Impact of ALK Inhibitors in Patients With *ALK*-Rearranged Nonlung Solid Tumors

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PURPOSE Anaplastic lymphoma kinase (*ALK*) rearrangement is a well-known driver oncogene in non–small-cell lung cancer and has also been identified in other types of tumors. However, there is limited evidence on the clinical response to ALK tyrosine kinase inhibitors (TKIs), such as alectinib and crizotinib, in rare tumors with ALK fusion. We evaluated the therapeutic effect of ALK-TKIs in rare *ALK*-rearranged tumors.

PATIENTS AND METHODS Between April 2012 and April 2019, clinical outcomes and characteristics of patients with *ALK*-rearranged nonlung solid tumors who received ALK-TKIs (alectinib and/or crizotinib) outside of clinical trials were reviewed. Expression and/or rearrangement of ALK was evaluated by immunohistochemistry, fluorescence in situ hybridization, and next-generation sequencing. The tumor response was assessed according to RECIST (version 1.1). Progression-free survival was estimated from initial ALK-TKI initiation until progression.

RESULTS We identified seven patients (inflammatory myofibroblastic tumors, n = 3; ALK-positive histiocytosis, n = 1; histiocytic sarcoma, n = 1; osteosarcoma, n = 1; and parotid adenocarcinoma, n = 1), with a median age of 17 years. Two rare *ALK* fusions, namely, *CTNNA1-ALK* and *ITSN2-ALK*, were identified. As initial ALK-TKI therapy, five patients received alectinib and two received crizotinib. The objective response rate for the initial ALK-TKI therapy was 85.7% (95% CI, 44 to 97), including two patients who received alectinib and achieved complete response. The median progression-free survival was 8.1 months (range, 1.7 to not estimable). There were no treatment interruptions or dose reductions because of adverse events caused by alectinib.

CONCLUSION This study highlights the potential benefit of ALK-TKIs, especially alectinib, in patients with *ALK*-rearranged nonlung solid tumors.

BACKGROUND

Anaplastic lymphoma kinase (*ALK*) rearrangement was first discovered as a potential actionable therapeutic oncogenic gene aberration in anaplastic large-cell lymphoma (ALCL).[1] The next disease linked to *ALK* was inflammatory myofibroblastic tumor (IMT), characterized by increased expression of the ALK protein and a rearranged *ALK* locus in a subset of cases.[2,3] Later, there were advances in *ALK*-targeted therapy because of the discovery of the *EML4-ALK* rearrangement in non–small-cell lung cancer (NSCLC),[4] which led to the discovery of *ALK* alterations in other solid tumors such as neuroblastomas, rhabdomyosarcomas, and anaplastic thyroid cancers.[5-7] Activation of the *ALK* gene can occur by rearrangements with partner genes, point mutations, or amplification. Ever since the discovery of the oncogenic role, *ALK* alterations, mainly rearrangements, have been a target for developing therapies, and Hiroyuki Mano[8] proposed the collective

name ALKoma to refer to tumors that develop because of *ALK* functioning abnormally as an oncogene.

The first-generation ALK-tyrosine kinase inhibitor (TKI) to be approved following clinical trials was crizotinib, which also acts as a mesenchymal epithelial transition factor and receptor tyrosine kinase-1 kinase inhibitor. It showed a dramatic effect in ALK-positive solid tumors and ALCLs.[9,10] A second-generation ALK inhibitor, alectinib, was subsequently approved and showed a higher response rate than crizotinib with minimal toxicity in patients with *ALK*-rearranged metastatic NSCLC.[11] Currently, ceritinib, brigatinib, and lorlatinib are approved in the clinical setting for *ALK*-rearranged NSCLC.[12-14]

In ALKomas other than NSCLC, a small sample size of phase II studies showed that crizotinib demonstrated antitumor efficacy and achieved a durable response, as anticipated.[15] However, there are limited reports on

CONTEXT

Key Objective

There is limited evidence on the clinical efficacy of anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (ALK-TKIs) in nonlung solid tumors with *ALK* rearrangements. This single institutional study aimed to evaluate the efficacy and tolerability of ALK-TKIs in a group of patients with *ALK*-rearranged rare solid tumor.

Knowledge Generated

Alectinib showed dramatic response for patients with *ALK*-rearranged nonlung solid tumors, and furthermore, sequential ALK-TKI therapy was acceptable for some patients. A patient with parotid tumor with *CTNNA1-ALK* rearrangement derived clinical benefit from alectinib.

Relevance

Our data revealed that *ALK* rearrangements are found in rare solid tumors and result in clinical benefit when treated with ALK-TKIs. This leads to a rationale for clinical trials targeting *ALK*-rearranged nonlung solid tumors to promote personalized medicine.

other ALK-positive solid tumors, and the efficacy and safety of alectinib for these tumors have only been described as case reports.[16-19] Thus, in this case series, we summarize the efficacy and tolerability of ALK-TKIs (alectinib and crizotinib) in patients with ALKomas.

PATIENTS AND METHODS

We retrospectively reviewed patients with *ALK*-rearranged nonlung solid tumors who received alectinib and crizotinib outside of clinical trials at the National Cancer Center Hospital between April 2012 and April 2019. Patient data were retrieved from electronic medical records. Alectinib and crizotinib were administered at the doses approved for NSCLC in Japan: 300 mg twice daily and 250 mg twice daily, respectively. Expression of ALK and/or rearrangement of *ALK* was evaluated by immunohistochemistry (IHC) (5A4, Abcam, Cambridge, UK, or ALK1, DAKO, Glostrup, Denmark), fluorescence in situ hybridization (FISH) using a break-apart probe (Vysis ALK Break Apart FISH Probe Kit, Abbott Molecular, Abbott Park, IL), or next-generation sequencing (NGS) using NCC Oncopanel v4.0, which detects gene rearrangements, base substitutions, short insertions or deletions, and copy number alterations in 114 genes.[20] The institutional ethics committee of the National Cancer Center Hospital approved this study (#2016-086). We also obtained documented informed consent from each patient before treatment. The response to ALK-TKI was assessed by two independent oncologists according to version 1.1 of the RECIST.[21] The response rate (ie, the proportion of patients with complete response (CR) or partial response [PR]) was calculated, and its 95% CI was estimated based on the Clopper-Pearson method. Time-to-event end points were summarized using the Kaplan-Meier method. Data were analyzed using JMP Pro version 13.0.0 (SAS Institute).

RESULTS

Among the patients treated with an ALK-TKI outside of a clinical trial during the study period, seven had nonlung solid tumors. Initial ALK-TKI treatment consisted of alectinib in five patients and crizotinib in two patients. Patient characteristics are shown in Table 1. The median follow-up time was 15.0 months.

There were five male and two female patients, and the mean age was 17 years (range, 14-60 years). The most common histology was IMT (n = 3), followed by ALK-positive histiocytosis (n = 1), histiocytic sarcoma (n = 1), osteosarcoma (n = 1), and parotid adenocarcinoma (n = 1). Three IMTs showed characteristic histology, including two epithelioid variants. In contrast to ALK-positive histiocytosis, the histiocytic sarcoma showed nuclear atypia and high mitotic activity with atypical mitoses. Osteosarcomas were of the conventional osteoblastic type with highly pleomorphic nuclei. One adenocarcinoma of the parotid gland showed a solid pattern without mucous secretion, and IHC was positive for S100, SOX10, and DOG1 and negative for NR4A3. IHC of ALK was positive for all tumors except osteosarcoma. The ALK staining patterns were nuclear membranous in patient 3 with IMT (epithelioid), plasma membranous in patient 7 with parotid adenocarcinoma, and cytoplasmic in the remaining patients (Table 2 and Fig 1).

The median number of lines of previous systemic pharmacotherapy was one (range, 0-2 lines). All seven patients showed an *ALK* rearrangement of some kind, and four patients were tested by NGS. Their clinicopathological features and detected fusions are listed in Table 2. The observed partner genes were *KIF5B* (n = 1), *CLTC* (n = 2), *ITSN2* (n = 1), and *CTNNA* (n = 1) (Appendix Figs A1A-C). Table 2 and Figure 2 illustrate the patients' clinical courses. Three patients died of cancer, one was lost to follow-up, and the remainder were still alive at last follow-up.

The best objective response rate (ORR) for initial ALK-TKI was 85.7% (95% CI, 43.65 to 96.99) (6 of 7 patients) with a disease control rate of 85.7% (6 of 7 patients), as summarized in Figure 3. The median progression-free survival

TABLE 1. Patient Characteristics

Characteristic	No. Patients (%)
Total patients treated	7
Age, median (range), years	17 (14-60)
Sex	
Male	5 (71)
Female	2 (29)
ECOG performance status	
0	4 (57)
1	2 (29)
2	1 (14)
Histology	
Inflammatory myofibroblastic tumor	3 (43)
ALK-positive histiocytosis	1 (14)
Histiocytic sarcoma	1 (14)
Osteosarcoma	1 (14)
Parotid adenocarcinoma	1 (14)
Median No. lines of prior systemic pharmacotherapy (range)	1 (0-2)
0 prior line	2 (29)
1 prior line	3 (43)
2 prior lines	2 (29)
Initial ALK-targeted therapy	
Alectinib	5 (71)
Crizotinib	2 (29)
Sequential ALK-targeted therapy beyond initial ALK-TKI	
Alectinib	1 (14)
Ceritinib	2 (29)

Abbreviations: ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor.

(PFS) was 8.1 months (range, 1.7 to not estimable). In patients receiving initial alectinib, the response rate was 80.0% (4 of 5 patients), including two patients with CR and another two with durable PR (Fig 4). In one 17-year-old patient with locally advanced bladder IMT (patient 2 in Table 2), it was possible to preserve the bladder because of the good response to crizotinib.[22] Three patients were treated with a second ALK-TKI, either alectinib or ceritinib. In one patient initially treated with crizotinib (patient 1), alectinib and ceritinib were subsequently administered. In this patient, alectinib failed to achieve clinical efficacy although ceritinib achieved PR. Overall, the clinical effect of sequential ALK-TKI therapy was mild in terms of the tumor response and short response duration.

Regarding the safety profile of ALK-TKI treatment, there were no treatment-related adverse events and no dose reductions or interruptions for any cause with alectinib therapy. One patient receiving crizotinib experienced grade 3 neutropenia that was considered to be drug related, and dose reduction was required.

DISCUSSION

The current case series clarified the efficacy of ALK-TKIs, including alectinib, a second-generation ALK-TKI, across different tumor types and fusion partners in patients with advanced, *ALK*-rearranged, nonlung solid tumors. For the first time, we report the response to ALK-TKI in tumors with two rare fusions, *ITSN2-ALK* and *CTNNA1-ALK*, and the clinical benefit and safety of alectinib in a pediatric patient with a solid tumor. Previous studies have shown that crizotinib, a first-generation ALK-TKI, is effective and achieves a durable response in ALK-positive tumors, excluding NSCLC.[10,23,24] In these studies, crizotinib resulted in ORRs of 66.7%-86.0% in patients with IMT and 11.8% in patients with other solid tumors excluding NSCLC. As for alectinib, a phase II trial for ALK-positive ALCL[25] led to regulatory approval in Japan, but no clinical trial data for alectinib to treat solid tumors have been reported so far. In our report, the ORR for initial ALK-TKI therapy was 85.7% (6 of 7 patients), which is comparable with the efficacy in previous crizotinib trials. Our ORR results are also similar to those from alectinib trials for NSCLC, although the PFS was shorter than that of the patients with NSCLC.[11] The shorter PFS could be explained by differences in histology, fusion partner genes, number of lines of previous pharmacotherapy, and number of patients. This report is the first to show the efficacy of alectinib as an initial ALK-TKI in a group of nonlung solid tumors, and the first to report the clinical benefit of alectinib in rare cancer types such as *ALK*-positive histiocytosis, histiocytic sarcoma, and parotid gland adenocarcinoma with *CTNNA-ALK*, in addition to tumors with known fusion types such as IMT with *CLTC-ALK* fusion.

The function of the protein derived from *CTNNA1-ALK* fusion was previously unknown, since only one study described *CTNNA1* as a fusion partner of *ALK* in a patient with salivary secretory carcinoma, and the treatment outcomes were not reported.[26] Our case of *CTNNA-ALK*–positive parotid adenocarcinoma demonstrated rearrangement in the canonical exon 20 recombination region and showed a clinical response to alectinib (Appendix Fig A1B and Table 2); this was consistent with the other cancer types in our series that had an *ALK* fusion in the same region and also demonstrated a response to alectinib. Also, previous studies have reported that this type of in-frame fusion to exon 20 of *ALK* generates an oncogenic protein, which suggests that this oncogenic protein is a possible therapeutic target of ALK inhibitors irrespective of cancer type.[4,8,27,28] The positive ALK IHC staining in the tumor cells of our patient with parotid adenocarcinoma and the response to ALK inhibitors suggest that this fusion was an oncogenic driver. Interestingly, ALK plasma membrane staining was characteristic of this patient, which suggests that this staining pattern may reflect CTNNA1 function and location. α-E-catenin, the protein product of *CTNNA1*, functions in a complex with
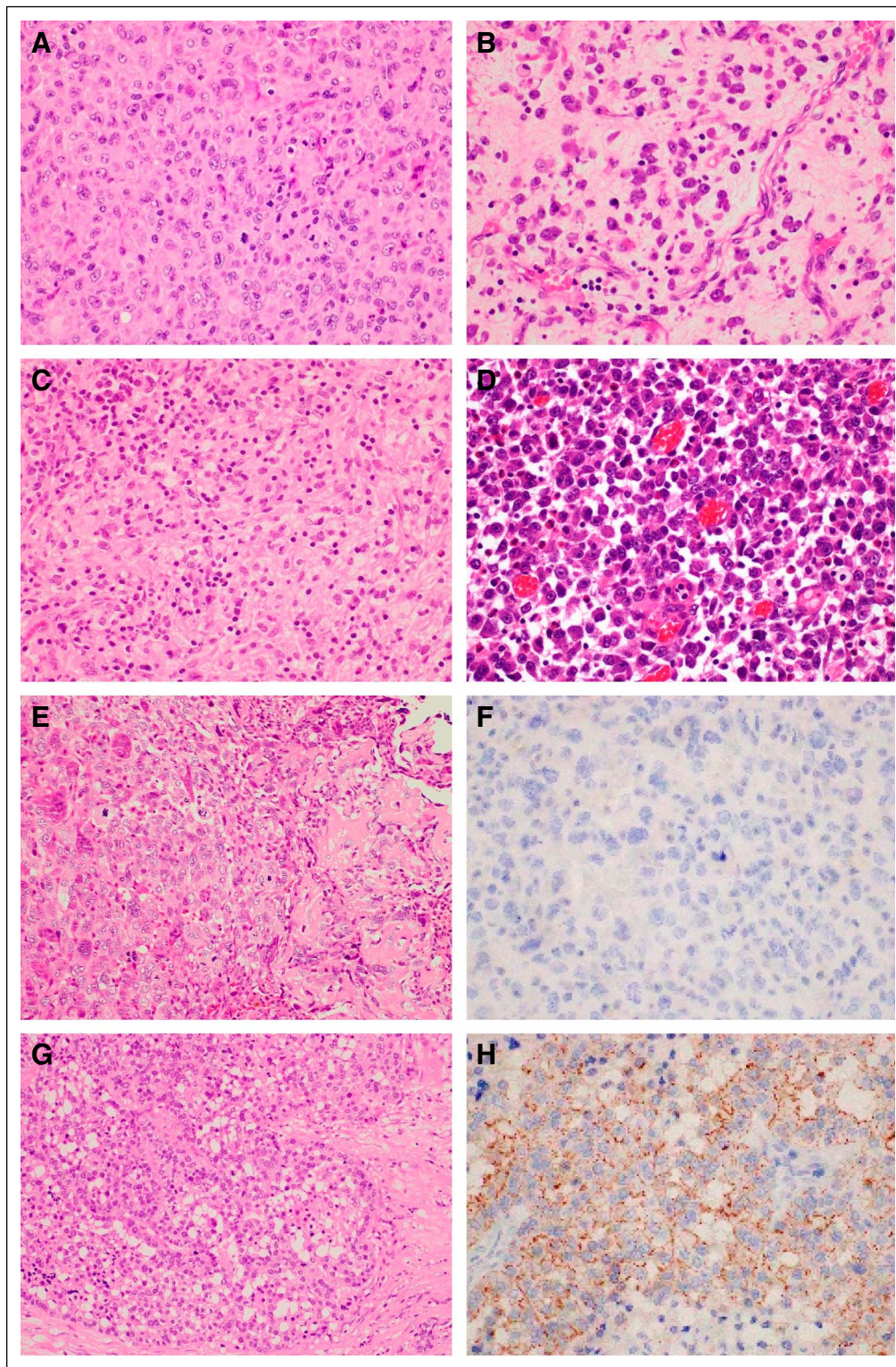
FIG 1. Histological features of representative cases. (A) Patient 1: histiocytic sarcoma, *CLTC|ALK* fusion; (B) patient 3: IMT (epithelioid); (C) patient 4: ALK-positive histiocytosis; (D) patient 5: IMT, *CLTC|ALK* fusion; (E) patient 6: osteosarcoma, *ITSN2|ALK* fusion; (F) patient 6: negative staining in ALK IHC; (G) patient 7: parotid adenocarcinoma, *CTNNA1|ALK* fusion; and (H) patient 7: plasma membrane staining in ALK IHC. ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; IMT, inflammatory myofibroblastic tumor.

TABLE 2. Clinicopathologic Features of Patients Treated With ALK-TKI (Crizotinib and Alectinib)

No.	Age (years), Sex	Histopathology	IHC	FISH	NGS	Tumor Location	Treatment	Duration (months)	Response	Follow-Up Time (months)/Outcome
1	44, F	Histiocytic sarcoma	Positive (cytoplasm)	Positive	CLTC-ALK	Multifocal: cervical LN, mediastinal LN, supraclavicular LN, hilar LN, and subcutaneous	Crizotinib	4.4	PR	18.4/death because of PD
2	17, M	IMT	Positive (cytoplasm)	Positive	NA	Unifocal: bladder	Crizotinib	40.0	PR	45.3/alive with disease
3	14, M	IMT (epithelioid)	Positive (nuclear membrane)	Positive	NA	Multifocal: peritoneal dissemination	Alectinib	44.2	CR	44.2/no evidence of disease
4	17, F	ALK-positive histiocytosis	Positive (cytoplasm)	Positive KIF5B-ALK	NA	Multifocal: breast and brain	Alectinib	29.9	CR	29.9/no evidence of disease
5	52, M	IMT (epithelioid)	Positive (cytoplasm)	Negative	CLTC-ALK	Multifocal: peritoneal dissemination and ascites fluid	Alectinib	6.9	PR	11.5/alive with disease
6	17, M	Osteosarcoma	Negative	Positive	ITSN2-ALK	Multifocal: lung and bone	Alectinib	1.7	PD	1.7/death because of PD
7	60, M	Parotid adenocarcinoma	Positive (plasma membrane)	NA	CTNNA1-ALK	Multifocal: cervical LN, axillary LN, and abdominal LN	Alectinib	8.1	PR	12.1/death because of PD

Abbreviations: ALK, anaplastic lymphoma kinase; CLTC, clathrin heavy chain; CR, complete response; F, female; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; IMT, inflammatory myofibroblastic tumor; LN, lymph node; M, male; NGS, next-generation sequencing; PD, progression disease; PR, partial response.
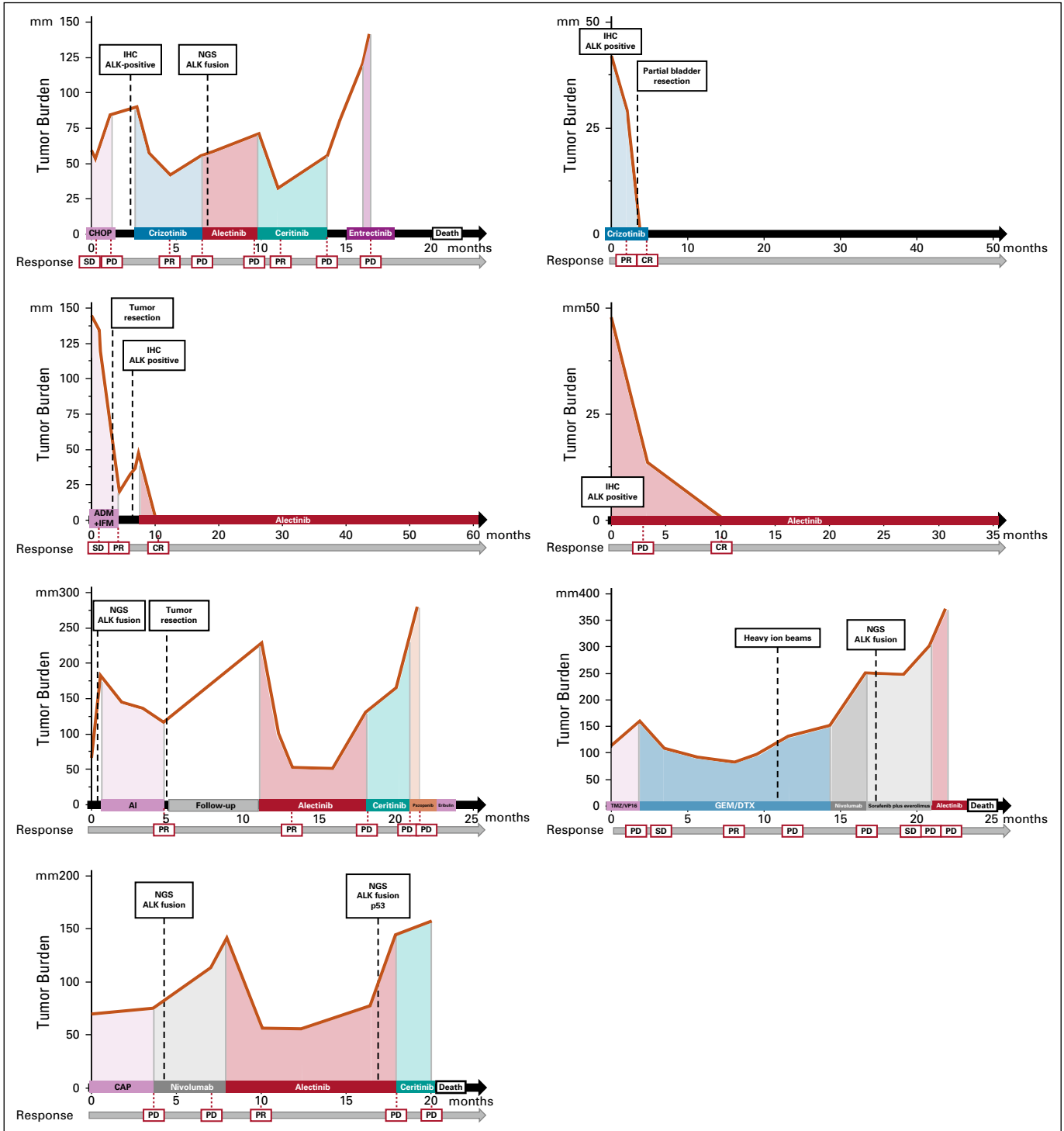
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FIG 2. Trends with tumor burden (sum of target lesions) and clinical courses for each case. ADM, adriamycin; AI, adriamycin/ifosfamide; ALK, anaplastic lymphoma kinase; CAP, cyclophosphamide/adriamycin/cisplatin; CHOP, cyclophosphamide/adriamycin/oncovin/prednisolone; CR, complete response; DTX, docetaxel; GEM, gemcitabine; IFM, ifosfamide; IHC, immunohistochemistry; NGS, next-generation sequencing; PD, progressive disease; PR, partial response; SD, stable disease; TMZ, temozolomide; VP-16, etoposide.
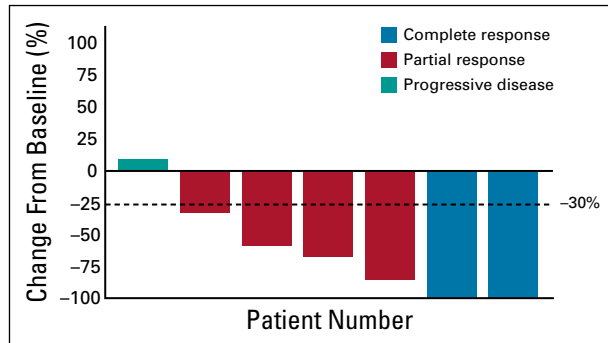
FIG 3. Waterfall plot of best response to initial ALK-TKI. ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor.

β-catenin and is responsible for organizing and tethering actin filaments at the zones of E-cadherin–mediated cell-cell contact, which can be seen in the cell membrane when stained by IHC for α-E-catenin.[29,30] Different ALK staining patterns have been described in *ALK*-rearranged tumors depending on the localization of the various fusion proteins.[31]

We also detected an *ITSN2-ALK* fusion in a patient with osteosarcoma who demonstrated poor sensitivity to alectinib. Although many previous studies have reported other *ALK* fusion partners and breakpoints, little is still known about the true oncogenic role of fusion variants other than the common fusions found in NSCLC,[32] let alone the clinical efficacy of ALK-TKIs for rare *ALK* fusion variants. The *ITSN2-ALK* fusion gene we identified by NGS resulted from a fusion between *ITSN2* (exon 32) and *ALK* (exon 14). However, IHC was negative despite FISH positivity with predominant isolated *ALK* 3′ signals, suggesting that this fusion may not be an activating alteration despite genomic rearrangement. Although our NGS analysis detected *ALK-ITSN2* fusion reads, that is, the possible reciprocal counterpart of *ITSN2-ALK*, it is possible that an *ITSN2-ALK* gene fusion also occurs. Since the fusion gene maintained the ALK kinase domain and the *ITSN2* portion of the fusion gene included the coiled coil domain, the rearranged gene might have resulted in production of an oncogenic fusion protein. However, given the negative IHC results and the poor response to alectinib, the rearrangement is unlikely to have produced the *ITSN2-ALK* fusion gene (Appendix Fig A1C). Only one other *ITSN2* (exon 29)-*ALK* (exon 18) fusion has been reported so far, specifically in a patient with thyroid cancer.[33] In that case, RNA-Seq showed overexpression of *ALK* exons 18-29 downstream of the fusion point; however, neither IHC results nor the therapeutic effects of ALK-TKIs were reported.

Next-generation ALK-TKIs such as alectinib, ceritinib, and lorlatinib have shown antitumor activity in patients with ALK-positive NSCLC who were previously treated with a different ALK-TKI.[34,35] In our study, two patients (one with *CLTC-ALK* and the other with *CTNAA-ALK*) who progressed on alectinib were treated with ceritinib. One patient (*CLTC-ALK*) achieved PR, confirming the clinical efficacy of ceritinib. This patient had initially responded to crizotinib, but did not show a response to subsequent alectinib. Since a previous study found that ceritinib was effective in patients with NSCLC treated with first-line alectinib, our results are in line with expectations about rechallenging with ALK-TKIs.[34] We could not examine the molecular mechanism of resistance to previous ALK-TKI treatment or the efficacy of lorlatinib, a third-generation ALK-TKI. Resistance to ALK inhibitors in *ALK*-rearranged NSCLC is known to result from secondary mutations such as gatekeeper mutations or the emergence of fusion-negative tumor cells.[36-38] Therefore, we conducted plasma NGS (Guardant360) in the patient with *CTNNA1-ALK* fusion–positive parotid adenocarcinoma at disease progression after he was treated with alectinib. We identified *TP53* T253A and *PIK3CA* E547A mutations but did not detect any *ALK*-related alterations, including the *ALK* fusion found in the tumor tissue. The failure to identify this *ALK* fusion in the serial biopsy may be a result of the alectinib treatment or the limited detection power of NGS when using cell-free DNA. Moreover, Petros et al reported that detection of *TP53* mutations was associated with poor TKI-response in patients with ALK-positive NSCLC.[39] These factors may explain the poor outcome after treatment with ceritinib in our patient with parotid adenocarcinoma.

This case series has several limitations. First, this was a retrospective study conducted at a single institution with a small sample size and a variety of malignant solid tumors. In addition, because of the lack of systematic strategy at the time to identify patients with rare cancer with a specific genomic characteristic, we did not systematically identify ALK-positive solid tumors. Therefore, there might have been ALK-positive cases that did not receive ALK-TKIs outside of this case series. However, these study characteristics are not unusual because of the nature of rare cancers and we have made improvements in the process by building a registry study for rare cancers. Second, we did not perform NGS sequencing in all patients, and therefore, it was not possible to demonstrate a clear correlation between the efficacy of ALK-TKI treatment and each *ALK* fusion partner. In the era of personalized medicine involving the idea of the $1,000 genome, such precise mechanisms may gradually become clarified, since only FISH was performed before the development of NGS. The MASTER KEY project[40] is a platform study being conducted in Japan that includes a prospective registry study and multiple clinical trials (UMIN000027552). One of the clinical trials is an investigator-initiated, single-arm, open-label, phase II trial of alectinib for patients with ALK-positive rare cancers (JMA-IIA00364). These platforms are essential since they centrally accumulate limited data in a comprehensive manner, as opposed to instances in which each patient with rare cancer is treated with a driver-directed therapy at a local hospital, and the valuable patient data are scattered.
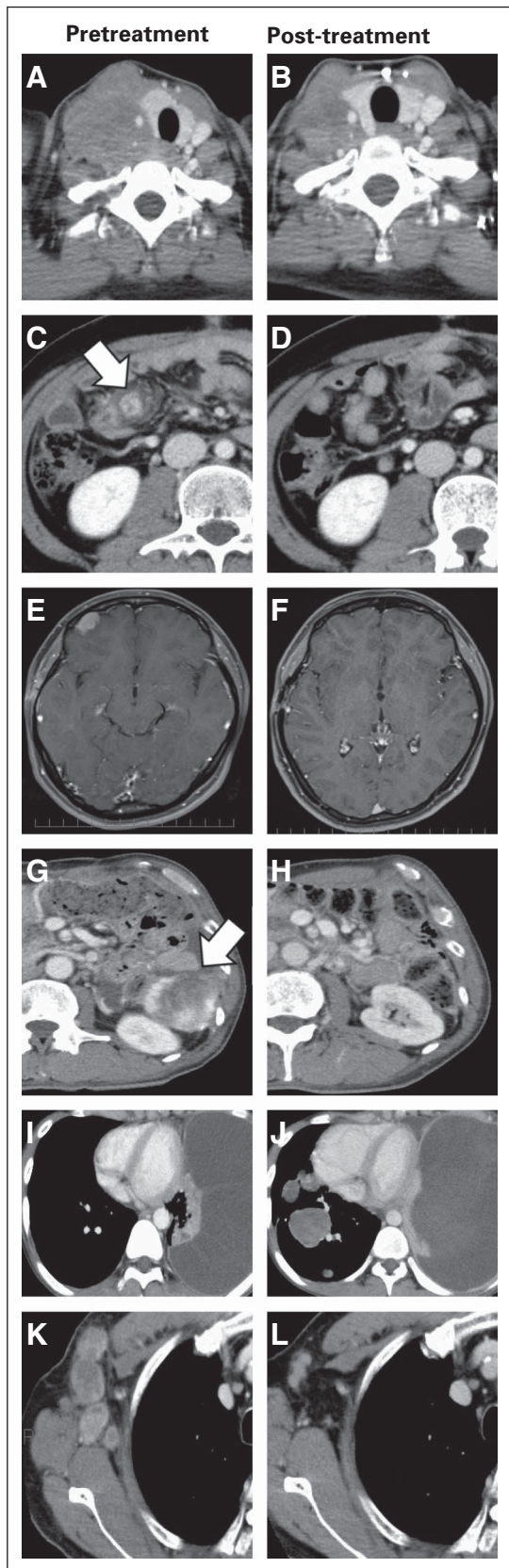
FIG 4. Diagnostic radiographic images of representative cases. (A and B) Patient 1: histiocytic sarcoma showing PR; (C and D) patient 3: IMT (epithelioid) showing CR; (E and F) patient 4: ALK-positive histiocytosis showing CR; (G and H) patient 5: IMT; (I and J) patient 6: osteosarcoma showing PD; and (K and L) patient 7: parotid adenocarcinoma showing PR. ALK, anaplastic lymphoma kinase; CR, complete response; PD, progressive disease; PR, partial response; IMT, inflammatory myofibroblastic tumor.

In conclusion, our data suggest that *ALK* fusions are found in rare solid tumors outside of NSCLC and will lead to clinical benefit for patients in the era of personalized medicine. The ongoing clinical phase II trial is expected to result in new evidence and treatment options for this small patient population.

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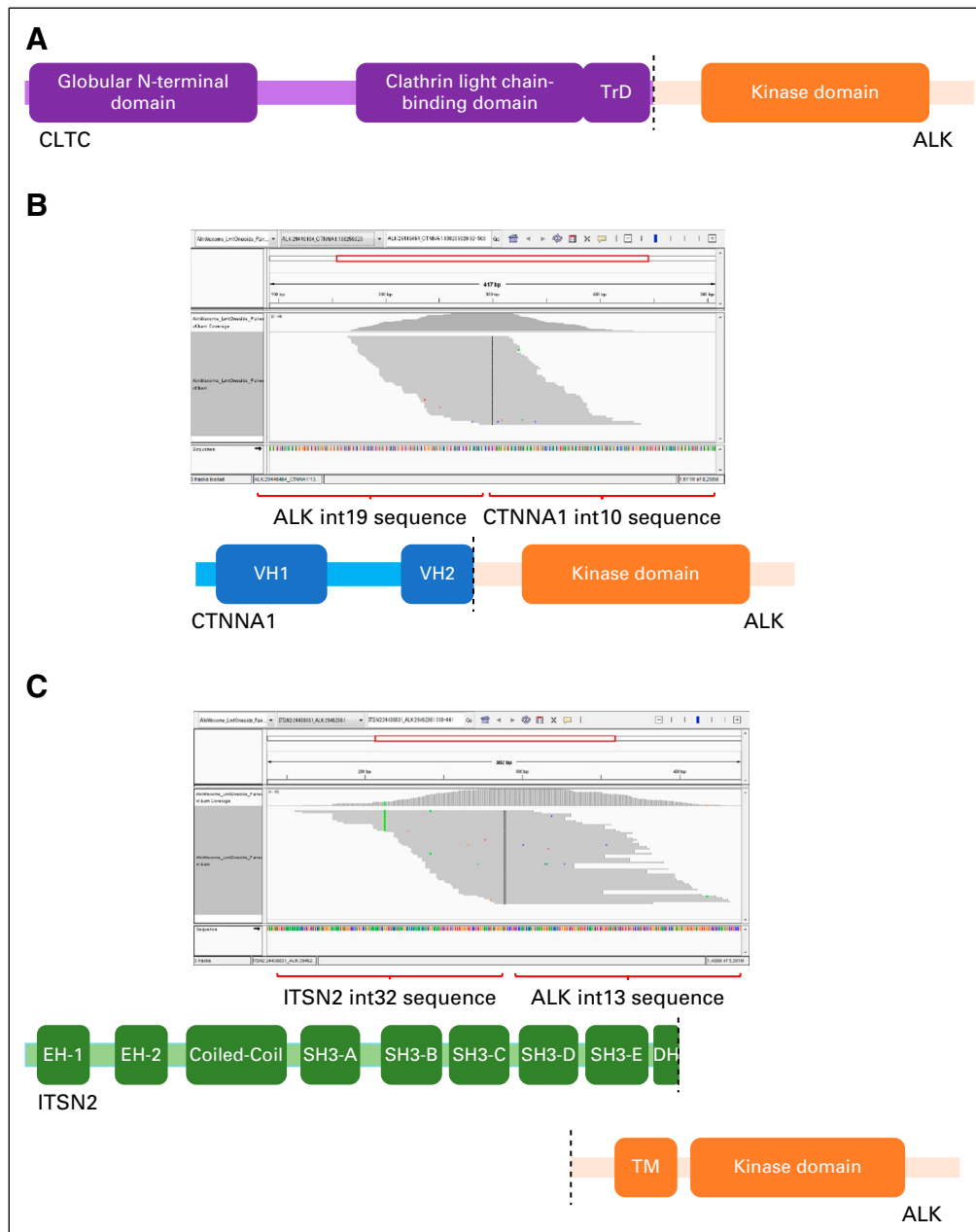
APPENDIX

FIG A1. (A) Schematic figures of gene fusions detected by NGS (patients 1 and 5): patient 1: *CLTC|ALK* fusion chr17: 57, 769, 218-chr2:29, 447, 574 (exon 31: exon 20) and patient 5: *CLTC|ALK* fusion chr 17:57, 768, 627-chr 2: 29,446,555 (exon 31: exon 20); (B) NGS sequencing results and schematic figure of patient 7: *CTNNA1-ALK* fusion. Patient 7: *CTNNA1|ALK* fusion chr5:138, 259, 019-chr2:29, 446, 464 (exon 10: exon 20); (C) NGS sequencing results and schematic figure of patient 6: *ITSN-ALK* fusion. Patient 6: ITSN2|ALK fusion chr2:29,462,361-chr2: 24,438,831 (exon 14: exon 32); ALK, anaplastic lymphoma kinase; chr2, chromosome 2; DH, Dbl homology domain; EH, Eps15 homology domain; IMT, inflammatory myofibroblastic tumor; ITSN2, intersectin 2; NGS, next-generation sequencing; SH3, Src three homology domain; TM, transmembrane domain; TrD, trimerization domain; VH1, vinculin homology one domain; VH2, vinculin homology two domain.