Antitumor activity of ABI-009 (*nab*-rapamycin) in combination with anti-PD1 antibody in a syngeneic mouse model of B16 melanoma

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ABSTRACT (#5872)

Background: mTOR pathway has been implicated in cell survival and proliferation and is an attractive target for cancer therapy. Loss of PTEN, a negative regulator of mTOR pathway, is frequently observed in multiple cancer types. Recent studies indicate that loss of PTEN promotes resistance to T cell-mediated immunotherapy. Since PTEN loss can result in downstream mTOR activation, we investigated the safety and efficacy of ABI-009 (*nab*-rapamycin, a novel mTOR inhibitor) in combination with anti-PD1 antibody in a syngeneic mouse model of B16 melanoma. ABI-009 (*nab*-rapamycin) is a nanoparticle form of human albumin-bound rapamycin with a mean particle size of approximately 100 nm developed with a proprietary nanoparticle albumin-bound (*nab*®) technology. ABI-009 is currently in phase 1 and 2 clinical studies for the treatment of malignant perivascular epithelioid cell carcinoma (PEComa), severe pulmonary arterial hypertension (PAH), nonmuscle-invasive bladder cancer, soft-tissue sarcomas, and various childhood cancers.

Methods: Syngeneic B16 melanoma tumors were implanted in immunocompetent C57BL/6 mice. ABI-009 was administered IV at 5 mg/kg 3 times weekly. Monoclonal anti-mouse PD-1 antibody (RMP1-14, BioXcell, West Lebanon, NH, USA) was administered IP at 250 μg every 2 days for 3 times. The study drugs were either administered as single agent or in combination with 3 different dosing schedules: concurrent (A), ABI-009 one week before anti-PD1 (B), or anti-PD1 one week before ABI-009 (C).

Results: Overall, all treatments were well tolerated with no significant body weight loss in any group. All treatment groups showed significant antitumor effect and longer survival compared with the saline control. Addition of ABI-009 simultaneously or after anti-PD1 significantly improved tumor growth suppression and survival compared with anti-PD1 alone. Tumor volumes were reduced 35.5% for group A and 44.8% for group C when compared with anti-PD1 alone ($p < 0.05$). Median survival were 26 days for group A and 26 days for group C vs 20 days for anti-PD1 alone ($p < 0.05$). On the other hand, group B failed to significantly improve antitumor effect and survival over anti-PD1 alone. The combination treatment regimen of anti-PD1 given before ABI-009 (group C) was the best schedule among the 3 schedules tested.

Conclusions: The combination of ABI-009 and anti-PD1 antibody was well tolerated. Results from this study support the treatment regimens of anti-PD1 immunotherapy, concurrent or followed by ABI-009. Pretreatment with ABI-009 followed by anti-PD1 is not recommended. A phase 1b investigation of safety/efficacy of nivolumab and ABI-009 in patients with advanced sarcoma has been initiated.

INTRODUCTION

- The mammalian target of rapamycin (mTOR) regulates cell growth, survival, and proliferation, and is often overexpressed in various cancers, making it a promising target in tumor therapy. [1]
- ABI-009 (*nab*-rapamycin), a nanoparticle albumin-bound rapamycin, was well tolerated and showed evidence of responses and stable disease in various solid tumors in a phase 1 study. [2]
- Loss of PTEN, a negative regulator of mTOR pathway, can result in downstream mTOR activation and also promote resistance to T cell-mediated immunotherapy. [3, 4]
- This study examined whether ABI-009 in combination with anti-PD1 antibody may have synergistic activity in a syngeneic mouse model of melanoma.

METHODS

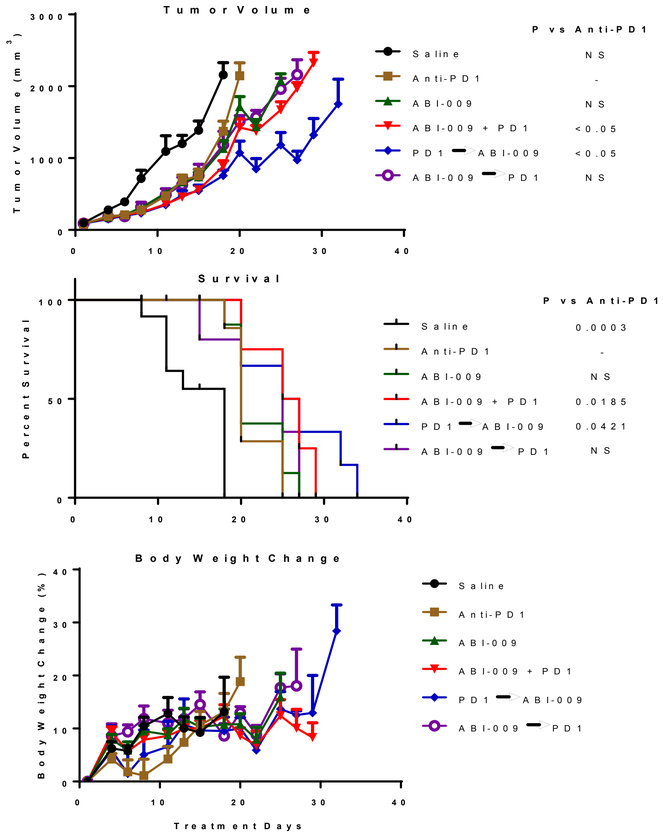
- Syngeneic mouse model of B16 melanoma tumors were implanted in immunocompetent C57BL/6 mice。
- Rat anti-mouse PD1 monoclonal antibody, clone RMP 1-14 (Hoelzel Biotech)
- Each group started with 12 mice, 2 mice per each group were sacrificed on treatment days 8, 15, and 20 for blood and tumor analysis
- Anti-PD1 antibody was given concurrently with ABI-009 from Week 1 D1, or 1 week before ABI-009, or 1 week after ABI-009.

RESULTS

Table 1. Treatment groups.

	Material	Dosing	Route	Frequency
1	Saline	0	IV*	3x weekly
2	Anti-PD1	250 μg/mouse	IP**	3x weekly
3	ABI-009	5 mg/kg	IV	3x weekly
4	Anti-PD1	250 μg/mouse	IP	3x weekly (from Week 1, D1)
	ABI-009 Concurrent	5 mg/kg	IV	3x weekly (from Week 1, D1)
5	Anti-PD1 Before	250 μg/mouse	IP	3x weekly (from Week 1, D1)
	ABI-009	5 mg/kg	IV	3x weekly (from Week 2, D1)
6	ABI-009 Before	5 mg/kg	IV	3x weekly (from Week 1, D1)
	Anti-PD1	250 μg/mouse	IP	3x weekly (from Week 2, D1)

Figure 1. Tumor volume, animal survival, and body weight following ABI-009 and anti-PD1 treatment



RESULTS

Table 2. Tumor growth inhibition and animal survival of each treatment group.

	Group	Tumor Growth				Animal Survival			
		vs Saline (Day 8)		vs Anti-PD1 (Day 18)			P vs		
	Treatment	TGI (%)	P	TGI (%)	P	Median (Days)	Saline	Anti-PD1	ABI-009
1	Saline	0	-	NA	NA	18	-	0.0003	0.0002
2	Anti-PD1	41.6	NS	0	-	20	0.0003	-	0.5314
3	ABI-009	51.5	<0.05	17.5	NS	20	0.0002	0.5314	-
4	ABI-009 + Anti-PD1	55.5	<0.01	35.5	<0.05	26	<0.0001	0.0185	0.0507
5	Anti-PD1 -> ABI-009	-	-	44.8	<0.05	26	0.0002	0.0421	0.0765
6	ABI-009 -> Anti-PD1	-	-	13.6	NS	25	0.0029	0.2191	0.4739

- All treatment groups showed significant antitumor effect and longer survival compared with saline control, with anti-PD1 treatment the least effective.
- The combination of ABI-009 and anti-PD1 treatment demonstrated better antitumor activity than either single agent ABI-009 or anti-PD1; however treatment sequence may be important:
  - ABI-009 given concurrently with anti-PD1 or given after anti-PD1 significantly improved tumor growth suppression and survival compared with anti-PD1 alone.
  - Pretreatment with anti-PD1 before combination with ABI-009 was more effective than anti-PD1 and ABI-009 concurrent treatment.
  - Pretreatment with ABI-009 before combination with anti-PD1 failed to improve antitumor effect and survival over anti-PD1 alone.
- All treatments were well tolerated, with no significant body weight loss in any group.

CONCLUSIONS

- Treatment with ABI-009 concurrently or following anti-PD1 antibody significantly improved the antitumor activity of anti-PD1 antibody.
- Overall, results from this study support the treatment regimen of anti-PD1 immunotherapy followed by ABI-009.
- Pretreatment with ABI-009 followed by anti-PD1 may not be optimal, based on results in this setting.
- The combination of mTOR inhibitors and immune checkpoint inhibitors is feasible and may offer clinical benefits.
- An ongoing phase 1b study (SOC-1701) investigates safety/efficacy of nivolumab (Opdivo®) and ABI-009 in patients with advanced sarcoma (NCT03190174).

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