STRN-ALK Fusion–Positive Case of Breast Cancer With Response to Alectinib

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Introduction

Anaplastic lymphoma kinase (*ALK*) fusion rearrangements were first described in anaplastic large cell lymphoma and subsequently defined in non–small-cell lung cancer (NSCLC) as capable of inducing malignant transformation.[1,2] Such fusion events in cancer involve numerous partner genes, but invariably retain the ALK kinase domain coded for by exon 20 and are present in about seven percent of NSCLC cases.[3,4] Recent data have demonstrated high overall response rates and improved progression-free survival with *ALK*-directed kinase inhibitors including entrectinib, alectinib, and brigatinib in NSCLC, but have limited data in other tumor types.[5-9] One recent study of 4,854 genomically sequenced breast cancer (BC) cases identified one *EML4-ALK* fusion in a patient with estrogen receptor–positive disease.[10] Another study using exon arrays identified another five cases with *EML4-ALK*; however, we are not aware of other published cases involving *EML4* or other *ALK* fusion partners.[11] Here, we report the first case of *STRN-ALK* fusion–positive BC in a patient who responded to alectinib.

Case Report

A 52-year-old woman presented with a breast mass. Whole-body computed tomography (CT) did not show evidence of distant metastasis and the patient was treated with mastectomy. Histopathology demonstrated grade 3 papillary adenocarcinoma, which was estrogen receptor–positive, progesterone receptor–negative, and human epidermal growth factor receptor 2–negative. She received adjuvant therapy with docetaxel, cyclophosphamide, epirubicin, and fluorouracil. She also underwent adjuvant radiation and received tamoxifen, with clinical stability for 9 months postsurgery. The patient subsequently presented with widespread advanced BC and received several further lines of systemic treatment. The patient progressed on docetaxel, experienced a partial response to paclitaxel and carboplatin, and progressed again on palbociclib with letrozole. Her condition continued to deteriorate. A schematic of this clinical history and lines of therapy is diagrammed in Figure 1A. She presented at Docrates Cancer Center in October 2020. A liver lesion was biopsied and sent for comprehensive genomic profiling using the FoundationOneCDx panel interrogating 324 genes involved in cancer (Foundation Medicine, Cambridge, MA).[12] The primary mastectomy specimen was also sent to Foundation Medicine for genomic profiling, and patient consent was obtained for publication of genomic and clinical data. The primary tumor and liver metastasis were both found to be GATA-binding protein 3–positive and thyroid transcription factor-1–negative.

The NGS results demonstrated an *STRN-ALK* fusion rearrangement (S3; A20, Fig 1B), a *TP53 R306** nonsense mutation, and an *MSH6* duplication involving exons 4-9 in both the primary and metastatic tissue samples. Despite a potentially inactivating *MSH6* alteration, both samples demonstrated a tumor mutation burden of three mutations per megabase and microsatellite stability (which was orthogonally confirmed by immunohistochemistry for mismatch repair proteins). Several low-level copy-number amplifications were also identified in the liver metastasis only (Table 1). The sequenced breast primary sample demonstrated relatively high tumor content (60% *v* 31% in liver metastasis), suggesting these copy-number alterations were likely acquired during tumor progression (rather than present but not detected in the breast primary). Based on the presence of the *STRN-ALK* fusion, the patient was started on alectinib with a baseline CT shown at day 7 of treatment (Fig 1C), and a baseline cell-free tumor DNA (cfDNA) measurement of 45.6 ng/mL. During follow-up on day 19 on alectinib, cfDNA was noted to be 5.82 ng/mL and whole-body CT imaging demonstrated partial response of lung and lymph node metastasis with mixed response in the liver and increased sclerosis of the bone metastasis (Fig 1C). At two-month follow-up, however, radiographic evidence of progression was noted in the liver with a new lung lesion also observed (Fig 1C). There appeared to be continued response in bone lesions and lymph nodes, with increased cfDNA to 19.45 ng/mL at the time of this writing, and the patient decided not to pursue additional lines of therapy or testing.

Written consent was obtained from the patient discussed in this manuscript that results from genetic profiling and subsequent and previous clinical data can be published. The consent was reviewed by appropriate outside ethics counsel that represents institutional review board for Docrates as a private hospital.

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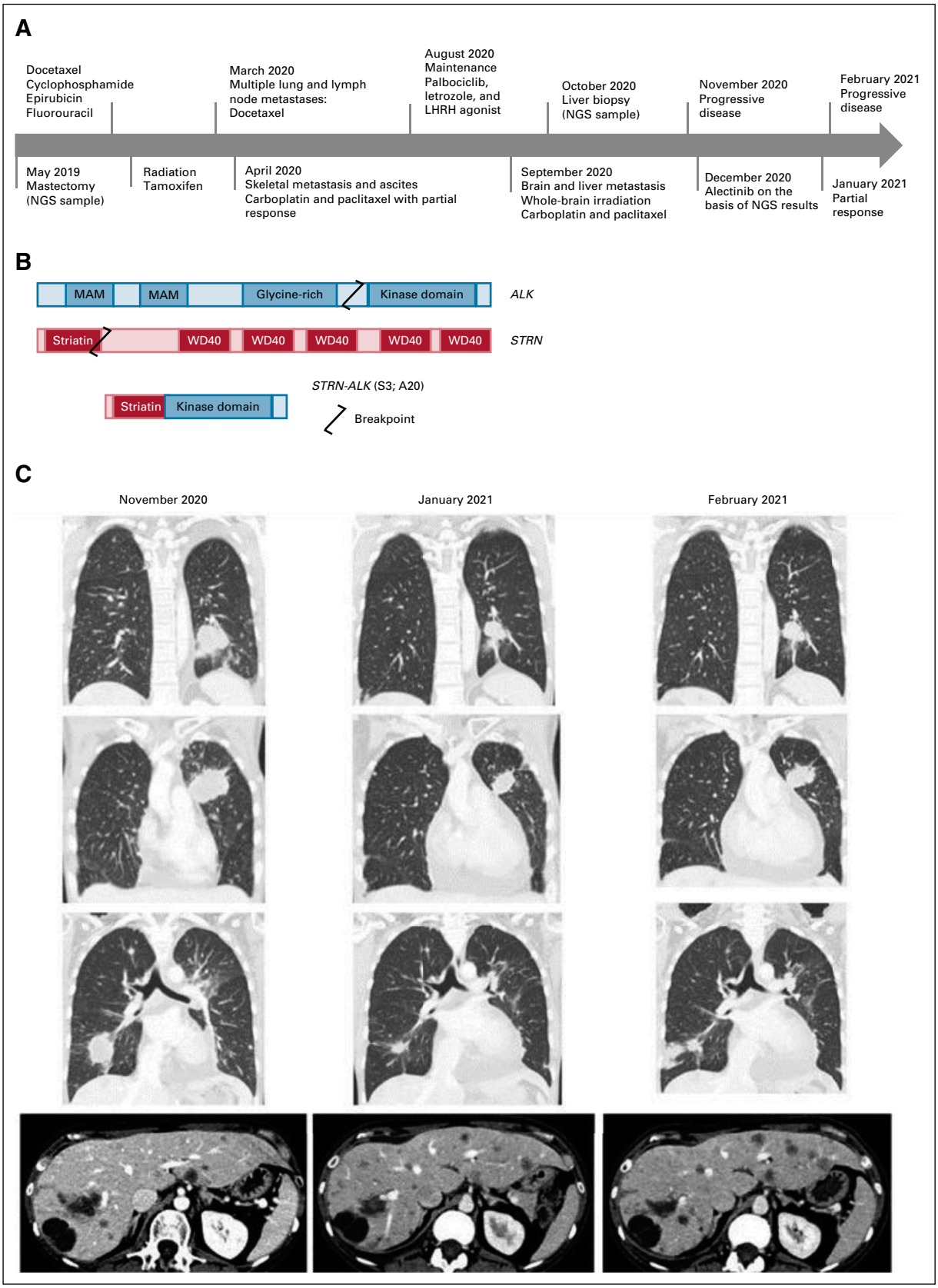

FIG 1. Clinical course of *STRN-ALK*–driven breast cancer: (A) timeline of therapies and patient response, (B) diagram of *STRN-ALK* fusion rearrangement, and (C) baseline and follow-up CT scans after initiating alectinib therapy. CT, computed tomography; LHRH, luteinizing hormone-releasing hormone; NGS, next generation sequencing.

TABLE 1. Genomic Alterations Detected by NGS

Breast Primary (estimated tumor purity = 60%)	Liver Metastasis (estimated tumor purity = 31%)
Microsatellite stable	Microsatellite stable
Tumor mutation burden = 3 mutations/megabase	Tumor mutation burden = 3 mutations/megabase
STRN-ALK fusion	*STRN-ALK* fusion
*TP53 R306** (variant allele frequency = 47.6%)	*TP53 R306** (variant allele frequency = 31.7%)
MSH6 duplication exons 4-9	*MSH6* duplication exons 4-9
	CCND2 amplification
	BRAF amplification
	FGF23 amplification
	FGF6 amplification
	KDM5A amplification
	KEL amplification
	LYN amplification—equivocal

Discussion

Alectinib is a selective tyrosine kinase inhibitor approved by the US Food and Drug Administration for *ALK*-positive NSCLC based on extensive clinical data showing high overall response rates and improved outcomes compared with crizotinib.[6] *ALK* fusion rearrangements in other tumor types are rare, and there are limited data supporting the role of *ALK*-directed agents in BC. The case report described here helps address at least two open questions. First, the most common *ALK* fusion partner described in solid tumors is *EML4*, and there are multiple distinct rearrangement breakpoints reported with different associations with clinical outcomes.[13] The rarity of *STRN* as a fusion partner has precluded large analyses to date evaluating sensitivity of *STRN-ALK*–positive solid tumors to ALK inhibitors with only a handful of published case reports. Several patients with lung adenocarcinoma positive for *STRN-ALK* were shown to respond to *ALK*-directed agents.[14-16] Another patient with malignant mesothelioma achieved a response to ceritinib.[17] This patient's response to alectinib suggests that the *STRN-ALK* (S3; A20) fusion is likely *ALK* inhibitor–sensitive. Second, *ALK* fusions are exceedingly rare in breast tumors, and this case identifies a novel initial driver event as demonstrated by the presence of *STRN-ALK* in both primary mastectomy and liver metastatic specimens. The existing published case of *EML4-ALK*–positive BC identified the fusion only in a posthormonal therapy progression sample, suggesting a mechanism of resistance, but not necessarily a tumor-initiating event. The presence of *STRN-ALK* in this patient's mastectomy sample—and the relative paucity of other alterations—suggests that in this case, the *STRN-ALK* fusion may have been the transforming event. Interestingly, this observation is in line with multiple analyses of colorectal carcinomas harboring kinase gene fusions, which demonstrate a relative lack of pathogenic alterations in other oncogenic drivers like *BRAF* or *KRAS*, and enrichment for microsatellite instability because of *MLH1* promoter methylation.[18-20] Although this patient had microsatellite stable disease, they also harbored an *MSH6* alteration affecting a similar region to a reported germline variant, potentially representing a shared molecular phenotype.[21]

The pattern of progression this patient experienced after two months on targeted therapy after response hints that genomic heterogeneity of metastatic sites could drive alectinib resistance, as multiple alterations were present in the liver but absent in the primary tumor. Because of the comparable sample quality and tumor content, it is unlikely that these differences were technical in nature. Of note, there were no identified *ALK* substitution mutations reported to cause kinase inhibitor resistance, but the amplification of wild-type *BRAF* represents at least a theoretical mechanism for bypass oncogenic signaling independent of *ALK* activity.[22] To our knowledge, amplification of wild-type *BRAF* has not been reported as a mechanism of resistance to alectinib, but merits further study. Because of patient preferences, additional sequencing at the time of progression on alectinib was not pursued; so, we are unable to determine whether any established mechanisms of acquired resistance were present. However, in the setting of lung adenocarcinoma, alectinib resistance has been reported in one *STRN-ALK*–positive patient who lacked known resistance mutations, suggesting alternative mechanisms may be responsible.[23]

In summary, to our knowledge, we present the first case of *STRN-ALK* fusion–driven BC with response to alectinib. This case highlights clinical actionability derived from comprehensive genomic profiling results outside standard-of-care BC management, which would not otherwise interrogate *ALK*. Patients with advanced BC harboring rare fusion rearrangements may benefit from therapies shown to benefit other more common fusion partners in other tumor types.

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