Bispecific T-Cell Engagers (BiTEs) in Hematologic Malignancies

Grand Rounds

January 6, 2023

Disclosures

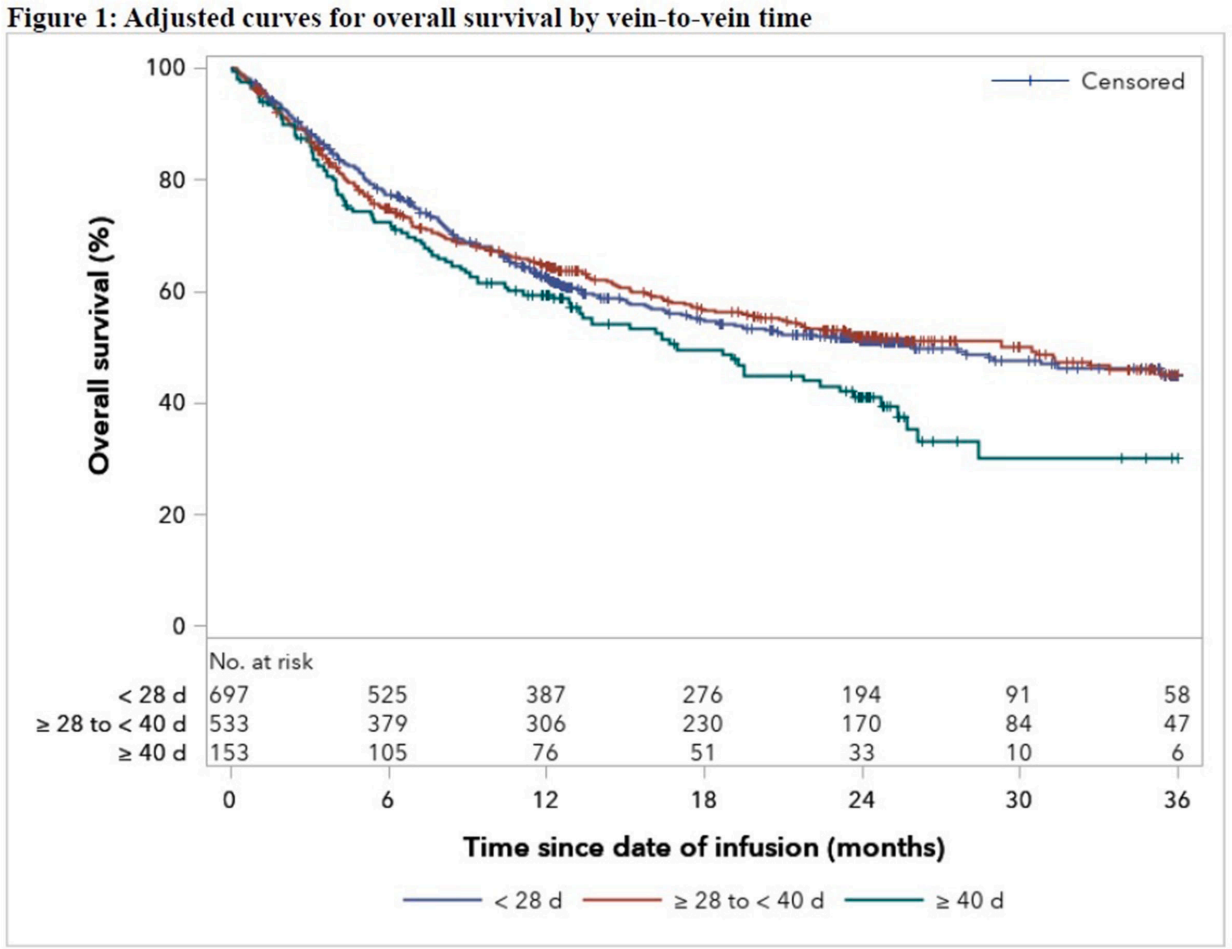
- None

Learning Objectives

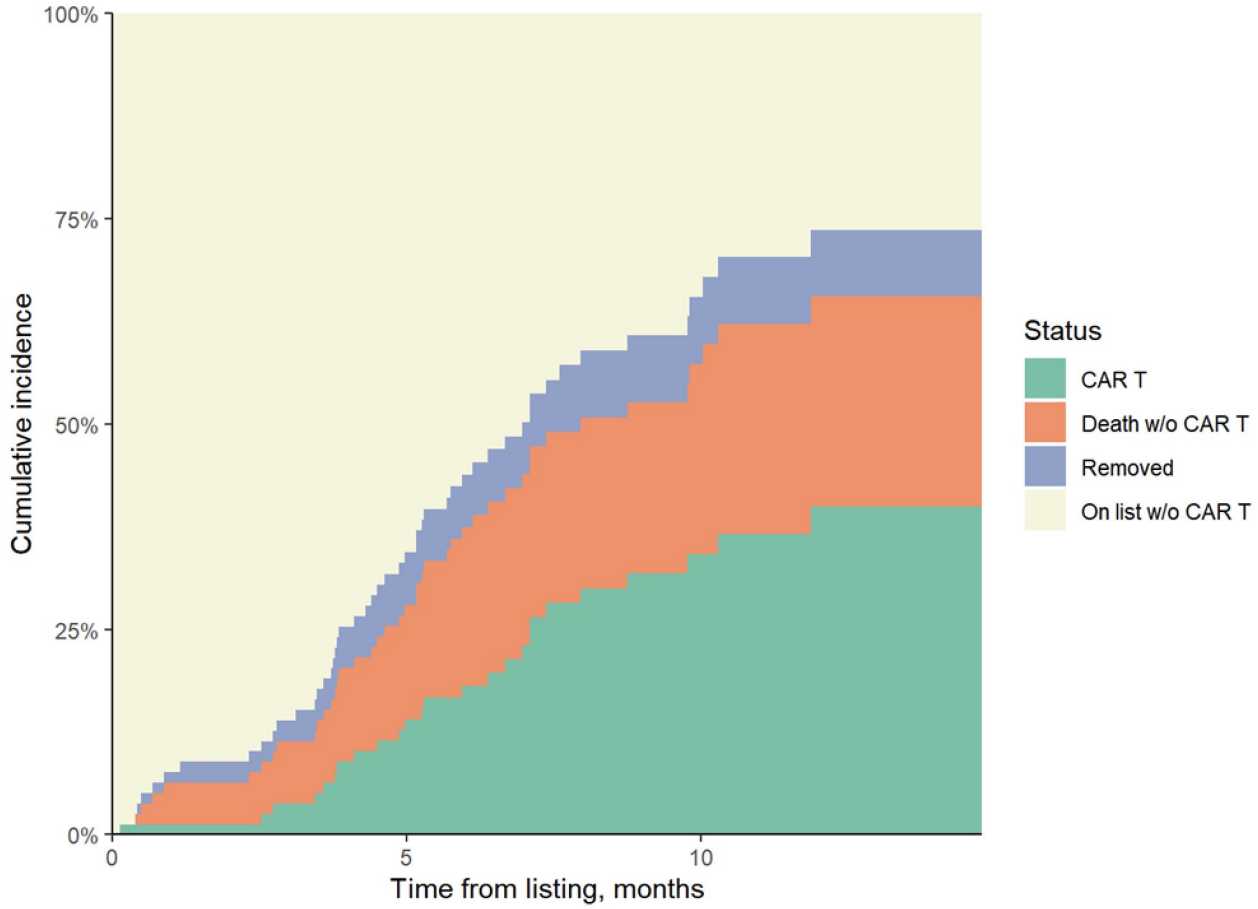
- Identify the need for accessible T effector cell immunotherapy in the treatment of relapsed/refractory DLBCL, FL, and MM
- Dissect the dosing regimens, CRS prophylaxis strategies, efficacy, and toxicity in four phase 2 BiTE trials published in 2022
- Compare the outcomes with BiTEs to CAR-T cell therapy in lymphoma and myeloma

Impact of commercial CAR-T wait times

CIBMTR analysis of commercial Axi-cel (n=1383)



UAMS/MCW wait list data for commercial Ide-cel (n=80)



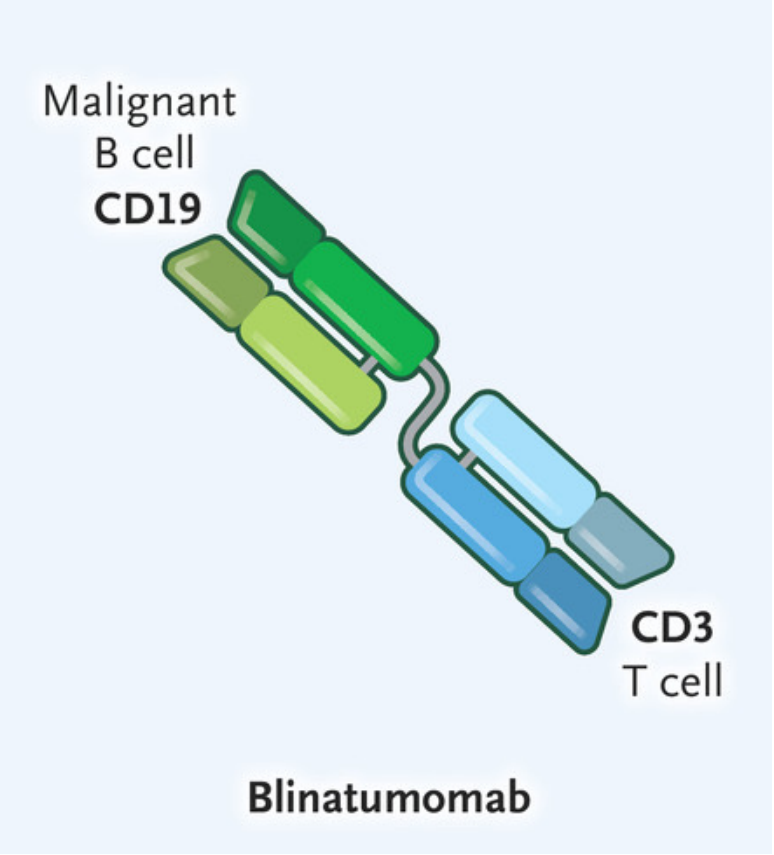
ASH 2022 Abstract 3345; ASH 2022 Abstract 3588

Overview

- Background: the success of blinatumomab (CD19xCD3 BiTE) in ALL
- Lymphoma (CD20xCD3 BiTEs)
  - Glofitamab *NEJM 12/15/22*
  - Epcoritamab *EPCORE NHL-1 JCO 12/22/22*
  - Ondronextamab *ELM-2 ASH 2022 ABSTRACTS 444 & 949*
  - Mosunetuzumab *Lancet Oncol 8/23/22*; *FDA APPROVED 12/22/22 for 3L R/R FL*
- Myeloma
  - Teclistamab (BCMAxCD3 BiTE) *MagisTEC-1 NEJM 8/11/22; FDA APPROVED 10/25/22 for 5L R/R MM*
  - Talquetamab (GPRC5DxCD3 BiTE) *MonumenTAL-1 NEJM 12/15/22*
  - Cevostamab (FcRH5xCD3 BiTE) *unpublished*

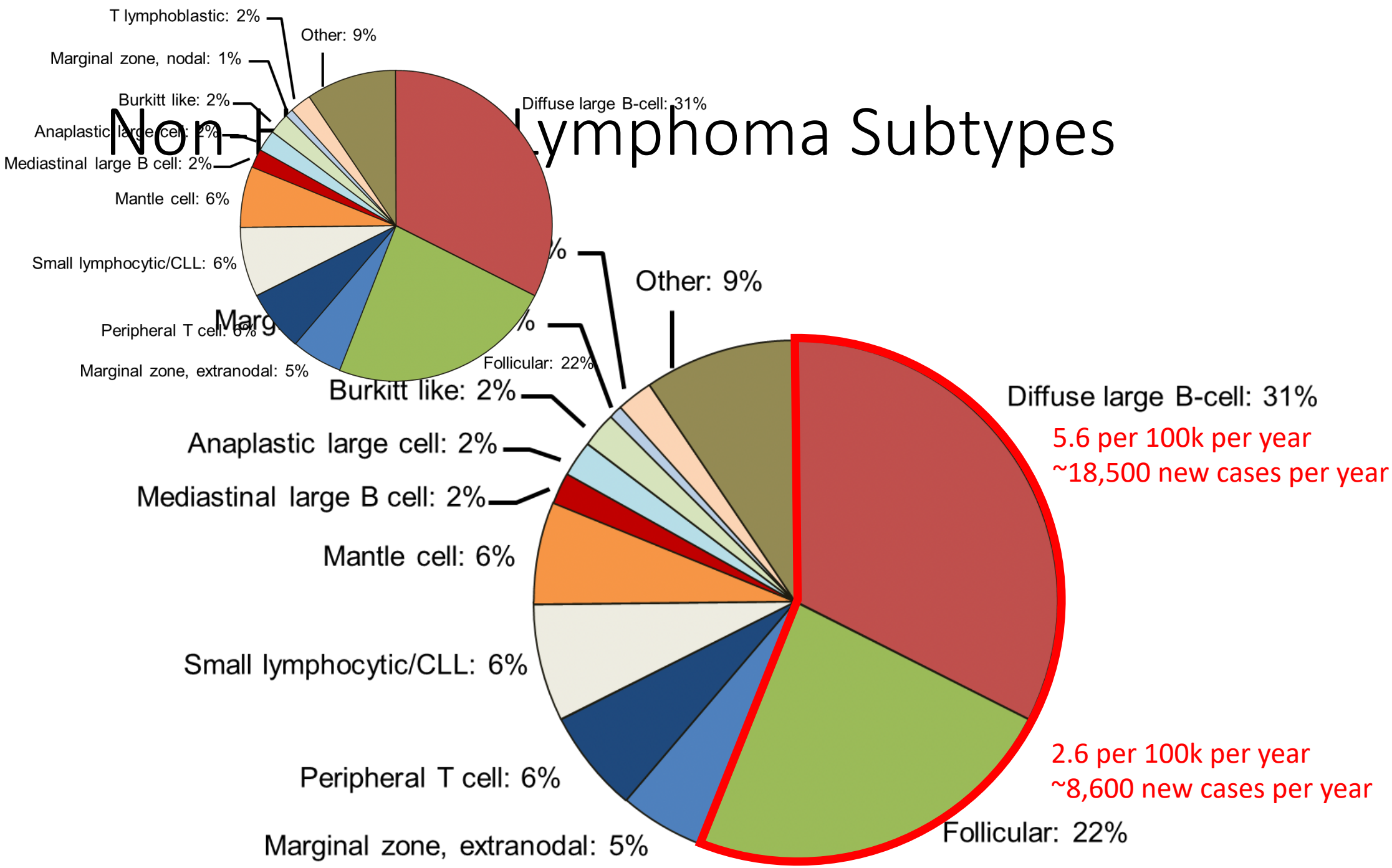
The success of Blinatumomab

- Derived from the term B lineage-specific anti-tumor mouse monoclonal antibody
- FDA approved for R/R Ph- B-ALL in 2014, then for Ph- B-ALL in MRD+ CR1 or CR2 in 2018
- Downside: small molecule with resultant short half life → requires continuous infusion



CD20xCD3 BiTEs in Non-Hodgkin Lymphomas

Non-Hodgkin Lymphoma Subtypes

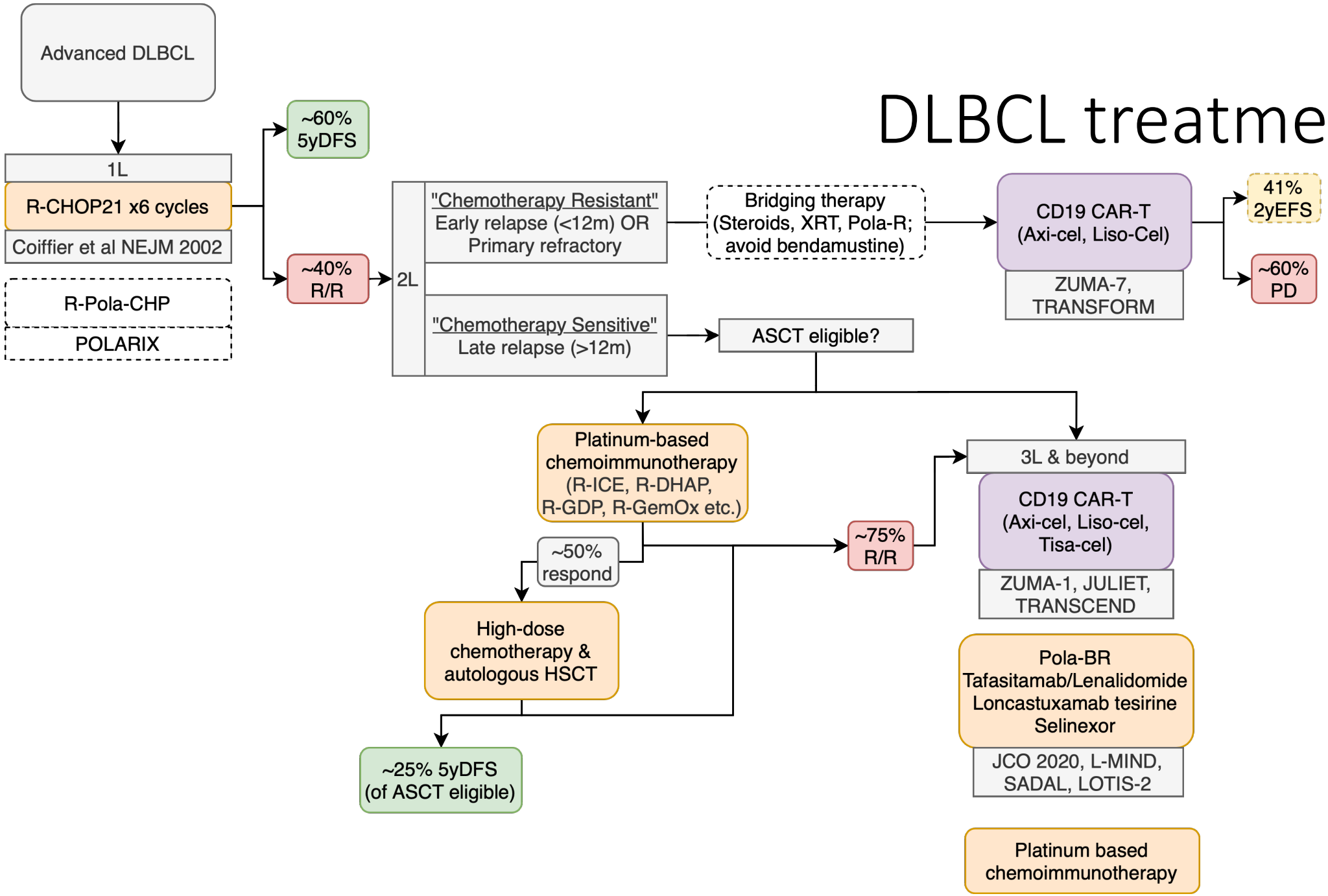


JCO 1998 Aug;16(8):2780-95, seer.cancer.gov

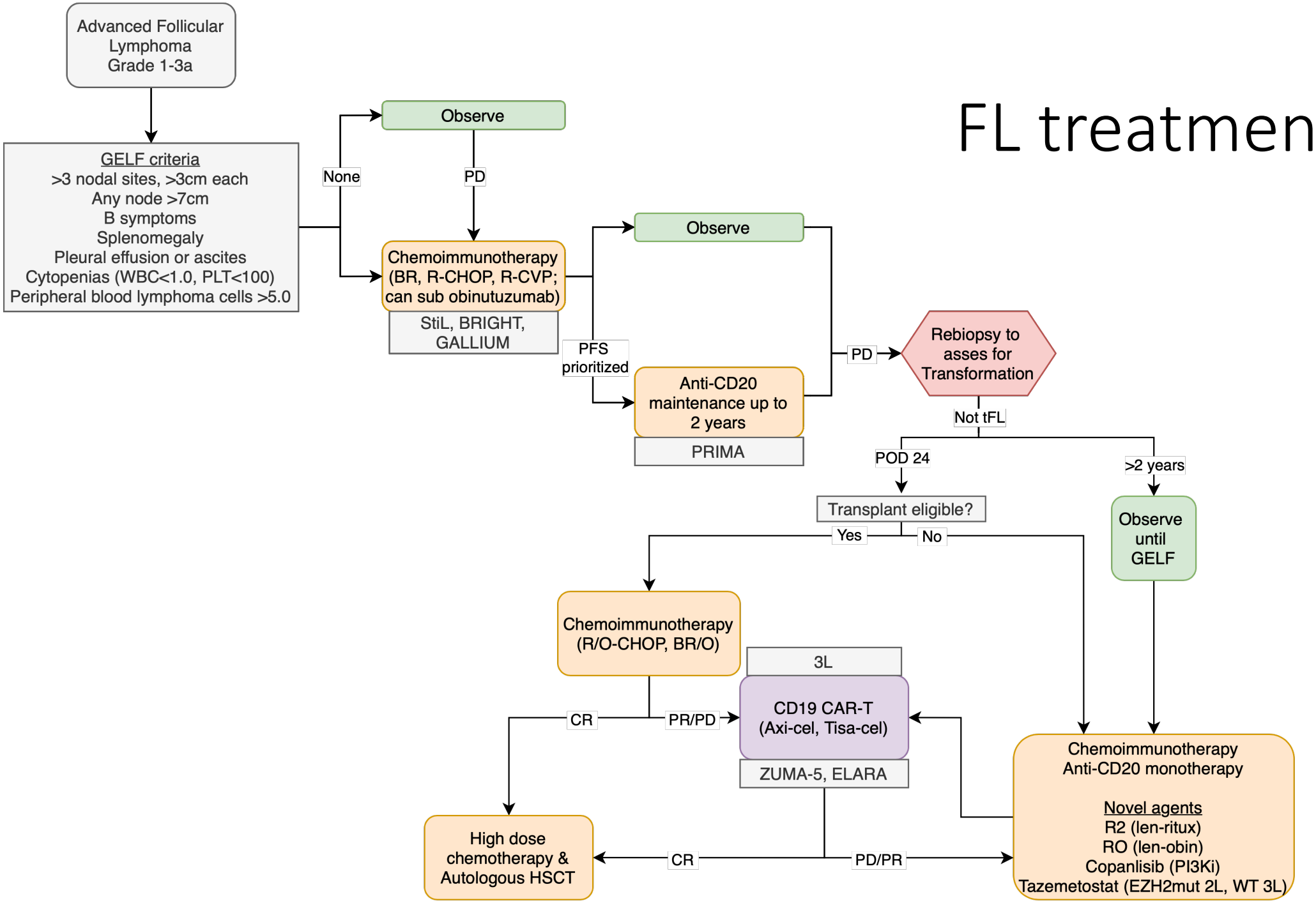
CD20xCD3 BiTEs: trial vs publication histology

- Glofitamab
  - NCT03075696: "…Relapsed/Refractory B-Cell Non-Hodgkin's Lymphoma"
    - Inclusion: a histologically-confirmed hematological malignancy that is expected to express CD20
    - Exclusion: CLL, Burkitt's, LPL, PCNSL
  - Dickinson et al. NEJM 2022: **DLBCL, HGBL, PMBL, tFL**
- Epcoritamab
  - NCT03625037: "…Relapsed, Progressive or Refractory B-Cell Lymphoma"
    - Inclusion: Documented CD20+ mature B-cell neoplasm (DLBCL, HGBL, PMBL, FL, MCL, SLL, MZL)
    - Exclusion: PCNSL or CNS involvement
  - Thieblemont et al. JCO 2022: **DLBCL, PMBL, HGBL, FL G3b**
- Mosunetuzumab
  - NCT02500407: "…Non-Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL)"
    - Inclusion: B-cell hematologic malignancies expected to express CD20
    - Exclusion: CNS lymphoma
  - Budde et al. Lancet Oncol. 2022: **FL G1-3a**

DLBCL treatment



FL treatment



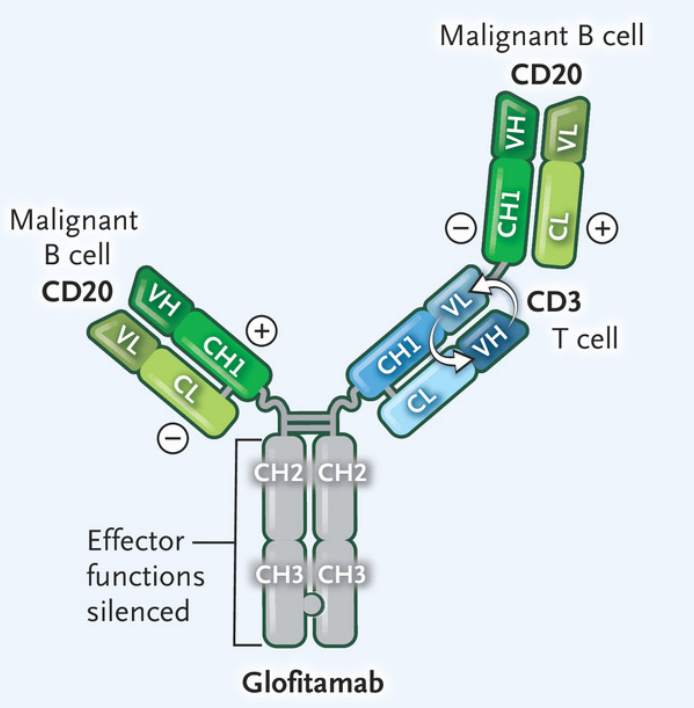
CD19 CAR-T

- No prior CD19 targeted therapy or T effector cell therapy

CD20xCD3 BiTEs

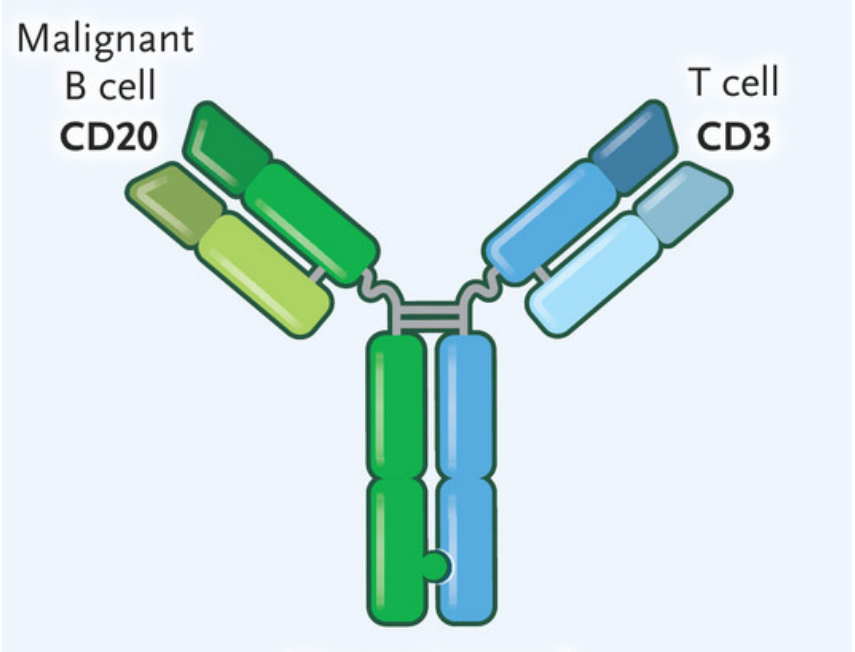
- Required prior CD20 therapy
- 30-40% prior CAR-T therapy in aggressive B-cell lymphoma trials

CD20xCD3 BiTEs



Glofitamab (bivalent)

Epcoritamab & Mosunetuzumab



Meaningful or marketing?

NEJM 2022; 387:2287-2290.

CD20xCD3 BiTE trials

	Glofitamab	Epcoritamab		Mosunetuzumab
Diagnosis	DLBCL, tFL, HGBL, PMBL	DLBCL, FL G3b, HGBL, PMBL		r/r FL G1-3a
Line	3L	3L		3L
Required prior therapy	anti-CD20 and anthracycline	anti-CD20 and prior or ineligible for ASCT		anti-CD20 and alkylating agent
Phase	2	2		2
Duration of therapy	Fixed	Continuous		Fixed
Route	IV	SQ		IV

Dosing Regimens, CRS ppx, and hospitalization

Glofitamab IV

Fixed duration, twelve 21-day cycles

Cycle 1 (step-up dosing)

- Day 1: Obinutuzumab 1000mg IV
- Day 8: Glofitamab 2.5mg IV
- Day 15: Glofitamab 10mg IV

Cycles 2 to 12

- Day 1: Glofitamab 30mg IV

Supportive Care:

- Methylprednisolone 80mg IV or equivalent cycles 1 and 2
  - Optional in later cycles unless develops CRS
- Acetaminophen 500-1000mg
- Diphenhydramine 50-100mg

- Hospitalized for first dose of Glofitamab, outpatient for subsequent doses unless G2 or higher CRS with first

Epcoritamab SC

Indefinite therapy, 28-day cycles

Cycle 1 (step-up dosing)

- Day 1: Epcoritamab 0.16mg SC priming dose
- Day 8: Epcoritamab 0.8mg SC intermediate dose
- Days 15 and 22: Epcoritamab 48mg SC full dose

Cycles 1 to 3: Epcoritamab 48mg SC weekly (days 1, 8, 15, 22)

Cycles 4 to 9: Epcoritamab 48mg SC every two weeks (days 1, 15)

Cycle 10 and beyond: Epcoritamab 48mg SC (day 1)

Supportive Care:

- Prednisolone 100mg PO daily x4 for each dose of cycle 1 (days 1-4, 8-11, 15-18, and 22-25)
  - If grade 2 or higher CRS after 4th dose of cycle 1, corticosteroids were given x4 days for each dose until CRS resolved
- Diphenhydramine 50mg
- Acetaminophen 650-1000mg

- Hospitalized 24h after 3rd dose (first full dose)

Mosunetuzumab IV

Fixed duration, up to seventeen 21-day cycles

Cycle 1 (step-up dosing)

- Day 1: Mosunetuzumab 1mg IV
- Day 8: Mosunetuzumab 2mg IV
- Day 15: Mosunetuzumab 60mg IV

Cycle 2

- Day 1: Mosunetuzumab 60mg IV

Cycle 3 onwards (to cycle 8 if CR, cycle 17 if PR/SD)

- Day 1: Mosunetuzumab 30mg IV

Supportive care:

- Corticosteroids (MP 80mg IV or Dex 20mg IV) cycles 1 and 2
  - Optional from cycle 3 on

- Hospital admission not mandatory

Baseline Characteristics

	Glofitamab	Epcoritamab
Enrollment	1/2020 to 9/2021	6/2020 to 1/2022
Data Cutoff	3/14/22	1/31/22
N	154	157
Age	66 (21-90)	64 (20-83)
Sex	65%M/35%F	60%M/40%F
Median prior LOT	3 (2-7)	3 (2-11)
Diagnosis	71% DLBCL 18% tFL 7% HGBL 4% PMBL	89% DLBCL (28% transformed) 6% HGBL 2% PMBL 3% FL3b
Primary refractory	58%	61%
Prior CAR-T	33%	38.9% (75% progressed <6m)
Prior ASCT	18%	19.7% (58% relapse <12m)

	Mosunetuzumab
Enrollment	5/2019 to 9/2020
Data Cutoff	8/27/21
N	90
Age	60 (53-67)
Sex	61%M/39%F
Median prior LOT	3 (2-4)
Prior therapy	100% alkylator 100% anti-CD20 82% anthracycline 19% PI3Ki 14% IMiD
POD24	52%
Prior CAR-T	3%
Prior ASCT	21%

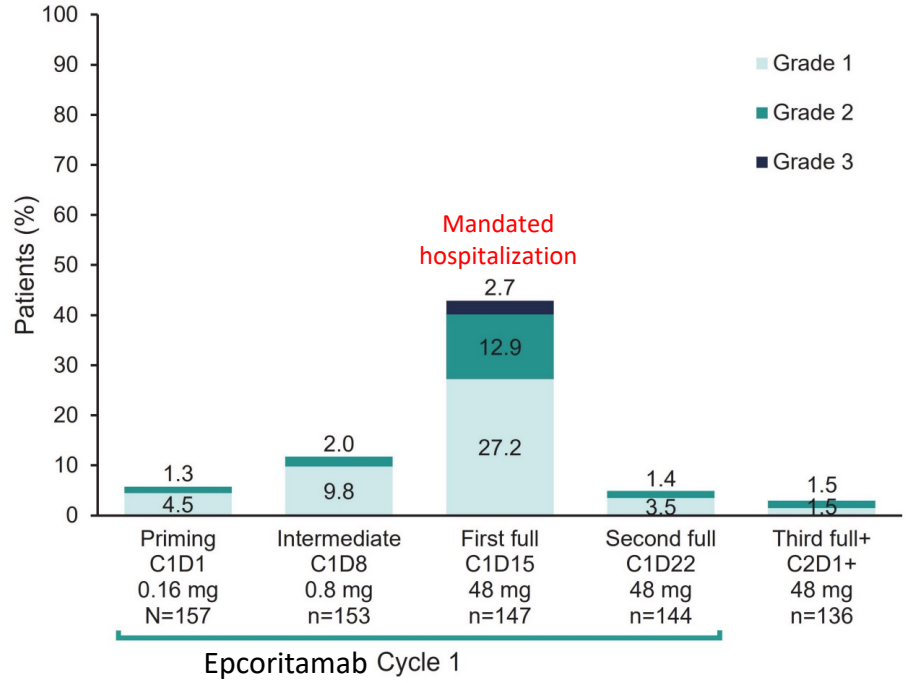
Outcomes

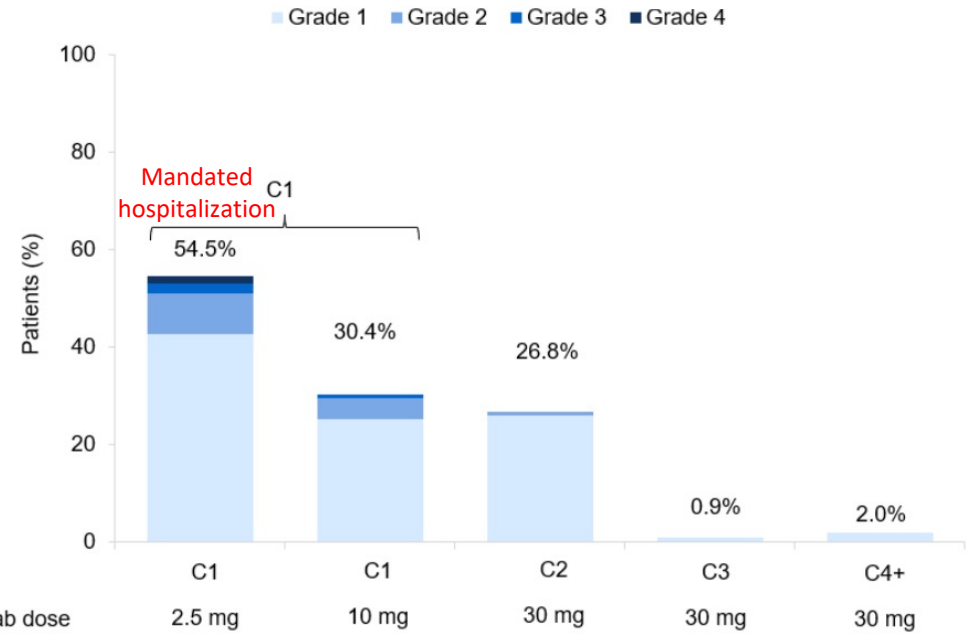
	Glofitamab	Epcoritamab	Mosunetuzumab
Median f/u	12.6 months	10.7 months	18.3 months
1º	CR	ORR	CR
ORR	52%	63%	80%
CR	39%	39%	60%
Median time to response	n/a	1.4 months (1.0-8.4)	1.4 months (1.2-2.9)
Median time to CR	42 days (31-308)	2.7 months (1.2-11.1)	3.0 months (1.4-5.7)
Duration of CR	78% at 12 months	89% at 9 months	63.7% at 18 months
Other		MRD (-) 45.9% (49 of 107 evaluable by clonoSEQ) 78% remained MRD (-) at 6 months	Treatment cycles received <8 cycles - 23% 8 cycles - 59% 8-17 cycles - 6% 17 cycles - 12%

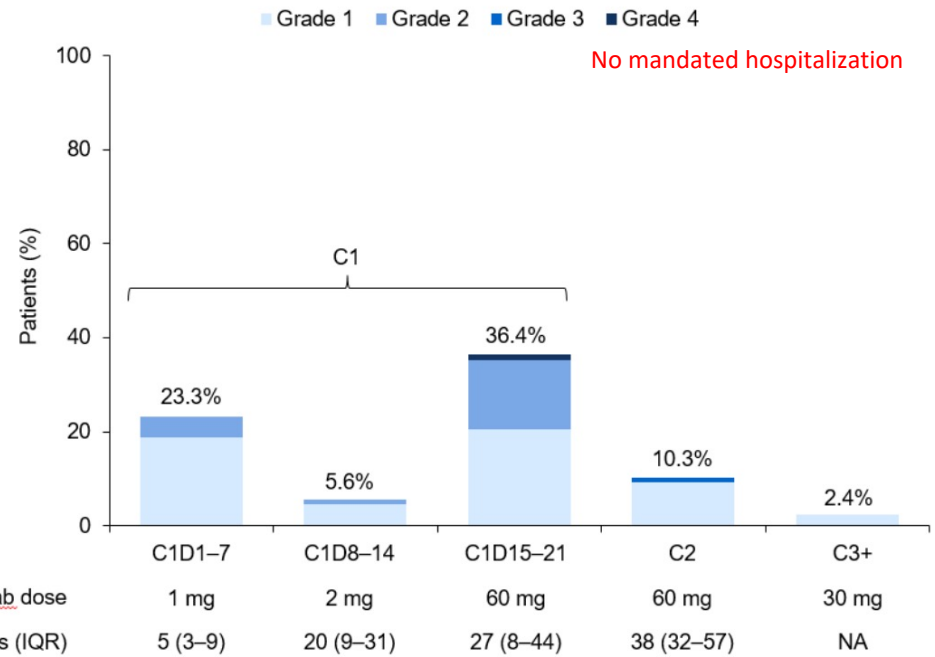
Toxicity: CRS/ICANS

	Glofitamab	Epcoritamab		Mosunetuzumab
Any CRS	63%	49.7%		44%
G1-2 CRS	60%	47.1%		26%/17%
G3-4 CRS	2.6%/1.3%	2.5%/0%		1%/1%
G5 CRS	none	none		none
Any ICANS	8%	6.4%		3%
G3-4 ICANS	2.6%	0%		0%
G5 ICANS	none	1 event		none
Anti-IL6	20%	28%		32.5% received either (8% tocilizumab alone, 15% steroids alone, 10% both)
Unplanned steroids	18%	20%		
Unplanned hospitalization	7% ICU admission	n/a		23%

CRS timing


Grade 1
Grade 2
Grade 3
Patients (%)
Mandated hospitalization
1.3
4.5
2.0
9.8
2.7
12.9
27.2
1.4
3.5
1.5
1.5
Priming C1D1 0.16 mg N=157
Intermediate C1D8 0.8 mg n=153
First full C1D15 48 mg n=147
Second full C1D22 48 mg n=144
Third full+ C2D1+ 48 mg n=136
Epcoritamab Cycle 1


Grade 1
Grade 2
Grade 3
Grade 4
Patients (%)
Mandated hospitalization
C1
54.5%
30.4%
26.8%
0.9%
2.0%
Glofitamab dose
C1 2.5 mg
C1 10 mg
C2 30 mg
C3 30 mg
C4+ 30 mg


Grade 1
Grade 2
Grade 3
Grade 4
No mandated hospitalization
Patients (%)
C1
23.3%
5.6%
36.4%
10.3%
2.4%
Mosunetuzumab dose
C1D1–7 1 mg
C1D8–14 2 mg
C1D15–21 60 mg
C2 60 mg
C3+ 30 mg
Median time to CRS onset, hours (IQR)
5 (3–9)
20 (9–31)
27 (8–44)
38 (32–57)
NA

Toxicity: Hematologic/Infectious

	Glofitamab	Epcoritamab		Mosunetuzumab
G3-4 Anemia	6%	10%		8%
G3-4 Thrombocytopenia	8%	6%		4%
G3-4 Neutropenia	27%	15%		27%
G-CSF	n/a	10%		20%
Febrile Neutropenia	3% ≥G3	3%		n/a
Infection	38% (15% G3-4)	14.6% (1.3% G3-4)		20% (14% G3-4)
COVID19	2.6% (1.3% G5)	6.4% (1.3% G5)		4% (no G5)
Any G5 AE	5% (0 of 8 attributed to glofitamab)	? At least 1		2.2% (0 of 2 attributed to mosunetuzumab)
Other	6% G3-4 hypophosphatemia	n/a		8% G3-4 hyperglycemia 17% G 3-4 hypophosphatemia 8% anemia

DLBCL CD19 CAR-T and CD20xCD3 BiTEs

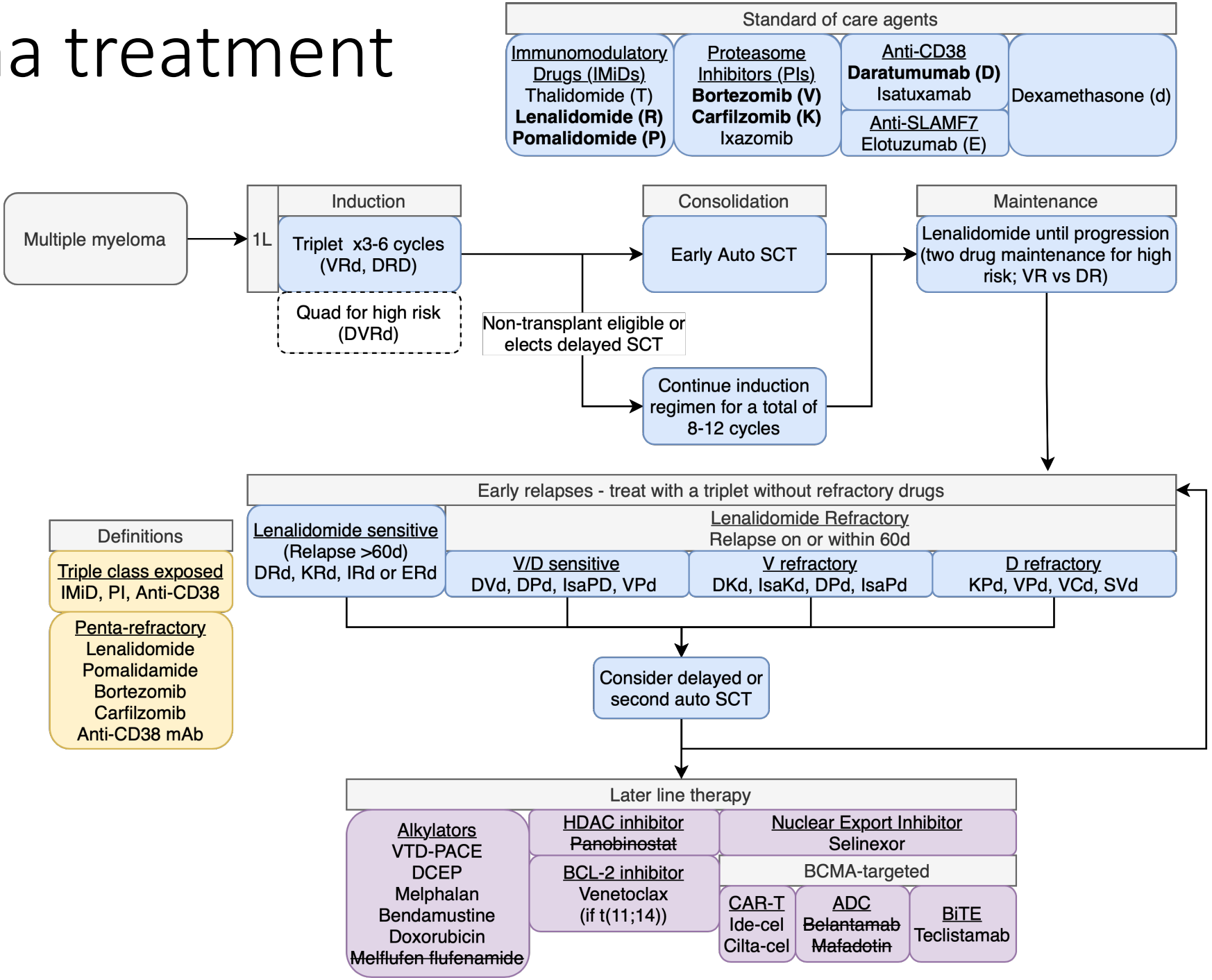
	DLBCL							
	Axi-cel		Liso-cel		Tisa-cel		Glofitamab	Epcoritamab
Trial	ZUMA-7	ZUMA-1	TRANSFORM	TRANSCEND	BELINDA	JULIET	NEJM 2022	EPCORE NHL1
Target	CD19	CD19	CD19	CD19	CD19	CD19	CD20xCD3	CD20xCD3
Line of therapy	2L	3L	2L	3L	3L	3L	3L	3L
Phase	3	2	3	2	3	2	2	2
N	359	111	184	256	322	93	154	157
ORR	83%	82%	86%	73%	46%	52%	52%	63%
CR	65%	54%	61%	53%	28%	40%	39%	39%
Any CRS (≥G3)	92% (6%)	93% (13%)	49% (1%)	42% (2%)	61% (5%)	57% (23%)	63% (4%)	50% (3%)
ICANS (≥G3)	60% (21%)	64% (28%)	12% (4%)	30% (10%)	10% (2%)	20% (11%)	8% (3%)	6% (0%)

FL CD19 CAR-T and CD20xCD3 BiTEs

	FL		
	Axi-cel	Tisa-cel	Mosenutuzumab
Trial	ZUMA-5	ELARA	Lancet Oncol 2022
Target	CD19	CD19	CD20xCD3
Line of therapy	3L	3L	3L
Phase	2	2	2
N	86	90	90
ORR	94%	86%	80%
CR	79%	69%	60%
Any CRS (≥G3)	78% (6%)	53% (0%)	44% (2%)
ICANS (≥G3)	59% (19%)	4% (1%)	3% (0%)

BiTEs in Multiple Myeloma

Myeloma treatment



LocoMMotion study

- Prospective, non-interventional study of triple-class exposed R/R MM (N=248)
- ECOG 0-1

Time from initial MM diagnosis, median (range) years	6.3 (0.3–22.8)
Number of prior lines of therapy, median (range)	4.0 (2–13)
Prior lines of therapy, *n* (%)	
2	16 (6.5)
3	48 (19.4)
4	62 (25.0)
≥5	122 (49.2)
Previous stem cell transplant, *n* (%)	
Autologous	160 (64.5)
Allogeneic	11 (4.4)
Triple-class exposed,[c] *n* (%)	248 (100)
Refractory status, *n* (%)	
Any PI	197 (79.4)
Any IMiD	234 (94.4)
Any anti-CD38 mAb	228 (91.9)
Triple-class refractory	183 (73.8)
Penta-drug refractory	44 (17.7)

Leukemia. 2022 May;36(5):1371-1376

LocoMMotion study

- ORR 29.8%
  - Only one CR and no stringent CR
- mPFS 4.6 months
  - 3.9 months in triple-class refractory vs 8.2 months in triple-class exposed
- mOS 12.4 months

Table S1. SOC treatment regimens in patients (excluding subsequent therapy).

SOC treatment	n (%)
Number of regimens	92
Doublet drug combinations	105 (42.3)
Combinations of ≥3 drugs	160 (64.5)
Regimens (given to ≥4 patients)	
Carfilzomib–dexamethasone	34 (13.7)
Pomalidomide–cyclophosphamide–dexamethasone	33 (13.3)
Pomalidomide–dexamethasone	28 (11.3)
Ixazomib–lenalidomide–dexamethasone	14 (5.6)
Panobinostat–bortezomib–dexamethasone	11 (4.4)
Bendamustine–bortezomib–dexamethasone	7 (2.8)
Carfilzomib–cyclophosphamide–dexamethasone	7 (2.8)
Elotuzumab–pomalidomide–dexamethasone	6 (2.4)
Lenalidomide–dexamethasone	6 (2.4)
Doxorubicin–bortezomib–dexamethasone	5 (2.0)
Carfilzomib–lenalidomide–dexamethasone	5 (2.0)
Carfilzomib–pomalidomide–dexamethasone	5 (2.0)
Melphalan	5 (2.0)
Belantamab mafodotin	4 (1.6)
Bendamustine–prednisone	4 (1.6)
Cyclophosphamide–dexamethasone	4 (1.6)

Leukemia. 2022 May;36(5):1371-1376

Caution with MM accelerated approvals

Standard of Care

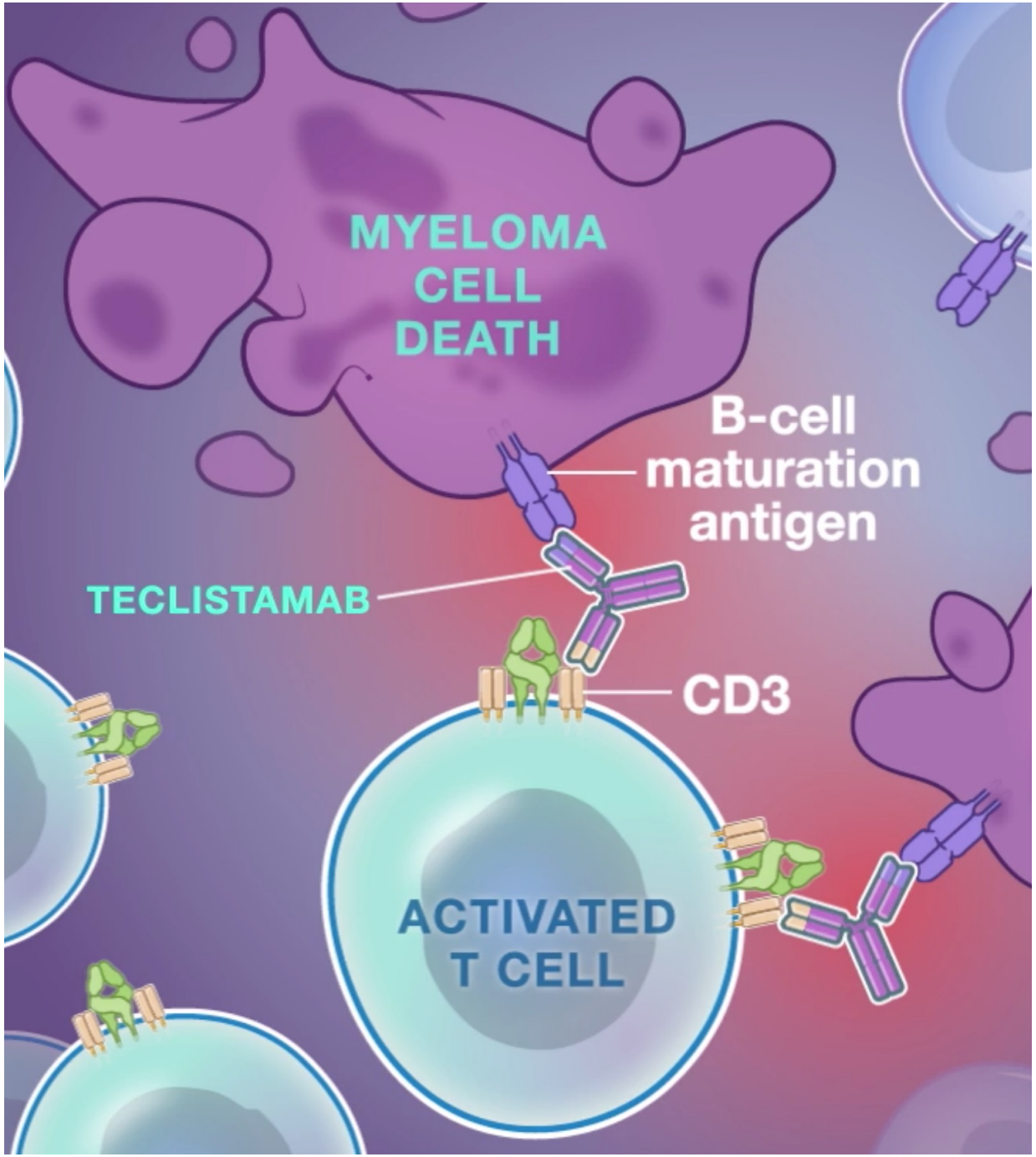
- 2003 Bortezomib
- 2012 Carfilzomib
- 2013 Pomalidomide
- 2015 Daratumumab

Withdrawn

- 2015 Panobinostat
  - 2/2015 accelerated approval based on phase 3 PANORAMA 1 trial (PFS benefit, nonsignificant OS benefit)
  - 11/2021 withdrawn after “not feasible to complete” confirmatory trial
- 2020 Belantamab Mafadotin
  - 8/2020 accelerated approval based on phase 2 DREAMM-2 trial (single agent ORR 31%)
  - 11/2022 withdrawn after phase 3 DREAMM-3 trial showed no PFS benefit vs pom-dex
  - DREAMM-7 and DREAMM-8 trials ongoing
- 2021 Melphalan Flufenamide
  - 2/2021 accelerated approval based on phase 2 HORIZON trial (single agent ORR 24%)
  - 10/2021 withdrawn after phase 3 OCEAN trial showed PFS benefit but worse OS

2019/2020 Selinexor (TBD)

Teclistamab



Dosing regimen, CRS ppx, and hospitalization

Teclistamab SC

Indefinite therapy, 28 day cycles

- Step up doses of 0.06mg/kg and 0.3 mg/kg separated by 2-4 days
- Teclistamab 1.5mg/kg SC weekly (days 1, 8, 15, 22)

- Hospitalization and dexamethasone 16mg for step up doses and first full dose

Trial design and baseline characteristics

	Teclistamab
Diagnosis	R/R MM, triple-class exposed
Line	4L
Required prior therapy	IMiD, PI, Anti-CD38
Phase	2
Duration of therapy	Continuous
Route	SC

Baseline Characteristics	
Enrollment	3/3/20 to 8/13/21
Data Cutoff	3/16/22
N	125
Age	64 (33-83)
Sex	56%M/44%F
Median prior LOT	5 (2-14) 78% triple-class refractory 70% penta-drug expose 30% penta-drug refractory
Median time since diagnosis	6 years (0.8 to 22.7)
High-risk cytogenetics	26% (16% del(17p) 11% t(4;14) 3% t(14;16))
Prior CAR-T	none
Prior ASCT	82%

Outcomes and toxicity

Outcomes	
Median f/u	14.1 months
1º	ORR
ORR	63%
CR	39%
Median time to response	1.2 months (0.2 to 5.5)
Median time to best response	3.8 months (1.1 to 16.8)
mDOR	not yet mature
mPFS	11.3 months (8.8 to 17.1)
MRD (-)	27% (46% in pts with CR)

Adverse Events	
Any CRS	72%
G3-4 CRS	0.6%/0%
G5 CRS	none
Neurotoxicity	15%
Any ICANS	3% (5 patients had 9 events)
G3-5 ICANS	none
Anti-IL6	36%
Unplanned steroids	8.50%

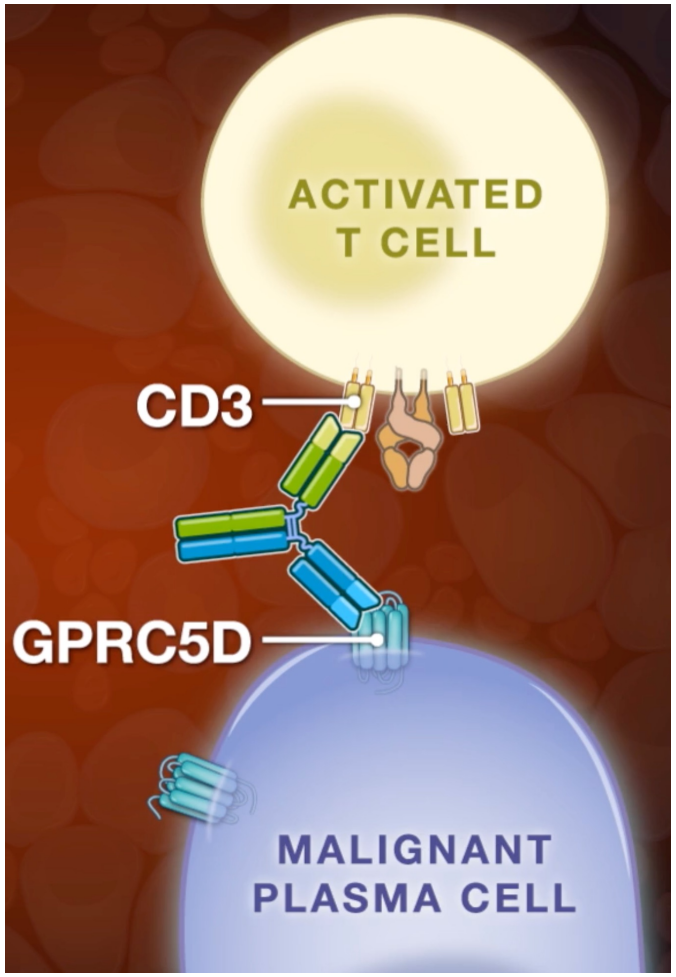
Hematologic/Infectious Adverse Events	
G3-4 Anemia	37%
G3-4 Thrombocytopenia	21%
G3-4 Neutropenia	64%
G-CSF	55%
Febrile Neutropenia	2%
Hypogammaglobulinemia	75%
IVIg	39%
Infection	76% (44% G3-4) • 18% COVID19 (7% G5) • 4% PJP • 1 bacterial meningitis c/b G4 seizure • 1 PML • 1 G3 adenovirus PNA • 1 G4 PML

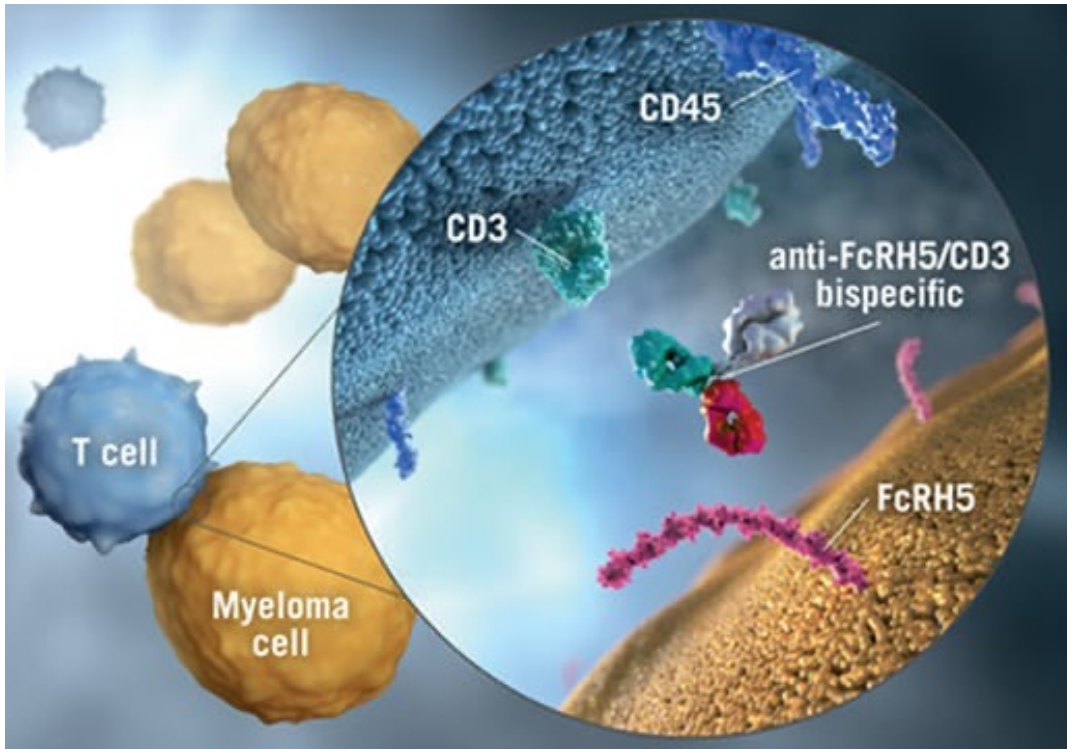
- G-CSF as indicated, consider neutropenia ppx
- Consider PJP ppx
- Monitor IgG, IVIg as indicated
- COVID vaccines and preventative antibodies
- Flu, pneumococcal, meningococcal vaccines
- ?Acyclovir ppx
- Screen for HIV/HBV/HCV, strongyloides?

MM BCMA CAR-T and BCMAxCD3 BiTE

	MM		
	Ide-cel	Cilta-cel	Teclistamab
Trial	KarMMA	CARTITUDE-1	MagesTEC-1
Target	BCMA	BCMA	BCMA
Line of therapy	4L	4L	4L
Phase	2	2	2
N	128	97	165
ORR	78%	98%	63%
CR	33%	83%	39%
Any CRS (≥G3)	84% (5%)	95% (4%)	72% (1%)
ICANS (≥G3)	18% (3%)	21% (9%)	3% (0%)

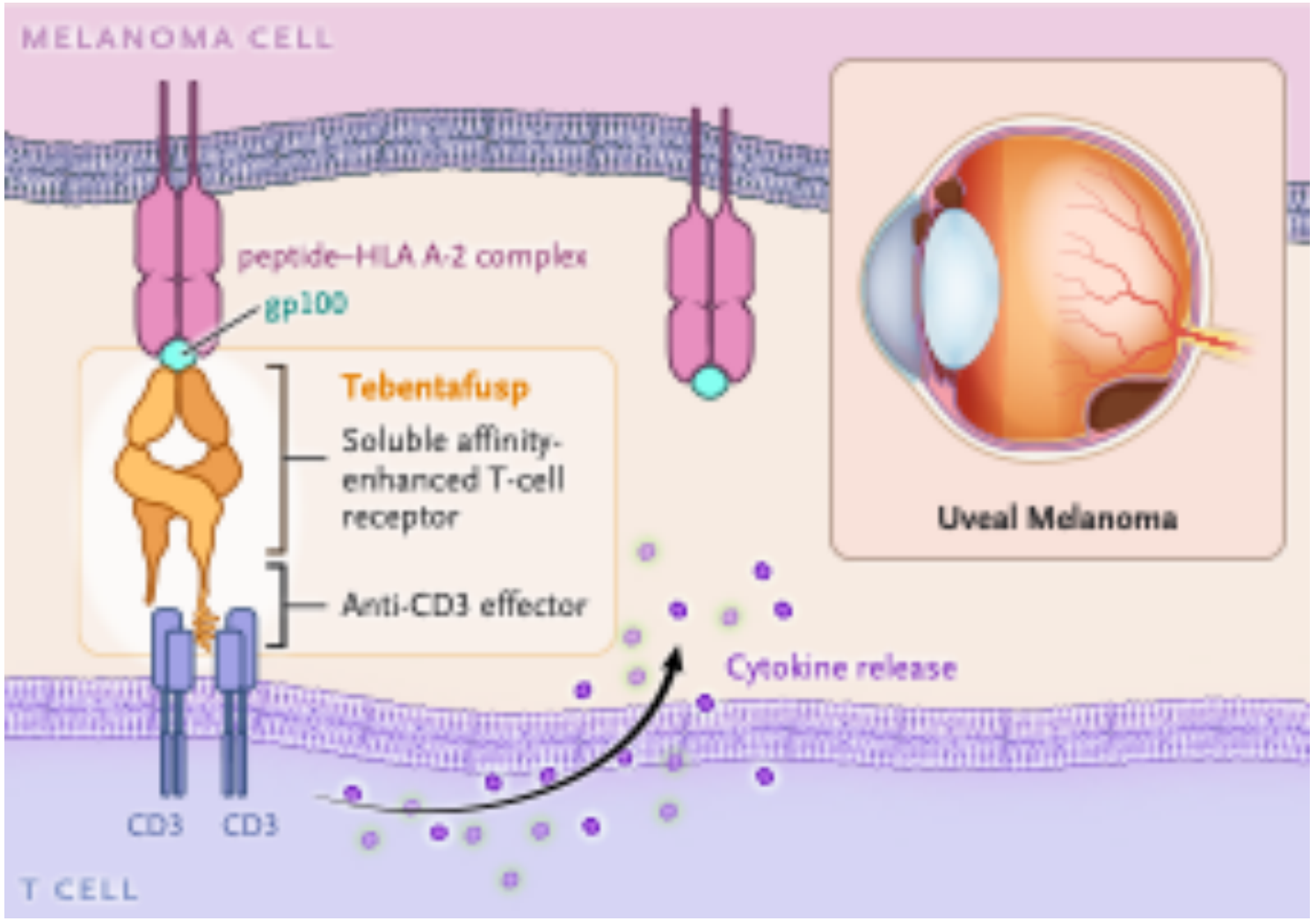
Talquetamab and Cevostamab novel targets





Non-antibody BiTEs in solid tumors

Tebentafusp (gp100xCD3)
Unresectable/metastatic uveal melanoma
FDA approved 1/25/22



Conclusions

- BiTEs induced rapid, deep (often MRD-) responses in a subset (~40%) of patients with relapsed/refractory DLBCL (including post-CAR-T), FL, and MM
  - IV and SC administrations appear to be equally efficacious with similar toxicity
  - Glofitamab CD20 bivalency doesn't confer a visible benefit
- CR to BiTEs has early durability, but long term durability is yet to be determined, particularly with fixed-duration therapy
- Teclistamab may require more intensive infection prophylaxis and treatment
- As monotherapy, CD20xCD3 and BCMAxCD3 BiTEs are adjuncts (not alternatives) to CD19 and BCMA CAR-T therapy
- Questions
  - Will BiTEs be tolerable in older frailer patients not fit for CAR-T?
  - Logistics
    - Community/university coordination – Initiate therapy at a cell therapy center, then transition to community?
    - Community training on CRS/ICANS identification and management
    - REMS certification for each individual drug – there many in the pipeline