# Managing CAR T Cell Toxicity: Strategies and Insights

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09/23/2023

# Conflict of Interests

Attended Ad Board of Cardinal Health

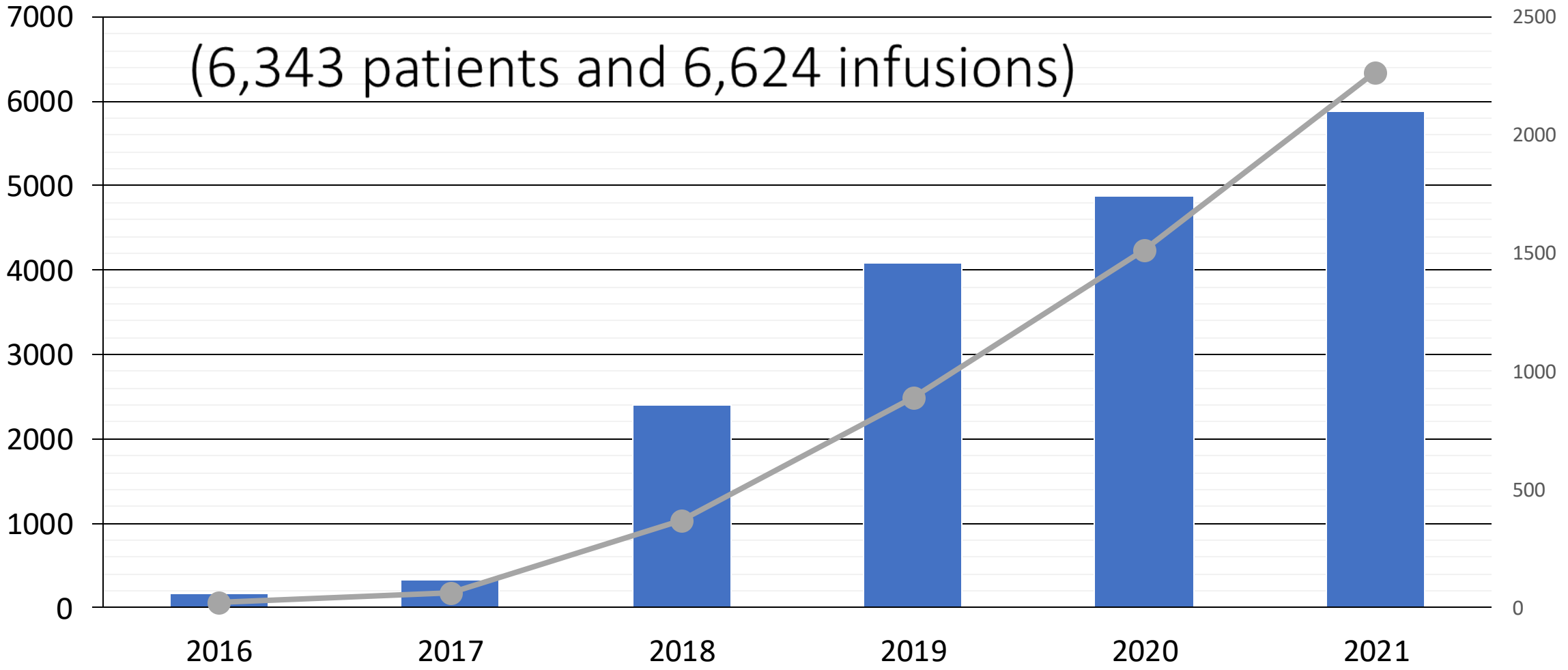
# Approved CAR T Cells

Summary of FDA-approved CAR T cell therapies for B cell malignancies and multiple myeloma.

| Company name Brand name Generic name | Date of approval | Target antigen/ Antibody | Hinge/ transmembrane | Costimulatory domains | Vector promoter | Targeted cancers | Pivotal trial | No. of Patients | Outcomes | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Novartis Kymriah Tisagenlecleucel | Aug 30, 2017 | CD19 Mouse FMC63 | CD8α/CD8α | 4-1BB + CD3ζ | Lentiviral EF1α | R/R B-ALL | ELIANA (NCT02228096) | 75 | 81% overall remission | (Maude et al., 2018) |
| Kite Yescarta Axicabtagene ciloleucel | Oct 18, 2017 | CD19 Mouse FMC63 | CD8α/CD8α | CD28 + CD3ζ | Gammaretroviral LTR | R/R LBCL | ZUMA-1 (NCT02348216 ) | 108 | 58% complete response | (Locke et al., 2019) |
| Kite Tecartus Brexucabtagene autoleucel | Jul 24, 2020 | CD19 Mouse FMC63 | CD28/CD28 | CD28 + CD3ζ | Gammaretroviral LTR | R/R MCL | ZUMA-2 (NCT02601313) | 68 | 67% complete response | (Wang et al., 2020) |
| Juno Breyanzi Lisocabtagene maraleucel | Feb 5, 2021 | CD19 Mouse FMC63 | IgG4/CD28 | 4-1BB+ CD3ζ | Lentiviral EF1α | R/R LBCL | Transcend NHL001 (NCT02631044) | 269 | 53% complete response | (Abramson et al., 2020) |
| Bluebird Abecma Idecabtagene vicleucel | Mar 26, 2021 | BCMA Mouse BB2121 | CD8α/CD8α | 4-1BB+ CD3ζ | Lentiviral MND | R/R MM | KarMMa (NCT03361748) | 128 | 33% complete response | (Munshi et al., 2021) |
| J&J and Legend Carvykti | Feb 28, 2022 | BCMA dual camel single-domain antibodies | CD8α/CD8α | 4-1BB + CD3ζ | Lentiviral EF1α | R/R MM | CARTITUDE-1 (NCT03548207) | 68 | 82.5% complete response | (Martin et al., 2023) |

From Bench to Bedside: The History and Progress of CAR T Cell Therapy. Mitra A. et. al. Frontiers in Immunology. May 2023.

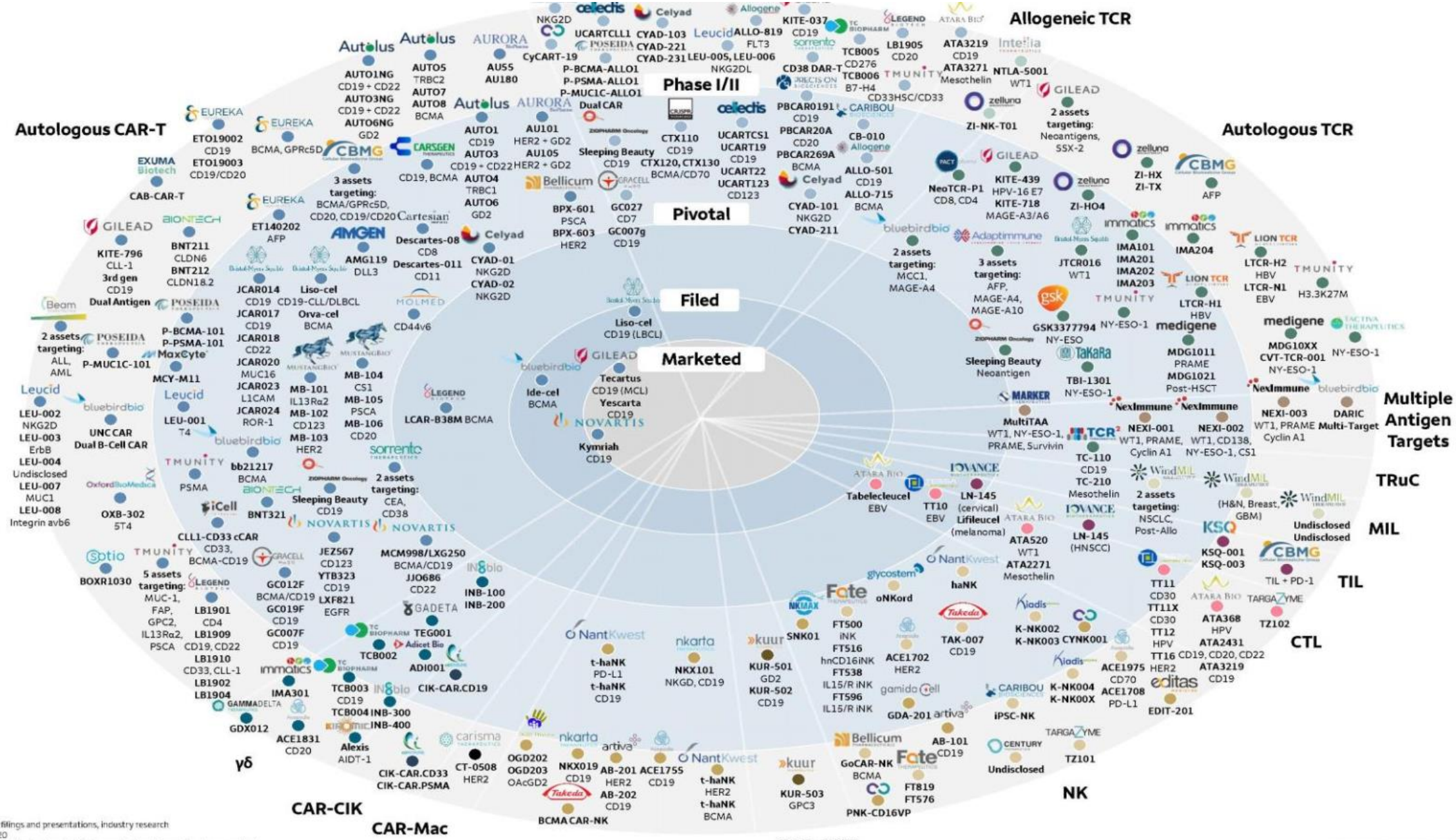
# Number of CAR T cell infusions: 2016-2021




Data Incomplete for 2020 & 2021

Cumulative

Moskop, A, Jacobs B, Pasquini MC. **Current uses of CAR T cell Therapies in the US: CIDR summary slides, 2021.** http://www.cibmtr.org accessed 9/19/2023


Autologous CAR-T
Allogeneic TCR
Autologous TCR
Multiple Antigen Targets
TRuC
MIL
TIL
CTL
NK
CAR-CIK
CAR-Mac
CAR-NK
CAR-NKT
γδ
Phase I/II
Pivotal
Filed
Marketed
AUTO1NG CD19 + CD22
AUTO3NG CD19 + CD22
AUTO6NG GD2
AUTO5 TRBC2
AUTO7
AUTO8 BCMA
AU55
AU180
CyCART-19
P-BCMA-ALLO1
P-PSMA-ALLO1
P-MUC1C-ALLO1
Dual CAR
AUTO1 CD19
AUTO3 CD19 + CD22
AUTO4 TRBC1
AUTO6 GD2
AU101 HER2 + GD2
AU105 HER2 + GD2
Sleeping Beauty CD19
CTX110 CD19
CTX120, CTX130 BCMA/CD70
UCARTCS1
UCART19 CD19
UCART22
UCART123 CD123
CB-010
PBCAR0191 CD19
PBCAR20A CD20
PBCAR269A BCMA
ALLO-501 CD19
ALLO-715 BCMA
CYAD-101 NKG2D
CYAD-211
UCARTCLL1
CYAD-103
CYAD-221
CYAD-231
ALLO-819 FLT3
LEU-005, LEU-006 NKG2DL
KITE-037 CD19
TCB005 CD276
TCB006 B7-H4
CD38 DAR-T
CD33HSC/CD33
LB1905 CD20
ATA3219 CD19
ATA3271 Mesothelin
NTLA-5001 WT1
ZI-NK-T01
2 assets targeting: Neoantigens, SSX-2
ZI-HX
ZI-TX
ZI-HO4
AFP
NeoTCR-P1 CD8, CD4
KITE-439 HPV-16 E7
KITE-718 MAGE-A3/A6
2 assets targeting: MCC1, MAGE-A4
3 assets targeting: AFP, MAGE-A4, MAGE-A10
JTCR016 WT1
GSK3377794 NY-ESO
Sleeping Beauty Neoantigen
TBI-1301 NY-ESO-1
IMA101
IMA201
IMA202
IMA203
NY-ESO-1
IMA204
LTCR-H1 HBV
LTCR-H2 HBV
LTCR-N1 EBV
H3.3K27M
MDG1011 PRAME
MDG1021 Post-HSCT
MDG10XX
CVT-TCR-001 NY-ESO-1
NY-ESO-1
NEXI-003 WT1, PRAME Cyclin A1
DARIC Multi-Target
MultiTAA WT1, NY-ESO-1, PRAME, Survivin
TC-110 CD19
TC-210 Mesothelin
NEXI-001 WT1, PRAME, Cyclin A1
NEXI-002 WT1, CD138, NY-ESO-1, CS1
LN-145 (cervical) Lifileucel (melanoma)
LN-145 (HNSCC)
ATA520 WT1
ATA2271 Mesothelin
2 assets targeting: NSCLC, Post-Allo
Tabelecleucel EBV
TT10 EBV
(H&N, Breast, GBM)
Undisclosed
Undisclosed
KSQ-001
KSQ-003
TIL + PD-1
TT11 CD30
TT11X CD30
TT12 HPV
TT16 HER2
ATA368 HPV
ATA2431 CD19, CD20, CD22
ATA3219 CD19
TZ102
EDIT-201
ACE1975 CD70
ACE1708 PD-L1
K-NK002
K-NK003
CYNK001
K-NK004
K-NK00X
iPSC-NK
TZ101
Undisclosed
haNK
TAK-007 CD19
oNKord
FT500 iNK
FT516 hnCD16iNK
FT538 IL15/R iNK
FT596 IL15/R iNK
ACE1702 HER2
GDA-201
AB-101 CD19
SNK01
KUR-501 GD2
KUR-502 CD19
KUR-503 GPC3
GoCAR-NK BCMA
FT819
FT576
PNK-CD16VP
t-haNK PD-L1
t-haNK CD19
NKX101 NKGD, CD19
t-haNK HER2
t-haNK BCMA
NKX019 CD19
AB-201 HER2
AB-202 CD19
ACE1755 CD19
OGD202
OGD203 OAcGD2
BCMA CAR-NK
CT-0508 HER2
CIK-CAR.CD33
CIK-CAR.PSMA
GDX012
ACE1831 CD20
Alexis
AIDT-1
IMA301
TCB003 CD19
TCB004
INB-300
INB-400
CIK-CAR.CD19
TCB002
TEG001
ADI001
INB-100
INB-200
JJO686 CD22
MCM998/LXG250 BCMA/CD19
JEZ567 CD123
YTB323 CD19
LXF821 EGFR
GC012F BCMA/CD19
GC019F CD19
GC007F CD19
CLL1-CD33 cCAR CD33, BCMA-CD19
5 assets targeting: MUC-1, FAP, GPC2, IL13Rα2, PSCA
LB1901 CD4
LB1909 CD19, CD22
LB1910 CD33, CLL-1
LB1902
LB1904
BOXR1030
OXB-302 5T4
BNT321
bb21217 BCMA
Sleeping Beauty CD19
2 assets targeting: CEA, CD38
PSMA
MB-101 IL13Rα2
MB-102 CD123
MB-103 HER2
MB-104 CS1
MB-105 PSCA
MB-106 CD20
MCY-M11
P-BCMA-101
P-PSMA-101
MaxCyte
P-MUC1C-101
UNC CAR Dual B-Cell CAR
LEU-001 T4
LEU-002 NKG2D
LEU-003 ErbB
LEU-004 Undisclosed
LEU-007 MUC1
LEU-008 Integrin avb6
2 assets targeting: ALL, AML
CAB-CAR-T
KITE-796 CLL-1
3rd gen CD19 Dual Antigen
BNT211 CLDN6
BNT212 CLDN18.2
ET0190002 CD19
ET0190003 CD19/CD20
ET140202 AFP
3 assets targeting: BCMA/GPRc5D, CD20, CD19/CD20
BCMA, GPRc5D
CD19, BCMA
AMG119 DLL3
Descartes-08 CD8
Descartes-011 CD11
CD44v6
JCAR014 CD19
JCAR017 CD19
JCAR018 CD22
JCAR020 MUC16
JCAR023 L1CAM
JCAR024 ROR-1
Liso-cel CD19-CLL/DLBCL
Orva-cel BCMA
CYAD-01 NKG2D
CYAD-02 NKG2D
BPX-601 PSCA
BPX-603 HER2
GC027 CD7
GC007g CD19
Liso-cel CD19 (LBCL)
Ide-cel BCMA
Tecartus CD19 (MCL)
Yescarta CD19
Kymriah CD19
LCAR-B38M BCMA
Source: Company filings and presentations, industry research
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# CAR T Landscape

- More commercial CAR-T cell /Cellular Therapies likely to be approved in next few years (including solid tumors).

- Various CAR-T cell/Cellular Therapy trials ongoing for Colo-rectal Cancer, Melanoma, Prostate Cancer and Hepatomas.

- 1228 CAR- T trials ( Clinicaltrials.gov. Accessed on 9/17/2023)

# Challenges

- Short /Long term side effects.
- Several rate limiting factors.
- Financial Toxicity.
- Resistance.

# Toxicities

- Cytokine Release Syndrome- CRS
- ICANS
- Hemophagocytic lymphohistiocytosis.
- Persistent cytopenias
- Infections
- Hypogammaglobulinemia
- Second cancers?

# Early CAR toxicities

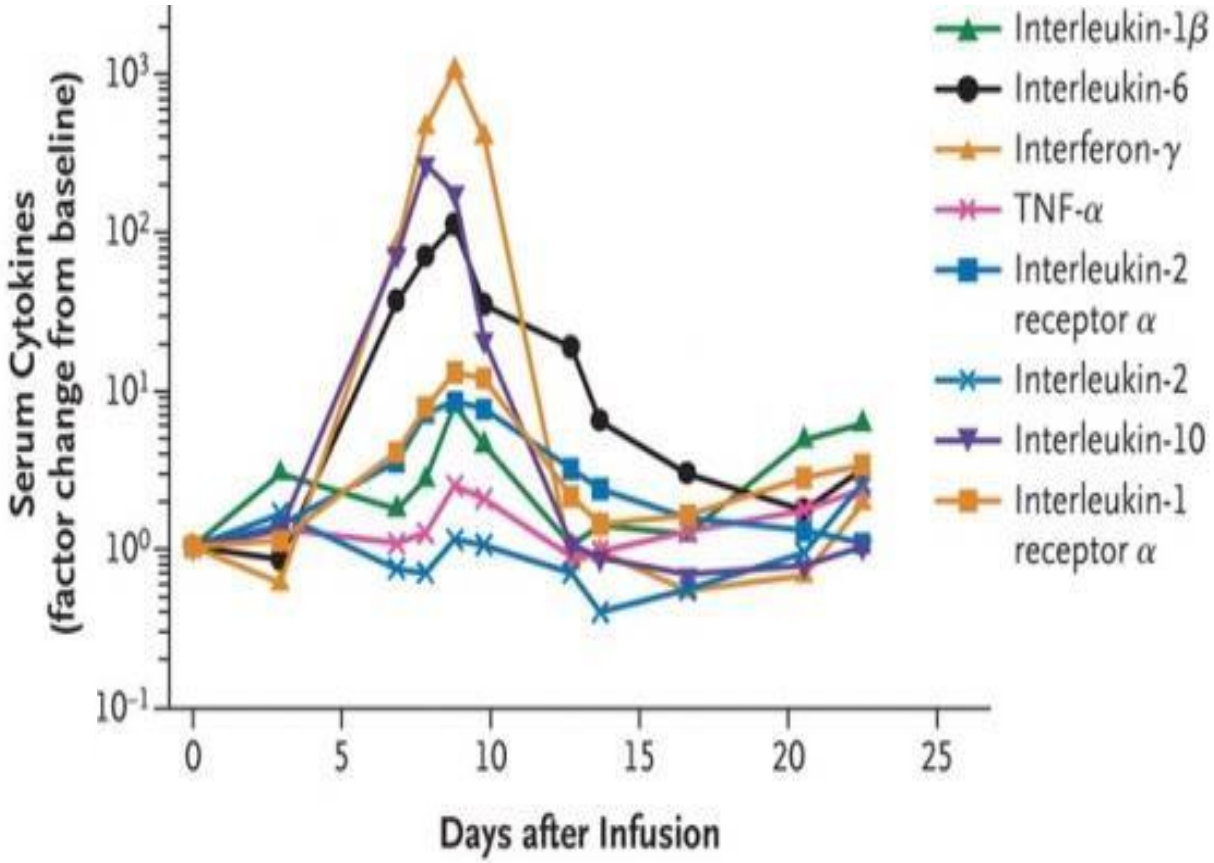
- The result of activation or engagement of endogenous or transferred T cells and/or other immune cells

| Cytokine Release Syndrome (CRS) | Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) |
|---|---|
| • Supraphysiologic systemic inflammatory response following immune therapy<br>• Manifestations likely mediated by high levels of circulating cytokines, e.g. IL-6 and IL-1<br>• Fever is a cardinal symptom | • Pathologic process involving the central nervous system<br>• Symptoms or signs include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema. |

Adapted from Lee *et al.,* Biol Blood Marrow Transplant 2019

# Cytokine Release Syndrome

- Manifestations include:
  - Fever
  - Hypotension
  - Hypoxia (capillary leak)
  - End organ dysfunction
    - Liver, kidney, heart, coagulopathy, …
- Laboratory findings include:
  - Elevated inflammatory markers
    - C-reactive protein, ferritin
    - Often lags behind clinical changes
  - Coagulopathy




*Grupp et al., NEJM 2013*

# CRS

- 74-100%
- Fever at onset
- 1-7 days
- Can last 1-2 weeks
- Earlier Onset CD28− (axi-cel and brexu-cel) compared with 4-1BB-costimulated(Tisa-cel)
- Severity- On disease burden, Cardiac disease, Higher doses of CAR-T cells

*J Immunother Cancer.* 2020;8(2):e001511

# CRS incidence in larger trials

| | Tisagenlecleucel[1] | Axicabtagene ciloleucel[2] | Tisagenlecleucel[3] | Lisocabtagene maraleucel[4] |
|---|---|---|---|---|
| **Disease** | Ped/AYA ALL | Adult DLBCL | Adult DLBCL | Adult DLBCL |
| **Patients treated** | 75 | 101 | 111 | 114 |
| **CRS** | **DIFFERENT GRADING SCALES WERE USED!!!** | | | |
| **Time to onset** | 3 d (1-22) | 2 d (1-12) | 3 d (1-9) | 5 d (2-12) |
| **Duration** | 8 d (1-36) | 8 d (NR) | 7 d (2-30) | 5 d (NR) |
| **All grades** | 77% | 93% | 58% | 42% |
| **Grade 3 or 4** | 47% | 13% | 23% | 2% |
| **Tocilizumab use** | 51% | 43% | 16% | 21% |
| **Vasopressor use** | 33%* | 17% | 6%* | NR |
| **Steroid use** | NR | 27% | 11% | 17% |

*High dose

[1]Maude *et al.* (ELIANA), N Engl J Med 2018; [2]Locke *et al.* (ZUMA-1), Lancet Oncol 2019;
[3]Schuster *et al.* (JULIET), N Engl J Med 2019; [4]Abramson *et al.* (TRANSCEND), LANCET 2020

# CRS grading – ASBMT/ASTCT

| Parameter | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Fever** | T ≥ 38°C | T ≥ 38°C | T ≥ 38°C | T ≥ 38°C |
| | | with | | |
| **Hypotension** | None | Not requiring vasopressors | Requiring one pressor (± vasopressin) | Requiring multiple vasopressors (excluding vasopressin) |
| | | and/or | | |
| **Hypoxia** | None | Low-flow nasal cannula (NC) or blow-by | High-flow NC, face mask, non-rebreather or Venturi mask | Positive pressure (e.g., CPAP, BiPAP, intubation, ventilation) |

(organ toxicities should be graded using CTCAE but do not inform CRS grade)

Lee *et al.,* Biol Blood Marrow Transplant 2019

# Management

- Supportive Care

- Tocilizumab-IL-6 Blocking antibody- approved in 2017

- Adults - ASTCT grade 2 CRS or higher.

- Earlier for Elderly or Extensive co-morbidities.

- For pediatric patients at ASTCT grade 3 CRS .

- Persistent Grade 1 CRS > 3 days

*J Immunother Cancer. 2020;8(2):e001511*
*Oncologist 2018;23:943–7*
*N Engl J Med Overseas Ed 2013;368:1509–18*
*Nat Rev Clin Oncol 2018;15:47–62.*

# Management

- Refractory CRS after 1 dose of tocilizumab, administer steroids with second dose of tocilizumab
- Refractory CRS third-line agents, including anakinra and high-dose methylprednisolone.
- Rule out/re-evaluate for infections.
- Rapid taper steroids once symptoms begin to improve.

*Blood* 2016;127:3321–30.
*Biol Blood Marrow Transplant* 2019; ;25:e123–7
*N Engl J Med* 2014;371:1507–17.

# IEC-Associated Neurotoxicity Syndrome (ICANS)

- 42-87%
- 4-6 days onset
- Can last 2 weeks
- Concurrent or after CRS
- Rarely before CRS

Lee *et al.,* Biol Blood Marrow Transplant 2019

# ICANS pathophysiology

- Thought to be secondary to high levels of cytokines and endothelial activation in the CNS

- Human and animal data suggest:
  - Increased permeability of blood-brain barrier (BBB) allows access of cytokines to pericytes
  - Risk factors include:

  Tumor burden, high CAR-T cell dose, CRS, pre-existing neurologic comorbidities

Gust et al. Cancer Discov 2017;
Kenderian et al. Blood, 2019

# ICANS

- A spectrum of neurologic abnormalities associated with CNS dysfunction
  - Confusion, delirium, aphasia, obtundation, seizure, cerebral edema
  - Possibly fatal
  - Other neurotoxicities (such as headache and myoclonus) are excluded from ICANS
- Occurs during or after CRS, rarely before

# ICANS incidence in larger trials

| | Tisagenlecleucel[1] | Axicabtagene ciloleucel[2] | Tisagenlecleucel[3] | Lisocabtagene maraleucel[4] |
|---|---|---|---|---|
| **Disease** | Ped/AYA ALL | Adult DLBCL | Adult DLBCL | Adult DLBCL |
| **Patients treated** | 75 | 101 | 111 | 114 |
| **Neurotoxicity** | **DIFFERENT GRADING SCALES WERE USED!!!** | | | |
| **Time to onset** | Within 8 wks | 5 d (1-17) | 6 d (1-17) | 10 d (3-23) |
| **Median duration** | NR | 17 d | 14 d | 11 d |
| **All grades** | 40% | 64% | 21% | 30% |
| **Grade ≥ 3** | 13% | 28% | 12% | 10% |

NR: not reported

[1]Maude *et al.* (ELIANA), N Engl J Med 2018; [2]Locke *et al.* (ZUMA-1), Lancet Oncol 2019;
[3]Schuster *et al.* (JULIET), N Engl J Med 2019; [4]Abramson *et al.* (TRANSCEND), Lancet 2020

# ICANS grading – ASBMT/ASTCT

| Parameter | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **ICE score*** | 7-9 | 3-6 | 0-2 | 0 (unable to do) |
| **Level of consciousness** | Awakens spontaneously | Awakens to voice | Awakens to tactile stimulus | Unarousable, stupor or coma |
| **Seizure** | — | — | Focal or generalized, resolving quickly | Life threatening, prolonged, status |
| **Motor findings** | — | — | — | Deep focal weakness |
| **Cerebral edema** | — | — | Focal edema on imaging | Diffuse edema on imaging or signs of increased ICP |

*Immune effector Cell-associated Encephalopathy score: ❶ Oriented to year, month, city and hospital (4 points). ❷ Names 3 objects (3 points). ❸ Follows simple commands (1 point). ❹ Writes standard sentence (1 point). ❺ Able to count backwards from 100 by 10 (1 point).

Adapted from Lee *et al.,* Biol Blood Marrow Transplant 2019

# ICANS management

- All stress comprehensive supportive care:
  - Frequent neurologic assessment
  - Imaging(Brain CT/MRI) and EEG as appropriate
  - Adequate management of increased intracranial pressure

- All recommend for grade ≥ 2:
  - Steroids (dexamethasone)- dosing product specific
  - Methylprednisone 1 g X 3 days Grade 4
  - Rapid taper
  - Prophylactic Levetiracetam
  - Tocilizumab does not cross BBB and is not effective

Kite Yescarta package insert, 2017. *United States FDA*.
*Cancer Discov* 2018;8:958–71

# ICANS management

- Other potential drugs:
  - Anakinra
    -Therapeutic
    -Prophylactic
  - Situximab
  - Case reports- IT chemotherapy

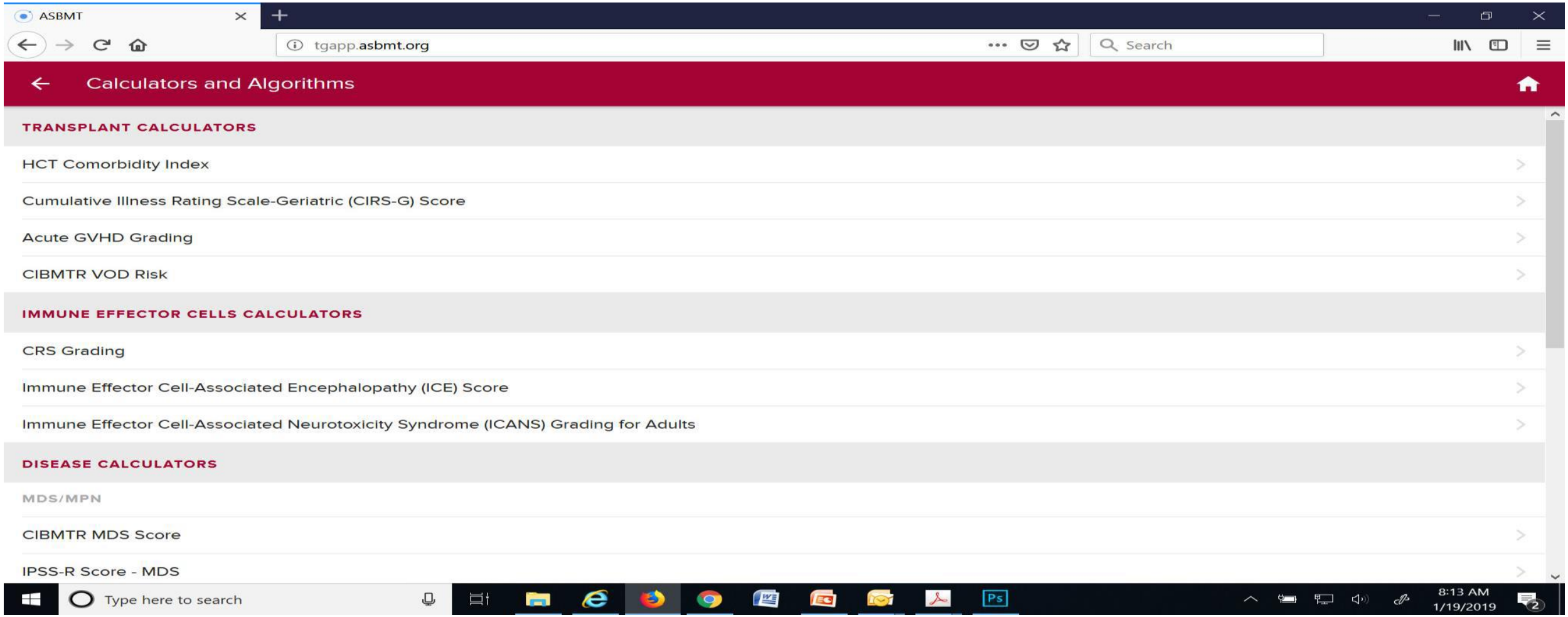
*J Immunother Cancer*. 2022;10(1)
*Blood Adv*. 2020;4(13):3123-3127
*Blood*. 2021;138(suppl 1). Abstract 96
*Blood Adv* . 2020;4(10):2119-2122

# Dexamethasone Prophylaxis

- ZUMA- 1, Cohort -6
- 3 days (day 0 -2)
- Levetiracetam starting day 0
- CRS in 80% of patients (all grade ≤2).
- Any grade and grade 3 or higher Neurologic events in 58% and 13%

Br J Haematol. 2021 Aug;194(4):690-700

# ASTCT App


ASBMT
tgapp.asbmt.org
Search
Calculators and Algorithms
TRANSPLANT CALCULATORS
HCT Comorbidity Index
Cumulative Illness Rating Scale-Geriatric (CIRS-G) Score
Acute GVHD Grading
CIBMTR VOD Risk
IMMUNE EFFECTOR CELLS CALCULATORS
CRS Grading
Immune Effector Cell-Associated Encephalopathy (ICE) Score
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grading for Adults
DISEASE CALCULATORS
MDS/MPN
CIBMTR MDS Score
IPSS-R Score - MDS
Type here to search
8:13 AM
1/19/2019

# IEC-Hemophagocytic Lymphohistiocytosis-like Syndrome

- Rare
- More common with CD 22 CAR T cells
- Rising Ferritin, CRS resolves
- Recurrence of fever
- Coagulation abnormalities
- Transaminitis
- Hemophagocytosis on BM biopsy
- Anakinra/Steroids

*Br J Haematol*. 2021;194(4):701-707
*Blood*. 2021;138(24):2469-2484

# Other early CAR toxicities

- Coagulopathy
  - Potentially leading to cerebral hemorrhage
  - Part of CRS
  - Part of IEC-HS

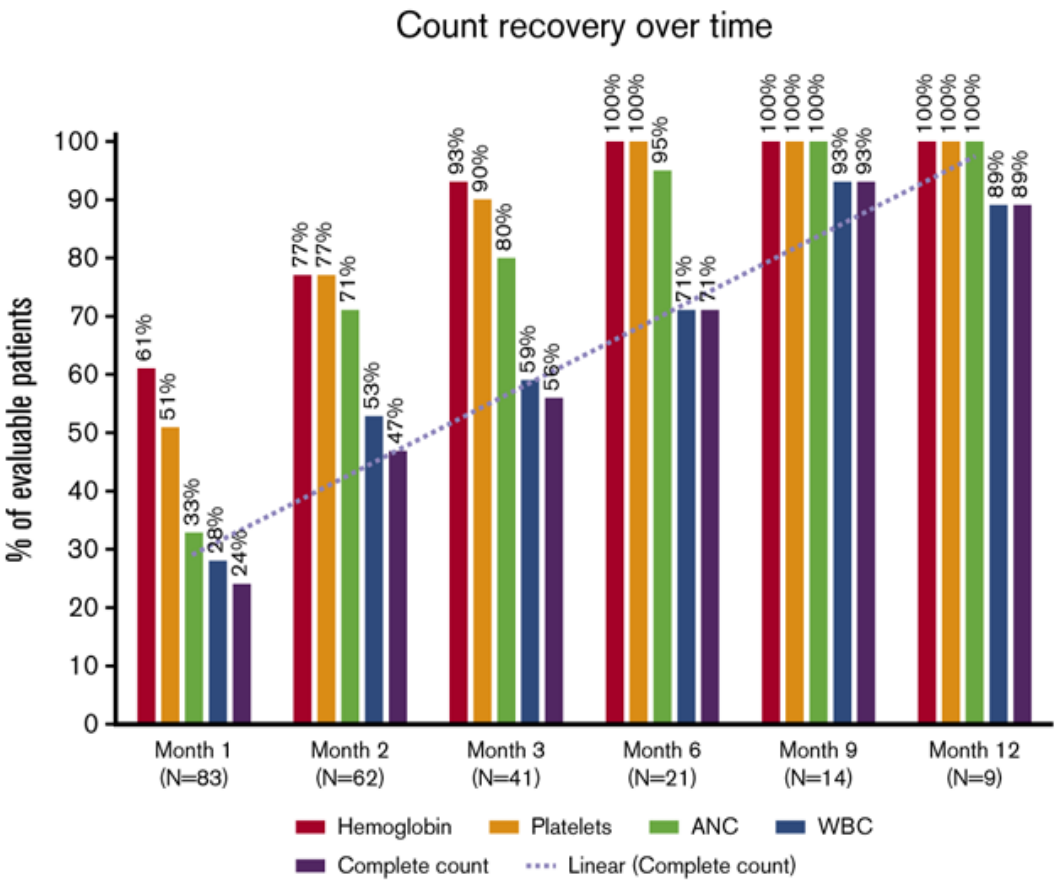
- These can be life threatening acute toxicities but are excluded from definitions of CRS and ICANS

# Late CAR toxicities

- Some are due to lymphodepleting chemotherapy (and possibly inflammatory sequelae of CRS)
  - Persistent cytopenias (can be prolonged)
  - Infections

- Others can result from on-target off-tumor effects of CAR
  - Toxicities from cells may persist and worsen
  - CD19 CARTs: B cell aplasia and hypogammaglobulinemia

# CAR T Associated Cytopenias

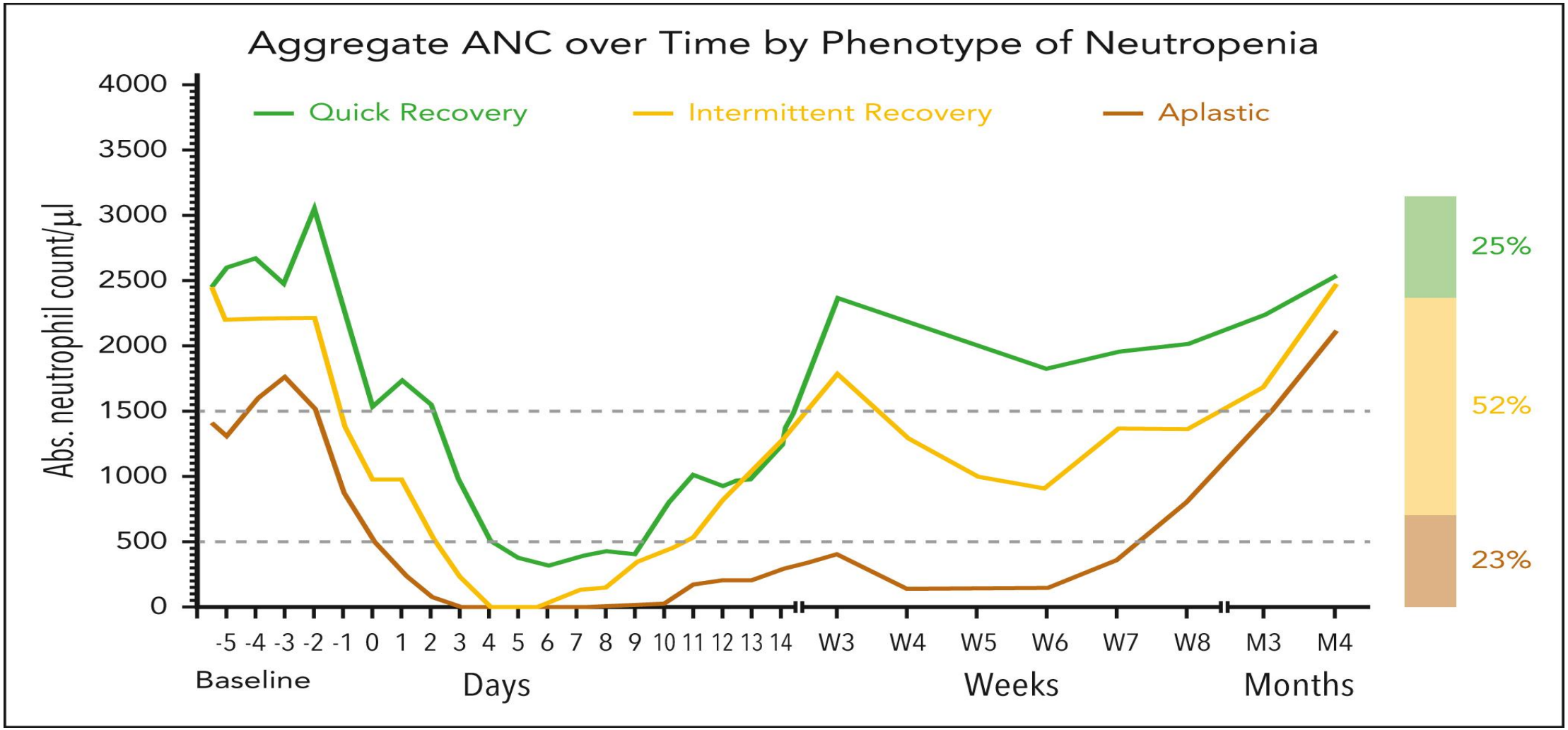



Grade 3-4 CRS/ICANS → Lower liklihood of recovering blood counts at 1 month

| | ≤ Grade 2 CRS/ICANS (n=50) | Grade 3-4 CRS/ICANS (n=33) | Cochran-Mantel-Haenszel p-value |
|---|---|---|---|
| **Baseline cytopenia** | | | **0.002** |
| No (n=10) | 5/7 (71%) | 1/3 (33%) | |
| Yes (n=73) | 13/43 (30%) | 1/30 (3%) | |
| **CAR construct** | | | **0.01** |
| Axicabtagene ciloleucel (n=30) | 5/19 (26%) | 0/11 (0%) | |
| Tisagenlecleucel (n=10) | 7/10 (70%) | - | |
| 19-28z CAR T (n=37) | 6/16 (38%) | 1/21 (5%) | |
| anti-BCMA CAR T (n=6) | 0/5 (0%) | 1/1 (100%) | |

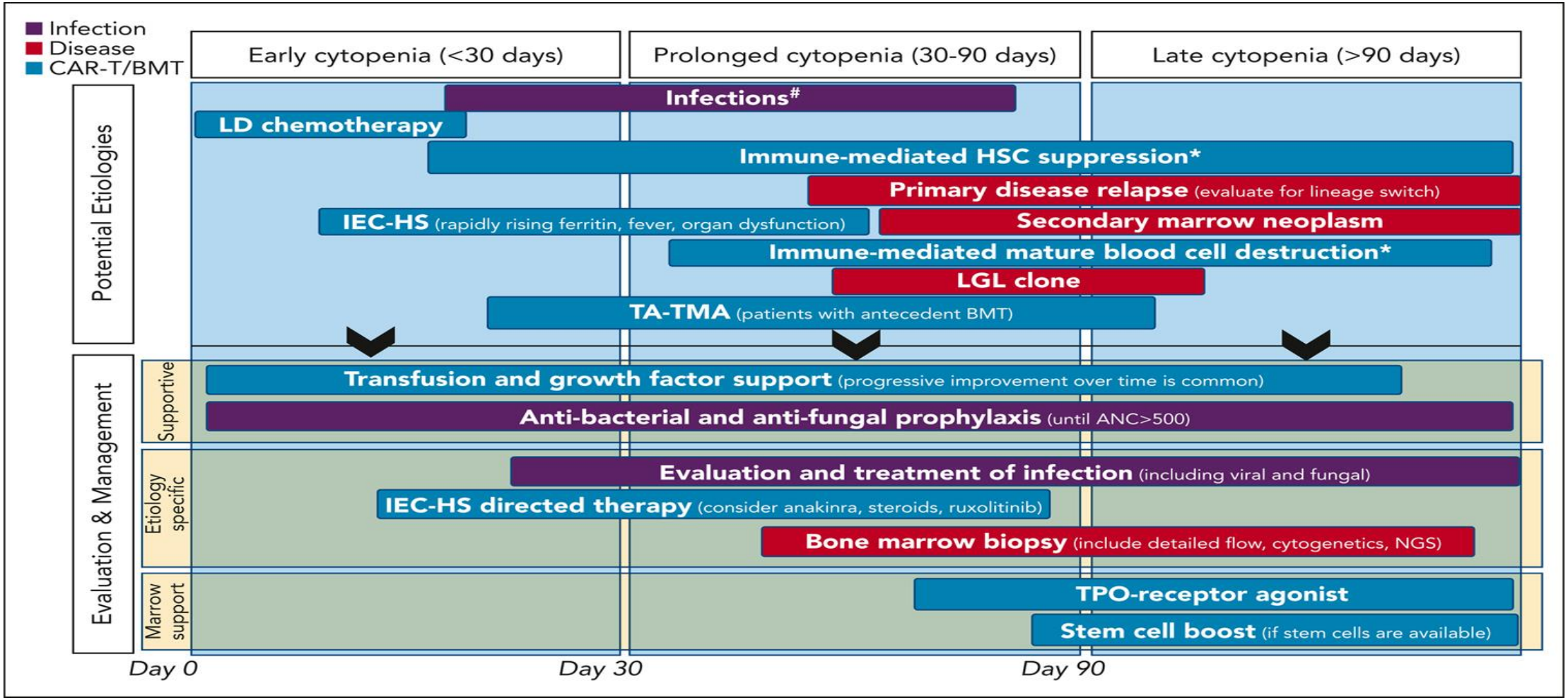
*Adopted from Jain. T et al. Blood Adv* (2020) 4 (15): 3776–3787.

# CAR T Associated Cytopenias




*Adopted from Blood* (2023) 141 (20): 2460–2469

# CAR T Associated Cytopenias




*Adopted from Blood* (2023) 141 (20): 2460–2469

# Hypogammaglobulinemia/B Cell Aplasia

- Persistence of CAR T cells
- Recovery median ~ 6.7 months
- Previous therapies increase risk
- IV Ig for IgG <400
- Subcutaneous may be an option

*J Immunother Cancer. 2020;8(2):e001511*

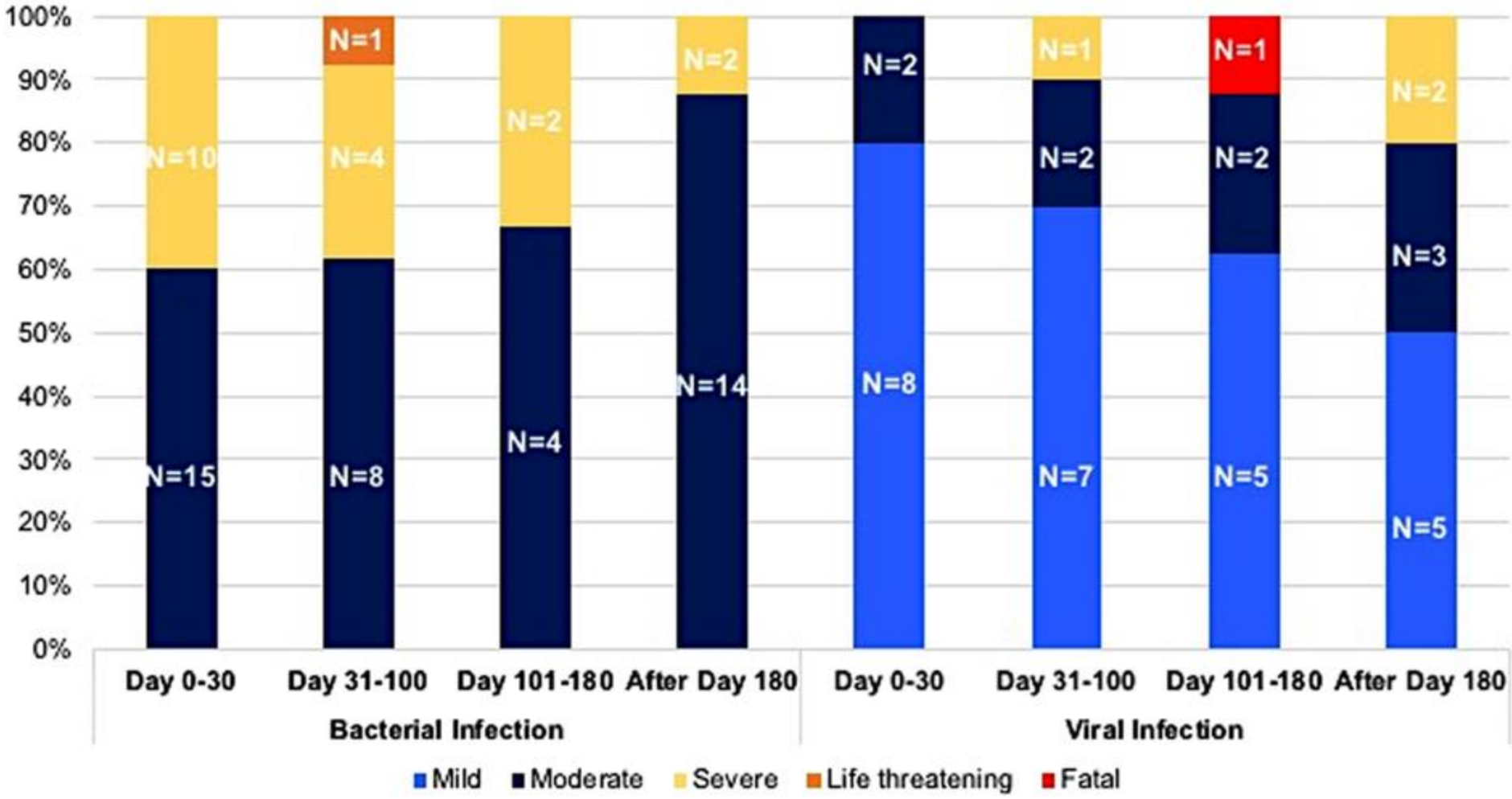
*N Engl J Med* 2017;377:2545–54.

# Infections

- Previous therapies
- Lymphodepeletion Chemotherapy
- Bacterial /Fungal/Viral- prophylaxis
- PJP- Prophylaxis
- CRS/ICANS Therapies
- Hypogammaglobulinemia

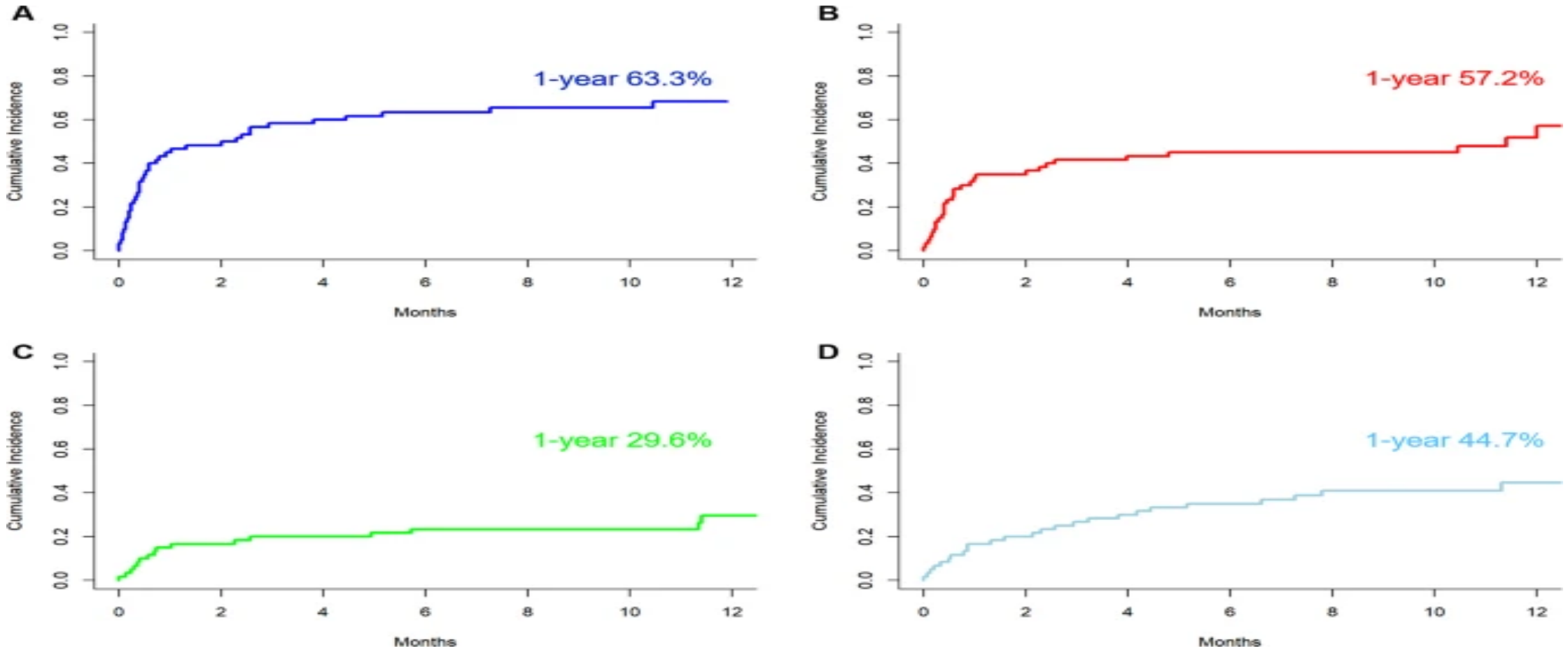
*J Immunother Cancer. 2020;8(2):e001511*

# Infections- CD 19 CAR T cells




*Adopted from Wudhikarn. Blood Cancer J.* **10**, 79 (2020)

# Cumulative Infections




*Adopted from Wudhikarn. Blood Cancer J.* **10**, 79 (2020)

# Financial Toxicity/Access

- Social Worker evaluation
- Patient education
- Family support
- Call Parameters
- Infection prophylaxis.

# Novel Strategies- ? Better

- Bispecific / Trispecific CAR T cells
- Allogeneic CAR T cells
- NK-CAR cell Therapies
- Safety switch

# Regulations

## ASTCT 80/20 Taskforce

**1. Mission**

- **Advocate** for standardization
- **Identify 80% common workflows** (contrasting **20% product-specific**)
- **Streamline** auditing and education
- **Leverage** existing entities


**2. Taskforce Activities**

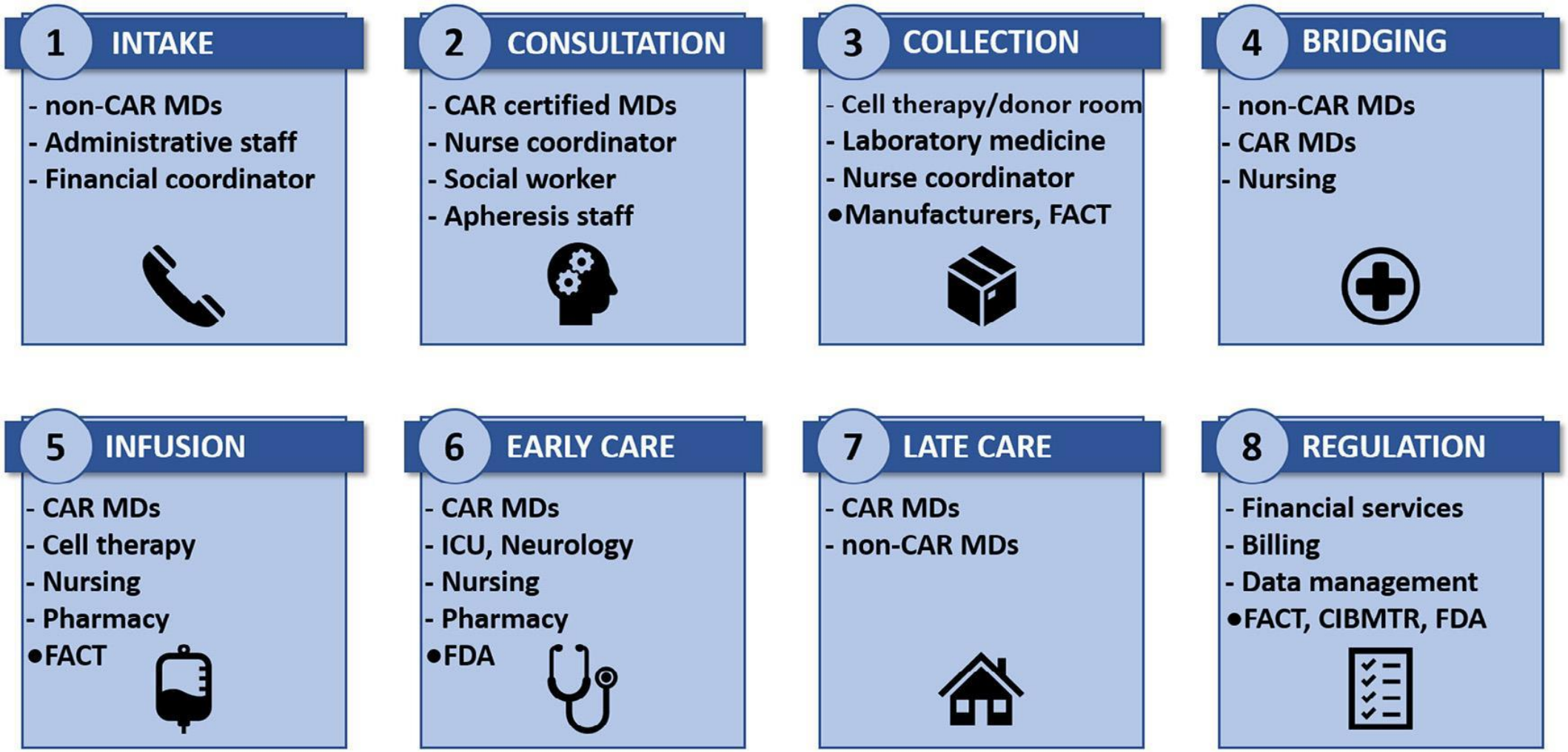
- 80/20 Stakeholder Interviews
- AcCELLerate Forum Session
- 80/20 Workshop

**3. Potential Solutions to Challenges**

- Eliminate duplication in accreditation and auditing
- Define standard expectations for managing toxicities
- Streamline education, testing, data reporting - REMS
- Centralize IT platforms for logistics and feedback
- Use common nomenclature across manufacturers

Transplant Cell Ther. 2023 Apr;29(4):228-239

# Essentials of CAR T Program




Perica et al. Biol Blood Marrow Transplant. 2018 Jun;24(6):1135-1141

# Thank you