MUTAZIONI DI *CSF3R* NELLA NEUTROPENIA CONGENITA: ANALISI DEL REGISTRO ITALIANO

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Disclosures of Agnese Roveta

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

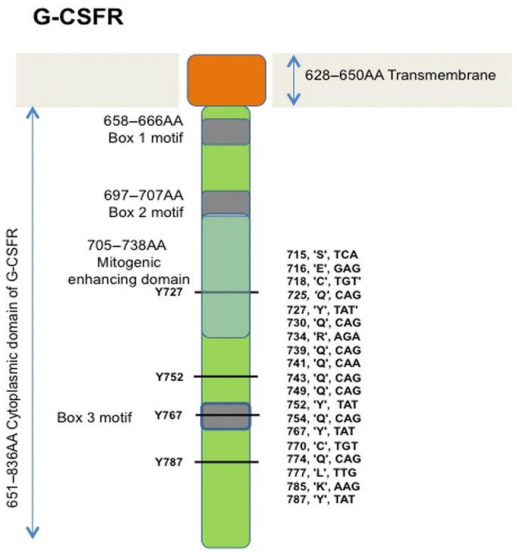
Background

Severe congenital neutropenia → intrinsic risk of developing myelodysplasia and/or acute leukemia (6-31% according to treatment duration)

Acquired, gain of function mutations in the intracellular part of *CSF3R* occur >30% of SCN patients

Cytoplasmatic domain mutations
→ premature stop codons
→ truncated receptor
→ resistance to apoptosis and maturational block

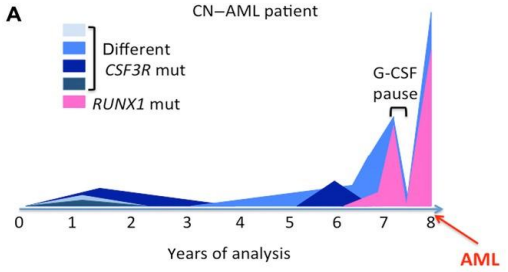
>80% of SCN patients who develop MDS/AML have *CSF3R* mutations



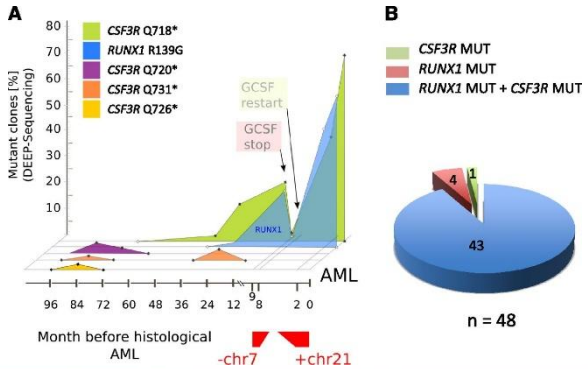
Klimiankou M, Ann NY Acad Sci. 2016

Background

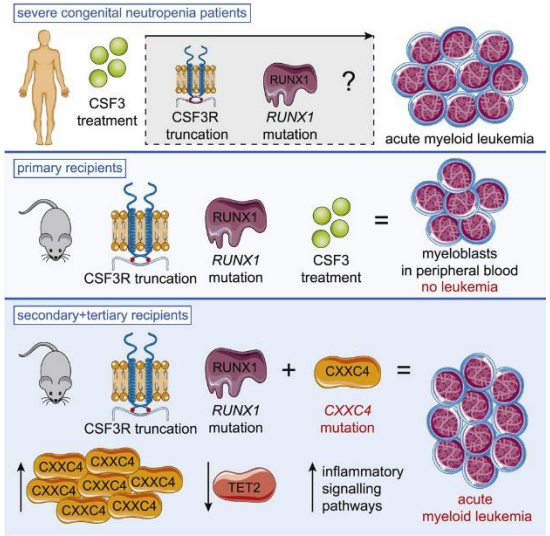
Multiple and dynamic *CSF3R* clones



Cooperativity of *RUNX1* and *CSF3R* mutations



Additional *CXXC4* mutation with downregulation of TET2 activity



Klimiankou M, Ann NY Acad Sci 2016
Skokowa J, Blood 2014
Olofsen PA, Cell Rep Med 2020

Methods - *Population*

Observational study

Pediatric and adults patients with SCN tested for *CSF3R* somatic mutations

Retrospective Prospective Study (Hematology Unit – IRCCS Istituto Giannina Gaslini)

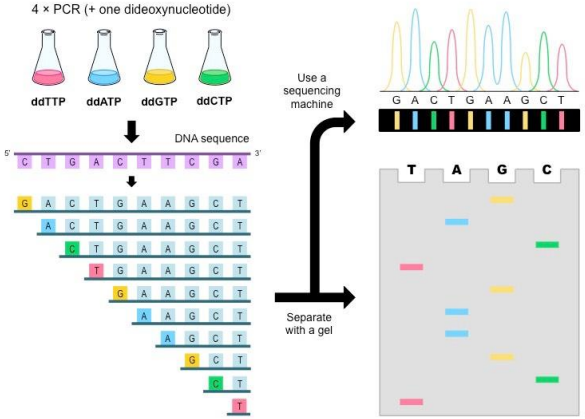
Inclusion criteria:

- Diagnosis of SCN
- Treatment with G-CSF
- At least one determination of *CSF3R* clones during the follow-up period
- Available data on clinical presentation, treatment and outcome (follow-up ≥ 1 year)

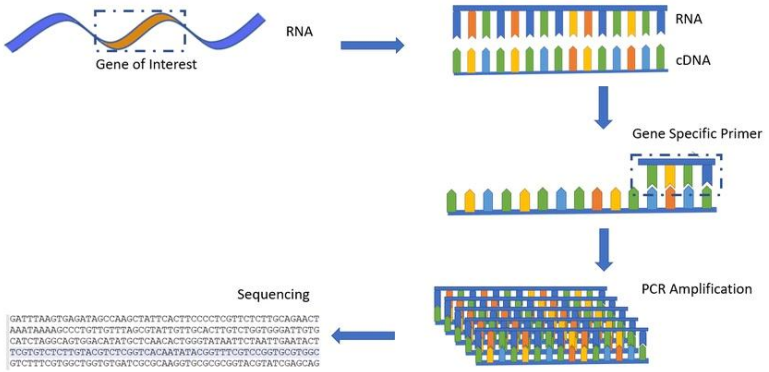
Methods – *Clone detection*

Sequencing of exon 17 of *CSF3R* gene (AOU Meyer IRCCS)

Cloning
(≥ 100 clones per patient)



Next Generation Amplicon Sequencing
(1% sensitivity)



2004 — 2013 — 2025

Reteng P, BMC Res Notes 2017
Lopez-Rincon A, Sci Rep 2020

Results – *Patients*

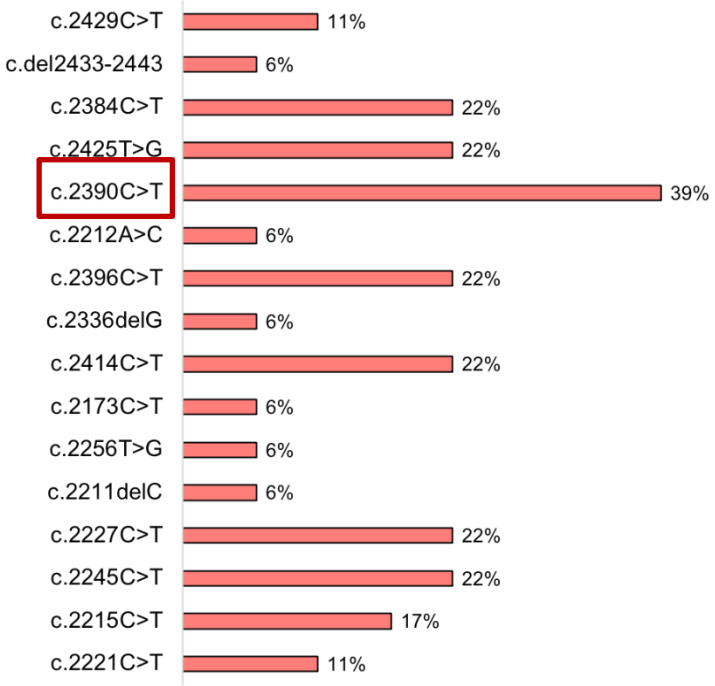
57 patients (1985-2025)

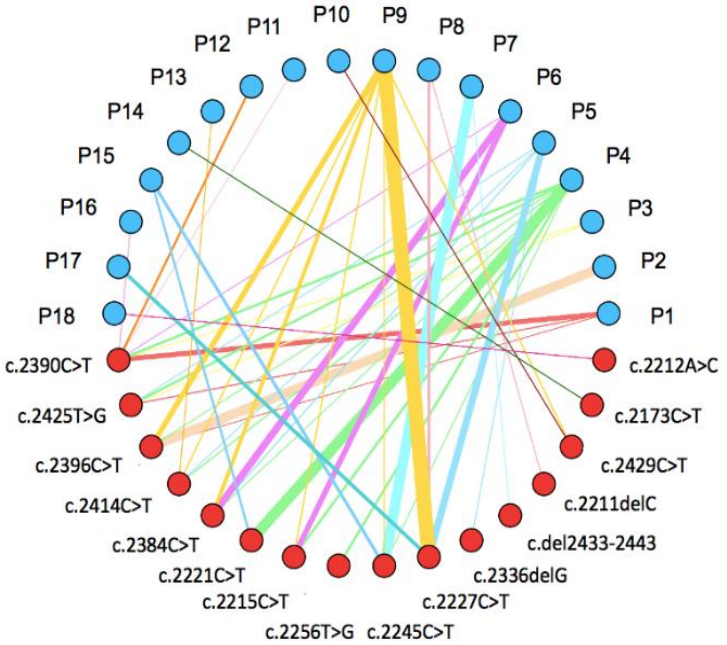
12 centers

Genova	14
Monza	12
Firenze	6
Padova	6
Bari	4
Perugia	4
Pisa	4
Brescia	2
Catania	1
Napoli	1
Palermo	1
Parma	1
Verona	1

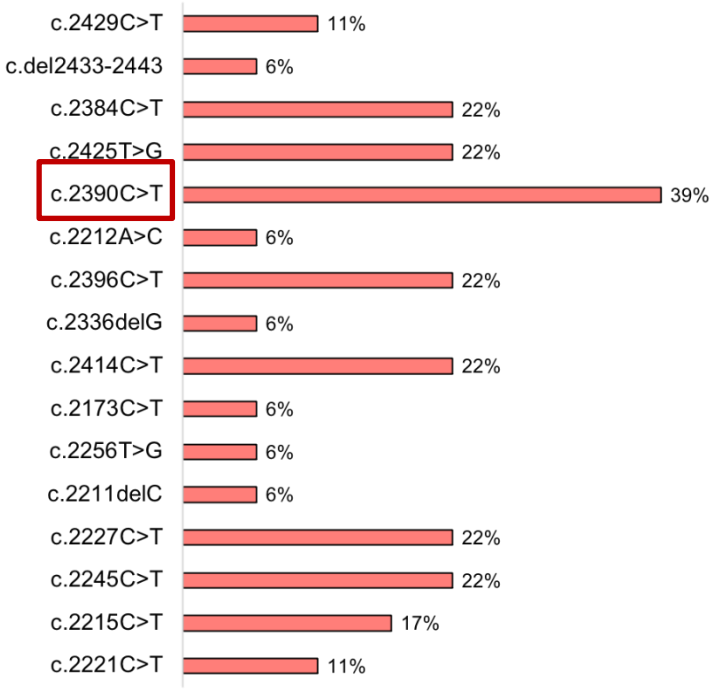
	All patients (n=57)	Patients with *CSF3R* mutations (n=18)	Patients without *CSF3R* mutations (n=39)	*p*-value[#]
Female sex, n (%)	29 (51)	8 (44)	21 (54)	0.708
Median age at diagnosis, months (IQR)	12 (3-65)	12 (3-80)	12 (3-60)	0.757
SCN mutated gene, n (%)				
ELANE	35 (61)	13 (72)	22 (57)	0.397
HAX1	2 (4)	2 (11)	0 (0)	NA
SRP54	3 (5)	1 (6)	2 (5)	0.569
Gene orphan	10 (18)	2 (11)	8 (21)	0.622
Others	7 (12)	0 (0)	7 (18)	NA
Median age at the beginning of G-CSF treatment, months (IQR)	12 (3-51)	12 (4-51)	12 (3-48)	0.472
Median age at the last follow-up, years (IQR)	14 (7-22)	20 (14-31)	11 (6-20)	**0.014**
Evolution to MDS/AML, n (%)	7 (12)	6 (33)	1 (3)	**0.004**
Median age at MDS/AML, years (IQR)	17 (8-19)	18 (11-20)	1 (1-1)	NA
HSCT, n (%)	14 (25)	6 (33)	8 (21)	0.475
Median age at HSCT, years (IQR)	3 (2-15)	15 (7-19)	3 (1-3)	**0.022**
Deaths at last follow-up, n (%)	6 (11)	3 (17)	3 (8)	0.574
Causes of death, n (%)				
MDS/AML	1 (2)	1 (6)	0 (0)	NA
Infection	1 (2)	0 (0)	1 (3)	NA
TRM	3 (5)	2 (11)	1 (3)	0.481
Others	1 (2)	0 (0)	1 (3)	NA

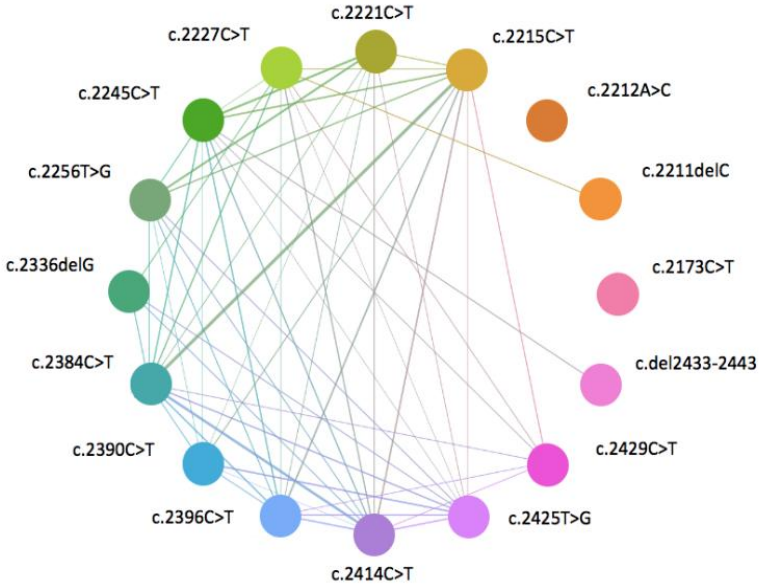
Results – *CSF3R clones*





Results – *CSF3R clones*

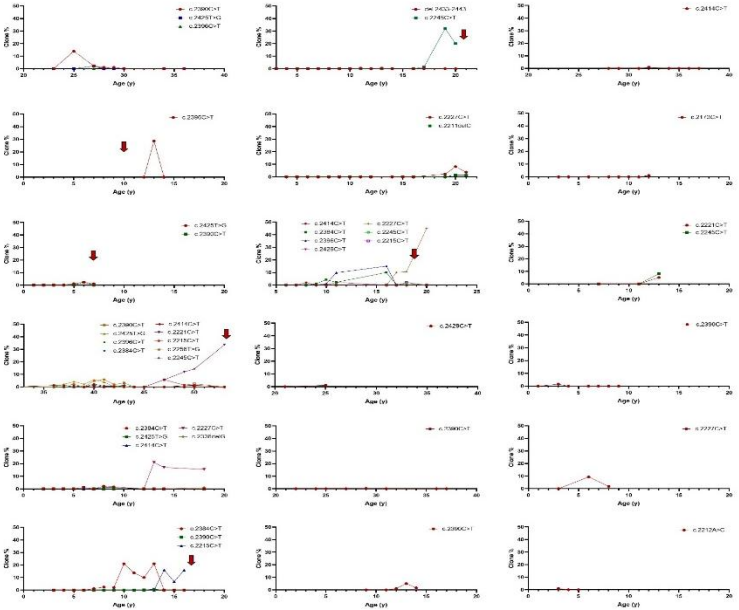


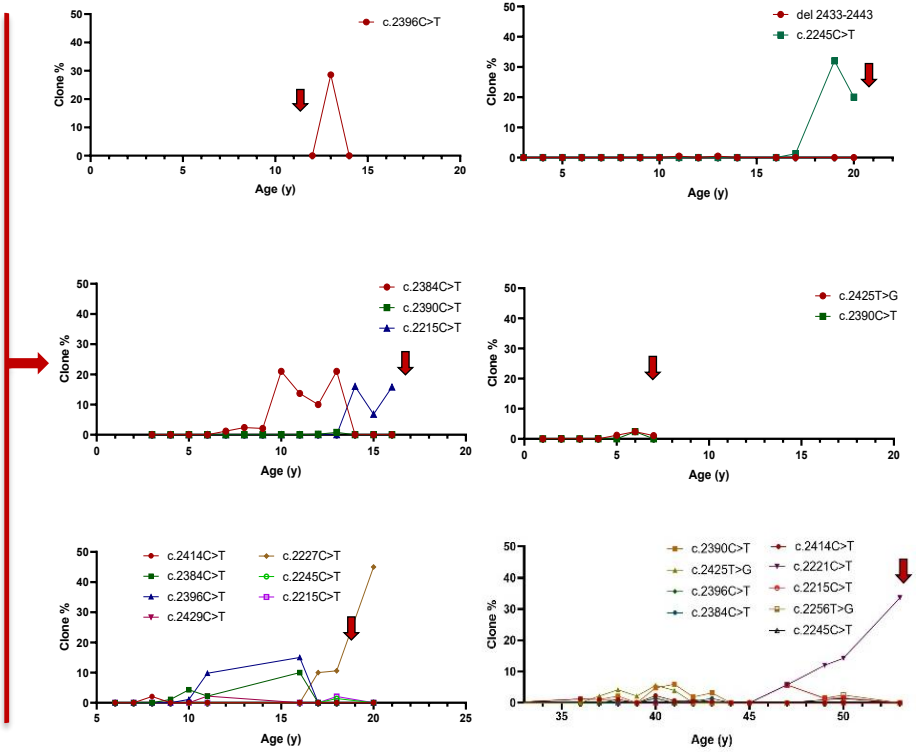


Results – *Clinical implications of CSF3R clones*

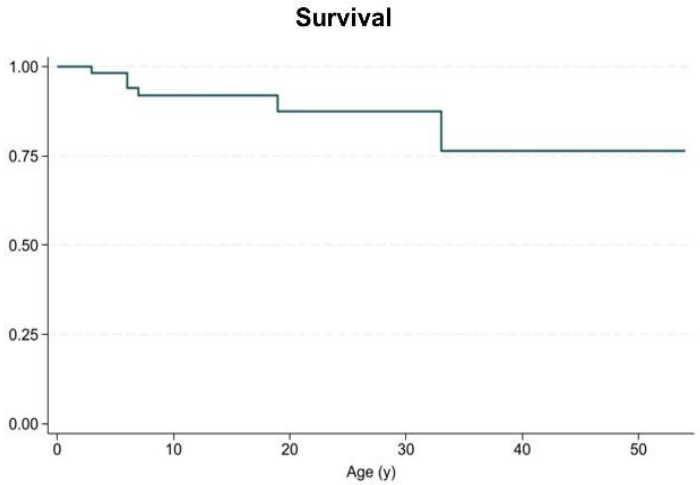
	Patients with *CSF3R* mutations (n=18)	MDS/AML evolution (n=6)	No MDS/AML evolution (n=12)	*p*-value[#]
Median age at the first *CSF3R* clone detection, months (IQR)	142 (72-277)	117 (89-158)	148 (67-294)	0.928
Median number of clones per patient (IQR)	2 (1-3)	3 (2-6)	1 (1-2)	0.061
Patients with >1 clones, n (%)	9 (50)	5 (83)	4 (33)	0.131
CSF3R clone, n (%)				
c.2245C>T°	4 (22)	3 (50)	1 (8)	0.083
c.2227C>T°	4 (22)	1 (17)	3 (25)	1.000
c.2215C>T°	3 (17)	3 (50)	0 (0)	**0.025**
c.2221C>T°	2 (11)	1 (17)	1 (8)	1.000
c.2211delC°	1 (6)	0 (0)	1 (8)	1.000
c.2256T>G°	1 (6)	1 (17)	0 (0)	0.333
c.2173C>T°	1 (6)	0 (0)	1 (8)	1.000
c.2414C>T°°	4 (22)	2 (33)	2 (17)	0.569
c.2396C>T°°	4 (22)	3 (50)	1 (8)	0.083
c.2336delG°°	1 (6)	0 (0)	1 (8)	1.000
c.2212A>C°°	1 (6)	0 (0)	1 (8)	1.000
c.2390C>T	7 (39)	3 (50)	4 (33)	0.627
c.2425T>G	4 (22)	2 (33)	2 (17)	0.569
c.2384C>T	4 (22)	3 (50)	1 (8)	0.083
c.2429C>T	2 (11)	1 (17)	1 (8)	1.000
c.del2433-2443	1 (6)	1 (17)	0 (0)	0.333
Median value of maximum clone size per patient (IQR)	8.4 (1.2-21)	30.3 (22.9-33.2)	3.3 (1.1-8.9)	**0.009**

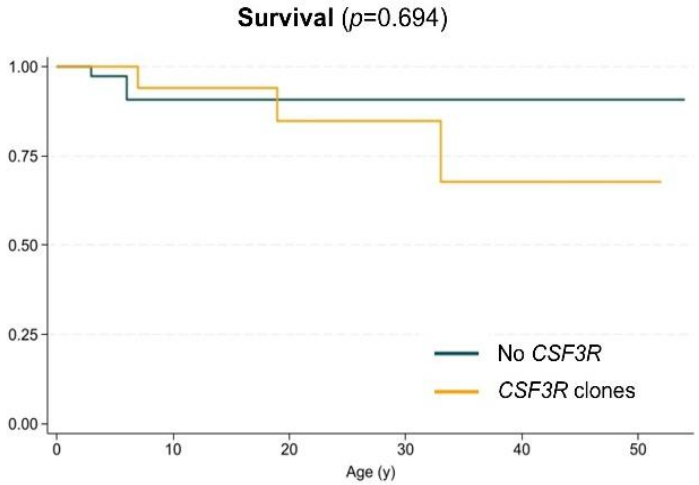
Results – *Clone dynamics*



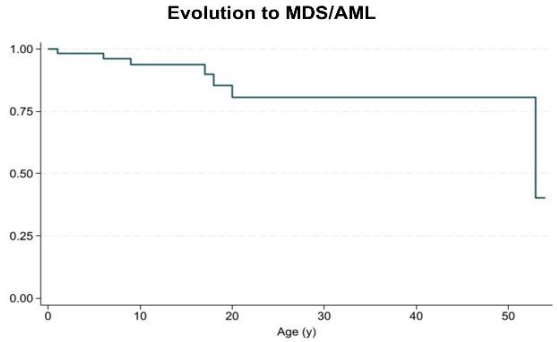


Results – *Survival*





Results – *Evolution to MDS/AML*



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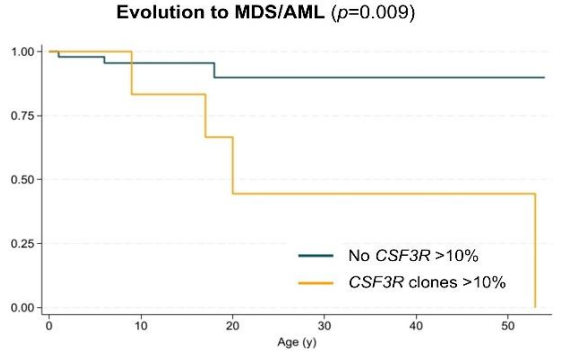

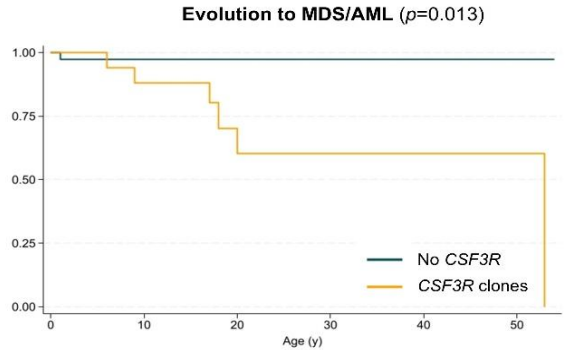

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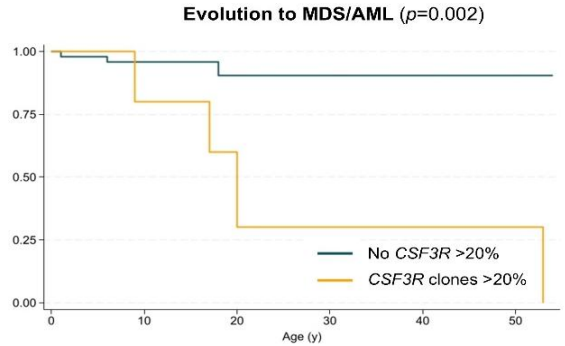

Conclusions & discussion

- MDS/AML trasformation in SCN patients is significantly associated with large *CSF3R* clones
- **Longitudinal monitoring** to detect *CSF3R* clones and clonal expansion → potential biomarkers of transformation
- **Registry-based** follow-up
- Ongoing evaluation of **additional factors** contributing to leukemic evolution (somatic mutations, type of *ELANE* mutation, G-CSF treatment duration)

Acknowledgements

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