# Combined inhibition of KRAS G12C and PD1 boosts the therapeutic efficacy via conditioning of tumor microenvironment in pre-clinical humanized NSCLC mouse models

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## Introduction

RAS is one of the most frequently mutated oncogenes in lung cancer. The KRAS G12C mutation is present in approximately 39% of KRAS-mutant NSCLC1. Mutant KRAS is linked to PD-L1 expression, and oncogenic RAS signaling promotes an immunosuppressive tumor microenvironment by upregulating PD-L1 expression. Consequently, combining KRAS G12C inhibitors with immune checkpoint blockers shows promising benefits. Highly immunodeficient mice are transplanted with human PBMC or CD34+ cells, providing an opportunity to evaluate candidates targeting the human immune system in pre-clinical tumor models. In this study, we evaluated the combination efficacy of KRAS G12C inhibitor AMG 510 and anti-PD-1 antibody nivolumab in humanized NSCLC mouse models, revealing strong rationale for clinical practice.

## Methods

LU-01-0361 is a patient-derived xenograft model of NSCLC that exhibits both KRAS G12C mutation and high PD-L1 expression. To better understand the mechanisms underlying the combined inhibition of AMG 510 and nivolumab, LU-01-0361 tumor model was established using human PBMC (A) and CD34+ cells (B) transplanted into humanized mice. Tumor growth and body weight were monitored, blood and tumor samples were collected. Immune profiling analysis of human immune cell reconstitution and infiltration were conducted by flow cytometry, spatial transcriptomics and CITE-seq.

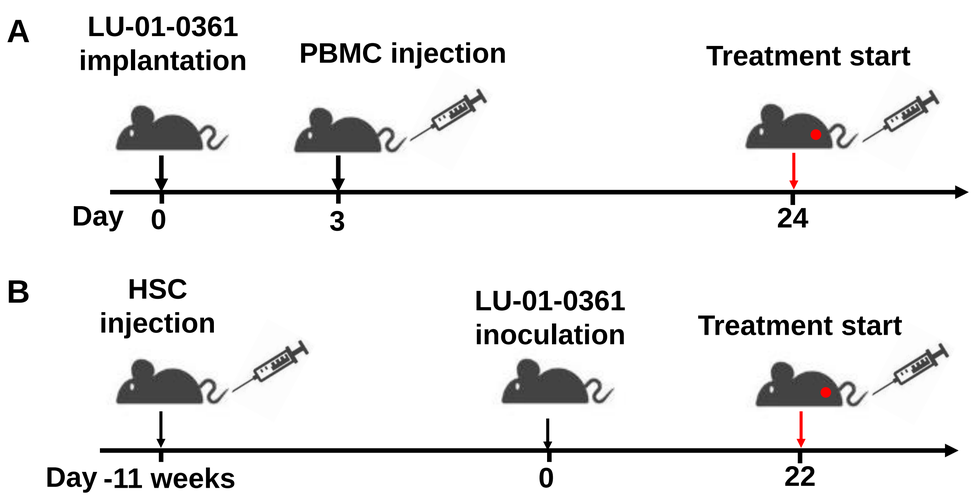


**Figure 1. Graphic overview of humanized model construction. (A, B)** Schematic diagram showing the *in vivo* treatment program in PBMC-LU-01-0361 (A) and CD34+-LU-01-0361 (B) humanized models.

## Results

In both PBMC-LU-01-0361 and CD34+-LU-01-0361 models, adding nivolumab to AMG 510 delayed tumor growth compared with AMG 510 alone. In PBMC-LU-01-0361 model, tumor regression (TR=82%) occurred in all mice after AMG 510 plus nivolumab treatment (A). Similarly, *in vivo* tumor growth inhibition (TGI= 56%) was observed after combination treatment compared with AMG 510 alone in the CD34+-LU-01-0361 model (B). Furthermore, the administration of AMG 510 sensitized the tumor microenvironment by upregulating antigen presentation and immune activation related genes, enhancing MHC-related antigen presentation signal pathways and immune cell activation signal pathways compared with nivolumab alone (C, D, E). The combination treatment of AMG 510 and nivolumab greatly improved the benefits of immunotherapy.

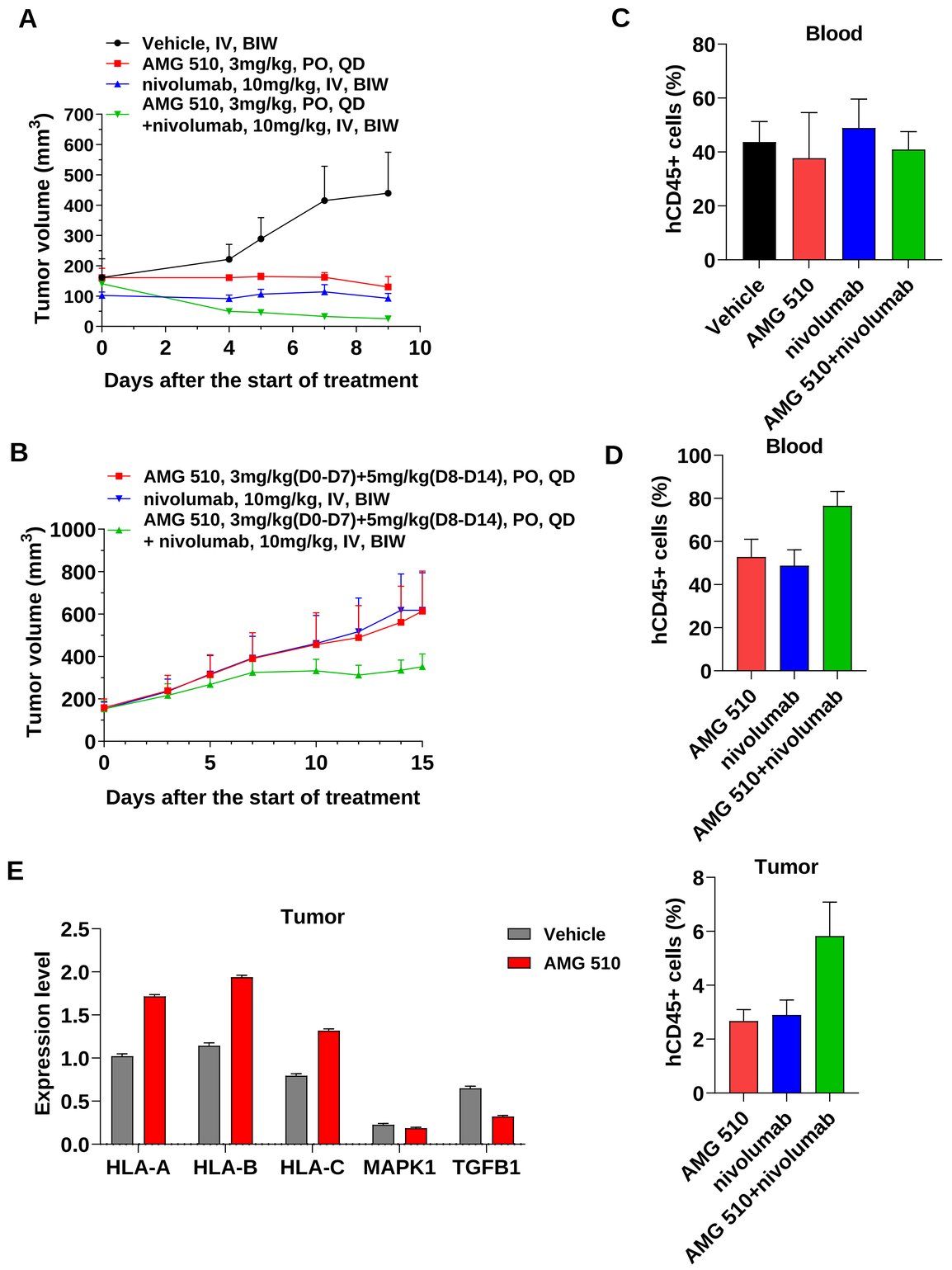


**Figure 2. Therapeutic efficacy of AMG 510 combined with nivolumab in LU-01-0361 humanized models. (A, B)** Tumor growth curves after the start of treatment in PBMC-LU-01-0361 (A) and CD34+-LU-01-0361 (B) humanized models. **(C, D)** Summary of percentages of hCD45+ cells in peripheral blood and tumors from mice in PBMC-LU-01-0361 (C) and CD34+-LU-01-0361 (D) humanized models. **(E)** The MHC-related antigen presentation was detected by scRNA-Seq in the tumors treated with Vehicle and AMG 510 for 7 days in CD34+-LU-01-0361 humanized model . Data are presented as the mean ± SEM.

## Conclusions

KRAS G12C mutation and PD-L1 overexpression in cancer patients contribute to immune suppression. Combination therapy of KRAS G12C inhibitor AMG 510 and anti-PD-1 antibody nivolumab demonstrated significant anti-tumor activities in pre-clinical humanized NSCLC mouse models. Notably, AMG 510 provided complementary immune modulatory benefits that support the mechanism of nivolumab. The findings suggest that combining KRAS G12C inhibitor with anti-PD-1 antibody holds a promising therapeutic potential for NSCLC patients.

## References

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