Antitumor Efficacy and Immune Profiling of the Mouse Ortholog of Nemvaleukin Alfa, a Novel Engineered IL-2 Fusion Protein, in an Orthotopic Mouse Model of Small Cell Lung Cancer Alone or in Combination with Standard Chemotherapy

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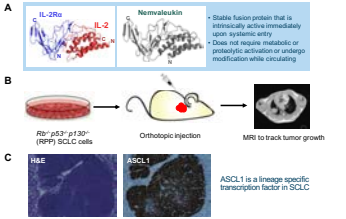
#3326

INTRODUCTION

- Lung cancer remains the leading cause of cancer death worldwide.
- Small cell lung cancer (SCLC) is a deadly cancer with a 5-year survival of less than 7%, accounting about 15% of all lung cancer.
- Immune checkpoint blockade was recently approved in SCLC but survival benefits are limited.
- Agents that induce immunogenic cell death may offer synergistic advantages in combination with nemvaleukin.
- Nemvaleukin alfa ('nemvaleukin'; also known as ALKS 4230) is a novel engineered IL-2 fusion protein currently under phase 1/2 study, that preferentially expands tumor-killing CD8+ T and NK cells by selectively binding the intermediate-affinity IL-2 receptor (IL-2R) (**Fig. 1A**).[1, 3, 4]
- Here, a novel SCLC murine model[2] was used to investigate the effects of RDB 1462, the murine ortholog of nemvaleukin, on tumor growth and the immune microenvironment when administered alone and in combination with cisplatin/etoposide chemotherapy.

FIGURE 1: Structure of Nemvaleukin Alfa and Schematic Illustration of SCLC Model

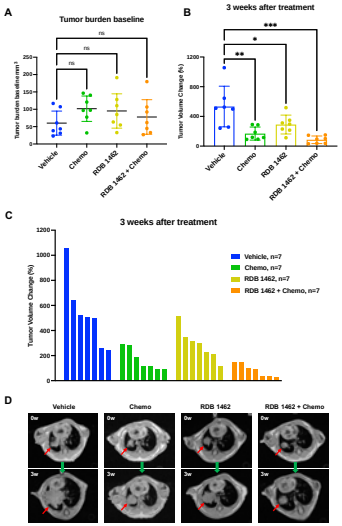


METHODS

- A novel syngeneic *Rb1*$^{-/-}$ *p53*$^{-/-}$ *p130*$^{-/-}$ (RPP) SCLC model that closely mimics human disease was generated.[2] In brief, RPP SCLC cell lines were derived from genetically engineering mouse models (GEMMs). Ultrasound-guided transthoracic injection of RPP cells was performed to generate the orthotopic model (**Fig. 1B**). SCLC histology was confirmed by H&E staining and immunohistochemistry (IHC) of ASCL1 expression (**Fig. 1C**).
- After confirming tumor burden by magnetic resonance imaging (MRI), mice were treated with RDB 1462 alone (every 4 days at 6mg/kg for 3 weeks) or in combination with standard chemotherapy (cisplatin 5mg/kg q.w. + etoposide 10mg/kg t.i.w. for 3 weeks).Tumor growth was measured by MRI and survival was recorded.
- Upon RDB 1462 mono- and combination treatment regimens, the frequencies and functionality of tumor-infiltrating and peripheral blood immune cells were analyzed by flow cytometry.
- Statistical analyses were performed using GraphPad Prism 9 software. Data are presented as mean with SEM. Statistical comparisons were performed using one way ANOVA (* p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001).

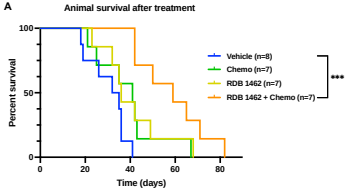
RESULTS

FIGURE 2: RDB 1462 Treatment Significantly Delayed Tumor Growth in the SCLC Model



- After orthotopic injection of RPP SCLC cells, tumor burden was confirmed by MRI. Mice were then randomized into different treatment arms. Tumor burden baseline was similar among the 4 treatment arms (**Fig. 2A**).
- Changes in tumor volume were calculated 3 weeks after treatment initiation. Chemotherapy (cisplatin + etoposide), RDB 1462 monotherapy and combination therapy significantly delayed tumor growth. The combination therapy achieved the most significant antitumor effects. (**Fig. 2 B and C**).
- Representative MRI images of tumor baseline and 3 weeks after treatment initiation (**Fig. 2D**). The red arrowheads indicate the location of lung tumors.

FIGURE 3: RDB 1462 Treatment Improved Survival in the SCLC animal model

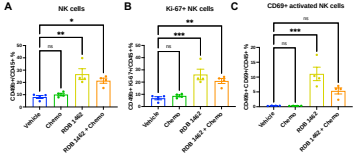


B

Treatment arms	Vehicle	Chemo	RDB 1462	RDB 1462 + Chemo
Median survival (days)	33.5	41	36	59

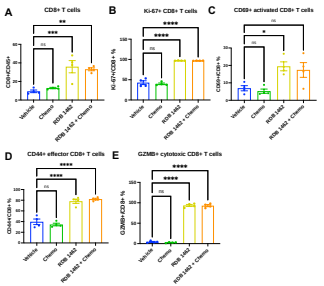
- Kaplan-Meier survival curve for RPP SCLC model after indicated treatment. Chemotherapy and RDB 1462 monotherapy modestly prolonged animal survival. Combining RDB 1462 with chemotherapy provided the most significant survival benefits among all treatment groups (**Fig. 3A**).
- Median survival days after treatment are shown in table (**Fig. 3B**).

FIGURE 4: RDB 1462 Treatment Significantly Expanded Tumor-Infiltrating NK Cells in the SCLC Model



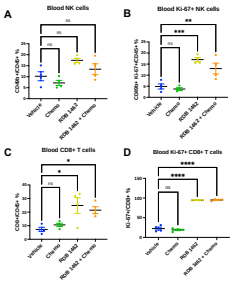
- Tumor-infiltrating lymphocytes from RPP SCLC model were analyzed at day 7 after treatment. RDB 1462 mono- and combination treatments increased the total number of tumor-associated NK cells, the percentage of NK cells expressing the proliferation marker Ki-67, and the activation marker CD69 (**Fig. 4 A-C**).

FIGURE 5: RDB 1462 Treatment Significantly Expanded Tumor-Infiltrating CD8+ T Cells in the SCLC Model



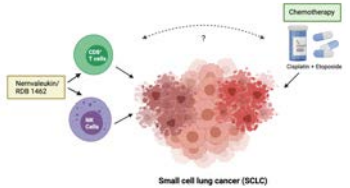
- RDB 1462 treatment increased the total number of tumor-infiltrating CD8+ T cells expressing markers of proliferation (Ki-67), activation (CD69), effector (CD44), and cytotoxic (GZMB) function. (**Fig. 5 A-E**)

FIGURE 6: RDB 1462 Treatment Also Expanded the Proliferating NK Cells and CD8+ T Cells in the Peripheral Blood in the SCLC Model



- Peripheral blood lymphocytes from RPP SCLC model were analyzed at day 7 after treatment. RDB 1462 treatment expanded NK cells expressing the proliferation marker Ki-67. RDB 1462 also increased the total number and proliferating CD8+ T cells (**Fig. 6 A-D**).

FIGURE 7: Schematic Illustration of Nemvaleukin/RDB 1462 and Chemotherapy on Treating SCLC



- Cytotoxic agents like cisplatin and etoposide induce direct antitumor effects as well as immunogenic tumor-cell death.
- Nemvaleukin increases tumor-killing NK and CD8+ T cells in the tumor.
- Nemvaleukin may enhance the efficacy of chemotherapy in SCLC, which requires further investigation.

CONCLUSIONS

- The mouse ortholog of nemvaleukin, RDB 1462, demonstrated antitumor immunity in a murine model of SCLC.
- RDB 1462 reduced SCLC growth and prolonged survival in mice, which was further enhanced by combining with standard chemotherapy.
- RDB 1462 increases NK cells and CD8+ T cells in both tumor tissues and peripheral blood.
- These data support further evaluation of nemvaleukin in combination with chemotherapy in the clinic.

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Disclosures

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