Bispecific Antibodies in the Lymphoma Outpatient Setting

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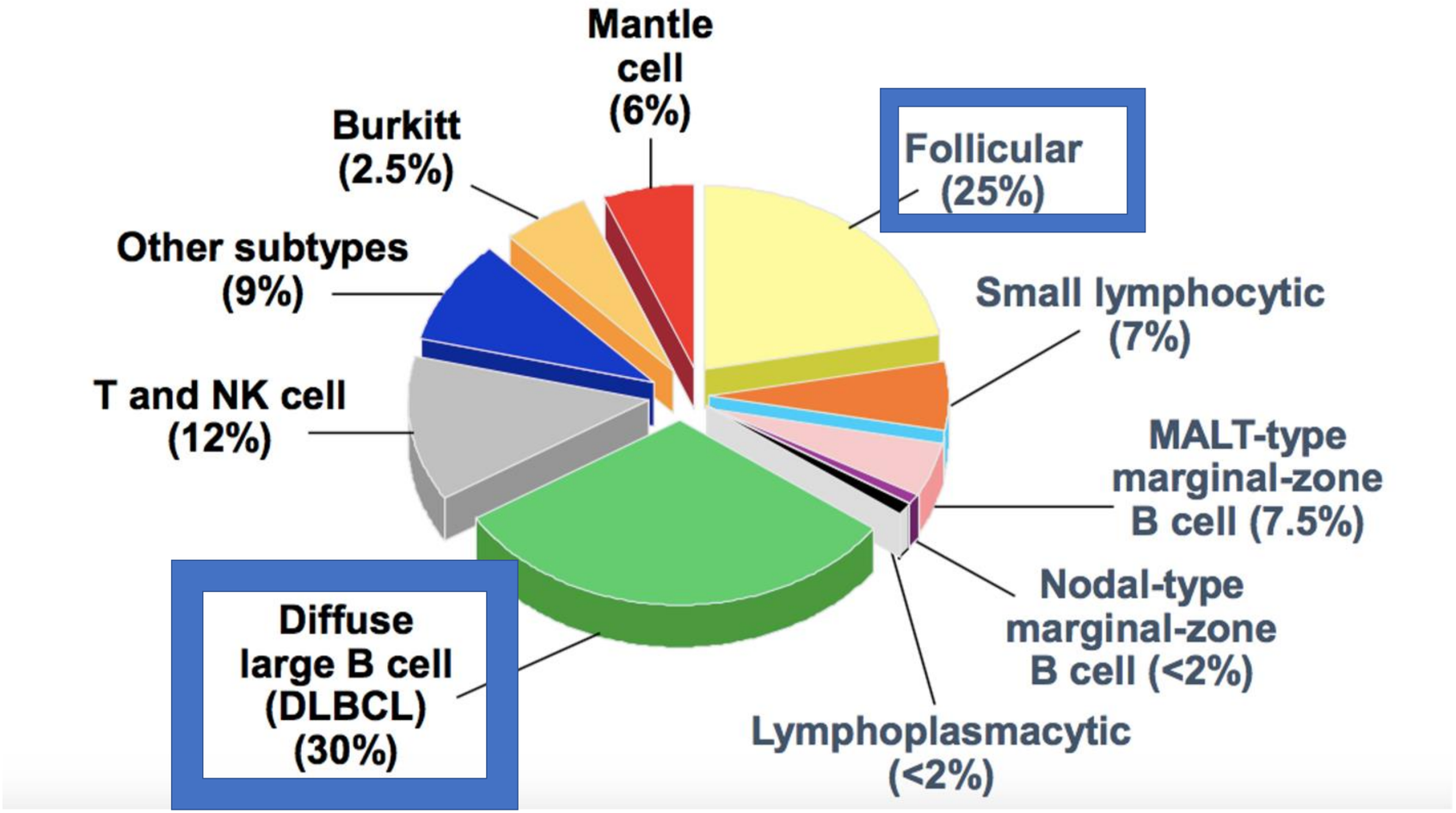
LOUISIANA ONCOLOGY SOCIETY

Disclosures

None

Most Common Subtypes of Non Hodgkin Lymphoma



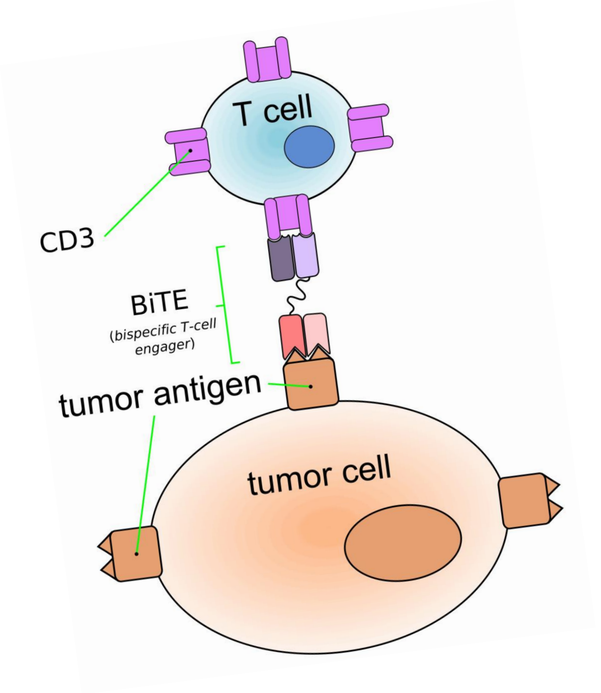
Lichtman MA. *Williams Hematology*. 7th ed. New York, NY: McGraw Hill. 2006;1408.

What is a BiSpecific T Cell Engager (BiTEs)

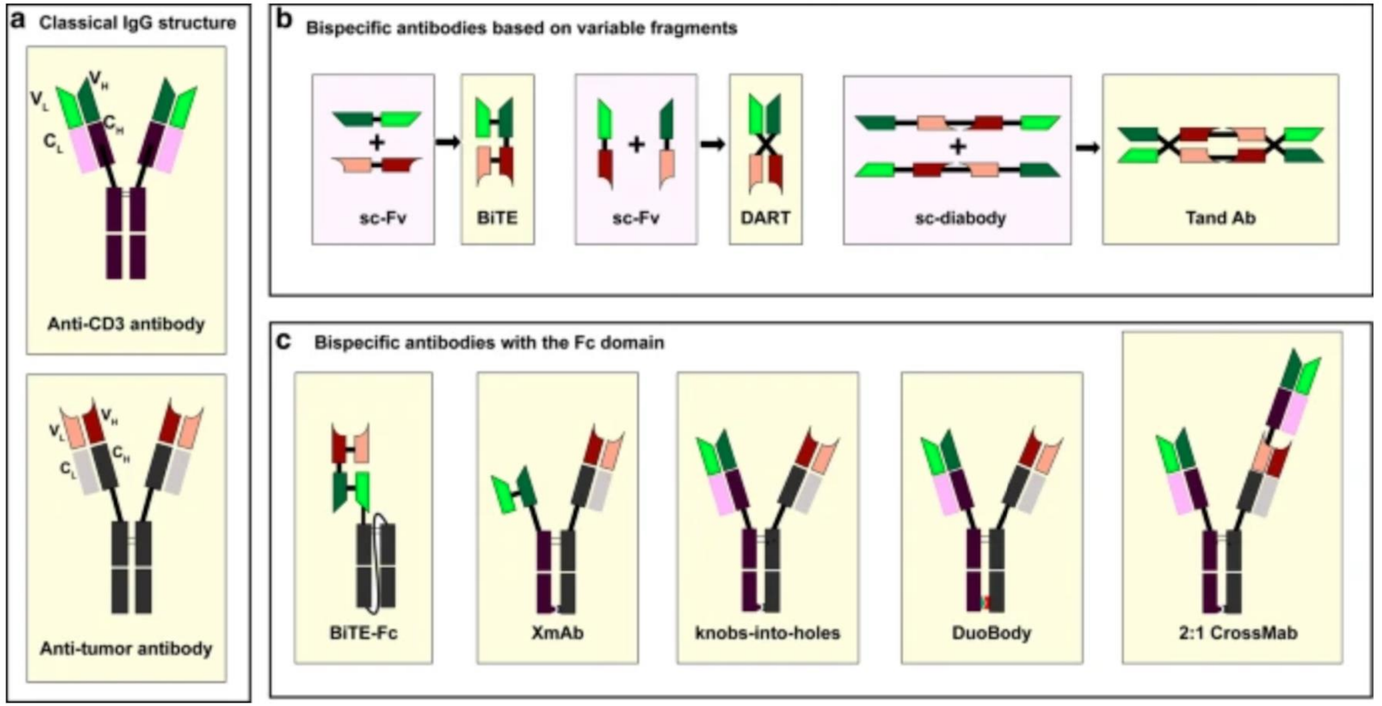
- Concept first appeared in the early 1960s

- First example constructed in 1985

- BiTEs activate T cells without the need for co-stimulation
- Preferentially activate memory T cells
- Their small size allows for:
  - Allow more rapid tumor and tissue penetration
  - Rapid clearance through the kidneys
- BiTEs are unique in that they lack an Fc-binding portion
- They do not activate immune cells:
  - macrophages, neutrophils, or natural killer cells



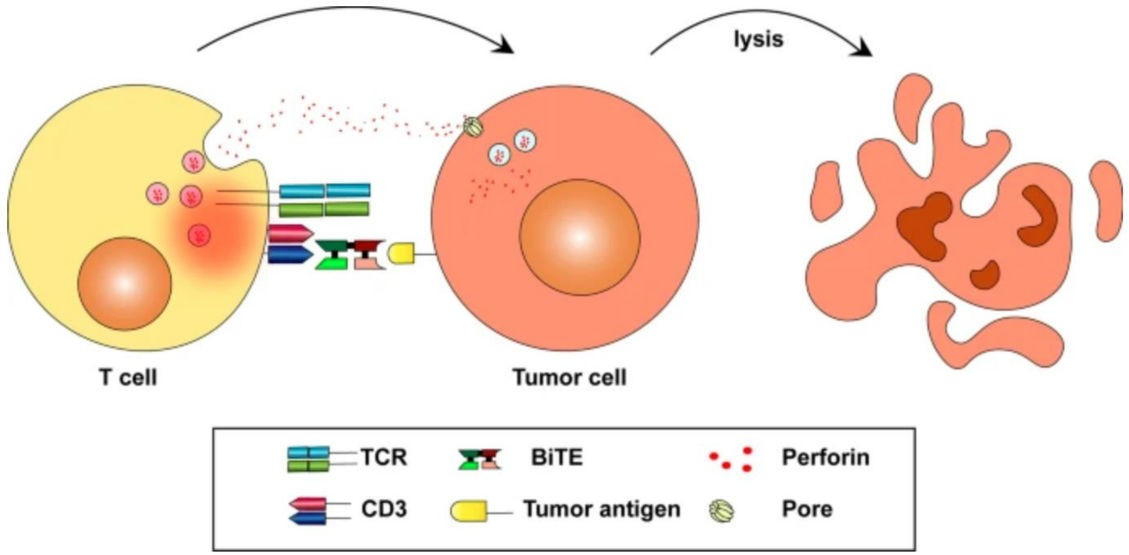
Mechanism of BiTE Action



- BiTEs can redirect T cells to specific tumor antigens and activate T cells directly [preferentially memory T cells]
- Targeting one tumor antigen and one CD3 molecule simultaneously. The CD3 molecule non-covalently associates with the T cell receptor (TCR) and participates in antigen-specific signals transduction which can induce the activation of T cells

Tian, Z., Liu, M., Zhang, Y. *et al.* Bispecific T cell engagers: an emerging therapy for management of hematologic malignancies. *J Hematol Oncol* **14**, 75 (2021)

Achieving Tumor Lysis

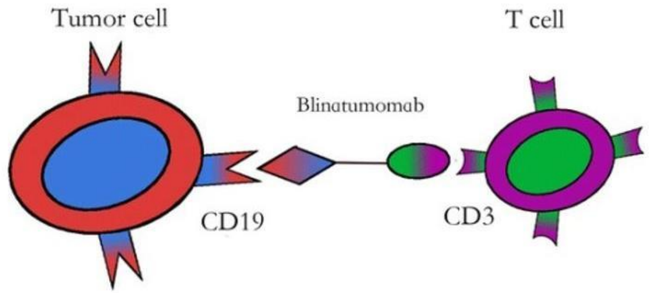


Mechanisms of tumor cell lysis mediated by the BiTEs. BiTEs can redirect T cells to tumor cells and active T cells. Activated T cells release perforin and other granzymes through immunological synapses. These cytolytic proteins can form endosomes in tumor cells and lyse tumor cells ultimately

- Activated T cells secrete perforin and other granzymes through immunological synapses These cytolytic proteins can form pores on cancer cell membrane
- During the process of membrane self-repair, perforin, and other granzymes are endocytosed by cancer cells and then form endosomes.
- Perforin inside endosomes can form pores on the endosomal membrane and cause the release of granzymes inside targeted cells, then cancer cells are lysed

Tian, Z., Liu, M., Zhang, Y. *et al.* Bispecific T cell engagers: an emerging therapy for management of hematologic malignancies. *J Hematol Oncol* **14**, 75 (2021)

Best known BiTE to date



Blinatumomab

- FDA approved in December 2014 for Adult Philadelphia chromosome negative relapsed or refractory B-cell Acute Lymphoblastic Leukemia
- transiently links CD3-positive T cells to CD19-positive B cells
- Inducing T-cell activation followed by serial T-cell–mediated lysis of tumor cells and concomitant T-cell proliferation

BiTE vs CAR-T

BiTE drugs furthest along in development for B-cell lymphoma
are directed to CD20
compared
with the CD19 target used in the approved CAR T-cell products

Sequential therapy with CAR T cells and BiTEs is feasible. In fact, preliminary reports of the BiTE agents describe durable responses after failure of CAR T-cell therapy

Comparison to CAR-T

COMPARISON OF BISPECIFIC T-CELL ENGAGER THERAPY AND CAR T CELLS

CLASS	SCHEDULE	LOCATION	ADVANTAGES	DISADVANTAGES
BITE	STEP-UP, WEEKLY AND THEN VARIABLE	MOSTLY OP	"OFF THE SHELF", VERY LOW SEVERE CRS, ICANS	LOWER CR THAN CAR T, ONGOING DOSING, DURATION OF RESPONSE (?) FINANCIAL (?)
CAR T	"ONE AND DONE"	HOSPITAL* X 2 WEEKS, ACADEMIC MEDICAL CENTER(?)	POTENTIAL CURE IN LYMPHOMA, REMISSION BUT NOT CURE IN MYELOMA	TIME NEEDED FOR MANUFACTURING SEVERE CRS, ICANS, FINANCIAL

OP; OUTPATIENT, CRS; CYTOKINE RELEASE SYNDROME, ICANS; IMMUNE EFFECTOR CELL–ASSOCIATED NEUROTOXICITY SYNDROME, CR; COMPLETE RESPONSE
* FEASIBLE TO GIVE LISOCABTAGENE, TISAGENLECLEUCEL AS OUTPATIENT BUT NOT FOR AXICABTAGENE, IDECABTAGENE AT CURRENT TIME

Cooper, Dennis. https://www.onclive.com/view/bites-more-than-a-nibble-for-lymphoma-and-myeloma. July 2021

Comparison of Blinatumomab vs CD19 CAR T cells

	Bispecific antibody constructs	CAR T cells
FDA approval	Blinatumomab: pediatric and adult patients with r/r ALL, MRD$^+$ (0.1%) ALL (first or second remission)	Axicel: adult with r/r (>2 prior Tx lines) DLBCL, PMBCL
		Tisacel: r/r ALL <26 y of age, adults with r/r (>2 prior Tx lines) DLBCL
Design	Recombinant soluble protein	Retro- or lentiviral-transduced CAR T cells
Availability	**Off the shelf**	17-54 d from patient presentation to CAR T transfusion (national vs international patient recruitment, different trial design)
Manufacturing failures	Not applicable	≤10%[38]
Manufacturing and dosing variability	Not applicable	CAR T-cell product variability due to differences in T-cell subset composition, CAR transduction efficacy, number of viable CAR T cells; number of transfused CAR T cells differs from 0.2×10^6 to 6×10^8[8,26]
Lymphodepletion prior to start of therapy	No lymphodepletion required	Lymphodepletion with cyclophosphamide and fludarabine prior to CAR T-cell transfusion mandatory (tisa-cel: exceptions in case of WBCs $<1\times10^9$/L within 1 wk prior to transfusion)
Safety: AE ≥III	**CRS:4.9%,** ICANS: 9%, hematotoxicity: neutropenia: 28%; lymphopenia: 1.5%; decrease in white-cell count: 5.2%; decrease in platelet count: 6.4% (lower rate of infections compared with SOC; short half-life (<2 h), interruption possible[4]	**CRS: 46%;** ICANS: 12%-32%; hematotoxicity: ≤23%-45%; JULIET trial: cytopenia not resolved by day 28: 32%, CAR T cells persist for months/years[6,7]
B-cell aplasia	Recovery after completion of infusion: 6-18 mo	Months to years depending on persistence of functional CAR T cells; hypogammaglobulinemia for months to years
ORR	44% in r/r ALL, 78% in MRD$^+$ ALL[4]	81% in r/r ALL, 54%-82% in r/r DLBCL
Financial toxicity	**Product: US$72 000**; average no. of cycles: 1-2; in-hospital days: r/r setting: 9 d within the first cycle (MRD setting: 3 d), 2 d second cycle; additional costs: pump equipment, possible IgG-replacement therapy for 6-12 mo	**Products: > US$350 000**; no. of treatment applications: 1; additional costs: logistics, leukapheresis, lymphodepleting chemotherapy, average 10-d in-hospital stay (outpatient to long-term stay, including ICU), possible IgG-replacement therapy for months to years
Target antigen	CD19 target antigen loss: 3%-21%	CD19 target antigen loss: 7%-35%
T-cell exhaustion	Potentially, reversal through treatment-free intervals (induction: 4 wk on, 2 wk off; maintenance: 4 wk on, 8 wk off)	Preclinical work: drug-induced cessation of CAR receptor signaling to prevent or reverse exhaustion; genetically engineered CAR T cells to counteract exhaustion

Marion Subklewe; BiTEs better than CAR T cells. *Blood Adv* 2021; 5 (2): 607–612

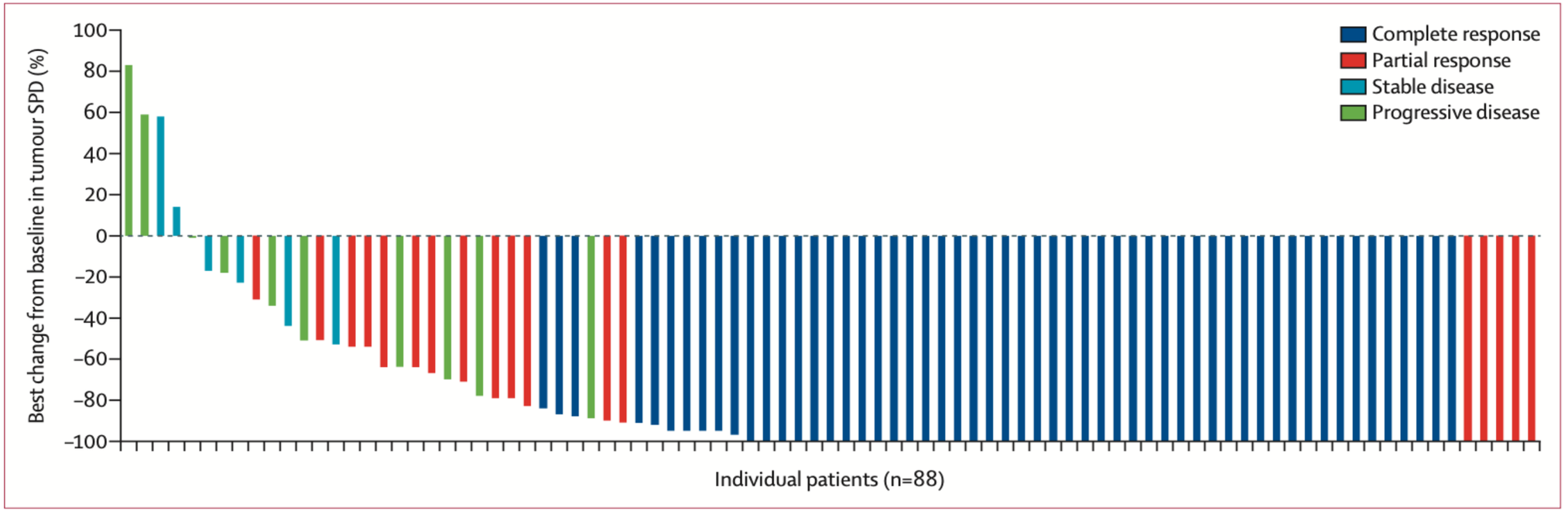
Current Options

ANTI-CD20 X ANTI-CD3 BISPECIFIC ANTIBODIES

AGENT	OUTCOMES	TOXICITY	COMMENTS; INTERESTING ONGOING TRIALS
MOSUNETUZUMAB	INDOLENT: 63% ORR, 43% CR AGGRESSIVE: 37% ORR, 19% CR	CRS 29%, NEARLY ALL GRADE 1-2, BRIEF NEUROTOXICITY 4%	FDA BREAKTHROUGH DESIGNATION 7/20 1) FIRST-LINE FOLLICULAR AND MARGINAL ZONE 2) COMBINATION WITH LENALIDOMIDE R/R FOLLICULAR 3) COMBINATION WITH CHEMO RELAPSED DLBCL 4) AFTER CAR T
ODRONEXTAMAB	INDOLENT: 90% ORR, 70% CR AGGRESSIVE 55% ORR AND CR 42%	64% CRS, SEVERE 7.5%	FDA PAUSE IN THERAPY BECAUSE OF CASES OF SEVERE CRS, TRIAL RESTARTED
GLOFITAMAB	AGGRESSIVE: 65.1% ORR AND 57.1% CR AT RP2D	50.3% CRS BUT ONLY 1.2% GRADE 3	OBINUTUZUMAB PRETREATMENT. 1) COMBINED WITH CHEMOTHERAPY R/R DISEASE AND NEWLY DIAGNOSED DISEASE 2) AFTER CAR T CELL THERAPY 3) COMBINED WITH LENALIDOMIDE
EPCORITAMAB	AGGRESSIVE: 66.7% ORR, 33% CR	GRADE 1-2 CRS, NO GRADE 3, TRANSIENT NEUROTOXICITY	SUBCUTANEOUS ADMINISTRATION PHASE 3 VS INVESTIGATOR'S CHOICE OF CHEMOTHERAPY R/R DISEASE

Cooper, Dennis. https://www.onclive.com/view/bites-more-than-a-nibble-for-lymphoma-and-myeloma. July 2021

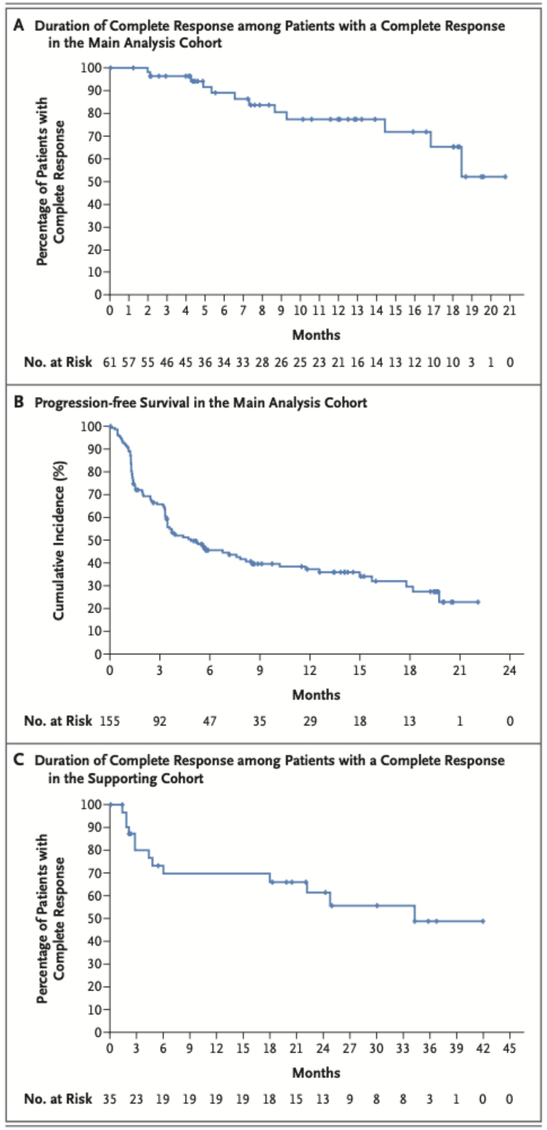
Mosunetuzumab



- Single-arm, multicenter phase 2 study
- 90 patients with Follicular Lymphoma relapsed after at least two prior lines of treatment
- 60% complete response
- 20% partial response
- After failure of CAR T-cell therapy 22% achieving CR
- Median duration of response of 23 months

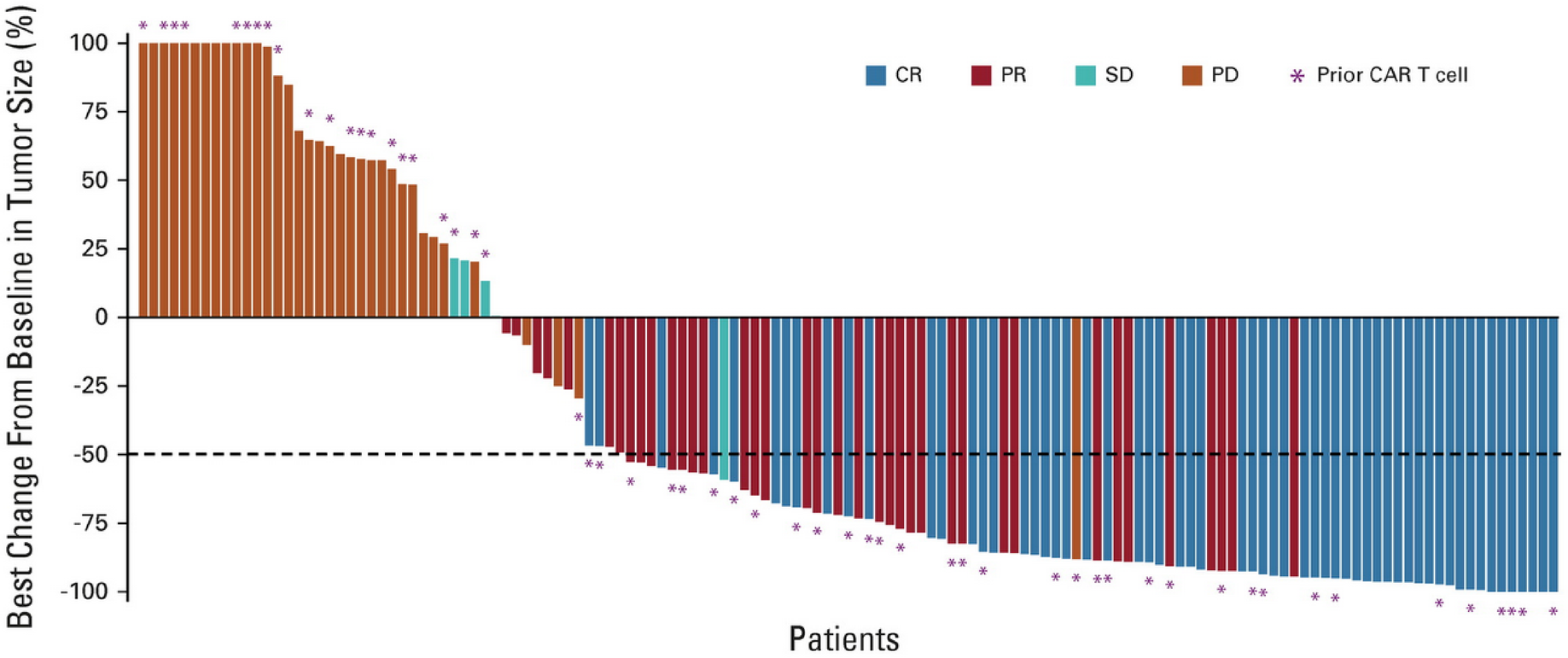
Budde LE, Sehn LH, et all. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. *Lancet Oncol*. 2022;23(8):1055. Epub 2022 Jul 5

Glofitamab



- Phase 2 study
- Relapsed or refractory DLBCL who had received at least two lines of therapy
- Patients received pretreatment with obinutuzumab to mitigate cytokine release syndrome, followed by fixed-duration monotherapy (12 cycles total)
- RESULTS: Of the 155 patients who were enrolled, 154 received at least one dose of any study treatment (obinutuzumab or glofitamab)
- At a median follow-up of 12.6 months, **39% of the patients had a complete response**
- Results were consistent among the 52 patients who had previously received chimeric antigen receptor T-cell therapy (35% of whom had a complete response)
- The median time to a complete response was 42 days
- **78% of complete responses were ongoing at 12 months**
- **The 12-month progression-free survival was 37%**

Dickinson MJ, Carlo-Stella C, et all. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2022;387(24):2220. Epub 2022 Dec 11.



Epcoritamab

- Phase I/II study for relapsed or refractory CD20⁺ large B-cell lymphoma and at least two prior therapy lines
- 157 patients were treated
- median age, 64 years
- median of three prior therapy lines
- 61% primary refractory disease
- 39% prior chimeric antigen receptor (CAR) T-cell exposure
- At a median follow-up of 10.7 months:
- **63% overall response rate**
- **39% complete response rate**
- **The median duration of response was 12.0 months**

Thieblemont C, Phillips T,et all. Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. J Clin Oncol. 2022 Dec 22

Conclusions

- BiTE therapy for many B cell lymphomas induce high rates of complete responses
  - Many CRs last more than one year
  - Readily available as off-the-shelf products
  - More cost effective than CAR-T currently
  - Primarily administered as an outpatient regimen
  - More than half of patient had an adverse event

Questions

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