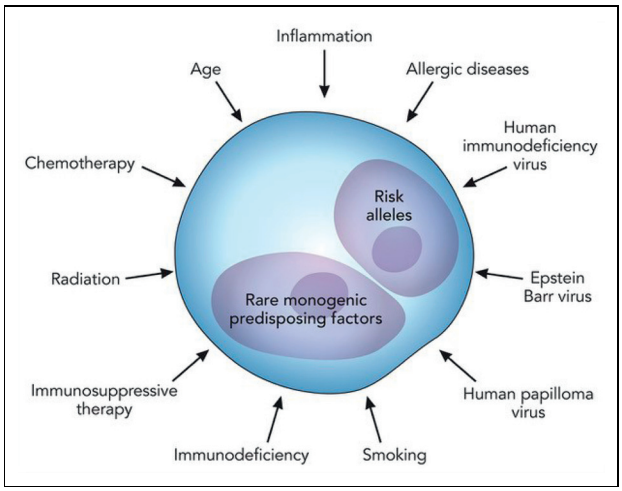

Risk factors for Hodgkin lymphoma, including established extrinsic risk factors with postulated genetic intrinsic risk factors. Professional illustration by Patrick Lane, ScEYEnce Studios.

(in *GATA3* and *PAX5*), highlighting the importance of undertaking a comprehensive analysis with whole genome sequencing to permit examination of the DNA outside of the coding regions. *GATA3* and *PAX5* were considered novel predisposing loci, whereas *KDR* and *KLHDC8B* had been described previously. Most remaining risk variants identified were unique to a single pedigree, and so constitute private, rare variants.

Given the spectrum and rarity of postulated HL risk variants and the probable polygenic manner in which most will confer a HL predisposition, we are currently unable to neatly categorize a genetic predisposition to HL in the same way we can for several forms of hereditary MDS and AML. This factor presents challenges for how we counsel, test, and manage patients and families with a suspected familial HL predisposition. Flerlage et al have suggested 44 HL risk variants that may now be further evaluated in functional and translational research studies. The publication of these findings also permits the interrogation of other HL cohorts for the presence of these postulated HL risk variants. There is potential for this work alongside other datasets and future research efforts, to permit design of a multifaceted risk score for HL predisposition or development. Flerlage et al state that the genomic landscape of familial HL remains incompletely characterized. This publication represents an important step toward understanding the familial clustering that may occur with this disease.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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LYMPHOID NEOPLASIA

Comment on Schavgoulidze et al, page 1308

Del(1p32): prime time in (ultra) high-risk myeloma

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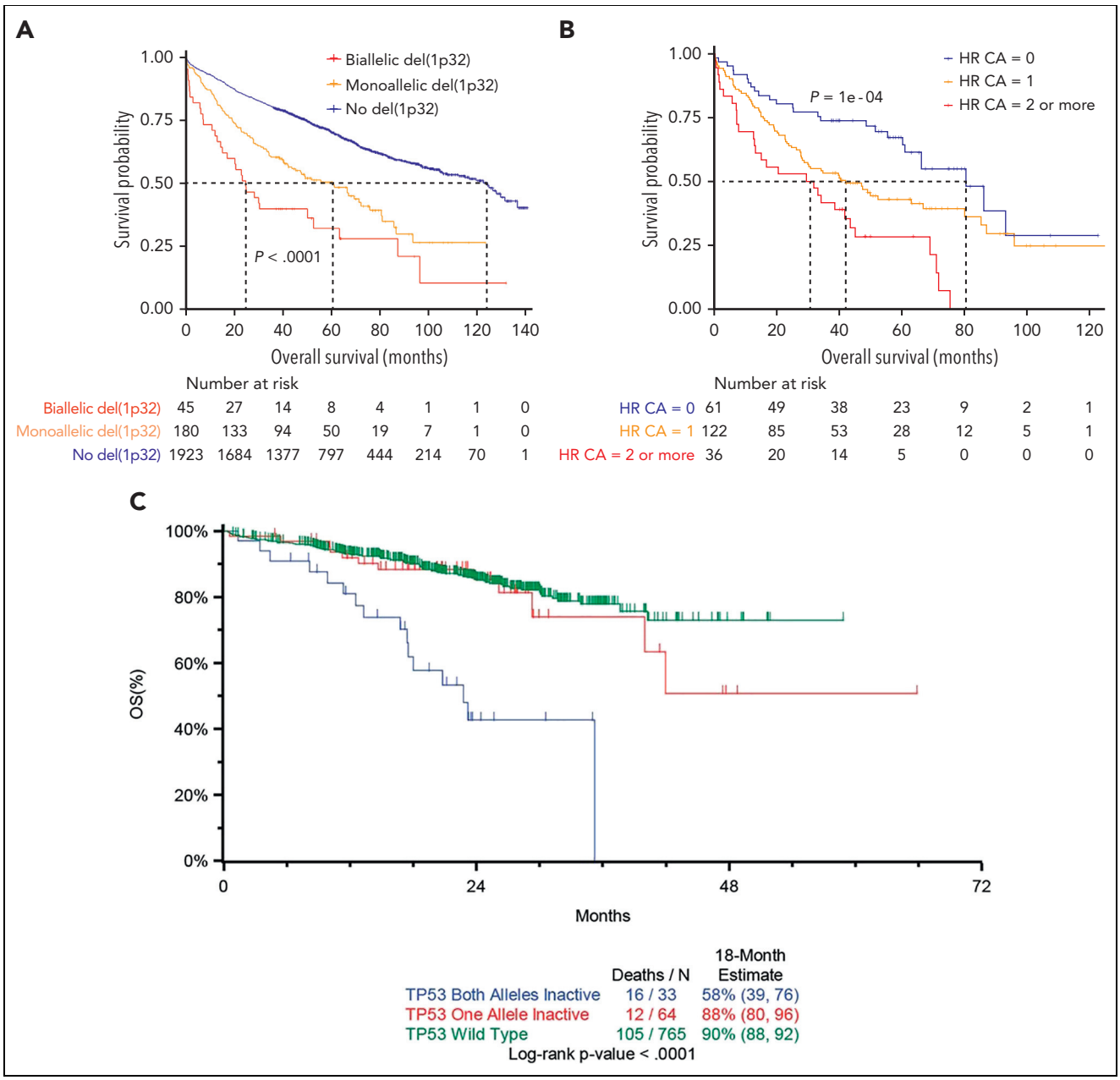
In this issue of *Blood*, Schavgoulidze et al validate the importance of the cytogenetic abnormality del(1p32) in risk stratification by analyzing a large cohort of patients with newly diagnosed multiple myeloma (NDMM). Importantly, the study also identifies an ultra high-risk group (UHR) with biallelic deletion, which demonstrates significantly adverse outcomes following current standard frontline treatment.[1]

The addition of cytogenetic criteria (del(17p) and/or t(4;14) and/or t(14;16)) as part of the revised International Staging System (R-ISS) represented a major advance towards improving risk stratification in patients with newly diagnosed myeloma.[2] Subsequently, the importance of additional cytogenetic and genomic abnormalities such as 1q gain/amplification and *TP53* mutation status has been highlighted in defining cohorts of patients with particularly poor outcomes following non–risk-adapted therapeutic strategies. A UHR population of double-hit patients was identified in a report from the Myeloma Genome Project, based on biallelic inactivation of *TP53* and amplification of *CKS1B* (1q21), which was associated with a median overall survival (OS) of only 21 months.[3]

Also, the deleterious impact of certain criteria in the R-ISS such as t(4;14) and/or t(14;16) appear to be abrogated by current standard-of-care triplet treatment regimens, which combine immunomodulatory drugs, proteasome inhibitors, and autologous stem cell transplant (ASCT), in eligible patients and maintenance strategies. Therefore, the criteria for risk stratification need ongoing reevaluation in light of new data pertaining to disease biology and treatment outcomes.

Significant progress in the availability of new therapeutic options over the past 2 decades has been associated with a marked improvement in progression-free survival and OS for the majority of patients with newly diagnosed myeloma.[4] Unfortunately, these non–risk-adapted empiric strategies have not been successful in a subgroup of patients, who continue to have an OS <5 years.

A consensus clinical definition for these high-risk (HR) groups is a median OS <5 years and <3 years for UHR patients.[5] The median OS of 25 months for patients with biallelic 1p32 deletion in the current study satisfies the criterion for inclusion in the UHR category (see figure panel A). It also highlights the importance of



(A) Kaplan-Meier overall survival curve of newly diagnosed multiple myeloma patients according to del(1p32) status. See Figure 2A in the article by Schavgoulidze et al that begins on page 1308. (B) Kaplan-Meier overall survival curve of newly diagnosed multiple myeloma patients with del(1p32) according to the association with other high-risk cytogenetic abnormalities, defined by the presence of del(17p), t(4;14), and/or gain(1q). See Figure 4 in the article by Schavgoulidze et al that begins on page 1308. (C) Kaplan-Meier overall survival curve by *TP53* biallelic, monoallelic, or wild-type status. Reproduced from Walker et al,[3] published under a CC BY 4.0 license (http://creativecommons.org/licenses/by/4.0/).

monoallelic deletion (median OS, 60 months) and the cytogenetic abnormality of del(1p32) (median OS, 49 months) in identifying HR NDMM patients. Notably, this finding is observed in a substantial proportion, 11%, of patients at diagnosis. These findings need to be considered in updated risk-stratification criteria, around which prospective risk-adapted clinical trials can be designed. The phase 2 Optimum/Muknine trial for UHR patients included del(1p) in the criteria for eligibility and showed a benefit for an intensified treatment approach using a quintuplet induction (daratumumab, bortezomib, lenalidomide, cyclophosphamide, and dexamethasone), augmented ASCT, and quadruplet (daratumumab, bortezomib, lenalidomide, and dexamethasone) consolidation strategy.[6]

This study also corroborates the negative prognostic impact of multiple HR cytogenetic abnormalities (see figure panel B), adding to the authors' previous work in this area,[7] and suggests that the biallelic deletion of 1p32 may have a similar prognostic impact to biallelic *TP53* mutations, a well-recognized marker of UHR myeloma, in which the median OS is 24 months (see figure panel C).[3] Another key message is the specification of the importance of the locus of del(1p), with only del(1p32) appearing to be useful in prognostication.

An additional important finding from the current analysis includes the equivalence of the different platforms (FISH/SNP arrays/NGS) used, which will help in discussions regarding standardization of methodology and cutoffs; this is essential if cytogenetic and genomic criteria are to be incorporated into risk-adapted treatment strategies outside of clinical trials.

However, it must be noted that this is a retrospective analysis of a large intergroup cohort of patients, with its attendant caveats, including missing data, and, therefore, corroboration of the impact of del(1p32) on outcomes from prospective clinical trial data sets is required, along with analysis of its impact on other known genomic negative prognostic markers, mainly *TP53* mutations and 1q amplification.

It is anticipated that the results of this study will be pivotal in the effort to accurately define HR and UHR myeloma patients at diagnosis and disease progression, adding to data provided by the mSMART, EMC92/SKY92, UAMS GEP70, and CoMMpass criteria.[8] This information will aid the design of prospective risk-adapted clinical trials to eventually improve outcomes for patients in this area of high unmet need.

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MYELOID NEOPLASIA

Comment on Schnegg-Kaufmann et al, page 1316

The kids are alright: MDS clones mature

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In this issue of *Blood*, Schnegg-Kaufmann et al[1] demonstrate that highly mutated hematopoietic stem and progenitor cells contribute to normal hematopoiesis in myelodysplastic neoplasms (MDS) and chronic myelomonocytic leukemia (CMML) with or without azacytidine (AZA) treatment.

Myeloid malignancies represent a highly diverse set of diseases, including myeloproliferative neoplasms, MDS, and acute myeloid leukemia (AML). Notably, many genetic mutations are shared across different myeloid malignancies (*TET2, TP53*), whereas others are unique to a specific type (*NPM1*[c]). These different mutations ultimately promote abnormal self-renewal of hematopoietic stem and progenitor cells (HSPCs) and/or block their maturation into normal myeloid cells such as granulocytes or monocytes. This block in maturation ultimately results in a major morbidity in MDS/CMML cytopenias, which make patients transfusion dependent.

Importantly, concepts from 1 disease are frequently applied to other myeloid malignancies. For example, minimal residual disease (MRD) measurement in chronic myeloid leukemia is standard of care,[2] and a similar concept for risk stratification is emerging in AML.[3] The fundamental paradigm to emerge from