ELSEVIER

Blood 142 (2023) 4068–4070

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

503.CLONAL HEMATOPOIESIS, AGING AND INFLAMMATION

Sole *DNMT3A/TET2/ASXL1* Mutations Define a Distinct Clinical Trajectory for Patients with Clonal Hematopoiesis

Shyam Ajay Patel, MDPhD[1], *William K Gerber*[2], *Rena Zheng, MDPhD*[2], *Shrinkhala Khanna, MD*[2], *Lloyd Hutchinson*[2], *Jan Cerny, MDPhD*[2], *Brandon Dasilva, MD*[3], *Tian Y. Zhang, MD PhD*[4], *Salwa Khedr, MD*[2], *William Selove*[5], *Bruce Woda, MD*[2], *Gregory A Abel, MD MPH*[6], *Patricia Minehart Miron, PhD*[2], *Anne Higgins*[2], *Jonathan M. Gerber, MD*[2]

[1]Department of Medicine - Hematology/Oncology, UMass Chan Medical School, Worcester, MA
[2]UMass Chan Medical School, Worcester, MA
[3]Department of Medicine, Stanford University School of Medicine, Stanford, CA
[4]Division of Hematology, Department of Medicine, Stanford University School of Medicine, Stanford, CA
[5]UMass Memorial Medical Center, Whitinsville, MA
[6]Dana-Farber Cancer Institute, Boston, MA

Background: Clonal hematopoiesis of indeterminate potential (CHIP) is a clinically defined entity that is recognized by the 2022 International Consensus Classification and the 5 th Edition of the WHO. While the Clonal Hematopoiesis Risk Score (CHRS) incorporates 8 variables that underlie a prognostic framework for prediction of risk for progression to myeloid neoplasm (MN) (Weeks LD *et al., NEJM Evidence* 2023), there remains debate as to the role of mutations in epigenetic regulators, such as *DNMT3A, TET2* and *ASXL1* ("DTA"), with respect to clinical outcomes in the real-world setting. Although DTA mutations often occur early in myeloid pathogenesis, the persistence of these mutations as age-related clonal hematopoiesis (CH) might not significantly influence clinical course (Jongen-Lavrencic M *et al., NEJM* 2018). We have previously observed impaired clearance of DTA-mutant clones with hypomethylating agent or intensive chemotherapy for myelodysplastic neoplasms and acute myeloid leukemia (ASH abstract 4122; *Blood* (2022) 140 (Supplement 1): 9150-9151), and we now seek to understand the impact of sole DTA mutations in patients with CH.
Methods: We studied a pre-selected group of patients who had an indication for undergoing bone marrow evaluation. Such indications included cytopenia(s), elevated blood cell count(s), staging/workup for lymphoma, and radiographic marrow abnormalities. Patients with CH were identified via concurrent morphologic, cytogenetic, and molecular diagnostics of bone marrow aspirates reviewed by UMass and Stanford Hematopathology from 2013 to 2023. CH was defined as presence of a somatic mutation with variant allele frequency (VAF) $\geq$ 2% on molecular diagnostics or non-myelodysplastic syndrome (MDS)-defining clonal cytogenetic aberration in a patient without morphologic evidence of MN. A total of 79 patients with CH were identified, then segregated based on presence or absence of sole DTA mutations.
Results: We assessed the clinical trajectory of patients with CH who did not exclusively have DTA mutations ("non-sole DTA;" $n = 58$) **(Panel A)** compared to patients with CH who had DTA mutations alone without any other concurrent mutations ("sole DTA;" $n = 21$) **(Panel B)**. The median age at detection of CH for sole DTA vs. non-sole DTA was 71.0 $\pm$ 2.11 years vs. 71.5 $\pm$ 1.45 years, respectively ($p = 0.454$). Median number of mutations for sole DTA vs. non-sole DTA patients was 1.24 $\pm$ 1.2 vs. 2.24 $\pm$ 0.18, respectively ($p < 0.0001$). Median follow-up for all patients was 450 days, and the median overall survival was not reached for either group. For non-sole DTA patients, 44 of 58 patients (76%) did not progress, while 14 of 58 patients (24%) progressed to frank MN at the time of analysis. Types of frank MN in the 14 progressors included MDS (50%), MDS/myeloproliferative neoplasm (MPN) overlap (28.6%), AML (14.3%), and MPN (7.1%). For sole DTA patients, 0 of 21 patients (0%) progressed. Regarding distribution of VAFs for sole DTA patients vs. non-sole DTA patients, mean VAF was 13.5% $\pm$ 1.91% vs. 31.6% $\pm$ 2.18%, respectively ($p < 0.001$). For patients with both DTA mutations plus additional mutations, mean VAF for non-progressors vs. progressors was 30.4% $\pm$1.47% vs. 38.6% $\pm$ 2.97%, respectively ($p = 0.206$). For patients without any DTA mutations but with other somatic mutations, mean VAF for non-progressors vs. progressors was 29.7% $\pm$1.67% vs. 35.2% $\pm$ 2.26%, respectively ($p = 0.160$).
Conclusion: In this study of pre-selected patients with CH, DTA mutations alone were insufficient for progression to frank MN. Progressors included patients with either (1) DTA mutations plus concurrent mutations, or (2) patients without DTA mutations but presence of mutations in other gene clusters. The clinical trajectory of patients with CH in our study differs from that of patients from large consortia possibly because our patients presented with an indication for testing, reflecting real-world data.

A limitation of our analysis is the variability in time to recognition and diagnosis of CH, which reflects the high heterogeneity of these patients. Still, our data suggest the need for large-scale studies in the real-world setting to better prognosticate the relevance of DTA mutations for this patient population.

Disclosures Patel: *UMass Center for Clinical and Translational Science (CCTS) Pilot Project Program grant (NIH / NCATS Grant UL1TR001453:* Research Funding; *Bristol Myers Squibb:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. **Cerny:** *ICON- Allovir:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *ICON-Prolacta:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Bristol Myers Squibb:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *MERIT CRO:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Actinium Pharmaceuticals:* Current holder of *stock options* in a privately-held company; *BlueBird Bio, Inc:* Current holder of *stock options* in a privately-held company; *Cellectar Sciences:* Current holder of *stock options* in a privately-held company; *Dynavax Technologies:* Current holder of *stock options* in a privately-held company; *Gamida Cell:* Current holder of *stock options* in a privately-held company; *Atyr Pharma:* Current holder of *stock options* in a privately-held company; *Novavax Inc:* Current holder of *stock options* in a privately-held company; *Ovid Therapeutics Inc:* Current holder of *stock options* in a privately-held company; *Sorreto Therapeutics:* Current holder of *stock options* in a privately-held company; *Veru Inc:* Current holder of *stock options* in a privately-held company; *Viridian Therapeutics:* Current holder of *stock options* in a privately-held company; *Vaxart Inc:* Current holder of *stock options* in a privately-held company; *2Seventy Bio Reg SHS:* Current holder of *stock options* in a privately-held company. **Zhang:** *Abbvie:* Consultancy; *Rigel:* Consultancy; *Servier:* Consultancy; *Bristol Myers Squibb:* Research Funding; *Stanford University:* Current Employment. **Gerber:** *Bristol Myers Squibb:* Research Funding; *Hutchmed:* Research Funding; *Stemline Therapeutics, Inc.:* Research Funding; *AbbVie:* Divested equity in a private or publicly-traded company in the past 24 months; *Novartis:* Honoraria, Research Funding.

https://doi.org/10.1182/blood-2023-182881

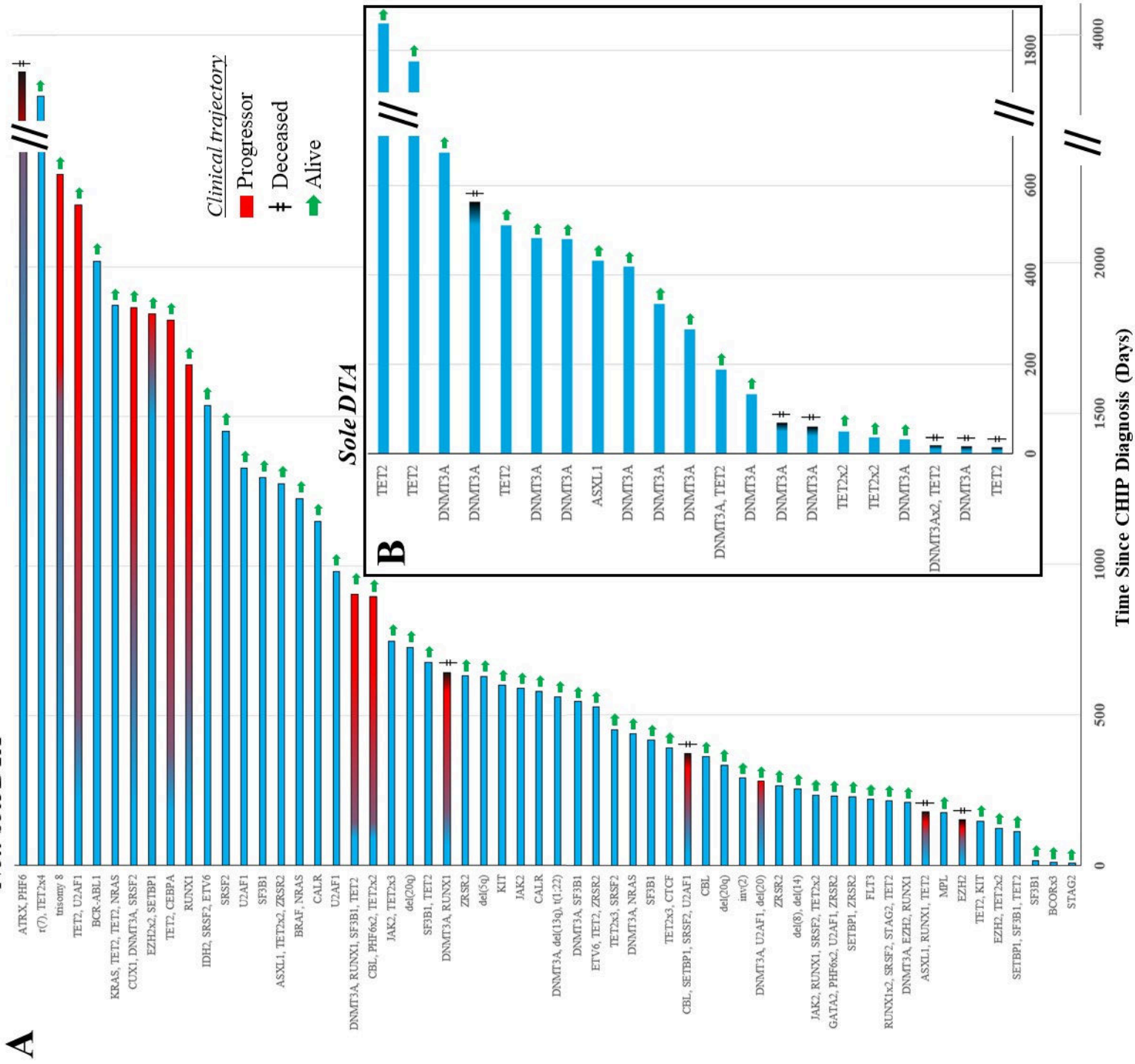

Figure 1