POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

SINDROMI MIELODISPLASTICHE
Biologia e prognosi

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Disclosures of LUCA MALCOVATTI

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NA	NA	NA	NA	NA	NA	NA	NA

Congress at a glance

1. PLENARY SESSION

2. ORAL SESSIONS:

503. Clonal Hematopoiesis, Aging and Inflammation

506. Bone Marrow Microenvironment

636. Myelodysplastic Syndromes - Basic and Translational

637. Myelodysplastic Syndromes - Clinical and Epidemiological

Tips & trends

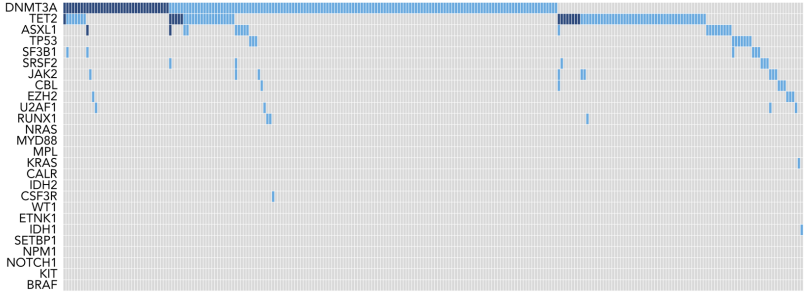
- **Preclinical states and early clonal dynamics (early diagnosis and therapeutic intervention).**
- **Extra-clonal variables (BM microenvironment, germline predisposition).**
- **Clinical implications of mutation profiles.**
- **Pre-clinical investigation of actionable genetic defects.**

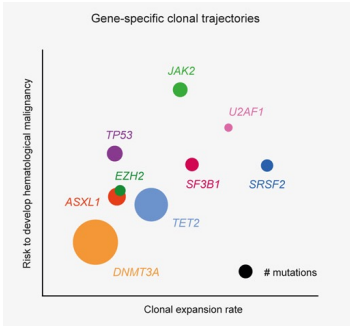
503. Clonal Hematopoiesis, Aging and Inflammation

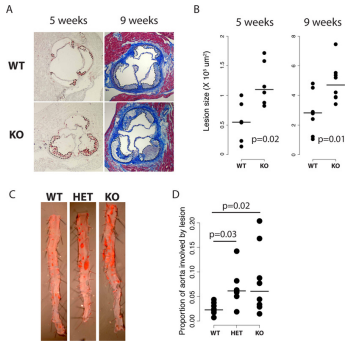
Mechanisms and Therapeutic Strategies to Reverse *TET2* Mutant Clonal Hematopoiesis and the Risk of MDS, AML, and Atherosclerotic Cardiovascular Disease

Nicole Prutsch, Amélie Vromman, Brittaney Leeper, Mengyu Chen, Shuning He, Siyang Ren, Christopher J. Walker, Mark W. Zimmerman, Mariana Janini Gomes, Eduardo J. Folco, Philipp J. Rauch, Prafulla C. Gokhale, Brian J. Abraham, Donna S. Neuberg, Benjamin L. Ebert, Peter Libby, A. Thomas Look

Background





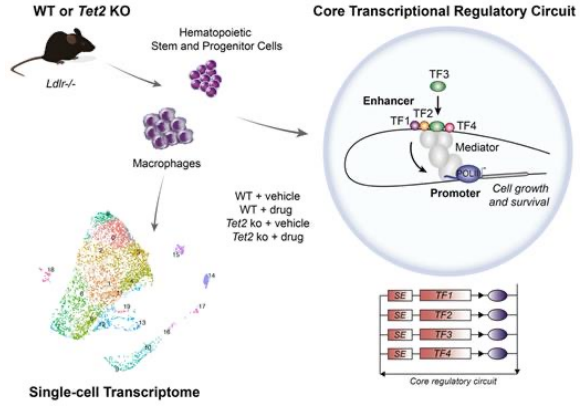


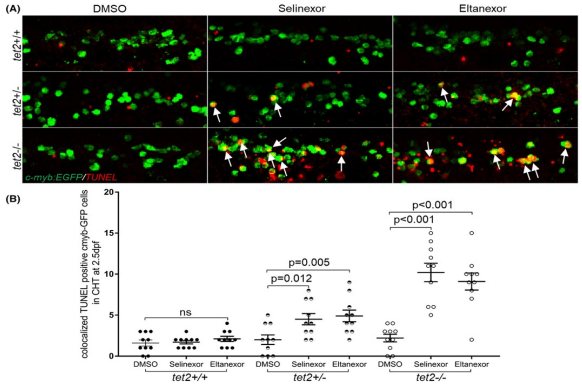
NEJM 2017; Blood. 2020; Cancer Cell. 2023

Rationale and aim of the study

- Administration of drugs that selectively suppress the growth of mutant CHIP clones in the bone marrow might reduce the risk of
  i) progression to MDS or hematologic malignancy,
  ii) atherosclerotic cardiovascular disease.

- This study focused on identifying drugs that reverse the inflammatory and atherosclerotic properties of *TET2*-mutant macrophages.





Results

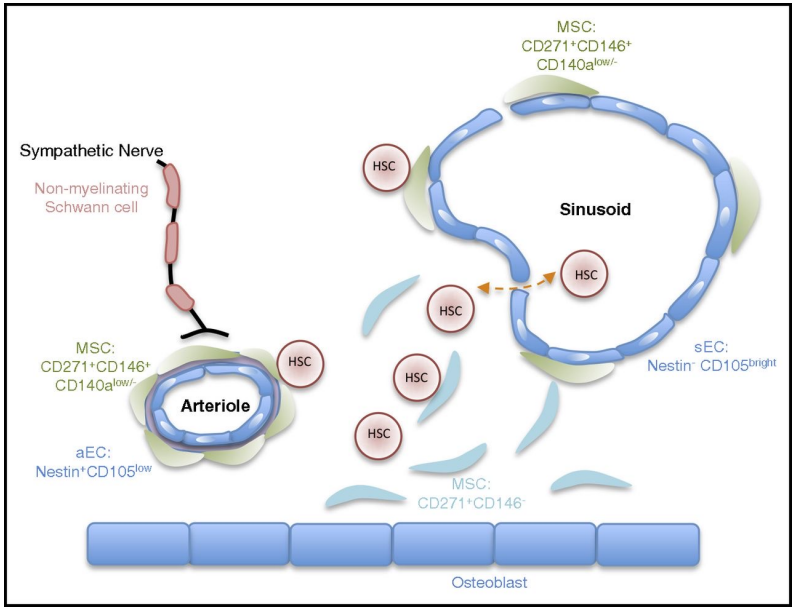
- Eltanexor selectively reduces Tet2-mutant circulating monocytes while having no effect on WBC counts.
- Single-cell CITE-seq analysis showed that eltanexor selectively reduces the percentage of Tet2+/- HSPCs and of pro-inflammatory macrophages in the arterial wall, along with a decrease in IL-1β expression.
- The investigation also revealed that binding of ATF3 (negative regulator of the macrophage inflammatory response) with IL-1β was significantly diminished in Tet2-mutant macrophages. Remarkably, **treatment with eltanexor restored the binding of ATF3 to IL1β, providing a mechanism of the anti-inflammatory effect of eltanexor.**

506. Bone Marrow Microenvironment

Chronic TNF in the Aging Microenvironment Exacerbates *TET2*-loss-of-Function Myeloid Expansion

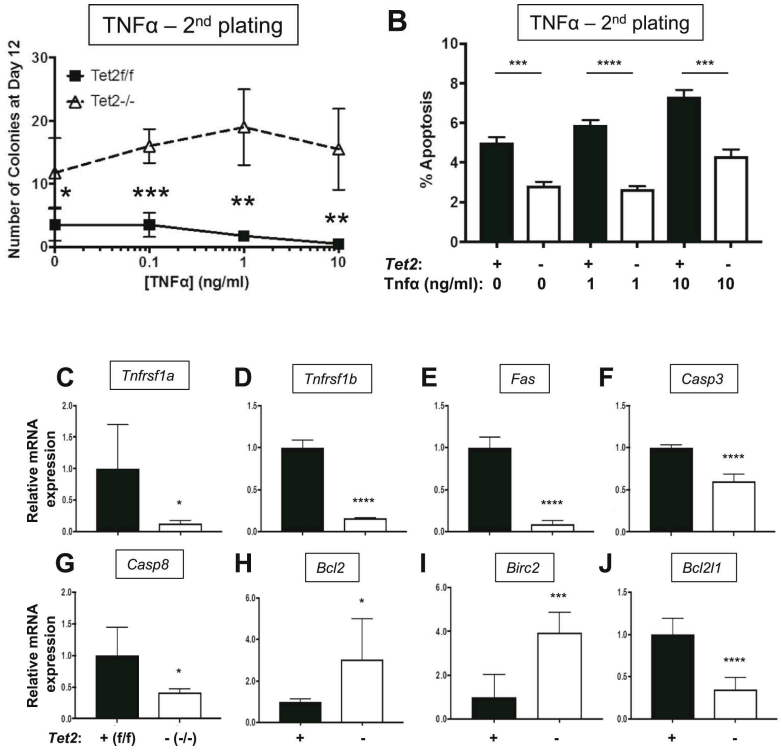
Candice Quin, Erica DeJong, Amy J. M. McNaughton, Marco M. Buttigieg, Salman Basrai, Sagi Abelson, Margaret Larche, Michael J. Rauh, Dawn ME Bowdish

Background



Rationale and aim of the study

- Despite its role in unhealthy aging, the extrinsic mechanisms driving *TET2*-mutant CHIP clonal expansion remain unclear.
- Working hypothesis: age-related increases in TNF may provide an advantage to HSC and progeny with *TET2*-mutations in vivo.



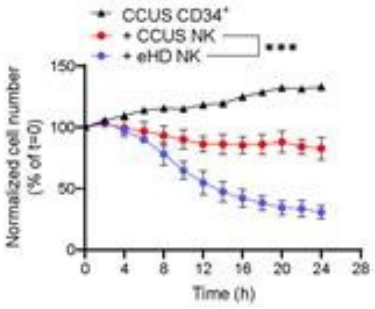
Results

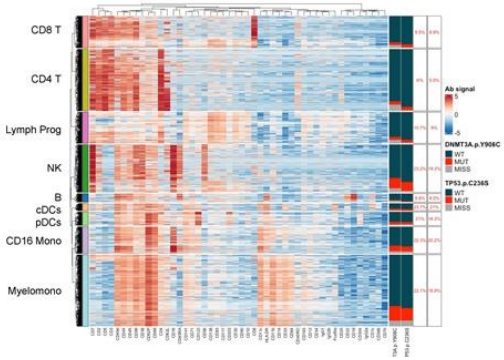
- Age-associated increase in TNF significantly increased the proportion of HSC in old recipient mice, with myeloid lineage skewing and expansion of Tet2-/- monocytes and neutrophils. This aberrant myelomonocytic advantage was mitigated in old TNF -/- recipient mice, suggesting that TNF signalling in the BM is essential for Tet2-mutant myeloid expansion.
- Age-associated TNF predisposed Tet2-/- HSC to the development of high inflammatory monocytes, further exacerbating an inflammatory environment in favor of Tet2-mutant expansion.
- Preliminary in vivo evidence suggests that anti-TNF therapy (adalimumab) may induce reduction in CHIP clone size between 3 and 6 months.

506. Bone Marrow Microenvironment

Mutant Natural Killer Cell Dysfunction Enables the Immune Escape of Premalignant MDS Cell Clones

Irene Ganan-Gomez, Bijender Kumar, Juan Jose Rodriguez Sevilla, Feiyang Ma, Yi June Kim, Kelly S. Chien, Kate Nelson, Hui Yang, Roselyn Tan, Zongrui Li, Tomoyuki Tanaka, Hidetaka Uryu, Rashmi Kanagal-Shamanna, Sanam Loghavi, Gheath Alatrash, Rafael Bejar, Katayoun Rezvani, Koichi Takahashi, Guillermo Garcia-Manero, May Daher, MD, Simona Colla





Results

- NK cells from CCUS had a significantly (P<0.0001) impaired cytolytic capacity against leukemic cells, and failed to kill both heterotypic and isotypic CCUS CD34 + cells ex vivo.
- Joint targeted single-cell DNA sequencing and immunophenotypic analyses of MNCs from CCUS with *DNMT3A* or *TET2* mutations revealed that NK cells were enriched in aberrant clones and had mutational burdens similar to those of myelomonocytes.
- Deletion of *DNMT3A* or *TET2* by CRISPR/Cas9 in cord blood-derived NK cells showed a significant (P<0.0001) progressive loss of cytolytic capacity with tumor re-challenging in knock-out NK cells, which demonstrated that LOF mutations in those genes are a direct cause of NK cell dysfunction.

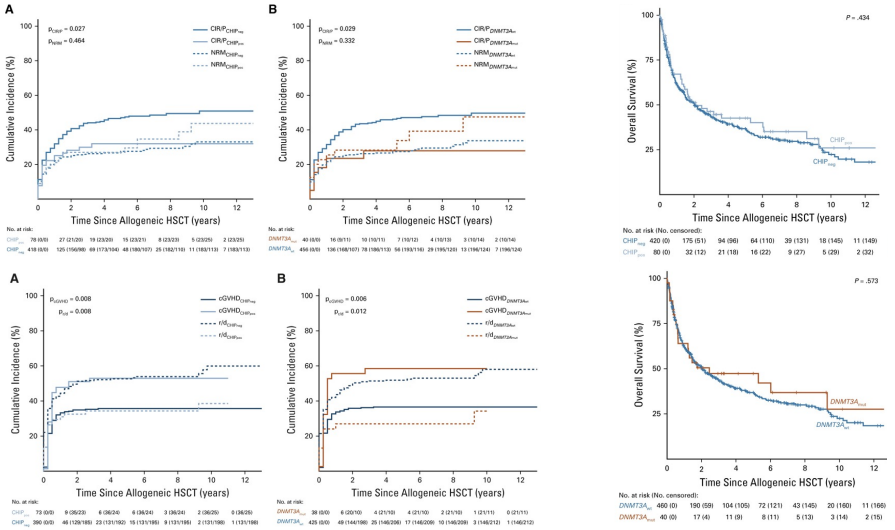
503. Clonal Hematopoiesis, Aging and Inflammation

Clonal Hematopoiesis Is Common in Unrelated Stem Cell Donors but Has No Impact on Patient Outcome after Hematopoietic Stem Cell Transplantation

Johannes Schetelig, Frederik Damm, Ulf - Peter Günther, Henning Baldauf, Carina Rave, Linda Koster, Gerhard Schöfl, Anja Klussmeier, Kamal Menghrajani, Kelly L. Bolton, Elke Rücker-Braun, Falk Heidenreich, Marie Münn, Markus Fuhrmann, Ilaria Visco, Mareike Frick, Raphael Hablesreiter, Christopher Maximilian Arends, Liesbeth C. de Wreede, Olena Nesterenko, Matthias Stelljes, Gesine Bug, Thomas Schröder, Ivan Sergeevich Moiseev, Helene Schoemans, Christian Koenecke, Raphael Teipel, Malte von Bonin, Lars Bullinger, Martin Bornhäuser, Marcel R.M. van den Brink, Alexander H. Schmidt, Vinzenz Lange, Zinaida Peric, Olaf Penack

Background and rationale of the study

Term	Definition and significance
Genetic measurable MRD	MN-related genetic abnormality detectable after transplantation
CHIP	Non-MN–related somatic genetic abnormality detectable after transplantation
New clonally unrelated MN	MDS, MPN, MDS/MPN or AML with genetic features that are entirely different from the antecedent MN; considered to be a therapy-related myeloid neoplasm
Donor-derived CHIP	CH shown to be of donor hematopoietic cell origin, detected after HCT for AML (Figure 1I)
Donor-derived MN	MDS, MPN, MDS/MPN or AML shown to be of donor hematopoietic cell origin, developing after HCT



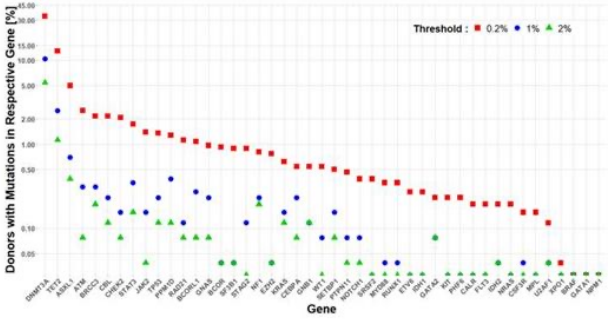
J Clin Oncol. 2019;37:375-385.

Methods

- Data from 2584 unrelated donor-recipient pairs.
- Median patient follow-up after alloHCT: 60 months.
- Median donor age: 46 years (39-61 years).
- Median patient age: 54 years (0-79 years).
- Indications for alloHCT: AML (44%), ALL (10%), MDS (10%), MPN (6%), B-cell lymphoma (6%), Multiple Myeloma (5%), CML 3%, inherited disorders (3%), CLL 2% and other (13%). Transplantations were performed between 2005 and 2018.
- In vivo or ex vivo T-cell depletion (TCD) in 81% of transplants, PTCY in 5% and no TCD in 14%

Results

Panel A. Rate of CH in Stem Cell Donors by Gene and Variant Allele Frequency



Panel B. Impact of Total Donor CH on Clinical Endpoints by Different Cutoffs

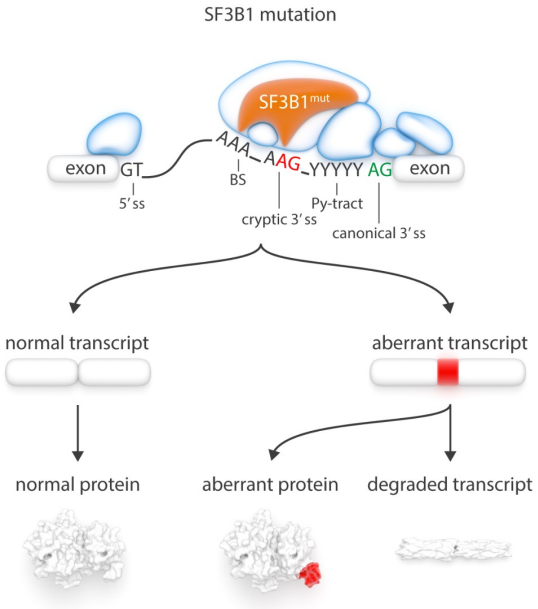
VAF	N_{neg}	N_{pos}	OS		EFS		Relapse		NRM		aGvHD		cGvHD	
			HR [95%-CI]	p	HR [95%-CI]	p	HR [95%-CI]	p	HR [95%-CI]	p	HR [95%-CI]	p	HR [95%-CI]	p
≥0.2% vs <0.2%	1140 (44.1%)	1444 (55.9%)	1.01 [0.90-1.12]	.92	1.02 [0.92-1.14]	.69	1.14 [0.97-1.33]	.11	0.93 [0.79-1.08]	.33	1.02 [0.88-1.18]	.79	0.99 [0.85-1.16]	.94
≥1% vs <1%	2170 (84%)	414 (16%)	1.16 [1.00-1.34]	.05	1.15 [0.99-1.33]	.07	1.12 [0.91-1.38]	.29	1.18 [0.96-1.44]	.12	1.11 [0.92-1.33]	.29	0.92 [0.75-1.14]	.47
≥2% vs <2%	2366 (84%)	218 (16%)	1.22 [1.01-1.48]	.04	1.27 [1.05-1.52]	.01	1.24 [0.95-1.62]	.12	1.30 [1.00-1.69]	.05	1.19 [0.94-1.52]	.14	0.84 [0.62–1.12]	.22
≥5% vs <5%	2514 (91.6%)	70 (8.4%)	1.04 [0.73–1.48]	.82	1.08 [0.77-1.51]	.67	0.96 [0.57-1.6]	.87	1.20 [0.76-1.88]	.44	1.24 [0.84-1.84]	.28	0.89 [0.56-1.43]	.64
≥5% vs <0.2%	1140 (94.2%)	70 (5.8%)	1.04 [0.73–1.49]	.81	1.09 [0.77–1.54]	.63	1.03 [0.61–1.74]	.91	1.14 [0.72–1.81]	.57	1.25 [0.83–1.87]	.28	0.89 [0.55–1.44]	.65

1. PLENARY SESSION

Synthetic Introns Identify the Novel RNA Splicing Factor GPATCH8 As Required for Mis-Splicing Induced By *SF3B1* Mutations

Salima Benbarche, Jose Maria Bello Pineda, Laura Baquero Galvis, Bo Liu, Jeetayu Biswas, Eric Wang, K. Ashley Lyttle, Alexander M. Lewis, Martina Sarchi, Sanjoy Mehta, Ralph Garippa, Juliana Ortiz-Pacheco, Zhuoning Li, Mara Monetti, Robert Stanley, Sergei Doulatov, Robert K. Bradley, Omar Abdel-Wahab

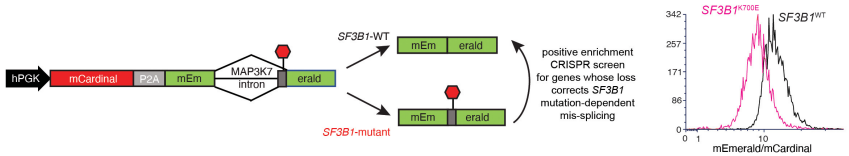
Background



Blood 2011; Blood 2015; Blood 2020; Blood 2022

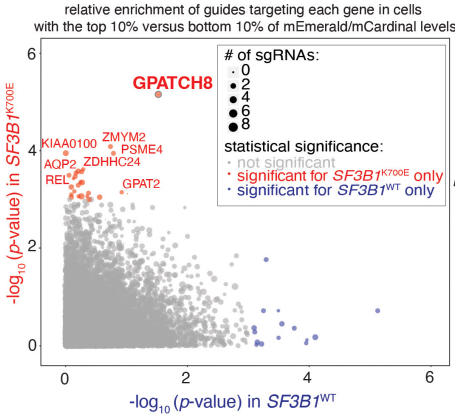
Methods

- Synthetic intronic splicing assays: synthetic intron uniquely recognized by mutant *SF3B1* that interrupts the coding sequence of the fluorescent protein mEmerald.
- This fluorescent splicing reporter was used to perform positive enrichment whole genome CRISPR screens to identify genes whose deletion corrects SF3B1 mutant aberrant splicing.

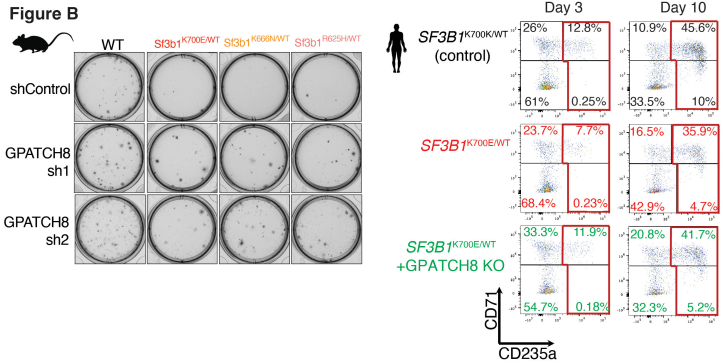


Results

- GPATCH8: domains characteristic of RNA splicing factors activating RNA helicases and potential role in 3' splice site recognition.



- Deletion of GPATCH8 corrects SF3B1 mutant mis-splicing.
- Silencing of Gpatch8 rescued colony formation from hematopoietic precursors (and was tolerated by normal hematopoietic precursors).
- GPATCH8 deletion rescued erythroid differentiation in SF3B1 K700E-edited adult CD34 + cells.



637. Myelodysplastic Syndromes - Clinical and Epidemiological

Molecular Taxonomy of Myelodysplastic Syndromes and Its Clinical Implications

Elsa Bernard, Robert Hasserjian, Peter L. Greenberg, Juan E Arango Ossa, Maria Creignou, Yasuhito Nannya, Heinz Tuechler, Juan S Medina-Martínez, Max F Levine, Martin Jädersten, Ulrich Germing, Guillermo Sanz, Arjan A. van de Loosdrecht, Olivier Kosmider, Matilde Yung Follo, Felicitas Thol, Lurdes Zamora, Ronald Feitosa Pinheiro, Andrea Pellagatti, Harold K Elias, Detlef Haase, Maria Sirenko, Christina Ganster, Lionel Ades, Magnus Tobiasson, Laura Palomo, Matteo Giovanni Della Porta, Pierre Fenaux, Monika Belickova, Michael R. Savona, Virginia M. Klimek, Fabio P. S. Santos, Jacqueline Boultwood, Ioannis Kotsianidis, Valeria Santini, Francesc Sole, Uwe Platzbecker, Michael Heuser, Peter Valent, Carlo Finelli, Maria Teresa Voso, Lee-Yung Shih, Michaela Fontenay, Joop H. Jansen, Jose Cervera, Norbert Gattermann, Benjamin L. Ebert, Rafael Bejar, Luca Malcovati, Mario Cazzola, Seishi Ogawa, Eva Hellstrom Lindberg, Elli Papaemmanuil

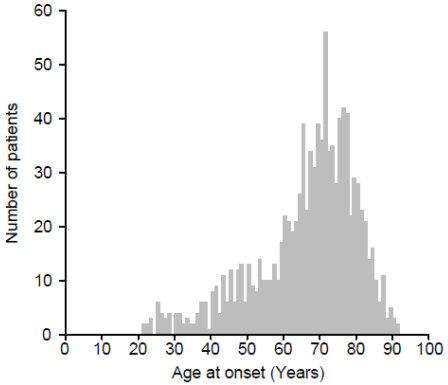
636. Myelodysplastic Syndromes - Basic and Translational

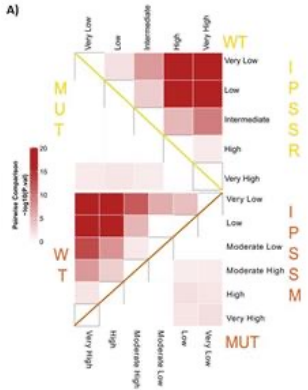
Outcome Prediction in *DDX41*-Mutant Myelodysplastic Syndromes Is Not Possible with General Disease Schemes and Requires a Dedicated Risk Scoring System

Carmelo Gurnari, Hideki Makishima, Arda Durmaz, Ryunosuke Saiki, Guilherme Mendes Sapinho, Alex Bataller, Lukasz P. Gondek, Yasuhito Nannya, Steve Best, Pramila Krishnamurthy, Hussein Awada, Enrico Attardi, Valeria Visconte, Maria Teresa Voso, Amy E. DeZern, Guillermo Garcia-Manero, Austin Kulasekararaj, Jaroslaw P. Maciejewski, Seishi Ogawa

Results

- Median age at MDS diagnosis: 69 years (IQR 61-76)
- Strong male predominance (4.4 M:F ratio).





- No survival difference between cases with germline alone vs germline plus somatic configuration.
- Significantly worse survival outcomes and faster leukemia evolution in cases carrying truncating and/or p.R525H mutations.