

Cluster of differentiation 33 single nucleotide polymorphism rs12459419 is a predictive factor in patients with nucleophosmin1-mutated acute myeloid leukemia receiving gemtuzumab ozogamicin

Katrin Teich,¹ Julia Krzykalla,² Silke Kapp-Schwoerer,³ Verena I. Gaidzik,³ Richard F. Schlenk,^{4,5} Peter Paschka,³ Daniela Weber,³ Walter Fiedler,⁶ Michael W. M. Kühn,⁷ Thomas Schroeder,⁸ Karin Mayer,⁹ Michael Lübbert,¹⁰ Dhanya Ramachandran,¹¹ Axel Benner,² Arnold Ganser,¹ Hartmut Döhner,³ Michael Heuser,¹ Konstanze Döhner³ and Felicitas Thol¹

¹Department of Hematology, Hemostaseology, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover; ²Division of Biostatistics, German Cancer Research Center Heidelberg, Heidelberg; ³Department of Internal Medicine III, University Hospital of Ulm, Ulm; ⁴Nationales Centrum für Tumorerkrankungen Trial Center, National Center of Tumor Diseases, German Cancer Research Center, Heidelberg; ⁵Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg; ⁶Department of Internal Medicine II, University Medical Center Hamburg-Eppendorf, Hamburg; ⁷Department of Hematology, Medical Oncology and Pneumology, University Medical Center Mainz, Mainz; ⁸Department of Hematology, Oncology, and Clinical Immunology, University of Düsseldorf, Medical Faculty, Düsseldorf; ⁹Internal Medicine III, University Hospital of Bonn, Bonn; ¹⁰Klinik für Innere Medizin I, Universitätsklinikum Freiburg, Faculty of Medicine, Freiburg and ¹¹Department Molecular Gynecology, Hannover Medical School, Hannover, Germany

Correspondence: KATRIN TEICH - teich.katrin@mh-hannover.de

doi:10.3324/haematol.2021.278894

Supplemental Data

Supplemental Table 1: Patient and disease characteristics according to randomization and CD33 genotype.

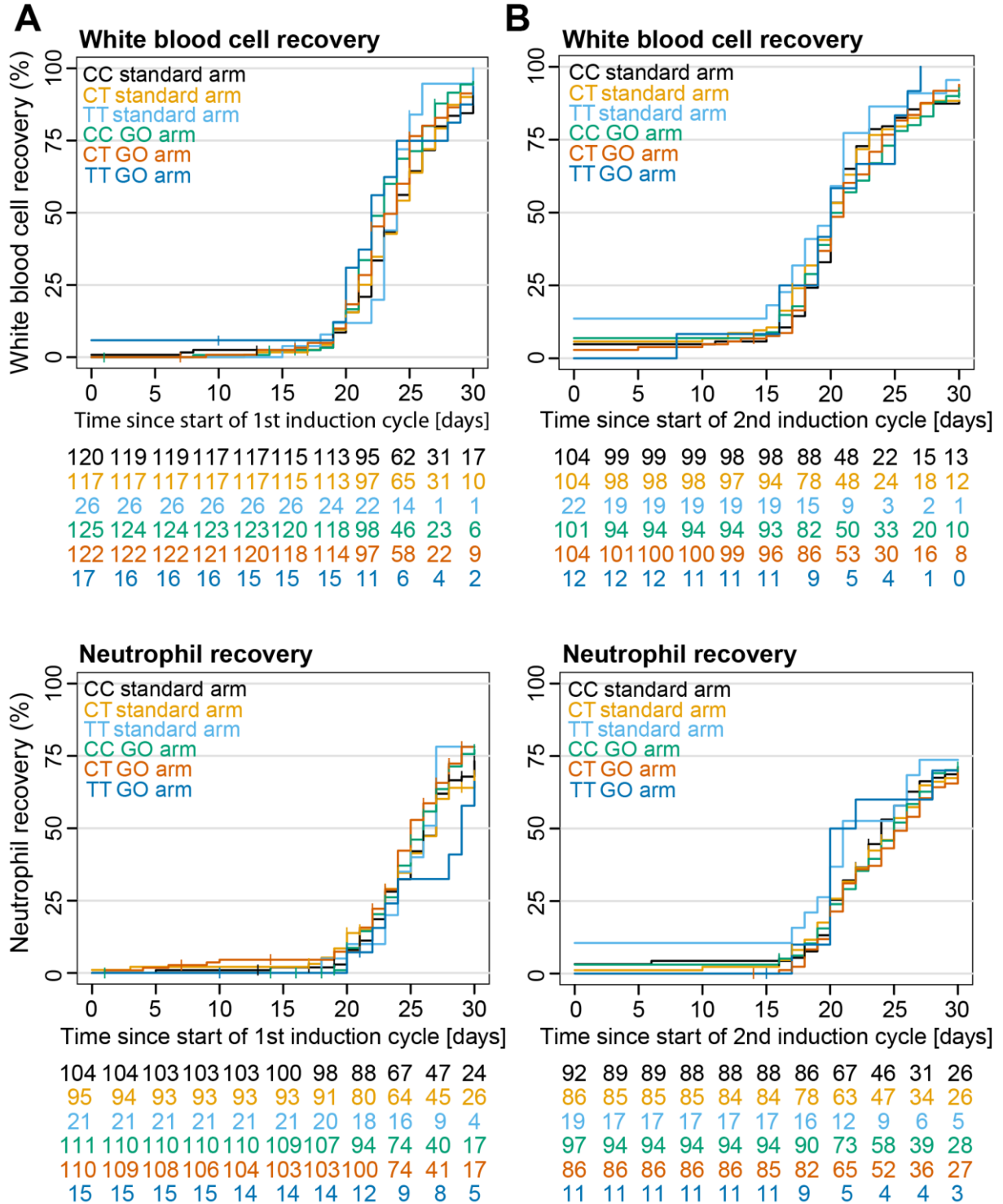
Parameter	Standard arm			GO arm		
	CC (N=123, 45%)	CT (N=120, 44%)	TT (N=29, 11%)	CC (N=128, 46%)	CT (N=127, 45%)	TT (N=18, 9%)
Age (years)						
Mean (SD)	57.3 (12.6)	58.0 (12.7)	57.0 (15.3)	58.0 (12.1)	58.3 (11.7)	61.9 (14.1)
Median [Min, Max]	57.6 [20.9, 77.3]	58.6 [21.9, 78.4]	60.7 [22.1, 80.2]	57.6 [25.7, 78.3]	59.9 [19.3, 82.3]	62.8 [18.4, 76.2]
Sex						
Male	55 (45%)	57 (47%)	17 (59%)	63 (49%)	48 (38%)	8 (44%)
Female	68 (55%)	63 (53%)	12 (41%)	65 (51%)	79 (62%)	10 (56%)
ECOG performance status						
0	48 (39%)	42 (35%)	11 (38%)	37 (29%)	49 (39%)	6 (33.3%)
1	62 (50%)	65 (54%)	15 (52%)	79 (62%)	66 (52%)	6 (33.3%)
2	13 (11%)	13 (11%)	3 (10%)	12 (9%)	12 (9%)	6 (33.3%)
FAB subtype						
M0	6 (6%)	2 (2%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)
M1+M2	44 (46%)	42 (46%)	16 (67%)	48 (47.5%)	46 (44%)	7 (54%)
M3	1 (1%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)
M4+M5	43 (44%)	45 (50%)	7 (29%)	48 (47.5%)	52 (51%)	5 (38)
M6+M7	3 (3%)	2 (2%)	0 (0%)	4 (4%)	4 (4%)	1 (8%)
Missing	26 (21%)	29 (24%)	5 (17%)	27 (21%)	24 (19%)	5 (28%)
Type of AML						
de novo	110 (90%)	110 (91%)	26 (90%)	115 (90%)	113 (89%)	17 (94%)
secondary	7 (6%)	8 (7%)	2 (7%)	10 (8%)	11 (9%)	1 (6%)
therapy-related	5 (4%)	2 (2%)	1 (3%)	3 (2%)	3 (2%)	0 (0%)
Missing	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ELN 2010						
Favorable	84 (74%)	81 (78%)	18 (70%)	80 (68%)	93 (81%)	11 (65%)
Intermediate-I	16 (14%)	12 (12%)	4 (15%)	18 (15%)	11 (10%)	5 (29%)
Intermediate-II	13 (11%)	8 (8%)	4 (15%)	18 (15%)	10 (9%)	1 (6%)
Adverse	1 (1%)	2 (2%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Missing	9 (7%)	17 (14%)	3 (10%)	10 (8%)	13 (10%)	1 (6%)
HSCT						
no	79 (64%)	85 (71%)	23 (79%)	103 (81%)	97 (76%)	13 (72%)
yes	44 (36%)	35 (29%)	6 (21%)	25 (19%)	30 (23%)	5 (28%)

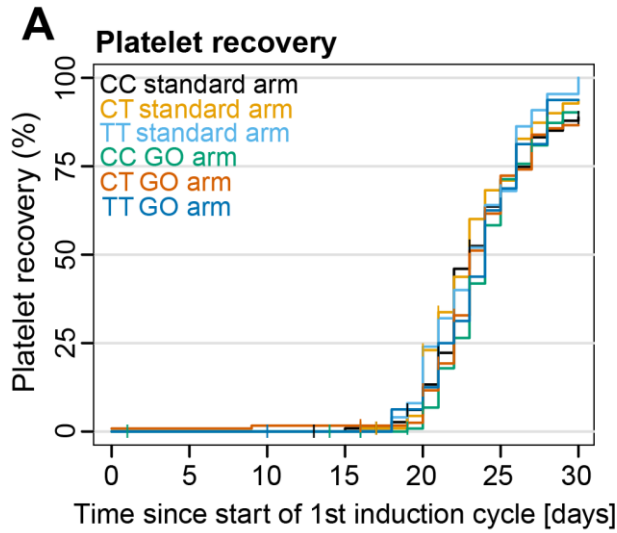
HSCT Type						
Matched related	9 (21%)	11 (32%)	1 (17%)	7 (28%)	7 (23%)	2 (40%)
Matched unrelated	33 (79%)	20 (59%)	5 (83%)	18 (72%)	23 (77%)	3 (60%)
Haploidentical	0 (0%)	3 (9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	81 (66%)	86 (72%)	23 (79%)	103 (81%)	97 (76%)	13 (72%)
HSCT-Phase						
CR1	14 (34%)	13 (40%)	2 (33%)	14 (56%)	14 (47%)	2 (40%)
CR2	11 (26%)	12 (38%)	3 (50 %)	7 (28%)	5 (17%)	1 (20%)
PR1	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)
RD1	1 (2%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Relapse1	14 (34%)	6 (19%)	1 (17%)	4 (16%)	10 (33%)	2 (40%)
Relapse2	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	81 (66%)	88 (73%)	23 (79%)	103 (81%)	97 (76%)	13 (72%)
Peripheral blood blasts						
Mean (SD)	34.7 (32.7)	38.1 (34.0)	44.2 (34.3)	38.3 (33.0)	34.4 (31.2)	35.6 (32.6)
Median [Min, Max]	24.0 [0, 99.0]	32.0 [0, 98.0]	39.0 [0, 97.0]	30.0 [0, 99.0]	26.0 [0, 97.0]	29.0 [0, 88.0]
Missing	6 (5%)	3 (2 %)	0 (0%)	5 (4%)	7 (6%)	1 (6%)
Bone marrow blasts						
Mean (SD)	65.6 (23.5)	67.6 (24.9)	63.5 (27.6)	68.7 (25.4)	64.0 (24.5)	66.8 (26.8)
Median [Min, Max]	70.0 [16.0, 100]	79.0 [20.0, 100]	80.0 [3.0, 94.0]	80.0 [0, 100]	70.0 [0, 100]	72.5 [15.0, 100]
Missing	5 (4%)	5 (4%)	0 (0%)	3 (2%)	4 (3%)	2 (11%)
WBC count (x 10⁹/l)						
Mean (SD)	39.9 (46.4)	42.0 (55.0)	45.1 (53.9)	40.1 (49.9)	33.1 (47.6)	27.0 (21.1)
Median [Min, Max]	23.4 [0.7, 243]	20.2 [0.6, 296]	23.3 [1.4, 207]	20.2 [0.9, 251]	15.6 [0.6, 254]	30.4 [2.1, 64.7]
Hemoglobin (g/L)						
Mean (SD)	9.34 (1.98)	9.61 (1.80)	9.20 (1.65)	9.24 (1.81)	9.15 (1.86)	9.29 (1.43)
Median [Min, Max]	9.25 [4.3, 19.3]	9.40 [5.5, 14.6]	8.80 [6.2, 12.4]	8.75 [5.8, 15.0]	9.10 [4.4, 13.1]	9.35 [7.0, 12.1]
Missing	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Platelet count						
Mean (SD)	97.6 (82.4)	103 (100)	77.5 (67.0)	84.0 (69.3)	102 (72.6)	64.8 (33.9)
Median [Min, Max]	75.0 [9.0, 533]	72.0 [12.0, 660]	56.0 [16.0, 376]	64.5 [7.0, 314]	91.0 [13.0, 404]	59.0 [15.0, 134]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
LDH						
Mean (SD)	554 (330)	605 (502)	572 (346)	667 (1090)	533 (417)	657 (577)
Median [Min, Max]	454 [147, 1630]	442 [86.0, 3100]	469 [210, 1490]	421 [151, 9670]	438 [137, 3120]	409 [250, 2420]
Missing	2 (2%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Cytogenetics by MRC						
Favorable	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Intermediate	115 (99%)	113 (99%)	29 (100%)	126 (98%)	121 (100%)	17 (100%)
Adverse	1 (1%)	1 (1%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Missing	7 (6%)	6 (5%)	0 (0%)	0 (0%)	6 (5%)	1 (6%)
<i>FLT3</i>-ITD						
Wildtype	102 (83%)	98 (82%)	23 (79%)	106 (83%)	109 (86%)	13 (72%)
Mutated	21 (17%)	22 (18%)	6 (21%)	22 (17%)	18 (14%)	5 (28%)
<i>FLT3</i>-TKD						
Wildtype	107 (87%)	110 (92%)	23 (79%)	108 (84%)	111 (87%)	17 (94%)
Mutated	16 (13%)	10 (8%)	6 (21%)	20 (16%)	16 (13%)	1 (6%)
<i>NPM1/FLT3</i> mutation risk group						
High risk	21 (17%)	22 (18%)	6 (21%)	22 (17%)	18 (14%)	5 (28%)
How risk	102 (83%)	98 (82%)	23 (79%)	106 (83%)	109 (86%)	13 (72%)
<i>DNMT3A</i>						
Wildtype	47 (52%)	49 (59%)	15 (75%)	40 (46%)	48 (57%)	6 (55%)
Mutated	43 (48%)	34 (41%)	5 (25%)	46 (54%)	37 (43%)	5 (45%)
Missing	33 (27%)	37 (31%)	9 (31%)	42 (33%)	42 (33%)	7 (39%)

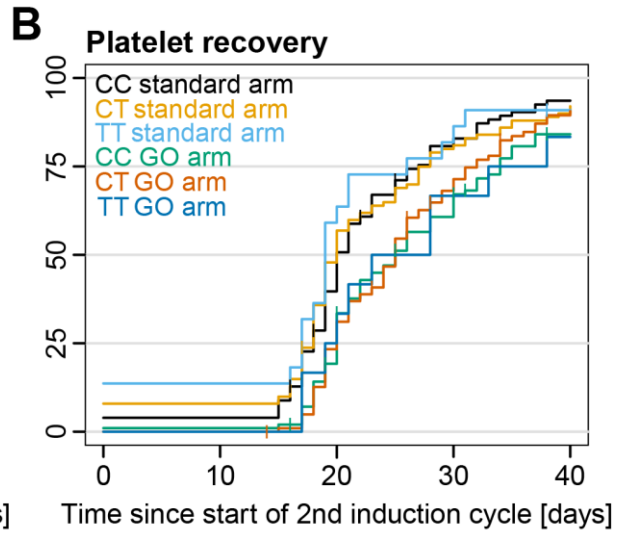
Abbreviations: AML, acute myeloid leukemia; CR, complete remission; *DNMT3A*, DNA methyltransferase 3A; ECOG, Eastern Cooperative Oncology Group; ELN, European Leukemia Net; FAB, French-American-British; *FLT3*-ITD, FMS-like tyrosine kinase 3 gene internal tandem duplication; *FLT3*-TKD, FMS-like tyrosine kinase 3 gene tyrosine kinase domain mutation; GO, Gemtuzumab ozogamicin; HSCT, hematopoietic stem cell transplantation; LDH, lactate dehydrogenase; MRC, Medical Research Council; *NPM1*, nucleophosmin1; PR, partial remission; RD, resistant disease; Secondary AML, AML after previous myelodysplastic syndrome or myeloproliferative neoplasm; WBC, white blood cell count

Supplemental Figure 1: Time to hematological recovery in the two treatment arms according to the three genotypes A) after first induction cycle and B) after second induction cycle.





118 118 118 118 118 116 113 97 51 27 13
 115 115 115 115 115 115 112 86 44 19 8
 26 26 26 26 26 26 25 19 12 3 1
 124 123 123 123 123 122 120 109 67 28 10
 121 120 120 120 119 119 118 105 56 29 15
 17 17 17 17 16 16 16 14 9 3 1

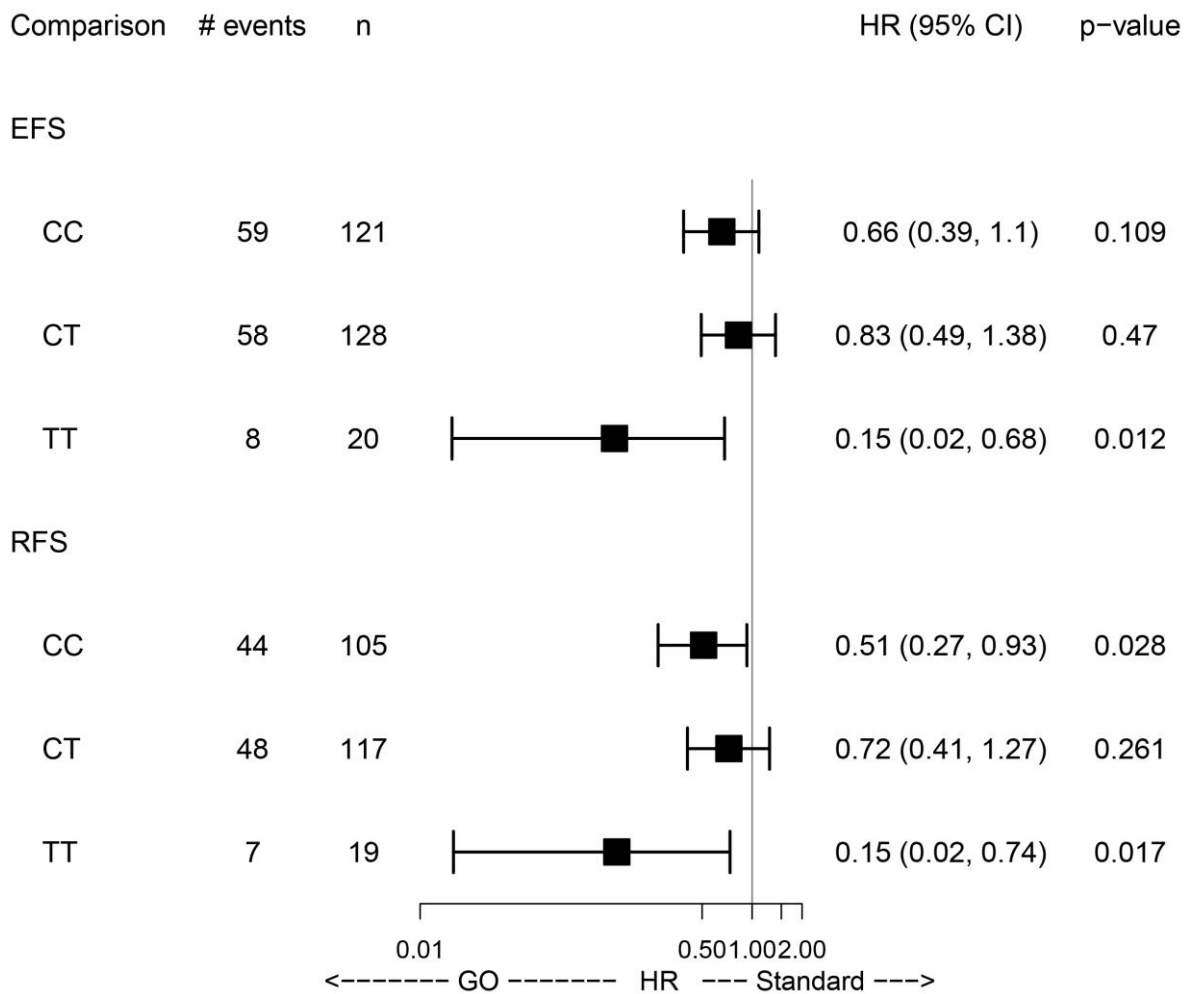


102 98 98 98 93 60 32 23 16 9 6
 101 93 93 93 91 52 36 25 17 12 10
 22 19 19 19 19 9 6 5 2 2 1
 100 99 99 99 98 79 53 41 28 17 12
 104 104 104 104 102 79 60 35 23 14 9
 12 12 12 12 12 9 6 6 4 3 2

Supplemental Figure 2: Separate analysis comparing GO vs. Standard arm for female (A) and male (B) patients in the three subgroups defined by the genotypes with regard to the endpoints event-free survival (EFS) and relapse-free survival (RFS). There was no significant correlation of the SNP with age or sex. Analysis of EFS and RFS for female patients (A) showed a trend towards a genotype-independent benefit in female patients treated with GO whereas male patients (B) show a trend to better EFS and RFS only for c.41 C/C genotype.

A

Treatment effect of GO vs. Standard by CD33 SNP Genotype for female patients



B

Treatment effect of GO vs. Standard by CD33 SNP Genotype for male patients

