

Supplements

Differential impact of IDH1/2 mutational subclasses on outcome in adult AML: Results from a large multicenter study

Table 1

Parameter	<i>IDH1</i> R132C	<i>IDH1</i> R132H	<i>IDH2</i> R140Q	<i>IDH2</i> R172
<i>IDH</i> VAF, median/mean (SD/IQR/range)	37.5/32.67 (12.53/ 27.6-41.3/ 0.9-58)	38/31.66 (14.91/ 23.35-42.75/ 0.14-52.5)	39.3/36.88 (12.43/ 32.98-44.92/ 0.3-76.78)	39/36.73 (10.97/ 32.25-44.97/ 9-58)

VAF – variant allele frequency; SD – standard deviation; IQR – interquartile range

Table 2

Parameter	wtIDH	IDH1	IDH2	p-value	adjusted p-value
patients, n	3946	423	561		
age, median (IQR)	55 (44-65)	59 (48-67)	59 (51-68)	<0.0001	<0.0001
VAf, median (IQR)		38.3 (26-42.6)	39.2 (32.9-45)	0.0006	0.0054
sex, n (%)				0.1674	0.6846
male	2018 (51.1)	196 (46.3)	287 (51.2)		
female	1928 (48.9)	227 (53.7)	274 (48.8)		
AML type, n (%)				0.1141	0.6846
de novo	3168 (81)	353 (83.6)	467 (84)		
sAML	511 (13.1)	50 (11.8)	65 (11.7)		
tAML	234 (6)	19 (4.5)	24 (4.3)		
lab values					
WBC in GPt/l, median (IQR)	15.3 (3.9-50.5)	10.5 (2.3-46.1)	11.6 (2.8-45.3)	0.0015	0.012
PLT in GPt/l, median (IQR)	51 (28-92)	67 (33-121)	68 (38-131)	<0.0001	<0.0001
Hb in mmol/l, median (IQR)	5.7 (4.9-6.6)	5.6 (5-6.5)	5.8 (5-6.6)	0.5514	1.0
LDH in U/l, median (IQR)	435 (274-784)	419 (255-707)	382 (236-586)	<0.0001	<0.0001
BM blasts in %, median (IQR)	63 (40-80)	73 (54-86)	70 (44-84)	<0.0001	<0.0001
Cytogenetics, n (%)				<0.0001	<0.0001
normal karyotype	1897 (51)	277 (73.3)	365 (70.5)		
complex karyotype	525 (13.8)	14 (3.5)	20 (3.7)		
ELN2017 risk				<0.0001	<0.0001
favorable	1234 (33.7)	162 (44)	182 (35)		
intermediate	1280 (35)	143 (38.9)	205 (39.4)		
adverse	1143 (31.3)	63 (17.1)	133 (25.6)		
Molecular markers					
mNPM1, n (%)	1110 (28.4)	211 (50.1)	224 (40)	<0.0001	<0.0001
FLT3-ITD, n (%)	890 (22.7)	83 (19.7)	115 (20.5)	0.2321	0.6963
FLT3-Ratio, median (IQR)	0.6 (0.2-0.8)	0.6 (0.2-0.8)	0.5 (0.2-0.7)	0.1203	0.6846
mCEBPA, n (%)	288 (7.4)	12 (2.9)	24 (4.3)	0.0001	0.001

wt – wild-type; m – mutated; IQR – interquartile range; sAML – secondary acute myeloid leukemia; tAML – therapy-associated acute myeloid leukemia; WBC – white blood cell count; PLT – platelet count; Hb – hemoglobin; BM – bone marrow; N/n - number

Table 3

1) CR rate for <i>IDH1</i> -R132C compared to other <i>mIDH1</i>			
	Odds ratio	95%-CI	adjusted <i>p</i> -value
age	0.96	0.95-0.96	<0.001
log(WBC)	0.65	0.58-0.74	<0.001
sAML	0.63	0.51-0.79	<0.001
tAML	0.47	0.35-0.64	<0.001
ELN2017 favorable	2.02	1.63-2.49	<0.001
ELN2017 adverse	0.41	0.34-0.49	<0.001
<i>IDH1</i> -R132C	0.63	0.43-0.92	0.016
<i>IDH1</i> -R132H	0.77	0.51-1.18	0.232
<i>IDH1</i> -R132G, -R132S, -R132L	0.54	0.29-1.00	0.052
2) CR rate for <i>IDH1</i> -R132G, -R132S, -R132L			
	Odds ratio	95%-CI	adjusted <i>p</i> -value
age	0.96	0.95-0.96	<0.001
log(WBC)	0.61	0.53-0.69	<0.001
sAML	0.65	0.51-0.81	<0.001
tAML	0.50	0.37-0.68	<0.001
ELN2017 favorable	2.08	1.58-2.75	<0.001
ELN2017 adverse	0.43	0.35-0.52	<0.001
<i>mNPM1</i>	1.06	0.76-1.47	0.747
<i>FLT3</i> -ITD	1.44	1.09-1.91	0.01
<i>IDH1</i> -R132C	0.65	0.45-0.95	0.026
<i>IDH1</i> -R132H	0.77	0.50-1.19	0.241
<i>IDH1</i> -R132G, -R132S, -R132L	0.52	0.28-0.96	0.036
3.1) RFS for <i>IDH2</i> -R172K compared to other <i>mIDH1</i> / <i>mIDH2</i> variants			
	Hazard ratio	95%-CI	adjusted <i>p</i> -value
age	1.02	1.02-1.03	<0.001
log(WBC)	1.14	1.16-1.33	<0.001
sAML	0.99	0.85-1.14	0.839
tAML	0.94	0.75-1.18	0.614
ELN2017 favorable	0.52	0.47-0.58	<0.001

ELN2017 adverse	1.43	1.28-1.60	<0.001
IDH1-R132C	0.93	0.72-1.21	0.578
IDH1-R132H	1.30	1.02-1.65	0.033
IDH1-R132G, -R132S, -R132L	1.18	0.79-1.77	0.425
IDH2-R172K	0.68	0.50-0.92	0.013
IDH2-R140Q	1.06	0.91-1.23	0.473
3.2) OS for IDH2-R172K compared to other mIDH1/mIDH2 variants			
	Hazard ratio	95%-CI	adjusted <i>p</i> -value
age	1.03	1.028-1.034	<0.001
log(WBC)	1.30	1.23-1.38	<0.001
sAML	1.10	0.99-1.23	0.081
tAML	1.46	1.25-1.71	<0.001
ELN2017 favorable	0.53	0.48-0.59	<0.001
ELN2017 adverse	1.61	1.47-1.76	<0.001
<i>IDH1</i> -R132C	1.15	0.95-1.40	0.162
<i>IDH1</i> -R132H	1.27	1.03-1.56	0.027
<i>IDH1</i> -R132G, -R132S, -R132L	1.18	0.85-1.65	0.317
<i>IDH2</i> -R172K	0.737	0.57-0.95	0.018
<i>IDH2</i> -R140Q	0.95	0.84-1.09	0.476
4) IDH2-R172K compared to wtIDH1/2			
	Hazard ratio	95%-CI	adjusted <i>p</i> -value
age	1.03	1.027-1.035	<0.001
log(WBC)	1.32	1.24-1.41	<0.001
sAML	1.07	0.95-1.20	0.255
tAML	1.45	1.22-1.72	<0.001
ELN2017 adverse	1.63	1.49-1.78	<0.001
<i>IDH1</i> -R132C	1.16	0.93-1.43	0.19
<i>IDH1</i> -R132H	1.31	0.95-1.81	0.11
<i>IDH1</i> -R132G, -R132S, -R132L	1.26	0.81-1.97	0.303
<i>IDH2</i> -R172K	0.72	0.56-0.93	0.012
<i>IDH2</i> -R140Q	0.86	0.73-1.01	0.065

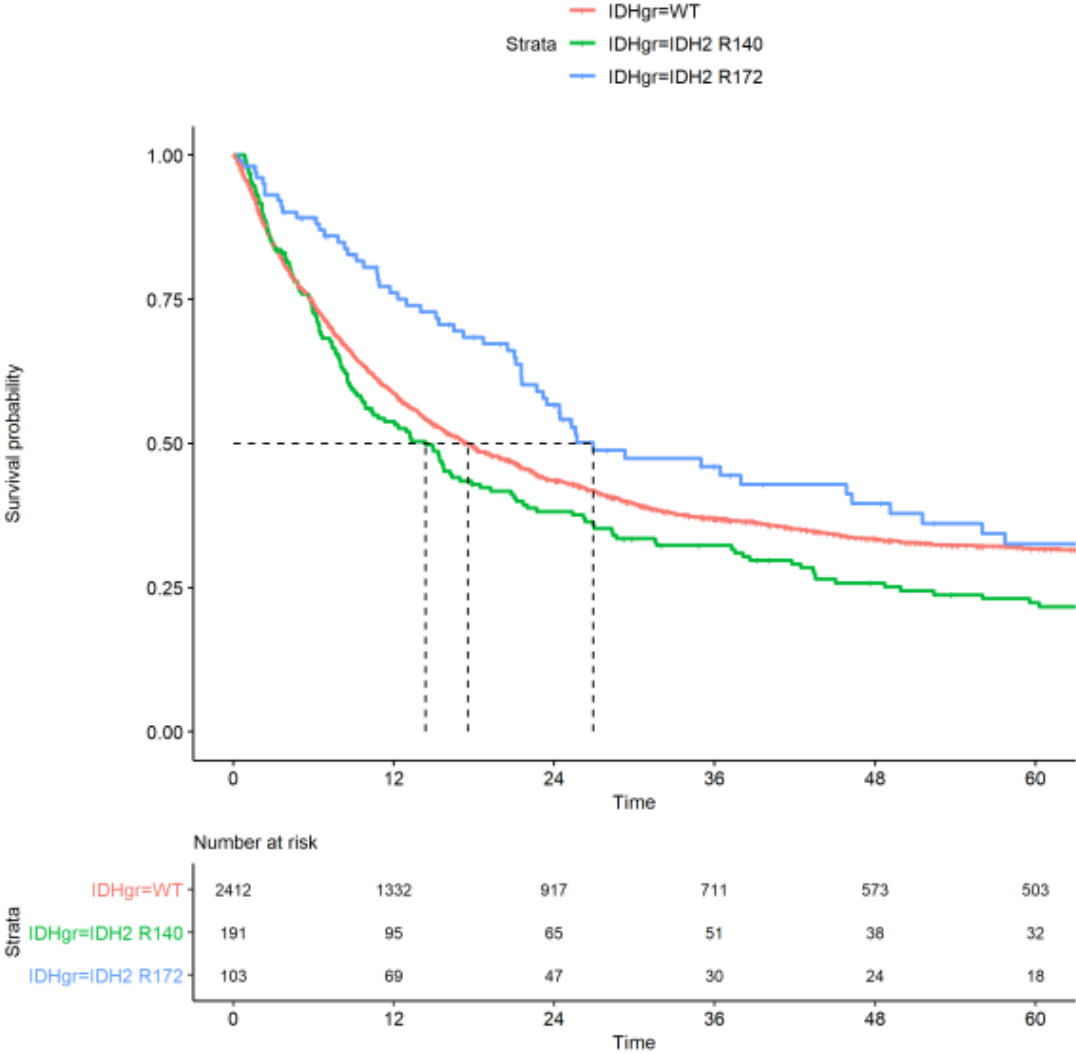
Multivariable analysis for outcome of mIDH1/2 variants. CI: confidence interval; CR: complete remission; m-: mutated; OS: overall survival; RFS: relapse-free survival; sAML: secondary AML; tAML: therapy-associated AML; WBC: white blood cell count; wt: wildtype

Table 4

Parameter	IDH1-R132G	IDH1-R132L	IDH1-R132S	p-value
patients, n	28	18	20	
CR/Cri, n	19	13	14	0.9512
OS in months, median (CI)	18.7 (12 – Inf)	16.9 (12.4 – Inf)	21.2 (13.2 – Inf)	0.9802
RFS in months, median (CI)	19 (13.1 – Inf)	11.4 (7.6 – Inf)	18.7 (12.3 – Inf)	0.9761

CR – complete remission; CRi – complete remission with incomplete regeneration; OS – overall survival; RFS – relapse-free survival; CI - confidence interval (at 95% confidence); N/n – number; Inf - infinity

Figure 1



Kaplan-Meier plot for overall survival between wild-type *IDH*, mutated *IDH2* R140 and mutated *IDH2* R172 AML; time in months.