Supplementary Figure legends

Supplementary Fig. 1. ATRA alone is sub-toxic at physiological/therapeutic relevant concentrations in HT-29, HCT116, and SKBR3 cells. Relative cell viability in cells incubated with increasing ATRA concentrations (0–100 μM) for 48 hours. Data presented as mean of three experiments ± S.E.

Supplementary Fig. 2. ATRA pre-conditioning enhances fimaporfin-PDT in MDA-MB-231 and MC-38 cells. Left panel, relative cell viability of MDA-MB-231 cells after 18 hrs co-incubation with 10 μM ATRA and 0.4 μg/mL $TPCS_{2a}$ prior to light exposure (PDT). Viability (MTT) was assessed 48 hours after PDT. Representative experiment of three independent experiments, data presented as mean of triplicates ± S.D Right panel, relative cell viability of MC-38 cells after 42 hrs pre-incubation of 1 μM ATRA including 18 hrs co-incubation with 0.6 μg/mL TPCS2a prior to light exposure (PDT). Viability (MTT) was assessed 24 hours after PDT. Representative experiment of three independent experiments, data presented as mean of triplicates ± S.D. * $p<0.05$, *** $p<0.001$

Supplementary Fig. 3. ATRA do not enhance fimaporfin-PDT when given after light. ATRA incubation for 48 hours after PDT does not induce enhanced cytotoxicity. HT-29 (left panel) and MC-38 cells (right panel) were incubated with 1 μM and 10 μM ATRA, respectively. Representative experiment of three independent experiments, data presented as mean of triplicates ± S.D.

Supplementary Fig. 4. ATRA+light is non-toxic and no phototoxic products are generated after light exposure of ATRA and fimaporfin ($TPCS_{2a}$) in a cell-free system.

(A) ATRA alone in HT-29 (0.1 μM) and MDA-MB-231 (10 μM) cells exposed to increasing light exposure. Viability evaluated 48 hours post-light exposure. (**B)** 0.1 μM ATRA and 0.4 μg/mL fimaporfin ($TPCS_{2a}$) exposed to light ex vivo and subsequently incubated for 48 hours in HT-29 cells. Representative experiment of at least two experiments, data presented as mean of triplicates ± S.D.

Supplementary Fig. 5. Sub-lethal ATRA concentrations does not significantly affect the differential marker alkaline phosphatase and the stem cell marker CD133.

(A) Alkaline phosphatase expression per mg protein and (**B),** relative CD133 expression in HCT116, SKBR3 and HT-29 incubated with 0.1–1 μM ATRA for 42 hours. Data presented as mean of three experiments ± S.E.

Supplementary Fig. 6. Drug-protein and protein-protein interaction network of retinoic acid and DEGs (ATRA+PDT versus ATRA) of at least 1 log_2-fold change.

(A) The drug-gene and protein-protein interaction network from the STITCH database of retinoic acid. The block represents the drug and circle represents gene. Associations are indicated with a line. Stronger associations are represented by thicker lines. (**B)** Protein-protein network from the STRING database. Each circle represents a protein. Association between the proteins is indicated with a line.

Supplementary Fig. 7. Treatment response following systemic ATRA and fimaporfin-PDT (ATRA+PDT) in HT-29 -tumor bearing mice.

(A) Relative body weight in the ATRA-treatment group. The animals received ATRA i.p. once a day for five days. The weight of each animal was normalized to the weight at the day -4. **(B)** ATRA+PDT group received five doses of ATRA prior to light treatment. 10 mg/kg ATRA was delivered intraperitoneally once a day for five days. TPCS2a (5 mg/kg) was delivered as a single dose intravenously three days prior to laser exposure with a light dose of 15 J/cm^2 using an irradiance of 90 mW/cm^2. The Kaplan-Meier survival curve shows the treatment response and the table shows the estimated time to reach endpoint in the different treatment groups. Note that ATRA+PDT group is only 2 animals as 4 animals had severe toxic effects after systemic delivery of ATRA. Consequently, it was decided to co-deliver ATRA and fimaporfin/TPCS2a by intratumoral injections in the further experiments (Figure 5 + Supplementary Fig.8). **(C)** Mean tumor volume (mm^3), and **(D)** waterfall plots of each treatment group at 5, 10, and 20 days post-treatment. Each bar indicate an individual animal and percentage change of tumor size compared to day 0. NT, ATRA and PDT: 6 mice per group, except for ATRA+PDT where n = 2. Data presented as mean ± S.E.

Supplementary Fig. 8. Survival and tumor response following intratumoral injection of ATRA and fimaporfin, and photochemical treatment.

(A) Waterfall plots of each treatment group at 5, 10 and 20 days post-treatment. Each bar indicate an individual animal. The tumor size at indicated time-point relative to tumor size at treatment start (day 0). **(B)** Tumor volume (mm^3) of individual animal in each treatment group up to 90 days post-treatment. Each line represents one animal. **(C)** Survival curve of treatment response and table of estimated mean time (days) to reach endpoint for each treatment groups. For all treatment groups n = 5, except for NT where n = 6. Survival evaluated using log-rank (Mantel-Cox) ***** $p \leq 0.05$. **(D)** Tumor size (mm^3) of animals in each group that reached day 90.