Highlights from
IMS 20th meeting 2023

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Emopoiesi Clonale

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

DISCLOSURE

Nothing to disclose

AGENDA

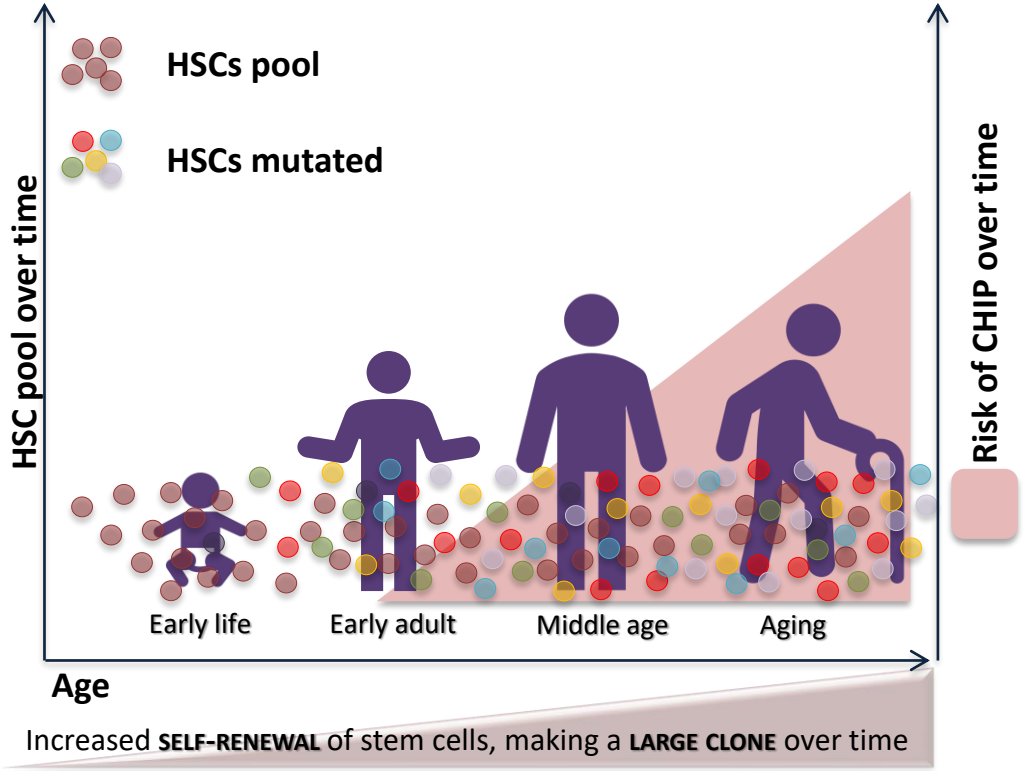
GAME OF CLONES: *type of CH*

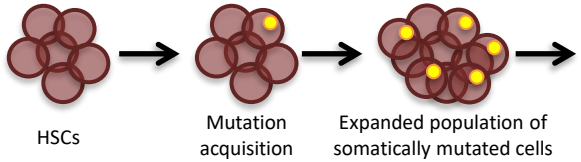
PREVALENCE OF CH IN MM

→ *Pre-neoplastic phase*
→ *Diagnosis*
→ *At the time of ASCT*

CH THERAPY: *Does therapy influence CH evolution?*

GAME OF CLONES: CLONAL HEMATOPOIESIS (CH)





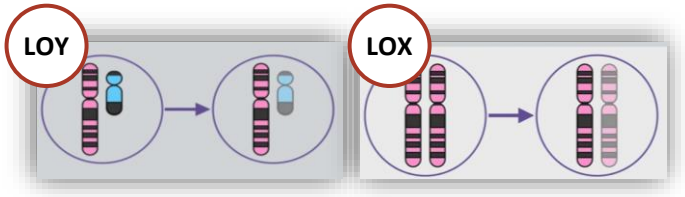
Clonal Hematopoiesis (CH)

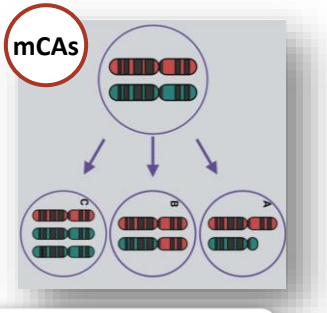
Expansion of HSCs clones (& progeny) in the BM, following the acquisition of somatic mutations

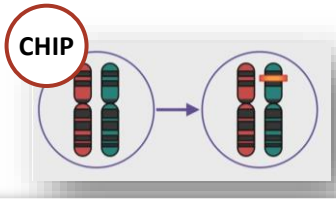
➔ **common** at diagnosis is patients with **blood cancers**, due to:

- clock-like mutational process ongoing at a steady-state rate throughout life
- prior chemotherapy and/or radiation exposure
- smoking
- inflammation

TYPE OF CLONAL HEMATOPOIESIS







Loss of Chromosome Y (LOY)

- **Absence** of the **Y** chromosome in a clonal population of blood cells in men
- **Increases** with advancing age
- Genetic determinants highlight genes involved in cell-cycle regulation, somatic drivers of tumor growth, and cancer susceptibility

Loss of Chromosome X (LOX)

- **Absence** of an **X** chromosome in a clonal population of blood cells in women
- **Increases** with advancing age

Autosomal Mosaic Chromosomal Alterations (mCAs)

- **Large structural alterations** present across all autosomal chromosomes in both males and females
- **Increases** with advancing age

A. **Genomic deletions** are the partial or full loss of a chromosome arm

B. **Copy neutral loss of heterozygosity (CNLOH)** is a deletion and subsequent duplication of chromosomal arms resulting in no net change in copy number

C. **Genomic duplications** are partial or full gain of a chromosomal arm

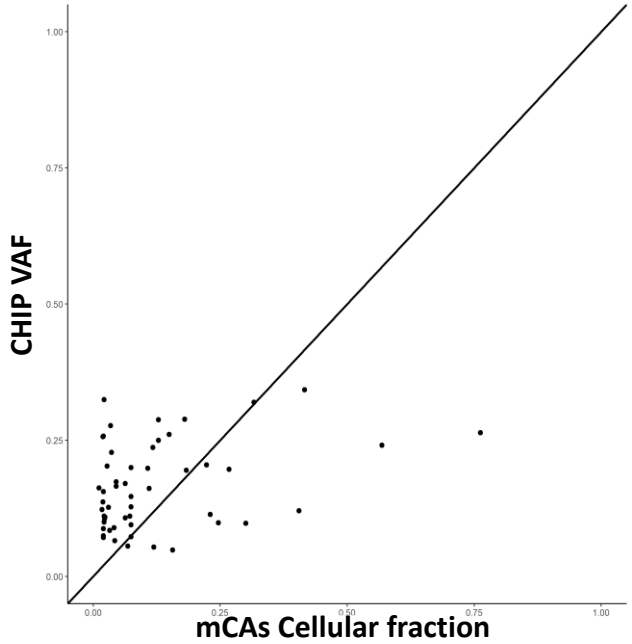
Clonal Hematopoiesis of Indeterminate Potential (CHIP)

- **Clonal expansion** of blood cells carrying somatic blood cacner **driver mutations** in individual with normal blood parameters
- Mutations are frequently observed in ***DNMT3A***, ***TET2***, ***ASXL1***, ***JAK2***, ***TP3***, etc
- Genetic determinants are related to **increased self-renewal** of hematopoietic stem cells and telomerase activity

D.W. Brown et al., Nature Communications 2023

CHIP PRECEDES MCAS ACQUISITION

→ higher estimated CHIP VAF than estimated mCA cellular fraction in a majority of co-localizing mutations, suggesting the acquisition of the CHIP mutation preceded the acquisition of autosomal mCAs



Derek W. Brown et al., Nat Comm (2023)

«Second hit»

Cross-sectional observations of cellular fraction indicate the **CHIP mutations often precede autosomal mCAs**, which can lead to **preferential clonal expansion of mCAs containing CHIP** mutations (i.e., a "**SECOND HIT**")

Multi-hit hypothesis in driving Clonal Evolution

Unknown

DISTINCTION OF LYMPHOID AND MYELOID CH

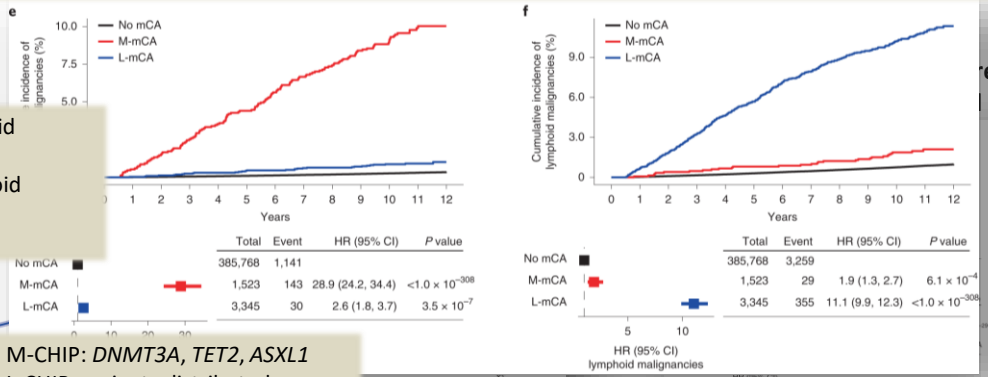
CH Mutations

- ***TET2*** mutations have been found to be more frequent in **Myeloid** lineage
- ***DNMT3A*** mutations tend to be more **multipotent** and frequently affect both Myeloid and Lymphoid lineage
- Certain CH can be characterized as **Myeloid CH** and others as **Lymphoid CH** → **highly predictive** of patients being at **risk of Myeloid or Lymphoid** malignancies

→ Somatic variants in both myeloid and lymphoid driver genes using WES data from 46,706 unrelated individuals aged 40–70 years (median, 58 years) with no previous hematologic malignancy diagnosis

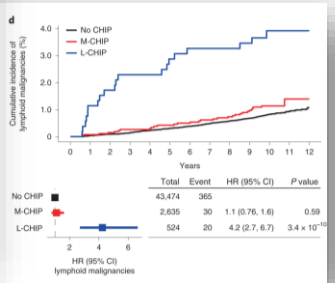
M-CHIP and L-CHIP increase with age

→ M-mCAs increased the risk of Myeloid malignamìncies
→ L-mCAs increased the risk of Lymphoid malignancies
→ A-mCAs increased the risk of both



→ M-CHIP: *DNMT3A*, *TET2*, *ASXL1*
→ L-CHIP: variants distributed more envely across genes

…ease the risk of Myeloid or … malignancies



A. Niroula et al., Nature Medicine (2021)

PREVALENCE OF CHIP IN PATIENTS WITH MYELOMA

The prevalence of CHIP has been studied at various TIME POINTS along the Myeloma disease spectrum

- → **pre-neoplastic phase**
- → **at Myeloma Diagnosis**
- → **at the time of ASCT**

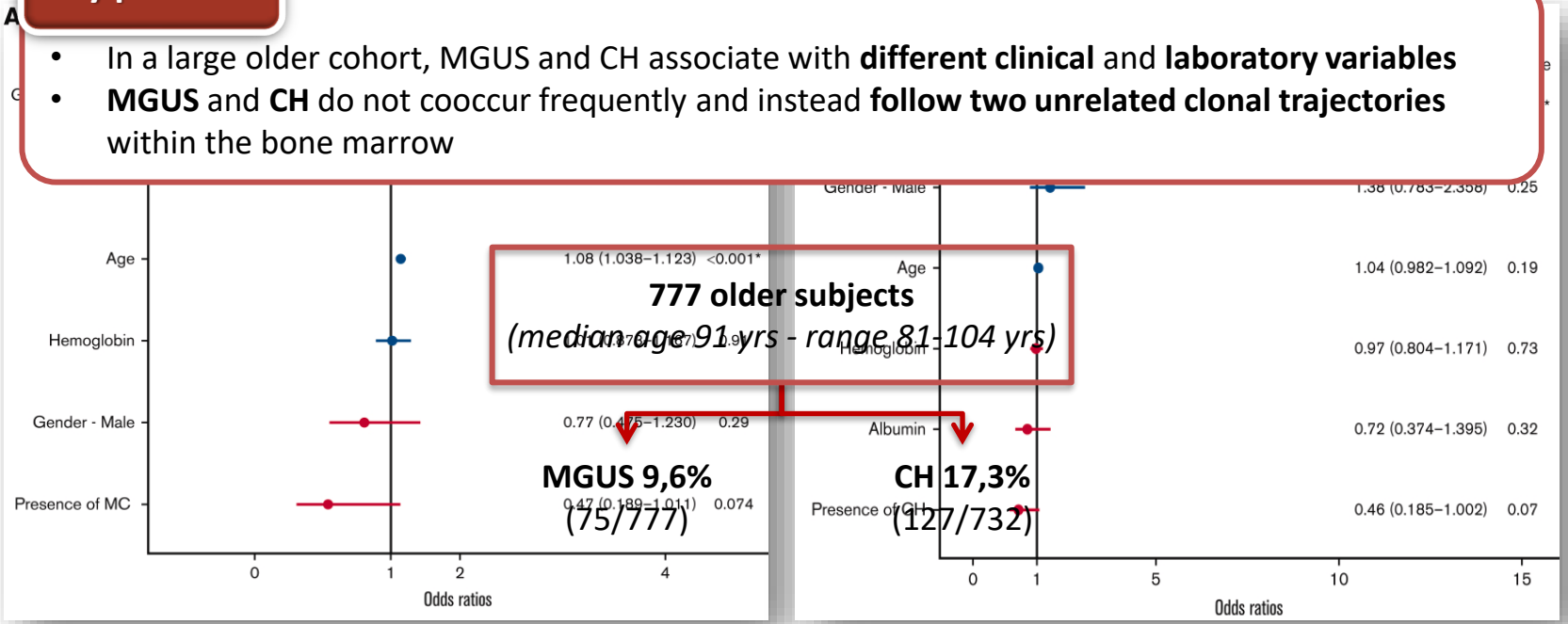
CHIP AND MM: PRE-NEOPLASTIC PHASE

No association between MGUS and CH → tendency toward their mutual exclusivity

D and laboratory covariates → develop along independet biological trajectories

Key points

- In a large older cohort, MGUS and CH associate with **different clinical** and **laboratory variables**
- **MGUS** and **CH** do not cooccur frequently and instead **follow two unrelated clonal trajectories** within the bone marrow



777 older subjects

(median age 91 yrs - range 81-104 yrs)

MGUS 9,6% (75/777)

CH 17,3% (127/732)

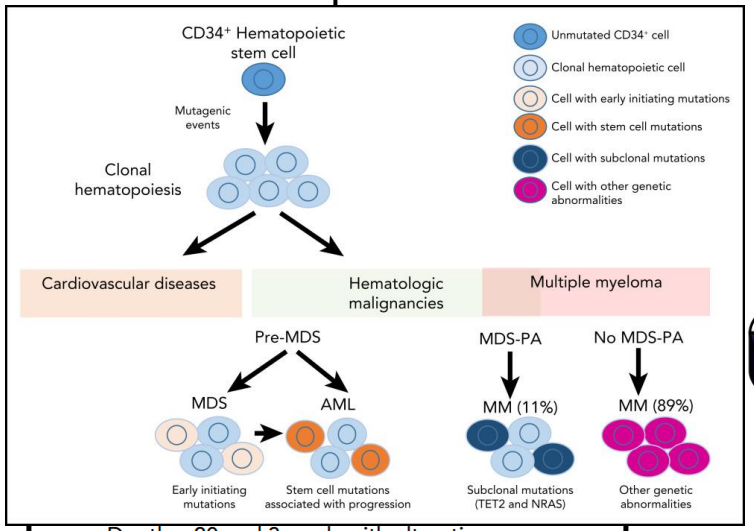
Da Vià M. C. et al., Hematopoiesis and stem cells (2020)

CHIP AND MM: DIAGNOSIS

67 patients

285 NDMM enrolled in the PETHEMA and/or GEM2012MENOS65

11,6% of MM cases displayed MDS-PA phenotype



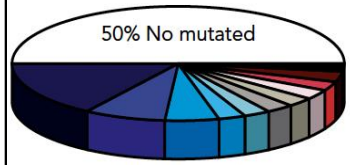
- Depth > 20 and 3 reads with alteration
- MAF < 0.01
- 0.05 ≤ VAF ≤ 0.35
- In COSMIC database

Maia C. et al., Hematopoiesis and stem cells (2020)

Prevalence of CHIP by NGS

Median VAF= 9%

Patients with MDS–PA

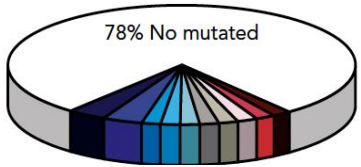


- *TET2* (23.1%)
- *NRAS* (11.5%)
- *GATA2* (7.7%)
- *JAK3* (3.8%)
- *CDKN2A* (3.8%)
- *CALR* (3.8%)
- *NPM1* (3.8%)
- *ZRSR2* (3.8%)
- *ATRX* (3.8%)
- *PPM1D* (3.8%)
- *DNMT3A* (3.8%)

50% mutated

Median VAF=7%

Patients without MDS-PA



- *KRAS* (4.9%)
- *NOTCH1* (4.9%)
- *NRAS* (2.4%)
- *TET2* (2.4%)
- *IKZF1* (2.4%)
- *ASXL1* (2.4%)
- *DNMT3A* (2.4%)
- *CBL* (2.4%)
- *ABL1* (2.4%)
- *JAK3* (2.4%)

22% mutated

In either case, the overall prevalence of CHIP in this NDMM population was high at 33%

Neri P. et al., Hematopoiesis and stem cells (2020)

CHIP AND MM: DIAGNOSIS

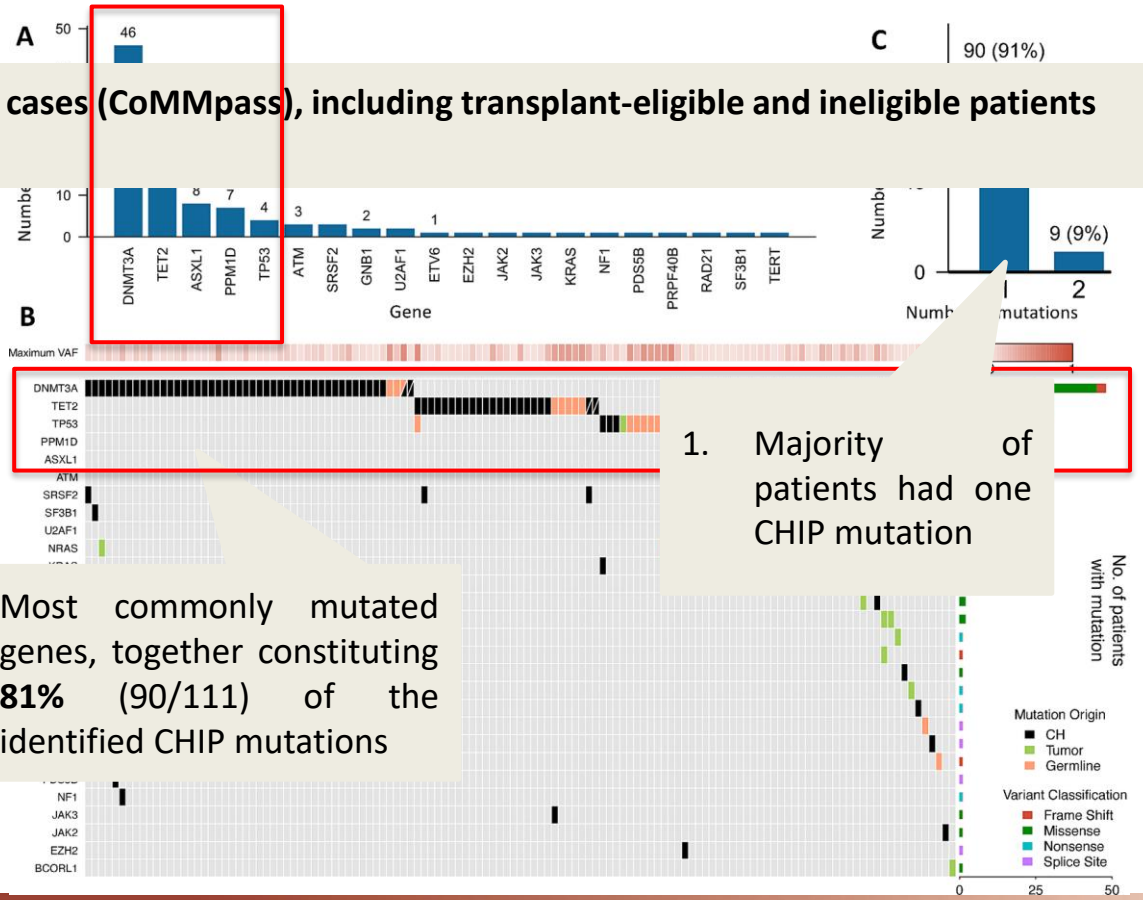
→ **A large multi-center cohort of 986 NDMM cases (CoMMpass), including transplant-eligible and ineligible patients**

→ **WES data of PB and BM**

1. *Idetified **111 CHIP** mutations - **99**/986 (**~10%**) CHIP*
2. *Median **VAF 7%** - Mean 10,9%*

→ *Transplant (**40**/529 – **7,56%**)*
→ *Non-Transplant (**59**/457 – **12,91%**)*

3. *Most patients had **only a sigle** CHIP mutation (**9** had 2 CHIP mutations)*



1. Majority of patients had one CHIP mutation

1. Most commonly mutated genes, together constituting **81%** (90/111) of the identified CHIP mutations

Mouhieddine T.H. et al., Cancer Research Comm (2023)

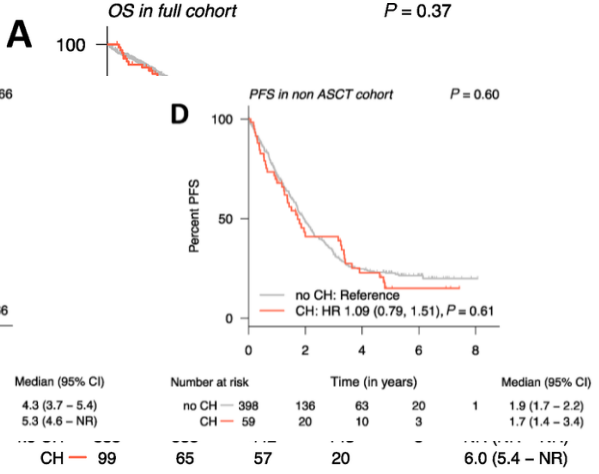
CLINICAL ASSOCIATION WITH CHIP IN NDMM

→ **Across the full cohort, they did not see a significant association between CHIP and OS or PFS**

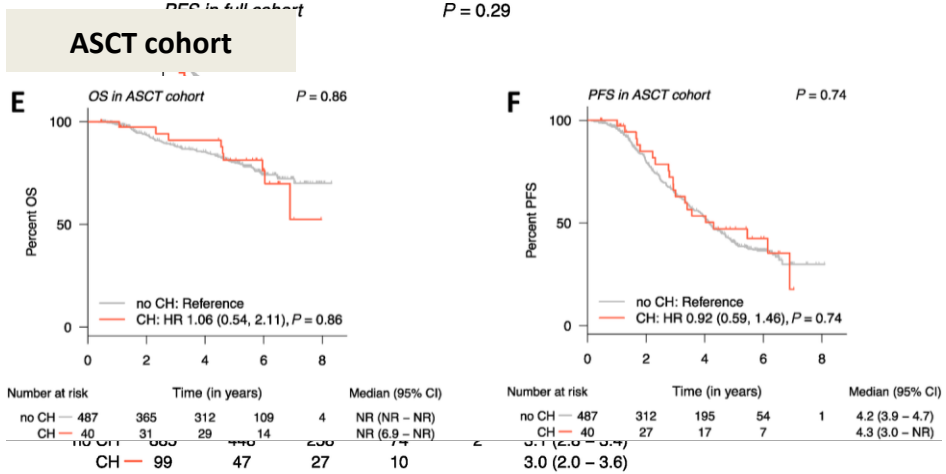
→ Among the 457 non-transplanted patients, the presence of CHIP was not significantly associated with OS or PFS

→ Similarly, among the 527 transplanted patients, the presence of CHIP was not significantly associated with OS or PFS

Non ASCT cohort



ASCT cohort



Mouhieddine T.H. et al., Cancer Research Comm (2023)

EVOLUTION OF CHIP DURING TREATMENT

- → **Sequential PB samples**
- → **Target bait panel of 586 genes (Pan-cancer and Myeloid associated genes)**

52 MM

48 patients had 2 timepoints

3 patients had 3 or

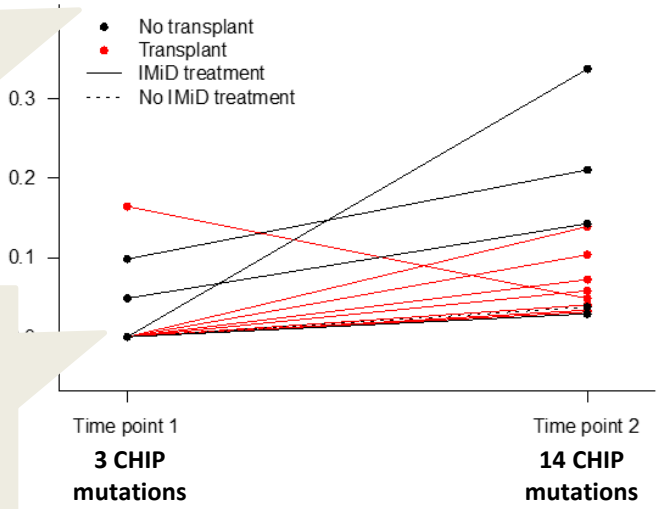
36 ASCT

The median time
first and second
3.12 years (range
years

1. **3/52** (5,76%) had CHIP at diagnosis
2. Following therapy, **CHIP** mutations were present in **additional 10 patients** (13/52 – 25%)

1. Common **emergent mutation** was in ***DNMT3A*** (5/10)
2. Most patients with expanded or emerging clones
3. 1 patient *DNMT3A* clone dropped down under Lena

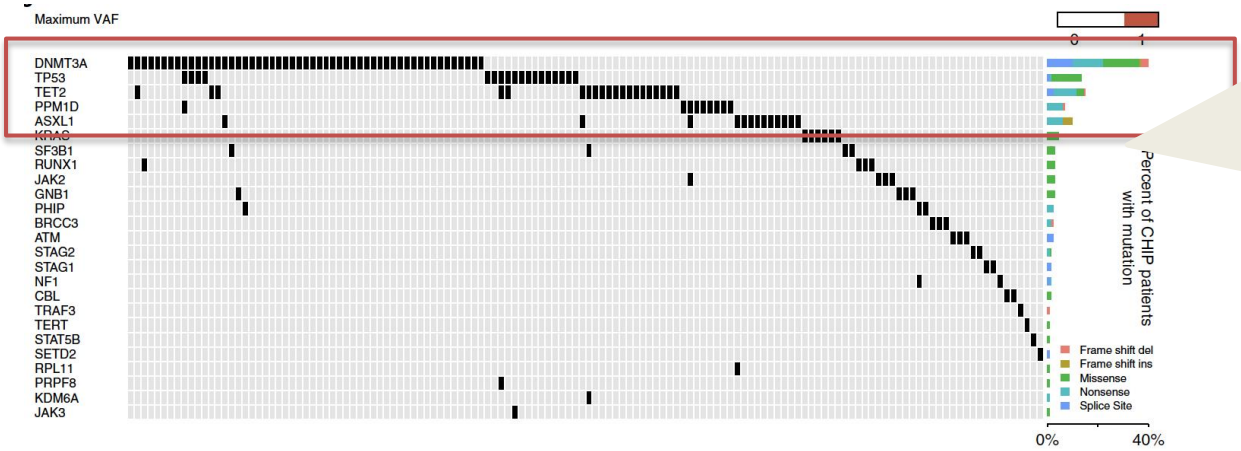
Change in prevalence and VAF of CHIP clones between 2 time points



Mouhieddine T.H. et al., Cancer Research Comm (2023)

CHIP AND MM: AT THE TIME OF ASCT

- **Checked for CHIP from stem cell products mobilized right before ASCT of 629 MM**
- **Target bait panel of 224 genes (pan-cancer, MM and Myeloid)**



1. Commonly mutated genes included: ***DNMT3A***, ***TP53***, ***TET2***, ***PPM1D*** and ***ASXL1***
2. CHIP prior to ASCT was not associated with an increased risk of TMN
3. Majority of MM patients have only **one mutation (116/136)** (**20/136** – **14,7%** had 2 or more)

- **88**/629 MM patients (**14%**) with mutation with a VAF ≥ 0.02
- **136**/629 MM patients (**22%**) with mutation with a VAF ≥ 0.01

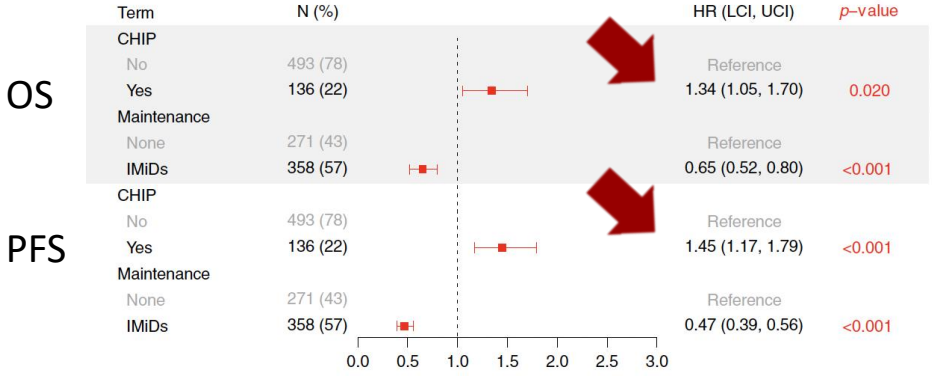
  24/629 MM patients (**4%**) had VAF ≥ 0.1

➔ median VAF = 0.027 (very low plasma cells contamination)

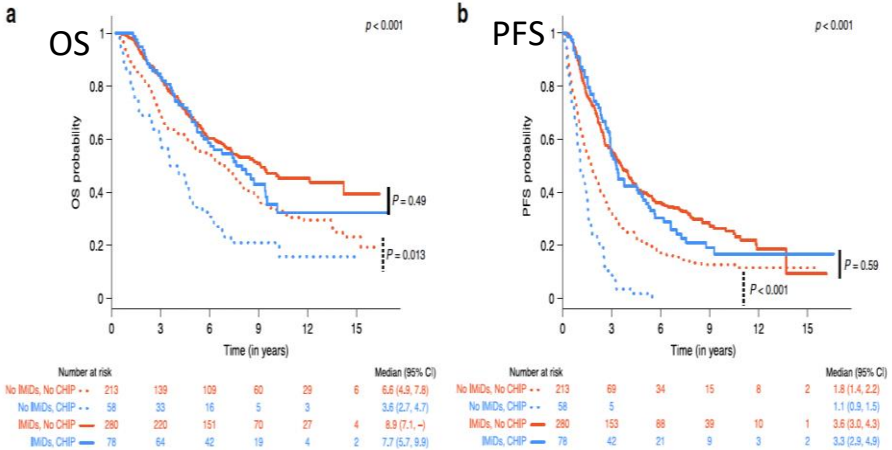
Mouhieddine T.H. et al., Nat Comm (2020)

CHIP AND MM: AT THE TIME OF ASCT (CLINICAL OUTCOMES)

CHIP at the time of ASCT has been shown to be associated with decreased OS and PFS in MM patients



	median OS	median PFS
CHIP	5.3 years	2.2 years
no CHIP	7.5 years	2.6 years



ADVERSE IMPACT ON OUTCOME WAS COMPLETELY ABROGATED BY LEN

INCREASED RISK FOR MYELOMA PROGRESSION IN PATIENTS WITH CHIP

Mouhieddine T.H. et al., Nat Comm (2020)

DOES THERAPY INFLUENCE CH EVOLUTION? CAN CH BE TRACKED?

1. In spite of the enormous benefits of chemotherapy, it can plant the seed for the development of a secondary neoplasm years or decades later

2. Unresolved question is whether chemotherapy directly induces the *acquisition of new driver mutations or whether it selects for existing pre-leukemic clones*

MUTATIONAL SIGNATURE TO TRACK CH EVOLUTION

Innovative Aspects of the study

Use of MUTATIONAL SIGNATURES as TEMPORAL BARCODES that perm[it] mutagenic exposure in a patient's lifetime

Assembled a **DATASET** of **20 MM** ← **WGS** on a cohort of **40 tMNs** ← Imported **tMN** and ***DE NOVO AML*** data from public datasets (Cancer Genome Atlas and Beat AML)

Quantified mutational processes, starting with SINGLE-BASE SUBSTITUTIONS (SBSs)

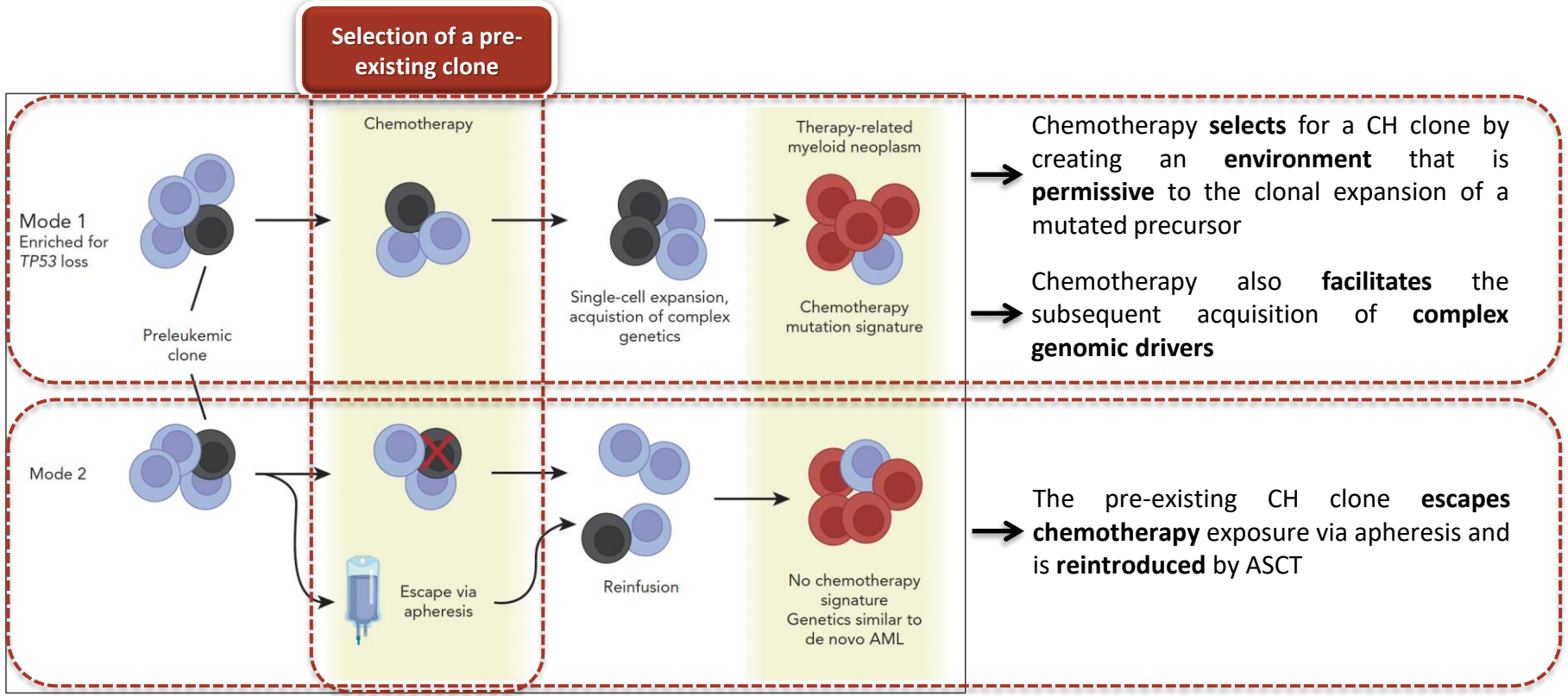
- **SBS1, SBS-HSC – Related to AGE**
- **SBS31, SBSS35 – Related to Platinum-based CT**
- **SBS-MM1 – Related to Melphalan**

→ All **tMNs exposed to prior platinum-based therapy** harbored the **platinum signature**, consistent with a model in which **one cell survived** platinum-based DNA damage and expanded to clonal dominance.

→ Conversely, only **41% of tMNs exposed to prior melphalan-based therapy** harbored the **melphalan signature**, consistent with the **secondary malignancy** being driven by **subclonal populations**, lack of melphalan driven mutagenesis, or escape from melphalan exposure.

B. Diamond et al., Blood (2023)

MUTATIONAL SIGNATURES REVEAL CLONAL EVOLUTION



Y.S. Lee and P. van Galen, Blood (2023)

TAKE HOME MESSAGE

1. CH is ***common*** in MM patients at all time points in their disease course and tends to become more common after treatment

2. CH may confer ***worse outcomes*** in patients undergoing ASCT → worse outcome is abrogated by IMiDs maintenance

3. CH is associated with an ***increased risk*** of subsequent hematologic malignancies

4. Different clonal trajectories that lead to tMNs, showing emergence from pre-existing clones that either harbour chemotherapy mutation signature or escaped exposure *via* apheresis