Outcomes and genetic dynamics of acute myeloid leukemia at first relapse

Alex Bataller,[1] Hagop Kantarjian,[1] Alexandre Bazinet,[1] Tapan Kadia,[1] Naval Daver,[1] Courtney D. DiNardo,[1] Gautam Borthakur,[1] Sanam Loghavi,[2] Keyur Patel,[2] Guilin Tang,[2] Koji Sasaki,[1] Nicholas J. Short,[1] Musa Yilmaz,[1] Ghayas C. Issa,[1] Yesid Alvarado,[1] Guillermo Montalban-Bravo,[1] Abhishek Maiti,[1] Hussein A. Abbas,[1] Koichi Takahashi,[1] Sherry Pierce,[1] Elias Jabbour,[1] Guillermo Garcia-Manero[1] and Farhad Ravandi[1]

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

Correspondence: F. Ravandi
fravandi@mdanderson.org

Received: January 12, 2024.
Accepted: April 19, 2024.
Early view: May 2, 2024.

https://doi.org/10.3324/haematol.2024.285057

Supplementary material

Outcomes and genetic dynamics of acute myeloid leukemia in first relapse

Alex Bataller[1], Hagop Kantarjian[1], Alexandre Bazinet[1], Tapan Kadia[1], Naval Daver[1], Courtney D. DiNardo[1], Gautam Borthakur[1], Sanam Loghavi[2], Keyur Patel[2], Guilin Tang[2], Koji Sasaki[1], Nicholas J. Short[1], Musa Yilmaz[1], Ghayas C. Issa[1], Yesid Alvarado[1], Guillermo Montalban-Bravo[1], Abhishek Maiti[1], Hussain A. Abbas[1], Koichi Takahashi[1], Sherry Pierce[1], Elias Jabbour[1], Guillermo Garcia-Manero[1], and Farhad Ravandi[1]

Contents

Tables

Table S1. 81-gene NGS panel

Gene	Exons (codons) tested
ANKRD26(NM_014915)	1 (1-6)
ASXL1 (NM_015338)	11-12 (362-1542)
ASXL2 (NM_018263)	11-12 (381-1436)
BCOR (NM_017745)	2-4 (1-512), 4-6 (514-1080), 7 (1122-1124), 7 (1091-1099), 7-15 (1124-1722)
BCORL1 (NM_021946)	1-6 (1-1261), 6 (1264-1323), 6-11 (1326-1600), 11-12 (1614-1699), 12 (1706-1712)
BRAF (NM_004333)	11 (439-478), 15 (581-620)
BRINP3 (NM_199051)	2-8 (1-471), 8 (475-767)
CALR (NM_004343)	9 (352-418)
CBL (NM_005188)	7-9 (336-477)
CBLB (NM_170662)	7-10 (282-469)
CBLC (NM_012116)	7-9 (336-454), 10 (464-475)
CEBPA (NM_004364)	1 (1-56), 1 (59-91), 1 (96), 1 (128-143), 1 (146-175), 1 (178-201), 1 (249-358)
CREBBP (NM_004380)	2-8 (29-608), 9-10 (615-705), 12-16 (724-1084), 17-31 (1094-1943), 31 (1950-2235), 31 (2238-2443)
CSF3R (NM_156039)	14 (575-622), 17 (681-864)
CUX1 (NM_181552)	2-6 (11-172), 6-9 (174-241), 10-12 (248-359), 13-14 (367-408)
DDX41 (NM_016222)	1-10 (1-366), 11 (369-410), 12-17 (420-623)
DNMT3A (NM_022552)	8-22 (286-862), 23 (866-913)
EED (NM_003797)	1-2 (1-69), 2-8 (71-287), 9-12 (289-442)
ELANE (NM_001972)	1-2 (5-46), 2 (69-75), 4-5 (123-268)
ETNK1 (NM_018638)	3 (228-275)
ETV6 (NM_001987)	1-6 (1-378), 7-8 (385-453)
EZH2 (NM_004456)	2-5 (1-158), 6 (162-205), 7 (209-217), 8-13 (243-512), 14 (516-538), 14-19 (547-732), 20 (752)
FBXW7 (NM_033632)	9-12 (413-708)
FLT3 (NM_004119)	11-17 (437-709), 18-20 (736-847)
GATA1 (NM_002049)	2-3 (1-84)
GATA2 (NM_032638)	2-5 (1-377), 5-6 (379-481)
GFI1 (NM_005263)	2 (2-39)
GNAS (NM_000516)	8 (200-202), 11 (315-324)
HNRNPK (NM_002140)	3-7 (1-96), 7 (101-106), 8-17 (111-465)
HRAS (NM_005343)	2-3 (1-60), 3-4 (87-150)
IDH1 (NM_005896)	4 (132-133)
IDH2 (NM_002168)	4 (125-178)
IKZF1 (NM_006060)	2-8 (1-443), 8 (445-518)
IL2RG (NM_000206)	1-2 (1-45), 2-8 (51-340), 8 (360-370)
IL7R (NM_002185)	5-7 (180-292)
JAK1 (NM_002227)	3-9 (3-445), 10 (453-465), 10-22 (470-1023), 22-24 (1026-1123)
JAK2 (NM_004972)	10 (405-442), 12-14 (505-622), 16 (665-711), 18 (762-802)

JAK3 (NM_000215)	2-23 (1-1069)
KDM6A (NM_021140)	1-19 (1-971), 19-21 (976-1070), 22-29 (1080-1402)
KIT (NM_000222)	8-9 (411-514), 11 (550-592), 17 (788-828)
KMT2A (NM_005933)	2-4 (145-1075), 4-13 (1081-1561), 14-15 (1566-1665), 27 (2178-2195), 27 (2201-2362), 27 (2365-2715), 27 (2721-3216), 27 (3219-3327), 27 (3336-3505), 27 (3521-3582)
KRAS (NM_004985)	2-4 (1-150)
MAP2K1 (NM_002755)	2 (27-90), 3 (98-146)
MPL (NM_005373)	10 (490-522), 12 (552-636)
NF1 (NM_001042492)	2-4 (21-160), 5 (165-190), 6 (201-218), 8-13 (244-468), 13-14 (478-547), 15-17 (568-667), 18 (674-728), 18-22 (746-992), 23-26 (997-1146), 26-30 (1160-1330), 30-31 (1353-1378), 31-34 (1382-1493), 34-35 (1512-1550), 35 (1563-1575), 36-38 (1601-1868), 39 (1870-1884), 39-40 (1886-1947), 40-47 (1952-2322), 47-49 (2325-2438), 50-51 (2441-2491), 51-52 (2494-2555), 53-58 (2580-2840)
NOTCH1 (NM_017617)	26 (1529-1600), 26-28 (1604-1795), 34 (2061-2228), 34 (2234-2274), 34 (2290-2309), 34 (2290-2556), 34 (2061-2228), 34 (2234-2274), 34 (2309-2556)
NPM1 (NM_002520)	11 (283-295)
NRAS (NM_002524)	2-4 (1-150)
PAX5 (NM_016734)	1-10 (1-392)
PHF6 (NM_032458)	2-3 (1-79), 4-10 (81-366)
PIGA (NM_002641)	2 (1-6), 2-5 (15-396), 6 (399-485)
PML (NM_033238)	3 (201-255)
PRPF40B (NM_001031698)	2-19 (2-609), 19-20 (611-658), 20-24 (661-807), 25-26 (815-893)
PTEN (NM_000314)	7-8 (212-340)
PTPN11 (NM_002834)	3-4 (46-125), 7 (253-285), 12 (460-462), 12-13 (465-533)
RAD21 (NM_006265)	2-12 (1-540), 13 (544-560), 14 (569-632)
RARA (NM_000964)	6-7 (211-338)
RUNX1 (NM_001754)	2-9 (1-419), 9 (426-437), 9 (456-474)
SETBP1 (NM_015559)	4 (838-885)
SF1 (NM_004630)	1-2 (1-31), 2 (39-54), 3-12 (57-524), 13 (544-578), 13 (596-600), 13 (605-640)
SF3A1 (NM_005877)	2-7 (22-322), 7-9 (355-424), 9-12 (427-646), 13-16 (651-794)
SF3B1 (NM_012433)	13-16 (574-790)
SH2B3 (NM_005475)	2 (1-40), 2 (43-119), 2 (132-164), 2-6 (233-374), 6-8 (380-576)
SMC1A (NM_006306)	1-25 (1-1234)
SMC3 (NM_005445)	1 (1-5), 2-6 (19-110), 6-11 (113-299), 11-15 (308-477), 15-16 (498-504), 16-17 (507-580), 17-19 (591-706), 20-25 (708-975), 25 (979-1035), 26-29 (1038-1217)
SRSF2 (NM_003016)	1 (1-38), 1 (45-121)
STAG1 (NM_005862)	2 (1-5), 3-5 (10-101), 5-12 (121-392), 13-20 (402-703), 21-22 (724-738), 22-27 (740-953), 27 (955-979), 28 (985-1008), 29-34 (1022-1259)
STAG2 (NM_006603)	2-8 (1-273), 9-16 (287-518), 16 (521-539), 17-22 (547-751), 23-33 (756-1232)
STAT3 (NM_139276)	17 (489-509), 17-22 (521-715)
STAT5A (NM_003152)	3-6 (1-177), 6-7 (181-189), 8-20 (261-795)
STAT5B (NM_012448)	16 (636-673)

SUZ12 (NM_015355)	1 (20-44), 1 (46-84), 2 (92-97), 4-5 (129-169), 7-11 (198-431), 12-16 (468-740)
TERC (NR_001566)	1 (1-36)
TERT (NM_198253)	1-2 (1-172), 2 (258-342), 2 (349-474), 2-4 (477-630), 4-5 (633-692), 6 (711-749), 6-12 (753-954), 12-16 (957-1133)
TET2 (NM_001127208)	3 (1-77), 3 (91-92), 3 (98-815), 3 (829-853), 3-10 (867-1453), 10-11 (1465-2003)
TP53 (NM_000546)	2 (1-25), 4-11 (80-394)
U2AF1 (NM_006758)	2 (15-44), 6 (117-161)
U2AF2 (NM_007279)	1-5 (1-161), 6-12 (163-437), 12 (441-476)
WT1 (NM_024426)	1 (1-5), 1 (7-63), 1-10 (127-518)
ZRSR2 (NM_005089)	1-4 (1-90), 5 (105-130), 6-8 (134-257), 9-11 (260-419), 11 (465-483)

Table S2. Baseline characteristics of all AML patients

	All patients (n = 875)
Age, years	65 (18-94)
Male sex, n (%)	468 (53.5)
Race/ethnicity, n (%)	
White	654 (74.7)
Black	73 (8.3)
Asian	42 (4.8)
Other	72 (8.2)
Unknown/NA	34 (3.9)
WBC	3.4 (0.1-336)
Hgb	8.7 (3.5-14.3)
Platelets	36 (1-1625)
BM blasts	45 (1-97)
Cytogenetics	
Diploid	291 (35.5)
-5/-5q	151 (18.4)
-7/-7q	112 (13.7)
+8	80 (9.8)
inv16/t(16;16)	45 (5.5)
t(8:21)	27 (3.3)
*KMT2A*r	47 (5.7)
*MECOM*r	11 (1.2)
Complex/Monosomal	208 (25.4)
ELN 2022	
Favorable	175 (20.7)
Intermediate	199 (23.6)
Adverse	470 (55.7)
Mutations	
ASXL1	108 (12.8)
BCOR	40 (4.8)
BCORL1	26 (3.1)
DNMT3A	198 (23.5)
EZH2	28 (3.3)
FLT3-ITD	140 (16.6)
IDH1	71 (8.4)
IDH2	119 (14.1)
NPM1	183 (21.8)
PTPN11	82 (9.8)
RUNX1	108 (12.8)
SRSF2	122 (14.5)
TET2	132 (15.7)
TP53	190 (22.6)
U2AF1	62 (7.4)
WT1	61 (7.3)
ZRSR2	17 (2.0)
Treatment	
IT	348 (39.8)
IT + Ven	144 (41.4)*
LIT	527 (60.2)
LIT + Ven	379 (71.9)*

* Percentages calculated by treatment subgroup (IT or LIT).

Table S3. Emergence and clearance rates of mutations and cytogenetic findings

Emergence rate = n of patients with acquired mutation at relapse / n of patients without mutation at diagnosis

Clearance rate = n of patients with acquired mutation at relapse / n of patients without mutation at diagnosis

	All patients		Intensive chemotherapy		Low intensity chemotherapy	
Gene mutation	Emergence rate	Clearance rate	Emergence rate	Clearance rate	Emergence rate	Clearance rate
ASXL1	6/137 (4.4%)	1/19 (5.3%)	2/48 (4.2%)	0/5	4/89 (4.5%)	1/14 (7.1%)
ASXL2	1/156 (0.6%)	0/0	0/53	0/0	1/103 (1%)	0/0
BCOR	3/148 (2%)	2/8 (25%)	0/50	1/3 (33.3%)	3/98 (3.1%)	1/5 (20%)
BCORL1	4/153 (2.6%)	2/3 (66.7%)	0/53	0/0	4/100 (4%)	2/3 (66.7%)
BRAF	0/154	1/2 (50%)	0/53	0/0	0/101	1/2 (50%)
BRINP3	1/155 (0.6%)	0/1	0/53	0/0	1/102 (1%)	0/1
CALR	1/155 (0.6%)	0/1	1/53 (1.9%)	0/0	0/102	0/1
CBL	2/150 (1.3%)	2/6 (33.3%)	1/52 (1.9%)	0/1	1/98 (1%)	2/5 (40%)
CBLC	0/155	1/1 (100%)	0/52	1/1 (100%)	0/103	0/0
CEBPA	1/149 (0.7%)	3/7 (42.9%)	1/50 (2%)	2/3 (66.7%)	0/99	1/4 (25%)
CREBBP	1/156 (0.6%)	0/0	0/53	0/0	1/103 (1%)	0/0
CSF3R	2/154 (1.3%)	0/2	1/52 (1.9%)	0/1	1/102 (1%)	0/1
DDX41	1/150 (0.7%)	1/6 (16.7%)	1/50 (2%)	0/3	0/100	1/3 (33.3%)
DNMT3A	9/106 (8.5%)	4/50 (8%)	3/34 (8.8%)	1/19 (5.3%)	6/72 (8.3%)	3/31 (9.7%)
ETV6	2/155 (1.3%)	0/1	2/53 (3.8%)	0/0	0/102	0/1
EZH2	5/152 (3.3%)	2/4 (50%)	2/52 (3.8%)	1/1 (100%)	3/100 (3%)	1/3 (33.3%)
FBXW7	0/155	1/1 (100%)	0/53	0/0	0/102	1/1 (100%)
FLT3_TKD	3/141 (2.1%)	11/15 (73.3%)	1/44 (2.3%)	6/9 (66.7%)	2/97 (2.1%)	5/6 (83.3%)
FLT3_ITD	6/132 (4.5%)	14/24 (58.3%)	1/41 (2.4%)	5/12 (41.7%)	5/91 (5.5%)	9/12 (75%)
GATA2	4/153 (2.6%)	0/3	1/52 (1.9%)	0/1	3/101 (3%)	0/2
GNAS	1/155 (0.6%)	1/1 (100%)	1/53 (1.9%)	0/0	0/102	1/1 (100%)
IDH1	4/144 (2.8%)	4/12 (33.3%)	1/47 (2.1%)	2/6 (33.3%)	3/97 (3.1%)	2/6 (33.3%)
IDH2	3/137 (2.2%)	2/19 (10.5%)	1/48 (2.1%)	1/5 (20%)	2/89 (2.2%)	1/14 (7.1%)
IKZF1	4/151 (2.6%)	2/5 (40%)	1/51 (2%)	0/2	3/100 (3%)	2/3 (66.7%)
JAK1	1/156 (0.6%)	0/0	0/53	0/0	1/103 (1%)	0/0
JAK2	1/153 (0.7%)	2/3 (66.7%)	0/53	0/0	1/100 (1%)	2/3 (66.7%)
JAK3	1/156 (0.6%)	0/0	0/53	0/0	1/103 (1%)	0/0
KDM6A	2/155 (1.3%)	0/1	2/53 (3.8%)	0/0	0/102	0/1
KIT	0/152	3/4 (75%)	0/49	3/4 (75%)	0/103	0/0
KMT2A	1/155 (0.6%)	0/1	0/53	0/0	1/102 (1%)	0/1
KRAS	3/145 (2.1%)	5/11 (45.5%)	1/49 (2%)	2/4 (50%)	2/96 (2.1%)	3/7 (42.9%)
MPL	1/156 (0.6%)	0/0	0/53	0/0	1/103 (1%)	0/0
NF1	2/146 (1.4%)	6/10 (60%)	0/49	2/4 (50%)	2/97 (2.1%)	4/6 (66.7%)
NOTCH1	0/155	1/1 (100%)	0/53	0/0	0/102	1/1 (100%)
NPM1	0/129	4/27 (14.8%)	0/40	2/13 (15.4%)	0/89	2/14 (14.3%)
NRAS	5/130 (3.8%)	8/26 (30.8%)	1/44 (2.3%)	5/9 (55.6%)	4/86 (4.7%)	3/17 (17.6%)
PHF6	3/150 (2%)	3/6 (50%)	2/51 (3.9%)	0/2	1/99 (1%)	3/4 (75%)
PIGA	0/155	0/1	0/53	0/0	0/102	0/1
PRPF40B	2/155 (1.3%)	0/1	0/53	0/0	2/102 (2%)	0/1
PTPN11	1/149 (0.7%)	3/7 (42.9%)	1/49 (2%)	2/4 (50%)	0/100	1/3 (33.3%)

RAD21	2/154 (1.3%)	0/2	1/51 (2%)	0/2	1/103 (1%)	0/0
RUNX1	5/126 (4%)	4/30 (13.3%)	0/46	2/7 (28.6%)	5/80 (6.2%)	2/23 (8.7%)
SETBP1	0/152	2/4 (50%)	0/53	0/0	0/99	2/4 (50%)
SF3B1	1/150 (0.7%)	0/6	0/51	0/2	1/99 (1%)	0/4
SH2B3	1/155 (0.6%)	0/1	0/52	0/1	1/103 (1%)	0/0
SMC1A	3/155 (1.9%)	0/1	2/53 (3.8%)	0/0	1/102 (1%)	0/1
SMC3	1/155 (0.6%)	0/1	1/52 (1.9%)	0/1	0/103	0/0
SRSF2	1/129 (0.8%)	1/27 (3.7%)	1/49 (2%)	1/4 (25%)	0/80	0/23
STAG1	0/155	1/1 (100%)	0/53	0/0	0/102	1/1 (100%)
STAG2	2/150 (1.3%)	1/6 (16.7%)	2/51 (3.9%)	1/2 (50%)	0/99	0/4
STAT5A	1/155 (0.6%)	0/1	0/53	0/0	1/102 (1%)	0/1
STAT5B	0/155	1/1 (100%)	0/52	1/1 (100%)	0/103	0/0
SUZ12	0/155	1/1 (100%)	0/52	1/1 (100%)	0/103	0/0
TERT	0/155	1/1 (100%)	0/53	0/0	0/102	1/1 (100%)
TET2	10/128 (7.8%)	1/28 (3.6%)	5/44 (11.4%)	0/9	5/84 (6%)	1/19 (5.3%)
TP53	8/107 (7.5%)	2/49 (4.1%)	7/45 (15.6%)	1/8 (12.5%)	1/62 (1.6%)	1/41 (2.4%)
U2AF1	0/145	1/11 (9.1%)	0/51	0/2	0/94	1/9 (11.1%)
U2AF2	0/155	0/1	0/53	0/0	0/102	0/1
WT1	7/149 (4.7%)	2/7 (28.6%)	3/49 (6.1%)	1/4 (25%)	4/100 (4%)	1/3 (33.3%)
ZRSR2	2/154 (1.3%)	2/2 (100%)	1/52 (1.9%)	1/1 (100%)	1/102 (1%)	1/1 (100%)
	All patients		**Intensive chemotherapy**		**Low intensity chemotherapy**	
CG finding	**Emergence rate**	**Clearance rate**	**Emergence rate**	**Clearance rate**	**Emergence rate**	**Clearance rate**
Normal CG	5/100 (5%)	14/49 (28.6%)	4/29 (13.8%)	9/21 (42.9%)	1/71 (1.4%)	5/28 (17.9%)
Complex	6/100 (6%)	2/45 (4.4%)	2/43 (4.7%)	0/7	4/57 (7%)	1/42 (2.4%)
Chr 5 abn	3/104 (2.9%)	2/45 (4.4%)	0/43	0/7	3/61 (4.9%)	2/38 (5.3%)
Chr 7 abn	11/110 (10%)	3/39 (7.7%)	6/46 (13%)	0/4	5/64 (7.8%)	3/35 (8.6%)
Chr 17 abn	6/120 (5%)	2/29 (6.9%)	2/46 (4.3%)	0/4	4/74 (5.4%)	2/25 (8)
t(8;21)	0/147	0/5	0/48	0/2	0/0	0/0
inv(16)	0/143	0/6	0/44	0/6	0/0	0/0
***KMT2A*r**	0/144	0/144	0/48	0/2	0/96	0/3
***MECOM*r**	0/142	1/7 (14.3%)	0/47	1/3 (33.3%)	0/95	0/4
t(6;9)	0/147	0/2	0/49	0/1	0/98	0/1

Table S4. Salvage treatments for rAML

Therapy intensity	therapy type	FLT3i	IDHi	Immunotherapy	Other	Treatment
IT	**Chemotherapy IT (n = 23)**	Gilteritinib (n = 2)	Ivosidenib (n = 1)	GO (CD33 ADC) (n = 2)	LY2606368 (CHEK1 inh) (n = 1)	HDAC: 1 (4.3%) Ara-C + VP16: 1 (4.3%) CLIA: 2 (8.7%) CLIA + GO: 3 (13%) CLIA + decitabine: 1 (4.3%) CPX-351 + GO: 4 (17.3%) CPX-351 + ivosidenib: 1 (4.3%) FA + LY2606368: 1 (4.3%) FAI: 1 (4.3%) FAI + gilteritinib: 2 (4.3%) FAI + GO: 1 (4.3%) FA BID: 1 (4.3%) FLAG: 1 (4.3%) FLAG + Ida: 1 (4.3%) FLAG + Ida + GO: 1 (4.3%) Direct HSCT: 1 (4.3%)
	Chemo IT + Ven (n = 9)	-	-	-	-	FLAG+Ida+Ven: 1 (11.1%) CPX-351+Ven: 6 (55.5%) BID FA+Ven: 1 (11.1%) FAI+Ven: 1 (11.1%)
LIT	**LIT (n = 35)**	Gilteritinib (n = 1) Quizartinib (n = 5) Sorafenib (n = 2)	Enasidenib (n = 6) Ivosidenib (n = 1)	GO (CD33 ADC) (n = 1) Avelumab (PD-L1) (n = 1) Magrolimab (CD47) (n = 3) Nivolumab (PD1) (n = 6) Ipilimumab (CTLA-4) (n = 5)	BGB324 (AXL1 inh) (n = 1) DS-3032B (MDM2 inh) (n = 1) Imatinib (n = 1) Palbociclib (CDK4/6 inh) (n = 1) PLX51107 (BET inh) (n = 1)	Aza + quizartinib: 1 (%) Aza + nivolumab + ipilimumab: 5 (16.1%) Aza + nivolumab: 1 (3.2%) Aza + sorafenib + enasidenib: 1 (3.2%) Aza + sorafenib: 1 (3.2%) Aza + enasidenib: 5 (16.1%) Aza + DS-3032B: 1 (3.2%) Aza + ivosidenib + imatinib: 1 (3.2%) Aza + PLX51107: 1 (3.2%) Aza + avelumab + GO: 1 (3.2%) Aza + magrolimab: 3 (9.7%) Dec: 4 (%) Dec + palbociclib: 1 (3.2%) Dec + quizartinib: 3 (9.7%) SGI + Ida: 1 (3.2%) LDAC + Quizartinib: 1 (%) LDAC + BGB324: 1 (%) Clad + LDAC + gilteritinib: 1 (20%) Clad + LDAC: 1 (%) Aspacytarabine: 1 (%)

	LIT + Ven (n = 64)	Gilteritinib (n = 5) Midostaurin (n = 1) Sorafenib (n = 1)	Enasidenib (n = 4) Ivosidenib (n = 1)	GO (CD33 ADC) (n = 2) Avelumab (PD-L1) (n = 2) Magrolimab (CD47) (n = 1) IMGN632 (CD123 ADC) (n = 1)	Trametinib (MEK inh) (n = 1) DS-3032B (MDM2 inh) (n = 1)	Aza + Ven: 7 (%) Aza + Ven + avelumab: 2 (%) Aza + Ven + GO: 1 (2.1%) Aza + Ven + enasidenib: 3 (4.7%) Aza + Ven + magrolimab: 1 (2.1%) Aza + Ven + trametinib: 1 (2.1%) Aza + Ven + IMGN632: 1 (2.1%) Aza + Ven + gilteritinib: 2 (4.2%) Aza + Ven + ivosidenib: 1 (2.1%) Dec + Ven: 18 (%) Dec 10d + Ven: 3 (6.2%) Dec + Ven + Enasid: 1 (2.1%) Dec + Ven + GO: 1 (2.1%) Dec + Ven + gilteritinib: 3 (%) Dec + Ven + sorafenib: 1 (2.1%) Dec + Ven + midostaurin: 1 (2.1%) Clad LDAC + Dec Ven: 1 (6.2%) LDAC + Ven: 3 (%) LDAC + Ven + DS3032b: 1 (6.2%) Clad LDAC + Ven: 10 (62.5%) HHT + Ven: 1 (6.2%) Sapacitabine + Ven: 1 (2.1%)
	Ven (n = 4)	Quizartinib (n = 1)	Ivosidenib (n = 1)	-	APR-246 (TP53mut) (n = 1) CYC065 (CDK inh) (n = 1)	Ivosidenib + Ven: 1 (25%) APR-246 + Ven: 1 (25%) CYC065 + Ven: 1 (25%) Quizartinib + Ven: 1 (25%)

	Other (n = 29)	-	Enasidenib (n = 2) Ivosidenib (n = 2)	AGS62P1 (FLT3 ADC) (n = 1) AMG330 (CD33-CD3) (n = 2) AMV564 (CD33-CD3) (n = 2) MGD006 (CD123-CD3) (n = 1) HU8F4 (PR1) (n = 1) IMGN632 (CD123 ADC) (n = 6) MCLA-117 (CLL1-CD3) (n = 1) Nivolumab (PD1) (n = 2) Ipilimumab (CTLA-4) (n = 2) NKX101 (NK therapy) (n = 1) FT538 (NK therapy) (n = 2)	APTO-253 (cMyc inh) (n = 1) BTX-A51 (CK1a inh) (n = 1) CA4948 (IRAK4 inh) (n = 2) CB-5339 (VCP inh) (n = 1) DS-1594b (Menin inh) (n = 1)	**Enasidenib:** 2 (6.9%) **Ivosidenib:** 2 (6.9%) **Nivolumab + Ipilimumab:** 2 (3.4%) **IMGN632:** 6 (20.7%) **AGS62P1:** 1 (3.4%) **AMG330:** 2 (6.9%) **AMV564:** 2 (6.9%) **APTO-253:** 1 (3.4%) **BTX-A51:** 1 (3.4%) **CA-4948:** 2 (6.9%) **CB-5339:** 1 (3.4%) **DS-1594b:** 1 (3.4%) **NKX101:** 1 (3.4%) **FT538:** 2 (6.9%) **HU8F4:** 1 (3.4%) **MCLA-117:** 1 (3.4%) **MGD006:** 1 (3.4%)

Figures

Figure S1

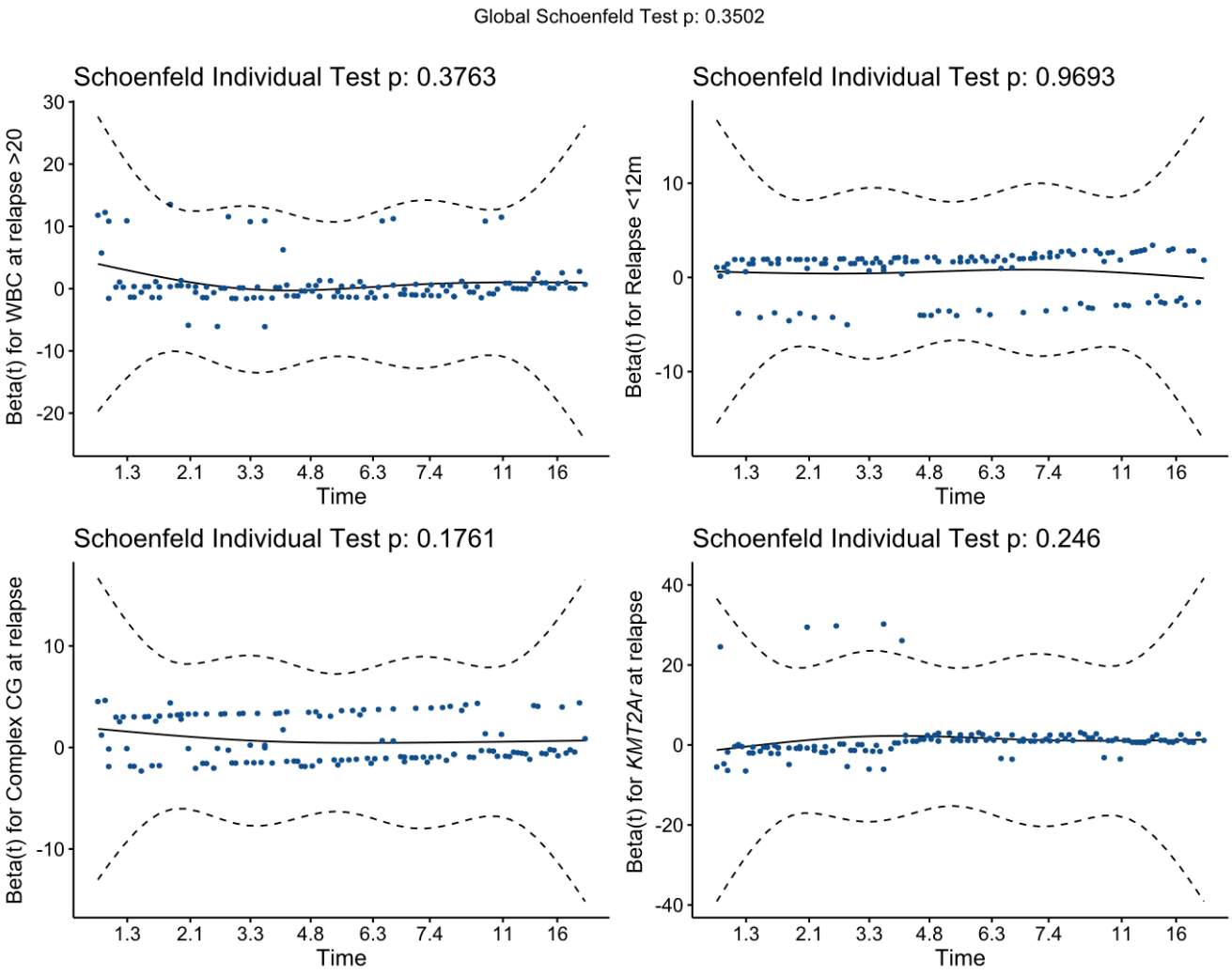

Figure S1. Schoenfeld residuals for variables included in the multivariate analysis for all patients.

Figure S2

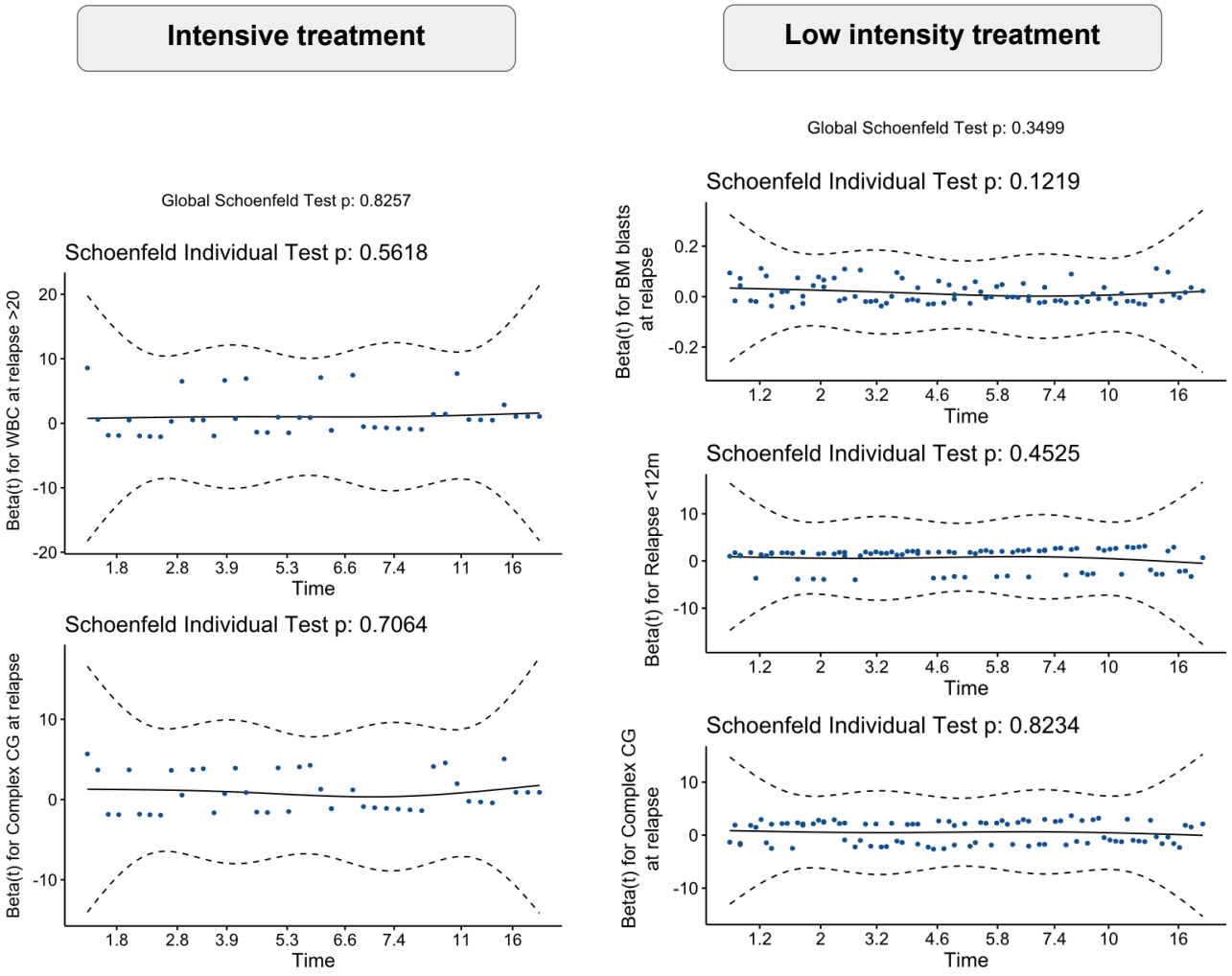

Figure S2. Schoenfeld residuals for variables included in the multivariate analysis for patients treated with intensive and low intensity treatment.

Figure S3

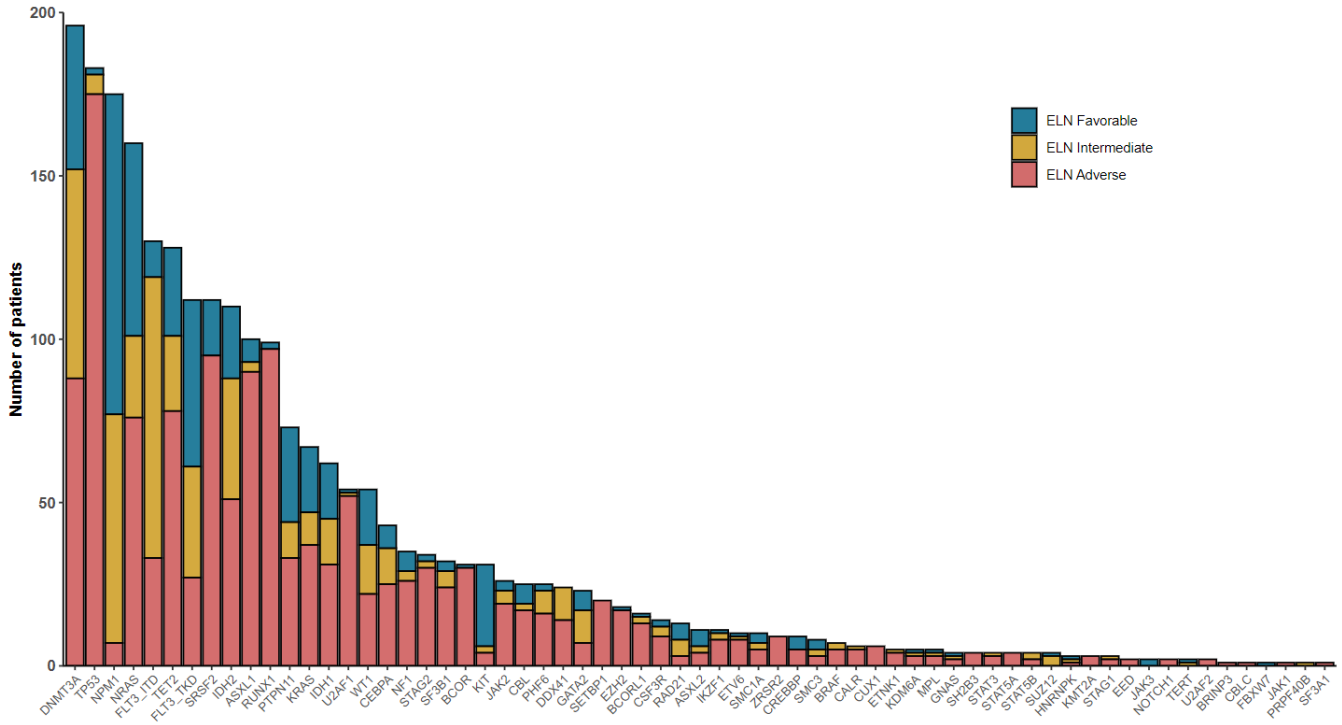

Figure S3. Bar plot describing all mutations detected in all patients at diagnosis, stratified by ELN 2022 risk.

Figure S4

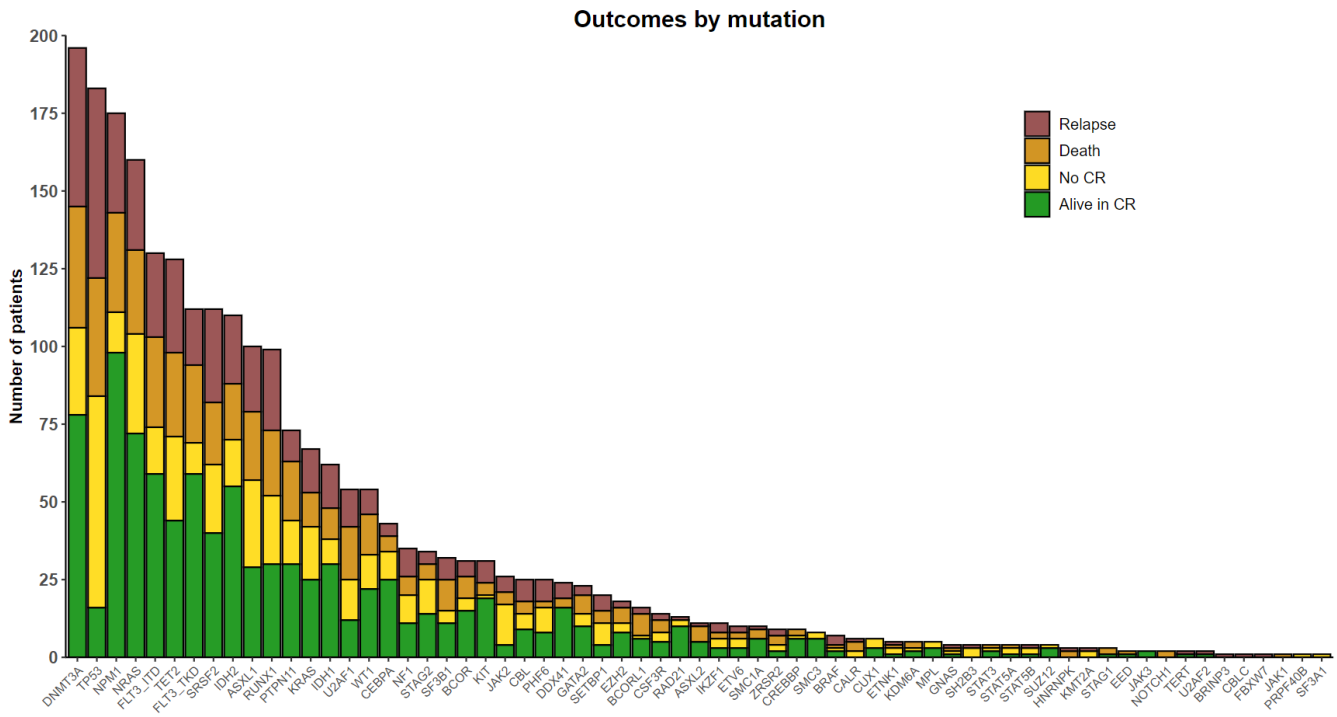

Figure S4. Bar plot describing all mutations detected in all patients at diagnosis, by the outcome of each patient.

Figure S5

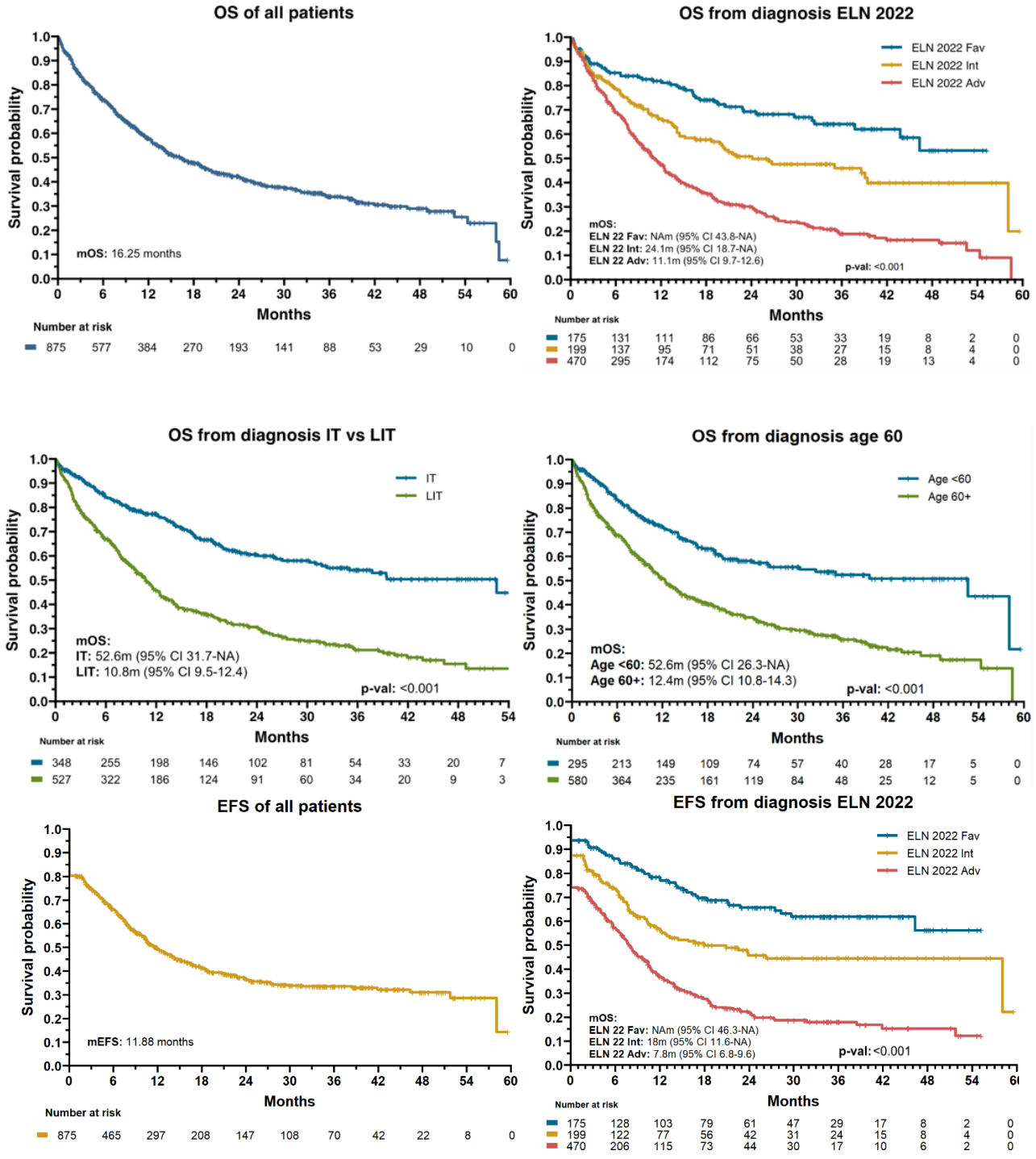

Figure S5. (A) OS of the entire cohort. (B) OS of the entire cohort stratified by the ELN 2022 risk classification. (D) OS of the entire cohort stratified by frontline treatment received. (E) OS of the entire cohort by age. Event-free survival (EFS) of all patients (left) and according to the ELN 2022 classification (right).

Figure S6

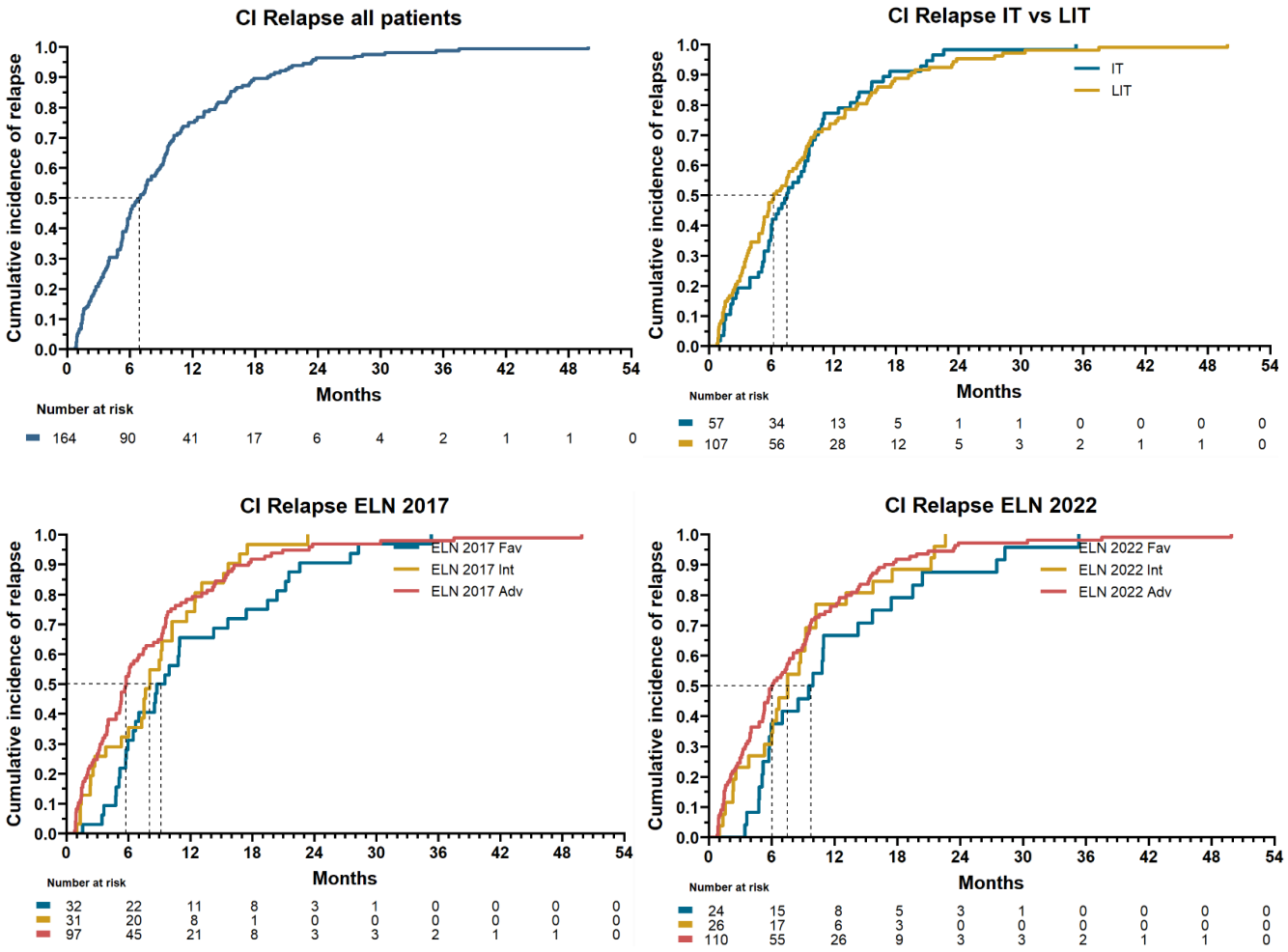

Figure S6. Cumulative incidence of relapse of all rAML patients (upper left), according to therapy received (upper right), according to ELN 2017 (lower left), and according to ELN 2022 (lower right).

Figure S7

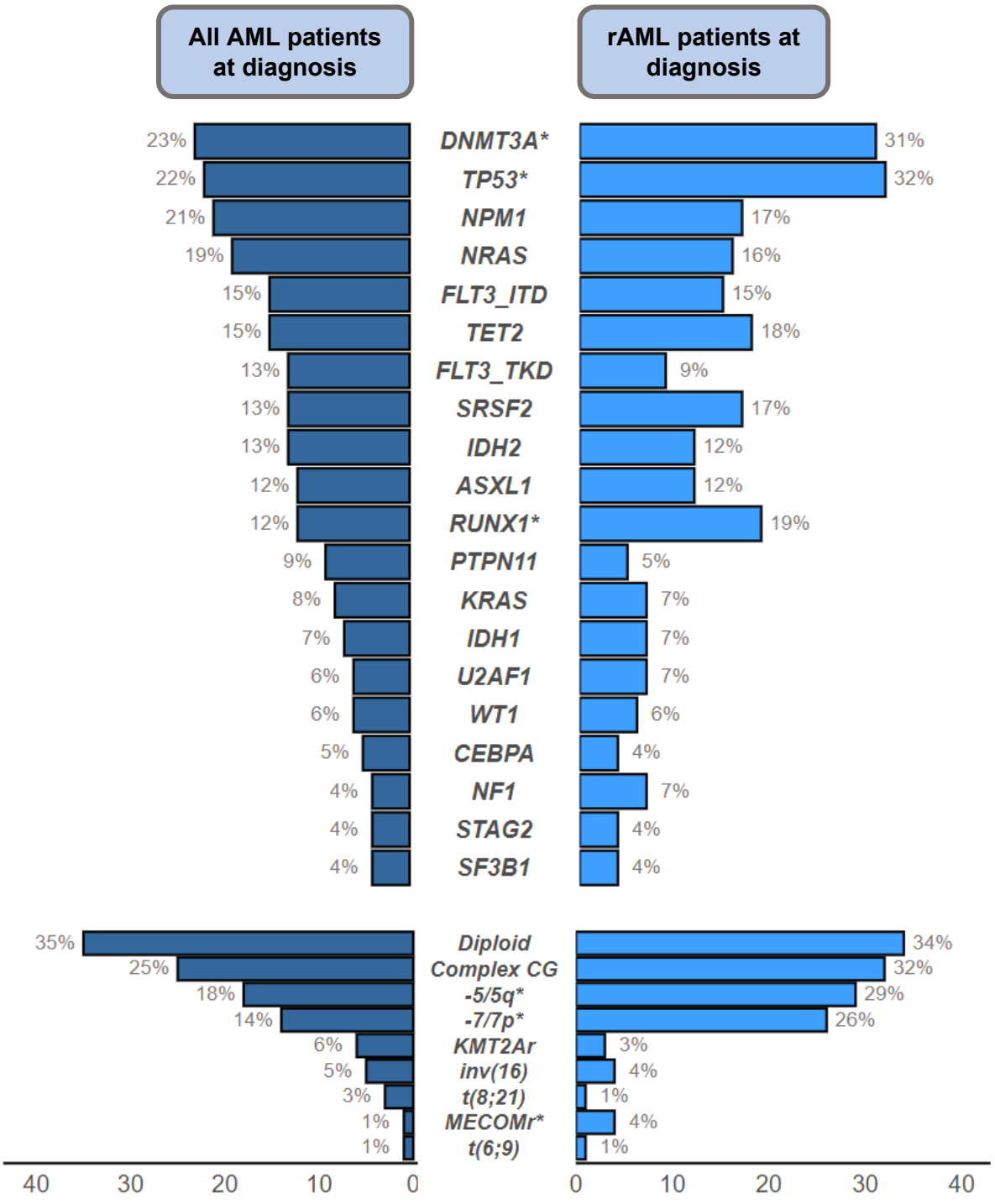

Figure S7. Frequency of mutations and cytogenetic findings in all patients at diagnosis vs rAML patients at diagnosis. An asterisk specifies genes/cytogenetic findings with significant proportion changes.

Figure S8

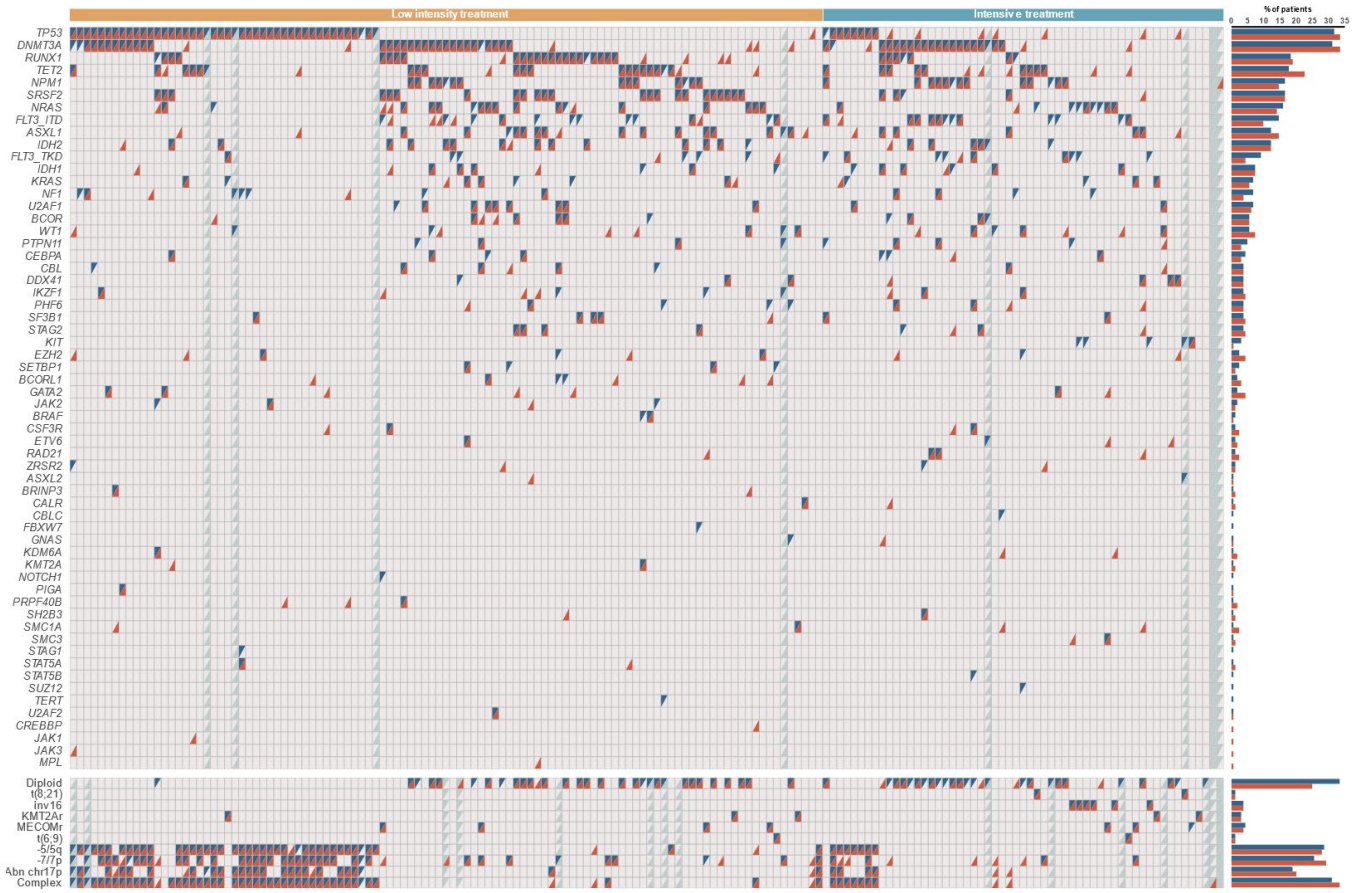

Figure S8. Oncoplot describing mutations at cytogenetic abnormalities at diagnosis (blue) and relapse (red). Patients with no data available are highlighted in grey.

Figure S9

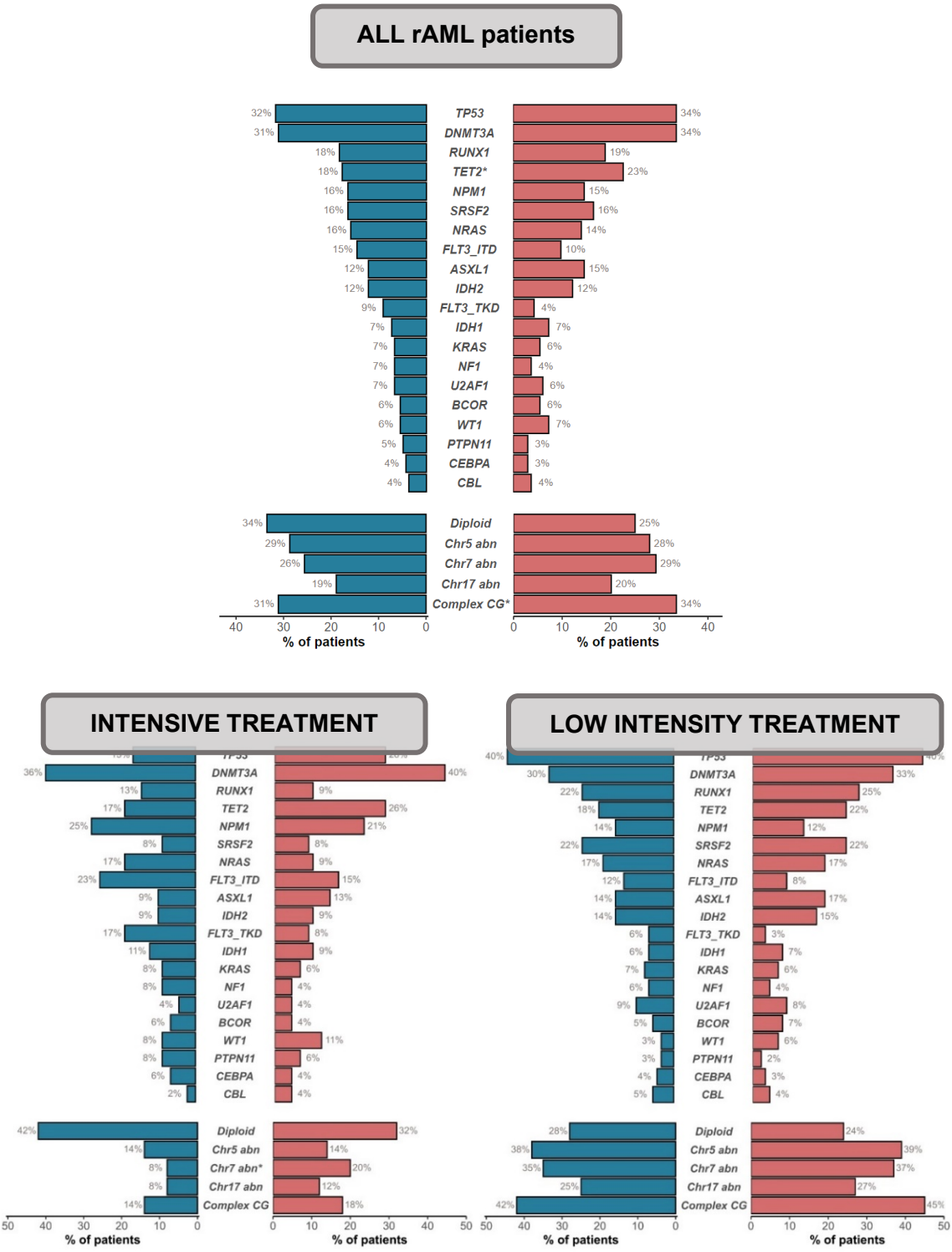

Figure S9. Frequency of mutations and cytogenetic findings at diagnosis and relapse in rAML patients with paired samples. An asterisk specifies genes/cytogenetic findings with significant proportion changes using a paired-sample approach with the McNemar test.

Figure S10

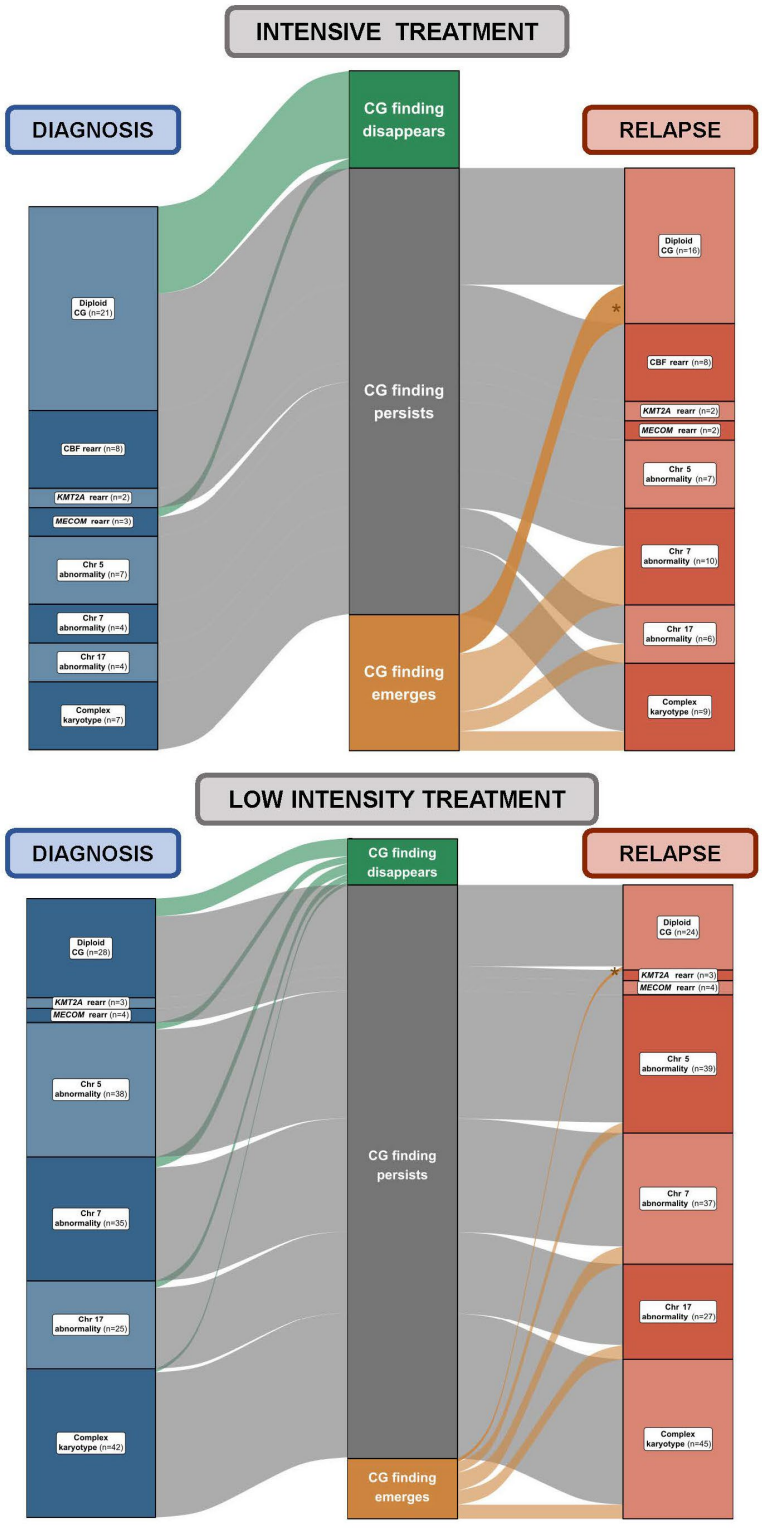

Figure S10. Cytogenetic dynamics from diagnosis to relapse of patients treated with IT (top) or treated with LIT (bottom).

Figure S11

Variable	Total n / Events	HR (90% CI)	p-val	mOS	p-val
Sex (male)	n=78, events=71 (Female) vs n=86, events=78 (Male)	1.01 (0.73-1.4)	0.94	5.5 months (Female) vs 5.1 months (Male)	0.938
Age at relapse (≥60)	n=40, events=35 (No) vs n=124, events=114 (Yes)	1.36 (0.93-1.99)	0.116	6.5 months (No) vs 5.1 months (Yes)	0.113
trAML	n=127, events=115 (No) vs n=37, events=34 (Yes)	1.1 (0.75-1.62)	0.614	5.5 months (No) vs 4.7 months (Yes)	0.613
Prior alloSCT	n=129, events=116 (No) vs n=35, events=33 (Yes)	0.87 (0.59-1.28)	0.484	4.8 months (No) vs 6.6 months (Yes)	0.481
LIT (vs IT)	n=57, events=49 (IT) vs n=107, events=100 (LIT)	1.38 (0.98-1.95)	0.066	6.6 months (IT) vs 4.9 months (LIT)	0.065
Prior Ven	n=81, events=70 (No) vs n=83, events=79 (Yes)	1.16 (0.84-1.6)	0.38	5.6 months (No) vs 4.8 months (Yes)	0.378
Time from CR to Rel (cont)	n=164 events=149	0.98 (0.95-1)	0.055		
<12m from CR to Rel	n=41, events=35 (No) vs n=123, events=114 (Yes)	1.8 (1.22-2.64)	0.003	8.1 months (No) vs 4.3 months (Yes)	0.002
WBC (cont)	n=158 events=143	1.01 (1-1.02)	0.019		
WBC > 20x10^9/L	n=143, events=128 (No) vs n=15, events=15 (Yes)	2.37 (1.38-4.08)	0.002	5.6 months (No) vs 2.8 months (Yes)	0.001
ANC (cont)	n=158 events=143	1.11 (1.03-1.2)	0.005		
Hgb (cont)	n=158 events=143	0.86 (0.77-0.96)	0.008		
Plt (cont)	n=158 events=143	1 (0.99-1)	0.444		
BM blast (cont)	n=157 events=142	1.01 (1-1.01)	0.027		
Diploid CG	n=111, events=101 (No) vs n=41, events=36 (Yes)	0.63 (0.43-0.93)	0.019	4.7 months (No) vs 7 months (Yes)	0.018
Chr5 abn	n=106, events=93 (No) vs n=46, events=44 (Yes)	1.68 (1.17-2.41)	0.005	6.5 months (No) vs 3.8 months (Yes)	0.004
Chr7 abn	n=104, events=92 (No) vs n=48, events=45 (Yes)	1.75 (1.21-2.52)	0.003	6.5 months (No) vs 4.8 months (Yes)	0.003
Chr17 abn	n=119, events=107 (No) vs n=33, events=30 (Yes)	1.33 (0.89-2)	0.169	5.8 months (No) vs 5.1 months (Yes)	0.168
KMT2Ar	n=147, events=132 (No) vs n=5, events=5 (Yes)	3.85 (1.53-9.65)	0.004	5.8 months (No) vs 2.6 months (Yes)	0.002
CBFr	n=144, events=132 (No) vs n=8, events=5 (Yes)	0.53 (0.22-1.31)	0.171	5.5 months (No) vs 7.3 months (Yes)	0.165
Complex CG	n=83, events=71 (No) vs n=69, events=66 (Yes)	1.8 (1.28-2.53)	0.001	6.7 months (No) vs 4.2 months (Yes)	0.001
ASXL1	n=133, events=119 (No) vs n=24, events=24 (Yes)	1.26 (0.81-1.95)	0.313	5.5 months (No) vs 5.2 months (Yes)	0.312
BCOR	n=148, events=134 (No) vs n=9, events=9 (Yes)	1.01 (0.51-1.99)	0.974	5.3 months (No) vs 6.5 months (Yes)	0.973
CBL	n=151, events=137 (No) vs n=6, events=6 (Yes)	1.12 (0.49-2.54)	0.792	5.5 months (No) vs 4.4 months (Yes)	0.787
CEBPA	n=152, events=139 (No) vs n=5, events=4 (Yes)	0.65 (0.24-1.78)	0.405	5.5 months (No) vs 3.1 months (Yes)	0.402
DDX41	n=151, events=138 (No) vs n=6, events=5 (Yes)	0.7 (0.28-1.71)	0.431	5.2 months (No) vs 8.1 months (Yes)	0.431
DNMT3A	n=102, events=94 (No) vs n=55, events=49 (Yes)	0.81 (0.57-1.14)	0.227	4.7 months (No) vs 6.6 months (Yes)	0.226
EZH2	n=150, events=137 (No) vs n=7, events=6 (Yes)	1.03 (0.45-2.35)	0.938	5.3 months (No) vs 7.3 months (Yes)	0.934
FLT3 TKD	n=150, events=136 (No) vs n=7, events=7 (Yes)	1.78 (0.83-3.82)	0.138	5.5 months (No) vs 3.8 months (Yes)	0.137
FLT3 ITD	n=141, events=128 (No) vs n=16, events=15 (Yes)	0.95 (0.55-1.62)	0.84	5.2 months (No) vs 6.5 months (Yes)	0.834
GATA2	n=150, events=137 (No) vs n=7, events=6 (Yes)	0.73 (0.32-1.65)	0.447	5.5 months (No) vs 5.1 months (Yes)	0.443
IDH1	n=145, events=135 (No) vs n=12, events=8 (Yes)	0.57 (0.28-1.16)	0.123	5.2 months (No) vs 7.7 months (Yes)	0.118
IDH2	n=137, events=124 (No) vs n=20, events=19 (Yes)	0.75 (0.46-1.21)	0.24	5.1 months (No) vs 7.3 months (Yes)	0.239
KRAS	n=148, events=135 (No) vs n=9, events=8 (Yes)	1.56 (0.76-3.2)	0.228	5.5 months (No) vs 3.9 months (Yes)	0.221
NPM1	n=133, events=121 (No) vs n=24, events=22 (Yes)	1.06 (0.67-1.68)	0.789	5.2 months (No) vs 5.8 months (Yes)	0.795
NF1	n=151, events=137 (No) vs n=6, events=6 (Yes)	2.5 (1.09-5.75)	0.031	5.5 months (No) vs 3.2 months (Yes)	0.026
NRAS	n=134, events=121 (No) vs n=23, events=22 (Yes)	1.09 (0.69-1.72)	0.709	5.5 months (No) vs 4.9 months (Yes)	0.707
RUNX1	n=126, events=115 (No) vs n=31, events=28 (Yes)	0.83 (0.55-1.26)	0.389	5.1 months (No) vs 6.7 months (Yes)	0.389
SF3B1	n=150, events=136 (No) vs n=7, events=7 (Yes)	0.61 (0.28-1.31)	0.204	5.2 months (No) vs 11.7 months (Yes)	0.199
SRSF2	n=130, events=118 (No) vs n=27, events=25 (Yes)	1.12 (0.72-1.72)	0.617	5.5 months (No) vs 5.3 months (Yes)	0.617
STAG2	n=150, events=136 (No) vs n=7, events=7 (Yes)	1.02 (0.47-2.18)	0.967	5.5 months (No) vs 5.1 months (Yes)	0.968
TET2	n=120, events=108 (No) vs n=37, events=35 (Yes)	1.11 (0.76-1.63)	0.577	5.5 months (No) vs 5.1 months (Yes)	0.574
TP53	n=102, events=91 (No) vs n=55, events=52 (Yes)	1.72 (1.21-2.43)	0.002	6.3 months (No) vs 4.2 months (Yes)	0.002
U2AF1	n=147, events=133 (No) vs n=10, events=10 (Yes)	1.17 (0.61-2.22)	0.642	5.5 months (No) vs 4.8 months (Yes)	0.636
WT1	n=145, events=131 (No) vs n=12, events=12 (Yes)	1.26 (0.7-2.29)	0.439	5.5 months (No) vs 5 months (Yes)	0.439

Figure S11. Univariate analysis for OS in all patients.

Figure S12

Variable	Total n / Events	HR (90% CI)	p-val	mOS	p-val
Sex (male)	n=30, events=26 (Female) vs n=27, events=23 (Male)	0.82 (0.47-1.44)	0.49	6.2 months (Female) vs 6.6 months (Male)	0.482
Age at relapse (≥60)	n=36, events=31 (No) vs n=21, events=18 (Yes)	1.24 (0.69-2.23)	0.477	6.5 months (No) vs 6.6 months (Yes)	0.469
trAML	n=51, events=43 (No) vs n=6, events=6 (Yes)	1.04 (0.44-2.44)	0.932	6.6 months (No) vs 5.9 months (Yes)	0.926
Prior alloSCT	n=37, events=30 (No) vs n=20, events=19 (Yes)	1.01 (0.56-1.82)	0.967	5.1 months (No) vs 6.7 months (Yes)	0.986
Prior Ven	n=41, events=33 (No) vs n=16, events=16 (Yes)	1 (0.55-1.84)	0.987	6.5 months (No) vs 7 months (Yes)	0.987
Time from CR to Rel (cont)	n=57 events=49	0.99 (0.95-1.04)	0.805		
<12m from CR to Rel	n=13, events=11 (No) vs n=44, events=38 (Yes)	1.54 (0.78-3.05)	0.21	11.1 months (No) vs 6.2 months (Yes)	0.206
WBC (cont)	n=54 events=46	1.01 (1-1.02)	0.136		
WBC > 20x10^9/L	n=47, events=39 (No) vs n=7, events=7 (Yes)	2.09 (0.91-4.78)	0.08	6.7 months (No) vs 4.1 months (Yes)	0.073
ANC (cont)	n=54 events=46	1.09 (0.97-1.22)	0.158		
Hgb (cont)	n=54 events=46	0.9 (0.76-1.06)	0.206		
Plt (cont)	n=54 events=46	1 (0.99-1.01)	0.6		
BM blast (cont)	n=53 events=45	1 (0.99-1.02)	0.466		
Diploid CG	n=35, events=29 (No) vs n=16, events=14 (Yes)	0.69 (0.36-1.32)	0.263	6.2 months (No) vs 7.6 months (Yes)	0.26
Chr5 abn	n=44, events=36 (No) vs n=7, events=7 (Yes)	1.9 (0.84-4.31)	0.123	6.6 months (No) vs 3.2 months (Yes)	0.116
Chr7 abn	n=41, events=34 (No) vs n=10, events=9 (Yes)	2.42 (1.12-5.25)	0.025	7.1 months (No) vs 4.2 months (Yes)	0.021
Chr17 abn	n=45, events=38 (No) vs n=6, events=5 (Yes)	1.58 (0.61-4.12)	0.345	6.6 months (No) vs 4.8 months (Yes)	0.339
KMT2Ar	n=49, events=41 (No) vs n=2, events=2 (Yes)	4.15 (0.95-18.25)	0.059	6.6 months (No) vs 3.1 months (Yes)	0.041
CBFr	n=43, events=38 (No) vs n=8, events=5 (Yes)	0.66 (0.26-1.68)	0.381	6.6 months (No) vs 7.3 months (Yes)	0.378
Complex CG	n=36, events=29 (No) vs n=15, events=14 (Yes)	2.19 (1.13-4.24)	0.02	7.1 months (No) vs 4.1 months (Yes)	0.017
ASXL1	n=47, events=40 (No) vs n=7, events=7 (Yes)	1.63 (0.72-3.68)	0.237	6.6 months (No) vs 4.6 months (Yes)	0.229
BCOR	n=52, events=45 (No) vs n=2, events=2 (Yes)	0.81 (0.19-3.35)	0.769	6.2 months (No) vs 9.9 months (Yes)	0.773
CBL	n=52, events=45 (No) vs n=2, events=2 (Yes)	2.43 (0.56-10.44)	0.234	6.6 months (No) vs 4.4 months (Yes)	0.219
CEBPA	n=52, events=46 (No) vs n=2, events=1 (Yes)	0.2 (0.03-1.48)	0.116	6.2 months (No) vs 16.9 months (Yes)	0.082
DDX41	n=50, events=43 (No) vs n=4, events=4 (Yes)	1.08 (0.38-3.06)	0.881	6.2 months (No) vs 7.2 months (Yes)	0.878
DNMT3A	n=33, events=30 (No) vs n=21, events=17 (Yes)	0.67 (0.37-1.22)	0.192	4.1 months (No) vs 6.7 months (Yes)	0.185
EZH2	n=52, events=45 (No) vs n=2, events=2 (Yes)	1.42 (0.34-5.95)	0.63	6.5 months (No) vs 6 months (Yes)	0.627
FLT3 TKD	n=50, events=43 (No) vs n=4, events=4 (Yes)	1.7 (0.6-4.77)	0.315	6.6 months (No) vs 4.5 months (Yes)	0.323
FLT3 ITD	n=46, events=40 (No) vs n=8, events=7 (Yes)	0.78 (0.35-1.75)	0.554	5.5 months (No) vs 6.6 months (Yes)	0.537
GATA2	n=52, events=45 (No) vs n=2, events=2 (Yes)	0.58 (0.14-2.41)	0.453	6.2 months (No) vs 13.3 months (Yes)	0.449
IDH1	n=49, events=45 (No) vs n=5, events=2 (Yes)	0.55 (0.13-2.3)	0.415	6.5 months (No) vs NA months (Yes)	0.41
IDH2	n=49, events=42 (No) vs n=5, events=5 (Yes)	1 (0.39-2.54)	0.995	6.2 months (No) vs 6.6 months (Yes)	0.993
KRAS	n=51, events=44 (No) vs n=3, events=3 (Yes)	4.04 (1.15-14.11)	0.029	6.6 months (No) vs 3 months (Yes)	0.018
NPM1	n=42, events=36 (No) vs n=12, events=11 (Yes)	1.22 (0.61-2.45)	0.574	5.4 months (No) vs 6.6 months (Yes)	0.592
NF1	n=52, events=45 (No) vs n=2, events=2 (Yes)	1.68 (0.4-7.1)	0.478	6.5 months (No) vs 5.6 months (Yes)	0.486
NRAS	n=49, events=42 (No) vs n=5, events=5 (Yes)	1 (0.39-2.58)	1	6.6 months (No) vs 2.8 months (Yes)	0.991
RUNX1	n=49, events=42 (No) vs n=5, events=5 (Yes)	1.83 (0.71-4.7)	0.212	6.6 months (No) vs 4.6 months (Yes)	0.204
SF3B1	n=52, events=45 (No) vs n=2, events=2 (Yes)	0.65 (0.16-2.69)	0.551	6.2 months (No) vs 12.5 months (Yes)	0.551
SRSF2	n=50, events=43 (No) vs n=4, events=4 (Yes)	3.04 (1.03-8.98)	0.044	6.6 months (No) vs 4.3 months (Yes)	0.034
STAG2	n=51, events=44 (No) vs n=3, events=3 (Yes)	0.67 (0.21-2.17)	0.504	6.5 months (No) vs 13.3 months (Yes)	0.505
TET2	n=40, events=35 (No) vs n=14, events=12 (Yes)	0.87 (0.45-1.68)	0.679	5.5 months (No) vs 7.1 months (Yes)	0.686
TP53	n=40, events=34 (No) vs n=14, events=13 (Yes)	1.25 (0.65-2.39)	0.504	6.5 months (No) vs 6.4 months (Yes)	0.495
U2AF1	n=52, events=45 (No) vs n=2, events=2 (Yes)	0.84 (0.2-3.47)	0.806	6.5 months (No) vs 9.3 months (Yes)	0.81
WT1	n=48, events=41 (No) vs n=6, events=6 (Yes)	1.92 (0.8-4.61)	0.147	6.6 months (No) vs 5 months (Yes)	0.139

Figure S12. Univariate analysis for OS in patients receiving IT at diagnosis.

Figure S13

Variable	Total n / Events	HR (90% CI)	p-val	mOS	p-val
Sex (male)	n=48, events=45 (Female) vs n=59, events=55 (Male)	1.13 (0.76-1.68)	0.551	5.3 months (Female) vs 4.3 months (Male)	0.549
Age at relapse (≥60)	n=4, events=4 (No) vs n=103, events=96 (Yes)	0.86 (0.31-2.35)	0.764	5.8 months (No) vs 4.9 months (Yes)	0.77
trAML	n=76, events=72 (No) vs n=31, events=28 (Yes)	1.03 (0.66-1.59)	0.902	5 months (No) vs 4.7 months (Yes)	0.9
Prior alloSCT	n=92, events=86 (No) vs n=15, events=14 (Yes)	0.84 (0.48-1.48)	0.548	4.5 months (No) vs 5.8 months (Yes)	0.548
Prior Ven	n=40, events=37 (No) vs n=67, events=63 (Yes)	1.06 (0.7-1.59)	0.788	5.5 months (No) vs 4.2 months (Yes)	0.791
Time from CR to Rel (cont)	n=107 events=100	0.97 (0.95-1)	0.037		
<12m from CR to Rel	n=28, events=24 (No) vs n=79, events=76 (Yes)	1.95 (1.22-3.11)	0.005	8 months (No) vs 4 months (Yes)	0.004
WBC (cont)	n=104 events=97	1.05 (1.02-1.07)	<0.001		
WBC > 20x10^9/L	n=96, events=89 (No) vs n=8, events=8 (Yes)	3.52 (1.68-7.33)	0.001	5.3 months (No) vs 1.5 months (Yes)	<0.001
ANC (cont)	n=104 events=97	1.19 (1.07-1.33)	0.002		
Hgb (cont)	n=104 events=97	0.83 (0.71-0.97)	0.023		
Plt (cont)	n=104 events=97	1 (0.99-1)	0.183		
BM blast (cont)	n=104 events=97	1.01 (1.01-1.02)	0.001		
Diploid CG	n=76, events=72 (No) vs n=25, events=22 (Yes)	0.63 (0.39-1.01)	0.056	4.3 months (No) vs 6.9 months (Yes)	0.054
Chr5 abn	n=62, events=57 (No) vs n=39, events=37 (Yes)	1.48 (0.97-2.24)	0.068	5.8 months (No) vs 4 months (Yes)	0.066
Chr7 abn	n=63, events=58 (No) vs n=38, events=36 (Yes)	1.53 (1-2.35)	0.052	5.2 months (No) vs 4.8 months (Yes)	0.051
Chr17 abn	n=74, events=69 (No) vs n=27, events=25 (Yes)	1.19 (0.75-1.88)	0.463	5.2 months (No) vs 5.1 months (Yes)	0.461
KMT2Ar	n=98, events=91 (No) vs n=3, events=3 (Yes)	3.99 (1.22-12.99)	0.022	5.3 months (No) vs 2.6 months (Yes)	0.013
Complex CG	n=47, events=42 (No) vs n=54, events=52 (Yes)	1.54 (1.02-2.33)	0.039	6.3 months (No) vs 4.3 months (Yes)	0.038
ASXL1	n=86, events=79 (No) vs n=17, events=17 (Yes)	1.09 (0.64-1.84)	0.752	5 months (No) vs 5.3 months (Yes)	0.751
BCOR	n=96, events=89 (No) vs n=7, events=7 (Yes)	1.06 (0.49-2.3)	0.879	5.1 months (No) vs 5.1 months (Yes)	0.879
CBL	n=99, events=92 (No) vs n=4, events=4 (Yes)	0.87 (0.32-2.38)	0.787	5.1 months (No) vs 7.7 months (Yes)	0.79
CEBPA	n=100, events=93 (No) vs n=3, events=3 (Yes)	4.38 (1.33-14.36)	0.015	5.2 months (No) vs 2 months (Yes)	0.008
DDX41	n=101, events=95 (No) vs n=2, events=1 (Yes)	0.33 (0.05-2.35)	0.266	5 months (No) vs 10.9 months (Yes)	0.242
DNMT3A	n=69, events=64 (No) vs n=34, events=32 (Yes)	0.94 (0.61-1.44)	0.785	5 months (No) vs 5.5 months (Yes)	0.787
EZH2	n=98, events=92 (No) vs n=5, events=4 (Yes)	0.9 (0.33-2.45)	0.831	5.1 months (No) vs 8.1 months (Yes)	0.832
FLT3 TKD	n=100, events=93 (No) vs n=3, events=3 (Yes)	2.2 (0.69-7.02)	0.181	5.1 months (No) vs 2.5 months (Yes)	0.171
FLT3 ITD	n=95, events=88 (No) vs n=8, events=8 (Yes)	1.31 (0.63-2.73)	0.463	5.1 months (No) vs 4.9 months (Yes)	0.461
GATA2	n=98, events=92 (No) vs n=5, events=4 (Yes)	0.83 (0.3-2.26)	0.71	5.2 months (No) vs 5 months (Yes)	0.709
IDH1	n=96, events=90 (No) vs n=7, events=6 (Yes)	0.59 (0.26-1.35)	0.21	4.8 months (No) vs 7.7 months (Yes)	0.204
IDH2	n=88, events=82 (No) vs n=15, events=14 (Yes)	0.63 (0.36-1.12)	0.118	4.5 months (No) vs 7.9 months (Yes)	0.115
KRAS	n=97, events=91 (No) vs n=6, events=5 (Yes)	1.13 (0.46-2.81)	0.787	5.1 months (No) vs 4.7 months (Yes)	0.784
NPM1	n=91, events=85 (No) vs n=12, events=11 (Yes)	1.02 (0.54-1.93)	0.941	5.1 months (No) vs 3.9 months (Yes)	0.94
NF1	n=99, events=92 (No) vs n=4, events=4 (Yes)	3.51 (1.24-9.94)	0.018	5.2 months (No) vs 2.5 months (Yes)	0.012
NRAS	n=85, events=79 (No) vs n=18, events=17 (Yes)	1.08 (0.64-1.83)	0.771	5.1 months (No) vs 5 months (Yes)	0.77
RUNX1	n=77, events=73 (No) vs n=26, events=23 (Yes)	0.66 (0.41-1.05)	0.079	4.2 months (No) vs 6.9 months (Yes)	0.076
SF3B1	n=98, events=91 (No) vs n=5, events=5 (Yes)	0.57 (0.23-1.41)	0.225	5 months (No) vs 11.7 months (Yes)	0.218
SRSF2	n=80, events=75 (No) vs n=23, events=21 (Yes)	0.91 (0.56-1.48)	0.7	4.8 months (No) vs 5.5 months (Yes)	0.699
STAG2	n=99, events=92 (No) vs n=4, events=4 (Yes)	1.94 (0.7-5.41)	0.202	5.2 months (No) vs 3.8 months (Yes)	0.198
TET2	n=80, events=73 (No) vs n=23, events=23 (Yes)	1.31 (0.82-2.1)	0.259	5.3 months (No) vs 3.3 months (Yes)	0.255
TP53	n=62, events=57 (No) vs n=41, events=39 (Yes)	1.93 (1.26-2.95)	0.002	6 months (No) vs 3.6 months (Yes)	0.002
U2AF1	n=95, events=88 (No) vs n=8, events=8 (Yes)	1.25 (0.6-2.59)	0.547	5.1 months (No) vs 3.8 months (Yes)	0.544
WT1	n=97, events=90 (No) vs n=6, events=6 (Yes)	1 (0.44-2.29)	1	5.1 months (No) vs 5.1 months (Yes)	0.996

Figure S13. Univariate analysis for OS in patients receiving LIT at diagnosis.

Figure S14

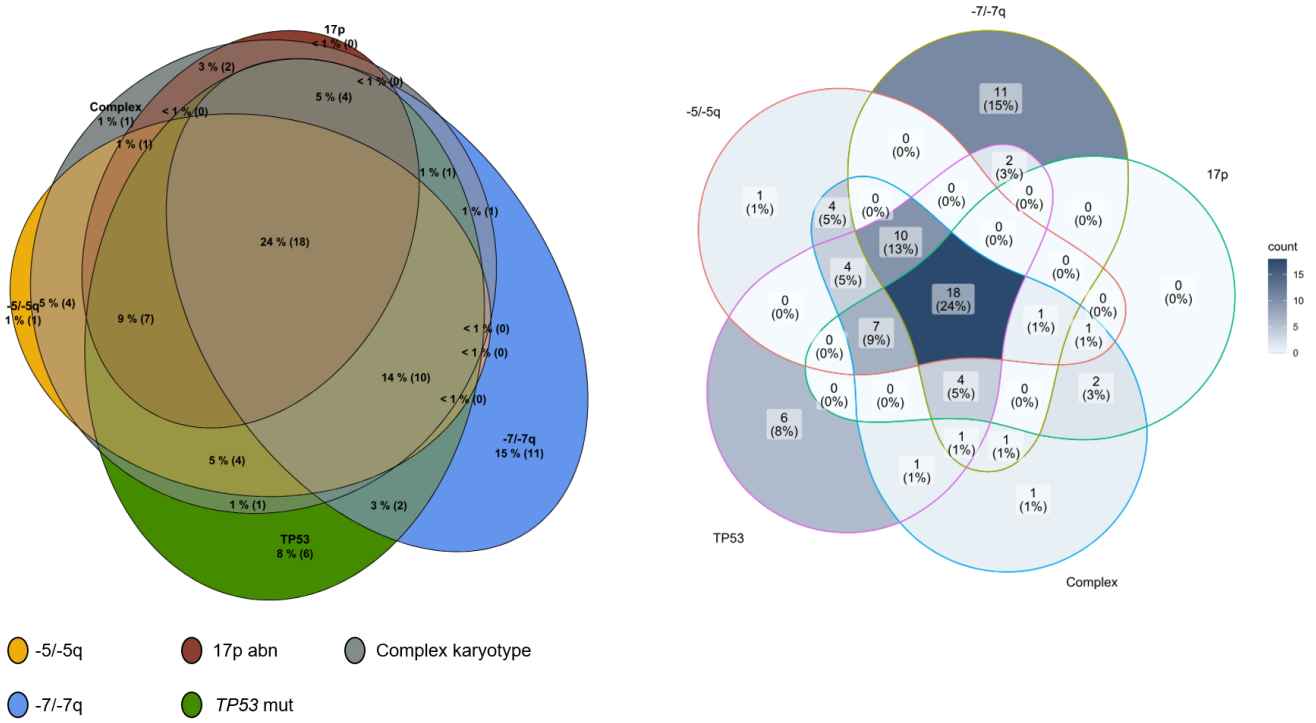

Figure S14. Venn diagram (left) and Euler plot (right) describing cooccurrence of cytogenetic and molecular abnormalities (Chr5, Chr7 and Chr17 abnormalities, complex karyotype, and TP53 mutation). In the Venn diagram, area of interaction is proportional to the number of patients.

Supplementary analysis 1 (SA1)

Patients receiving FLT3 inhibitors

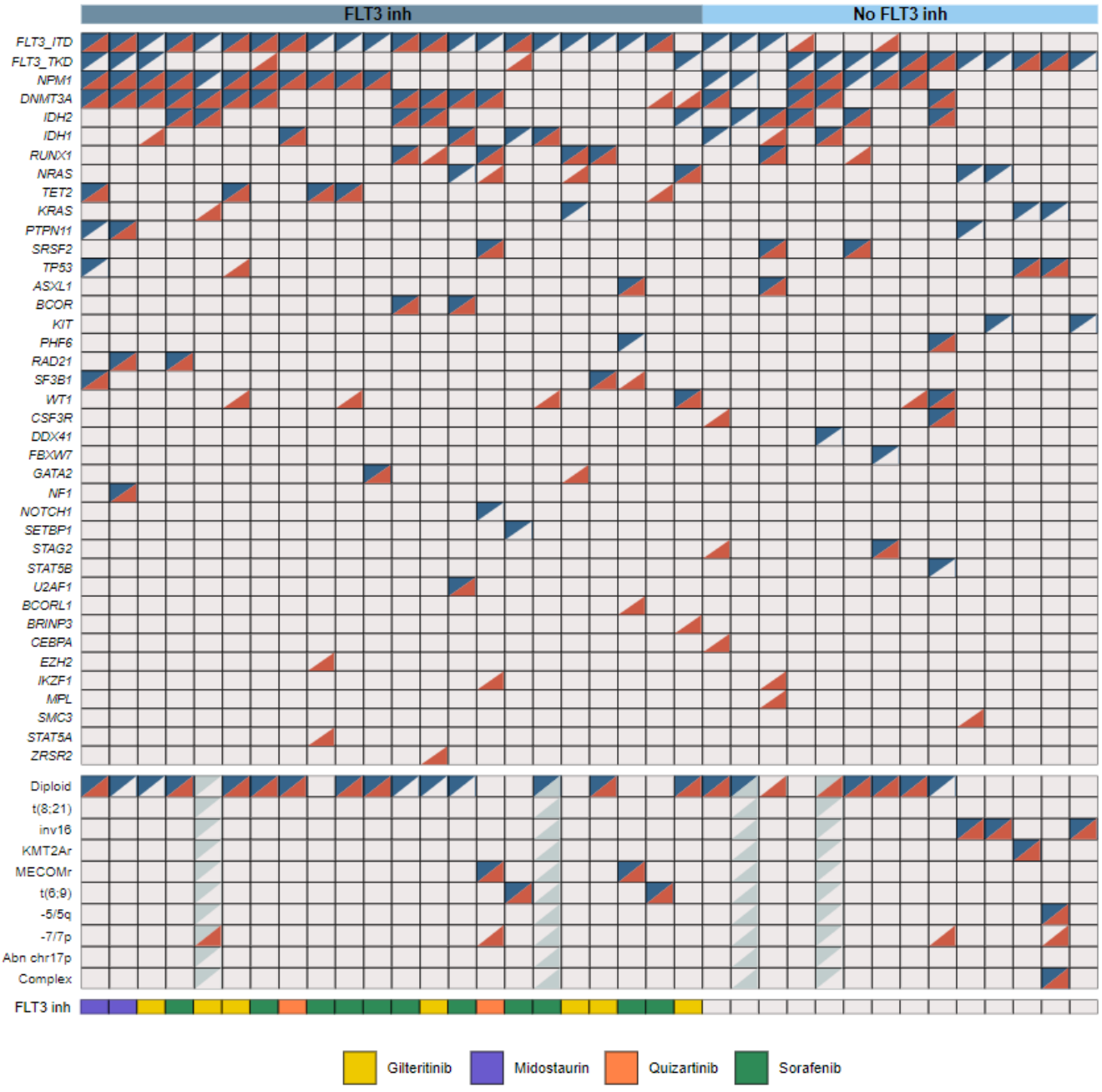

Figure S15. Mutations and cytogenetics at diagnosis and relapse in patients with *FLT3* (ITD and TKD mutations), stratified by therapy (FLT3 inhibitor).

	FLT3 inhibitor (n=22)		No FLT3 inhibitor (n=134)	
Gene	**Emergence rate**	**Clearance rate**	**Emergence rate**	**Clearance rate**
ASXL1	0/21 (0%)	0/1 (0%)	6/116 (5.2%)	1/18 (5.6%)
BCOR	0/20 (0%)	0/2	3/128 (2.3%)	2/6 (33.3%)
BCORL1	1/22 (4.5%)	0/0	3/131 (2.3%)	2/3 (66.7%)
BRINP3	1/22 (4.5%)	0/0	0/133	0/1
DNMT3A	2/11 (18.2%)	0/11	7/95 (7.4%)	4/39 (10.3%)
EZH2	1/22 (4.5%)	0/0	4/130 (3.1%)	2/4 (50%)
FLT3_TKD	2/18 (11.1%)	4/4 (100%)	1/123 (0.8%)	7/11 (63.6%)
FLT3_ITD	0/1	11/21 (52.4%)	6/131 (4.6%)	3/3 (100%)
GATA2	1/21 (4.8%)	0/1	3/132 (2.3%)	0/2
IDH1	1/18 (5.6%)	1/4 (25%)	3/126 (2.4%)	3/8 (37.5%)
IDH2	0/17	1/5 (20%)	3/120 (2.5%)	1/14 (7.1%)
IKZF1	1/22 (4.5%)	0/0	3/129 (2.3%)	2/5 (40%)
KRAS	1/21 (4.8%)	1/1 (100%)	2/124 (1.6%)	4/10 (40%)
NF1	0/21	0/1	2/125 (1.6%)	6/9 (66.7%)
NOTCH1	0/21	1/1 (100%)	0/134	0/0
NPM1	0/11	1/11 (9.1%)	0/118	3/16 (18.8%)
NRAS	2/20 (10%)	1/2 (50%)	3/110 (2.7%)	7/24 (29.2%)
PHF6	0/21	1/1 (100%)	3/129 (2.3%)	2/5 (40%)
PTPN11	0/20	1/2 (50%)	1/129 (0.8%)	2/5 (40%)
RAD21	0/20	0/2	2/134 (1.5%)	0/0
RUNX1	1/18 (5.6%)	0/4	4/108 (3.7%)	4/26 (15.4%)
SETBP1	0/21	1/1 (100%)	0/131	1/3 (33.3%)
SF3B1	1/20 (5%)	0/2	0/130	0/4
SRSF2	0/21	0/1	1/108 (0.9%)	1/26 (3.8%)
STAG1	0/22	0/0	0/133	1/1 (100%)
TET2	1/18 (5.6%)	0/4	9/110 (8.2%)	1/24 (4.2%)
TP53	1/21 (4.8%)	1/1 (100%)	7/86 (8.1%)	1/48 (2.1%)
U2AF1	0/21	0/1	0/124	1/10 (10%)
WT1	3/21 (14.3%)	0/1	4/128 (3.1%)	2/6 (33.3%)
ZRSR2	1/22 (4.5%)	0/0	1/132 (0.8%)	2/2 (100%)

Table S5 Mutations and cytogenetic abnormalities at diagnosis and relapse in patients with *FLT3* (ITD and TKD mutations), stratified by therapy (FLT3 inhibitor).

Supplementary analysis 2 (SA2)

Patients with normal karyotype

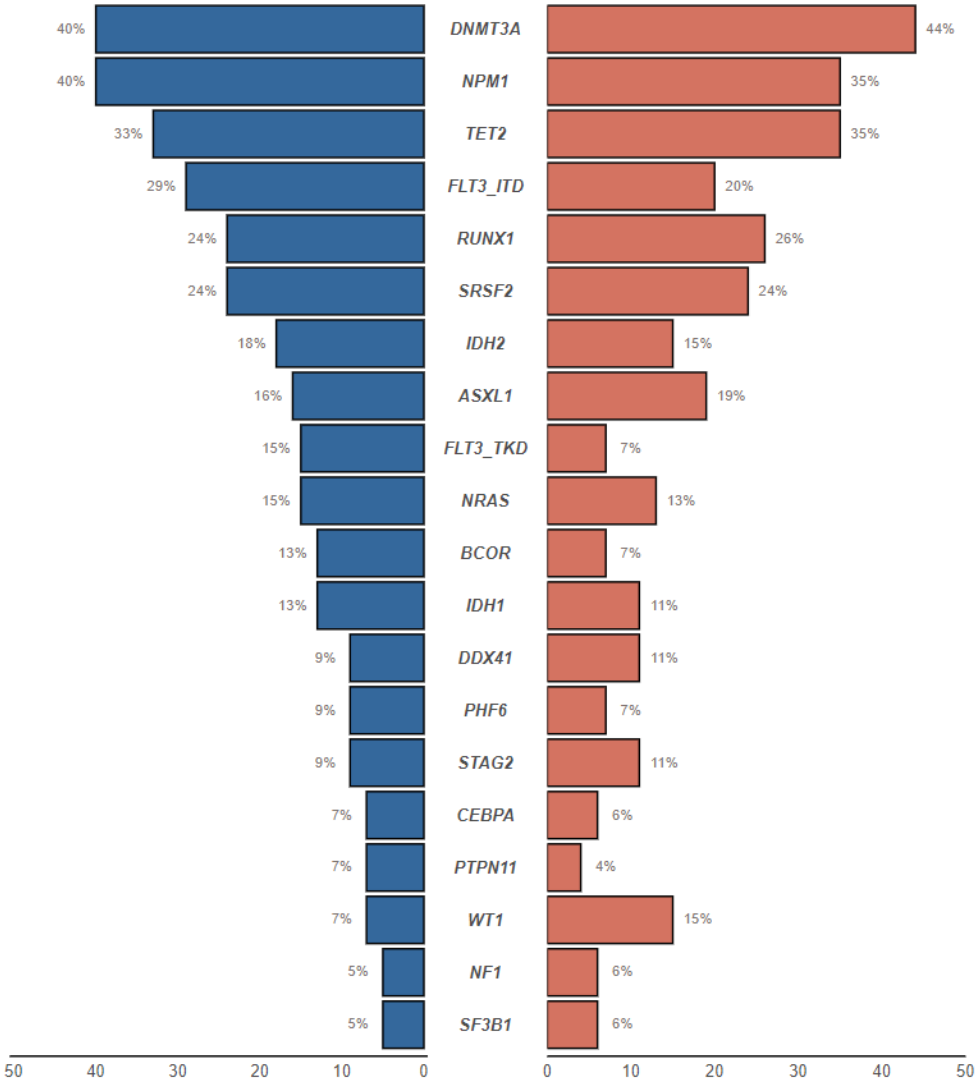

Figure S16. Mutations and cytogenetics at diagnosis (blue) and relapse (red) in rAML patients with *normal karyotype at the moment of diagnosis.*

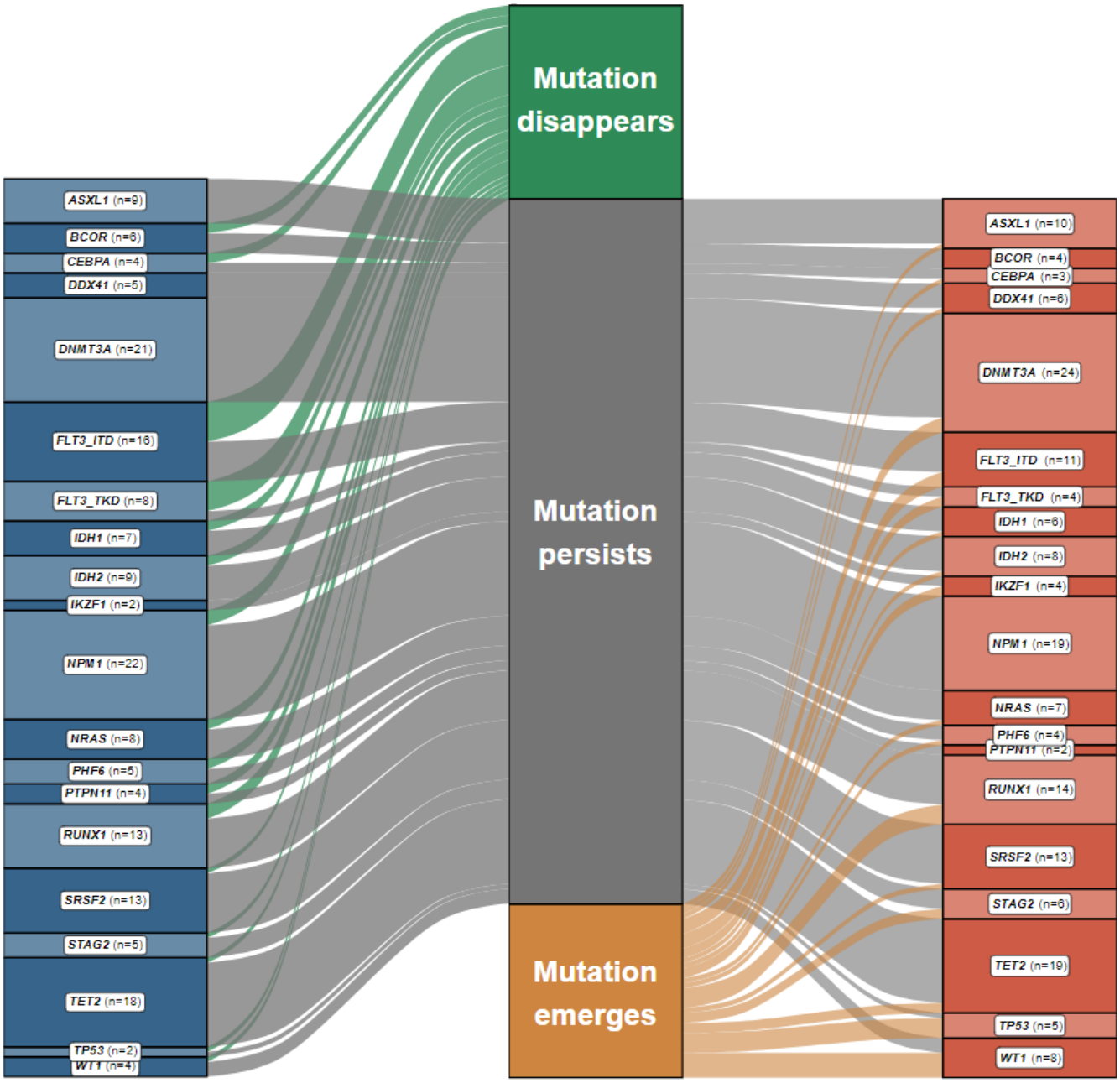

Figure S17. Mutation dynamics between diagnosis and relapse in patients with normal karyotype.

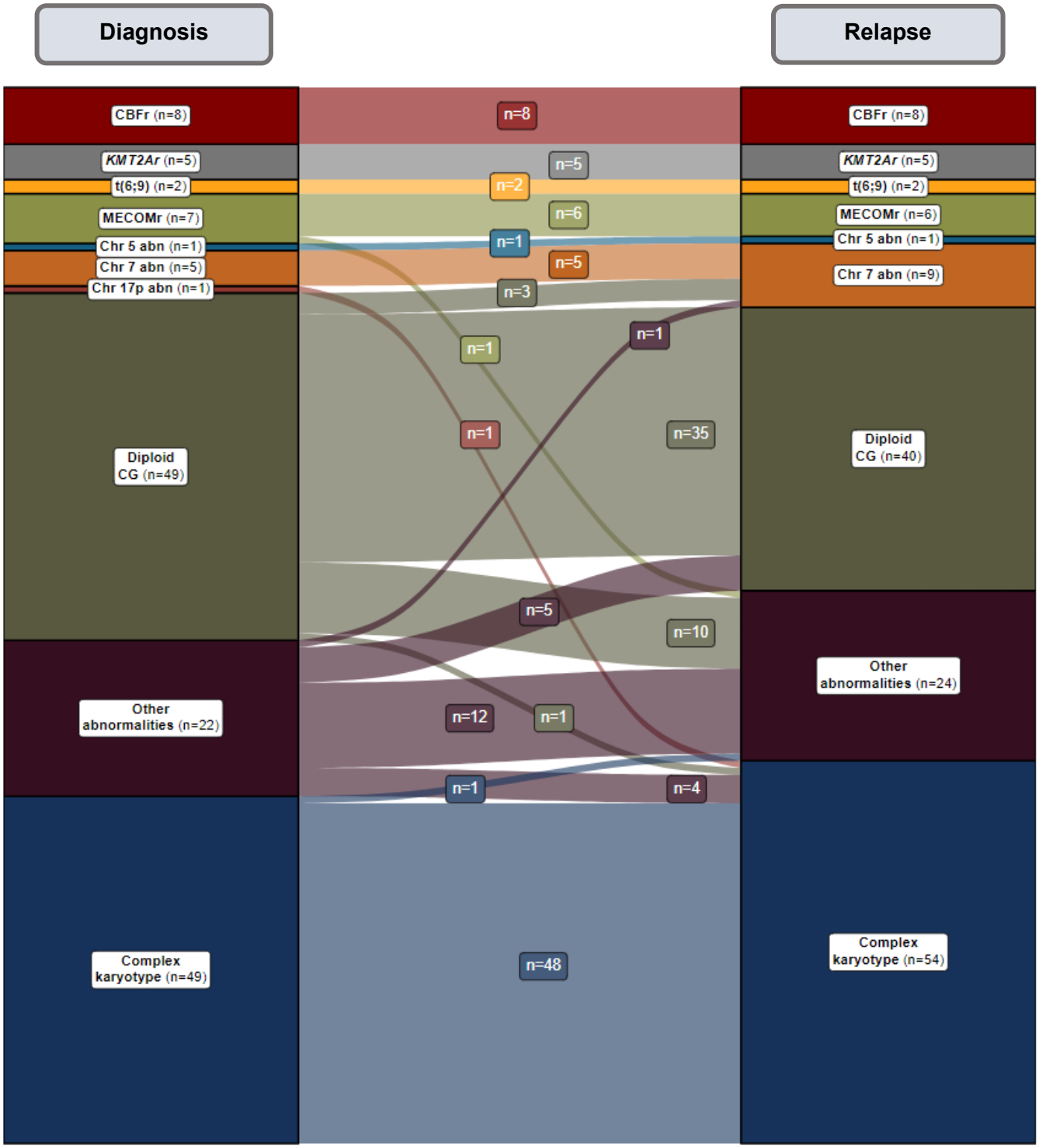

Figure S18. Flow of all patients according to their cytogenetic classification at diagnosis and at relapse. Numbers in the labels represent the number of patients.

ID	CG diagnosis	CG Relapse
9	46,XY[20]	46,XY[18]
20	46,XY[20]	46,XY[20]
24	46,XY,t(4;15)(q21;q21)[1]/46,XY[19]	46,XY[20]
26	46,XY[20]	45,XY,der(5;17)(p10;q10),add(7)(q22),del(12)(p12)[6]/ 44,XY,der(5;17)(p10;q10),-7[14]
34	46,XX[20]	46,XX[20]
35	46,XY[20]	46,XY[20]
37	46,XX[18]	46,XX[20]
38	46,XX[20]	46,XX[20]
43	47,XX,+mar[1]/46,XX[19]	NA
48	46,XX[20]	46,XX[20]
49	46,XY[20]	47,XY,+6[3]/48,idem,+8[2]/46~50,idem,+8,+13[cp3]/ 46,XY[12]
51	46,XY[20]	46,XY[20]
52	46,XY[20]	46,XY[20]
57	46,XY[20]	46,XY[20]
61	46,XX[20]	41,X,-X,-4,add(11)(q24),add(16)(q24)[1]/46,XX[19]
63	46,XX[20]	46,XX[20]
65	46,XY[20]	46,XY[20]
67	46,XY[20]	46,XY[20]
75	46,XX[20]	46,XY[20]
77	46,XX[19]	47,XX,+8[1]/46,XX[19]
78	46,XX,del(7)(p15)[1]/46,XX[19]	46,XX,inv(1)(p13q44)[1]/46,XX,t(1;18)(q22;p11.3)[1]/ 46,XX,-13,+mar[1]/46,XX[15]//46,XY[2]
80	46,XY[20]	46,XY,dup(1)(q21q32)[13]/46,XY,der(6)t(1;6)(q21;p23)[1]/ 46,XY[6]
83	46,XY[20]	46,XY[11]
89	46,XX,add(2)(q21),add(19)(p13.3)[1]/ 46,XX[19]	46,XX[19]/46,XY[1]
90	46,XY[20]	46,XX[20]
92	46,XX[20]	46,XX,t(9;20)(p22;p13)[2]/46,XX,add(9)(p24),-18[1]/46,XX[5]//46,XY[12]
93	46,XX[20]	50,XX,+6,+8,+8,+8[17]/46,XX[3]
94	46,XY[20]	46,XY[20]
95	46,XY[20]	46,XY[20]
97	46,XX[3]	46,XX[20]
98	46,XY[20]	46,XY,del(1)(q21q22)[5]/46,Y,del(X)(q24q26)[1]/ 46,XY[14]
101	46,XX[20]	46,XX,t(4;17)(q12;q25)[15]/46,XX[5]
104	46,XY[20]	46,XY[20]
109	46,XX[20]	46,XX[20]
110	46,XY[20]	47,XY,+8,add(17)(p13)[12]/46,XY[8]
111	46,XY[20]	46,XY,t(6;22)(q25;q11.2)[20]
112	47,XY,+mar[2]/46,XX[18]	46,XY[20]
113	47,XY,+mar[1]/46,XY[19]	46,XY[20]
115	46,XX[20]	45,XX,-7[14]/45,XX,der(7;17)(q10;q10)[2]// 46,XY,inv(9)(p12q13)[6]
117	46,XY[20]	46,XY[20]
123	46,XY[20]	47,XY,+1[1]/46,XY[19]
125	47,XY,+11[1]/46,XY[19]	46,XY[20]
126	46,XY[20]	NA

129	48,XY,+12,+14[1]/46,XY[19]	NA
133	46,XX[20]	46,XX[20]
134	46,XY[20]	48,XY,+8,+21[3]/49,idem,+13[1]/46,XY[16]
136	46,XX[20]	47,XX,+4[17]/46,XX,del(7)(q22)[2]/46,XX[1]
137	46,XY[20]	46,XY[20]
140	46,XX[20]	46,XX[20]
141	46,XX[20]	NA
144	42,XY,-6,-7,-7,+8,add(15)(q24), add(19)(q13.3),-21,-21[1]/46,XY[19]	NA
145	47,XX,+mar[1]/46,XX[19]	47,XX,+11[9]/46,XX,del(7)(q22)[8]/46,XX[3]
150	47,XY,del(2)(p12),-3,+2mar[1]/ 45,XY,der(14;21)(q10;q10)[1]/46,XY[18]	46,XY[20]
161	46,XX[20]	46,XX,del(12)(p13p12)[9]/46,XX[11]
162	46,XY[20]	NA

Table S6. Karyotypes at diagnosis and relapse in patients with normal karyotype. Non-class defining abnormalities found in only one metaphase were not considered clonal.

Supplementary analysis 3 (SA3)

Prognostic scores for rAML

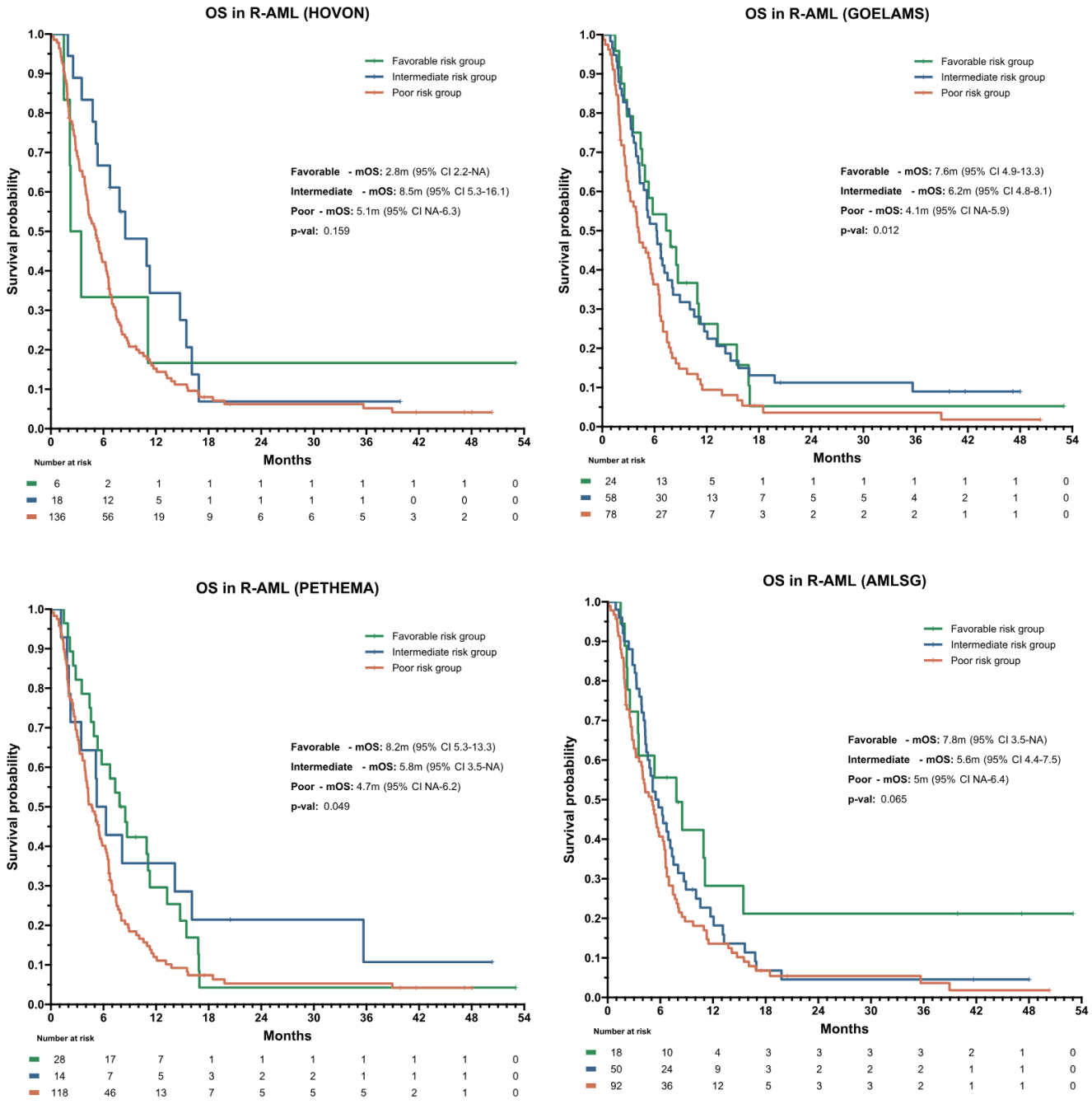

Figure S19. OS according to different prognostic scores. Upper left: HOVON (Breems et al, J Clin Oncol 2005). Upper right: GOELAMS (Chevallier et al, Leukemia 2011). Lower left: PETHEMA (Bergua et al, Br J Haematol 2016). Lower right: AMLSG (Schlenk et al, Leukemia 2017).

	Breems et al J Clin Oncol 2005	Chevallier et al Leukemia 2011	Bergua et al Br J Haematol 2016	Schlenk et al Leukemia 2017	Van der Maas NG et al ASH 2023
Relapse-free interval	Yes (6 - 18m)	Yes (12m)	Yes (12m)	Yes (6 - 18m)	Yes (12m)
Cytogenetics	CBF vs other	Adverse vs non-adverse	Inv16 vs Int vs High risk + t(8;21)	CBF (fav)	*MLL*, Complex karyotype (unfav)
Age	Yes (35 – 45yo)	No	Yes (60yo)	Yes	Yes (60yo)
Previous SCT	Yes (unfav)	No	Yes (AutoSCT unfav, alloSCT no effect)	Yes (unfav)	Yes (unfav)
WBC at diagnosis	No	No	No	No	Yes (>10K)
***FLT3*-ITD**	NA	Yes (unfav)	Yes (unfav)	Yes (unfav)	Yes (unfav)
***TP53* mut**	NA	NA	NA	No	Yes
***CEBPA* mut**	NA	NA	NA	Yes (fav)	No

Table S7. Summary of the different prognostic scores for rAML with the variables included in each classification.

	HOVON			GOLEAMS			PETHEMA			AMLSG		
	n	mOS (months)	1-yr OS	n	mOS (months)	1-yr OS	n	mOS (months)	1-yr OS	n	mOS (months)	1-yr OS
Low risk	6	2.8	17%	24	7.6	26%	28	8.2	30%	18	7.8	28%
Intermediate risk	18	8.5	34%	58	6.2	24%	14	5.8	36%	50	5.6	20%
High risk	136	5.1	15%	78	4.1	9%	118	4.7	12%	92	5	13%
P value (log-rank)	0.159			0.012			0.049			0.065		
Harrell's C-index	0.535			0.575			0.554			0.553		

Table S8. Overall survival, log-rank test and Harrel's C-index for each prognostic score evaluated.

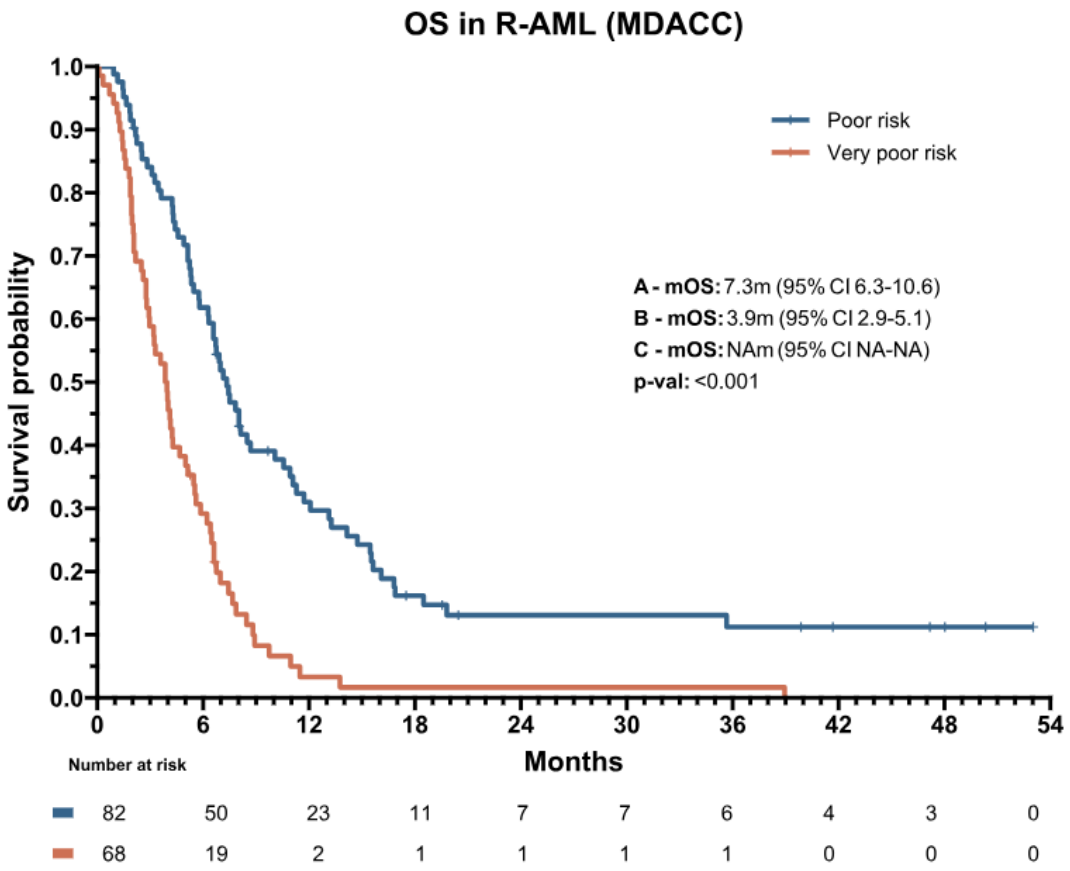

Figure S20. OS according to an exploratory analysis looking at risk groups defined the multivariate analysis. Patients with no or one risk factor (poor risk) vs patients with two or more risk factors (very poor risk). Risk factors are defined by time in remission < 12 months, adverse cytogenetics or *KMT2A* rearrangement at relapse, and a WBC > 20 x 10^9/L at relapse