## Supplementary Materials

Supplementary Figure 1. Genetic profile of advanced breast cancer subtypes

A) Percentage and type of mutations, per gene, identified in the ABC-Bio study presented by tumour subtype. *Left hand panel*: HR+/HER2-; *Middle panel*: TNBC; *Right hand panel*: HER2. B) Comparison of the incidence of mutations identified in ABC-Bio (green bars) with the TCGA primary breast cancer (grey bars), presented by HR+/HER2- (*left hand panel*), TNBC (*centre panel*) and HER2+ (*right hand* panel). q value, Fisher’s exact test with Benjamini Hochberg false discovery correction. C) Comparison of the incidence of mutations identified in ABC-Bio (green bars) with primary (left hand panel) and metastatic (right hand panel) tumours from the MSKCC dataset. q value, Fisher’s exact test with Benjamini Hochberg false discovery correction. D) Contingency tables, *top panel,* of HER2 expression (IHC/ISH) versus *HER2* amplification determined with ABC-Bio sequencing and *bottom panel*, HER2 expression (IHC/ISH) versus *HER2* mutation status determined with ABC-Bio sequencing.

Supplementary Figure 2. Genetic profile of ER positive primary breast cancers that ‘switch’ to triple negative recurrent advanced breast cancer

A) *Top panel,* percentage incidence of mutations identified in genes by subtype of primary tumour, indicating 10 primary HR+/HER2- tumours that were later identified as TNBC in their metastatic tumour sample. *Bottom panel*, comparison of mutation profiles (%) by subtype, gene order as in top panel. r and p values as indicated, Spearman correlation.

Supplementary Figure 3. *NCOR* expression in *NF1* mutated cancers

A) Gene expression analysis of TCGA data, showing effect of truncating and missense mutations in *NF1* gene, on gene expression (p=0.000159, Wilcoxon test)*.* B) Expression of *NCOR1* gene from TCGA data, showing effect of truncating *NF1* mutations (p=0.105, Wilcoxon test)*.* C) Expression of *NCOR2* gene from TCGA data, showing effect of truncating *NF1* mutations (p=0.85, Wilcoxon test)*.*

Supplementary Figure 4. *NCOR* expression following NF1 loss

A) Western blot of whole cell lystates from MCF7 and T47D cells following transient transfection with individual siRNAs and SMARTpool targeting NF1, probed for NF1 and βtubulin as a loading control. B) Bliss Independence score was calculated for the effect of *NF1* knockdown on endocrine therapies in MCF7 (top, n=8) and T47D (bottom, n=4) cells. C) Western blot of whole cell lysates from MCF7-LucB2.2, MCF7-shNF1 14B2.2 and MCF7 17B2.2, probed for NF1 and phospho-ERK1,2. D) ddPCR analysis of gene expression of *NF1*, *NCOR1* and *NCOR2* in MCF7-LucB2.2, MCF7-shNF1 14B2.2 and MCF7 17B2.2. Target gene expression relative to *GUSB* housekeeping gene. E) Western blot of MCF7 cells treated with vehicle or trametinib (100nM) for 1, 8, 24, 48 and 72h. Whole cell lysates were blotted for the indicated proteins. F) Western blot of MCF7 cells transfected with siCON or siNF1 and treated for 72hr with and without trametinib (100nM). Whole cell lysates were blotted and probed for the indicated proteins. G) Gene expression, from RT2 ER profiler array, of *MYC* in MCF7 cells transfected 96 hours earlier with siRNA against *NF1 and* treated with trametinib (100nM) or vehicle for 72 hours. q values, t Test with Benjamini Hochberg false discovery correction.

Supplementary Figure 5. CDK4/6 inhibition partly overcomes NF1 loss in T47D cells

A) Colony formation assay of T47D with siCON or siNF1 and treated with either fulvestrant, tamoxifen or oestradiol depletion on their own or in combination with palbociclib for 7 days. Drugs were washed off and colonies allowed to grow for an addition 14 days. Mean SEM, n=3; 2 way ANOVA with Sidak multiple comparisons, p values as indicated. B) Bliss Independence score was calculated for the effect of palbociclib on endocrine therapies in MCF7 (left hand panel) and T47D cells (right hand panel). C) Bliss Independence score was calculated for the effect of *NF1* knockdown on endocrine therapies in MCF7 (left hand panel) and T47D cells (right hand panel). D) *NF1* mutation status on overall survival in patients enrolled in the PALOMA-3 trial treated with fulvestrant.

Supplementary Table 1. Targets of The Breast NGS v1.0 capture panel.

Supplementary Table 2. Gene list of NanoString nCounter™ custom codeset.

Supplementary Table 3. Gene list of Human Estrogen Receptor RT2 Profiler PCR Array (330231, PAHS-005ZA-24, Qiagen)

Supplementary Table 4. Lines of treatment of patients with *ESR1* and *NF1* mutations.

Supplementary Table 5. Disease free survival for mutated genes with incidence ≥5% presented by HR+/HER2-, HER2+ and TNBC subtype.

Supplementary Table 6. Advanced overall survival for mutated genes with incidence ≥5% presented by HR+/HER2-, HER2+ and TNBC subtype.