### Title

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# Repotrectinib in a Patient With *NTRK* Fusion-Positive Pancreatic Carcinoma and Congenital Long QT Syndrome

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## Introduction

Neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusions are potential targets for cancer therapy. Entrectinib and larotrectinib are first-generation TRK tyrosine kinase inhibitors (TKIs) currently approved for the treatment of patients with pretreated metastatic or unresectable cancer harboring *NTRK* fusions.[1,2] However, acquired resistance invariably develops on TRK TKIs. Repotrectinib (Bristol Myers Squibb, Princeton, NJ) is a next-generation TRK inhibitor and currently being studied in the phase I/II TRIDENT-1 trial. Repotrectinib leverages its compact macrocyclic structure to bind inside the ATP-binding pocket and overcome steric hindrance from TRK solvent front and gatekeeper resistance mutations.[3] Here, we describe a case of metastatic *NTRK* fusion–positive pancreatic carcinoma with secondary resistance to larotrectinib and tolerance to repotrectinib in the setting of congenital long QT syndrome.

## Case Report

Our patient is a 62-year-old female with a history of congenital long QT syndrome type 1 and metastatic *NTRK* fusion–positive pancreatic acinar cell carcinoma. Family history was significant for a son who had a sudden cardiac arrest at age 17 years and long QT syndrome. Using cascade genetic testing, the patient and her other son were also found to have long QT syndrome (type 1 genotype). Given her personal history of syncopal episodes and sudden cardiac arrest in her son, the patient received placement of an automatic implantable cardioverter defibrillator (AICD) in 2017. Of note, none of the patient's electrocardiograms (ECGs) had QTc prolongation, although QTc interval may be normal in up to 40% of genotype-positive patients.[4]

Clinical course for this patient's pancreatic carcinoma was complicated by progression on three prior lines of chemotherapy (Fig 1). Molecular profiling using Tempus (Chicago, IL) of tumor DNA in a liver biopsy obtained after the third cancer progression showed an *ETV6-NTRK3* fusion. Subsequently, the patient started fourth-line therapy with larotrectinib and achieved a partial response. However, she progressed after 8 months on larotrectinib. Gemcitabine and nab-paclitaxel were added to larotrectinib with the hopes of treating larotrectinib-resistant tumor cells, but her disease continued to progress on combination chemotherapy and larotrectinib.

The patient expressed interest in participating in the phase I/II TRIDENT-1 trial (ClinicalTrials.gov identifier: NCT03093116) but was excluded because of her congenital long QT syndrome. A request for a single patient investigational new drug for compassionate use of repotrectinib was submitted and approved by the US Food and Drug Administration (FDA) and UC San Diego Institutional Review Board. She was switched to single-agent repotrectinib in August 2021 without any washout period. Before the initiation of repotrectinib, the patient had an Eastern Cooperative Oncology Group performance status of 1. She reported abdominal pain, nausea, decreased appetite, headaches, and 30 lb weight loss over the course of 3 months. Pretreatment ECG showed a QTc interval of 421 ms. Repotrectinib was initiated at 160 mg once daily. After 2 weeks without any reported toxicities on once daily dosing, repotrectinib was increased to 160 mg twice a day, consistent with the recommended phase II dose in TRIDENT-1.[4] Computed tomography (CT) scans on repotrectinib showed a partial response (Fig 2). Her cancer-related symptoms completely resolved after 3 weeks on repotrectinib. Side effects from repotrectinib included grade 1 dizziness and grade 1 diarrhea, neither of which affected treatment continuation. Her dizziness was stable with observation, and diarrhea was controlled

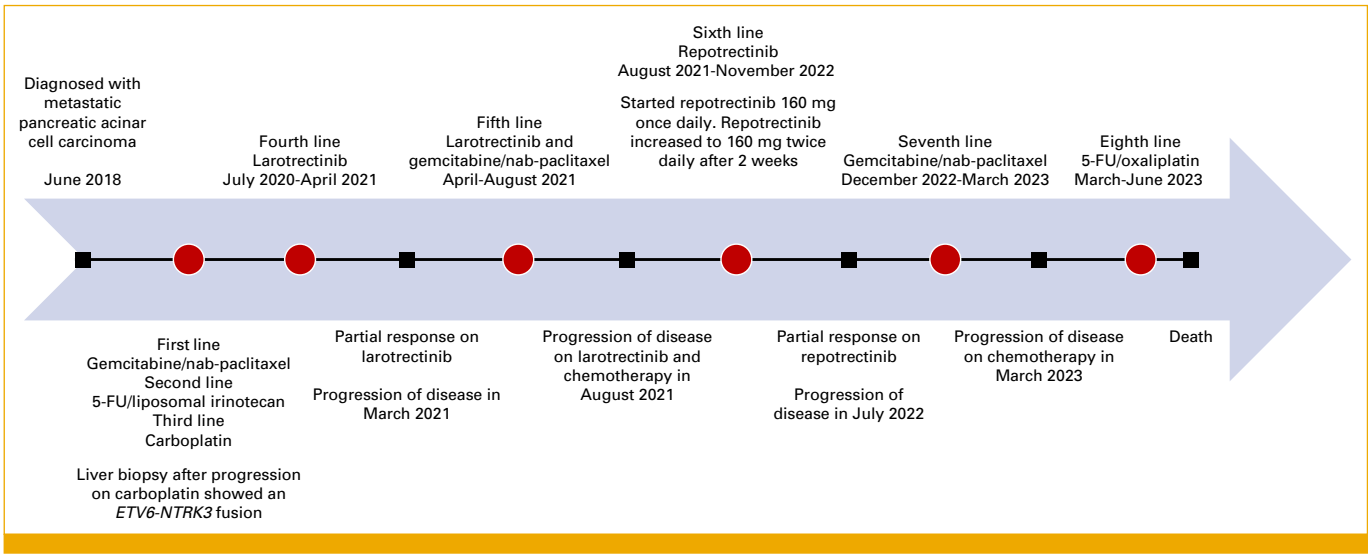


**FIG 1.** Timeline of clinical course. FU, fluorouracil.

on antidiarrheals. She did not have any QTc prolongation on repotrectinib with QTc intervals <440 ms on ECGs performed every 8 weeks, and there were no AICD therapies. After a duration of response (DOR) of 11.5 months on repotrectinib, CT scans demonstrated disease progression. Repotrectinib was stopped in November 2022. A postprogression biopsy showed the original *ETV6-NTRK3* fusion and did not identify a mechanism of resistance to repotrectinib. Unfortunately, the patient's disease progressed on subsequent chemotherapy, and she passed away in July 2023.

## Informed Consent

Informed consent was obtained from the patient described in this case report. We confirm that we have permission from the patient, as required by the law and by our institution, to

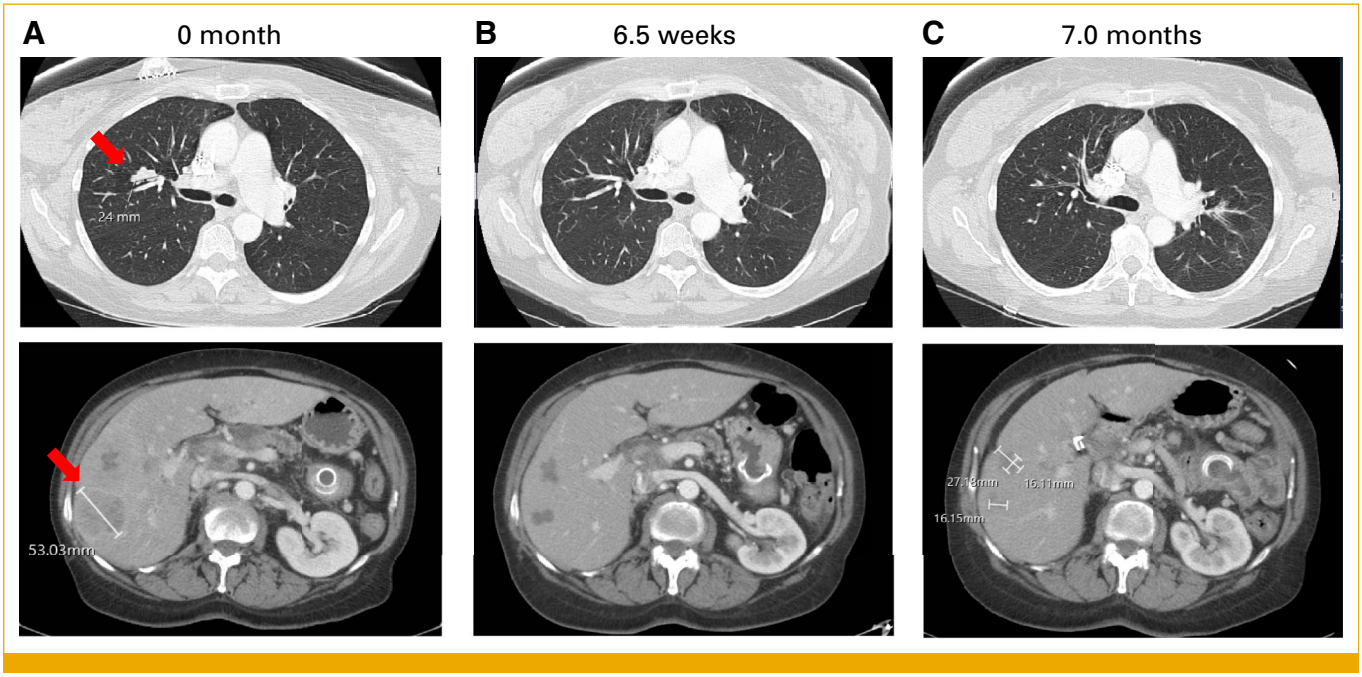


**FIG 2.** (A) Pretreatment CT of the chest and abdomen/pelvis. (B) CT of the chest and abdomen/pelvis after 6.5 weeks on repotrectinib shows resolution of pulmonary nodules and partial response of liver metastases. (C) CT of the chest and abdomen/pelvis after 7.0 months on repotrectinib shows partial response to therapy. CT, computed tomography.

 

publish details of her medical condition, treatment, and images in *JCO Precision Oncology*.

A single patient investigational new drug for compassionate use of repotrectinib was approved by the FDA and UC San Diego Institutional Review Board for the patient described in this case report.

## Discussion

*NTRK* fusions are oncogenic drivers found in <2% of pancreatic cancers.[5] Pancreatic cancers harboring *CTRC-NTRK1*, *ETV6-NTRK3*, *LMNA-NTRK1*, *TPR-NTRK1*, and *SEL1L-NTRK1* fusions have been described, and efficacy has been observed in patients treated with entrectinib and larotrectinib.[5-8] A pooled analysis of phase I/II clinical trials with entrectinib in four patients with *NTRK* fusion–positive pancreatic carcinoma demonstrated an objective response rate (ORR) of 75%, median DOR of 12.9 months, median progression-free survival of 12.8 months, and median overall survival of 22.0 months.[9] Case reports of two patients with *NTRK* fusion–positive pancreatic carcinoma both demonstrated partial responses to larotrectinib.[5,8] Across various *NTRK* fusion–positive solid tumors, acquired resistance to TRK TKIs can arise through amino acid substitutions in the solvent front, activation loop xDFG, or gatekeeper residues of TRKA or TRKC.[10] Off-target mechanisms of resistance to TRK inhibition can also occur through alterations in the MAPK pathway via *BRAF V600E* mutations, *KRAS G12D* mutations, and *MET* amplifications.[11] Specifically in *NTRK* fusion–positive pancreatic carcinoma, *NTRK1 A608D* and *BRAF V600E* resistance mutations have been reported.[8,12]

Repotrectinib is a next-generation ROS1/TRK/ALK inhibitor, and its efficacy in advanced *NTRK* fusion–positive solid tumors is currently being studied in the phase I/II TRIDENT-1 trial.[3] Preliminary data from TRIDENT-1 in TRK TKI-naïve patients receiving repotrectinib showed an ORR of 54% while in TRK TKI-pretreated patients, the ORR was 43.2%. Dizziness (61.3%), dysgeusia (49.3%), and constipation (36.7%) were the most common treatment-emergent adverse events. A majority of the dizziness events were grade 1 (73.2%), and none of these resulted in treatment discontinuation.[13] Our patient developed grade 1 dizziness as a side effect from repotrectinib. She was counseled on avoiding standing or moving her head suddenly. Her dizziness remained stable on repotrectinib.

One unique feature of this case is the use of repotrectinib in a patient with congenital long QT syndrome. QTc prolongation has been reported with entrectinib. Of 504 patients in clinical trials, 4.0% of patients had QTc prolongation of >60 ms after starting entrectinib and 2.8% of patients had a QTc interval of >500 ms.[13] Conversely, to our knowledge, no cases of QTc prolongation to date have been reported with larotrectinib or repotrectinib. Our patient tolerated repotrectinib with no cardiac events or QTc prolongation seen on ECGs despite her history of congenital long QT syndrome. Although data within this population is extremely limited, our experience in this case is encouraging and suggests that with a certain risk tolerance, repotrectinib could be considered in patients with long QT syndrome. Of importance, the risks of QT prolongation should be carefully weighed against the risks from cancer. Careful risk stratification and close ECG monitoring are important aspects of managing patients with prolonged QT or at risk for QT prolongation. ECG and electrolytes should be assessed at baseline, at steady-state concentrations (after three to five elimination half-lives), and at the time of any dose titration.[14] Cardiac arrest due to torsades de pointes (TdP) is the main risk associated with QT prolongation and that risk is proportional to the duration of QTc interval.[15,16] Data from patients with long QT syndrome and drug-induced TdP indicate that QTc >500 ms is associated with the highest risk for TdP, cardiac arrest, and sudden death.[15,16] Hence, repotrectinib should be avoided in patients with QTc >500 ms, and it is also advised to discontinue QT prolonging agents if QT prolongs to >500 ms or >60 ms from baseline.[14]

Significant QTc prolongation (>500 ms) is extremely rare with conventional chemotherapy while the incidence is 0%-5% with targeted therapies.[17] Overall, arrhythmias and sudden cardiac death from chemotherapy and targeted therapies are rare.[17] E14 FDA guidelines on the evaluation of QT interval prolongation for nonantiarrhythmic drugs recommend a thorough QT/QTc study early in clinical development of any novel therapeutic.[18] However, that type of study is typically carried out in healthy volunteers, making it not feasible for cancer therapeutics. To protect patient safety, the FDA suggests excluding patients with prolonged QTc interval (>450 ms), congenital QT syndrome, heart failure, or family history of long QT syndromes until the effects of a drug on the QT interval has been characterized.[18] Consequently, this often prevents this subpopulation from benefiting from novel therapeutics before commercial approval.

Cardiovascular comorbidities are common among oncology patients, and the paucity of clinical trial data in this vulnerable patient group makes their management even more challenging. Higher cardiovascular risk patients and patients with preexisting cardiovascular conditions are generally underrepresented in oncology clinical trials, leading to the limited generalizability of findings to the broader patient population. Excluding patients with cardiac comorbidities or renal dysfunction might influence a study population's sensitivity to QT prolongation. As a result, extrapolating phase I and II study results with stringent exclusion criteria to the real-world population who are more prone to QTc prolongation is challenging. Real-world application of clinical trial data is crucial in advancing patient care, and early-phase clinical trials should be designed to maximize the generalizability of study results. Clinical trial eligibility criteria should be expanded such that patients with otherwise stable cardiac disease are not automatically excluded. A companion arm allowing enrollment of higher risk patients

with significant comorbidities who would otherwise not meet safety criteria should be considered for phase II and III clinical trials as information on the risk-benefit ratio of investigational drugs would be very valuable for practicing oncologists once study drugs are approved. Companion arms in clinical trials may give patients with life-threatening cancer diagnoses an earlier opportunity to access novel drugs and provide a more comprehensive assessment on the safety of a compound. Such companion arms could be designed to require more frequent laboratory or clinical assessments tailored to the specific risk concerns as well as evaluations by other disease specialists who can help monitor these risks. Regarding QT intervals, companion arms could potentially have less stringent exclusion criteria on the basis of the QTc interval duration. Furthermore, postmarketing studies and pharmacovigilance databases are also important in assessing the real-world risk of QT prolongation.

In conclusion, repotrectinib is a promising novel therapy in patients with advanced *NTRK* fusion–positive solid tumors. Our case highlights the efficacy and tolerability of repotrectinib in a patient with secondary resistance to larotrectinib and congenital long QT syndrome. Future studies will need to investigate the optimal sequence of therapy in treating advanced *NTRK* fusion–positive solid tumors and evaluate their safety among a broader patient population, including those with preexisting cardiovascular conditions.

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**Manuscript writing:** All authors
**Final approval of manuscript:** All authors
**Accountable for all aspects of the work:** All authors

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted.
I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.
Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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