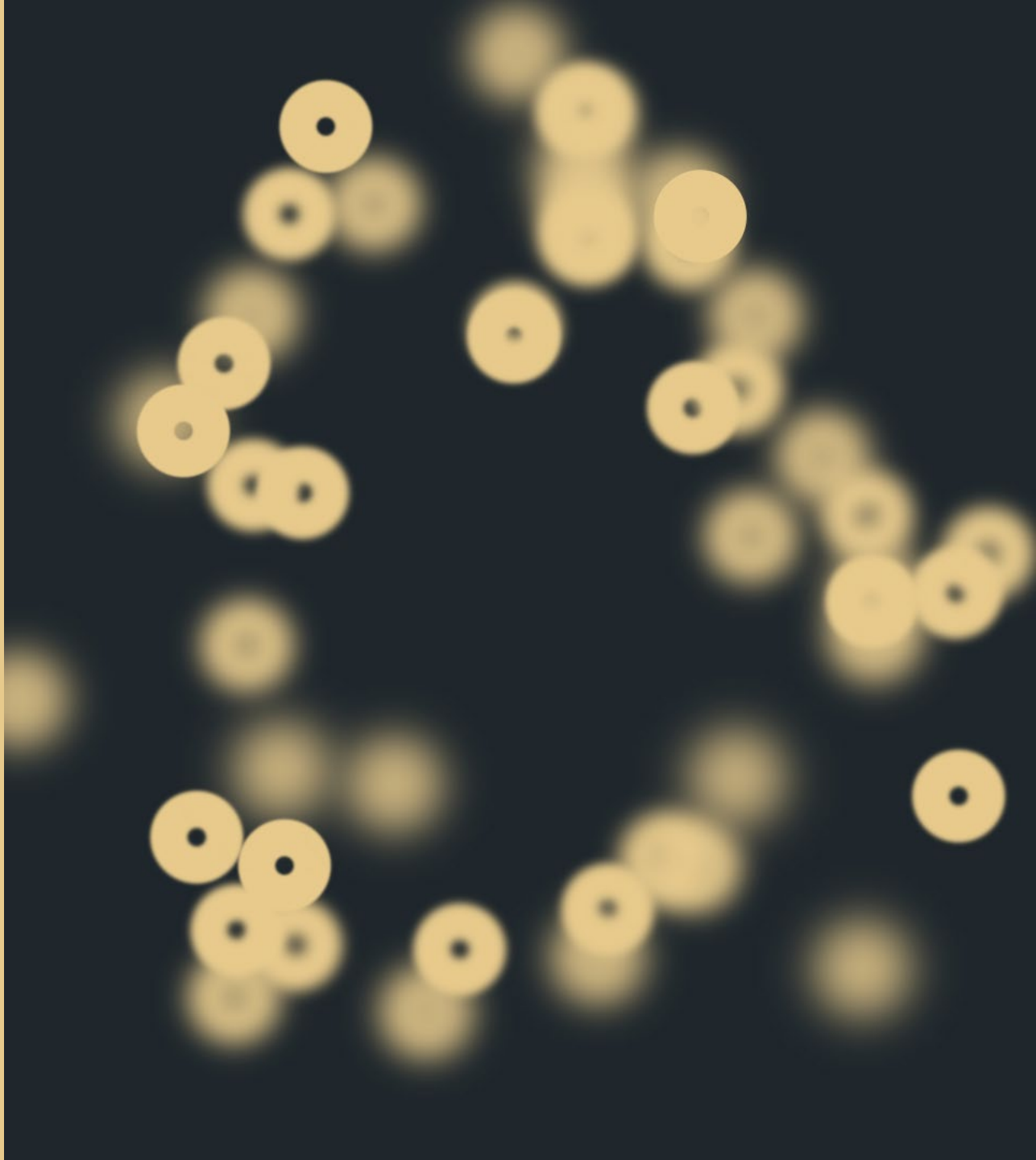
eha

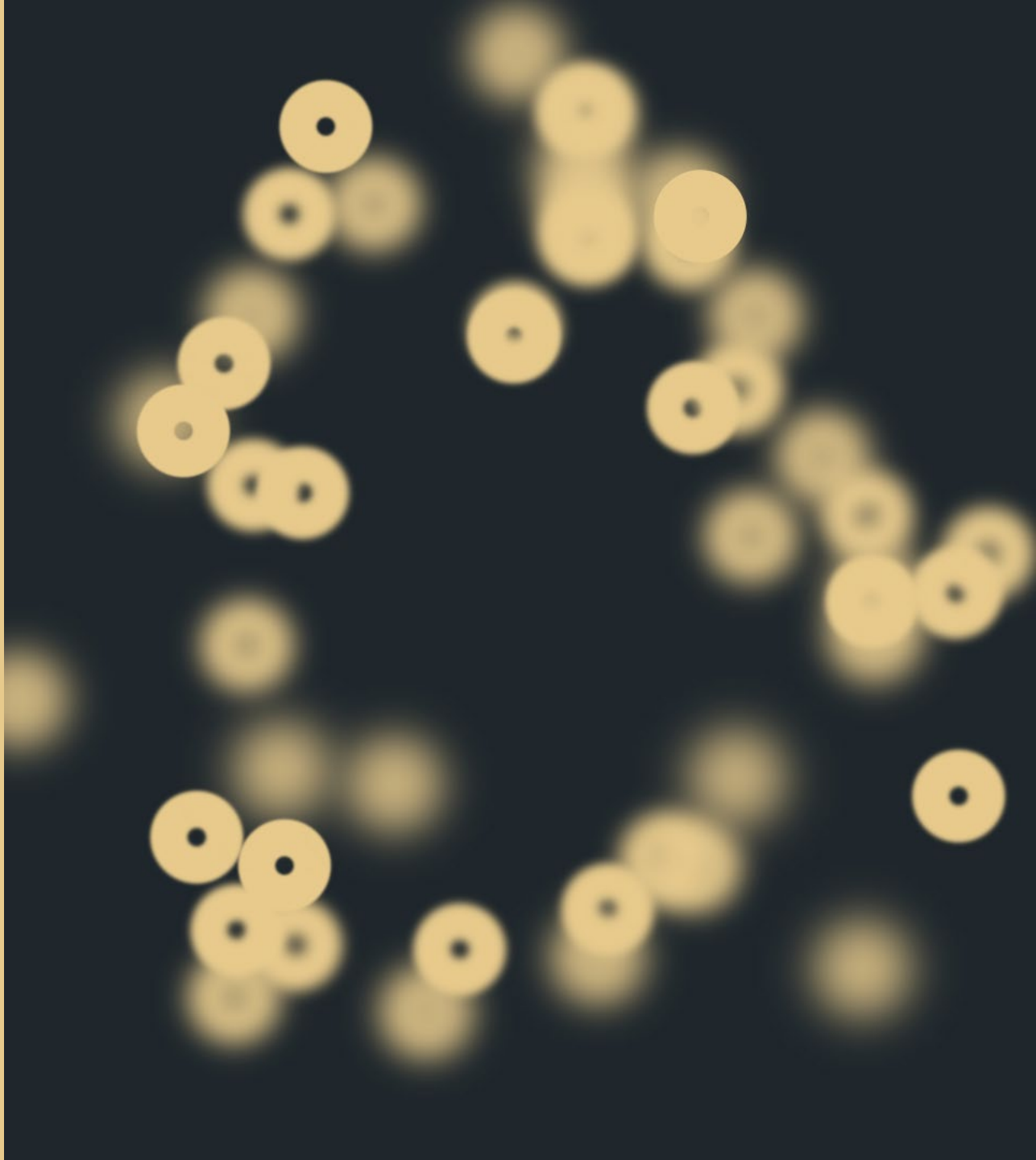
EHA-SWG Scientific Meeting on Recent Advances in the Pathogenesis and Treatment of Secondary Acute Myeloid Leukemias

Berlin, Germany
April 25-26, 2025



CHIP and clinical management

25.04.2025 Kirsten Grønbæk

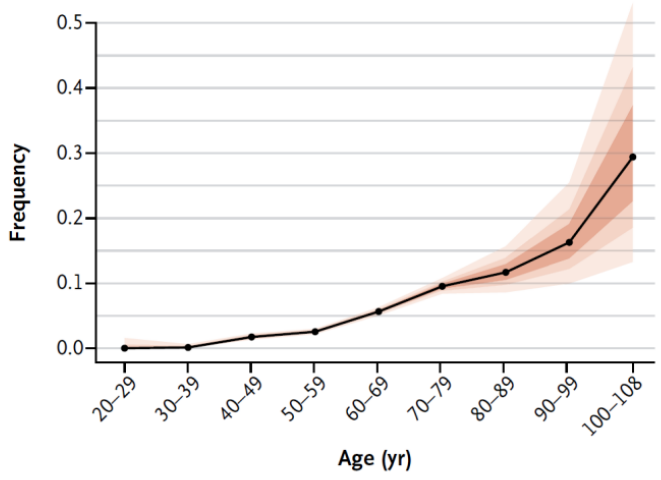


Today's talk

- CHIP and CCUS in the general population, the risk of myeloid neoplasms and death.
- Therapy related CHIP (t-CHIP) and therapy related CCUS (t-CCUS), the risk of therapy related myeloid neoplasms (t-MN) and other complications
- Could CHIP and CCUS clinical interception trials improve outcome?

CHIP and CCUS in the general population

Clonal hematopoiesis



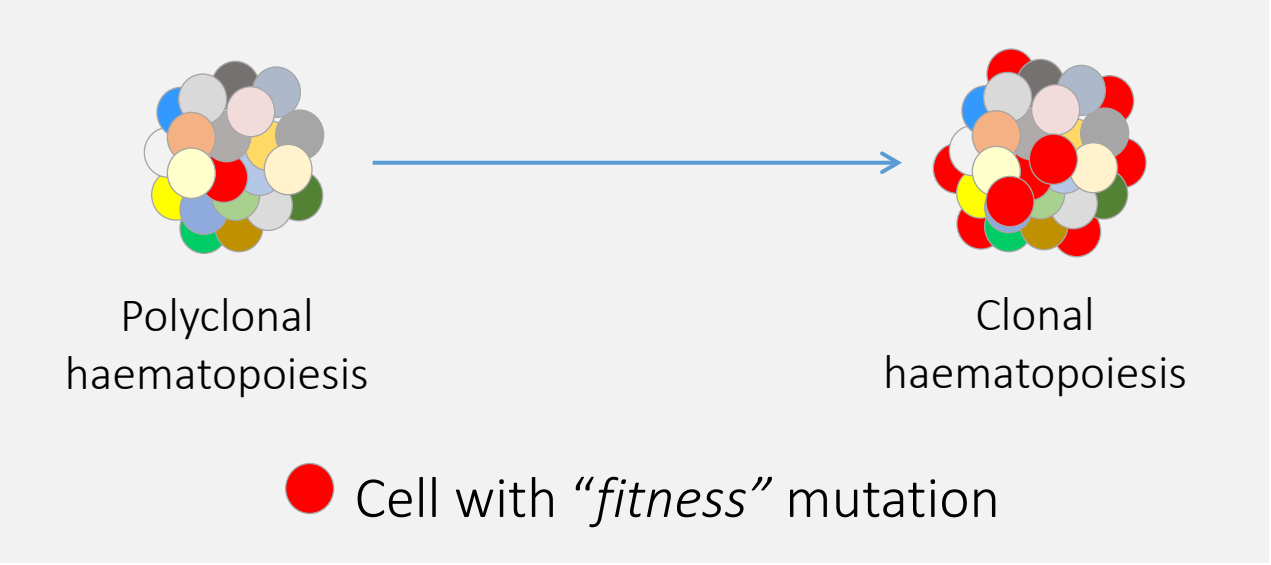
No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

Figure 1. Prevalence of Somatic Mutations, According to Age.
Colored bands, in increasingly lighter shades, represent the 50th, 75th, and 95th percentiles.

- **Increased risk of hematological cancer**
- **Increased risk of cardiovascular disease**
- **Higher mortality**

Jaiswal NEJM 2014

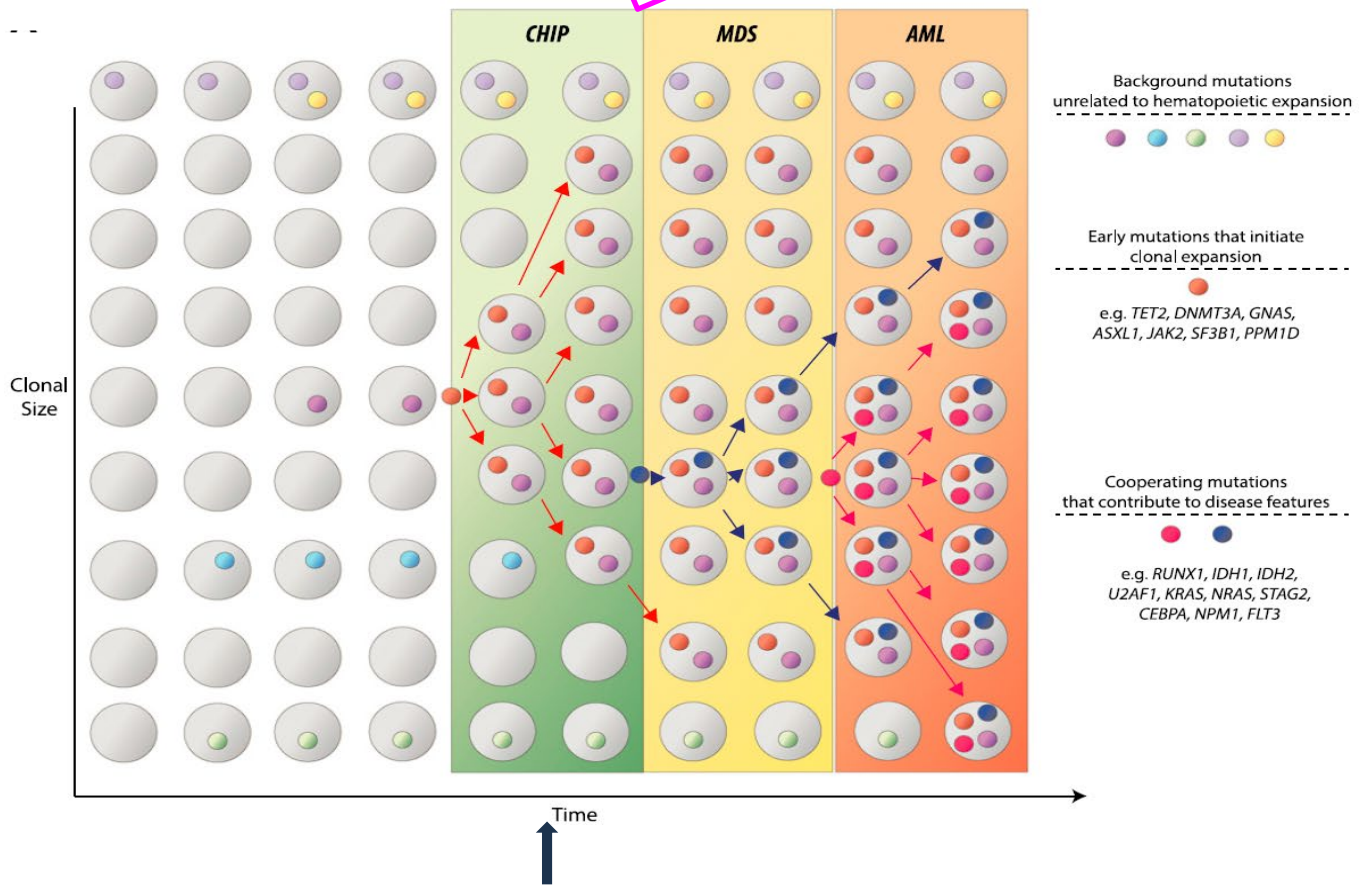
Clonal Hematopoiesis (CH)



Mutated genes: *DNMT3A, TET2, ASXL1, JAK2, SF3B1, SRSF2, TP53, PPM1D*
Prevalence: *15-20% of people aged >60 years*

Jaiswal et al, NEJM 2014; Genovese et al, NEJM 2014; Xie et al, Nat Med 2014, McKerrell et al, Cell Reports 2015.

CCUS:
A window of 1-10 Years
Before MDS/AML



Germline, Aging, Genotoxic stress

CHIP: Clonal Hematopoiesis of Indeterminate Potential
CCUS: Clonal Cytopenia of Unknown Significance

modified from Steensma et al. Blood 2015

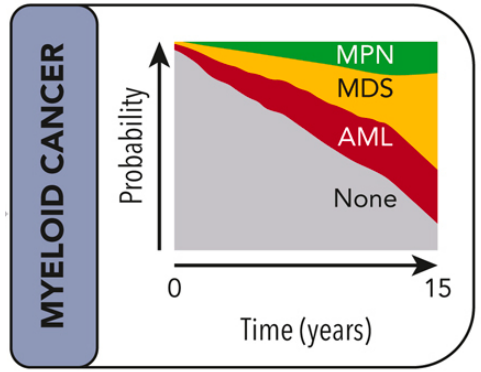
What have we learned from epidemiological studies?

- The risk of progression of CHIP to a hematological malignancy is 0,5-1%/year
- The role of CH in cardiovascular and other diseases is still debated
- High-risk CHIP of MN progression - We can use:

  - CHRS (clonal hematopoiesis risk score) (Weeks et al., NEJM evidence 2023 ;2(5)
  - Multiparameter prediction of myeloid neoplasia risk

    (Gu et al., Nature Genetics 2023; 55 (1523-1530))
  - CCRS (Risk prediction for clonal cytopenia)

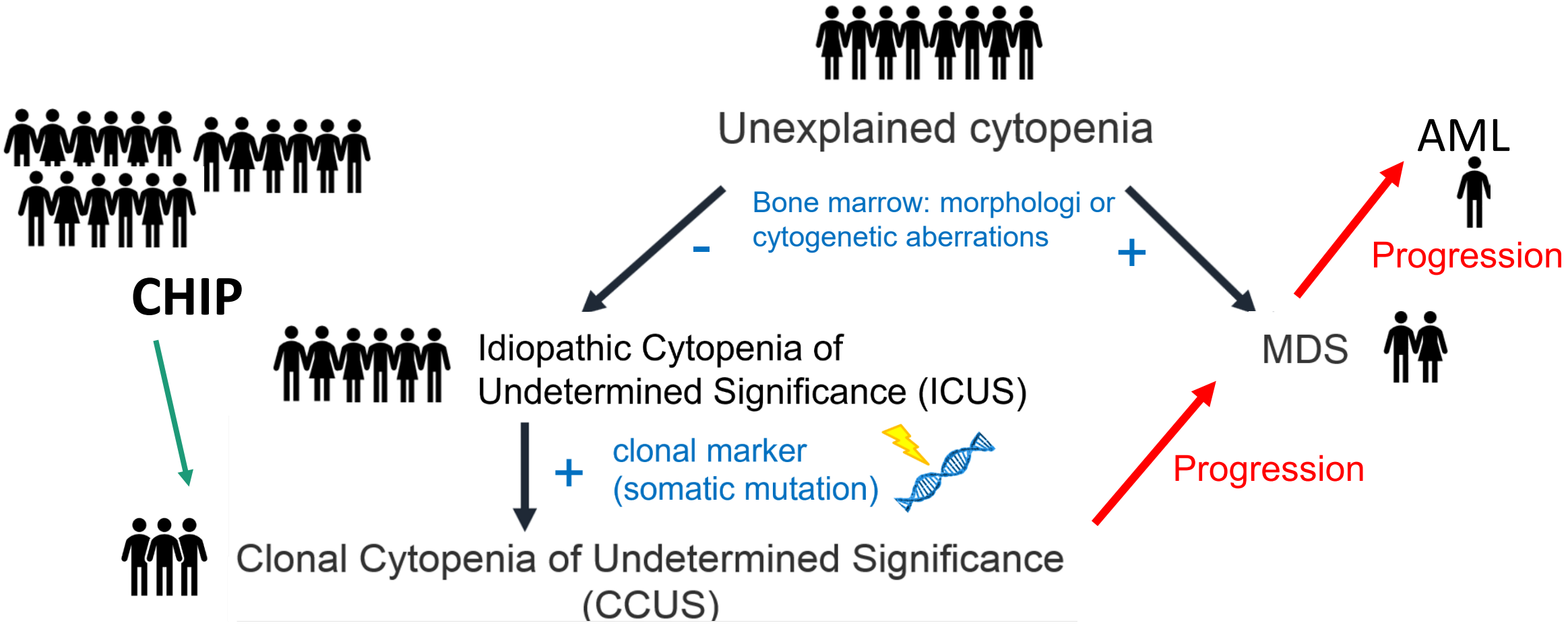
    (Xie z et al Blood 2024;144(19):2033-2044)



What about unselected patients referred with unexplained cytopenia?

Hansen JW, Træden D et al., submitted

Myeloid cancer and precursor conditions

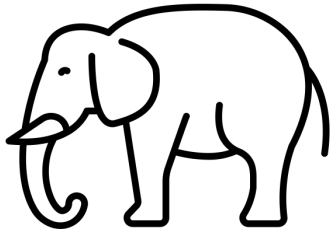


Open questions

- Are deaths not related to myeloid cancer progression also related to the mutated clones?
- Can we prevent or postpone progression/death?
- Can we prevent or postpone comorbidities/causes of death not related to myeloid cancer progression?
- Is this best done by targeting the factor that stimulates the clone, the clone itself, or the downstream effectors of clonal mutations?

What about structural aberrations?

The role of mosaic chromosomal aberrations?

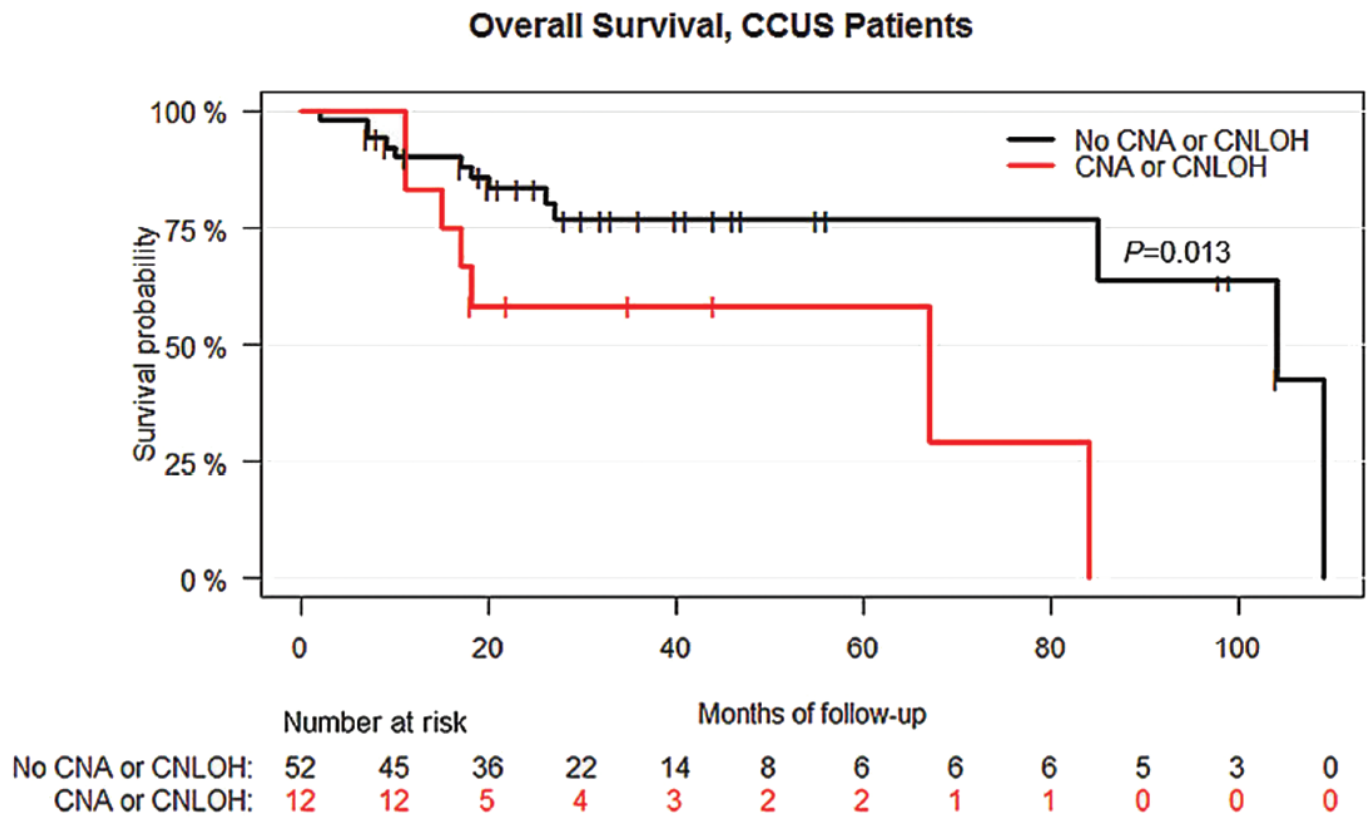


- CHIP (clonal hematopoiesis of indeterminate potential)
- Next-generation sequencing
  - WGS/WES/**targeteret panel**
- SNV/indels, punktmutationer
  - Missense
  - Frameshift
  - Nonsense
  - Splice site

- mCA (mosaic chromosomal alterations)
- **SNP array**/WGS
- Strukturelle varianter/copy number variations (SV/CNV)
  - losses
  - gains
  - Copy-neutral loss of heterozygosity/uniparentel disomi (CNLOH/UPD)
  - (Translocations)

CCUS with combined point mutations and structural aberrations

Mutations + CNA or CN-LOH are associated with overall survival



CNA: Copy number aberrations
CN-LOH: Copy neutral loss of heterozygosity

Mikkelsen SU et al., Haematologica 2021 Jun 1;106(6):1762-1766

Who to follow and how?

- Patients referred with long lasting cytopenia should have a full diagnostic work up
- We need to identify high-risk CHIP/CCUS – high risk of progression vs high risk of death
- CHRS, MN Predict and CCRS can identify cases that progress, but is not efficient for predicting survival in an elderly population (our study and *)
- Structural aberrations/mCA and germline genetics not included in prediction models – could they be helpful?
- CCUS with anemia + one cytopenia should be followed like LR-MDS
- Very few CCUS patients progress to high-risk disease within 5 years
- SYMPTOMS may be the most important follow-up parameter, particularly in the elderly population
- Beware of co-morbidities - the main causes of death, particularly in the elderly population

*Huber et al., Leukemia (2024) 38:1634 – 1637

Therapy related CHIP and CCUS
(t-CHIP and t-CCUS)

blood

LETTER TO BLOOD | MAY 28, 2020

Clonal hematopoiesis evolves from pretreatment clones and stabilizes after end of chemotherapy in patients with MCL

Christian Winther Eskelund , Simon Husby , Francesco Favero , Tobias Wirenfeldt Klausen , Francisco German Rodriguez-Gonzalez , Arne Kolstad , Lone Bredo Pedersen , Riikka Katariina Räty , Christian H. Geisler , Mats Jerkeman , Joachim Weischenfeldt , Kirsten Grønbæk

Blood (2020) 135 (22): 2000–2004.

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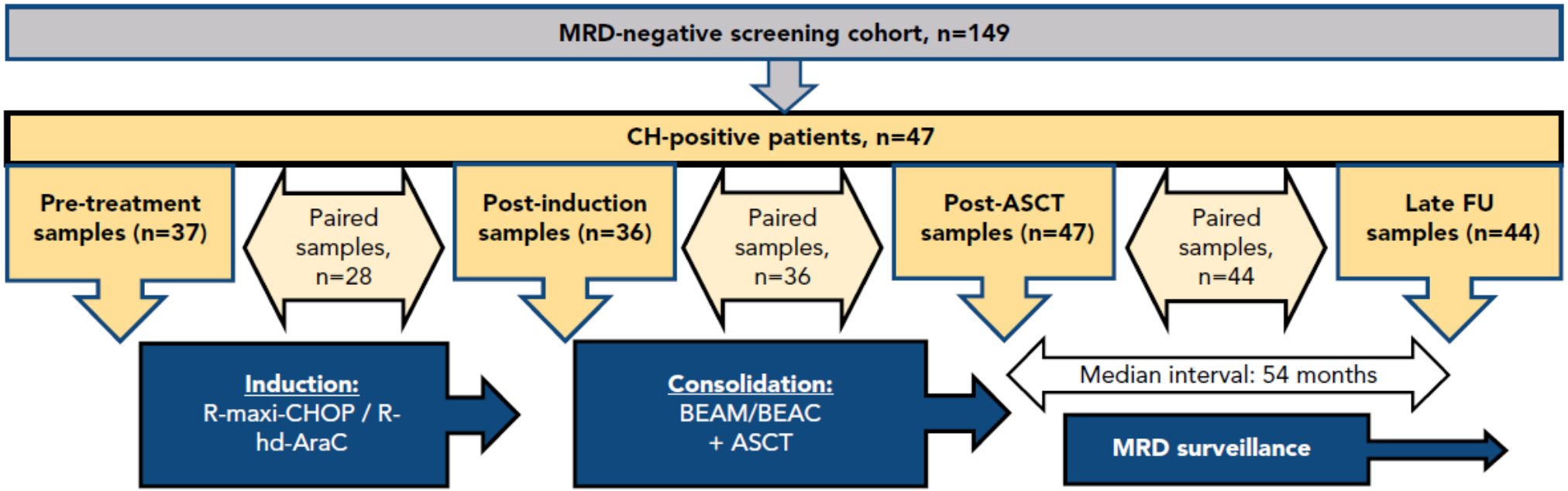
Main Research Question:

Is CHIP in lymphoma caused by the chemotherapy and how do clones evolve during treatment?

Eskelund, Husby* et al. – Blood 2020*

t-CHIP in pts from the Nordic Mantle Cell Lymphoma (MCL) 2+3 trials



Approach:

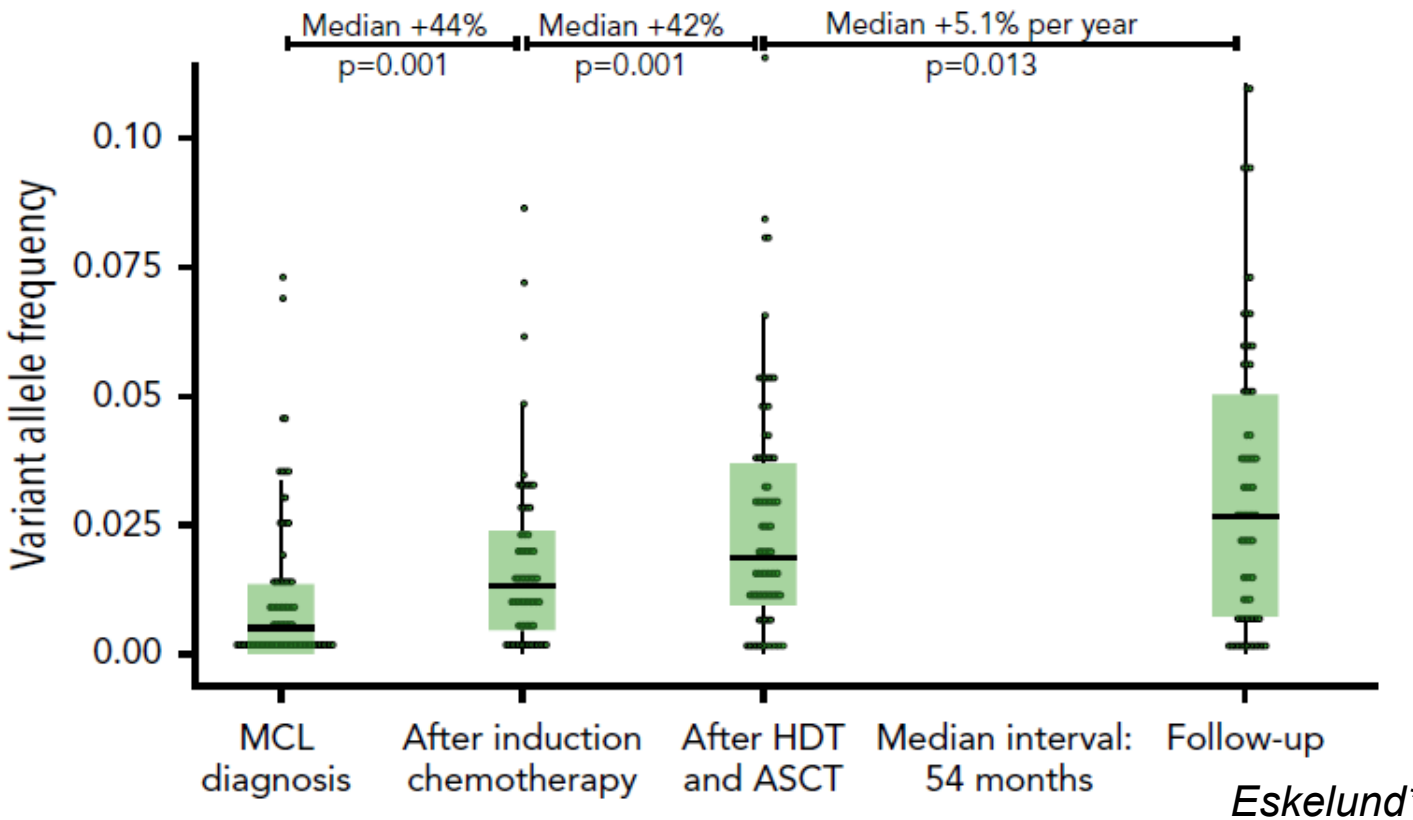
335 samples from 149 cases

In 47 **CH positive** and **MRD negative** cases consecutive samples were investigated by NGS and ddPCR to follow the clonal evolution.

Eskelund, Husby* et al. – Blood 2020*

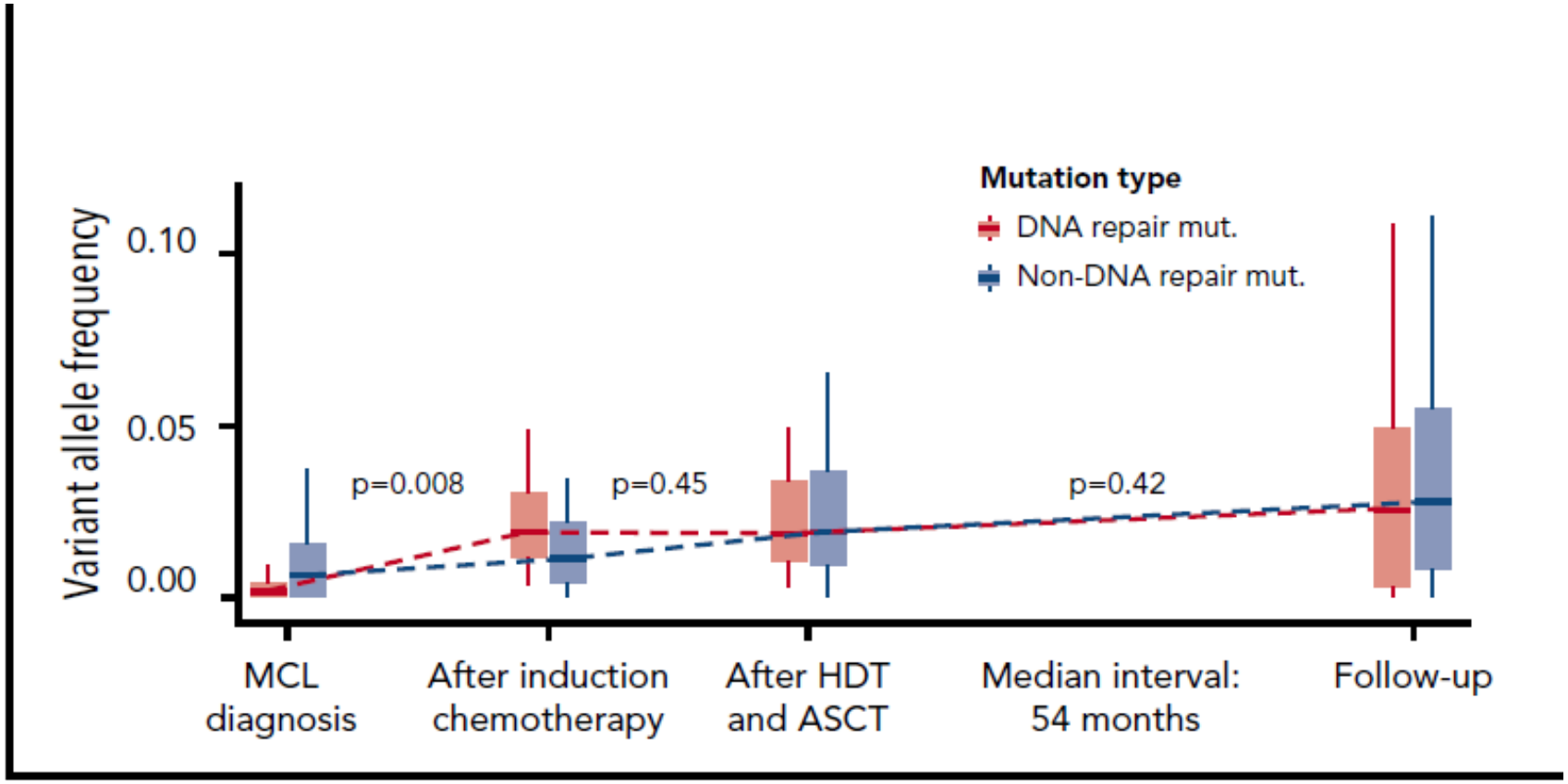
MCL pts,1st line tx; Nordic Regimen

- CHIP mutations grow under treatment chemotherapy



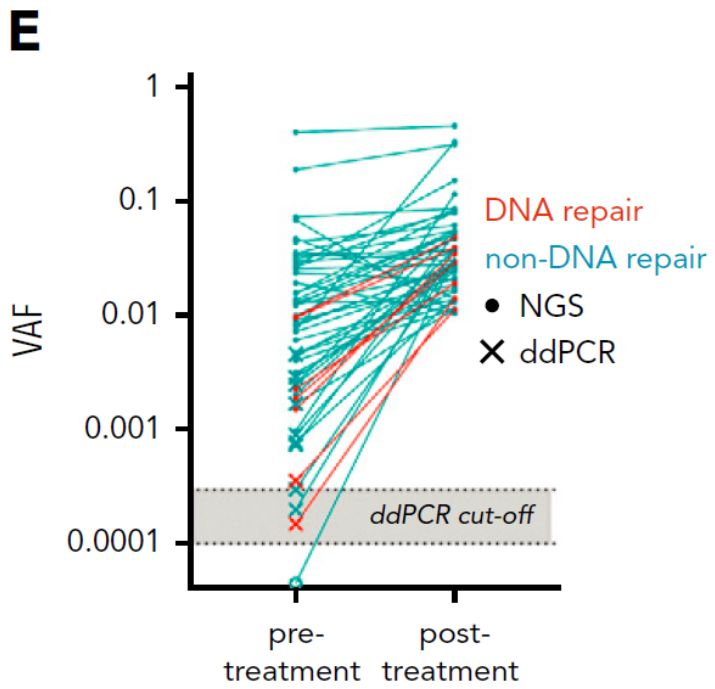
Eskelund, Husby* et al. – Blood 2020*

Evolution of clones with DNA repair mutations vs other CH mutations



Eskelund, Husby* et al. – Blood 2020*

All but one mutation were detectable before any treatment was initiated



Eskelund, Husby* et al. – Blood 2020*

Clonal evolution of CHIP under the pressure of immuno-chemotherapy:

- CHIP clones are present at low levels even before chemotherapy (CT) is given**
- The clones expand during the pressure of CT, and stabilizes when CT is removed
- Specifically clones with mutations in DNA repair genes expand during induction chemotherapy**
- In MCL with ASCT as part of induction regimen tMN are rare, even in expanding clones after long term follow up (none at median 7.7 years)

Eskelund, Husby* et al. – Blood 2020*

* *Similar results on clonal evolution during chemo:
Wong et al Nature. 2015 February 26; 518(7540): 552–555.
Wong et al NATURE COMMUNICATIONS | (2018) 9:455
Nead KT, Kim T, Joo L, et al. Blood Adv. 2024;8(19):5215-5224

ARTICLE

Lymphoma

Clinical impact of clonal hematopoiesis in patients with lymphoma undergoing ASCT: a national population-based cohort study

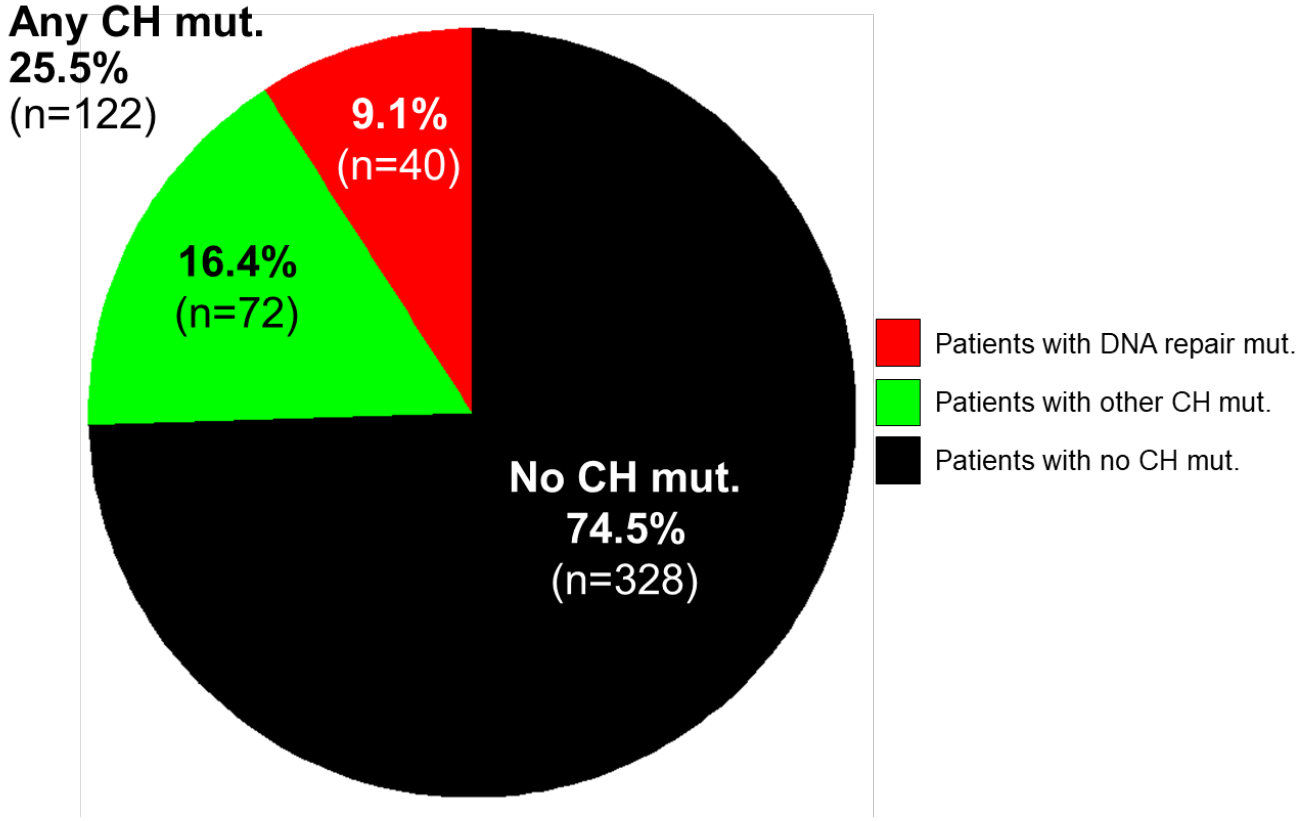
Simon Husby[1,2] · Francesco Favero[2,3] · Christian Nielsen[4,5] · Betina S. Sørensen[6] · John Bæch[7] · Kathrine Grell[8,9] · Jakob W. Hansen[1,2,10] · Francisco G. Rodriguez-Gonzalez[2,3] · Eva K. Haastrup[11] · Anne Fischer-Nielsen[11] · Pernille Andersen[12] · Bente Arboe[1] · Susanne G. Sækmose[13] · Per B. Hansen[14] · Ilse Christiansen[15] · Erik Clasen-Linde[16] · Lene Meldgaard[17] · Lene H. Ebbesen[18] · Erik K. Segel[18] · Pär Josefsson[17] · Michael Thorsgaard[18] · Tarec C. El-Galaly[15] · Peter Brown[1] · Joachim Weischenfeldt[2,3] · Thomas S. Larsen[5,19] · Kirsten Grønbæk[1,2,10]

Main Research Question: Does CHIP influence the outcome of treatment after HD chemotherapy and ASCT for lymphoma

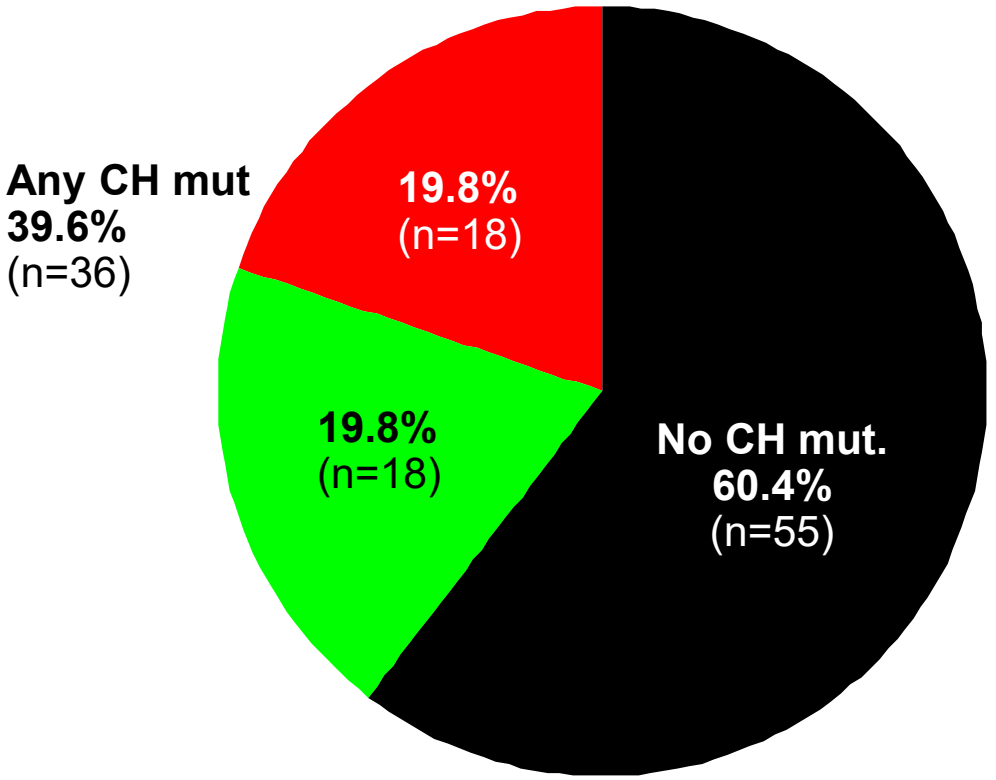
Approach: Nation-wide study of CHIP in BM samples from **440 pts treated** with HD chemo and ASCT

Husby et al Leukemia 2020 Dec;34(12):3256-3268

The full national HDT cohort (median 56y, 45% 1. line)

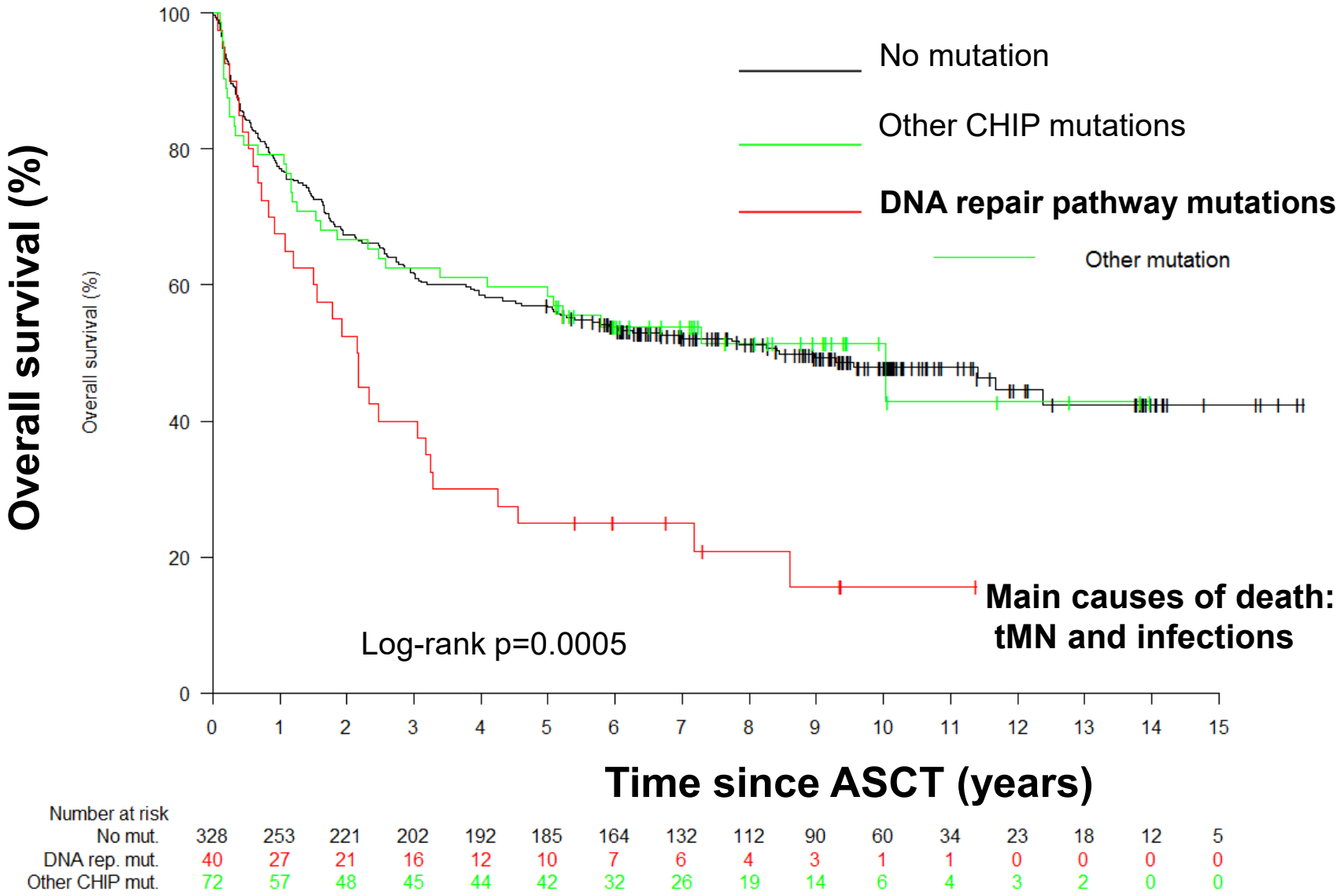


Subcohort (60-70 y, min. 2. line treatment)



Husby et al., Leukemia 2020 Dec;34(12):3256-3268

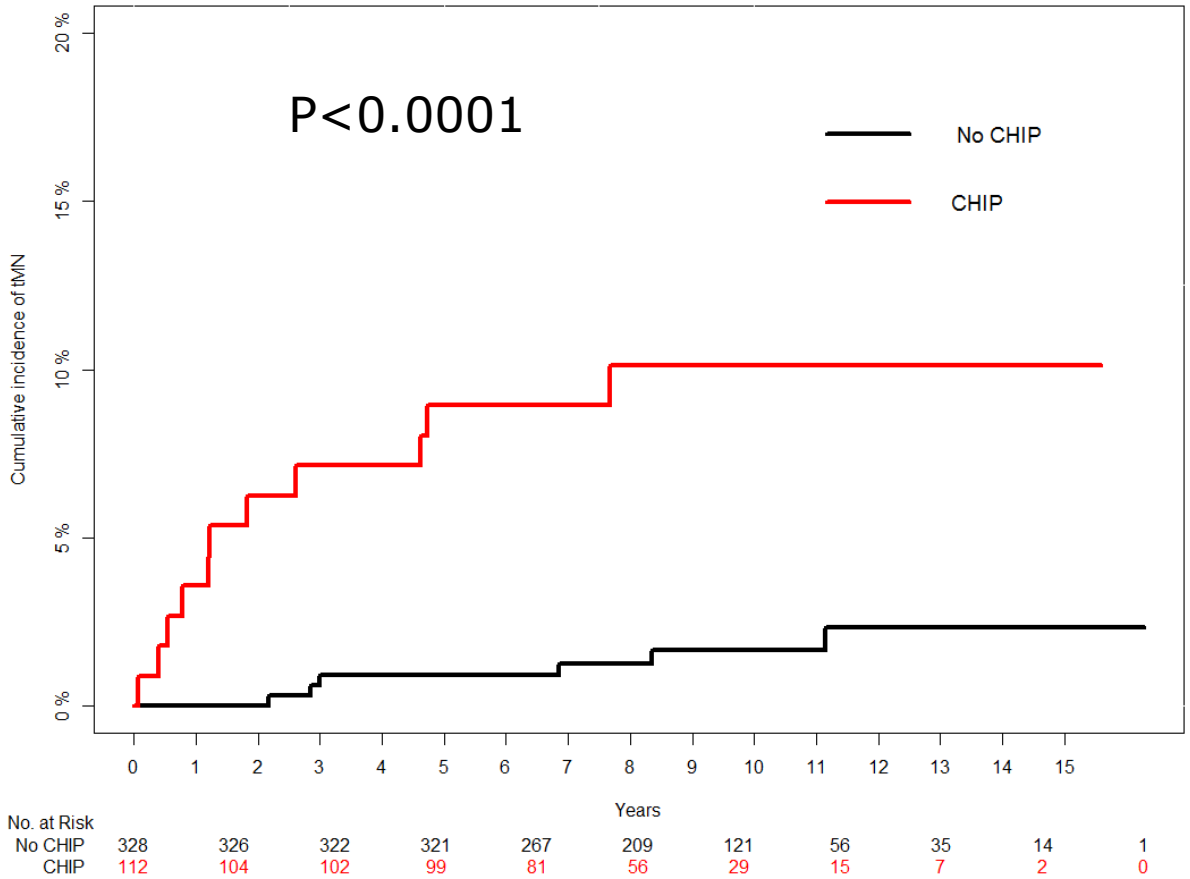
t-CHIP after HD chemo and ASCT for lymphoma



Number at risk																
No mut.	328	253	221	202	192	185	164	132	112	90	60	34	23	18	12	5
DNA rep. mut.	40	27	21	16	12	10	7	6	4	3	1	1	0	0	0	0
Other CHIP mut.	72	57	48	45	44	42	32	26	19	14	6	4	3	2	0	0

Husby et al., Leukemia 2020 Dec;34(12):3256-3268

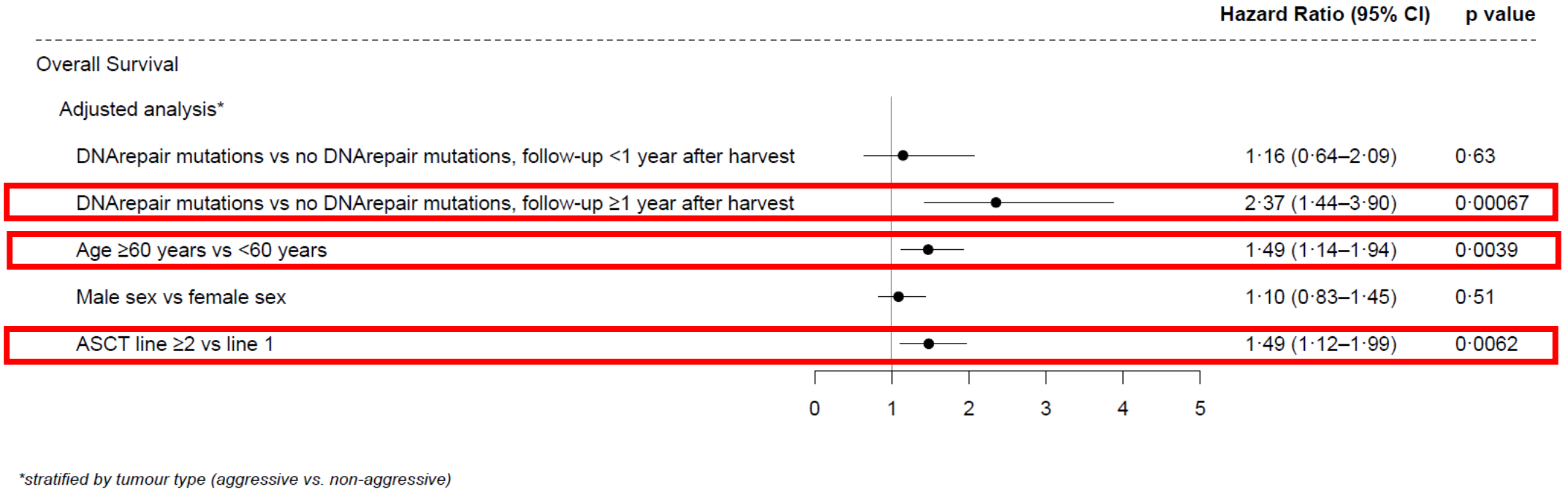
Cumm Incidence of therapy related MN



- **CHIP is associated with increased risk of therapy related MN**

Husby et al., Leukemia 2020 Dec;34(12):3256-3268

Multivariate analysis
(Cox proportional hazards model)



**stratified by tumour type (aggressive vs. non-aggressive)*

Husby et al., Leukemia 2020 Dec;34(12):3256-3268

t-CHIP in lymphoma treated with HD chemo and ASCT

- t-CHIP-DNA repair mutations are associated with poor survival after autologous stem cell transplantation*- but other t-CHIP mutations do not impact survival after ASCT
- The number of previous series of chemotherapy is critical
- Age > 60 + t-CHIP is associated with poor outcome
- t-CHIP +mCA is associated with exceedingly poor outcome

**Similar results from Gibson et al JCO 2017*

Unanswered questions

- How common is t-CHIP in elderly lymphoma pts? (at time of relapse)
- Impact on treatment toxicity and/or dose-reductions?
- Could these mutations identify elderly patients with poor outcomes after chemotherapy who should be offered alternative treatment regimens?

Whats next ? DELPHI study

Timeline

1. series 2. series 3. series 4. series 5. series 6. series

EOT

Relapse/Progression

DELPHI study
Information and consent

DELPHI
1x EDTA (9mL)
1x STRECK(10mL)
Questionaire
(via E-boks)

Real-time NGS analysis
for subclinical t-MDS/AML

DELPHI
1x EDTA (9mL)
1x STRECK(10mL)
Questionaire
(via E-boks)

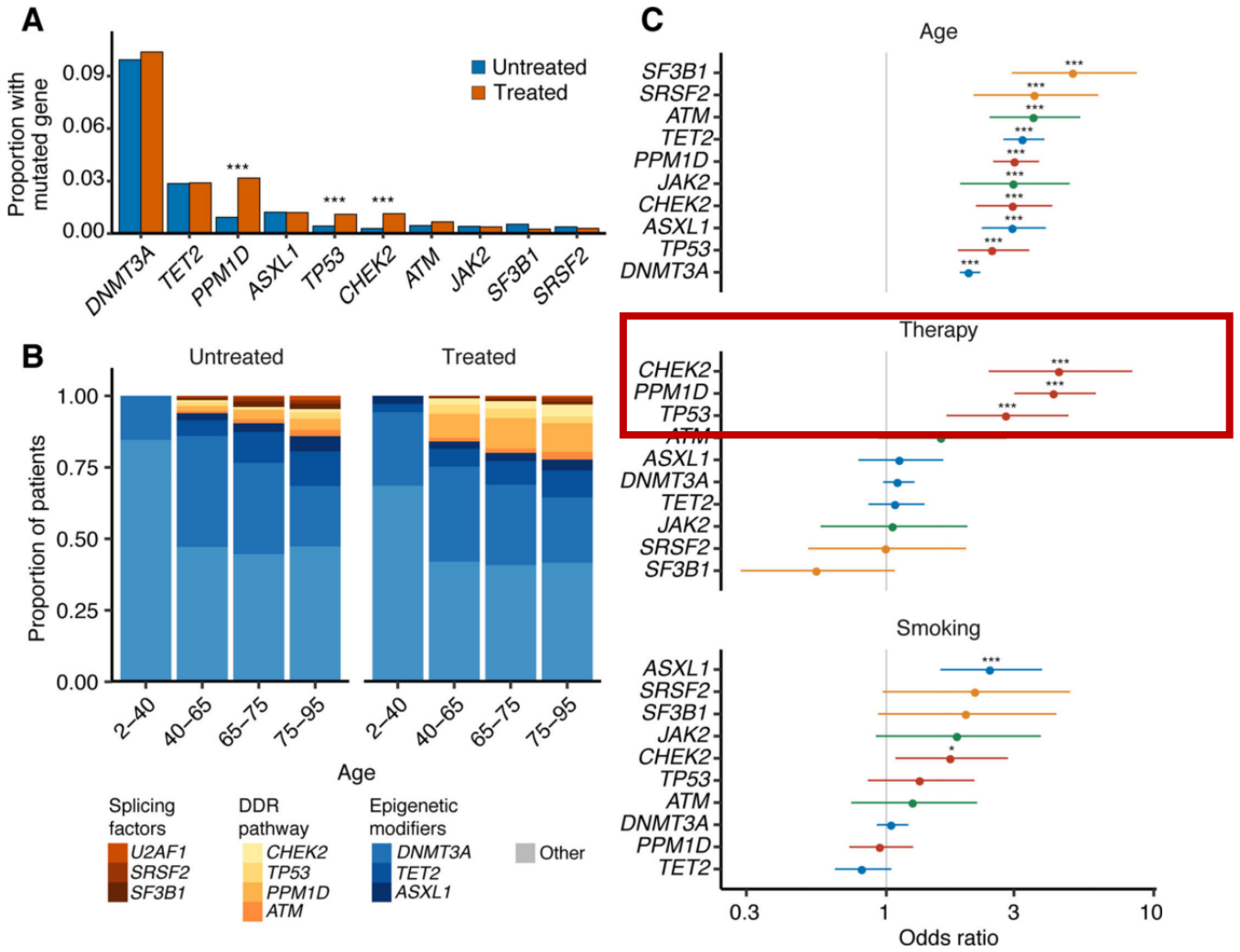
Sample saved in case of drop out

DELPHI
1x EDTA (9mL)
1x STRECK(10mL)
Questionaire
(via E-boks)

Real-time NGS analysis
for subclinical t-MDS/AML

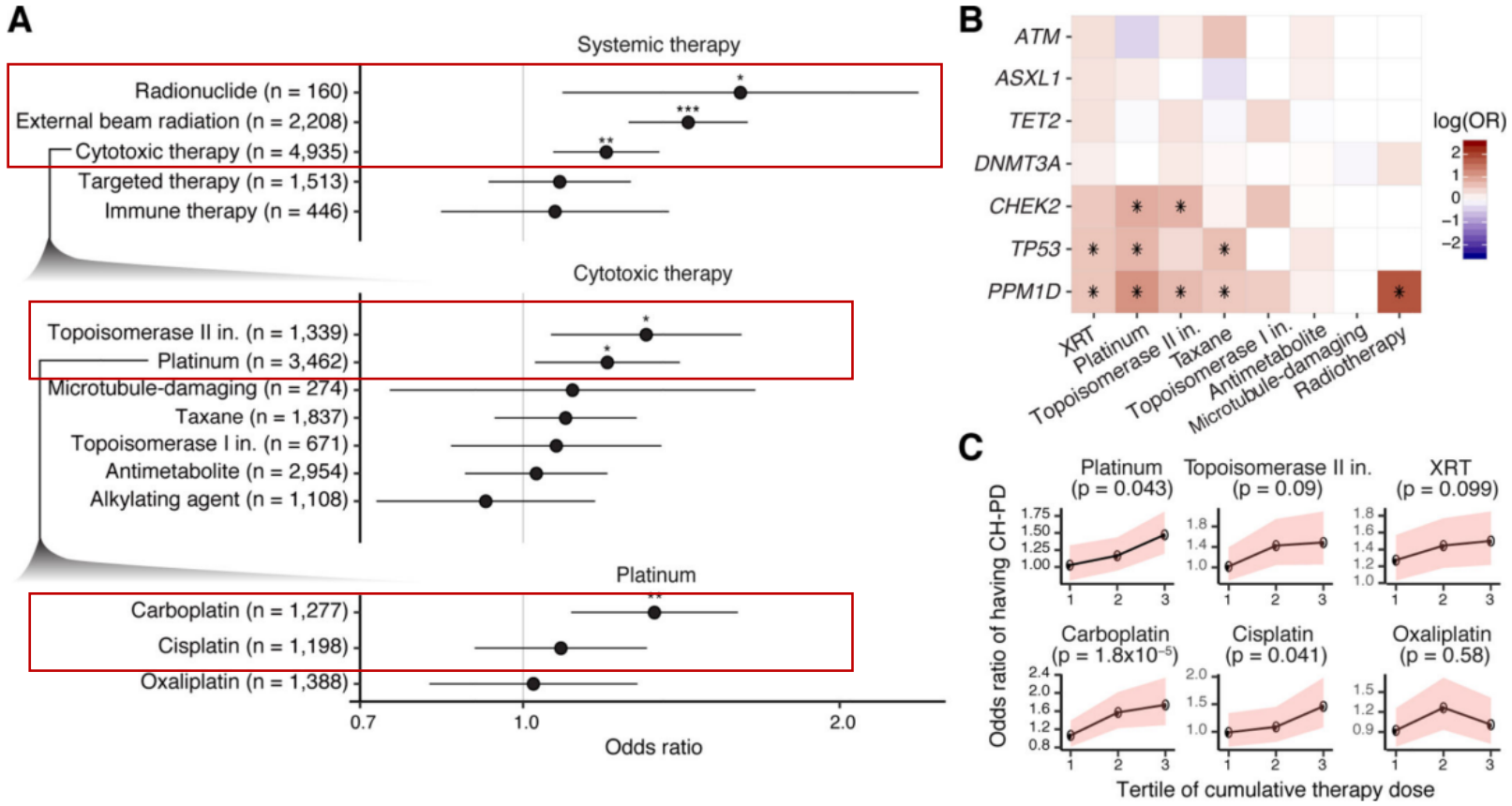
Solid tumors, treatment and clonal hematopoiesis

Before blood drawing:
5,978 patients (59%)
exposed to cancer therapy
4,160 (41%)
treatment-naive.



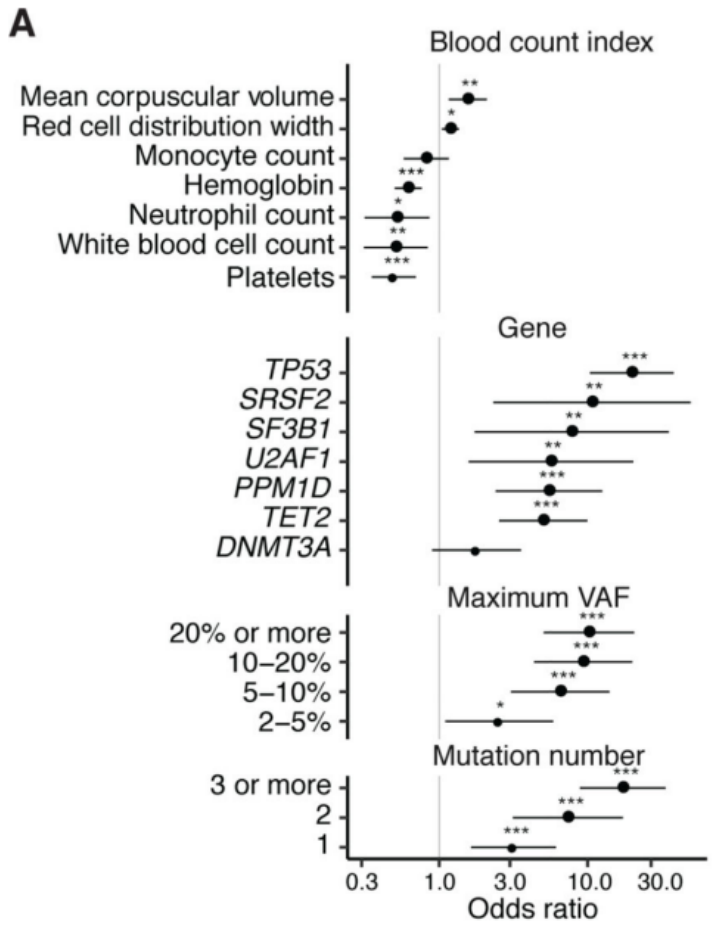
Bolton KL, Ptashkin RN, Gao T, et al. Nat Genet. 2020;52(11):1219-1226.

Specific cancer therapies and the development of CH with putative cancer-driver mutations



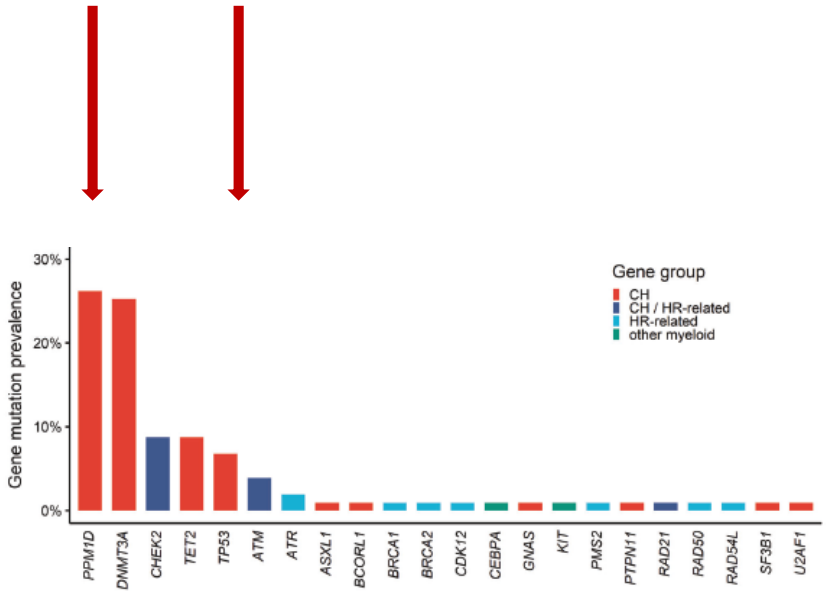
Bolton KL, Ptashkin RN, Gao T, et al. Nat Genet. 2020;52(11):1219-1226.

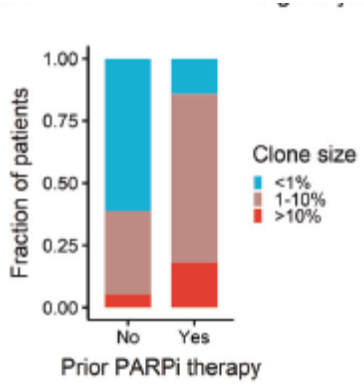
Risk of AML or MDS by clinical and CH mutational characteristics in patients with solid tumors

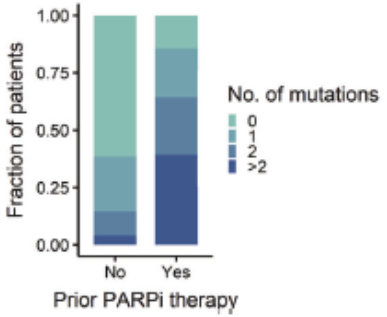


Bolton KL, Ptashkin RN, Gao T, et al. Nat Genet. 2020;52(11):1219-1226.

PARP inhibitors are associated with increased clone size, and more CH mutations





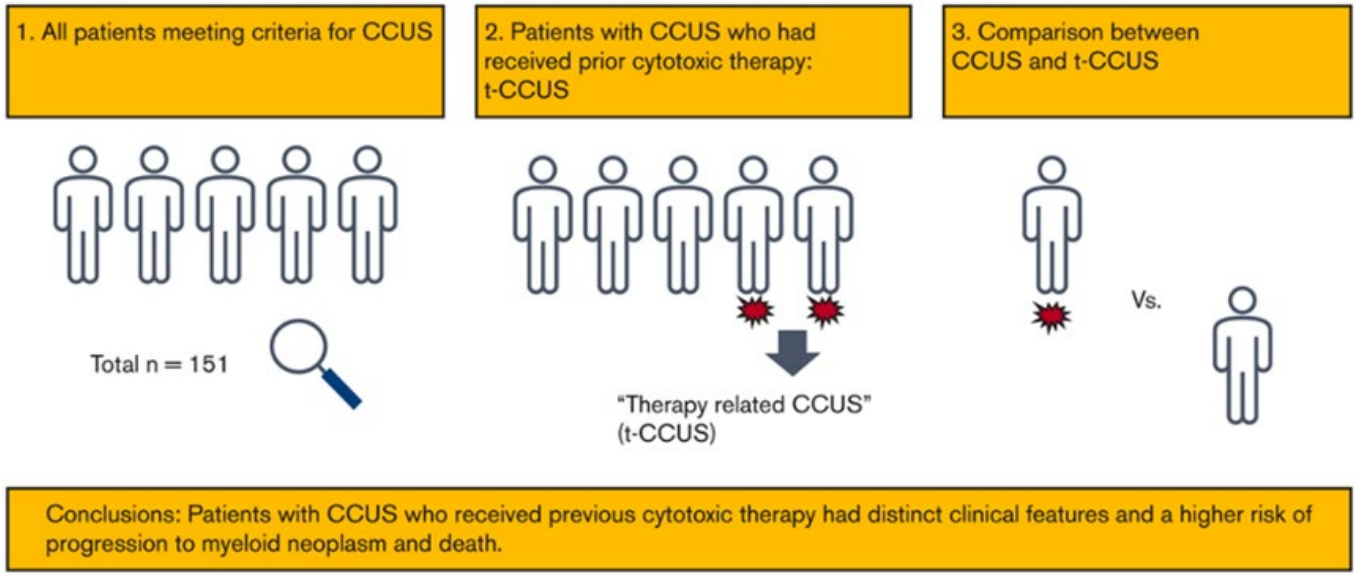


- OBS: cfDNA analyses also detects clonal hematopoiesis – thus mutations in buffy coat must be subtracted

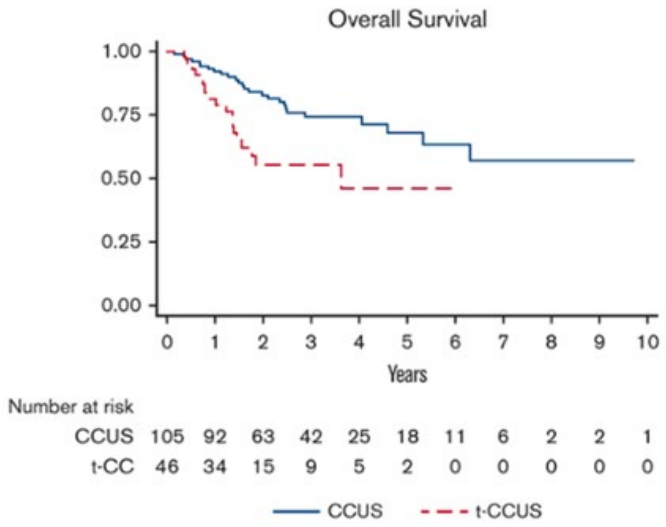
Arends CM, Kopp K, Hablesreiter R, et al. Leukemia. 2024;38(6):1378-1389.

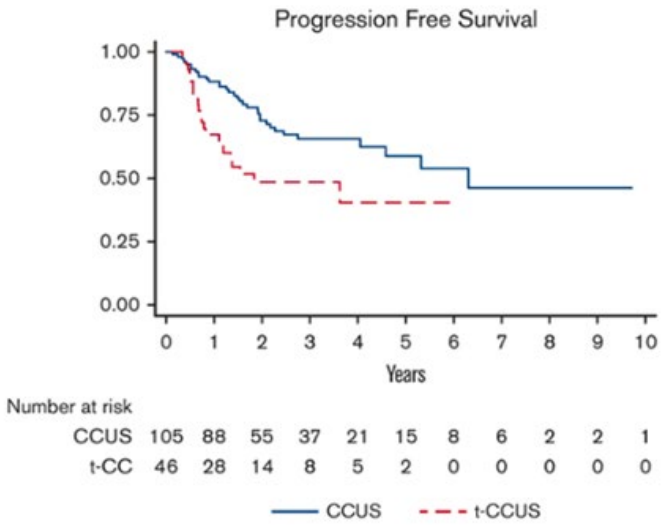
PARPi and MDS/AML: Reviewed in Lancet Hematology 2021,;8 .e122-34

Patients with t-CCUS have higher risk of progression and death



Conclusions: Patients with CCUS who received previous cytotoxic therapy had distinct clinical features and a higher risk of progression to myeloid neoplasm and death.





Li M, Baranwal A, Gurney M, et al. Blood Adv. 2024;8(12):3130-3139.

t-CHIP/t-CCUS – when does it matter?

- t-CHIP mutations in DNA repair genes (*TP53 PPM1D* and *CHEK2*) are associated with poor outcome
- tCHIP +mCA are associated with poor outcome
- Treatment with radiation, platinum, topoisomerase inhibitors, PARP inhibitors and lenalidomide particularly select for clones with mutated DNA repair genes
- CAR-T?
- Age > 60 + t-CHIP is associated with poor outcome
- t-CCUS have poorer outcome than CCUS
- Solution? – Elderly patients with relapse tested for t-CHIP before 2.line + chemo is initiated, and alternative lesser toxic regimens could be considered
- Clinical trials?

Could CHIP and CCUS clinical interception trials improve outcome?

What would be required from pre-emptive therapy in CHIP/CCUS?

- Cautious genetic testing – based on informed consent
- Identification of high-risk patients is essential
- Drugs should be largely non-toxic, without affecting the individuals' quality of life

Ongoing clinical intervention trials in CCUS/LR-MDS

- NCT05102370: **Enasidenib** for Patients With Clonal Cytopenia of Undetermined Significance and Mutations in IDH2 (single arm, Phase 2, 15 pts)
- NCT05030441: **Ivosidenib** Clonal Cytopenia of Undetermined Significance and Mutations in IDH1 (single arm phase 2, 20pts)
- NCT05483010: **Statins** in Patients with Clonal Cytopenia of Undetermined Significance (CCUS) and Myelodysplastic Syndromes (MDS) (single arm, Phase 2, 16 pts)
- NCT06063486: **Curcumin** to Improve Inflammation and Symptoms in Patients With Clonal Cytopenia of Undetermined Significance, Low Risk Myelodysplastic Syndrome, and Myeloproliferative Neoplasms (randomized, Phase 2, 30 pts)
- NCT05641831: A Randomized **Double-Blinded Placebo-Controlled Phase II** Multi-Center Study of Inflammation Modification of **Canakinumab** to Prevent Leukemic Progression of Clonal Cytopenias of Unknown Significance (CCUS): IMPACT Study (randomized Phase 2, 94 pts)
- NCT06802146: Early Intervention in High Risk CCUS. Open-label, multicenter pilot study testing the feasibility and safety of early pharmacologic intervention, **decitabine/cedazuridine**, in participants with higher-risk clonal cytopenia of unknown significance (CCUS)(pilot 30 in the intervention arm total 108)

NCT04741945: Repurposing **Metformin** as a leukemia-preventive drug in CCUS and LR-MDS (Phase 2 single arm 40 pts; 40/40 enrolled)

NCT03682029: Epigenetics, **Vitamin C,** and Abnormal Blood Cell Formation - Vitamin C in Patients With Low-Risk Myeloid Malignancies (EVITA) (A **randomized, placebo-controlled**, blinded, parallel-group clinical phase 2 study, 109 pts, enrollment completed).

(ClinicalTrials.gov)

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All patients and their families

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Danish and Nordic Lymphoma groups
Mats Jerkeman
Tarec El-Galaly
Christian Geisler
- all the others

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Casey O'Connell

Dept. of Hematology, Rigshospitalet
Bo Kok Mortensen

Dept. of Hematology, Aalborg University Hospital
Marianne Tang Severinsen

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The Danish Cancer Society
Independent Research Fund Denmark
Greater Copenhagen Health Science Partners

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EPIGENETICS DREAM TEAM

Danish Cancer Society

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