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# *ATM*-Mutated Pancreatic Cancer

## *Clinical and Molecular Response to Gemcitabine/Nab-Paclitaxel After Genome-Based Therapy Resistance*

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**Abstract:** Metastatic pancreatic cancer (PC) is an aggressive malignancy, with most patients deriving benefit only from first-line chemotherapy. Increasingly, the recommended treatment for those with a germline mutation in a gene involved in homologous recombination repair is with a platinum drug followed by a poly (ADP-ribose) polymerase (poly adenosine phosphate-ribose polymerase [PARP]) inhibitor. Yet, this is based largely on studies of *BRCA1/2* or *PALB2* mutated PC. We present the case of a 44-year-old woman with *ATM*-mutated PC who achieved stable disease as the best response to first-line fluorouracil, leucovorin, irinotecan, and oxaliplatin, followed by progression on a PARP inhibitor. In the setting of jaundice, painful hepatomegaly, and a declining performance status, she experienced rapid disease regression with the nonplatinum regimen, gemcitabine plus nab-paclitaxel. Both physical stigmata and abnormal laboratory values resolved, imaging studies showed a reduction in metastases and her performance status returned to normal. Measurement of circulating tumor DNA for *KRAS G12R* by digital droplet polymerase chain reaction confirmed a deep molecular response. This case highlights that first-line treatment with a platinum-containing regimen followed by PARP inhibition may not be the best choice for individuals with *ATM*-mutated pancreatic cancer. Additional predictors of treatment response are needed in this setting.

**Key Words:** pancreatic cancer, homologous recombination deficiency, ATM mutation, PARP inhibitor, mutant KRAS ct DNA

**Abbreviations:** CT - computed tomography,
ctDNA - circulating tumor DNA,
FOLFIRINOX - fluorouracil, leucovorin, irinotecan, and oxaliplatin,
HRR - homologous recombination repair,
MRI - magnetic resonance imaging,
PARP - poly(adenosine phosphate-ribose) polymerase,
RECIST - response evaluation criteria in solid tumors

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal of human malignancies, with most patients presenting in the advanced stages where median survivals are less than 1 year. This is due in large part to the failure of PDAC to benefit from newer immunotherapy approaches or drugs that target driver mutations.[1] Recent inroads have been made, however, in those harboring germline (*g*) mutations in genes involved in homologous recombination repair (HRR) of DNA double-strand breaks, such as *BRCA1/2, ATM, PALB2, CHEK1/2*, *RAD51*, and *ATR*.[2,3] The identification of an HRR gene mutation can inform the choice of treatment, as well as the health of family members, leading some groups to recommend universal genetic testing of all PDAC patients.[4,5]

Advanced PDAC is typically treated first with either 1 of 2 chemotherapeutic regimens, the platinum-containing 5-fluorouracil, leucovorin, irinotecan, oxaliplatin (FOLFIRINOX) or the nonplatinum gemcitabine plus nab-paclitaxel (G/N).[6,7] Although the alternative regimen is commonly utilized in the second-line, a real-world analysis showed that only 24% of patients receive second-line chemotherapy and the response is poor.[8] Despite the critical importance of the first-line choice, physicians have had no biomarkers to inform their decision making, until recently.

Accumulating evidence indicates that PDAC patients with an HRR gene mutation have a superior response to platinum-based chemotherapy and may respond to poly adenosine phosphate-ribose polymerase (PARP) inhibitors.[2–4,9] The recently published (Pancreas Cancer Olaparib Ongoing) study demonstrated that gBRCA1/2 patients who responded to platinum-based chemotherapy may have prolonged disease control with olaparib[10]; a similar finding was demonstrated for those with germline or somatic *BRCA1/2* or *PALB2* mutations treated with rucaparib.[11] This genome-based strategy is being extended to other gHRR gene mutations, although few full reports exist regarding the treatment of non–BRCA1/BRCA2/PALB2-mutated patients.

Here, we describe a patient with a *gATM* mutation in whom treatment choices were based on identification of this mutation. The limited response to predicted, genome-based therapies but robust response to the alternative chemotherapy regimen highlights the present limitations of this approach.

## CASE REPORT

### Pathologic and Genetic Features

Informed written consent was obtained from the patient for publication of this case report.

A vigorous 44-year-old woman presented to her gynecologist with left-sided pelvic pain. Transvaginal ultrasound revealed a left ovarian mass, and she underwent a left salpingo-oophorectomy and right salpingectomy. The left ovary contained a 12-cm multiloculated cyst consistent with a mucinous borderline tumor, intestinal type, with focal areas of invasive mucinous adenocarcinoma in the cyst wall. The bilateral fallopian tubes contained detached clusters of mucinous adenocarcinoma, identical to that

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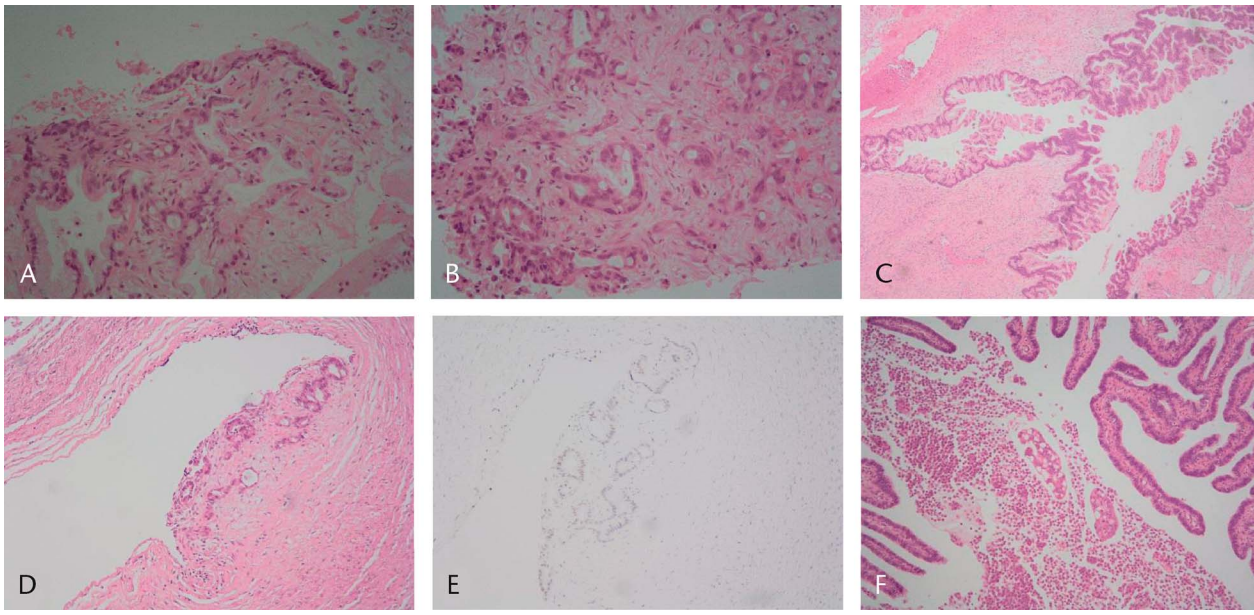



**FIGURE 1.** Hematoxylin-eosin-stained sections of the pancreatic cancer primary and metastatic sites. A, Cell block from pancreatic FNA biopsy with moderately differentiated adenocarcinoma (20×). B, Cell block from liver FNA biopsy with moderately differentiated adenocarcinoma with identical morphology to pancreas tumor and ovary (40×). C, Primary mucinous borderline tumor of left ovary showing epithelial complexity and nuclear crowding (10×). D, Invasive mucinous adenocarcinoma in ovarian cyst wall with a morphology similar to the pancreatic tumor (10×). E, Immunohistochemical stain for CDX2 showing weak positivity in the invasive carcinoma in the ovarian cyst wall, suggesting gastrointestinal/pancreaticobiliary origin (20×). F, Metastatic adenocarcinoma floating in fallopian tube lumen with a morphology similar to the pancreatic tumor (20×).

found in the ovary; immunohistochemistry positive for B72.3, BerEP4, WT-1, CK7, CK20, and p16 and negative for p53, ER, PAX8, calretinin, and D2–40. Because the invasive adenocarcinoma was most consistent with a gastrointestinal origin, computed tomography (CT) of the chest, abdomen, and pelvis was performed which revealed numerous hepatic metastases, the largest 1.8 cm, and a 3.5 cm mass in the pancreatic body/tail junction. Endoscopic ultrasound with fine-needle aspiration (FNA)/biopsy of the pancreatic mass and liver showed adenocarcinoma, consistent with stage IV PDAC to the liver and fallopian tubes (Fig. 1). The carbohydrate antigen (CA) 19–9 = 216 U/mL.

Her family history was notable for ovarian and gastric cancers and a sister with an *ATM* germline mutation but no personal history of cancer. The patient underwent germline (myRISK; Myriad Genetics, Inc., Salt Lake City, Utah), and somatic tumor (FOUNDATIONONE CDx; Foundation Medicine, Inc., Cambridge, Mass) genetic testing as shown in Table 1. The germline *ATM* mutation was splice site c.8585-2A > C, which results in loss of function.[12] The *ATM* mutation allele frequency was 47.6%, the MSI (microsatellite instability) status stable, and the PDL-1 tumor proportion score was 0%.

## Clinical Course

A timeline of the patient's treatment course and response by imaging, response evaluation criteria in solid tumor (RECIST) 1.1 measurements and CA 19–9 levels is shown in Figure 2A. Treatment was initiated with the FOLFIRINOX regimen every 14 days. A total of 10 cycles was administered over 20 weeks. The CA 19–9 declined throughout this period while imaging showed stable disease in the pancreas and liver as the best response at 8 weeks. By 14 weeks, CT showed hepatic steatosis and a mixed response in the liver with the possible development of small new lesions. Because of perceived clinical benefit and declining CA 19–9, the regimen was continued through 20 weeks at which point imaging showed progression of disease. Therapy was changed to olaparib 300 mg po bid (off protocol expanded access). After 2 months, CT scan showed progression of disease, and the CA 19–9 began to rise. She then enrolled in a clinical trial of a PARP inhibitor plus an ataxia-telangiectasia and Rad-3 related (ATR) inhibitor at another institution.

After 3 months of PARP/ATR inhibitor therapy, she returned to our clinic significantly weaker with jaundice, fatigue, tender hepatomegaly and a new 3-cm Sister Mary Joseph's nodule. The bilirubin was 5 mg/dL; alkaline phosphatase, 935 U/L; alanine aminotransferase, 256 U/L; aspartate aminotransferase, 249 U/L; and CA 19–9 markedly elevated. Abdominal magnetic resonance imaging (MRI) showed significant growth of hepatic metastases causing intrahepatic cholestasis (Fig. 2A, month 13). She began chemotherapy with gemcitabine/nab-paclitaxel at a reduced dose on day 1, 8 schedules every 21 days. She experienced prompt symptom relief and improvement in her performance status along with resolution of hepatomegaly, the Sister Mary Joseph's nodule and hyperbilirubinemia/transaminitis. The CA 19–9 rapidly declined, and MRI at 14 weeks showed a 20% reduction by RECIST (which includes the pancreatic primary) and a 35% reduction in hepatic metastases (last image panel).

## MATERIALS AND METHODS

The patient participant provided written informed consent for blood collection on a biobanking protocol approved by the Western CT Health Network institutional review board. Cell free DNA (cfDNA) was extracted from 1 mL of serum using QiAamp Circulating Nucleic Acid Kit (Qiagen, Hilden, Germany) and eluted with 105 μL of Qiagen elution buffer AVE. The isolation of germline DNA from peripheral blood mononuclear cells and DNA quantification were performed as previously described.[13]

**TABLE 1.** Molecular Alterations Identified in the Patient

| Genomic Alterations Identified | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Gene Symbol** | **Mutation Type** | **Chromosome** | **Position (hg38)** | **End Position (hg38)** | **Cytoband** | **Reference Allele** | **Sample Allele** | **ACMG Classification** | **Variation Type** | **Gene Region** | **Protein Variant** | **Inferred Activity** | **Translation Impact** | **dbSNP ID** | **COSMIC ID** |
| *ATM* | Germline | 11 | 108347277 | 108347277 | q22.3 | A | C | Pathogenic | SNV | Splice site | – | Loss | – | 1060501700 | – |
| *CDKN2A* | Somatic | 9 | 21974696 | 21974696 | p21.3 | G | – | Pathogenic | Deletion | Exonic | p.Y44* | Loss | Frameshift | 1131691187 | 4448823 |
| *KRAS* | Somatic | 12 | 25245351 | 25245351 | p12.1 | C | G | Pathogenic | SNV | Exonic | p.G12R | Gain | Missense | 121913530 | 1157797 |
| *TP53* | Somatic | 17 | 7673728 | 7673728 | p13.1 | G | T | VUS | SNV | Exonic | p.E298Q | Normal | Missense | 201744589 | 10710 |
| Microsatellite status | | | | | | | | | Tumor mutation burden | | | | | | |
| The tumor seen here is MSS | | | | | | | | | The tumor seen here harbors a low TMB, 1 muts/Mb. On average, pancreatic carcinoma harbors a median TMB of 2.5 muts/Mb | | | | | | |

The variant annotation and interpretation analyses shown in the table were generated through the use of Ingenuity Variant Analysis software https://www.qiagenbioinformatics.com/products/ingenuity-variant-analysis from QIAGEN, Inc.

ACMG indicates American College of Medical Genetics; MSS, microsatellite stable; muts/Mb, mutations per megabase; SNV, single nucleotide variation; VUS, variant of uncertain significance.

*KRAS G12R* Mutant Detection-Custom TaqMan Assays were designed using the Life Technologies web-based design tool (http://www.thermofisher.com/order/custom-genomic-products/tools/genotyping/). TaqMan Assays were developed to quantitate copy number variants of mutants using droplet digital polymerase chain reaction (PCR) (ddPCR; RainDance Technologies, Billerica, Mass). Assays included VIC- or FAM-labeled probes, which were selected for wild-type and mutant variants, respectively. The specificity of each assay was first validated by Quantstudio7 Flex Real Time PCR System (Applied Biosystems, Foster City, Calif). A standard curve was developed to establish sensitivity, linearity, and the lower limits of detection of mutants in ddPCR assays. For this purpose, serial dilutions of synthesized *KRAS G12R* double-stranded DNA gene fragments (Integrated DNA Technologies, Coralville, Iowa) ranging from 2 to 2000 copies were spiked into a background of 50,000 copies of genomic KRAS wild type DNA. Once the lower limit of detection was established for each assay, ddPCR was performed on cf/germline DNA extracted from longitudinally collected patient serum/peripheral blood mononuclear cell samples. Ten nanograms of eluted cell free/germline DNA was used for each PCR reaction. Droplets were synthesized using RainDrop Source instrumentation. The total PCR reaction volume was 50 μL resulting in $10^6$ droplets. Cycling with a Gene Touch Thermocycler (Portsmouth, NC) was performed using the following parameters: 95°C for 10 minutes for 1 cycle; 95°C (15 seconds), and 60°C (1 minute) with a step for 45 cycles each; and 98°C (10 minutes). PCR products were loaded into the RainDrop Sense instrument (RainDance Technologies) for quantification of wild type and mutant copy numbers and analyzed with RainDrop Analyst II software (RainDance Technologies) as described.[13] Each DNA sample was represented by at least 2 replicates.

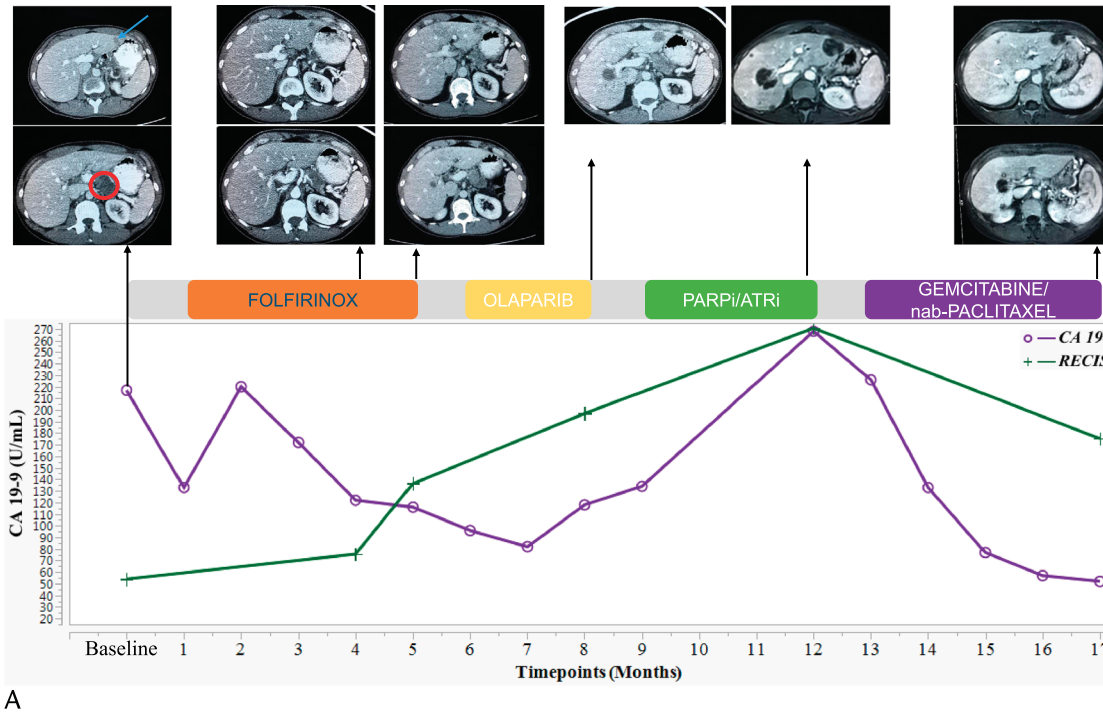
## RESULTS

The measurement of circulating levels of mutant *KRAS* ctDNA (circulating tumor DNA) has been shown to be a highly sensitive method to aid in the determination of prognosis and response to treatment in PDAC.[14] In addition to the patient's clinical condition, imaging studies and CA 19–9 levels, we were able to further assess our patient's response to treatment by measuring serum levels of mutant *KRAS G12R* ctDNA. As shown in Figure 2B, the rise in *KRAS G12R* ctDNA levels preceded the rise in CA 19–9 while the patient was receiving FOLFIRINOX (see month 5). Mutant *KRAS G12R* ctDNA became undetectable after month 14, confirming that gemcitabine/nab-paclitaxel resulted in a deeper and more durable response than prior therapies.

## DISCUSSION

Treatment options for advanced PDAC are extremely limited. Fewer than 1% of patients qualify for immunotherapy based on microsatellite instability status,[15] and there are no effective protein kinase inhibitors or monoclonal antibody therapies. Chemotherapy, therefore, remains the mainstay of treatment, and the best responses are obtained with the first-line regimen. Since there are 2 main first-line choices, FOLFIRINOX or G/N, it is important to choose the "right" treatment for each patient. Until recently, this choice was guided primarily by a patient's age, performance status, and comorbidities rather than an objective predictive biomarker.[8] Accumulating evidence suggests that identification of a germline mutation in a gene involved in HRR can guide the choice of therapy.[2–4,10,11]

Several recent analyses indicate that mutations in the *ATM* gene are among the most commonly occurring cancer susceptibility gene mutations in PDAC. Investigators at the Mayo Clinic

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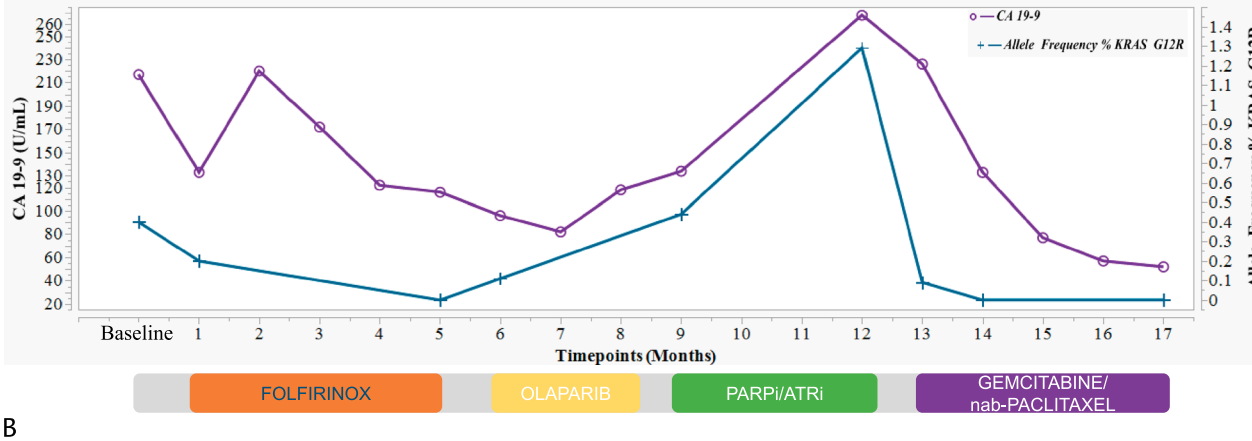


B

**FIGURE 2.** Clinical pattern of response to treatment. A, RECIST measurements and CA 19–9 levels corresponding to the timeline showing therapy (I = inhibitor). Top panels show corresponding axial CT and MRI images. Red circle indicates the pancreatic primary, and the blue arrow indicates a liver metastasis. B, Comparison of CA 19–9 values and allele frequency of *KRAS* c34G > C (G12R) ctDNA demonstrating a complete molecular response to gemcitabine/nab-paclitaxel.

compared 3030 patients with pancreatic cancer to reference controls and found mutations in 6 genes that significantly increased the risk of PDAC, affecting 5.5% of all patients: *ATM* (2.3%), *BRCA2* (1.9%), *BRCA1* (0.6%), *CDKN2A* (0.3%), *TP53* (0.2%), and *MLH1* (0.13%); *PALB2* (0.4%) did not increase the risk of pancreatic cancer compared with controls.[16] Cancer of the Pancreas Screening program investigators at Johns Hopkins Hospital found mutations in 15 (4.3%) of 345 individuals with familial pancreatic cancer: 9 *ATM*, 2 *BRCA2,* 1 *BRCA1*, 1 *PALB2*, 1 *TP53*, and 1 *CPA1*.[17] Perhaps, because of prior experience with other *BRCA*-associated cancers (especially ovarian and breast), there have been numerous case reports, small series and clinical trials on the use of platinum drugs and PARP inhibitors in PDAC patients with *BRCA1/2* and *PALB2* mutations.[10,11,18,19] As a result of the favorable data reported, leading guidelines now recommend first-line platinum drugs for patients with 1 of these 3 mutations.[20] Yet, despite its relatively high incidence, there is a paucity of clinical reports, and no guideline recommendations for those with *ATM* mutations.

Ataxia-telangiectasia mutated (ATM) is a protein kinase that is central to the DNA damage response pathway. Recruited to sites of double-strand breaks, ATM coordinates HRR through interactions with multiple proteins, including BRCA1/2, ATR, and TP53.[21] *ATM*-mutant cells are defective in DNA repair and predicted to have sensitivity to platinum drugs (which induce double-strand DNA breaks) and PARP inhibitors (which induce synthetic lethality).[21,22] There have been no clinical trials specifically targeting *ATM*-mutated PDAC nor have there been

published case reports. Kondo et al[9] included *ATM*-mutated patients among a group of HRR-gene mutated PDAC and reported that the group as a whole had improved disease free survival with oxaliplatin-based chemotherapy, compared with those without mutations. Aguirre et al[4] utilized a novel PancSeq protocol to discover *g*DDR mutations in 18% of their patient cohort. Five of 8 patients with an *ATM*, *ATR*, or *CHEK2* mutation who were treated with oxaliplatin-based chemotherapy were deemed to derive clinical benefit (defined as stable disease or better at 8 weeks). One *ATM*-mutated patient received a PARP inhibitor but the response was not noted.

To our knowledge, this is the first case report of *gATM*-mutated pancreatic cancer. Our patient is notable for deriving stable disease for 14 weeks as the best response to first-line FOLFIRINOX, no response to PARP (and ATR) inhibition, but an unexpectedly robust response to third-line therapy with the nonplatinum regimen of gemcitabine plus nab-paclitaxel. This superior response was confirmed by a decline in the CA 19–9 to its lowest level and the lack of detectable *KRAS G12R* ctDNA. It was only owing to her young age and previous fit condition that we could treat her with third-line cytotoxic chemotherapy in the setting of rapidly progressive disease; many patients would be appropriately offered palliative care and hospice at this point in their cancer course. Although we cannot account for the response to third-line gemcitabine/nab-paclitaxel, we speculate that her suboptimal response to genome-based therapies may be related in part to preservation of the normal ATM allele (absence of loss-of-heterozygosity) and resultant lack of enrichment for the homologous recombination deficiency/COSMIC3 mutational signature.[4,23]

In conclusion, this case report suggests that the detection of a germline *ATM* mutation in advanced pancreatic cancer may not be sufficient evidence to choose a first-line platinum regimen or treatment with a PARP inhibitor. This is in contrast to the detection of a *BRCA1/2* or *PALB2* mutation. Improved methods of assessing homologous recombination deficiency and/or novel pharmacogenomic approaches, such as gene expression profiling from patient-derived organoids[24] or from circulating tumor and invasive cells,[25] offer the promise of better predictive tools to help oncologists choose the most effective treatments for their patients with pancreatic cancer.

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