La gestione del paziente che non risponde

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1 Introduction

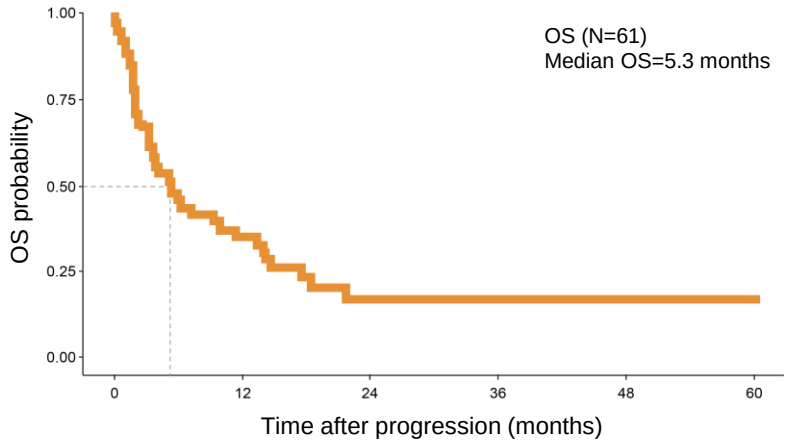
Relapsed/refractory patients after CAR-T cells

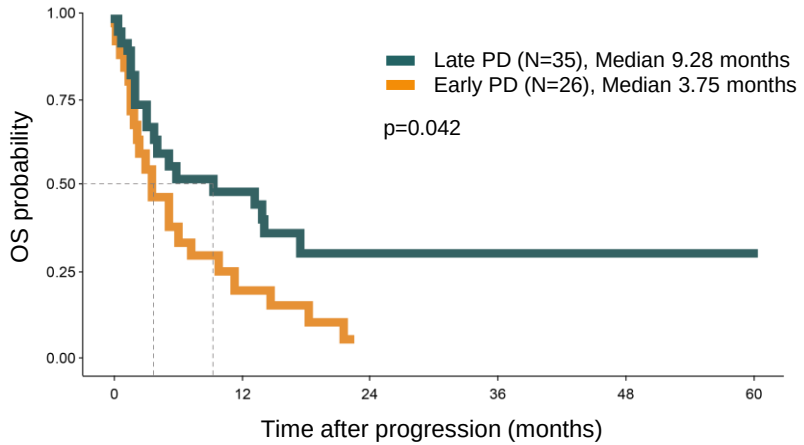
Issues for salvage treatment

- 60% of DLBCL patients failed CAR-T cell treatment
- Some of them have rapidly progressive disease and no time for salvage treatment
- 20–30% of the patients experienced prolonged cytopenia
- Hypogammaglobulinemia and increased infectious risk
- Few options available
- Few studies and some case reports
- Need of early recognition of poor outcome

CD19-specific CAR-T cell therapy: Progressive disease

61 patients with DLBCL, PMBCL, HGBCL



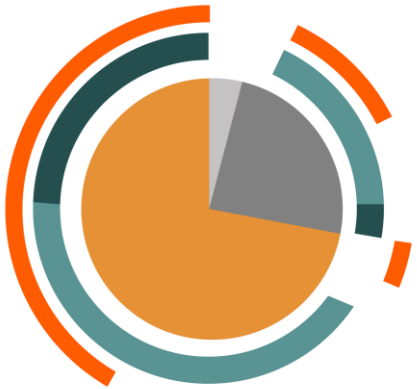


- 46 (75%) received subsequent therapies
- Initial therapies included: Second CAR-T of same construct (14), novel/targeted therapy (14), chemotherapy +/− rituximab (7), radiotherapy (5), PD1-inhibitors (4), intrathecal chemotherapy (1), and allogeneic HSCT (1)
- At time of progression, 16% (N=10) and 26% (N=16) of patients in our population were noted to have grade ≥3 neutropenia and thrombocytopenia
- 9 patients alive and in remission for ≥12 months after progression. Last line of therapy included radiotherapy (2), allogeneic HSCT (2), ibrutinib (2), subsequent CD19- specific CAR-T (1), nivolumab (1), and lenalidomide (1)

DLBCL: diffuse large B-cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma; HGBCL: high-grade B-cell lymphoma; OS: overall survival: HSCT: hematopoietic stem cell transplantation PD: progression disease

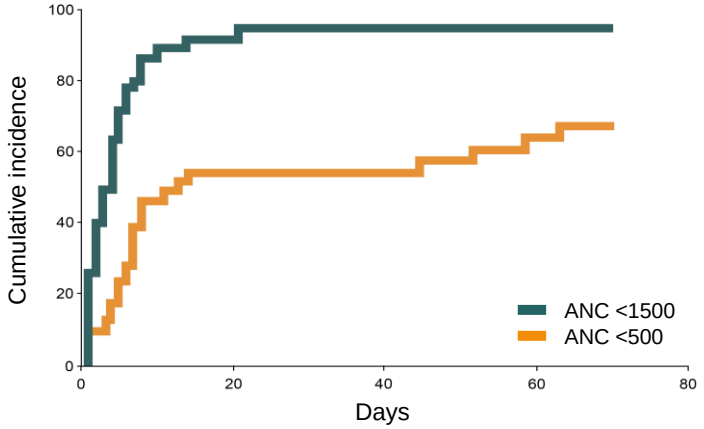
Mod. da Chow WA, et al. Am J Hematol 2019; 94: E209–E213

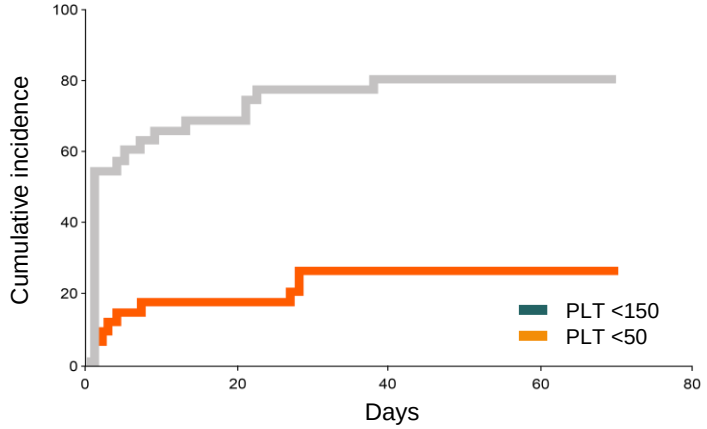
Early and late hematologic toxicity following CD19 CAR-T cells

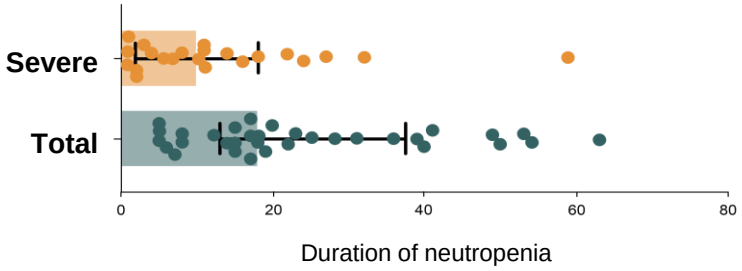


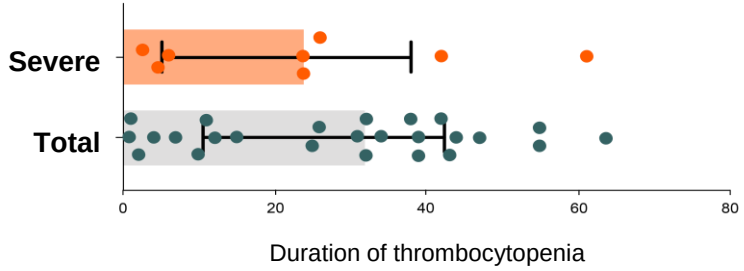
Neutropenia
- None (n=1)
- Mild (n=7)
- Severe (n=21)

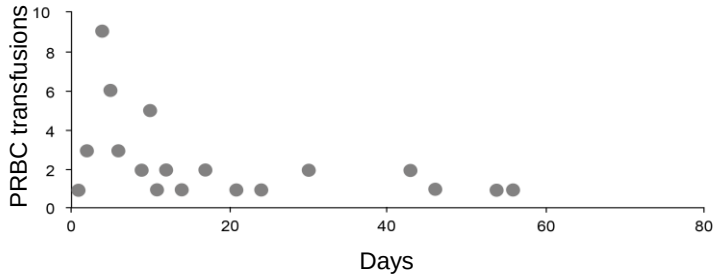
Thrombocytopenia
- Mild (n=17)
- Severe (n=8)
- Anemia (n=16)











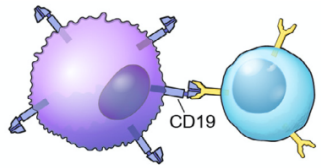
ANC: absolute neutrophil count; PLT: platelet; PRBC: packed red blood cell

Mod. da Fried S, et al. Bone Marrow Transplantation 2019; 54: 1643–1650

Mechanisms of CAR-T cell failure

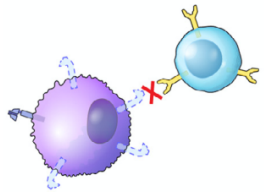
Proposed/known mechanisms of CAR T-cell treatment failure and potential treatment strategies

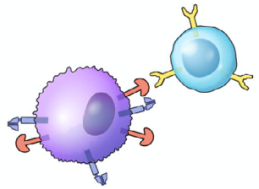
Standard chimeric antigen receptor treatment

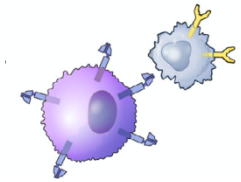


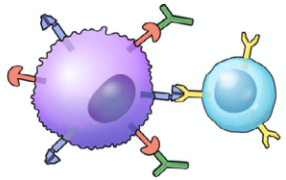
B-cell lymphoma CAR-T cell

Potential mechanisms of CAR-T failure	Potential treatment strategies
CD19 epitope loss Loss of CD19 epitope by uncertain mechanisms in lymphoma	**Alternative CAR-T cells** CAR-T cells against alternative targets; allogeneic transplantation for patients able to achieve post relapse remission
Host or tumor factors Upregulation of negative regulatory receptors on CAR-T cells or ligands on tumor or microenvironment; high tumor burden and inadequate target to effector ratio.	**Checkpoint inhibitors** Checkpoint blockade, immuno modulation with ImiDs, ITKi, o other agents; additional CD19 CAR-T cell therapy
T cell specific factors Inadequate central memory and/or stem central memory CAR-T cells; pre-manufacture T cell dysfunction due to disease or prior therapy; inadequate cytokine profile; paucity of CD4 CAR-T cells; insufficient CAR-T cell expansion or persistence.	**Immunomodulation** Immunomodulation with IMIDs ITKi, or other off the shelf CAR-T cell strategies.









Mod. da Byrne M, et al. Biol Blood Marrow Transplant 2019; 25: 344–351

2

Relapsed/refractory patients after CAR-T cells: Possible treatments

2.1
Bispecific antibodies

Bispecific antibodies

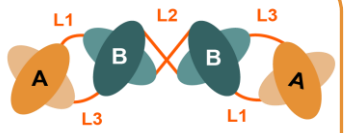
CD19 x CD3

Blinatumomab

Bispecific
Bivalent

Size 54 kDA
Half-life 2 h

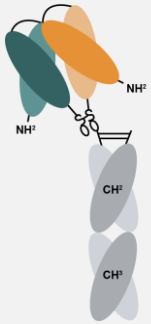
AFM11



Bispecific
Tetravalent

Size 105 kDA
Half-life 20 h
CD3 affinity ↑

MGD011



Bispecific
Bivalent

Size 110 kDA
Half-life
340-460h

AMG562

Bispecific
Bivalent

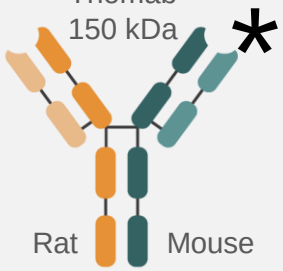
Half-life
extended

CD20 x CD3

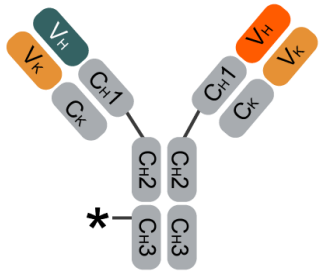
FBTA05

(Lymphomun)

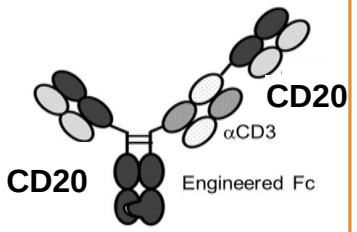
Triomab
150 kDa



RGN1979

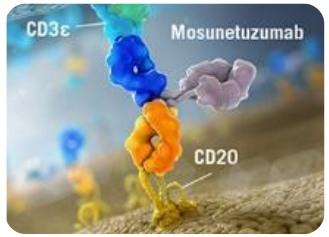


RG6026 «TCB»

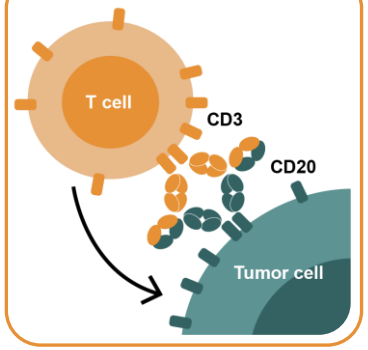


RG7828 «TDB»

(Mosunetuzumab)



GEN3013



GO29781: Mosunetuzumab in R/R NHL

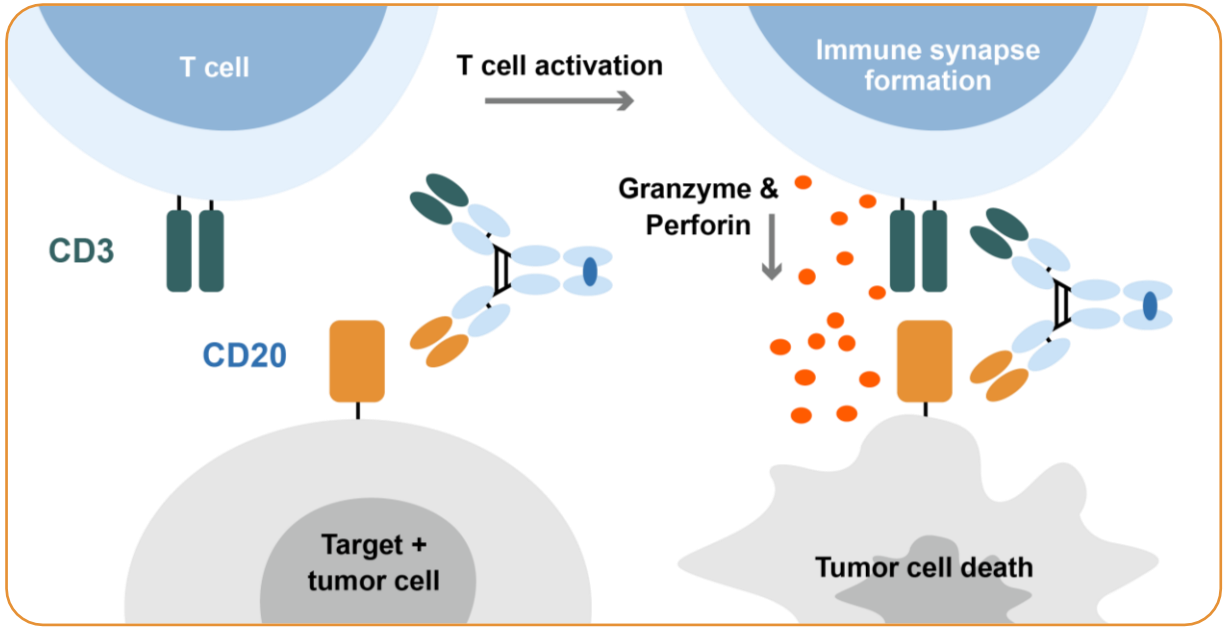
Mosunetuzumab (RG7828; BTCT4465A)

- Full-length, fully humanized IgG1 bispecific antibody[1]
- Redirects T cells to engage and eliminate B cells; T-cell activation, cytokine elevation and increase in TILs observed *(Hernandez et al. ASH 2019 P-1585)*
- No ex-vivo T cell manipulation required ('off-the-shelf' and no delay in treatment)

GO29781

- Phase I/Ib dose-escalation and expansion study in heavily pre-treated R/R B-cell NHL
- Cycle 1 step-up dosing: Mitigates CRS, allowing dose escalation to maximize therapeutic potential[2,3]

Are reported data for 270 R/R B-cell NHL patients, including 30 patients with prior CAR-T



Registry number: NCT02500407

CRS: cytokine release syndrome; NHL: non-Hodgkin lymphoma; R/R: relapsed/refractory; TILs: tumor-infiltrating lymphocytes

Mod. da Schuster SJ, et al. Blood 2019; 134 (Suppl_1): 6

1. Sun LL, et al. Sci Transl Med 2015; 7: 287ra70; 2. Budde LE, et al. Blood 2018; 132 (Suppl_1): 399; 3 Bartlett NL, et al. J Clin Oncol 2019; 37 (Suppl_15): 7518

GO29781: Patient population

n (%)	N=270*	
Median age, years (range)	62	(19–96)
Male	172	(63.7%)
ECOG PS 1 at baseline	164	(61.2%)†
Aggressive NHL	180	(66.7%)
DLBCL	117	(43.3%)
trFL	32	(11.9%)
MCL	23	(8.5%)
Other	8	(3.0%)
Indolent NHL	85	(31.5%)
FL	82	(30.4%)
Other	3	(1.1%)
Median prior systemic therapies, n (range)	3	(1–14)†
Prior CAR-T therapy	30	(11.1%)
Prior autologous SCT	77	(28.5%)
Refractory‡ to last prior therapy	194	(71.9%)
Refractory‡ to prior anti-CD20 therapy	233	(86.3%)

CCOD (clinical cut-off date): Aug 9, 2019
**safety evaluable patients; †n=268, as two patients did not have data entered by CCOD; ‡no response (PR or CR) or PD within ≤6 months of treatment*
trFL: transformed follicular lymphoma; MCL: mantle cell lymphoma; SCT: stem cell transplantation

30 patients with prior CAR-T therapy

- 17 DLBCL, 8 trFL, 5 FL
- Median 5 lines of prior systemic therapies (range 3–14)
- 29 patients (96.7%) refractory to prior anti-CD20 therapy
- 25 patients (83.3%) refractory to last prior therapy
- 22 patients (73.3%) refractory to prior CAR-T therapy

Mod. da Schuster SJ, et al. Blood 2019; 134 (Suppl_1): 6

GO29781: Safety

	Safety evaluable N=270	Prior CAR-T N=30
CRS (Lee et al. 2014)	29%	27%
Grade 1/2	28%	23%
Grade 3	1%	3%
NT	44%	43%
Grade 1/2	40%	33%
Grade 3	4%	10%
Potential ICANS	1%	0%

- 95% of AEs occurred in cycle 1; no cumulative or chronic toxicity
- Neutropenia was responsive to GCSF; rate of febrile neutropenia was low (3%)
- CRS onset was a median of 4 days (range 1–43) after dosing and lasted a median of 2 days (range 1–59)
- 97% of CRS events resolved by the cutoff date; tocilizumab was used in 3% of cases
- No CRS during retreatment
- The most common NAEs were headache (16%), insomnia (9%), and dizziness (9%)
- ICANS-like AEs included 2 confusion (1 related) and 1 lethargy (related); all resolved within 3 days

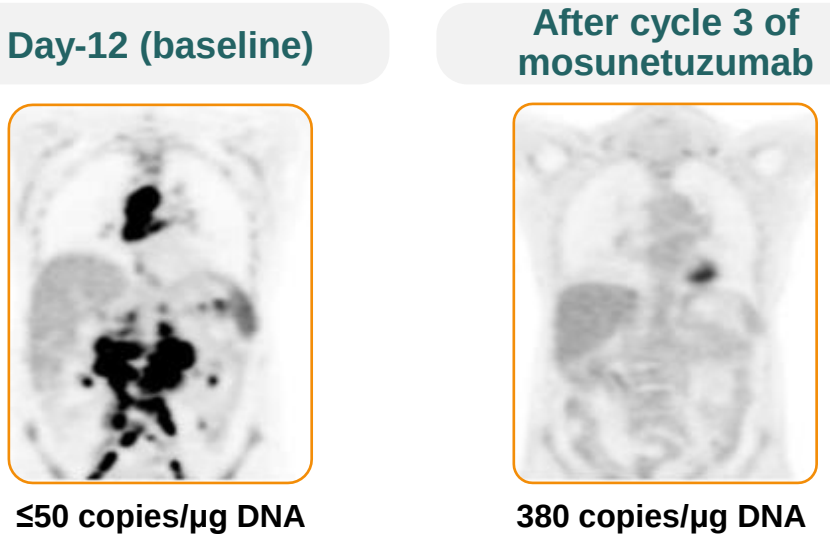
NT: neurotoxicity; NAEs: neurological adverse events; ICANS: immune effector cell-associated neurotoxicity syndrome; GCSF: granulocyte colony-stimulating factor

Mod. da Schuster SJ, et al. Blood 2019; 134 (Suppl_1): 6

GO29781: Patients with prior CAR-T therapy

Efficacy

	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%)



- *8 months in CR off treatment*

Case

- 58-year old patient with R/R FL
- 8 prior lines of systemic treatment
  - Refractory to prior anti-CD20 and alkylating agents
  - Relapsed after CD19-CAR-T therapy
  - Progressed on checkpoint inhibitor and no response to PI3K inhibitor

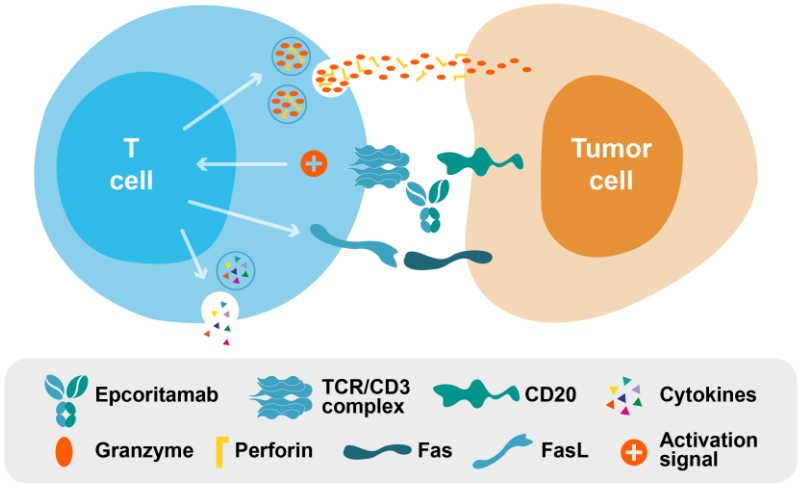
Exploratory biomarkers

- Expansion of lymphocytes (including residual CAR-T cells in 2/8 tested patients)
- CR to mosunetuzumab observed **with** or **without** CAR-T expansion

**efficacy-evaluable patients: patients who were enrolled for at least 3 months, or had response data available at any time, or discontinued treatment for any cause*
CCOD: Aug 9, 2019

Mod. da Schuster SJ, et al. Blood 2019; 134 (Suppl_1): 6

Escalating dose of subcutaneous epcoritamab in R/R B-cell NHL: High rate of complete response and favorable safety profile



Epcoritamab (DuoBody®-CD3xCD20) is a subcutaneously administered bispecific antibody that induces T cell-mediated killing of CD20-expressing tumors

- Induces T cell activation by binding to CD3 on T cells and CD20 on malignant B cells
- Promotes immunological synapse between bound cells, resulting in apoptosis of B cells
- Binds to a distinct epitope on CD20, different from the epitopes of rituximab and obinutuzumab

Response by histology

Response	DLBCL (n=46)		FL (n=12)		MCL
	12–60 mg (n=23)	48–60 mg (n=12)	0.76–48 (n=11)	12–48 (n=5)	0.76–48 mg (n=4)
Evaluable patients, n	**22**	**11**	**10**	**5**	**4**
ORR, n (%)	15 (68)	10 (91)	9 (90)	4 (80)	2 (50)
CR	10 (46)	6 (55)	5 (50)	3 (60)	1 (25)
PR	5 (23)	4 (36)	4 (40)	1 (20)	1 (25)
Stable disease, n (%)	1 (5)	0	0	0	1 (25)
Progressive disease, n (%)	5 (23)	0	1 (10)	1 (20)	0

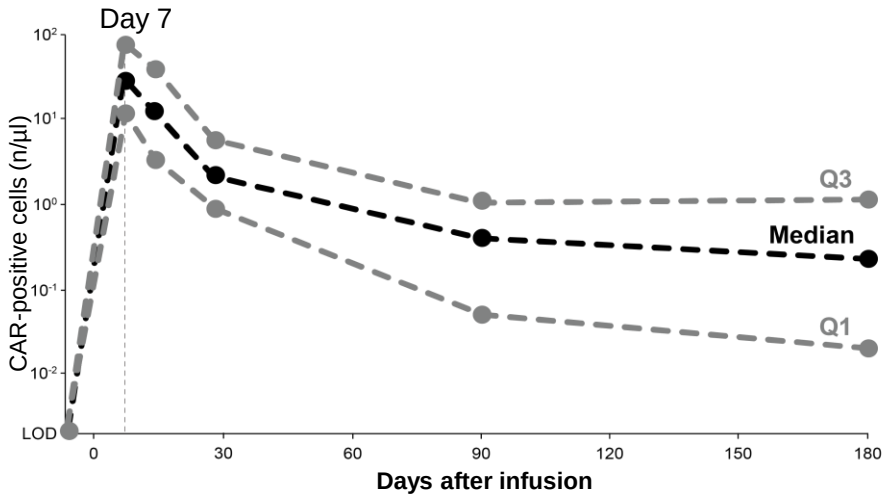
ORR: overall response rate; CR: complete response; PR: partial response

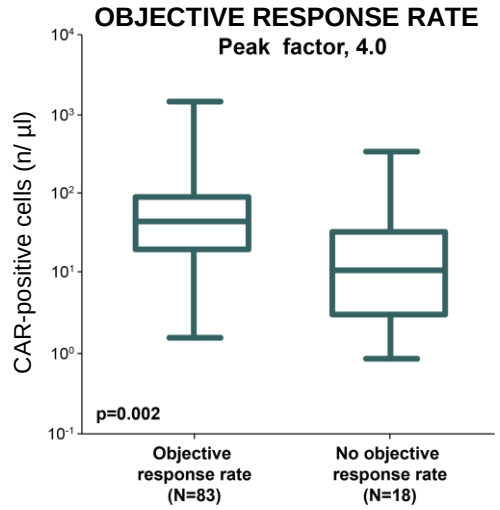
Mod. da Hutchings M, et al. Blood 2020; 136 (Suppl_1): 45–46

2.2
Checkpoint inhibitors

Possible mechanisms of resistance to CAR-T

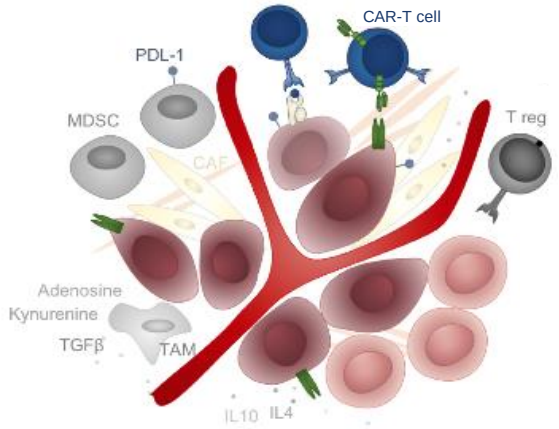
CAR-T expansion correlates with response





Tumor immunosuppressive microenvironment

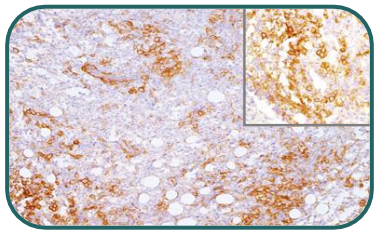
- Treg lymphocytes interaction
- Cytochine inhibition
- Pro-apoptotic signals against CAR-T



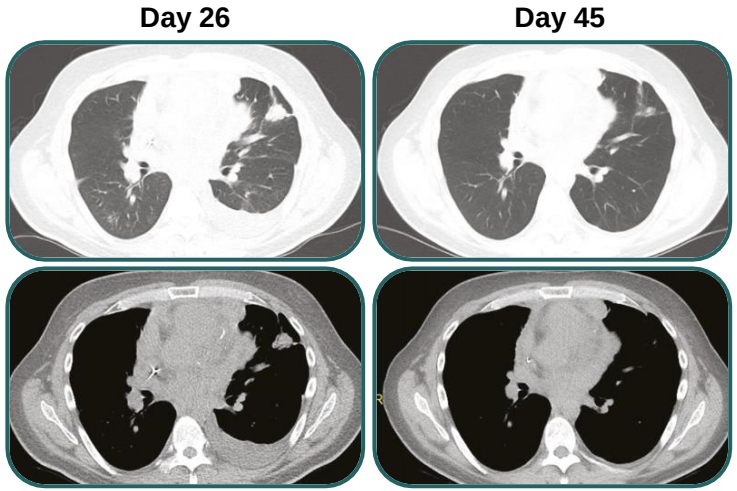
Mod. da Neelapu SS, et al. N Engl J Med 2017; 377: 2531–2544

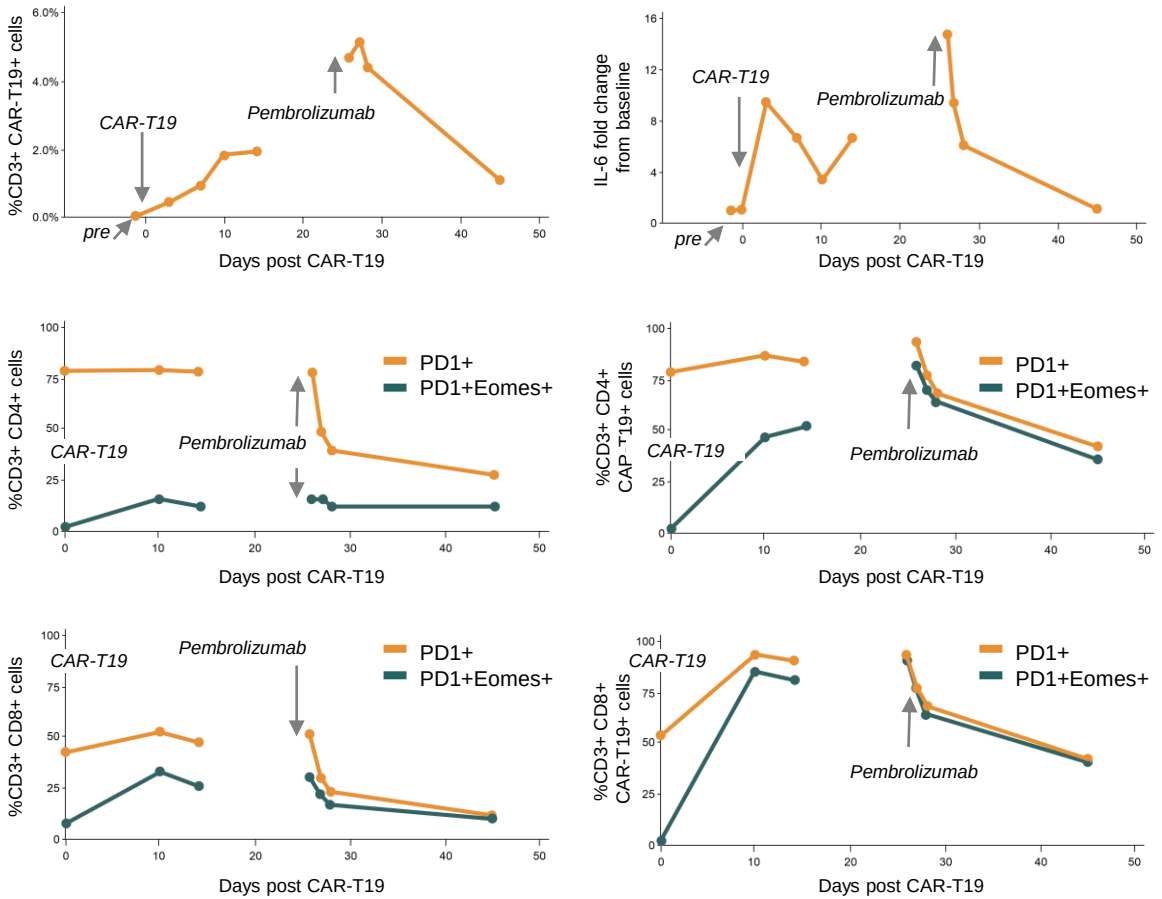
Relapse after CAR-T infusion: Pembrolizumab

35-year old man with multiple refractory PMBCL with multiple extranodal involvement treated with CAR-T19 cells, progressed at day +26. He received pembrolizumab, 2 mg/kg, on day 26 after CAR-T19 cell infusion and then every 3 weeks. PET at day 186 PMR



	Day 14	Day 26	Day 45
Clone 1	6.10%	6.10%	13.11%
Clone 2	2.35%	2.90%	6.45%
Clone 3	0.00%	0.27%	3.57%
Clone 4	0.40%	0.40%	2.15%
Clone 5	0.12%	0.27%	1.49%
Clone 6	0.00%	0.04%	1.46%
Clone 7	0.57%	0.91%	1.31%
Clone 8	0.07%	0.32%	1.23%
Clone 9	1.08%	0.81%	0.99%





Mod. da Chong EA, et al. Blood 2017; 23: 1039–1041

Relapse after CAR-T infusion: Nivolumab

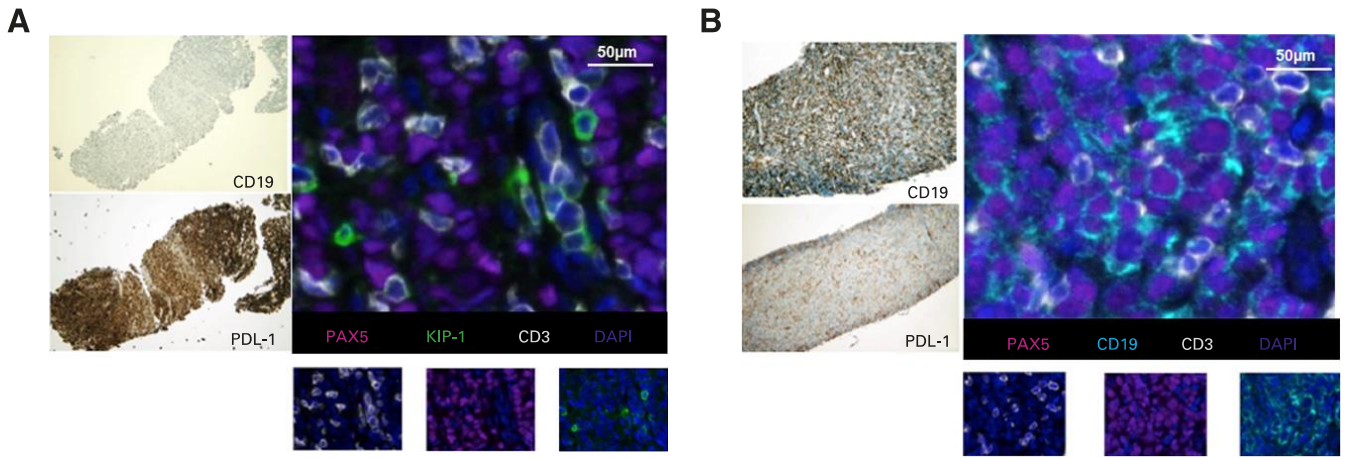
- **46 years old with DLBCL PDL1+ refractory to 3 lines of therapy**
- **Treated in Zuma-1 trial with rapid progression after CAR-T cell infusion**
- **On day 11 he received nivolumab 3 mg/kg with grade 3 CRS**
- **Rapid tumor regression after 1 cycle of nivolumab associated with rapid re-expansion of CAR-T cells**

Mod. da Hill BT, et al. Blood 2017; 130 (Suppl_1): 2825

CAR-T cell therapy + pembrolizumab

- **Single phase 2 trial for R/R B-cell NHL after treatment with CAR-T19**
- **12 patients (11 DLBCL, 1 FL).**
- **Median PFS after CAR-T: 2.2 months**
- **Pembrolizumab fixed dose 200 mg every 3 weeks**
- **CRS 1 patient**
- **Few side effects: Neutropenia, fatigue, pleural effusion**
- **ORR 27% (1 CR, 2 PR, 1 SD, 7 PD)**
- **9/12 showed a re-expansion peak in peripheral blood CAR-T19 cells**
- **Maximum CAR transgene copy number did not correlate with response, but responding had more than one re-espansion peak**

Different pattern of resistance after CAR-T cell treatment. CD19 loss and PDL-1 upregulation

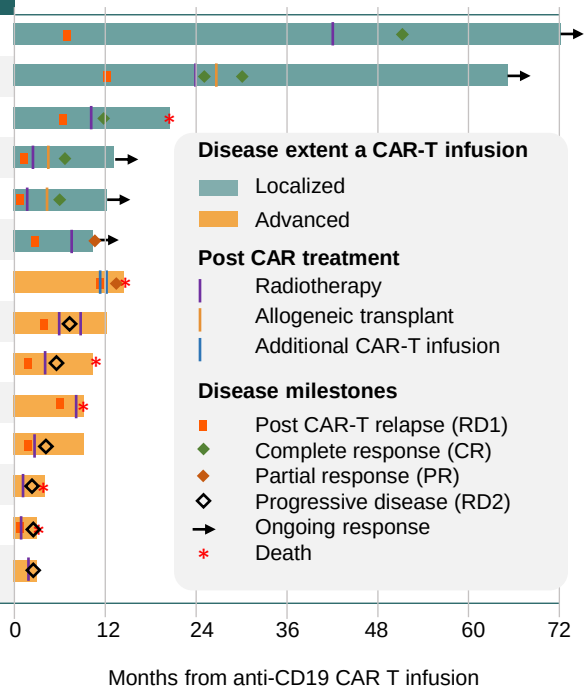


Mod. Da Chong EA, et al, Blood 2018; 132: 4198; Jacobson CA, et al. J Clin Oncol 2020: 38: 3095–3106

2.3
Radiotherapy

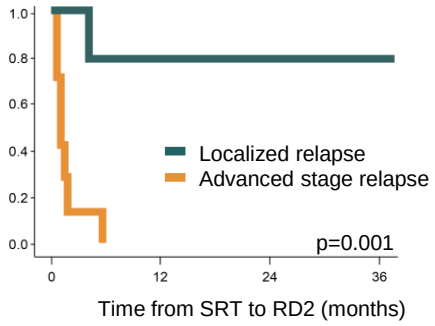
Early experience using salvage radiotherapy for relapsed/refractory non-Hodgkin lymphomas after CD19 chimeric antigen receptor (CAR)-T cell therapy: 14 patients at MSKCC

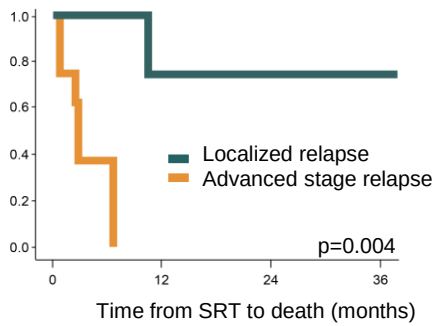
	CAR-T product	Best post CAR-T response	Indication for SRT	Irradiated site	SRT Dose (Gy)	SRT fract.
14	CAR 19-28z	CR	Focal relapse. follicular histology	Upper mediastinum	46	23
13	CAR 19-28z	CR	Bridge to alloSCT	Chest wall	36	18
12	JCAR017	PR	Focal relapse, chemorefractory	Mesentery	30	20
11	JCAR017	PR	Bridge to alloSCT	Mediastinum, manubrium	45	26
10	Tisa-cel	PD	Bridge to alloSCT	Mesentery	45	30
9	Tisa-cel	CR	Focal relapse, palliation	Thoracic paraspinal	20	5
8	JCAR017	PR	Augment CAR response	Mesentery/perinephrin	20	5
7	Tisa-cel	CR	Palliation of neuro symptoms	WBRT	30	10
6	JCAR017	PR	Palliation airway compromise	Larynx	30	10
5	Armored	CR	Palliation	Gluteal soft tissue	20	5
4	JCAR017	PR	Dominant site of progression	Mesentery	36	20
3	Axi-cel	PD	Palliation of cord compression	Thoracolumbar spine	20	5
2	JCAR017	PD	Palliation airway compromise	Bilateral neck	20	10
1	JCAR017	PR	Palliation	Thigh cutaneous/soft tissue	30	15

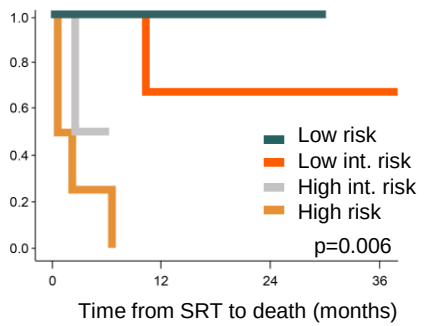


Discussion points

- Post CAR-T failure: 79% relapsed/progressed in previous PET-avid sites. Need for RT consolidation to high risk lesions sites after/before CAR-T?
- Preclinically, low-dose RT conditioning can sensitize antigen-negative tumour cells to CAR-T-mediated elimination by activated CAR-T secretion of TRAIL cytokines.
- RT-CAR-T synergy may be via abscopal effects producing enhanced tumour-specific immunity against irradiated and distant sites







Mod. da Imber BS, et al Br J Haemat 2020; 190: 45–51

2.4

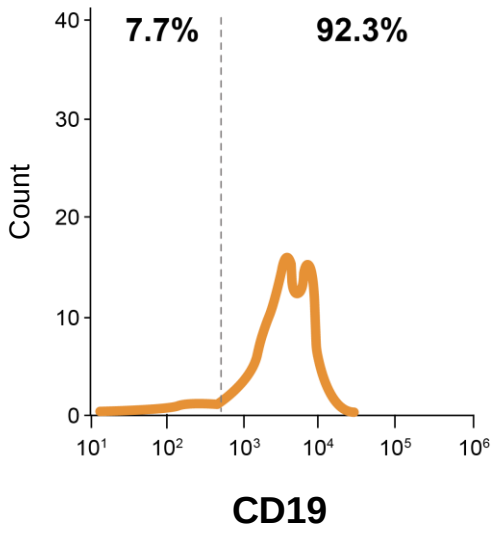
Bispecific CAR-T

Relapses after CAR-T cells: 30% down-regulation of CD19 antigen and development of CD19 clone

- Mutations resulting in CD19 expression loss
- Selection of pre-existing CD19 negative clones

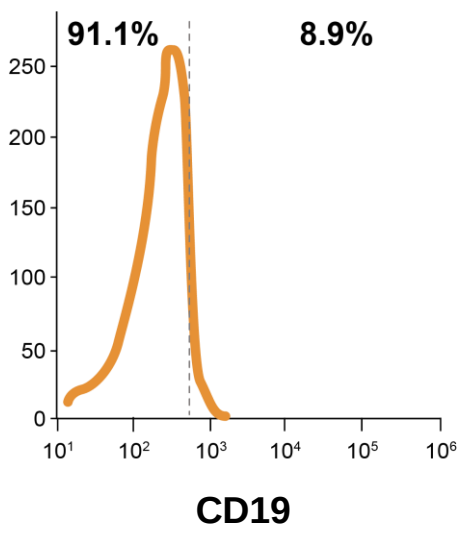
Before infusion

CD45+>SSC low>CD34+



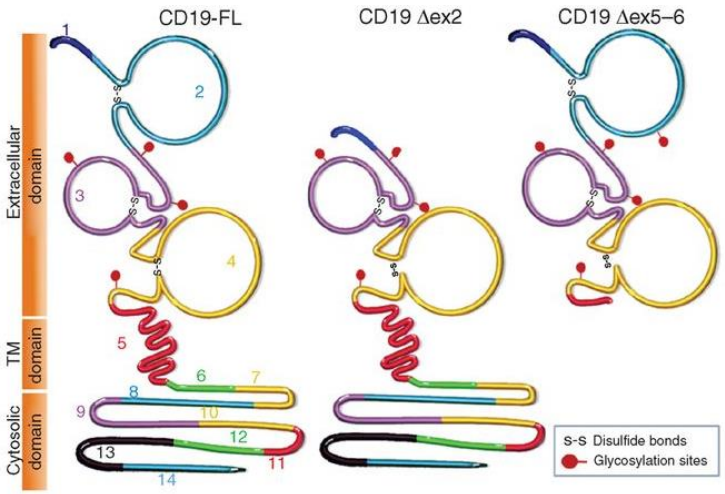
At the time of relapse

CD45+>SSC low>CD34+

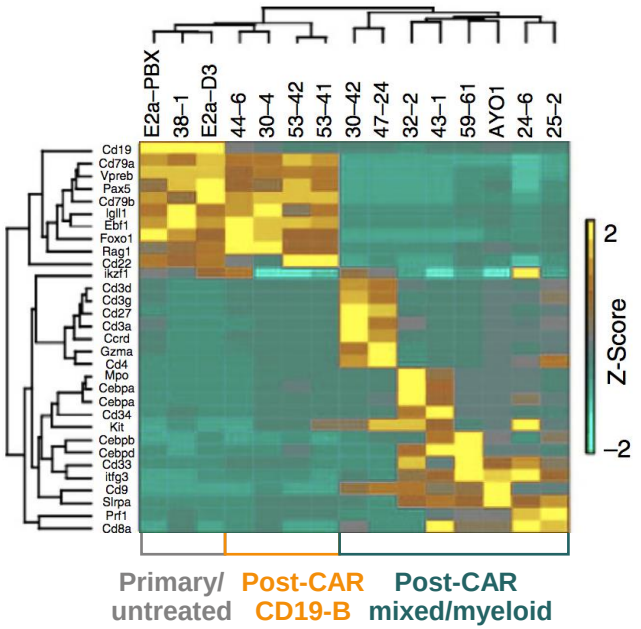


CD19 variant not targeted by CAR-T (exon 2 splicing)

Predicted protein products for CD19 isoforms



Phenotypic switch

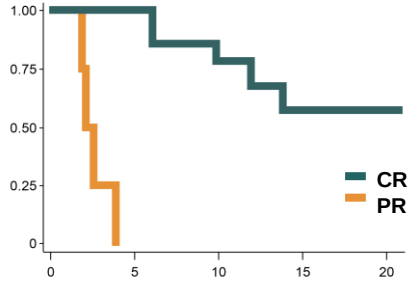


Mod. da Grupp SA, et al. N Engl J Med 2014; 371: 1507–1517; Sotillo E, et al. Cancer Discov 2015; 5: 1282–1295; Jacoby E, et al. Nat Commun 2016; 7: 12320

Bispecific anti-CD20, anti-CD19 CAR-T

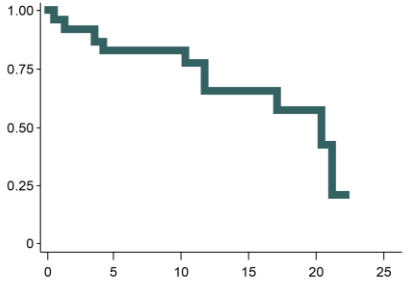
Baseline characteristics	*n=22 (%)*
Age at infusion in years, median (range)	57 (38–72)
Male sex	19 (86 %)
Race	
European ancestry	19 (86%)
Other	3 (14%)
Histology	
DLBCL	11 (50%)
Richter's transformation	2 (9%)
MYC rearrangement	5 (23%)
MCL	7 (32%)
CLL	3 (14%)
FL	1 (4%)
Baseline LDH, median (range)	229 (121–2074)
Refractory to last line of treatment	18 (82%)
Lines of prior therapy, median (range)	4 (2–12)
History of prior autologous HCT	8 (37%)
History of prior allogeneic HCT	3 (14%)
History of prior anti-CD19 CAR-T cell therapy	1 (5%)
Prior BTK inhibitor treatment (patients with MCL or CLL only; n=10)	10 (100%)
Dose (max body weight of 80 kg)	
2.5 x 10^5 cells per kg	3 (14%)
7.5 x 10^5 cells per kg	3 (14%)
2.5 x 10^6 cells per kg	16 (73%)
Non-cryopreserved infusion	15 (68%)
Split infusion (30% on day 0, 70% on day 1)	16 (73%)
Clinical outcomes at day 28	
Day 28: ORR, all dose levels (n=22)	18 (82%)
CR	14 (64%)
PR	4 (18%)
Day 28 ORR, dose of 2.5x10^6 cells per kg (n=16)	14 (88%)
CR	12 (75%)
PR	2 (13%)
Day 28 ORR, dose of 2.5x10^6 cells per kg, fresh infusion (n=12)	12 (100%)
CR	11 (92%)
PR	1 (8%)
DLBCL day 28 ORR (n=11)	10 (91%)
CR	7 (64%)
PR	3 (27%)
MCL day 28 ORR (n=7)	4 (57%)
CR	4 (57%)
PR	0
CLL day 28 ORR (n=3)	3 (100%)
CR	2 (66%)
PR	1 (33%)
FL day 28 ORR (n=1)	1 (100%)
CR	1 (100%)
Median IgG at day 28 (mg/mL)	4.72 (0.99–7.71)
Received IVIG for hypogammaglobulinemia post-CAR infusion	15 (68%)

DURATION OF RESPONSE BY DAY 28 OUTCOME



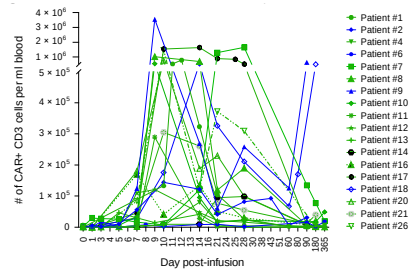
Months from LV20, 19 CAR-T cell infusion

OVERALL SURVIVAL

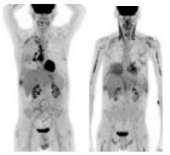


Months from LV20, 19 CAR-T cell infusion

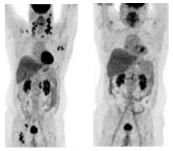
CD3 CAR+ T cells for CR/PR patients



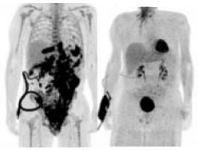
SUBJECT 01: Pre/post CAR-T cell PET/CT



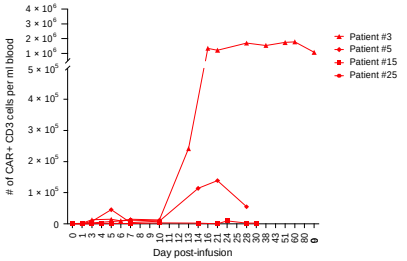
SUBJECT 11: Pre/post CAR-T cell PET/CT



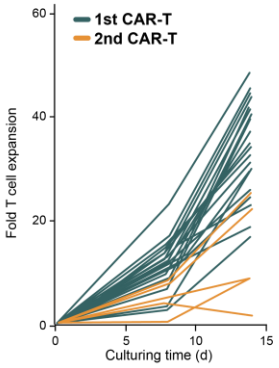
SUBJECT 26: Pre/post CAR-T cell PET/CT



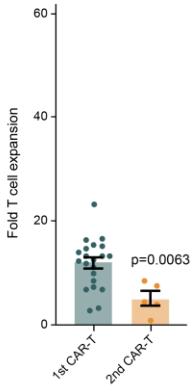
CD3 CAR+ T cells for PD patients



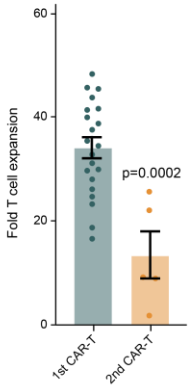
Fold T cell expansion



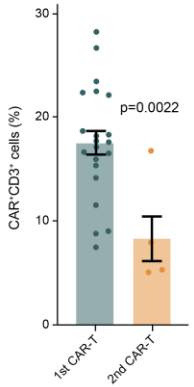
Day 8 - T cell exp.



Day 14 - T cell exp.



Percent of CAR+ T cells



These data suggest that dual targeting of CD19 and CD20 is a promising combination to over-come antigen loss in B cell NHL and CLL

Mod. da Shah NN, et al. Nat Med 2020; 26: 1569–1575

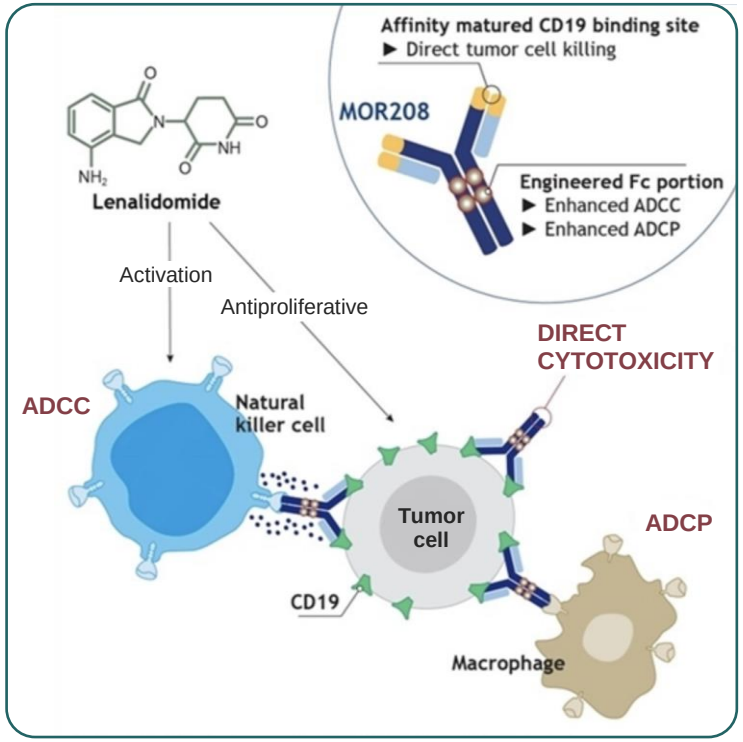
2.5

New biological treatments for R/R DLBCL possibly with low hematological toxicity

L-MIND: A multicentre, prospective single-arm, phase II study

MOR208
Fc-enhanced, anti-CD19 mAb

- ADCC ↑
- ADCP ↑
- Direct cell death
- Encouraging single agent activity in NHL patients with long DoR in R/R DLBCL



Lenalidomide

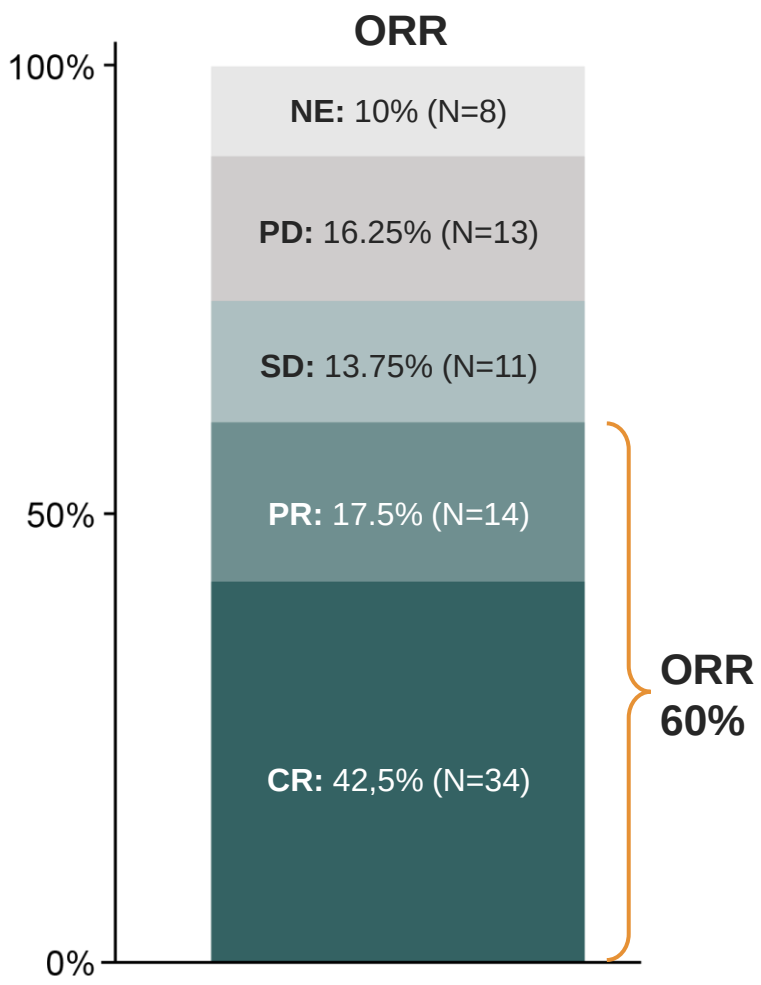
- T and NK cell activation/expansion
- Direct cell death
- Demonstrated activity as an anti-lymphoma agent, alone or in combination
- Approved for treatment of MCL and FL/MZL

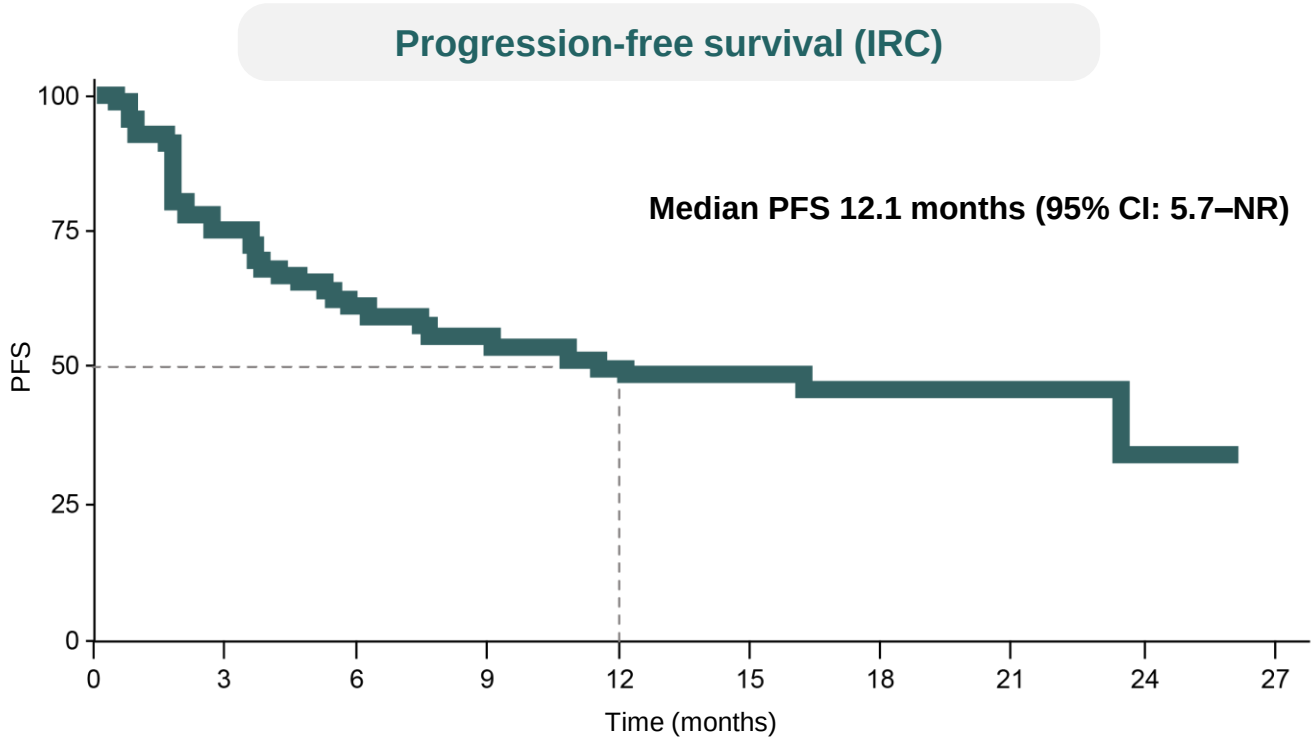
Potentiation of activity by combining tafasitamab and LEN in vivo and in vitro

Mod. Da Salles G, et al. Lancet Oncol 2020; 21: 978–988

Horton HM, et al. Cancer Res 2008; Awan FT, et al. Blood 2010; Richter J, et al. Blood 2013; MorphoSys data on file; Wu L, et al. Clin Cancer Res 2008; Lapalombella R, et al. Blood 2008; Zhang L H, et al. Br J 2013, Wiernik PH, et al. J Clin Oncol 2008; Witzig TE, et al. Ann Oncol 2011; Czuczman MS, et al. Clin Cancer Res 2017; Jurczak W, et al. Ann Oncol 2018

Tafasatinib + lenalidomide in 80 patients with R/R DLBCL





- Median follow-up time 17.3 months
- 39 PFS events recorded
- 28 patients still ongoing with study treatment

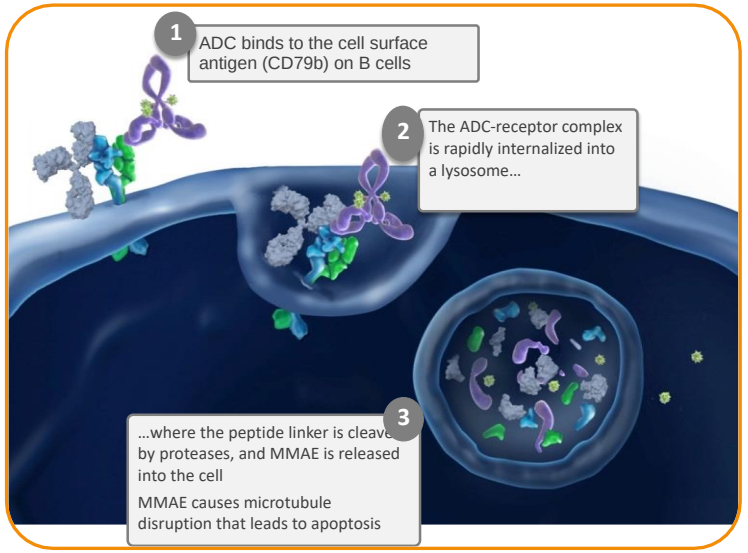
Mod. da Salles G, et al. Lancet Oncol 2020; 21: 978–988

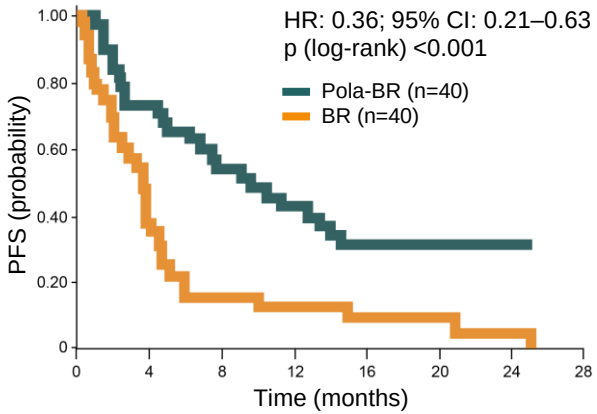
Polatuzumab vedotin in R/R DLBCL

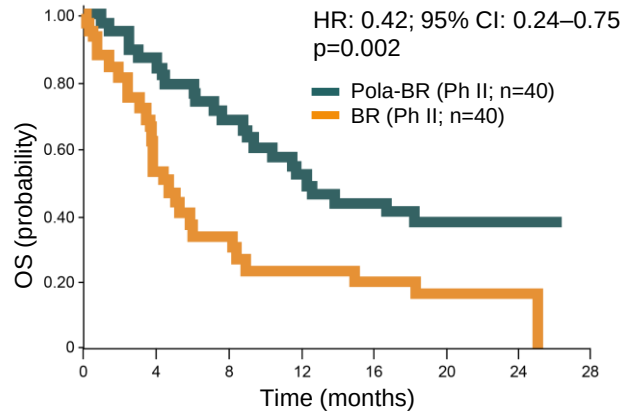
Phase 2 randomized study in 80 transplant ineligible R/R DLBCL patients: BR ± Pola

ADVERSE EVENTS IN PATIENTS TREATED WITH POLA-BR COMPARED WITH BR

Adverse event	Pola-BR (n=39)		BR (n=39)	
	All grades, N (%)	Grade 3–4, N (%)	All grades, N (%)	Grade 3–4, N (%)
Blood and lymphatic system disorders				
Anemia	21 (53.8)	11 (28.2)	10 (25.6)	7 (17.9)
Neutropenia	21 (53.8)	18 (46.2)	15 (38.5)	13 (33.3)
Thrombocytopenia	19 (48.7)	16 (41.0)	11 (28.2)	9 (23.1)
Lymphopenia	5 (12.8)	5 (12.8)	0	0
Febrile neutropenia	4 (10.3)	4 (10.3)	5 (12.8)	5 (12.8)
GI disorders				
Diarrhea	15 (38.5)	1 (2.6)	11 (28.2)	1 (2.6)
Nausea	12 (30.8)	0	16 (41.0)	0
Constipation	7 (17.9)	0	8 (20.5)	1 (2.6)
General disorders and administration site conditions				
Fatigue	14 (35.9)	1 (2.6)	14 (35.9)	1 (2.6)
Pyrexia	13 (33.3)	1 (2.6)	9 (23.1)	0
Metabolism and nutrition disorders				
Decreased appetite	10 (25.6)	1 (2.6)	8 (20.5)	0
Peripheral neuropathy				
Peripheral neuropathy	17 (43.6)	0	3 (7.7)	0







Mod. da Sehn LH, et al. J Clin Oncol 2019; 38: 155–165

2.6

Role of allogeneic transplantation

Allogeneic transplantation?

- **Innovative strategies for patients who fail CAR-T include: Kinase inhibitors, polatuzumab, bispecific antibodies, checkpoint inhibitors**
- **All these agents provide short-lived response**
- **Investigating allo-HCT consolidation for sensitive post-CAR-T relapse is worthwhile**
- **However, in a real-word study only 5/61 patients underwent allo-HCT post CAR-T failure**

Mod. da Dreger P, et al. Biol Blood Marrow Transplant 2020; 26: 77–85