Cancer Care and a Tale of Three Molecular "Genomic" Tests

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Introduction

- The practice of oncology has largely evolved to treating cancer based on tumor genomics.
- Genetic testing for hereditary cancer predisposition syndromes and somatic tumor testing for targeted therapy selection have advanced patient care.
- More recently, cell free DNA analysis has been leveraged to develop patient-specific, bespoke assays for detecting circulating tumor DNA (ctDNA) in cancer patients, allowing monitoring for molecular residual disease, recurrence, and treatment response.[1-4]
- Specific to those diagnosed with metastatic disease and treated with single-agent pembrolizumab, we have previously demonstrated a strong correlation between changes in ctDNA levels with overall survival, progression free survival, received clinical benefit, and overall response rate.[5]

Aim

- To present a patient diagnosed with cancer where three individual molecular tests with unique purpose were utilized in the care continuum.

Figure 1. Signatera Molecular Protocol

Sequence tumor tissue to identify unique signature of tumor mutations

Custom design and manufacture personalized mPCR assay for each patient targeting clonal mutations found in tumor

Use personalized assay to test patient's blood for presence of circulating tumor DNA (ctDNA)

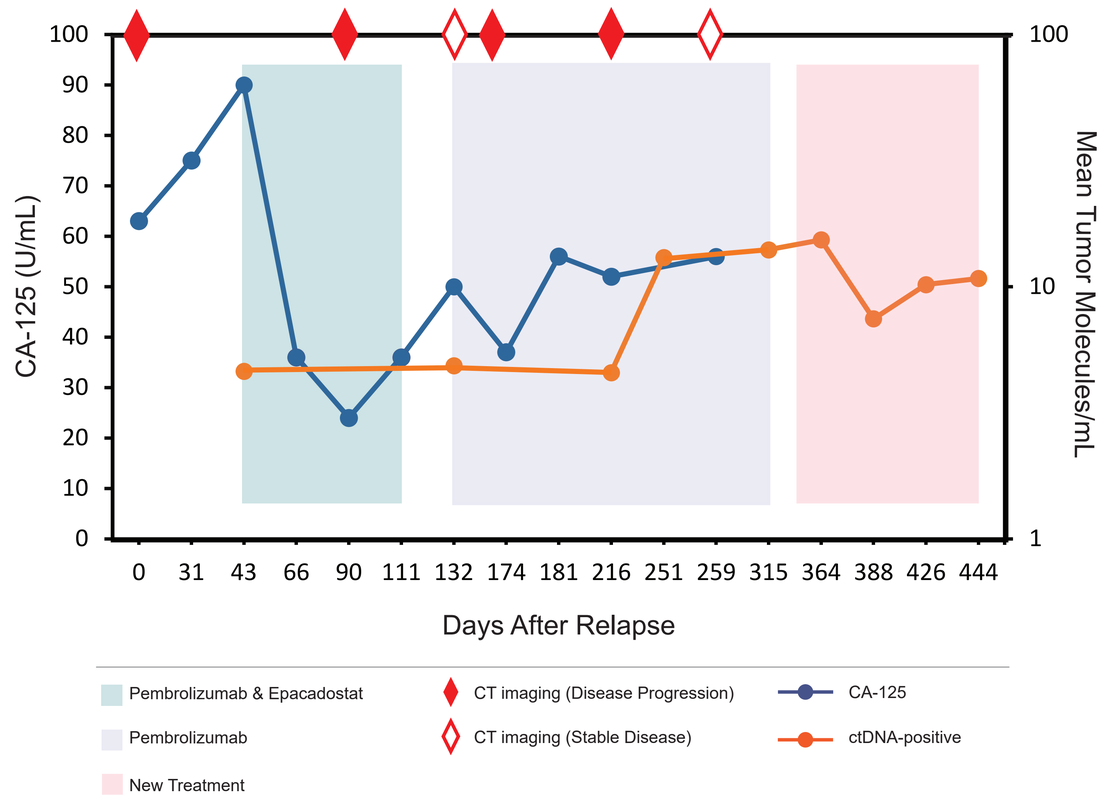
Case Presentation

- A 56 year old caucasian female diagnosed with stage IIIc ovarian clear cell carcinoma, treated with total abdominal hysterectomy with bilateral salpingo-oophorectomy,omentectomy, appendectomy, lymph node sampling, peritonectomy, and optimal tumor debulking in June 2018.
- Following diagnosis, the patient was assessed with tumor molecular comprehensive genomic profiling (CGP) and hereditary cancer predisposition syndrome diagnostic testing **(Table 1)** to identify potential inherited predisposition risk and to inform on treatment selection, available clinical trials, and potential use of PARP inhibitor therapy.
  - The CGP test included evaluation of microsatellite instability status, tumor mutation burden, and NGS of exons for 315 genes, as well as introns of 28 genes involved in rearrangements.
- The patient's germline testing was negative for mutations associated with hereditary cancer predisposition syndromes, including germline variants in *BRCA1/BRCA2*, which if present, could have suggested a response to PARP inhibitors.
- CGP results identified the following somatic genomic alterations: *PIK3CA* (E545K), *ARID1A* (T118fs*275), *PPP2R1A* (R183Q)
- CGP results did not identify a FDA-approved therapy specific to the patient's tumor type, however, Everolimus (Afinitor)/Temsirolius is FDA-approved for use in patients identified with *PIK3CA* somatic variants in other tumor types. In addition, 11 clinical trials were identified based on the somatic profile.
- Treatment with first line adjuvant chemotherapy concluded October 2018. In Jan 2019, the patient relapsed and enrolled in clinical trial (NCT03602586), receiving pembrolizumab infusions with oral epacadostat. Due to severe reactions to epacadostat, beginning May 2019, the patient received pembrolizumab infusions only.
- In December 2019, the patient progressed off of clinical trial NCT03602586 and began a new clinical trial
- From February 2019 to March 2020, the patient has been assessed using personalized, tumor-informed ctDNA assay (Signatera, bespoke mPCR NGS assay) **(Figure 1)**.
- **Figure 2** shows varied ctDNA levels measured in mean tumor molecules/mL compared to CA-125 levels from February 2019 to March 2020.
- Positive ctDNA results allow the opportunity to monitor treatment response and trending disease burden through longitudinal screening of ctDNA levels.

Table 1. Genes Analyzed for Sequence Alterations and Exonic Deletions/Duplications to Test for Hereditary Cancer Predisposition Syndromes

ATM	*BARD1*	*BRCA1*	*BRCA2*
BRIP1	*CDH1*	*CHEK2*	*DICER1*
EPCAM (del/dup only)	*MLH1*	*MSH2*	*MSH6*
NBN	*NF1*	*PALB2*	*PMS2*
PTEN	*RAD50*	*RAD51C*	*RAD51D*
SMARCA4	*STK11*	*TP53*	

Figure 2. Serial ctDNA Measurements for Therapy Response Monitoring



Discussion

- Here we present an oncology patient where three unique molecular tests informed a patient's treatment selection and monitoring:
  - Negative germline *BRCA1/2* testing and CGP testing suggested lack of therapeutic response to PARP inhibitors.
  - CGP aided in the identification of available clinical trials.
  - Throughout treatment with pembrolizumab, disease burden and treatment response were monitored via ctDNA analysis.

Conclusions

- It is important that genetics professionals become familiar with the increasing number of molecular genomic tests being incorporated into oncology, as each has a unique purpose in the patient care continuum.
- Patients and physicians may seek consultation from clinical genetics professionals to differentiate between molecular genomic tests encountered in their care or practice.

References

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Disclosures

UD is an ex-employee of Natera. All other authors are employees of Natera, Inc. with stock/options to own stock in the company.

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