Research Article

Title:

Anti-VEGF antibody protects against alveolar exudate leakage caused by vascular hyperpermeability, resulting in mitigation of pneumonitis induced by immunotherapy

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Running title:

Anti-VEGF antibody relieves immune-related pneumonitis

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26 Abstract

27 Immune-related pneumonitis is an important toxicity associated with checkpoint inhibitor therapy
28 with anti-PD-1 or anti-PD-L1 antibodies, often necessitating discontinuation of treatment.
29 Development of methods to mitigate checkpoint inhibitor–related pneumonitis is required.
30 The contributions of PD-L1, PD-L2, and VEGF to the pathogenesis of pneumonitis were examined
31 in an IL-2- plus IL-18-induced mouse pneumonitis model (IL pneumonitis model). Furthermore, the
32 incidences of pneumonitis were retrospectively examined in non–small-cell lung cancer patients
33 treated with the anti-PD-L1 monoclonal antibody atezolizumab plus chemotherapy, with or without
34 the anti-VEGF monoclonal antibody bevacizumab, in the phase III IMpower150 trial.
35 PD-1 signal blockade by anti-PD-L1 and anti-PD-L2 antibodies aggravated pneumonitis in the IL
36 pneumonitis model. An anti-VEGF antibody prevented PD-1 signal blockade from aggravating
37 pneumonitis in this model. PD-1 signal blockade induced interstitial T cell infiltration in the lungs,
38 but VEGF blockade did not affect this T cell infiltration. The anti-VEGF antibody protected against
39 vascular-to-alveolar leakage of protein and fluid due to PD-1 signal blockade in a murine model. In
40 the IMpower150 trial, incidence rates of pneumonitis of any grade were 4.3% in the group without
41 bevacizumab and 2.8% in the group with bevacizumab. In patients with pneumonitis, outcomes of
42 “Not recovered / Not Resolved” were reported for 29.4% in the group without bevacizumab
43 compared with 9.1% in the group with bevacizumab.
44 Our findings suggest that anti-VEGF antibodies in combination with checkpoint inhibitors may be a
45 treatment method that can control checkpoint inhibitor–related pneumonitis.
47 **Introduction**

Programmed cell death 1 receptor (PD-1) on T cells plays a major role in suppressing the host’s antitumor immune response by interaction with PD-L1 or PD-L2 on tumor cells, macrophages or dendritic cells, and treatment with anti-PD-1 or anti-PD-L1 antibodies generally has high clinical benefit in cancer patients (1). However, the use of anti-PD-1 or anti-PD-L1 antibodies is often associated with potentially fatal immune-related pneumonitis, an important autoimmune toxicity with significant morbidity and mortality, often necessitating discontinuation of therapy (2) (3).

Meta-analyses of published clinical trials of PD-1 and PD-L1 inhibitor therapy for non–small-cell lung cancer (NSCLC) patients show that the incidence of pneumonitis of any grade is significantly higher in patients treated with PD-1 inhibitors than in patients treated with PD-L1 inhibitors (4) (5), indicating that the appropriate clinical selection of these agents may be one of the options for reducing the risk of pneumonitis in NSCLC; however, even when using a PD-L1 inhibitor, the risk of pneumonitis remains. Therefore, the development of a method for controlling pneumonitis is required.

VEGF is an angiogenic factor (6) and also a potent inducer of vascular permeability (7) (8). It has been reported that VEGF plays a significant role in the development of several lung disorders, including chronic obstructive pulmonary disease, pulmonary hypertension, and acute lung injury (9). However, the role of VEGF in checkpoint inhibitor–related pneumonitis has not been investigated.

In this study, we used an IL-2- plus IL-18-induced mouse pneumonitis model (10) to investigate the roles of PD-L1, PD-L2, and VEGF in pneumonitis, and we investigated whether an anti-VEGF antibody has a mitigation effect on checkpoint inhibitor–related pneumonitis in the phase 3 IMpower150 trial.

69 **Materials and Methods**

**Mice**

Female 6-week-old C57BL/6 mice were obtained from Japan SLC (Hamamatsu, Shizuoka, Japan). All animals were allowed to acclimatize and recover from shipping-related stress for 1 week prior to the study. The animals were allowed free access to chlorinated water and irradiated food, and were kept under a controlled light–dark cycle (12 h–12 h). All animal procedures were approved by the
Institutional Animal Care and Use Committee at Chugai Pharmaceutical Co., Ltd., and conformed to the Guide for the Care and Use of Laboratory Animals published by the Institute of Laboratory Animal Resources (ILAR).

Mouse pneumonitis model

Mice were treated once a day with an intraperitoneal injection of 10,000 IU/head rhIL-2 (PeproTech, Cranbury, NJ, USA) and 1 μg/head rmIL-18 (R&D Systems, Minneapolis, MN, USA). These cytokines were suspended in 200 μL of sterile phosphate-buffered saline (PBS), and mice treated with 200 μL PBS were used as controls. Anti-mouse PD-L1 antibody (10F.9G2; BioLegend, San Diego, CA, USA), anti-mouse PD-L2 antibody (TY25; BioLegend), anti-mouse VEGF antibody (B20-4.1.1; gifted from Genentech) or Rat IgG (MP Biomedicals, Santa Ana, CA, USA) was administered intraperitoneally to the mice at a dose of 10 mg/kg three times from the day before cytokine treatment. Wet lung weight and moist rale were measured after 5 days of the treatment.

Flow cytometric analysis

For analysis of lung-infiltrating inflammatory cells, lung tissue was excised from treated mice after 5 days of the treatment, and single-cell suspensions were obtained by mincing lung tissues and homogenizing them by disruption and digestion with a gentleMACS Dissociator and a Lung Dissociation Kit for mice (Miltenyi Biotec, Bergisch Gladbach, Germany). Single-cell suspensions were incubated with anti-Fcγ receptor antibodies (Tonbo Biosciences, San Diego, CA, USA) and the fixable viability dye FVD506 or FVD780 (eBioscience, San Diego, CA, USA) at room temperature for 5 minutes, and stained with the following monoclonal antibodies: mouse CD45 (30-F11), CD4 (RM4-5), CD8α (53-6.7), NK1.1 (PK136), CD11c (HL3), CD103 (M290), CD11b (M1/70), Gr-1 (RB6-8C5), F4/80 (T45-2342), PD-L1 (MIH5), and PD-L2 (TY25) from BioLegend or BD Biosciences (Franklin Lakes, NJ, USA). The appropriate conjugated isotype-matched immunoglobulin G (IgG) was used as the control for each. Cells were analyzed using an LSRFortessa X-20 cell analyzer (BD Biosciences) and FlowJo 10 software (Tree Star, San Carlos, CA, USA).
Lung tissue was excised from treated mice after 4 days of treatment. The trachea was surgically
exposed and intubated with a syringe catheter. The lungs were subjected to lavage with 0.5 mL PBS
3 times. BALF was obtained from each mouse and cells in BALF were pelleted by centrifugation
(500 g, 5 min). The supernatants were stored at −80°C for later measurements.

Histological examination

Lung tissue was excised from treated mice after 5 days of treatment. After opening of the thorax, the
lungs were immediately fixed by intratracheal instillation of 10% neutral buffered formalin. After
gross examination, the excised tissues were placed in 10% formalin. Sections (4 µm thickness) were
cut from paraffin-embedded tissues. Deparaffinized sections were stained with hematoxylin and
eosin (HE).

Immunoassays

Concentrations of mouse SP-D were measured with a Quantikine ELISA kit (R&D Systems). VEGF
was quantified by using a Quantikine ELISA kit (R&D Systems). Albumin was quantified by using a
specific ELISA kit (Bethyl Laboratories, Montgomery, AL, USA).

Clinical study design

The IMpower150 trial (NCT02366143) was a randomized phase 3 study that evaluated the safety
and efficacy of atezolizumab in combination with carboplatin + paclitaxel with or without
bevacizumab compared with treatment with carboplatin + paclitaxel + bevacizumab in metastatic
NSCLC (11). The IMpower150 study was done in full accordance with the guidelines for Good
Clinical Practice and the Declaration of Helsinki, and all patients gave their written informed
consent. We performed the human investigations after approval by the research ethics committee of
Chugai Pharmaceutical Co., Ltd. Participants were randomized in a 1:1:1 ratio to the ACP arm
(atezolizumab + carboplatin + paclitaxel), the ABCP arm (atezolizumab + carboplatin + paclitaxel +
bevacizumab), and the BCP arm (carboplatin + paclitaxel + bevacizumab).
Statistical analysis

To evaluate statistical significance in the mouse model experiments, data was analyzed with the Wilcoxon test. For two groups, \( P < 0.05 \) was considered to indicate a significant difference. For multiple groups, \( P \) values were adjusted by the Holm–Bonferroni method (12) by using JMP version 10 software (SAS Institute, Cary, NC, USA).

Results

PD-1 signal blockade aggravated pneumonitis and VEGF blockade improved the pneumonitis in the immune-related pneumonitis model

Bronchoalveolar lavage fluid (BALF) of patients with checkpoint inhibitor–related pneumonitis often suggests lymphocytic inflammation of the alveoli, and BALF cytology often presents an increased proportion of lymphocytes (13). Therefore, to investigate immune-related mechanisms for pneumonitis aggravated by PD-1 signal blockade, we examined the effects of anti-PD-L1 and anti-PD-L2 antibodies in an IL-2- plus IL-18-induced murine pneumonitis model with symptoms of interstitial lymphocyte infiltration in the lungs. The wet lung weight was significantly higher in the group with dual PD-L1/PD-L2 blockade compared with that in the IL-2 plus IL-18 alone group (Fig. 1A). Serum pulmonary surfactant protein-D (SP-D) is a useful clinical biomarker for the diagnosis and management of pneumonitis and it also increases in patients with checkpoint inhibitor–related pneumonitis (14-16). In the current model, the serum SP-D level was significantly higher in the group with dual PD-L1/PD-L2 blockade compared with that in the IL-2 plus IL-18 alone group (Fig. 1B).

Next, to investigate the relation between VEGF signaling and checkpoint inhibitor–related pneumonitis, we examined the effect of VEGF blockade in the IL-2- plus IL-18-induced pneumonitis model. The wet lung weight was significantly lower in the VEGF blockade group compared with the group with dual PD-L1/PD-L2 blockade (Fig. 1A). The level of SP-D in serum was also significantly decreased by the addition of VEGF blockade (Fig. 1B).
PD-L1 and PD-L2 blockade induced interstitial T cell infiltration in the lungs, but VEGF blockade did not prevent T cells from infiltrating

To investigate the mechanism of action through which dual PD-L1/PD-L2 blockade aggravated pneumonitis in the IL-2- plus IL-18-induced pneumonitis murine model, we analyzed the expressions of PD-L1 and PD-L2 in lung tissues of mice. In normal lung tissue, PD-L1 and PD-L2 were expressed most strongly on CD103− CD11c+ dendritic cells (DCs) (Fig. 2). IL-2 plus IL-18 treatment upregulated PD-L1 expression on CD103− DCs, CD103+ DCs, CD11b+ Gr1high neutrophils, and F4/80+ CD11c− macrophages. In contrast, IL-2 plus IL-18 treatment did not upregulate PD-L2 expression on these cells (Fig. 2).

Next, we analyzed the inflammatory condition of the lung tissue. Histological evaluation of mice treated with IL-2 + IL-18 + anti-PD-L1 antibody + anti-PD-L2 antibody revealed that the alveolar wall and interstitium had large interstitial infiltration of mononuclear cells and granulocytes (Fig. 3).

Flow cytometry analysis revealed that IL-2 plus IL-18 significantly increased CD3− NK1.1+ NK cells, neutrophils, and macrophages in the lungs and significantly decreased CD8α+ T cells, while addition of dual PD-L1/PD-L2 blockade significantly increased CD8α+ T cells and CD4+ T cells (Fig. 4). However, additional treatment with anti-VEGF antibody did not change the number of inflammatory cells in the lung tissues (Fig. 4).

Anti-VEGF antibody protected against alveolar exudate leakage due to dual PD-L1/PD-L2 blockade

Although treatment with the anti-VEGF antibody prevented the increases in wet lung weight and serum SP-D level—an index useful for the evaluation of pneumonitis—it did not change inflammatory cell infiltration into lung tissues. A characteristic of this immune-related pneumonitis model is a moist rale caused by air mixing with fluid exudate in the bronchial tubes. A moist rale is also a typical clinical finding in patients with checkpoint inhibitor–related pneumonitis. The mice with symptoms of moist rale showed that alveolar exudate formed in the lung tissue (Fig. 3). Moist rale occurred in the group with PD-L1 blockade and in the group with dual PD-L1/PD-L2 blockade, but it did not occur in the group with PD-L1 + PD-L2 + VEGF blockade (Fig. 5A).
To ascertain whether VEGF blockade protects against vascular-to-alveolar leakage in this model, we measured the albumin concentration in BALF. The albumin concentration in the group with dual PD-L1/PD-L2 blockade was significantly higher than in the IL-2 plus IL-18 group and in the PD-L1 blockade group (Fig. 5B). Addition of VEGF blockade to the dual PD-L1/PD-L2 blockade treatment significantly decreased the albumin concentration in BALF (Fig. 5B).

Because VEGF blockade protected against vascular-to-alveolar leakage, we evaluated the expression of VEGF in lung tissues, expecting to see an increase. Unexpectedly, IL-2 plus IL-18 significantly decreased VEGF levels in the lung tissue and dual PD-L1/PD-L2 blockade did not change these decreased VEGF levels (Fig. 5C).

**Bevacizumab reduced the incidence of checkpoint inhibitor–related pneumonitis and improved the rate of recovery from pneumonitis in NSCLC patients**

We showed that VEGF blockade prevented immune-related pneumonitis from aggravating in the murine model. Therefore, to investigate whether VEGF modulates the risk of immune-related pneumonitis in NSCLC patients treated with immune checkpoint blockade therapy, we compared the status of pneumonitis between the atezolizumab + carboplatin + paclitaxel (ACP group) and the atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP group) in the phase 3 IMpower150 trial. Incidence rates of pneumonitis of any grade were 4.3% in the ACP group and 2.8% in the ABCP group (Fig. 6). Incidence of symptomatic Grade 2–4 pneumonitis was 3.8% in the ACP group and 2.0% in the ABCP group (Table 1). Rates of “Not recovered / Not Resolved” outcomes in patients with pneumonitis were 29.4% in the ACP group and 9.1% in the ABCP group (Fig. 6).

Among patients with pneumonitis, 5.9% in the ACP group and 27.3% in the ABCP group did not use steroids (Table 2).

**Discussion**

We demonstrated that dual treatment with anti-PD-L1 antibody plus anti-PD-L2 antibody worsened the index for evaluation of pneumonitis in an IL-2- plus IL-18-induced murine pneumonitis model. Because pneumonitis does not develop in PD-1−/−C57BL/6 mice but is accelerated by PD-1 deficiency in the MRL background which has the risk of the autoimmune damage in lung (17), the
aggravation of pneumonitis due to dual PD-L1/PD-L2 blockade may need a pre-existing inflammatory immune microenvironment in the lungs. In patients with NSCLC, pre-existing pulmonary fibrosis is reported to be a risk factor for anti-PD-1–related pneumonitis, supporting this hypothesis (18,19). It has been reported that PD-L2 plays a role in the homeostasis of inflammation in the lungs (20). Our data showed that PD-L2 was expressed on DCs in murine lung tissue in a steady state and that that expression continued without a change even under the inflammatory conditions induced by IL-2 plus IL-18. Expression of PD-L1, on the other hand, was upregulated under the IL-2- plus IL-18-induced inflammatory conditions. These results suggest that not only PD-L2 but PD-L1 also may be active in the lungs under inflammatory conditions. In fact, we demonstrated that not only dual PD-L1/PD-L2 blockade but also blockade of PD-L1 alone caused symptoms such as moist rale under the IL-2- plus IL-18-induced inflammatory conditions. Although there is a higher incidence of pneumonitis with the use of PD-1 inhibitors than with the use of PD-L1 inhibitors (4), it is necessary to be prepared for pneumonitis also when using PD-L1 inhibitors.

With regard to the role of VEGF in checkpoint inhibitor–related pneumonitis, we demonstrated that anti-VEGF antibody could control symptoms of checkpoint inhibitor–related pneumonitis in the murine model, especially the vascular-to-alveolar leakage and moist rale due to the leakage. Although moist rales/crackles are not very commonly manifested symptoms in the patients with immune checkpoint inhibitor-related pneumonitis, they has been listed as one of the clinical findings suspecting the onset of severe pneumonitis recommending a chest CT(21,22). Furthermore, we demonstrated that in NSCLC patients, the incidence of symptomatic pneumonitis induced by atezolizumab plus chemotherapy was lower in the group also treated with bevacizumab than in the group without bevacizumab. And even in the broadly defined pneumonitis, including interstitial lung disease, pulmonary fibrosis and etc., this trend does not change (23). Therefore, it is suggested that checkpoint inhibitor–related pneumonitis occurs when two conditions are both met: presence of intrinsic VEGF and aggravation of pre-existing inflammation caused by PD-1 signal blockade. On the other hand, our results showed that the level of VEGF expression in lung tissues decreased in the IL-2 + IL-18 + anti-PD-L1/PD-L2 antibody-induced pneumonitis model. Although the lungs have the highest level of VEGF gene expression among all normal tissues (24), VEGF levels in BALF from acute lung injury patients are reported to be lower than levels in normal BALF, and a possible explanation for these decreased levels of VEGF may be dilution resulting from alveolar
flooding (25). Therefore, the same phenomenon may be happening in our pneumonitis model, and our study demonstrated that despite this lowered level of VEGF, it is still sufficient and critical for the massive alveolar exudate leakage seen in the immune-related pneumonitis model. Since increase in immune cell infiltration caused by PD-1 signal blockade was not affected by co-administration of anti-VEGF antibody, it may not be considered as a fundamental treatment measure to cure immune-related pneumonitis at least from the results using current mouse pneumonitis model. However, as there has been little information about the precise roles of infiltrated immune cells in immune checkpoint inhibitor-related pneumonitis, further studies are required to understand the contribution of each type of immune cells to the development of each symptom.

Although checkpoint inhibitor–related pneumonitis is one of the most serious immune-related adverse events, no preventive measures have been established. Although steroid therapy is an effective treatment, it carries the risk of suppressing the antitumor effect of checkpoint inhibitors (26). We demonstrated that among NSCLC patients, the clinical outcome of pneumonitis induced by atezolizumab plus chemotherapy was better in patients treated with bevacizumab than in those without bevacizumab. Furthermore, the percentage of patients with pneumonitis who used steroids was lower in the group treated with bevacizumab than in the group without. Anti-VEGF antibodies such as bevacizumab are reported to have additive or synergistic effects when administered in combination with anti-PD-L1 antibodies (such as atezolizumab) in NSCLC, renal cell carcinoma, and hepatocellular carcinoma (11,27,28). Anti-VEGF antibodies plus checkpoint inhibitors may be a treatment method that can control at least a part of checkpoint inhibitor–related pneumonitis without loss of therapeutic effects. On the other hands, mechanism of checkpoint inhibitor–related pneumonitis is not clear and there is a limit what we can learn from our research in an IL-2–plus IL-18-induced murine pneumonitis model and the particular group of patients. Further study will be needed to clarify the clinically relevant mitigation effects of bevacizumab on immune-related pneumonitis.

In conclusion, we have shown that an anti-VEGF antibody protected against vascular-to-alveolar leakage of protein and fluid, resulting in mitigation of checkpoint inhibitor–related pneumonitis in a murine model. Our findings suggest that bevacizumab may be a meaningful therapeutic option for patients receiving checkpoint inhibitors, not only in terms of enhancing their anti-tumor effect but also in terms of reducing some side effects.
Acknowledgments

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REFERENCES


### TABLES

#### Table 1. Severity of pneumonitis in the IMpower150 trial

<table>
<thead>
<tr>
<th>Grade</th>
<th>ACP (n=400)</th>
<th>ABCP (n=393)</th>
<th>BCP (n=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis Any grade</td>
<td>17 (4.3%)</td>
<td>11 (2.8%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>4</td>
<td>2 (0.5%)</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>6 (1.5%)</td>
<td>4 (1.0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>2</td>
<td>7 (1.8%)</td>
<td>3 (0.8%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>1</td>
<td>2 (0.5%)</td>
<td>3 (0.8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

ACP: atezolizumab + carboplatin + paclitaxel group
ABCP: atezolizumab + bevacizumab + carboplatin + paclitaxel group
BCP: bevacizumab + carboplatin + paclitaxel group

#### Table 2. Steroid use in patients with pneumonitis in the IMpower150 trial

<table>
<thead>
<tr>
<th>Use</th>
<th>ACP (n=17)</th>
<th>ABCP (n=11)</th>
<th>BCP (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid No</td>
<td>1 (5.9%)</td>
<td>3 (27.3%)</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td>Yes</td>
<td>16 (94.1%)</td>
<td>8 (72.7%)</td>
<td>2 (66.7%)</td>
</tr>
</tbody>
</table>

ACP: atezolizumab + carboplatin + paclitaxel group
ABCP: atezolizumab + bevacizumab + carboplatin + paclitaxel group
BCP: bevacizumab + carboplatin + paclitaxel group
FIGURE LEGENDS

Figure 1. Effect of PD-L1/PD-L2/VEGF blockade on lung weight and SP-D level in mice with lung damage induced by IL-2 plus IL-18

(A) Lung weights. Data are shown as the mean ± SD (n=13–18/group). Statistical analysis used Wilcoxon rank sum test. *, P < 0.05; NS, not significant. (B) Levels of pulmonary surfactant protein-D (SP-D) in serum. Data are shown as the mean ± SD (n=10–15/group). Statistical analysis used Wilcoxon rank sum test. *, P < 0.05; NS, not significant.

Figure 2. Expression of PD-L1 or PD-L2 on inflammatory cells in mouse lung tissue

(A) PD-L1 expression and (B) PD-L2 expression in mouse lung tissues in the control group and the IL-2- plus IL-18-treated group. Cells were determined by flow cytometric analysis. DCs, dendritic cells.

Figure 3. Histopathological examination of lung tissue stained with HE


Figure 4. Infiltration of inflammatory cells into lung tissue of treated mice

Number of NK cells (NK1.1+), CD8α+ cells, CD4+ cells, neutrophils (CD11b+ Gr-1high), macrophages (F4/80+), CD103+ DCs (CD103+ CD11c+), and CD103- DCs (CD103- CD11c-) in lung tissues after the indicated treatment (n=7–12/group). Statistical analysis used Wilcoxon rank sum test. *, P < 0.05; NS, not significant. Data are shown as the mean ± SD.
Figure 5. Effect of anti-VEGF antibody on alveolar exudate leakage due to dual PD-L1/PD-L2 blockade

(A) Incidence of moist rale (n=18–24/group). (B) Albumin concentration in BALF (n=11–16/group).

Data are shown as the mean + SD. Statistical analysis used Wilcoxon rank sum test and the Holm–Bonferroni method. *, P < 0.05; NS, not significant. (C) VEGF concentration in lung tissues (n=6/group). Data are shown as the mean + SD. Statistical analysis used Wilcoxon rank sum test and the Holm–Bonferroni method. *, P < 0.05; NS, not significant.

Figure 6. Incidence rates of pneumonitis and outcome rates of patients with pneumonitis in the phase III IMpower150 trial

Incidence rates of pneumonitis and rates of “Not recovered / Not resolved” outcomes in patients with pneumonitis in the atezolizumab + carboplatin + paclitaxel group (ACP, n=400) and in the atezolizumab + bevacizumab + carboplatin + paclitaxel group (ABCP, n=393).
Fig. 2

A  PD-L1

Macrophages (F4/80+ CD11c−)

CD103+ DCs (CD103+ CD11c+)

CD103− DCs (CD103− CD11c+)

Neutrophils (CD11b+ Gr1high)

B  PD-L2

Control  IL-2/18

Control  IL-2/18

Isotype Stain

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Fig. 3

A. Around blood vessel

B. Alveoli

Control

C. IL-2/18 + anti-PD-L1 + anti-PD-L2

D.

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Fig. 6

ACP (n=400)

- Pneumonitis: 4.3% (17)
- Not Recovered / Not Resolved: 29.4% (5)

ABCP (n=393)

- Pneumonitis: 2.8% (11)
- Not Recovered / Not Resolved: 9.1% (1)
Molecular Cancer Therapeutics

Anti-VEGF antibody protects against alveolar exudate leakage caused by vascular hyperpermeability, resulting in mitigation of pneumonitis induced by immunotherapy

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