Supplementary Methods

Immunohistochemical staining of XRCC1, ATM, ATR, WEE1 and BRCA1 in clinical breast cancers

The study was performed in a consecutive series of 1650 patients with primary invasive breast carcinomas who were diagnosed between 1986 and 1999 and entered into the Nottingham Tenovus Primary Breast Carcinoma series. All patients were treated in a single institution and have been investigated in a wide range of biomarker studies (9, 10, 19, 22, 23). Supplemental Table S1 summarizes patient demographics. All patients were treated in a uniform way in a single institution with standard surgery (mastectomy or wide local excision), followed by Radiotherapy. Prior to 1989, patients did not receive systemic adjuvant treatment (AT). After 1989, AT was scheduled based on prognostic and predictive factor status, including Nottingham Prognostic Index (NPI), oestrogen receptor-α (ER-α) status, and menopausal status. Patients with NPI scores of <3.4 (low risk) did not receive AT. In pre-menopausal patients with NPI scores of ≥3.4 (high risk), classical Cyclophosphamide, Methotrexate, and 5-Flurouracil (CMF) chemotherapy was given; patients with ER-α positive tumours were also offered endocrine therapy. Postmenopausal patients with NPI scores of ≥3.4 and ER positivity were offered endocrine therapy, while ER negative patients received classical CMF chemotherapy. Median follow up was 111 months (range 1 to 233 months). Breast cancer specific survival (BCSS) data was maintained on a prospective basis. Breast cancer specific survival (BCSS) was defined as the number of months from diagnosis to the occurrence of BC related-death. Survival was censored if the patient was still alive at the time of analysis, lost to follow-up, or died from other causes.

IHC protocol: Immunohistochemical staining was performed using the Thermo Scientific Shandon Sequenza chamber system (REF: 72110017), in combination with the Novolink Max

Polymer Detection System (RE7280-K: 1250 tests), and the Leica Bond Primary Antibody Diluent (AR9352), each used according to the manufacturer's instructions (Leica Microsystems). Leica Autostainer XL machine was used to dewax and rehydrate the slides. Pre-treatment antigen retrieval was performed on the TMA sections using sodium citrate buffer (pH 6.0) and heated for 20 minutes at 95^0C in a microwave (Whirpool JT359 Jet Chef 1000W). Negative and positive (by omission of the primary antibody and IgG-matched serum) controls were included for each marker in each run. The negative control ensured that all the staining was produced from the specific interaction between antibody and antigen. HER2 expression was assessed according to the new ASCO/CAP guidelines using IHC and fluorescence in situ hybridisation (FISH) {Wolff, 2007 #19}. Supplementary Table S2 summarizes antigens, primary antibodies, clone, source and optimal dilution used for each immunohistochemical marker (XRCC1, ATM, ATR and WEE1).

Evaluation of immune staining: Whole field inspection of the core was scored and intensities of nuclear staining for DNA repair markers were grouped as follows: 0 = no staining, 1 = weak staining, 2 = moderate staining, 3 = strong staining. The percentage of each category was estimated (0-100%). H-score (range 0-300) was calculated by multiplying intensity of staining and percentage staining for ATR, WEE1 and XRCC1 expression. H-score of ≥ 60 was taken as the cut-off for high ATR expression. Low WEE1 expression was defined by H-score of ≤100. Low/negative XRCC1 expression was defined by H-score of ≤90. The percentage of ATM positive cells was used, with a cut off of <25% cells being classed as low, and ≥25% as high for nuclear ATM protein level. For BRCA1, H score of less than 100 was considered as low/negative expression.

The Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) criteria, recommended by McShane et al (24), were followed throughout this study. This work was approved by Nottingham Research Ethics Committee.

Supplementary Table S1: Percentage of cells in various stages of the cell cycle.

Cell line	G1 (Mean ± SD*)	S phase (Mean ± SD*)	G2/M (Mean ± SD*)
MDA-MB-231 (C) _UT	45 ± 0.8	44 ± 2.4	8.4 ± 2.1
MDA-MB-231(C) _Olaparib	39 ± 1.5	45 ± 0.5	16 ± 1.4
MDA-MB-231(C) _AZD6738	38 ± 1.3	50 ±5.4	16.5 ±4.8
MDA-MB-231(C) _AZD6738+Olaparib	28.5 ± 1.2	50.5 ±2.3	12 ± 2.1
MDA-MB-231(C) _AZD1775	36 ± 4.3	47 ± 23	17 +1.2
MDA-MB-231(C) _AZD1775+Olaparib	37 ± 2.3	56.5 ± 5.6	9.5 ±3.5
MDA-MB-231(C) _AZ31	36 ± 1.6	46 ± 1.2	21 ± 4.2
MDA-MB-231(C) _AZ31+Olaparib	69.5 ± 3.1	28 ± 2.5	1 ± 2.1
MDA-MB-231 (XRRC1 _KO) _UT	36 ± 2.1	46.5 ± 3.2	17.5 ± 5.6
MDA-MB-231(XRRC1 _KO) _Olaparib	30 ± 4.5	24.5 ± 3.6	43 ± 1.5
MDA-MB-231(XRRC1 _KO) _AZD6738	27 ± 1.8	64 ± 2.1	11 ± 3.2
MDA-MB-231(XRRC1 _KO) _AZD6738+Olaparib	22.5 ± 3.2	74 ± 6.2	4 ±1.4
MDA-MB-231(XRRC1 _KO) _AZD1775	35 ± 2.6	59 ±3.6	6 ± 2.1
MDA-MB-231(XRRC1 _KO) _AZD1775+Olaparib	12 ± 3.1	82 ± 4.2	7 ± 1.2
MDA-MB-231(XRRC1 _KO) _AZ31	51.5 ± 2.1	35 ± 3.6	5.8 ± 5.2
MDA-MB-231(XRRC1 _KO) _AZ31+Olaparib	72.5 ± 3.5	28.5 ± 2.5	1.5 ± 0.8
MDA-MB-157_UT	45 ± 2.6	32 ± 1.8	23 ±3.8
MDA-MB-157_Olaparib	33.5 ± 5.1	56.5 ± 4.9	9.5 ± 3.5
MDA-MB-157_AZD6738	49 ± 3.8	55 ± 7.2	7 ±6
MDA-MB-157_AZD6738+Olaparib	24 ± 2.1	66 ± 2.3	8.8 ± 4.5
MDA-MB-157_AZD1775	37 ± 1.9	46 ± 3.1	16.5 ± 3.5
MDA-MB-157_AZD1775+Olaparib	3 ± 2	72 ± 3.2	26 ± 8.4
MDA-MB-157_AZ31	53 ± 4.2	43 ± 3.1	2 ± 1.2
MDA-MB-157_AZ31+Olaparib	69 ± 1.6	28 ± 5.1	1 ± 3.2
HeLa_control_ UT	49 ± 1.2	43 ± 1.5	6.5 ± 1.6
HeLa_control_ Olaparib	28 ± 4.2	51± 1.4	12.5 ±1.2
HeLa_control_ AZD6738	38.5 ± 4.6	51 ± 6.2	9.5 ± 2.1
HeLa_control_ AZD6738+Olaparib	41 ±3.1	45 ± 2.4	13 ± 1.6
HeLa_control_ _AZD1775	46 ± 3.1	48 ± 1.5	4.8 ± 4
HeLa_control_ _AZD1775+Olaparib	38 ± 3.2	52 ± 1.4	9 ±2.8
HeLa_control_ _AZ31	51 ± 1.6	39 ± 2.6	8.5 ± 3.2
HeLa_control_ AZ31+Olaparib	40 ± 3.1	52 ± 5.1	8 ± 4
HeLa_XRCC1_KD_ UT	42 ± 1.3	44.5 ± 1.2	12.5 ± 2.2
HeLa_XRCC1_KD Olaparib	24 ± 1.5	68 ± 1.8	4 ± 2.1
HeLa_XRCC1_KD AZD6738	35 ± 2.4	59.5 ± 3.2	5 ± 4.1
HeLa_XRCC1_KD AZD6738+Olaparib	8 ± 7.8	65 ± 3.2	25 ± 3.6
HeLa_XRCC1_KD _AZD1775	32 ± 2.4	53.5 ± 1.8	15 ± 4.2
HeLa_XRCC1_KD _AZD1775+Olaparib	16 ± 6.1	72 ± 3.6	10 ± 2
HeLa_XRCC1_KD _AZ31	59 ± 2.1	35 ± 4.2	5 ± 1.2
HeLa_XRCC1_KD AZ31+Olaparib	70 ± 2.6	22 ± 8.1	8.5 ± 3.2

Supplementary Table S2: Combination index for drug interaction

Combination	Cell line	Combination index
AZD31 +Olaparib	MDA-MB-231_XRCC1_KO	0.62
	MDA-MB-157	0.75
	HeLa_KD	0.266
AZD6738+Olaparib	MDA-MB-231_KO	0.225
	MDA-MB-157	0.162
	HeLa_XRCC1_KD	0.52
AZD1775+Olaparib	231_KO	0.25
	MDA-MB-157	0.9
	HeLa_XRCC1_KD	0.5

Supplementary Table S3: Clinicopathological characteristics of whole breast cancer cohort

Variable	n*	Cases	(%)
Menopausal status	1650		
Pre-menopausal		612	(37.0)
postmenopausal		1038	(63.0)
Tumour Grade (NGS)	1650		
G1		306	(18.5)
G2		531	(32.2)
G3		813	(49.3)
Lymph node stage	1650		
Negative		1056	(64.0)
Positive (1-3 nodes)		486	(29.5)
Positive (>3 nodes)		108	(6.5)
Tumour size (cm)	1650		
T1 a + b (≤1.0)		187	(11.0)
T1 c (>1.0 -2.0)		868	(53.0)
T2 (>2.0-5)		5729	(35.0)
T3 (>5)		16	(1.0)
Tumour type	1650		
IDC-NST		941	(57)
Tubular		349	(21)
ILC		160	(10)
Medullary (typical/atypical)		41	(2.5)
Others		159	(9.5)
NPI subgroups	1650		
Excellent PG(2.08-2.40)	Low risk	207	(12.5)
Good PG(2.42-3.40)		331	(20.1)

Moderate I PG(3.42 to 4.4)	High risk	488	(29.6)
Moderate II PG(4.42 to 5.4)		395	(23.9)
Poor PG(5.42 to 6.4)		170	(10.3)
Very poor PG(6.5–6.8)		59	(3.6)
Survival at 20 years	1650		
Alive and well		1055	(64.0)
Dead from disease		468	(28.4)
Dead from other causes		127	(7.6)
Adjuvant systemic therapy (AT)	1602		
No AT		665	(42.0)
Hormone therapy (HT)		642	(41.0)
Chemotherapy		307	(20.0)
Hormone + chemotherapy		46	(3.0)

* Number of cases for which data were available.

NPI; Nottingham prognostic index, PG; prognostic group

Supplementary Table S4: Antigens, primary antibodies, clone, source, optimal dilution and scoring system used for each immunohistochemical marker

Antigen	Antibody	Clone	Source	Antigen Retrieval	Dilution / Incubation Time	Distribution	Scoring system	Cut-offs
ER	Mouse MAb anti-ER-α	SP1	Dako-Cytomation	Citrate pH6	1:150 30 min	Nuclear	Allred score	≥3 (positive)
ER	Mouse MAb anti-ER-α	EP1	Dako-Cytomation	Citrate pH6	1:80 30 min	Nuclear	% positive cells	≥1% positive
PR	Mouse MAb anti-PR	PgR636	Dako-Cytomation	Citrate pH6	1:125 30 min	Nuclear	% positive cells	≥1% positive
CK14	Mouse MAb anti-Ck14	LL002	Novocastra	Citrate pH6	1:40 60 min	Cytoplasm	% of positive cells	≥10% (positive)
Ck5/6	Mouse MAb anti-Ck5/6	D5/161B4	Dako-Cytomation	EDTA pH8	1:100 60 min	Cytoplasm	% of positive cells	≥10% (positive)
Ck17	Mouse MAb anti-Ck17	E3	Dako-Cytomation	Citrate pH6	1:100 60 min	Cytoplasm	% of positive cells	≥10% (positive)
Ck18	Mouse MAb anti-Ck18	DC10	Dako-Cytomation	Citrate pH6	1:100 60 min	Cytoplasm	% of positive cells	≥10% (positive)
HER2	Rabbit antihuman c-erbB2	polyclonal	Dako-Cytomation	None	1:400 60 min	Membrane	See text	See text

All sections were pre-treated with microwave antigen retrieval using 0.1% citrate buffer (pH 6) except for HER2 (no pre-treatment)

Supplementary Table S5: Clinicopathological significance of WEE1 expression.

	WEE1 expression		**P- value**	***P -Value** (Adjusted)
	WEE1 -	WEE1+		
A) Pathological Parameters				
Tumour Size				
<1cm	65 (59.6%)	38 (40.4%)		**0.0330**
>1-2cm	229 (46.9%)	259 (54.1%)	**0.027**	
>2-5cm	155 (42.5%)	210 (57.5%)		
>5cm	7 (42.5%)	6 (46.2)		
Tumour Stage				
1	286 (47.6%)	315 (52.4%)	0.119	1.309
2	130 (47.1%)	146 (52.9%)		
3	30 (35.7%)	54 (64.3%)		
Tumour Grade				
G1	100 (62.5%)	60 (37.5%)	**0.00134×10^{-8}**	**<0.0001**
G2	169 (58.1%)	122 (41.9%)		
G3	178 (34.9%)	332 (65.1%)		
NPI			**0.00725×10^{-4}**	
≤ 3.4	173 (61.3%)	109 (38.7%)		**<0.0001**
>3.4	255 (40%)	382 (60%)		
Mitotic Index				
M1 (low; mitoses < 10)	194 (63%)	114 (37%)	**0.00411×10^{-7}**	**<0.0001**
M2 (medium; mitoses 10-18)	79 (47.6%)	87 (52.4%)		
M3 (high; mitosis >18)	156 (34.3%)	299 (65.7%)		
Tubule Formation				
1 (>75% definite tubule)	26 (52%)	24 (48%)	**0.057**	**0.0627**
2 (10%-75% definite tubule)	157 (51%)	151 (49%)		
3 (<10% definite tubule)	246 (43.1%)	325 (56.9%)		
Pleomorphism				
1 (small-regular uniform)	13 (76.5%)	4 (23.5%)	**0.00234×10^{-6}**	**<0.0001**
2 (Moderate variation)	208 (60.1%)	138 (39.9%)		
3 (Marked variation)	207 (36.8%)	356 (63.2%)		
Tumour Type				
IDC-NST	225 (39.3%)	347 (60.7%)		
Tubular	96 (50.5%)	94 (49.5%)	**0.00179×10^{-5}**	**<0.0001**
Medullary	4 (17.4%)	19 (82.6%)		
ILC	68 (78.2%)	19 (21.8%)		
Others	13 (65%)	7 (35%)		
Mixed NST &lobular/ special type	27 (56.3%)	21 (43.8%)		
HER-2 overexpression			**0.000196**	**0.0003**
No	402 (49.1%)	417 (50.9%)		
Yes	38 (29.2%)	92 (70.8%)		
ER				
Negative	78 (31.5%)	170 (68.5%)	**0.0042×10^{-6}**	**<0.0001**
Positive	363 (51.9%)	337 (48.1%)		
PR				**<0.0001**
Negative	147 (37.5%)	245 (62.5%)	**0.00807×10^{-5}**	
Positive	284 (52.1%)	261 (47.9%)		

Supplementary Table S6: Clinicopathological significance of ATR and XRCC1 expression

	ATR and XRCC1 expression				P- value	*P -Value (Adjusted)
	ATR+/ XRCC1+	ATR +/ XRCC1-	ATR -/ XRCC1+	ATR -/ XRCC1-		
A) Pathological Parameters						
Tumour Size					0.385	0.4235
<1cm	12 (33.3%)	3 (8.3%)	17 (47.2%)	4 (11.1%)		
>1-2cm	87 (38.5%)	13 (5.8%)	108 (47.8%)	18 (8%)		
>2-5cm	95 (45%)	19 (5.7%)	83 (39.3%)	14 (6.6%)		
>5cm	5 (50%)	2 (20%)	2(20%)	1 (10%)		
Tumour Stage						
1	120(44.3%)	22(8.1%)	106(39.1%)	23(8.5%)	0.451	4.9610
2	63(38.2%)	12(7.3%)	78(47.3%)	12(7.3%)		
3	18(36.0%)	3(6.0%)	27(54.0%)	2(4%)		
Tumour Grade						
G1	23(37.7%)	2(3.3%)	31(50.8%)	5(8.2%)	0.00031	**0.0017**
G2	52(35.9%)	5(3.4%)	84(57.9%)	4(2.8%)		
G3	125(45%)	30(10.8%)	95(34.2%)	28(10.1%)		
NPI					0.045	0.0707
≤ 3.4	42 (36.8%)	4 (3.5%)	61 (53.5%)	7 (6.1%)		
>3.4	147 (42.5%)	31 (9%)	139 (40.2%)	29 (8.4%)		
Mitotic Index						
M1 (low; mitoses < 10)	3(60%)	0(0%)	2(40%)	0(0%)	0.004	**0.0110**
M2 (medium; mitoses 10-18)	55(34%)	7(4.3%)	91(56.2%)	9(5.6%)		
M3 (high; mitosis >18)	142(45.1%)	30(9.5%)	115(36.5%)	28(8.9%)		
Tubule Formation						
1 (>75% definite tubule)	8(38.1%)	2(9.5%)	9(42.9%)	2(9.5%)	0.00000	**0.0001**
2 (10%-75% definite tubule)	64(38.3%)	84(50.3%)	84(50.3%)	8(4.8%)	7	
3 (<10% definite tubule)	128(43.5%)	115(39.1%)	115(39.1%)	27(9.2%)		
Pleomorphism						
1 (small-regular uniform)	3(60%)	0(0%)	2(40%)	0(0%)	0.004	**0.0110**
2 (Moderate variation)	55(34%)	7(4.3%)	91(56.2%)	9(5.6%)		
3 (Marked variation)	142(45.1%)	30(9.5%)	115(36.5%)	28(8.9%)		
Tumour Type					0.168	0.2310
IDC-NST	134 (42.4%)	29 (9.2%)	129 (40.8%)	24 (7.6%)		
Tubular	33 (38.4%)	6 (7%)	40 (46.5%)	7 (8.1%)		
Medullary	3(33.3%)	0 (0%)	3 (33.3%)	3 (33.3%)		
ILC	13 (38.2%)	1 (2.9%)	20 (58.8%)	0 (0%)		
Others	1 (33.3%)	0 (0%)	1 (33.3%)	1 (33.3%)		
Mixed NST & Lobular/special type	12 (40%)	1 (3.3%)	15 (50%)	2 (6.7%)		
Her2 overexpression					0.310	0.3789
No	159 (39.7%)	32 (8%)	181(45.1%)	29 (7.2%)		
Yes	39 (49.4%)	6 (7.6%)	27 (34.2%)	7 (8.9%)		
ER status					0.011	**0.0202**
Negative	48 (41.4 %)	16 (13.8%)	40 (34.5%)	12(10.3%)		
Positive	151 (41.7%)	22 (6.1%)	166 (45.9%)	23 (6.4%)		
PR					0.002	**0.0073**
Negative	71 (38.8%)	24 (13.1%)	70(38.3%)	18 (9.3%)		
Positive	120 (43.2%)	13 (4.7%)	130 (46.8%)	15(5.4%)		

Supplementary Table S7: Clinicopathological significance of ATM and XRCC1 expression

	ATM and XRCC1 expression				**P- value**	***P - Value** (Adjusted)
	ATM+/ XRCC1+	ATM +/ XRCC1-	ATM -/ XRCC1+	ATM -/ XRCC1-		
A) Pathological Parameters						
Tumour Size					0.174	
<1cm	29 (40.3%)	5 (6.9%)	30 (41.7%)	8 (11.1%)		**0.4785**
>1-2cm	198 (46.8%)	22 (5.2%)	169 (40%)	34 (8%)		
>2-5cm	102 (36.2%)	16 (5.7%)	128 (45.4%)	36 (12.8%)		
>5cm	3 (25%)	0 (0%)	7 (58.3%)	2 (16.7%)		
Tumour Stage						
1	220(45.6%)	28(5.8%)	194(40.2%)	40(8.3%)		
2	91(37.9%)	13(5.4%)	104(43.0%)	34(14%)	0.046	**0.1687**
3	22(33.3%)	2(3%)	36(54.5%)	6(9.1%)		
Tumour Grade						**<0.0001**
G1	79(64.2%)	7(5.7%)	35(28.5%)	2(1.6%)		
G2	123(46.1%)	4(1.5%)	127(47.6%)	13(4.9%)	1.539	
G3	131(32.8%)	32(8%)	172(43%)	65(16.3%)	X 10^{-13}	
NPI						**<0.0001**
≤ 3.4	127 (55.9%)	8 (3.5%)	85 (37.4%)	7 (3.1%)	1.7958	
>3.4	194 (36.5%)	33 (6.2%)	233 (43.9%)	71 (13.4%)	X 10^{-7}	
Mitotic Index						**<0.0001**
M1 (low; mitoses < 10)	144(54.5%)	8(3%)	105(39.8%)	7(2.7%)	8.3X10	
M2 (medium; mitoses 10-18)	66(44.3%)	5(3.4%)	62(41.6%)	16(10.7%)	$^{-10}$	
M3 (high; mitosis >18)	116(32.1%)	30(8.3%)	158(43.8%)	57(15.8%)		
Tubule Formation						**<0.0001**
1 (>75% definite tubule)	15(41.7%)	5(13.9%)	16(44.4%)	0(0%)	4.3	
2 (10%-75% definite tubule)	144(54.5%)	6(2.3%)	97(36.7%)	17(6.4%)	X10 $^{-17}$	
3 (<10% definite tubule)	167(35.2%)	32(6.8%)	212(44.7%)	63(13.3%)		
Pleomorphism						
1 (small-regular uniform)	10(55.6%)	2(11.1%)	6(33.3%)	0(0%)	0.0000	**<0.0001**
2 (Moderate variation)	149(49.7%)	9(3%)	128(42.7%)	14(4.7%)	07	
3 (Marked variation)	165(36.4%)	32(7.1%)	190(41.9%)	66(14.6%)		
Tumour Type					0.0000	
IDC-NST	183 (38.1%)	27 (5.6%)	208 (43.3%)	62 (12.9%)	06	**0.0001**
Tubular	87 (56.5%)	8 (5.2%)	54 (35.1%)	5 (3.2%)		
Medullary	7 (28%)	3 (12%)	7 (28%)	8 (32%)		
ILC	25 (35.7%)	2 (2.9%)	41 (58.6%)	2 (2.9%)		
Others	3 (37.5%)	0 (0%)	5 (62.5%)	0 (0%)		
Mixed NST & Lobular/special type	24 (51.1%)	3 (6.4%)	17 (36.2%)	3 (6.4%)		
Her2 overexpression					0.176	**0.4785**
No	293 (43.7%)	35 (5.2%)	276 (41.2%)	66 (9.9%)		
Yes	35 (32.4%)	7 (6.5%)	54 (50%)	12 (11.1%)		
ER status					8.318	**<0.0001**
Negative	61 (28.8%)	20 (9.4%)	86 (40.6%)	45 (21.2%)	X 10^{-13}	
Positive	270 (47.6%)	21 (3.7%)	243 (42.9%)	33 (5.8%)		
PR					3.0047	**<0.0001**
Negative	103 (32.5%)	24 (7.6%)	133 (42%)	57 (18%)	X 10^{-11}	
Positive	219 (49.2%)	15 (3.4%)	191 (42.9%)	20 (4.5%)		

Supplementary Table S8: Clinicopathological significance of WEE1 expression and XRCC1.

	WEE1 and XRCC1 expression				P- value	*P -Value (Adjusted)
	WEE1+/ XRCC1+	WEE1+/ XRCC1-	WEE1-/ XRCC1+	WEE1-/ XRCC1-		
A) Pathological Parameters						
Tumour Size						
<1cm	20 (35.1%)	3 (5.3%)	28 (49.1%)	5 (10.5%)		
>1-2cm	172 (48%)	33 (9.2%)	130 (36.3%)	23 (6.4%)	0.138	0.7590
>2-5cm	127 (45.7%)	35 (12.6%)	92 (33.1%)	24 (8.6%)		
>5cm	2 (18.2%)	2 (18.2%)	6 (54.5%)	1 (9.1%)		
Tumour Stage						
1	194 (45.6%)	41 (9.6%)	159 (37.4%)	31 (7.3%)		0.803
2	89 (41.8%)	28 (13.1%)	80 (37.6%)	16 (7.5%)	0.292	
3	39 (57.4%)	5 (74%)	18 (26.5%)	6 (8.8%)		
Tumour Grade						
G1	37 (34.3%)	7 (6.5%)	57 (52.8%)	7 (6.5%)		**<0.0001**
G2	80 (38.1%)	8 (3.8%)	111 (52.9%)	11 (5.2%)	7.45 X	
G3	205 (53%)	58 (15%)	88 (22.7%)	36 (9.3%)	10^{-7}	
NPI						**<0.0001**
≤ 3.4	67 (34.5%)	11 (5.7%)	106 (54.6%)	10 (5.2%)	7.25 X	
>3.4	240 (49.9%)	60 (12.5%)	139 (28.9%)	42 (8.7%)	10^{-9}	
Mitotic Index						**<0.0001**
M1 (low; mitoses < 10)	73 (34.9%)	9 (4.3%)	115 (55%)	12 (5.7%)	4.0115 X	
M2 (medium; mitoses 10-18)	46 (43.1%)	11 (8.5%)	50 (38.5%)	13 (10%)	10^{-12}	
M3 (high; mitosis >18)	185 (53.8%)	52 (15.1%)	79 (23%)	28 (8.1%)		
Tubule Formation						
1 (>75% definite tubule)	15 (46.9%)	2 (6.3%)	12 (37.5%)	3 (9.4%)	0.171	**0.6270**
2 (10%-75% definite tubule)	103 (45.2%)	16 (75)	4 (41.2%)	15 (6.6%)		
3 (<10% definite tubule)	196 (46.3%)	54 (12.3%)	138 (32.6%)	35 (8.3%)		
Pleomorphism						
1 (small-regular uniform)	3 (30 %)	0 (0 %)	6 (60%)	1 (10%)	2.333 X	**<0.0001**
2 (Moderate variation)	90 (35.9%)	11 (4.4%)	132 (52.6%)	18 (7.2%)	10^{-11}	
3 (Marked variation)	219 (52.3%)	61 (14.6%)	105 (25.1%)	34 (8.1%)		
Tumour Type						
IDC-NST	218 (50.3%)	50 (11.5%)	125 (28.9%)	40 (9.2%)		**<0.0001**
Tubular	62 (47.3%)	10 (7.6%)	52 (39.7%)	7 (5.3%)		
Medullary	9 (45%)	7 (35%)	2 (10%)	2 (10%)	01.79x1	
ILC	10 (16.7%)	2 (3.3%)	47 (78.3%)	1 (1.7%)	0^{-10}	
Others	2 (25%)	1 (12.5%)	4 (50 %)	1 (12.5%)		
Mixed NST & Lobular/special type	15 (38.5%)	3 (7.7%)	18 (46.2%)	3 (7.7%)		
Her2 overexpression						
No	258 (42.6%)	64 (10.6%)	239 (39.4%)	45 (7.4%)		**0.0216**
Yes	61 (64.2%)	8 (8.4%)	17 (17.9%)	9 (9.5%)	0.00196	
ER status						
Negative	89 (48.4%)	41 (22.3%)	38 (20.7%)	16 (8.6%)	4.1958 X	**<0.0001**
Positive	228 (44.5%)	32 (6.3%)	216 (42.2%)	36 (7%)	10^{-11}	
PR						
Negative	139 (47.9%)	53 (18.3%)	75 (25.5%)	24 (8.3%)	8.0747 X	**<0.0001**
Positive	176 (43.7%)	21 (5.2%)	180 (44.7%)	26 (6.5%)	10^{-10}	

Supplementary Table S9: Correlation between XRCC1 and BRCA1 in sporadic breast cancers.

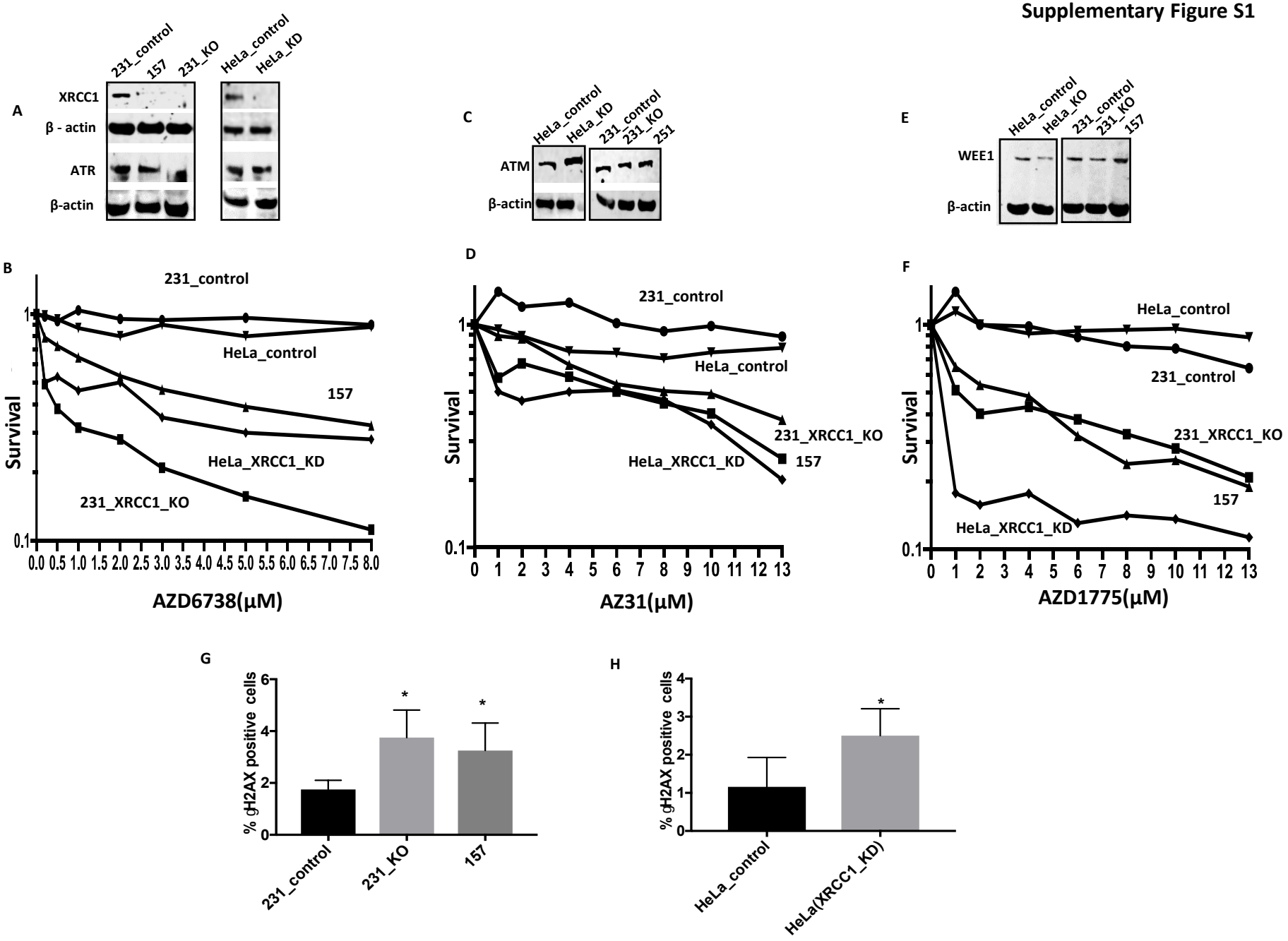
	Low XRCC1	**High XRCC1**	**P-Value**
BRCA1 Negative	105 (23.0%)	352(77.0%)	0.0001
BRCA1 Positive	63 (11%)	509 (89%)	
Total (n=1029)	168 (16.3%)	861 (87.3%)	

Supplementary Figure Legends:

Supplementary Figure S1: (A) Western blot of ATR and XRCC1 levels in HeLa control, HeLa XRCC1_KD, 231 control, 231 (XRCC1_KO) and 157 cells**. (B)** Clonogenic survival assay for AZD6738 monotherapy in 231control, 231 (XRCC1_KO), 157 cells, HeLa control and HeLa XRCC1_KD cells. **(C)** Western blot of ATM levels in 231control, 231 (XRCC1_KO), 157 cells, HeLa control and HeLa XRCC1_KD cells**. (D)** Clonogenic survival assay for AZ31 monotherapy in 231control, 231 (XRCC1_KO), 157 cells, HeLa control and HeLa XRCC1_KD cells. **(E)** Western blot of WEE1 levels in 231control, 231 (XRCC1_KO), 157 cells, HeLa control and HeLa XRCC1_KD cells**. (F)** Clonogenic survival assay for AZD1775 monotherapy in 231control, 231 (XRCC1_KO), 157 cells, HeLa control and HeLa XRCC1_KD cells. **(G)** Quantification of basal γH2AX levels by flow cytometry in 231control, 231 (XRCC1_KO) and 157 cells. **(H)** Quantification of basal γH2AX levels by flow cytometry in HeLa control and HeLa XRCC1_KD cells

Supplementary Figure S2: Kaplan Meier curves for WEE1 protein expression showing breast cancer specific survival (BCSS).

Supplementary Figure S1



Supplementary Figure S2