

Supplementary Table 1

Customised breast cancer NGS panel			
<i>AKT1</i>	<i>ERCC2</i>	<i>MEN1</i>	<i>SDHD</i>
<i>AKT2</i>	<i>ERCC3</i>	<i>MET</i>	<i>SF3B1</i>
<i>AKT3</i>	<i>ERCC4</i>	<i>MLH1</i>	<i>SMO</i>
<i>ALK</i>	<i>ERCC5</i>	<i>MSH2</i>	<i>STK11</i>
<i>APC</i>	<i>ESR1</i>	<i>MSH6</i>	<i>TBX3</i>
<i>ARID1A</i>	<i>EXT1</i>	<i>MUTYH</i>	<i>TMEM127</i>
<i>ATM</i>	<i>FANCA</i>	<i>NBN</i>	<i>TP53</i>
<i>AXIN2</i>	<i>FANCC</i>	<i>NCOR1</i>	<i>TSC1</i>
<i>BAP1</i>	<i>FANCG</i>	<i>NF2</i>	<i>TSC2</i>
<i>BLM</i>	<i>FBXW7</i>	<i>NOTCH1</i>	<i>VHL</i>
<i>BMPRIA</i>	<i>FGFR1</i>	<i>NOTCH2</i>	<i>WT1</i>
<i>BRAF</i>	<i>FGFR2</i>	<i>NRAS</i>	<i>XPA</i>
<i>BRCA1</i>	<i>FGFR3</i>	<i>PALB2</i>	<i>XPC</i>
<i>BRCA2</i>	<i>FGFR4</i>	<i>PDGFRA</i>	
<i>BRIP1</i>	<i>FH</i>	<i>PIK3CA</i>	
<i>BUB1B</i>	<i>FLCN</i>	<i>PIK3R1</i>	
<i>CASP8</i>	<i>FOXA1</i>	<i>PIK3R3</i>	
<i>CBFB</i>	<i>GATA3</i>	<i>PMS2</i>	
<i>CCND1</i>	<i>HRAS</i>	<i>PRKARIA</i>	
<i>CCND2</i>	<i>IGF1R</i>	<i>PTCH1</i>	
<i>CDC73</i>	<i>INPP4B</i>	<i>PTEN</i>	
<i>CDH1</i>	<i>KIT</i>	<i>PTPN11</i>	
<i>CDK4</i>	<i>KRAS</i>	<i>RAD51C</i>	
<i>CDKN2A</i>	<i>KMT2C</i>	<i>RAD51D</i>	
<i>CHEK2</i>	<i>KMT2D</i>	<i>RB1</i>	
<i>CTNNB1</i>	<i>MAP2K1</i>	<i>RECQL4</i>	
<i>DDB2</i>	<i>MAP2K4</i>	<i>RET</i>	
<i>EGFR</i>	<i>MAP3K1</i>	<i>RUNX1</i>	
<i>ERBB2</i>	<i>MAX</i>	<i>SDHA</i>	
<i>ERBB3</i>	<i>MCL1</i>	<i>SDHB</i>	
<i>ERBB4</i>	<i>MDM2</i>	<i>SDHC</i>	

Supplementary Table 1 - Table listing the target genes for the customised breast NGS panel that was utilised for tumour samples from SOFT.

Supplementary Table 2

	BIG 1-98			SOFT		
	HER2-low (N=203)	HER2-zero (N=317)	P-value	HER2-low (N=274)	HER2-zero (N=1001)	P-value
Tumour size						
≤ 2 cm	112 (67)	179 (62)	0.50	179 (65)	654 (65)	0.94
> 2 cm	89 (32)	135 (37)		89 (33)	332 (33)	
Unknown	2 (1)	3 (<1)		6 (2)	15 (2)	
Nodal status						
Positive	111 (39)	166 (35)	0.41	91 (33)	339 (34)	0.87
Negative	92 (61)	151 (65)		183 (67)	659 (66)	
Unknown	0 (0)	0 (0)		0 (0)	3 (<1)	
Grade						
Grade 1	21 (11)	52 (27)	0.003	55 (20)	257 (26)	0.13
Grade 2	100 (60)	182 (55)		158 (58)	556 (56)	
Grade 3	82 (29)	81 (17)		60 (22)	188 (19)	
Unknown		2 (<1)		1 (<1)	0 (0)	

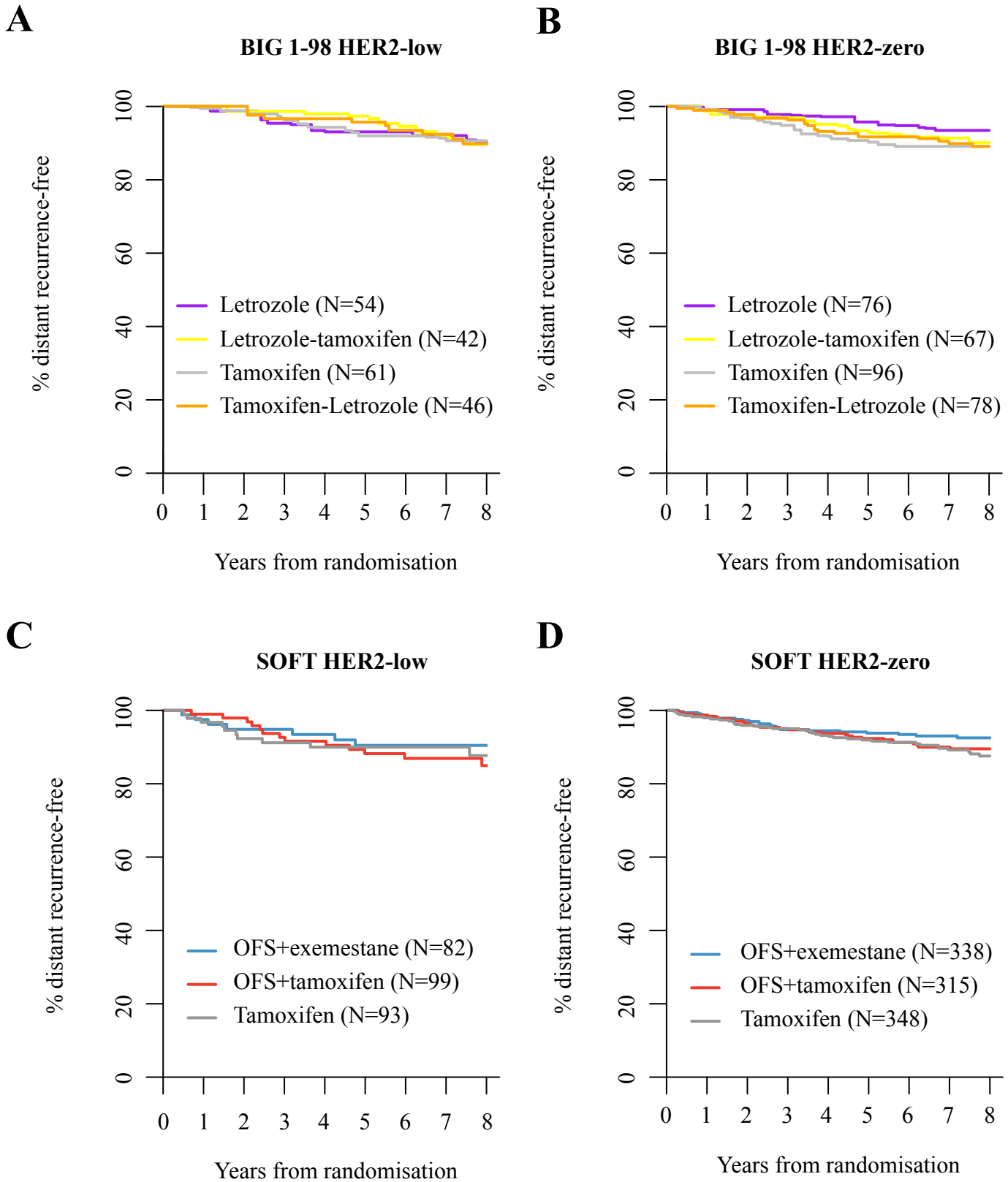
Supplementary Table 2 - Table demonstrating the association of tumour characteristics size, nodal status, and grade with HER2-low status. The number of patients with each characteristic are listed with the proportion in brackets. For BIG 1-98, the proportions displayed are weighted proportions.

Supplementary Table 3

Genomic alteration	BIG 1-98			SOFT		
	Frequency in HER2-low tumours (N=203)	Frequency in HER2-zero tumours (N=317)	q-value	Frequency in HER2-low tumours (N=274)	Frequency in HER2-zero tumours (N=1001)	q-value
<i>PIK3CA</i> mutation	48%	49%	0.97	41%	44%	0.66
<i>GATA3</i> mutation	13%	11%	0.77	21%	16%	0.29
<i>MAP3K1</i> mutation	5%	19%	0.002	6%	11%	0.080
<i>BRCA2</i> mutation	4%	1%	0.22	9%	5%	0.078
<i>CDH1</i> mutation	12%	12%	0.97	5%	8%	0.64
<i>TP53</i> mutation	16%	15%	0.97	5%	4%	0.78
<i>MAP2K4</i> mutation	9%	3%	0.46	1%	2%	0.64
<i>SPEN</i> mutation	2%	7%	0.22	2%	2%	0.83
<i>PTEN</i> mutation	5%	4%	0.97	7%	6%	0.74
<i>BRCA1</i> mutation	2%	0%	0.22	2%	3%	0.66
<i>AKT1</i> mutation	3%	5%	0.77	4%	5%	0.66
<i>CCND1</i> amplification	17%	17%	0.97	14%	15%	0.78
<i>FGF19</i> amplification	13%	16%	0.77	13%	15%	0.74
<i>EMSY</i> amplification	9%	7%	0.77	4%	5%	1.00
<i>FGFR1</i> amplification	11%	7%	0.55	15%	9%	0.073
<i>MYC</i> amplification	16%	8%	0.16	8%	6%	0.68

Supplementary Table 3 - Table demonstrating the frequency of genomic driver alterations with HER2-low status. q-value is the P value adjusted for multiple testing.

Supplementary Figure 1

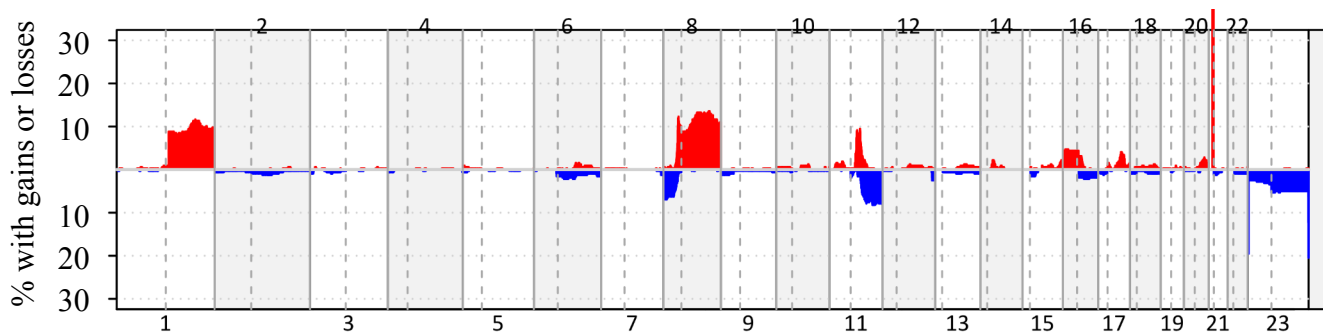


Supplementary Figure 1 - Kaplan Meier plot for distant recurrence-free interval by HER2-low status and treatment assignment in BIG 1-98 (panel A, B) and SOFT (C,D). Abbreviations: OFS, ovarian function suppression.

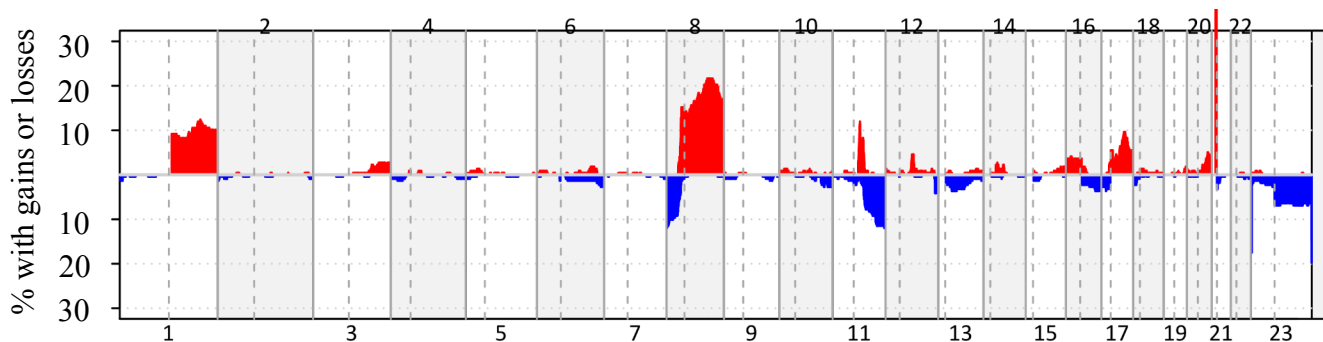
Supplementary Figure 2

BIG 1-98

HER2-zero

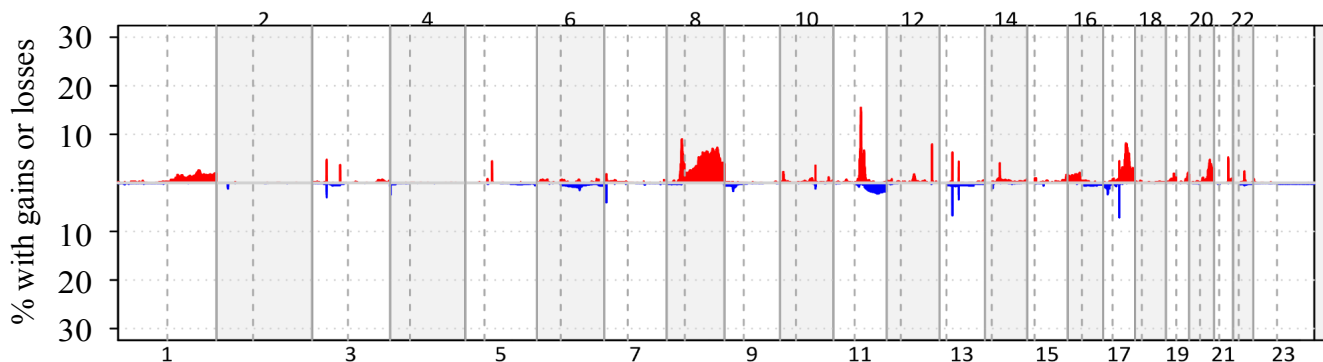


HER2-low

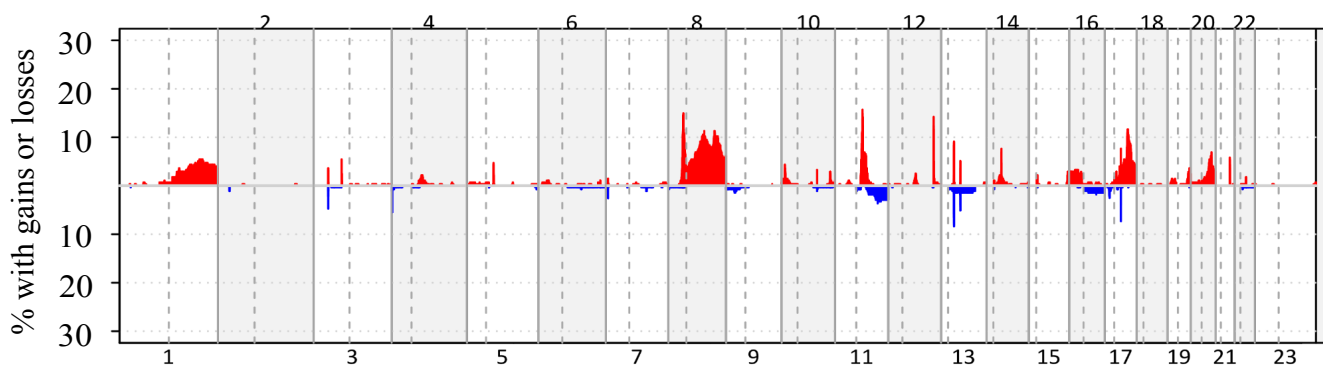


SOFT

HER2-zero



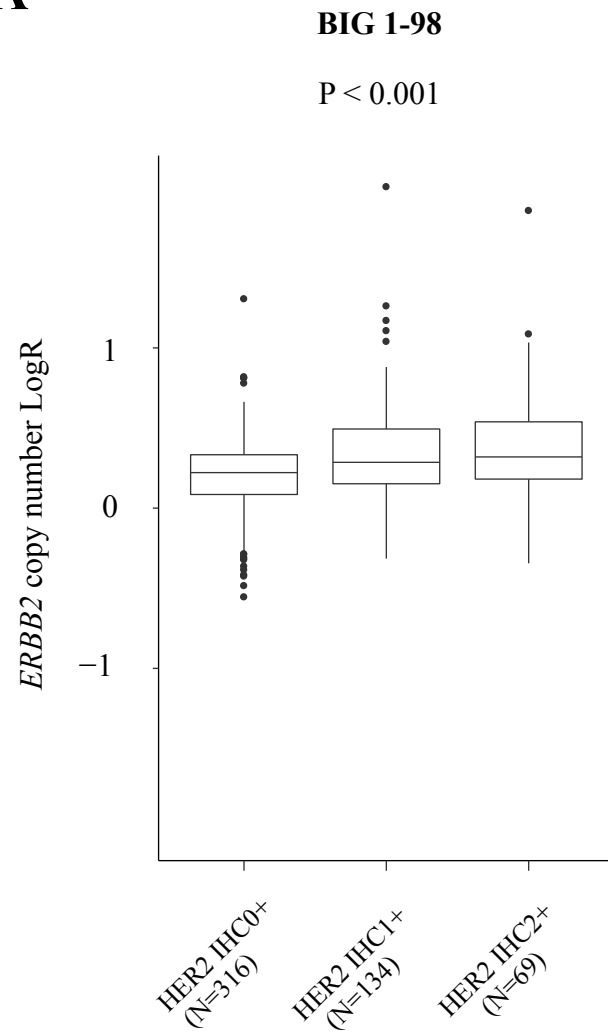
HER2-low



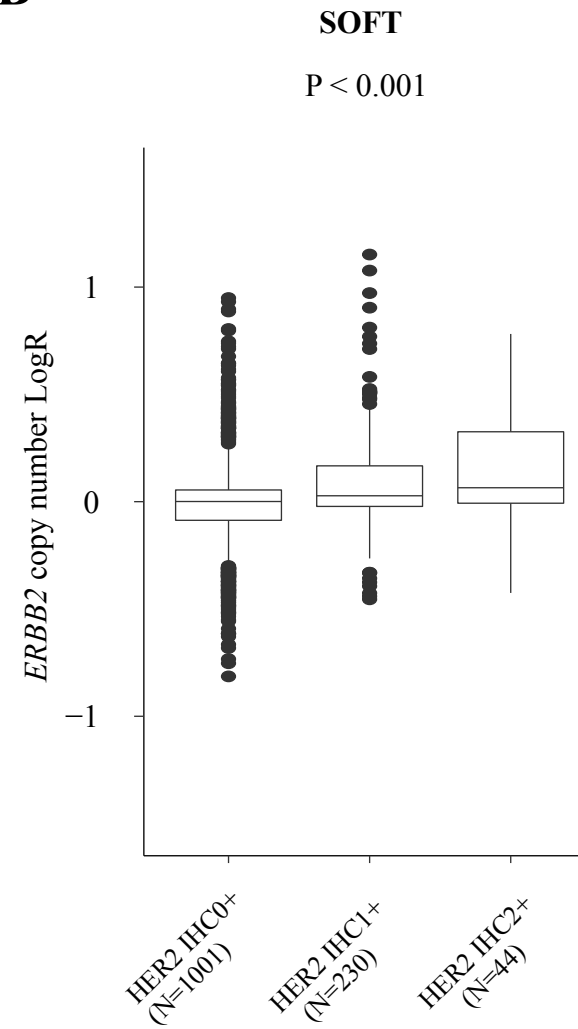
Supplementary Figure 2 - Plots demonstrating whole genome copy number profiles in BIG 1-98 (top two panels) and SOFT (bottom two panels) by HER2-low status. A copy number LogR value of 0.75 and -0.75 were used to determine gains or losses respectively.

Supplementary Figure 3

A



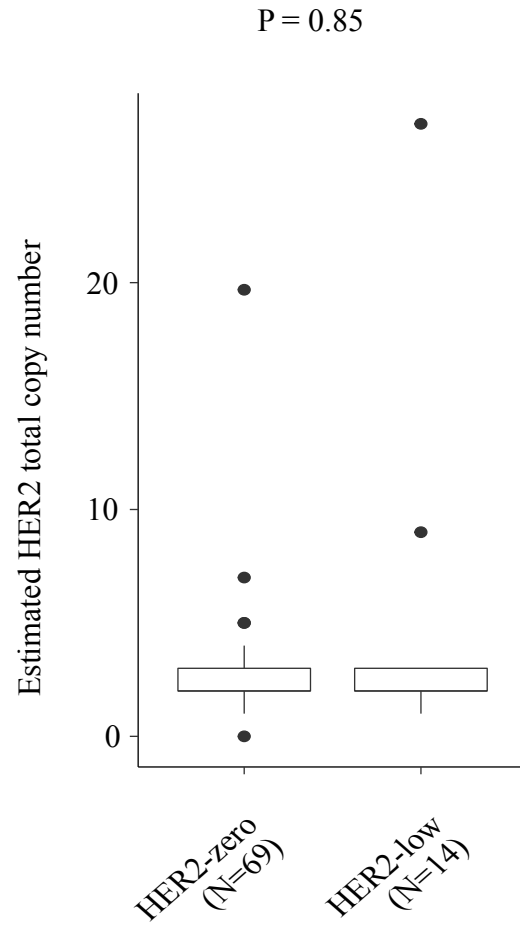
B



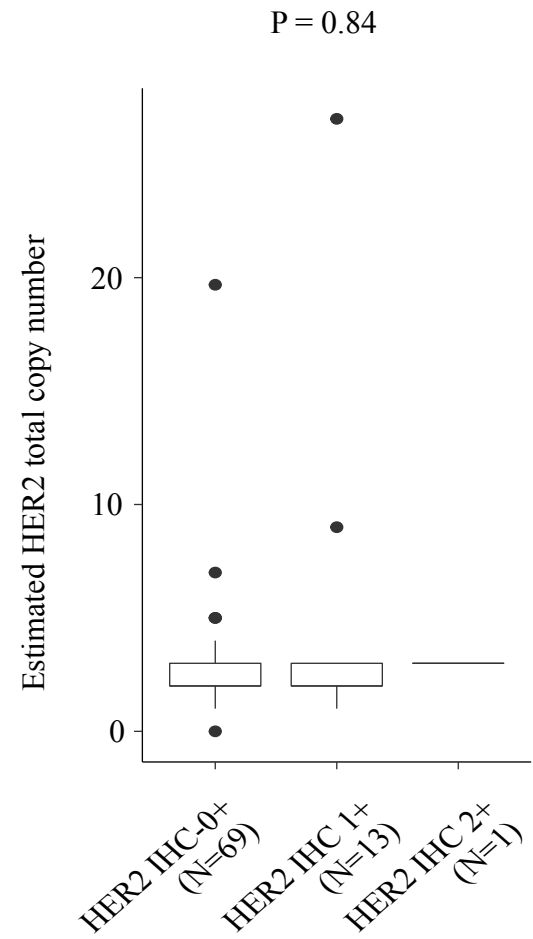
Supplementary Figure 3 - Boxplots demonstrating *ERBB2* copy number LogR by HER2 immunohistochemistry score in BIG 1-98 (Panel A) and SOFT (Panel B).

Supplementary Figure 4

A

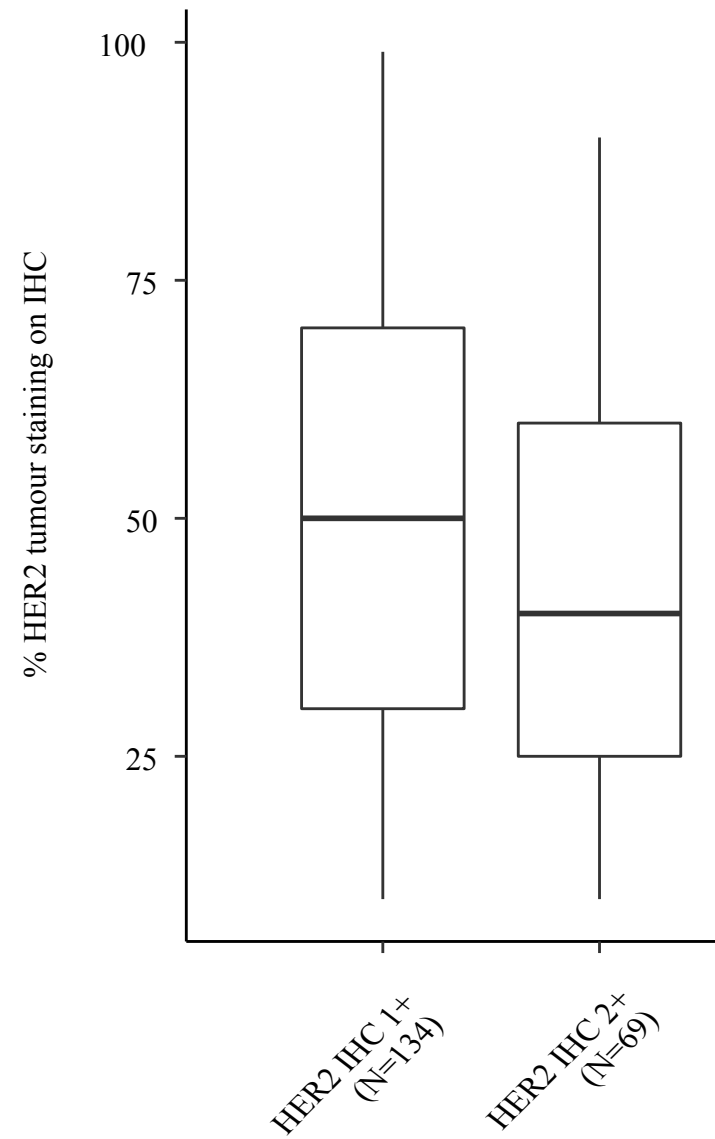


B



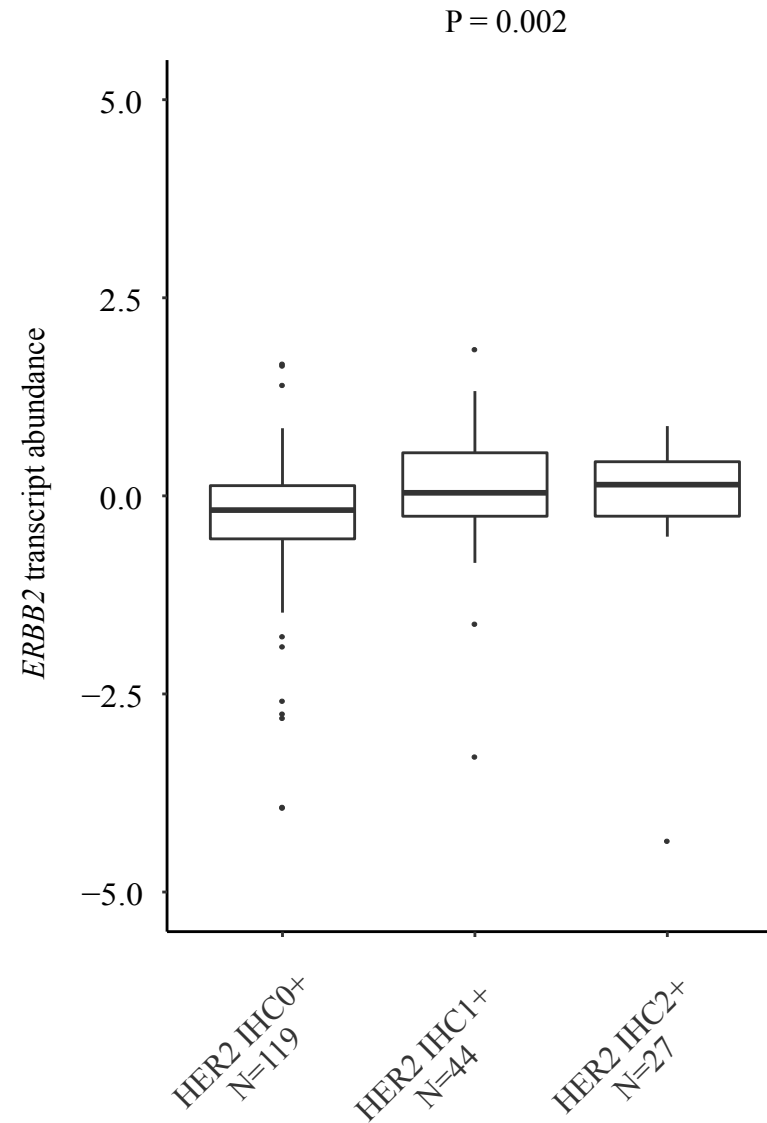
Supplementary Figure 4 - Boxplots demonstrating estimated HER2 total copy number from allele specific copy number analysis in a subset of SOFT tumours that underwent whole exome sequencing by HER2-low status (Panel A) and HER2 immunohistochemistry score (Panel B)

Supplementary Figure 5



Supplementary Figure 5 - Boxplots demonstrating % HER2 tumour staining by IHC by HER2 immunohistochemistry score. Abbreviations: IHC, immunohistochemistry.

Supplementary Figure 6



Supplementary Figure 6 - Boxplots demonstrating *ERBB2* transcript abundance by HER2 immunohistochemistry score.