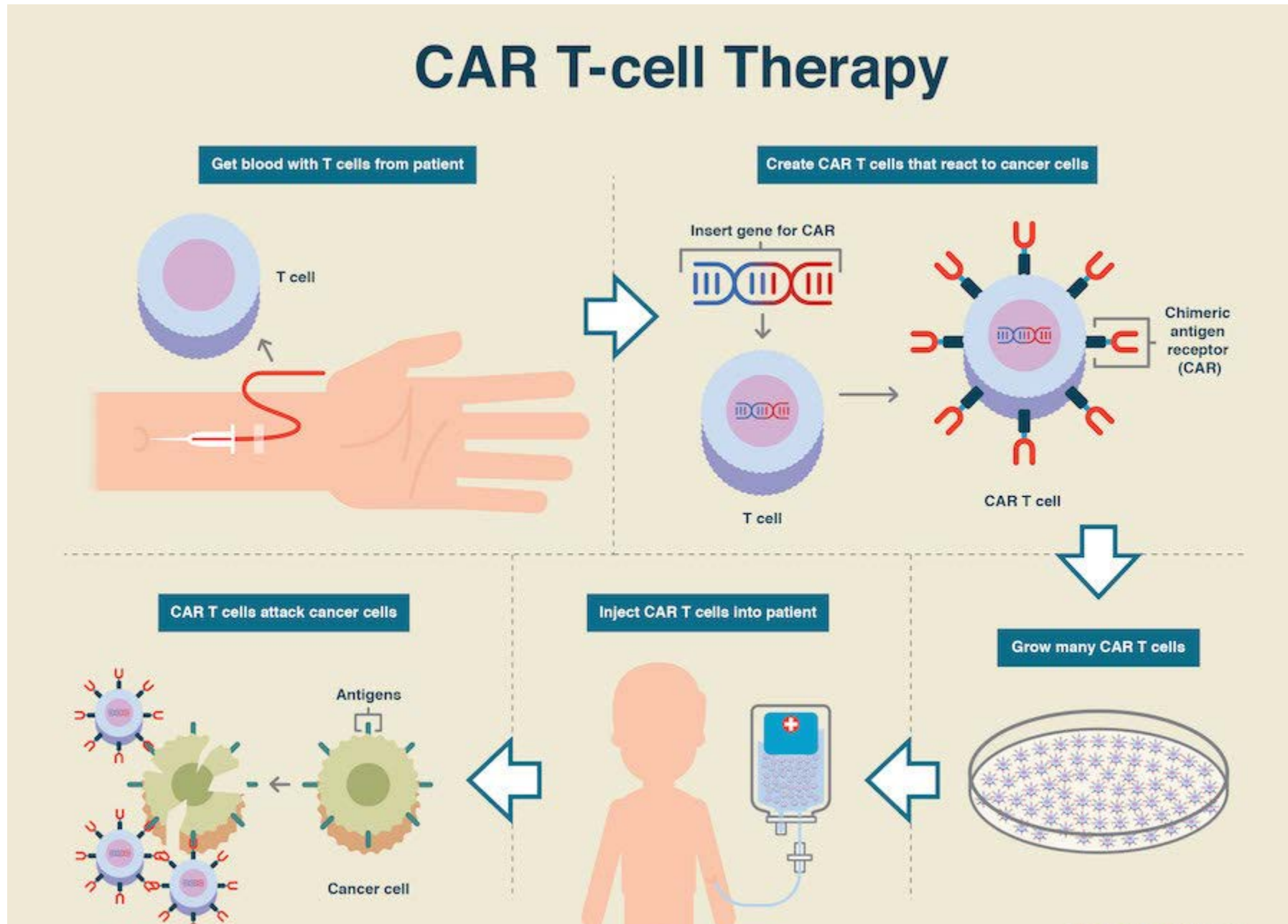


Advances in CAR T-Cell therapy for DLBCL and other lymphomas

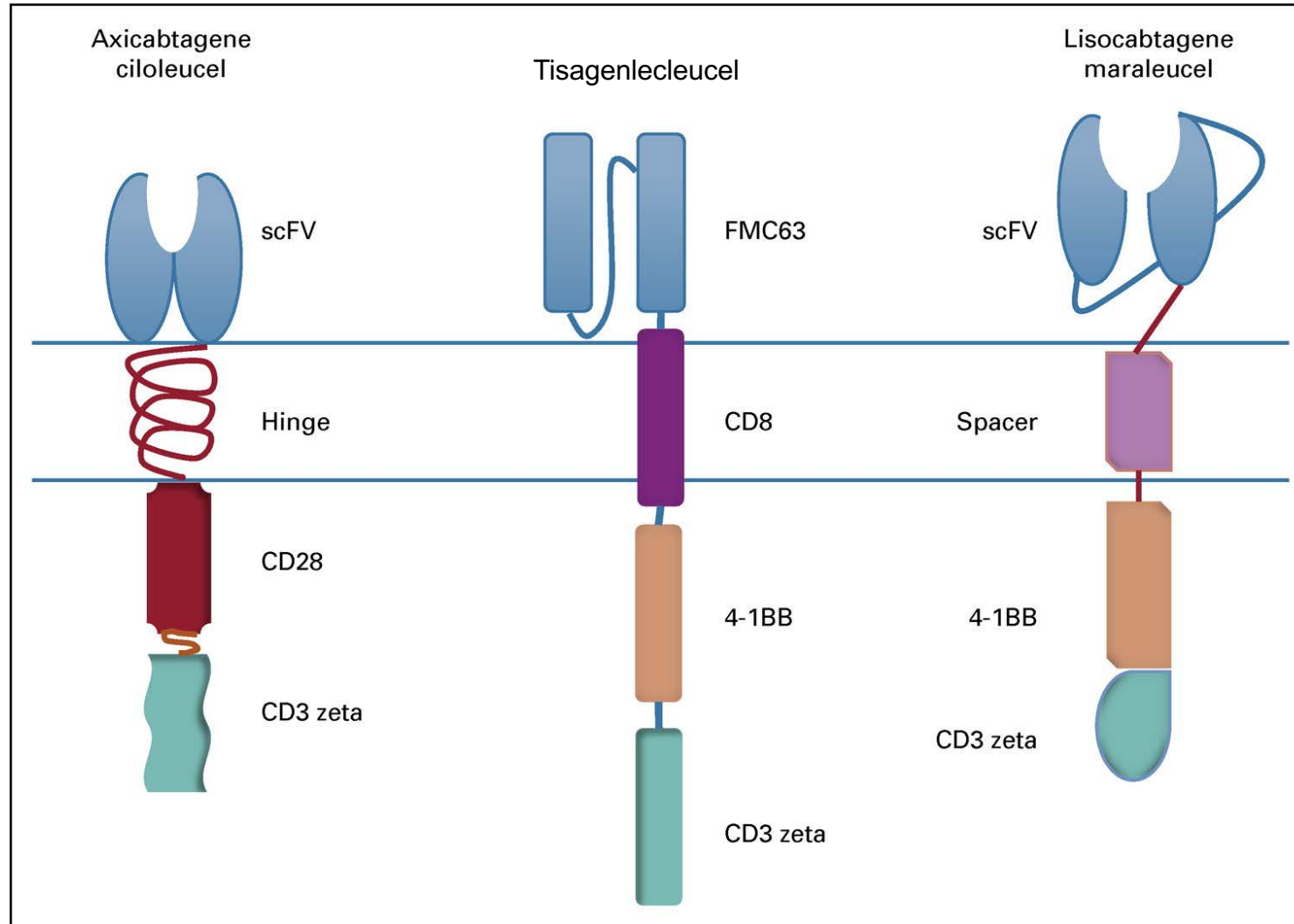
Jonathan W. Friedberg M.D.
Samuel Durand Professor of Medicine



CAR T-cell Therapy



CAR T-cell therapy products targeting CD19



CD19 CAR T-cell therapy FDA-approved products

Axicabtagene ciloleucel

Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy

Tisagenlecleucel

Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Brexucabtagene autoleucel

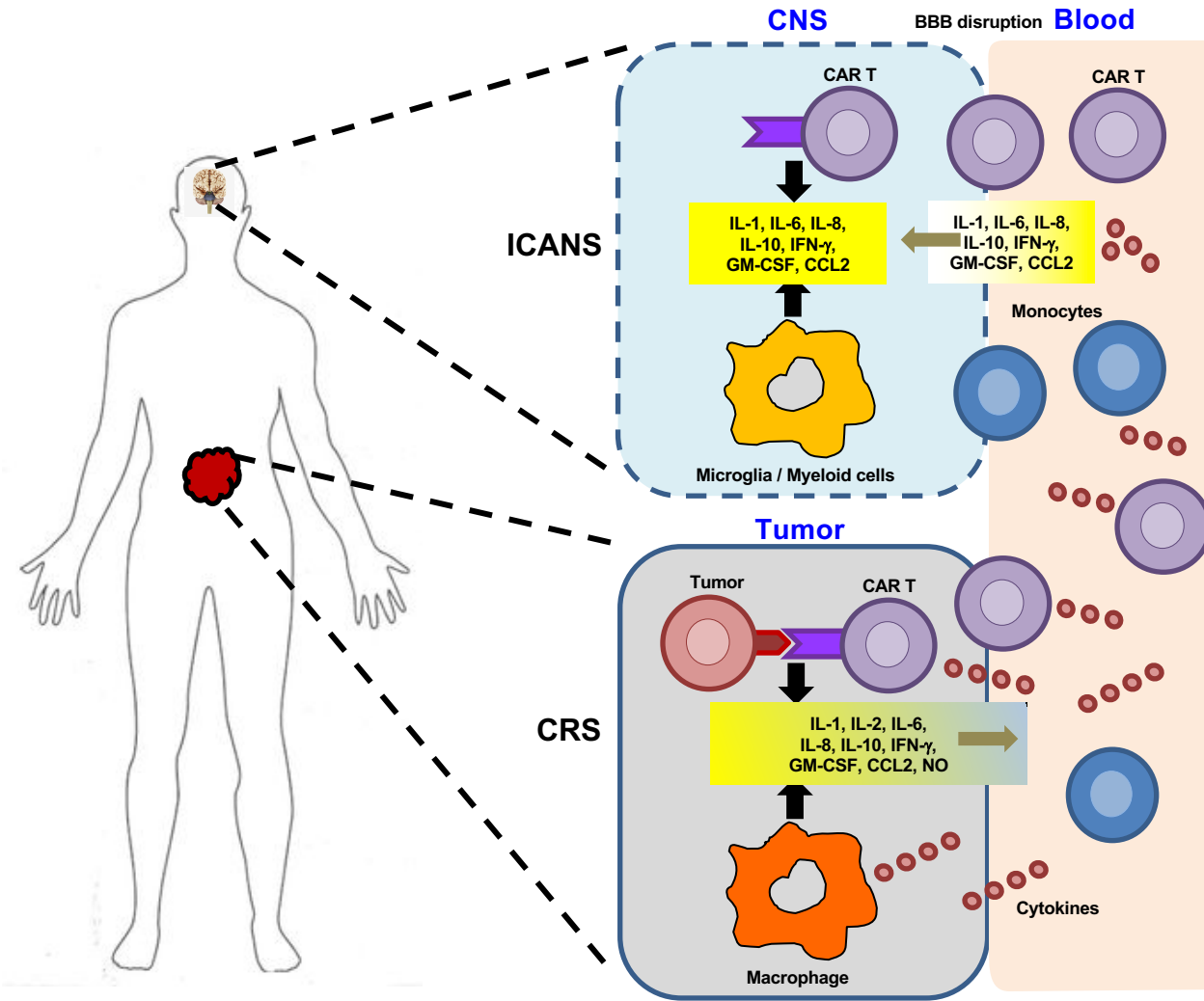
For the treatment of adult patients with relapsed/refractory mantle cell lymphoma.



Challenges of comparing CAR T-cell products: Efficacy summary

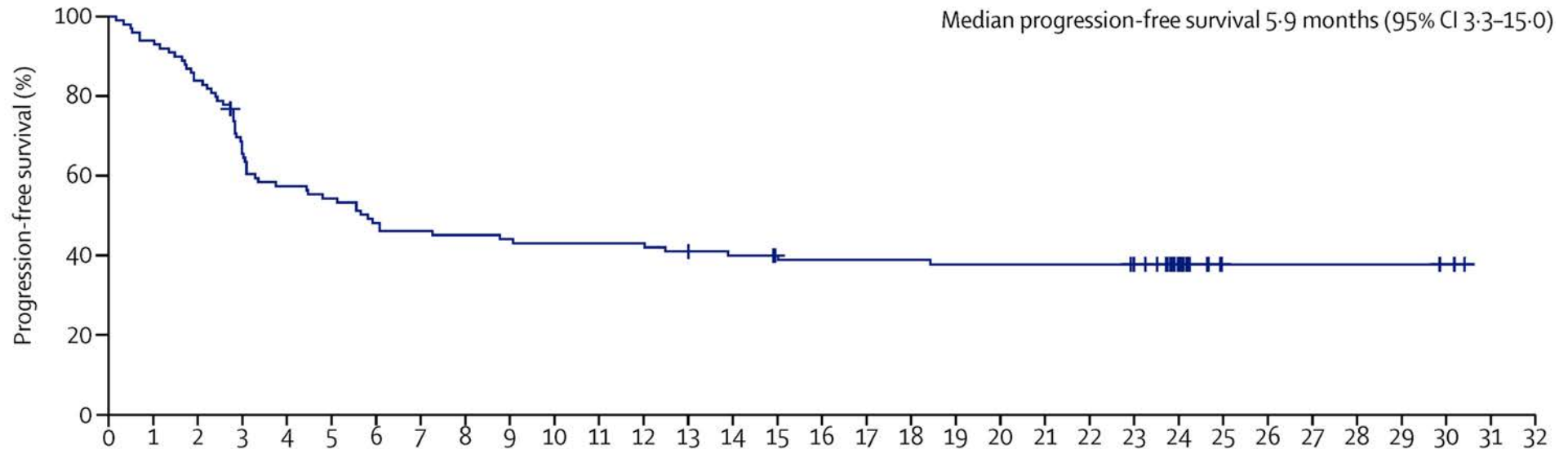
Variable	ZUMA-1 (axi-cel [KTE-C19])	JULIET (t-cel [CTL019])
No. pheresed	111	165
No. treated	101	111
No. evaluable	101	93
No. never treated (%)	10 (9) of 111	50 (31) of 161
Bridging treatment, %	0	92
ORR, %	82	52
CR, %	54	40
6-Month ORR, %	41	37*
6-Month CR, %	36	30*
ITT ORR (%)	83 (75) of 111	48 (30) of 161

Pathophysiology of CAR T-cell-associated neurotoxicity and cytokine release syndrome



Long-term safety and efficacy of axicabtagene ciloleucel in refractory DLBCL (ZUMA-1)

Progression-free survival: Median follow-up 27 months

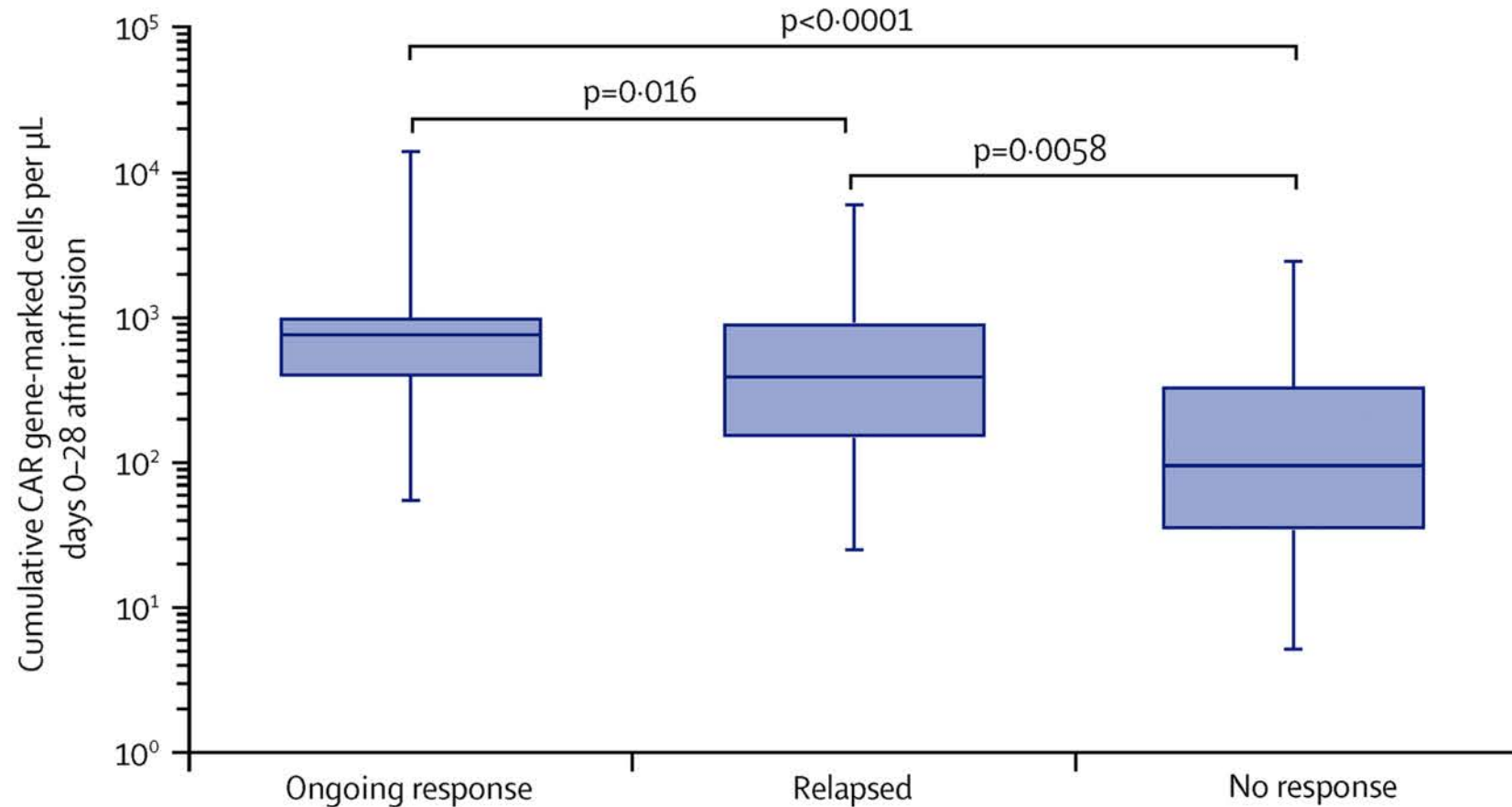


In patients with CR at 3 months, 24 month PFS was 72%

Median OS not reached

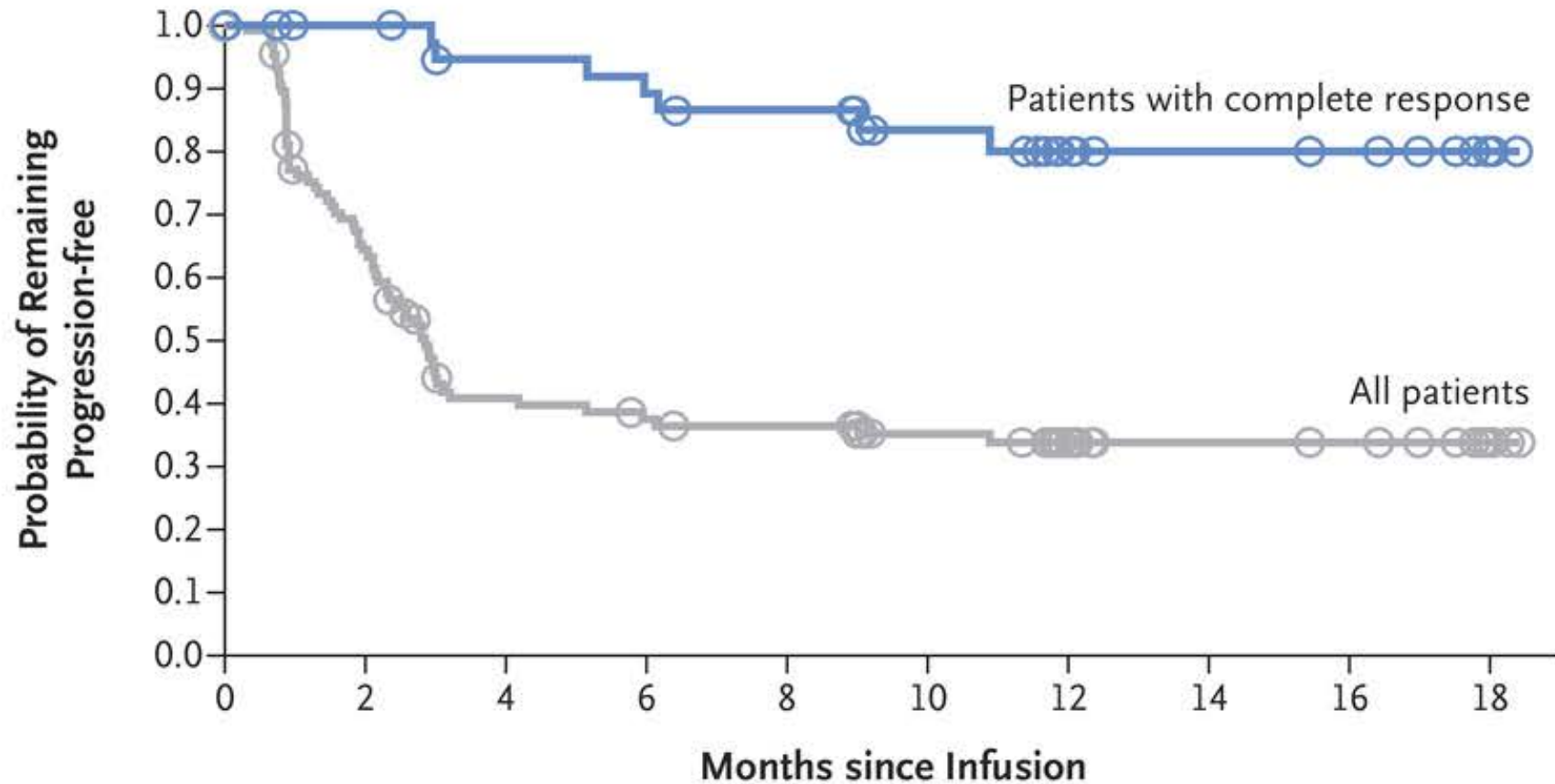


Durable responses are correlated with persistent CAR T-cells: ZUMA-1

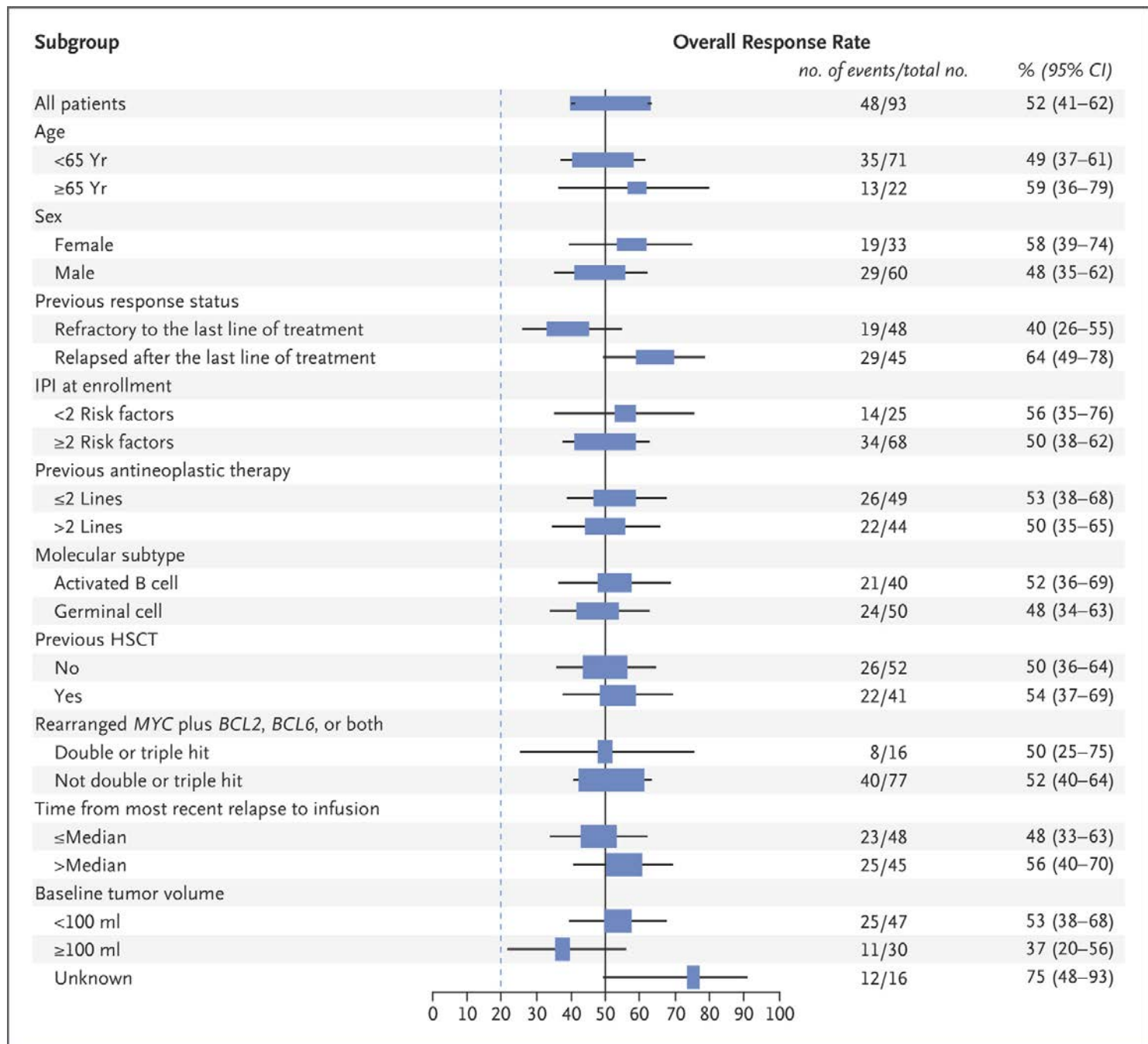


Tisagenlecleucel for DLBCL: JULIET trial

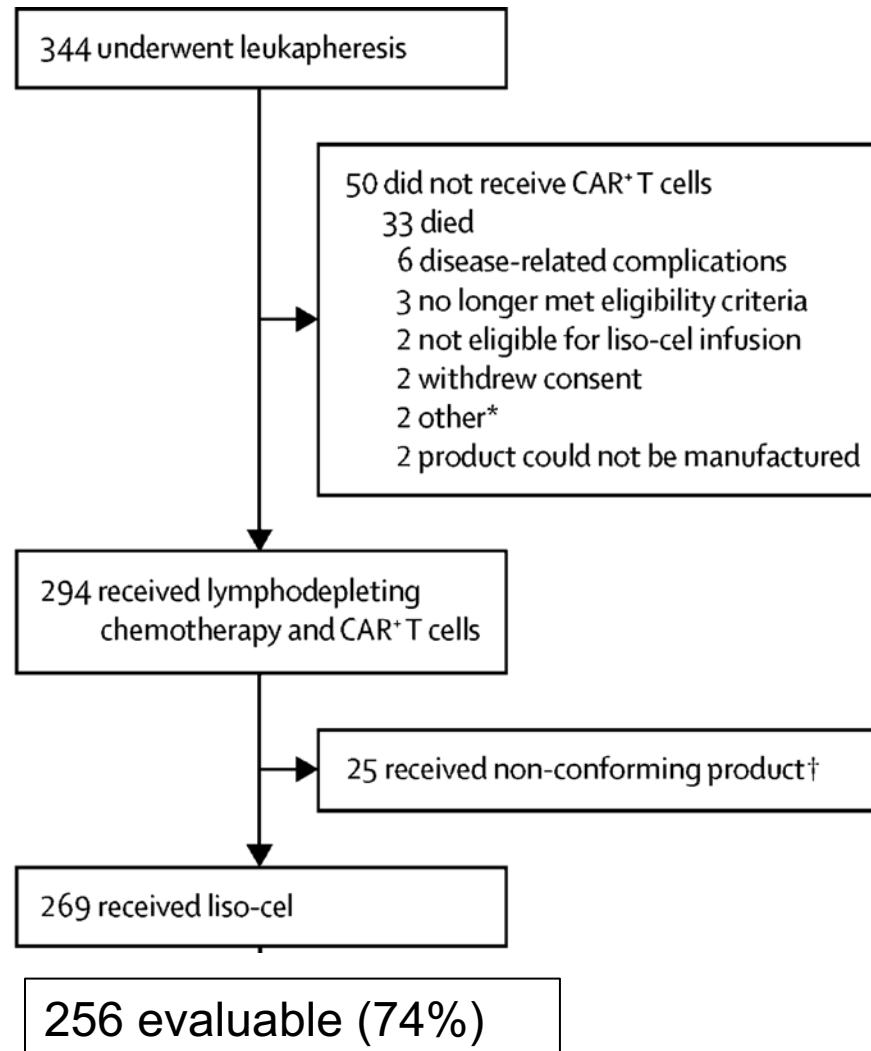
Median follow-up 14 months



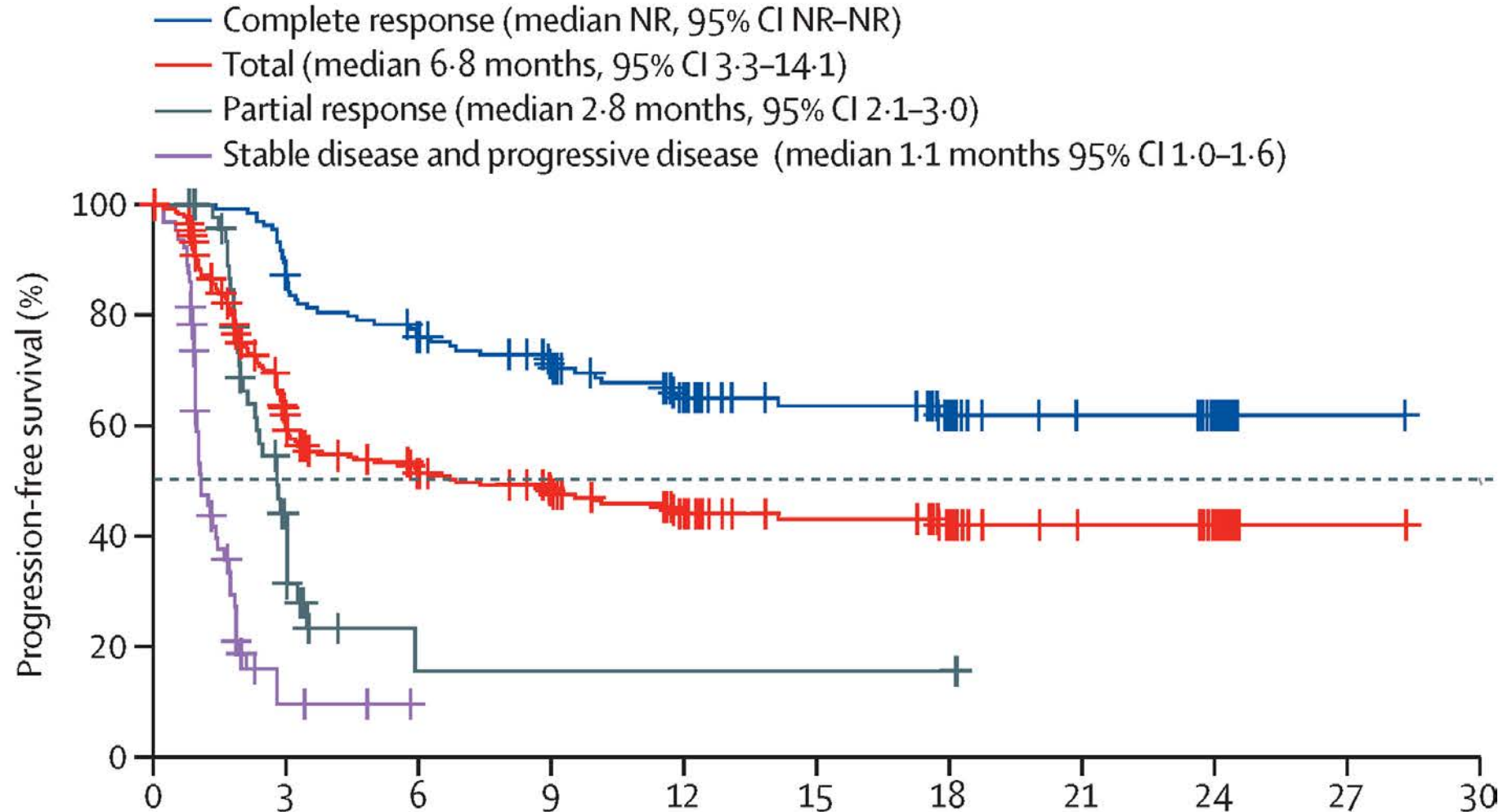
JULIET Trial of Tisagenlecleucel for R/R DLBCL



Lisocabtagene maraleucel for relapsed/refractory large cell lymphoma: TRANSCEND NHL 001



TRANSCEND NHL 001 trial of lisocabtagene maraleucel for large cell lymphoma: Progression-free survival median follow-up 18 mos.



“Real world” results with axicabtagene ciloleucel

- Jacobson et al (JCO 38:3095-3106 2019):
 - Response rates similar on ZUMA-1 eligible and ineligible groups
 - Grade 3 toxicities:
 - Cytokine release syndrome 16%
 - Neurotoxicity 35%
 - ***“Axi-cel yields similar rates of overall response and toxicity in commercial and trial settings”***
- Nastoupil et al (JCO 38:3119-28 2019):
 - 43% of patients would not have been eligible for ZUMA-1
 - Grade 3 toxicities:
 - Cytokine release syndrome 7%
 - Neurotoxicity 31%
 - ***“Safety and efficacy of axi-cel in SOC setting comparable to ZUMA registrational trial”***

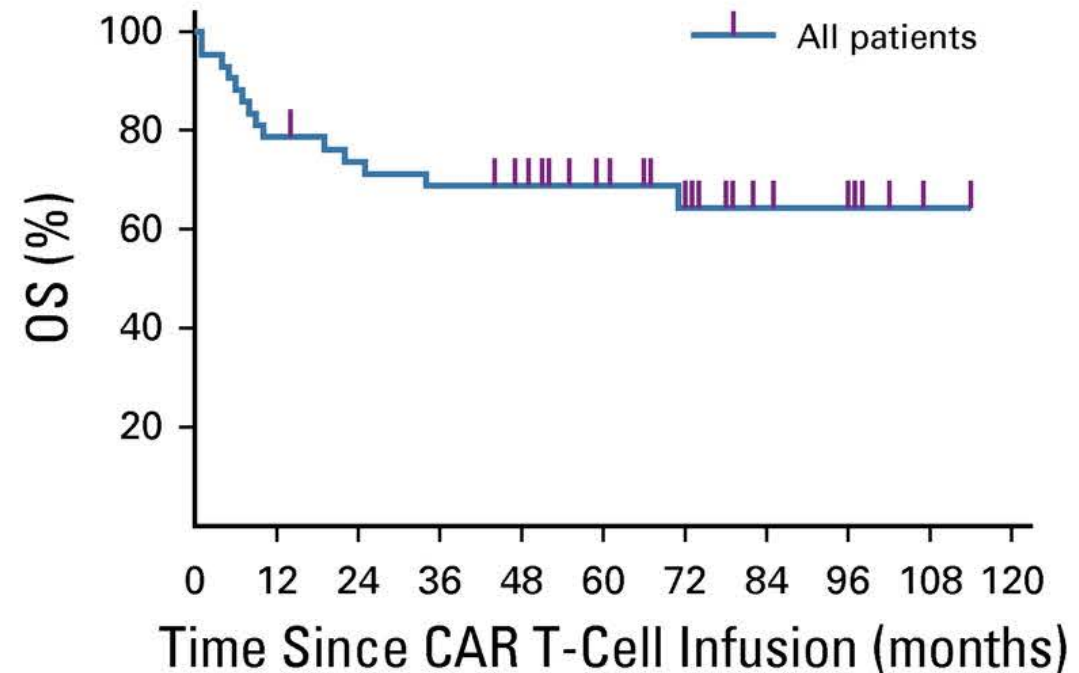


Are CAR T-cells curative?

Long-term follow-up of NCI experience

Median follow-up 42 months

- No patient with PR/SD as best response had a durable response
- 19/25 CRs (76%) are ongoing
- Overall 51% of CAR T-cell treatments resulted in DOR > 3 years

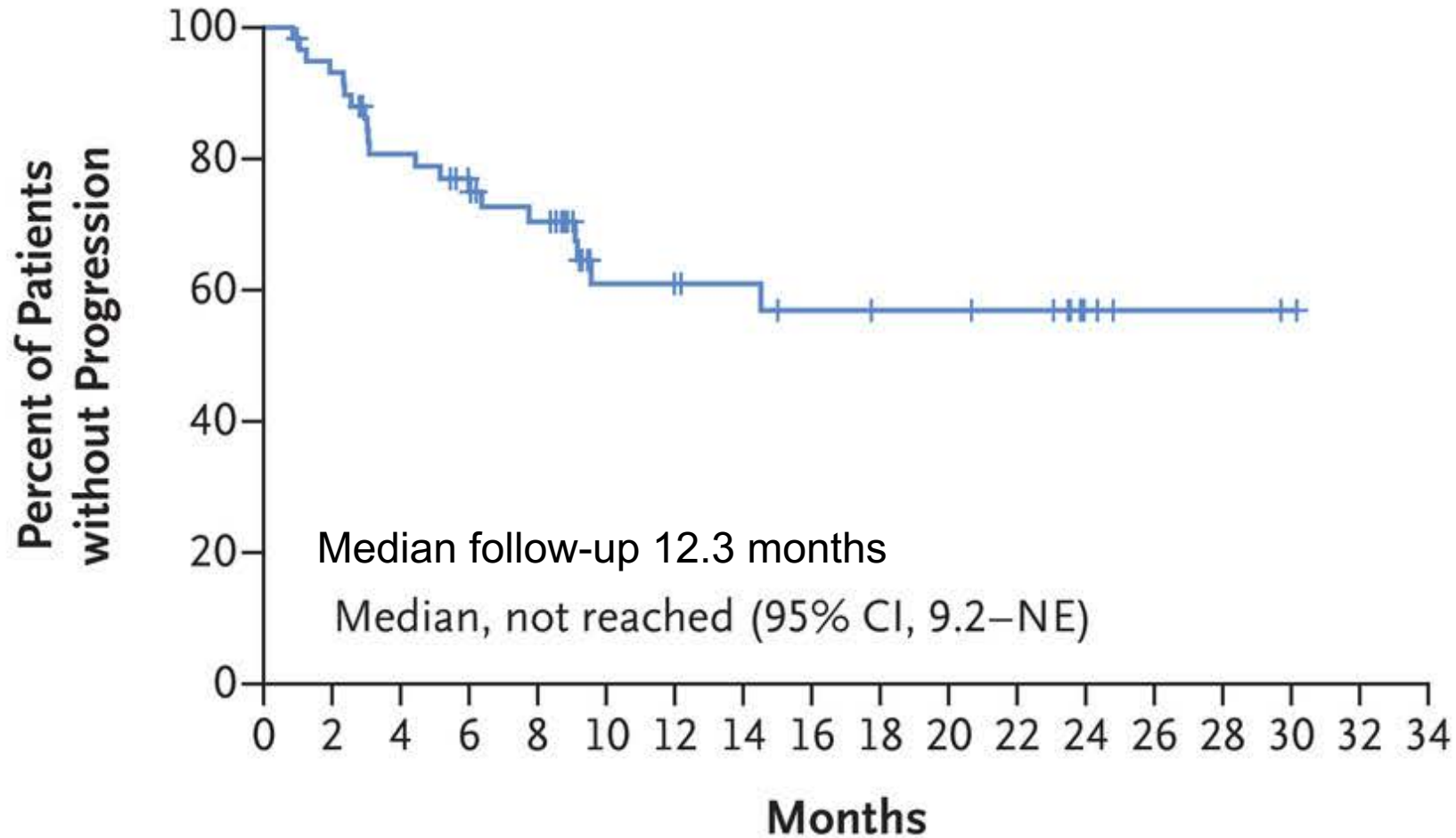


CAR T-cell therapy in mantle cell lymphoma: KTE-X19 (Brexucabtagene autoleucel)

- ◆ Relapsed/refractory mantle cell lymphoma
 - ◆ Up to 5 previous therapies
 - ◆ All patients had prior BTK inhibitor
- ◆ 74 patients enrolled
 - ◆ Successful manufacture in 71 patients
 - ◆ Administered to 68 patients (92%)
- ◆ ORR 85%; CR 59%
- ◆ Two grade 5 events



Brexucabtagene autoleucel in mantle cell lymphoma: Progression-Free Survival



ZUMA-5 trial of axicabtagene ciloleucel: CAR-T cell therapy for FL

- High risk Indolent lymphoma:
 - ≥ 2 prior lines of therapy
 - 66% POD24
 - 73% refractory to last treatment

N=80 patients with follicular lymphoma

ORR 95%

68% of patients with ongoing responses

CRS grade 3+: 11%

Neuro grade 3+: 19%

Grade 5 events: 2



ZUMA-5 trial: CAR-T cell therapy for FL

- High risk Indolent lymphoma:
 - ≥ 2 prior lines of therapy
 - 66% POD24
 - 73% refractory to last treatment

N=80 patients with follicular lymphoma

ORR 95%

68% of patients with ongoing responses

CRS grade 3+: 11%

Neuro grade 3+: 19%

Grade 5 events: 2

A supplemental Biologics License Application (sBLA) has been submitted to the FDA to expand the indication for axicabtagene ciloleucel.



Anti-CD30 CAR-T cell therapy in relapsed/refractory Hodgkin lymphoma

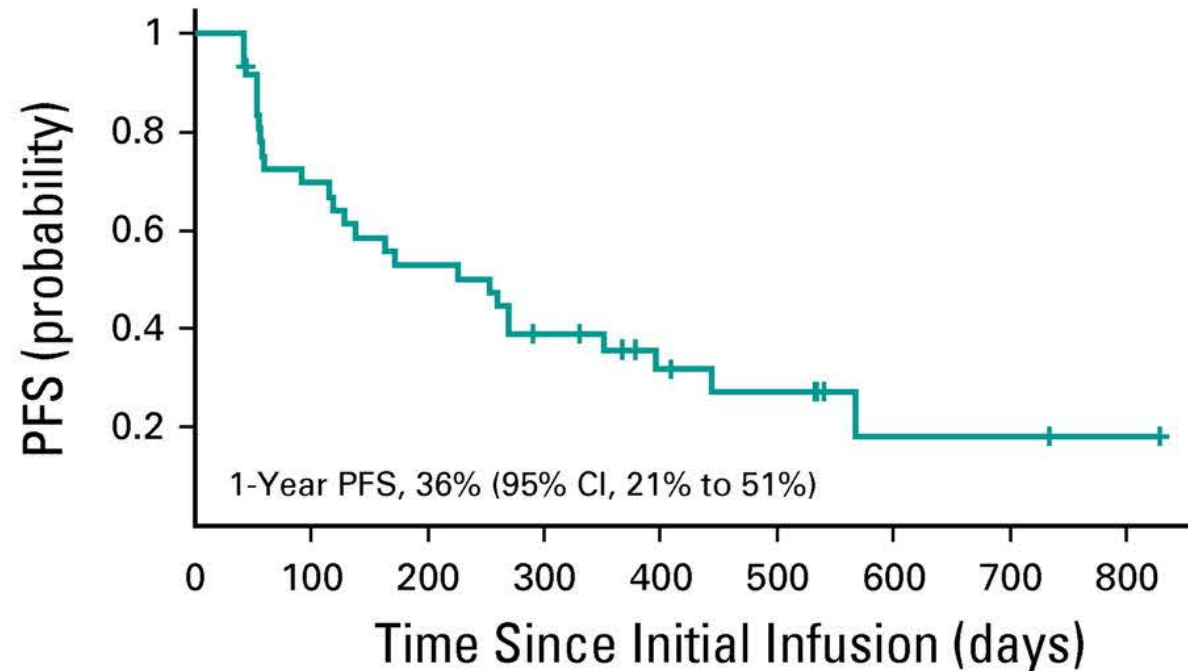
41 patients

Median 7 prior lines of therapy: Checkpoint inhibitors, Brentuximab ASCT/alloSCT.

Low grade CRS; no neurologic toxicity; common skin rash

ORR 72%; CR 59%

One year PFS: 36%



Patient identification and appropriate referral for CAR-T cell therapy

- EARLY referral is most important
 - Numerous open trials in novel settings
- Considerations:
 - Avoid lymphotoxic therapy (purine analogs, bendamustine)
 - Avoid immunosuppressive therapy, including steroids
 - (?) avoid tafasitamab and other CD19-targeting agents
- For DLBCL:
 - Refer before starting salvage therapy
 - New products may allow treatment of older individuals
 - “Real world” experiences variable



Clinical trials in CAR T-cell therapy: summary

- Randomized trials comparing CAR T-cell therapy to salvage + ASCT
- Post CAR-T treatment interventions
 - Immune checkpoint inhibitors
 - Immunomodulators
- Novel histologies
- New constructs
 - Outpatient therapy
 - Minimizing toxicity

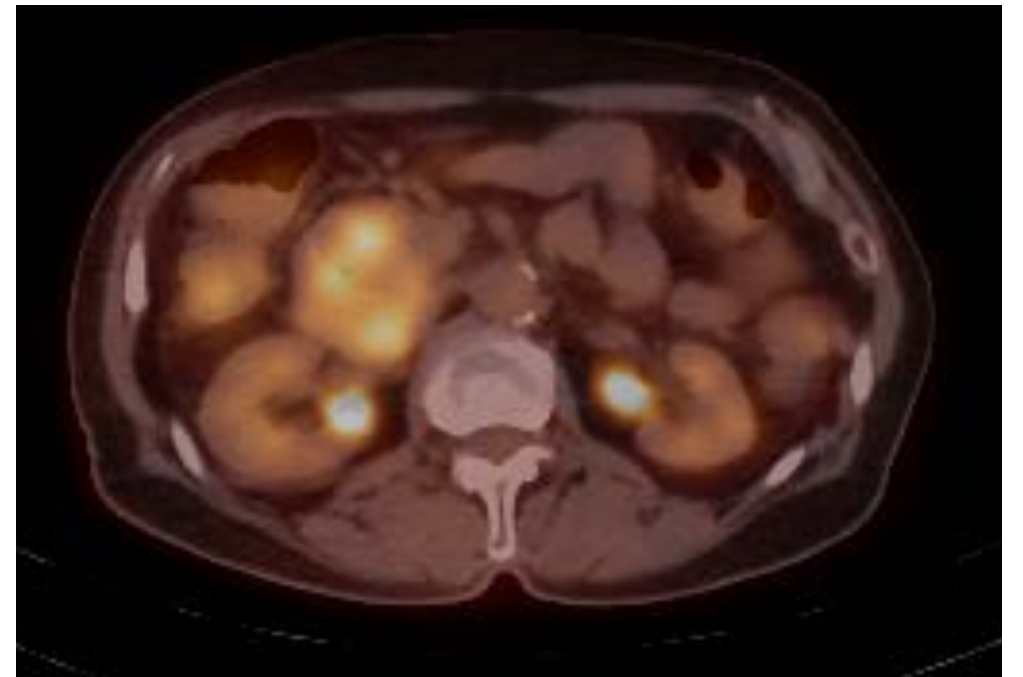
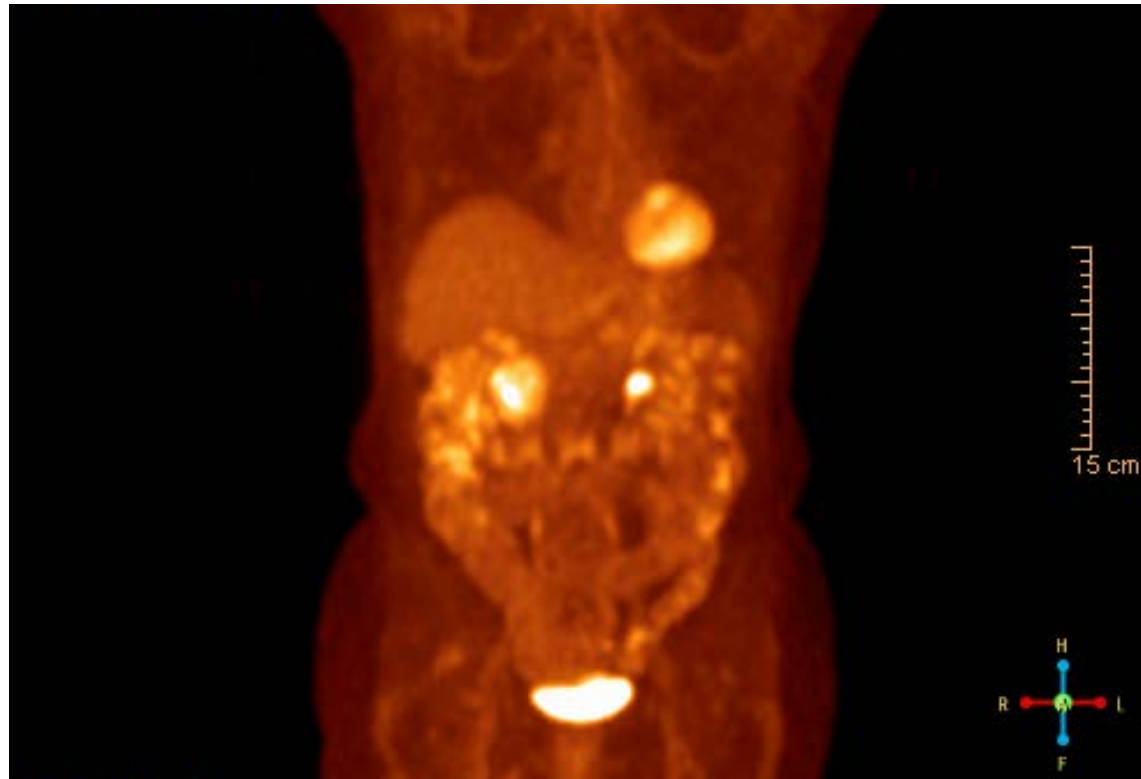


Case 1

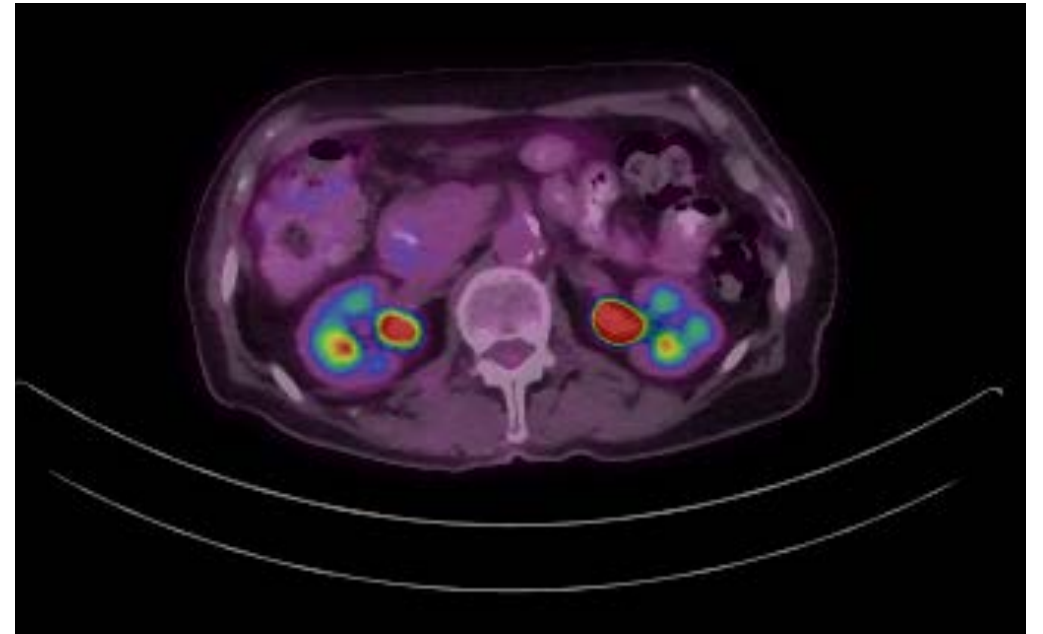
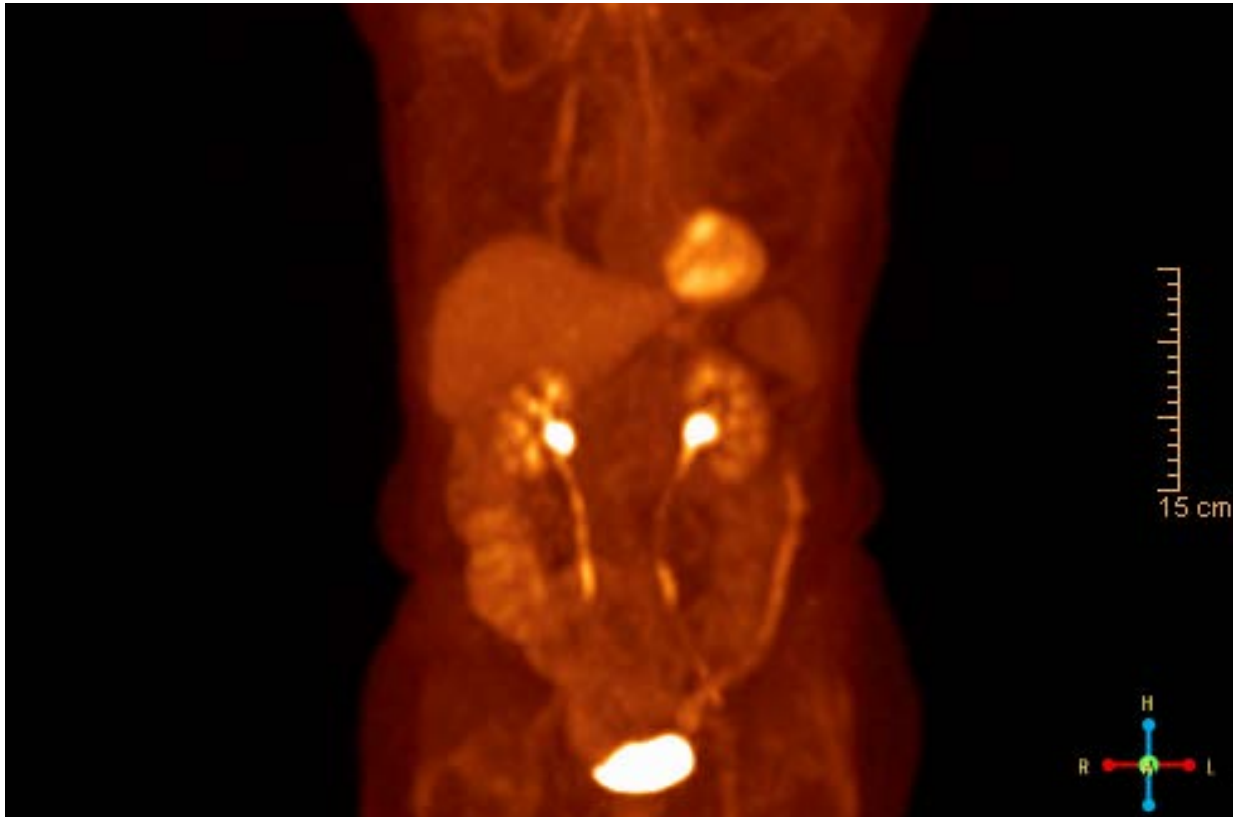
Patient is a 70 y.o. female with history of transformed follicular lymphoma (MYC & BCL-2 translocations) with recurrent disease s/p ASCT.

- 2007: Follicular lymphoma, Fludarabine/rituximab x 5
- 2012: Fludarabine/rituximab
- 2013: Double hit transformation, RCHOPx4 followed by BEAM and ASCT
- 7/18/2017: Recurrent transformed follicular lymphoma, Completed 2 cycles of RCHOP initiated then 2 cycles of miniRCHOP due to neutropenic fever
- 11/9/17: Initiated Lenalidomide
- 3/21/2018: Started lymphodepleting chemotherapy with fludarabine and cyclophosphamide
- 3/26/2018: Received axicabtagene ciloleucel 2×10^6 cells/kg
- Tolerated treatment well; low grade fever after infusion.
- Remains in complete remission.

Case 1: PET/CT Pre CAR T-cell Therapy



Case 1: PET/CT Post CAR T-cell Therapy



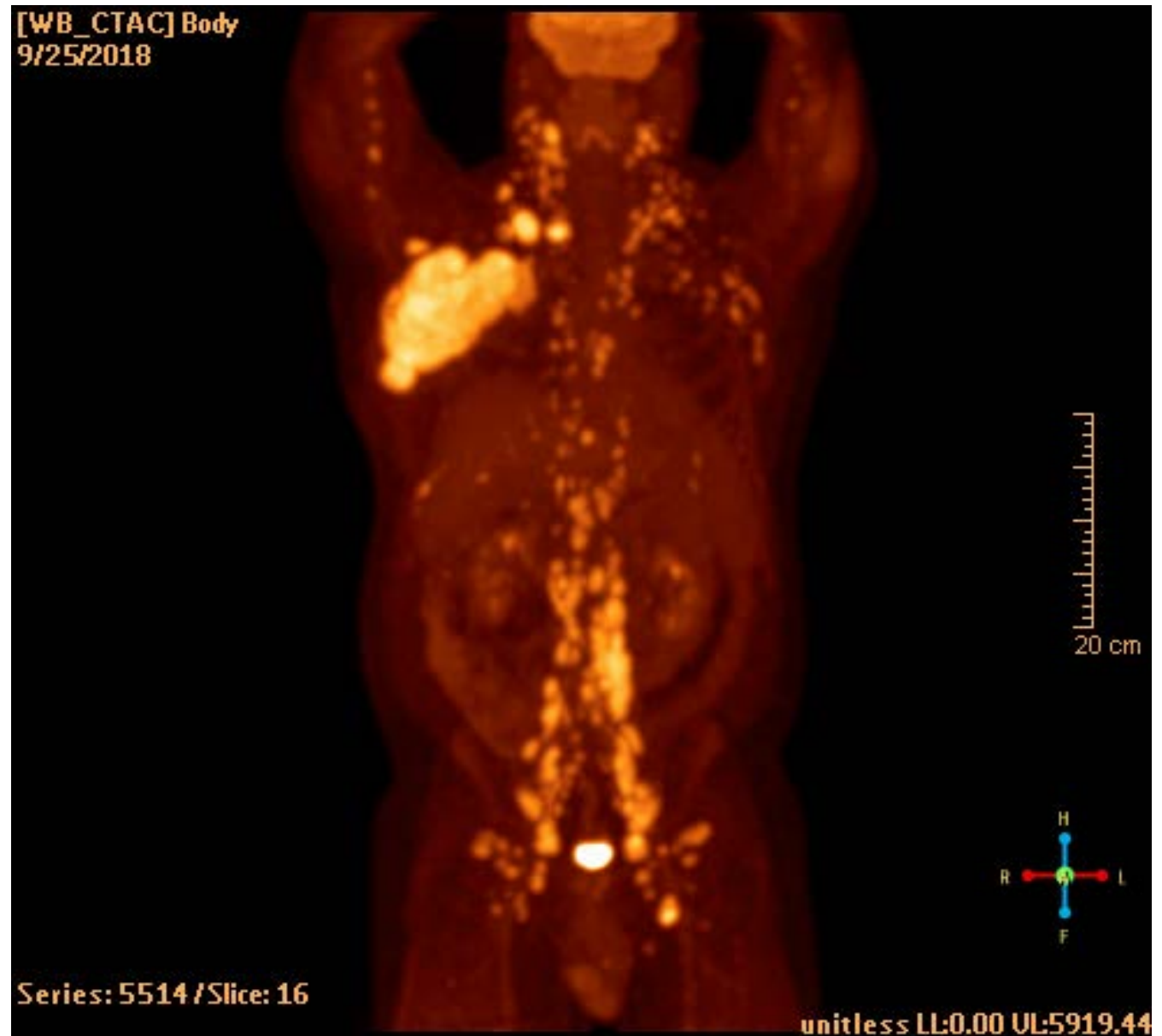
Case 2

55 y.o. male physician with mantle cell lymphoma.

Treatment history:

- 5/16: Diagnosis; p53 deleted MCL
- Nordic regimen (maxiCHOP with cytarabine/rituximab) followed by BEAM ASCT; completed 9/15/16
- Rituximab maintenance
- 11/17: disease progression on surveillance imaging
- 12/17: acalabrutinib started
- 2018: disease progression; Cyclophosphamide/fludarabine followed by axicabtagene ciloleucel (10/01 infusion; on ZUMA-2 trial)
- Severe Neurologic toxicity, requiring ICU stay.
- Complete response; now back at work after rehabilitation.

Case 2:
PET/CT Pre
CAR T-cell Therapy



Case 2: PET/CT Post CAR T-cell Therapy



Thank you!
Questions



WILMOT
CANCER INSTITUTE