Efficacies of programmed cell death 1 ligand 1 blockade in non-small cell lung cancer patients with acquired resistance to prior programmed cell death 1 inhibitor and development of diabetic ketoacidosis caused by two different etiologies: a retrospective case series

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Abstract. The programmed cell death 1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) axis is vital for immune resistance during tumor development, while PD-L1 inhibitors can also inhibit the PD-L1/B7-1 (CD80) interaction, indicating one of the molecular differences between PD-1 and PD-L1 inhibitors. However, the clinical benefits of PD-L1 inhibitors in patients previously treated with PD-1 inhibitors remain unknown. In this study, we retrospectively analyzed the clinical data of eight patients with non-small cell lung cancer who received the PD-L1 inhibitor atezolizumab and previously treated with the PD-1 inhibitor nivolumab. The median progression-free survival was 2.1 months (1.8–18.7 months), and 4 of 8 patients achieved at least stable disease. In two of these patients, atezolizumab treatment resulted in longer progression-free survival (PFS) compared with that of nivolumab. Conversely, one patient exhibited grade 4 diabetic ketoacidosis (DKA) within 2 weeks after the initial administration of atezolizumab. Another patient had developed type 1 diabetes mellitus (T1DM) during the prior nivolumab treatment and then developed DKA due to an infection after the initiation of atezolizumab. Both of them had high-risk human leukocyte antigen-DR/DQ types relevant to T1DM. These results demonstrate the potential efficacy of PD-L1 inhibitors to some tumors that have acquired resistance to PD-1 inhibitors and suggest that appropriate managements are required for not only a newly onset of T1DM but also blood glucose control after the development of T1DM during a reiteration of the PD-1/PD-L1 blockade.

Key words: Reiteration of the programmed cell death 1/programmed cell death 1 ligand 1 immune blockade, Type-1 diabetes mellitus, Diabetic ketoacidosis, Non-small cell lung cancer

Rapid Communication

DEVELOPMENT OF IMMUNE CHECKPOINT INHIBITORS (ICIs) results in prolonged survival in patients with various cancers. Programmed cell death 1 (PD-1) is highly expressed in tumor-infiltrating lymphocytes, and its ligands (PD-L1) are constitutively expressed or upregulated in many different types of tumor cells. The PD-1/PD-L1 axis is vital for innate and adaptive immune resistance during tumor development.

PD-L1 also interacts with B7-1 (CD80) leading to the promotion of tumor immune tolerance [1, 2]. Meanwhile, PD-1 also interacts with programmed cell death 2 (PD-L2), which is primarily restricted to antigen-presenting cells and is inducibly expressed on other hematopoietic cells [3]. Therefore, PD-1 inhibitors block both the interaction of PD-1/PD-L1 and PD-1/PD-L2, whereas PD-L1 inhibitor does not bind to PD-L2, indicating less disruption of peripheral immune homeostasis. These molecular differences represent a distinctive feature of PD-L1 inhibitors compared with PD-1 inhibitors.

The anti-PD-L1 monoclonal antibody, atezolizumab, increases T cell-mediated immunity against tumors by blocking the interaction of PD-L1 with PD-1 and B7-1.
Phase III clinical trials (OAK) have shown a statistically significant superiority of atezolizumab over docetaxel in non-small cell lung cancer (NSCLC) patients who had failed prior platinum therapy, and atezolizumab is associated with a favorable safety profile [4]. The incidence of immune-related adverse events (irAEs) in PD-L1 monotherapy has been shown to be approximately 30% (5.0%–6.0% grade 3/4) [4, 5]. Of these, the incidence of severe metabolic disorders, including diabetic ketoacidosis (DKA) and type-1 diabetes mellitus (T1DM), was reported as less than 1.0% [6-8]. The efficacy and safety profile of atezolizumab after platinum therapy failure is well characterized; however, the clinical benefits of atezolizumab in patients previously treated with PD-1 inhibitors remain unknown. We retrospectively reviewed our patient cohort to evaluate the efficacy and safety of atezolizumab in NSCLC patients previously treated with the PD-1 inhibitor, nivolumab. The results included two cases of DKA with extremely acute onset after atezolizumab administration.

Materials and Methods

This retrospective cohort study was conducted with the approval of the ethical review committee of Nagoya University Hospital and was in accordance with the guidelines of the Declaration of Helsinki [9, 10]. We retrospectively reviewed the medical records of patients between September 2015 and February 2020. Patients enrolled for this study were selected based on the following eligibility criteria: (1) diagnosed as having stage III/IV or recurrent NSCLC as confirmed by histological or cytological examination, (2) Eastern Cooperative Oncology Group (ECOG) performance status 0–1, and (3) having received atezolizumab after prior nivolumab monotherapy. The demographic and clinical information of eligible patients, including age, sex, smoking history, histological subtype, clinical stage of disease at diagnosis, performance status, treatment outcome, and PD-L1 status, were retrospectively obtained from medical records. Clinical stages were assigned according to the seventh edition of the American Joint Committee on Cancer. Objective tumor responses were evaluated as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and irAEs were assessed according to the Common Terminology Criteria for Adverse Events, version 5.0. PD-L1 expression was assessed in formalin-fixed tumor samples by immunohistochemistry using the 22C3 pharmDx assay (Agilent, Santa Clara, CA, USA).

Cases 1, 2, 4, 5, 6, 7, and 8 were included in a previous study for analyzing the development of thyroid dysfunction induced by anti-PD-1 antibodies [11]. All cases were included in another study analyzing the association of internal echo patterns in the thyroid associated with the development of thyroid dysfunction [12].

PFS was estimated by the Kaplan-Meier method and was defined as the time from the start of ICI treatment to disease progression or death, whichever was earlier. The data were censored at the last follow-up date. Statistical analyses were performed using GraphPad Prism software (Version 7.0).

Results

The efficacy and safety of atezolizumab in NSCLC patients previously receiving nivolumab

To investigate the clinical benefits of atezolizumab monotherapy in patients previously treated with nivolumab, we retrospectively analyzed the clinical data of 8 eligible patients with advanced NSCLC. The median patient age was 60.5 years and the performance status was 0 for seven patients (Table 1). PD-L1 tumor proportion scores (TPS) were ≥50% for 3 patients and 1%–49% for 1 patient. Nivolumab treatment was discontinued in 7 patients due to disease progression, and the other one was changed to other regimen because of this side effect. The treatment profile is shown in Fig. 1 and Table 2. The median number of cycles for atezolizumab monotherapy was 2.5 cycles (range 1–27 cycles), and the median progression-free survival (PFS) and disease control rate (DCR) were 2.1 months (range 1.8–18.7 months) and 50%, respectively. In two patients (Case 1 and 2), atezolizumab showed longer PFS than those of nivolumab, including one patient (Case 2) with SD over 5 months, although he experienced disease progression during the prior nivolumab monotherapy within 1.5 months. The two patients had not received radiation therapy during the prior nivolumab to atezolizumab transition period. The adverse events are summarized in Table 3. During the course of treatment with atezolizumab, DKA was observed in two cases with acute onset after the initial administration. One patient had not experienced any symptoms during prior nivolumab treatment at 8.0 months (Case 3), while the other patient had grade 4 hyperglycemia after 14 cycles of prior nivolumab monotherapy (Case 4). Furthermore, we performed human leukocyte antigen (HLA) typing in the patients and found that both of them had the HLA-DRB1*04:05 and -DQB1*04:01 haplotype, which are associated with a high-risk of TIDM in Asian patients [13] (Table 4).
Table 1  Patients characteristics

| Characteristics         |       |
|-------------------------|-------|
| Age (years)             | 60.5  (50–74) |
| Body Mass Index (kg/m²) | 22.0  (15.78–27.15) |
| Brinkman index          | 1,046 (0–1,800) |

| Sex          | Count |
|--------------|-------|
| male         | 6     |
| female       | 2     |

| Histopathology                  | Count |
|---------------------------------|-------|
| Adenocarcinoma                  | 3     |
| Squamous cell carcinoma         | 2     |
| Large cell carcinoma            | 2     |
| Pleomorphic carcinoma           | 1     |

| Performance status  | Count |
|---------------------|-------|
| 0                   | 7     |
| 1                   | 1     |

| PD-L1 expression          | Count |
|---------------------------|-------|
| TPS 50%≤                  | 3     |
| 1% ≤ TPS < 50%            | 1     |
| <TPS 1%                   | 2     |
| Unmeasurable              | 2     |

| Clinical staging              | Count |
|-------------------------------|-------|
| Stage IIIIB                   | 1     |
| Stage IV                      | 1     |
| Recurrence                    | 6     |

EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; TPS, tumor proportion score

Case presentation with DKA

Case 3

A 62-year-old man was diagnosed with recurrent lung squamous cell carcinoma with a TPS of 30%–40%, 23.7 months after right lower lobe lobectomy. He had no other underlying diseases such as diabetes mellitus. As 4th line treatment, he received nivolumab for 18 cycles and was discontinued after 8.2 months due to disease progression. Thereafter, he received docetaxel; however, his tumor grew rapidly. Then, atezolizumab monotherapy was administered. Although his fasting blood glucose was 72 mg/dL before atezolizumab treatment, just 15 days after the first administration, he was hospitalized with thirst, vomiting, high fever, and extremely high serum glucose levels with acidemia (Fig. 2A and Table 5). He was diagnosed with DKA and fulminant T1DM as an irAE. After one-month treatment of intensive insulin therapy consisting of four injections per day, his blood glucose level had stabilized. Despite the severe adverse effects, the tumor exhibited a partial remission for 3.7 months.

Case 4

A 51-year-old man with type-2 diabetes mellitus (T2DM) was diagnosed with recurrent stage IA large cell carcinoma with a TPS of ≥50%, 36.7 months after left upper lung lobectomy. As 3rd line treatment, he received nivolumab monotherapy. Although T2DM was controlled and stable for two decades with oral diabetes drugs, his fasting blood glucose suddenly increased after 14 cycles (Fig. 2B and Table 5). At this time, serum levels of c-peptide were preserved (2.84 ng/mL). Subsequent evaluation of his endogenous insulin secretion revealed the development of insulin dependence (serum c-peptide; <0.1 ng/mL). Based on these data, he was diagnosed with T1DM irAE induced by nivolumab. Blood glucose levels were controlled by intensive insulin therapy, while the nivolumab monotherapy was continued for 51 cycles until disease progression. Thereafter, he received cytotoxic chemotherapy, but the tumor rapidly recurred. As 6th line treatment, atezolizumab was initiated. He experienced a high fever, thirst, and lightheadedness 13 days after the initial administration, and was urgently hospitalized with an extremely high blood glucose level (Fig. 2B and Table 5). He was diagnosed with preshock and DKA caused by an infectious fever. Although the results of the bacteria culture tests of his blood, sputum, and urine samples were all negative, we speculated septic fever caused by stent-associated cholangitis because he had a medical history of cholangitis because of bile duct stenosis. We adjusted the insulin dose and simultaneously treated him using broad-spectrum antibiotics; thereafter, the ketoacidosis immediately improved, and the patient gradually recovered. Once his blood glucose level had been stabilized, atezolizumab treatment was restarted for...
two retrospective studies investigated the effectiveness of switching therapy from PD-1 inhibitors to atezolizumab as an ICI rechallenge, however, their clinical efficacies are limited due to disease progression. Hence, ICI rechallenge may represent a rational therapeutic option for subsequent regimens. Recently, two retrospective studies investigated the effectiveness of primarily PD-1 inhibitor retreatment in advanced NSCLC, and showed that PFS and DCR were 1.6–3.1 months and 21.4%–41.7%, respectively [15, 16]. Most of the responsive cases included radiation therapy before PD-1 inhibitor retreatment, suggesting that abscopal effects influenced the clinical results. On the other hand, Kitagawa et al. reported the clinical efficacies of switching therapy from PD-1 inhibitors to atezolizumab as an ICI rechallenge, and the PFS and DCR were 4.0 months and 58.8%, respectively, indicating that the switching treatment strategy showed some clinical benefits [17]. In our dataset, 2 out of 8 cases exhibited longer PFS for atezolizumab therapy compared with those with prior nivolumab without radiation. In case 1, the prior nivolumab

### Table 2 Clinical courses after nivolumab monotherapy

| Case | 2C3 TPS (%) | Cycles | PFS (months) | Best response | Regimens | Cycles (Interval months) | RT (Gy) | Best response | Cycles | PFS (months) | Best response |
|------|-------------|--------|--------------|---------------|----------|--------------------------|---------|---------------|--------|--------------|---------------|
| Case 1 | <1 | 9 | 11.6 | SD | — | — | — | — | 27 | 18.7 | SD |
| Case 2 | <1 | 5 | 1.4 | PD | DTX + RAM | 12 (19.1) | — | PR | 7 | 5.5 | SD |
| Case 3 | 30–40 | 18 | 8.2 | SD | DTX | 3 (8.7) | 30 | SD | 1 | 3.7 | SD |
| Case 4 | 50≤ | 51 | 26.4 | PR | S-1/CPT-11 | 5/2 (25.0) | 39 | SD/PD | 1 | 1.8 | PD |
| Case 5 | not measured | 48 | 24.0 | SD | — | — | — | — | 1 | 2.0 | SD |
| Case 6 | not measured | 3 | 1.8 | PD | — | — | — | — | 4 | 2.2 | PD |
| Case 7 | 50≤ | 34 | 16.1 | SD | S-1/VNB | 2/16 (31.7) | — | NE/SD | 3 | 2.0 | PD |
| Case 8 | 70 | 15 | 8.1 | SD | S-1/DTX/VNB | 14/4/4 (23.8) | — | SD/SD/SD | 2 | 1.8 | PD |

Anti-PD-L1, anti-programmed death-ligand 1; anti-PD-1, anti-programmed death 1; ICI, immune checkpoint inhibitors; TPS, tumor proportion score; PFS, progression-free survival; RT, radiotherapy; PR, partial response; SD, stable disease; NE, not evaluable; VNB, vinorelbine; DTX, docetaxel; RAM, ramucirumab

### Table 3 Profiles of adverse events

| Immune-related adverse events | Nivolumab | Atezolizumab |
|------------------------------|-----------|--------------|
| G1-2 | G3 | G4 | G1-2 | G3 | G4 |
| Rash maculopapular | 1 | 0 | 0 | 1 | 0 | 0 |
| Fatigue | 2 | 0 | 0 | 2 | 0 | 0 |
| Cough | 1 | 0 | 0 | 0 | 0 | 0 |
| Fever | 1 | 0 | 0 | 4 | 0 | 0 |
| Infection | 0 | 0 | 0 | 0 | 0 | 0 |
| Arthritis | 2 | 0 | 0 | 1 | 0 | 0 |
| Acidosis | 0 | 0 | 0 | 0 | 0 | 2 |
| Hyperglycemia | 0 | 1* | 0 | 0 | 0 | 2** |
| Hyperthyroidism | 1 | 0 | 0 | 0 | 0 | 0 |
| Hypothyroidism | 0 | 0 | 0 | 1 | 0 | 0 |
| Ileus | 0 | 0 | 0 | 0 | 1 | 0 |
| Adrenal insufficiency | 0 | 1 | 0 | 0 | 0 | 0 |
| Autoimmune disorder | 0 | 0 | 0 | 0 | 1 | 0 |

* One patient exhibited hyperglycemia due to an immune-related adverse event after the atezolizumab administration. ** The other patient who had developed type 1 diabetes induced by nivolumab exhibited hyperglycemia due to an infection after atezolizumab administration.

### Discussion

Currently, a large number of patients with advanced NSCLC receive ICIs upfront in combination with platinum-based chemotherapy. Nevertheless, the majority are unable to continue initial ICI treatment due to progressive disease. Therefore, clinicians must select subsequent therapeutic regimens despite the paucity of clinical evidence to support their efficacy. As cytotoxic agents, pemetrexed, tegafur-gimeracil-oteracil, or docetaxel ± ramucirumab are generally considered as 2nd line treatment, however, their clinical efficacies are limited [14]. Hence, ICI rechallenge may represent a rational therapeutic option for subsequent regimens. Recently, two retrospective studies investigated the effectiveness of primarily PD-1 inhibitor retreatment in advanced NSCLC, and showed that PFS and DCR were 1.6–3.1 months and 21.4%–41.7%, respectively [15, 16]. Most of the responsive cases included radiation therapy before PD-1 inhibitor retreatment, suggesting that abscopal effects influenced the clinical results. On the other hand, Kitagawa et al. reported the clinical efficacies of switching therapy from PD-1 inhibitors to atezolizumab as an ICI rechallenge, and the PFS and DCR were 4.0 months and 58.8%, respectively, indicating that the switching treatment strategy showed some clinical benefits [17]. In

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Table 4  Human leukocyte antigen (HLA) alleles of the 8 cases

| Case | HLA-A      | HLA-B      | HLA-C      | HLA-DRB1 | HLA-DQ1B | HLA-DPB1 |
|------|------------|------------|------------|----------|----------|----------|
| 1    | A*02:01   | A*11:01   | B*15:18    | C*01:02  | DRB1*04:05 | DQB1*03:01 | DPB1*05:01 |
| 2    | A*01:01   | A*24:02   | B*37:01    | C*01:02  | DRB1*04:05 | DQB1*04:01 | DPB1*05:01 |
| 3    | A*24:02   | A*31:01   | B*40:06    | C*08:01  | DRB1*12:01 | DQB1*04:01 | DPB1*14:01 |
| 4    | A*02:07   | A*24:02   | B*35:01    | C*01:02  | DRB1*04:05 | DQB1*03:01 | DPB1*05:01 |
| 5    | A*24:02   | A*24:02   | B*15:07    | C*01:02  | DRB1*04:03 | DQB1*06:01 | DPB1*14:01 |
| 6    | A*24:02   | A*24:02   | B*52:01    | C*12:02  | DRB1*15:02 | DQB1*03:02 | DPB1*09:01 |
| 7    | A*11:01   | A*24:02   | B*13:01    | C*07:02  | DRB1*12:02 | DQB1*03:01 | DPB1*05:01 |
| 8    | A*11:01   | A*31:01   | B*15:01    | B*56:03  | DRB1*15:01 | DQB1*03:01 | DPB1*05:01 |

HLA alleles associated with susceptible to spontaneous T1DM filled with light gray, and protective to spontaneous T1DM with dark gray.
had developed T1DM irAE during the prior nivolumab treatment, infection after the initiation of atezolizumab was a trigger of DKA. It is well known that patients with T1DM can develop DKA when they are sick, including infections. Our results indicate that patients with T1DM irAE require an appropriate management of blood glucose control and sick-days for prolonged periods. A previous study showed that immune blockade rechallenges using different types of ICIs confer a high risk of irAE recurrence, which had occurred during the initial ICI treatment, while most of them were mild and manageable [17, 27]. In our dataset, 4 of 8 cases had some irAEs such as arthritis, T1DM, hypothyroidism, and secondary adrenal insufficiency during the prior nivolumab treatment (Table 3). However, in the later atezolizumab treatments, further exacerbation was not observed. To address the clinical benefits of switching the ICI treatment in cases with irAE development, further study would be required.

**Conclusion**

Our results indicate that the anti-PD-L1 antibody, atezolizumab, is potentially effective to some tumors that have acquired resistance to the anti-PD-1 antibodies, nivolumab and that appropriate managements are required for not only a newly onset of T1DM but also blood glucose control after the development of T1DM during a reiteration of the PD-1/PD-L1 blockade. Further large-scale studies are warranted to address the clinical benefits of ICI retreatment.

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**Conflicts of Interest Statements**

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Table 5  Laboratory data of Case 3 and 4 on diagnosis with hyperglycemia

|                         | Case 3 14 days after atezolizumab administration | Case 4 32 weeks after nivolumab administration | Case 4 On the day of atezolizumab administration | 13 days after atezolizumab administration | Reference |
|-------------------------|--------------------------------------------------|-------------------------------------------------|-------------------------------------------------|------------------------------------------|-----------|
| Blood                   |                                                  |                                                 |                                                |                                          |           |
| Glucose, mg/dL          | 1,041                                            | 394                                             | 169                                             | 788                                      | 73–109    |
| HbA1c, %                | 6.9                                              | 8.9                                             | 8.9                                             | 9.3                                      | 4.9–6.0   |
| Urea, mg/dL             | 61.5                                             | 16.9                                            | 13.4                                            | 30.3                                     | 8.0–20.0  |
| Creatinine, mg/dL       | 3.11                                             | 0.78                                            | 0.65                                            | 1.16                                     | 0.65–1.07 |
| eGFR (mL/min/1.73 m²)   | 16.8                                             | 81.5                                            | 97.9                                            | 51.9                                     |           |
| Na, mmol/L              | 120.0                                            | 138.0                                           | 139.0                                           | 127.0                                    | 138.0–145.0 |
| K, mmol/L               | 7.2                                              | 5.3                                             | 4.5                                             | 5.6                                      | 3.6–4.8   |
| Cl, mmol/L              | 80.0                                             | 100.0                                           | 102.0                                           | 86.0                                     | 101.0–108.0 |
| CRP, mg/L               | 4.86                                             | 0.50                                            | 0.71                                            | 21.02                                    | <0.14     |
| Platelet, ×10⁹/μL       | 231                                              | 257                                             | 245                                             | 57                                       | 158–348   |
| Hb, g/dL                | 14.2                                             | 14.0                                            | 13.0                                            | 16.3                                     | 13.7–16.8 |
| WBC, ×10⁹/μL            | 20.4                                             | 7.0                                             | 4.6                                             | 3.2                                      | 3.3–8.6   |
| TSH, μU/mL              | 1.768                                            | 1.599                                           | 3.675                                           | 2.317                                    | 0.350–4.940 |
| FT3, ng/dL              | <1.50                                            | 3.13                                            | 2.69                                            | <1.50                                    | 1.88–3.18 |
| FT4, ng/dL              | 0.73                                             | 1.16                                            | 0.99                                            | 0.76                                     | 0.7–1.48  |
| Total ketone, μmol/L    | 13,100.0                                         | not measured                                    | not measured                                    | 43.6                                     | 26.0–122.0 |
| Insulin, μU/mL          | 11.0                                             | not measured                                    | not measured                                    | 120.0                                    | ≤18.7     |
| C-peptide, ng/mL        | 0.20                                             | 2.84                                            | <0.1                                           | <0.1                                     | 0.6–1.8   |
| GADA, U/mL              | <5.0                                             | not measured                                    | <5.0                                            | <5.0                                     | <5.0      |
| Insulin Ab, % binding   | <0.4                                             | not measured                                    | <0.4                                            | <0.4                                     | <0.4      |
| Arterial blood gas      |                                                  |                                                 |                                                |                                          |           |
| pH                      | 6.938                                            | not measured                                    | not measured                                    | 7.200                                    | 7.350–7.450 |
| PaCO₂, mmHg             | 11.0                                             | not measured                                    | not measured                                    | 23.0                                     | 35.0–48.0 |
| PaO₂, mmHg              | 128.0                                            | not measured                                    | not measured                                    | 109.0                                    | 83.0–108.0 |
| HCO₃, mmol/L            | 6.5                                              | not measured                                    | not measured                                    | 9.0                                      | 22.0–26.0 |
| Base excess, mmol/L     | −26.9                                            | not measured                                    | not measured                                    | −17.1                                    | −2, +2     |
| Lactate, mmol/L         | 7.6                                              | not measured                                    | not measured                                    | 5.4                                      | 0.7–2.1   |
| Urine                   |                                                  |                                                 |                                                |                                          |           |
| Protein                 | 3+                                               | –                                               | –                                               | +/−                                      |           |
| Glucose                 | 4+                                               | 4+                                              | –                                               | 4+                                      |           |
| Ketone                  | 2+                                               | –                                               | –                                               | 3+                                      |           |
| C-peptide, μg/day       | <2.0                                             | not measured                                    | <1.1                                           | <1.3                                     | 20.1–155.0 |

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