

Supplementary Table S1. Pathogenic or likely pathogenic SNVs *

NB driver genes		Variant type
<i>CASZ1</i> c.4966 del G		frameshift
<i>PBX2</i> c.41 G>A		missense
<i>FGFR1</i> c.1625 del A		frameshift
<i>DMBT1</i> c.7217 del C		frameshift
<i>PTPN11</i> c.1508 G>T		missense
Other mutated genes		
<i>HTR1D</i> c.680 G>A		missense
<i>TYW1</i> c.1273 C>T		missense
<i>LRP1B</i> c.13686 T>G		stop gained
<i>MAST2</i> c.1301 C>A		missense
<i>GNG12</i> c.202 del A		frameshift
<i>BARHL2</i> c.865 C>T		missense
<i>KCNA10</i> c.352 de lA		frameshift
<i>KCNA10</i> c.352 A>G		missense
<i>INKA2</i> c.559 del G		frameshift
<i>GON4L</i> c.5490 delA		frameshift
<i>FCRL6</i> c.1302 C>A		stop gained
<i>ADCY10</i> c.4518 C>A		splice region
<i>TDRD5</i> c.1907 del T		frameshift
<i>CEP350</i> c.4361 A>G		missense
<i>RBBP5</i> c.997 G>A		missense
<i>PKDCC</i> c.254G>T		missense
<i>ATP6V1B1</i> c.33 del G		frameshift
<i>DOK1</i> c.245 del C		frameshift
<i>AFF3</i> c.1696 del G		frameshift
<i>EN1</i> c.820 G>A		missense
<i>MYO7B</i> c.6313 C>T		stop gained
<i>SAP130</i> c.1787 T>A		missense
<i>PTPN18</i> c.826 C>T		stop gained
<i>MCM6</i> c.1825 G>T		missense
<i>VIL1</i> c.2035 C>T		stop gained
<i>TUBA4A</i> c.355 C>T		splice region
<i>TMEM198</i> c.653 G>T		missense
<i>MTMR14</i> c.1490 del C		frameshift
<i>ZBTB47</i> c.1634 A>G		missense
<i>LAMB2</i> c.2882 C>T		missense
<i>IFRD2</i> c.955_956 AA>CC		missense
<i>PBRM1</i> c.3520 T>C		missense
<i>SI</i> c.1882 C>A		missense
<i>EVC2</i> c.24 del G		frameshift
<i>CRMP1</i> c.381+4323 A>G		initiator codon
<i>SRD5A3</i> c.312 del T		frameshift
<i>PARM1</i> c.784 A>C		missense
<i>PRDM8</i> c.822 C>T		splice region
<i>ANK2</i> c.10367 dup G		frameshift
<i>CCNA2</i> c.293 C>T		missense
<i>PCDH10</i> c.49 T>C		missense

AGXT2 c.1421 G>A	missense
NUP155 c.166 A>C	missense
ITGA1 c.87 C>A	missense
IK c.814 C>G	missense
PDE6A c.2381 A>G	missense
TCOF1 c.2873 del C	frameshift
NPM1 c.527 A>G	missense
NSD1 c.2903 del A	frameshift
SLC22A23 c.1864 A>T	frameshift
SLC22A23 c.932 del C	missense
ARFGEF3 c.2096 C>A	missense
ARFGEF3 c.4207 del G	frameshift
ARFGEF3 c.4207 G>T	missense
SASH1 c.1756 del A	frameshift
SYNE1 c.11394 del A	frameshift
ANLN c.523 C>T	missense
SEPTIN14 c.775 del A	frameshift
SAMD9 c.3559 del A	frameshift
KLHDC10 c.604 A>G	missense
PLXNA4 c.5573 G>A	missense
ADAM9 c.883 C>T	missense
PARP10 c.1829 A>G	missense
FAM189A2 c.1157 C>T	missense
C5 c.3479 C>T	missense
HMCN2 c.8956 G>A	missense
FUBP3 c.566 A>G	missense
CEL c.2171 del C	frameshift
TRAF2 c.26 del C	frameshift
ITGA8 c.1344 C>T	splice region
ADRA2A c.1019 A>T	missense
TRPM5 c.2906 T>G	missense
CARS1 c.1265 del A	frameshift
EIF3F c.1034 A>G	missense
MRPL48 c.222 del A	frameshift
EED c.770 A>T	missense
JHY c.2216 del A	frameshift
CACNA1C c.2336 C>T	missense
STK38L c.710 G>T	missense
CAND1 c.674 del A	frameshift
BTBD11 c.2570 A>G	missense
HNF1A c.1463 C>A	missense
MYCBP2 c.1173 C>T	splice region
CCDC168 c.17048 del A	frameshift
CCDC168 c.12092 del A	frameshift
SOX1 c.342 G>A	splice region
CUL4A c.1952 G>T	missense
ABCD4 c.868 G>A	missense
RTF1 c.1098 G>A	splice region
TBC1D24 c.1531 G>A	missense
SRL c.734 G>A	missense
GLYR1 c.874 A>G	missense
ITGAM c.856 G>T	missense
ZNRF1 c.199 del G	frameshift
KIAA0513 c.73 G>T	stop gained

TRPV3 c.353 G>A		missense
ENO3 c.313 A>C		missense
DHX33 c.1393 C>G		missense
NLGN2 c.1967 A>G		missense
SLC35G6 c.997_998 GA>AC		missense
DHRS7C c.141 A>G		splice region
KSR1 c.146 A>G		missense
MED1 c.1172 C>T		missense
NR1D1 c.610 C>T		missense
OTOP2 c.1456 del A		frameshift
CCDC137 c.799 C>T		stop gained
ZBTB7C c.1435 C>G		missense
ATP8B1 c.2441 A>G		missense
RTTN c.2303 dup A		frameshift
SF3A2 c.337 G>A		missense
ARHGEF18 c.434 A>T		missense
AP1M1 c.546+1201 G>T		stop gained
MYO9B c.4154 del A		frameshift
ZNF682 c.146 delA		frameshift
TDRD12 c.3378 dup G		frameshift
KIRREL2 c.606 del T		frameshift
LTBP4 c.3958 G>T		missense
CTU1 c.166 G>A		missense
ZSCAN18 c.1418 dup G		frameshift
RTF2 c.340 C>A		missense
TIAM1 c.3284 A>G		missense
RIPK4 c.27 G>T		missense
TRPM2 c.1273 G>A		missense
FOXRED2 c.1663 C>T		missense
BAIAP2L2 c.1392 del C		frameshift
NPTXR c.1 C>A		initiator codon
GTPBP6 c.170 T>A		missense
TAB3 c.1772 C>T		missense
PPP1R2C c.202 G>A		missense
SASH3 c.14 A>C		missense

Legend: * Pathogenicity of SNVs was checked using multiple web-based applications evaluating DNA sequence variants for their disease-causing potential

- Mutation detected only in tumor onset DNA
- Mutation detected only in exo-DNA at onset
- Mutation detected only in exo-DNA at progression
- Concordant mutation in tumor DNA and in exo-DNA at progression
- Concordant mutation in tumor DNA, in exo-DNA at onset and in exo-DNA at progression

Supplementary Table S2. Survival of 786 NB patients in relation to *KLRB1* expression levels by *MYCN* status.

Overall Survival	N/D	OS	95%CI	<i>p</i>
<i>MYCN normal</i>				
Cut-off based on the median value				0.002
≤ 1.559	314/74	77.1	72.0 – 81.4	
> 1.559	315/45	84.6	79.7 – 88.4	
Cut-offs based on tertile values				< 0.001
≤ 1.174	209/58	72.2	65.5 – 77.9	
1.174 – 1.945	210/32	85.1	79.3 – 89.5	
> 1.945	210/29	85.2	79.2 – 89.6	
<i>MYCN amplified</i>				
Cut-off based on the median value				0.537
≤ 0.391	76/54	28.5	18.7 – 39.0	
> 0.391	77/54	29.9	20.1 – 40.2	
Cut-offs based on tertile values				0.803
≤ 0.152	51/36	29.0	17.2 – 41.8	
0.152 – 0.825	51/31	39.2	26.0 – 52.2	
> 0.825	51/41	19.6	10.1 – 31.4	
Event Free Survival	N/E	EFS	95%CI	<i>p</i>
<i>MYCN normal</i>				
Cut-off based on the median value				0.027
≤ 1.559	307/116	62.5	56.8 – 67.7	
> 1.559	307/91	70.3	64.9 – 75.1	
Cut-offs based on tertile values				0.001
≤ 1.174	203/87	57.6	50.5 – 64.1	
1.174 – 1.945	206/62	69.9	63.1 – 75.7	
> 1.945	205/58	71.7	65.0 – 77.3	
<i>MYCN amplified</i>				
Cut-off based on the median value				0.390
≤ 0.391	75/56	24.2	14.9 – 34.9	
> 0.391	76/55	27.6	18.2 – 37.9	
Cut-offs based on tertile values				0.837
≤ 0.152	51/39	21.9	11.1 – 34.9	
0.152 – 0.825	50/31	38.0	24.8 – 51.1	
> 0.825	50/41	18.0	8.9 – 29.7	

N/D = Number of patients/ Deaths. OS = Ten-year Overall Survival, N/E Number of patients/ Events. EFS = Ten-year Event Free Survival, 95%CI: 95% confidence interval.

Supplementary Table S3. Survival of 786 NB patients in relation to *KLRB1* expression levels by INSS stage.

Overall Survival	N/D	OS	95%CI	<i>p</i>
<i>Localized stage</i>				
Cut-off based on the median value				0.007
≤ 1.556	186/25	86.5	80.7 – 90.7	
> 1.556	187/10	94.6	90.2 – 97.1	
Cut-offs based on tertile values				0.002
≤ 1.196	124/21	83.1	75.2 – 88.6	
1.196 – 1.952	124/7	94.2	88.3 – 97.2	
> 1.952	125/7	94.4	88.6 – 97.3	
<i>Stage 4</i>				
Cut-off based on the median value				< 0.001
≤ 1.120	160/107	33.6	26.4 – 41.0	
> 1.120	160/76	51.3	42.7 – 59.2	
Cut-offs based on tertile values				< 0.001
≤ 0.468	106/73	31.9	23.3 – 40.9	
0.468 – 1.582	107/61	44.4	34.7 – 53.6	
> 1.582	107/49	50.7	39.8 – 60.6	
<i>Stage 4S</i>				
Cut-off based on the median value				0.113
≤ 1.474	46/8	81.4	65.8 – 90.4	
> 1.474	46/3	93.5	81.1 – 97.9	
Cut-offs based on tertile values				n.e.
≤ 0.882	30/5	n.e.	n.e.	
0.882 – 1.800	31/5	n.e.	n.e.	
> 1.800	31/1	n.e.	n.e.	
Event Free Survival	N/E	EFS	95%CI	<i>p</i>
<i>Localized stage</i>				
Cut-off based on the median value				0.011
≤ 1.556	184/54	70.7	63.5 – 76.7	
> 1.556	180/32	82.2	75.8 – 87.1	
Cut-offs based on tertile values				0.004
≤ 1.196	122/41	66.4	57.3 – 74.0	
1.196 – 1.952	122/24	80.3	72.1 – 86.4	
> 1.952	120/21	82.5	74.4 – 88.2	
<i>Stage 4</i>				
Cut-off based on the median value				0.002
≤ 1.120	157/112	29.1	22.2 – 36.4	
> 1.120	157/94	40.1	32.4 – 47.7	
Cut-offs based on tertile values				0.002
≤ 0.468	104/77	26.6	18.4 – 35.4	
0.468 – 1.582	104/66	36.5	27.4 – 45.7	
> 1.582	106/63	40.6	31.2 – 49.7	
<i>Stage 4S</i>				
Cut-off based on the median value				0.759
≤ 1.474	44/14	68.2	52.3 – 79.8	
> 1.474	46/13	71.7	56.4 – 82.5	
Cut-offs based on tertile values				0.672
≤ 0.882	29/9	69.9	48.8 – 82.5	
0.882 – 1.800	30/10	66.7	46.9 – 80.5	
> 1.800	31/8	74.2	55.0 – 86.2	

N/D = Number of patients/ deaths. OS = Overall Survival, 95%CI: 95% confidence interval of OS. n.e. = not evaluable

Supplementary Table S4. Survival of 786 NB patients in relation to *FANCA* expression levels by *MYCN* status.

Overall Survival	N/D	OS	95%CI	<i>p</i>
<i>MYCN normal</i>				
Cut-off based on the median value				<i>< 0.001</i>
≤ 3.277	314/42	86.0	81.4 – 89.5	
> 3.277	315/77	75.8	70.5 – 80.3	
Cut-offs based on tertile values				<i>< 0.001</i>
≤ 2.960	209/29	85.7	80.0 – 89.9	
2.960 – 3.580	210/32	84.0	78.0 – 88.5	
> 3.580	210/58	73.0	66.2 – 78.6	
<i>MYCN amplified</i>				
Cut-off based on the median value				<i>0.927</i>
≤ 3.945	76/53	29.6	19.6 – 40.3	
> 3.945	77/55	28.6	19.0 – 38.9	
Cut-offs based on tertile values				<i>0.975</i>
≤ 3.715	51/38	24.4	13.3 – 37.2	
3.715 – 4.151	51/31	39.2	26.0 – 52.2	
> 4.151	51/39	23.5	13.0 – 35.8	
Event Free Survival	N/E	EFS	95%CI	<i>p</i>
Cut-off based on the median value				<i>< 0.001</i>
≤ 3.277	304/72	76.3	71.1 – 80.7	
> 3.277	310/135	56.7	51.0 – 62.0	
Cut-offs based on tertile values				<i>< 0.001</i>
≤ 2.960	202/46	77.2	70.8 – 82.4	
2.960 – 3.580	205/57	72.2	65.5 – 77.8	
> 3.580	207/104	50.2	43.2 – 56.8	
<i>MYCN amplified</i>				
Cut-off based on the median value				<i>0.793</i>
≤ 3.945	74/54	25.8	16.0 – 36.7	
> 3.945	77/57	26.0	16.8 – 36.1	
Cut-offs based on tertile values				<i>0.960</i>
≤ 3.715	49/37	24.5	13.6 – 37.1	
3.715 – 4.151	51/34	31.8	19.0 – 45.3	
> 4.151	51/40	21.6	11.6 – 33.6	

N/D = Number of patients/ Deaths. OS = Ten-year Overall Survival, N/E Number of patients/ Events. EFS = Ten-year Event Free Survival, 95%CI: 95% confidence interval.

Supplementary Table S5. Survival of 786 NB patients in relation to *FANCA* expression levels by INSS stage.

Overall Survival	N/D	OS	95%CI	<i>p</i>
<i>Localized stage</i>				
Cut-off based on the median value				< 0.001
≤ 3.221	186/7	96.2	92.2 – 98.2	
> 3.221	187/28	85.0	79.0 – 89.4	
Cut-offs based on tertile values				< 0.001
≤ 2.897	124/2	98.4	93.7 – 99.6	
2.897 – 3.518	124/9	92.7	86.4 – 96.1	
> 3.518	125/24	80.7	72.6 – 86.6	
<i>Stage 4</i>				
Cut-off based on the median value				0.001
≤ 3.657	160/79	49.4	40.9 – 57.3	
> 3.657	160/104	35.5	28.1 – 43.1	
Cut-offs based on tertile values				< 0.001
≤ 3.314	106/51	49.2	38.4 – 59.1	
3.314 – 3.949	107/56	48.8	38.9 – 58.0	
> 3.949	107/76	29.2	20.7 – 38.2	
<i>Stage 4S</i>				
Cut-off based on the median value				0.822
≤ 3.307	46/6	87.0	73.3 – 93.9	
> 3.307	46/5	87.5	71.7 – 94.8	
Cut-offs based on tertile values				n.e.
≤ 3.134	30/4	n.e.	n.e.	
3.134 – 3.672	31/4	n.e.	n.e.	
> 3.672	31/3	n.e.	n.e.	
Event Free Survival	N/E	EFS	95%CI	<i>p</i>
<i>Localized stage</i>				
Cut-off based on the median value				< 0.001
≤ 3.221	179/22	87.7	81.9 – 91.7	
> 3.221	185/64	65.4	58.1 – 71.8	
Cut-offs based on tertile values				< 0.001
≤ 2.897	118/11	90.7	83.8 – 94.7	
2.897 – 3.518	123/23	81.3	73.2 – 87.2	
> 3.518	123/52	57.7	48.5 – 65.9	
<i>Stage 4</i>				
Cut-off based on the median value				0.003
≤ 3.657	155/90	41.9	34.1 – 49.6	
> 3.657	159/116	27.3	20.5 – 34.5	
Cut-offs based on tertile values				< 0.001
≤ 3.314	105/59	43.8	34.2 – 53.0	
3.314 – 3.949	102/65	36.9	27.5 – 46.2	
> 3.949	107/82	23.4	15.9 – 31.7	
<i>Stage 4S</i>				
Cut-off based on the median value				0.748
≤ 3.307	44/13	70.5	54.6 – 81.7	
> 3.307	46/14	69.6	54.1 – 80.7	
Cut-offs based on tertile values				0.221
≤ 3.134	29/7	75.9	55.9 – 87.7	
3.134 – 3.672	30/9	70.0	50.3 – 83.1	
> 3.672	31/11	64.5	45.2 – 78.5	

N/D = Number of patients/ deaths. OS = Overall Survival, 95%CI: 95% confidence interval of OS. n.e. = not evaluable

Supplementary Table S6. Survival of 786 NB patients in relation to MPAK3 expression levels by MYCN status.

Overall Survival	N/D	OS	95%CI	<i>p</i>
<i>MYCN normal</i>				
Cut-off based on the median value				0.195
≤ 3.880	314/53	83.5	78.9 – 87.3	
> 3.880	315/66	78.1	72.8 – 82.5	
Cut-offs based on tertile values				0.235
≤ 3.696	209/37	82.5	76.5 – 87.1	
3.696 – 4.057	210/35	83.5	77.6 – 87.9	
> 4.057	210/47	76.6	69.7 – 82.0	
<i>MYCN amplified</i>				
Cut-off based on the median value				0.194
≤ 3.625	76/51	32.9	22.7 – 43.5	
> 3.625	77/57	24.2	14.6 – 35.2	
Cut-offs based on tertile values				0.220
≤ 3.494	51/37	27.5	16.1 – 40.0	
3.494 – 3.894	51/30	41.2	27.7 – 54.2	
> 3.894	51/41	21.6	11.6 – 33.6	
Event Free Survival	N/E	EFS	95%CI	<i>p</i>
Cut-off based on the median value				0.923
≤ 3.880	314/106	66.5	61.0 – 71.5	
> 3.880	300/101	66.3	60.7 – 71.4	
Cut-offs based on tertile values				0.940
≤ 3.696	209/74	64.6	57.7 – 70.6	
3.696 – 4.057	210/63	70.5	63.8 – 76.2	
> 4.057	195/70	64.1	56.9 – 70.4	
<i>MYCN amplified</i>				
Cut-off based on the median value				0.280
≤ 3.625	76/54	28.4	18.6 – 38.9	
> 3.625	75/57	24.0	15.1 – 34.1	
Cut-offs based on tertile values				0.480
≤ 3.494	51/38	25.5	14.6 – 37.9	
3.494 – 3.894	51/34	31.8	19.0 – 45.3	
> 3.894	49/39	20.4	10.5 – 32.6	

N/D = Number of patients/ Deaths. OS = Ten-year Overall Survival, N/E Number of patients/ Events. EFS = Ten-year Event Free Survival, 95%CI: 95% confidence interval.

Supplementary Table S7. Survival of 786 NB patients in relation to MAPK3 expression levels by INSS stage.

Overall Survival	N/D	OS	95%CI	<i>p</i>
<i>Localized stage</i>				
Cut-off based on the median value				0.112
≤ 3.868	186/22	88.1	82.5 – 92.0	
> 3.868	187/13	93.0	88.2 – 95.9	
Cut-offs based on tertile values				0.027
≤ 3.652	124/20	83.9	76.1 – 89.3	
3.652 – 4.038	124/5	95.9	90.4 – 98.3	
> 4.038	125/10	91.9	85.5– 95.6	
<i>Stage 4</i>				
Cut-off based on the median value				0.715
≤ 3.817	160/88	44.9	36.9– 52.6	
> 3.817	160/95	40.0	32.0 – 47.9	
Cut-offs based on tertile values				0.926
≤ 3.619	106/61	42.8	33.1 – 52.1	
3.619 – 4.005	107/57	47.4	37.6 – 56.5	
> 4.005	101/65	36.7	26.7 – 46.8	
<i>Stage 4S</i>				
Cut-off based on the median value				0.003
≤ 3.822	46/1	97.8	85.6 – 99.7	
> 3.822	46/10	77.8	60.6 – 87.0	
Cut-offs based on tertile values				n.e.
≤ 3.686	30/0	n.e.	n.e.	
3.686 – 4.057	31/7	n.e.	n.e.	
> 4.057	31/4	n.e.	n.e.	
Event Free Survival	N/E	EFS	95%CI	<i>p</i>
<i>Localized stage</i>				
Cut-off based on the median value				0.083
≤ 3.868	186/51	72.6	65.6 – 78.4	
> 3.868	178/35	80.3	73.7 – 85.5	
Cut-offs based on tertile values				0.136
≤ 3.652	124/37	70.2	61.3 – 77.4	
3.652 – 4.038	124/24	80.7	72.5 – 86.6	
> 4.038	116/25	78.5	69.8 – 84.9	
<i>Stage 4</i>				
Cut-off based on the median value				0.372
≤ 3.817	160/108	32.8	25.6 – 40.2	
> 3.817	154/98	36.4	28.8 – 43.9	
Cut-offs based on tertile values				0.469
≤ 3.619	106/71	32.4	23.5 – 41.5	
3.619 – 4.005	107/70	35.5	26.6 – 44.5	
> 4.005	101/65	35.6	26.5 – 44.9	
<i>Stage 4S</i>				
Cut-off based on the median value				0.032
≤ 3.822	46/9	80.4	65.8 – 89.3	
> 3.822	44/18	59.1	43.2 – 71.9	
Cut-offs based on tertile values				0.101
≤ 3.686	30/5	83.3	64.5 – 92.7	
3.686 – 4.057	31/11	64.5	45.2 – 78.5	
> 4.057	29/11	62.1	42.1 – 76.9	

N/D = Number of patients/ deaths. OS = Overall Survival, 95%CI: 95% confidence interval of OS. n.e. = not evaluable

Supplementary Table S8. Main characteristics of the 786 NB patients selected for the analyses.

Patient characteristics	N	%
<i>Age at diagnosis</i>		
< 18 months	449	57.1
≥ 18 months	337	42.9
<i>Disease extension</i>		
Localized	373	47.5
Disseminated	412	52.4
Missing	1	0.1
<i>INSS stage</i>		
1	143	18.2
2	125	15.9
3	105	13.4
4	320	40.7
4S	92	11.7
Missing	1	0.1
<i>MYCN status</i>		
Not amplified	629	80.0
Amplified	153	19.5
Missing	4	0.5
Events ¹	320	40.7
Deaths	229	29.1

¹ 17 missing for the Event Free Survival.