

Tossicità acute legate ai nuovi trattamenti - Tossicità da nuovi approcci immunoterapici



Fondazione IRCCS
San Gerardo dei Tintori

Sistema Socio Sanitario



Regione
Lombardia



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Disclosures:

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CENTRO MARIA LETIZIA VERGA



Tossicità da nuovi approcci immunoterapici

11:15 – 11:30

- CAR T cells: CRS, ICANS, ICAHT, IEC-HS, Ig deficiency
- Brentuximab/Nivolumab: neuropathy

11:30 -11:35 Q & A



Tossicità da nuovi approcci immunoterapici

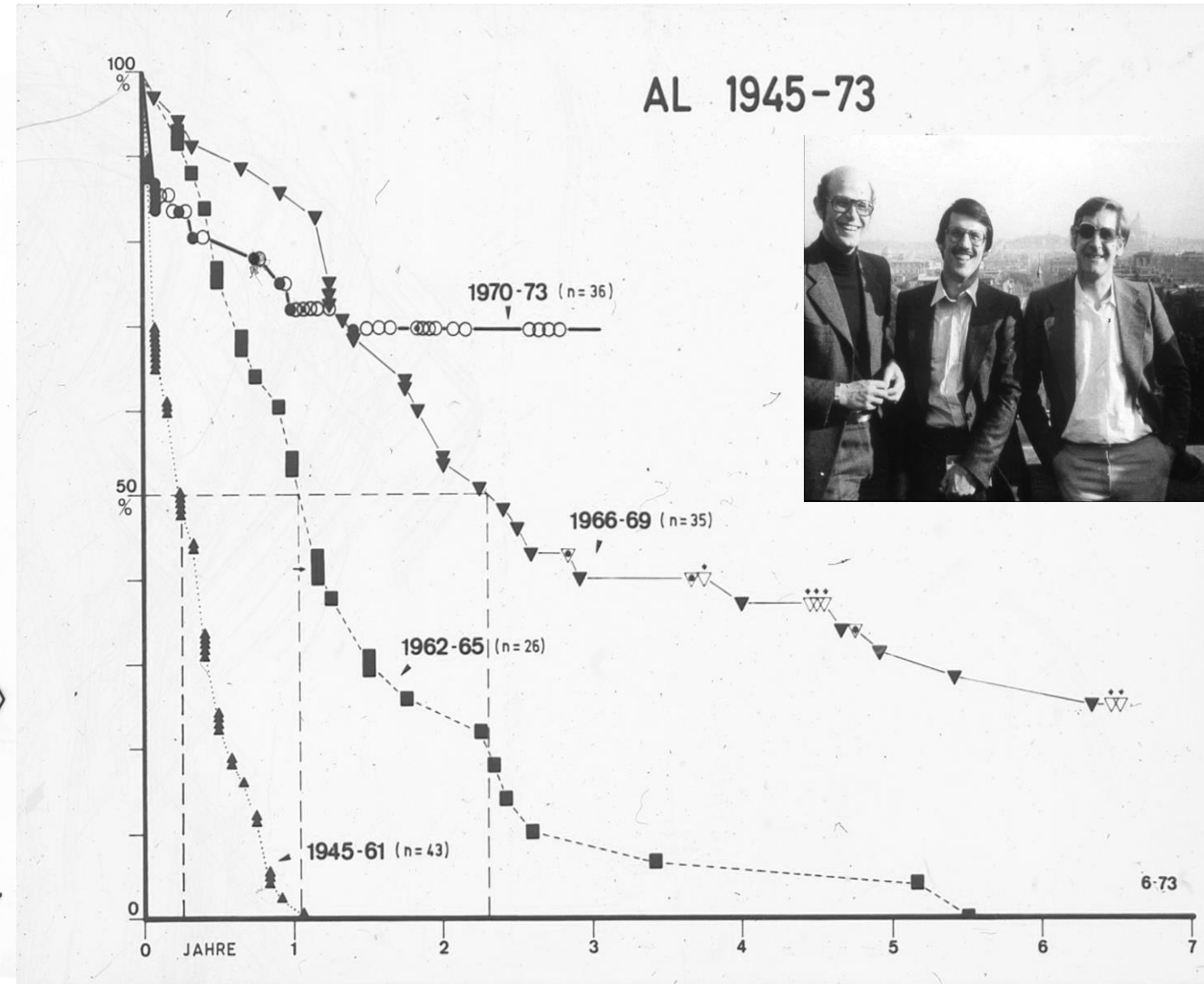
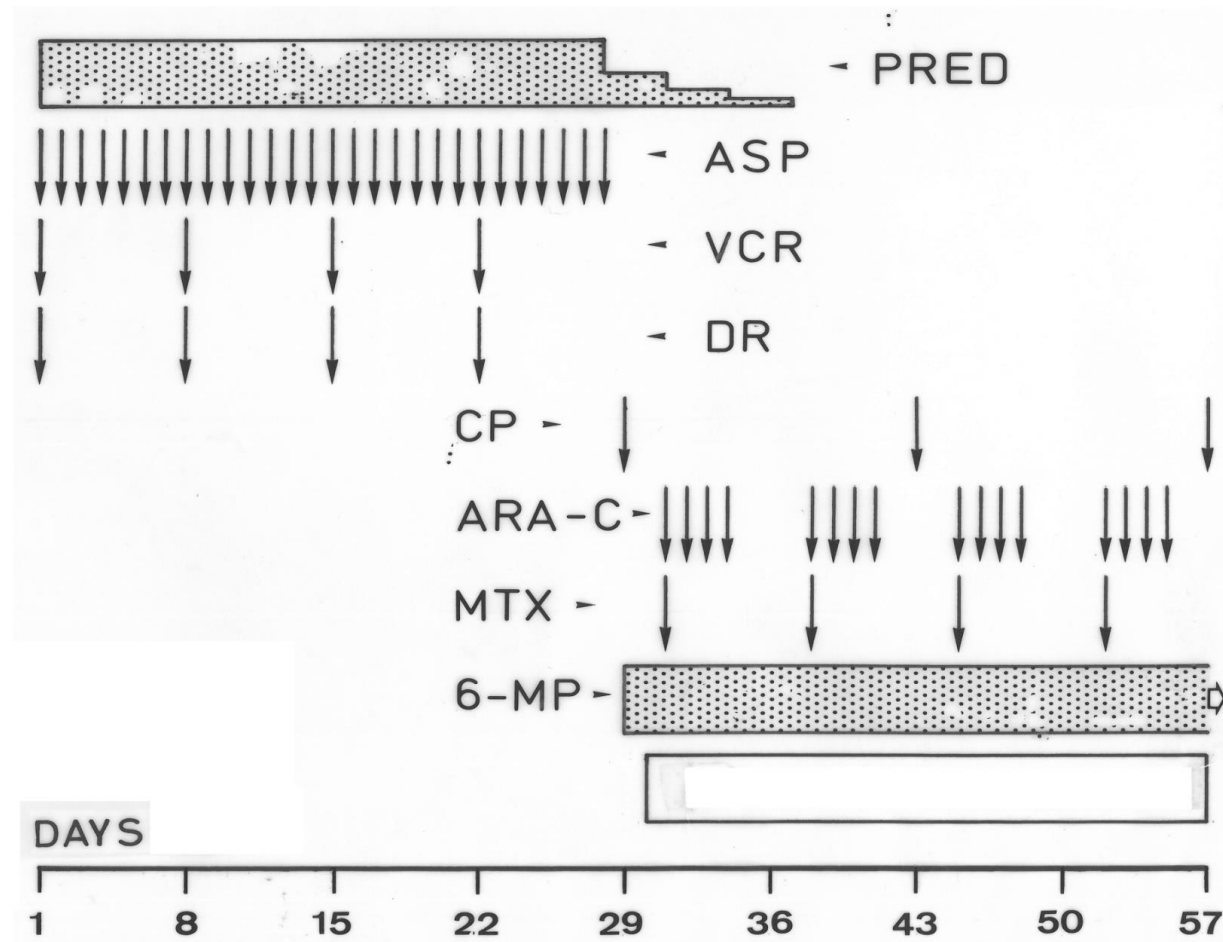
11:15 – 11:30

- **CAR T cells: CRS, ICANS, ICAHT, IEC-HS, Ig deficiency**
- Brentuximab/Nivolumab: neuropathy

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History of Childhood ALL - a story of success: cure rate from 3% to 90%



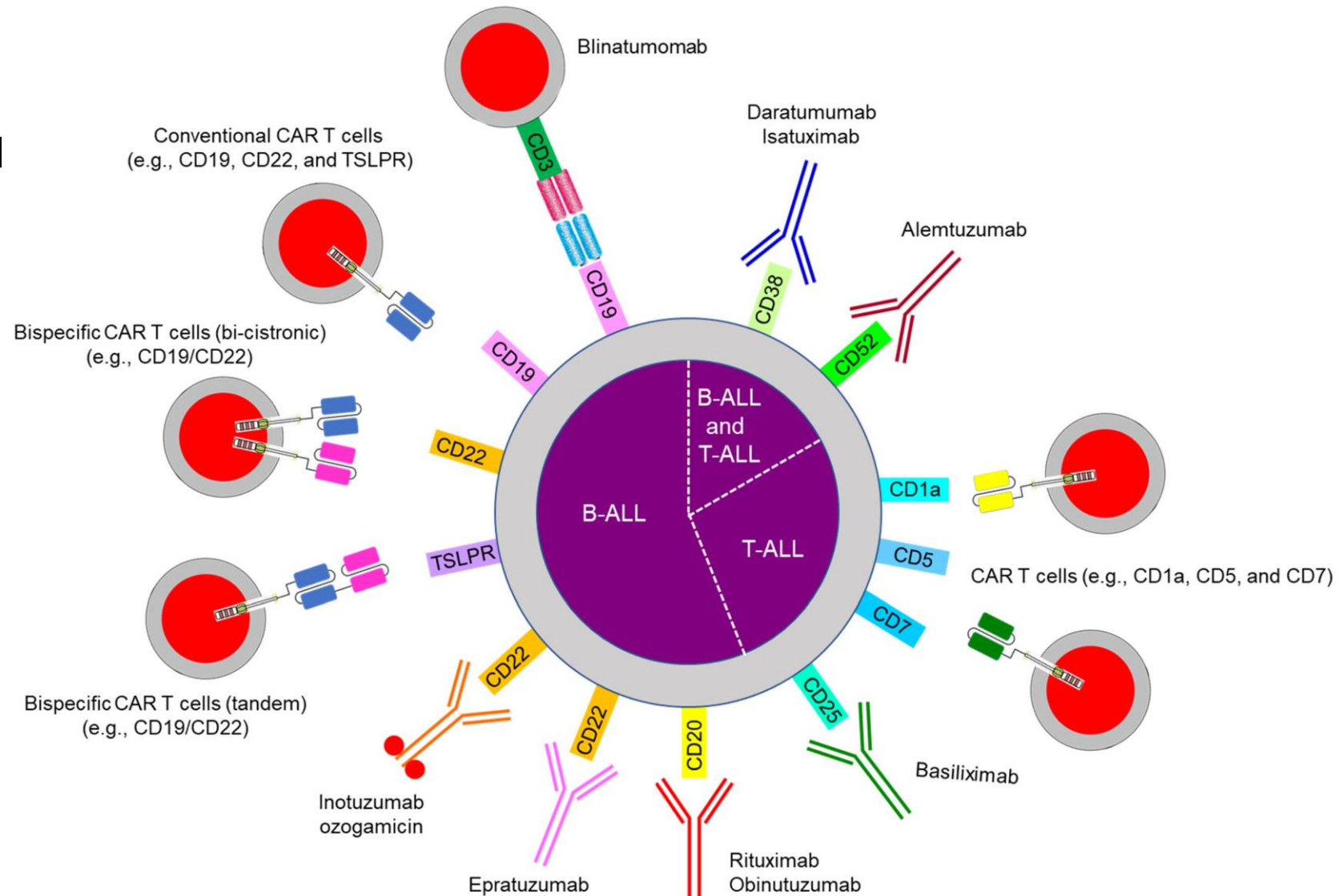
- targeted treatments may overcome disease resistance and/or might replace standard treatment elements, even in children with chemosensitive ALL, to decrease toxicity^{1,2}

ALL, acute lymphoblastic leukemia; CR, complete remission; R/R, relapsed/refractory.

1. Pui CH, et al. Childhood Acute Lymphoblastic Leukemia: Progress Through Collaboration. J Clin Oncol. 2015 Sep 20;33(27):2938-48.

2. Inaba H, Pui CH. Advances in the Diagnosis and Treatment of Pediatric Acute Lymphoblastic Leukemia. J Clin Med. 2021 Apr 29;10(9):1926

Immunotherapy TARGET



CAR T-Cell Therapy: Tisagenlecleucel (CTL019)

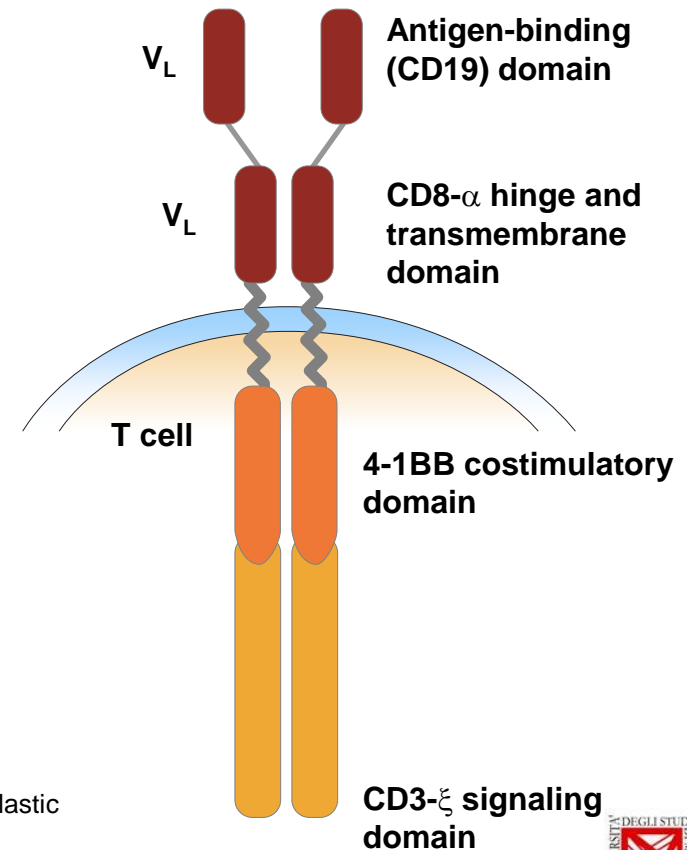
- a second-generation CAR-T-cell therapy targeting the CD19 antigen expressed on the surface of cells, manufactured from autologous T cells transduced to express a 4-1BB costimulatory domain and a CD3 ζ T-cell activation signaling domain¹⁻⁴



- FDA approval in the United States**
 - Aug 2017: for patients up to 25 years of age with r/r BCP ALL
- EMA approval in Europe**
 - August 2018: for patients up to 25 years of age with r/r BCP ALL
- AIFA approval in Italy**
 - August 2019: refunding & regulatory strategies defined within the National Healths System

Grupp S et al, N Engl J Med 2013

<https://emilywhiteheadfoundation.org>



CAR, Chimeric Antigen Receptor; DLBCL, diffuse large B-cell lymphoma; EU, European Union; peds ALL, pediatric acute lymphoblastic leukemia; r/r, relapsed/refractory.

1. Milone MC, et al. *Mol Ther*. 2009;17:1453-1464; 2. Zhang H, et al. *J Immunol*. 2007;179:4910-4918; 3. Kalos M, et al. *Sci Transl Med*. 2011;3:95ra73; 4. Maude SL, et al. *N Engl J Med*. 2018;378(5):439-448.

Indicazioni attuali AIFA

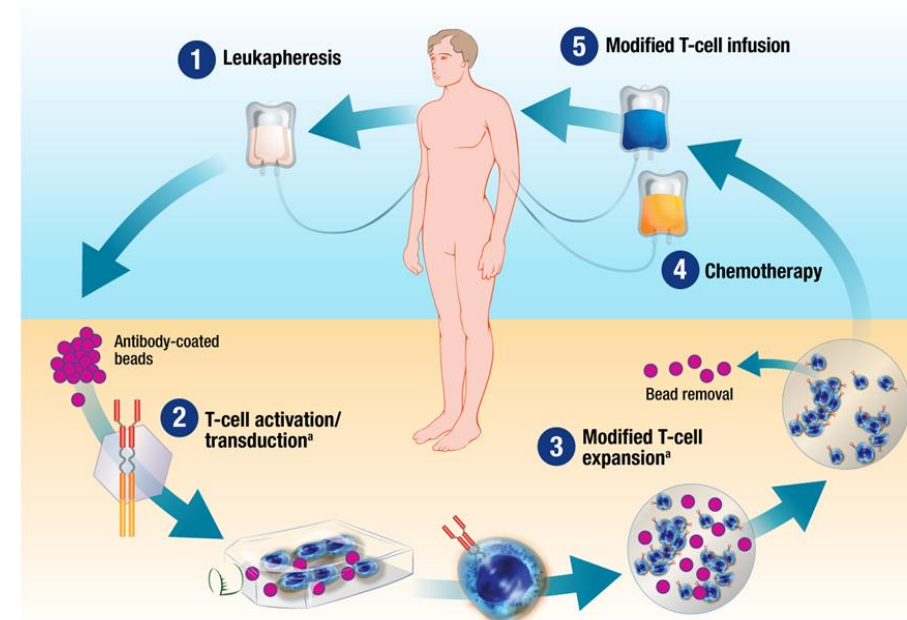
Eligibilità a Kymriah si declina diversamente in ogni paese

- pazienti pediatrici e giovani adulti fino a 25 anni di età affetti da leucemia linfoblastica acuta a cellule B CD19+ :
 - Refrattaria
 - in recidiva dopo trapianto di cellule staminali emopoietiche allogeniche
 - in II o III recidiva
 - Non più necessario 5% di blasti ma solo definizione di recidiva*

** nella prescrizione di AIFA - farmaci soggetti a monitoraggio - non si possono scrivere decimali, quindi necessariamente >1% ($\geq 0.5\%$)*

CAR, Chimeric Antigen Receptor; ALL, acute lymphoblastic leukemia; R/R, relapsed/refractory.

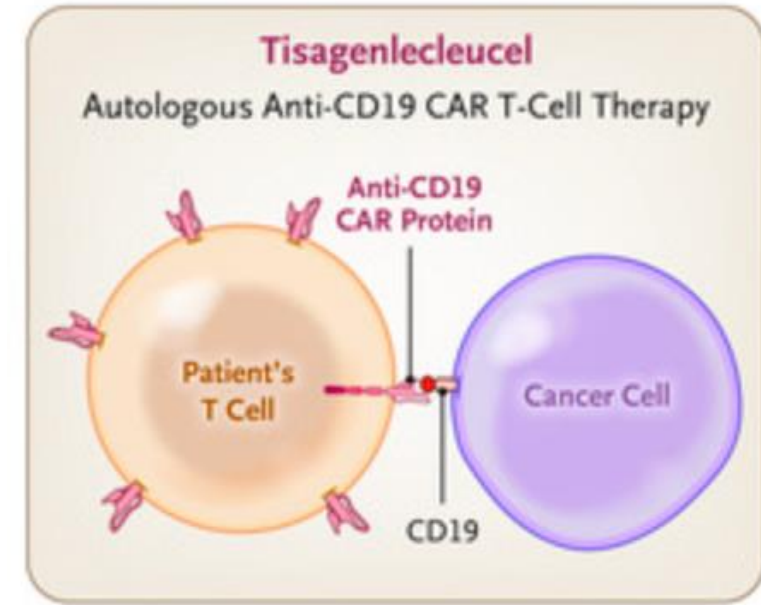
1. Maude SL, et al. *N Engl J Med*. 2018;378(5):439-448.
2. Baruchel A, et al. EHA 2020. Oral S118
3. Ghorashian S, et al. *Blood*. 2020;136(Suppl. 1):1016
4. Schultz LM, et al. *Blood*. 2020;136(Suppl. 1):14–15
5. Pasquini. *Blood Adv*. 2020 Nov 10;4(21):5414-5424



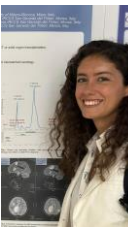
^a Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

Case 1: ALL, 5 ms, female

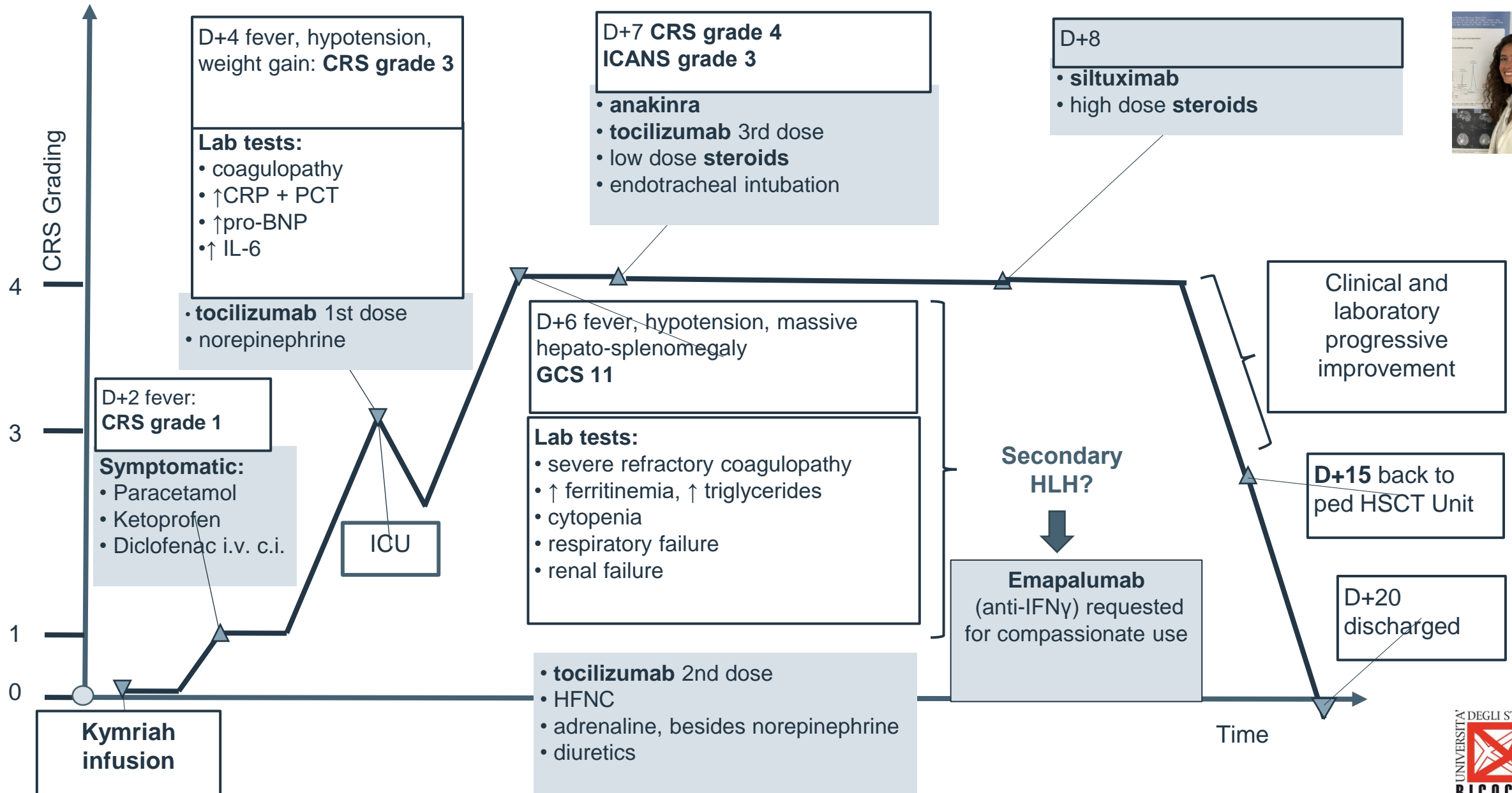
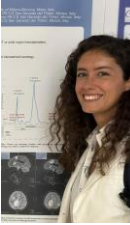
- Diagnosis:
 - WBC $180 \times 10^9/L$
 - KMT2A/AFF1 rearranged BI-ALL, CNS1
- AIEOP-BFM ALL 2017 protocol → early-HR
- 10 ms: refractory relapse
- Eligible for autologous anti-CD19 CAR-T cells (Tisagenlecleucel-Kymriah)
- Apheresis under sedation, femoral access
- Lymphodepletion: cyclophosphamide and fludarabine
- BM blasts: pancytopenic, punctio sicca (last assessment 60%), CNS neg



Adapted from: Bishop MR et al., NEJM, 2022

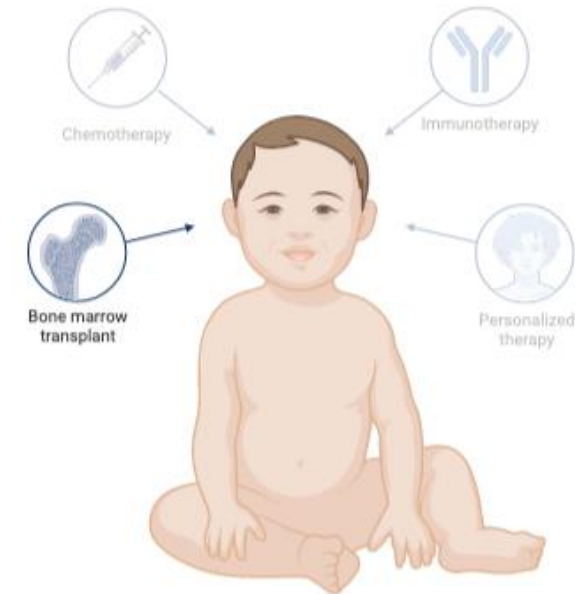


Case 1: ALL, 13 ms at the time of tisa infusion

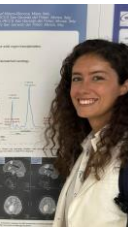


Case 1: ALL, 13 ms at the time of tisa infusion, outcome

- D+7: Severe immune effector cell associated HLH-like syndrome:
a case report of successful treatment in a pediatric patient after CAR-T cell infusion
- D+28 CR:
 - Morphological, flow and molecular remission
 - 312/uL CAR-T cells on PB
- D+78 BM:
 - morphological remission
 - B-cell aplasia and CAR-T cell persistence
 - poor BM cellularity, suspected CD19- blasts in flow
 - PCR-MRD negative
- D+105 after CAR-T infusion: haploidentical HSCT due to highest risk of CD19-/lineage switch relapse
- +18 ms: alive in CR2, chronic GVHD requiring multiple lines of tx, partially responsive to MSC

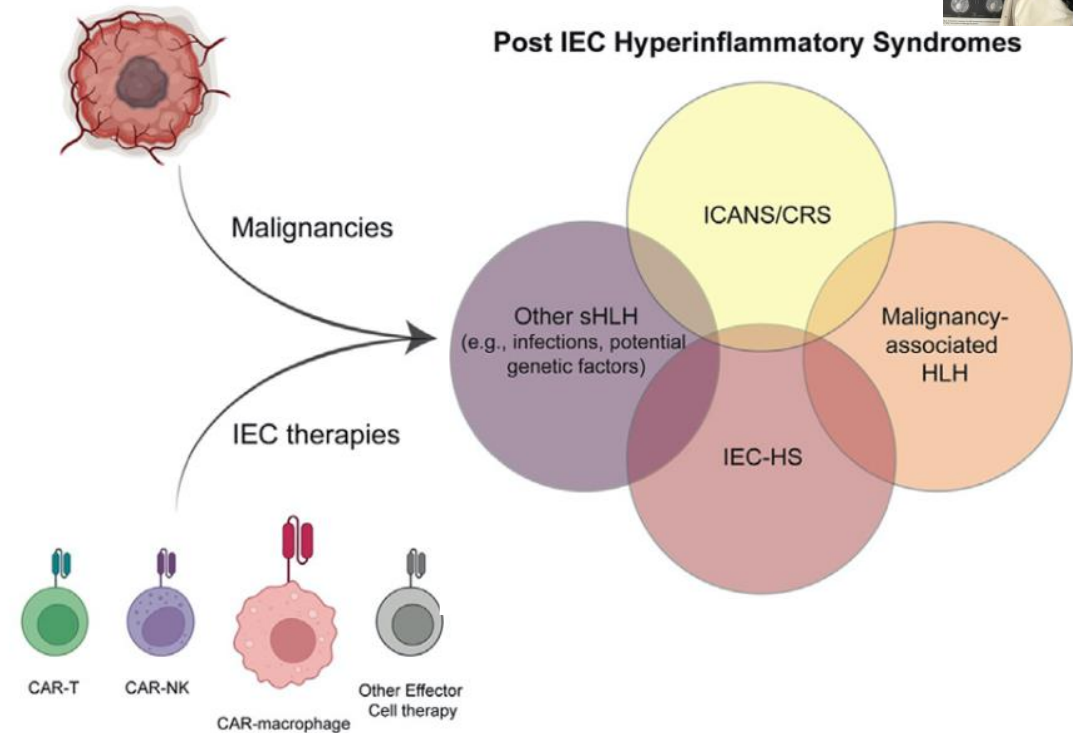


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CAR T-cell toxicities

- **CRS:** Cytokine release syndrome
- **ICANS:** immune effector cell associated neurotoxicity
- **IEC-HS:** immune effector cell associated HLH-like syndrome - recently described
- **ICAHT²:** immune effector cell associated hematotoxicity
- Immunodeficiency²



Adapted from: Hines MR et al., *Transplant Cell. Ther.*, 2023

1: Hines MR et al., *Transplant Cell. Ther.*, 2023

2: Rejeski K, Subklewe M, Aljurf M et al., *Blood*, 2023

CAR-T early toxicities

1: Morris, E.C et al., Nat Rev Immunol, 2022; 2: Hines MR et al., *Transplant Cell. Ther.*, 2023

	CRS ¹	ICANS ¹	IEC-HS ²
Symptoms & signs	Fever, malaise, anorexia → hypotension, hypoxia and/or organ dysfunction	Word-finding difficulty, confusion, dysphasia, aphasia, impaired fine motor skills, somnolence → seizures, motor weakness, cerebral oedema, coma	Fever, respiratory failure, hypotension, hepato-splenomegaly
Lab tests	Elevated inflammatory markers (IFN-γ, IL-6, IL-10, soluble IL-2Rα), pro-BNP, liver/renal function abnormalities	Elevated inflammatory markers (LDH, ferritin, CRP, ESR, IL-2, IL-6, IL-15, IFN-γ, TNF-α), CSF normal or mild protein elevation and pleocytosis	Cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or liver function abnormalities
Management	<ul style="list-style-type: none"> • Symptomatic drugs: paracetamol, ketoprofen, diclofenac, intravenous fluids • Anti-IL6 ± steroids • Others: anakinra 	<ul style="list-style-type: none"> • Supportive care • Corticosteroids 	<ul style="list-style-type: none"> • Anakinra ± steroids • Ruxolitinib ± alternative agents (etoposide/emapalumab)

- CRS, ICANS and IEC-HS are life-threatening complications of CAR-T cell therapy
- Prompt diagnosis and treatment initiation are crucial for patient outcomes
- New strategies targeting cytokines pathways may be considered in patients refractory to first line therapies

IEC-HS

- Fever, hypotension, hypoxia, hepatosplenomegaly

Hines MR,
*Transplant Cell.
Ther.*, 2023

- Cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or liver function abnormalities
- Clinical independence from CRS and ICANS



EMERGENT CAR T-CELL TOXICITIES

How I treat refractory CRS and ICANS after CAR T-cell therapy

Michael D. Jain,^{1,*} Melody Smith,^{2,*} and Nirali N. Shah³

¹Department of Blood and Cellular Therapy, Dana-Farber Cancer Institute, Boston, MA

The clinical use of CAR T-cell therapy for hematologic malignancies is rapidly expanding. However, the lack of consensus on the diagnosis and management of emergent toxicities, such as CRS and ICANS, may impact patient safety and outcomes. This review discusses the current state of knowledge on the diagnosis and management of CRS and ICANS, and provides recommendations for the treatment of these toxicities.

Open access

Journal for
Immunotherapy of Cancer

Short report

Single-center experience using anakinra for steroid-refractory immune effector cell-associated neurotoxicity syndrome (ICANS)

Marc Wehrli^{1,2}, Kathleen Gallagher^{1,2}, Yi-Bin Chen^{1,2,3}, Mark B Leick^{1,2,3}, Steven L McAfee^{2,3}, Areej R El-Jawahri^{2,3}, Zachariah DeFilipp^{1,2,3}, Nora Horick^{2,3}, Paul O'Donnell^{2,3}, Thomas Spitzer^{2,3}, Bimal Dey^{2,3}, Daniella Cook^{1,3}, Michael Traylor^{1,3}, Kevin Lindell^{1,3}, Marcela V Maus^{1,2,3}, Matthew J Frigault^{1,2,3}

14 JUNE 2022 • VOLUME 6, NUMBER 11

RESEARCH LETTER

blood advances

TO THE EDITOR:

Anakinra utilization in refractory pediatric CAR T-cell associated toxicities

Caroline Diorio,^{1,*} Anant Vatsayan,^{2,*} Aimee C. Talleur,³ Colleen Annesley,⁴ Jennifer J. Jaroscak,⁵ Haneen Shalabi,⁶ Amanda K. Ombrello,⁷ Michelle Hudspeth,⁵ Shannon L. Maude,¹ Rebecca A. Gardner,⁴ and Nirali N. Shah⁶

nature communications (2023)14:3423

Article

<https://doi.org/10.1038/s41467-023-38723-y>

Neutralizing IFN γ improves safety without compromising efficacy of CAR-T cell therapy in B-cell malignancies

Received: 23 March 2022

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Published online: 09 June 2023

Check for updates

Simona Manni^{1,5}, Francesca Del Bufalo^{1,5}, Pietro Merli¹, Domenico Alessandro Silvestri¹, Marika Guercio¹, Simona Caruso¹, Sofia Reddel¹, Laura Iaffaldano¹, Michele Pezzella¹, Stefano Di Cecca¹, Matilde Sinibaldi¹, Alessio Ottaviani¹, Maria Cecilia Quadraccia¹, Mariasole Aurigemma¹, Andrea Sarcinelli¹, Roselia Ciccone¹, Zeinab Abbaszadeh¹, Manuela Ceccarelli¹, Rita De Vito², Maria Chiara Lodi¹, Maria Giuseppina Cefalo¹, Angela Mastronuzzi¹, Biagio De Angelis¹, Franco Locatelli^{1,3,5} & Concetta Quintarelli^{1,4,5}

- presenting symptom: typically fever, usually within 5–7 days after infusion, with critical illness arising 12–96 h later, if at all
- malaise, fatigue, myalgias
- hypotension
- hypoxia
- capillary-leak syndrome
- fluid retention

Table 1. Clinical signs and symptoms associated with CRS

Organ system	Symptoms
Constitutional	Fever \pm rigors, malaise, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia \pm bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dymetria, altered gait, seizures

How I Treat

Current concepts in the diagnosis and management of cytokine release syndrome

Daniel W. Lee,¹ Rebecca Gardner,² David L. Porter,³ Chrystal U. Louis,⁴ Nabil Ahmed,⁴ Michael Jensen,² Stephan A. Grupp,^{3,5} and Crystal L. Mackall¹

¹Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD; ²Seattle Children's Hospital, Seattle, WA; ³Division of Hematology-Oncology, University of Pennsylvania, Philadelphia, PA; ⁴Texas Children's Hospital, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX; and ⁵Children's Hospital of Philadelphia Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

CAR-T toxicity - CRS

1

2

3

4

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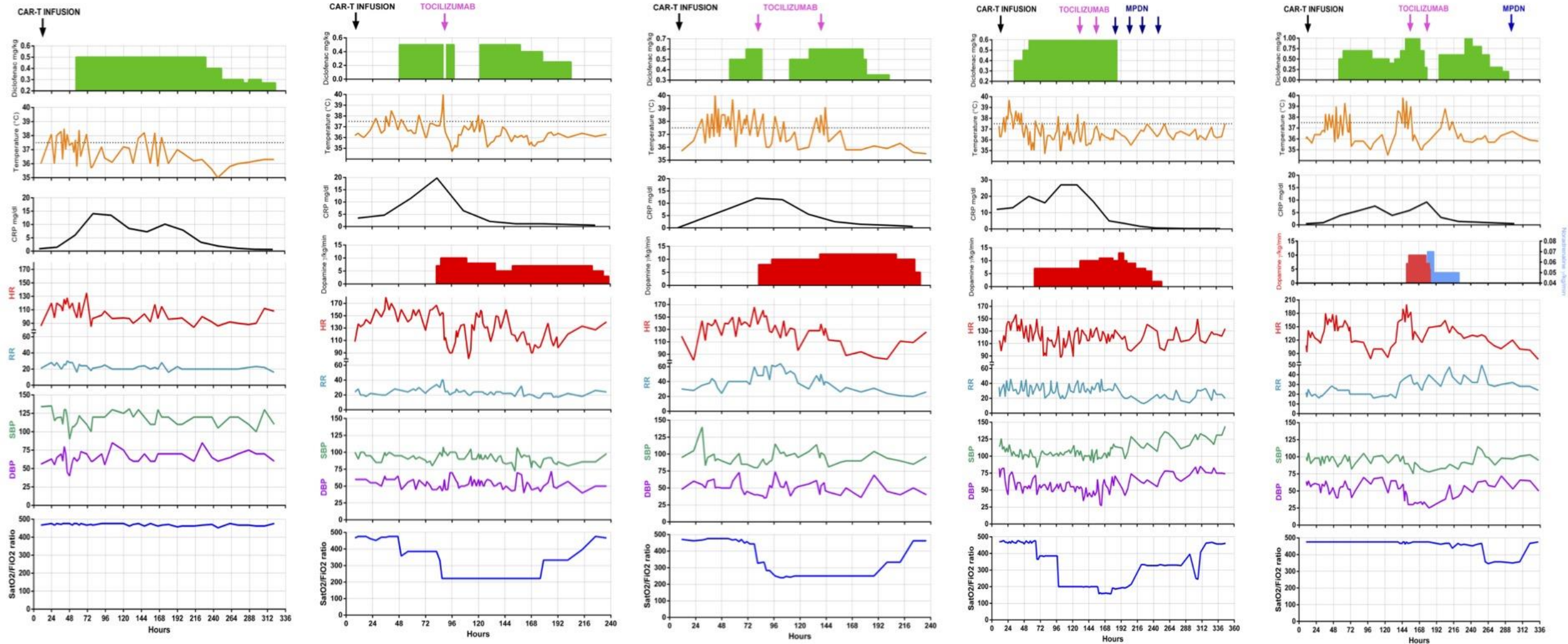


Figure 1. CRS course overtime in the five patients

Diclofenac mg/Kg: intravenous continuous infusion (i.v. c.i.) daily dose is indicated; body temperature (°C); CRP levels (mg/dL); Dopamine infusion; HR: heart rate; RR: breath rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; SpO2/FiO2 ratio

CAR-T toxicity - CRS ASTCT Scoring

Table 2
ASBMT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
With Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or [†] Hypoxia	None	Requiring low-flow nasal cannula [‡] or blow-by	Requiring high-flow nasal cannula [‡] , facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[†] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C , hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[‡] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

ASBMT, American Society for Blood and Marrow Transplantation; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events.

Lee DW, et al. *Biol Blood Marrow Transplant* 2018; pii: S1083-8791(18):31691–4 [Epub ahead of print].

CAR-T toxicity: CRS Management Algorithm

Grading and management of cytokine release syndrome

ASBMT CRS Grade	Defining Features of Grade	Management
Grade 1	Fever with temperature $\geq 38^{\circ}\text{C}$ but no hypotension or hypoxia	<ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• 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)	<ul style="list-style-type: none">• 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, biphasic positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome

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

CAR-T toxicity: CRS Management

- presenting symptom: typically fever, usually within 5–7 days after infusion, with critical illness arising 12–96 h later, if at all
- supportive therapy, i.v. fluids
- first-line specific therapy: tocilizumab
- methylprednisolone at 1-2 mg/Kg per day in case of no response to tocilizumab (up to 4 doses) better than i.v. dexamethasone
- consider steroid sparing to limit the risk of jeopardizing CAR-T cells
- escalation to siltuximab, anakinra, HD-steroid for refractory severe CRS
- no G-CSF (?)

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

CAR-T toxicity: ICANS

Immune cell associated neurotoxicity syndrome*

- onset generally when CRS improves
- median 6-7 ds, lasts 4 days
- ranges from mild abnormalities and tremor, to encephalopathy/delirium, expressive aphasia, ataxia, obtundation,
- consider levetiracetam prophylaxis (in case of previous CNS-related issues/disease)
- tocilizumab not active - consider if underlying CRS
- no steroids for low-grade neurotoxicity
- treatment decisions tailored to the type of neurotoxicity
- higher-grade neuro- toxicity might deserve treatment
 - seizures well controlled by anti-epileptic drugs should not be treated in the same way as increased intracranial pressure and cerebral oedema
- steroid use might vary by CAR-T product
- anti-IL-6 therapy is often not effective for neurotoxicity
- using failure to IL-6 blockade to determine the next line of therapy is not appropriate

** management mainly fits tisagenlecleucel*

CAR-T toxicity: ICANS

Table 3
Neurologic and Psychiatric Adverse Reactions Reported with Approved CAR T Products

Tisagenlecleucel (Kymriah)	Axicabtagene ciloleucel (Yescarta)
<p>Encephalopathy: includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, and automatism</p> <p>Delirium: includes delirium, agitation, hallucination, hallucination visual, irritability, restlessness</p> <p>Headache: includes headache and migraine</p> <p>Anxiety</p> <p>Sleep disorder: includes sleep disorder, insomnia, nightmares</p>	<p>Encephalopathy: includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbed attention, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor</p> <p>Delirium: includes agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness</p> <p>Headache</p> <p>Dizziness: includes dizziness, presyncope, syncope</p> <p>Aphasia: includes aphasia, dysphasia</p> <p>Motor dysfunction: includes muscle spasms, muscular weakness</p> <p>Tremor</p> <p>Ataxia</p> <p>Seizure</p> <p>Dyscalculia</p> <p>Myoclonus</p>

A disorder characterized by a pathologic process involving the CNS following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive and may include aphasia, altered consciousness, impairment of cognitive skills, motor weakness, seizures and cerebral oedema

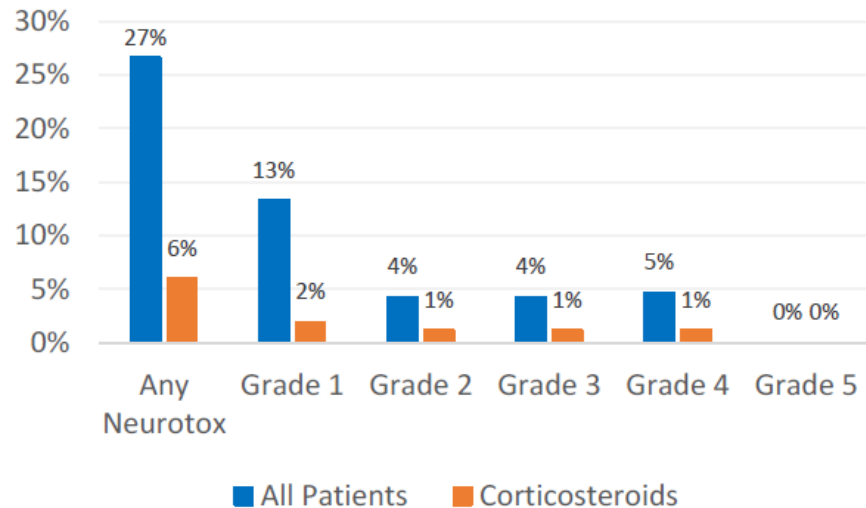
Lee et al. ASTCT Consensus Grading for CRS and Neurologic Toxicity Associated with Immune Effector Cells. *BBMT*. 2019 Apr;25(4):625-638

Frequency of ICANS with Tisagenlecleucel

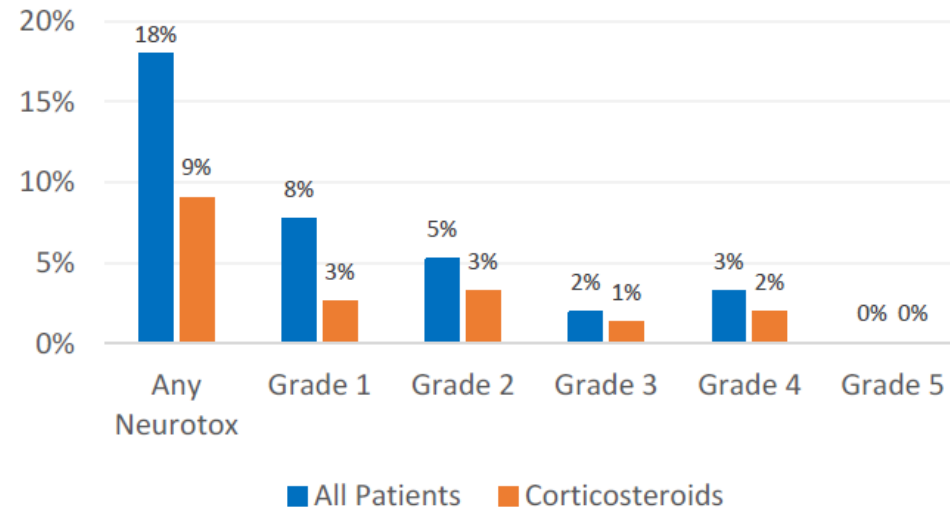
D

Endpoint	ALL		NHL	
	CIBMTR (N=255)	ELIANA (N=79)	CIBMTR (N=155)	JULIET (N=115)
Neurotoxicity				
Any, n (%)	69 (27.1)	31 (39.2)	28 (18.1)	23 (20.0)
Grade ≥3, n (%)	23 (9.0)	10 (12.7)	8 (5.1)	13 (11.3)
Median time to onset in days (range)	7 (1-80)	8 (2-489)	8 (2-33)	6 (1-323)
Median duration in days (range)	7 (1-94)	7	6.5 (1-50)	13

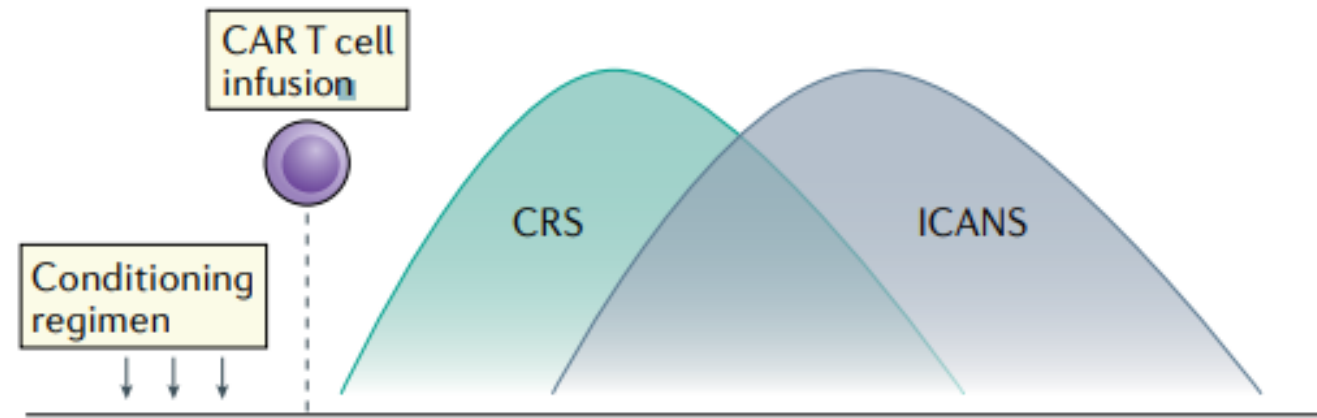
E: Acute Lymphoblastic Leukemia



F: Non-Hodgkin Lymphoma



Timing of ICANS



- ICANS typically manifests as a toxic encephalopathy and starts with word-finding difficulty, confusion, dysphasia, aphasia, impaired fine motor skills and somnolence
 - Earliest symptoms tremor dysgraphia, mild difficulties with expressive speech, mild lethargy, headache aspecific.
 - Expressive aphasia is a very specific symptom of ICANS and can progress to global aphasia (they are awake but cannot speak or follow command)
 - in more severe cases, seizures (10/15%) , motor weakness, cerebral oedema and coma have been noted
 - Focal neurologic symptoms are less common, although EEG commonly shows focal abnormalities
 - Rarely, cortical cytotoxic oedema seen during acute ICANS can evolve into chronic injury with persistent focal dysfunction, and evidence of gliosis on histopathology
-
- The typical course of ICANS is monophasic, with symptoms quickly increasing to the max and improving over time, rarely there is waxing and waning of the symptoms.
 - Symptoms tend to start day +3-6 reach their peak in the second week post CART cells and resolve by the third fourth week.
 - Neurologic adverse events typically occur after the onset of CRS, and it is not unusual for ICANS to develop in the setting of improving or resolved CRS.

Mechanism of neurotoxicity

Disruption of BBB

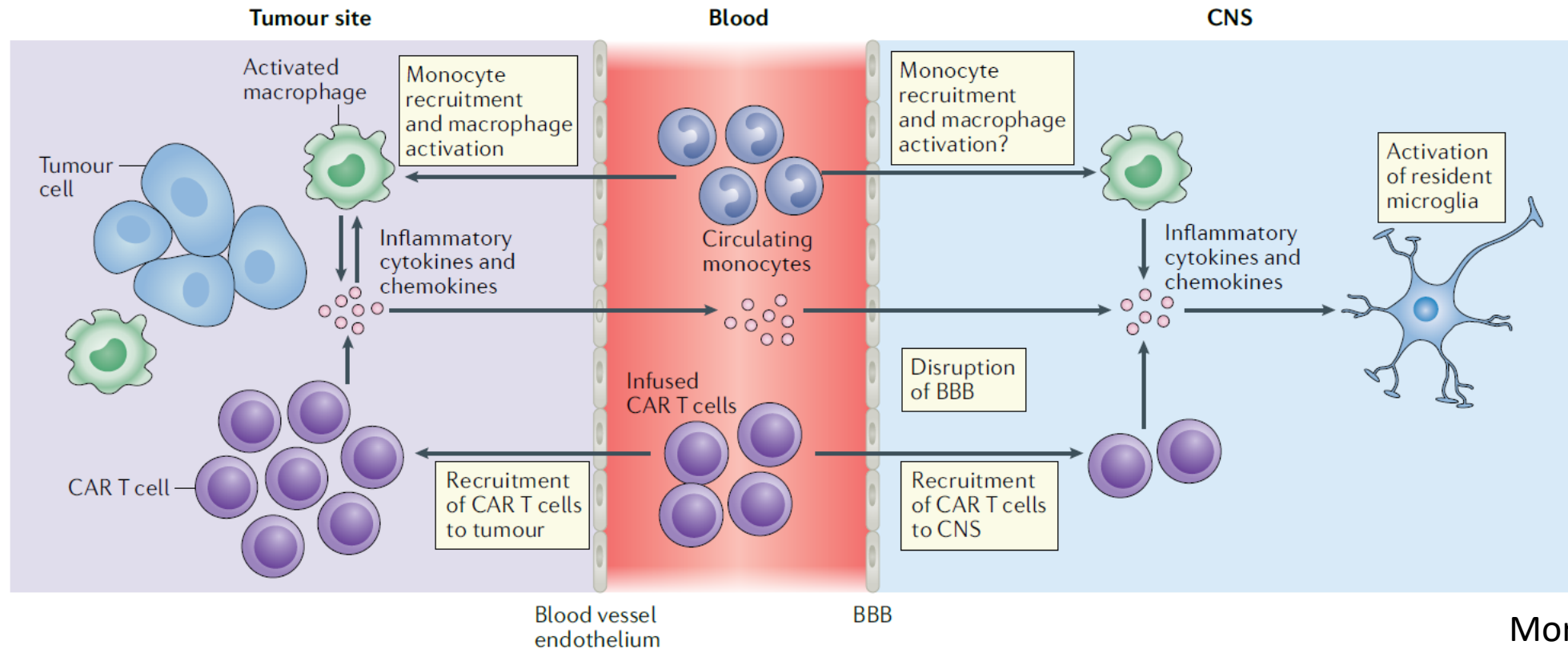
Raised protein, CD4, CD8, CART in CSF

Endothelial activation/damage

Raised serum ANG1/ANG2 ratio

Astroglial cell injury

Raised GFAP and S100b in CSF



Risk factors for ICANS

- Early/severe CRS
- Increased serum levels of various cytokines and the risk of developing ICANS
- Rapid peak of IL6 concentration early after CAR-T cell infusion
- Increased serum ANG2/ANG1 ratios prior to lymphodepletion
- Circulating/CNS CART cells
- Role of pre CART CNS toxicity/exposure to potential neurotoxic drug is speculative but very relevant (example IT MTX or fludarabine)

Investigations for neurotoxicity

6.2 Investigations to be performed if ICANS is suspected

Daily assessment of neurological and cognitive function including fundoscopy, writing, gait GCS and age-appropriate cognitive test (see appendix 6.4), where available
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FBC

Coagulation profile including d-dimers, fibrinogen
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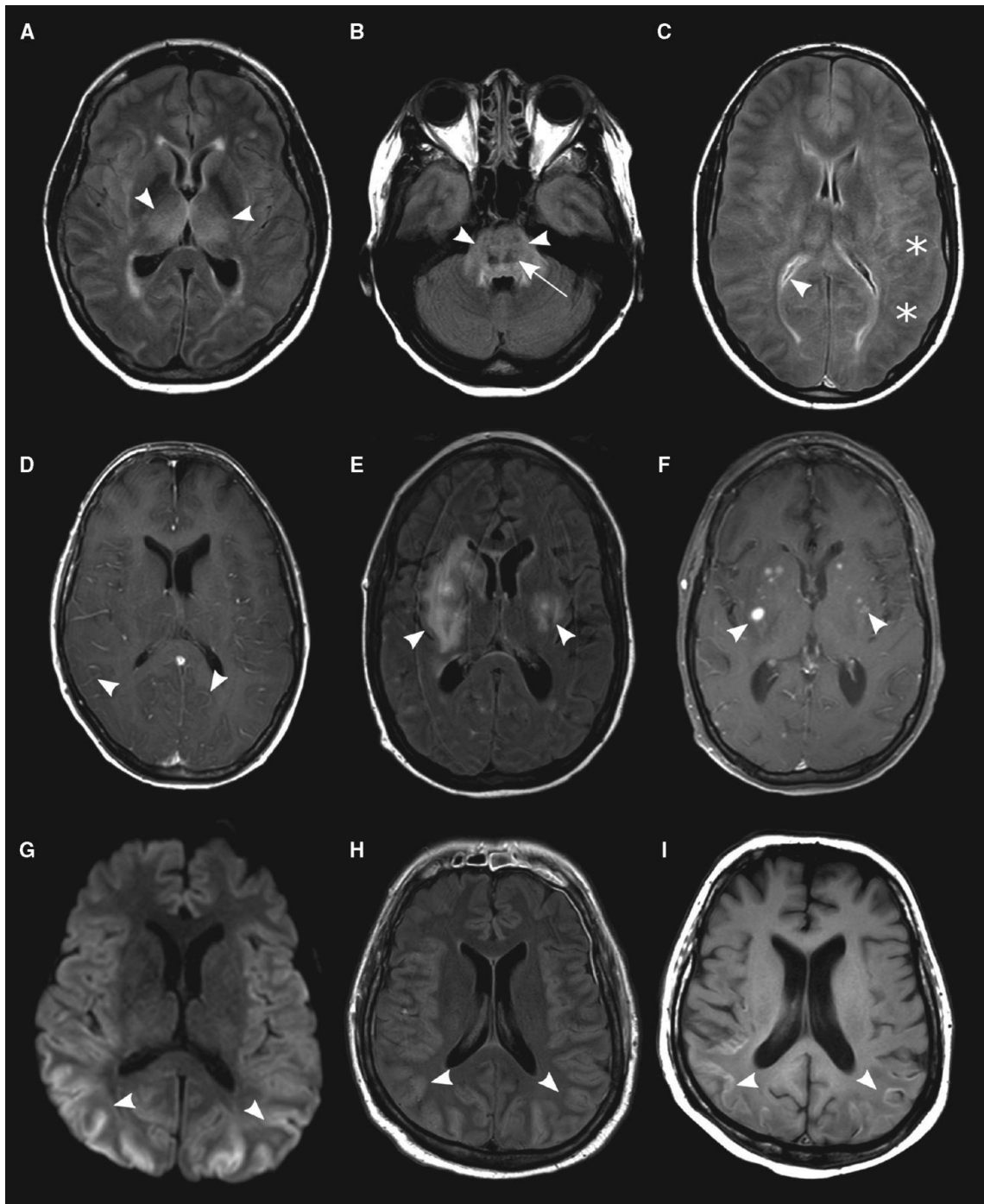
Serum Biochemistry including renal, liver, bone profile

CRP, ferritin

Neuroimaging, ideally MRI brain + contrast with T2/FLAIR (CT brain if MRI not feasible)

EEG (where appropriate and in consultation with neurology team)

Lumbar puncture with CSF opening pressure, protein, glucose as well as culture, sample for microbial PCR, cytopsin and flow, where possible/indicated



leptomeningeal enhancement and T2 hyperintensity in the cerebral sulci

T2 hyperintensity and swelling of the bilateral thalami, indicative of interstitial or vasogenic edema

symmetric T2 hyperintensities in the supratentorial white matter, diffusion restriction in patchy areas or cortex and/or white matter, and reversible interstitial edema in areas of prior CNS injury such as from radiation or medication toxicity

changes are typically symmetric, and have a predilection for thalami and deep grey matter

Differential diagnosis

- Chemotherapy related toxicity:

there is no unequivocal or pathognomonic pathological hallmark to differentiate potential CAR-T toxicity from fludarabine injury.

Consider: time of onset, risk factors, progression, response to treatment

- Infectious complication:

rule out / treat possible infections

(consider NGS sequencing of the brain biopsy for off microbiological entities)

Take home message

- Neurotox can be significant in a minimal number of patients and risk factors must be taken into account (GFR for fludarabine)
- Clinical evaluation of the patient is paramount in detecting early signs of neurotoxicity
- Treatment of severe neurotoxicity is not established beyond steroid
- More specific risk factors/pathogenesis are still being investigated

Safety issues observed in Eliana, B2001X, real world UK, USA, CIBMTR

	Protocols		Real world		
Parameter (%)	Eliana	B2001X	UK	USA	CIBMTR
No. infused/enrolled	79/97	67/73	49/60	185/200	255
CRS, any-grade	77	64	88		55
CRS, grade ≥ 3	49	28	20	19	16
Tocilizumab	39		45		25
Steroids	20				6
ICU admissions	48	28	22		
High-dose vasopressors	24	22			22
Intubation	15	7			
ICANS, any-grade	39	24	31		27
ICANS, grade ≥ 3	13	10	10	7	9

CRS: 0

What makes the difference...
better efficacy or just less toxicity?
Quality of life assessment in the short term...



**ongoing
blinatumomab
infusion**

**+28 days post-
tisagenlecleucel**



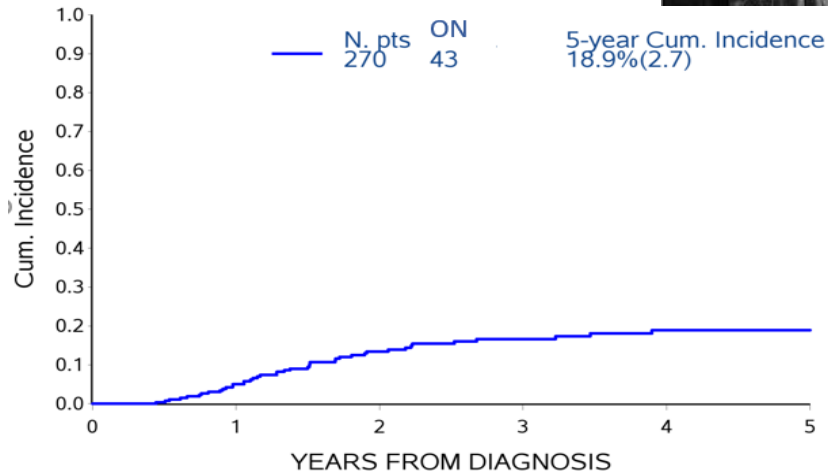
What makes the difference... is mainly quality of life in the long term...

- Secondary malignancies
- Osteonecrosis
- Neurocognitive sequelae
- Cardiomyopathy
- Insulin dependent diabetes (pancreatitis)
- Chronic GvHD
- Chronic immune deficiency (also post-CAR-T)

Osteonecrosis

Cumulative incidence:
AIEOP BFM 2009:
270 frontline patients
(relapse and transplant
not censored)

270 patients



Chronic GVHD



Second tumor



CAR-T cells in pediatric AL - Conclusions

- CAR-T cell therapy can provide benefits for patients with refractory disease, especially in cases where no alternative options exist
- Management of CAR-T cell-related adverse events can be achieved even in cases with multiple comorbidities
- Successful CAR-T cell therapy requires well trained teams and supportive ICU collaboration
- Crucial role: nurse staff !!!

Tossicità da nuovi approcci immunoterapici

11:15 – 11:30

- CAR T cells: CRS, ICANS, ICAHT, IEC-HS, Ig deficiency
- **Brentuximab/Nivolumab: neuropathy**

11:30 -11:35 Q & A



Case 6: HL, 15 ys, male

- Diagnosis:
 - Hodgkin lymphoma (mixed cellularity) diagnosed Jan 2018, stage IIIB
 - EuroNet-PHL-C2, progression after frontline treatment
 - Bendamustine, Gemcitabine (4 cycles), Vinorelbine (2 cycles), DHAP (1 cycle), Brentuximab (2+4+3+7 doses)
 - HSCT from HLA compatible father (IS discontinued +90)
 - pre-emptive DLI+CIK (5 infusions) and Nivolumab, discontinued after bladder toxicity/cystitis
 - post-HSCT refractory relapse, disease progression involving mediastinal sites, histologically confirmed
 - Nivolumab cycles resumed (total 35 cycles), well tolerated
 - disease progression involving mediastinal, spleen, retrocaval sites
 - radiation: 34 Gy in 17 fractions to refractory nodal sites mediastinum, pulmonary hylum, subcarenal, retrocaval, 24 Gy in 12 fractions to spleen, 21.6 Gy in 12 fractions to previous mediastinal and abdominal nodal sites
 - CT scan + PET: anatomic and metabolic remission of the previously involved areas

Focus:

- Treatment:
 - nivolumab anti-PD-L1 - fully human immunoglobulin G4 monoclonal antibody inhibiting programmed death-1 (PD-1)/PD-L1 binding
 - brentuximab anti-CD30 antibody drug conjugate
- peripheral neuropathy after brentuximab & nivolumab

peripheral neuropathy after brentuximab

Brentuximab vedotin for paediatric relapsed or refractory Hodgkin's lymphoma and anaplastic large-cell lymphoma a multicentre, open-label, phase 1/2 study

Franco Locatelli, Christine Mauz-Koerholz, Kathleen Neville, Anna Llori, Auke Beishuizen, Stephen Daw, Marta Pilon, Nathalie Aladjidi, Thomas Klingebiel, Judith Landman-Parker, Aurora Medina-Sanson, Keith August, Jessica Sachs, Kristen Hoffman, Judith Kinley, Sam Song, Gregory Song, Stephen Zhang, Ajit Suri, Lia Gore

Lancet Oncology 2020

- 36/41 pts (7-17 ys) enrolled
 - 19 HL
 - 17 ALCL
- study period 2012-2016
- dose finding
 - 1.4 mg/kg phase I
 - 1.8 mg/kg phase I-II
- overall response:
 - HL 47% (CI 21-73)
 - ALCL 53% (CI 28-77)
- 12 (33%) transient limited severity peripheral neuropathy

	1.4 mg/kg phase 1 only (n=3)	1.8 mg/kg phase 1 and 2 cHL only (n=16)	1.8 mg/kg phase 1 and 2 sALCL only (n=17)	1.8 mg/kg phase 1 and 2 sALCL in first relapse only (n=10)	1.8 mg/kg all patients (n=33)	All patients (N=36)
Any TEAE	3 (100%)	16 (100%)	17 (100%)	10 (100%)	33 (100%)	36 (100%)
Grade 3 or worse TEAE	0	11 (69%)	5 (29%)	3 (30%)	16 (48%)	16 (44%)
SAE	0	7 (44%)	1 (6%)	0	8 (24%)	8 (22%)
Drug-related TEAE	2 (67%)	13 (81%)	10 (59%)	6 (60%)	23 (70%)	25 (69%)
Drug-related grade 3 or worse TEAE	0	6 (38%)	3 (18%)	3 (30%)	9 (27%)	9 (25%)
Drug-related SAE	0	3 (19%)	0	0	3 (9%)	3 (8%)
TEAE leading to study-drug discontinuation	0	2 (13%)	0	0	2 (6%)	2 (6%)
On-study death	0	1 (6%)	0	0	1 (3%)	1 (3%)
PN	1 (33%)	7 (44%)	4 (24%)	1 (10%)	11 (33%)	12 (33%)
Worst PN grade*						
Grade 1	1 (100%)	5 (71%)	3 (75%)	..	8 (73%)	9 (75%)
Grade 2	0	1 (14%)	1 (25%)	..	2 (18%)	2 (17%)
Grade 3	0	1 (14%)	0	..	1 (9%)	1 (8%)
PN outcome*						
Resolved	1 (100%)	5 (71%)	4 (100%)	..	9 (82%)	10 (83%)
Improved	0	1 (14%)	0	..	1 (9%)	1 (8%)
Not resolved or improved	0	1 (14%)	0	..	1 (9%)	1 (8%)

Data are n (%). cHL=classical Hodgkin's lymphoma. PN=peripheral neuropathy. SAE=serious adverse event. sALCL=systemic anaplastic large-cell lymphoma. TEAE=treatment-emergent adverse event. *Percentages use number of patients with peripheral neuropathy in this category as the denominator.

Table 4: Summary safety data by intervention group (safety population)

peripheral neuropathy after brentuximab

Pediatr Blood Cancer, 2022 Oct;69(10):e29801

Brentuximab vedotin in the treatment of paediatric patients with relapsed or refractory Hodgkin's lymphoma: Results of a real-life study

Davide Massano¹ | Elisa Carraro¹ | Lara Mussolin^{2,3} | Salvatore Buffardi⁴ |
Veronica Barat⁵ | Daniele Zama⁶ | Paola Muggeo⁷ | Francesca Vendemini⁸ |
Antonella Sau⁹ | Maria Luisa Moleti¹⁰ | Federico Verzegnassi¹¹ |
Salvatore D'Amico¹² | Tommaso Casini¹³ | Alberto Garaventa¹⁴ |
Elisabetta Schiavello¹⁵ | Monica Cellini¹⁶ | Luciana Vinti¹⁷ | Piero Farruggia¹⁸ |
Katia Perruccio¹⁹ | Simone Cesaro²⁰ | Raffaella De Santis²¹ |
Maddalena Marinoni²² | Irene D'Alba²³ | Rosa Maria Mura²⁴ | Roberta Burnelli²⁵ |
Maurizio Mascarin²⁶ | Marta Pillon¹

- 68 pts (7-17 ys) enrolled
- study period 2011-2020
- median 9 doses
 - 31 monotherapy
 - 37 in combination
- phase:
 - 12 post-HSCT
 - 18 pre-HSCT
 - 15 pre and post HSCT
- overall response rate 66%
- 3-yr PFS 58%, 3-yr OS 75%
- 46% 3-4 adverse events
 - —> discontinuation in 5 pts
 - 21% neuropathy, 9% grade 3-4

TABLE 3 Summary of the adverse events according to Common Terminology Criteria for AEs v4.0

Adverse events	Grade			
	G1	G2	G3	G4
Peripheral sensory neuropathy	4	4	4	2
Neutropenia	6	5	10	7
Anaemia	1	10	6	1
Thrombocytopenia	7	4	5	2
Infection	1	3	6	0
Pneumonia	3	1	1	0
Diarrhoea	3	2	1	0
Vomiting	4	6	0	0
Cardiac conduction disorder	0	1	0	0
GGT increase	0	0	3	0
Subocclusion	0	1	0	0
Temporo-mandibular pain	0	1	0	0
Chronic kidney disease	0	0	0	1
Total	29	38	36	13

- peripheral neuropathy after brentuximab/nivolumab

Zinzani, JCO. 2019



Nivolumab Combined With Brentuximab Vedotin for Relapsed/Refractory Primary Mediastinal Large B-Cell Lymphoma: Efficacy and Safety From the Phase II CheckMate 436 Study

Pier Luigi Zinzani, MD, PhD¹; Armando Santoro, MD²; Giuseppe Gritti, MD, PhD³; Pauline Brice, MD⁴; Paul M. Barr, MD⁵; John Kuruvilla, MD⁶; David Cunningham, MD⁷; Justin Kline, MD⁸; Nathalie A. Johnson, MD⁹; Neha Mehta-Shah, MD¹⁰; Thomas Manley, MD¹¹; Stephen Francis, MS¹²; Manish Sharma, MD¹²; and Alison J. Moskowitz, MD¹³

- 30 R/R PMBL NHL pts enrolled
- expansion cohort of phase I/II CheckMate 436:
 - q 3 weeks
 - nivolumab 240 mg i.v.
 - brentuximab 1.8 mg/kg i.v.
 - until progression/toxicity
- overall response rate 73% (95CI 54-88)
- 25 pts (83%) AE; 16 (53%) 3-4 SAE
 - 3 (10%) neuropathy

TABLE 2. Treatment-Related Adverse Events

Treatment-Related Adverse Events	All Treated Patients (N = 30)	
	Any Grade	Grade 3-4
All	25 (83)	16 (53)
Neutropenia	9 (30)	9 (30)
Peripheral neuropathy	8 (27)	3 (10)
Thrombocytopenia	4 (13)	3 (10)
Rash	4 (13)	1 (3)
Peripheral sensory neuropathy	4 (13)	0
Hyperthyroidism	4 (13)	0
Pyrexia	3 (10)	0
Decreased neutrophil count	2 (7)	2 (7)
Hypersensitivity	2 (7)	1 (3)
Maculopapular rash	1 (3)	1 (3)
Colitis	1 (3)	1 (3)
Immune-mediated hepatitis	1 (3)	1 (3)

NOTE. Data reported as No. (%). Treatment-related adverse events reported in $\geq 10\%$ of patients or grade 3 to 4 treatment-related adverse events reported in any patient.

- peripheral neuropathy after brentuximab

Nivolumab combined with brentuximab vedotin for R/R primary mediastinal large B-cell lymphoma: a 3-year follow-up

Pier Luigi Zinzani,^{1,2} Armando Santoro,³ Giuseppe Gritti,⁴ Pauline Brice,⁵ Paul M. Barr,⁶ John Kuruvilla,⁷ David Cunningham,⁸ Justin Kline,⁹ Nathalie A. Johnson,¹⁰ Neha Mehta-Shah,¹¹ Julie Lisano,¹² Rachael Wen,¹³ Alev Akyol,¹³ and Alison J. Moskowitz¹⁴

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- 29 R/R PMBL NHL pts enrolled
- expansion cohort of phase I/II CheckMate 436, med f-up: 40 ms
 - q 3 weeks
 - nivolumab 240 mg i.v.
 - brentuximab 1.8 mg/kg i.v.
 - until progression/toxicity
- 4 pts (13%) neuropathy

Table 3. Any-grade TRAEs reported in greater than or equal to 10% of patients who received treatment and grade 3/4 TRAEs in all patients with R/R PMBL who received treatment

Any-grade TRAEs reported in ≥ 10% patients who received treatment, and grade 3/4 TRAEs in any patients, n (%)	Any grade	Grade 3/4
Total	25 (83.3)	16 (53.3)
Neutropenia	14 (43.3)	13 (40.0)
Pyrexia	9 (30.0)	1 (3.3)
Arthralgia	6 (20.0)	0
Thrombocytopenia	5 (16.7)	3 (10.0)
Rash	5 (16.7)	1 (3.3)
Peripheral sensory neuropathy	5 (16.7)	0
Peripheral neuropathy	4 (13.3)	3 (10.0)
Hyperthyroidism	4 (13.3)	0
Decreased neutrophil count	2 (6.7)	2 (6.7)
Colitis	1 (3.3)	1 (3.3)
Immune-mediated hepatitis	1 (3.3)	1 (3.3)
Maculopapular rash	1 (3.3)	1 (3.3)

- peripheral neuropathy after brentuximab/nivolumab

Nivolumab plus brentuximab vedotin for relapsed/refractory peripheral T-cell lymphoma and cutaneous T-cell lymphoma

Pier Luigi Zinzani,¹ Gilles Salles,² Alison J. Moskowitz,² Armando Santoro,³ Amitkumar Mehta,⁴ Paul M. Barr,⁵ Neha Mehta-Shah,⁶ Graham P. Collins,⁷ Stephen M. Ansell,⁸ Joshua D. Brody,⁹ Eva Domingo-Domenech,¹⁰ Nathalie A. Johnson,¹¹ David Cunningham,¹² Silvia Ferrari,¹³ Julie Lisano,¹⁴ Jennifer Krajewski,¹⁵ Rachael Wen,¹⁵ Alev Akyol,¹⁵ Russell Crowe,¹⁵ and Kerry J. Savage¹⁶

- >18 ys
 - 34 R/R PTCL
 - 30 CTCL
- 5 pts (15%) neuropathy, 1 grade 3/4

Zinzani, Blood Adv. 2024

Table 2. Safety data in patients with R/R PTCL and CTCL

TRAEs in ≥5% of patients,* n (%)	PTCL (n = 33)		CTCL (n = 29)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
All TRAEs	28 (84.8)	15 (45.5)	26 (89.7)	13 (44.8)
Fatigue	8 (24.2)	2 (6.1)	4 (13.8)	0
Nausea	6 (18.2)	0	6 (20.7)	0
Pyrexia	6 (18.2)	0	5 (17.2)	0
Neutropenia	5 (15.2)	5 (15.2)	0	0
Peripheral neuropathy	5 (15.2)	1 (3.0)	8 (27.6)	0
Diarrhea	5 (15.2)	1 (3.0)	6 (20.7)	1 (3.4)
Anemia	5 (15.2)	1 (3.0)	1 (3.4)	0
Increased aspartate aminotransferase	5 (15.2)	0	3 (10.3)	1 (3.4)
Paresthesia	5 (15.2)	0	1 (3.4)	0
Thrombocytopenia	4 (12.1)	2 (6.1)	1 (3.4)	1 (3.4)
Peripheral sensory neuropathy	4 (12.1)	1 (3.0)	2 (6.9)	0
Infusion-related reaction	4 (12.1)	0	6 (20.7)	1 (3.4)
Pruritis	4 (12.1)	0	2 (6.9)	0
Arthralgia	4 (12.1)	0	1 (3.4)	0
Rash	3 (9.1)	0	4 (13.8)	2 (6.9)

A family ... behind each child

A whole team of nurses taking care of each child



Thank you for your attention!



Comitato
Maria Letizia Verga

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