Immune checkpoint inhibitors for invasive mucinous adenocarcinoma: A case series

TATSUYA KATO[1], TAKAHIRO MITSUMURA[1], EIYU TSUBOI[1], HIROSHI NAKAHAMA[1], YUI TAKAHASHI[1], YUICHIRO NEI[1], SHIGEO HANADA[1], ATSUSHI MIYAMOTO[1], HIRONORI URUGA[2,3], TAKESHI FUJII[2] and MEIYO TAMAOKA[1]

[1]Department of Respiratory Medicine, Respiratory Center, Toranomon Hospital, Tokyo 105-8470, Japan; [2]Department of Diagnostic Pathology, Toranomon Hospital, Tokyo 105-8470, Japan; [3]Okinaka Memorial Institute for Medical Research, Tokyo 105-8470, Japan

Received November 27, 2025; Accepted April 29, 2026

DOI: 10.3892/ol.2026.15674

Abstract. Invasive mucinous adenocarcinoma (IMA) is a rare subtype of lung adenocarcinoma that frequently harbors *KRAS* mutations and exhibits low programmed death-ligand 1 (PD-L1) expression. As evidence on the use of immune checkpoint inhibitors (ICIs) for IMA is limited, the present study aimed to describe the clinical features, treatment patterns and outcomes to evaluate the effectiveness of ICIs for IMA. The present retrospective study included 15 patients with advanced or recurrent IMA who were treated at Toranomon Hospital (Tokyo, Japan) between April 2014 and March 2025. The present report focuses on 7 patients who received first-line ICI-based therapy. Patient characteristics, molecular and pathological features, treatments administered, and outcomes were summarized, and responses were assessed using the Response Evaluation Criteria in Solid Tumors version 1.1. Among the 15 patients, *KRAS* mutations were identified in 6 patients (40%), PD-L1 expression was positive in 2 patients (13%), negative in 7 patients (47%) and unknown in 6 patients (40%). Of the 7 patients receiving first-line ICI-based therapy, 4 received dual ICIs and 3 received a single-agent ICI. The best overall response among these patients was partial response (PR) in 1 patient (14%), stable disease in 5 patients (71%) and progressive disease in 1 patient (14%). A total of 5 patients (71%) experienced immune-related adverse events leading to treatment discontinuation. In conclusion, first-line ICI-based therapies showed limited effectiveness overall. However, 3 patients treated with dual ICIs and chemotherapy achieved a 100% disease control rate, with 1 patient achieving a PR. Therefore, specific ICI-based combination therapies may be a viable option for the treatment of IMA.

Correspondence to: Dr Takahiro Mitsumura, Department of Respiratory Medicine, Respiratory Center, Toranomon Hospital, 2-2-2 Toranomon, Minatoku, Tokyo 105-8470, Japan
E-mail: mitsumura@toranomon.gr.jp

Key words: invasive mucinous adenocarcinoma, immune checkpoint inhibitor, *KRAS*

Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Invasive mucinous adenocarcinoma (IMA), a rare subtype of lung adenocarcinoma, is characterized by frequent *KRAS* mutations, low expression of programmed death-ligand 1 (PD-L1) and thyroid transcription factor 1 (TTF-1), and infrequent *EGFR* mutations (1).

Immune checkpoint inhibitors (ICIs) are important therapeutic options for non-small cell lung cancer (NSCLC) and are used as monotherapy or combination therapy. The effectiveness of ICIs varies based on several factors, such as PD-L1 expression levels and the presence of specific gene mutations, including *KRAS* (2). Combination therapies such as dual ICIs (durvalumab plus tremelimumab or nivolumab plus ipilimumab) with or without chemotherapy (platinum plus pemetrexed or taxanes) are promising options for overcoming the immunosuppressive microenvironment, especially for patients with low PD-L1 expression (3).

Considering the rarity of IMA and its distinct molecular profile, evidence for the efficacy of ICIs in IMA is limited. We retrospectively reviewed 15 patients with advanced or recurrent IMA at our institution to characterize treatment patterns and outcomes. This study aims to identify effective therapeutic strategies using ICIs for this challenging subtype.

Case report

Patients and methods. This retrospective study included 15 patients with advanced or recurrent IMA who were treated at our institution (Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo, 105-8470, Japan) between April 2014 and March 2025. The patient characteristics are summarized in Table I, and the molecular features and treatment outcomes are summarized in Table II. Treatment responses were assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. PD-L1 expression [Tumor Proportion Score (TPS)] was evaluated using the PD-L1 IHC 22C3 pharmDx assay

(Agilent Technologies) and was defined as the percentage of viable tumor cells showing partial or complete membrane staining at any intensity.

Results. The molecular and pathological features were as follows: *KRAS* mutations were identified in six patients (40%); PD-L1 expression was positive (TPS 1-49%) in two patients (13%), negative (TPS <1%) in seven patients (47%), and unknown in six patients (40%). TTF-1 expression was positive in three patients (20%), negative in 11 (73%), and not assessed in one patient (7%). Seven of the fifteen patients received first-line ICI-based therapy, three received ICI therapy in later lines, and five did not receive any ICI therapy. Of the seven patients who received first-line ICI-based therapy, four received dual ICIs (PD-1/PD-L1 and cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] inhibitors) and three received a single-agent ICI (PD-1 inhibitor). The best overall response included one partial response (PR), five stable diseases (SD), and one progressive disease (PD).

Five representative cases were selected from the seven patients who received first-line ICI-based therapy to highlight diverse clinical scenarios, treatment outcomes and complications. These include primary resistance with early, severe immune-related adverse events (irAEs) (Case 1), successful management of severe irAEs leading to a partial response (Case 3), and atypical response patterns (Case 5). Furthermore, to illustrate the potential for durable benefits with ICI therapy in IMA, we describe two cases, the only ones with positive PD-L1 in this cohort, which achieved remarkable long-term survival: one treated with ICI plus chemotherapy (Case 6) and another with a single ICI (Case 7). The remaining two cases (Cases 2 and 4) were not described in detail. Case 2 was a clinically complex case with baseline interstitial pneumonia previously treated with immunosuppressive therapy for an acute exacerbation. The treatment was discontinued early due to worsening respiratory status, and the patient ultimately died of pulmonary failure, with acute exacerbation, infection and grade 3 irAE pneumonitis, all considered in the differential diagnosis. Regarding Case 4, although grade 2 irAE thyroid dysfunction and infectious complications led to treatment discontinuation, the clinical course was relatively typical, achieving SD, and sotorasib was considered for future disease progression.

Table I. Baseline characteristics of 15 patients with advanced or recurrent invasive mucinous adenocarcinoma.

Characteristics	Value
Median age, years (IQR)	70 (67-77)
Sex, n (%)	
Male	10 (67)
Female	5 (33)
ECOG PS, n (%)	
0	10 (67)
1	3 (20)
2	2 (13)
3	0 (0)
4	0 (0)
Smoking history, n (%)	
Current	0 (0)
Former	12 (80)
Never	3 (20)
Stage, n (%)	
IV	6 (40)
Postoperative recurrence	9 (60)
Timing of ICI treatment, n (%)	
First-line	7 (47)
Second-line or later	3 (20)
Not used	5 (33)
KRAS mutation, n (%)	6 (40)
PD-L1 (22C3), n (%)	
<1%	7 (47)
1-49%	2 (13)
≥50%	0 (0)
Unknown	6 (40)
TTF-1, n (%)	
Positive	3 (20)
Negative	11 (73)
Unknown	1 (7)

ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; PD-L1, programmed death-ligand 1; TTF-1, thyroid transcription factor 1.

Case 1. A 68-year-old male presented to our hospital and was diagnosed with left lower lobe IMA (cT4N2aM1a, Stage IVA). No common driver mutations were identified, and the PD-L1 expression (TPS) was <1%. The patient was administered dual ICIs (nivolumab and ipilimumab) but developed grade 3 liver enzyme elevation and grade 2 creatine kinase elevation during the first cycle. The patient required treatment with immunosuppressive agents. The lung cancer progressed rapidly following the discontinuation of the therapy, and the patient received best supportive care. Due to respiratory failure secondary to disease progression and impaired consciousness caused by carbon dioxide narcosis, the patient was discharged for palliative care with ventilatory support.

Case 3. A 75-year-old male presented with multifocal IMAs in the left upper, right middle, and right lower lobes. The patient underwent surgical resections for all three lesions. Histopathological examination revealed three distinct primary tumors with the following pathological stages: pT1aN0M0, pT1bN0M0, and pT4N0M0. Following three cycles of postoperative adjuvant chemotherapy (cisplatin and vinorelbine), bilateral pulmonary metastases developed. No common driver mutations were identified, and PD-L1 expression (TPS) was <1%. The patient was administered dual ICIs (durvalumab and tremelimumab) combined with chemotherapy (carboplatin and nab-paclitaxel). After two cycles, the patient showed SD, which improved to PR after the fourth cycle (Fig. 1). Before the maintenance cycle, the patient developed grade 2 irAE colitis, which required prednisolone escalation. Concurrently, the patient developed a disturbance of consciousness. Magnetic resonance imaging of the brain and spinal cord revealed no abnormalities. Cerebrospinal

Table II. Summary of 15 invasive mucinous adenocarcinoma cases: Baseline characteristics, molecular features, lines of ICI administration, first-line regimens, number of first-line cycles, BOR to first-line therapy, overall survival and irAEs.

Case	Age, years	Sex	PS	Smoking history	Stage	Gene mutations	PD-L1, %	TTF-1	Line of ICI administration	First-line regimen	Cycles	BOR	OS, months	irAEs (grade)
1	68	M	2	Former	IVA	None[a]	<1	-	First	Nivo + Ipi	1	PD	5 (alive)	Liver injury (G3), myositis (G2)
2	68	F	0	Former	IVA	None[b]	<1	Focal+	First	CBDCA + nabPTX+ Dur + Tre	2	SD	6	Dermatitis (G2), pneumonitis (G3)
3	75	M	0	Former	PO	*KRAS* G12D; *CTNNB1* S45P[a]	<1	Focal+	First	CBDCA + nabPTX + Dur + Tre	4	PR	13 (alive)	Colitis (G2), encephalitis (G4)
4	70	F	0	Never	PO	*KRAS* G12C[c]	<1	Focal+	First	CBDCA + PEM + Pembro	6	SD	15 (alive)	Thyroid dysfunction (G2)
5	70	F	0	Never	IVA	*KRAS* G12V[a]	<1	-	First	CDDP + PEM + Dur + Tre	7 (ongoing)	SD	15 (alive)	None
6	78	M	0	Former	PO	None[d]	5	-	First	CBDCA + PEM + Pembro	6	SD	53 (lost to follow up)	Pneumonitis (G3)
7	58	M	1	Former	PO	None[d]; *ABL1* S882del, *MSH2* E251K, *MSH2* N596S, *NFE2L2* S103Y[e]	5	-	First	Pembro	4	SD	66 (alive)	None
8	78	M	1	Former	PO	*KRAS* G12S[a]	<1	-	No ICI treatment	TS-1	27	SD	23	No ICI treatment
9	77	M	0	Former	PO	None[d]	UK	-	No ICI treatment	CBDCA + PEM	4	SD	10	No ICI treatment
10	68	M	2	Former	IVA	None[d]	<1	-	No ICI treatment	CBDCA + nabPTX	4	SD	8	No ICI treatment
11	75	F	1	Former	IVA	None[d]	UK	-	Third	CBDCA + PEM	5	SD	8	No ICI treatment
12	46	F	0	Never	IVA	None[f]	UK	-	Third	CBDCA + PEM	10	SD	18	No ICI treatment
13	81	M	0	Former	PO	None[f]	UK	UK	-	PEM	4	SD	8	No ICI treatment
14	67	M	0	Former	PO	*KRAS* mutation[f]	UK	-	Fifth	CBDCA + nabPTX	5	SD	21	No ICI treatment
15	59	M	0	Former	IVA	*KRAS* mutation[f]	UK	-	-	CDDP + PEM	8	SD	15	No ICI treatment

Gene mutations were evaluated using: [a]Oncomine™ DxTT; [b]Lung Cancer Compact Panel™; [c]AmoyDx® Pan Lung Cancer PCR Panel; [d]Sanger sequencing or cobas® EGFR Mutation Test v2.0 (for *EGFR*); [e]FoundationOne® CDx; [f]Sanger sequencing (for *EGFR* and *KRAS*). Stage was determined using the 8th edition of the TNM Classification (Union for International Cancer Control, 2017). PD-L1 expression was evaluated using clone 22C3 (tumor proportion score). In the Gene mutation column, driver mutations and co-mutations are separated by semicolons; 'None' indicates the absence of identified driver mutations. BOR, best overall response; CBDCA, carboplatin; CDDP, cisplatin; Dur, durvalumab; F, female; G, grade; ICI, immune checkpoint inhibitor; Ipi, ipilimumab; irAE, immune-related adverse event; LDT, laboratory developed test; M, male; nabPTX, nab-paclitaxel; Nivo, nivolumab; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PEM, pemetrexed; Pembro, pembrolizumab; PO, postoperative recurrence; PR, partial response; PS, performance status; SD, stable disease; Tre, tremelimumab; TS-1, tegafur/gimeracil/oteracil; TTF-1, thyroid transcription factor 1; UK, unknown.

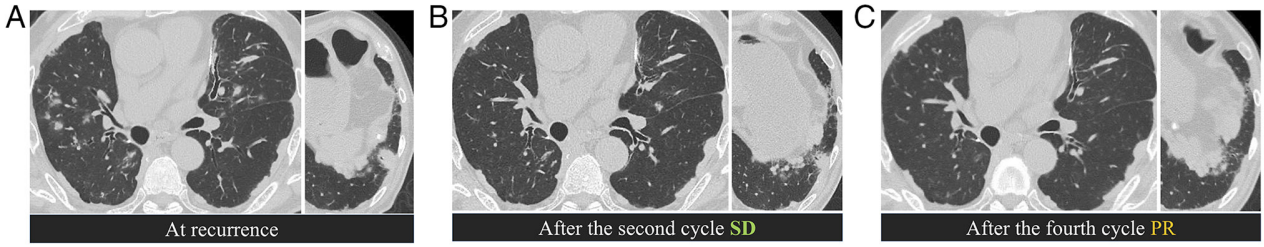

Figure 1. CT images for case 3. (A) CT scan at recurrence, demonstrating multiple metastatic nodules throughout both lungs. (B) CT scan after the second cycle of dual immune checkpoint inhibitors (durvalumab and tremelimumab) combined with chemotherapy (carboplatin and nab-paclitaxel), showing SD. (C) CT scan after the fourth cycle, showing partial response. CT, computed tomography; PR, partial response; SD, stable disease.

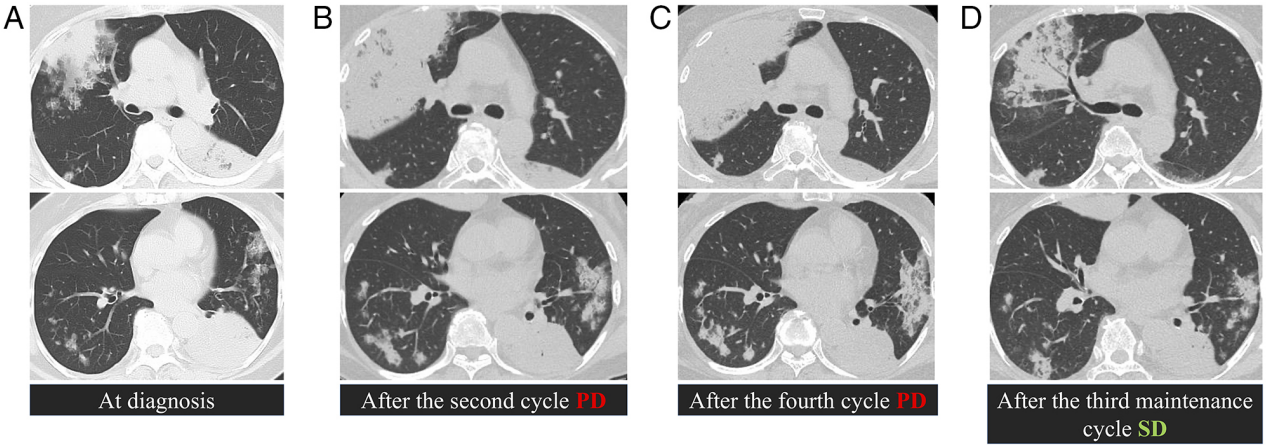

Figure 2. CT images for case 5. In each panel, the top and bottom rows display different axial slices obtained at the same corresponding time point. (A) CT scan at diagnosis, demonstrating consolidation in the left lower lobe and multiple metastatic nodules and consolidation in both lungs, including the right upper lobe. CT scans after the (B) second and (C) fourth cycles of dual immune checkpoint inhibitors (durvalumab and tremelimumab) combined with chemotherapy (cisplatin and pemetrexed), showing PD. (D) CT scan after the third cycle of maintenance therapy, showing SD. CT, computed tomography; PD, progressive disease; SD, stable disease.

fluid analysis revealed pleocytosis and elevated protein levels. A comprehensive meningitis/encephalitis panel was negative for infectious etiology. Owing to deteriorating consciousness, the patient was diagnosed with grade 4 irAE encephalitis. The patient was aggressively managed with two courses of high-dose intravenous methylprednisolone (1 g/d for 3 d each), a 5-d course of intravenous immunoglobulin, and a single dose of tocilizumab (8 mg/kg). Approximately 2 weeks after the initial high-dose steroid therapy, his consciousness began to improve, allowing for gradual prednisolone tapering. Once stabilized, the patient was transferred to a rehabilitation facility.

Case 5. A 70-year-old female presented with left lower lobe IMA (cT4N0M1a, Stage IVA). No common driver mutations were identified, and the PD-L1 expression (TPS) was <1%. The patient was administered dual ICIs (durvalumab and tremelimumab) combined with chemotherapy (cisplatin and pemetrexed). Despite the initial assessment of PD after the second cycle, the treatment regimen was continued. This decision was based on the patient's stable performance status and preference, as well as the mixed response observed among the different target lesions. The disease remained PD after the fourth cycle but achieved SD after the third cycle of maintenance therapy (Fig. 2). At the time of this report, the patient was continuing maintenance therapy.

Case 6. A 78-year-old male presented with a pneumonia-like consolidation in the right lower lobe during follow-up for testicular cancer. Tumor markers were elevated, and the patient was diagnosed with IMA by bronchoscopy. The patient underwent a right lower lobe resection (pT3N0M0, Stage IIB). No *EGFR* mutation was found, *ALK* and *ROS1* were negative with immunohistochemistry, and the PD-L1 expression (TPS) was 5%. The patient declined postoperative adjuvant chemotherapy based on personal preference. Approximately one year after surgery, recurrent lesions appeared in the right lung pleura and left lower lobe. The patient was administered an ICI combined with chemotherapy, (pembrolizumab plus carboplatin and pemetrexed). After four cycles of induction and two cycles of maintenance therapy, the disease achieved SD; however the patient was admitted to the hospital with dyspnea and was diagnosed with grade 3 irAE pneumonitis. After intravenous methylprednisolone (1 g for 3 days) was administered, the patient was discharged with oral prednisolone (25 mg/day) and home oxygen therapy (HOT). The dose of prednisolone was eventually tapered to zero, and HOT was no longer needed. However, given the patient's age, he did not restart additional treatment for the cancer and moved to another hospital. The patient was lost to follow-up, but there was no record of death.

Case 7. A 58-year-old male presented with right upper lobe IMA and underwent a partial resection (pT2aN0M0, Stage IB). No *EGFR* mutation was identified, *ALK* and *ROS1* were negative with immunohistochemistry, and the PD-L1 expression (TPS) was 5%. About 1.5 years after surgery, the disease progressed with recurrence at the surgical resection site. A single ICI (pembrolizumab) was administered, and the disease showed PD after four cycles. Following this, TS-1, pemetrexed, and docetaxel were administered. FoundationOne® CDx, a comprehensive genomic profiling assay designed to detect alterations in 324 genes, as well as select gene rearrangements and genomic signatures, was negative for treatable mutations. After the disease showed PD, gemcitabine was administered.

Discussion

IMA account for approximately 2-10% of lung adenocarcinomas (4) and 3-10% of invasive adenocarcinomas (1); however, it is sometimes misdiagnosed due to its pneumonia-like features. IMA is characterized by molecular features distinct from those of non-mucinous adenocarcinoma (4), including a high frequency of *KRAS* mutations (28-87%, particularly G12D and G12V) and *NRG1* fusions (7-27%, particularly in those without *KRAS* mutations), low frequency of *EGFR* mutations (0-5%), and low expression rates of PD-L1 (0-6.1%) and TTF-1 (11-27.5%).

While the general predictors of ICI effectiveness include PD-L1 expression, tumor mutational burden (TMB), and tumor-infiltrating lymphocytes, their role in IMA requires further investigation. *KRAS*-mutated NSCLC is generally considered responsive to ICIs, however clinical efficacy varies significantly depending on the specific *KRAS* subtype and co-mutation profile (5,6). *KRAS* G12C mutations, which are common in smokers, are often associated with high TMB and PD-L1 expression, making them more sensitive to immunotherapy. In contrast, *KRAS* G12D mutations, the predominant subtype in IMA, are frequently found in non-smokers and typically exhibit low PD-L1 expression and an immunologically 'colder' tumor microenvironment (TME). This TME is less immunogenic, characterized by impeded effective T-cell infiltration and the enhanced recruitment of myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and cancer-associated fibroblasts (CAFs). Furthermore, the presence of co-mutations is a critical factor: while *TP53* co-mutations can prime the tumor for ICI responsiveness by creating a 'hot' TME, other loss-of-function co-mutations, such as *STK11* and *KEAP1*, foster a 'colder' TME. There are conflicting reports regarding the effectiveness of ICIs in IMA treatment. Jang *et al* (7) suggested that immunotherapy may lead to better outcomes than chemotherapy for IMA, reporting significantly better overall survival (median OS undefined vs. 17.0 months, P<0.001). Conversely, Kim *et al* (8) observed no significant difference in overall survival (OS) after immunotherapy (P=0.992). A phase II trial by Chae *et al* (9) showed promising results for the combination of dual ICIs (ipilimumab and nivolumab) in IMA and non-mucinous lepidic adenocarcinoma, reporting an overall response rate of 25% and a clinical benefit rate of 62.5%. Dual ICIs are commonly used for NSCLC, particularly for those with low PD-L1 expression, and chemotherapy is often administered for early tumor reduction. However, evidence for the efficacy of this combination therapy for IMA remains limited.

This case series included 15 patients with advanced or recurrent IMA. Molecular characteristics, including the frequency of *KRAS* mutations and TTF-1 positivity, were largely consistent with those reported previously. The rate of positive PD-L1 expression (TPS ≥1%) in this cohort was 13%, which is slightly higher than that reported previously. This may be attributed to the six patients whose PD-L1 status was unknown.

Among the seven patients who received first-line ICI-based therapy, the overall response rate was modest at 14%, but the disease control rate (DCR) was high at 86%. For the two PD-L1-positive patients, a single ICI was administered, one in combination with chemotherapy and the other without. Although one of these patients was lost to follow-up, both demonstrated a longer OS compared to the rest of the cohort. This aligns with previous reports from pembrolizumab studies, indicating that higher PD-L1 expression correlates with longer OS. Notably, three patients treated with a combination of dual ICIs and chemotherapy were PD-L1 negative yet achieved a 100% DCR. The clinical benefit of dual ICIs in IMA may be largely explained by the synergistic effect of anti-PD-1/PD-L1 and anti-CTLA-4 antibodies in modulating the 'cold' TME. Anti-CTLA-4 antibodies (such as tremelimumab and ipilimumab) act complementarily to PD-1 inhibition by enhancing T-cell priming in the lymph nodes and potentially reducing the immunosuppressive influence of intratumoral Tregs. For mucin-rich tumors like IMA, where the mucin barrier typically hinders immune cell infiltration, combining chemotherapy might play an important role in enhancing the efficacy of immunotherapy.

Regarding chemotherapy selection, two of the seven ICI-treated patients received nab-paclitaxel as part of a dual ICI regimen. The only patient who achieved a PR harbored a *KRAS* G12D mutation and was treated with dual ICIs (durvalumab and tremelimumab) plus nab-paclitaxel. The addition of paclitaxel for *KRAS*-G12D-mutant NSCLC has been reported to induce the secretion of Th1-type chemokines, including CXCL10 and CXCL11, which facilitate the infiltration of CD8+ T cells into the tumor (10). This combination of chemotherapy-induced T-cell recruitment and CTLA-4-mediated TME modulation could be crucial for overcoming the primary resistance of *KRAS*-G12D-mutated IMA to immunotherapy. However, due to concerns regarding taxane-related adverse effects, Patient 5 in this cohort received pemetrexed. Although pemetrexed generally has limited efficacy in TTF-1-negative cases (11), the disease subsequently stabilized following an initial PD assessment, and SD was achieved after the third maintenance cycle. Evaluating the responses in some IMA cases may be challenging using RECIST version 1.1. The characteristic growth pattern of IMA, involving multifocal lesions and airspace spread, complicates the selection and measurement of target lesions, potentially leading to an inaccurate response assessment. Similar to the development of iRECIST for evaluating atypical responses to ICIs (12), a modified evaluation framework may be required for IMA.

However, this promising effectiveness of ICIs was accompanied by a high incidence of irAEs; five of the seven patients (71%) experienced irAEs, leading to treatment discontinuation. Despite these toxicities, the survival outcomes were highly encouraging. Five of the seven patients (71%) remained alive at

the time of analysis, with one patient continuing first-line treatment. While irAEs are a significant concern, these findings suggest that ICI-based regimens, especially the combination of dual ICIs with chemotherapy, may offer clinical benefits and prolong the survival of patients with IMA.

Specific genetic subsets of IMA present unique therapeutic challenges. Patient 4 harbored a *KRAS* G12C mutation, for which sotorasib was the standard second-line therapy for NSCLC. However, the efficacy of sotorasib in the treatment of the IMA subtype remains unclear. A case report (13) suggested that *VEGF-A* overexpression could be a mechanism of sotorasib resistance in IMA, indicating the complex biology of this disease.

Previous case reports (14,15) indicated that bevacizumab, a monoclonal antibody against vascular endothelial growth factor, may offer therapeutic benefit for IMA when combined with platinum and pemetrexed. Although bevacizumab is widely used to treat various malignancies, notably NSCLC, it is often administered in combination with chemotherapy and immunotherapy. Since none of the patients in this cohort received bevacizumab, we could not evaluate its potential synergistic effects with other ICIs. This remains an important issue for future clinical investigations.

This study has several limitations. First, the sample size was small (n=15) due to the rarity of IMA, and the study was conducted retrospectively at a single institution. Second, there was heterogeneity in the treatment regimens. Among the four patients treated with dual ICIs, three were administered concurrent platinum-based cytotoxic chemotherapy, while one received dual ICIs alone. Finally, this study did not assess the presence of *NRG1* fusions or co-mutations (*TP53*, *STK11* and *KEAP1*), which might have influenced treatment outcomes. An exception was Patient 7, in whom the absence of these co-mutations was confirmed by FoundationOne® CDx.

Further studies are required to optimize the balance between therapeutic benefits and irAE risk by identifying patients who are most likely to respond to immunotherapy while minimizing severe toxicity. In addition, the development of targeted therapies for specific alterations, including distinct *KRAS* subtypes and *NRG1* fusions, may provide promising alternatives for patients with this challenging lung cancer subtype.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study are not publicly available due to patient privacy protection but may be requested from the corresponding author.

Authors' contributions

TK and TM wrote the manuscript and conducted the background research. TK, TM, ET, HN, YT, YN, SH, AM and MT were the attending physicians and contributed to acquiring the patient data. TK, TM and MT were involved in study design and interpreting the clinical outcomes. HU and TF performed the pathological examinations. TK and TM confirm the authenticity of all the raw data. TM and MT supervised the study and manuscript writing. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present retrospective study was approved by the Institutional Review Board of Toranomon Hospital (approval no. 2694; Tokyo, Japan). Informed consent was obtained via an opt-out method, wherein patients were provided with information about the study and given the opportunity to decline participation.

Patient consent for publication

Consent for the publication of clinical information and images was obtained via an opt-out method, as approved by the Institutional Review Board.

Competing interests

SH reports personal fees from AstraZeneca, outside the submitted work. The other authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools (Gemini, Google LLC) were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tool as necessary, taking full responsibility for the ultimate content of the present manuscript.

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