PB030

TARGETING ACIDOSIS TO IMPROVE IMMUNOTHERAPY IN A PANCREATIC DUCTAL ADENOCARCINOMA MODEL

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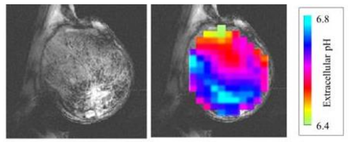
BACKGROUND

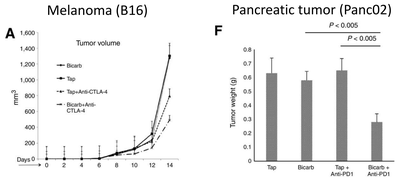
Solid tumors are acidic due to the combination of high rates of glycolysis with poor perfusion [1].



DCE of MDA-435 pHe map of MDA-435

Van Sluis et al., MRM, 2001

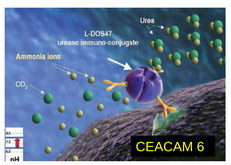
Sodium bicarbonate buffer therapy effectively neutralizes tumor acidity and has been shown pre-clinically to be synergistic or additive to checkpoint blockades [2].



Pilon-Thomas et al. 2016

✓ But… phase I/IIa clinical trials with bicarbonate failed due to poor patient compliance.

✓ **The aim is to test clinically translatable alternative agents to bicarbonate in order to improve the response of PDAC to immune checkpoint blockade**



L-DOS47

→ a urease enzyme immunoconjugate targeted to CEACAM6, a cell surface protein highly expressed in GI and lung cancers. There, urease cleaves endogenous urea into two NH_4^+ and one CO_2, raising local pH [3].

→ Has been well-tolerated in phase I/IIa trials [4,5].

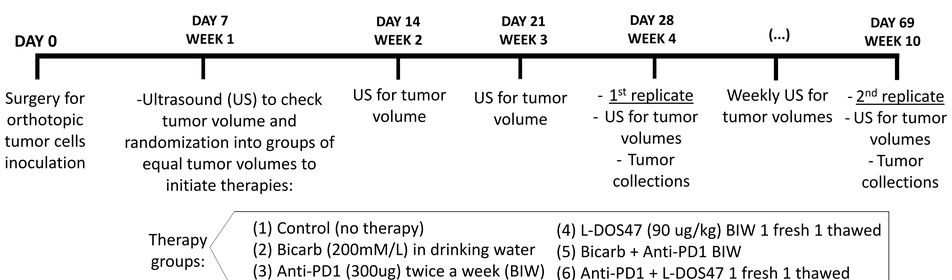
METHODS

✓ Immunocompetent B6.129 mice were inoculated orthotopically with murine pancreatic KPC961 cells transfected to express human CEACAM6 (clone 1B6).

✓ Two biological replicates:

1st replicate = To monitor tumor growth changes up to day 28;

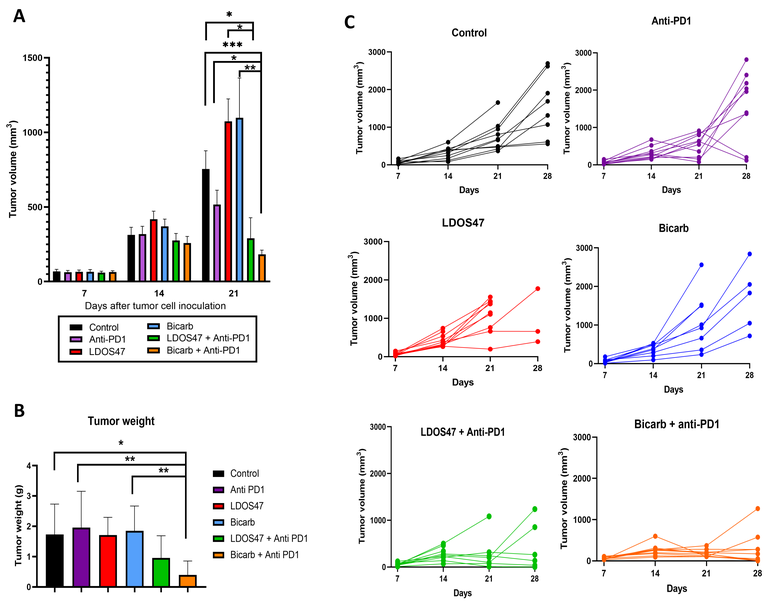
2nd replicate = To analyze overall survival with an endpoint tumor volume of 750 mm^3.



RESULTS

1st replicate:

✓ **Combining anti-PD1 with L-DOS47 or bicarbonate delayed tumor growth; tumor regression was evident in both groups**

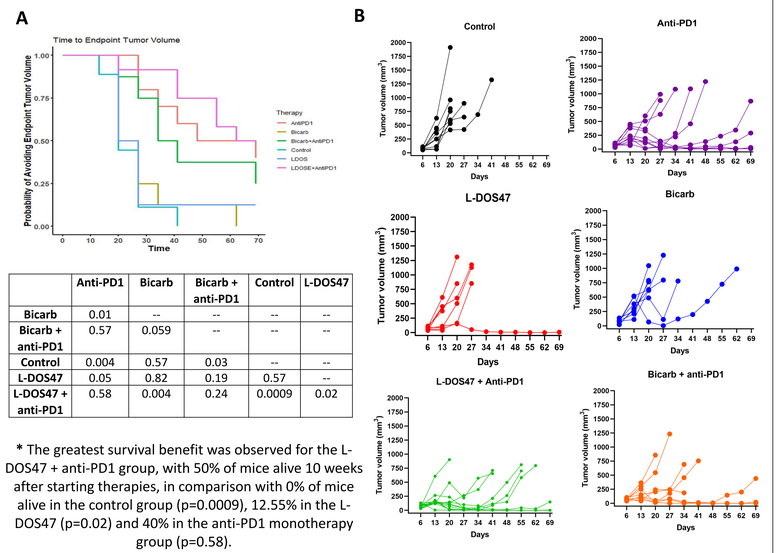


Therapy efficacy in KPC961-1B6 orthotopic tumors.
A. Comparison of tumor volume for each therapy group up to day 21.
B. Comparison of tumor weight measured at endpoint (day 28).
C. Individual tumor growth for each mouse in each therapy group up to day 28 (study endpoint). * $p < 0.05$; ** $p < 0.005$; *** $p < 0.0005$

2nd replicate:

✓ **Anti-PD1 monotherapy or combination therapy with L-DOS47 or bicarbonate increased survival compared with control**

✓ **The greatest survival benefit was observed for the combination of anti-PD1 and L-DOS47***



	Anti-PD1	Bicarb	Bicarb + anti-PD1	Control	L-DOS47
Bicarb	0.01	--	--	--	--
Bicarb + anti-PD1	0.57	0.059	--	--	--
Control	0.004	0.57	0.03	--	--
L-DOS47	0.05	0.82	0.19	0.57	--
L-DOS47 + anti-PD1	0.58	0.004	0.24	0.0009	0.02

* The greatest survival benefit was observed for the L-DOS47 + anti-PD1 group, with 50% of mice alive 10 weeks after starting therapies, in comparison with 0% of mice alive in the control group (p=0.0009), 12.55% in the L-DOS47 (p=0.02) and 40% in the anti-PD1 monotherapy group (p=0.58).

Survival analyzes in the KPC961-1B6 orthotopic tumor model.
A. Kaplan Meier survival plot and results of curve comparisons using Log-Rank test.
B. Individual tumor growth for each mouse in each therapy group up to endpoint tumor volume.

CONCLUSION

Preliminary results suggest that neutralizing acidic tumor pH enhances immune checkpoint blockade responses in an orthotopic pancreatic tumor model. Further experiments are underway.

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