#1553 Combining PD-1 Blockade with DLL3-Targeted T Cell Engager Potentiates Antitumor Efficacy in Small Cell Lung Cancer

Tongxin Huo, Ting Ni, Jingjing Wang, Panpan Wang, Yuhe Han, Yawen Zhang, Jian Xiang, Zhixiang Zhang
In Vivo Pharmacology Unit, WuXi Biology, WuXi AppTec, China

WuXi AppTec

WuXi Biology

Abstract

Small cell lung cancer (SCLC) is an aggressive neuroendocrine malignancy characterized by rapid proliferation, early metastasis, and poor prognosis. Despite initial sensitivity to chemotherapy and immune checkpoint blockade, most patients experience disease relapse, highlighting the urgent need for novel therapeutic strategies. Delta-like ligand 3 (DLL3) is highly expressed on the surface of SCLC cells but minimally on normal tissues, making it an ideal target for T cell-engaging therapies. However, limited immune infiltration and the immunosuppressive tumor microenvironment often restrict the efficacy of TCEs in SCLC. Given the complementary mechanism of TCE (T cell engager) mediated cytotoxicity and PD-1 blockade induced T cell activation, our research found that combining a DLL3-targeted TCE with PD-1 inhibition could enhance antitumor immune responses significantly and improve therapeutic outcomes in SCLC.

In PBMC-humanized mouse models bearing SHP77 (DLL3-high expression) or NCI-H69 (DLL3-low expression) xenografts, DLL3 TCE combined with pembrolizumab achieved significant antitumor efficacy than DLL3 TCE monotherapy. To elucidate the underlying mechanisms, we found a marked increase infiltration of human CD45$^+$ immune cells in tumors after combination treatment. In tumors treated with DLL3 TCE alone, PD-1 expression on tumor-infiltrated T cells was upregulated, suggesting T-cell activation accompanied by the inhibitory immune regulation. Notably, PD-1 expression decreased upon co-administration with pembrolizumab, indicating that PD-1 blockade effectively reversed immunosuppressive microenvironment and enhanced immune-mediated tumor clearance. Furthermore, the combination treatment not only promoted T-cell priming and activation but also enhanced recognition between cancer cells and T cells within the tumor microenvironment, indicating a more inflamed immunologically active phenotype.

This strategy provides a strong preclinical rationale for clinical evaluation of DLL3-targeted TCEs in combination with immune checkpoint inhibitors for the treatment of SCLC.

A

Cell line	DLL3 expression	
	log2(TPM+1)	FPKM
SHP77	7.33	53.84
NCI-H524	6.73	20.87
NCI-H510A	7.24	70.78
NCI-H82	5.08	21.66
NCI-H196	0.16	0
NCI-H69	4.46	5.41

log2(TPM+1) values from CCLE.
FPKM values from WuXi AppTec.

B

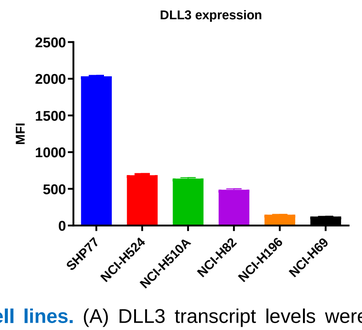

Figure 1. Expression of DLL3 in human SCLC cell lines. (A) DLL3 transcript levels were determined by RNA-seq to assess gene expression across SCLC cells. (B) Cell surface DLL3 protein expression was further evaluated by flow cytometry. Notably, surface protein levels may not fully reflect total cellular DLL3 expression, as a substantial fraction of DLL3 is localized intracellularly.

Results

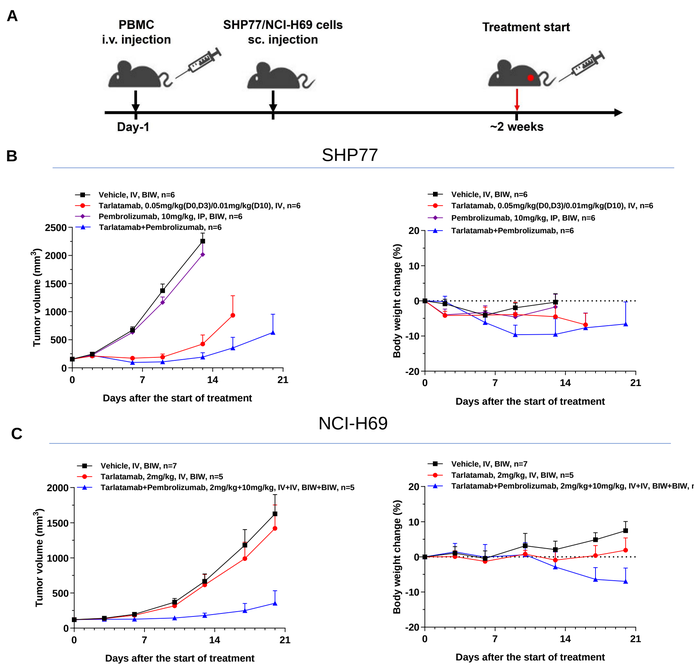

Figure 2. Combination of DLL3 TCE and Pembrolizumab enhances antitumor efficacy. (A) Schematic diagram showing the *in vivo* treatment program in PBMC-SHP77/NCI-H69 humanized models. (B and C) Tumor volume and body weight change of xenografts treated with Tarlatamab and Pembrolizumab. In both SHP77 and NCI-H69 models, adding Pembrolizumab to Tarlatamab delayed tumor growth compared with either Pembrolizumab or Tarlatamab alone.

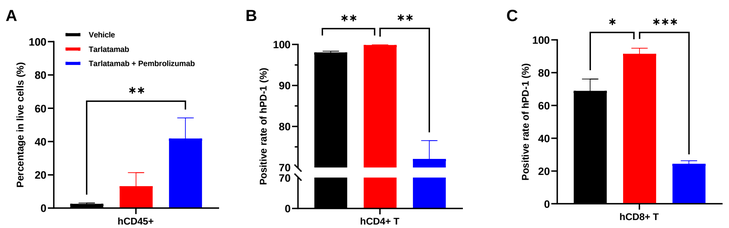

Figure 3. Combination treatment increases immune cell infiltration and reverses PD-1 mediated immune suppression (A) In NCI-H69 tumors, hCD45+ immune cells infiltration was increased in the combination treatment group. (B and C) hPD-1 expression on tumor-infiltrated hCD4+ T and hCD8+ T cells was upregulated after Tarlatamab treatment and reversed by adding Pembrolizumab.

Results

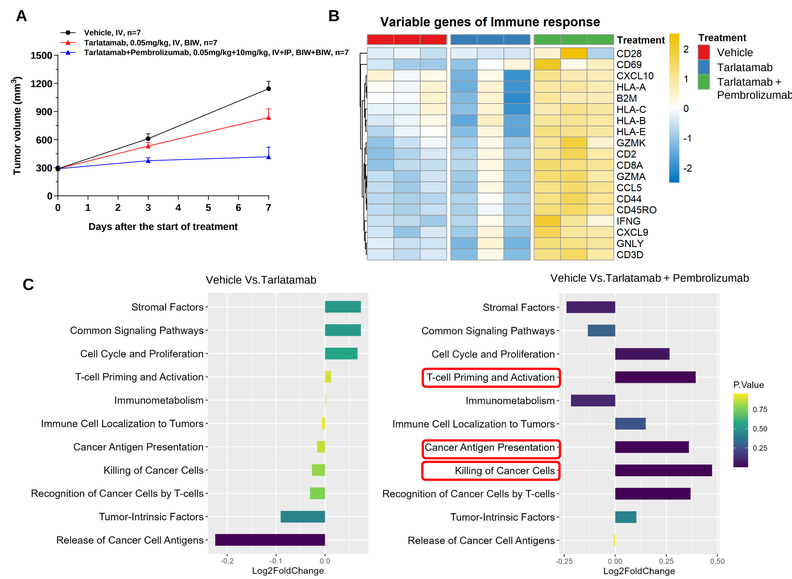

Figure 4. Combination of DLL3 TCE and Pembrolizumab promotes an active immune microenvironment. (A) hPBMC-SHP77 tumors were collected after treatment for NanoString analysis. (B and C) NanoString analysis using- NanoString PanCancer Human IO360 Panel and Gene Set Variation Analysis (GSVA). Combination therapy upregulated gene expression in the antigen presentation and T cell priming/activation pathways.

Conclusion

The combination of Tarlatamab and Pembrolizumab exhibited robust antitumor efficacy in preclinical humanized SCLC models. Mechanistically, this regimen enhanced antitumor immunity by reshaping the tumor microenvironment toward a more activated and immune-supportive phenotype. Collectively, these results support the clinical development of DLL3-targeted T-cell engagers in combination with PD-1 blockade as a novel therapeutic approach for SCLC.

References

1. Challenges of small cell lung cancer heterogeneity and phenotypic plasticity. Nat Rev Cancer. 2025 Jun;25(6):447-462.
2. Delta-like ligand 3: A promising target against small cell lung cancer. Aging Med (Milton). 2024 May 28;7(3):283-286.
3. A Bispecific DLL3/CD3 IgG-Like T-Cell Engaging Antibody Induces Antitumor Responses in Small Cell Lung Cancer. Clin Cancer Res. 2020 Oct 1;26(19):5258-5268

Contact Us USA: mahnaz_arjomand@wuxiapptec.com EU/UK/Israel: dave_madge@wuxiapptec.com Japan: fumio_itoh@wuxiapptec.com Korea: sycho@wuxiapptec.com China/Singapore/Australia: xu_longji@wuxiapptec.com