20TH INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

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Bispecific Antibodies in Follicular Lymphoma

20TH ULTMANN
CHICAGO LYMPHOMA SYMPOSIUM

THE UNIVERSITY OF CHICAGO
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Disclosures

None

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Follicular lymphoma

- Slow growing tumor, with overall 10-year survival rate approaching 80%. 5 yr OS is 90% for patients who remain progression free for >24 months.
- 2nd most common lymphoma accounting for 20-22% of all NHL cases.
- Indolent course, combined with older age patients (most dx over 60yo) frequently leads to “watch and wait” approach.
- For individuals who have progression of disease within 24 months (POD24) after completing 1st line hemoimmunotherapy, the 5 year OS is down to 50% and about 20% of FL patients have a persistent relapsing course.
- Every year 2-4% of FL patients will progress to an aggressive, high-grade disease

Follicular Lymphoma

Advanced-stage disease usually incurable.

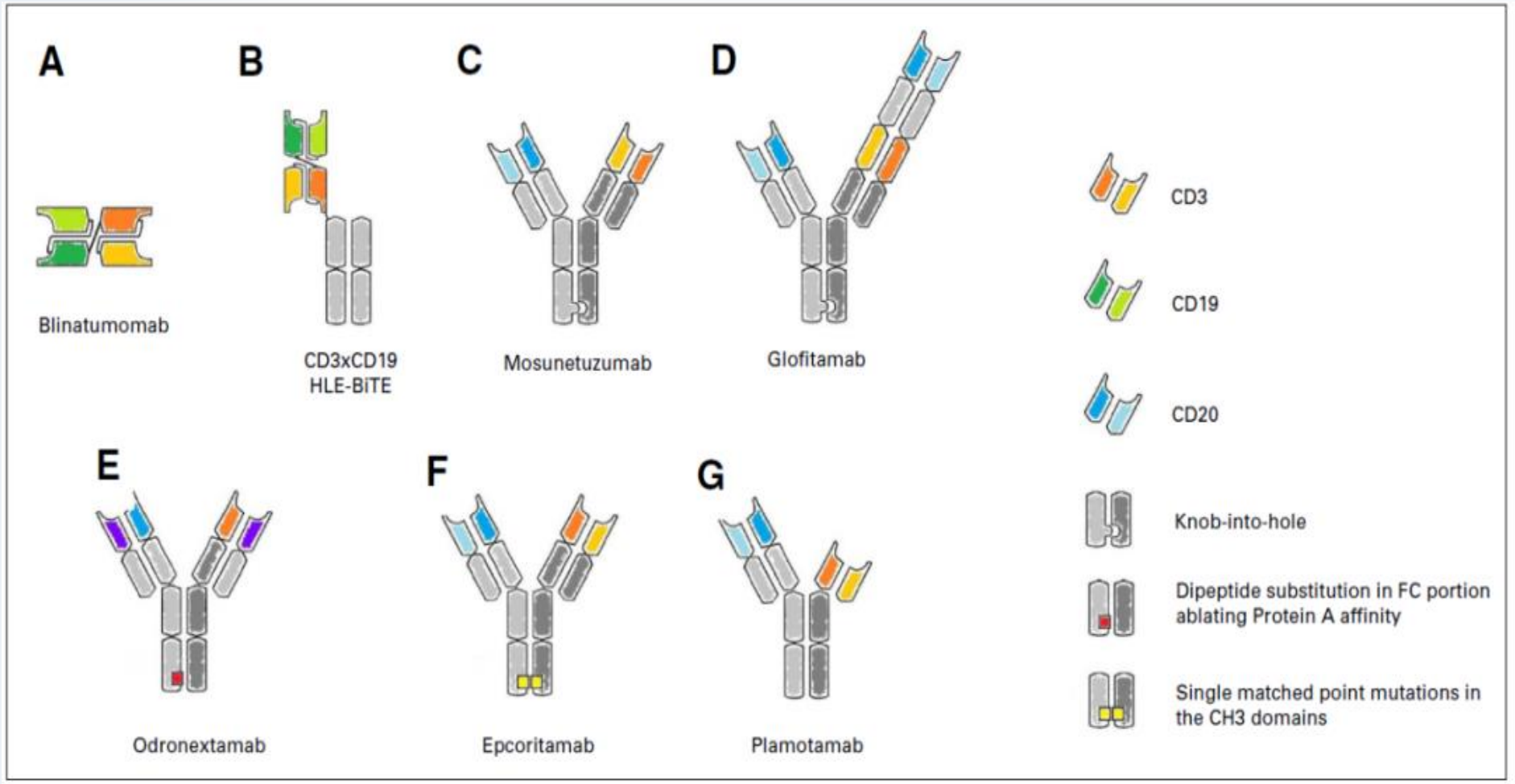
Prior to the introduction of targeted therapies (mAb), OS had not changed significantly

mAbs (e.g. rituximab, obinatuzumab, etc) appear to change the natural history of the disease

Wide range of treatment options:

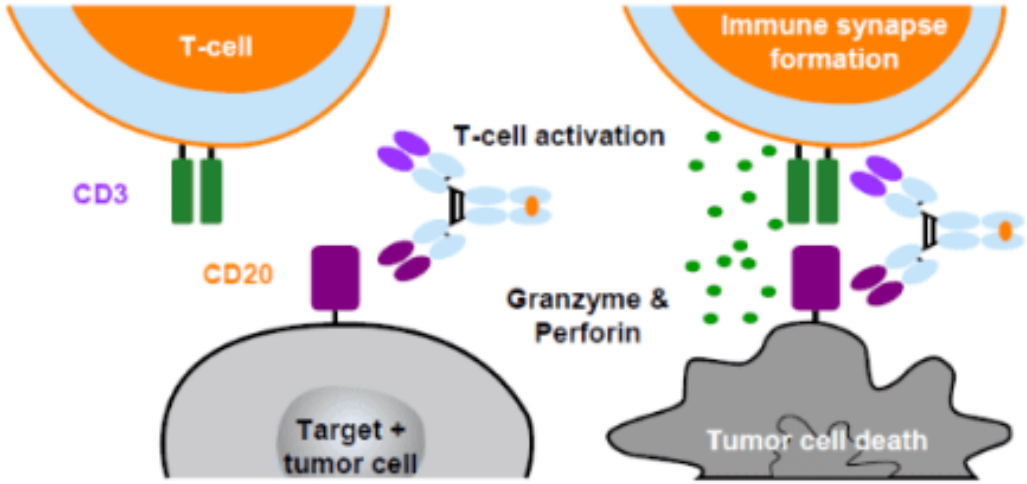
Observation, mAb alone, mAb+chemo, small molecule targeted therapy, such as PI3K (copanlisib) or BTK inhibitors, lenalidomide + mAb (R2), tazemetostat (EZH2 inhibitor), CAR-T, autologous HCT, allogeneic HCT. Now adding BiTEs for R/R FL with >2 prior treatments

Structures of BiTEs for Lymphomas



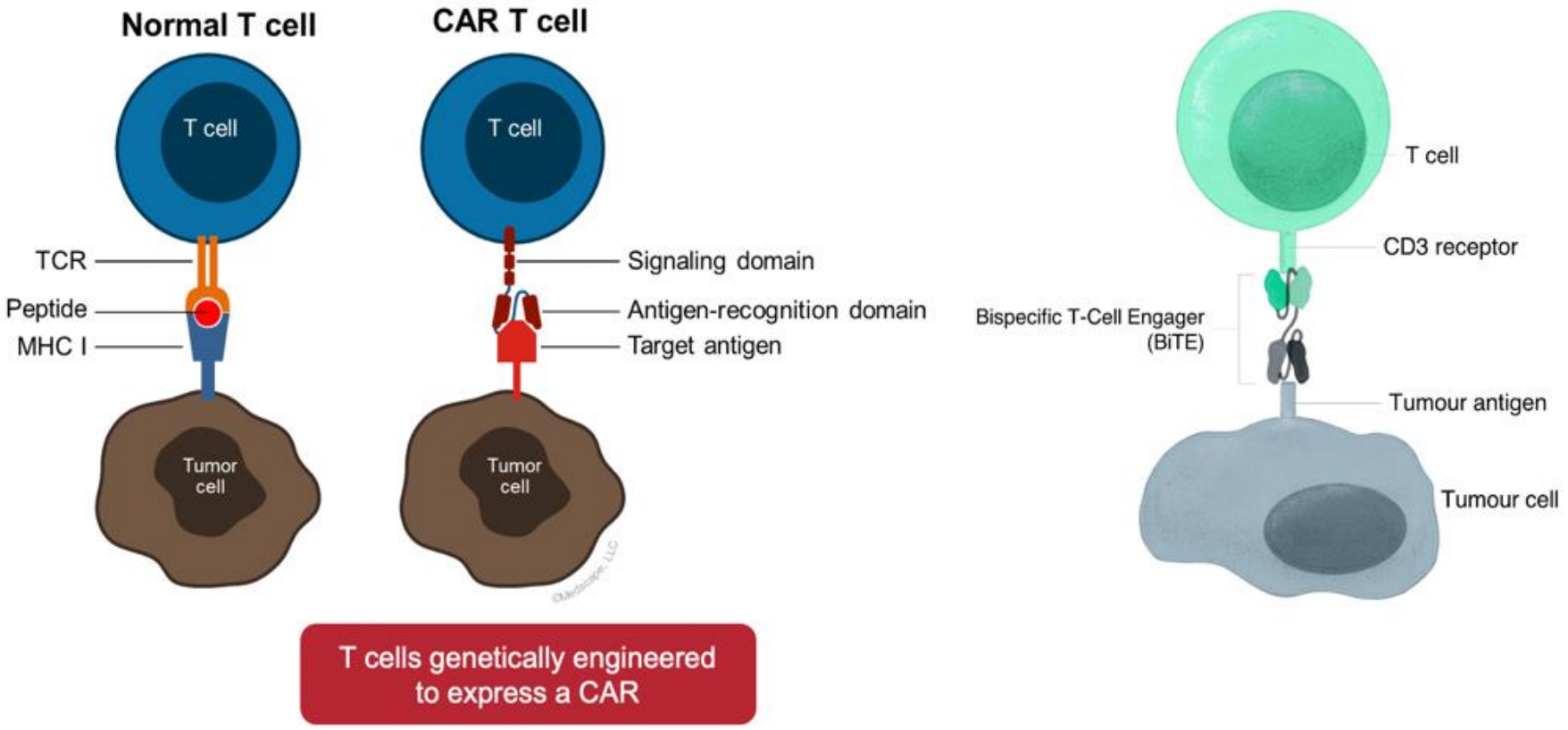
Anti-CD20/CD3 bispecific antibody simultaneously bind T-cells and B-cells

mosunetuzumab



- Optimized binding affinities for improved therapeutic index
- Fast, universal, off-the-shelf solution, with mAb dosing and PK properties
- Potential for use as a single agent and in combination with manageable CRS and neurotoxicity profiles

Tumor Antigen Recognition: T-cell v. CAR T v. BiTE



T cells genetically engineered to express a CAR

Hinrichs CS. Nat Biotechnol. 2013;31:999-1008.

Potential Adverse Events with BiTEs

1. CRS (Cytokine release syndrome) which can be life threatening if it progresses to hypotension/hypoxemia/organ dysfunction. Most patients experience fever (40-98%), chills (35%), and flu-like symptoms. Use step up dosing so dosing is slowly increased to control T cell engagement and the cytokine reaction. Many BiTEs also use corticosteroid premedication for the first cycles. Also exploring SC administration instead of IV for some BiTEs for slower steadier absorption
2. Neutropenia (27-30%) and infections
3. Fatigue (around 40%)
4. Neurotoxicity (ICANS)—confusion, decreased attention. Rare (1-3%). No seizure, aphasia, encephalopathy has been seen in studies.
5. Headache (25-31%)
6. Tumor flare (3%)

Multiple CD3/CD20 BiTEs in Development

	Patients (N)	ORR / CR Rate	Durability	Toxicity Gr 1-2 / Gr 3-4	Comments
Mosunetuzumab (ASH 2019)[1,2]	N=218 141 aNHL, 72 iNHL 23 prior CAR-T	aNHL 35% / 21% iNHL 67% / 36% Prior CAR 44% / 25%	Med DoCR **>6-8 mo**	CRS: 27% / 1% ICANS: ?/ 3%	Genentech; RG7828 Fully humanized
Odronextabmab (ASH 2020)[3]	N=127 71 DLBCL, 37 FL	[3]5% / 22% DLBCL Higher at ↑ doses	Med DoCR **≈ 4-8 mo**	CRS: 62% / 7% ICANS: ? / 4%	Regeneron; REGN1979; Fully humanized 7/24 resp in prior CART
Epcoritamab (ASH 2020)[4]	N=67 45 DLBCL	76% / 44% DLBCL ↑ dose	**?**	CRS: 58% / 0% ICANS: 6% / 3%	Genmab SQ route
Plamotamab[5] (ASH2019) (ASH 2021)	N=44 36 NHL N=14 with 4 FL	ORR 33% All NHL ORR 66.7%, CR 33.3%; FL: ORR 100%; CR 50%	**?**	CRS: 39% / 3% ICANS: 0% ?	Xencor; XmAb1376
Glofitamab (ASH 2020)[6]	N=38 28 aNHL	50% / 29% aNHL	**?**	CRS: 55% / 3% ICANS: ? / 0%	Roche; RG6026; Full Ab 2:1 CD20:CD3 sites Obin dose prior

[1]Bartlett ASCO 2019; [2]Schuster ASH 2020 #6; [3]Bannerji ASH 2020 #400; [4]Hutchings, ASH 2020 #402;
[5]Patel, ASH 2019 #4079 ; [6]Hutchings, ASH 2020 #403;
Patel , ASH 2021

Mosunetuzumab in R/R FL

- Mosunetuzumab (Mosun) is a CD20xCD3 bispecific antibody (Ab). In ph I/II study,Mosun was highly active and well tolerated in R/R FL patients (pts) who had received =2 prior lines of therapy (3L+ R/R FL) when given IV with Cycle 1 step-up dosing for mitigation of CRS
- This is data from the same study from a large expansion cohort of R/R FL pts who received Mosun monotherapy at the recommended Phase II dose (1/2/60/30mg).
- R/R to at least 2 prior lines of therapy including an anti (a)-CD20 Ab and an alkylator
- 90 pts were enrolled. Median number of prior lines of therapy was 3 (range: 2–10). 82% with prior anthracycline; 21% with prior auto-HCT. 69% refractory to prior line of therapy. 52% had POD24.

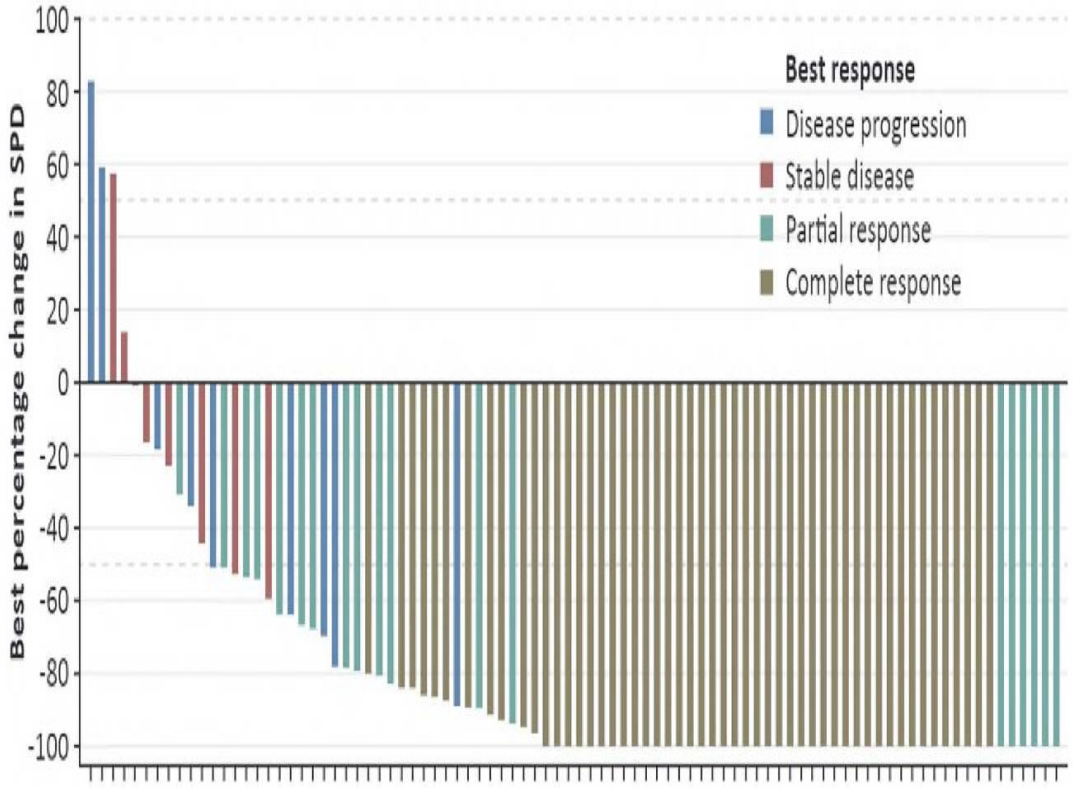
Budde et al, ASH 2021, Abstract 127

Mosunetuzumab for R/R Follicular lymphoma

- Best ORR was 79% and CR rate was 58%
- Median duration of response was not reached; Median PFS was 17.9 months (95% CI: 12.0–not estimable).
- CRS seen in 44%, mostly on C1 and Gr 3-4 only in 2 patients. All CRS events resolved after median duration of 3 days. Toci and steroids used in some pts.
- Common (=5%) Gr 3–4 AEs (66.7% overall) were neutropenia (26.6%), hypophosphatemia (13.3%), hyperglycemia and anemia (7.8% each), and elevated ALT (5.6%).
- Gr 3 neurologic events were uncommon (4.4%) and no Gr 4–5 events occurred.

Budde et al, ASH 2021, Abstract 127

Figure. Waterfall plot of best percentage change in SPD as assessed by PET/CT and independent review facility in all 3L+ R/R FL pts



Glofitamab in R/R Follicular lymphoma

- Glofitamab is a T-cell-engaging, CD20xCD3 bispecific, full-length, 2:1 format antibody with bivalent binding to CD20 (B cells) and monovalent binding to CD3 (T cells).
- Glofitamab monotherapy with obinutuzumab pretreatment or combined with obinutuzumab has shown efficacy and manageable safety in heavily pretreated R/R NHL.
- Here, updated results of glofitamab with three different step-up dosing (SUD) regimens as monotherapy (mono) or combined with obinutuzumab (combo) in R/R FL.
- Obinutuzumab (1000mg) was given 7 days prior to the first dose of glofitamab.
- For the 3 mono cohorts, intravenous glofitamab SUD was given on Days (D) 1 and 8 of Cycle (C) 1; then at target dose on C2, or as SUD on C1D1, C1D8, C2D1 and target dose on C3D1.
- For the combo cohort, glofitamab SUD was given on D1 and D8 of C1, then at target dose combined with obinutuzumab 1000mg from C2D1 and onwards (every 21 days for up to 12 cycles). Response rates were based on the Lugano criteria (Cheson *et al*. J Clin Oncol 2014).

Morschhauser et al, ASH 2021, Abstract 128

Glofitamab in R/R Follicular lymphoma

- 53 pts received glofitamab mono SUD (2.5/10/16mg, n=3; 2.5/10/30mg, n=21; 0.5/2.5/10/30mg, n=29)
- 19 pts received glofitamab combo SUD (2.5/10/30mg).
- median number of prior therapies was 3 (range 1–12) and 2 (range 1–5), respectively. A total of 19 (36%) pts in the mono cohorts and 10 (53%) pts in the combo cohort had experienced POD24.
- In the mono cohorts, overall response rate (ORR) was 81% (n=43) and complete metabolic response rate (CMR) was 70% (n=37), with 72% (n=21) CMR in the 0.5/2.5/10/30mg cohort and 67% CMR in both the 2.5/10/16mg (n=2) and 2.5/10/30mg (n=14) cohorts. In the combo cohort, ORR was 100% (n=19) and CMR was 73.7% (n=14).
- CRS seen in 66% and 79% in the mono and combo cohorts, respectively. 1 pt had a Gr 3 event in the mono cohort and none in the combo cohort. All CRS events were manageable and had resolved at data cut-off.
- Neurologic AEs were seen in 26 pts (16 mono, 10 combo; 36%); all Gr 1 (n=17) or Gr 2 (n=9). No ICANS-like events related to glofitamab were reported.

Table: CMR rates with glofitamab as monotherapy or in combination with obinutuzumab by high-risk subgroup

	CMR rate	
Patients n (%)	Glofitamab monotherapy (n=53)	Glofitamab in combination with obinutuzumab (n=19)
Double-refractory*	8/16 (50%)	3/7 (43%)
POD24	11/19 (58%)	7/10 (70%)
PI3Ki-refractory	3/7 (43%)	1/2 (50%)
SPD ≥3000mm^2	15/24 (63%)	3/7 (43%)

*Pts refractory to anti-CD20 antibodies and alkylating agents

Morschhauser et al, ASH 2021, Abstract 128

Plamotamab

- Step dosing to get to flat dose with C2

-ORR (all B-cell lymphomas)51.1%, CR 25.5%.

(R/R FL with 4 prior treatments: ORR: 100%, CR 50%.

- Study in DLBCL combining plamotamab + tafasitimab + lenalidomide—including those lymphomas arising from low grade lymphoma. Dual Ag targeting may reduce resistance to single Ag loss. Lenalidomide based immune modulation may improve efficacy.

Patel, ASH 2021

Odronextamab

- In R/R FL ORR 78% all doses. With doses of 5 mg or greater: 91%
- CR: 63% CR: 72%

- Median progression free survival: 17.1 mos (range 7.5-not reached)

Bispecific Antibodies (T-cell engagers)

- Promising efficacy in patients with relapsed B-NHL
- Feasible in the community setting
- AEs of interest primarily occur early
- Potentially effective in patients with high risk features
- -previous CAR-T
- -previous stem cell transplant
- -previous anti-CD20 Ab
- -previous alkylating agents
- -pervious targeted therapy
- Complete response is achievable
- Responses are potentially durable
- Can be combined with novel agents or chemotherapy

How do we utilize BiTEs?

1. Currently 3rd line treatment for R/R FL. Will this improve if given earlier?
2. Sequencing questions: give before or after CAR-T or HCT?
3. Give in conjunction with other treatments (mAb, lenalidomide, chemotherapy, other targeted therapy)
4. Looking at SC administration in some BiTEs to slow the absorption and decrease CRS/ICANs