Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Clinical Practice Guideline Webinar –

Immune Effector Cell-related Adverse Events

Friday, March 5, 2021

3:00 PM – 4:00 p.m. EST

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer

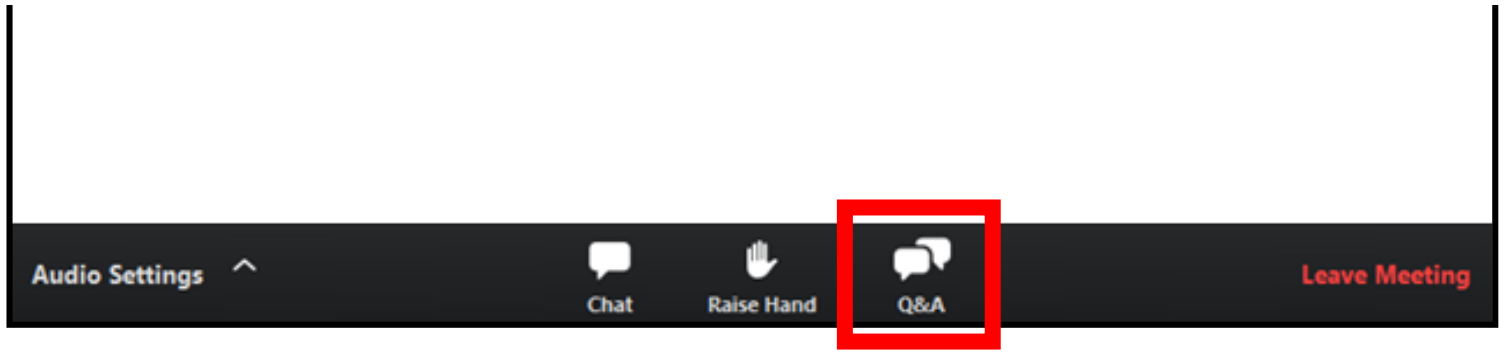
This webinar is supported, in part, by independent medical education grant funding from Amgen, AstraZeneca Pharmaceuticals LP, Celgene Corporation and Merck & Co., Inc.

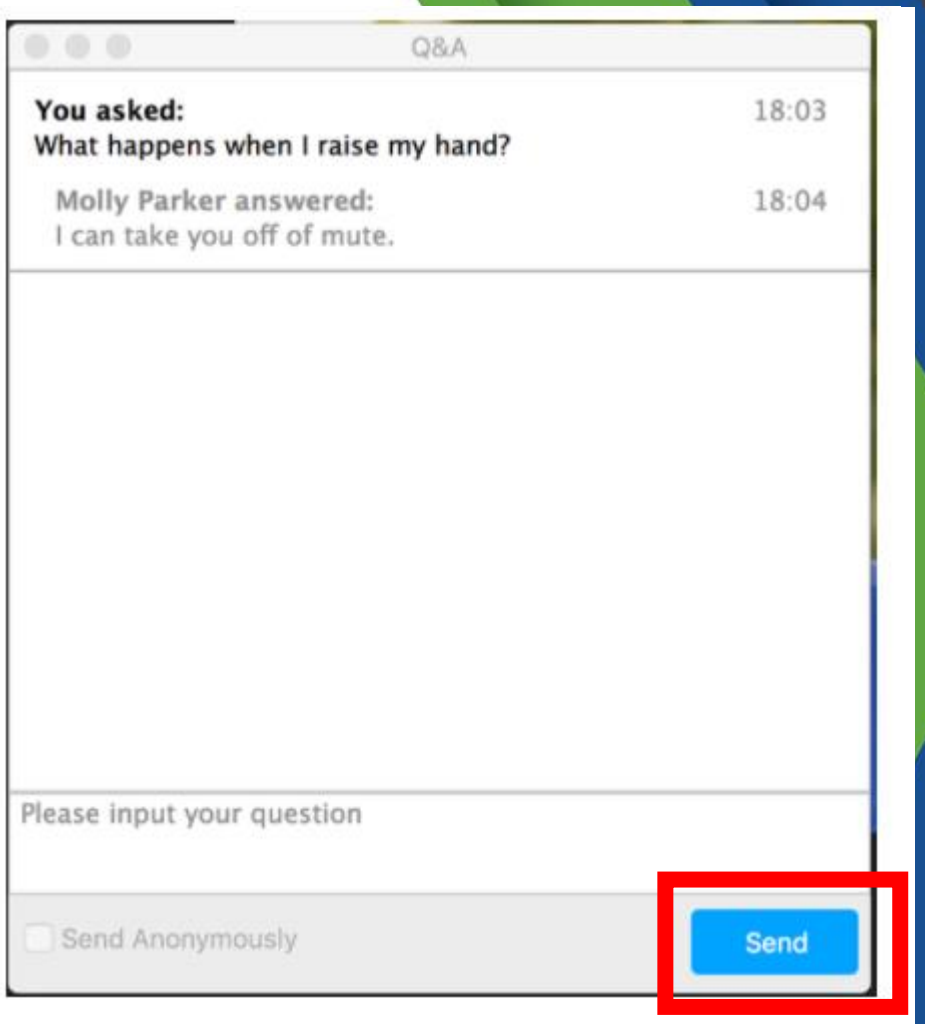
Webinar Agenda

3:00 – 3:05 p.m. ET	Overview: Welcome and Introductions
3:05 – 3:45 p.m. ET	Presentation and discussion of guideline content
3:45 – 3:55 p.m. ET	Question and Answer Session
3:55 – 4:00 p.m. ET	Closing Remarks

How to Submit Questions

- Click the “Q&A” icon located on at the bottom of your Zoom control panel
- Type your question in the Q&A box, then click “Send”
- Questions will be answered in the Question & Answer session at the end of the webinar (as time permits)





Webinar faculty

Stephan Grupp, MD, PhD
Children's Hospital of Philadelphia and University of Pennsylvania

Matthew J. Frigault, MD, MSc
Massachusetts General Hospital

Frederick L. Locke, MD
H. Lee Moffitt Cancer Center & Research Institute

Bianca D. Santomasso, MD, PhD
Memorial Sloan Kettering Cancer

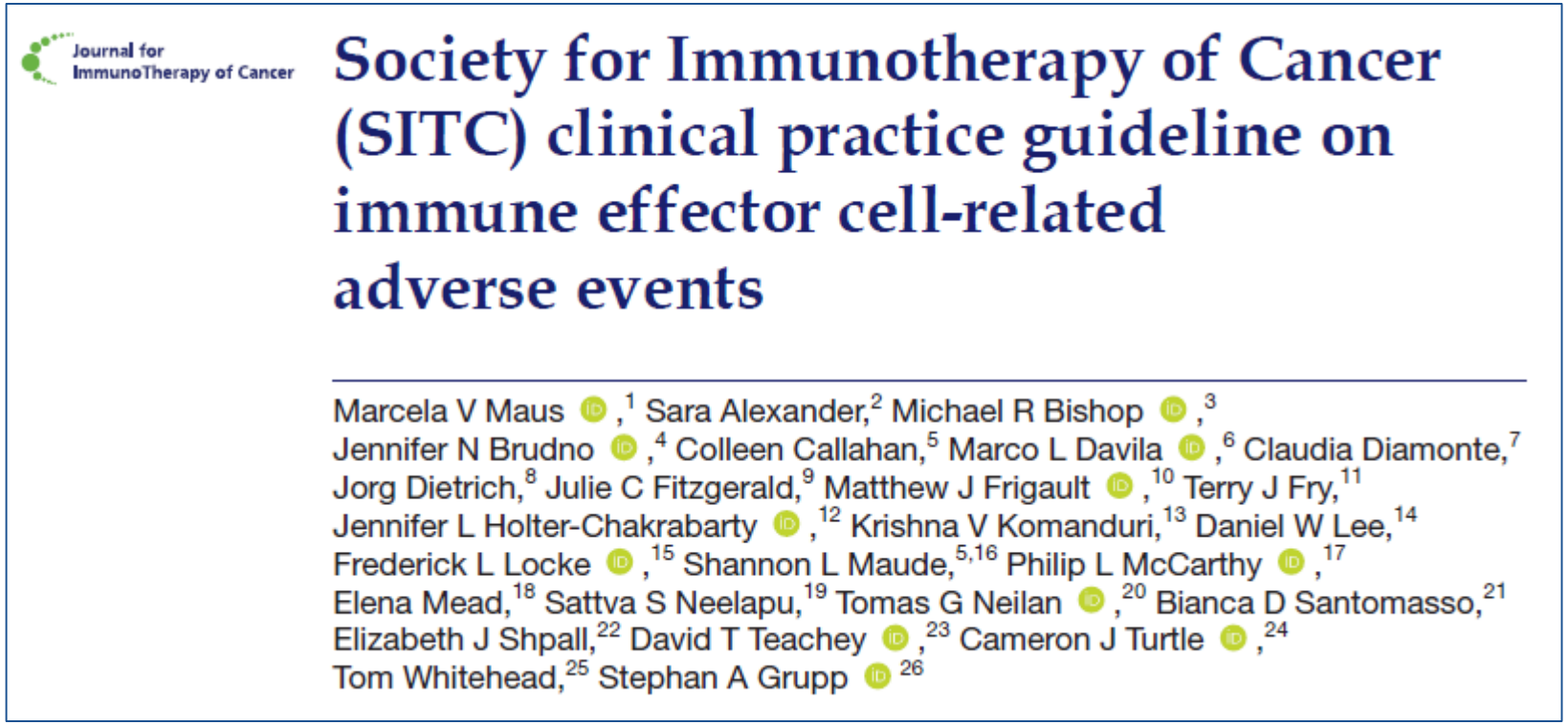
Learning objectives

- Properly monitor patients receiving immune effector cell therapies for treatment-related adverse events and identify those at high risk
- Identify common and uncommon toxicities that may occur with immune effector cell therapies
- Determine appropriate management techniques for common adverse events resulting from immune effector cell therapies

Development of the guideline

- Panel of 26 members, including physician, nursing, and patient advocacy perspectives
- Representatives from several organizations participated:
  - American Society of Hematology (ASH)
  - American Society for Transplantation and Cellular Therapy (ASTCT)
  - Foundation for the Accreditation of Cellular Therapy (FACT) at the University of Nebraska Medical Center
  - Emily Whitehead Foundation
- All recommendations based on literature where available, and panel experience and consensus where applicable

Development of the guideline



Journal for ImmunoTherapy of Cancer

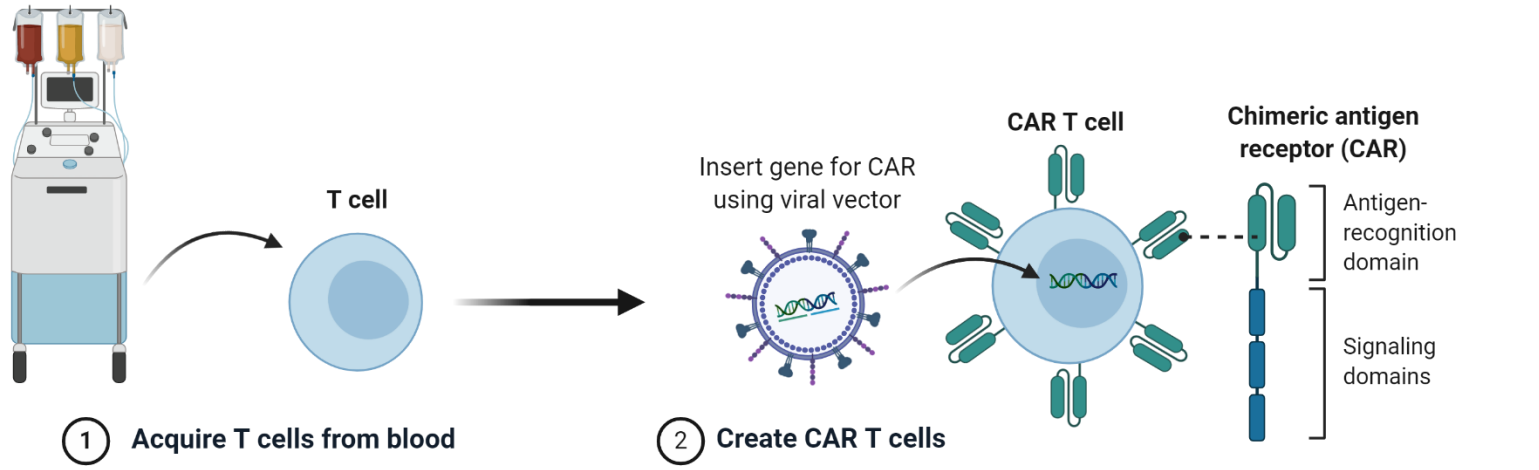
Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events

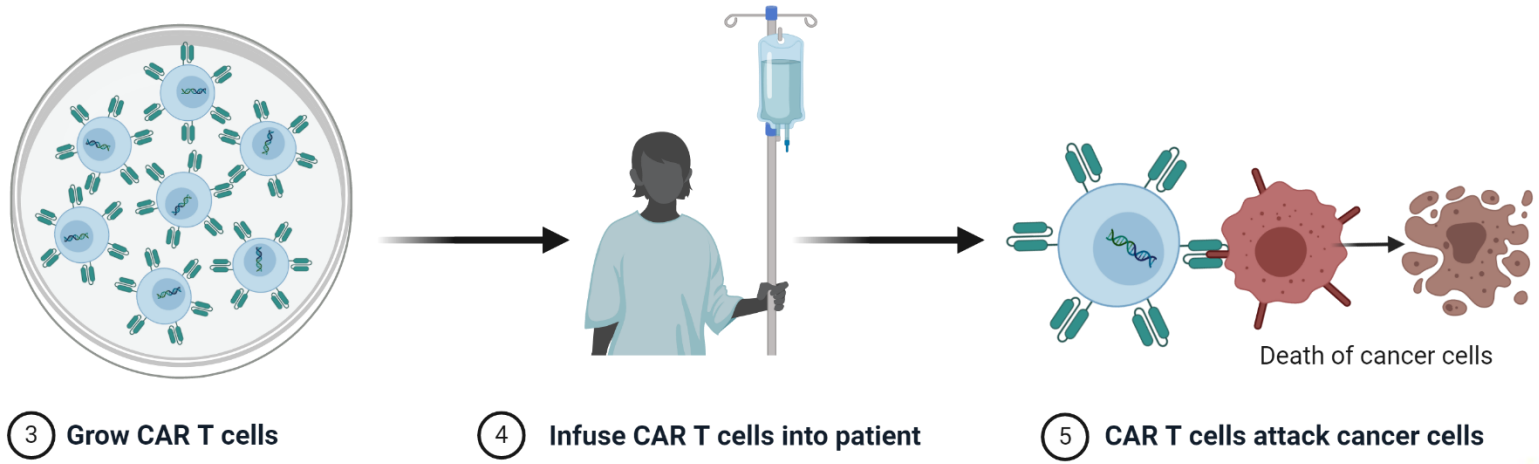
Marcela V Maus [1], Sara Alexander,[2] Michael R Bishop [3], Jennifer N Brudno [4], Colleen Callahan,[5] Marco L Davila [6], Claudia Diamonte,[7] Jorg Dietrich,[8] Julie C Fitzgerald,[9] Matthew J Frigault [10], Terry J Fry,[11] Jennifer L Holter-Chakrabarty [12], Krishna V Komanduri,[13] Daniel W Lee,[14] Frederick L Locke [15], Shannon L Maude,[5,16] Philip L McCarthy [17], Elena Mead,[18] Sattva S Neelapu,[19] Tomas G Neilan [20], Bianca D Santomasso,[21] Elizabeth J Shpall,[22] David T Teachey [23], Cameron J Turtle [24], Tom Whitehead,[25] Stephan A Grupp [26]

Webinar outline

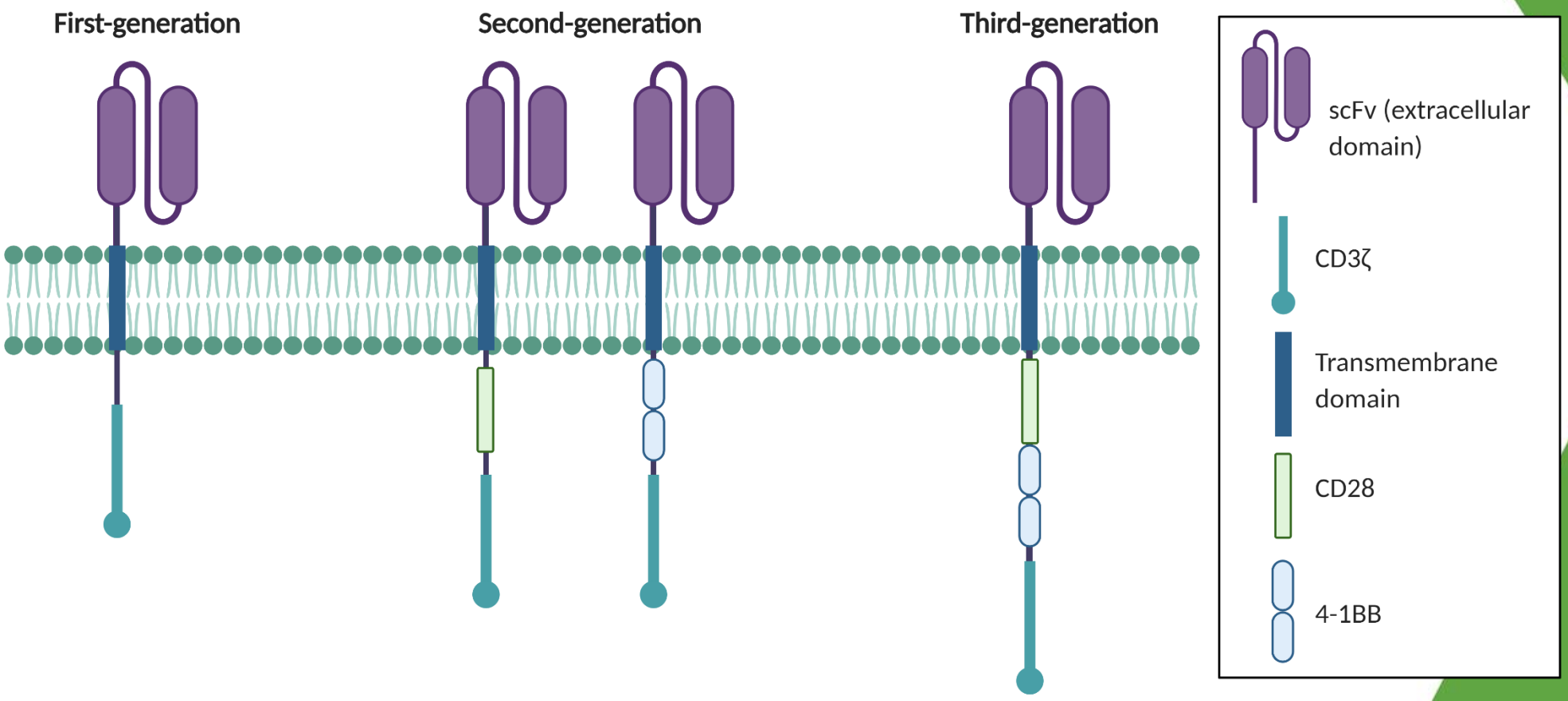
- Introduction to CAR T therapy
- Screening and selecting patients for IEC therapy
- Common adverse events with IEC therapy
  - CRS – cytokine release syndrome
  - ICANS – immune effector cell-associated neurotoxicity syndrome
  - Cytopenias

CAR T therapy





Evolution of CAR constructs



FDA-approved CAR T therapies

Drug	Target/co-stimulatory domain	Indication	Dose
Axicabtagene ciloleucel	CD19/CD28	Adults with r/r large B-cell lymphoma, Including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	2 x 10^6 CAR-positive, viable T cells per kg bodyweight (up to 2x10^8)
Tisagenlecleucel	CD19/4-1BB	Patients ≤25 yr with refractory B-cell acute lymphoblastic leukemia or in 2+ relapse	0.2-0.5x10^6 CAR-positive, viable T cells per kg if under 50 kg 0.1-2.5x10^8 CAR-positive, viable T-cells if over 50 kg
Tisagenlecleucel	CD19/4-1BB	Adults with r/r large B-cell lymphoma after 2+ therapies Including DLBCL, high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma	0.6-6.0 x 10^8 CAR-positive, viable T cells
Brexucabtagene autoleucel	CD19/CD28	Adults with mantle cell lymphoma (MCL) who have not responded to or who have relapsed following other treatments	2 x 10^6 CAR-positive, viable T cells per kg bodyweight (up to 2x10^8)
Lisocabtagene maraleucel* **not approved at time of guideline development*	CD19/4-1BB	Adults with r/r large-B-cell lymphoma after 2+ therapies Including DLBCL, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B	50 to 110x10^6 CAR-positive, viable T cells (consisting of 1:1 CAR-positive viable CD4 and CD8 T cells)

Clinical trials of CAR T therapies

Trial	Indication	Treatment	ORR	Landmark OS	Grade 3+ toxicity rates
ZUMA-2	R/R mantle cell lymphoma	Brexucabtagene autoleucel (KTE-X19)	86% CRR: 57%	1-year: 86%	CRS: 18% ICANS: 46%
ZUMA-1	Refractory large B cell lymphoma	Axicabtagene ciloleucel	83% CRR: 58%	2-year: 50%	CRS: 11% ICANS: 32%
JULIET	R/R diffuse large B cell lymphoma	Tisagenlecleucel	52% CRR: 40%	1-year: 49%	CRS: 22% ICANS: 12%
ELIANA	R/R B cell acute lymphoblastic leukemia	Tisagenlecleucel	82% CRR: 62%	18-month: 70%	CRS: 48% ICANS: 13%
TRANSCEND	R/R diffuse large B cell lymphoma	Lisocabtagene maraleucel	73% CRR: 53%	1-year: 57%	CRS: 4% ICANS: 12%

Wang, ASH 2019; Locke, Lancet Oncol 2019; Schuster, N Engl J Med 2019; Grupp, Biol Blood Mar Trans 2019. Abramson, Lancet 2020

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Patient selection considerations

- Treatment decisions should be **risk-adapted** to take into account characteristics of individual patients and products.
- Patients who have previously undergone allo-HSCT, BiTE therapy, anti-CD19 mAb therapy, and other mAb therapy may be treated with CAR T, provided the patient's disease **still expresses the target antigen**.
- Toxicity and timing of toxicities **may vary for different products**, depending on costimulatory or other structural domains.

Maus, J Immunother Cancer 2020

Patient selection considerations

- Patients with **higher pre-treatment disease burden** are at increased risk of toxicity.
- **ECOG performance status** should be taken into account, due to the high risk of toxicity.
- CAR T therapy may be appropriate for patients with **stable disease or in CR** with high relapse risk.
- Some CAR T products can be given in outpatient setting, but **admission should be considered** at first signs of toxicity.

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Pre-treatment evaluations

- Similar to auto-SCT
- Pre-treatment tests should include:
  - C-reactive protein (CRP)
  - Ferritin
  - Lactate dehydrogenase (LDH)
  - Complete blood count
  - Comprehensive metabolic panel
  - Transthoracic echocardiogram or multigated acquisition scan
  - Neurological evaluation
  - Disease burden assessment

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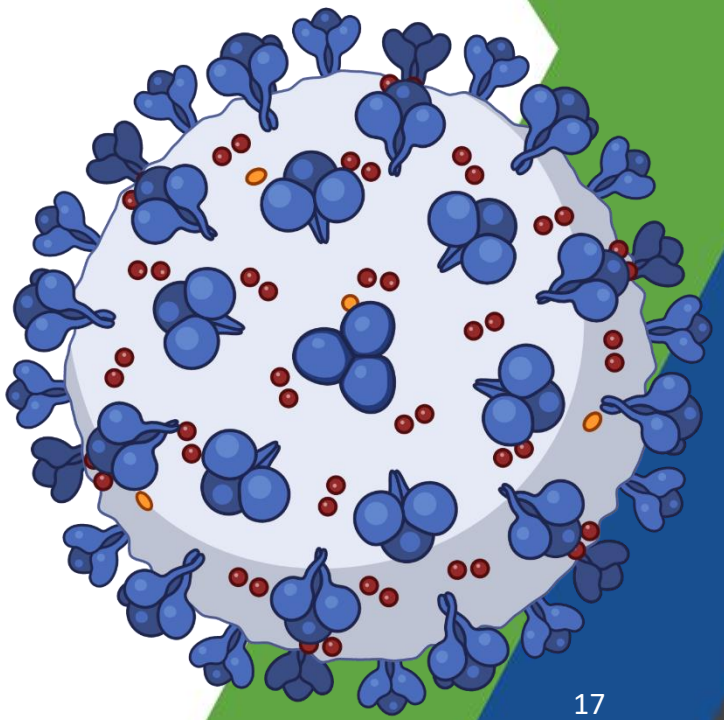
Considerations during the COVID-19 pandemic

- Treatment plans for cancer patients must take into account potential limitations in hospital resources
- Delaying CAR T may not be an option in some cases
- Make sure tocilizumab is readily available
- Ensure adequate staffing and supportive care



Maus, J Immunother Cancer 2020; Bachanova, Biol Blood Marrow Transpl 2020.

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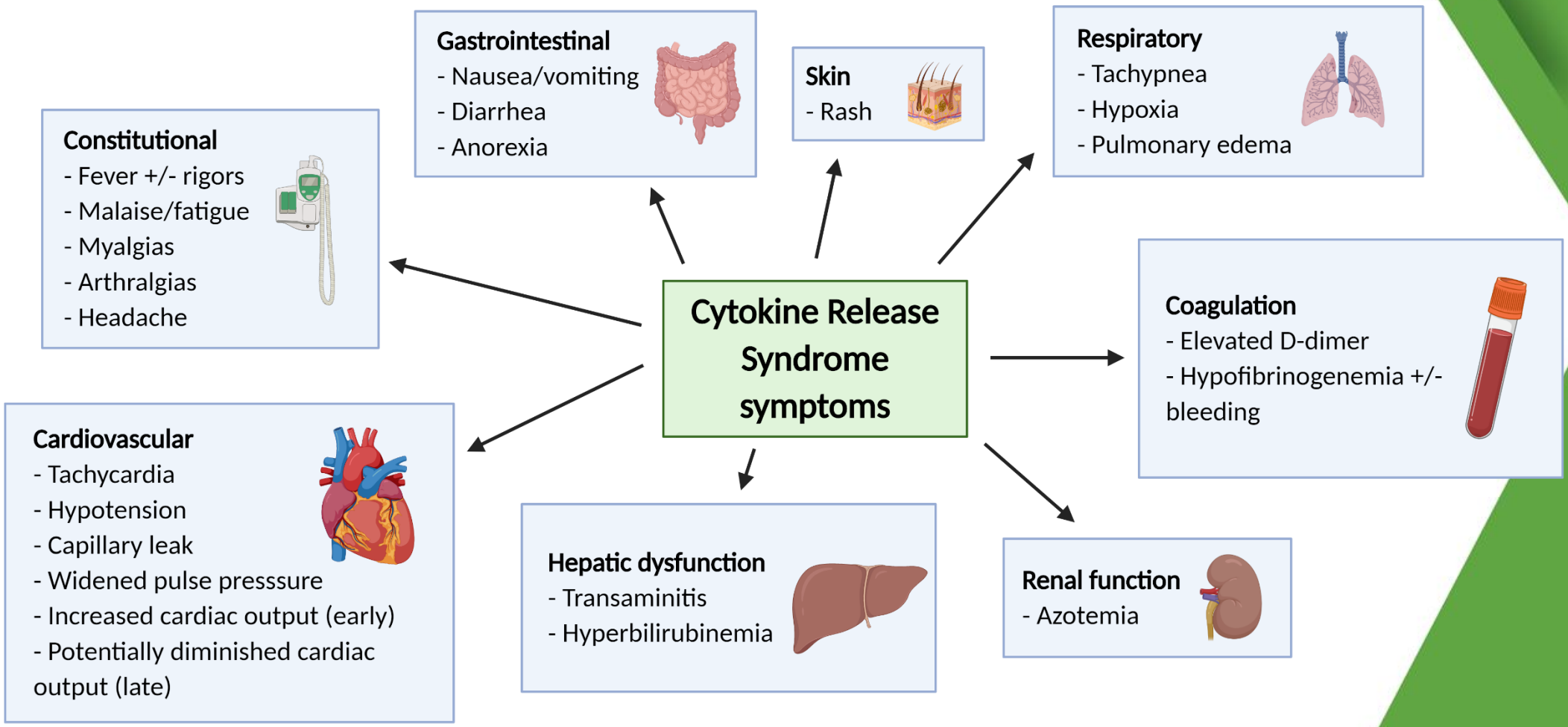
Cytokine release syndrome



ASTCT CRS grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	≥ 38°C	≥ 38°C	≥ 38°C	≥ 38°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, face mask, non-rebreather mask or venturi mask	Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

Lee, Santomasso, Biol Blood Marrow Transpl 2018

Monitoring for CRS

- Events requiring physician notification include:
  - Deviations from baseline systolic blood pressure
  - Heart rate >120 or <60 bpm
  - Arrythmia
  - Respiratory rate >25 or <12 breaths/minute
  - Arterial oxygen saturation <92% on room air
  - Upward trend in blood creatinine or liver function tests
  - Tremors or jerky movements in extremities
  - Altered mental status
  - Temperature ≥ 38°C

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Management of CRS

Grade 1	Grade 2	Grade 3	Grade 4	Tocilizumab-unresponsive	Tocilizumab + steroids-unresponsive
Close monitoring and supportive care	Consider tocilizumab	Tocilizumab	Tocilizumab + steroids	If CRS does not respond to 1 dose of tocilizumab, combine steroids + tocilizumab	Options include: Anakinra, siltuximab, HD methylprednisone

- For **elderly patients or those with significant co-morbidities**, tocilizumab should be considered earlier in the treatment course.
- If CRS does not improve after tocilizumab + steroids, **infections** should be considered and managed appropriately.
- If steroids are used, a **rapid taper** should be employed once symptoms begin to improve.

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ASTCT ICANS grading - adults

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7–9	3–6	0–2	0 (patient is unarousable)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min), repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

Lee, Santomasso, Biol Blood Marrow Transpl 2018

ASTCT ICANS grading - pediatric

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score (age ≥12 years)	7–9	3–6	0–2	0 (patient is unarousable)
CAPD score (age <12 years)	1–8	1–8	≥9	Unable to perform CAPD
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse
Seizure (any age)	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min), repetitive clinical or electrical seizures without return to baseline in between
Motor weakness (any age)	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema (any age)	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

Lee, Santomasso, Biol Blood Marrow Transpl 2018

Immune effector cell-associated encephalopathy (ICE) score

- **Orientation**: Orientation to year, month, city, hospital: 4 points (1 point each)
- **Naming**: Name 3 objects (e.g., clock, pen, button): 3 points (1 point each)
- **Following commands**: (e.g., Show me 2 fingers or close your eyes and stick out your tongue): 1 point
- **Writing**: Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point
- **Attention**: Count backwards from 100 by 10: 1 point
- **Total scale**: 0-10

Monitoring for ICANS

- Altered mental status defines the onset of ICANS
- Work-up should include:
  - CRP
  - CBC
  - CMP
  - Fibrinogen
  - Prothrombin time test
  - PT/INR
- Head CT, EEG, and brain MRI may be considered

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Management of ICANS

- **4-1BB** CAR T agents: consider steroids at grade 2 ICANS; administer steroids for grades 3-4 ICANS
- **CD28** CAR T agents: administer steroids for grades 2-4 ICANS
- Management of neurotoxicity **may take precedence** over low-grade CRS, due to possibility of tocilizumab worsening ICANS
  - For example: in the case of a patient with concomitant grade 1 CRS (fever) and grade 2 ICANS, steroids should be given. This does not apply to higher-grade CRS.
- If **steroids** are used, administer at least two doses and employ a fast taper
- **Levetiracetam** is recommended for management of seizures

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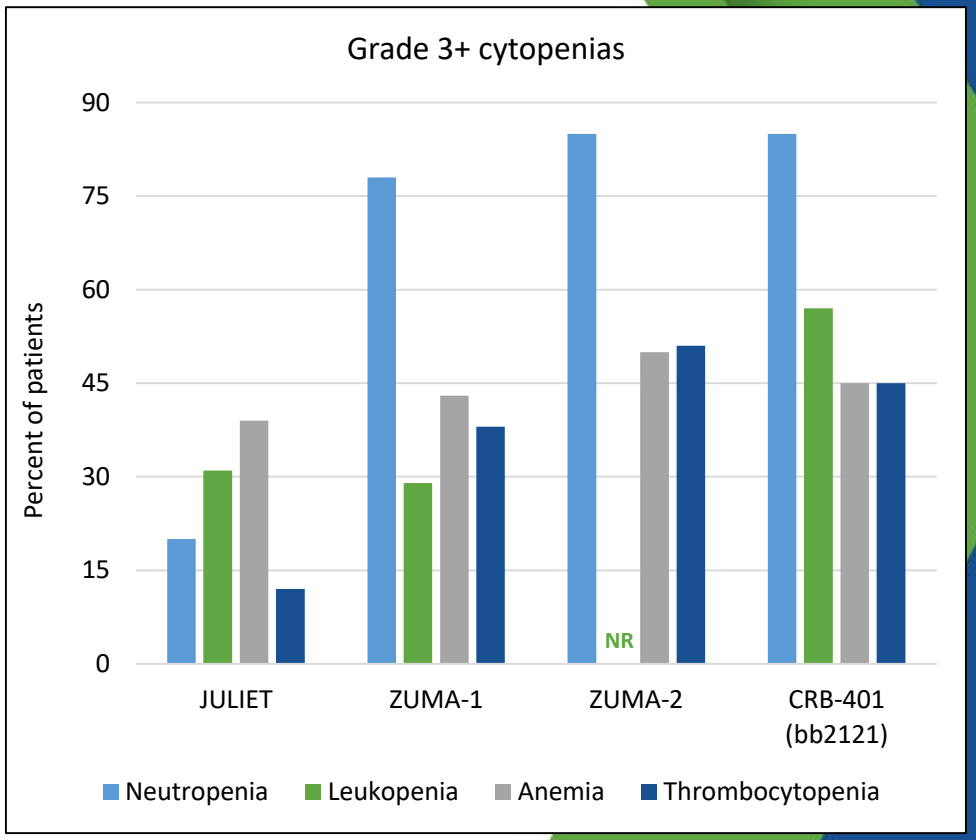
Cytopenias with CAR T therapy

- Short-term cytopenias are expected with lymphodepletion
- Timing and persistence of cytopenias may vary by product
- Important to consider myelodysplastic syndromes in differential diagnosis
- Risk factors include high disease burden, prior HSCT and high grade CRS



Schuster, N Engl J Med 2019; Neelapu, N Engl J Med 2017; Wang, N Engl J Med 2020; Raje, N Engl J Med 2019.

Monitoring & management of cytopenias

- For cytopenias occurring within **first 28 days**, CBC may be adequate for follow-up
- For cytopenias persisting **>28 days**, bone marrow biopsy and aspiration should be performed
- Patients should be **hospitalized** if they develop active infections or febrile neutropenia
- Consider **holding growth factors** until day 14 from CAR T infusion, or once CRS has resolved
- Growth factors should be considered for **persistent cytopenias**

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Infection precautions and prophylaxis

- Any bacterial or fungal infections should be treated and CAR T held until **infections are controlled**
- All patients should undergo **pneumocystis pneumonia** prophylaxis
- The decision for antibacterial, antiviral and/or antifungal prophylaxis should be **risk-adjusted** by patient characteristics
- For patients with **high-risk historical features**, antibacterial/ antifungal prophylaxis should be strongly considered
- Patients with **persistent neutropenia** should receive antibacterial/antifungal prophylaxis

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Additional toxicities with CAR T therapies

- HLH/MAS
- Cerebral edema
- Cardiac toxicities
- On-target toxicities: Hypogammaglobulinemia
- Tumor lysis syndrome

These toxicities will be discussed in the upcoming "**Practical management pearls for immune effector cell-related adverse events**" webinar

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Conclusions

- High disease burden correlates with higher likelihood of adverse events
- Most common IEC-related adverse events include CRS, ICANS and cytopenias
- Incidence, timing and severity of adverse events varies by product and patient characteristics

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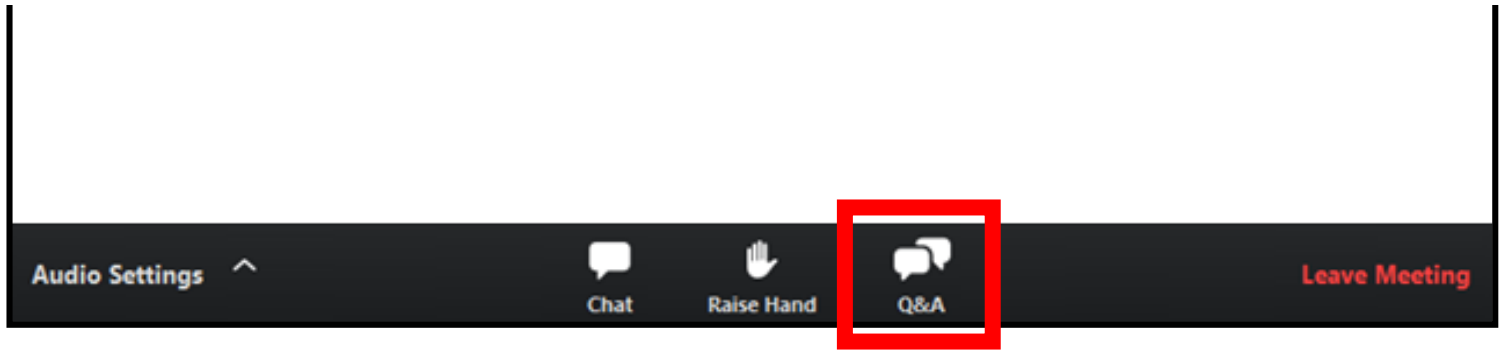

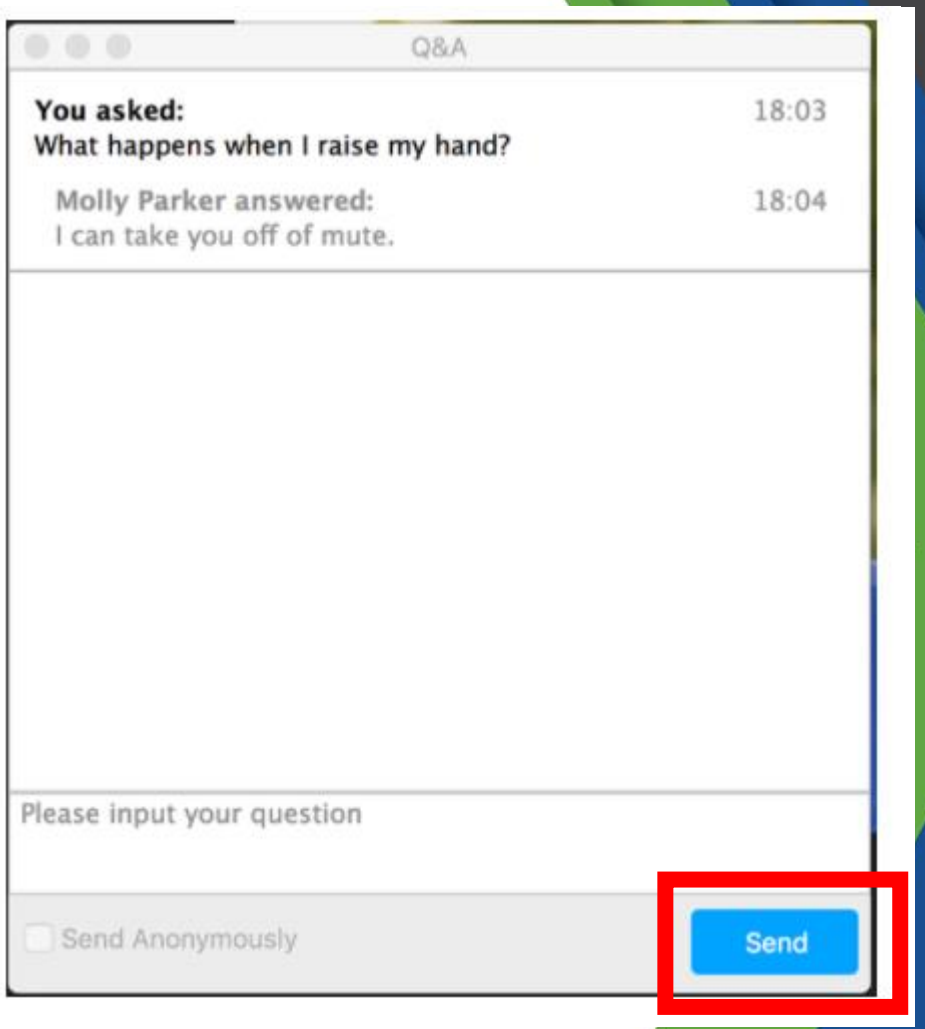

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Upcoming Webinar:

Advances in Cancer Immunotherapy™ Webinar – Clinical Updates from SITC 2020

Tuesday, March 30 at 4 – 5 p.m. ET

Faculty:

Jason Luke, MD – *University of Pittsburgh Medical Center*
Diwakar Davar, MD – *University of Pittsburgh Medical Center*
Karl Lewis, MD – *University of Colorado*
Ignacio Melero, MD, PhD – *Fundación para la Investigación Médica Aplicada*
Hussein Tawbi, MD, PhD – *MD Anderson Cancer Center*

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Advances in Cancer Immunotherapy™ Virtual Programs

Saturday, March 20

Thursday, April 8

Tuesday, April 27

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Continuing Education Credits

- Continuing Education Credits are offered for Physicians, PAs, NPs, RNs and Pharmacists
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- Questions and comments: connectED@sitcancer.org

Thank you for attending the webinar!

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Acknowledgements

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