CASE 1: GENOMIC ANALYSIS AND MANAGEMENT OF METASTATIC PANCREATIC CANCER WITH AN ACTIONABLE ABERRATION

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QUESTION #1:

- The percent of pancreatic cancers that harbor potentially "actionable" alterations (for which there is an FDA approved therapy [in pancreatic cancer OR other disease types]) is:
  A. 3 – 5%
  B. 10%
  C. 25%
  D. 40%

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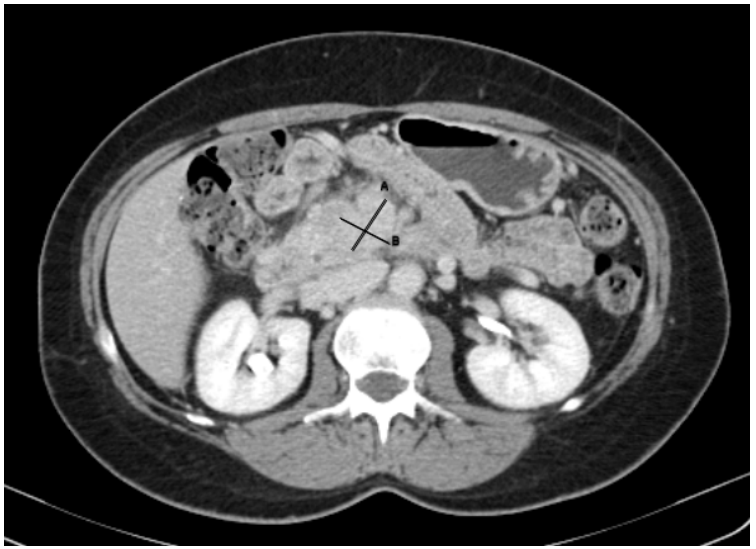
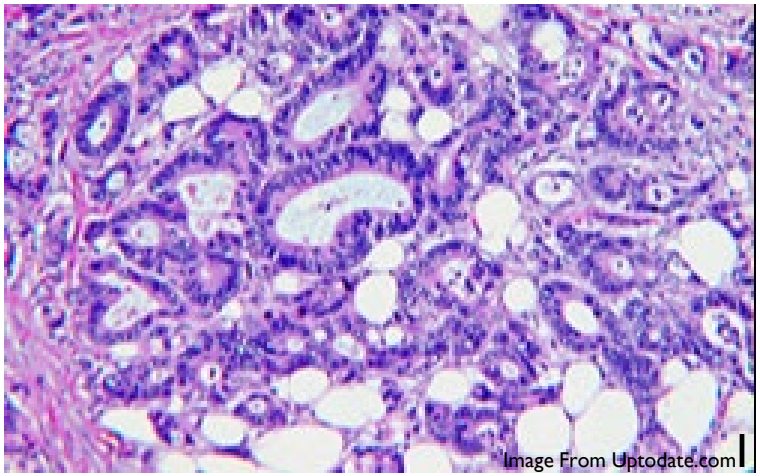
HISTORY OF PRESENT ILLNESS

- Previously healthy 51 year old female presented with abdominal pain in 2014
- No medical or surgical history
- No tobacco or ETOH use
- Family history: father with lung cancer

DIAGNOSIS

- CT Scan (and a subsequent MRI/MRCP) showed a 2.9 x 2.6cm pancreatic head mass encasing the SMA
- EUS-FNA pathology: well-differentiated adenocarcinoma
- Diagnosis: locally advanced unresectable pancreatic adenocarcinoma





TREATMENT TIMELINE

- Frontline FOLFOX 12/2014 - 10/2016
  - Held oxaliplatin after Cycle 6 for neuropathy
- Incorporated SBRT to the mass in 03/2015
- October, 2016 restaging scan: large right ovarian tumor (12 x 10 x 12cm)
  - Resected in 11/2016 – pathology consistent with a metastasis from the pancreatic primary
- Reinitiated FOLFOX 11/2016
  - Oxaliplatin stopped after only 4 additional cycles for an allergy

QUESTION #2:

- Is the presence of a germline *BRCA1/2* mutation in pancreatic cancer know to be:
  A. Prognostic
  B. Predictive of a response to platinum-based therapy
  C. Both A and B
  D. Neither A nor B

QUESTION #2:

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  - A. Prognostic
  - **B. Predictive of a response to platinum-based therapy**
  - C. Both A and B
  - D. Neither A nor B

Golan, et al, BJC, 2014; Pishvaian, et al, JCO PO, manuscript in press, 2019

MOLECULAR PROFILING OF THE METASTASIS

- *BRCA1* & *BRCA2* non-mutated
- ***ATM* mutation in exon 25 p.L1238fs**
- *KRAS* mutation in exon 2 p.Gt2D
- *SMAD4* mutation in exon 10 p.V387fs
- *MET* mutation in exon 2 p.P164A
- MS-stable
- Total mutational burden: 10 mutations/Mb

QUESTION #3:

- The most common potentially "actionable" alteration in pancreatic cancer is a (an):
  - A. *KRAS* mutation
  - B. *BRCA1* or *-2* mutation
  - C. *ATM* mutation
  - D. Defect in mismatch repair (MMR deficient/MSI-high)
  - E. *NTRK* fusion

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  - B. *BRCA1* or *-2* mutation
  - **C. *ATM* mutation – 6.2% across multiple publications**
  - D. Defect in mismatch repair (MMR deficient/MSI-high)
  - E. *NTRK* fusion

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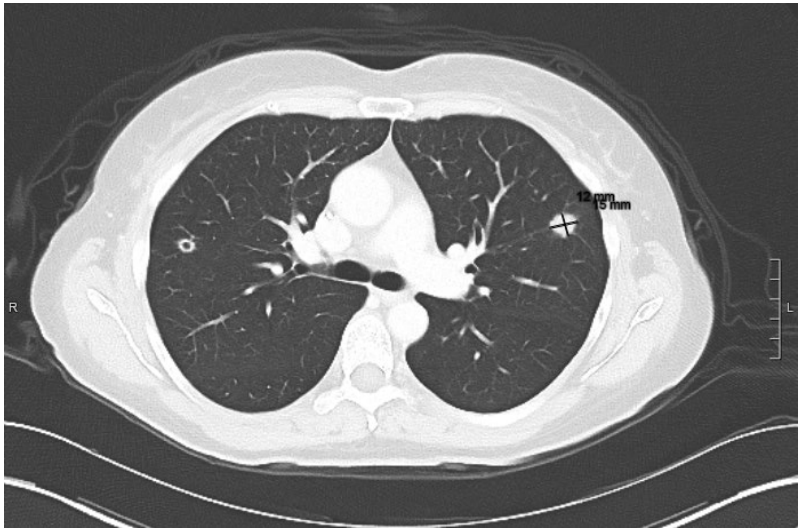
TREATMENT TIMELINE - CONTINUED



- Transitioned to maintenance capecitabine 2/2017-6/2018
- February, 2018 restaging scan: prepubic soft tissue mass (3.2 x 2.4 cm)
  - Suprapubic metastasectomy 3/15/2018
- May, 2018 restaging scan showed pulmonary metastatic disease

TREATMENT TIMELINE - CONTINUED

- Phase I trial of carboplatin plus niraparib 6/2018-8/2018
  - No benefit: August, 2018 restaging scan showed an enlarged cervix, and a pelvic exam revealed a 4 cm cervical lesion
- Radiation to the cervical metastasis 9/2018
- Gemcitabine plus nab-paclitaxel 11/2018-1/2019
- At progression enrolled in a Phase I trial of irinotecan, veliparib and the ATR inhibitor VX-970
  - Disease stable on trial through 6 months

IMPORTANCE OF GENOMIC SEQUENCING

- Identify therapeutically relevant alterations in ~25% of PDACs
  - The majority of mutations identified are in the DNA damage response and repair (DDR) genes
- DDR mutations render cells more sensitive to DNA damage
  - Classically *BRCA1/2* mutations respond to platinums and PARPi
  - But…..not all DDR mutations are the same
- Research needed to identify how to treat different mutations

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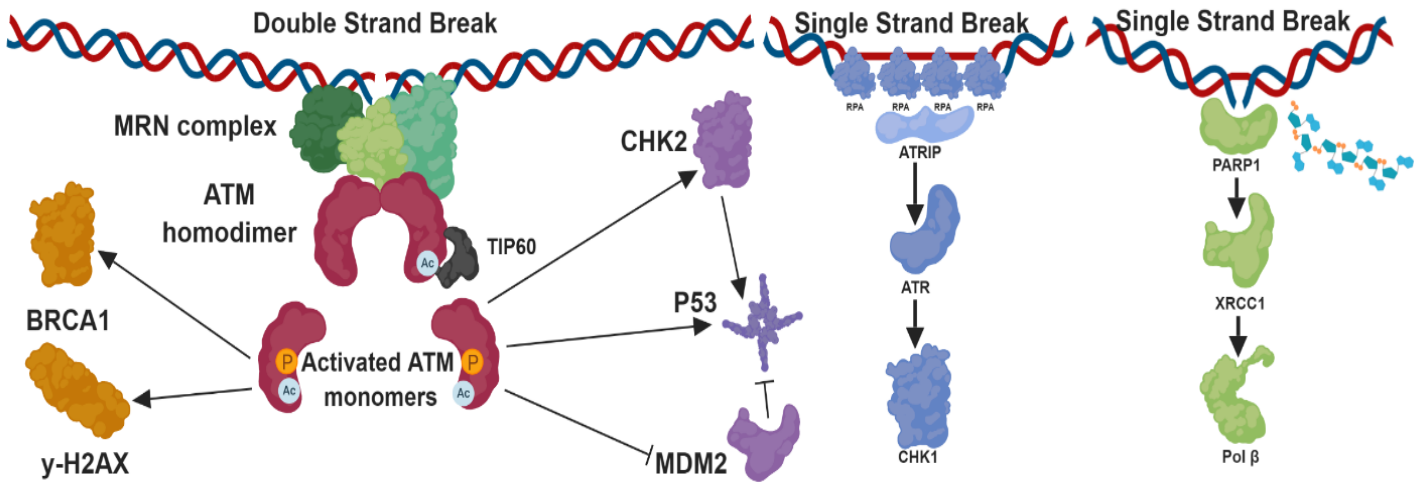
ATM MUTATIONS IN PDAC

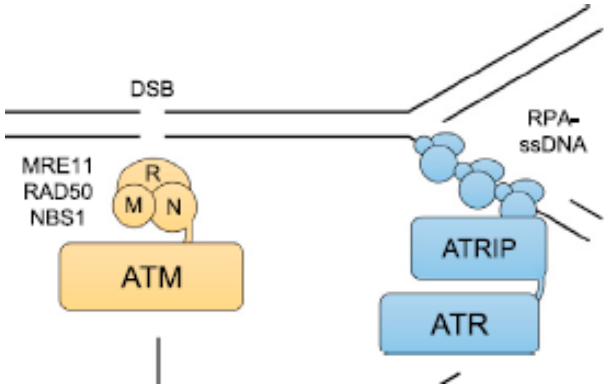


- ATM's Function:
  - Cell cycle checkpoint kinase
  - Regulate downstream proteins
  - Respond to DNA damage for genome stability
- ATM is one of the most commonly mutated DDR genes in PDAC
  - Somatic mutations 2 - 18%
  - Germline mutations 1 - 34%

Armstrong et al, Manuscript in Press, Molecular Cancer Research

THERAPEUTIC SIGNIFICANCE OF *ATM* MUTATIONS

- Uniquely sensitive to radiation therapy
  - As seen in this case - prolonged control with SBRT
- Unlike *BRCA1/2* mutations, *ATM* mutations are not always responsive to platinum agents and PARP inhibitors
  - As seen in this case - rapid progression on platinum + a PARPi
- Synthetic lethality with an ATR inhibitor in the context of an *ATM* mutation



Armstrong et al, Manuscript in Press, Molecular Cancer Research; Blackford and Jackson, Molecular Cell 66, June 15, 2017

TAKE AWAY POINTS

- Genetic profiling is crucial in every pancreatic cancer patient
- Not all DDR mutations are the same, we still need to identify how to treat each mutation differently
- Promising preclinical data utilizing ATR inhibition +/- chemotherapy in *ATM*-mutated tumors