Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Case Studies in Immunotherapy for the Treatment of Lymphoma

Wednesday, July 7, 2021
5:30-6:30 p.m. EDT

This webinar is supported, in part, by independent medical education grant funding from

AMGEN MERCK

(as of 6/7/21)

Webinar faculty

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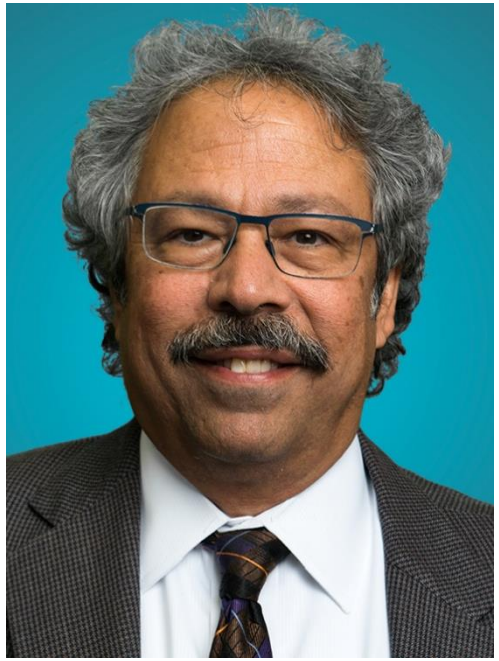


Mitchell S. Cairo, MD –
New York Medical College at Maria Fareri Children's Hospital

Case #1 – presentation and diagnosis

- 31 year-old woman, presenting with persistent cough, 30 lb weight loss, drenching night sweats, pleural effusion, and bulky anterior mediastinal mass in March, 2017.
- Core needle biopsy of mass revealed cHL, nodular sclerosis subtype
- PET scan was consistent with stage IV, bulky disease with osseous involvement. Initial stage: IVBX
- IPS was 3/7

Case #1 – first-line therapy

- Patient was treated with 6 cycles of ABVD
- Interim PET scan after 3 cycles showed complete response
- Post-therapy PET scan in October, 2017 confirmed complete response
- Observation was recommended

Case #1 - recurrence

- Patient presented with acute shortness of breath in February, 2018
- Chest CT scan revealed extensive soft tissue nodularity
- Patient underwent numerous thoracenteses for recurrent pleural effusion. Pleural fluid cytology revealed no evidence of malignancy
- PET/CT revealed hypermetabolic lesions in mediastinum, pericardium, hilium, and paratracheal nodes
- Patient underwent VATS and biopsy, which revealed recurrent cHL

Case #1 – second-line treatment

- Patient underwent salvage therapy with ICE followed by planned ASCT
- Patient achieved a likely CR (with mild residual FDG activity in the chest) after cycle 2
- Cycle 3 of ICE was administered and autologous stem cells were collected
- PET/CT after cycle 3 of ICE demonstrated disease progression

Case #1 – Question 1

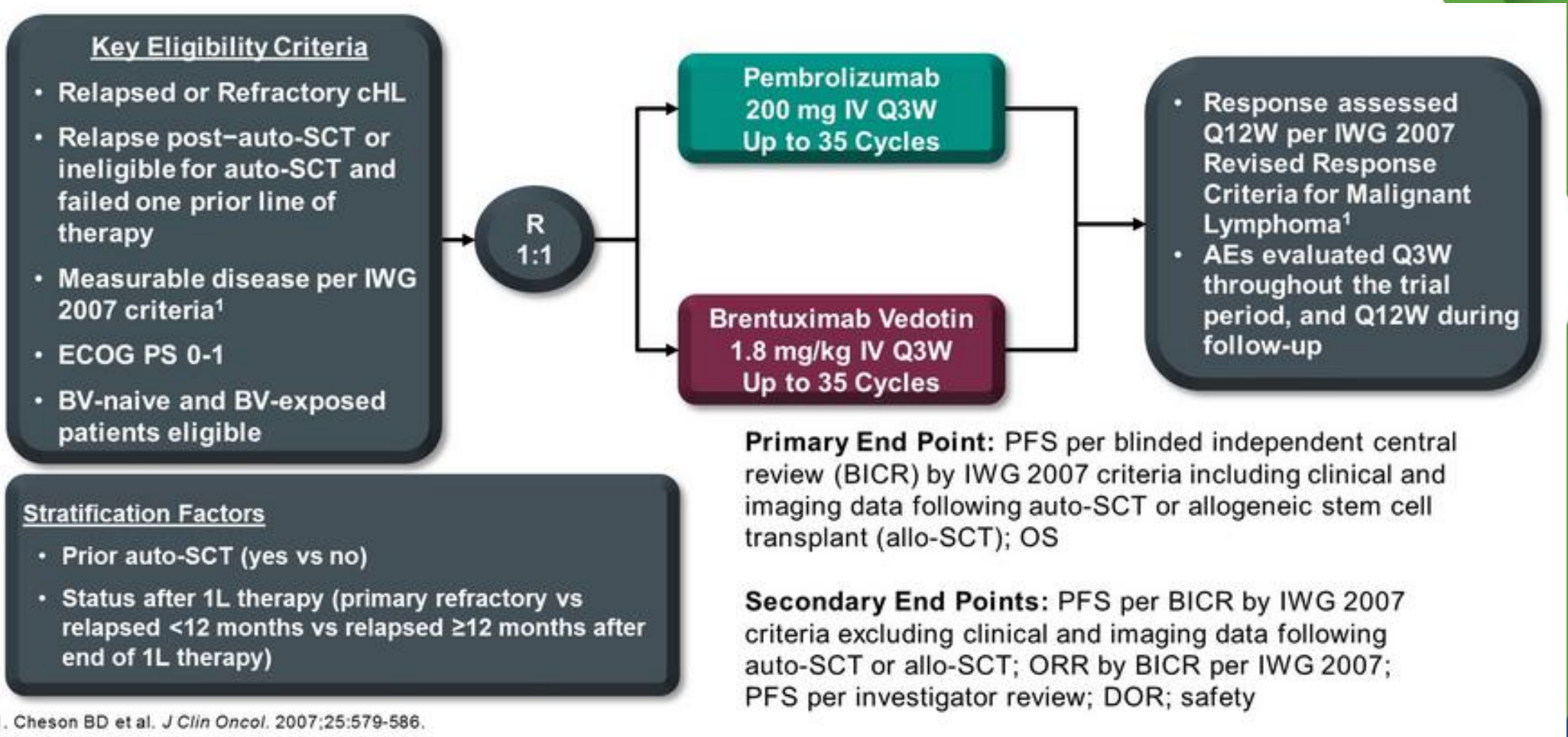
What treatment would have the highest likelihood of improved PFS at this time?

A. Pembrolizumab
B. Brentuximab vedotin
C. ASCT
D. Bendamustine and brentuximab vedotin
E. Conventional salvage chemotherapy (GND, GDP, etc)

Case #1 – third-line treatment

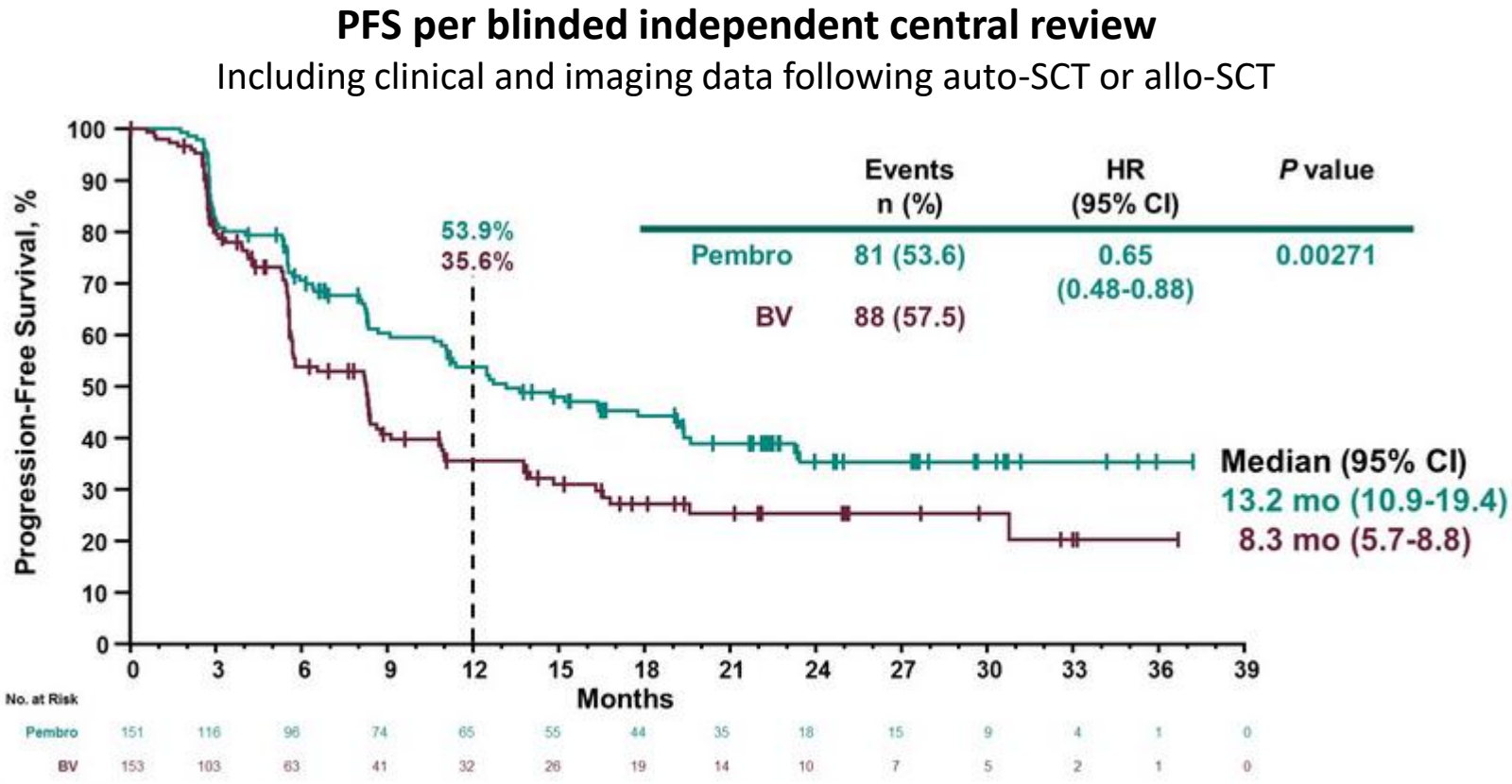
- Patient enrolled onto study of pembrolizumab vs BV (KEYNOTE-204) and was randomized to pembrolizumab arm
- After 4 cycles of therapy, PET/CT revealed a complete metabolic response

KEYNOTE-204: Pembrolizumab vs brentuximab vedotin



Kuruvilla, ASCO 2020

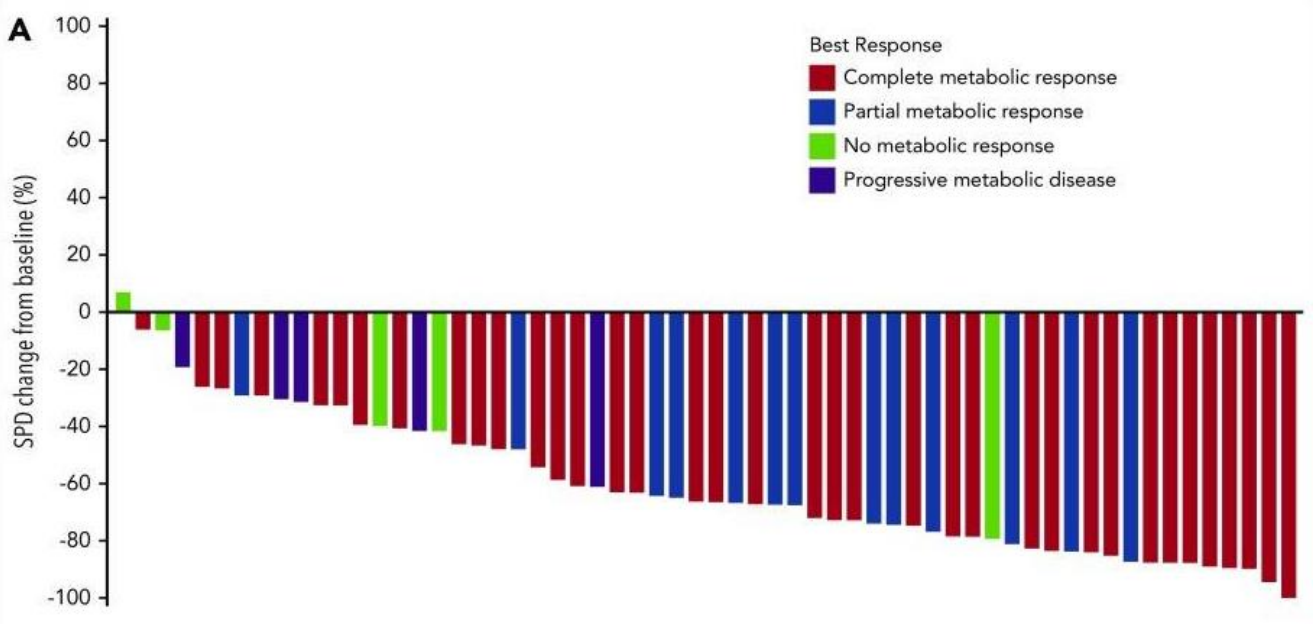
KEYNOTE-204: Pembrolizumab vs brentuximab vedotin



	Pembrolizumab	Brentuximab vedotin
ORR	65.6%	54.2%
mDOR	20.7 mo	13.8 mo

Kuruvilla, ASCO 2020

Nivolumab + brentuximab vedotin



Adverse event	Grade 1-2	Grade 3-4
Nausea	49%	0%
Fatigue	40%	2%
IRRs	41%	3%
Pruritus	29%	2%
Diarrhea	25%	2%
Peripheral sensory neuropathy	15%	0%

Herrera, Blood 2018

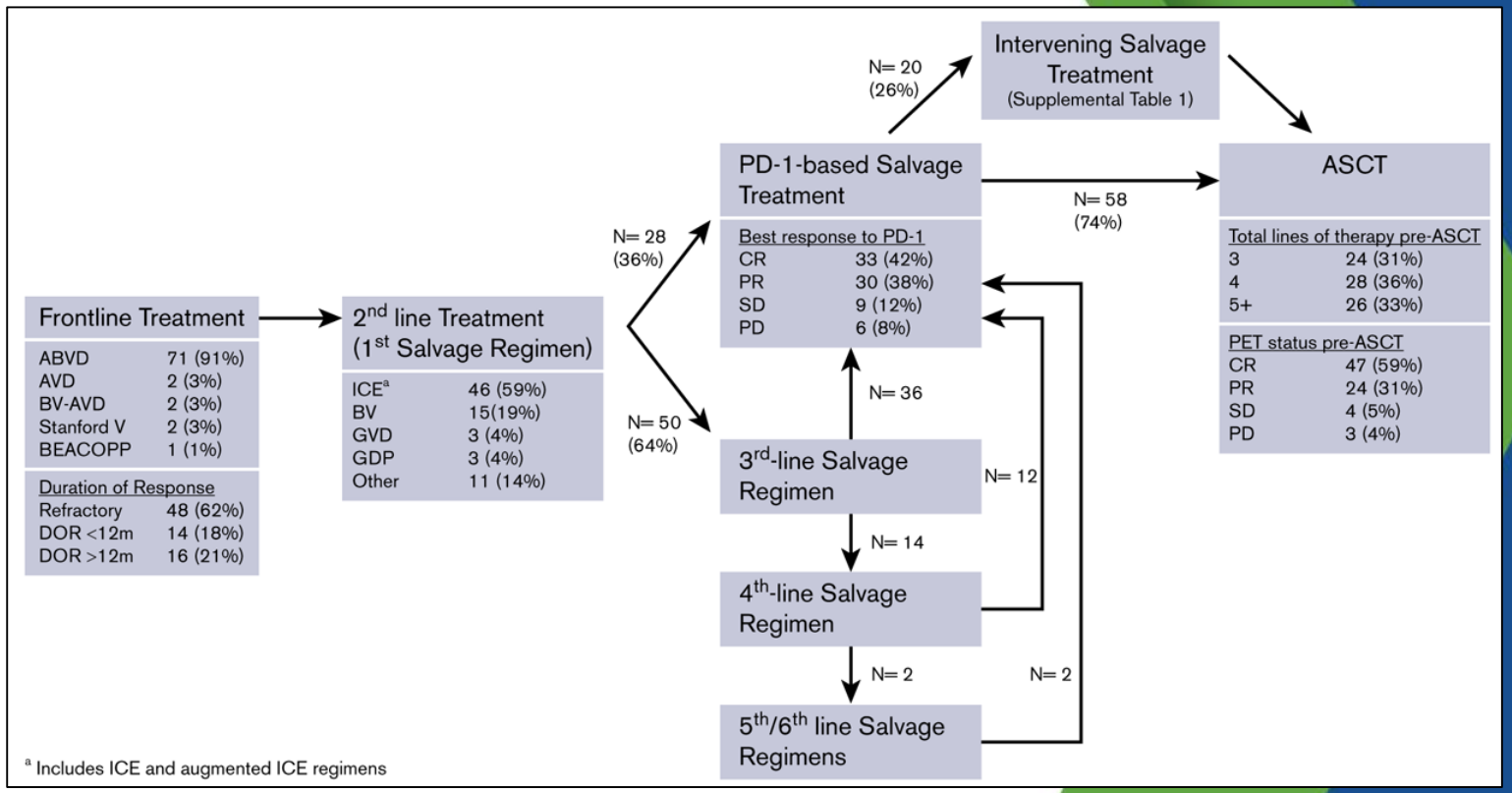
Case #1 – Question 2

What treatment approach(es) can be considered at this point in treatment?

A. Autologous stem cell transplant
B. Continued treatment with pembrolizumab
C. Observation
D. Allogeneic stem cell transplant

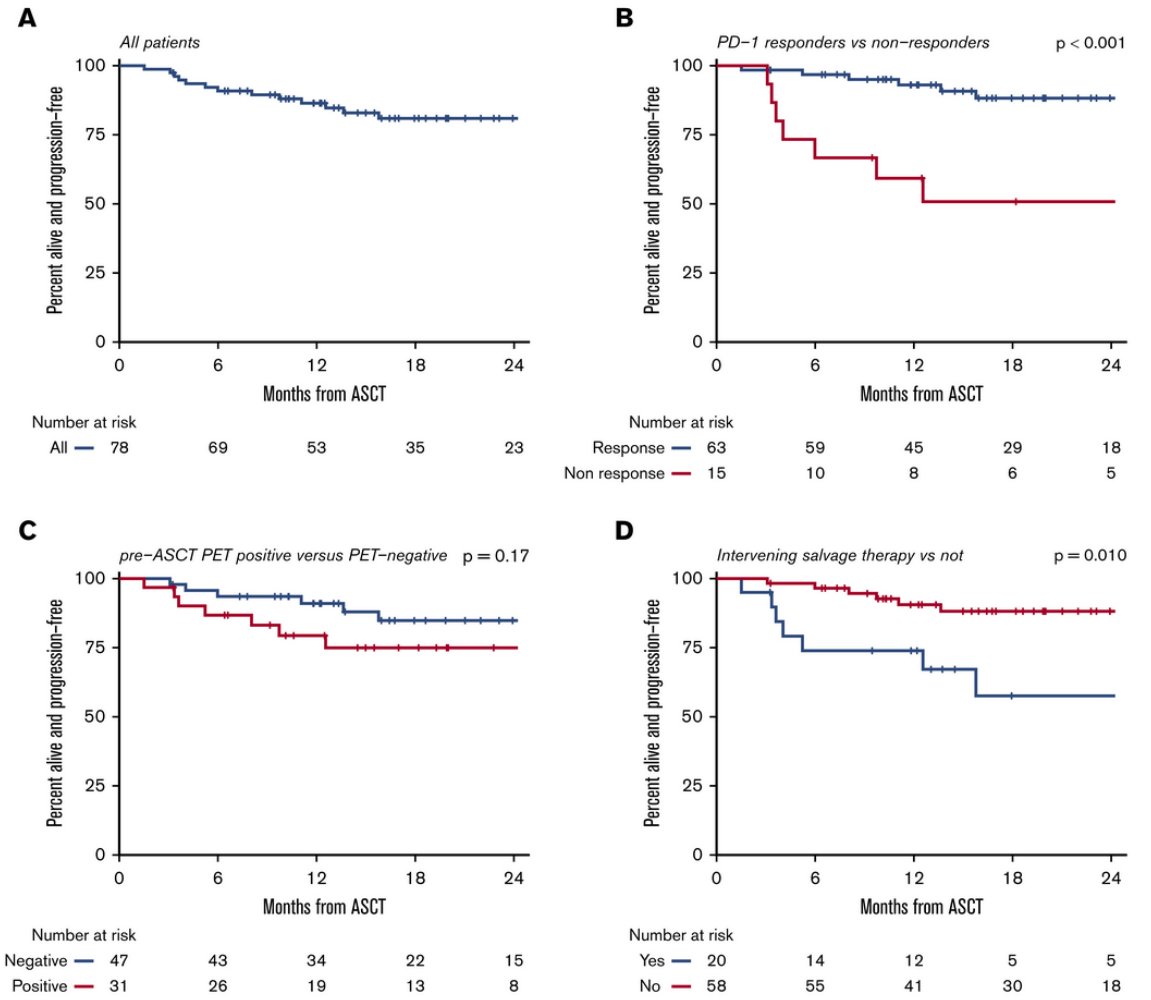
ASCT after checkpoint inhibitors

- ASCT in cHL traditionally requires demonstration of chemosensitivity with salvage therapy
- Study question: What is the role of immune checkpoint inhibitors prior to ASCT?

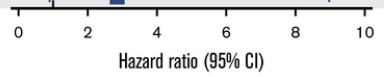


Merryman, Blood Adv 2021

ASCT after checkpoint inhibition



Term	N (%)	18−month PFS (95% CI)	HR (95% CI)	p−value
Age at time of ASCT				
10−year increment	78 (100)	–	1.69 (1.18, 2.41)	0.004
Refractory to pre anti−PD−1 treatment				
No	23 (29)	87 (72 – 100)	Reference	
Yes	55 (71)	78 (67 – 91)	1.73 (0.49, 6.15)	0.40
Refractory to two lines prior to anti−PD−1 treatment				
No	36 (46)	84 (72 – 98)	Reference	
Yes	42 (54)	78 (66 – 93)	1.33 (0.47, 3.73)	0.59
Refractory to three lines prior to anti−PD−1 treatment				
No	60 (77)	85 (75 – 96)	Reference	
Yes	18 (23)	67 (48 – 92)	2.22 (0.79, 6.25)	0.13
Refractory to all prior lines of therapy before anti−PD−1 treatment				
No	49 (63)	83 (72 – 95)	Reference	
Yes	29 (37)	78 (64 – 95)	1.20 (0.43, 3.39)	0.72
Refractory to two or more lines of salvage therapy				
No	48 (62)	85 (74 – 97)	Reference	
Yes	30 (38)	75 (60 – 93)	1.72 (0.62, 4.77)	0.30
Line received anti−PD−1 therapy				
Line 1−3	28 (36)	95 (87 – 100)	Reference	
Line 4+	50 (64)	73 (61 – 88)	3.69 (0.83, 16.42)	0.087
PD−1 regimen				
Combination	18 (23)	84 (65 – 100)	Reference	
Monotherapy	59 (77)	81 (72 – 93)	1.20 (0.26, 5.50)	0.82
PD−1 responders				
Response	63 (81)	88 (80 – 98)	Reference	
Non response	15 (19)	51 (30 – 86)	6.31 (2.28, 17.48)	< 0.001
Patients who received intervening salvage therapy				
No	58 (74)	88 (80 – 98)	Reference	
Yes	20 (26)	58 (37 – 90)	3.58 (1.28, 10.06)	0.015
Pre−ASCT PET response				
Negative	47 (60)	85 (74 – 97)	Reference	
Positive	31 (40)	75 (60 – 93)	2.00 (0.72, 5.52)	0.18
ASCT conditioning regimen				
Other	25 (32)	87 (73 – 100)	Reference	
BEAM	53 (68)	78 (67 – 92)	1.46 (0.46, 4.60)	0.52
No. of PD−1 half−lives				
0−5	67 (87)	84 (75 – 94)	Reference	
>5	10 (13)	60 (36 – 100)	2.85 (0.90, 8.97)	0.074



Merryman, Blood Adv 2021

Case #1 – stem cell transplant

- Decision was made to proceed to ASCT in CR2 after pembrolizumab
- Patient received BEAM conditioning and was infused with her autologous stem cells
- Day 30 PET/CT was consistent with ongoing CR
- Patient received 16 cycles of maintenance BV
- Ongoing clinical remission since that time

Case #1 - conclusions

- Standard of care therapy for relapsed or primary refractory cHL remains second-line therapy and ASCT
- Negative PET/CT prior to ASCT is highly predictive of a favorable outcome following ASCT
- Approach to salvage therapy prior to ASCT has classically been to use chemotherapy (ICE, GND)
- Newer options include BV/bendamustine, BV/nivolumab
- Patients with relapsed/refractory cHL who enter remission with PD-1 blockade therapy appear to do well after ASCT

Case #2 – presentation and diagnosis

- 62 year old woman with history of hypertension, diabetes, and obesity
- Patient noticed right axillary swelling in 12/2017
- Core needle biopsy revealed follicular lymphoma (diffuse type) grade 2
- PET/CT demonstrated lesions above and below the diaphragm, indicating stage 3A disease

Case #2 – transformed FL

- Biopsy in 12/2018 revealed DLBCL (50%) arising from FL
  - Grade 3B
  - With sclerosis, and areas with necrosis
  - Positive for: CD20, CD79a, CD10, BCL2, BCL6, M1B1/Ki67 = 70-80%
  - Negative for: CD30, CD3, CD5, CD43, MYC, BCL1, MUM1, Kappa, Lambda, CD23

Case #2 – Initial treatments

- Patient treated with 6 cycles of R-CHOP, which she tolerated well
- PET/CT in 3/2019 indicated resolution of axillary, abdominal, RP and pleural base nodules (Deauville 2)
- PET/CT in 4/2020 indicated new hypermetabolic nodules in subcutaneous tissue of right chest
- Axillary biopsy showed FL grade 2
- PET/CT in 12/2020 revealed increased nodules (Deauville 5)
- Chest mass biopsy indicated DLBCL, GC type

Case #2 – next treatments

- Patient treated with 3 cycles of RICE
- PET/CT revealed some responding lesions (Deauville 2) and some non-responding lesions (Deauville 4)

Case #2 – Question #1

What treatment would you consider next for this patient?

A. ASCT
B. CD20xCD3 bispecific agent
C. CD30 antibody-drug conjugate
D. Chemotherapy

Case #2 – bispecific treatment

- Patient was treated with gemcitabine + oxaliplatin + epcoritamab, with epcoritamab step-up dosing
- Following first full dose, patient exhibits fever, hypotension and tachycardia, consistent with Grade 2 cytokine release syndrome

Case #2 – Question 2

What management approaches would you use for this patient's Grade 2 CRS?

A. IV fluids + acetaminophen + ibuprofen
B. Steroids
C. Tocilizumab
D. Vasopressors
E. More than one of above

Case #2 – Question 3

What management approaches would you use if a patient developed Grade 3 CRS?

A. IV fluids + acetaminophen + ibuprofen
B. Steroids
C. Tocilizumab
D. Vasopressors
E. More than one of above

Grading and management of CRS

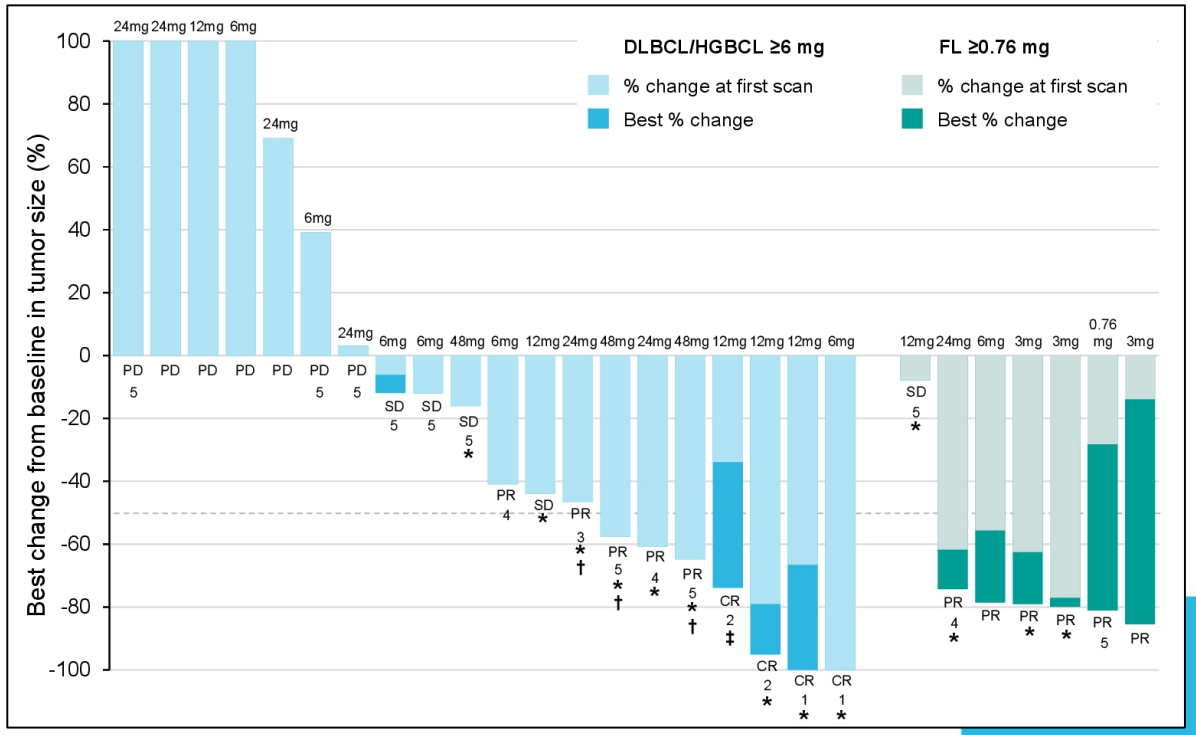
CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	≥ 38°C	≥ 38°C	≥ 38°C	≥ 38°C
with				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
and/or				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, face mask, non-rebreather mask or venturi mask	Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

Management of CRS (one algorithm):

- **Grade 1** *Tocilizumab*: No. *Steroids*: No.
- **Grade 2** *Tocilizumab*: No (yes, if comorbidities). *Steroids*: No (consider, if comorbidities).
- **Grade 3** *Tocilizumab*: Yes. *Steroids*: Consider.
- **Grade 4** *Tocilizumab*: Yes. *Steroids*: Yes

Lee, Santomasso, Biol Blood Marrow Transpl 2018

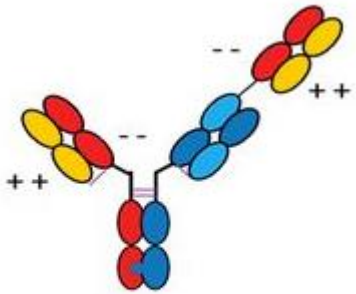
Bispecifics in NHL - Epcoritamab

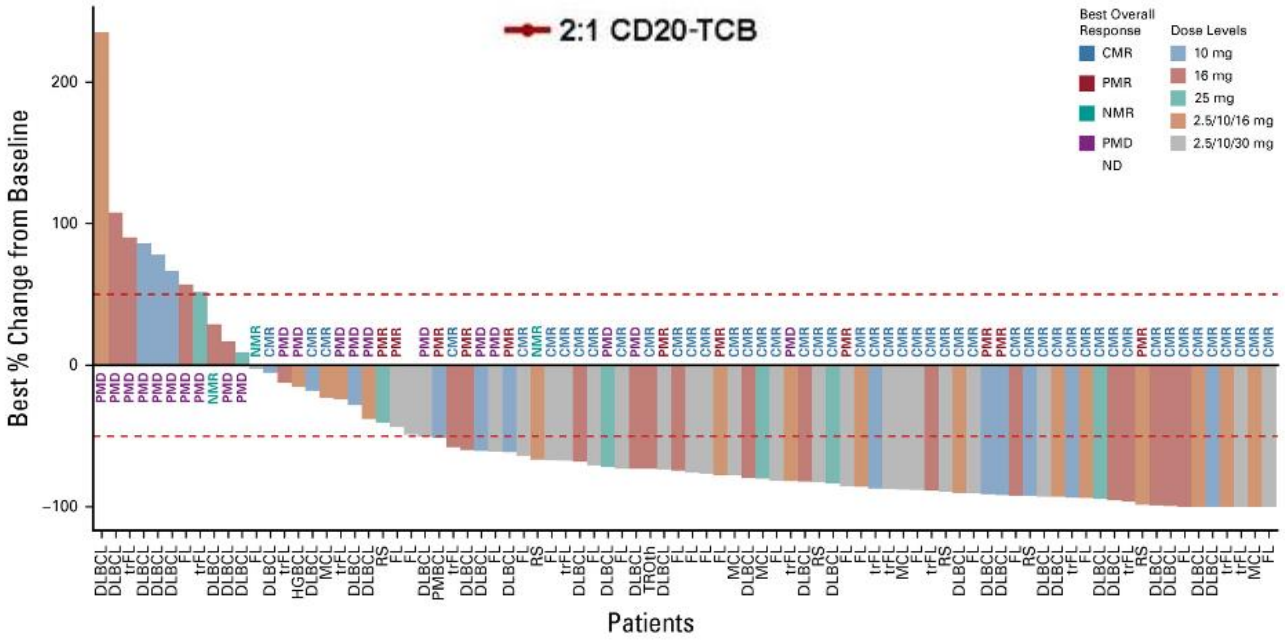


	DLBCL ≥12 mg			FL ≥0.76 mg
	All DLBCL	De novo*	Transformed	
Evaluable patients, n†	14	8	6	7
Overall response rate, n (%)	7 (50.0%)	5 (62.5%)	2 (33.3%)	6 (85.7%)
Complete response	3 (21.4%)	2 (25.0%)	1 (16.7%)	0 (0%)
Partial response	4 (28.6%)	3 (37.5%)	1 (16.7%)‡	6 (85.7%)§
Stable disease, n (%)	2 (14.3%)¶	1 (12.5%)	1 (16.7%)	1 (14.3%)¶
Progressive disease, n (%)	5 (35.7%)	2 (25.0%)	3 (50.0%)	0 (0%)

Hutchings, ASCO 2020

Bispecifics in NHL - Glofitamab



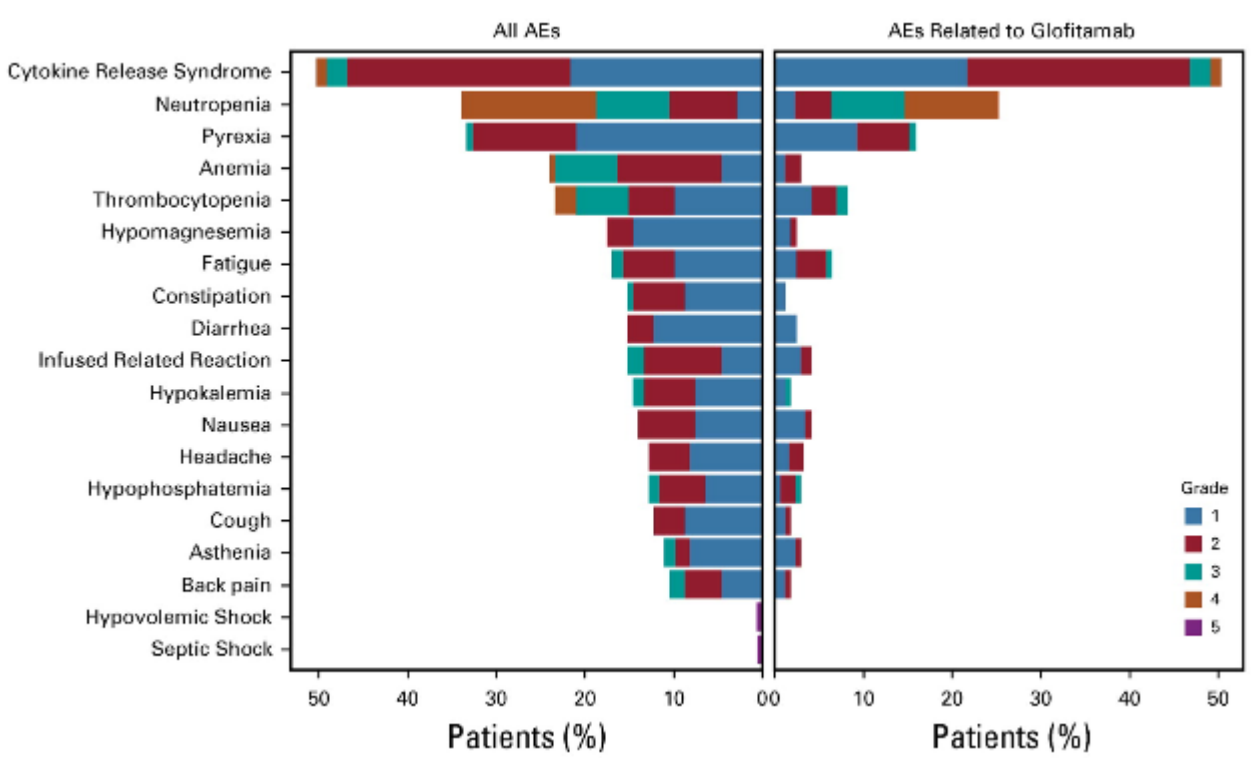


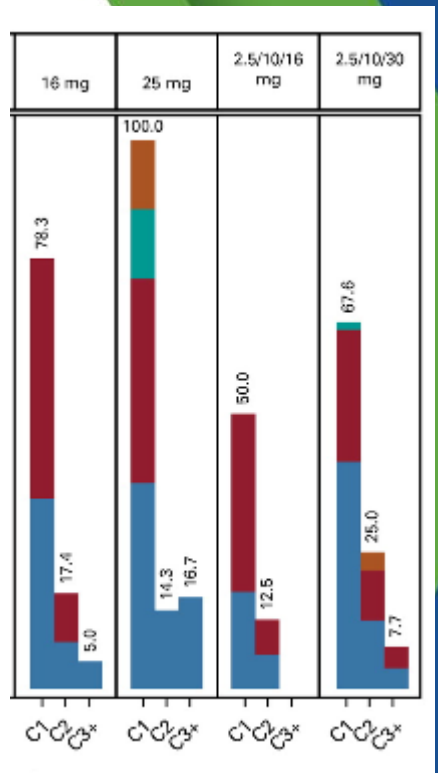
Response	All Histologies	aNHL[a]	DLBCL	trFL	FL (Gr 1-3A)
All cohorts, No.	171	127	73	29	44
Overall response rate[b]					
No. (%)	92 (53.8)	61 (48.0)	30 (41.4)	16 (55.2)	31 (70.5)
95% CI	46.0 to 61.4	39.1 to 57.1	29.7 to 53.2	35.7 to 73.6	54.8 to 83.2
CR					
No. (%)	63 (36.8)	42 (33.1)	21 (28.8)	10 (34.5)	21 (47.7)
95% CI	29.6 to 44.5	25.0 to 42.0	18.8 to 40.6	17.9 to 54.3	32.5 to 63.3
PR					
No. (%)	29 (17.0)	19 (15.0)	9 (12.3)	6 (20.7)	10 (22.7)
95% CI	11.7 to 23.4	9.3 to 22.4	5.8 to 22.1	8.0 to 39.7	11.5 to 37.8
≥ 10 mg cohorts, No.	98	69	38	14	29
Overall response rate[b]					
No. (%)	62 (63.3)	42 (60.9)	21 (55.3)	9 (64.3)	20 (69.0)
95% CI	52.9 to 72.8	48.4 to 72.4	38.3 to 71.4	35.1 to 87.2	49.2 to 84.7
CR					
No. (%)	51 (52.0)	34 (49.3)	16 (42.1)	9 (64.3)	17 (58.6)
95% CI	41.7 to 62.2	37.0 to 61.6	26.3 to 59.2	35.1 to 87.2	38.9 to 76.5
PR					
No. (%)	11 (11.2)	8 (11.6)	5 (13.2)	0	3 (10.3)
95% CI	5.7 to 19.2	5.1 to 21.6	4.4 to 28.1	—	—
RP2D 2.5/10/30 mg, No.	35	14	5	3	21
Objective response rate[b]					
No. (%)	23 (65.7)	10 (71.4)	3 (60.0)	3 (100.0)	13 (61.9)
95% CI	47.8 to 80.9	41.9 to 91.6	—	—	38.4 to 81.9
CR					
No. (%)	20 (57.1)	9 (64.3)	2 (40.0)	3 (100.0)	11 (52.4)
95% CI	39.4 to 73.7	35.1 to 87.2	—	—	29.8 to 74.3
PR					
No. (%)	3 (8.6)	1 (7.1)	1 (20.0)	0	2 (9.5)
95% CI	1.8 to 23.1	0.2 to 33.9	—	—	1.2 to 30.4

Hutchings, J Clin Oncol 2021

Bispecifics in NHL - safety

Epcoritamab	All patients (N=58)
CRS, n (%)	33 (56.9%)
Grade 1	17 (29.3%)
Grade 2	16 (27.6%)
Grade ≥3	0 (0%)
Symptoms of CRS (≥10%)	
Pyrexia	33 (56.9%)
Hypotension	12 (20.7%)
Hypoxia	9 (15.5%)
Tachycardia	8 (13.8%)
Chills	6 (10.3%)
Neurotoxicity, n (%)	4 (6.9%)
Grade 1	2 (3.4%)
Grade 2	0 (0%)
Grade 3	2 (3.4%)





Hutchings, ASCO 2020; Hutchings, J Clin Oncol 2021

Case #2 - conclusions

- Standard of care therapy for 3rd line DLBCL is undefined
- CAR-T, tafastiamab + lenalidomide, loncastuximab tesirine, polatuzumab+rituximab+bendamustine, selinexor, all recently approved for these patients
- Possibly, bispecific mAb will be approved in the near-term, off-the-shelf T cell-based therapy targeting different antigen than current CAR-T options
- Multiple agents (glofitamab, epcoritamab, mosunetuzumab, odronextamab) all with high ORR and CR rates, a majority of CRs appears to be durable, e.g. > 2 years

Case #3 – presentation and diagnosis

- 67 year old woman with hepatitis C
- 9/2017: PET/CT showed extensive lymph node uptake – mediastinal, gastrohepatic, peri-pancreatic, aortocaval, RP, mesenteric
- Biopsy of RP LN showed DLBCL, GCB
- Ureteral stent placed for hydronephrosis due to RP mass compression

Case #3 – first treatments

- 10/2017-2/2018: Patient received DA-REPOCH x 6 cycles
- 11/2018: PET/CT showed relapse with diffuse LN uptake
- Patient recommended for second-line chemotherapy
- Deferred chemotherapy due to history of low platelets and poor tolerance of REPOCH
- 9/2019: progression
- 11/2019: treated with R-DHAP x 2 cycles
- R-DHAP was tolerated poorly, with two hospitalizations for febrile neutropenia

Case #3 – next treatment

- 4/2020: Partial response (Deauville 4)
- 6/2020: Disease progression with ~70% increase in tumor bulk

Case #3 – Question 1

What treatment would be appropriate at this point?

A. Allogeneic Stem Cell Transplantation

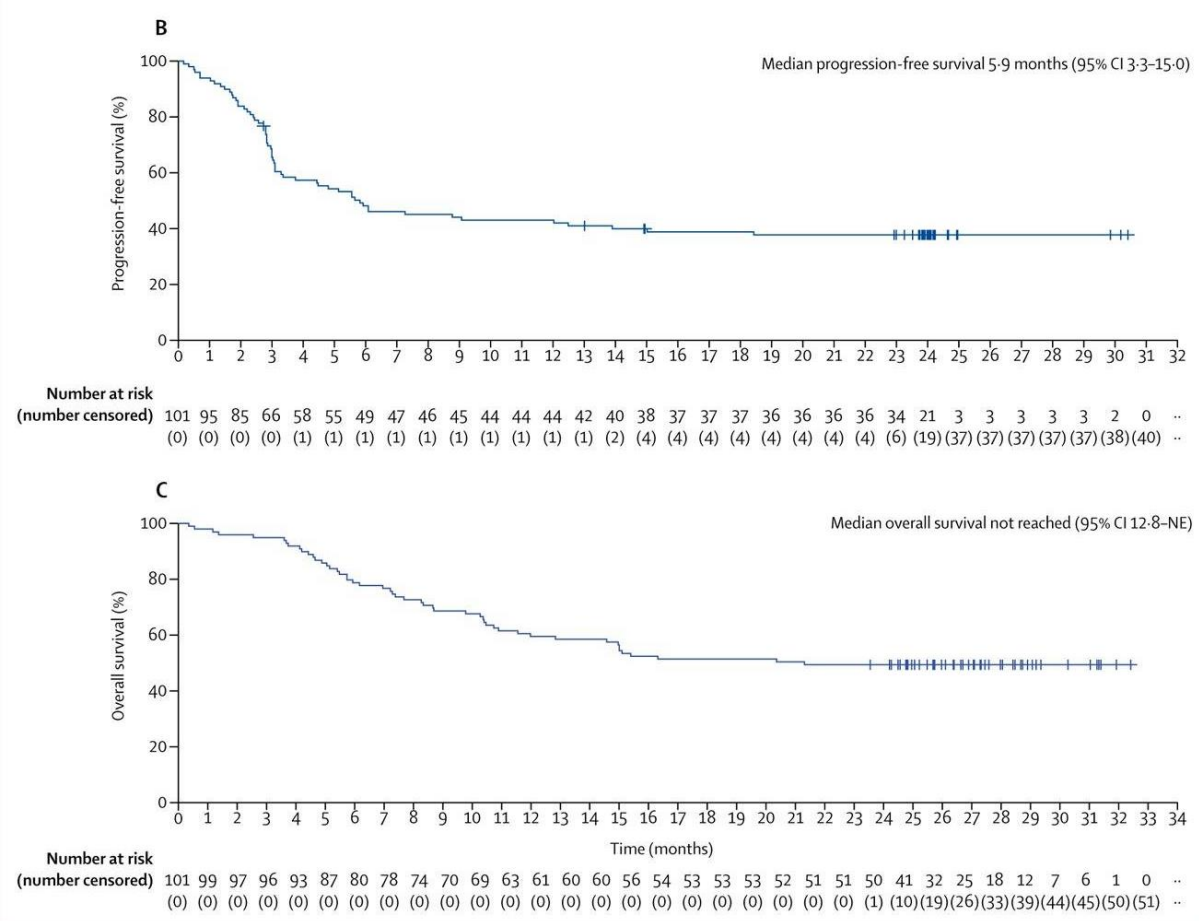
B. CD30 x CD3 Bispecific Agent

C. CD19 CAR-T cells

D. Chemotherapy

Curative potential of CAR T

ZUMA-1: axicabtagene ciloleucel in large B cell lymphoma



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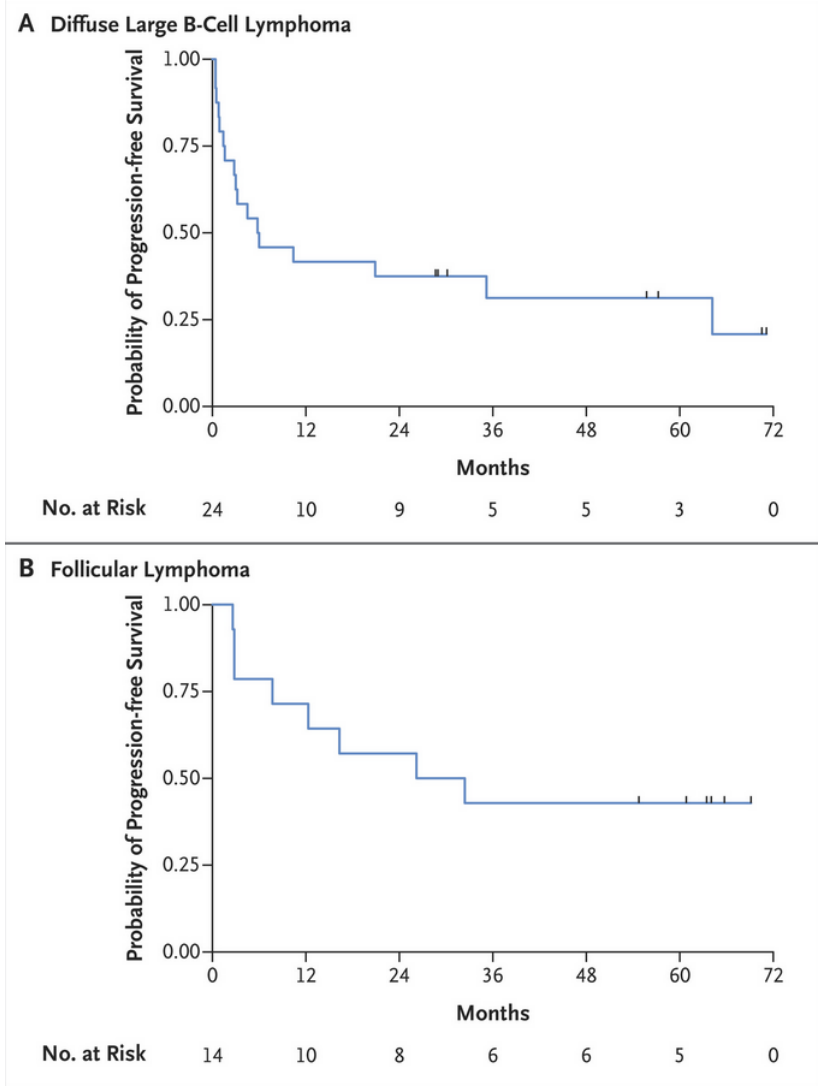

Chong, NEJM 2021
Jacobson, ASH 2020

Potential of CAR T: real-world evidence

	ZUMA-1	Real-world use*
ORR	83%	70%
CRR	58%	50%
mDOR	11.1 months	11.0 months
mPFS	5.9 months	4.5 months
mOS	NR (f/u 27.1 months)	NR (f/u 10.4 months)
CRS G3+	11%	16%
ICANS G3+	32%	35%
Treatment-related deaths	1.9% (2/108)	6%

**62% of patients in this study were ZUMA-1-eligible*

Locke, Lancet Oncol 2019
Jacobson, JCO 2020

Emerging data for CD19 CAR T in LBCL

- TRANSFORM trial (NCT03575351): randomized, multicenter Phase 3 trial evaluating lisocabtagene maraleucel compared to current standard of care regimens in second line
- Press release in June 2021: study met its primary endpoint of demonstrating a clinically meaningful and statistically significant improvement in event-free survival
- Peer-reviewed report pending
- **Implications**: CD19 CAR T may move to second line therapy for R/R DLBCL, replacing autologous stem cell transplant

Press release

Case #3 – CAR T treatment

- Patient received flu-cy lymphodepletion
- Treated with axicabtagene ciloleucel
- Patient developed Grade 3 cytokine release syndrome and Grade 3 neurotoxicity

Case #3 – Question 2

What treatment approach is appropriate for managing the patient's Grade 3 CRS and Grade 3 ICANS?

A. High-dose corticosteroids
B. Tocilizumab
C. Anti-pyretics and vasopressors
D. Both A and B

Common CAR T toxicities: CRS and ICANS

Cytokine release syndrome

- Fever, hypotension, hypoxia
- Manage with tocilizumab and steroids
- Supportive care as needed: vasopressors, oxygen support

Immune effector cell-associated neurotoxicity syndrome

- Confusion, delirium, aphasia, headache, tremors, seizures
- Manage with steroids
- Monitor patients daily for mental status changes

SITC recommends the ASTCT grading systems for CRS and ICANS.

Check out the SITC clinical practice guideline on immune effector cell-related adverse events for more guidance

Maus, J Immunother Cancer 2020

Case #3 - post-CAR T

- 8/2020: 1 month post-CAR T, PET/CT showed complete response (Deauville 2)
- 11/2020: PET/CT shows external iliac LNs, biopsy indicates DLBCL

Case #3 – Question 3

What treatment would you consider for this patient with progression after CAR T?

A. Allogeneic Stem Cell Transplantation
B. Radiation Therapy
C. Anti CD20xCD3 Bispecific T-Cell Engager
D. Chemotherapy

Case #3 - Conclusions

- CD19 CAR T-Cells are safe and effective in patients with DLBCL as third care treatment
- Emerging data suggests CD19 CAR T-cells may become the treatment of choice in patients with DLBCL requiring 2nd line therapy
- Grade III/IV complications such as CRS and ICANS can occur in patients with DLBCL treated with CD19 CAR T-cells

Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Practical Management Pearls for Immune Effector Cell-related Adverse Events

August 12, 2021, 5:30-6:30 p.m. EDT

Immune Checkpoint Inhibitor-related Adverse Events

August 13, 2021, 10-11 a.m. EDT

Learn more and register at:
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