case reports

Response to Cabozantinib Following Acquired Entrectinib Resistance in a Patient With *ETV6-NTRK3* Fusion-Positive Carcinoma Harboring the *NTRK3*^{G623R} Solvent-Front Mutation

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INTRODUCTION

Recently, neurotrophic tyrosine receptor kinase (NTRK) inhibitors have been highlighted as the first small molecule inhibitors to receive tissue-agnostic US Food and Drug Administration approval. Targeting oncogenic *NTRK* fusions, which appear at low frequencies across a broad range of cancer entities,[1–3] this class of inhibitors has demonstrated impressive clinical efficacy, achieving overall remission rates up to 75% regardless of the underlying tumor histology.[3–7] Nevertheless, development of acquired resistance to tyrosine kinase inhibitors (TKIs) occurs in a large proportion of patients and limits the duration of response.[8] Entrectinib has been developed as an ALK inhibitor overcoming acquired resistance to first-generation TKIs such as crizotinib and ceritinib, [9]but was also found to potently inhibit *ROS1* and *NTRK1-3*.[10,11] However, the duration of response is often limited by acquired resistance. Structural analyses identified the solvent-front motif—a conserved region that is shared by different tyrosine kinases (TKs) and gets in direct contact with the inhibitor—as a frequent site of resistance inducing mutations.[12] As a consequence of conserved amino acid sequences within the TK domains, homologies between distinct mutations across different receptor TKs are observed. The *NTRK3*^{G623R} mutation was initially reported in patients with *ETV6-NTRK3* fusion-positive mammary analogue secretory carcinoma or infantile fibrosarcoma that had experienced secondary resistance to NTRK inhibitors[13,14] and was found to be homologous to *NTRK1*^{G595R} and *NTRK2*^{G639R} (ref. 15) as well as *ALK*^{G1202R} and *ROS1*^{G2032R} mutations[16] that all convey resistance to entrectinib (Table 1). Although the *ROS1*^{G2032R} mutation has been reported to exhibit sensitivity to the US Food and Drug Administration–approved agents cabozantinib and foretinib, its homologue *NTRK1*^{G595R} was tested to be highly resistant to entrectinib, larotrectinib, as well as cabozantinib in preclinical models.[17–19] Therefore, it was assumed that no currently approved NTRK-targeting TKI would be able to overcome acquired resistance to NTRK inhibitors conveyed by the *NTRK3*^{G623R} solvent-front mutation.[14,20,21]

Here, we report a case of marked response to cabozantinib in a secondary entrectinib-resistant tumor harboring the *ETV6-NTRK3* fusion with a G623R solvent-front mutation. Written consent to publish the information contained in this article was obtained from the patient.

CASE REPORT

A 41-year-old male was referred to our department because of progressive pulmonary and cervical metastases. Sixteen months before (October 2016), the patient presented with a plum-sized tumor behind the right sternocleidomastoid muscle and was diagnosed with a carcinoma of unknown primary. Following tumor resection, histopathologic assessment of two completely resected lymph nodes demonstrated metastatic infiltration by a heterogeneously differentiated tumor consisting of a moderately well-differentiated TTF-1-positive adenocarcinoma with partly mucinous differentiation, single psammomatous calcifications, and areas of glandular as well as papillary differentiation. Additionally, it showed sarcomatous components with expression of myogenic markers (Figs 1A-1F). Because of the suspected diagnosis of a dedifferentiated thyroid carcinoma, a total thyroidectomy and cervical lymphonodectomy was performed followed by radioiodine ablation (Appendix Fig A1). Histopathologic work-up revealed a chronic lymphocytic thyroiditis but no malignant cells within the thyroid tissue. The patient relapsed three months later with a soft tissue metastasis of the right neck and underwent surgical resection once again. Histopathology at this timepoint indicated a sarcomatoid dedifferentiation with absence of the primarily observed adenocarcinomatous parts. Because of repeated local recurrence, cervical tumor manifestations were

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TABLE 1. Homologous Receptor Tyrosine Kinase Variants

Type	Gene	SNV	Entity	Resistant	Sensitive
Solvent-front mutation	*NTRK1*	p.G595R	*LMNA–NTRK1*-rearranged colorectal cancer	Entrectinib (PMID 26546295), larotrectinib (PMID 28578312), cabozantinib, nintedanib, foretinib, ponatinib, merestinib (PMID 30333516)	LOXO-195 (selitrectinib) (PMID 28578312), TPX-0005 (repotrectinib) (doi: 10.1158/1535-7163, 10.1158/1535-7163.TARG-17-B185)
	NTRK2	p.G639R	Preclinically engineered: Ba/F3 cells		TPX-0005 (repotrectinib) (PMID 30093503)
	NTRK3	p.G623R	*ETV6–NTRK3*-rearranged infantile fibrosarcoma, MASC	Entrectinib (PMID 26884591), larotrectinib (PMID 28578312)	LOXO-195 (selitrectinib) (PMID 28578312), TPX-0005 (repotrectinib) (doi: 10.1158/1535-7163)
		p.G623E	MASC	Entrectinib (PMID 30093503)	TPX-0005 (repotrectinib) (PMID 30093503)
	ALK	p.G1202R	NSCLC	Crizotinib (PMID 24675041, PMID 23401436), ceritinib, alectinib, brigatinib (PMID 27432227), entrectinib (PMID 26939704)	Lorlatinib effective in EML4-ALK Ba/F3 cells (PMID 27432227, 26144315)
		p.G1202del	BA/F3 *EML4-ALK*-cell line	Moderate resistance to ceritinib, alectinib, brigatinib (PMID 30892989)	Crizotinib potency only slightly affected (PMID 27432227)
	ROS1	p.G2032R	NSCLC	Crizotinib (PMID 23724914), entrectinib, ceritinib, brigatinib, ensartinib (PMID 30093503)	Cabozantinib, foretinib, TAE684 (PMID 25351743), TPX-0005 (repotrectinib) (PMID 30093503)
		p.D2033N	Lung adenocarcinoma	Crizotinib (PMID 26673800), entrectinib, ceritinib, brigatinib, ensartinib (PMID 26673800)	Cabozantinib (PMID 26673800), lorlatinib, TPX-0005 (repotrectinib, PMID 30093503), repotrectinib slightly less potent than cabozantinib but more potent than lorlatinib in Ba/F3 cells (PMID 30093503)
xDFG mutation	*NTRK1*	p.G667C	Colorectal cancer (PMID 26546295)	Larotrectinib, weaker entrectinib resistance induction than G595R (PMID 26546295), belizatinib (TSR-011) (PMID 30333516)	Cabozantinib, foretinib (PMID 29463555), ponatinib, nintedanib (PMID 28751539, 30333516) even higher sensitivity than wild-type NTRK1, LOXO-195 (selitrectinib) (PMID 28578312), merestinib, entrectinib (PMID 29568395)
	NTRK3	p.G696A	Preclinical: NIH 3T3 cell lines (PMID 28578312)	Larotrectinib (PMID 28578312)	LOXO-195 (selitrectinib) BA/F-3 cells with ETV6-NTRK3-fusion (PMID 28578312)
	ROS1	p.G2101	Preclinical (PMID 2875139)		
	ALK	p.G1269A	ALK-rearranged lung cancer	Crizotinib (PMID 23344087), larotrectinib, entrectinib (PMID 28578312)	

Abbreviations: MASC, mammary analogue secretory carcinoma; NIH, National Institutes of Health; NSCLC, non–small-cell lung cancer; SNV, single nucleotide variant.

resected twice and adjuvant chemotherapy with carboplatin and paclitaxel for four cycles was administered. Upon appearance of lung metastases 4 months later, the patient was admitted to our clinic in February 2018. We performed one more cycle of carboplatin and paclitaxel and simultaneously conducted a molecular analysis of formalin-fixed paraffin-embedded tissue of the sarcomatoid dedifferentiated cervical tumor that was resected in February 2017. Gene panel sequencing (Ignyta Trailblaze Pharos) revealed an oncogenic *ETV6-NTRK3* rearrangement. Based on this finding, we started a therapy with entrectinib in the context of the STARTRK-2 trial (NCT02568267) in April 2018. Follow-up computed tomography (CT) scans (Figs 2A-2E) after 4 weeks of entrectinib treatment demonstrated a partial remission of the pulmonary and cervical metastases. Twelve weeks after initiation of entrectinib, all manifestations were continuously responding, except for the cervical tumor (Fig 2F) that was resected (R0). From October 2018 onward, we observed a disease acceleration with progression of the cervical and pulmonary metastases. The cervical metastasis was irradiated and additional foci appeared in December 2018 and February 2019, which included pectoral and gluteal soft tissue metastases, a hepatic lesion, and tumor manifestations affecting the right adrenal gland and hepatoduodenal ligament. Observing the rapid development of resistance, we performed a

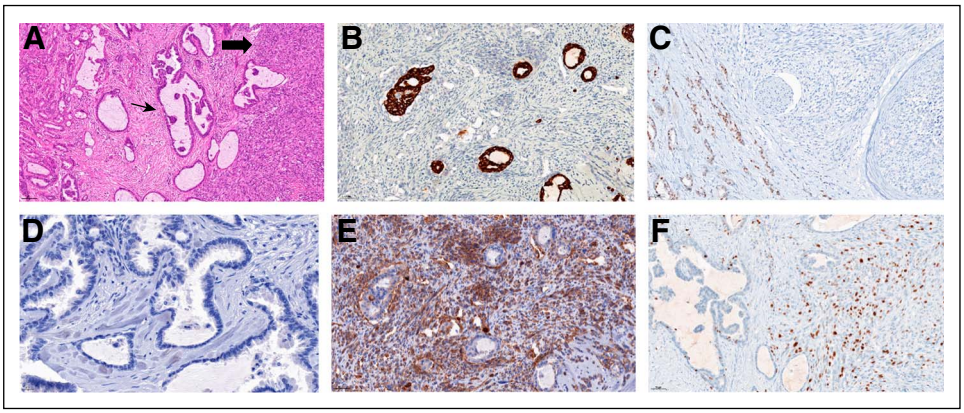

FIG 1. Histopathologic assessment. (A) Hematoxylin and eosin (10×) of a cervical lymph node metastasis (October 2016) with adenocarcinomatous (thin black arrow) and sarcomatous (thick black arrow) differentiation harboring the same *ETV6-NTRK3* fusion; (B and C) CK7- and TTF1-expression in adenocarcinomatous parts of the metastasis (20×); (D) no expression of MUC4 (or CEA, not shown) in adenocarcinomatous parts of the metastasis (40×); (E) expression of caldesmon in sarcomatous parts of the metastasis (20×); (F) difference in proliferation activity between carcinomatous and sarcomatous parts of the metastasis (Ki67, 20×).

molecular analysis of a left-sided pectoral metastasis by whole-genome sequencing (Illumina HiSeq X, San Diego, CA) in the context of the MASTER (Molecularly Aided Stratification for Tumor Eradication Research) program, a prospective multicenter precision oncology platform that addresses the comprehensive molecular characterization and mechanism-based treatment of advanced malignancies.[22–25] Because of the limited accessibility of next-generation NTRK inhibitors at that time and based on reports demonstrating the efficacy of cabozantinib in preclinical models with acquired resistance to entrectinib,[20] we started a treatment with cabozantinib that induced a significant clinical response. CT scans after 6 weeks as well as 4 months after initiation of cabozantinib revealed a distinct regression of all lesions including the pectoral metastasis that harbored the G623R mutation

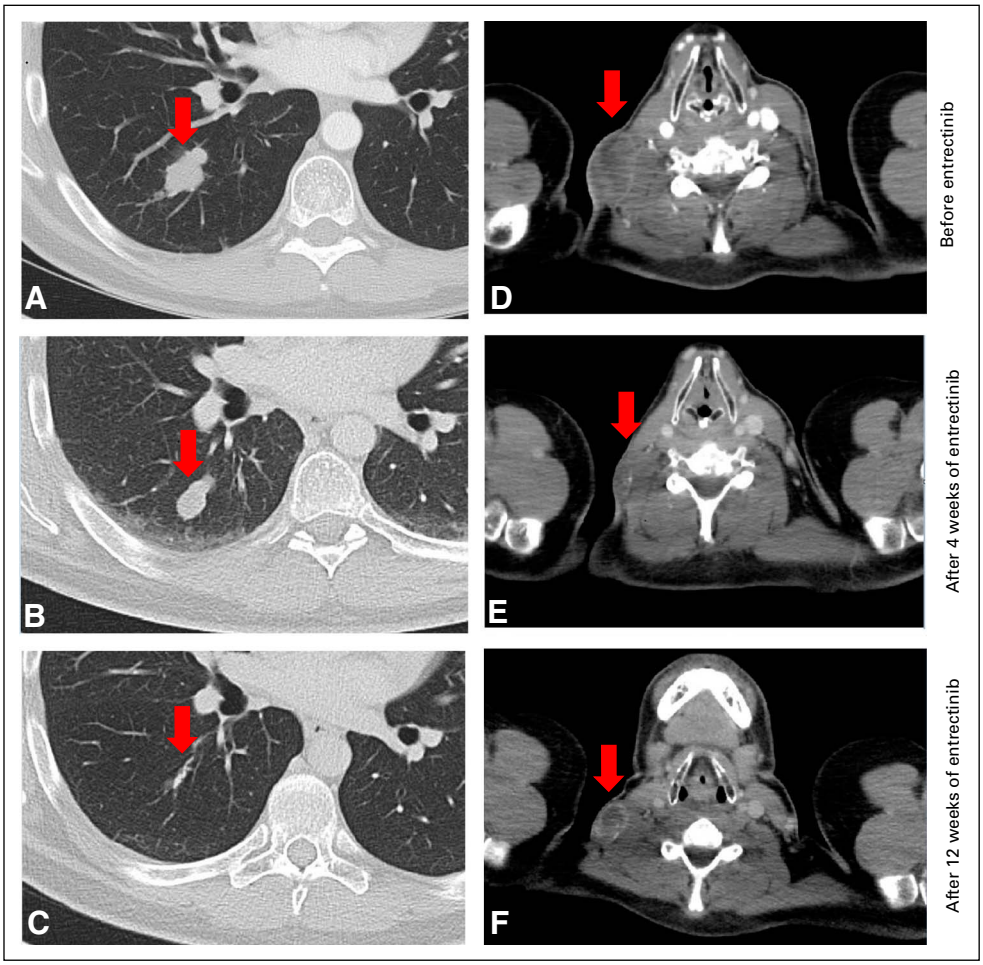

FIG 2. Response to entrectinib. (A-C) Computed tomography (CT) of the lung showing a pulmonary metastasis in the right lower lobe (A) before entrectinib (April 2018) that (B) decreased in size (May 2018) and (C) showed a near-complete response in July 2018. (D-F) CT (April 2018) of the neck (arterial phase) showing a solid cervical lesion dorsal to the right sternocleidomastoid muscle (D) before entrectinib treatment, that (E) decreased in size in a subsequent CT scan (May 2018; venous phase) 4 weeks after onset of entrectinib and (F) increased in size after 12 weeks of entrectinib (July 2018; venous phase).

(Figs 3A-3H). Nonresponding was only a newly appeared metastasis of the left adrenal gland (Figs 3I and 3J). Furthermore, we observed a clinically impressive regression of the additionally irradiated pectoral and cervical metastases, while shedding in the area of the melting cervical metastasis produced a prolonged ulceration.

Our whole-genome sequencing results confirmed the known *ETV6-NTRK3* fusion and revealed a triploid genome harboring 30 exonic single-nucleotide variants (SNVs) and four small insertions or deletions. With regard to therapeutically relevant alterations, we observed a homozygous loss of *CDKN2A/B*. Most importantly, we identified an *NTRK3*^{G623R} solvent-front mutation (chr15:g.88476265C>T; reference genome hg19, ENST00000394480.2: c.G1867A; tumor variant frequency 23%; tumor cell purity estimated 54%) affecting the kinase domain of the *ETV6-NTRK3* fusion gene as the obvious mechanism of acquired resistance to entrectinib.[13] Sequencing data were deposited in the European Genome-phenome Archive (EGAS00001004494).

Based on corresponding preclinical data and case reports,[14] the molecular tumor board recommended a therapy with the next-generation NTRK inhibitor LOXO-195 (selitrectinib) in case of progressive disease. Because of the ongoing response to cabozantinib, we decided to continue the treatment until progression. Eighteen weeks after initiation of cabozantinib and 2 weeks after the last CT scan displaying response to therapy, the patient died from septic organ failure probably caused by either pneumogenic sepsis or associated with a soft-tissue defect caused by the melting metastases.

To verify that the antitumor effect of cabozantinib in our case was based on its activity against *NTRK3*^{G623R} rather than on off-target effects, we transduced Ba/F3 cells with *ETV6-NTRK3* wild-type and *ETV-NTRK3*^{G623R} fusion constructs (Data Supplement). Treatment of the transduced cells with entrectinib and cabozantinib confirmed a resistance of G623R-mutated cells against entrectinib while sensitivity against cabozantinib was retained in *NTRK3*-rearranged cells harboring the G623R mutation clearly demonstrating the on-target activity of cabozantinib in this setting (Figs 4A-4C).

DISCUSSION

The introduction of next-generation inhibitors designed to target wild-type as well as mutant *NTRK* has significantly improved therapeutic options in NTRK-positive tumors that have acquired on-target resistance. Nevertheless, because of the low incidence of *NTRK* fusions, clinical data on the most appropriate second-line inhibitor are lacking or refer to small case series. The discovery of homologies between distinct mutations affecting different receptor TKs has improved our understanding of resistance mechanisms and allows, to a certain extent, to predict TKI efficacy across diverse receptor TKs that harbor homologous resistance-mediating SNVs.

Currently, there is no approved NTRK inhibitor to overcome acquired resistance conveyed by the *NTRK3*^{G623R} substitution,[14] while the potential of next-generation inhibitors such as LOXO-195 and repotrectinib is investigated in clinical trials.[12,15,26,27] To our knowledge, there are no data on the

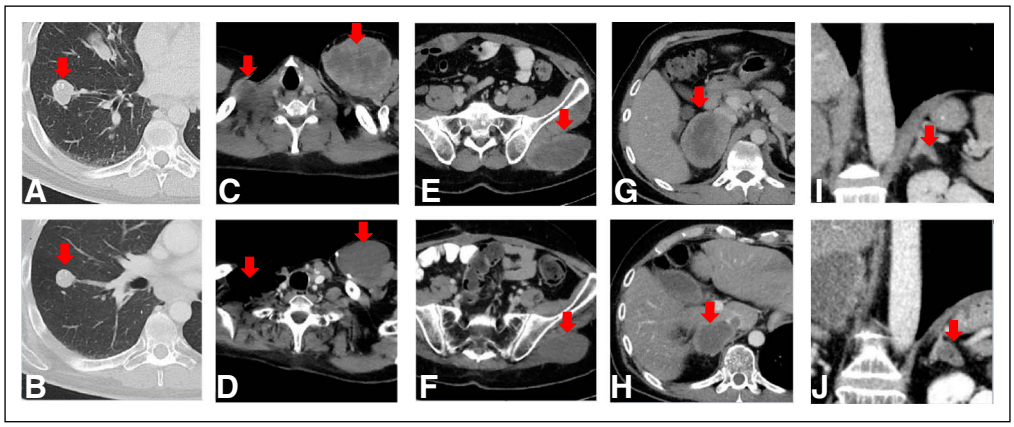

FIG 3. Response to cabozantinib. Serial computed tomography (CT) imaging of the same lesions vertically ordered before cabozantinib and after 4 months of cabozantinib treatment shows a pulmonary metastasis in the right lower lobe (A) before cabozantinib (February 2019) that (B) decreased in size during therapy (June 2019). Bilateral periclavicular metastases in a CT scan of the neck and upper thorax (C) before cabozantinib (February 2019; venous phase) (D) decreased in size (left) leaving a soft tissue defect (right) after 4 months of cabozantinib (June 2019; venous phase). CT of the pelvis demonstrating a left gluteal metastasis (E) before cabozantinib (February 2019; venous phase), (F) decreasing in size in the course of cabozantinib treatment (June 2019; venous phase). CT of the upper abdomen indicating a right adrenal metastasis (G) before cabozantinib (February 2019; venous phase) that (H) decreased in size after 4 months of cabozantinib (June 2019; venous phase). CT of the upper abdomen showing no left adrenal metastasis (I) before cabozantinib (February 2019; venous phase), followed by appearance of (J) a left adrenal metastasis detected after 4 months of cabozantinib treatment (June 2019; venous phase).

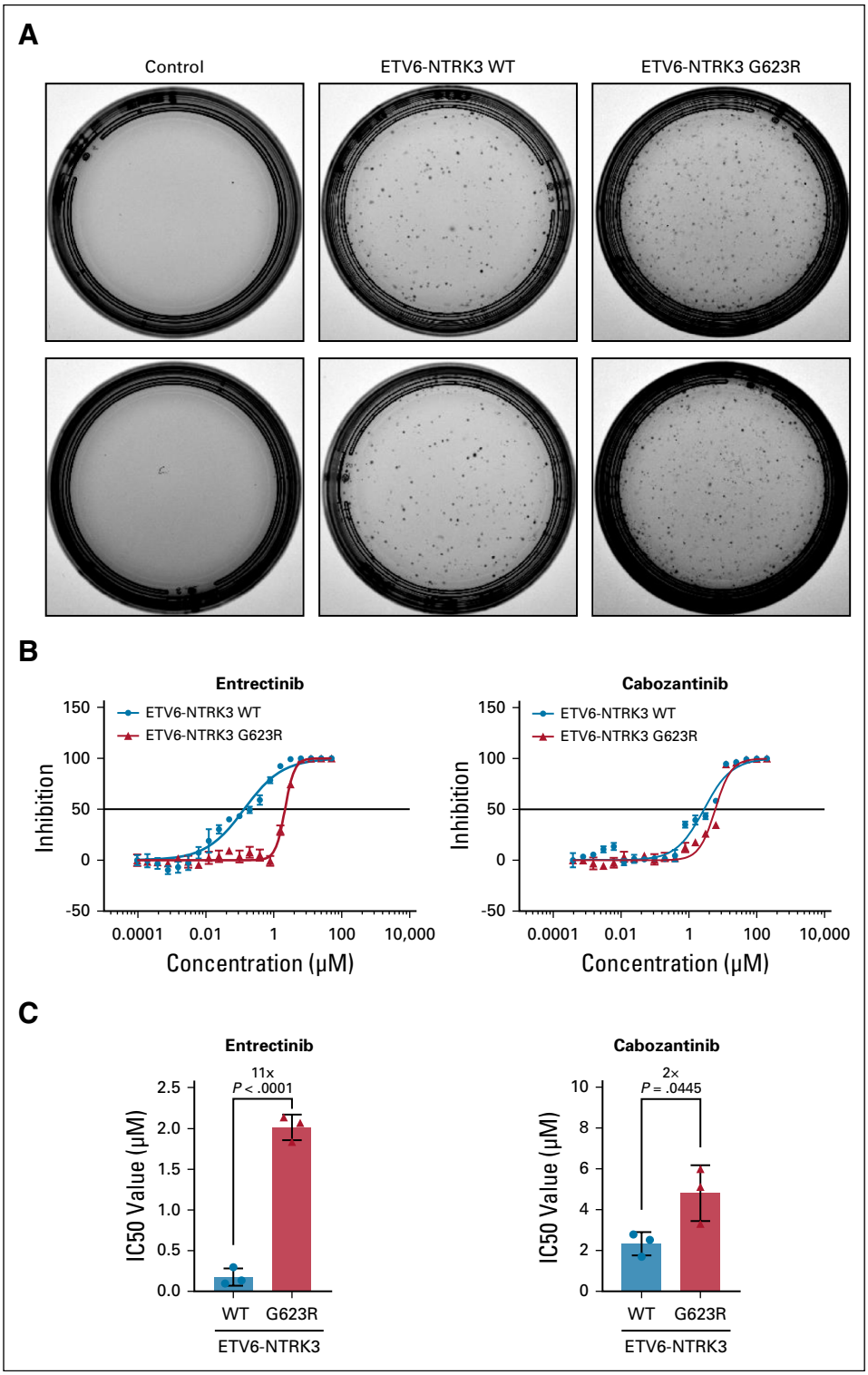

FIG 4. Expression of the *ETV6-NTRK3* WT or G623R fusion gene in Ba/F3 cells induces interleukin 3 (IL-3)-independent growth and sustains sensitivity toward cabozantinib. (A) Colony-forming units of Ba/F3 cells transduced with lentiviral vectors encoding for eGFP only (control), *ETV6-NTRK3* WT, or *ETV6-NTRK3* G623R after 7 days of cultivation in MethoCult M3231 in the absence of IL-3 in technical duplicates. (B) Representative IC50 curves of entrectinib- or cabozantinib-treated Ba/F3 cells expressing either *ETV6-NTRK3* WT (blue) or *ETV6-NTRK3* G623R (red) determined after 96 hours. Data points are shown as mean ± standard deviation (SD) from technical quadruplicates. (C) IC50 values of entrectinib- and cabozantinib-treated Ba/F3 cells expressing either WT or G623R *ETV6-NTRK3* fusion constructs including the fold change between entrectinib (11×, 0.1761 μM *v* 2.017 μM) or cabozantinib (2×, 2.335 μM *v* 4.810 μM) treated WT and G623R cells calculated from mean IC50 values from three independent biologic replicates. Data shown as mean ± SD, *P* values were determined using two-tailed unpaired Student's *t*-test. WT, wild-type.

efficacy of cabozantinib in *NTRK3*^{G623R}-mutant tumors so far. However, because of the homologies with amino acid substitutions in other kinases, sensitivity would not have been predicted conclusively.[20] Although cabozantinib exhibited inhibitory capacity against *NTRK1*^{G667C} mutation and the *NTRK3*^{G623R} homologue *ROS1*^{G2032R}, no efficacy against the closest homologue *NTRK1*^{G595R} was observed so far.[14]

The reported case illustrates that our knowledge on homologies between different TK residues alone is not sufficient to predict drug sensitivity. Therefore, the most appropriate treatment needs to be assessed carefully with regard to the distinct genetic alteration and context of the underlying tumor entity. Next-generation inhibitors and approved TKIs may serve as salvage therapy upon

conformational changes to the ATP-binding pocket induced by SNVs mediating secondary resistance.

Furthermore, histopathologic reassessment with knowledge of *ETV6-NTRK3* rearrangement did not reveal a clear primary tumor and confirmed a histopathologically heterogeneous tumor, which might explain the mixed response of different lesions during NTRK inhibitor therapy.

Our observations emphasize the diagnostic and therapeutic impact arising from the diagnosis of *NTRK* fusions and underline the feasibility of individualized targeted treatments in cancers of unresolved diagnosis. Given the steadily increasing number of effective NTRK inhibitors and the dramatic responses that have been observed in a variety of *NTRK*-rearranged malignancies, implementation of regular *NTRK* testing into routine clinical care should be considered. The possible efficacy of cabozantinib in secondary resistant *NTRK* rearranged tumors warrants further study.

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Data Sharing Statement

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

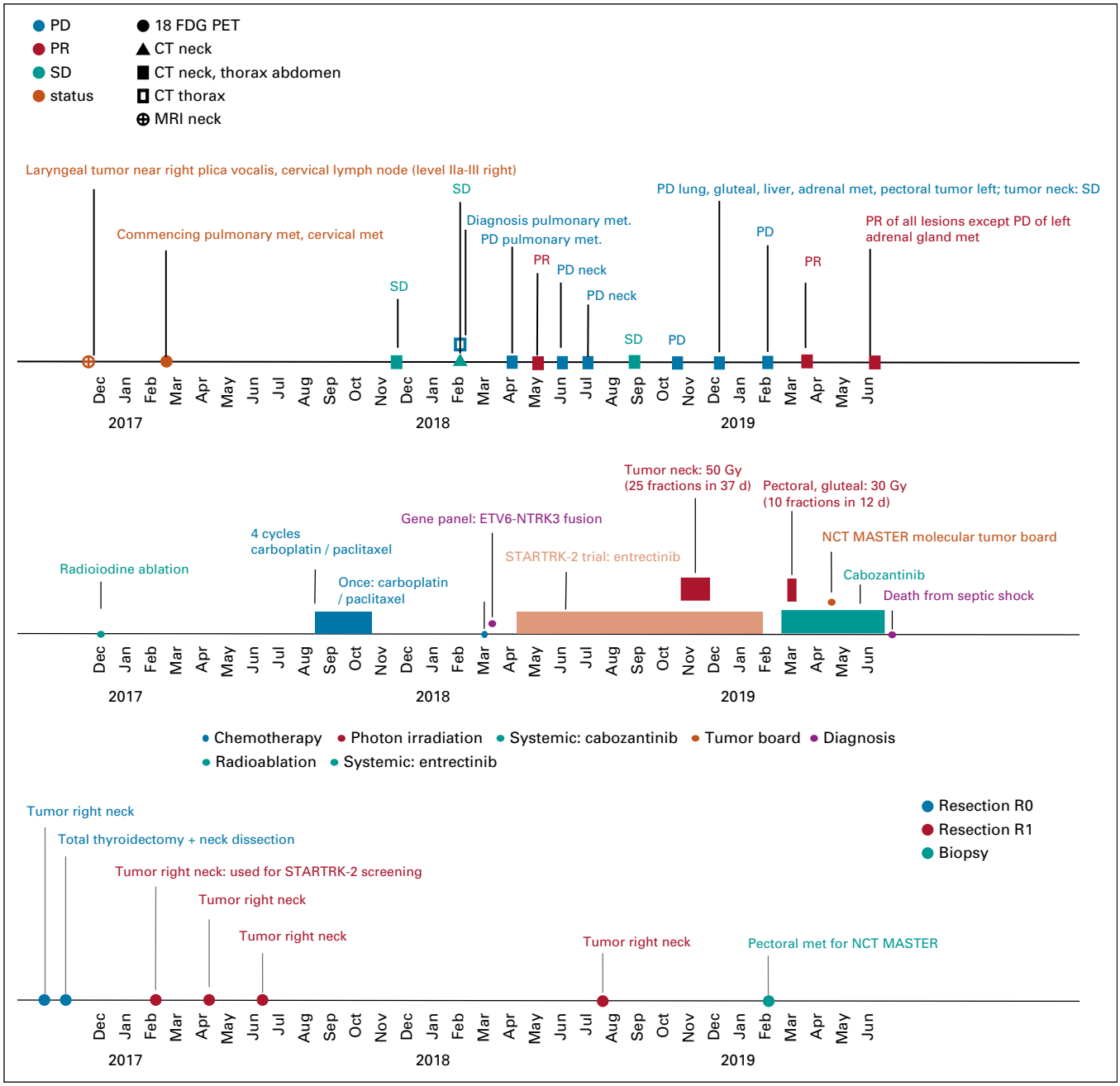

FIG A1. Clinical course displayed in three timeline plots showing main therapeutic events on top, imaging results in the middle, and surgical procedures in a timely aligned stacked layout. CT, computed tomography; FDG, fluorodeoxyglucose; met, metastasis: MRI, magnetic resonance imaging; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

