Un cambio a la deriva, terapia que redirecciona células

María-Victoria Mateos

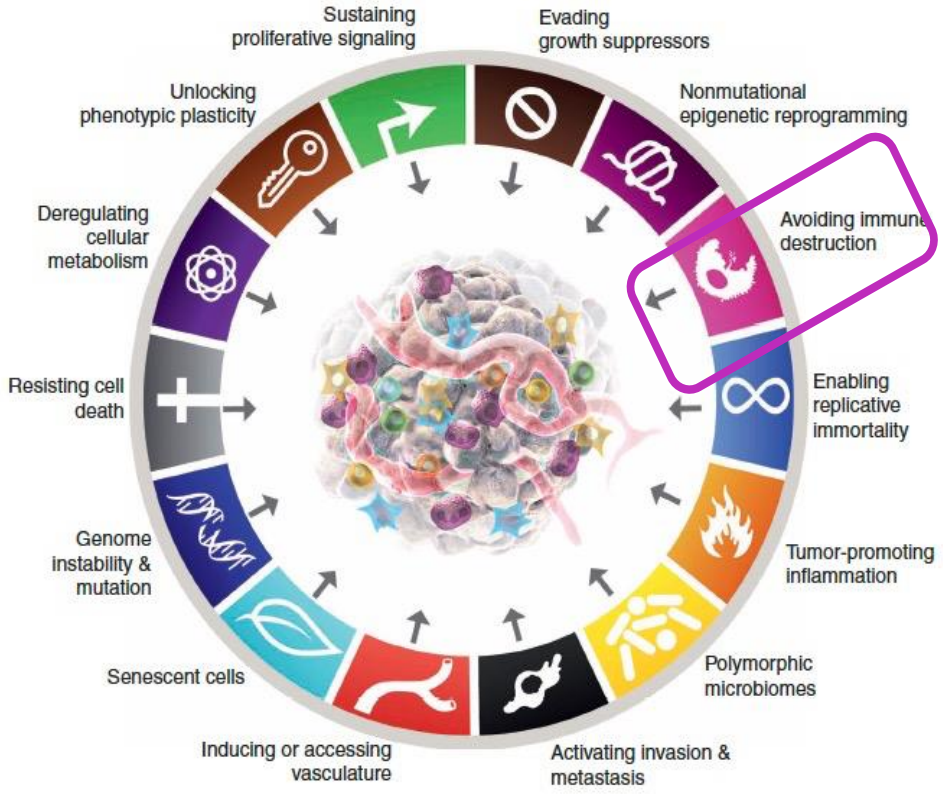
Hospital Universitario de Salamanca

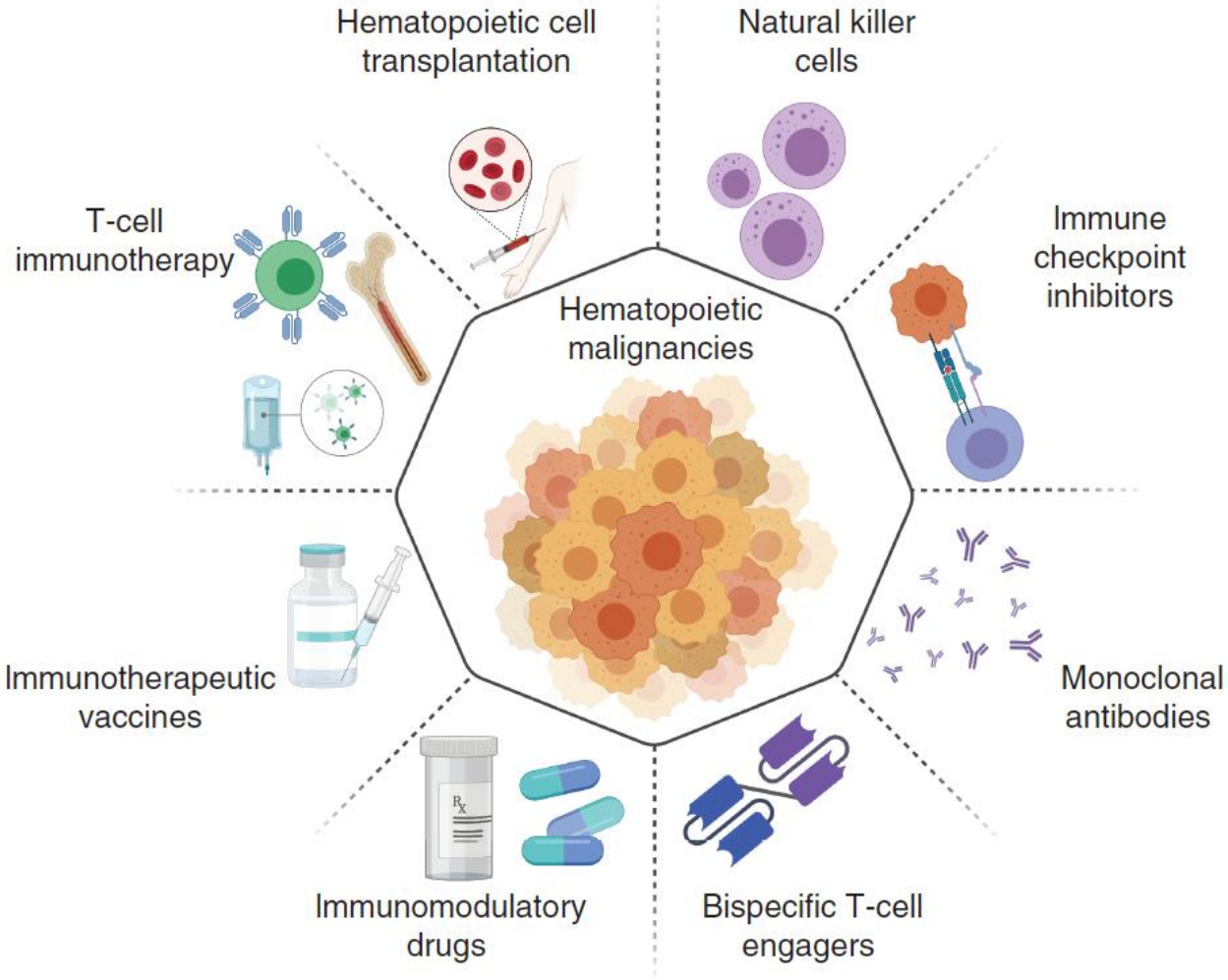
Disclosures

- Honoraria derived from lectures and participation in advisory boards from Janssen, Celgene, Takeda, Amgen, GSK, AbbVie, Pfizer, Regeneron, Roche, Sanofi, Oncopeptides, Seagen

Hallmarks in Cancer

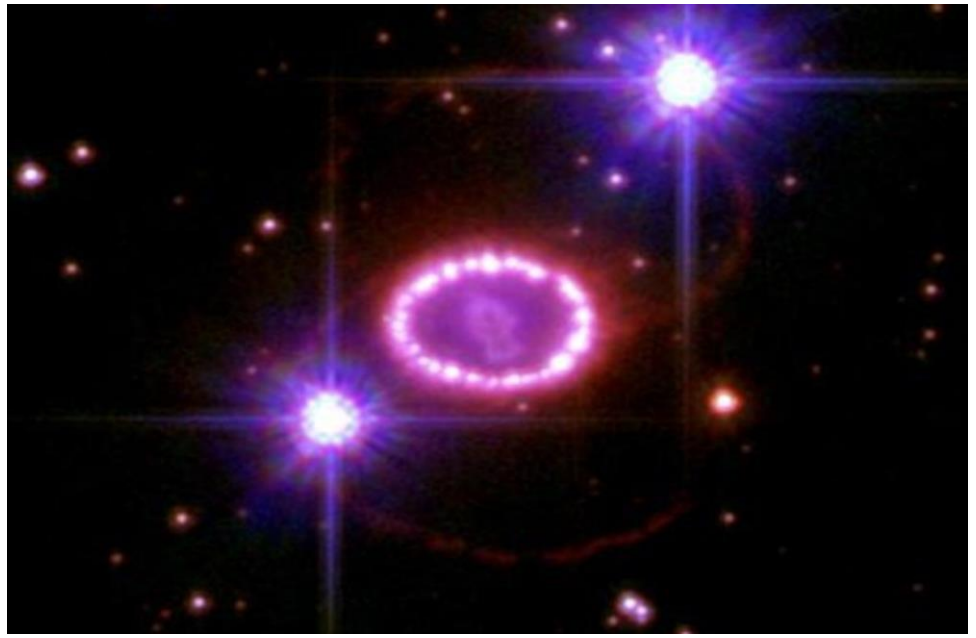
Immunotherapy in hematological cancers





Hablemos de supernovas

Supernova

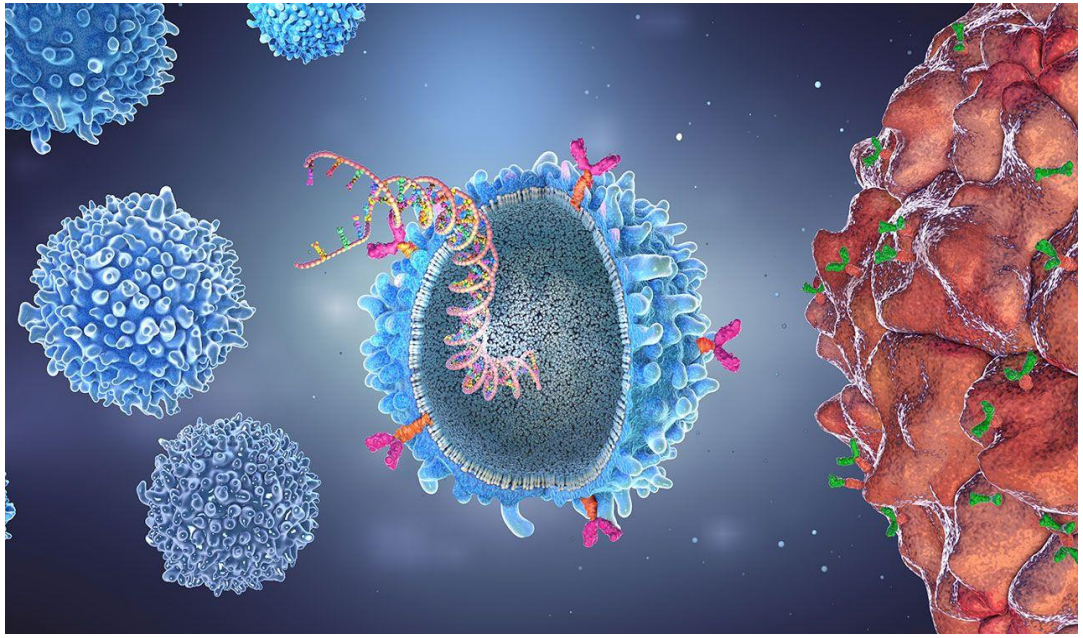


- Una supernova es la explosión de una estrella.
- Generalmente son estrellas muy masivas que expulsan todo el material que está en su interior por medio de una onda choque y esto - llamado un remanente de supernova - se expande, y arrastra el material que encuentra a su paso.

Hablemos de supernovas

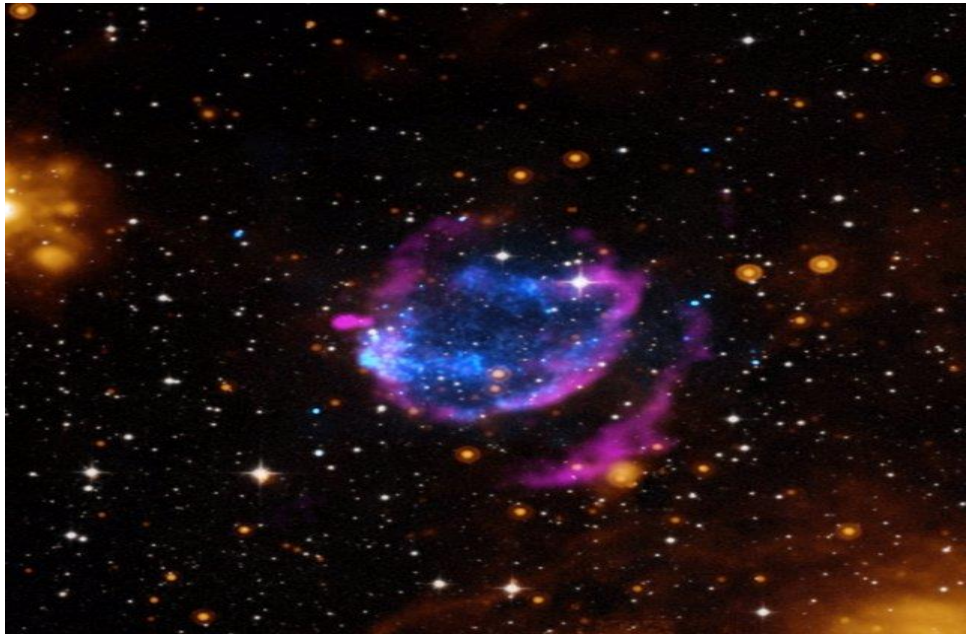
Terapias que modifican células…

CAR-T cells



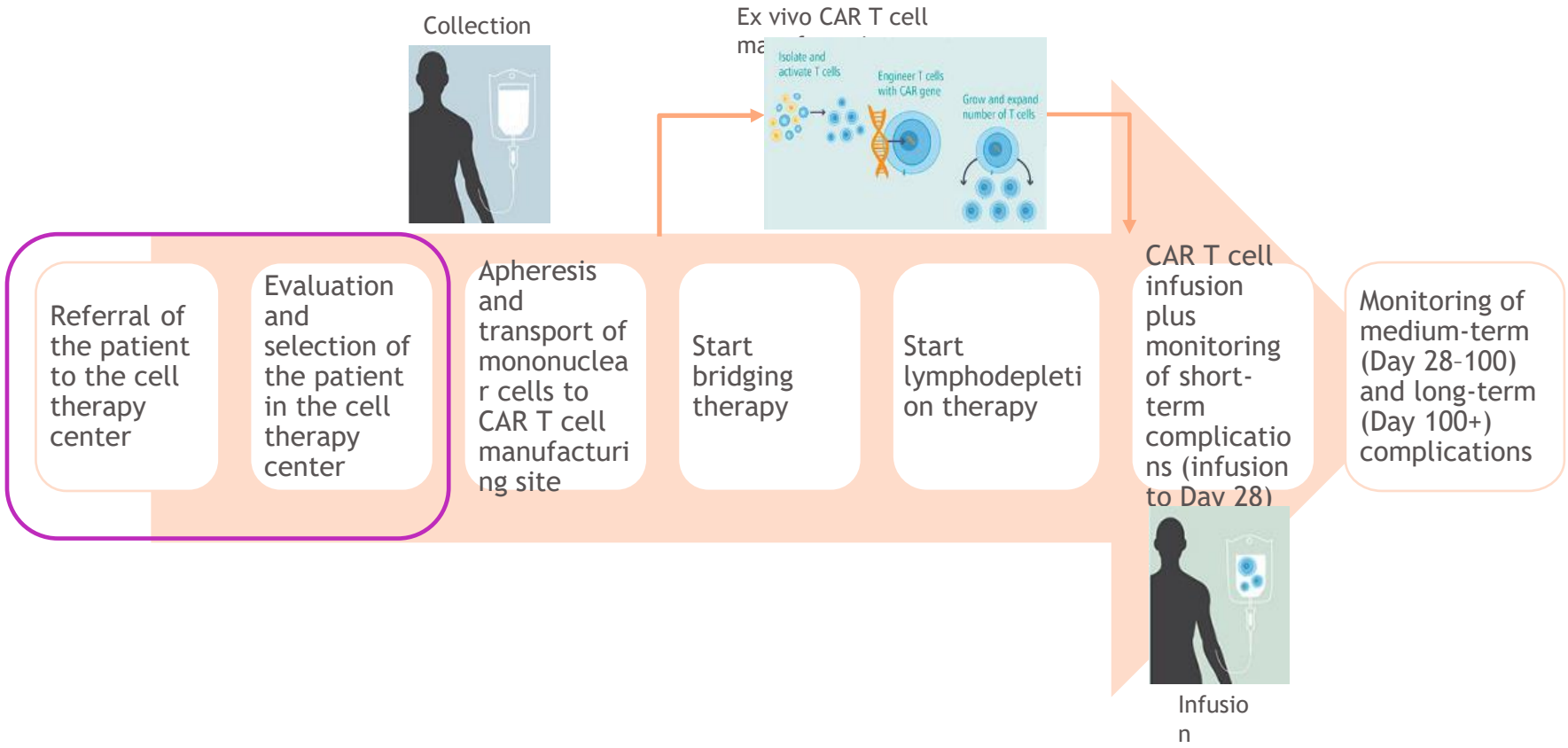
- Estas terapias que modifican células son como las supernova….. Iluminan los Servicios, las consultas… y hasta los ojos de los pacientes… y son efectivas y hasta curan a algunos pero…..

Supernova



- Estas explosiones se producen en promedio dos veces por siglo en la Vía Láctea, aunque es cierto que generan enormes cantidades de energía y son tan brillantes como una galaxia entera.

CAR T cells in haematological cancers:



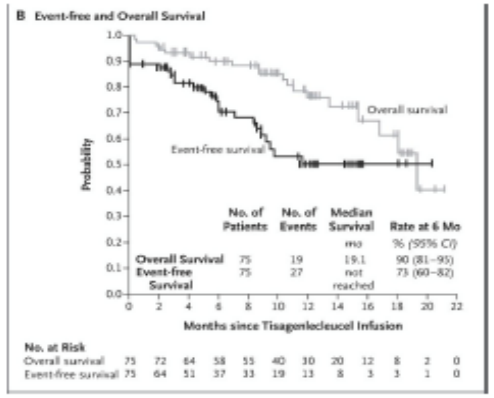
Limitations

- Slot availability
- Cost
- Affordability
- Referal process
- Manufacturing timing
- Being eligible

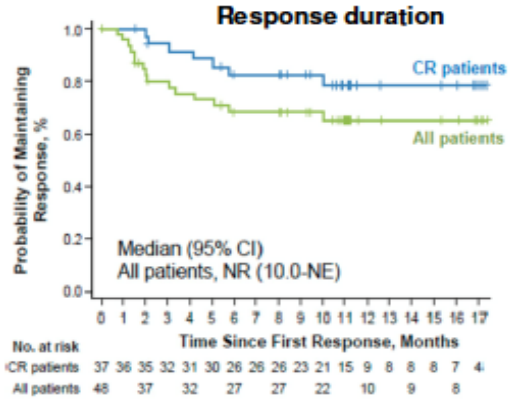
CAR T cells in haematological cancers: efficacy results

- **Comparison to CART-19**

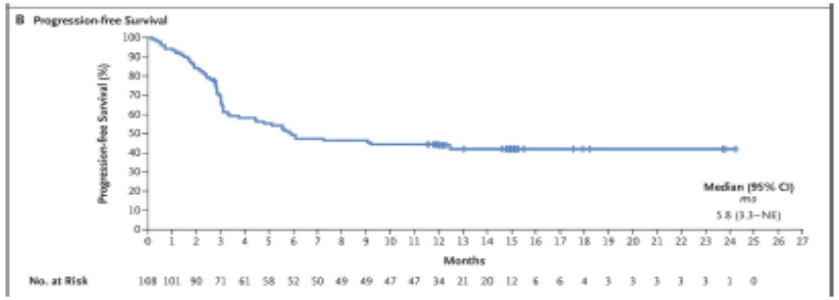
ALL ph2
ELIANA



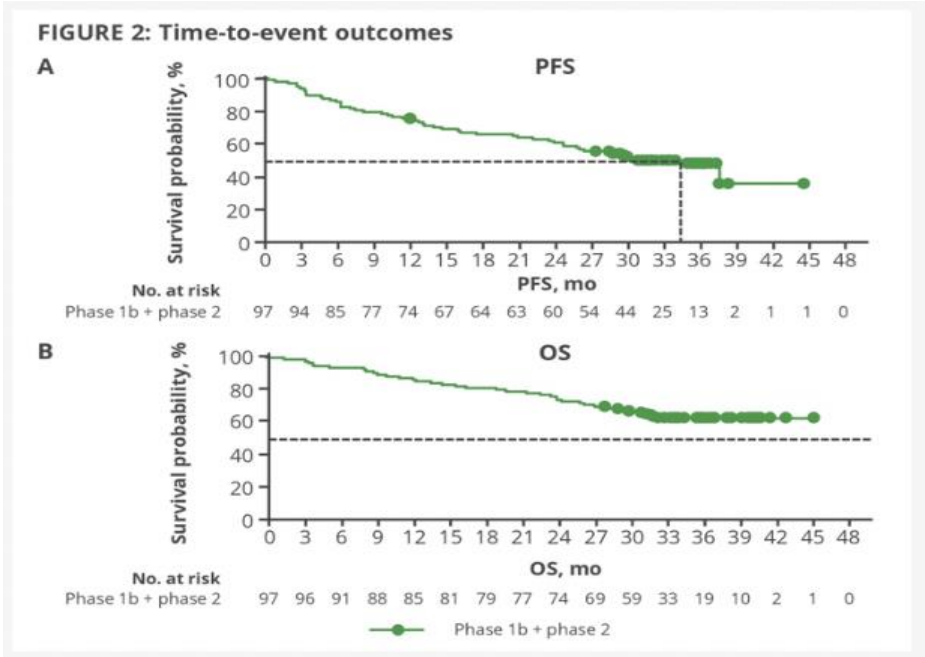
DLBCL ph2
JULIET



DLBCL ph2
ZUMA-1



- CART-BCMA in Myeloma

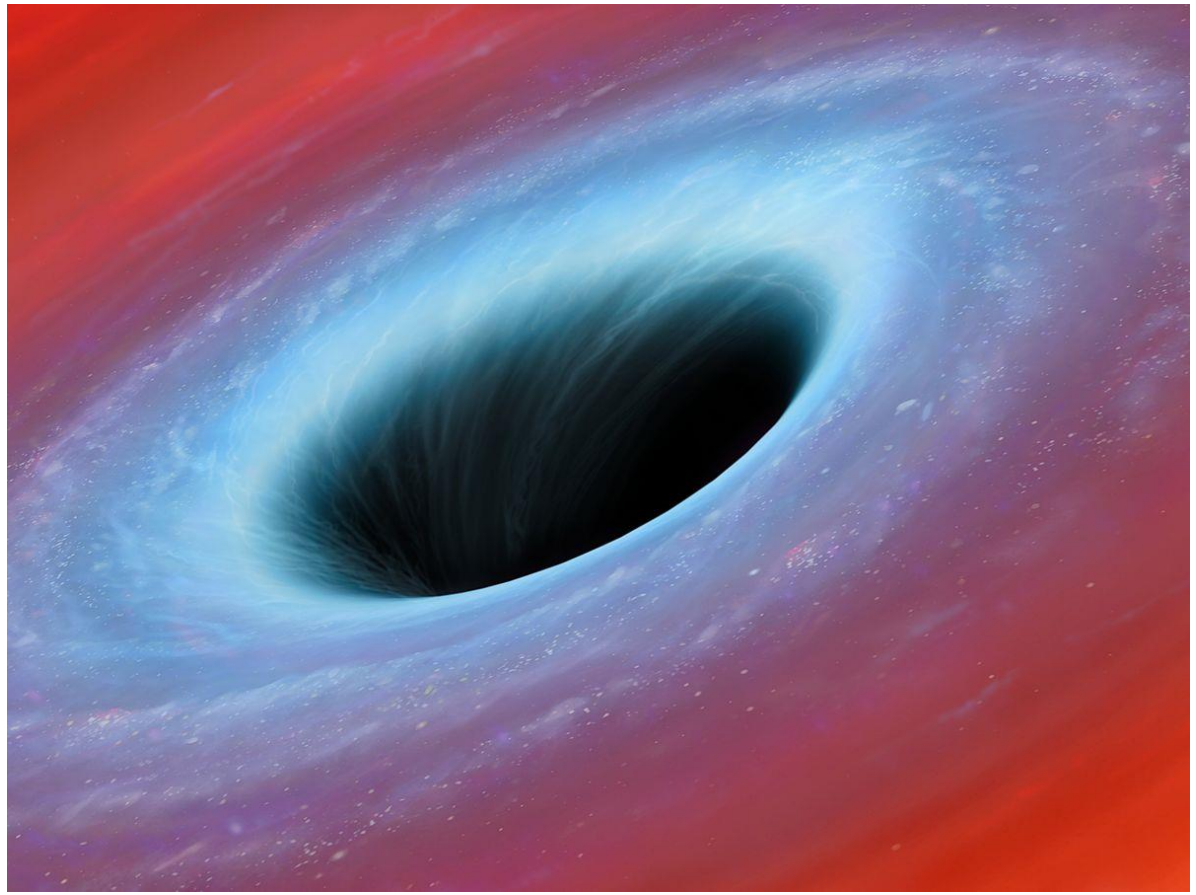


Is CAR-T a curable strategy for all hematological cancers?

Nuestras grandes deudas pendientes

Nuestros agujeros negros

Agujeros negros



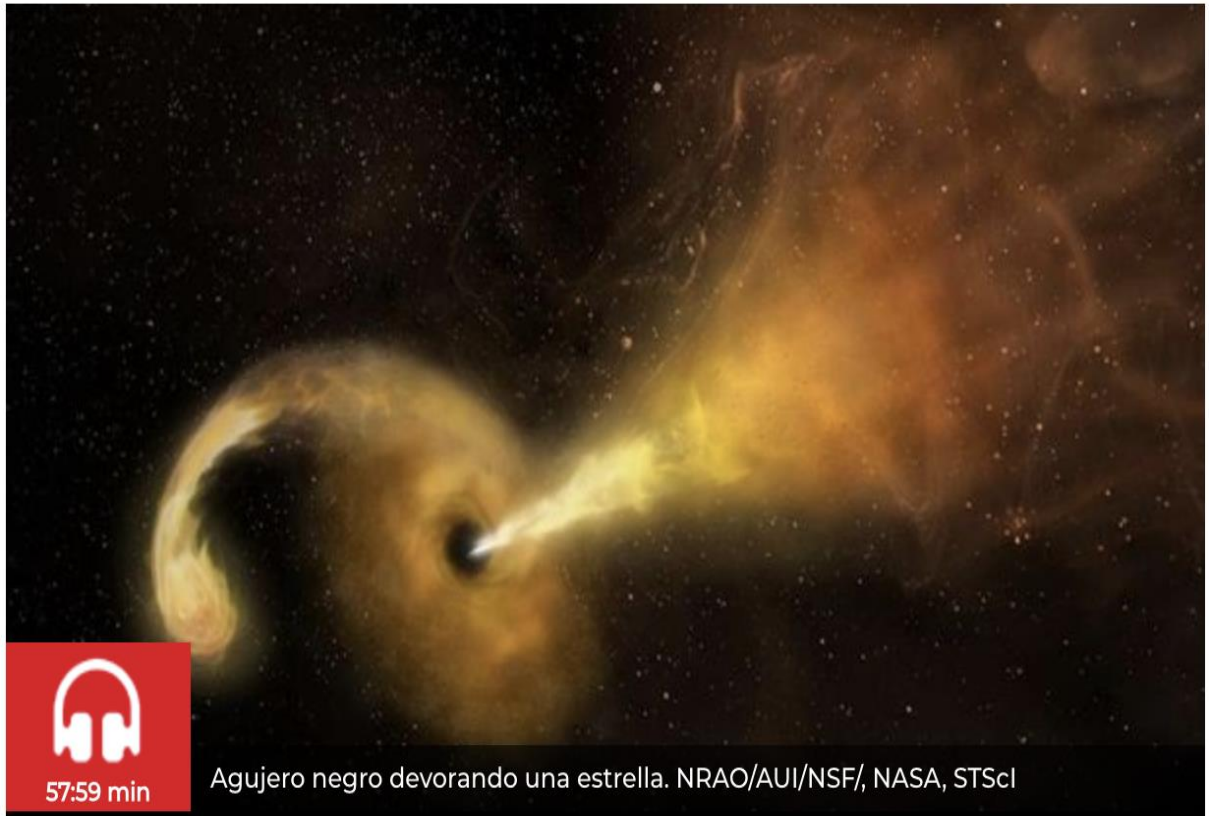
- Aun y a pesar de la eficacia de las supernovas y de su gran iluminación…..
- Los agujeros negros son los restos fríos de antiguas estrellas, tan densas que ninguna partícula material, ni siquiera la luz, es capaz de escapar a su poderosa fuerza gravitatoria.
- Serían nuestros grandes enemigos… porque si caemos en el agujero negro… no salimos…. Pero.. Por qué no aprovechar esto como una gran oportunidad????

Nuestras grandes deudas pendientes

Nuestros agujeros negros

Agujeros negros/Hematological cancers

Investigadores del IAA observaron el primer agujero negro hipermasivo atrapando una estrella. Nobel de Química 2019. Mujeres e investigación del cáncer. Luz de sincrotrón para la ataxia de Friedrich.



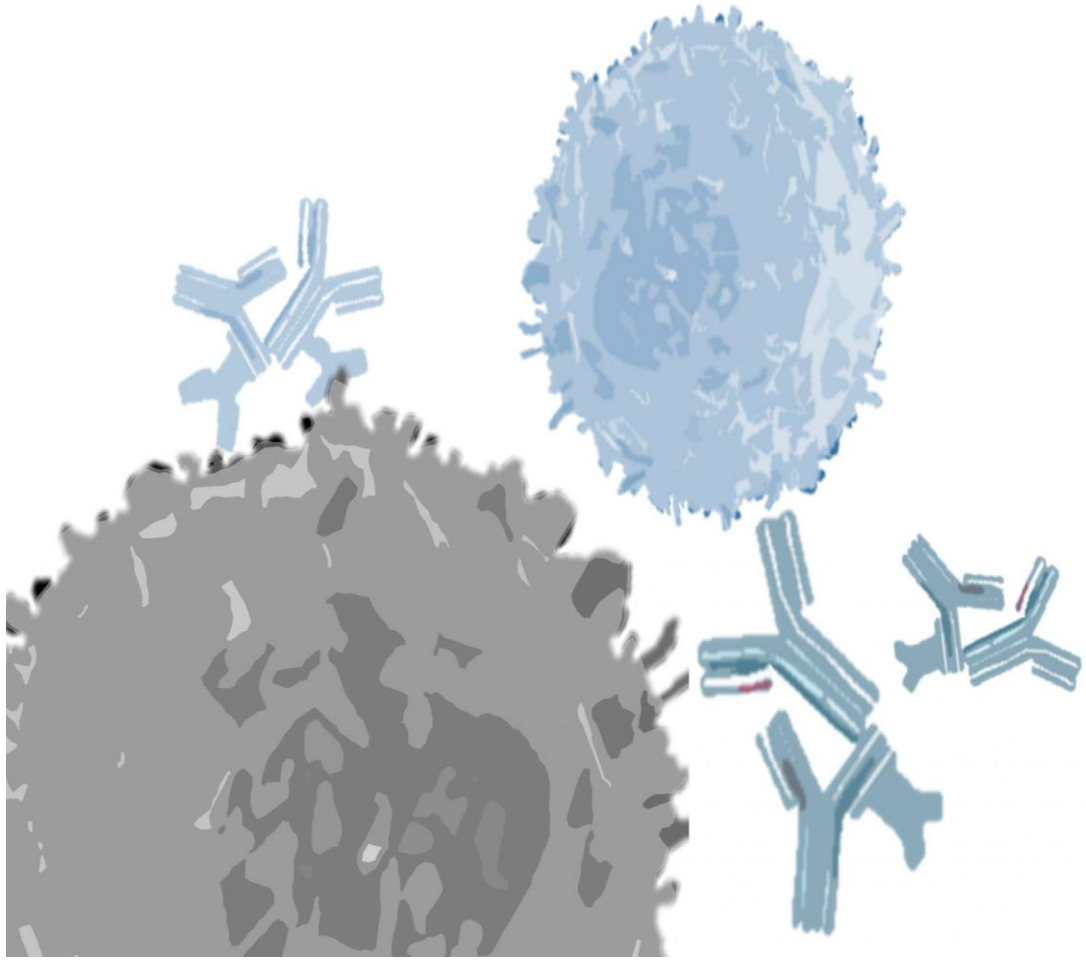
- Vamos a utilizar los agujeros negros como estrategia.
- Vamos a redireccionar los agujeros negros a las células tumorales o las células tumorales a los agujeros negros para que sean destruidos

- Esto es posible???

Terapia que redirecciona células

Anticuerpos monoclonales biespecíficos

Format	Properties
BiTE	• Two scFvs (heavy and light chain variable regions) joined together by a linker • Format allows for short distance between tumor cells and T cells • Short serum half-life due to small size • Potent and can induce specific anti tumoral cytotoxicity at low picomolar concentrations in cell culture[1,2,3] • Examples: blinatumomab, AMG420 (BCMA BiTE)
DART With Fc and without Fc	• Criss-cross format (heavy chain of one arm joined to light chain of second arm) • Short serum half-life that can be lengthened if Fc region present • Examples may target T cells or CD16-bearing effector cells • Potency has been shown to be superior to BiTEs[4] • Examples: MGD006 S80880, MDG011
TandAb	• Molecular weight exceeds the renal clearance threshold, offering a longer half-life than BiTEs or DARTs • Examples may target T cells or CD16-bearing effector cells • Potent with cytotoxicity at low picomolar concentrations *in vitro* • Example: AFM11
Full-length IgG With Fc effector function (Trioma®s) Without Fc effector function	• Full-length IgG confers long half-life • Recruit T cells and Trioma®s also activate monocytes, macrophages, dendritic, and NK cells by binding to the Fc region • Formats have also been developed with Fc region that does not bind Fc receptor (effector null) • Examples: catumaxomab (Trioma®), PF-06863135 (full-length IgG (effector null))
BiKEs TriKEs	• BiKEs are similar in design to BiTEs, but target CD16 on NK cells, rather than T cells • TriKEs incorporate IL-15 sandwiched into the design to drive NK cell expansion *in vivo* • Both formats direct NK cells to tumors to trigger antibody-dependent cell-mediated cytotoxicity • Examples: 1633-BiKE, 161533 TriKE

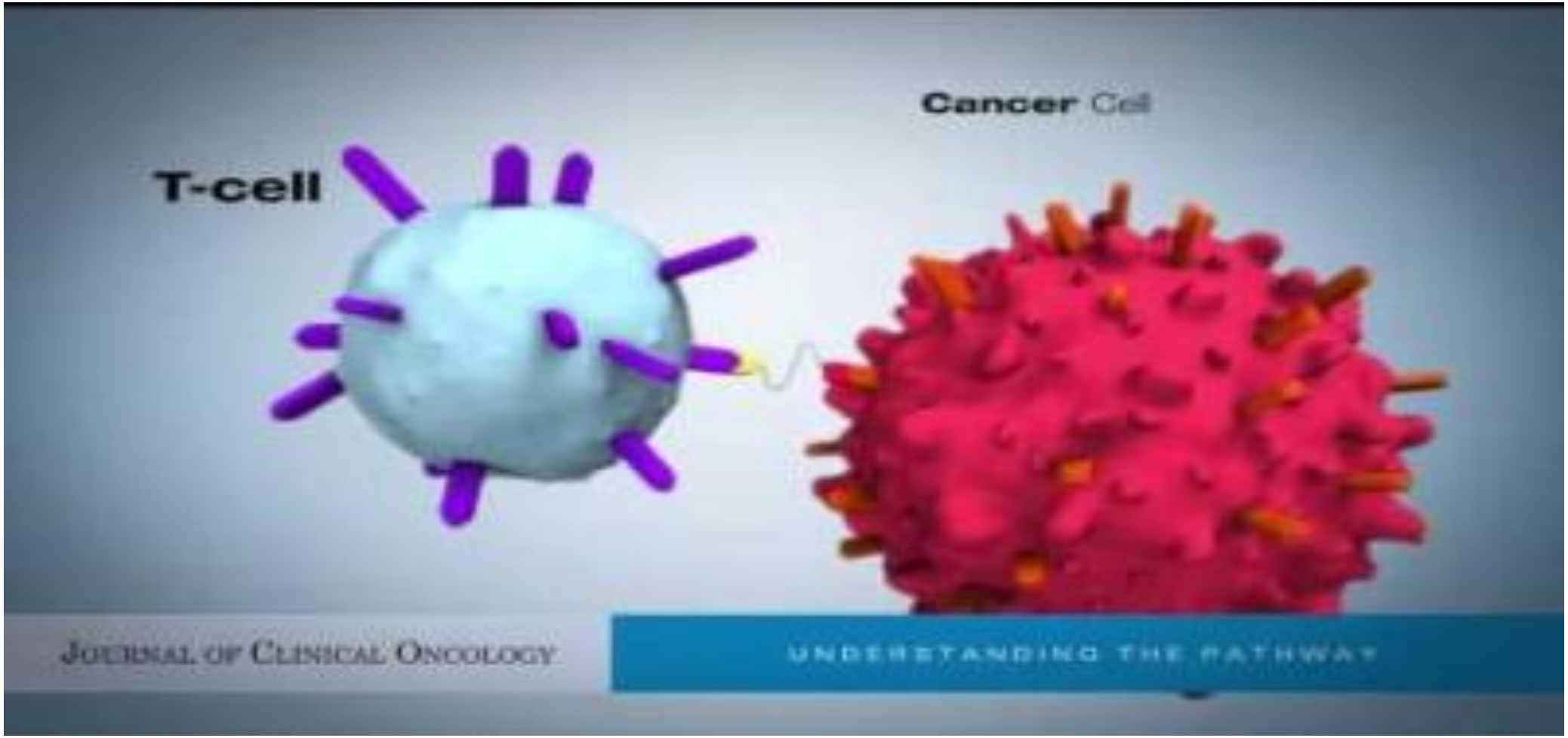


Terapia que redirige células

BiTEs

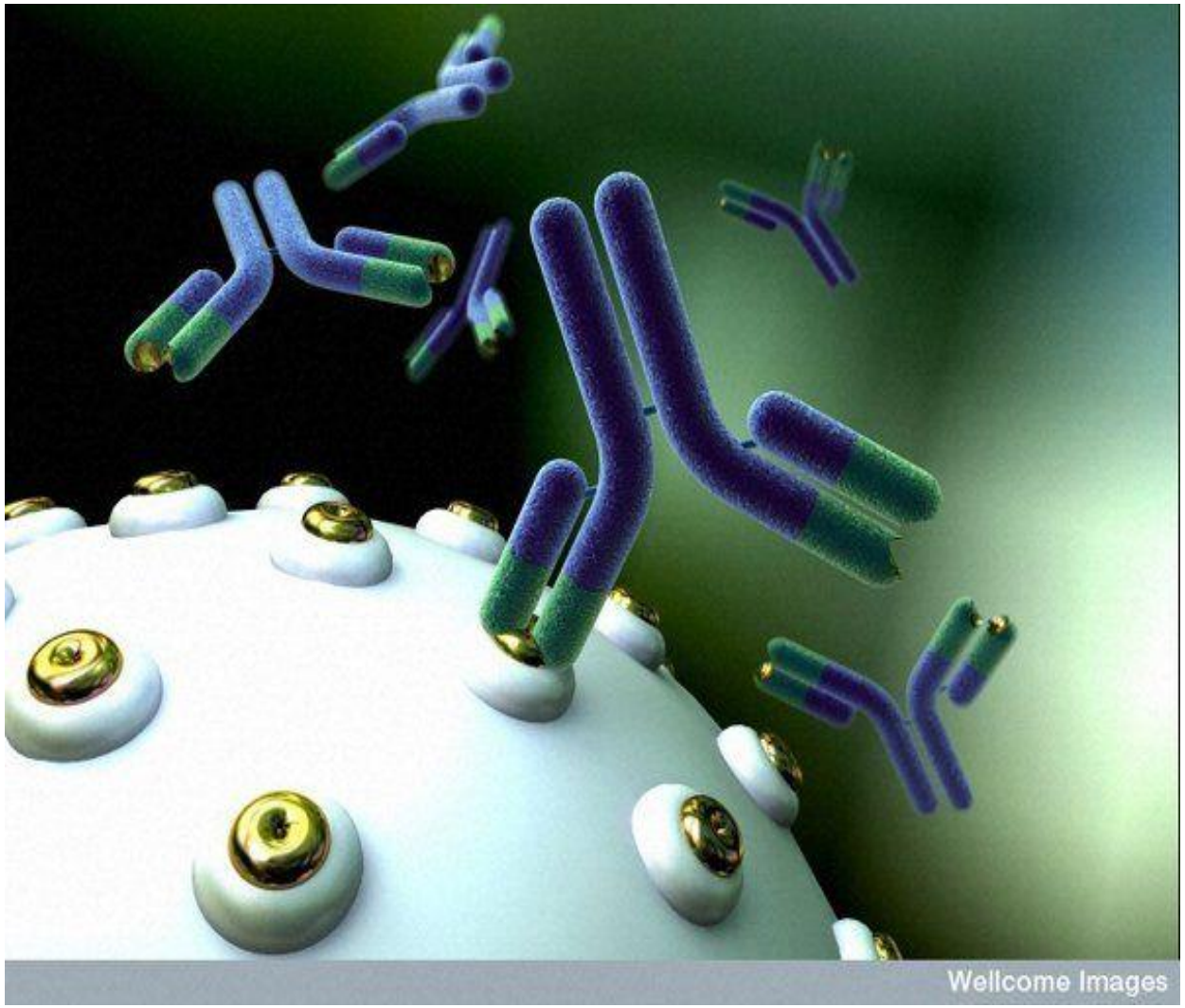
Terapia que redirige células

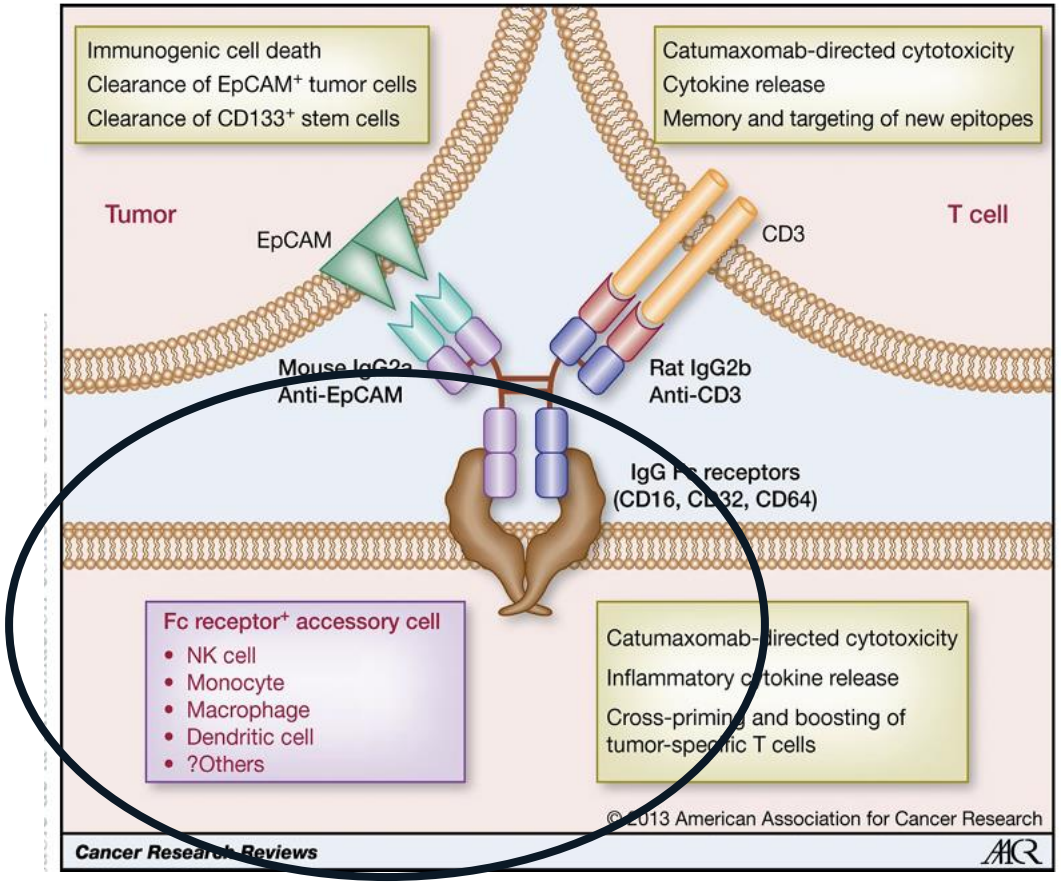
BiTEs



Terapia que redirecciona células

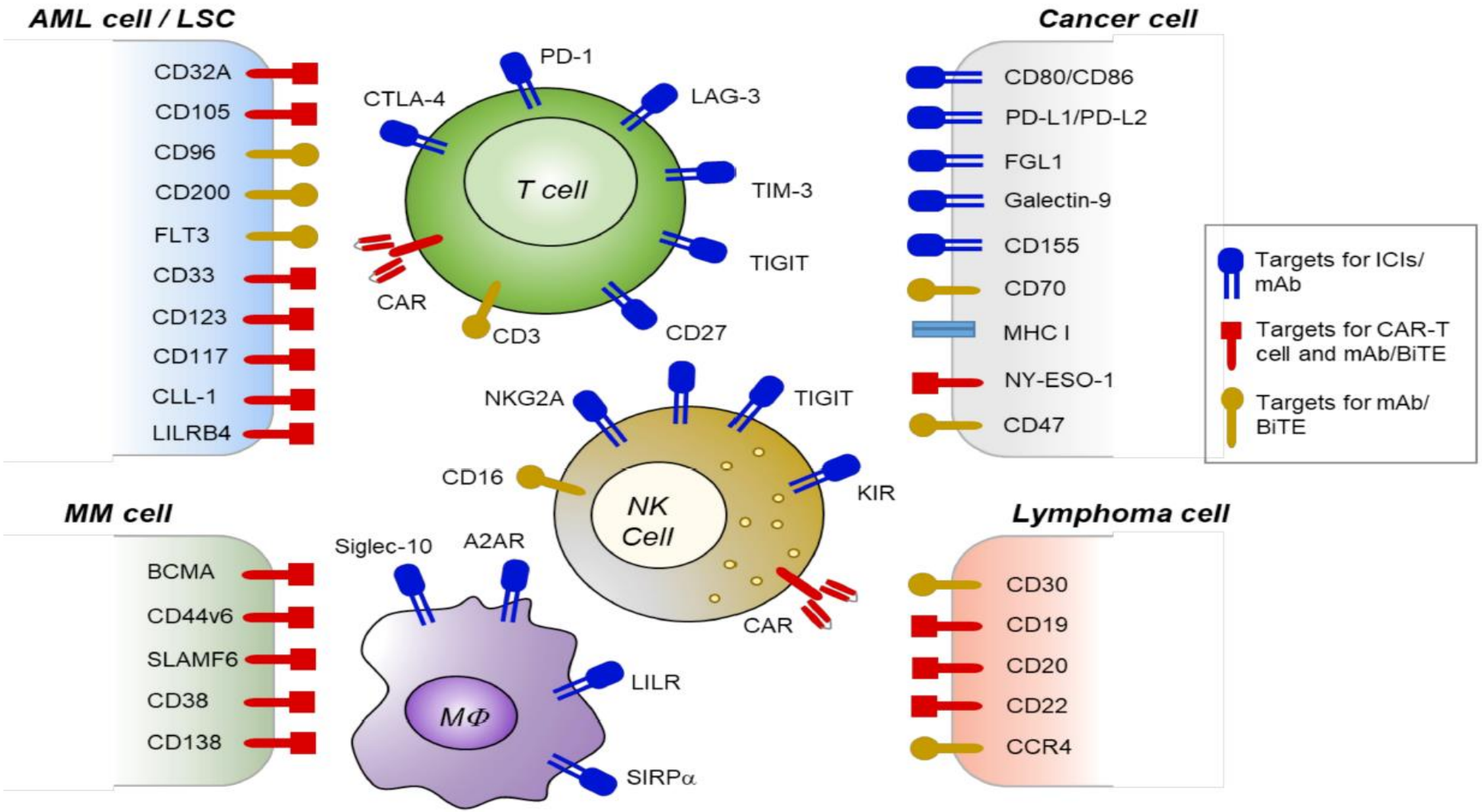
Anticuerpos biespecíficos





Terapia que redirige células

BiTEs y Anticuerpos monoclonales biespecíficos



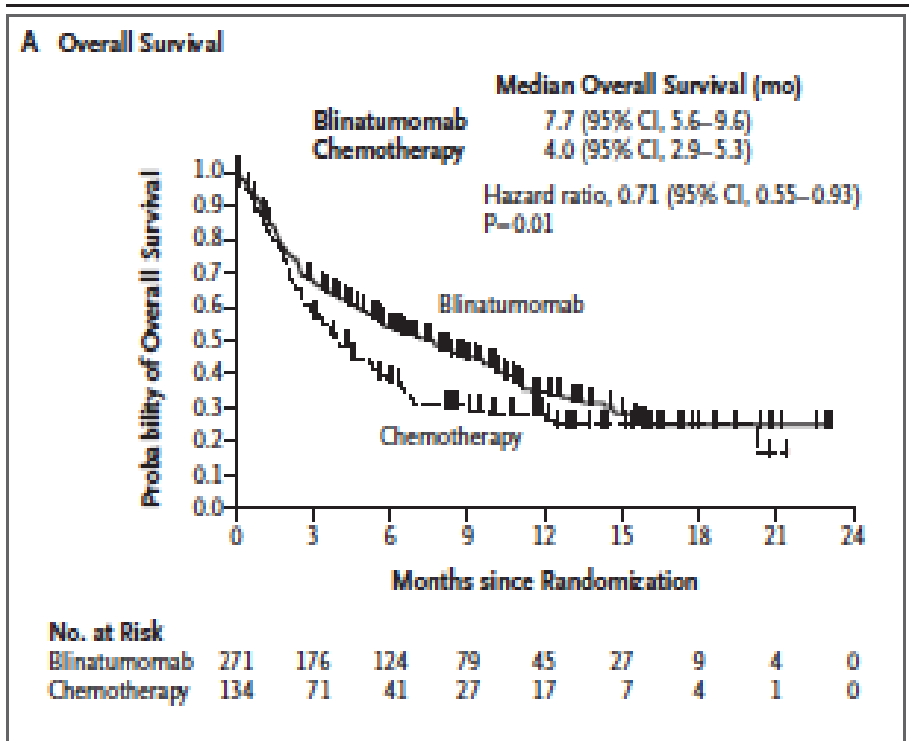
Terapia que redirecciona células

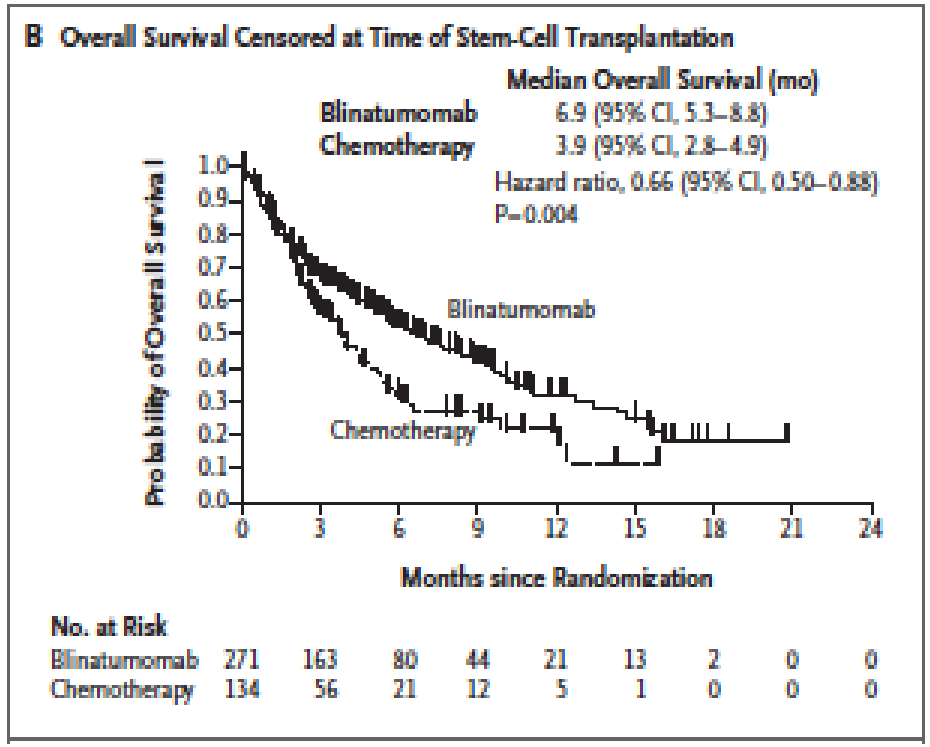
BiTEs en Leucemia Linfoblástica aguda-B

- **BLINATUMOMAB**
  - Relapse refractory patients (Ph neg/Ph pos)
  - MRD positive patients
  - Combination with TKI in Ph pos patients
    - Relapse/refractory
    - Frontline
  - Blinatumomab in newly diagnosed Ph neg ALL patients

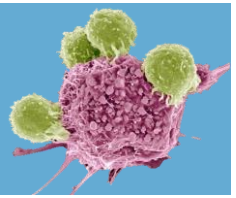
Blinatumomab: Relapsed/refractory patients

- **EC Phase 3 (TOWER): Results**
  - Improvement in OS
  - When censored at the moment of AlloSCT, the advantage in OS is more clear

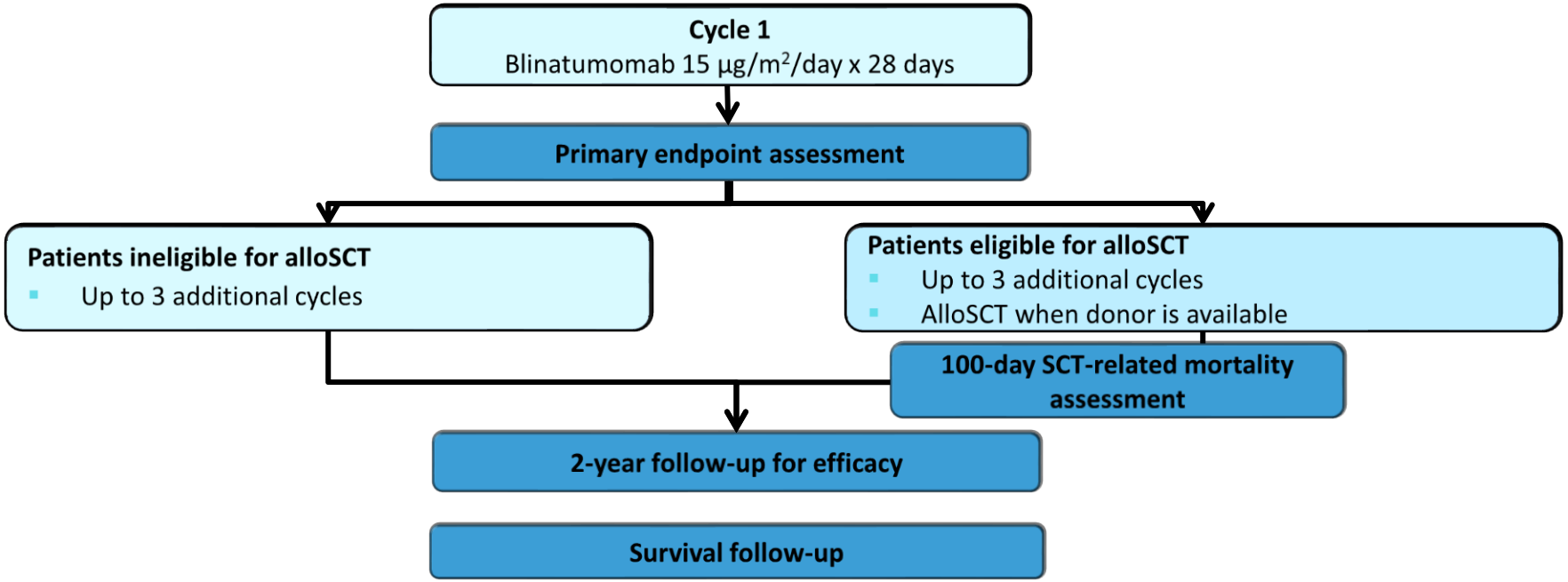




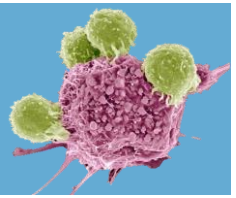
Blinatumomab: MRD positive



- **Phase 2 trial (BLAST) n=116** *(Gokbuget et al, Blood 2018)*
- CR MRD positive (patients > 10^{-3})
  - Including Ph positive ALL
  - Excludes CNS infiltration



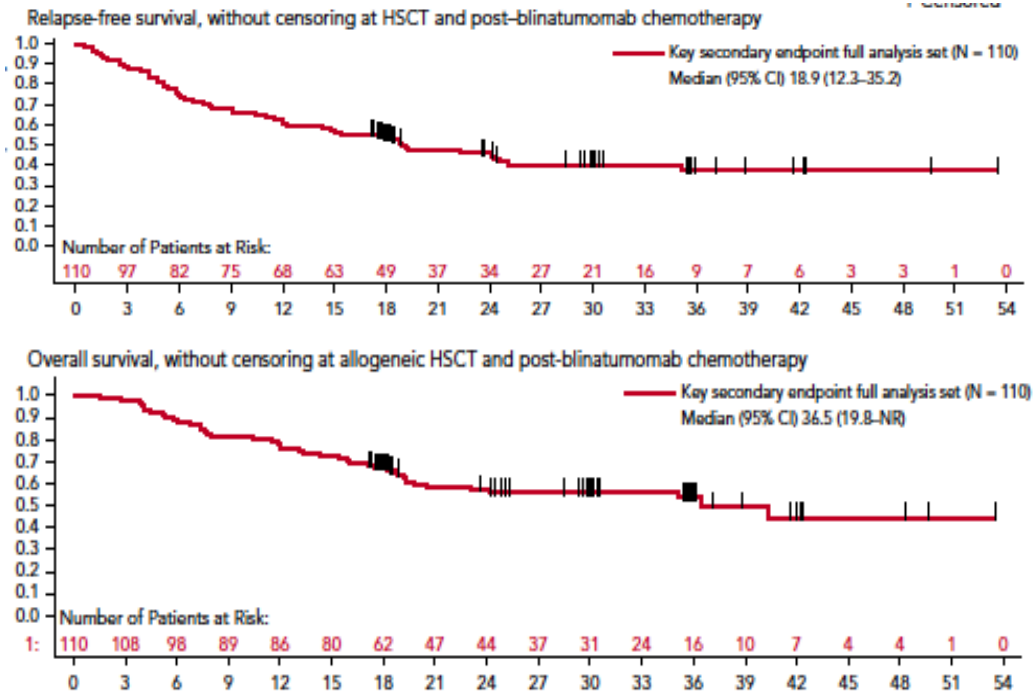
Blinatumomab: MRD positive



Phase 2 trial (BLAST)

Characteristic	N=116
Male, n (%)	68 (59)
Median age, years (range)	45.0 (18–76)
Age, n (%)	
≥18 to <35 y	36 (31)
≥35 to <55 y	41 (35)
≥55 to <65 y	24 (21)
≥65 y	15 (13)
Time from prior treatment, months (range)	1.3 (0–45)
Relapse history, n (%)	
1st CR	75 (65)
2nd CR	39 (34)
3rd CR	2 (2)
Baseline MRD levels, n (%)*	
$\geq 10^{-1}$ to <1	9 (8)
$\geq 10^{-2}$ to $<10^{-1}$	45 (39)
$\geq 10^{-3}$ to $<10^{-2}$	52 (45)

- **88 patients (78%) achieved MRD negative CR.**
- 86/88 after 1st cycle.
- No differences based on age, MRD level or disease status (CR1 vs CR2-3).



Terapia que redirecciona células

Linfoma no Hodgkin

A Rampotas, G Sangha *et al.*

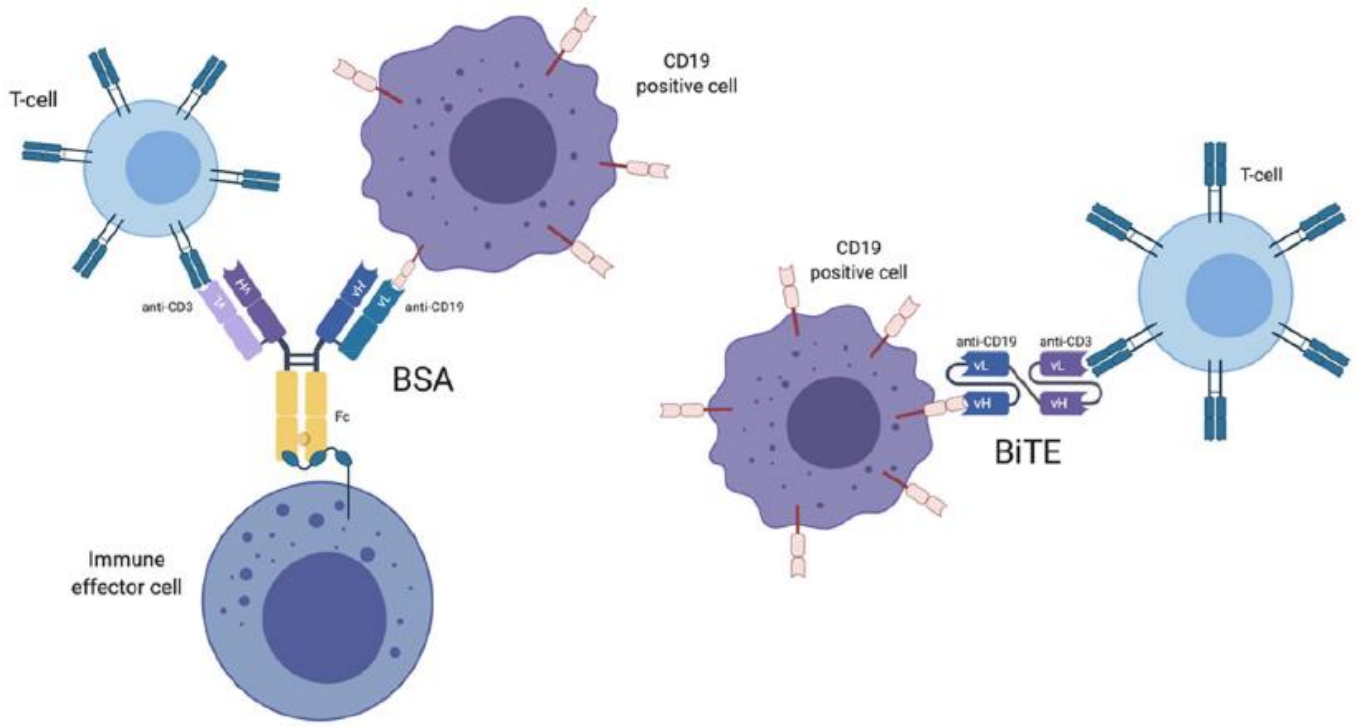
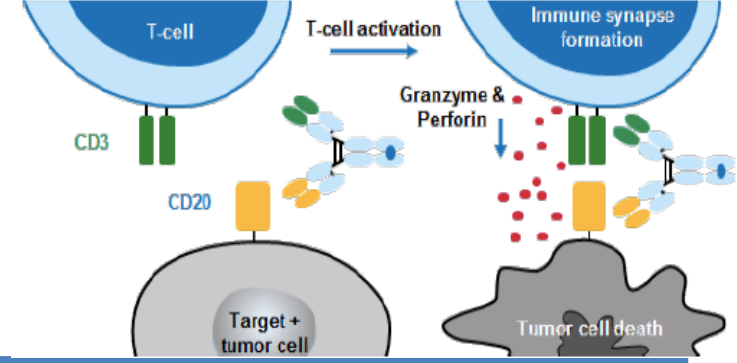


Figure 3. Bispecific antibodies comparison to Bispecific T-cell Engager. BiTEs target a tumour-specific antigen and CD3 which is present in T-cells 'bringing them' together and facilitating an immune response by the T-cell towards the tumour. BSAs work in a similar manner, but they also retain the Fc receptor which enables them to induce a broader immune response by other immune effector cells as well. Their larger size makes them less prone to renal excretion avoiding the need for a continuous infusion that BiTEs require.
BiTE, bi-specific T-cell engager; BSA, bispecific antibodies.

Biespecifics CD3 x CD20 in R/R DLBCL: Overview

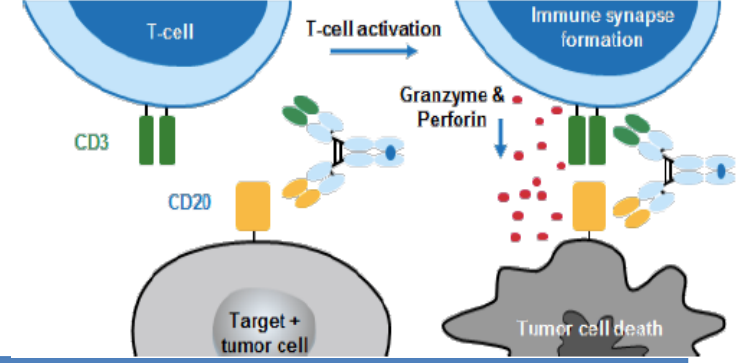


Response, n (%)	Mosunetuzumab[1] (N = 124)	Odronextamab[2] (N = 140)	Glofitamab[3] (N = 154)	Epcoritamab[4] (N=157)
Patient characteristics				
Prior lines, median	3 (1-14)	2 (2-8)	3 (2-7)	3 (2-11)
Refractory	72%	86%	86%	83%
Efficacy				
ORR	37%	49%	52%	63%
CR	19%	31%	39%	39%
Toxicity (grade ≥3)				
CRS	1.1%	4.3%	3.9%	2.5%
ICANS	3.7%	0.7%	2.6%	0.6%

Some of these patients had been previously treated with SUPERNOVAS

1. Schuster SJ et al, ASH 2019, Abs. 6 (doses ≥2.5 mg); 2. Kim SW, et al. ASH 2022, Abs. 444 (phase 2 ELM-2 study); 3. Dickinson M, et al. EHA 2022, #S220 (phase 2); NEJM 2022; 4. Thieblemont C, et al. EHA 2022, #LB2364; JCO 2022 (phase 2)

Biespecifics CD3 x CD20 in R/R DLBCL: Overview



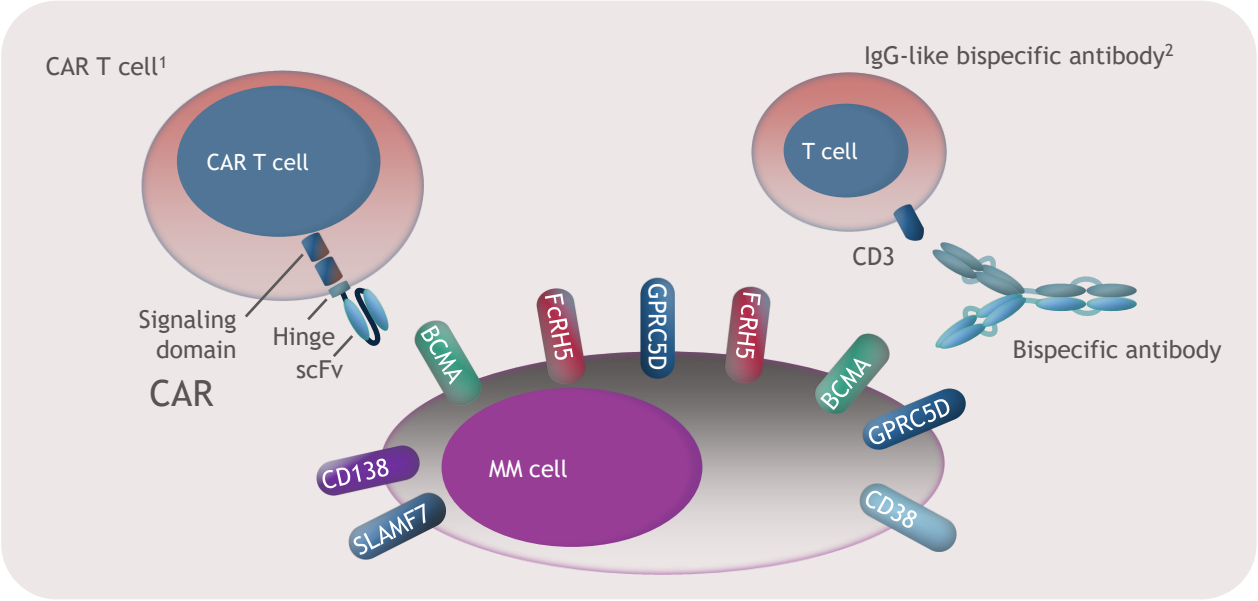
Response, n (%)	Mosunetuzumab[1] (N = 124)	Odronextamab[2] (N = 140)	Glofitamab[3] (N = 154)	Epcoritamab[4] (N=157)
Patient characteristics				
Prior lines, median	3 (1-14)	2 (2-8)	3 (2-7)	3 (2-11)
Refractory	72%	86%	86%	83%
Efficacy				
ORR	37%	49%	52%	63%
CR	19%	31%	39%	39%
Toxicity (grade ≥3)				
CRS	1.1%	4.3%	3.9%	2.5%
ICANS	3.7%	0.7%	2.6%	0.6%

Some of these patients had been previously treated with SUPERNOVAS

1. Schuster SJ et al, ASH 2019, Abs. 6 (doses ≥2.5 mg); 2. Kim SW, et al. ASH 2022, Abs. 444 (phase 2 ELM-2 study); 3. Dickinson M, et al. EHA 2022, #S220 (phase 2); NEJM 2022; 4. Thieblemont C, et al. EHA 2022, #LB2364; JCO 2022 (phase 2)

Terapia que redirecciona células

Mieloma Múltiple



- Bispecifics:
  AMG701
  Teclistamab, talquetamab
  Elranatamab
  REGN5458
  TNB-383B
  CC-93269
  Cevostamab

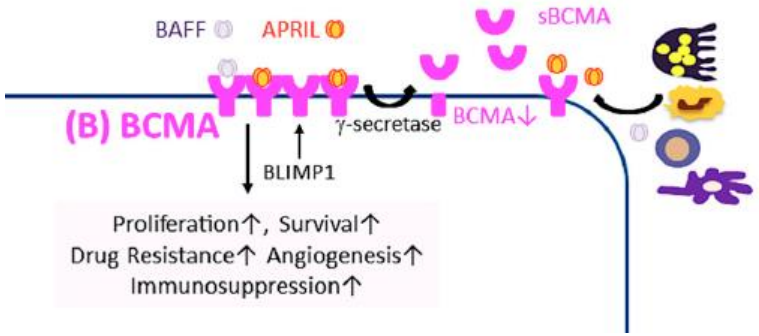
BCMA:[3]
- Selectively overexpressed in plasma cells
- Promotes proliferation and survival of MM cells

GPRC5D:[4,5]
- Highly and selectively expressed in MM
- Distribution is similar to but independent of BCMA

FCRH5:[6]
- High levels of expression on MM cells
- Normally expressed in plasma cells only

BCMA as target in Myeloma

BCMA is extensively studied and is an approved target



BCMA expression in PC

In normal physical functions

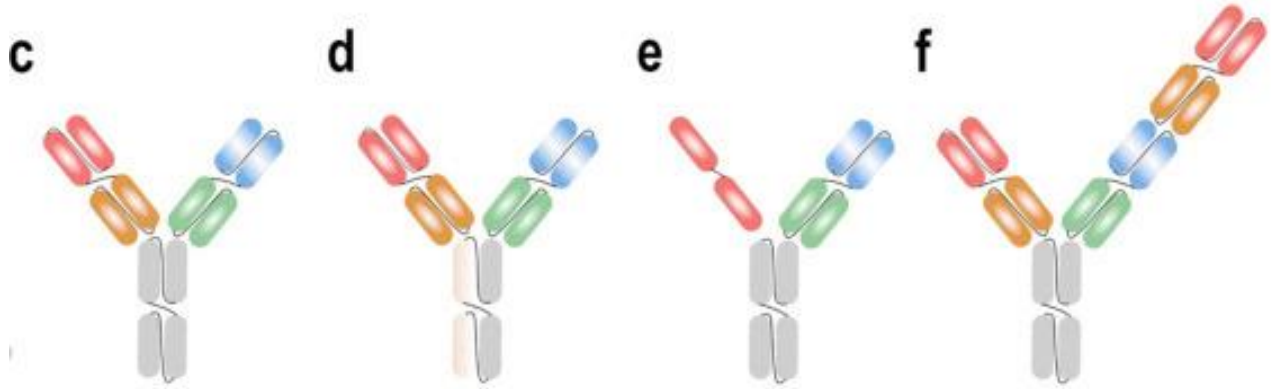
- Support survival of long-lived PCs
- Production of antibodies
- Class switch of immunoglobulin

In MM

- Promote proliferation and survival of MM cells
- Associated with immunosuppressive BM microenvironment
- Increased sBCMA level is associate with disease progression and poorer outcome

Yu B et al. JHematol Oncol 2020;doi:10.1186/s13045-020-00962-7

BCMA BsmAbs under development in MM



BCMA-targeting regions are colored red, CD3-targeting regions are blue. Fc regions are colored grey.

(c) Bispecific antibody, IgG4 Fc region (REGN5458, Elranatamab). (d) Bispecific antibody, IgG4 Fc region (DuoBody®, Teclistamab). (e) Bispecific antibody, IgG4 Fc region, dual BCMA binding domains (TNB-383B). (f) Bispecific antibody, IgG1 Fc region, bivalent anti-BCMA arm (CC-93269).

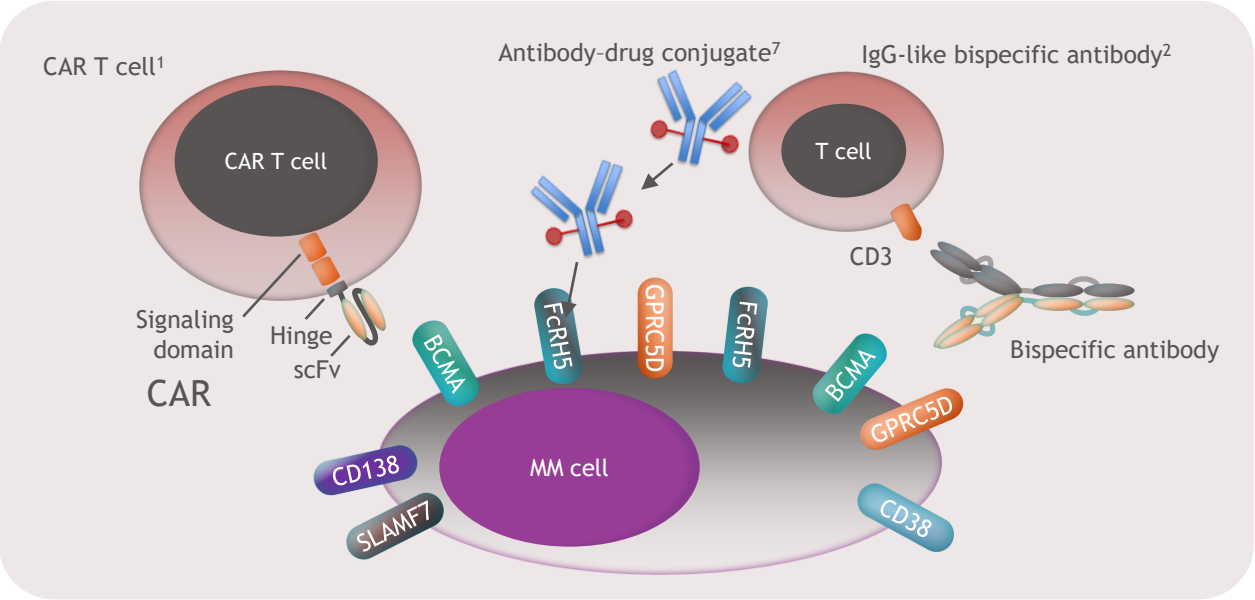
BCMA-bispecific mAbs: Efficacy

Product	n	PL/TCR	Efficacy at the RP2D	PFS/DoR (m)	Schedule of administration
Alnuctamab	68	4PL 63%	ORR 53% (23% CR) @10,15,30,60 mg(n=55) [65% (19%CR) @ 30 mg n=26]	NR/90% or responders continue on treatment	MTD not reached yet **SC** weekly C1-C2; every other week C3-C6; monthy from C7
Teclistamab	165	5PL 77.6%	ORR 63% RC/RCs: 39.4%	11.3 /18.4	0.06-0.3-1.5 mg/kg Weekly and **SC**
Elranatamab	123	5PL 96.7%	ORR 61% RC/RCs: 28%	58.5%@12m/ 71.6%@12m	12-33-76 **SC** weekly From C7, every other week
Linvoseltamab	252	5PL/ 81%	64% (24% CR) @ 200mg (n=58) 50% (20%) @ 50 (n=104)	NR/ 89%@6m(200mg) NR/ 60%@16m(50m)	5-25-200 mg Weekly **IV** C1-C3 Every other week C4-C5 Monthly later if ≥VGPR
ABBV-383	174	5 PL 80%	56% (25% CR) in all pts 58% (13% CR) @ 40mg 61% (34% CR) @ 60mg	9.7m/NR 13.7m/NR 11.2m/19.4m	RP2d not defined yet IV every 3 weeks

Most of BCMA×CD3 bispecifics abs have been evaluated in TCR MM patients.
ORR ranges 50-60% and covers the unmet need. PFS is approx 1 year

1. Wong ASH 2022 Abstract 162; 2.Moreau et al.. NEJM 2022; 3. Bahlis N et al. ASH 2022: Abstr 158; 4. Bumma et al. ASH 2022; Abstract 4555; 5. Voorhes et al. ASH 2022;Absttract 1919

New-generation immunotherapies in MM



- **ADC:**
  Belantamab
- **Bispecifics:**
  Teclistamab,
  talquetamab
  Elranatamab
  Linvoseltamab
  TNB-383B
  Alnuctamab
  Cevostamab
- **CAR T:**
  Ide-cel
  Cilta-cel
  p-BCMA-101
  CT053
  ALLO-715

BCMA:[3]
- Selectively overexpressed in plasma cells
- Promotes proliferation and survival of MM cells

GPRC5D:[4,5]
- Highly and selectively expressed in MM
- Distribution is similar to but independent of BCMA

FCRH5:[6]
- High levels of expression on MM cells
- Normally expressed in plasma cells only

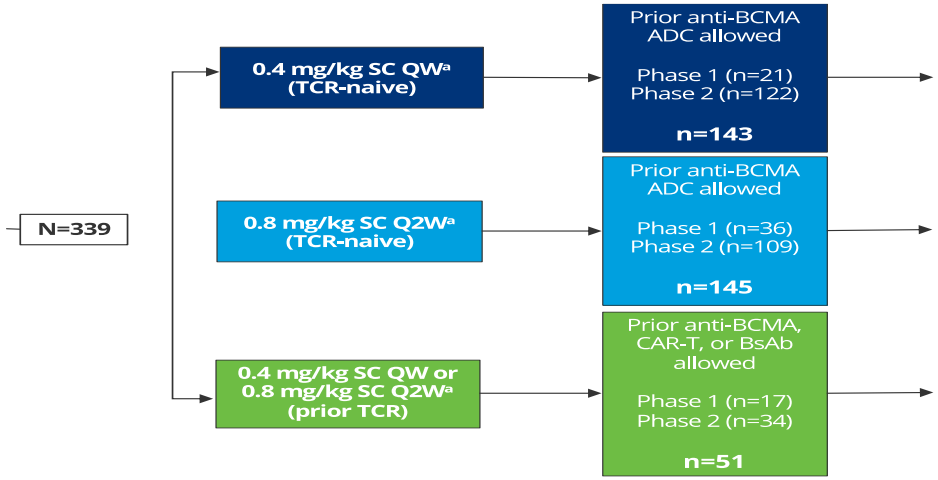
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; FcRH5, Fc receptor-like 5; GPRC5D, ide-cel, idecabtagene vicleucel; GPRC5D, G-protein coupled receptor family C group 5 member D; Ig, immunoglobulin; scFv, single chain variable fragment.

1. Rodríguez-Lobato LG, et al. Front Oncol. 2020;10:1243. 2. Pillarisetti K, et al. Blood Adv. 2020;4:4538-49. 3. Yu B, et al. J Hematol Oncol. 2020;13:125. 4. Verkleij et al. Blood Advances, 2020;5(8);2195-2215. 5. Smith EL, et al. Sci Transl Med. 2020;11:eaau7746. 6. Li J, et al. Cancer Cell. 2017;31;383-395. 7. Bruins WSC, et al. Front Immunol. 2020;11:1155.

Images adapted from Verkleij CPM, et al. Curr Opin Oncol. 2020;32:664-71 and Bruins WSC, et al. Front Immunol. 2020;11:1155.

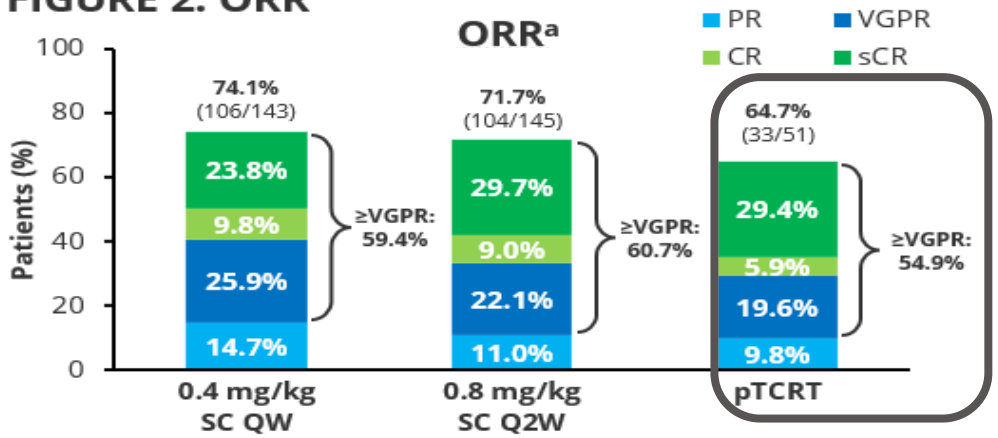
MonumenTAL-1 study: Talquetamab, GPRC5D-CD3 bsAb in RRMM patients[1]

- RRMM patients; median 5–6 PL and ~70% TCR



- ORR was maintained across patient subgroups, except patients with EMD

FIGURE 2: ORR



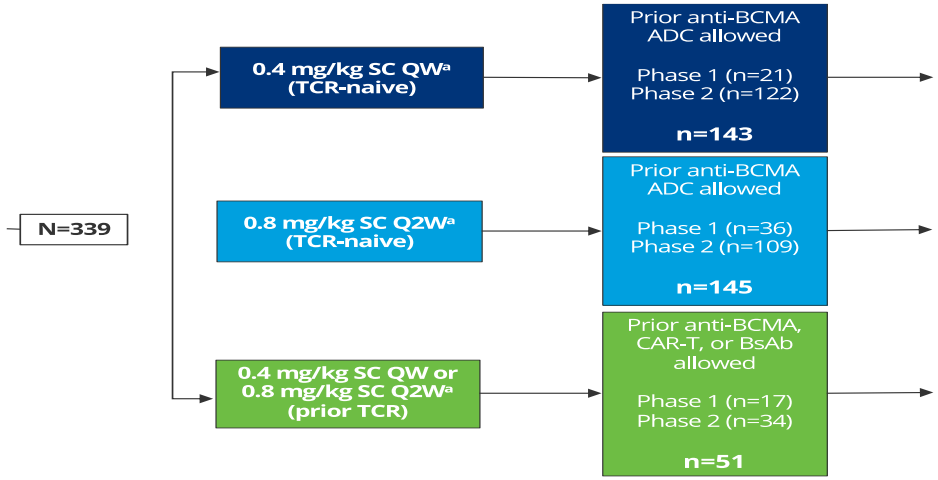
Outcome	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=145)	Prior TCR (n=51)
mFU, mo	18.8	12.7	14.8
12-mo DOR rate in patients with ≥CR, %	78.9	90.5	80.5
mPFS, mo (95% CI)	7.5 (5.7–9.4)	14.2 (9.6–NE)[b]	5.1 (3.4–12.3)
12-mo PFS rate, %	34.9	54.4	38.1
12-mo OS rate, %	76.4	77.4	62.9

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CD, cluster of differentiation; CI, confidence interval; CR, complete response; DOR, duration of response; EMD, extramedullary disease; FU, follow-up; GPRC5D, G protein coupled-receptor Class 5 group 5; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression–free survival; PL, prior lines; PR, partial response; Q2W, every 2 weeks; QW, weekly; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; sCR, stringent complete response; TCR, T-cell redirection; VGPR, very good partial response.

1. Schinke CD, et al. ASCO 2023 (Abstract No. 8036 – poster).

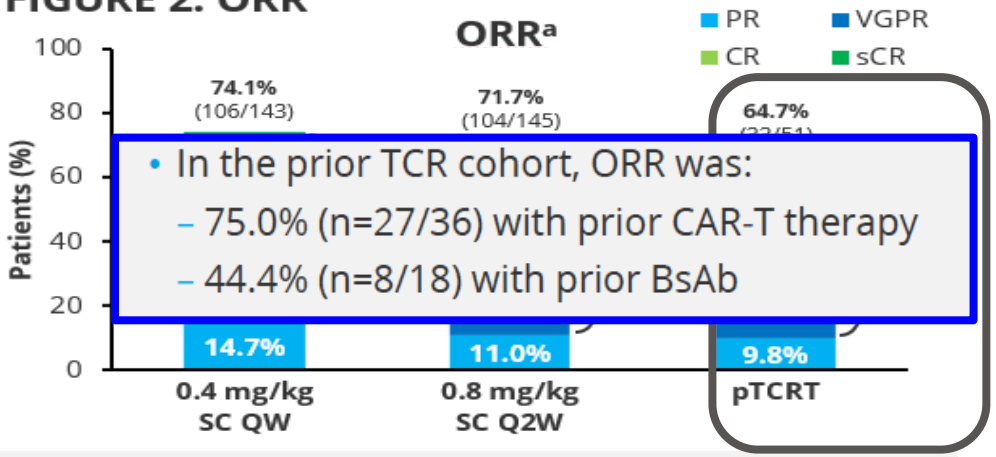
MonumenTAL-1 study: Talquetamab, GPRC5D-CD3 bsAb in RRMM patients[1]

- RRMM patients; median 5–6 PL and ~70% TCR



- ORR was maintained across patient subgroups, except patients with EMD

FIGURE 2: ORR



Outcome	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=145)	Prior TCR (n=51)
mFU, mo	18.8	12.7	14.8
12-mo DOR rate in patients with ≥CR, %	78.9	90.5	80.5
mPFS, mo (95% CI)	7.5 (5.7–9.4)	14.2 (9.6–NE)[b]	5.1 (3.4–12.3)
12-mo PFS rate, %	34.9	54.4	38.1
12-mo OS rate, %	76.4	77.4	62.9

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CD, cluster of differentiation; CI, confidence interval; CR, complete response; DOR, duration of response; EMD, extramedullary disease; FU, follow-up; GPRC5D, G protein coupled-receptor Class 5 group 5; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression–free survival; PL, prior lines; PR, partial response; Q2W, every 2 weeks; QW, weekly; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; sCR, stringent complete response; TCR, T-cell redirection; VGPR, very good partial response.

1. Schinke CD, et al. ASCO 2023 (Abstract No. 8036 – poster).

Cevostamab (BFCR4350A, FcRH5 × CD3 bispecific antibody):
Phase 1 results in RRMM (n = 157); summary of key data

Key inclusion criteria: RRMM for which no standard therapy is available

Key baseline characteristics: median age 64 (33-82) years; median prior lines: 6 (2-18); 84.5% were triple-class refractory, 68.3% penta-drug refractory; **prior BCMA: 33.5%**

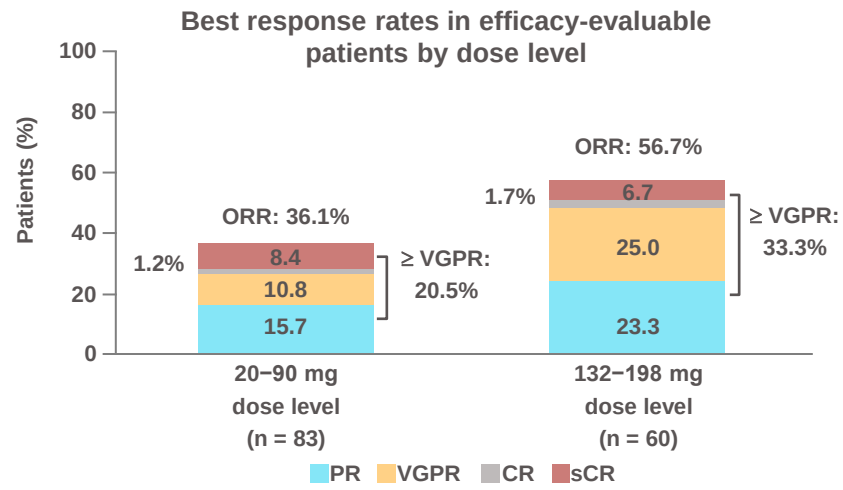
2 schedules:

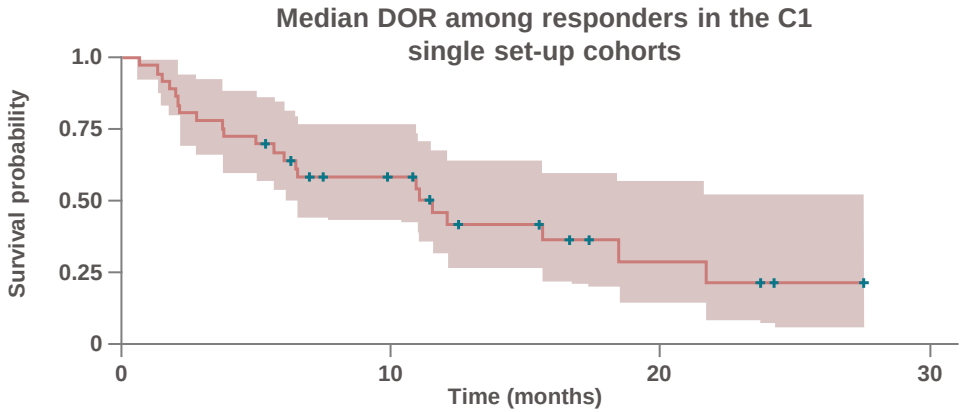
Single-step up (dose range: 0.05-3.6 mg) C1D[8]+ 0.15-198 mg (q3w, i.v. infusion)

⇒ Expansion single step-up C1D1 3.6 mg/C1D8 90 mg (C2+ q3w) (n = 31)

Double-step up C1D1: 0.3-1.2 mg/C1D8 3.6 mg/C1D15 60-180 mg/C2+ q3w

⇒ Expansion C1D1 0.3 mg/C1D8 3.6 mg/C1D15 160 mg (n = 31)





Median DOR: 11.5 (95% CI: 6.0–18.4) months

Most frequent TRAEs, overall (Grade ≥ 3)
- Neutropenia 40% (mostly grade 3/4)
- Thrombocytopenia 26% (18%)

- CRS: 80.7% (1.2%);
- Median time to onset: 1 day

- ICANS :14.3% (0.6%)
- Infections: 48% (19%)

Cevostamab is given for up to 17 cycles

Trudel S, et al. Blood. 2021;138 (Suppl 1):157.

Nuestras grandes deudas pendientes

Nuestros agujeros negros

Agujeros negros/Hematological cancers

Investigadores del IAA observaron el primer agujero negro hipermasivo atrapando una estrella. Nobel de Química 2019. Mujeres e investigación del cáncer. Luz de sincrotrón para la ataxia de Friedrich.

- Vamos a utilizar los agujeros negros como estrategia.
- Vamos a redireccionar los agujeros negros a las células tumorales o las células tumorales a los agujeros negros para que sean destruidos

- Esto es posible???

Nuestras grandes deudas pendientes

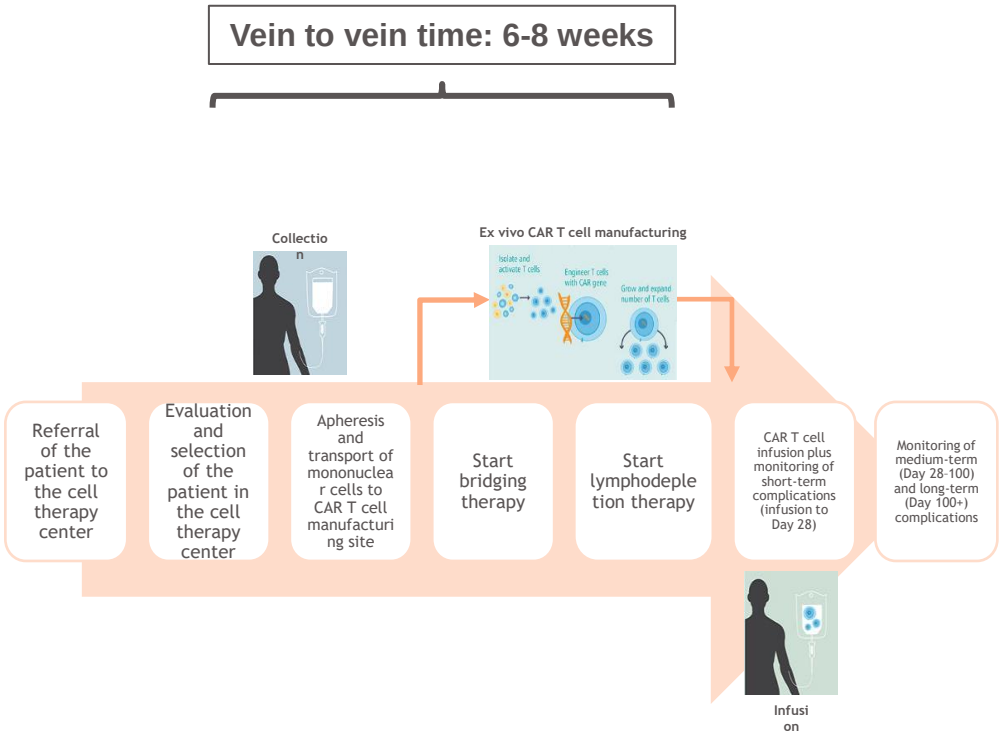
Nuestros agujeros negros

Agujeros negros/Hematological cancers

Investigadores del IAA observaron el primer agujero negro hipermasivo atrapando una estrella. Nobel de Química 2019. Mujeres e investigación del cáncer. Luz de sincrotrón para la ataxia de Friedrich.

- No hay duda sobre la eficacia de los anticuerpos monoclonales biespecíficos en las diferentes neoplasias hematológicas
- La mayoría ya están aprobados y en fase de investigación en líneas precoces, en primera línea e incluso en combinación con otros fármacos

What about disease morbidity for the selection of bi-specific in MM?



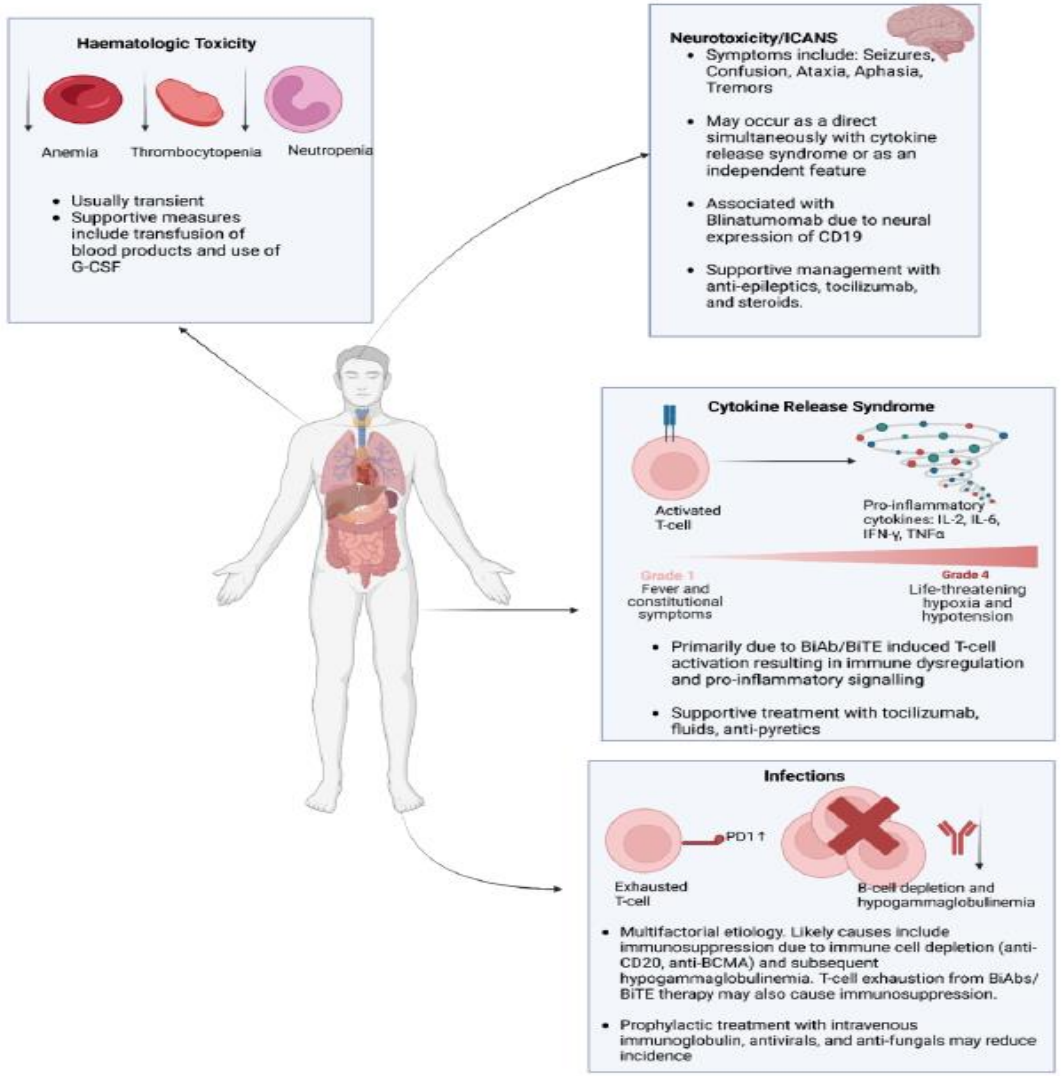
Slot availability, eligibility, vein to vein time……..
Specialized center…..

Which BsAb do you want? They are ready to be administered

BsAbs are off the self drugs broadly available and can be delivered in all centers, including comunity-based hospitals

Terapia que redirige células

Toxicidad



Cytokine release syndrome

Neurotoxicity/ICANS

Hematological toxicity

Infections

What about Cytokine Release Syndrome?

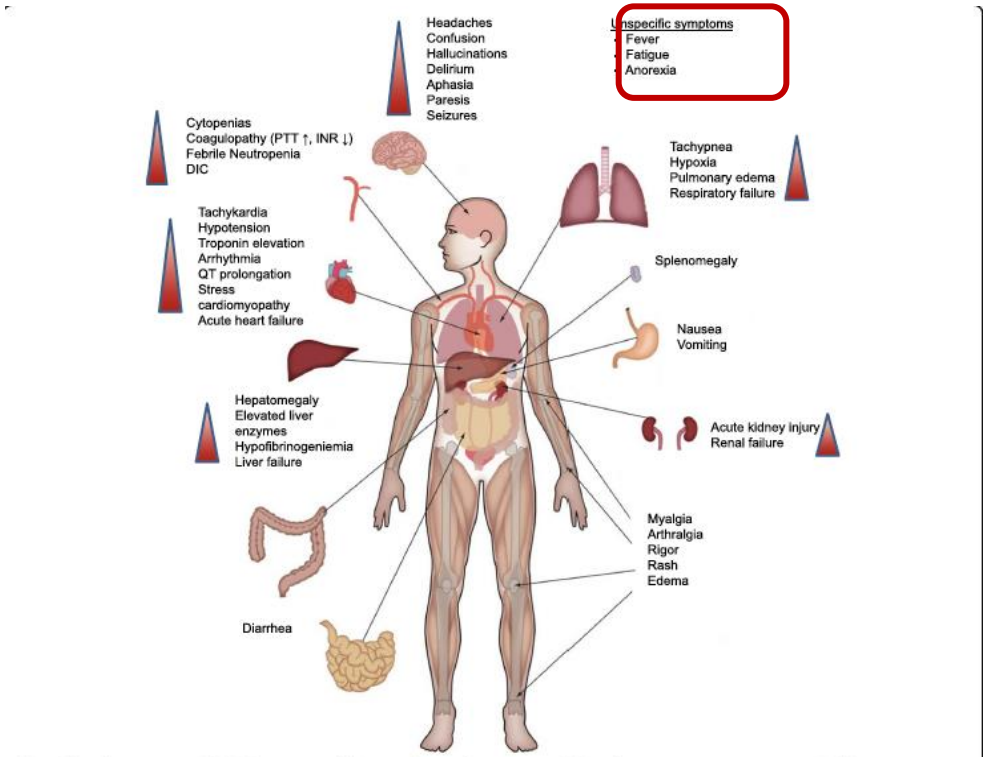


Fig. 1 Clinical presentation of CRS. Beginning with fever and unspecific symptoms CRS might impact most organ systems. Mild cases can present as flu-like illness. Grade °II to IV shows signs of life threatening cardiovascular, pulmonary and renal involvement. Neurotoxicity can occur concurrent or with delay. Abbreviations: DIC: disseminated intravascular coagulation; INR: international normalized ratio; PTT: partial thromboplastin time

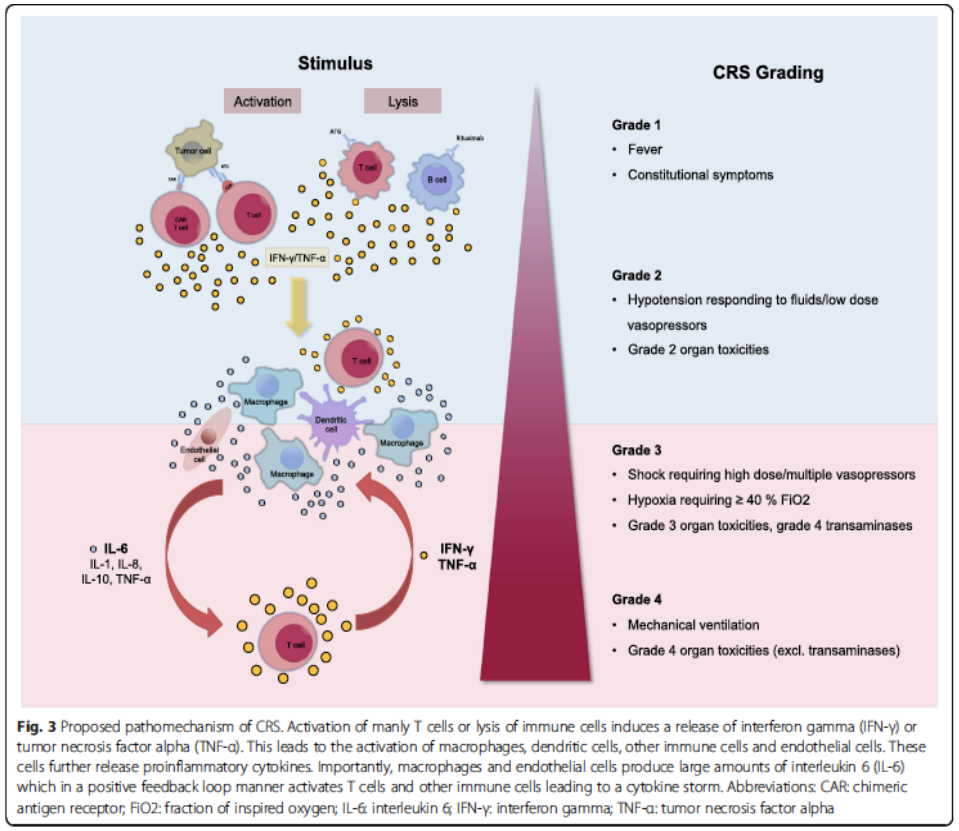


Fig. 3 Proposed pathomechanism of CRS. Activation of manly T cells or lysis of immune cells induces a release of interferon gamma (IFN-γ) or tumor necrosis factor alpha (TNF-α). This leads to the activation of macrophages, dendritic cells, other immune cells and endothelial cells. These cells further release proinflammatory cytokines. Importantly, macrophages and endothelial cells produce large amounts of interleukin 6 (IL-6) which in a positive feedback loop manner activates T cells and other immune cells leading to a cytokine storm. Abbreviations: CAR: chimeric antigen receptor; FiO2: fraction of inspired oxygen; IL-6: interleukin 6; IFN-γ: interferon gamma; TNF-α: tumor necrosis factor alpha

CRS is very frequent with all BsABs and fever is the first symptom

Strategies to mitigate CRS

Schedule: teclistamab s.c

Week 1: Step 1: 0.06 mg/kg;

Step 2: 0.3 mg/kg;

Step up doses are separated by 2 to 4 days before the first full dose

C1+: 1.5 mg/kg weekly subcutaneously in abdomen

If patients are in at least CR for 6 months or longer, it is possible to move to Tec 1.5 mg/Kg Q2W

Cycles of 28 days

Hospitalization and premedication with:

- Dexamethasone 16 mg
- Acetaminophen 1 g
- Diphenhydramine 6 mg

Before each step-up dose and for the first full dose

Patients should be hospitalized for 48 hours after administration of all doses within the teclistamab-cqyv step-up dosing schedule.

Early detection and gradation is crucial to start therapy

Table 2 ASTCT CRS consensus grading (adapted from Lee *et al*/ASTCT, *BBMT*, 2019[75])

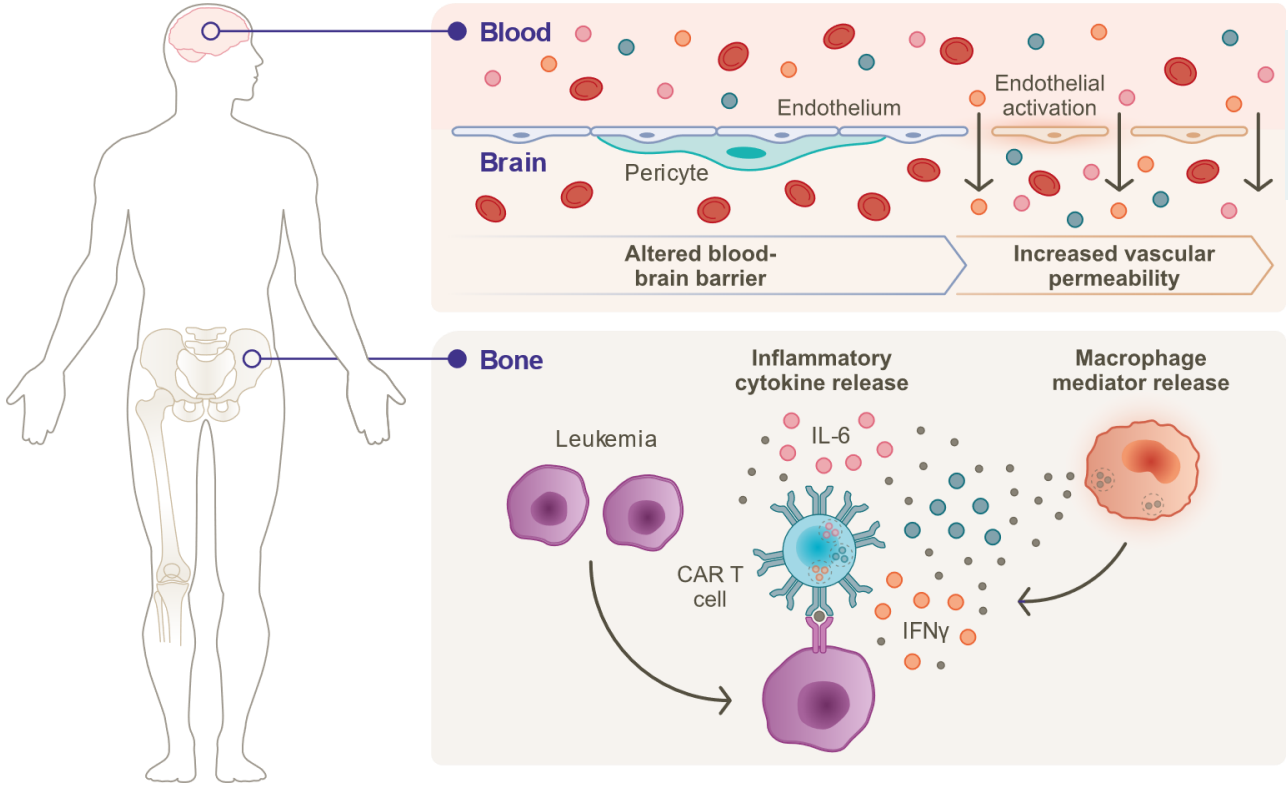
CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or†				
Hypoxia	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 (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE V.5.0, but they do not influence CRS grading.
*Fever is defined as a temperature of ≥38°C not attributable to any other cause. In patients who have CRS who then undergo antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
†CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5°C, hypotension requiring one vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome.

- G-CSF is not recommended during the step-up doses and first full dose
- It is not recommended to give more than 2 doses of tocilizumab because of the blockade of IL-6R
- The TLS can be prevented with adequate hydration and allopurinol as part of the routine.
- In selected patients with high tumor burden, it would be recommended to prescribe rasburicase as prophylaxis. If TLS is suspected it is highly recommended to prescribe rasburicase.

- G1: symptomatic treatment
- G1 persistent or G2: tocilizumab
  Toci can be considered earlier on in elderly patients with comorbidities
- If CRS does not improve, steroids should be given with a second dose of tocilizumab
- If CRS does not improve, third line can include high-dose MP, siltuximab, anakinra.... But it would be highly recommended to consider other diagnosis
- There are some trials using toci prophylactic to prevent CRS

ICANS pathophysiology



Commonly associated with CRS ← potential mechanistic link[1,2]

Elevated CNS levels of cytokines

Encephalopathy
Seizures
Focal signs

Raised ICP

Systemic inflammation & high levels of circulating cytokines → ENDOTHELIAL CELL ACTIVATION & BLOOD BRAIN BARRIER DISRUPTION → INFLAMMATORY CASCADE WITHIN THE CNS → cortical & subcortical dysfunction +/- cerebral edema[1,2]

ICANS is not frequent and it is reported in no more than 5% of patients and always G1-2

CAR, chimeric antigen receptor; CNS, central nervous system; CRS, Cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; IFN, interferon; IL, interleukin.

1. June C et al. Science 2018;359(6382):1361–1365; 2. Santomasso B, et al. Am Soc Clin Oncol EDUC Book. 2019;39:433–444.

Early detection or suspect of NTX/ICANSc

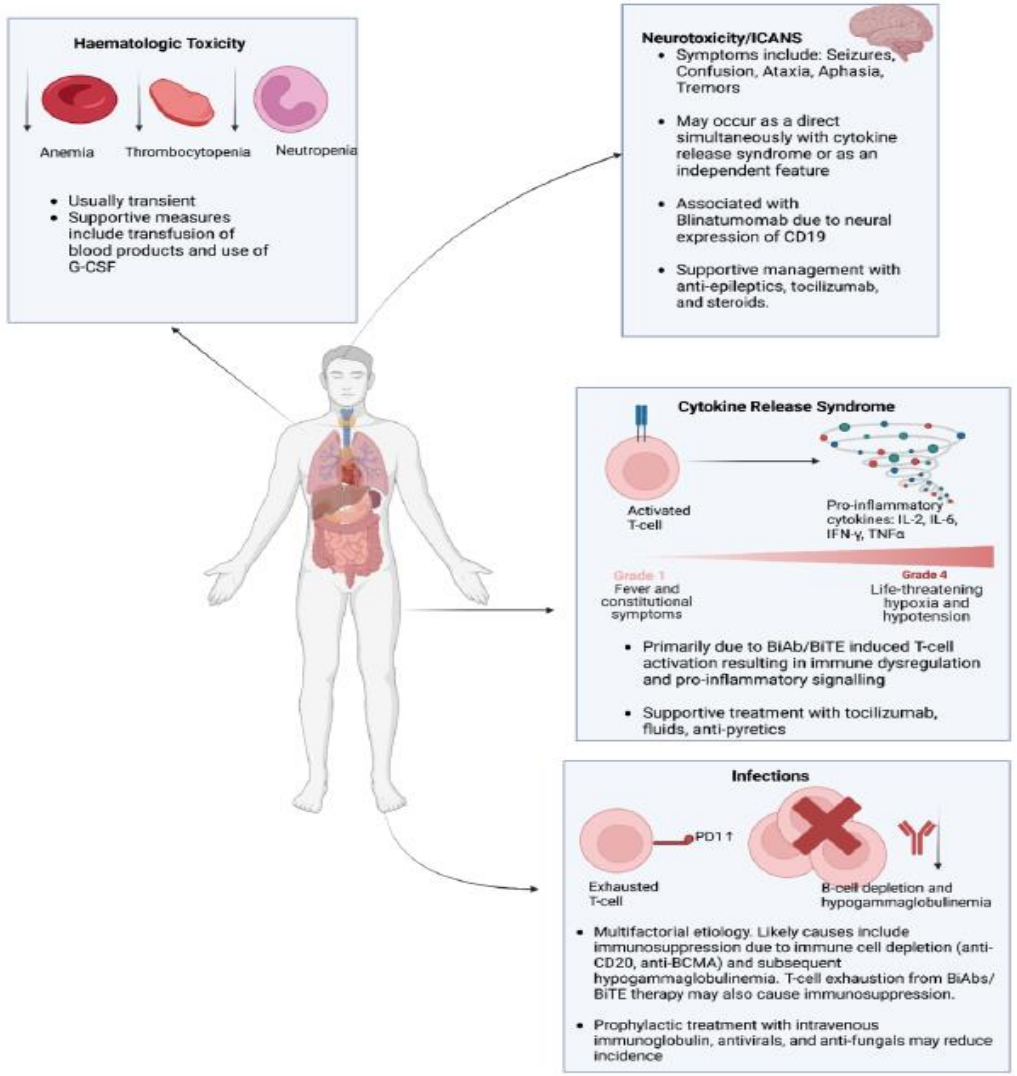
- ICANS usually follows CRS or in the context of CRS, some hours/days after the onset of CRS
- Cinical examination is crucial every day or every 8-12 hours during the priming doses and especially if CRS occurs

- As early detection is crucial, patient but especially caregiver should be aware about any of the most common symptoms to inform to the physician
- **Expressive aphasia** with impaired naming of objects, paraphasias, hesitant speech and verbal perseveration that may progress to global aphasia

Neurologist do not evaluate the patient receiving BsAbs unless necessary
Hematologists and caregivers shoud interact to detect the NTX

Terapia que redirige células

Toxicidad



Cytokine release syndrome

Neurotoxicity/ICANS

Hematological toxicity

Infections

Incidence and Severity of Clinically Relevant Infections During Teclistamab Treatment: BCMA-bsAb

- Majority of grade ≥3 infections were COVID-19 and respiratory infections
  - Study enrollment overlapped with peak of COVID-19 pandemic
  - 13/165 patients (7.9%) received a COVID-19 vaccine prior to the first teclistamab dose
  - **18/165 patients (10.9%) died due to COVID-19**
- All 7 PJP infections were grade 3/4 and all resolved
  - No PJP prophylaxis in 4/7 patients
- Most viral, GI, and fungal infections were grade 1/2

Patients, n (%)	N=165		
	Any Grade	Grade 3/4	Grade 5
Any infection	132 (80.0)	91 (55.2)	21 (12.7)
Respiratory infections	95 (57.6)	32 (19.4)	2 (1.2)
COVID-19 infection	48 (29.1)	35 (21.2)	18 (10.9)
Key viral infections[a]	20 (12.1)	7 (4.2)	1 (0.6)
GI infections	15 (9.1)	2 (1.2)	0
Fungal infections[b]	9 (5.5)	0	0
PJP	7 (4.2)	7 (4.2)	0
HBV reactivation	1 (0.6)	1 (0.6)	0

Infections were selected based on categories of clinically relevant infections typically occurring in patients with relapsed/refractory multiple myeloma using MedDRA version 24.0. Patients were counted once for any given event, regardless of the number of times they experienced the event. If toxicity grade was missing for a specific infection, the patient was only counted in the total percentage for that infection.
[a]Excluding COVID-19. [b]Excluding PJP. GI, gastrointestinal; HBV, hepatitis B virus; MedDRA, Medical Dictionary for Regulatory Activities; PJP, *Pneumocystis jirovecii* pneumonia.

Summary of Key Recommendations for Managing Infections During Teclistamab Treatment

Before starting teclistamab, patients should be up to date with all vaccinations (including COVID-19) and screened for HBV, HCV, and HIV

Teclistamab should not be initiated in patients with any active infections

Based on experience from MajesTEC-1[1,2] and in line with recently published consensus guidelines[3-5]

Patients should be closely monitored for a range of infection types during treatment to facilitate prompt investigation and intervention

Teclistamab should not be given to patients with any active infections

Prophylaxis for PJP, HSV, and VZV should be given to all patients

Other prophylactic antimicrobials should be administered per institutional guidelines

IgG replacement should be used to maintain IgG ≥400 mg/dL

IgG replacement should be administered prophylactically and/or for treatment of life-threatening infections, and for serious or recurrent infections, per institutional guidelines

Growth factors should be considered for grade ≥3 neutropenia with infection/fever and grade 4 neutropenia

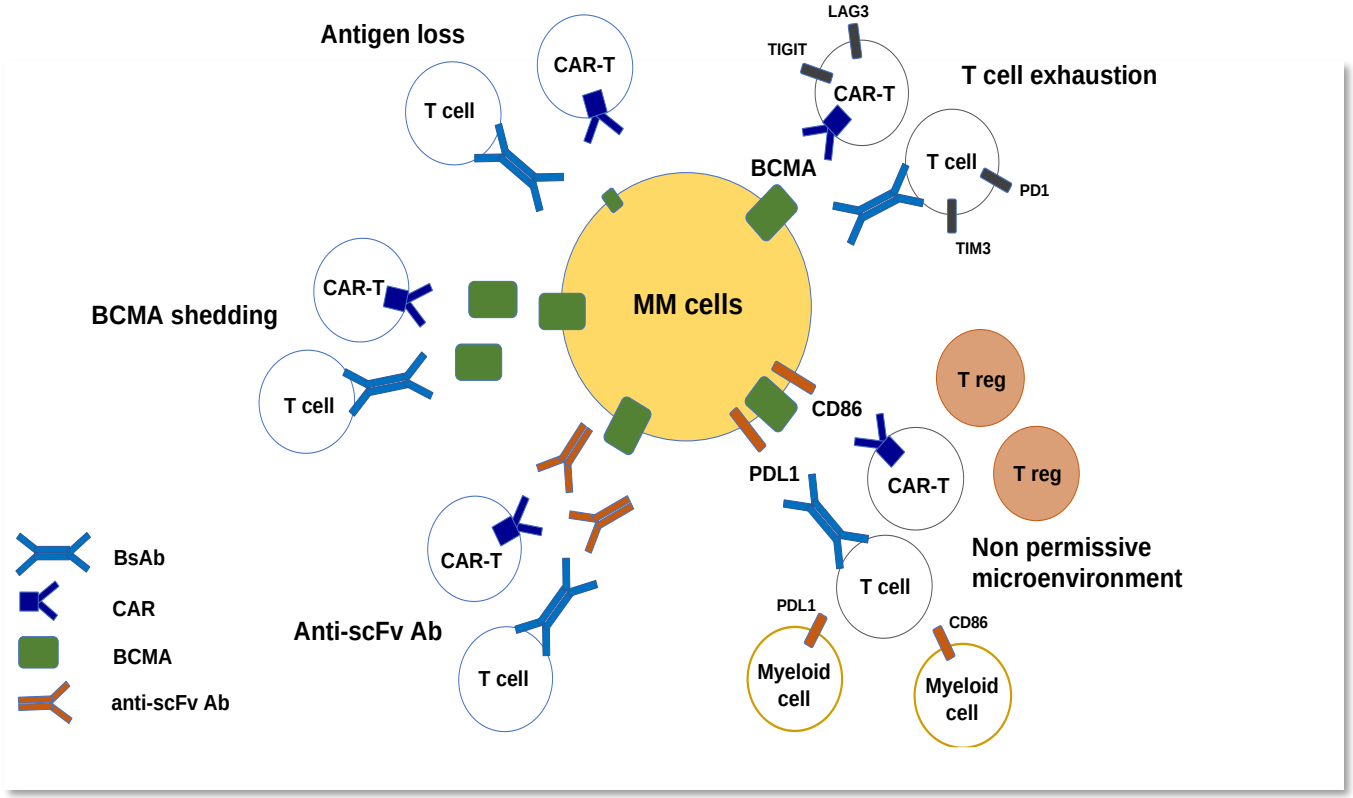
Growth factors should not be given during step-up dosing or during cytokine release syndrome

HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; IgG, immunoglobulin G; PJP, *Pneumocystis jirovecii* pneumonia; VZV, varicella-zoster virus.
1. Moreau P, et al. *N Engl J Med* 2022;387:495-505. 2. van de Donk NWCJ, et al. *J Clin Oncol* 2023;41(16 Suppl):8011. 3. Raje N, et al. *Lancet Haematol* 2022;9:143-61. 4. Ludwig H, et al. *Lancet Oncol* 2023;24:e255-69. 5. Raje N, et al. *Blood Cancer J* 2023;13:116.

Other toxicities to consider: On target off tumor toxicities

- GPRC5D is expressed in epithelial cells of the hair follicles in the skin (the number of hair follicles in skin samples explains the variability in RNA expression), and at the base of the epithelial columns supporting the filiform papillae (keratinized structures in the tongue)
- GPRC5D-targeted therapy does induce in approx 50% of patients: nails abnormalities, skin abnormalities and dysgeusia
- Trials ongoing to mititgate these side effects

Is it possible to sequence Supernovas and Agujeros negros? Understanding mechanism of resistance



- Target dependent
  - Antigen loss
  - Antigen shedding
  - Anti-scFv Ab
- T cell dependent
  - T cell exhaustion
  - Non-permissive microenvironment

- Potentiate the fitness of T-Cells with intermediate therapies including IMiD's or check point inhibitors….

BsAb: bispecific antibody; Treg: regulatory T cells.
Gazeau N, et al. Blood Adv. 2021;5:3016-20.

Summary

Terapias que redireccionan células

- Although CAR-T or therapy modifying cells are extremely atractives like Supernovas, there are currently some limitations for their use…
- Bispecific monoclonal antibodies are an excellent complement to the Supernovas, especially because:
  - Off the self
  - Broadly available
  - More patients are eligible for BsABs
- Bispecific monoclonal antibodies do require from optimization in some diseases and based on Fixed duration of therapy, more flexible Schedule of administrations..
- Supernovas and Agujeros Negros, CAR-T and BsAbs can be used together and BsAbs can serve as bridging therapy or consolidation after CAR-T