Novel combinations of aplitabart, a DR5 agonist IgM antibody, with ADCs or chemotherapeutic agents lead to robust anti-tumor responses in solid tumor models

Poster #1899

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Background

- Aplitabart (IGM-8444) is a multivalent IgM agonist that targets tumor necrosis factor (TNF) receptor superfamily member death receptor DR5, which requires multimerization to induce tumor cell apoptosis.
- Aplitabart exhibits anti-tumor activity in preclinical models with a favorable in vitro and in vivo safety profile, making it a potentially promising combination partner with standard of care treatment regimens. Aplitabart is currently being evaluated in a randomized Phase 1b clinical trial with FOLFIRI + bevacizumab in patients with metastatic colorectal cancer (NCT04553692).
- We have evaluated novel combinations of aplitabart in preclinical tumor models with the chemotherapeutic agents, carboplatin and paclitaxel, and with the anti-TROP2 antibody drug conjugate, TRODELVY®.

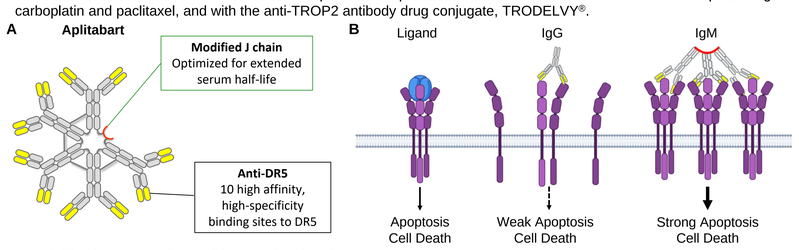

Figure 1. Structure and function of DR5 agonist aplitabart.
A) Aplitabart is a monospecific recombinant pentameric IgM antibody with 10 binding sites to DR5. **B)** Schematic illustrating ability of multivalent IgM to efficiently cluster DR5 and induce tumor apoptosis and cell death. Created with BioRender.com.

Aplitabart Synergizes with Paclitaxel and Carboplatin in Breast Cancer and Non-Small Cell Lung Cancer Cell Lines in Vitro

A

Average Bliss Synergy Scores

■ Synergistic ■ Weakly synergistic □ Additive

Cell line	Indication	Paclitaxel + Aplitabart	Carboplatin + Aplitabart
MDA-MB-231	TNBC	6.7	5.7
CAL120	TNBC	6.0	6.9
BT20	TNBC	5.9	6.1
HCC1187	TNBC	3.2	3.8
SKBR3	breast	1.5	10.6
HCC15	NSCLC	22	16.0
SK-MES-1	NSCLC	10.9	12.8
NCI-H1373	NSCLC	9.2	12.6
HCC1588	NSCLC	6.8	4.8
NCI-H1703	NSCLC	0.4	5.2

B

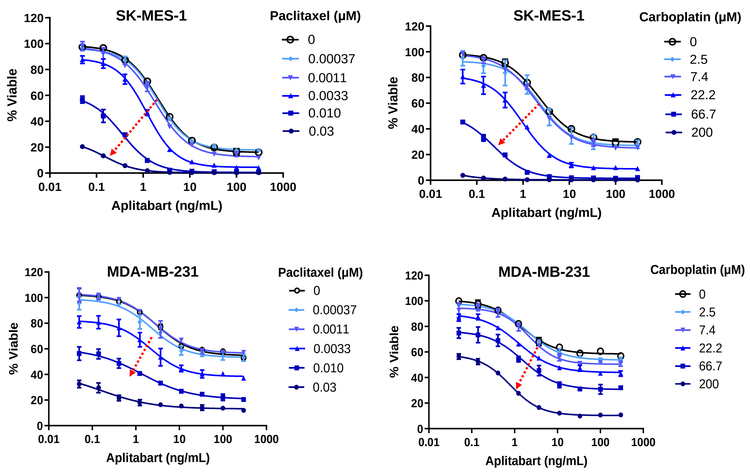

Figure 2. Synergistic cytotoxicity of aplitabart with paclitaxel and with carboplatin was observed in a range of breast and non-small cell lung cancer cell lines in vitro
Ten human breast or lung cancer cell lines were treated with aplitabart in combination with paclitaxel or carboplatin, and viability was measured after 72 hours using CellTiter-Glo. **A)** Synergy was calculated using Bliss scores, where an average Bliss score greater than 10 indicates synergy and an average Bliss score between 5 and 10 suggests weak synergy (Ianevski et al., 2017, Bioinformatics 33(15), 2413-2415; Malyutina et al. 2019, PLoS Comput Biol 15(5): e1006752). Aplitabart combination with paclitaxel and carboplatin showed similar synergy scores on most of the cell lines tested. **B)** The combinatorial activity of aplitabart with paclitaxel or carboplatin is shown for the SK-MES-1 NSCLC and MDA-MB-231 TNBC cell lines. Dotted red arrow indicates EC50 shift, suggestive of synergy.

Aplitabart and Paclitaxel / Carboplatin Combination Enhances Anti-Tumor Responses in the MDA-MB-231 Xenograft TNBC Model

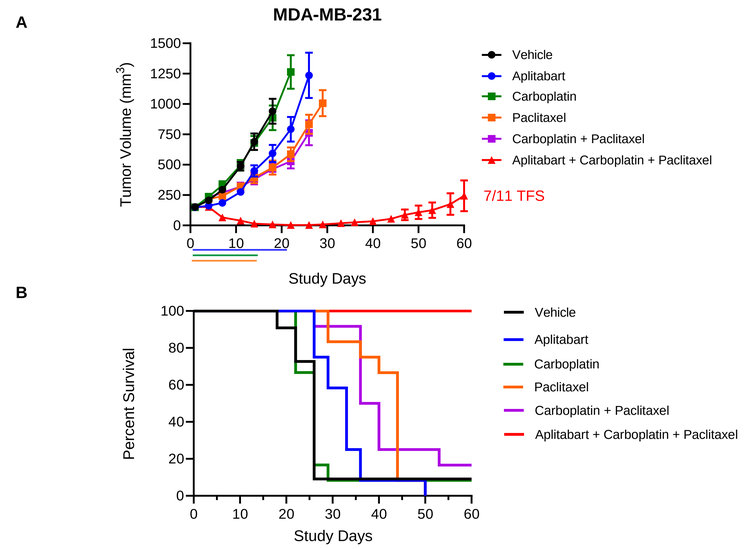

Figure 3. Aplitabart in combination with paclitaxel/carboplatin enhances anti-tumor responses and extends overall survival in the partially sensitive MDA-MB-231 TNBC xenograft model
A) MDA-MB-231 TNBC cells were implanted subcutaneously and mice were dosed with vehicle q2d x 11 i.v., 5 mg/kg of aplitabart q2d x 11 i.v., 20 mg/kg of carboplatin qw x 3 i.p., 10 mg/kg of paclitaxel qw x 3 i.v., or a combination of the aplitabart and carboplatin/paclitaxel dosing regimens. Horizontal bars in the lower left of the graph indicate the dosing period. Tumor volumes (mean ± SEM) are plotted. Combination of aplitabart with paclitaxel/carboplatin resulted in an enhanced anti-tumor response with over half of the animals being tumor free survivors (TFS) by study end compared to single agents or the standard-of-care combination alone. **B)** The combination of aplitabart with paclitaxel/carboplatin significantly extended overall survival in the MDA-MB-231 mouse xenograft tumor model.

Paclitaxel Induces ER Stress Resulting in Activation of the Unfolded Protein Response and Up-Regulation of DR5

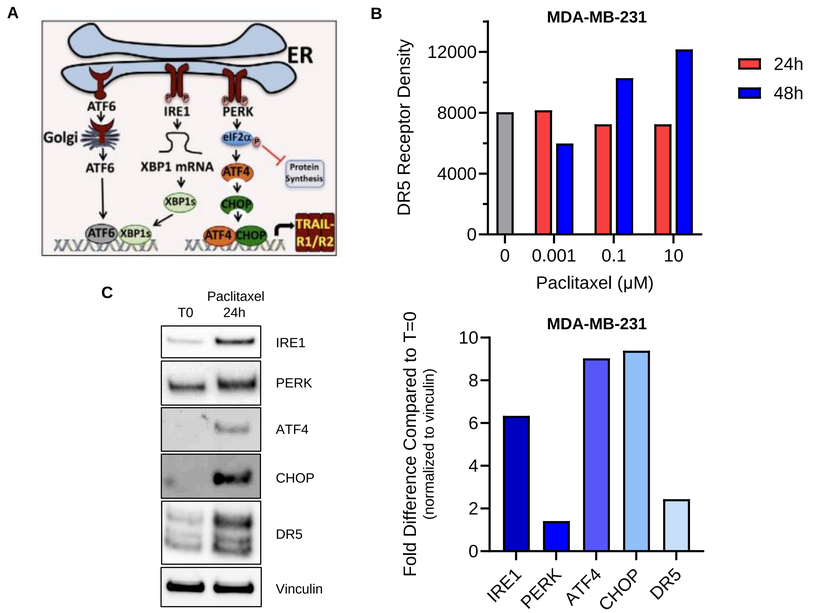

Figure 4. Paclitaxel induces ER stress resulting in upregulation or IRE1, ATF4, CHOP and DR5
A) Schematic representation of the unfolded protein response (UPR) pathway (Sullivan et al., 2020, Developmental Cell 52, 714–730). **B)** MDA-MB-231 cells were treated in vitro with increasing concentrations of paclitaxel for 24 or 48 hours. Cell surface DR5 expression was assessed by flow cytometry and DR5 receptor density was quantitated using PE Quantibrite PE beads. Cell surface DR5 up-regulation was most pronounced 48 hours post-treatment with paclitaxel. **C)** MDA-MB-231 cells were treated with 100 μM paclitaxel for 24 hours. Cell lysates were run on a reducing gel and analyzed for the indicated UPR proteins, DR5 or for vinculin loading control by western blot. Blots were quantitated using ImageJ software.

Aplitabart Synergizes with the anti-TROP2 ADC TRODELVY® on TNBC and NSCLC Cell Lines in Vitro

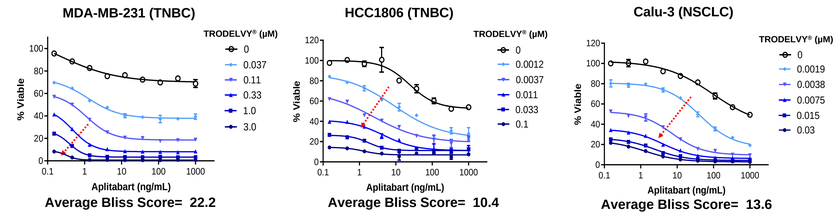

Figure 5. Aplitabart combined with the anti-TROP2 ADC, TRODELVY® (sacituzumab govitecan-hziy), shows synergy on TNBC and NSCLC cell lines.
TRODELVY® is an anti-TROP2 ADC that contains the potent topoisomerase I inhibitor SN-38 as the drug conjugate. Two TNBC and one NSCLC cell lines were treated with aplitabart in combination with TRODELVY® and viability was measured after 72 hours using CellTiter-Glo. Synergy was calculated using Bliss scores, where an average Bliss score greater than 10 indicates synergy and an average Bliss score between 5 and 10 suggests weak synergy Sacituzumab (Ianevski et al., 2017, Bioinformatics 33(15), 2413-2415; Malyutina et al. 2019, PLoS Comput Biol 15(5): e1006752). Dotted red arrow indicates EC50 shift, suggestive of synergy.

Aplitabart and TRODELVY® Combination Inhibits Tumor Growth in the Calu-3 Xenograft NSCLC Model

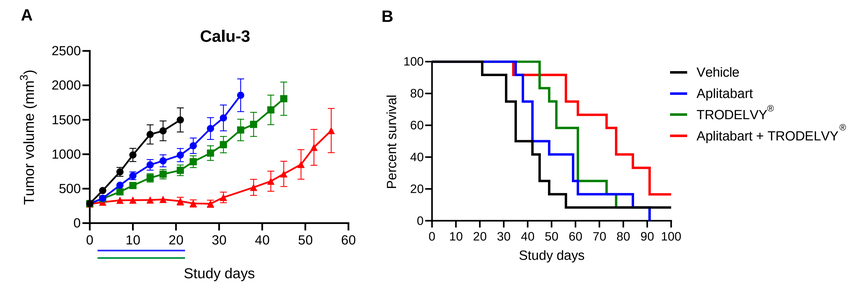

Figure 6. Aplitabart in combination with TRODELVY® leads to potent inhibition of tumor growth in the partially sensitive Calu-3 xenograft NSCLC model
A) Calu-3 NSCLC cells were implanted subcutaneously and mice were dosed with vehicle q2d x 11 i.v., 5 mg/kg of aplitabart q2d x 11 i.v., 250 μg of TRODELVY® qw x 4 i.p., or a combination of the aplitabart and TRODELVY® dosing regimens. Horizontal bars in the lower left of the graph indicate the dosing period. Tumor volumes (mean ± SEM) are plotted. Combination of aplitabart with TRODELVY® resulted in an enhanced anti-tumor response compared to either single agent. **B)** The combination of aplitabart with TRODELVY® significantly extended overall survival compared to the vehicle group (P = 0.007). The difference in overall survival was also significant between the aplitabart single agent group and the combination group (P = 0.02), and between the TRODELVY® treatment group and the aplitabart combination group (P = 0.04).

The Topoisomerase Inhibitor, SN-38, Up-Regulates DR5 Expression, a Potential Mechanism for Aplitabart Synergy

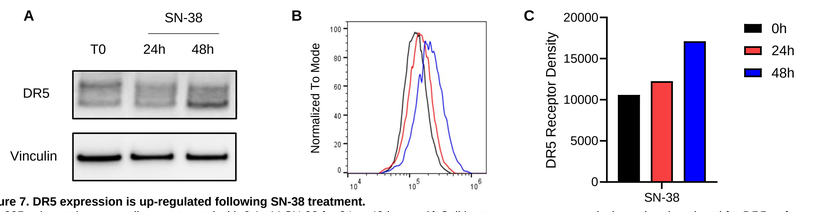

Figure 7. DR5 expression is up-regulated following SN-38 treatment.
Colo205 colorectal cancer cells were treated with 0.1 μM SN-38 for 24 or 48 hours. **A)** Cell lysates were run on a reducing gel and analyzed for DR5 or for vinculin loading control by western blot. **B)** Cell surface DR5 expression was assessed by flow cytometry, and **C)** DR5 receptor density was quantitated using PE Quantibrite beads. DR5 up-regulation was most pronounced 48 hours post-treatment with SN-38.

Summary

- The combination of aplitabart with FOLFIRI + bevacizumab is currently under evaluation in a randomized Phase 1b clinical trial in patients with metastatic colorectal cancer (NCT04553692).
- Preclinical studies were conducted to evaluate new drug combinations for aplitabart, potentially expanding use beyond CRC.
- Aplitabart was screened in combination with the chemotherapeutic agents, paclitaxel and carboplatin, and the ADC TRODELVY®. All combinations showed synergy on breast and NSCLC cell lines in vitro.
- The combination of aplitabart with paclitaxel/carboplatin also enhanced anti-tumor responses in vivo in the MDA-MB-231 xenograft breast cancer model, resulting in long-term tumor-free survivors in the combination group.
- The combination of aplitabart with TRODELVY® showed inhibition of tumor growth in the Calu-3 xenograft NSCLC model.
- Chemotherapy treatment can up-regulate DR5 expression, providing a potential mechanistic rationale for the enhanced anti-tumor activity observed when these agents are combined with aplitabart.