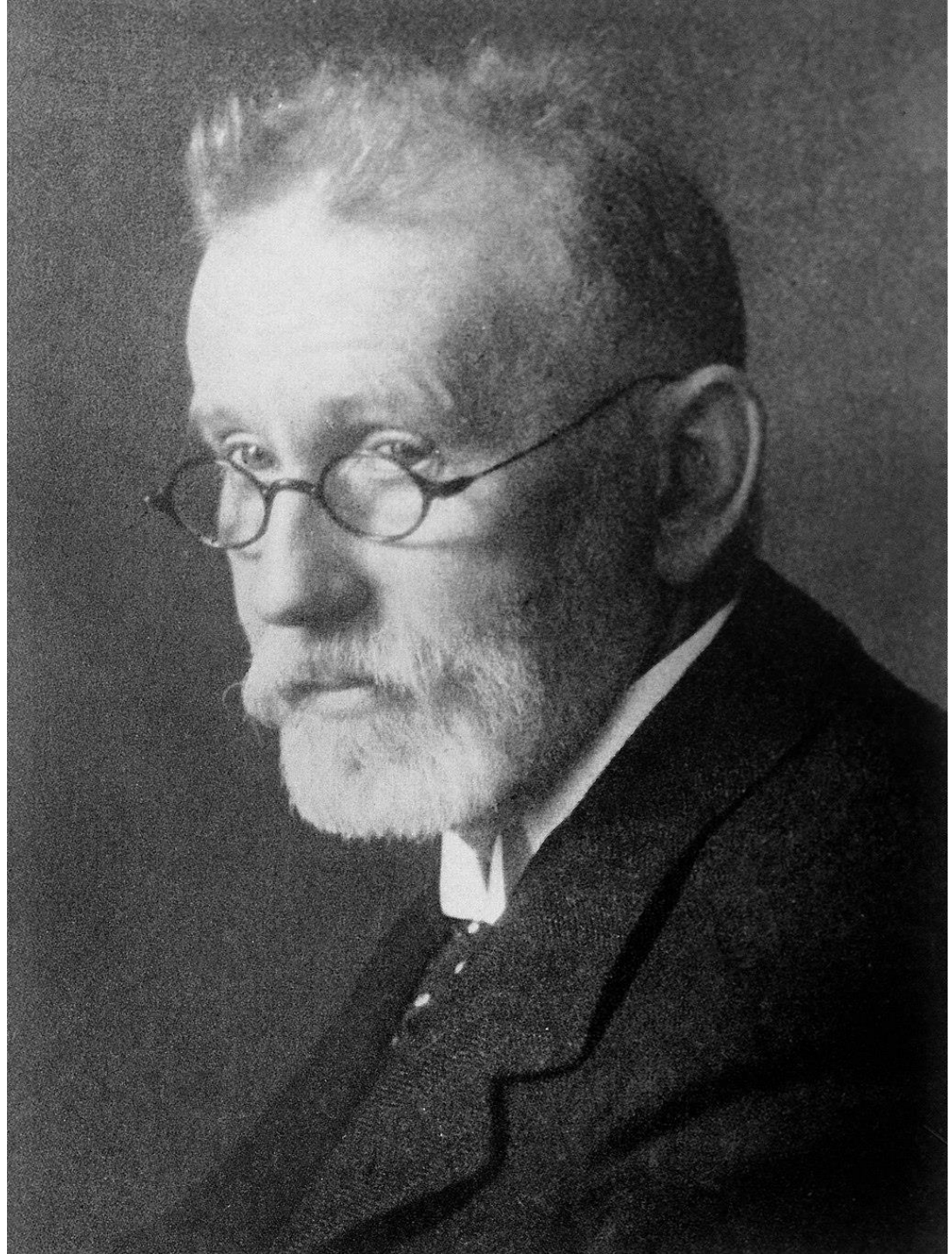
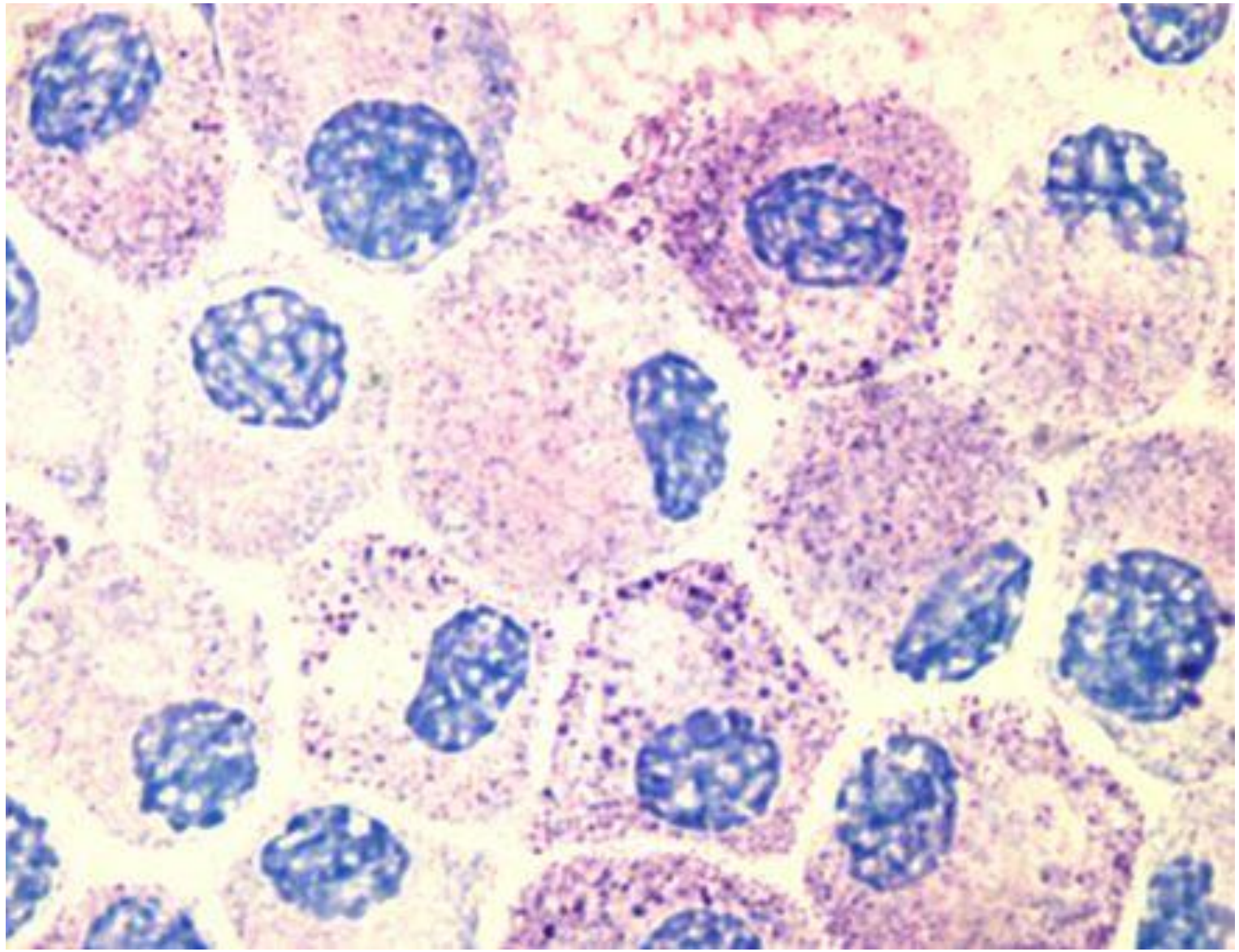
# De weg naar non-chemo

Fritz Offner

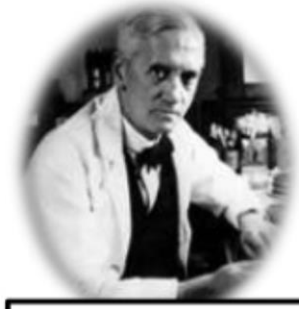
UZ Gent Hemato



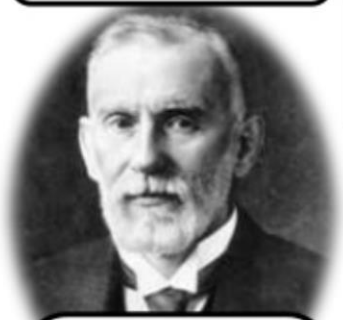
Paul Ehrlich 1854-1915



# Timeline history of chemotherapy development



1908- Discovery of Arsphenamine

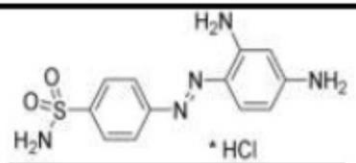


Alexander Fleming 1928- Penicillin

**Paul Ehrilich**
Father of Chemotherapy

Gerhard Domagk 1939- Sulfonamidochrysoidine (Prontosil)

1900- *Paul Ehrilich* Chemotherapy Animal model developed




1932- Prontosil- First sulfonamide- Bayer's Laboratory

1943- Nitrogen mustard in lymphomas

1944- Waksman *et al.*, discovered streptomycin.

1948- Anitfolates

1951- Thiopurines

1957- 5-Fluorouracil

1958- Methotrexate

1959- Antitumor antibiotics

1962- nalidixic acid

1963- Vinca alkaloids

1963 to 1970- Treatment for Hodgkin's disease

1996- Imatinib

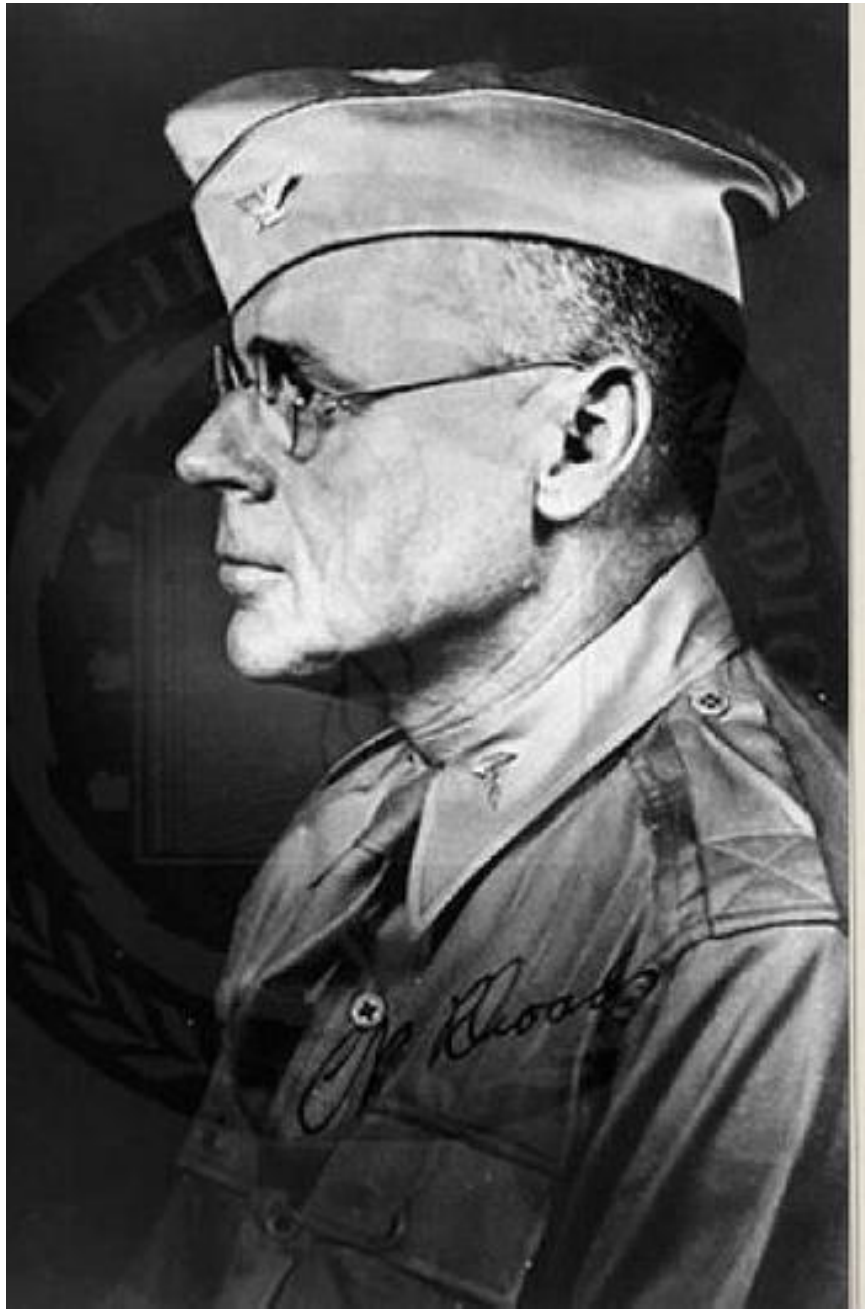
1997- Monoclonal antibody approved for the treatment of tumor.

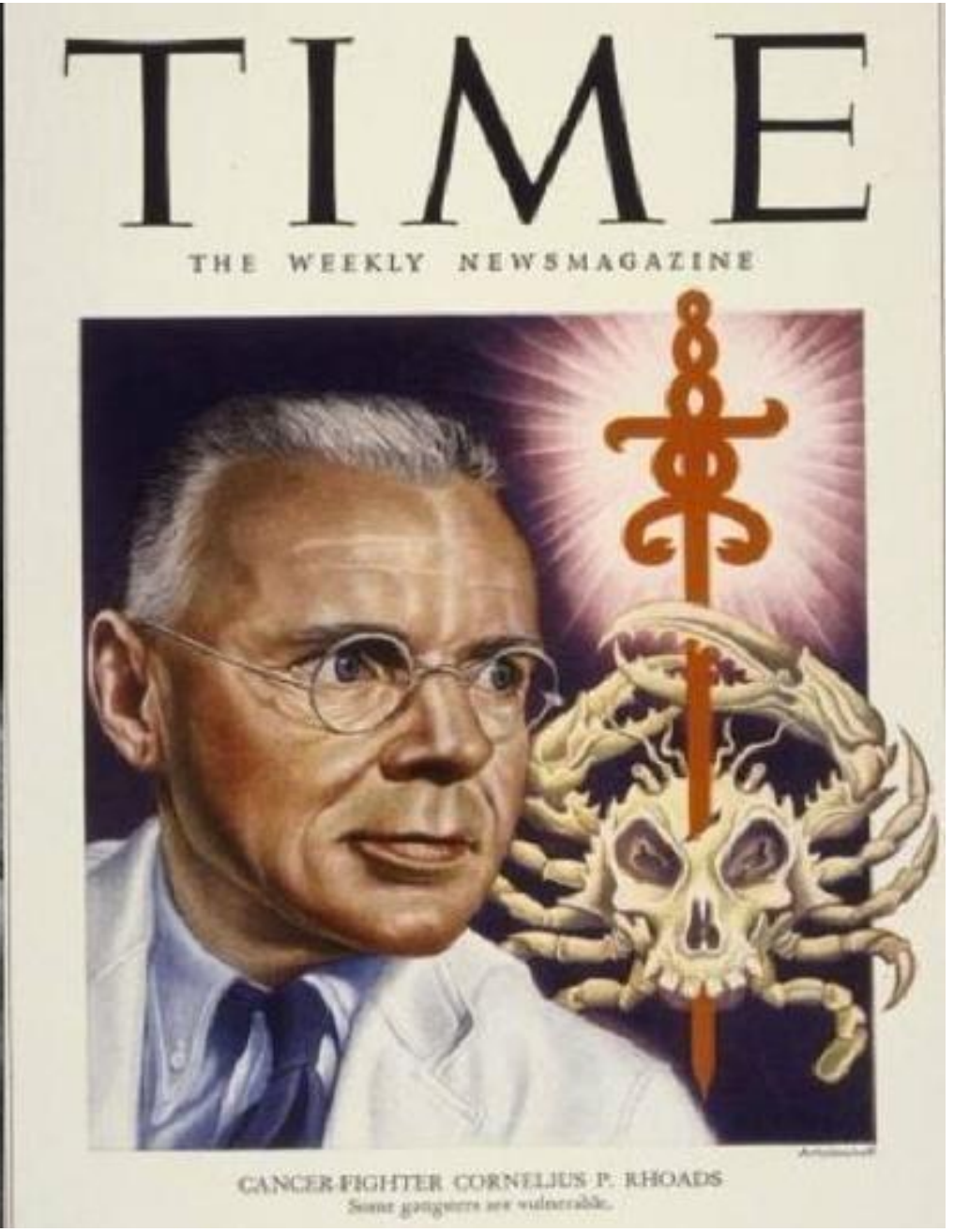
2005- Tyrosine kinase inhibitors

2007- Target specific screens

1900 1920 1940 1960 1980 2015


U.S.

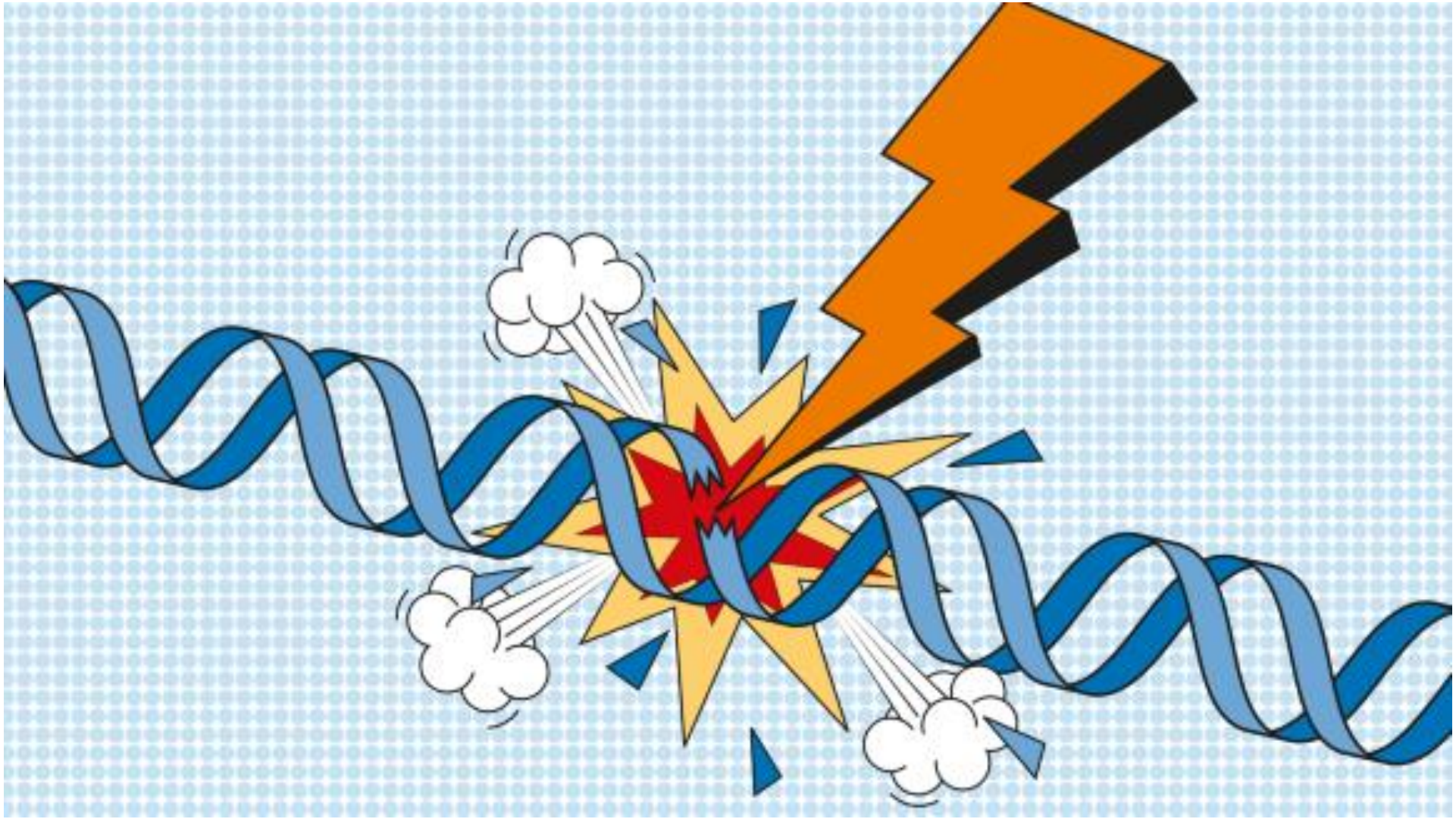


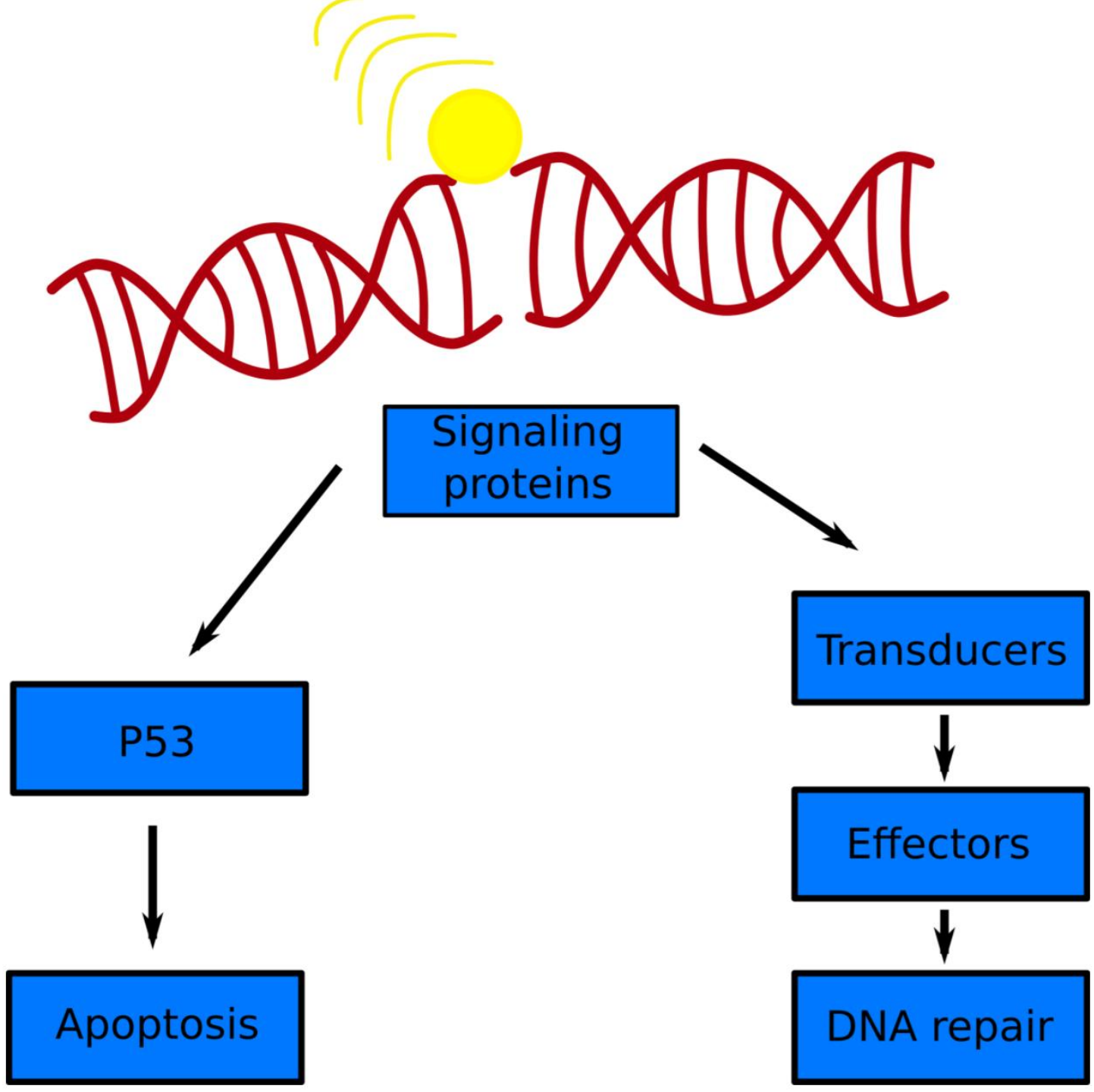

TIME
THE WEEKLY NEWSMAGAZINE
CANCER-FIGHTER CORNELIUS P. RHOADS

# THE GREAT SECRET

## The Classified WWII Disaster that Launched the War on Cancer

JENNET CONANT




Signaling proteins
P53
Apoptosis
Transducers
Effectors
DNA repair

# Neveneffecten chemotherapie :

- Korte termijn :
  - Haarverlies
  - Ontsteking en infecties
  - Moeheid
  - Misselijkheid, braken
  - Fertiliteit
  - Specifieke effecten : hart, long, zenuw,…
- Lange termijn :
  - Fertiliteit, hormonaal
  - Myelodysplasie

# De bijdrage van chemotherapie in lymfoom (1950-1990)

- Ziekte van Hodgkin : 90-95% genezing
- Non Hodgkin lymfoom :
- DLBCL : 50-70% , na rituximab toevoeging 60-85% genezing
- Folliculair NHL : na rituximab toevoeging heeft 80% van de pt voor de eerste 10 jaar dezelfde vooruitzichten als hun leeftijdsgenoten
- Mantelcellymfoom : matig effect met enkel chemo (3,5 jr overleving), beter met R-chemo (>7jaar)
- Marginale zone lymfoom : beperkte bijdrage
- T-cel lymfomen : toch nog steeds 40% genezing

# De opkomst van non-chemotherapie behandelingen

- Interferon, cytokines, LAK en TIL 1980 : de gaspedaal van het immuun stelsel
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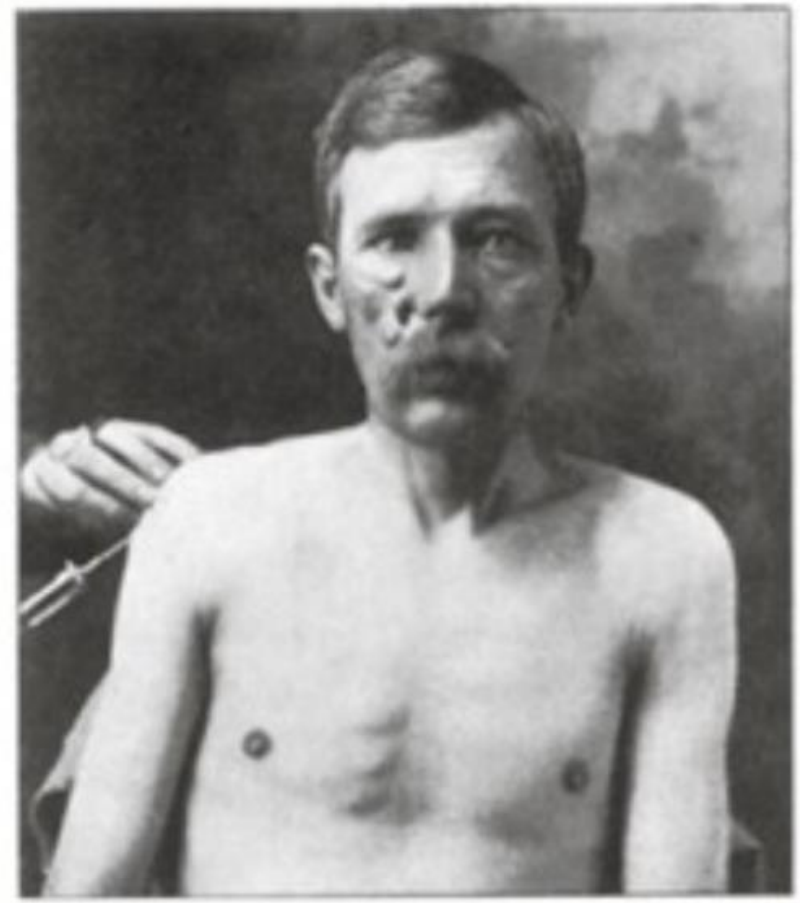
- Optimalisatie van Moabs : immunotoxines, bispecifieke Ab en CART

a

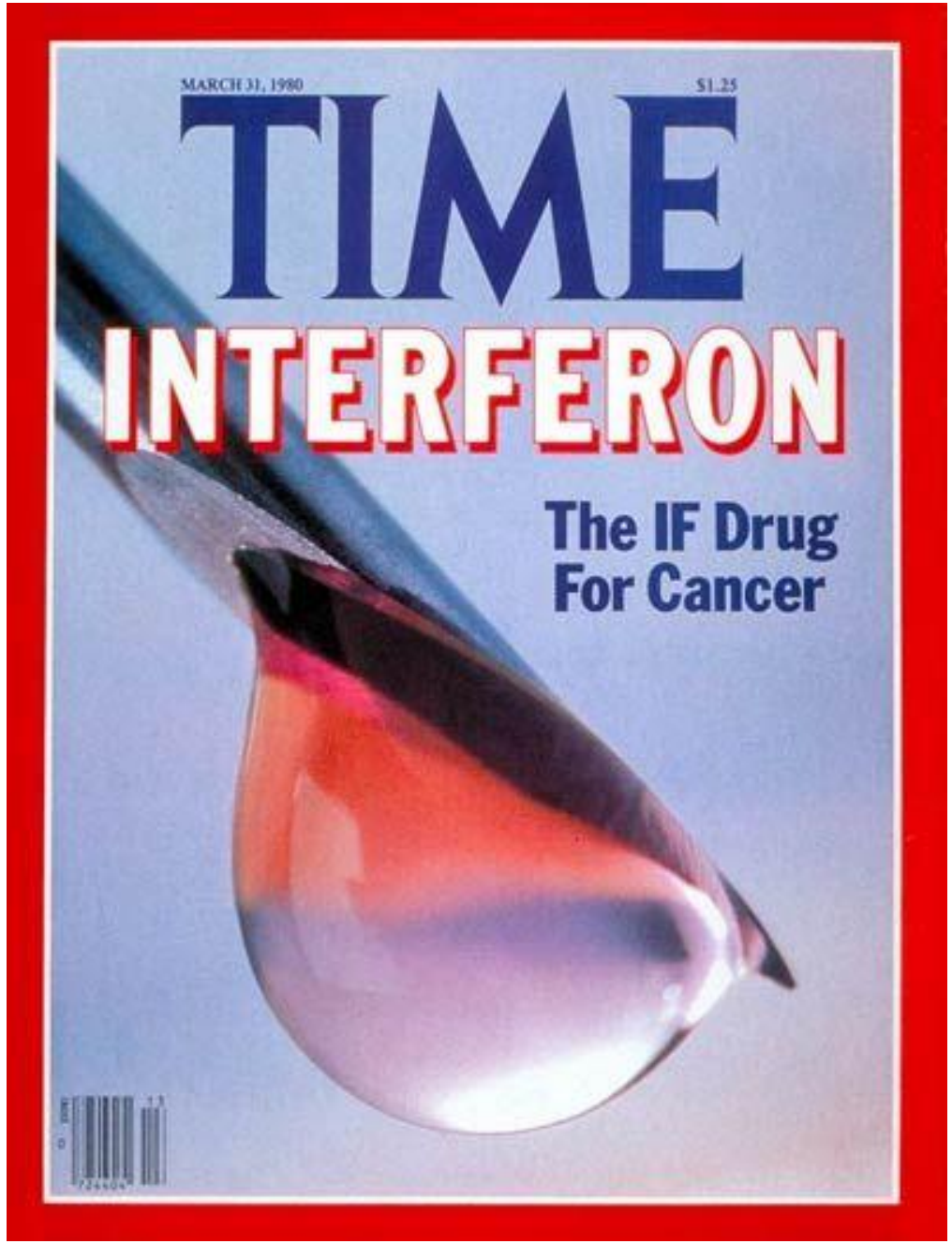
b

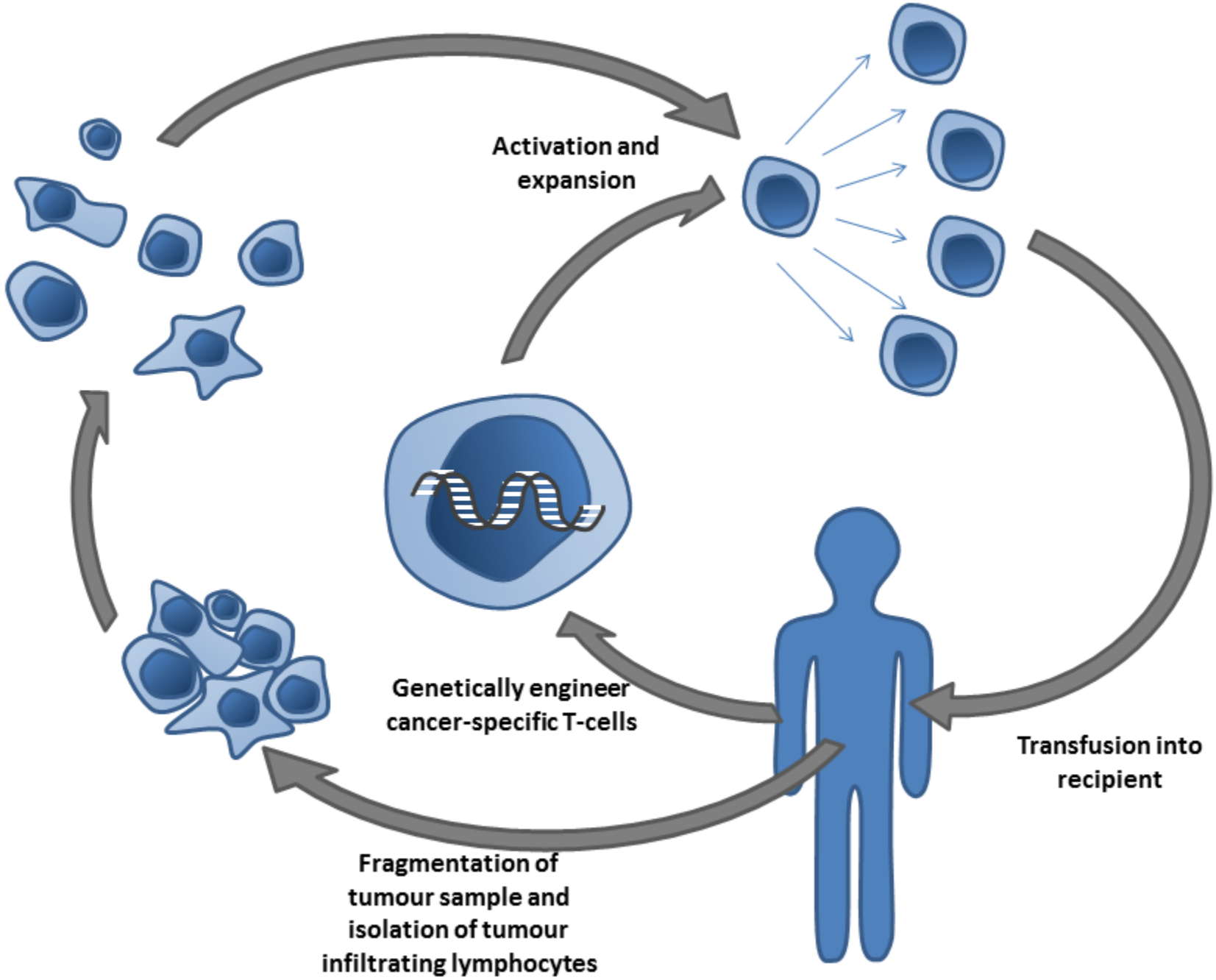


Pre-ILP TM-LLP

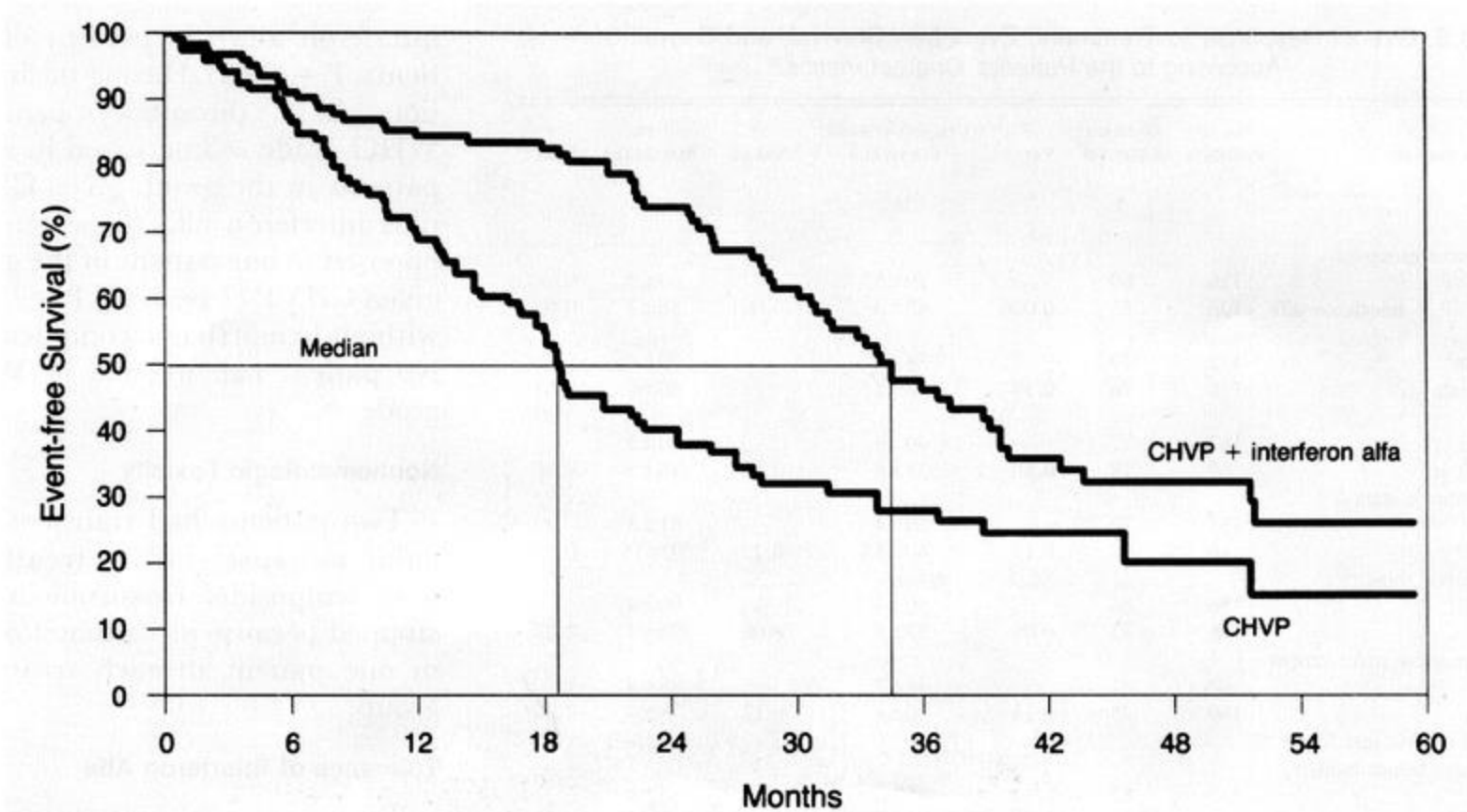
2 months after TM-ILP

Ongoing response 9 months after TM-ILP

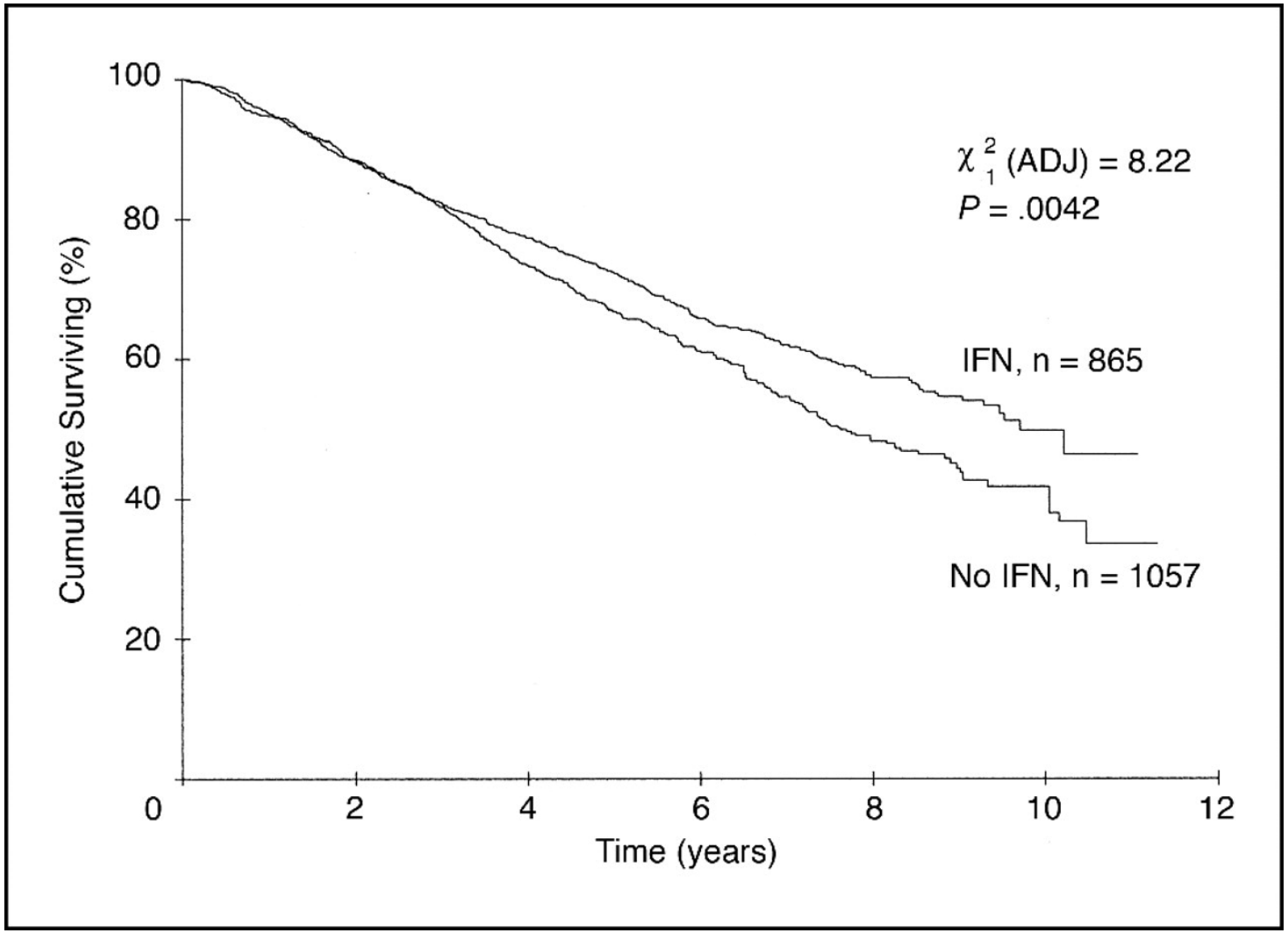

MARCH 31, 1980
$1.25
TIME
INTERFERON
The IF Drug
For Cancer


Activation and expansion
Genetically engineer cancer-specific T-cells
Transfusion into recipient
Fragmentation of tumour sample and isolation of tumour infiltrating lymphocytes

GELF: IFN onderhoud in folliculair NHL , NEJM 1993




| Group | No. of Patients | No. with Events | Median Event-free Survival (95% CI) | P Value |
|---|---|---|---|---|
| CHVP | 119 | 83 | 19 mo (17–23) | |
| CHVP + interferon alfa | 123 | 65 | 34 mo (31–39) | <0.001 |




Published in: A.Z.S. Rohatiner; W.M. Gregory; B. Peterson; E. Borden; P. Solal-Celigny; A. Hagenbeek; R.I. Fisher; M. Unterhalt; R. Arranz; T. Chisesi; A. Aviles; T.A. Lister; *Journal of Clinical Oncology* 2005 232215-2223.
DOI: 10.1200/JCO.2005.06.146

# Interferon

- TNF/IFN gamma waren erg toxisch behalve lokaal
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- IFN alfa wordt (nog steeds) gebruikt als antiviraal middel
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- 2005 : opkomst van de Imids in MM, werkingsmechanisme onbekend
- 2014 : lenalidomide heeft een IFN signature, en stimuleert de IFN pathway, én wordt veel beter verdragen dan IFN.

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- Immuun modulatoren (Imid's) 2005-heden
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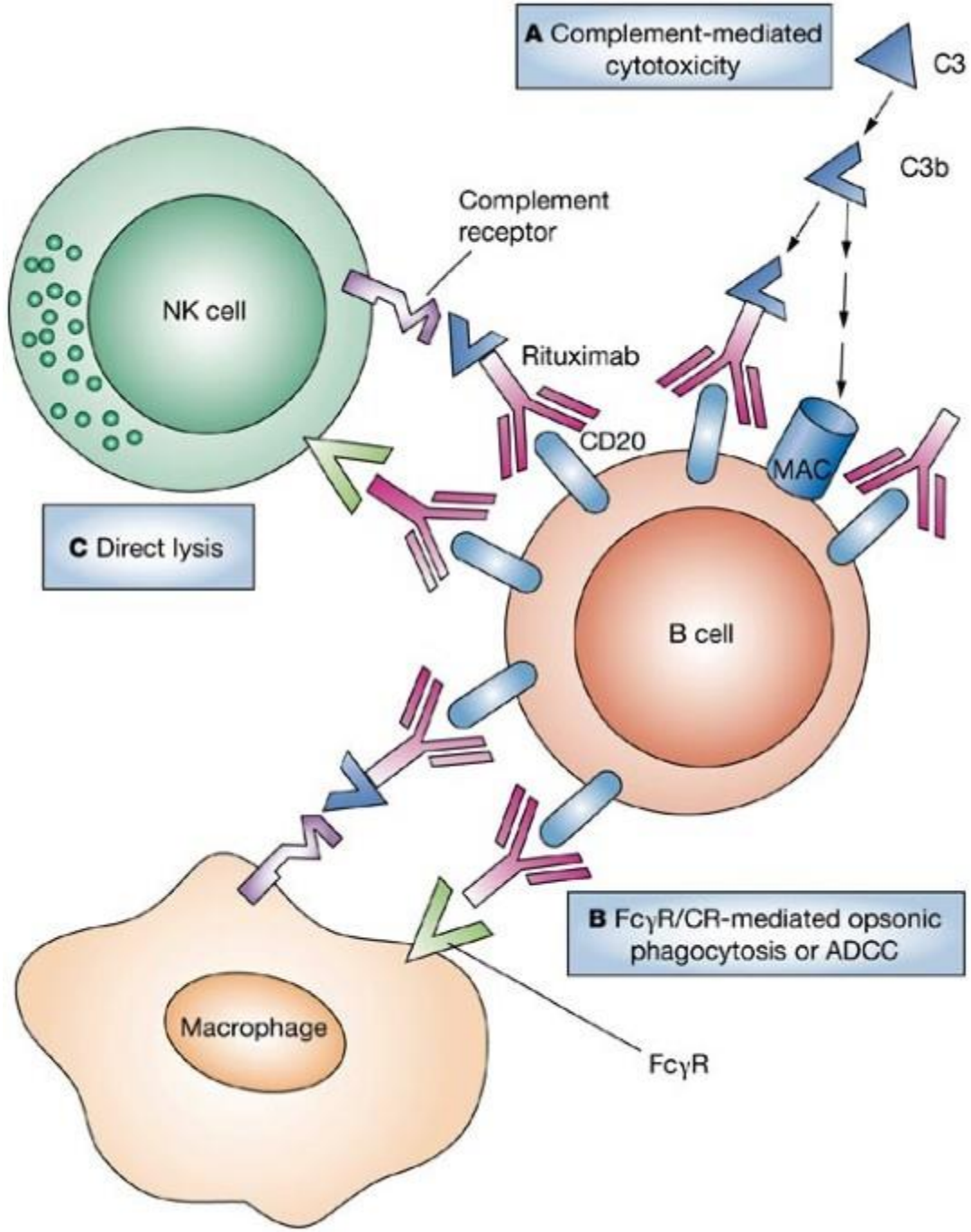
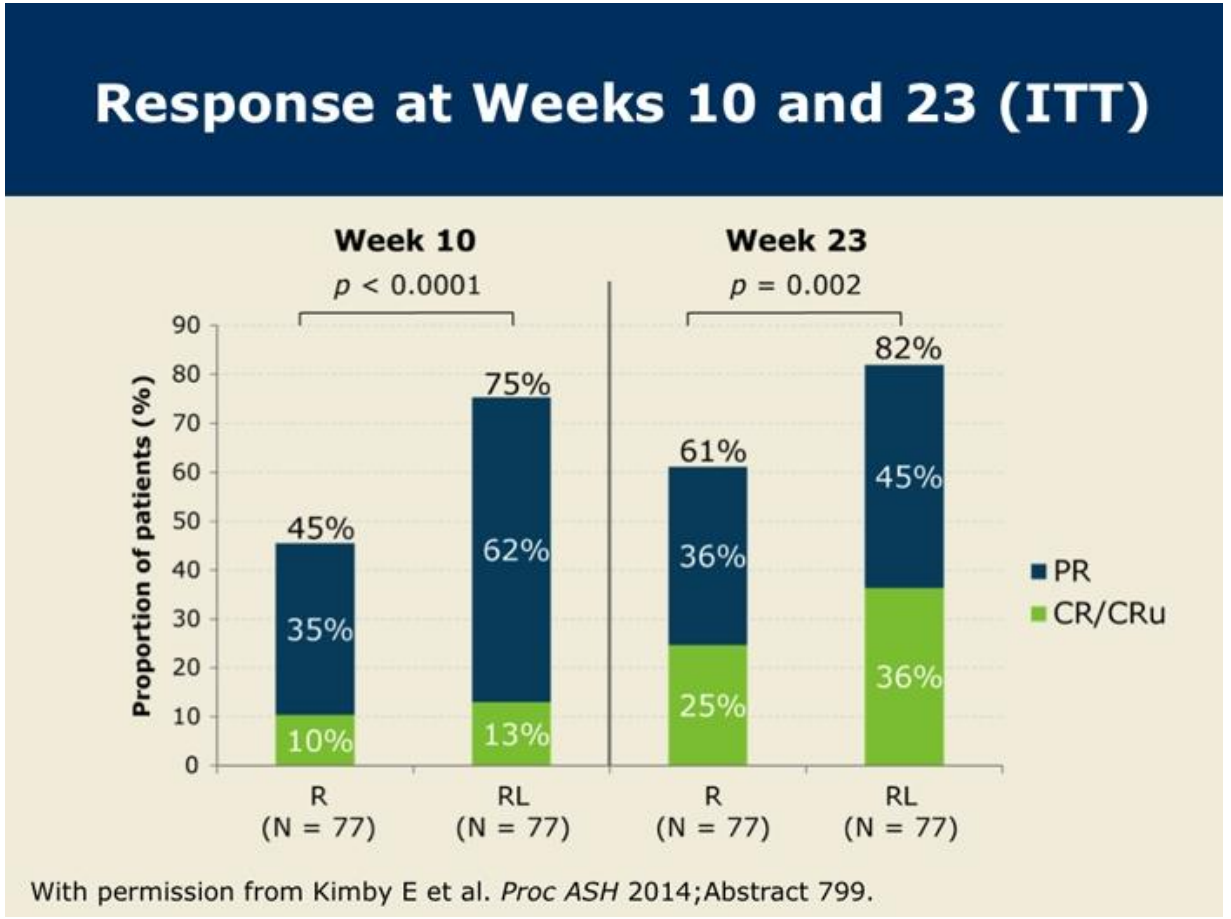
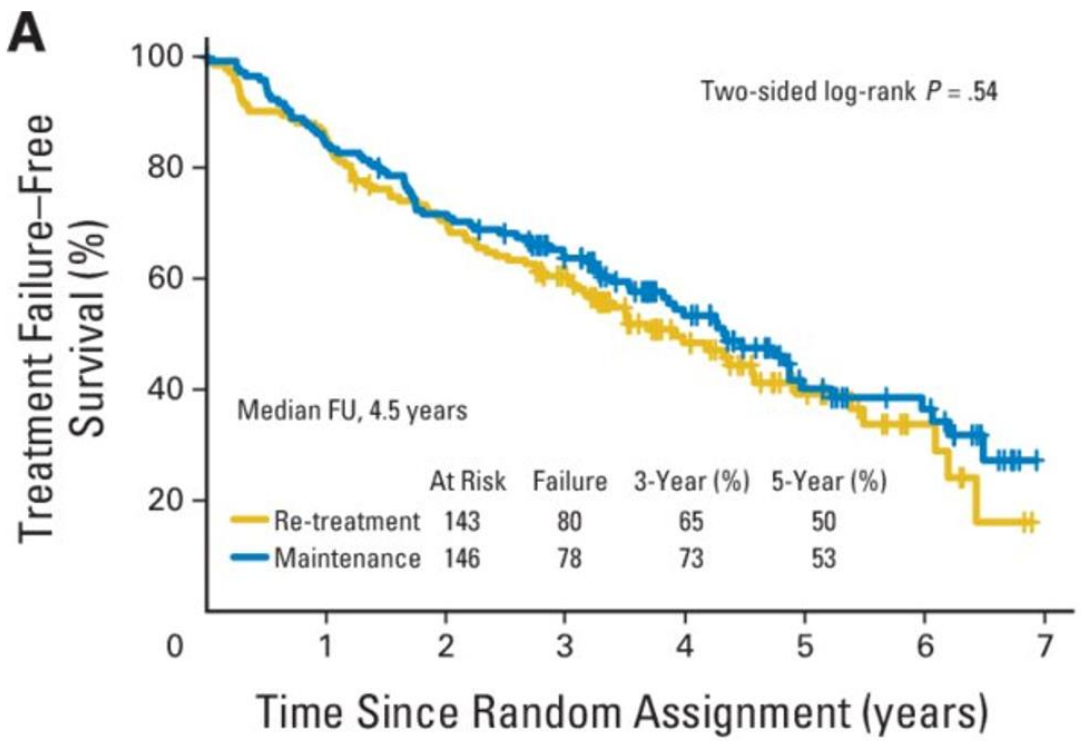
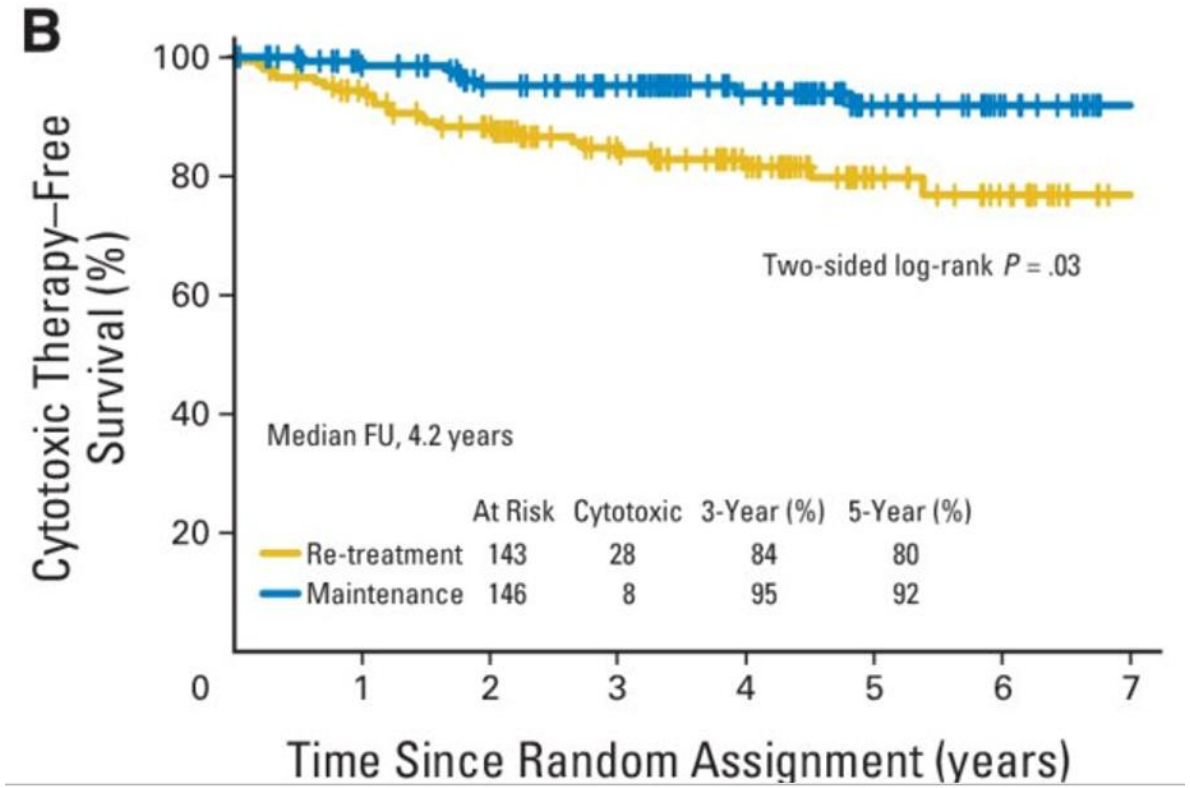

A Complement-mediated cytotoxicity
C3
C3b
Complement receptor
NK cell
Rituximab
CD20
MAC
C Direct lysis
B cell
B FcγR/CR-mediated opsonic phagocytosis or ADCC
Macrophage
FcγR

# Rituximab monotherapie in FL 1994-2014 : de controle groep

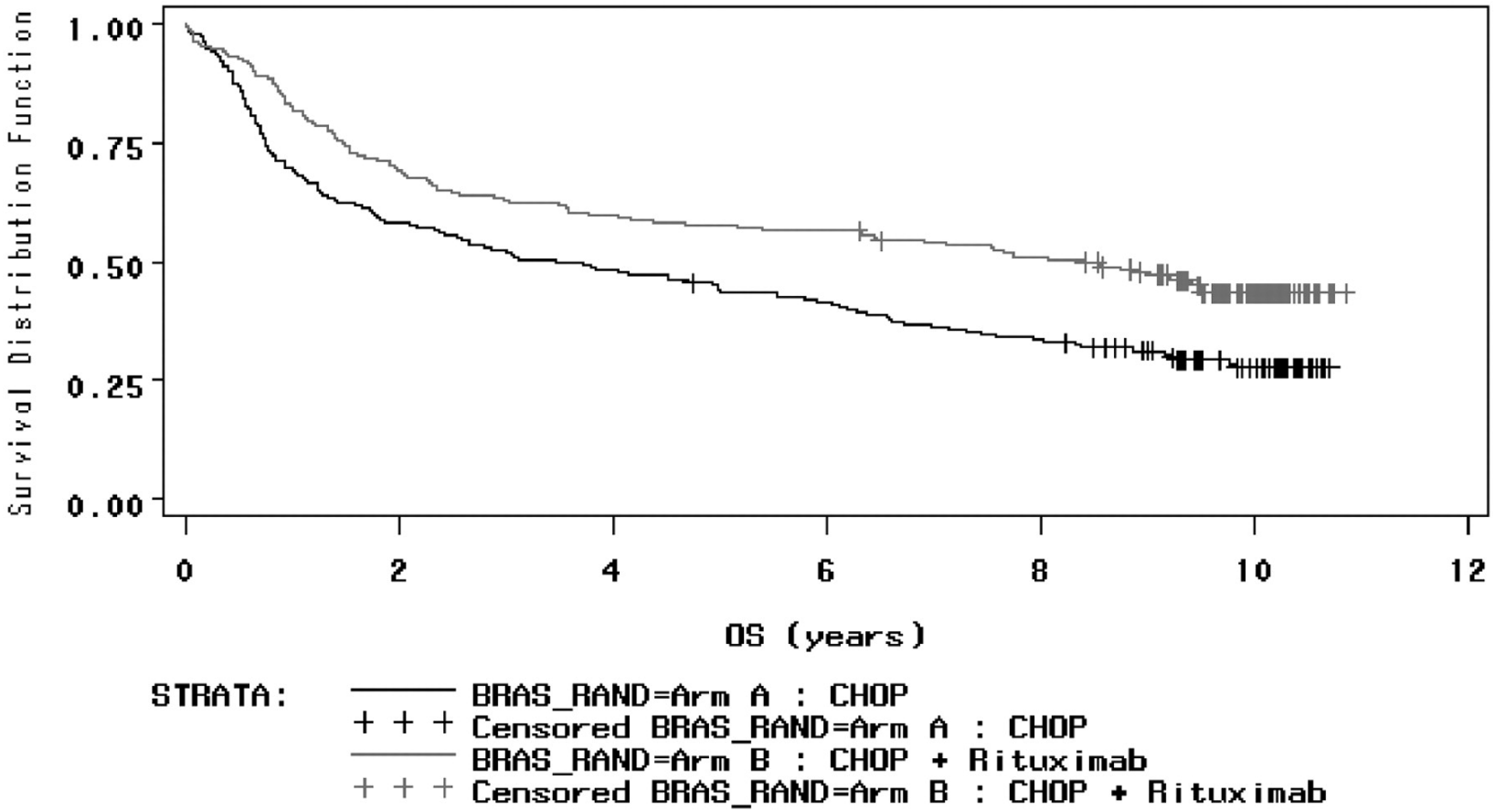


Stelt rituximab monotherapie chemotherapie uit in FL ? (SWOG-studie)



# DLBCL : Overall survival in patients treated with CHOP and R-CHOP(10 years FU)



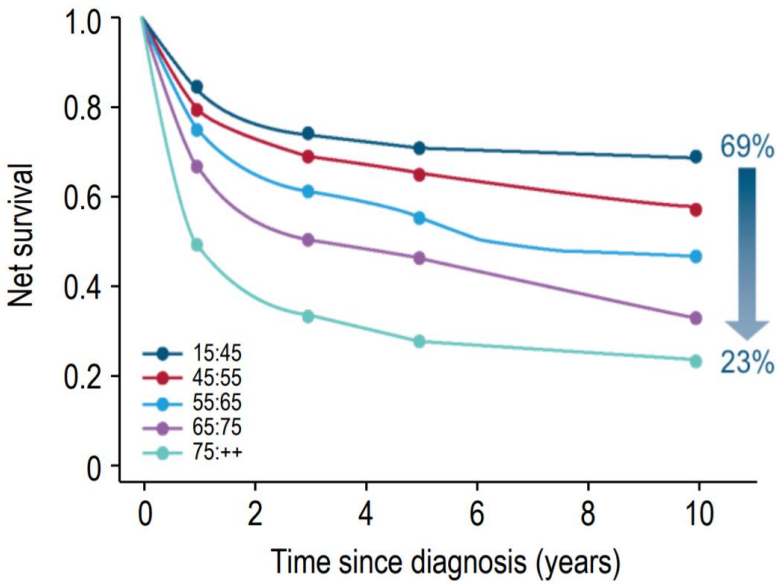

*Coiffier, B. et al. Blood 2010;116:2040-2045*

# DLBCL PROGNOSIS

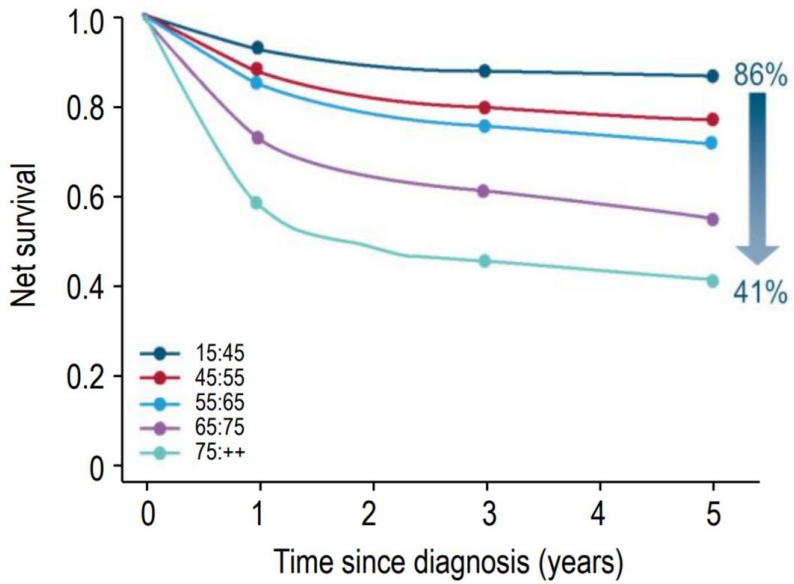
Overall Survival according to age and time period

Events occur early….

**1989–2007**[1]




**2005–2010**[2]





1. Monnereau A, *et al.,* Survie des personnes atteintes de cancer en France 1989-2007. Lymphomes diffus à grandes cellules. Études à partir des registres des cancers du réseau FRANCIM.
2. Monnereau A, *et al.,* Lymphome diffus à grandes cellules B. Available on invs.santepubliquefrance.fr

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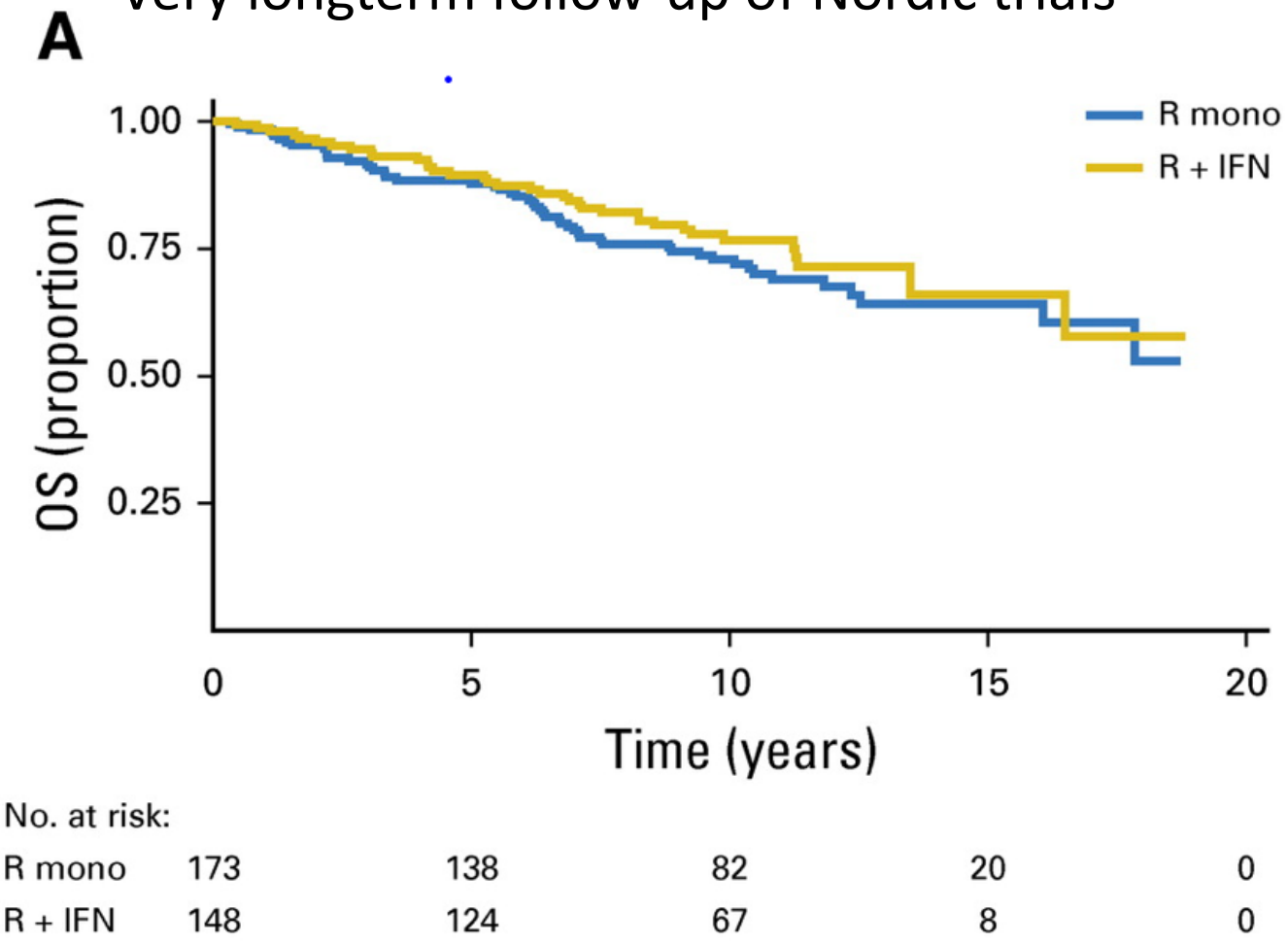
# Very longterm follow-up of Nordic trials




Published in: Sandra Lockmer; Bjørn Østenstad; Hans Hagberg; Harald Holte; Ann-Sofie Johansson; Björn Engelbrekt Wahlin; Karin Fahl Wader; Chloé Beate Steen; Peter Meyer; Martin Maisenhølder; Karin Ekström Smedby; Peter Brown; Eva Kimby; *Journal of Clinical Oncology* 2018 363315-3323.
DOI: 10.1200/JCO.18.00262

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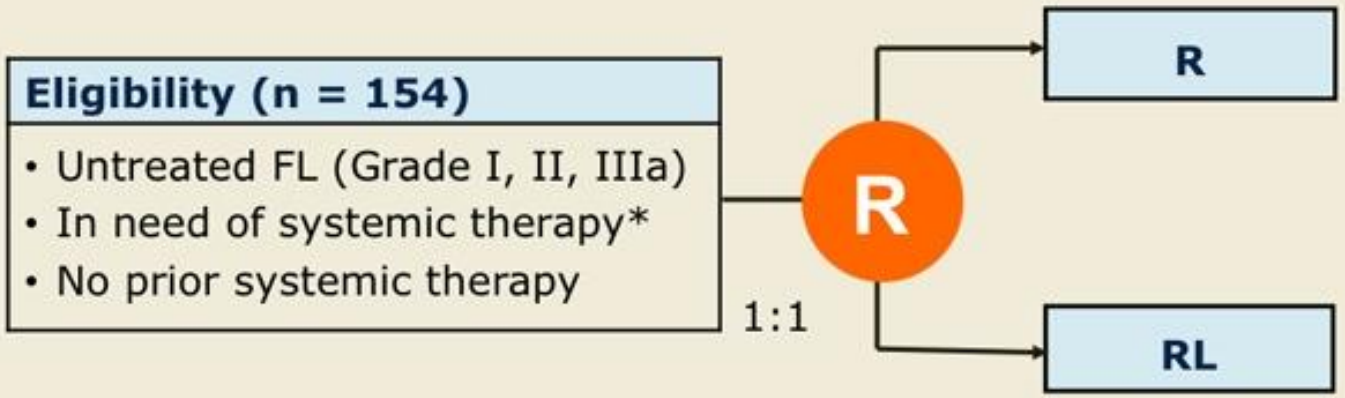
# De evolutie naar non-chemo in FL

## Phase II SAKK 35/10 Design




R: 375 mg/m$^2$, IV, d1, wk 1, 2, 3, 4, 12, 13, 14 and 15

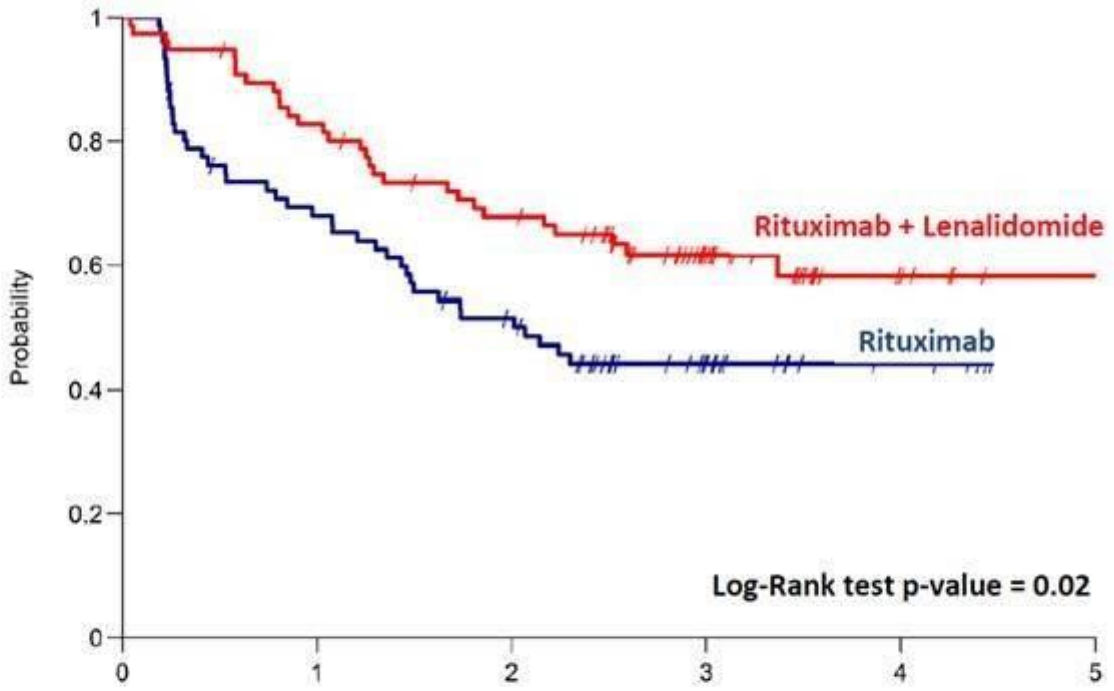
L: 15 mg, PO, 14 d before first R dose, continuously until 14 d after last R dose

- **Primary endpoint:** Complete response rate (CR/unconfirmed CR) at week 23

* At least 1 of the following: symptomatic enlarged lymph node, spleen or other FL manifestations, clinically significant progression over ≥6 mo, bulky disease ≥6 cm in long diameter, clinically significant progressive anemia/thrombocytopenia due to FL, B symptoms

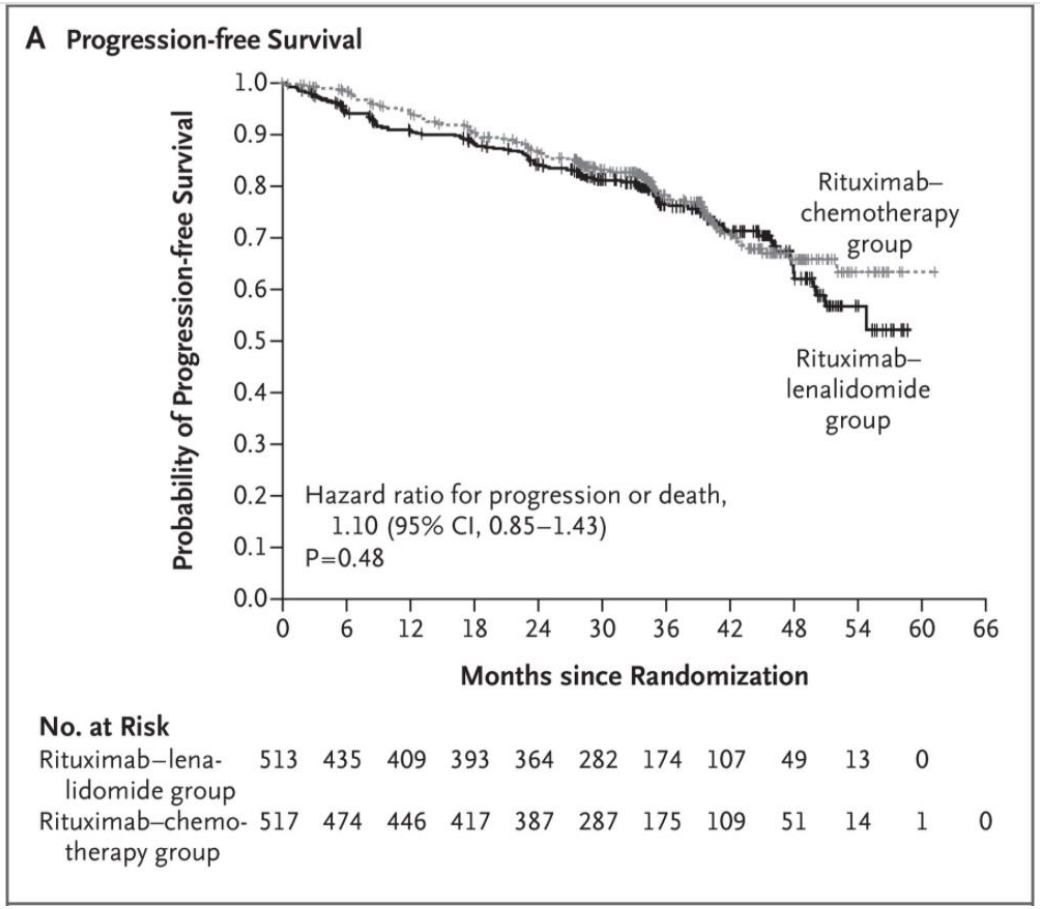
Kimby E et al. *Proc ASH* 2014;Abstract 799.

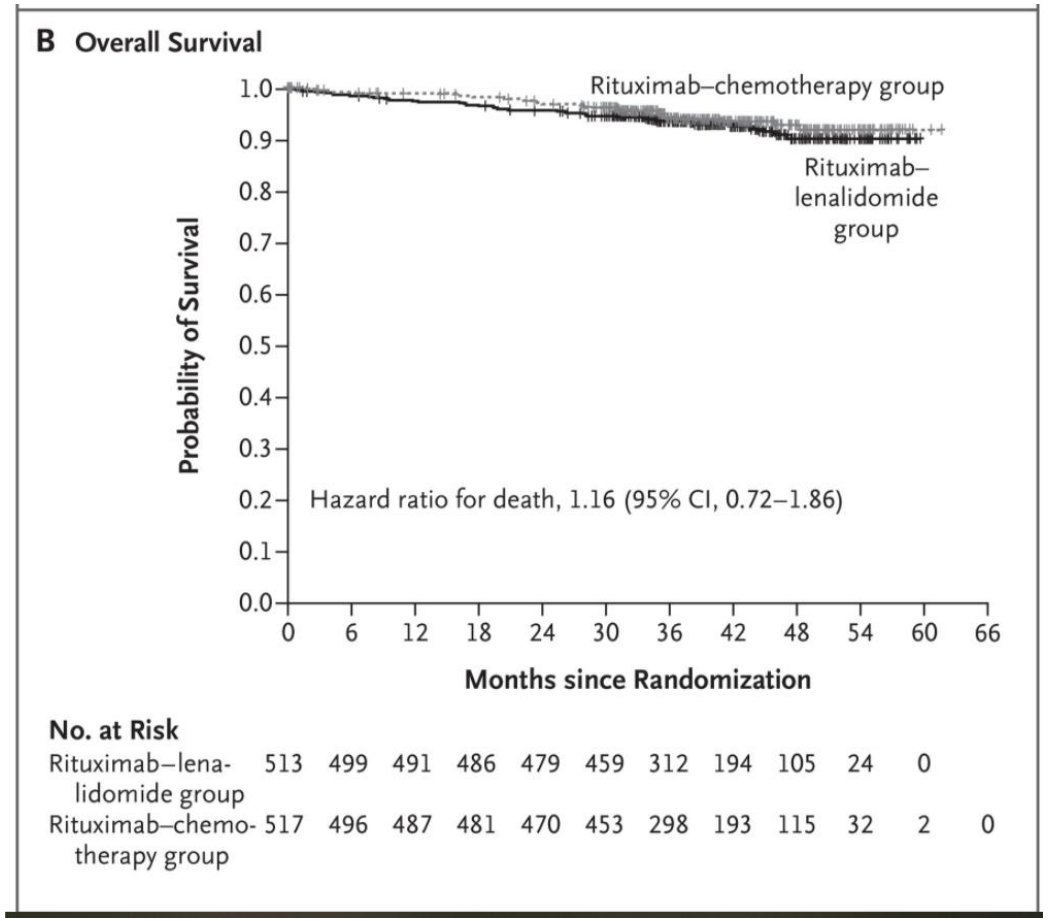
# SAKK 35/85 follow-up of 2016



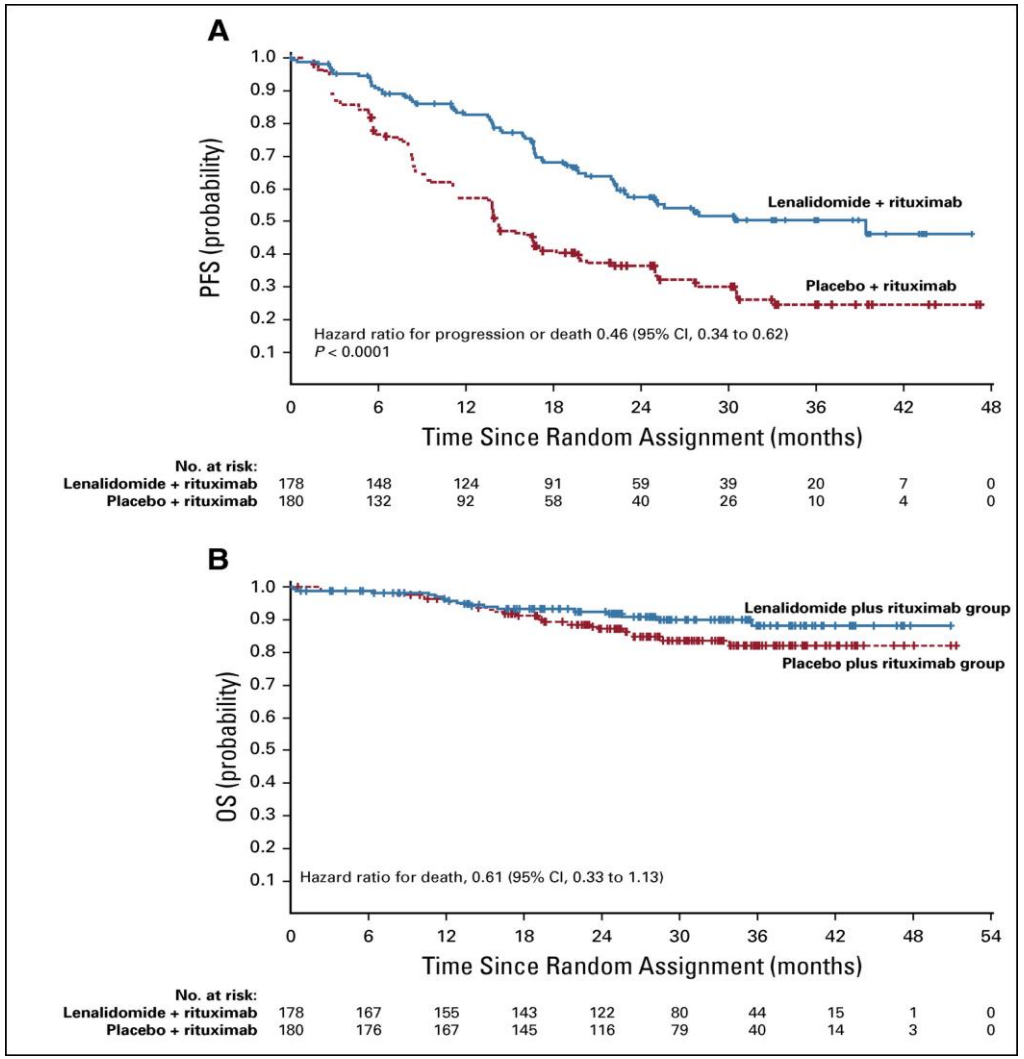

| # at risk | | | | | | |
|---|---|---|---|---|---|---|
| Rituximab | 77 | 50 | 36 | 15 | 5 | 0 |
| Rituximab + Lenalidomide | 77 | 62 | 49 | 25 | 6 | 1 |

# Relevance R-chemo versus R-lenalidomide



# Augment trial : lenalidomide-rituximab in relapse indolent en FL




Published in: John P. Leonard; Marek Trneny; Koji Izutsu; Nathan H. Fowler; Xiaonan Hong; Jun Zhu; Huilai Zhang; Fritz Offner; Adriana Scheliga; Grzegorz S. Nowakowski; Antonio Pinto; Francesca Re; Laura Maria Fogliatto; Phillip Scheinberg; Ian W. Flinn; Claudia Moreira; José Cabeçadas; David Liu; Stacey Kalambakas; Pierre Fustier; Chengqing Wu; John G. Gribben; *Journal of Clinical Oncology* 2019 371188-1199.
DOI: 10.1200/JCO.19.00010

# De opkomst van non-chemotherapie behandelingen : wat heeft gewerkt ?

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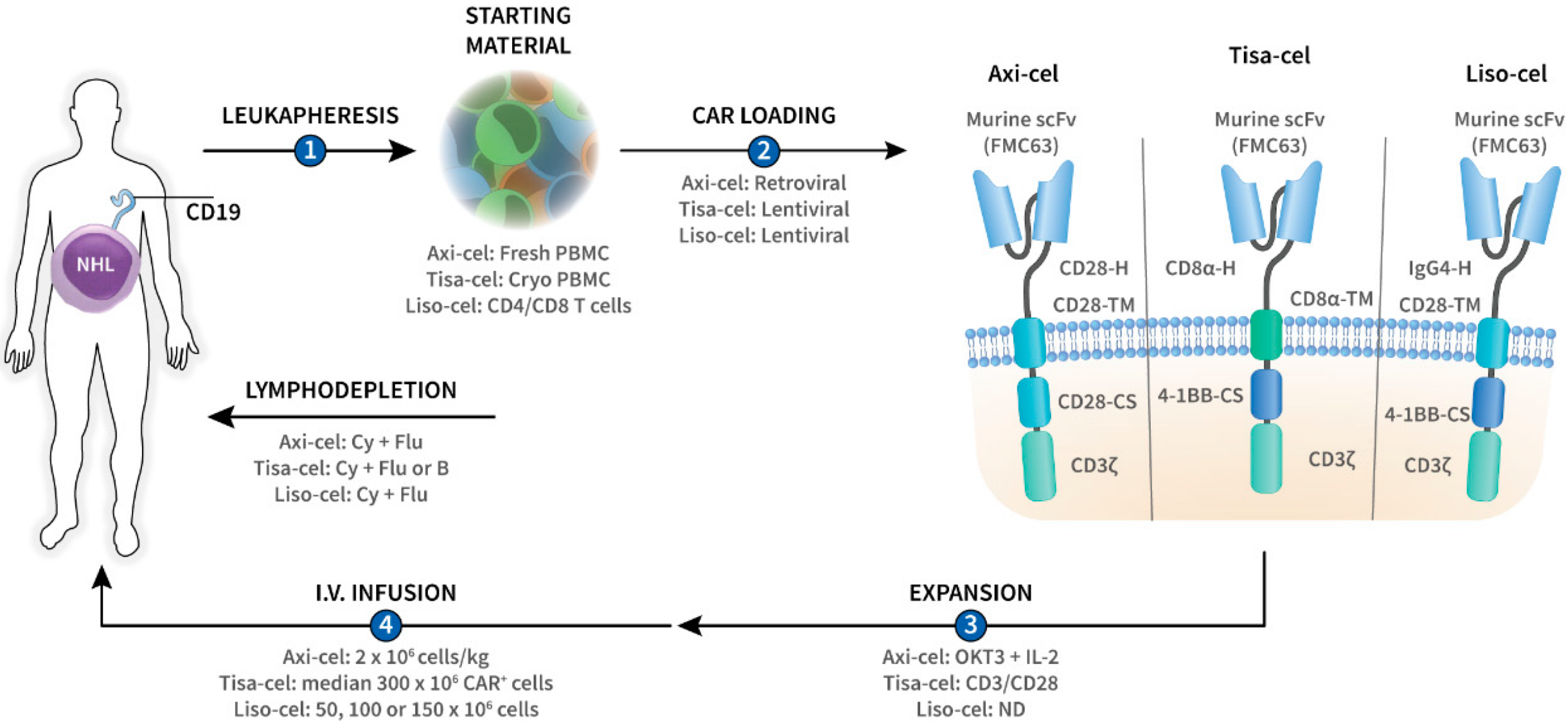
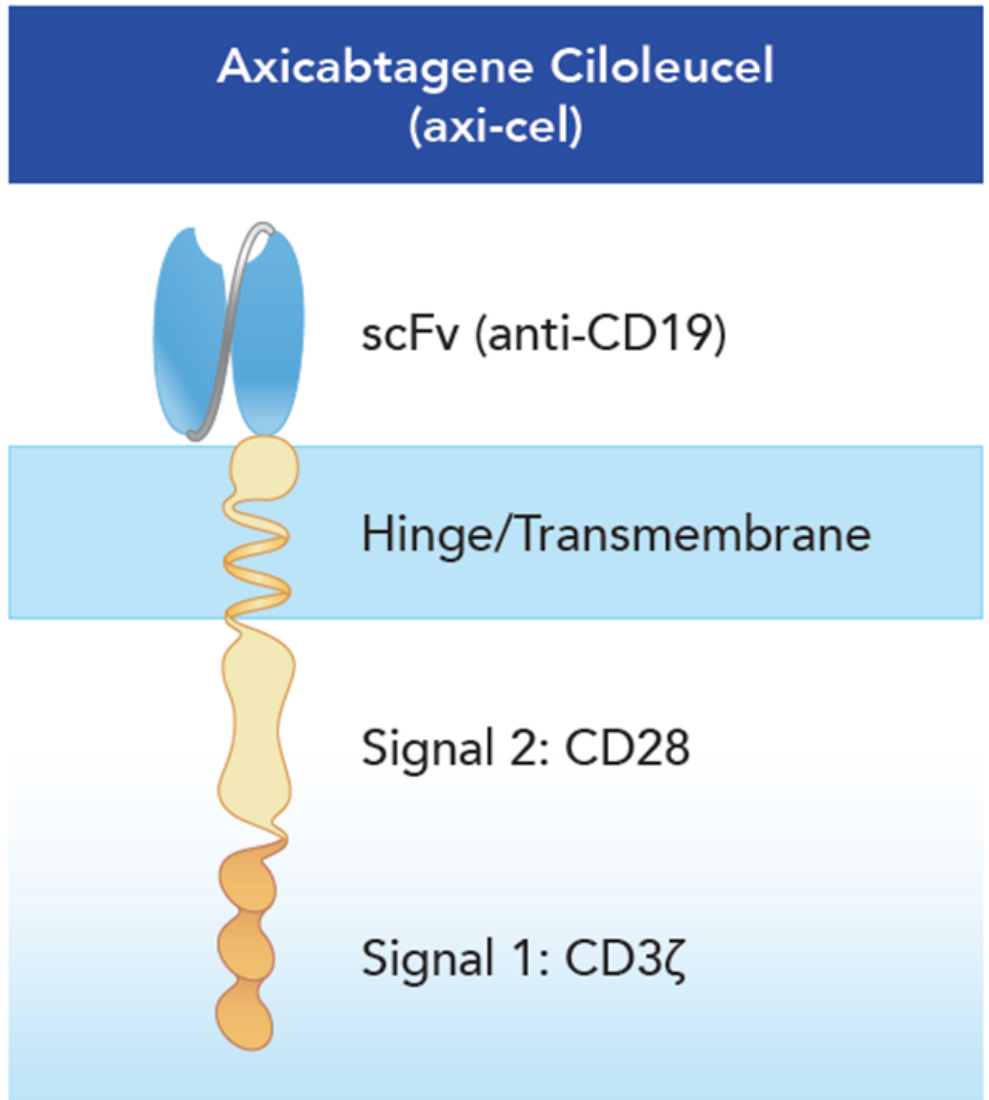
# De opkomst van non-chemotherapie behandelingen : wat heeft niet gewerkt in NHL ?

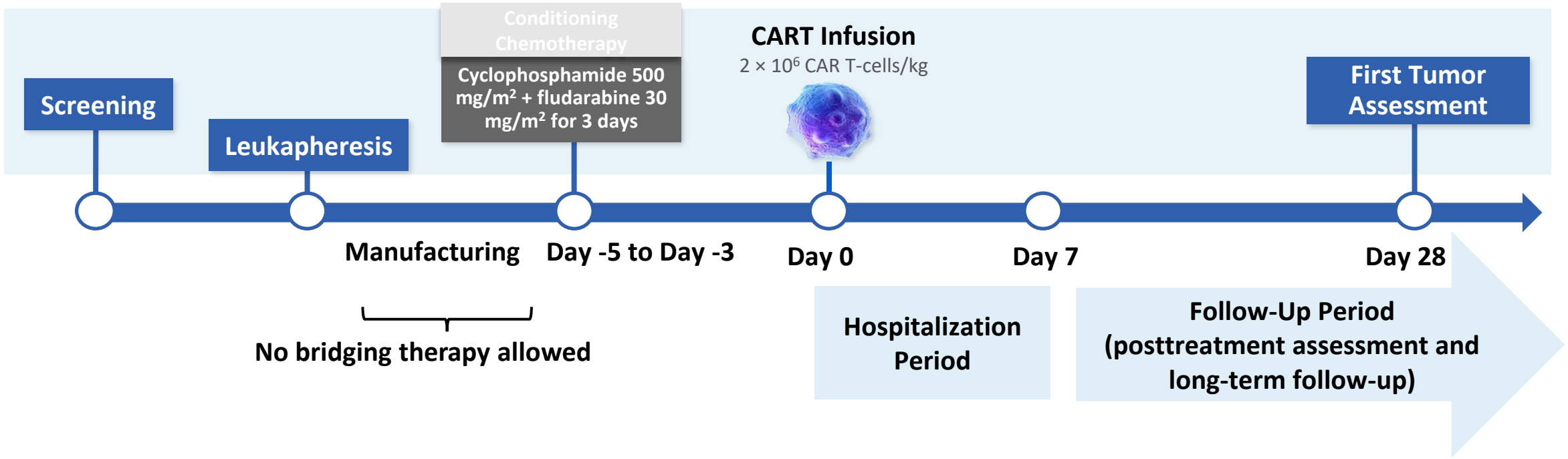
- Interferon, cytokines, LAK en TIL 1980 : de gaspedaal van het immuun stelsel :
- Monoclonale antilichamen (Moabs) 1995
- Immunochemotherapie 1995-2005 G-CHOP in DLBCL, A-CHOP ,G-CHOP in FL
- Targeted treatment 2000-heden bortezomib, PI-3K inh, ibrutinib in DLBCL, R-ibrutinib in FL
- Immuun modulatoren (Imid's) 2005-heden
- Combinatie Moab-Imid 2015-heden R-CHOP plus Imid of TT in DLBCL
- Checkpoint-inhibitoren : loslaten van de handrem van het immuunstelsel, goede resultaten in HL, PMBCL, CNS lymfoom, werkt niet in DLBCL
- Optimalisatie van Moabs : immunotoxines, bispecifieke Ab en CART

# De opkomst van non-chemotherapie behandelingen

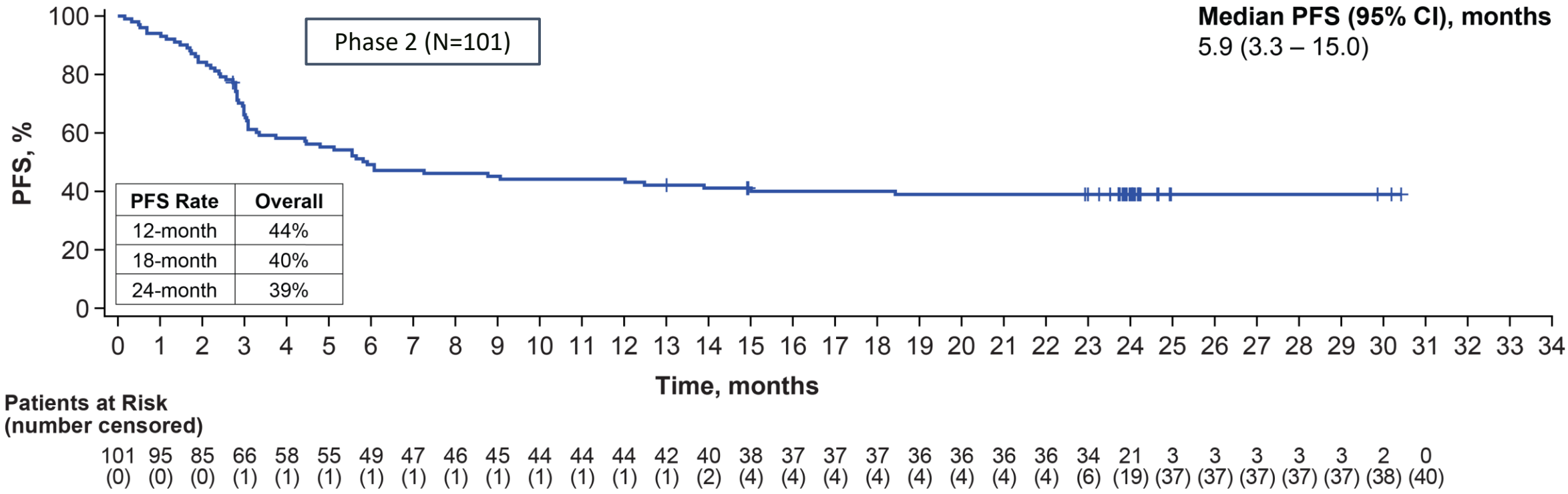
- Combinatie Moab-Imid 2010-heden
- Checkpoint-inhibitoren : loslaten van de handrem van het immuunstelsel
- Optimalisatie van Moabs :
- Immunotoxines
- Bispecifieke Ab
- CART


STARTING MATERIAL
LEUKAPHERESIS
1
CD19
NHL
Axi-cel: Fresh PBMC
Tisa-cel: Cryo PBMC
Liso-cel: CD4/CD8 T cells
CAR LOADING
2
Axi-cel: Retroviral
Tisa-cel: Lentiviral
Liso-cel: Lentiviral
Axi-cel
Tisa-cel
Liso-cel
Murine scFv (FMC63)
Murine scFv (FMC63)
Murine scFv (FMC63)
CD28-H
CD28-TM
CD28-CS
CD3ζ
CD8α-H
CD8α-TM
4-1BB-CS
CD3ζ
IgG4-H
CD28-TM
4-1BB-CS
CD3ζ
LYMPHODEPLETION
Axi-cel: Cy + Flu
Tisa-cel: Cy + Flu or B
Liso-cel: Cy + Flu
I.V. INFUSION
4
Axi-cel: 2 x 10⁶ cells/kg
Tisa-cel: median 300 x 10⁶ CAR⁺ cells
Liso-cel: 50, 100 or 150 x 10⁶ cells
EXPANSION
3
Axi-cel: OKT3 + IL-2
Tisa-cel: CD3/CD28
Liso-cel: ND


Axicabtagene Ciloleucel
(axi-cel)
scFv (anti-CD19)
Hinge/Transmembrane
Signal 2: CD28
Signal 1: CD3ζ

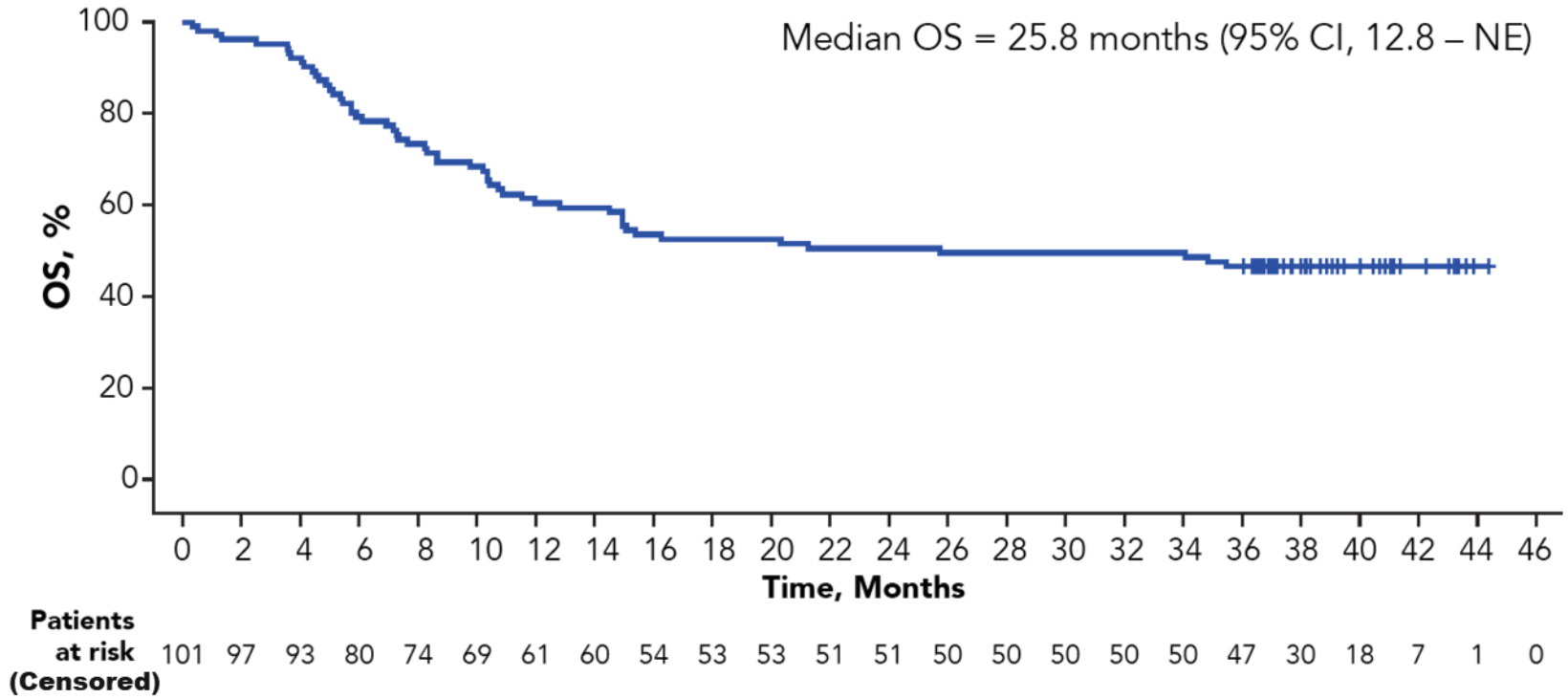

Screening
Leukapheresis
Conditioning Chemotherapy
Cyclophosphamide 500 mg/m² + fludarabine 30 mg/m² for 3 days
CART Infusion
2 × 10⁶ CAR T-cells/kg
First Tumor Assessment
Manufacturing
Day -5 to Day -3
Day 0
Day 7
Day 28
No bridging therapy allowed
Hospitalization Period
Follow-Up Period (posttreatment assessment and long-term follow-up)

# PFS by Investigator Assessment (Yescarta, Zuma trial)




The 6-month plateau was largely maintained, with only 10 patients progressing beyond the 6-month follow-up

# With a Median of 39.1 Months Follow-up, Median Overall Survival[a] was 25.8 Months

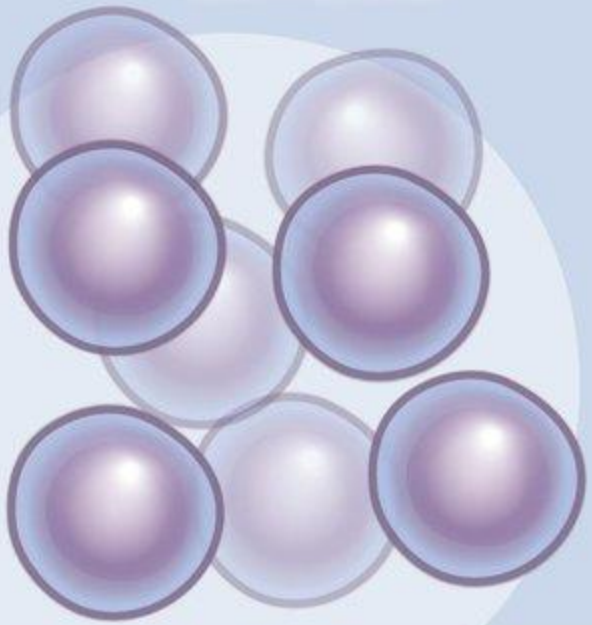



- With 39.1 months median follow-up:
  - 25.8 months median OS
  - 47% 3-year OS rate

# CAR T-Cell Therapy for Refractory Large B-Cell Lymphoma

MULTICENTER, PHASE 2 CLINICAL TRIAL

## CAR T-cell Therapy
N=101



**82% Objective response**

**54% Complete response**

(20% Objective response in historical controls)

**52% Overall survival at 18 months**

**96 Patients**
Had grade ≥3 adverse events:

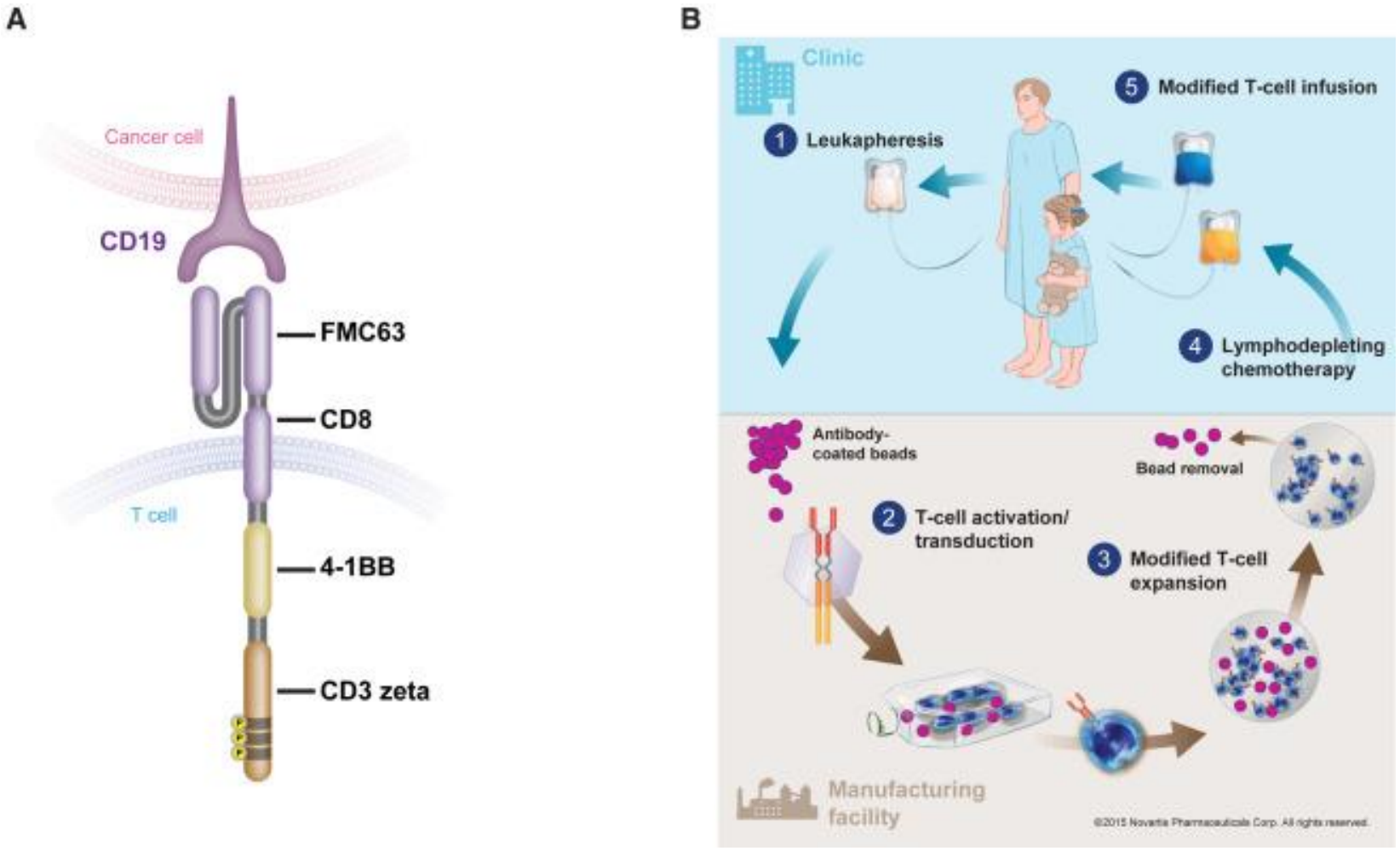
**13 Patients**
Had cytokine release syndrome (including 2 deaths)

**28 Patients**
Had neurologic events

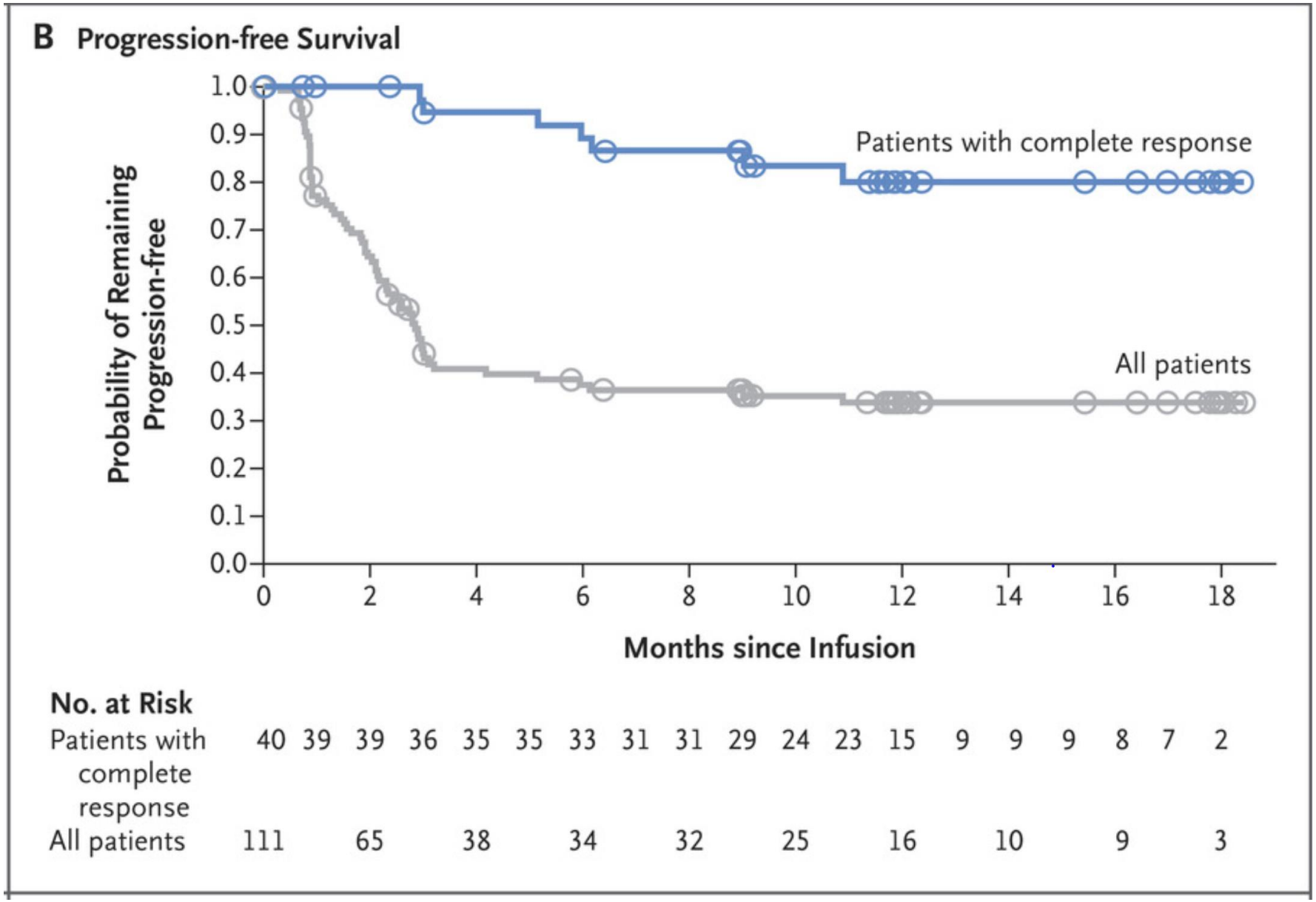
The NEW ENGLAND JOURNAL of MEDICINE

Neelapu et al. 2017

# Tisa-cel, Kymriah

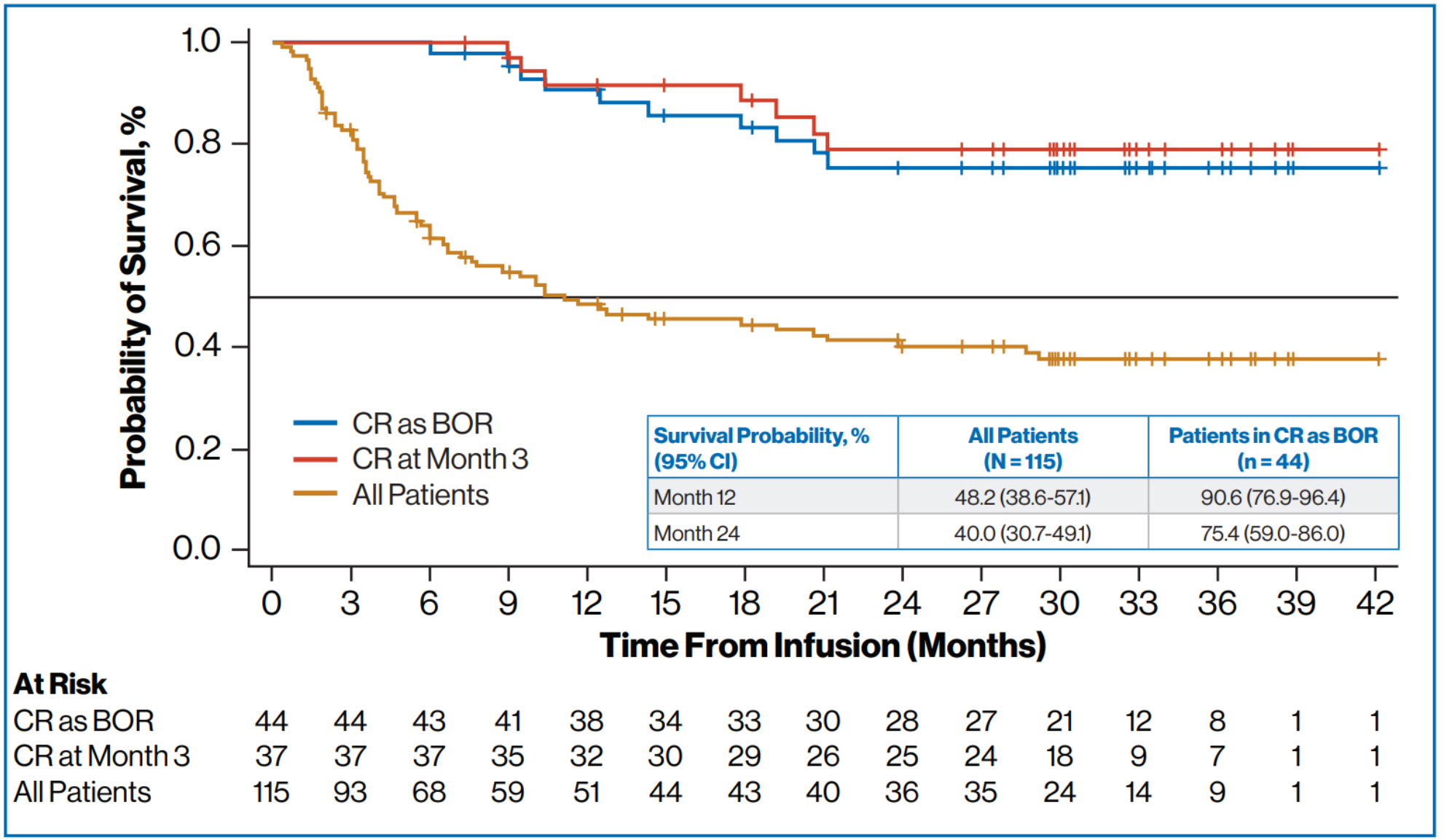


# Kymriah PFS


B Progression-free Survival
Probability of Remaining Progression-free
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
10
12
14
16
18
Months since Infusion
Patients with complete response
All patients
No. at Risk
Patients with complete response 40 39 39 36 35 35 33 31 31 29 24 23 15 9 9 9 8 7 2
All patients 111 65 38 34 32 25 16 10 9 3

Juliet trial Kymriah

**Figure 2. Overall Survival for Patients in CR and All Patients in the Full Cohort**



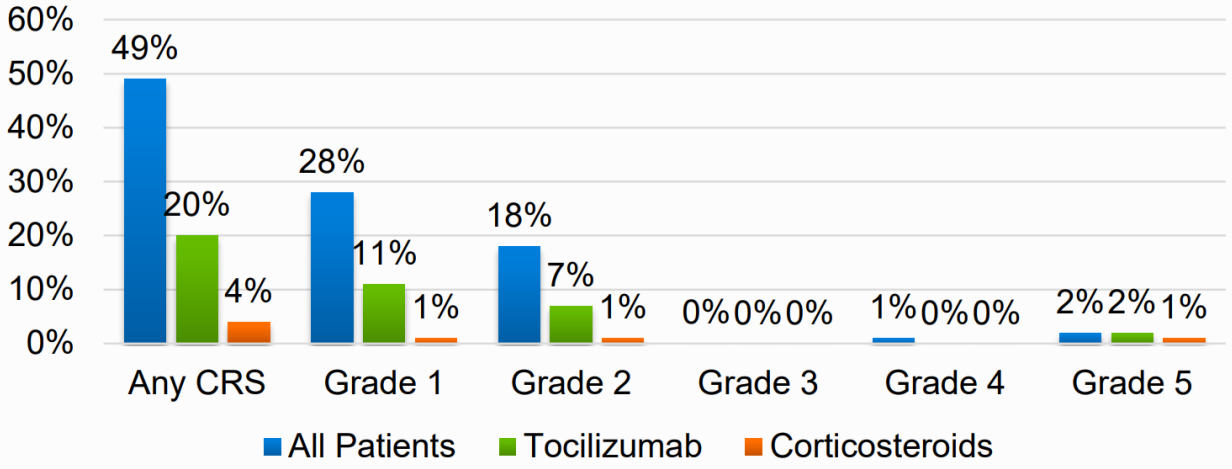

| Survival Probability, % (95% CI) | All Patients (N = 115) | Patients in CR as BOR (n = 44) |
|---|---|---|
| Month 12 | 48.2 (38.6-57.1) | 90.6 (76.9-96.4) |
| Month 24 | 40.0 (30.7-49.1) | 75.4 (59.0-86.0) |

**At Risk**

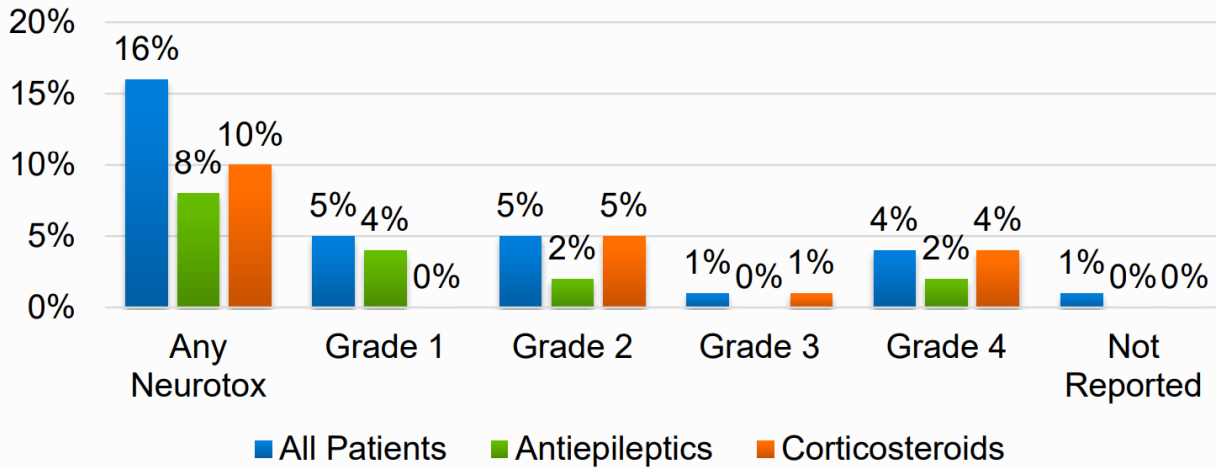
| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CR as BOR | 44 | 44 | 43 | 41 | 38 | 34 | 33 | 30 | 28 | 27 | 21 | 12 | 8 | 1 | 1 |
| CR at Month 3 | 37 | 37 | 37 | 35 | 32 | 30 | 29 | 26 | 25 | 24 | 18 | 9 | 7 | 1 | 1 |
| All Patients | 115 | 93 | 68 | 59 | 51 | 44 | 43 | 40 | 36 | 35 | 24 | 14 | 9 | 1 | 1 |

# Safety

## Frequency of CRS by Grade (ASTCT scale)




## Frequency of Neurotoxicity by Grade (ICANS scale)




| Timing | CRS | Neurotoxicity |
|---|---|---|
| Median time to onset in days (range) | 4 (2-14) | 8 (4-27) |
| Median duration in days (range) | 5 (4-8) | 14 (5-25) |

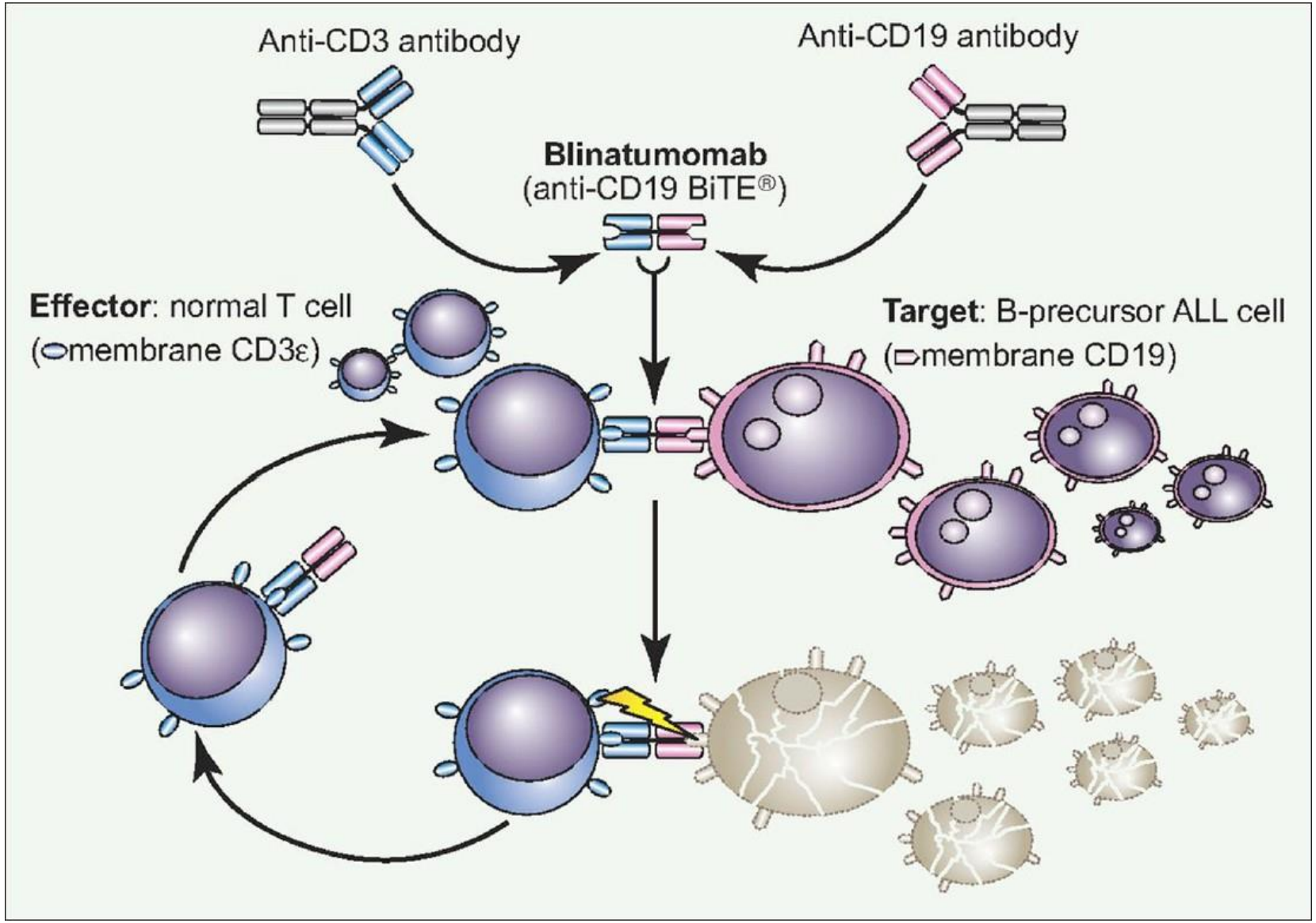
# Toekomst CART

- Combinatie met anti-PD1
- Combinatie lenalidomide ?
- Combinatie van targets
- Technische verbetering van de CART : overlevingsduur, type T cellen
- NK cellen ?
- Combinatie ibrutinib : verbetert de T cellen waarvan CART worden gemaakt
- Preventie CRS, neurotoxiciteit

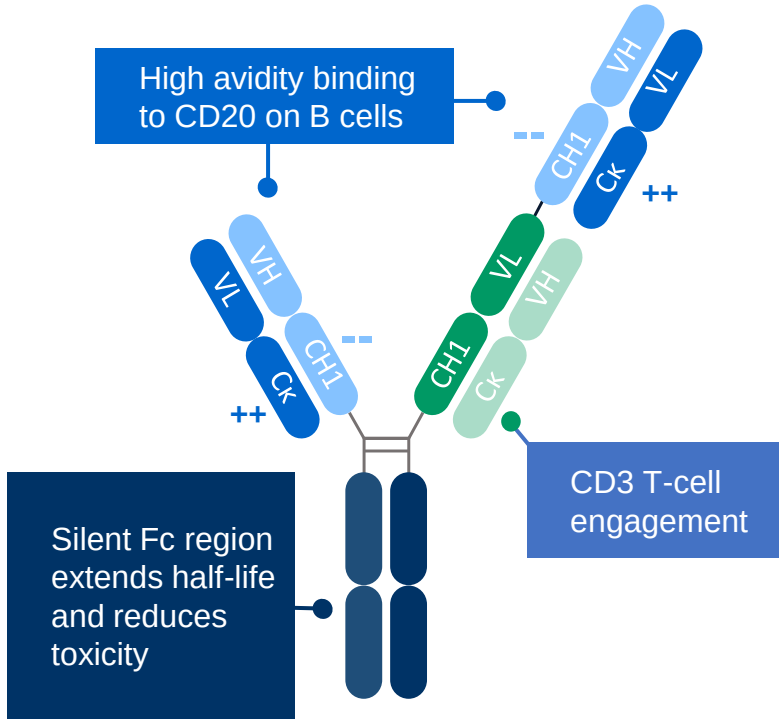
# De opkomst van non-chemotherapie behandelingen

- Combinatie Moab-Imid 2010-heden
- Checkpoint-inhibitoren : loslaten van de handrem van het immuunstelsel
- Optimalisatie van Moabs :
- Immunotoxines
- Bispecifieke Ab
- CART

# Bispecifieke antilichamen



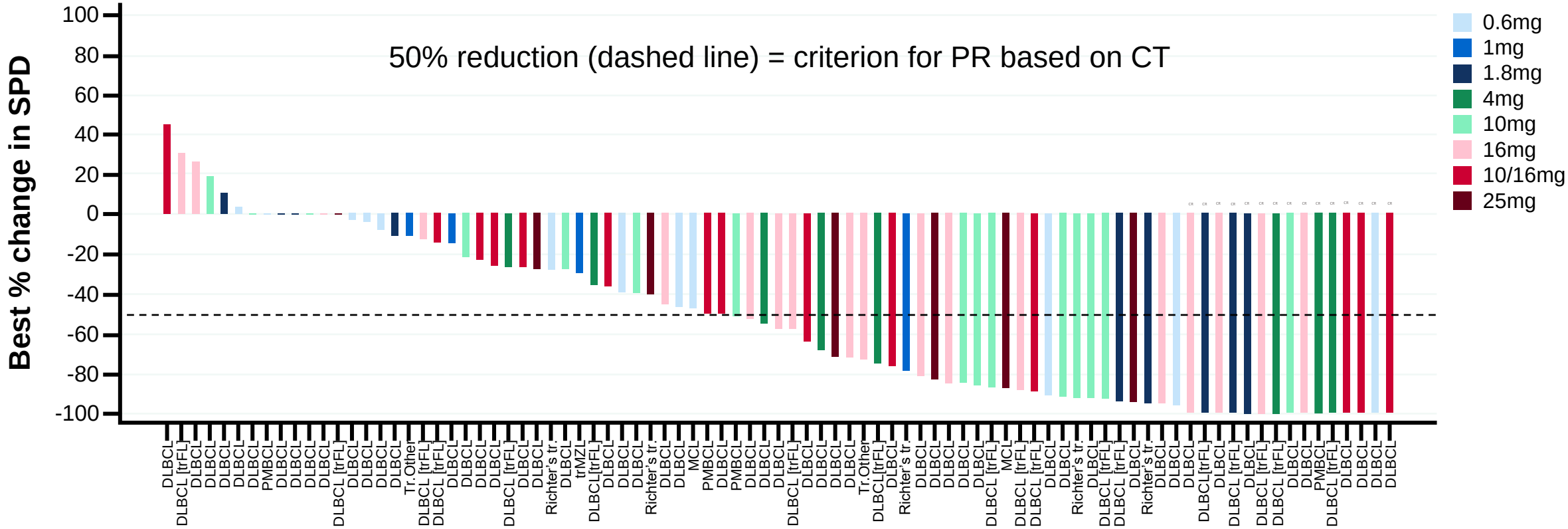
# Glofitamab




1. Crump M, et al. Blood 2017;130:1800–8
2. MacDonald D, et al. Curr Oncol 2016; 23: 407–17
3. Bacac M, et al. Clin Cancer Res 2018;24:4785–97
4. Morschhauser F, et al. 61st ASH Annual Meeting & Exposition, December 7–10, 2019 [P-1584]

CH1, constant heavy 1; CK, kappa light chain; Fc, fragment crystallisable; VH, variable heavy; VL, variable light

# Antitumor activity in aggressive non-Hodgkin lymphoma*



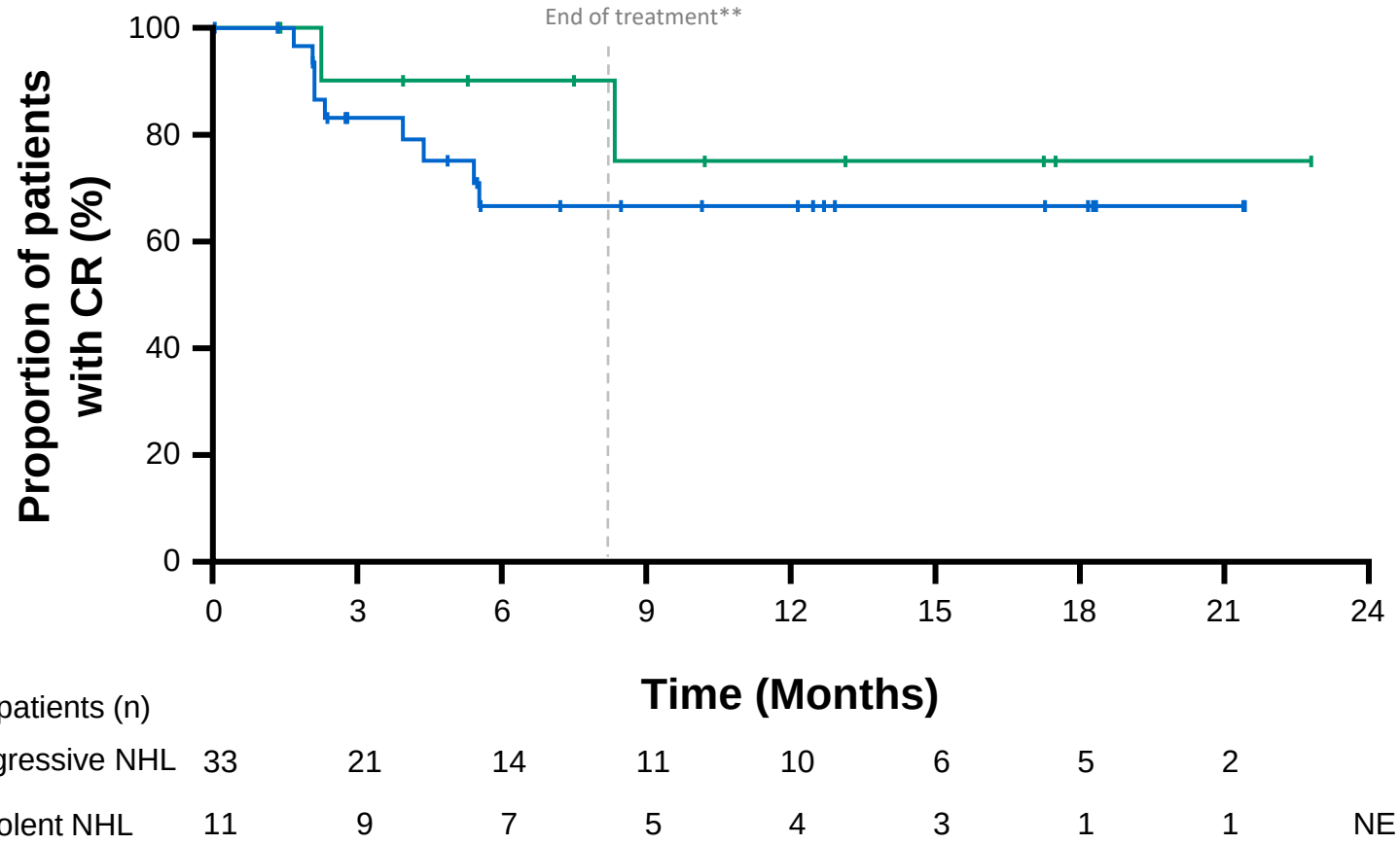

Clinical cut-off date: 17 April 2020. n.b. Patients enrolled in the 10/16mg cohort after September 2019 are not included

*≥0.6mg cohorts only; assessed by computed tomography (CT) and Lugano criteria.[1] Aggressive NHL includes DLBCL, transformed FL, PMBCL, MCL, transformed MZL and Richter's transformation

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; PR, partial response; Richter's transf, Richter's transformation; SPD, sum of the longest diameters; tr, transformed

1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68

# Durable complete responses* were seen in patients with indolent and aggressive NHL (≥0.6mg cohorts)




Clinical cut-off date: 17 April 2020. n.b. Patients enrolled in the 10/16mg cohort after September 2019 are not included

*Best response CR; **patients received glofitamab IV Q2W for up to 12 14-day cycles or Q3W (from 10mg) for 8–12 21-day cycles;

## Aggressive NHL†

- Median follow-up (months): **10.2 (95% CI: 5.6, 17.3)**
- Median DOCR (months): **NR (95% CI: 5.5, NE)**
- 24 ongoing CRs:
  **10 CRs for >12 months**
  **14 CRs for <12 months**

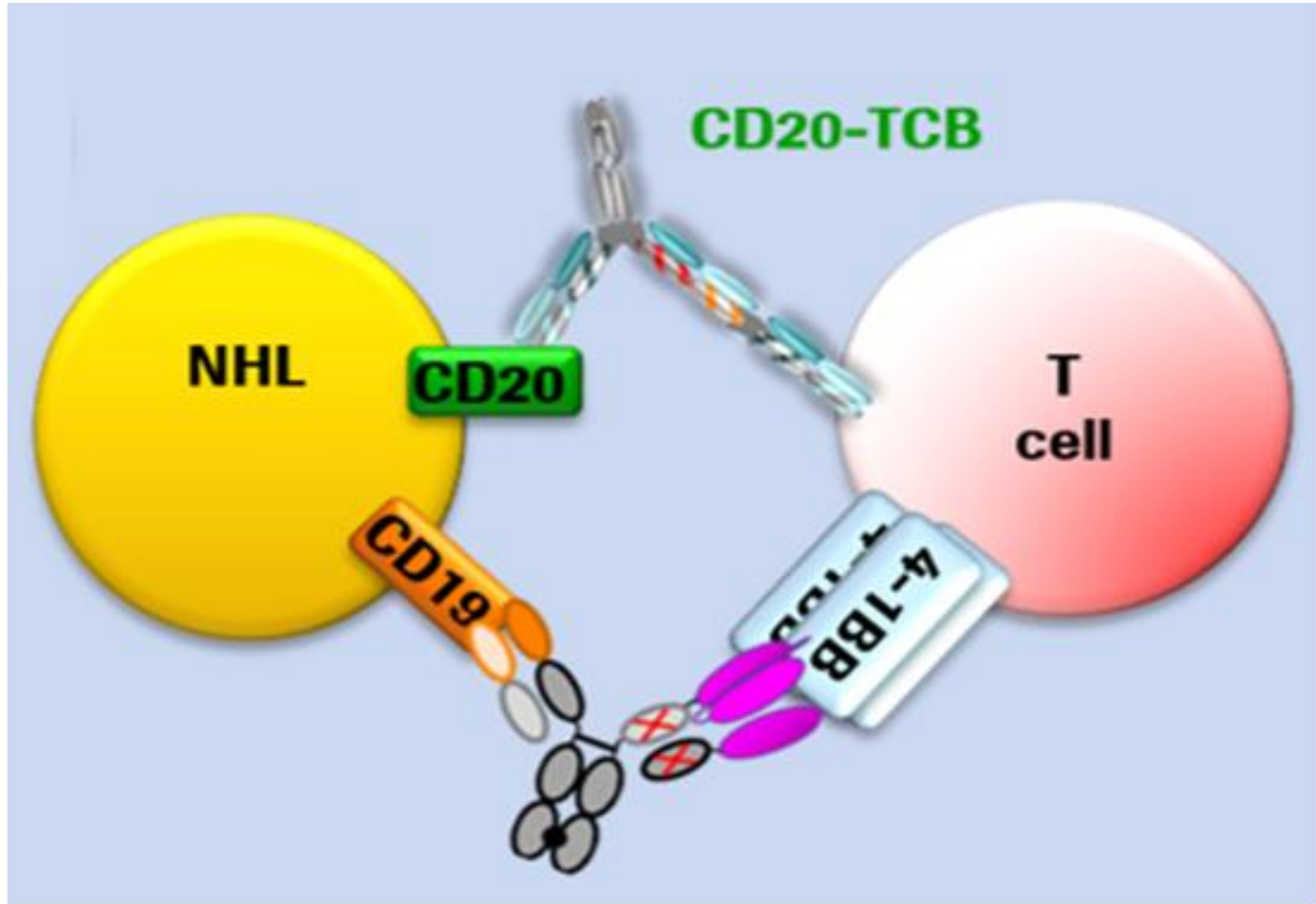
## Indolent NHL‡

- Median follow-up (months): **10.2 (95% CI: 5.3, NE)**
- Median DOCR (months): **NR (95% CI: 8.4, NE)**
- 9 ongoing CRs:
  **4 CRs >12 months**
  5 CRs <12 months

†aggressive NHL includes diffuse large B-cell lymphoma, transformed FL, primary mediastinal large B-cell lymphoma, MCL, transformed marginal zone lymphoma and Richter's transformation; ‡indolent NHL includes patients with FL Grade 1–3a or unknown Grade. CI, confidence interval; CR, complete response; DOCR, duration of complete response; FL, follicular lymphoma; MCL, mantle cell lymphoma; NE, non-estimable; NHL, non-Hodgkin lymphoma; NR, not reached

# Toekomst bispecifieke Al

- Combinatie met chemo
- Combinatie met anti-PD1
- Combinatie lenalidomide ?
- Combinatie antiCD19-4.1BB
- Combinatie van verschillende doelwitten vb CD 22, CD 19, CD 20

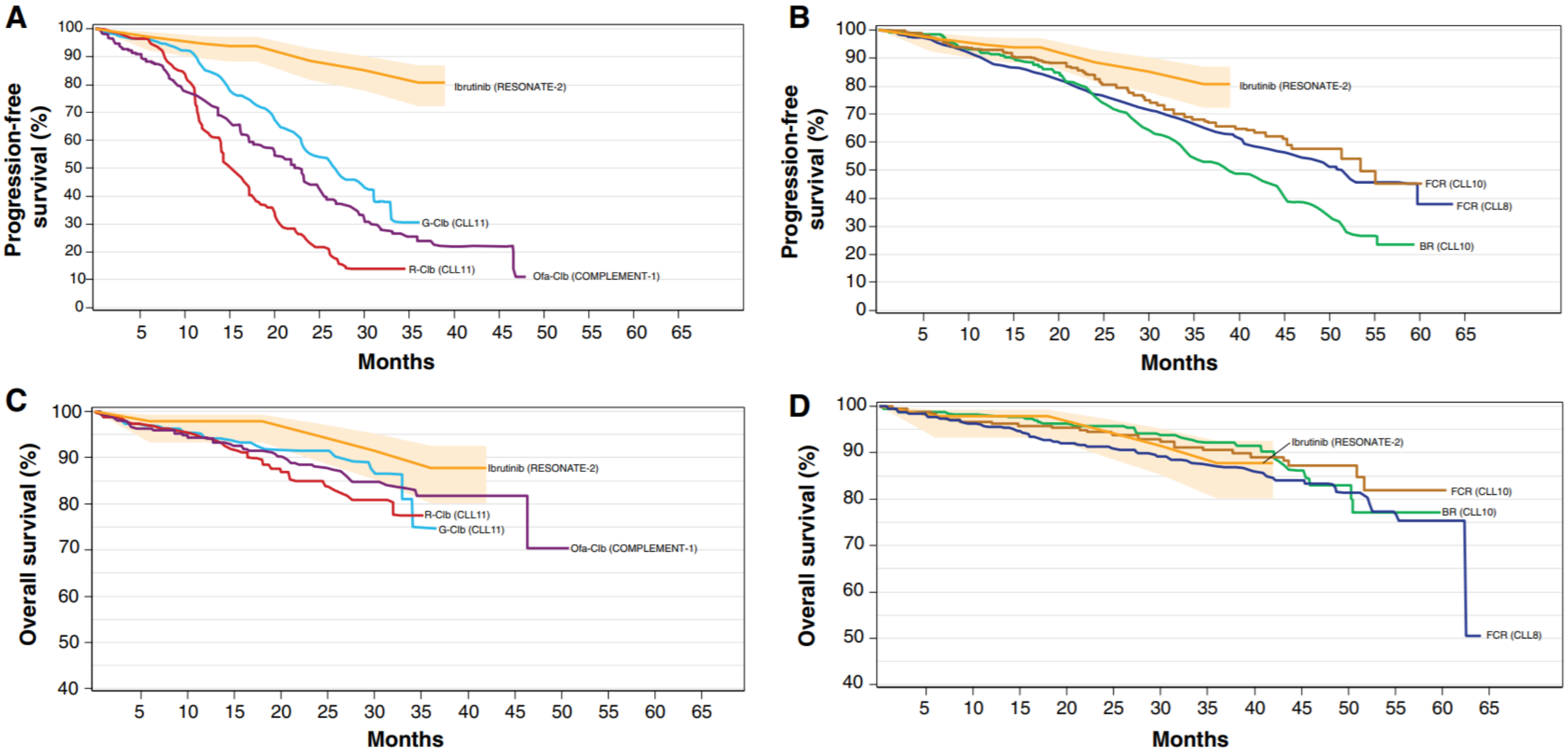

CD20-TCB
NHL
CD20
T
cell
CD19
4-1BB

# Evolutie naar non-chemo

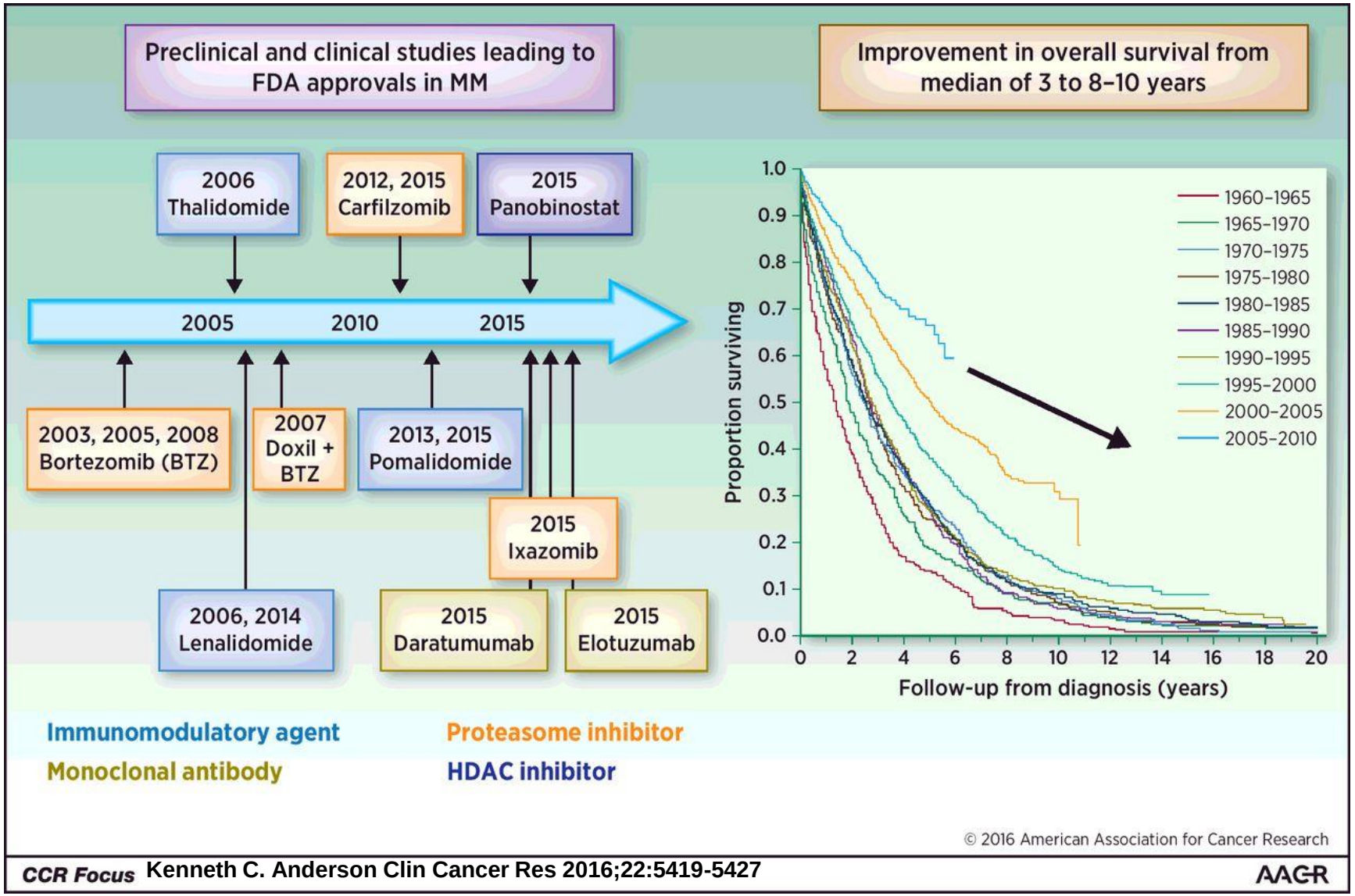
| | 1980-2000 | 2000-2010 | 2010-2020 |
|---|---|---|---|
| Hodgkin | ABVD/Rescue autoTx | ABVD/rescue autoTx | ABVD/rescue autoTx |
| | | Adcetris (immunotoxine) | Adcetris |
| | | | Nivolumab/ Pembrolizumab |
| Folliculair NHL | CHOP/CVP | R-CHOP/R-CVP/R-Benda | R-CHOP/R/G-benda |
| | | | R-lenalidomide |
| | | R maintenance | R-ibrutinib/R-idelalisib |
| Diffuus grootecellig NHL | CHOP/rescue autoTx | R-CHOP/rescue autoTx | R-CHOP/rescue autoTx |
| | | | CART/Bispecific |

# Evolutie naar non-chemo

| | 1980-2000 | 2000-2010 | 2010-2020 |
|---|---|---|---|
| CLL | Chl-FC | RFC | ibrutinib |
| | | | R-venetoclax |
| MCL | CHOP/DHAP autoTX | R-CHOP/R-DHAP autoTx | R-CHOP/R-DHAP autoTx/maintenance R |
| | | | Ibrutinib |
| MZL | Chl/CVP | R-CVP/R-Benda | R-CVP/R-benda |
| | | R-mono | R-lenalidomide |
| | | | R-ibrutinib/R-idelalisib |
| Multipel myeloom | MP, VAD, autoTx | VTD autoTx, MPV | VTD autoTx, MPV |
| | | | DVd, DRd |
| | | | CART/Bispecific |


A
Progression-free survival (%)
Ibrutinib (RESONATE-2)
G-Clb (CLL11)
R-Clb (CLL11)
Ofa-Clb (COMPLEMENT-1)
Months
B
Progression-free survival (%)
Ibrutinib (RESONATE-2)
FCR (CLL10)
FCR (CLL8)
BR (CLL10)
Months
C
Overall survival (%)
Ibrutinib (RESONATE-2)
R-Clb (CLL11)
G-Clb (CLL11)
Ofa-Clb (COMPLEMENT-1)
Months
D
Overall survival (%)
Ibrutinib (RESONATE-2)
FCR (CLL10)
BR (CLL10)
FCR (CLL8)
Months

# Bench-to-bedside translation of novel agents in myeloma.




CCR Focus Kenneth C. Anderson Clin Cancer Res 2016;22:5419-5427