



CAR-T

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Everyone have
their mics on?



Nya/godkända (FDA/EMA) behandlingar 2011-2021

ca 35

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Table 1. Features of the tyrosine kinase (TK) inhibitors approved by the Food and Drug Administration (FDA) from 2011 to 2021. The order of drugs is tabulated in order of most recent to oldest registration date.

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Reference
1	Zanubrutinib	BELICIA Celgene Bridgewater, NJ, USA	14th FDA approval 14 May 2019		BRK ¹	Oral	Multiple Cell Lymphomas	Diarrhea, cough, vomiting, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[145]
2	Acalabrutinib	CALQUENCE Celgene Bridgewater, NJ, USA	15 October 2017 15 November 2019		BRK ¹	Oral	Multiple Cell Lymphomas	Diarrhea, cough, vomiting, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[145,14]
3	Brutinib	IMBRUVICA AstraZeneca Bull, H, USA	13 May 2017 23 October 2014		BRK ¹	Oral	Multiple Cell Lymphomas	Diarrhea, cough, vomiting, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[145,14]
4	Brutinib	SKCEL Novartis East Hanover, NJ, USA	14 November 2012 23 March 2015		Ser ¹ / Akt ¹	Oral	Chronic Myeloid Leukemia	Diarrhea, cough, vomiting, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[145,17]

¹ BRK: Bruton's tyrosine kinase. ² Ser: serine/threonine kinase. ³ Akt: Serine/threonine kinase.

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Table 6. Features of the enzyme inhibitors approved by the Food and Drug Administration (FDA) from 2011 to 2021. The order of drugs is tabulated in order of most recent to oldest registration date.

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Reference
1	Acatinib	OSI-030 Novartis East Hanover, NJ, USA	17 May 2011 19 June 2012		DNMT3 ¹	Oral	Acute Myeloid Leukemia	Neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[151,16]
2	Yescarta	SLY512 Celgene Bridgewater, NJ, USA	29 May 2017 28 May 2019		CD20 ¹	Oral	Epitopedal B-cell Lymphoma	Diarrhea, cough, vomiting, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[145,16]
3	Inotuzumab	INOTUZUMAB Genentech Sunnyvale, CA, USA	22 May 2017 22 May 2019		CD20 ¹	Oral	Acute Myeloid Leukemia	Diarrhea, cough, vomiting, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[145,17]
4	Enasclorin	ENASCLORIN Novartis East Hanover, NJ, USA	14 August 2017 14 August 2019		DNMT3 ¹	Oral	Acute Myeloid Leukemia	Neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[151,16]

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Table 7. Features of the protein translation inhibitor approved by the Food and Drug Administration (FDA) from 2011 to 2021.

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Reference
1	Onasemnogene	SYNROBO Teva Pharmaceuticals North Wales, UK	17 October 2012 17 October 2012		Protein level	Subcutaneous injection	Chronic Myelogenous Leukemia	Thrombocytopenia, neutropenia, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[145,16]

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Table 2. Features of the small kinase inhibitors approved by the Food and Drug Administration (FDA) from 2011 to 2021. The order of drugs is tabulated in order of most recent to oldest registration date.

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Reference
1	Enzalutamide	ENZA Novartis East Hanover, NJ, USA	14 August 2014 8 February 2011		JAK2 ¹	Oral	Myeloid Leukemia	Diarrhea, cough, vomiting, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[151,17]
2	Gilteritinib	XOVALTA Novartis East Hanover, NJ, USA	17 November 2019 24 September 2019		RET ¹ / ALK ¹ / ALK2 ¹	Oral	Acute Myeloid Leukemia	Diarrhea, cough, vomiting, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[145,16]
3	Meklinotinib	PM23347 Pharmaceutical Research and Manufacturers of America Washington, DC, USA	28 February 2017 15 September 2017		RET ¹ / ALK ¹ / ALK2 ¹ / VEGFR2 ¹	Oral	Acute Myeloid Leukemia	Diarrhea, cough, vomiting, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[151,17]

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Table 4. Features of the various protease inhibitors approved by the Food and Drug Administration (FDA) from 2011 to 2021.

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Reference
1	Pomalidomide	IMN102 Pharmaceutical Research and Manufacturers of America Washington, DC, USA	22 February 2013 14 August 2015		IKZF1 ¹	Oral	Multiple Myeloma	Neutropenia, thrombocytopenia, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[151,16]
2	Belcastatam	BELECASTAM Pharmaceutical Research and Manufacturers of America Washington, DC, USA	7 February 2021 7 February 2021		IKZF1 ¹	Oral	Multiple Myeloma	Neutropenia, thrombocytopenia, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[151,16]

¹ DNMT3: DNA methyltransferase. ² IKZF1: Interferon regulatory factor 1. ³ IKZF3: Interferon regulatory factor 3. ⁴ IKZF4: Interferon regulatory factor 4. ⁵ IKZF5: Interferon regulatory factor 5. ⁶ IKZF6: Interferon regulatory factor 6. ⁷ IKZF7: Interferon regulatory factor 7. ⁸ IKZF8: Interferon regulatory factor 8. ⁹ IKZF9: Interferon regulatory factor 9. ¹⁰ IKZF10: Interferon regulatory factor 10. ¹¹ IKZF11: Interferon regulatory factor 11. ¹² IKZF12: Interferon regulatory factor 12. ¹³ IKZF13: Interferon regulatory factor 13. ¹⁴ IKZF14: Interferon regulatory factor 14. ¹⁵ IKZF15: Interferon regulatory factor 15. ¹⁶ IKZF16: Interferon regulatory factor 16. ¹⁷ IKZF17: Interferon regulatory factor 17. ¹⁸ IKZF18: Interferon regulatory factor 18. ¹⁹ IKZF19: Interferon regulatory factor 19. ²⁰ IKZF20: Interferon regulatory factor 20.

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Table 6. Features of the immunomodulatory drug approved by the Food and Drug Administration (FDA) from 2011 to 2021.

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Reference
1	Pomalidomide	IMN102 Pharmaceutical Research and Manufacturers of America Washington, DC, USA	22 February 2013 14 August 2015		IKZF1 ¹	Oral	Multiple Myeloma	Neutropenia, thrombocytopenia, constipation, upper respiratory tract infection, upper extremity edema, headache, back pain, fatigue, weight loss	[151,16]

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Table 2. Features of the phosphatidylinositol-3-kinase (PI3K) inhibitors approved by the Food and Drug Administration (FDA) from 2011 to 2021. The order of drugs is tabulated in order of most recent to oldest registration date.

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Reference
4	Pirotinib	KLINGON Pharmaceutical Research and Manufacturers of America Washington, DC, USA	14 August 2017 14 July 2019		PI3K ¹ / PI3K ² / PI3K ³ / PI3K ⁴ / PI3K ⁵ / PI3K ⁶ / PI3K ⁷ / PI3K ⁸ / PI3K ⁹ / PI3K ¹⁰ / PI3K ¹¹ / PI3K ¹² / PI3K ¹³ / PI3K ¹⁴ / PI3K ¹⁵ / PI3K ¹⁶ / PI3K ¹⁷ / PI3K ¹⁸ / PI3K ¹⁹ / PI3K ²⁰ / PI3K ²¹ / PI3K ²² / PI3K ²³ / PI3K ²⁴ / PI3K ²⁵ / PI3K ²⁶ / PI3K ²⁷ / PI3K ²⁸ / PI3K ²⁹ / PI3K ³⁰ / PI3K ³¹ / PI3K ³² / PI3K ³³ / PI3K ³⁴ / PI3K ³⁵ / PI3K ³⁶ / PI3K ³⁷ / PI3K ³⁸ / PI3K ³⁹ / PI3K ⁴⁰ / PI3K ⁴¹ / PI3K ⁴² / PI3K ⁴³ / PI3K ⁴⁴ / PI3K ⁴⁵ / PI3K ⁴⁶ / PI3K ⁴⁷ / PI3K ⁴⁸ / PI3K ⁴⁹ / PI3K ⁵⁰ / PI3K ⁵¹ / PI3K ⁵² / PI3K ⁵³ / PI3K ⁵⁴ / PI3K ⁵⁵ / PI3K ⁵⁶ / PI3K ⁵⁷ / PI3K ⁵⁸ / PI3K ⁵⁹ / PI3K ⁶⁰ / PI3K ⁶¹ / PI3K ⁶² / PI3K ⁶³ / PI3K ⁶⁴ / PI3K ⁶⁵ / PI3K ⁶⁶ / PI3K ⁶⁷ / PI3K ⁶⁸ / PI3K ⁶⁹ / PI3K ⁷⁰ / PI3K ⁷¹ / PI3K ⁷² / PI3K ⁷³ / PI3K ⁷⁴ / PI3K ⁷⁵ / PI3K ⁷⁶ / PI3K ⁷⁷ / PI3K ⁷⁸ / PI3K ⁷⁹ / PI3K ⁸⁰ / PI3K ⁸¹ / PI3K ⁸² / PI3K ⁸³ / PI3K ⁸⁴ / PI3K ⁸⁵ / PI3K ⁸⁶ / PI3K ⁸⁷ / PI3K ⁸⁸ / PI3K ⁸⁹ 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Forts. 2021

CAR T

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Table 16. Features of the chimeric antigen receptor T-cells (CAR-T cells) drugs approved by the Food and Drug Administration (FDA) from 2011 to 2021. The order of drugs is tabulated in order of most recent to oldest registration date.

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approved Date	Class	Molecular Target	Route of Administration	Indication	Adverse Effects	Reference
1	Brexucabtagene autiximab [†]	YECARTUS Kite, a Celgene Company, Foster City, CA, USA	FDA: 24 July 2020 EMA: 14 December 2020	Genetically modified autologous T cells	CD19 [†]	Intravenous	Multiple Myeloma	Cytokine release syndrome, cytopenias, hypotension, anaphylaxis, fever, fatigue, tachycardia, arrhythmias, infection with pathogen unspecified, chills, hypoxia, cough, tumor, musculoskeletal pain, headache, nausea, edema, constipation, constipation, diarrhea, decreased appetite, dyspnea, rash, neutropenia, bilateral effusion, aphasia, Cytokine release syndrome, fever, hypotension, osteophalopathy, leukopenia, fatigue, headache, febrile neutropenia, nausea, infection with pathogen unspecified, decreased appetite, chills, diarrhea, tumor, musculoskeletal pain, cough, hypoxia, constipation, vomiting, arthralgias, dizziness, Cytokine release syndrome, infectious pathogen unspecified, pyrexia, decreased appetite, hypogammaglobulinemia, headache, osteophalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury, edema, cough, delirium	[293,294,295]
2	Axicabtagene ciltecel	YESCARTA Kite Pharma, Inc., Los Angeles, CA, USA	FDA: 18 October 2017 EMA: 23 August 2018	Genetically modified autologous T cells	CD19 [†]	Intravenous	Large B Cell Lymphoma, Follicular Lymphoma	febrile neutropenia, nausea, infection with pathogen unspecified, decreased appetite, chills, diarrhea, tumor, musculoskeletal pain, cough, hypoxia, constipation, vomiting, arthralgias, dizziness, Cytokine release syndrome, infectious pathogen unspecified, pyrexia, decreased appetite, hypogammaglobulinemia, headache, osteophalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury, edema, cough, delirium	[296,297]
3	Tisagenlecleumab	KYMRIAH Novartis Pharmaceuticals Corporation, Basel, Switzerland	FDA: 30 August 2017 EMA: 23 August 2018	Genetically modified autologous T cells	CD19 [†]	Intravenous	Acute Lymphoblastic Leukemia, Large B Cell Lymphoma	hypotension, hypoxia, tachycardia, constipation, vomiting, arthralgias, dizziness, Cytokine release syndrome, infectious pathogen unspecified, pyrexia, decreased appetite, hypogammaglobulinemia, headache, osteophalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury, edema, cough, delirium	[298,299]

[†] CD19 cluster of differentiation 19.

2022: 9 nya godkännanden

Orencia (abatacept), aGvHD-profylax

Oxbryta (voxelotor), SCA 4-11 år

Enjaymo (sutmilimab-jome) CAD

Carvytki (cilta-cel), MM R/R, 5e linjen

Yescarta (axi-cel), LBCL ref/rel inom 12 mån

Vidaza (azacitidine) JMML

Kymriah (tisa-cel), FL 3e linjens beh

Breyanzi (liso-cel), LBLC ref/rel inom 12 mån

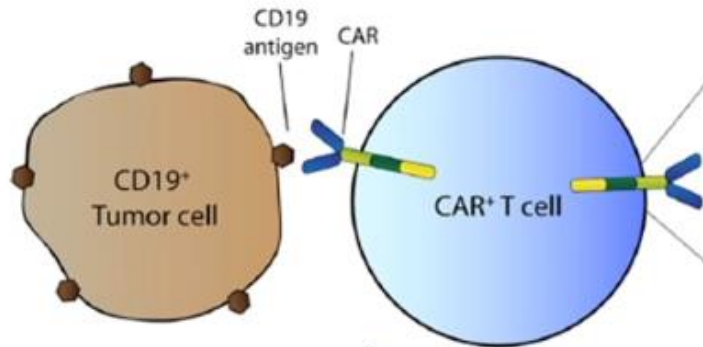
Tecyvali (teclistamab), MM ref/rel 4e linjens beh



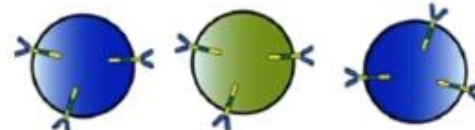
Chimeric Antigen Receptor
(CAR)
+
T-celler
=
Genmodifierade T-celler

CAR-T cell therapy mechanism of action

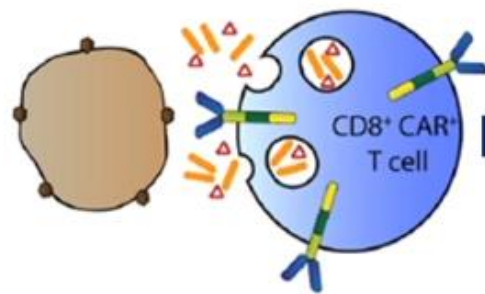
Tumor cell recognition
CAR mediated T cell activation



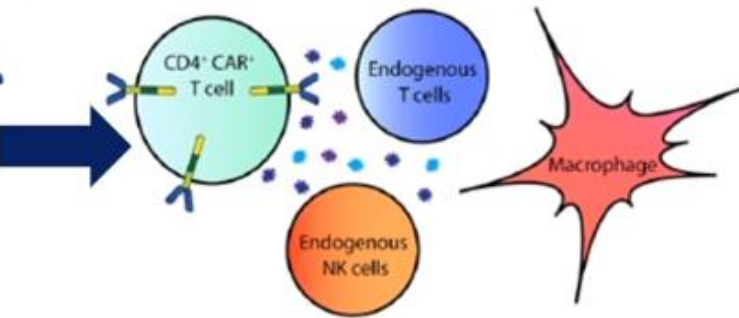
Memory T cell formation
Long-lived tumor specific memory T cells remain



Activation of Cytotoxic T cells
Release of Perforin (|) and Granzymes (Δ)

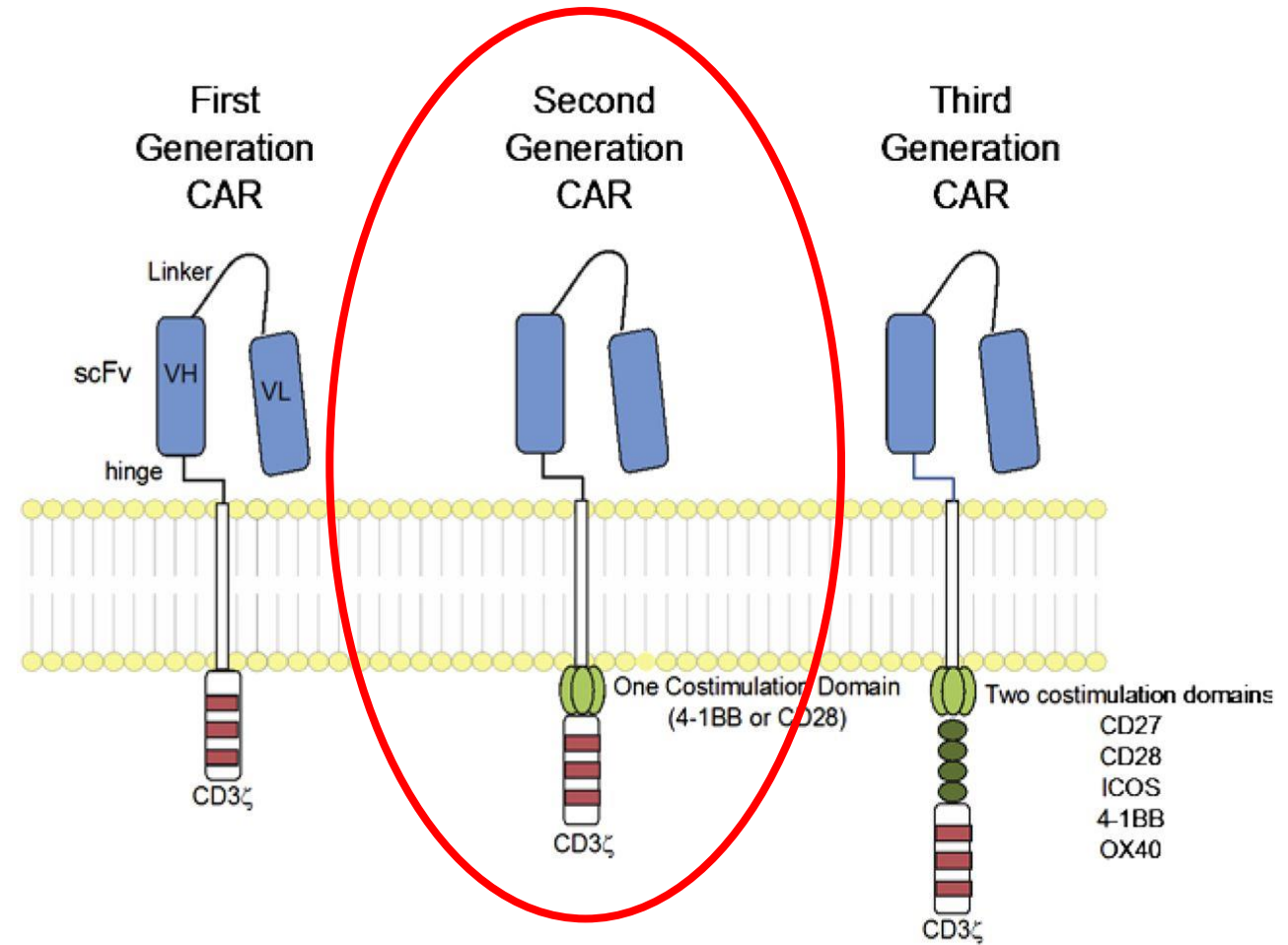


Cytokine Release
Cytokines (•) recruit endogenous immune cells



CAR-T

”Andra generationen”
Tumörantigen CD19, BCMA...
(=målstruktur)

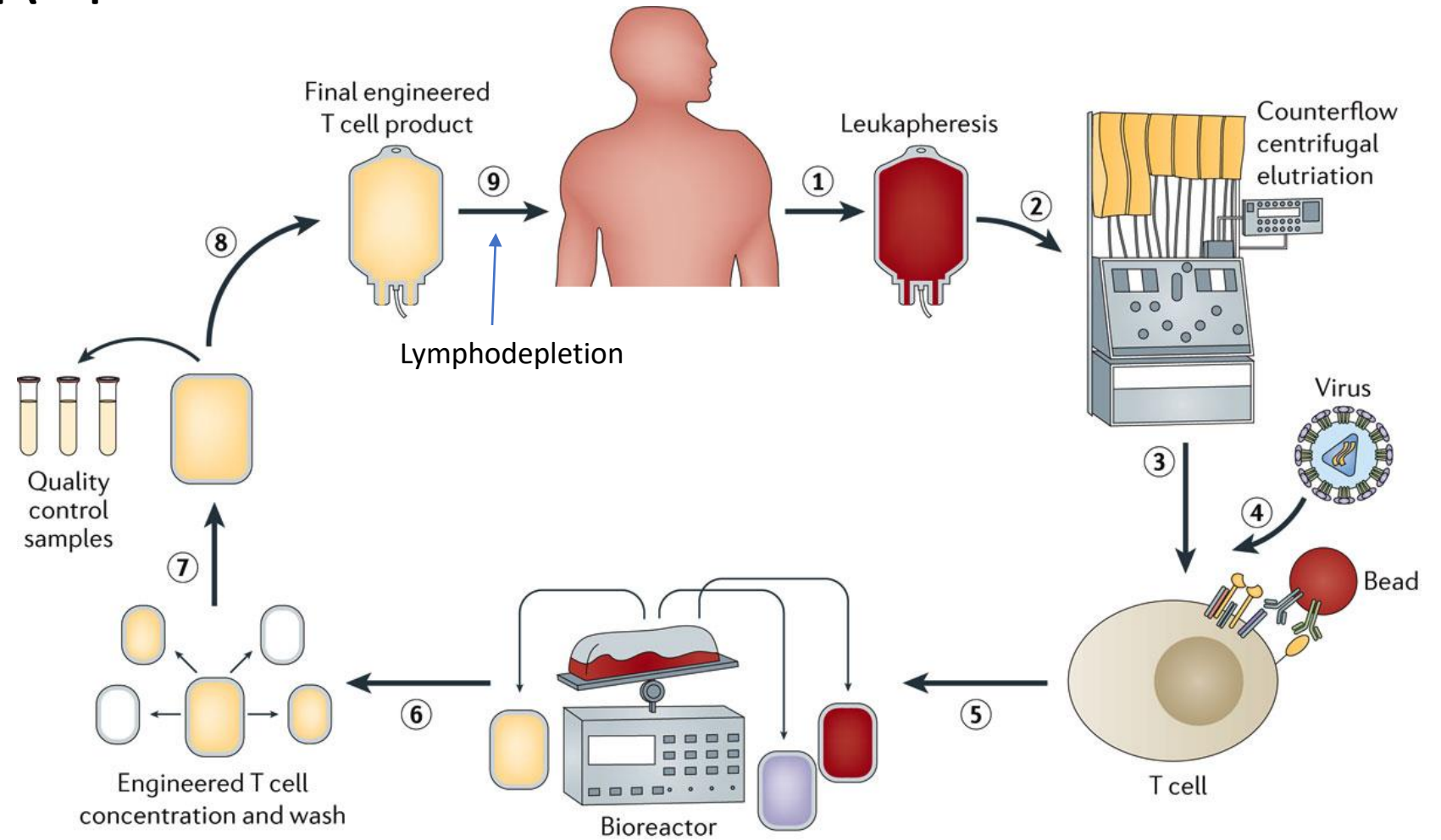


Shannon L. Maude et al. *Blood* 2015;125:4017-4023

©2015 by American Society of Hematology

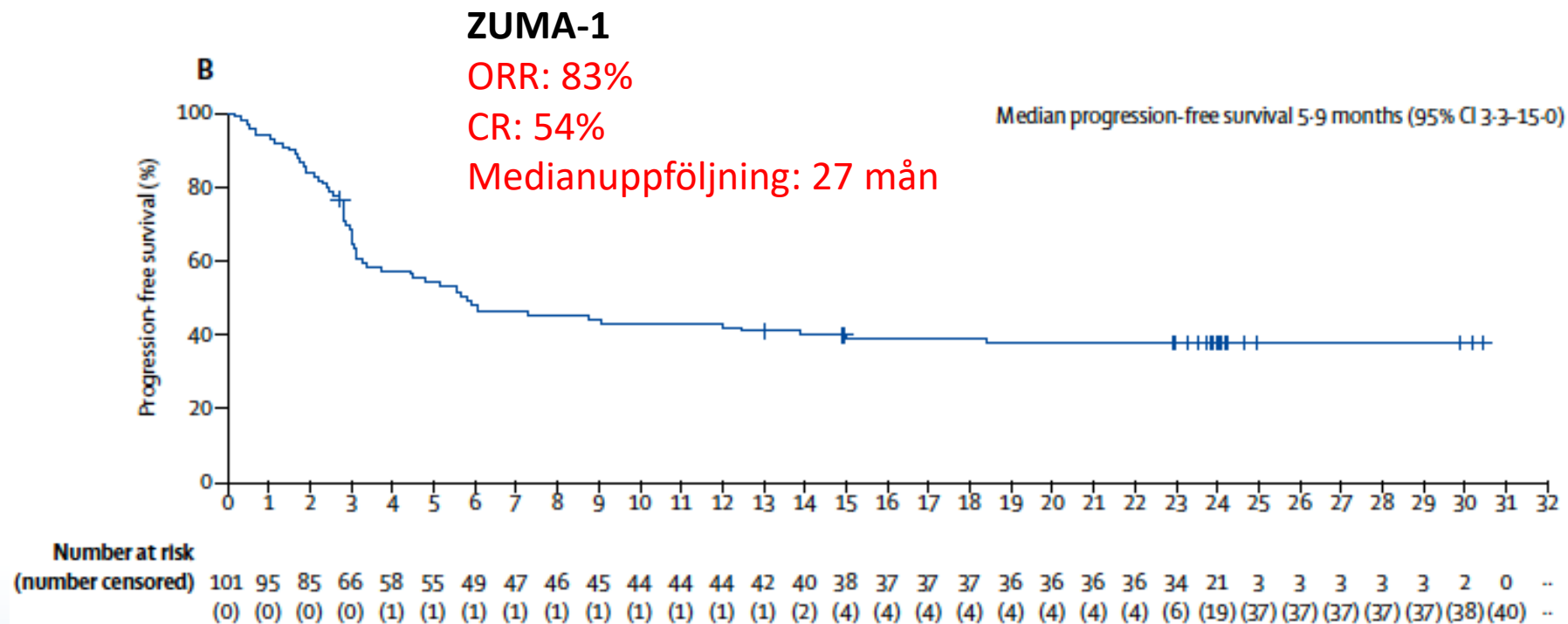
Tillverkning CAR-T

- Autologa T-celler
- Skörd på SU/S
- Produktion USA, EU
- 3-4 v leveranstid
- Infusion på SU/S



CAR-T: "What's the fuzz?"

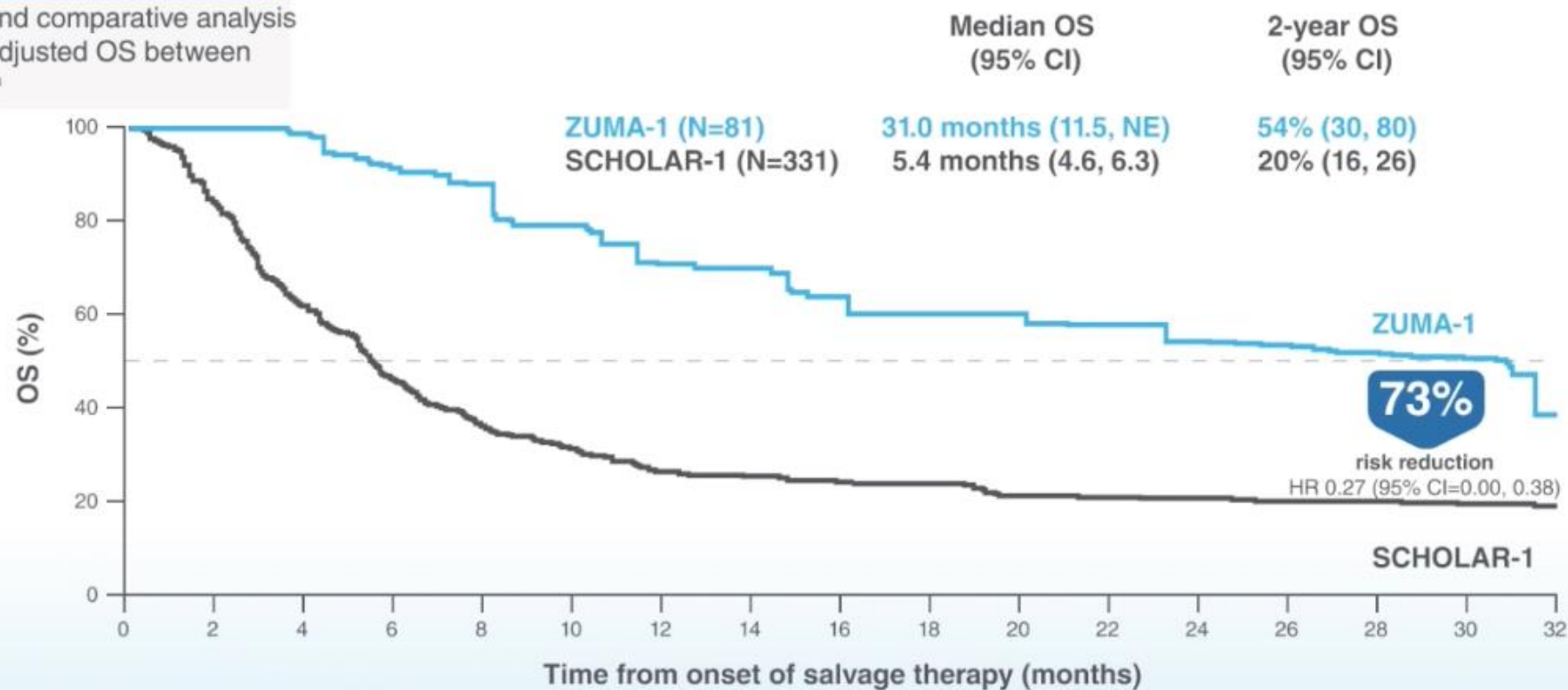
B-cellslymfom



”Unmet need”: SOC har dålig prognos

ZUMA-1 (axicabtagene ciloleucel) /SCHOLAR-1 (SoC)

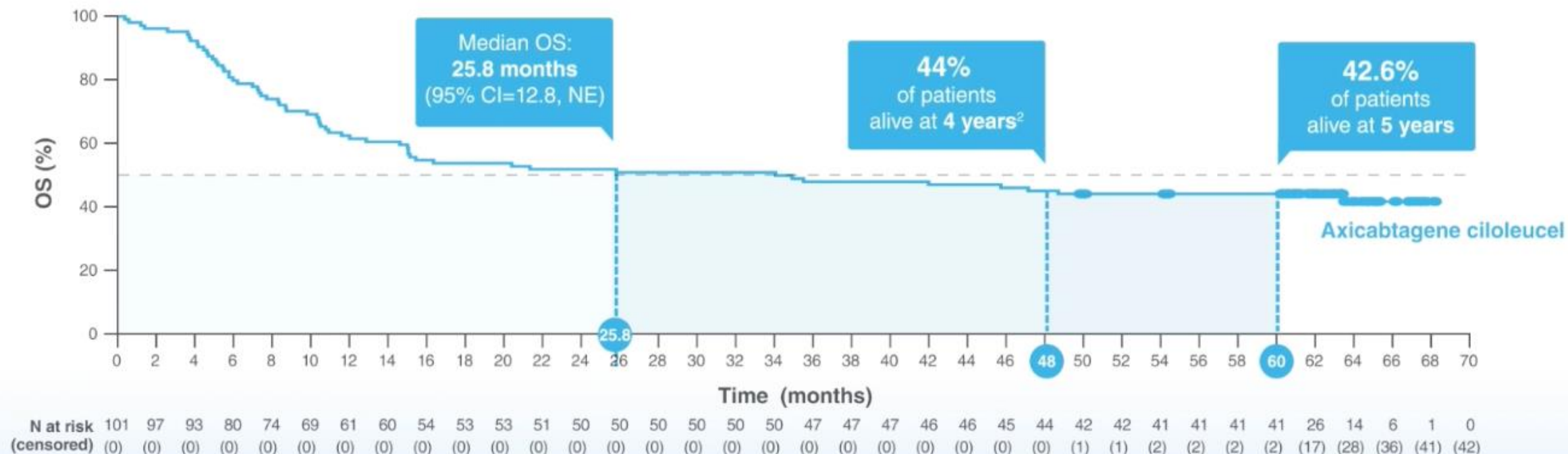
Retrospective and comparative analysis
of confounder-adjusted OS between
the two studies^a



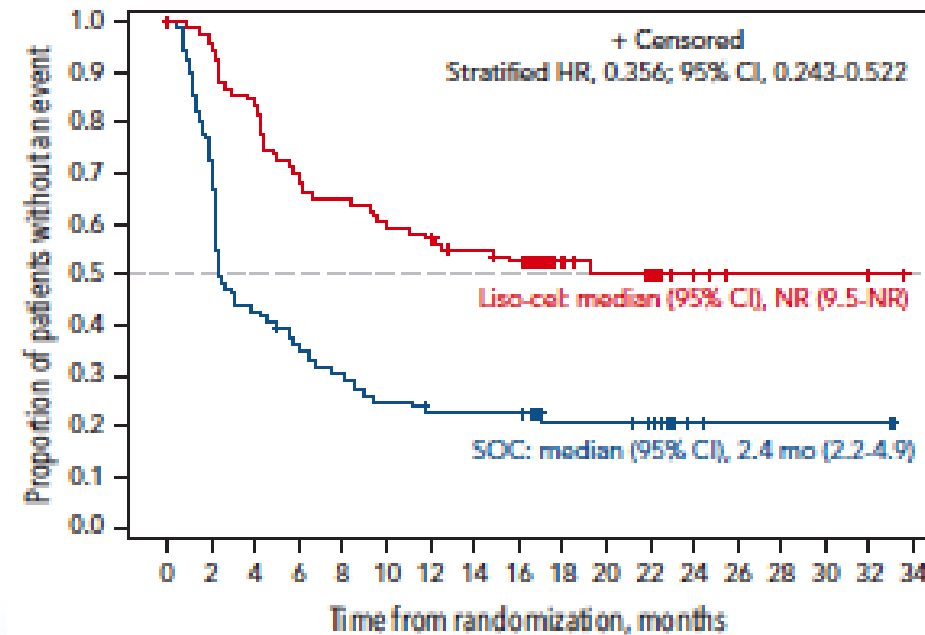
5-årsuppföljning

ZUMA-1

OS at median 63.1 months' follow-up (N=101)¹

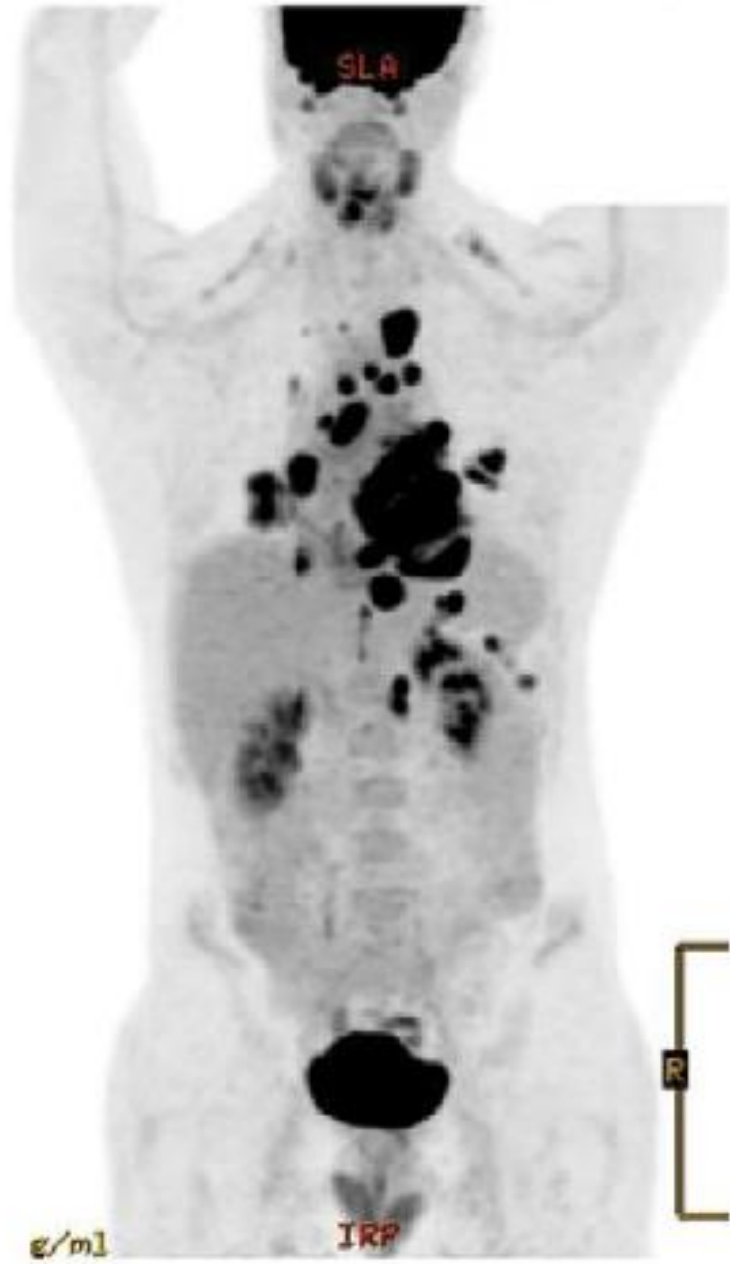


17,5 mos follow-up



No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
SOC	92	66	39	32	27	22	19	19	19	12	12	10	3	2	2	2	2	0
Liso-cel	92	87	76	62	59	55	52	48	45	24	20	17	5	3	3	3	3	0

CR 74% for liso-cel (vs 43%)
EFS NR for liso-cel vs (2.4 mos)



B-ALL

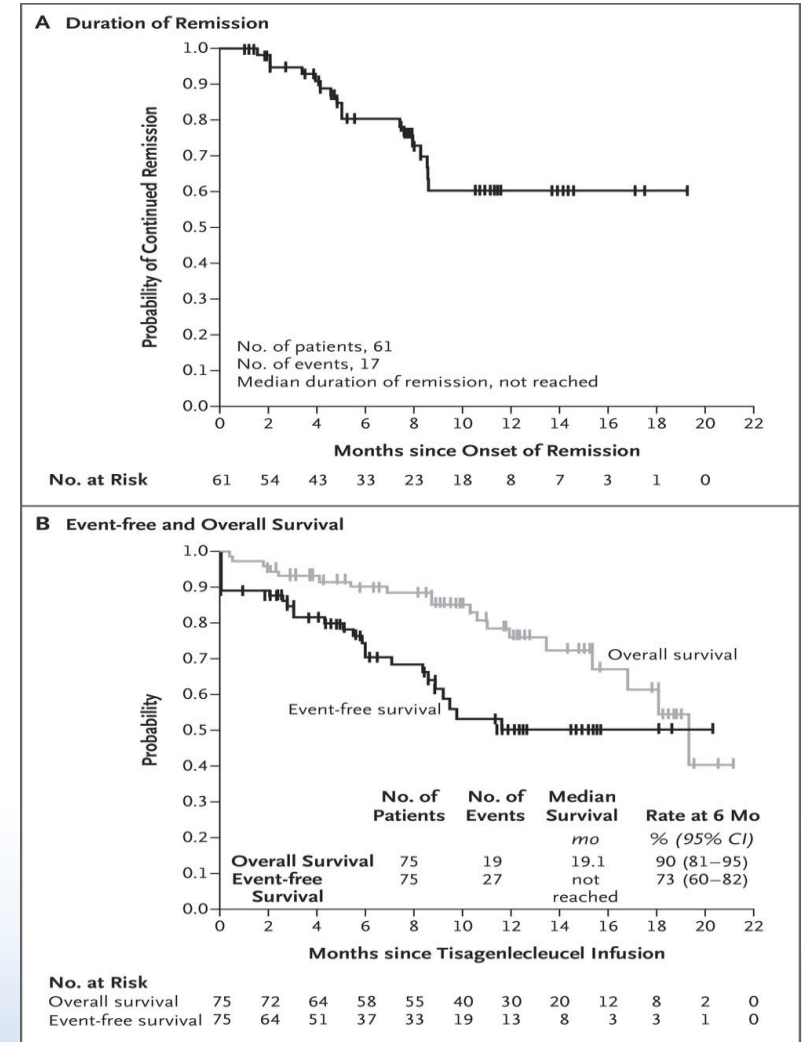
ALL

Kymriah®/tisa-cel/Novartis

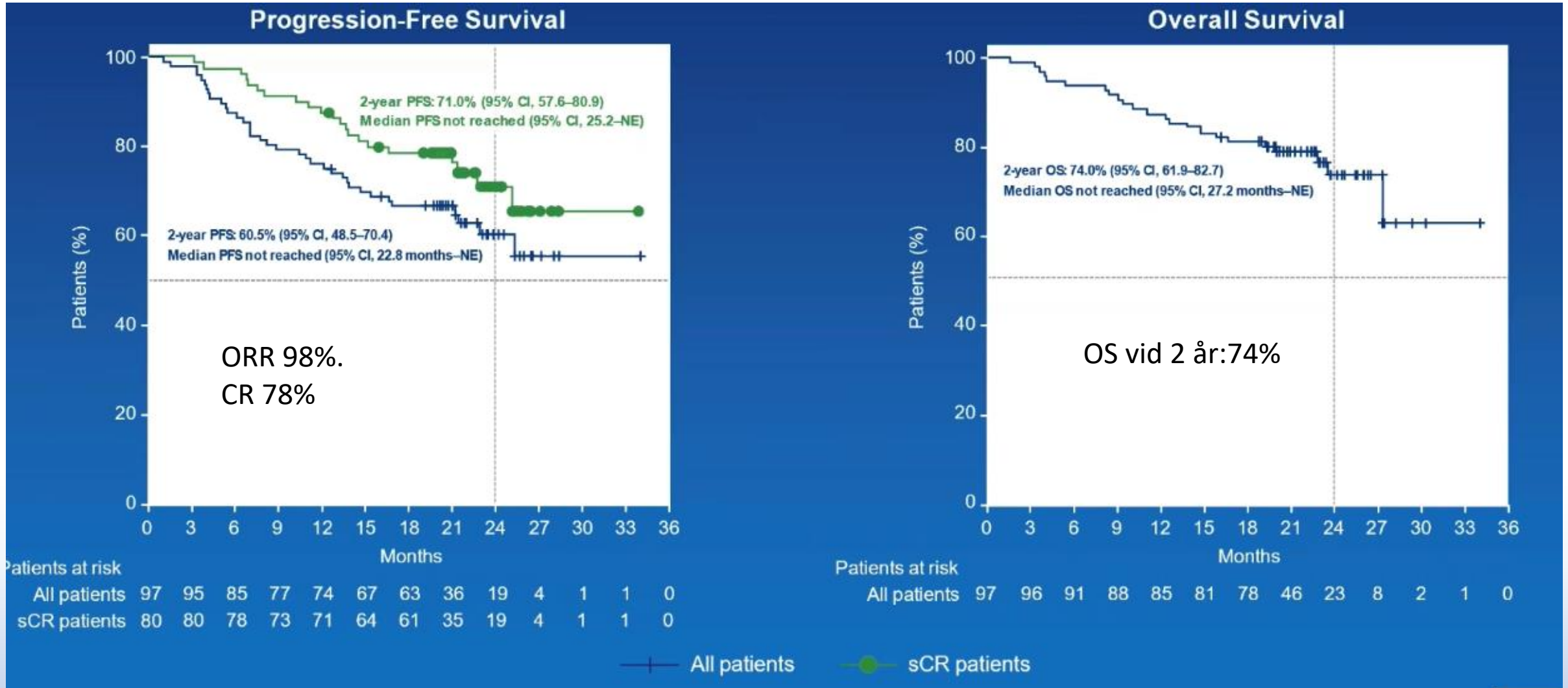
Median-follow-up: 38,8 mos

ORR 82%. 59% of responders rel-free at 12 months.

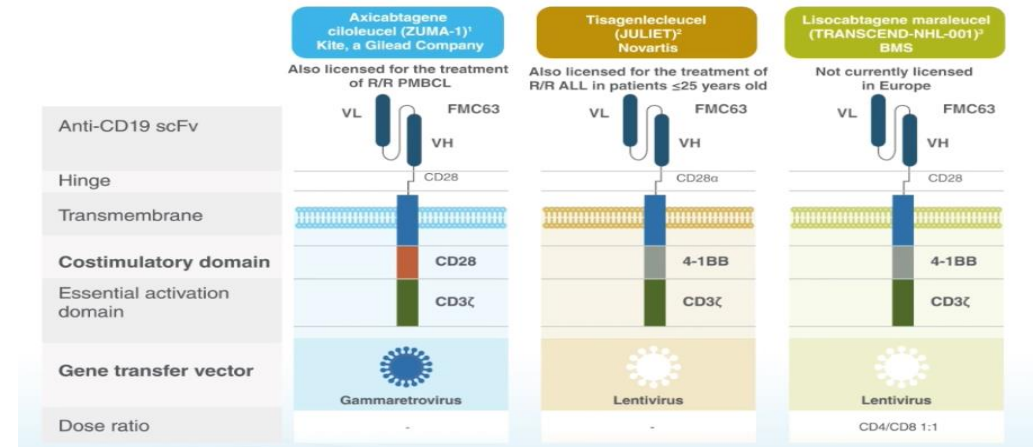
3-yrs: EFS 44%, OS 63%



Myelom

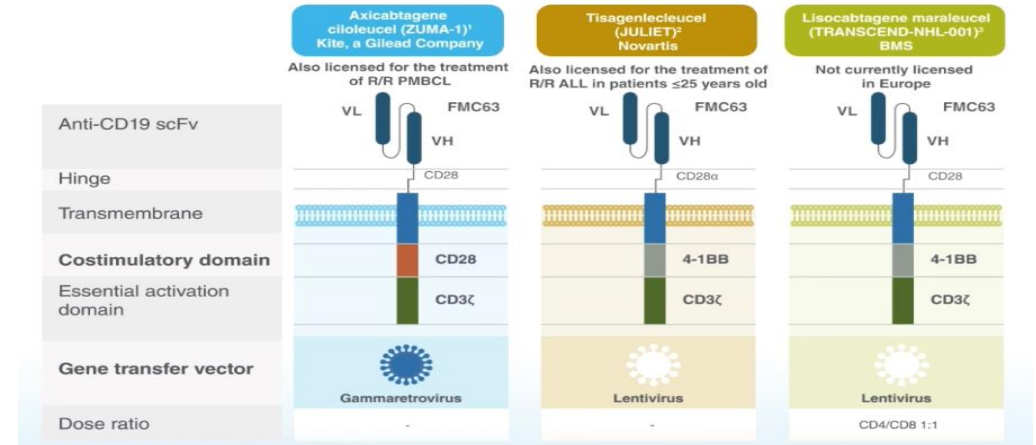


- **ZUMA**-studierna
(LBCL, MCL, ALL, indolenta lymfom, KLL)
Axicaptagene ciloleucel (**Yescarta**[®])
Brexucaptagene autoleucel (**Tecartus**[®])
- **JULIET**, **ELIANA** och **BELINDA** (LBLCL, ALL)
Tisagenlecleucel (**Kymriah**[®])
- **TRANSCEND** och **TRANSFORM** (LBCL)
Lisocaptagene maraleucel (**Breyanzi**[®])



- **KARMMA**-studierna (MM)
Idecabtagene vicleucel (**Abecma**[®])
- **CARTITUDE**-studierna (MM)
Ciltacabtagene autoleucel (**CARVYTKI**[®])

- **ZUMA**-studierna
(LBCL, MCL, ALL, indolenta lymfom, KLL)
Axicaptagene ciloleucel (**Yescarta**[®])
Brexucaptagene autoleucel (**Tecartus**[®])
- **JULIET**, **ELIANA** och **BELINDA** (LBLCL, ALL)
Tisagenlecleucel (**Kymriah**[®])
- **TRANSCEND** och **TRANSFORM** (LBCL)
Lisocaptagene maraleucel (**Breyanzi**[®])



- **KARMMA**-studierna (MM)
Idecabtagene vicleucel (**Abecma**[®])
- **CARTITUDE**-studierna (MM)
Ciltacabtagene autoleucel (**CARVYTKI**[®])

Indikationer i Sverige

Aggressiva lymfom **Yescarta**[®] (axi-cel)

- Rel/ref, 3e linjen
- Vuxna
- 5-10 patienter/år på SU

Mantelcellslymfom **Tecartus**[®] (brexu-cel)

- Rel/ref, 3e linjen, inkl TKI
- Vuxna
- 1-2 patienter/år på SU

Akut lymfatisk leukemi **Kymriah**[®] (Tisa-cel)

- Rel/ref
- Barn & vuxna upp till 25år
- 0-2 patienter år



Approvals as standard of care

- Sweden
 - Tisa-cel – ALL - Stockholm, Gothenburg
 - Axi-cel – DLBCL, PMBCL - Lund, Gothenburg, Uppsala, Stockholm, Linköping
- Norway
 - Tisa-cel – ALL – Oslo
 - Axi-cel – DLBCL, PMBCL
- Denmark
 - Tisa-cel – ALL - Copenhagen
- Finland
 - Tisa-cel – ALL and lymphoma – Helsinki
 - Axi-cel – DLBCL, PMBCL, FL - Helsinki, Oulu, Turku
 - Brexu-cel – MCL – soon Helsinki, Oulu, Turku

Nya indikationer på gång
Myelom, LBCL, ALL och FL

LBCL som 2a linjensbeh ref/rel inom 12 mån

Yescarta[®] (axi-cel) - ZUMA-7

Breyanzi[®] (liso-cel) - TRANSFORM

Swedish CAR T/TCR treatments: Now 133 patients

Currently treated nationally;
137 infusions (4 RI) – 12 children

- CAR T treatment centre
- Standard of Care - SOC
- Academic Clinical Trial - ACT
- Industry Clinical Trial - ICT
- GMP manufacture

RI = Reinfusion

Uppsala (50 infusions)

- Academic trial 3rd generation CAR T since 2014
- First ACT 2014 – Now 39 patients
- First SOC Nov 2022 – Now 11 patients
- *First Mantle Cell Lymphoma patient April 2023*

Gothenburg (12 infusions)

- First SOC Oct 2020 – Now 10 patients
- First ICT Oct 2022 – Now 1 patient, 1 RI

Umeå

- Upcoming treatment center

Stockholm (44 infusions)

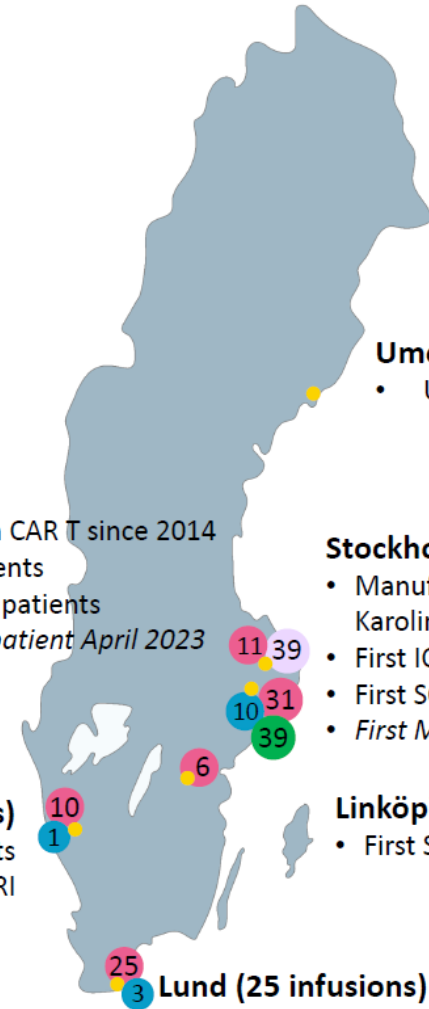
- Manufacture 3rd generation CAR T since 2014 – Karolinska/Vecura – 39 GMP batches
- First ICT Aug 2019 – Now 10 patients
- First SOC Nov 2019 – Now 31 patients, 3 RI
- *First Mantle Cell Lymphoma patient March 2023*

Linköping (6 infusions)

- First SOC Jan 2020

Lund (25 infusions)

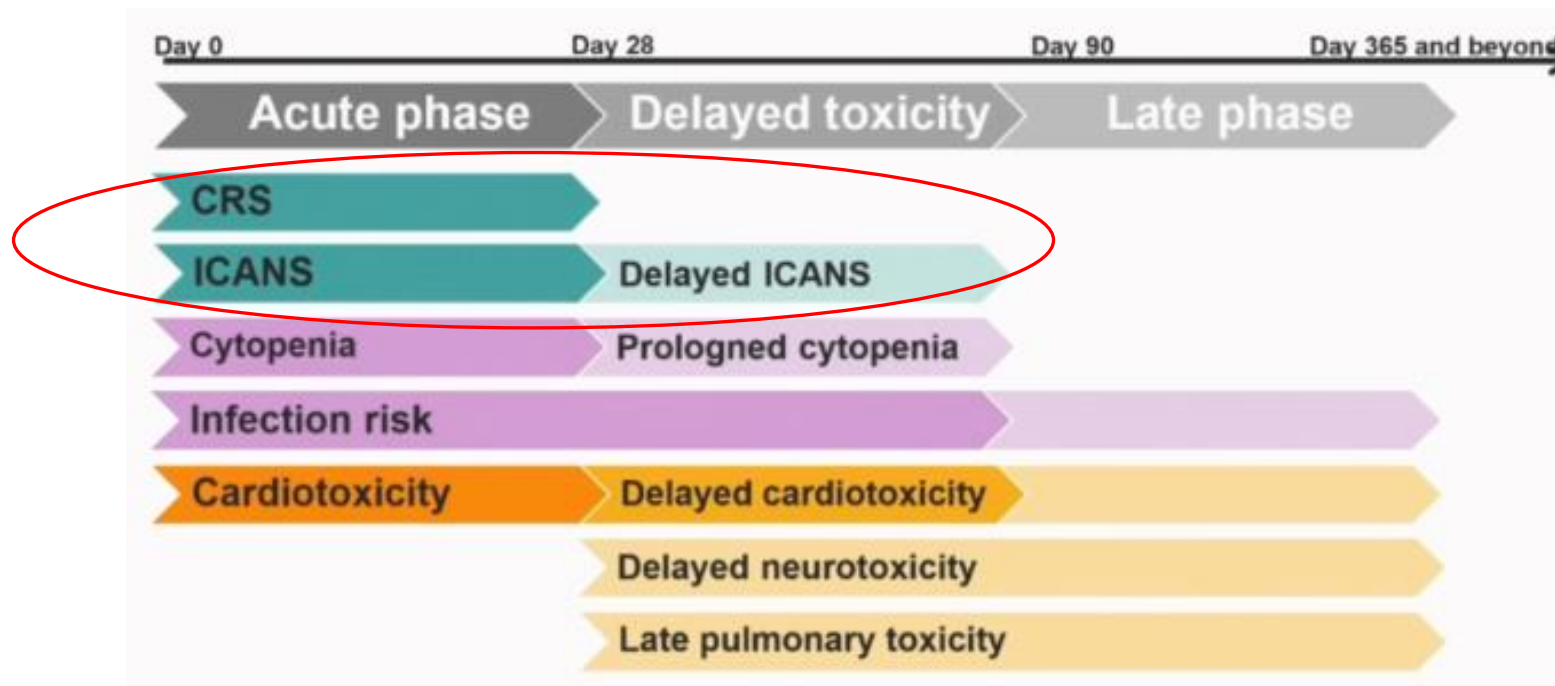
- First SOC Jan 2020 – Now 22 patients
- First ICT Nov 2021 – Now 3 patients



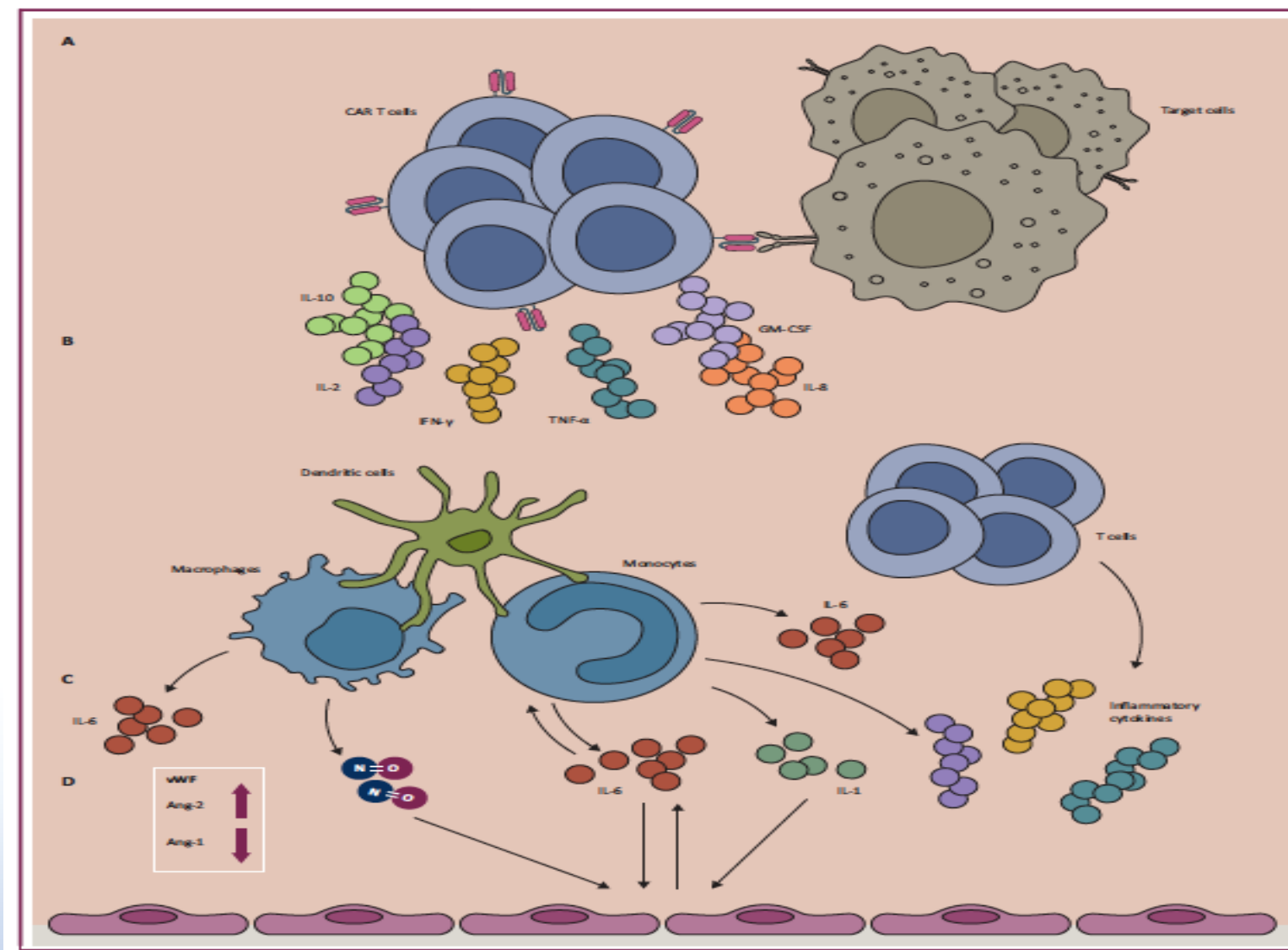
Data from SWECARNET Updated March 6th 2023

Komplikationer och biverkningar efter CAR-T/BiTe

- CRS
- ICANS
- Cytopenier
- Infektioner
- Organtoxicitet
- TLS
- CAR-T-cellsassocierad HLH



CRS patofysiologi



- >90% av patienterna (grad ≥ 3 ca 30%)
- Debutsymptom: feber
- Kan snabbt försämrans
- Behandlas tidigt -> oftast god prognos
- Liknar infektion/sepsis

Symptom	Grad 1	Grad 2	Grad 3	Grad 4
Feber	≥38°C	≥38°C	≥38°C	≥38°C
tillsammans med:				
Lågt blodtryck	-	Svarar på vätska iv. Ej behov av vasopressorer	Behov av 1 vasopressor	Behov av flera vasopressorer (exkl vasopressin)
och/eller:				
Låg saturation	-	Syrgas på gramma ≤ 6 L/min	Syrgas >6 L/min på mask eller högflöde nasalt	CPAP, BiPAP, Respirator

CRS-inducerad organtoxicitet

Lever

Njurar – Kan kräva dialys

Andningsvägar

Hjärtat

Blodkärl – kapillärläckagesyndrom

Långvariga cytopenier

Koagulopati med hypofibrinogenemi –

DIC. **Obs:** Övervaka även efter CRS.

Symptom	Grad 1	Grad 2	Grad 3	Grad 4
Feber	≥38°C	≥38°C	≥38°C	≥38°C
Upp till 30% av alla				
tillsammans med:				
Lågt blodtryck	-	Svarar på vätska iv. Ej behov av vasopressorer	Behov av 1 vasopressor	Behov av flera vasopressorer (exkl vasopressin)
och/eller:				
Låg saturation	-	Syrgas på gramma ≤ 6 L/min	Syrgas >6 L/min på mask eller högflöde nasalt	CPAP, BiPAP, Respirator

CRS-inducerad organtoxicitet

Lever

Njurar – Kan kräva dialys

Andningsvägar

Hjärtat

Blodkärl – kapillärläckagesyndrom

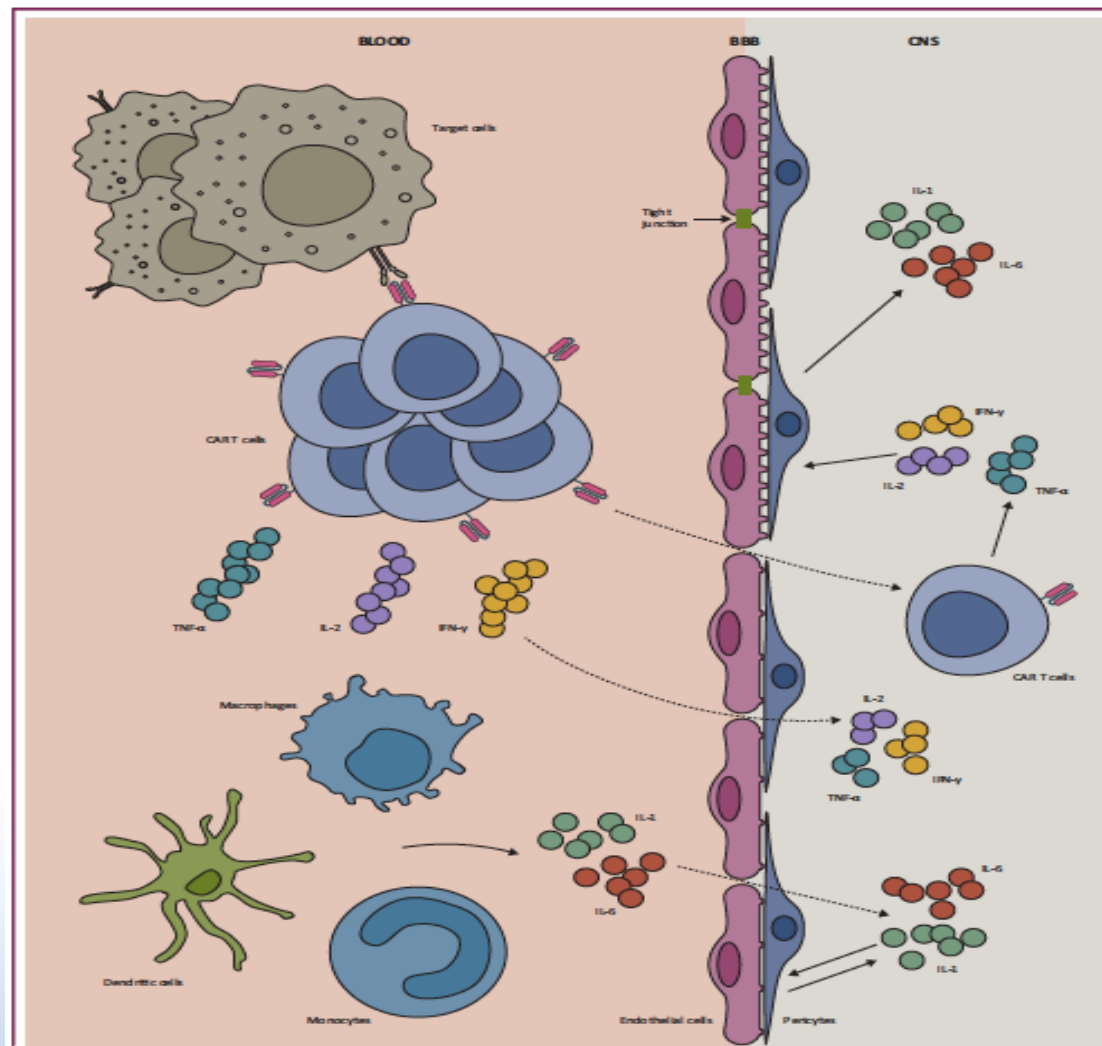
Långvariga cytopenier

Koagulopati med hypofibrinogenemi –

DIC. **Obs:** Övervaka även efter CRS.

CRS	Grad 1	Grad 2	Grad 3	Grad 4
Symptom	Milda	Måttliga	Allvarliga	Livshotande
Understödjande	Paracetamol, iv vätska, Antiemetika (Ev. antibiotika)	Paracetamol, iv vätska (bolus vb) Syrgas på gramma Kontakta MIG-team	<u>Intensivvård</u>	
Tocilizumab	Ej bättre inom 24 tim	Var 8:e tim till förbättring. Max 4 totalt doser.		
Steroider	Ej aktuellt	Om ej bättre efter 4 doser tocilizumab: Dexametason 10mg iv x4 i 1-3 dygn	Dexametason 10mg iv x4 i 1-3 dygn	Dexametason 20mg iv x4 i 3 dygn
Utvärdering, fortsatt vård	Ej bättre inom 24 tim, överväg beh enl grad 2	Efter 24h: Förbättring, fortsätt enl. grad 1. Ej förbättring, fortsätt enl. grad 3.	Förbättring, fortsätt enl. grad 2. Fortsätt med steroider till grad 1. Trappa ut. Ej förbättring, fortsätt enl. grad 4	Förbättring, fortsätt enl grad 3. Fortsätt med steroider till grad 1. Trappa ut. Ej förbättring, metylprednisolon (iv) 1000mg x1 i 3 dygn. Trappa ned. Överväg andra immunosuppressiva läkemedel.

ICANS patofysiologi



M.-L. Schubert et al. "Side-effect management of chimeric antigen receptor (CAR) T-cell therapy." *Annals of oncology*

- Upp till 70% (ca 35% grad 3-4)
- Tidiga tecken: tremor, dysfasi, dysgrafi, apraxi, slöhet
- Kan snabbt försämrans: Konfusion, krampanfall, motorisk svaghet och medvetandepåverkan
- Hjärnödem, blödningar, t.o.m. dödsfall
- Tidig intervention viktig

Day 3

I love my family

MMSE
29/30

Day 4

I love my family

27/30

2 hours post
dexamethasone 10 mg
IV

I love my family

27/30

Day 5

I love my family

29/30

ICE (*Immune effector Cell Encephalopathy score*)

Test	Poäng
Orientering till år, månad, stad, sjukhus	4
Benämning: förmåga att benämna tre föremål (tex, bord, säng, lampa, kudde)	3
Följa en uppmaning: förmåga att följa en enkel uppmaning (tex vinka, blunda)	1
Skriva: förmåga att skriva en enkel mening (tex, Jag gillar att simma)	1
Kognition: förmåga att räkna baklänges från 100 med 10-tal	1

ICANS	Grad 1	Grad 2	Grad 3	Grad 4
ICE poäng	7-9	3-6	0-2	0 (kan ej bedömas)
Medvetandegrad	Vaknar spontant (RLS 1)	Vaknar vid tilltal (RLS 2)	Vaknar vid beröring, men ej tilltal (RLS 2-3)	Medvetslös (RLS \geq 4)
Krampanfall	-	-	Krampanfall eller icke-konvulsivt på EEG med epileptiform aktivitet och svarar på intervention	Livshotande kramp (>5 min), status epilepticus eller uppreprepade krampanfall eller icke-konvulsivt på EEG utan normalisering emellan
Motoriskt bortfall	-	-	Nej	Fokalt motoriskt bortfall, hemipares/parapares
Intrakraniellt tryck/hjärnödem	-	-	Radiologiska tecken på fokalt ödem	Diffust hjärnödem (enl. CT/MR); decerebrerings-/dekortikalissymtom; papillödem; abducenspare; Cushings triad

Upp till 35% av alla				
ICANS	Grad 1	Grad 2	Grad 3	Grad 4
ICE poäng	7-9	3-6	0-2	0 (kan ej bedömas)
Medvetandegrad	Vaknar spontant (RLS 1)	Vaknar vid tilltal (RLS 2)	Vaknar vid beröring, men ej tilltal (RLS 2-3)	Medvetslös (RLS \geq 4)
Krampanfall	-	-	Krampanfall eller icke-konvulsivt på EEG med epileptiform aktivitet och svarar på intervention	Livshotande kramp (>5 min), status epilepticus eller upprepade krampanfall eller icke-konvulsivt på EEG utan normalisering emellan
Motoriskt bortfall	-	-	Nej	Fokalt motoriskt bortfall, hemipares/parapares
Intrakraniellt tryck/hjärnödem	-	-	Radiologiska tecken på fokalt ödem	Diffust hjärnödem (enl. CT/MR); decerebrerings-/dekortikalissymtom; papillödem; abducenspare; Cushings triad

Behandling	Grad 1	Grad 2	Grad 3	Grad 4
Tocilizumab	Endast vid samtidigt CRS, oavsett grad.			
Steroider	Nej	Dexametason 10mg x4 iv i 1-3 dygn	Dexametason 20mg x2 iv i 1-3 dygn	Metylprednisolon 1000mg x1 iv i 3 dygn, därefter nedtrappning. Ej bättre inom 24 tim, överväg alternativ immunhämmande behandling.
Vårdsnivå	Vårdavdelning	Avgörs individuellt	Intensivvård	

CRS

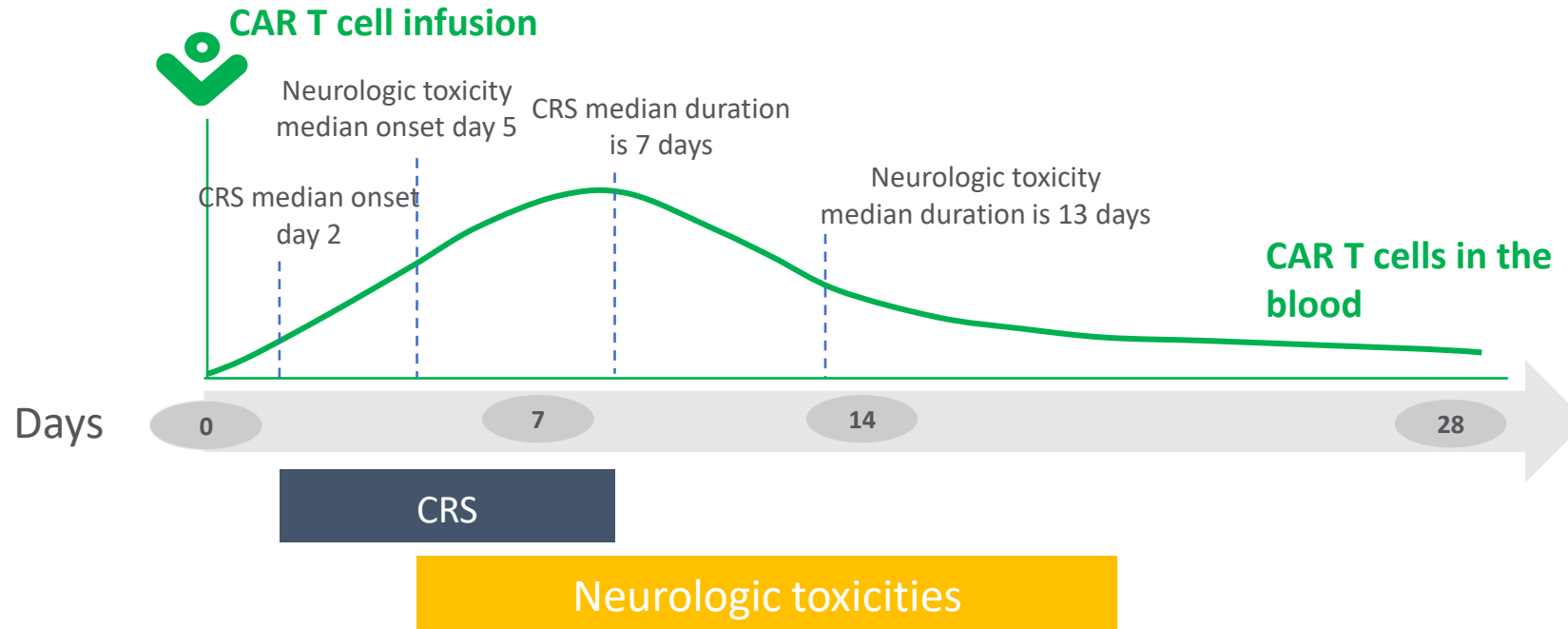
- Hög tumörbörda
- Trombocytopeni
- Infektion/CRP
- CAR-T-produkt (Yescarta>Kymriah)

ICANS

Som för CRS och:

- CRS
- ALL
- CNS-sjukdom

Onset and Resolution of CRS and ICANS

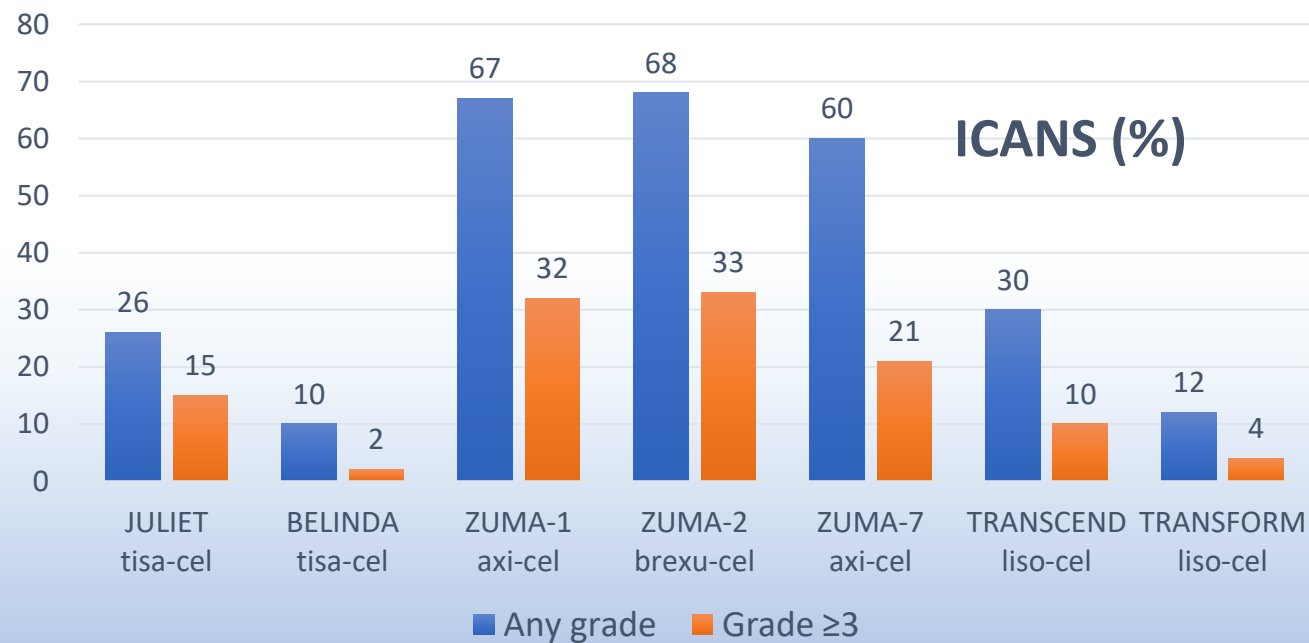
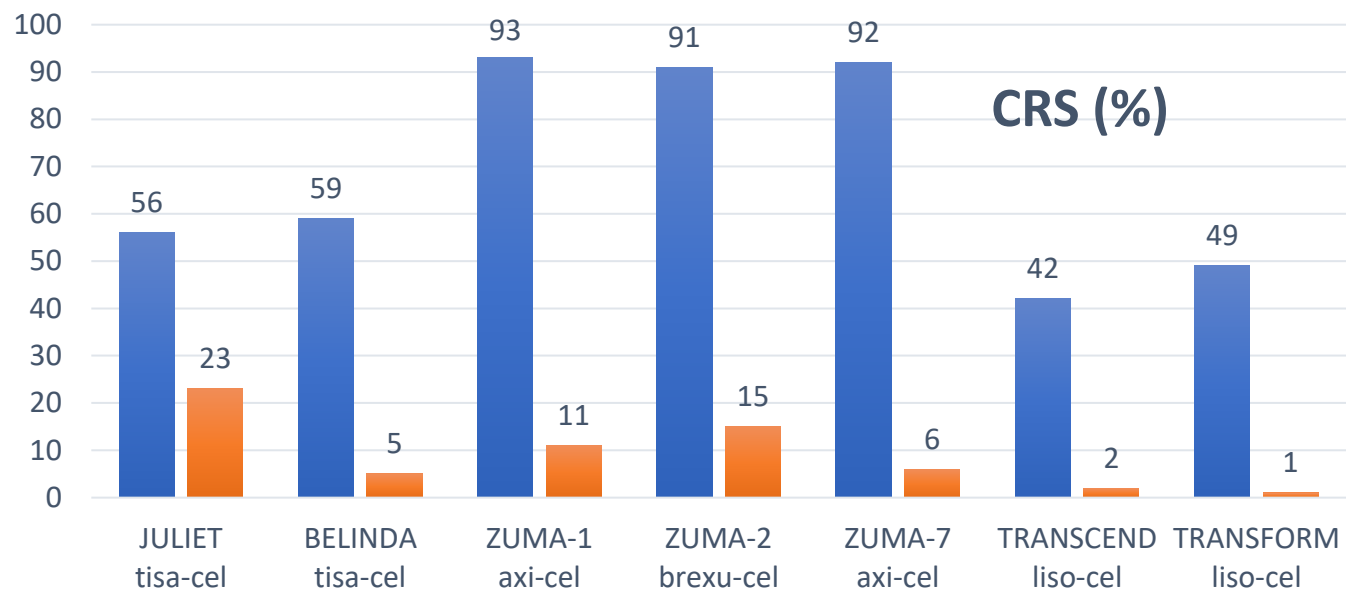


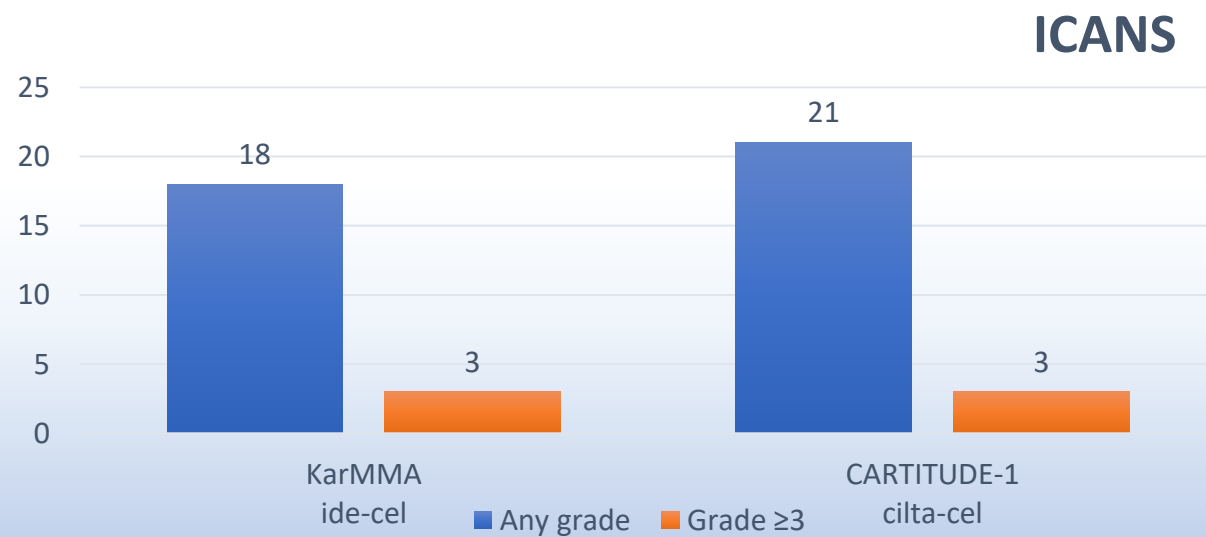
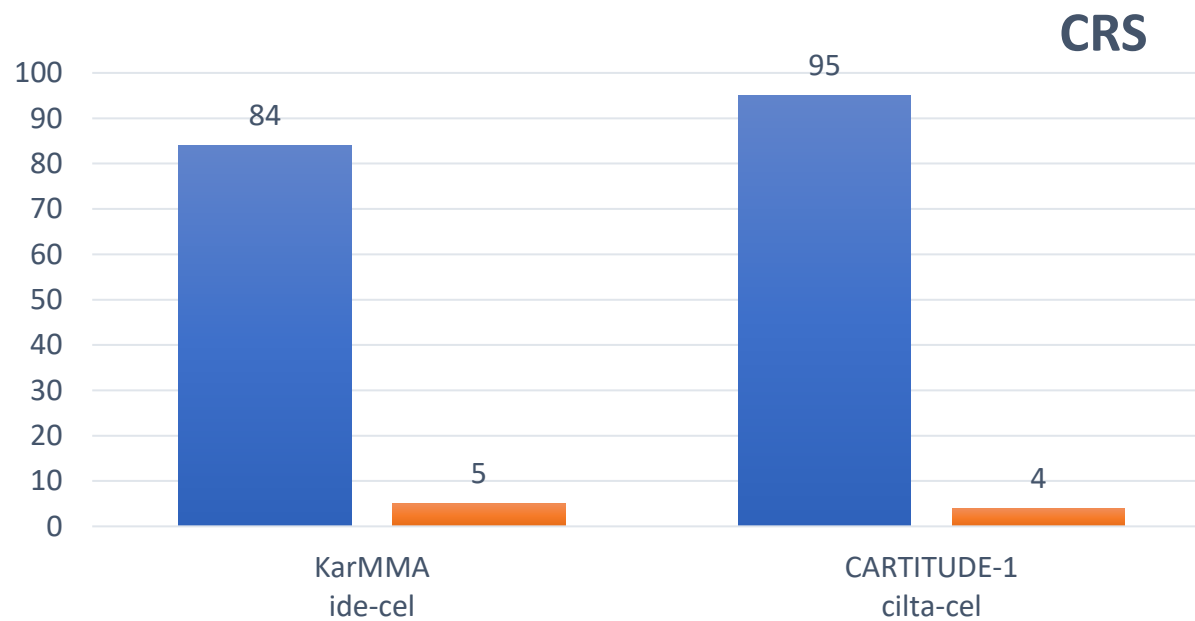
- May occur within minutes or hours but generally appear within days or weeks^{1, 2}
 - Coincide with maximal T cell expansion¹
- Generally reversible in most patients; rare cases of long-term symptoms¹

CAR, chimeric antigen receptor; CRS, cytokine release syndrome.

1. Lee DW, et al. *Blood*. 2014;124:188-195. 2. YESCARTA (axicabtagene ciloleucel) SmPC April 2019.

CRS och ICANS (lymfom)



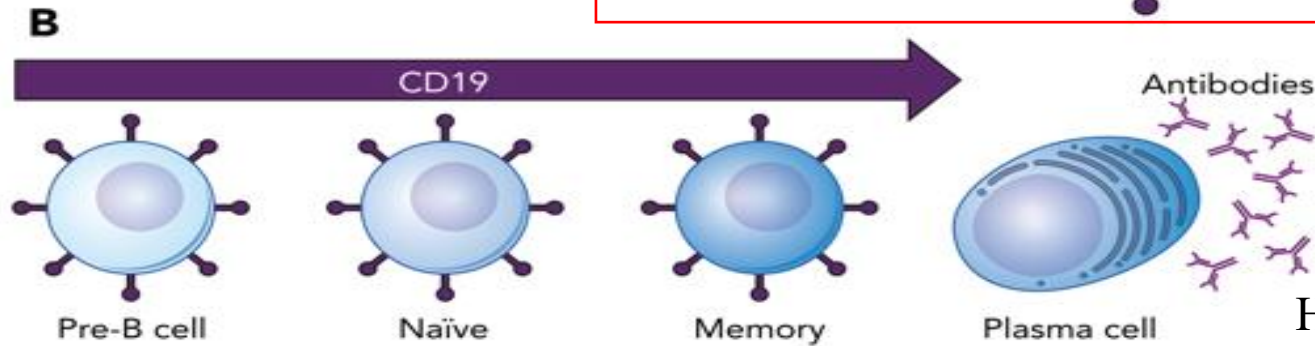
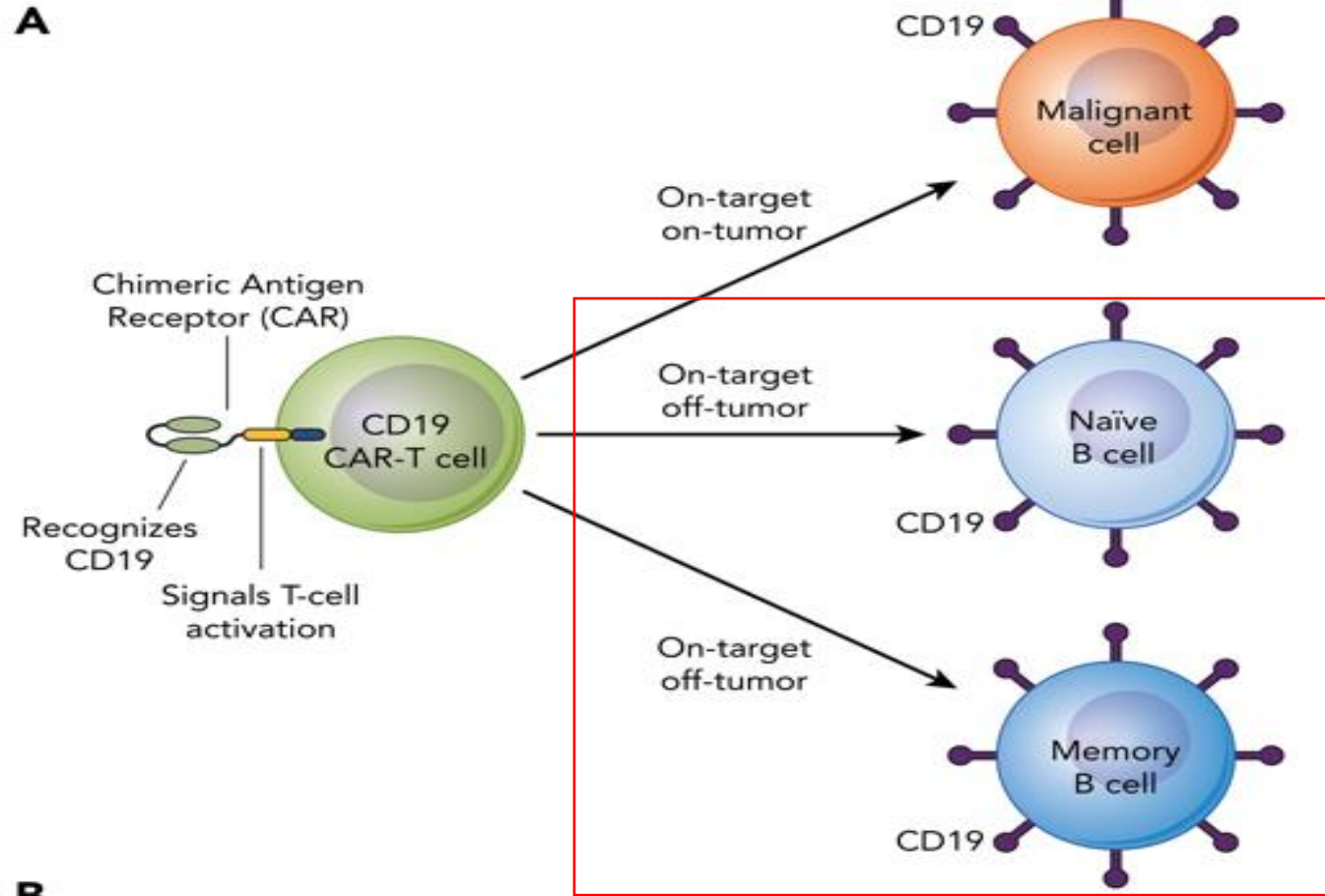


Parkinson-liknande biverkningar

- BCMA-riktade CAR-T (myelom)
- Neurokognitiva störningar + hypokinetiska rörelsemönster
- Kan komma flera månader efter infusion
- BCMA uttrycks i hjärnan

CD19-CAR-T

B-cellshypoplasi:
On-target,
Off-tumor effect



Hill JA et al. *Blood* 2020

B-cellsaplasti och hypogammaglobulinemi

Efter 12 mån: ca 50%

B Cell and Immunoglobulin Recovery in Patients with Complete Remission after CAR-Ts

	3 Months	6 Months	9 Months	12 Months	24 Months
<i>Percentage of patients with detectable B cells</i>					
Axicabtagene ciloleucel ZUMA-1 [4]	17	~24	61	~52	75
Tisagenlecleucel single-institution study [23] *	–	40	–	60	80
<i>Percentage of patients with IgG increase from nadir in the absence of IVIG</i>					
Tisagenlecleucel single-institution study [23],*	–	30	–	40	100

* This study only reported results for patients achieving complete remission.

Cytopenier

”Real world”:

Uttalad neutropeni ca 80-90% (ses ofta första veckan)

Ofta ihållande (upp till 1/5 dag+90)

Neutropen feber 80-87% första månaden

Frequency and Duration of Cytopenias after FDA Approved CD19 CAR-T Products

	Neutropenia \geq Grade 3			Anemia \geq Grade 3			Thrombocytopenia \geq Grade 3		
	Percentage of Patients at Any Time*	At \geq 28 Days [†]	At \geq 3 Months	Percentage of Patients at Any Time*	At \geq 28 Days [†]	At \geq 3 Months	Percentage of Patients at Any Time*	At \geq 28 Days [†]	At \geq 3 Months
Axicabtagene ciloleucel, ZUMA-1 [4],*	93	26	11	65	10	3	58	24	7
Tisagenlecleucel, JULIET [2],*	81	24	0	58	Not reported	Not reported	54	41	38

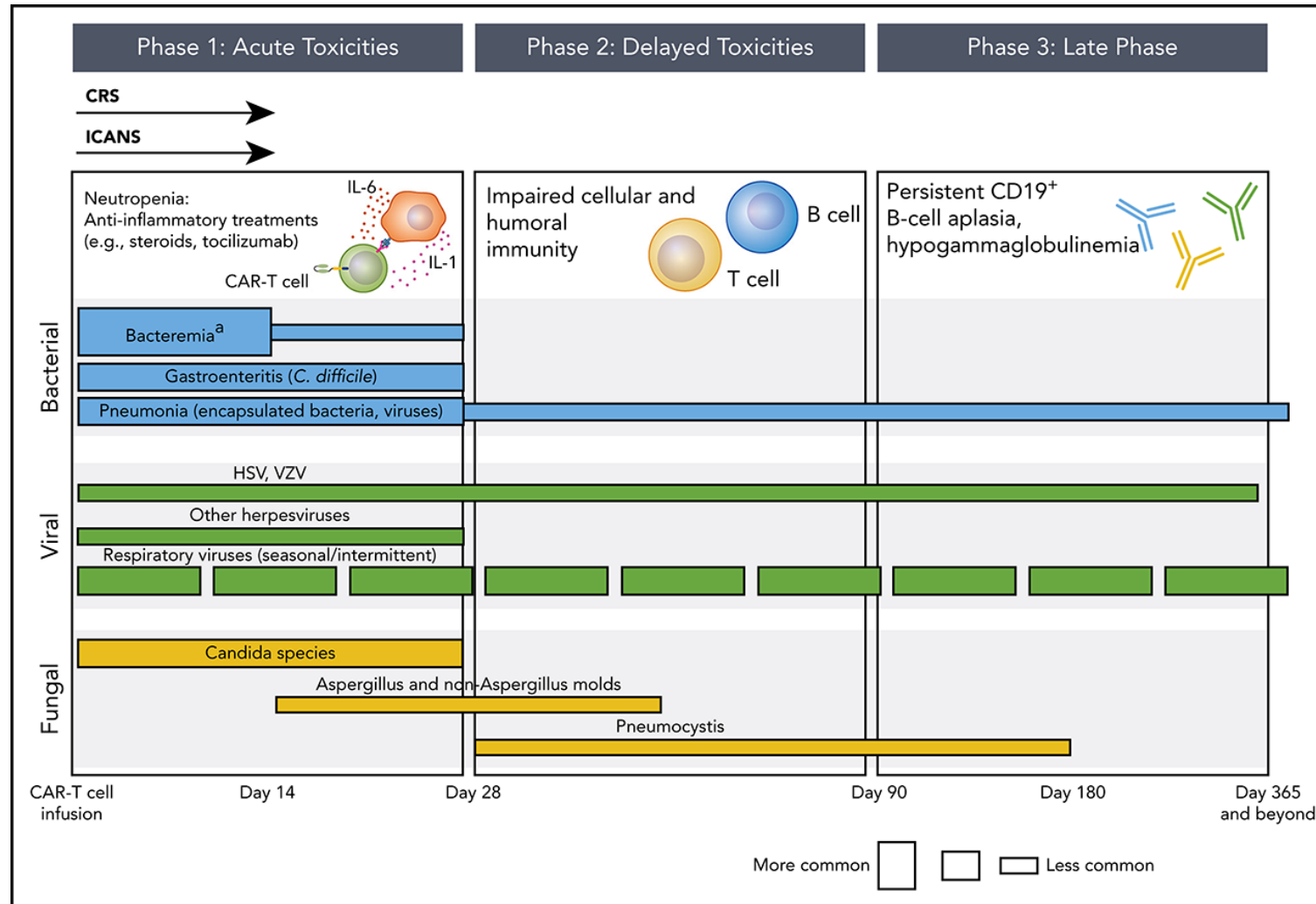
* Data from package insert, all other data from studies.

[†] \geq 30 day outcomes reported for ZUMA-1, \geq 28 day outcomes reported for JULIET.

Cytopenier

- Pancytopeni >4 veckor vanligt
- Långsam återhämtning (veckor till månader)
- G-CSF kan ges vid neutropeni:
 - uttalad ($<0,2 \times 10^9/L$)
 - ihållande
 - infektion
 - försiktighet vid CRS/ICANS grad 3-4
- Bestrålade blodprodukter t.o.m. 12 månader

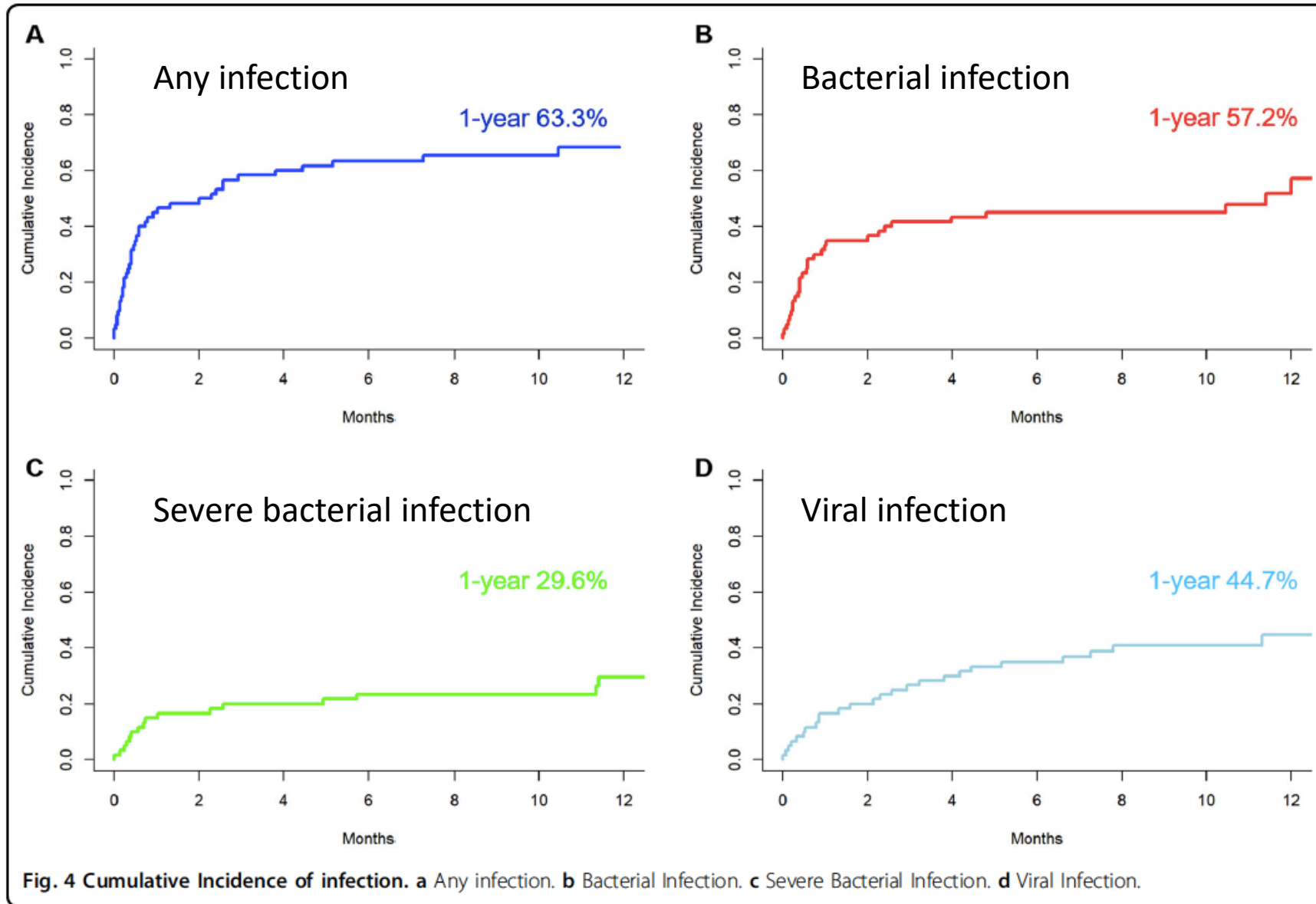
CAR-T-celler/timeline för infektion



Hill JA et al. *Blood* 2020

Kumulativ incidens av infektioner 1a året efter CAR-T

Retrosp, DLBCL
CD19-CAR-T
N=60



- Fram till dag+28: inom 2 timmars avstånd från SU
- Omedelbart uppsöka läkarvård om symtom på CRS/ICANS
- Påminn patienten att ej behandla sina egna symptom
- Ej framföra fordon, använda maskiner under 8 veckor
- Kolla temp \times 2 under 3–4 veckor ->Vid feber inom 14 dagar: återinläggning

Take-home message: efter CAR-T/BitE

Feber+cytopenier:

- ✓ Behandla som neutropen feber
- ✓ CRP kan vara lågt om tozilizumab
- ✓ Kontakta hemajour – CRS-behandling?

Neurologiska symptom:

- ✓ Neurologisk utredning
- ✓ Kontakta hemajour – ICANS-behandling?

Gäller även om lång tid sedan CAR-T-infusion!!



TACK