# CAR-T en la LAL pediátrica

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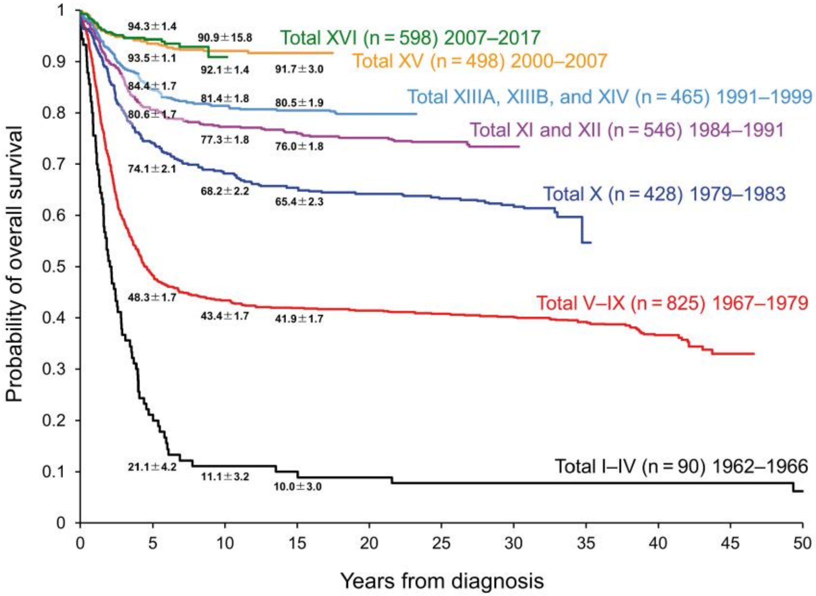
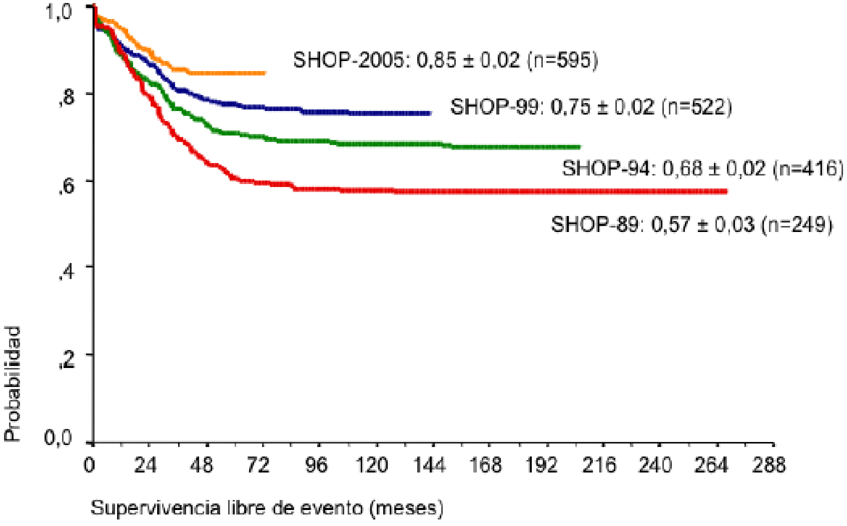
# Leucemia aguda linfoblástica (LAL)

- Cáncer más frecuente en niños (85% inmunofenotipo B)
- Incremento significativo de la supervivencia global (> 90 %)

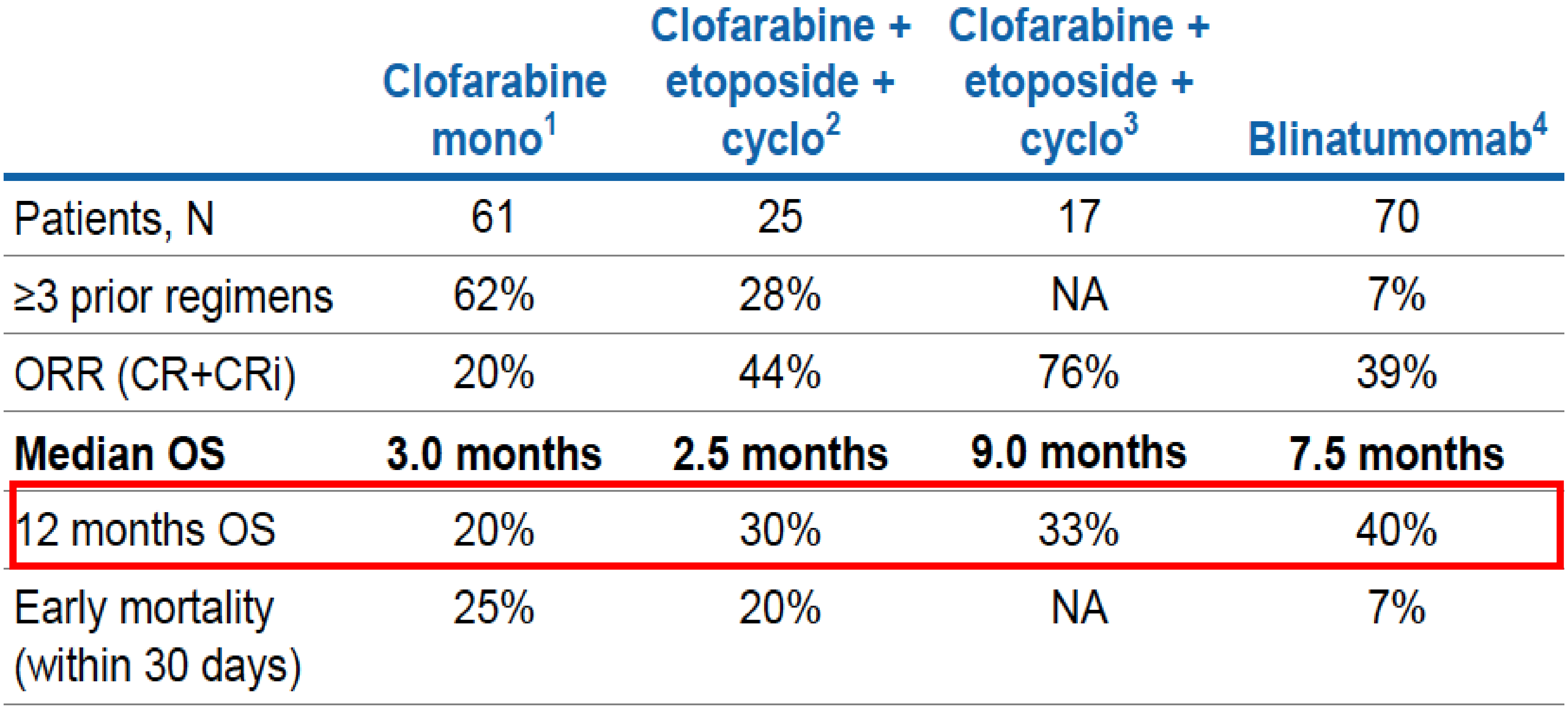


St Jude Total Therapy studies.
Inaba H, Mulligan CH et al. 2020



Protocolos Soc. Esp. Hematología y Oncología Pediátrica
Inaba H, Mulligan CH et al. 2020

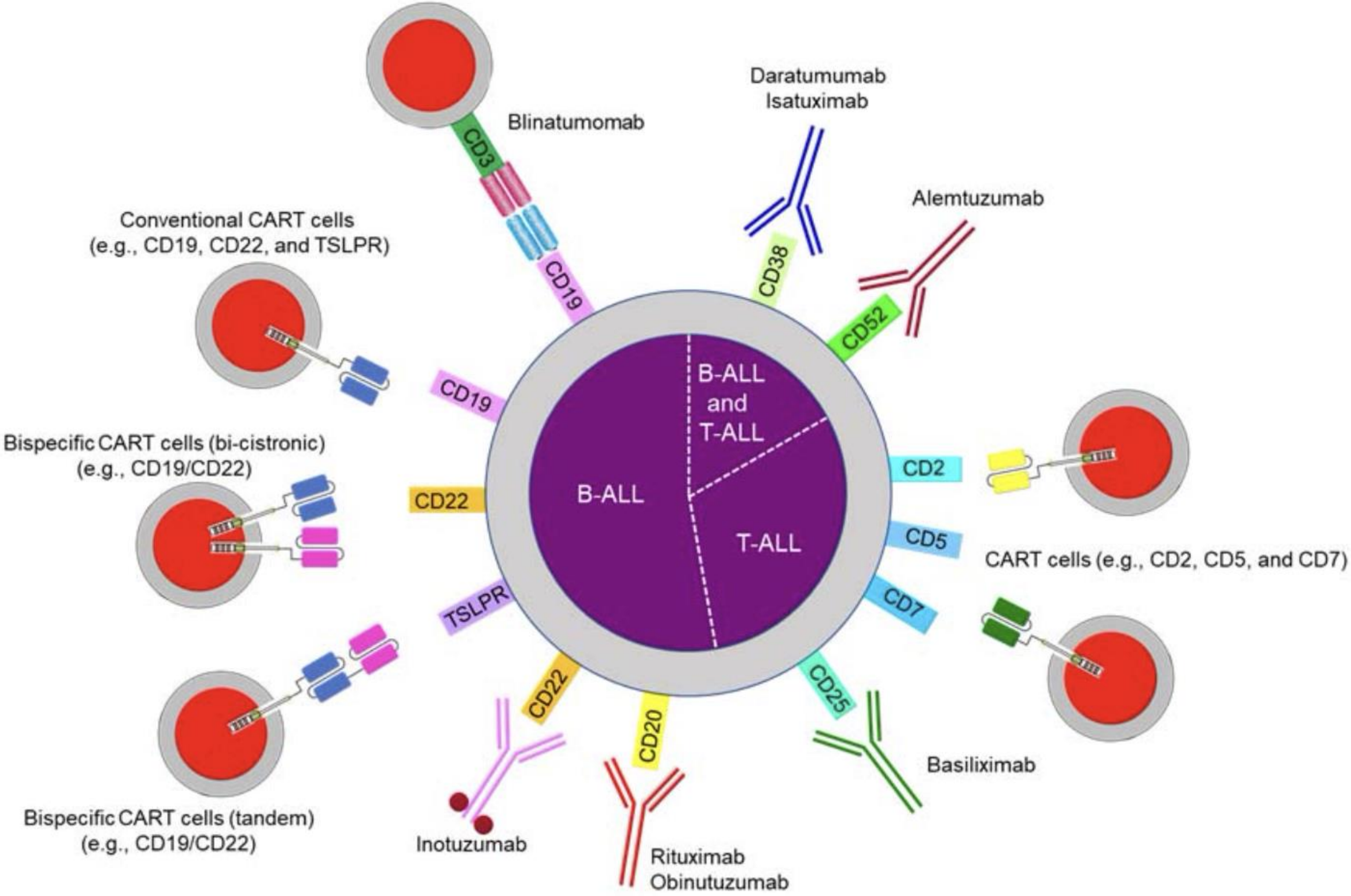
# Eficacia de los tratamientos disponibles antes de los CAR-T en pacientes con LLA-B R/R



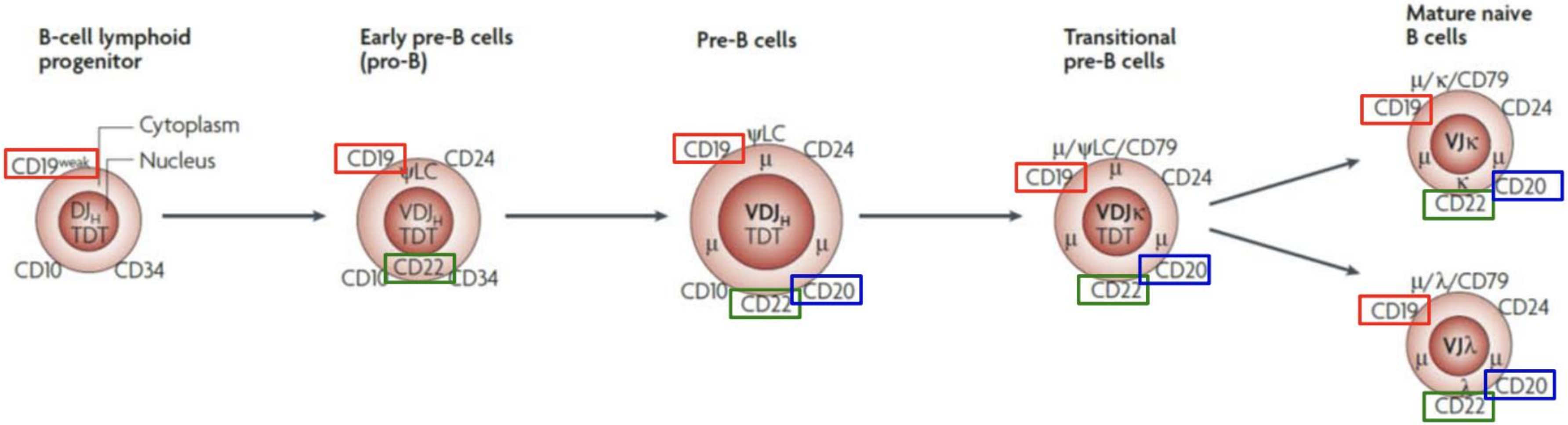
| | Clofarabine mono[1] | Clofarabine + etoposide + cyclo[2] | Clofarabine + etoposide + cyclo[3] | Blinatumomab[4] |
|---|---|---|---|---|
| Patients, N | 61 | 25 | 17 | 70 |
| ≥3 prior regimens | 62% | 28% | NA | 7% |
| ORR (CR+CRi) | 20% | 44% | 76% | 39% |
| **Median OS** | **3.0 months** | **2.5 months** | **9.0 months** | **7.5 months** |
| 12 months OS | 20% | 30% | 33% | 40% |
| Early mortality (within 30 days) | 25% | 20% | NA | 7% |

1. Jeha S et al J Clin Oncol. 2006; 24:1917-23
2. Hijiya N et al. Blood 2011; 118: 6043 -6049
3. Locatelli F et al Br J Haematol. 2009;147(3):371-378
4. Von Stackelberg J et al. J Clin Oncol. 2016; 34:4381-4389

# Inmunoterapia para la LAL


Blinatumomab
CD3
CD19
Daratumumab
Isatuximab
CD38
Alemtuzumab
CD52
Conventional CART cells
(e.g., CD19, CD22, and TSLPR)
CD19
B-ALL
and
T-ALL
B-ALL
T-ALL
CD2
CD5
CD7
CART cells (e.g., CD2, CD5, and CD7)
Bispecific CART cells (bi-cistronic)
(e.g., CD19/CD22)
CD22
TSLPR
CD22
CD20
CD25
Basiliximab
Bispecific CART cells (tandem)
(e.g., CD19/CD22)
Inotuzumab
Rituximab
Obinutuzumab

# Marcadores de superficie de los linfocitos B


B-cell lymphoid progenitor
Cytoplasm
Nucleus
CD19weak
DJH
TDT
CD10
CD34
Early pre-B cells (pro-B)
CD19
CD24
ψLC
VDJH
TDT
CD10
CD22
CD34
Pre-B cells
CD19
ψLC
CD24
μ
VDJH
TDT
μ
μ
CD10
CD22
CD20
Transitional pre-B cells
μ/ψLC/CD79
CD19
μ
CD24
VDJκ
TDT
μ
μ
CD22
CD20
Mature naive B cells
μ/κ/CD79
CD19
CD24
VJκ
μ
μ
κ
CD22
CD20
μ/λ/CD79
CD19
CD24
VJλ
μ
μ
λ
CD22
CD20

CD19, CD20 y CD22 no se expresan sobre las células madre hematopoyéticas o otros tejidos.

# CAR-T en investigación en LAL pediátrica

**Tisagenlecleucel (CTL019)**
- **August 30, 2017:** approved for R/R B-cell precursor ALL (pediatric or young adult patients aged ≤25 y)[1]

**KTE-X19**
- Currently in phase 2 testing

**FHCRC CD19-4-1BB CAR**
- Phase 1/2

**UCART19**
- Phase 1

# CAR-T aprobados EMA

| | **Tisagenlecleucel**<br>**(Tisa-cel, CTL019)**<br>**Kymriah ®** | **Axicabtagene Ciloleucel**<br>**(Axi-cel, KTE-C19)**<br>**Yescarta ®** | **Brexucabtagene Autoleucel**<br>**(KTE-X19)**<br>**Tecartus ®** |
|---|---|---|---|
| **US FDA Indication** | Ped/young adult ALL<br>Adult DLBCL | Adult LBCL | Adult MCL |
| **CAR Type** | CD19/4-1BB/CD3z | CD19/CD28/CD3z | CD19/CD28/CD3z |
| **Costimulatory Domain** | 4-1BB (CD 137) | CD28 | CD28 |
| **Vector** | Lentivirus | Retrovirus | Retrovirus |
| **Pivotal Trial** | ELIANA (ALL),<br>JULIET (DLBCL) | ZUMA-1 (LBCL) | ZUMA-2 (MCL) |

tisagenlecleucel

brexucabtagene autoleucel
TECARTUS

# Resultados de los tratamientos con CART

# Diseño estudio ELIANA

**Estudio de fase 2 multicéntrico, abierto y de un solo brazo para evaluar la eficacia y seguridad de tisagenlecleucel (CTL019) en pacientes pediátricos y adultos jóvenes con LAL B R / R (N = 75)**

QT linfodepleción

- Fludarabina 30 mg/m2 IV diaria x 4 días (1-4)
- Ciclofosfamida 500 mg/m2 IV diaria x 2 días (1-2)

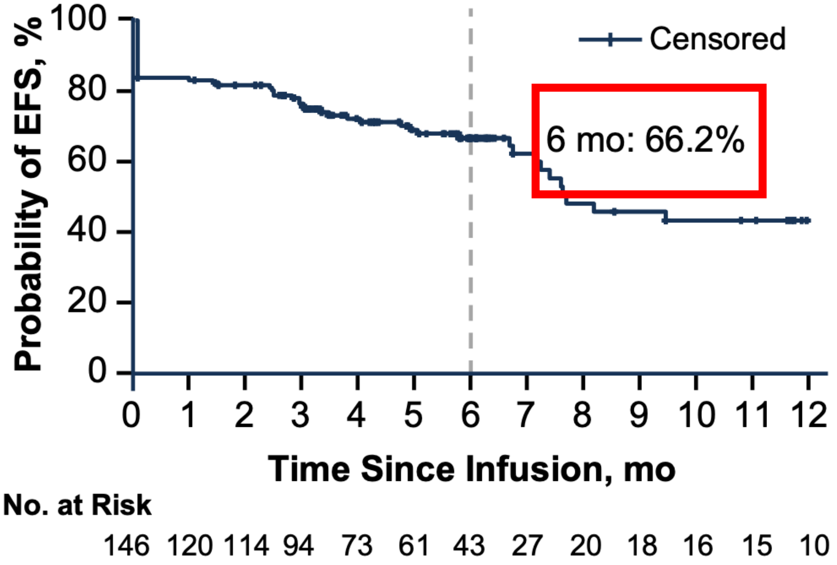
DosiS única CTL019 (2-14 días después de completar la QT linfodepleción):

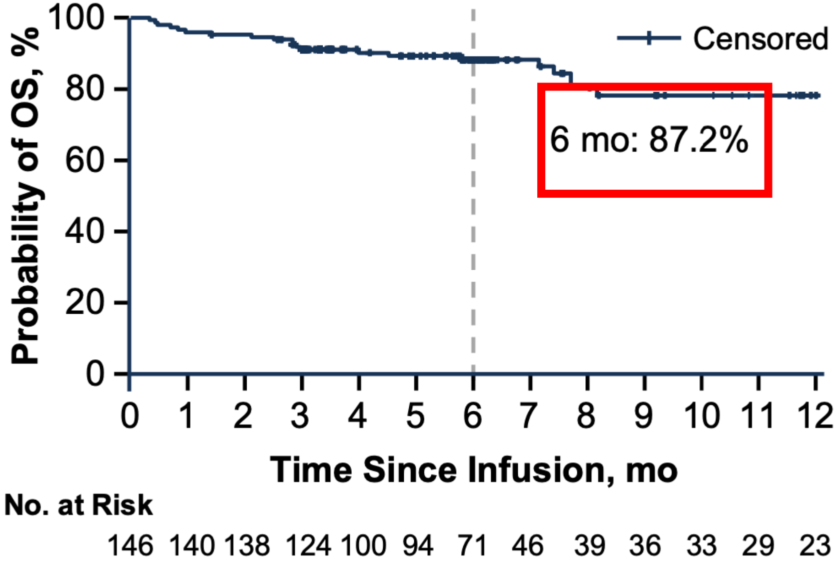
- 0,2 a 5 x $10^6$ AR+ T cel/Kg (para pacientes <= 50 Kg)
- 0,1 a 2,5 x $10^8$ cel/Kg cel /Kg (para pacientes > 50 Kg)

- Objetivo principal: tasa respuesta completa (CR/CRi) a los 3 meses
- Objetivos secundarios: duración de respuesta, supervivencia libre de evento, supervivencia global, supervivencia libre de recaída

Maude SL et al. NEJM 2018.

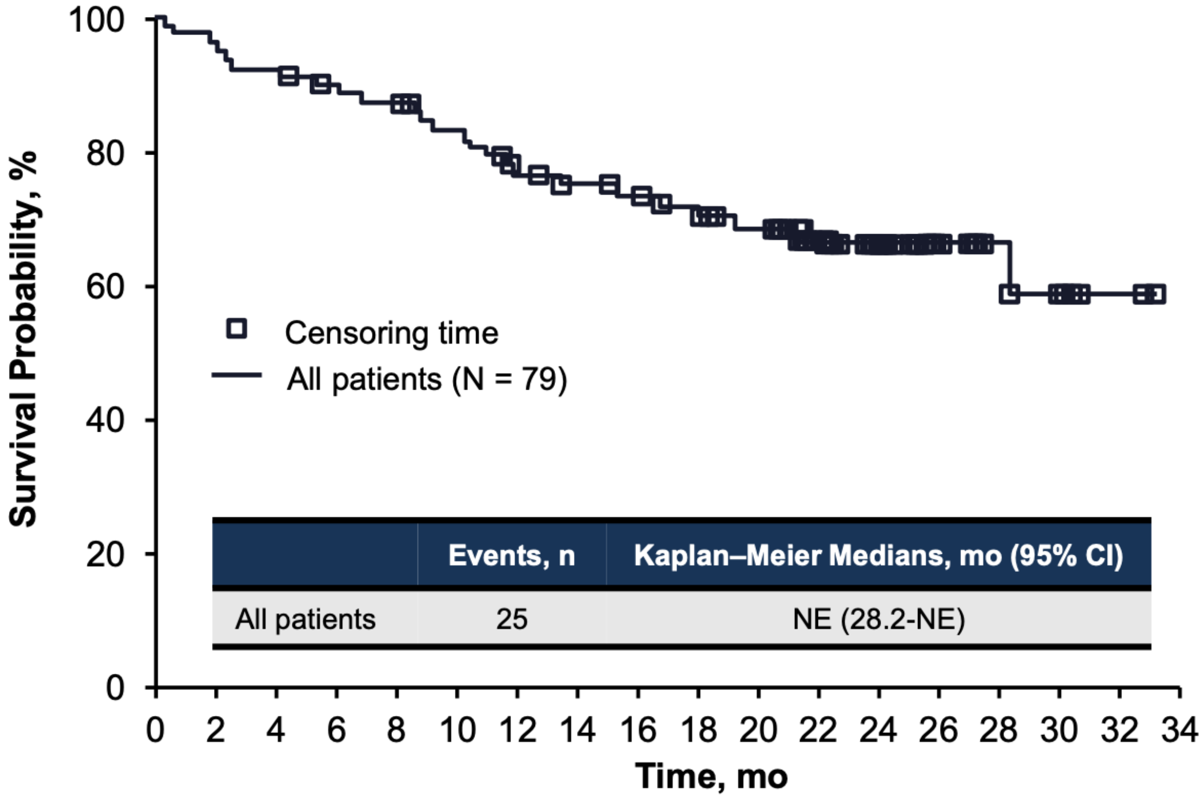
# ELIANA : resultados supervivencia libre de evento y supervivencia global


**EFS for Patients With ALL at the First Infusion**


**Overall Survival for Patients With ALL at the First Infusion**

Tasa de remisión (3 meses) : 82% (todos EMR-)

# ELIANA: resultados SG con mayor seguimiento



| | Events, n | Kaplan–Meier Medians, mo (95% CI) |
|---|---|---|
| All patients | 25 | NE (28.2-NE) |

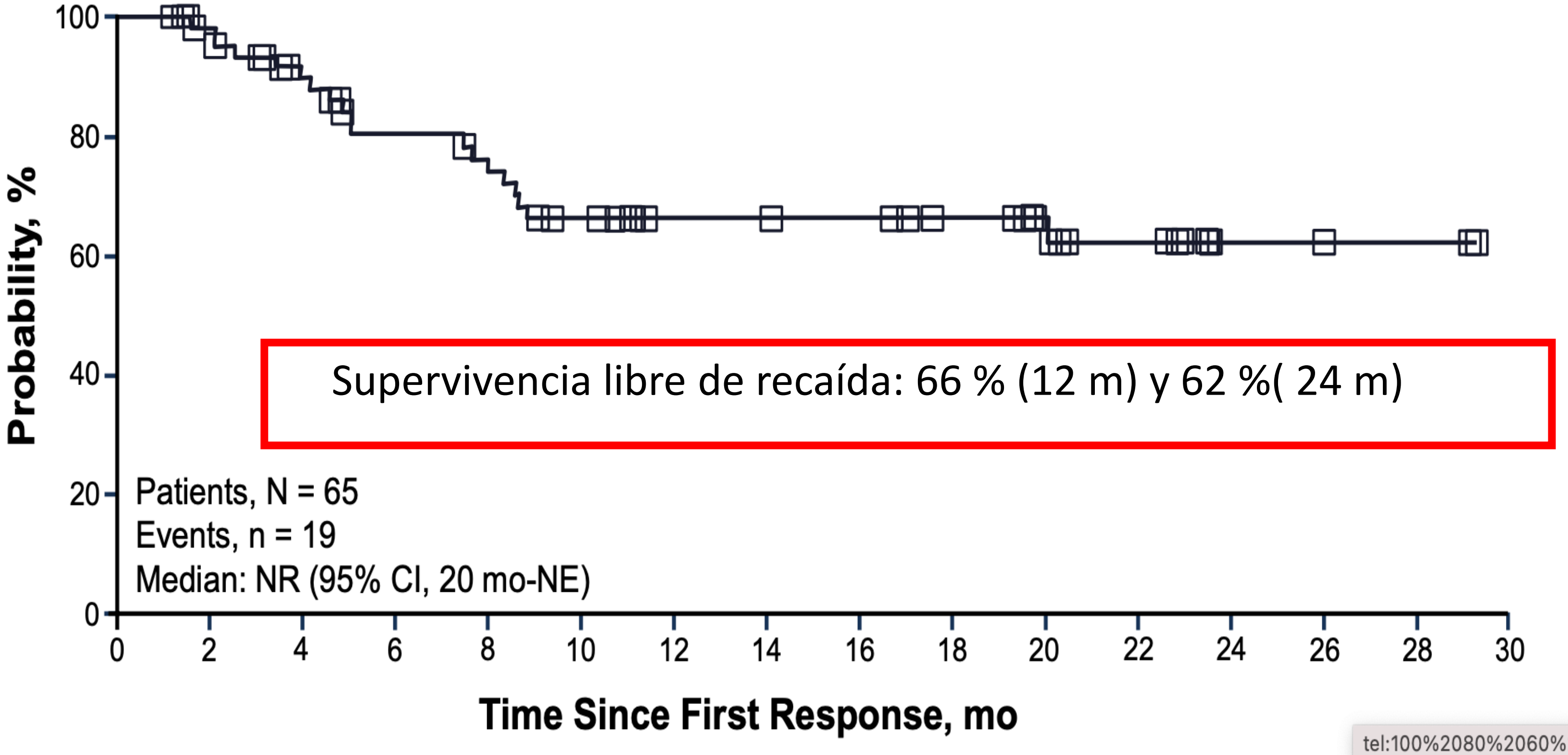
| No. at Risk | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| All patients | 79 | 76 | 73 | 68 | 67 | 62 | 55 | 52 | 47 | 42 | 39 | 26 | 21 | 14 | 9 | 5 | 2 | 0 |

**OS Rates Among Infused Patients**

- **12 month:** 76% (95% CI, 65-85)
- **18 month:** 70% (95% CI, 58-79)
- **24 month:** 66% (95% CI, 54-76)

Grupp SA et al . SHD 2018. Abstr. 895

# ELIANA : resultados SLE con mayor seguimiento



Supervivencia libre de recaída: 66 % (12 m) y 62 %( 24 m)

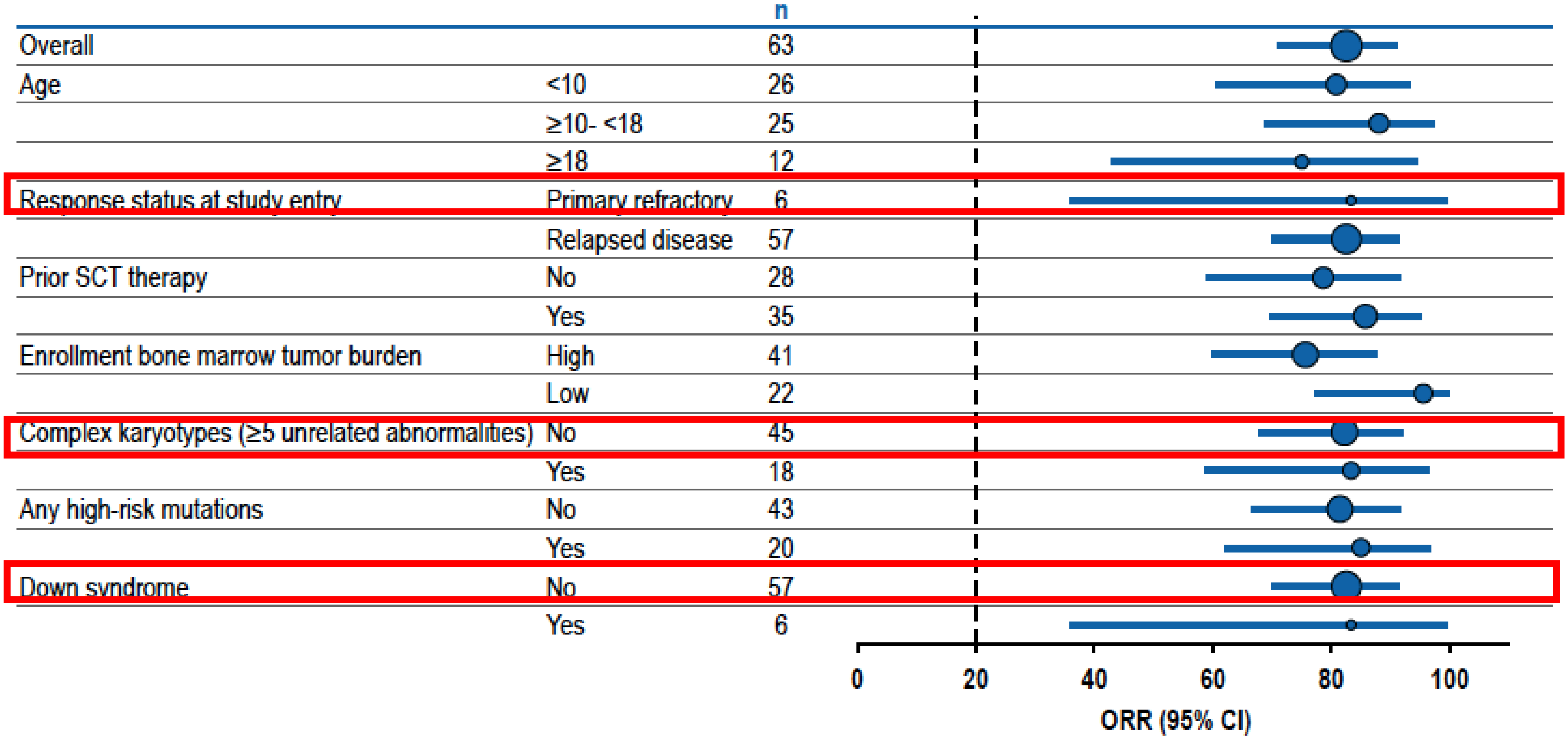
Patients, N = 65
Events, n = 19
Median: NR (95% CI, 20 mo-NE)

tel:100%2080%2060%2040

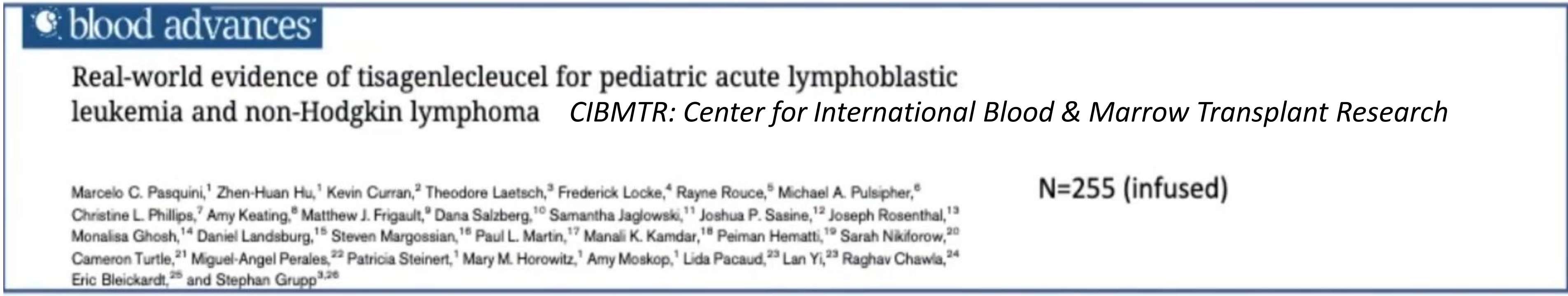
- La mayoría de las recaídas ocurren en los primeros meses.
- Las recaídas son a menudo CD19 negativas (escape)

Grupp SA et al . ASH 2018. Abstr. 895

# ELIANA: todos los subgrupos se benefician del tratamiento



# *Real world :* Tisagenlecleucel en LAL pediátrica



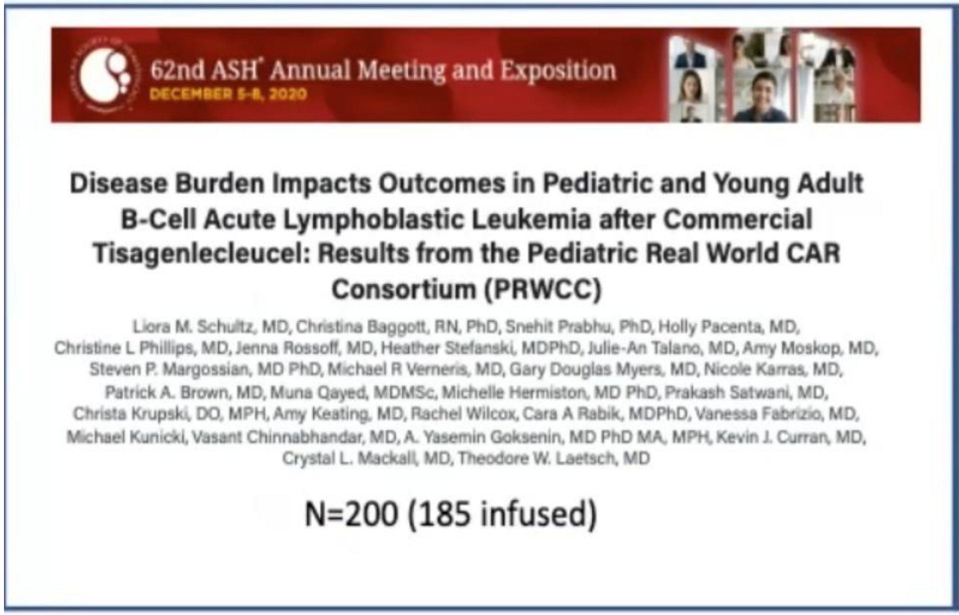
blood advances

## Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma

*CIBMTR: Center for International Blood & Marrow Transplant Research*

Marcelo C. Pasquini,[1] Zhen-Huan Hu,[1] Kevin Curran,[2] Theodore Laetsch,[3] Frederick Locke,[4] Rayne Rouce,[5] Michael A. Pulsipher,[6] Christine L. Phillips,[7] Amy Keating,[8] Matthew J. Frigault,[9] Dana Salzberg,[10] Samantha Jaglowski,[11] Joshua P. Sasine,[12] Joseph Rosenthal,[13] Monalisa Ghosh,[14] Daniel Landsburg,[15] Steven Margossian,[16] Paul L. Martin,[17] Manali K. Kamdar,[18] Peiman Hematti,[19] Sarah Nikiforow,[20] Cameron Turtle,[21] Miguel-Angel Perales,[22] Patricia Steinert,[1] Mary M. Horowitz,[1] Amy Moskop,[1] Lida Pacaud,[23] Lan Yi,[23] Raghav Chawla,[24] Eric Bleickardt,[25] and Stephan Grupp[3,26]

N=255 (infused)

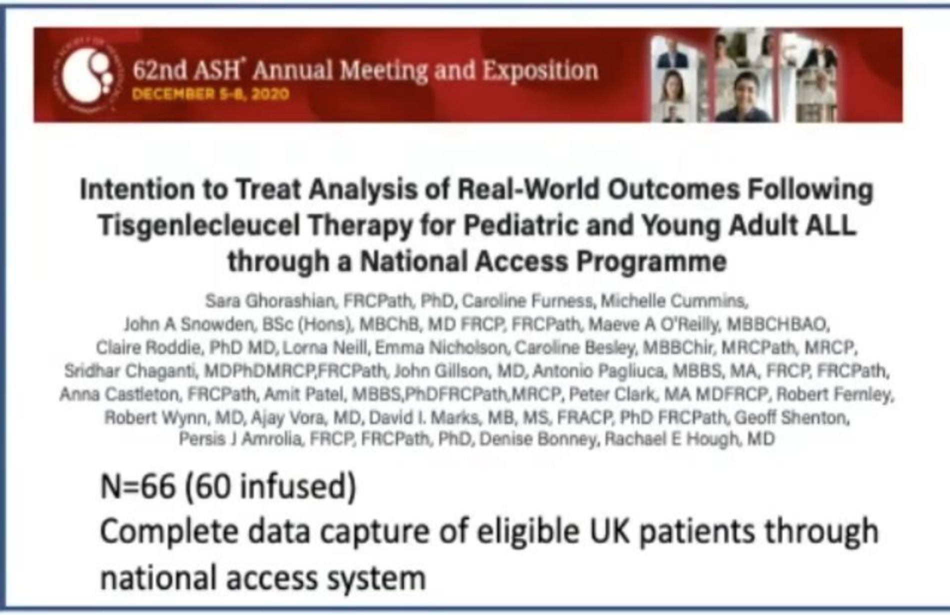


62nd ASH® Annual Meeting and Exposition
DECEMBER 5-8, 2020

## Disease Burden Impacts Outcomes in Pediatric and Young Adult B-Cell Acute Lymphoblastic Leukemia after Commercial Tisagenlecleucel: Results from the Pediatric Real World CAR Consortium (PRWCC)

Liora M. Schultz, MD, Christina Baggott, RN, PhD, Snehit Prabhu, PhD, Holly Pacenta, MD, Christine L Phillips, MD, Jenna Rossoff, MD, Heather Stefanski, MDPhD, Julie-An Talano, MD, Amy Moskop, MD, Steven P. Margossian, MD PhD, Michael R Verneris, MD, Gary Douglas Myers, MD, Nicole Karras, MD, Patrick A. Brown, MD, Muna Qayed, MDMSc, Michelle Hermiston, MD PhD, Prakash Satwani, MD, Christa Krupski, DO, MPH, Amy Keating, MD, Rachel Wilcox, Cara A Rabik, MDPhD, Vanessa Fabrizio, MD, Michael Kunicki, Vasant Chinnabhandar, MD, A. Yasemin Goksenin, MD PhD MA, MPH, Kevin J. Curran, MD, Crystal L. Mackall, MD, Theodore W. Laetsch, MD

N=200 (185 infused)



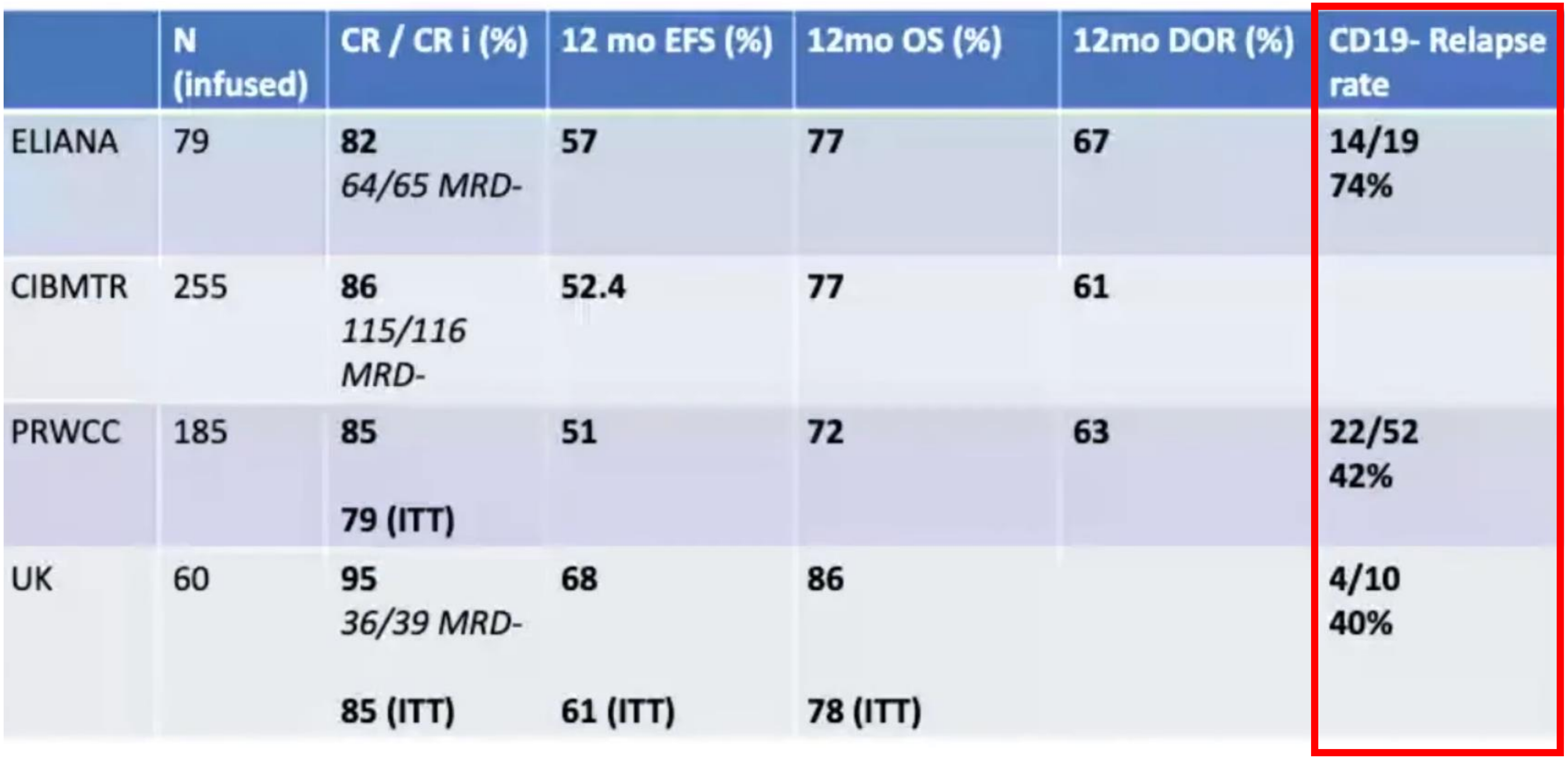
62nd ASH® Annual Meeting and Exposition
DECEMBER 5-8, 2020

## Intention to Treat Analysis of Real-World Outcomes Following Tisgenlecleucel Therapy for Pediatric and Young Adult ALL through a National Access Programme

Sara Ghorashian, FRCPath, PhD, Caroline Furness, Michelle Cummins, John A Snowden, BSc (Hons), MBChB, MD FRCP, FRCPath, Maeve A O'Reilly, MBBCHBAO, Claire Roddie, PhD MD, Lorna Neill, Emma Nicholson, Caroline Besley, MBBChir, MRCPath, MRCP, Sridhar Chaganti, MDPhDMRCP,FRCPath, John Gillson, MD, Antonio Pagliuca, MBBS, MA, FRCP, FRCPath, Anna Castleton, FRCPath, Amit Patel, MBBS,PhDFRCPath,MRCP, Peter Clark, MA MDFRCP, Robert Fernley, Robert Wynn, MD, Ajay Vora, MD, David I. Marks, MB, MS, FRACP, PhD FRCPath, Geoff Shenton, Persis J Amrolia, FRCP, FRCPath, PhD, Denise Bonney, Rachael E Hough, MD

N=66 (60 infused)
Complete data capture of eligible UK patients through national access system

# *Real world :* Tisagenlecleucel el LAL pediátrica

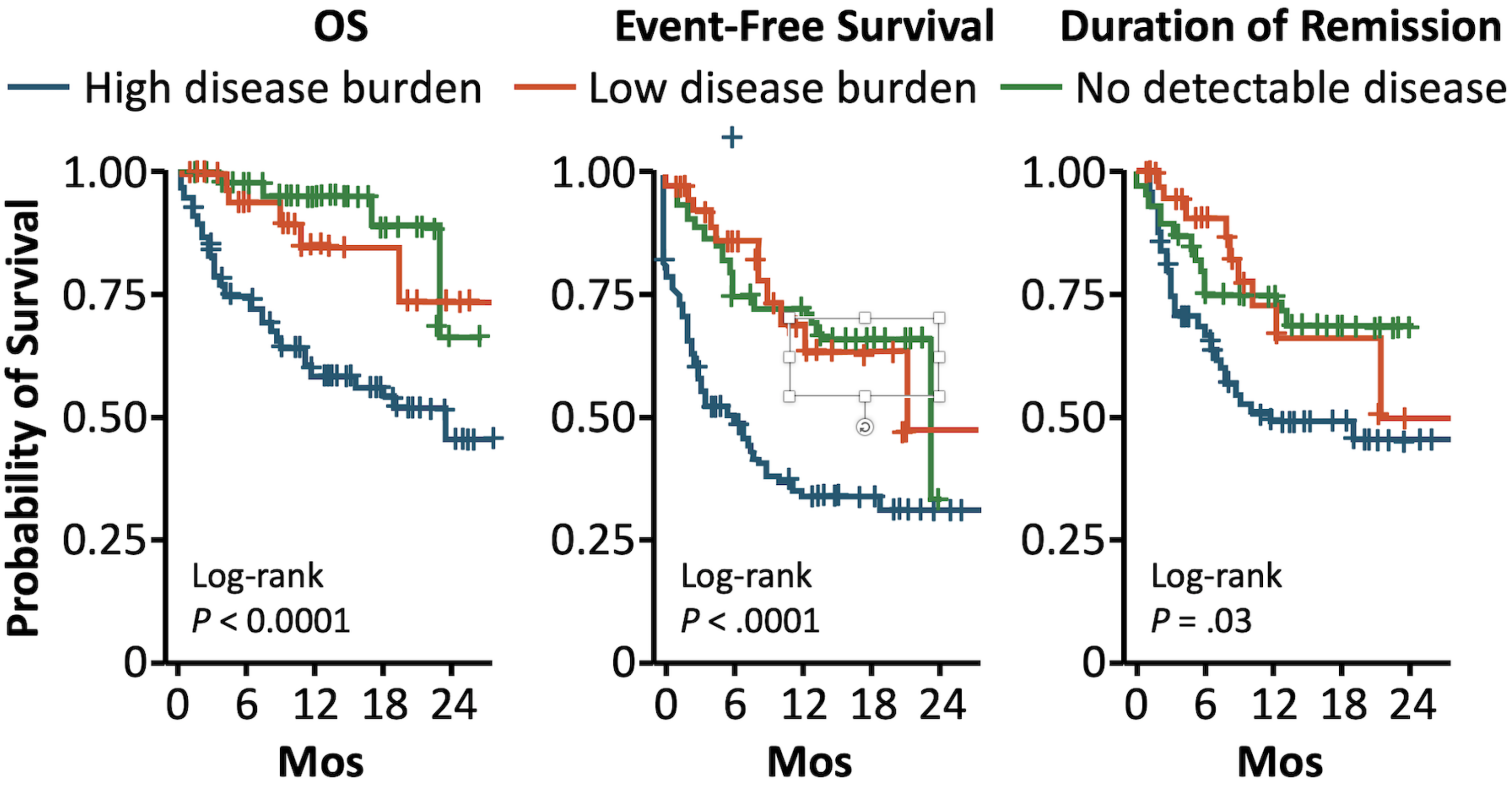


| | N (infused) | CR / CR i (%) | 12 mo EFS (%) | 12mo OS (%) | 12mo DOR (%) | CD19- Relapse rate |
|---|---|---|---|---|---|---|
| ELIANA | 79 | **82**<br>*64/65 MRD-* | **57** | **77** | **67** | **14/19**<br>**74%** |
| CIBMTR | 255 | **86**<br>*115/116 MRD-* | **52.4** | **77** | **61** | |
| PRWCC | 185 | **85**<br>**79 (ITT)** | **51** | **72** | **63** | **22/52**<br>**42%** |
| UK | 60 | **95**<br>*36/39 MRD-*<br>**85 (ITT)** | **68**<br>**61 (ITT)** | **86**<br>**78 (ITT)** | | **4/10**<br>**40%** |

*CIBMTR: Center for International Blood & Marrow Transplant Research*

*Pediatric Real World CAR T Consortium (PRWCC)*

# *Real world :* Tisagenlecleucel el LAL pediátrica



*Pediatric Real World CAR Consortium* (PRWCC)

Schultz, ASH 2020. Abstr. 468

# Identificación y manejo de las toxicidades de las CAR-T

# ELIANA: efectos adversos

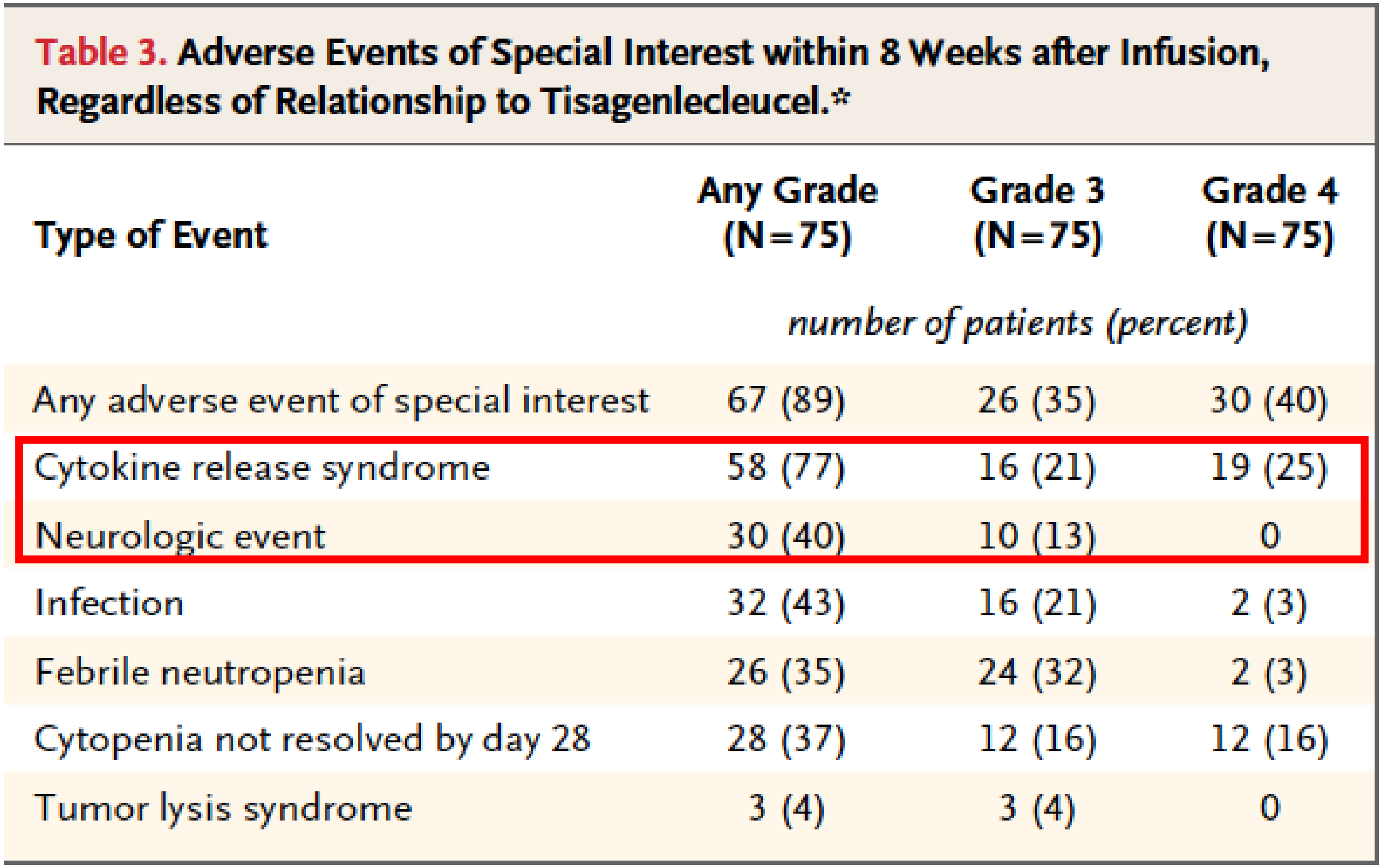
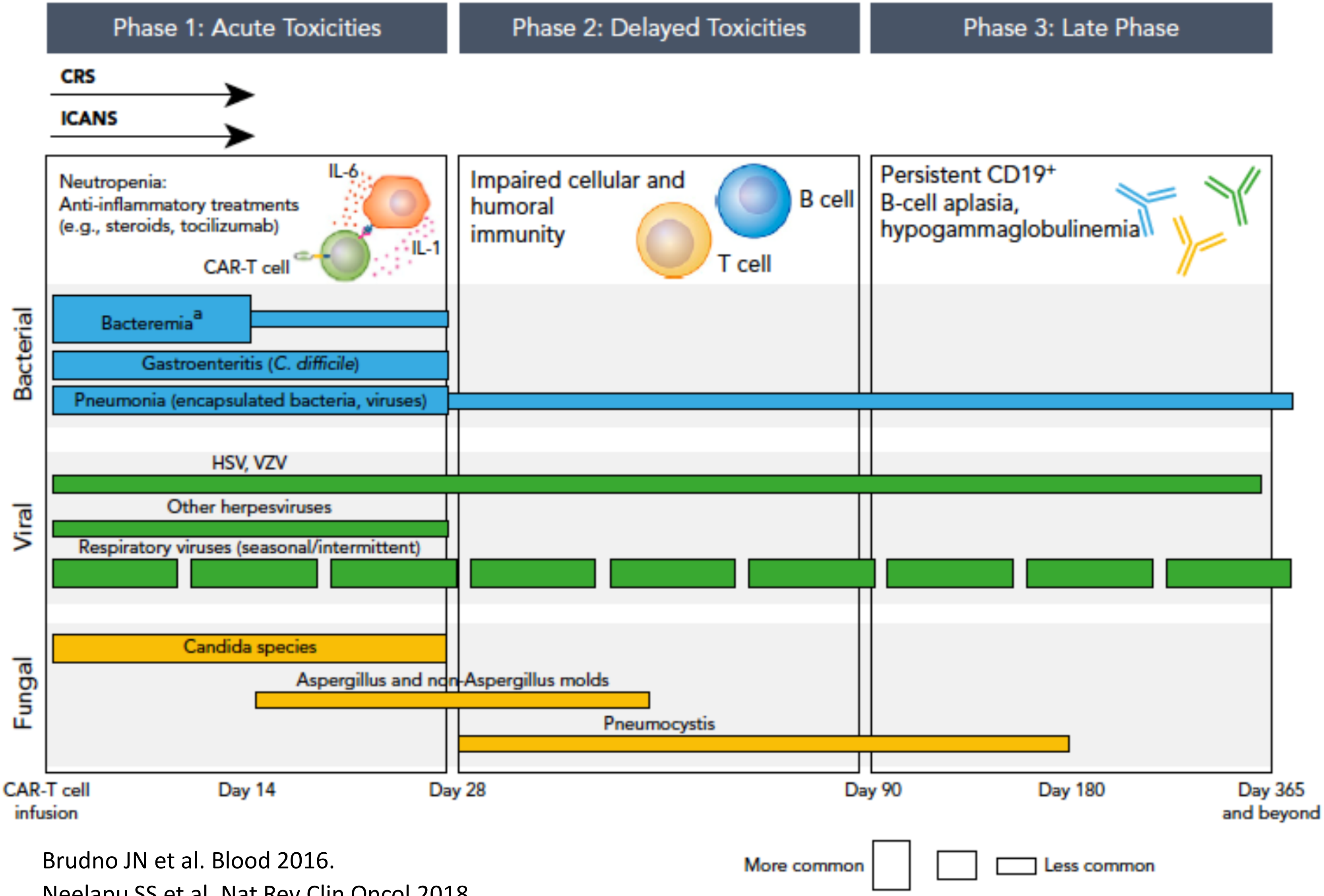


**Table 3. Adverse Events of Special Interest within 8 Weeks after Infusion, Regardless of Relationship to Tisagenlecleucel.***

| Type of Event | Any Grade (N=75) | Grade 3 (N=75) | Grade 4 (N=75) |
|---|---|---|---|
| | *number of patients (percent)* | | |
| Any adverse event of special interest | 67 (89) | 26 (35) | 30 (40) |
| Cytokine release syndrome | 58 (77) | 16 (21) | 19 (25) |
| Neurologic event | 30 (40) | 10 (13) | 0 |
| Infection | 32 (43) | 16 (21) | 2 (3) |
| Febrile neutropenia | 26 (35) | 24 (32) | 2 (3) |
| Cytopenia not resolved by day 28 | 28 (37) | 12 (16) | 12 (16) |
| Tumor lysis syndrome | 3 (4) | 3 (4) | 0 |

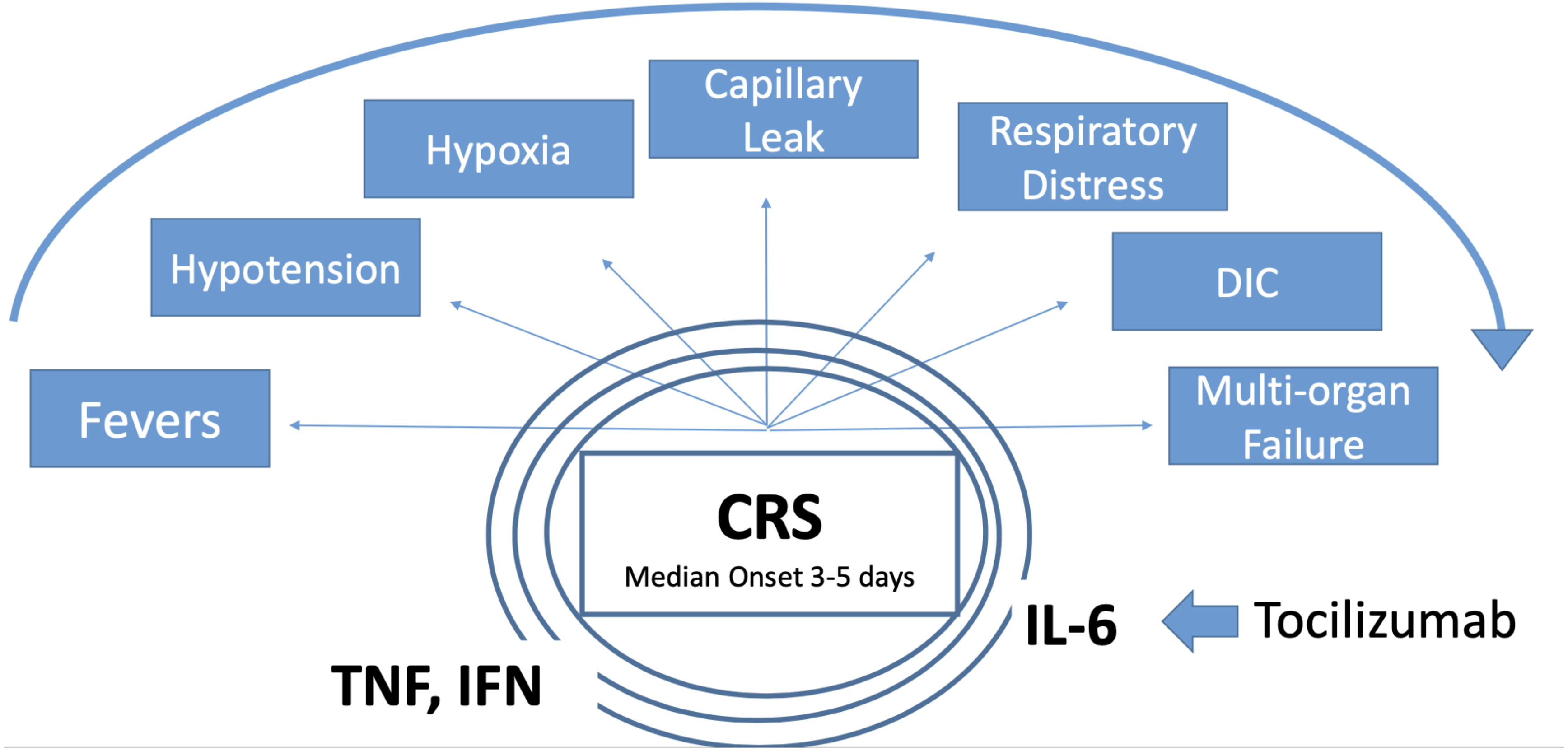
# Efectos adversos de las CAR T


Phase 1: Acute Toxicities
Phase 2: Delayed Toxicities
Phase 3: Late Phase
CRS
ICANS
Neutropenia:
Anti-inflammatory treatments
(e.g., steroids, tocilizumab)
IL-6
IL-1
CAR-T cell
Impaired cellular and humoral immunity
B cell
T cell
Persistent CD19+
B-cell aplasia,
hypogammaglobulinemia
Bacterial
Bacteremia[a]
Gastroenteritis (C. difficile)
Pneumonia (encapsulated bacteria, viruses)
Viral
HSV, VZV
Other herpesviruses
Respiratory viruses (seasonal/intermittent)
Fungal
Candida species
Aspergillus and non-Aspergillus molds
Pneumocystis
CAR-T cell infusion
Day 14
Day 28
Day 90
Day 180
Day 365 and beyond
More common
Less common

Brudno JN et al. Blood 2016.

Neelapu SS et al. Nat Rev Clin Oncol 2018

# Síndrome de liberación de citoquinas (SLC)



Hypoxia

Capillary Leak

Respiratory Distress

Hypotension

DIC

Fevers

Multi-organ Failure

**CRS**

Median Onset 3-5 days

**IL-6**

Tocilizumab

**TNF, IFN**

# Gradación del SLC (ASTCT)

| **Parameter** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
|---|---|---|---|---|
| Fever | Temp ≥ 38°C | Temp ≥ 38°C | Temp ≥ 38°C | Temp ≥ 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, facemask, nonrebreather mask, or Venturi mask | Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation) |

- Objetivo: prevenir daño orgánico
- Evitar retraso en soporte, peores resultados: considerar paso a UCI con un grado 2
- Manejo hipotensión: fluidos IV, uso de vasopresores
- Uso de fármacos anti interleuquina, no reducen la respuesta antitumoral

Lee DW et al . Biol Blood Marrow Transplant. 2019

# Inhibición de las interleuquinas

| | Tocilizumab | Siltuximab | Anakinra |
|---|---|---|---|
| **Description** | Humanized IL-6 receptor antagonist | Chimeric anti-IL-6 | Recombinant human IL-1 receptor antagonist |
| **Mechanism of Action** | Inhibits IL-6 mediated signaling by binding to both soluble & membrane bound human **IL-6 receptors** | **Binds to human IL-6** preventing an interaction with both soluble & membrane bound IL-6 receptors | Competitive antagonist of the IL-1 receptor, regulates actions of IL-1 by prevention of signal transduction |
| **Dose** | < 30 kg: 12 mg/kg<br>≥30 kg: 8 mg/kg<br>Max dose of 800 mg<br>Every 8 hours, max 4 doses total | 11 mg/kg | *Under investigation* |
| **Administration** | IV over one hour<br>No premedication needed | IV over one hour | *Under investigation* |

Neelapu SS et al Nat Rev Clin Oncol. 2018

# ICANS (*immune effector cell asssociated neurotoxicity syndrome*)

- Disminución atención, alteración lenguaje, confusión, desorientación, temblores, convulsiones y encefalopatía.
- Fisiopatología no del todo establecido, síndrome de fuga capilar y disrupción de BHE, otras causas.
- Inicio 4-6 días, y duración 14-17 días, +/-SLC.
- Autolimitante y la mayoría de pacientes recuperan sin secuelas neurológicas a largo plazo.
- Profilaxis con levetiracetam .

# ICANS (Immune efectos cell-associated neurotoxicity syndrome)

| 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 nonconvulsive seizures on EEG that resolve with intervention | Life-threatening prolonged seizure (> 5 mins) or 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; or cranial nerve VI palsy; or papilledema; or Cushing's triad |

Lee DW et al. Biol Blod Marrow Transplant 2019

# Recaída post infusión CAR T

# Recaída post infusión CAR T

- Recaída CD19+ (tempranas), falta de persistencia de los CAR-T
  - Dominio co-estimulador : 4 -1BB > CD 28
  - Rechazo inmunomediado (componente murino)
    - CAR T humanizados
  - Agotamiento de la célula T
  - Producción: pacientes intensamente tratados
    - Avanzar la aféresis a una etapa más temprana
    - Mejora de las técnicas ex vivo

# Recaída post infusión CAR T

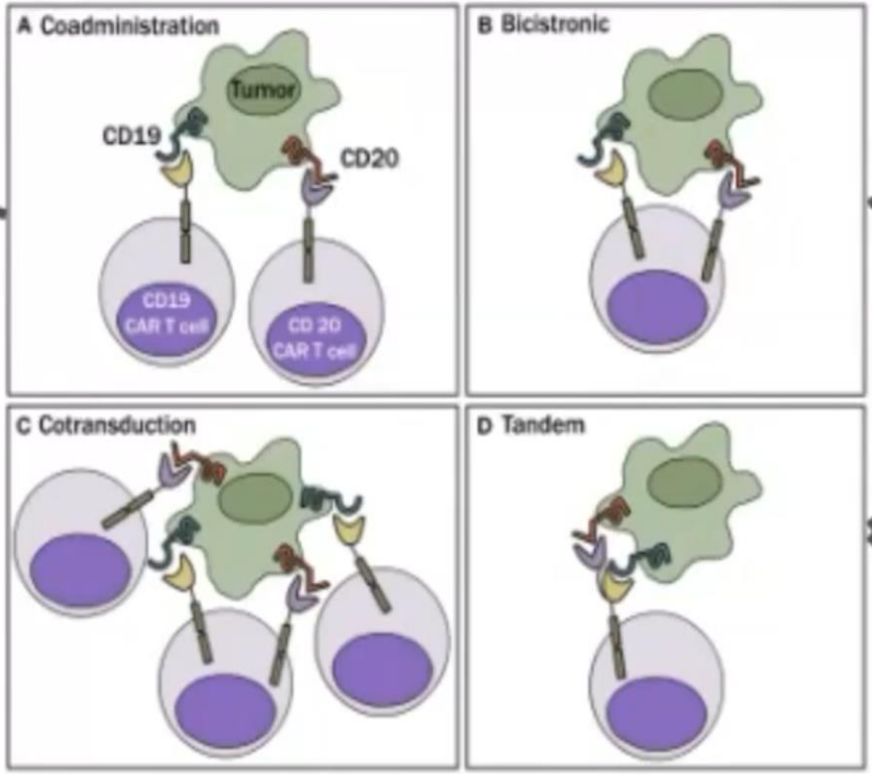
- Recaída CD19 -, pérdida del antígeno diana durante la aplasia de linfos B:
  - Mutaciones en los exones 2-5 de CD19
  - Tráfico inefectivo de CD19 de membrana
  - Previa tratamiento con blinatumomab o inotuzumab ozogamicina ¿?
    - Múltiple o bispecifico CAR T (eg CD19/22)

# CAR T duales

CD19/CD22 Cocktail
(Wang, N et al Blood 2019)
51 infused – 96% CR
PFS 13.6 months

**Short In Vivo persistence of CAR T cells**

24 relapses
1 CD19-CD22dim
23 CD19+CD22+


A Coadministration
Tumor
CD19
CD20
CD19 CAR T cell
CD 20 CAR T cell
B Bicistronic
C Cotransduction
D Tandem

Nirav Shah et al, Front in Onc 2018

AUTO3 - Great Ormond Street
(Amrolia PJ, et al. ASH 2019)

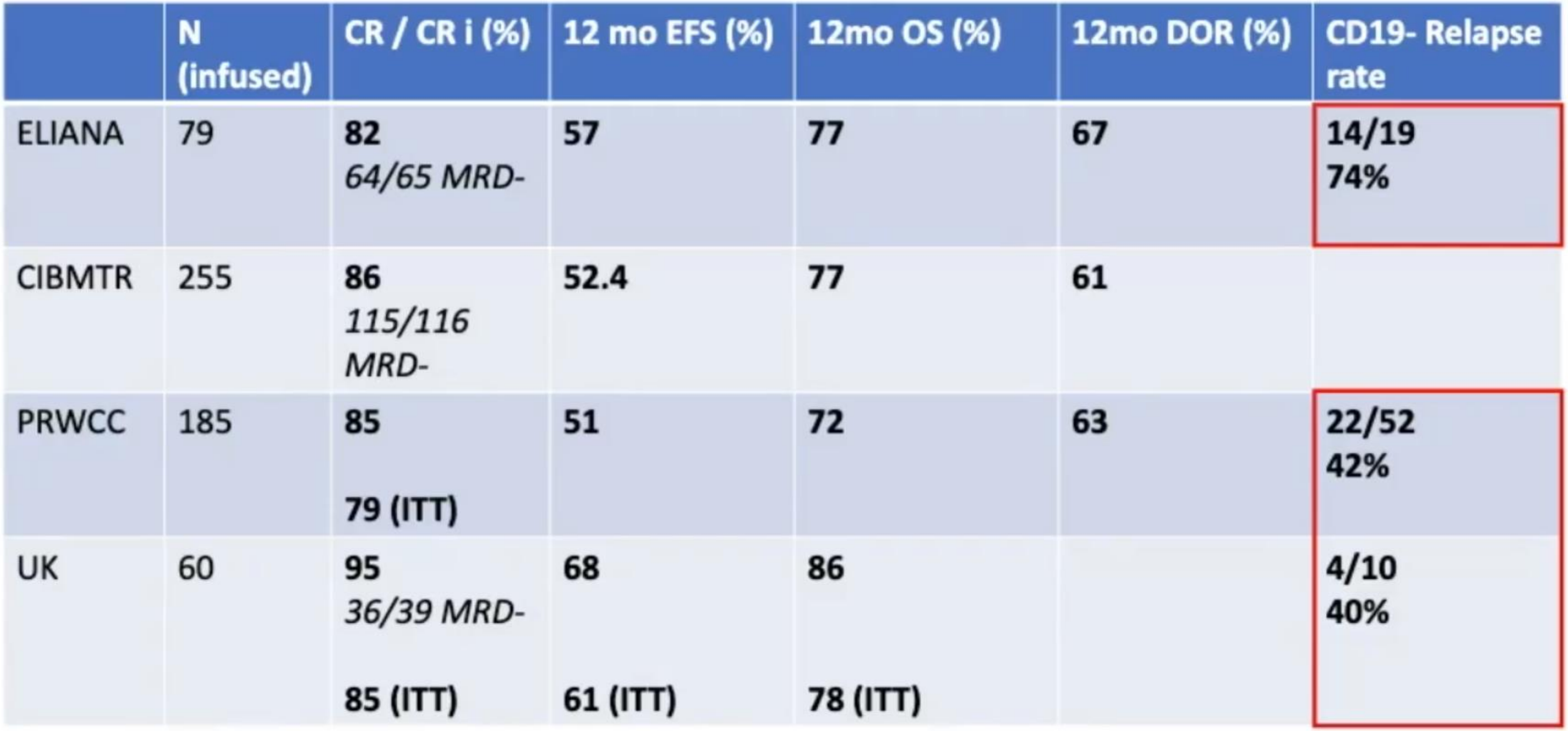
7/7 MRD neg CR

**Short persistence is seen**
CD19+antigen relapse seen

Stanford
(Schultz L et al. ASH2019)
92% MRD negative CR
**Short persistence is seen**
CD19+ relapses

Beijing
(Dai, H et al. J Hem Onc 2020)
6/6 MRD negative CR
5/6 **lost persistence** prior to 6 months

# ELIANA: Tisagenlecleucel en LAL-B niños, adolescentes y adultos jóvenes recaída o refractaria



| | **N (infused)** | **CR / CR i (%)** | **12 mo EFS (%)** | **12mo OS (%)** | **12mo DOR (%)** | **CD19- Relapse rate** |
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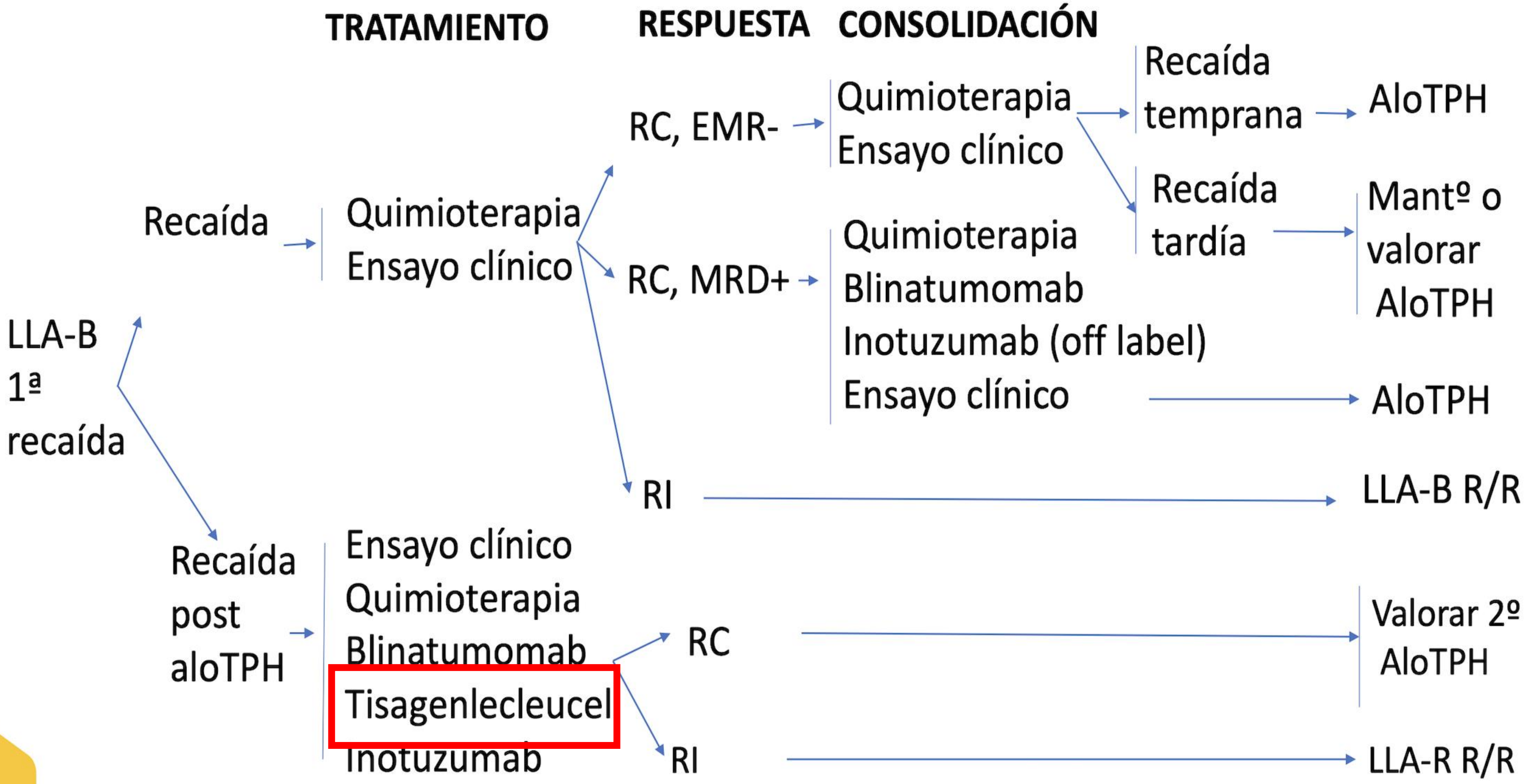
| CIBMTR | 255 | **86**<br>*115/116 MRD-* | **52.4** | **77** | **61** | |
| PRWCC | 185 | **85**<br>**79 (ITT)** | **51** | **72** | **63** | **22/52**<br>**42%** |
| UK | 60 | **95**<br>*36/39 MRD-*<br>**85 (ITT)** | **68**<br>**61 (ITT)** | **86**<br>**78 (ITT)** | | **4/10**<br>**40%** |

- La mayoría (73,7%) son CD19- que ocurren en contexto de persistencia de aplasia linfos B.

# Algoritmo de tratamiento LAL B primera recaída



**TRATAMIENTO** **RESPUESTA** **CONSOLIDACIÓN**

LLA-B 1ª recaída

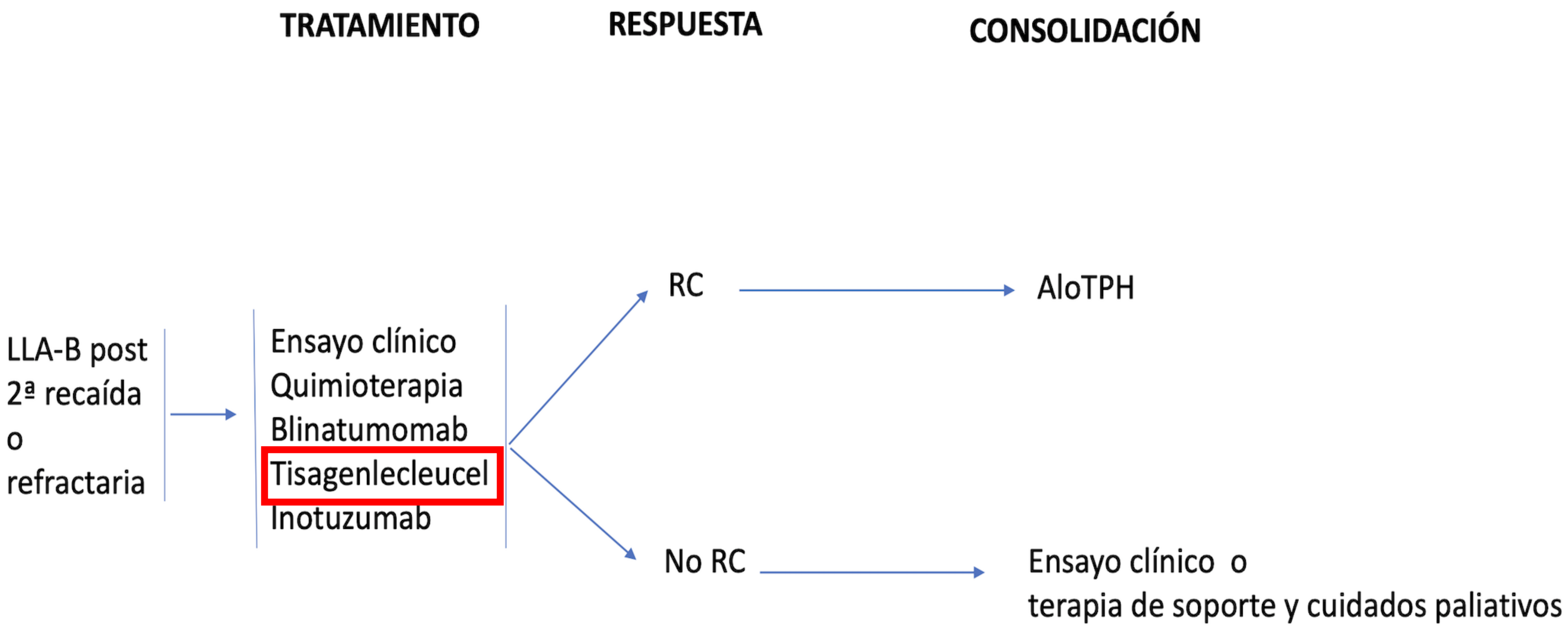
Recaída → Quimioterapia, Ensayo clínico

- RC, EMR- → Quimioterapia, Ensayo clínico
  - Recaída temprana → AloTPH
  - Recaída tardía → Mantº o valorar AloTPH
- RC, MRD+ → Quimioterapia, Blinatumomab, Inotuzumab (off label), Ensayo clínico → AloTPH
- RI → LLA-B R/R

Recaída post aloTPH → Ensayo clínico, Quimioterapia, Blinatumomab, Tisagenlecleucel, Inotuzumab

- RC → Valorar 2º AloTPH
- RI → LLA-R R/R

# Algoritmo de tratamiento LAL B
# 2ª recaída o refractaria



**TRATAMIENTO** | **RESPUESTA** | **CONSOLIDACIÓN**

LLA-B post 2ª recaída o refractaria →

Ensayo clínico
Quimioterapia
Blinatumomab
Tisagenlecleucel
Inotuzumab

→ RC → AloTPH

→ No RC → Ensayo clínico o terapia de soporte y cuidados paliativos

# Conclusiones

- La tisagenlecleucel ha demostrado en ensayos clínicos y *real world* inducir remisiones rápidas y duraderas siendo una potencial terapia definitiva en pacientes con remisiones prolongadas.
- Presentan un mecanismo de acción y un perfil de toxicidad únicos que requieren una monitorización estrecha y terapia de soporte agresivo y manejo en centros especializados.
- Es necesario conocer la seguridad y eficacia a largo plazo, y vencer algunos hándicaps como la pérdida del CAR T o vencer los mecanismos de resistencia.

# Gracias

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