**NRG1 Gene Fusions Are Recurrent, Clinically Actionable Gene Rearrangements in KRAS Wild-Type Pancreatic Ductal Adenocarcinoma**

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**Abstract**

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

**Experimental Design:** Forty-seven 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 pretreatment and post-treatment PET/CT imaging.

**Results:** Three of 47 (6%) patients with advanced pancreatic ductal adenocarcinoma were identified as KRAS wild type by whole-genome sequencing. All KRAS wild-type tumors were positive for gene fusions involving the ERBB3 ligand NRG1. Two of 3 patients with NRG1 fusion-positive tumors 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 tumors harboring NRG1 gene fusions may benefit from treatment with afatinib.

See related commentary by Aguirre, p. 4589

**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 harbored an ATPI81–NRG1 gene fusion who responded favorably to treatment with the HER-family kinase inhibitor afatinib (2). However, not all tumors 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, pancreatic ductal adenocarcinoma (PDAC) is defined by the presence of KRAS driver mutations in the vast majority of cases, and is 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 tumor biopsies from 47 PDAC patients, 91% of which were characterized by clonal KRAS gain-of-function.
Translational Relevance

Gene fusions involving neuregulin 1 (NRG1) have been noted in multiple cancer types and have potential therapeutic implications. Here, we describe 3 patients with advanced, KRAS wild-type pancreatic ductal adenocarcinoma (PDAC) who were comprehensively profiled by whole-genome and transcriptome sequencing. All 3 tumors were positive for gene fusions involving the EBB3 ligand NRG1. Two of the 3 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.

Written informed consent was obtained from each patient prior to genomic profiling. Guidelines. Written informed consent was obtained from each patient prior to genomic pro-

Materials and Methods

Whole-genome and transcriptome analysis

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, H16-00291) 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 was 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

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 40× and 80×, respectively, and a transcriptome of approximately 200M reads generated from the tumor sample. Somatic point mutations, small insertions and deletions (indels), and copy-number alterations, present in the tumor DNA but not in the germ line were identified (7–9). Detection of structural rearrangements was achieved by merging and annotating structural variants (SV) detected by de novo assembly (Trans-AbysS; ref. 10) and existing SV callers—deFuse (11), DELLY (12), Chimerascan (13), and Manta (14)—using MAVIS (15). Fusion and RNA sequencing (RNA-seq) alignment visualization were generated using MAVIS. Publicly available transcriptome sequencing data from The Cancer Genome Atlas (TCGA; ref. 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 and colleagues (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 nonnegative least-squares decomposition implemented in the R package "nnls."

Molecular subtyping

Molecular subtyping was performed based on gene-expression signatures detailed in Moffin and colleagues (18), Bailey and colleagues (19), and Collisson and colleagues (20). Given the relatively small cohort size, RNA-seq data from 130 TCGA PAAD samples were 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). Den- drograms were cut, and branches were labeled to assign subtypes according to relative expression levels of subtyping gene sets.

Sequencing data availability

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

NRG1 fluorescent in situ hybridization protocol

Fluorescent in situ hybridization (FISH) 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 63× objective, and z-stack images were captured using Metasystems software (MetaSystems Group Inc.; for details, see Supplementary Methods).

NRG1 fusion RT-PCR

Total RNA was extracted from 6 × 5 μm scrolls of FFPE material with a High Pure FFPE RNA Isolation Kit (Roche). First-strand cDNA was prepared from 200 to 500 ng RNA with standard procedures for Superscript IV reverse transcriptase and random hexamer oligonucleotides (Thermo Fisher Scientific). Based on whole-genome and transcriptome data, oligonucleotide primers were designed to ATP1B1 exon 2 (FWD: 5′-CATCGGAACCATCGGAATGTA-3′) and exon 3 (FWD: 5′-TTCCTGCCTTAAGTGACCCCAAGAC-3′) and NRG1 exon 2 (FWD: 5′-CATCGGAACCATCGGAATGTA-3′) and exon 6

NRG1 Gene Fusions in PDAC Are Clinically Actionable
sequencing data were performed using MAVIS (15). Transloca-

S1). Subsequent targeted read alignment of known

nucleotide variant analysis (patients 44

G12D in the genome and transcriptome, respectively).

TGCA fusion data review

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

Results

Genomic and transcriptomic analysis

As part of the POG study, metastatic tumors 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 tumor samples (Fig. 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 tumors (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 assembly data, additional genomic breakpoints – CAGTGGTGGATGTAGATGTAGC–3′). Each case was assessed by standard Platinum Taq polymerase PCR protocol (Thermo Fisher Scientific) 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; for details, see Supplementary Methods).

SV analysis and annotation from genome and transcriptome sequencing data were performed using MAVIS (15). Translocations affecting NRG1 were identified in 3 KRAS wild-type tumor samples (Fig. 1A; Supplementary Table S2). Notably, we did not detect oncogenic mutations or SVs 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 tumor suppressors CDKN2A, TP53, and SMAD4 were absent in tumors positive for NRG1 fusions (Fig. 1A; Supplementary Tables S1 and S3). Additionally, expression-based subtyping revealed that all 3 KRAS wild-type, NRG1 fusion–positive samples were consistent with the classic subtype of PDAC (Fig. 1A; Supplementary Table S4; ref. 18). Somatic SNVs were predominantly C>G>T>A and T>A>C>G transitions, similar to the majority of the cohort (Fig. 1A), and were compared with a catalog of previously described mutation signatures (http://cancer.sanger.ac.uk/cosmic/signatures). Somatic SNVs from all 3 NRG1 fusion–positive tumors were most highly attributed to COSMIC mutation signatures 1 and 5, which are ubiquitous across cancer types (ref. 24; Supplementary Table S5).

NRG1 fusions in advanced PDMC

Patient 44 is a 55-year-old man with a family history of GI cancers (gastric and colorectal cancers), who presented with stage IV PDAC with metastases. No prior germ line 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 tumor 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 NRG1 fusion that was supported by both the genome and transcriptome data (Fig. 1B; Supplementary Table S2). Expression analysis of the NRG1 gene revealed the tumor sample from patient 44 was a high expression outlier compared with a cohort of primary pancreatic adenocarcinoma samples, suggesting increased expression of NRG1 as a result of the fusion transcript. Alignment of RNA-seq 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 (Fig. 2B). This patient remains on first-line therapy.

Patient 45 is a 59-year-old man with a family history of prostate and colon cancers, who presented with stage IV PDAC with multiple metastases to the liver. No prior germ line 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 tumor 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 NRG1 fusion that was supported by both the genome and transcriptome data (Fig. 1B; Supplementary Table S2). 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 tumor sample from patient 45, which was a significant outlier when compared with the cohort of primary PDAC, as described above (Fig. 2A). In agreement with the fusion breakpoints detected in this sample, aligned RNA-seq reads across the NRG1 gene revealed an increase in expression of exons 2 to 7 (Fig. 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 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 Fig. 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 tumor 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 tumor 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 (Fig. 1B; Supplementary Table S2). Expression analysis indicated the fusion transcript resulted in increased expression of exons 6 and 7 of the NRG1 gene and outlier expression compared with the primary PDAC cohort (Fig. 2).

All 3 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 (Fig. 1B; refs. 25, 26). Moreover, alignment of the RNA-seq reads revealed a striking increase in expression of EGF-like domain-containing exons 6 and 7 in all 3 cases (Fig. 2B). Both fusion partners, ATP1B1 and APP, encode integral membrane proteins and donate transmembrane domains to the predicted NRG1 fusion proteins (Fig. 1B). Finally, a query of gene fusions detected in transcriptome data from TCGA (http://www.tumorfusions.org; ref. 22) 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 \textit{ATP1B1} and exon 2 of \textit{NRG1}, identical to the structure of the gene fusion identified in patient 45 (Fig. 1B).

Clinical response to afatinib in \textit{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 (Fig. 3A, left). 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 7246 (Fig. 3C). Clinically, he appeared much better with significant improvements in pain and performance status. He had minor skin rash and minor diarrhea related to the afatinib. He had a CT at 3 months after 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.

Table 1. In-frame \textit{ATP1B1-NRG1} gene fusions detected in transcriptome data from TCGA and POG and described in the published literature

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Sample</th>
<th>Fusion pair</th>
<th>Frame</th>
<th>(5') Gene junction</th>
<th>(5') Exon</th>
<th>(3') Gene junction</th>
<th>(3') Exon</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDAC</td>
<td>POG-Patient 44</td>
<td>\textit{ATP1B1-NRG1}</td>
<td>In-frame</td>
<td>Chr1:169094277/1</td>
<td>Chr8:32585467/1</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>PDAC</td>
<td>POG-Patient 45</td>
<td>\textit{ATP1B1-NRG1}</td>
<td>In-frame</td>
<td>Chr1:169080736/1</td>
<td>Chr8:32453346/1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>PDAC</td>
<td>POG-Patient 46</td>
<td>\textit{APP-NRG1}</td>
<td>In-frame</td>
<td>Chr2:7277336/1</td>
<td>Chr8:32585467/1</td>
<td>30.7</td>
<td>6.16</td>
</tr>
<tr>
<td>CHOL</td>
<td>POG-Patient 5(2)</td>
<td>\textit{ATP1B1-NRG1}</td>
<td>In-frame</td>
<td>Chr1:169080736/1</td>
<td>Chr8:32453346/1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>PDAC</td>
<td>TCGA.3A.A915.01A</td>
<td>\textit{ATP1B1-NRG1}</td>
<td>In-frame</td>
<td>Chr1:169080736/1</td>
<td>Chr8:32453346/1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>PDAC</td>
<td>NCT/DTK MASTER(6)</td>
<td>\textit{ATP1B1-NRG1}</td>
<td>In-frame</td>
<td>Chr1:169080736/1</td>
<td>Chr8:32453346/1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>BLCA</td>
<td>TCGA.FD.ASRB.01A</td>
<td>\textit{CDK-1NRG1}</td>
<td>In-frame</td>
<td>Chr1:62539960/1</td>
<td>Chr8:32585467/1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>HNSC</td>
<td>TCGA.CG.0534.01A</td>
<td>\textit{PDE7A-NRG1}</td>
<td>In-frame</td>
<td>Chr1:6669965/1</td>
<td>Chr8:32585467/1</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>LUAD</td>
<td>TCGA.8E.7964.01A</td>
<td>\textit{SDC4-NRG1}</td>
<td>In-frame</td>
<td>Chr2:43935006/1</td>
<td>Chr8:32585467/1</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>LUAD</td>
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<td>\textit{SDC4-NRG1}</td>
<td>In-frame</td>
<td>Chr2:43935006/1</td>
<td>Chr8:32585467/1</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: BLCA, bladder urothelial carcinoma; CHOL, cholangiocarcinoma; HNSC, head and neck squamous cell carcinoma; LUAD, lung adenocarcinoma; nd, no data.
metastatic lymph nodes and liver metastasis (Fig. 3B, left). 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 (Fig. 3B, right). 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 after 8 weeks following treatment initiation, and a CT scan done 5 months after treatment initiation showed ongoing response. He continues on treatment at the time of manuscript preparation.

Discussion

In this report, we describe ATP1B1–NRG1 gene fusions in 2 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 harbored NRG1 fusions. A fourth was identified in a review of publicly 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 function. The absence of potential alternative drivers of PDAC in NRG1 fusion–positive tumors 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 tumor will respond. Alternatively, the genomic context of the gene fusion may be the relevant factor indicating the importance of comprehensive genomics 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 pretreated NRG1 fusion–positive PDAC.
Upregulation 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 harboring an NRG1 gene fusion and a model of NRG1 fusion–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 1 and phase II clinical trials continues to grow. However, given the rarity and structural complexity of NRG1–1 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, 2 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 preclinical setting.

Disclosure of Potential Conflicts of Interest

H.I. Lim is a consultant/advisory board member for Bristol-Myers Squibb, Roche, Ipsen, Eisai, Taiho, and Amgen. S. Yip is a consultant/advisory board member for Bayer, Pfizer, and Roche. J.J. Knox receives reporting other commercial research support from Merck, and is a consultant/advisory board member for Merck and Bristol-Myers Squibb. J. Laskin reports receiving other remuneration from Roche Canada and Bi Canada. D.J. Renouf reports receiving speakers bureau honoraria from Servier and Celgene, and is a consultant/advisory board member for Servier, Celgene, Ipsen, Bayer, and Taiho. No potential conflicts of interest were disclosed by the other authors.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Goytain, H.J. Lim, M.J. Moore, H.L. Wong, A.J. Mungall, Y. Ma, S. Gallinger

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References


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