

## Supplementary methods

### *Whole exome sequencing*

For the generation of standard exome capture libraries, the Agilent SureSelect Target Enrichment protocol was used for Illumina paired-end sequencing library (ver. B.3, June 2015) together with 200 ng input FFPE DNA. The quantification and quality of DNA were measured by PicoGreen and Nanodrop. Fragmentation of 1 µg of genomic DNA was performed using adaptive focused acoustic technology (AFA; Covaris, Woburn, MA, USA). The fragmented DNA was repaired, an 'A' was ligated to the 3' end, and Agilent adapters were then ligated to the fragments. Once ligation had been verified, the adapter-ligated product was PCR amplified. The final purified product was then quantified using qPCR according to the qPCR Quantification Protocol Guide and qualified using the TapeStation DNA Screentape (Agilent). For exome capture, 250 ng of DNA library was mixed with hybridization buffers, blocking mixes, RNase block, and 5 µl of SureSelect all exon capture library, according to the standard Agilent SureSelect Target Enrichment protocol. Hybridization to the capture baits was conducted at 65°C using a heated thermal cycler lid option at 105°C for 24 hours on the PCR machine.

The captured DNA was then amplified. The final purified product was quantified using qPCR according to the qPCR Quantification Protocol Guide and qualified using the TapeStation DNA Screentape (Agilent). Finally, the DNA was sequenced using the HiSeq™ 2500 platform (Illumina, San Diego, USA).

Supplementary Table 1. Dose level and schedule in the phase Ib trial.

Dose level	Gemcitabine mg/m <sup>2</sup> (day 1 and 8)	Cisplatin mg/m <sup>2</sup> (day 1 and 8)	Everolimus (mg) (daily)
-1	800	20	5 mg QOD
1	800	30	5 mg QOD
2	800	30	5 mg daily
3	800	30	10 mg daily

Supplemental Table 2. Digital PCR results of *PI3KCA* mutations

Number	Primary breast cancer			Cell-free DNA		
	E542K	E545K	H1047R	E542K	E545K	H1047R
Ph1-1	0.00	0.70 (0.1/12.1)	0.70 (0.1/11.3)	0.00	0.00	0.17 (0.1/75.0)
Ph1-2	NA	NA	NA	0.00	0.02 (0.2/725.0)	0.16 (1.1/706.0)
Ph1-3	NA	NA	NA	0.00	0.00	0.03 (0.1/355.0)
Ph1-4	0.60 (0.3/45.6)	0.18 (0.1/48.1)	0.30 (0.2/47.9)	0.00	0.11 (0.2/208.0)	0.26 (0.5/195.0)
Ph1-5	2.80 (0.2/7.2)	28.00 (2.2/5.7)	0.00	0.00	0.00	0.15 (0.2/103.0)
Ph1-6	NA	NA	NA	0.06 (0.1/168.0)	0.00	0.25 (0.4/157.0)
Ph1-7	NA	NA	NA	0.01 (0.1/1139.0)	0.02 (0.2/1117.0)	0.15 (1.7/1129.0)
Ph1-8	0.00	7.20 (2.2/28.1)	0.29 (0.1/26.1)	0.06 (0.1/192.0)	0.00	0.22 (0.4/173.0)
Ph1-9	1.40 (0.2/12.0)	0.00	0.00	0.02 (0.1/371.0)	0.07 (0.2/360.0)	0.20 (0.7/351.0)
Ph2-1	0.00	0.00	0.00	0.00	0.14 (0.2/115.0)	0.09 (0.1/112.0)
Ph2-2	0.00	5.00 (0.1/1.4)	0.00	0.07 (0.1/148.0)	0.00	0.28 (0.4/125.0)
Ph2-3	NA	NA	NA	0.00	0.00	0.37 (0.1/29.9)
Ph2-4	0.00	0.00	0.00	0.00	0.00	0.29 (0.2/66.3)
Ph2-5	0.00	0.00	0.00	0.00	0.00	0.13 (0.3/221.0)
Ph2-6	0.00	1.10 (0.1/6.5)	0.00	0.17 (0.1/52.2)	0.00	0.38 (0.2/52.5)
Ph2-7	NA	NA	NA	0.00	0.00	0.08 (0.1/138.0)
Ph2-8	0.00	0.60 (0.1/23.8)	1.10 (0.3/28.8)	0.38 (0.1/29.2)	0.00	6.16 (1.7/25.9)
Ph2-9	0.00	0.00	0.00	0.00	0.00	0.07 (0.1/135.0)
Ph2-10	0.00	0.00	0.00	0.00	0.00	0.00
Ph2-11	NA	NA	NA	0.00	0.00	0.00
Ph2-12	NA	NA	NA	0.10 (0.1/103.0)	0.08 (0.1/98.0)	0.09 (0.1/102.0)
Ph2-13	NA	NA	NA	0.00	0.00	0.00
Ph2-14	0.00	0.00	0.00	0.02	0.00	0.19 (0.7/376.0)

Fractional abundance (%) (FAM positive / [FAM positive +HEX positive]), 0.1% and more evaluated as mutation positive