Linfomi aggressivi in recidiva: terapia CART. Risultati, criteri di selezione e di riferimento dei pazienti

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Disclosures: Annalisa Chiappella

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Major Stockholder	N/A
Conferences/Educational Activities	Celgene, Janssen, Roche, Servier
Scientific Advisory Board	Celgene, IQONE, Janssen

CLINICAL TRIALS AND OBSERVATIONS

Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study

Michael Crump,[1] Sattva S. Neelapu,[2] Umar Farooq,[3] Eric Van Den Neste,[4] John Kuruvilla,[1] Jason Westin,[2] Brian K. Link,[3] Annette Hay,[1] James R. Cerhan,[5] Liting Zhu,[1] Sami Boussetta,[4] Lei Feng,[2] Matthew J. Maurer,[5] Lynn Navale,[6] Jeff Wiezorek,[6] William Y. Go,[6] and Christian Gisselbrecht[4]

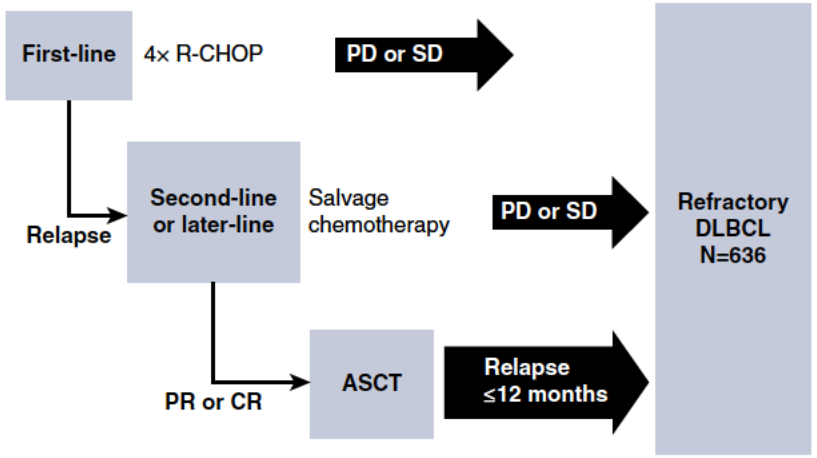
blood

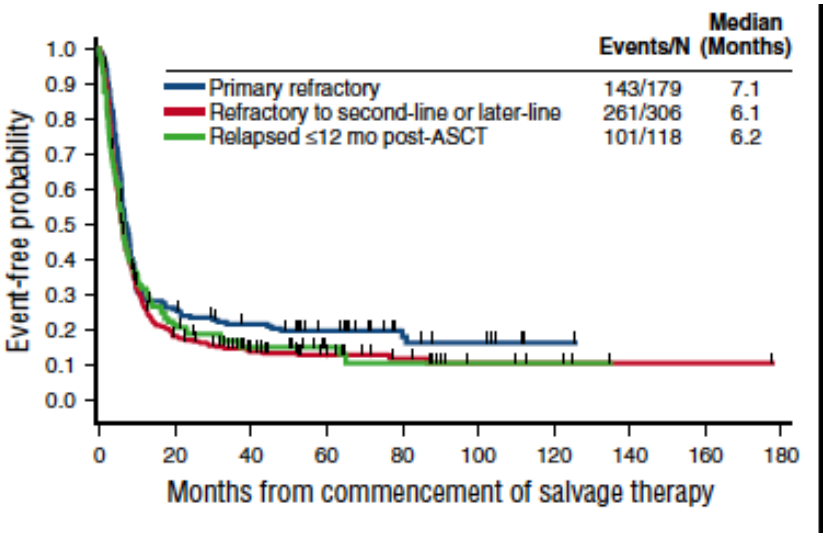
BLOOD, 19 OCTOBER 2017 • VOLUME 130, NUMBER 16

Large retrospective analysis of outcomes in 636 refractory DLBCL

How did these patients with refractory DLBCL respond to the next line of therapy?

- ✓ ORR 26% (CR 7%)
- ✓ Median OS 6.3 months





CAR-T

CAR-T

- ✓ CAR-T products
- ✓ Manifacturing process

Clinical trial and real-word experiences

- ✓ Efficacy
- ✓ Toxicity
- ✓ Predictors of response and toxicity

INT experience

CAR-T

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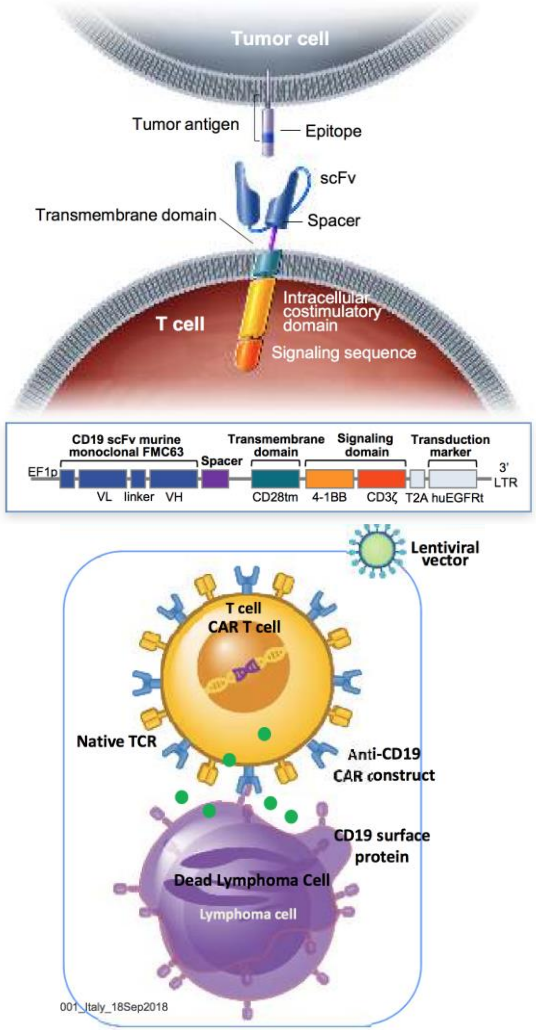
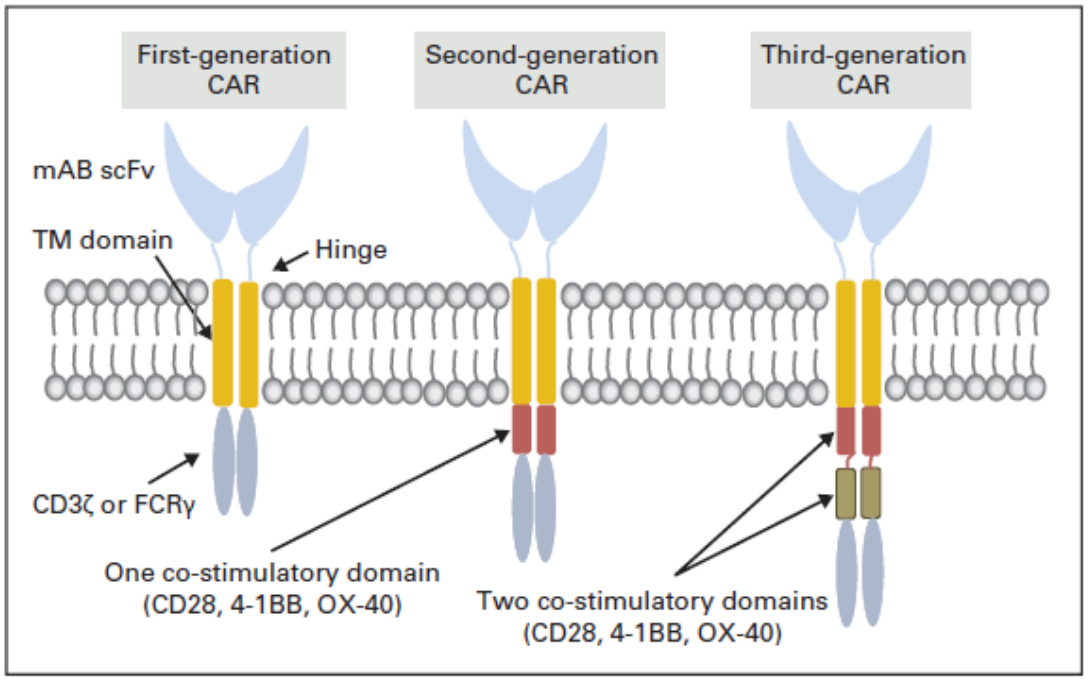
INT experience

Chimeric Antigen Receptor T-cell Therapy (CAR-T)

Adoptive immunotherapy that incorporates T cells that have been genetically engineered to express a chimeric antigen receptor for the pan–B-cell CD19 antigen.



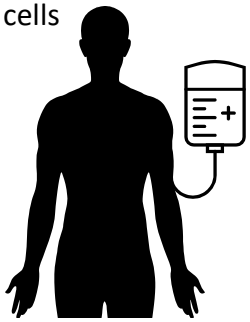


Brentjens et al *JCO* 2015

CAR T-Cell Therapy: Vein to Vein process

Leukapheresis

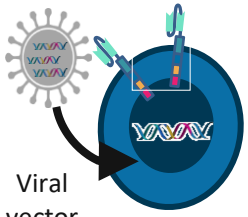
Collect patient's white blood cells

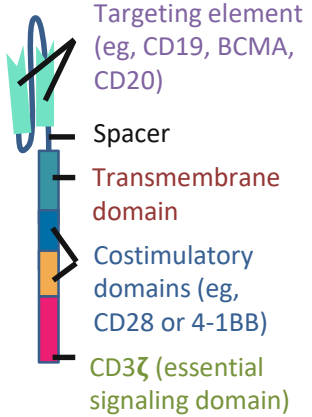


Manufacturing

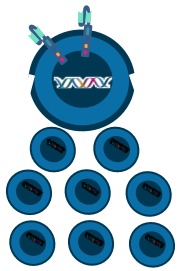
Isolate and activate T-cells

Engineer T-cells with CAR gene





Expand CAR T-cells

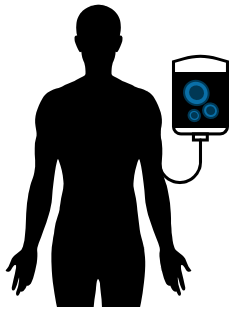


Median manufacturing time: 17-28 days

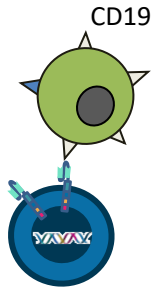
Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

Infusion

Infuse same patient with CAR T-cells



Activity



Majors. EHA 2018. Abstr PS1156. Lim. Cell. 2017;168:724. Sadelain. Nat Rev Cancer. 2003;3:35.
Brentjens. Nat Med. 2003;9:279. Park. ASH 2015. Abstr 682. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

CAR-T

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Clinical trial and real-word experiences

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- ✓ **Toxicity**
- ✓ **Predictors of response and toxicity**

INT experience

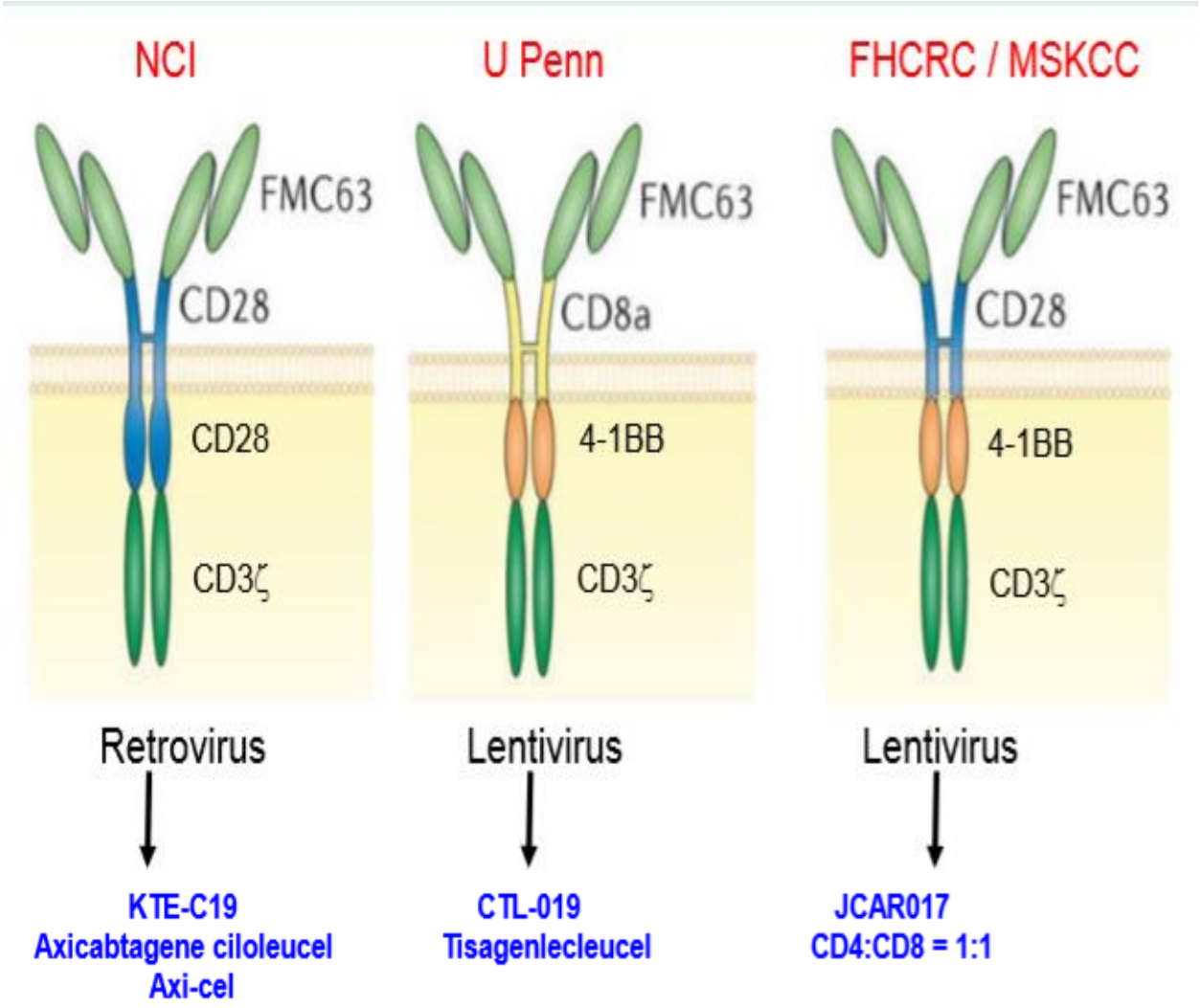
CD19 CAR-T products in pivotal trials in NHL

Antigen-binding (CD19) domain

CD8-alpha hinge and transmembrane

Costimulatory domain

CD3-zeta signaling domain



Adapted from van der Steegen et al. Nat Rev Drug Discov, 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiezorek, and W.Y. Go

ZUMA-1 study

111 enrolled patients
101 treated

Adult patients with large B-cell lymphoma (DLBCL, PMBCL, or TFL); refractory disease (SD/PD with previous chemotherapy or relapsed within 12 mos of ASCT) (N = 111)

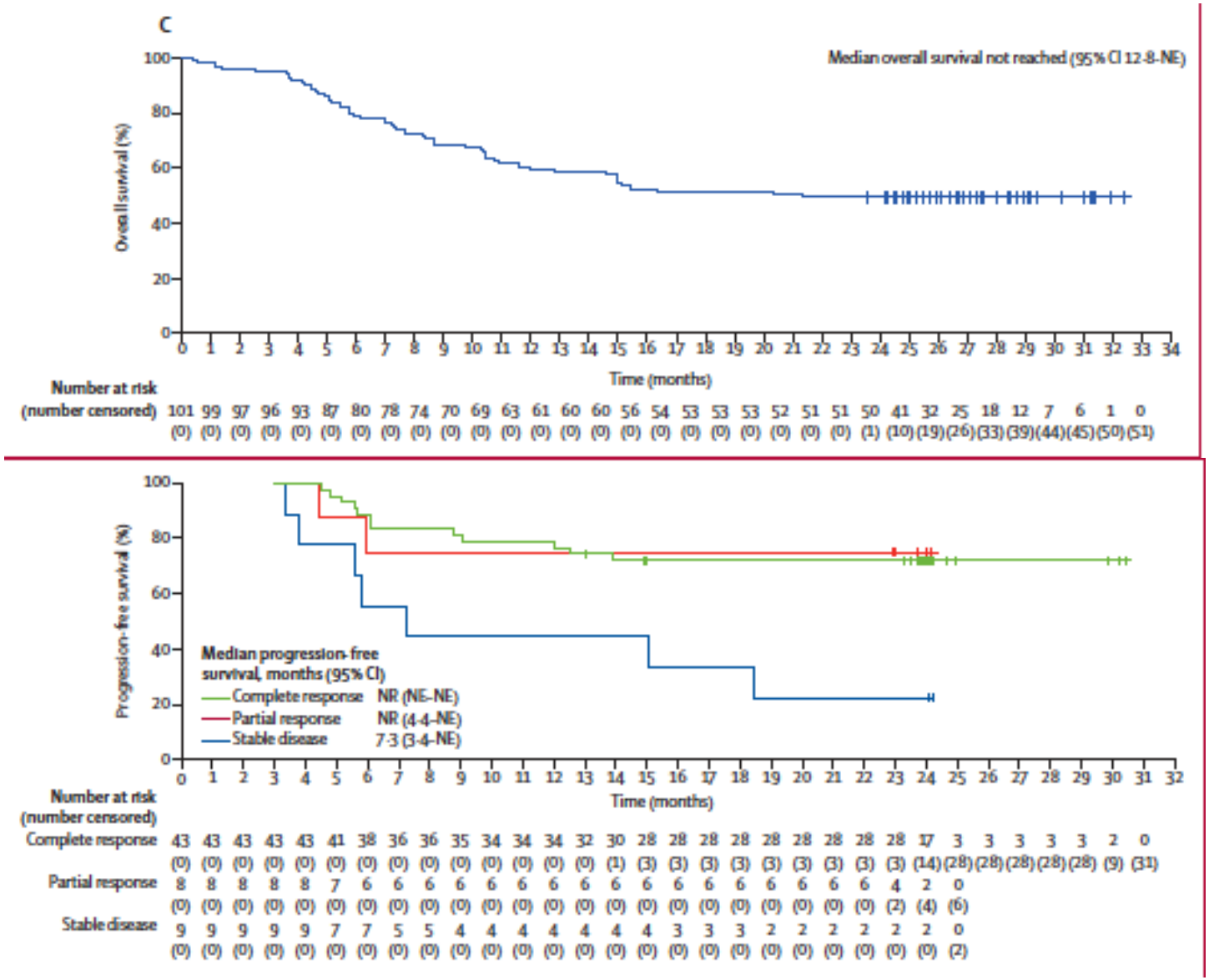
→ **Leukapheresis** → **Axicabtagene ciloleucel manufacturing and lymphodepletion*** → **Axicabtagene ciloleucel infusion** (2×10^6 cells) → **Posttreatment Follow-up**

*Fludarabine and cyclophosphamide on days −5, −4, and −3 before administration of single dose of CAR T-cell therapy; no bridging chemotherapy allowed.

- Primary endpoint: ORR; secondary endpoints: DoR, OS, safety
- Baseline: median prior therapies, 3; primary refractory, 26%; relapsed after autologous SCT, 21%

Neelapu. NEJM. 2017;377:2531.

ZUMA-1 study. ORR 83%, median DO 11.1 months



Locke FL et al, Lancet Oncol 2019

JULIET study, first global CAR-T cells study in DLBCL: Tisagenlecleucel in Refractory B-NHL

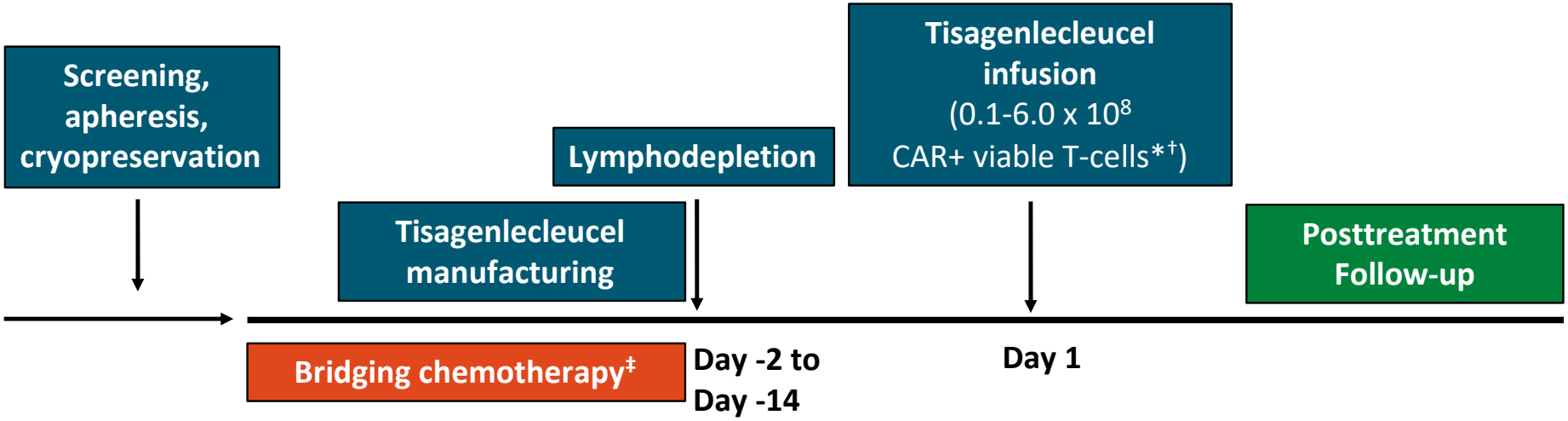
Key eligibility criteria

- ≥ 18 years of age
- Central confirmation of histology
- ≥ 2 prior lines of therapy for DLBCL
- PD after or ineligible for auto-SCT
- No prior anti-CD19 therapy
- No active CNS involvement

Endpoints

- **Primary endpoint:** best overall response rate (ORR: CR + PR)
  - Lugano criteria used for response assessment by IRC[1]
- **Secondary endpoints:** DOR, OS, safety

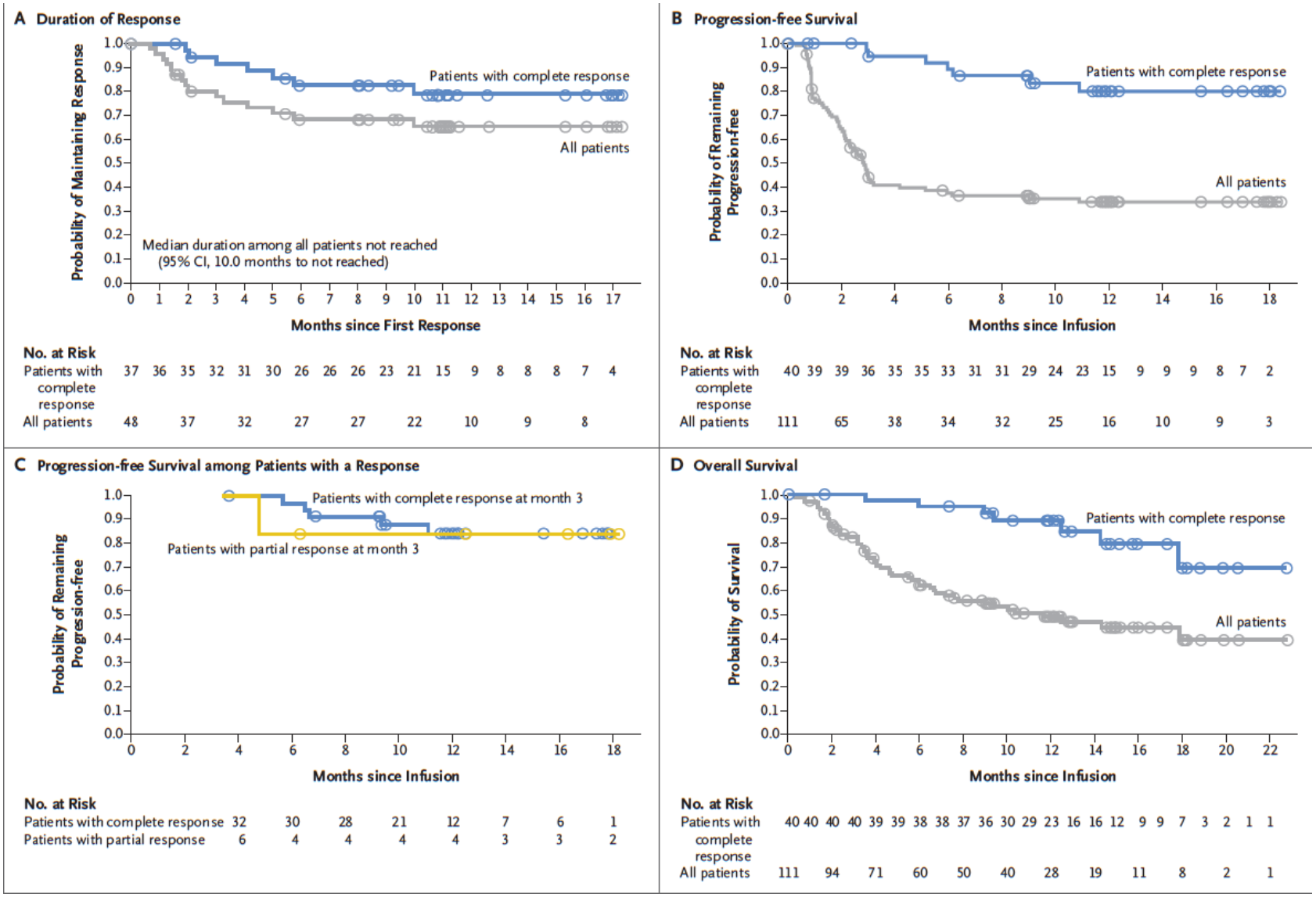
238 screened patients
111 treated



*Inpatient or outpatient infusion. †D/c before infusion: n = 50 (inability to manufacture, n = 12; other reasons, n = 38).
‡When needed.

Shuster SJ et al, NEJM 2019

JULIET study. ORR 52%; ORR (3 mo) 38%; ORR (6 mo) 33%



Shuster SJ et al, NEJM 2019

JULIET study. Special Interest Adverse Events

	(N = 111)		
AESI[a]	All Grades, %	Grade 3, %	Grade 4, %
Cytokine release syndrome[b]	58	14	8
Neurological events	21	7	5
Prolonged cytopenia[c]	44	16	16
Infections	34	18	2
Febrile neutropenia	15	13	2

[a] Occurring within 8 weeks of tisagenlecleucel infusion. [b] Cytokine release syndrome was graded using the Penn scale. [c] At day 28.

	Patients (N = 111)
Time to onset, median (range), days[a]	3 (1-9)
Duration, median (range), days[a]	7 (2-30)
Hypotension that required intervention, %	26
High-dose vasopressors	6
Intubated, %	7
Anticytokine therapy, %	16
Tocilizumab	15
Corticosteroids	11

[a] Calculated based only on patients who had cytokine release syndrome (n = 64), excluding 1 patient who had onset on day 51.

No deaths due to tisagenlecleucel, CRS or cerebral edema

The most common neurological events were:

- Confusional state (8% any grade; 2% grade 3)
- Encephalopathy (6% any grade; 1% grade 3 and 4% grade 4)

Tocilizumab administered according to a protocol-specific treatment algorithm (CRS graded per the Penn scale[1])

- 3% of patients with grade 2 CRS
- 50% with grade 3 CRS
- 100% with grade 4 CRS

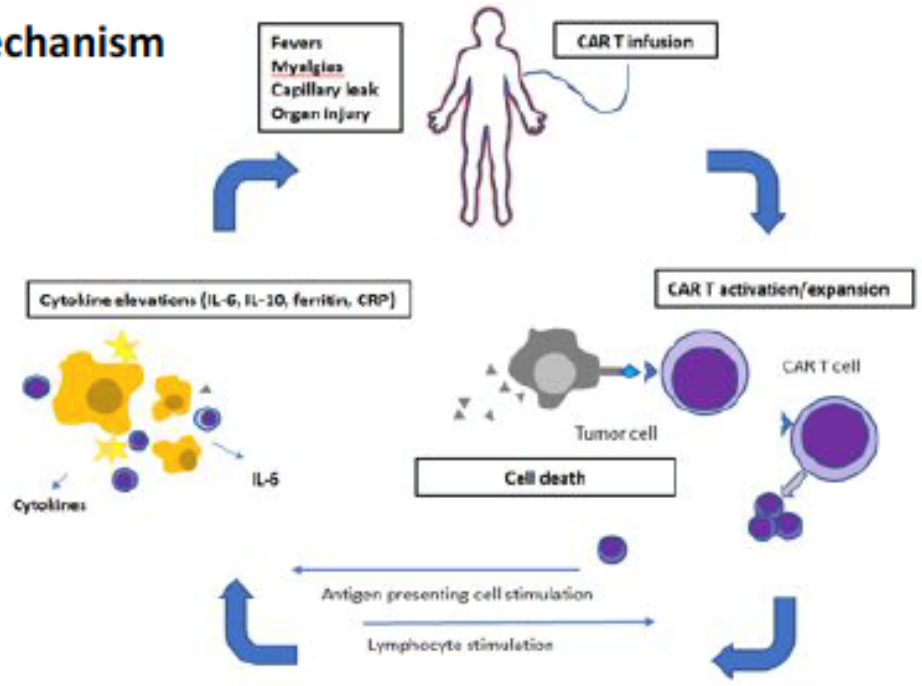
Shuster SJ et al, NEJM 2019

CRS: cytokine release syndrome

G	PENN GRADING SCALE[1]
1	Mild reaction: treated with supportive care such as antipyretics, antiemetics
2	Moderate reaction: some signs of organ dysfunction related to CRS and not attributable to any other condition. Need for IV therapies (not including fluid resuscitation for hypotension)
3	More severe reaction: symptoms related to organ dysfunction related to CRS; hypotension treated with intravenous fluids (defined as multiple fluid boluses for blood pressure support) or low-dose vasopressors, coagulopathy requiring FFP/cryo, and hypoxia requiring supplemental O2
4	Life-threatening complications such as hypotension requiring high-dose Vasopressors or hypoxia requiring mechanical ventilation

1. Porter DL *et al. Sci Transl Med*. 2015

Mechanism



Symptoms

Onset 1-14 days after infusion, duration 1-10 days

Fevers come first and get very high (105ºF/41ºC)

Myalgias, fatigue, anorexia, capillary leak, hypoxia, hypotension

Management

Supportive care

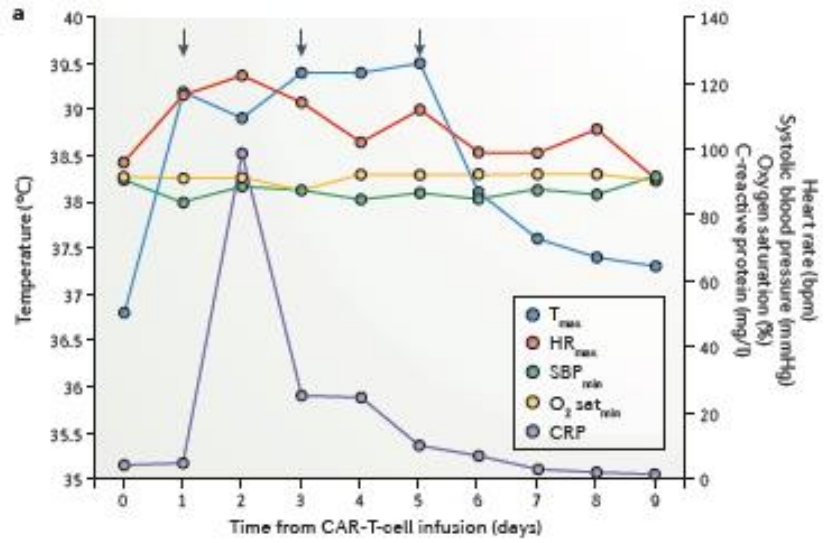
Anti-cytokine interventions

Neurologic toxicity

Chimeric antigen receptor T-cell therapy — assessment and management of toxicities

Sattva S. Neelapu[1], Sudhakar Tummala[2], Partow Kebriaei[3], William Wierda[4], Cristina Gutierrez[5], Frederick L. Locke[6], Krishna V. Komanduri[7], Yi Lin[8], Nitin Jain[4], Naval Daver[4], Jason Westin[1], Alison M. Gulbis[9], Monica E. Loghin[2], John F. de Groot[2], Sherry Adkins[1], Suzanne E. Davis[10], Katayoun Rezvani[3], Patrick Hwu[10], Elizabeth J. Shpall[3]

NATURE REVIEWS | CLINICAL ONCOLOGY 2017



Mechanism

T cell vs. cytokine mediated (endothelial activation)

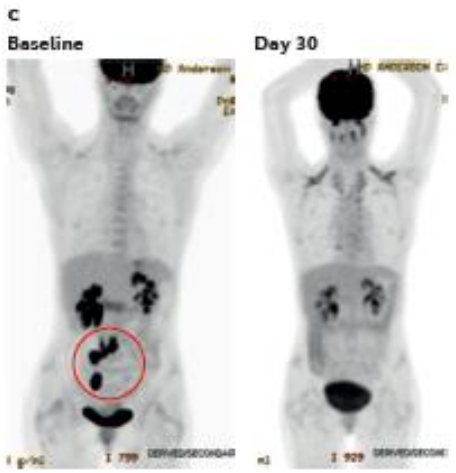
CAR T cells are seen in the CSF[1-5]

Symptoms

Aphasia, delirium, encephalopathy, seizures

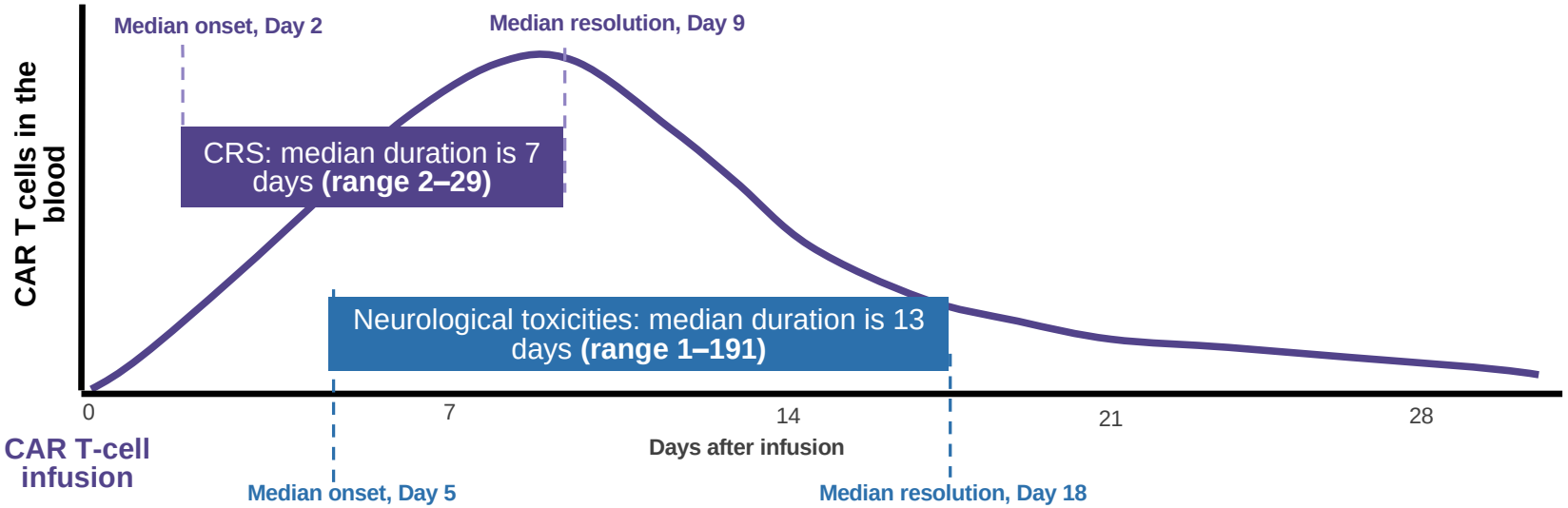
Management

No clear response to anti-cytokine treatment



Timing and duration of acute adverse events

CRS coincides with maximal T-cell expansion[1] CRS may occur within minutes but more typically within days[1,2]



CRS and NEs are acute adverse events

AE: adverse event; CAR: chimeric antigen receptor; CRS: cytokine release syndrome; SmPC: Summary of Product Characteristics; NE: neurological event; RMM: risk minimisation measure

1. Lee DW, *et al. Blood* 2014; 124:188–195. 2. Yescarta SmPC (May 2019; available at www.ema.europa.eu).

CD19-targeted CAR-T cells: Late Effects

Clinical characteristics	N = 59 (%), median FU after CAR-T 23 months
Median age	60 (range, 34 – 73)
NHL/CLL	42 (71%) / 17 (29%)
Median prior lines	4 (range, 1 – 8)
One CAR T infusion	35 (59%)
Two/Three CAR T infusions	22 (37%); 2 (3%)
Salvage Therapy after CAR T	29 (49)

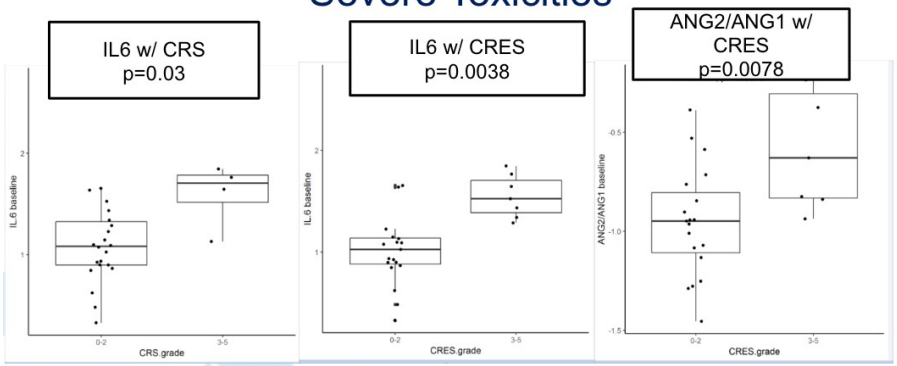
Adverse Events	
Cytopenia beyond 90 days	**25%**
Subsequent malignancies	**14%**
Neuropsychiatric disordes	**8%**
Cardiovascular Events	**8%**
Severe hypogammaglobulinemia	**41%**
Hospital admission due to infections	**46%**

3/59 pts died of non-relapse causes
(2 due to infection after allo HCT, and 1 due to duodenal ulcer and gut perforation)

Cordeiro A et al, ASH 2018

Axi-cells in Real World: Predictors of Response, Resistance and Toxicity

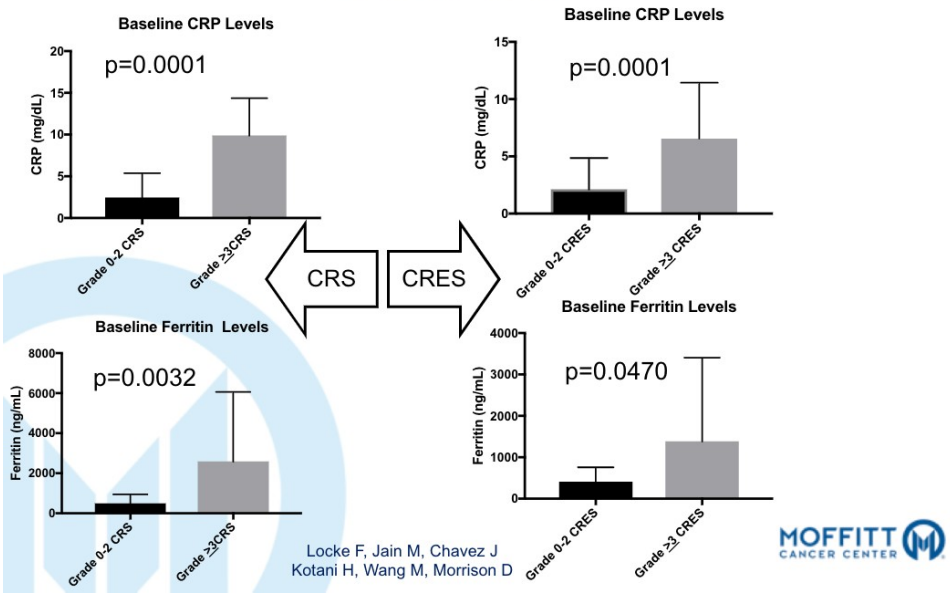
Pre-infusion Cytokines in Patients with Severe Toxicities



Locke F, Jain M, Chavez J
Kotani H, Wang M, Morrison D

MOFFITT CANCER CENTER

Pre-infusion Biomarkers in Patients with Severe Toxicities



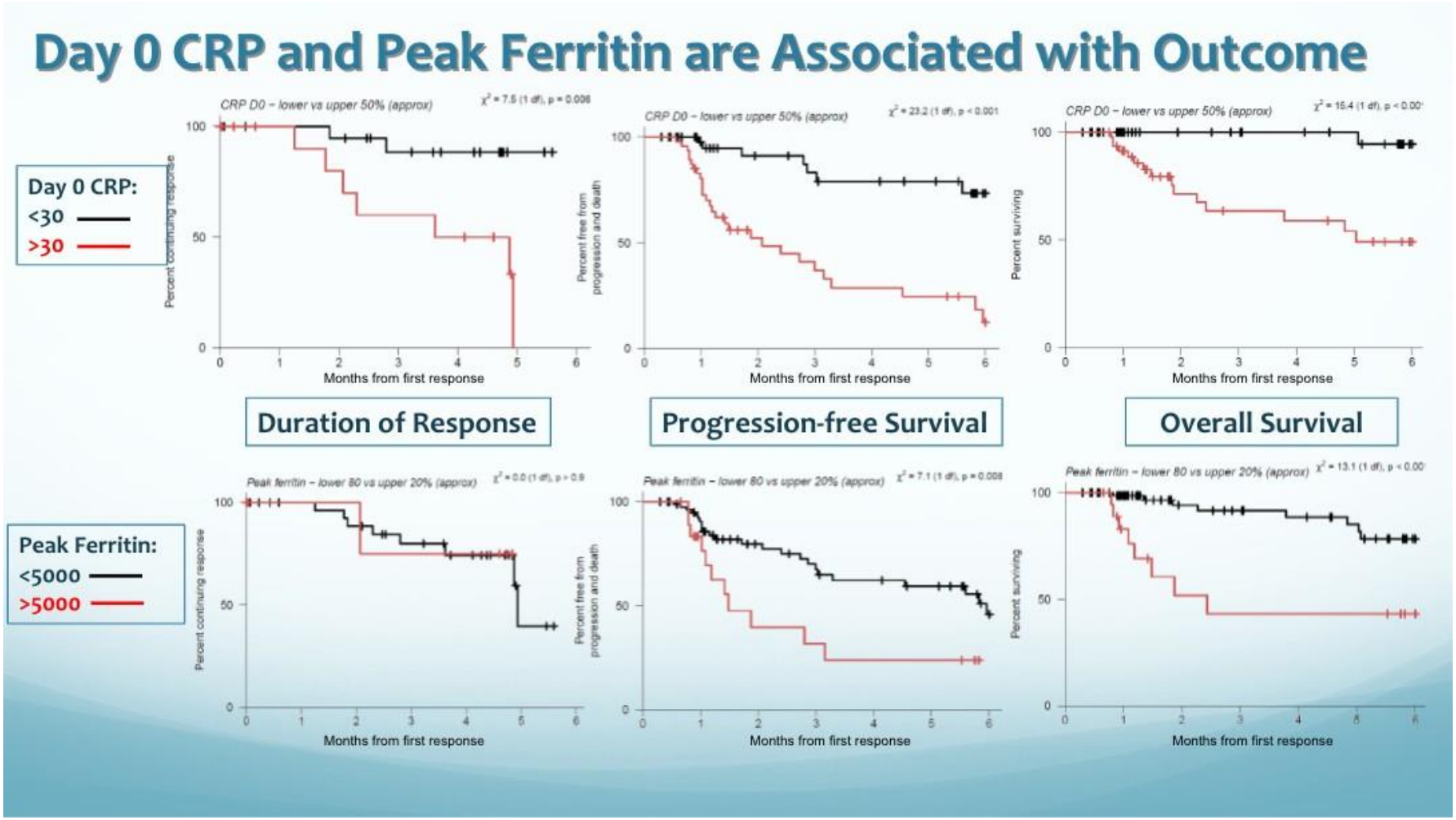
Locke F, Jain M, Chavez J
Kotani H, Wang M, Morrison D

MOFFITT CANCER CENTER

Patients with severe neuro-toxicity (≥grade 4) manifested **higher ANG2 levels and higher ANG2:ANG1** ratios, which predicts Endothelial Cells activation

Faramand R et al, ASH 2018

Axi-cells in Real World: Predictors of Response, Resistance and Toxicity



Jacobson CA et al, ASH 2018

CAR-T

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- ✓ CAR-T products
- ✓ Manifacturing process

Clinical trial and real-word experiences

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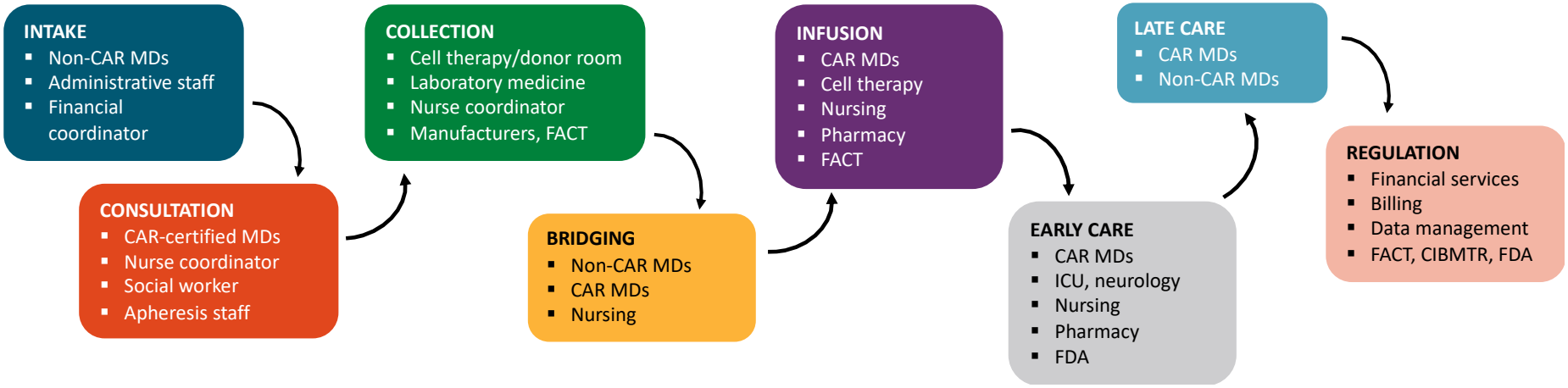
INT experience

CAR-T Team

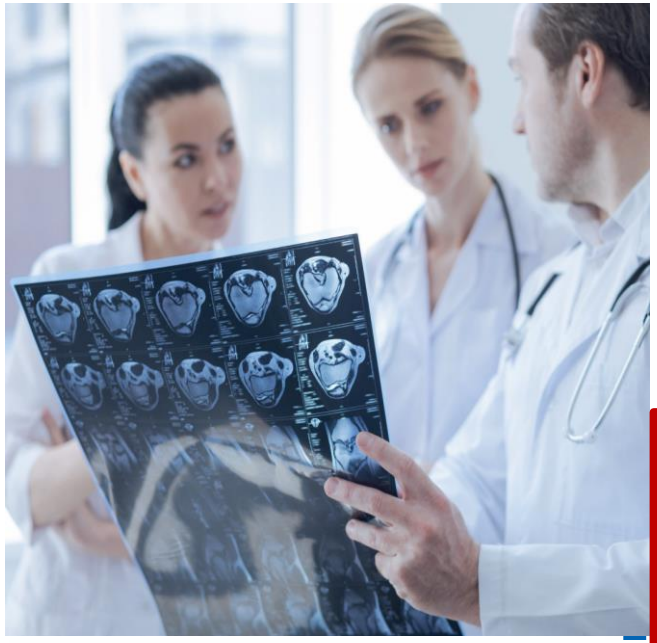
- **Consider the therapy and refer early**: Plan patient's treatment course early; consider when more chemotherapy may be appropriate vs commercially approved CAR T-cell therapy or CAR T-cell therapy clinical trial
- **Maintain clear communication** prior to leukapheresis, during bridging chemotherapy, and prior to T-cell infusion to ensure successful collection and manufacturing of T-cells and safe administration
- All physicians, pharmacists, nurses, and other midlevel providers interacting with patients receiving CAR T-cell therapy **must have FDA-mandated training**

Essential Steps and Required Personnel for the MSKCC CAR T-Cell Program



Perica. Biol Blood Marrow Transplant. 2018;24:1135.

CAR-T Clinical facilities



THE PROCESS OF CAR T CELL THERAPY IN EUROPE

EHA Guidance Document

EUROPEAN HEMATOLOGY ASSOCIATION

For more information, please visit ehaweb.org

EHA | POWERED BY YOU!

BOX 3: Clinical facilities required for safe administration of CAR T cell therapy

Clinical hematology unit (inpatient and outpatient). CAR T cell therapy can be administered in a hematology ward, in a hematopoietic transplantation unit, or in a specific CAR T cell patient facility.

Intensive care unit with sufficient capacity and staff who are trained in all stages of the use of CAR T cells, from the start of lympho-depletive chemotherapy to completion of therapy.

Emergency department with on-site medical resuscitation specialists that guarantees an immediate response when needed.

Neurology department on site or able to be rapidly engaged, if necessary. A referral neurologist needs to be appointed to discuss monitoring and care protocols. Performing magnetic resonance imaging (MRI) before baseline initiation could be left to the discretion of the hematologist and/or referral neurologist but is highly recommended for pediatric indications.

On-site medical imaging service with MRI. The full-time (24 hours per day, 7 days per week [24/7]) presence of a professional trained to use the facility's MRI equipment is essential. Performing magnetic resonance imaging (MRI) before initiation of CAR T cell therapy is recommended, particularly for pediatric indications. The hospital should have a radiographic brain MRI patient protocol under CAR T cells (written locally) to allow a radiographer to start MRI in the absence of a radiologist (e.g., at night) without loss of time. An on-site, on-call, radiologist or tele-diagnosis protocol is also highly recommended.

Pharmacy available and able to deliver (24/7) all necessary drugs to treat CAR T cell therapy recipients, including those needed for complications of the therapy.

Transfusion service able to supply blood components at any time (24/7).

EHA Guidance Document 2019, Hemasphere 2019

Three major CD19 CAR-T products in DLBCL

Product	Trial	Construct	Lymphodepleting chemotherapy	Cell dose	Toxicities	Outcomes
Axicabtagene ciloleucel	ZUMA-1	Anti-CD19 CD3ζ CD28	Cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) for 3 days	2×10^6 cells/kg	CRS: 93% (≥grade 3: 13%) ICANS: 64% (≥grade 3: 28%)	Best ORR; 82% Best CR rate: 58% CR at 2 years: 37% 2-year PFS: 39% 2-year OS: 51%
Tisagenecleucel	JULIET	Anti-CD19 CD3ζ 4-1BB	Fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2) for 3 days, or bendamustine (90 mg/m^2) for 2 days	Median dose: 3×10^8 cells	CRS: 58% (≥ grade 3: 22%) ICANS: 21% (≥ grade 3: 12%)	Best ORR: 52% CR: 40% Median OS: 12 months
Lisocabtagene maraleucel	TRANSCEND	Anti-CD19 CD3ζ 4-1BB Fixed 1 : 1 CD4 : CD8 ratio	Cyclophosphamide (300 mg/m^2) and fludarabine (30 mg/m^2) for 3 days	1×10^8 cells (flat dose)	CRS: 35% (≥grade 3: 1%) ICANS: 19% (≥grade 3: 12%)	Best ORR: 80% Best CR rate: 59% 1-year OS: 69%

CR, complete response; CRS; cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ORS, objective response rate; OS, overall survival; PFS, progression-free survival.

August 7th, 2019: Tisa-cel
November 12th, 2019: Axi-cel

Patient selection is primarily guided by the EMA and AIFA approved indications

Caution for use or no use in patients with:

- **Histotypes according to product specification**
- Active uncontrolled infections → no use
- ECOG > 1 → no use
- HBV/HCV/HIV active infection → no use
- Venous thrombosis in the last six months → no use
- CNS disorder or primary CNS lymphoma → no use
- Previous allo-SCT → no use
- Inadequate renal, hepatic, pulmonary or cardiac function
- Prior anti-CD19 therapy → repeat biopsy to prove the presence of CD19
- ANC > 1000, Hb > 8, PLTS > 75.000, **ALC according to product specification**

SIE STUDY

Principal Investigator: Prof Paolo Corradini

A multicenter prospective observational study on Chimeric Antigen Receptor (CAR) T-cell therapy for lymphoma: monitoring feasibility, efficacy, toxicity and biomarkers in a real life setting

Primary Objective:

- Feasibility and efficacy of the treatment in the real life practice

Secondary Objectives:

- Evaluation of Outcome [Response rate (ORR), Overall survival (OS), Progression free survival (PFS), duration of response (DoR) non-relapse mortality (NRM)].
- Evaluation of safety (CRS, neurotoxicity, infections, cytopenias, B cell aplasia)
- Comparison of the two different CAR T-cell products (time from patient screening to infusion, disease response and safety)
- Characterization of biomarkers of early response (circulating tumor cell free DNA versus PET and CT scans)
- Characterization of toxicity biomarkers
- Analysis of immune reconstitution

Conclusions

- ✓ Refractory DLBCL represents an unmeet clinical need
- ✓ CAR-T cells are able to determine high rate of response and promising PFS (Juliet trial, ZUMA trial, real world data)
- ✓ Patient eligible to CAR-T therapy should be carefully identified
- ✓ CRS and neurotoxicity are manageable, if promptly recognized and treated by an experienced staff
- ✓ Further studies and longer follow-up are needed to identify predictors of response and toxicities

Acknowledgments

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Luca Pappalettera
Giulia Perrone
Martina Pennisi
Chiara Rusconi

Reparto VI piano
Giorgia Gobbi

Reparto VIII piano
Lucia Saracino

Infermiere di ricerca
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