Optimizing Outcomes for CD19-directed CAR-T Therapy in Refractory B-cell Lymphomas

Stephen J. Schuster, MD

Professor of Medicine
Perelman School of Medicine of the University of Pennsylvania

Director, Lymphoma Program & Lymphoma Translational Research
Abramson Cancer Center of the University of Pennsylvania

2nd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Scientific board:
Marco Ladetto (Alessandria)
Umberto Vitolo (Candiolo-TO)

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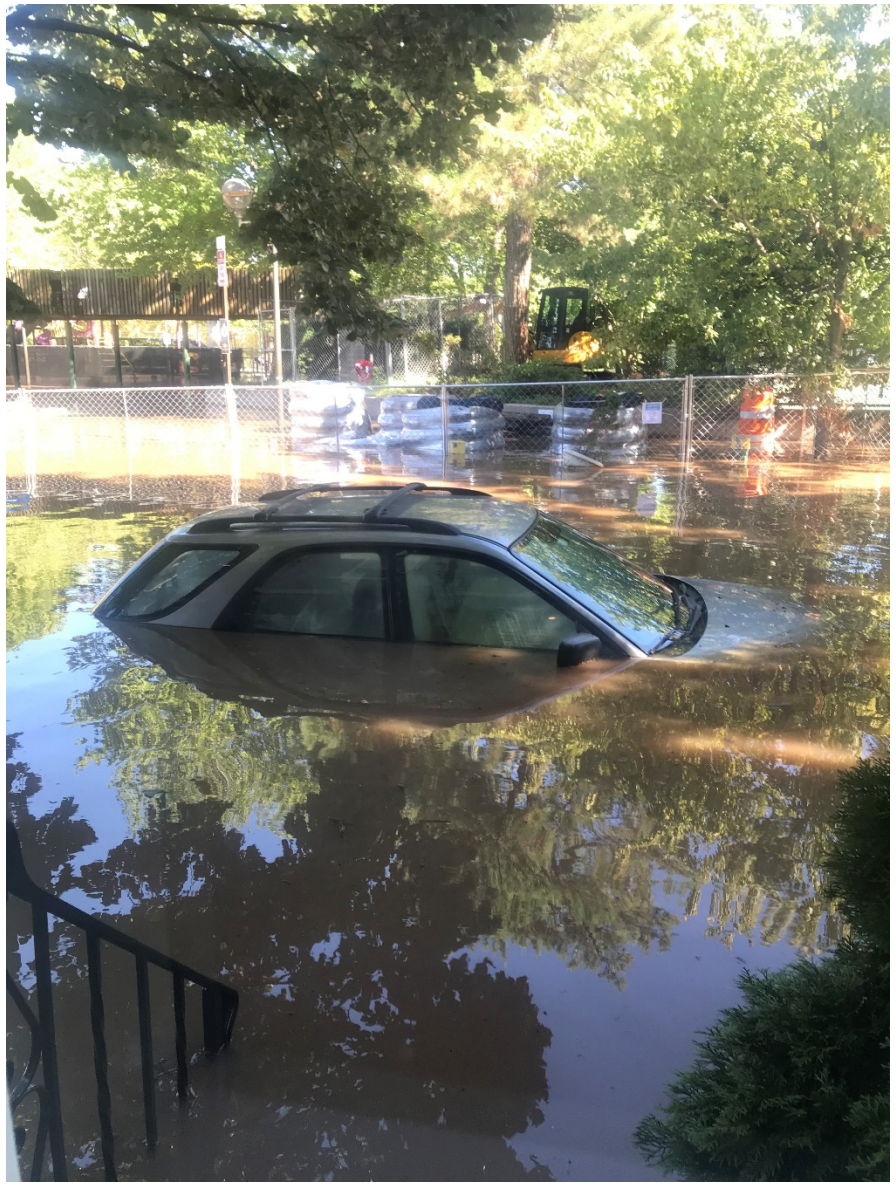
Hurricane Ida: View from my first floor



Optimizing CAR-T Therapy Outcomes

Lecture Outline

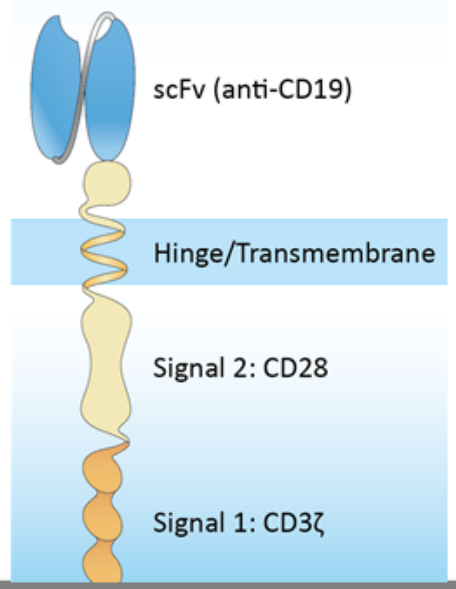
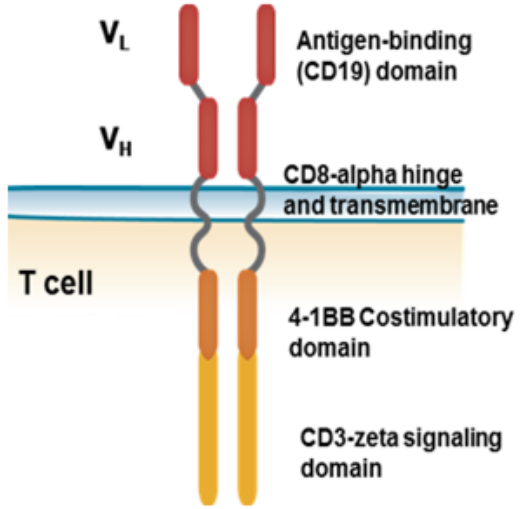
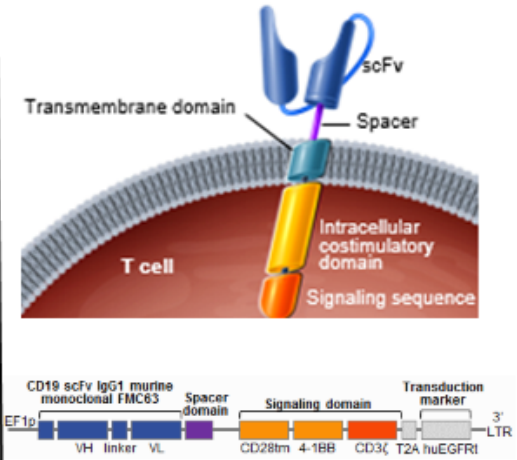
1. Current Status of CD19-directed CAR-T therapies in relapsed or refractory B-cell lymphomas
    - Large B-cell lymphomas
    - Follicular lymphoma
    - Mantle cell lymphoma

2. Optimizing CAR-T therapy outcomes in clinical practice: minimizing toxicities and optimizing efficacy
    - 3 phases of CAR-T therapy: opportunities to improve outcomes

Phase 1	Phase 2	Phase 3
Pre-infusion evaluation & management	**Early periinfusion period**	**Late post-treatment period**
• assess patient and T cell fitness	• assess risks of CAR T-related toxicities	• response assessment
• determine bridging therapy	• management of CAR T-related toxicities	• potential late CAR T-related toxicities

Current Status of CD19-CAR-T: Large B-cell Lymphomas

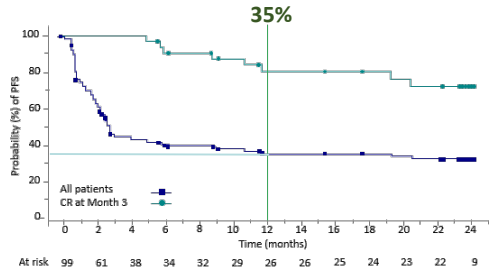
Three CD19-CAR-T Products for Relapsed/Refractory Large B-cell Lymphomas

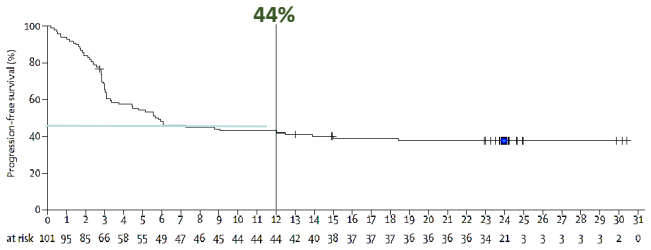
KTE-C19 *axicabtagene ciloleucel* *(axi-cel)*	CTL019 *tisagenlecleucel* *(tisa-cel)*	JCAR017 *lisocabtagene maraleucel* *(liso-cel)*
		
axi-cel	**tisa-cel**	**liso-cel**
scFv = anti-CD19	scFv = anti-CD19	scFv = anti-CD19
CD28-CD3ζ	4-1BB-CD3ζ	4-1BB-CD3ζ
ZUMA-1 trial	JULIET trial	TRANSCEND-NHL-001 trial

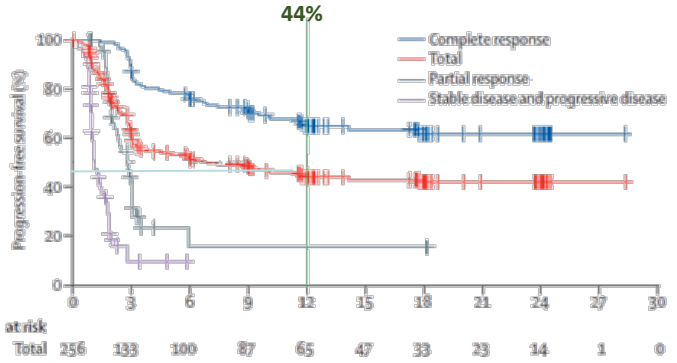
Current Status of CD19-CAR-T: Large B-cell Lymphomas

Progression-free Survival

Tisagenlecleucel* (JULIET)		Axicabtagene ciloleucel** (ZUMA-1)		Lisocabtagene maraleucel*** (TRANSCEND NHL 001)				
r/r DLBCL/HGBCL	r/r tFL	r/r DLBCL/HGBCL	r/r tFL/PMBCL	r/r DLBCL	t iNHL	PMBCL	HGBCL	FL3B
89 (80%)	22 (20%)	77 (76%)	24 (24%)	137 (51%)	78 (29%)	15 (6%)	36 (13%)	3 (1%)
DLBCL/HGBCL : other LBCL, JULIET = 4:1		DLBCL/HGBCL : other LBCL, Zuma = 3:1		DLBCL/HGBCL : other LBCL, TRANSCEND = 2:1				







*Bachanova V, et al. ICML 2019. Abstract 254; ** Locke FL, et al. Lancet Oncol. (2019)20:31-42; ***Abramson JS, et al. Lancet. (2020)396 839-852.

Current Status of CD19-CAR-T: Large B-cell Lymphomas

	Tisagenlecleucel*		Axicabtagene ciloleucel**		Lisocabtagene maraleucel***				
Disease state	r/r DLBCL	r/r tFL	r/r DLBCL	r/r tFL/PMBCL	r/r DLBCL	t iNHL	PMBCL	HGBCL	FL3B
Response evaluable pts, n	89	22	77	24	137	78	15	36	3
Follow-up, median	14 months		15.4 months		12.3 months				
Efficacy	n = 93		n = 101		n = 256				
ORR / CR	52% / 40% [best]		82% / 54% [best]		73% / 53% [best]				
% PFS for CR @ 12 months	78.5%		79%		65%				
DOR (CR/PR; median)	not reached		11.1 months (NR by IRC)		not reached (NR for PMBCL & tFL; DLBCL 5.6 mo.; HGBCL 10.8 mo.)				
DOR (CR; median)	not reached		not reached		not reached				
Safety	n = 111		n = 101		n = 269				
CRS	22% grade 3/4[a]		13% grade $\geq$ 3[b]		2% grade 3/4[b]				
Neurotoxicity	12% grade 3/4		28% grade $\geq$ 3		10% grade 3/4				

[+]These data are not intended for cross-trial comparisons since patient characteristics were not matched and protocol designs differed.

[a]Penn scale; [b]Lee scale

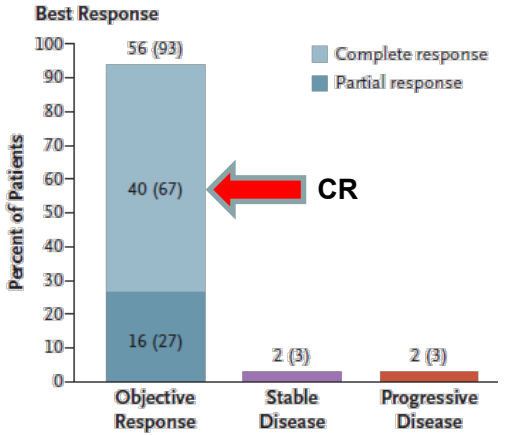
*Schuster SJ et al. *N Engl J Med.* 2019;380:45-56.; **Neelapu, SS et al. *N Engl J Med.* 2017; 377:2531-2544; **Locke FL et al. *Lancet Oncol.* 2019; 20: 31–42.; ***Abramson J et al. *Lancet.* 2020; 396: 839–52.

Current Status of CD19-CAR-T: Mantle Cell Lymphoma

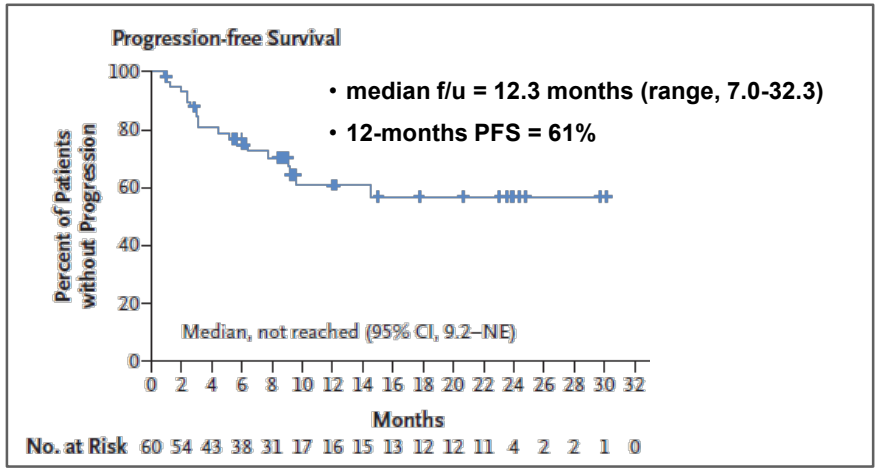
CAR-T (KTE-X19) in Relapsed or Refractory Mantle Cell Lymphoma

Table 1. Baseline Characteristics of All 68 Treated Patients.*

Characteristic	Patients
Median age (range) — yr	65 (38–79)
Intermediate or high risk according to Simplified MIPI — no. (%)†‡	38 (56)
Blastoid or pleomorphic morphologic characteristics of MCL — no. (%)	21 (31)
Ki-67 proliferation index ≥30% — no./total no. (%)‡	40/49 (82)
TP53 mutation — no. (%)	6/36 (17)
Positive CD19 status — no./total no. (%)	47/51 (92)
Median no. of previous therapies (range)§	3 (1–5)
≥3 Previous lines of therapy — no. (%)	55 (81)
Previous autologous stem-cell transplantation — no. (%)	29 (43)
Previous BTK inhibitor therapy — no. (%)§	68 (100)
Ibrutinib	58 (85)
Acalabrutinib	16 (24)
Both	6 (9)
Relapsed or refractory disease — no. (%)	
Relapse after autologous stem-cell transplantation	29 (43)
Refractory to most recent previous therapy	27 (40)
Relapse after most recent previous therapy	12 (18)
Disease that relapsed or was refractory to BTK inhibitor therapy — no. (%)	68 (100)
Refractory to BTK inhibitor therapy	42 (62)
Relapse during BTK inhibitor therapy	18 (26)
Relapse after BTK inhibitor therapy	5 (7)
Could not take BTKi therapy because of adverse events	3 (4)



Event	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	number of patients (percent)					
Symptom of cytokine release syndrome						
Any	62 (91)	20 (29)	32 (47)	8 (12)	2 (3)	0
Neurologic event	43 (63)	13 (19)	9 (13)	15 (22)	6 (9)	0



Wang M, et al. New Engl J Med (2020) 382:1331-42.

Current Status of CD19-CAR-T: Follicular Lymphoma

ZUMA-5: Axi-cel in r/r Indolent B-cell Lymphomas

- r/r low-grade follicular lymphoma (grade 1-3a), marginal zone lymphoma

- Multicenter, single arm, phase 2 trial

Eligibility:

- r/r FL grades 1-3a or MZL (nodal or extranodal)
- ≥ 2 prior lines of therapy including anti-CD20 combined with alkylating agent

Enrollment:

- 151 enrolled → 146 treated (124 FL, 22 MZL)

Response Rates

FL: 94% ORR (79/84)

- **80% CR (67/84), 14% PR (12/84)**
- **median f/u: 18.5 months**
- **12-month DOR: 77%**

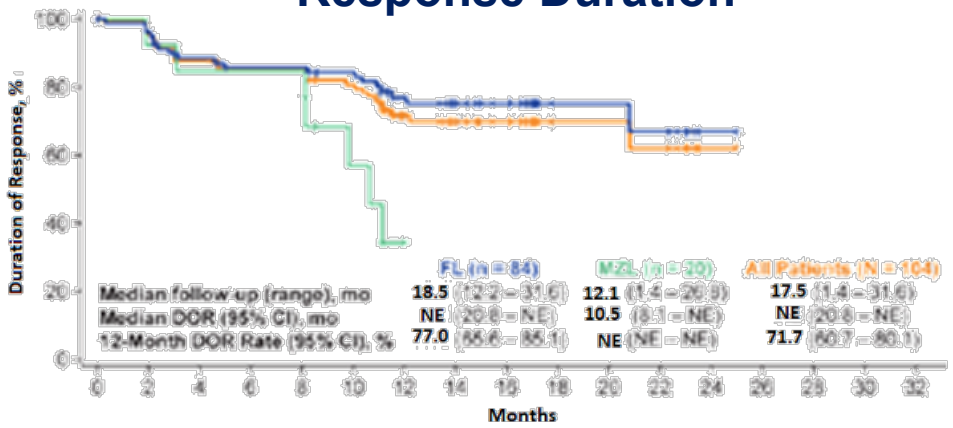
MZL: 85% ORR (17/20)

- **60% CR (12/20), 25% PR (5/20)**
- **median f/u: 12.1 months**
- **median DOR: 10.6 months**

Adverse Events

Parameter	FL (n = 124)	MZL (n = 22)	All Patients (N = 146)
CRS, n (%)			
Any grade	97 (78)	22 (100)	119 (82)
Grade ≥ 3	8 (6)	2 (9)	10 (7)
AE management, n (%)			
Tocilizumab	56 (45)	15 (68)	71 (49)
Corticosteroids	19 (15)	6 (27)	25 (17)
Parameter	**FL (n = 124)**	**MZL (n = 22)**	**All Patients (N = 146)**
Neurologic events, n (%)[a]			
Any grade	70 (56)	17 (77)	87 (60)
Grade ≥ 3	19 (15)	9 (41)	28 (19)
AE management, n (%)			
Corticosteroids	38 (31)	14 (64)	52 (36)
Tocilizumab	7 (6)	2 (9)	9 (6)

Response Duration



Jacobson C, et al. ASH 2020. Abstract 700.

Optimizing CAR-T Therapy: Pre-infusion

Phase 1: Pre-infusion evaluation & management

- **assess patient and T cell fitness**
  - *life expectancy ≥ 8 weeks*
  - *ECOG performance status 0 or 1*
  - *expected CAR-T efficacy (related to tumor bulk, serum LDH and performance status)*
  - *absolute lymphocytes >300/mm^3, or absolute CD3+ T cells 150/mm^3 for tisagenlecleucel (recommended)*
  - *absolute lymphocytes >100/mm3 for axicabtagene ciloleucel (recommended)*
- **determination of bridging therapy**
  - *avoid T cell cytotoxic therapy (e.g., bendamustine) until after apheresis*
  - *consider BTKi for non-GC DLBCL and MCL*
  - *consider PD-1 blockade for DLBCL*
  - *consider PI3Ki for FL*
  - *consider radiation therapy to bulky lesions in advance of LD chemotherapy*

Optimizing CAR-T Therapy: Early Management

Phase 2: Early periinfusion period

- **assess risks of CAR T-related toxicities**
  - *antecedent cytopenias vis-à-vis lymphodepletion plan*
  - *antecedent neurological disorders*
  - *CNS involvement by lymphoma*
  - *anatomic sites of involvement by lymphoma (blood, spleen, marrow)*
- **management of CAR T-related toxicities**
  - *CRS grading and management*
  - *ICANS grading and management*

Optimizing CAR-T Therapy: Early Management

CRS grading and management

Grading and management of cytokine release syndrome

ASBMT CRS Grade	Defining Features of Grade	Management
Grade 1	Fever with temperature ≥38°C but no hypotension or hypoxia	• Antipyretics and IV hydration • Diagnostic work-up to rule out infection • Consider growth factors and antibiotics if neutropenic
Grade 2	Fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula	• Supportive care as in grade 1 • IV fluid boluses and/or supplemental oxygen • Tocilizumab +/− dexamethasone or its equivalent of methylprednisolone
Grade 3	Fever with hypotension requiring one vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula, facemask, non-rebreather mask, or venturi mask	• supportive care as in grade 1 • consider monitoring in intensive care unit • vasopressor support and/or supplemental oxygen • tocilizumab + dexamethasone 10-20 mg IV q 6 hrs or its equivalent of methylprednisolone
Grade 4	Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	• Supportive care as in grade 1 • Monitoring in intensive care unit • Vasopressor support and/or supplemental oxygen via positive pressure ventilation • Tocilizumab + methylprednisolone 1000 mg/day

ASBMT, American Society for Blood Marrow Transplant; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; IV, intravenous.

- For hypotension requiring *any* dose of vasopressor and/or hypoxia requiring more than low-flow oxygen related to CRS, tocilizumab is strongly recommended

Neelapu S. Hematol Oncol (2019) 37(S1)

Optimizing CAR-T Therapy: Early Management

ICANS grading and management

ASBMT ICANS Grade	Defining Features of Grade	Management
Grade 1	• ICE score 7-9 and/or depressed level of consciousness but awakens spontaneously • No seizures, motor weakness, or raised ICP/cerebral edema	• Aspiration precautions and IV hydration • Seizure prophylaxis with levetiracetam • EEG • Imaging of brain • Consider tocilizumab if there is concurrent CRS
Grade 2	• ICE score 3-6 and/or depressed level of consciousness but awakens to voice. • No seizures, motor weakness, or raised ICP/cerebral edema	• Supportive care as in grade 1 • Consider dexamethasone or its equivalent of methylprednisolone
Grade 3	• ICE score 0-2 and/or depressed level of consciousness but awakens to tactile stimulus • Any clinical seizure focal or generalized that resolves rapidly, or nonconvulsive seizures on EEG that resolve with intervention • No motor weakness • Focal/local edema on neuroimaging	• Supportive care as in grade 1 • Dexamethasone 10-20 mg IV q 6 hours or its equivalent of methylprednisolone • Control seizures with benzodiazepines (for short-term control) and levetiracetam +/− phenobarbital and/or lacosamide • High-dose methylprednisolone 1000 mg/day for focal/local edema
Grade 4	• ICE score 0 and patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse or stupor or coma • Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between • Deep focal motor weakness such as hemiparesis or paraparesis • Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad	• Supportive care as in grade 1 • High-dose methylprednisolone 1000 mg/day • Control seizures with benzodiazepines (for short-term control) and levetiracetam +/− phenobarbital and/or lacosamide • Imaging of spine for focal motor weakness • Lower ICP by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt in patients with cerebral edema

ASBMT, American Society for Blood and Marrow Transplant; EEG, electroencephalograph; ICE, immune effector cell-associated encephalopathy; ICP, intracranial pressure; m, modified.

Neelapu S. Hematol Oncol (2019) 37(S1)

Optimizing CAR-T Therapy: Late Management

Phase 3: Late post-treatment period

- **response assessment**
  - **PET/CT should be used to confirm CR per 2007 or 2014 International Working Group Criteria**
  - **Routine PET/CT or CT at 1 month post infusion is not prognostically useful. First response assessment in clinically improving patients should be performed at 3 months *(data to be discussed)***
  - **Usefulness of baseline TMTV or change in TMTV is still under investigation.**

- **potential late CAR T-related toxicities**
  - **To date, there are no new safety signals.**
  - **We recently published 5-year follow up for a cohort of patients in sustained CR after CTL019 (tisagenlecleucel)[1]:**

I. ***Time to resolution of all cytopenias: median = 56 days (IQR: 27-139)***
II. ***Within 2 years, 11/16 (67%) recovered B cells; 9/16 (82%) had detectable CAR19 transgene at B cell recovery***
III. ***At 5 years, 11/16 (69%) had normal IgM, 9/16 (56%) normal IgA, and 6/16 (38%) normal IgG levels***
IV. ***All patients in remission > 1 year recovered normal CD3, CD4, and CD8 T-cell counts (median CD3 recovery time 4.6 months, range: IQR 3.9-4.9)***
V. ***Secondary malignancies occurred in 6/38 patients (16%): 1 AML; 1 MDS; 1 melanoma; 2 lung cancer; 1 prostate cancer***

[1] Chong EA, Ruella M, Schuster SJ. New Engl J Med (2021) 384(7):673-4.

Current PET/CT response criteria used in DLBCL trials

Revised Response Criteria (2007)[1]

Response	Nodal Masses
CR	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative
PR	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site

Deauville Score	[^{18}F]FDG Uptake
1	No uptake
2	≤ Mediastinal blood pool
3	> Mediastinum and ≤ liver
4	Moderately more than liver at any site
5	Markedly more* than liver at any site and/or new sites of disease

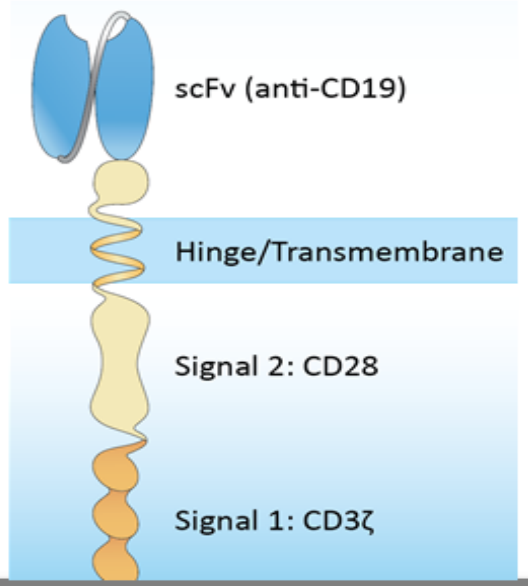
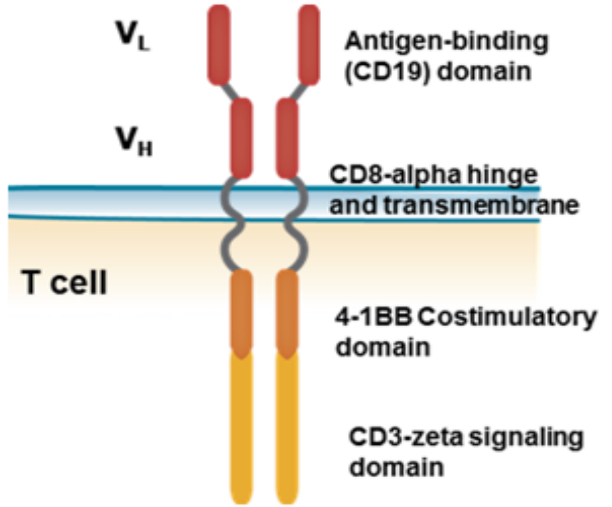
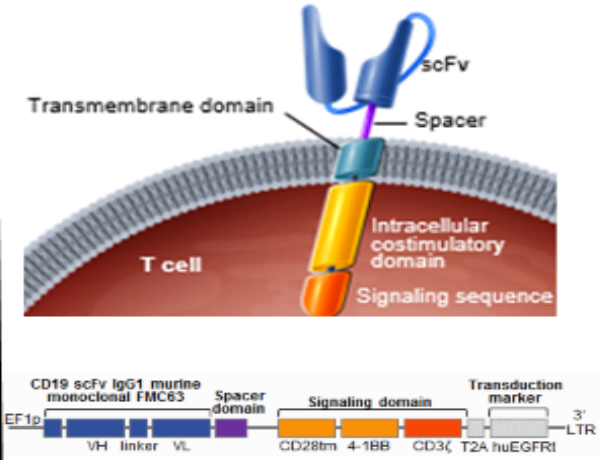
*Maximum standardized uptake value of the lesion more than two times liver uptake.

Lugano Classification (2014)[2]

Response and Site	PET-CT–Based Response
Complete	Complete metabolic response
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS
Nonmeasured lesion	Not applicable
Organ enlargement	Not applicable
New lesions	None
Bone marrow	No evidence of FDG-avid disease in marrow
Partial	Partial metabolic response
Lymph nodes and extralymphatic sites	Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease
Nonmeasured lesions	Not applicable
Organ enlargement	Not applicable
New lesions	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline

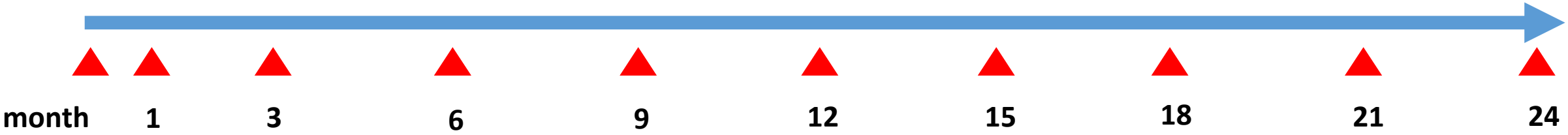
[1] Cheson BD, et al. (2007) J Clin Oncol 25:579-586.
[2] Cheson BD, et al. (2014) J Clin Oncol 32(27):3059-68.

How was PET/CT used in 3 registrational CAR-T trials?

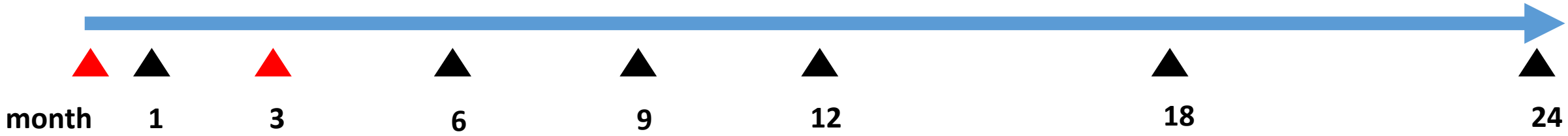
	KTE-C19 *axicabtagene ciloleucel* *(axi-cel)*	CTL019 *tisagenlecleucel* *(tisa-cel)*	JCAR017 *lisocabtagene maraleucel* *(liso-cel)*
			
	axi-cel	tisa-cel	liso-cel
	scFv = anti-CD19	scFv = anti-CD19	scFv = anti-CD19
	CD28-CD3ζ	4-1BB-CD3ζ	4-1BB-CD3ζ
Name of trial →	ZUMA-1 trial	JULIET trial	TRANSCEND-NHL-001 trial

PET/CT requirements in 3 registrational CAR-T trials

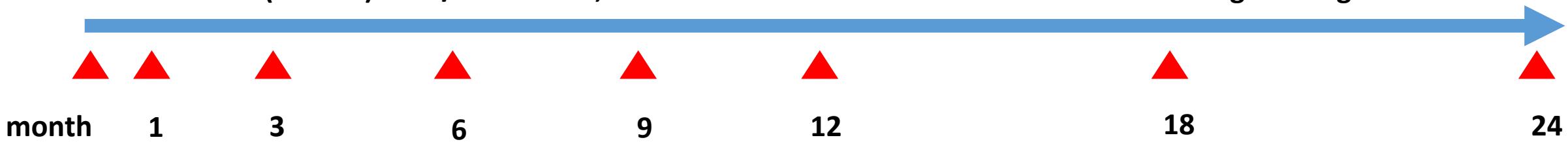
ZUMA 1[1,2] (axi-cel): PET/CT at baseline, at 4 weeks, at month 3 and every 3 months up to 2 years post–infusion



JULIET[3] (tisa-cel): PET/CT at baseline (within 4 weeks of infusion before lymphodepletion) and at month 3



TRANSCEND[4] (liso-cel): PET/CT until CR, then CT or PETCT at the discretion of the treating investigator



▲ = PET/CT

▲ = CT/MRI

[1]Neelapu SS, *et al.* N Engl J Med (2017) 377:2531-44.
[2]Locke FL, *et al.* Lancet Oncol (2019) 20:31-42.
[3]Schuster SJ, *et al*. N Engl J Med (2019) 380(1):45-56.
[4]Abramson J, *et al.* Lancet (2020) 396:839-52.

PET/CT use in 3 CAR-T clinical trials

1. PET/CT detects more late response conversions than CT

	JULIET[1]	ZUMA-1[2]	TRANSCEND[3,6]
Response evaluable pts*, n	**68**	**101**	**192**
Median time to response (CR or PR)	**0.9 months (range, 0.7-3.3)**	**0.9 months (range, 0.8-6.2)**	**1 month (range, 0.7-8.9)**

*no bridging chemotherapy or imaging with measurable disease after completion of bridging chemotherapy, prior to CAR-T

2. PET/CT or CT response assessment at Month-1 is not prognostically useful due to subsequent conversions of PR to CR

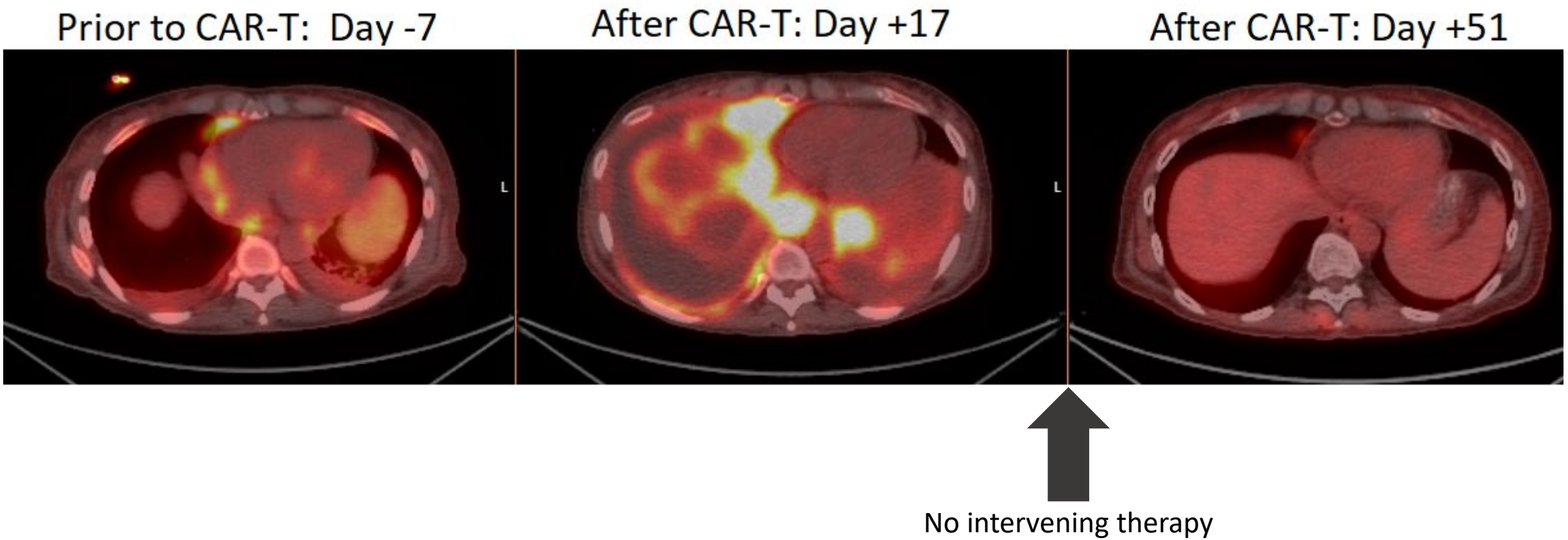
PR conversions to CR	JULIET[4] (Month-1 CT)	ZUMA-1[5] (Month-1 PET/CT)
Month-1 PR converting to CR, n/N, total Month-1 PR	**12/24 (54%)**	**11/33 (33%)**
Median time from PR to CR conversion	**2 months (range, 1-17.0)**	**not reported** (most by 6 months)

*JULIET used CT for Month-1 response assessment; ZUMA-1 and TRANSCEND used PET/CT for Month-1 response assessment

1. https://www.fda.gov/media/107296
2. https://www.fda.gov/media/108377
3. https://www.fda.gov/media/145711
4. Schuster SJ, *et al*. N Engl J Med (2019) 380(1):45-56.
5. Locke FL, *et al.* Lancet Oncol (2019) 20:31-42.
6. Abramson J, *et al.* Lancet (2020) 396:839-52.

Case

53-year-old woman with refractory large cell transformation of marginal zone lymphoma.



PET/CT: beyond response assessment

- **Can we use PET/CT to predict the outcome of CAR-T therapy before T cell infusion?**

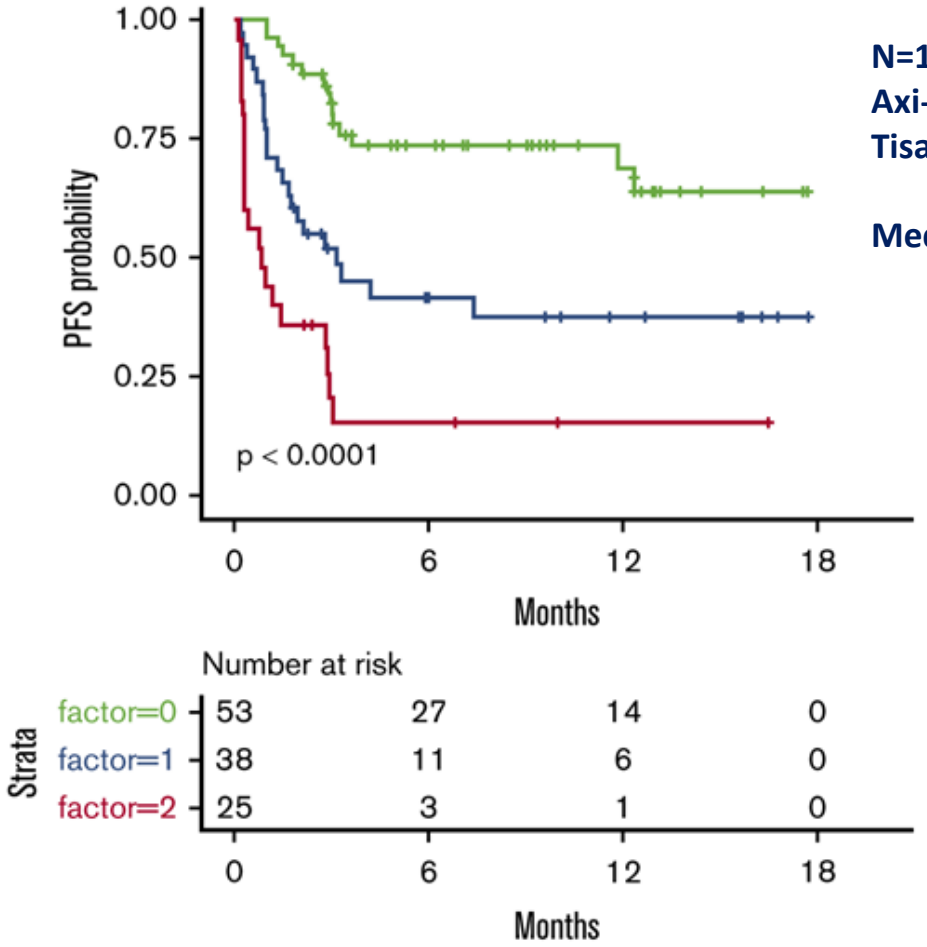
Independent risk factors for early post CAR-T progression of disease by multivariate analysis

- **Extranodal (EN) sites ≥ 2**
- **High CRP**
- **TMTV41% > 80 mL**

Three prognostic groups are defined by the sum of two prognostic factors:

- **EN sites ≥ 2**
- **TMTV 41% > 80 mL**

0 = very good; 1 = good; 2 = poor



N=116
Axi-cel, n= 49
Tisa-cel, n = 67

Median FU = 8.2 months

Vercellino L, et al. Blood Adv. (2020) 4(22): 5607-5615.

Radiologic imaging: beyond response assessment

*"Images Are More than Pictures, They Are Data"**

Objective:

- use data from PET or CT images, including data beyond our visual perception, to ***improve decision support***

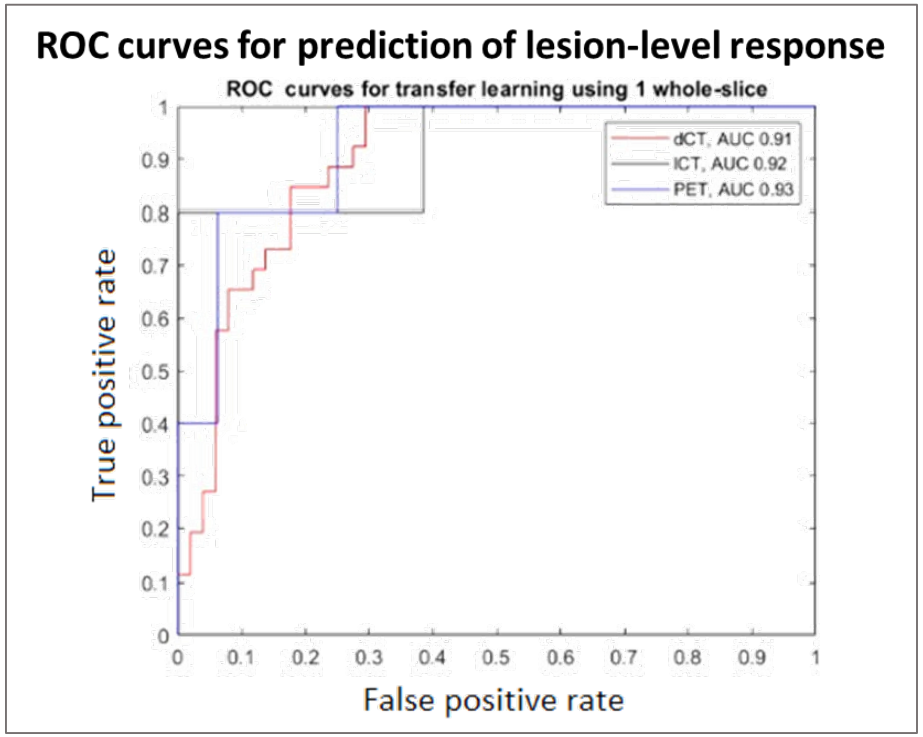
Approach:

- *extract quantitative features* (data) from PET or CT images using data characterization algorithms
  - *Semantic features* (common radiology lexicon)
  - *Agnostic features* (quantitative mathematical descriptors)
- *create a database of correlative quantitative features*, which can be analyzed vis-à-vis outcomes
- finally, prospective validation of the utility of these quantitative features for predicting outcomes

*R. J. Gillies

Prediction of Lymphoma Response to CAR-T by Image Analysis

- Apply machine (deep) learning-based image analysis to ***pre-treatment*** diagnostic CT (dCT) images, low-dose CT (lCT) images, and ^{18}FDG-PET images to predict lesion-level treatment response to CAR T-cell therapy
- Transfer learning was performed by loading a pre-trained artificial neural network (AlexNet), modifying its output layers by replacing the last 3 layers with a fully connected layer and a binary classification output layer (CR or < CR), and retraining the network with specific training samples. We studied 770 nodal lesions: 402 by dCT, 214 by lCT and 154 by PET images from 39 patients with B-NHLs treated with CAR-T (13 FL; 26 DLBCL).
- Lesion-level response prediction was performed using volume of interest (VOI)-based and whole slice-based (non-VOI) approaches with CAVASS software; the whole slice approach had the best diagnostic accuracy for response prediction.



	diagnostic CT				low-dose CT				PET			
input	Acc.	Sens	Spec	AUC	Acc.	Sens	Spec	AUC	Acc.	Sens	Spec	AUC
1 whole-slice	0.82	0.87	0.77	0.91	0.91	0.94	0.75	0.92	0.87	0.90	0.77	0.93
	±0.05	±0.07	±0.12	±0.03	±0.06	±0.06	±0.32	±0.08	±0.06	±0.06	±0.19	±0.07

Tong, Udupa, Schuster, Torigian: *preliminary data*

Conclusions

- **CD19-directed CAR-T therapies have already improved the outcomes for relapsed or refractory large B-cell, follicular, and mantle cell lymphomas.**
- **Clinical outcomes of CAR-T cell approaches can be further improved by appropriate patient selection and toxicity management.**
- **As our experience with CAR-T therapies grows, clinical outcomes will continue to improve.**

Many Thanks !

2nd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Scientific board:
Marco Ladetto (Alessandria)
Umberto Vitolo (Candiolo-TO)