

# CAR-T Cells in Hodgkin Lymphoma

Carlos A. Ramos *et al.*

Professor of Medicine

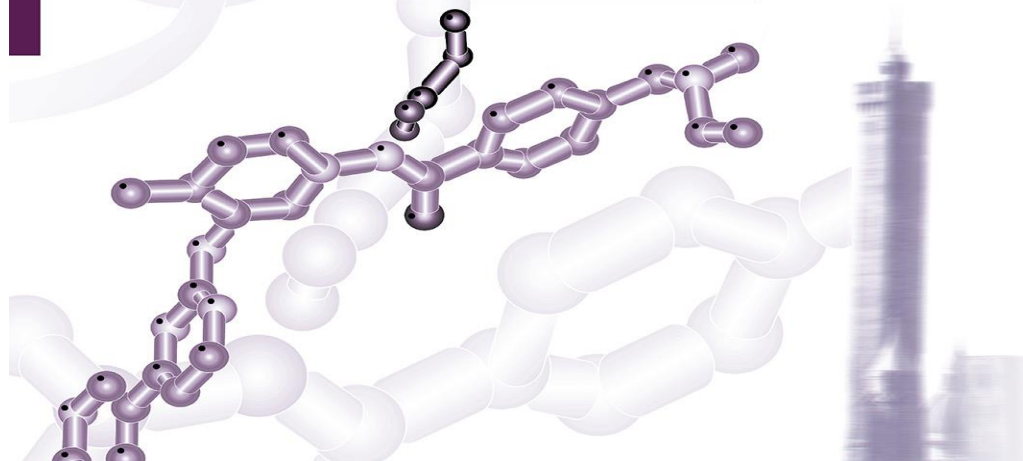




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UNIVERSITÀ DI BOLOGNA  
DIPARTIMENTO DI MEDICINA SPECIALISTICA  
DIAGNOSTICA E SPERIMENTALE

POLICLINICO DI  
**SANT'ORSOLA**

SERVIZIO SANITARIO REGIONALE  
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Azienda Ospedaliero - Universitaria di Bologna



# New Drugs in Hematology

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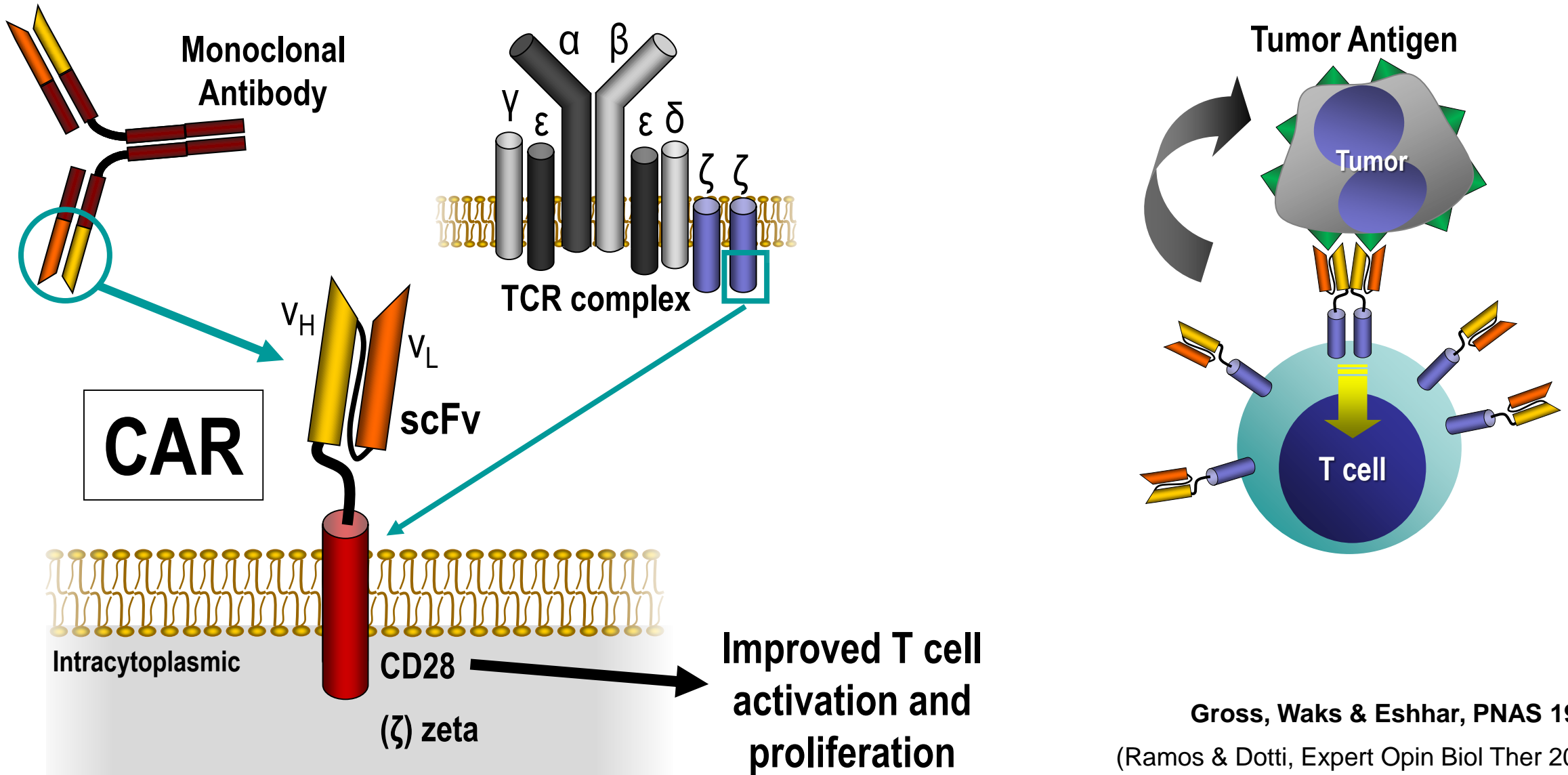
Bologna,  
Royal Hotel Carlton

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## Disclosures of CARLOS RAMOS

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis						✓	
Genentech			✓				
Tessa Therapeutics	✓						✓
Athenex, Inc.	✓						
CRISPR Therapeutics			✓				

# Chimeric Antigen Receptors

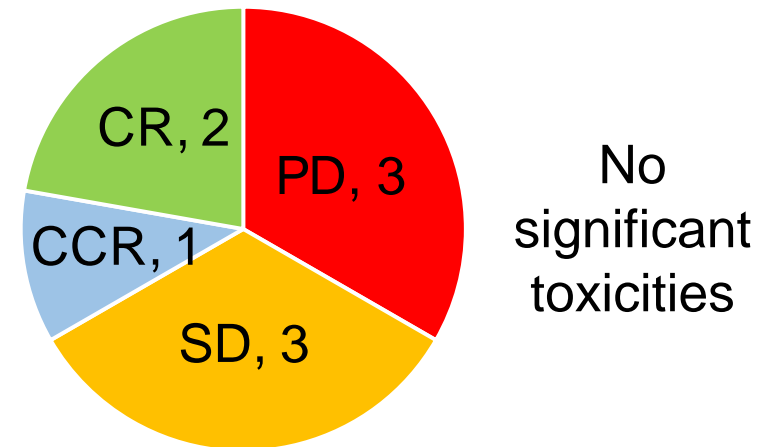
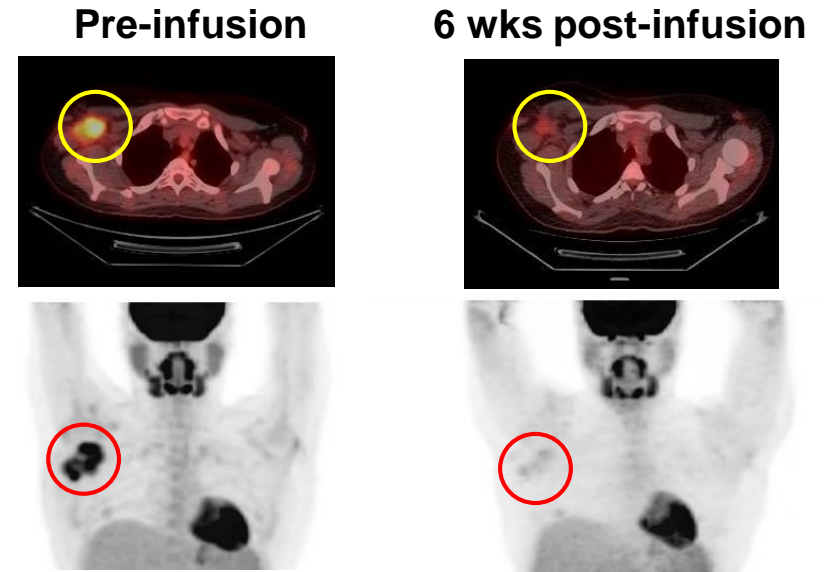
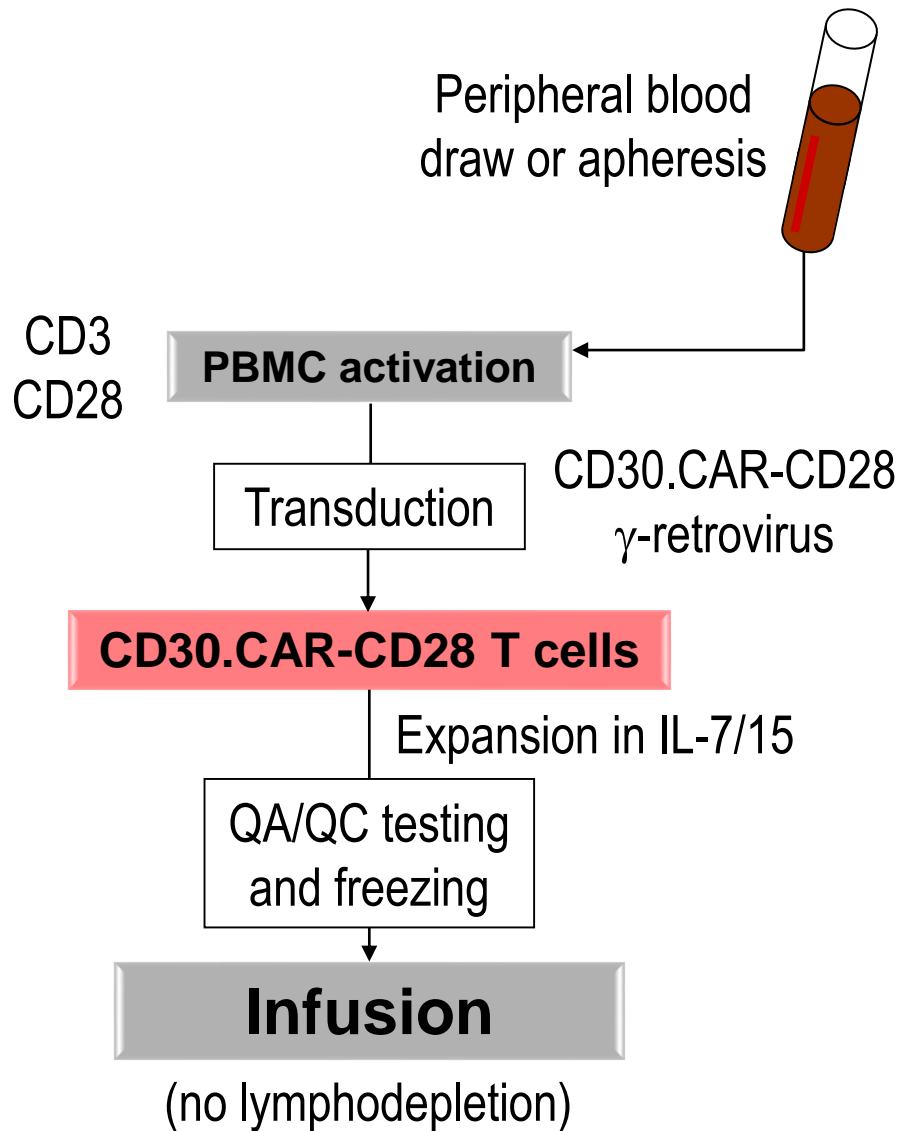


Gross, Waks & Eshhar, PNAS 1989  
(Ramos & Dotti, Expert Opin Biol Ther 2011)

# Targeting CD30 with a CAR

- CD19-specific (and BCMA) CAR-T cells are highly successful against B-cell NHL and ALL (and myeloma)
- Adequate targets for other disorders have been more difficult to define
- CD30 has been validated as an immune target (e.g. brentuximab vedotin)
- A CD30-specific CAR (CD30.CAR) has activity in pre-clinical models of HL (Hombach, Ca Res 1998; Savoldo, Blood 2007)

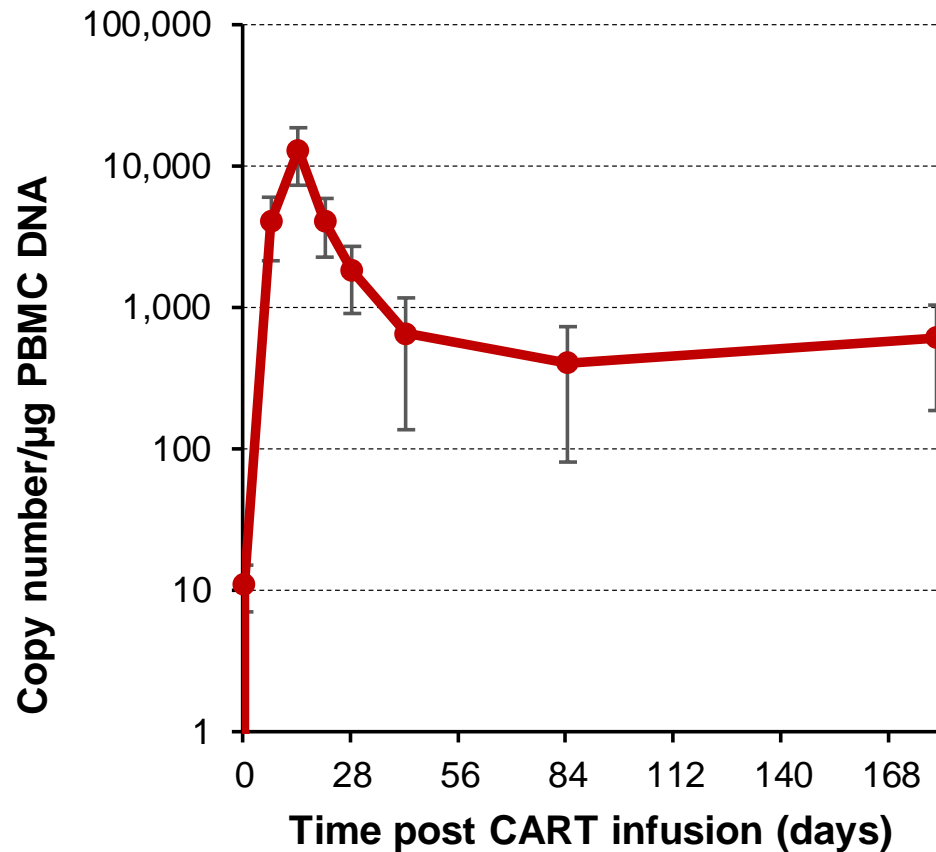
# CART CD30 trial (NCT01316146)



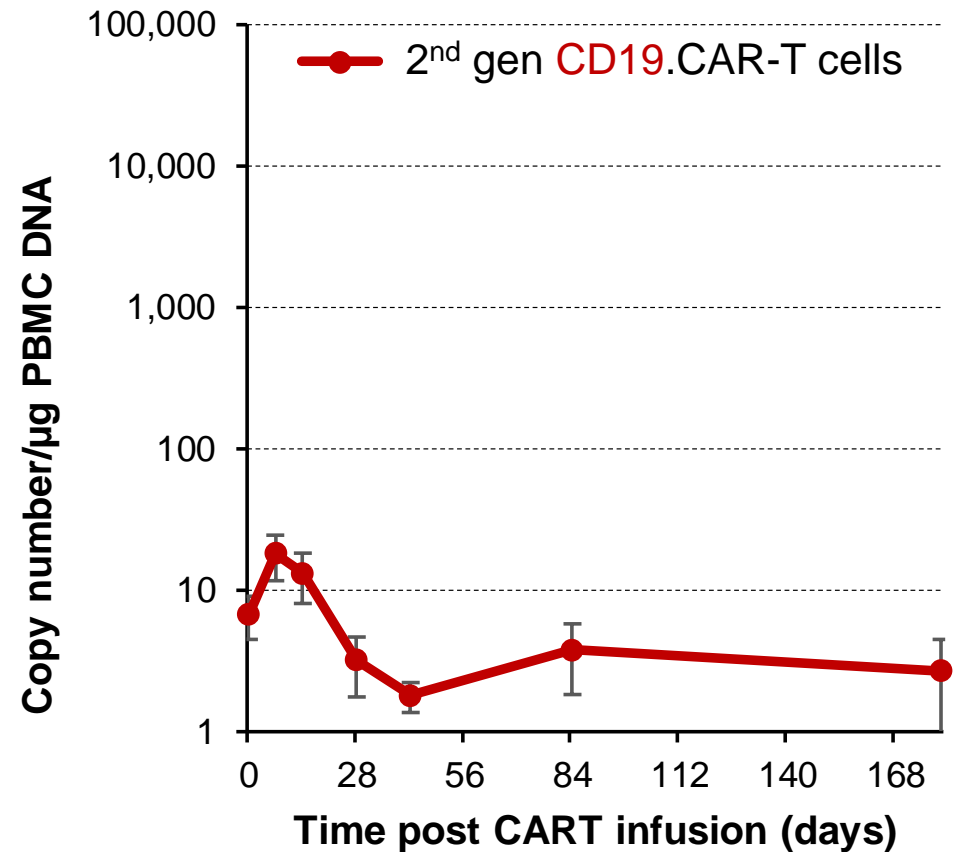
(Ramos *et al.*, J Clin Invest 2017)

# Lymphodepleting chemotherapy improves CAR-T expansion

## Cyclophosphamide + fludarabine

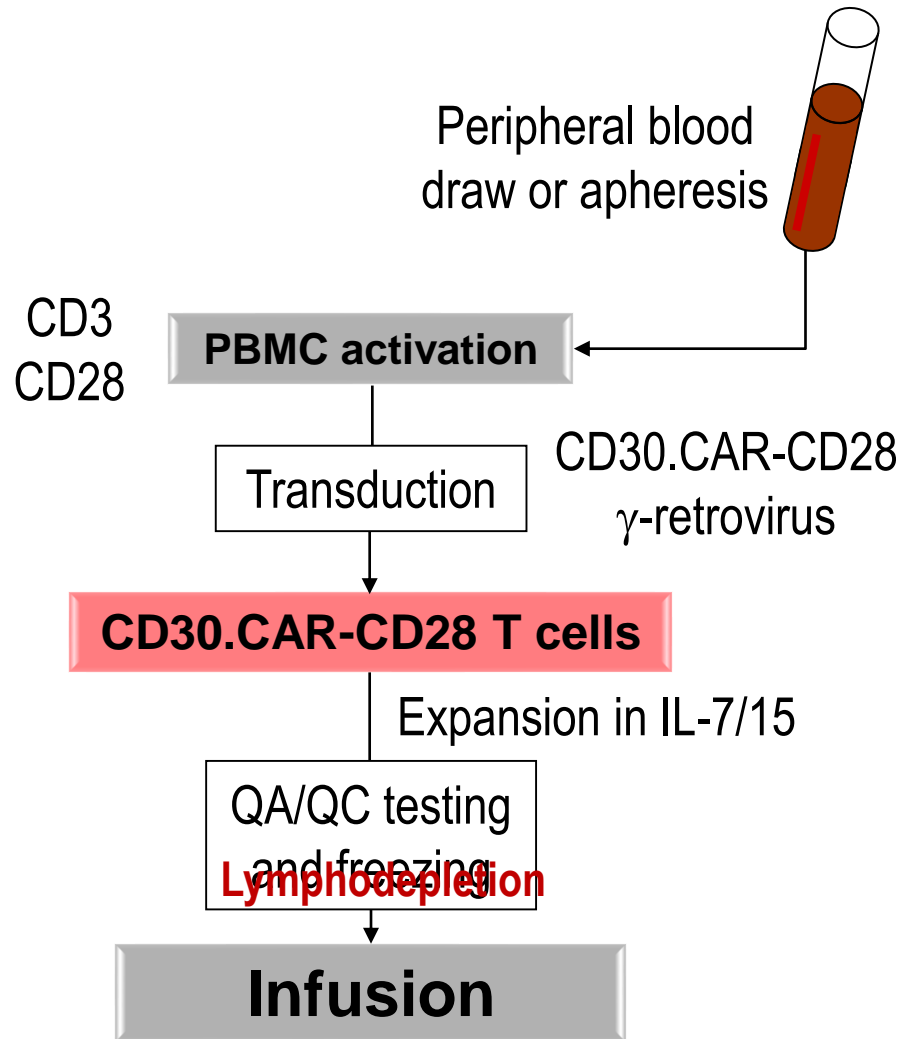


## No preceding chemotherapy



(Ramos *et al.*, Mol Ther 2018)

# ATLAS (UNC) & RELY-30 (BCM) trials



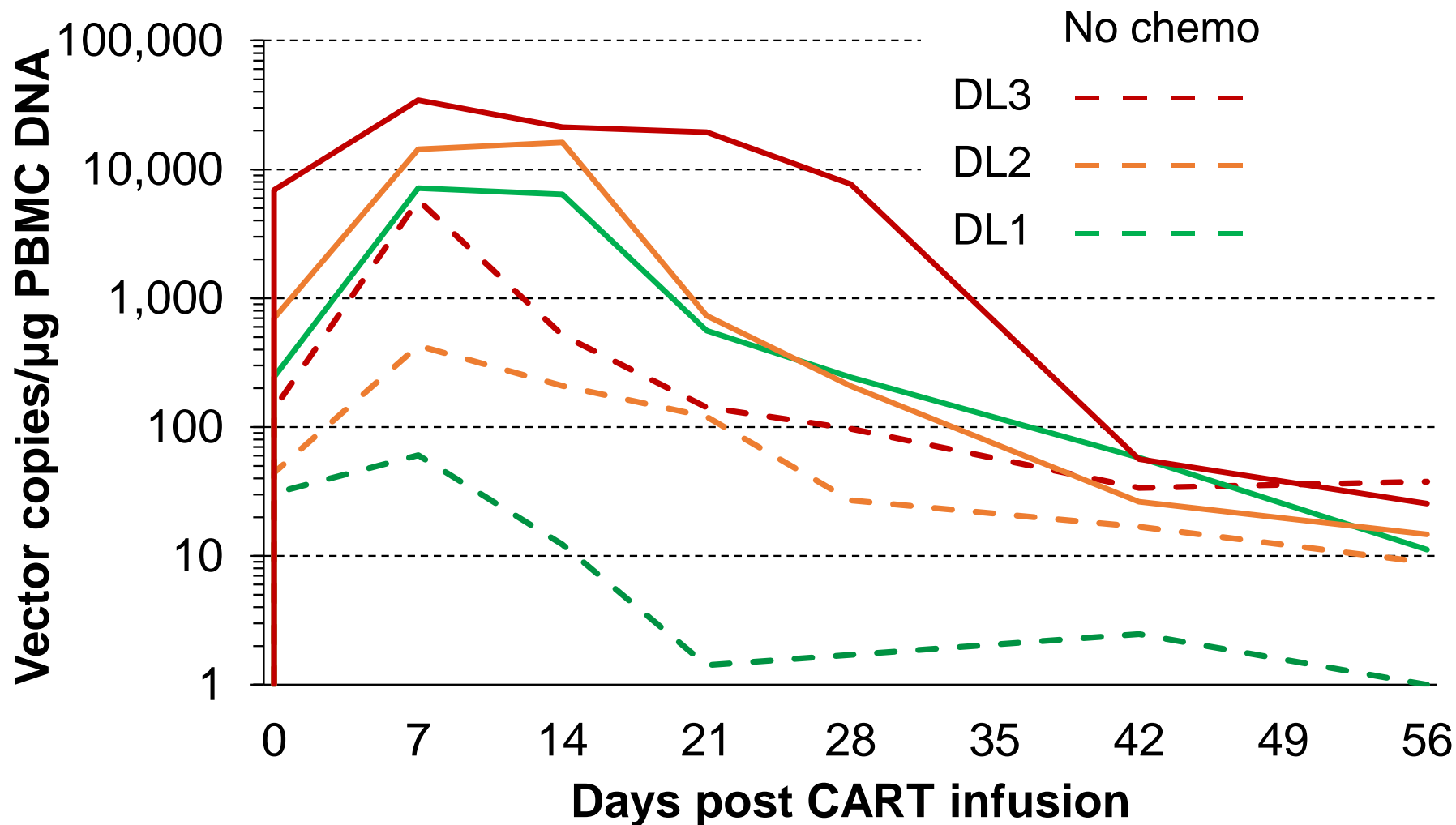
- Phase 1 trials
- CD30<sup>+</sup> malignancies
  - Active disease
  - Failure of standard treatment
- Lymphodepleting chemotherapy prior to CART infusion
  - Bendamustine ± fludarabine (UNC)
  - Cyclophosphamide + fludarabine (BCM)
- Primary objective: safety
- Secondary: response per Lugano
  - Initial assessment at week 6

# ATLAS/RELY-30 patients characteristics

- 41 HL patients
  - 13 F
  - 28 M
- Subtypes
  - NS (32)
  - MC (4)
  - “NOS” (5)
- Age
  - Median 35 yrs  
(range 17-69 yrs)
- Prior treatments
  - Median 7 regimens (range 2-23)
  - PD-1 inhibitor in 34 patients
  - Brentuximab vedotin in 38 patients
  - HDT/ASCT in 32 patients
  - Allotx in 10 patients

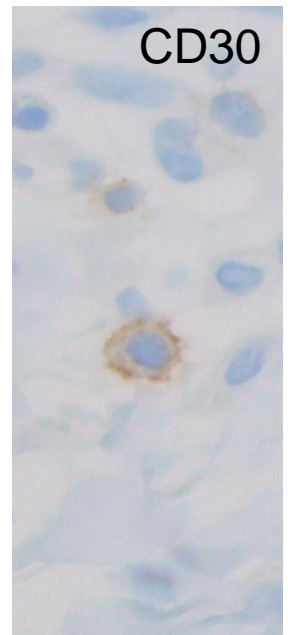
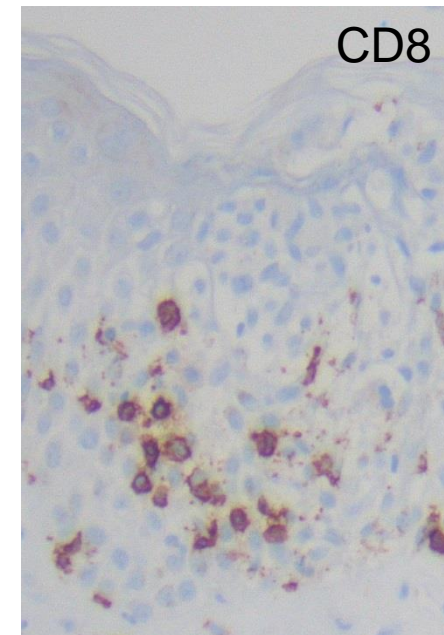
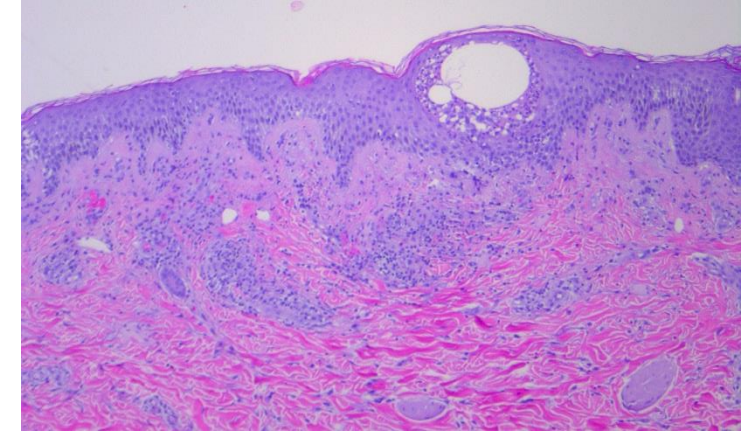


# CD30.CART expansion is increased by lymphodepleting chemotherapy



# CD30.CART main toxicities

- No neurotoxicity
- CRS in 10 pts
  - all grade 1
  - all resolved spontaneously
- Rash in 20 pts
  - all resolved spontaneously
  - 3 baseline rashes



Patient B9

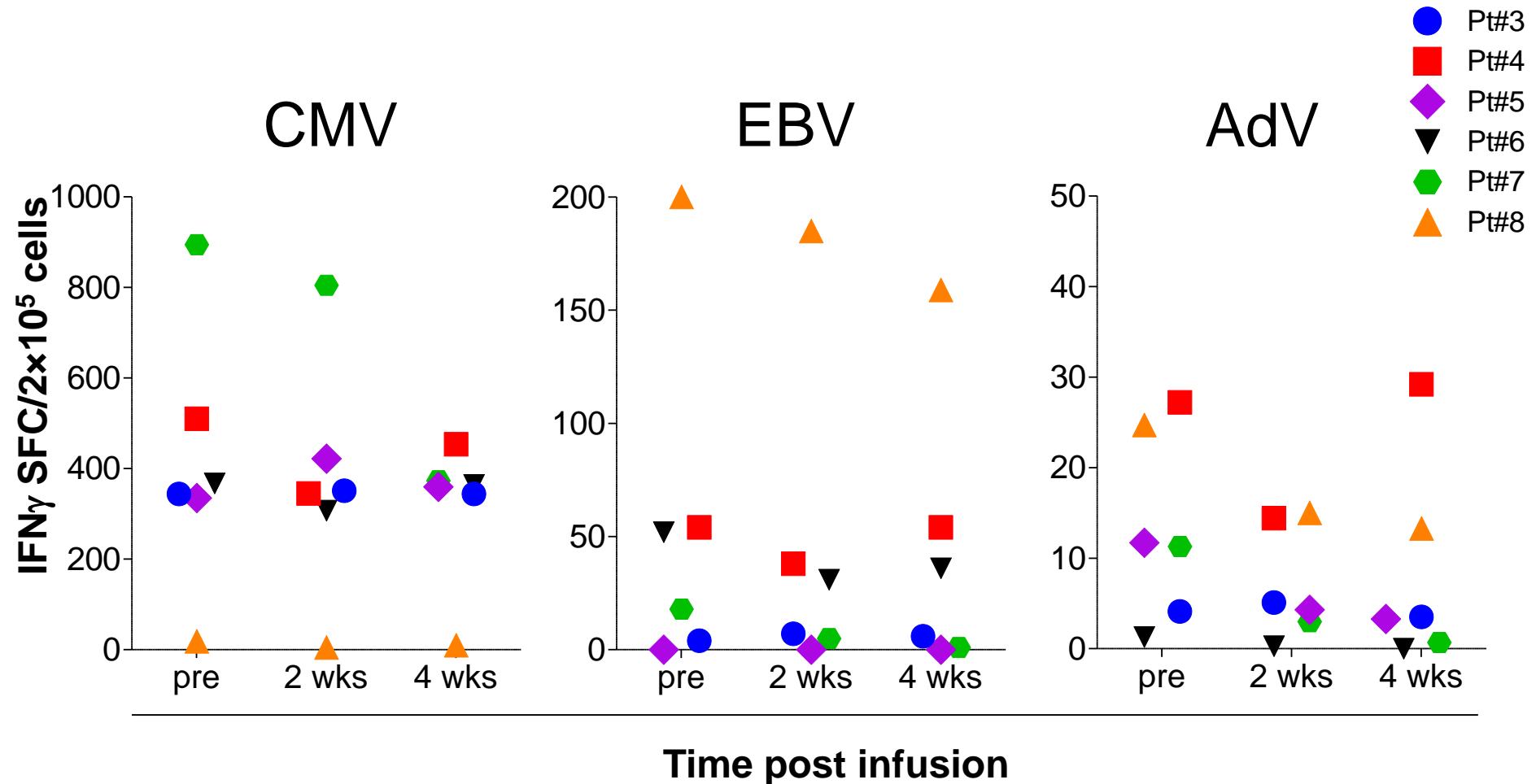
# Grade 3 or higher toxicities

<b>Toxicity (N= 42)</b>	<b>Grade 3/4 N (%)</b>	<b>Not resolved &gt;28 d N (%)</b>	<b>Not resolved &gt;3 mo N (%)</b>
<b>Lymphopenia</b>	42 (100)	-	-
<b>Neutropenia</b>	20 (48)	4 (10)	0
<b>Thrombocytopenia</b>	11 (26)	10 (24)	4 (10)
<b>Anemia</b>	5 (12)	0	0
<b>Pneumonia</b>	1 (2)	-	-
<b>Hypoalbuminemia</b>	3 (7)	-	-
<b>Hyponatremia</b>	2 (5)	-	-

# Other potential concerns related to CD30 targeting

- CD30 is preferentially and/or constitutively expressed by Th2 or Tc2 cells
  - CD30 is expressed transiently by activated T cells after exposure to cognate antigen
- ⇒ Need to ensure that CD30.CAR-T cells do not eliminate activated (viral) antigen-specific T cells in vivo:
- pre and post infusion virus-specific immune response monitoring

# Viral immunity is not compromised

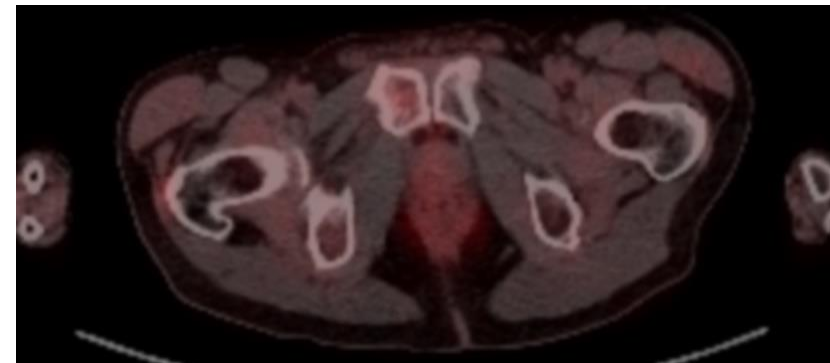
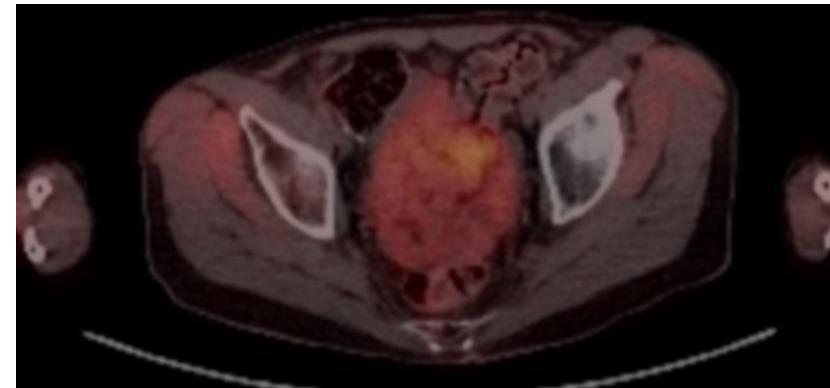
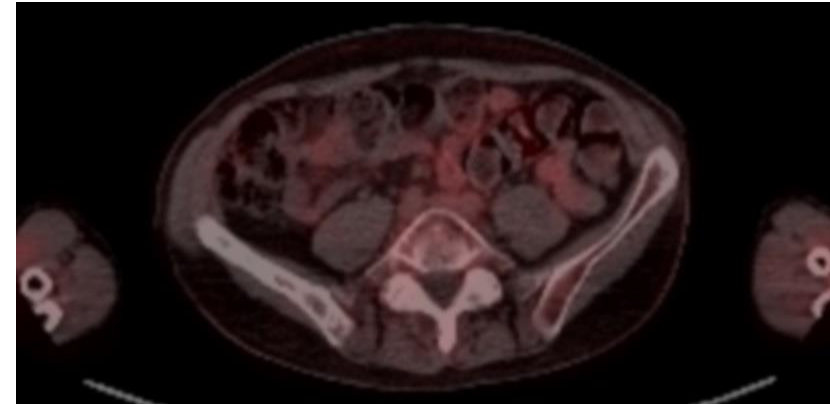
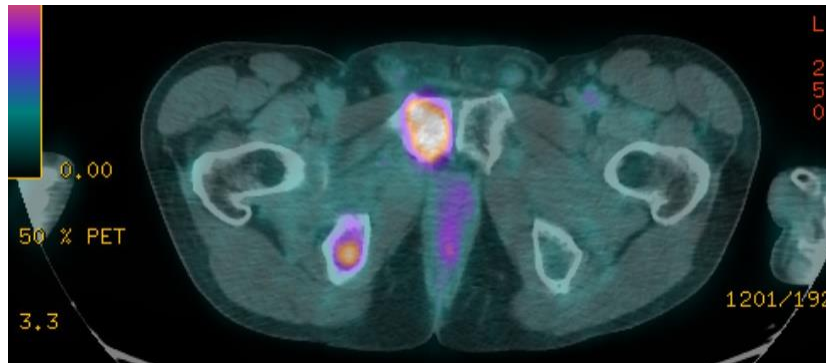
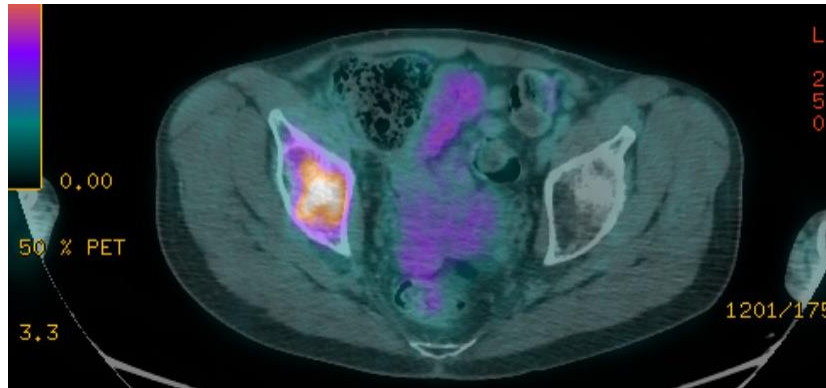
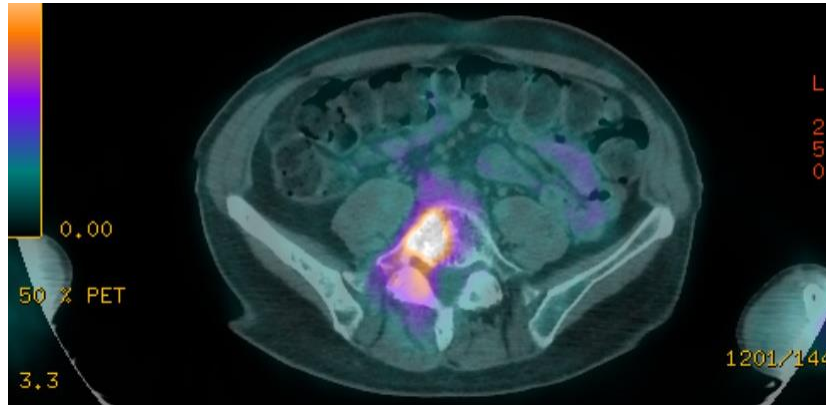


# Clinical responses in patients with measurable disease at treatment

		All patients (N = 37)	Benda (N = 5)	Flu/Benda (N = 15)	Flu/Cy (N = 17)
<b>ORR: N (%)</b>	<b>CR + PR</b>	22 (59%)	0 (0%)	12 (80%)	11 (65%)
<b>RR: N (%)</b>	<b>CR</b>	19 (51%)	0 (0%)	11 (73%)	8 (47%)
	<b>PR</b>	4 (11%)	0 (0%)	1 (7%)	3 (18%)
	<b>SD</b>	4 (11%)	1 (20%)	1 (7%)	2 (11%)
	<b>PD</b>	8 (27%)	4 (80%)	2 (13%)	4 (24%)

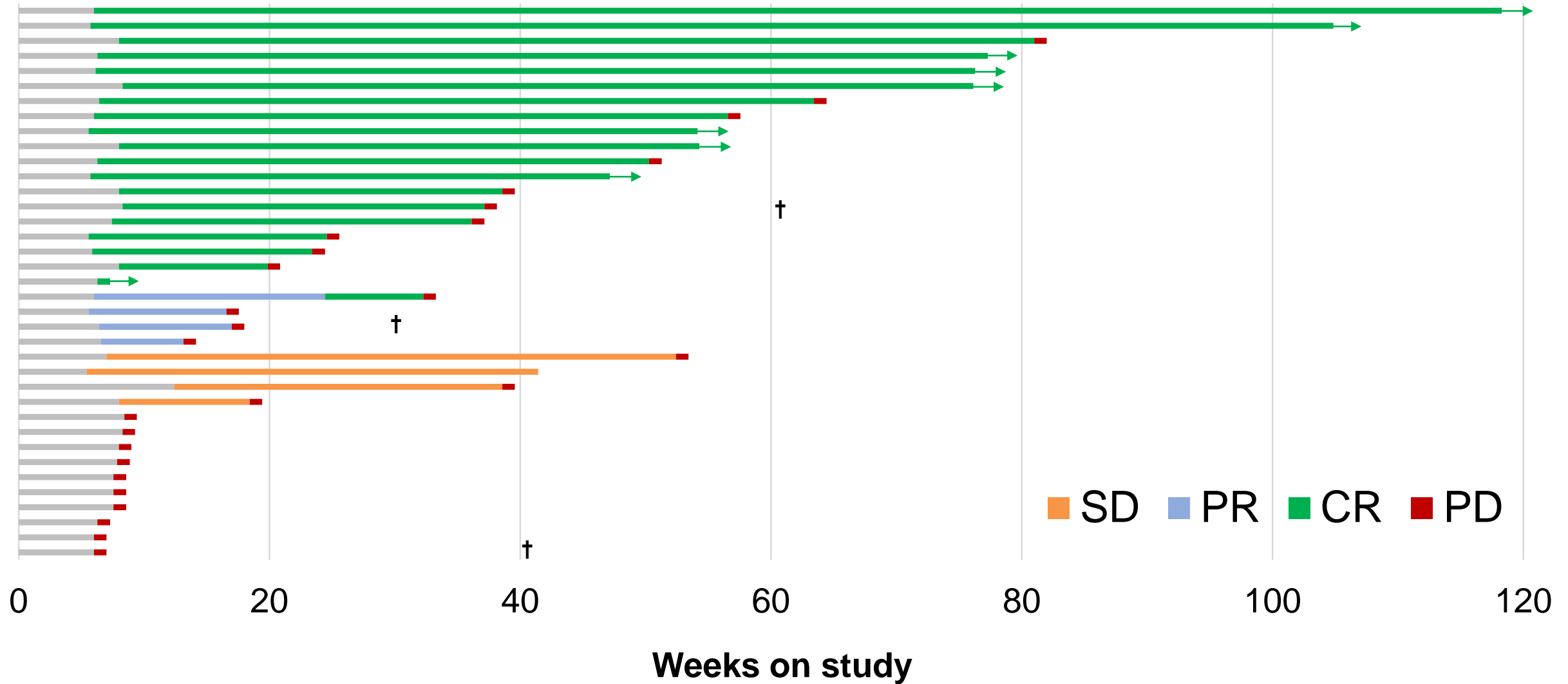
# CD30.CART tumor response (patient #B1)

**Pre-  
infusion**



**6 wks  
post-  
infusion**

# ATLAS & RELY-30 outcomes





# CHARIOT (NCT04268706) trial

## Study Population

Patients with R/R cHL:

- 12-75 years old
- Failed  $\geq 3$  lines of therapy including:
  - Chemotherapy
  - Brentuximab vedotin,<sup>@</sup> and
  - PD-1 inhibitor<sup>@</sup>

May have received an autologous or allogeneic stem cell transplant

## Study Treatment

(Pilot: n = >12,  
Pivotal: n = 82)

### LD (3 days)\*

- Fludarabine 30 mg/m<sup>2</sup>/day
- Bendamustine 70 mg/m<sup>2</sup>/day

### CD30.CAR-T#

Allowable dose range:  
2.0-2.7 x 10<sup>8</sup> cells/m<sup>2</sup>

## Endpoints

### Primary

- Pilot: Safety
- Pivotal: ORR

### Secondary

- Pilot:  
ORR, DOR,  
PFS, OS, HRQoL
- Pivotal:  
Safety, DOR,  
PFS, OS, HRQoL

# CHARIOT interim results

Response Assessments (N = 14)		By IRRC N (%)	By Investigators N (%)
ORR (CR+PR)		10 (71.4)	13 (92.9)
Best Overall Response	CR	8 (57.1)	6 (42.9)
	PR	2 (14.3)	7 (50.0)
	SD	1 (7.1)	1 (7.1)
	PD	3 (21.4)	0 (0)

(data courtesy of Ivan Horak, Tessa Therapeutics, ASH 2021)

# Conclusions & Future directions

- Adoptive transfer of autologous CD30.CAR-T cells is feasible, safe and clinically effective
- Expansion and persistence is dose-dependent
- Responses are improved with lymphodepleting chemotherapy
- Increased expansion may be associated with CRS and limited skin toxicity
- Confirmatory multicenter phase 1/2 trial ongoing
- Allogeneic phase 1 trial ongoing...

# Grazie!

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## **QA**

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## ***NGVL for RCR***

## **All patients**

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