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Efficacy of ASC60, an Oral Fatty Acid Synthase Inhibitor,in Two Tumor Mouse Models

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Introduction

Fatty acid synthase (**FASN**) is the only enzyme in the human body capable of converting metabolized sugar into a fatty acid, palmitate, a process called **De Novo Lipogenesis (DNL)** as shown in **Figure 1A**. FASN is overexpressed in many cancers, and studies have shown that FASN inhibition can disrupt lipid synthesis in tumor cells and disrupt tumor-associated signal transduction, suggesting that FASN inhibition can serve as a potential treatment for cancer.

ASC60 is an orally bioavailable FASN inhibitor, which binds to and blocks FASN. *In vitro* studies in rats showed that treatment with ASC60 could reduce the new palmitate synthesis as shown in **Figure 1B**.

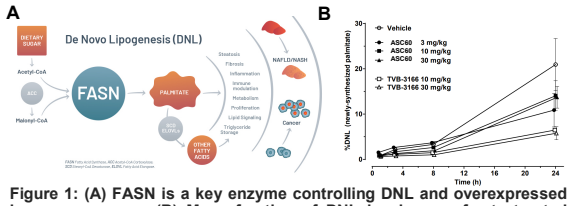

Figure 1: (A) FASN is a key enzyme controlling DNL and overexpressed in many cancers. (B) Mean fraction of DNL in plasma of rats treated orally with ASC60, TVB-3166, or Vehicle.

ASC60 can block FASN, and thus prevent the synthesis of palmitate needed for tumor cell growth and survival. Here we report the *in vivo* efficacy data of ASC60 either as a single agent or in combination with mouse programmed cell death-1 (mPD-1) antibody in two tumor mouse models. Although *in vitro* studies showed that inhibition of palmitate synthesis by ASC60 was less efficient in mouse than in human based on the IC_{50} values shown in **Table 1**, results of the present studies showed that ASC60 could still suppress tumor growth in the tumor mouse models either alone or in combination with mPD-1 antibody. ASC60 would possibly demonstrate much better efficacies in human than in mouse.

Table 1: Inhibition of ASC60 on palmitate synthesis in different cell lines.

Cell lines	IC_{50} (μM)
Human (Hela, 22Rv1, PANC-1, MRC-5, Pfeiffer, Raji, Toledo)	0.005 ~ 0.026
Mouse (LA4, MPEC, CT26, C57BL6-MEF)	1.36 ~ 3.55
Rat (NMU)	0.296

In vivo efficacy evaluation of ASC60 in breast cancer brain metastasis patient-derived orthotopic xenograft model in NUNU mice

Luciferase labelled breast cancer brain metastasis patient-derived xenograft (PDX) derived cells (LD1-2009-362541-Luc) were transplanted into the brain of nude mice. Tumor volumes were estimated by the luciferase reporter signal. When the average signal reached 4.12X10^7 photon/sec, mice were randomized equally into 4 groups treated with ASC60 (20, 60, and 100 mg/kg) or vehicle once daily (QD) for 4 weeks as shown in **Table 2**. Body weights and tumor volumes were measured and estimated regularly, and tumor growth inhibitions (TGI) of different groups were compared.

Table 2: Groups and treatment information.

Group	N	Treatment	Dose (mg/kg)	Dosing Route	Dosing Schedule
1	8	Vehicle Control	--	PO	QD × 28 days
2	8	ASC60	20	PO	QD × 28 days
3	8	ASC60	60	PO	QD × 28 days
4	8	ASC60	100	PO	QD × 28 days

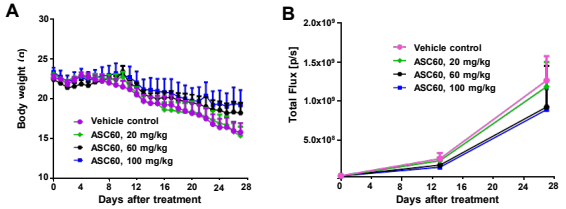

Figure 2: (A) Changes of body weights during the treatment period of this study. (B) The tumor growth curves.

Table 3: *In vivo* imaging results of mouse bioluminescence (Mean)

Group	Dose (mg/kg)	photon intensity (x 10^8 photon/s)		TGI%		T/C%	
		D13	D27	D13	D27	D13	D 27
Vehicle	--	2.61	12.6	--	--	--	--
ASC60	20	2.36	11.8	10.83	6.46	92.29	95.44
ASC60	60	1.8	10	36.95	21.27	69.09	79.63
ASC60	100	1.52	8.91	49.21	30.47	59.73	72.22

T/C: tumor volume of treatment/tumor volume of vehicle control

Body weight changes during the treatment period were shown in **Figure 2A**. During this experiment, from Day 12 after the initial treatment, including the mice in the vehicle control group, most mice showed continuous body weight losses, which should be caused by the tumor progression of LD1-2009-362541-Luc breast cancer brain metastasis patient-derived orthotopic xenograft model. Mice treated with higher doses of ASC60 (60 and 100 mg/kg) showed less body weight losses compared to those treated with vehicle control or a lower dose of ASC60 (20 mg/kg).

ASC60 suppressed tumor growth in LD1-2009-362541-Luc breast cancer brain metastasis patient-derived orthotopic xenograft model in mice as shown in **Figure 2B**. Mice treated with ASC60 (20, 60, and 100 mg/kg) showed dose dependent TGI values of 10.83%, 36.95% and 49.21% on Day 13 (D13) and of 6.46%, 21.27% and 30.47% on Day 27 (D27), respectively, as shown in **Table 3**.

In vivo efficacy evaluation of ASC60 combined with mPD-1 antibody in subcutaneous MC38 colon cancer model in C57BL/6 mice

MC38 cells (1 x 10^6) were subcutaneously inoculated at the right flank region of female C57BL/6 mice. Ten days after inoculation when the average tumor volume reached approximately 62 mm^3, 32 mice were randomized equally into 4 groups with different treatment regimens as shown in **Table 4**. ASC60 (60 or 100 mg/kg) or vehicle was given once daily (QD) for 3 weeks, while mPD-1 antibody (1 mg/kg) was given twice a week (BIW) for 2 weeks. Body weights and tumor volumes were measured regularly, and TGI of different groups were compared.

Table 4: Group and treatment plan.

Group	N	Treatment	Dose (mg/kg)	Dosing Route	Schedule
1	8	Vehicle	-	PO	QD × 3 weeks
2	8	mPD-1	1	IP	BIW × 2 weeks
3	8	ASC60 + mPD-1	60 + 1	PO + IP	QD × 3 weeks + BIW x 2 weeks
4	8	ASC60 + mPD-1	100 + 1	PO + IP	QD × 3 weeks + BIW x 2 weeks

Tumor volumes of different treatment groups on Day after treatment were shown in **Table 5**. On Day13, the tumor volume in the vehicle control mice reached 626 mm^3. mPD-1 antibody showed significant antitumor effects as shown in **Table 6**. TGI values in mice treated with ASC60 (60 and 100 mg/kg) combined with mPD-1 antibody were 91.86% and 99.88% respectively, showing that ASC60 has a dose-dependent antitumor effect. Furthermore, TGI values of mice treated with ASC60 (60 or 100 mg/kg) in combination with mPD-1 antibody were higher than those of mice treated with mPD-1 alone (91.86%, 99.88% vs 89.84), suggesting that combination of ASC60 with mPD-1 would enhance the antitumor activity of mPD-1 antibody.

Table 6: Combination with ASC60 would enhance the antitumor activity of mPD-1 antibody in the MC38 mouse model

Group	Tumor volume on Day 13 after treatment (mm^3)	TGI (%)	p
Vehicle	626 ± 108	-	-
mPD-1 (1 mg/kg BIW)	119 ± 48	89.84	< 0.001
ASC60 (60 mg/kg QD) + mPD-1 (1 mg/kg BIW)	102 ± 36	91.86	< 0.001
ASC60 (100 mg/kg QD) + mPD-1 (1 mg/kg BIW)	69 ± 20	99.88	< 0.001

Table 5: Tumor volumes of different groups on Day after treatment

Day after treatment	Vehicle	mPD-1 (1 mg/kg BIW)	ASC60 (60 mg/kg QD) + mPD-1 (1 mg/kg BIW)	ASC60 (100 mg/kg QD) + mPD-1 (1 mg/kg BIW)
0	62 ± 6	62 ± 6	62 ± 6	62 ± 7
2	87 ± 8	84 ± 7	85 ± 8	85 ± 9
4	115 ± 9	102 ± 9	110 ± 11	113 ± 13
6	158 ± 16	97 ± 10	111 ± 9	110 ± 15
9	253 ± 35	71 ± 17	83 ± 15	71 ± 12
11	413 ± 70	76 ± 27	83 ± 21	67 ± 13
13	626 ± 108	119 ± 48	102 ± 36	69 ± 20
16	963 ± 201	188 ± 74	115 ± 42	105 ± 42
18	1335 ± 313	265 ± 100	156 ± 58	155 ± 68
20	2016 ± 670	371 ± 135	130 ± 55	138 ± 53
23	2033 ± 534	564 ± 242	283 ± 130	242 ± 93

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