Pancreatic Cancer - Case Study 2

Real Patients, Real Results

56-Year-Old Male

BRCA SOMATIC RESULTS

"This case brings up two treatment decisions. What chemotherapy and what, if any, maintenance therapy?" - Dr. Paul Walker, Chief Medical Officer, Former Director of Thoracic Oncology at East Carolina University

SUMMARY OF RESULTS

Gene(s) Tested:	52
Alteration(s) Detected:	4
FDA-Approved Targeted Therapies:	0
Additional Therapies:	0
Open Clinical Trials:	16

IMMUNOTHERAPY TEST RESULTS

		FDA GUIDANCE
MSI-H	Not Detected	

These alterations, relevant in pancreatic cancer, were tested and determined to be Detected/Not Detected or Test Not Performed

Result	Gene	Variant	Alteration
Detected	BRCA1 (somatic)		c.4675+2T>C
Not detected	BRCA2 (somatic)		
Not detected	BRCA1 (germline)		
Not detected	BRCA2 (germline)		
Not detected	MLH1 (germline)		
Not detected	MSH2 (germline)		
Not detected	MSH6 (germline)		
Not detected	PMS2 (germline)		
Not detected	MSI		

Reference complete BRCA and/or hereditary panel report for additional and complete information about BRCA and/or hereditary marker tests. Reference "Immunotherapy & RNA Test Result" section for MSI results.

In germline BRCA-mutated advanced pancreatic cancers, it is clearly established that platinum-based chemotherapy and maintenance PARP inhibitors can be notably effective. In the POLO trial published in the NEJM July 2019 issue, there was a significant progression-free survival and prolonged median duration of response of 25 months with the use of the maintenance PARP inhibitor Olaparib. FOLFIRINOX or cisplatin-gemcitabine with notable response and disease control rates of 70% and 100% in germline BRCA patients would be the recommended chemotherapy approaches over gemcitabine-abraxane.

In this case, there is a somatic BRCA1 mutation along with three other ctDNA mutations not yet having any known effective targeted therapy approach. Somatic BRCA-mutated patients showed a similar PR with one CR benefit of the PARP inhibitor Rucaparib after previous chemotherapy in platinum-sensitive disease supporting the use of maintenance PARP inhibitor in this patient.

"Not to be overlooked is the benefit of plasma NGS monitoring of treatment response and potential actionable resistance pathways to keep going forward with his best possible treatment and outcome."

Sources:
- Dr. Paul Walker, Chief Medical Officer, Former Director of Thoracic Oncology at East Carolina University
- J Clin Oncol 38:1378-1388. © 2020 by American Society of Clinical Oncology
- N Engl J Med 2019;381:317-27. DOI: 10.1056/NEJMoa1903387
- ascopubs.org/journal/po JCO™ Precision Oncology

73-Year-Old Patient

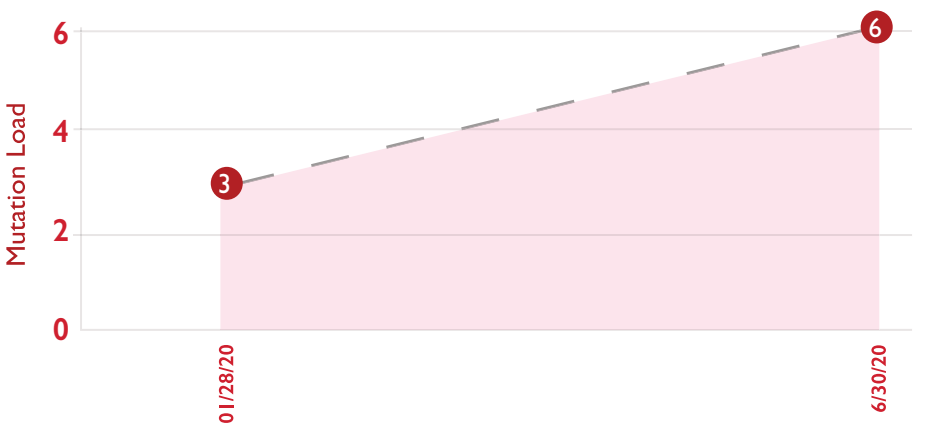
ATM, INCREASING ctDNA MUTATIONS

"Using plasma NGS in monitoring treatment response in pancreatic - and all - cancers can be notably impactful in helping patients live longer and live better. Plasma ctDNA can identify responding or progressing cancer activity before it is radiographically evident, avoiding continuation of ineffective therapy with needless toxicity. It can also identify resistance pathways, guiding a potentially more effective precision treatment approach. In a seminal study comparing tissue biopsies of multiple tumor sites with tissue NGS versus paired plasma NGS, the plasma ctDNA was far superior in identifying more resistant pathways and identified more mutations that are otherwise limited by tissue heterogeneity.

SUMMARY OF RESULTS

Gene(s) Tested:	52
Alteration(s) Detected:	6
FDA-Approved Targeted Therapies:	0
Additional Therapies:	0
Open Clinical Trials:	23

MUTATIONAL TRENDING



ALTERATIONS DETECTED

GENE	ALTERATION	MUTANT FRACTION	FDA TARGETED THERAPIES (pancreatic cancer)	FDA TARGETED THERAPIES (for other indications)	CLINICAL TRIALS (details below)
ATM	p.R337C; c.1009C>T	34.2%	None	None	6

ATM Description

The protein encoded by this gene belongs to the PI3/PI4-kinase family. This protein is an important cell cycle checkpoint kinase that phosphorylates; thus, it functions as a regulator of a wide variety of downstream proteins, including tumor suppressor proteins p53 and BRCA1, checkpoint kinase CHK2, checkpoint proteins RAD17 and RAD9, and DNA repair protein NBS1. This protein and the closely related kinase ATR are thought to be master controllers of cell cycle signaling pathways that are required for cell response to DNA damage and for genome stability. Mutations in this gene are associated with ataxia telangiectasia, an autosomal recessive disorder. [provided by RefSeq, Aug 2010]

Very unfortunately, based upon this second plasma NGS, there is clearly active and progressing pancreatic cancer with the number of ctDNA mutations increasing from 3 to 6. If her cancer were responding, her ctDNA load should have been decreasing by 4-6 weeks after starting treatment. Continuing the same ineffective therapy at this point is pure toxicity without any benefit.

Although none of the mutations are directly targetable, they can be actionable in making a next-treatment-step recommendation and decision. The "Know Your Tumor" study was a profound proof of principle of this with a markedly better survival in those patients who received 'matched' therapy guided by molecular testing. ATM is a DNA damage response and repair pathway gene. ATM mutations can heighten potential response to chemotherapy, gemcitabine-abraxane in particular, PARP inhibitors and radiation therapy. The next best therapy step needs to be guided by and 'match' the evolving tumor biology and progressing disease findings. Certainly, a clinical trial targeting ATM is also a possibility, if available.

Precision oncology is knowing the tumor biology. Personalized cancer treatment is providing the best possible cancer treatment to get the best possible outcome for your patient. You will not know the tumor biology if you do not test it. Plasma NGS is the best monitor of cancer activity and evolving tumor biology."

- Dr. Paul Walker, Chief Medical Officer, Former Director of Thoracic Oncology at East Carolina University

Sources:
- Pancreas Journal, Volume 49, Number 1, January 2020
- Pancreas (Fairfax). 2019 ; 3(1): e5–e8. doi:10.17140/POJ-3-e011
- Michael Ayars, James Eshleman & Michael Goggins (2017). Susceptibility of ATM-deficient pancreatic cancer cells to radiation, Cell Cycle, 16:10, 991-998, DOI: 10.1080/15384101.2017.1312236
- The Lancet Oncology, March 2020