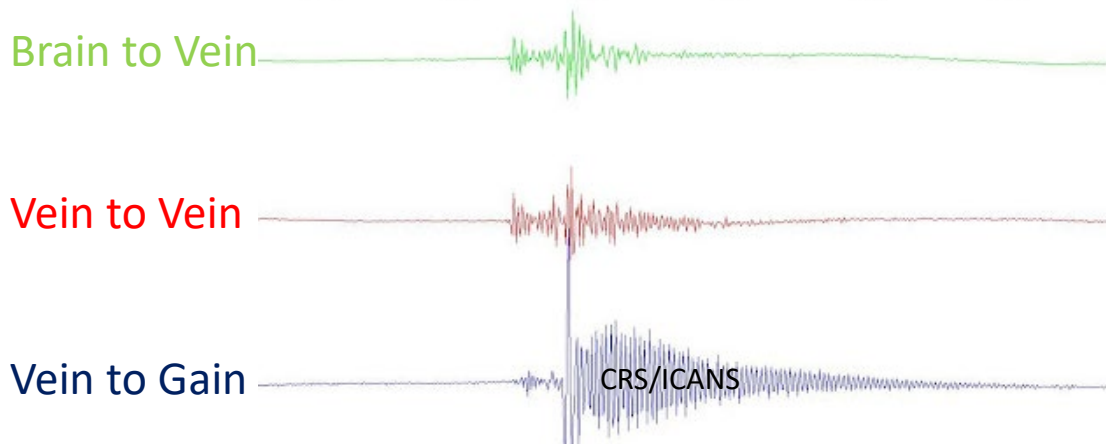


Cellular Therapy for Lymphoma: Efficacy and Managing Adverse Reactions



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4/29/2022



Disclosures

Updated 3/2023	
Research Support	BMS, Curis
Consultancy	AbbVie, Acrotech, Astellas, AZ, BMS, Caribou, CRISPR, Diiachi Sankyo, Fate Therapeutics, Genentech, Genmab, Ipsen, Janssen, Kite, Loxo, Miltenyi, Morphosys, Nurix, Pharmacyclics, Regeneron, Sanofi, Seagen, Takeda
Employment	NONE
Stock/Equity	NONE
Speakers Bureau	NONE



Objectives

- Highlight challenges in the management of pre-CAR-T patients in different stages of the CAR-T journey
- Provide an update from the POSITIVE 2nd line CAR-T pivotal trials
- Discuss the post-CAR-T complications that can occur after the acute setting (infusion to D+28)



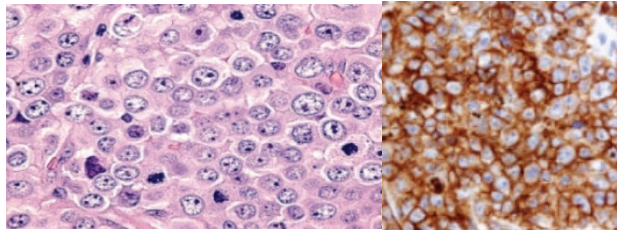
Case of the Day

- Before Covid (BC) is a 44 y.o. woman who noted unintentional weight loss of 10 kgs in 2 months.
- Husband notes she has been “sweating the bed” and he now chooses to sleep on the couch.
- Exam: Multiple enlarged lymph nodes in his cervical, supraclavicular, and inguinal lymph nodes.
- No reported fevers or night sweats
- She continues to work but is tired by end of the day



Case of the Day

- Excision biopsy: Right supraclavicular lymph node.
- Pathology: Effacement of nodal architecture by large cleaved cells
- IHC: CD20+, CD10+, MYC 90%, Ki-67 90%
- FISH: Positive for MYC and BCL2
- Dx: High grade B-cell lymphoma with MYC and BCL-2 rearrangement (Double Hit)

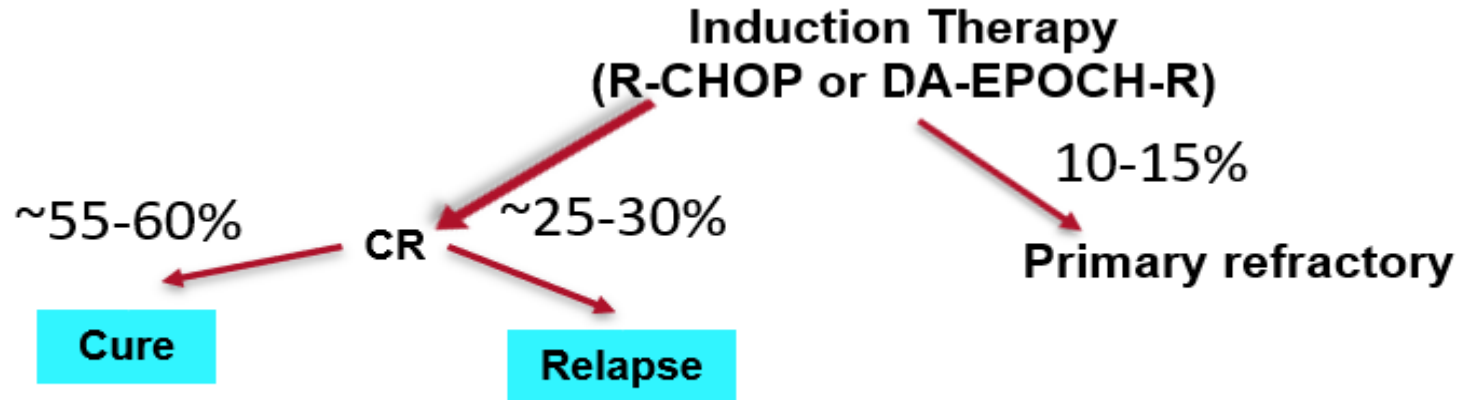


Case of the Day

- PET/CT demonstrates adenopathy above and below the diaphragm with lytic bone lesions.
- Normal CBC
- Normal CMP but elevated LDH
- Bone marrow: Deferred
- Stage: IVA

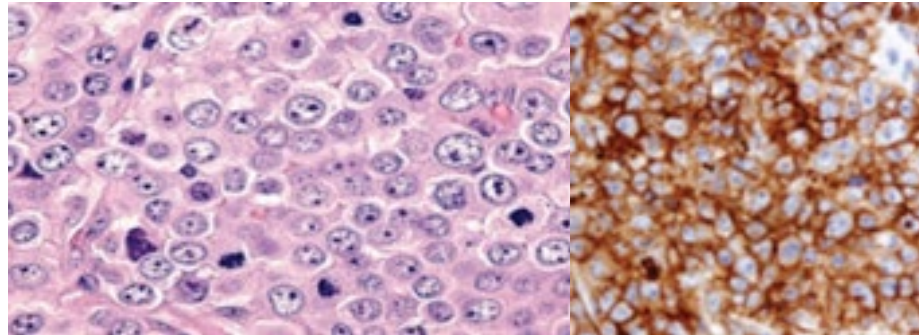


DLBCL

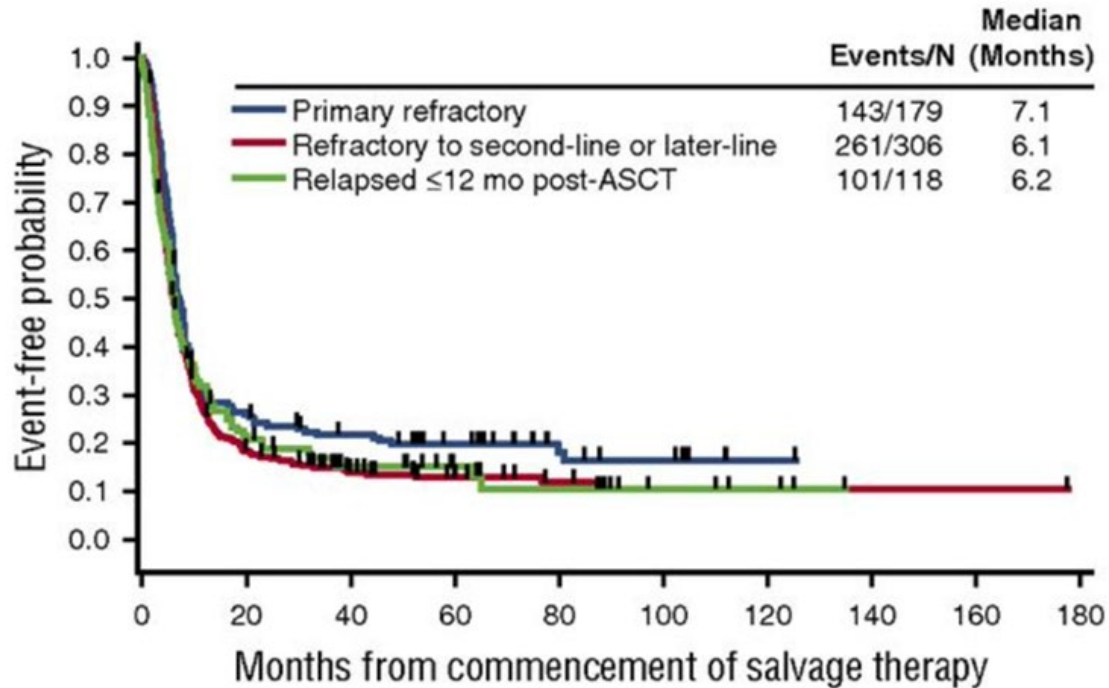


Case of Day XY&!

- Enlargine lymph nodes at 3 month visit post chemotherapy
- PET/CT confirms avid and new sites of nodal disease (Deauville 5)
- Biopsy: Large cleaved cells
- IHC: CD20+, CD10+, CD30+ (30%), MYC 90%, Ki-67 90%
- Dx: DLBCL-NOS but given hx and IHC HGBCL with MYC/BL2 rearrangements



Her Current Prognosis: YIKES



Are they an autologous transplant candidate?



Yes



Maybe

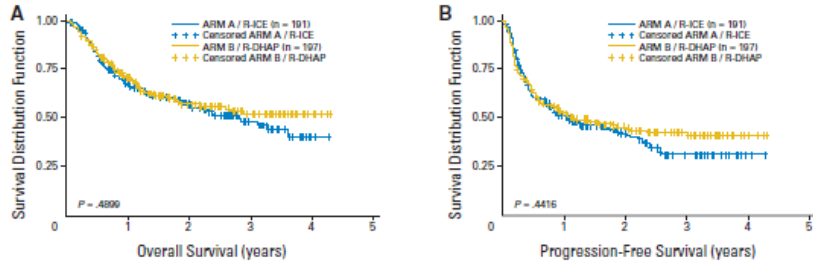


No

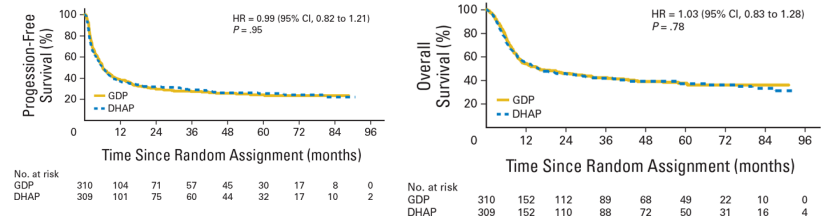


2nd Line Outcomes

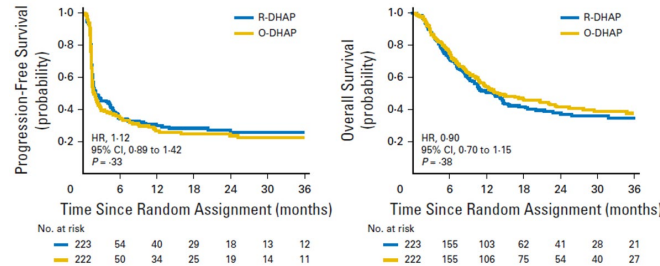
Coral (R-ICE vs R-DHAP)



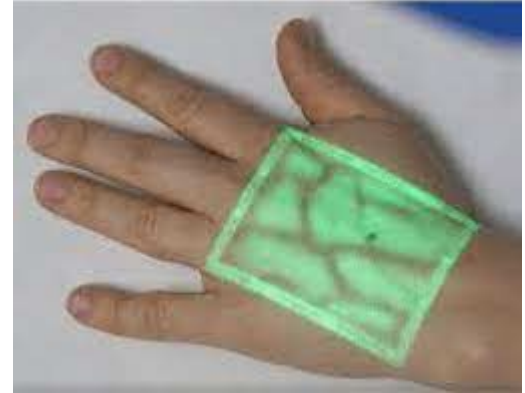
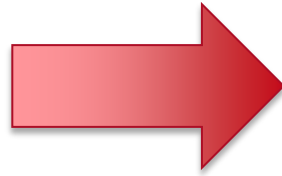
LY12 (GDP vs DHAP)



ORCHARDD



CAR-T ASAP?



Brain to Vein: Intent to CAR is Not CAR

- Need to bridge
 - Yes or No
- Insurance
 - Private, Medicare, Medicaid (State), TriCare
- Apheresis Date
 - Immediate access
 - Out of specification trend
- Early bridging (Brain to Vein)
 - Yes or No
- Late bridging (Vein to Vein)
 - Yes or No or unknown



Brain to Vein: Using YOUR Institutional History

- Private insured (weeks to months)
 - How long did it take for prior single case agreement (SCA)
 - Extra inclusion criterion
 - TTE, PFTs, HCSCT markers
- Medicare (days to months)
 - Managed plans require a SCA
 - If Medicare with supplement, then move quickly to apheresis
- Medicaid (weeks to months)
 - Managed plan requires SCA
 - Differs state to state regarding approval process
- Tricare (Unknown)
 - Referred to VA center (Vanderbilt in Nashville, TN)



Brain to Vein: My Internal Debate

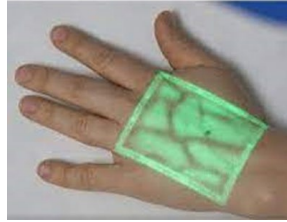
- Insurance
 - **Private**
- Need to bridge
 - **Yes** or No
- Prior treatment
 - **DA-EPOCH-R**, R-CHOP or Pola-R-CHP or Clinical Trial
- Early bridging (Brain to Vein)
 - **Yes** or No
- Late bridging (Vein to Vein)
 - Yes or No or **Unknown**



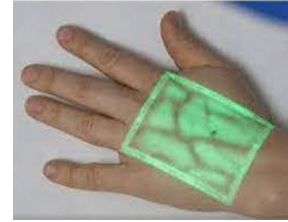
Is This A Line of Treatment?

- Polatuzumab vedotin single agent (1.8 mg/kg)
- Nodal disease remain prominent but non-progressive
- CBC with persistent anemia (hgb 10.5) and transient thrombocytopenia
- No neuropathy seen





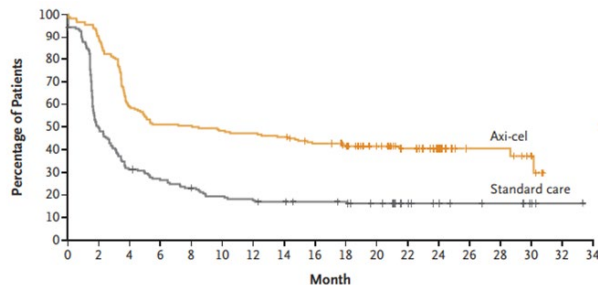
to



- Apheresis Date
 - Riding your house (SCA)
 - Online portal...
 - Phone calls may matter
- Vein to vein
 - Know the timing
- Late bridging (Vein to Vein)
 - Yes or No
 - None
 - Steroids
 - XRT
 - Another cycle



Vein to Gain: Axi-cel

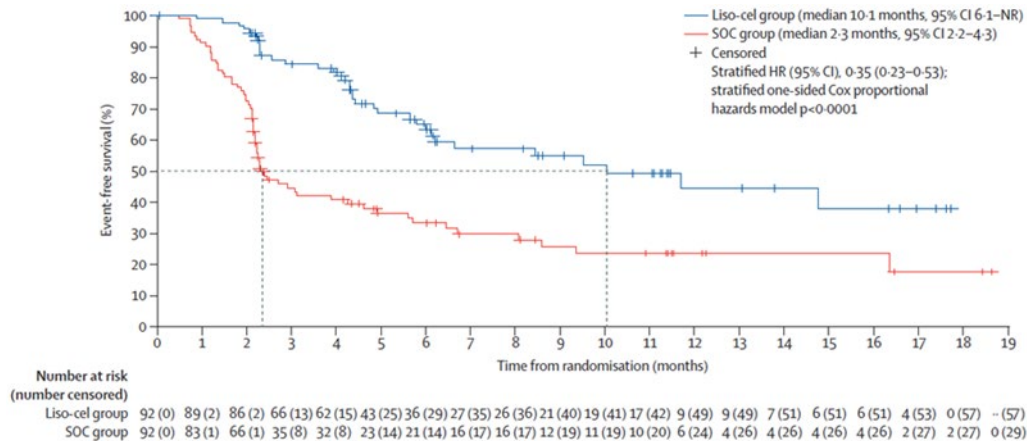


No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6		
Standard care	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

	ASCT (n = 179)	Axi-cel (n = 180)
mEFS; months (95% CI)	2.0 (1.6-2.8)	8.3 (4.5-15.8)
mPFS; months (95% CI)	3.7 (18.5-NE)	14.7 (2.9-3.9)
mOS; months (95% CI)	35.1 (18.5-NE)	NR (28.3-NE)



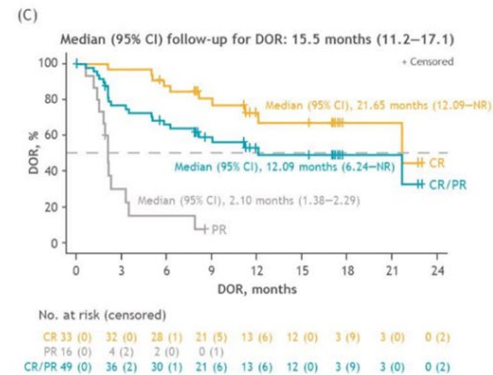
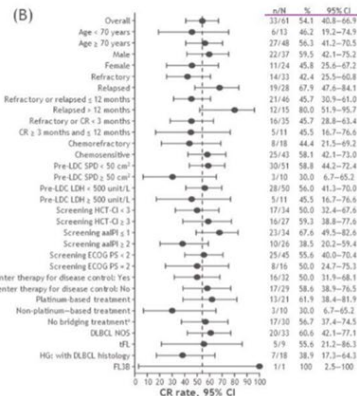
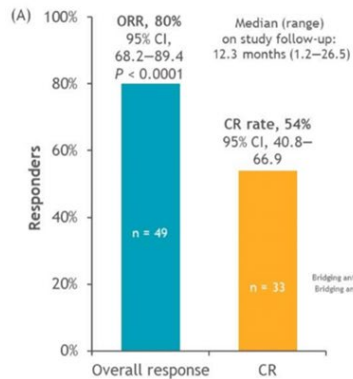
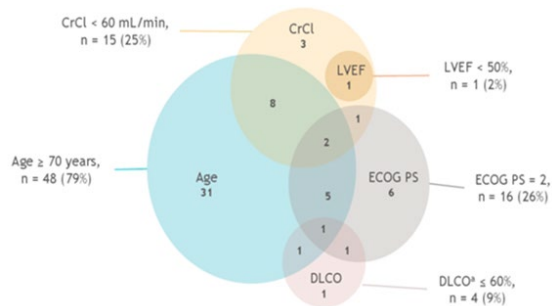
Vein to Gain: Liso-cel



	ASCT (n = 92)	Liso-cel (n = 92)
mEFS; months (95% CI)	2.3 (2.2-4.3)	10.1 (6.1-NR)
mPFS; months (95% CI)	5.7 (3.9-9.4)	14.8 (6.6-NR)
mOS; months (95% CI)	16.4 (11.0-NR)	NR (15.8-NR)



Vein to Gain: Liso-cel



Vein to Gain: CRS/ICANS

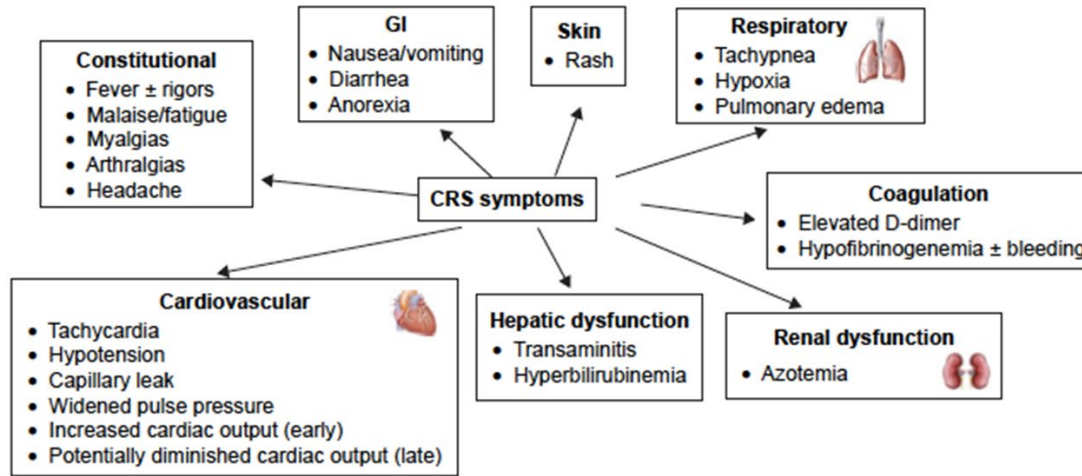


Figure 1 Symptoms of CRS.

Notes: CRS affects a number of organ systems. It requires fever at a minimum but is frequently associated with any of the symptoms shown. Additional manifestations may also rarely occur.

Abbreviations: GI, gastrointestinal; CRS, cytokine release syndrome.



CRS Management

Grading (on the basis of ASTCT consensus grading) ¹⁰	Management
<p>G1: Fever^a: temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause Hypotension: none Hypoxia: none</p>	<p>Offer supportive care with antipyretics, IV hydration, and symptomatic management of organ toxicities and constitutional symptoms May consider empiric broad-spectrum antibiotics if neutropenic. May consider G-CSF in accordance with product guidelines. Note: GM-CSF is not recommended In patients with persistent (> 3 days) or refractory fever, consider managing as per G2</p>
<p>G2: Fever^a: temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause <i>plus</i> Hypotension: not requiring vasopressors <i>And/or</i> Hypoxia: requiring low-flow nasal cannula (ie, oxygen delivered at ≤ 6 L/min) or blowby</p>	<p>Continue supportive care as per G1 and include IV fluid bolus and/or supplemental oxygen as needed Administer tocilizumab⁴²⁻⁴⁴ 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours if no improvement in signs and symptoms of CRS; limit to a maximum of three doses in a 24-hour period, with a maximum of four doses total In patients with hypotension that persists after two fluid boluses and after one to two doses of tocilizumab, may consider dexamethasone 10 mg IV (or equivalent) every 12 hours for one to two doses and then reassess Manage per G3 if no improvement within 24 hours of starting tocilizumab</p>
<p>G3: Fever^a: temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause <i>plus</i> Hypotension: requiring a vasopressor with or without vasopressin <i>And/or</i> Hypoxia: requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask</p>	<p>Continue supportive care as per G2 and include vasopressors as needed Admit patient to ICU If echocardiogram was not already performed, obtain ECHO to assess cardiac function and conduct hemodynamic monitoring Tocilizumab as per G2 if maximum dose is not reached within 24-hour period plus dexamethasone 10 mg IV every 6 hours (or equivalent) and rapidly taper once symptoms improve If refractory, manage as per G4</p>
<p>G4: Fever^a: temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause <i>plus</i> Hypotension: requiring multiple vasopressors (excluding vasopressin) <i>And/or</i> Hypoxia: requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)</p>	<p>Continue supportive care as per G3 plus mechanical ventilation as needed Administer tocilizumab as per G2 if maximum is not reached within 24-hour period Initiate high-dose methylprednisolone at a dose of 500 mg IV every 12 hours for 3 days, followed by 250 mg IV every 12 hours for 2 days, 125 mg IV every 12 hours for 2 days, and 60 mg IV every 12 hours until CRS improvement to G1 If not improving, consider methylprednisolone 1,000 mg IV 2 times a day or alternate therapy^b</p>

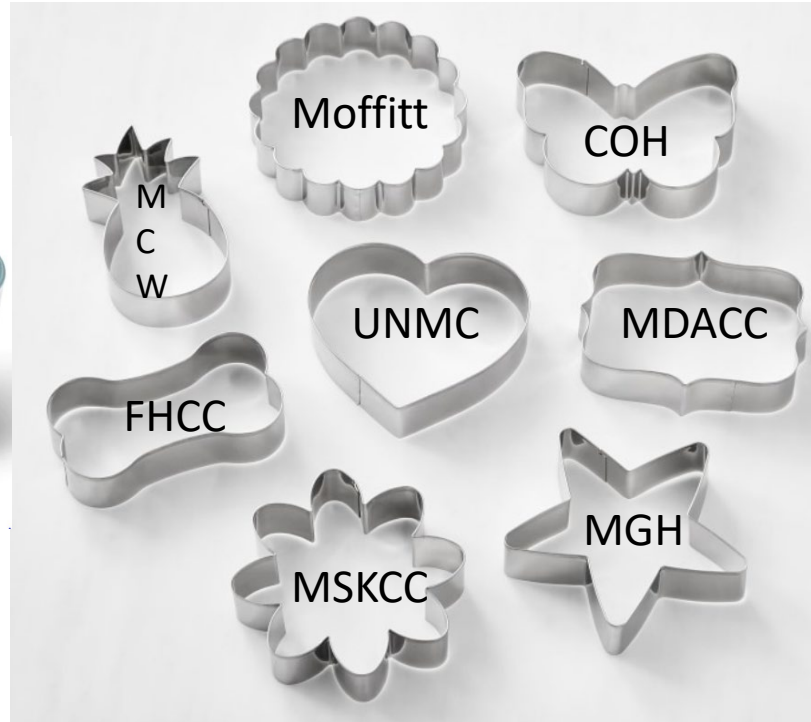


ICANS MANAGEMENT

<p>G1: ICE score^a: 7-9 with no depressed level of consciousness</p>	<p>No concurrent CRS Offer supportive care with IV hydration and aspiration precautions With concurrent CRS Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours as needed. Limit to a maximum of three doses in a 24-hour period; maximum total of four doses. Caution with repeated tocilizumab doses in patients with ICANS. Consider adding corticosteroids to tocilizumab past the first dose</p>
<p>G2: ICE score^a: 3-6 And/or Mild somnolence awaking to voice</p>	<p>No concurrent CRS Offer supportive care as per G1 For high-risk products or patients, consider dexamethasone 10 mg IV x two doses (or equivalent) and reassess. Repeat every 6-12 hours if no improvement.^a Rapidly taper steroids as clinically appropriate once symptoms improve to G1^a With concurrent CRS Consider ICU transfer if ICANS associated with ≥ G2 CRS Administer tocilizumab as per G1 If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6-12 hours) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement to grade 1, and then rapidly taper as clinically appropriate^a</p>
<p>G3: ICE score^a: 0-2 And/or Depressed level of consciousness awakening only to tactile stimulus And/or Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention And/or Focal or local edema on neuroimaging</p>	<p>All G3 patients: Transfer patient to ICU No concurrent CRS Administer dexamethasone (10 mg IV every 6-12 hours) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). With concurrent CRS Administer tocilizumab as per grade 1 If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6-12 hours) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement to grade 1, and then rapidly taper as clinically appropriate^a</p>
<p>G4: ICE score^a: 0 (patient is unarousable and unable to perform ICE) And/or Stupor or coma And/or Life-threatening prolonged seizure (> 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between And/or Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilloedema, cranial nerve VI palsy, or Cushing's triad</p>	<p>All G4 patients: Admit patient to ICU if not already receiving ICU care. Consider mechanical ventilation for airway protection No concurrent CRS Administer high-dose methylprednisolone IV 1,000 mg one to two times per day for 3 days If not improving, consider 1,000 mg of methylprednisolone two to three times per day or alternate therapy^a Continue corticosteroids until improvement to grade 1, and then taper as clinically appropriate^a Status epilepticus to be treated as per institutional guidelines With concurrent CRS Administer tocilizumab as per grade 1 in addition to methylprednisolone 1,000 mg IV one to two times per day for 3 days If not improving, consider 1,000 mg of methylprednisolone IV two to three times a day or alternate therapy^a Continue corticosteroids until improvement to grade 1, and then taper as clinically appropriate^a</p>



2023: CRS/ICANS Management

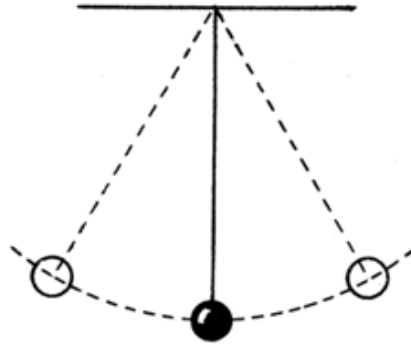


2023 CRS/ICAN: Experience Matters

ZUMA-1



Cohort 1 → Cohort 4 → Cohort 6

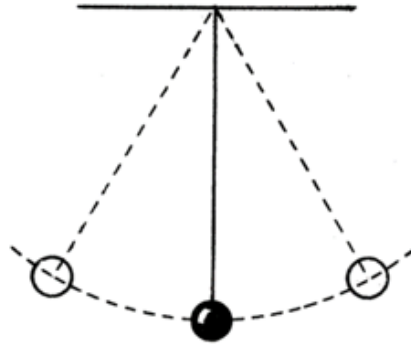


2023 CRS/ICAN: Experience Matters

TRANSCEND



CRS < 72 hours or CRS > 72hours



PARTING PRINCIPALS: 100 Consecutive Patients

- All pts with CRS had some degree of CNS symptoms
- All pts with NT had CRS
- Earlier onset CRS: greater likelihood & higher grade of ICANS
- Baseline/peak CRP higher in pts developing ICANS
- LP unhelpful unless given triple treatment (steroids, MTX, Ara-C)
- EEG- diffuse slowing common, seizure activity 30%





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