25ο ΕΤΗΣΙΟ ΣΕΜΙΝΑΡΙΟ ΣΥΝΕΧΙΖΟΜΕΝΗΣ ΙΑΤΡΙΚΗΣ ΕΚΠΑΙΔΕΥΣΗΣ
ΓΝΑ «Ο ΕΥΑΓΓΕΛΙΣΜΟΣ»
ΑΘΗΝΑ, 17 ΦΕΒΡΟΥΑΡΙΟΥ 2020

ΕΚΠΑΙΔΕΥΤΙΚΟ ΣΥΜΠΟΣΙΟ:
Νεότερες ανοσοθεραπείες στην αντιμετώπιση των αιματολογικών κακοηθειών:
Καινοφανείς τοξικότητες – Αντιμετώπιση.

ΑΝΤΙΜΕΤΩΠΙΣΗ ΤΗΣ ΤΟΞΙΚΟΤΗΤΑΣ ΤΩΝ CAR-T CELLS

Στέλιος Κόκκορης, MD, PhD
Παθολόγος-Εντατικολόγος
Επιμελητής Α΄
Α΄ ΚΕΘ ΙΑΤΡΙΚΗΣ ΣΧΟΛΗΣ ΕΚΠΑ
ΓΝΑ 'Ο ΕΥΑΓΓΕΛΙΣΜΟΣ'

Δεν υπάρχει σύγκρουση συμφερόντων με τις Χορηγούς Εταιρείες:

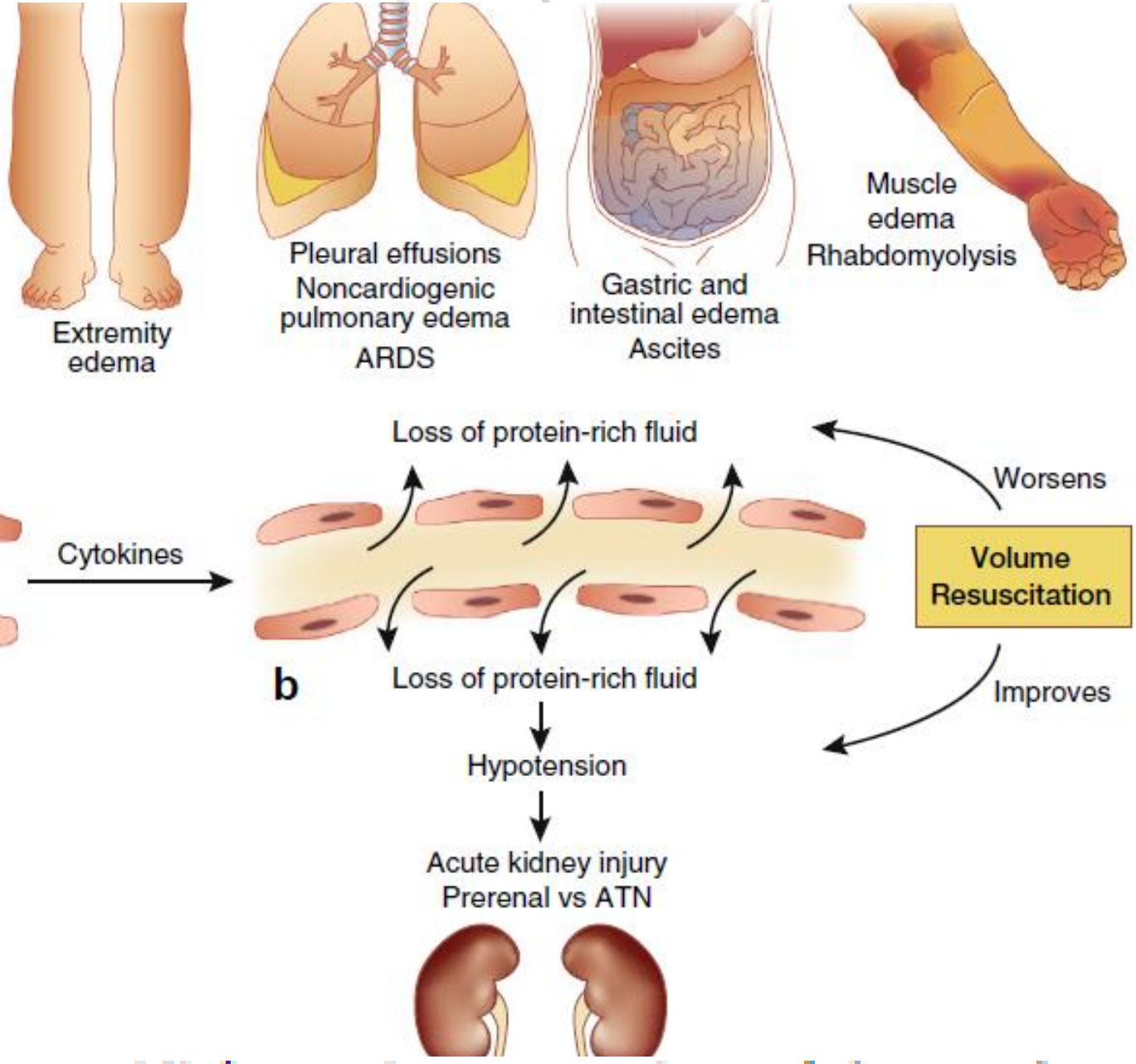
NOVARTIS
Roche
astellas
WinMedica
Serving Health for Life
GILEAD
MEDIWAY
Pfizer Oncology
SANDOZ A Novartis Division
Bristol-Myers Squibb
abbvie
Abbott
AMGEN
cardio innovation
GENESIS pharma
Janssen Oncology
Pfizer Hospital
Boehringer Ingelheim
Lilly ΦΑΡΜΑΣΕΡΒ
SERVIER
Baxter
DEMO ABEE ΒΙΟΜΗΧΑΝΙΑ ΦΑΡΜΑΚΩΝ
emergy
AENORASIS
Rontis
Specifar A Teva Company

Table 2. Reported Toxic Effects of CAR T Cells.

CAR Specificity and Adverse Effect
CD19 CAR
B-cell aplasia and hypogammaglobulinemia
Cytokine release syndrome
Dermatitis
Hematophagocytic lymphohistiocytosis and macrophage activation syndrome
Neurologic effects such as ataxia and aphasia
Cerebral edema
B-cell maturation antigen CAR: the cytokine release syndrome
Mesothelin CAR: anaphylaxis (antibody to murine single-chain variable fragments)
Carbonic anhydrase IX CAR: cholangitis (on-target)
HER2/neu CAR: lethal cytokine release syndrome
Carcinoembryonic antigen–related cell-adhesion molecule 5 (CEACAM5) CAR: hemorrhagic colitis (on-target)

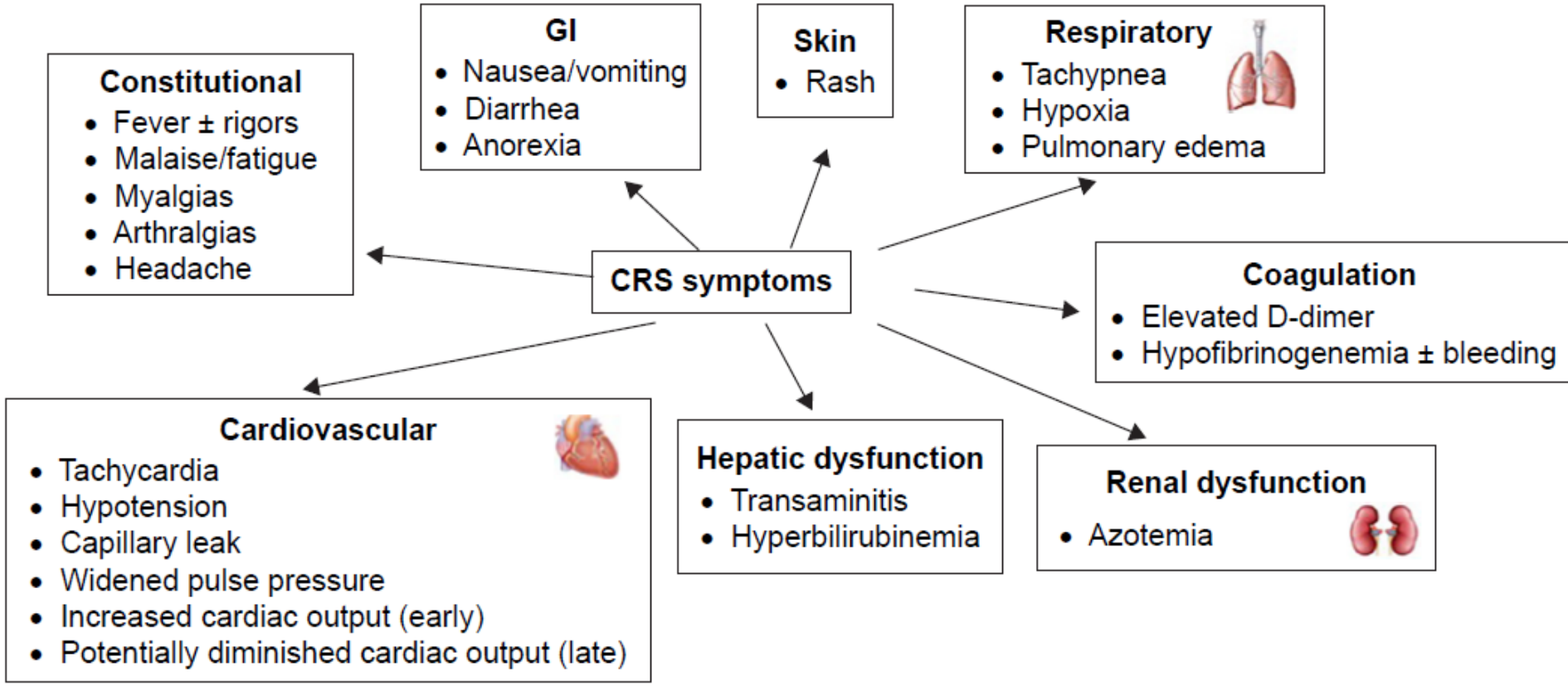
N Engl J Med 2018;379

Clinical manifestations of capillary leak syndrome.



Kidney International (2017) **92**

Symptoms of CRS.



D/D: Sepsis, TLS, MAS

Therapeutics and Clinical Risk Management 2019:15

Table 1 Incidence and treatment of CAR-T-related cytokine release syndrome and neurotoxicity in published clinical trials

Study	CAR-T construct	Diseases	Number of patients	Rate of CRS	Grade III-IV CRS	Death from CRS	Rate of neuro-toxicity	Grade III-IV neurotoxicity	Death from neurotoxicity
Borchmann et al. (2018) (JULIET) [8]	CD19-4-1BB (tisagenlecleucel; CTL019)	DLBCL	111	57 (58%)	23 (23%)	0	23 (21%)	12 (12%)	0
Maude et al. (2018) (ELI-ANA) [19]	CD19-4-1BB	B-ALL	75	58 (77%)	35 (46%)	1 (1%)	30 (40%)	10 (13%)	0
Neelapu et al. (2017) (ZUMA-1) [6]	CD19-28-ζ (axicabtagene ciloleucel; axi-cel, KTE-C19)	DLBCL	101	94 (93%)	13 (13%)	2 (2%)	65 (64%)	28 (28%)	0
Schuster et al. (2017) (Novartis/U. Penn) [7]	CD19-4-1BB	DLBCL	28	16 (57%)	5 (18%)	0	11 (39%)	3 (11%)	1 (4%)
Abramson et al. (2018) (TRAN-SCEND NHL 001) [45]	CD19-4-1BB (lisocabtagene maraleucel; liso-cell; JCAR017)	DLBCL	102	38 (37%)	1 (1%)	0	23 (23%)	13 (13%)	0
Park et al. (2018) (MSKCC) [43]	CD19-28-ζ	B-ALL	53	45 (85%)	14 (26%)	1 (2%)	23 (43%)	22 (42%)	0
Maude et al. (2014) (U. Penn) [20]	CD19-4-1BB	B-ALL	30	30 (100%)	8 (27%)	0	13 (43%)	NA	0
Ghorashian et al. (2017) (NHS) [64]	CD19-4-1BB (low affinity)	B-ALL	8	8 (100%)	0	0	3 (38%)	0	0
Qasim et al. (2017) (NHS) [75]	CD19-4-1BB with RQR8 safety switch (allogeneic CAR-T)	B-ALL	5	5 (100%)	1 (20%)	0	2 (40%)	0	0
Gust et al. (2017) (Juno) [39, 51]	CD19-4-1BB	B-ALL, NHL, CLL	133	93 (70%)	16 (12%)	5 (4%)*	53 (40%)	28 (21%)	4 (3%)
DeAngelo et al. (2017) (ROCKET) [40]	CD19-28-ζ (JCAR015)	B-ALL	38	NA	8 (21%)	0	NA	20 (52%)	5 (13%)
Cohen et al. (2017) (U. Penn) [58]	BCMA-4-1BB	MM	21	18 (86%)	6 (29%)	0	3 (14%)	1 (5%)	0
Raje et al. (2018) [55]	BCMA-4-1BB	MM	43	27 (63%)	2 (5%)	0	14 (33%)	1 (2%)	0

CONSENSUS GRADING OF CRS (2018)

ASBMT CRS Grade	Defining Features of Grade
Grade 1	Fever with temperature ≥38°C but no hypotension or hypoxia
Grade 2	Fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula
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
Grade 4	Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Hematological Oncology. 2019;

TOCILIZUMAB

anti-IL6-R Ab

MAX. DOSE=800mg

Tocilizumab is infused over 60 min at a dose of 12 mg/kg for patients with a body weight < 30 kg and 8 mg/kg for patients weighing ≥ 30 kg. The FDA-approved dosing strategy includes the ability to administer up to three additional doses if there is no clinical improvement in the signs and symptoms of CRS, with a minimum of 8 h between consecutive doses.

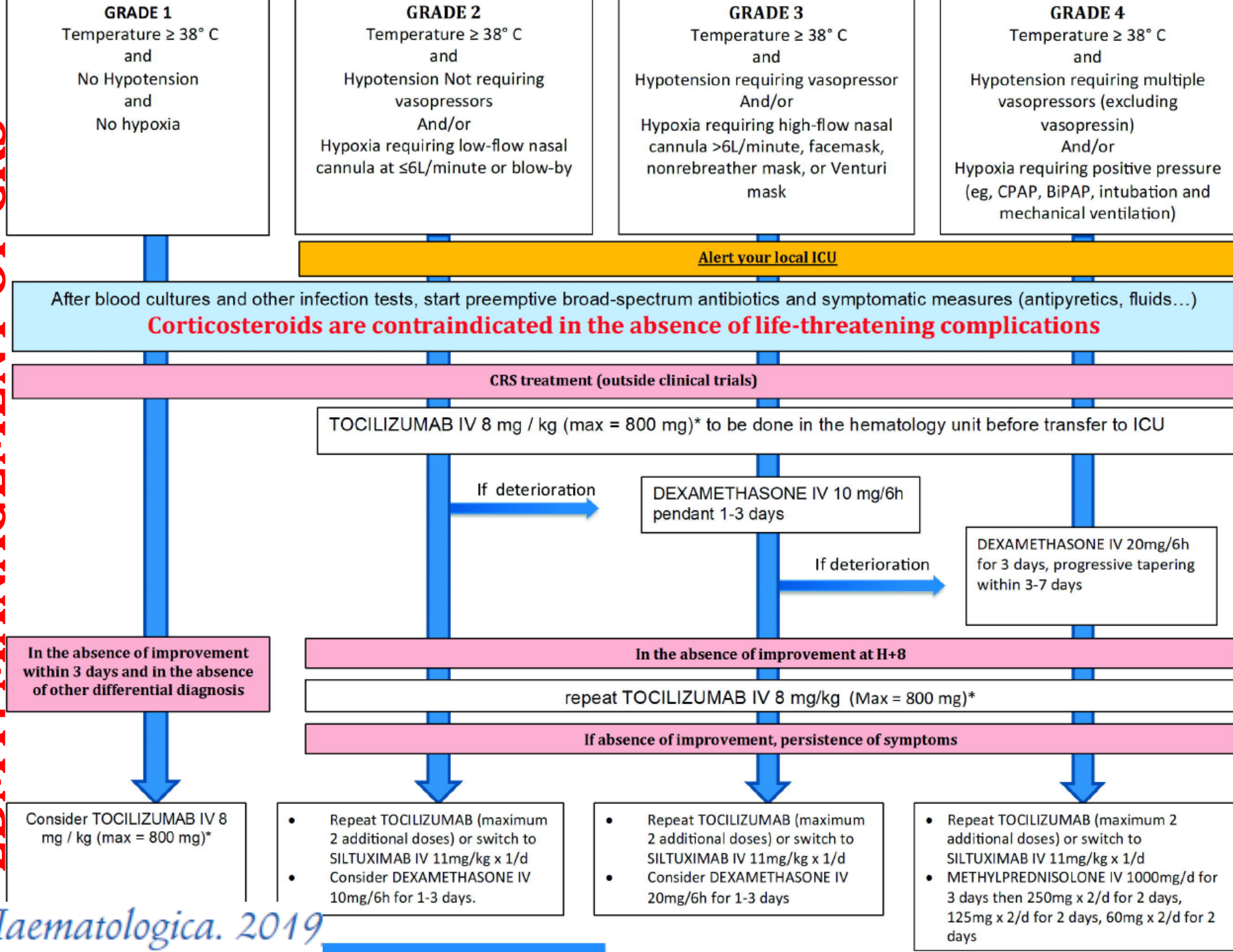
BioDrugs 2018

ASBMT: MANAGEMENT OF CRS

ASBMT CRS Grade	Management
Grade 1	• Antipyretics and IV hydration • Diagnostic work-up to rule out infection • Consider growth factors and antibiotics if neutropenic
Grade 2	• Supportive care as in grade 1 • IV fluid boluses and/or supplemental oxygen • Tocilizumab +/− dexamethasone or its equivalent of methylprednisolone
Grade 3	• 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	• 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

Hematological Oncology. 2019

EBMT: MANAGEMENT OF CRS



Haematologica. 2019

ICANS:

Immune Effector Cell-Associated Encephalopathy

ICE Score

Παράμετρος	Βαθμοί
Προσανατολισμός (Συνολικά 4 βαθμοί)	
• Έτος	1
• Μήνας	1
• Πόλη	1
• Νοσοκομείο	1
Κατονομασία αντικειμένων (Συνολικά 3 βαθμοί)	
• 1ο αντικείμενο	1
• 2ο αντικείμενο	1
• 3ο αντικείμενο	1
Εκτέλεση εντολών (Συνολικά 1 βαθμός)	
• «Χαμογελάστε» ή «ανοίξτε το στόμα σας»	1
Ικανότητα να γράψει μια σταθερή πρόταση (Συνολικά 1 βαθμός)	
• πχ. «Χαίρομαι όταν είμαι μαζί με την οικογένειά μου»	1
Προσοχή (Συνολικά 1 βαθμός)	
• Μέτρηση από το 100 και κάτω ανά 10 μονάδες	1
ΣΥΝΟΛΙΚΟ SCORE (Μέγιστο: 10 βαθμοί)	……

Lee et al, Biol Blood Marrow Transplant 2019

CONCENSUS GRADING OF ICANS

ASBMT ICANS Grade	Defining Features of Grade
Grade 1	• ICE score 7-9 and/or depressed level of consciousness but awakens spontaneously • No seizures, motor weakness, or raised ICP/cerebral edema
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
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
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

Hematological Oncology. 2019;37

ASBMT: MANAGEMENT OF ICANS

ASBMT ICANS Grade	Management
Grade 1	• Aspiration precautions and IV hydration • Seizure prophylaxis with levetiracetam • EEG • Imaging of brain • Consider tocilizumab if there is concurrent CRS
Grade 2	• Supportive care as in grade 1 • Consider dexamethasone or its equivalent of methylprednisolone
Grade 3	• 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	• 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

Hematological Oncology. 2019;37

EBMT: MANAGEMENT OF ICANS

GRADE 1	GRADE 2	GRADE 3	GRADE 4
- Decreased level of consciousness (Awakens spontaneously) - ICE Score (age ≥ 12) = 7-9 or CAPD (age<12) = 1-8	- Alteration level of consciousness affecting activities of daily living (Awakens to voice) - ICE Score (age ≥ 12) = 3-6 or CAPD (age<12) = 1-8	- Very altered level of consciousness (Awakens only to tactile stimulus) - Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention - Focal/local oedema on neuroimaging - ICE Score (age ≥ 12) = 0-2 or CAPD (age<12) > 8	- Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. 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- Cerebral oedema Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad - ICE score or CAPD impossible

Contact your local ICU,
Alert your referral neurologist

Symptomatic measures: raised head 30 °, suspend oral nutrition, replace oral drugs by IV

Specific ICANS treatment (outside clinical trials)

- Systematic EEG in 1st place
- MRI and LP as clinically indicated (differential diagnosis)
- Close monitoring

- Daily EEG, fundus, MRI and then LP in the absence of CI, transfer to ICU

- If seizure (clinically or EEG): CLONAZEPAM IV 1 mg (0.015 mg / Kg up to 1 mg), and introduce levetiracetam 500 mg x2 (paediatric dose 30 mg / Kg x 2, max 3g daily)
- If persistence or recurrence of seizure, repeat clonazepam 5 min once, otherwise, to be treated as a "état de mal"

- If papillary oedema : consider ACETAZOLAMIDE IV 1000 mg then 250-1000 mg/12h (5 mg/Kg/12h)

- If cerebral oedema: consider hyperosmolar therapy

If associated with CRS grade ≥ 1 (fever): TOCILIZUMAB IV 8 mg / kg (max = 800 mg); see management of CRS

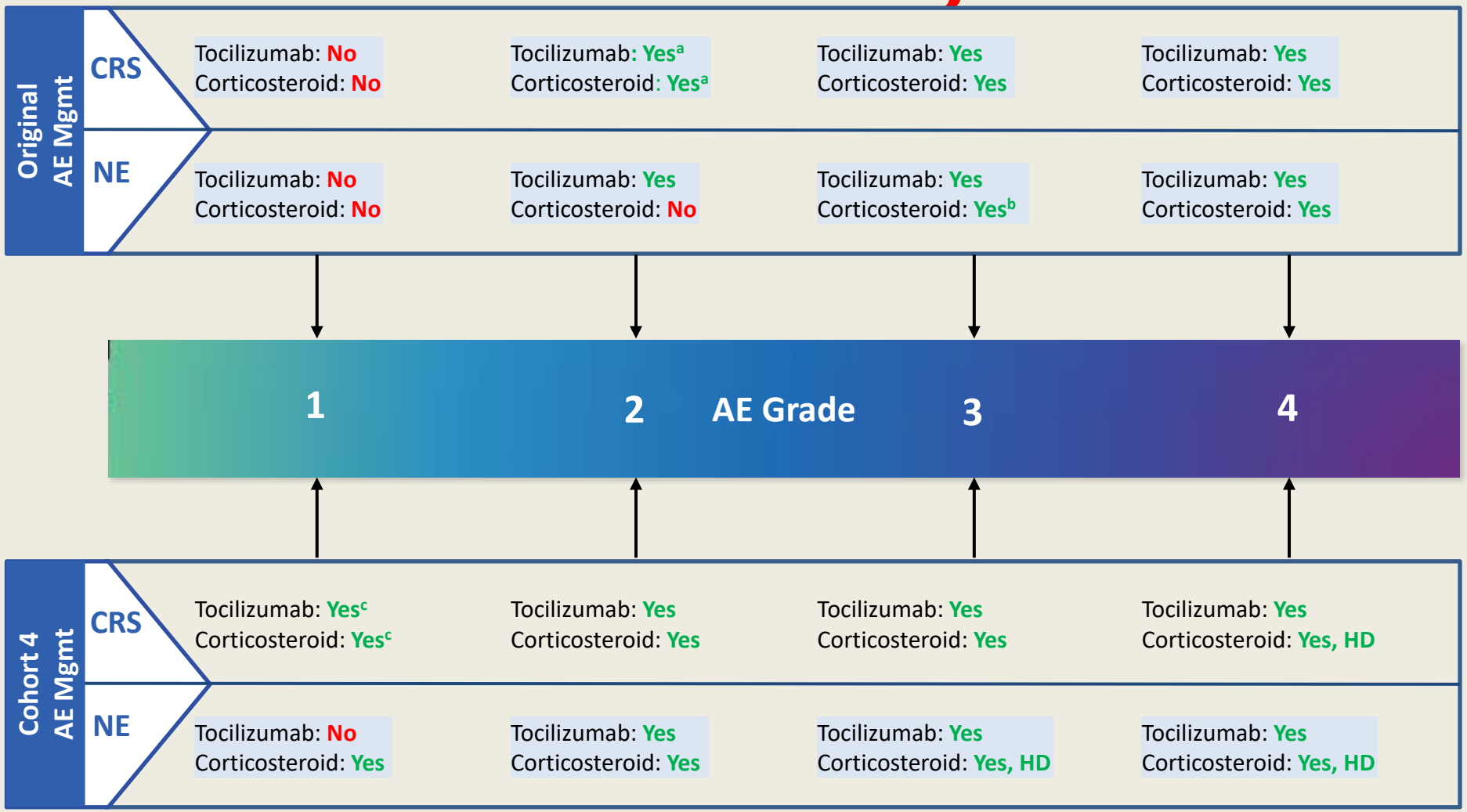
If ICANS without CRS (afebrile): consider corticosteroid therapy

- DEXAMETHASONE IV 10 mg/6h for 1-3 d
- DEXAMETHASONE IV 20 mg/12h for 1-3 d
- METHYLPREDNISOLONE IV 1000 mg/4h for 3 d then 250 mg x 2/d for 2 d, 125 mg x 2/d for 2 d, 60 mg x 2/d for 2 d
- Discuss other alternative: high dose cyclophosphamide, anti-IL1R (Anakinra), antiIL6 (Siltuximab)

EEG monitoring until resolution: if seizure: e.g. ICANS grade 2
Daily fundus until resolution: if papillary oedema: e.g ICANS grade 3
MRI and LP to be reassessed according to evolution
CAR-T cell checklist 2 times a day*

Haematologica. 2019

AE Management in ZUMA-1 (AxiCell-YESCARTA®)



[a] Only in case of comordbidities or older age. [b] Only if no improvement to tocilizumab, use standard dose. [c] If not improvement after 3 days.
AE, adverse event; CRS, cytokine release syndrome; HD, high dose; mgmt, management; NE neurologic event.

Topp, ASH 2019

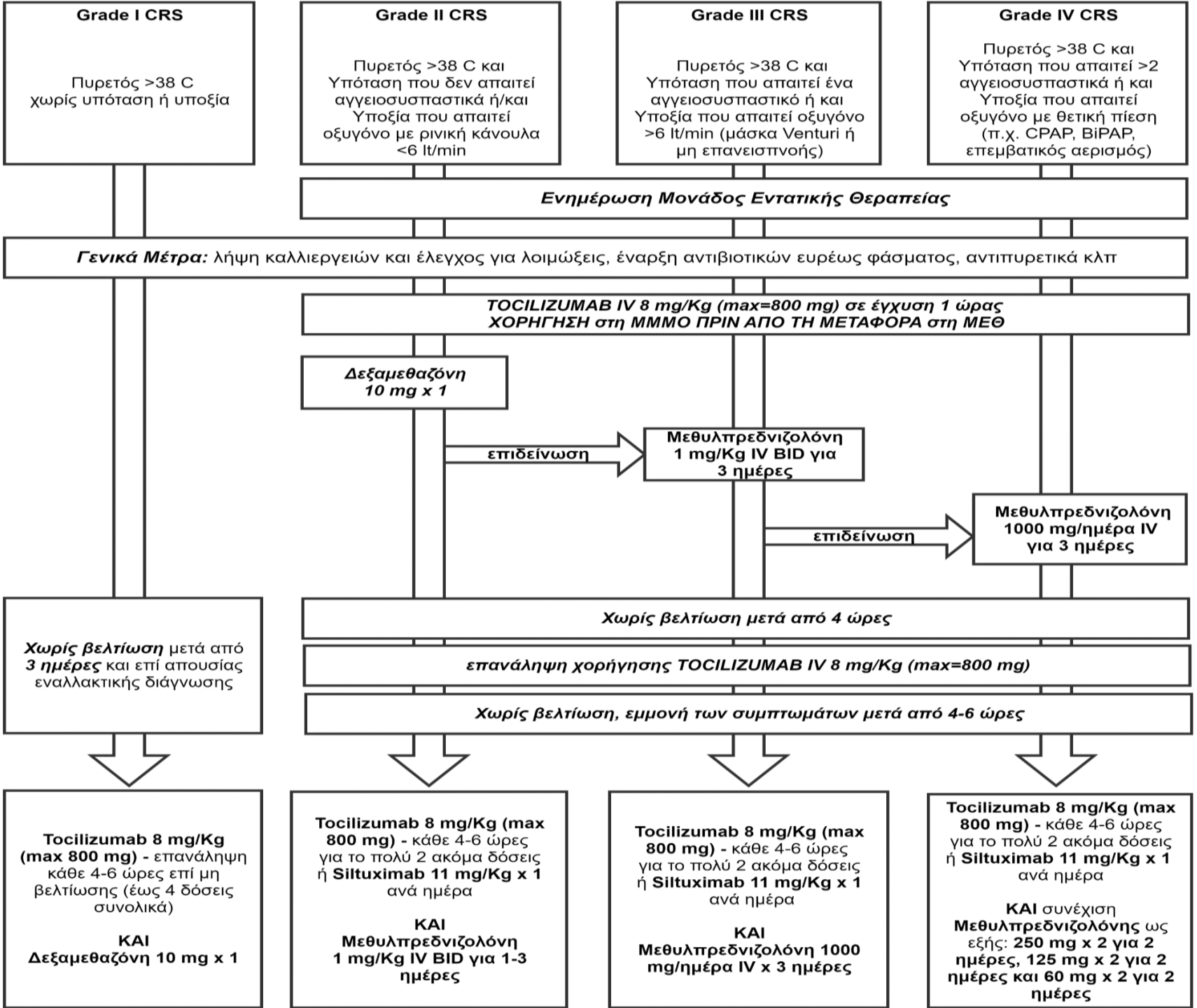
Conclusions from the ZUMA-1 study, cohort 4 (AxiCell- YESCARTA®) in patients with R/R DLBCL

<u>Earlier steroid intervention has the potential to :</u>

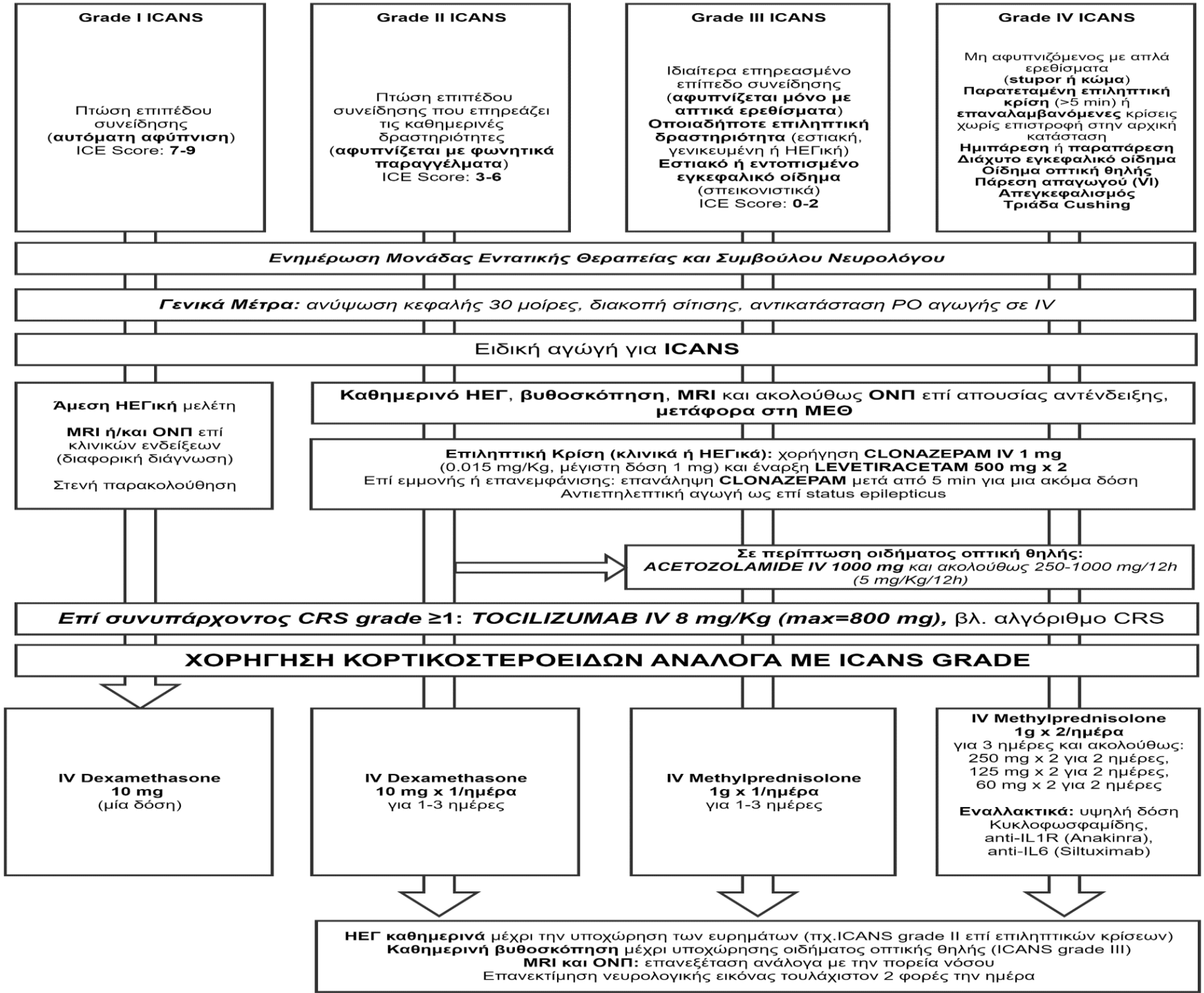
- **Lower rate of CRS and NEs in Cohort 4 versus Cohorts 1+2**
- **No impact on the expansion of CAR T cells**
- **No impact on ongoing response rates (ORR)**

Topp, ASH 2019

MANAGEMENT OF CRS due to YESCARTA®



MANAGEMENT OF ICANS due to YESCARTA®



CART RELATED CEREBRAL EDEMA

Box 4 | **Recommendation for management of raised intracranial pressure (ICP) after CAR-T-cell therapy**

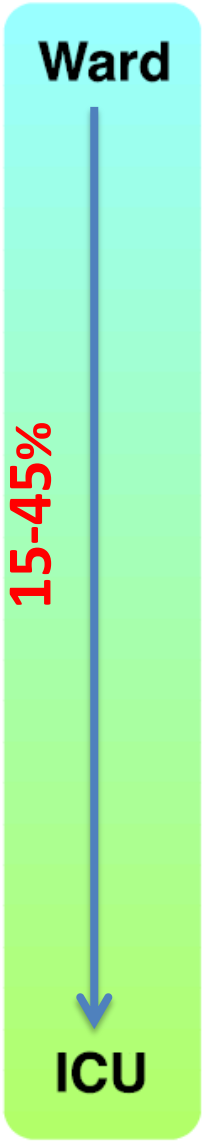
Stage 3, 4, or 5 papilloedema*, with any sign of cerebral oedema on imaging studies, or a CSF opening pressure of ≥20 mmHg

- Use high-dose corticosteroids with methylprednisolone IV 1 g/day, as recommended for grade 4 CAR-T-cell-related encephalopathy syndrome (CRES; BOX 2)
- Elevate head end of the patient's bed to an angle of 30 degrees
- Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 28–30 mmHg, but maintained for no longer than 24 h
- Hyperosmolar therapy with either mannitol (20 g/dl solution) or hypertonic saline (3% or 23.4%, as detailed below)
  - Mannitol: initial dose 0.5–1 g/kg; maintenance at 0.25–1 g/kg every 6 h while monitoring metabolic profile and serum osmolality every 6 h, and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40
  - Hypertonic saline: initial 250 ml of 3% hypertonic saline; maintenance at 50–75 ml/h while monitoring electrolytes every 4 h, and withhold infusion if serum Na levels reach ≥155 mEq/l
  - For patients with imminent herniation: initial 30 ml of 23.4% hypertonic saline; repeat after 15 min, if needed
- If patient has ommaya reservoir, drain CSF to target opening pressure of <20 mmHg
- Consider neurosurgery consultation and IV anaesthetics for burst-suppression pattern on electroencephalography
- Metabolic profiling every 6 h and daily CT scan of head, with adjustments in usage of the aforementioned medications to prevent rebound cerebral oedema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension

NATURE REVIEWS | CLINICAL ONCOLOGY 2017

A Critical Care View of CAR-T cell therapy

CAR-T cells



Consultation from an ICU specialist upon scheduling (eligiblity, assessment of functional status/organ dysfunction, preventive measures, information of patient and relatives)

Application of a common information network to share important dates of events and day-to-day information

Reach agreement among ICU and hematology teams about the goals of care

-

Time-limited ICU trial should be considered for every patient

CRS and neurological symptoms have to be assessed clinically several times per day for at least 7 days

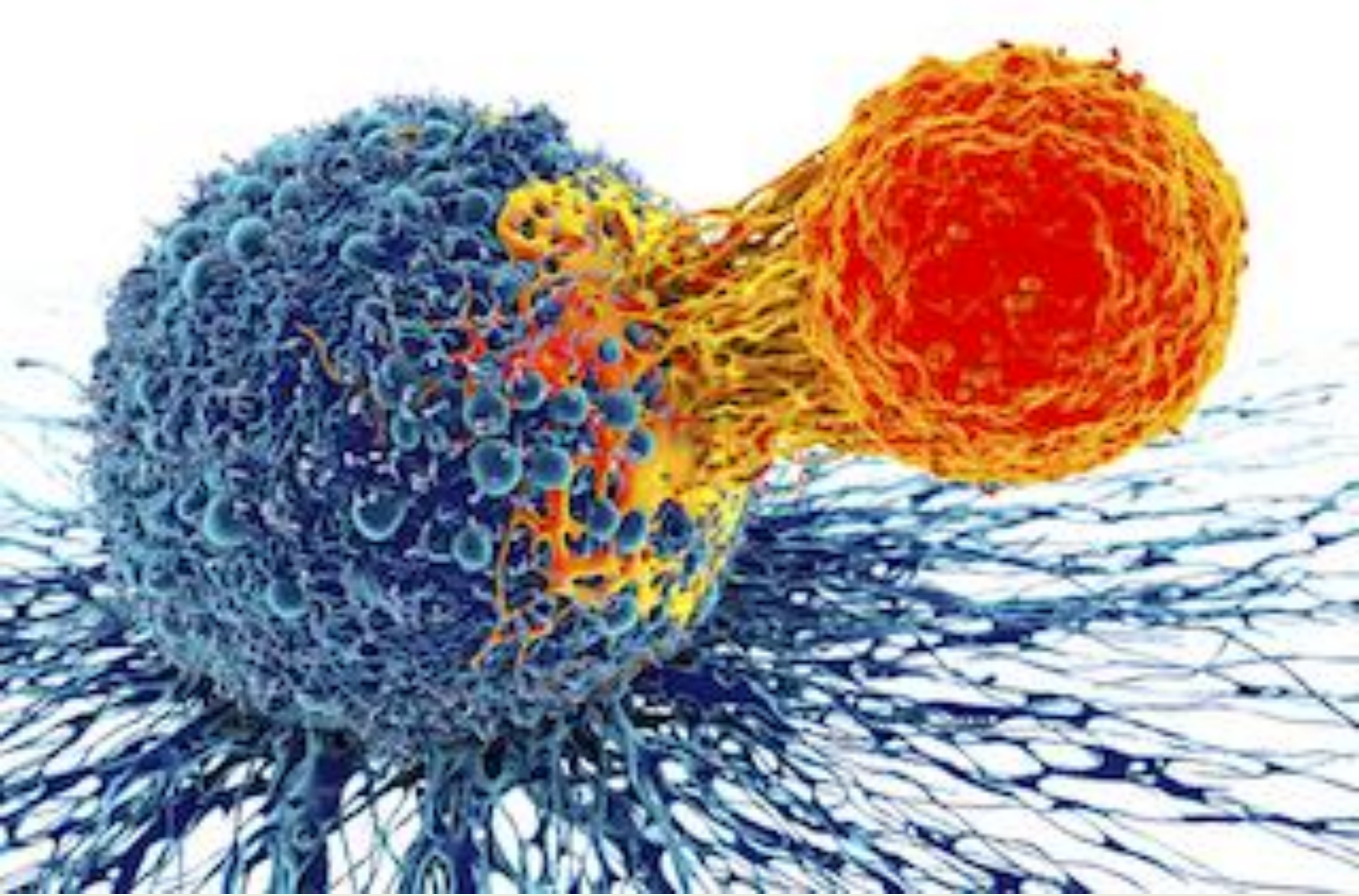
Elicit prompt ICU admission once diagnosis of grade II CRS is made. Do not delay ICU admission

Leverage the latest advances in critical care managment and technology for the benefit of critically ill patients undergoing CART therapy

Liase with all clinicians and researchers involved in the development and evaluation of CART therapy to facilitate translational research on detection and treatment of CART-related toxicities

Share experiences with other specialists dedicated to the care of hematology/oncology patients

Azoulay, AJRCCM 2019



ΕΥΧΑΡΙΣΤΩ