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Comprehensive genomic profiling of pancreatic acinar cell carcinomas identifies recurrent RAF fusions and frequent inactivation of DNA repair genes

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Background: Pancreatic acinar cell carcinomas (PACCs) account for ~1% (~500 cases) of pancreatic cancer diagnoses annually in the United States. Oncogenic therapuetic targets have proven elusive in this disease, and chemotherapy and radiation have demonstrated limited efficacy against these tumors.
Materials and Methods: We performed comprehensive genomic profiling of a large series of PACCs (n = 44), including closely related mixed acinar carcinomas (16 pure PACC, 14 mixed acinar/neuroendocrine, 6 mixed acinar/ductal, 2 mixed acinar/neuroendocrine/ductal, and 6 samples with incomplete histological analysis), using FoundationOne®, a next-generation sequencing (NGS)-based platform. DNA was analyzed for base substitutions, insertions/deletions, copy number alterations, and select rearrangements; eleven samples had sufficient material for broad fusion detection using targeted RNA-sequencing.
Results: Recurrent rearrangements involving *BRAF* and *RAF1* (*CRAF*) were observed in 10 samples (23%) of mixed and pure histology, and were mutually exclusive with other known driver events. Biochemical characterization of the most prevalent fusion, *SND1-BRAF* (n = 5), resulted in activation of the mitogen activated protein kinase (MAPK) pathway which could be abrogated with MEK inhibition. *SND1-BRAF* was transforming, and cells dependent on this fusion were sensitive to treatment with the MEK inhibitor, trametinib. Broad analysis of recurrent cancer-related genomic alterations in PACC revealed a unique genomic landscape compared to other subtypes of pancreatic cancer. Notably, we observed lower frequencies of *KRAS* and *NF1* alterations compared to pancreatic ductal adenocarcinoma and neuroendocrine tumors, respectively. Inactivating alterations in DNA repair genes were observed in 45% of PACCs, including mixed and pure histologies, and were mutually exclusive with *RAF* genomic alterations.
Conclusions: These findings have immediate clinical impact for PACC patients. *RAF* fusions in other diseases have demonstrated clinical sensitivity to targeted inhibitors; these agents may represent potential treatment options for the 23% of PACCs driven by these fusions. To our knowledge, this is the first report of *RAF* fusions in any form of pancreatic cancer. DNA repair deficiencies (45% of PACCs) are associated with sensitivity to platinum-based therapies and may also predict susceptibility to PARP inhibitors currently in late-stage clinical development. Although these alterations have been implicated in other forms of pancreatic cancer, they have been described only rarely in PACC. Collectively, these data suggest multiple potential therapeutic options for over two-thirds of PACC patients, and provide a rationale for using personalized therapies in this disease.

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A combined in vitro and mathematical modelling approach for understanding the impact of an inhibitor of ATR on DNA damage and repair after ionising radiation

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Background: AZD6738 is a potent specific inhibitor of ATR. As part of clinical development it is planned to investigate the combination of AZD6738 with ionising radiation (IR) in head and neck cancer patients. We have developed a novel cell cycle model to predict cellular responses to combination AZD6738/IR treatment.
Materials and Methods: A simple mathematical model of the cell cycle, incorporating DNA damage and repair, was proposed. The model was formulated so that AZD6738 was assumed to inhibit the repair of replication stress induced damage during S-phase of the cell cycle. The model was calibrated using *in vitro* dose–response data generated using a colon carcinoma cell line. gH2AX biomarker data was used to measure DNA damage, with cell count as the indicator of tumour proliferation. The *in vitro* calibrated model was incorporated into a solid tumour growth model and AZD6738 time-varying concentration informed by observed plasma pharmacokinetics in the mouse. Validation of model predictions was against gH2AX changes over time in the same tumour cell line xenografted in mice *in vivo* and the resulting efficacy after repeated doses of AZD6738 and IR
Results: The model was successfully parameterised using *in vitro* data generated at a range of concentrations of AZD6738 as well as after replenishing with AZD6738 free media to simulate drug washout. The resulting *in vivo* tumour growth model was capable of accurately predicting *in vivo* mouse xenograft data, without requiring any additional modification of model parameters.
Conclusions: Our prediction of AZD6738/IR combination efficacy has informed on the minimum dosing levels required in the clinic to be pharmacologically active. Minimum efficacious dose will minimize the risk of overdosing and so toxicological effects such as mucositis. The model also predicts drug efficacy and tumour proliferation rates in response to intermittent dose schedules, thus optimizing drug exposure for tumour regression. The model provides a framework that can be extended across other targetted therapy classes, supplementing mathematical models of low throughput *in vivo* data with high throughput *in vitro* assays.

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The DNA damage response gene Schlafen 11 (SLFN11) is a transcriptional target of ETS transcription factors in Ewing's sarcoma and other cancers

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SLFN11 is a critical determinant of response to DNA targeted therapies including topoisomerase I and II inhibitors (camptothecins, etoposide, doxorubicin) and cisplatin. Ewing's sarcoma (EWS), which is characterized by expression of the chimeric transcription factor EWS-FLI1, has notably high SLFN11 expression. This led us to investigate whether EWS-FLI1 is causative for elevated SLFN11 expression. ChIP-Seq analysis of EWS-FLI1 in A673 EWS cells showed that EWS-FLI1 binds near the transcription start site of *SLFN11*. We further demonstrate that EWS-FLI1 is a positive transcriptional regulator for *SLFN11* and that EWS-FLI1-mediated SLFN11 overexpression is responsible for high sensitivity of EWS to the topoisomerase I inhibitor camptothecin. The correlated expression between SLFN11 and FLI1 extends to leukemia, pediatric, breast and prostate cancers. These analyses suggest that, in addition to FLI1, several ETS members, including ETS1 regulate SLFN11 expression. Together, our results suggest the emerging relevance of SLFN11 for therapeutic response to DNA damaging agents in ETS-activated cancers.

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Phase 1 correlative study of ARQ761, a β-lapachone analogue that promotes NQ01-mediated programmed cancer cell necrosis

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Background: NAD(P)H:quinone oxidoreductase 1 (NQO1) is a two-electron oxidoreductase expressed in multiple tumor types at levels 5- to 200-fold above normal tissue. ARQ761 (ArQule, Woburn, MA, USA) is a highly soluble intermediate β-lapachone hydroquinone analogue, complexed in hydroxypropyl-β-cyclodextrin, that exploits the unique elevation of NQO1 found in solid tumors to cause tumor-specific cell death by eliciting a futile redox cycle generating high levels of reactive oxygen species and ultimately PARP1 hyperactivation-dependent cell death.
Materials and Methods: We initiated a 3+3 dose escalation study of 3 schedules (weekly, every other week, 2/3 weeks) of ARQ761 monotherapy as a 1-hr or 2-hr infusion. Eligible patients had refractory advanced solid