CAR-T cell therapy: setting the scene

Prof. dr. Sébastien Anguille

Laboratory of Experimental Hematology
Vaccine & Infectious Disease Institute
University of Antwerp

Healixia event | 21 Nov 2025

What is CAR-T cell therapy?

- CAR-T cells
  - T cells: immune effector cells / “soldiers” of our immune system
  - CAR: weaponized with a “**C**himeric **A**ntigen **R**eceptor”

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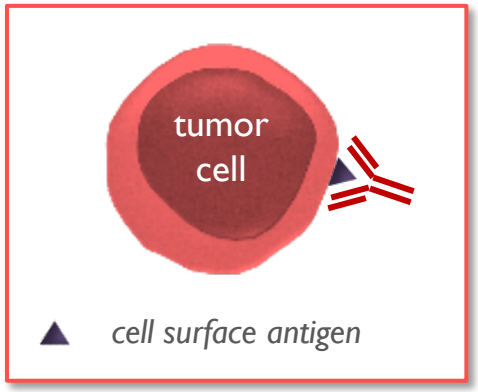
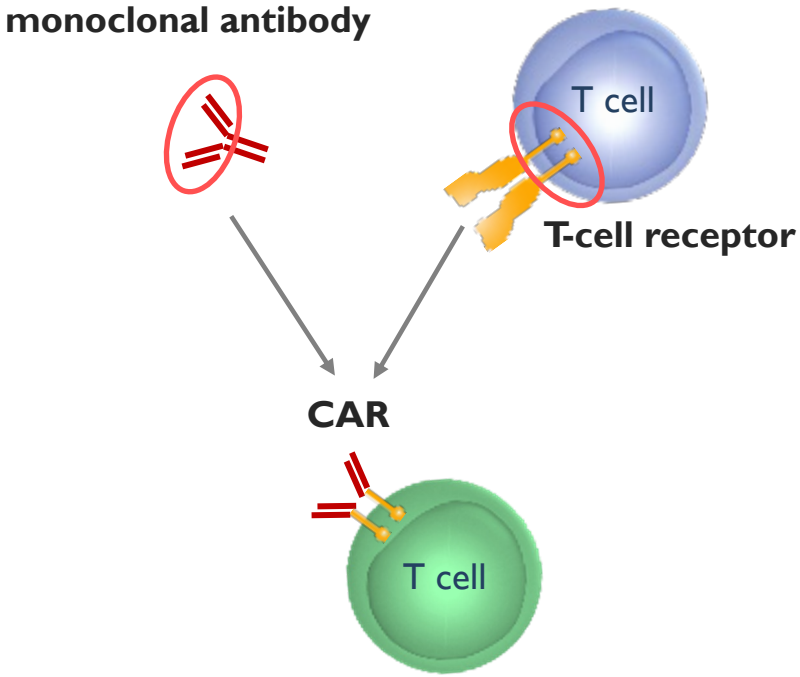
  - CAR: weaponized with a “**C**himeric **A**ntigen **R**eceptor”
    - Synthetic receptor composed of 2 main parts:





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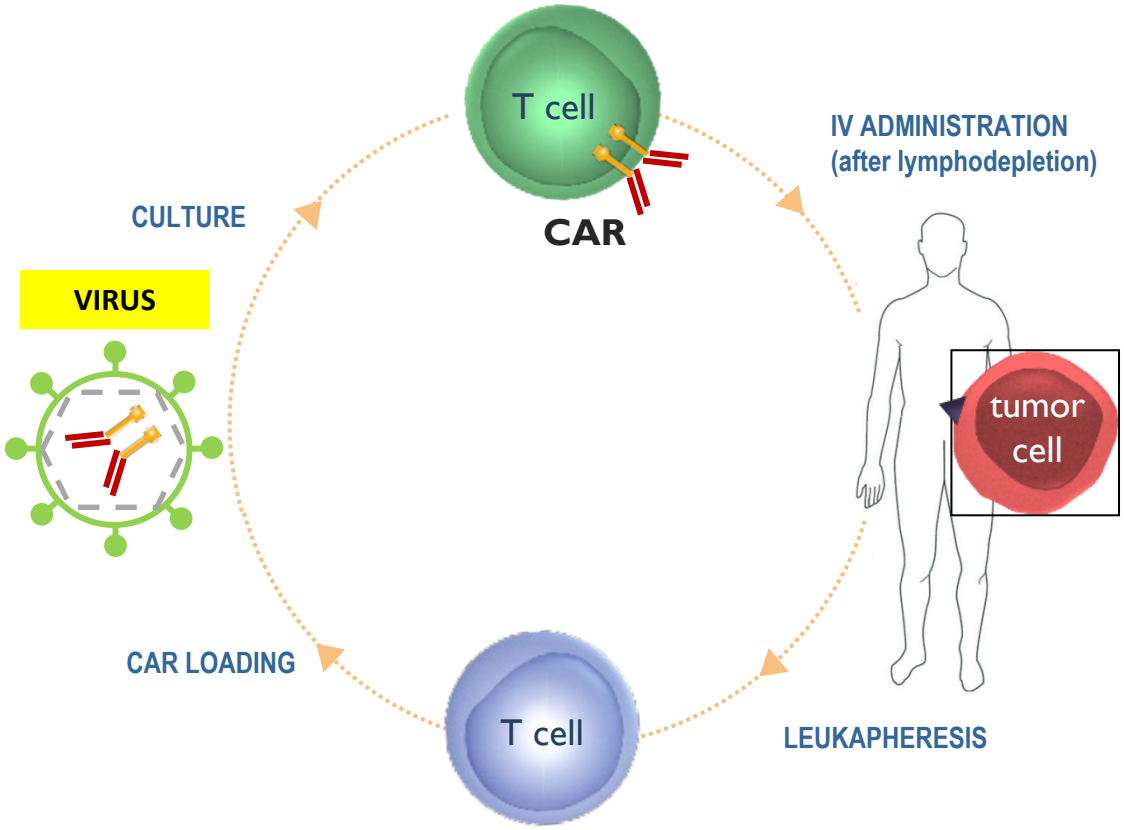

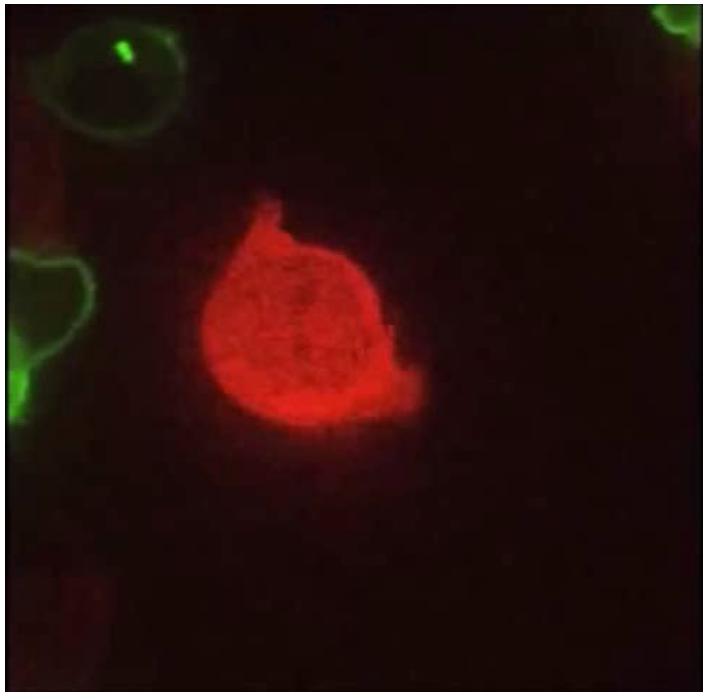

CAR-T cell therapy in Belgium

Knack Rubrieken ▾ Het magazine Voordelen voor abonnees Abonneren

Nieuwe generatie immunotherapie vanaf 1 juni terugbetaald

Vanaf 1 juni 2019 wordt de behandeling met CAR-T-cellen terugbetaald voor twee groepen patiënten.

Maggie De Block

CAR-T-therapie, een nieuwe generatie immunotherapie, wordt vanaf 1 juni 2019 terugbetaald voor de behandeling van twee types bloedkanker. Dat heeft minister van Volksgezondheid Maggie De Block beslist.

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Goed nieuws voor in totaal 140 patiënten die tot voor kort 'uitbehandeld' waren. Want naast innovatief is de therapie ook immens duur.

Bij CAR-T-therapie worden de eigen witte bloedcellen genetisch aangepast om kankercellen aan te vallen. Vanaf 1 juni 2019 wordt de behandeling met CAR-T-cellen terugbetaald voor twee groepen patiënten.

De eerste groep zijn kinderen en jongvolwassenen met acute lymfatische leukemie bij wie een andere behandeling niet of onvoldoende aanslaat.

De tweede groep zijn volwassenen met diffuus grootcellig B-cellymfoom (een agressieve vorm van lymfeklierkanker) bij wie een andere behandeling niet of onvoldoende aanslaat.

HEMATOLOGICAL MALIGNANCIES

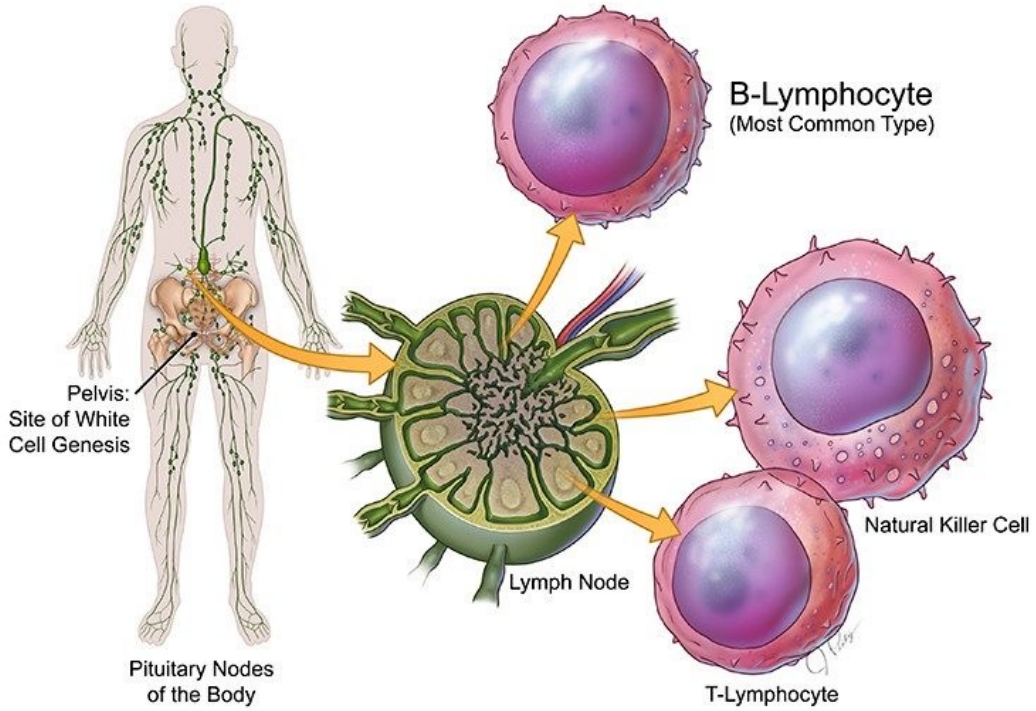
Reimbursed: acute lymphoblastic leukemia (pediatric ALL) and lymphoma

CAR-T cell therapy in Belgium

> Since May 1, 2025, CAR-T cell therapy is also reimbursed for the treatment of **multiple myeloma**, in addition to its established indications in ALL and certain lymphomas.

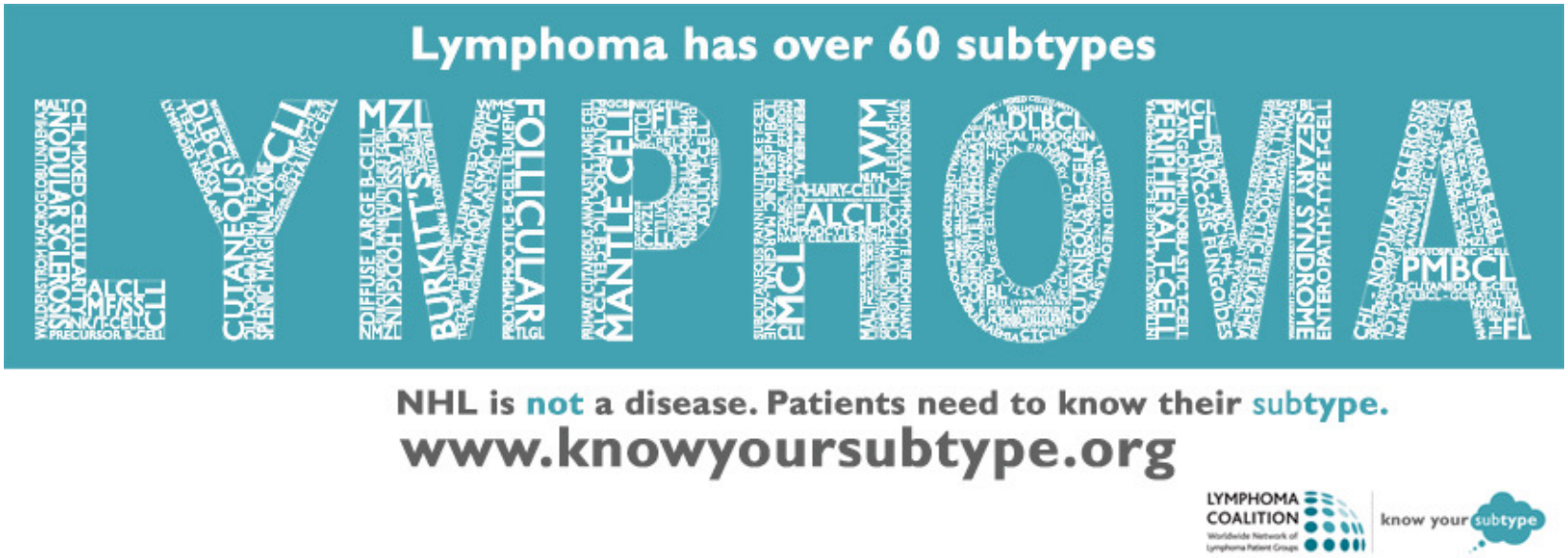
CAR-T cell therapy for lymphoma

- Lymphoma
  - B-cell non-Hodgkin lymphoma (B-NHL)



CAR-T cell therapy for lymphoma

- Lymphoma
  - B-cell non-Hodgkin lymphoma (B-NHL)

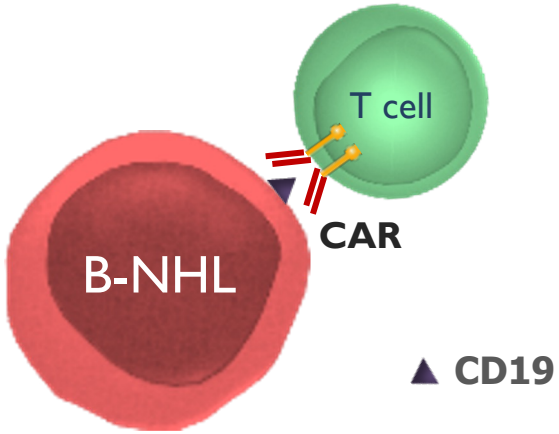


  - *Indolent* lymphoma (e.g. follicular lymphoma)
  - *Agressive* lymphoma (e.g. DLBCL, PMBCL)

CAR-T cell therapy for lymphoma

- Lymphoma
  - B-cell non-Hodgkin lymphoma (B-NHL)

    -> expresses CD19



- Currently reimbursed in Belgium
  - Axicabtagene ciloleucel (axi-cel, Yescarta®)
  - Brexucabtagene autoleucel (brexu-cel, Tecartus®)
    - CAR-T directed towards CD19
    - Pharmaceutical company: Gilead/Kite

CAR-T cell therapy for lymphoma

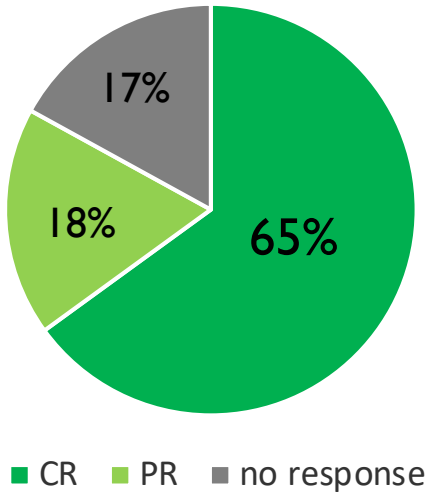
- Currently reimbursed in Belgium

	Axi-cel 2L	Axi-cel 2L+	Brexu-cel 2L+ (≤5L)
Diffuse large B-cell lymphoma (DLBCL) or High-grade B-cell lymphoma (HBCL)	☑	☑	☒
Primary mediastinal B-cell lymphoma (PMBCL)	☒	☑	☒
Mantle cell lymphoma (MCL)	☒	☒	☑

CAR-T cell therapy for lymphoma

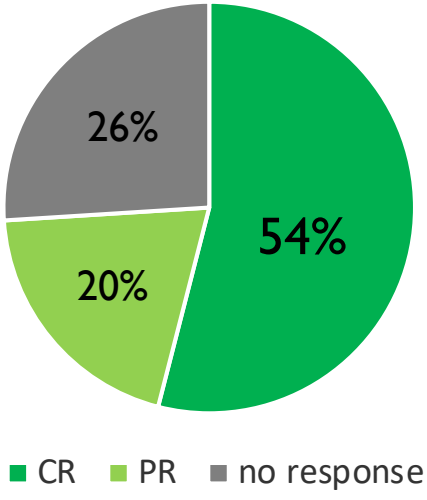
- Efficacy
  - Response rate

Axi-cel 2L



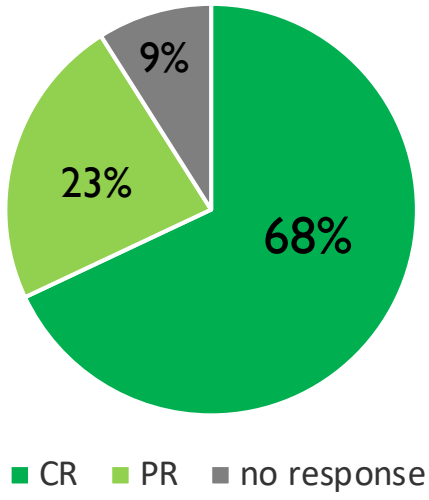
Locke et al. *NEJM* (2022)

Axi-cel 2L+



Locke et al. *Lancet Oncol* (2019)

Brexu-cel

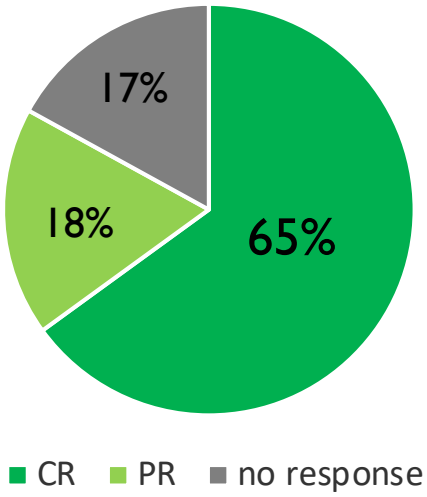


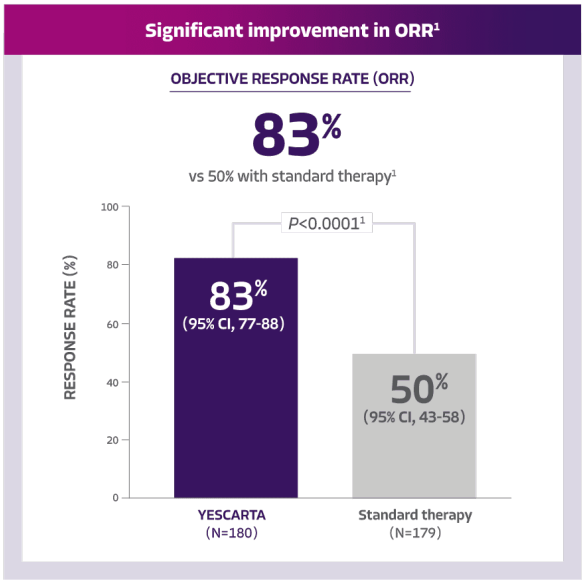
Wang et al. *JCO* (2023)

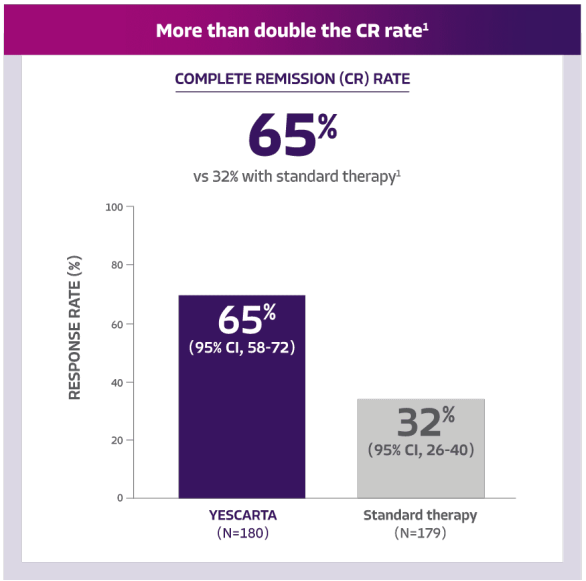
CAR-T cell therapy for lymphoma

- Efficacy
  - Response rate

Axi-cel 2L



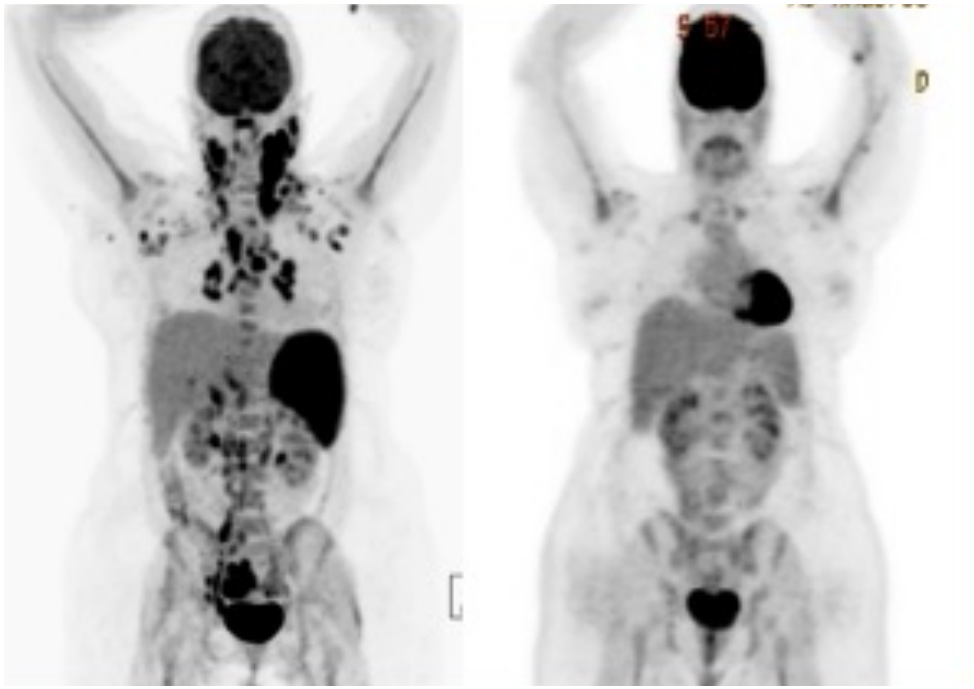




Locke et al. *NEJM* (2022)

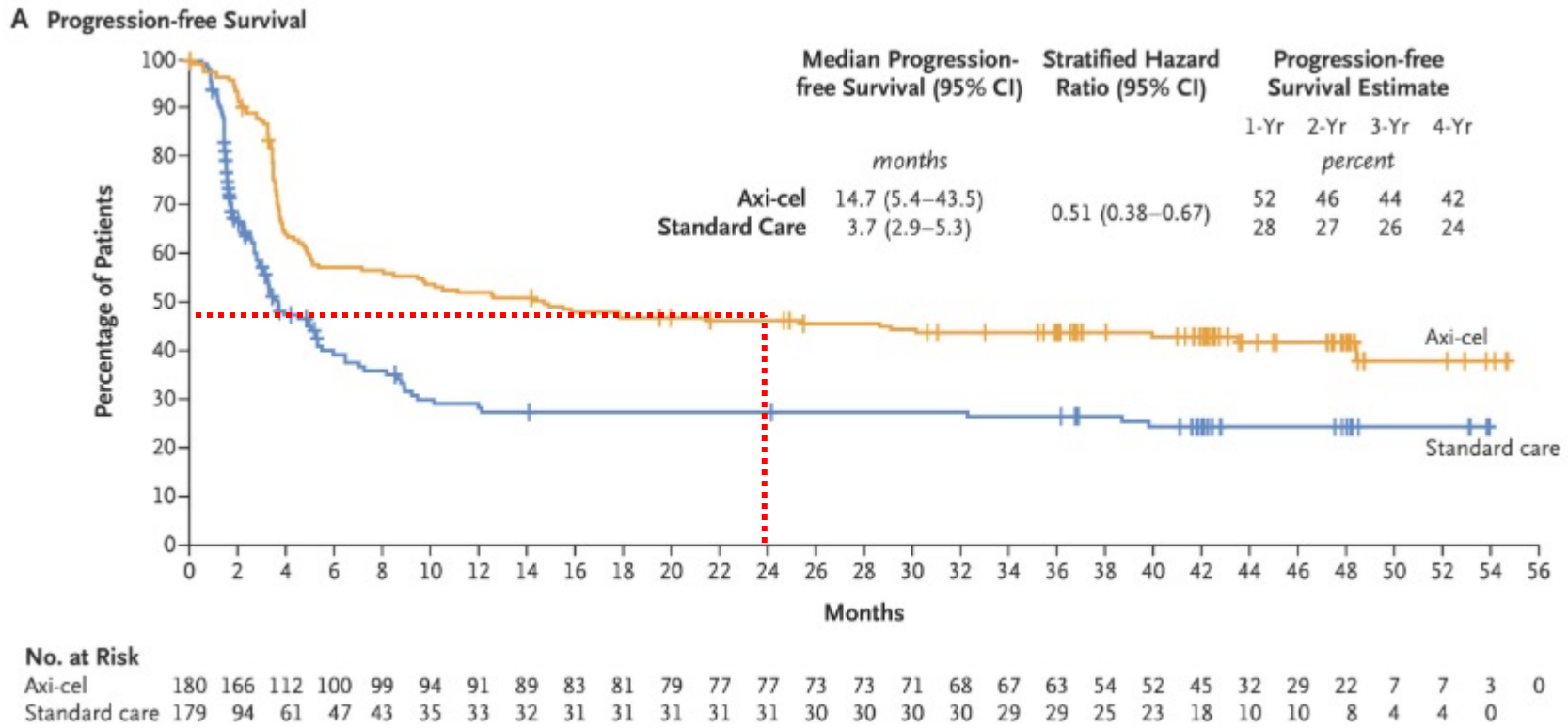
CAR-T cell therapy for lymphoma

- Efficacy
  - Response rate



CAR-T cell therapy for lymphoma

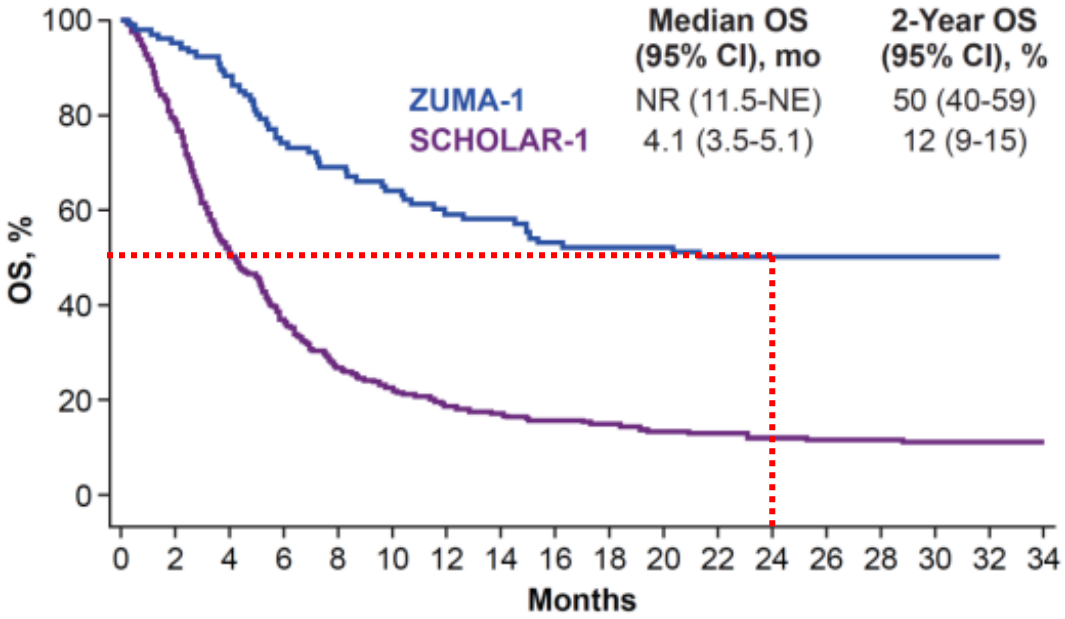
- Efficacy
  - Progression-free survival: e.g. axi-cel 2L



Westin et al. *NEJM* (2023)

CAR-T cell therapy for lymphoma

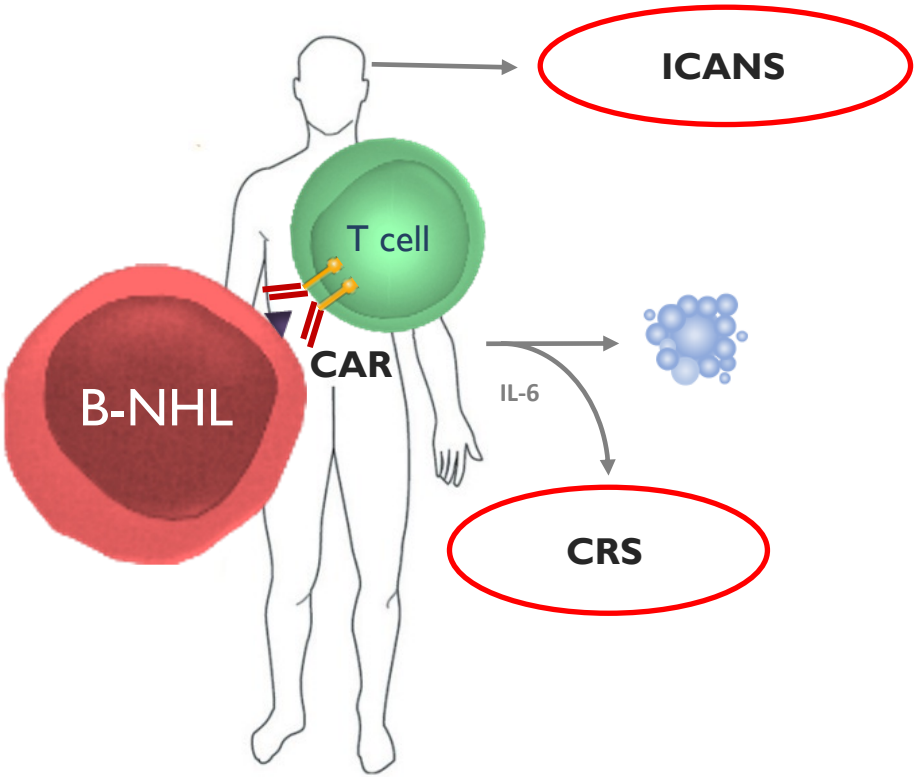
- Efficacy
  - Overall survival: e.g. axi-cel 2L+



Neelapu et al. *Blood Adv* (2021)

CAR-T cell therapy for lymphoma

- Toxicities
  - CRS = cytokine release syndrome
  - ICANS = immune effector cell-associated neurotoxicity syndrome



CAR-T cell therapy for lymphoma

- Toxicities
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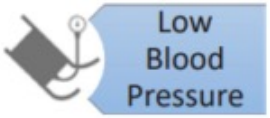
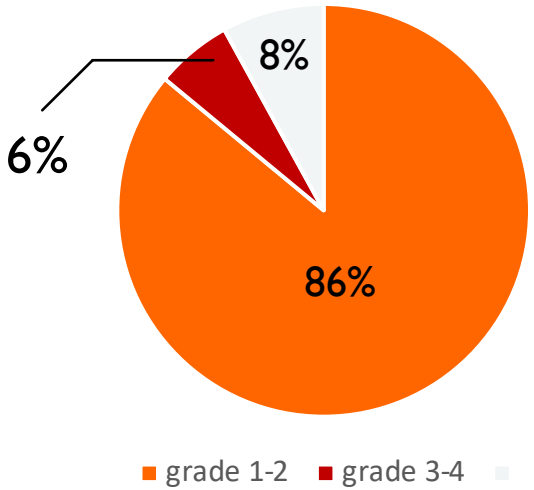
			
Grade 1	☑	☒	☒
Grade 2	☑	☑ No vasopressor	*and/or* ☑ ≤6L O_2
Grade 3	☑	☑ 1 vasopressor	*and/or* ☑ >6L O_2
Grade 4	☑	☑ ≥ 2 vasopressors	*and/or* ☑ PAP ventilation

Yáñez L et al. *ESMO Open* (2020)

CAR-T cell therapy for lymphoma

- Toxicities
  - CRS = cytokine release syndrome

e.g. axi-cel 2L

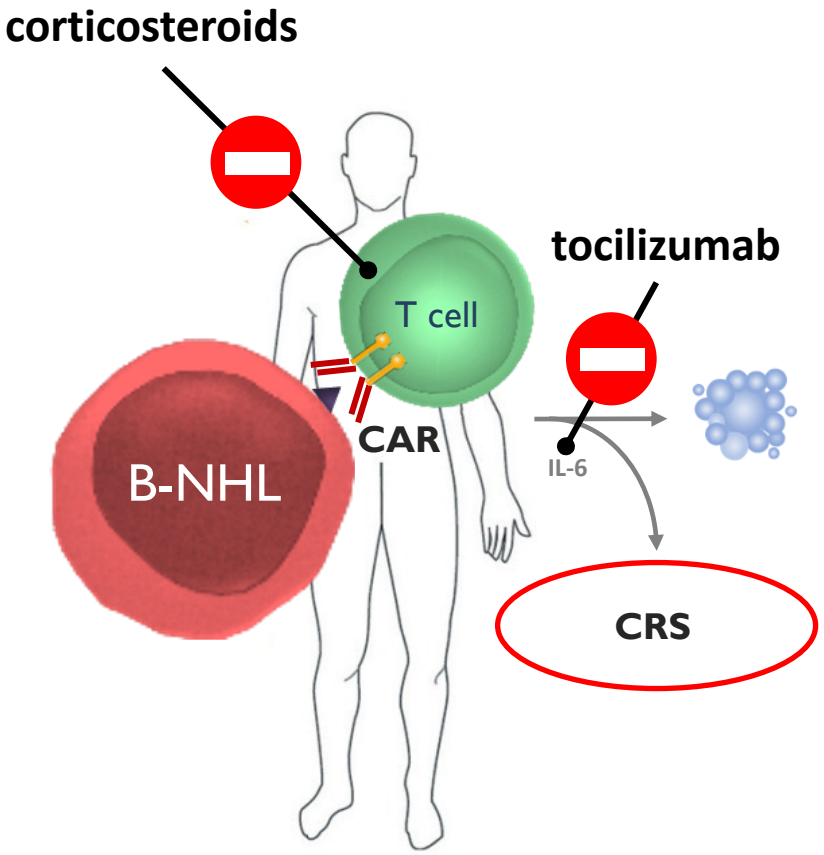


- Median time to onset: 3 days (1-10)
- Median duration: 7 days

Locke et al. *NEJM* (2022)

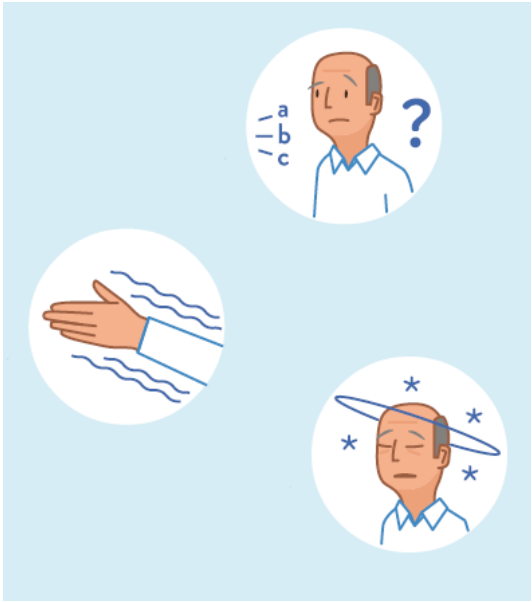
CAR-T cell therapy for lymphoma

- Toxicities
  - CRS = cytokine release syndrome
    - Treatment



CAR-T cell therapy for lymphoma

- Toxicity
  - ICANS = immune effector cell-associated neurotoxicity syndrome
    - Confusion
    - Somnolence -> coma
    - Difficulty speaking / understanding / writingjven
    - Seizures
    - Agressive behaviour
    - …



CAR-T cell therapy for lymphoma

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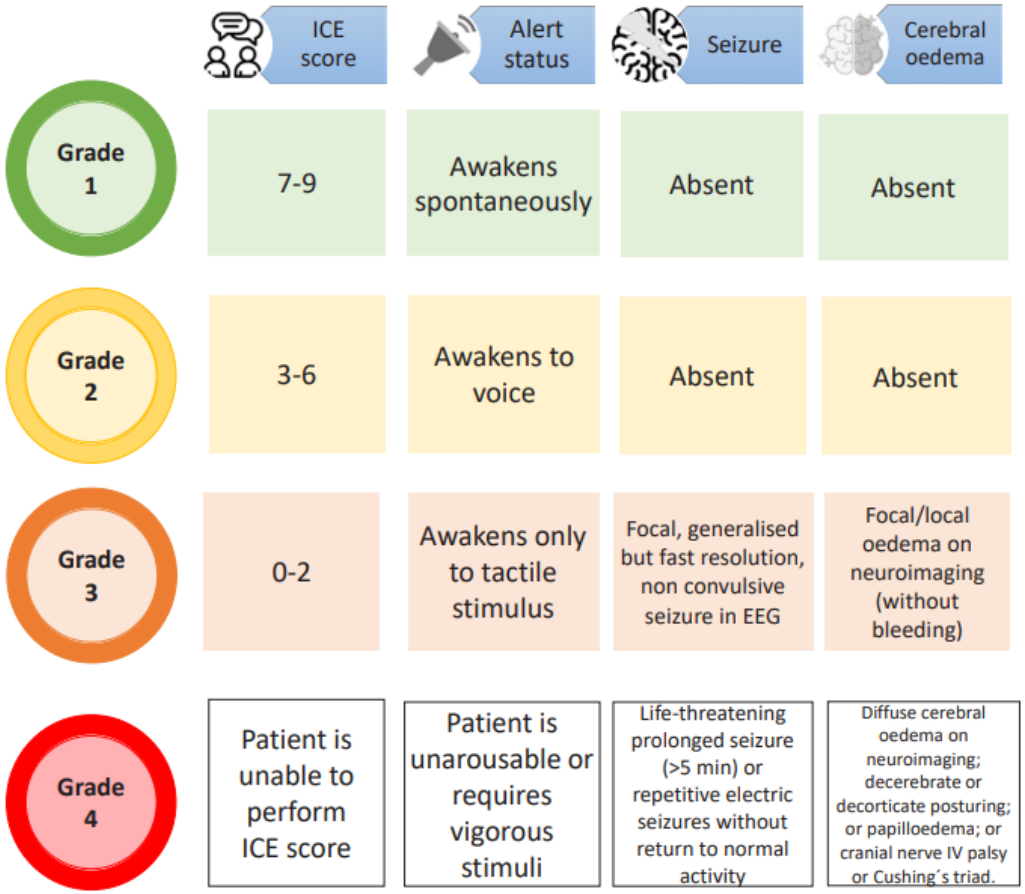

	ICE score	Alert status	Seizure	Cerebral oedema
Grade 1	7-9	Awakens spontaneously	Absent	Absent
Grade 2	3-6	Awakens to voice	Absent	Absent
Grade 3	0-2	Awakens only to tactile stimulus	Focal, generalised but fast resolution, non convulsive seizure in EEG	Focal/local oedema on neuroimaging (without bleeding)
Grade 4	Patient is unable to perform ICE score	Patient is unarousable or requires vigorous stimuli	Life-threatening prolonged seizure (>5 min) or repetitive electric seizures without return to normal activity	Diffuse cerebral oedema on neuroimaging; decerebrate or decorticate posturing; or papilloedema; or cranial nerve IV palsy or Cushing´s triad.

CAR-T cell therapy for lymphoma

- Toxicities
  - ICANS = immune effector cell-associated neurotoxicity syndrome

Dagelijkse evaluatie van neurotoxiciteit via ICE/CARTOX-10 gradering

Patiëntidentificatie (patiënt etiket)

Naam van patiënt
Geboortedatum

	Jaar	Maand	Stad	Hospitaal	Koning *CARTOX-10*	Voorwerp 1	Voorwerp 2	Voorwerp 3	Instructie *ICE*	100 > 10 In 10 "	SCORE	
Datum en tijd 3/??/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	*CARTOX-10*	*ICE*
Naam VK	**Handschrift** → IK BEN NIET GRAAG IN HET ZIEKENHUIS										10	10
	Jaar	Maand	Stad	Hospitaal	Koning *CARTOX-10*	Voorwerp 1	Voorwerp 2	Voorwerp 3	Instructie *ICE*	100 > 10 In 10 "	SCORE	
Datum en tijd 10/1/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	*CARTOX-10*	*ICE*
Naam VK	**Handschrift** IK BEN NIET GRAAG IN HET ZIEKENHUIS										10	10
	Jaar	Maand	Stad	Hospitaal	Koning *CARTOX-10*	Voorwerp 1	Voorwerp 2	Voorwerp 3	Instructie *ICE*	100 > 10 In 10 "	SCORE	
Datum en tijd 13/1/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	*CARTOX-10*	*ICE*
	Handschrift IK BEN NIET GRAAG IN HET ZIEKEN HUIS										10	10
	Jaar	Maand	Stad	Hospitaal	Koning *CARTOX-10*	Voorwerp 1	Voorwerp 2	Voorwerp 3	Instructie *ICE*	100 > 10 In 10 "	SCORE	
Datum en tijd 17/1/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	*CARTOX-10*	*ICE*
	Handschrift IK BEN NIET GRAAG IN HET ZIEKENHUIS										10	10
	Jaar	Maand	Stad	Hospitaal	Koning *CARTOX-10*	Voorwerp 1	Voorwerp 2	Voorwerp 3	Instructie *ICE*	100 > 10 In 10 "	SCORE	
Datum en tijd 24/01/23	1	1	1	1	1	1	1	1	1	1	*CARTOX-10*	*ICE*
	Handschrift → IK BEN NIET GRAAG IN HET ZIEKENHUIS										10	10

CAR-T cell therapy for lymphoma

- Toxicities
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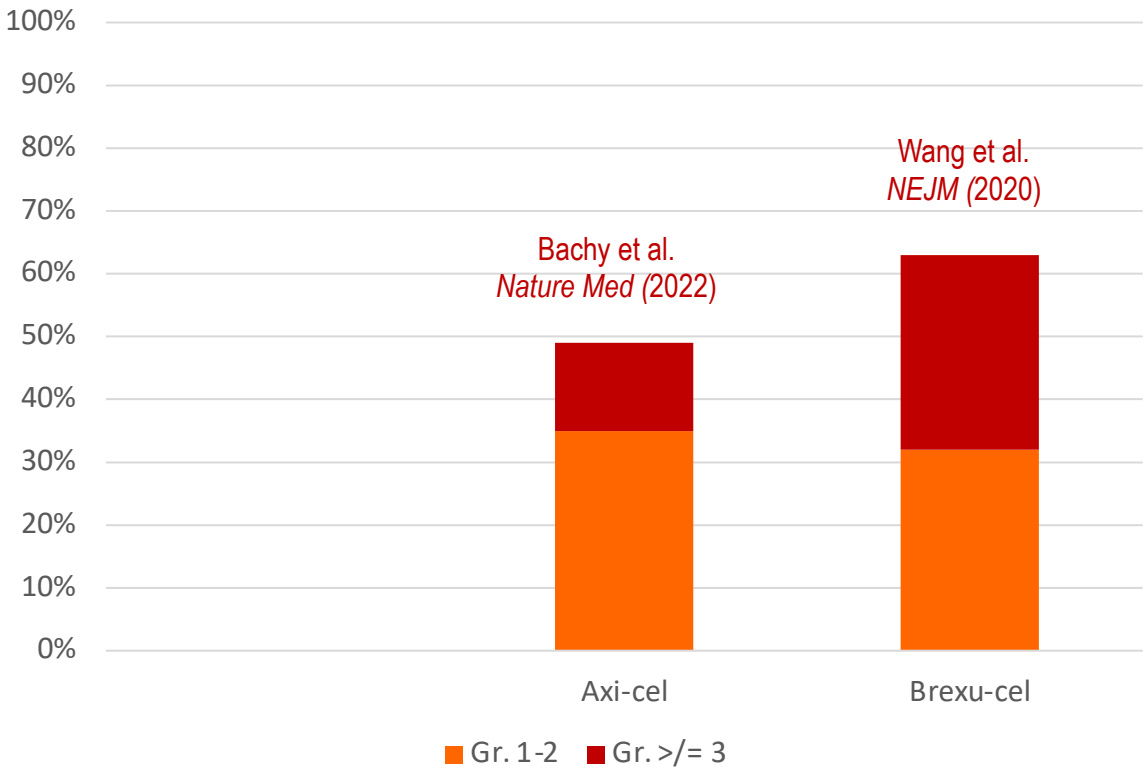
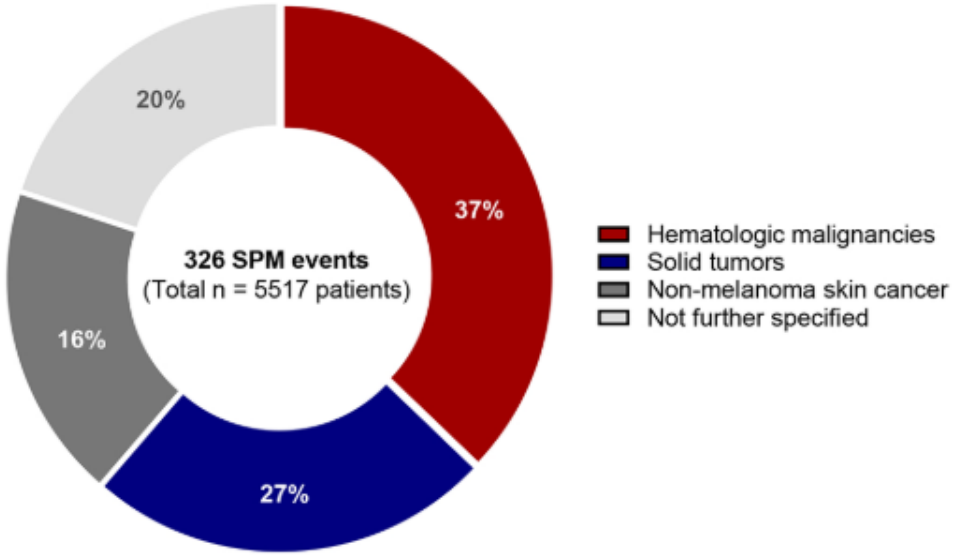


  - Median time to onset: 7 days

CAR-T cell therapy for lymphoma

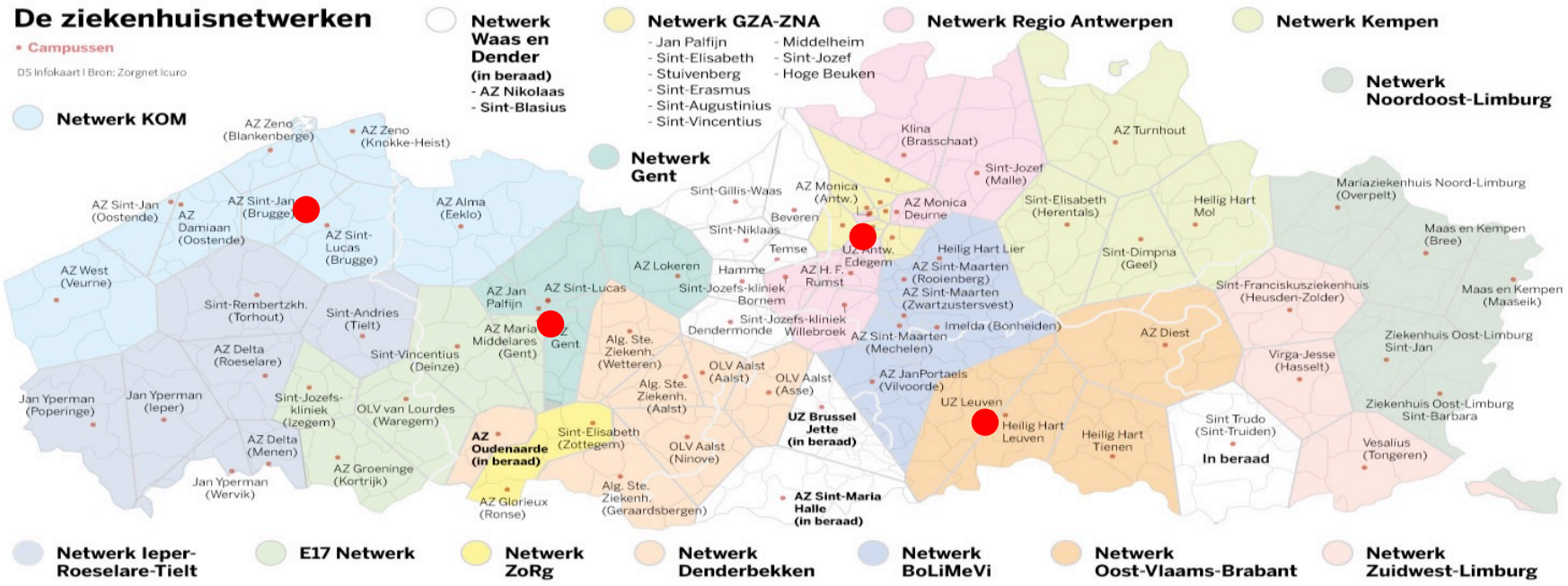
- Toxicities
  - Cytopenias
  - Infections
    - Due to ↓ white blood cells
    - Due to hypogammaglobulinemia
  - Second cancers
    - 6%
    - MDS most common
    - (CAR-)T cell lymphoma
      = rare



Tix et al. *Clin Cancer Res* (2025)

CAR-T cell therapy for lymphoma

- Availability in Flanders/Belgium: **reimbursed** in CAR-T infusion centers
  - Axi-cel (Yescarta®) and brexu-cel (Tecartus®)



CAR-T cell therapy for lymphoma

- Availability in Flanders/Belgium: via **clinical trials**

DeMorgen.

POLITIEK | BETER LEVEN | TV & CULTUUR | VOOR U UITGELEGD

Nieuws Kankeronderzoek

UZA behandelt als eerste Belgisch ziekenhuis kankerpatiënt met lokaal geproduceerde CAR-T-cellen

Beeld photonews

Het Universitair Ziekenhuis Antwerpen (UZA) heeft voor het eerst een lymfeklierkanker-patiënt behandeld met CAR-T-cellen die lokaal geproduceerd werden. CAR-T-celtherapie is een vorm van kankerbehandeling die gebruik maakt van het afweersysteem van de patiënt.

CAR-T cell therapy for lymphoma

- Availability in Flanders/Belgium: via **clinical trials**
  - Local, decentralized manufacturing model in Galapagos Atalanta-1 study

Universiteit Antwerpen

UZA
kennis / ervaring / zorg

anicells
advancing innovative cell therapy solutions to the patient

Galápagos

CAR-T cell therapy for lymphoma

- Availability in Flanders/Belgium: via **clinical trials**
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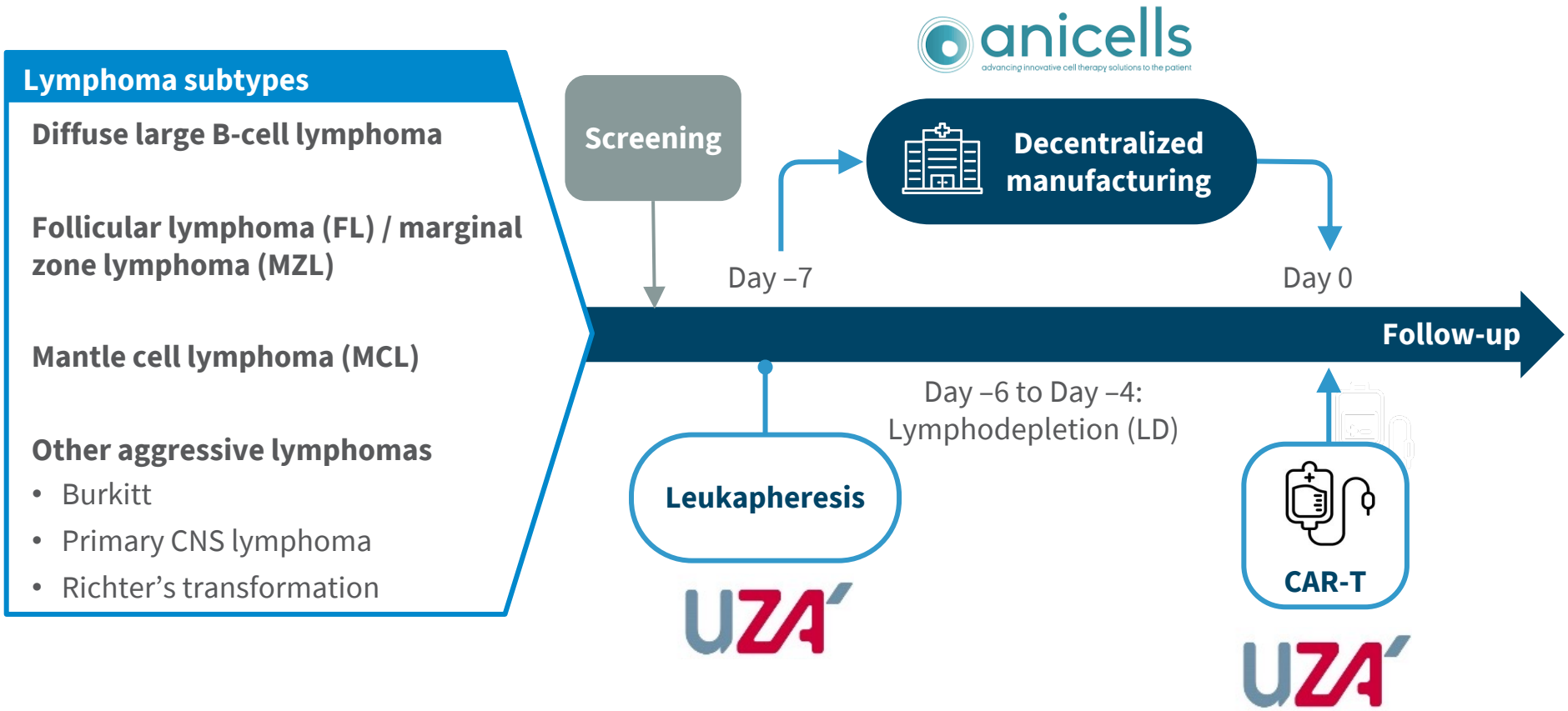

CAR-T cell therapy for lymphoma

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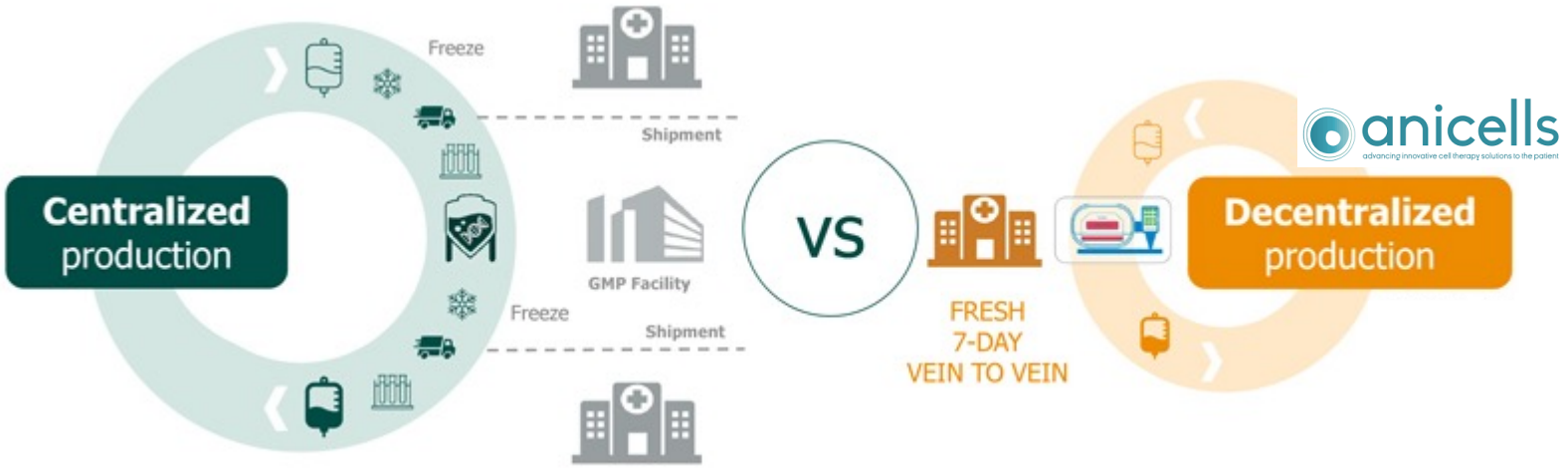


Local manufacturing

-> bypassing complex logistic chain

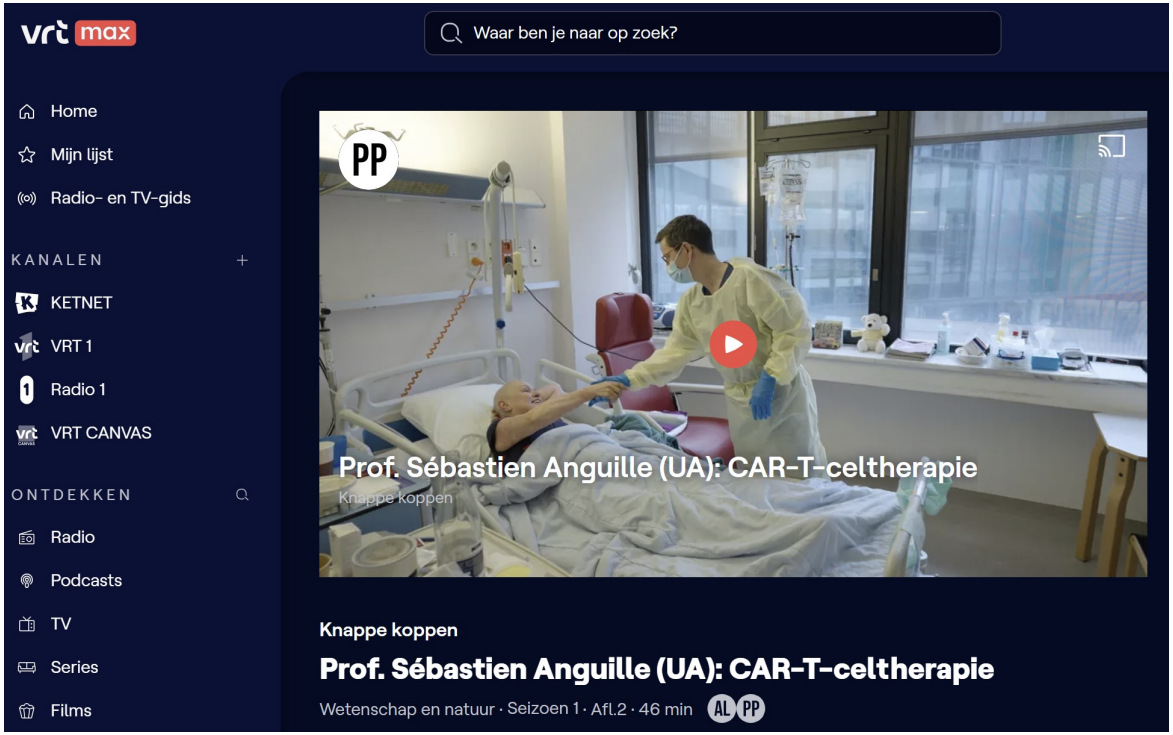
CAR-T ready for infusion in **one week**

Decreased costs

CAR-T cell therapy for lymphoma

- Availability in Flanders/Belgium: via **clinical trials**
  - Local, decentralized manufacturing model in Galapagos Atalanta-1 study

- **First patient**, Tom, was treated in March, 2022

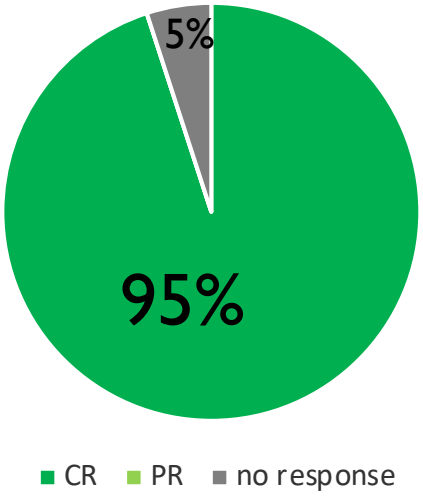


CAR-T cell therapy for lymphoma

- Availability in Flanders/Belgium: via **clinical trials**
  - Local, decentralized manufacturing model in Galapagos Atalanta-1 study

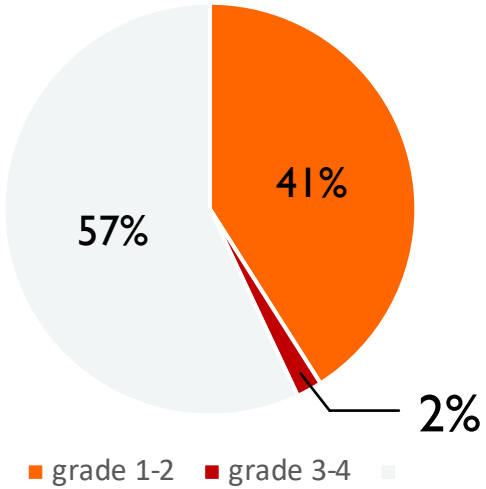
- As of Nov, 2025, **100 patients were dosed** in the Atalanta-1 study

Efficacy in FL/MZL (n=21)

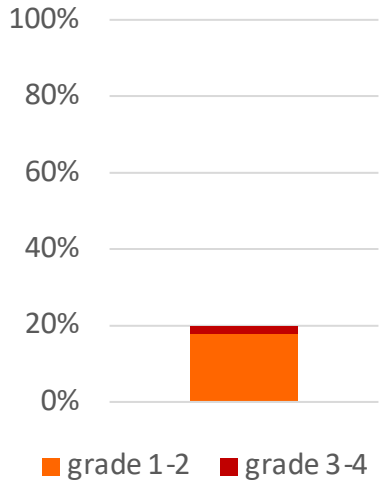


Kersten et al. *ASH* (2024)

CRS (n=61)



ICANS (n=61)



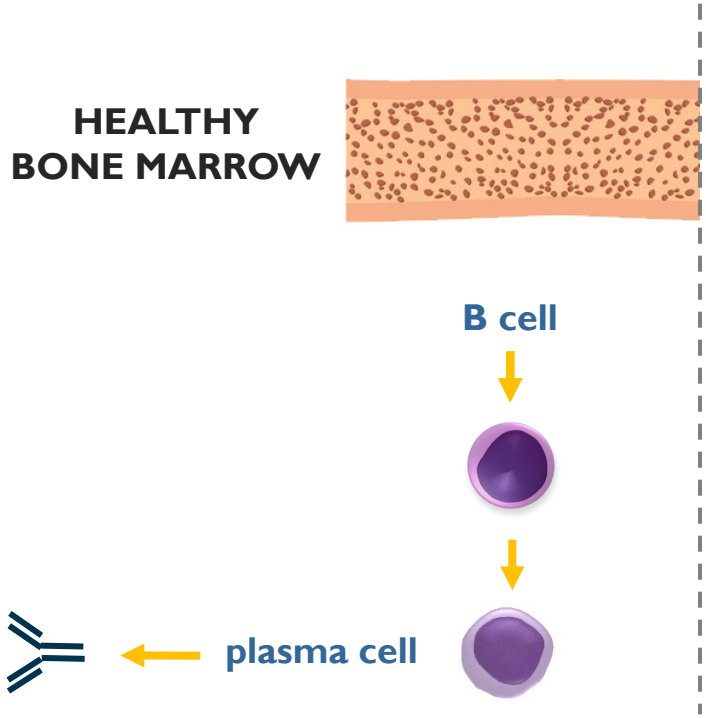
Vermaat et al. *EHA* (2025)

CAR-T cell therapy for lymphoma

- Availability in Flanders/Belgium: via **clinical trials**
  - IMMENSI-T2 study (expected 2026)
    - Pharmaceutical company: Kite
    - Phase 3: Bispecific CAR-T directed towards CD19 and CD20 vs axi-cel 2L
  - Bowery study (expected 2026)
    - Pharmaceutical company: J&J
    - Phase 3: Bispecific CAR-T directed towards CD19 and CD20 vs axi-cel 2L

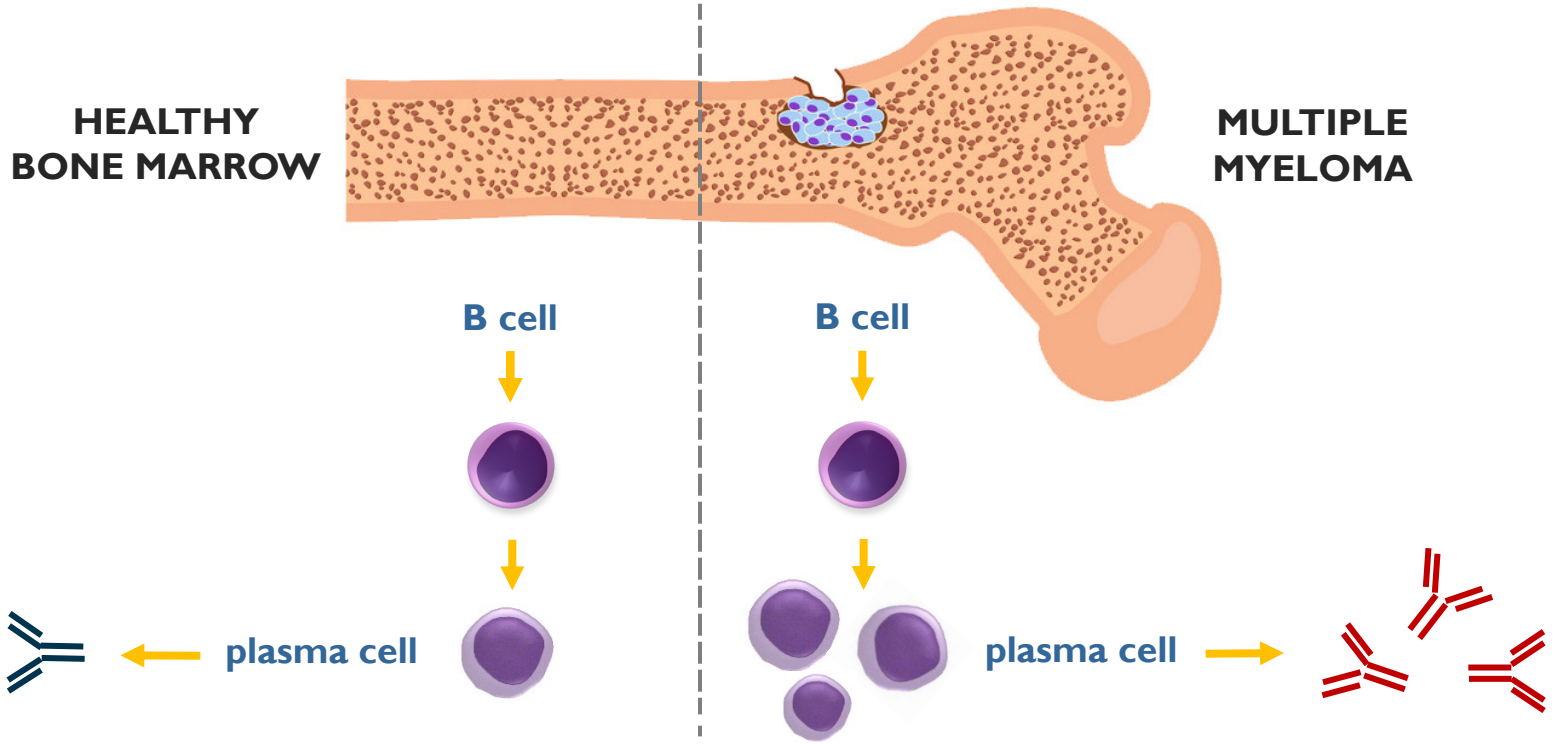
CAR-T cell therapy for multiple myeloma

- Multiple myeloma
  - 2nd most common hematological malignancy
  - Malignant proliferation of plasma cells in the bone marrow



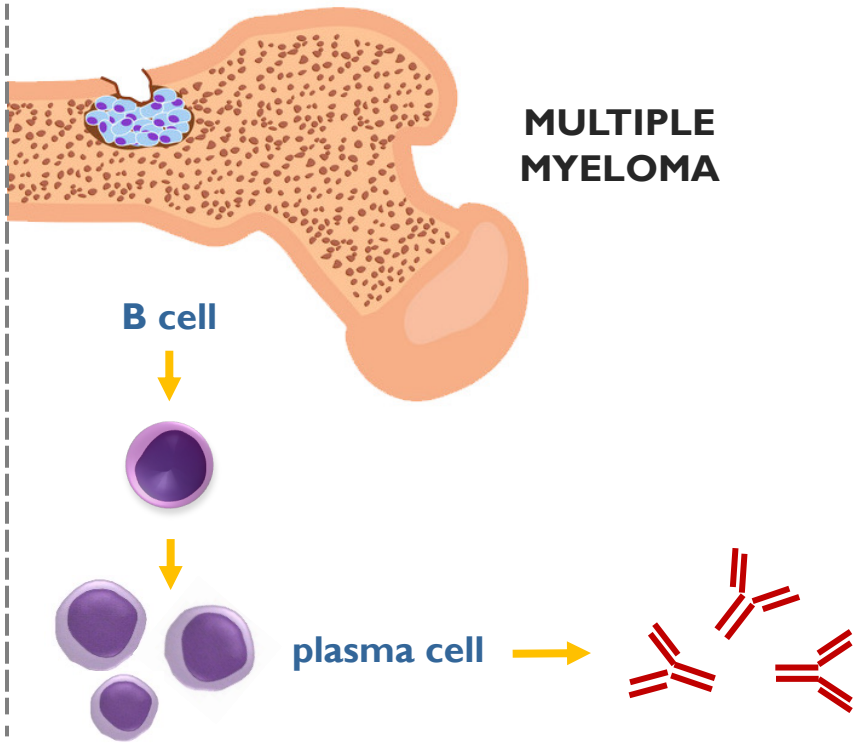
CAR-T cell therapy for multiple myeloma

- Multiple myeloma
  - 2nd most common hematological malignancy
  - Malignant proliferation of plasma cells in the bone marrow



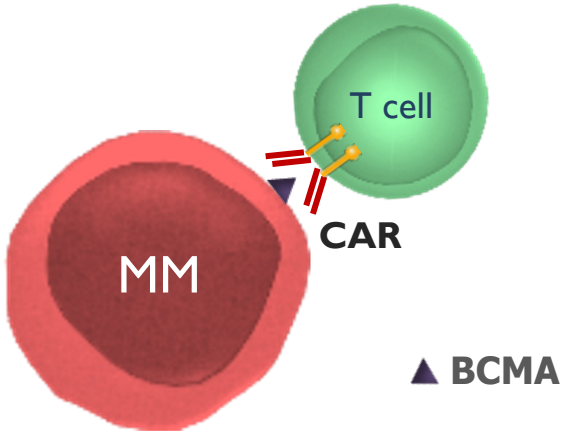
CAR-T cell therapy for multiple myeloma

- Multiple myeloma
  - 2nd most common hematological malignancy
  - Malignant proliferation of plasma cells in the bone marrow



CAR-T cell therapy for multiple myeloma

- Multiple myeloma (MM)
  - Expresses B-cell maturation antigen (BCMA)



- Currently reimbursed in Belgium
  - Ciltacabtagene autoleucel (cilta-cel, Carvykti®)
    - CAR-T directed towards BCMA
    - Pharmaceutical company: J&J
    - Essential reimbursement criteria
      - at least 1 line of prior systemic therapy including a PI and IMiD
      - patients must be lenalidomide-refractory
      - no need for prior exposure to anti-CD38 antibody
      - prior BCMA-targeted therapy is not allowed
      - prior GPRC5D-targeted therapy (e.g. talquetamab) is not allowed

CAR-T cell therapy for multiple myeloma

Home > Actueel > Nieuws >

3 dure geneesmiddelen vooralsnog niet vergoed

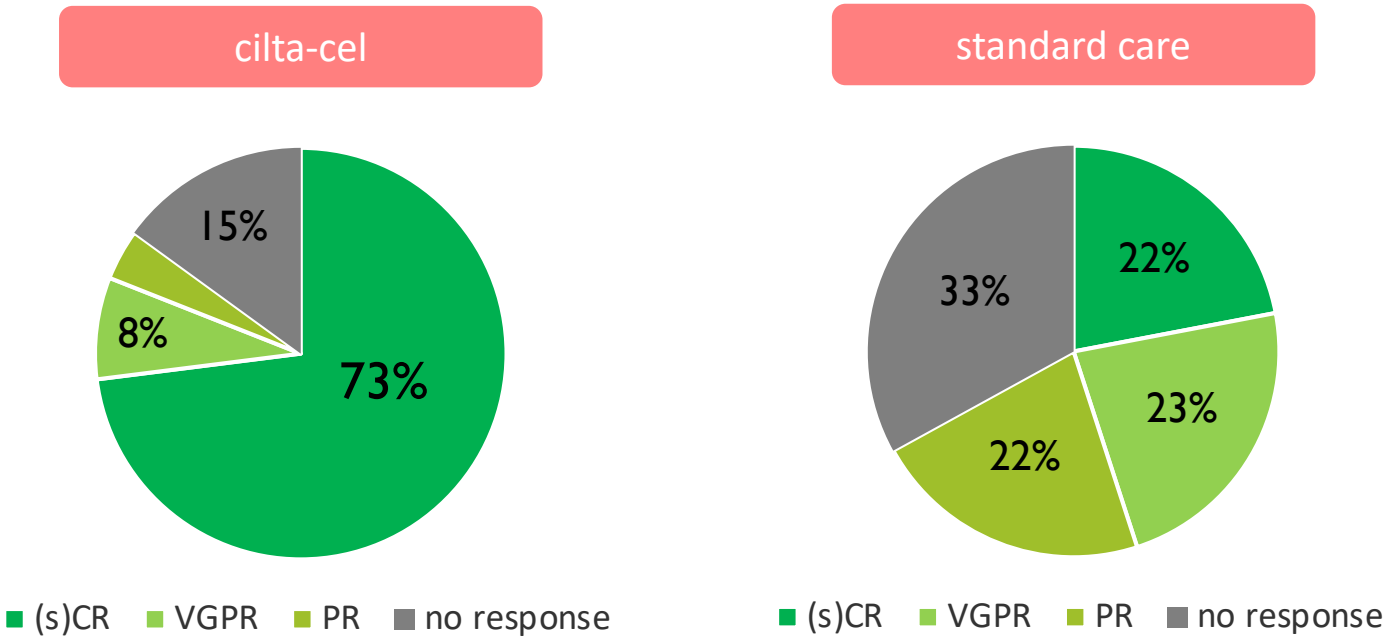
Nieuwsbericht | 11-11-2025 | 17:00

Minister Jan Anthonie Bruijn van Volksgezondheid, Welzijn en Sport (VWS) heeft besloten de sluisplaatsing van 3 dure geneesmiddelen te verlengen, omdat de onderhandelingen met de leveranciers op dit moment niet hebben geleid tot een maatschappelijk aanvaardbare prijs. Dit betekent dat de geneesmiddelen vooralsnog niet opgenomen worden in het basispakket van de zorgverzekering.

Het gaat om de geneesmiddelen Xenpozyme (olipudase alfa), Carvykti (ciltacabtagene autoleucel) en Enhertu (trastuzumab deruxtecan). In het geval van het geneesmiddel Enhertu gaat het om de behandeling van HER2-low borstkanker. Enhertu blijft wél vergoed voor de behandeling van HER2-positieve borstkanker.

CAR-T cell therapy for multiple myeloma

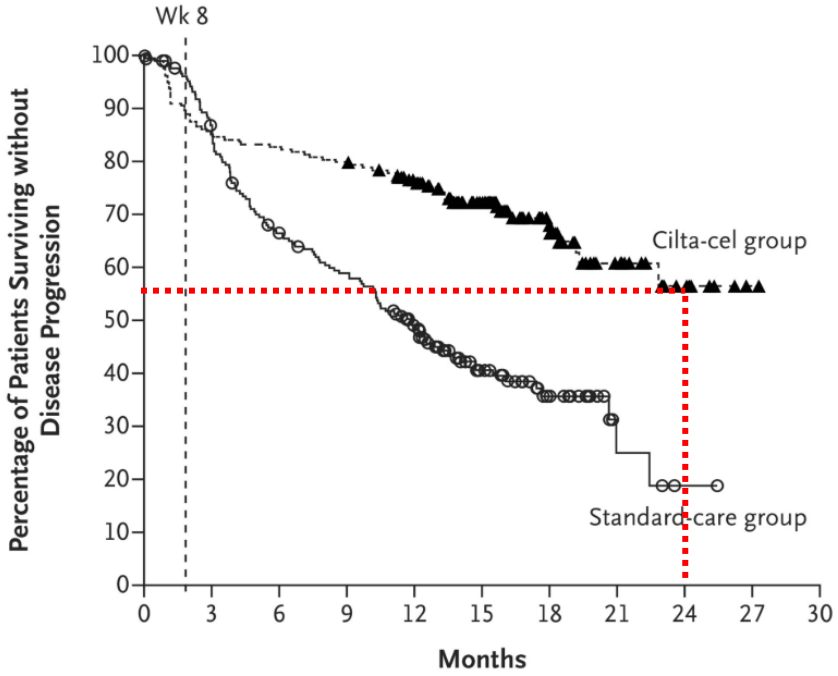
- Efficacy
  - Response rate



San-Miguel et al. *NEJM* (2023)

CAR-T cell therapy for multiple myeloma

- Efficacy
  - Progression-free survival



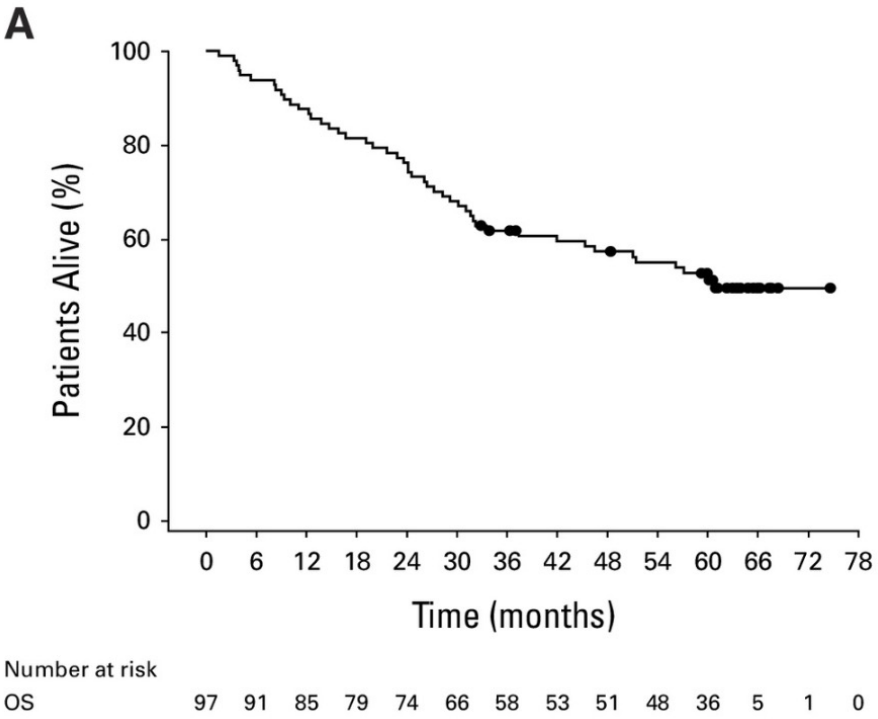
No. at Risk

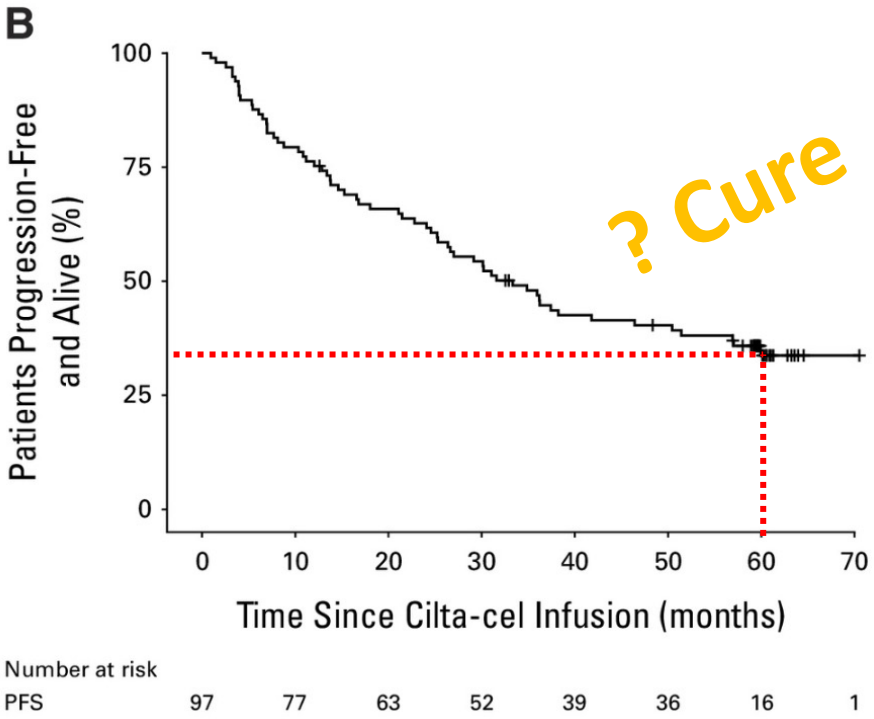
Cilta-cel group	208	177	172	166	146	94	45	22	9	1	0
Standard-care group	211	176	133	116	88	46	20	4	1	0	0

San-Miguel et al. *NEJM* (2023)

CAR-T cell therapy for multiple myeloma

- Efficacy
  - Overall survival

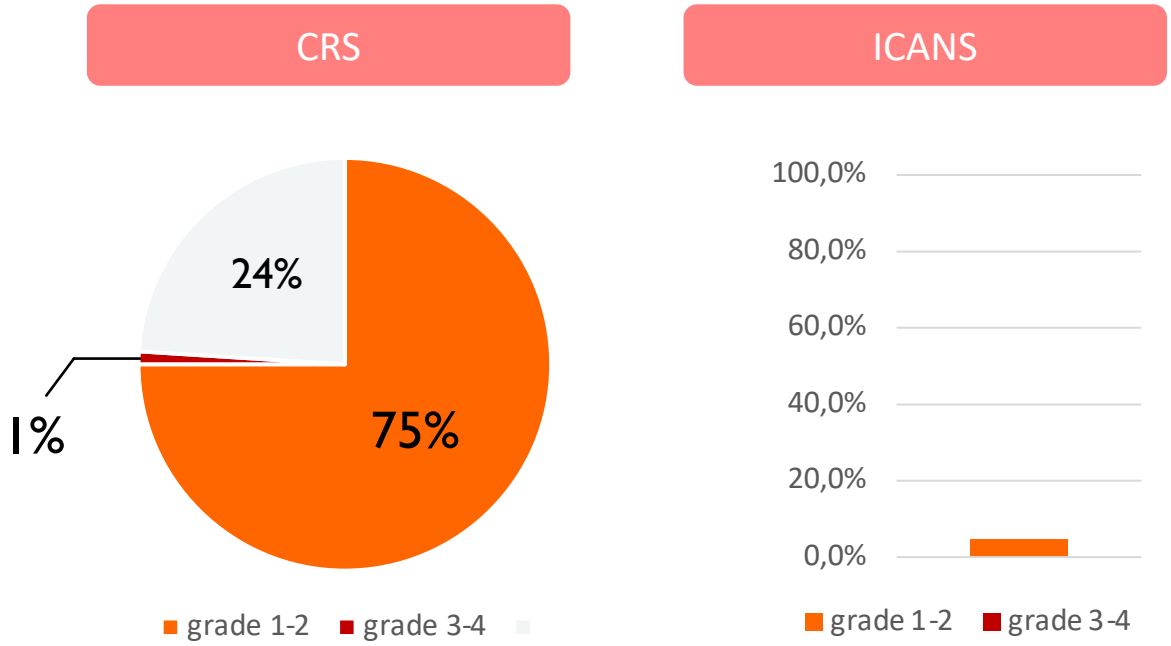




Jagannath et al. *JCO* (2025)

CAR-T cell therapy for multiple myeloma

- Toxicities
  - CRS and ICANS



- Median time to onset: 8 days (1-23)
- Median duration: 3 days

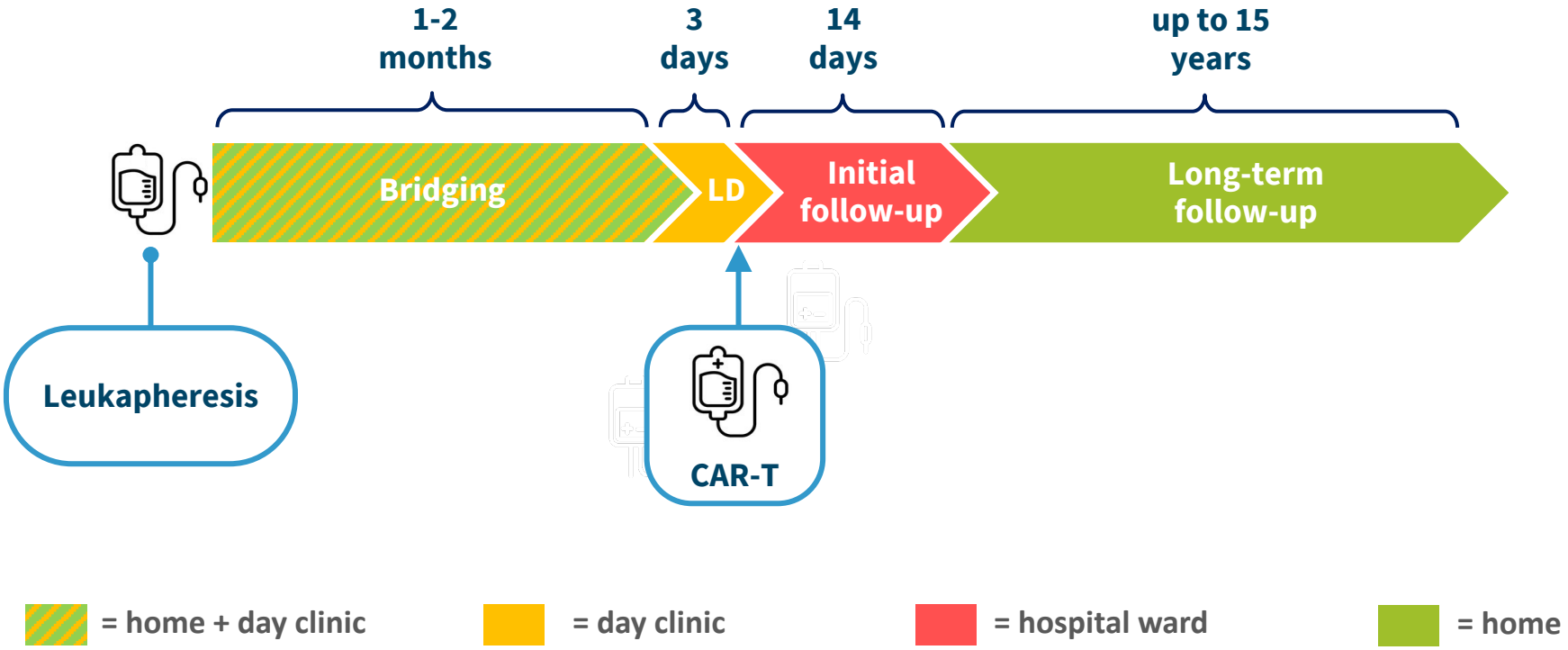
San-Miguel et al. *NEJM* (2023)

CAR-T cell therapy for multiple myeloma

- Toxicities
  - Non-ICANS neurotoxicity (NINT)
    - 10-20% of patients
    - After 14d
    - Cranial nerve palsy
    - Guillain-Barré syndrome
    - Movement and Neurocognitive Events (MNT)
      - <5% of patients
      - Can be reversible
      - Linked to high CAR-T cell expansion
    - Other

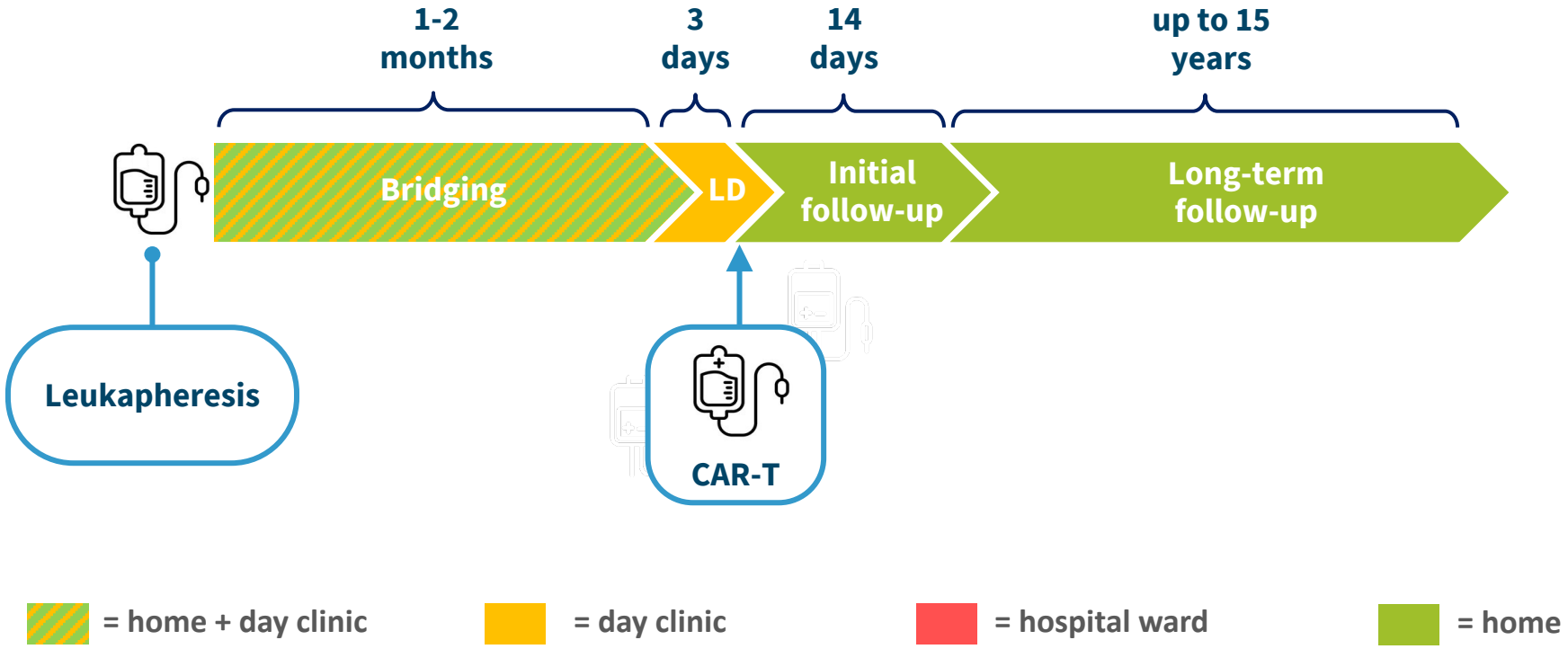
CAR-T cell therapy for multiple myeloma

- Toxicities
  - CRS and ICANS currently requires **inpatient** monitoring



CAR-T cell therapy for multiple myeloma

- Toxicities
  - CRS and ICANS monitoring in near-future in an **outpatient** setting



CAR-T cell therapy for multiple myeloma

- Toxicities
  - CRS and ICANS monitoring in near-future in an **outpatient** setting

ICANS scoring (2x/day)

CRS parameters (4x/day)

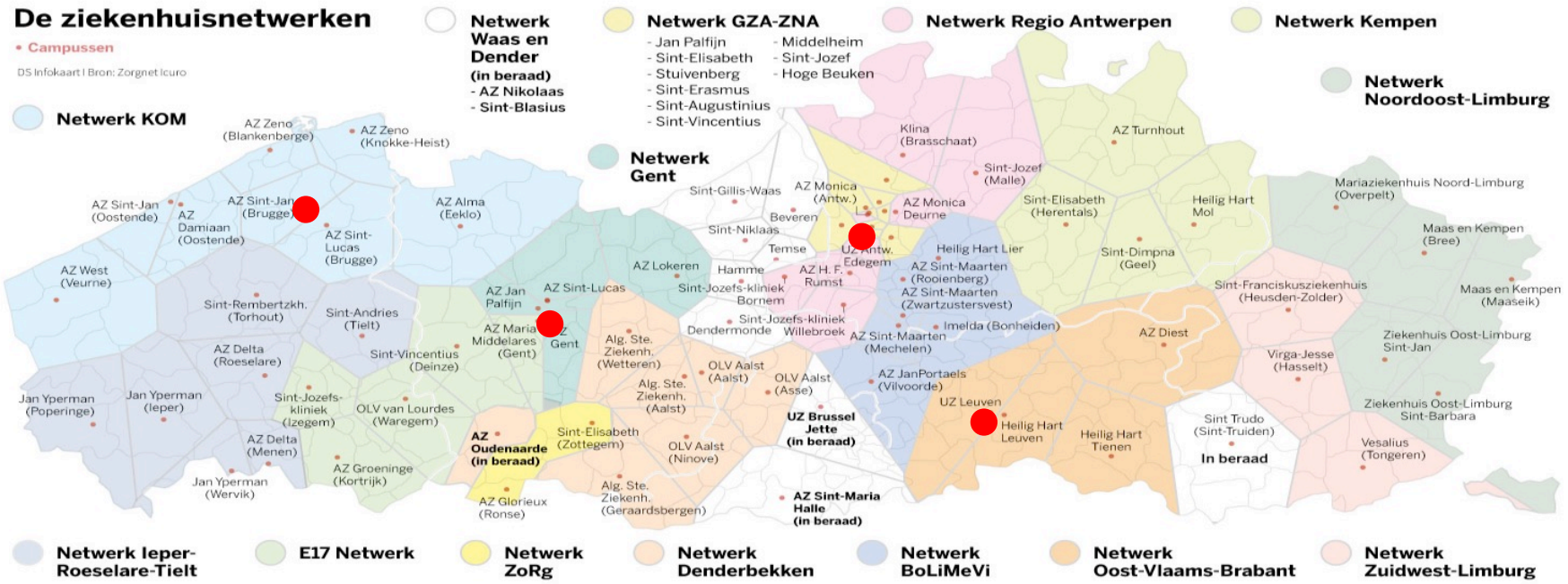
Blood draw @home (3x/week)

UZA

Rapid Response & Telemonitoring team

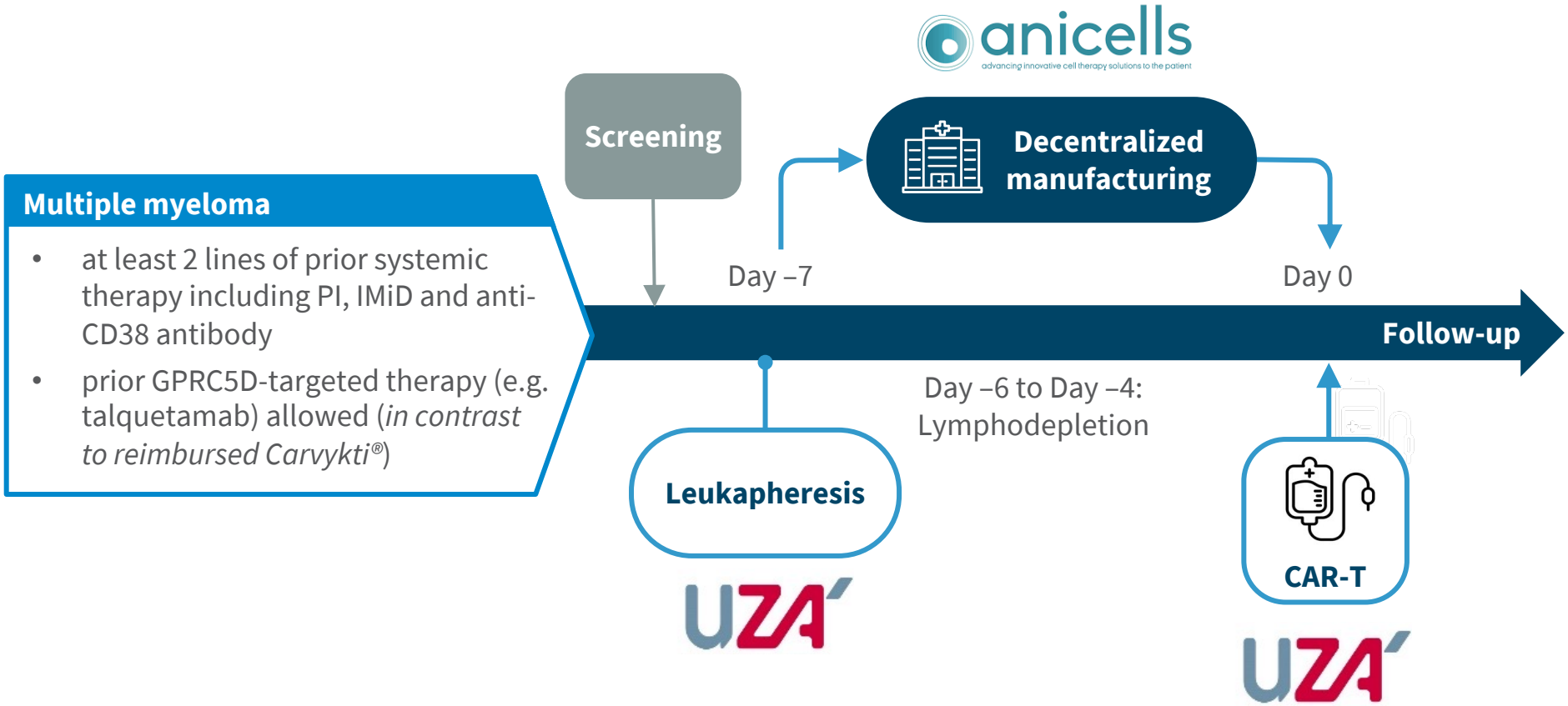
CAR-T cell therapy for multiple myeloma

- Availability in Flanders/Belgium: **reimbursed** in CAR-T infusion centers
  - Cilta-cel (Carvykti®)



CAR-T cell therapy for multiple myeloma

- Availability in Flanders/Belgium: via **clinical trials**
  - Local, decentralized manufacturing model in Galapagos Papilio-1 study



  - First patient, Christiane, was treated in December, 2023

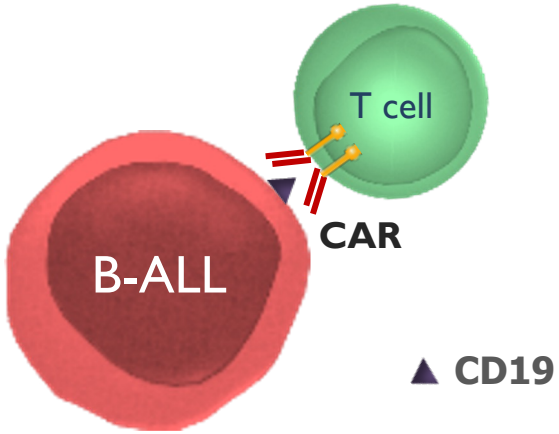
CAR-T cell therapy for multiple myeloma

- Availability in Flanders/Belgium: via **clinical trials**
  - iMMagine-3 study
    - Pharmaceutical company: Kite
    - Phase 3: CAR-T directed towards BCMA (anito-cel) vs standard care
    - 1-3 prior lines of therapy, including PI, IMID and anti-CD38 antibody
    - no need for lenalidomide-refractoriness (in contrast to reimbursed Carvykti®)
    - no cases of MNT (Parkinsonism) were observed so far
  - QUINTESSENTIAL-2 study
    - Pharmaceutical company: BMS
    - Phase 3: CAR-T directed towards GPRC5D (arlo-cel) vs standard care
    - 1-3 prior lines of therapy, including PI, IMID and anti-CD38 antibody
    - Patients must be refractory to lenalidomide
    - prior BCMA allowed (in contrast to reimbursed Carvykti®)

CAR-T cell therapy for ALL

- Acute lymphoblastic leukemia (ALL)
  - B-cell ALL (B-ALL)

    -> expresses CD19



- Currently reimbursed in Belgium
  - Tisagenlecleucel (tisa-cel, Kymriah®)
    - CAR-T directed towards CD19
    - Pharmaceutical company: Novartis
    - Only for children and young adults up to the age of 25 years

CAR-T cell therapy for ALL

- Efficacy

2012.11
6 months after CR

CAR-T cell therapy for ALL

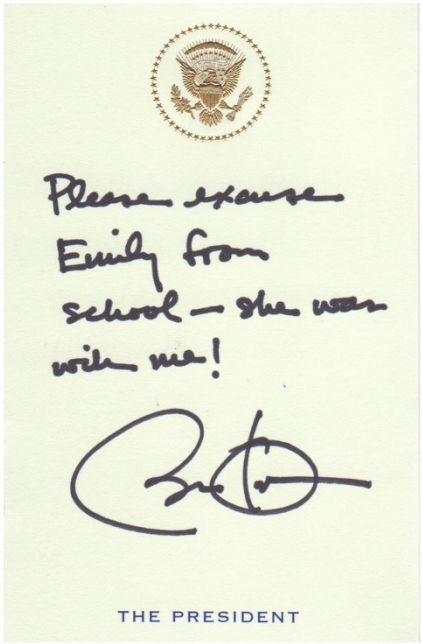
- Efficacy

CAR-T cell therapy for ALL

- Efficacy

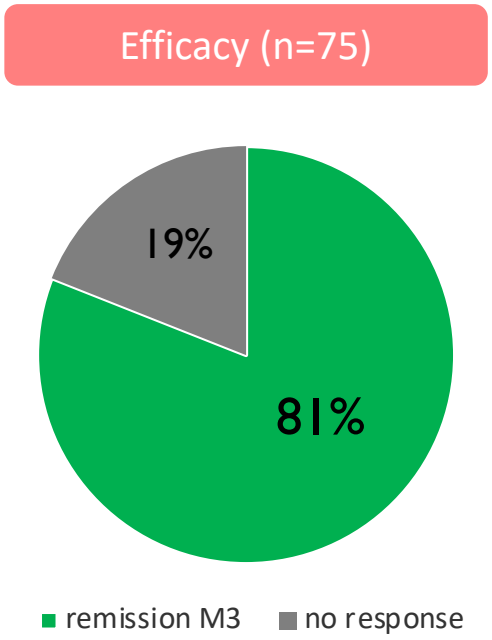
CAR-T cell therapy for ALL

- Efficacy



CAR-T cell therapy for ALL

- Efficacy
  - Response rate

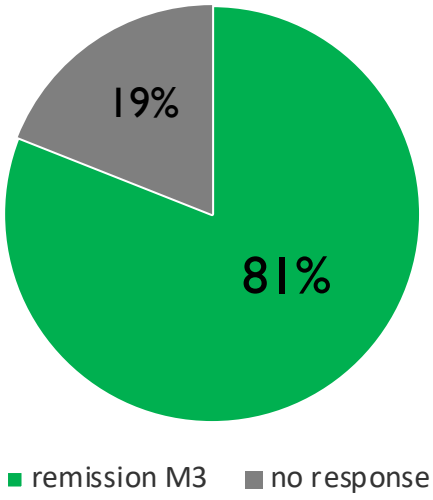


Maude et al. *NEJM* (2018)

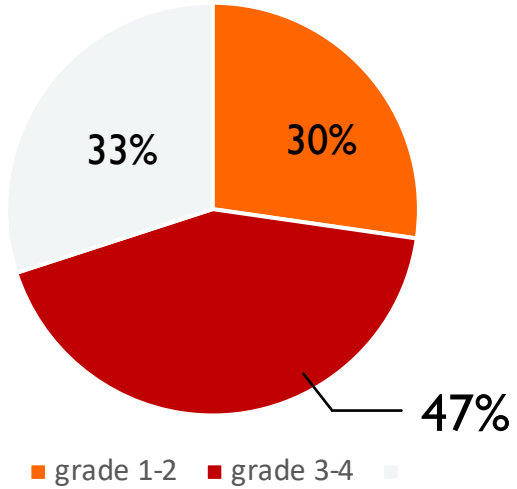
CAR-T cell therapy for ALL

- Efficacy and toxicity
  - Response rate / CRS / ICANS

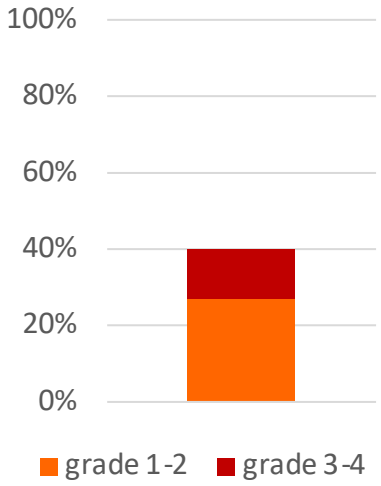
Efficacy (n=75)



CRS (n=75)



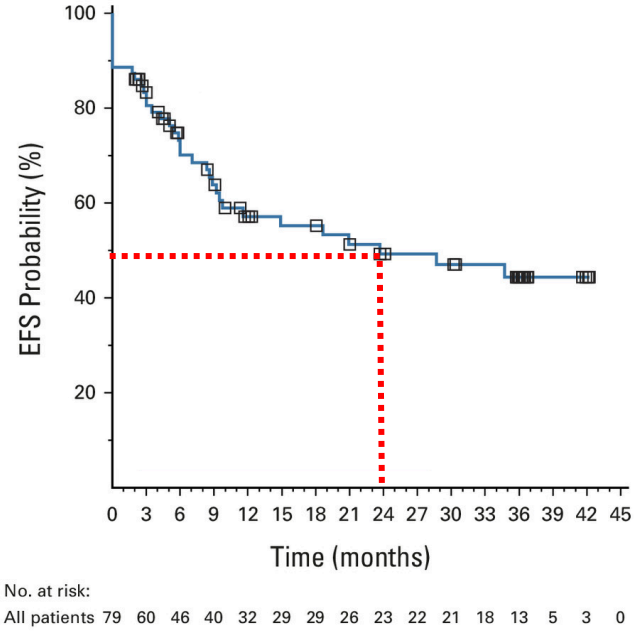
ICANS (n=75)

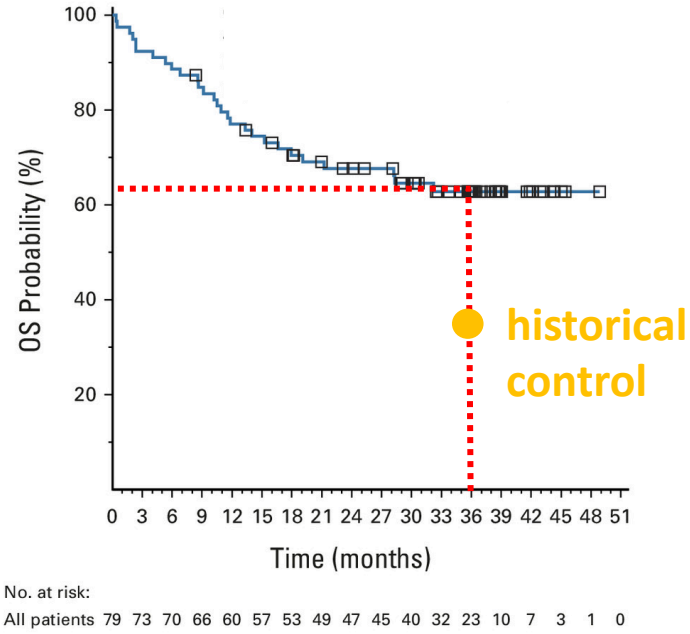


Maude et al. *NEJM* (2018)

CAR-T cell therapy for ALL

- Efficacy
  - Progression-free survival and overall survival

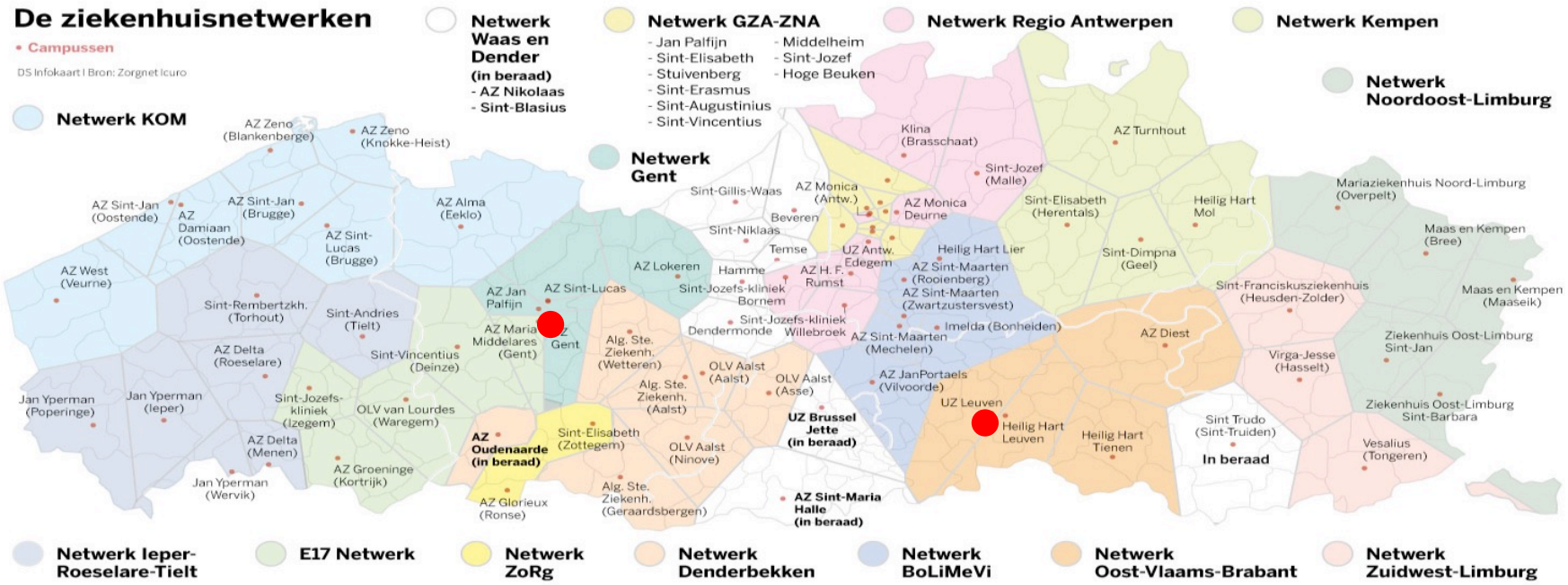




Laetsch et al. *JCO (*2023)
V Stackelberg et al. *Leukemia* (2023)

CAR-T cell therapy for ALL

- Availability in Flanders/Belgium: **reimbursed** in CAR-T infusion center
  - Tisa-cel (Kymriah®)



CAR-T cell therapy for ALL

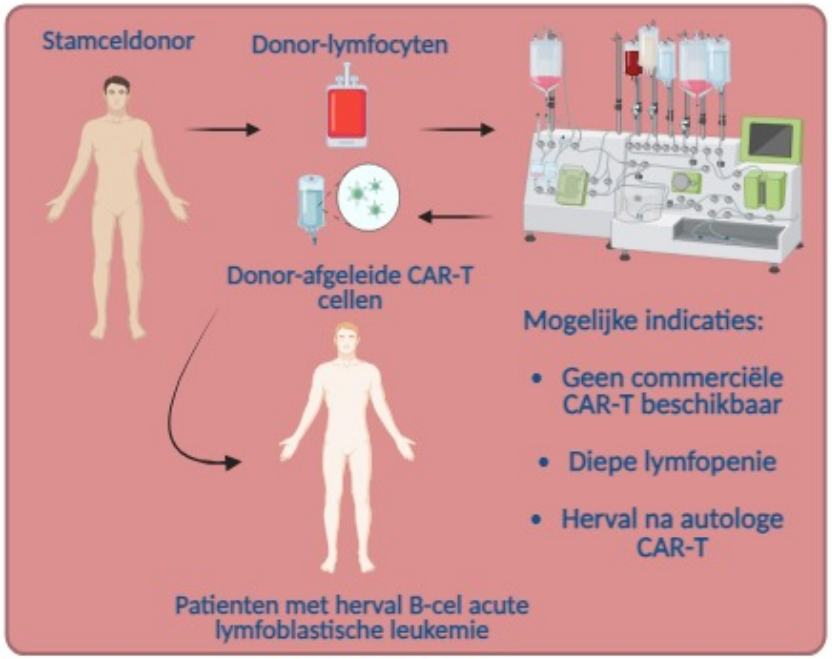
- Availability in Flanders/Belgium: **reimbursed** for B-ALL ≤25 yr

EU member state	Tisa-cel *ALL ≤25 yr*	Brexu-cel *ALL >25 yr*
Germany		
Austria		
France		
Italy		
Czech Republic		
Greece		
Finland		
Greece		
Spain		
Luxembourg*		
Belgium		
Slovakia		
Portugal		
Poland		
Sweden		
Netherlands**		
Ireland		
Slovenia		
Romania		
Croatia		
Denmark		
Hungary		
Malta***		
Bulgaria		
Estonia		
Lithuania		
Latvia		
Cyprus		

CAR-T cell therapy for ALL

- Availability in Flanders/Belgium: via **clinical trials**
  - CAR-DLI study
    - National academic study, with funding from Stand up Against Cancer
    - Phase 1: allogeneic CAR-T directed towards CD19

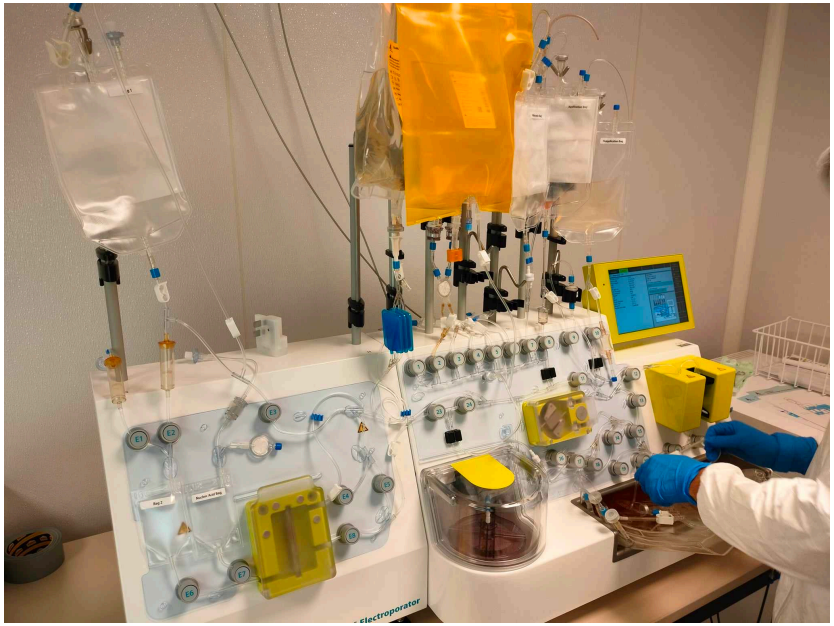
ALLOGENEIC



NON-VIRAL

CAR-T cell therapy for ALL

- Availability in Flanders/Belgium: via **clinical trials**
  - CAR-DLI study
    - National academic study, with funding from Stand up Against Cancer
    - Phase 1: allogeneic CAR-T directed towards CD19



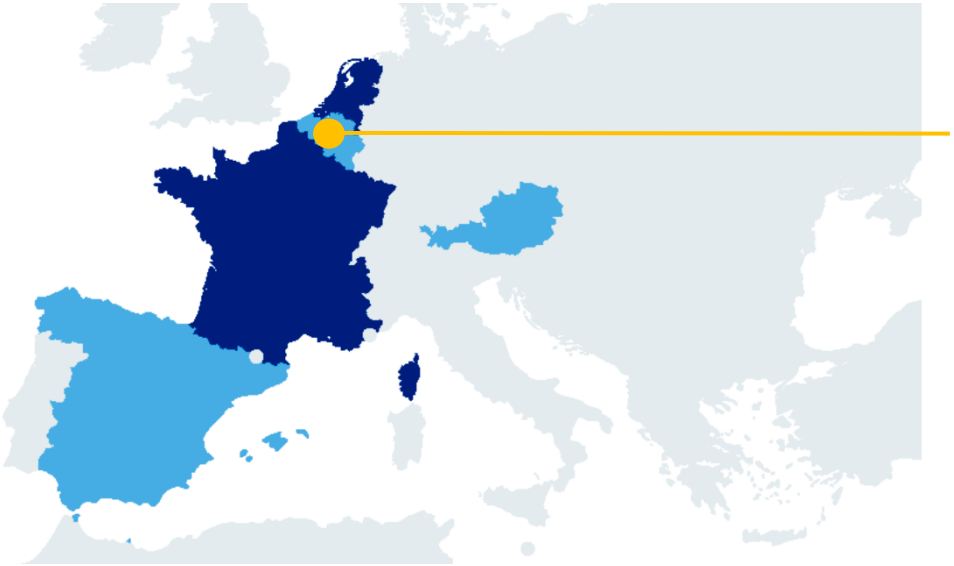
HOME GROWN

anicells
advancing innovative cell therapy solutions to the patient

CAR-T cell therapy for ALL

ATTRACT
Accelerate Together Rare Cancer Treatment

- Availability in Flanders/Belgium: via **clinical trials**
  - CARTALLEU study
    - Multinational academic study, with funding from ATTRACT
    - Phase 2: autologous CAR-T directed towards CD19 (varnimcabtagene autoleucel, var-cel)
    - Local, decentralized manufacturing



anicells
advancing innovative cell therapy solutions to the patient

CAR-T cell therapy for solid cancers

B-cell hematological malignancies (lymphoma, multiple myeloma, ALL), for which **CAR-T** cell therapies are **available**, account for **<10%** of **all cancers**

CAR-T cell therapy for solid cancers

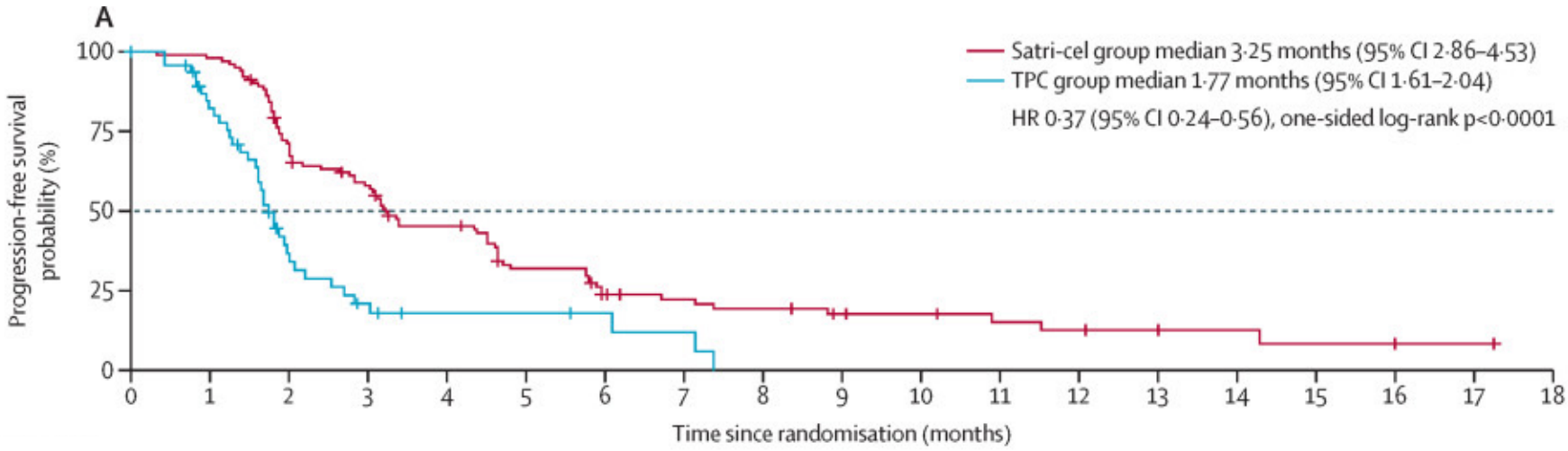
- To date, **no** CAR-T cell therapy has been granted **regulatory approval** for solid cancers

- In 2025, >250 **clinical trials** of CAR-T cell therapy for solid tumors were registered on ClinicalTrials.gov

- Only a limited number of studies have currently entered the **late phase clinical trial** stage

CAR-T cell therapy for solid cancers

- To date, only one late-stage RCT of CAR-T cell therapy in solid tumors has been published
  - Claudin-18.2-targeted CAR-T for gastric cancer
  - Phase 2, randomized



Qi et al. *Lancet* (2025)

CAR-T cell therapy for solid cancers

Clinical Trial › JAMA Oncol. 2024 Nov 1;10(11):1532-1536. doi: 10.1001/jamaoncol.2024.3891.

Chimeric Antigen Receptor T Cells Targeting CD19 and GCC in Metastatic Colorectal Cancer: A Nonrandomized Clinical Trial

Naifei Chen [1], Chengfei Pu [2], Lingling Zhao [1], Wei Li [1], Chang Wang [1], Ruihong Zhu [2], Tingting Liang [1], Chao Niu [1], Xi Huang [2], Haiyang Tang [2], Yizhuo Wang [1], Hang Yang [2], Beibei Jia [2], Xianyang Jiang [2], Guiting Han [2], Wensheng Wang [2], Dongqi Chen [2], Yiming Wang [2], Eric K Rowinsky [3], Eugene Kennedy [4], Victor X Lu [3], Guozhen Cui [1], Zhao Wu [2], Lei Xiao [3], Jiuwei Cui [1]

Abstract

Importance: Chimeric antigen receptor (CAR) T-cell therapy (CART) has transformed the treatment landscape of hematologic cancer, but has negligible effects for adult solid cancers. In this trial, an autologous CAR T-cell product demonstrated antitumor activity in heavily pretreated patients with metastatic colorectal cancer (mCRC).

Objective: To evaluate the safety and efficacy of guanylate cyclase-C (GCC19) CART in participants with metastatic colorectal cancer (mCRC).

Design, setting, and participants: This single-arm, nonrandomized, phase 1 trial was conducted at the First Hospital of Jilin University from December 3, 2020, to April 13, 2022. Data analysis was conducted from May 2022 to April 2024. Adults with relapsed and refractory mCRC expressing GCC were treated with GCC19CART, a mixture of autologous CAR T cells transduced with lentiviral vectors expressing genes that encode either CD-19 CAR or GCC CAR.

Main outcomes and measures: Safety and tolerability of CAR T-cell therapy targeting GCC in patients with mCRC without therapeutic options is capable of conferring a reasonable likeliness of clinical benefit. Other outcomes included objective response rate, progression-free survival, overall survival, and immune activation.

Results: Of 15 patients 9 (60%) were women, and the median (range) age was 44 (33-61) years. Treatment with GCC19CART was associated with the development of cytokine release syndrome and diarrhea in most patients, all of which were self-limited and manageable. The objective response rate was 40%, with a partial response in 2 of 8 and 4 of 7 CAR-T cell therapy for solid ca... 106 cells/kg or 2 × 106 cells/kg. Median overall survival was 22.8 months (95% CI, 13.4-26.1) at data cutoff; the median progress-free survival was 6.0 months in the high dose level group (95% CI, 3.0 to not available).

Conclusions and relevance: The results of this nonrandomized clinical trial suggest that GCC19CART was safe and tolerable in heavily pretreated patients with mCRC and is the first CAR T-cell therapy known to produce objective clinical activity in refractory cancer. Given the paucity of effective therapeutics developed for colorectal cancer in recent decades, the observation that CD-19 CART target engagement can robustly induce GCC19CART target engagement sufficient to produce objective activity may serve as a foundation to develop effective cellular therapy in mCRC and other solid cancers.

CAR-T cell therapy for solid cancers

Clinical Trial › Nature. 2025 Jan;637(8047):940-946. doi: 10.1038/s41586-024-08261-8. Epub 2024 Nov 27.

Interleukin-15-armoured GPC3 CAR T cells for patients with solid cancers

David Steffin [1 2 3 4], Nisha Ghatwai [1 2], Antonino Montalbano [1 2], Purva Rathi [1 2], Amy N Courtney [1 2 3], Azlann B Arnett [2 5], Julien Fleurence [1 3], Ramy Sweidan [4], Tao Wang [3], Huimin Zhang [4], Prakash Masand [6], John M Maris [7], Daniel Martinez [8], Jennifer Pogoriler [8], Navin Varadarajan [9], Sachin G Thakkar [4], Deborah Lyon [4], Natalia Lapteva [4 10 11], Mei Zhuyong [4], Kalyani Patel [11], Dolores Lopez-Terrada [11], Carlos A Ramos [3 4], Premal Lulla [3 4], Tannaz Armaghany [3], Bambi J Grilley [1 2 3 4], Stephen Gottschalk [12], Gianpietro Dotti [13], Leonid S Metelitsa [1 2 3 4], Helen E Heslop [3 4], Malcolm K Brenner [3 4], Pavel Sumazin [1 3], Andras Heczey [14 15 16 17 18]

Abstract

Interleukin-15 (IL-15) promotes the survival of T lymphocytes and enhances the antitumour properties of chimeric antigen receptor (CAR) T cells in preclinical models of solid neoplasms in which CAR T cells have limited efficacy[1-4]. Glypican-3 (GPC3) is expressed in a group of solid cancers[5-10], and here we report the evaluation in humans of the effects of IL-15 co-expression on GPC3-expressing CAR T cells (hereafter GPC3 CAR T cells). Cohort 1 patients (NCT02905188 and NCT02932956) received GPC3 CAR T cells, which were safe but produced no objective antitumour responses and reached peak expansion at 2 weeks. Cohort 2 patients (NCT05103631 and NCT04377932) received GPC3 CAR T cells that co-expressed IL-15 (15.CAR), which mediated significantly increased cell expansion and induced a disease control rate of 66% and antitumour response rate of 33%. Infusion of 15.CAR T cells was associated with increased incidence of cytokine release syndrome, which was controlled with IL-1/IL-6 blockade or rapidly ameliorated by activation of the inducible caspase 9 safety switch. Compared with non-responders, tumour-infiltrating 15.CAR T cells from responders showed repression of SWI/SNF epigenetic regulators and upregulation of FOS and JUN family members, as well as of genes related to type I interferon signalling. Collectively, these results demonstrate that IL-15 increases the expansion, intratumoural survival and antitumour activity of GPC3 CAR T cells in patients.

CAR-T cell therapy for solid cancers

CAR-T cell therapy for solid ca...

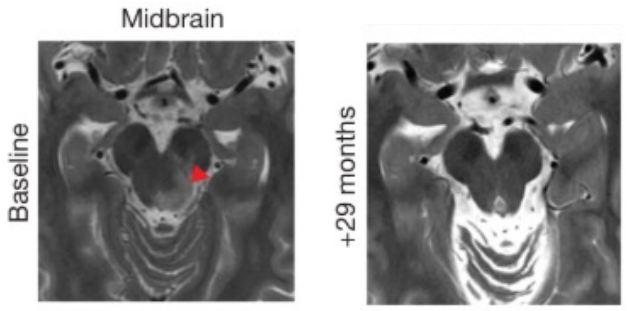
Clinical Trial › Nature. 2025 Jan;637(8046):708-715. doi: 10.1038/s41586-024-08171-9. Epub 2024 Nov 13.

Intravenous and intracranial GD2–CAR T cells for H3K27M$^+$ diffuse midline gliomas

Michelle Monje [1 2 3 4 5 6], Jasia Mahdi [7 8], Robbie Majzner [9 8], Kristen W Yeom [7 10 11], Liora M Schultz [9 8], Rebecca M Richards [9 8], Valentin Barsan [9 8], Kun-Wei Song [7 8], Jen Kamens [9 8], Christina Baggott [8], Michael Kunicki [8], Skyler P Rietberg [8], Alexandria Sung Lin Agnes Reschke [9 8], Sharon Mavroukakis [8], Emily Egeler [8], Jennifer Moon [8], Shabnum Patel [8], Harshini Chinnasamy [8], Courtney Erickson [8], Ashley Jacobs [8], Allison K Duh [10], Ramya Tunuguntla [8], Dorota Danuta Klysz [8], Carley Fowler [8], Sean Green [9], Barbara Beebe [8], Casey Carr [8], Michelle Fujimoto [8], Annie Kathleen Brown [8], Ann-Louise G Petersen [8], Catherine McIntyre [12], Aman Siddiqui [12], Nadia Lepori-Bui [12], Katlin Villar [12], Kymhuynh Pham [1] Rachel Bove [12], Eric Musa [12], Warren D Reynolds [8], Adam Kuo [8], Snehit Prabhu [8], Lindsey Rasmussen [13], Timothy T Cornell [13], Sonia Partap [7], Paul G Fisher [7], Cynthia J Campen [7] Gerald Grant [10], Laura Prolo [10], Xiaobu Ye [14], Bita Sahaf [8], Kara L Davis [9 8], Steven A Feldman [8] Sneha Ramakrishna [15 16], Crystal Mackall [17 18 19 20]

Abstract

H3K27M-mutant diffuse midline gliomas (DMGs) express high levels of the disialoganglioside GD2 (ref. [1]). Chimeric antigen receptor-modified T cells targeting GD2 (GD2-CART) eradicated DMGs in preclinical models[1]. Arm A of Phase I trial no. NCT04196413 (ref. [2]) administered one intravenous (IV) dose of autologous GD2-CART to patients with H3K27M-mutant pontine (DIPG) or spinal DMG (sDMG) at two dose levels (DL1, 1×10^6 kg^{-1}; DL2, 3×10^6 kg^{-1}) following lymphodepleting chemotherapy. Patients with clinical or imaging benefit were eligible for subsequent intracerebroventricular (ICV) intracranial infusions (10-30 $\times 10^6$ GD2-CART). Primary objectives were manufacturing feasibility, tolerability and the identification of maximally tolerated IV dose. Secondary objectives included preliminary assessments of benefit. Thirteen patients enroled, with 11 receiving IV GD2-CART on study (n = 3 DL1 (3 DIPG); n = 8 DL2 (6 DIPG, 2 sDMG)). GD2-CART manufacture was successful for all patients. No dose-limiting toxicities occurred on DL1, but three patients experienced dose-limiting cytokine release syndrome on DL2, establishing DL1 as the maximally tolerated IV dose. Nine patients received ICV infusions, with no dose-limiting toxicities. All patients exhibited tumour inflammation-associated neurotoxicity, safely managed with intensive monitoring and care. Four patients demonstrated major volumetric tumour reductions (52, 54, 91 and 100%), with a further three patients exhibiting smaller reductions. One patient exhibited a complete response ongoing for over 30 months since enrolment. Nine patients demonstrated neurological benefit, as measured by a protocol-directed clinical improvement score. Sequential IV, followed by ICV GD2-CART, induced tumour regressions and neurological improvements in patients with DIPG and those with sDMG.



CAR-T cell therapy for solid cancers

Clinical Trial > Nat Med. 2025 Mar;31(3):861-868. doi: 10.1038/s41591-024-03451-3. Epub 2025 Jan 7.

Intracerebroventricular B7–H3–targeting CAR T cells for diffuse intrinsic pontine glioma: a phase 1 trial

Nicholas A Vitanza [1 2 3], Rebecca Ronsley [4 5 6], Michelle Choe [4 5], Kristy Seidel [6], Wenjun Huang [6], Stephanie D Rawlings-Rhea [6], Madison Beam [6], Leonel Steinmetzer [6], Ashley L Wilson [6], Christopher Brown [6], Adam Beebe [6], Catherine Lindgren [6], Joshua A Gustafson [6], Amy Wein [5], Susan Holtzclaw [5], Corrine Hoeppner [5], Hannah E Goldstein [7], Samuel R Browd [7], Jason S Hauptman [7], Amy Lee [7], Jeffrey G Ojemann [7 8], Erin E Crotty [4 5], Sarah E S Leary [4 5], Francisco A Perez [9], Jason N Wright [9], Marta M Alonso [10], Matthew D Dun [11 12 13], Jessica B Foster [14 15], Diana Hurst [5], Ada Kong [16], Alison Thomsen [5], Rimas J Orentas [4 5], Catherine M Albert [4 5], Navin Pinto [4 5], Colleen Annesley [4 5 6], Rebecca A Gardner [4 5 6], On Ho [6], Sowmya Pattabhi [6], Juliane Gust [8 17], Jason P Wendler [6], Julie R Park [4 5 6 18], Michael C Jensen [6]

Abstract

Diffuse intrinsic pontine glioma (DIPG) is a fatal central nervous system (CNS) tumor that confers a median survival of 11 months. As B7-H3 is expressed on pediatric CNS tumors, we conducted BrainChild-03, a single-center, dose-escalation phase 1 clinical trial of repetitive intracerebroventricular (ICV) dosing of B7-H3-targeting chimeric antigen receptor T cells (B7-H3 CAR T cells) for children with recurrent or refractory CNS tumors and DIPG. Here we report results from Arm C, restricted to patients with DIPG. The primary objectives were to assess feasibility and tolerability, which were both met. Secondary objectives included assessments of CAR T cell distribution and survival. A total of 23 patients with DIPG enrolled, and 21 were treated with repeated doses of ICV B7-H3 CAR T cells using intra-patient dose-escalation regimens without previous lymphodepletion. Concurrent tumor-directed therapy, including re-irradiation, was not allowed while on protocol therapy. We delivered a total of 253 ICV doses and established the highest planned dose regimen, DR4, which escalated up to 10×10^7 cells per dose, as the maximally tolerated dose regimen. Common adverse events included headache, fatigue and fever. There was one dose-limiting toxicity (intratumoral hemorrhage) during DR2. For all treated patients (n = 21), the median survival from their initial CAR T cell infusion was 10.7 months and the median survival from diagnosis was 19.8 months with 3 patients still alive at 44, 45 and 52 months from diagnosis. Ultimately, this completed first-in-human trial shows that repetitive ICV dosing of B7-H3 CAR T cells in pediatric and young adult patients with DIPG is tolerable, including multiyear repeated dosing, and may have clinical efficacy that warrants further investigation on a multisite phase 2 trial. ClinicalTrials.gov registration: NCT04185038 .

CAR-T cell therapy for solid cancers

Clinical Trial > Nat Med. 2025 Nov;31(11):3689-3699. doi: 10.1038/s41591-025-03874-6. Epub 2025 Aug 21.

GD2–targeting CAR T cells in high–risk neuroblastoma: a phase 1/2 trial

Franco Locatelli [1 2], Daria Pagliara [3], Maria A De Ioris [3], Marco Becilli [3], Giada Del Baldo [3], Annalisa Serra [3], Angela Mastronuzzi [3], Maria G Cefalo [3], Giuseppina Li Pira [3], Giovanna Leone [4], Valentina Bertaina [3], Francesco Fabozzi [3], Matteo Di Nardo [5], Chiara Rosignoli [3], Maria Luisa D'Andrea [6], Alessandro Crocoli [7], Sabina Vennarini [8], Matilde Sinibaldi [3], Stefano Di Cecca [3], Marika Guercio [3], Laura Iaffaldano [3], Barbarella Lucarelli [3], Mattia Algeri [3 9], Pietro Merli [3], Giovanna S Colafati [6], Biagio De Angelis [3], Concetta Quintarelli [# 3 10], Francesca Del Bufalo [# 3]

Abstract

Antidisialoganglioside (GD2), third-generation chimeric antigen receptor (CAR) T cells (GD2-CART01) have shown encouraging efficacy in children with high-risk metastatic, relapsed, or refractory neuroblastoma in the interim analysis of a phase 1/2 clinical trial. We now present the final results obtained in all 35 patients enrolled and in 19 additional children selected with the same criteria of the trial and treated in a hospital exemption setting. Primary endpoints for the trial were safety, maximum tolerated dose, overall response rate (ORR) and complete remission rate at various timepoints. Secondary endpoints included 5-year overall survival (OS) and persistence of GD2-CART01. No new safety signals were observed. Grade 3 immune effector cell-associated neurotoxicity syndrome was diagnosed in four children and rapidly controlled with the activation of the inducible caspase-9 suicide gene by rimiducid. The maximum tolerated dose was 10×10^6CAR$^+$ cells per kg. The ORR of the patients enrolled in the clinical trial was 66% (21/32-excluding the three patients treated in nonevidence of disease). The complete remission rate at 6 weeks, 3 months and 6 months reached 37%, 34% and 40%, respectively. GD2-CART01 persisted ≥12 months in 64% of the patients enrolled in the clinical trial. With a median follow-up of 4.2 years, the 5-year OS for the trial cohort was 42.67%. In total, 38 of 54 children were treated with low disease burden at 10×10^6 GD2-CART01 cells per kg (defined as the target population), including eight patients consolidated in nonevidence of disease after the first line. The ORR in the target population was 77%, the 5-year OS and event-free survivals were 68% and 53%, respectively. Substantially superior 5-year OS and event-free survivals were observed in patients treated after one or two lines of therapy versus those treated after ≥3 lines of therapy. Better results were observed in patients whose lymphocyte collection was performed at the time of diagnosis. These results confirm that GD2-CART01 can induce durable remissions in children with high-risk metastatic, relapsed, or refractory neuroblastoma. ClinicalTrials.gov identifier: NCT03373097 .

CAR-T cell therapy for solid cancers

Clinical Trial > Nat Med. 2025 Apr;31(4):1125-1129. doi: 10.1038/s41591-025-03513-0. Epub 2025 Feb 17.

Long-term outcomes of GD2-directed CAR-T cell therapy in patients with neuroblastoma

Che-Hsing Li [1 2 3], Sandhya Sharma [1], Andras A Heczey [1 2 4], Mae L Woods [1], David H M Steffin [1 4], Chrystal U Louis [1], Bambi J Grilley [1 4], Sachin G Thakkar [1], Mengfen Wu [4], Tao Wang [4], Cliona M Rooney [1 4], Malcolm K Brenner [1 4], Helen E Heslop [5 6]

Abstract

In a phase 1 clinical trial open to accrual from 2004 to 2009, we treated children with neuroblastoma with Epstein-Barr virus (EBV)-specific T lymphocytes and CD3-activated T cells-each expressing chimeric antigen receptors (CARs) targeting GD2 but without an embedded co-stimulatory sequence (first-generation CARs). These CARs incorporated barcoded sequences to track each infused population. We previously reported outcomes up to 5 years and now report long-term outcomes up to 18 years. Of 11 patients with active disease at infusion, three achieved a complete response that was sustained in two patients, one for 8 years until lost to follow-up and one for more than 18 years. Of eight patients with no evidence of disease at the time of CAR-T administration, five are disease free at their last follow-up between 10 years and 15 years after infusion. Intermittent low levels of transgene were detected during the follow-up period with significantly greater persistence in those who were long-term survivors. Despite using first-generation vectors that are no longer employed because of the lack of co-stimulatory domains, patients with relapsed/refractory neuroblastoma achieved long-term disease control after receiving GD2 CAR-T cell therapy, including one patient now in remission of relapsed disease for more than 18 years.ClinicalTrials.gov identifier: NCT00085930 .

CAR-T cell therapy for auto-immune diseases

- To date, **no** CAR-T cell therapy has been granted **regulatory approval** for auto-immune diseases

- Early **clinical trials** indicate that CAR-T cell therapy can represent a **curative** paradigm shift

CAR-T cell therapy for auto-immune diseases

> Autoreactive B-cells play a key role in the pathogenesis of **auto-immune diseases**, providing a strong rationale for **B-cell-directed CAR-T** cell therapies in these disorders

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CAR-T cell therapy for auto-immune diseases

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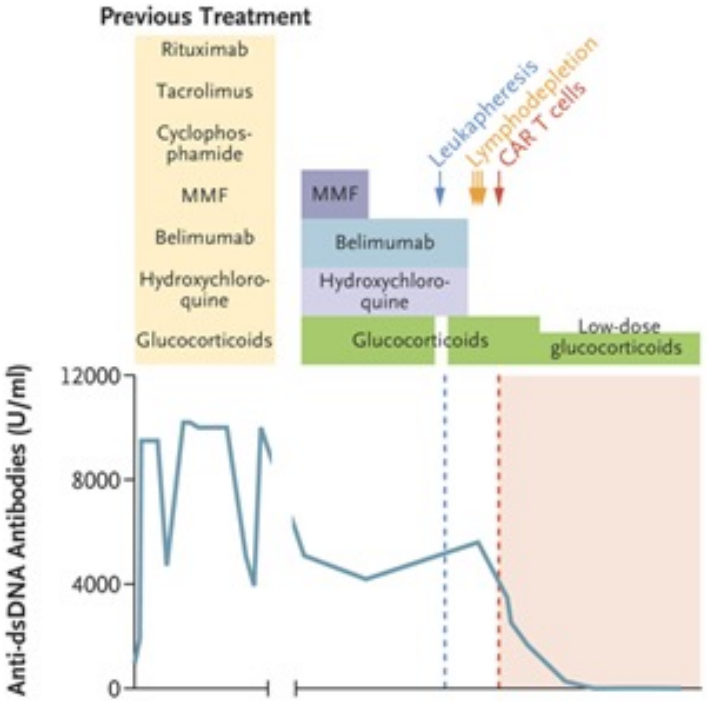
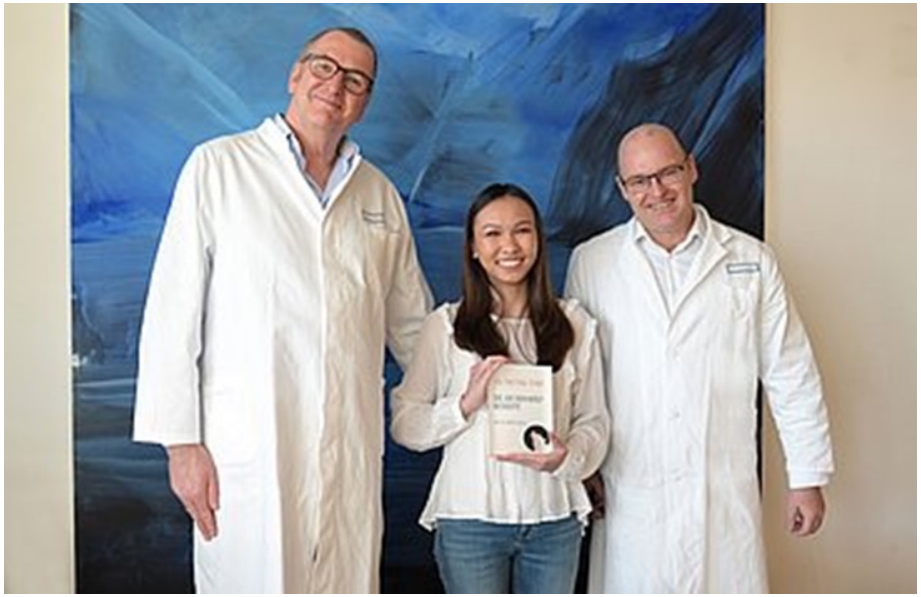
- Early **clinical trials** indicate that CAR-T cell therapy can represent a **curative** paradigm shift

- Examples are systemic **lupus** erythematosus (SLE), rheumatoid arthritis (RA), auto-immune neurological diseases (myasthenia gravis, **multiple sclerosis**, etc.)

CAR-T cell therapy for auto-immune diseases

- First patient possibly **cured** of severe refractory **lupus** by CD19-directed CAR-T cells





Mougiakakos et al. *NEJM* (2021)

CAR-T cell therapy for auto-immune diseases

Motte et al. *Lancet Neurol* (2025)

Laboratory of Experimental Hematology
Vaccine & Infectious Disease Institute
University of Antwerp