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Activity of Brigatinib in Crizotinib and Ceritinib-Resistant *ROS1*-Rearranged Non–Small-Cell Lung Cancer

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ASSOCIATED CONTENT

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INTRODUCTION

One to two percent of non–small-cell lung cancers (NSCLCs) harbor *ROS1* gene rearrangements.[1–3] *ROS1* gene rearrangement leads to constitutive activation receptor tyrosine kinase that activates downstream mitogen-activated protein kinase, phosphoinositide-3 kinase, signal transducer and activator of transcription 3, and other pathways leading to oncogenesis.[4]

Because *ROS1* shares 49% amino acid sequence homology with anaplastic lymphoma kinase *(ALK)* in the kinase domain, *ROS1* rearranged (*ROS1*-positive) NSCLC tends to be sensitive to ALK inhibitors.[5] Crizotinib, a mesenchymal epithelial transition factor (MET)/ALK/ROS1 tyrosine kinase inhibitor (TKI), is the only US Food and Drug Administration–approved drug for *ROS1*-positive NSCLC.[6] Ceritinib and brigatinib, second-generation ALK inhibitors, have demonstrated activity in crizotinib-naÏve *ROS1*-positive NSCLC but lacked activity in patients who were crizotinib resistant in anecdotal cases.[7,8] However, the efficacy of both ceritinib and brigatinib in patients who are crizotinib resistant remains unclear. We previously reported the preliminary systemic and intracranial activity of ceritinib in a crizotinib-refractory patient.[9] Herein, we report the activity of brigatinib in the same patient (Fig 1A).

CASE REPORT

A 77-year-old white man with a prior history of smoking presented with shortness of breath. Chest radiograph revealed a right lower lobe (RLL) nodule. Computed tomography (CT) scan of the chest confirmed a 1.5-cm irregular nodular opacity within the RLL. Biopsy indicated a cytokeratin 7– and thyroid transcription factor-1-positive adenocarcinoma. He underwent RLL lobectomy, which confirmed T2aN1M0, stage IIA NSCLC. Hot spot molecular testing was negative for *EGFR, KRAS,* and *BRAF* mutations, and fluorescence in situ hybridization was negative for *ALK* gene rearrangement. He received adjuvant carboplatin and pemetrexed. Fludeoxyglucose positron emission tomography–CT scan after completing four cycles of chemotherapy showed increasing pleural nodularity. Comprehensive next-generation sequencing of tumor tissue obtained revealed a *CD74-ROS1* rearrangement (Fig 1B). Crizotinib 250 mg orally twice daily was initiated. After two cycles of crizotinib, positron emission tomography–CT imaging showed resolution of metastatic disease. He remained disease free for 13 months until a follow-up CT scan of the chest showed relapse, with two RLL nodules. He received stereotactic ablative radiotherapy to two RLL nodules (50 Gy in four fractions). Chest CT scan performed 1 month after stereotactic ablative radiation showed treatment response in one of the two RLL nodules but multiple new pleural nodules. Magnetic resonance imaging (MRI) of the brain also demonstrated new bilateral cerebellar enhancing lesions. Each of the two cerebellar lesions was treated with gamma knife radiosurgery (20 Gy to 50% isodose), and the patient was enrolled in an anti–cytotoxic T-cell lymphocyte-4 antibody ipilimumab and radiation trial (ClinicalTrials.gov identifier: NCT02239900). As per trial protocol, he received external beam radiotherapy to the RLL lesion (60 Gy in 10 fractions) with concurrent ipilimumab. There was disease progression noted in mediastinal lymph nodes and pleural metastasis while on the aforementioned trial. In addition, he developed auto-immune hypophysitis and was off

therapy for 3 months.[10] Restaging confirmed progression in multiple sites. He was then enrolled in the modular phase II basket SIGNATURE (ClinicalTrials.gov identifier: NCT02186821) trial with ceritinib for *ROS1*-aberrant cancers at 750 mg orally daily.[11] Restaging scans after two cycles and once again after four cycles confirmed a partial response (PR; 56% decrease) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. In addition, MRI showed reduction in brain metastasis. He continued to have PR while receiving ceritinib for 8 months, until it had to be held for grade 3 elevation in AST and ALT. During this treatment hiatus, he developed new brain metastases and had to be taken off the trial. He received whole-brain radiation therapy (30 Gy in 10 fractions). After multidisciplinary consensus, given his prior response to ceritinib, he restarted ceritinib at 600 mg orally daily off-label. Ceritinib continued to clinically benefit the patient, demonstrating both systemic and CNS activity for another 17 months. Eventually, he experienced progression in brain metastases, mediastinal lymph nodes, and RLL lesions. Plasma cell-free DNA (cfDNA) testing (Guardant panel, Guardant Health, Redwood, CA) showed *NOTCH S2435S, TP53 G245A,* and *P190T,* as well as *FBXW7 G477S* mutations but no *CD74-ROS1* fusions or other *ROS1* pathway aberrations. Given the preclinical activity of brig-atinib in *ROS1* fusion-positive cancers,[12] he was administered brigatinib 90 mg orally once daily 12 days after discontinuing ceritinib. Four days after starting brigatinib, it was held because of grade 2 fatigue (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03). Brigatinib was restarted 3 weeks later at 30 mg orally once daily and escalated to 90 mg over the course of 3 days. He continued to receive brigatinib 90 mg daily for 2 more months, with grade 1 fatigue and no other adverse effects. Restaging MRI after two cycles of brigatinib showed stable brain metastases and no new lesions. CT scan of the chest also showed 59% decrease in target lesions by RECIST 1.1 criteria (unconfirmed PR), with decrease in RLL lesions and resolution of mediastinal lymphadenopathy (Fig 1C). Unfortunately, 1 month later he experienced a fall, leading to hospitalization. MRI at this juncture continued to show stable brain metastases with no new lesions. However, owing to a significant decline in performance status (Eastern Cooperative Oncology Group score, 4) due to other comorbidities and prolonged hospitalization, he was transitioned to hospice care.

DISCUSSION

To our knowledge, this is the first report of crizotinib-resistant *ROS1*-positive NSCLC responding for an extended period of time (25 months), to ceritinib[9] and sub-sequently to brigatinib. Mechanisms of resistance to crizotinib in *ROS1*-positive NSCLC include mutations involving the *ROS1* kinase domain and activation of bypass signaling pathways.[13–15] The most common of the *ROS1* resistance mutations is the G2032R solvent front mutation that causes steric interference to crizotinib binding.[15,16] The G2032R mutation occurs in close to 50% of crizotinib-resistant NSCLC.[15] In vitro studies have demonstrated that both ceritinib and brigatinib are unable to overcome the common G2032R resistance mutation.[12,17] Various other mutations in the *ROS1* kinase domain confer resistance to crizotinib.[18–21] Of these, the L2026M gatekeeper mutation maintains sensitivity to ceritinib and brigatinib.[12,20] Brigatinib is a TKI that has preclinical activity against *ROS1.*[12] In an in vitro kinase inhibitory screen of more than 300 kinases, *ALK*(half maximal inhibitory

concentration[IC_{50}]; 0. 6 nM) was the only kinase inhibited with an IC_{50} less than 1 nM. Excluding *ALK* variants, 10 kinases (3% of those assayed) were inhibited by brigatinib with an IC_{50} within 10fold of *ALK* (ie, less than 6 nM), including *ROS1* (IC_{50}, 1.9 nM). Brigatinib potently inhibited viability of Ba/F3 cells expressing *FIG-, CD74-, SDC4-,* or *EZR-ROS1* fusions (IC_{50} from 16 nM to 41 nM) with potency similar to that of crizotinib (IC_{50}, 17 to 52 nM). Introduction of a mutation at the gatekeeper residue (L2026M) of a *CD74-ROS1* fusion had no effect on the potency of brigatinib, whereas crizotinib potency was reduced five-fold.[12] Bio-chemical potency of crizotinib, ceritinib, and brigatinib, all of which our patient received, is listed in Appendix Table A1. One explanation is the presence of L2026M or another mutation that conferred resistance to crizotinib but remained sensitive to ceritinib and brigatinib. Another possibility is the re-emergence of the *CD74-ROS1* fusion during ipilimumab plus radiation and the subsequent 3-month treatment hiatus because of lack of selection pressure in the absence of crizotinib, rendering the tumor sensitive to ceritinib. However, the lapse between ceritinib and brigatinib therapy was only 12 days, making such a phenomenon less likely.

One of the major limitations of this study is the lack of on-and post-progression biopsies, which are critical to understanding response and/or resistance mechanisms. These were not performed because the patient declined biopsy, considering advanced age, comorbidities, clinical urgency of treatment at progression, and the risk of pneumothorax. Instead, we obtained cfDNA testing (Guardant panel) at disease progression, which was nondiagnostic, either because of *ROS1* cfDNA suppression by ongoing ceritinib treatment or limited sensitivity of the cfDNA platform in detecting the *ROS1* fusion. Evolving cfDNA platforms will improve our ability to detect these fusions.[22,23]

Apart from *ROS1* resistance mutations, poor CNS penetration of crizotinib is a frequent cause of CNS progression and failure of therapy.[24,25] In a phase II study of ceritinib in ROS1-positive NSCLC, 25% and 63% of patients had intracranial response and intracranial disease control, respectively.[7] Brigatinib demonstrated superior CNS activity in both preclinical and clinical studies of ALK-rearranged NSCLC.[12,26] In an exploratory analysis of the phase I/II ALTA (ClinicalTrials.gov identifier: NCT02094573) trial, brigatinib intracranial response rate was 53%.[26] Intracranial response rate was similar in both patients without prior irradiation and those who had progressed after radiation. Although CNS activity of brigatinib in *ROSI*-positive NSCLC is not documented, it is likely superior to crizotinib and possibly even ceritinib, given the findings in *ALK*-rearranged NSCLC. The CNS activity of both ceritinib and brigatinib in our patient is noteworthy. Ceritinib induced a response in previously irradiated CNS lesions, and brigatinib was able to maintain intracranial disease control in twice-irradiated CNS metastases. Our patient was refractory to ipilimumab and radiation but responded promptly to subsequent *ROSI*-directed therapy, once again highlighting the lack of benefit of second-line immune checkpoint monotherapy in patients with certain subsets of oncogene-driven NSCLC.[27,28]

Several *ROSI*-directed TKIs are being studied in clinical trials (Table 1). While outcomes of these trials are awaited, ceritinib and brigatinib may still have a role in the treatment of crizotinib-resistant *ROSI*-positive NSCLC. This report further emphasizes the need for

efficacious *ROSI* inhibitors with activity against resistance mutations and better CNS penetrance.

APPENDIX

TABLE A1.

Biochemical Potency of US Food and Drug Administration–Approved ALK Inhibitors With *ROS1* Inhibitory Activity Against *ROS-1* and *ROS-1* Mutants

	Cellular Assay* IC_{50} (nM)		
Compound	***CD74-ROS1***	***CD74-ROS1 (G2032R)***	***CD74-ROS1 (L2026M)***
Crizotinib[12]	25	1,600	127
Ceritinibt	72.9	1,900	ND
Brigatinib[12]	18	1,100	17

Abbreviations: ALK, anaplastic lymphoma kinase; IC_{50}, half maximal inhibitory concentration; ND, not determined.

*Potency assessed by viability assays using Ba/F3 cells, whose survival was dependent on activity of the indicated fusion protein.

†Davare MA, et al: Proc Natl Acad Sci USA 112:E5381-E5390, 2015

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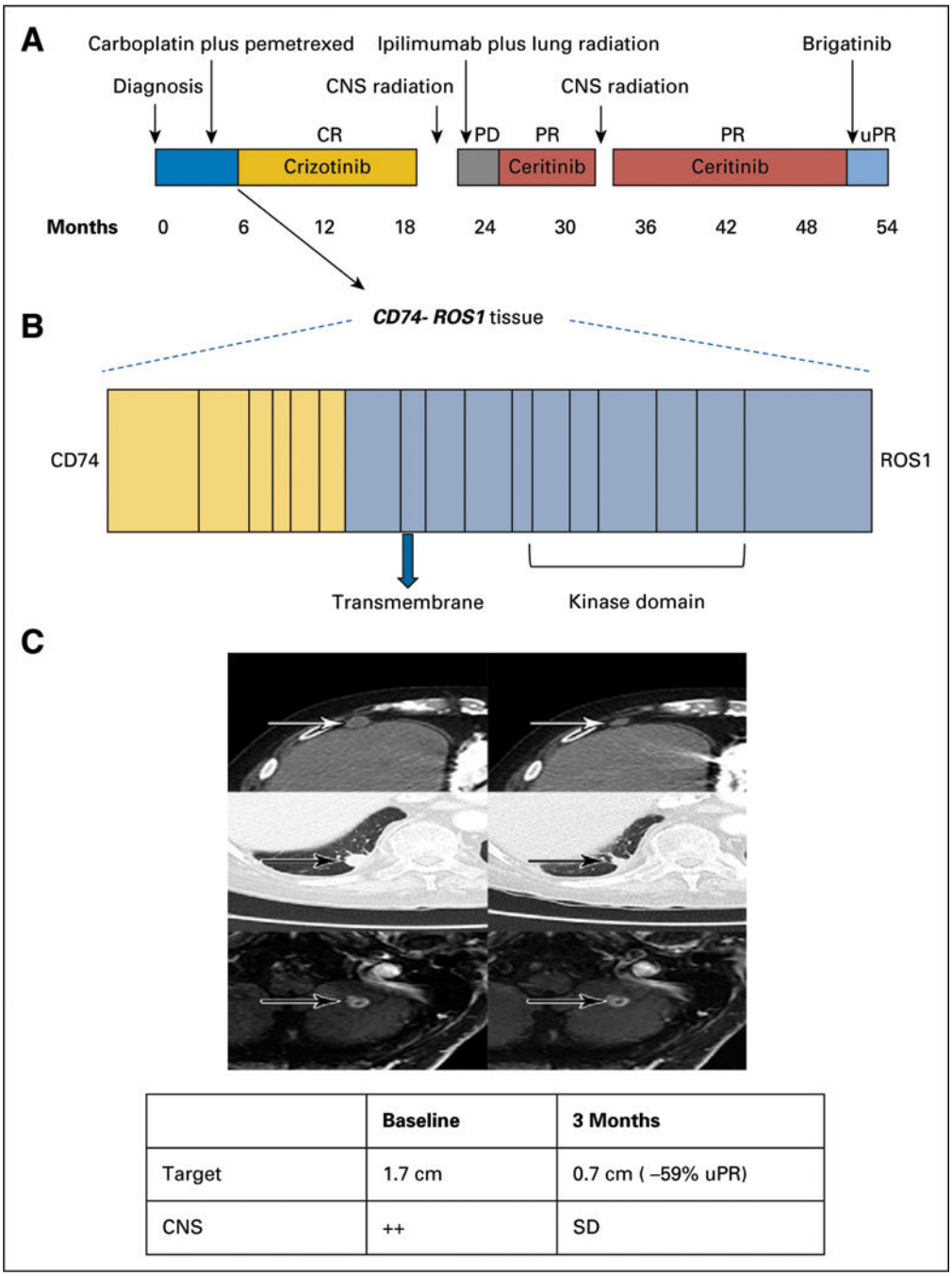

	Baseline	3 Months
Target	1.7 cm	0.7 cm (–59% uPR)
CNS	++	SD

FIG 1.

Clinical activity of brigatinib in crizotinib-and ceritinib-resistant *ROS1*-positive non–small-cell lung cancer. (A) The various treatments the patient received for metastatic *ROS1*-positive non–small-cell lung cancer, along with the duration of and best response to each treatment. (B) Fusion event: 5′-*CD74*(x1–6 NM_004355)-3′-*ROS1*(x33–43 NM_002944) breakpoints *CD74* intron 6, *ROS1* intron 32. (C) Computed tomography and magnetic resonance images of the patient's right anterior diaphragmatic lymph node, right lower lobe nodule, and left cerebellar metastases before and at the indicated times after he initiated

treatment with brigatinib. A radiologic unconfirmed partial response by Response Evaluation Criteria in Solid Tumors 1.1 was achieved after 3 months in the target lesion (right lower lobe nodule), with concurrent response in the right anterior diaphragmatic lymph node and stable cerebellar metastases. CR, complete response; PD, progressive disease; PR, partial response; uPR, unconfirmed partial re-sponse; SD, stable disease.

TABLE 1.

Ongoing Clinical Trials of ROS1-Targeted Agents

Drug	Phase	Study	In Vitro Activity Against G2032R
Cabozantinib	II	NCT01639508	Yes[20]
Lorlatinib	I	NCT01970865	Conflicting[29,30]
	II	NCT02927340	
Repotrectinib	I/II	NCT03093116	Yes[31]
DS-6051b	I	NCT002279433	Unknown
Entrectinib	I	ALKA-372–001	No[32,33]
	I	STARTRK-1	
	II	STARTRK-2	
Brigatinib	I/II	NCT01449461	No[12]