Lymfekræft og CLL

Hvad kan vi tilbyde af behandling i dag, og hvad er der udsigt til?

F.d'Amore
Hæmatologisk afd.R, ÅUH

14.April 2018

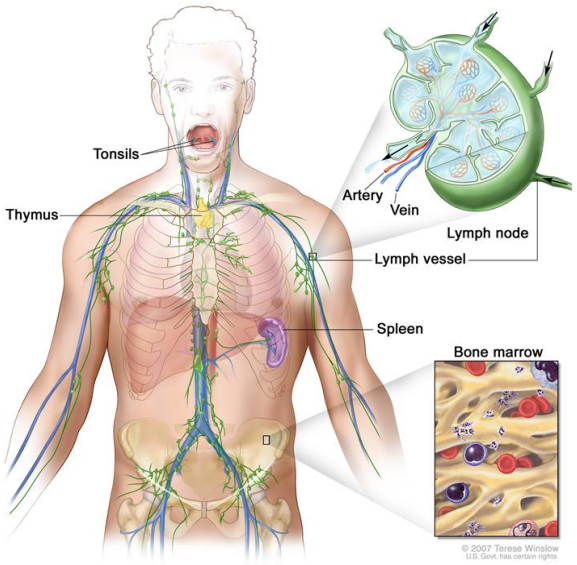
Emner

- Lymfomtyper
- Det kliniske billede
- Risikoprofilen
- Behandling

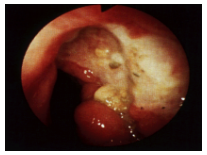

LYMPHOMA
MALT
NODULAR SCLEROSIS
PRECURSOR B-CELL
CUTANEOUS
CLL
MZL
BURKITT'S
FOLLICULAR
MANTLE CELL
MCL
ALCL
HAIRY-CELL
WM
DLBCL
CLASSICAL HODGKIN
PERIPHERAL T-CELL
SEZARY SYNDROME
ENTEROPATHY-TYPE T-CELL
PMBCL
© Lymphoma Coalition

Maligne lymfomer – WHO klassifikation 2001/2008/2017

International klassifikation baseret på objektivt verificerbare biologiske egenskaber



Mavesæk

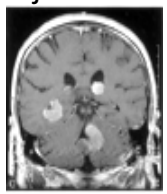


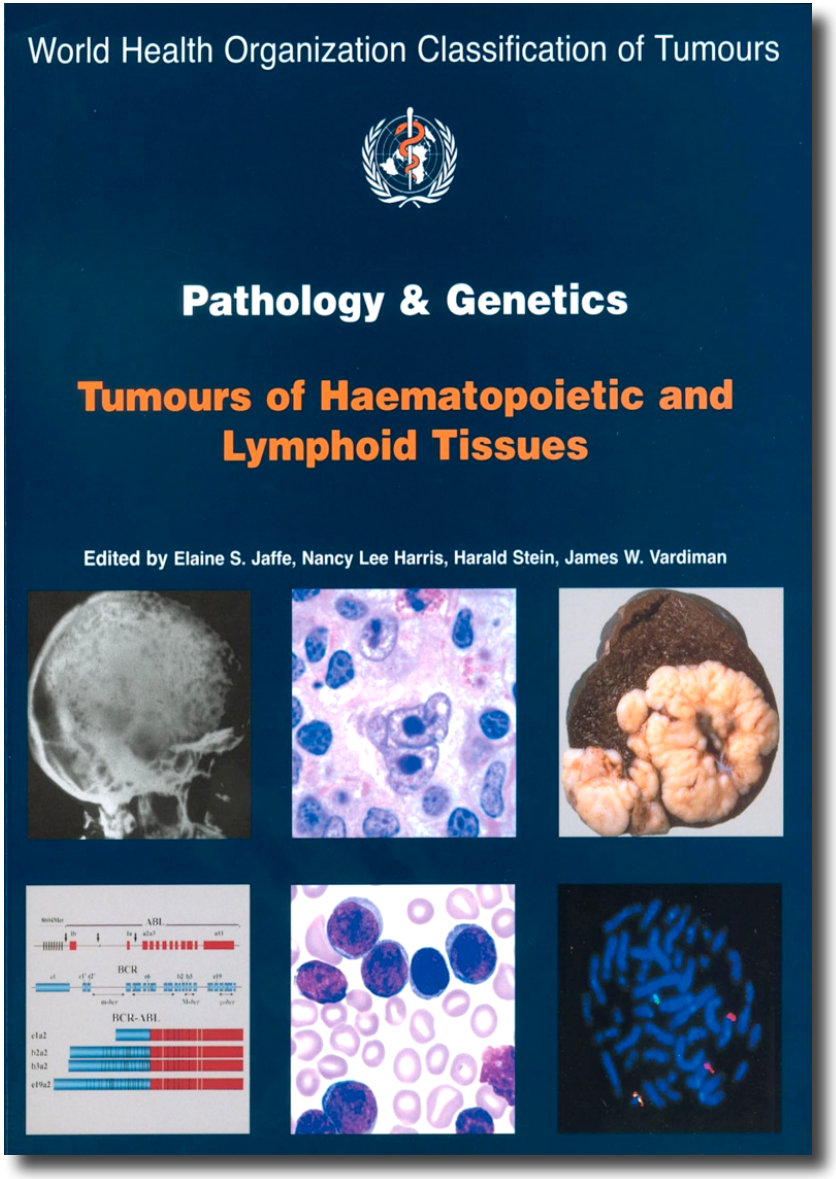
Tyndtarm

Hud

Næse

hjerne





- **B-celle lymfomer**
- **T/NK-celle lymfomer**
- **Hodgkin lymfom**
- **Lymfomer ved medfødt eller erhvervet immunsvækkelse**

WHO klassifikationen for B- og T-celle lymfomer

B-cell neoplasms (85-90%)

Precursor:

B-lymphoblastic lymphoma/leukemia

Mature B-cell neoplasms:

CLL/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma/Waldenström
Splenic marginal zone lymphoma
Hairy cell leukaemia
Plasma cell neoplasms
Extranodal marginal zone (MALT) lymphoma
Nodal marginal zone lymphoma
Follicular lymphoma **(25%)**
Mantle cell lymphoma
Diffuse large B-cell lymphoma **(35-40%)**
Mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary effusion lymphoma
Burkitt lymphoma

T-/NK-cell neoplasms (10-15%)

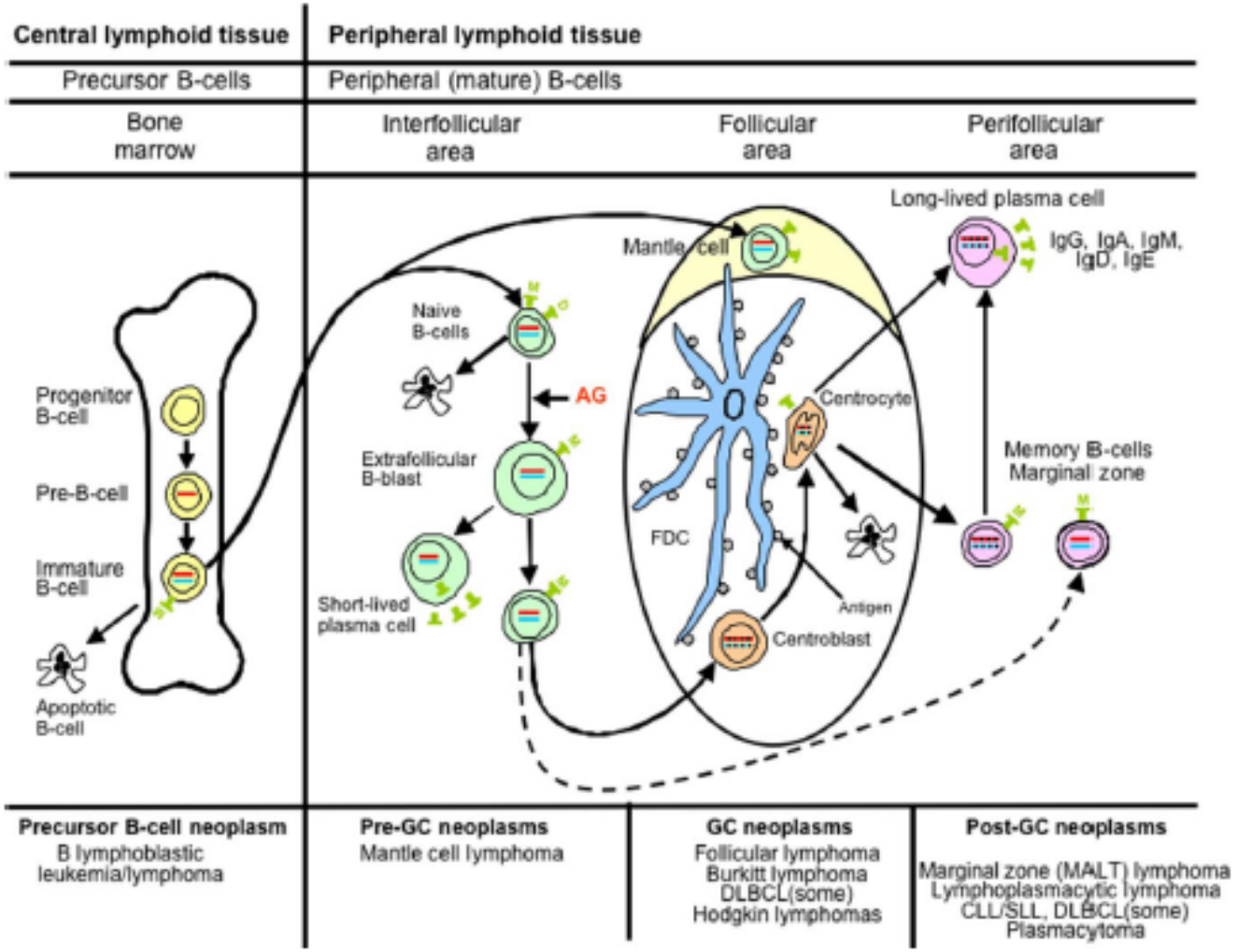
Precursor:

T-lymphoblastic lymphoma/leukemia

Mature (peripheral) T/NK-cell neoplasms:

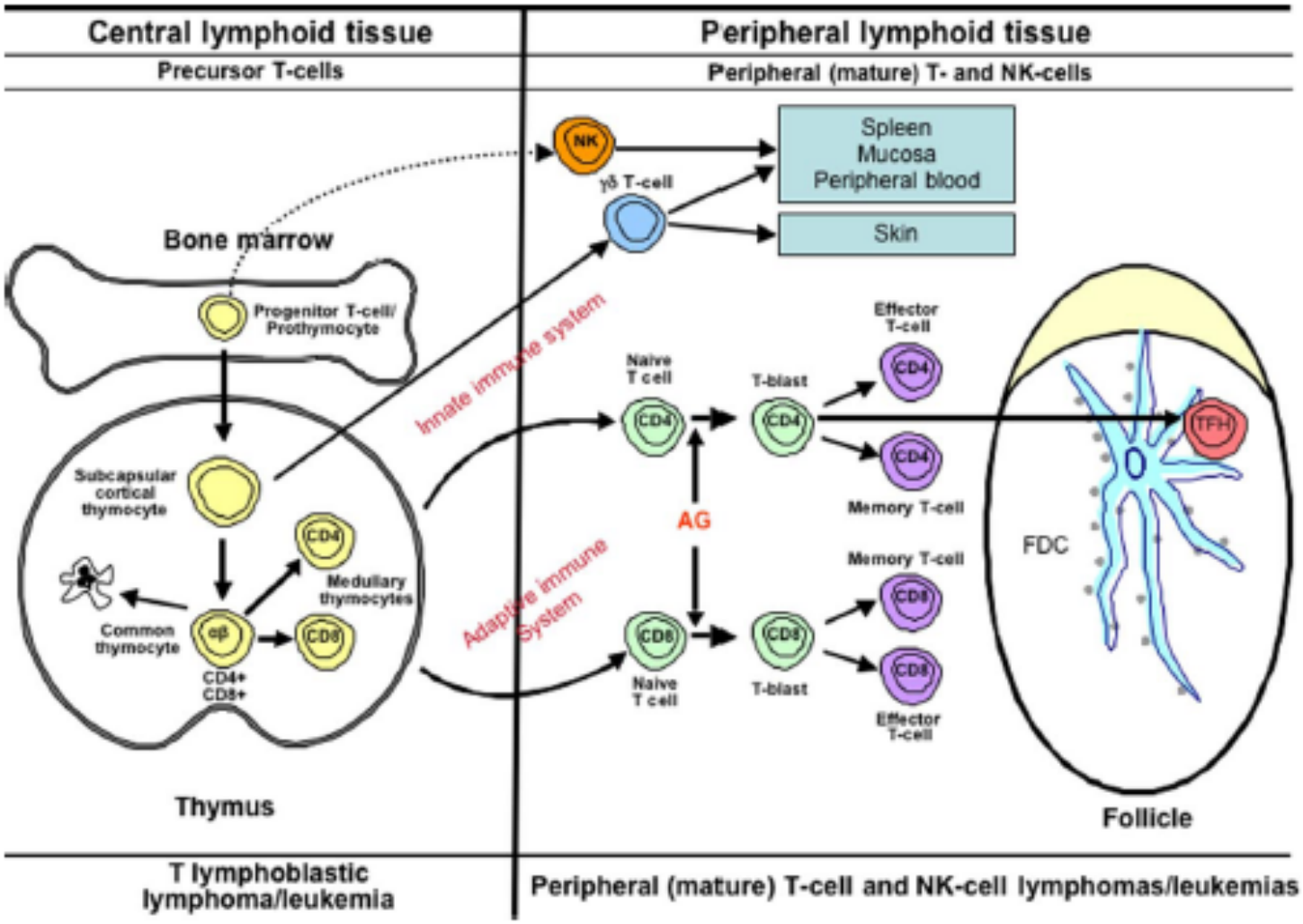
T-PLL
T-cell granular lymphocytic leukemia
Aggressive NK-cell leukemia
ATL (HTLV-1 +)
Extranodal NK-/T-cell, nasal type
Enteropathy-type
Hepatosplenic gamma/delta
Subcutaneous panniculitis-like
ALC T/O, primary cutaneous
Mycosis fungoides/Sézary
PTCL, unspecified (ca 50% af alle PTCL)
Angioimmunoblastic
ALC T/O, primary systemic

B-celle modning



BLOOD, 1 DECEMBER 2008 • VOLUME 112, NUMBER 12

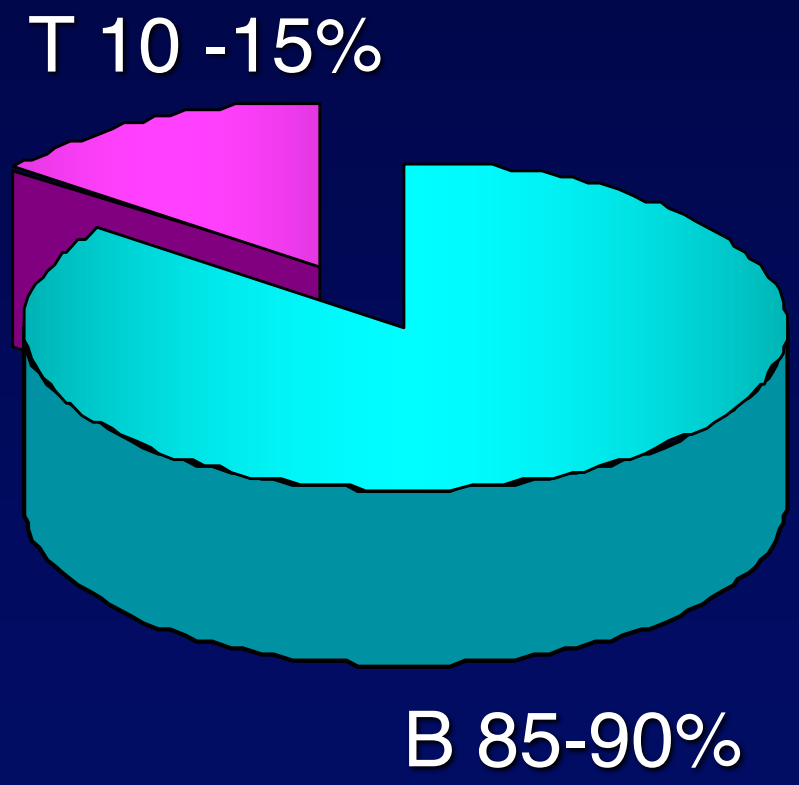
T-celle modning



BLOOD, 1 DECEMBER 2008 • VOLUME 112, NUMBER 12

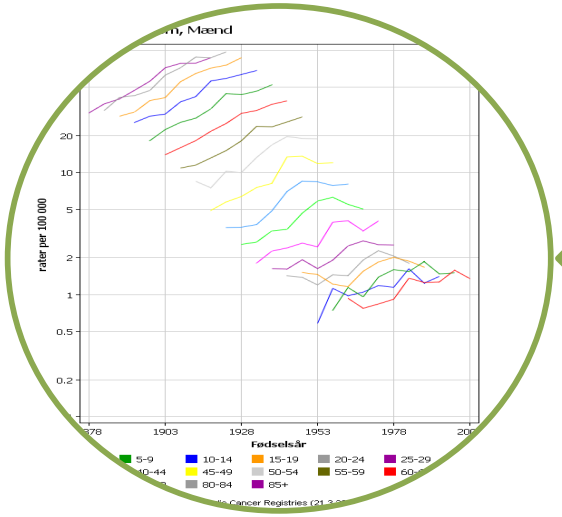
Frekvens af T- vs B-celle NHL

- T-celle NHL udgør ca. 15% af alle NHL i Vesten
- PTCL ca 7-8%

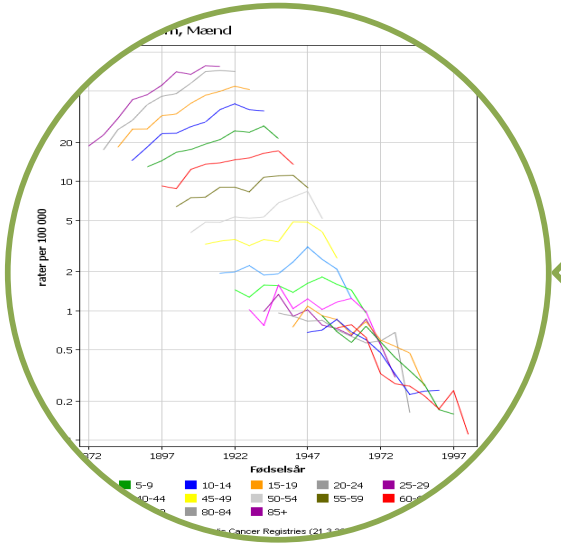


Status og facit for lymfekræft anno 2018

Status



Øget incidens



Faldende dødelighed

Facit

Bedre forebyggelse

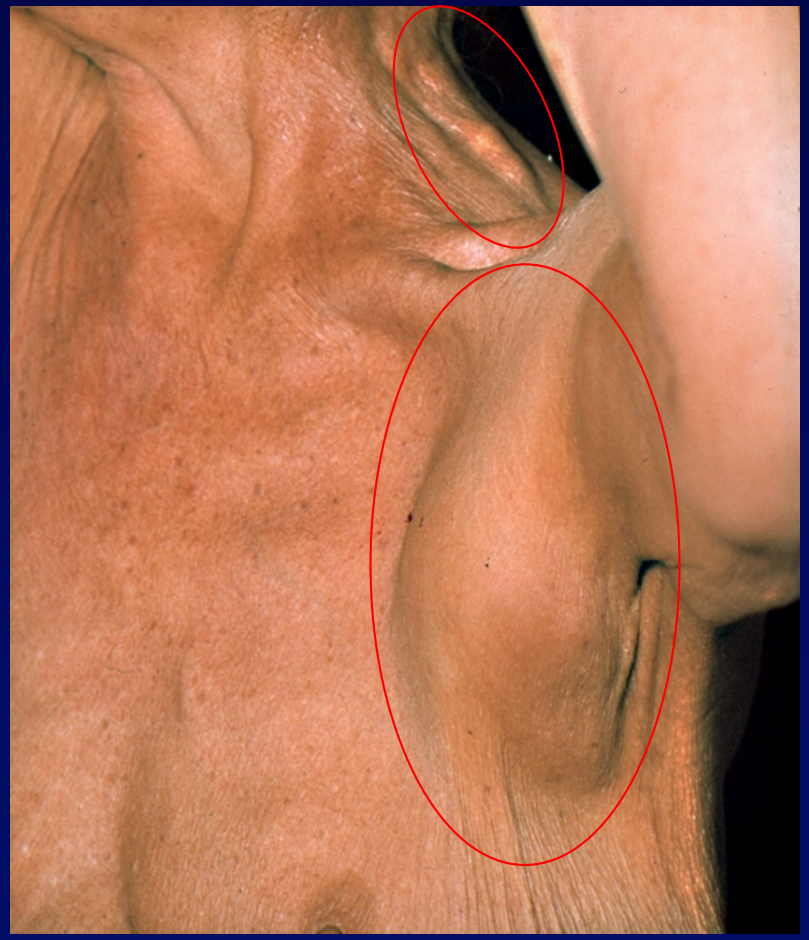
Bedre diagnostik, prædiktering og behandling

Emner

- Lymfomtyper
- Det kliniske billede
- Risikoprofilen
- Behandling

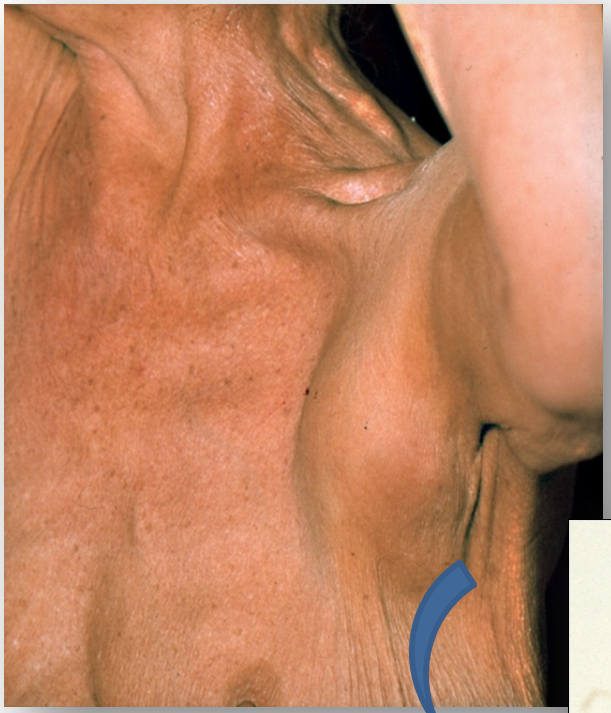
Lymfom – Udredningsprocessen

70-årig kvinde med ca 2 mdr varende hævelse i ve armhule og ve side af halsen. Nattesved, utilsigtet væggtab på ca 4 kg og let tp.forhøjelse (38-38,5C) uden oplagte infektionstegn



1. **Hvad fejler pt?**
   - **Optagelse af sygehistorie**
   - **Lægeundersøgelse**
   - **Vævsprøve-baseret diagnose**
2. **Hvor udbredt er sygdommen?**
   - **Lægeus., scanning, KM evt. m.m.**
3. **Hvad gør vi ved det?**
   - **Behandlings- og opfølgningsplan**

Det kliniske billede - I

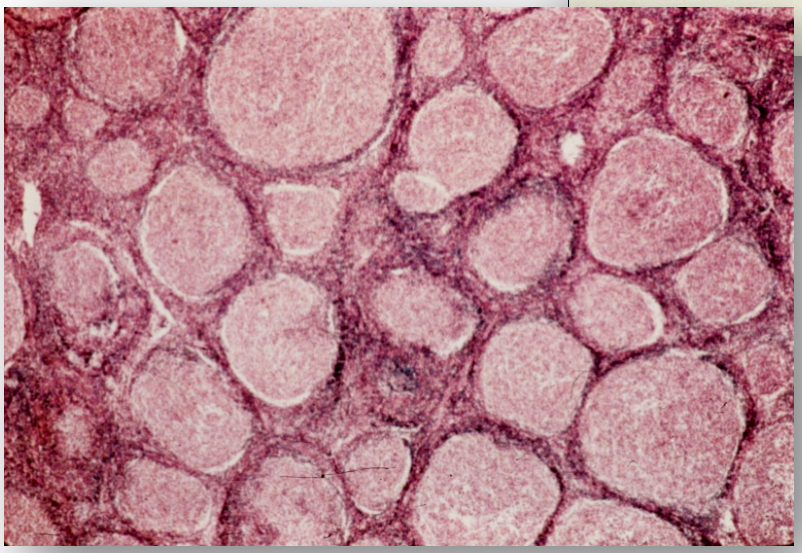


Det mest almindelige symptom på lymfekræft er hævede og uømme lymfeknuder

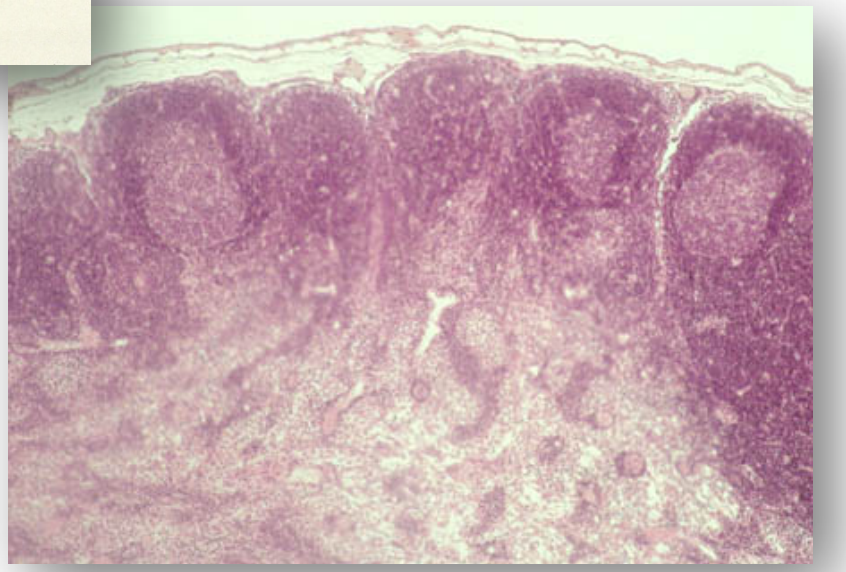
Sygdommen ledsages i 30-40% af tilfældene af svedetendens, feber og vægttab, og, mindre ofte, af intens hudkløe

Diagnosen hviler ofte på en lymfeknudebiopsi. Fjernelse af en hel lymfeknude bør, så vidt mulig, foretrækkes frem for nålebiopsier, for at give patologen mulighed for at vurdere hele vævsarkitekturen og dermed stille en mere sikker diagnose.

Follikulært lymfom



Normal lymfeknude



Fra mistanke til endelig diagnose

Klinisk fremgangsmåde

Diagnose

- Diagnostisk biopsi (excision eller grovnål)
- Histologisk revision (hvis relevant)
- Identifikation af lymfomundertype

Udbredning + prognostisk profil

- Sygdomsudbredning (lok. vs diss.) >> helst PET/CT
- Involvering af vigtige extranodale organer >> 'ad hoc'
- Biokemisk profil >> husk s-LDH
- Generel klinisk vurdering/co-morbiditet
- Lymfom-specifik prognosticering >> IPI (aggr.), IPS (HL), FLIPI (FL)

Terapeutisk strategi

- Behandlingsplan (kurativ vs palliativ)
- Behandlingstargets (e.g. CD20, CD30, ABC signatur)

Emner

- Lymfomtyper
- Det kliniske billede
- Risikoprofilen
- Behandling

Faktorer med relevans for behandlingsplanen

- Sygdomsudbredning (lokaliseret/udbredt)
- Sygdom udenfor lfkn (ekstranodal)?
- Risikoprofil (Alder, AT, blodprøver, tumorbiologi)
- Generel klinisk vurdering (fx. co-morbiditet)

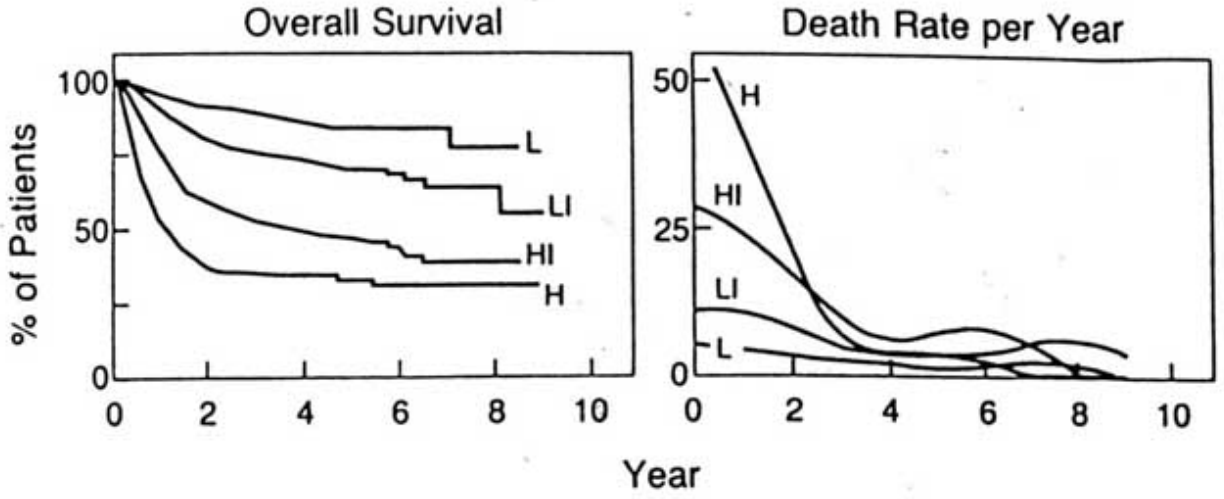
Den Internationale Prognostiske Index (IPI) for aggressive lymfomer

Ugunstige faktorer:

- alder >60
- diss. sygdom (stadie >II)
- PS >1
- forhøjet s-LDH
- >1 extranodal lok

Risk Group	Risk Factors (*n*)	Patients* (%)	Complete Response (%)	2-Yr Relapse-Free Survival (%)	5-Yr Relapse-Free Survival (%)	2-Yr Survival (%)	5-Yr Survival (%)
Low	0 or 1	35	87	79	70	84	73
Low-Intermediate	2	27	67	66	50	66	51
High-Intermediate	3	22	55	59	49	54	43
High	4 or 5	16	44	58	40	34	26

*Patients total 2031, including 1385 in the training sample and 646 in the validation sample.
Adapted from The International Non-Hodgkin's Lymphoma Prognostic Factors Project: "A predictive model for aggressive non-Hodgkin's lymphoma." *N Engl J Med* 329(14):987–994, 1997.



International prognostic score (IPS) for HL

A PROGNOSTIC SCORE FOR ADVANCED HODGKIN'S DISEASE

DIRK HASENCLEVER, PH.D., AND VOLKER DIEHL, M.D.,
FOR THE INTERNATIONAL PROGNOSTIC FACTORS PROJECT ON ADVANCED HODGKIN'S DISEASE*

International Prognostic Score (IPS)

- Male sex
- Hb < 6.5 mmol/l
- Stage IV
- Age ≥ 45 years
- Leucocytes >16 * 10^9/l
- Lymphocytopenia < 0.6 x 10^9/L
- Albumin < 40 g/L

IPS Score: 0-7

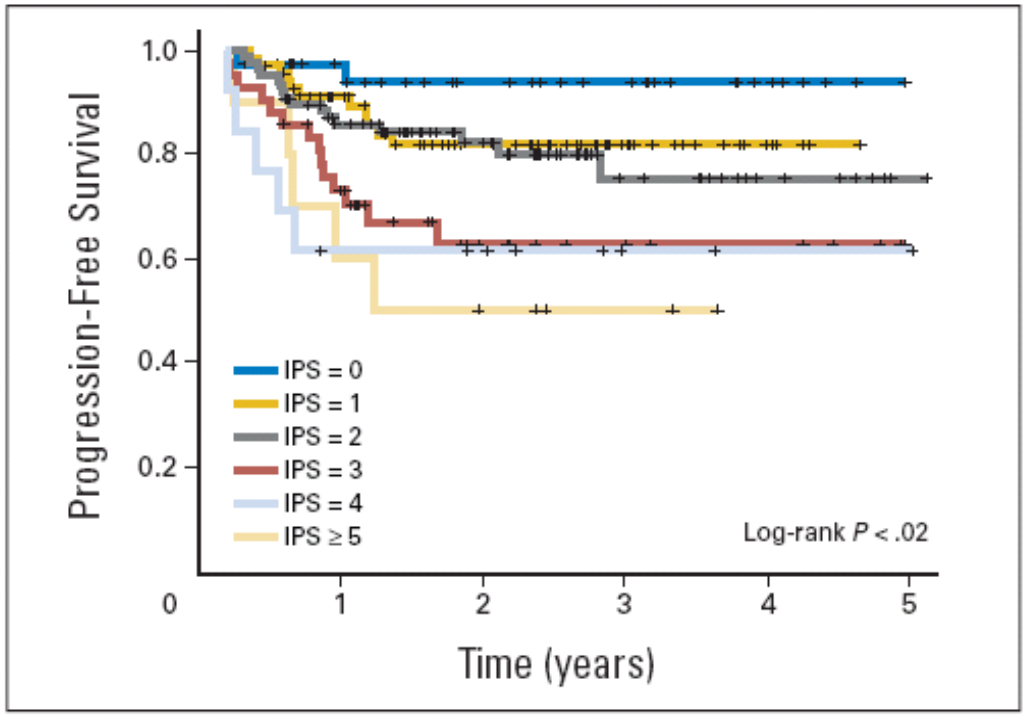


Fig 2. Kaplan-Meier plot showing the progression-free survival according to International Prognostic Score (IPS) group.

PET som prognostisk faktor

Gallamini et al, **Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study.**

J Clin Oncol. 2007 Aug 20;25(24):3746-52.

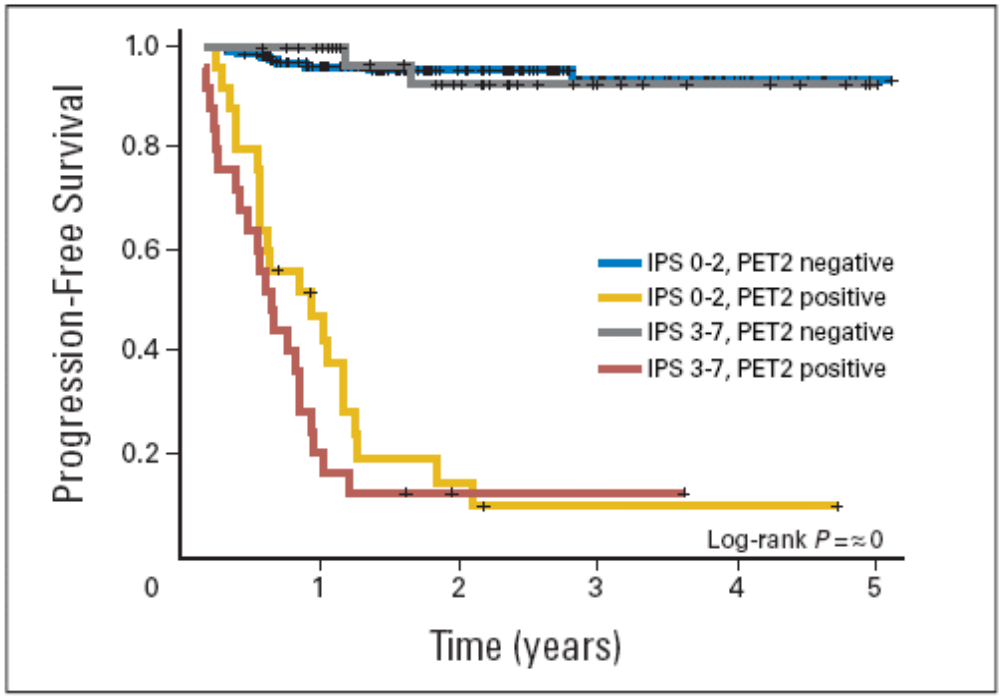


Fig 3. Kaplan-Meier plot showing the progression-free survival according to International Prognostic Score (IPS) group and positron emission tomography results after two cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine).

To hovedsignaturer indenfor lymfomtypen ’diffust storcellet B-celle lymfom’ (DLBCL)

Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling

Ash A. Alizadeh[1,2], Michael B. Eisen[2,3,4], R. Eric Davis[5], Chi Ma[5], Izidore S. Lossos[6], Andreas Rosenwald[5], Jennifer C. Boldrick[1], Hajeer Sabet[5], Truc Tran[5], Xin Yu[5], John I. Powell[7], Liming Yang[7], Gerald E. Marti[8], Troy Moore[9], James Hudson Jr[9], Lisheng Lu[10], David B. Lewis[10], Robert Tibshirani[11], Gavin Sherlock[4], Wing C. Chan[12], Timothy C. Greiner[12], Dennis D. Weisenburger[12], James O. Armitage[13], Roger Warnke[14], Ronald Levy[6], Wyndham Wilson[15], Michael R. Grever[16], John C. Byrd[17], David Botstein[4], Patrick O. Brown[1,18] & Louis M. Staudt[5]

Departments of [1]Biochemistry, [3]Genetics, [14]Pathology, [6]Medicine, [10]Pediatrics and [11]Health Research & Policy and Statistics, and [18]Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, California 94305, USA
[5] Metabolism Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA
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[9] Research Genetics, Huntsville, Alabama 35801, USA
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[15] Medicine Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA
[16] Johns Hopkins Oncology Center, Johns Hopkins School of Medicine, Baltimore, Maryland 21287, USA
[17] Walter Reed Army Medical Center, Washington, DC 20307, USA
[2] These authors contributed equally to this work

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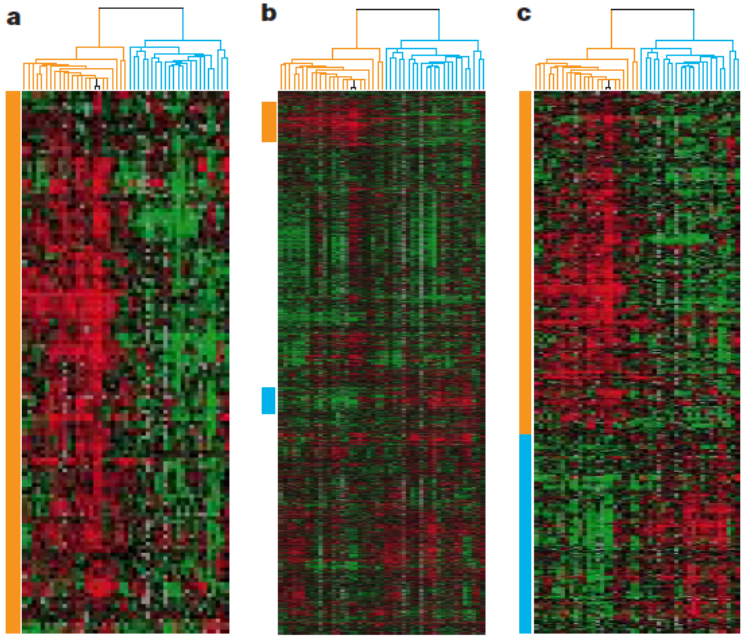
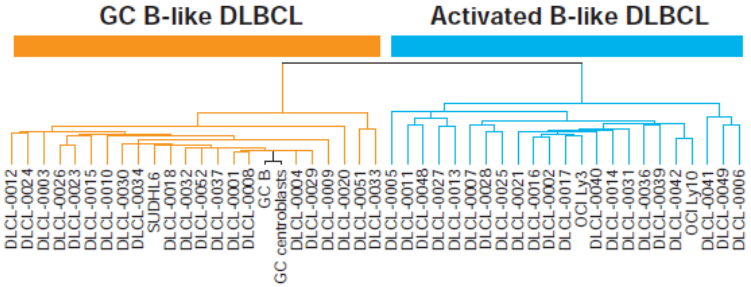




GCB vs ABC (non-GCB)

Gen-ekspressionssignatur i forhold til IPI

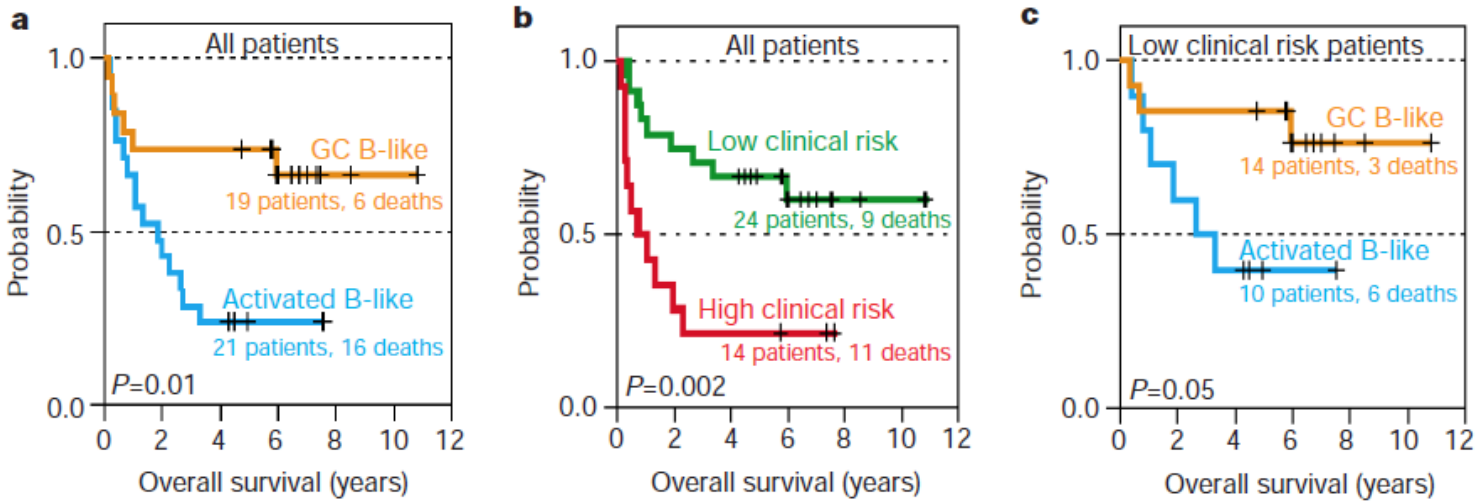


Figure 5 Clinically distinct DLBCL subgroups defined by gene expression profiling. **a**, Kaplan–Meier plot of overall survival of DLBCL patients grouped on the basis of gene expression profiling. **b**, Kaplan–Meier plot of overall survival of DLBCL patients grouped according to the International Prognostic Index (IPI). Low clinical risk patients (IPI score 0–2) and high clinical risk patients (IPI score 3–5) are plotted separately. **c**, Kaplan–Meier plot of overall survival of low clinical risk DLBCL patients (IPI score 0–2) grouped on the basis of their gene expression profiles.

Emner

- Lymfomtyper
- Det kliniske billede
- Risikoprofilen
- Behandling

Lymfom obs pro/Nydiagnosticeret lymfom

Klinisk fremgangsmåde

Diagnose

- Ledsagende symptomer?
- Biopsi (hele lfkn? grovnål? finnål?)
  - Hvilken type lymfom?

Udbredning + risikoprofil

- Sygdomsudbredning (lokaliseret/udbredt)
- Sygdom udenfor lfkn (ekstranodal)?
- Risikoprofil (alder, AT, blodprøver)
- Generel vurdering (fx. andre sygdomme?)

Behandlings- og opfølgningsplan

- Hvilken behandling (Strålebehandling? Traditionel kemoterapi? Nye molekyler?)? Kontrolhyppighed under og efter behandling? Hvilke undersøgelser?

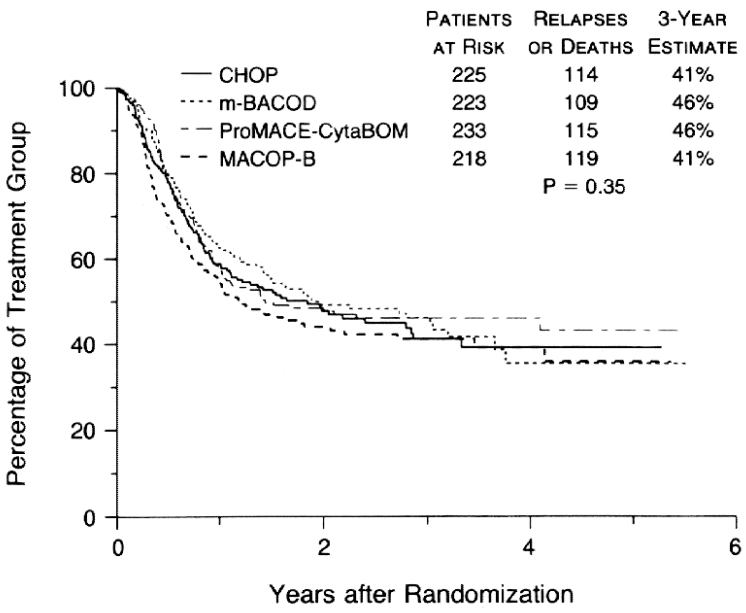
Kemoterapi er stadig et værdifuldt værktøj for at opnå helbredelse
Eks.: CHOP kemoterapi

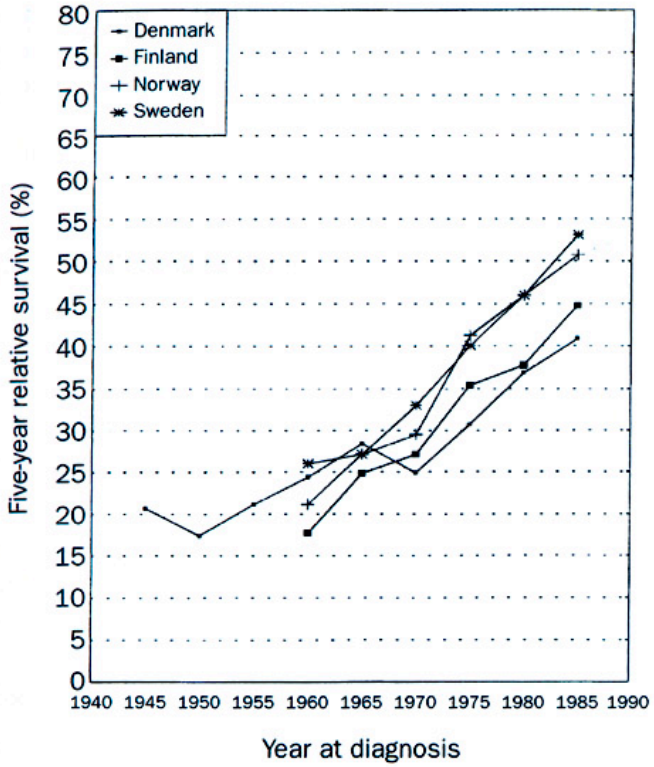
Ann Intern Med. 1976 Oct;85(4):417-22.
Bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisone (BACOP) combination chemotherapy in the treatment of advanced diffuse histiocytic lymphoma.
Schein PS, DeVita VT Jr, Hubbard S, Chabner BA, Canellos GP, Berard C, Young RC

Comparison of a Standard Regimen (CHOP) with Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma

Richard I. Fisher, Ellen R. Gaynor, Steve Dahlberg, Martin M. Oken, Thomas M. Grogan, Evonne M. Mize, John H. Glick, Charles A. Coltman, and Thomas P. Miller

N Engl J Med 1993, 328:1002-1006





ABVD (ABVD/COPP) kemoterapi for Hodgkin lymfom

COMBINATION CHEMOTHERAPY OF HODGKIN'S DISEASE WITH ADRIAMYCIN, BLEOMYCIN, VINBLASTINE, AND IMIDAZOLE CARBOXAMIDE VERSUS MOPP

GIANNI BONADONNA, MD,* ROBERTO ZUCALI, MD,† SILVIO MONFARDINI, MD,‡ MARIO DE LENA, MD,§ AND CARLO USLENGHI, MD‖

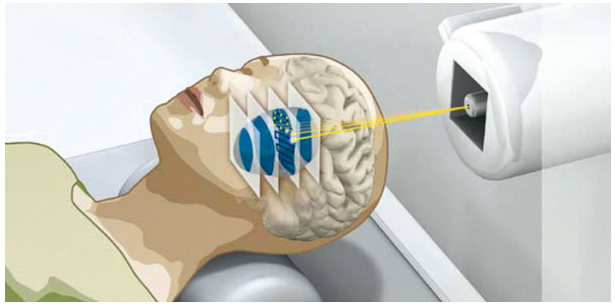
Cancer 36:252–259, 1975.

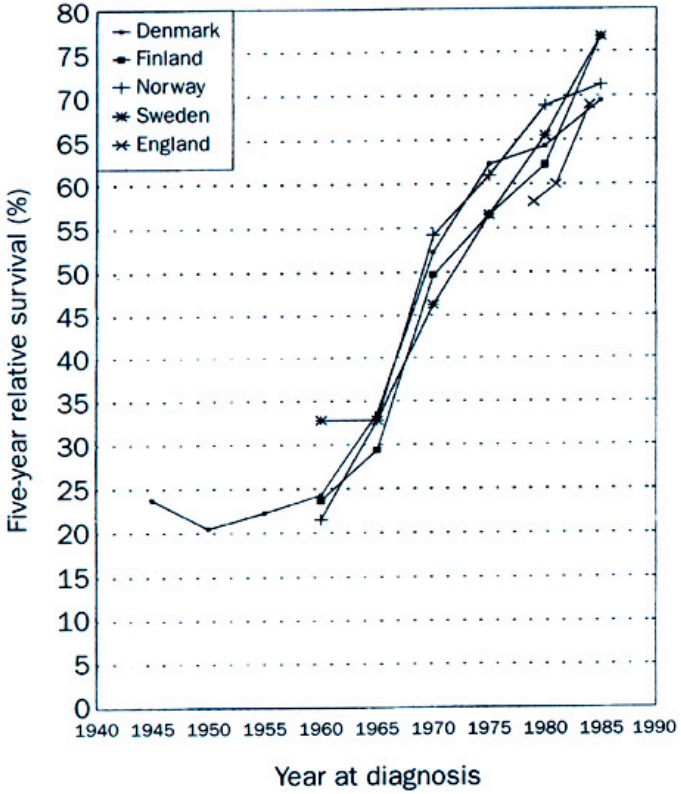
Megavoltage stråleterapi for Hodgkin lymfom

Ca start 1970-1975

Partikelterapi

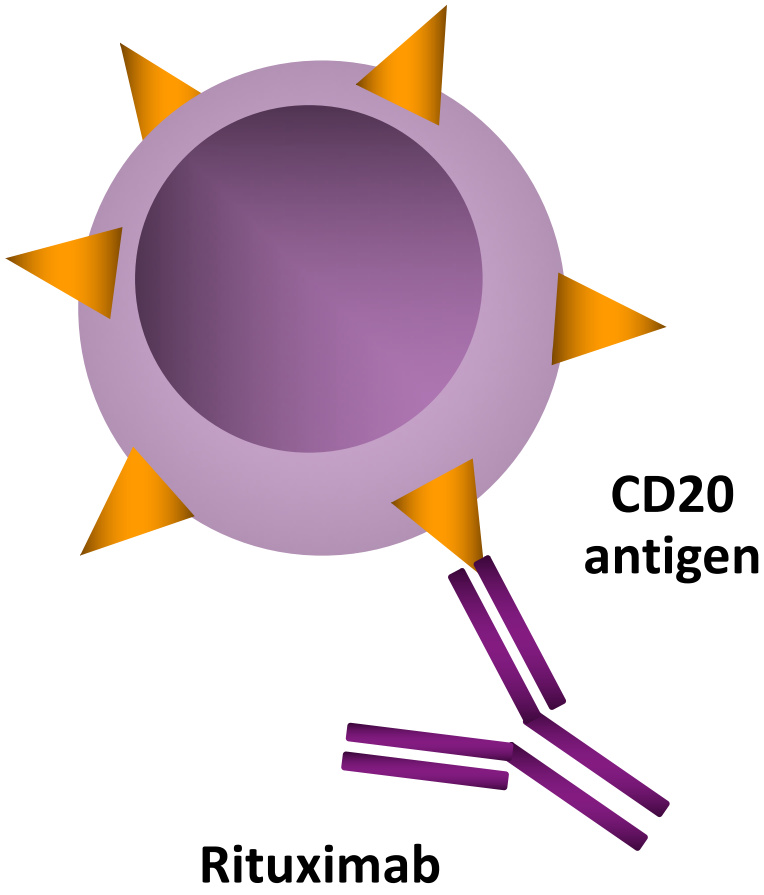
2019-…





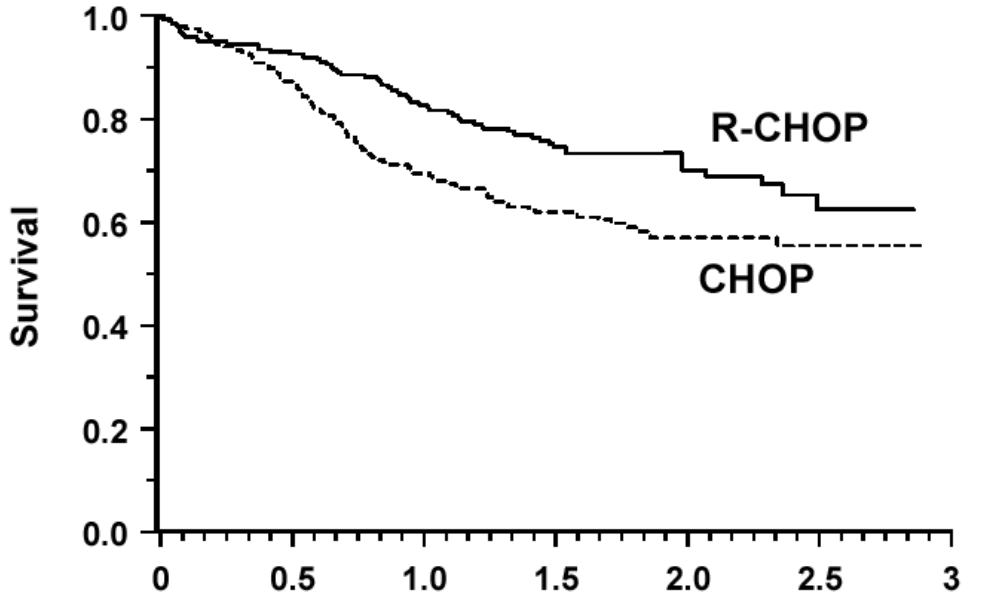
CD20 som eksempel på en ideal målskive immunterapi

- CD20 antigen:
  - Egnet mål for lymfombehandling
  - Udtrykt af de fleste B-celler
  - 'Fælder' ikke fra cellens overflade ('shedding')
  - Bliver ikke 'skjult' af kræftcellen efter binding af antistoffet ('modulering')



DLBCL: rituximab forbedrer overlevelsen

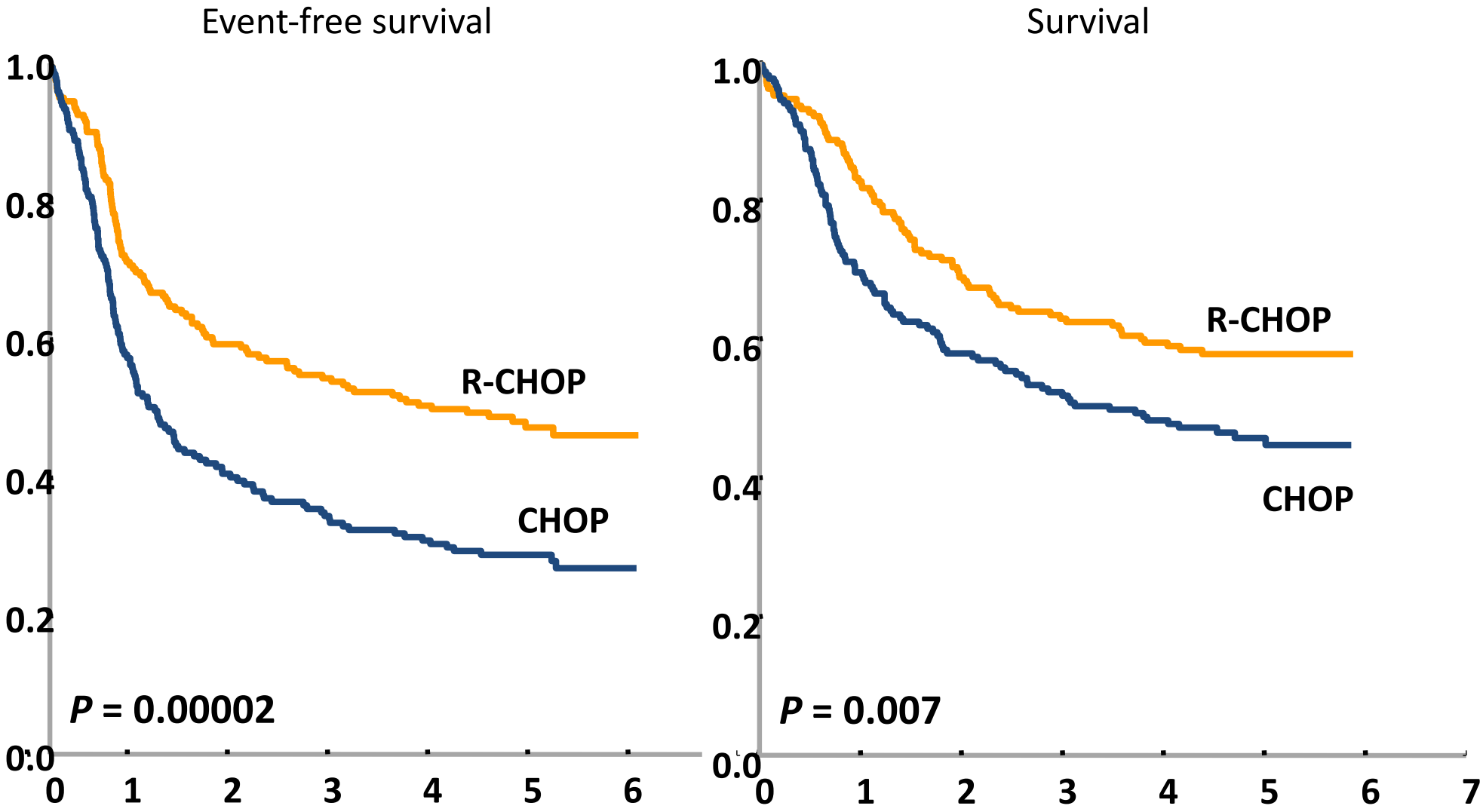
Figure 2. Overall survival of the 399 patients entered in the 98.5 study comparing CHOP regimen to CHOP plus rituximab (R-CHOP) (P = 0.007).



No at Risk						
R-CHOP	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

Coiffier, NEJM 2002

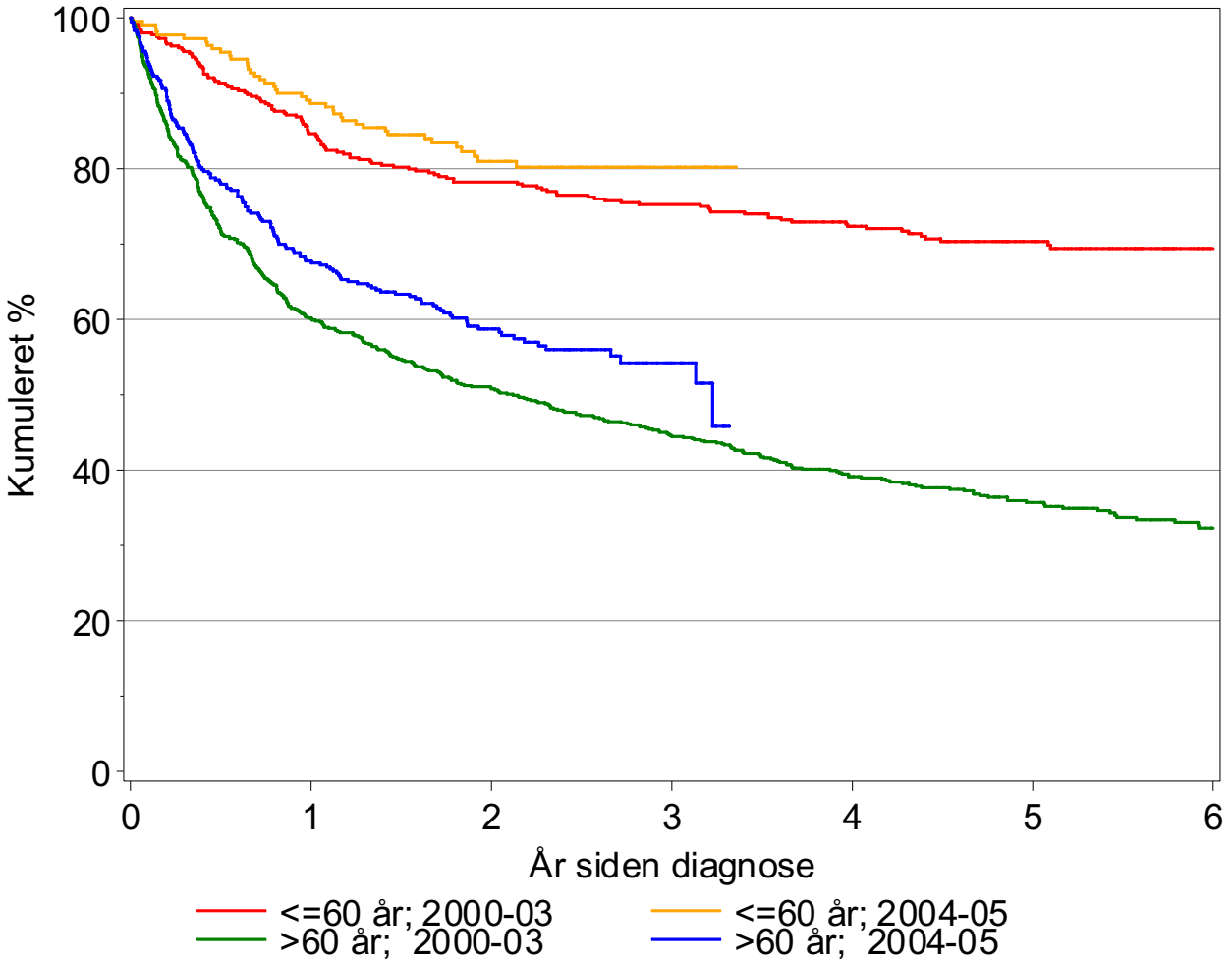
GELA-LNH 98.5 Studie: Median Follow-up 5 år



Gela

Feugier P, et al. *J Clin Oncol* 2005; 23: 4117-4126.

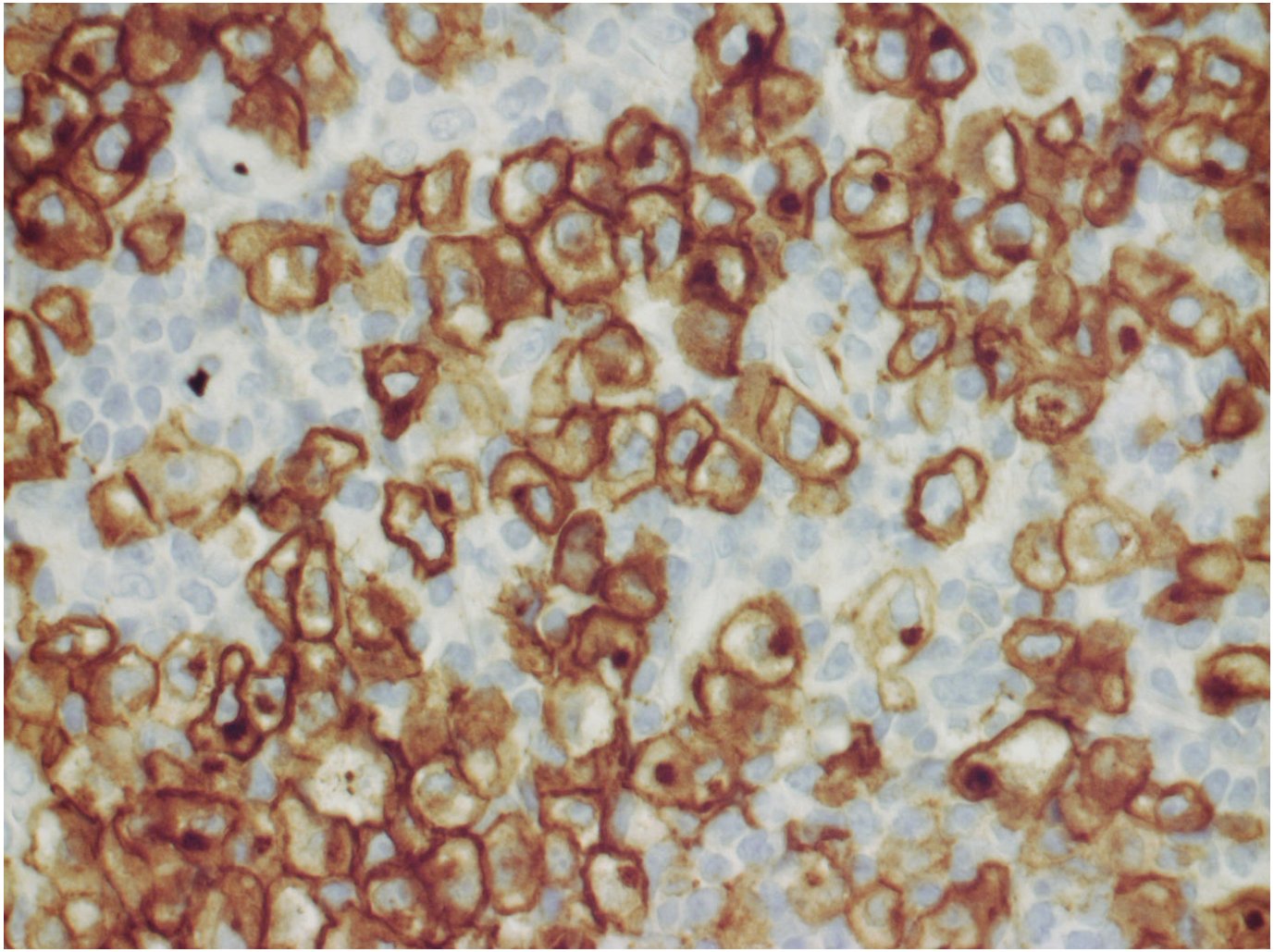
DLBCL: rituximab forbedrer overlevelsen også i opgørelser foretaget i populations-baserede registre



DLGs Årsrapport 2006
www.lymphoma.dk

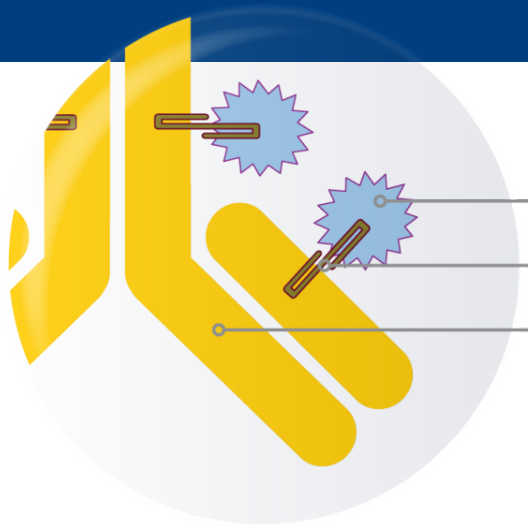
Hodgkin og T-celle lymfom

Proteinet CD30 som målskive



ALCL, CD30

Brentuximab Vedotin - Virkningsmekanisme

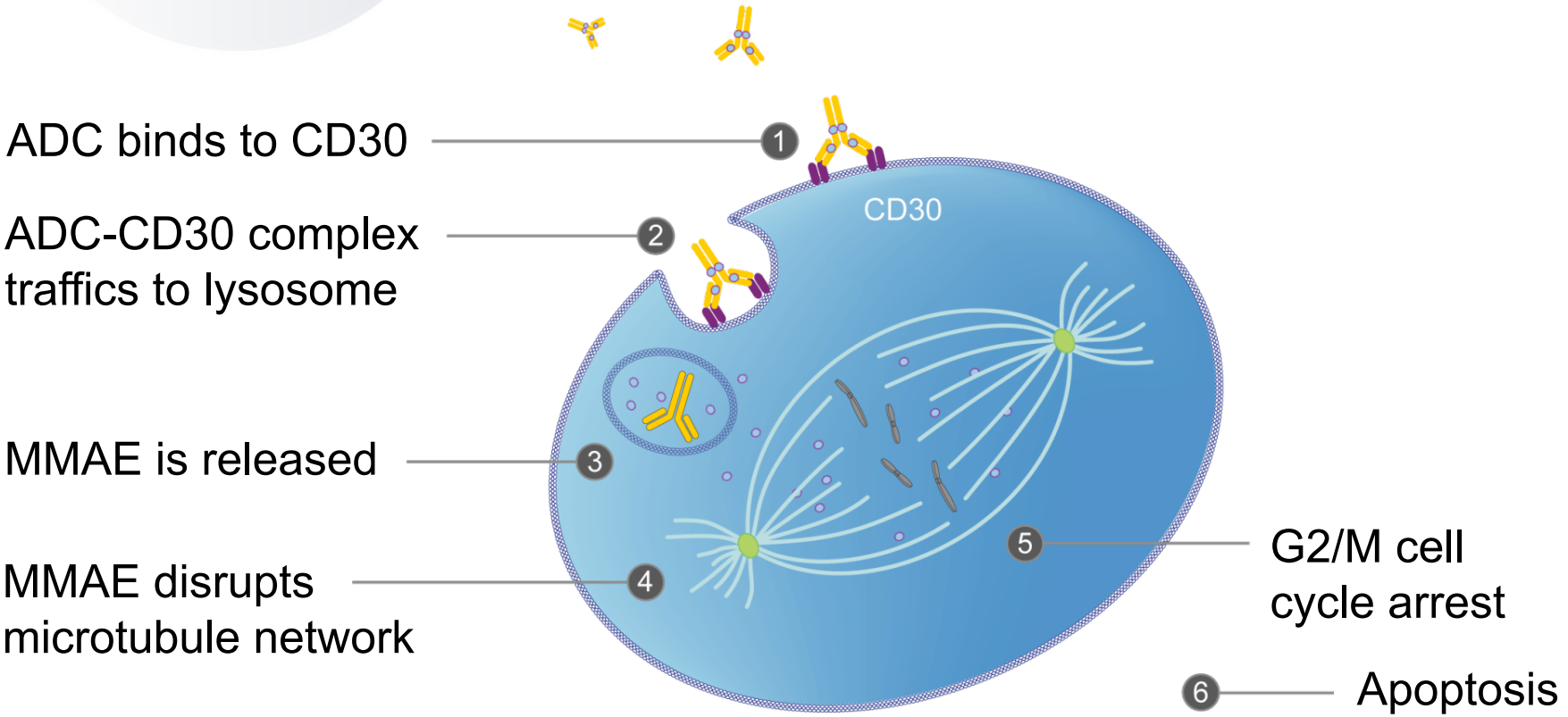


Brentuximab vedotin (SGN-35) ADC

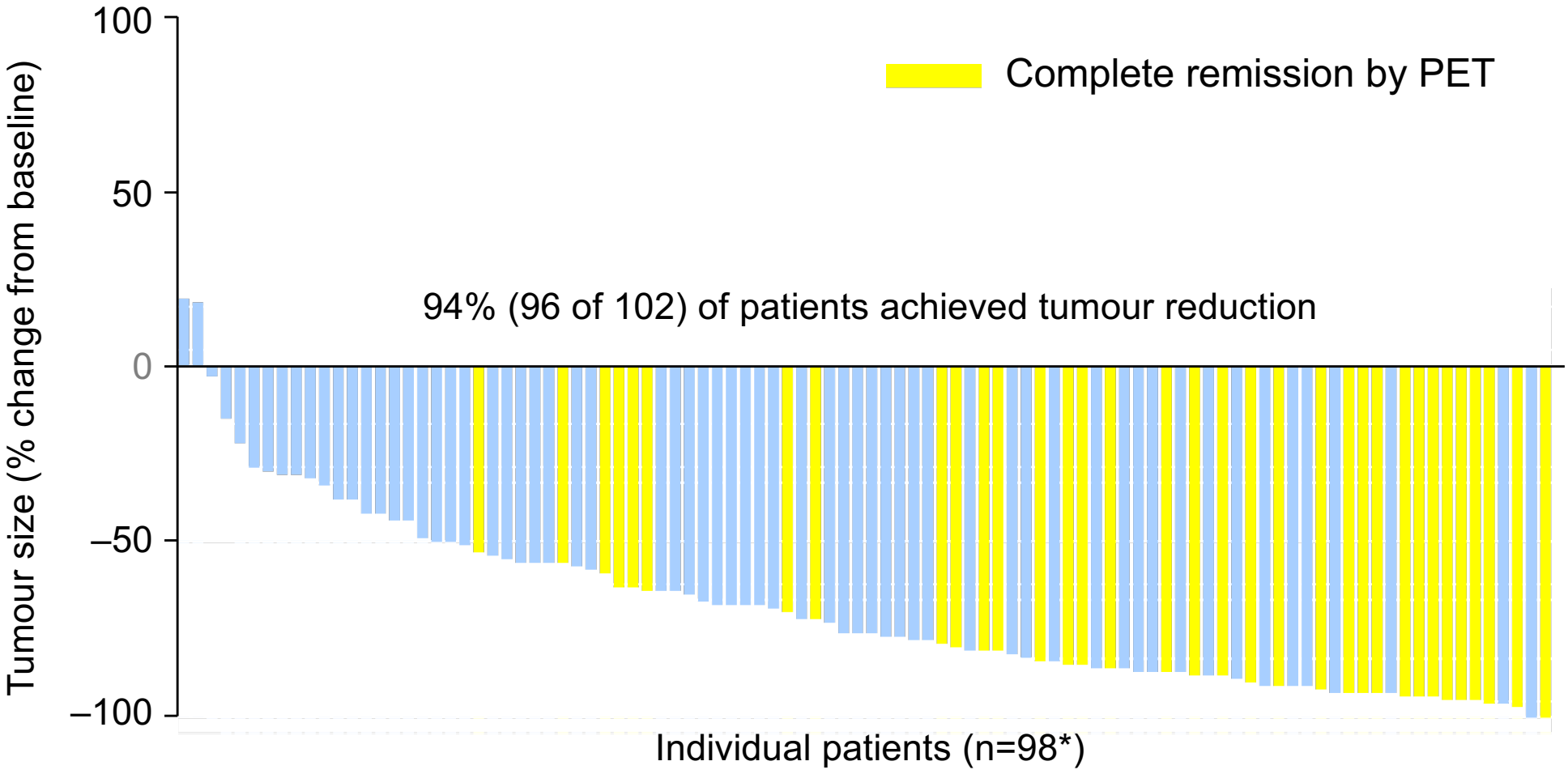
monomethyl auristatin E (MMAE), potent antitubulin agent

protease-cleavable linker

anti-CD30 monoclonal antibody



Tumour reduction in heavily pre-treated ALCL pts[1]



1. Chen RW *et al*. Presented at American Society of Clinical Oncology annual meeting, Chicago, USA; 4–6 June 2011: Oral presentation Abstract #.8031

Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling

Ash A. Alizadeh[1,2], Michael B. Eisen[2,3,4], R. Eric Davis[5], Chi Ma[5], Izidore S. Lossos[6], Andreas Rosenwald[5], Jennifer C. Boldrick[1], Hajeer Sabet[5], Truc Tran[5], Xin Yu[5], John I. Powell[7], Liming Yang[7], Gerald E. Marti[8], Troy Moore[9], James Hudson Jr[9], Lisheng Lu[10], David B. Lewis[10], Robert Tibshirani[11], Gavin Sherlock[4], Wing C. Chan[12], Timothy C. Greiner[12], Dennis D. Weisenburger[12], James O. Armitage[13], Roger Warnke[14], Ronald Levy[6], Wyndham Wilson[15], Michael R. Grever[16], John C. Byrd[17], David Botstein[4], Patrick O. Brown[1,18] & Louis M. Staudt[5]

Departments of [1]Biochemistry, [3]Genetics, [14]Pathology, [6]Medicine, [10]Pediatrics and [11]Health Research & Policy and Statistics, and [18]Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, California 94305, USA
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[16] Johns Hopkins Oncology Center, Johns Hopkins School of Medicine, Baltimore, Maryland 21287, USA
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[2] These authors contributed equally to this work

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To hovedsignaturer indenfor NHL af typen 'diffust storcellet B-celle lymfom'

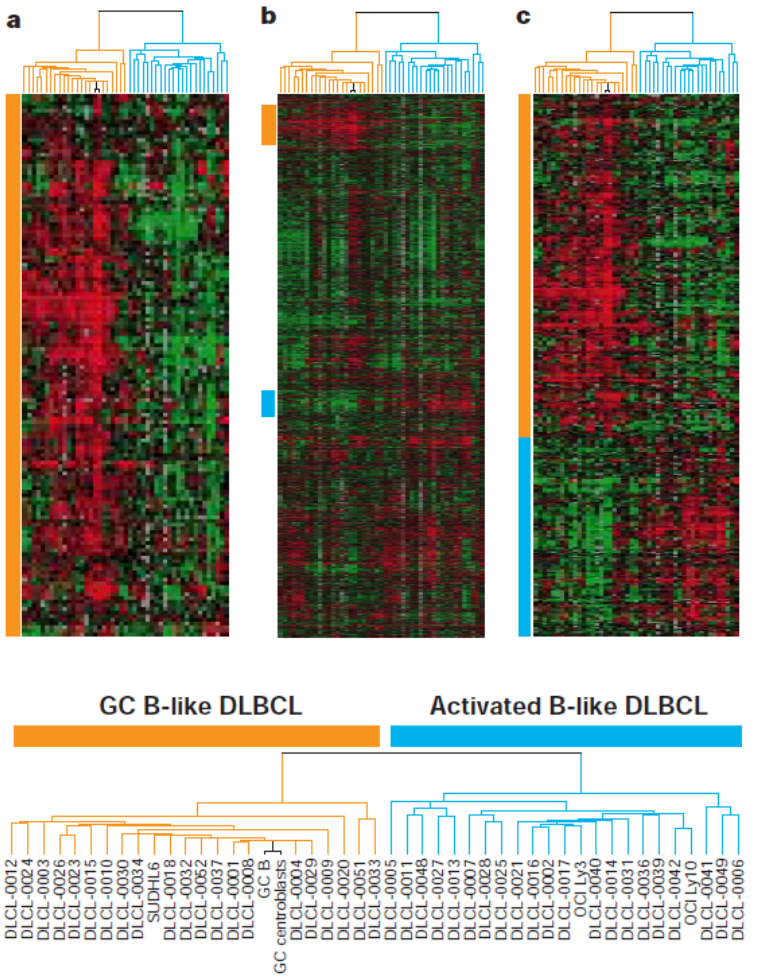
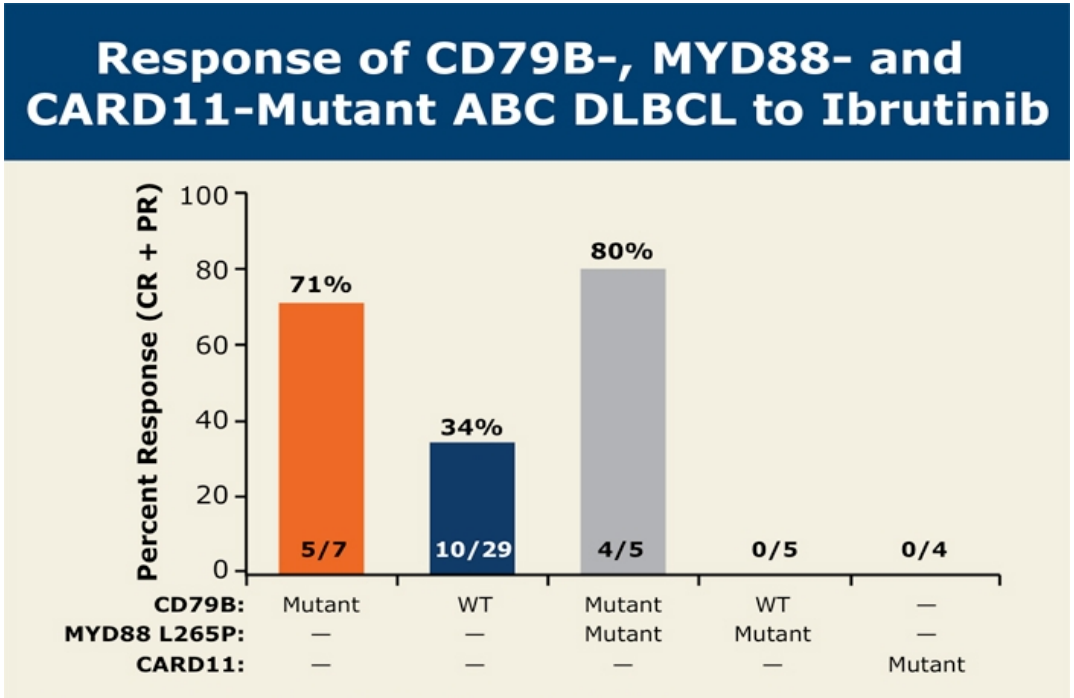
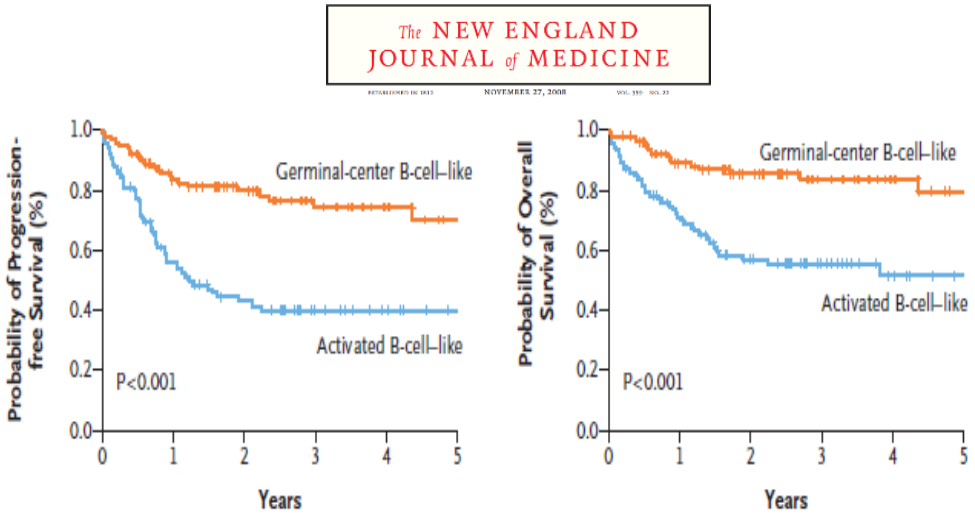


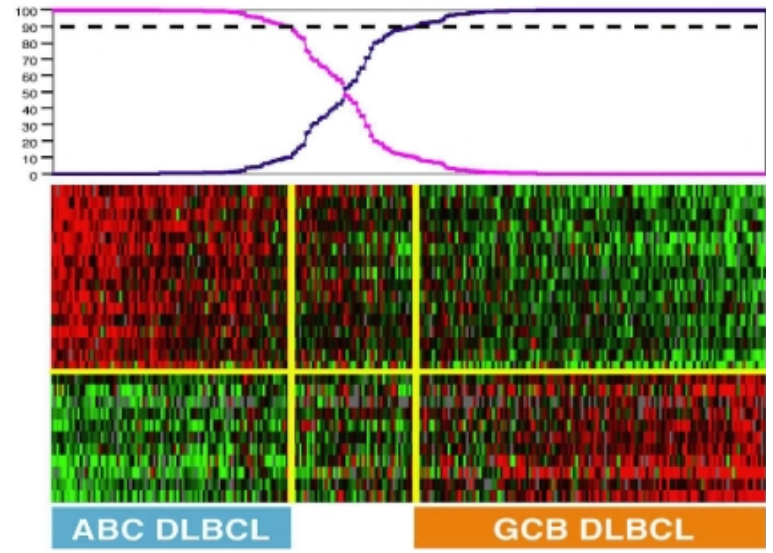
Figure 3 Discovery of DLBCL subtypes by gene expression profiling. The samples used in this clustering analysis are shown at the bottom. **a**, Hierarchical clustering of DLBCL cases (blue and orange) and germinal centre B cells (black) based on the genes of the germinal centre B-cell gene expression signature shown in Figs 1 and 2. Two DLBCL subgroups, GC B-like DLBCL (orange) and activated B-like DLBCL (blue) were defined by this process. **b**, Discovery of genes that are selectively expressed in GC B-like DLBCL and activated B-like DLBCL. All genes from Fig. 1, with the exception of the genes in the proliferation, T-cell and lymph-node gene expression signatures, were ordered by hierarchical clustering while maintaining the order of samples determined in Fig. 3a. Genes selectively expressed in GC B-like DLBCL (orange) and activated B-like DLBCL (blue) are indicated. **c**, Hierarchical clustering of the genes selectively expressed in GC B-like DLBCL and activated B-like DLBCL, which was determined from Fig. 3b.

Biomarkør-dreven behandling

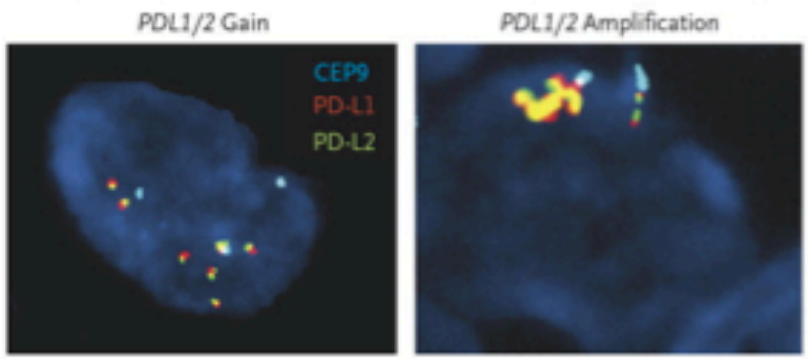
- Ibrutinib ved non-GCB DLBCL
- Phoenix fase 3 studie
- R-CHOP vs R-CHOP+IBR

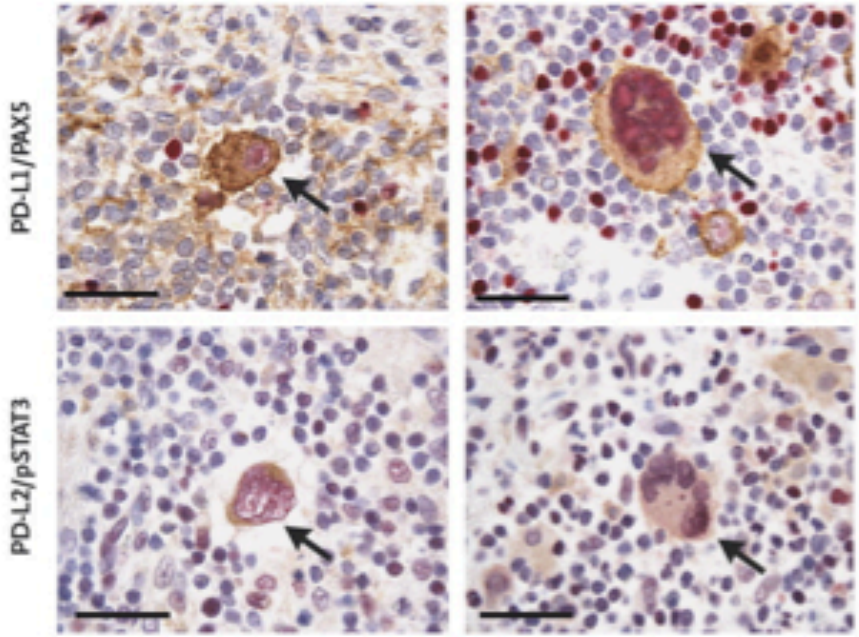




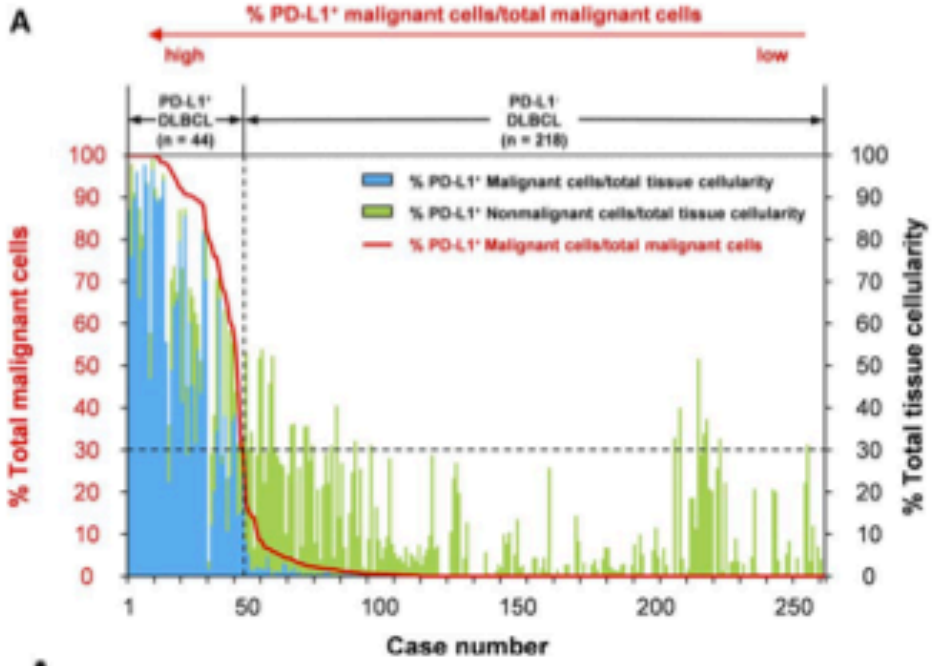


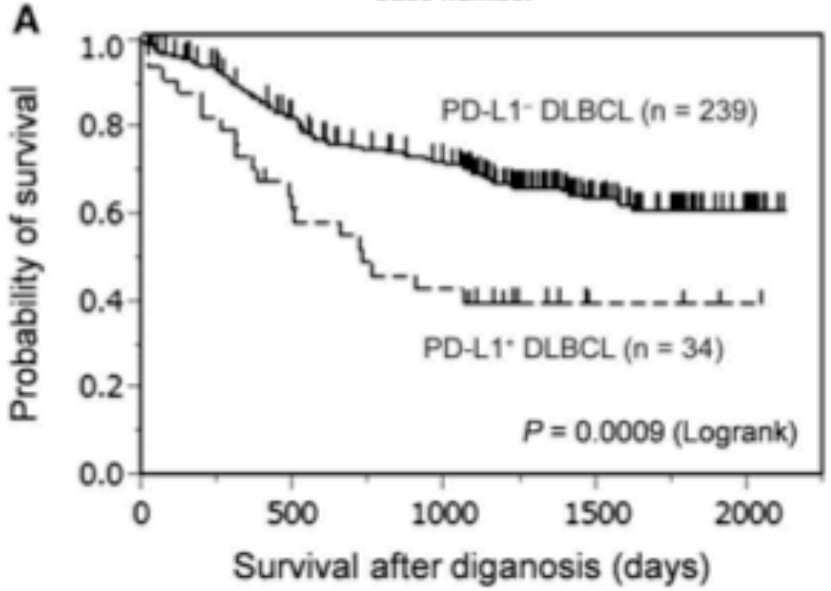
Øget ekspression af PD-L1 and PD-L2 på Lymfomceller



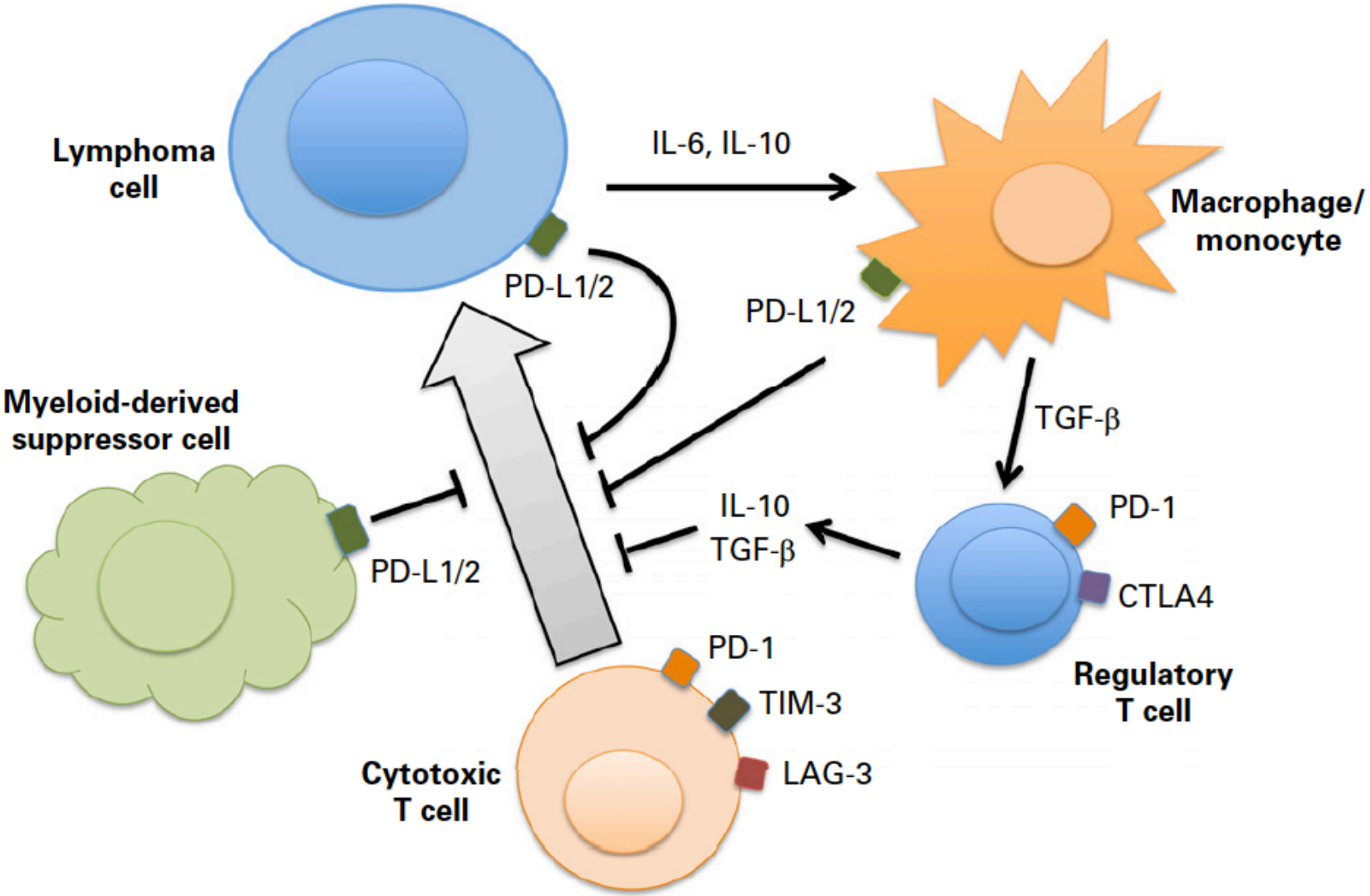


Ansell et al. N Engl J Med. 2015;372:311-319
Roemer et al. ASH 2015 abstract #176
Kiyasu et al. Blood 2015;126:2193-2201





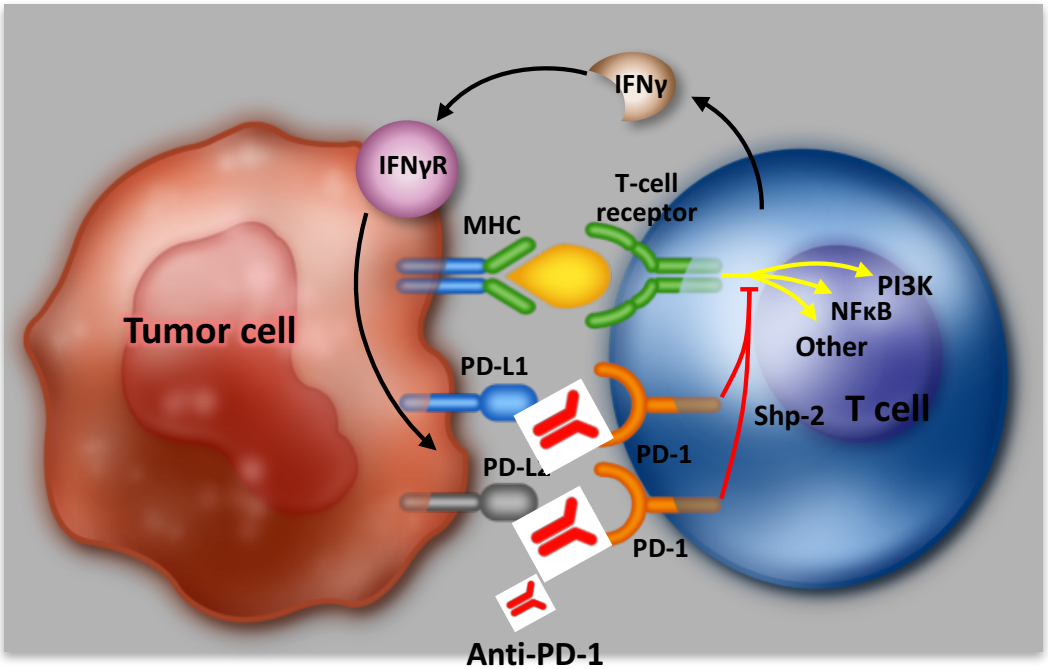
Hvordan kunne man re-aktivere den svækkede immunresponse mod tumorcellerne?



Ansell SM. J Oncol Pract. 2016 Feb;12(2):101-6.

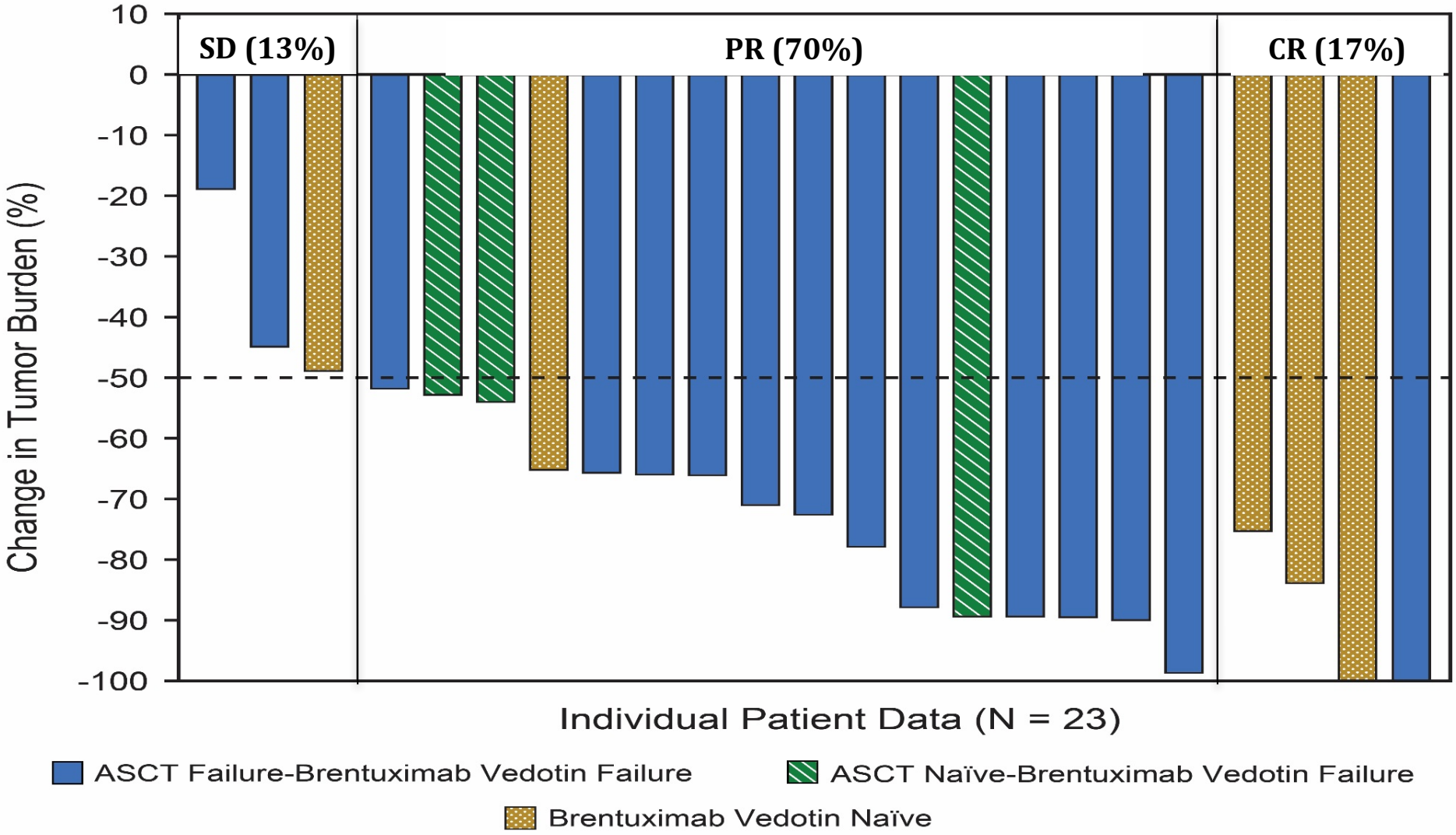
Immune Checkpoint Blokering:
Blokering af PD-1

- PD-1 ligands are overexpressed in inflammatory environments and attenuate the immune response via PD-1 on immune effector cells.[1]
- PD-L1 expressed on malignant cells and/or in the tumor microenvironment suppresses tumor infiltrating lymphocyte activity.[2]



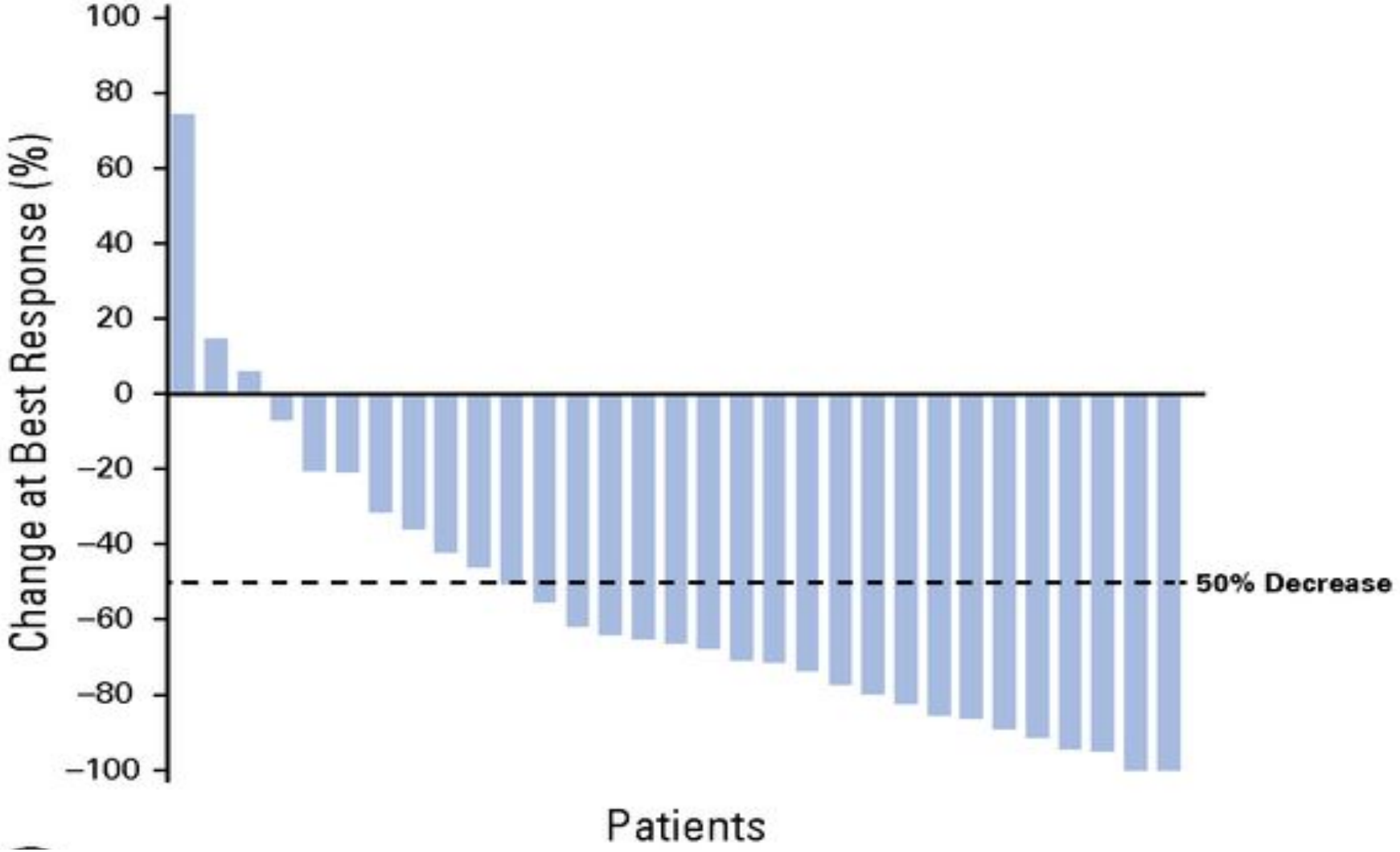
[1]Francisco LM et al. J Exp Med 2009;206:3015-29.
[2]Andorsky DJ et al. Clin Cancer Res 2011;17:4232-44

Hodgkin Lymfom – Response på Nivolumab



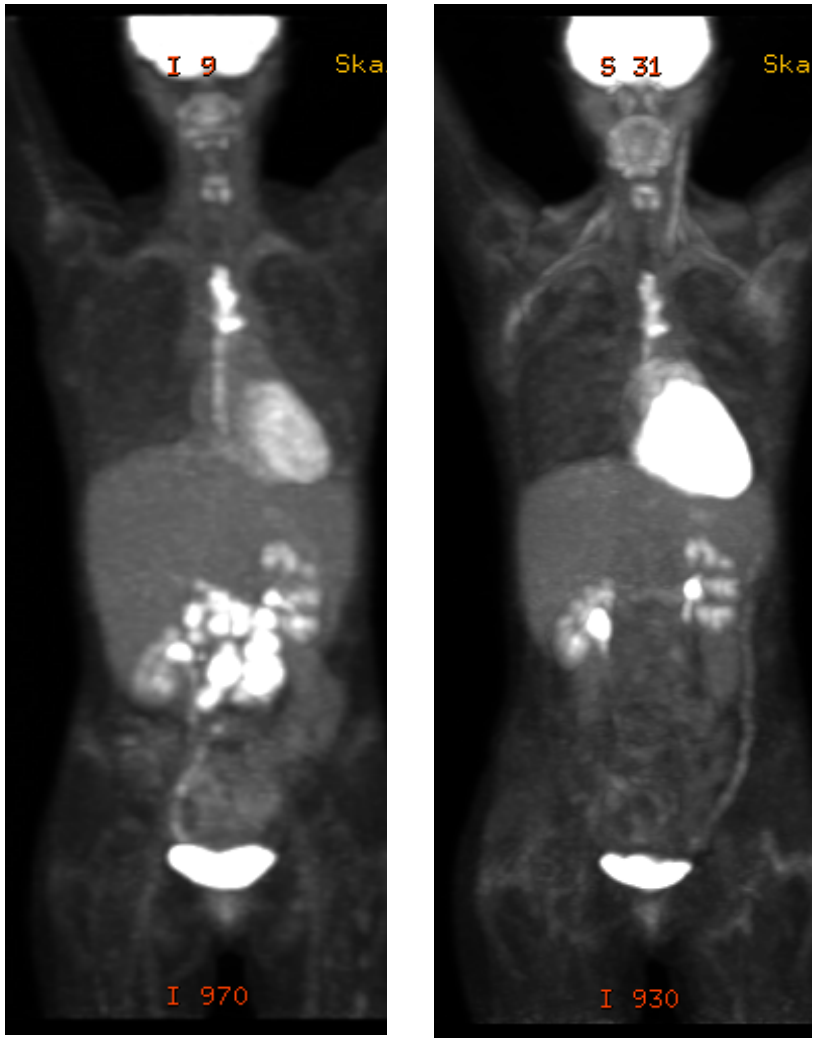
Ansell et al. N Engl J Med. 2015;372(4):311-9.

Lignende Resultater med andre anti-PD1 Antistoffer ved Hodgkin Lymfom - Pembrolizumab

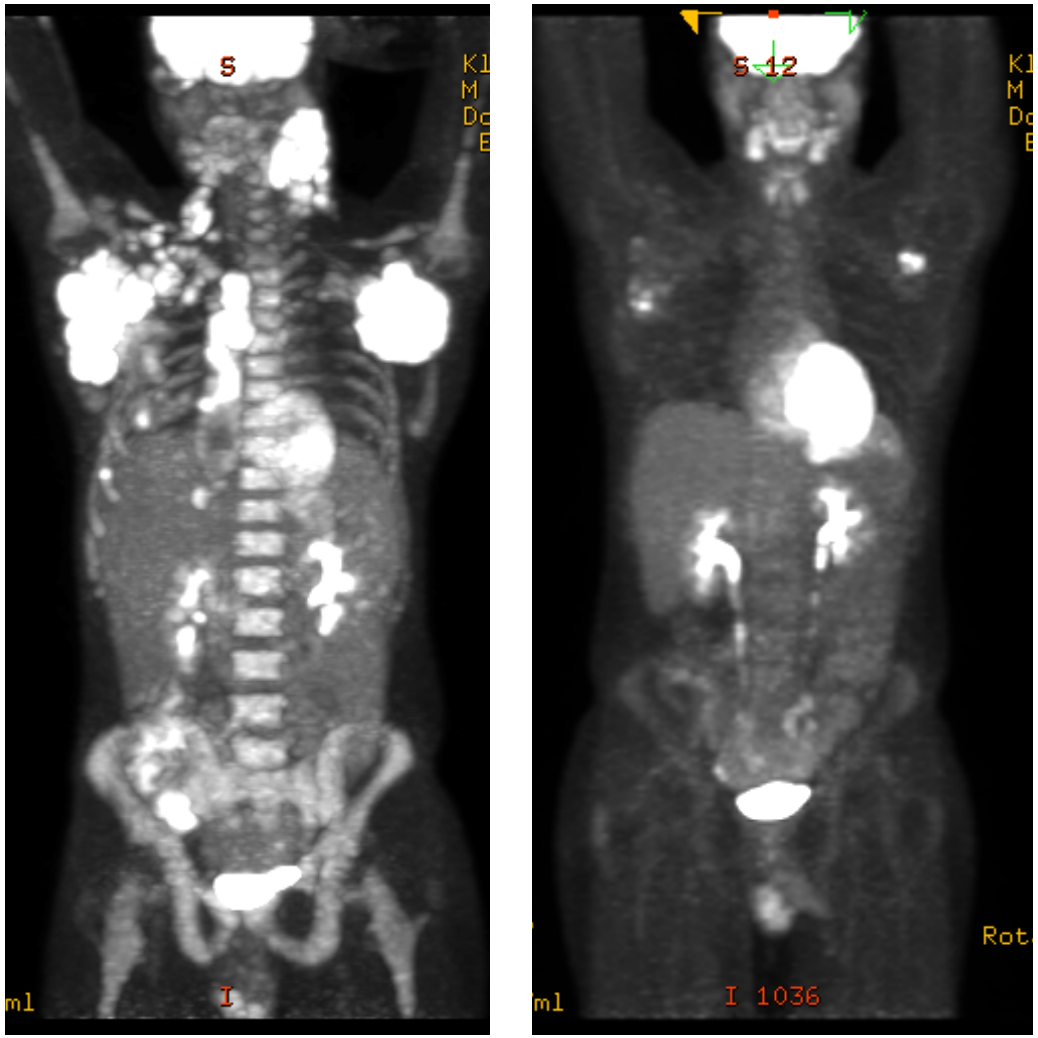


Armand et al. J Clin Oncol. 2016 Jun 27. pii: JCO673467. [Epub ahead of print]

Virker Blokering af PD-1 i praksis?



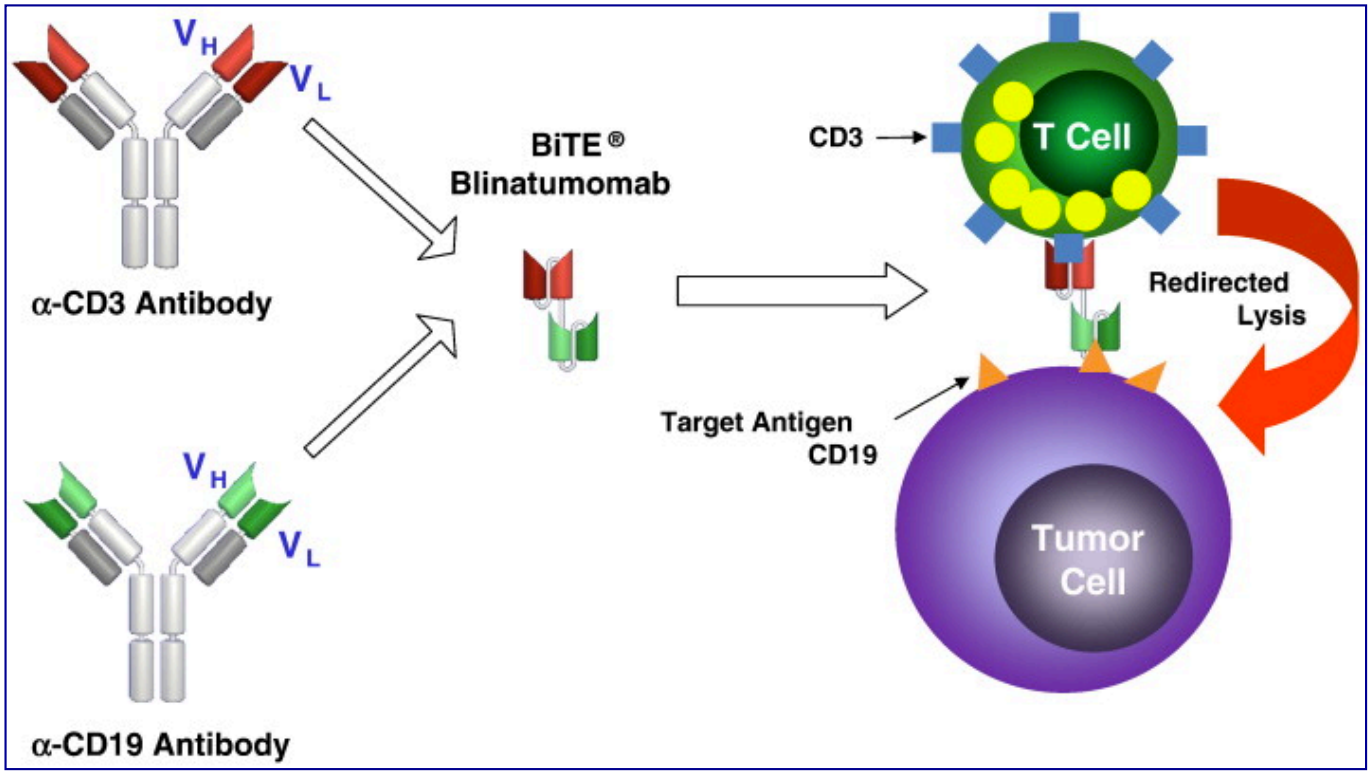
42 year old female – Hodgkin lymphoma

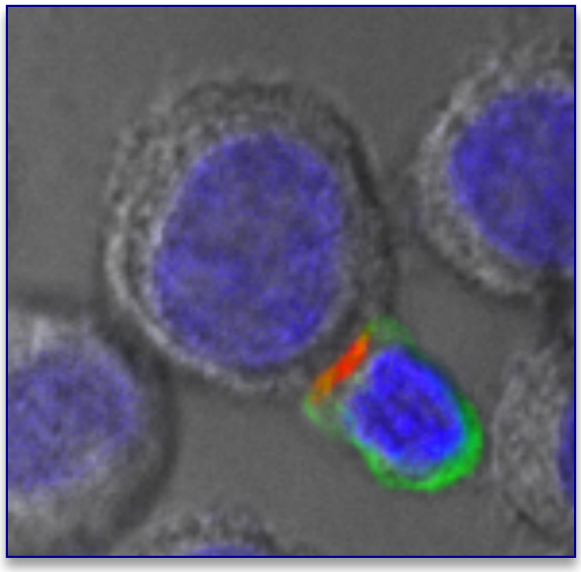


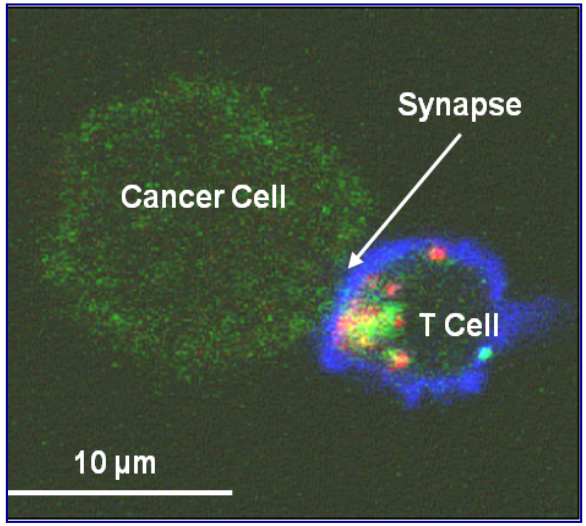
26 year old male – Hodgkin lymphoma

Courtesy of SM Ansell, Mayo Clinic

BiTE: formation of cytolytic synapse
serial killing

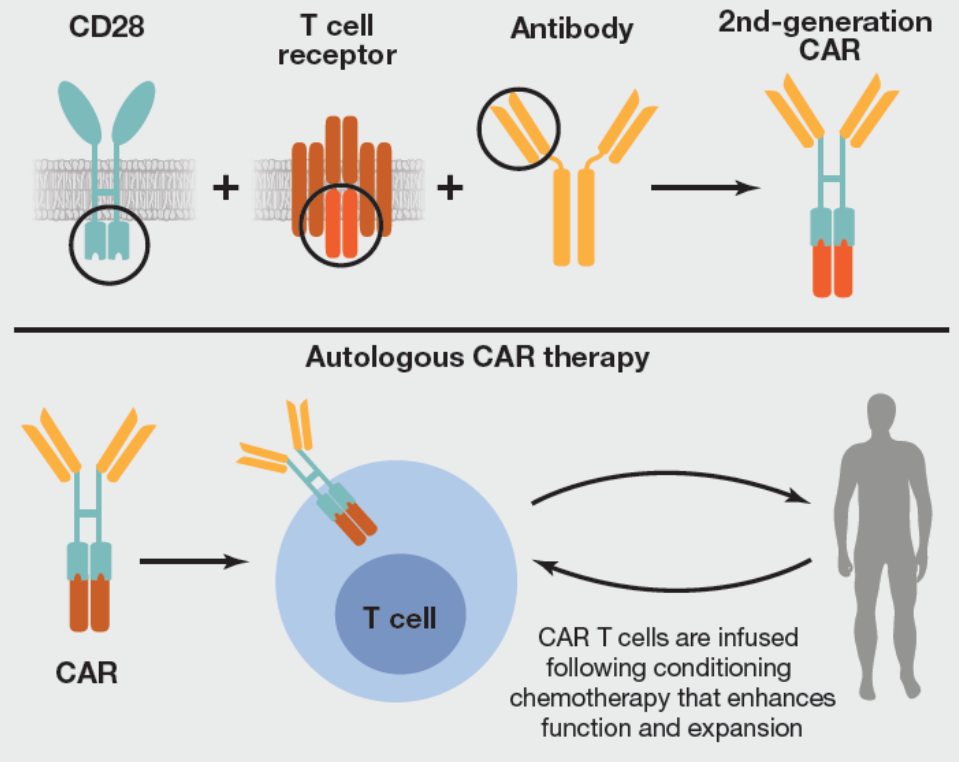






Offner Mol Immunol 2008

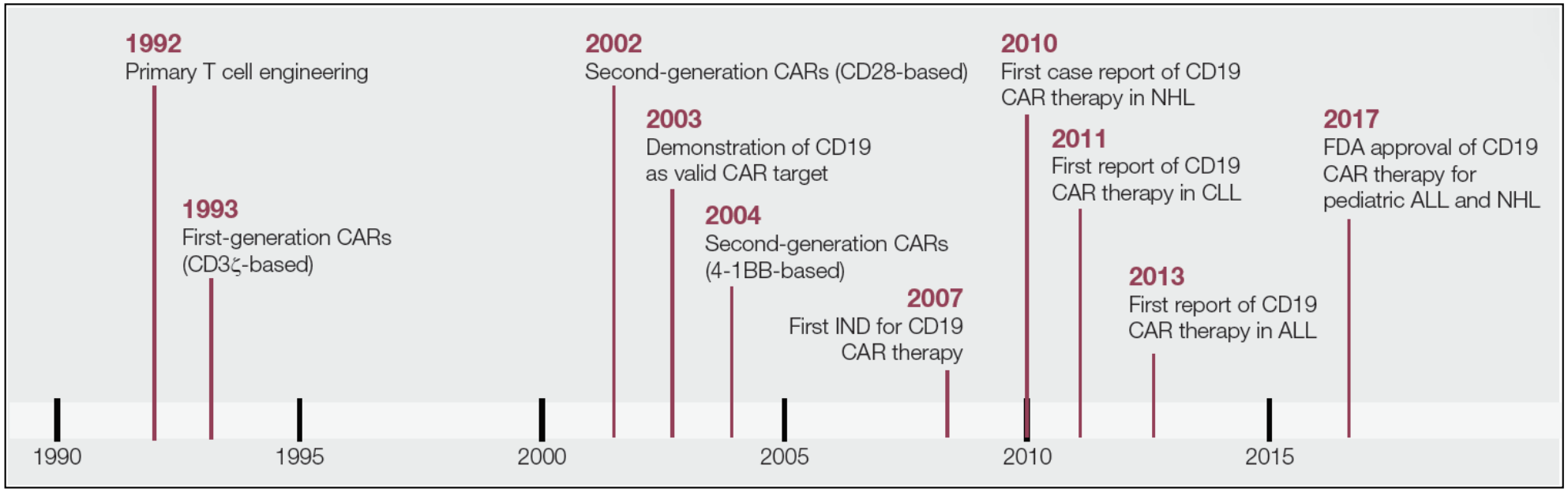
Chimeric antigen receptors (CARs)



Sadelain et al., Cell 2017

- CARs are synthetic receptors that reprogram immune cells for therapeutic purposes
- CARs comprise three canonical domains
  - Antigen recognition
  - T cell activation
  - Costimulation
- The CAR cDNA is genetically integrated in the T cell genome

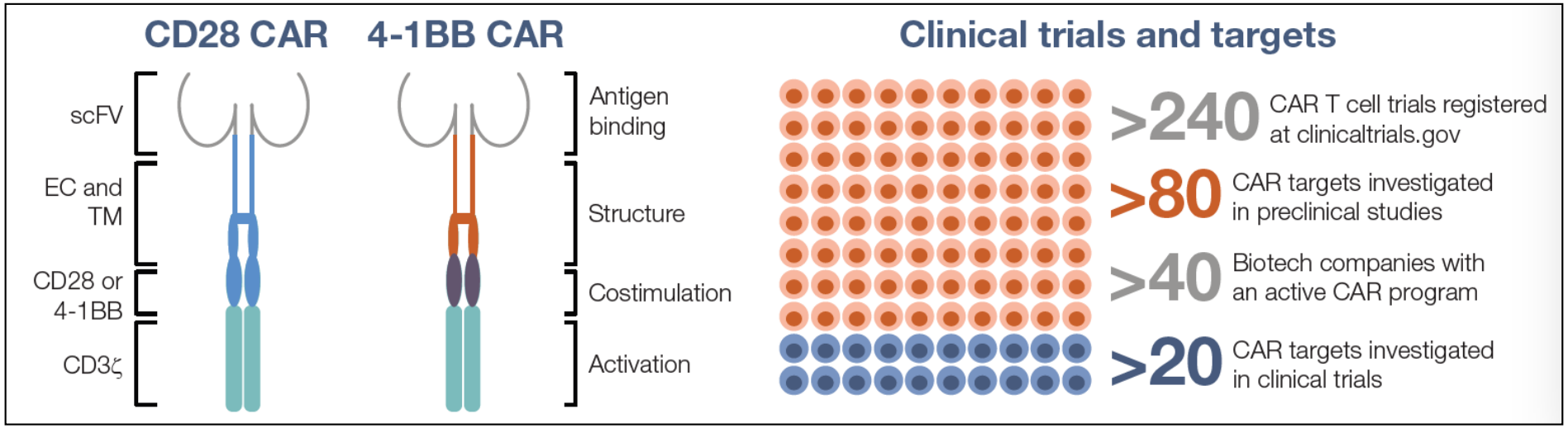
Historie



Sadelain et al., Cell 2017

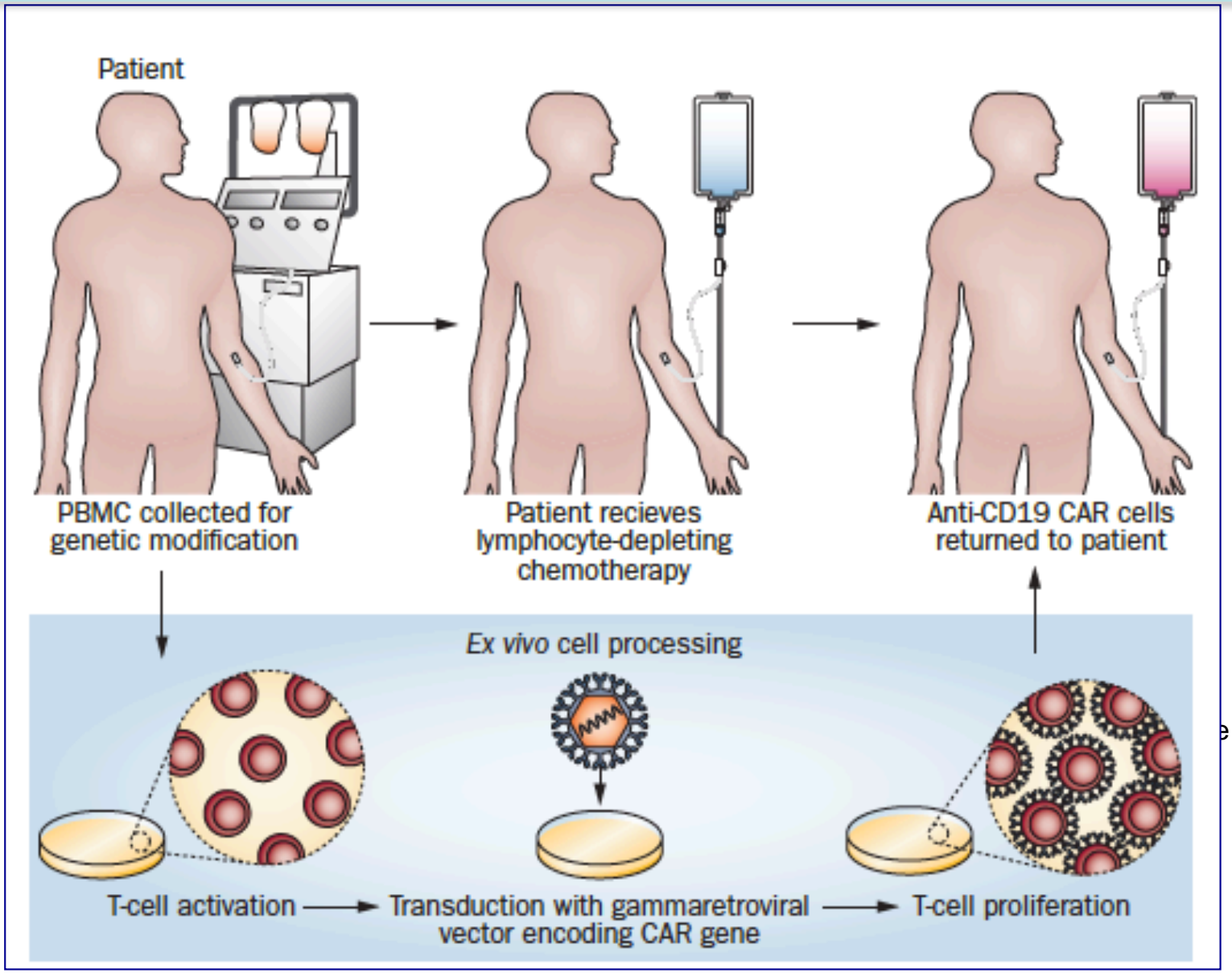
2017

V 2017 FDA approved the first two CD19-targeted CARs, Kymriah (Novartis) and Yescarta (Kite Pharma/Gilead)



Sadelain et al., Cell 2017

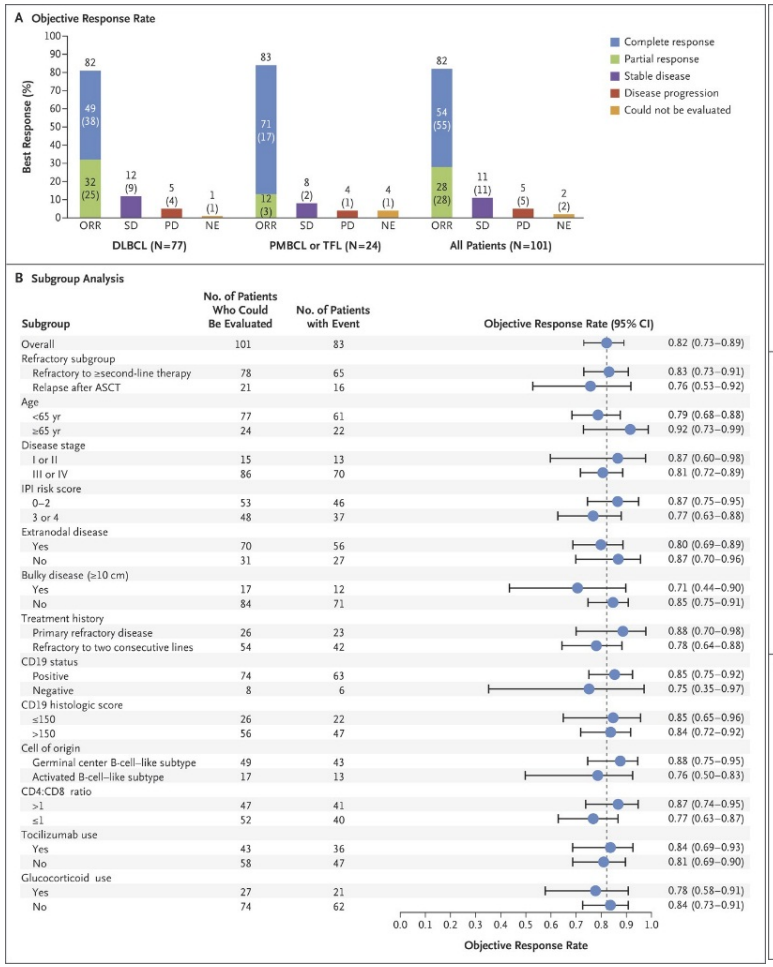
CAR-T cells: behandlingstrin

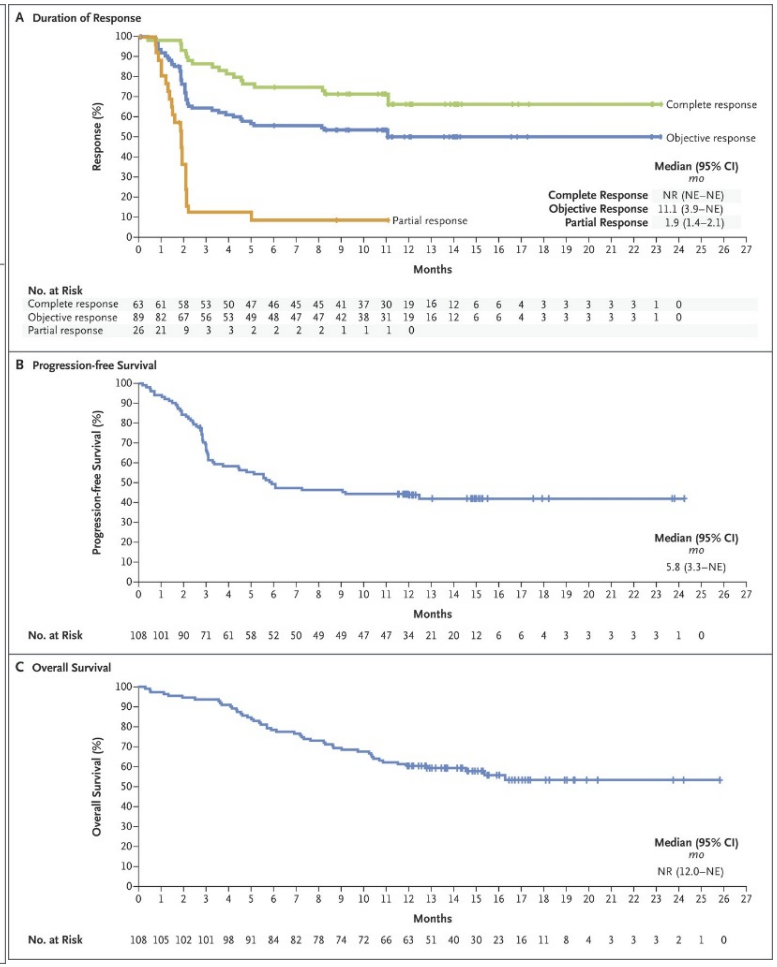


Multicenter trial experiences

- **ZUMA-1**
- **JULIET**
- **TRANSCEND NHL 001**

Zuma-1 trial – Responses and survival





Median DOR 11.1 mo

1 year PFS 41%

1 year OS 52%

Neelapu et al., NEJM 2017

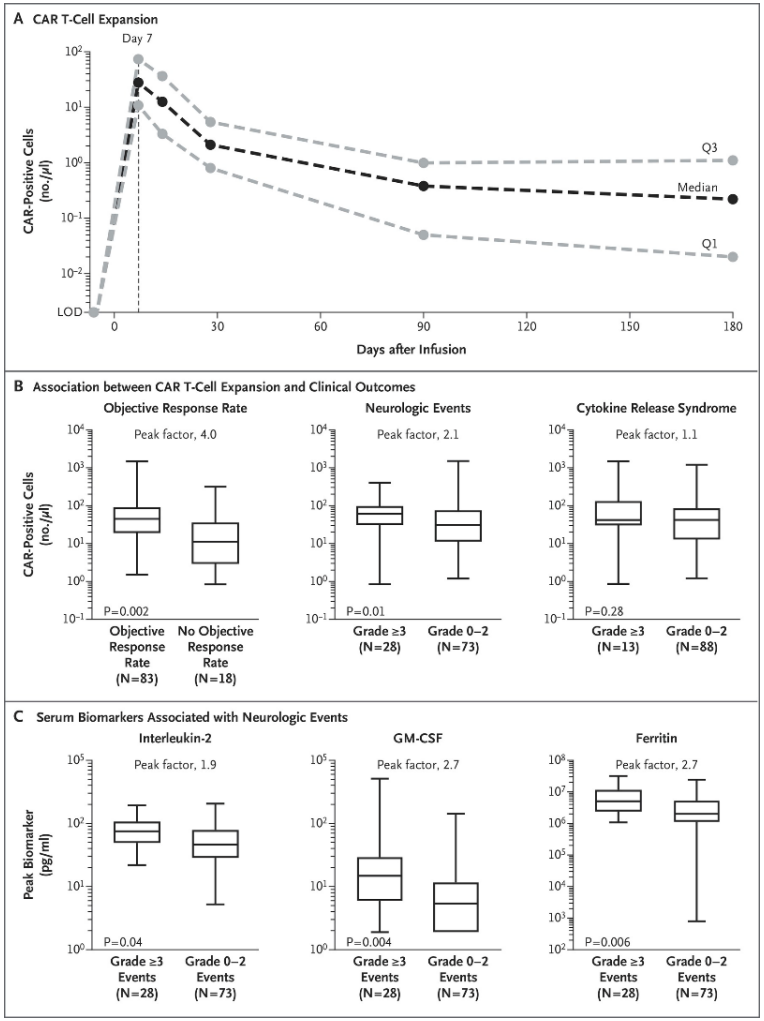
Zuma-1 trial -AEs

Major AEs (Any grades)

- CRS 93%
- Pyrexia 85%
- Neutropenia 84%
- Anemia 66%
- Neurologic events 64%

AEs Grade ≥3

- Neutropenia 78%
- Anemia 43%
- Trombocytopenia 38%
- Febrile neutropenia 31%
- Neurologic events 28%
- CRS 13%



CAR-T cell expansion and correlations with response and AEs

Neelapu et al., NEJM 2017

Næste steps

- Randomized multicenter Phase 3 trials to compare the efficacy and safety of CAR-T cells to standard of care in adult subjects with high-risk, transplant-eligible relapsed or refractory aggressive B-cell non-Hodgkin lymphomas
- CAR-T cells with other targets
  - CD30 (CD30+ HL and NHL)
  - CD20 (CD20+ B- cell lymphomas)
  - CD22 (B-cell NHL)
  - BCMA (Multiple myeloma)
  - CD33 (AML)
  - CD123 (AML)
  - Solid tumors

AARHUS · DENMARK
24–25 MAY 2018

3rd nordic Meeting on Tumor Microenvironment in Lymphoma

Welcome to the 3rd Nordic Meeting
on Tumor Microenvironment in Lymphoma
in Aarhus, Denmark on 24-25 May 2018

We cordially invite you to participate and contribute to the 3rd Nordic Meeting on Tumor Micro-environment in Lymphoma, which will take place at Comwell Congress Center, Aarhus, Den-mark on May, 24-25, 2018.

The primary goal of the meeting is to bring together experts from around the world and from the Nordic countries to discuss the latest breakthroughs within the field, establish the highest prio-rities for investigations and present cutting-edge experiences with novel therapeutic agents.

A faculty consisting of world leading experts in the field will present the scientific program, which will combine keynote lectures on basic microenvironment biology with presentations on specific lymphoma entities.

We look very much forward to welcoming you in Aarhus!
Best regards,
Christian Steidl MD and Francesco d'Amore MD
Conference Chairmen

http://nordictumormicroenvironment.org

DLBCL

DLBCL	Behandling
70K, st 2 (hals+axil), ingen B-symptomer, GCB, lav IPI	R-CHOP-21x3 + IFRT
42M, st 4 (lkn+bihuler+milt), non-GCB og myc+, høj IPI	R-CHOEP-14x6 + 2x interponeret hdMTX (som forebyggelse mod spredning til CNS) (>>Ibrutinib? >Phoenix studie)
1ste relaps 6 mdr senere	R-DHAP + HDT/ASCT
2nden relaps 1 år senere	Recidivkemo evt. + ibrutinib, ved response alloSCT; eller henvisning til udlandet mhp>>CAR-T

FL

FL	Behandling
62M, st 2 (bækken+lyske), ingen bulk, ingen B-sympt, lav FLIPI	Observation uden behandling
70K, st 4 (Lkn+KM), B-sympt, høj FLIPI, co-morbiditet med let hjertepumpesvigt og type2 diabetes med neuropati	R-CHOP/R-CVP/R-Bendamustin>> R-Bendamustin x (4)-6 + vedligeholdelse rituximab i 2 år
62M, vækst af nye lfkn (hals) 3 år senere, fortsat asymptomatisk, normale bl.pr.	PET/CT + biopsi af lfkn. + KM. Er der sket en transformation?
70K, recidiv 3 år senere med lfkn hals, axil, bughule, bækken,lyske, B-symptomer, forhøjet LDH	Biopsi viser transformation: nyt anti-CD20 antistof+recidivkemo (obs hjertetox) + ibrutinib/venetoclax/ radioimmunoterapi/

MCL

MCL	Behandling
57M MCL st 4 (+KM), ingen B-symptomer, ingen co-morbiditet	R-CHOP+R-hdAraC+HDT/ASCT
1ste relaps 1 år senere	R+ recidiv-kemo; Overvej ibrutinib
Senere relapser	Ibrutinib/venetoclax/lenalidomid/bortezomib

Hodgkin

Klassisk HL	Behandling
27K klHL-NS, st III, intermediær IPS	ABVDx2 >> ny PET/CT >> ved mCR, da AVDx4; ved PR/NC, da esc BEACOPPx4-6
1ste relapse	Brentuximab vedotin holdig strategi
2nden relapse	PD1 hæmmere
75M klHL-NS, st IV, høj IPS	AVD+ Brentuximab

CLL/Waldenström

Yngre CLL, p53 muteret	R-FC Undersøg evt beslægtet donormulighed
Richter transformation	Recidiv-kemo eftefulgt af alloSCT Hvis ikke egnet til Tx, overvej PD1 hæmmere
Recidivbehandlingsmuligheder med: Ibrutinib, venetoclax, idelalisib	
80M MbW, træt afkræftet ofte søvnig, hurtigt forværring af AT, IgM 60 g/l (M-komp 50 g/l) – svær co-morbiditet	>>Hyperviskositet! Plasmaferese MYD-88 muteret >> ibrutinib monoterapi

The PANTHEON trial