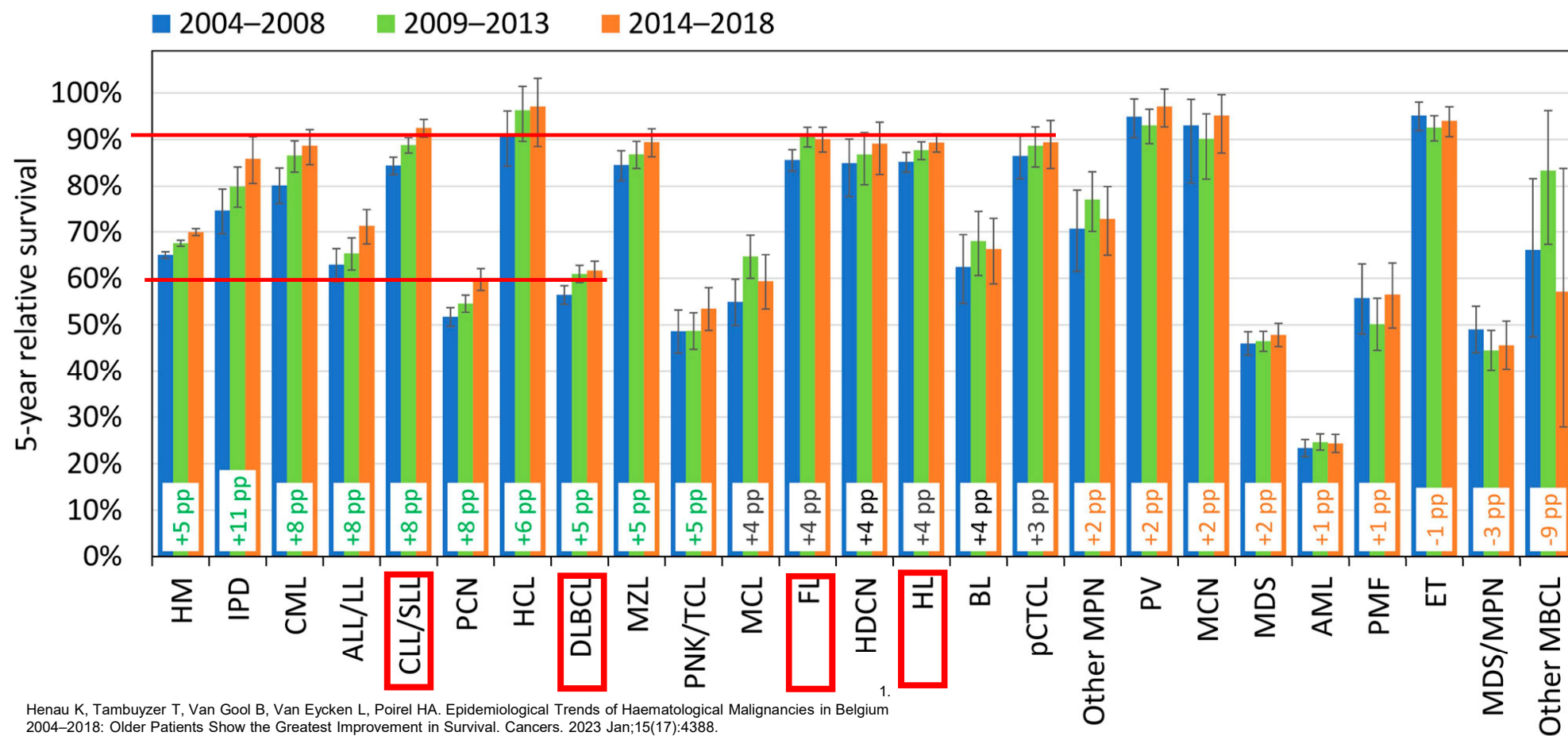


Overzicht van de behandelingen en nevenwerkingen

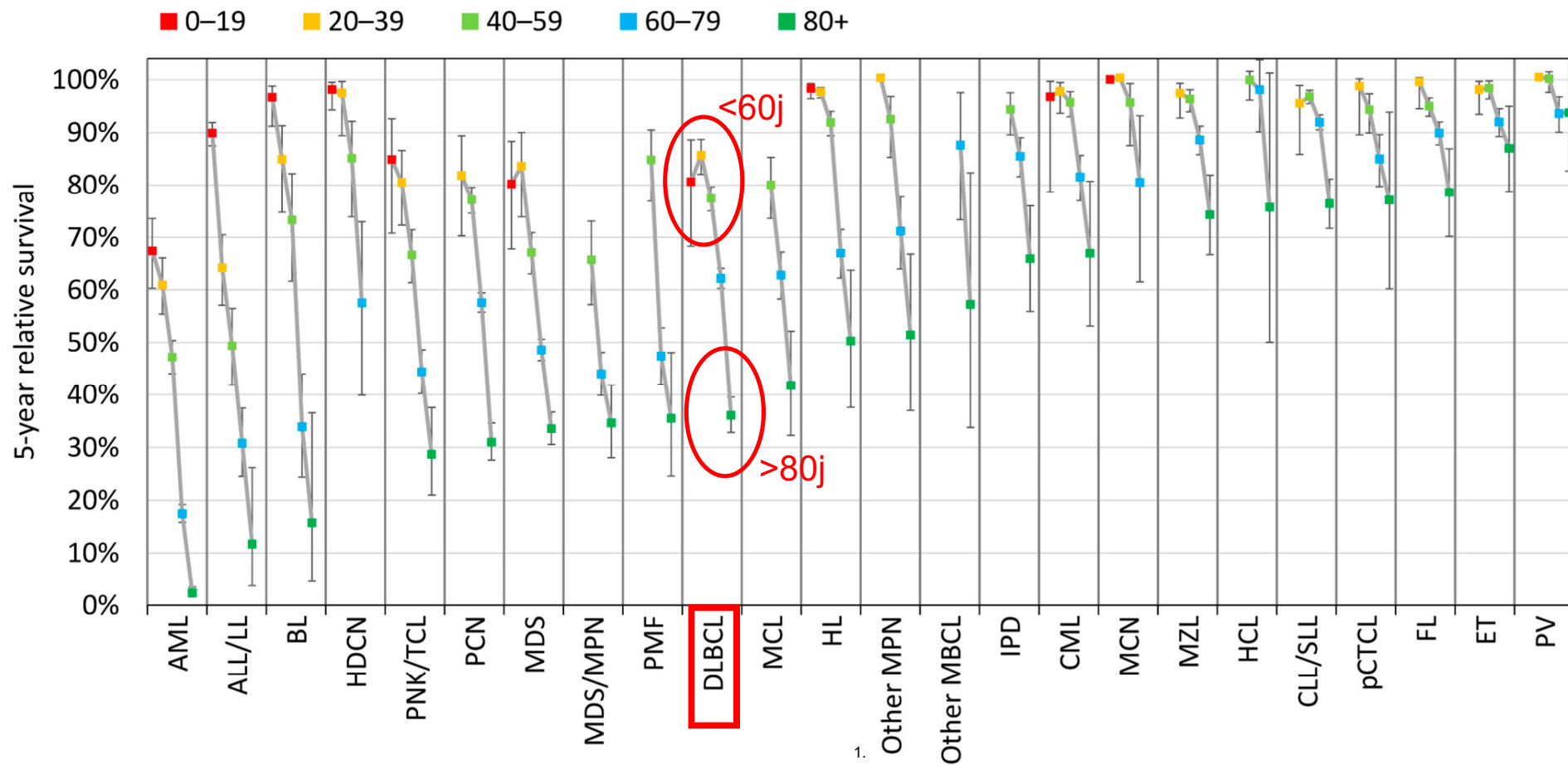
Viering 40 jaar LVV: symposium lymfeklierkanker
12 September 2026

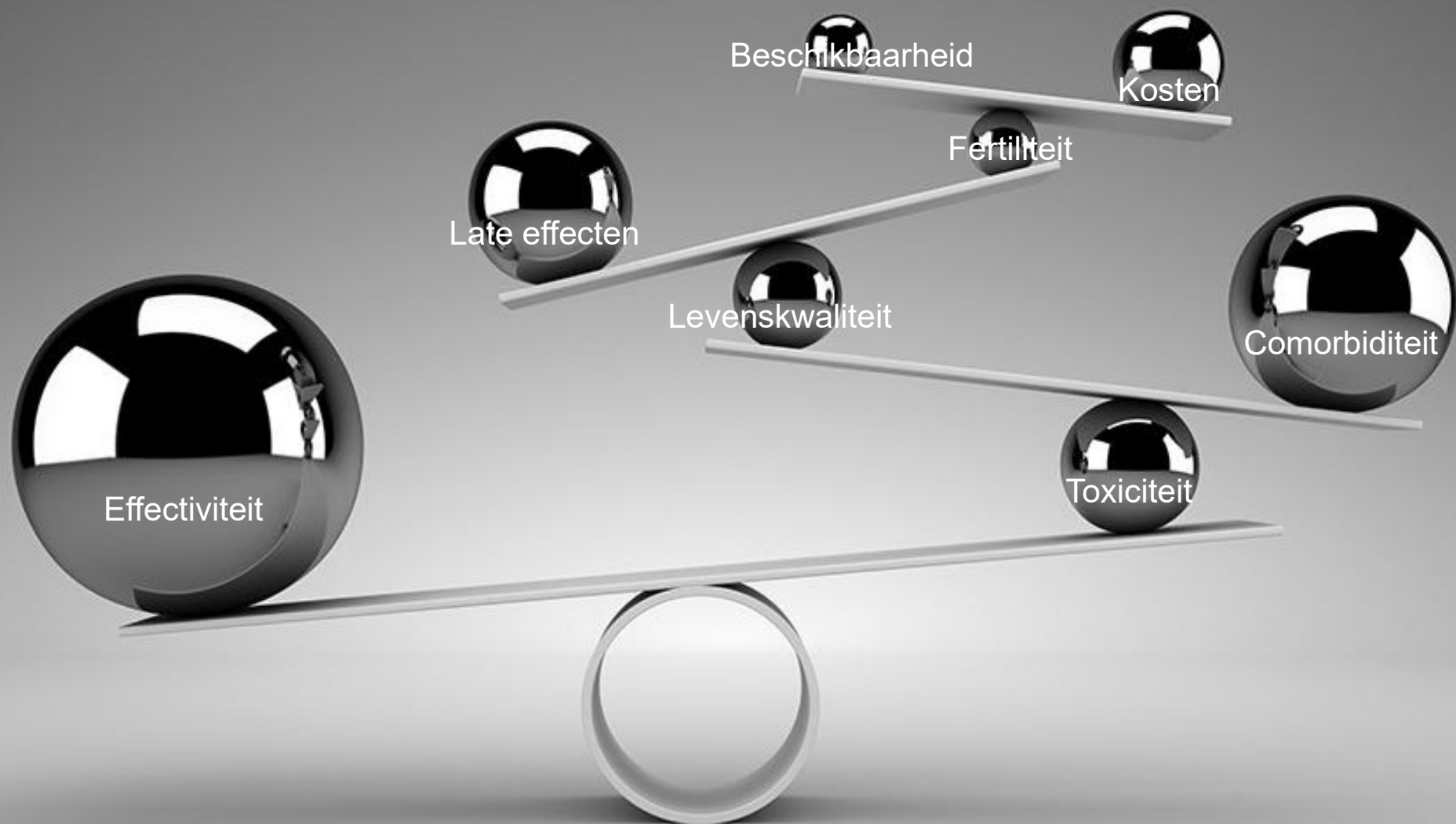
Overleving is verbeterd voor bijna alle hematologische kankers



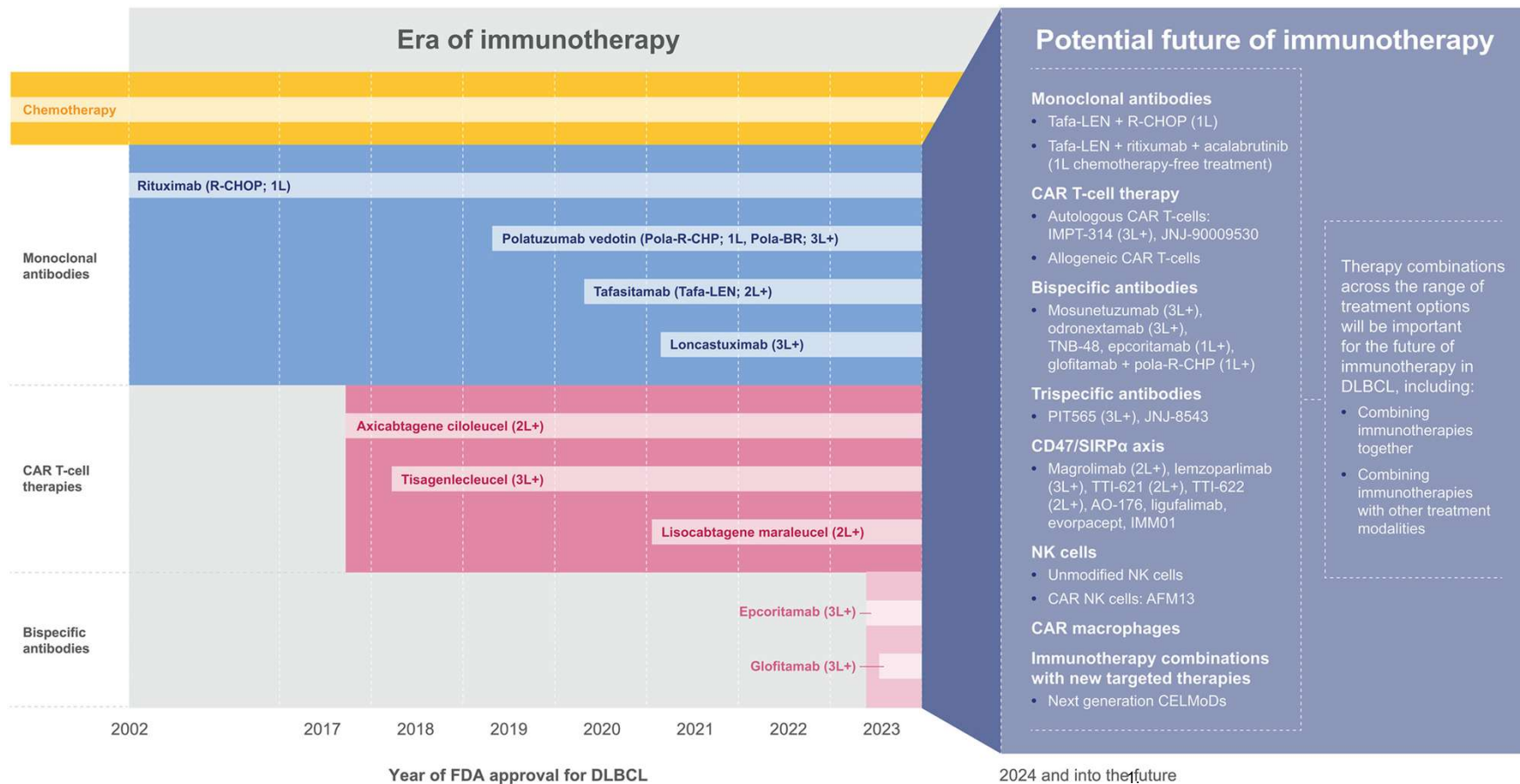
Henau K, Tambuyzer T, Van Gool B, Van Eycken L, Poirel HA. Epidemiological Trends of Haematological Malignancies in Belgium 2004–2018: Older Patients Show the Greatest Improvement in Survival. *Cancers*. 2023 Jan;15(17):4388. doi:10.3390/cancers15174388

Wel groot verschil ifv leeftijd bij diagnose





Veel nieuwe behandelingen (bv DLBCL)



Overzicht

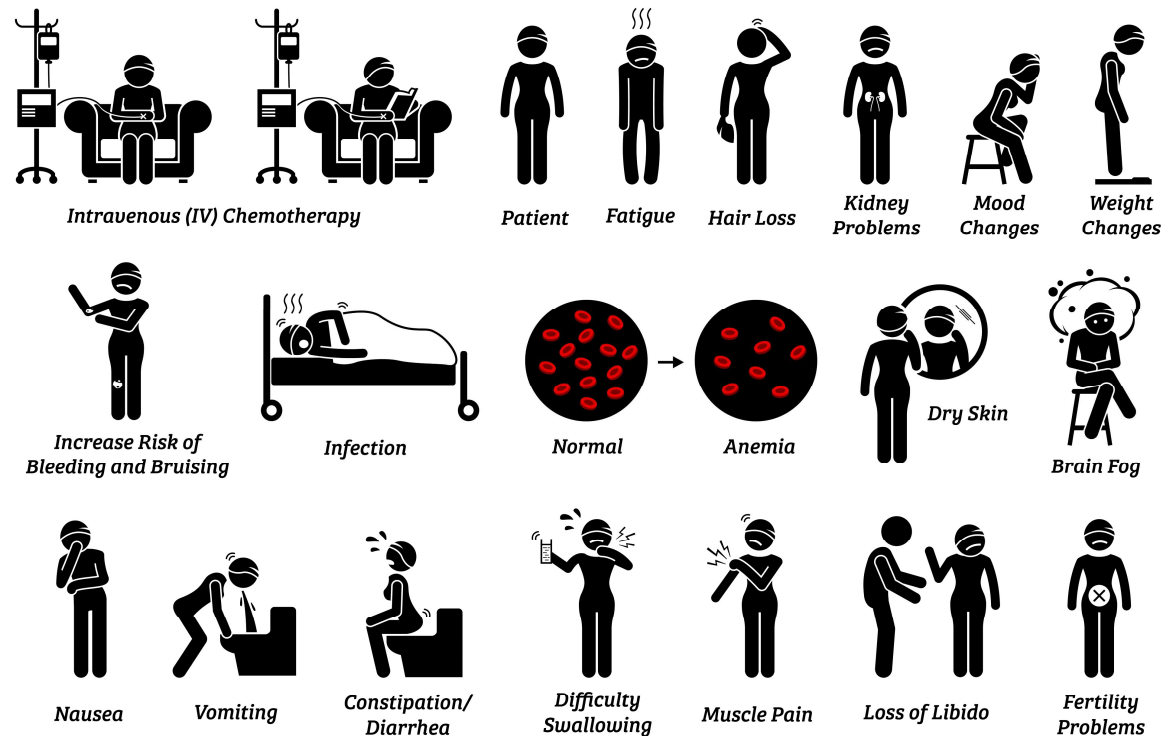
- ▶ Chemotherapie
 - ▶ Doelgerichte chemotherapie
- ▶ Radiotherapie
- ▶ Stamceltransplantatie
 - ▶ Autoloog
 - ▶ Allogeen
- ▶ Doelgerichte therapie
 - ▶ BTK-inhibitoren
 - ▶ BCL2-inhibitoren
 - ▶ Lenalidomide
- ▶ Immunotherapie
 - ▶ Monoklonale antilichamen
 - ▶ Check-point-inhibitoren
 - ▶ Bispecifieke antilichamen
 - ▶ CAR-T cel therapie



Nevenwerkingen

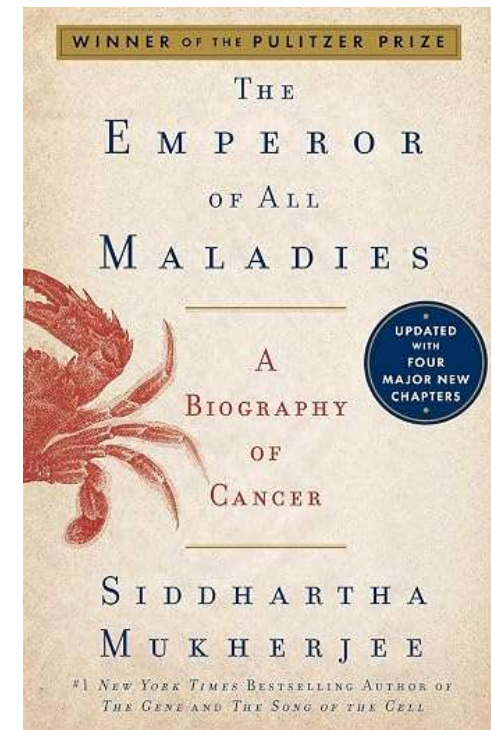
- ▶ Misselijkheid en braken
- ▶ Haaruitval (alopecia)
- ▶ Zenuwaantasting (neuropathie)
- ▶ Koorts en infecties
- ▶ Bloedarmoede (anemie)
- ▶ Laag aantal bloedplaatjes (trombopenie)
- ▶ Huidafwijkingen
- ▶ Diarree
- ▶ Auto-immuniteit
- ▶ Laattijdige effecten
 - ▶ Cardiale toxiciteit
 - ▶ Fertiliteit
 - ▶ Andere tumoren

Chemotherapy Side Effect



Chemotherapie

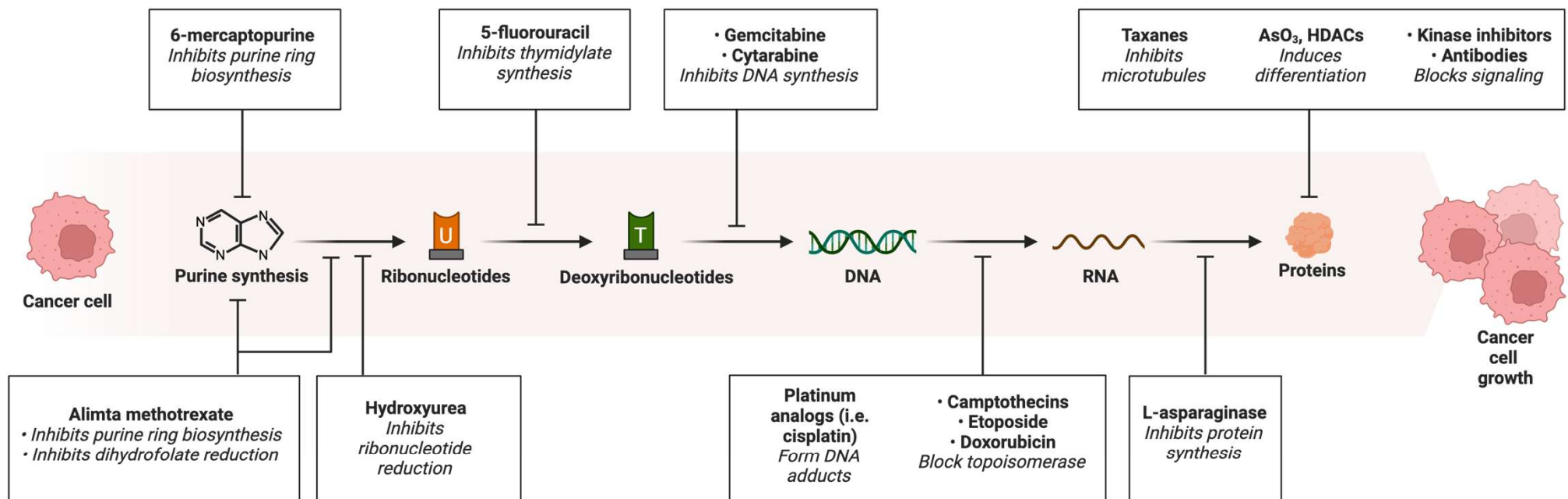
- ▶ Vroeger enigste beschikbare lymfoombehandeling
- ▶ Evolutie naar meer “chemovrije” behandeling
 - ▶ Minder “klassieke” bijwerkingen
 - ▶ Minder laattijdige bijwerkingen
 - ▶ Chemo-vrij ≠ bijwerkingen-vrij
- ▶ Voorlopig nog belangrijke plaats in behandeling
 - ▶ Hoge slaagkansen voor veel ziekten
 - ▶ “Time-limited” therapie
 - ▶ (veel) goedkoper dan nieuwe behandelingen
- ▶ Vaak combinatietherapie (afkortingen)
 - ▶ Beter effect (synergie, voorkomen resistentie, ...)
 - ▶ Ook combinatie van bijwerkingen!
 - ▶ Bijwerkingen afh. van type en dosis!



Werking chemotherapie

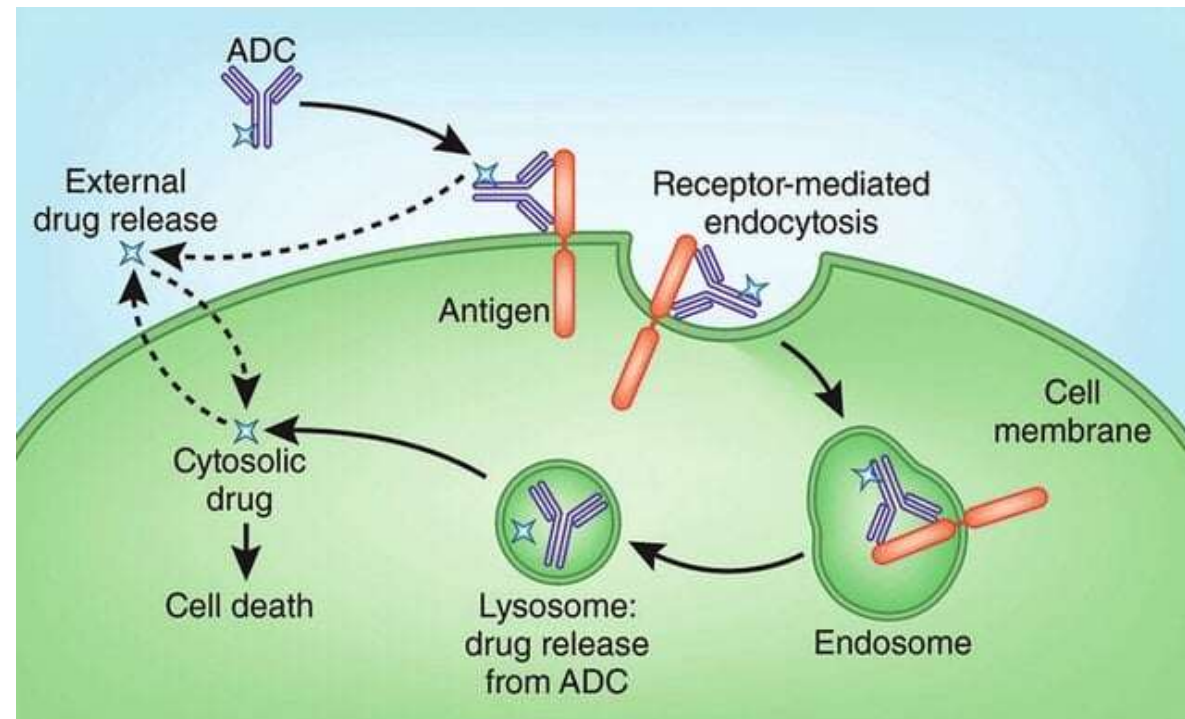
Vooral effect op “snel” delende cellen

- ➔ Kankercellen
- ➔ Bloedcellen
- ➔ Haren -> haaruitval
- ➔ Slijmvliezen -> mucositis / misselijkheid



Doelgerichte chemotherapie (Antibody-Drug-Conjugate : ADC)

- ▶ Gericht naar doelwit op tumorcel
 - ▶ Niet altijd beschikbaar!
 - ▶ Bijwerkingen als ook op niet-tumorcel
- ▶ Minder bijwerkingen
 - ▶ Zenuwaantasting!
- ▶ Verbetering uitkomsten
 - ▶ Polatuzumab-Vedotin (CD79b)
 - DLBCL
 - ▶ Brentuximab-Vedotin (CD30)
 - Hodgkin lymfoom
 - T cel lymfoom (sALCL, CTCL)



Misselijkheid en braken

- ▶ Verschillende types (chemo)therapie hebben ander risico profiel

Table 2. MASCC—ESMO emetic risk groups 2023			
Intravenous agents ^a	Emetic risk	Oral agents ^b	Emetic risk
High	Risk in nearly all patients (>90%)	High/moderate	Risk in 30% or more of patients
Moderate	Risk in 30%-90% of patients		
Low	Risk in 10%-30% of patients	Low/minimal	Risk in fewer than 30% of patients
Minimal	Fewer than 10% at risk		

- ▶ Ifv risico andere anti-emetica
 - ▶ Hoog risico : Akynzeo® + Corticoiden + Olanzapine (Zyprexa®)
 - ▶ Gemiddeld risico: Palonsetron + Corticoiden
 - ▶ Laag risico : Ondansetron of Litican® of Primperan® of corticoiden
- ▶ Aandacht voor constipatie bij gebruik Akynzeo®/Palonsetron/Ondansetron!

Misselijkheid en braken

Table 3. Emetogenic potential of single intravenous antineoplastic agents

High	Anthracycline/cyclophosphamide combination^a CHOP Carmustine Chlormethine (mechlorethamine) Cisplatin DHAP Cyclophosphamide ≥ 1500 mg/m² Dacarbazine Streptozocin
------	--

Low	Aflibercept Amivantamab Axicabtagene—ciloleucel Belinostat Blinatumomab Bortezomib Brentuximab—vedotin
-----	--

Moderate Alemtuzumab

Arsenic trioxide

Azacitidine

Bendamustine

Busulfan

Carboplatin^b

Clofarabine

Cyclophosphamide < 1500 mg/m²

Cytarabine > 1000 mg/m²

Cytarabine/daunorubicin liposomal

Minimal Asparaginase (calaspargase pegol)

Atezolizumab

Avelumab

Belantamab—mafodotin

Bevacizumab

Bleomycin

Cemiplimab

Cladribine (2-chlorodeoxyadenosine)

Daratumumab

Nivolumab

Obinutuzumab

Ofatumumab

Pembrolizumab

Pixantrone

Polatuzumab—vedotin

Pralatrexate

Ramucirumab

Rituximab

Misselijkheid en braken

Misselijkheid bij R-CHOP bij gebruik Akynzeo®

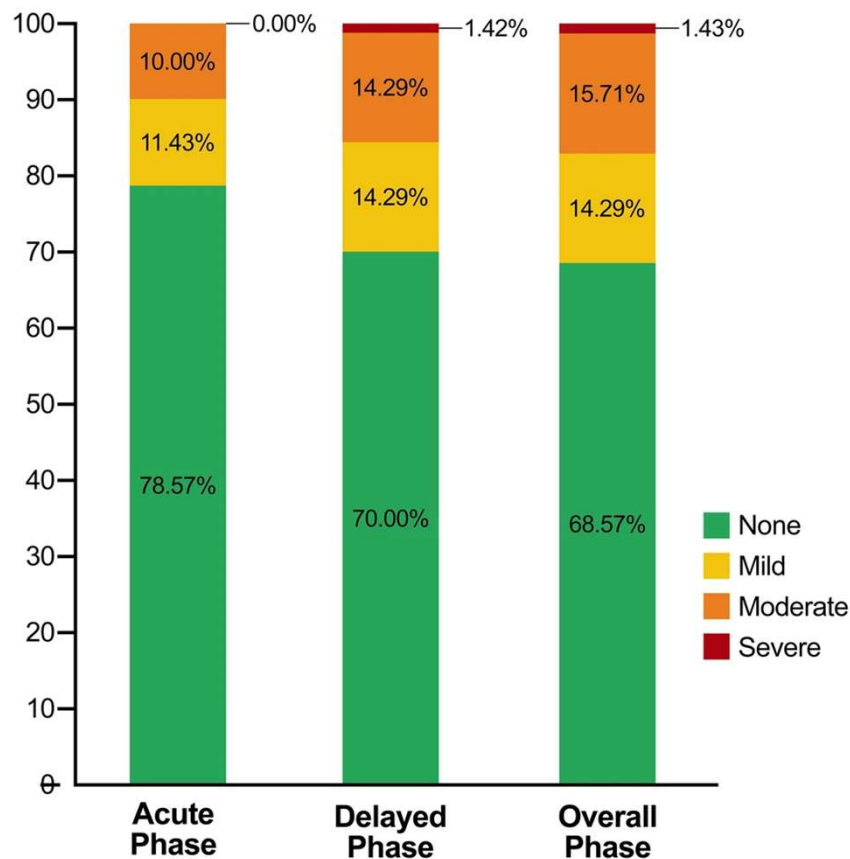


Table 3. Emetogenic potential of single intravenous antineoplastic agents

High	Anthracycline/cyclophosphamide combination ^a	CHOP
	Carmustine	
	Chlormethine (mechlorethamine)	
	Cisplatin	DHAP
	Cyclophosphamide $\geq 1500 \text{ mg/m}^2$	
	Dacarbazine	
	Streptozocin	

Zonder medicatie quasi 100% braken
Met juiste medicatie slechts minderheid

Haaruitval (alopecia)

- ▶ Afhankelijk van type chemo
- ▶ Haarverlies vs uitdunnen
 - ▶ Meestal na 3 tal weken
- ▶ Groeit meestal terug 1-3 maand na einde therapie

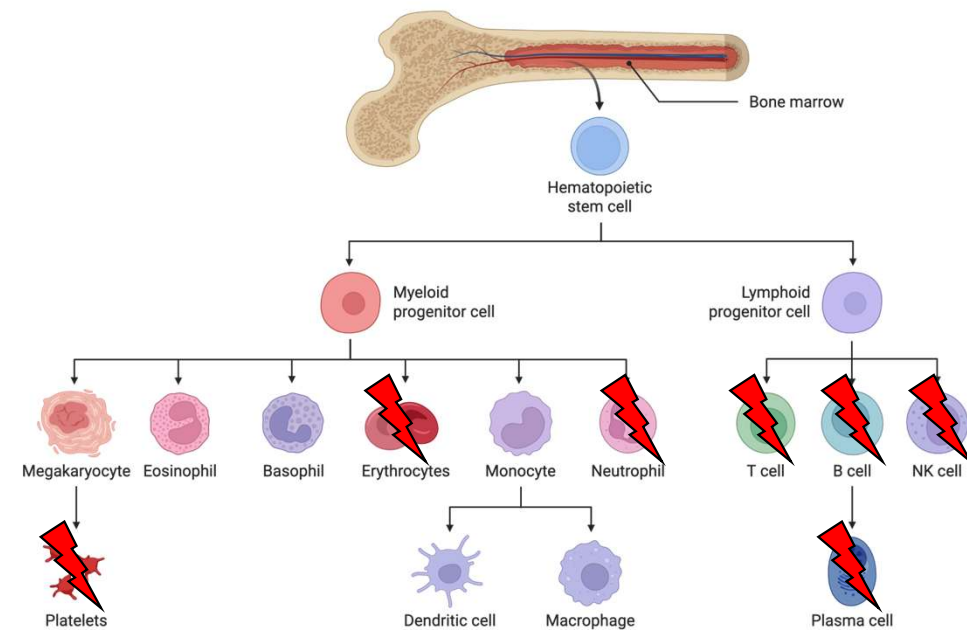
Table 1. Cytotoxic drugs that cause chemotherapy-induced alopecia

Mild alopecia (0.1%–1% of patients experience alopecia)	Moderate alopecia (1%–10% of patients experience alopecia)	Severe alopecia (>10% of patients experience alopecia)
Bortezomib	Bleomycin	Busulfan
Cabazitaxel	Cyclophosphamide	Docetaxel
Carboplatin	Epirubicin	Doxorubicin
Catumaxomab	Trastuzumab	Etoposide
Cisplatin	Panitumumab	Gemcitabine
Cytarabine		Idarubicin
Dactinomycin		Ifosfamide
Ixabepilone		Irinotecan
Lomustine		Mitomycin
Methotrexate		Oxaliplatin
Pemetrexed		Paclitaxel
		Topotecan
		Vinorelbine
		Procarbazine

Data from Investigator's Brochure (IB).

Verlaagd aantal bloedcellen (Cytopenie)

- ▶ Te laag aantal rode bloedcellen (anemie)
 - ▶ Vermoeidheid
 - ▶ Kortademigheid
 - ▶ Concentratiestoornissen
 - ▶ Bleke huidskleur
- ▶ Te laag aantal bloedplaatjes (trombopenie)
 - ▶ Bloedingen
 - Blauwe plekken
 - Neusbloedingen
 - Maag en darm bloedingen
- ▶ Te laag aantal witte bloedcellen (neutropenie)
 - ▶ Infecties
 - Viraal (van buitenaf)
 - Bacterieel (vaak vanuit eigen lichaam)
 - ▶ Bij neutropene koorts -> dringende noodzaak therapie met antibiotica!



Infecties

- ▶ Zeer frequente complicatie!
- ▶ Belangrijke doodsoorzaak
- ▶ Therapie gericht op eigen immuuncellen
 - ▶ Lymfopenie
 - ▶ Hypogammaglobulinemie (lage antistoffen)
- ▶ Verstoorde barrières en effect chemotherapie
 - ▶ Catheters
 - ▶ Slijmvliesontsteking (mucositis)
 - ▶ Neutropenie

CLL

Drug Class	(%) ernstige infecties
BTKi	19.86 %
PI3Ki	30.89 %
2e generatie anti-CD20	13.46 %
Rituximab	19.85 %
Anti-BCL2	17.49 %
Lenalidomide	13.33 %
anti-CD52	45.09 %

Years since diagnosis

Time point	Probability of death due to infection (95% CI)
1 year	5.0% (3.6%-7.1%)
2 years	7.2% (5.3%-9.8%)
3 years	8.3% (6.1%-11.2%)
4 years	9.4% (6.9%-12.8%)
5 years	11.1% (7.9%-15.5%)

DLBCL behandeld met R-CHOP

Infecties

► Belang van vaccinaties!

- Griep
- Covid-19
- Longontstekingen : pneumococcen + RSV
- Zona (gordelroos) : Shingrix®

► Belang van profylactische medicatie (ifv therapie)

- Aciclovir voor herpes / zona
- Eusaprim/Bactrim voor PCP-infectie (ernstige longinfectie bij personen met lage immuniteit)
- Fluconazole/Posaconazole voor schimmelinfecties

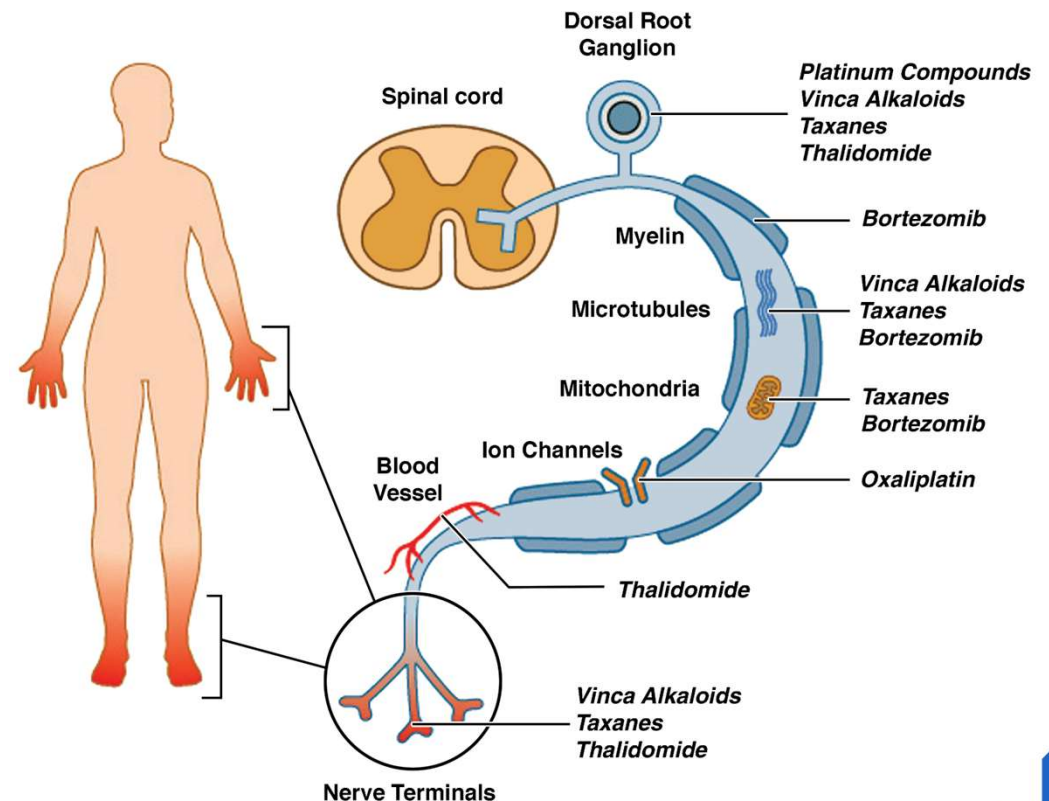
► Vermijden van infectiebronnen

- Zieke personen
- Grote massa's (mogelijks zieke personen)
- Handhygiene
- Voedselveiligheid



Zenuwaantasting (neuropathie)

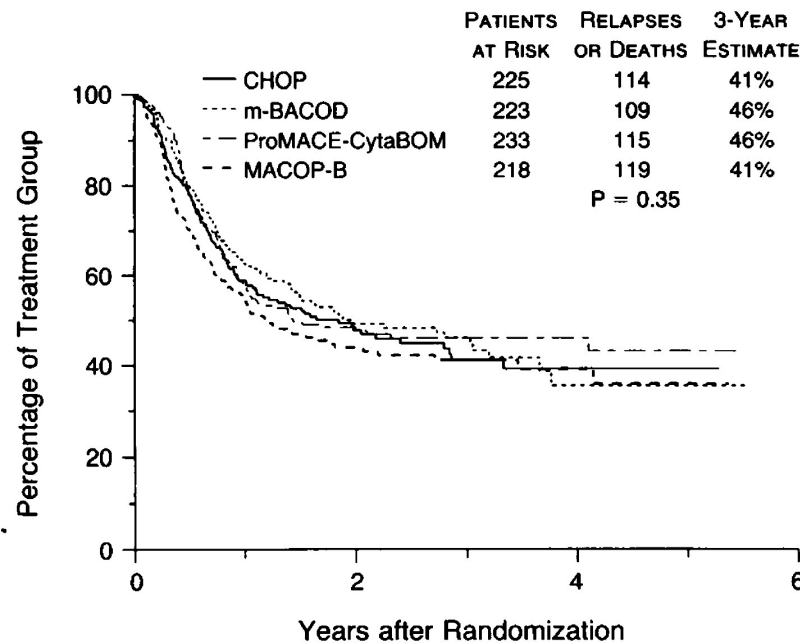
- ▶ Typische bijwerking van sommige chemotherapie
 - ▶ Vincristine
 - ▶ Bortezomib
 - ▶ Polatuzumab-Vedotin
 - ▶ Brentuximab-Vedotin
 - ▶ Platinum-derivaten
- ▶ Klassiek begin thv handen en voeten
 - ▶ Doofheid/gevoelsstoornis -> pijn / motoriek
- ▶ Soms ook gehoorschade (cisplatinum)
- ▶ Soms noodzaak dosisaanpassing / weglaten deel therapie
- ▶ Vaak deels recuperatie na stop therapie
 - ▶ Soms permanent
- ▶ Behandeling vooral symptomatisch



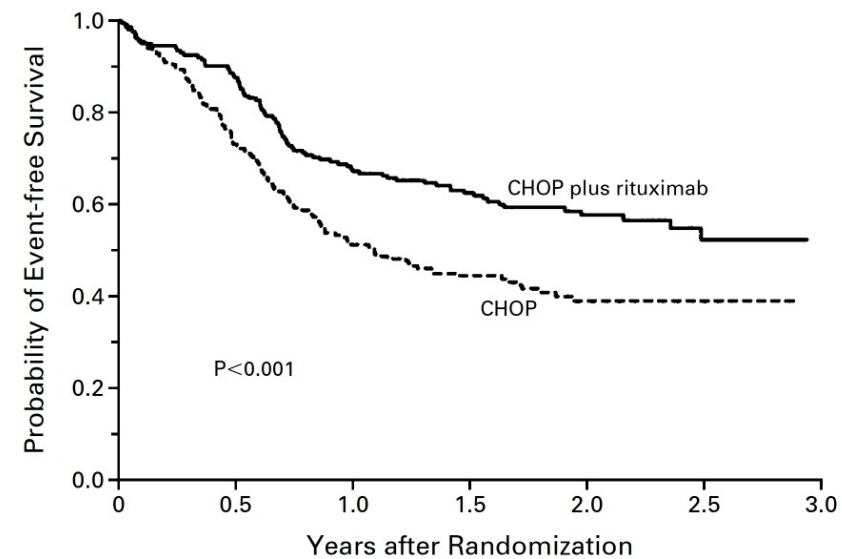
Vruchtbaarheid (sub-/infertiliteit)

- ▶ Risico voornamelijk met chemotherapie
 - ▶ Sommige meer dan andere (vb ABVD 10%)
 - ▶ Vaak nog recuperatie na 1-2 jaar
 - ▶ Sommige quasi 100% infertiliteit (bv stamceltransplantatie)
 - Belangrijk om toch voorzorgsmaatregelen te nemen cfr soms toch zwangerschap mogelijk
- ▶ Effect op fertiliteit/afwijkingen baby van doelgerichte therapie vaak ongekend
 - ▶ Soms gekende ernstige risico's (bv Thalidomide)
 - ▶ Meestal afgeraden om kinderen te krijgen tijdens “actieve” therapie
- ▶ Belang van fertiliteitspreservatie vooraf indien mogelijk
 - ▶ Man : spermastaal: soms door ziekte reeds slechte staalkwaliteit
 - ▶ Vrouw: eikel pickup : noodzaak stimulatie met risico's en uitstel therapie

R-CHOP = standaardbehandeling voor DLBCL en FL



Fisher et al, NEJM 1993



Coiffier, NEJM 2002

1. Fisher, Richard I., Ellen R. Gaynor, Steve Dahlberg, Martin M. Oken, Thomas M. Grogan, Evonne M. Mize, John H. Glick, Charles A. Coltman, en Thomas P. Miller. 'Comparison of a Standard Regimen (CHOP) with Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma'. *New England Journal of Medicine* 328, nr. 14 (8 april 1993): 1002-6. <https://doi.org/10.1056/NEJM199304083281404>.
2. Coiffier, Bertrand, Eric Lepage, Josette Briere, Raoul Herbrecht, Hervé Tilly, Reda Bouabdallah, Pierre Morel, e.a. 'CHOP Chemotherapy plus Rituximab Compared with CHOP Alone in Elderly Patients with Diffuse Large-B-Cell Lymphoma'. *New England Journal of Medicine* 346, nr. 4 (24 januari 2002): 235-42. <https://doi.org/10.1056/NEJMoa011795>.

CHOP (en CHOP-like therapie)

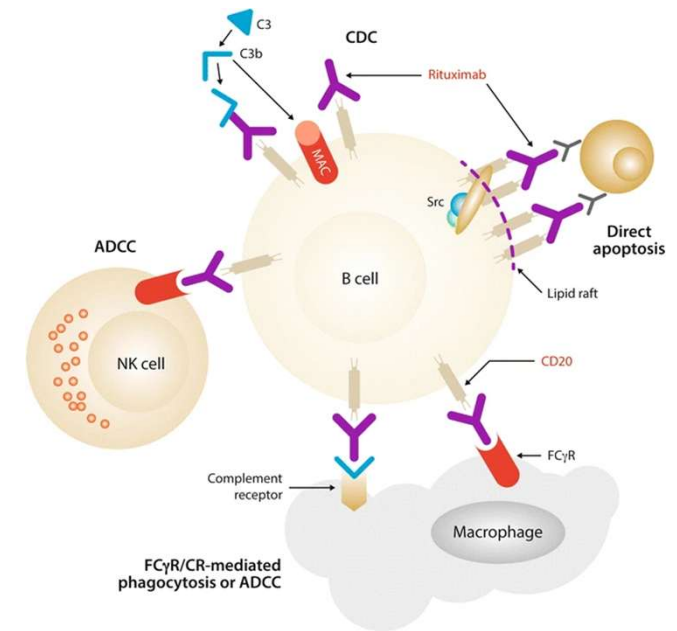
Toediening op 1 dag
Elke 3 weken herhaald
4-8 keer (meestal 6)

- ▶
- ▶
- ▶ **C** = Cyclofosfamide
 - ▶ Lage bloedcellen
 - ▶ Infectie risico
 - ▶ Misselijkheid
 - ▶ Haaruitval
- ▶ **H** = Hydroxodaunoribicine = doxorubicine
 - ▶ Hartfalen
- ▶ **O** = Oncovin® = Vincristine
 - ▶ Zenuwaantasting
- ▶
- ▶ **P** = Prednisolone = cortisone (vb Medrol®).
 - ▶ Gejaagdheid, spierverlies, slapeloosheid, suikerziekte, ...

R-CHOP

- ▶
- ▶ **R** = Rituximab
- ▶ **C** = Cyclofosfamide
- ▶ **H** = Hydroxodaunoribicine = doxorubicine
- ▶ **O** = Oncovin® = Vincristine
- ▶
- ▶ **P** = Prednisolone = cortisone (vb Medrol®).

Infusie-reacties
Infectie risico



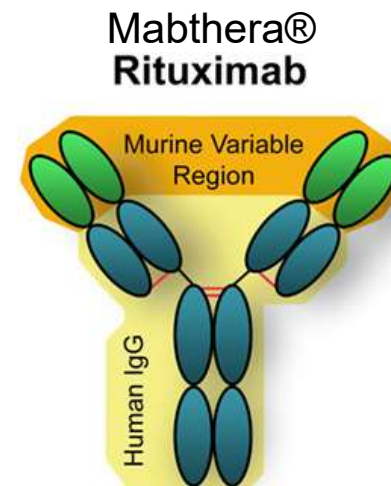
Immunotherapie : monoclonale antilichamen (vb CD20)

► Belangrijkste bijwerkingen

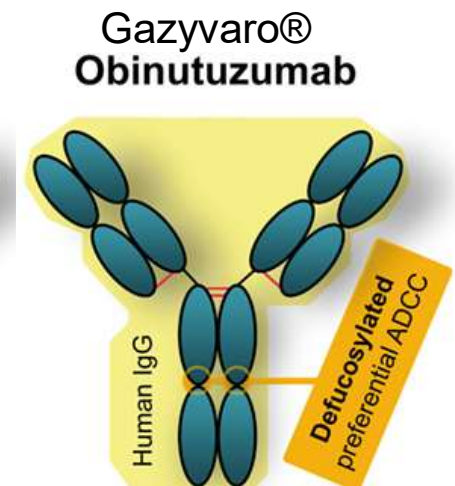
- Infusie-reacties!! Vooral/uitsluitend eerste toediening -> premedicatie
 - Nadien zeer goed verdragen
- B-cel depletie -> verhoogd infectierisico / slechtere respons op vaccinaties
- Lokale reactie op SC toediening
- (Soms laag aantal witte bloedcellen)

► Rituximab vs Obinutuzumab

- Anti-CD20 op B cellen / B cel lymfomen
- Rituximab IV -> SC / Obinutuzumab enkel IV
- Obinutuzumab “krachtiger” maar ook meer bijwerkingen
 - Voor CLL vaak 1^e toedieningen via hospitalisatie
 - In andere lymfomen geen duidelijk betere uitkomsten



Type I	
Direct Killing	+
CDC	+++
ADCC	++
ADP	++



Type II	
Direct Killing	+++
CDC	+
ADCC	+++
ADP	+++

Bijwerkingen van R-CHOP

Dag na chemotherapie groeifactoren spuiten!
Lonquex®, Neulasta®, ...

	6xCHOP-14 (n=307)	8xCHOP-14 (n=305)	6xR-CHOP-14 (n=306)	8xR-CHOP-14 (n=304)	p
Leucocytopenia*	93/193 (48)	93/195 (48)	<u>103/197 (52)</u>	108/218 (50)	0.8017
Thrombocytopenia	18/187 (10)	34/198 (17)	23/192 (12)	33/212 (16)	0.1242
Anaemia	46/284 (16)	66/287 (23)	45/283 (16)	77/283 (27)	0.0013
Arrhythmia	13/280 (5)	8/281 (3)	11/281 (4)	18/287 (6)	0.2437
Cardiac function	5/277 (2)	5/281 (2)	<u>7/279 (3)</u>	8/284 (3)	0.7917
Neuropathy	20/279 (7)	30/284 (11)	<u>20/284 (7)</u>	24/290 (8)	0.3946
Mucositis	8/281 (3)	18/283 (6)	<u>15/282 (5)</u>	25/288 (9)	0.0278
Infection	83/284 (29)	88/286 (31)	<u>79/287 (28)</u>	101/291 (35)	0.2784
Red-blood-cell transfusions	116/286 (41)	148/291 (51)	134/288 (47)	150/291 (52)	0.0312
Platelet transfusions	7/285 (2)	13/290 (4)	9/286 (3)	11/289 (4)	0.5840
Antibiotics—interventional	131/288 (45)	161/291 (55)	<u>151/285 (53)</u>	180/289 (62)	0.0008

Data are numbers of patients with toxicity or therapeutic intervention/number of patients with information and percentage of patients. p values are over all treatment regimens. *Common Toxicity Criteria grade 4 only.

Table 4: Grade 3 and 4 Common Toxicity Criteria toxicities and therapeutic interventions

R-miniCHOP

Dosis verlagen

Mogelijkheid tot behandelen bij 80+

- ▶
- ▶ **R** = Rituximab
- ▶ **C** = Cyclofosfamide
- ▶ **H** = Hydroxodaunoribicine = doxorubicine
- ▶ **O** = Oncovin® = Vincristine
- ▶
- ▶ **P** = Prednisolone = cortisone (vb Medrol®).

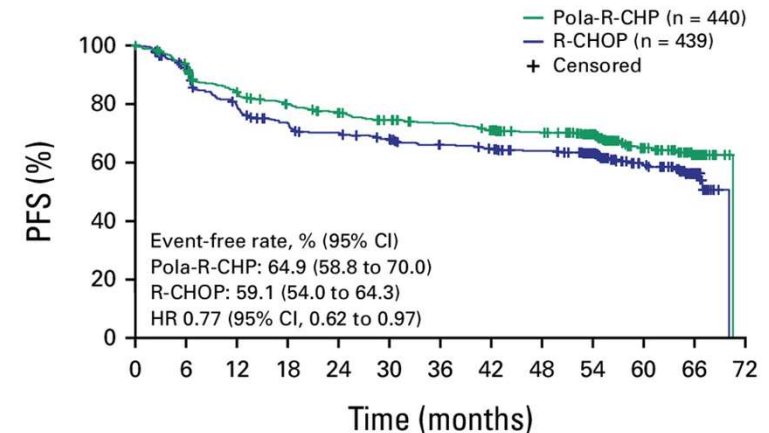
R-CVP / R-COP

- ▶ Weglaten doxorubicine
Mogelijkheid tot behandelen bij hartproblemen
 - ▶ **R** = Rituximab
 - ▶ **C** = Cyclofosfamide
 - ▶
 - ▶ **O/V** = Oncovin® = Vincristine
 - ▶
 - ▶ **P** = Prednisolone = cortisone (vb Medrol®).
- 

Pola-R-CHP

- ▶ **P** = Polatuzumab-Vedotin
- ▶ **R** = Rituximab
- ▶ **C** = Cyclofosfamide
- ▶ **H** = Hydroxodaunoribicine = doxorubicine
- ▶
- ▶
- ▶ **P** = Prednisolone = cortisone (vb Medrol®).

Vincristine vervangen door Polatuzumab
Betere resultaten bij hoog risico DLBCL

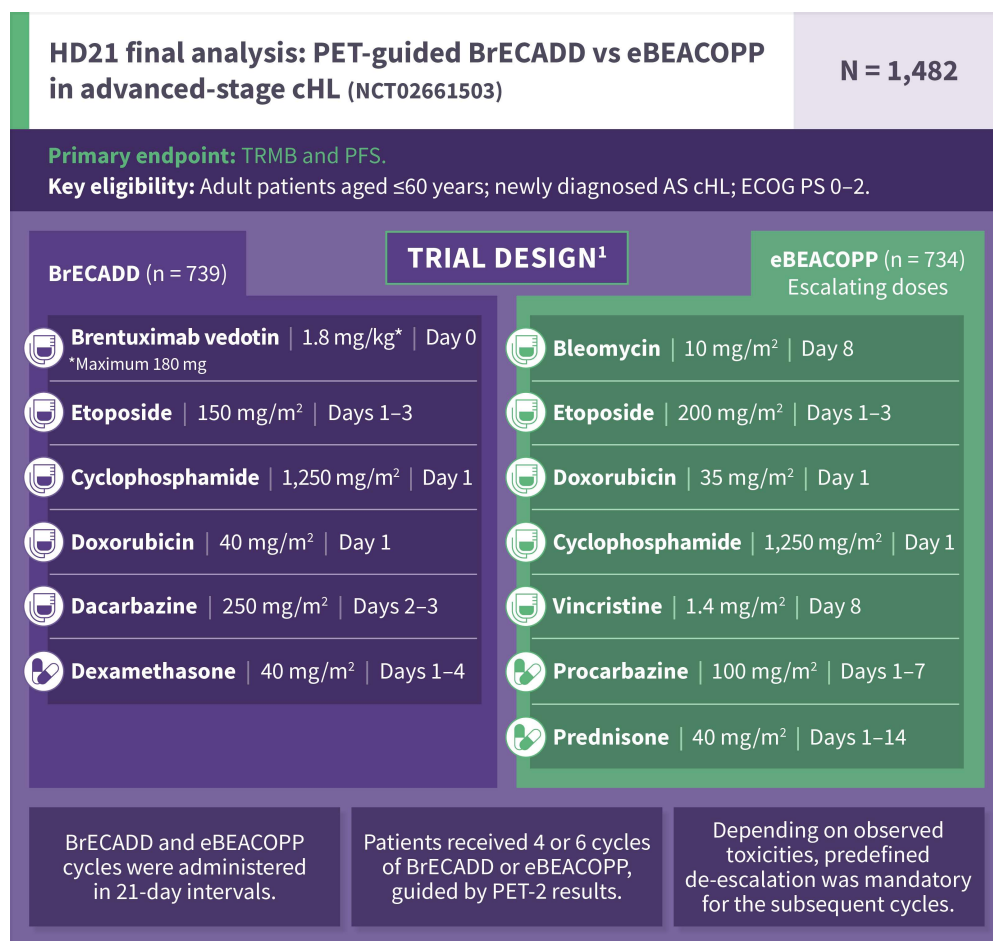


DA-R-EPOCH

Toediening over 5 dagen (opname)
Toevoegen etoposide
Bij agressieve lymfomen
Mogelijkheid tot dosisaanpassingen

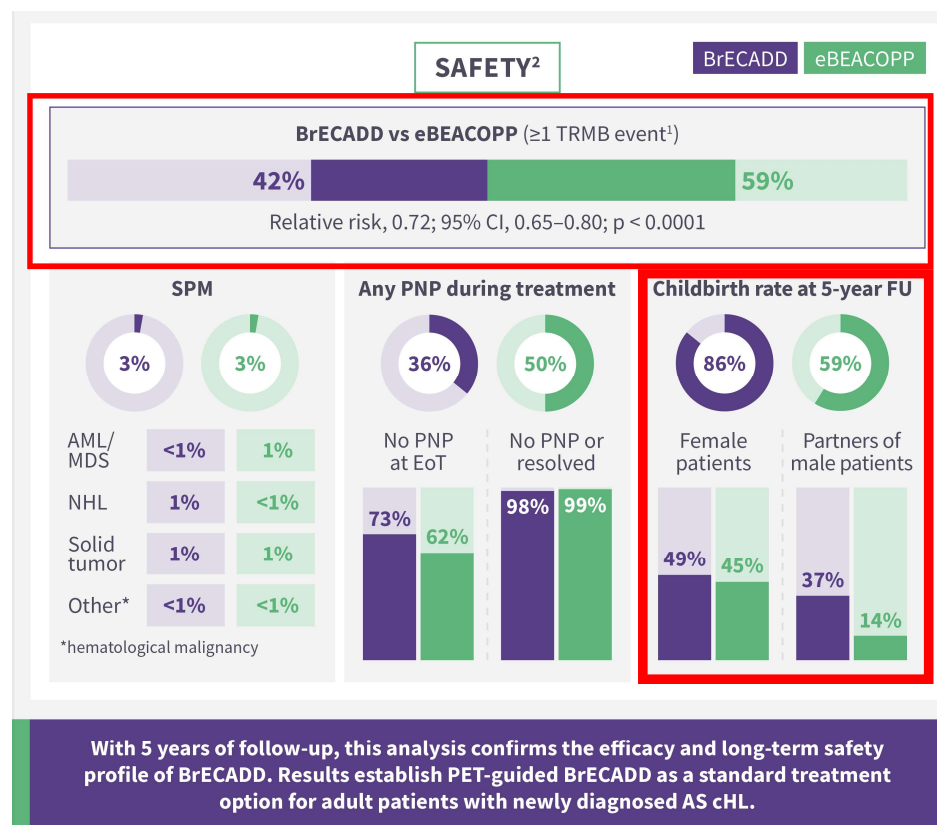
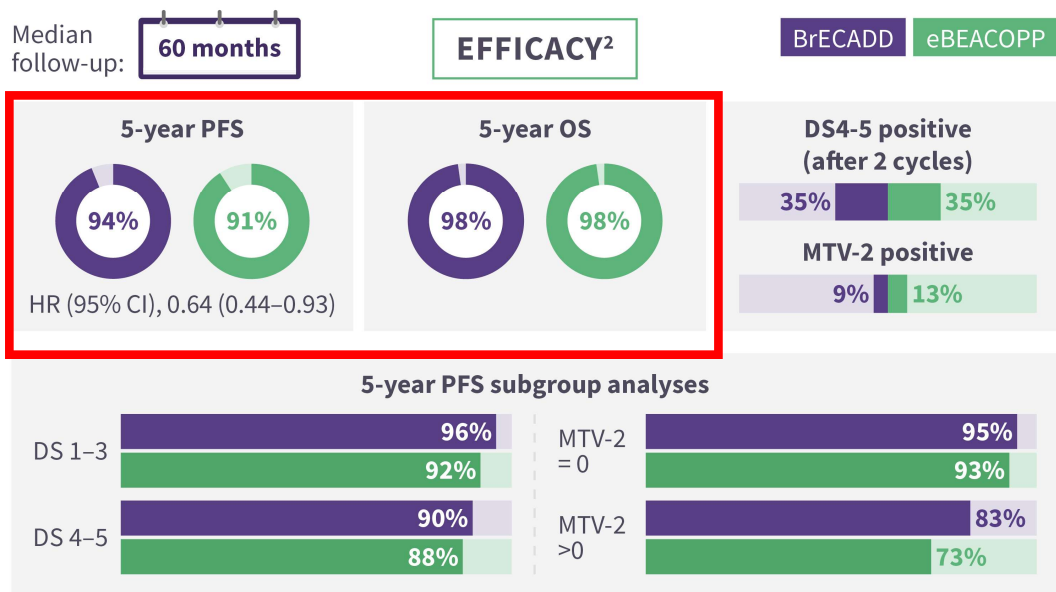
- ▶ **DA** = 'Dose-adjusted'
- ▶ **R** = Rituximab
- ▶ **C** = Cyclofosfamide
- ▶ **H** = Hydroxodaunoribicine = doxorubicine
- ▶ **O** = Oncovin® = Vincristine
- ▶ **E** = Etoposide
- ▶ **P** = Prednisolone = cortisone (vb Medrol®).

Hodgkin : BrECADD vs eBEACOPP



- ▶ Poging om effectiviteit therapie te behouden met minder bijwerkingen
 - ▶ Toevoegen Brentuximab (betere effectiviteit)
 - ▶ Weglaten vincristine (zenuwaantasting)
 - ▶ Weglaten bleomycine (long)
 - ▶ Vervangen procarbazine met dacarbazine (fertiliteit)
- ▶ (Nog niet terugbetaald in België)

BrECADD vs eBEACOPP



Radiotherapie

▶ Indicaties

- ▶ Ziekte van hodgkin
- ▶ Gelimiteerde ziekte indolent lymfoom
- ▶ Tumoraal CTCL
- ▶ Consolidatie
- ▶ Palliatie
- ▶ Bepaalde zeldzame types zoals ENKTCL

▶ Redenering

▶ Bijwerkingen

▶ Lange termijn effecten

Stamceltransplantatie

▶ Autoloog (Grieks : *autos* = zelf/eigen)

▶ Doel : hoge dosis chemotherapie om ziekte (langdurig) te controleren

▶ Praktisch

- Stamcel collectie -> hoge dosis chemotherapie -> teruggave stamcellen
- 4-6 weken in ziekenhuis voor opvangen complicaties
- Revalidatie achteraf
- Hervaccinatie

▶ Minder indicaties dan voorheen + enkel voor fitte patienten

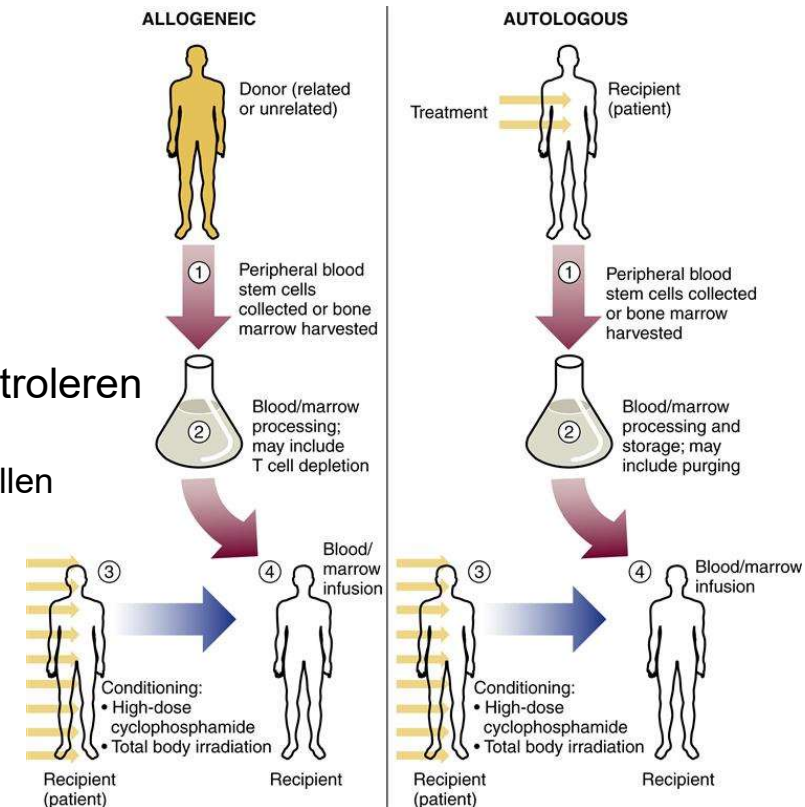
▶ Allogeen (Grieks : *allos* = ander)

▶ Doel : ziekte controle door immuuncellen van donor

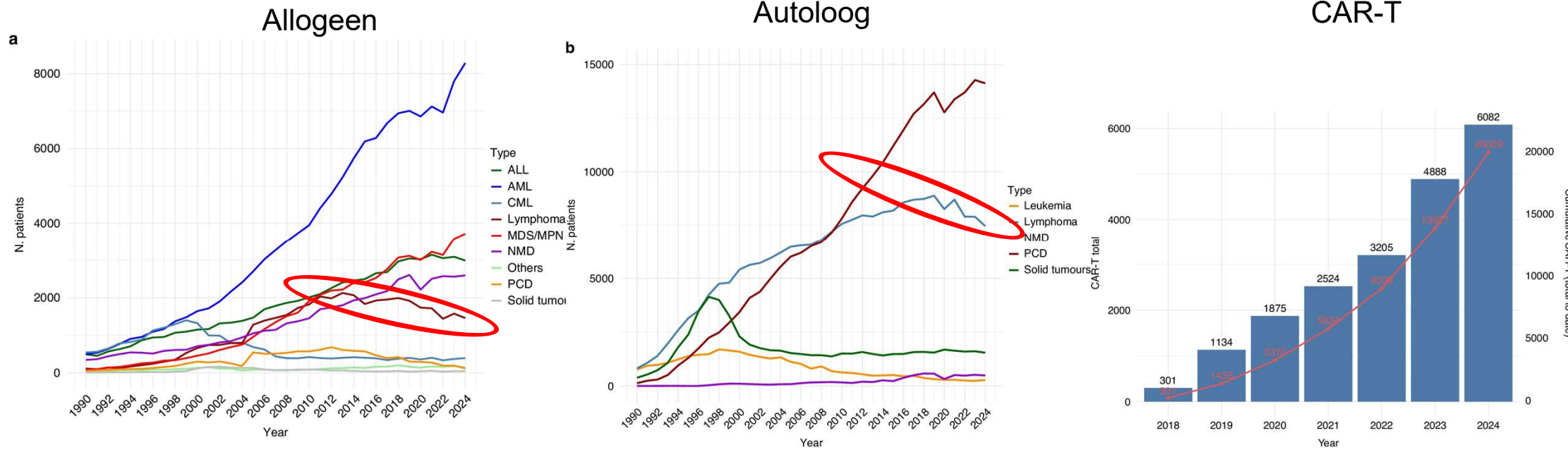
▶ Praktisch:

- Noodzaak donor : familielid of uit wereldwijde donorbank (niet altijd mogelijk!)
- Chemotherapie om donorcellen te accepteren (+/- om ziekte extra te behandelen)
- 4-6 weken in ziekenhuis voor opvangen complicaties
- Groot risico's op afstoting en infecties tot jaren nadien

▶ Beperkt gebruikt voor lymfoom omwille van risico's + noodzaak fitte patient.



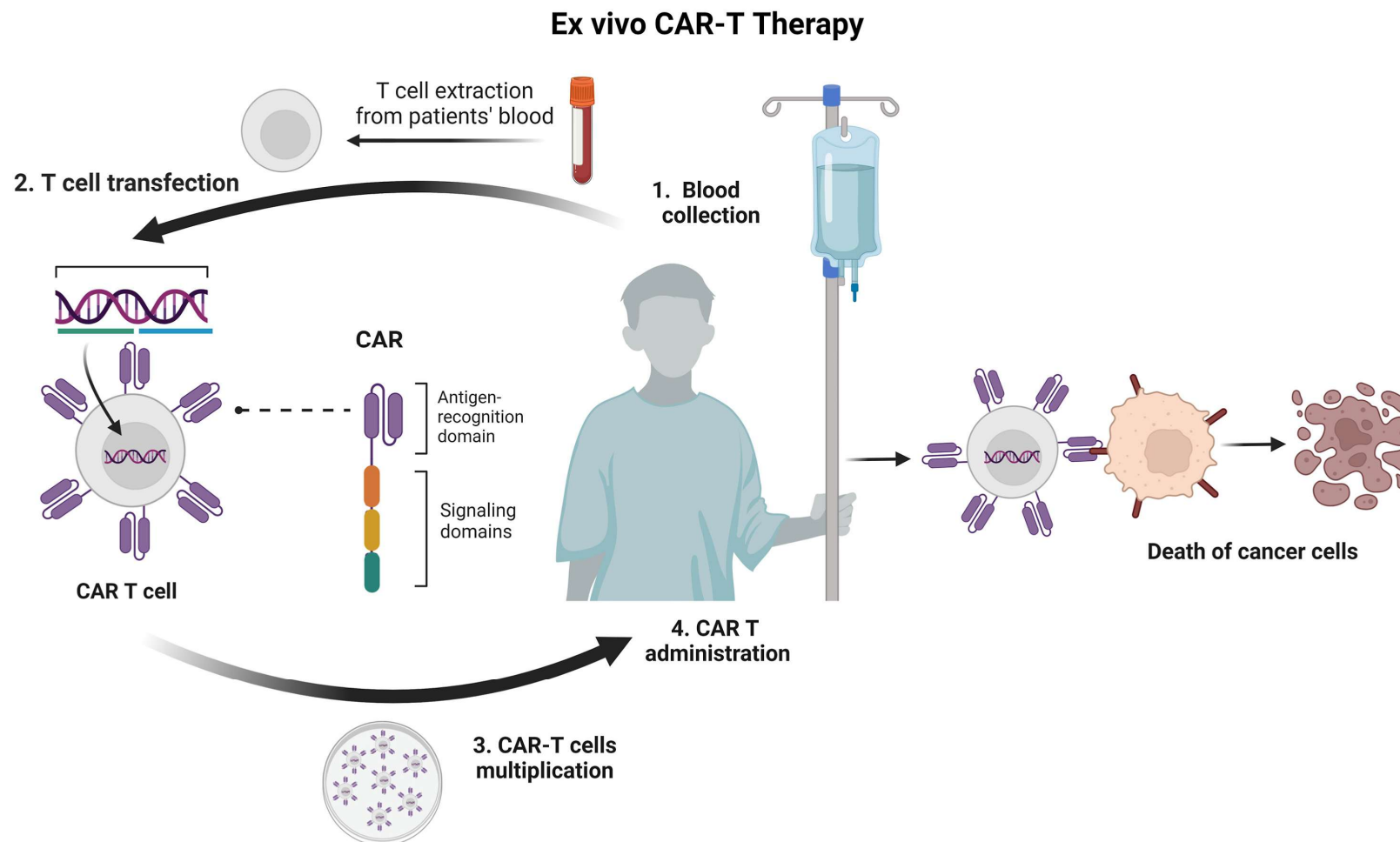
Transplantatie en CAR-T (EBMT data)



1.

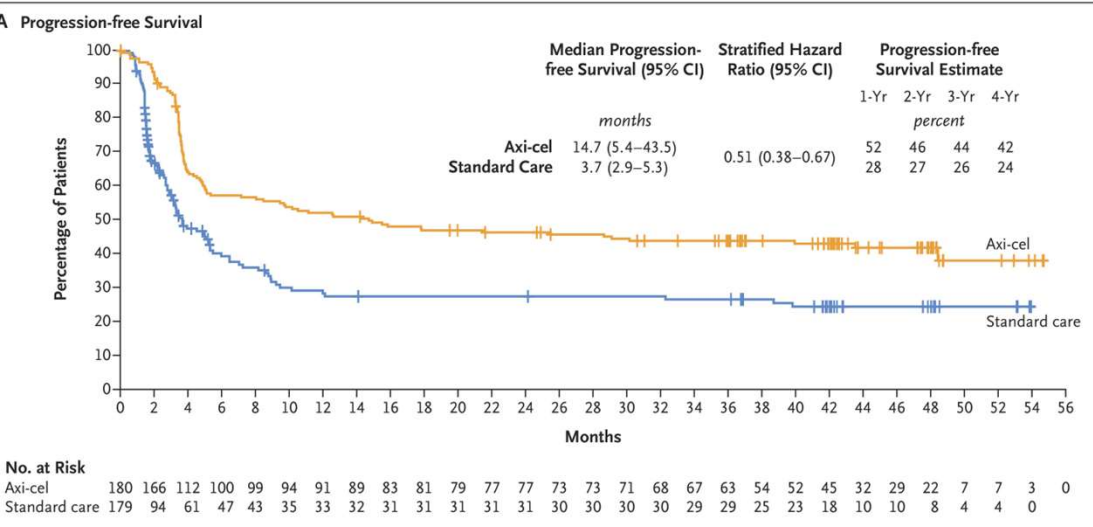
Greco R, Sánchez-Ortega I, Risitano AM, Kalwak K, Ruggeri A, Kleovoulou I, et al. The 2024 EBMT activity report: crossing one million HCTs and 20,000 CAR-T. A landmark in cellular therapy. Bone Marrow Transplant. 2026 Jul;61(7):899–912. doi:[10.1038/s41409-026-02919-9](https://doi.org/10.1038/s41409-026-02919-9)

Immunotherapie : CAR-T cell therapie

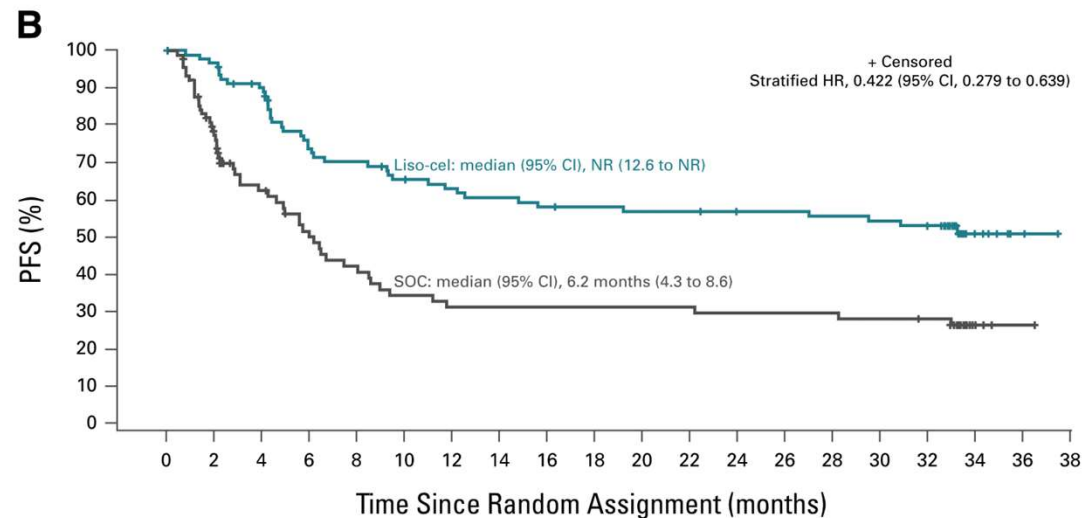


Effectiviteit bij vroeg herval CAR-T vs standaard chemo + stamceltransplantatie

ZUMA-7 Axi-cel



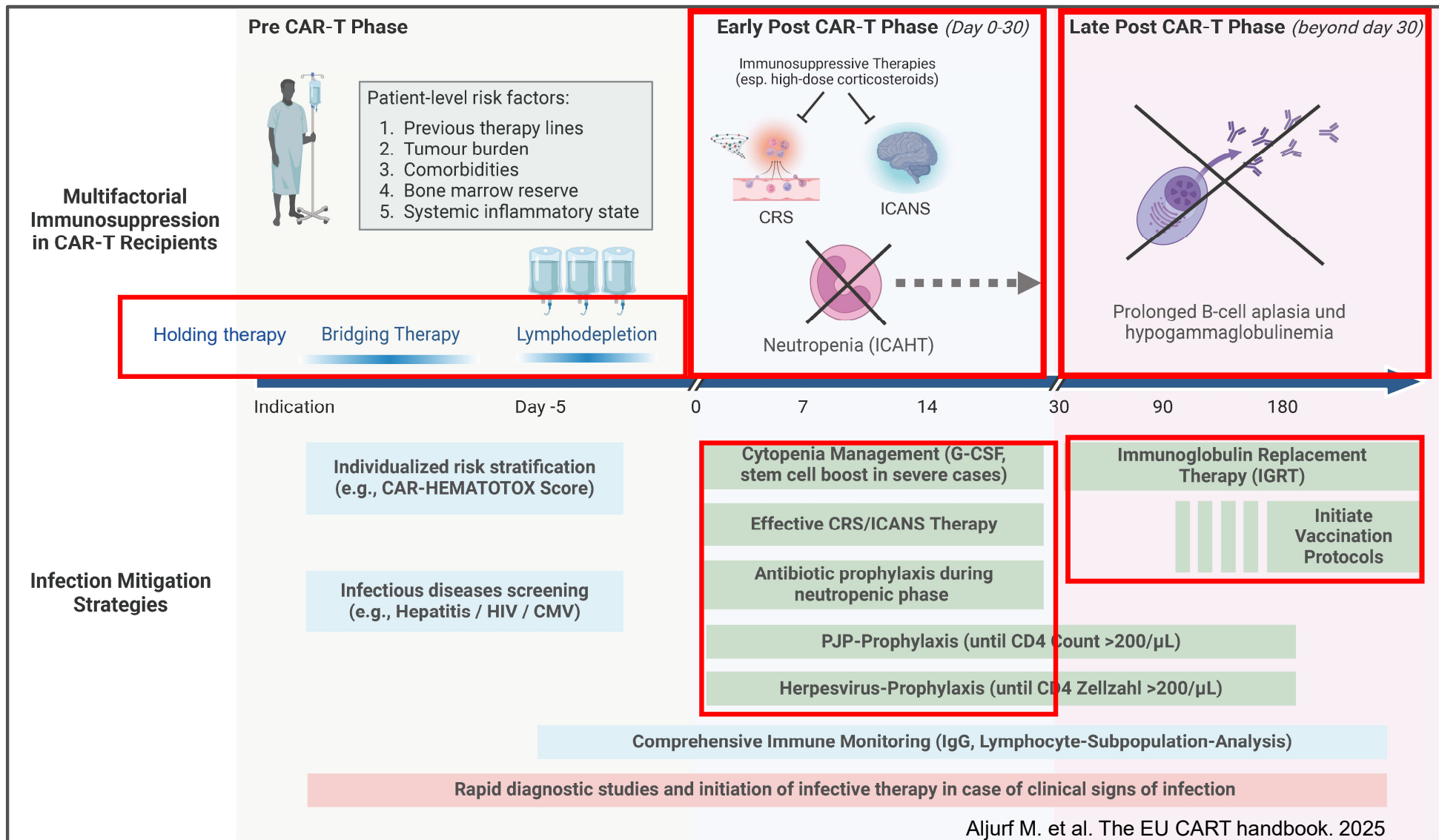
TRANSFORM Liso-cel



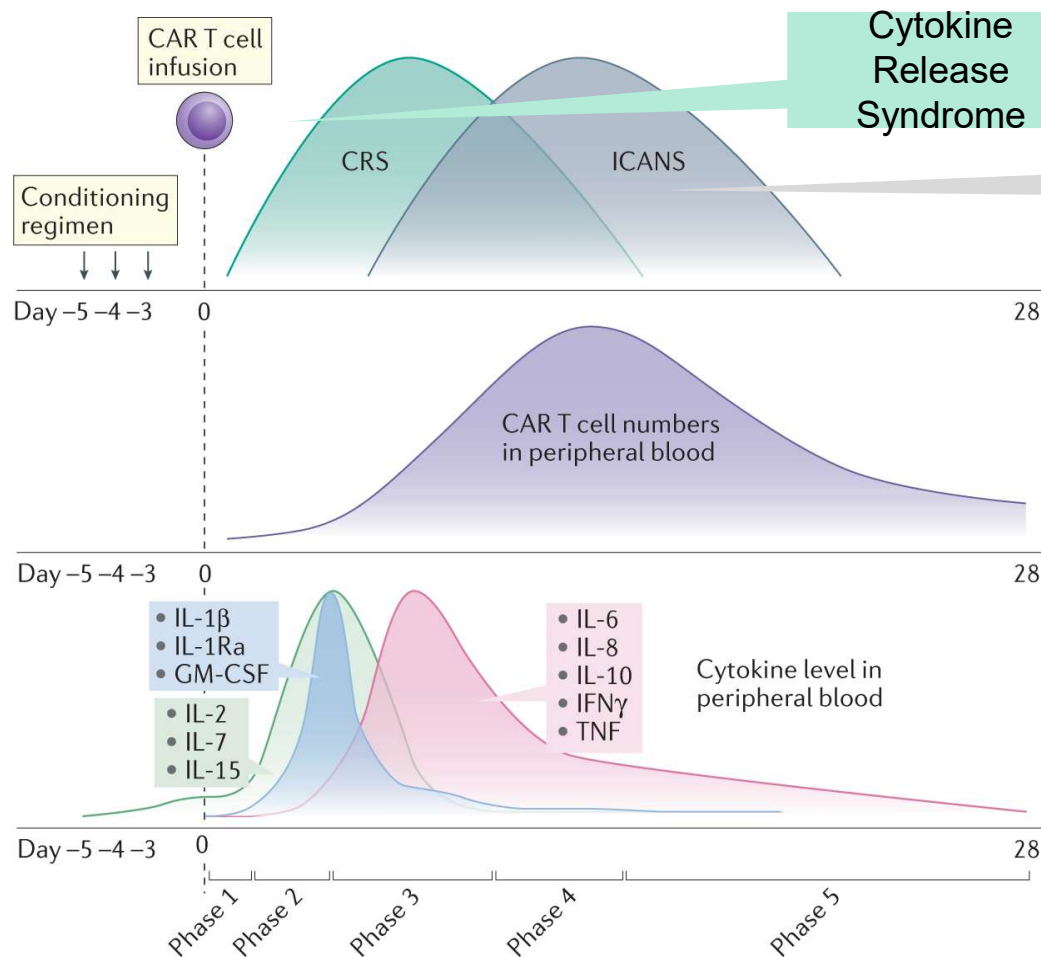
Westin JR, Oluwole OO, Kersten MJ, Miklos DB, Perales MA, Ghobadi A, et al. Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. N Engl J Med. 2023 Jul 13;389(2):148–57. doi:[10.1056/NEJMoa2301665](https://doi.org/10.1056/NEJMoa2301665)

Kamdar M, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene Maraleucel Versus Standard of Care for Second-Line Relapsed/Refractory Large B-Cell Lymphoma: 3-Year Follow-Up From the Randomized, Phase III TRANSFORM Study. J Clin Oncol. 2025 Aug 20;43(24):2671–8. doi:[10.1200/JCO-25-00399](https://doi.org/10.1200/JCO-25-00399)

Bijwerkingen CAR T-cell therapie



Bijwerkingen CAR-T : CRS en ICANS



Immune Effector Cell
Associated Neurologic Toxicity
Syndrome

CRS

Koorts

+/- zuurstofnood

+/- lage bloeddrukken

Mogelijks levensbedreigend

ICANS

20-30% IZ opname

Verwardheid

Zelden epilepsie / coma

Geen restletsels

Bijwerkingen CAR-T

► CRS

- >90%
- <10% ernstig (ifv type!)

► ICANS

- 60%
- 10-30% ernstig

► Infecties!

- 15-30% in studies

► Verlaagd aantal bloedcellen

- 20-40% langdurige tekorten
 - Transfusienood
 - Infecties

Table 2. Most Common Adverse Events, Cytokine Release Syndrome, and Neurologic Events.*

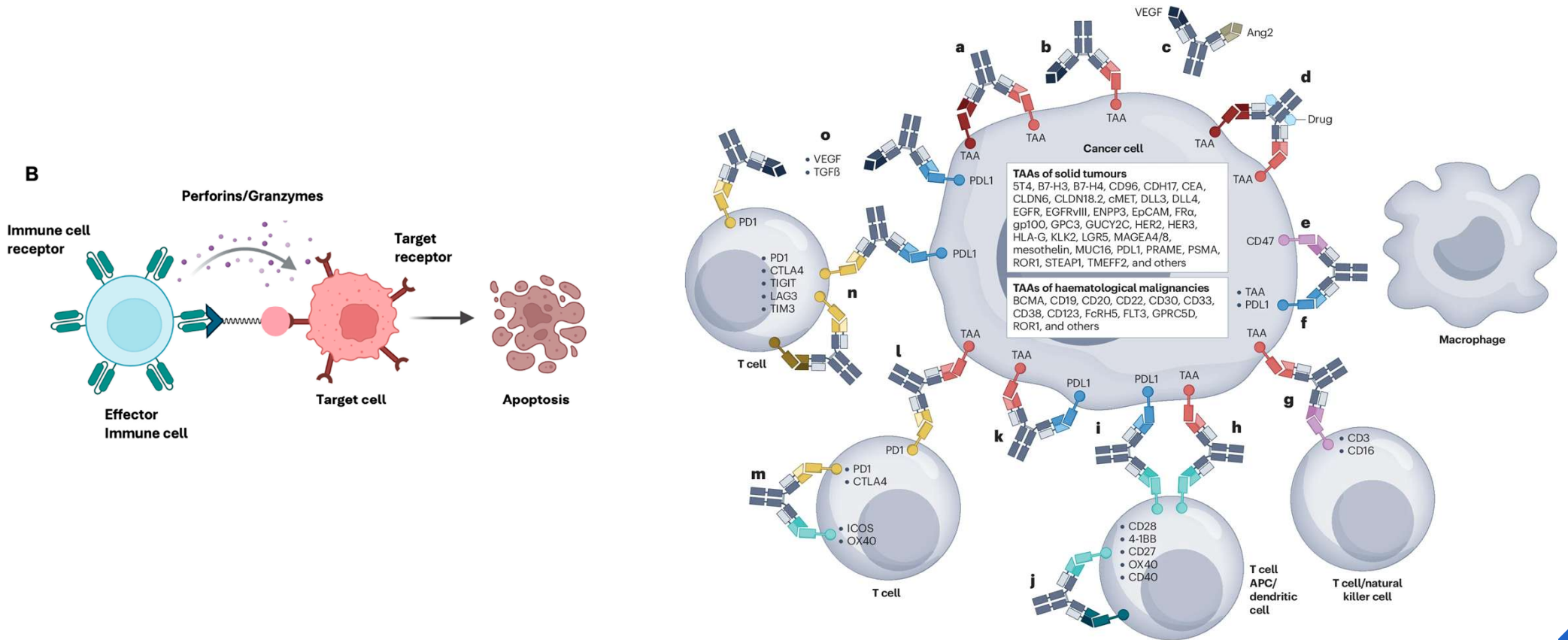
Event	Axi-cel (N = 170)		Standard Care (N = 168)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse event — no. (%)	170 (100)	155 (91)	168 (100)	140 (83)
Pyrexia	158 (93)	15 (9)	43 (26)	1 (1)
Neutropenia†	121 (71)	118 (69)	70 (42)	69 (41)
Hypotension	75 (44)	19 (11)	25 (15)	5 (3)
Fatigue	71 (42)	11 (6)	87 (52)	4 (2)
Anemia	71 (42)	51 (30)	91 (54)	65 (39)
Diarrhea	71 (42)	4 (2)	66 (39)	7 (4)
Headache	70 (41)	5 (3)	43 (26)	2 (1)
Nausea	69 (41)	3 (2)	116 (69)	9 (5)
Sinus tachycardia	58 (34)	3 (2)	17 (10)	1 (1)
Leukopenia‡	55 (32)	50 (29)	43 (26)	37 (22)
Thrombocytopenia§	50 (29)	25 (15)	101 (60)	95 (57)
Chills	47 (28)	1 (1)	14 (8)	0
Hypokalemia	44 (26)	10 (6)	49 (29)	11 (7)
Hypophosphatemia	45 (26)	31 (18)	29 (17)	21 (12)
Cough	42 (25)	1 (1)	18 (11)	0
Decreased appetite	42 (25)	7 (4)	42 (25)	6 (4)
Hypoxia	37 (22)	16 (9)	13 (8)	7 (4)
Dizziness	36 (21)	2 (1)	21 (12)	1 (1)
Constipation	34 (20)	0	58 (35)	0
Vomiting	33 (19)	0	55 (33)	1 (1)
Febrile neutropenia	4 (2)	4 (2)	46 (27)	46 (27)
Cytokine release syndrome — no. (%)	157 (92)	11 (6)	—	—
Pyrexia — no./total no. (%)	155/157 (99)	14/157 (9)	—	—
Hypotension — no./total no. (%)	68/157 (43)	18/157 (11)	—	—
Sinus tachycardia — no./total no. (%)	49/157 (31)	3/157 (2)	—	—
Chills — no./total no. (%)	38/157 (24)	0/157	—	—
Hypoxia — no./total no. (%)	31/157 (20)	13/157 (8)	—	—
Headache — no./total no. (%)	32/157 (20)	2/157 (1)	—	—
Neurologic event — no. (%)	102 (60)	36 (21)	33 (20)¶	1 (1)
Tremor	44 (26)	2 (1)	1 (1)	0
Confusional state	40 (24)	9 (5)	4 (2)	0
Aphasia	36 (21)	12 (7)	0	0
Encephalopathy	29 (17)	20 (12)	2 (1)	0
Paresthesia	8 (5)	1 (1)	14 (8)	0
Delirium	3 (2)	3 (2)	5 (3)	1 (1)

1.

Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022 Feb 17;386(7):640–54. doi:10.1056/NEJMoa2116133

CAR-T

- ▶ Terugbetaald in DLBCL en MCL (en MM)
 - ▶ In studies voor FL, MZL, CLL, auto-immuunziekten, ...
 - ▶ Voornaamste bijwerkingen
 - ▶ CRS
 - ▶ ICANS
 - ▶ Infecties
 - ▶ Langdurig verlaagde bloedplaatjes of witte bloedcellen
 - ▶ Eventuele laattijdige effecten
 - ▶ Noodzaak hospitalisatie (10-14 dagen) gezien potentieel ernstige bijwerkingen
 - ▶ Ondanks vele complicaties mogelijkheid tot genezing deel patienten met anders zeer slechte prognose.
- 



Klein, C., Brinkmann, U., Reichert, J.M. *et al.* The present and future of bispecific antibodies for cancer therapy. *Nat Rev Drug Discov* **23**, 301–319 (2024). <https://doi.org.libugent.idm.oclc.org/10.1038/s41573-024-00896-6>

Kwizera, R., Kanduluru, A. K., & Srinivasarao, M. (2026). Recent Advances in the Exploitation of Cell Surface Receptors for Targeted Cell Therapies. *Receptors*, 5(3), 27. <https://doi.org/10.3390/receptors5030027>

Bijwerkingen CD20-Bispec

- ▶ CRS
 - ▶ >50% - lager mits voorbereiding
 - ▶ Slechts <5% ernstig
- ▶ ICANS
 - ▶ <10% - slechts <1% ernstig
- ▶ Infecties!
 - ▶ >30% in studies
- ▶ Tumorlyse
- ▶ Tumor flare

1.

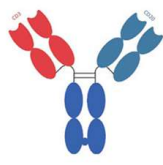
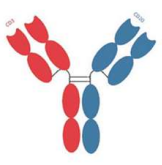
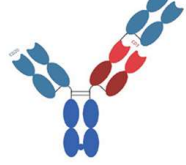
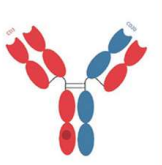
Table 3. Adverse Events in All the Patients Treated at the Phase 2 Dose (Safety Population).^{*,†}

Event	Patients (N = 154) no. (%)
Any adverse event	152 (99)
Most common adverse events	
Cytokine release syndrome, per ASTCT	97 (63)
Cytokine release syndrome, per Lee et al. ²⁸	101 (66)
Neutropenia	58 (38)
Anemia	47 (31)
Thrombocytopenia [‡]	38 (25)
Any glofitamab-related adverse event	140 (91)
Any grade 3 or 4 adverse event	87 (56)
Most common grade 3 or 4 adverse events	
Neutropenia	41 (27)
Anemia	10 (6)
Thrombocytopenia	12 (8)
Any glofitamab-related grade 3 or 4 adverse event	64 (42)
Any serious adverse event	73 (47)
Most common serious adverse events [‡]	
Cytokine release syndrome, per ASTCT	32 (21)
Sepsis	6 (4)
Tumor flare	5 (3)
Covid-19–related pneumonia	5 (3)
Covid-19	4 (3)
Adverse events of special interest	
Cytokine release syndrome, grade ≥2 per ASTCT	24 (16)
Cytokine release syndrome, grade ≥2 per Lee et al. ²⁸	28 (18)
Infection, any grade	59 (38)
Neurologic event, grade ≥2	23 (15)
Event grade consistent with ICANS, any grade [§]	12 (8)
Tumor flare, grade ≥2	11 (7)
AST, ALT, or total bilirubin elevation, grade ≥2	11 (7)
Febrile neutropenia, grade ≥3	4 (3)
Tumor lysis syndrome, grade ≥3	2 (1)
Any grade 5 adverse event	8 (5)
Any glofitamab-related grade 5 adverse event	0
Any adverse event leading to discontinuation of glofitamab	14 (9)
Any glofitamab-related adverse event leading to discontinuation of glofitamab	5 (3)
Any adverse event leading to interruption in glofitamab treatment	28 (18)
Any glofitamab-related adverse event leading to interruption in glofitamab treatment	14 (9)

Dickinson MJ, Carlo-Stella C, Morschhauser F, Bachy E, Corradini P, Iacoboni G, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *New England Journal of Medicine*. 2022 Dec 14;387(24):2220–31. doi:[10.1056/NEJMoa2206913](https://doi.org/10.1056/NEJMoa2206913)

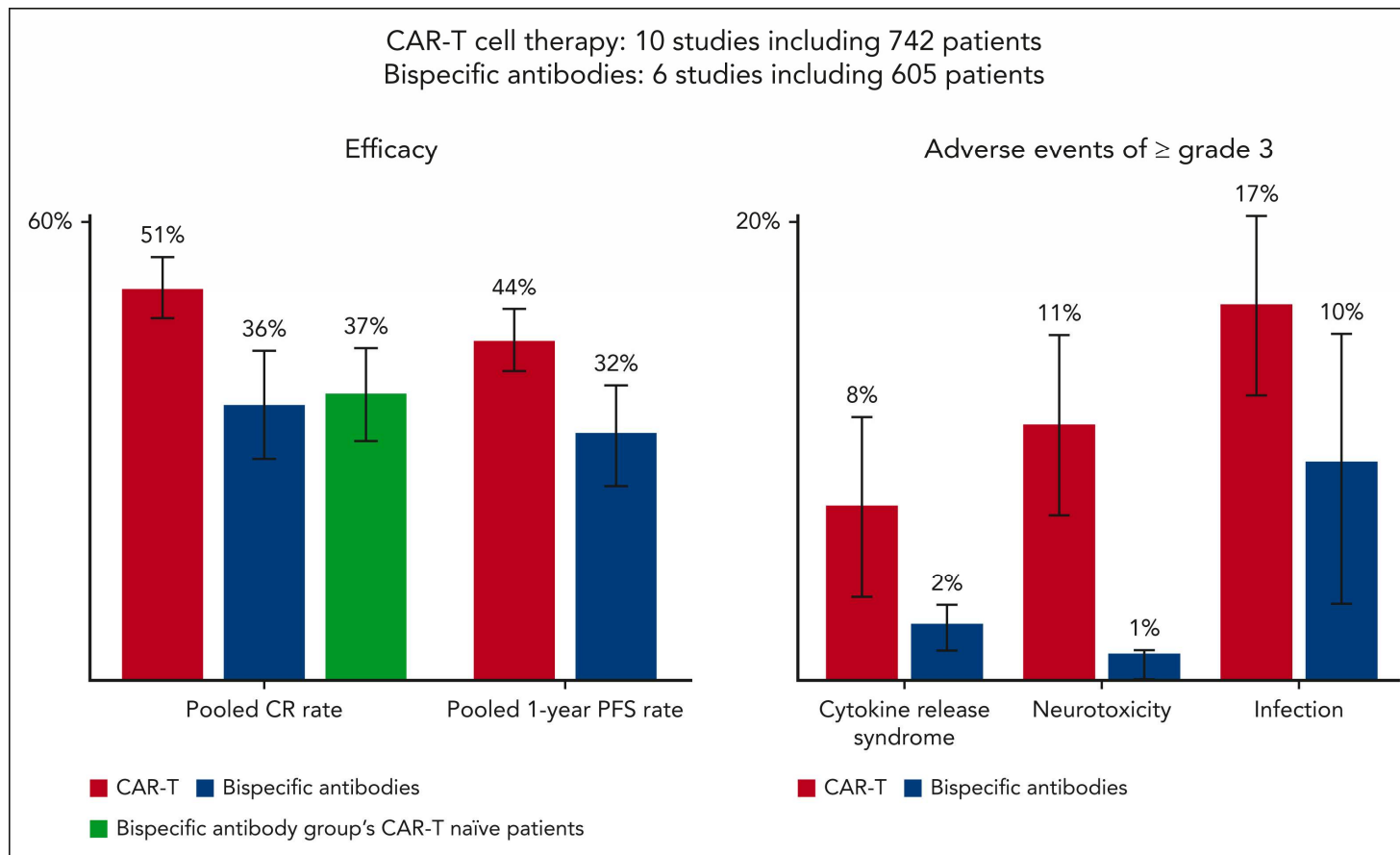
Bispecifieke antilichamen

- ▶ Terugbetaald in DLBCL (en MM)
 - ▶ Verschillende studies lopende in FL, MZL, CLL, ...

	BLINATUMOMAB	MOSUNETUZUMAB	EPCORITAMAB	GLOFITAMAB	ODRONEXTAMAB
TARGET	CD3xCD19	CD3xCD20	CD3xCD20	CD3x(CD20) ₂	CD3xCD20
DESIGN					
	• Monovalent CD3 and monovalent CD19 binding • Two murine scFv-joined by a glycine-serine linker	• Monovalent CD3 and monovalent CD20 binding • Humanized mouse IgG1-based antibody	• Monovalent CD3 and monovalent CD20 binding • Humanized mouse IgG1-based antibody	• Monovalent CD3 and bivalent CD20 binding • Humanized mouse IgG1-based antibody	• Monovalent CD3 and monovalent CD20 binding • Fully human IgG4-based antibody

- ▶ Voornaamste bijwerkingen vergelijkbaar met CAR-T doch minder frequent
 - ▶ CRS
 - ▶ (ICANS)
 - ▶ Tumor flare
 - ▶ Infecties
- ▶ Noodzaak step-up dosing
- ▶ Vaak noodzaak hospitalisatie in het begin – nadien ambulant
- ▶ Langdurige therapie IV of SC

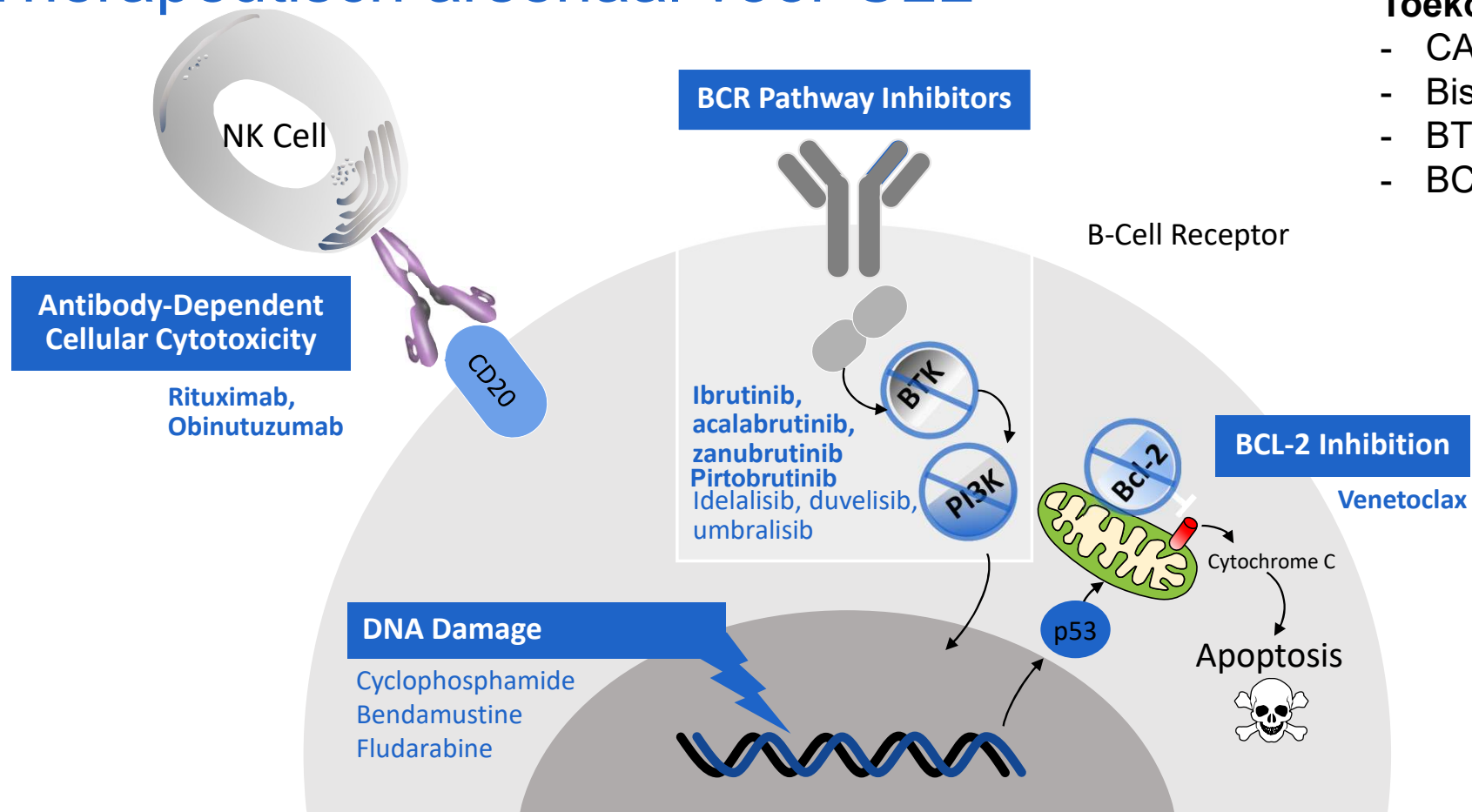
CAR-T vs bispecifieke antilichamen



Keuze tussen CAR-T en Bispecifieke antilichamen

- ▶ Voordeel bispecifieke antilichamen
 - ▶ Off-the-shelf (<-> delay CAR-T)
 - ▶ Geen problemen met afname eigen cellen en productie CAR-T cellen
 - ▶ Geen chemotherapie voor lymfodepletie
 - ▶ Minder bijwerkingen zoals CRS en ICANS
 - Toepasbaar voor meer patienten
 - Mogelijkheid om ambulant toe te dienen
 - ▶ Mogelijk in verschillende ziekenhuizen (CAR-T slechts in 8 centra in België – voornamelijk UZ)
 - ▶ Combinaties mogelijk met chemotherapie, doelgerichte therapie, lenalidomide,...
 - ▶ Minder “late” bijwerkingen
 - ▶ Stop behandeling → Stop bijwerkingen (CAR-T is “levend medicijn” en kan je moeilijk “stoppen”)
- ▶ Voordeel CAR-T
 - ▶ Eenmalige therapie vs langdurige behandeling
 - ▶ Betere uitkomsten (vermoedelijk)
 - ▶ Langere opvolging beschikbaar
- ▶ Open vragen
 - ▶ Ideale volgorde CAR-T / BiSp ?
 - Beide zijn mogelijk

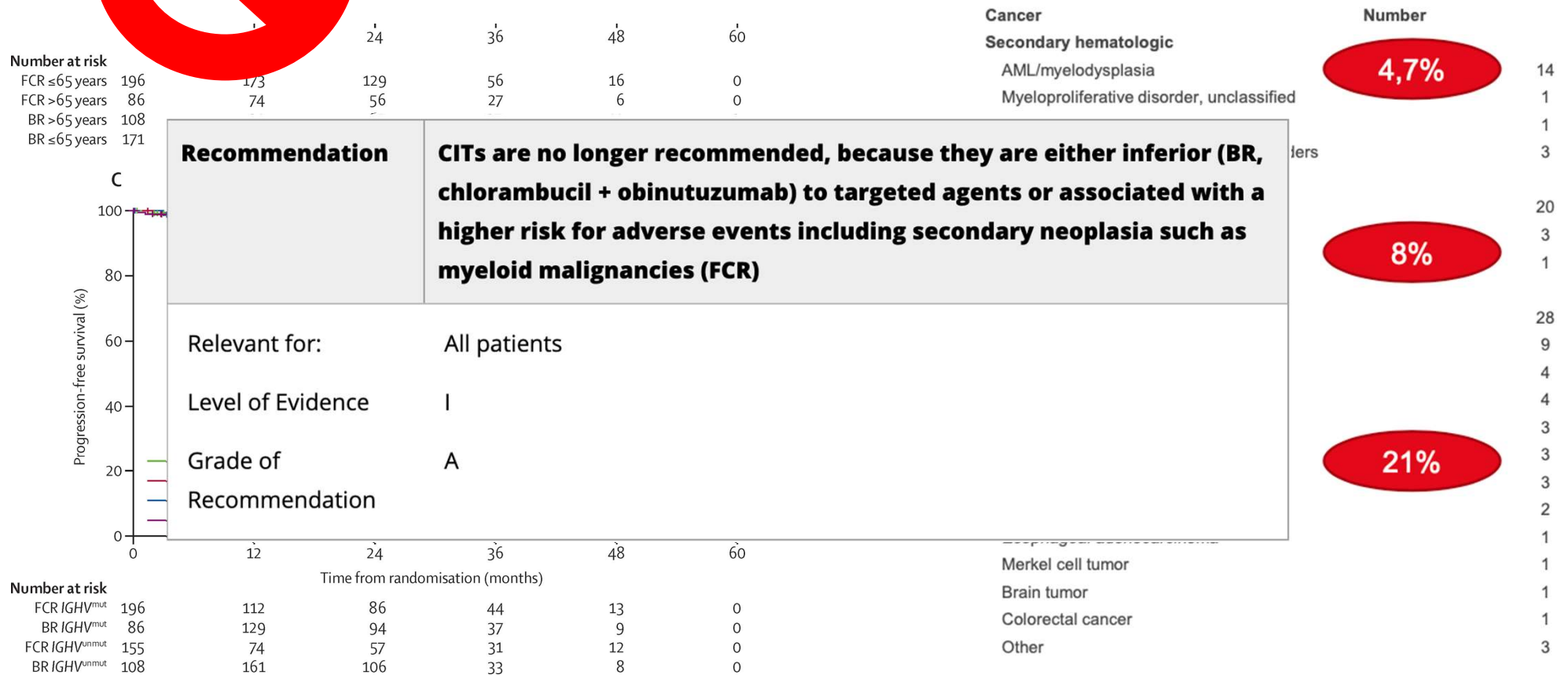
Therapeutisch arsenaal voor CLL



Toekomst

- CAR-T
- Bispecifics
- BTK-degrader
- BCL2-degraders

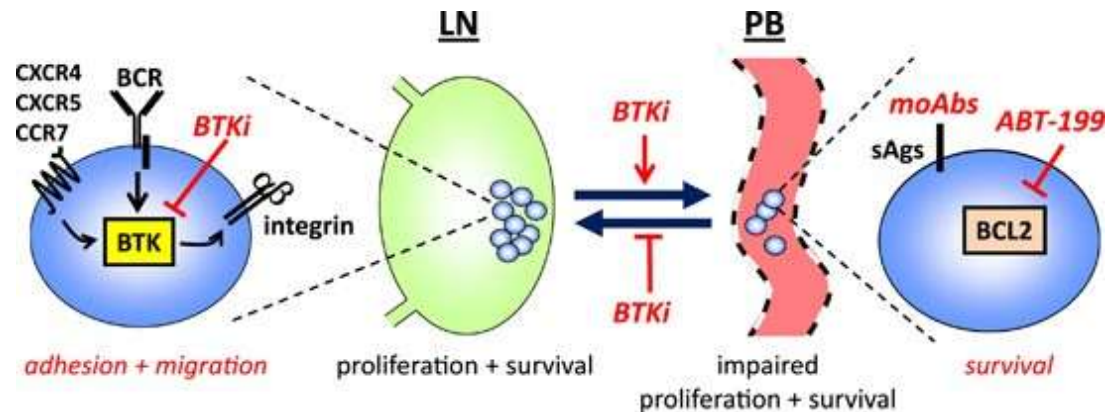
Chemotherapy (FCR) in IgHV mutated CLL



1. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial Eichhorst, Barbara et al. The Lancet Oncology, Volume 17, Issue 7, 928 – 942

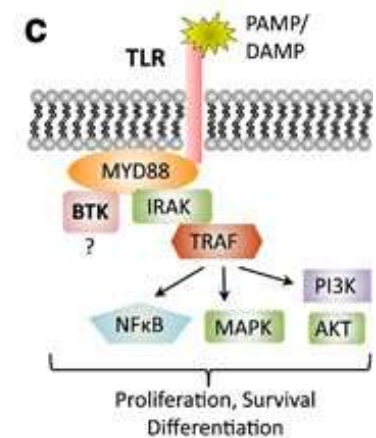
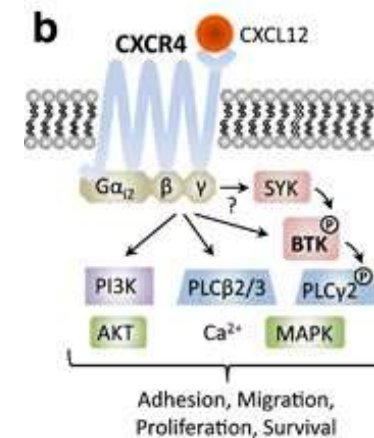
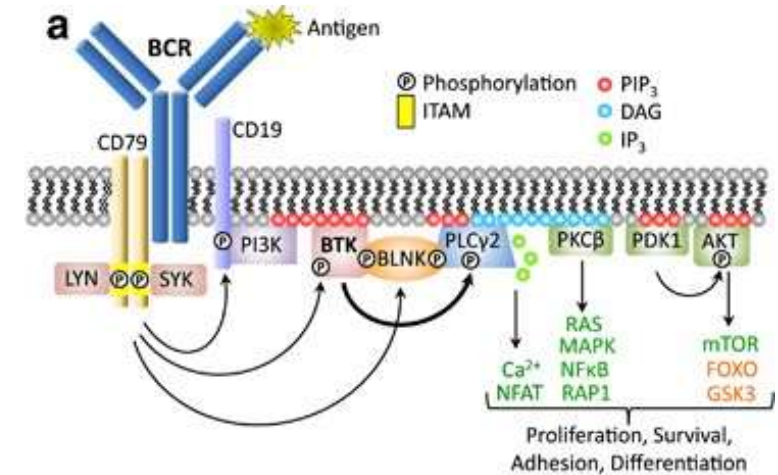
2. Eichhorst B, Ghia P, Bosch F, Clifford R, Gregor M, Guieze R, et al. EHA Guidelines on management of chronic lymphocytic leukemia and Richter transformation. HemaSphere. 2026;10(6):e70403. doi:10.1002/hem3.70403

BTKi



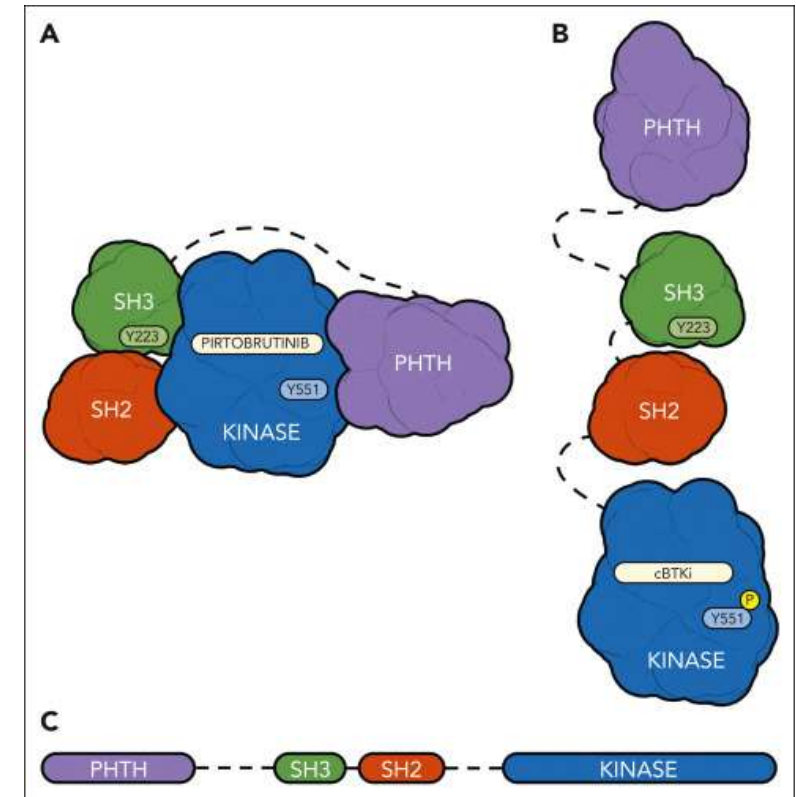
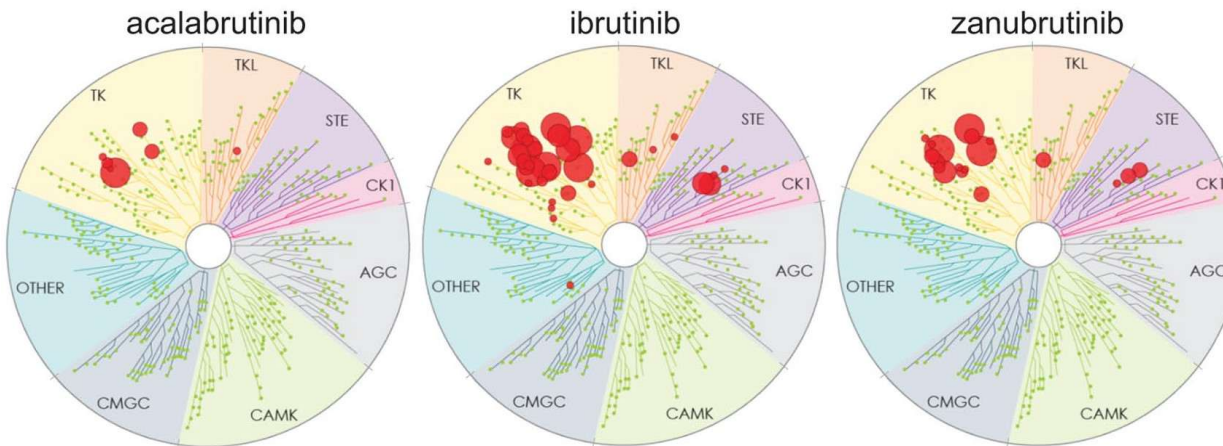
BTK inhibitie zorgt voor:

- Verminderde retentie in lymfeklieren
 - >Redistributielymfocytose
- Weghalen van survival / proliferatie pathways



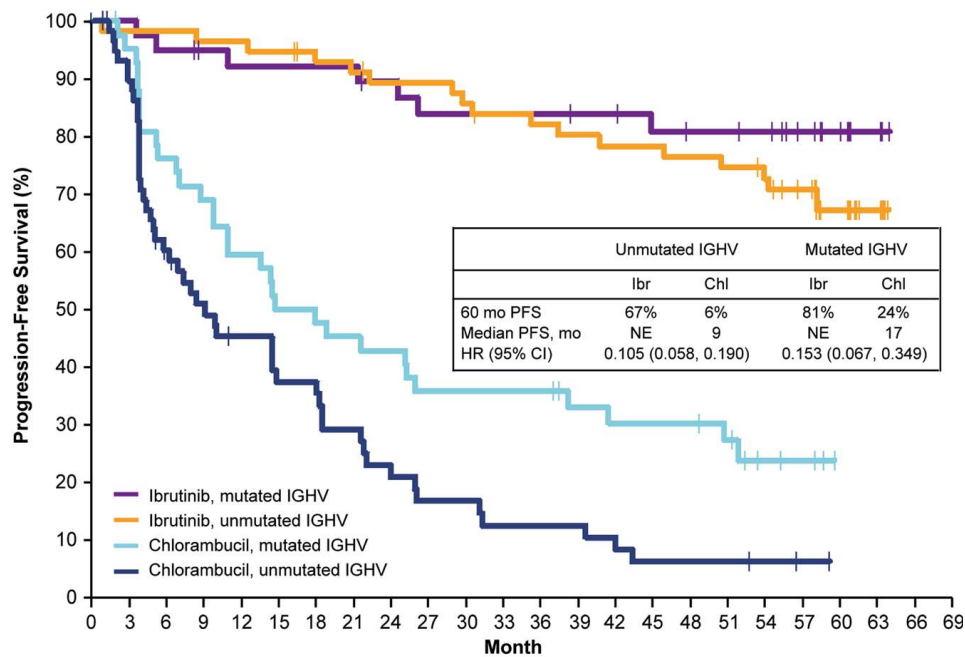
BTKi

- Per orale medicatie (pillen)
- In begin stijging aantal witte bloedcellen (uit klieren)
- Covalente BTKi (Ibrutinib / Acalabrutinib / Zanubrutinib)
 - Verschillende effecten op andere kinasen
 - Sommige bijwerkingen verschillend
 - Efficiëntie verschillend?
- NonCovalante BTKi (Pirtobrutinib)
 - Kan sommige BTKi mutaties overwinnen
 - Meer specifiek – minder bijwerkingen (?)



Doelgerichte therapie : BTKi – Ibrutinib (first in class)

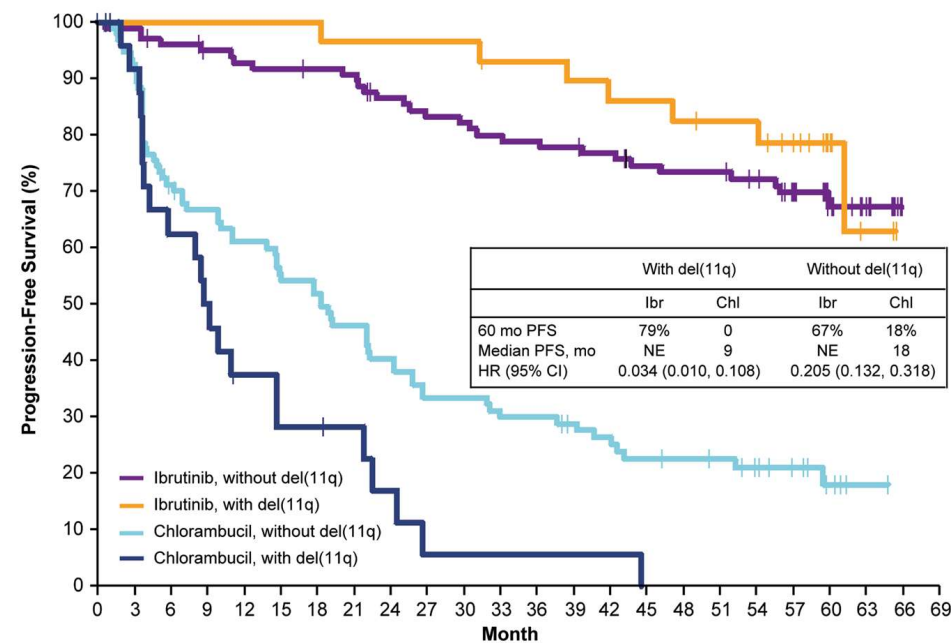
B



Patients at Risk

Ibrutinib, mutated IGHV	40	39	37	35	34	34	34	34	32	30	30	30	30	29	28	27	26	25	24	14	6	1
Ibrutinib, unmutated IGHV	58	57	57	56	56	55	53	52	49	49	48	45	45	43	42	41	41	40	36	18	11	
Chlorambucil, mutated IGHV	42	40	32	29	25	22	21	19	18	15	15	15	13	12	11	11	10	7	5	2		
Chlorambucil, unmutated IGHV	60	52	33	27	23	20	19	14	11	8	8	6	6	6	5	3	3	3	2	1		

A



Patients at Risk

Ibrutinib, without del(11q):	101	98	94	91	89	88	87	86	80	77	76	74	73	72	70	65	64	64	61	56	24	12	1
Ibrutinib, with del(11q):	29	29	29	29	29	29	28	28	28	28	26	26	26	25	24	24	23	22	22	19	7	2	
Chlorambucil, without del(11q):	96	87	64	59	54	48	45	40	35	29	29	27	26	23	21	18	17	15	13	10	4	1	
Chlorambucil, with del(11q):	25	22	15	12	8	6	6	5	3	1	1	1	1	1	1	0							

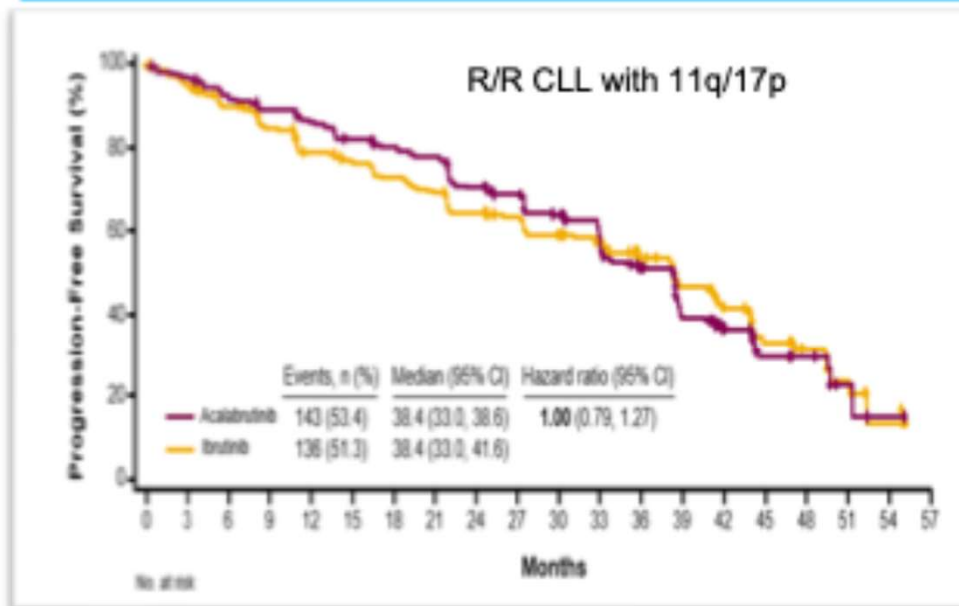
Effectiviteit Ibrutinib vs Acalabrutinib of Zanubrutinib

median number of previous treatments: 2
discontinuations due to AEs: Acala 14.7%/Ibr 21.3%
still on Acala 46.3% vs. Ibr 41.1%

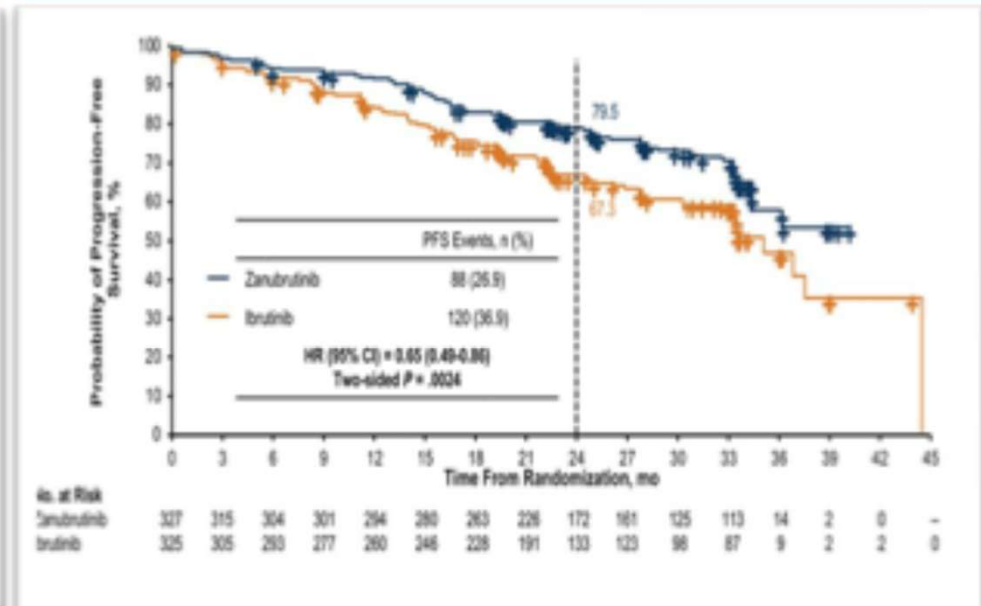
Median number of previous treatments: 1
discontinuations due to AEs: Zanu 21,45%/ Ibr 28,3%

ELEVATE R/R: m fu 41mo
mPFS 38.4 mos

ALPINE: m fu 42,5 mo
3 yrs PFS: 64,5% vs. 54,4%

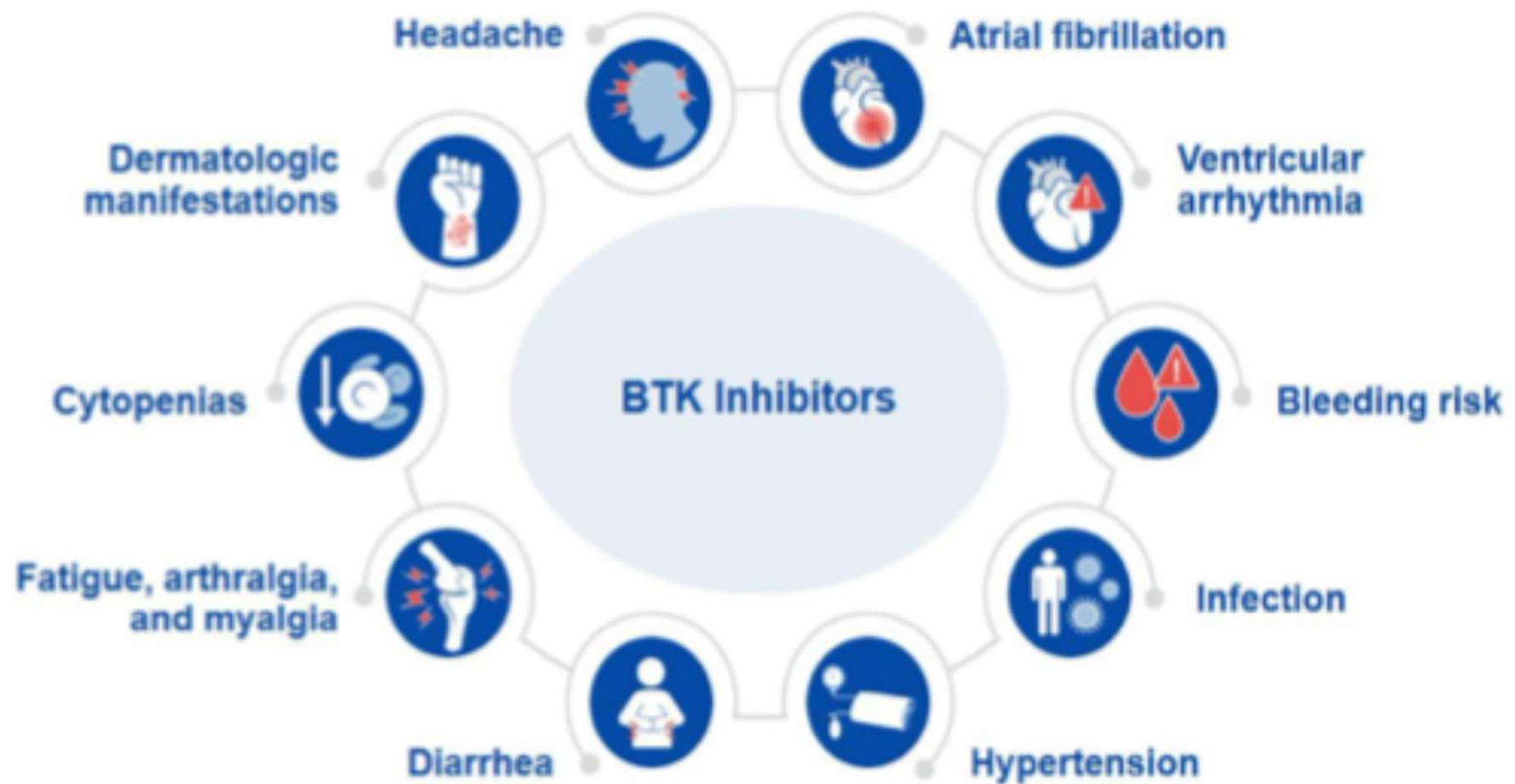


Byrd et al. J Clin Oncol 2021



Brown et al. NEJM 2023- Blood 2024

BTKi – bijwerkingen



Verskil in bijwerkingen tussen BTKi's

Adverse events	Pooled ibru N = 756 Ref ²³	ibru ALPINE/ ASPEN N = 422 Ref ²⁴	ibru ELEVATE R/R N = 263 Ref ²⁵	Pooled acala N = 1040 Ref ²⁴	acala ELEVATE R/R N = 266 Ref ²⁵	Pooled zanu N = 1550 Ref ²⁶	Pooled zanu N = 779 Ref ²⁷
Atrial fibrillation	6%	14.7%	16%	4.4%	9%	4.6%	3%
Hypertension	10%	24.6%	23%	8%	9%	15.2%	12%
Bleeding	38%	45.3%	51%	46%	38%	50.6%	65%
Major bleeding	3%	6.2%	5%	3%	5%	5.2%	4%
Anaemia	21%	17.1%	19%	14%	22%	15.2%	18%
Neutropenia	33%	23%	25%	12.3%	21%	29.5%	36%
Thrombocytopenia	21%	15.6%	13%	9%	15%	17.1%	21%
Infections	70%	68%	81%	67%	78%	70.7%	76%
Headache	13%	NR	20%	37.8%	35%	NR	13%
Diarrhoea	39%	NR	46%	36.7%	35%	NR	23%
Arthralgia	13%	NR	23%	19.1%	16%	NR	24%

N: number of patients; R/R: relapsed/refractory; NR: not reported; ibru: ibrutinib; acala: acalabrutinib; zanu: zanubrutinib.

If intolerant:

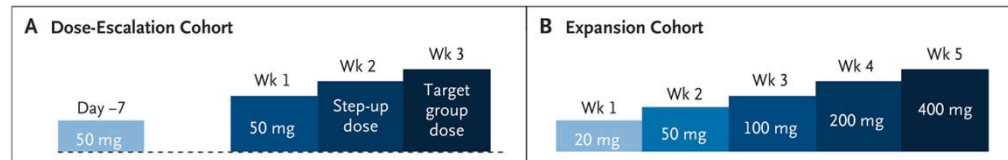
- Dose reductions
- Change between cBTKis

Neefs et al. BJH 2024

Bijwerkingen BCL2i (Venetoclax)

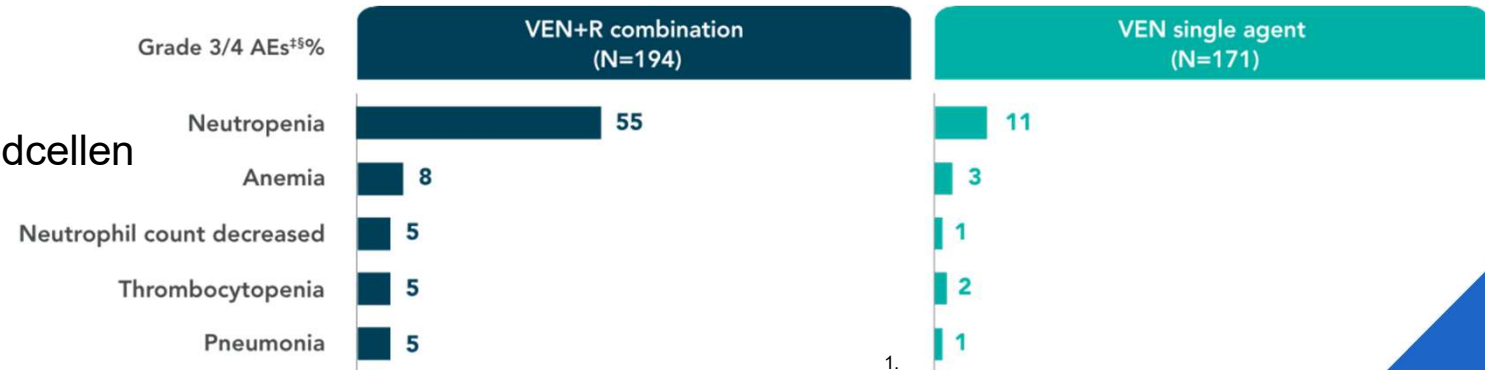
► Tumor lysis syndrome (TLS)

- Zonder ramp-up : 3/3 ernstig TLS met 1 overlijden
- Snelle ramp-up : 13% TLS zonder ernstige complicaties
- “Standaard 5 weken ramp-up” : <2%



► Lage bloedcellen

- Vooral lage witte bloedcellen
- Infecties!



1.
2.

venclexta [Internet]. [cited 2026 Sep 10]. Venetoclax + acalabrutinib for CLL | VENCLEXTA® HCP. Available from: <https://www.venclextahcp.com/ven-a.html>

Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, et al. Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. New England Journal of Medicine. 2016 Jan 28;374(4):311–22. doi:10.1056/NEJMoa1513257

Aandacht voor interacties!

Strong CYP3A4 inhibitors	Moderate CYP3A4 inhibitors	CYP3A4 inducers
clarithromycin	amiodarone	carbamazepine
ketoconazole	diltiazem	phenytoin
posaconazole	verapamil	rifampicin
voriconazole	erythromycin	rifabutin
HIV medication	fluconazole	phenobarbital
Nirmatrelvir/ritonavir (Paxlovid®)	isavuconazole	enzalutamide
Grape fruit (juice), Sevilla oranges		St John's wort
[BTKis/venetoclax] ↑↑	[BTKis/venetoclax] ↑	[BTKis/venetoclax] ↓

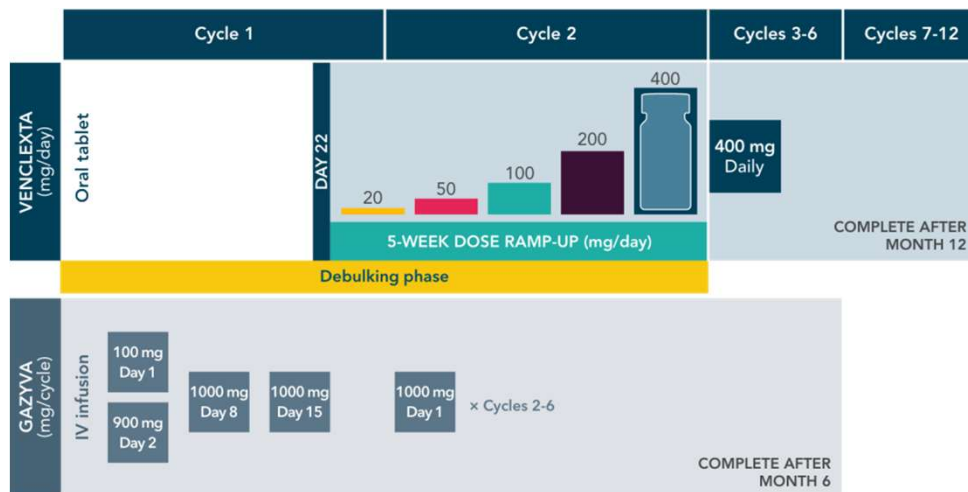
Stimulate patients to declare the use of additional nutrients, herbs & other complimentary agents

Re-check drug-drug interactions at the start of each new treatment, ideally with your clinical pharmacist



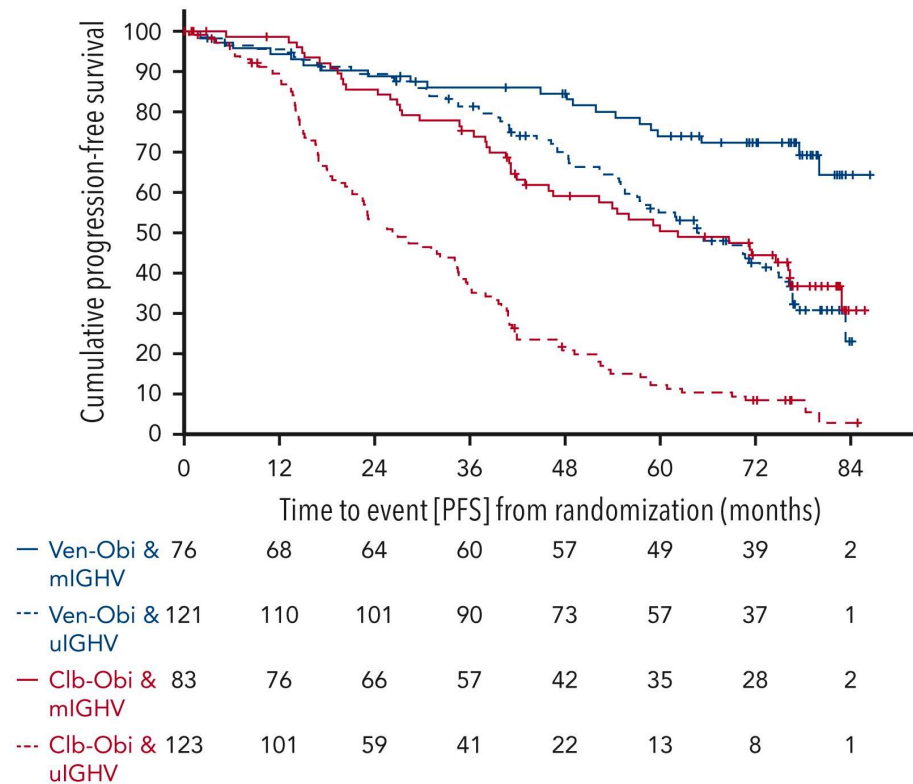
VenG (Venclyxto + Gazyvaro / Venetoclax + Obinutuzumab) (1jaar)

- ▶ Beginnen met IV Obi in ziekenhuis
 - ▶ Risico op infusiereacties
- ▶ Nadien “ramp-up” venetoclax
 - ▶ Risico op tumorlyse
- ▶ -> Frequent in ziekenhuis in begin
- ▶ Slechts 1 jaar behandeling



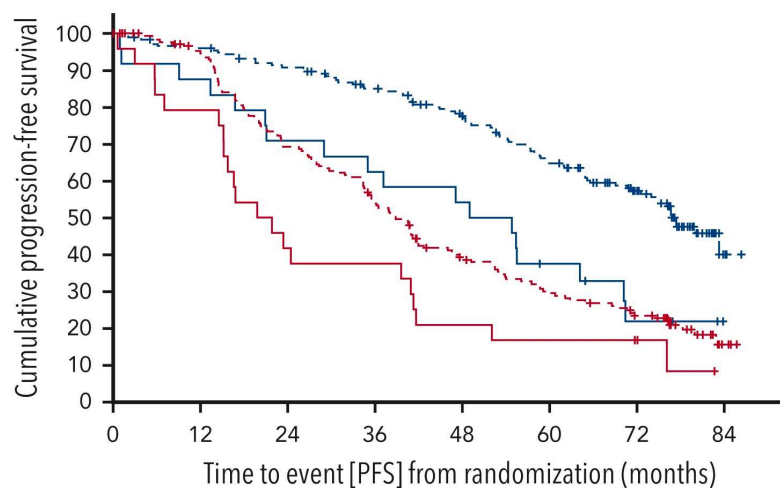
Graphic not to scale. Each cycle is 28 days.

C



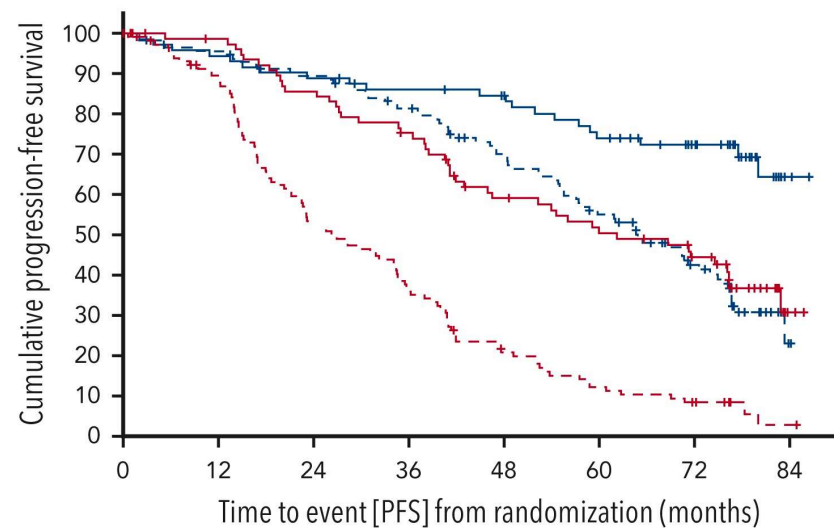
VenG (CLL14 : frontline)

B



	0	12	24	36	48	60	72	84
— Ven-Obi & TP53 del/mut	25	21	17	15	13	8	4	0
- - - Ven-Obi & no TP53 del/mut	184	168	157	142	123	101	73	3
— Clb-Obi & TP53 del/mut	24	19	10	9	5	4	3	0
- - - Clb-Obi & no TP53 del/mut	184	160	117	90	60	45	33	3

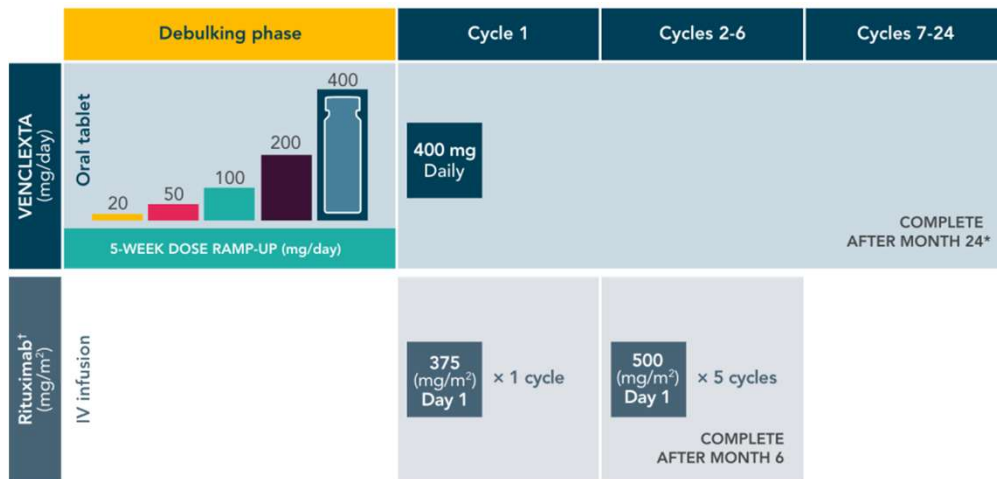
C



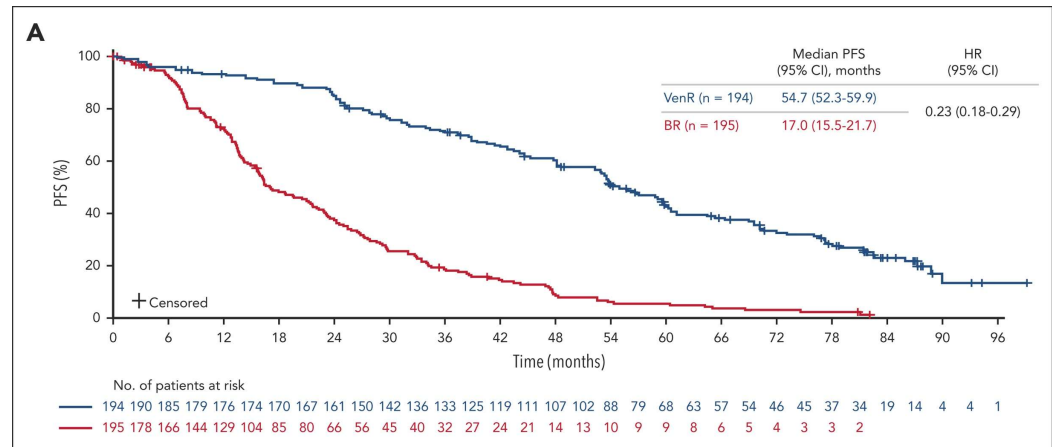
	0	12	24	36	48	60	72	84
— Ven-Obi & 76 mIGHV	76	68	64	60	57	49	39	2
- - - Ven-Obi & 121 uIGHV	110	101	90	73	57	37	1	
— Clb-Obi & 83 mIGHV	83	76	66	57	42	35	28	2
- - - Clb-Obi & 123 uIGHV	123	101	59	41	22	13	8	1

VenR (Venetoclax + Rituximab) / MURANO (2 jaar)

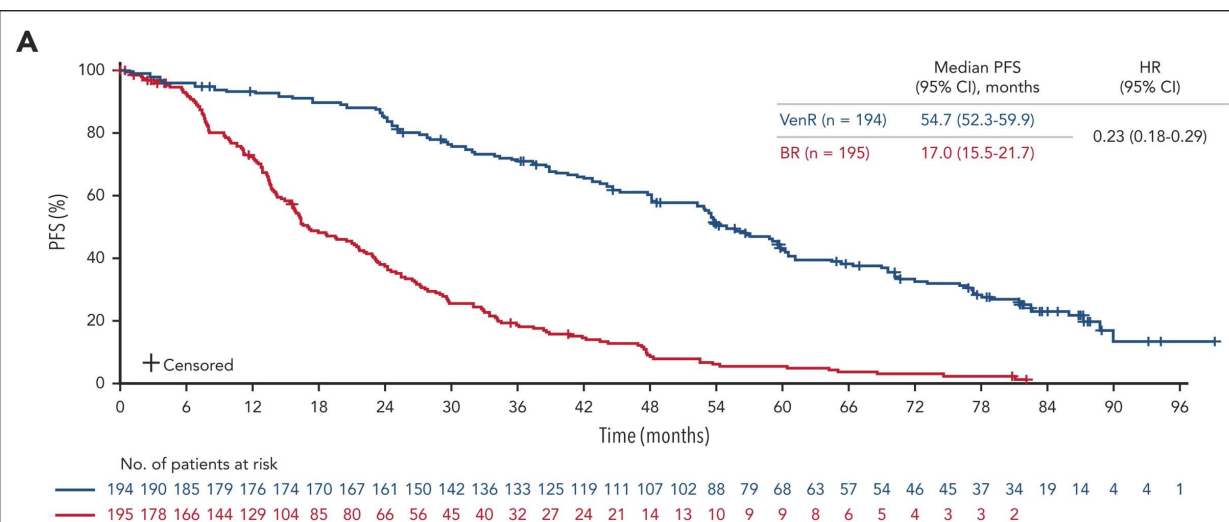
- ▶ “Ramp-up” venetoclax
 - ▶ Risico op tumorlyse
 - ▶ Frequent in ziekenhuis eerste 5 weken
- ▶ Opstart Rituximab via dagkliniek nadien (6 keer)
- ▶ 2 jaar behandeling
- ▶ Mogelijkheid om te herhalen als lange tijd goed effect gehad



Graphic not to scale. Each cycle is 28 days.



VenR (MURANO) - Relapsed

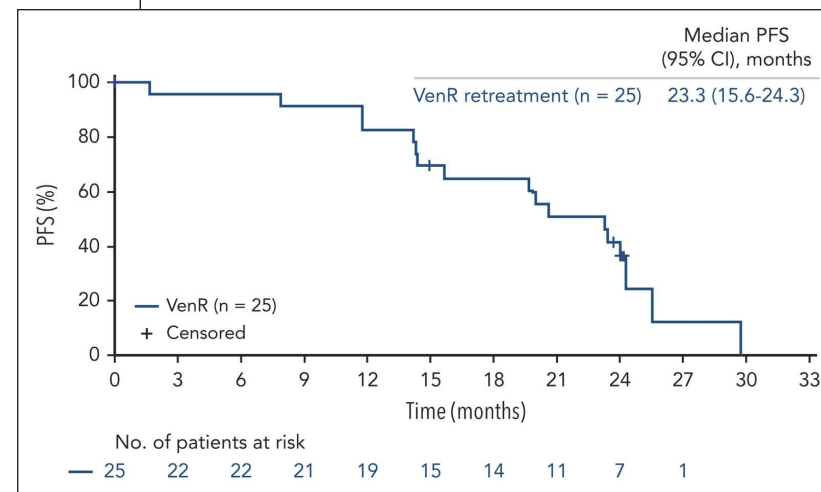


7-year PFS rate 23.0%

- Lower in high-risk features
 - del(17p) and/or *TP53* mutation : 5%
 - NOTCH1 mutations : 11%
 - unmutated IGHV was 16.3%

Retreatment possible

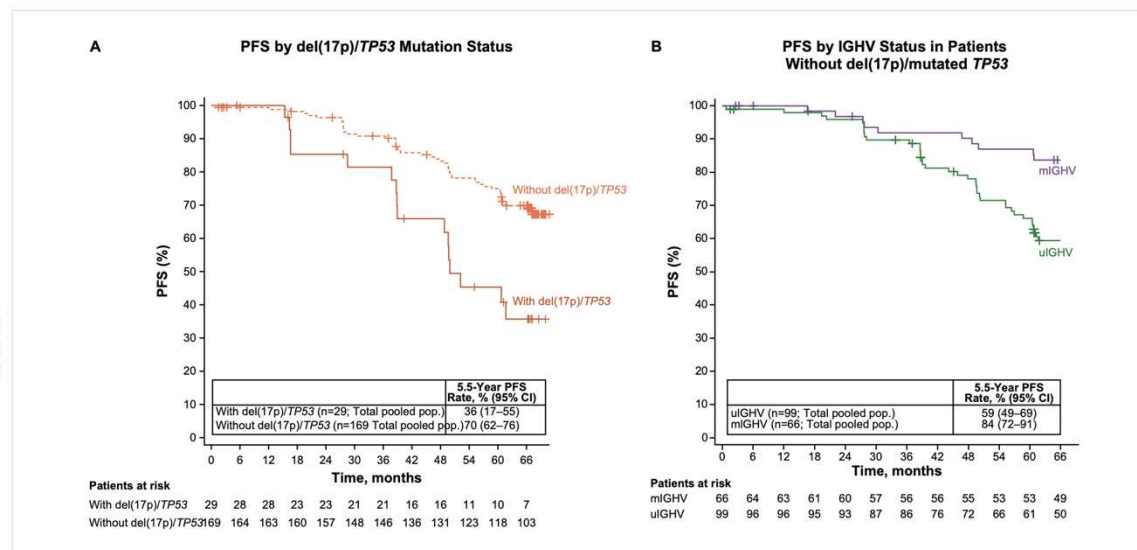
- ORR 72%
- 32% achieved uMRD
- mPFS 23m



I+V (Ibrutinib + Venetoclax) (15 maand)

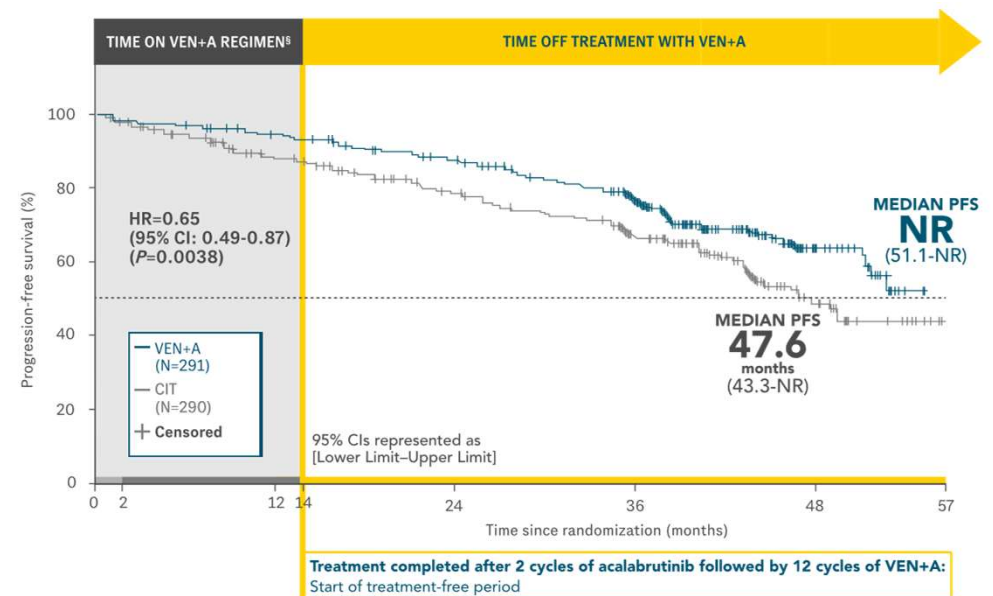
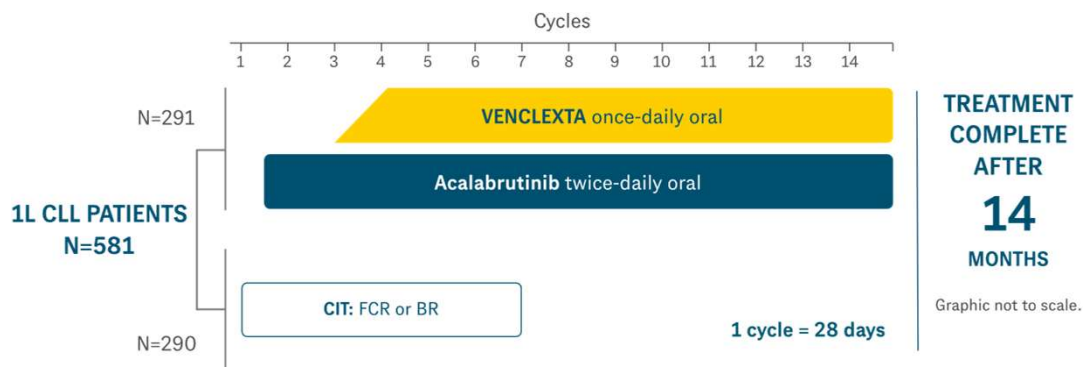
- ▶ Volledig orale behandeling
- ▶ 15 maand therapie
- ▶ Vooral nuttig in IgHV-unmutated CLL
- ▶ Bijwerkingen van 2 producten

Impact of del(17p)/mutated *TP53* and IGHV Status on Long-Term PFS (Total Pooled Population)



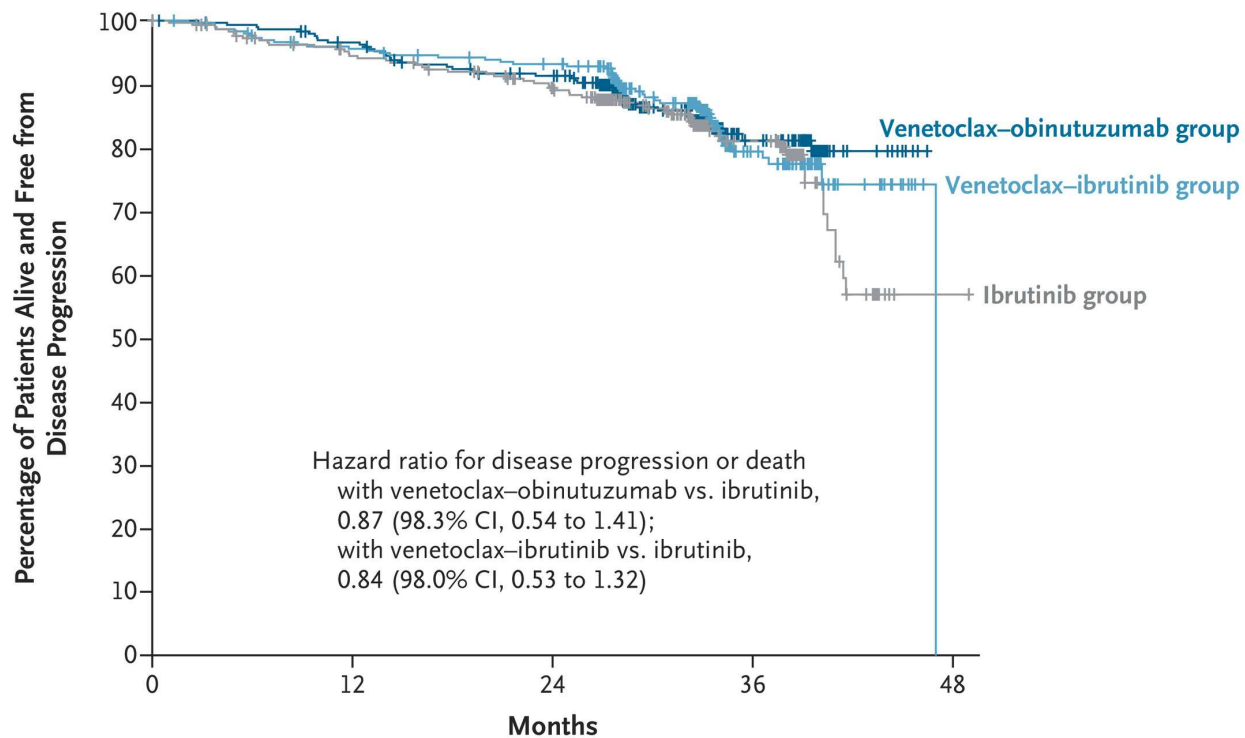
A+I (Venetoclax + Acalabrutinib) – 14 maand

- ▶ Volledig orale behandeling
- ▶ 14 maand therapie
- ▶ Vooral nuttig in patiente met vrees voor (cardiale) bijwerkingen Ibrutinib



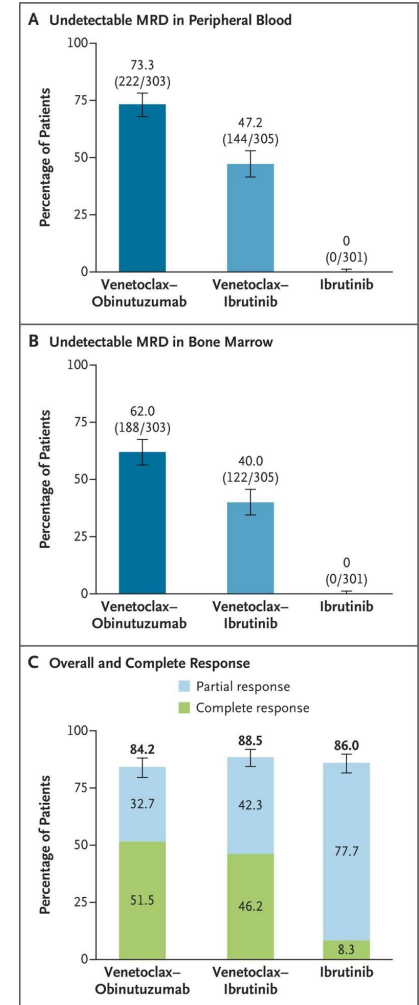
Number of patients at risk										
VEN+A	291	282	269	251	237	219	177	102	35	3
CIT	290	236	208	189	170	154	127	66	28	6

Hoe kiezen? CLL 17 (nog) geen overtuigende verschillen !



No. at Risk

Venetoclax-obinutuzumab	303	278	256	77	0
Venetoclax-ibrutinib	305	278	267	82	0
Ibrutinib	301	267	243	94	1



CLL First-Line

Integrated vision of individual features to guide treatment decision

	Biological Profile			Infection risk	Ease of treatment	Concomitant comorbidities & comedication			
	M-IGHV	UM-IGHV	TP53mut/del(17p)			Cardio-vascular Disease	Impaired Renal Function	Anticoagulation/bleeding risk	Drug Interactions
Venetoclax - Obinutuzumab	A	A	B	C	C	A	B ²	A	Assess specific interactions
Venetoclax + Ibrutinib ¹	A	A	B	B	B	C	B ²	B ³	
Venetoclax + Acalabrutinib	A	A	B	B	B	B	B ²	B ³	
Venetoclax + Acalabrutinib + obinutuzumab	A	A	B	C	C	C	B ²	B ³	
Acalabrutinib	B	A	A	A	A	B	A ²	B ³	
Zanubrutinib	B	A	A	A	A	B	A ²	B ³	
Ibrutinib	B	A	A	A	A	C	A ²	B ³	

A= Strongly recommended; **B**= Recommended; **C**= consider alternatives.

¹: This combination appears particularly effective in UM-IGHV when used within an MRD-guided strategy, but is not currently approved.

²: caution with CrCl < 50 mL/min for venetoclax and < 30 mL/min for BTKi. For venetoclax recommended TLS preventions should be followed in patients with CrCl 50 -79 mL/min.

³: contraindicated with anti-Vitamin K.

Recommendation	CITs are no longer recommended, because they are either inferior (BR, chlorambucil + obinutuzumab) to targeted agents or associated with a higher risk for adverse events including secondary neoplasia such as myeloid malignancies (FCR)
Relevant for:	All patients
Level of Evidence	I
Grade of Recommendation	A

Recommendation	Time-limited targeted therapies should be preferred over continuous therapy in patients with CLL without <i>TP53</i> aberrations (Figure 1)
Relevant for:	All patients
Level of Evidence	I
Grade of Recommendation	A

Recommendation	The selection of combination therapy should take into consideration the biological profile of the CLL and the adverse event profile of the agents, as well as the patient's comorbidities, co-medications, history of infections, and ease of treatment (Figure 2). In particular, in patients with CLL and mutated IGHV status, continuous therapy should be avoided
----------------	---

Conclusies

- ▶ Overleving lymfeklierkanker gaat vooruit!
 - ▶ Deels door betere behandelingen.
 - ▶ Veel verschillende behandelingsmogelijkheden
 - ▶ Elk met eigen bijwerkingsprofiel
 - ▶ Afstemmen op profiel patient! (ziekte, leeftijd, comorbiditeiten,...)
 - ▶ Vaak combinaties immunotherapie +/- chemotherapie +/- doelgerichte therapie
 - ▶ Ook combinaties bijwerkingen
 - ▶ Evolutie naar meer doelgerichte / chemovrije therapie
 - ▶ Soms andere soort bijwerkingen
 - ▶ Samenwerking met behandelend team om
 - ▶ geïnformeerd te zijn van mogelijke bijwerkingen
 - ▶ te voorkomen!
 - ▶ pro-actief aan te pakken
- 

DR. WILLEM DANEELS

Hematoloog

Dienst hematologie

Universitair Ziekenhuis Gent
C. Heymanslaan 10 | B 9000 Gent
T +32 (0)9 332 21 11
E info@uzgent.be

www.uzgent.be

Volg ons op

