



# Combination Synergy of a Spliceosome Modulator ADC with a K-RAS Inhibitor in K-RAS Mutated Pancreatic Cancers

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## Background:

AKTX-101 is a TROP2 ADC containing the spliceosome modulator payload, PH1(1). PH1 can target oncogenic driver splice variants such as AR-v7 and WT Androgen Receptor in prostate cancer. Alternative splicing of K-Ras results in two isoforms, 4A and 4B. When K-Ras WT carcinoma cells were treated with PH1, exon skipping of KRAS RNA was altered in a region common to both isoforms (2). AKTX-101 exhibited single digit nM potency in NCI-H441 lung cancer model with a K-Ras G12V driver mutation.

## Methods:

To investigate the potential efficacy of AKTX-101 in pancreatic cancer, in vitro cytotoxicity assays were performed using 4 cell lines with oncogenic K-Ras G12C or G12D mutations. Here we tested AKTX-101 vs 3 TROP2 ADCs bearing topoisomerase I-payloads, alone, and in combination with adagrasib. In the combination experiments, ADCs were fixed at their IC50 concentrations, or at 20nM if IC50 was not reached, and adagrasib was varied from a top concentration of 100uM with nine 4-fold serial dilutions. The mean for the Bliss Independence scores was used to determine combination index: Bliss scores of > 5 indicated synergy and < -5 reflected antagonism.

## Results:

In KRAS G12C and G12D mutant pancreatic cancer cell lines, the combination of AKTX-101 and adagrasib exhibited synergistic cell killing not seen with the other TROP2 ADC/adagrasib combinations. Mean Bliss scores were > 10 for the AKTX-101+ adagrasib combination, vs. primarily negative Bliss scores for the competitor TROP2 ADCs/adagrasib combinations, suggesting synergy may be due to novel biology of PH1 targeting splicing.

## Conclusion:

The TROP2 ADC, AKTX-101 exhibited synergistic efficacy with adagrasib in K-Ras G12C and G12D mutated pancreatic cancer cell lines. This synergy may be linked to PH1-specific effects on K-Ras splicing and may have contributed to improved adagrasib efficacy in G12D-mutated pancreatic cancer, where currently adagrasib is not approved.

Table: In vitro combinations of Trop2 ADCs with adagrasib

| K-Ras mutation | Cell line  | AKTX- 101 IC50(nM) | Adagrasib (Ada)IC50 (nM) | Bliss Mean <b>AKTX-101</b> +Ada | Bliss Mean <b>SG</b> +Ada | Bliss Mean <b>Dato-DXd</b> +Ada | Bliss Mean <b>Sac-TMT</b> +Ada |
|----------------|------------|--------------------|--------------------------|---------------------------------|---------------------------|---------------------------------|--------------------------------|
| G12C           | PA1266     | >20.0              | 2288.5                   | 15.95                           | -6.18                     | -3.87                           | -5.22                          |
| G12D           | HPAF-II    | >20.0              | 3346.7                   | 17.55                           | -13.73                    | -11.63                          | -12.16                         |
| G12D           | Panc 10.05 | >20.0              | 4387.7                   | 17.51                           | -5.87                     | 8.23                            | -3.29                          |
| G12D           | SW-1990    | >20.0              | 2529.5                   | 6.78                            | -5.20                     | -4.74                           | -7.66                          |

Where SG = Sacituzumab govectin, Dato-DXd = Datopotamab deruxecan, Sac-TMT = Sacituzumab tirumotecan, Ada = Adagrasib

References:  
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2. Mitra SK, Jammalamadaka V, Kang J, Losic T, Tuffy G, Liang TW, Tipton K, Lopez A, Savage S, Monteith W, Haskins WE, Jurica MS, Satyal S, Do M. Development of a splicing modulator-based ADC payload class with immune stimulatory properties for cancer therapy. Cancer Res. 2021;81(13\_Supplement):1832.