Supplementary Information

Additional gene mutations may refine the 2017 European LeukemiaNet classification in adult patients with de novo acute myeloid leukemia aged <60 years

Ann-Kathrin Eisfeld,[1] Jessica Kohlschmidt,[2,3] Alice Mims,[1] Deedra Nicolet,[2.3] Christopher J. Walker,[2] James S. Blachly,[1,2] Andrew J. Carroll,[4] Dimitrios Papaioannou,[1] Jonathan E. Kolitz[5], Bayard E. Powell[6], Richard M. Stone,[7] Albert de la Chapelle,[2] John C. Byrd,[1,2] Krzysztof Mrózek,[2] and Clara D. Bloomfield[2]

1. Division of Hematology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA
2. The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA
3. Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN, USA
4. University of Alabama at Birmingham, Birmingham, AL, USA
5. Monter Cancer Center, Zucker School of Medicine at Hofstra/Northwell, Lake Success, NY, USA
6. Wake Forest Baptist Comprehensive Cancer Center, Winston-Salem, NC, USA
7. Dana-Farber/Partners CancerCare, Boston, MA, USA

Running title: Mutations refining the 2017 ELN classification of AML

PARTICIPATING INSTITUTIONS

The following Cancer and Leukemia Group B (CALGB)/Alliance for Clinical Trials in Oncology (Alliance) institutions participated in this study and contributed at least five patients. For each of these institutions, the current or last principal investigator and the cytogeneticists who analyzed the cases are listed as follows:

The Ohio State University Medical Center, Columbus, OH: Claire F. Verschraegen, Karl S. Theil, Diane Minka and Nyla A. Heerema; North Shore University Hospital, Manhasset, NY: Jonathan E. Kolitz, Prasad R. K. Koduru, Ayala Aviram-Goldring and Chandrika Sreekantaiah; Wake Forest University School of Medicine, Winston-Salem, NC: Heidi D. Klepin, P. Nagesh Rao, Wendy L. Flejter and Mark Pettenati; Dana Farber Cancer Institute, Boston, MA: Harold J. Burstein, Ramana V. Tantravahi, Cynthia C. Morton and Paola Dal Cin; Washington University School of Medicine, St. Louis, MO: Nancy L. Bartlett, Michael S. Watson, Eric C. Crawford, Jaime Garcia-Heras, Peining Li and Shashikant Kulkarni; University of North Carolina, Chapel Hill, NC: Matthew I. Milowsky and Kathleen W. Rao; University of Maryland Greenebaum Cancer Center, Baltimore, MD: Heather D. Mannuel, Joseph R. Testa, Maimon M. Cohen, Judith Stamberg and Yi Ning; University of Chicago Medical Center, Chicago, IL: Hedy L. Kindler, Diane Roulston, Katrin M. Carlson, Yanming Zhang and Michelle M. LeBeau; Roswell Park Cancer Institute, Buffalo, NY: Ellis G. Levine and AnneMarie W. Block; University of Iowa Hospitals, Iowa City, IA: Umar Farooq and Shivanand R. Patil; Dartmouth Medical School, Lebanon, NH: Konstantin H. Dragnev, Doris H. Wurster-Hill and Thuluvancheri K. Mohandas; Duke University Medical Center, Durham, NC: Jeffrey Crawford, Sandra H. Bigner, Mazin B. Qumsiyeh and Barbara K. Goodman;

Ft. Wayne Medical Oncology/Hematology, Ft. Wayne, IN: Sreenivasa Nattam and Patricia I. Bader; SUNY Upstate Medical University, Syracuse, NY: Stephen L. Graziano, Larry Gordon and Constance K. Stein; Weill Medical College of Cornell University, New York, NY: Scott T. Tagawa, Ram S. Verma, Prasad R.K. Koduru, Andrew J. Carroll and Susan Mathew; Christiana Care Health Services, Inc., Newark, DE: Gregory A. Masters, Digamber S. Borgaonkar, Jeanne M. Meck, and Kathleen Richkind; Western Pennsylvania Hospital, Pittsburgh, PA: Gene G. Finley and Gerard R. Diggans; University of Vermont Cancer Center, Burlington, VT: Peter A. Kaufman, Elizabeth F. Allen and Mary Tang; Rhode Island Hospital, Providence, RI: Howard P. Safran, Teresita Padre-Mendoza, Hon Fong L. Mark, Shelly L. Kerman and Aurelia Meloni-Ehrig; University of Massachusetts Medical Center, Worcester, MA: William V. Walsh, Philip L. Townes, Vikram Jaswaney, Kathleen Richkind, Patricia Miron and Michael J. Mitchell; Mount Sinai School of Medicine, New York, NY: Michael A. Schwartz and Vesna Najfeld; Eastern Maine Medical Center, Bangor, ME: Sarah J. Sinclair and Laurent J. Beauregard; University of California San Diego Moores Cancer Center, San Diego, CA: Lyudmila A. Bazhenova, Renée Bernstein and Marie L. Dell'Aquila; University of Alabama at Birmingham, Birmingham, AL: Robert Diasio and Andrew J. Carroll; Long Island Jewish Medical Center, Lake Success, NY: Jonathan E. Kolitz dman, Prasad R. K. Koduru, Ayala Aviram-Goldring and Chandrika Sreekantaiah; Walter Reed National Military Medical Center, Bethesda, MD: Karen G. Zeman, Rawatmal B. Surana, Digamber S. Borgaonkar, Karl S. Theil and Kathleen E. Richkind; Massachusetts General Hospital, Boston, MA: David Ryan, Justin Gainor, Cynthia C. Morton and Paola Dal Cin; University of Puerto Rico, San Juan, Puerto Rico: Eileen I. Pacheco, Leonard L. Atkins, Cynthia C. Morton and Paola Dal Cin; University of California at San Francisco, San Francisco, CA: Charalambos Andreadis and Kathleen E. Richkind; Virginia Commonwealth University,

Richmond, VA: Steven R. Grossman, Mary H. Hackney and Colleen Jackson-Cook; University of Minnesota, Minneapolis, MN: Anne H. Blaes, Diane C. Arthur and Betsy A. Hirsch; University of Illinois, Chicago, IL: John G. Quigley, Maureen M. McCorquodale, Kathleen E. Richkind and Valerie Lindgren; University of Missouri/Ellis Fischel Cancer Center, Columbia, MO: Puja Nistala and Tim Hui-Ming Huang; University of Nebraska Medical Center, Omaha, NE: Apar K. Ganti and Warren G. Sanger.

TREATMENT PROTOCOLS

Patients in this study received intensive cytarabine/daunorubicin-based therapy on one of the following Cancer and Leukemia Group B (CALGB) frontline treatment protocols: 19808[1] (n=295), 10503[2] (n=257), 9621[3] (n=137), 8525[4] (n=35), 9222[5] (n=72), 10603[6] (n=55), 9022[7] (n=5), 8821[8] (n=6).

Patients enrolled on CALGB 19808 were randomly assigned to receive induction chemotherapy with cytarabine, daunorubicin, and etoposide with or without PSC-833 (valspodar), a multidrug resistance protein inhibitor.[1] On achievement of complete remission (CR), patients were assigned to intensification with high-dose cytarabine and etoposide for stem-cell mobilization followed by myeloablative treatment with busulfan and etoposide supported by autologous peripheral blood stem-cell transplantation (HSCT). Patients enrolled on CALGB 10503 were assigned to receive induction chemotherapy consisting of cytarabine, daunorubicin, and etoposide. Upon achievement of CR, patients received high-dose cytarabine and etoposide for stem-cell mobilization followed by myeloablative treatment with busulfan and etoposide supported by autologous peripheral HSCT. Patients not eligible for HSCT received high-dose cytarabine

(HiDAC). After intensification, patients received the DNA methyltransferase inhibitor decitabine for maintenance.[2] Patients enrolled on CALGB 9621 were treated similarly to those on CALGB 19808, as previously reported.[3] Patients on CALGB 8525 were treated with induction chemotherapy consisting of cytarabine in combination with daunorubicin and were randomly assigned to consolidation with different doses of cytarabine followed by maintenance treatment.[4] Patients on protocol CALGB 9222 received induction chemotherapy consisting of cytarabine in combination with daunorubicin followed by consolidation with one cycle of HiDAC. Different doses of mitoxantrone were explored, and the consolidation treatment was randomized to three cycles of monotherapy with HiDAC or consolidation with one cycle of HiDAC, a cycle of cyclophosphamide and etoposide, and one cycle of mitoxantrone and diaziquone.[5] In CALGB 10603, cytarabine and daunorubicin followed by consolidation with high-dose cytarabine was applied with or without PKC-412.[6] Patients enrolled onto CALGB 9022 received induction chemotherapy consisting of cytarabine in combination with daunorubicin followed by consolidation with one cycle of HiDAC, a cycle of cyclophosphamide and etoposide, and one cycle of mitoxantrone and diaziquone.[7] After induction consisting of cytarabine in combination with daunorubicin, the patients enrolled on CALGB 8821 received intensive post remission therapy with cytoxan/etoposide and diazaquone/mitoxantrone.[8]

DEFINITION OF CLINICAL ENDPOINTS

CR required an absolute neutrophil count $\geq 1.5 \times 10^9$/l with the exception for protocols CALGB 10503 and 10603, which required an absolute neutrophil count of $\geq 1.0 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, no leukemic blasts in the blood, bone marrow (BM) cellularity >20% with maturation of

all cell lines, no Auer rods, <5% BM blast cells, and no evidence of extramedullary leukemia, all of which had persisted for at least one month. Relapse was defined by ≥5% BM blasts, circulating leukemic blasts, or the development of extramedullary leukemia. Disease-free survival (DFS) was measured from the date of CR until the date of relapse or death; patients alive and relapse-free at last follow-up were censored. Overall survival (OS) was measured from the date on study until the date of death, and patients alive at last follow-up were censored.[9]

MUTATIONAL PROFILING

Cytogenetic analyses of pretreatment BM and/or blood samples subjected to short-term (24- or 48-h) unstimulated cultures were performed by CALGB/Alliance-approved institutional laboratories, and the results were confirmed by central karyotype review. Mononuclear cells were enriched through Ficoll-Hypaque gradient centrifugation and cryopreserved until use. Genomic DNA was extracted using the DNeasy Blood and Tissue Kit (QIAGEN, Hilden, Germany). The mutational status of 80 protein coding genes (*AKT1*, *ARAF*, *ASXL1*, *ATM*, *AXL*, *BCL2*, *BCOR*, *BCORL1*, *BRAF*, *BRD4*, *BRINP3*, *BTK*, *CBL*, *CCND1*, *CCND2*, *CSNK1A1*, *CTNNB1*, *DNMT3A*, *ETV6*, *EZH2*, *FBXW7*, *FLT3* [for *FLT3* tyrosine kinase domain mutations (*FLT3*-TKD)], *GATA1*, *GATA2*, *GSK3B*, *HIST1H1E*, *HNRNPK*, *IDH1*, *IDH2*, *IKZF1*, *IKZF3*, *ILR7*, *JAK1*, *JAK2*, *JAK3*, *KIT*, *KLHL6*, *KMT2A*, *KRAS*, *MAPK1*, *MAPK3*, *MED12*, *MYD88*, *NF1*, *NOTCH1*, *NPM1*, *NRAS*, *PHF6*, *PIK3CD*, *PIK3CG*, *PLCG2*, *PLEKHG5*, *PRKCB*, *PRKD3*, *PTEN*, *PTPN11*, *RAD21*, *RAF1*, *RUNX1*, *SAMHD1*, *SETBP1*, *SF1*, *SF3A1*, *SF3B1*, *SMARCA2*, *SMC1A*, *SMC3*, *SRSF2*, *STAG2*, *SYK*, *TET2*, *TGM7*, *TP53*, *TYK2*, *U2AF1*, *U2AF2*, *WT1*, *XPO1*, *ZMYM3*, *ZRSR2*) was determined by targeted amplicon sequencing using the MiSeq platform (Illumina, San Diego, CA). DNA library preparations were performed according to the manufacturer's instructions. Briefly, samples

were pooled and run on the MiSeq machine using the Illumina MiSeq Reagent Kit v3. Sequenced reads were aligned to the hg19 genome build using the Illumina Isis Banded Smith-Waterman aligner. Single nucleotide variant and indel calling were performed using MuTect and VarScan, respectively.[10,11] The MuCor algorithm was used as the baseline for integrative mutation assessment.[12] We only considered non-synonymous variants not listed in either the 1000 Genome database or dbSNP142-common variants as mutations. All called variants underwent visual inspection of the aligned reads using the Integrative Genomics Viewer (Broad Institute).[14] All variants that occurred with variant allele fractions of <0.10 were considered wild-type; all variants that were sequenced to a depth of <15 reads were excluded from the analysis. In addition, variants were excluded when they occurred only in 1 read direction if sequenced in both directions, if the region contained many variants with low quality scores, or if they occurred in all analyzed samples including run controls. In addition, samples with high background noise were entirely excluded from analysis. Samples were considered non-evaluable for a specific gene if ≥85% of the amplicons covering the target regions within the coding sequence of the gene were sequenced to a depth of <15 reads.

Gene mutations were assigned to previously described functional groups[8] as follows: chromatin remodeling (*ASXL1*, *BCOR*, *BCORL1*, *EZH2* and *SMARCA2*), cohesin complex (*RAD21*, *SMC1A*, *SMC3* and *STAG2*), kinases [*AXL*, *FLT3*-ITD, *FLT3* tyrosine kinase domain mutations (*FLT3*-TKD), *KIT* and *TYK2*], methylation-related (*DNMT3A*, *IDH1/2* and *TET2*), NPM1 (*NPM1*), RAS pathway (*CBL*, *KRAS*, *NRAS* and *PTPN11*), spliceosome (*SF3B1*, *SRSF2*, *U2AF1* and *ZRSR2*), transcription factors (*CEBPA*, *ETV6*, *GATA2*, *IKZF1*, *NOTCH1* and *RUNX1*) and tumor suppressors (*PHF6*, *TP53* and *WT1*).

STATISTICAL ANALYSES

Patients enrolled into the various study protocols listed above were combined for analyses. To verify that we did not have a time-dependent bias, we compared outcomes of patients enrolled in the six protocols that comprised at least eight patients included in our study (CALGB 8525, 9222, 9621, 10503, 10603 and 19808). We show that there were no statistically significant differences in CR rates (P=0.71), DFS (P=0.31) and OS (P=0.08) among patients enrolled in these protocols.

Patients who died within 30 days after starting therapy were excluded from the study as treatment response could not be evaluated. We used a limited backwards selection technique for multivariable modeling for achievement of CR and Cox proportional hazard stepwise regression for modeling for DFS and OS. In our outcome analyses, we used *P*-values adjusted to control for per family error rate (probability of a Type I error) for all variables considered in univariable analyses. The families were all variables considered in each outcome analysis and only variables whose likelihood ratio test adjusted P-value was <0.20 from the univariable models were considered in the multivariable analyses. To identify variables associated with achievement of CR, DFS and OS, the following parameters were included in the modeling of the outcome analyses (univariable and multivariable) for ELN 2017 Favorable-risk non-CBF-AML patients: hemoglobin, platelet counts, white blood cell (WBC) counts, % blood blasts, % BM blasts, age, race, sex, extramedullary involvement, *FLT3*-TKD and mutations in the *BCOR*, *DNMT3A*, *EZH2*, *GATA2*, *IDH1*, *IDH2*, *KIT*, *KRAS*, *NRAS*, *PLCG2*, *PTPN11*, *RAD21*, *SETBP1*, *SMARCA2*, *SMC1A*, *SMC3*, *TET2*, *WT1* and *ZRSR2* genes. To identify variables associated with achievement of CR, DFS and OS, the following parameters were included in the modeling of outcome analyses (univariable and multivariable) for ELN 2017 Favorable-risk CBF-AML patients: hemoglobin, platelet counts, WBC counts, % blood blasts, % BM blasts, age, race, sex, extramedullary

involvement, *FLT3*-TKD, and mutations in *KRAS*, *NRAS* and *WT1*. To identify variables associated with achievement of CR, DFS and OS, the following parameters were included in the modeling for outcome analyses (univariable and multivariable) for ELN 2017 Intermediate-risk patients: hemoglobin, platelet counts, WBC counts, % blood blasts, % BM blasts, age, race, sex, extramedullary involvement, *FLT3*-TKD, and mutations in *DNMT3A*, *IDH1*, *IDH2*, *JAK1*, *KRAS*, *NRAS*, *PTPN11*, *SMC3*, *TET2*, *WT1* and *ZRSR2*. To identify variables associated with achievement of CR, DFS and OS, the following parameters were included in the modeling for outcome analyses (univariable and multivariable) for ELN 2017 Adverse-risk patients: hemoglobin, platelet counts, WBC counts, % blood blasts, % BM blasts, age, race, sex, extramedullary involvement, *FLT3*-TKD, and mutations in *BCOR*, *DNMT3A*, *GATA2*, *IDH1*, *IDH2*, *KRAS*, *NRAS*, *PHF6*, *PLCG2*, *PTPN11*, *SF3B1*, *SMARCA2*, *SMC1A*, *SRSF2*, *STAG2*, *TET2*, *WT1* and *ZRSR2*.

Supplementary references

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Supplementary Table S1. Frequencies of gene mutations in younger adult patients with *de novo* acute myeloid leukemia assigned to the genetic-risk groups according to the 2017 ELN classification

Gene[a]	All patients n=863	Favorable-risk n=423	Intermediate-risk n=189	Adverse-risk n=251	*P*-value[b]
ASXL1, n (%)					<0.001
Mutated	34 (4)	2 (0)	0 (0)	32 (13)	
Wild-type	829 (96)	421 (100)	189 (100)	219 (87)	
AXL, n (%)					0.72
Mutated	16 (2)	9 (2)	4 (2)	3 (1)	
Wild-type	847 (98)	414 (98)	185 (98)	248 (99)	
BCOR, n (%)					<0.001
Mutated	40 (5)	9 (2)	8 (4)	23 (9)	
Wild-type	823 (95)	414 (98)	181 (96)	228 (91)	
BCORL1, n (%)					0.66
Mutated	22 (3)	9 (2)	6 (3)	7 (3)	
Wild-type	841 (97)	414 (98)	183 (97)	244 (97)	
BRINP3, n (%)					0.14
Mutated	14 (2)	4 (1)	6 (3)	4 (2)	
Wild-type	849 (98)	419 (99)	183 (97)	247 (98)	
CBL, n (%)					0.90
Mutated	16 (2)	9 (2)	3 (2)	4 (2)	
Wild-type	847 (98)	414 (98)	186 (98)	247 (98)	
CCND2, n (%)					0.004
Mutated	13 (2)	12 (3)	1 (1)	0 (0)	
Wild-type	850 (98)	411 (97)	188 (99)	251 (100)	
CEBPA, n (%)					<0.001
Mutated	73 (9)	73 (19)	0 (0)	0 (0)	
Wild-type	723 (91)	321 (81)	184 (100)	218 (100)	
DNMT3A, n (%)					<0.001
Mutated	199 (23)	101 (24)	63 (33)	35 (14)	
R882	139	70	44	25	
Non-R882	61	32	19	10	
Wild-type	664 (77)	322 (76)	126 (67)	216 (86)	
ETV6, n (%)					0.61
Mutated	18 (2)	7 (2)	4 (2)	7 (3)	
Wild-type	845 (98)	416 (98)	185 (98)	244 (97)	
EZH2, n (%)					0.88
Mutated	22 (3)	12 (3)	4 (2)	6 (2)	
Wild-type	841 (97)	411 (97)	185 (98)	245 (98)	
FLT3-ITD, n (%)					<0.001
Present	191 (23)	40 (10)	89 (47)	62 (28)	
Absent	637 (77)	377 (90)	100 (53)	160 (72)	
FLT3-TKD, n (%)					<0.001
Present	72 (8)	52 (12)	12 (6)	8 (3)	
Absent	784 (92)	369 (88)	175 (94)	240 (97)	
GATA2, n (%)					0.13
Mutated	49 (6)	31 (7)	7 (4)	11 (4)	
Wild-type	814 (94)	392 (93)	182 (96)	240 (96)	

Gene[a]	All patients n=863	Favorable-risk n=423	Intermediate-risk n=189	Adverse-risk n=251	*P*-value[b]
IDH1, n (%)					0.04
Mutated	63 (7)	40 (9)	12 (6)	11 (4)	
Wild-type	800 (93)	383 (91)	177 (94)	240 (96)	
IDH2, n (%)					0.03
Mutated	74 (9)	27 (6)	24 (13)	23 (9)	
Wild-type	789 (91)	396 (94)	165 (87)	228 (91)	
IKZF1, n (%)					0.02
Mutated	13 (2)	2 (0)	6 (3)	5 (2)	
Wild-type	850 (98)	421 (100)	183 (97)	246 (98)	
JAK1, n (%)					0.04
Mutated	9 (1)	8 (2)	1 (1)	0 (0)	
Wild-type	854 (99)	415 (98)	188 (99)	251 (100)	
KIT, n (%)					<0.001
Mutated	44 (5)	36 (9)	3 (2)	5 (2)	
Wild-type	796 (95)	381 (91)	179 (98)	236 (98)	
KMT2A, n (%)					0.19
Mutated	14 (2)	4 (1)	3 (2)	7 (3)	
Wild-type	849 (98)	419 (99)	186 (98)	244 (97)	
KRAS, n (%)					0.47
Mutated	38 (4)	18 (4)	6 (3)	14 (6)	
Wild-type	825 (96)	405 (96)	183 (97)	237 (94)	
MED12, no. (%)					0.53
Mutated	11 (1)	4 (1)	2 (1)	5 (2)	
Wild-type	852 (99)	419 (99)	187 (99)	246 (98)	
NF1, no. (%)					0.54
Mutated	32 (6)	15 (5)	7 (5)	10 (7)	
Wild-type	539 (94)	292 (95)	122 (95)	125 (93)	
NOTCH1, n (%)					0.53
Mutated	14 (2)	5 (1)	3 (2)	6 (2)	
Wild-type	849 (98)	418 (99)	186 (98)	245 (98)	
NPM1, n (%)					<0.001
Mutated	299 (35)	216 (51)	79 (42)	4 (2)	
Wild-type	561 (65)	207 (49)	110 (58)	244 (98)	
NRAS, n (%)					<0.001
Mutated	131 (15)	86 (20)	17 (9)	28 (11)	
Wild-type	732 (85)	337 (80)	172 (91)	223 (89)	
PHF6, n (%)					0.001
Mutated	21 (2)	4 (1)	3 (2)	14 (6)	
Wild-type	842 (98)	419 (99)	186 (98)	237 (94)	
PIK3CG, n (%)					0.57
Mutated	11 (1)	7 (2)	1 (1)	3 (1)	
Wild-type	852 (99)	416 (98)	188 (99)	248 (99)	
PLCG2, n (%)					0.78
Mutated	22 (3)	10 (2)	4 (2)	8 (3)	
Wild-type	841 (97)	413 (98)	185 (98)	243 (97)	
PTPN11, n (%)					0.07
Mutated	68 (8)	42 (10)	9 (5)	17 (7)	
Wild-type	795 (92)	381 (90)	180 (95)	234 (93)	

Gene[a]	All patients n=863	Favorable-risk n=423	Intermediate-risk n=189	Adverse-risk n=251	*P*-value[b]
RAD21, n (%)					0.03
Mutated	19 (2)	11 (3)	7 (4)	1 (0)	
Wild-type	844 (98)	412 (97)	182 (96)	250 (100)	
RUNX1, n (%)					<0.001
Mutated	61 (7)	2 (0)	1 (1)	58 (23)	
Wild-type	802 (93)	421 (100)	188 (99)	193 (77)	
SETBP1, n (%)					0.96
Mutated	23 (3)	12 (3)	5 (3)	6 (2)	
Wild-type	840 (97)	411 (97)	184 (97)	245 (98)	
SF3B1, n (%)					0.009
Mutated	26 (3)	8 (2)	3 (2)	15 (6)	
Wild-type	837 (97)	415 (98)	186 (98)	236 (94)	
SMARCA2, n (%)					0.12
Mutated	26 (3)	13 (3)	2 (1)	11 (4)	
Wild-type	837 (97)	410 (97)	187 (99)	240 (96)	
SMC1A, n (%)					0.36
Mutated	34 (4)	21 (5)	5 (3)	8 (3)	
Wild-type	829 (96)	402 (95)	184 (97)	243 (97)	
SMC3, n (%)					0.17
Mutated	30 (3)	15 (4)	10 (5)	5 (2)	
Wild-type	833 (97)	408 (96)	179 (95)	246 (98)	
SRSF2, n (%)					<0.001
Mutated	23 (3)	4 (1)	3 (2)	16 (6)	
Wild-type	836 (97)	417 (99)	185 (98)	234 (94)	
STAG2, n (%)					0.11
Mutated	17 (2)	5 (1)	3 (2)	9 (4)	
Wild-type	846 (98)	418 (99)	186 (98)	242 (96)	
TET2, n (%)					0.42
Mutated	79 (9)	43 (10)	18 (10)	18 (7)	
Wild-type	784 (91)	380 (90)	171 (90)	233 (93)	
TP53, n (%)					<0.001
Mutated	42 (5)	2 (0)	1 (1)	39 (16)	
Wild-type	821 (95)	421 (100)	188 (99)	212 (84)	
TYK2, n (%)					0.85
Mutated	16 (2)	7 (2)	4 (2)	5 (2)	
Wild-type	847 (98)	416 (98)	185 (98)	246 (98)	
U2AF1, n (%)					0.29
Mutated	18 (2)	6 (1)	6 (3)	6 (2)	
Wild-type	845 (98)	417 (99)	183 (97)	245 (98)	
WT1, n (%)					0.18
Mutated	77 (9)	36 (9)	23 (12)	18 (7)	
Wild-type	786 (91)	387 (91)	166 (88)	233 (93)	
ZRSR2, n (%)					0.49
Mutated	44 (5)	18 (4)	12 (6)	14 (6)	
Wild-type	819 (95)	405 (96)	177 (94)	237 (94)	
Total number of mutations					0.10

Gene[a]	All patients n=863	Favorable-risk n=423	Intermediate-risk n=189	Adverse-risk n=251	*P*-value[b]
Median	3	3	3	2	
Range	(0, 9)	(0, 9)	(0, 9)	(0, 9)	

Abbreviation: ELN, European LeukemiaNet; n, number.

[a] Listed are only those genes that were found mutated in at least 2% of patients in at least one of the risk groups. The following genes were mutated in <2%: *AKT1*, *ARAF*, *ATM*, *BRAF*, *BRD4*, *BTK*, *CCND1*, *CTNNB1*, *FBXW7*, *GSK3B*, *HIST1H1*, *HNRNPK*, *IKZF3*, *IL7R*, *JAK2*, *JAK3*, *KLHL6*, *MAPK3*, *MYD88*, *PIK3CD*, *PLEKHG5*, *PRKCB*, *PRKD*3, *PTEN*, *RAF1*, *SAMHD1*, *SF1*, *SF3A1*, *SYK*, *TGM7* and *XPO1*. No patient harbored a mutation in any of the following genes analyzed: *BCL2*, *CSNKN1A*, *GATA1*, *MAPK1, U2AF2*, or *ZMYM3.*

[b] *P*-values for categorical variables are from Fisher's exact test. *P*-values for continuous variables are from the Wilcoxon rank sum test and they are comparing the three risk groups: Favorable, Intermediate and Adverse.

Supplementary Table S2. Frequencies of gene mutations assigned to functional groups in younger adult patients with *de novo* acute myeloid leukemia assigned to the genetic-risk groups according to the 2017 ELN classification

Functional groups[a]	All patients n=863	Favorable-risk n=423	Intermediate-risk n=189	Adverse-risk n=251	*P*-value[b]
Chromatin remodeling, n (%)					<0.001
Mutated	132 (15)	44 (10)	17 (9)	71 (28)	
Wild-type	731 (85)	379 (90)	172 (91)	180 (72)	
Cohesin complex, n (%)					0.36
Mutated	99 (11)	51 (12)	25 (13)	23 (9)	
Wild-type	764 (89)	372 (88)	164 (87)	228 (91)	
Kinases, n (%)					<0.001
Mutated	316 (39)	137 (33)	102 (56)	77 (35)	
Wild-type	497 (61)	273 (67)	79 (44)	145 (65)	
Methylation-related, n (%)					<0.001
Mutated	328 (38)	165 (39)	96 (51)	67 (27)	
Wild-type	535 (62)	258 (61)	93 (49)	184 (73)	
NPM1, n (%)					<0.001
Mutated	298 (35)	216 (51)	78 (41)	4 (2)	
Wild-type	562 (65)	207 (49)	111 (59)	244 (98)	
RAS Pathway, n (%)					<0.001
Mutated	242 (28)	148 (35)	35 (19)	59 (24)	
Wild-type	621 (72)	275 (65)	154 (81)	192 (76)	
Spliceosome, n (%)					<0.001
Mutated	104 (12)	34 (8)	21 (11)	49 (20)	
Wild-type	755 (88)	387 (92)	167 (89)	201 (80)	
Transcription factors, n (%)					<0.001
Mutated	190 (24)	92 (23)	17 (9)	81 (36)	
Wild-type	612 (76)	302 (77)	167 (91)	143 (64)	
Tumor suppressor, n (%)					<0.001
Mutated	135 (16)	41 (10)	26 (14)	68 (27)	
Wild-type	728 (84)	382 (90)	163 (86)	183 (73)	

Abbreviations: ELN, European LeukemiaNet; n, number.

[a] Gene mutations were assigned to functional groups as follows: chromatin remodeling (*ASXL1*, *BCOR*, *BCORL1*, *EZH2* and *SMARCA2*), cohesin complex (*RAD21*, *SMC1A*, *SMC3* and *STAG2*), kinases [*AXL*, *FLT3* internal tandem duplications (*FLT3*-ITD), *FLT3* tyrosine kinase domain mutations (*FLT3*-TKD), *KIT* and *TYK2*], methylation-related (*DNMT3A*, *IDH1/2* and *TET2*), NPM1 (*NPM1*), RAS pathway (*CBL*, *KRAS*, *NRAS* and *PTPN11*), spliceosome (*SF3B1*, *SRSF2*, *U2AF1* and *ZRSR2*), transcription factors (*CEBPA*, *ETV6*, *GATA2*, *IKZF1*, *NOTCH1* and *RUNX1*) and tumor suppressors (*PHF6*, *TP53* and *WT1*).

[b] *P*-values for categorical variables are from Fisher's exact test and they are comparing the three risk groups: Favorable, Intermediate and Adverse.

Supplementary Table S3. Clinical outcome of younger adult patients with *de novo* acute myeloid leukemia classified according to the proposed refinements of the 2017 ELN risk classification with additional gene mutations

Outcome	New Favorable-risk n=371	New Intermediate-risk n=131	New Adverse-risk n=361	*P*-value[a]
Complete remission, n (%)	348 (92)	95 (77)	212 (59)	<0.001
Disease-free survival				<0.001
Median, years	7.7	1.1	0.7	
% Disease-free at 3 years (95% CI)	57 (51-62)	32 (23-41)	10 (7-15)	
Overall survival				<0.001
Median, years	12.9	1.8	1.0	
% Alive at 3 years (95% CI)	69 (64-73)	41 (33-49)	19 (15-23)	

Abbreviation: CI, confidence interval; ELN, European LeukemiaNet; n, number.

[a] *P*-values for categorical variables are from Fisher's exact test , *P*-values for the time to event variables are from the log-rank test and they are comparing the three risk groups: New Favorable, New Intermediate and New Adverse.