Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Practical Management Pearls for Immunotherapy for the Treatment of Lymphoma

Monday, June 21, 2021

4 – 5 p.m. EST

This webinar is supported, in part, by independent medical education grant funding from

AMGEN MERCK

(as of 6/7/21)

Webinar faculty

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Weill Cornell Medicine

Outline

- Prioritizing therapies in lymphoma
  - Current options
  - Role of CAR T and stem cell transplant
  - Sequencing ICIs and stem cell transplant
- CAR T in lymphoma
  - Curative potential
  - Predicting success or failure
  - Earlier use of CAR T
  - Toxicities of CAR T

SITC Lymphoma Guideline

Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of lymphoma

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Guideline development

- *The Institute of Medicine's Standards for Developing Trustworthy Practice Guidelines* were used to develop these recommendations
- Panel consisted of 12 participants, including medical oncologists, a pediatric oncologist, a nurse practitioner, and a patient advocate
- Recommendations come from literature evidence, supplemented with clinical experience of the panel members where necessary
- Consensus defined as ≥75% agreement

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Approved immunotherapies for non-Hodgkin lymphoma

For more information on these drugs, view the “Immunotherapy for the Treatment of Lymphoma” SITC webinar.

Immunotherapy options include:

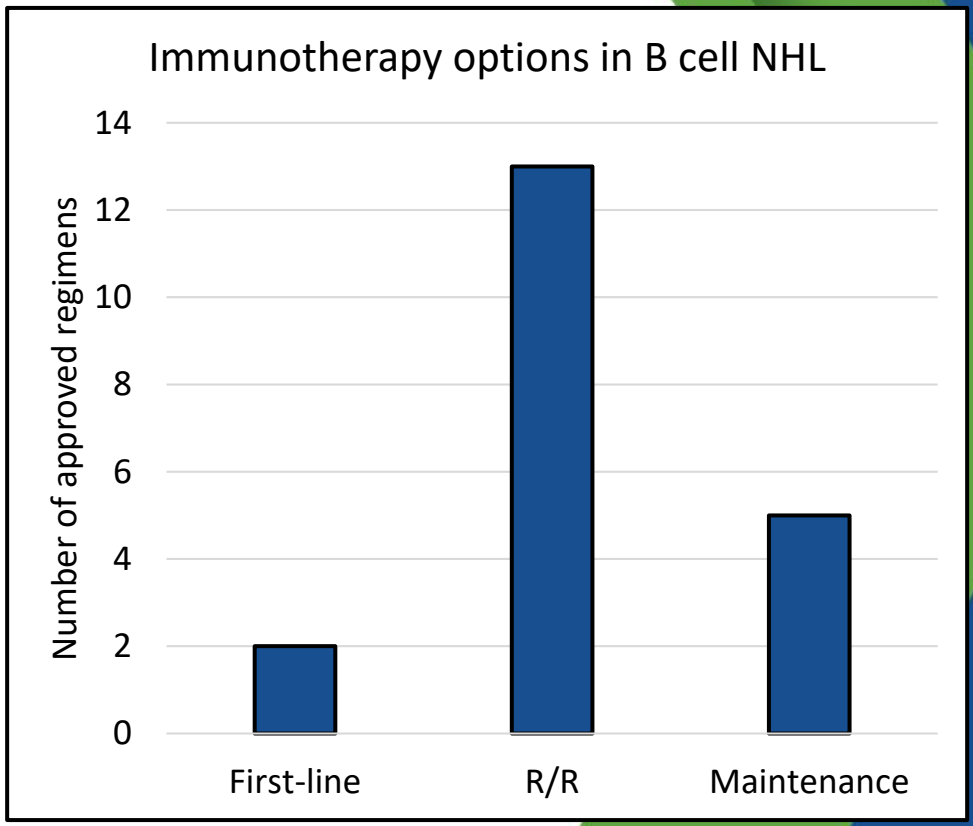
- Monoclonal antibodies
  - Rituximab (CD20)
  - Obinutuzumab (CD20)
  - Mogamulizumab-kpkc (CCR4)
  - Tafasitamab-cxix (CD19)
- Antibody-drug conjugates
  - Ibritumomab tiuxetan (CD20)
  - Brentuximab vedotin (CD30)
  - Polatuzumab vedotin-piiq (CD79)
  - Loncastuximab tesirine (CD19)
- Cellular therapies
  - Axicabtagene ciloleucel (CD19)
  - Tisagenlecleucel (CD19)
  - Brexucabtagene autoleucel (CD19)
  - Lisocabtagene maraleucel (CD19)
- Immunomodulators
  - Lenalidomide
- Immune checkpoint inhibitors
  - Pembrolizumab (PD-1)

Approved immunotherapies for Hodgkin lymphoma

Agent	Therapy type	Target	Indication(s)
Brentuximab vedotin	ADC	CD30	First-line stage III-IV cHL (combination with doxorubicin, vinblastine and dacarbazine)
			Consolidation therapy for cHL after autoSCT and high risk of relapse
			R/R cHL after autoSCT
Nivolumab	ICI	PD-1	R/R cHL after autoSCT and brentuximab vedotin
			R/R cHL after 3+ prior therapies
Pembrolizumab	ICI	PD-1	R/R cHL after 3+ prior therapies

Sequencing therapies in lymphoma

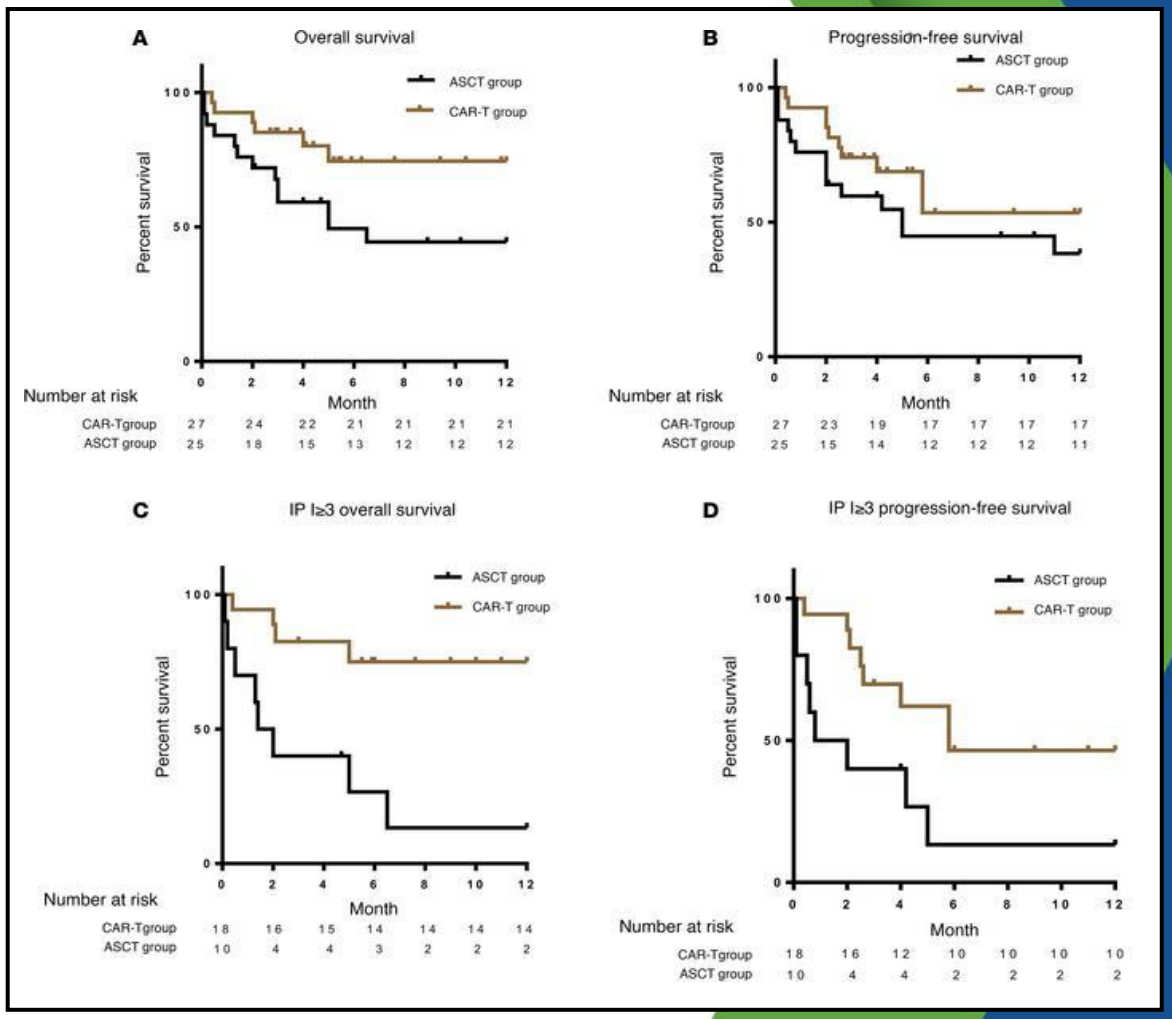
- Even among the Expert Panel, the question of how to sequence therapies for lymphoma remains largely debatable.
  - Example: “The panel did not reach consensus on second-line or later lines of treatment for patients with MCL. Treatment options include brexucabtagene autoleucel, proteasome inhibitors, BTK inhibitors, BTK inhibitors+rituximab, or lenalidomide+rituximab.”
- Choice of therapy sequence may depend on patient characteristics, disease characteristics and response to prior therapies.



Neelapu, J Immunother Cancer 2020

Stem cell transplant vs CAR T

- There is debate as to the potential of CAR T to be used in conjunction with or to replace traditional autoSCT.
- Here, 29 patients receiving anti-CD19 CART are compared with contemporaneous 27 patients who underwent autologous transplant.
- Larger studies are ongoing (i.e. ZUMA-7, BELINDA, TRANSFORM).



Li, JCI Insight 2019;4(17):e130195

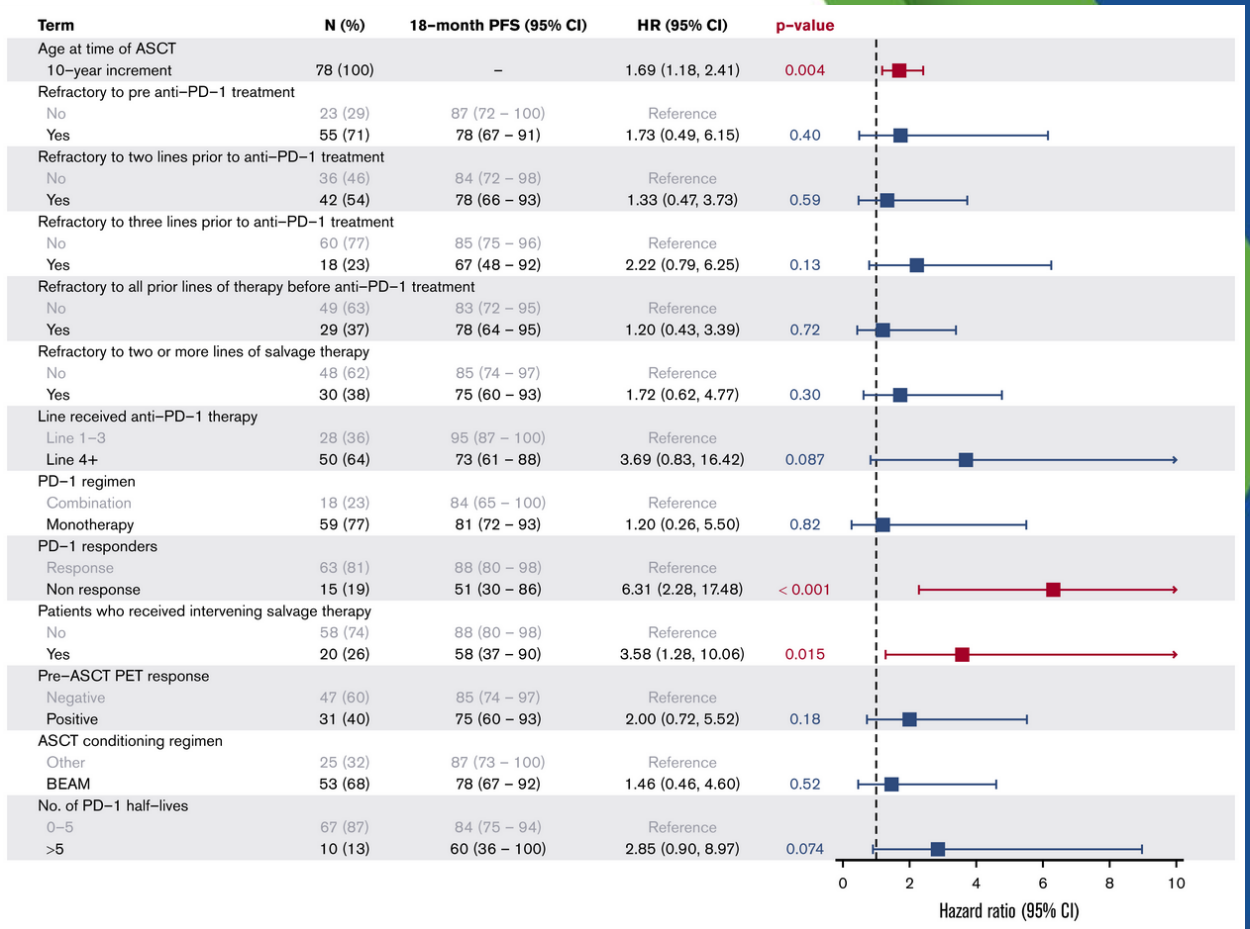
Emerging data for CD19 CAR T in LBCL

- TRANSFORM trial (NCT03575351): randomized, multicenter Phase 3 trial evaluating lisocabtagene maraleucel compared to current standard of care regimens in second line
- Press release in June 2021: study met its primary endpoint of demonstrating a clinically meaningful and statistically significant improvement in event-free survival
- Peer-reviewed report pending
- **Implications**: CD19 CAR T may move to second line therapy for R/R DLBCL, replacing autologous stem cell transplant

Press release

Immune checkpoint inhibitors (ICIs) and SCT

- There is limited data on ICI use prior to autoSCT.
  - This study included 78 patients with prior ICI treatment who then underwent autoSCT.
- There is a theoretical risk of GVHD exacerbation with ICIs used before/after alloSCT.
- ICIs appear to be safe after autoSCT.

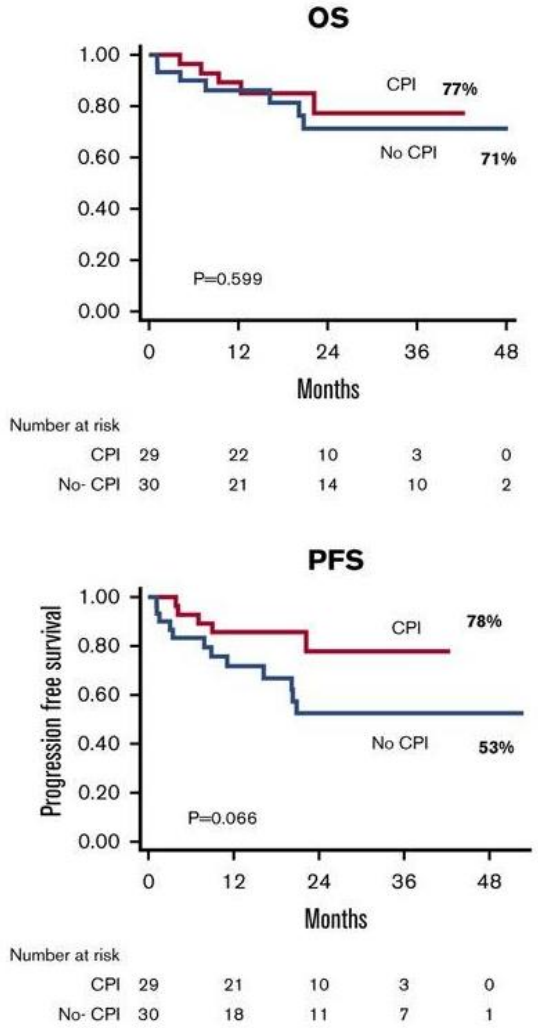


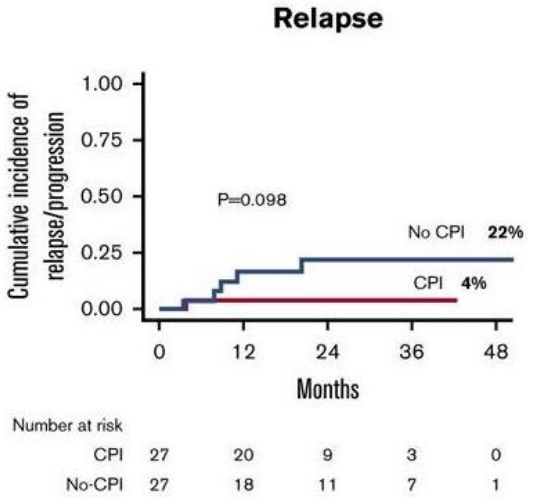
Term	N (%)	18–month PFS (95% CI)	HR (95% CI)	p–value
Age at time of ASCT				
10–year increment	78 (100)	–	1.69 (1.18, 2.41)	0.004
Refractory to pre anti–PD–1 treatment				
No	23 (29)	87 (72 – 100)	Reference	
Yes	55 (71)	78 (67 – 91)	1.73 (0.49, 6.15)	0.40
Refractory to two lines prior to anti–PD–1 treatment				
No	36 (46)	84 (72 – 98)	Reference	
Yes	42 (54)	78 (66 – 93)	1.33 (0.47, 3.73)	0.59
Refractory to three lines prior to anti–PD–1 treatment				
No	60 (77)	85 (75 – 96)	Reference	
Yes	18 (23)	67 (48 – 92)	2.22 (0.79, 6.25)	0.13
Refractory to all prior lines of therapy before anti–PD–1 treatment				
No	49 (63)	83 (72 – 95)	Reference	
Yes	29 (37)	78 (64 – 95)	1.20 (0.43, 3.39)	0.72
Refractory to two or more lines of salvage therapy				
No	48 (62)	85 (74 – 97)	Reference	
Yes	30 (38)	75 (60 – 93)	1.72 (0.62, 4.77)	0.30
Line received anti–PD–1 therapy				
Line 1–3	28 (36)	95 (87 – 100)	Reference	
Line 4+	50 (64)	73 (61 – 88)	3.69 (0.83, 16.42)	0.087
PD–1 regimen				
Combination	18 (23)	84 (65 – 100)	Reference	
Monotherapy	59 (77)	81 (72 – 93)	1.20 (0.26, 5.50)	0.82
PD–1 responders				
Response	63 (81)	88 (80 – 98)	Reference	
Non response	15 (19)	51 (30 – 86)	6.31 (2.28, 17.48)	< 0.001
Patients who received intervening salvage therapy				
No	58 (74)	88 (80 – 98)	Reference	
Yes	20 (26)	58 (37 – 90)	3.58 (1.28, 10.06)	0.015
Pre–ASCT PET response				
Negative	47 (60)	85 (74 – 97)	Reference	
Positive	31 (40)	75 (60 – 93)	2.00 (0.72, 5.52)	0.18
ASCT conditioning regimen				
Other	25 (32)	87 (73 – 100)	Reference	
BEAM	53 (68)	78 (67 – 92)	1.46 (0.46, 4.60)	0.52
No. of PD–1 half–lives				
0–5	67 (87)	84 (75 – 94)	Reference	
>5	10 (13)	60 (36 – 100)	2.85 (0.90, 8.97)	0.074

Merryman, Blood Adv 2021

Use of ICIs before alloSCT

Characteristics	All patients	No CPI	CPI	P value
N	59	30 (51%)	29 (49%)	
Median age	30 (19-64)	31 (19-64)	30 (21-61)	0.896
Previous auto-SCT	49 (83%)	27 (90%)	22 (76%)	0.181
Previous lines of therapy (median)	5 (2-11)	4 (2-11)	6 (3-9)	<0.001
Disease status at Haplo-SCT CR PR SD/PD	 40 (68%) 14 (24%) 5 (8%)	 22 (73%) 5 (17%) 3 (10%)	 18 (62%) 9 (31%) 2 (7%)	0.355
Stem cells source BM PBSC	 17 (29%) 42 (71%)	 7 (23%) 23 (77%)	 10 (36%) 19 (64%)	0.345
Conditioning regimen Non myeloablative Reduced toxicity	 45 (76%) 14 (24%)	 24 (80%) 6 (20%)	 21 (72%) 8 (28%)	0.495
HCT-CI 0-2 3-5	 31 (52%) 28 (48%)	 14 (47%) 16 (53%)	 17 (59%) 12 (41%)	0.358





Toxicity	CPI	No CPI	P value
Grade 2-4 aGVHD	41%	33%	NS
1 year-mod-sev cGVHD	7%	8%	NS
Febrile syndrome	10%	0%	NS
MAS	3%	0%	NS
VOD	0%	3%	NS
2 year-NRM	15%	21%	NS

De Philippis, Blood Adv 2020

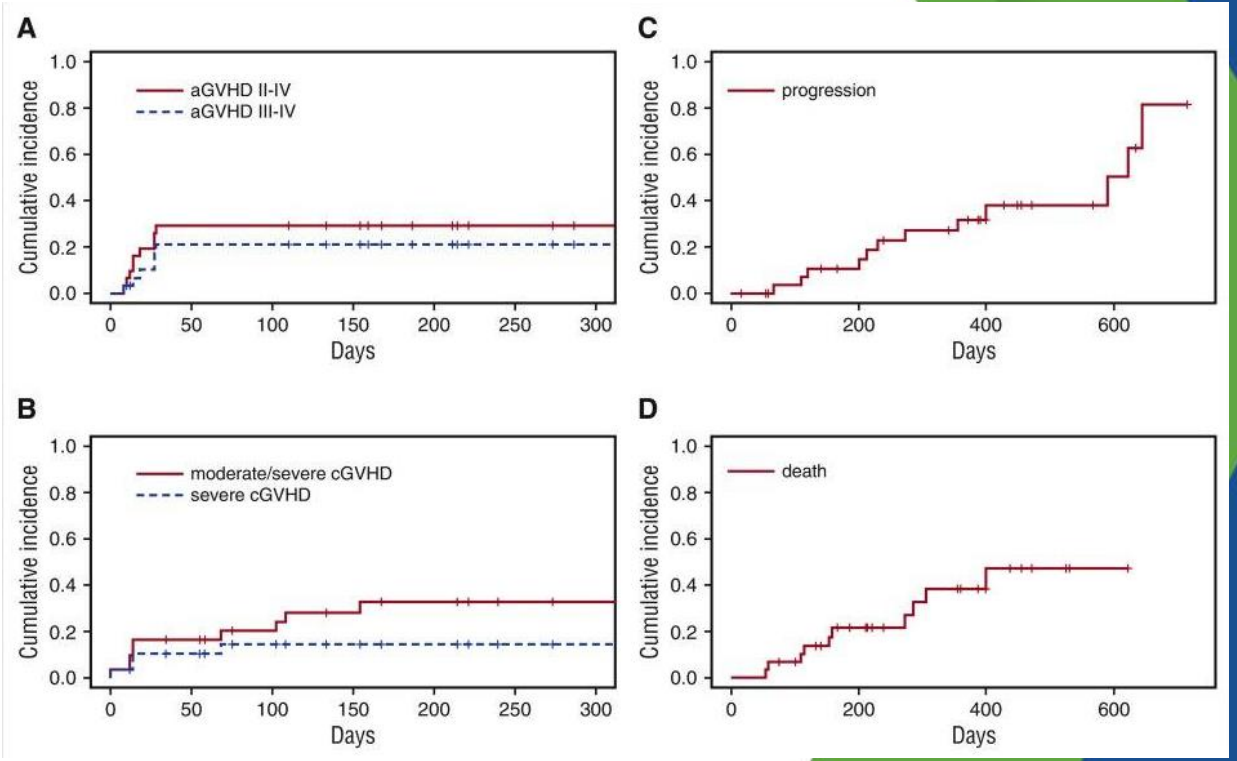
Use of ICIs after alloSCT (1)

	Patient 1	Patient 2	Patient 3
Age	47	25	55
Sex	Male	Male	Male
Prior therapies (no.)	6	6	5
Stem cell source	Matched-related	Matched-related	Haploidentical and umbilical cord blood
Conditioning regimen	Reduced intensity	Reduced intensity	Reduced intensity
T cell depleted graft	Yes	Yes	Yes
Prior GVHD	No	Chronic GVHD of gut	Chronic oral GVHD
Days to relapse following AlloHSCT (no.)	181	2456	389
Localization and size of relapse	Diffuse bone and splenic involvement	Multifocal adenopathy in mediastinum, retroperitoneum and pelvis. Largest lymph node 2.3 × 1.5 cm in mediastinum	Multifocal adenopathy in neck, chest, abdomen and pelvis. Largest lymph node 4.2 × 1.8 cm in right axilla
Prior DLI	No	Yes	No
Immune-related adverse events	Grade 2 Keratoconjunctivitis	Grade 3 Inflammatory polyarthritis and grade 2 keratoconjunctivitis	Grade 1 Rash
Response to nivolumab	Partial response	Partial response	Partial response
Duration of response	6 Months+	10 Months+	14 Months+
Donor $CD3^+$ chimerism before and after treatment	18 to 49%	Not available	Not available

Godfrey, J Immunother Cancer 2017

Use of ICIs after alloSCT (2)

- 31 patients treated with PD-1 therapy for relapsed disease after allo-SCT
- ORR: 77%
- mPFS: 591 days
- mOS: not achieved
- Associated with risk of GVHD



Haverkos, Blood 2017

Panel recommendations for sequencing of therapies with SCT

- There was consensus that ICI and CAR T cell therapy are both acceptable **after a patient has received autoSCT**. The panel did not reach consensus on the subject of whether ICIs or CAR T cell therapy should be administered **prior to autoSCT**.
- There was consensus that CAR T cell therapy is safe and could be considered **following alloSCT,** if the patient does not have active GVHD or require immunosuppression. Caution should also be exercised for patients with a history of severe GVHD.
- The panel did not reach consensus on the subject of whether **ICIs should be considered contraindicated** before or after alloSCT.

Neelapu, J Immunother Cancer 2020

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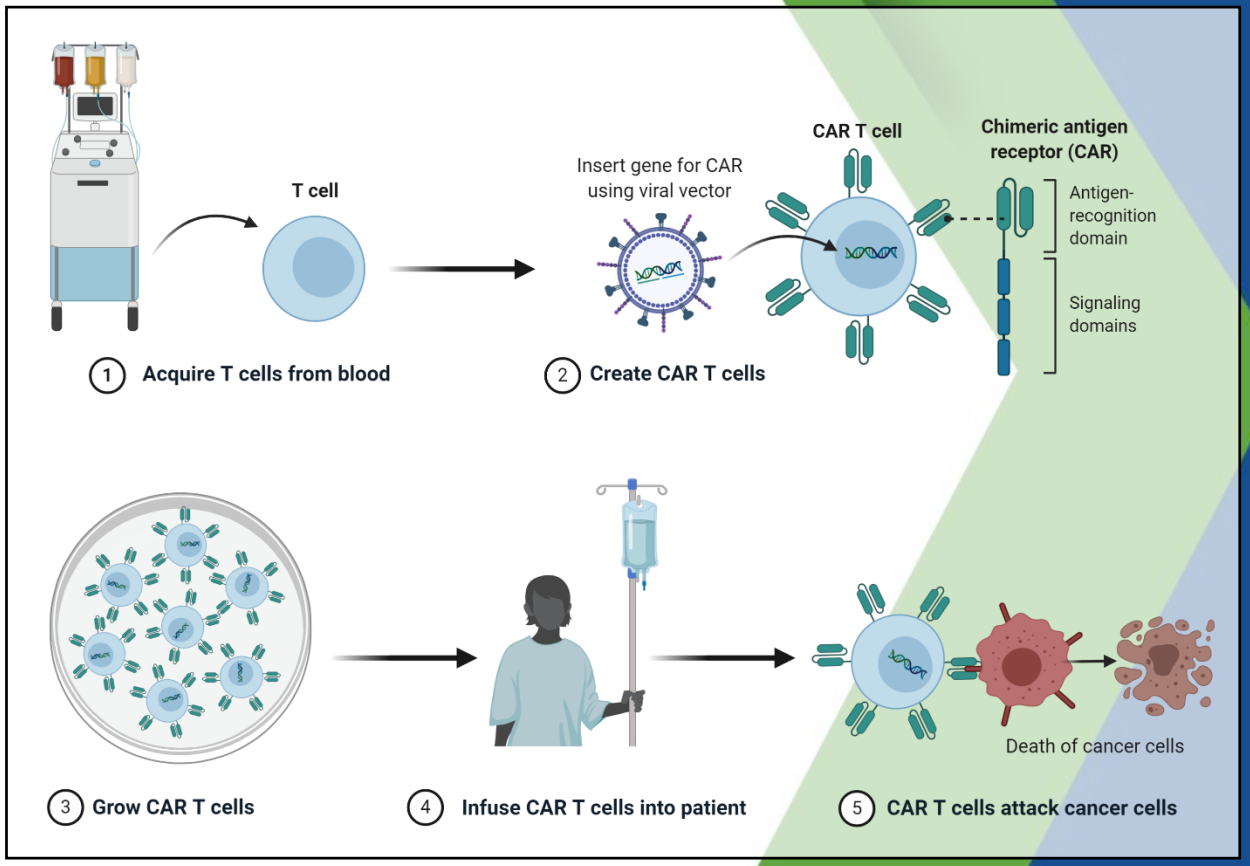
CAR T in lymphoma

CD19 CAR T therapies

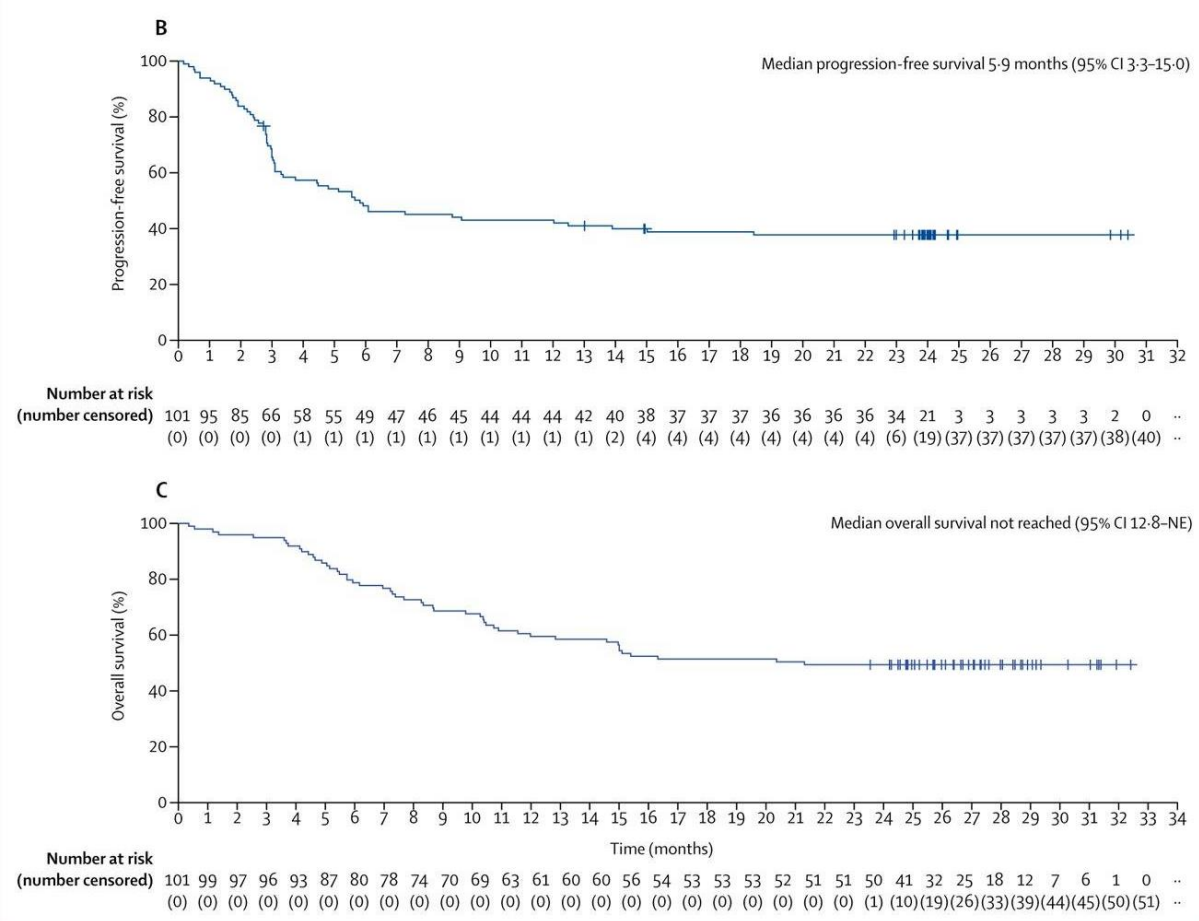
Agent	Approved indication
Axicabtagene ciloleucel	R/R large B cell lymphomas after 2+ prior therapies R/R follicular lymphoma after 2+ prior therapies
Tisagenlecleucel	R/R large B cell lymphomas after 2+ prior therapies
Lisocabtagene maraleucel	R/R large B cell lymphomas after 2+ prior therapies
Brexucabtagene autoleucel	R/R MCL

Axi-cel and brexu-cel have the same CAR construct; however, the manufacturing of brexu-cel involves enrichment of specific lymphocytes to improve therapeutic potential.

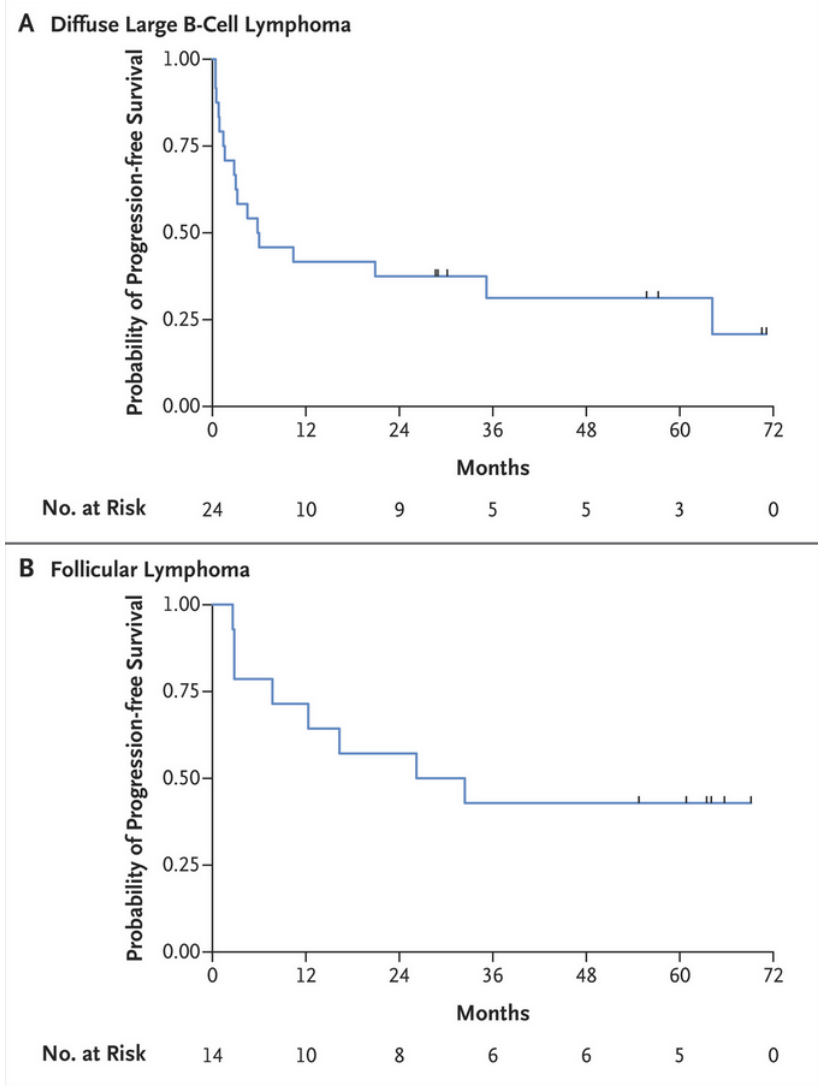


Curative potential of CAR T

ZUMA-1: axicabtagene ciloleucel in large B cell lymphoma



JULIET: tisagenlecleucel



Chong, NEJM 2021
Jacobson, ASH 2020

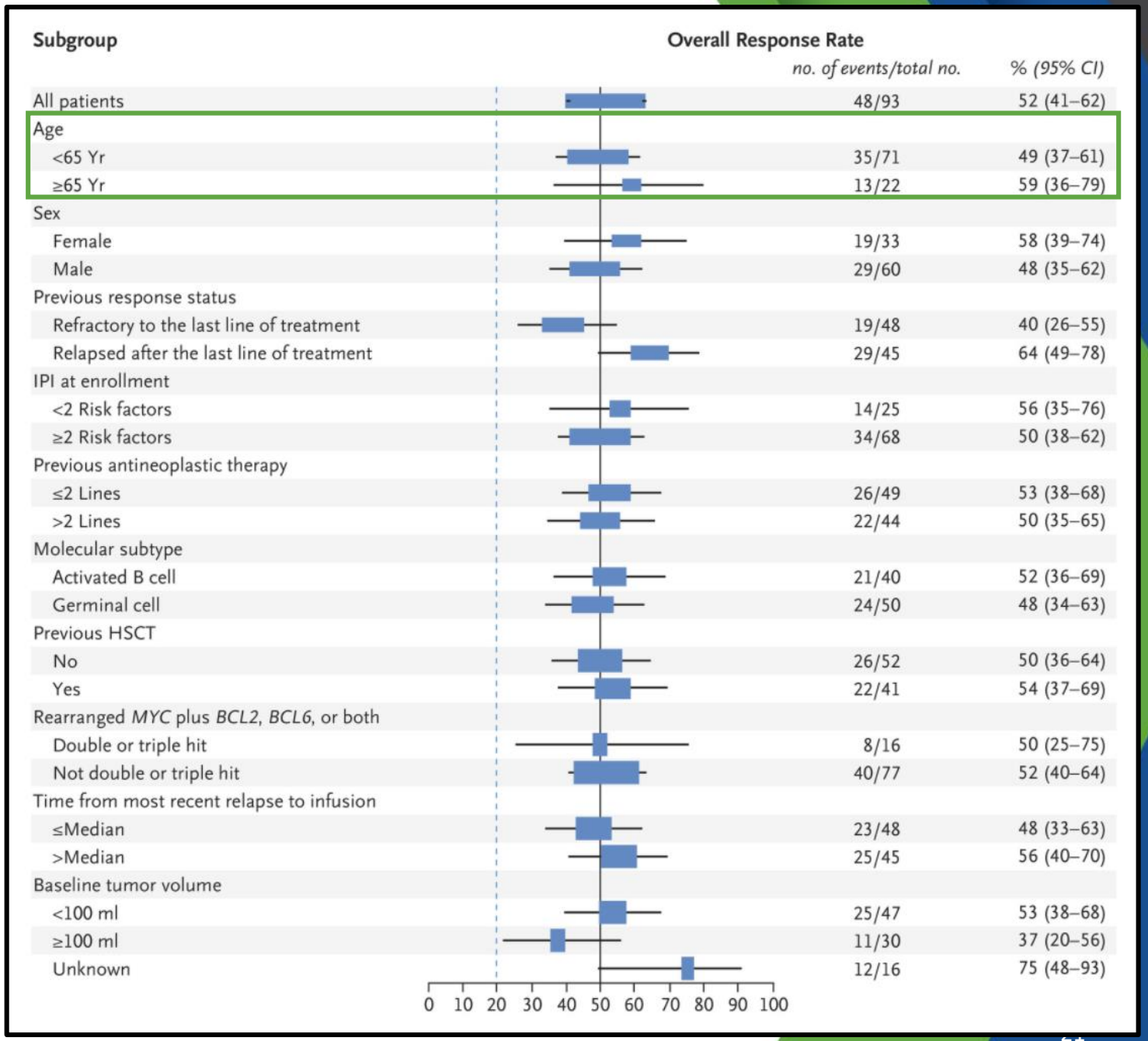
Potential of CAR T: real-world evidence

	ZUMA-1	Real-world use*
ORR	83%	70%
CRR	58%	50%
mDOR	11.1 months	11.0 months
mPFS	5.9 months	4.5 months
mOS	NR (f/u 27.1 months)	NR (f/u 10.4 months)
CRS G3+	11%	16%
ICANS G3+	32%	35%
Treatment-related deaths	1.9% (2/108)	6%

**62% of patients in this study were ZUMA-1-eligible*

Locke, Lancet Oncol 2019
Jacobson, JCO 2020

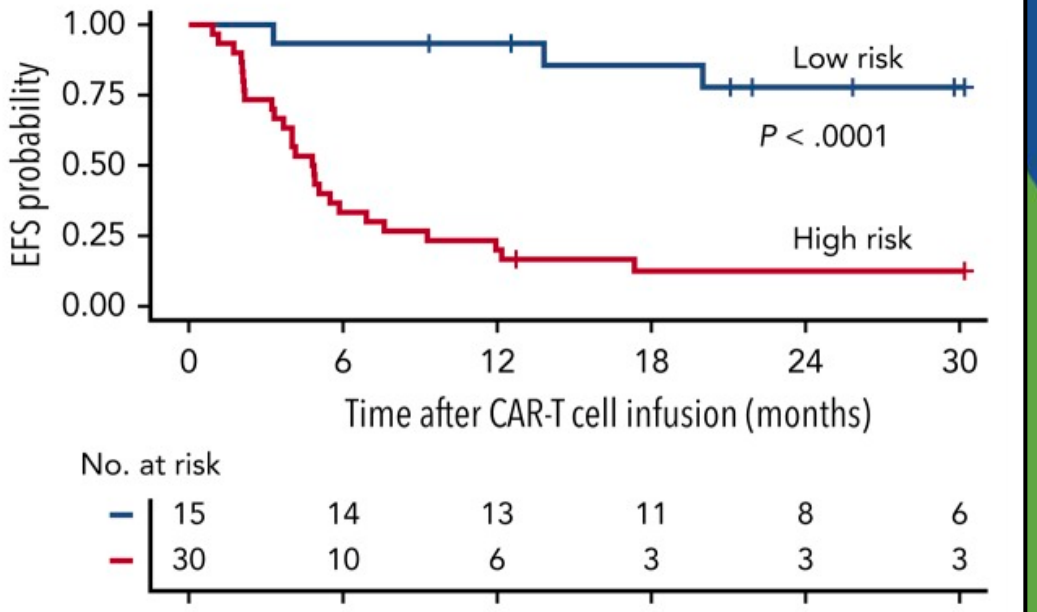
Predictors of success vs failure: early experience (JULIET)



Schuster, N Engl J Med 2019

Predictors of success vs failure: emerging evidence

- Response to CAR T therapy is impacted by:
  - **Disease** characteristics (LDH, tumor volume, metabolic activity)
  - **Patient** characteristics (performance status, prior therapies)
  - **CAR T product** characteristics (persistence, expansion)



Low risk: Pre-lymphodepletion LDH ≤ ULN; platelet count ≥ 100,000/uL; and use of fludarabine in lymphodepletion regimen

High risk: Pre-lymphodepletion LDH > ULN; platelet count < 100,000/uL; and no fludarabine in lymphodepletion regimen

Hay, Blood 2019

Common CAR T toxicities: CRS and ICANS

Cytokine release syndrome

- Fever, hypotension, hypoxia
- Manage with tocilizumab and steroids
- Supportive care as needed: vasopressors, oxygen support

Immune effector cell-associated neurotoxicity syndrome

- Confusion, delirium, aphasia, headache, tremors, seizures
- Manage with steroids
- Monitor patients daily for mental status changes

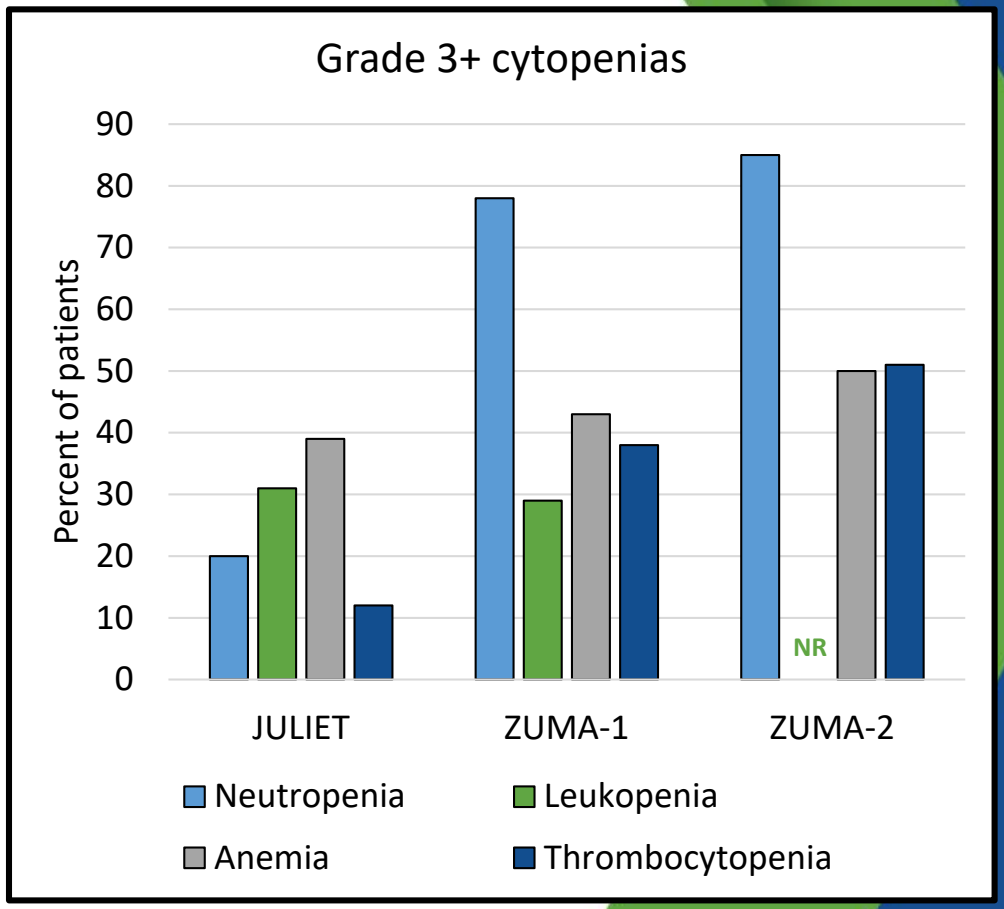
SITC recommends the ASTCT grading systems for CRS and ICANS.

Check out the SITC clinical practice guideline on immune effector cell-related adverse events for more guidance

Maus, J Immunother Cancer 2020

Common CAR T toxicities: cytopenias

- 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.

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

Maus, J Immunother Cancer 2020

Common CAR T toxicities: B cell aplasia and hypogammaglobulinemia

- Due to on-target killing of CD19-positive B cells
- Occurs in most patients who respond to CD19 CAR T therapy
- Can be long-lasting
- Managed with immunoglobulin replacement therapy

Maus, J Immunother Cancer 2020

Uncommon CAR T toxicities: HLH/MAS

- CRS and HLH/MAS substantially overlap.
- Late-onset, tocilizumab-refractory HLH/MAS-like symptoms may represent a distinct and separate pathology from conventional CRS.
- Delayed coagulopathy may be one hallmark of delayed onset HLH/MAS-like toxicity.
- Etoposide should only be administered to patients experiencing late-onset, tocilizumab-refractory HLH/MAS-like symptoms after CAR T cell therapy as a last resort.
- For treatment of late-onset, HLH/MAS-like pathology, which may be tocilzumab-refractory, third-line CRS agents such as anakinra and steroids may be considered.

Maus, J Immunother Cancer 2020

Conclusions

- SITC Clinical Practice Guideline panel consisted of 12 participants, including medical oncologists, a pediatric oncologist, a nurse practitioner, and a patient advocate
- Discussed numerous immunotherapies for lymphoma
- Many options are available, consensus often reached on best practices and safe use of immunotherapy
- Lack of consensus did not mean “disagreement” or “controversy”, but rather lack of data or multiple reasonable options and opinions.
- CAR T cells represent an exciting potent new approach to immunotherapy in lymphoma.
- Associated with significant and unique toxicities
- New information is allowing physicians to better predict which patients are most likely to benefit from CAR T cells.
- CAR T cells have curative potential in lymphoma.

Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Case Studies in Immunotherapy for the Treatment of Lymphoma

July 7, 2021, 5:30-6:30 pm ET

Learn more and register at:
https://www.sitcancer.org/research/cancer-immunotherapy-guidelines/webinars

Targets for Cancer Immunotherapy: A Deep Dive Seminar Series

Eight online seminars will address key questions in the field of cancer immunotherapy **drug development**

SEMINAR 2 – THE TIGIT PATHWAY: A DEEP DIVE IN CANCER IMMUNOTHERAPY TARGETS – June 29, 2021, 2-4 p.m. EDT

SEMINAR 3 – IL-2 VARIANTS AND IL-15: A DEEP DIVE IN CANCER IMMUNOTHERAPY TARGETS –July 19, 2021, 4:30-6:30 p.m. EDT

Learn more and register at:
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Clinical Updates from ESMO Immuno-Oncology Virtual Congress 2020

July 16, 2021, 12 – 1 PM ET

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Acknowledgements

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