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UTILITY OF TUMOR-INFORMED MOLECULAR RESIDUAL DISEASE ASSAYS IN PATIENTS WITH COMPLETE RESPONSE TO IMMUNE CHECKPOINT BLOCKADE
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Background Recent data suggests that responses in patients with mismatch repair deficient (dMMR) tumors tend to be durable and potentially curative. Typically immunotherapy is employed and approved only in metastatic settings. However, it is not uncommon now to consider usage in patients with dMMR tumors secondary to the hypermutated nature of these malignancies alongside the concerns that these do not respond to therapy either through a clinical trial or off-label compassionate access programs. As noted, in patients who have these dramatic and durable responses, the question of foregoing surgery and/or radiation comes up. There is no great test to help predict or guide who are these complete responders. Assessment of molecular residual disease or minimal residual disease through tumor-informed assays is one potential test that can be employed in this setting. We here show the feasibility of such an approach in patients with dMMR tumors who got immunotherapy in the advanced but not metastatic setting.

Methods We identified patients who were enrolled in the serial tumor informed molecular residual disease BESPOKE expanded access ctDNA testing program (Signatera 16-plex bespoke mPCR NGS assay) who got immunotherapy in the neoadjuvant setting and were also enrolled in our biobanking program.

Results We were able to serially do ctDNA analysis in 2 patients (1 with advanced but not metastatic esophageal adenocarcinoma and another patient with advanced but not metastatic nearly obstructing rectal adenocarcinoma with extensive nodal metastases in both situations) who got immunotherapy off-label per physician discretion and tumor board discussion. Of note both these patients also had germline oncology-based treatments and now includes sacituzumab govitecan, a novel antibody-chemotherapy conjugate.

Abstract 24 Figure 1 Ongoing response and negative ctDNA minimal residual disease to PD-1 blockade added to standard of care chemotherapy for a patient with advanced rectal cancer

REFERENCE

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LINE OF THERAPY ADJUSTMENT IN A PATIENT WITH ADVANCED TRIPLE-NEGATIVE BREAST CANCER (TNBC) BY USING PERSONALIZED CTDNA TEST FOR TREATMENT RESPONSE MONITORING
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Background Triple negative breast cancer (TNBC) is an aggressive form of breast cancer that is most difficult to treat due to the absence of hormone/growth factor receptors.1 2 Metastatic TNBC (mTNBC) is particularly challenging, given the limited efficacy and duration of response to chemotherapy.3 The repertoire of therapeutic options for mTNBC patients continues to increase with chemotherapeutic and immuno oncology based treatments and now includes sacituzumab govitecan, a novel antibody-chemotherapy conjugate.4

Methods Here we present a case study of a 40-year-old female who on biopsy of her left breast mass was diagnosed with TNBC. The patient underwent neoadjuvant chemotherapy with weekly administration of paclitaxel and carboplatin followed by dose-dense doxorubicin with cyclophosphamide. Following one-month, the patient underwent bilateral mastectomy, showing pathological staging ypT2 pN0. The patient underwent periodic radiological imaging along with the assessment of circulating tumor DNA in blood using a personalized and tumor-informed multiplex PCR, next-generation sequencing assay (Signatera bespoke, mPCR NGS assay) to identify the minimal residual disease (MRD) and treatment response.

Results After surgery, MRD assessment revealed ctDNA positive status (0.41 MTM/mL) prompting PET/CT scan that revealed liver metastasis. Continued ctDNA monitoring
showed continuous increase in ctDNA concentration (287.09 MTM/mL). Separate analyses indicated MSI-high and PD-L1 positive tumor status, leading to the initiation of the first line of therapy (nab-paclitaxel and Atezolizumab), which resulted in ctDNA decline (39.62 MTM/mL). Weekly ctDNA monitoring noted a rapid increase a month later (178 MTM/mL to 833.69 MTM/mL) within a 2-week interval, which corresponded to disease progression on imaging. Given non-responsiveness with the first-line therapy, the patient was initiated with sacituzumab govitcan. Following this, a rapid decline in the ctDNA level was observed within a week (364.07 MTM/mL) with a downward trend to 73.03 MTM/mL by two weeks. An interval PET/CT scan showed a mixed response. Continued monitoring of ctDNA demonstrated ctDNA levels <5MTM/mL for a period of two months before serially rising again (to 89.27 MTM/mL). PET-CT ordered in response to increasing ctDNA levels confirmed progression involving hepatic and lung lesions. A new line of therapy with nivolumab and ipilimumab was subsequently initiated.

Conclusions Serial monitoring of ctDNA enables early detection of therapy resistance and provides a rationale for treatment change/optimization/discontinuation as compared to periodic imaging that is currently the standard of care. The ease and convenience of using ctDNA-based testing as frequently as every week clearly identified earlier non-responsiveness to IO and also identified earlier acquired resistance to antibody-drug conjugate, enabling a prompt switch to alternative therapy.

Ethics Approval N/A
Consent N/A

REFERENCES


Abstract 26 Figure 1 ctDNA time-course demonstrating ctDNA kinetics

Time-point A represents the initial ctDNA assay, performed at the time of resection of peritoneal metastasis. An additional time-point (B) drawn a month later reveals a further increase in ctDNA. Time-point C represents a peak in ctDNA levels, concomitant with the new emergence of a PET avid cardiophrenic lymph node. Combination Immunotherapy (IO) was begun shortly after time-point C. Time-point D represents ctDNA clearance and radiographic resolution of lymph node metastasis after two cycles of IO. MTM/mL - mean tumor molecules/ megabase.