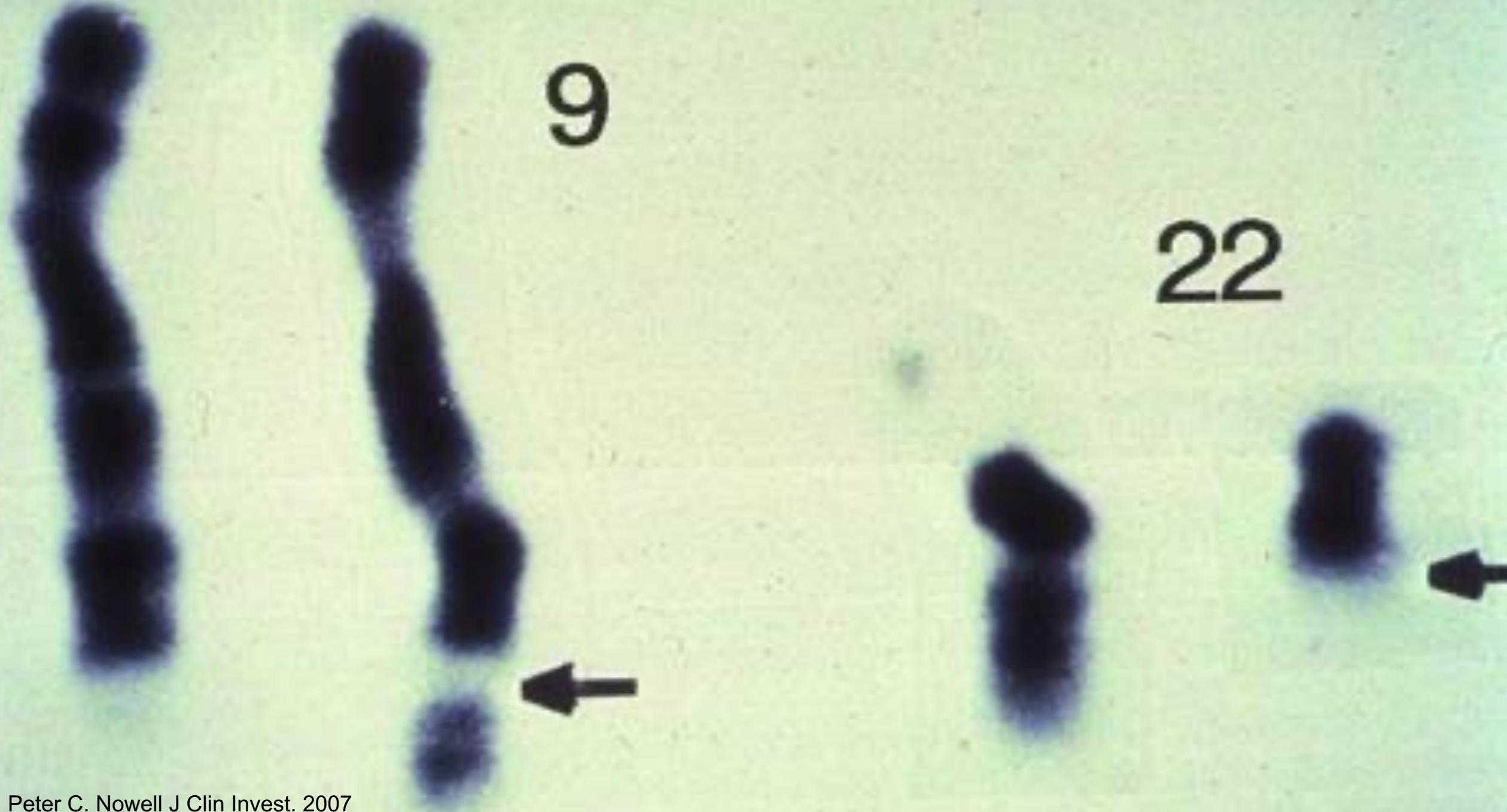


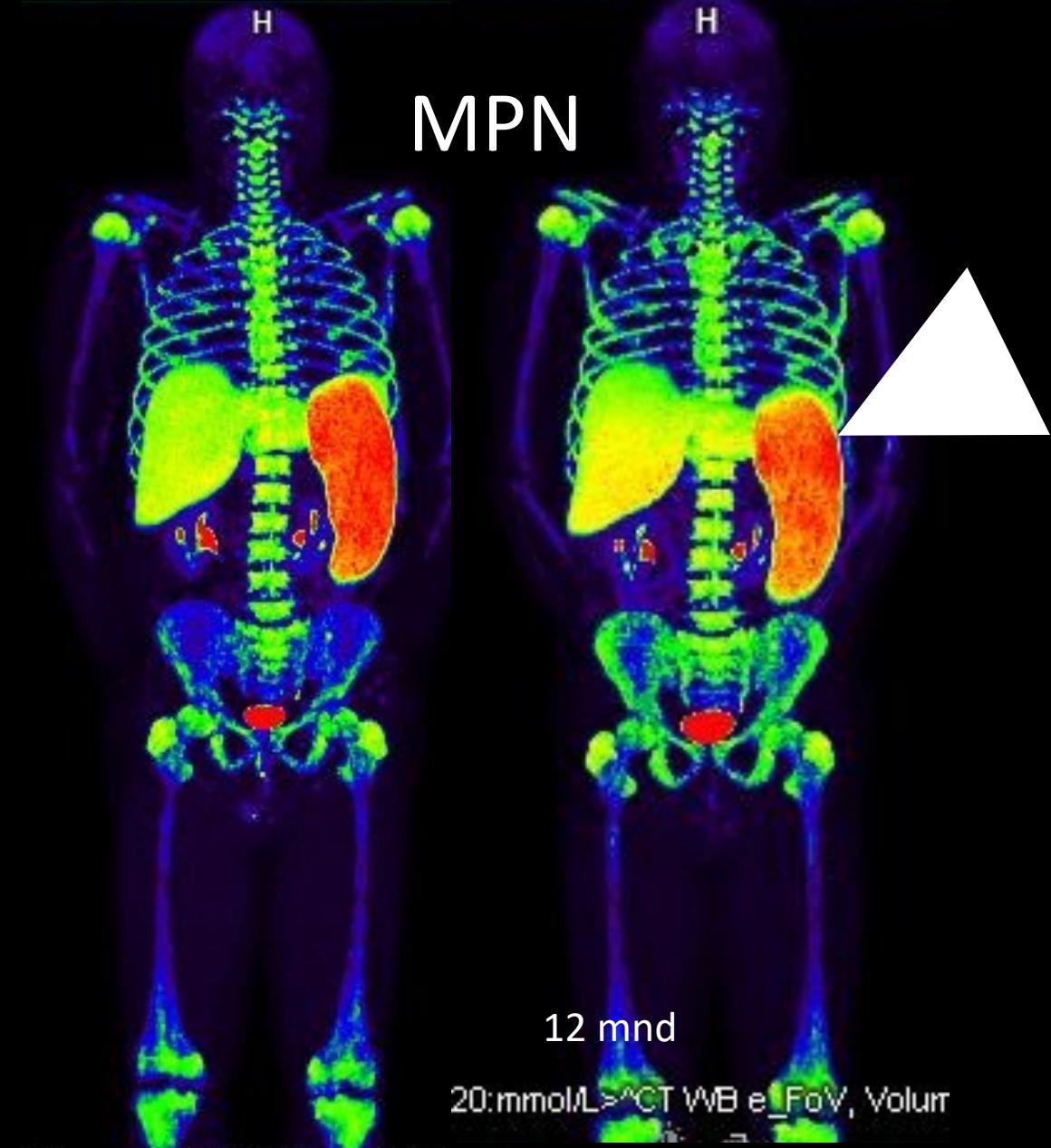
Myeloproliferative sykdommer (MPN)

Bjørn Tore Gjertsen

9

22



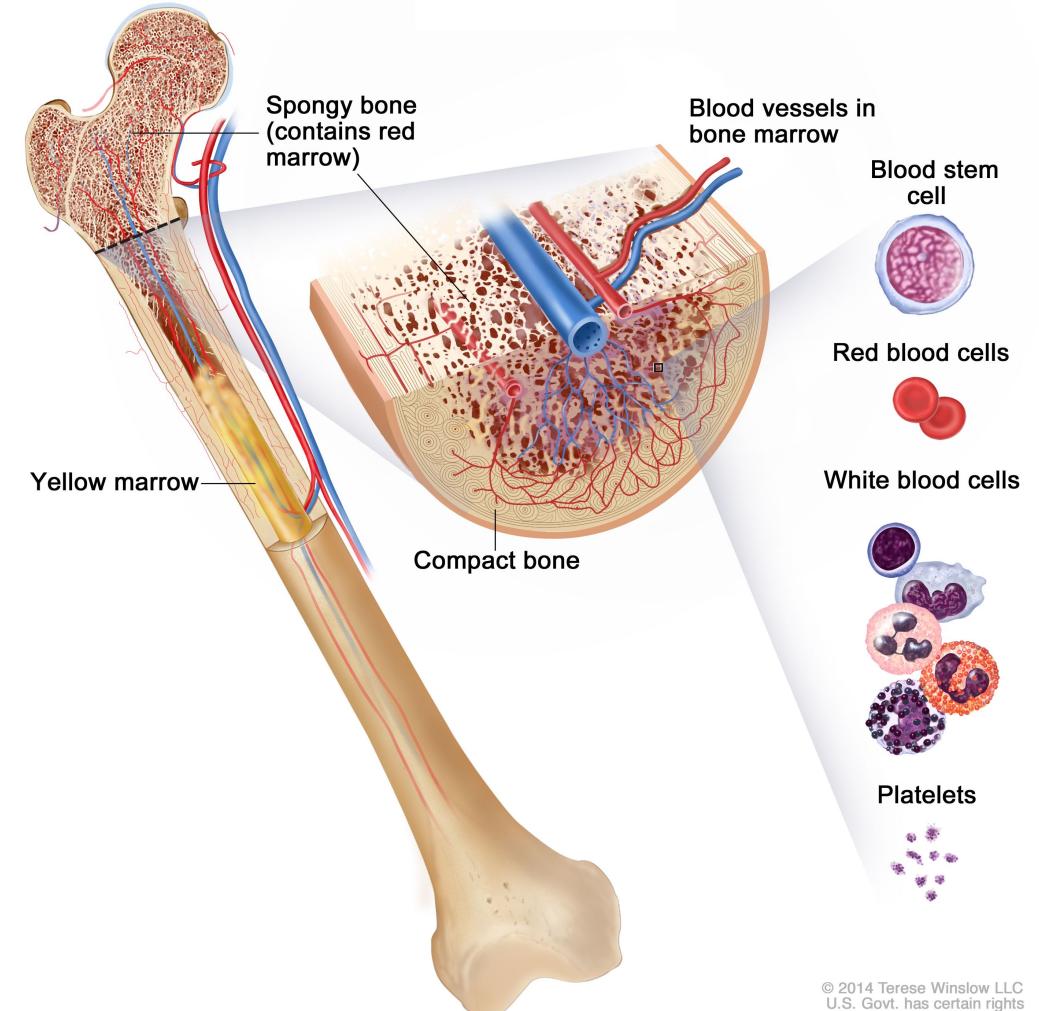


Myeloproliferativ neoplasi – diagnosene:

- Essensiell Trombocytose(ET)
- Polecytemia vera (PV)
- Myelofibrose(MF)

Behandlingsalternativer

Siste nytt – forskning

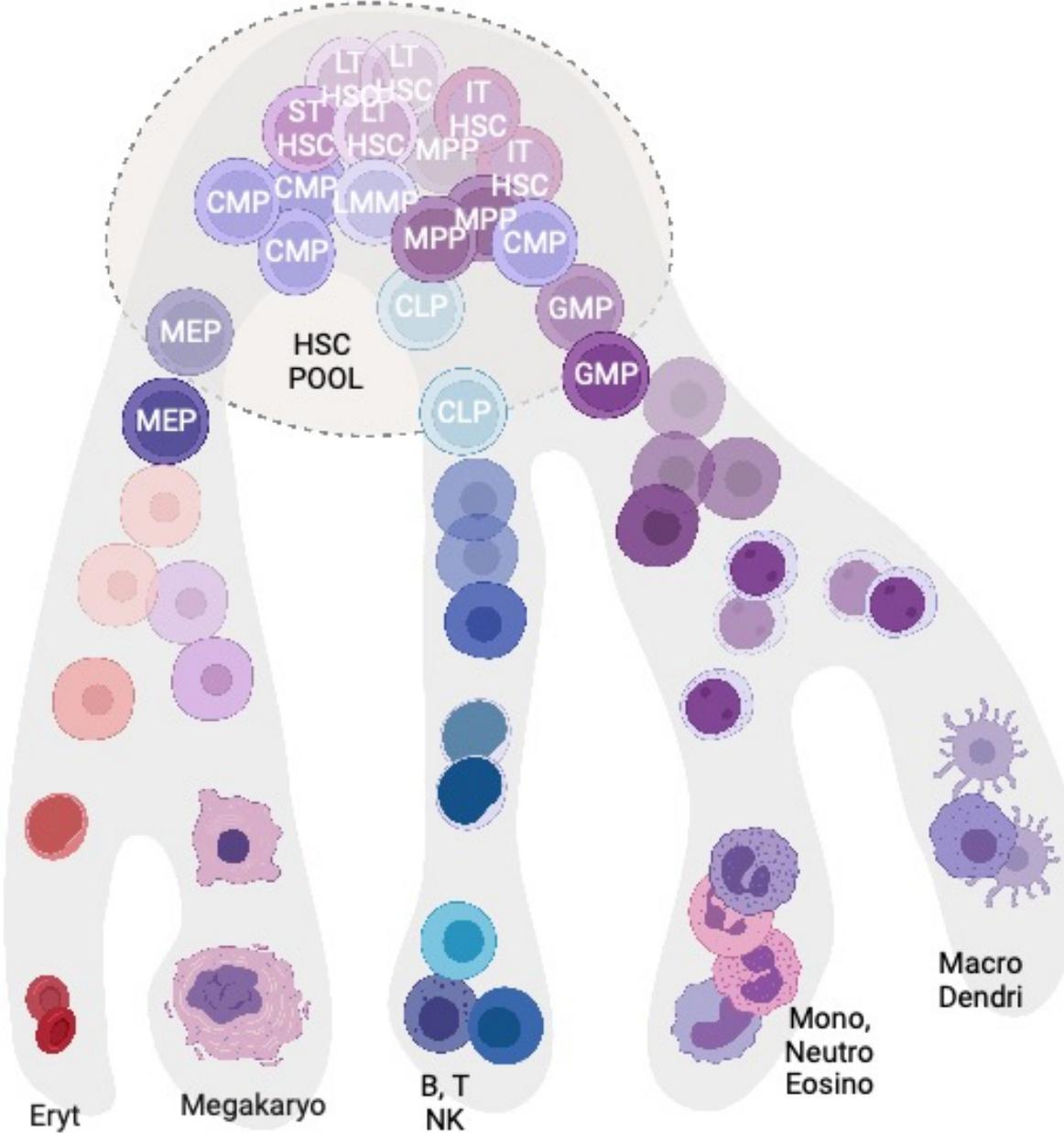


© 2014 Terese Winslow LLC
U.S. Govt. has certain rights

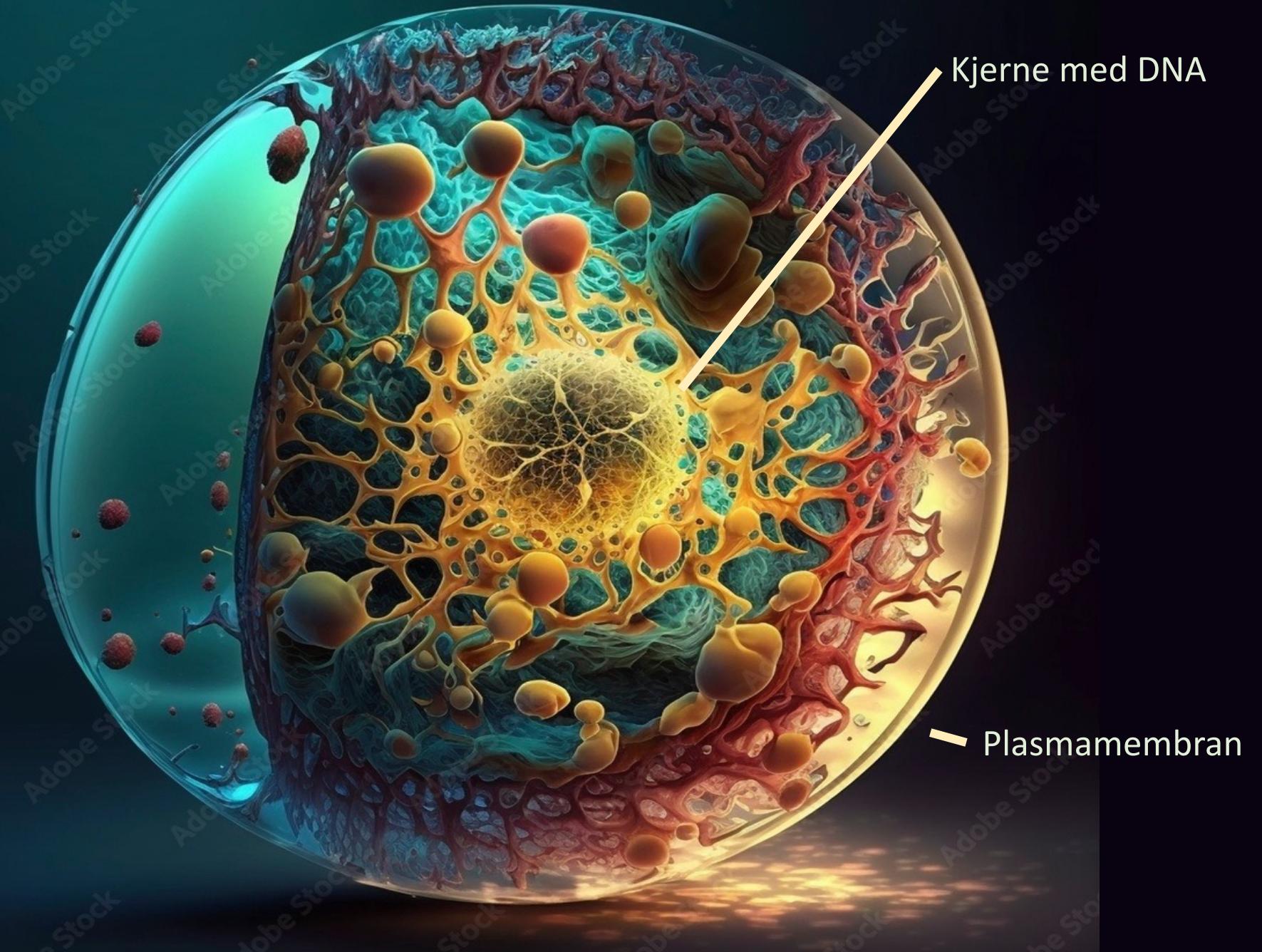
MPN – hva er typisk for sykdommene?

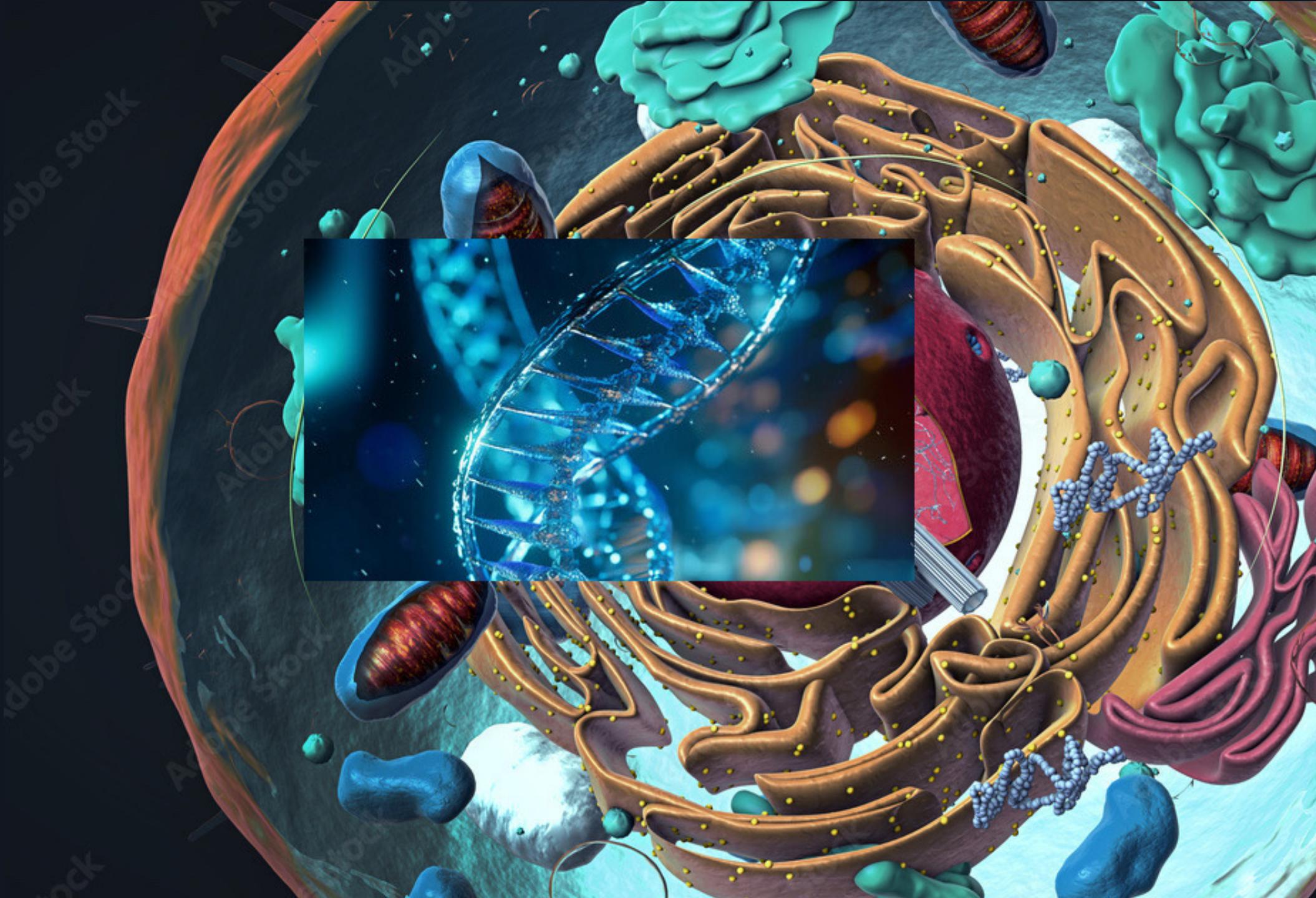
- Overproduksjon av en eller flere celletyper med en dominerende transformert celleklon
- Hypercellulær beinmarg /beinmargsfibrose
- Kromosomavvik og/eller mutasjoner i myeloide celler
- Tendens til trombose og/eller blødning
- Økt celleproduksjon og destruksjon -> urinsyre økt
- Sykdom utenfor beinmargen: Lever og milt
- Transformasjon til akutt leukemi
- Overlappende tegn og symptomer

Bloddannelse i beinmargen



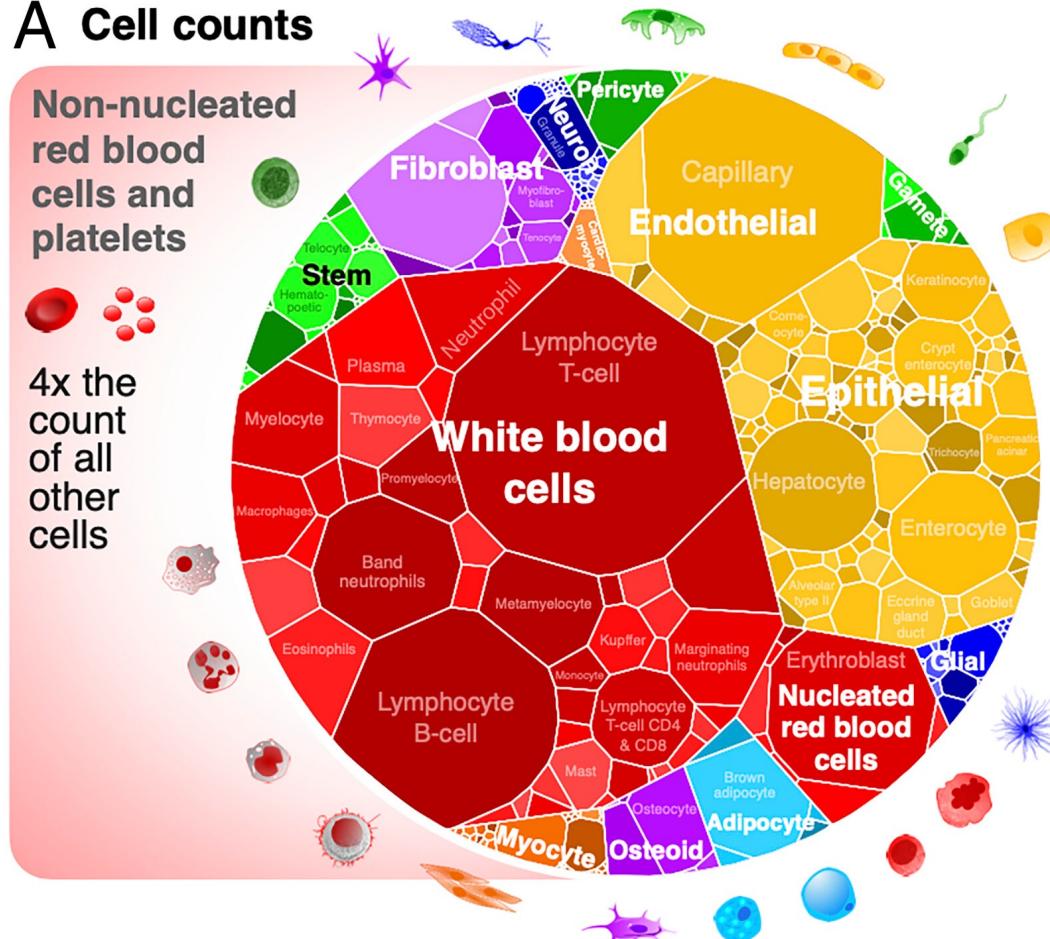
Cellen





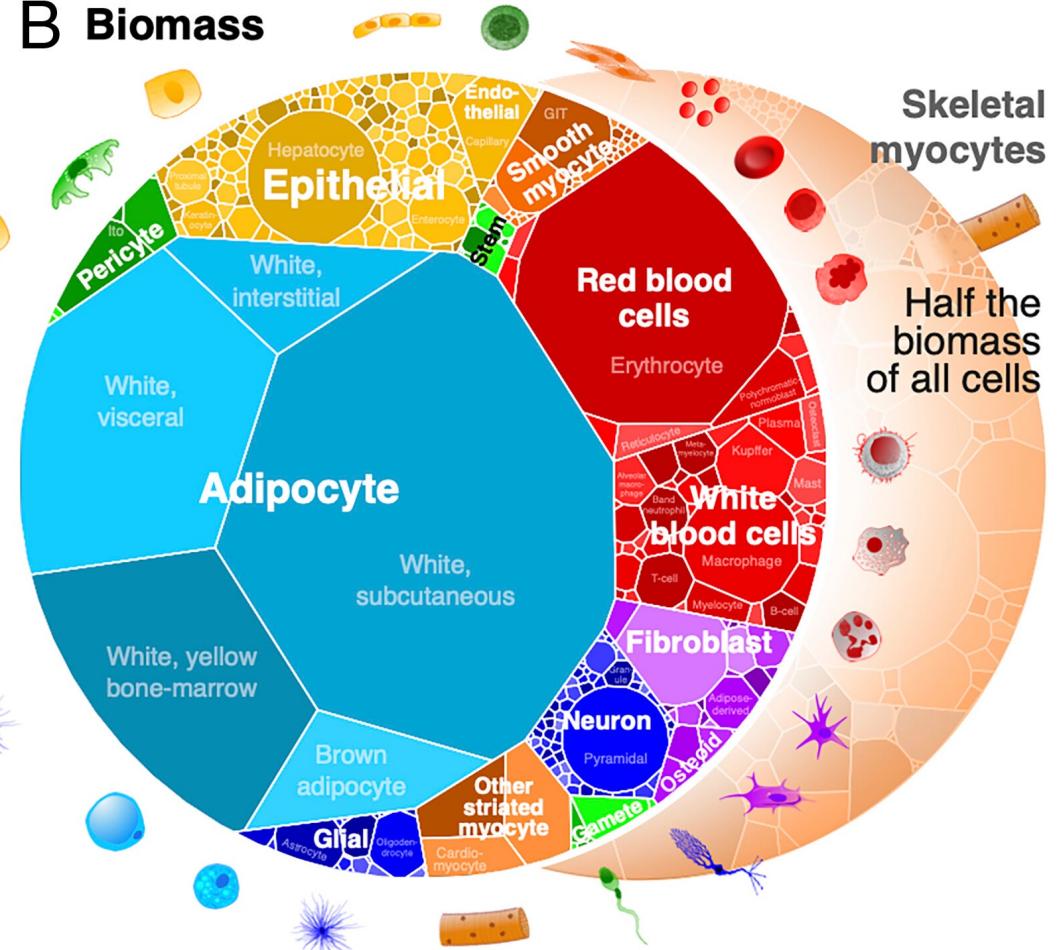
Celle-tall og biomasse-distribusjon etter celletype

A Cell counts



29 trillion non-nucleated + 7 trillion nucleated cells
= 36 trillion cells (+ 38 trillion bacteria)

B Biomass



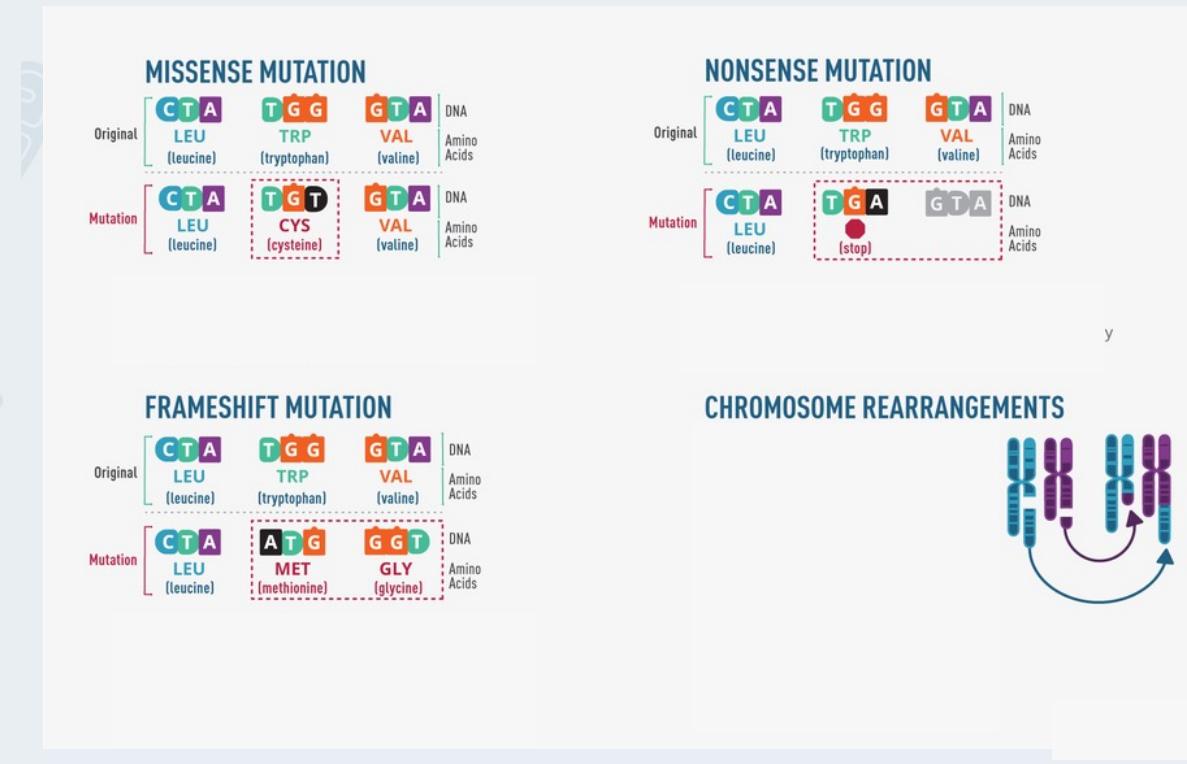
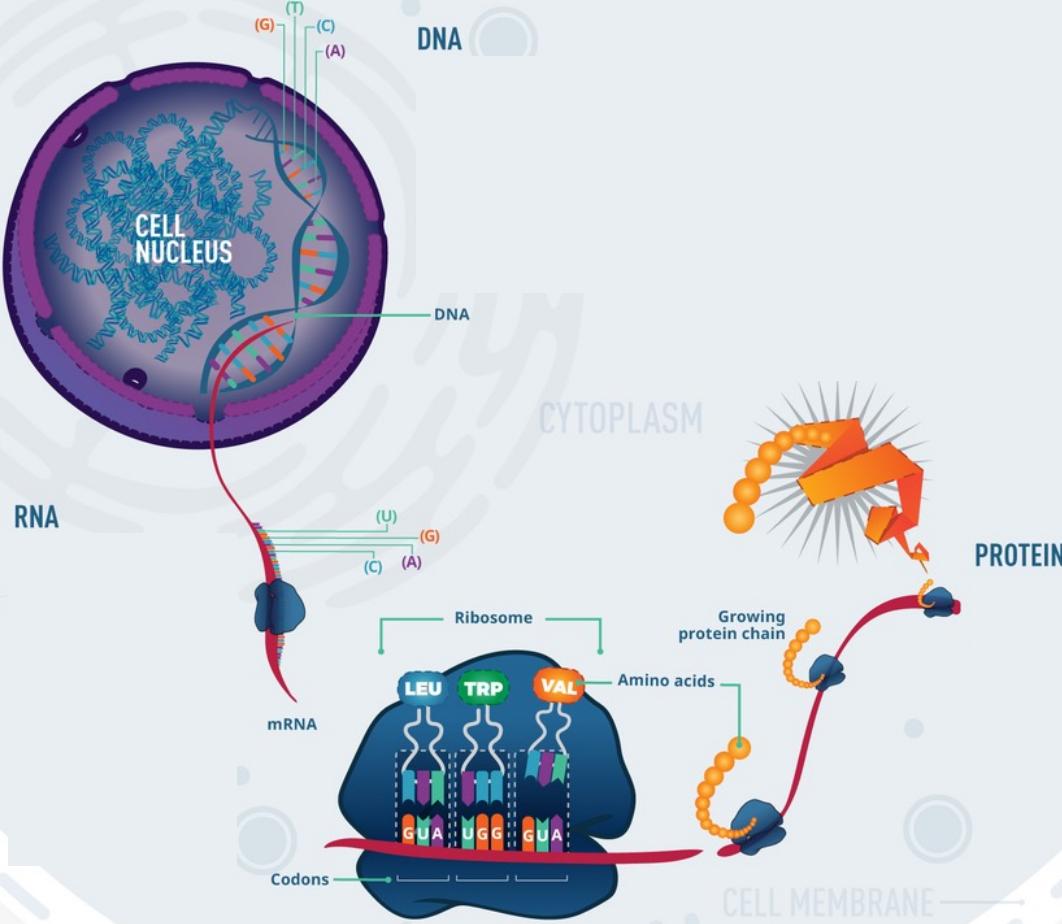
21.5 kg of skeletal myocytes + 23.5 kg of all other cells
= 45 kg cell biomass (of 70 kg total mass)



Genforandringer og kreft

- "Tull og tøys"-mutasjoner (missense)
- Nonsense-mutasjoner
- Rammeskiftmutasjoner (frameshift mutation)
- Kromosom rearrangement

Genforandringer og kraft





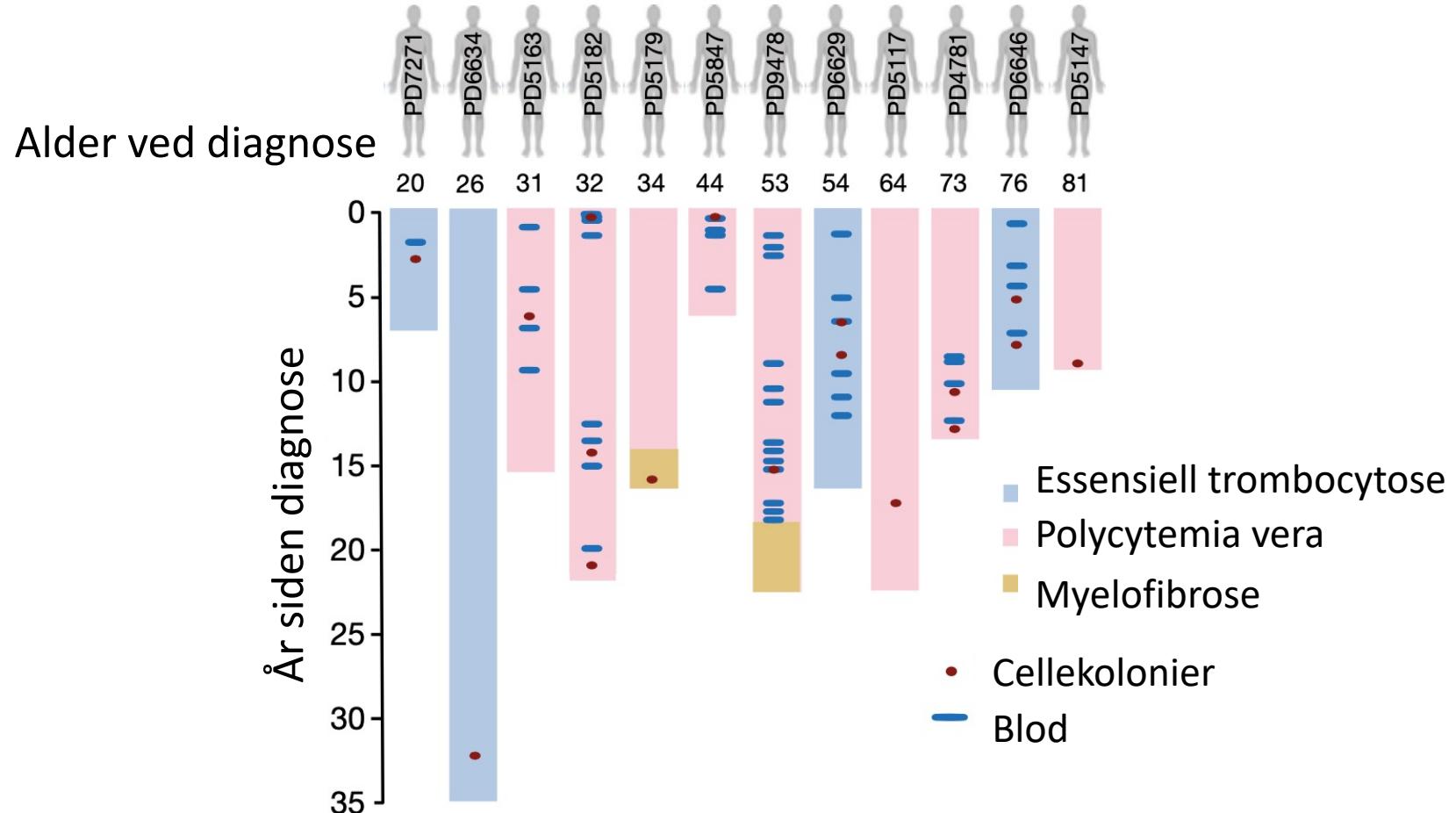
STORE MEDISINSKE LEKSIKON

klon

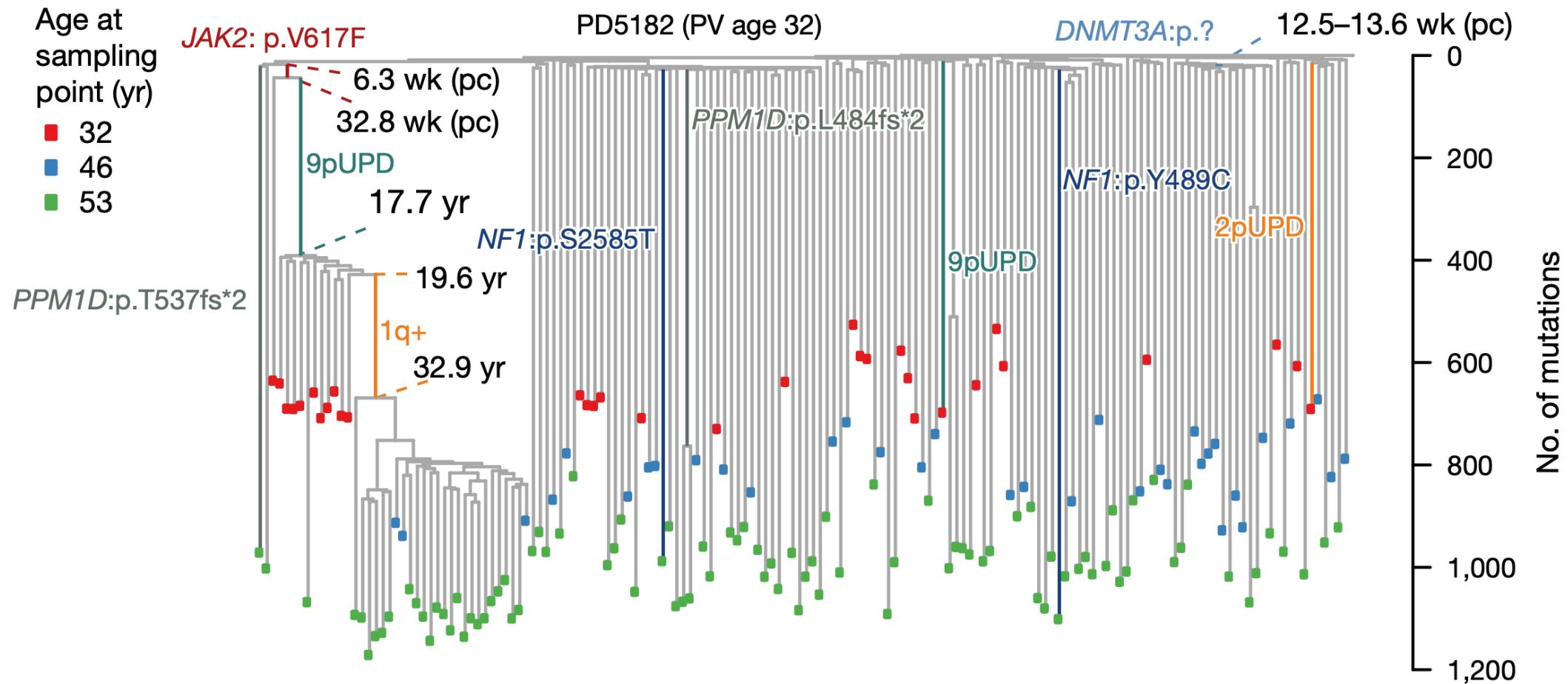
Klon er en ansamling av molekyler eller celler som alle skriver seg fra én enkelt utgangscelle.

Alle cellene i klonen er genetisk identiske med denne opphavscellen, det vil si at de har akkurat det samme arvematerialet.

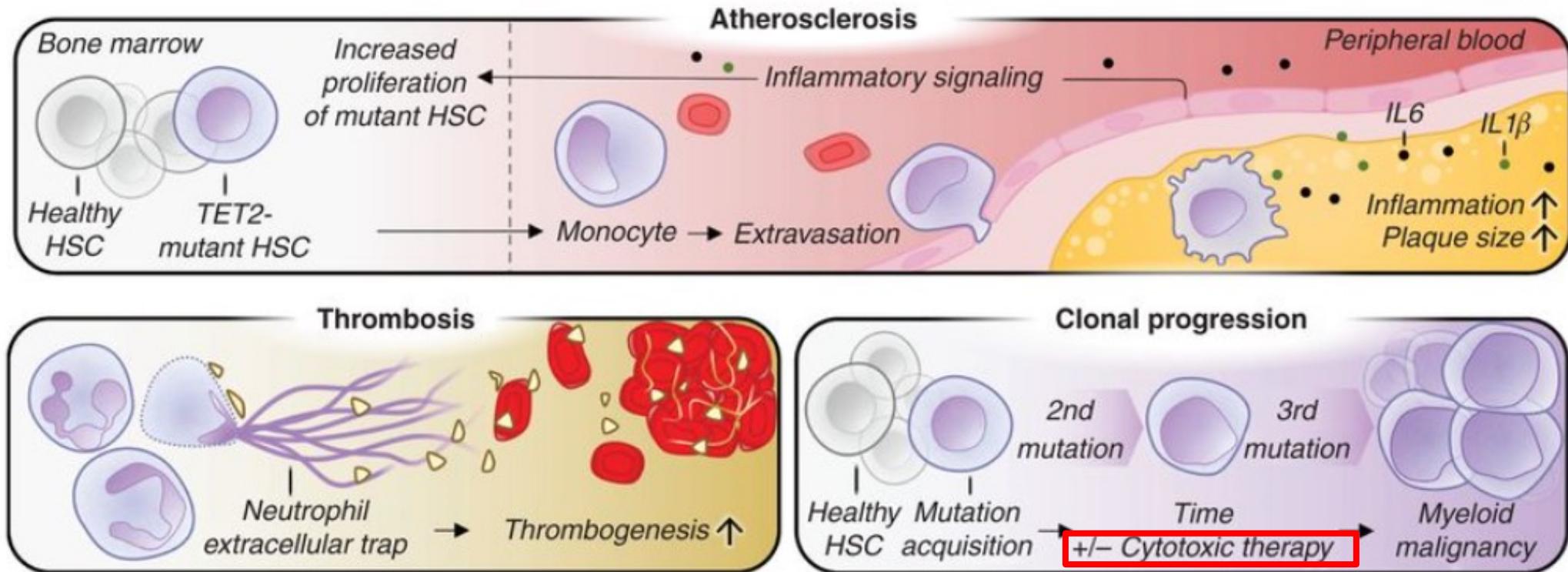
Livshistorie til sykdommen myeloproliferativ neoplas



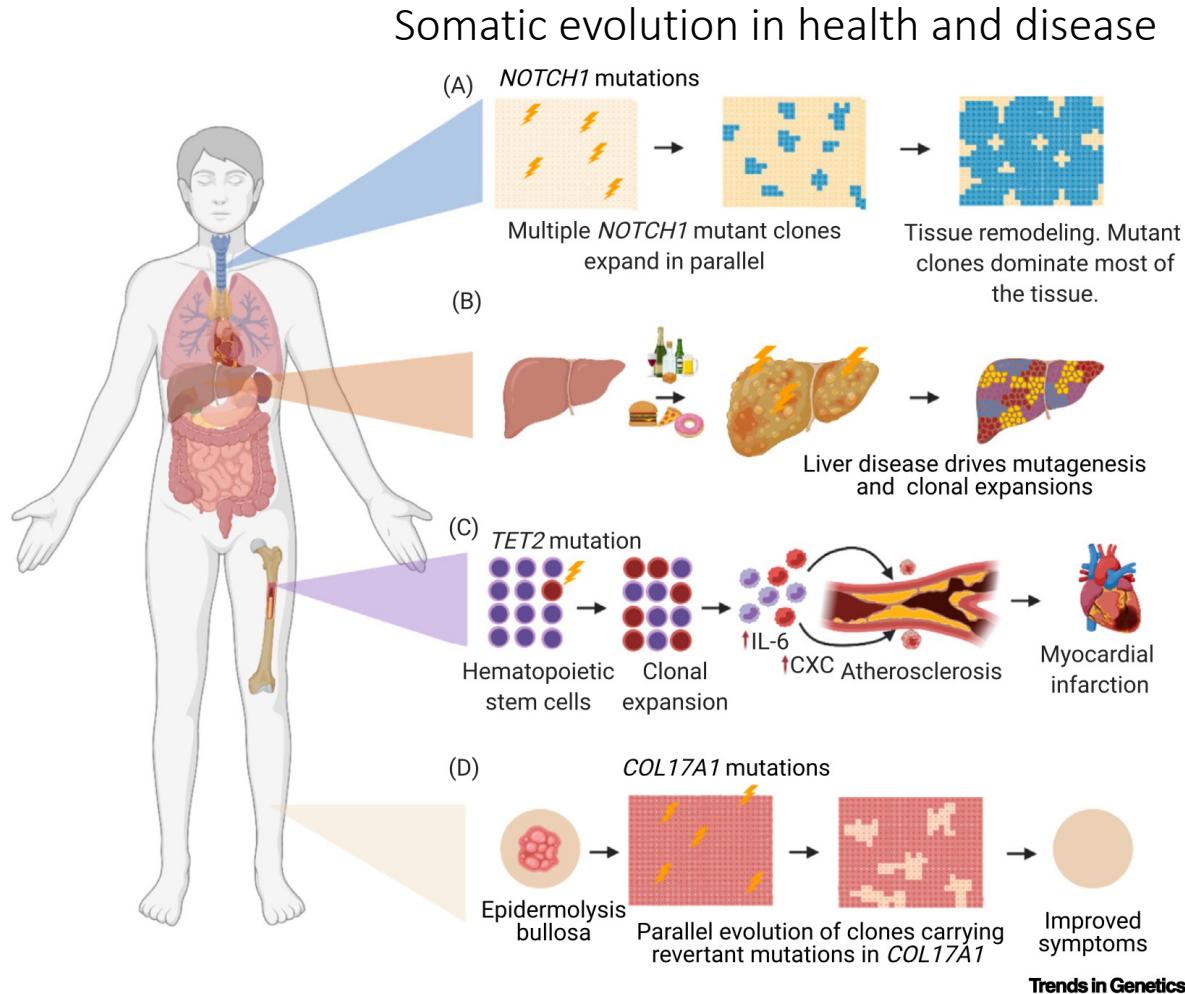
Utviklingstre for pasient med flere driver-mutasjoner



Somatiske mutasjoner i beinmargen og sykdom



Kunnskap om MPN gir kunnskap om andre sykdommer



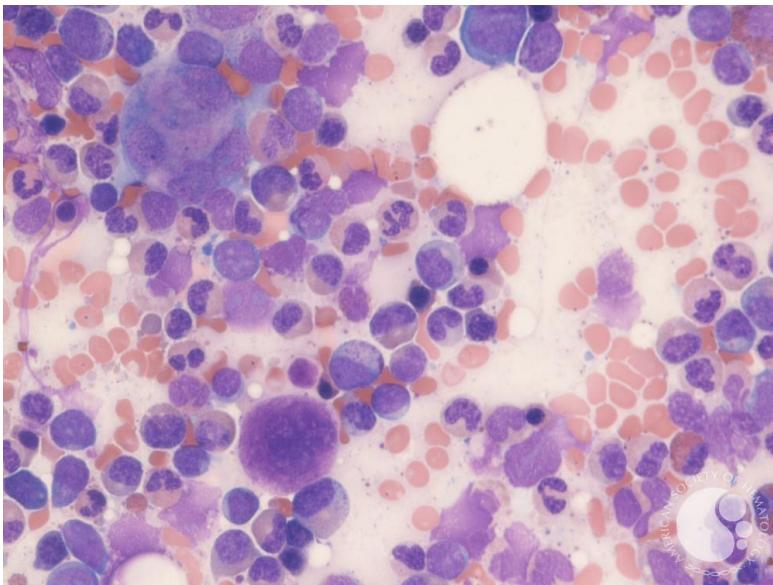
I hvilken grad er remodellering av vev vanlig i ved sykdom? Og i hvilke gener finnes det mutasjoner som gir fordeler for cellekloner som har slike mutasjoner?

MPN-diagnosene

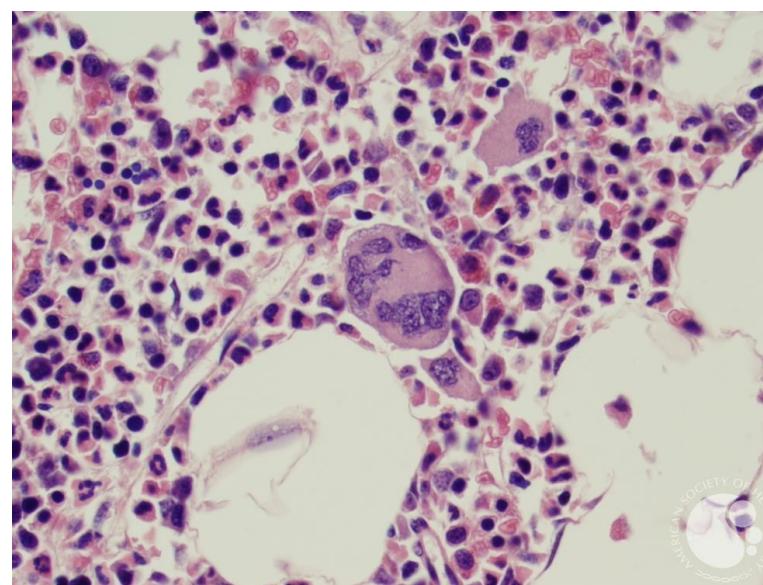
- Essensiell Trombocytose (ET)
- Polecytemia vera (PV)
- Myelofibrose(MF)



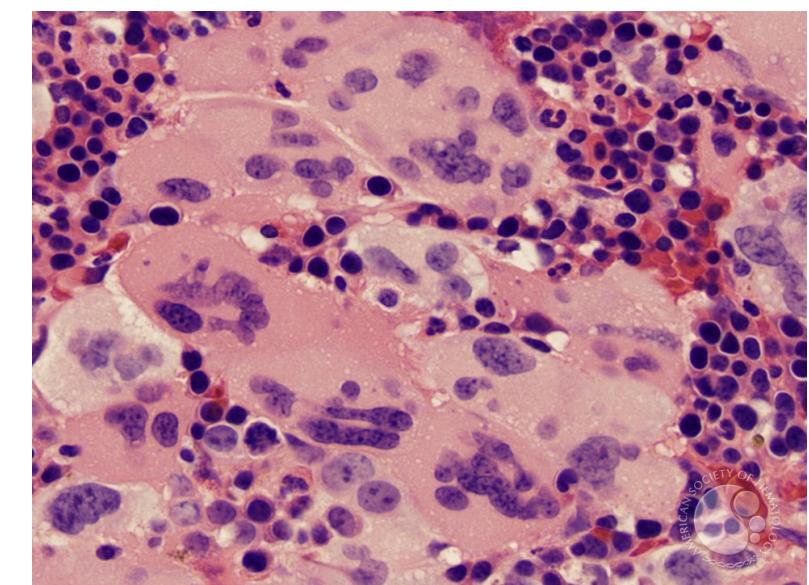
Beinmargshistologi – mikroanatomi av MPN



Polyctemia vera (PV)

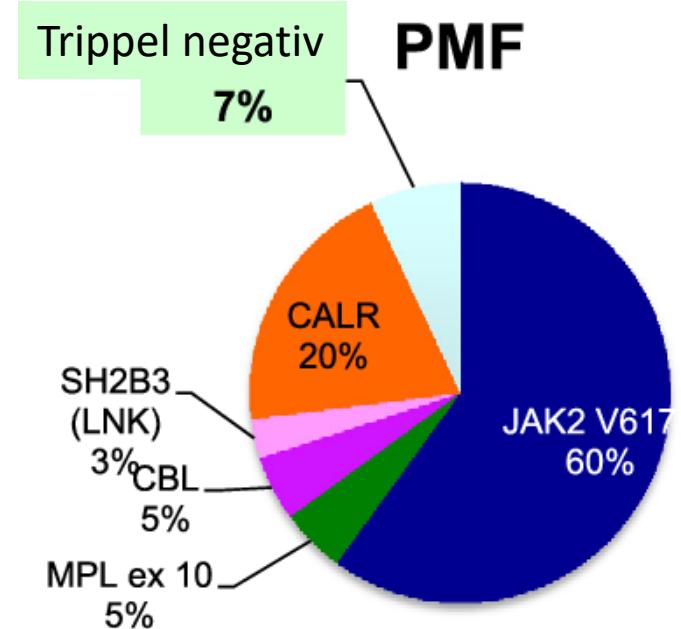
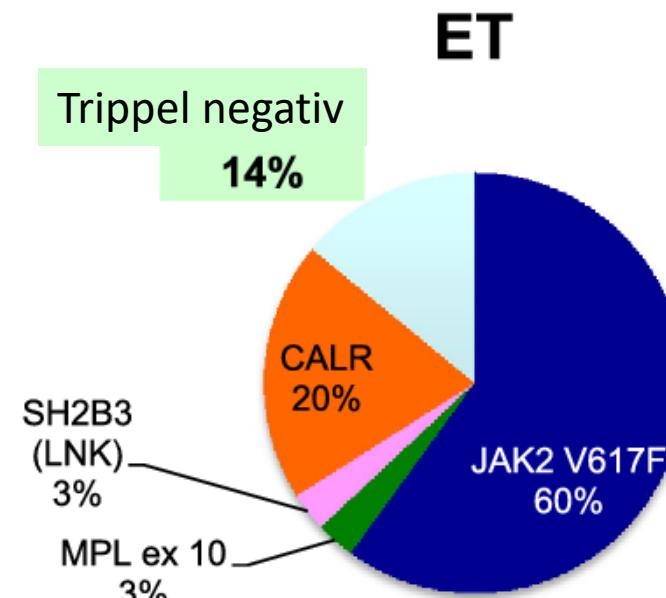
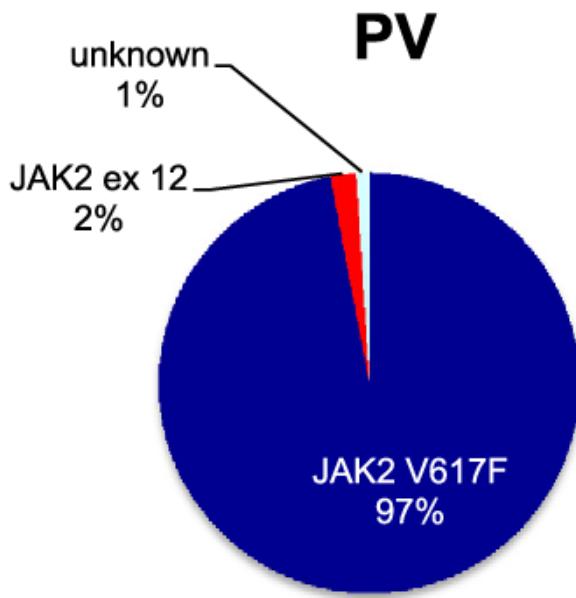


Essentiell Trombocytose(ET)



Myelofibrose(MF)

Myeloproliferative neoplasmer: JAK2 signalering

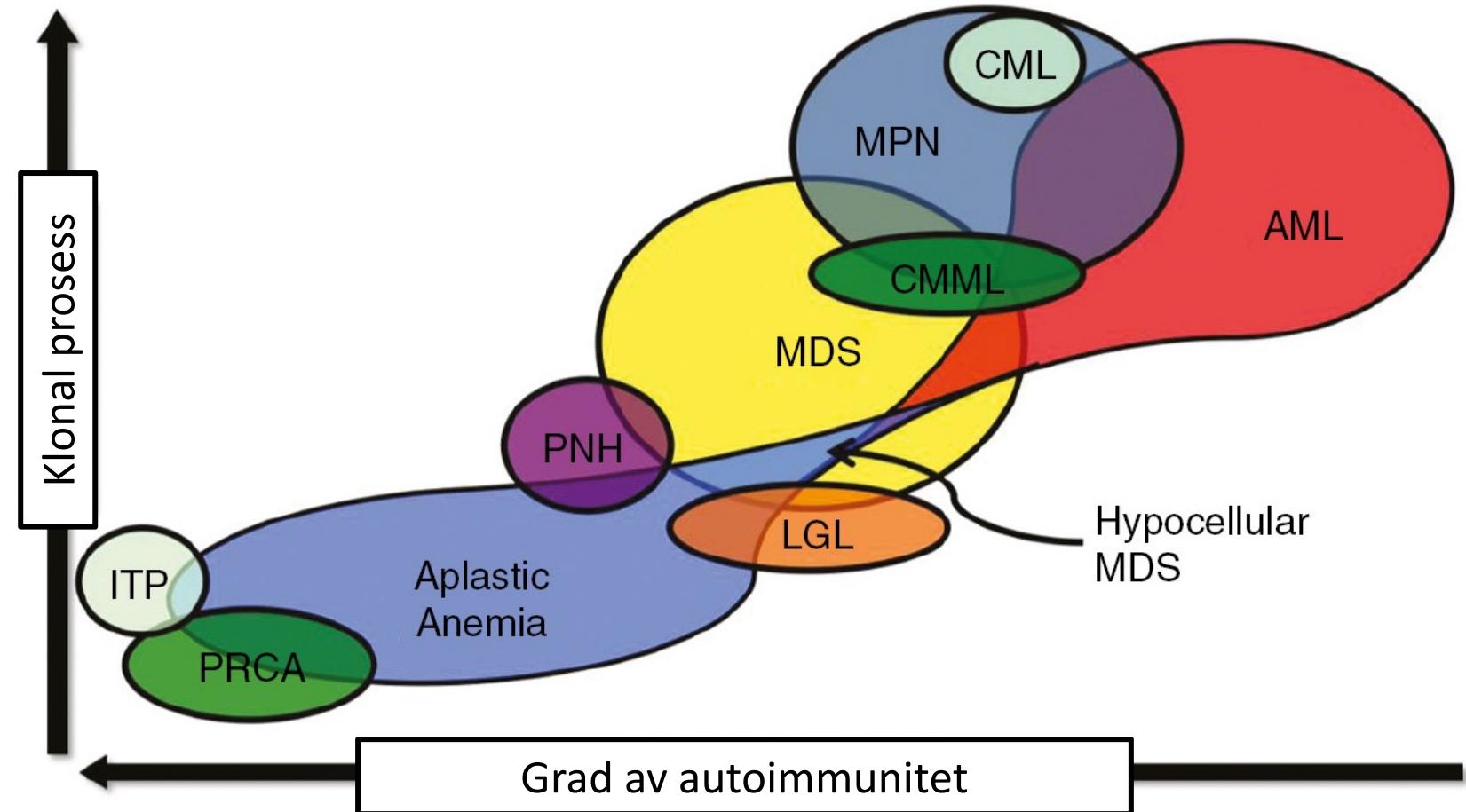


Polyctemia vera (PV)
AML risiko
i løpet av 10 år: 2.3-8.7%

Essensiell Trombocytose(ET)
0.7-4%

Myelofibrose(MF)
5.8-20.6%

Myeloide neoplasier: Overlapp mellom myelodysplastiske sykdom og myeloproliferativ neoplasier

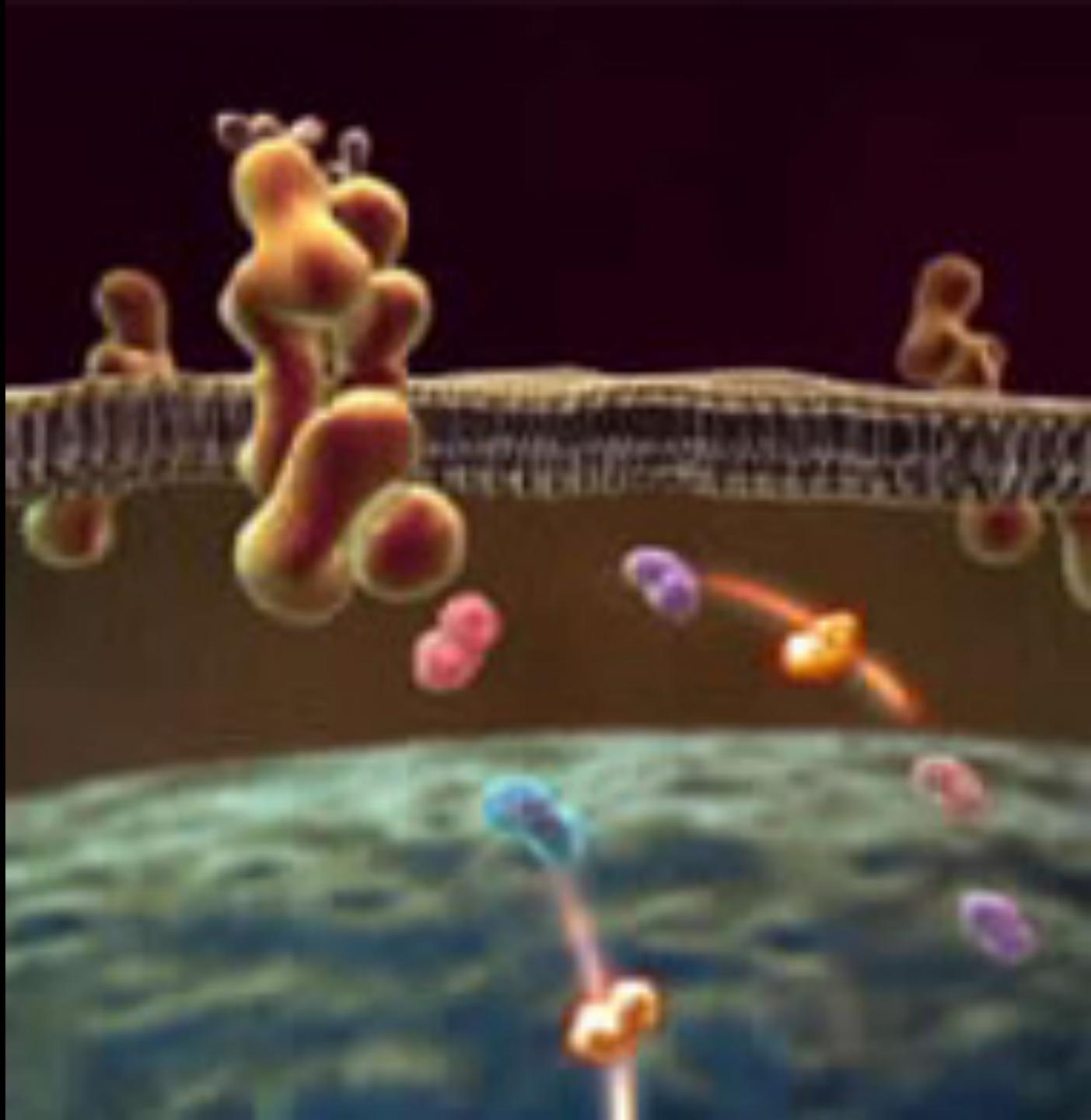


Behandling



Signalering – signalformidling i celler

Signalformidling er prosessen for mottak og videre bearbeiding av signaler som en celle mottar fra andre celler.

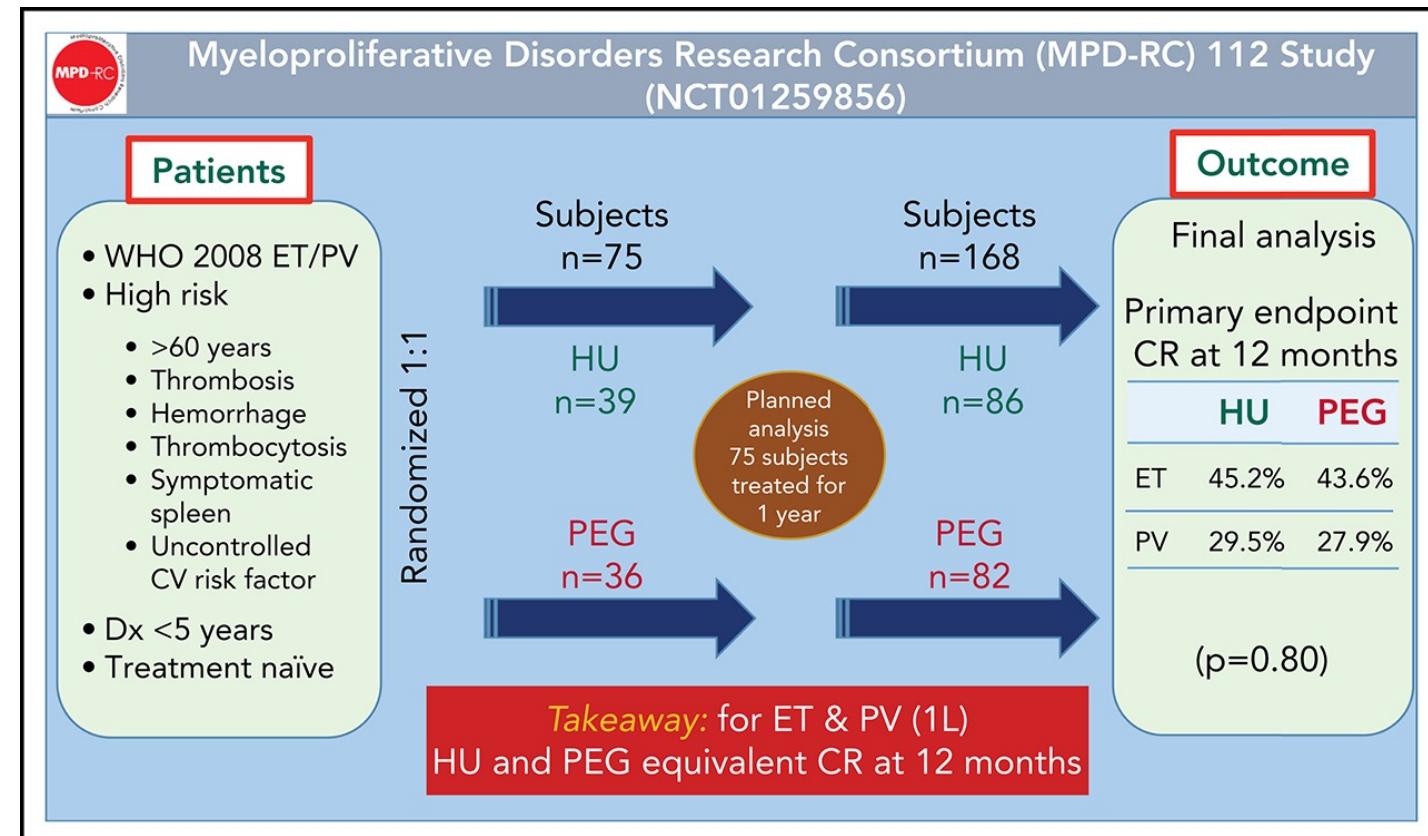


Immunterapi versus cytostatisk behandling PV og ET: interferon- α versus hydroxyurea i polycytemia vera and essensiel trombocytemi

Utprøving i 7,5 år med 51 voksne pasienter med PV. Gjennomsnittelig behandlingstid 5 år, og 61% hadde normalisering av blodverdier, normal miltstørrelse og ingen arterielle eller venøse blodpropper. FDA-godkjent november 2021.

Beslutning i Beslutningsforum for nye metoder (22.05.2023)

1. Ropéginterferon alfa-2b (Besremi) innføres ikke til behandling av voksne med polycytemia vera uten symptomatisk splenomegalie.
2. Det er ikke dokumentert en klinisk nytte som står i forhold til prisen på legemidlet.
3. Sykehusinnkjøp bes gjenoppta forhandlingene med leverandør.



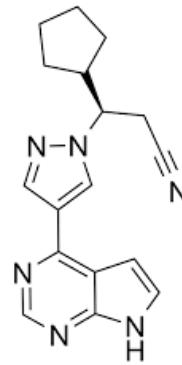
MF behandlingseffekt

- Miltvolum reduksjon 35% eller mer ved uke 24 oppnås hos 42% behandlet med ruxolitinib, 47% med fedratinib, 19% med pacritinib, og 27% med momelotinib.
- Allogen hematopoietisk stamcelletransplantasjon er den eneste kurative behandling med MF: 1 av 2 er helbredet ved 5 års vurdering.

Gupta et al. Biol Blood Marrow Transplant 2014



Ruxolitinib ved myelofibrose: kreftstamcellene forblir (persisterer)



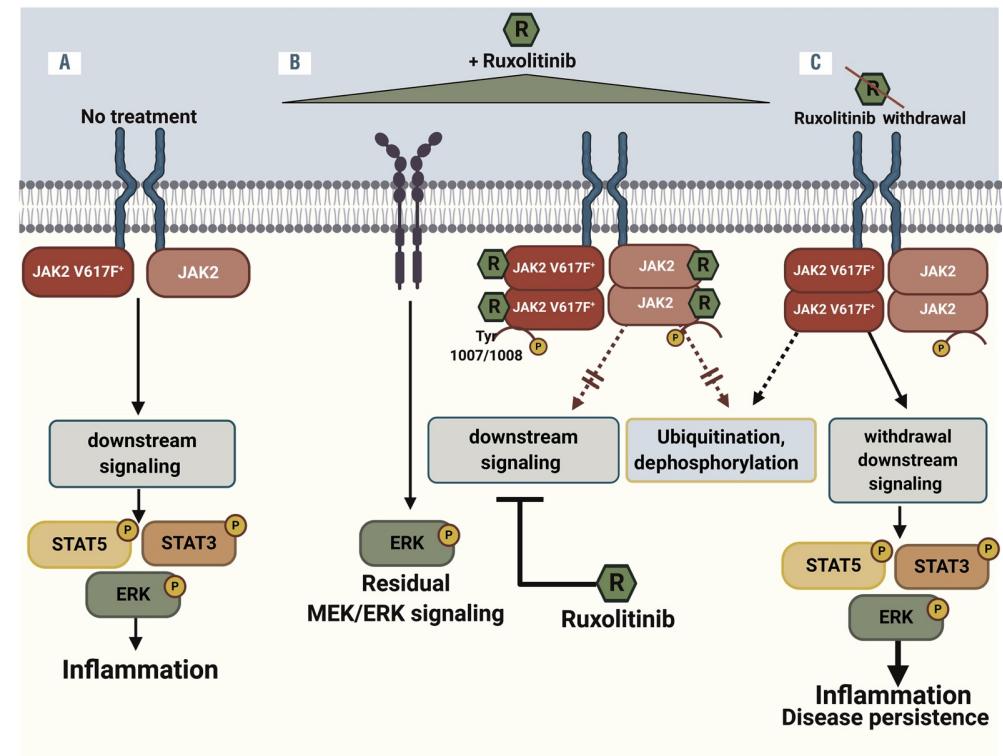
Indikasjoner:

- Sykdomsrelatert splenomegali eller symptomer hos voksne med primær MF, post-PV MF, post-ET MF
- PV resistente eller intolerante overfor hydroxyurea

Andel pasienter med respons ved 24 uker
(mer enn 35% reduksjon i miltvolum):

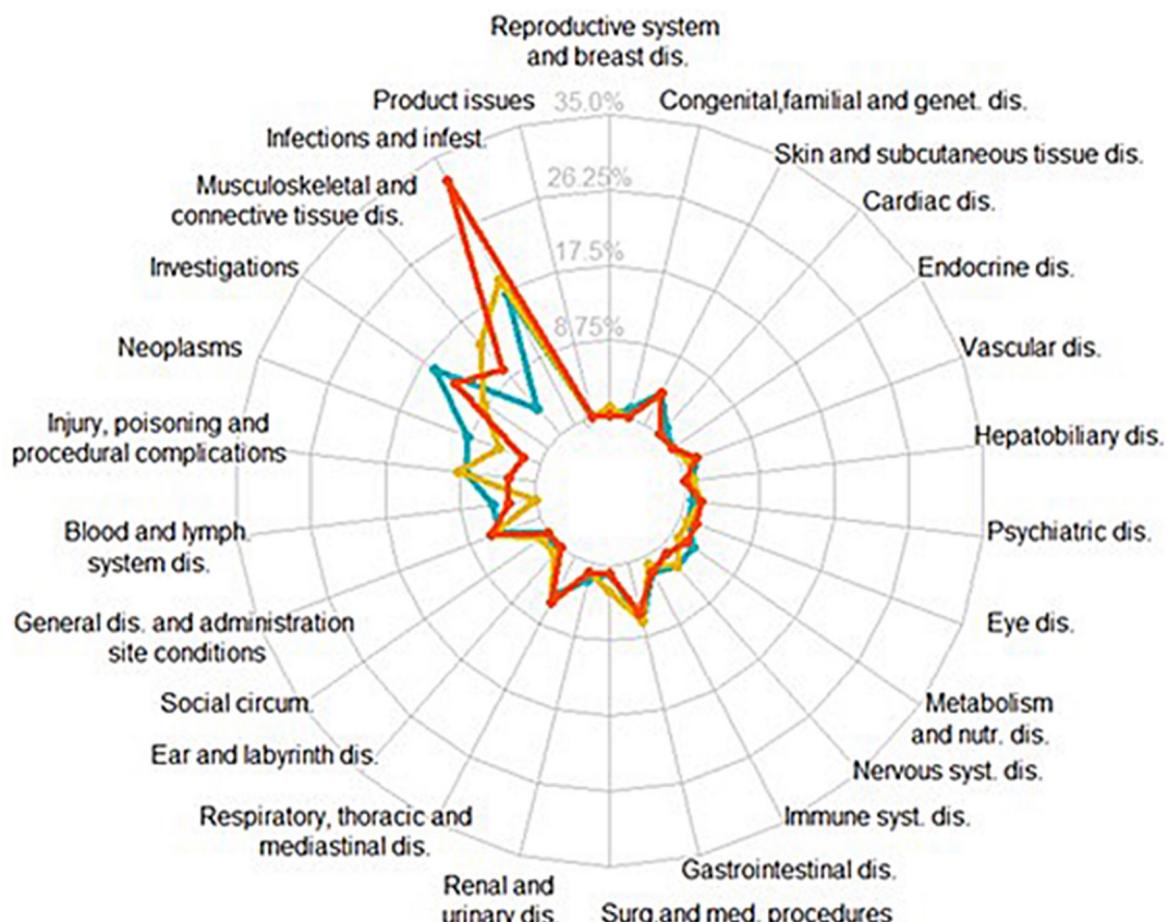
42% COMFORT-1 (v/placebo 0,7%)

32% COMFORT-2 (v/best supp. care 0)



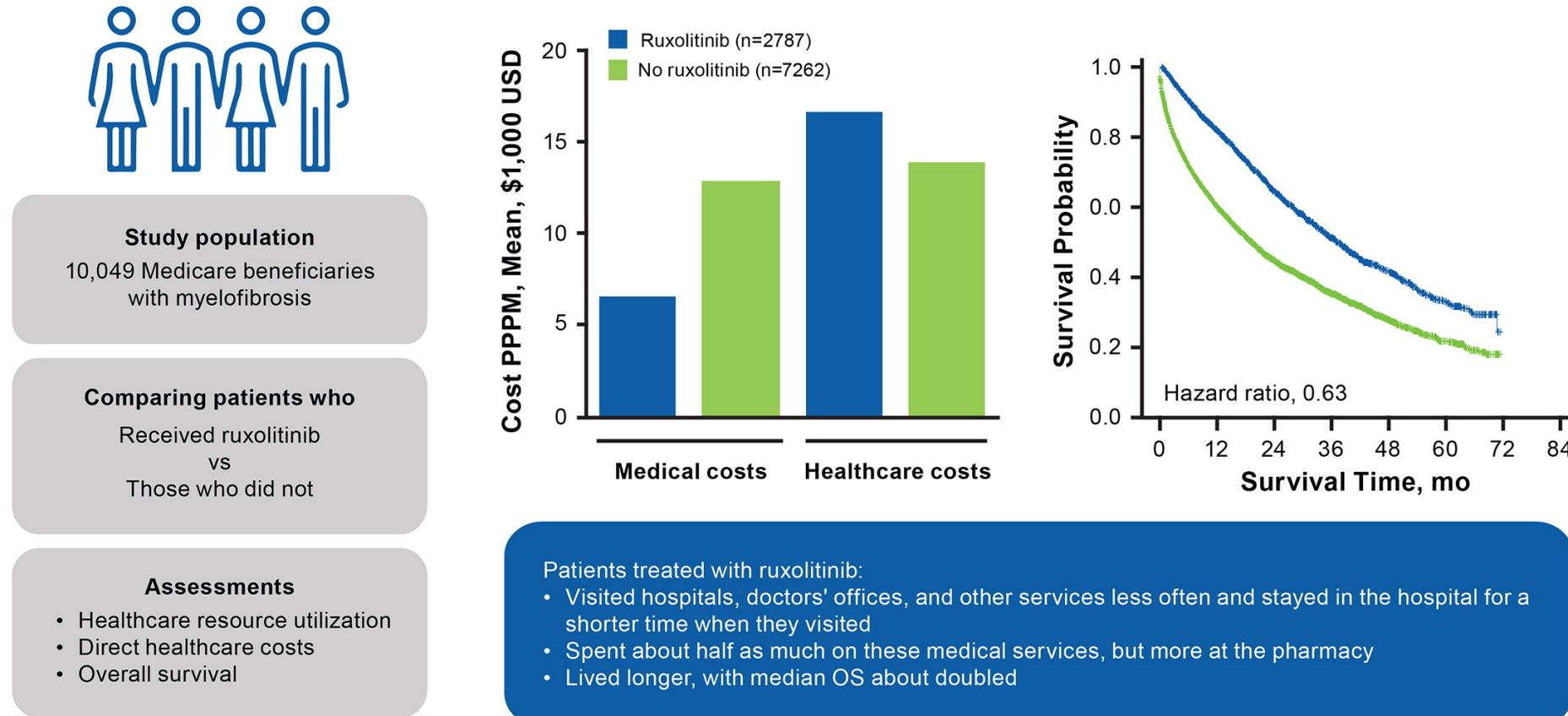
Ruxolitinib bivirkninger

	RESPONSE¹⁶	COMFORT-I¹⁷	COMFORT-II⁵⁴
	n=110	n=155	n=146
Bruising		18.7%	
Peripheral edema			22%
Asthenia			18%
Nasopharyngitis			16%
Pyrexia			14%/2%
Nausea			13%
Arthralgia			12%
Diarrhea	14.5%		23%
Dizziness		14.8%	
Headache		14.8%	10%
Dyspnea	10%/2.7%		16%
Muscle spasms	11.8%		
Abdominal pain	9.1%		11%/3%
Weight gain		7%	
Flatulence		5%	10%/2%



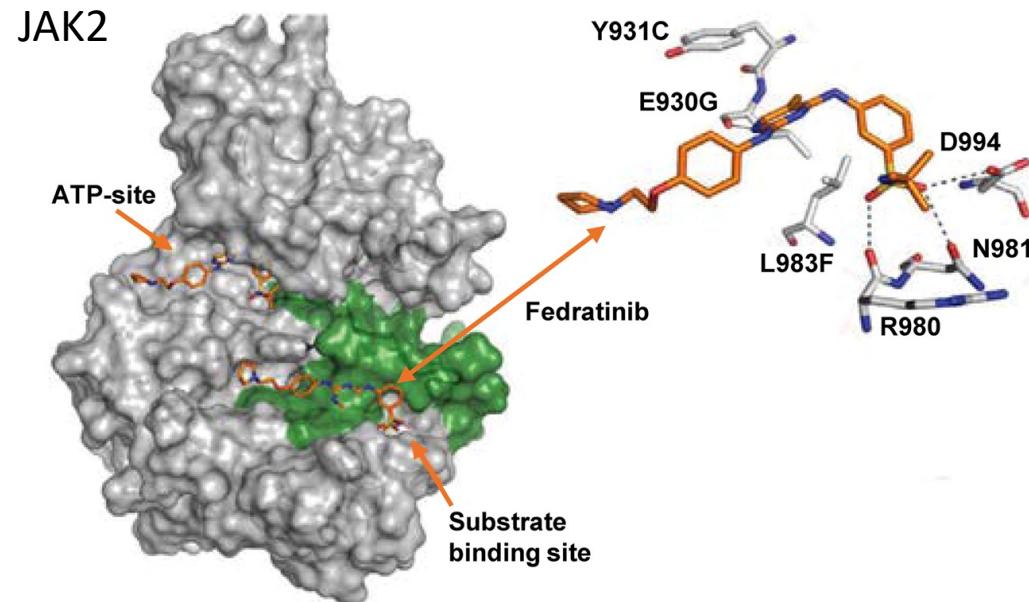
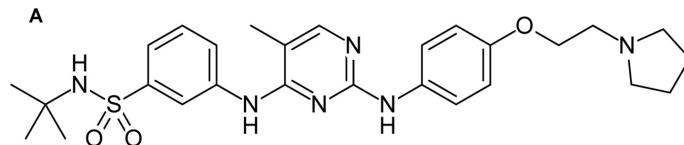
n=126,815 reports from the WHO pharmacovigilance database

Ruxolitinib mot MF hos eldre ikke-transplanterte: Ressurser og kostnader



PPPM, price per patient per month; USD, United States Dollar

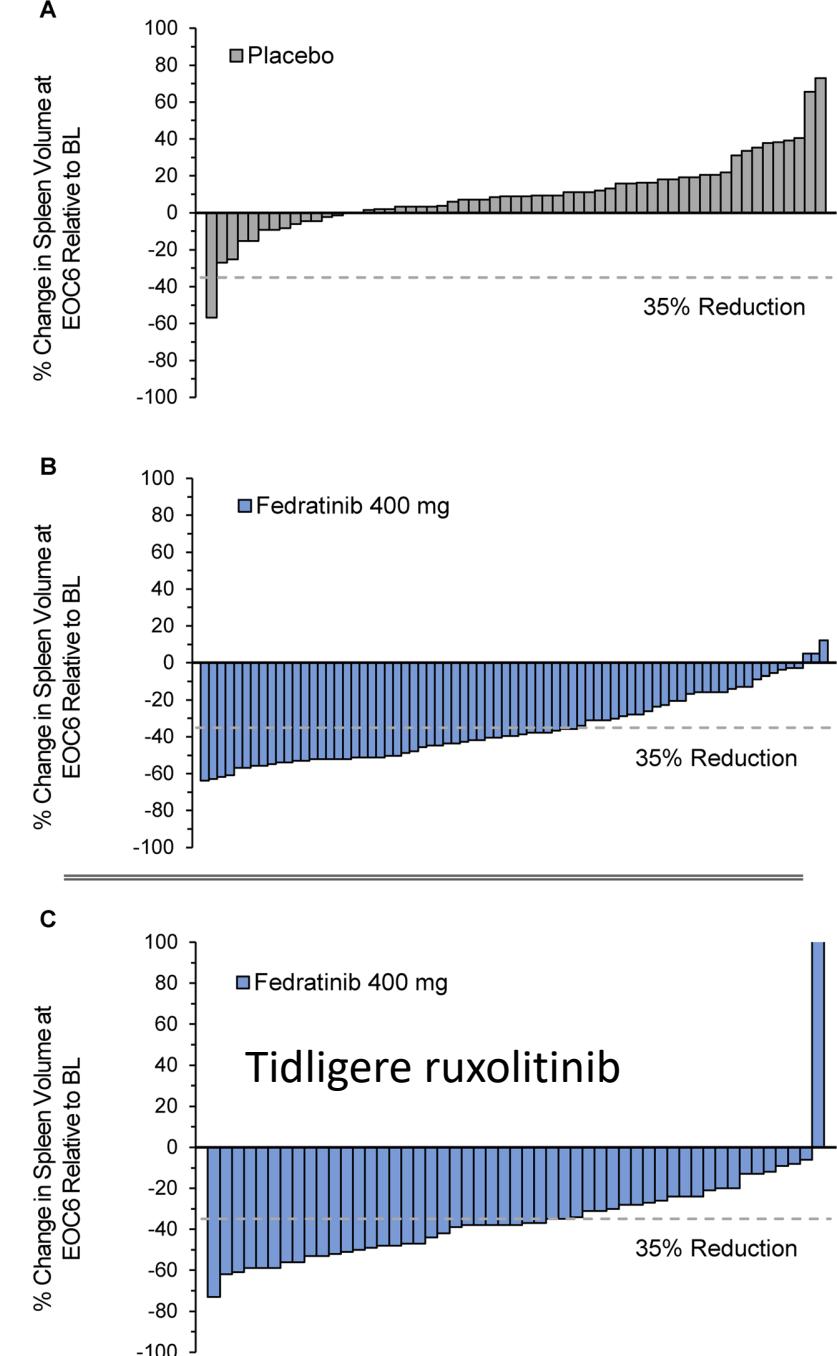
Fedratinib (Inrebec)



(26.09.2022)

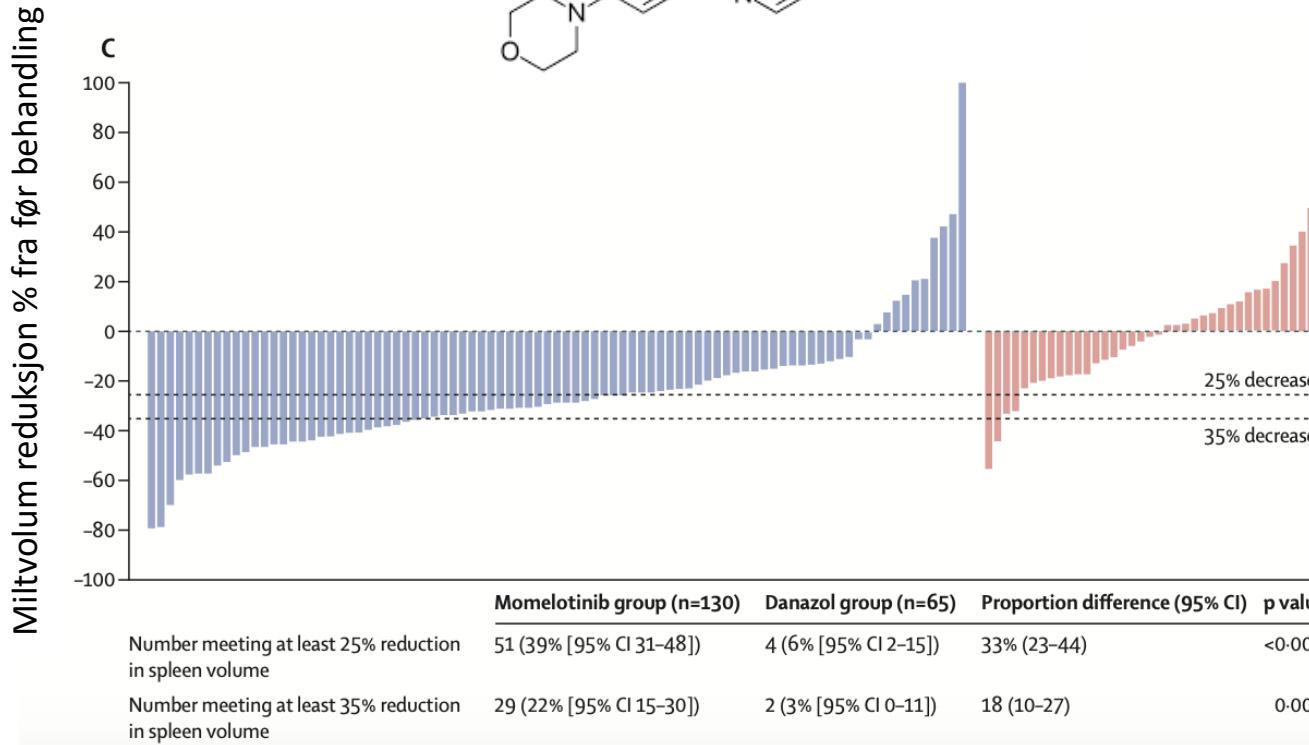
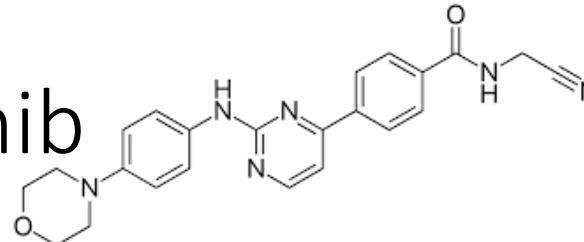
1. Fedratinib (Inrebec) innføres til behandling av primær myelofibrose, post polycytemia vera myelofibrose eller post essensiell trombocytose myelofibrose for JAK-hemmer-naive pasienter.

Impact Biomedicines. INREBIC® (fedratinib) prescribing information. Summit, NJ: Impact Biomedicines, Inc; 2019; Harrison et al. AM J Hematol 2020.



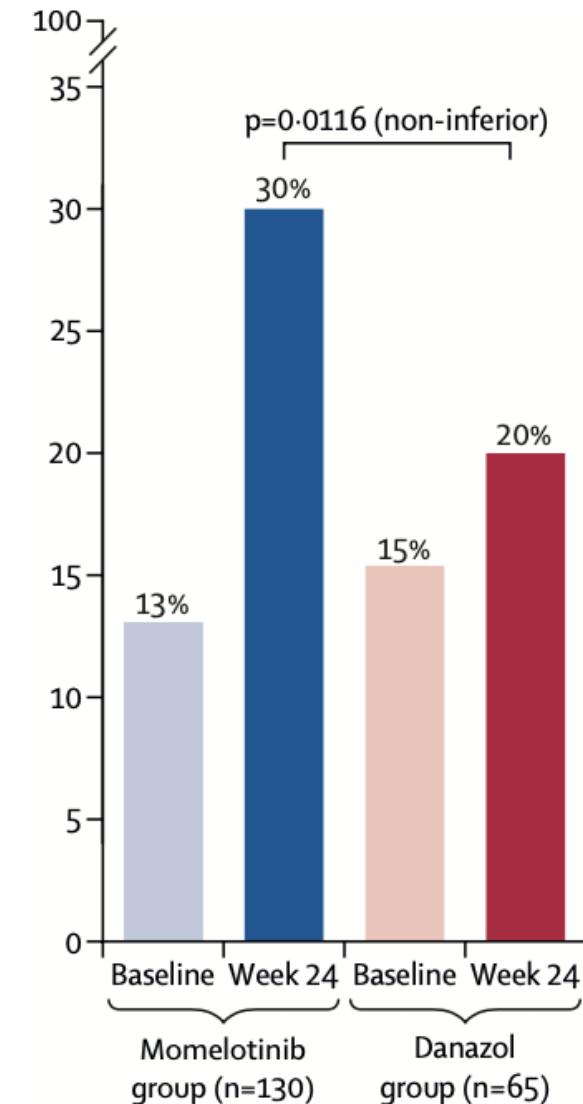
Includes patients with both baseline and week 24 assessments
EOC6, end of cycle 6; BL, baseline

Momelotinib



- Approval is for use in myelofibrosis patients with anaemia regardless of prior myelofibrosis therapy
- Nearly all myelofibrosis patients are estimated to develop anaemia over the course of the disease, and over 30% will discontinue treatment due to anemia
- Momelotinib addresses key manifestations of myelofibrosis, namely anaemia, constitutional symptoms and splenomegaly

Endring i transfusjons-uavhengighet fra baseline til uke 24



Momelotinib

	Momelotinib group (n=130)		Danazol group (n=65)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Non-haematological abnormalities (preferred term)				
Diarrhoea	29 (22%)	0	6 (9%)	1 (2%)
Nausea	21 (16%)	3 (2%)	6 (9%)	2 (3%)
Asthenia	17 (13%)	1 (1%)	6 (9%)	1 (2%)
Pruritus	14 (11%)	2 (2%)	7 (11%)	0
Weight decreased	14 (11%)	0	4 (6%)	0
Blood creatinine increased	10 (8%)	1 (1%)	10 (15%)	2 (3%)
Dyspnoea	10 (8%)	3 (2%)	9 (14%)	1 (2%)
Peripheral oedema	10 (8%)	2 (2%)	9 (14%)	0
Fatigue	8 (6%)	1 (1%)	7 (11%)	2 (3%)
Acute kidney injury	6 (5%)	4 (3%)	8 (12%)	6 (9%)
Haematological abnormalities*				
Anaemia	129 (99%)	79 (61%)	65 (100%)	
Thrombocytopenia	99 (76%)	36 (28%)	40 (62%)	
Neutropenia	38 (29%)	16 (12%)	17 (26%)	

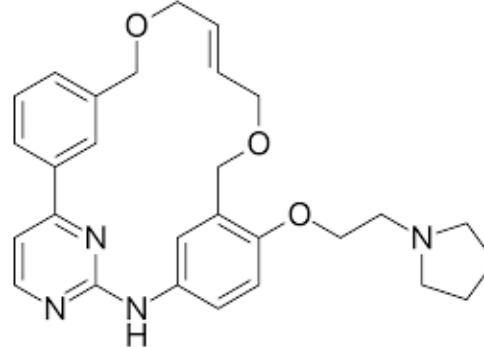
Data are n (%). *Haematological abnormalities are based on laboratory values. The data shown are for the worst grade during the 24-week randomised treatment phase of the study, regardless of whether this grade changed from baseline.

Table 3: Treatment-emergent adverse events observed in at least 10% of patients in either group during the 24-week randomised treatment period

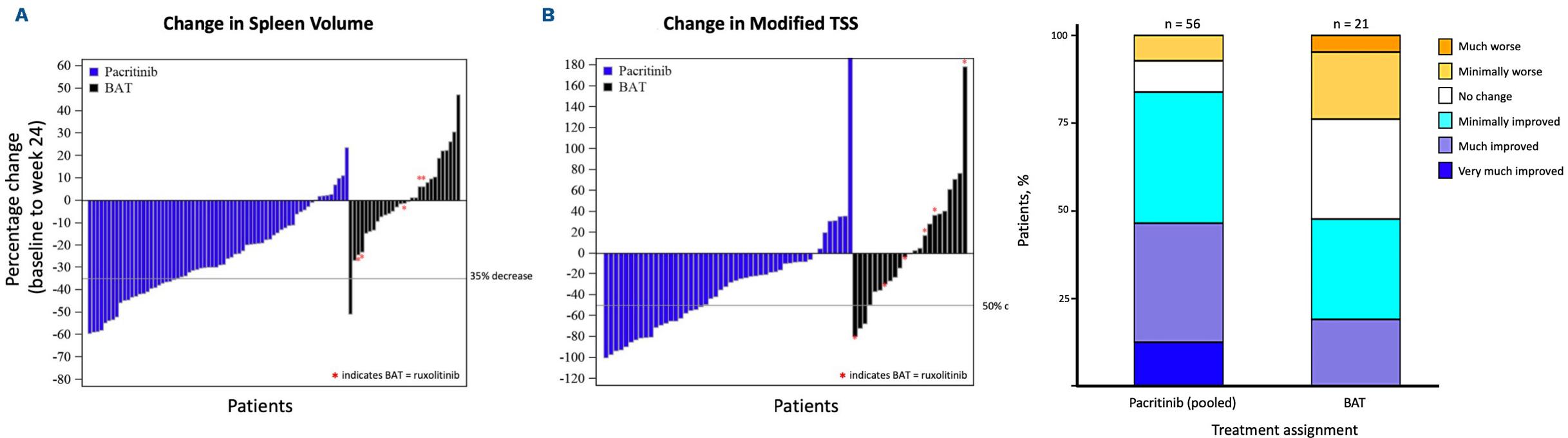
(19.06.2023)

Et prisnotat utarbeides av Sykehusinnkjøp HF, LIS for momelotinib (Omjara) til behandling av sykdomsrelatert splenomegali eller symptomer ved myelofibrose.

Pacritinib

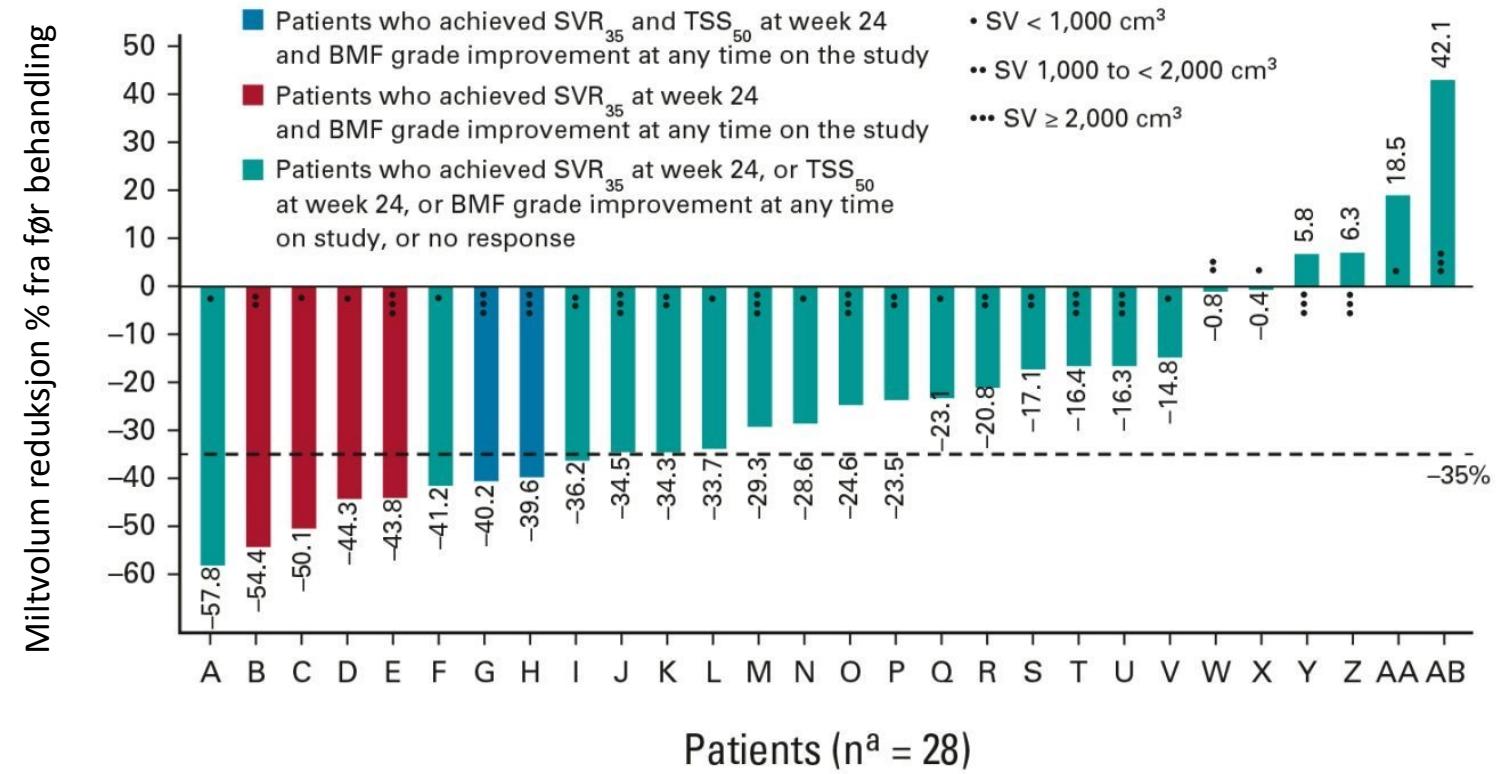


Selv-rapporterte symptomer hos pasienter ved uke 24 (Patient Global Impression of Change). Symptombedring større for pasienter på pacritinib (84% [47/56]) sammenlignet med beste tilgjengelige behandling (BAT) (48% [10/21])



Navitoklaks i tillegg til ruxolitinib for pasienter med myelofibrose med progresjon eller suboptimal respons (fase II)

- **navitoklaks + ruxolitinib** gir reduksjon i miltstørrelse og bedring av generelle symptomer hos pasienter refraktør til ruxolitinib monoterapi.
- Sikkerhetsprofilen av kombinasjonen er lik med ruxolitinib alene, med unntak av mer trombocytopeni



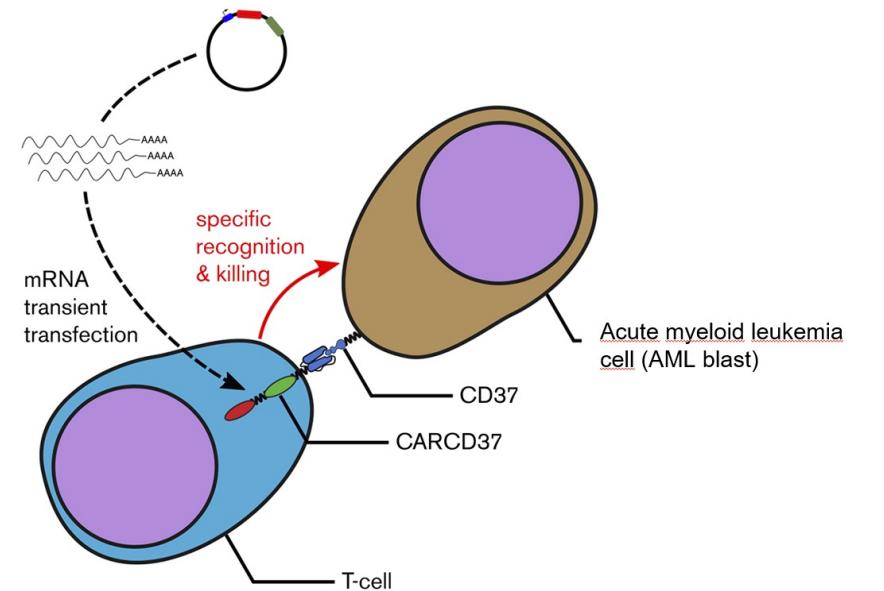
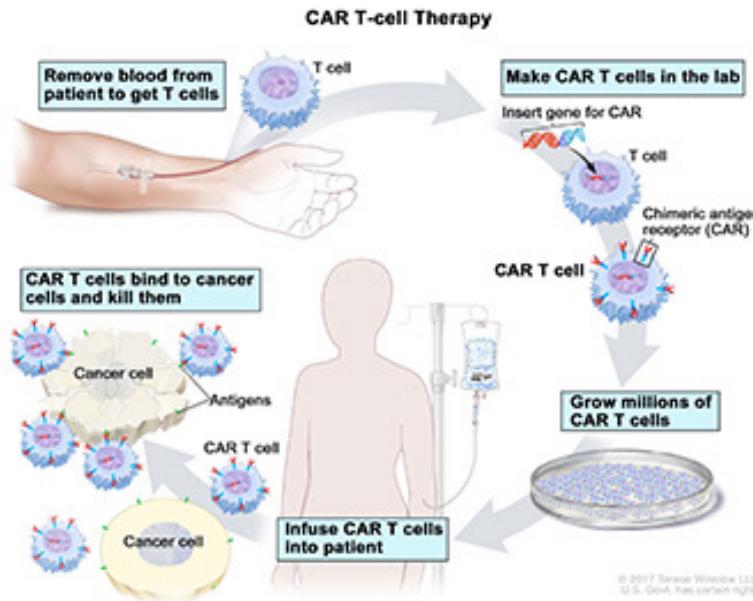
Kronisk tretthet - fatigue





forskning

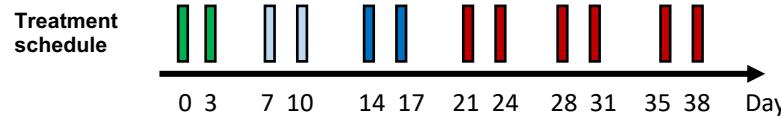
CAR T mot calreticulin (CALR) ved MF



Day 0 Day 10 Pretreatment Day of treatment

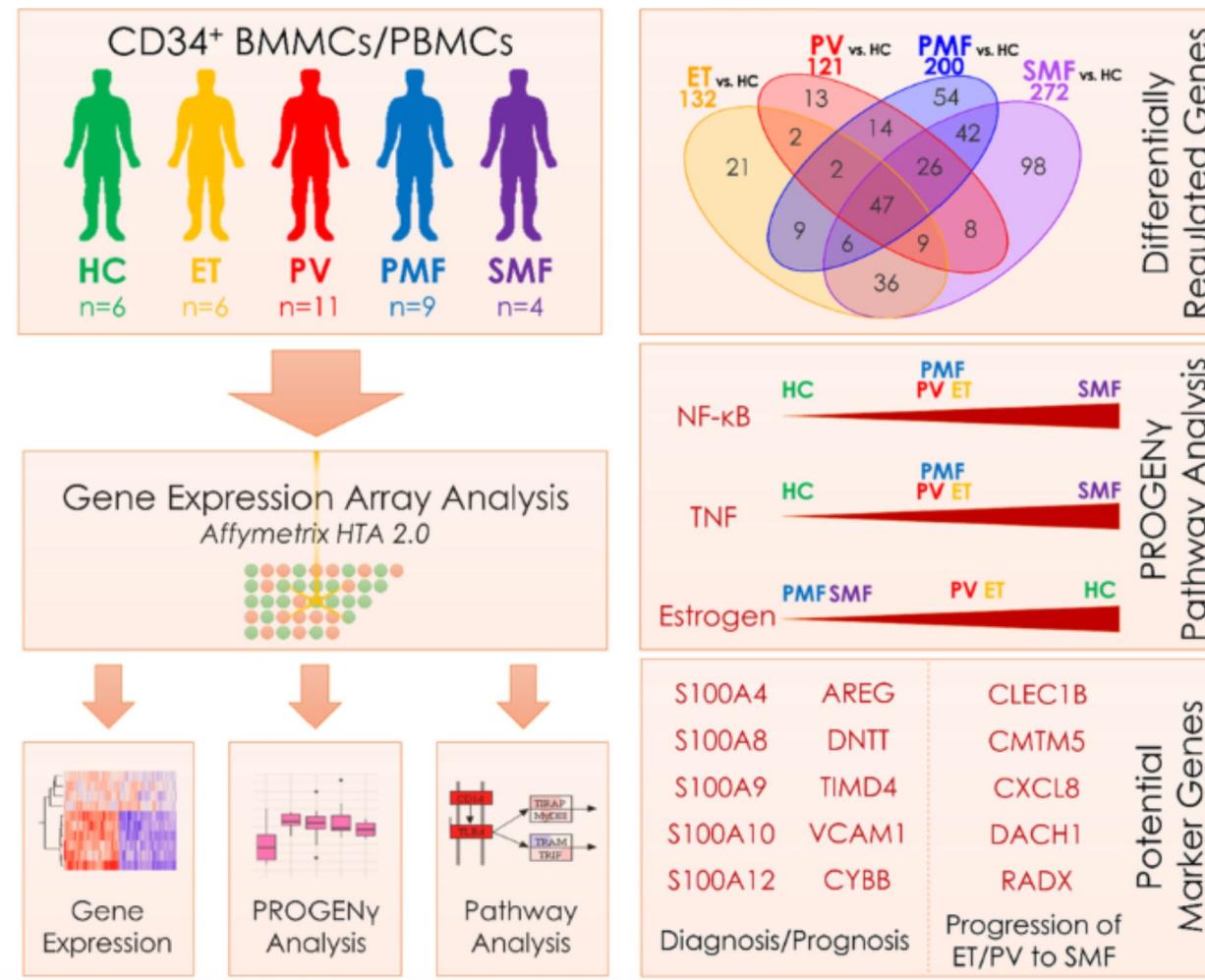
Leukapheresis → Elutriation and stimulation of T cells with anti-CD3/CD28 Dynabeads → Remove beads, harvest, wash, electroporation with Radium-4 mRNA construct. Cryopreserve → Quality testing and release. Potency testing. → Thaw aliquot of product. Infuse T cells iv.

- 1 x 10⁸ cells i.v.
- 3 x 10⁸ cells i.v.
- 1 x 10⁹ cells i.v.
- 2 x 10⁹ cells i.v.

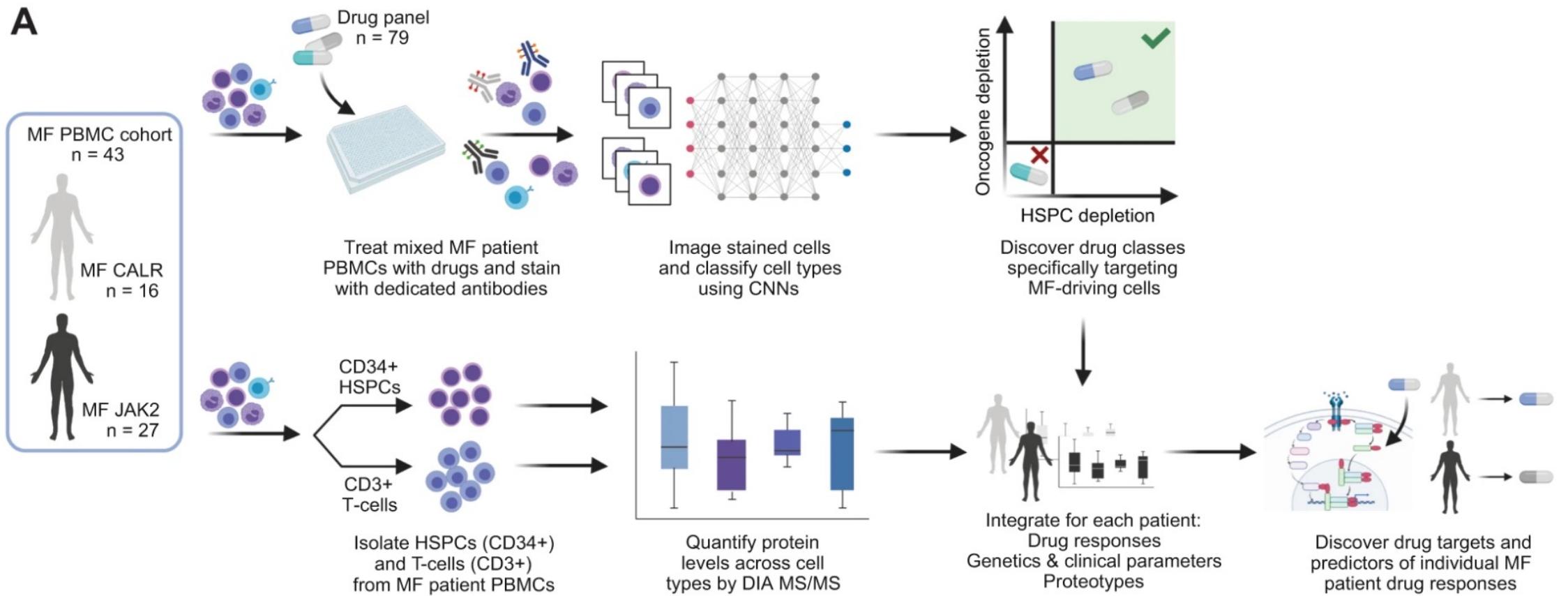


KlinBeForsk: CAR T CD37
mot AML med målbar
restsykdom som
uttrykker CD37

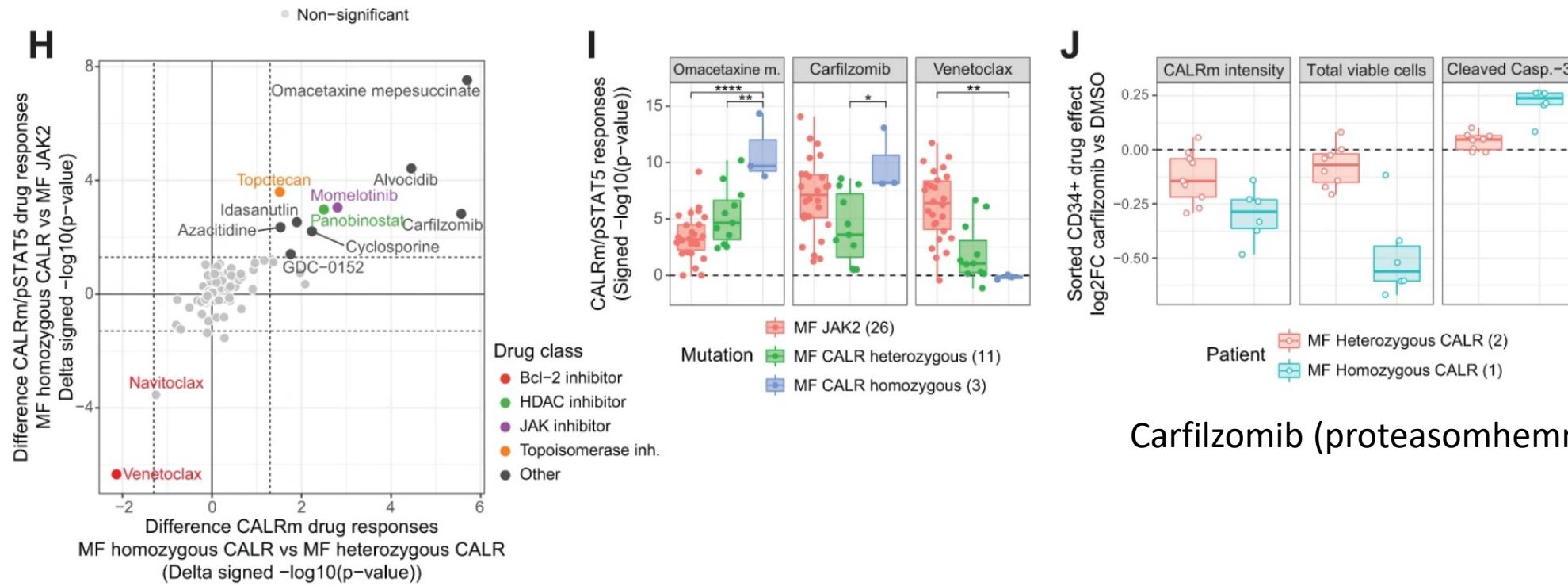
Tidlig og sene stadium av MPN: genuttrykk i CD34+ celler (kreftstamceller)



Protein-genetisk medisin-respons avdekker terapimål ved myelofibrose



Protein-genetisk medisin-respons avdekker terapimål ved myelofibrose

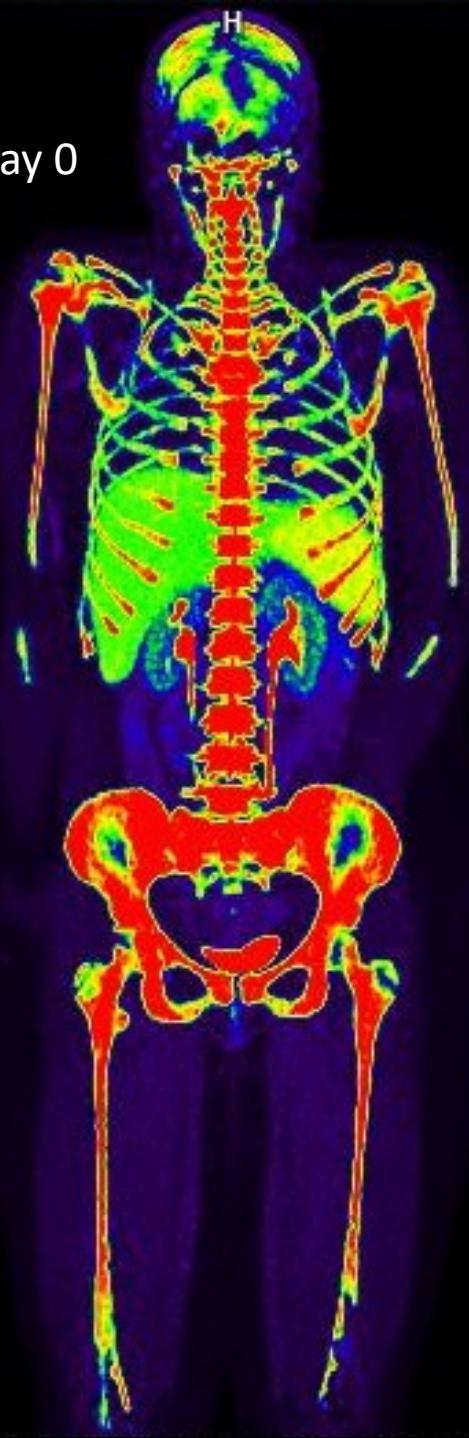


Responseevaluering som leder til endring i behandling er basert på tumor-mengde målt etter måneder med behandling.

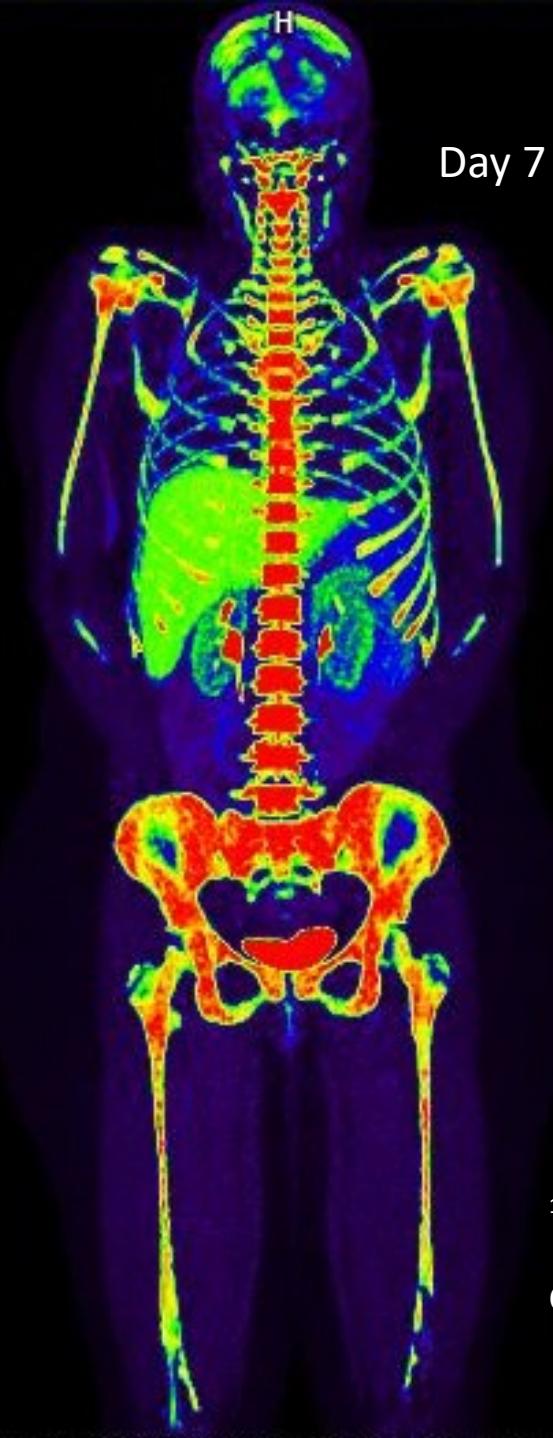
Dynamiske prosesser i kreftcellene som ligger bak terapi-responsen er for oss ukjent (black box).

Kan intracellulær signalering avdekke manglende respons i løpet av dager, og tillate oss hurtig tilpassing av behandlingen til noe som virker?

CML Day 0



Day 7 bosutinib



¹⁸F-FLT PET CT

Cecilie Rygh 2021

MPN-karakterisika

«Problemet med å lytte til kroppens signaler, er at man hører så utrolig mye. Og det meste er uten noen som helst betydning.»

Ingvar Wilhelmsen



Gjertsen lab

Vibeke Andresen
Stein-Erik Gullaksen
Maria Omsland (HVL)
Benedicte Tislevoll
Pål Tore Bentsen
Øystein Sefland
Kristine Sletta
Inga Motzfeld
Liv Thomsen
Tara Dowling
Reidun Kopperud
Tuyen Van Hoang
Gard Skarsten

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Satu Musjoki, Helsinki
Kimmo Porkka, Helsinki

Dominik Wolf, Innsbruck

UiB Flow cytometry Core
Jørn Skavland
Brit Bergum
Silke Appel

PET CT
Cecilie Brekke Rygh



Centre for
Cancer Biomarkers

••• HELSE BERGEN
Haukeland universitetssjukehus

Forskningsrådet

KREFTFORENINGEN

Immunotherapies

Interferon (IFN)

develop CAR T-cells for MF, targeting the mutated cell surface protein mutCALR (mutated Calreticulin) on the malignant cells. mutCALR is found in 25% of all cases of MF and represents an excellent potential target for CAR T-cells.



Navitoclax Added to Ruxolitinib Improves Spleen Volume and Symptoms in Myelofibrosis

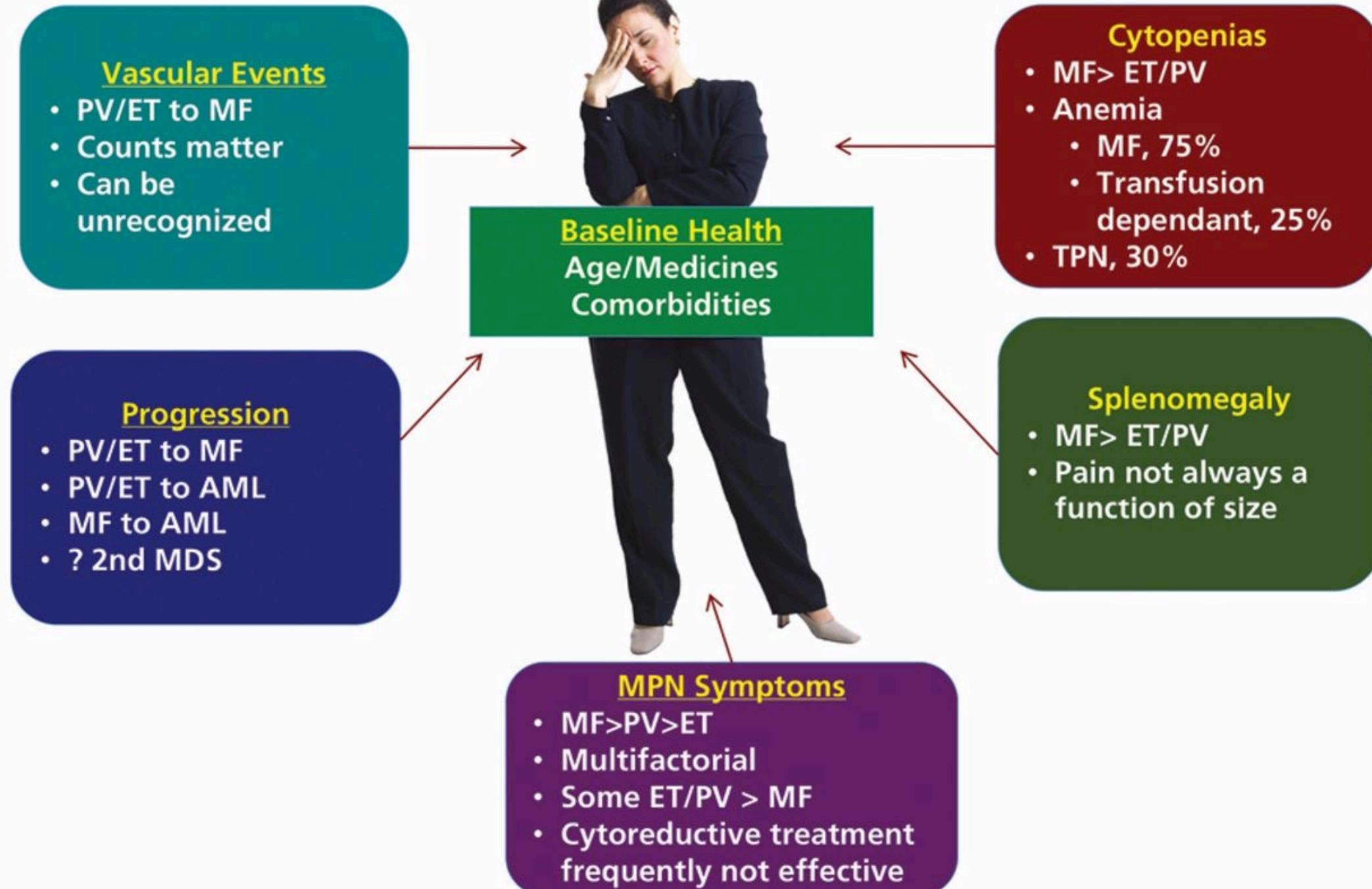
Results for the secondary end points showed that 28% of patients had a ≥ 1 grade reduction in BMF from baseline. Moreover, 22% patients had complete resolution of BMF. The median time to BMF reduction was 12.3 weeks (range, 12.1-24.1). Five of 14 evaluable patients showed a VAF reduction $\geq 50\%$ for driver gene mutations. The molecular responses to navitoclax/ruxolitinib occurred as early as 12 weeks into treatment.

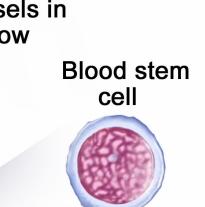
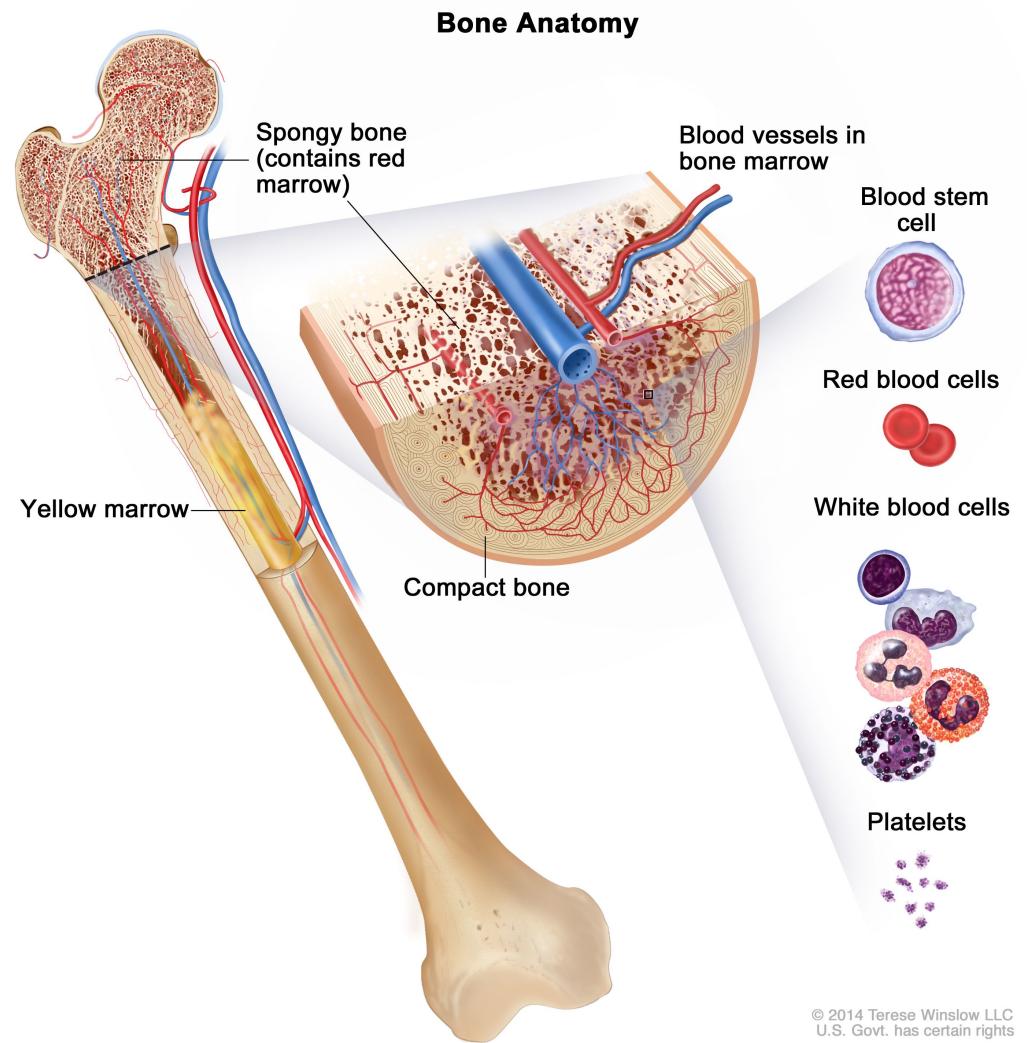
phase 2 REFINE trial (NCT03222609), treatment with navitoclax plus ruxolitinib (Jakafi) led to an improvement in bone marrow fibrosis (BMF) and reduction in variant allele frequency (VAF) in patients with myelofibrosis (MF) who progressed on or had suboptimal response with prior ruxolitinib monotherapy.¹

Median overall survival (OS) was not reached (NR) in patients who had at least 1 grade improvement in BMF vs those without at 28.5 months (95% CI, 19.6-NR; $P < .01$). Similarly, median OS was better in those with 20% or greater reduction in VAF vs without (NR vs 28.5 month, respectively; $P = .05$). No deaths were observed in patients with either BMF improvement or VAF reduction.

Passamonti F, Foran JM, Tandra A, et al. 237 The combination of navitoclax and ruxolitinib in jak inhibitor-naïve patients with myelofibrosis mediates responses suggestive of disease modification. *Blood*. 2022;140 (suppl 1): 583–585. doi:10.1182/blood-2022-157949

Pemmaraju N, Garcia J, Potluri J, et al. Addition of navitoclax to ruxolitinib mediates responses suggestive of disease modification in patients with myelofibrosis previously treated with ruxolitinib monotherapy. Presented at: American Association for Cancer Research (AACR) 2022 Annual Meeting; April 8-14, 2022; New Orleans, LA. Abstract LB108 /





White blood cells



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Myeloproliferative neoplasms (MPNs) are types of blood cancer that begin with an abnormal mutation (change) in a stem cell in the bone marrow. The change leads to an overproduction of any combination of white cells, red cells and platelets.



Essential Thrombocythemia

Essential Thrombocythemia (ET) Is a rare blood disease in which the bone marrow produces too many platelets. High numbers of platelets may lead to a thrombus, a blood clot that forms in a blood vessel.



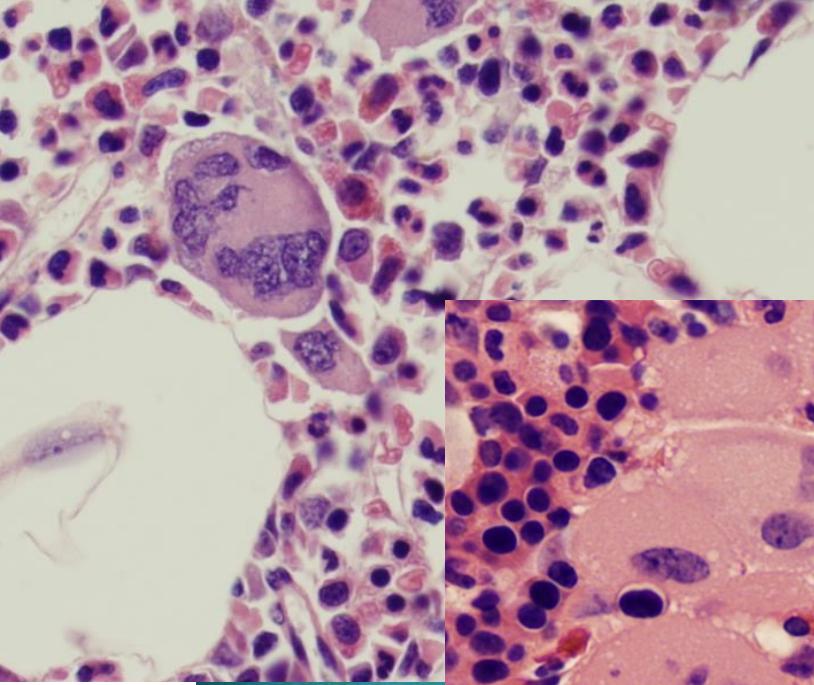
Myelofibrosis

Myelofibrosis (MF) Is a rare disorder in which abnormal blood cells and fibers build up in the bone marrow. Is one of a related group of blood cancers known as “myeloproliferative neoplasms (MPNs)” in which bone marrow cells that produce blood cells develop and function abnormally.

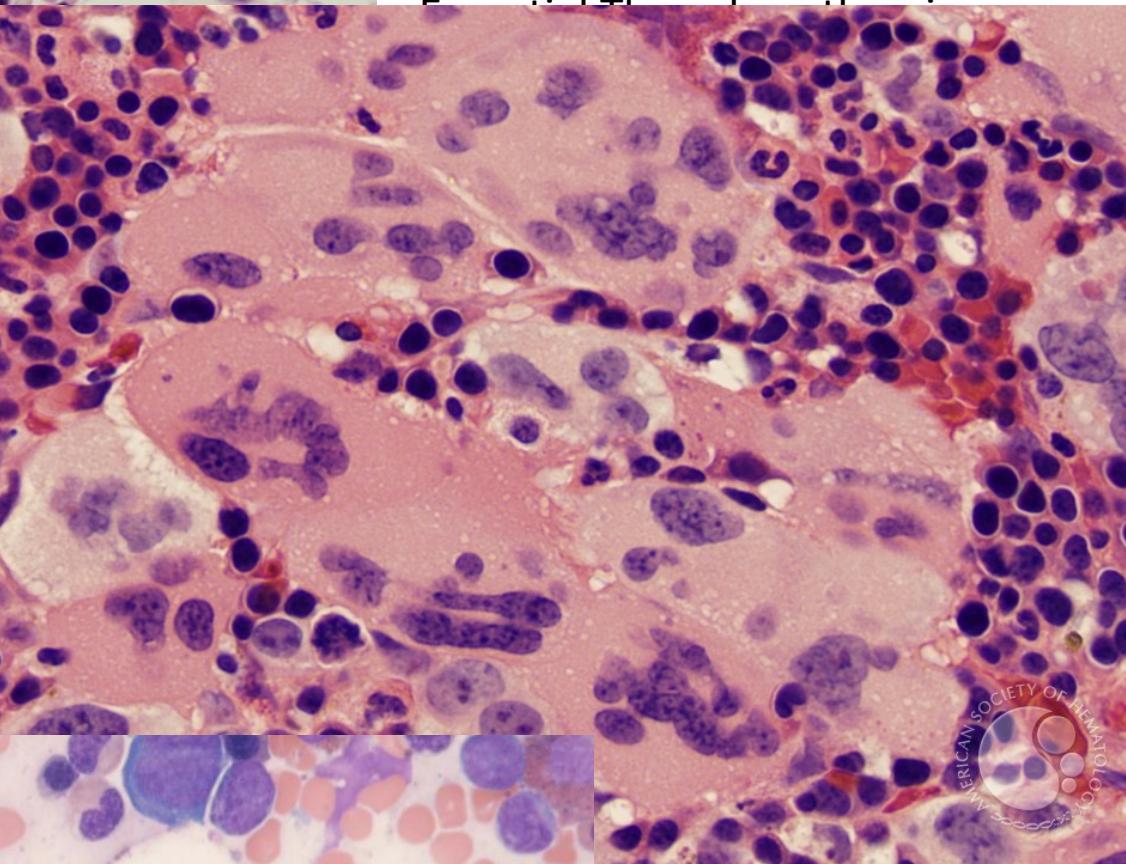


Polycythemia Vera

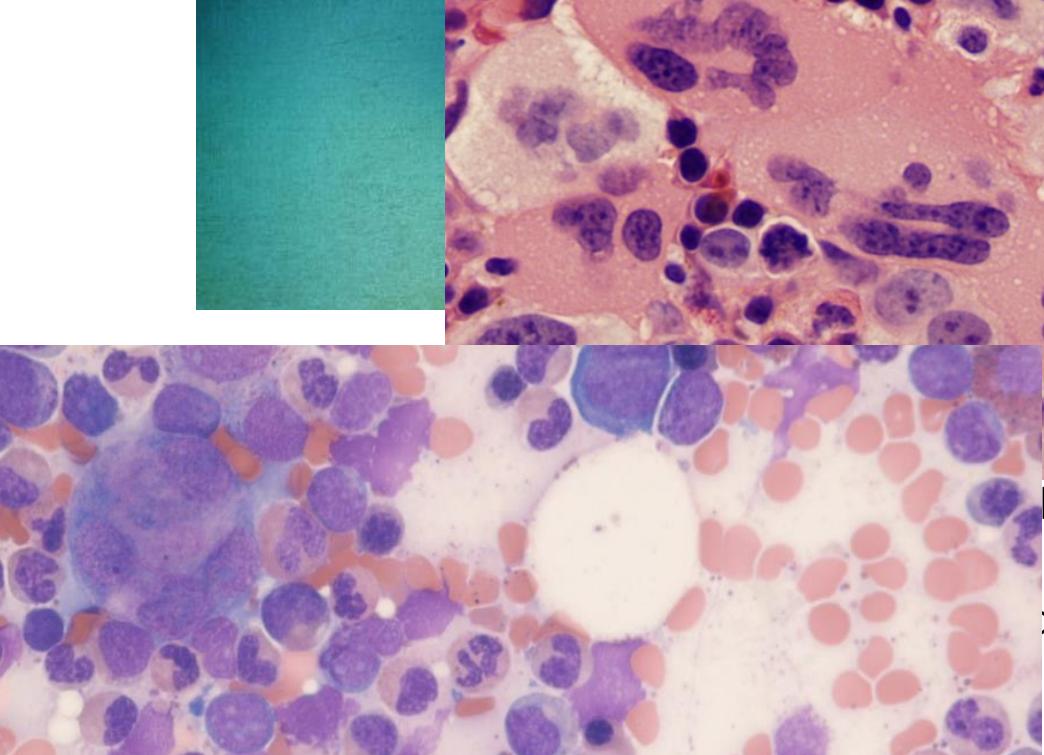
Polycythemia Vera (PV) Is one of a related group of blood cancers known as “myeloproliferative neoplasms” (MPNs). Too many red blood cells are made in the bone marrow and, in many cases, the numbers of white blood cells and platelets are also elevated.



roliferative neoplasms (MPNs) are types of blood cancer that begin with an initial mutation (change) in a stem cell in the bone marrow. The change leads to production of any combination of white cells, red cells and platelets.



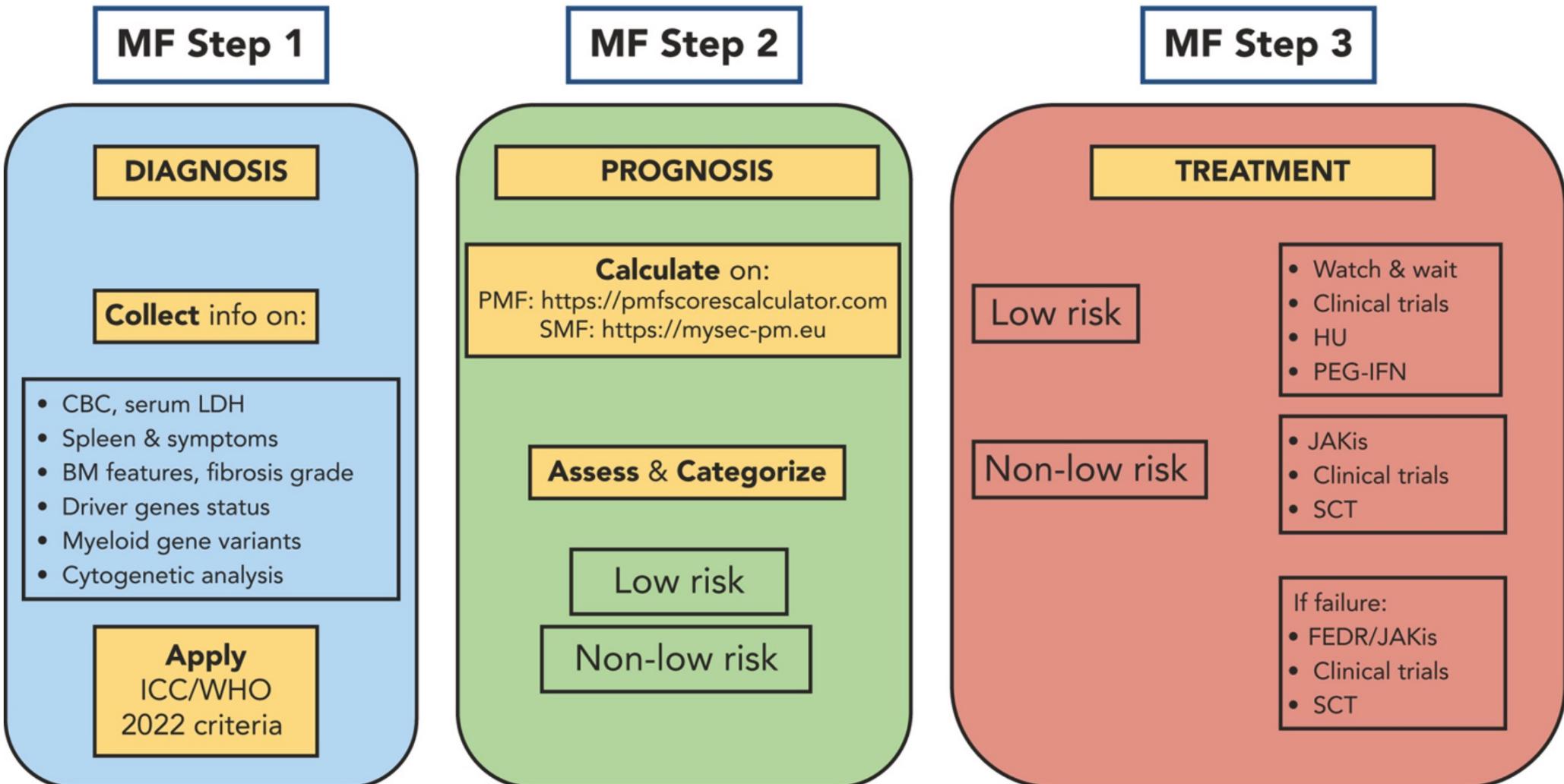
are blood disease in which the bone High numbers of platelets may lead s in a blood vessel.



in which abnormal blood cells and is one of a related group of blood neoplasms (MPNs)" in which bone s develop and function abnormally.

related group of blood cancers known loproliferative neoplasms" (MPNs). Too many red blood cells are the bone marrow and, in many cases, the numbers of white blood platelets are also elevated.

The 3 steps of MF management



Legend: BM= bone marrow; CBC= complete blood count; FEDR= fedratinib, HU= hydroxyurea; ICC= International Consensus Classification; JAKis= JAK inhibitors;
LDH= lactate dehydrogenase; MF= myelofibrosis; PEG-IFN= PEGylated interferon; PMF= primary myelofibrosis; SCT= stem cells transplantation; SMF= secondary myelofibrosis;
rmilde World Health Organization.

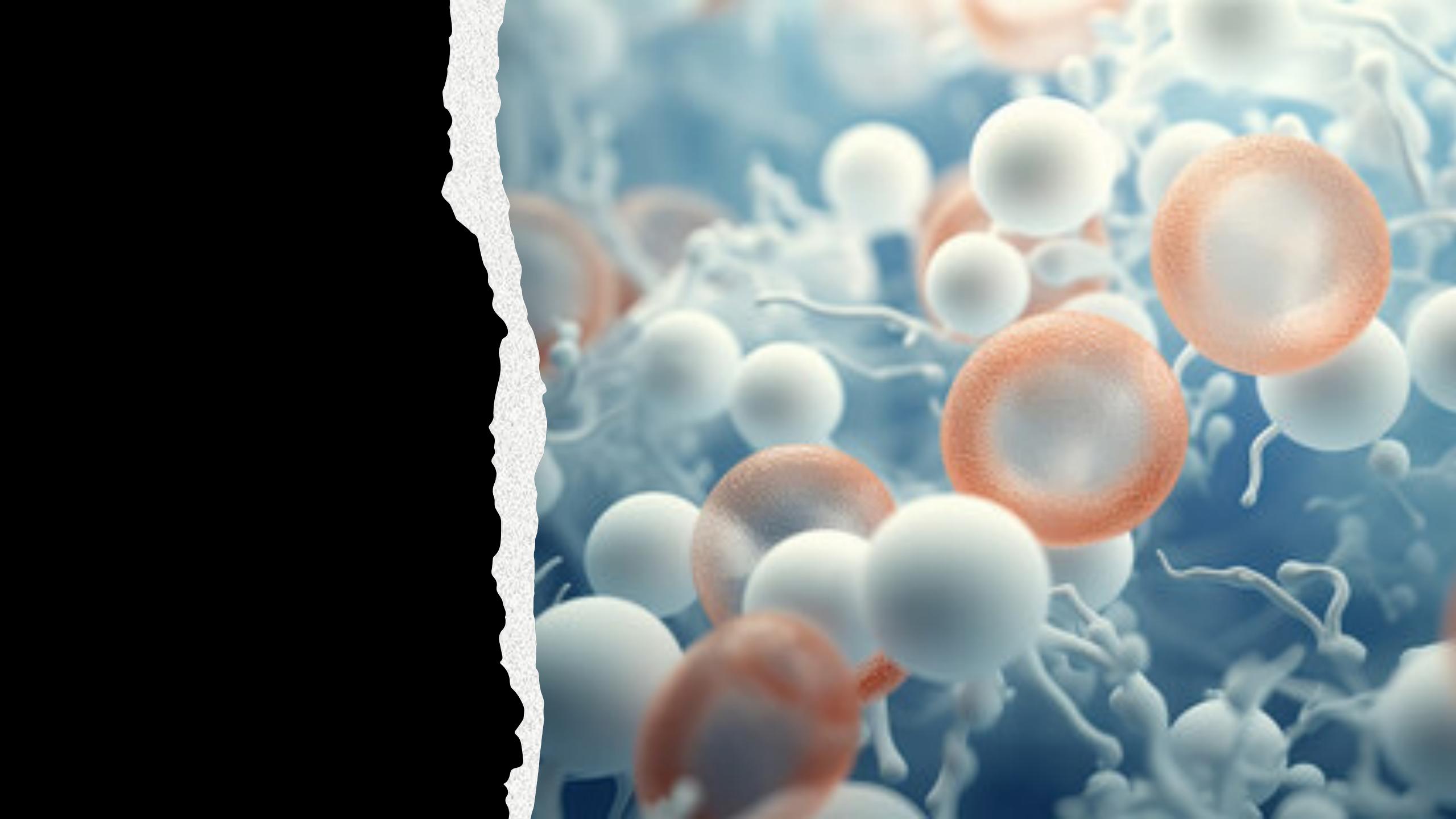


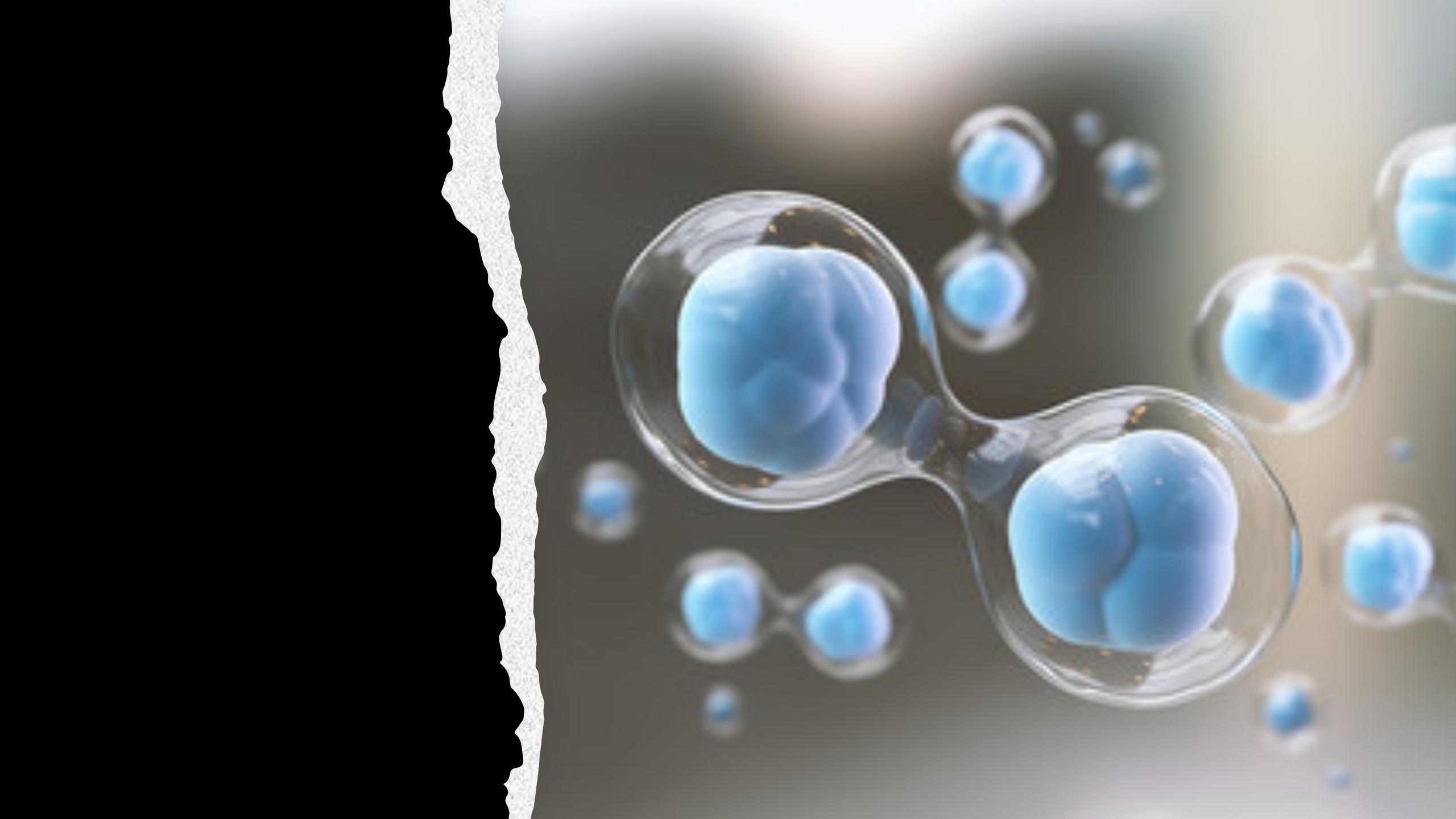
klon

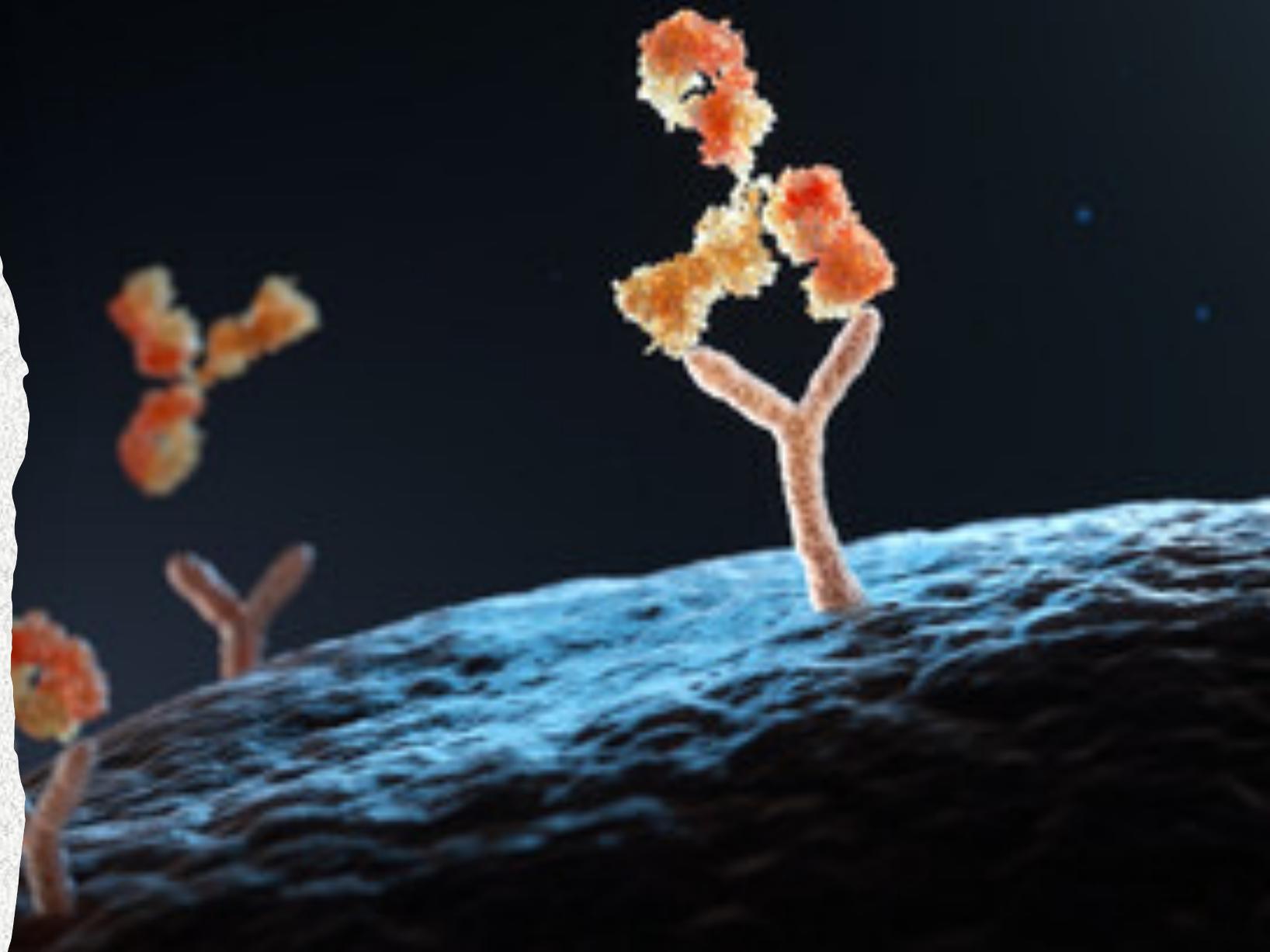
Klon er en ansamling av molekyler eller celler som alle skriver seg fra én enkelt utgangscelle.

Alle cellene i klonen er genetisk identiske med denne opphavscellen, det vil si at de har akkurat det samme arvematerialet.

Cellekulturer (kloner) som hver skriver seg fra en enkelt utgangscelle, kan lett fremstilles i laboratoriet.











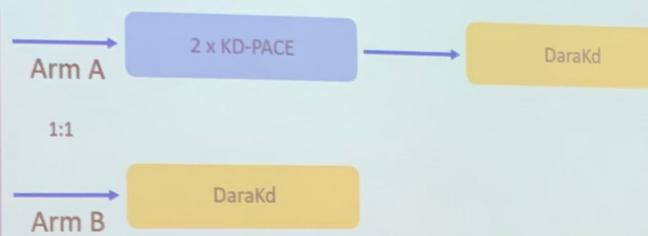
EHA•**CRTH**

CLINICAL RESEARCH TRAINING IN HEMATOLOGY

RD-PACE followed by DaraKd vs DaraKd as salvage treatment in multiple myeloma patients with early relapse (<12 months) following first-line treatment with autologous stem cell transplantation

A randomized controlled phase II trial

PD <12 months post ASCTH
Age > 18 years
ECOG 0-2
Not refractory to daratumumab or karfilzomib
Normal cardiac function
GFR >30
n=125



Hanne Marie Norseth





EHA CRTH
CLINICAL RESEARCH TRAINING IN HEMATOLOGY



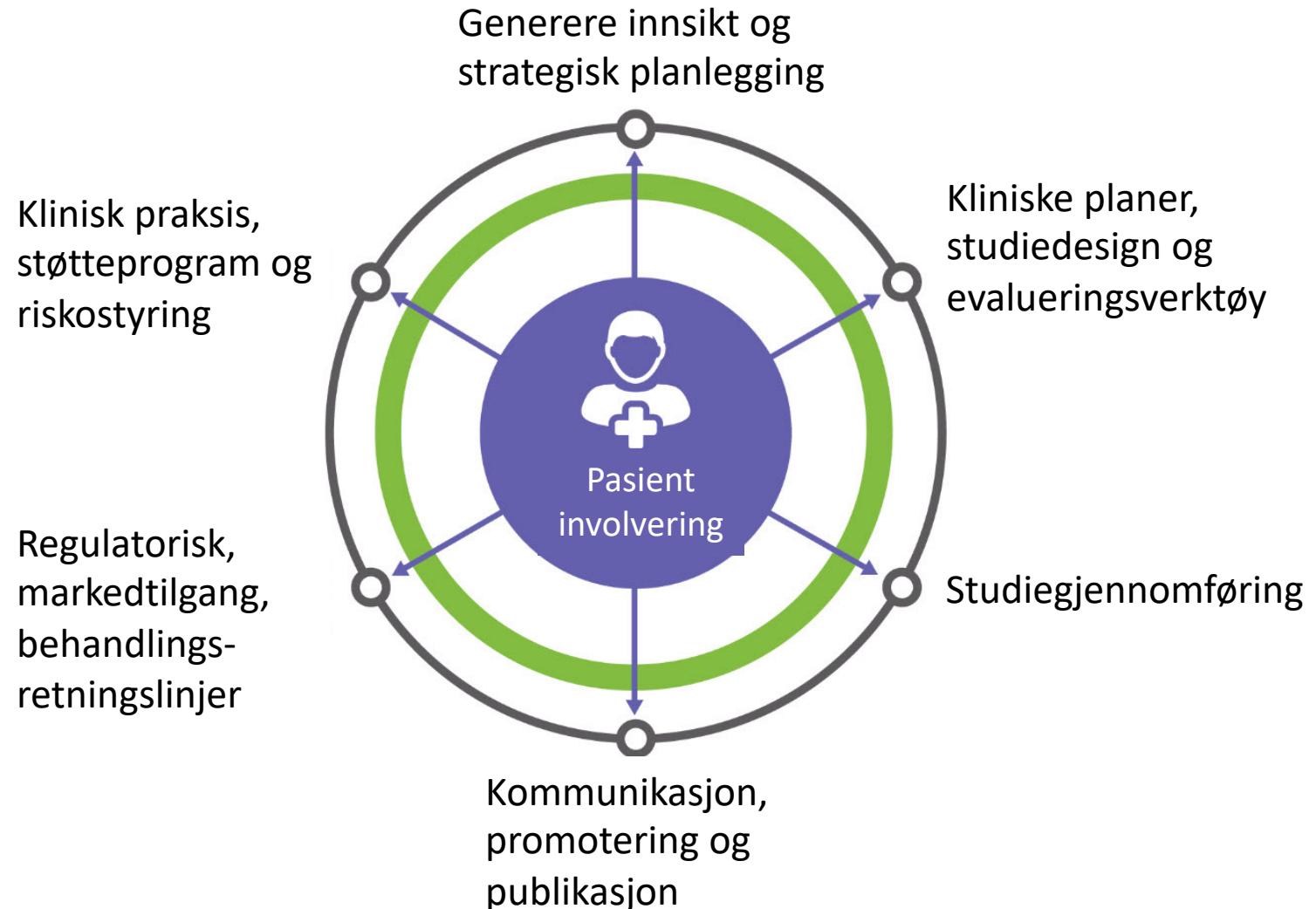


Ekstra prøver og biopsier ved klinisk utprøving:

“Etisk rettferdiggjøring viser til prosessen å etablere en moralsk posisjon ved å presentere tilstrekkelig begrunnelse”

- Min mening
- “Familie og venner-testen” Family and friends test”
- “Key Opinion Leader” mening
- Studiegruppe diskusjon (spesialister) Study group discussion
- Pasient, brukerrepresentanter sin involvering

Involvering av pasienter og brukergrupper





NORDIC
AML
GROUP

Welcome to the Nordic AML Meeting 2023

AUGUST 24.- 25 | RADISSON BLU ROYAL HOTEL, BERGEN



Daniel A. Polleyea



Kimmo Porkka



Gunnar Jullusson



Jeff Tyner



Satu Mustjoki



Martin Höglund



Sören Lehmann



Uwe Platzbecker



Eva Hellström-Lindberg

Mer info: www.helsekonferanser.no

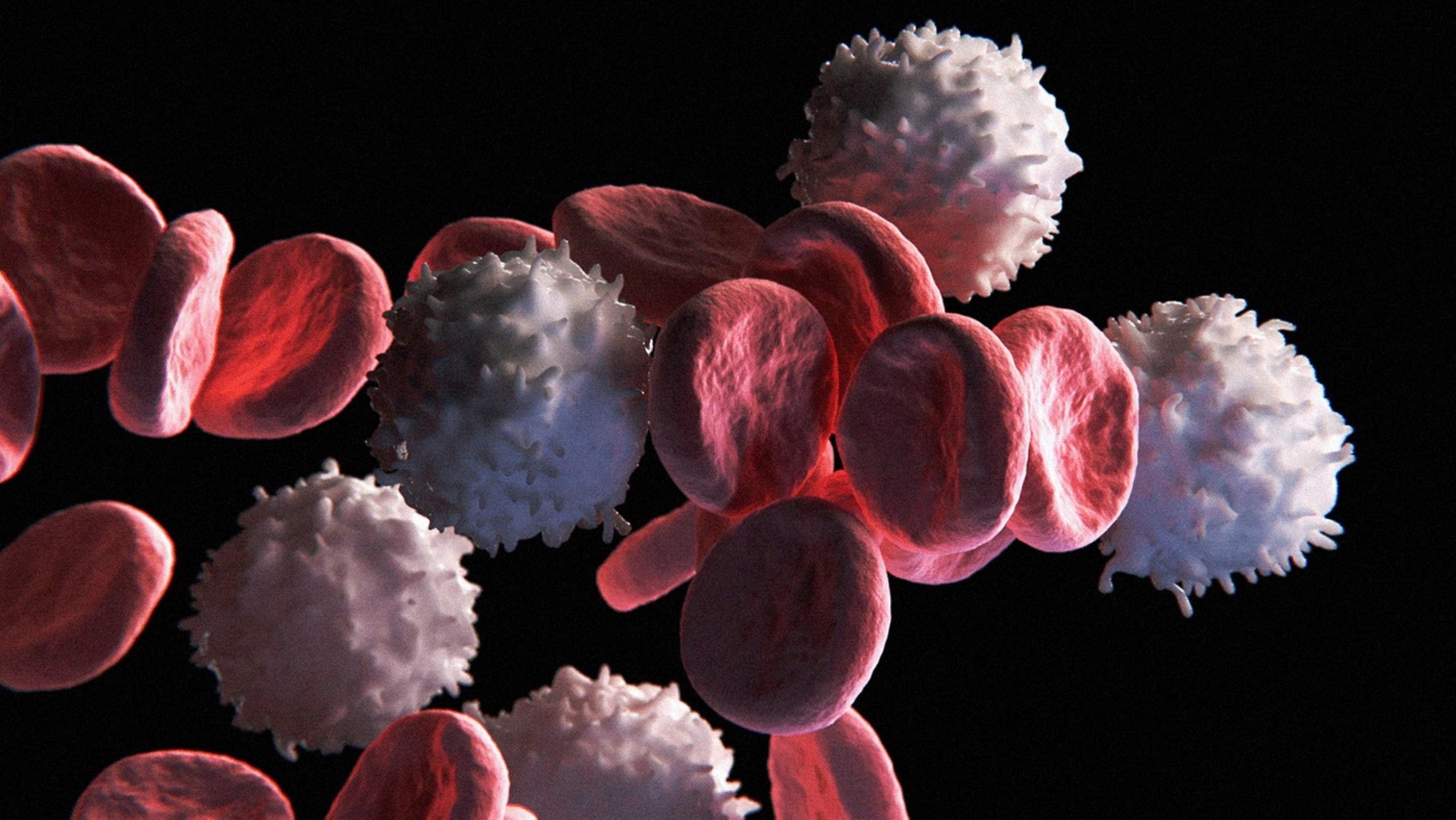


– en bloddraape en verden med solcenter og klober.

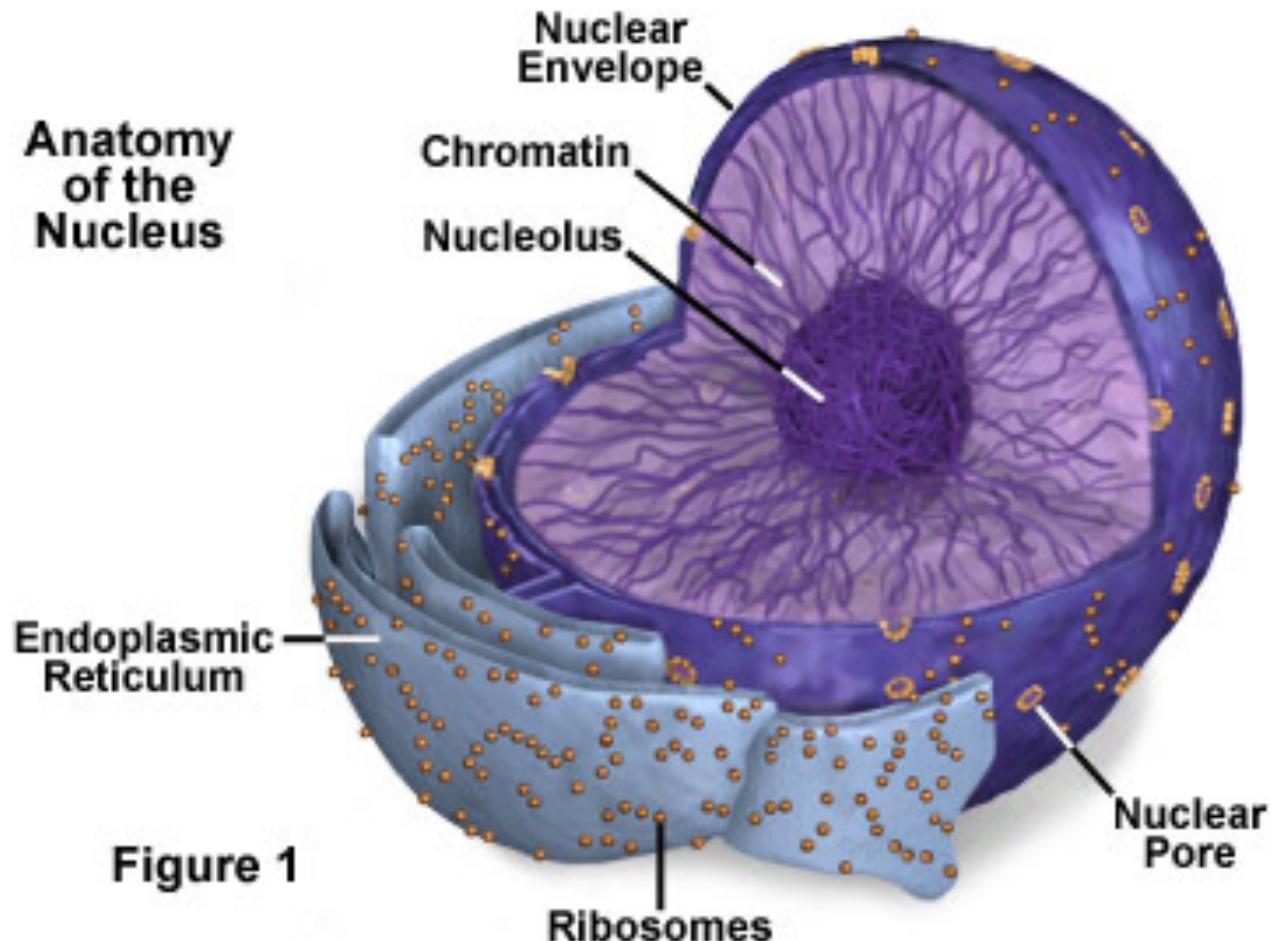
I os er verdener

Intet er litet intet er stort – I os er verdener. Det smaa deler sig i det store.
Det store i det smaa – en bloddraape en verden med solcenter og klober.
Havet en draape. En liden del av et legeme.

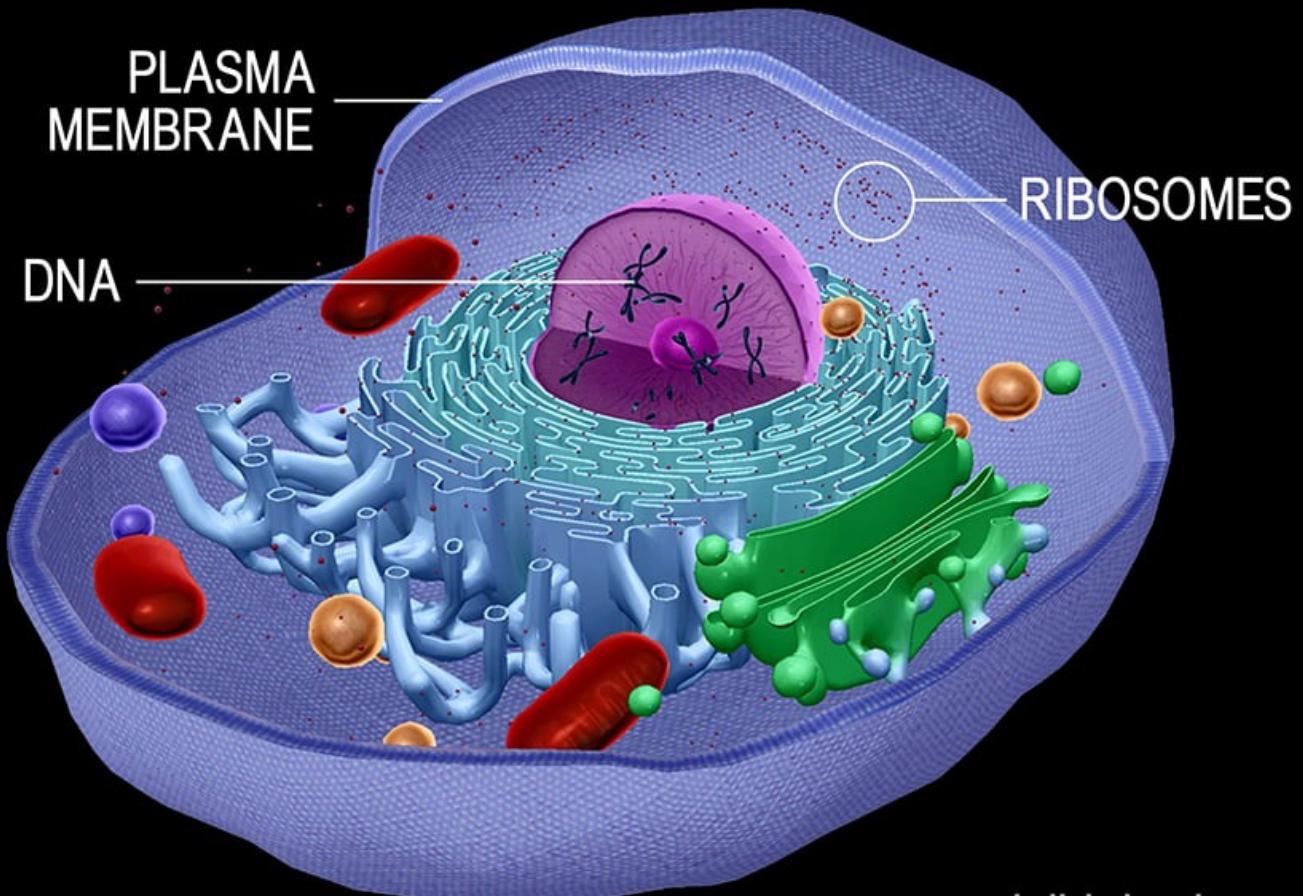
(Edvard Munch, udatert tekst)



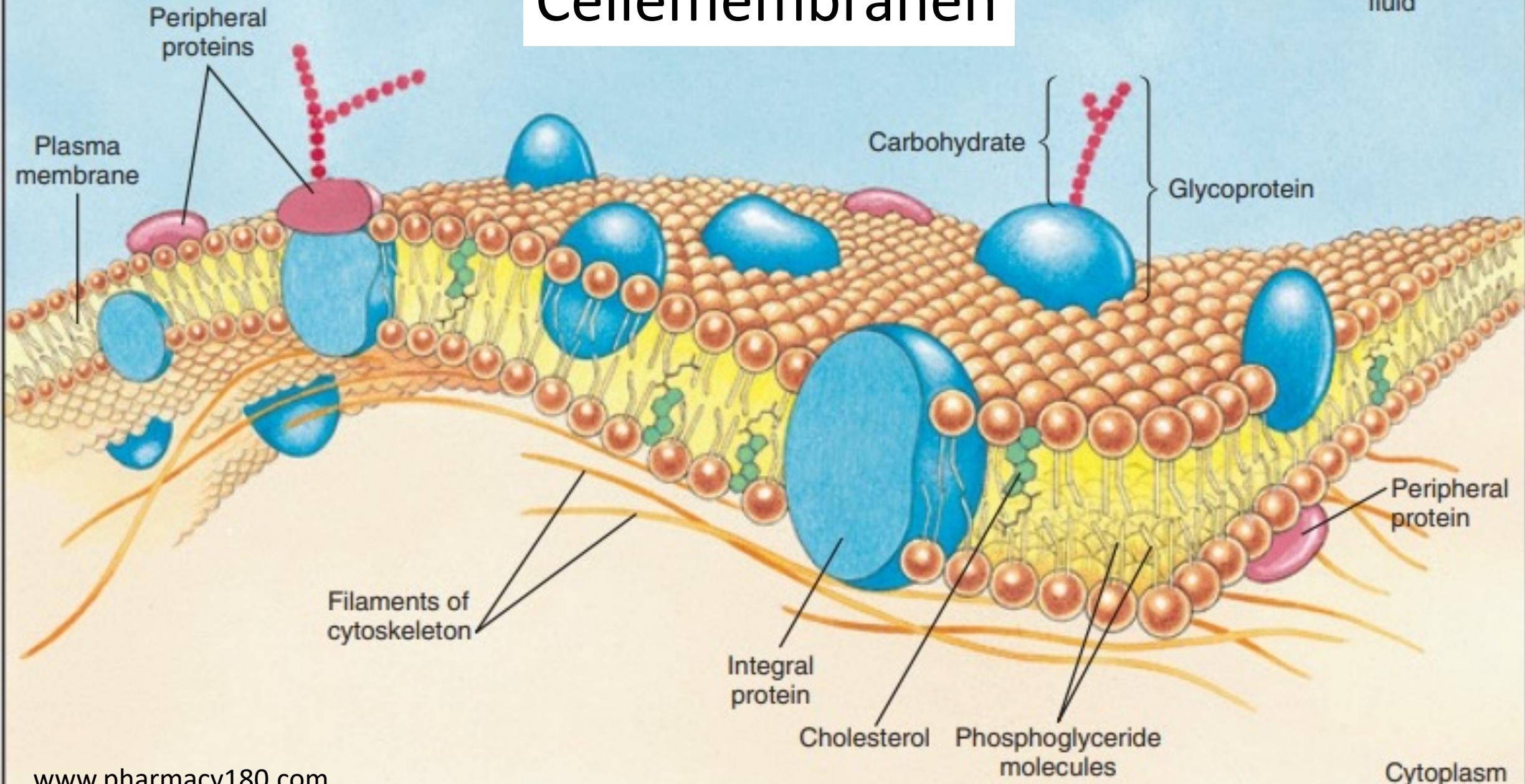
Kjerne-anatomi



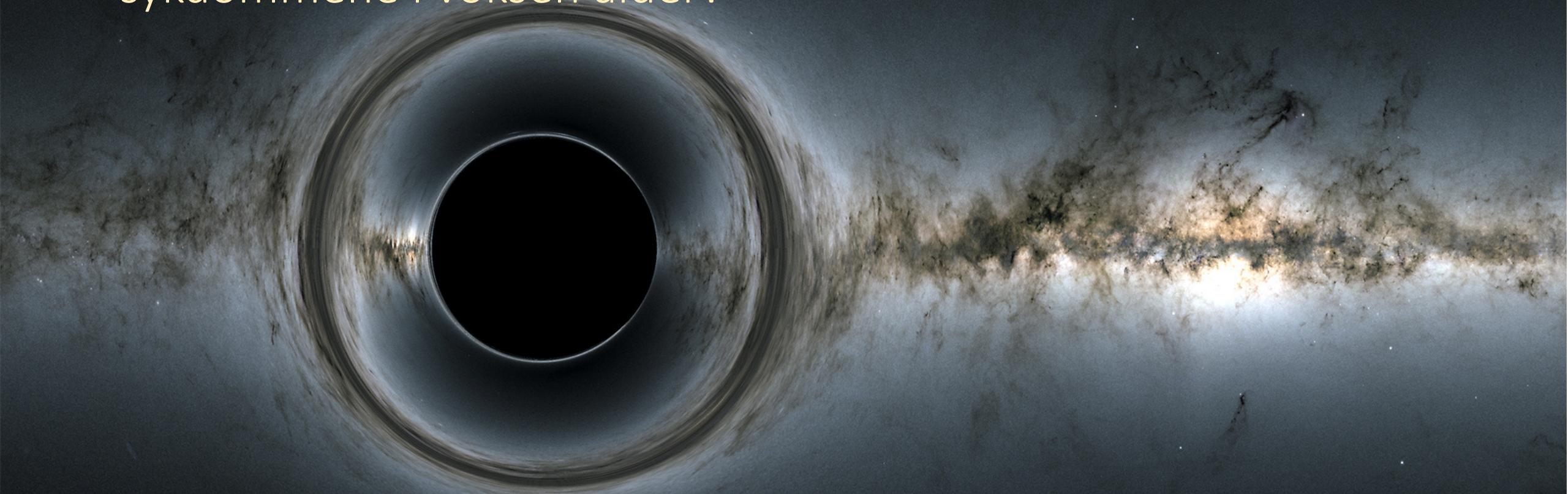
Celle-anatomi



Cellemembranen



Hypotese: det er cellene som mangler som gir de vanlige sykdommene i voksen alder?



Hva skjer innen forskning på blodkreft?

YoungEHA sesjon 8. juni 2023 vil handle om:

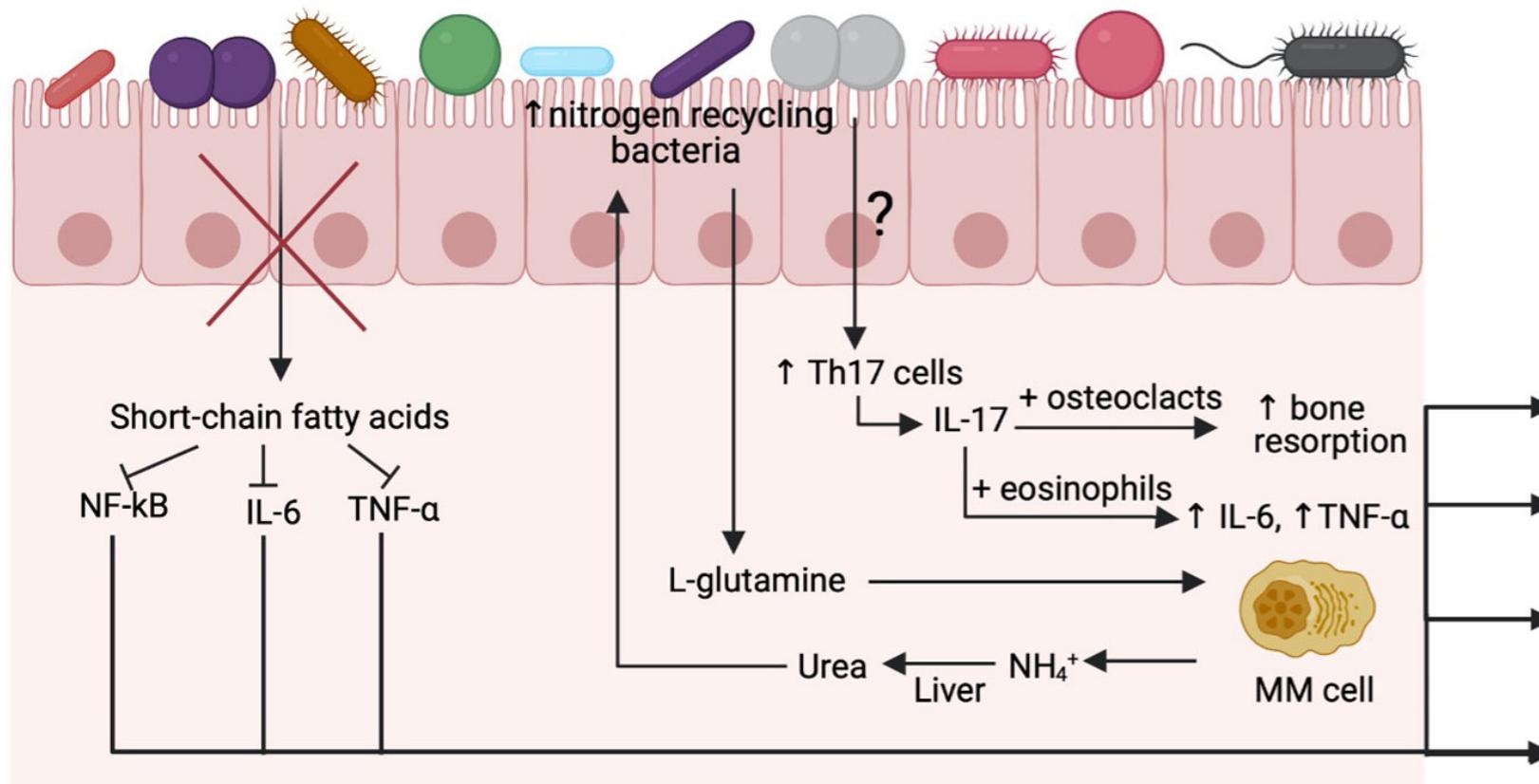
- cellealdring og celledød
- signalering, hormon- og cytokin-kontroll
- transkripsjonell kontroll
- mikrobiom/infeksjonssykdommer



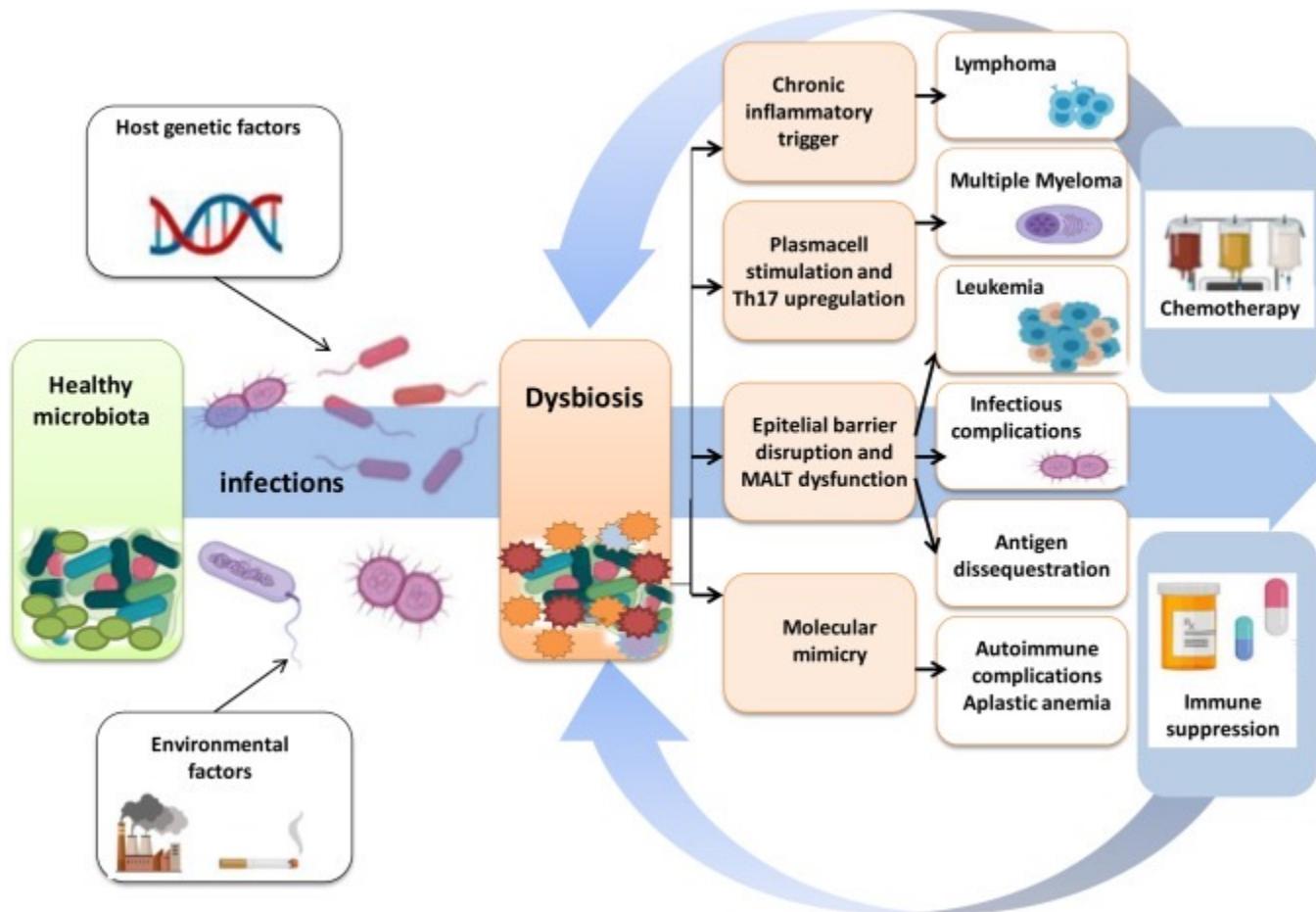
mikrobiom – definisjon

- Mikrobiom eller mikrobiota er den samlingen av alle mikroorganismer som lever på indre og ytre overflater hos mennesker, dyr, planter og sopp.
- Mikrobiomet hos mennesker består av 500–700 forskjellige arter mikroorganismer lokalisert til alle kroppens overflater og hulrom (all hud, nese, munnhule, fordøyelseskanalen, urinveier og vagina).

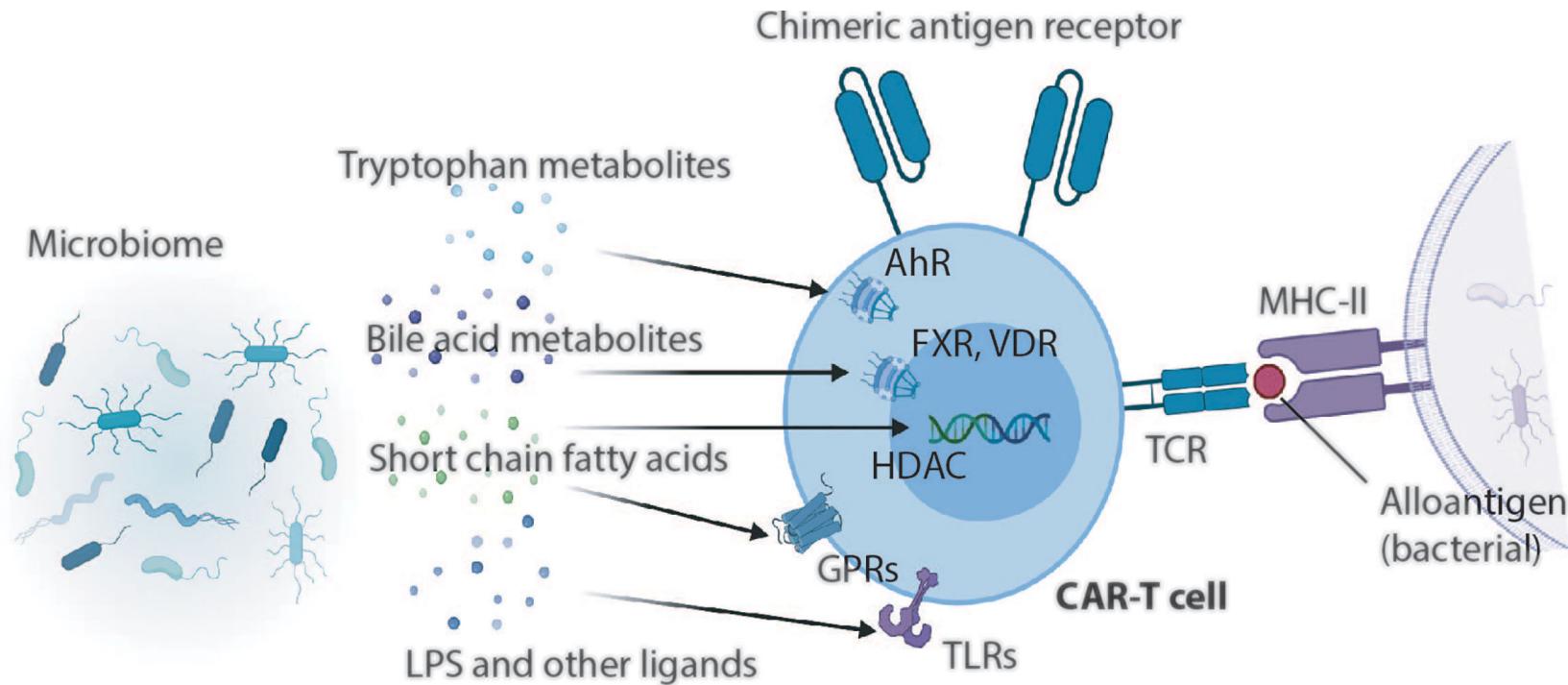
Mikrobiomet og myelomatose



Mikrobiomet og leukemi



Mikrobiomet og CAR T



YoungEHA sesjon 8. juni 2023:

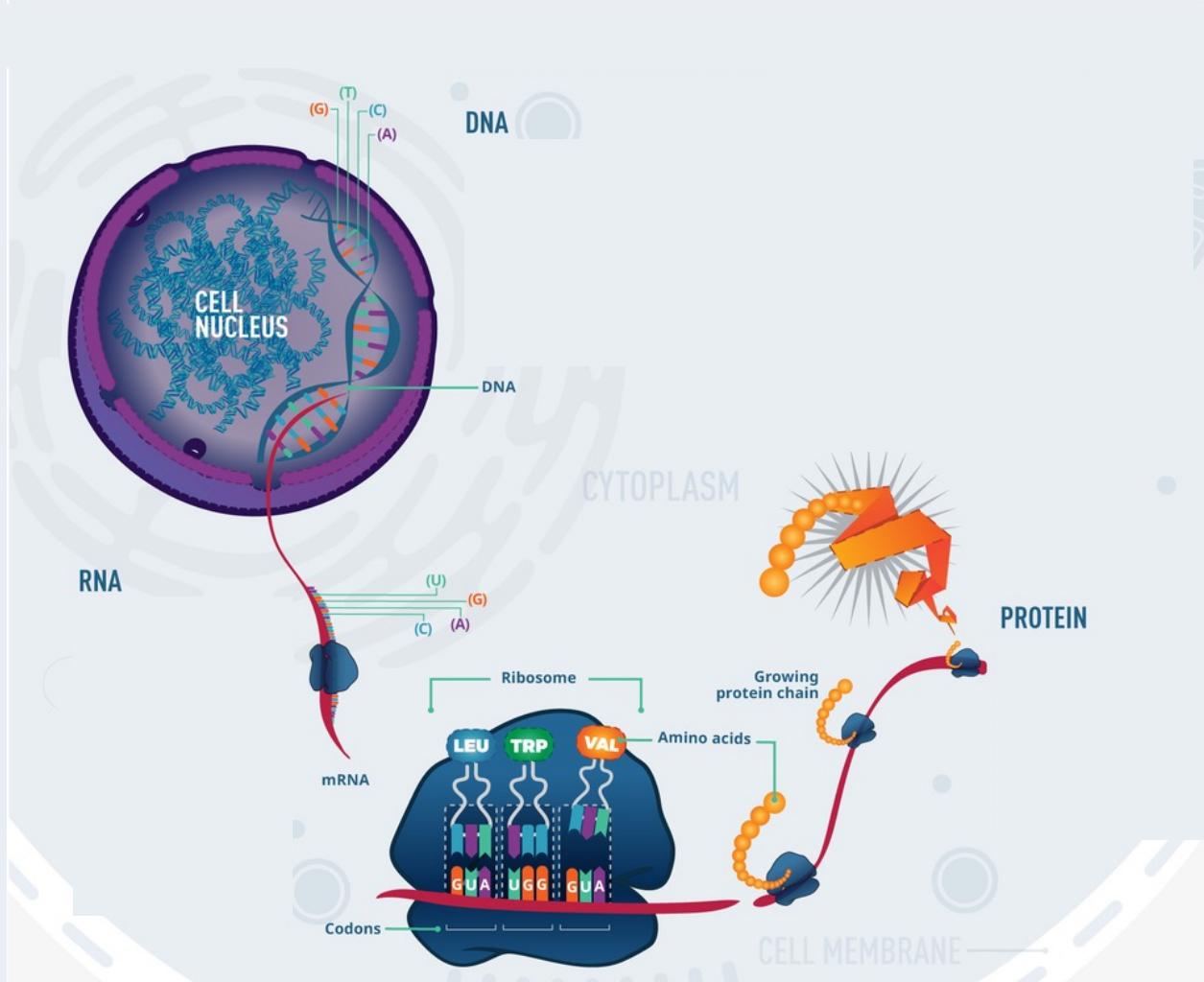
- cellealdring og celledød
- signalering, hormon- og cytokin-kontroll
- transkripsjonell kontroll
- mikrobiom/infeksjonssykdommer



Transkripsjon

- Transkripsjon er ein biologisk prosess der det blir laga ein RNA-kopi av ein gensekvens (DNA) som kodar for eit protein. RNA-kopien blir kalla mRNA (forkorting for messengerRNA på engelsk) eller bodbringar-RNA.
- Her: Kontroll av transkripsjon

Transkripsjonell kontroll og leukemi

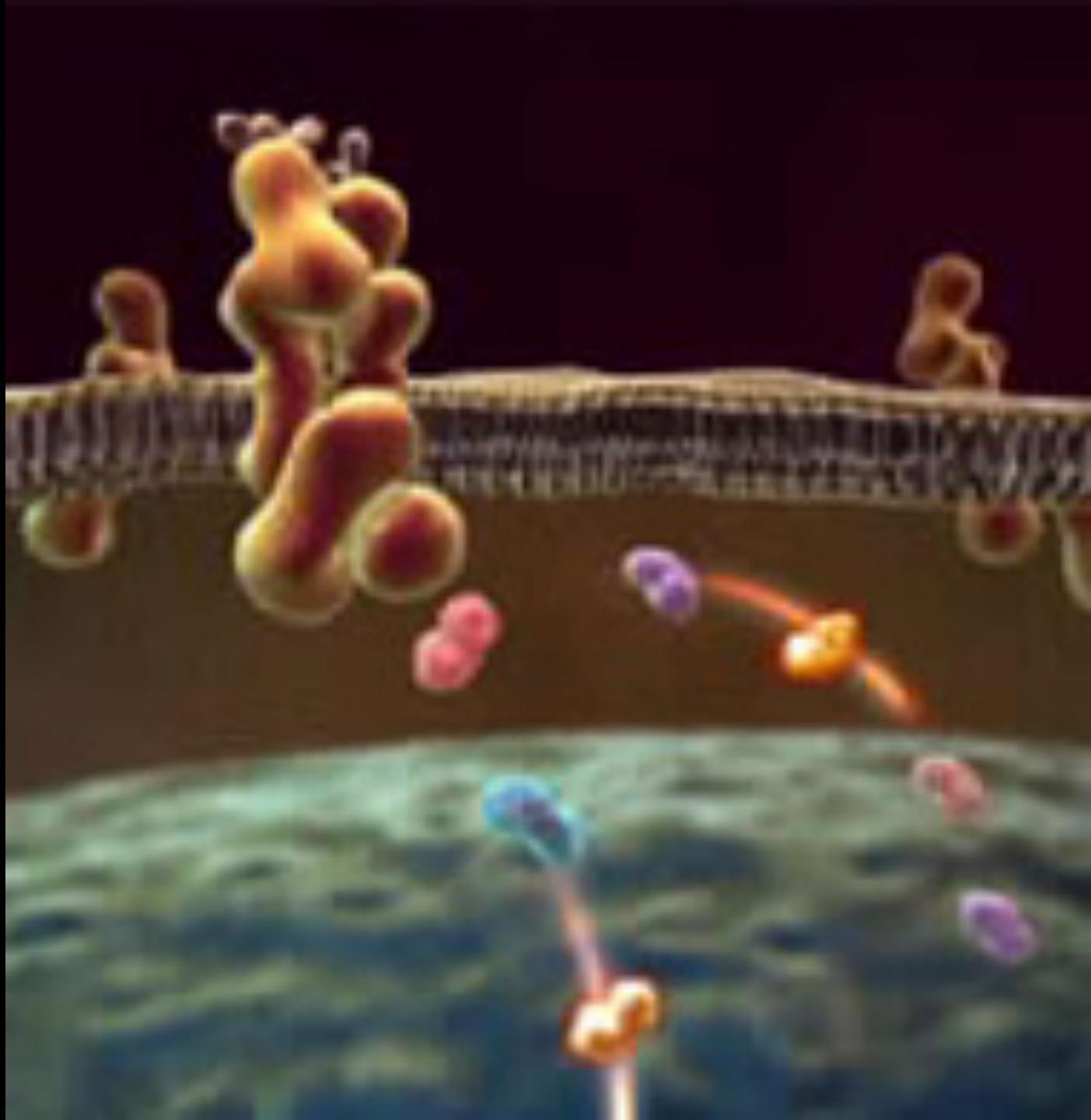


YoungEHA sesjon 8. juni 2023 vil inkludere:

- cellealdring og celledød
- signalering, hormon- og cytokin-kontroll
- transkripsjonell kontroll
- mikrobiom/infeksjonssykdommer

Signalering – signalformidling i celler

Signalformidling er prosessen for mottak og videre bearbeiding av signaler som en celle mottar fra andre celler.

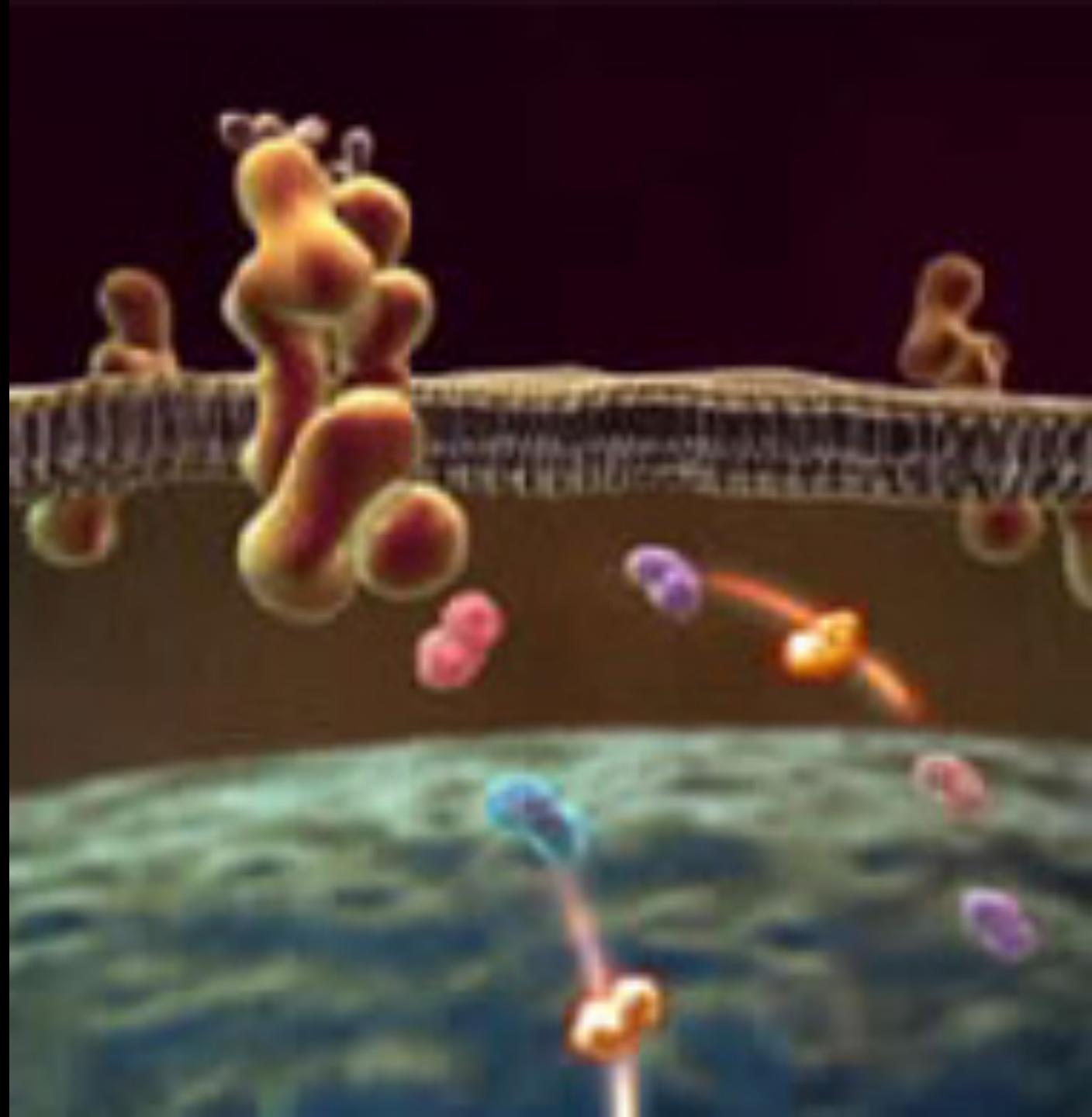


Signalerings mekanismer

Tid

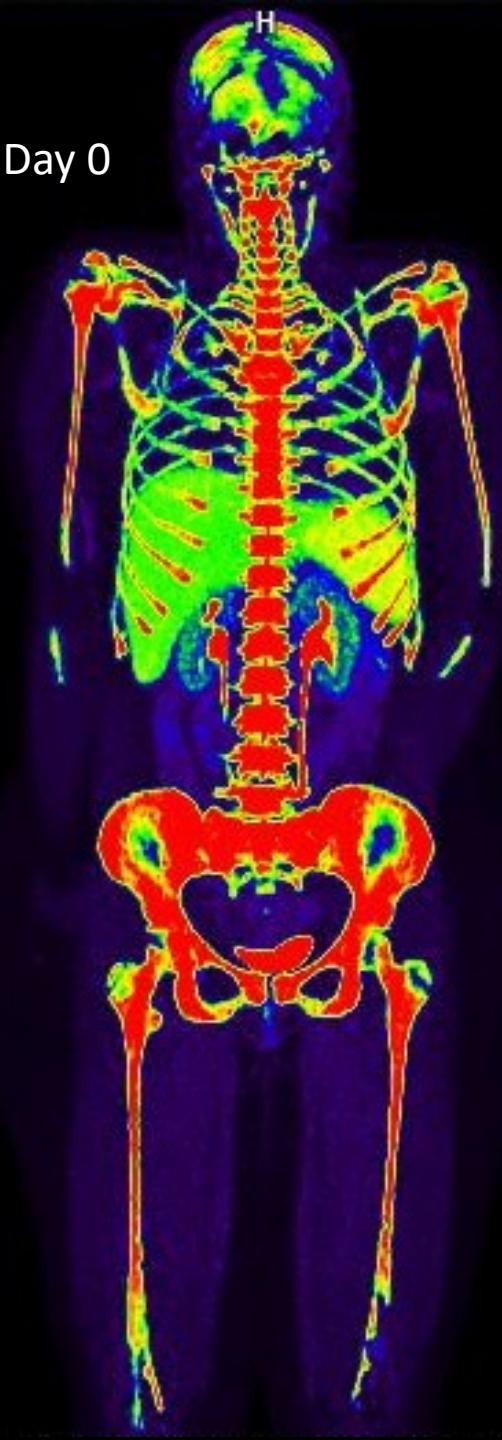
Rom

Kryss-tale



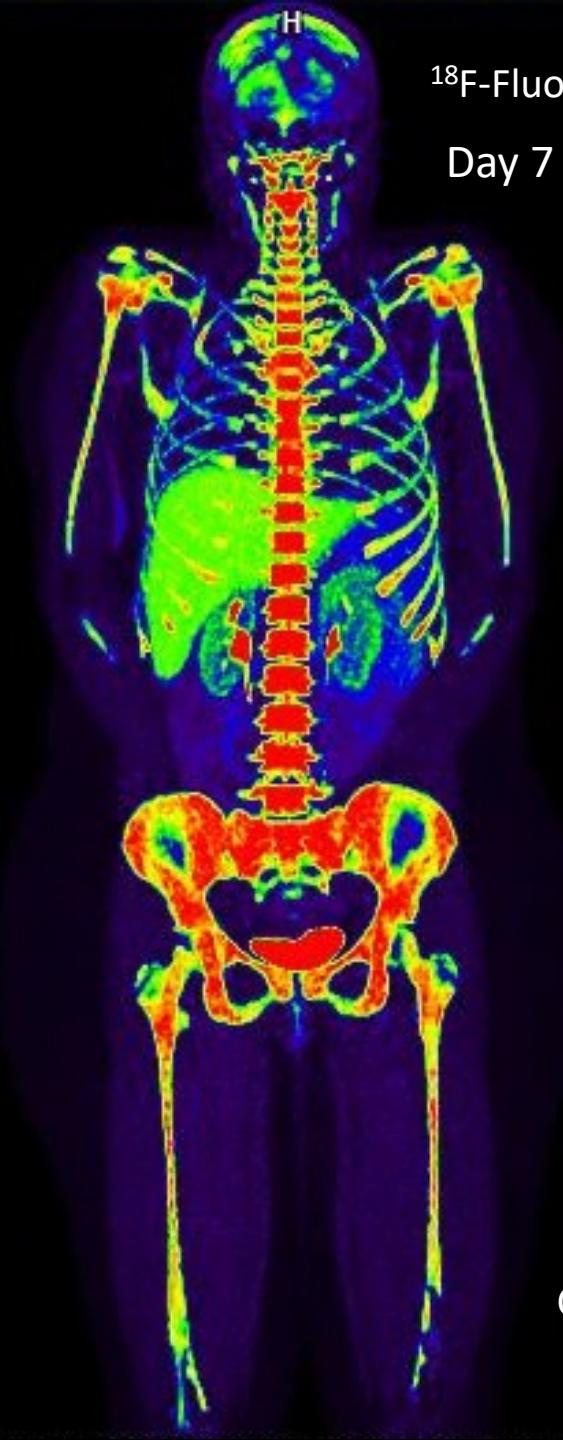
Ved aggressiv blodkreft: Vår kunnskap om de dynamiske molekylære mekanismene bak terapirespons er en «black box», noe som umuliggjør meningsfull responsevaluering og dermed fører til behandling som er justert og tilpasset for lite og for sent.

CML Day 0



¹⁸F-Fluorothymidine PET CT

Day 7 bosutinib

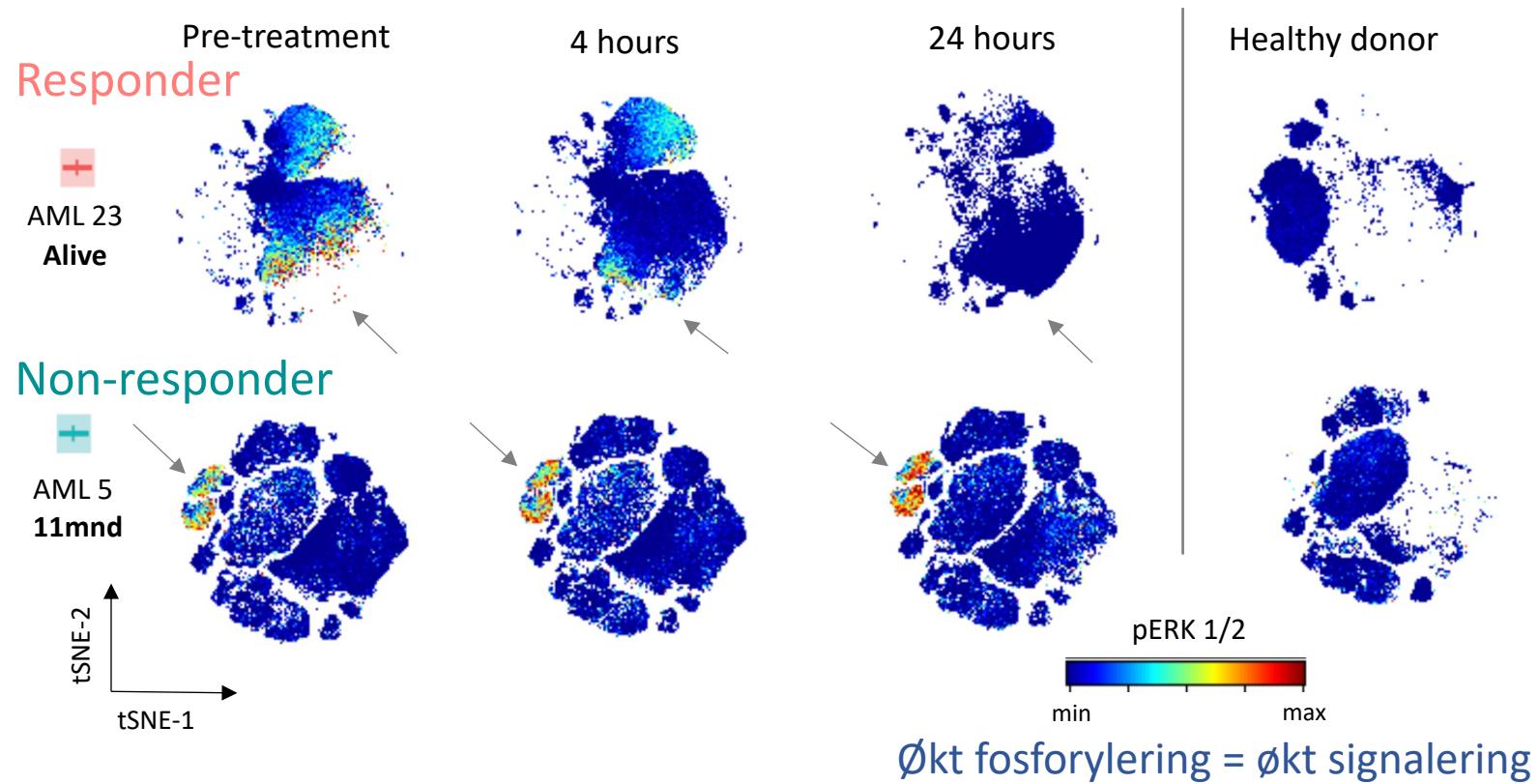




Benedicte Tislevoll

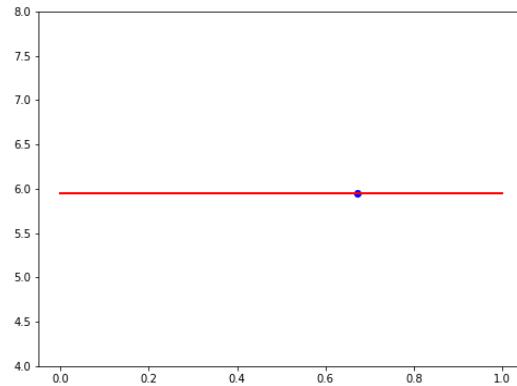
Økt fosforylering av ERK 1/2 de første 24 timene etter start av kjemoterapi hos halvparten av pasientene

Acute myeloid leukemia, de novo, fit for intensive therapy

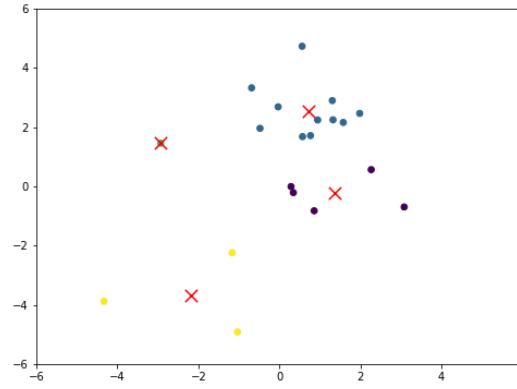


Machine learning by Self Organizing maps (SOMs) - FlowSOM

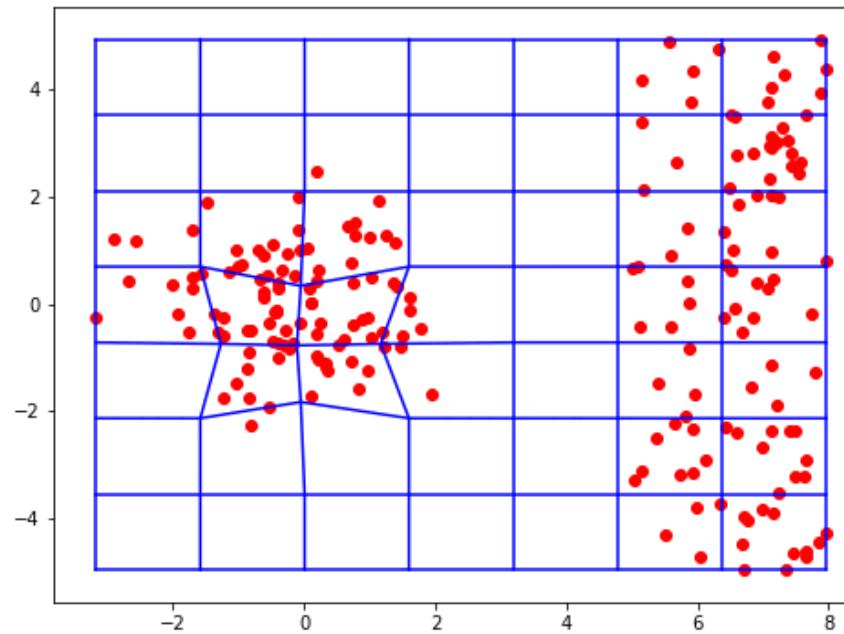
Linear regression



Cluster analysis

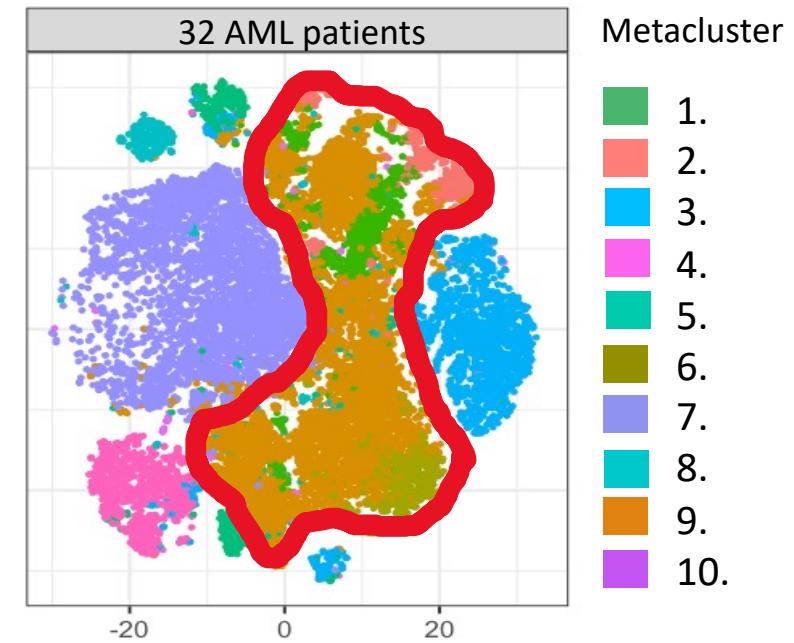


Self Organizing map (SOM)



LASSO regresjonsanalyse:

Modelvalg samtidig som regresjon: selection (finding most relevant variables) at the same time as regression: **Signalling som forutser overlevelse? pERK1/2 ved 24 timer behandling.**



- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.
- 9.
- 10.

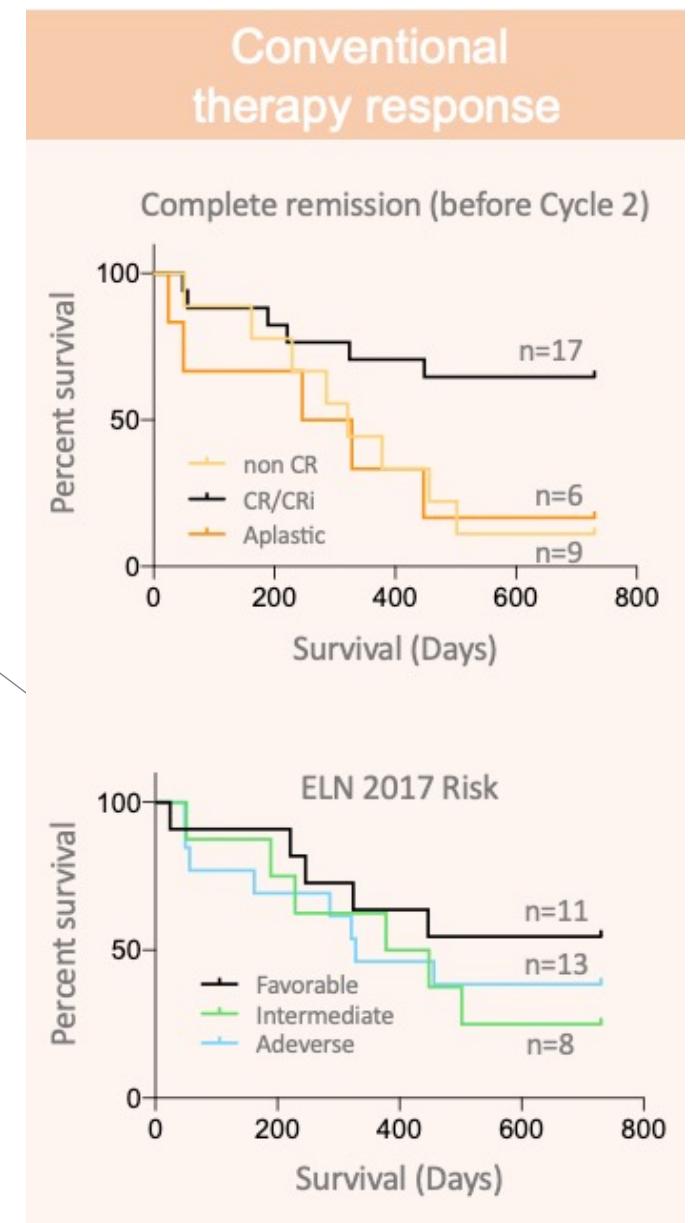
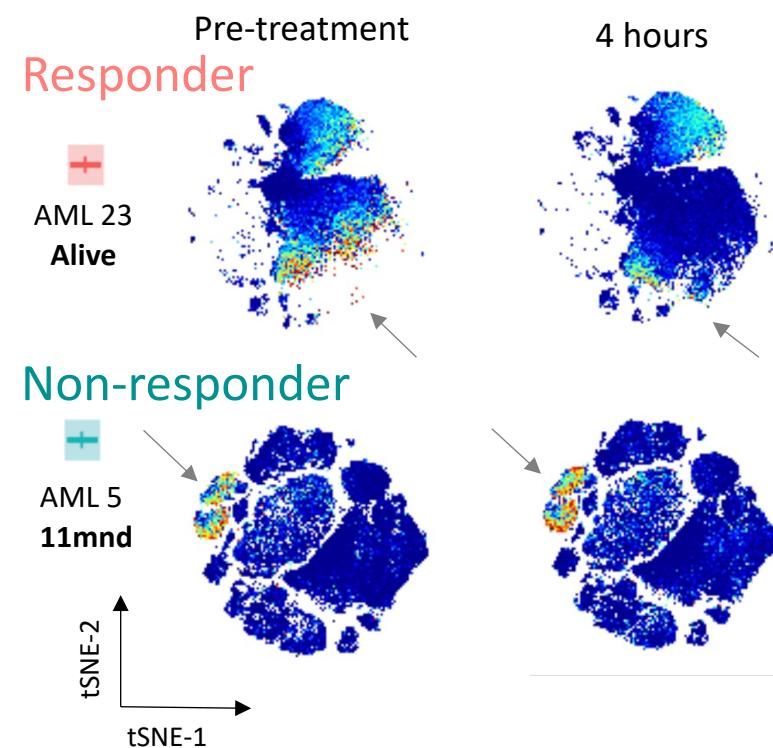
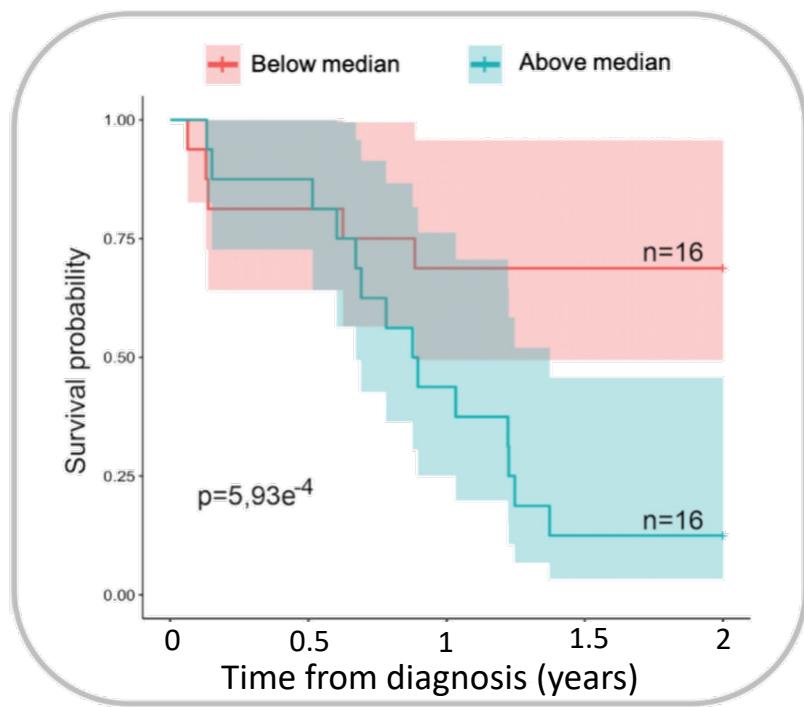


Benedicte Tislevoll

Increase in pERK 1/2 during the first 24 hours of therapy predict low patient survival

Acute myeloid leukemia, de novo, fit for intensive therapy

9. HLA-DR mid, CD33mid, CD64 mid Myeloid cells



Kliniske studier?

Signalmolekylet CD37 er et lovende mål i presisjonsbehandling av akutt myelogen leukemi

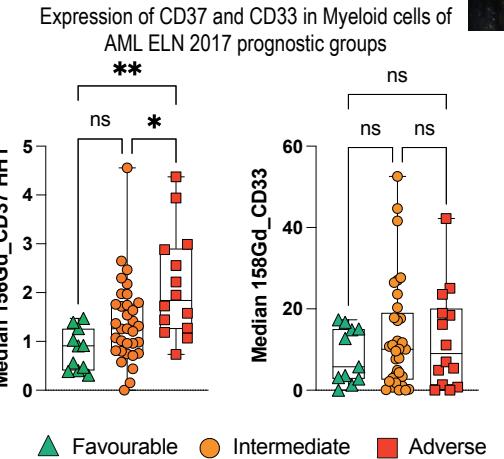
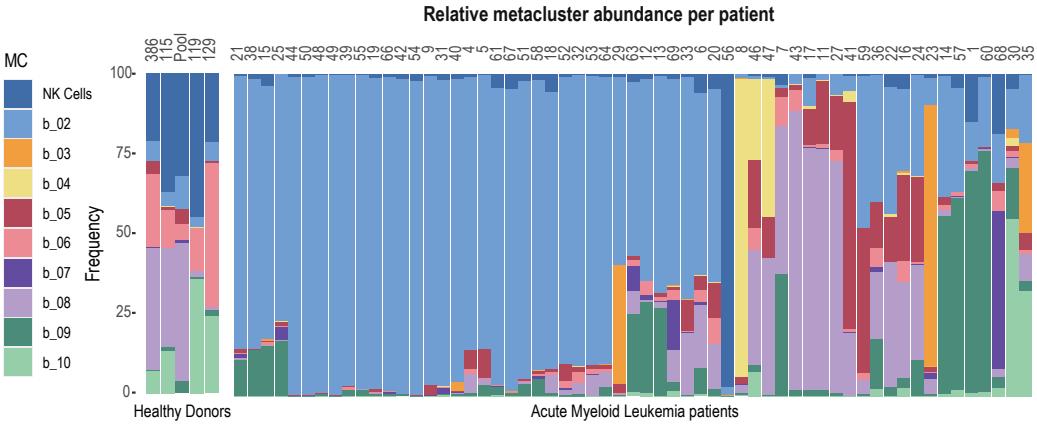
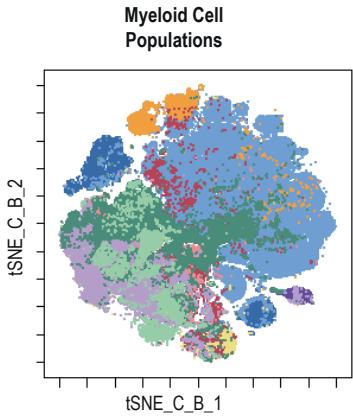
Tara Helén Steinsland
Dowling, MSc

PhD fellow

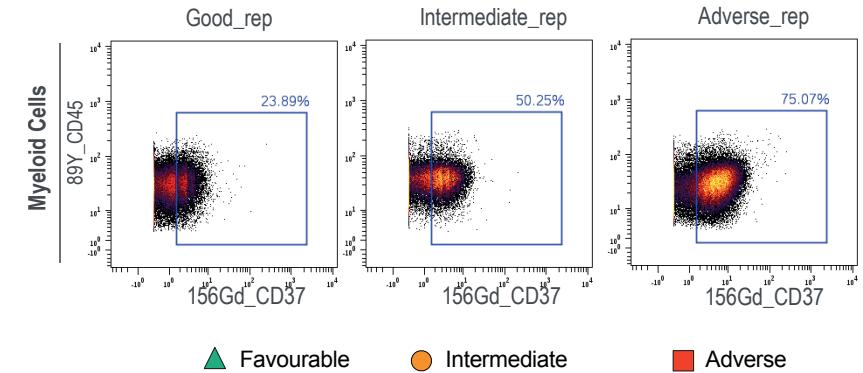
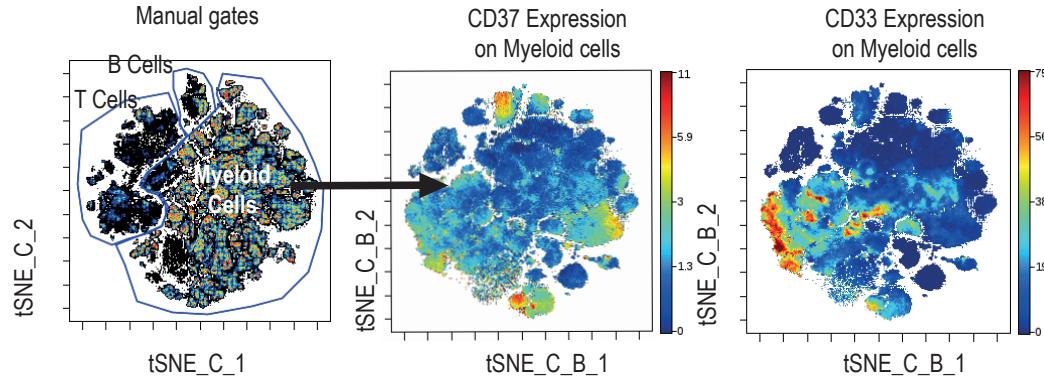


59 AML patients

5 Healthy donors



The CD37 expression of representative AML patient from each ELN 2017 prognostic group



▲ Favourable ● Intermediate ■ Adverse



Centre for
Cancer Biomarkers
Norwegian Centre of Excellence – University of Bergen

HELSE VEST

KREFTFORENINGEN

IMPRESS-Norway Melfalankohorten

Emil Nyquist, hematolog, SIV HF, Tønsberg



**IMPRESS
NORWAY**

Hypoplastisk høy-risiko MDS og AML



13



Irini Ktoridou-Valen

Actinomycin D treatment in patients with NPM-1 mutated AML and other myeloid malignancies



KlinBeForsk: CAR T CD37 mot AML med målbar restsykdom som uttrykker CD37

