Session 5

Pre-malignant clonal hematopoietic proliferations

Chairs: Frank Kuo and Valentina Nardi

Pre-malignant clonal hematopoietic proliferations

- *Clonal LYMPHOID proliferations:*

  - *Monoclonal gammopathy of undetermined significance (MGUS)*

  - *Monoclonal B-cell lymphocytosis (MBL)*

  - *In Situ Follicular Neoplasia (ISFN)*

  - *In Situ Mantle Cell Neoplasia (ISMCN)*

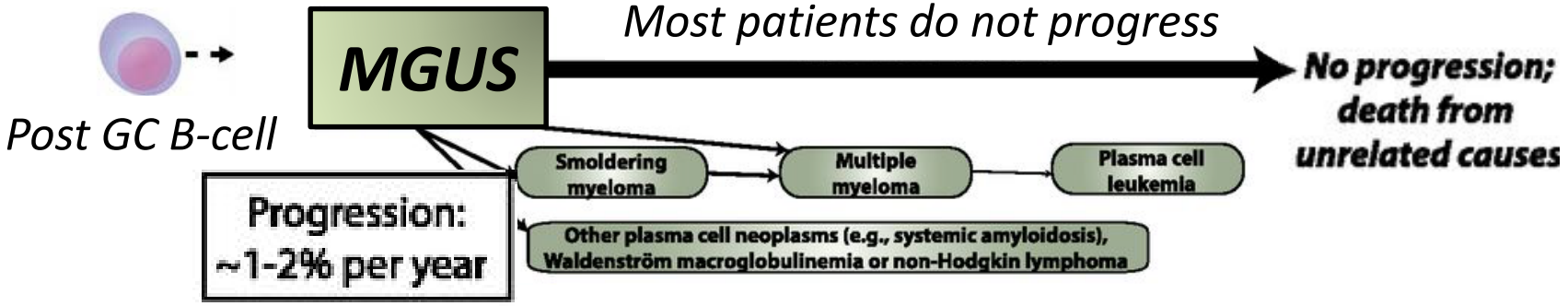
Pre-malignant clonal hematopoietic proliferations

- *Clonal MYELOID proliferations:*

  - *Clonal hematopoiesis of indeterminate potential (CHIP)*
  - *Clonal cytopenia of undeterminate significance (CCUS)*
  - *Small clones of cells with BCR-ABL1*

Premalignant clonal LYMPHOID proliferations

Monoclonal gammopathy of undetermined significance



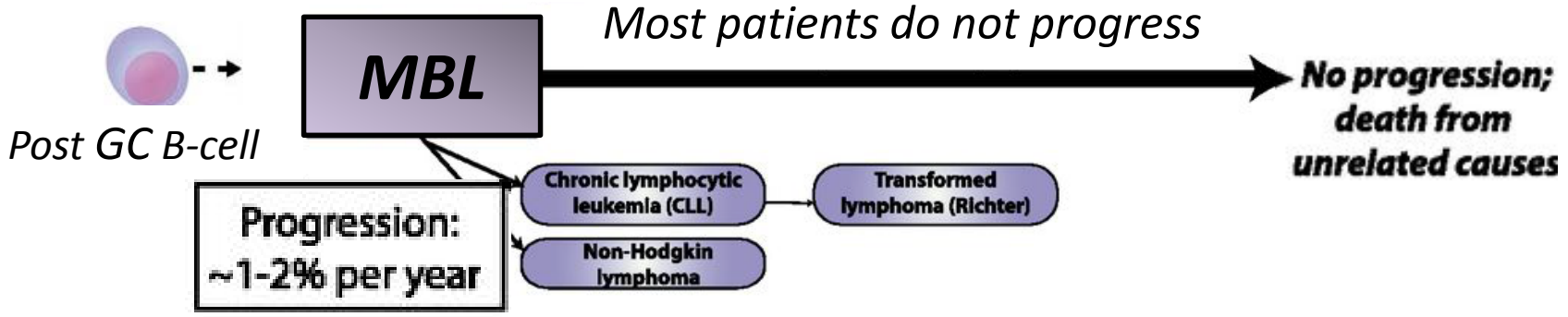
- *Non-IgM MGUS (plasma cell)*

- *IgM MGUS (mostly lymphoid/lymphoplasmacytic) - progresses to LPL/WM, other B-cell neoplasms, or primary amyloidosis*

Adapted from David P. Steensma et al. Blood 2015;126:9-16

Premalignant clonal LYMPHOID proliferations

Monoclonal B-cell lymphocytosis

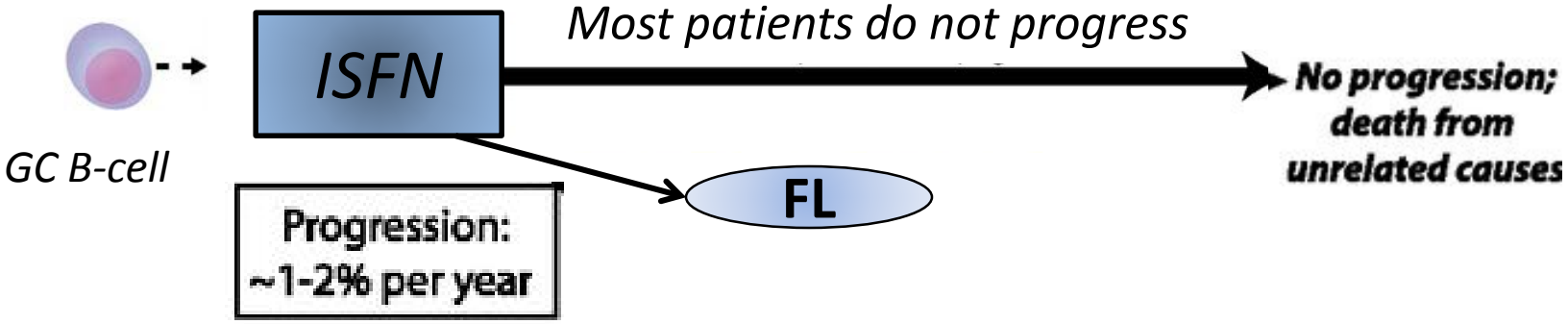


- *CLL-type, atypical CLL-type, non CLL-type*
- *Low count (<0.5 x10^9/L) vs High count (> 0.5 x10^9/L)*

Adapted from David P. Steensma et al. Blood 2015;126:9-16

Premalignant clonal LYMPHOID proliferations

In Situ Follicular Neoplasia

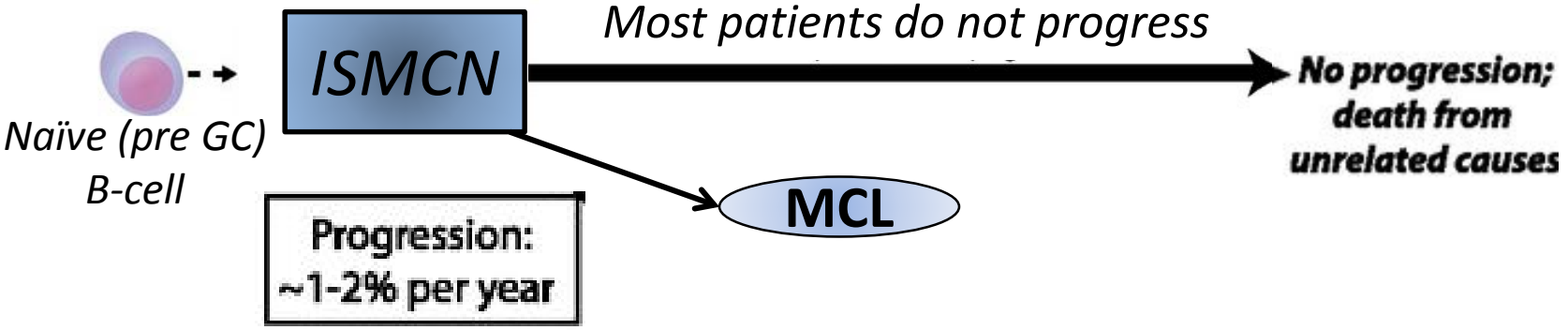


"Partial or total colonization of germinal centers by clonal B cells carrying the BCL2 translocation characteristic of FL in an otherwise reactive lymph node."

Adapted from David P. Steensma et al. Blood 2015;126:9-16

Premalignant clonal LYMPHOID proliferations

In Situ Mantle Cell Neoplasia

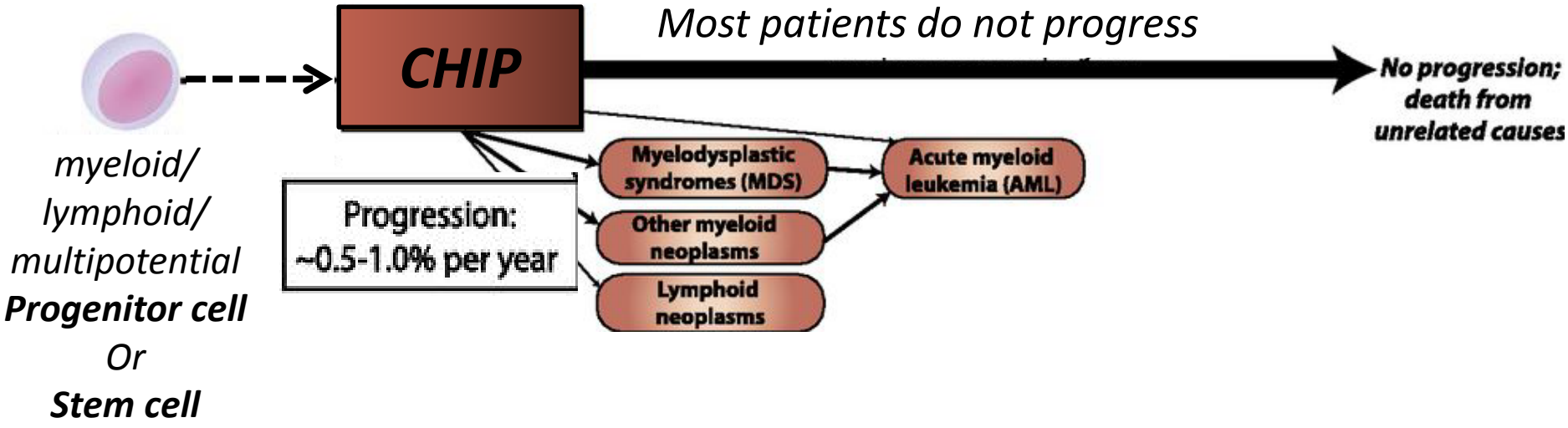


"Presence of cyclin D1– positive lymphoid cells with CCND1 rearrangements restricted to the mantle zones of otherwise hyperplastic-appearing lymphoid tissue."

Adapted from David P. Steensma et al. Blood 2015;126:9-16

Premalignant clonal MYELOID proliferations

Clonal hematopoiesis of indeterminate potential



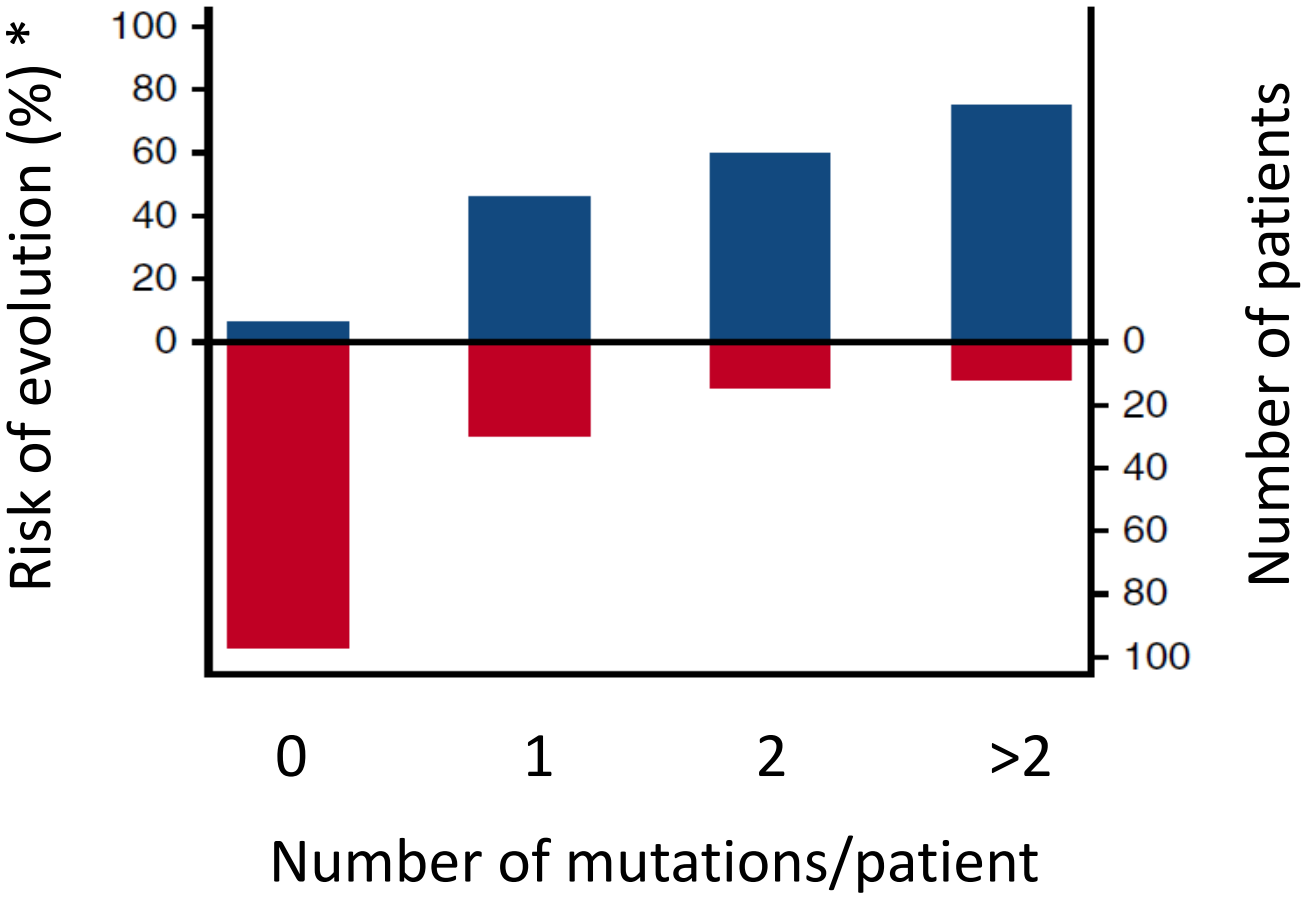
MDS-associated clonal gene mutations identified in haematopoietic cells without significant dysplasia on bone marrow examination and in the absence of cytopenias .

Adapted from David P. Steensma et al. Blood 2015;126:9-16

Significance of pre-malignant clonal hematopoietic proliferations

- *early involvement by a neoplasm*
- *precursor lesion*
- *inconsequential finding*

Somatic mutations in CCUS and risk of progression



**** Spliceosome gene mutations***

**** Co-mutation patterns involving DNMT3A, TET2 and ASL1***

Malcovati L. et al, Blood 2017

Pre-malignant clonal hematopoietic proliferations: cases selected for oral presentation

Case 269 *- Dr. Wood.*
Clonal cytopenia of undetermined significance.

Case 50 *- Dr. Thompson-Arildsen.*
Clonal cytopenia of undetermined significance with progression to myelodysplastic syndrome with excess blasts-2.

Case 350 *- Dr. Shanmugam.*
Clonal cytopenia of undetermined significance with progression to chronic myelomonocytic leukemia-1.

Case 28 *- Dr.Rjoop.*
Occult myeloid sarcoma (in a patient with lymphoplasmacytic lymphoma).

Case 256 *- Dr. Loghavi.*
1. Lymphoplasmacytic lymphoma. 2. Chronic myelomonocytic leukemia-1.

Case 332 *- Dr. Stuart.*
Paroxysmal nocturnal hemoglobinuria.

Clonality assessment for premalignant neoplasms

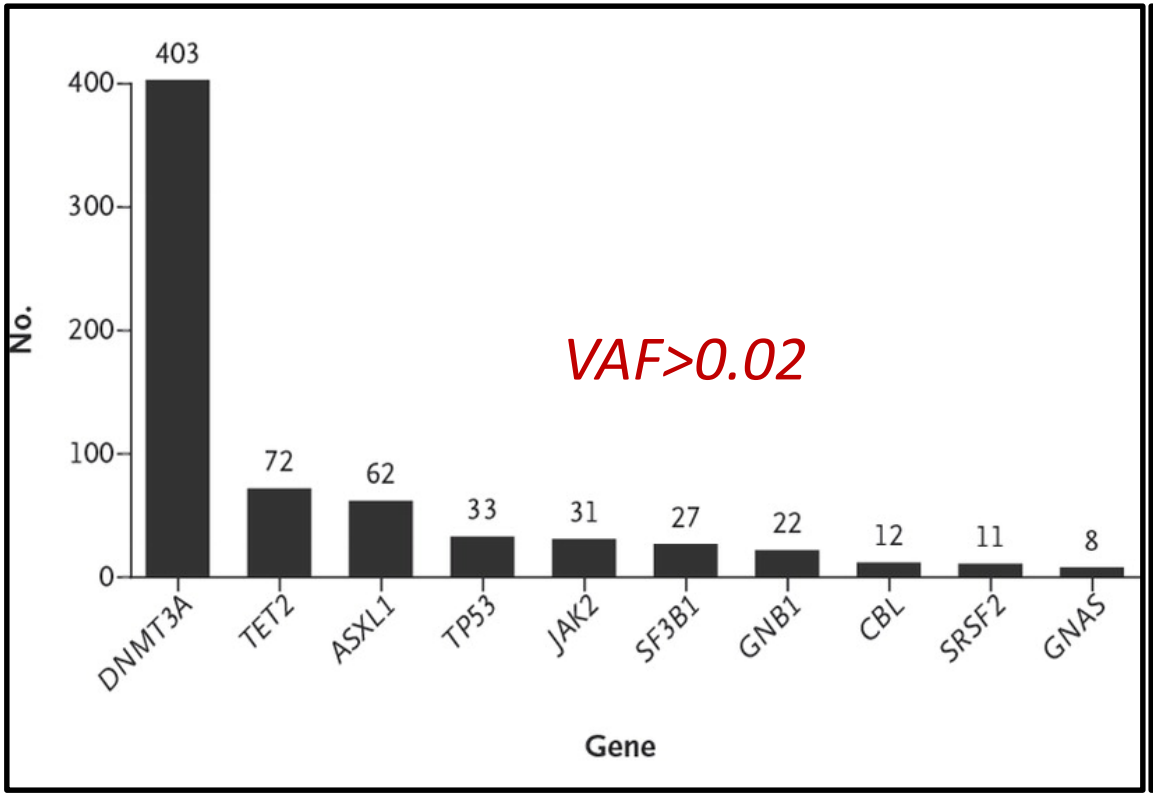
- *T/B cell clonality, flow cytometric analysis*
- *Chromosomal abnormality (karyotype, FISH, aCGH)*
- *Gene mutations (NGS)*
  - *same genes and mutations as myeloid /lymphoid neoplasms*
  - *variable allelic frequency (from low to high)*
  - *single or multiple*
  - *some confer higher risk of progression*

Premalignant (clonal) MYELOID proliferations

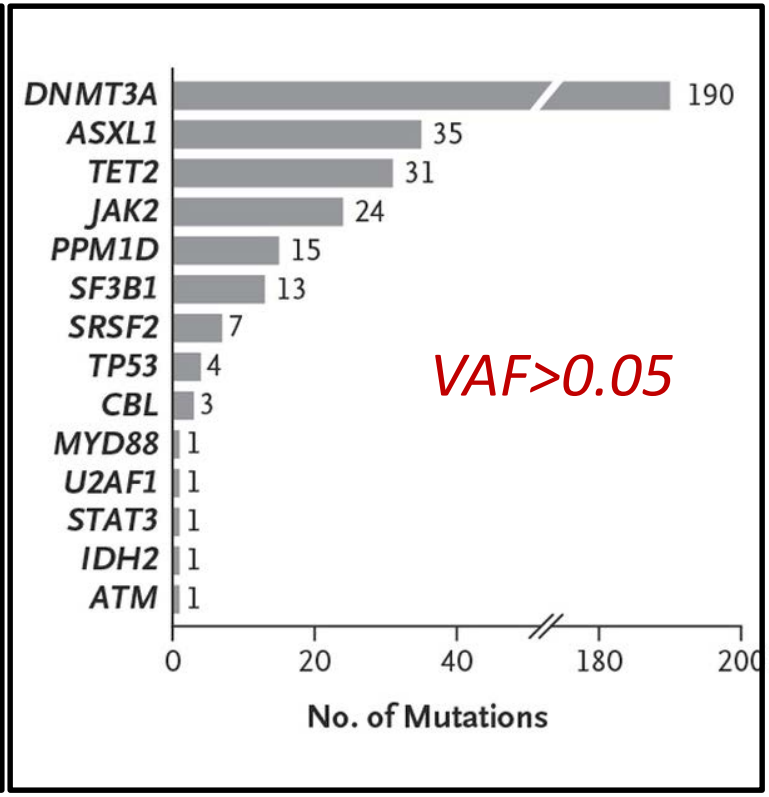
	ICUS	***CHIP***	***CCUS***
	Idiopathic Cytopenias of Undeterminate Significance	*Clonal Hematopoiesis of Indeterminate Potential*	*Clonal Cytopenias of Undeterminate Significance*
Clonality	-	+	+
Dysplasia	-	-	-
Cytopenias	+	-	+

Adapted from David P. Steensma et al. Blood 2015;126:9-16

Somatic mutations in CHIP



Jaiswal S., et al.
N Engl J Med 2014



Genovese G, et al.
N Engl J Med 2014

10% > age 70, 20%>age 90

DNMT3A, ASXL1 & TET2, most commonly mutated genes