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Indolent Lymphoma: 2024 Update on Immunotherapies

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MLS Seattle

DISCLOSURE

- Host of the Classical Music Clinic
- Sundays 1 pm Eastern on Clubhouse
- 3+ hours of classical music therapy
- https://www.clubhouse.com/@mxk214

OBJECTIVES/OUTLINE

- Brief background on indolent lymphoma (iNHL)
  - Age and iNHL
  - Basic pharmacology of anti-NHL agents
- **Targeted immune agents: mechanisms, indications, outcomes**
  - R/R disease: BiTE therapy
  - R/R disease: CAR T cells
- Conclusions and future directions
  - Unanswered questions in iNHL

AGE and iNHL: Epidemiology

- **Four WHO subtypes of iNHL**
- **All more common in older adults**

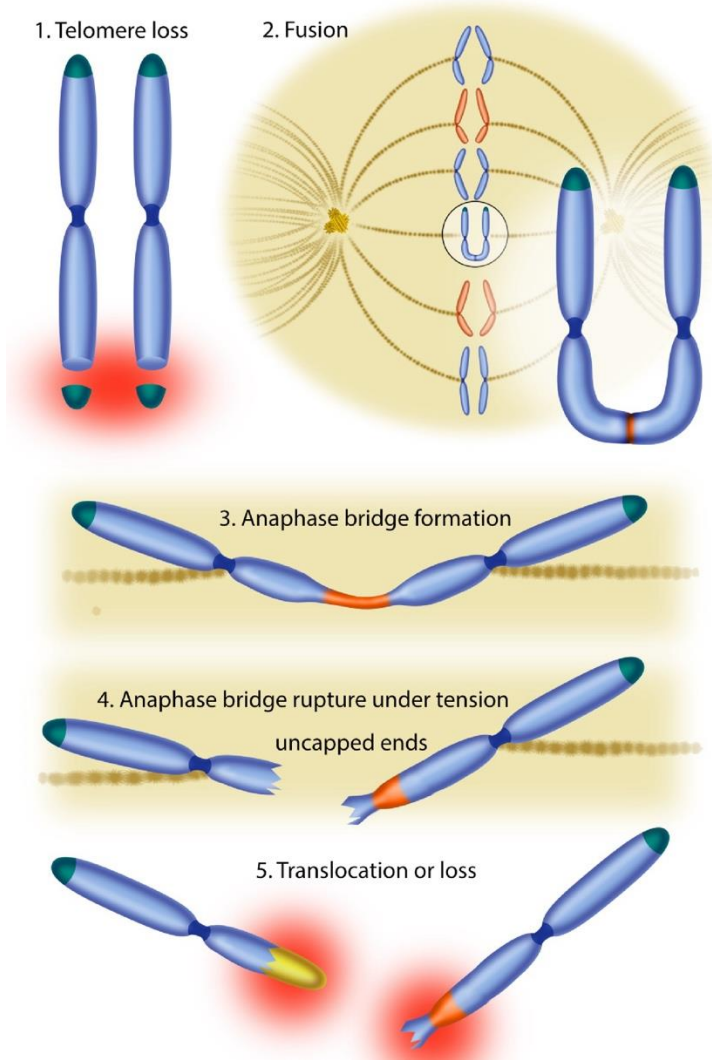
iNHL Subtype	Median Diagnosis Age (y)
Chronic lymphocytic leukemia **(CLL/SLL)**	72
Follicular lymphoma **(FL)**	65
Lymphoplasmacytic lymphoma **(LPL/WM)**	60 - 64
Marginal zone lymphoma **(MZL)**	72

Source: Garcia-Sanz et al. *Br J Haematol* 2001; Seng and Peterson *Oncology* 1997; Smith et al. *Br J Cancer* 2011

AGE and iNHL: Pathobiology

Aging predisposes to:

- **Telomere shortening and loss**



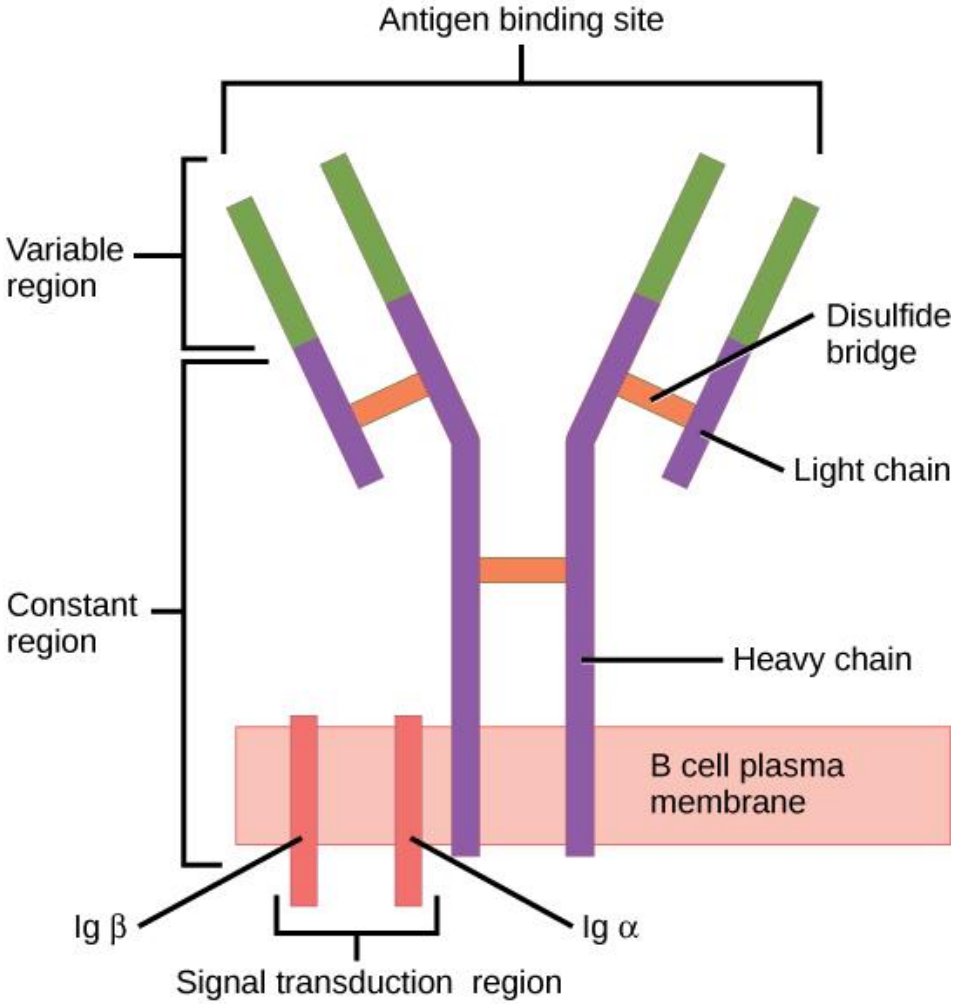
Source: Krem et al. *Br J Haematol* 2015

AGE and iNHL: Pathobiology

Aging predisposes to:

- Telomere shortening and loss

- **Loss of BCR diversity & growth of clones with tonic BCR signaling**

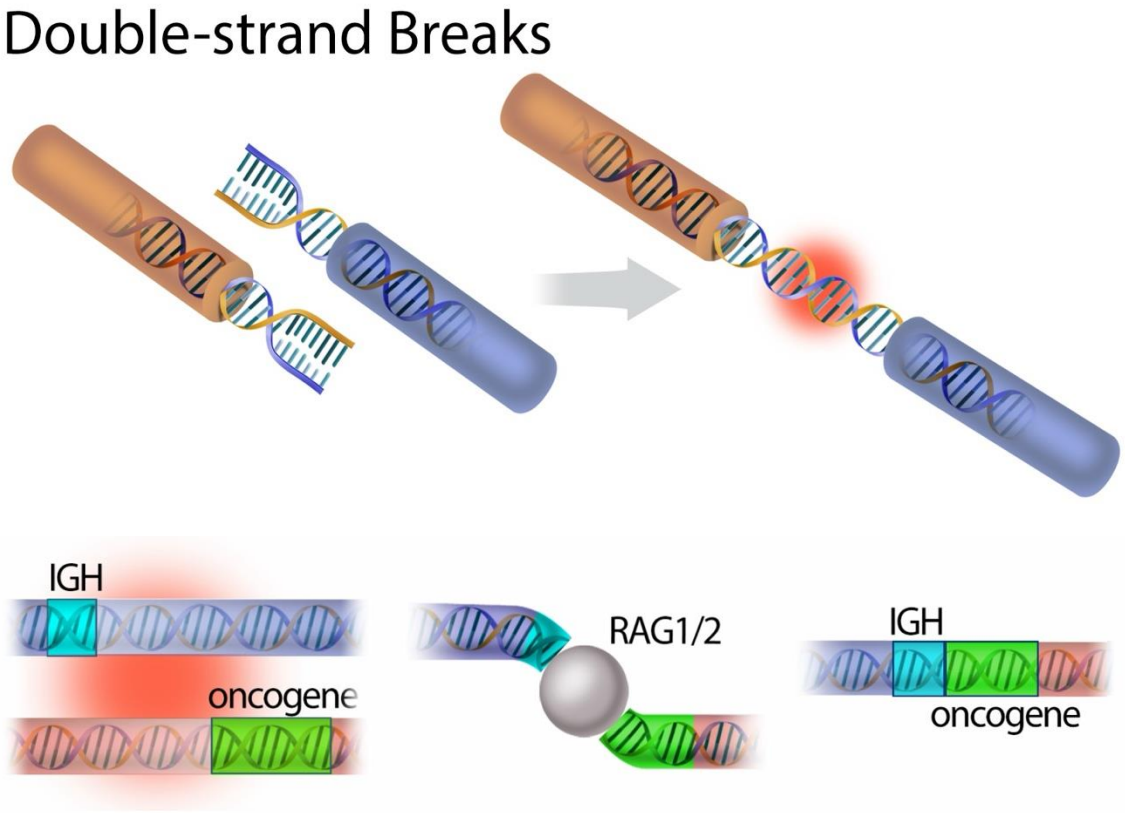


Source: Cancro et al. *Trends Immunol* 2009

AGE and iNHL: Pathobiology

Aging predisposes to:

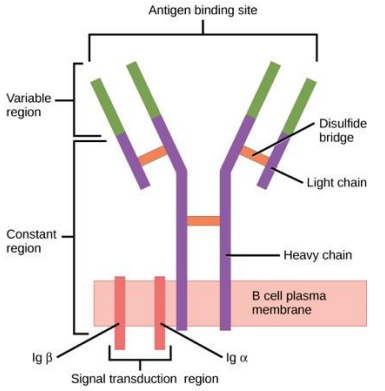
- Telomere shortening and loss
- Loss of BCR diversity & growth of clones with tonic BCR signaling
- **Chromosomal translocations**

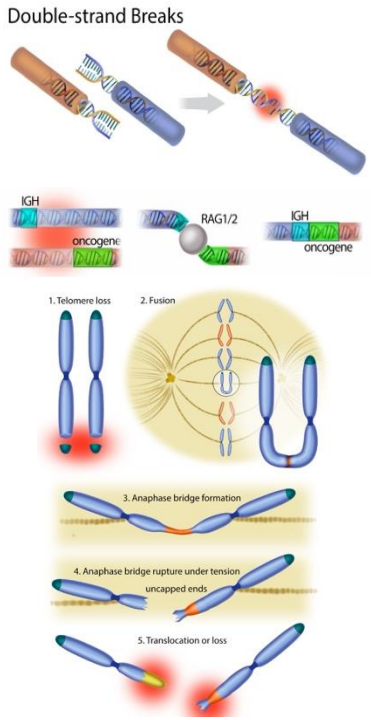


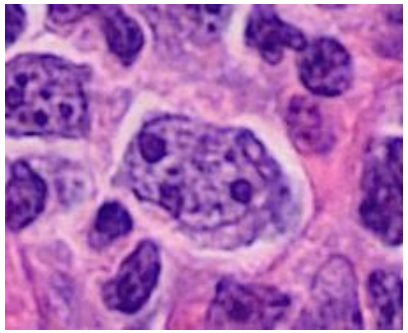
Source: Krem et al. *Br J Haematol* 2015; Rabkin et al. *J Natl Cancer Inst Monogr* 2008; Schuler et al. *Int J Cancer* 2009

AGE and iNHL: Pathobiology

Aging







- **Chromosomal instability (CIN)**
- **Chemo-refractory disease**

Source: Krem et al. *Br J Haematol* 2015

AGE and iNHL: Treatment Considerations

Connect CLL Registry: observational study of 1495 CLL patients

Risk factor	Age < 65	Age 65-75	Age > 75	p value
Charlson comorbidity index (CCI) score ≥ 3 (%)	35	46	52	< 0.0001
ECOG performance status 0 (%)	60	48	33	< 0.0001
Mean Cr clearance (mL/min)	101	74	53	< 0.0001

Source: Mato et al. *Br J Haematol* 2016; Sharman et al. ASH Meeting 2014

iNHL: The Toolbox

Major therapeutic drug classes in iNHL*:

Class	Representative Agent(s)
CD20 monoclonal antibody **(mab)**	rituximab, obinutuzumab
Immunomodulator **(IMiD)**	lenalidomide
Bruton tyrosine kinase inhibitor **(BTKi)**	zanubrutinib, pirtobrutinib
Cytotoxic chemotherapy	bendamustine
EZH2 (histone methylation) inhib. **(EZH2)**	tazemetostat
Immunotherapy	
BiTEs (CD20)	mosunetuzumab, epcoritamab
CAR T cells (CD19)	axi-cel, liso-cel

*not an exhaustive list

iNHL: Relapsed/Refractory Toolbox

Selected therapies for R/R iNHL*:

iNHL Subtype	Agents/Classes
CLL/SLL	BTKi (zanu, acala, pirto), CD20 mab, chemotherapy, venetoclax, idelalisib, CAR T
FL	CD20 mab, chemotherapy, tazemetostat, lenalidomide, zanubrutinib, mosunetuzumab, epcoritamab, CAR T, transplant
LPL/WM	BTKi (ibrutinib, zanu, acala[1]), CD20 mab, chemotherapy, bortezomib[1], transplant
MZL	CD20 mab, chemotherapy, lenalidomide, zanubrutinib, transplant

*Always evaluate for evidence of transformation.

1. Off-label indication

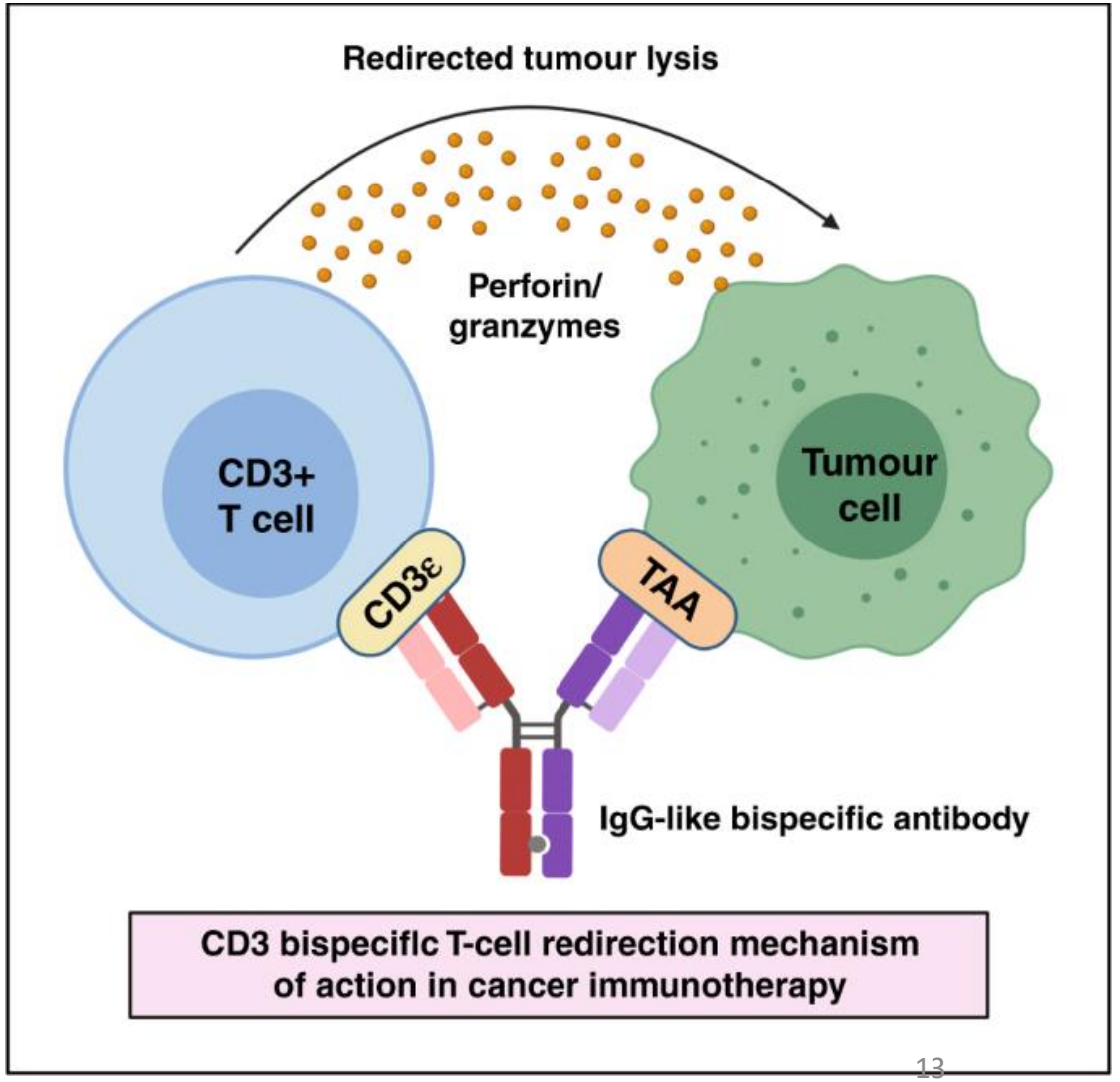
Aiming T-cells at Relapsed/Refractory iNHL

BiTE therapy and CAR T cells

T CELLS in R/R iNHL: BiTES

Bi-Specific T-cell Engagers (BiTEs):

- Target CD3 on T-cells AND tumor antigen
- E.g., CD20 on mature B-cells
- Activate T-cell/facilitate immunological synapse → Lysis of target tumor cells



Sources: Singh A et al. *Br J Cancer* 2021; Tian Z et al. *J Hematol Oncol* 2021

CD20 BiTE in R/R FL: Mosunetuzumab

GO29781:

- Phase 2 trial of mosunetuzumab, CD3-CD20 BiTE
- R/R disease
- Grade 1-3A
- N = 90
  - Age ≥ 18
  - ≥ 2 prior lines*, CD20 mab and alkylator
  - ECOG 0/1
  - **Premeds for 3 step-up doses:** **CRS, ICANS, REMS**
  - Primary endpoint: CR

*FDA approval Dec 2022: ≥ 2 prior lines

Source: Budde LE et al. *Lancet Oncol* 2022

GO29781: Mosunetuzumab

Study outcomes:

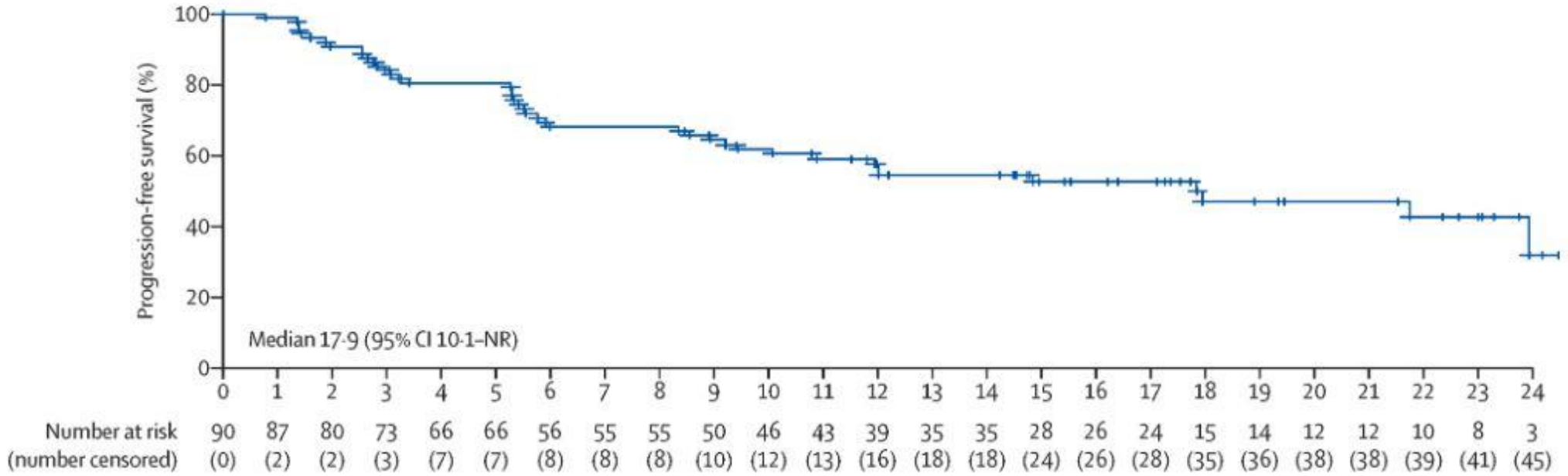
GO29781	Median age (y)	N	ORR (%)	CR (%)	DOR (months)	PFS (months)	18-month OS (%)	Grade ≥3 CRS (%)	Grade ≥3 neuro (%)	Toxic discont. (%)
Mosunetuzumab-axgb	60	90	80	**60**	23	18	90	2	0	4

*Other tox: Grade 1-2 CRS 42%, grade 1-2 neuro 5%, grade ≥ 3 infection 14%, tumor flare 3%

Sources: Budde LE et al. *Lancet Oncol* 2022; Schuster SJ et al. ASH Meeting 2023

GO29781: Mosunetuzumab

PFS entire cohort:



Source: Budde LE et al. *Lancet Oncol* 2022

CD20 BiTE in R/R FL: Epcoritamab

EPCORE NHL-1:

- Phase 1-2 trial of epcoritamab, CD3-CD20 BiTE
- R/R disease
- Grade 1-3A
- N = 128
  - Age **≥** 18
  - **≥** 2 prior lines, CD20 mab and alkylator or IMiD*
  - ECOG 0-2, GFR ≥ 45, no CV disease
  - **Premeds for 3 step-up doses:** **CRS, ICANS, REMS**
  - Primary endpoints: RR and DOR

*FDA approval 6-26-24: **≥** 2 prior lines

Source: Linton KM et al. *Lancet Haematol* 2024.

EPCORE NHL-1: Epcoritamab

Study outcomes:

EPCORE NHL-1	Median age (y)	N	ORR (%)	CR (%)	12-month DOR (%)	24-month PFS (%)	18-month OS (%)	Grade ≥3 CRS (%)	Grade ≥3 neuro (%)	Toxic discont. (%)
Epcoritamab-bysp	65	128	**82**	63	**68**	51	70	2	0	19

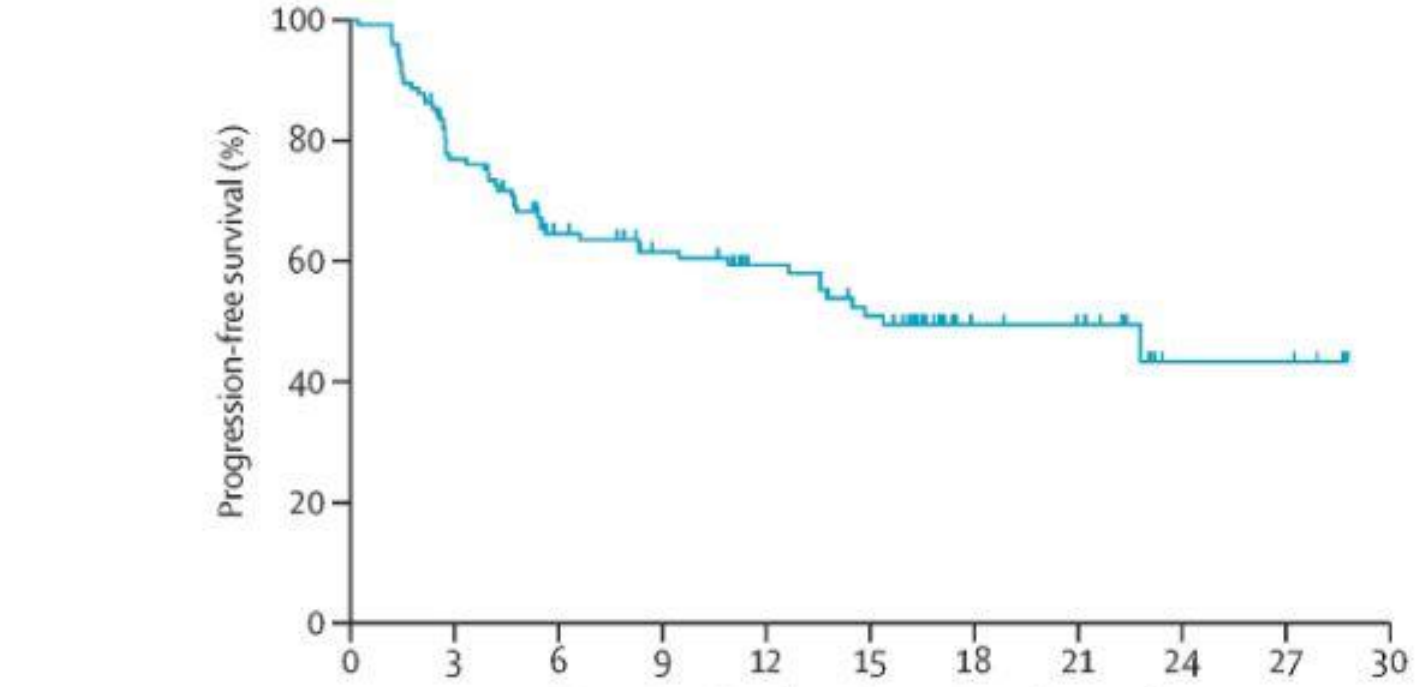
*Other tox: grade 1-2 CRS 65%, grade 1-2 neuro 6%, grade ≥ 3 infection 40%, incl. CMV and Covid

**86 pts received 3-step up doses in C1: grade 1-2 CRS 49%, no grade 3

Source: Linton KM et al. *Lancet Haematol* 2024.

EPCORE NHL-1: Epcoritamab

PFS, entire cohort:



Number at risk (number censored)											
Pivotal cohort	128 (0)	90 (10)	67 (19)	57 (26)	43 (38)	35 (40)	14 (60)	12 (62)	4 (69)	4 (69)	0 (73)

Source: Linton KM et al. *Lancet Haematol* 2024.

BiTES in R/R FL: Mosu and Epcor

BiTEs targeting CD20 in FL:

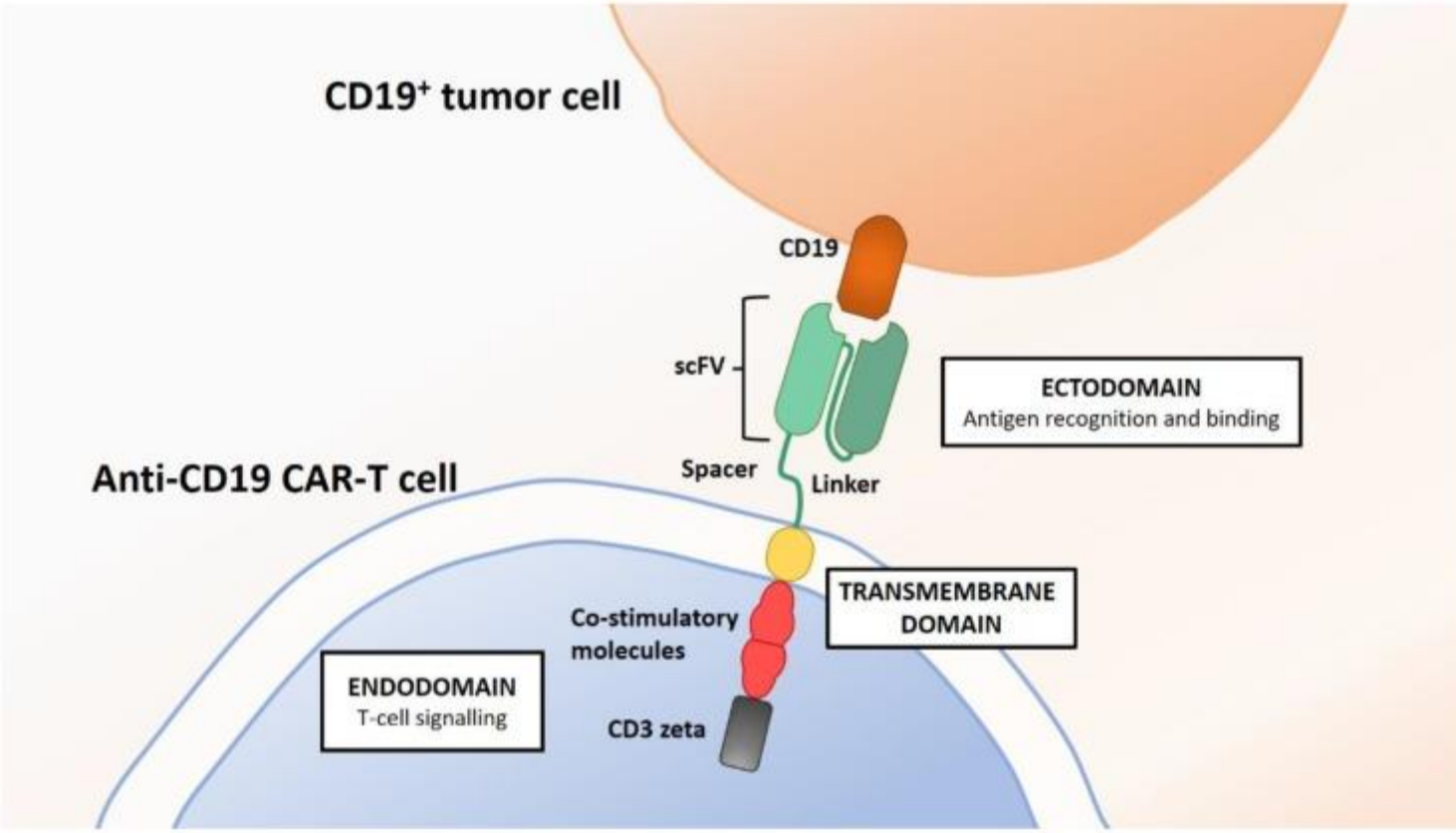
- Responses in CD20- and alkylator-refractory disease
- Option for POD24 disease
- CR and MRD-neg responses
- Option for non-CAR T-cell candidates
- Moderate inclusion of older/diverse populations
- Require toxicity-monitoring and premeds, but…
- Low rates of grade ≥3 CRS and ICANS
- Fixed-duration (8 vs 17 cycles) with mosu

*Current FDA approval for FL BiTES: **≥** 2 prior lines

CAR T CELLS in R/R FL: CD19

Chimeric antigen receptor (CAR) T cells:

- Autologous CD8 T cells, engineered TCR
- T cells bind tumor antigen
- MHC-independent T cell activation
- **CD19**; other targets in development
- Activate T cell and facilitate immunological synapse → Lysis of target tumor cells



Sources: Britten O, et al *Cells* 2019; Wang Z et al. *Front Immunol* 2022

CD19 CAR T CELLS: FL

Axicabtagene ciloleucel:

- R/R MZL and grade 1-3A FL
- ≥ 2 prior lines incl. CD20 mab + alkylator
- ECOG 0-1

ZUMA-5	Median age (y)	N	ORR (%)	CR (%)	18-month DOR (%)	18-month PFS (%)	18-month OS (%)	Grade ≥3 CRS (%)	Grade ≥3 neuro (%)	Toxic deaths (%)
Axi-cel	61	148	92	77	66	65	87	7	19	3

*Median V2V 17d. FL: 124, MZL: 24. Other tox: SAEs 74%, grade ≥ 3 infection 18%, 2nd malignancy 9%

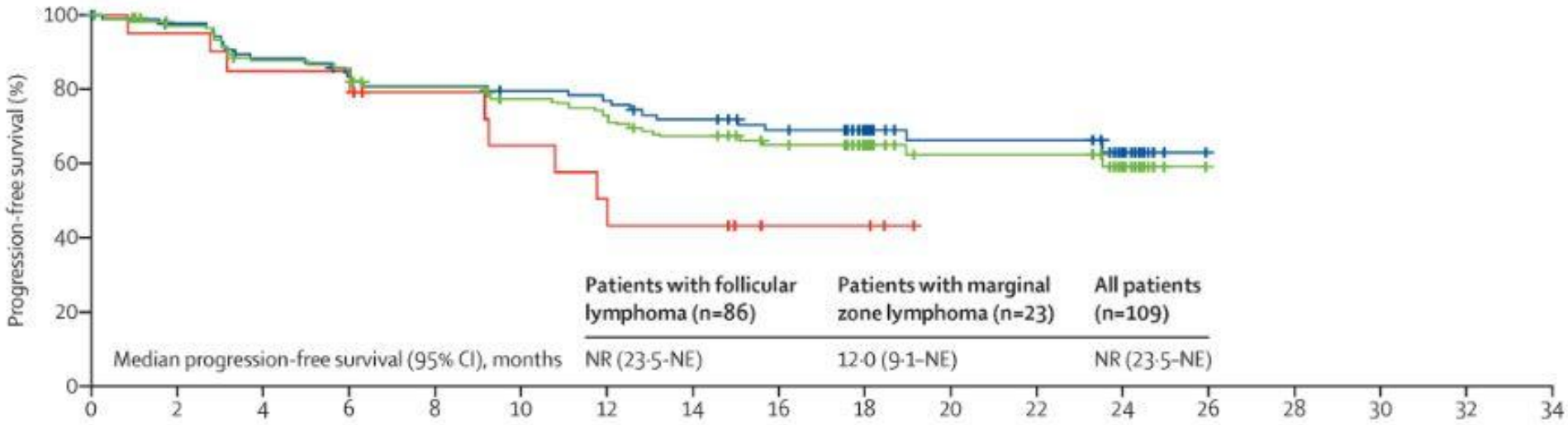
FDA approval 3-6-21: FL, ≥ 2 prior lines, warnings for CRS, ICANS, HLH, cytopenias, REMS

Source: Jacobson CA et al. *Lancet Oncol* 2022

CD19 CAR T CELLS: FL

Axicabtagene ciloleucel:

- R/R MZL and grade 1-3A FL



Number at risk (number censored)																		
Patients with follicular lymphoma	86 (0)	82 (2)	73 (3)	68 (4)	64 (6)	61 (8)	59 (8)	54 (9)	49 (12)	40 (21)	24 (36)	24 (36)	12 (47)	0 (59)	..	..	..	..
Patients with marginal zone lymphoma	23 (0)	19 (3)	16 (4)	15 (5)	11 (8)	9 (8)	7 (8)	6 (8)	3 (11)	3 (11)	0 (14)	..	..	..	..	..	..	..
All patients	109 (0)	101 (5)	89 (7)	83 (9)	75 (14)	70 (16)	66 (16)	60 (17)	52 (23)	43 (32)	24 (50)	24 (50)	12 (61)	0 (73)	..	..	..	..

Source: Jacobson CA et al. *Lancet Oncol* 2022

CD19 CAR T CELLS: FL

Lisocabtagene maraleucel:

- R/R FL
- ≥ 1 line incl. CD20 mab + alkylator; POD 24 in 2L cohort
- ECOG 0-1

TRANSCEND FL	Median age (y)	N	ORR (%)	CR (%)	12-month DOR (%)	12-month PFS (%)	12-month OS (%)	Grade =3 CRS (%)	Grade =3 neuro (%)	Toxic deaths (%)
Liso-cel	60	130	97	94	82	81	92	1	2	7

*Median V2V 29d. Other tox: prolonged cytopenia 22%, grade ≥ 3 infection 5%, 2nd malignancy 9%

FDA approval 5-15-24: ≥ 2 prior lines, warnings for CRS, ICANS, HLH, cytopenias, REMS

Sources: Morschhauser F et al. *Nat Med* 2024

CD19 CAR T CELLS: CLL

Lisocabtagene maraleucel:

- R/R CLL/SLL
- ≥ 3 lines (std risk cyto) or ≥ 2 lines (hi risk cyto) incl. BTKi ± venetoclax
- ECOG 0-1

TRANSCEND CLL 004	Median age (y)	N	ORR (%)	CR (%)	DOR (months)	PFS (months)	OS (months)	Grade =3 CRS (%)	Grade ≥3 neuro (%)	Toxic deaths (%)
Liso-cel	65	137	47	18	35	12	30	9	18	10

*Median V2V 36d. MRD-neg 64%. Other tox: prolonged cytopenia 54%, grade ≥ 3 infection 17%

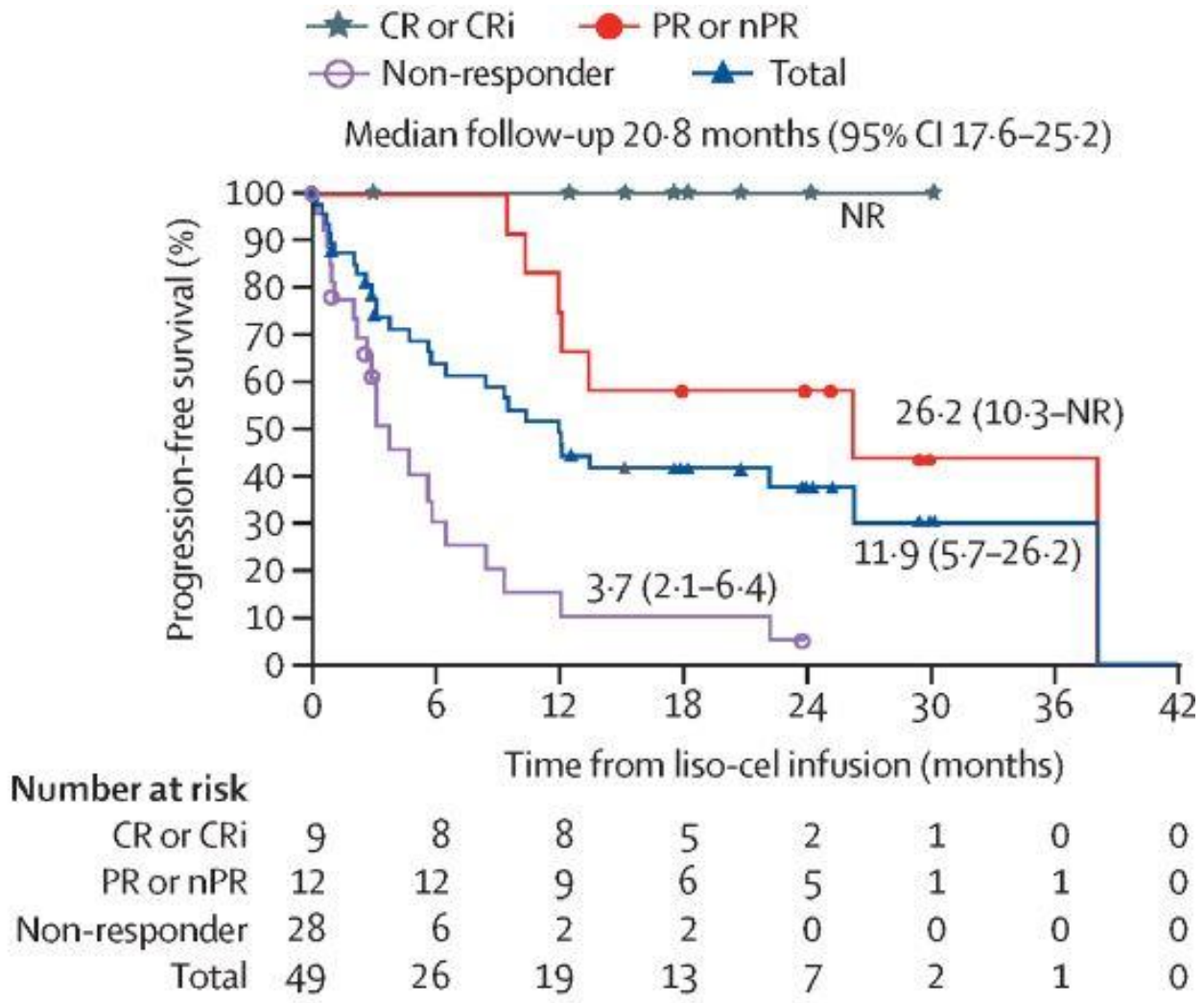
FDA approval 3-14-24: ≥ 2 prior lines, BTKi + ven, warnings for CRS, ICANS, HLH, cytopenias, REMS

Sources: Siddiqi T et al. *Blood* 2022; Siddiqi T et al. *Lancet* 2023

CD19 CAR T CELLS: CLL

Lisocabtagene maraleucel:

- R/R CLL/SLL



Source: Siddiqi T et al. *Lancet* 2023

CD19 CAR T CELLS: Richter Transformation

Retrospective study of CAR T in Richter transformation:

- N = 69, multicenter retrospective
- Median 4 prior lines incl. BTKi ± venetoclax

	Median age (y)	N	ORR (%)	CR (%)	DOR (months)	PFS (months)	OS (months)	Grade ≥3 CRS (%)	Grade ≥3 neuro (%)	NRM (%)
Axi-, tisa-, liso-, or brexu-cel	64	69	63	46	28	4.7	8.5	16	37	13

*Axi-cel = 44, tisa-cel = 17, liso-cel = 7, brexu-cel = 1. Grade ≥ 3 infection 20%

**Off-label use: warnings for CRS, ICANS, HLH, cytopenias, REMS

Sources: Kittai AS et al. *J Clin Oncol* 2024

R/R FL and CLL: CAR T cells

Axi-cel and liso-cel:

- Responses in relapsed/refractory disease
- Some responses are MRD-negative
- Option for cellular therapy (more robust) candidates
- Limited inclusion of older and diverse populations
- Requires cellular therapy-capable facility due to…
- Appreciable rates of grade ≥3 CRS and ICANS
- RRs appear lower in CLL and Richter transformation

*FDA approvals: **≥** 2 prior lines

AUTO-HCT and ALLO-HCT: Grade 3 FL

Retrospective study of autologous-HCT and RIC allogeneic-HCT in FL:

- N = 197, CIBMTR multicenter retrospective
- Rituximab-exposed; grade 3; 2000-2012

Cohort	Median age (y)	N	Median lines	100-day ANC (%)	100-day plt (%)	5-year PFS (%)	5-year OS (%)	5-year relapse (%)	3-year cGVHD (%)	NRM (%)
Auto-HCT	57	136	3	100	96	36	59	**61**	0	**4**
Allo-HCT	53	61	3	100	88	51	54	**20**	53	**27**

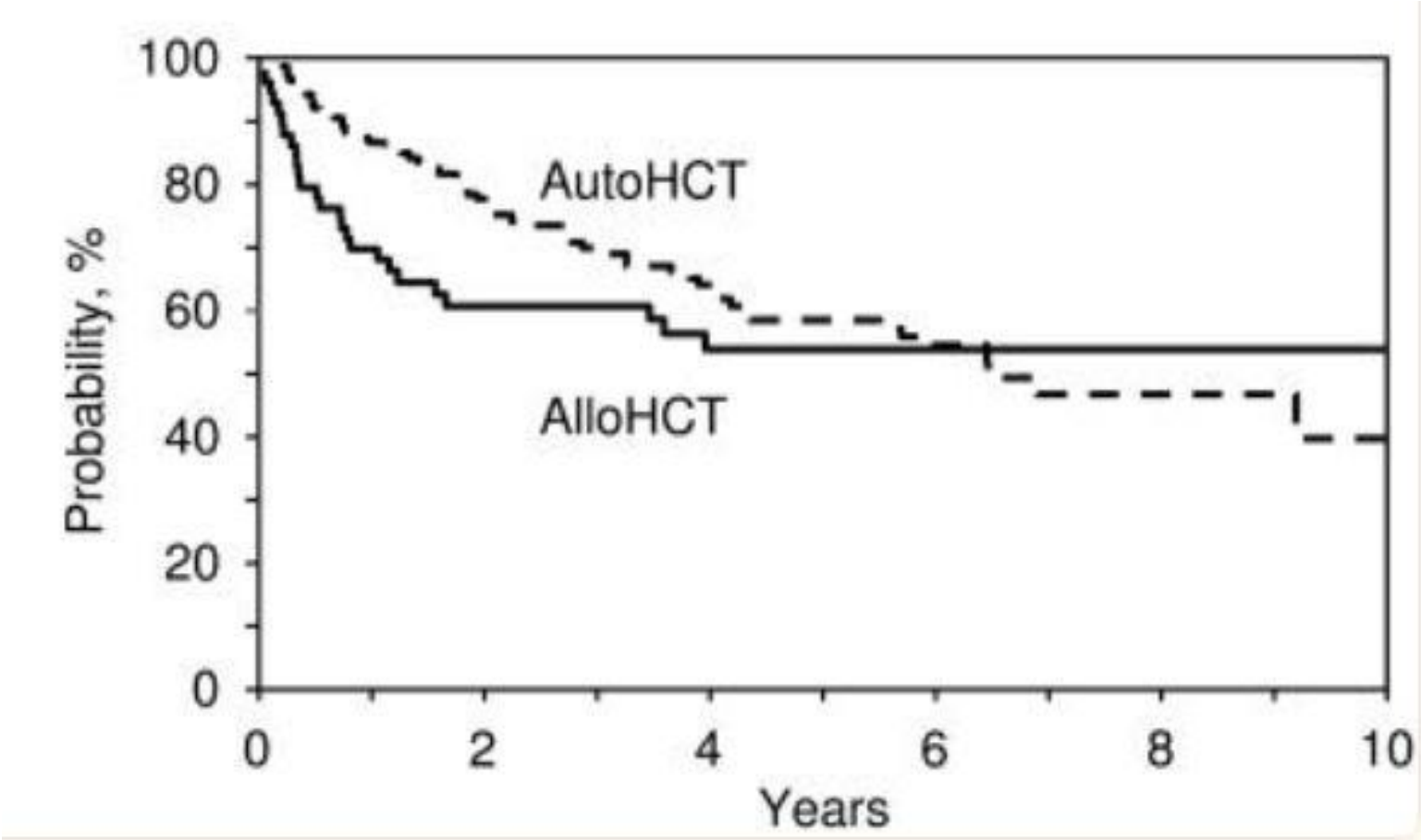
*RIC = reduced intensity and non-myeloablative conditioning.

Auto-HCT conditioning primarily BEAM and CBV

Source: Klyuchnikov E et al. *Bone Marrow Transplant* 2016

AUTO-HCT and ALLO-HCT: Grade 3 FL

CIBMTR study of auto-HCT and allo-HCT in FL:



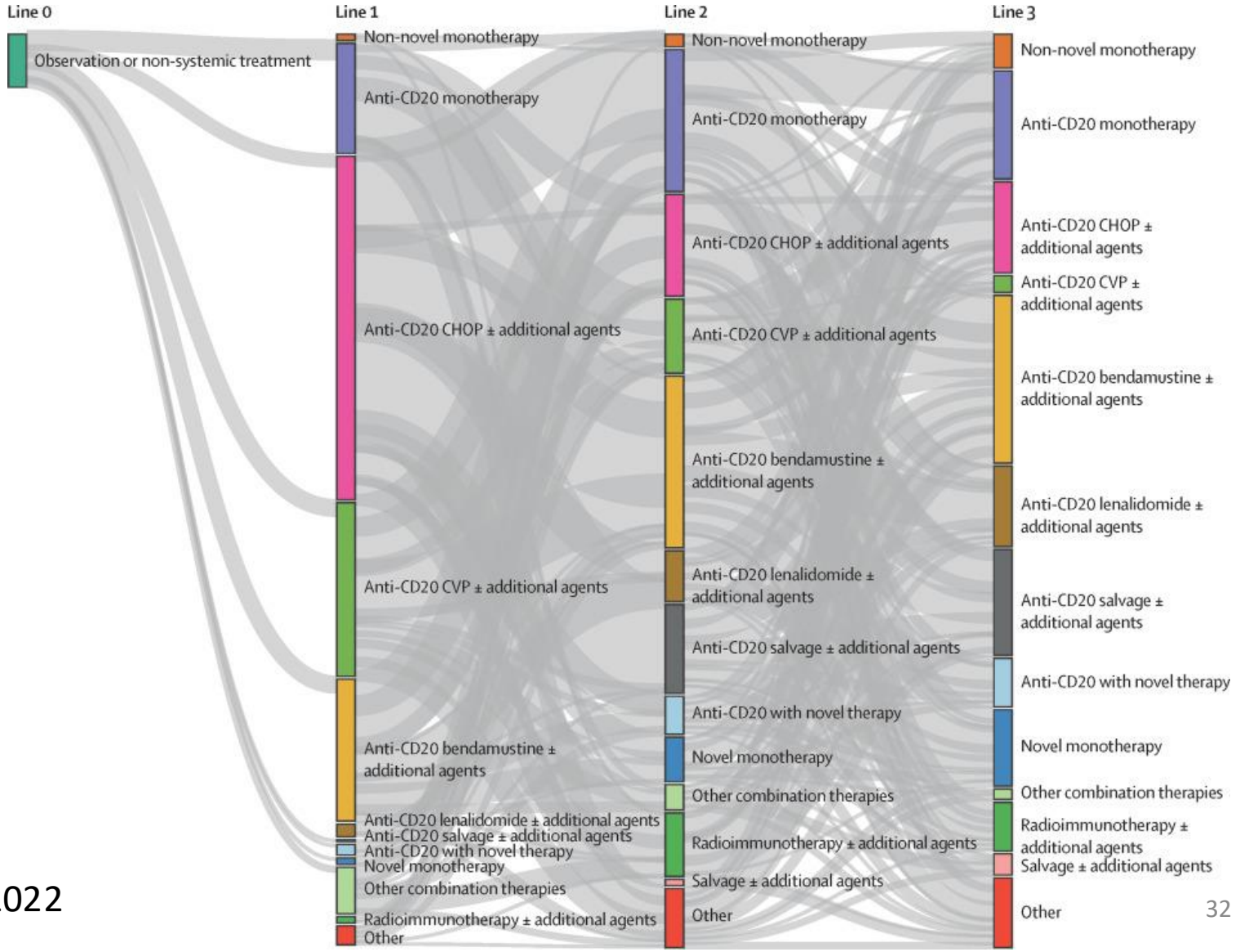
Source: Klyuchnikov E et al. *Bone Marrow Transplant* 2016

UNANSWERED QUESTIONS

Treatment landscape in R/R iNHL is complex!

- Optimal timing/sequencing of targeted therapies in iNHL
- Optimal CAR T cell in FL? **Liso-cel**, **axi-cel**, or **tisa-cel**?
- Which is the optimal BiTE in FL, **mosu** or **epcor**?
- Will T-cell therapies expand into other iNHL types, i.e. **MZL** and **LPL/WM**?

CHOICE OVERLOAD



Source: Casulo C, et al. *Lancet Haematol* 2022

CONCLUSIONS/FUTURE DIRECTIONS

Take-home points:

- Epidemiology and pathobiology of iNHL pose challenges
- BiTEs effective in R/R FL ≥ 2 lines
- CAR T cells effective in R/R FL and CLL ≥ 2 lines
- BiTEs and CAR T require specialized toxicity monitoring

Future directions:

- Real-world datasets
- Trials that incorporate:
  - Novel sequencing and combinations
  - More permissive ECOG and organ function criteria

ACKNOWLEDGMENTS

Our patients and their families/caregivers

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- Kansas City VAMC Hem/Onc Division
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