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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.

Table: In vitro combinations of Trop2 ADCs with adagrasib

K-Ras mutation	Cell line	AKTX- 101 IC50(nM)	Adagrasib (Ada)IC50 (nM)	Bliss Mean **AKTX-101** +Ada	Bliss Mean **Dato-DXd** +Ada	Bliss Mean **AKTX-101** +Ada	Bliss Mean **Sac-TMT** +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 govetican, Dato-DXd = Datopotamab deruxecan, Sac-TMT = Sacituzumab tirumotecan

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.

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.