Buparlisib (AN2025), a potential treatment option for anti-PD-1 non-responding tumors

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Background

Head and neck squamous cell carcinoma (HNSCC) is one of the most common cancers in the world [1]. Although anti-PD-1 antibodies have been approved by FDA and EMA, the response rates of nivolumab and pembrolizumab are both lower than 20% [2][3]. Treatment of anti-PD-1 Ab refractory patients remains to be an unmet medical need.

Buparlisib (AN2025, also known as BKM120), an oral pan-PI3K inhibitor, has shown promising efficacy in combination with paclitaxel in HNSCC BERIL-1 study, where the combination demonstrated a response rate of 39% compared with 14% with paclitaxel alone [4]. Considering the different mechanisms of Buparlisib and anti-PD-1 antibody, we proposed that Buparlisib (AN2025) could be a treatment option for anti-PD-1 Ab refractory tumors.

In order to understand the activity of Buparlisib in tumors refractory to anti-PD1 antibodies, we conducted this study.

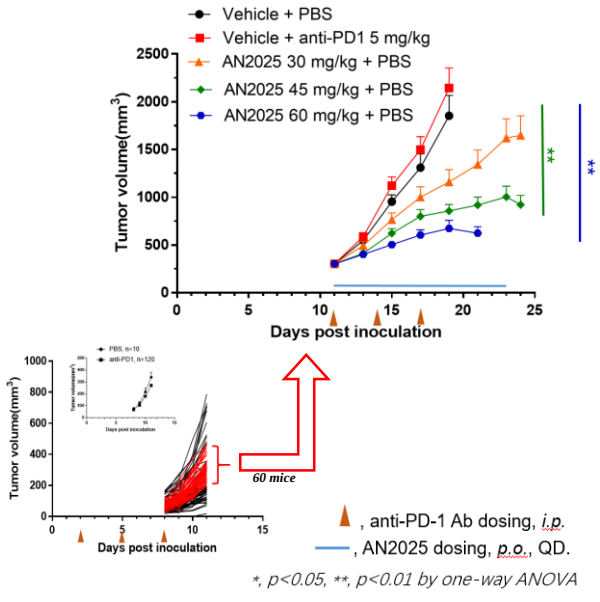
Methods

CT-26 cells were subcutaneously inoculated into 130 Balb/C mice. 2 days after cell inoculation, tumor bearing mice were grouped into PBS pretreated group, 10 mice, and anti-PD-1 Ab pretreated group, 120 mice. Grouped mice were treated with PBS buffer or anti-PD-1 Ab for 10 days. Then, 60 mice from anti-PD-1 Ab pretreated group were selected for 2nd stage treatment. The 60 mice were regrouped into 5 groups with 12 mice per group and then treated with vehicle, anti-PD-1 Ab or AN2025, respectively.

Anti-PD-1 Ab was dosed via *i.p.*, Q3D. and AN2025 was dosed via *p.o.*, QD.

Tumor growth inhibition (TGI) and T/C were calculated with day-11 and day-19 tumor volumes.

Results



*, p<0.05, **, p<0.01 by one-way ANOVA

	Treatment	T/C[a] (%)	TGI[a] (%)	p value[b]
1	Vehicle + PBS	--	--	--
2	Vehicle + 5mg/kg anti-PD-1 Ab	115.72	-18.8	0.8640
3	30mg/kg AN2025 + PBS	62.60	44.7	0.0803
4	45mg/kg AN2025 + PBS	46.22	64.2	0.0047
5	60mg/kg AN2025 + PBS	36.30	76.1	0.0011

a. Tumor growth inhibition was presented as T/C (TGI (%) = T_{TV}/ C_{TV}×100) and TGI (TGI (%) = [1-(T_{19}-T_{11})/ (C_{19}-C_{11})] ×100).

b. *p* value was calculated by tumor volume, one-way ANOVA, and Games-Howell method.

After regrouping, 45 mg/kg and 60 mg/kg AN2025 significantly inhibit tumor growth with a trend of dose response in anti-PD-1 refractory tumor bearing mice.

Conclusion and discussion

In anti-PD-1 Ab refractory tumor bearing mice, single agent treatment with Buparlisib (AN2025) significantly inhibits tumor growth in a dose range consistent with previous studies conducted with BMK120 by Novartis. This animal model result suggests Buparlisib (AN2025) could potentially be a treatment option for anti-PD-1 Ab refractory tumors.

This result, along with the promising outcome from the BERIL-1 study, is supporting the BURAN PhIII trial, which is underway to evaluate Buparlisib (AN2025) plus Paclitaxel versus Paclitaxel in refractory, recurrent or metastatic HNSCC patients who have progressed after prior platinum-based chemotherapy with or without prior anti-PD1/anti-PDL1 antibody treatment.

References

1. Forster MD, Devlin MJ. Front. in Oncol., 2018, 8:310.
2.Topalian SL, Sznol M, McDermott DF, Kluger HM, et al. J. Clin. Oncol., 2014, 32:1020–30.
3.Chow LQ, Haddad R, Gupta S, Mahipal A, Mehra R, Tahara M, et al. J. Clin. Oncol., 2016, 34:3838–45.
4.Souliè res D, Faivre S, Mesá R, Remenár É, et al. Lancet Oncol., 2017, 18:323-335.