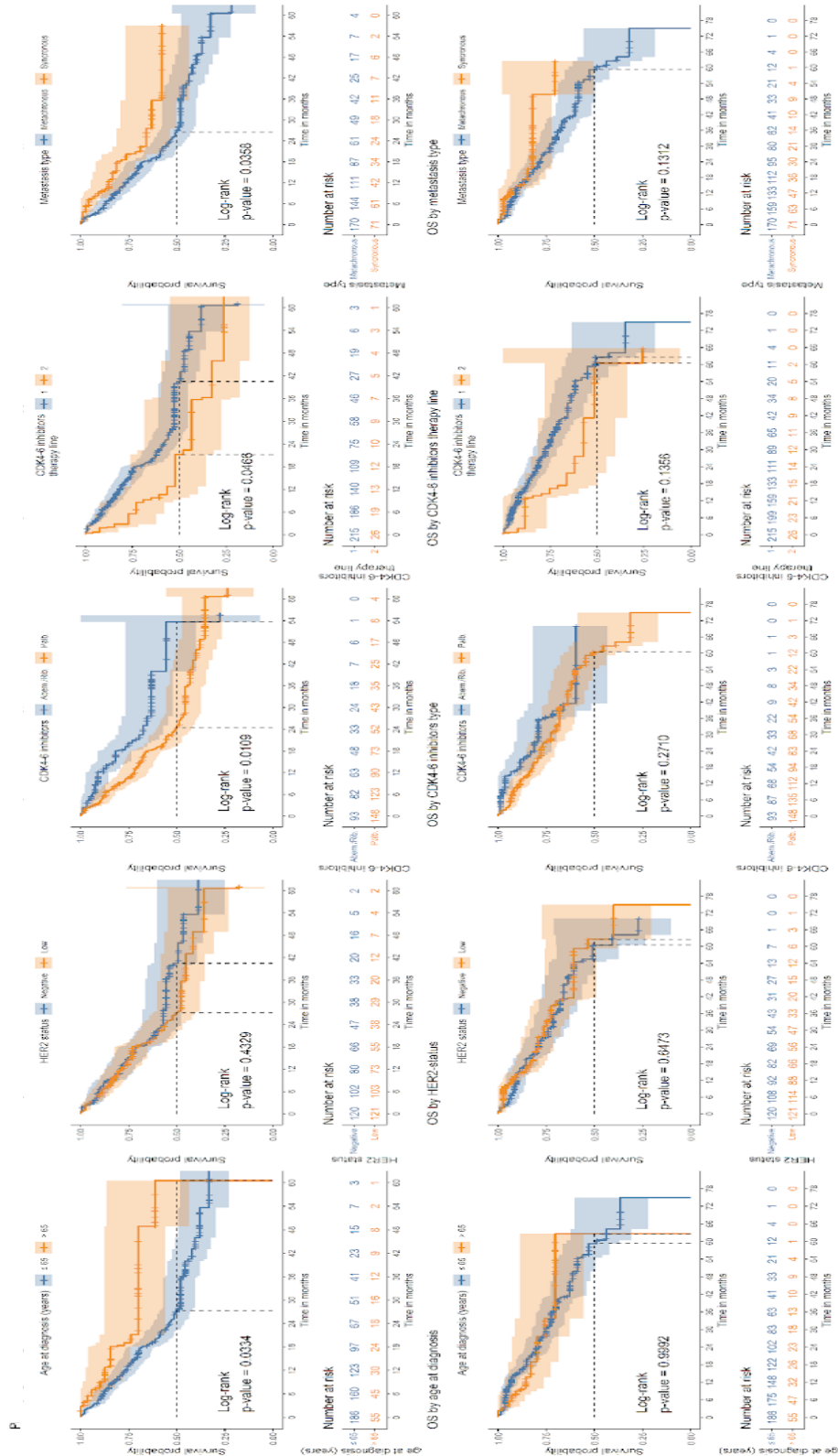# SUPPLEMENTARY MATERIALS

Supplementary Table 1. HER2 status from primary tumour and metastatic tissue biopsies. 'Subset' indicates the analysed subset of the whole dataset. 'Primary tumour tissue' indicates HER2 status deriving from the primary tumour tissue biopsy (and corresponding frequency). 'Metastatic tissue' indicates absolute and relative frequency (%) of HER2-low and HER2-negative patients from primary tumour tissue biopsy classified as HER2-low and HER2-negative from the metastatic tissue biopsy and not assayed.

Subset	Primary tumour tissue	Metastatic tissue		
		HER2-Low	HER2-negative	No biopsy
Overall (*n*=241)	HER2-low (*n*=112)	26 (23.21%)	13 (11.61%)	73 (65.18%)
	HER2-negative (*n*=129)	22 (17.05%)	38 (29.46%)	69 (53.49%)
Metachronous metastases (*n*=170)	HER2-low (*n*=72)	19 (26.39%)	12 (16.67%)	41 (56.94%)
	HER2-negative (*n*=98)	21 (21.43%)	36 (36.73%)	41 (41.84%)
Synchronous metastases (*n*=71)	HER2-low (*n*=40)	7 (17.50%)	1 (2.50%)	32 (80.00%)
	HER2-negative (*n*=31)	1 (3.23%)	2 (6.45%)	28 (90.32%)

Supplementary Table 2. Frequency of best response type by HER2 condition. Variable, analysed variable; n, number of non-missing observations; CR, absolute and relative (%) frequency of HER2-negative and HER2-low patients who had complete response as best response; PR, absolute and relative (%) frequency of HER2-negative and HER2-low patients who had partial response as best response; SD, absolute and relative (%) frequency of HER2-negative and HER2-low patients who had stable disease as best response; PD, absolute and relative (%) frequency of HER2-negative and HER2-low patients who had progressive disease as best response. *p* value obtained from the χ^2 test for independence.

Variable	*n*	CR	PR	SD	PD	*p* value
HER2-low at disease presentation or metastases	221					0.2756
No	113	10 (8.85%)	62 (54.87%)	28 (24.78%)	13 (11.5%)	
Yes	108	17 (15.74%)	52 (48.15%)	31 (28.7%)	8 (7.41%)	

Supplementary Figure 1. Progression-free and overall survival profiles by clinically relevant variables. Kaplan–Meier curves describing progression free (PFS) and overall survival (OS) profiles as function of age at diagnosis, HER2 status, of CDK4-6 inhibitors type, of CDK4-6 inhibitors therapy line, and of the metastasis type. The numbers reported in the table below each plot describe the number of subjects at risk at different time points by strata. Time is expressed in months. *p* value is derived from the log-rank test.

Supplementary Figure 2. Progression free and overall survival profiles by resistance type. Kaplan–Meier curves describing progression free (PFS) and overall survival (OS) profiles as function of resistance type on a subset of 47 subjects with primary or secondary resistance. The

numbers reported in the table below each plot describe the number of subjects at risk at different time points by strata. Time is expressed in months. The p value is derived from the log-rank test.

PFS by resistance type

Resistance type — Primary — Secondary

Log-rank
p-value = 0.3535

Number at risk

Resistance type	0	6	12	18	24	30	36	42	48	54	60
Primary	12	11	6	6	3	2	2	1	1	1	1
Secondary	35	30	24	18	14	9	9	5	4	1	1

OS by resistance type

Resistance type — Primary — Secondary

Log-rank
p-value = 0.1200

Number at risk

Resistance type	0	6	12	18	24	30	36	42	48	54	60	66	72	78
Primary	12	11	7	6	5	4	2	1	1	1	1	0	0	0
Secondary	35	31	27	22	19	16	14	9	7	5	3	1	1	0