Check for updates

Received: 23 May 2022 | Revised: 28 July 2022 | Accepted: 19 September 2022

DOI: 10.1002/cncr.34535

CONSENSUS STATEMENT

TP53-altered acute myeloid leukemia and myelodysplastic syndrome with excess blasts should be approached as a single entity

Rory M. Shallis MD[1] | Naval G. Daver MD[2] | Jessica K. Altman MD[3] | Robert P. Hasserjian MD[4] | Hagop M. Kantarjian MD[2] | Uwe Platzbecker MD[5] | Valeria Santini MD[6] | Andrew H. Wei MBBS, PhD, FRACP, FRCPA[7] | David A. Sallman MD[8] | Amer M. Zeidan MBBS, MHS[1]

[1]Section of Hematology, Department of Internal Medicine, Yale School of Medicine, Yale University, New Haven, Connecticut, USA

[2]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

[3]Division of Hematology and Oncology, Robert H. Lurie Comprehensive Cancer, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[4]Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

[5]Department of Hematology and Cellular Therapy, Medical Clinic and Policlinic I, Leipzig University Hospital, Leipzig, Germany

[6]MDS Unit, AOU Careggi, University of Florence, Florence, Italy

[7]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, Walter and Eliza Hall Institute of Medical Research and University of Melbourne, Melbourne, Victoria, Australia

[8]Department of Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA

Correspondence
Amer M. Zeidan, Section of Hematology, Department of Internal Medicine, Yale School of Medicine, Yale University, 333 Cedar St, PO Box 208028, New Haven, CT 06520-8028, USA.
Email: amer.zeidan@yale.edu

Funding information
National Institutes of Health, Grant/Award Number: P30 CA016672

Abstract

TP53-altered myelodysplastic syndrome with excess blasts and *TP53*-altered acute myeloid leukemia should be considered under one unifying classification term for their study in clinical trials. Ultimately, such a unification would simplify the screening processes for clinical trials and allow a focus on treating the patient for a genetically defined disorder rather than one based on an arbitrary blast threshold.

KEYWORDS
acute myeloid leukemia (AML), cutoff, excess blasts, myelodysplastic syndrome (MDS), p53, *TP53*

INTRODUCTION

There is increasing recognition that genetic and molecular characteristics are blurring the clinical boundaries traditionally dividing myelodysplastic syndrome with excess blasts-2 (MDS-EB2; 10%–19%) from acute myeloid leukemia (AML).[1–3] The nominal distinction between MDS-EB2 and AML is neither functionally impactful nor therapeutically validated, and it is subject to significant interobserver variability. This separation of a biologically defined population into two distinct subsets may also preclude patient candidacy for clinical trials and limit access to novel, effective drugs available for only MDS-EB2 or AML. Approximately 10%–20% of AML/myelodysplastic syndrome with excess blasts (MDS-EB) cases harbor a pathogenic *TP53* variant, and they represent a biological subset of disease with

The first two authors contributed equally to this article.

The last two authors contributed equally to this article.

 © 2022 American Cancer Society.

critical implications, regardless of the blast percentage, among all MDS-EB cases (i.e., with 5%–19% blasts).[4–7] In this article, we provide evidence and advocate for the unification of *TP53*-altered AML/MDS-EB as a single hematopathologic and clinical entity for disease classification and study in future clinical trials.

CONTRIVED BLAST ENUMERATION CONSTRAINTS

In 2001, the World Health Organization (WHO) eliminated the previously accepted French–American–British myelodysplastic syndrome (MDS) subcategory of refractory anemia with excess blasts in transformation (RAEB-t), which included patients with bone marrow blast percentages of 20%–29%, on the basis of similar outcomes for patients with RAEB-t and patients with AML with ≥30% blasts.[8,9] This change lowered the blast percentage threshold for defining AML to a new numerical cutoff of 20% and eliminated the entity RAEB-t.[10] In clinical practice, sampling inconsistency and interobserver variability between hematopathologists limit the precision of assigned blast percentages used to define patients as having either MDS-EB or AML.[11–13] Up to 20% of patients with MDS-EB have been reclassified as having AML upon tertiary center hematopathologic review, whereas the converse reclassification is rare.[12] Although providers may clinically elect to treat a patient with MDS-EB bordering on AML (e.g., 15%–19% blasts) with AML-directed therapy because of the accepted variance in blast enumeration, such patients are excluded from AML clinical trials requiring a bone marrow blast percentage of ≥20% as part of protocol-defined inclusion criteria, and thus patients are excluded from accessing important treatment options. Furthermore, there are frequent instances in which drugs, including targeted therapies, that are approved to treat AML are requested for treating patients with 15%–19% blasts but are denied coverage by insurance carriers because the patient does "not have AML." This issue is further accentuated by the recent approvals by the US Food and Drug Administration of nine new drugs for AML versus only two for MDS in the last 5 years. In fact, several of the drugs approved for AML (e.g., IDH1/2 inhibitors) have shown similarly promising clinical activity in single-arm studies/cohorts of MDS-EB.[14,15]

MOLECULAR UNIFORMITY OF *TP53*-ALTERED AML/MDS-EB

TP53-altered MDS-EB and AML have virtually indistinguishable biology. Although MDS/secondary AML–associated mutations co-occur with *TP53*-altered disease, including those in *DNMT3A*, *TET2*, *ASXL1*, *RUNX1*, and *SRSF2*, approximately 50%–70% of patients with *TP53*-altered MDS-EB and AML will not harbor any other common myeloid mutations.[6,16–20] These two currently separately defined subcategories of disease also have a paucity of driver mutations involving *NPM1* and *FLT3*.[6] In contrast, cytogenetic abnormalities are a hallmark of *TP53*-altered AML/MDS-EB. Specifically, complex/monosomal karyotypes are observed in 80%–90% of patients with either entity and often include aberrations of chromosomes 5, 7, and 17.[6,16,18] These cytogenetic abnormalities often raise an initial suspicion for *TP53*-altered disease, as a high proportion of MDS-EB or AML cases with a complex or monosomal karyotype will be *TP53*-altered[20–22] (Table 1).

UNIFORMLY POOR OUTCOMES IN *TP53*-ALTERED AML/MDS-EB

Perhaps the most important basis for establishing functional equivalence between *TP53*-altered MDS-EB and *TP53*-altered AML is the uniformly poor clinical outcome for patients affected by either. Patients with *TP53*-altered AML/MDS-EB have a median overall survival (OS) of 5–9 months, with only 5%–10% enjoying long-term survival, regardless of the therapy used (intensive induction, hypomethylating agent [HMA] monotherapy, or HMA with venetoclax).[18,23,24] Even with allogeneic hematopoietic stem cell transplantation (allo-HSCT), the expected survival is less than 12 months.[23,25,26] For example, in an analysis of 83 patients with *TP53*-mutated AML ($n = 45$) or MDS-EB ($n = 30$), the median OS was similar (6.7 vs. 5.5 months; $p = .10$).[24] In a large study of 230 patients with *TP53*-mutated myeloid malignancies, Grob et al.[18] showed that 186 patients with *TP53*-mutated AML had an OS similar to that of 44 patients with *TP53*-mutated MDS-EB, with both approximating 10 months ($p = .55$). Finally, Weinberg et al.[17] reported equally poor outcomes for patients with complex karyotype *TP53*-mutated AML ($n = 113$) and MDS-EB ($n = 91$; OS, 8.3 vs. 10.7 months; $p = .16$).

An important question is whether the spectrum of *TP53*-altered AML/MDS-EB is homogeneous. The existence of subgroups with disparate features defined by blast percentage thresholds could challenge the proposal to merge the two entities. The impact of a complex karyotype, the *TP53* variant allele frequency (VAF), the predicted *TP53* allele status (monoallelic vs. biallelic), responses to therapy, and post–allo-HSCT outcomes have been studied recently in cohorts of patients with *TP53*-altered AML/MDS-EB. Although a complex karyotype is associated with a higher proportion of marrow blasts among patients with *TP53*-altered MDS, a *TP53* mutation itself is a stronger determinant of outcome than a higher blast count (10%–29%) among patients with *TP53* wild-type MDS.[27] Furthermore, there is a negligible difference in the median OS among patients with *TP53*-altered AML/MDS-EB and the presence or absence of a complex karyotype.[18] The prognostic impact of the mutant *TP53* VAF in AML is controversial[19,27–31]; it appears to lose significance when one is specifically evaluating patients with complex karyotype, *TP53*-altered AML/MDS-EB.[16–18] This may be related to the likelihood that the *TP53* VAF and the complex karyotype are surrogates for the *TP53* allelic state, with biallelic *TP53* disruption resulting in a greater effect on the functional TP53 protein. Indeed, the Molecular Prognostic Scoring System for MDS, which underlines the importance of biallelic *TP53* alteration, predicts that a patient with biallelic *TP53* disruption and 6% marrow blasts will have the same prognosis as a patient with AML.[32] An estimated 55%–75% of *TP53*-altered

10970142, 2023, 2, Downloaded from https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.34535 by Universita Di Firenze Sistema, Wiley Online Library on [16/11/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Biological and outcome comparisons of *TP53*-mutated AML and *TP53*-mutated MDS-EB

		TP53-mutated MDS-EB		*TP53*-mutated AML	References
Biological features					
Cytogenetics	Monosomy 5/del(5q)	63%		44%–79%	18–20
	Monosomy 7/del(7q)	34%		26%–52%	18–20
	Monosomy 17/del(17p)	24%		21%–40%	18, 19
	Complex karyotype	90%		68%–90%	16, 18, 19
	Monosomal karyotype	85%		78%–87%	16, 18
Molecular	*FLT3* mutation	0%–2%		0%–7%	6, 16, 17, 19, 20
	NPM1 mutation	0%		0%–5%	6, 17, 19, 20
	IDH1/2 mutation	2%–3%		3%–14%	6, 16, 17, 19
	DNMT3A mutation	5%–14%		10%–14%	6, 16–19
	TET2 mutation	2%–9%		4%–9%	6, 16–19
	ASXL1 mutation	0%–5%		3%–10%	6, 16, 18, 19
	RUNX1 mutation	0%–6%		1%–6%	6, 16–19
	SRSF2 mutation	0%–2%		2%–10%	6, 18, 19
Allelic state	≥2 *TP53* mutations	30%		17%–19%	16, 18
	Median VAF	40%		43%–55%	16–18, 22
	Predicted biallelic loss	68%–75%		65%–77%	5, 17, 18, 20
Outcomes	*n* = 227	*n* = 186		*n* = 44	18
	Median OS, mo *n* = 204 (complex karyotype)	~10 *n* = 113	(*p* = .55)	~10 *n* = 91	17
	Median OS, mo *n* = 83	10.7 *n* = 30	(*p* = .16)	8.3 *n* = 45	24
	Median OS, mo *n* = 60 (sAML/MDS-EB)	5.5 *n* = 40	(*p* = .10)	6.7 *n* = 20	6
	Median OS, mo	7	(*p* = .97)	11	

Abbreviations: AML, acute myeloid leukemia; MDS-EB, myelodysplastic syndrome with excess blasts; OS, overall survival; sAML, secondary acute myeloid leukemia; VAF, variant allele frequency.

AML/MDS-EB cases have biallelic *TP53* defects.[5,17,18,20] Although exact copy number determination is imperfect with routinely performed techniques, clinical outcomes for patients with biallelic defects, inferred from the presence of double *TP53* mutations, the concurrent presence of a chromosome 17/17p abnormality, or a high VAF (i.e. > 40%–50%), are uniformly poor in patients with *TP53*-altered AML/MDS-EB.[17,18,33]

The absence of an effective standard-of-care induction and consolidation strategy in this group of patients diminishes the likelihood that currently available treatment approaches will influence outcomes, regardless of whether the given diagnosis is *TP53*-altered AML or *TP53*-altered MDS-EB.[16,18] For example, treatment outcomes for patients with *TP53*-altered AML receiving intensive chemotherapy are just as poor as those for patients with *TP53*-altered MDS-EB receiving HMA therapy in retrospective, propensity score–matched comparisons,[16,34] with the imbalanced effect of allo-HSCT limiting any conclusions regarding whether either approach is superior.[35] Disappointingly, the addition of venetoclax to frontline HMA therapy does not appear to improve OS in *TP53*-altered AML.[28,36,37] Because of the similar outcomes associated with intensive and less intensive treatment approaches for *TP53*-altered AML, there has been a progressive shift over the last decade toward the use of less intensive therapy for these patients regardless of age/fitness. The absence of a standard treatment approach for *TP53*-altered AML is reflected by the US Food and Drug Administration endorsement of either intensive or nonintensive chemotherapy as the control arm for a registration-enabling study for patients with *TP53*-altered AML (NCT04435691).

The adverse outcomes for patients with *TP53*-altered AML/MDS-EB should strongly encourage preferential enrollment of patients into experimental trials. This allows patients to access promising agents or combinations with the potential to improve outcomes. Unfortunately, clinical trial eligibility may be restricted by arbitrary blast thresholds despite pathobiological and prognostic similarities between *TP53*-altered MDS-EB and AML. In response to this limitation, a minority of trials have allowed patients with either MDS-EB

10970142, 2023, 2, Downloaded from https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.34535 by Universita Di Firenze Sistema, Wiley Online Library on [16/11/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

or what is colloquially known as oligoblastic AML (20%–29% blasts) to be enrolled.

There are additional logistical challenges, even after we consider the significant interobserver and time-based variability in blast enumeration and the absurdity of considering *TP53*-altered AML/MDS-EB with 19% blasts versus 20% blasts as different diseases, to use argumentum ad extremum. A frustration encountered in our clinical practice has been going through the often burdensome screening of a patient with MDS-EB for a trial compatible with the current WHO diagnostic blast cutoffs only to find that a patient initially eligible for an MDS trial has become ineligible just a few weeks later because of a peripheral blood or marrow blast count exceeding 20%. This delay is caused by the time required to make the diagnosis of *TP53*-mutated AML/MDS-EB, which requires one to wait for next-generation sequencing analysis, which can take up to 4 weeks at some institutions. However, recent validation of the use of mutant p53 protein expression patterns by immunohistochemistry to robustly inform the *TP53* mutation status and allelic state may soon allow a more expedient and reproducible means of disease risk assignment and treatment allocation.[38,39]

These realizations have prompted an appropriate rethinking of the classification of *TP53*-mutated AML/MDS-EB and the modern clinical approach. Although a ≥20% blast threshold to define AML is retained, the revised 2022 WHO classification states that *TP53*-mutated MDS with ≥10% marrow blasts (or ≥5% peripheral blood blasts) "may be regarded as AML-equivalent for therapeutic considerations and from a clinical trial design perspective when appropriate."[3] Furthermore, the most recent European LeukemiaNet 2022 recommendations and the new International Consensus Classification (ICC) now include an entity known as AML with mutated *TP53*, which requires a *TP53* VAF ≥10%, regardless of the allelic status.[3,40] The ICC further delineates *TP53*-mutated myeloid neoplasms by blast threshold and establishes those with 10%–19% blasts and a *TP53* VAF ≥ 10% as MDS/AML with mutated *TP53*; disease with up to 9% blasts, however, is still considered MDS, and a molecularly defined moniker excludes disease with predicted monoallelic *TP53* disruption.[3] The conception of a 10% blast and 10% VAF cutoff with allelic state restriction as well as an approach to *TP53*-altered AML with recurring or defining genetic abnormalities, albeit rare, requires further validation. Nonetheless, the efforts by European LeukemiaNet, WHO, and ICC are commended and will pave the way for a more inclusive and ergonomic approach to improving patient outcomes.

It is for these reasons that we believe that *TP53*-altered MDS-EB (5%–19% blasts) and *TP53*-altered AML should be considered under one unifying classification term. Laboratory studies such as RNA sequencing and proteomic analyses should be conducted across *TP53*-altered AML/MDS-EB rather than for separate entities to further support this contention. Ultimately, such a unification would simplify the screening processes for clinical trials and allow a focus on treating the patient for a genetically defined disorder rather than one based on an arbitrary blast threshold.

AUTHOR CONTRIBUTIONS

Rory M. Shallis: Conceptualization, writing–original draft, and writing–review and editing. **Naval G. Daver:** Writing–review and editing. **Jessica K. Altman:** Writing–review and editing. **Hagop M. Kantarjian:** Writing–review and editing. **Uwe Platzbecker:** Writing–review and editing. **Valeria Santini:** Writing–review and editing. **Andrew H. Wei:** Writing–review and editing. **David A. Sallman:** Writing–review and editing. **Amer M. Zeidan:** Conceptualization and writing–review and editing.

ACKNOWLEDGMENT

The University of Texas MD Anderson Cancer Center is supported by the National Institutes of Health (grant P30 CA016672).

CONFLICTS OF INTEREST

Rory M. Shallis has served as a member of an advisory board for Bristol-Myers Squibb and Gilead Sciences, Inc. Naval G. Daver has served in a consulting or advisory role for Astellas, AbbVie, Genentech, Daiichi-Sankyo, Novartis, Jazz, Amgen, Servier, Karyopharm, Trovagene, Trillium, Syndax, Gilead, Pfizer, Bristol-Myers Squibb, Kite, Actinium, Arog, Immunogen, Arcellx, and Shattuck; has served as a member of a data safety and monitoring committee for Kartos and Jazz; and has received research funding from Astellas, AbbVie, Genentech, Daiichi-Sankyo, Gilead, Immunogen, Pfizer, Bristol-Myers Squibb, Trovagene, Servier, Novimmune, Incyte, Hanmi, Fate, Amgen, Kite, Novartis, Astex, KAHR, Shattuck, and Sobi. Jessica K. Altman has served in a consulting or advisory role for Gilead Sciences, Kymera, AbbVie, Amgen, Astellas, Bluebird Bio, Curio Sciences, Daiichi-Sankyo, Kura Oncology, Stemline, Syros, and Theradex; has participated in speakers' bureaus for PeerView, prIME Oncology, and the France Foundation; has served as a member of a data safety and monitoring committee for GlycoMimetics; and has received research funding from ALX Oncology, Amgen, Aptos, Astellas, Aprea, BioSight, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Fujifilm, Immunogen, Kartos, Kura Oncology, Loxo, and Takeda. Robert P. Hasserjian reports acting as a consultant for Bluebird Bio. Hagop M. Kantarjian has served in a consulting or advisory role for AbbVie, Amgen, Ascentage, Astellas, AstraZeneca, Biologix, Curis, Ipsen Biopharmaceuticals, KAHR Medical, Novartis, Pfizer, Precision Biosciences, Shenzhen Target Rx, and Taiho Pharma Canada and has received research funding from AbbVie, Amgen, Ascentage, Bristol-Myers Squibb, Daiichi-Sankyo, Immunogen, Jazz, and Novartis. Uwe Platzbecker has served in a consulting or advisory role for Celgene/Bristol-Myers Squibb; has participated in speakers' bureaus for Celgene/Bristol-Myers Squibb and Novartis; has served as a member of a data safety and monitoring committee for Celgene; and has received research funding from Amgen, Celgene, Janssen Biotech, Merck, and Novartis. Valeria Santini has served in a consulting or advisory role for AbbVie, Celgene/Bristol-Myers Squibb, Geron, Gilead, Menarini, Novartis, Otsuka Pharmaceutical, Servier, and Takeda Oncology; has received travel support from Janssen Biotech; has participated in speakers' bureaus for Celgene/Bristol-Myers Squibb; and has received research funding from Celgene. Andrew H.

10970142, 2023, 2, Downloaded from https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.34535 by Universita Di Firenze Sistema, Wiley Online Library on [16/11/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Wei has served in a consulting or advisory role for Novartis, Astellas, Pfizer, Macrogenics, AbbVie, Genentech, Servier, Celgene, Amgen, AstraZeneca, and Janssen; has received research funding from Novartis, Celgene, AbbVie, Servier, AstraZeneca, and Amgen; and is a former employee of the Walter and Eliza Hall Institute and receives a fraction of its royalty stream related to venetoclax. David A. Sallman has served in a consulting or advisory role for Intellisphere, Molecular Partners AG, AvenCell Europe GmbH, Takeda Pharmaceutical Company, Shattuck Labs, Aprea, Janssen Global Services, PGEN Therapeutics, Zentalis, Syros Pharmaceuticals, Celyad, Agios, AbbVie, Bristol-Myers Squibb, Gilead Sciences, Intellia Therapeutics, Kite (a Gilead Company), Magenta Therapeutics, Novartis, and Syndax; has participated in speakers' bureaus for Agios, Incyte, and Bristol-Myers Squibb; has served as an independent contractor for Bluebird Bio and Servier; has received research funding from Aprea and Jazz Pharmaceuticals; and has an intellectual property patent for LB-100 in myelodysplastic syndrome. Amer M. Zeidan has served in a consulting or advisory role for Celgene, AbbVie, Acceleron, Agios, Amgen, Aprea, Astellas, AstraZeneca, BeyondSpring, Boehringer Ingelheim, Cardiff Oncology, Bristol-Myers Squibb, Daiichi-Sankyo, Epizyme, Genentech, Gilead, Kura, Incyte, Ionis, Loxo Oncology, Janssen, and Novartis; has served on clinical trial committees for AbbVie, BioCryst, Bristol-Myers Squibb, Geron, Gilead, Kura, Loxo Oncology, and Novartis; and has received research funding from AbbVie, Acceleron, ADC Therapeutics, Amgen, Aprea, Astex, Boehringer Ingelheim, Cardiff Oncology, Bristol-Myers Squibb, Incyte, Jasper, Jazz, Novartis, and Pfizer.

ORCID

Rory M. Shallis https://orcid.org/0000-0002-8542-2944
Naval G. Daver https://orcid.org/0000-0001-7103-373X
Amer M. Zeidan https://orcid.org/0000-0001-7017-8160

REFERENCES

1. Estey E, Hasserjian RP, Dohner H. Distinguishing AML from MDS: a fixed blast percentage may no longer be optimal. *Blood*. 2022;139(3):323-332. doi:10.1182/blood.2021011304
2. Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemia: integrating morphological, clinical, and genomic data. *Blood*. 2022;140(11):1200-1228. doi:10.1182/blood.2022015850
3. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia*. 2022;36(7):1703-1719. doi:10.1038/s41375-022-01613-1
4. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209-2221. doi:10.1056/nejmoa1516192
5. Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat Med*. 2020;26(10):1549-1556. doi:10.1038/s41591-020-1008-z
6. Chen X, Othus M, Wood BL, et al. Comparison of myeloid blast counts and variant allele frequencies of gene mutations in myelodysplastic syndrome with excess blasts and secondary acute myeloid leukemia. *Leuk Lymphoma*. 2021;62(5):1226-1233. doi:10.1080/10428194.2020.1861267
7. Sill H, Zebisch A, Haase D. Acute myeloid leukemia and myelodysplastic syndromes with TP53 aberrations—a distinct stem cell disorder. *Clin Cancer Res*. 2020;26(20):5304-5309. doi:10.1158/1078-0432.ccr-20-2272
8. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. French–American–British (FAB) Co-Operative Group. *Br J Haematol*. 1976;33(4):451-458. doi:10.1111/j.1365-2141.1976.tb03563.x
9. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol*. 1982;51(2):189-199. doi:10.1111/j.1365-2141.1982.tb08475.x
10. Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. IARC; 2017.
11. Matsuda A, Germing U, Jinnai I, et al. Difference in clinical features between Japanese and German patients with refractory anemia in myelodysplastic syndromes. *Blood*. 2005;106(8):2633-2640. doi:10.1182/blood-2005-01-0040
12. Naqvi K, Jabbour E, Bueso-Ramos C, et al. IImplications of discrepancy in morphologic diagnosis of myelodysplastic syndrome between referral and tertiary care centers. *Blood*. 2011;118(17):4690-4693. doi:10.1182/blood-2011-03-342642
13. Senent L, Arenillas L, Luno E, Ruiz JC, Sanz G, Florensa L. Reproducibility of the World Health Organization 2008 criteria for myelodysplastic syndromes. *Haematologica*. 2013;98(4):568-575. doi:10.3324/haematol.2012.071449
14. Ades L, Dimicoli-Salazar S, Sebert M, et al. Enasidenib (ENA) is effective in patients with IDH2 mutated myelodysplastic syndrome (MDS): the IDEAL phase 2 study by the GFM group. *Blood*. 2021;138(suppl 1):63. doi:10.1182/blood-2021-147898
15. Sebert M, Cluzeau T, Beyne Rauzy O, et al. Ivosidenib monotherapy is effective in patients with IDH1 mutated myelodysplastic syndrome (MDS): the IDIOME phase 2 study by the GFM group. *Blood*. 2021;138(suppl 1):62. doi:10.1182/blood-2021-146932
16. Badar T, Atallah E, Shallis RM, et al. Outcomes of TP53 mutated AML with evolving frontline therapies: impact of allogeneic stem cell transplantation on survival. *Am J Hematol*. 2022;97(7):E232-E235. doi:10.1002/ajh.26546
17. Weinberg OK, Siddon AJ, Madanat Y, et al. TP53 mutation defines a unique subgroup within complex karyotype de novo and therapy-related MDS/AML. *Blood Adv*. 2022;6(9):2847-2853. doi:10.1182/bloodadvances.2021006239
18. Grob T, Al Hinai AS, Sanders MA, et al. Molecular characterization of mutant TP53 acute myeloid leukemia and high-risk myelodysplastic syndrome. *Blood*. 2022;139(15):2347-2354. doi:10.1182/blood.2021014472
19. Prochazka KT, Pregartner G, Rucker FG, et al. Clinical implications of subclonal TP53 mutations in acute myeloid leukemia. *Haematologica*. 2019;104(3):516-523. doi:10.3324/haematol.2018.205013
20. Rucker FG, Schlenk RF, Bullinger L, et al. TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. *Blood*. 2012;119(9):2114-2121. doi:10.1182/blood-2011-08-375758
21. Kulasekararaj AG, Smith AE, Mian SA, et al. TP53 mutations in myelodysplastic syndrome are strongly correlated with aberrations of chromosome 5, and correlate with adverse prognosis. *Br J Haematol*. 2013;160(5):660-672. doi:10.1111/bjh.12203
22. Leung GMK, Zhang C, Ng NKL, et al. Distinct mutation spectrum, clinical outcome and therapeutic responses of typical complex/monosomy karyotype acute myeloid leukemia carrying TP53 mutations. *Am J Hematol*. 2019;94(6):650-657. doi:10.1002/ajh.25469
23. Shallis RM, Stahl M, Bewersdorf JP, Zeidan AM. The current understanding of and treatment paradigm for newly-diagnosed TP53-mutated acute myeloid leukemia. *Hemato*. 2021;2(4):748-763. doi:10.3390/hemato2040051

10970142, 2023, 2, Downloaded from https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.34535 by Universita Di Firenze Sistema, Wiley Online Library on [16/11/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

24. Bewersdorf JP, Shallis RM, Gowda L, et al. Clinical outcomes and characteristics of patients with TP53-mutated acute myeloid leukemia or myelodysplastic syndromes: a single center experience. *Leuk Lymphoma*. 2020;61(9):2180-2190. doi:10.1080/10428194.2020.1759051
25. Lindsley RC, Saber W, Mar BG, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. *N Engl J Med*. 2017;376(6):536-547. doi:10.1056/nejmoa1611604
26. Ciurea SO, Chilkulwar A, Saliba RM, et al. Prognostic factors influencing survival after allogeneic transplantation for AML/MDS patients with TP53 mutations. *Blood*. 2018;131(26):2989-2992. doi:10.1182/blood-2018-02-832360
27. Haase D, Stevenson KE, Neuberg D, et al. TP53 mutation status divides myelodysplastic syndromes with complex karyotypes into distinct prognostic subgroups. *Leukemia*. 2019;33(7):1747-1758. doi:10.1038/s41375-018-0351-2
28. Kim K, Maiti A, Loghavi S, et al. Outcomes of TP53-mutant acute myeloid leukemia with decitabine and venetoclax. *Cancer*. 2021;127(20):3772-3781. doi:10.1002/cncr.33689
29. Short NJ, Montalban-Bravo G, Hwang H, et al. Prognostic and therapeutic impacts of mutant TP53 variant allelic frequency in newly diagnosed acute myeloid leukemia. *Blood Adv*. 2020;4(22):5681-5689. doi:10.1182/bloodadvances.2020003120
30. Sallman DA, Komrokji R, Vaupel C, et al. Impact of TP53 mutation variant allele frequency on phenotype and outcomes in myelodysplastic syndromes. *Leukemia*. 2016;30(3):666-673. doi:10.1038/leu.2015.304
31. Montalban-Bravo G, Kanagal-Shamanna R, Benton CB, et al. Genomic context and TP53 allele frequency define clinical outcomes in TP53-mutated myelodysplastic syndromes. *Blood Adv*. 2020;4(3):482-495. doi:10.1182/bloodadvances.2019001101
32. Bernard E, Tuechler H, Greenberg PL, et al. Molecular international prognosis scoring system for myelodysplastic syndromes. *NEJM Evid*. 2022;1(7).
33. Ganster C, Schaab R, Shirneshan K, et al. TP53 status and outcome in myelodysplastic syndromes with complex aberrant karyotypes [abstract EP785]. Abstract presented at: 25th Congress of the European Hematology Association; June 12, 2020; Frankfurt, Germany.
34. Cherry EM, Abbott D, Amaya M, et al. Venetoclax and azacitidine compared with induction chemotherapy for newly diagnosed patients with acute myeloid leukemia. *Blood Adv*. 2021;5(24):5565-5573. doi:10.1182/bloodadvances.2021005538
35. Grenet J, Jain AG, Burkart M, et al. Comparing outcomes between liposomal daunorubicin/cytarabine (CPX-351) and HMA+venetoclax as frontline therapy in acute myeloid leukemia [abstract 32]. Abstract presented at: 2021 American Society of Hematology Annual Meeting; December 11–13, 2021; Atlanta, GA.
36. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629. doi:10.1056/nejmoa2012971
37. Matthews AH, Perl AE, Luger SM, et al. Real-world effectiveness of CPX-351 vs venetoclax and azacitidine in acute myeloid leukemia. *Blood Adv*. 2022;6(13):3997-4005. doi:10.1182/bloodadvances.2022007265
38. McGraw KL, Nguyen J, Komrokji RS, et al. Immunohistochemical pattern of p53 is a measure of TP53 mutation burden and adverse clinical outcome in myelodysplastic syndromes and secondary acute myeloid leukemia. *Haematologica*. 2016;101(8):e320-e323. doi:10.3324/haematol.2016.143214
39. Tashakori M, Kadia TM, Loghavi S, et al. TP53 copy number and protein expression inform mutation status across risk categories in acute myeloid leukemia. *Blood*. 2022;140(1):58-72. doi:10.1182/blood.2021013983
40. Dohner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 ELN recommendations from an international expert panel. *Blood*. 2022;140(12):1345-1377. doi:10.1182/blood.2022016867

How to cite this article: Shallis RM, Daver NG, Altman JK, et al. *TP53*-altered acute myeloid leukemia and myelodysplastic syndrome with excess blasts should be approached as a single entity. *Cancer*. 2023;129(2):175-180. doi:10.1002/cncr.34535

10970142, 2023, 2, Downloaded from https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.34535 by Universita Di Firenze Sistema, Wiley Online Library on [16/11/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License