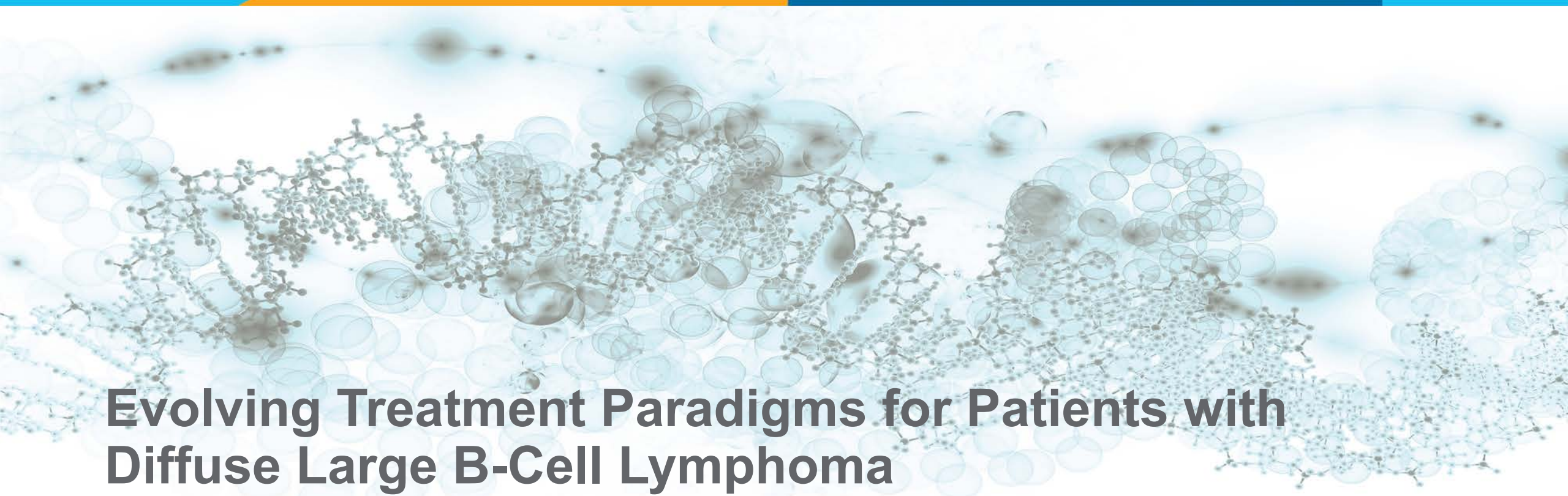


Evolving Treatment Paradigms for Patients with Diffuse Large B-Cell Lymphoma

Ann S. LaCasce, MD, MMSc

Case #1

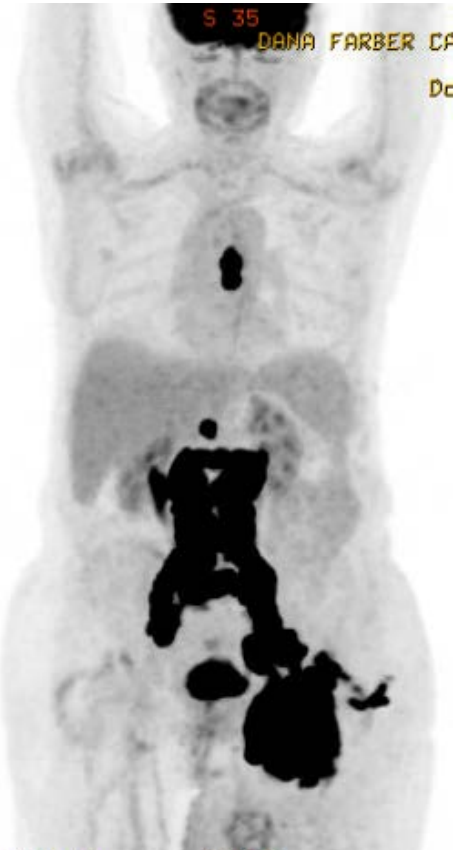
- 77-year-old woman initially presented with stage IV non-GCB DLBCL with extensive disease above and below the diaphragm with splenic and multi-focal bony disease. IPI 5. She was treated with RCHOP x 6 with systemic methotrexate x 3 cycles with a complete remission.

- Unfortunately, she developed recurrent disease 6 months later. She received RICE x 2. Subsequent PET scan showed improvement but with persistent uptake in a solitary soft tissue mass in the abdominal wall.

- She underwent T-cell pheresis, followed by lymphodepletion and CAR-T cell infusion. Her course was complicated by grade 2 CRS.

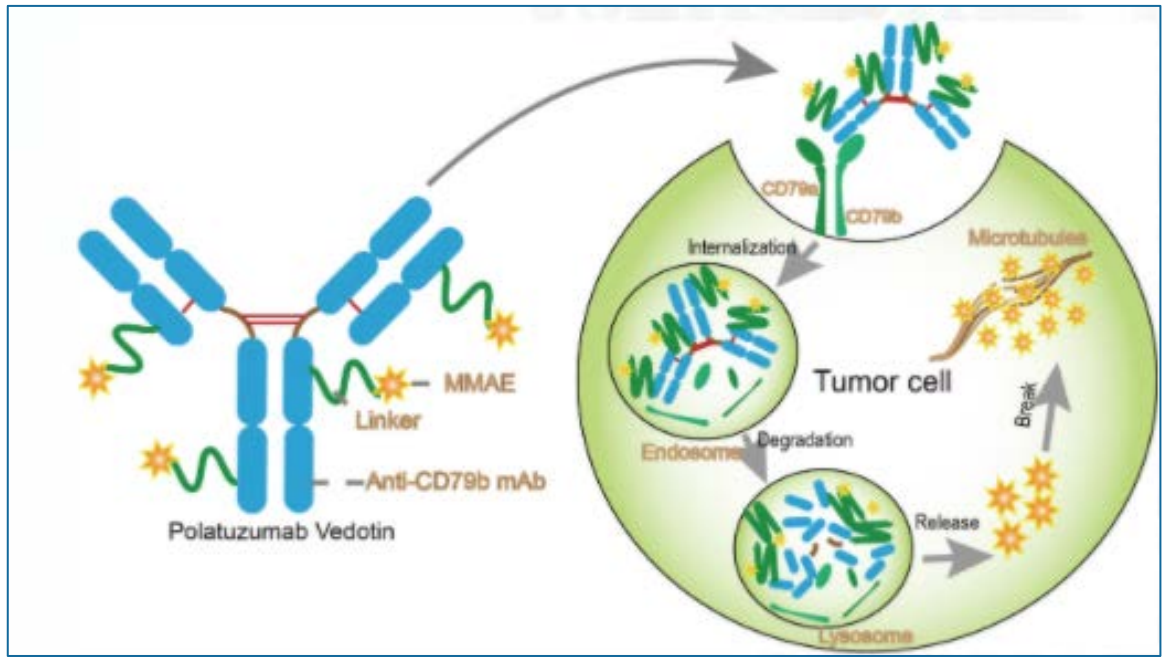
- One year later, she developed biopsy recurrent disease in the left thigh. She was enrolled on a clinical trial with a bi-specific antibody and achieved a near complete response. Her course was complicated by grade 1 neurotoxicity.

- Within 3 months, however, she had recurrent, severe leg swelling and scan showed high burden disease.

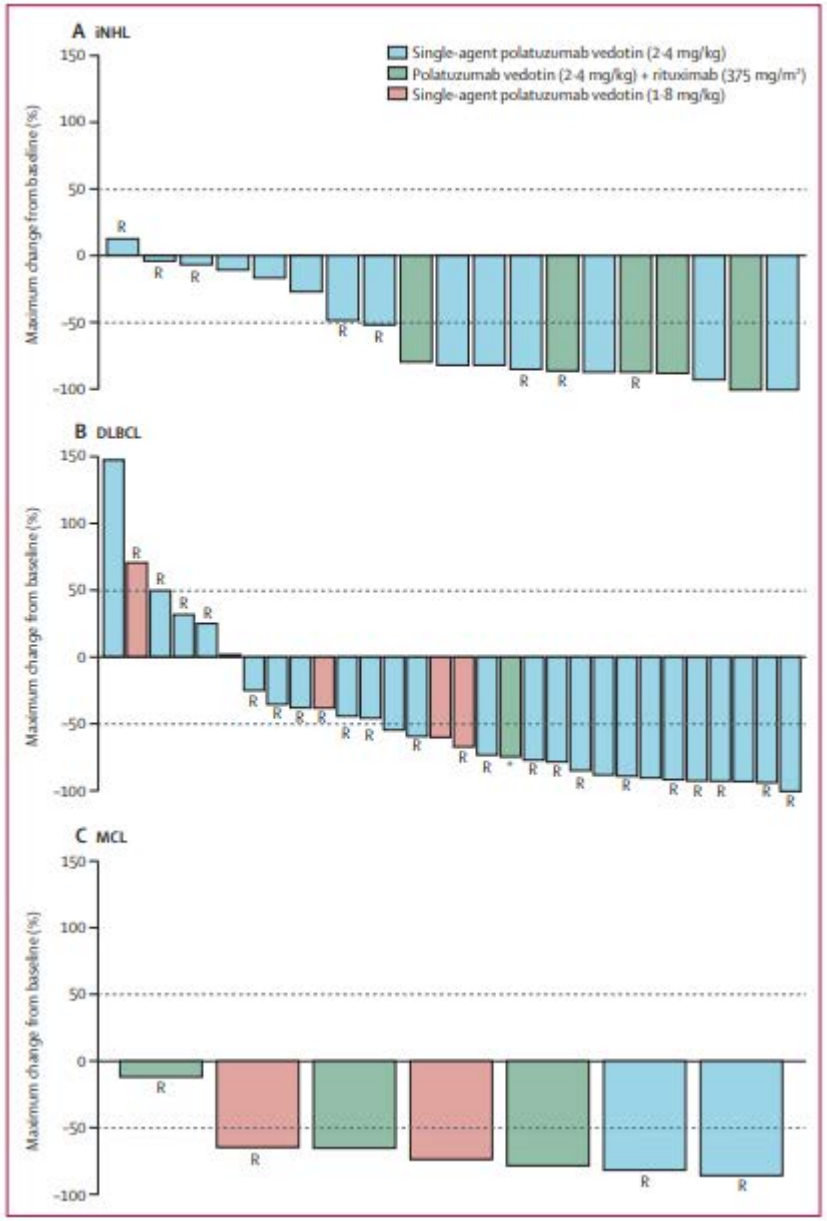


Courtesy of Ann S LaCasce, MD, MMSc

Polatuzumab vedotin phase I trial for R/R B-cell NHL and CLL



AEs in NHL 2.4 mg/kg	Gr 1-2	Gr 3	Gr 4
Neutropenia	4%	24%	16%
PN sensory	27%	7%	2%



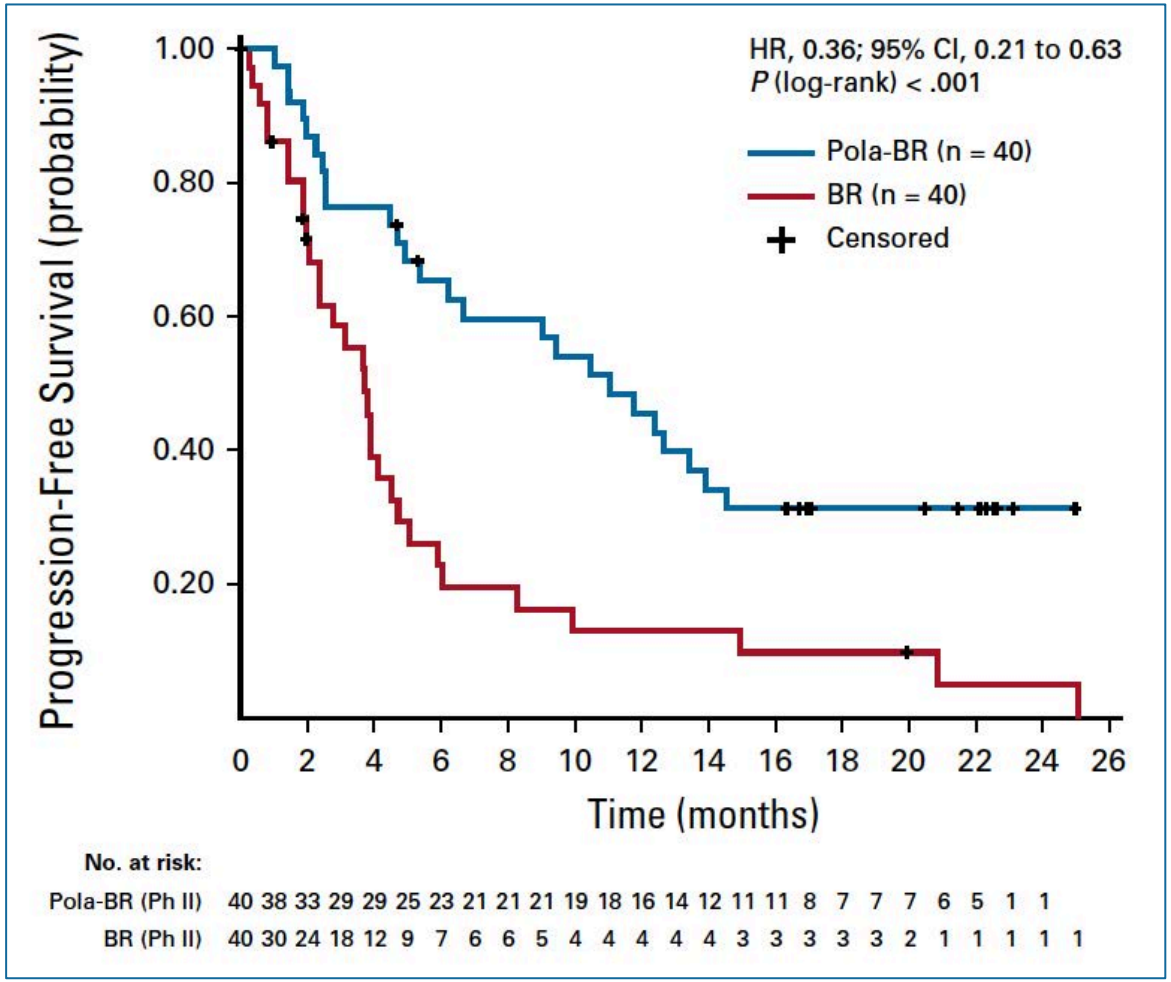
Palanca-Wessels et al. Lancet Oncol 2015

Courtesy of Ann S LaCasce, MD, MMSc

Polatuzumab vedotin + bendamustine + rituximab approved in relapsed/refractory DLBCL

Lines of prior therapy, median (range)	2 (1-7)	2 (1–5)
1	11 (27.5)	12 (30)
2	11 (27.5)	9 (22.5)
≥ 3	18 (45.0)	19 (47.5)
Prior bone marrow transplantation	10 (25.0)	6 (15.0)

ORR 62.5%
CR rate 50%



Sehn et al. JCO 2019

Courtesy of Ann S LaCasce, MD, MMSc

Phase 2 trial of polatuzumab vedotin plus RCHP in previously untreated DLBCL

		DLBCL subtypes by cell of origin			DLBCL subtypes by BCL2+/MYC+ immunohistochemistry	
	Polatuzumab vedotin (1·8 mg/kg) plus R-CHP or G-CHP group (n=66)	ABC subtype (n=16)	GCB subtype (n=28)	Unclassified (n=7)	DEL (n=13)	Non-DEL (n=28)
Overall response	59 (89%; 80–95)	14 (88%; 62–98)	28 (100%; 88–100)	5 (71%; 29–96)	12 (92%; 64–100)	26 (93%; 77–99)
Complete response	51 (77%; 65–87)	13 (81%; 54–96)	25 (89%; 72–98)	4 (57%; 18–90)	9 (69%; 39–91)	23 (82%; 63–94)
Partial response	8 (12%; 5–22)	1 (6%; 0–30)	3 (11%; 2–28)	1 (14%; 0–58)	3 (23%; 5–54)	3 (11%; 2–28)
Stable disease	..	..	..	..	..	..
Progressive disease	3 (5%; 1–11)	..	..	2 (29%; 4–71)	..	1 (4%; 0–18)
Missing	4 (6%; 2–15)	2 (13%; 2–38)	..	..	1 (8%; 0–36)	1 (4%; 0–18)

Morschhauser et al. Lancet Oncol 2019

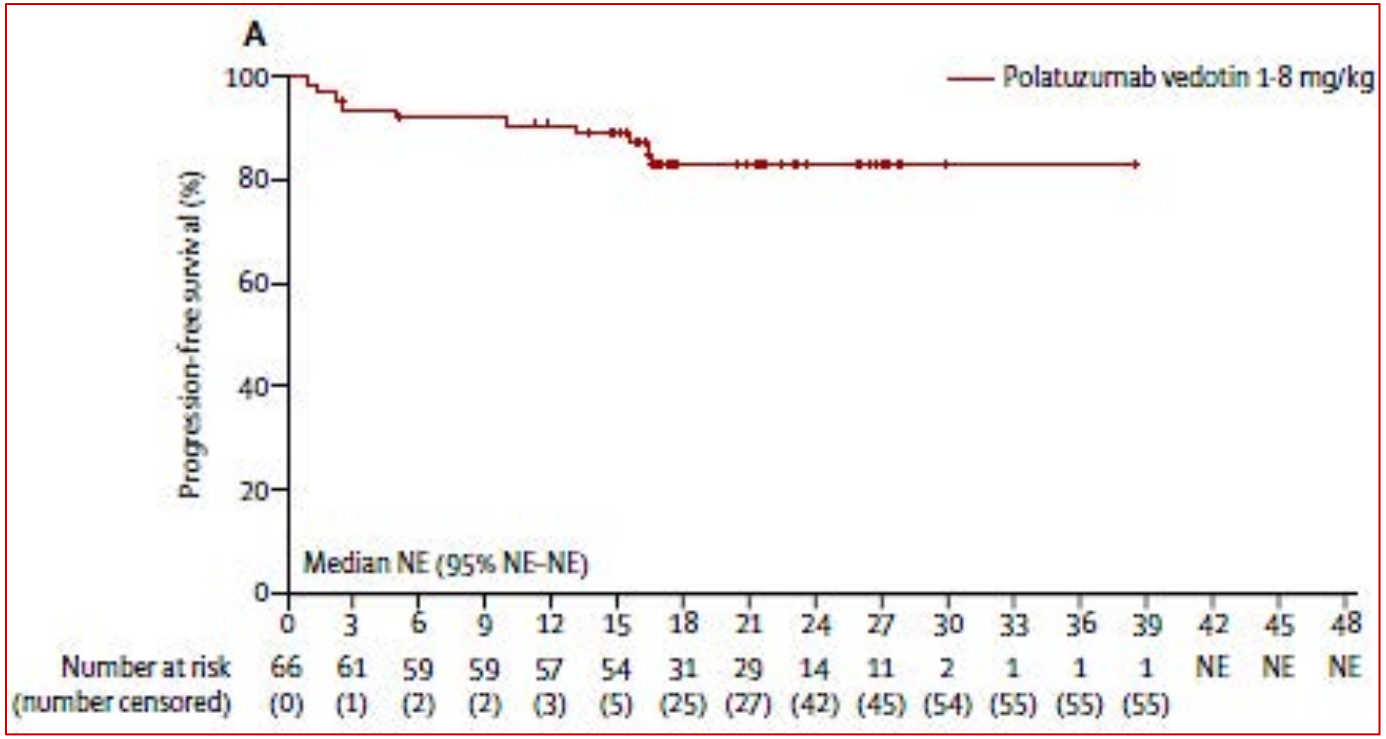
Courtesy of Ann S LaCasce, MD, MMSc

PFS favorable in Pola-RCHP with acceptable toxicity profile in previously untreated DLBCL

Toxicity of interest:

PN grade 1-2: 38%
PN grade 3: 3%

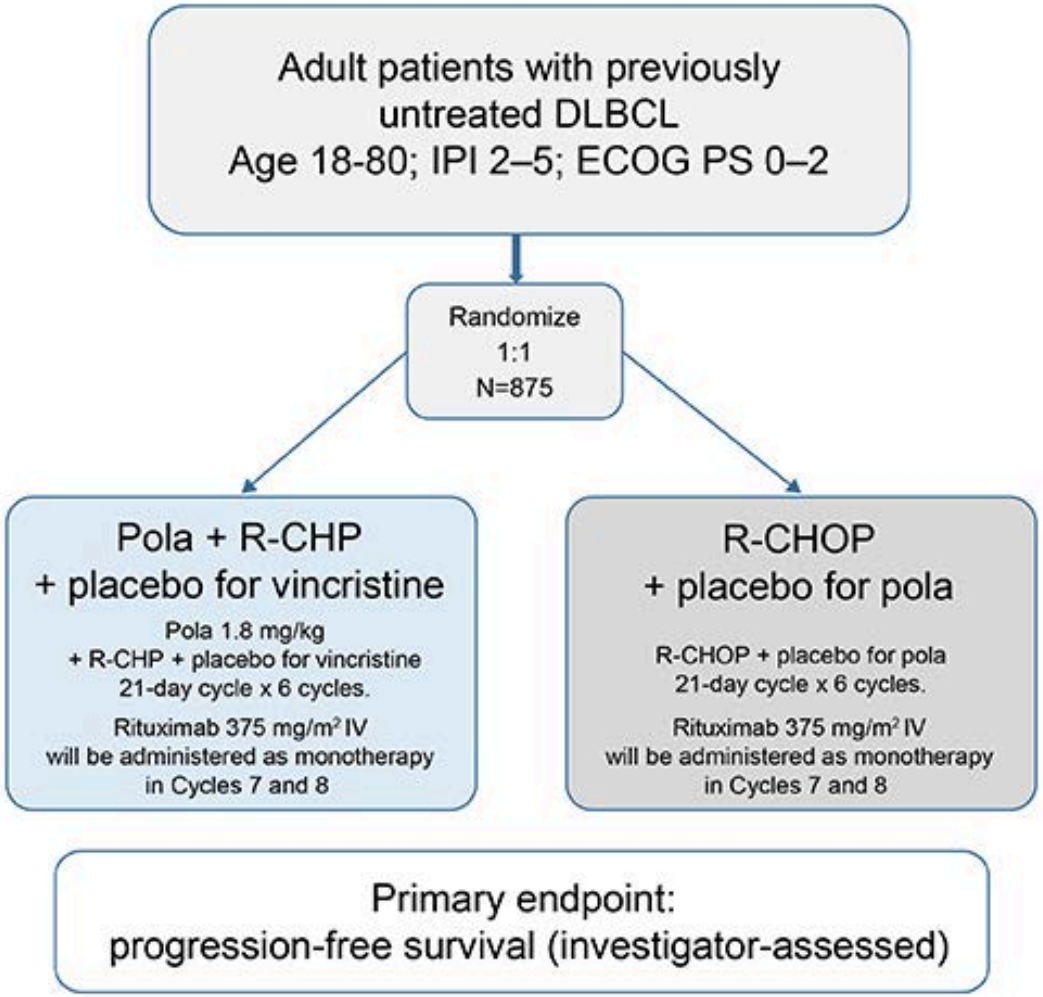
Febrile neutropenia gr 3/4: 19%



Morschhauser et al. Lancet Oncol 2019

Courtesy of Ann S LaCasce, MD, MMSc

Ongoing Phase 3 POLARIX Study DLBCL



Courtesy of Ann S LaCasce, MD, MMSc

Case # 1 (continued)

- She was treated with polatuzumab plus rituximab.
- Bendamustine was withheld given the persistent cytopenias after CAR-T and her prior therapies.
- She achieved a metabolic CR and had no toxicity.
- She remains in remission, now about 9 months post therapy.

Courtesy of Ann S LaCasce, MD, MMSc

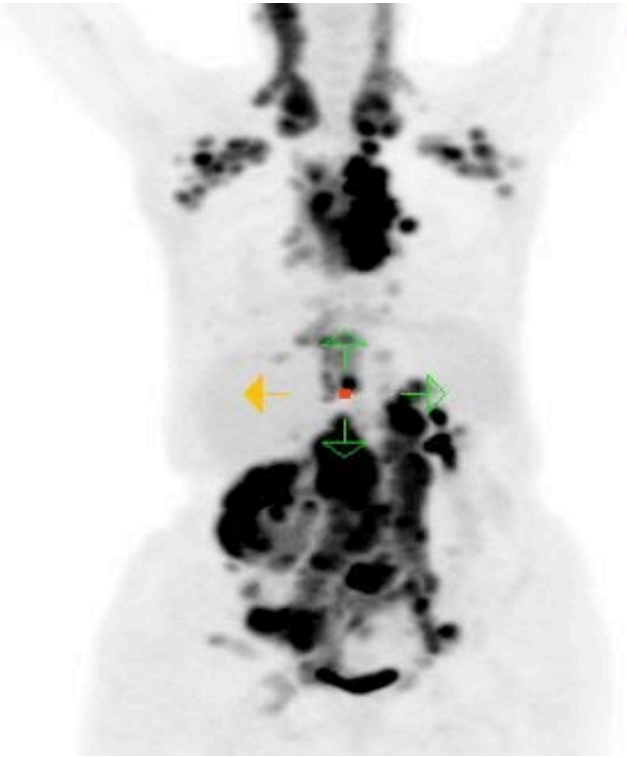
Case #2

A female patient in her mid-70s presented with left sided pleuritic chest pain. Chest CT revealed diffuse LAN. Excisional right axillary node bx showed DLBCL, non-GCB subtype with a ki-67 fraction of 80%.

PET scan with FDG-avid disease above and below the diaphragm with involvement of the right kidney with resultant hydronephrosis. She had bilateral pleural effusions R>L. IPI was a 5.

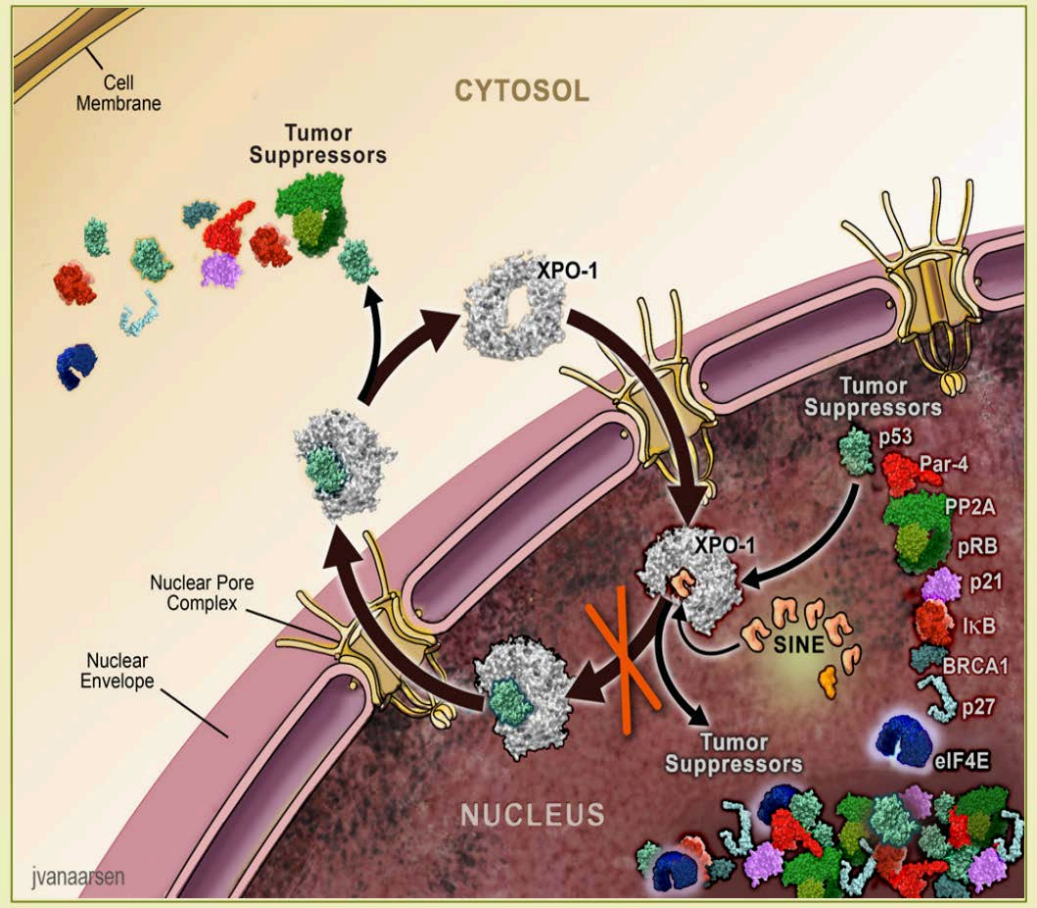
She received RCHOP x 6 with 2 of 3 cycles of systemic methotrexate with a metabolic CR.

She developed recurrent disease 9 months later.



Courtesy of Ann S LaCasce, MD, MMSc

Selinexor has a novel mechanism of action: XPO-1 inhibitor



XPO1 over-expressed in DLBCL and correlates with poor prognosis

Induces nuclear accumulation of tumor suppressors including p53, p73, IkBk and FOXO

Decreases production of oncoproteins including c-MYC, BCL2, BCL6 and BCL-XL

Kalakonda. Lancet Heme 2020

Courtesy of Ann S LaCasce, MD, MMSc

Phase II SADAL Trial: Selinexor in highly selected population of patients with DLBCL

60 mg D1,3 weekly

Key eligibility:
- **60 days after CR/PR**
- **98 days after refractory disease**

	Total (N=127)
Number of previous systemic regimens for DLBCL	
2	75 (59%)
>3	52 (41%)
Time since most recent progression from previous regimen to start of selinexor, weeks	8·1 (4·57–15·14)
Previous ASCT therapy for DLBCL	
Yes	38 (30%)
No	89 (70%)
Refractory to the most recent systemic treatment regimen for DLBCL	
Yes	91 (72%)
No	29 (23%)
Unknown	7 (6%)
Refractory or relapse DLBCL less than 1 year after last ASCT therapy	21 (17%)

Kalakonda. Lancet Heme 2020

Courtesy of Ann S LaCasce, MD, MMSc

SADAL: Activity is modest with high rates of low grade GI toxicity

	Overall response rate	Complete response	Partial response	Stable disease	Progressive disease or no response recorded
All patients	36/127 (28%) (20·7–37·0)	15 (12%) (6·8–18·7)	21 (17%) (10·5–24·2)	11 (9%) (4·4–15·0)	80 (63%) (54·0–71·4)
GCB subtype	20/59 (34%) (22·1–47·4)	8 (14%) (6·0–25·0)	12 (20%) (11·0–32·8)	7 (12%) (4·9–22·9)	32 (54%) (40·8–67·3)
Non-GCB subtype	13/63 (21%) (11·5–32·7)	6 (10%) (3·6–19·6)	7 (11%) (4·6–21·6)	3 (5%) (1·0–13·3)	47 (75%) (62·1–84·7)
Unclassified	3/5 (60%) (14·7–94·7)	1 (20%) (0·5–71·6)	2 (40%) (5·3–85·3)	1 (20%) (0·5–71·6)	1 (20%) (0·5–71·6)

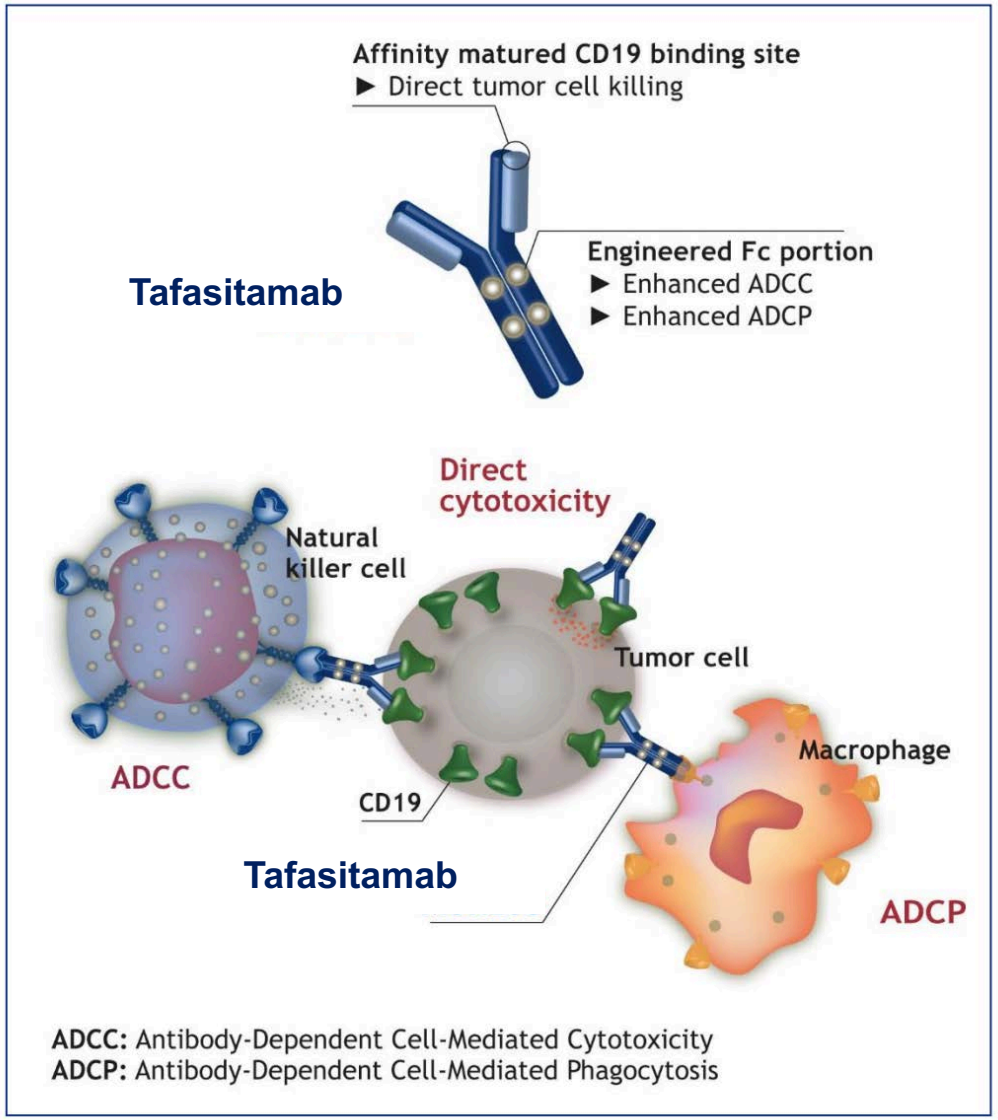
Data are n/N (%; 95% CI). Responses were adjudicated according to central imaging assessment. GCB=germinal centre B cell. See results section in main text for one-sided 97·5% CI.

Table 2: **Responses in evaluable patients**

On June 22, 2020, the FDA granted accelerated approval to selinexor for pts with R/R DLBCL, NOS, including DLBCL arising from FL, after at least 2 lines of systemic therapy.

	Grade 1–2	Grade 3	Grade 4
Thrombocytopenia	20 (16%)	39 (31%)	19 (15%)
Nausea	66 (52%)	8 (6%)	0
Fatigue	46 (36%)	14 (11%)	0
Anaemia	26 (21%)	27 (21%)	1 (1%)
Decreased appetite	42 (33%)	5 (4%)	0
Diarrhoea	41 (32%)	4 (3%)	0
Constipation	39 (31%)	0	0
Neutropenia	7 (6%)	20 (16%)	11 (9%)
Weight loss	38 (30%)	0	0
Vomiting	35 (28%)	2 (2%)	0
Pyrexia	23 (18%)	5 (4%)	0
Asthenia	21 (17%)	6 (5%)	0
Cough	23 (18%)	0	0
Upper respiratory tract infection	18 (14%)	1 (1%)	0
Dizziness	18 (14%)	0	0
Hypotension	13 (10%)	4 (3%)	0
Oedema peripheral	14 (11%)	1 (1%)	0
Dyspnoea	12 (10%)	1 (1%)	1 (1%)
Hyponatraemia	4 (3%)	10 (8%)	0

Tafasitamab (MOR208)



Lenalidomide enhances NK function with enhanced ADCC in vitro

Salles et al. Lancet Onc 2020

Courtesy of Ann S LaCasce, MD, MMSc

Tafasitamab (MOR208) plus lenalidomide active in relapsed/refractory DLBCL

Tafasitamab:
12 mg/kg weekly for 3 cycles.
Then q 14 days
until progression.
Lenalidomide: 25 mg for 12 cycles

	Patients in safety population (n=81)
Median age, years	72 (62–76)
Previous lines of systemic therapy	
Median (range)	2 (1–4)
1	40 (50%)
2	35 (43%)
3	5 (6%)
4	1 (1%)

LDH 56%
Prior ASCT 11%

Salles et al. Lancet Onc 2020

Phase II L-MIND Trial: Tafasitamab plus lenalidomide with durable responses in CR

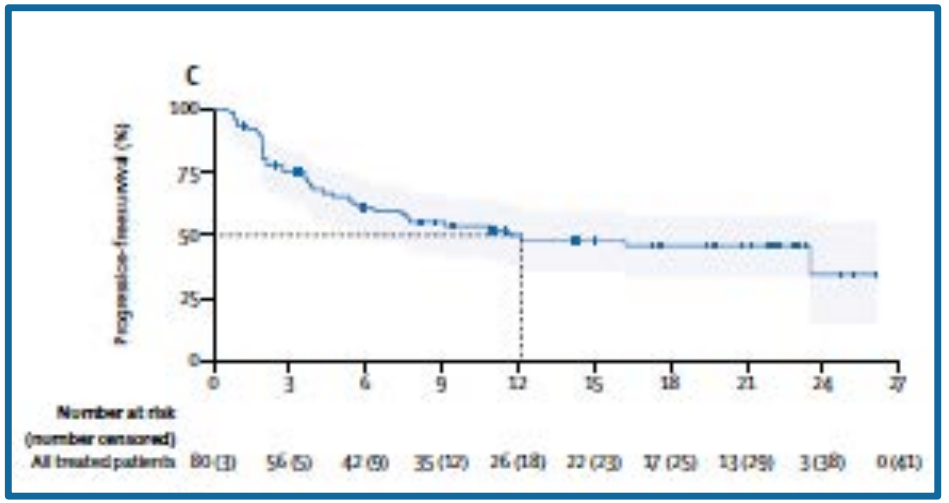
	Patients treated with tafasitamab plus lenalidomide (n=80)*
Best objective response	
Complete response	34 (43%; 32–54)
Partial response	14 (18%; 10–28)
Stable disease	11 (14%; 7–23)
Progressive disease	13 (16%; 9–26)
Not evaluable†	8 (10%; 4–19)
PET-confirmed complete response	30/34 (88%; 73–97)
Objective response‡	48 (60%; 48–71)
Disease control§	59 (74%; 63–83)

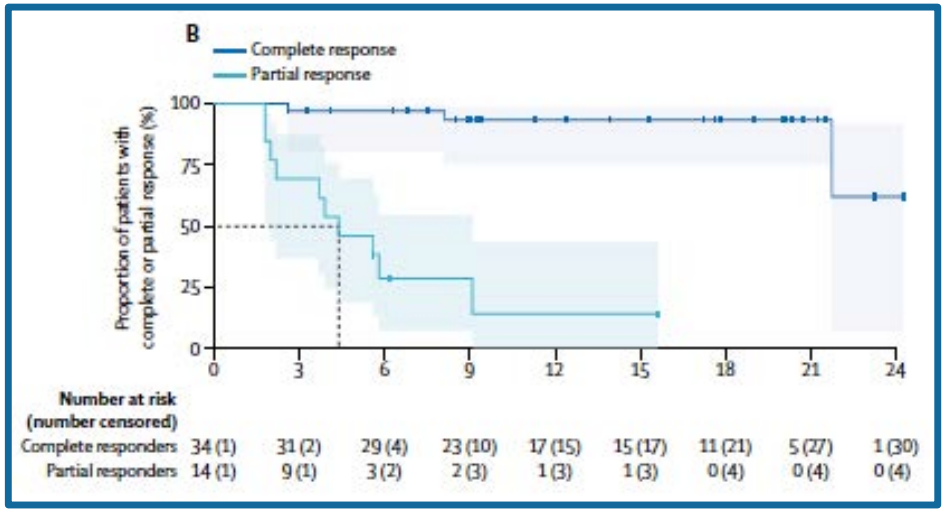
60% of patients received one year of both agents.

46% required dose reduction of lenalidomide and 22% permanently discontinued.

Most common TEAEs (Grade ≥3): Neutropenia, thrombocytopenia and febrile neutropenia

Serious AEs include pneumonia, febrile neutropenia, pulmonary embolism, bronchitis, atrial fibrillation and congestive cardiac failure



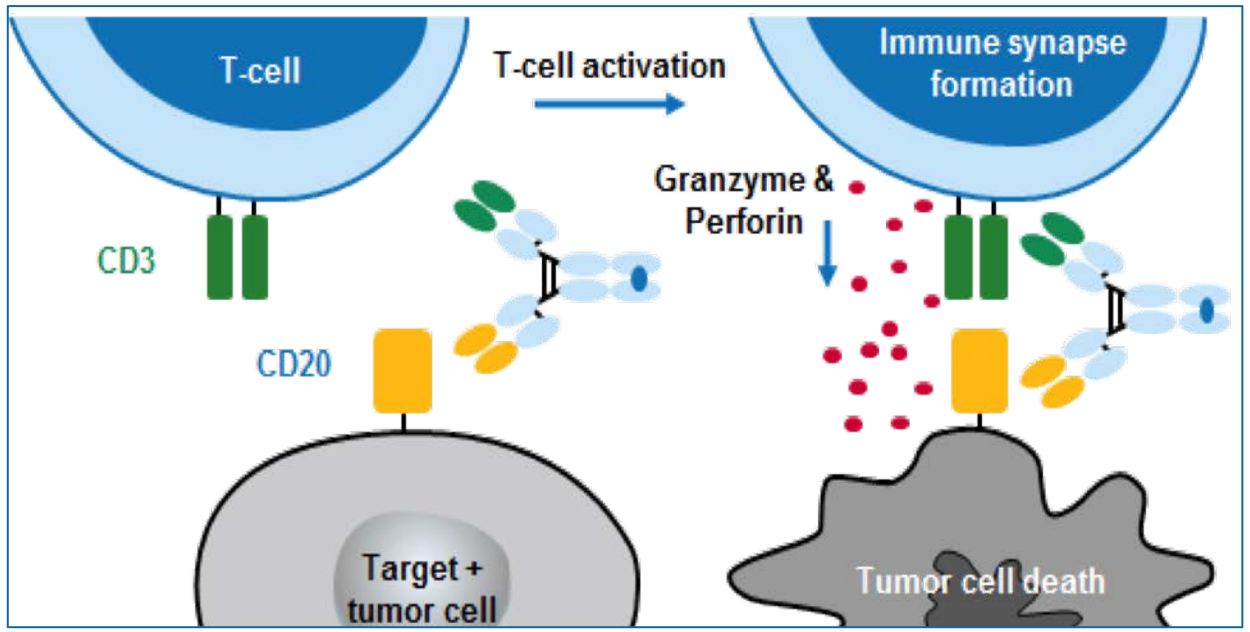


On July 31, 2020, the FDA granted accelerated approval to tafasitamab/len for R/R DLBCL NOS, including DLBCL arising from low-grade lymphoma, and pts who are not eligible for ASCT.

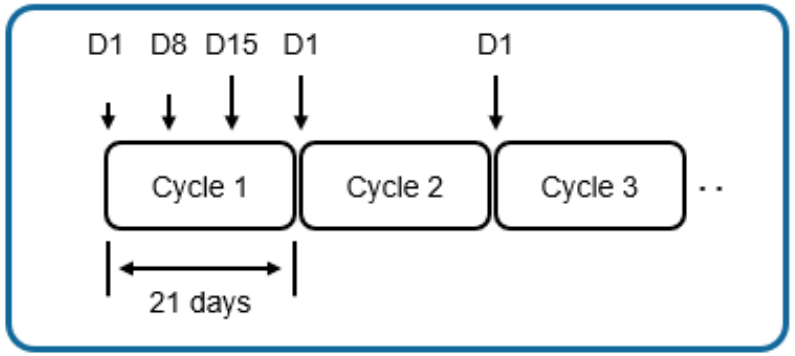
Salles et al. Lancet Onc 2020

Courtesy of Ann S LaCasce, MD, MMSc

Mosunetuzumab: full length CD20/CD3 bispecific antibody



Mosunetuzumab regimen



Phase I/Ib GO29781 Trial

Initial treatment = 8 cycles; if CR achieved, treatment discontinued; if PR or SD, treatment continued for up to 17 cycles

Retreatment allowed for CR patients who relapse

- Schuster et al. ASH 2019

Courtesy of Ann S LaCasce, MD, MMSc

GO29781 Trial: CRS is 30% and NT is 44% but mostly low grade

All Gr AEs in >15% pts	*N=270*
Cytokine release syndrome	78 (28.9%)
Neutropenia‡	65 (24.1%)
Fatigue	55 (20.4%)
Hypophosphatemia	52 (19.3%)
Diarrhea	45 (16.7%)
Pyrexia	44 (16.3%)
Headache	42 (15.6%)
Nausea	41 (15.2%)

Gr 3–4 AEs in >5% pts	*N=270*
Neutropenia‡	59 (21.8%)
Hypophosphatemia	36 (13.3%)
Anemia	24 (8.9%)

	NAEs	
n (%) with ≥1 AE	*Safety evaluable pts (N=270)*	*Prior CAR-T pts (n=30)*
Any Grade	118 (43.7%)	13 (43.3%)
Gr 1	74 (27.4%)	7 (23.3%)
Gr 2	34 (12.6%)	3 (10.0%)
Gr 3	10 (3.7%)	3 (10.0%)
Related Gr 3	3 (1.1%)	1 (3.3%)
ICANS-like NAE	3 (1.1%)	0
Gr 1	2 (0.7%)	0
Gr 2	1 (0.4%)	0
AE characteristics	• Most common NAEs: headache (15.6%), insomnia (9.3%), dizziness (9.3%) • ICANS-like NAEs: 2 confusion (1 related), 1 lethargy (related); all resolved ≤3 days	

GO29781 Trial: Efficacy in aggressive, indolent lymphoma and s/p CAR-T

Investigator-assessed best objective response (pooled data from 2.8mg to 40.5mg cohorts)

	N*	ORR, n (%)	CR, n (%)
Aggressive NHL	124	46 (37.1%)	24 (19.4%)
DLBCL/trFL after ≥ 2 lines	98	37 (37.8%)	20 (20.4%)
• Refractory to anti-CD20	88/98	32 (36.4%)	18 (20.5%)
• With prior auto SCT	32/98	17 (53.1%)	11 (34.3%)

s/p CAR-T	N*	ORR, n (%)	CR, n (%)
All histologies	18	7 (38.9%)	4 (22.2%)
• DLBCL	9	2 (22.2%)	2 (22.2%)
• trFL	5	1 (20.0%)	0 (0.0%)
• FL	4	4 (100%)	2 (50.0%)

Investigator-assessed best objective response (pooled data from 2.8mg to 13.5mg cohorts)

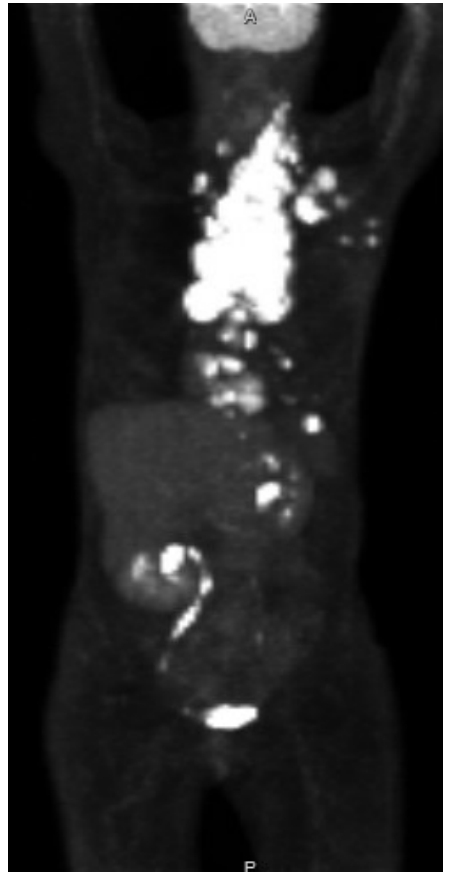
	N*	ORR, n (%)	CR, n (%)
Indolent NHL	67	42 (62.7%)	29 (43.3%)
FL after ≥ 2 lines	61	39 (63.9%)	27 (44.3%)
• Double refractory	43/61	28 (65.1%)	19 (44.2%)
• History of POD24	33/61	20 (60.6%)	14 (42.4%)
• PI3Ki refractory	9/61	8 (88.9%)	7 (77.8%)

Schuster et al. ASH 2019

Courtesy of Ann S LaCasce, MD, MMSc

Case #2 (Continued)

- She initially did not want to pursue infusional chemotherapy.
- We pursued oral BTK inhibitor therapy but there was several months delay given financial issues.
- She ultimately progressed relatively rapidly once she initiated the drug.
- Scan, shown here, showed extensive disease.
- She was started in polatuzumab vedotin plus BR but soon opted for hospice.
- At the time of her initial relapse, none of these 4 regimens was available.



Courtesy of Ann S LaCasce, MD, MMSc

Summary

- Multiple novel drugs recently approved and in trials for patients with DLBCL
- Polatuzumab/bendamustine/rituximab is an active regimen and appropriate for elderly patients. Cytopenias can be managed with dose reductions or holding bendamustine
- The POLARIX study should read out soon and may be the first change in upfront therapy since the introduction of rituximab with CHOP
- Selinexor is a novel XPO1 inhibitor with modest activity and low grade GI toxicity. It is appropriate for patients with less aggressive disease who prefer an oral regimen.
- Tafasitamab plus lenalidomide has favorable PFS, particularly in patients achieving CR. Dose reductions of lenalidomide common and schedule is intensive.
- Mosunetuzumab is active in multiple lymphoma subtypes in the relapsed/refractory setting. Ongoing upfront studies underway in DLBCL.

Courtesy of Ann S LaCasce, MD, MMSc