CAR-T cells in Hodgkin lymphoma: can we see the light at the end of the tunnel?

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Disclosures of Franco Locatelli

Name of Company	Research Support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Miltenyi					X		
Amgen					X	X	
Novartis					X	X	
BMS					X		
GILEAD					X		
MEDAC					X		
Sanofi						X	
SOBI					X		
Vertex						X	

Background

- Approximately 10-15% of patients with Hodgkin Lymphoma (HL) are either primary refractory or experience a relapse after first-line therapy
- Salvage chemotherapy followed by ASCT is the standard of care for relapsed/refractory (R/R) patients
- Brentuximab Vedotin (BV), an anti-CD30 ADC, improves the probability of survival after ASCT
- Approximately 50% of patients relapse after ASCT, and allo-HSCT represents the only treatment option offering long-term remissions; however, it is associated with a high burden of morbidity and mortality
- **Patients who fail ASCT, BV and anti-PD1 agents have poor chances to be cured**, with a median overall survival of 2 years
- **While CD30 is highly expressed in Hodgkin lymphoma (universally expressed by Reed-Sternberg cells), anaplastic large cell lymphoma and T-cell lymphomas, it is poorly expressed by healthy cells and seldom expressed in the CNS**
- CD30-targeting CAR T cells may represent a valuable alternative option for R/R patients who have failed both ASCT and BV, as well as for those not eligible for ASCT

Horie R, et al. Semin Immunol. 1998
Schirrmann T, et al. BioDrugs. 2014
Meng F, et al. BMC Cancer. 2025

Clinical Trials on CAR T cells for HL

Study	ID	Regimen	Study design	N	Mean of CD30 CAR-T	Age, median (range)	Male (%)	Disease	Stage at diagnosis		Previous therapies	
								HL	I-II	III-IV	ASCT	BV
Wang 2016 [17]	NCT02259556	CD30 CAR-T	Phase I, single-arm	17	1.56×10^{7}/kg	33 (13–77)	12 (70.6%)	cHL	1 (5.9%)	16 (94.1%)	9 (52.9%)	4 (23.5%)
Ramos 2017 [21]	NCT01316146	CD30 CAR-T	Phase I, single-arm	7	1.48×10^{8}/kg	31 (20–65)	5 (71.4%)	cHL	NA	NA	6 (85.7%)	5 (71.4%)
Ramos 2020 [18]	NCT02917083 /NCT02690545	CD30 CAR-T	Phase I/II, single-arm	42	1.66×10^{8}/kg	35 (17–69)	28 (66.7%)	cHL	14 (33.3%)	28 (66.7%)	32 (76.2%)	38 (90.5%)
Voorhees 2022 [15]	NCT02690545	CD30 CAR-T	Phase I/II, single-arm	27	1.81×10^{8}/kg	33 (15–67)	18 (66.7%)	cHL	9 (33.3%)	18 (66.7%)	22 (81.5%)	NA
Sang 2022 [16]	NCT03196830	CD30 CAR-T ±PD-1 inhibitor± HSCT	Phase II, single-arm	9	8.9×10^{8}/kg	24 (19–64)	6 (66.7%)	cHL	0 (0.0%)	9 (100.0%)	1 (11.1%)	0 (0.0%)
Zhang 2022 [22]	ChiCTR 2100053662	CD30 CAR-T + HSCT	Phase I, single-arm	5	NA	25 (18–30)	3 (60.0%)	cHL	2 (40.0%)	3 (60.0%)	0 (0.0%)	NA
Tschernia 2023 [14]	NCT02690545	CD30 CAR-T	Phase II, single-arm	23	1.87×10^{8}/kg	36 (23–70)	15 (65.2%)	CD30 + lymphomas	8 (34.8%)	15 (65.2%)	17 (73.9%)	22 (95.7%)
Brudno 2021 [20]	NCT03049449	CD30 CAR-T	Phase I, single-arm	21	3.47×10^{6}/kg	33 (18–64)	15 (71.4%)	CD30 + lymphomas	NA	NA	14 (66.7%)	21 (100%)

NA not available, *HL* Hodgkin lymphoma, *cHL* classic Hodgkin lymphoma, *ASCT* autologous stem cell transplantation, brentuximab vedotin

Meng F, et al. BMC Cancer. 2025

CD30-CART in R/R Hodgkin Lymphoma meta-analysis

8 studies (6 studies focused on cHL)
All phase I and/or phase II single-arm trials

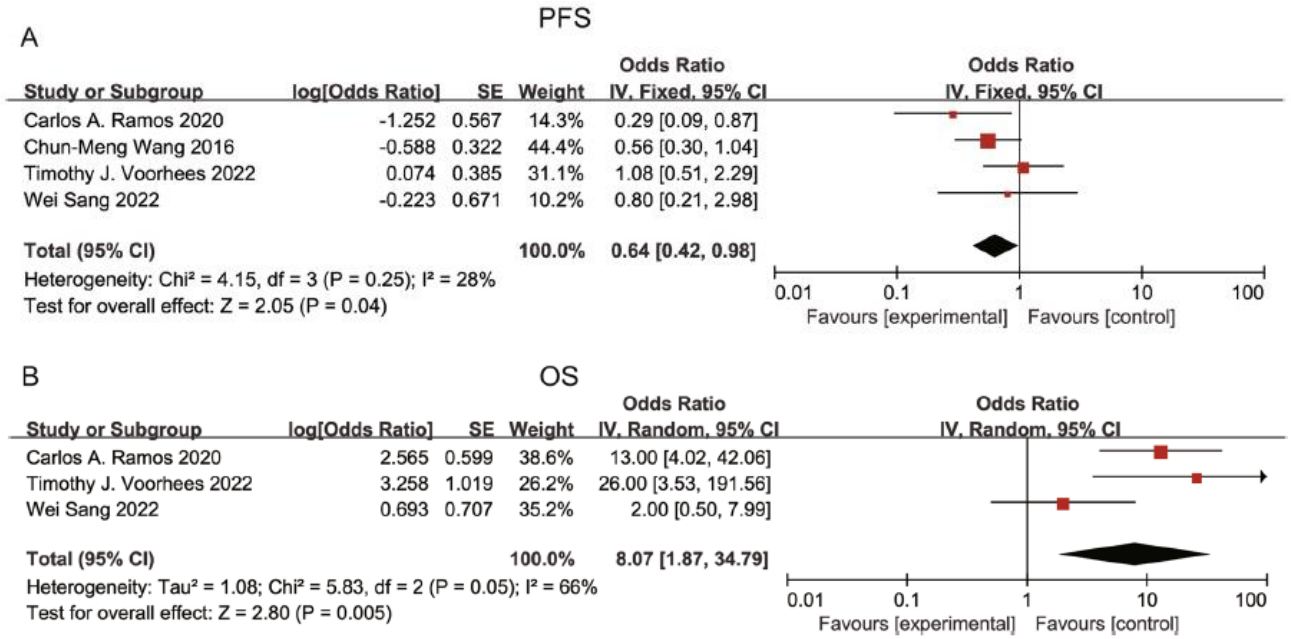
151 patients (147 cHL)

>60% stage III/IV
Several lines of prior therapies (7-14)
>50% had previously received ASCT
Most had PD before treatment

High
1-year PFS of 39% (95% CI: 0.30-0.49, p=0.04)
1-year OS of 89% (95% CI: 0.65-0.97, p=0.005)

Table 2 Efficacy outcomes of anti-CD30 CAR-T cell therapy in R/R cHL

Efficacy	Incidence	95% CI	*P*
ORR	0.57	0.36–0.76	0.50
CR	0.34	0.13–0.64	0.29
PR	0.32	0.15–0.55	0.12
SD	0.27	0.14–0.46	0.002



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CD30-CART in R/R Hodgkin Lymphoma

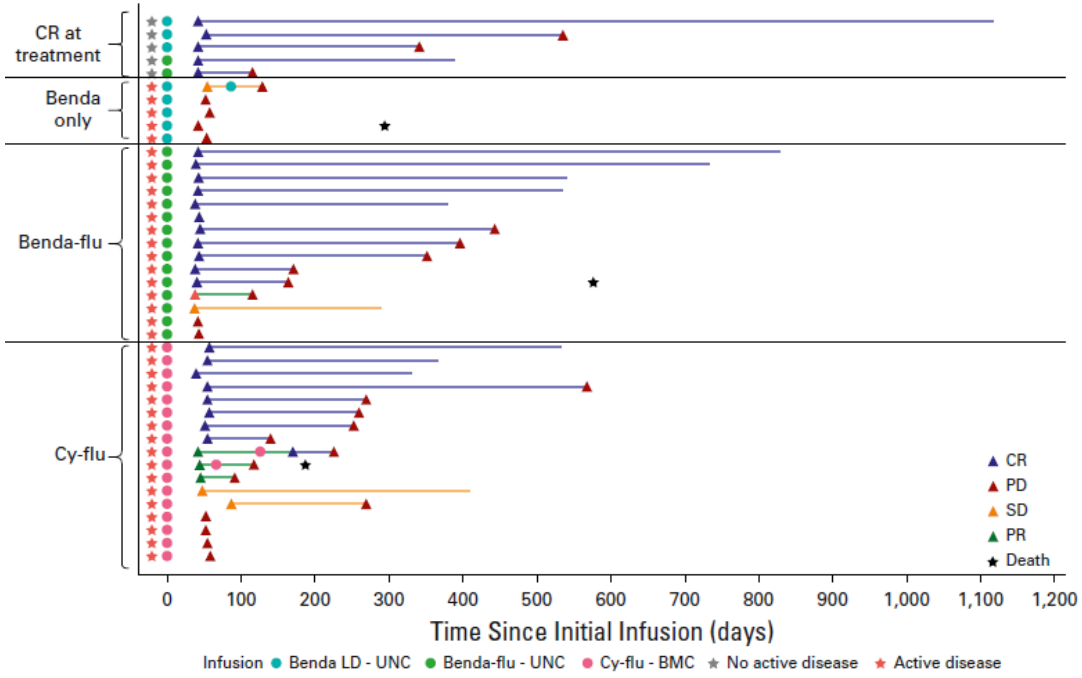
- 41 patients
- Two independent institutions (University of North Carolina and Baylor College of Medicine)
- 2 parallel phase I/II trials: NCT02690545; NCT02917083)
- Same **gamma retroviral vector** and manufacturing process

- **DL1: 2x10^7 CAR-T/m2**
- **DL2: 1x10^8 CAR-T/m2**
- **DL3: 2x10^8 CAR-T/m2**

Characteristic	All Patients (N = 42)[a]	Benda (n = 8)[a]	Benda-Flu (n = 17)	Cy-Flu (n = 17)[a]
HL subtype				
NS	32 (76)	6 (75)	10 (59)	16 (94)
MC	4 (10)	2 (25)	2 (12)	0
NOS	6 (14)	0	5 (29)	1 (6)
Stage at diagnosis				
I-II	14 (33)	1 (13)	7 (41)	6 (35)
III-IV	28 (67)	7 (88)	10 (59)	11 (65)
Median age (range), years	35 (17-69)	49 (23-67)	32 (23-45)	36 (17-69)
Male sex	28 (67)	5 (63)	13 (76)	10 (59)
ECOG PS ≥ 1	34 (81)	5 (63)	12 (71)	17 (100)
Median No. of prior therapies (range)	7 (2-23)	7.5 (5-17)	8 (3-23)	5 (2-10)
Bridging therapy	28 (67)	8 (100)	10 (59)	10 (59)
Prior BV	38 (90)	8 (100)	16 (94)	14 (82)
Progression on BV[b]	32 (84)	6 (75)	12 (75)	14 (100)
Prior CPI	34 (81)	7 (88)	13 (76)	14 (82)
Prior aSCT	32 (76)	7 (88)	14 (82)	11 (65)
Prior alloSCT	10 (24)	2 (25)	8 (47)	0 (0)
CAR-T cells/m^2				
2×10^7	3 (7)	0	0	3 (18)
1×10^8	9 (21)	3 (38)	0	6 (35)
2×10^8	30 (71)	5 (63)	17 (100)	8 (47)

Ramos CA, et al. J Clin Oncol. 2020

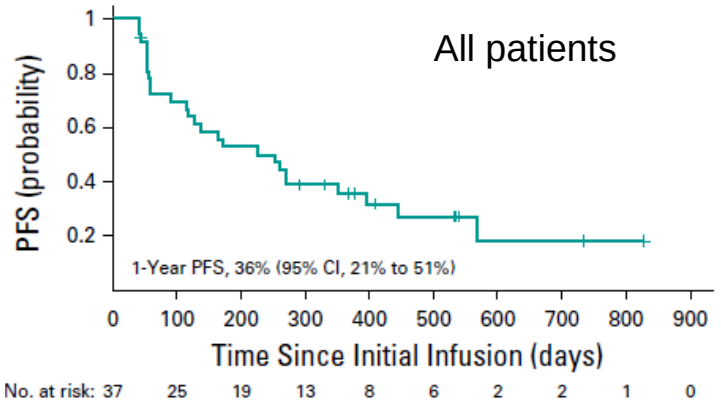
Antitumor activity of CD30-CAR T cells

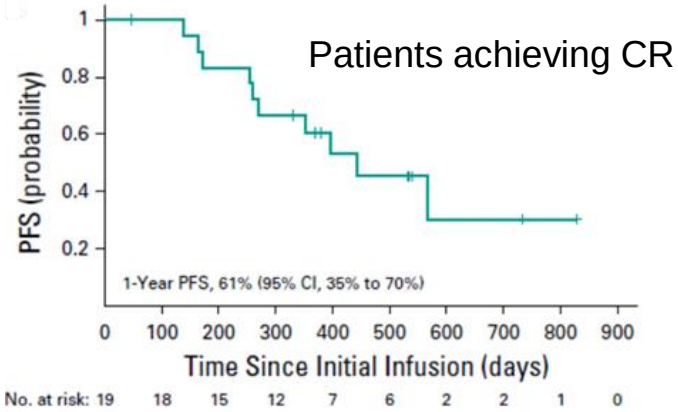


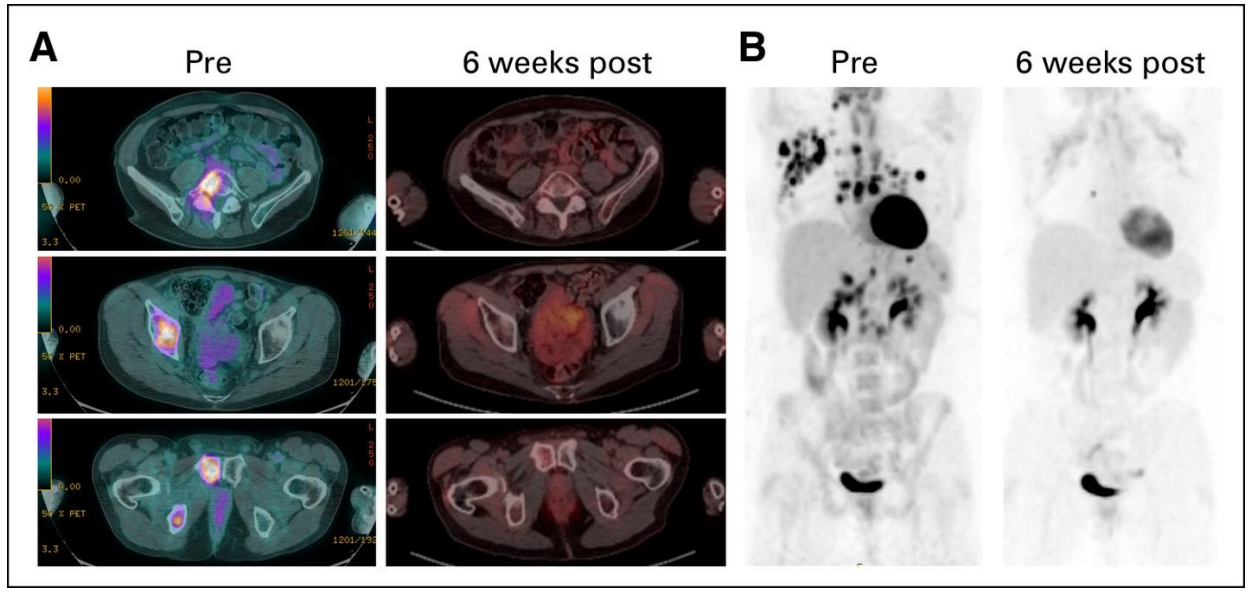
Response	All Patients (N = 37)	Benda (n = 5)	Benda-Flu (n = 15)	Cy-Flu (n = 17)
ORR				
CR + PR	23 (62)	0 (0)	12 (80)	11 (65)
Response rate				
CR	19 (51)	0 (0)	11 (73)	8 (47)
PR	4 (11)	0 (0)	1 (7)	3 (18)
SD	4 (11)	1 (20)	1 (7)	2 (11)
PD	10 (27)	4 (80)	2 (13)	4 (24)

Patients with measurable residual disease pre-LDP

Patients with measurable residual disease pre-LDP







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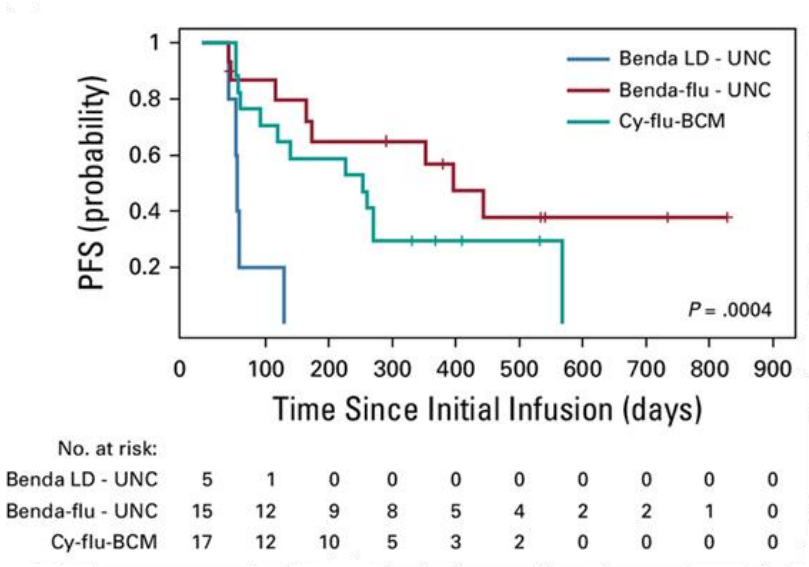
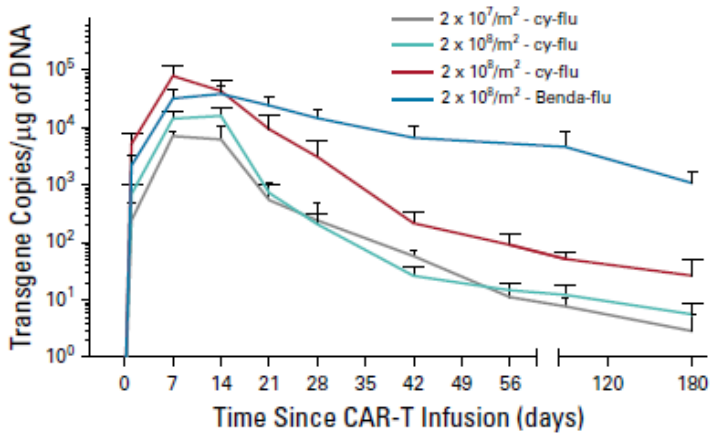
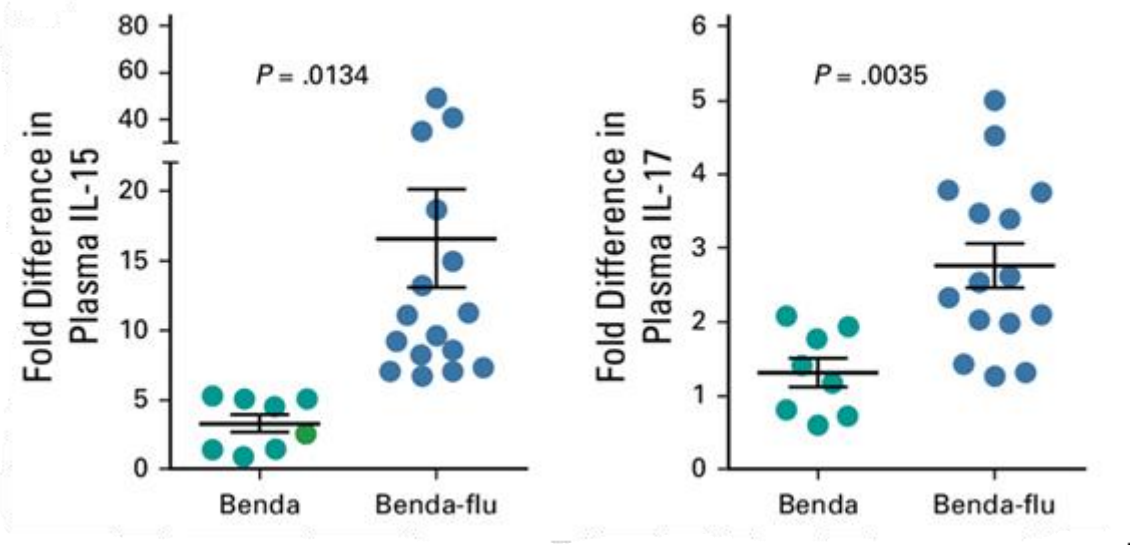
The role of lymphodepletion



- **Benda LD**: Bendamustine 90 mg/m^2/day x 2 days
- **Benda-flu**: Bendamustine 70 mg/m^2/day + Fludarabine 30 mg/m^2/day x 3 days
- **Cy-flu**: Cyclophosphamide 500 mg/m^2/day Fludarabine 30 mg/m^2/day x 3 days





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CD30-CAR T cells were also associated with lower efficacy and substantial toxicity

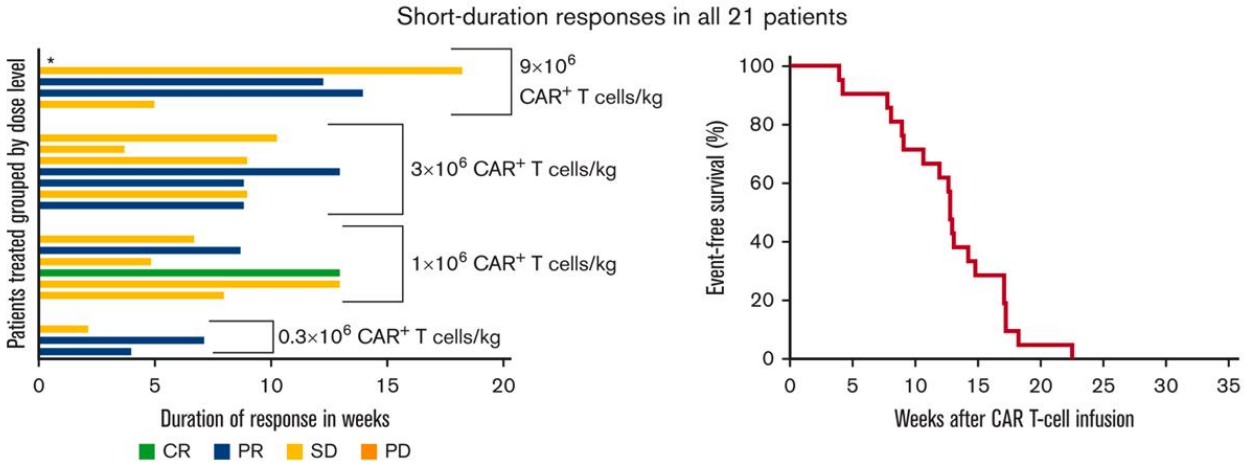
- Phase I clinical trial for refractory T-cell expressing lymphomas
- 5F11-28Z: human antibody–derived binding domain, CD28
- Lentiviral vector

- LDP: Cyclo 300 mg/m2 or 500 mg/m2 +
  Flu 30 mg/m2 day -5 to -3

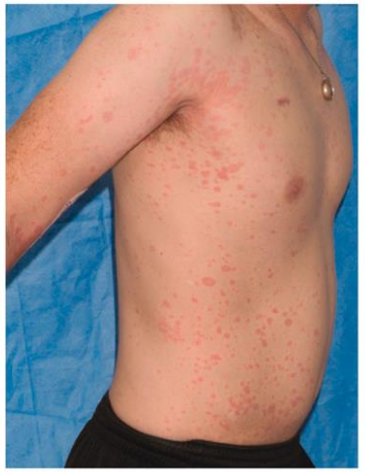
- **DL1: 0.3x10^6 CAR-T cells/kg**
- **DL2: 1x10^6 CAR-T cells/kg**
- **DL3: 3x10^6 CAR-T cells/kg**
- **DL4: 9x10^6 CAR-T cells/kg**

- 21 patients treated
- Median prior lines of therapy: 7 (range: 4-15)
- N=20 cHL; N=1 ALCL ALK+

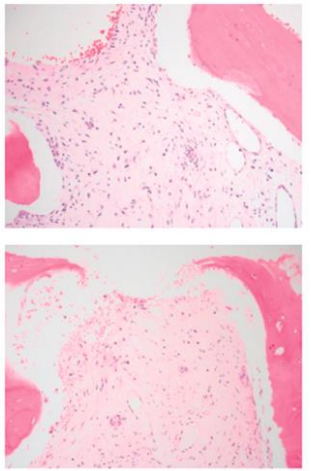
- Prior BV: 21/21; prior checkpoint inh: 18/21; prior ASCT: 14/21; prior alloHSCT: 3/21



Long-lasting grade 3 rashes in patients



Prolonged hematologic recovery in 5 patients
New bone marrow fibrosis in 3 patients



CRS: 11/21
(n=1 G3, no G4-5)
Minimal neurological toxicity

Brudno JN, et al. Blood Adv. 2024

CD30-CART as consolidation after ASCT in CD30+ Lymphomas at high-risk of relapse

Phase I, multicenter (2 sites in US), single-arm trial

Age ≥3 years, cHL (N=11) or CD30+ NHLs (N=6), max 18 pts

High risk categories:

a) primary refractory disease

b) relapse within 12 months of initial therapy

c) extranodal involvement at the start of pre-transplantation salvage therapy

gamma retroviral vector, CD28-cos. domain

Lymphocyte collection pre-mobilisation of PBSCs

- **DL1: 2x10^7 CAR-T/m^2**
- **DL2: 1x10^8 CAR-T/m^2**
- **DL3: 2x10^8 CAR-T/m^2**

- BEAM conditioning regimen pre-ASCT -> CD30.CART infusion at trilineage engraftment

	Patients who underwent cell collection (n=21)	Patients who received treatment (n=18)	Patients with Hodgkin lymphoma (n=11)
Median age, years	45	43	24
IQR	22–60	23–60	20–48
Range	12–76	16–76	17–61
Disease			
Hodgkin lymphoma	13 (62%)	11 (61%)	NA
ALK-positive ALCL	3 (14%)	3 (17%)	NA
ALK-negative ALCL	1 (5%)	1 (6%)	NA
AITL	1 (5%)	1 (6%)	NA
PTCL, NOS	1 (5%)	1 (6%)	NA
Grey zone lymphoma	1 (5%)	1 (6%)	NA
CD30⁺ large B-cell lymphoma	1 (5%)	0	NA
Number of systemic salvage therapies before autologous HSCT			
1	17 (81%)	15 (83%)	9 (81%)
2	4 (19%)	3 (17%)	2 (18%)
Received previous BV	16 (76%)	15 (83%)	9 (81%)
Refractory to previous BV§	2 (13%)	2 (13%)	1 (11%)
Received previous checkpoint inhibitor	2 (10%)	2 (11%)	2 (18%)
Disease status after front-line therapy			
Refractory	12 (57%)	9 (50%)	5 (45%)
Relapse <12 months	5 (24%)	5 (28%)	4 (36%)
Relapse ≥12 months	4 (19%)	4 (22%)	2 (18%)
Extranodal involvement at pre-HSCT relapse	10 (48%)	10 (56%)	5 (45%)
Disease status at HSCT			
Complete response	17 (81%)	16 (89%)	9 (81%)
Partial response	3 (14%)	2 (11%)	2 (18%)
Progressive disease	1 (5%)	0	0

Grover NS, et al. Lancet Haematol. 2024

CD30-CART as consolidation after ASCT in CD30+ Lymphomas at high-risk of relapse

	Grade 1–2	Grade 3	Grade 4
Anaemia	1 (6%)	1 (6%)	0
Aspartate aminotransferase increased	4 (22%)	0	0
Cytokine release syndrome	1 (6%)	0	0
Diarrhoea	3 (17%)	0	0
Dizziness	2 (11%)	0	0
Fatigue	3 (17%)	0	0
Headache	2 (11%)	0	0
Hypocalcaemia	2 (11%)	0	0
Lymphocyte count decreased	6 (33%)	2 (11%)	0
Nausea	6 (33%)	0	0
Neutrophil count decreased	3 (17%)	0	1 (6%)
Platelet count decreased	4 (22%)	1 (6%)	0
Rash maculopapular	1 (6%)	1 (6%)	0
Vomiting	2 (11%)	0	0
White blood cell count decreased	4 (22%)	2 (11%)	0

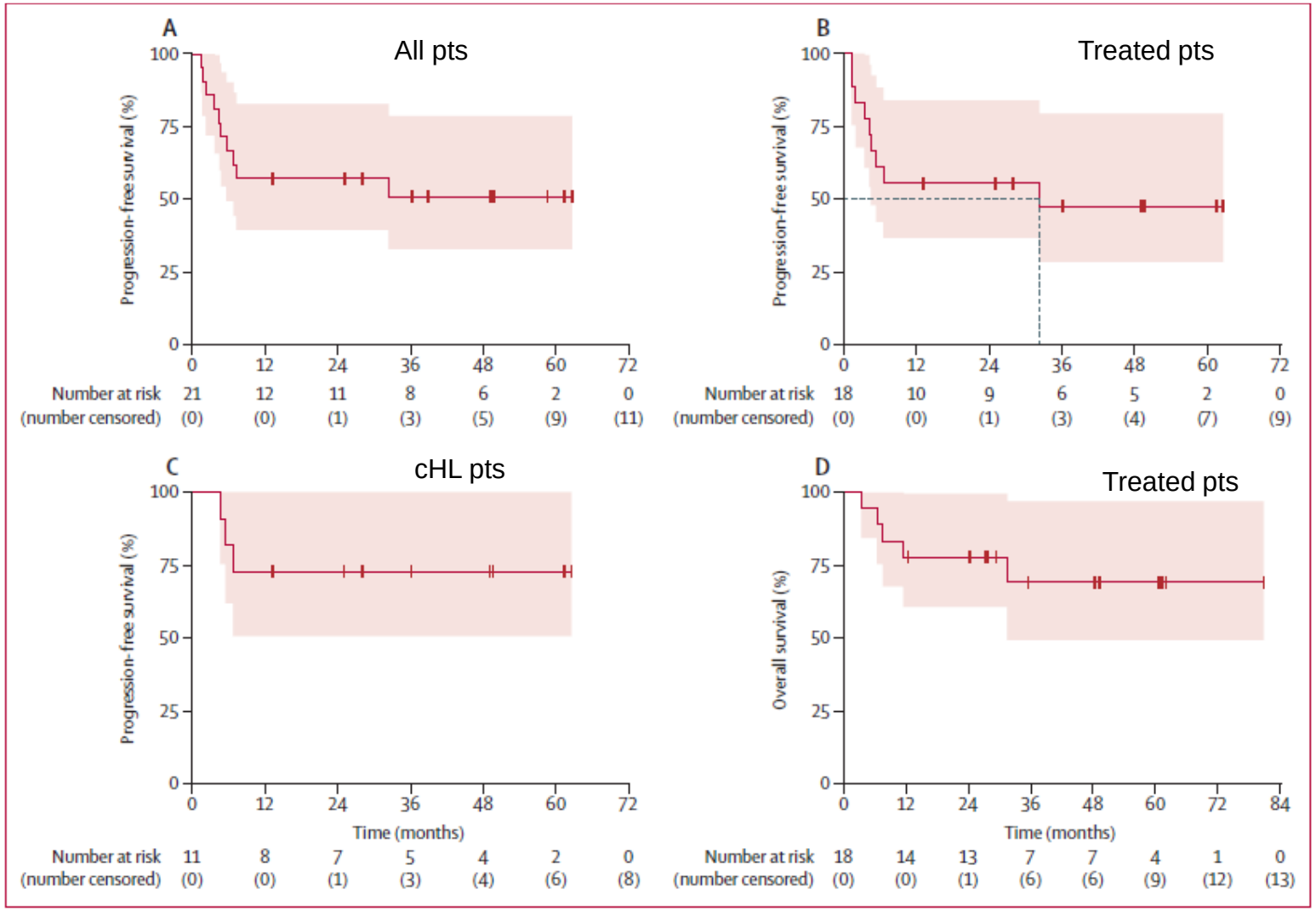
Data are n (%). The denominator for all percentages is 18 (the total number of treated patients). Table includes all grade 3 or worse adverse events and all grade 1–2 events occurring in ≥10% of patients as well as adverse events of special interest (cytokine release syndrome, rash). There were no fatal (grade 5) events.

Table 2: Treatment-emergent adverse events

	Patients who received treatment (n=18)	Dose level 1 (n=4)	Dose level 2 (n=5)	Dose level 3 (n=9)
Lymphopenia	2 (11%)	1 (25%)	0	1 (11%)
Leukopenia	2 (11%)	0	1 (20%)	1 (11%)
Neutropenia	1 (6%)	0	1 (20%)	0
Anaemia	1 (6%)	0	1 (20%)	0
Thrombocytopenia	1 (6%)	0	1 (20%)	0
Rash (grade 3)	1 (6%)	0	0	1 (11%)
Rash (any grade)	2 (11%)	0	0	2 (22%)
Cytokine release syndrome (grade 1)	1 (6%)	0	0	1 (11%)

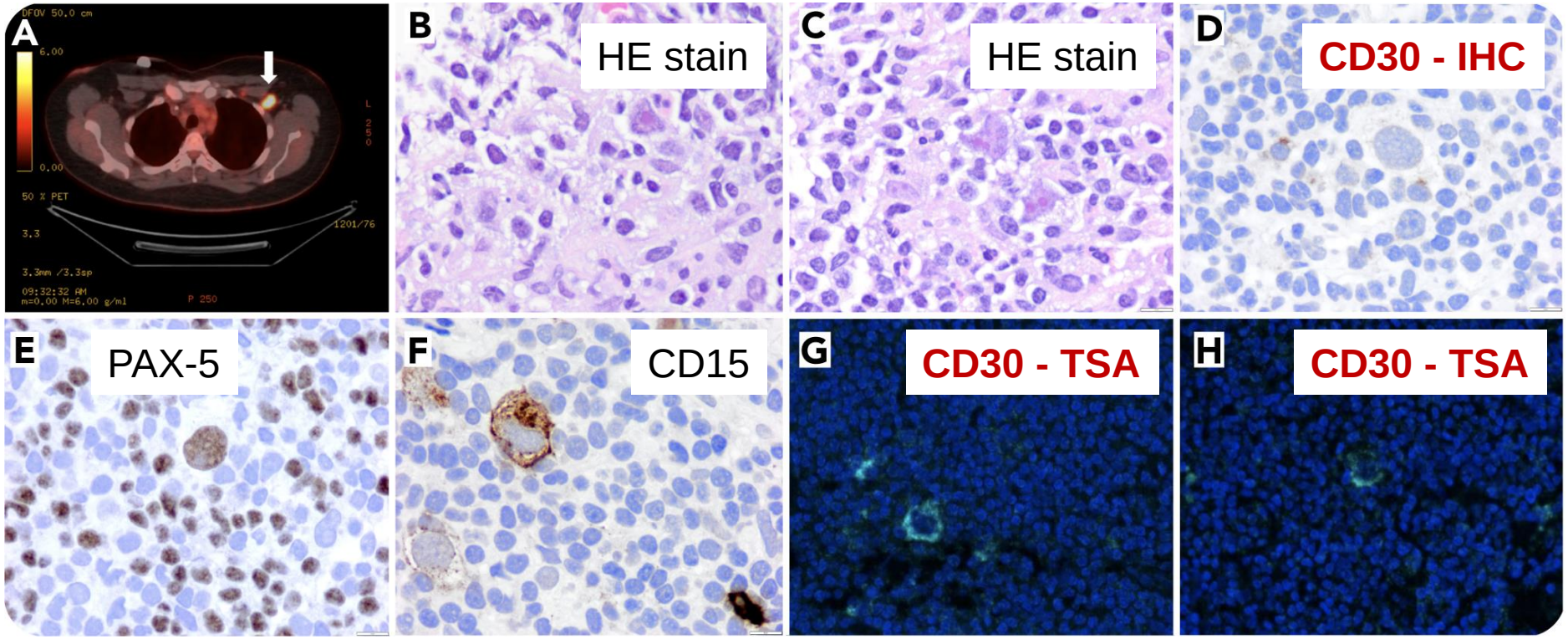
Data are n (%).

Table 3: Adverse events of special interest by dose level



Grover NS, et al. Lancet Haematol. 2024

Relapse after CD30-targeting immunotherapy may be related to a decreased expression of CD30



40 yo woman, cHL
6 ABVD, no RT
Relapse: Nivolumab - > BV -> CD30-CAR T cells
Relapse (chest wall/axillary lymph nodes)

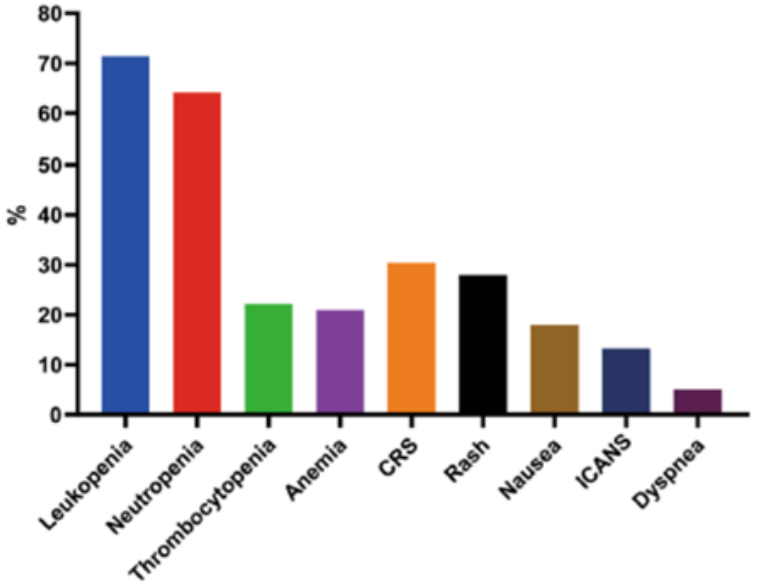
Kim DH, et al. Blood. 2022

Tolerability of CD30.CAR T cells meta-analysis

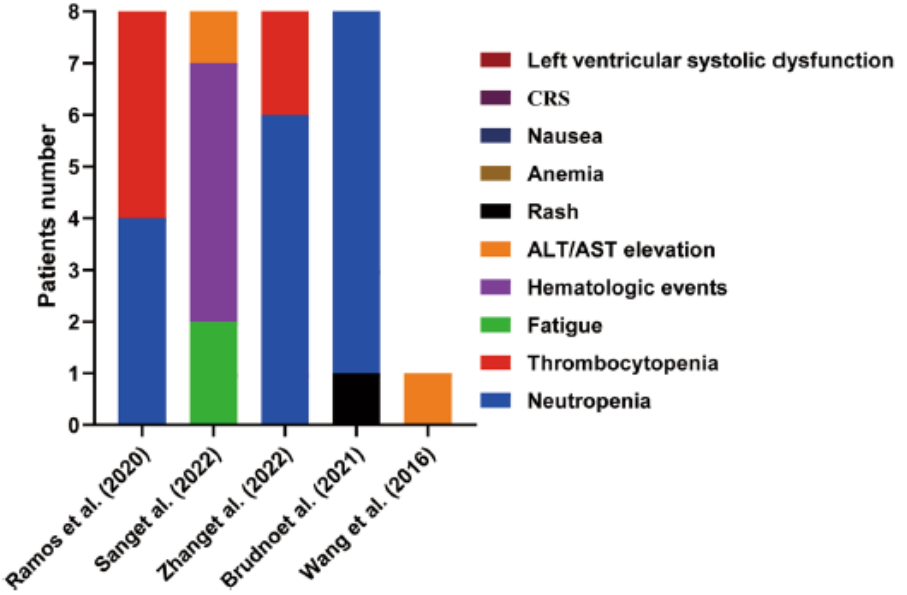
Safety	Incidence	95% CI	*P*
AEs			
CRS	0.43	0.14–0.76	0.69
Anemia	0.23	0.08–0.49	0.04
Thrombocytopenia	0.23	0.09–0.47	0.03
Leukopenia	0.72	0.50–0.87	0.05
Neutropenia	0.77	0.34–0.96	0.2
Dyspnea	0.07	0.03–0.15	0.00001
Rash	0.19	0.07–0.46	0.03
Nausea	0.22	0.12–0.36	0.0005
ICONS	0.14	0.02–0.57	0.09
Grade ≧3 AEs			
Neutropenia	0.65	0.06–0.98	0.73
Thrombocytopenia	0.28	0.07–0.68	0.27

CRS Cytokine release syndrome, *AEs* adverse events, *ICANS* immune effector cell-associated neurotoxicity syndrome

All grades adverse Events



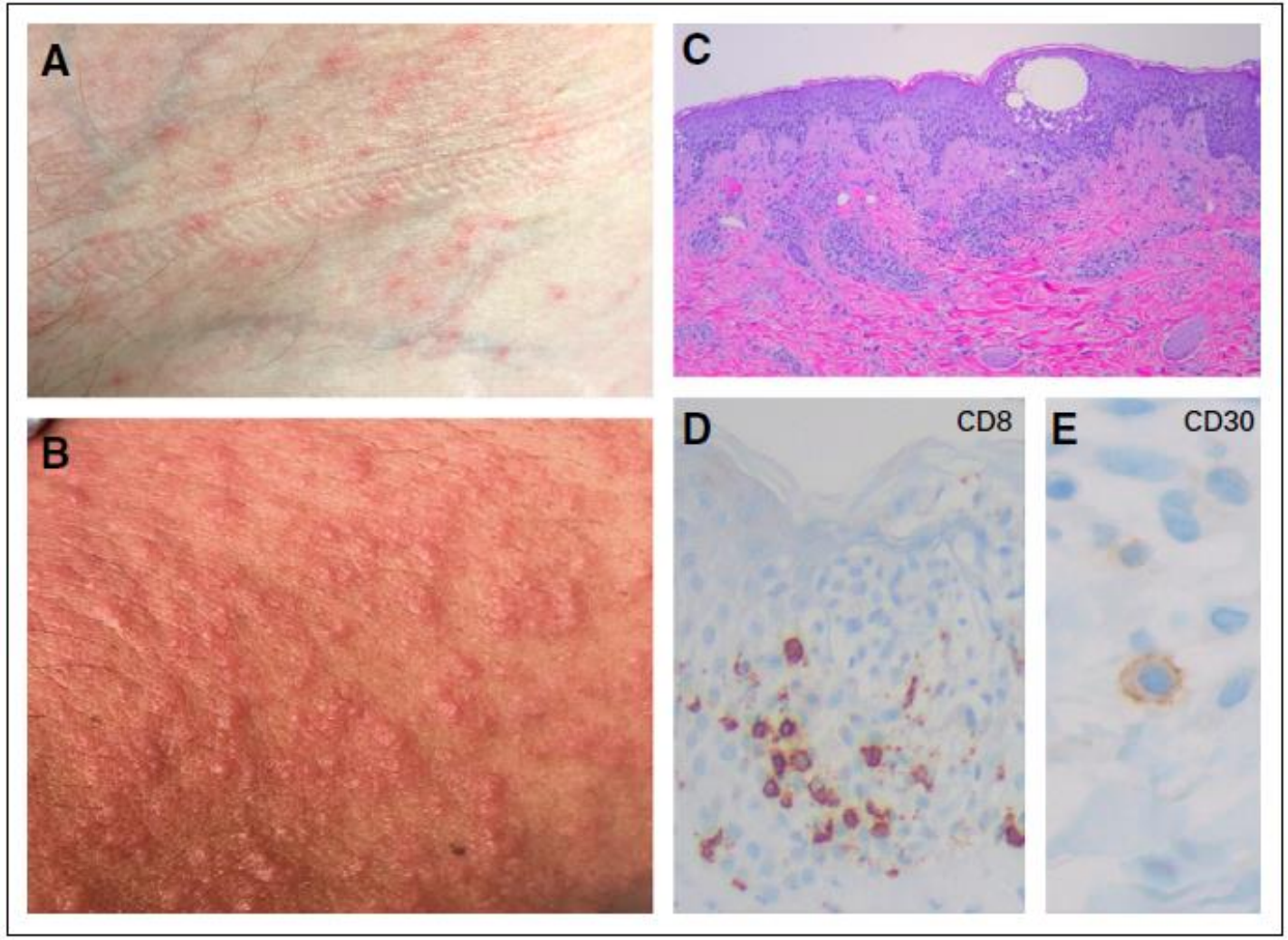
Grade 3/4 adverse Events



Meng F, et al. BMC Cancer. 2025

Skin rash and biopsy

- Characteristic rash that develops in some patients given CD30.CAR T cells **(A-B)**
- Spongiotic dermatitis with occasional eosinophils **(C)**
- Immunohistochemistry demonstrated a mixed population of lymphocytes with a CD4:CD8 ratio of approximately 1.5:1 **(D)**
- Apart from very rare scattered cells, CD30 stain was negative **(E)**
- Quantitative polymerase chain reaction for the CD30.CAR transgene was positive in DNA isolated from biopsy material



Ramos CA, et al. J Clin Oncol. 2020

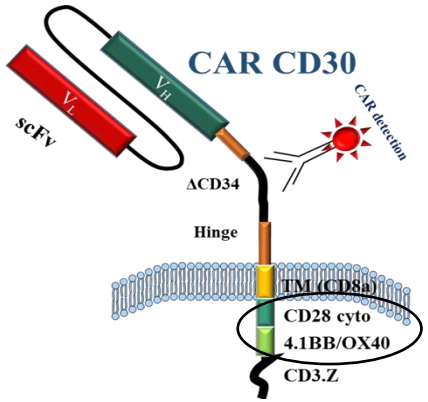
CD28.OX40 co-stimulatory combination to optimize CAR.CD30 T-cells

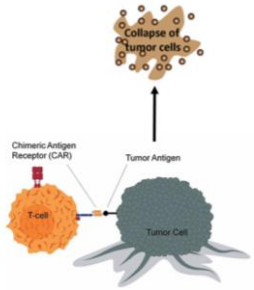
CD30+ Lymphomas

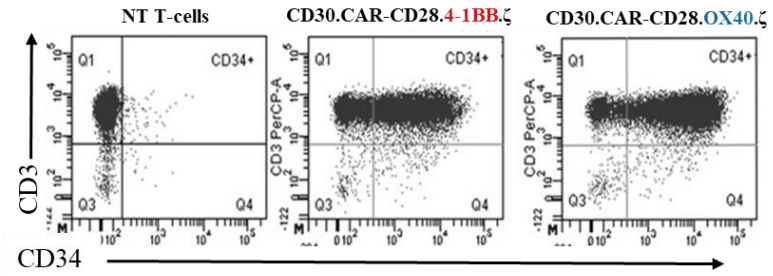
CD30 is promising target for immunotherapy as it is universally expressed in virtually all:

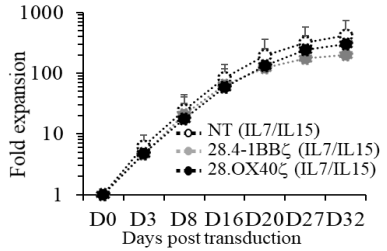
1. **Classical Hodgkin lymphomas (HL),**
2. **CD30+ anaplastic large cell lymphomas (ALCL)**
3. **CD30+ cutaneous T-cell lymphoma and diffuse large B cell lymphoma**
4. **Germinal tumors (solid tumor)**

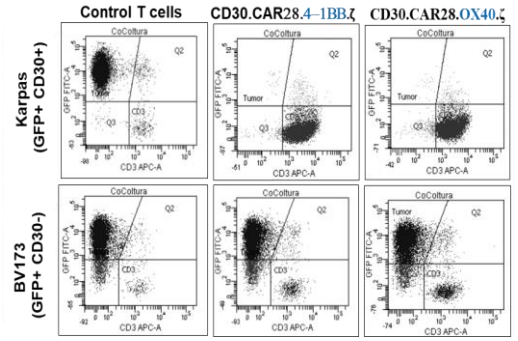
- Patients with HL failing chemotherapy, Brentuximab-vedotin (BV) and checkpoint inhibitors represent a clinical challenge, without effective options for cure.
- Approximately a quarter of patients do not respond, and prognosis after BV failure is poor for both HL and ALCL, with a median progression-free survival (PFS) of less than 6 months.

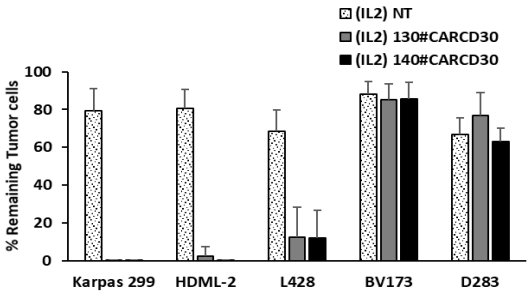






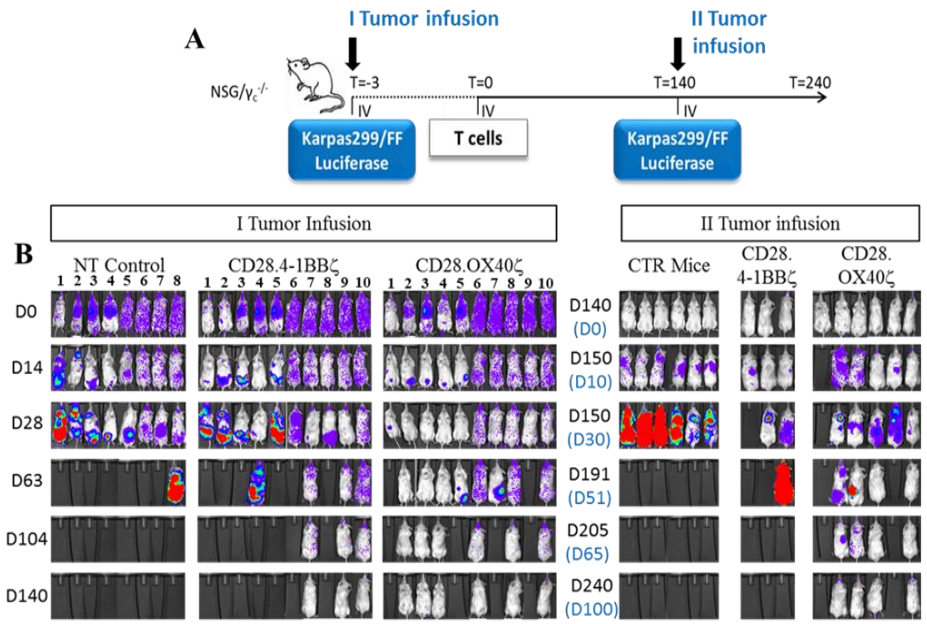


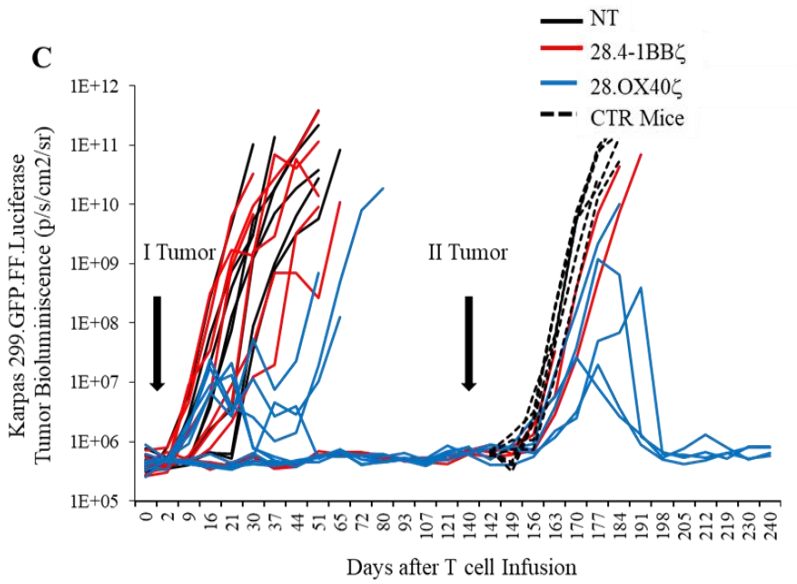


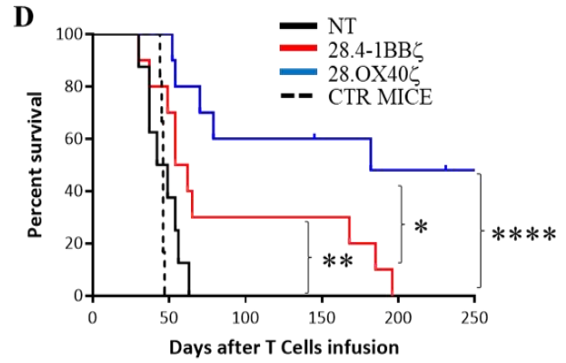


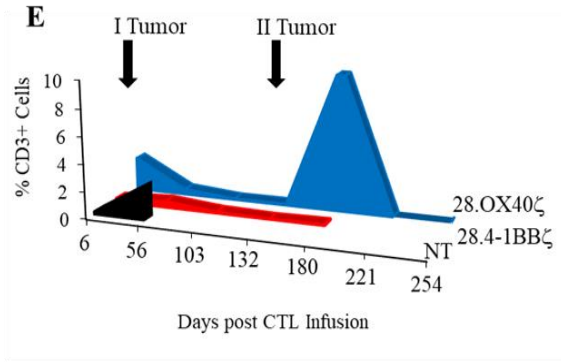
Guercio M et al. Haematologica 2021

CD28.OX40 co-stimulatory combination is associated with long in vivo persistence and high activity of CAR.CD30 T-cells









Cell Therapy & Immunotherapy

ARTICLE

CD28.OX40 co-stimulatory combination is associated with long *in vivo* persistence and high activity of CAR.CD30 T cells

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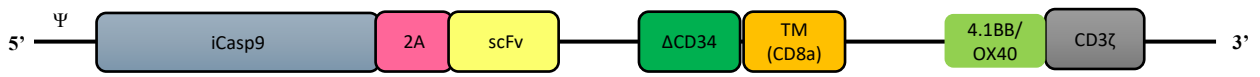
OPBG CD30.CAR-T product



SFG Retroviral Vector

Development of an innovative Chimeric Antigen Receptor therapy targeting CD30 in Hodgkin Lymphoma (HL) and CD30 positive T cell lymphomas: a first-in-human Phase I clinical trial

- Phase I, single-arm
- Autologous, third-generation CD28OX40-based CAR T cells
- Dose-finding study, BOIN design (max 12 pts)
- Four dose levels:
  - **DL1: 1.0x10^6 CAR-T/kg**
  - **DL2: 3.0 x 10^6 CAR-T/kg** ← **starting dose**
  - **DL3: 6.0 x 10^6 CAR-T/kg**
  - **DL4: 10.0 x 10^6 CAR-T/kg**
- **Sites:**
  - **OPBG, Rome F. Locatelli**
  - **AOU, Bologna P. Zinzani**
  - **INT, Milan P. Corradini**

PRIMARY END-POINTS

1. The MTD, defined as the dose level with an estimated Dose Limiting Toxicity (DLT) rate closest to the target toxicity rate (ϕ) of 0.28, provided that such dose is not exceeded based on the BOIN safety stopping rules
2. Number of patients experiencing DLTs during the MTD evaluation period

MAIN SECONDARY END-POINT

Overall Response Rate (ORR) at week 6 and month 3 after CD30-CART01 infusion, that include Complete Remission (CR) and Partial Response (PR) according to the Lugano Classification Revised Staging System for malignant lymphoma

OPBG CD30.CAR-T product

Main inclusion criteria

- Confirmed histological diagnosis of HL, or ALCL with **CD30 positive cells > 80%** as assayed in a CLIA certified pathology laboratory
- **Relapsed or refractory disease after ≥ 2 lines of chemotherapy, including brentuximab-vedotin (BV) and, only for HL patients, check-point inhibitors, and either having failed ASCT, or being ineligible for or not consenting to ASCT. Patients relapsing after allogeneic-HSCT will be eligible as well.**
- **Age 12 – 50 years**
- Subject has evidence of **adequate organ function** within 7 days of procurement as defined by:
  - Hemoglobin ≥ 8.0 g/dL (transfusion is allowed prior to procurement)
  - $CD3^+$ cells greater than 100/mcl
  - Total bilirubin ≤ 3 x ULN, unless attributed to Gilbert's Syndrome
  - AST ≤ 5 x ULN
  - ALT ≤ 5 x ULN
  - Creatinine ≤ 3 x ULN (adjusted value for age)
  - Estimated GFR > 30 ml/min
  - Pulse oximetry of > 90% on room air
- Imaging results from within 90 days prior to procurement to assess presence of active disease
- Patients receiving previous allogeneic stem cell transplantation are eligible only if 100 days have elapsed from the procedure, in the absence of graft-versus-host disease and must be not receiving any immune suppressive treatment
- Clinical performance status. Patients > 16 years of age: Karnofsky ≥ 60%; Patients ≤ 16 years of age: Lansky scale ≥ 60%

OPBG CD30.CAR-T product

Main exclusion criteria

- Pregnant or lactating woman
- **Severe, uncontrolled active bacterial, viral and fungal infections**, including HIV, or active HCV (<12 weeks between achievement of a sustained virological response to the specific treatment and apheresis) and/or HBV infection (either positive for Hepatitis B core antibody [HBcAb] or positive hepatitis B surface antigen [HBsAg] AND NAT tests), defined according to the American Association for the Study of Liver Diseases guidelines.
- **Concurrent or recent prior therapies, before apheresis**:
  - Systemic steroids (at a dose equivalent to or greater than 0,5 mg/kg/day prednisone) in the 2 weeks before apheresis collection. Recent or current use of inhaled/topical/non-absorbable steroids is not exclusionary.
  - Systemic chemotherapy in the previous 2 weeks preceding apheresis collection
  - Radiation therapy must have been completed at least 2 weeks prior to apheresis
  - **Anti-CD30 drug-conjugate antibody in the previous 7 days preceding apheresis collection and/or in the previous 6 weeks prior to LDP**
  - Checkpoint inhibitors in the previous 30 days preceding apheresis collection
  - Other anti-neoplastic investigational agents currently or within 30 days prior to start of protocol activities (i.e. before enrollment)
- Exceptions:
  - subjects receiving steroid therapy at physiologic replacement doses only are allowed, provided there has been no increase in dose for at least 2 weeks prior to apheresis.
  - there is no time restriction with regard to prior intrathecal chemotherapy, provided that there is complete recovery from any acute toxic effects of such.
- **Lymphocyte collection lower than 1 x 10^9 mononuclear cells will not be processed**

Conclusions

- CD30-targeting CAR T cells are overall well tolerated and demonstrate anti-lymphoma activity when infused following lymphodepleting therapy
- Prolonged hematologic toxicity and skin rashes are specific and significant adverse events
- Fludarabine-containing lymphodepletion seems to improve response rates
- Characterization of the CD30 expression lymphomas relapsing after a CD30-targeting therapy is of great relevance
- CD30 CAR T cells offer a valuable alternative treatment option for R/R cHL and CD30+ T-cell lymphomas, as pre-ASCT bridging therapy or for post-ASCT relapse prevention
- We are going to activate a Phase I trial with a third generation, retroviral construct in 3 academic Italian Institutions