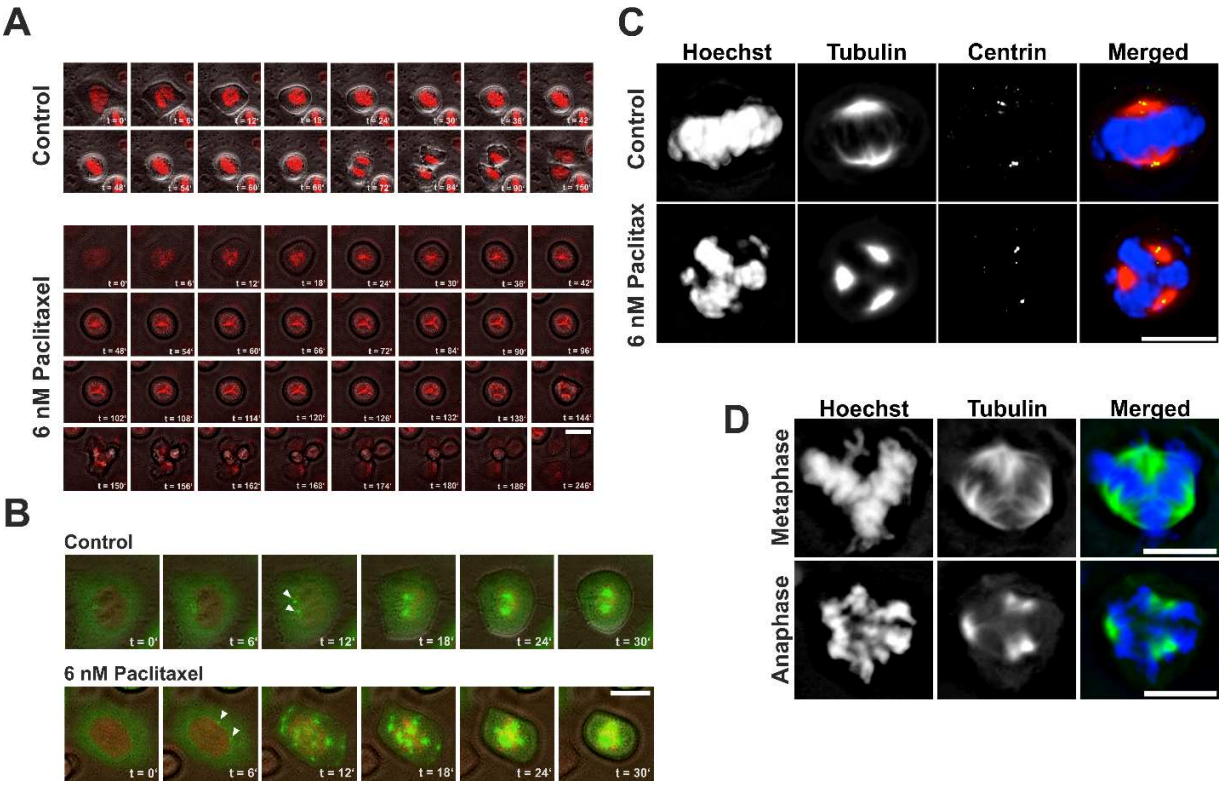
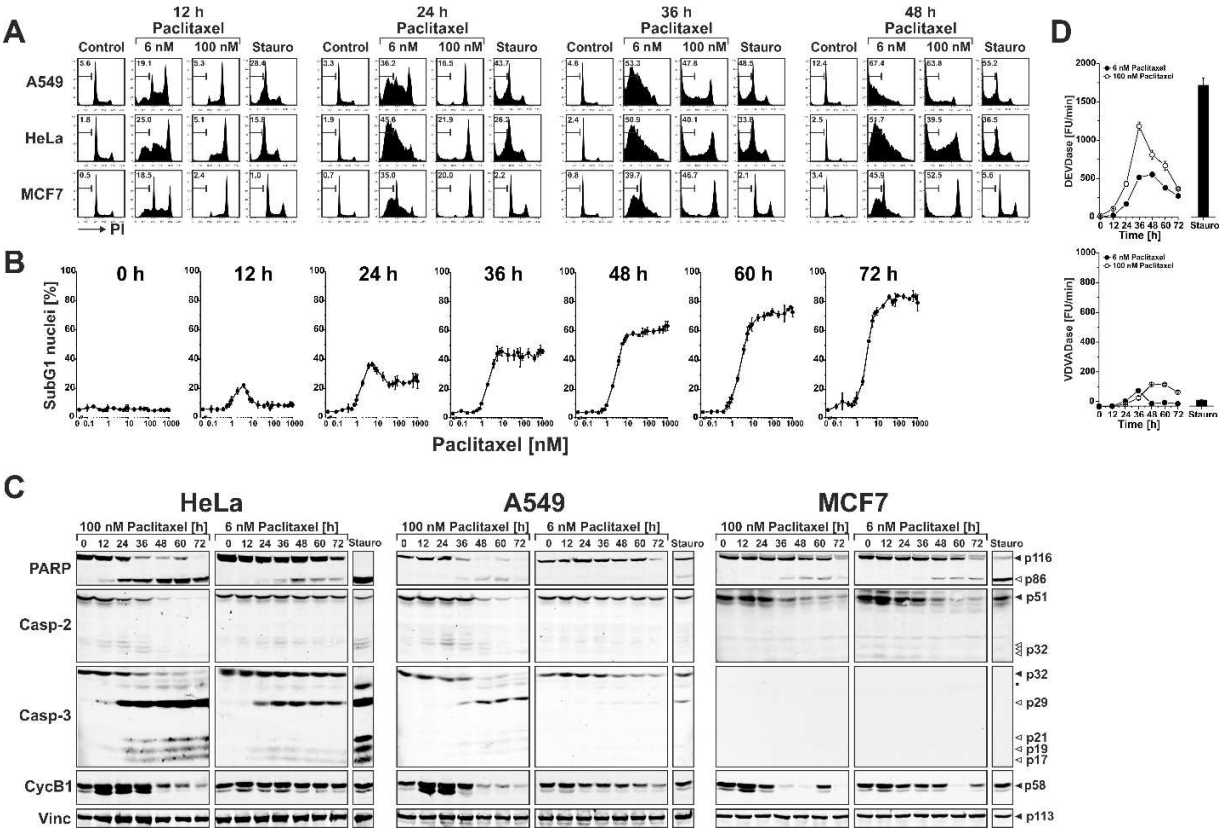
## Supplemental Material

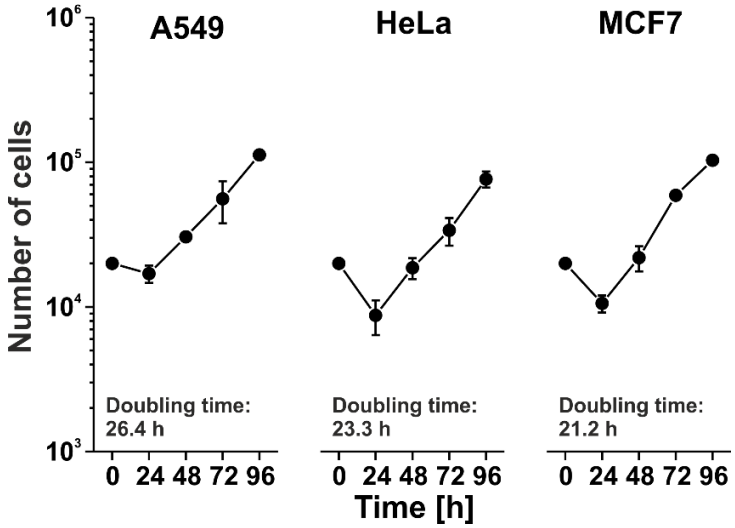



**Supplemental Figure 1. Microscopic characterization of the Paclitaxel-induced tripolar mitotic spindle phenotype.**
(**A**) Live-cell imaging showing tripartite and bipartite cell division in HeLa cells stably expressing mCherry-histone H2B (red) and EGFP-tubulin β (green) treated with 6 nM Paclitaxel or DMSO/ethanol as vehicle control. Time is indicated in minutes, and scale bar depicts 20 µm. Only the brightfield and the red channel are shown. (**B**) Live-cell imaging showing normal and ectopic formation of supernumerary microtubule-organizing centers at the beginning of mitosis upon treatment as in (A). (**C**) Immunofluorescence microscopy of metaphase HeLa cells treated with 6 nM Paclitaxel or DMSO/ethanol for 15 h and stained for tubulin (red), centrin (green), and DNA (blue). (**D**) Immunofluorescence microscopy of metaphase and anaphase HeLa cells treated as in (A) and stained for tubulin (green), and DNA (blue). Scale bars depict 10 µm.

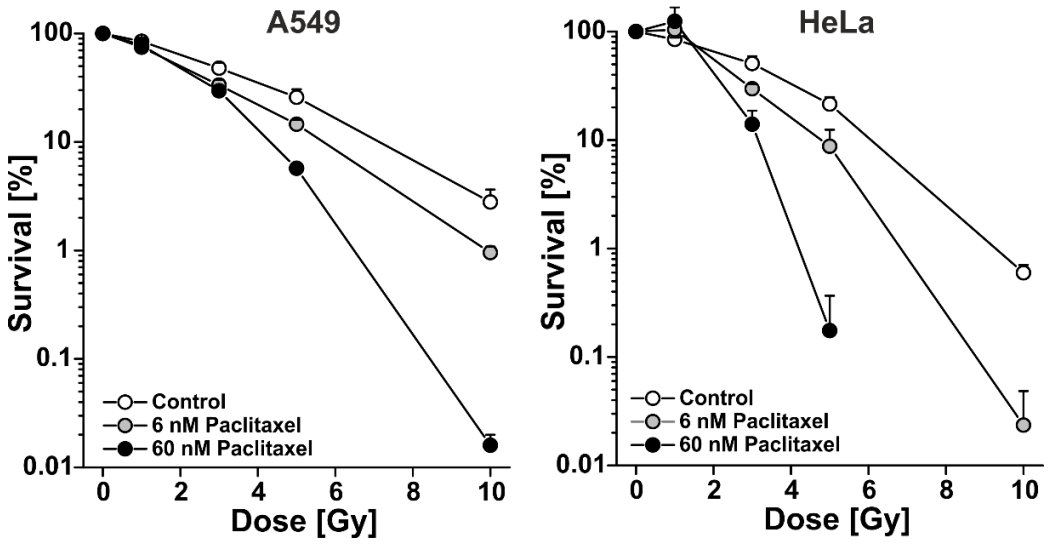



**Supplemental Figure 2. Occurrence of the tripolar spindle phenotype is followed by a delayed type of apoptotic response.**

(**A**) Flow cytometric analysis of DNA content in A549, HeLa, and MCF7 cells treated with 6 nM or 100 nM Paclitaxel for the indicated times. The percentage of subG1 cells is depicted in representative histograms. 2.5 µM Staurosporine served as a positive control for apoptosis induction (**B**) Quantification of HeLa cells with subG1 DNA content upon treatment with the indicated doses of Paclitaxel for 0-72 h. Means ± s.d. of four replicates are shown. (**C**) Western blot analyses of PARP, caspase-2 and caspase-3 cleavage, and Cyclin B1 levels in A549, HeLa, and MCF7 cells treated as in (A). Incubation with 5 µM Straurosporine (4-12 h) served as positive control for apoptosis induction. 300 or 20 µg of total protein were employed and vinculin was used as loading control. Filled arrow heads indicate the full-length forms and open arrow heads the processed forms with their respective molecular weights. (**D**) Measurement of DEVDase (for caspase-3/-7, upper panel) and VDVADase (for caspase-2, lower panel) activity in HeLa cells treated as in (C). Caspase activity is shown as increase in fluorescence over time (FU/min). Means ± s.d. of three replicates are displayed.

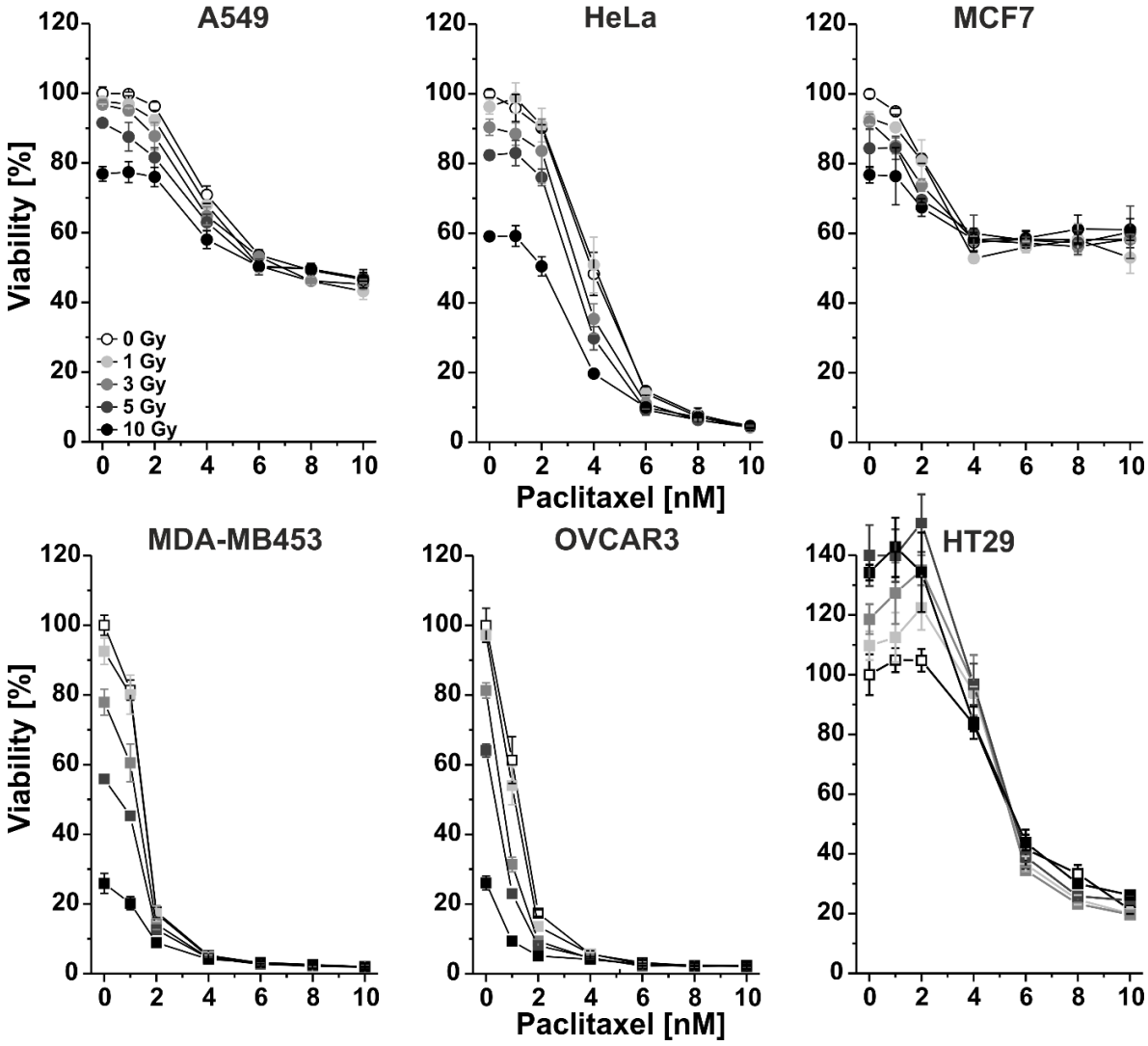



**Supplemental Figure 3. Estimation of individual doubling times.**
A549, HeLa, and MCF7 cells were seeded into 12-well plates at 0 h and cell numbers were determined in 24 h intervals using a Neubauer improved counting chamber. Means ± s.d. of four replicates are shown. The doubling times were calculated from the slopes of the regression lines in the exponential growth phase.



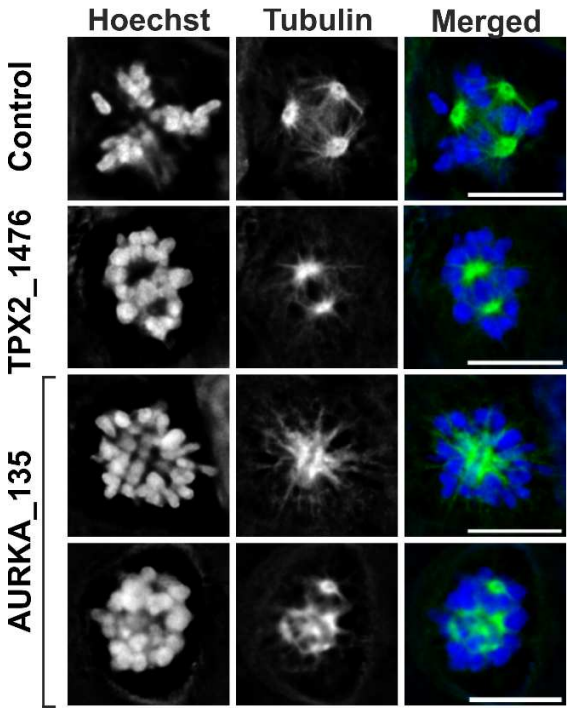

**Supplemental Figure 4. Radiosensitization by different concentrations of Paclitaxel.**

Clonogenic survival assay. A549 and HeLa cells were treated with 6 nM or 60 nM Paclitaxel or DMSO/ethanol, respectively, for one doubling time (Suppl. Fig. 3) prior to irradiation at the indicated doses. Means + s.d. of three independent replicates are shown.

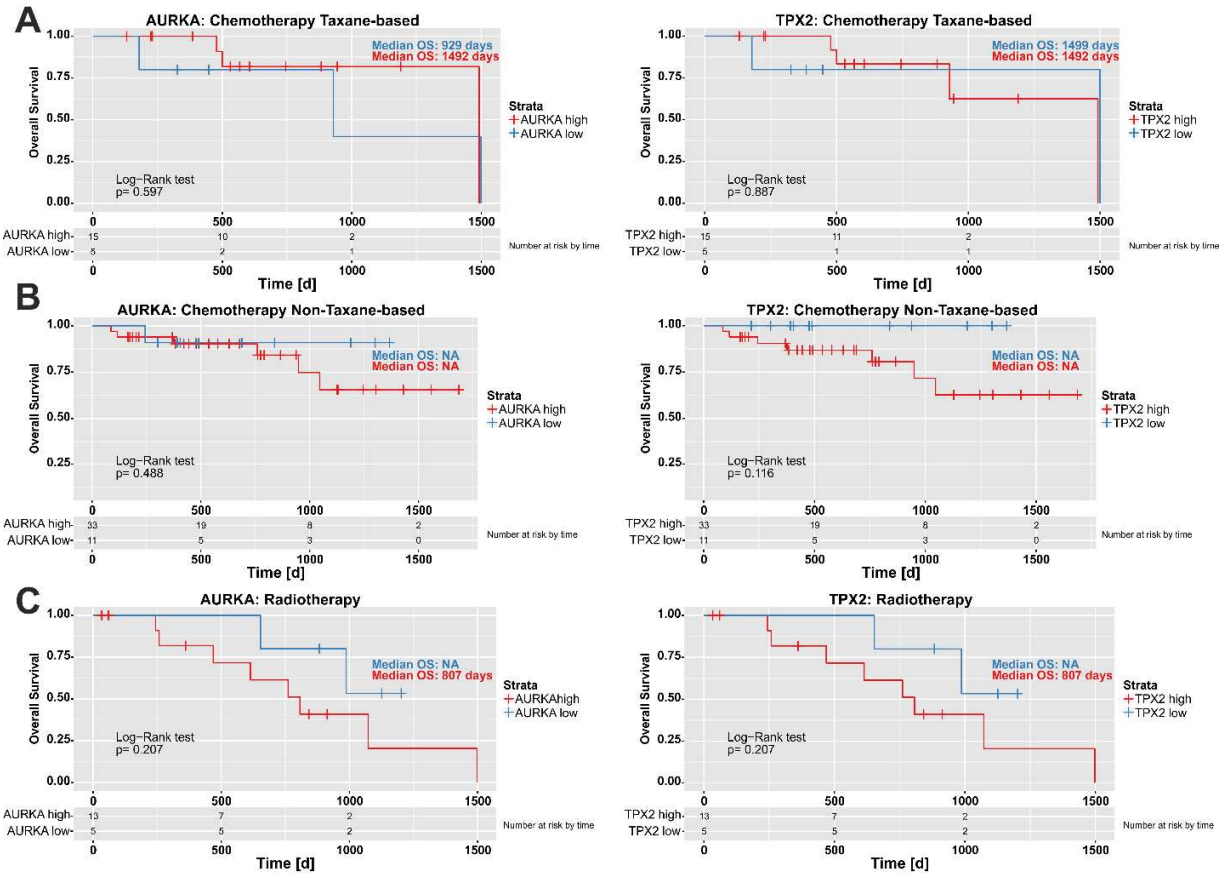



**Supplemental Figure 5. Viability screen to investigate the synergism between low-dose Paclitaxel and irradiation.**

A panel of human cancer cell lines (Suppl. Table 1) was treated with low nanomolar doses of Paclitaxel for 24 h and subsequently irradiated at the indicated doses. Viability was assessed 96 h after irradiation by Alamar blue reduction assays. Data of exemplary cell lines with (upper row) and without the tripolar mitotic phenotype (lower row) are shown as means ± s.d. of three replicates.

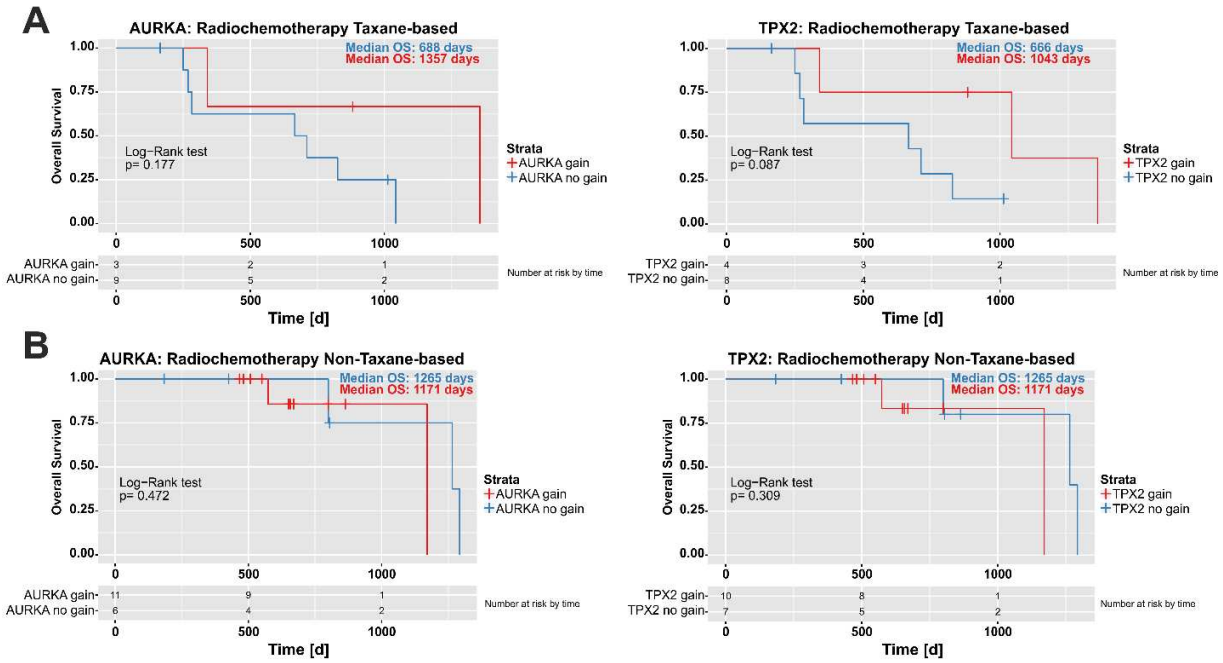



**Supplemental Figure 6. Mitotic phenotypes observed upon silencing of TPX2 and AURKA expression and subsequent treatment with low doses of Paclitaxel.** Immunofluorescence microscopy of early metaphase A549 cells treated with 6 nM Paclitaxel for 24 h after transfection with 3 nM TPX2_1476 or AURKA_135 siRNA. Cells were stained for tubulin (green) and DNA (blue). Scale bars correspond to 10 µm.




**Supplemental Figure 7. No predictive value of AURKA and TPX2 gene expression for the clinical outcome of chemotherapy and radiotherapy alone in the TCGA lung adenocarcinoma patient cohort.**

Kaplan-Meier overall survival analysis of patients with and without overexpression of AURKA and TPX2 undergoing taxane-based chemotherapy (**A**), non-taxane-based chemotherapy (**B**), or radiotherapy (**C**), in patients. Comparison was performed by Log-Rank test.




**Supplemental Figure 8. Association of AURKA and TPX2 gene copy numbers with clinical outcome of taxane-based and non-taxane-based radiochemotherapy in the TCGA lung adenocarcinoma cohort.**

Kaplan-Meier overall survival analysis upon taxane-based radiochemotherapy (**A**), and non-taxane-based radiochemotherapy (**B**) in patients with and without gene copy number gains (GISTIC 2.0 calls > 0) of AURKA and TPX2. Comparison was performed by Log-Rank test.

| Cell line | Cancer entity | Induction of tripolar phenotype by low dose Paclitaxel treatment |
|---|---|---|
| **A549** | Non-small cell lung carcinoma | YES |
| **HCT116** | Colon carcinoma | YES |
| **CaCo2** | Colon adenocarcinoma | YES |
| **HT29** | Colorectal adenocarcinoma | NO |
| **MCF7** | Mammacarcinoma | YES |
| **MDA-MB231** | Mammacarcinoma | YES |
| **MDA-MB453** | Mammacarcinoma | NO |
| **OVCAR3** | Ovarian adenocarcinoma | NO |
| **LN229** | Glioblastoma | YES |
| **T98G** | Glioblastoma | YES |
| **HeLa** | Cervix carcinoma | YES |

**Supplemental Table 1. Incidence of Paclitaxel-induced tripolar mitotic spindle formation in different human cancer cell lines.**
Cell lines were treated with 6 nM Paclitaxel for 15 h and analyzed for mitotic spindle morphology by immunofluorescence microscopy and for hypodiploid DNA contents by flow cytometry. Cells that showed tripolar spindle formation are highlighted in blue while cells that did not are displayed in pink.

**Cell lines with tripolar phenotype**

A549

| | 1 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| 1 | 1.29 | 1.30 | 0.93 | 0.90 | 1.08 | 1.02 |
| 3 | 1.56 | 1.29 | 0.99 | 1.06 | 1.17 | 1.08 |
| 5 | 1.18 | 1.23 | 1.09 | 1.09 | 1.36 | 1.11 |
| 10 | 1.29 | 1.50 | 1,26 | 1.35 | 1.61 | 1.10 |

HeLa

| | 1 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| 1 | 2.19 | 1.33 | 1.13 | 0.96 | 1.03 | 0.88 |
| 3 | 1.32 | 1.48 | 1.04 | 0.93 | 1.02 | 0.88 |
| 5 | 1.48 | 1.53 | 1.04 | 0.91 | 1.05 | 0.89 |
| 10 | 1.28 | 1.31 | 1.02 | 1.03 | 1.17 | 0.91 |

MCF7

| | 1 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| 1 | 1.60 | 1.18 | 0.54 | 0.92 | 1.33 | 1.08 |
| 3 | 1.32 | 0.92 | 0.74 | 1.02 | 1.28 | 1.35 |
| 5 | 1.62 | 0.85 | 0.88 | 1.12 | 1.40 | 1.48 |
| 10 | 1.35 | 1.03 | 0.97 | 1.32 | 1.86 | 1.53 |

MDA-MB231

| | 1 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| 1 | 1.23 | 1.25 | 0.92 | 1.00 | 0.99 | 0.97 |
| 3 | 1.27 | 1.35 | 0.98 | 1.05 | 1.11 | 1.03 |
| 5 | 1.03 | 1.08 | 1.05 | 1.05 | 1.17 | 1.04 |
| 10 | 1.18 | 1.30 | 1.16 | 1.32 | 1.31 | 1.12 |

CaCo2

| | 1 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| 1 | 1.50 | 1.83 | 0.85 | 1.08 | 1.32 | 1.18 |
| 3 | 1.58 | 0.97 | 0.90 | 1.13 | 1.36 | 1.16 |
| 5 | 1.04 | 0.92 | 0.94 | 1.21 | 1.36 | 1.16 |
| 10 | 1.34 | 1.19 | 1.08 | 1.27 | 1.49 | 1.20 |

HCT116

| | 1 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| 1 | 2.09 | 1.58 | 0.85 | 0.93 | 1.07 | 0.96 |
| 3 | 1.24 | 1.14 | 0.71 | 0.86 | 1.05 | 0.91 |
| 5 | 0.89 | 0.73 | 0.76 | 0.85 | 0.97 | 0.81 |
| 10 | 1.16 | 1.17 | 0.88 | 0.93 | 1.08 | 0.84 |

LN229

| | 1 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| 1 | 0.54 | 0.96 | 0.66 | 0.81 | 0.84 | 0.67 |
| 3 | 0.66 | 0.89 | 0.88 | 0.96 | 1.04 | 0.77 |
| 5 | 0.76 | 0.85 | 0.98 | 1.14 | 1.15 | 0.73 |
| 10 | 0.96 | 1.04 | 1.12 | 1.12 | 1.21 | 0.67 |

T98G

| | 1 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| 1 | n.d. | 1.79 | 0.96 | 1.01 | 1.16 | n.d. |
| 3 | 1.71 | 1.37 | 0.87 | 1.00 | 1.19 | 0.98 |
| 5 | 1.31 | 1.26 | 0.88 | 0.99 | 1.13 | 0.94 |
| 10 | 1.03 | 1.05 | 0.87 | 1.03 | 1.23 | 0.91 |

**Cell lines without tripolar phenotype**

MDA-MB453

| Gy | 1 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| 1 | 0.99 | 1.07 | 1.84 | 2.61 | 3.40 | 3.37 |
| 3 | 1.24 | 1.18 | 1.89 | 2.67 | 3.47 | 3.40 |
| 5 | 1.34 | 1.27 | 1.95 | 2.70 | 3.52 | 3.39 |
| 10 | 1.33 | 1.43 | 2.09 | 2.88 | 3.67 | 3.39 |

OVCAR3

| | 1 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| 1 | 0.73 | 1.05 | 1.88 | 2.64 | 3.50 | 3.47 |
| 3 | 0.86 | 1.12 | 1.92 | 2.70 | 3.50 | 3.47 |
| 5 | 0.96 | 1.20 | 2.00 | 2.71 | 3.60 | 3.48 |
| 10 | 1.03 | 1.31 | 2.16 | 2.91 | 3.71 | 3.49 |

HT29

| | 1 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| 1 | n.d. | n.d. | 2.48 | 1.87 | 1.98 | n.d. |
| 3 | n.d. | n.d. | 4.73 | 3.87 | 3.99 | n.d. |
| 5 | n.d. | n.d. | 6.78 | 5.93 | 6.05 | n.d. |
| 10 | n.d. | n.d. | 11.12 | 11.03 | 11.16 | n.d. |

Paclitaxel [nM]

**Supplemental Table 2. Combination indices obtained for low-dose Paclitaxel and irradiation in viability screens.**
Combination indices of low-dose Paclitaxel treatment and irradiation were calculated for each concentration/dose pair tested in viability screens (Suppl. Fig. 4). Combinations with indices < 1.0 were considered synergistic (red), while indices ≥ 1.0 were considered additive or sub-additive (black).