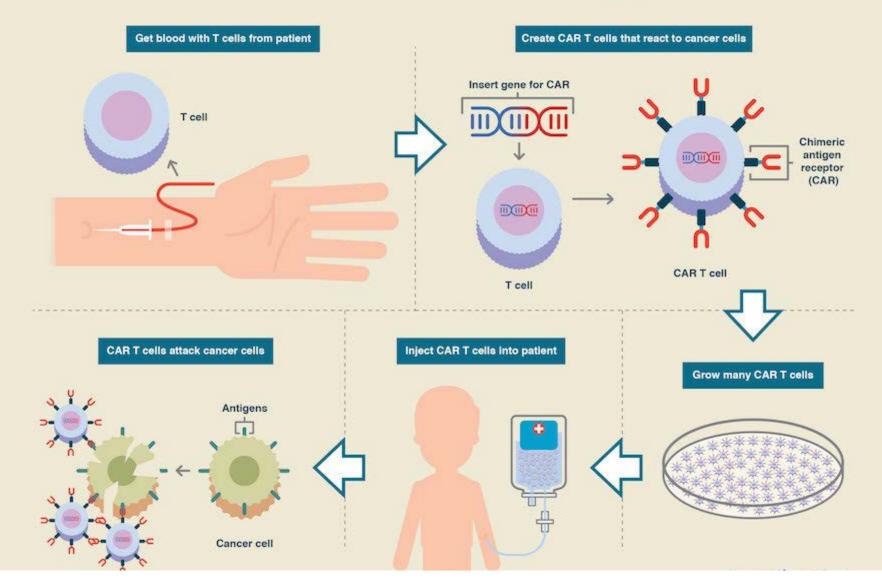
# Advances in CAR T-Cell therapy for DLBCL and other lymphomas

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



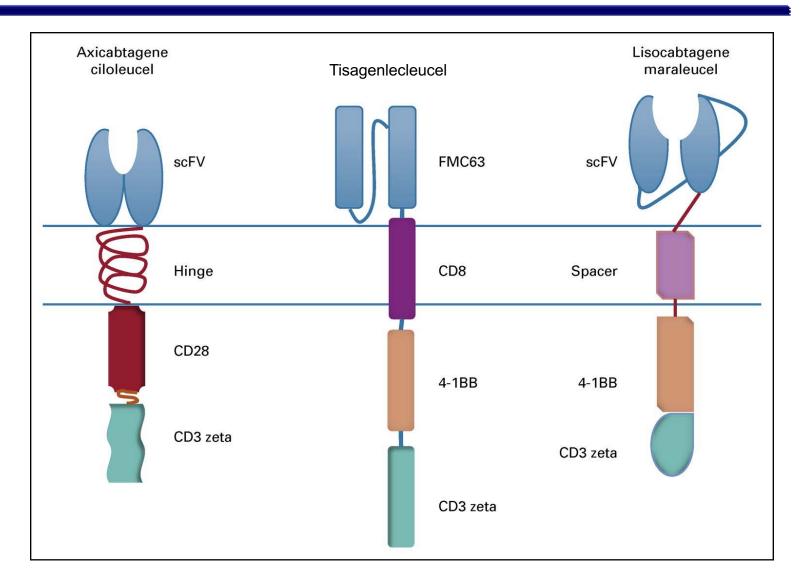
#### **CAR T-cell Therapy**



Courtesy of Jonathan W Friedberg, MD, MMSc

#### Medical Press Graphic

### CAR T-cell therapy products targeting CD19







Courtesy of Jonathan W Friedberg, MD, MMSc

Jacobson, JCO 37:328-35, 2019

#### 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.





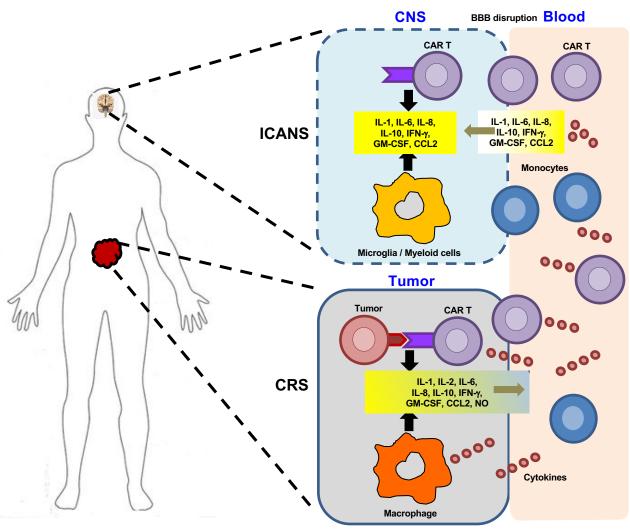
### Challenges of comparing CAR T-cell products: Efficacy summary

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

Courtesy of Jonathan W Friedberg, MD, MMSc

Jacobson, JCO 37:328-35, 2019

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





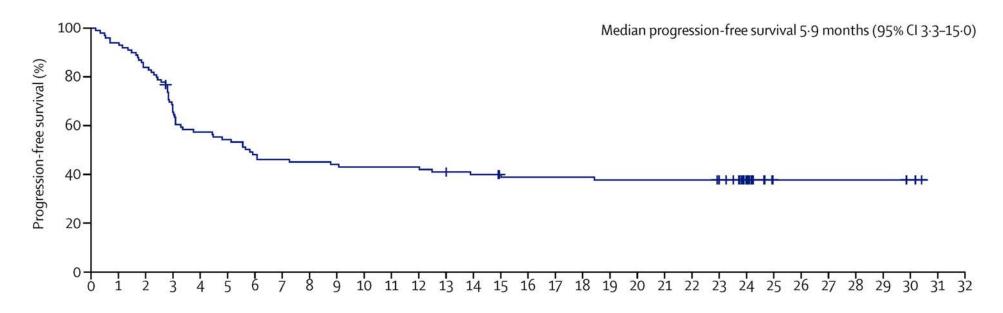


Courtesy of Jonathan W Friedberg, MD, MMSc

Reagan and Neelapu, JCO in press 2020

# 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

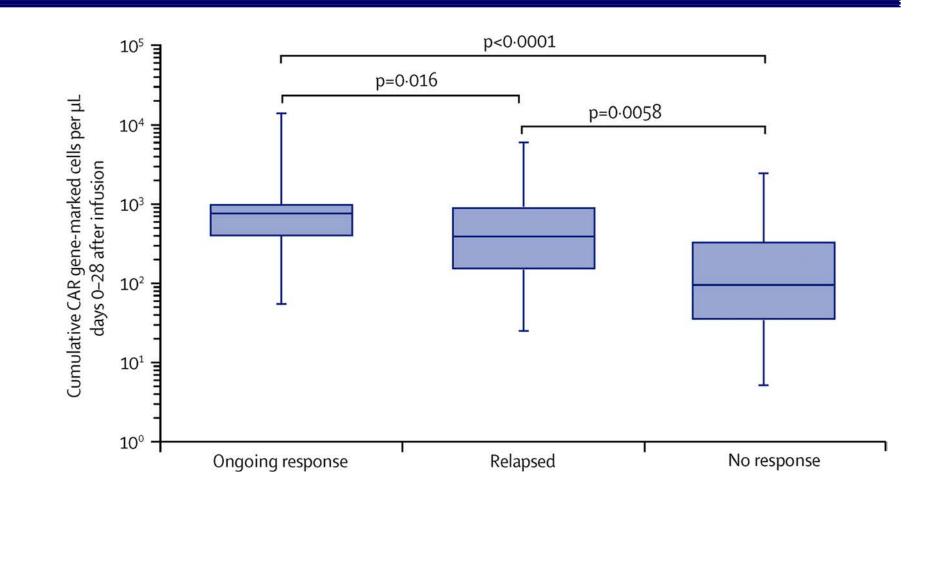


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Courtesy of Jonathan W Friedberg, MD, MMSc

Locke et al, Lancet Oncol 20:31-42 2019

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



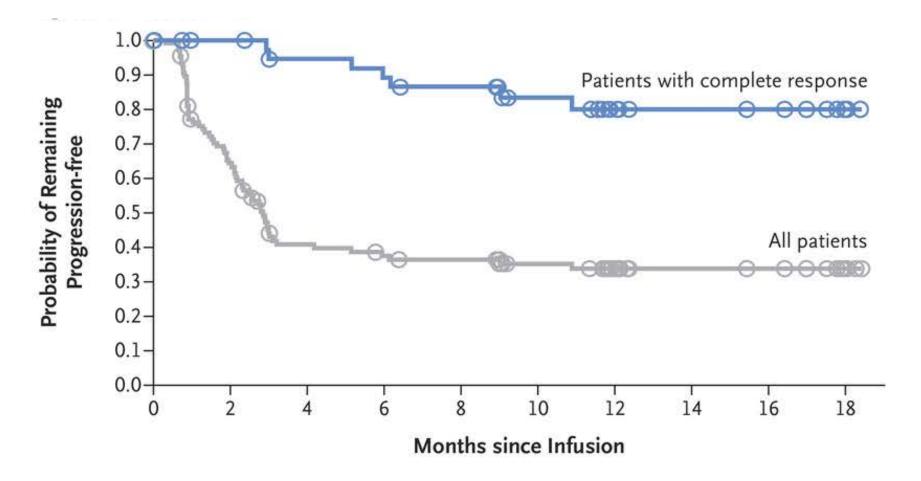
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Locke et al, Lancet Oncol 20:31-42 2019

#### Tisagenlecleucel for DLBCL: JULIET trial Median follow-up 14 months





Courtesy of Jonathan W Friedberg, MD, MMSc

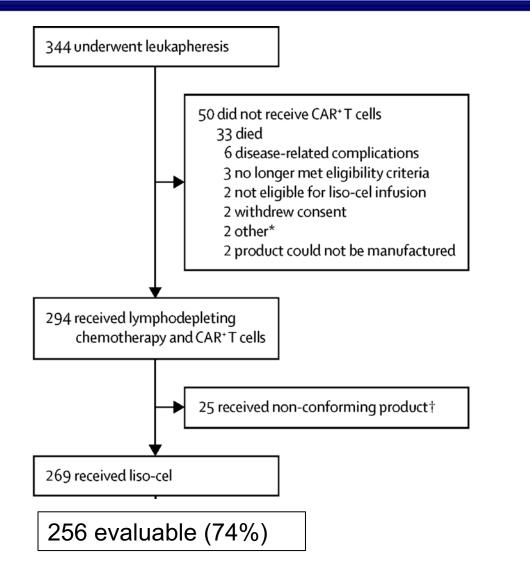
Schuster et al, *NEJM* 380:45-56 2019

#### JULIET Trial of Tisagenlecleucel for R/R DLBCL

Subgroup	Overall Response Rate	
	no. of events/total no.	% (95% CI)
All patients	48/93	52 (41-62)
Age		
<65 Yr	- 35/71	49 (37–61)
≥65 Yr	13/22	59 (36–79)
Sex		
Female	19/33	58 (39-74)
Male	<b>———</b> 29/60	48 (35–62)
Previous response status		
Refractory to the last line of treatment	19/48	40 (26–55)
Relapsed after the last line of treatment	29/45	64 (49-78)
IPI at enrollment		
<2 Risk factors	14/25	56 (35-76)
≥2 Risk factors	- 34/68	50 (38-62)
Previous antineoplastic therapy		
≤2 Lines	<b>——</b> 26/49	53 (38-68)
>2 Lines	22/44	50 (35-65)
Molecular subtype		
Activated B cell	21/40	52 (36–69)
Germinal cell	<u> </u>	48 (34-63)
Previous HSCT		
No	<b>— 26/52</b>	50 (36-64)
Yes	22/41	54 (37-69)
Rearranged MYC plus BCL2, BCL6, or both		
Double or triple hit	8/16	50 (25-75)
Not double or triple hit	- 40/77	52 (40-64)
Time from most recent relapse to infusion		
≤Median	23/48	48 (33-63)
>Median	25/45	56 (40-70)
Baseline tumor volume		
<100 ml	25/47	53 (38–68)
≥100 ml	11/30	37 (20-56)
Unknown	0 10 20 30 40 50 60 70 80 90 100	75 (48–93)

Schuster et al, *NEJM* 380:45-56 2019

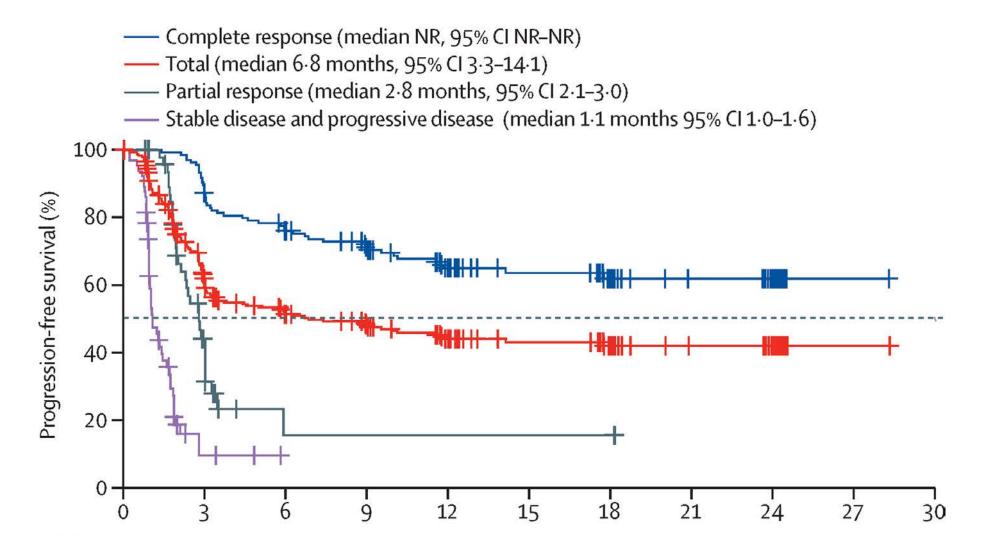
Lisocabtagene maraleucel for relapsed/refractory large cell lymphoma: TRANSCEND NHL 001



Courtesy of Jonathan W Friedberg, MD, MMSc

Abramson et al, *Lancet* 396:839-52 2020

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



Abramson et al, *Lancet* 396:839-52 2020

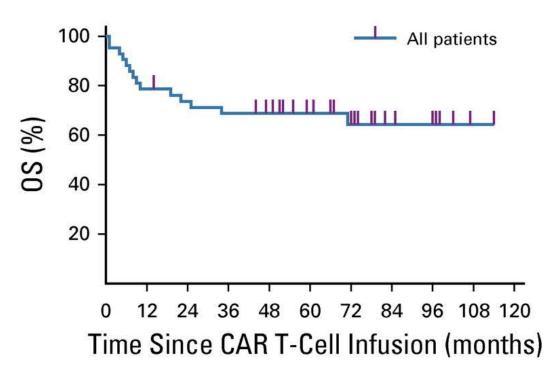
#### "Real world" results with axicabtagene ciloleucel

- 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"
- <u>Nastoupil et al (JCO 38:3119-28 2019)</u>:
  - 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%



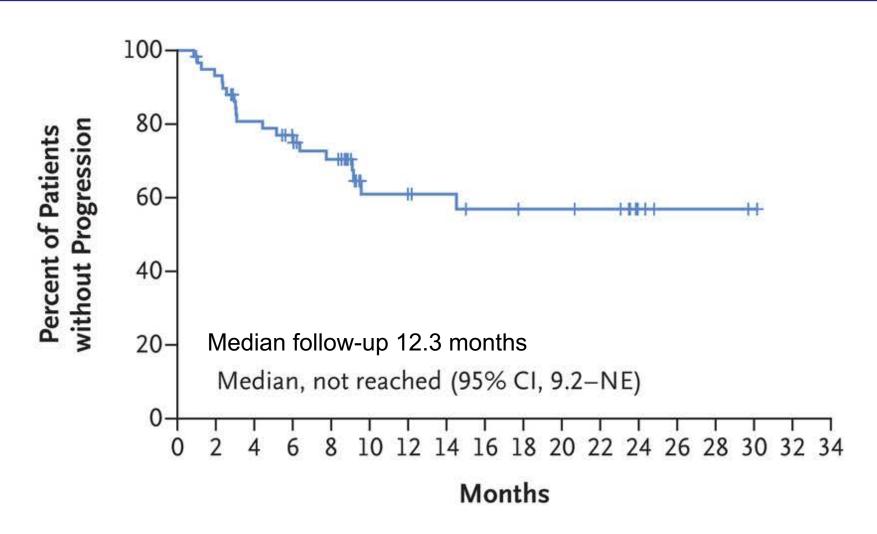
LMOT

Two grade 5 events

Courtesy of Jonathan W Friedberg, MD, MMSc

Wang et al, *NEJM* 382:1331-42 2020

#### Brexucabtagene autoleucel in mantle cell lymphoma: Progression-Free Survival







Courtesy of Jonathan W Friedberg, MD, MMSc

Wang et al, *NEJM* 382:1331-42 2020

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

- High risk Indolent lymphoma:
  - >/= 2 prior lines of therapy
  - 66% <u>POD24</u>
  - 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





Courtesy of Jonathan W Friedberg, MD, MMSc

Jacobson et al., Proc ASCO 2020

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

- High risk Indolent lymphoma:
  - >/= 2 prior lines of therapy
  - 66% <u>POD24</u>
  - 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.





Courtesy of Jonathan W Friedberg, MD, MMSc

Jacobson et al, Proc ASCO 2020

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

41 patients

Median 7 prior lines of PFS (probability) 0.8 Checkpoint therapy: inhibitors, **Brentuximab** 0.6 ASCT/alloSCT. 0.4 Low grade CRS; no 0.2 neurologic toxicity; common 1-Year PFS, 36% (95% CI, 21% to 51%) skin rash 0 100 200 300 400 500 600 700 800 Time Since Initial Infusion (days)

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:
  - <u>Refer before starting salvage therapy</u>
  - New products may allow treatment of older individuals
  - "Real world" experiences variable





Courtesy of Jonathan W Friedberg, MD, MMSc

Jain et al, BBMT 25:2305-21 2019

#### 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



CANCER INSTITUTE Courtesy of Jonathan W Friedberg, MD, MMSc

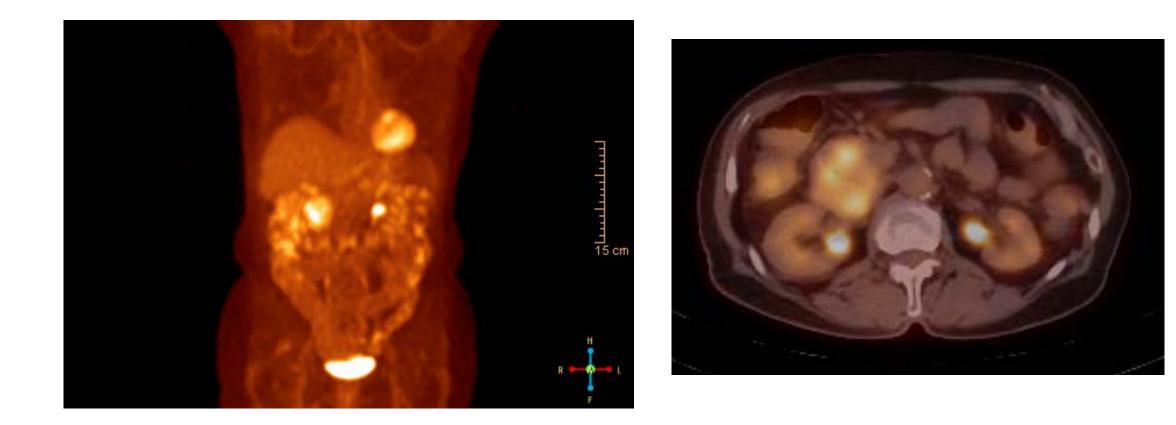
Kallam and Vose, Clin Leuk Lym Myeloma 19:751-57 2019

### Case 1

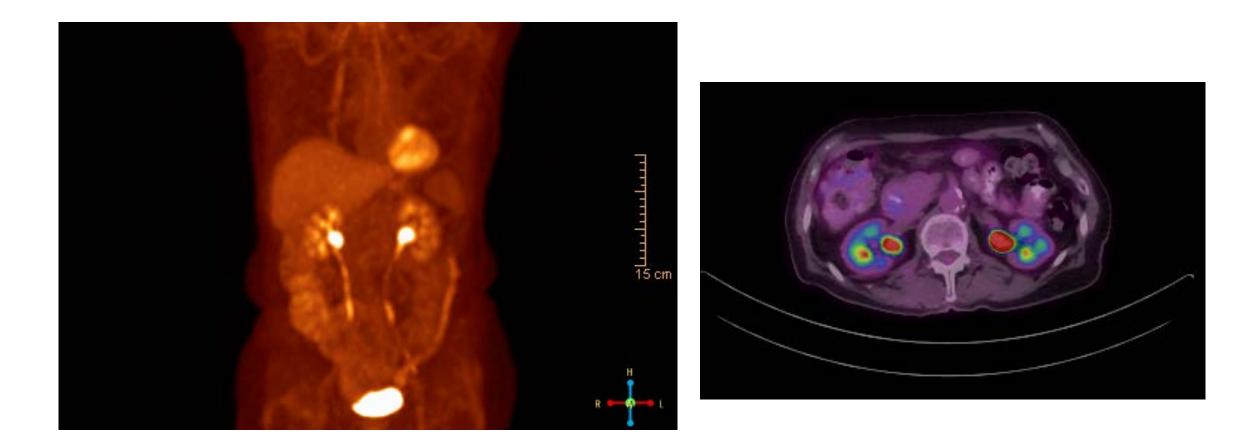
Patient is a 70 y.o. female with history of transformed follicular lymphoma (MYC & BCL-2 translocations) with recurrent disease s/p ASCT.

- 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 x 10<sup>6</sup> 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



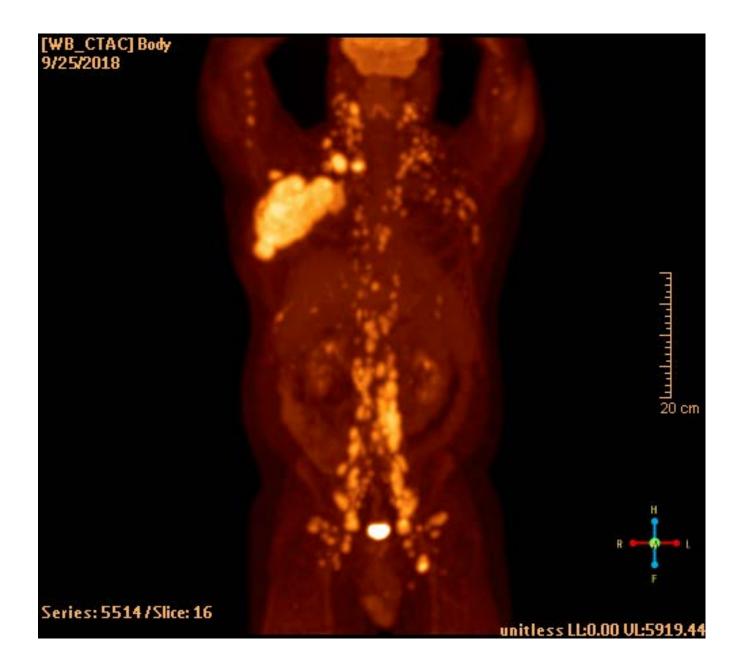
#### Case 2

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

