Supplementary Table 1. The sequence of si-RNAs

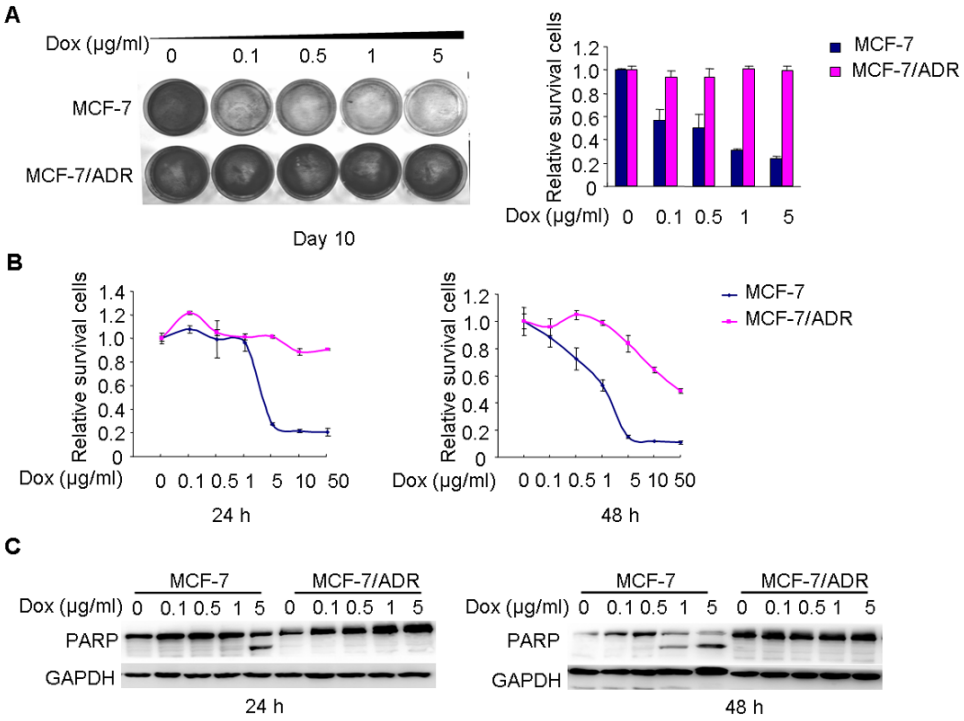
Gene name		Sequence (5'-3')
Axl	#1	Sense: CAAGAUUCUAGAUGAUUAAdTdT
		Anti-sense: UUAAUCAUCUAGAAUCUUGdTdT
	#2	Sense: UCGCGGUGCUGGGAGCUAAdTdT
		Anti-sense: UUAGCUCCCAGCACCGCGAdTdT
	#3	Sense: CGUGGAGAACAGCGAGAUUUAdTdT
		Anti-sense: UAAAUCUCGCUGUUCUCCACGdTdT
Akt	#1	Sense: CUGACCAAGAUGACAGCAUdTdT
		Anti-sense: AUGCUGUCAUCUUGGUCAGdTdT
	#2	Sense: GUGGUCAUGUACGAGAUGAdTdT
		Anti-sense: UCAUCUCGUACAUGACCACdTdT
	#3	Sense: CUCCUCAAGAAUGAUGGCAdTdT
		Anti-sense: UGCCAUCAUUCUUGAGGAGdTdT
β-catenin	#1	Sense: ACGACUAGUUCAGUUGCUUdTdT
		Anti-sense: AAGCAACUGAACUAGUCGUdTdT
	#2	Sense: CCUGGUGAAAAUGCUUGGUdTdT
		Anti-sense: ACCAAGCAUUUUCACCAGGdTdT
	#3	Sense: GUGCUAUCUGUCUGCUCUAdTdT
		Anti-sense: UAGAGCAGACAGAUAGCACdTdT
ZEB1	#1	Sense: CACAGAUACGGCAAAAGAUdTdT
		Anti-sense: AUCUUUUGCCGUAUCUGUGdTdT
	#2	Sense: CAGUGUUCCAUGCUUAAGAdTdT
		Anti-sense: UCUUAAGCAUGGAACACUGdTdT
	#3	Sense: UGACCUAAAGCAGCCUACUdTdT
		Anti-sense: AGUAGGCUGCUUUAGGUCAdTdT

Supplementary Table 2. Classification of breast cancer cell lines according to EMT markers

Order	Cell lines	Classfication
1	AU565	Epithelial
2	BT20	Epithelial
3	BT474	Epithelial
4	BT483	Epithelial
5	BT549	Mesenchymal
6	CAL120	Mesenchymal
7	CAL148	Epithelial
8	CAL51	Epithelial
9	CAL851	Epithelial
10	CAMA1	Epithelial
11	DU4475	Epithelial
12	EFM19	Epithelial
13	EFM192A	Epithelial
14	EVSAT	Epithelial
15	HCC1143	Epithelial
16	HCC1187	Epithelial
17	HCC1395	Epithelial
18	HCC1419	Epithelial
19	HCC1428	Epithelial
20	HCC1500	Epithelial
21	HCC1569	Epithelial
22	HCC1599	Epithelial
23	HCC1806	Epithelial
24	HCC1937	Epithelial
25	HCC1954	Epithelial
26	HCC202	Epithelial

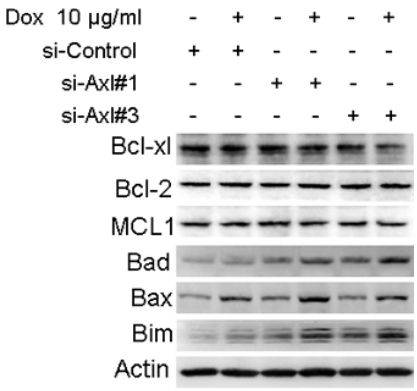
27	HCC2157	Epithelial
28	HCC2218	Epithelial
29	HCC38	Epithelial
30	HCC70	Epithelial
31	HDQP1	Epithelial
32	HMEL	Epithelial
33	HS274T	Mesenchymal
34	HS281T	Mesenchymal
35	HS343T	Mesenchymal
36	HS578T	Mesenchymal
37	HS606T	Mesenchymal
38	HS739T	Mesenchymal
39	JIMT1	Epithelial
40	KPL1	Epithelial
41	MCF7	Epithelial
42	MDAMB134VI	Epithelial
43	MDAMB157	Mesenchymal
44	MDAMB175VII	Epithelial
45	MDAMB231	Mesenchymal
46	MDAMB361	Epithelial
47	MDAMB415	Epithelial
48	MDAMB436	Mesenchymal
49	MDAMB453	Epithelial
50	MDAMB468	Epithelial
51	SKBR3	Epithelial
52	T47D	Epithelial
53	UACC812	Epithelial
54	UACC893	Epithelial
55	YMB1	Epithelial

56	ZR751	Epithelial
57	ZR7530	Epithelial



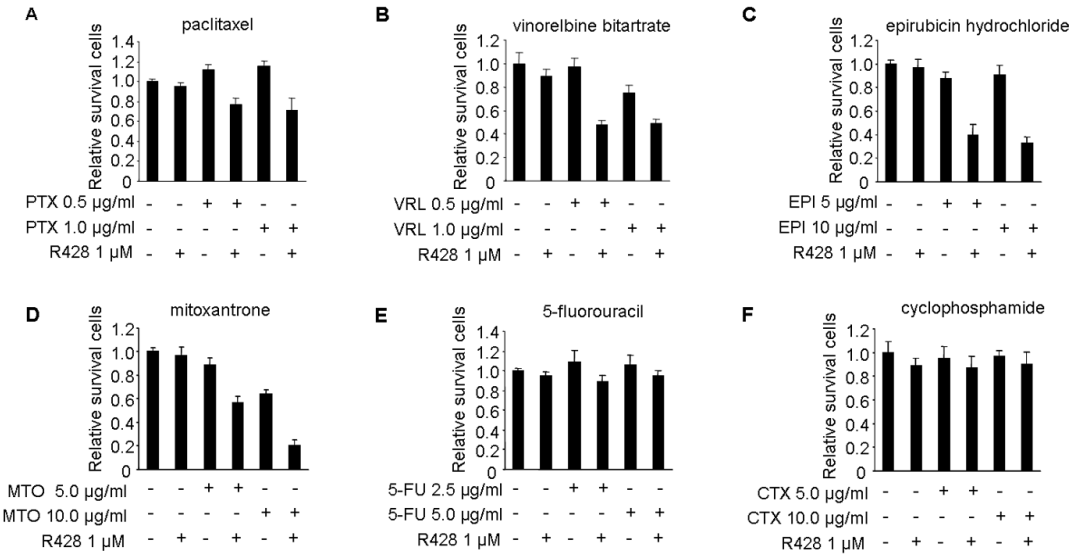
Supplementary Figure 1. Characterization of acquired Dox resistance in breast cancer cells

(A) Colony formation assay of cells treated continuously for 10 days with Dox. Histogram represents the relative analysis of survival of cells in parental (MCF-7) and drug-resistant cells (MCF-7/ADR) treated with increasing doses of Dox. **(B)** Cell viability assays of MCF-7 and MCF-7/ADR cells treated with increasing doses of Dox for 24 or 48 h. **(C)** Western blotting analysis for PARP in MCF-7 and MCF-7/ADR cells treated with increasing doses of Dox for 24 or 48 h.



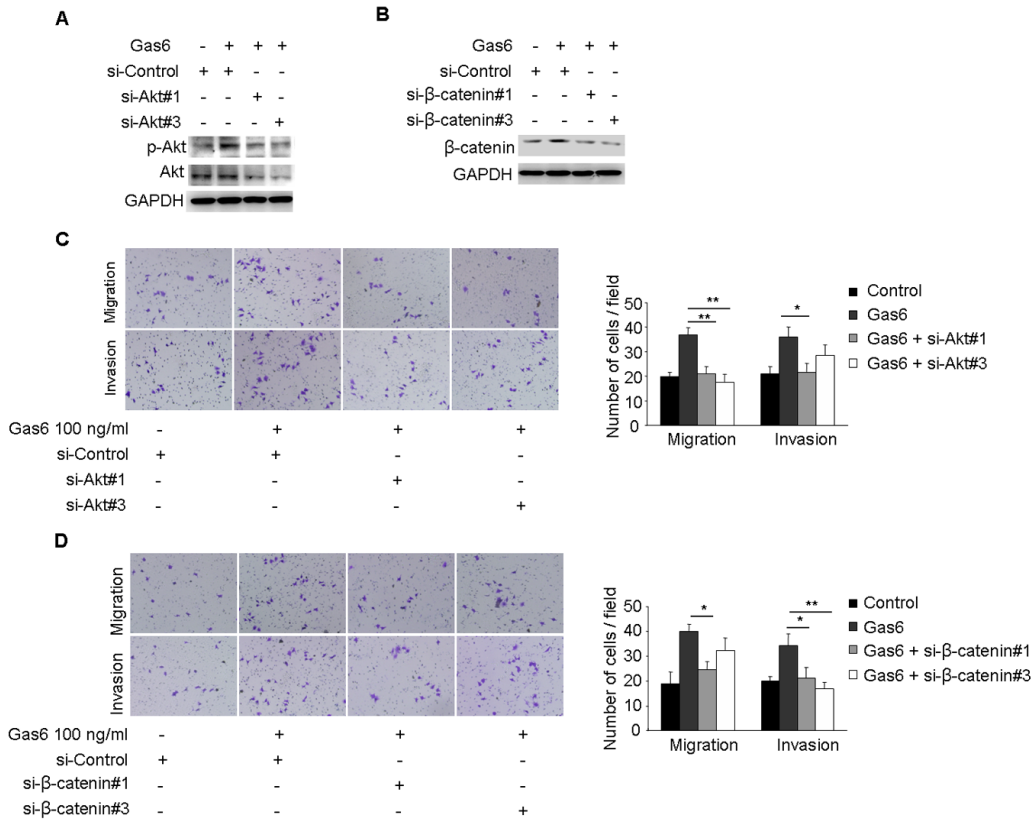
Supplementary Figure 2. Impact of Axl signaling pathway on survival/apoptotic factors.

MCF-7/ADR cells transfected with si-Axl or si-control were cultured in the absence or presence of 10 μg/ml Dox for 48 h. Changes of survival/apoptotic factors (Bcl-xl, Bcl-2, MCL-1, Bad, Bax, and Bim) were analyzed by Western blotting.



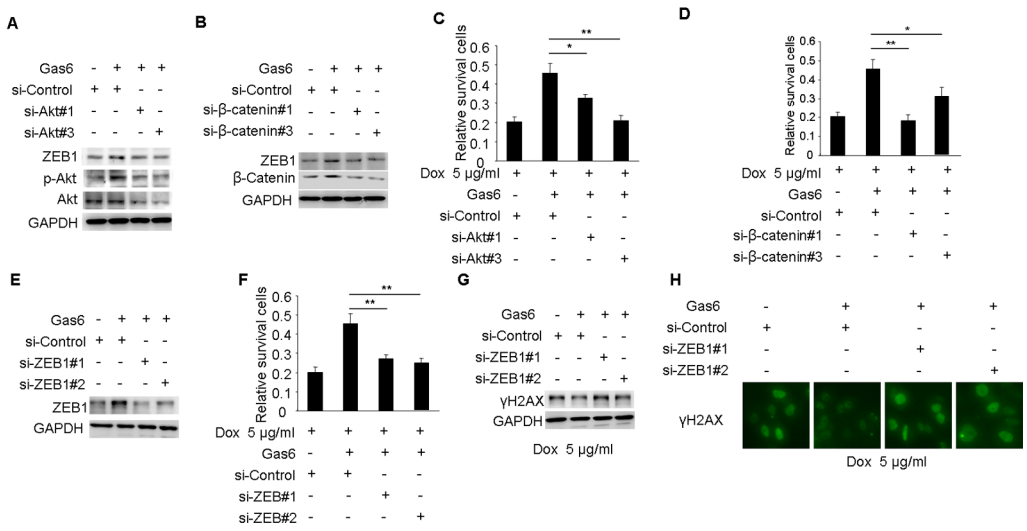
Supplementary Figure 3. R428 increased the chemosensitivity of several drugs in MCF-7/ADR cells

(A-D) Synergistic response of MCF-7/ADR cells to the combination of Axl inhibitor and several clinically used chemotherapeutic drugs (paclitaxel, vinorelbine bitartrate, epirubicin hydrochloride, and mitoxantrone). **(E-F)** Combination of Axl inhibitor R428 and 5-fluorouracil or cyclophosphamide exhibited no synergistic effects on MCF-7/ADR cells.



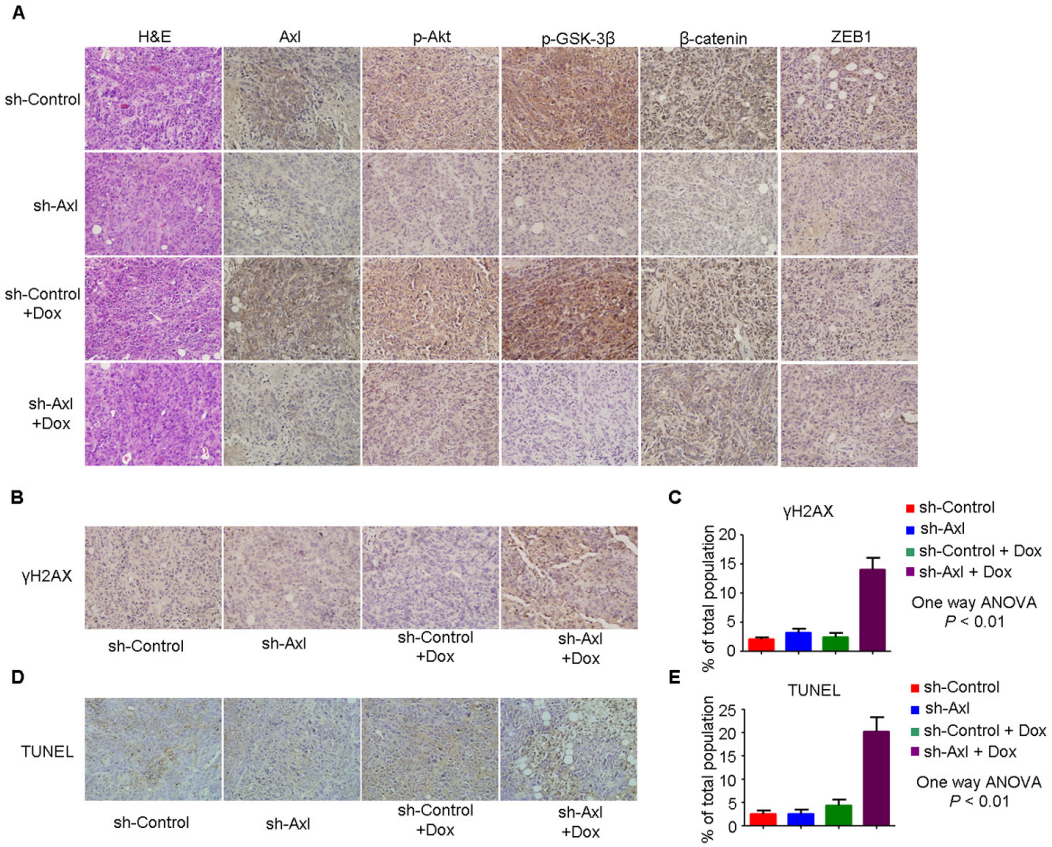
Supplementary Figure 4. Akt/GSK3β/β-catenin signaling is responsible for Gas6-induced cell invasion

(A-B) MCF-7 cells stimulated with 100 ng/ml Gas6 for 24 h were transfected with si-Akt, si-β-catenin or si-control. Whole-cell lysates from indicated cells were analyzed by Western blot for Akt, p-Akt, and β-catenin. **(C-D)** Migratory and invasive behaviors of the indicated cells were analyzed using transwell and matrigel invasion assays (magnification, ×200). **P*<0.05, ***P*<0.01.



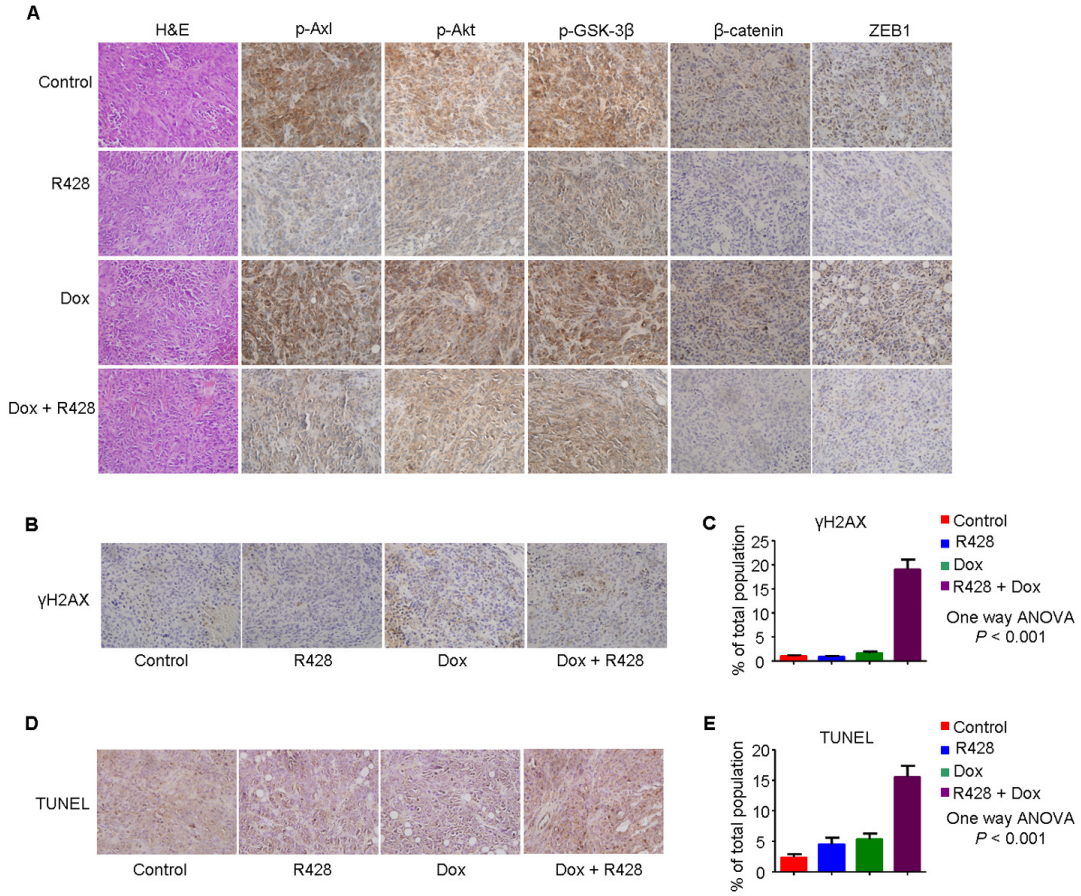
Supplementary Figure 5. Akt/GSK3β/β-catenin/ZEB1 signaling is responsible for Gas6-mediated drug resistance

(A-B) MCF-7 cells stimulated with 100 ng/ml Gas6 for 24 h were transfected with si-Akt, si-β-catenin or si-control. Whole-cell lysates from indicated cells were analyzed by Western blot for Akt, p-Akt, β-catenin and ZEB1. **(C-D)** MCF-7 cells stimulated by Gas6 were transfected with si-Akt, si-β-catenin or si-control and cultured in the presence of 5 μg/ml Dox for 24 h. Relative cell survival was analyzed by CCK8 assays. **(E-F)** MCF-7 cells stimulated with 100 ng/ml Gas6 for 24 h were transfected with si-ZEB1 and cultured in the presence of 5 μg/ml Dox for 24 h. Relative cell survival was analyzed by CCK8 assays. **(G-H)** Gas6 stimulated MCF-7 cells were transfected by si-ZEB1 or si-control and cultured in the presence of 5 μg/ml Dox for 24 h. Western blot analysis and immunofluorescent staining for γH2AX were performed. **P*<0.05, ***P*<0.01.



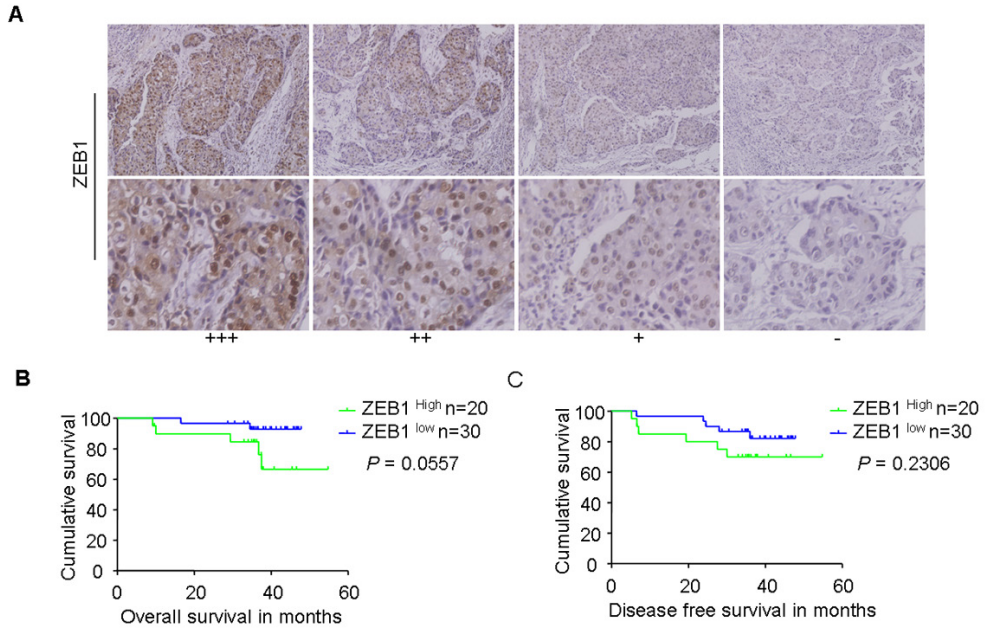
Supplementary Figure 6. *In vivo* mechanism of antitumor activity of Axl knockdown combined with Dox in xenograft models

(A) Representative immunohistochemical images of Axl, p-Akt, p-GSK3β, β-catenin, and ZEB1 in subcutaneous control or Axl-silenced MCF-7/ADR xenografts during 21 days of therapy with vehicle or Dox (2 mg/kg i.p. twice weekly). **(B-C)** Representative immunohistochemical images and quantifications of γH2AX-positive cells in subcutaneous control or Axl-silenced MCF-7/ADR xenografts. **(D-E)** Quantification of TUNEL-positive cells in control or Axl-silenced MCF-7/ADR xenografts treated with vehicle or Dox (2 mg/kg i.p. twice weekly) for 21 days.



Supplementary Figure 7. *In vivo* mechanism of antitumor activity of R428 combined with Dox in xenograft models

(A) Representative immunohistochemical images of p-Axl, p-Akt, p-GSK3β, β-catenin, and ZEB1 in subcutaneous MCF-7/ADR xenografts during 21 days of therapy with vehicle, R428 (25 mg/kg orally twice daily), Dox (2 mg/kg i.p. twice weekly), or combination treatment. **(B-C)** Representative immunohistochemical images and quantifications of γH2AX levels in subcutaneous MCF-7/ADR xenografts after 21 days of the combination therapy described in (A). **(D-E)** Quantification of TUNEL-positive cells in vehicle, R428, Dox, or combination treatment groups.



Supplementary Figure 8. Predictive significance of ZEB1 expression on overall survival and disease-free survival in breast cancer patients treated with Dox-based adjuvant chemotherapy

(A) Representative immunohistochemical images for ZEB1 in tumor specimens (score +++: strong positive; score ++: moderate positive; score +: weak positive; score -: negative). **(B-C)** Kaplan-Meier analysis of overall survival and disease-free survival in breast cancer cases based on ZEB1 expression levels.