10th POSTGRADUATE
Lymphoma
Conference

Has the dream of having effective CAR-Ts for HL faded?

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President:
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Disclosures

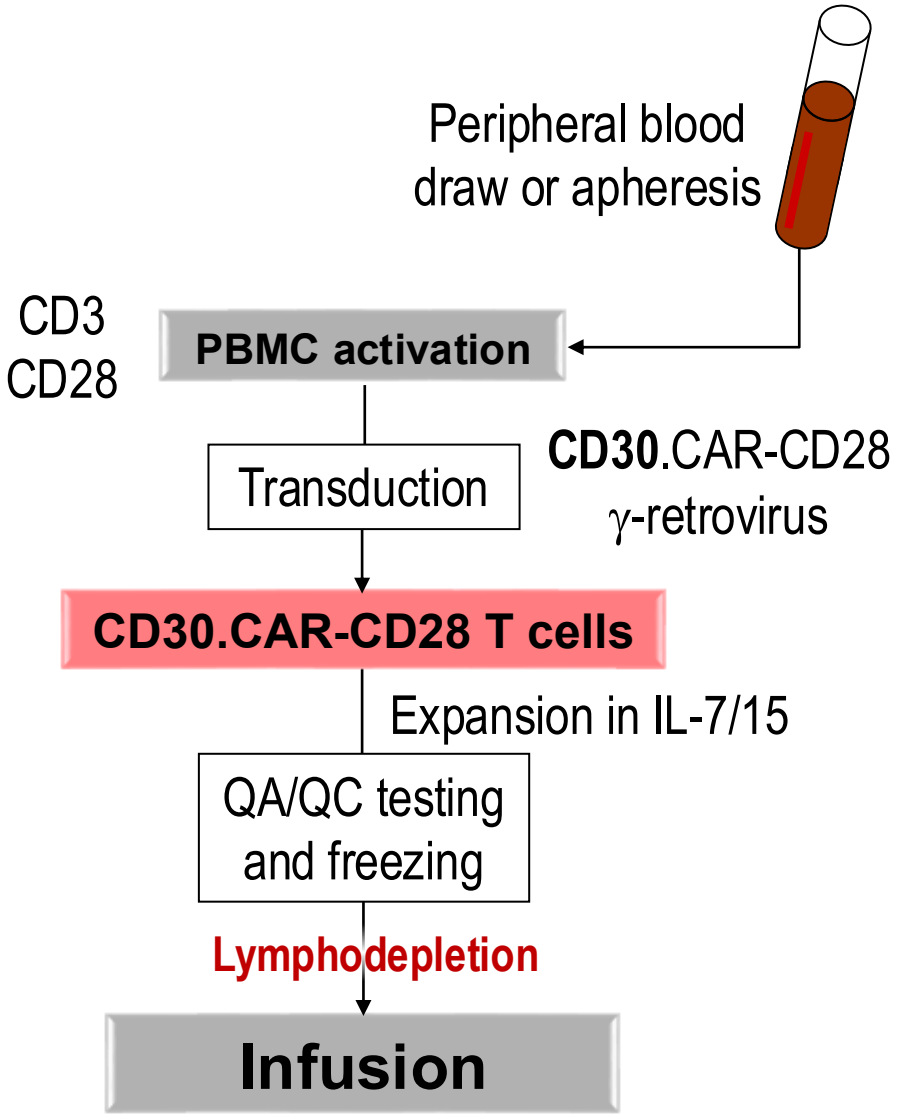
Disclosures of Carlos A. Ramos

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Tessa Therapeutics	×						
Athenex, Inc.	×						

Targeting CD30 in HL 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)

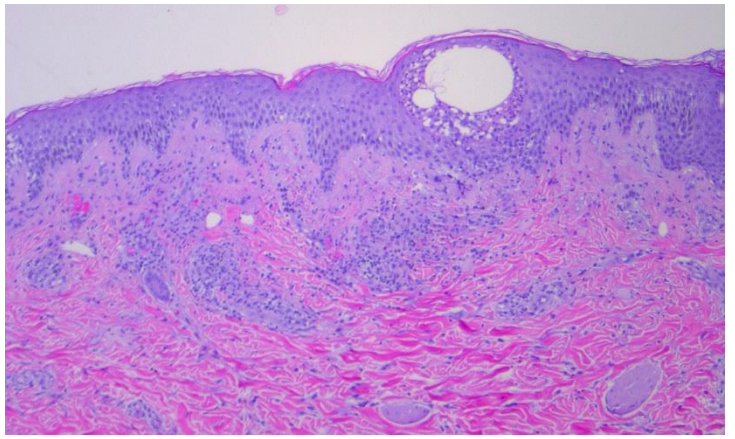
ATLAS (UNC) & RELY-30 (BCM) trials

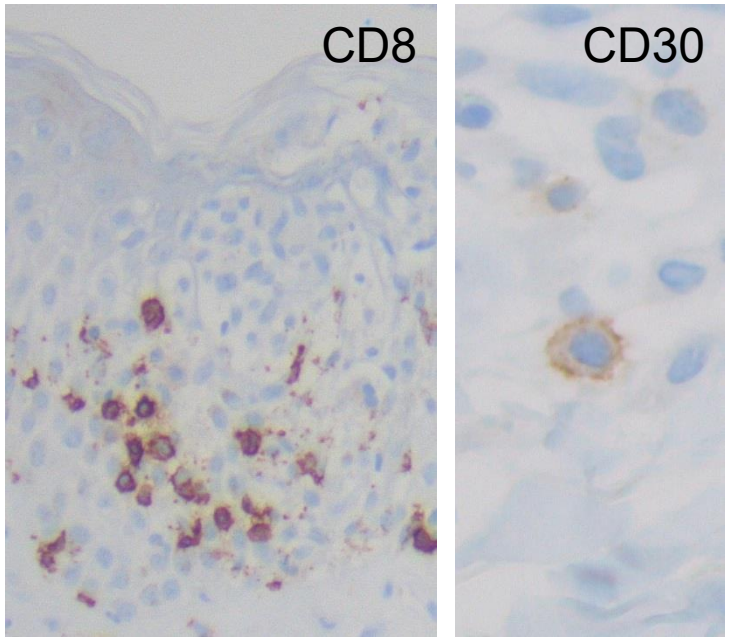


- 41 enrollments
- Gender
  - 13 F, 28 M
- Diagnoses
  - Hodgkin lymphoma (41)
    - Nodular sclerosis (32)
    - Mixed cellularity (4)
    - "NOS" (5)
- Median age 35 yrs (range 17-69)
- Median 7 prior treatments (range 2-23)
  - PD-1 inhibitor (34), brentuximab vedotin (38), HDT/ASCT (32), allo-SCT (10)

Autologous 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





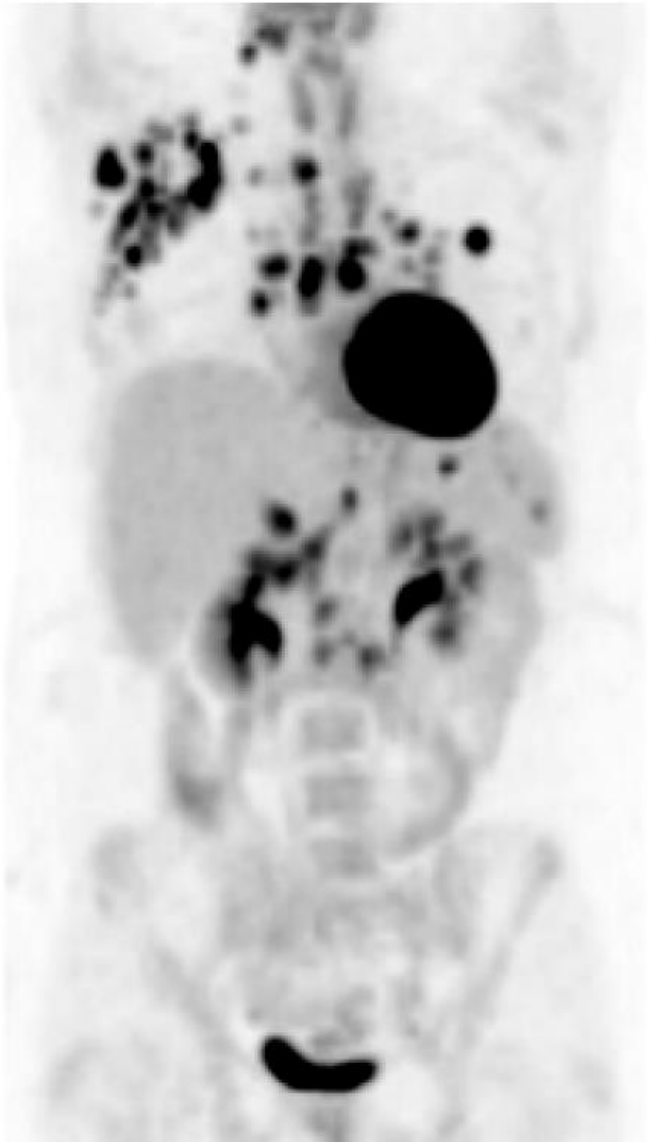
Patient B9

Grade 3 or higher toxicities

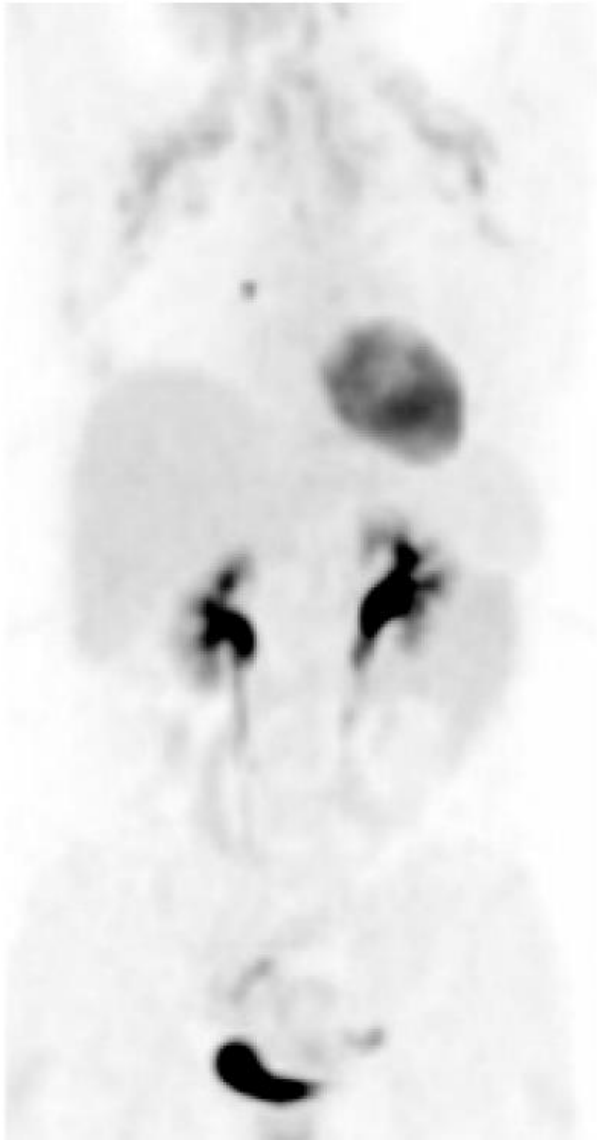
Toxicity (N= 42)	Grade 3/4 N (%)	Not resolved >28 d N (%)	Not resolved >3 mo N (%)
Lymphopenia	42 (100)	-	-
Neutropenia	20 (48)	4 (10)	0
Thrombocytopenia	11 (26)	10 (24)	4 (10)
Anemia	5 (12)	0	0
Pneumonia	1 (2)	-	-
Hypoalbuminemia	3 (7)	-	-
Hyponatremia	2 (5)	-	-

Response to autologous CD30.CART

Pre-infusion

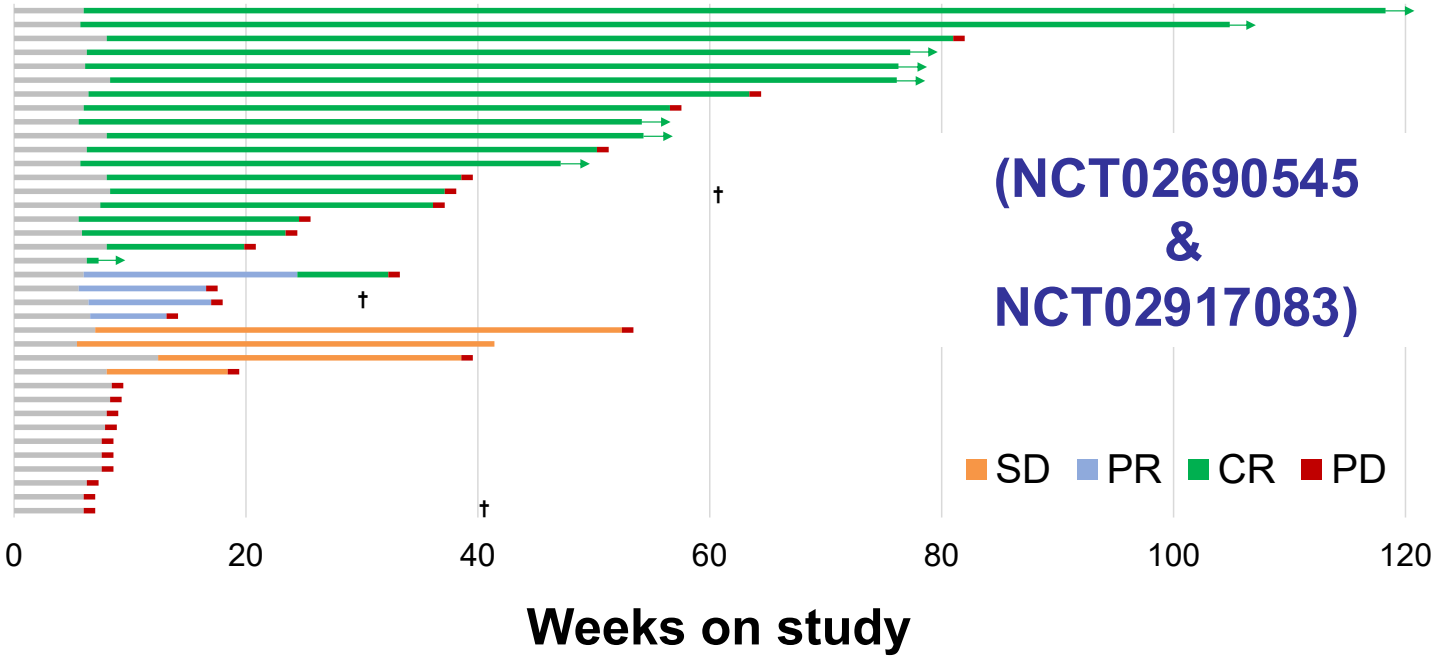


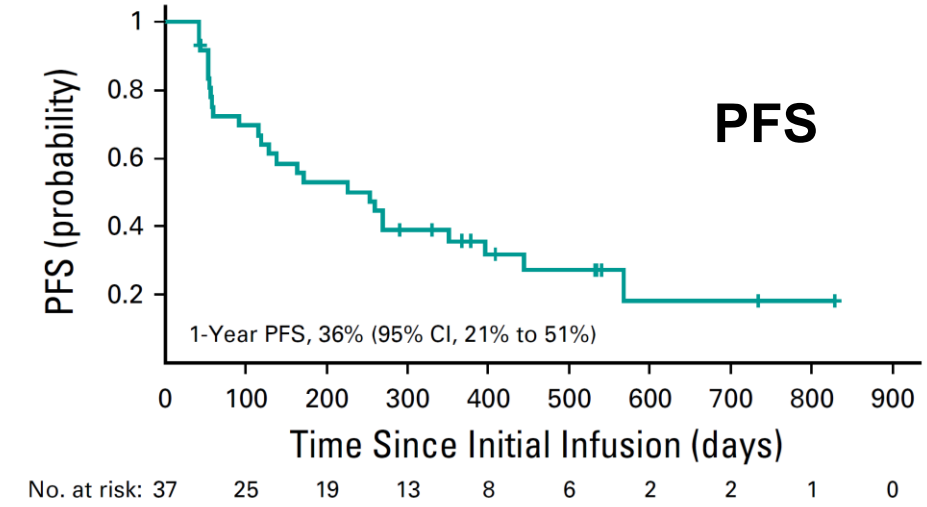
6 wks post-infusion

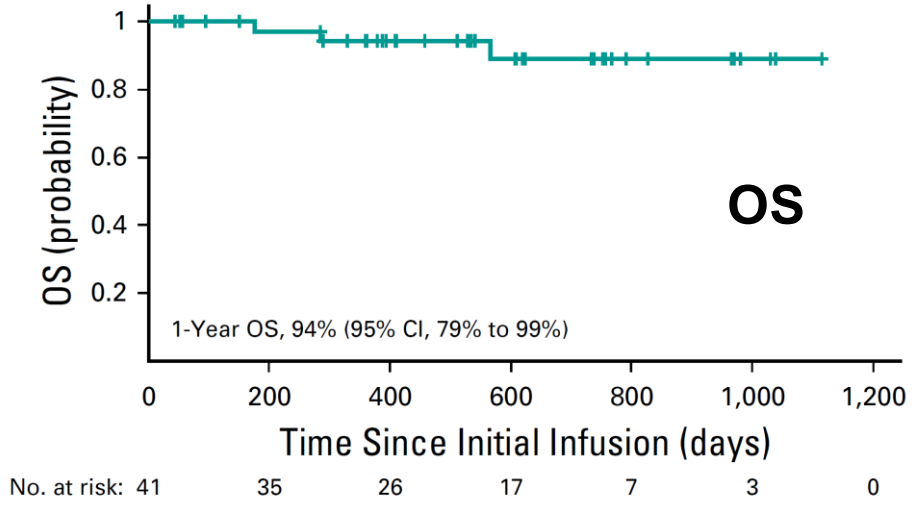


Autologous CD30.CAR-T cells in HL (BCM/UNC)

- With optimal lymphodepletion:
  - 72% overall response rate
  - 59% complete responses





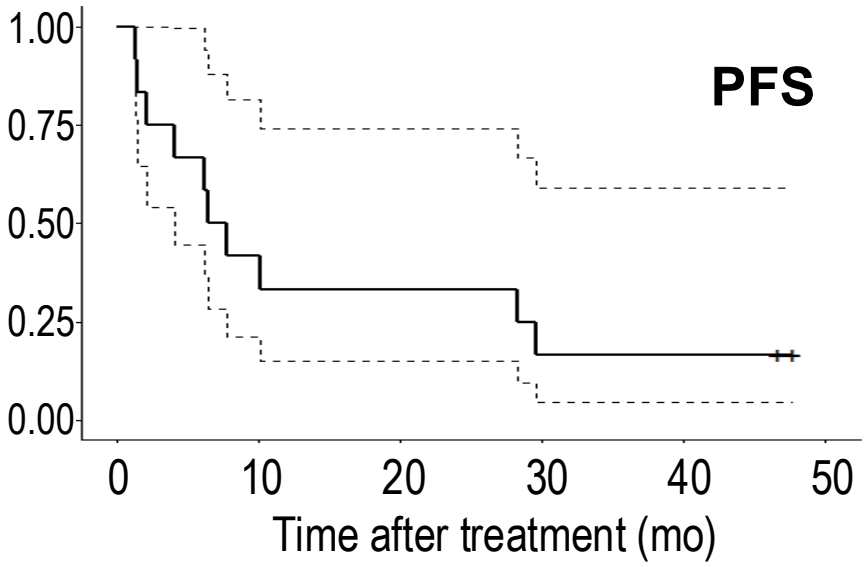


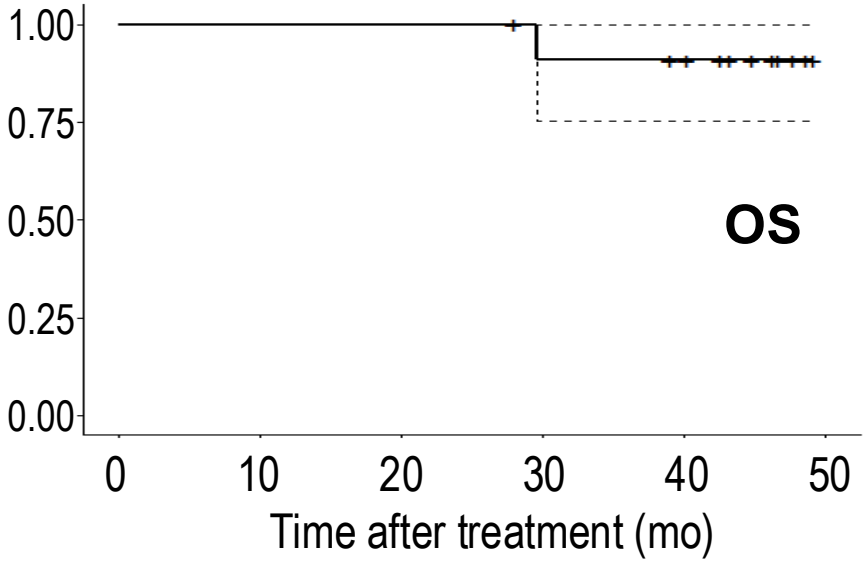
(Ramos, Grover *et al.*, J Clin Oncol 2020)

Long term follow-up of CHARIOT trial (NCT04268706)

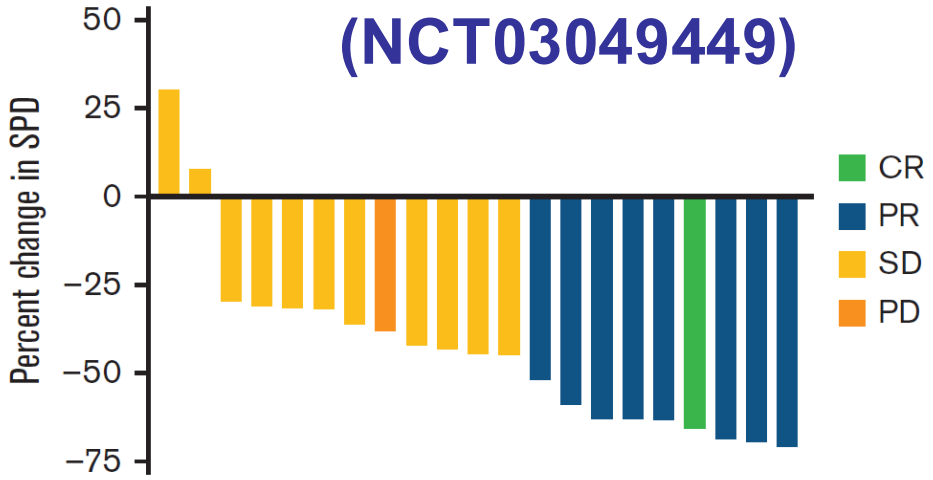
Response (data available for 12 pt)	N (%)
Objective response rate (ORR)	9 (75%)
Complete remission (CR)	6 (50%)
Partial response (PR)	3 (25%)
Median duration of response (range)	8.8 months (2.7–45.3 months)

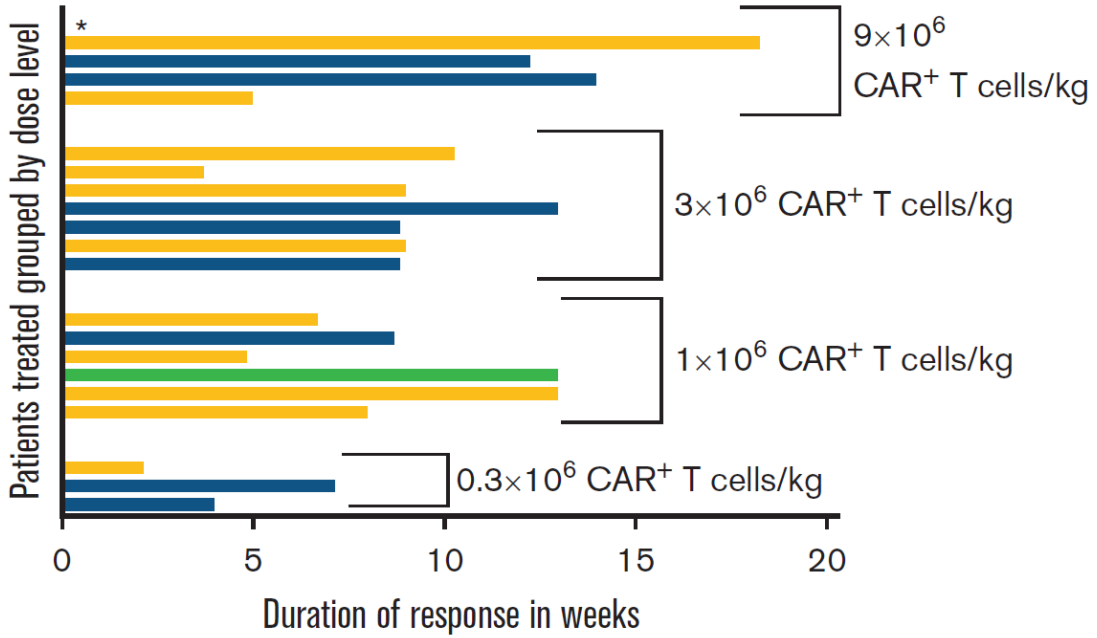
(Ahmed *et al.*, ASH 2025)





Experience at NIH, Bethesda



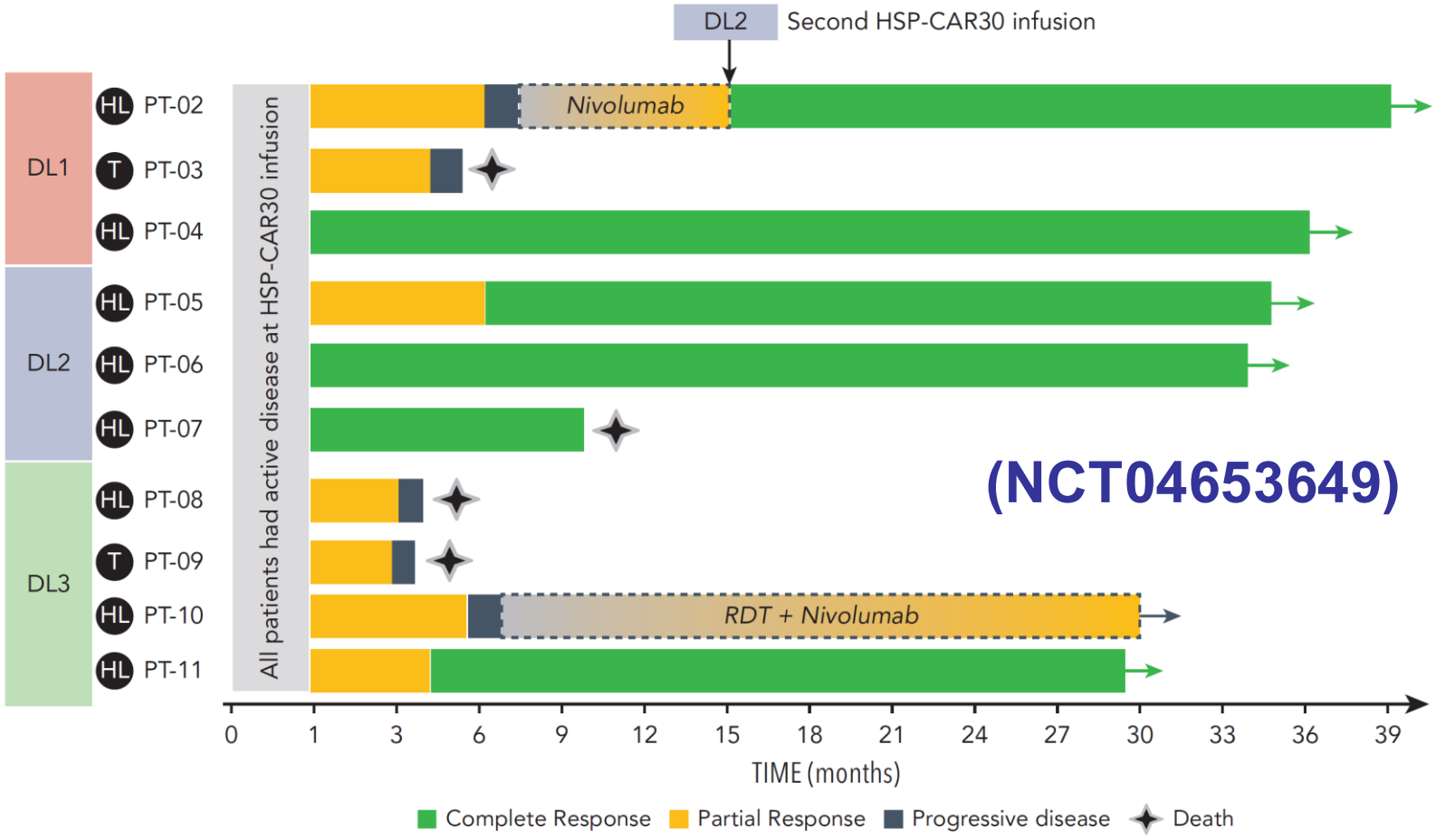


- 20 HL patients treated in phase 1 trial
- More toxicities, 2 dose-limiting:
  - 9 patients had rash, but 2 required prolonged steroid course
  - 5 had grade 3-4 cytopenias, with 2 complicated by life-threatening sepsis
- ORR 43%,CRR 5%, median DOR ~9 wks
- Further development was discontinued

(Brudno *et al.*, Blood Adv 2024)

Experience at H. Sant Pau, Barcelona

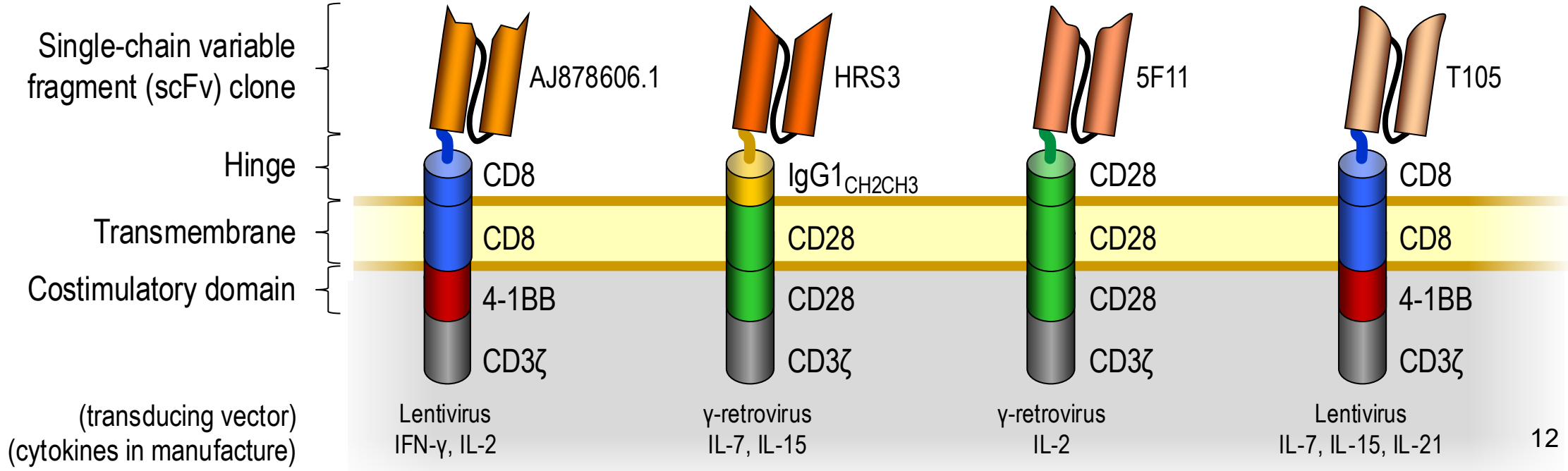
- 8 HL patients
  - Fresh product
  - Less “differentiated” CARTs (IL-21 in culture)
  - More bendamustine
- Limited toxicity
- ORR 100%, CRR 63%
- All complete responses ongoing after a mean follow-up of 34 months



(Caballero *et al.*, Blood 2025)

Autologous CD30.CART studies in cHL

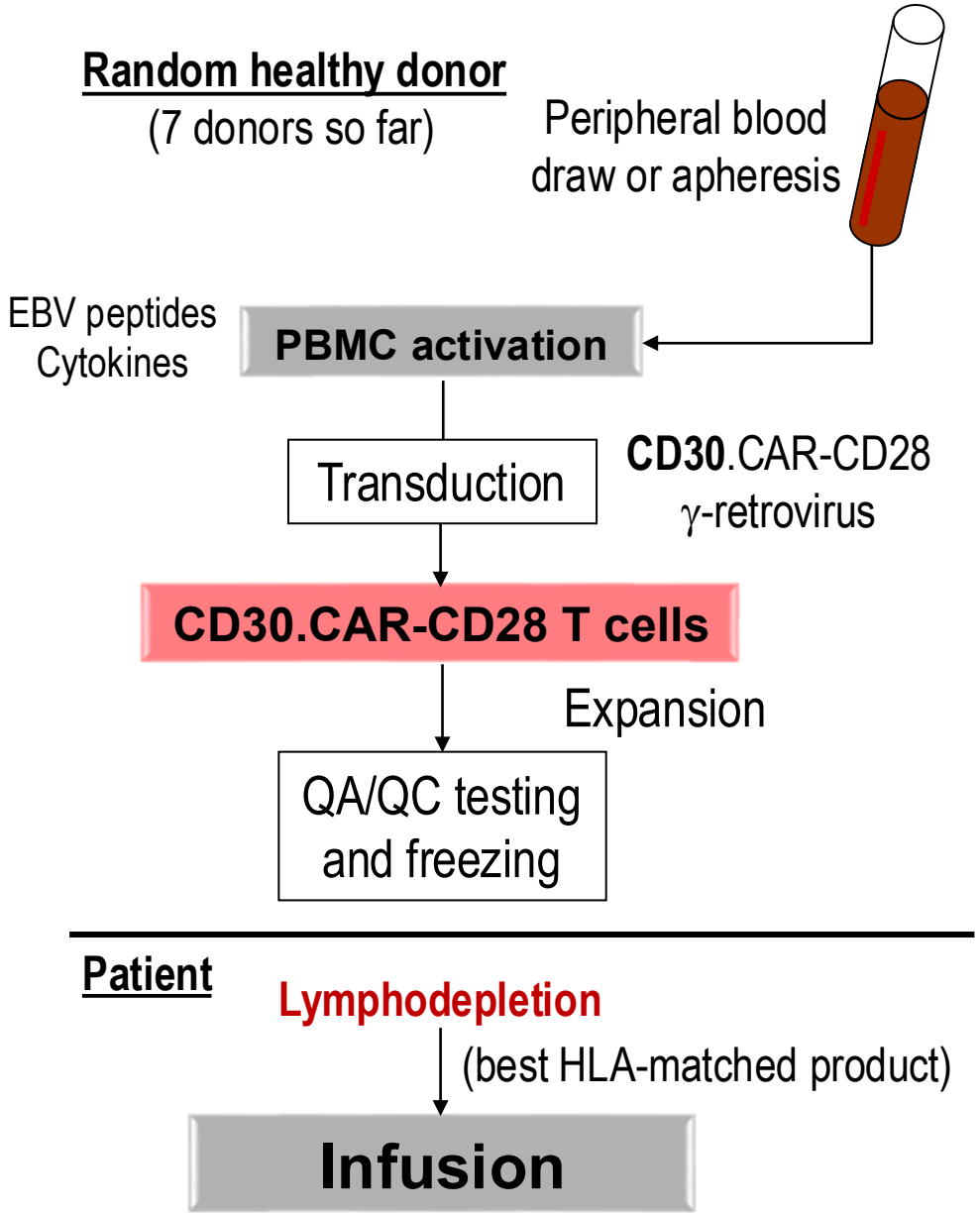
Study (year)	Wang *et al.* (2017)	Ramos *et al.* (2021)	Brudno *et al.* (2024)	Caballero *et al.* (2025)
Number of HL patients	17	42	20	8
Median age (range)	31 (13-55)	35 (17-69)	33 (18-64)	46 (21-63)
ORR | CR (%)	35 | 0	72 | 59	43 | 5	100 | 63
G3+ CRS | ICANS (%)	0 | 0	0 | 0	1 | 0	0 | 0
Other toxicities	Transient cytopenias	Transient rash Cytopenias	Rash requiring therapy Longer cytopenias	Transient rash Cytopenias, Infections



Allogeneic CD30.CAR-EBVSTs instead?

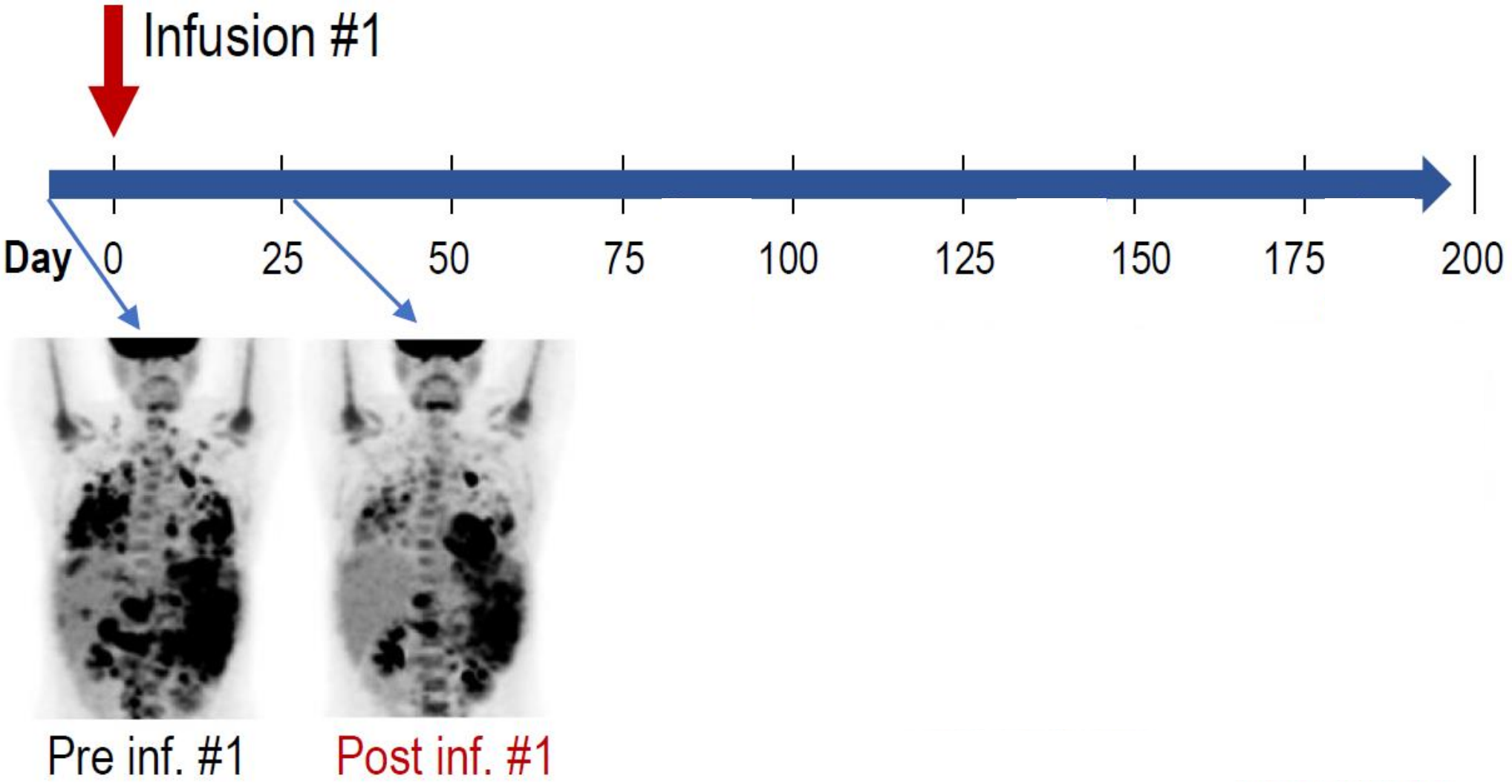
- Manufactured from healthy individuals; readily available
- Allogeneic EBV-specific T cells (EBVSTs) are safe in SCT and non-SCT recipients (Heslop, Sharma, Rooney, JCO 2021)
  - Many patients treated in several trials without GVHD
- Activated T cells express CD30
  - Recipient T cells reacting against donor CAR-T cells may be killed by CD30.CAR-T cells
- May avoid GVHD and be protected from rejection

BESTA clinical trial (NCT04288726)



- 26 enrollments (23 patients)
- Gender
  - 10 F, 13 M
- Diagnoses
  - Hodgkin lymphoma (21)
    - Nodular sclerosis (19)
    - Mixed cellularity (2)
  - Composite/gray zone lymphoma (2)
- Median age 35 yrs (range 22-62)
- Median 5 prior treatments (range 3-8)
  - PD-1 inhibitor (21), brentuximab vedotin (23), HDT/ASCT (12), allo-SCT (2), CD30.CAR-EBVST (3)

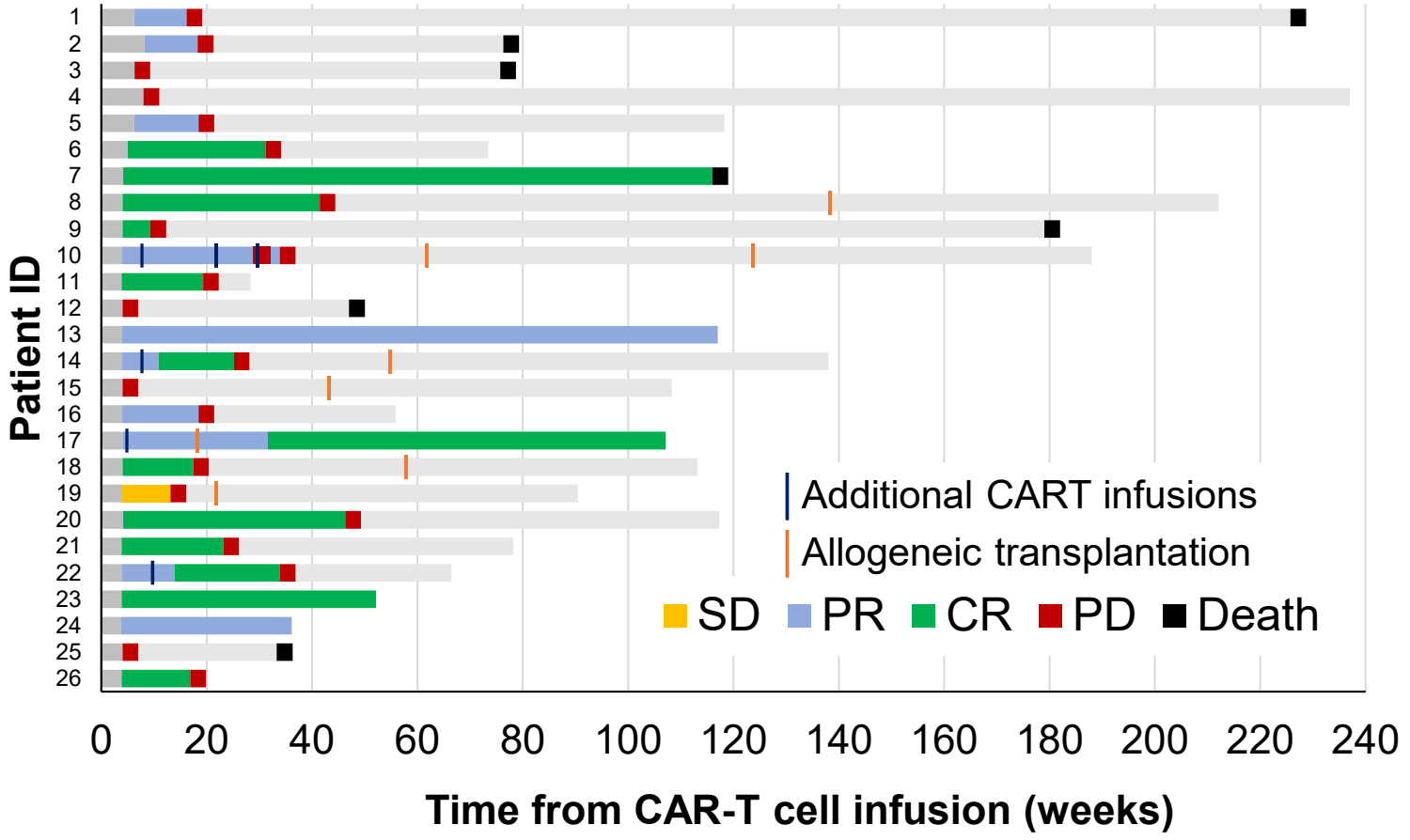
Response to allogeneic CD30.CARTs



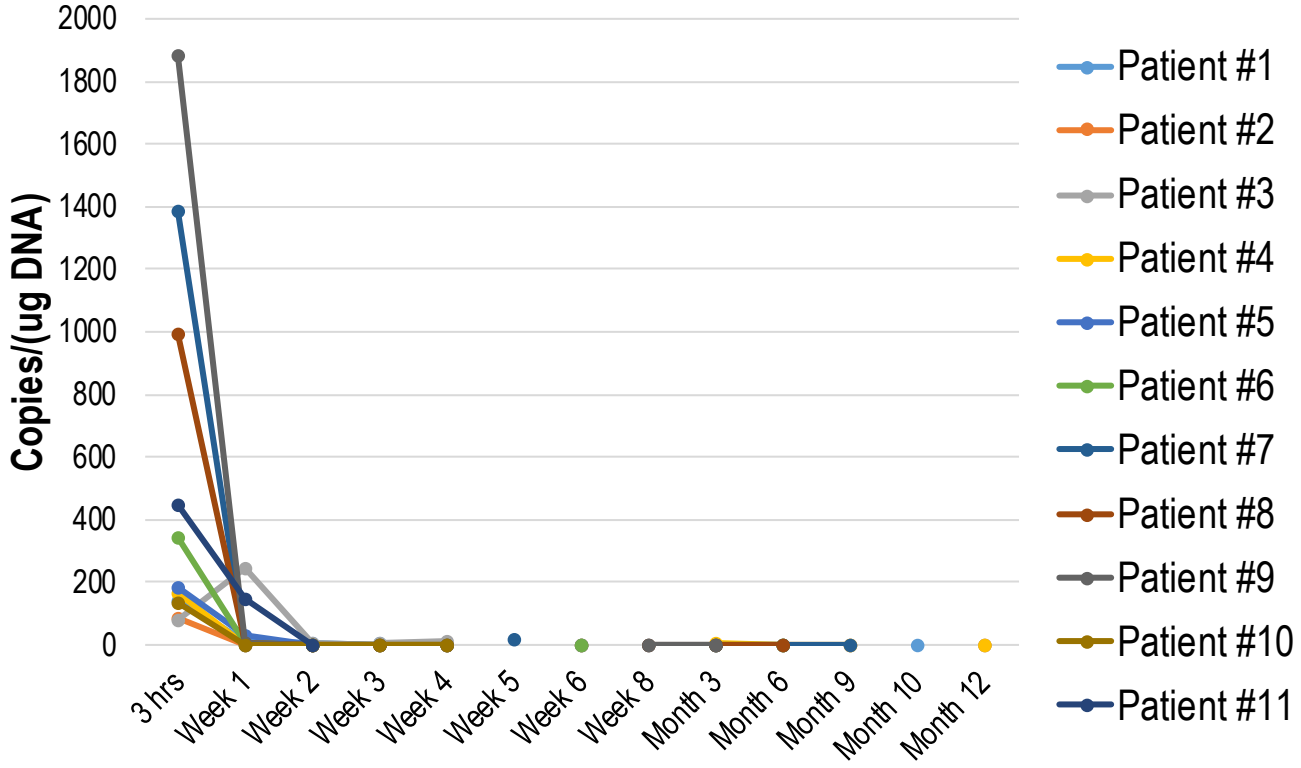
Allo CD30.CAR-EBVST safety & response data

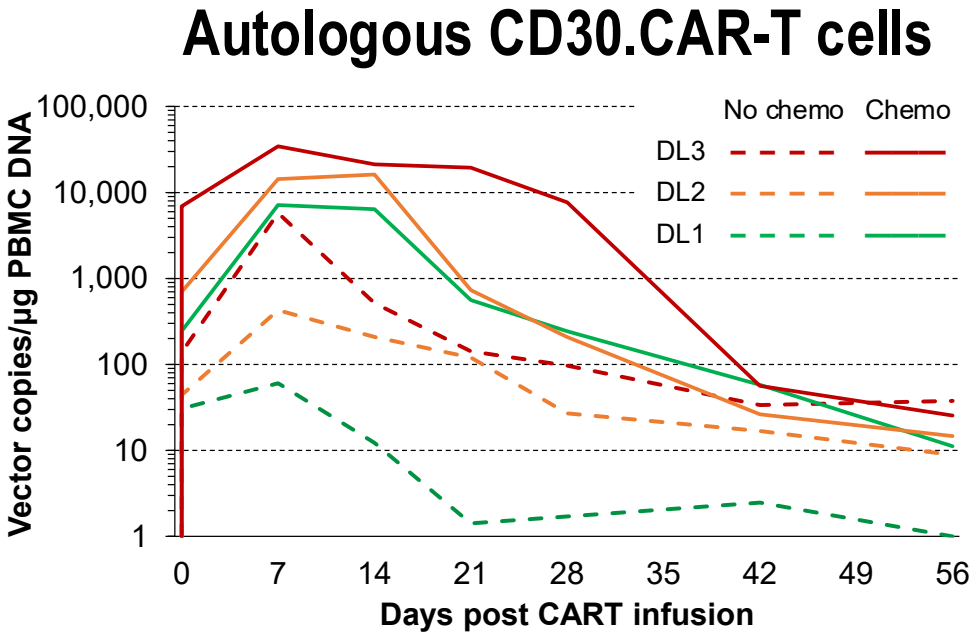
- No GVHD
  - Median 2 HLA matches
  - Range 1-7
- 9 episodes of CRS
  - All grade 1
- No ICANS
- Other AEs:
  - Mostly cytopenia due to chemo
    - 2 prolonged thrombocytopenias

77% ORR (20/26), 46% CR (12/26)



Allogeneic CD30.CAR-EBVSTs have limited persistence in peripheral blood

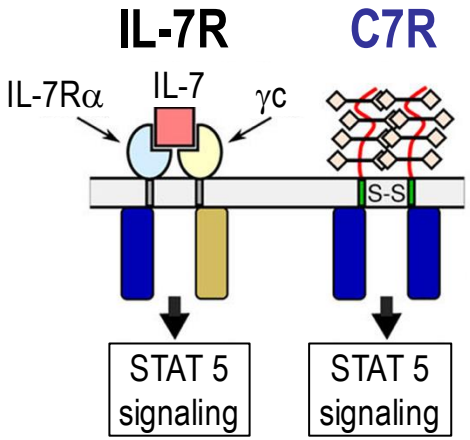




Ramos CA, *et al.* JCI (2017) & JCO (2020)

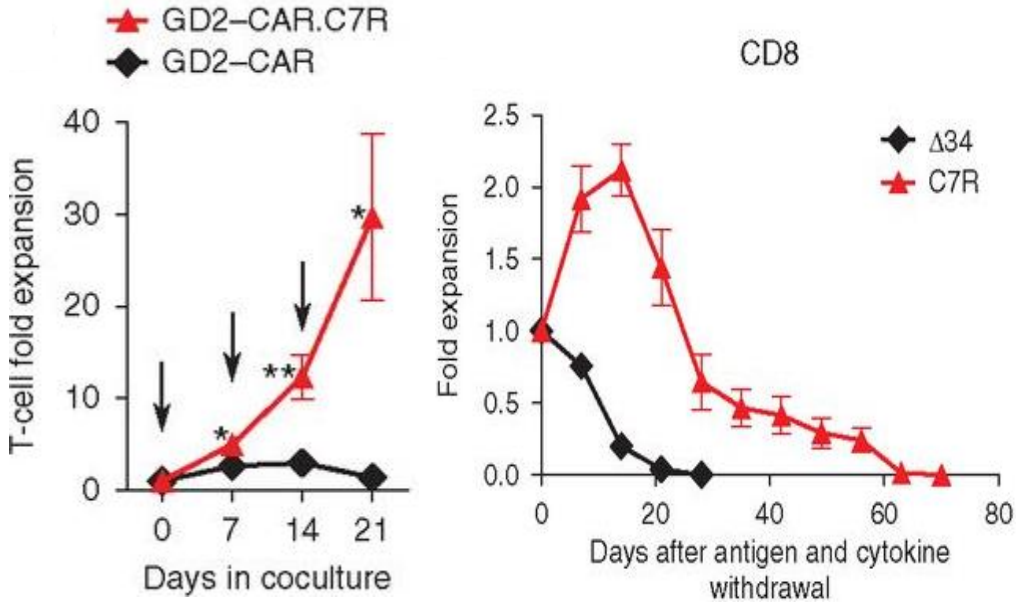
- Most patients show rapid loss of CD30.CAR EBVSTs in blood compared to autologous CD30.CAR-T cells with median DOR of ~24 vs 44 weeks
- Strategies to improve persistence are being developed:
  - E.g., constitutively active IL7 receptor expression in EBVSTs

Constitutive IL-7R in CD30.CAR-EBVSTs



Ectodomain
CD34
Transmembrane
IL-7Rα w/ S-S bridge
Endodomain
IL-7Rα

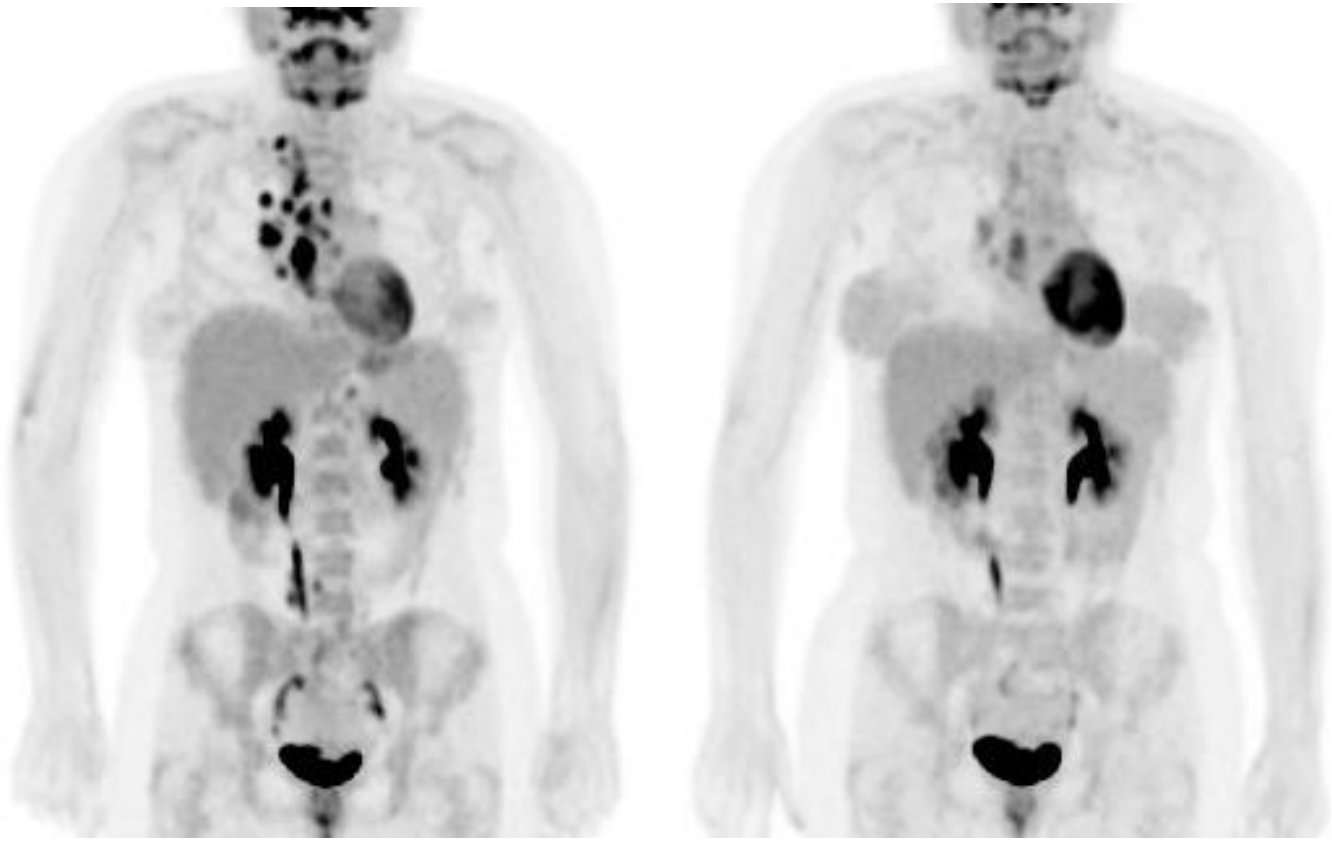
(wild type)



(Shum *et al.*, Cancer Discov 2017)

CABAL2 trial (NCT06176690)

Pre-infusion **6 wks post-infusion**



Conclusions

- Adoptive transfer of autologous and allogeneic CD30.CARTs is feasible, safe, and potentially clinically effective in HL
  - CRS and ICANS limited; maculopapular rash is seen often
- However, overall results are worse than those seen with autologous CD19.CART in NHL
  - Though some products may have better activity
- But has the dream of having effective CAR-Ts faded? I hope not…
  - Cellular immune therapy seems to work for HL, but how can we develop it?
    - Industry? Academia? Hybrid model?
  - Additional strategies are being explored to improve these results
  - But more patients and longer follow-up will be needed for validation

Grazie!

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