Annals of Clinical and Medical Case Reports®

ISSN 2639-8109 Volume 15

Case Report Open Access

Proof of Efficacy and Safety of Activated NK Cell Immunotherapy (ANK Therapy) for Various Types of Cancer, and Investigation into The Possibility That PD-L1 Is Useful as A Biomarker for Predicting Efficacy

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Received: 16 Jan 2026
Accepted: 03 Feb 2026
Published: 06 Feb 2026
J Short Name: ACMCR

Citation:

Kenjiro Nagai, Proof of Efficacy and Safety of Activated NK Cell Immunotherapy (ANK Therapy) for Various Types of Cancer, and Investigation into The Possibility That PD-L1 Is Useful as A Biomarker for Predicting Efficacy. Ann Clin Med Case Rep® 2026; V15(11): 1-4

1. Introduction

Activated natural killer cell immunotherapy (ANK therapy) is a treatment in which NK cells are extracted from the patient's own blood, expanded, activated, and then returned to the body, enhancing their ability to attack cancer. ANK therapy is theoretically considered to be effective against all types of cancer. Since there have been reports [1] that it is particularly effective against blood cancers, we investigated whether it is effective against adult T-cell lymphoma (ATL) and malignant lymphoma, etc., and although there have been reports of cases in which it is extremely effective against certain solid cancers, we investigated what types of cases are likely to be effective, the mechanism by which ANK therapy is effective, and whether there are any biomarkers, etc., and published the results in a paper.

2. Cases, Results, and Discussion

2.1. Case 1

HTLV-1-associated bronchiolo-alveolar disorder (HABA), a lung lesion in smoldering ATL, 81-year-old female with dyspnea and coughing symptoms [2], Case 2: 91-year-old female with advanced diffuse large B-cell lymphoma (DLBCL), stage II with multiple enlargement of the right axillary and subclavian lymph nodes [3], and Case 3: 71-year-old male with prostate cancer diagnosed with multiple bone metastases [4]. ANK therapy was performed on three cases. ANK therapy was highly effective for cases 1, 2, and 3. Images and respiratory function test changes for case 1 are shown in Figure 1&2. Images for case 2 are shown in Figure 3. Images for case 3 are shown in Figure 4. It has been reported that ANK cells kill PD-L1-positive tumor cells [5], and it has been reported that structures with deleted or enhanced PD-L1 3'-UTR are frequently found in ATL, and that PD-L1 expression is significantly increased [6]. Therefore, ANK therapy is thought to be effective against ATL. In addition, the following reasons may be considered for its effectiveness against DLBCL: 1. There are many PD-L1-positive tumor cells [7] 2. Repeated administration of NK cells can reduce the immunosuppressive state mediated by the PD-1PD-L1 pathway [8,9]. The reports so far suggest that the higher the PD-L1 positivity rate, the higher the therapeutic effect of ANK therapy.The third case of solid cancer, prostate cancer, is likely to be highly effective, as the PD-L1 positivity rate may be high, and PD-L1 immunostaining was confirmed in biopsied tissue Figure 5.

In the guideline treatment for ATL and DLBCL, combination therapy with cytotoxic antitumor drugs is the mainstream, and because of the difficulty of side effects, it may not be possible to treat elderly patients. However, ANK therapy is a safe treatment with few side effects.

Pulmonary function tests				
	Before treatment		After treatment	
	Measured value	% predicted value	Measured value	% predicted value
Vital Capacity (VC)	0.93 L	46.5%	1.54 L	78.6%
Forced Vital Capacity (FVC)	0.88 L	44%	1.18 L	60.2%
Forced Expiratory Volume in one second (FEV1.0)	0.83 L	57.6%	1.12 L	82.4%
%Forced Expiratory Volume in one second (FEV1.0%)	94.3%	127%	94.9%	128.5%

Figure 1: Pulmonary function test findings before and after treatment in a case of HABA with smoldering ATL.

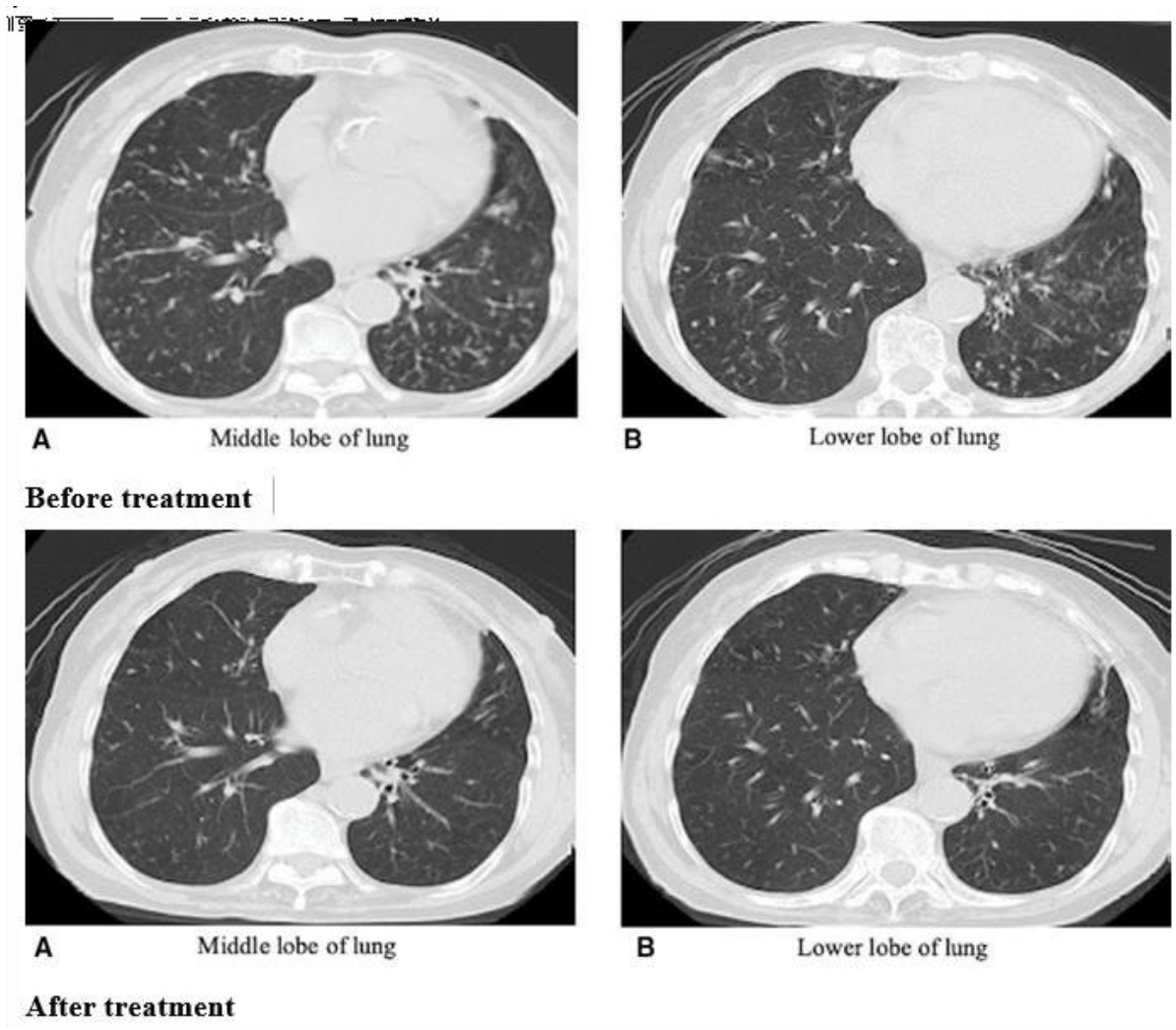
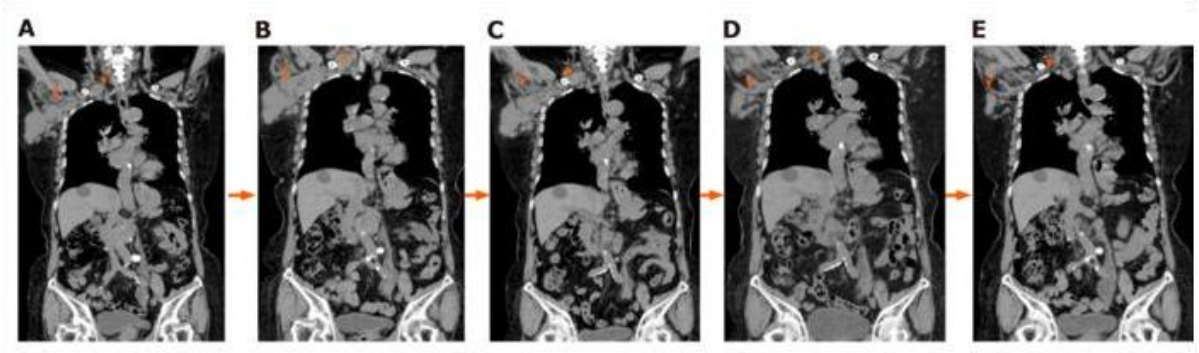


Figure2: CT imaging findings before and after treatment of a case of HABA with smoldering ATL.



A: At diagnosis B: Before treatment C, D: After treatment started E: After treatment ended.

Figure3: CT image changes before and after ANK therapy for DLBCL.

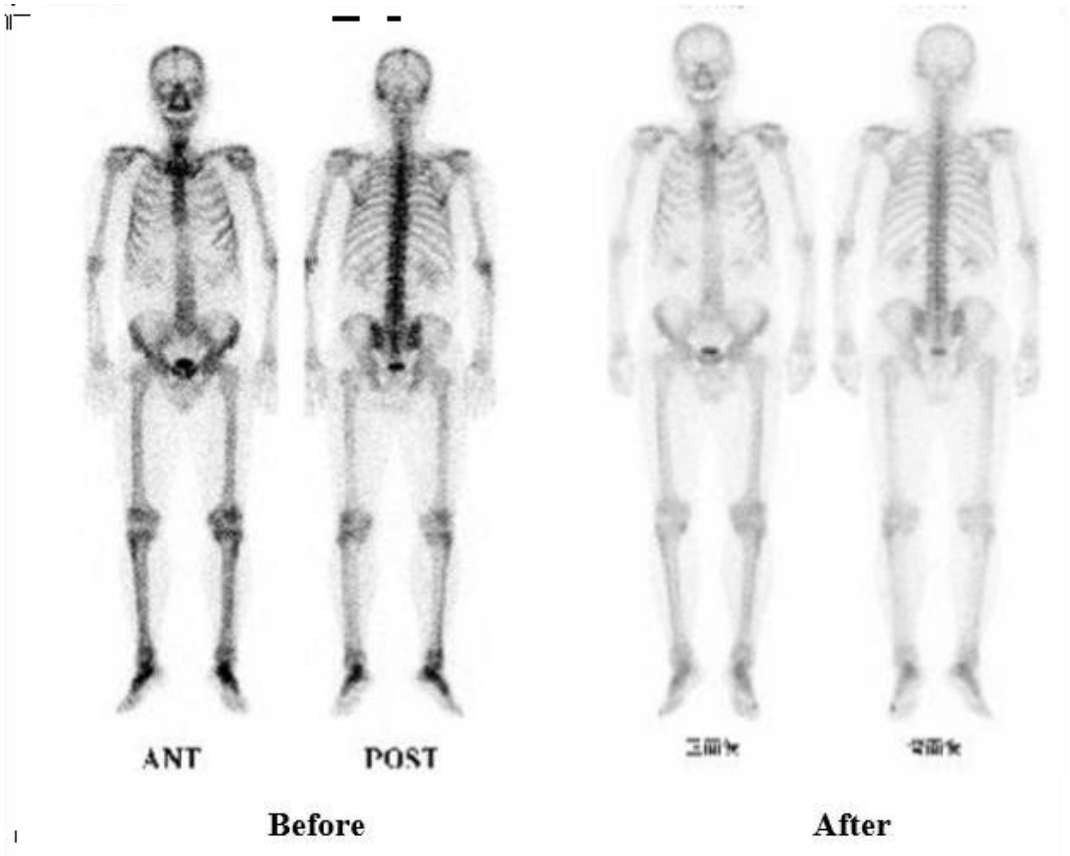


Figure 5: PD-L1 IHC 28-8 pharmDx ×200 Brown PD-L1 positive cells are generally observed in the cytoplasm of tumor cells.

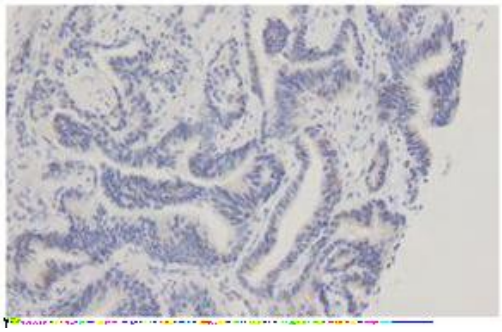


Figure 4:Bone scintigraphy findings before and after treatment in patients with multiple bone metastases from prostate cancer.

3. Summary

From the papers reported so far, ANK therapy is particularly effective for ATL and DLBCL, which have many PD-L1 positive tumor cells, and it may be possible to predict the effectiveness of treatment using the PD-L1 positivity rate as a biomarker for solid cancers, such as gastric cancer, esophageal cancer, and cervical cancer, which may have many PD-L1 positive tumor cells. In terms of safety, it uses non-cytotoxic NK cells, which have fewer side effects than existing cytotoxic antitumor drugs, and it may be possible for even elderly people to undergo treatment without having to give up.Right axillary lymph node swelling and subclavian lymph node swelling significantly reduced after ANK treatment.

4. Acknowledgement

Thank you to Professor. Fukumoto Manabu for consulting me about pathology findings.

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