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Case Report

Case Report: Immune Checkpoint Inhibitor Elicited Complete Response in a Heavily Pretreated Patient with Metastatic Endometrial Carcinoma with a High Tumor Mutation Burden (TMB)

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Abstract

We report a unique case example of a patient with advanced metastatic endometrial cancer who failed standard of care options before presentation to our translational program for targeted experimental options. Molecular profile analysis (FoundationOne™ testing, Cambridge, MA) of this patient revealed several genomic alterations potentially associated with therapeutic opportunities. In particular, the tumor mutation burden (TMB) and microsatellite instability (MSI) was high (>20 mutations load per megabase of DNA) with the presence of a *MSH2* loss-of-function mutation and PD-L1 expression <1%. We hypothesized that this group of genomic aberrations would likely indicate an increased neoantigen load and consequently a heightened probability of sensitivity to immune checkpoint inhibitors. Therefore, the patient entered a phase I study of the immune checkpoint inhibitor durvalumab. This heavily pretreated patient achieved a complete and long lasting clinical response to immunotherapy with no significant side effects. Follow up analysis of 266 additional patients identified 29 with TMB >20 mutations (mu)/Mb DNA. Six of these received immunotherapy and all 6 demonstrated response whereas only 1 of 21 other high TMB patients who did not receive immunotherapy achieved response. Genomic analysis has emerged as an important predictive component to maximize proportionate therapeutic benefit to immunotherapy and to help prioritize amongst investigative therapeutic options when available.

Keywords: Tumor mutation burden, Molecular signal, Endometrial, Immunotherapy, checkpoint

Case Report

Patient #103884 is a 61 year-old woman who presented in May 2007 with widely metastatic endometrial carcinoma to liver, lungs and omentum. She achieved a complete response (5/2008) following total hysterectomy, bilateral salpingectomy and subsequent adjuvant cisplatin/taxol. Seven years later, in May 2014, disease recurred (histologically confirmed) comprising multiple lung nodules, a large liver mass (7.8 x 7.0 x 8.5 cm), extensive omental and peritoneal nodules, and expanding ascites. Carboplatin/taxol was reinstituted but followed by rapidly progressive disease (8/2014). Adriamycin was then started but was discontinued after one cycle due to intolerability manifested as tachycardia and pruritus. She underwent a palliative partial hepatectomy and diaphragm nodule resection on October 8, 2014. Pathology confirmed the recurrence was morphologically consistent with the primary disease by histologic review. On the basis of high estrogen/progesterone receptor levels in the malignant tissue she received megestrol hormonal therapy but in the face of enlarging residual and new disease documented in January 2015 megestrol was discontinued and metformin/exemestane started.

After consultation at Mary Crowley Cancer Research Center (MCCRC) the October 2014 malignant tissue was sent to Foundation Medicine for bio-molecular analysis using FoundationOne™. Relevant results included a high tumor mutation burden (TMB; (i.e. >20 mutations/Mb DNA)), 24.3 mutations/Mb; a MSI-H (microsatellite instability-high) signal and *MSH2* mutation (Although germline mutational status was not assessed in patient #103884, two of her three daughters subsequently underwent germline testing and were positive). Additional genomic alterations identified included *ERBB2, FBXW7*, *NF1*, *PALB2*, *PIK3R2*, *PTEN*, *NOTCH3*, *ACVR1*, *ARID1A*, *CHEK2*, *CIC*, *CTCF*, *MLL2*, *MLL3*, *RB1* and *SPEN*, a number of which offered FDA approved therapeutic opportunities (Table 1).

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A September 2015 CT scan confirmed disease progression in the lung, abdomen, pelvis, peritoneum and liver involving multiple lesions ranging from 3.3 x 2.0 cm to 5.9 x 2.8 cm in size. Based on the high TMB and mismatch repair deficiency, the decision was made to proceed with immunotherapy. PD-L1 expression status was not known at that time; however, on September 26, 2017 PD-L1 expression as assessed using SP263 (Biomedical Laboratories, Dallas, TX) was <1% of malignant cells. In September 2015, following informed consent, she started treatment per MCCRC study 13-18, a phase I study of the PD-L1 inhibitor durvalumab (10 mg/kg IV every 2 weeks). A December 2015 computed tomography (CT) scan revealed a 42% reduction of disease by RECIST 1.1 criteria (Figure 1), in March 2016 a 58% reduction of disease and, ultimately, in May 2016, a CT scan showed no evidence of disease (NED). Durvalumab was stopped September 2016. Subsequent CT scans in November 2016 and February 2017 remained NED and PET scan in May 2017 showed no abnormal uptake of fluorodeoxyglucose (FDG) thereby validating complete response. This patient remains in complete response as of September 2017.

Table 1: Genomic Alteration and Potential Signal Pathway Treatment Option (Patient #103884 Involving 10/2014 Tissue, Foundation One Report).

Genomic Alteration	Therapy Option
ERBB2, NF1, PIK3R2, PTEN	Ado-trastuzumab emtansine, Afatinib, Lapatinib, Pertuzumab, Trastuzumab
FBXW7	Everolimus, Temsirolimus
PALB2	Olaparib
NF1	Trametinib

Our experience with patient #103884 prompted the review of 266 MCCRC patients with advanced cancer who had undergone Foundation One biomolecular analysis. We identified 29 of these patients with TMB >10 mu/Mb DNA, six of whom had received immune therapy (Table 2). All six achieved clinical benefit response (CBR; CR, PR or SD >6 months) as defined prospectively by RECIST 1.1. Of the 21 other patients with TMB >10 mu/Mb DNA who did not receive immunotherapy, only one experienced CBR. Two of the patients were unevaluable for response.

Discussion

Recent reports have defined the human cancer TMB

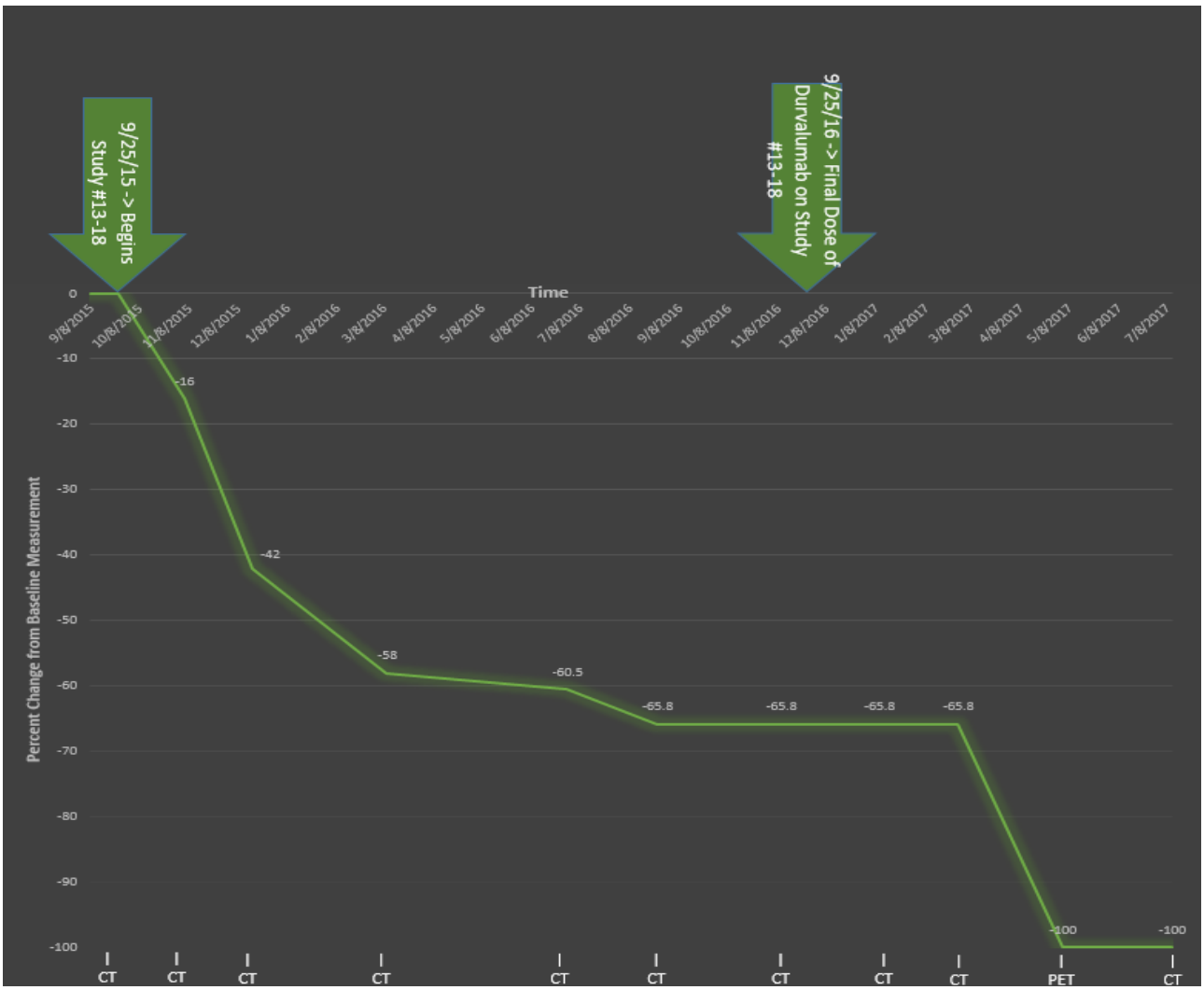

Figure 1: Change in maximum tumor diameter by RECIST 1.1 over time via third party (central image) tracking.

Table 2: MCCRC High TMB Correlated Patient Response to Immunotherapy (6/6 Responses)*

Patient	Disease	TMB	Prior Treatment	DNA Repair Defect	Experimental Immune Treatment	Response
052369	Melanoma	74	Surg, XRT	SF3B1	Vigil [20]	SD > 6 mo
103884	Endometrial ca	24	Chemo x4, surg	MSH2	Durvalumab	PR > 6 mo
035096	Unk prim	40	Chemo x2, surg	PBRM1	TVEC [21]	CR > 3 yr
137097	Unk prim	105	Surg, XRT	SF3B1	TVEC [21]	SD > 18 mo
PW	Melanoma	101	Chemo x2, immune, surg	MSH2	TVEC [21]	PR > 2 yr
076418	NSCLC (ad)	12	Chemo x5, XRT, surg	STK11	Durvalumab	SD > 6 mo

*Low TMB patients associated with 1/21 responses

landscape [1] as well as a quantitative correlation between TMB level and immunotherapeutic response and survival [2], particularly with PD-L1/PD-1 axis checkpoint inhibitor therapy. For example, Rizvi, et al. [3] showed that a higher response rate (PR/CR/ or SD) to pembrolizumab correlated with TMB in NSCLC patients and that progression free survival (PFS) was also prolonged in high vs low TMB patients (14.5 mo vs 3.7 mo; p=0.01). As would be expected, high mutation rates, TMB and correlated immune mediated responses were associated with mutations of DNA repair genes (i.e. *POLD1*, *POLE*, *MSH2*, *MSH6*, *MLH1* and *MLH2*). Rizvi addressed the underlying mechanism by hypothesizing (as others have) that a higher TMB is a surrogate for a higher probability of cancer-specific neo-antigens, formed as a consequence of somatic mutations (particularly missense). They then characterized the neo-antigen tumor landscape on these same patients and found a direct quantitative correlation of immunotherapeutic response and survival advantage with TMB ($p < 0.0001$). Cancers (regardless of histologic type) with a mean mutational load of >20 somatic mutations/Mb of coding DNA were more likely to have a burden of neo-antigens of which one or more subsets are effectively immunogenic [4,5]. Both our retrospective analysis involving 29 patients with TMB >10/Mb and the correlation of higher TMB to response (median 12.4/Mb responders vs. 6.4/Mb non-responders; p = 0.0001) and survival (p = 0.0012) in a phase III trial of atezolizumab in metastatic urothelial cancer failing or progressing after frontline cisplatin based chemotherapy [6] are in accord with this hypothesis. Insofar as bio-relevant "neo-antigens" can elicit antitumor immune responses, they also have the potential to induce off-setting counter responses including CTLA4, PD-1, and PD-L1 [7], thus explaining the benefit derived from checkpoint inhibitors and, possibly, other immunotherapies.

DNA mismatch repair (MMR) defects and high MSI defects, comprising 20-40% and 9-43% of uterine endometrioid cancers, respectively [8,9], appear to correlate with high TMB signal, neo-antigen load and PD-L1 expression [10,11]. MMR proteins correct polymerase errors by forming a complex that binds to the mismatched section of DNA then excises the mismatched section and inserts the correct sequence in its place [12]. Cells with abnormally functioning MMR have hyper mutability and are unable to correct certain error types (primarily base-base mismatches and insertion/deletion mispairs) that occur during DNA replication resulting in an increased TMB. Although germline evaluation is not available in the patient, the presence of germline *MSH2* mutations in two of her three daughters is highly suggestive of Lynch Syndrome in which PD-L1 expression is as high as 70% [11]. In our patient PD-L1 tumor expression was <1%; however, studies have shown that PD-L1 expression is not an invariably reliable predictor of response to treatment with anti-PD-1/PD-L1 antibodies [13,14]. Further, PD-L1 assessment may be subject to the vagaries of heterogeneity or discordance [15]. In addition, recurrent endometrial carcinoma has been shown to have a high rate of PD-L2 expression [16]. Not only does PD-L2 expression not appear to be associated with resistance to anti-PD-L1 therapy [17], but also responses have been seen with the PD-L1 inhibitor atezolizumab in PD-L2 high expression patients [18].

In an analysis of responses to PD-1 blockade (pembrolizumab), Le, et al. (2015) reported a 78% immune related PFS for MMR deficient patients versus 11% in MMR proficient patients [19]. In addition, there was a 40% PR vs 0% PR, in the two groups, respectively. Finally the FDA recently (05/23/17) expanded product indication of pembrolizumab for any advanced solid tumor with either deficient mismatch repair protein function by immunohistochemistry or MSI-H gene defect and nivolumab (8/2017) for MSI-H colorectal cancer that has progressed after standard frontline and second line treatment. A landmark decision as the first indication based on the molecular signature of a tumor independent of site of origin or histology. This case report adds to the growing clinical database demonstrating the effectiveness of immune checkpoint inhibitors and, in addition, supports the incorporation of genomic analysis, TMB signal, and neo-antigen load as important predictive components to maximize proportionate therapeutic benefit and help prioritize amongst investigative therapeutic options.

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