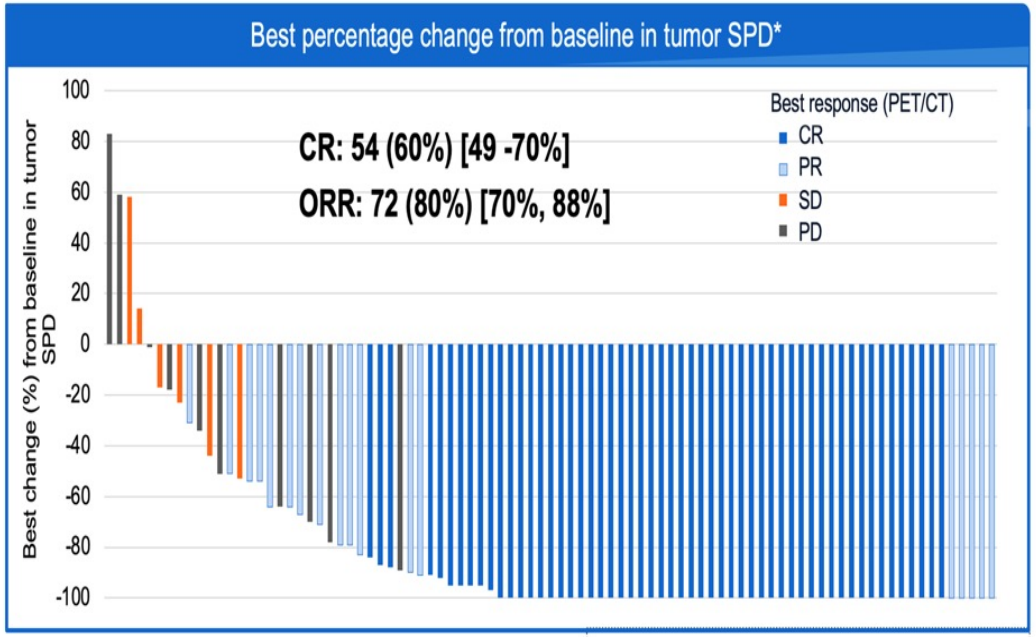
Mosunetuzumab for r/r FL

N	**90**
Median age	**60 (53-67)**
Prior lines	**3 (2-4)**
Prior CAR-T	**3%**
Prior ASCT	**21%**
Bulky disease (>6cm)	**34%**
POD24	**52%**

Route	IV
Cycles	21 days
Duration	7-17 cycles

Budde, Lancet, 2022

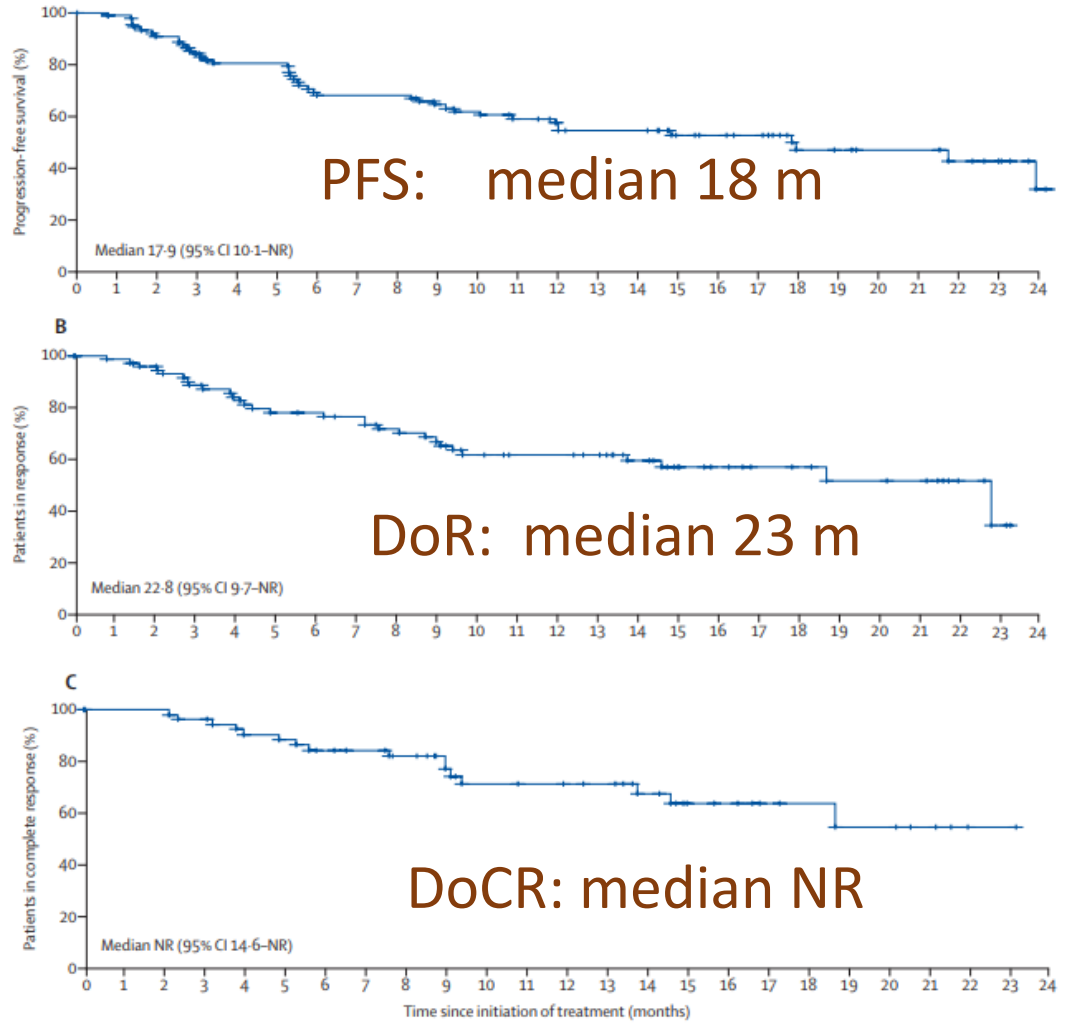
Mosunetuzumab for r/r FL



Median time to CR:
3 mo (1.2, 18.9)

Median DoR:
22.8 months (range: 9.7, NE)

Median PFS:
17.9 months (95% CI: 10.1, NE)



Budde, Lancet, 2022

Mosunetuzumab for r/r FL

N (%)	N=90
AE	90 (100%)
Mosunetuzumab related*	83 (92.2%)
Grade 5 (fatal) AE	2 (2.2%)†
Mosunetuzumab related*	0
AE leading to discontinuation of treatment	4 (4.4%)‡
Mosunetuzumab related*	2 (2.2%)‡
ICANS*	4 (4.4%)
Grade 3†	0

N (%)	N=90
CRS (any Grade)*	40 (44.4%)
Grade 1	23 (25.6%)
Grade 2	15 (16.7%)
Grade 3	1 (1.1%)
Grade 4	1 (1.1%)†
Serious AE of CRS (any Grade)	21 (23.3%)‡
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–23.7)
C1D15–21	26.6 (0.1–390.9)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	10 (11.1%)
Tocilizumab for CRS management	7 (7.8%)

- **Mosunetuzumab had a manageable safety profile. AEs leading to discontinuation were uncommon.**

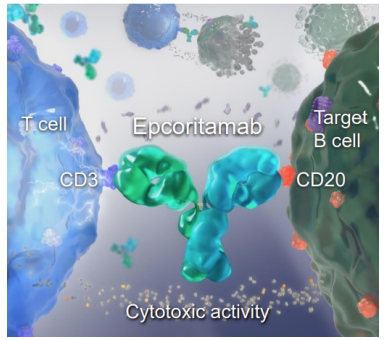
*AE considered related to treatment by the investigator; †mosunetuzumab unrelated: malignant neoplasm progression and unexplained death (1 patient each); ‡mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Esptein-Barr viremia and Hodgkin's disease (1 patient each); AE, adverse event; Gr, Grade ;

Budde, Lancet, 2022

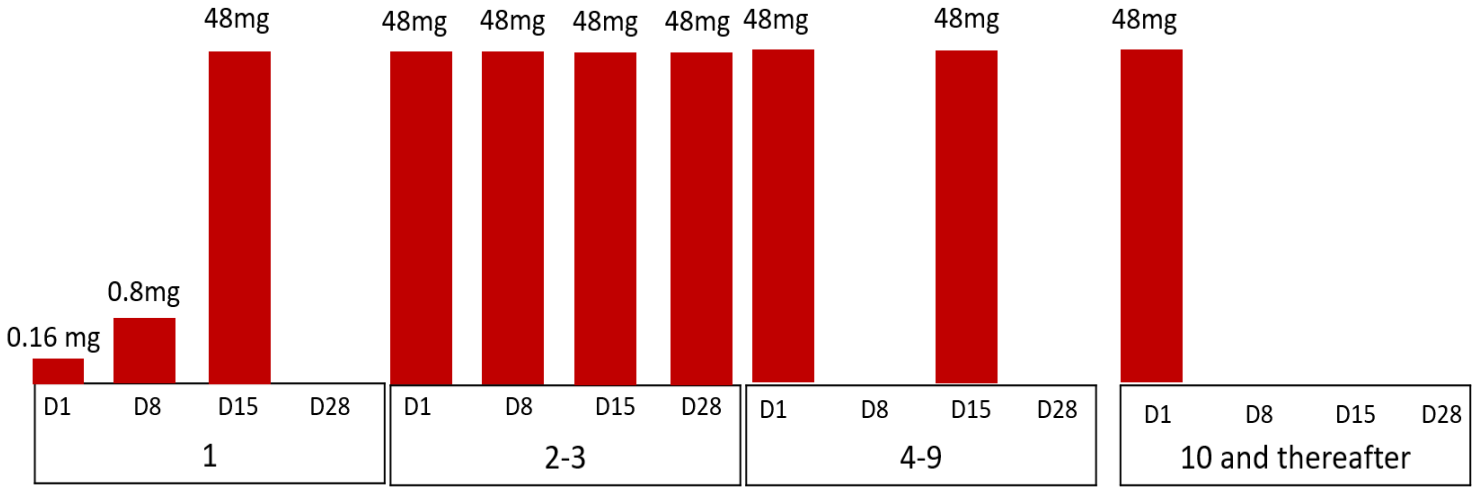
Mosunetuzumab study: Take home points

- Mosunetuzumab is an effective and time-limited IV (SC in future) for patients with relapsed FL
- Alternative to CAR-T
- Based on this study, the drug received accelerated approval in patients with relapsed FL after 2 prior lines of treatment

Epcoritamab for R/R DLBCL



N	**157**
Median age	**64 (20-83)**
Prior lines	**3 (2-11)**
Prior CAR-T	**38.9%**
Prior ASCT	**19.7%**
Primary refractory	**61.1%**
Refractory to previous treatment	**82.8%**

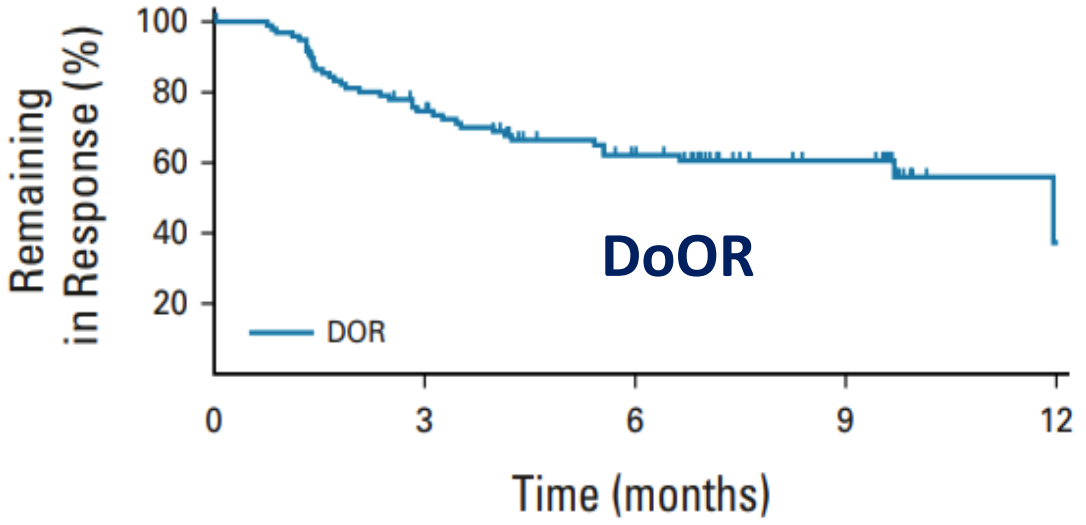


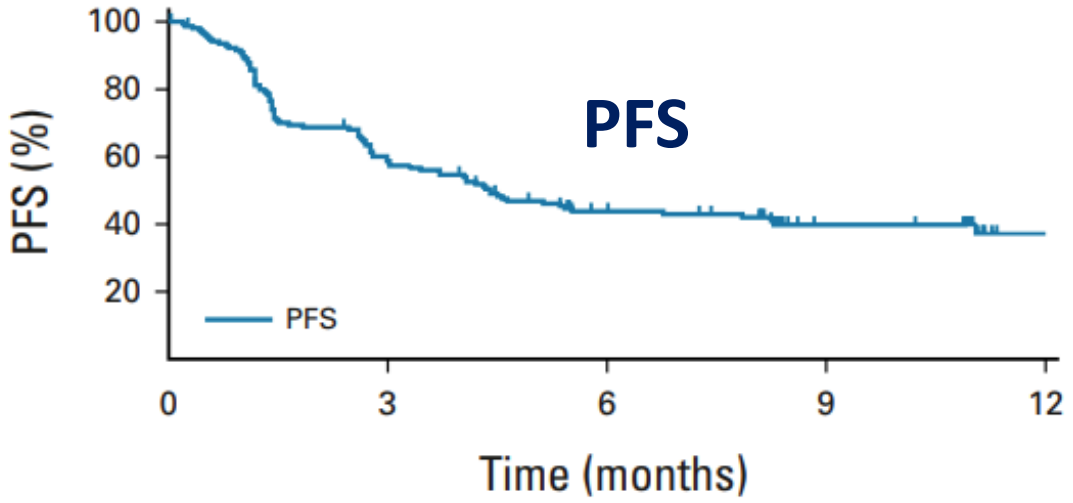
Route	SubQ
Cycles	28 days
Duration	Until PD or intolerance

Thieblemont, JCO, 2022

Epcoritamab for R/R DLBCL

CR	38.9%
CR in pts with prior CAR-T	34.4%
DoCR months	12 (9.7-NR)
CR at 12 months	-
ORR	63%
DoOR	12 (6.6-NR)
OR at 12 months	-
Median PFS (months)	4.4 (3.0-7.9)
12-month PFS	-
Median OS (months)	NR (11.3-NR)
12-month OS	-
Median time to response	1.4 months
Median time to CR	2.7 months



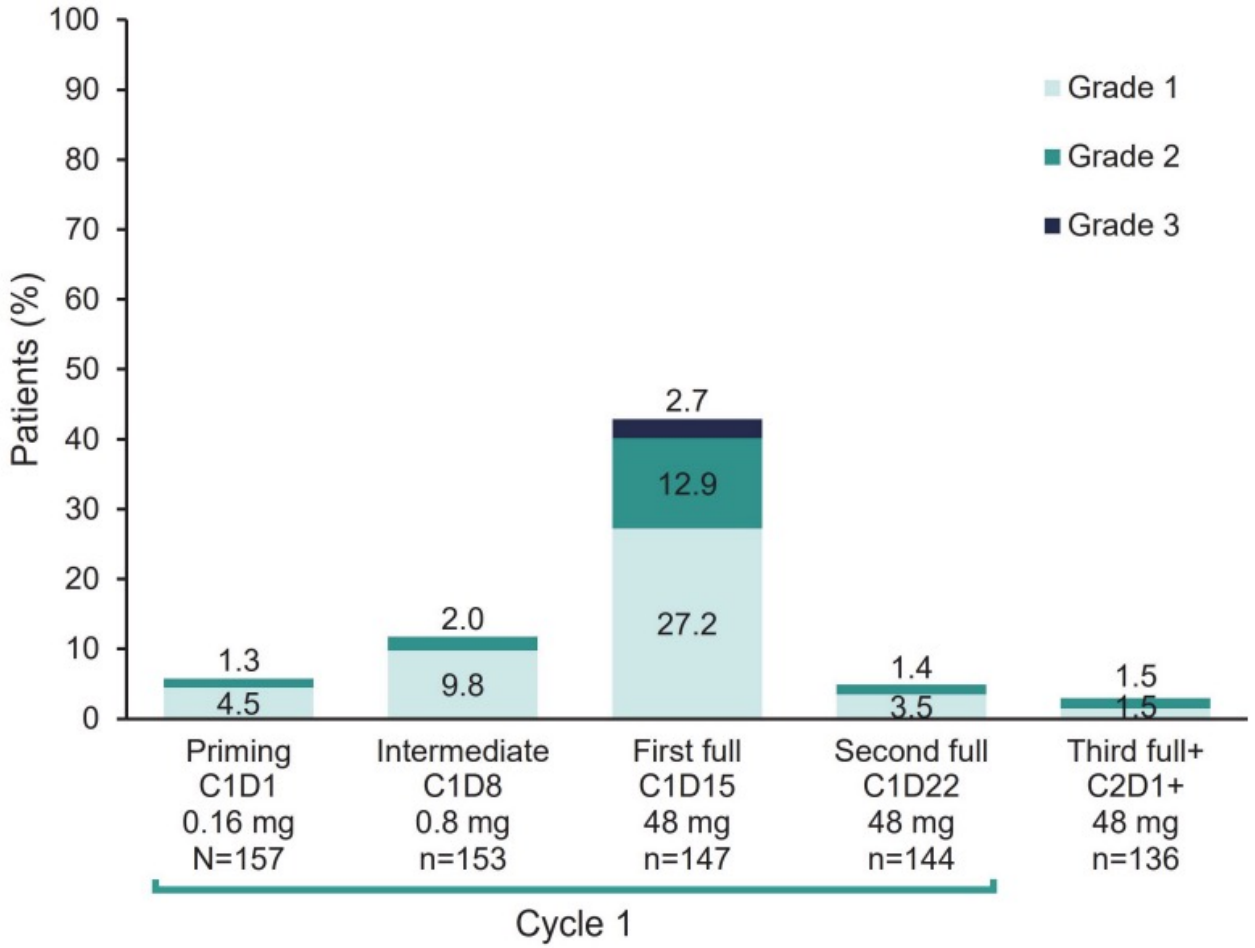


median follow-up of 10.7 months

Thieblemont, JCO, 2022

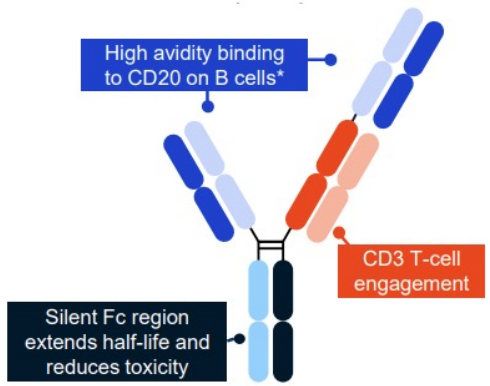
Epcoritamab for R/R DLBCL

CRS (ASTCT)	**49.7%**
G1	31.8%
G2	15.2%
G3	2.5%
G4	0
ICANS	**6.4%**
G1	4.4%
G2	1.3%
G3	0
G4	0
G5	0.6%

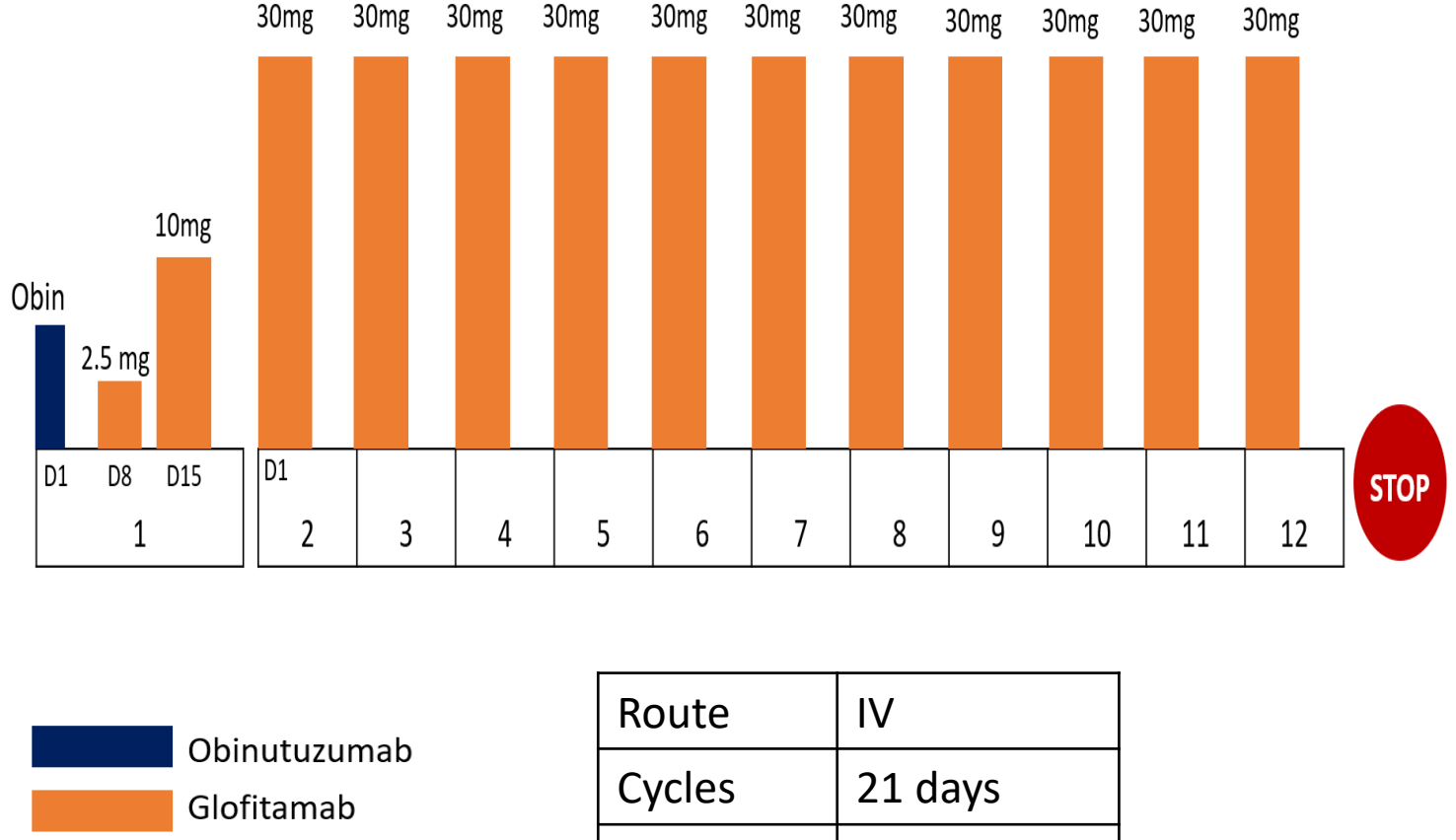


Thieblemont, JCO, 2022

Glofitamab for R/R DLBCL



N	154
Median age	66 (21-90)
Prior lines	3 (2-7)
Prior CAR-T	33%
Prior ASCT	18%
Primary refractory	58%
Refractory to previous treatment	90%

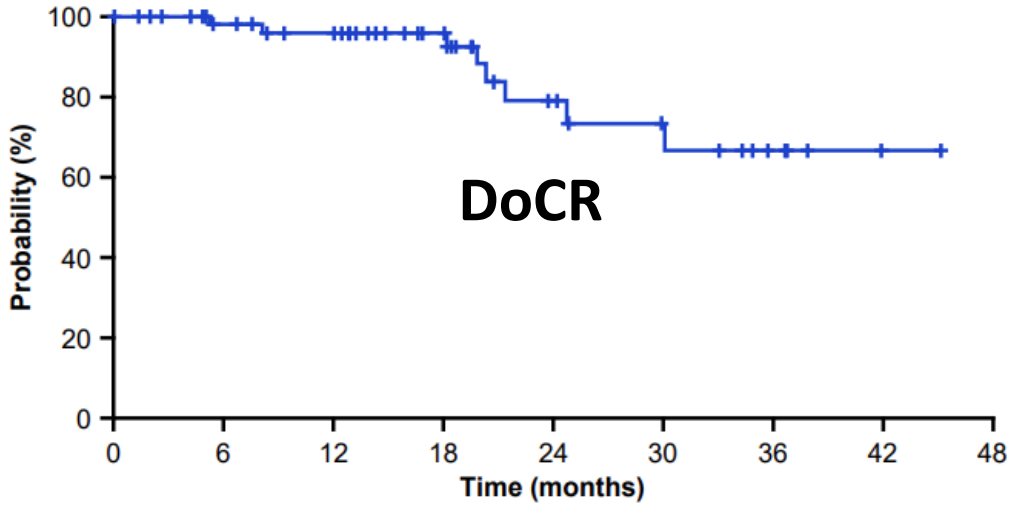


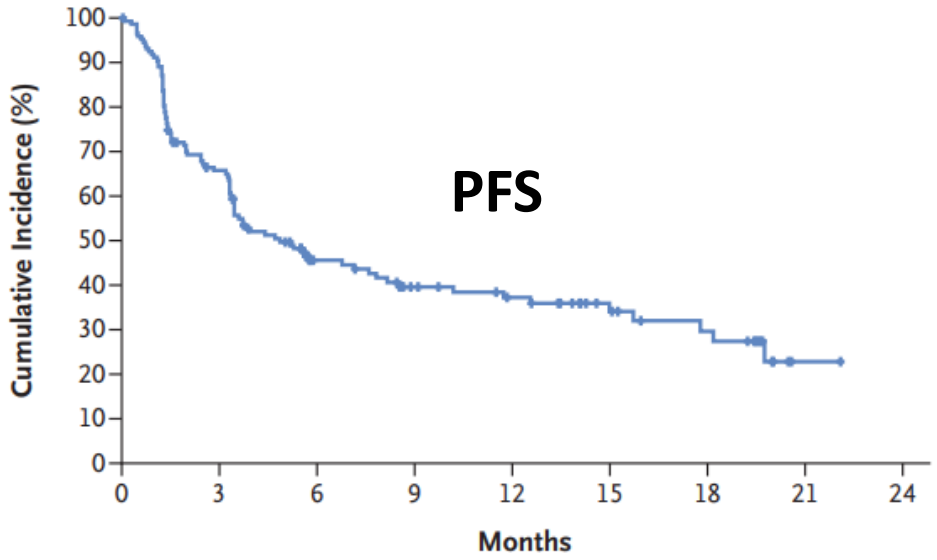
Route	IV
Cycles	21 days
Duration	12 cycles

Dickinson, NEJM, 2022

Glofitamab for R/R DLBCL

CR	39%
CR in pts with prior CAR-T	35%
DoCR	NR (30.1-NR)
CR at 24 months	79%
ORR	52%
DoOR	18.4 (13.7-NR)
OR at 12 months	64%
Median PFS (months)	4.9 (3.4-8.1)
12-month PFS	37%
Median OS (months)	11.5 (7.9-15.7)
12-month OS	50%
Median time to response	-
Median time to CR	1.4



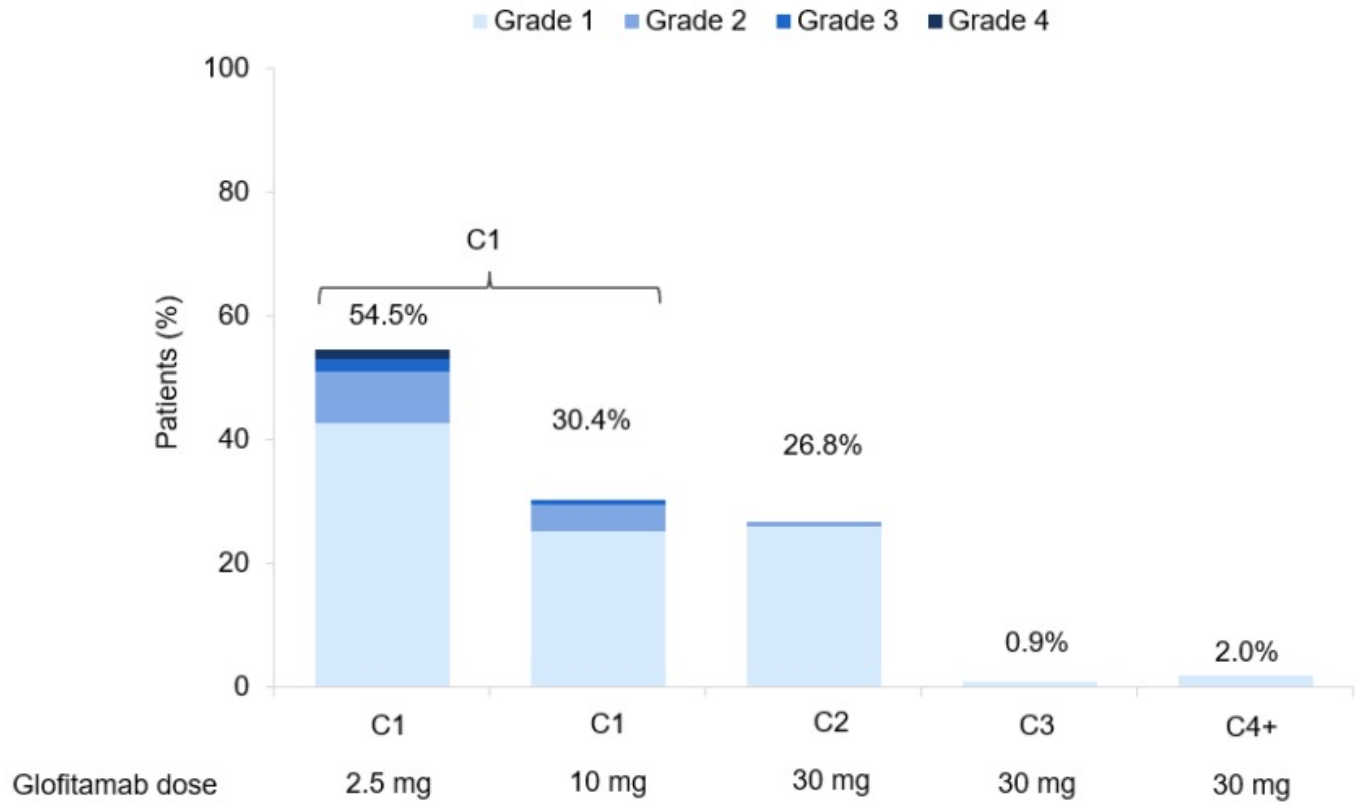


median follow-up of 12.6 months

ɔn, NEJM, 2022; Hutchings, ASH, 2022

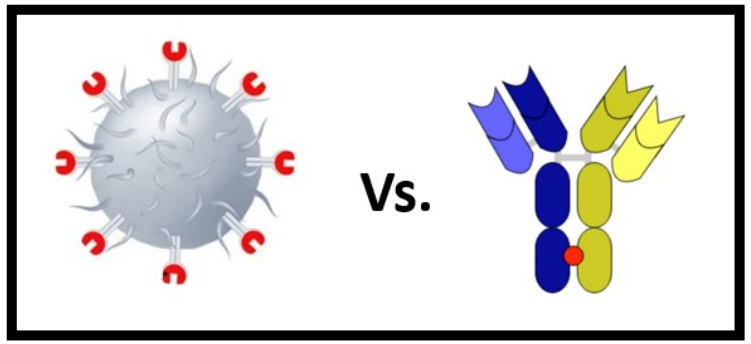
Glofitamab for R/R DLBCL

CRS (ASTCT)	**63%**	
G1		**47%**
G2		**12%**
G3		**3%**
G4		**1%**
ICANS	**8%**	
G1		
G2	**5%**	
G3	**3%**	
G4		

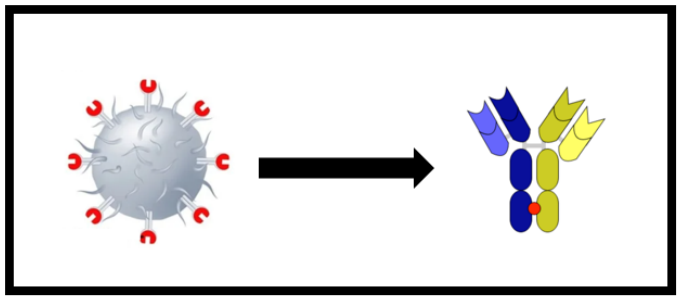


Dickinson, NEJM, 2022

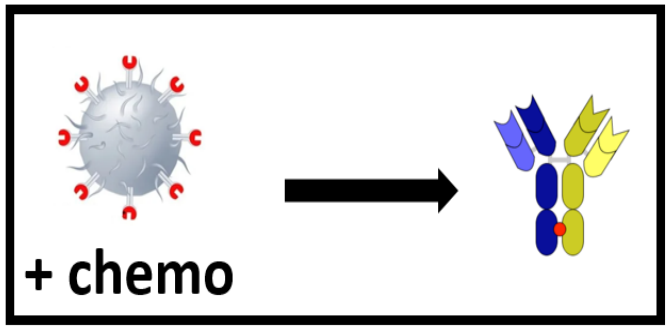
BsAb in 1st line



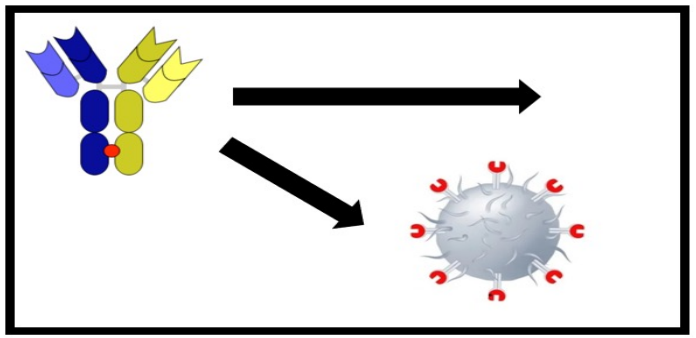
3rd line



Post-CAR-T relapse



CAR-T in 1st line



BsAb as a bridge vs. destination

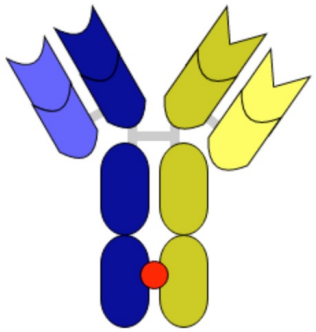
BsAb=bispecific antibody

- Data: N of studies, follow-up, RWE
- One time treatment!
- Established in second line (OS benefit)

- Intent-to-treat results?
- Logistical challenges
  - Healthcare related
  - Patient related

- Off-the-shelf
- Patient convenience
- High potential for combination
- Retreatment potential

- Shorter follow-up
- Long-term AEs (infections, cytopenia, etc.)
- Physicians' comfort level?
- Approval in earlier lines?



Right treatment? Vs. Right sequence?

Summary

- CLL
  - **Zanubrutinib** for first-line and relapsed CLL **(FDA approved)**
- MCL
  - **Pirtobrutinib** for 3rd line MCL (after cBTKi) **(FDA approved)**
- FL
  - **Mosunetuzumab** for 3rd line FL **(FDA approved)**
- DLBCL
  - **Polatuzumab Vedotin** for 1st line DLBCL **(FDA approved)**
  - **Epcoritamab** for 3rd line DLBCL **(Approval is expected)**
  - **Glofitamab** for 3rd line DLBCL **(Approval is expected)**

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Thank you

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UW Medicine