SUPPLEMENTARY MATERIALS AND METHODS

Mice

KB1P mammary tumors were generated and genotyped as described (Liu *et al.* Proc Natl Acad Sci U S A 2007;104:12111-6). To produce KB1PM mammary tumors on a FVB/N genetic background, FVB.129P2-Abcb1a<sup>tm1Bor</sup>Abcb1b<sup>tm1Bor</sup>, FVB-Tg(KRT14-cre)8Bbm, FVB.129P2-Trp53<sup>tm1Bor</sup>, or FVB.129P2-Brca1<sup>tm1Bor</sup> mice were backcrossed on FVB/N animals for at least 8 generations (the first 5 generations using marker-assisted breeding) and eventually crossed to generate FVB.Cg-Abcb1a<sup>tm1Bor</sup>Abcb1b<sup>tm1Bor</sup>Trp53<sup>tm1Bor</sup>Brca1<sup>tm1Bor</sup>Tg(KRT14-cre)8Bbm/A compound mice. Abcb1a<sup>36-7</sup>/6-7 and Abcb1b<sup>3-4</sup>/3-4 genotypes were confirmed by PCR with specific primers (forward-Abcb1a: 5'-GTGCATAGACCACCCTCAAGG-3'; forward-Abcb1b: 5'-AAGCTGTGCATGATTCTGGG-3') for wildtype (reverse-Abcb1a: 5'-GTCATGCACATCAAACCAGCC-3'; reverse-Abcb1b: 5'-' GAGAAACGATGTCTCTCCAG-3') and deleted alleles (reverse-Abcb1a: 5'-GGAGCAAAGCTGCTATTGGC-3'). Orthotopic transplantations, mammary tumor measurements and sampling were performed as explained previously (Rottenberg *et al.* Proc Natl Acad Sci U S A 2007;104:12117-22), and allowed us to collect response data for docetaxel, cisplatin and doxorubicin for 36 individual KB1P tumors. In addition, KB1PM mammary tumors were transplanted into FVB/N animals. Deletion of Brca1 and p53 of orthotopically transplanted tumors was confirmed by PCR (absence of Brca1<sup>F5-13/F5-13</sup>;p53<sup>F2-10/F2-10</sup> alleles and presence of Brca1<sup>F5-13/F5-13</sup>;p53<sup>F2-10/F2-10</sup> alleles) as described (Liu *et al.* Proc Natl Acad Sci U S A 2007;104:12111-6).

Drugs and treatment of tumor-bearing animals

Docetaxel (Taxotere, 10 mg/ml in Tween80/ethanol/saline 20:13:67 vol/vol/vol; Aventis, Antony Cedex, France) was diluted with saline to 5 mg/ml before injection. Cisplatin (1 mg/ml in saline-mannitol) originated from Mayne Pharma (Brussels, Belgium). Doxorubicin (Adriblastina; Amersham Pharmacia Netherlands, Woerden, The Netherlands) was diluted to 1 mg/ml in saline (Braun, Emmer-Compascuum, The Netherlands). When mammary tumors reached a volume of 150-250mm<sup>3</sup> (0.5 × length × width<sup>2</sup>) 25mg docetaxel per kg (days 0, 7, 14), 6mg cisplatin per kg (day 0) or 5mg doxorubicin per kg (day 0) were injected i.v. as initial treatment. To avoid accumulating toxicity of repeated injections, an additional treatment was not given during the recovery time of 7 days in case
the tumor responded to the treatment (tumor size <50% of the original volume, partial response).
Treatment was continued once the tumor relapsed to its original size (100%). For tumors with a
volume ≥50% after the recovery time, an additional treatment with the same dose as mentioned above
was given.

Histology

Tissues were fixed in 4% formaldehyde overnight, embedded in paraffin, and cut in 4μm
sections. After deparaffinization and rehydration, sections were stained with hematoxylin and eosin
according to standard procedures.

Processing and Analysis of the Microarray Data

Data normalization of the dual channel MEEBO arrays was carried out as described (Yang et al.
Nucleic Acids Res 30:e15, 2002). We then used a modified Rosetta error model (Weng et al.
the average ratio per gene and a P value indicating the chance a gene is falsely classified. For the
single channel Illumina arrays background correction was performed using the bg.adjust method from
between arrays the robust spline method was applied. Filtering of probes on the single channel arrays
was performed using the detection p-value (significantly different from background in at least one
sample), which reduced the number of reporters from 45,281 to 26,352. For filtering probes of the dual
channel arrays the p-value from the rosetta error model was used (fold change significantly different
from 0 in at least one sample). In addition, probes with missing data points in more than 10% of the
hybridizations were excluded. This reduced the number of reporters from 38,784 to 21,791. The TIGR
Multiexperiment Viewer 4.6 software (TMV4.6, www.tm4.org/mev.html) was used to perform the SAM
analysis. Unsupervised hierachical clustering analysis was carried out using the pvclust software
(www.is.titech.ac.jp/~shimo/prog/pvclust/). The hierachical clustering algorithm was based on
Euclidean distance and average linkage was applied to group tumor samples according to similarity in
the pattern of gene expression.

For the SAM in Figure 2D T5doce-res, T6doce-res, T12*doce-res, T18*doce-res, T20*doce-res,
T21*doce-res, T22*doce-res, T24*doce-res, T28*doce-res, T29*doce-res, T30*doce-res, T31*doce-
res, T34*doce-res, T35*doce-res, and T38*doce-res were used. These tumors with acquired docetaxel resistance were compared to the corresponding docetaxel-sensitive controls. T42 and T43 were not included, because docetaxel-resistant tumors of these were not available at the time of analysis. The microarray data reported in this article have been deposited in the Array Express database, www.ebi.ac.uk/arrayexpress (accession no. E-MTAB-413 [Illumina] and E-MTAB-415 [MEEBO]).

Reverse Transcription-Multiplex ligation-dependent probe amplification (RT-MLPA)
From snap frozen mouse tumors total RNA was isolated with Trizol (Invitrogen) according to the manufacturer’s protocol. RNA from FFPE human breast cancers was isolated using the High Pure RNA Paraffin Kit (Roche, Woerden, The Netherlands) as described in the instruction manual. Reverse transcription, hybridization, ligation, PCR amplification and fragment analysis by capillary electrophoresis were carried out as reported previously (19;20). The Abcb1 gene expression levels were normalized to the internal reference genes Actinβ and Hprt1. The average expression of Abcb1a or Abcb1b was lower than that of (Hprt1+Actinβ)/2. To simplify Fig. 4A all Abcb1a/[Hprt1+Actinβ]/2 ratios were multiplied with the factor 24.8, those of Abcb1b/[Hprt1+Actinβ]/2 with a factor of 25.8 and those of (Abcb1a+Abcb1b)/([Hprt1+Actinβ]/2) with a factor of 12.6. A list of the human-specific RT-MLPA probes is provided in Supplementary Table S4.

For normalization of XIST gene expression, we used the mean of 8 reference probes detecting β2M, GAPDH (2x), LDH, FAU, OAZ1, BIRC2 and ARHGDIA gene expression. The cut-off to determine low XIST expression was defined as 2 times the SD below the average expression of normal breast tissue (Supplementary Fig. S6).

TaqMan low density arrays (TLDA)
Synthesis of cDNA from 1 μg total RNA in a 20 μl reaction volume was carried out using the High Capacity cDNA kit with RNAse inhibitor (Applied Biosystems, Foster City, CA, USA) as per the manufacturer’s instructions. The reverse transcription conditions were as follows: 10 minutes at 25°C, 120 minutes at 37°C, 5 minutes at 85°C. Following reverse transcription, cDNA was stored at 4°C. Expression levels of 49 murine Abc transporter genes were measured using custom-made Taqman Low Density Arrays (Applied Biosystems, Foster City, CA, USA). cDNA was mixed with 2X Taqman Universal PCR Master Mix (Applied Biosystems, Foster City, CA, USA), loaded on the TLDA card
(125ng per port), and run on an ABI Prism 7900 HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA) as per the manufacturer’s instructions. For Abca14, Abca15, Abca16, Abca17, Abcb5, Abcb11 and Abcg8 no expression was detected in the mouse tumors.

**FISH**

Sections were deparaffinized with xylene and treated with 1M sodium thiocyanate for 10 minutes at 80°C to remove crosslinks. Cells were permeabilized with 750 U/ml pepsin (Sigma-Aldrich) for 8 minutes. RNF12-specific DNA FISH probes were prepared from RP11 BAC clones. BAC DNA was digested and labeled using random primer labeling (Invitrogen) with Bio-16-dUTP or (Roche). Probes were validated using control metaphases. XIST RNA FISH probe was prepared from a plasmid containing 12kb of the XIST sequence and labeled with DIG-11-dUTP (Roche). Digoxigenin- or biotin-labeled probes were detected using a FITC-labeled mouse anti-DIG antibody or Alexa 594-labeled streptavidin, respectively.

**Patients**

In a previous study stage-III HER2-negative breast cancer patients were randomly selected from a large randomized controlled trial (RCT) performed in the Netherlands between 1993 and 1999 (29) and analyzed for aCGH classification (35). Patients were randomized between conventional chemotherapy (5*FEC: 5-fluorouracil 500mg/m², epirubicin 90mg/m², cyclophosphamide 500mg/m²) and intensive platinum-based chemotherapy (4*FEC, followed by 1*CTC: cyclophosphamide 6000mg/m², thiotepa 480mg/m² and carboplatin 1600mg/m²). From the aCGH study we selected those patients of whom BRCA1-mutation status was available (n=60 from the previous study (35) and 13 additionally analyzed). Of 13 patients no fragments could be visualized upon electrophoresis due to poor FFPE RNA quality, resulting in a subset of 60 patients of whom RT-MLPA data was available. For statistical analyses recurrence-free survival (RFS) was calculated from randomization to appearance of local or regional recurrence, metastases or to death from any cause. All other events were censored. Differences between groups of interest were tested using Fisher’s exact tests. Survival curves were generated using the Kaplan-Meier method and compared using log-rank tests. Hazard ratios (HR) were calculated using Cox-proportional hazards regression.