Immunterapi ved hematologiske kreftformer

Alexander Fosså

Oslo Universitetssykehus


OUR MANAGER IS YOUNG ENOUGH TO HAVE FRESH NEW IDEAS!
AND I'M OLD ENOUGH TO HAVE SEEN THEM ALL BEFORE!
CARTOONSTOCK
Search ID: dbcn752

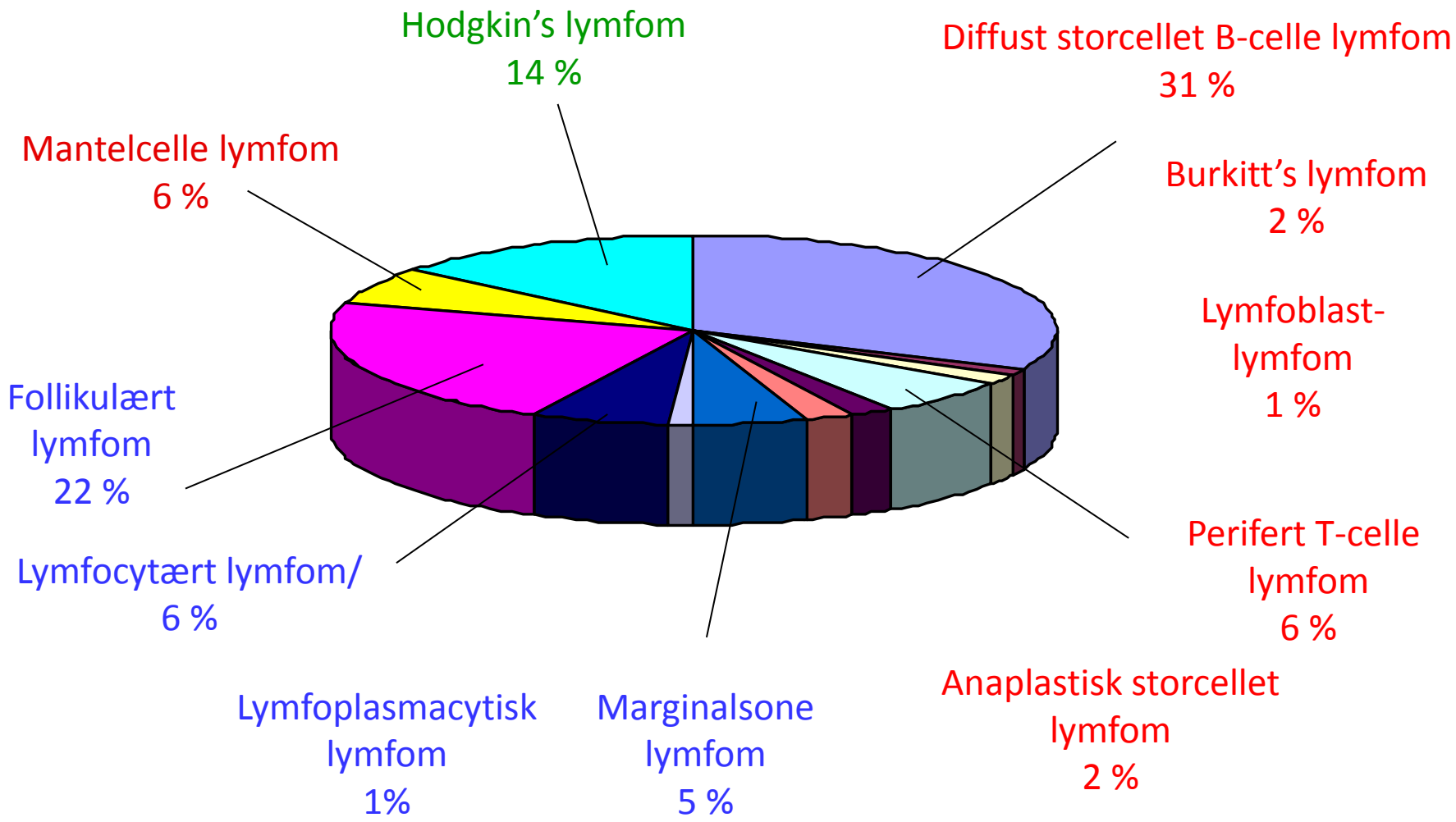
Hvorfor tror vi i det hele tatt at immunterapi skal hjelpe ved lymfom?

- Økt forekomst av lymfom ved immunsuppresjon
  - HIV
  - Organtransplantasjon
  - Medfødte immundefekter
- Monoklonale antistoffer (rituximab, obinituzumab)
- Graft versus lymphoma effect
- …

Tre nye strategier for immunterapi ved lymfom

- Checkpoint hemming i klassisk Hodgkin lymfom
- Kimær antigen reseptor T-celler (CAR-T-celler) ved lymfom
- Bispesifikke antistoffer

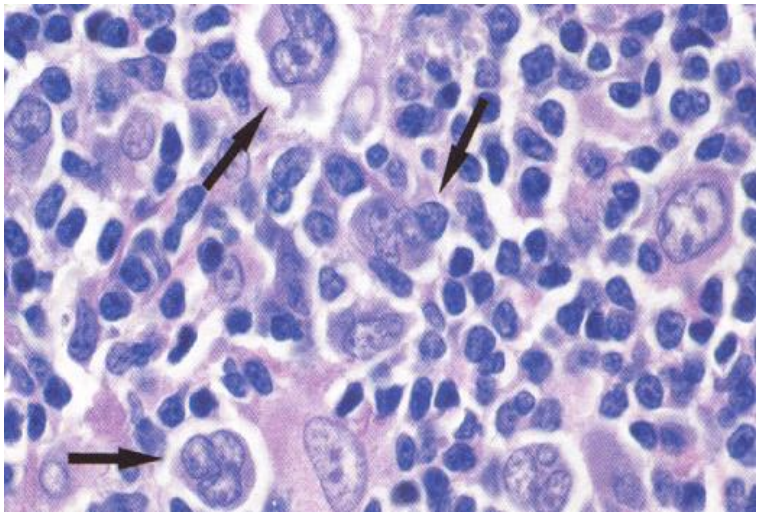
WHO for dummies…



Adaptert fra Nasjonalt handlingsprogram maligne lymfomer, januar 2019

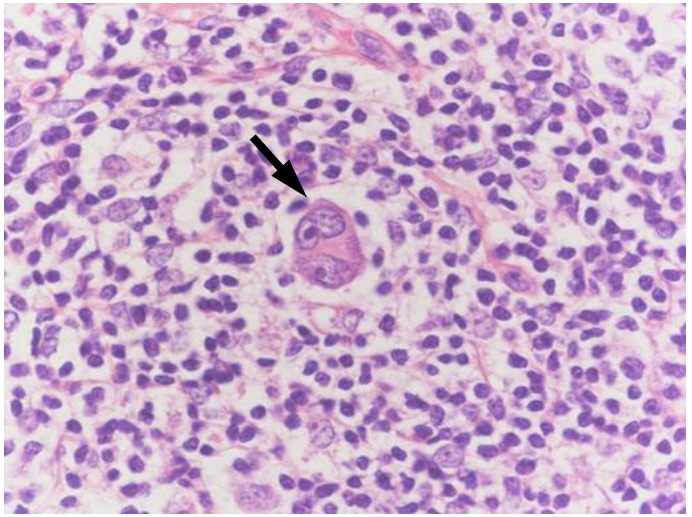
Hodgkins lymfom
-en malign B-celle sykdom

Nodulært lymfocyttrikt HL
5%



Lymphocytic/histiocytic cells
(L&H celler; popcorn celler)

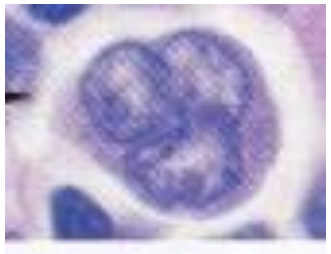
Klassisk HL
95%



Hodgkin celler
Reed-Sternberg celler

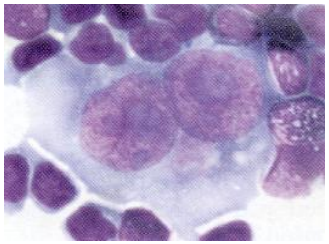
Hodgkins lymfom
-en malign sykdom

L&H celler



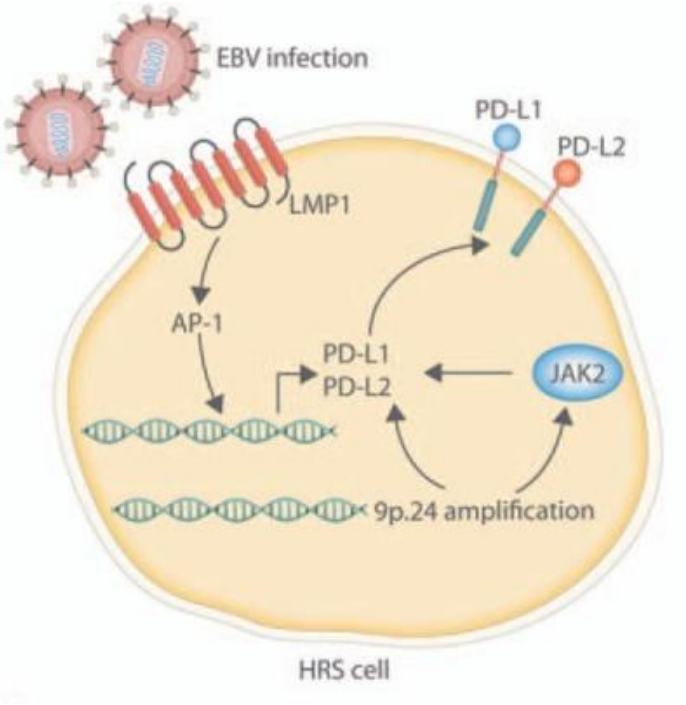
B-celle genotype
Monoklonale
Delvis bevart B-celle fenotype
CD20, CD79a, Pax5
Oct2, BOB.1
Kan være Ig+
Mangler CD30 og CD15

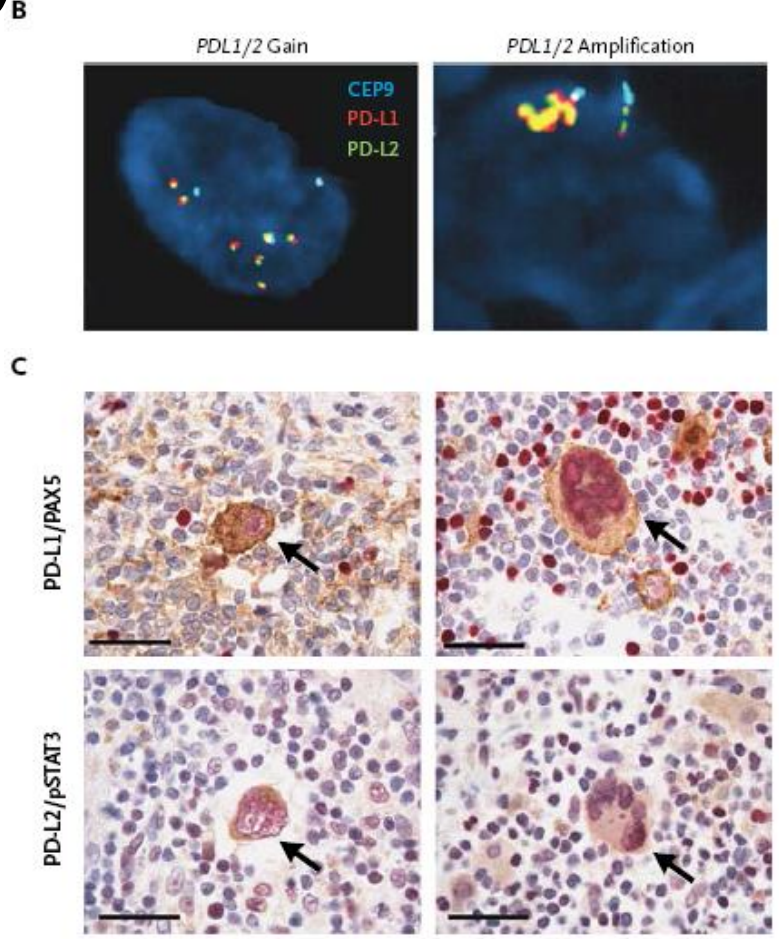
RS celler



B-celle genotype (>98%)
Monoklonale
Mistet B-celle fenotype
CD20, CD79a, Pax5
Oct2, BOB.1
Kan være Ig+
Ekspresjon av **CD30** og CD15 (>85%)
Opphav i germinalcenter celle
Apoptosedefekt? (NFκB, IκB, IκBK, TRAF1, LMP1, EBV)
Overuttrykk av PDL1 og L2
«Kringsatt av fiender – immune escape»

PD-L1 og L2 er overuttrykt i klassisk Hodgkin lymfom

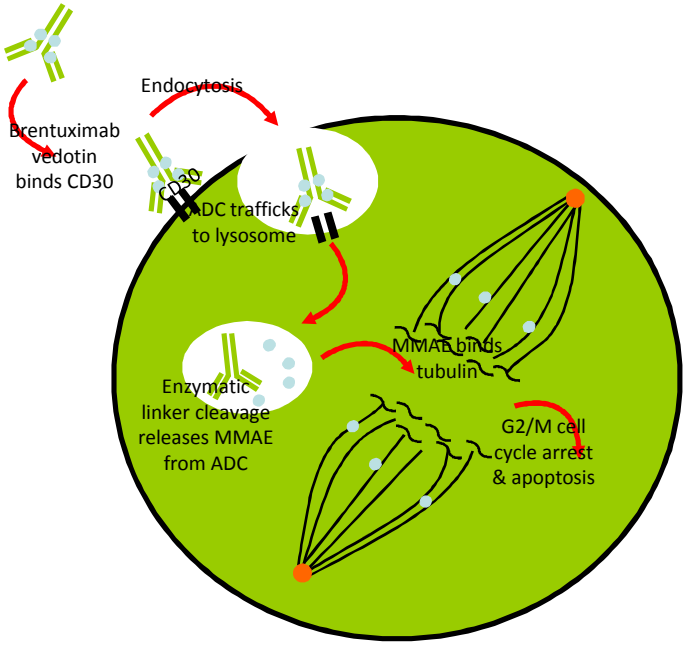


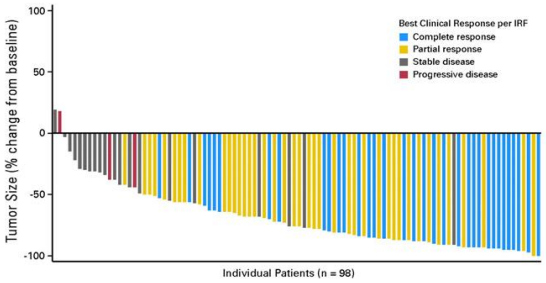


Ansell et al 2014; Roemer at al 2018

Nye behandlingformer for klassisk Hodgkin lymfom

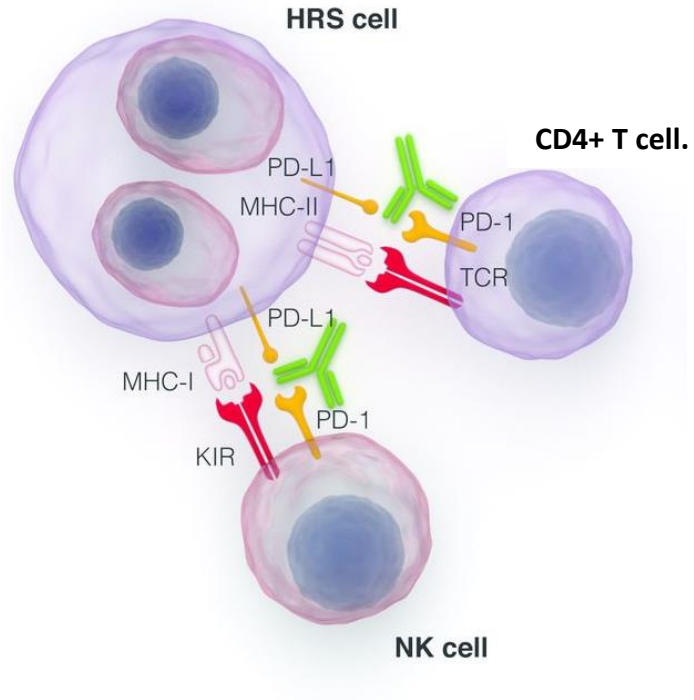
Brentuximab vedotin
Antibody-Drug Conjugate

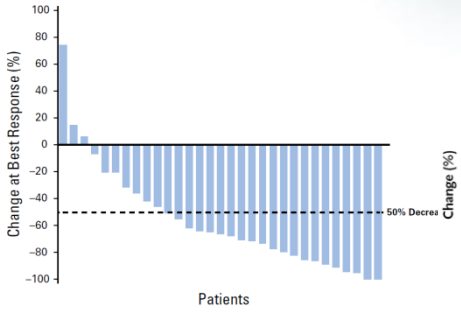




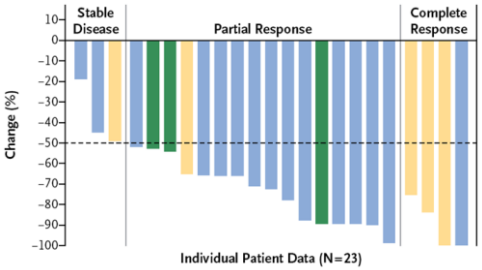
Younes et al; 2012

PD-1 inhibitorer
Nivolumab, Pembrolizumab



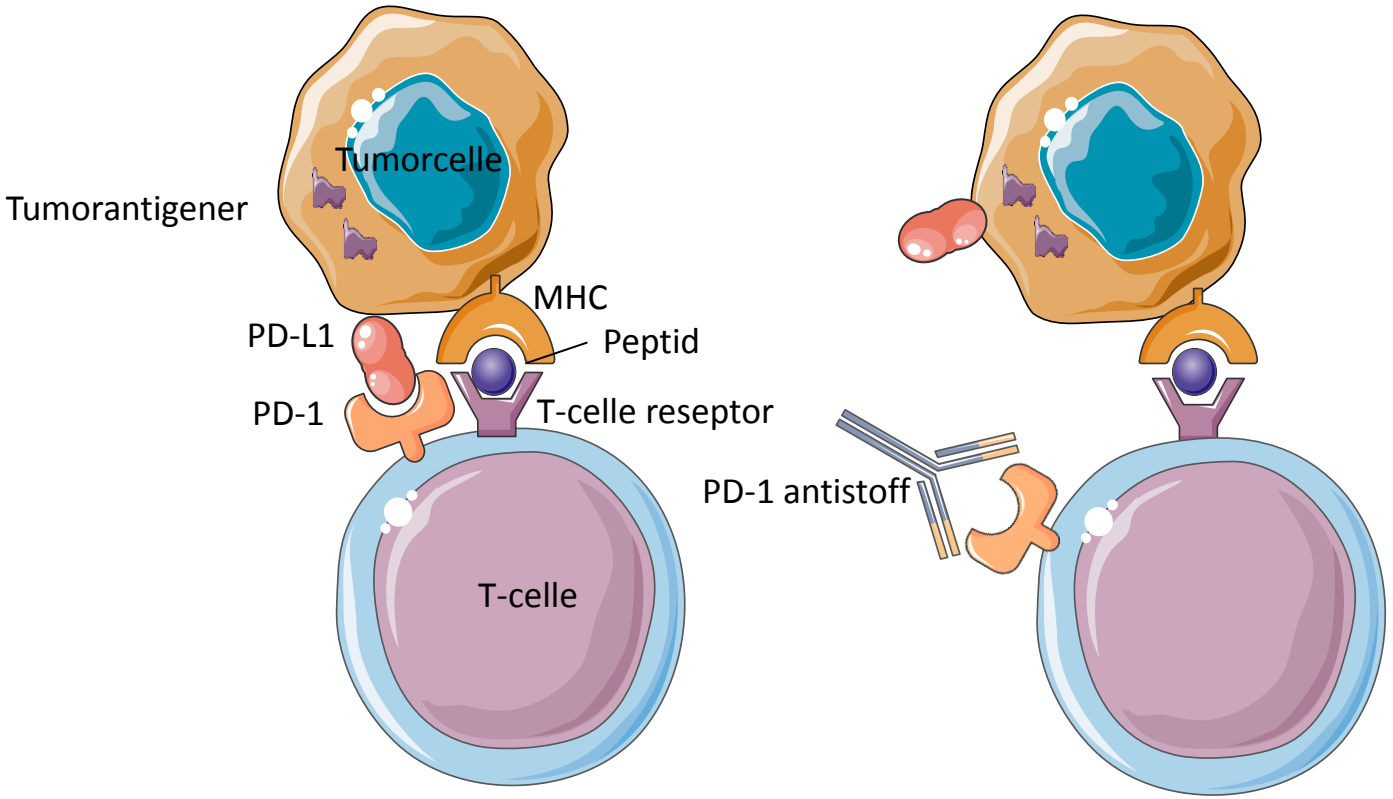


Armand et al; 2016



Ansell et al; 2015.

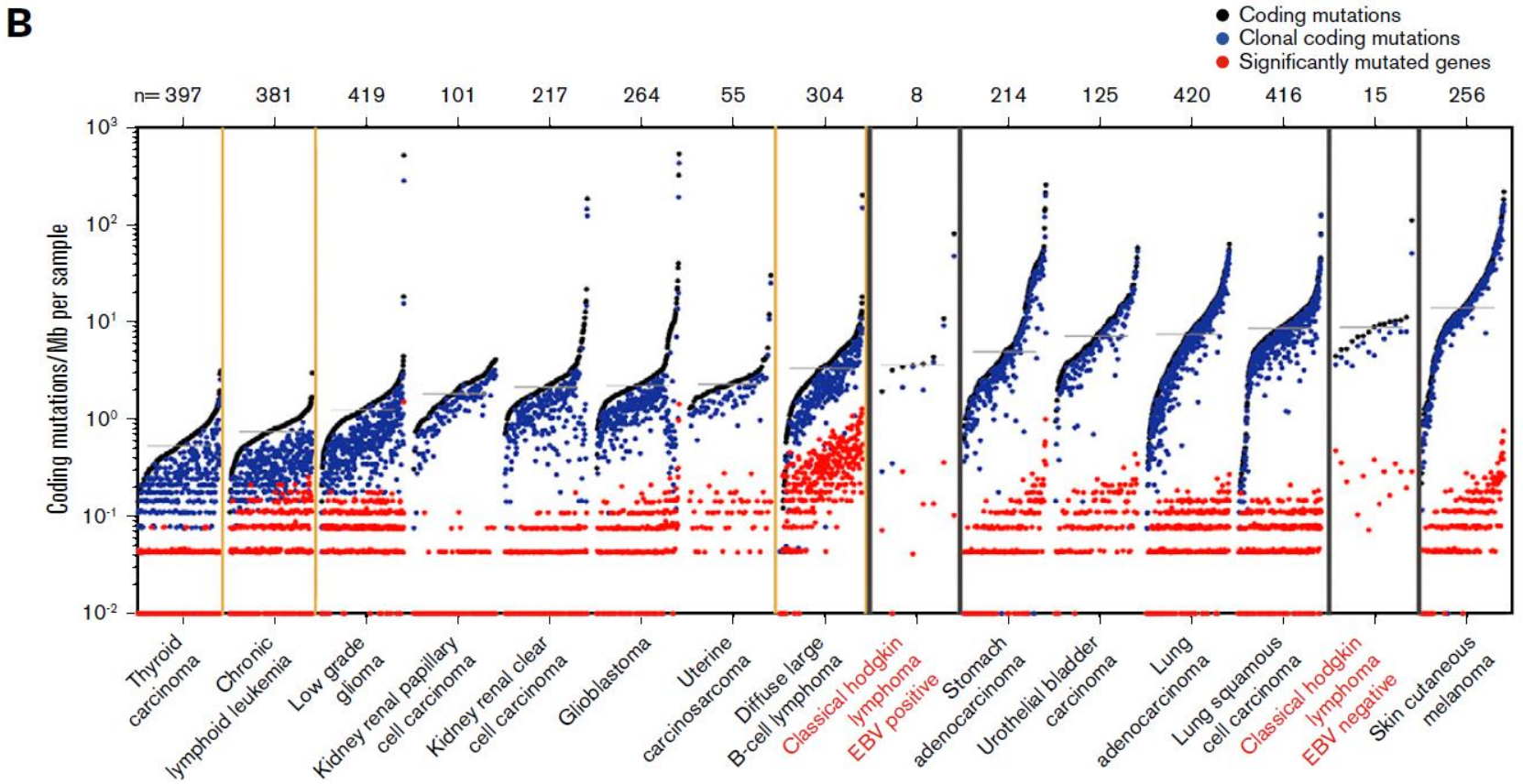
Virkningsmekansime for PD-1 hemmere



PD-1: Programmed death receptor; PD-L1: Programmed death ligand 1; MHC: Major histocompatibility antigen

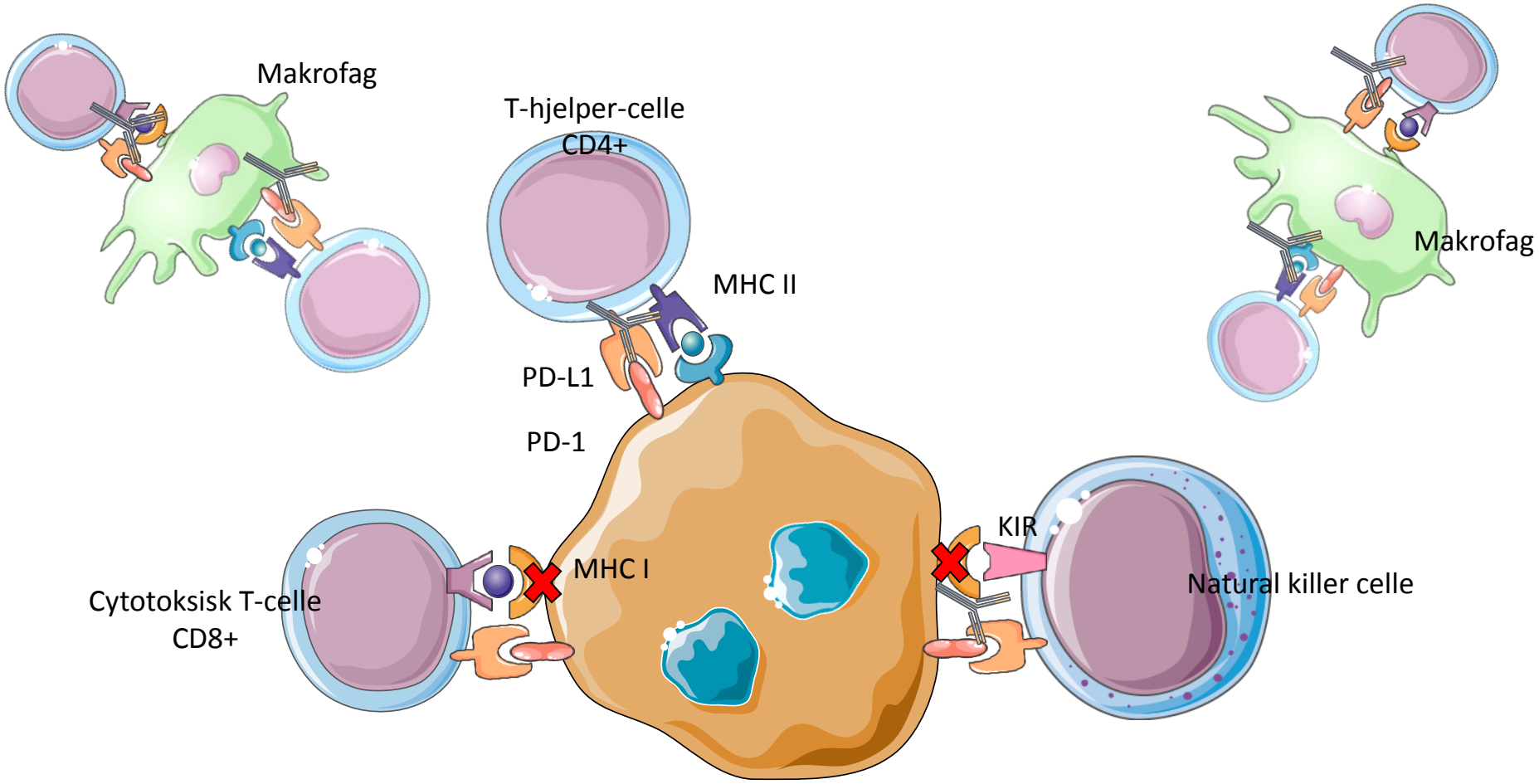
Fra Aamdal E

»Mutational burden» i Hodgkin og Reed Sternberg celler



Wienand et al 2019

Alternativ mekanisme of PD-1 hemmer i klassisk Hodgkin?

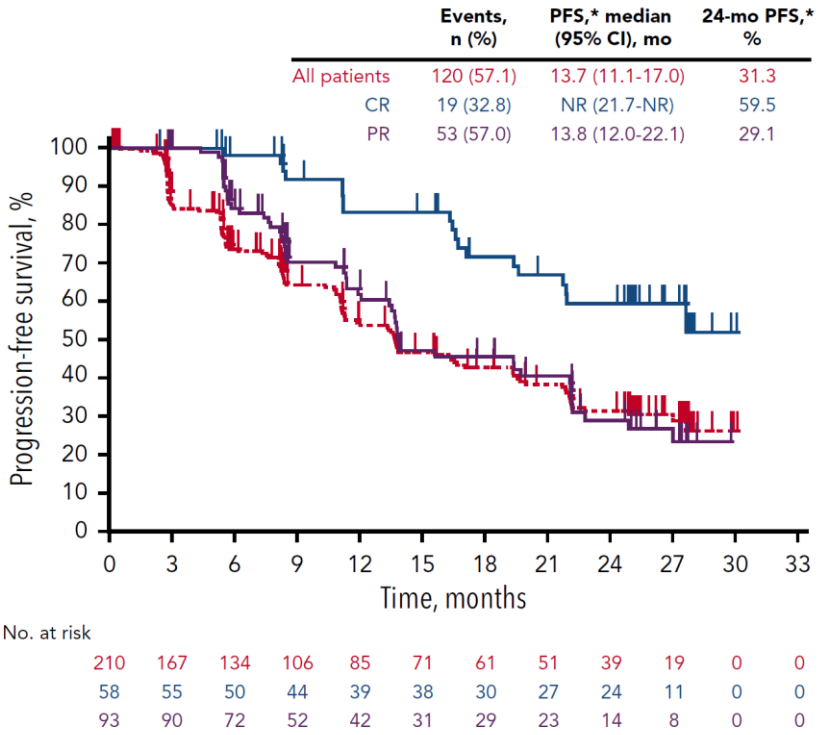


PD-1: Programmed death receptor; PD-L1: Programmed death ligand 1; MHC I/II: Major histocompatibility antigen class I/II; KIR; Killer immunoglobulin-like receptor

Carey et al 2017; Roemer at al 2018, Cader et al 2020

Fase II Pembrolizumab – Keynote 087

	All patients (N = 210)	
	n (%)	95% CI*
ORR	151 (71.9)	65.3-77.9
CR†	58 (27.6)	21.7-34.2
PR	93 (44.3)	37.5-51.3
SD	23 (11.0)	7.1-16.0
PD	32 (15.2)	10.7-20.8
No assessment	4 (1.9)	0.5-4.8

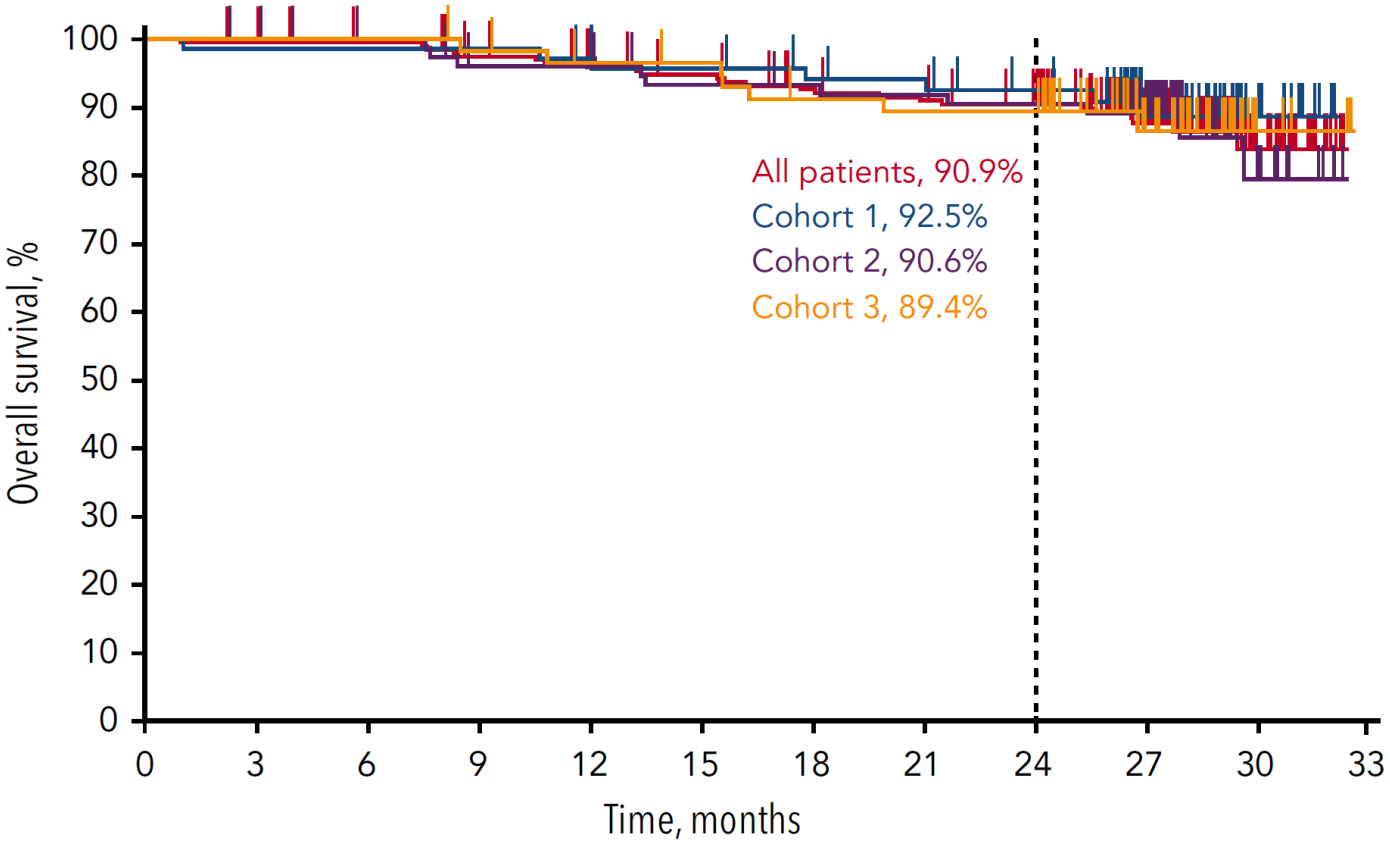


Chen et al 2019

HELSE SØR-ØST

Oslo universitetssykehus

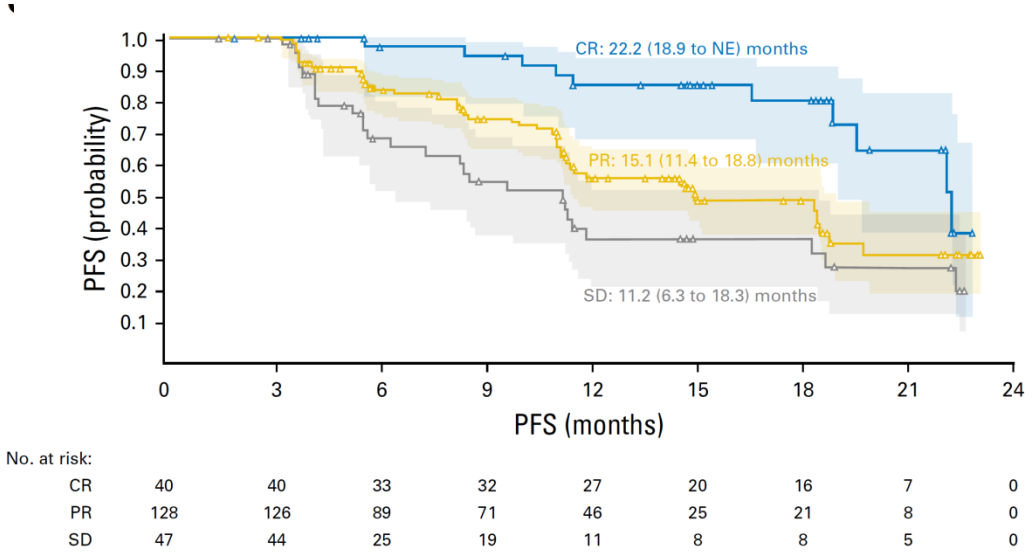
Fase II Pembrolizumab – Keynote 087 – endrer PD-1 hemming biologien?



Chen et al 2019

Fase II Nivolumab – Checkmate 205

Response	All patients (N = 243)
ORR, % (95% CI)	69 (63-75)
Best overall response	
Complete remission	40 (16)
Partial remission	128 (53)
Stable disease	47 (19)
Progressive disease	23 (9)
Unable to determine	5 (2)



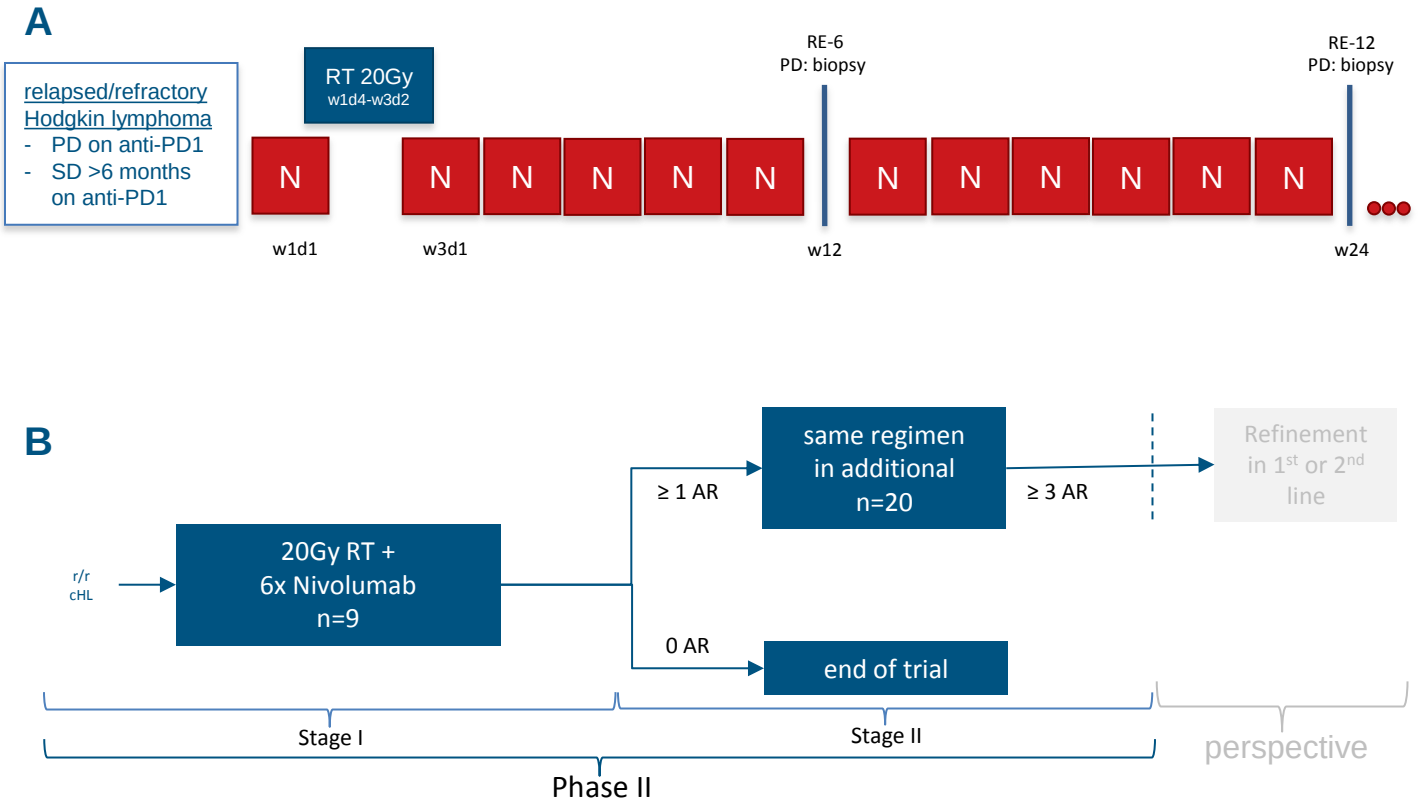
Armand et al 2018

PD-1 hemmere i klassisk Hodgkin lymfom

Trial Intervention	Phase	Status; Estimated Completion Date	ClinicalTrials.gov NCT Reference
Combined with chemotherapy			
Nivolumab and AVD in early-stage unfavorable HL	II	Recruiting; December 2020	NCT03004833
A(B)VD followed by nivolumab as frontline therapy	II	Recruiting; January 2020	NCT03033914
Nivolumab with ICE as second-line therapy	II	Recruiting; April 2019	NCT03016871
Pembrolizumab with ICE as second-line therapy	II	Recruiting; February 2020	NCT03077828
Pembrolizumab and combination chemotherapy in untreated patients	II	Not yet recruiting	NCT03226249
Combined with brentuximab vedotin			
Nivolumab plus brentuximab vedotin vs brentuximab alone in relapsed/refractory HL	III	Recruiting; July 2023	NCT03138499
Nivolumab and brentuximab vedotin with or without ipilimumab in relapsed/refractory HL	I/II	Recruiting; June 2018	NCT01896999
Nivolumab and brentuximab vedotin in older patients with untreated HL	II	Recruiting; May 2024	NCT02758717
Nivolumab and brentuximab vedotin after SCT in patients with relapsed/refractory HL	II	Recruiting; April 2019	NCT03057795
Combined with BTK inhibitors			
Ibrutinib and nivolumab in relapsed or refractory HL	II	Recruiting; May 2020	NCT02940301
ACP-196 (acalabrutinib) with pembrolizumab	Ib/II	Ongoing; April 2021	NCT02362035
Combined with immunodulatory agents			
Nivolumab and lenalidomide in relapsed or refractory NHL or HL	I/II	Suspended; April 2020	NCT03015896
Pembrolizumab and lenalidomide in relapsed NHL and HL	I/II	Recruiting; August 2023	NCT02875067
Combined with HDAC inhibitors			
Pembrolizumab and vorinostat in relapsed or refractory DLBCL, FL, or HL	I	Recruiting; July 2019	NCT03150329
Combined with radiotherapy			
Pembrolizumab and ISRT for early-stage relapsed or primary refractory HL	II	Recruiting; June 2020	NCT03179917

ABVD = adriamycin, bleomycin, vinblastine, dacarbazine, AVD = doxorubicin, vinblastine, and dacarbazine, BTK = Bruton tyrosine kinase, DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, HDAC = histone deacetylase, HL = Hodgkin lymphoma, ICE = ifosfamide, carboplatin, etoposide, ISRT = involved-site radiation therapy, NHL = non-Hodgkin lymphoma, SCT = stem cell transplant.

THE ABSCOPAL EFFECT OF RADIOTHERAPY AND NIVOLUMAB TRIAL



Fra Bröckelmann P

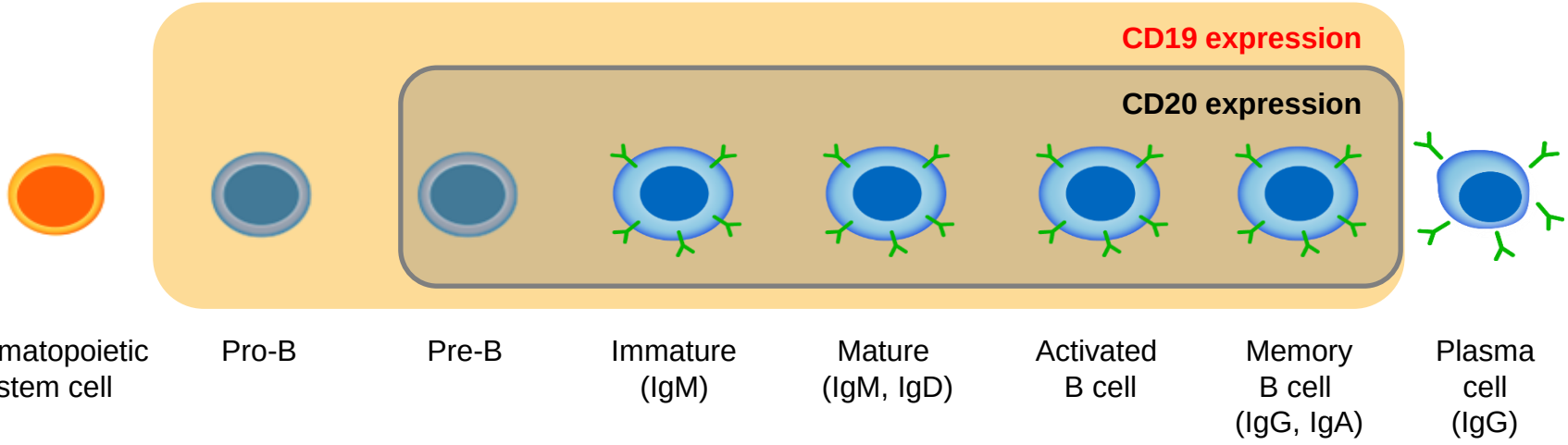
PD-1 hemmere i andre former for lymfom

Type lymfom	Antall pasienter	Overall response rate	Referanse
PMBCL	17	41	Zinzani PL et al, 2017
MF/SS	24	38	Khodadoust MS et al, 2020
RT	9	4	Ding W et al, 2017
PTCL	5	40	Lesokhin AM et al, 2016
FL	10	40	Lesokhin AM et al, 2016
DLBCL	11	36	Lesokhin AM et al, 2016
PTL	?		
PCNSL	?		
CLL	16	0	Ding W et al, 2017
Myelomatose	27	1	Lesokhin AM et al, 2016

PMBCL, Primary mediastinal B-cell lymphoma; MF, Mycosis fungoides; SS, Sezary syndrome; PTCL, Peripheral T-cell lymphoma; FL, Follicular lymphoma; DLBCL, Diffuse large B-cell lymphoma; PTL, Primary Testicular Lymphoma; PCNSL, Primary central nervous system lymphoma; CLL, Chronic lymphocytic leukemia

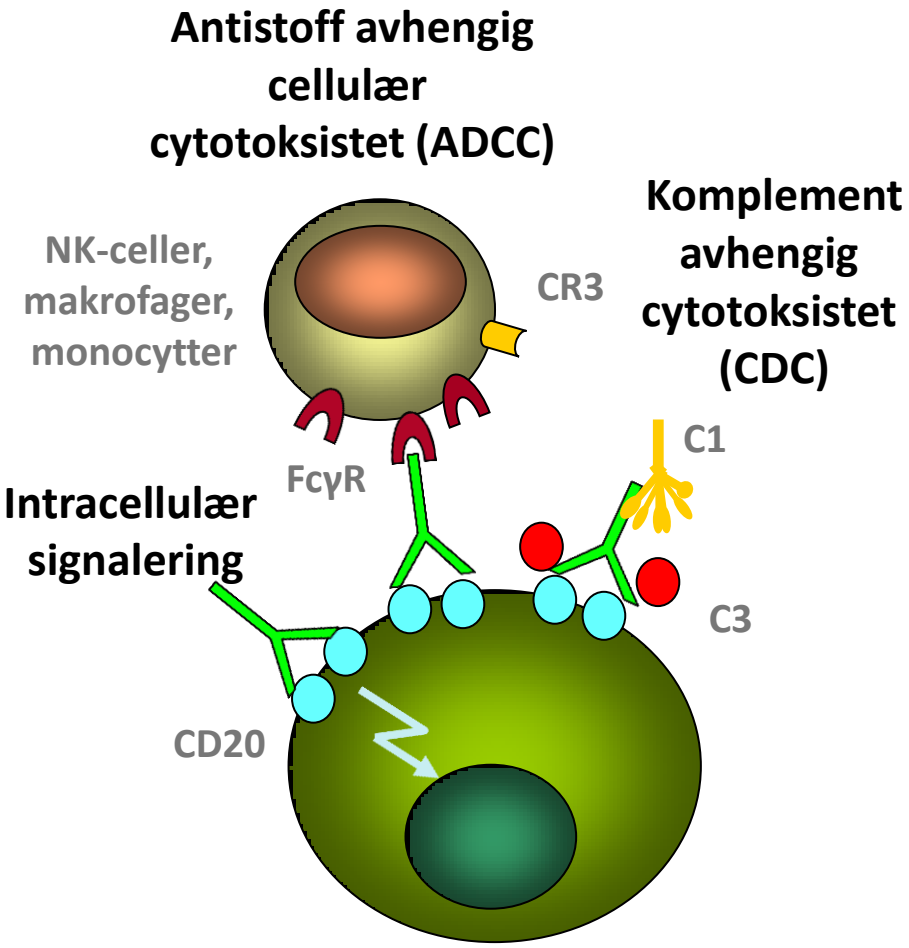
CD19 og CD 20: Gode mål for immunterapi ved B-celle neoplasier

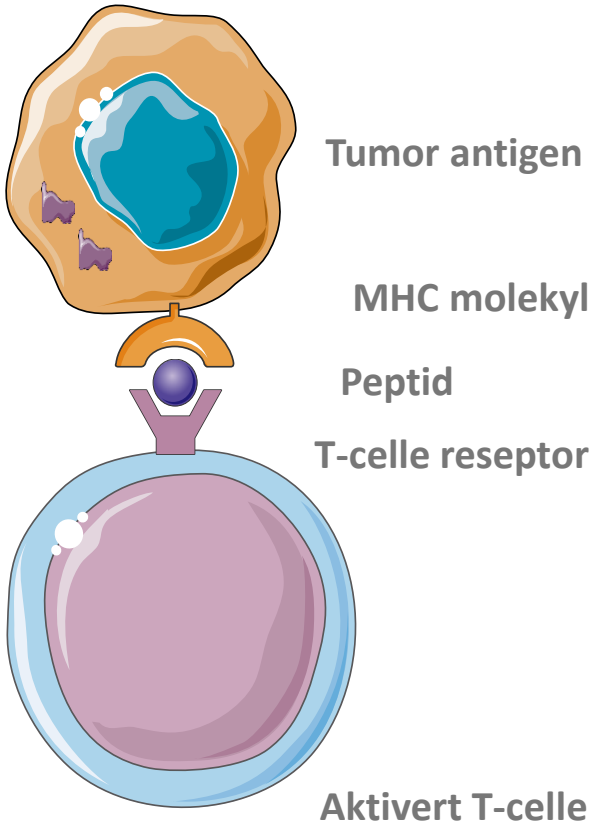
- CD19/CD20 ekspresjon er begrenset til B-celler og B-celle forstadier[1]
  - er ikke uttrykt på hematopoietiske stamceller eller plasmaceller [1]
- Mennesker kan klare seg uten B-celler
- CD19/CD 20 er uttrykt på de fleste B-celle neoplasier
  - KLL, B-ALL, DLBCL, FL, MCL[1]



1. Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397
Image adapted from Janeway CA, Travers P, Walport M, et al. *Immunobiology*. 5th ed. New York, NY: Garland Science; 2001:221-293; Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397; and Feldman M, Marini JC. Cell cooperation in the antibody response. In: Roitt I, Brostoff J, Male D, eds. *Immunology*. 6th ed. Maryland Heights, Missouri: Mosby;2001:131-146.

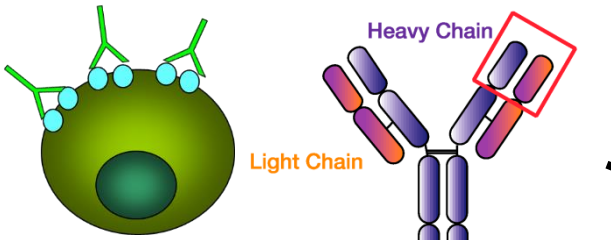
Rituximab - virkningsmekanismer

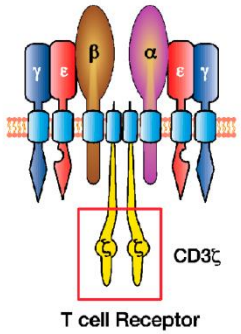


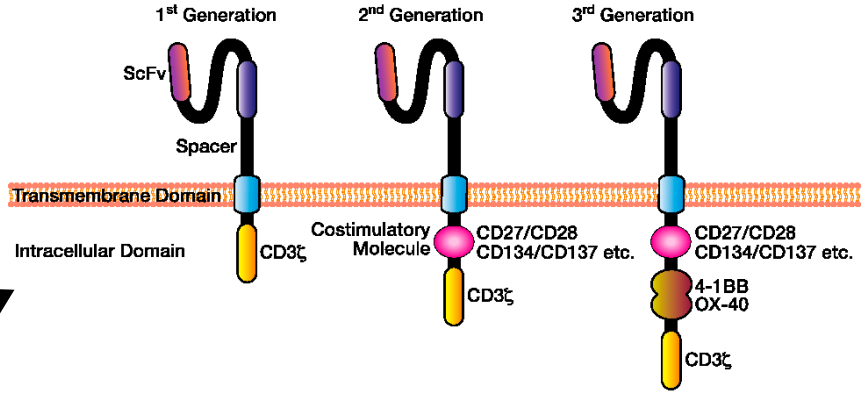


FcγR: Fc gamma reseptor; CR3: Komplementreseptor 3; C1 og C3: Komplementfaktorer 1 og 3; NK-celler: Natural killer celler

T-celle reseptor eller antistoffer?
Kimære antigen reseptorer



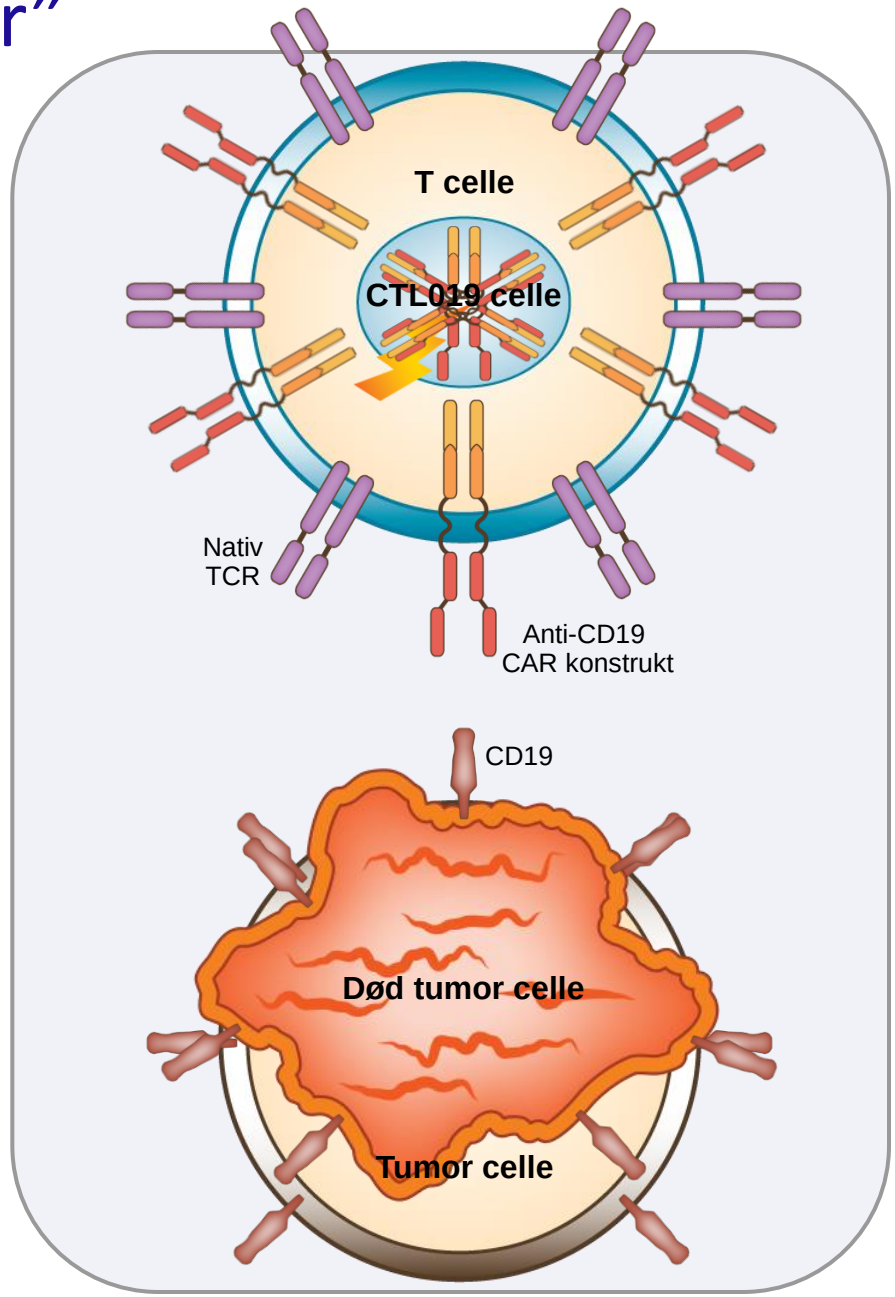




Adaptert fra Milne AA 1926; Hughes-Parry et al 2019

CAR T-celler: Pasientens egne T celler får nye "kimære antigen reseptorer"

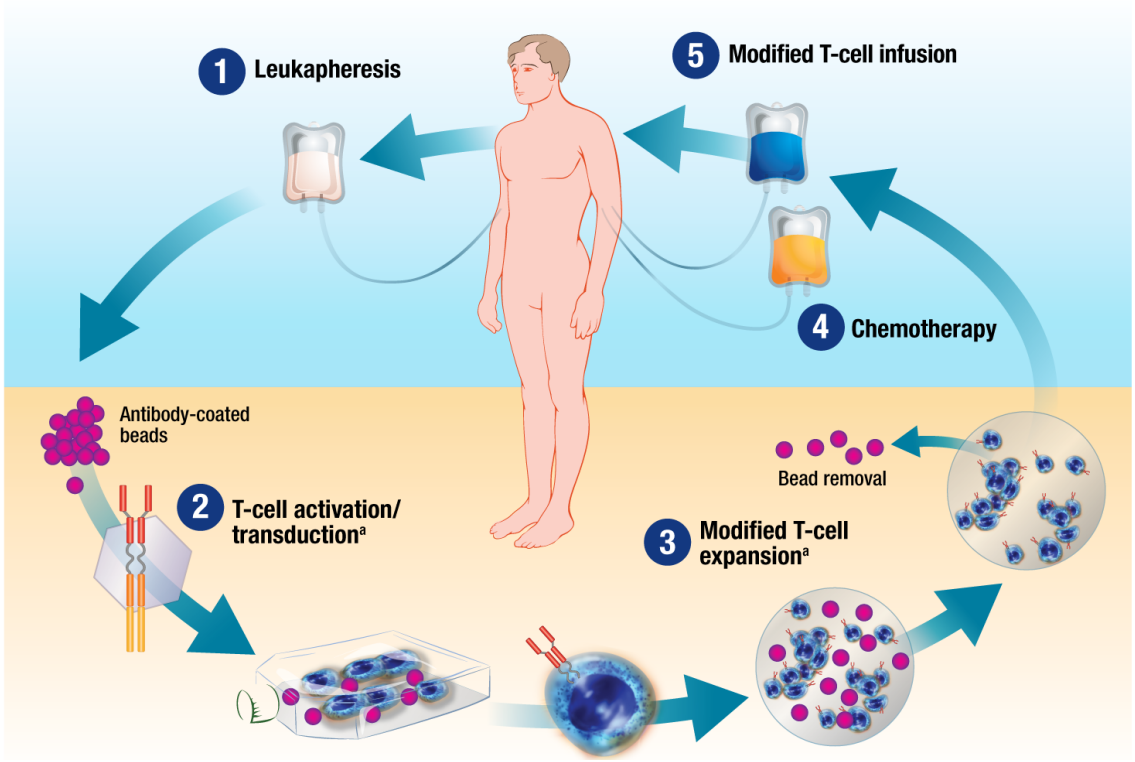
- Flere firma har utviklet CAR T-celler mot CD19, ettervhert flere andre targets
- Gen-terapi som setter inn nye kimære reseptorer mot CD 19 på T celler
- CAR19 T celler ment å drepe alle celler med CD19 på overflaten
- CAR19 cellene ment å overleve i pasienten over tid



Adaptert fra Holte H

CAR-T behandling i klinikken

- CTL019 terapi innebærer adoptiv overføring av autologe T celler som er genetisk modifisert til å uttrykke den kimære anti-CD19 reseptoren



1. **Leukaferese:** pasientens T celler høstes[1-3]
2. **T celler blir genetisk trandusert og aktivert ex vivo** med genkonstrukt som koder for anti-CD19 CAR[1-3]
3. **CTL019 celler blir ekspandert ex vivo** på antistoff-dekkede magnetiske kuler[1-3]
4. **Pasienten får kjemoterapi for lymfodeplesjon -** en lymfotoksisk kjemoterapi rett før reinfujson[1-3]
5. **CTL019 celler blir reinfudert** pasienten[1-3]

[a] Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

1. Kalos M, et al. *Sci Transl Med.* 2011;3(95):95ra73.
2. Porter DL, et al. *J Cancer*. 2011;2:331-332.
3. Porter DL, et al. *New Engl J Med.* 2011;365(8):725-733.

Adaptert fra Holte H

Mange CAR T celle studier i akutt lymfatisk leukemi: Klinisk respons hos ca 80%

Nyheter > Verden

Nyheter | Verden

Kurerte kreft med HIV-virus

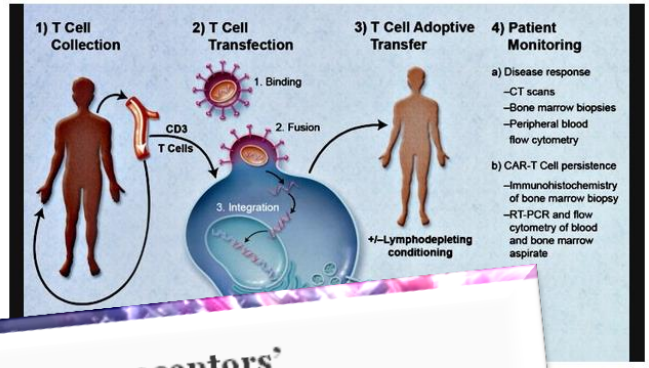
Emma Whitehead er nå tilbake på skolen, og er helt kreftfri. Moren Kari
tilbake.
Foto: JEFF SWENSEN/New York Times

Sju år gamle Emma Whitehead led av leukemi, og var
kreftfri etter å ha blitt behandlet med viruset som forå

The New York Times

UPenn and Novartis form alliance on T Cell therapy for cancer patients

CANCER RESEARCH | AUGUST 6, 2012 | BY: YVONNE P MAZZULO | + Subscribe



Posts Tagged 'chimeric antigen receptors'

Center for Advanced Cellular Therapies at U Penn gets $20MM funding from Novartis

Posted in CANCER BIOLOGY & Innovations in Cancer Ther
Molecular Genetics & Pharmaceutical, Pharm

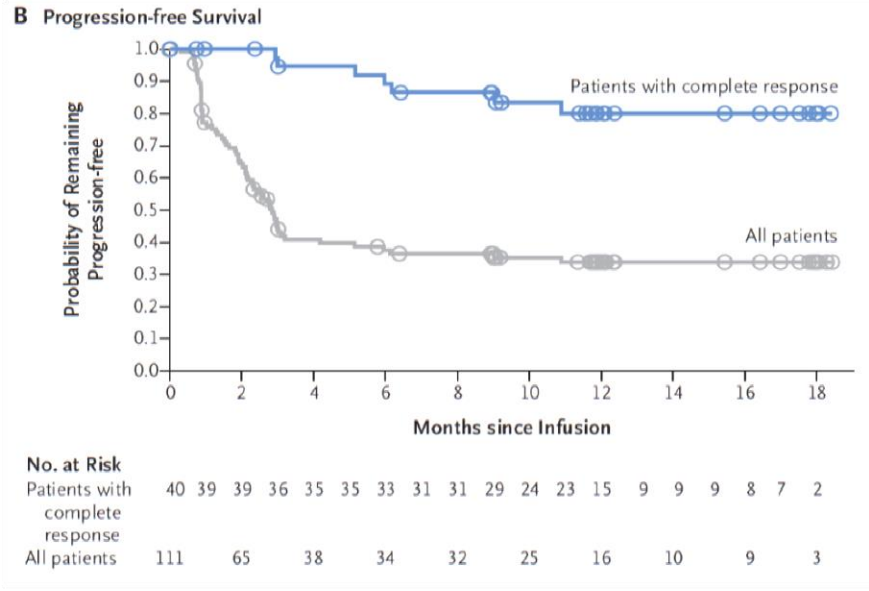
Science Translational Medicine
AAAS

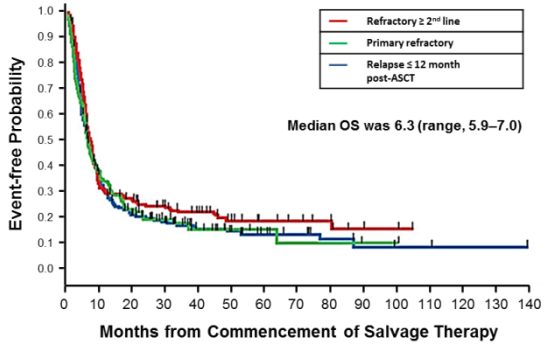
CD19-Targeted T Cells Rapidly Induce Molecular Re
with Chemotherapy-Refractory Acute Lymphoblastic
Renier J. Brentjens *et al.*
Sci Transl Med **5**, 177ra38 (2013);
DOI: 10.1126/scitranslmed.3005930

JULIET: CAR19 for refraktært/residivert diffust storcellet B-celle lymfom

Objektiv tumor respons

	Rate	95 % Confidence interval
Overall	52%	41-62%
Complete response	40 %	
Partial response	12 %	

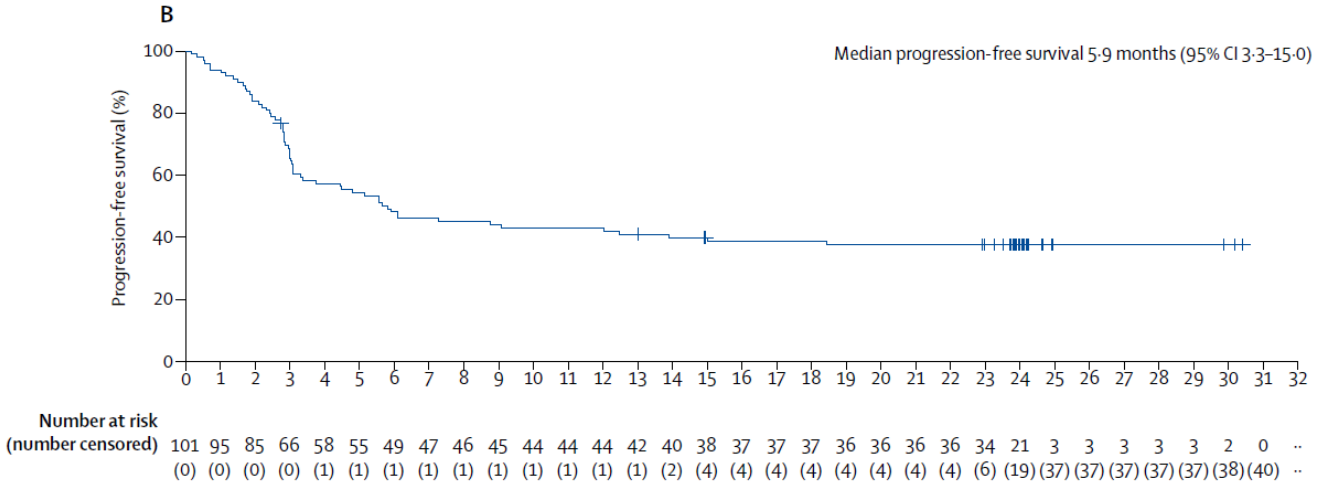




Schuster et al 2019; Crump et al 2017

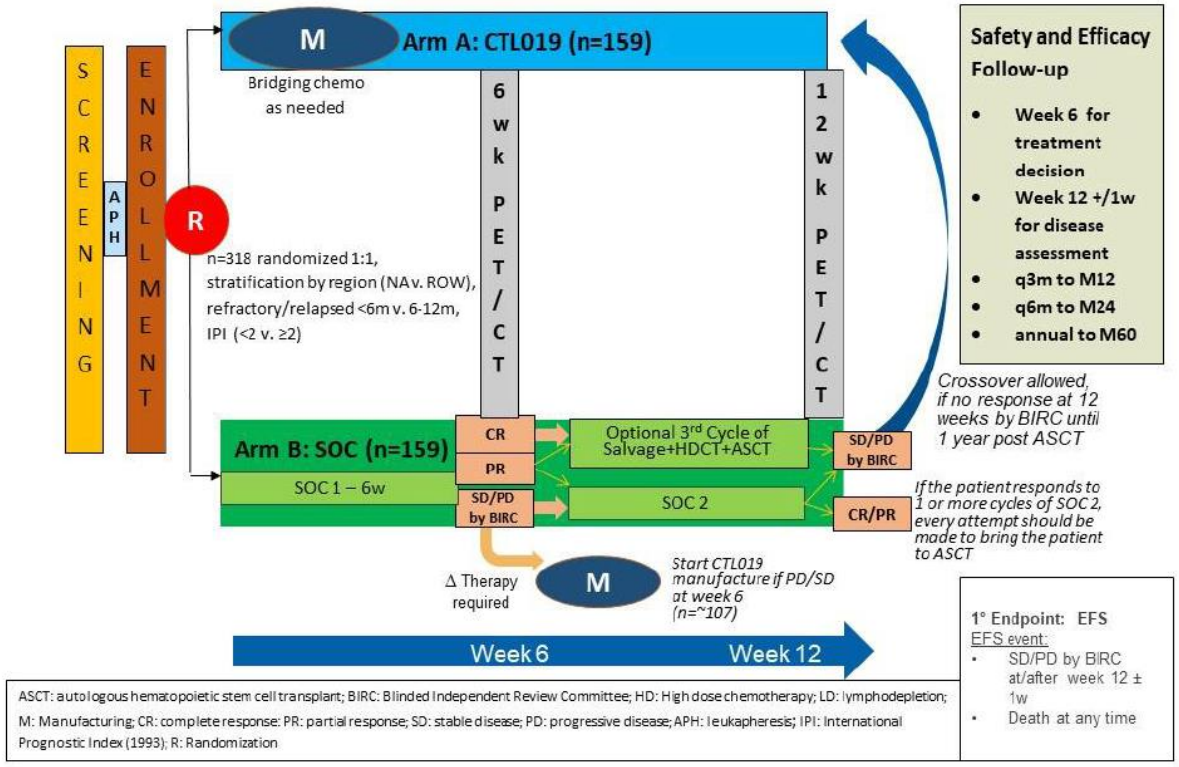
Zuma-1: CAR19 for refraktært/residivert diffust storcellet B-celle lymfom

	Investigator-assessed (n=101)	IRC-assessed (n=101)
Objective response*	84 (83%)	75 (74%)
Complete response†	59 (58%)	55 (54%)
Partial response	25 (25%)	20 (20%)
Ongoing response‡	39 (39%)	36 (36%)
Complete response	37 (37%)	35 (35%)
Partial response	2 (2%)	1 (1%)



Locke et al 2019

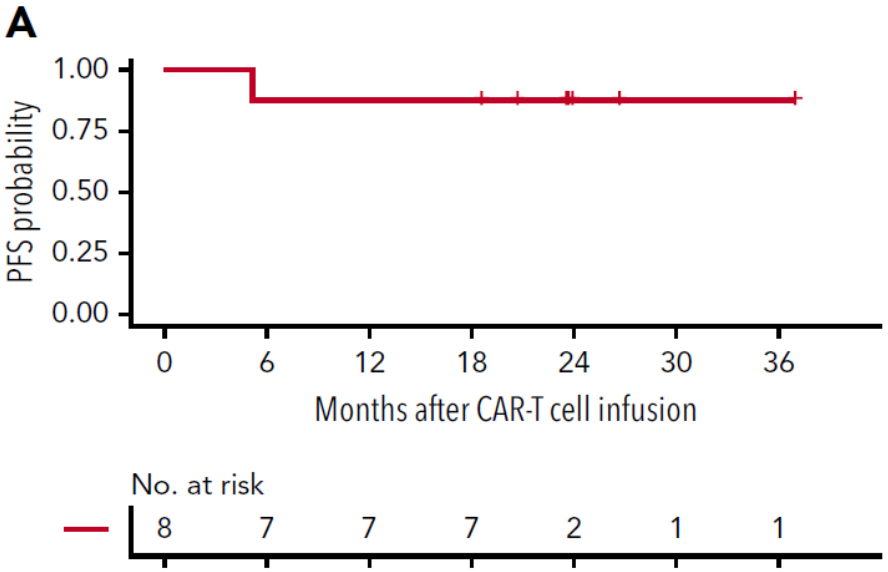
Belinda: CAR19 for refraktært/residivert diffust storcellet B-celle lymfom

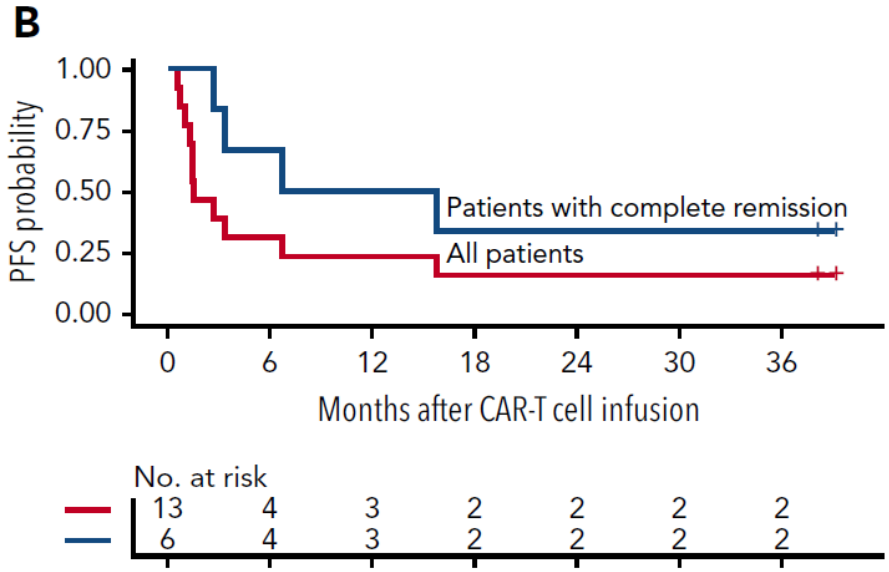


CAR 19 T-celler i follikulære lymfomer

Follikulære lymfomer n=8
Rate komplett remisjon 88 %

Transformerte lymfomer n=13
Rate komplett remisjon 46 %

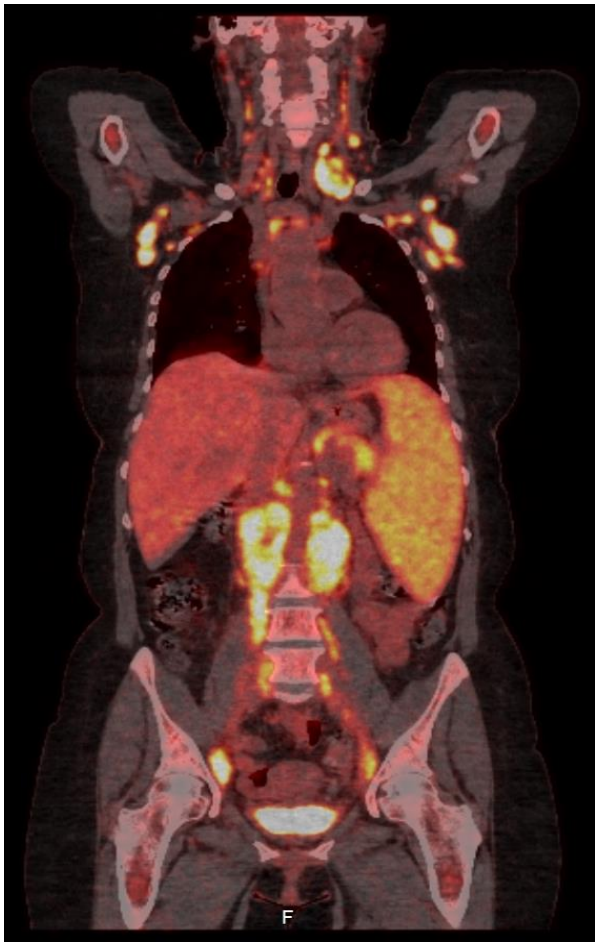




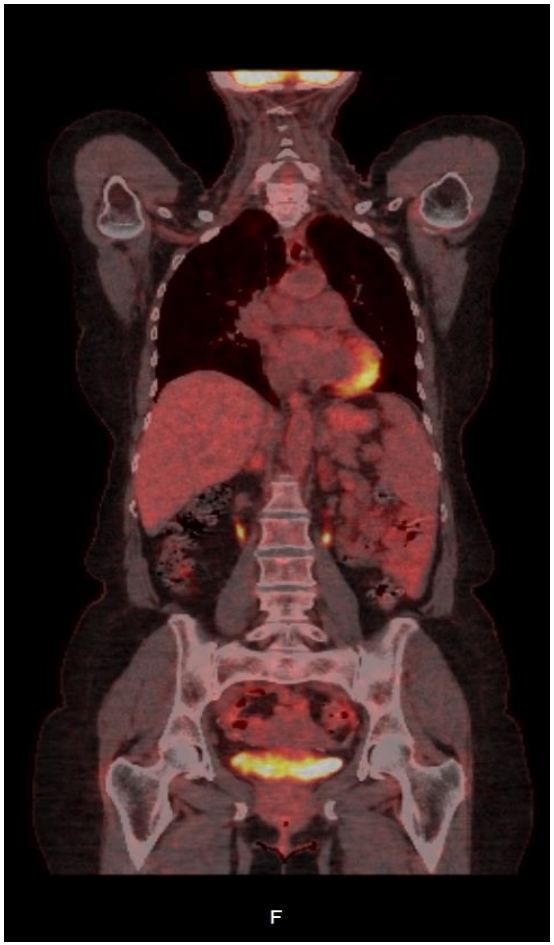
Hirayama et al 2019

ELARA-studien: Første norske pasient

Før Kymriah®
(Tisagenlecleucel)



3 måneder etter Kymriah®



2004 Follikulært lymfom

2004 Oral kjemoterapi

2011 R-CHOP x 6

2011-13 R vedlikehold

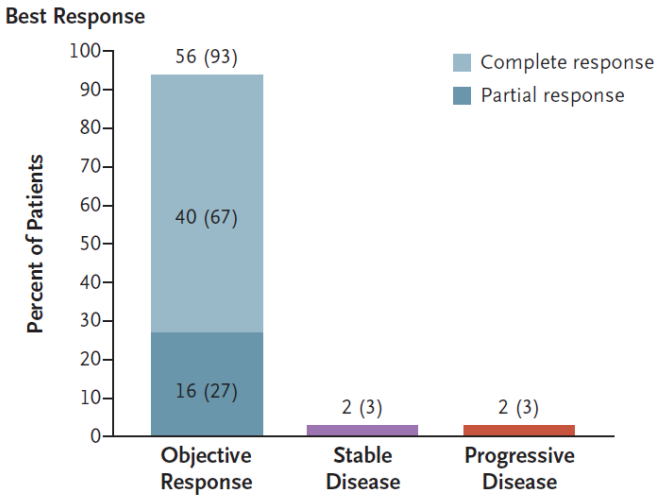
2017 HMAS

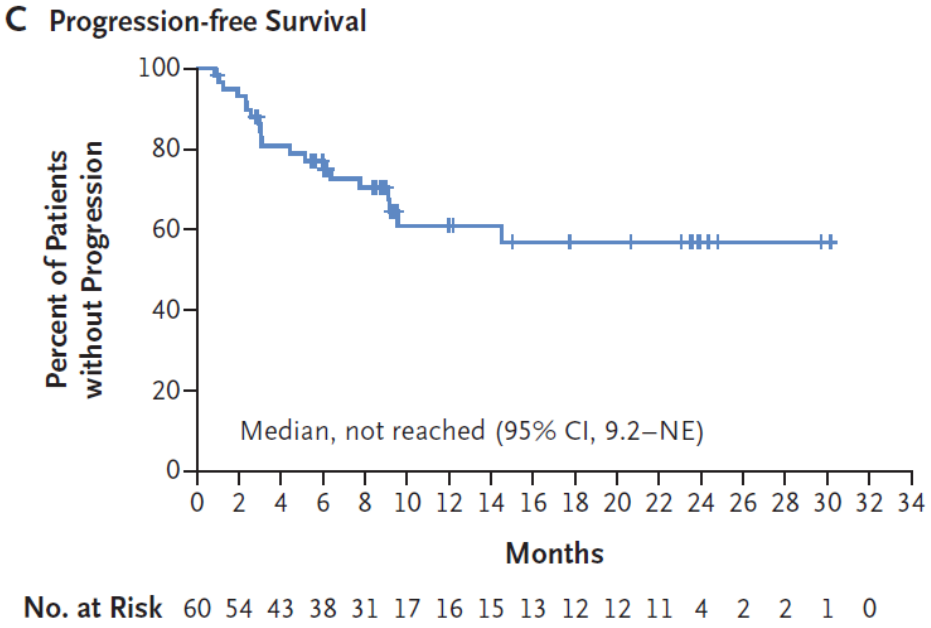
2018 Tilbakefall

2019 CAR19 T-celler i Elara studien

Desember 2020
Komplett remisjon

CAR 19 T-celler i mantelcelle lymfomer





Wang et al 2020

Toksisitet ved CAR19 T-celle terapi

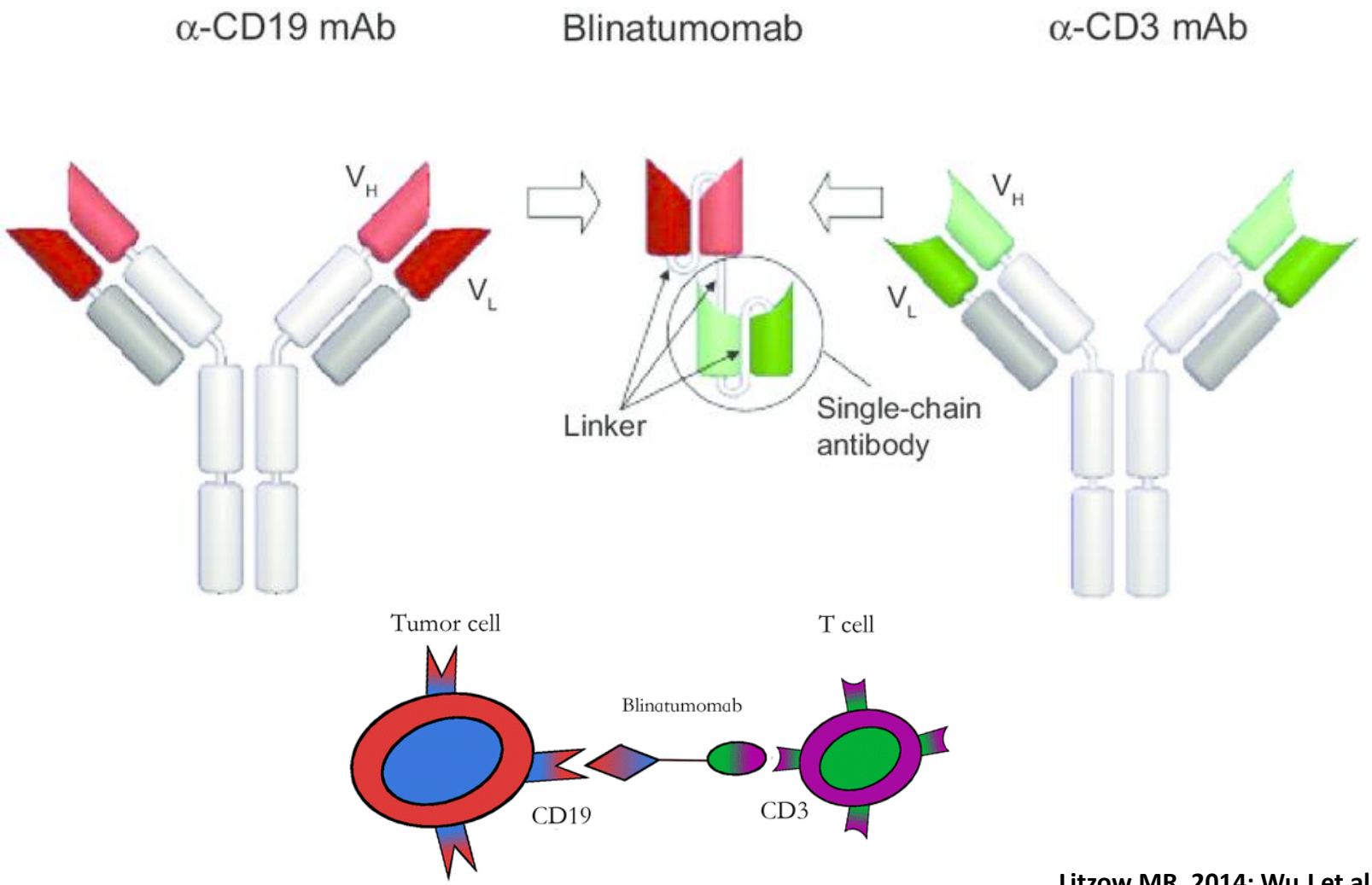
- Cytokine release syndrom (CRS)
  - Reversibel, «on target» toksisitet
  - Relatert til tumor byrde
  - Feber, blodtrykksfall, respirasjonsproblemer…overvåkning!
  - Sannsynlig i stor grad relatert til Interleukin-6
  - Tidlig behandling med tocilizumab +/- steroider
- Nevrotoksistet
  - Mange mulige symptomer, monitorering
  - Mekanismene uklare*
  - Steroider
- Tumor lyse syndrom
- B-celle aplasi med behov for gammaglobuliner

***Hunter et al 2019**

Table 6-2 CRS management

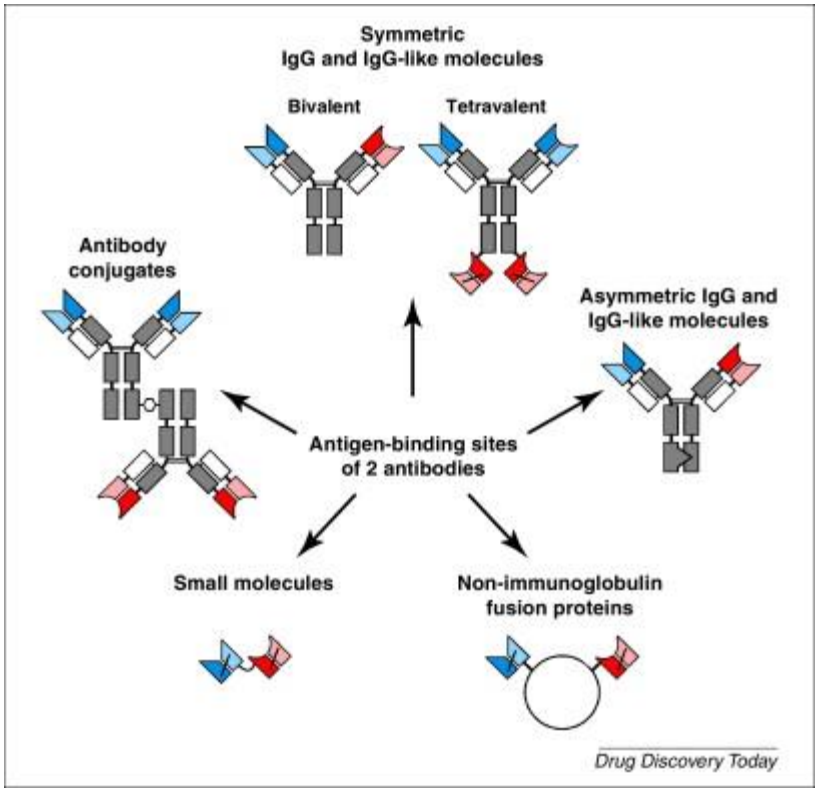
CRS severity	Symptomatic treatment	Tocilizumab	Corticosteroids
Mild symptoms requiring symptomatic treatment only e.g. low fever, fatigue, anorexia, etc.	1 Exclude other causes (e.g. infection) and treat specific symptoms with e.g. antipyretics, anti-emetics, anti-analgesics, etc. If neutropenic, administer antibiotics per local guidelines	Not applicable	Not applicable
Symptoms requiring moderate intervention: - high fever - hypoxia - mild hypotension	2 Antipyretics, oxygen, intravenous fluids and/or low dose vasopressors as needed.	If no improvement after symptomatic treatment administer tocilizumab i.v. over 1 hour: - 8 mg/kg (max. 800 mg) if body weight ≥ 30 kg - 12 mg/kg if body weight <30 kg	If no improvement within 12-18 hours of tocilizumab, administer a daily dose of 2 mg/kg i.v. methylprednisolone (or equivalent) until vasopressor and oxygen no longer need, then taper**
Symptoms requiring aggressive intervention: Hypoxia requiring high-flow oxygen supplementation or	3 High-flow oxygen Intravenous fluids and high-dose* vasopressor/s		
Hypotension requiring high-dose or multiple vasopressors	Treat other organ toxicities as per local guidelines	If no improvement, repeat every 8 hours (max total of 4 doses)**	
Life-threatening symptoms: – Hemodynamic instability despite i.v. fluids and vasopressors – Worsening respiratory distress – Rapid clinical deterioration	4 Mechanical ventilation Intravenous fluids and high-dose* vasopressor/s Treat other organ toxicities as per local guidelines		

Kan bispesifikke antistoffer være fremtiden?

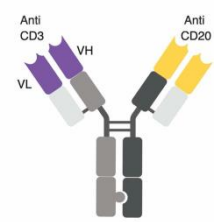


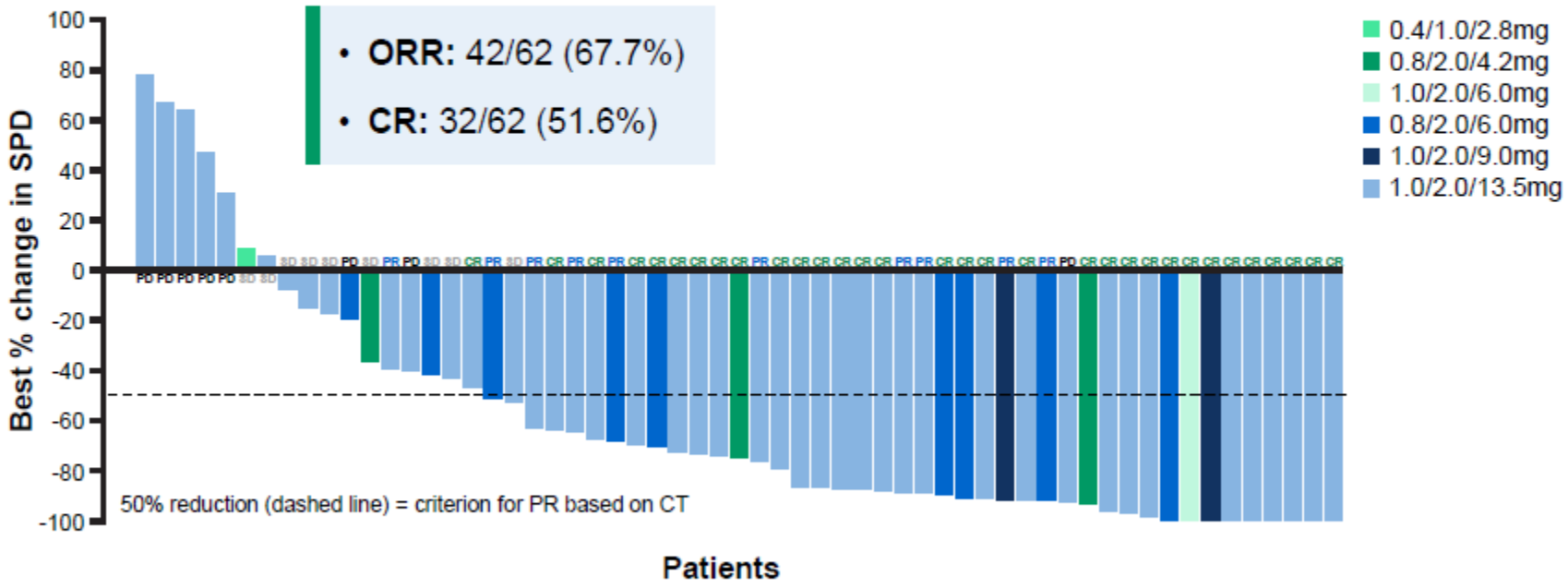
Litzow MR, 2014; Wu J et al, 2015

Mange varianter av bispesifikke antistoffer



Mosunetuzumab antitumor activity in patients with R/R FL across dose levels





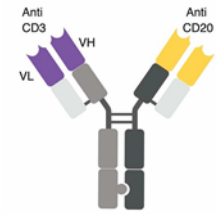
Assessment of higher dose levels is ongoing

SPD, sum of product diameter

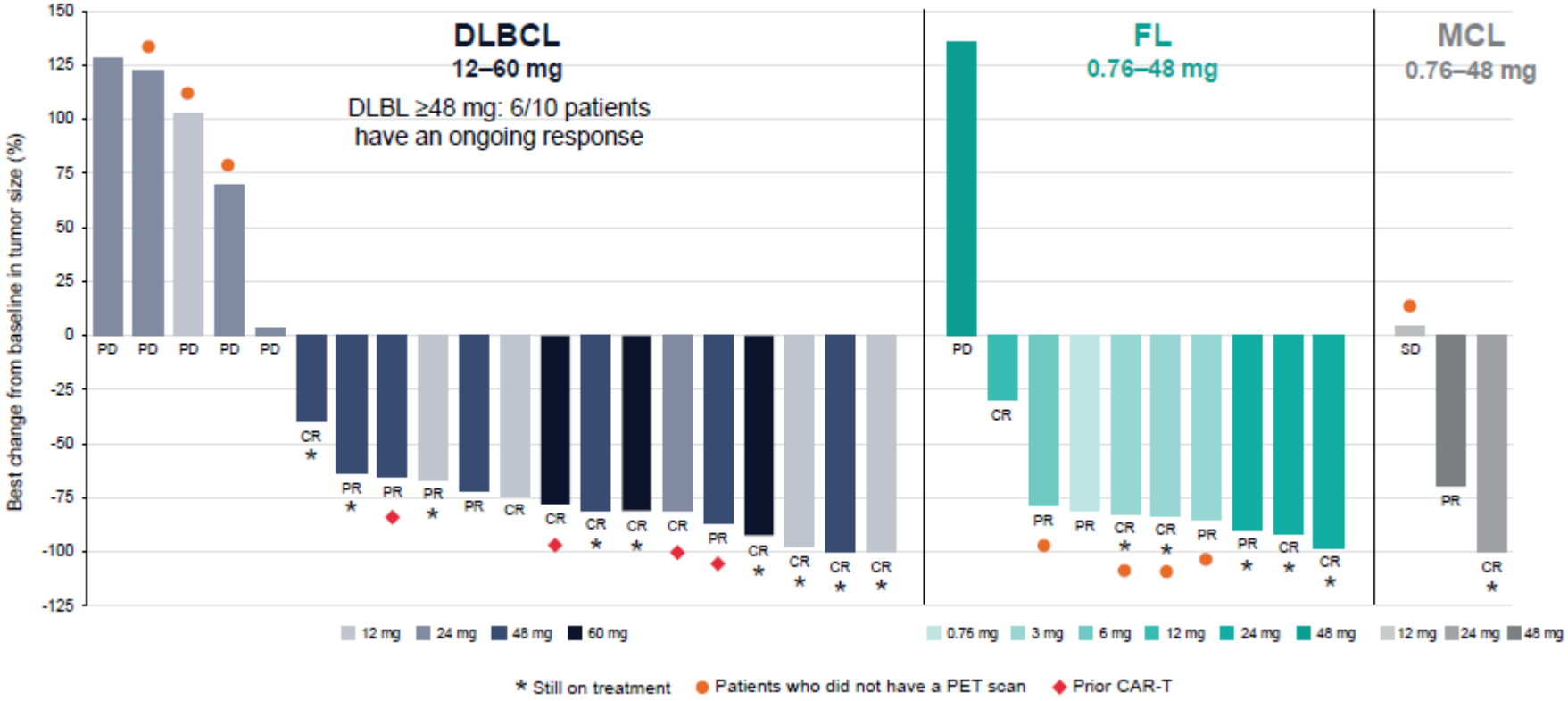
1. Cheson BD, et al. J Clin Oncol 2007; 25(5):579–86.

Assouline S et al, 2020

Subcutaneous epcoritamab in relpased/refractory B-cell Non Hodgkin lymphomas

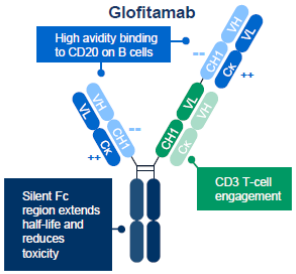


Best percent change from baseline in tumor size

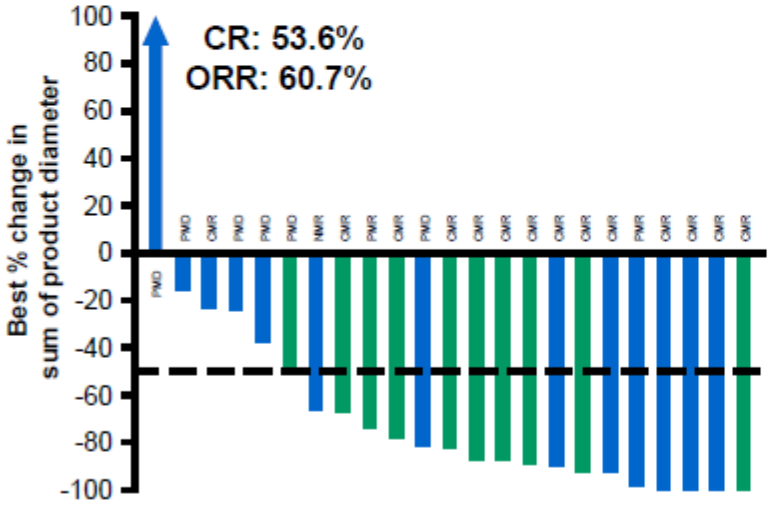


Hutchings M et al, 2020

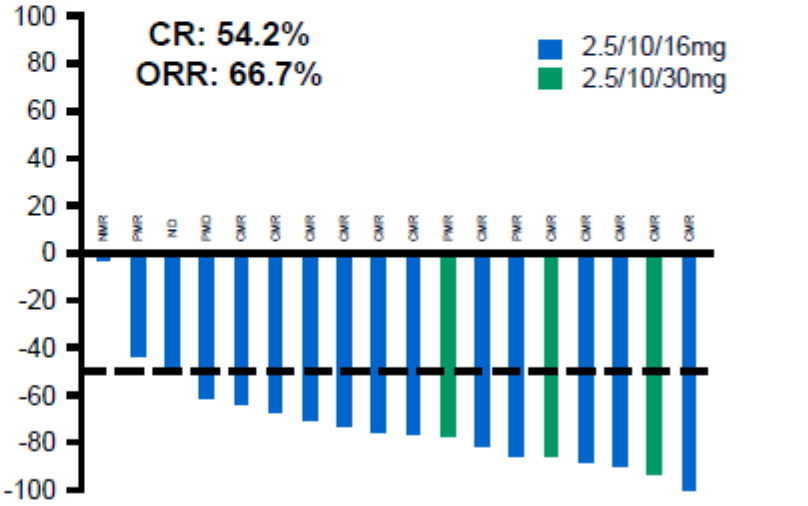
Glofitamab Step-Up Dosing Induces High Response Rates in Patients with Hard-to-treat Refractory or Relapsed (R/R) Non-Hodgkin Lymphoma (NHL)



Aggressive NHL*



Indolent NHL†



Patients assessed by CT and Lugano criteria.[1] Dashed lines represent 50% reduction in sum of product paramaters (criterion for PR based on CT).
*N=23; 2 patients did not have a response assessment and 3 did not have baseline SPD reported at time of CCOD.
†N=18; 6 patients did not have a response assessment at time of CCOD.

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