

Improved outcomes with pembrolizumab treatment in two cases of double cancer  
including non-small cell lung cancer

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## Short Running title

Pembrolizumab in double cancer including non-small cell lung cancer

## Abbreviations

PD-1: Programmed death-1

NSCLC: Non-small cell lung cancer

FDA: The Food and Drug Administration

## **Abstract**

Lung cancer is a major health concern worldwide, but new immunotherapeutic treatments for lung cancer have shown great promise and the prognosis for many severe cancers including lung cancer has been improving. In May 2017, the Food and Drug Administration's approved pembrolizumab, a therapeutic antibody that blocks lymphocytic programmed death-1 (PD-1), as a first-line treatment for any solid tumor with specific genetic features. Pembrolizumab is a therapeutic antibody that blocks lymphocytic programmed death-1 (PD-1), the ligand of which (PD-L1) is expressed on tumor cells and which can prevent the immune system from recognizing and destroying tumors. Here, we report 2 cases of double cancer (Case 1: lung and bladder cancer; Case 2: gastric and lung cancer) in which Pembrolizumab was effective for treatment of both cancers in each patient.

## **Introduction**

Lung cancer is a major health concern worldwide—with an estimated 1.8 million new cases globally in 2012 representing 12.9% of all new cancer cases [1, 2]. New immunotherapeutic treatments for lung cancer that exploit or protect immune surveillance have shown great promise. The immune system can recognize and destroy tumors, but can be prevented from doing so by programmed death ligand-1 (PD-L1) that is expressed on tumor cells. PD-L1 binds to programmed death-1 (PD-1) on cytotoxic T cells to inhibit their activity and up to 68% of non-small cell lung cancer (NSCLC) cases reportedly express PD-L1 [3-6]. In 2014, the Food and Drug Administration (FDA) approved pembrolizumab, a therapeutic antibody that blocks lymphocytic PD-1, for the treatment of advanced NSCLC. However, there is currently no standard treatment for double cancer (which is usually diagnosed in older people) as it is difficult to perform a large-scale study. As various treatment modalities are being developed, the prognosis of many severe cancers (including lung cancer) is improving and FDA approval (May 2017) of pembrolizumab as a first-line treatment for any solid tumor with certain genetic features has contributed to that improvement.

Here, we report 2 cases of double cancer involving NSCLC in which pembrolizumab was effective for treatment of both cancers. In Case 1, during lung

cancer treatment, symptoms related to another solid tumor progressed. In Case 2, during gastric cancer treatment, symptoms due to lung cancer progression were observed.

## **Case presentation**

### Case 1

An 83-year-old man presented with an abnormal opacity on chest radiography during a health check. He had a 63 pack-year history of smoking and a history of cerebellar infarction, diabetes, and lumbar disc herniation. No obvious family history for cancer was found. Chest CT revealed a 33-mm mass at the S3 region of the left lung and the subaortic lymph node was swollen (24 mm). Bronchoscopic lung biopsy was performed and he was diagnosed with stage IIIA squamous cell carcinoma (cT2aN2M0). Because evidence for chemoradiotherapy is poor for people over the age of 80, chemotherapy alone was performed with 4 cycles of carboplatin in addition to paclitaxel. Evaluation at the end of the fourth course showed that the disease remained progressive but the patient and his family requested a second-line treatment other than cytotoxic anticancer drugs. PD-1 inhibitors have demonstrated durable clinical responses in patients with lung squamous cell carcinoma; therefore, Nivolumab, the only immune-checkpoint inhibitor available in Japan at that time, was adopted as a

second-line treatment. By the end of the second course of nivolumab treatment, rapid shrinking of the lung tumor was observed. At the end of the fifth course of nivolumab, however, the patient was hospitalized for general malaise and an increase in inflammatory response. After hospitalization, no evidence of regrowth of the lung tumor was found, however, the patient exhibited hematuria. Whole-body computed tomographic examination found a protruding tumor in the bladder—a finding consistent with the presence of bladder cancer. Urothelial carcinoma was diagnosed with cytology. As the examined lung tissue was 70% positive for PD-L1 expression, pembrolizumab was selected as a third-line therapy. Interestingly, there is also evidence suggesting that pembrolizumab may be effective for urological cancer [7]. After pembrolizumab treatment, the macroscopic hematuria was almost fully resolved. The patient is currently receiving a thirteenth course of pembrolizumab without major side effects. The lung tumor has not increased in size and bladder cancer progression has not been observed (Figure 1, 2).

## Case 2

A 78-year-old man with a history of diabetes and hypertension who had received oxaliplatin in addition to S-1 treatment for stage IV gastric cancer was



examined in our hospital. During the course of chemotherapy for gastric cancer, a small nodule (5 mm) at the S3 region of the left lung was found on chest CT. Although the gastric cancer and the intraperitoneal lymph node showed good response to the chemotherapy, the lung tumor gradually increased to 31 × 25 mm in size with enlargement of a mediastinal lymph node and a right adrenal gland tumor. The lung tumor was diagnosed as stage IVB (cT4N2M1b) squamous cell carcinoma. Obstruction in the left main lung bronchus occurred due to the increasing size of the left lung tumor and the patient's general condition showed deterioration (ECOG status 2). While waiting for the results of PD-L1 expression testing, chemotherapy with carboplatin in addition to nab-paclitaxel (adjusted for lung and gastric cancer) was administered. However, on day 6, pneumonia-triggered septic shock occurred for which noradrenaline was administered, making continuation of the chemotherapy difficult. As the PD-L1 expression of the examined lung cancer tissue was 90% positive after 2 weeks, pembrolizumab was administered as a second-line treatment. The lung tumor shrank rapidly thereafter and the gastric cancer also resolved without recurrence (verified by endoscopic examination) (Figures 3 and 4). There were no major side effects and the patient is currently receiving a fourth pembrolizumab course.

## **Discussion**

We have introduced 2 cases of double cancer that showed good response to pembrolizumab. In the first case, the lung cancer was successfully treated with another immune checkpoint inhibitor, but the comorbid bladder cancer progressed, and the patient's general condition worsened. In the second case, the treatment of the gastric cancer was efficacious with another cytotoxic agent, but the lung cancer progressed, and the patient's general condition worsened. The findings of these 2 cases might appear contradictory, but in such cases of double cancer in elderly people, the initially diagnosed cancer is more likely than the second cancer to be treated effectively. Although lung cancer treatment is developing rapidly, the increasing complexity of multiple metastases, genetic components, and comorbidities confound standardization of therapy. To this end, it has been proposed that treatments be classified based on presence or absence of brain metastasis, since the blood brain barrier, as well as genetic mutations could be important complicating factors [8].

The KEYNOTE-010 Study (NCT01905657) was a randomized, open-label, phase II and III clinical trial comparing the safety and efficacy of pembrolizumab with that of docetaxel in patients with PD-L1-expressing NSCLC tumors [9]. Pembrolizumab demonstrated an improved overall survival (OS) benefit at both the tested doses in the

total population compared with docetaxel. Pembrolizumab also had a better safety profile than docetaxel, with fewer high-grade adverse effects [9]. Many studies have reported the efficacy of pembrolizumab in bladder cancer and, recently, its economic effects have also been reported [10-12]. Additionally, as with other immune checkpoint inhibitors like nivolumab, the efficacy of pembrolizumab even for gastric cancer cases was reported in the KEYNOTE-059 study [13]. Compared to relatively rare cancers such as malignant melanoma, simultaneous occurrence of secondary cancer is more frequently observed with lung cancer due to the larger number of patients.

Due to global aging, it is likely that pulmonologists will have to treat increasing numbers patients diagnosed with multiple cancers. In the past, for patients with lung cancer who developed other uncontrolled cancers, palliative care was the only option when the lung cancer did not respond to general anticancer drugs. However, as it is now possible to use immune checkpoint inhibitors, which have few side effects and are indicated for many solid tumors, more patients with double cancer can be successfully treated as in the cases presented here. Recently, attempts have been made to combine several target molecules for treatment [14,15]. Lung cancer itself is a heterozygous disorder and has been considered difficult to control even when targeting a single molecule. However, there is a possibility that such multicarrier targeted

anticancer drugs combined with checkpoint inhibitors will enable the more effective treatment of multiple cancers. In the literature, it seems as if immunity checkpoint inhibitors are only compared to cytotoxic anticancer drugs but even in multiple cancers we can firmly diagnose the molecular features of cancer by biopsy. This leads to the idea that using dual (or multi)-targeted proteins based on individualized molecular features might be more effective than blanket antibody or cytotoxic treatments and this possibility remains to be fully investigated.

Because pembrolizumab requires a pathological assessment via biopsy of the lung tumor or its metastatic lesion, these cases have primarily come to the respiratory medicine departments of hospitals. However, immune checkpoint inhibitors may be used more often for the treatment of multiple cancers in many clinical departments as knowledge regarding their indication increases.

## **Conclusion**

With the rapidly aging global population, diagnoses of double cancer cases are increasing and palliative care was, until recently, the only option for many of these patients. However, as demonstrated in the 2 cases presented here, innovative new treatments for solid tumors (such as immune checkpoint inhibitors like pembrolizumab)

have opened further avenues to treat lung cancer more effectively, even when it is comorbid with other cancers.

## Supplementary

### Detailed treatment information case 1

1<sup>st</sup> line CBDCA+PTX #1-4

2<sup>nd</sup> line Nivolumab #1-5

3<sup>rd</sup> line Pembrolizumab #1-

### Detailed treatment information case 2

1<sup>st</sup> line CBDCA+nabPTX #1

2<sup>nd</sup> line Pembrolizumab #1-

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## Conflict of interest

The authors report no conflict of interest.

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## Figures

### Figure 1

(a) Chest X-ray before Nivolumab treatment. A tumor can be observed in the left hilar area.

(b) Chest X-ray after the 13th course of Pembrolizumab. The tumor showed a marked shrinkage in size.

### Figure 2

(a) Lower abdomen CT after 5 Nivolumab courses. A protruding tumor can be observed in the bladder. Because of hematuria, a catheter was placed in the bladder.

(b) Lower abdomen CT after the end of 13 courses of Pembrolizumab. Macroscopic hematuria has disappeared. The bladder mass has remained, but without increase in size.

### Figure 3

(a) Chest X-ray before Pembrolizumab treatment. A tumor can be observed in the left hilar area.

(b) Chest X-ray after the 4th course of Pembrolizuma. The tumor showed a marked shrinkage in size.

Figure 4

(a) (b) Gastric fiber findings before any treatment. Blood is accumulated in the stomach.

A Borrmann type III lesion is recognized on the wall just behind the cardia. Bleeding continues from the ulcer. A biopsy was conducted from the surrounding embankment, which confirmed gastric cancer.

(c) Gastric fiber findings after 4 courses of Pembrolizumab. Gastric cancer at the same location cannot be confirmed with the camera. (d) Narrow band imaging findings from the same site.