NRG1 gene fusions are recurrent, clinically actionable gene rearrangements in KRAS wild-type pancreatic ductal adenocarcinoma

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Translational Relevance

Gene fusions involving Neuregulin 1 (NRG1) have been noted in multiple cancer types, and have potential therapeutic implications. Here we describe three patients with advanced, KRAS wild-type, pancreatic ductal adenocarcinoma (PDAC) that were comprehensively profiled by whole genome and transcriptome sequencing. All three tumours were positive for gene fusions involving the ERBB3 ligand, NRG1. Two of the three patients were treated with the HER-family kinase inhibitor afatinib and demonstrated a significant and rapid response while on therapy. This work adds to a growing body of evidence that NRG1 gene fusions are recurrent, therapeutically actionable, genomic events in hepatobiliary/pancreatic cancers. Based on the clinical outcomes described here, patients with KRAS wild-type PDAC would benefit from routine testing for NRG1 gene fusions.
Abstract

Purpose:

Gene fusions involving Neuregulin 1 (NRG1) have been noted in multiple cancer types, and have potential therapeutic implications. While varying results have been reported in other cancer types, the efficacy of HER-family kinase inhibitor afatinib in the treatment of NRG1 fusion positive pancreatic ductal adenocarcinoma is not fully understood.

Experimental Design:

47 patients with pancreatic ductal adenocarcinoma received comprehensive whole genome and transcriptome sequencing and analysis. Two patients with gene fusions involving NRG1 received afatinib treatment, with response measured by pre- and post-treatment PET/CT imaging.

Results:

3/47 (6%) of patients with advanced pancreatic ductal adenocarcinoma were identified as KRAS wild-type by whole genome sequencing. All KRAS wild-type tumours were positive for gene fusions involving the ERBB3 ligand NRG1. 2/3 patients with NRG1 fusion positive tumours were treated with afatinib and demonstrated a significant and rapid response while on therapy.

Conclusions:

This work adds to a growing body of evidence that NRG1 gene fusions are recurrent, therapeutically actionable, genomic events in pancreatic cancers. Based on the clinical outcomes described here, patients with KRAS wild-type tumours harbouring NRG1 gene fusions may benefit from treatment with afatinib.
Introduction

Oncogenic gene fusions involving Neuregulin 1 (NRG1) are recurrent across a variety of different cancer types and have emerged as clinically actionable genomic events in lung cancers and cholangiocarcinoma (1–4). As part of the ongoing Personalized OncoGenomics (POG; NCT02155621) and Prospectively Defining Metastatic Pancreatic Ductal Adenocarcinoma Subtypes by Comprehensive Genomic Analysis (PanGen; NCT02869802) clinical trials at our site, patients with advanced cancers undergo comprehensive genomic analysis including whole genome sequencing and transcriptome analysis (WGTA). We have previously described a patient with cholangiocarcinoma that harboured an ATP1B1-NRG1 gene fusion who responded favorably to treatment with the HER-family kinase inhibitor, afatinib (2). However, not all tumours with NRG1-fusions are responsive to afatinib, as evidenced by a lack of therapeutic benefit reported in a series of NRG1-fusion positive lung cancers (4), highlighting the need for further research in this area.

At a genomic level, PDAC is defined by the presence of KRAS driver mutations in the vast majority of cases, and are for the most part highly resistant to molecularly targeted therapeutic strategies. There is however a subset of PDACs that are KRAS wild-type. As part of the POG study, we have sequenced tumour biopsies from 47 PDAC patients, 91% of which were characterized by clonal KRAS gain of function mutations. KRAS wild-type PDAC tumours are thought to be dependent upon alternate oncogenic drivers that, though poorly understood (5), may provide opportunities for selective intervention with appropriate targeted therapies. Here we present 3 cases of KRAS wild-type PDAC that harbour oncogenic NRG1 fusions, with two cases demonstrating a significant response when treated with the HER-family kinase inhibitor afatinib. NRG1 fusions were highly expressed, retained the functional EGF-like domain required for HER-family kinase activation and involved transmembrane domain-containing fusion partners. A study published by Heining et al. similarly identified 3 NRG1-fusion
positive cases in their cohort of 17 PDAC tumours, one of which also demonstrated a reduction in
tumour size in response to treatment with afatinib(6). Together, these observations provide evidence
for the recurrent nature of oncogenic NRG1 fusions in KRAS wild-type PDAC and for the beneficial
treatment of afatinib in such cases, supporting further investigation of its use in this setting.
Materials and Methods

Patients were enrolled in the POG trial at BC Cancer in Vancouver, British Columbia. Patient biopsy samples received whole genome and transcriptome profiling in order to identify potentially clinically actionable genomic events. The study was approved by the University of British Columbia Research Ethics Committee (REB# H12-00137, H14-00681) and was conducted in accordance with international ethical guidelines. Written informed consent was obtained from each patient prior to genomic profiling. Patient identity was anonymized and an identification code assigned to the case for communicating clinically relevant information to physicians. Patients consented to potential publication of findings. Raw sequence data and downstream analytics were maintained within a secure computing environment.

Whole-genome and transcriptome analysis

Whole-genome and transcriptome analysis (WGTA) was performed as previously described(2). Briefly, a fresh tumor biopsy and blood sample were collected and sequenced to a mean redundant depth of coverage of 40x and 80x, respectively and a transcriptome of approximately 200M reads generated from the tumour sample. Somatic point mutations, small insertions and deletions (indels), and copy-number alterations, present in the tumor DNA but not in the germline were identified(7–9). Detection of structural rearrangements was achieved by merging and annotating SVs detected by de novo assembly (Trans-ABySS)(10) and existing SV callers; deFUSE(11), DELLY(12), Chimerascan(13) and Manta(14); using MAVIS(15). Fusion and RNAseq alignment visualization were generated using MAVIS. Publicly available transcriptome sequencing data from The Cancer Genome Atlas (TCGA)(16) were used to evaluate the expression profile of gene transcripts.

Mutation Signature Analysis
The mutation signature profile was determined by classifying all genomic SNVs into 96 classes based on variant and 3’/5’ mutation context to obtain a mutation catalog vector as described by Alexandrov et al.(17). In order to determine the best fit to a consensus set of 30 mutation signatures (available at http://cancer.sanger.ac.uk/cosmic/signatures), we performed non-negative least squares decomposition implemented in the R package “nnls”.

Molecular Subtyping

Molecular subtyping was performed based on gene expression signatures detailed in Moffit et al., 2015(18), Bailey et al. 2016(19), and Collisson et al., 2011(20). Given the relatively small cohort size, RNAseq data from 130 TCGA PAAD samples was leveraged in order to increase sample size and enable more robust clustering. Data were normalized using an empirical Bayesian method provided by ComBat(21). Consensus clustering of z-scores (of \( \log_{10}(x +1) \)) was performed, where x was RPKM for POG samples and TPM for TCGA samples(5). Dendrograms were cut and branches labelled to assign subtypes according to relative expression levels of subtyping gene sets.

Sequencing data availability

Genomic and transcriptomic datasets have been deposited at the European Genome-phenome Archive (EGA, http://www.ebi.ac.uk/ega/) under accession numbers EGAD00001004717 (patient 44), EGAD00001004718 (patient 45) EGAD00001004716 (patient 46).

NRG1 fluorescent in situ hybridization (FISH) protocol

Fluorescent in situ hybridization was performed as previously described(2) using the Dako Histology FISH Accessory Kit as per manufacturer’s protocol. Slides were scored manually using an oil immersion 63x
objective and z-stack images were captured using Metasystems software (MetaSystems Group Inc.,
Belmont, MA, USA) (for details, see Supplemental Methods).

NRG1 fusion RT-PCR

Total RNA was extracted from 6x5 micron scrolls of FFPE material with a High Pure FFPET RNA Isolation
kit (Roche, Mannheim, Germany). First strand cDNA was prepared from 200-500ng RNA with standard
procedures for Superscript IV reverse transcriptase and random hexamer oligonucleotides (Thermo
Fisher Scientific, Waltham, Massachusetts, USA). Based on whole genome and transcriptome data,
oligonucleotide primers were designed to ATP1B1 exon 2 (FWD:5’-CATCGGAACCATCCAAGTGA-3’) and
exon 3 (FWD:5’-TTTCGTCCTAATGATCCCAAGAG-3’) and NRG1 exon 2 (RVS:5’-
CATTCCCATTCTTGAAACCACCTTG-3’) and exon 6 (RVS:5’-CAGTGGTGATGTAGATGTAGC-3’). Each case was
assessed by standard Platinum Taq polymerase PCR protocol (Thermo Fisher Scientific, Waltham,
Massachusetts, USA) at 55°C annealing with ATP1B1ex2FWD-NRG1ex2RVS and ATP1B1ex3FWD-
NRG1ex6RVS primer combinations. Positive PCR bands were Sanger sequenced to confirm the fusion
breakpoint (NAPS, Michael Smith Laboratories, UBC, Vancouver, BC, Canada. For details, see
Supplemental methods).

TGCA fusion data review

Additional NRG1 gene fusions were identified by querying the Tumour Fusion Gene Data Portal
(http://www.tumorfusions.org)(22); which uses the PRADA algorithm(23) to detect fusion transcripts.
Results

Genomic and Transcriptomic Analysis

As part of the POG study, metastatic tumours from 47 patients with advanced PDAC underwent WGTA. In agreement with previous genomic characterization studies of PDAC, clonal KRAS gain of function mutations were identified in 91% (43/47) of tumour samples (Figure 1A, supplementary Table S1). KRAS mutations were not identified in 4 samples by standard somatic single nucleotide variant analysis (patients 44-47) (supplementary Table S1). Subsequent targeted read alignment of known KRAS gain of function hotspots revealed 1 of the 4 initially described KRAS wild-type tumours (patient 47) had a KRAS gain of function mutation of low variant allele frequency, indicating a potential subclonal KRAS mutation (1 and 6 sequencing reads supporting a KRAS G12D in the genome and transcriptome, respectively). Three of the 47 samples were devoid of KRAS mutations based on our standard and targeted SNV calling protocols.

Structural variant (SV) analysis and annotation from genome and transcriptome sequencing data was performed using MAVIS(15). Translocations affecting NRG1 were identified in 3 KRAS wild-type tumour samples (Figure 1A, supplementary Table S3). Notably, we did not detect oncogenic mutations or structural variants in potentially actionable alternative drivers including BRAF, ERBB2, ROS1, ALK, NTRK1-3, BRCA1/2 or ATM. Furthermore, recurrent loss of function mutations and deletions affecting tumour suppressors CDKN2A, TP53 and SMAD4 were absent in tumours positive for NRG1 fusions (Figure 1A, supplementary Table S1 and S2). Additionally, expression-based subtyping revealed that all three KRAS wild-type, NRG1 fusion positive samples were consistent with the classical subtype of PDAC (Figure 1A, supplementary Table S4)(18). Somatic SNVs were predominantly C:G>T:A and T:A>C:G transitions, similar to the majority of the cohort (Figure 1A), and were compared to a catalogue of previously described mutation signatures (http://cancer.sanger.ac.uk/cosmic/signatures). Somatic SNVs
from all three NRG1 fusion positive tumours were most highly attributed to COSMIC mutation signature 1 and 5 which are ubiquitous across cancer types (24) (supplementary Table S5).

**NRG1 Fusions in Advanced PDAC**

Patient 44 is a 55-year old man with a family history of GI cancers (gastric and colorectal cancer), who presented with stage IV PDAC with liver metastases. No prior germline or somatic testing was performed and he was enrolled on a first line metastatic phase II clinical trial of gemcitabine and nab-paclitaxel vs gemcitabine, nab-paclitaxel and dual-checkpoint inhibitor therapy. WGTA was performed on a core needle biopsy from a metastatic lesion in the liver. Tumour content was estimated to be 40% by pathology. Analysis of the somatic data revealed 42 somatic mutations (SNVs and indels) (supplementary Table S6). The tumour was negative for KRAS mutations and none of the other mutations were determined to be of clinical relevance. SV analysis revealed a fusion of **ATP1B1** (exon 4) with **NRG1** (exon 6), that was supported by both the genome and transcriptome data (Figure 1B, supplementary Table S3). Expression analysis of the **NRG1** gene revealed the tumour sample from patient 44 was a high expression outlier compared to a cohort of primary pancreatic adenocarcinoma samples, suggesting increased expression of **NRG1** as a result of the fusion transcript. Alignment of RNAseq reads to the **NRG1** gene demonstrated a significant increase in expression of exons 6 and 7 downstream of the predicted breakpoint, indicating the translocation stimulated expression of the fusion transcript (Figure 2B). This patient remains on first line therapy.

Patient 45 is a 59-year old man with a family history of prostate and colon cancer, who presented with stage IV PDAC with multiple metastases to the liver. No prior germline or somatic testing was performed. He was consented and enrolled in the POG clinical trial after having received 10 cycles of standard treatment with oxaliplatin, irinotecan, and 5-FU (FOLFIRINOX), with some initial partial response and
subsequent progression. He was subsequently treated with 3 cycles of gemcitabine with progression.

WGTA analysis performed on a biopsy sample (pathology-estimated tumour content of 40%) from a metastatic lesion from the liver showed 52 somatic mutations (SNVs and indels) (supplementary Table S6), none of which were determined to be clinically relevant. SV analysis revealed an *ATP1B1-NRG1* gene fusion that was supported by both the genome and transcriptome data (Figure 1B, supplementary Table S3). The breakpoints identified in patient 45 resulted in fusion of exon 3 of *ATP1B1* with exon 2 of *NRG1*, and differed from those observed in patient 44. Similar to patient 44, *NRG1* transcripts were highly expressed in the tumour sample from patient 45, which was a significant outlier when compared to the cohort of primary PDAC, as described above (Figure 2A). In agreement with the fusion breakpoints detected in this sample, aligned RNAseq reads across the *NRG1* gene revealed an increase in expression of exons 2-7 (Figure 2B). *ATP1B1-NRG1* fusions were subsequently validated by RT-PCR followed by Sanger sequencing.

Testing by break-apart FISH did not confirm the presence of *ATP1B1-NRG1* fusions in patient 44 or patient 45. Upon examination of the genome assembly data additional genomic breakpoints downstream of the fusion junction were identified in each case. An analysis of the structural complexity determined that the fusions likely arise from the insertion of the C-terminal region of the *NRG1* gene from chromosome 8 into the *ATP1B1* locus on chromosome 1 (supplementary Figure S1).

Patient 46 is a 54-year old man who has a limited family history of cancer and presented with stage IV PDAC with metastasis to the liver. The patient was consented and enrolled in the POG and PanGen clinical trials and received gemcitabine with nab-paclitaxel as part of a clinical trial. WGTA analysis of the liver biopsy (pathology-estimated tumour content of 85%) revealed 120 somatic mutations (SNVs and indels) including homozygous frame shift mutations affecting *ARID1A* (p.Q1519fs) and *B2M* (p.S53fs) and
several variants of unknown significance affecting additional components of the antigen presenting class I MHC complex, \( HLA-A \) (p.V255M and p.D251H) and \( HLA-B \) (p.T162K) (supplementary Table S6). The tumour was negative for \( KRAS \) gain of function mutations. A complex structural rearrangement resulting in the insertion of exons 6 and 7 of \( NRG1 \) in between exons 15 and 16 of \( APP \) was detected in both the genome and transcriptome (Figure 1B, supplementary Table S3). Expression analysis indicated the fusion transcript resulted in increased expression of exons 6 and 7 of the \( NRG1 \) gene and outlier expression compared to the primary PDAC cohort (Figure 2). Similar to patients 44 and 45, insertion of the \( NRG1 \) genomic fragment containing exons 6 and 7 into the \( APP \) gene were predicted to not be detectable by break-apart FISH.

All three \( NRG1 \) fusions were predicted to be in-frame and the predicted fusion structure preserved the EGF-like domain, which has previously been shown to be required for \( NRG1 \) function(25, 26) (Figure 1B). Moreover, alignment of the RNA sequencing reads revealed a striking increase in expression of EGF-like domain containing exons 6 and 7 in all three cases (Figure 2B). Both fusion partners, \( ATP1B1 \) and \( APP \), encode integral membrane proteins and donate trans-membrane domains to the predicted NRG1 fusion proteins (Figure 1B). Finally, a query of gene fusions detected in transcriptome data from TCGA [http://www.tumorfusions.org/] identified a third \( ATP1B1-NRG1 \) in-frame gene fusion in a sample from a PDAC (Table 1). The fusion junction results in the fusion of exon 3 from \( ATP1B1 \) and exon 2 of \( NRG1 \), identical to the structure of the gene fusion identified in patient 45 (Figure 1B).

**Clinical Response to Afatinib in \( NRG1 \) Fusion Positive PDAC**

Following progression on gemcitabine, patient 45 obtained access to afatinib. At the time of starting therapy, he had significant ascites and was ECOG performance status 2. His CA19-9 was >120,000. A PET/CT scan was performed at baseline prior to initiating therapy (Figure 3A, left panels). He initiated
treatment at a dose of 40 mg daily but was switched to 30 mg during cycle 1 due to diarrhea. After 4 weeks, a repeat PET/CT was performed demonstrating a significant response to therapy. It was noted that the degree and extent of FDG avidity within supraclavicular, mediastinal, portocaval and liver had all improved. Repeat CA19-9 after 4 weeks dropped to 7,246 (Figure 3C). Clinically he appeared much better with significant improvements in pain and performance status. He had minor skin rash and minor diarrhoea related to the afatinib. He had a CT at 3 months post treatment initiation confirming ongoing response. At 5.5 months since treatment initiation he had a repeat CT that demonstrated disease progression.

Patient 46 did not tolerate gemcitabine and nab-paclitaxel and came off treatment after 1 cycle. At the time of starting afatinib he had significant progression of disease with PET/CT showing avidity in the pancreatic head mass, as well as in multiple metastatic lymph nodes and liver metastasis (Figure 3B, left panels). CA19-9 levels were within the normal range. He initiated treatment with afatinib at a dose of 30 mg daily. After 4 weeks, a repeat PET/CT was performed also showing significant response to therapy (Figure 3B, right panels). There was noted to be resolution of multiple hepatic metastases, and the degree of FDG avidity within the primary pancreatic mass had also decreased. He tolerated the treatment well with good energy and minimal toxicity other than minor facial rash and paronychia. Response was confirmed by CT imaging performed at 8 weeks post treatment initiation, and a CT scan done 5 months post treatment initiation showed ongoing response. He continues on treatment at the time of manuscript preparation.
In this report, we describe ATP1B1-NRG1 gene fusions in 2 out of the 47 PDAC samples sequenced as part of the ongoing POG trial at our institute. Within this cohort, 3 PDAC samples were KRAS wild-type and harboured NRG1 fusions. A fourth was identified in a review of publically available transcriptome and 3 additional cases were recently described in independent study data(6). Together these results indicate that NRG1 fusions occur in a small proportion of PDAC patients, potentially defining a new subtype of KRAS wild-type PDAC.

NRG1 activates the ERBB3 (HER3) receptor, which then forms a heterodimer with other HER-family receptors, regulating downstream signaling pathways. NRG1 gene fusions are prevalent in lung cancers and are thought to drive ectopic signaling through continuous stimulation of HER-family proteins leading to growth and proliferation(27, 28). It is then not surprising that NRG1 gene fusions could drive PDAC given that the majority of PDAC is driven by KRAS activation, providing continuous activation of signaling pathways including MEK, ERK and PI3K(29). This hypothesis is borne out by the emerging mutual exclusivity of NRG1 gene fusions and KRAS activating mutations, which suggests an overlapping functions. The absence of potential alternative drivers of PDAC in NRG1 fusion positive tumours provides further support for NRG1 fusions as a driver in PDAC.

Two patients were treated with afatinib as a result of the NRG1 fusions detected as part of this study. Both patients demonstrated a significant clinical response when treated with afatinib. This observation is interesting given that a recent publication described an observable lack of response in some lung cancers positive for NRG1 fusions(4). This perhaps suggests that the fusion partner or etiology has an influence on how well a given tumour will respond. Alternatively, the genomic context of the gene fusion may be the relevant factor indicating the importance of comprehensive genomic profiling to
determine if the gene fusions detected are likely to be the sole driver of the disease. Further work is required to explore these observations.

Patient 45 showed disease progression after 5.5 months on treatment, a response to afatinib broadly equivalent to that seen in an unselected population of patients with advanced NSCLC(30). This observation demonstrates the likelihood of resistance mechanisms arising in pre-treated NRG1 fusion-positive PDAC. Up-regulation of NRG1 is a well-documented mechanism of parallel pathway activation and resistance in HER2-positive breast cancer models(31, 32) and ALK-positive lung cancer(33, 34). Furthermore, it has been reported that PDAC cells treated with an ERK-specific inhibitor upregulated the parallel PI3K-AKT pathway through activating HER-family proteins(35). It is therefore perhaps likely that resistance mechanisms in HER-family driven PDAC will emerge from the acquisition of genomic alterations that activate parallel signaling pathways.

With respect to possible therapeutic strategies a recent study has demonstrated that concurrent inhibition or HER-family kinases synergizes with an ERK-specific inhibitor in suppressing PDAC cell growth in vitro and in vivo(35). This provides a rationale for testing combinations of targeted therapies in preclinical models, as has been demonstrated for cancers treated with BRAF inhibitors(36, 37). Also, given that NRG1 is the primary ligand of ERBB3(38) there is significant interest in targeting ERBB3 directly. A recent study using breast cancer cell lines harbouring an NRG1 gene fusion and a model of NRG1 fusion-positive ovarian cancer revealed potential complexities in responses to broad versus targeted HER-family kinase inhibitors in NRG1-fusion positive disease(4). However, establishing an NRG1 positive model of PDAC will be instrumental in investigating appropriate treatments strategies for this etiology. To date, no ERBB3-targeted therapy has been approved for cancer treatment though monoclonal antibodies are under clinical evaluation(39, 40) and the number of phase I and phase II
clinical trials continues to grow. However, given the rarity and structural complexity of NRG-1 fusions, developing targeted strategies to reliably detect these genomic events will be necessary to facilitate the appropriate interpretation of clinical trial outcomes.

Finally, in addition to a previously described SDC4-NRG1 gene fusion in a case of lung cancer two additional in-frame NRG1 gene fusions were identified in transcriptome data from TCGA; CDK1-NRG1 in a bladder urothelial carcinoma and PDE7A-NRG1 in a head and neck squamous cell carcinoma (Table 1). Though the evidence is currently limited, this finding suggests that broad screening for NRG1 gene fusions across different cancer types may reveal additional potentially clinically actionable oncogenic events that can be tested for their therapeutic relevance in a clinical or pre-clinical setting.
Acknowledgements

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Clinical trial information

Personalized OncoGenomics (POG) Program of British Columbia: Utilization of Genomic Analysis to Better Understand Tumour Heterogeneity and Evolution (NCT02155621); Prospectively Defining Metastatic Pancreatic Ductal Adenocarcinoma Subtypes by Comprehensive Genomic Analysis (PanGen; NCT02869802).
References:


Figure 1. **NRG1 fusions detected in KRAS wild-type PDAC.** A. Molecular alteration status of genes recurrently altered in PDAC and gene expression-based molecular subtyping in the advanced PDAC cohort (n=47). NRG1 fusions were detected in three KRAS wild-type patients. B. Fusion visualization diagrams for NRG1 gene fusions in KRAS wild-type patient tumours. Exons corresponding to NRG1 (ENST00000523534), ATP1B1 (ENST00000367816) and APP (ENST00000346798) incorporated in the fusion transcripts are indicated. Reading frame is indicated by the black bar below the fusion transcript model and EGF-like and transmembrane domains derived from NRG1 and the fusion partners respectively are highlighted by the dark blue and beige boxes.
Figure 2. Expression of NRG1 fusion transcripts. A. Histogram of NRG1 expression (log_{10}(RPKM)) across the primary TCGA pancreatic cohort with expression of NRG1 fusion positive PDAC patients indicated by the dashed lines. B. Density of RNAseq read alignment across the NRG1 transcript (ENST00000523534) for NRG1 fusion positive PDAC patient tumours.
Figure 3. Clinical response of NRG1 fusion positive PDAC with afatinib. A. PET/CT scans of patient 45 prior to treatment (left) and after 4 weeks on afatinib (right). B. PET/CT scans of patient 46 prior to treatment (left) and after 4 weeks on afatinib (right). C. CA19-9 levels pre and post-afatinib for patient 45.
Table 1: In-frame ATP1B1-NRG1 gene fusions detected in transcriptome data from TCGA and POG and described in published literature

<table>
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<th>5' Gene Junction</th>
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<th>3' exon</th>
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<td>Chr8:32585467/1</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>
PDAC = Pancreatic Ductal Adenocarcinoma, CHOL = Cholangiocarcinoma, BLCA = bladder urothelial carcinoma, HNSC = head and neck squamous cell carcinoma, LUAD = lung adenocarcinoma, nd = no data
Figure 2

A

B

Patient 44

Patient 45

Patient 46
Figure 3

A

pre-treatment

+ 4 weeks afatinib

B

pre-treatment

+ 4 weeks afatinib

C

baseline

post-afatinib

CA19-9 level

time (months)
Clinical Cancer Research

NRG1 gene fusions are recurrent, clinically actionable gene rearrangements in KRAS wild-type pancreatic ductal adenocarcinoma

Martin R Jones, Laura M Williamson, James T. Topham, et al.

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