



# Exceptional Response to Nivolumab and Stereotactic Body Radiation Therapy (SBRT) in Neuroendocrine Cervical Carcinoma with High Tumor Mutational Burden: Management Considerations from the Center For Personalized Cancer Therapy at UC San Diego Moores Cancer Center

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## ABSTRACT

Neuroendocrine carcinoma of the cervix is an ultra-rare malignancy with a poor prognosis and limited treatment options. Checkpoint blockade immunotherapy has rapidly developed into an emerging standard of care for several common disease types. Interestingly, in preclinical and retrospective clinical data, radiation therapy has been demonstrated to synergize with checkpoint inhibitors. Here we report a patient with metastatic, chemotherapy-refractory neuroendocrine carcinoma who presented with partial bowel obstruction due to a large tumor burden. Genomic analysis demonstrated a high number of alterations on

liquid biopsy (circulating tumor DNA [ctDNA]), which prompted treatment with stereotactic body radiation therapy (SBRT) combined with anti-programmed cell death protein 1 antibody. Tissue rebiopsy and comprehensive genomic profiling confirmed high tumor mutational burden and a mismatch repair gene defect. The patient manifested near-complete systemic resolution of disease, ongoing at 10+ months. We discuss the novel treatment modality of SBRT combined with a checkpoint inhibitor and the implications of molecular profiling and tumor mutational burden as potential predictors of response. *The Oncologist* 2017;22:631–637

## KEY POINTS

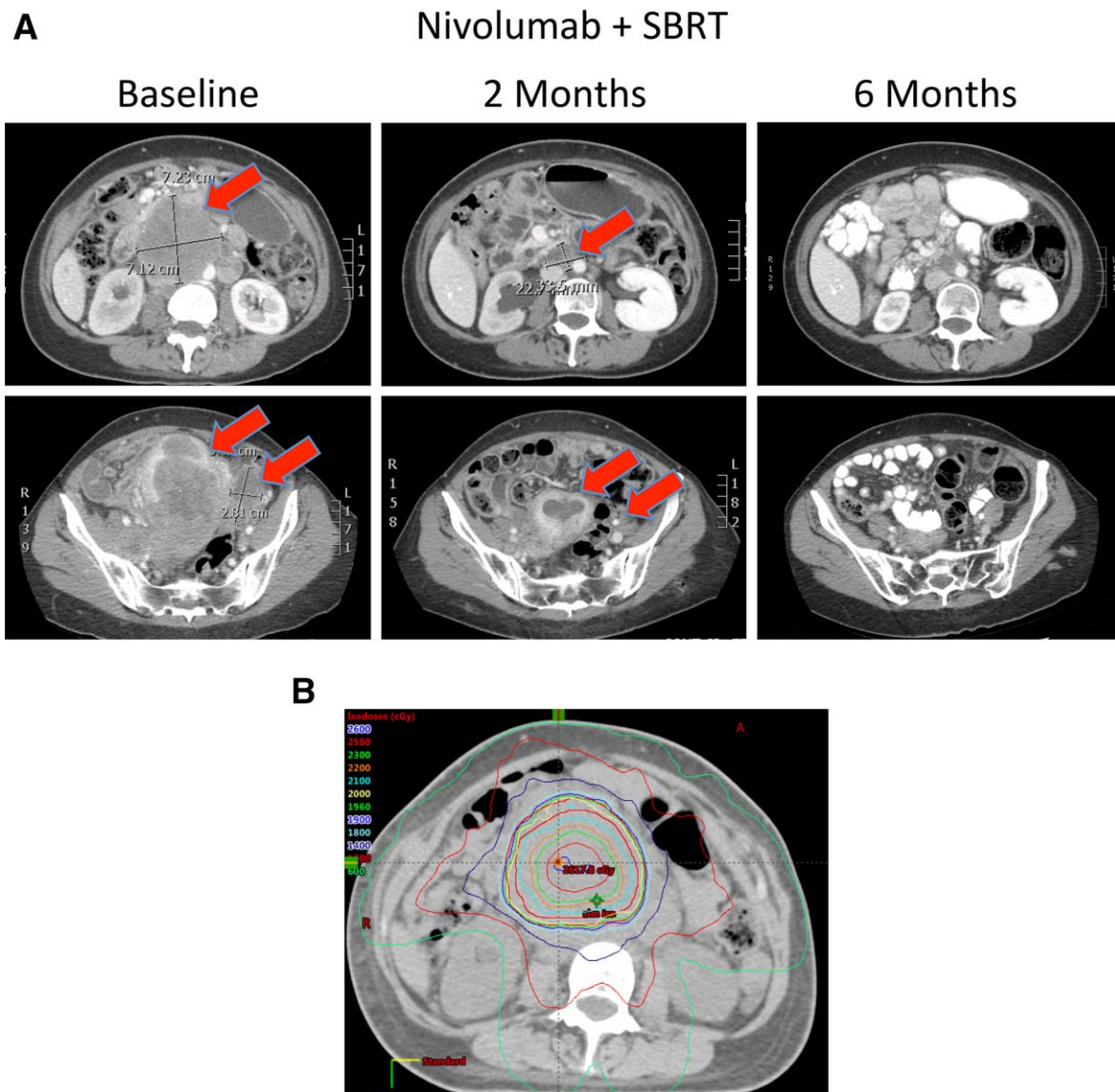
- High-grade, large-cell neuroendocrine carcinoma of the cervix is an ultra-rare malignancy that carries a grim prognosis.
- Next-generation sequencing may reveal key mutations in *MSH2* genes amongst others. *MSH2* mutations target the DNA mismatch repair process and can predispose patients to malignancies with high mutational burdens.
- Immunotherapy combined with radiation therapy can elicit a significant response, both within and outside the field of radiation. The latter is termed the “abscopal” effect, perhaps mediated by radiation-induced cross presentation of tumor antigens resulting in immune activation.
- Sequencing of blood-derived ctDNA showed a high number of alterations, and tissue sequencing confirmed a high tumor mutational burden as a consequence of a mismatch repair gene defect. This observation led to a therapeutic “match” with an anti-programmed cell death protein 1 antibody combined with SBRT, resulting in a durable (10+ months), near-complete remission in a patient with advanced chemotherapy-refractory disease.

## PATIENT STORY

In 2015, a 48 year-old woman underwent a myomectomy for presumed uterine fibroids. Upon biopsy, the patient was

diagnosed with high-grade, large-cell neuroendocrine cervical carcinoma. Neuroendocrine carcinoma of the cervix is an ultra-

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**Figure 1.** Sequential axial computerized tomographic (CT) imaging and radiation treatment plan of patient treated with SBRT combined with nivolumab. Patient shows excellent partial response at 2 months and near complete response at 6 months. After 11 months, response is ongoing with over 95% tumor regression. **(A):** Left panel: Axial CT of large 7.7-cm retroperitoneal mass (upper panels) and pelvic masses (lower panels) prior to treatment. Middle panel: 2 months after SBRT with significant systemic response. Right panel: 6 months after treatment with near complete response. **(B):** SBRT plan with concurrent nivolumab targeting the retroperitoneal mass (500cGyx4 fractions).

Abbreviation: SBRT, stereotactic body radiation therapy.

rare malignancy, representing less than 2% of cervical cancers, and carries a very poor prognosis [1–3]. Computerized tomographic (CT) scan showed a large infiltrating mass in the lower uterine segment and cervix with metastatic retroperitoneal and pelvic adenopathy. Initially, she was treated at an outside hospital in the Middle East with cisplatin and etoposide, along with two doses of radiation therapy, but showed rapidly progressive disease. The octreotide scan was positive. In January 2016, she was referred to the University of California San Diego (UCSD) Moores Cancer Center.

On initial examination, the patient presented with a very large mass that spanned the pelvic and abdominal regions, bilateral lower extremity edema, and gastrointestinal complaints consistent with intermittent partial small bowel obstruction. The patient's laboratory results indicated hypercalcemia,

which was treated with zoledronic acid. A rectovaginal exam revealed a large irregular mass that filled the entirety of the vagina. A CT scan showed a 7.8-cm cervical mass that obstructed the right ureter, leading to moderate hydronephrosis and compressed bilateral renal veins (Fig. 1A top). There were multiple metastatic lesions in the liver and pelvic region (Fig. 1A bottom). The right external iliac vein was compressed by metastatic lesions and there was evidence of the descending aorta being encased by para-aortic lymphadenopathy. There was no evidence of metastasis into the thoracic cavity. Doppler of the lower extremities showed no evidence of thrombosis.

As outside pathology was unavailable for review, a CT-guided core needle biopsy of the cervical mass was performed. The pathology was consistent with a high-grade, large-cell carcinoma with neuroendocrine differentiation that stained positive

**Table 1.** Profiling of patient with high-grade, large-cell neuroendocrine tumor

Test	Result	Comment
ctDNA from blood	<p><b>Characterized alterations</b></p> PTEN R130Q FBXW7 R465H PIK3CA E545D PIK3CA R88Q NRAS Q61R CTNNB1 S33A	70 gene panel <a href="http://www.guardanthealth.com">http://www.guardanthealth.com</a>
	<p><b>Variants of unknown significance and synonymous variants</b></p> ARID1A P600P ARID1A P427L BRCA2 L3184V NOTCH1 G309D NOTCH1 N2389N STK11 W332* APC Q767Q CDH1 A408A FGFR2 A260A ERBB2 I435F SMO T541T BRCA1 G1077R MET P325S	
Tissue next generation sequencing	FBXW7 R465H MSH2 E48* MSH2 Q324* PIK3CA E545D PTEN K267fs*9 PTEN R130Q STK11 W332* MEN1 R521fs*43 NOTCH1 R1586H ABL2 P497fs*7 ATRX D1940fs*15 BLM N515fs*16 FGF6 V127M JAK1 K860fs*16 JAK1 P430fs*2 MLL2 P2302fs*20 MLL3 K2797fs*26 PREX2 S565fs*3 QKI A338T SETD2 F636fs*6 SMARCA4 Q214* SMARCA4 T296fs*7 TET2 R1440fs*38 TET2 R550*	315 gene panel <a href="https://www.foundationmedicine.com">https://www.foundationmedicine.com</a>
Tumor mutational burden	High: 53 (>19 mutations per megabase considered high)	<a href="https://www.foundationmedicine.com">https://www.foundationmedicine.com</a>
MSI	High (MSI-H)	
PD-L1 (tumor) by immunohistochemistry	Low positive <sup>a</sup>	Spring Bioscience PD-L1 clone SP142 Pathline, <a href="https://www.foundationmedicine.com">https://www.foundationmedicine.com</a>
	Negative <sup>b</sup>	Spring Bioscience PD-L1 clone SP142 Caris <a href="http://www.carislifesciences.com">http://www.carislifesciences.com</a>

<sup>a</sup>Stained 1+ in 1%–24% of cells.<sup>b</sup>Positive = stained 2+ in 3% of cells.

Abbreviations: ctDNA, circulating tumor DNA; PD-L1, programmed death-ligand 1; MSI, microsatellite instability status.

for pancytkeratin, synaptophysin, CD99, EMA, and p16, markers commonly used to aid in the diagnosis of neuroendocrine cancer [4]. As part of the precision medicine program at UCSD Moores Cancer Center, genomic tests were performed in a clinical laboratory improvement amendment laboratory: blood test for circulating tumor DNA (ctDNA; 70 gene panel, <http://www.guardanthealth.com>) and tissue testing for next-generation sequencing (NGS; 315 gene panel, <https://www.foundationmedicine.com>; Table 1).

The patient's condition was deteriorating rapidly, so therapy was initiated based on blood ctDNA results and prior positive octreotide scan, before tissue genomic results were available. Because multiple alterations were seen in ctDNA (Table 1), it was suspected that the patient would have a high tumor mutational burden. Nivolumab 240 mg intravenously every 2 weeks was started along with sandostatin (100 mcg daily subcutaneously for 2 days and then b.i.d., with a later switch to the long-acting formulation). Two weeks after

immunotherapy was initiated, stereotactic body radiation therapy (SBRT) directed at the abdominal mass was given (500 centigray [cGy]) delivered over four sessions (2000 cGy total; Fig. 1B). The patient tolerated therapy well with no dose-limiting effects (although she later developed hypothyroidism due to nivolumab and was treated with thyroid hormone supplementation).

Tissue genomic results were available after initiating treatment; they showed mismatch repair gene (MMR) alterations (*MSH2* gene), as well as multiple other anomalies, a high tumor mutational burden (53 mutations per megabase [ $>19$  considered high]), and high microsatellite instability (MSI-H) status (Table 1).

### MOLECULAR TUMOR BOARD

A weekly Molecular Tumor Board has existed at the University of California Moores Cancer Center since November 2012 [5, 6]. Patients are presented by the physician, imaging is reviewed by the radiologist, pathology is reviewed by the pathologist, and the genomic results are discussed by the physician leader and basic/translational/clinical science attendees, as well as members of the UC San Diego Supercomputer Center. Patients treated according to the precision medicine paradigm are sometimes also presented to illustrate and discuss both responses and toxicities. If the physician feels that a presentation cannot wait, an ad hoc Molecular Tumor Board is convened over e-mail. A formatted case table that includes relevant patient details is distributed. Molecular Tumor Board discussions are documented in the patient chart and in minute meetings. Patients can give consent under a master institutional umbrella protocol (PREDICT UCSD ClinicalTrials.gov Identifier: NCT02478931).

### GENOTYPING RESULTS AND INTERPRETATION OF MOLECULAR RESULTS

The liquid biopsy ctDNA results (70 gene panel) showed 19 alterations. Tissue NGS results (315 gene panel) were available shortly after initiating treatment; they showed MSI-H status due to MMR alterations (*MSH2* gene), as well as multiple other anomalies ( $n = 24$  aberrations), and a high tumor mutational burden (53 mutations per megabase [ $>19$  considered high]; Table 1). The patient recently consented to germline testing for *MSH2* and is being referred for genetic counseling.

### FUNCTIONAL AND CLINICAL SIGNIFICANCE

Of special interest is the finding that the patient had alterations in an MMR (*MSH2*), accompanied by MSI-H and high tumor mutational burden. The high tumor mutational burden was first suspected on the basis of ctDNA results from a blood specimen, which showed a very high number of alterations ( $n = 19$ ). Because the patient had already failed chemotherapy and was declining rapidly, a treatment decision was made to initiate nivolumab and SBRT without waiting for tissue genomic testing results. High tumor mutational burden has previously been associated with lung cancer response to immunotherapy [7]. Once genomic tissue analysis was available, it was apparent that the patient did indeed have a high tumor mutational burden (53 mutations per megabase [high defined as over 19 mutations/megabase]) and MSI-H.

MSI usually arises from either germline mutations in components of the mismatch repair machinery (genes = *MSH2*, *MSH6*, *MLH1*, *PMS2*) or somatic hypermethylation of the

*MLH1* promoter. The result is a cancer with a 10- to 100-fold increase in mutations. Patients with colon cancer and this abnormality have poorly differentiated tumors, further characterized by an intense lymphocytic infiltrate [8]. Colorectal malignancies harboring DNA mismatch repair defects have higher response rates to anti-programmed cell death protein 1 (PD-1) immunotherapy: anecdotal cases of responses in other tumors types with mismatch repair deficiencies have also been described, though not, to our knowledge, in neuroendocrine tumors [7, 9].

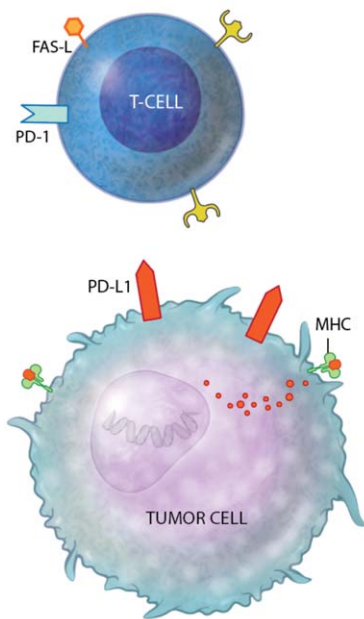
### PATIENT UPDATE

After treatment with SBRT, nivolumab, and sandostatin, the patient showed a remarkable response. CA-125, usually a marker for ovarian cancer, dropped from 78 U/mL to 31 by 3 months (normal  $<35$  U/mL) and stabilized [10]. From approximately 3 to 6 months on treatment, the patient's measured chromogranin A, a marker for neuroendocrine tumors, dropped from 151 to 87 (normal  $<39$  ng/L; no baseline was available) [11]. In April 2016, an abdominal CT scan showed a significant decrease in the size of the retroperitoneal mass, and a subsequent scan 4 months later showed continued regression (Fig 1A, middle and right side panels). There was a systemic response outside of the field of radiation therapy, as there was a decrease in size of the metastatic hepatic lesion, pelvic mass, and the pelvic and retroperitoneal lymph nodes. By October 2016, a 95% decrease in size of lesions was noted. The patient has had no significant toxicity other than hypothyroidism as a side effect from immunotherapy.

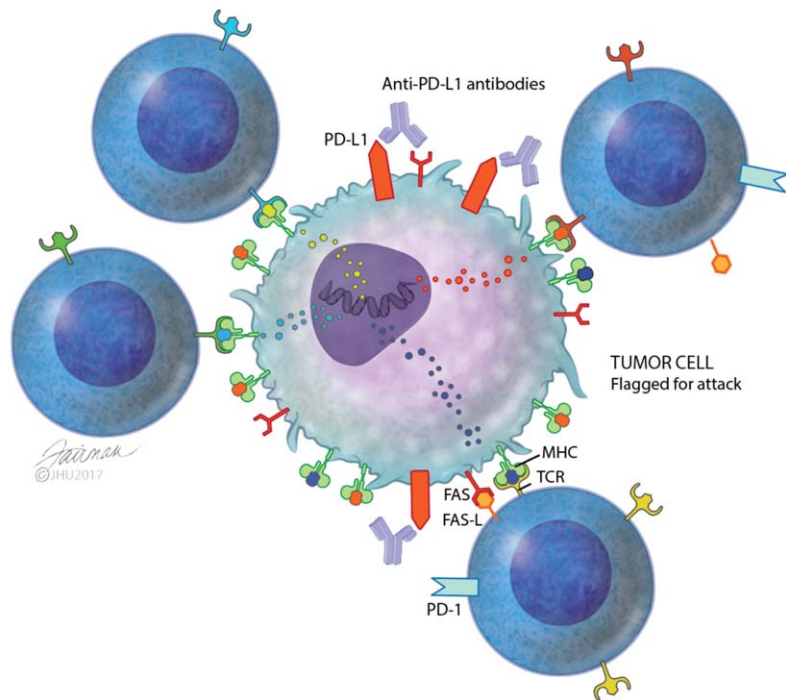
### POTENTIAL STRATEGIES TO TARGET THE PATHWAY AND IMPLICATIONS FOR CLINICAL PRACTICE

Immunotherapy is an emerging standard of care for several disease types. Monoclonal antibodies that target immune checkpoints, including key immunoregulatory molecules such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-1/programmed death ligand 1 (PD-L1) [12], are now FDA-approved for multiple disease types. For example, checkpoint blockade antibodies that target the PD-1/PD-L1 axis have indications in melanoma, non-small cell lung cancer, renal cancer, urothelial cancer, Hodgkin's lymphoma, and head and neck cancers. PD-1 is a protein that is highly expressed on activated T cells and other cells [13, 14]. PD-L1 is normally expressed at low levels on various hematopoietic and non-hematopoietic cells, but is upregulated by various solid tumor cells as well as antigen-presenting cells [15, 16]. Elevated PD-L1 expression shields the tumor cells from the endogenous antitumor response by dampening tumor-specific T cells, developing resistance to CD8+ T cell-mediated death and Fas-ligand associated apoptosis, and creating a subset of T regulatory cells [15]. PD-L1 expression has been investigated as a predictive biomarker, and across tumor types and anti-PD-1/PD-L1 agents, PD-L1-negative tumors had response rates that ranged from 0% to 17%, while PD-L1-positive tumors had response rates from 36% to 100% [17, 18]. Our patient's tumor did express PD-L1, albeit at low positive levels (Table 1). Responses to immunotherapy are also generally higher in the presence of certain genomic alterations. For instance, colorectal cancers that have MMR alterations, which are accompanied by a high tumor mutational burden, have significantly improved responses to anti-PD-1

## Low Mutational Burden



## High Mutational Burden



**Figure 2.** Schematic diagram of tumor cell with high mutational burden and enhanced immune cell recognition compared with tumor cell with low mutational burden.

Abbreviations: FAS-L, Fas ligand; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; TCR, T-cell receptor.

agents compared with patients who are MMR proficient [19]. Emerging evidence suggests that tumor mutational burden may be an important predictive factor for response to checkpoint blockade across different disease types (Fig. 2) [7, 20].

It has been previously demonstrated that immunotherapy combined with radiation therapy can elicit a significant response, both within and outside the field of radiation; the latter is termed the “abscopal effect” [21, 22]. The abscopal effect defines a phenomenon where a patient receives local radiation therapy but shows a reduction in tumor burden at a distant site [23]. This effect is mediated by the immune system, as radiation therapy vastly alters the expression of cell-surface molecules and enhances cross-presentation of tumor antigens [24]. Pre-clinical models have shown that radiation therapy combined with anti-PD-1 immunotherapy can induce an endogenous antigen-specific immune response, where the radiation therapy serves to prime the immune system [25]. Previously, ipilimumab combined with radiation therapy has been used to treat mucosal melanoma of the gynecologic tract; however, due to the rarity of neuroendocrine cancer of the cervix, there are no reported cases, to our knowledge, of this type of malignancy being treated with immunotherapy plus SBRT [26, 27]. Nivolumab itself is being tested in a clinical trial for use in treating cervical cancers (ClinicalTrials.gov Identifier: NCT02257528).

However, it is important to note that this patient may have responded to nivolumab with or without SBRT. Retrospective data have reported significant improvements in overall survival in patients with metastatic melanoma treated with ipilimumab and radiation compared to ipilimumab alone [28, 29].

Nevertheless, we await the data from ongoing prospective randomized clinical trials that aim to determine whether SBRT enhances systemic response rates to immunotherapy (ClinicalTrials.gov Identifier: NCT02843165). Regarding safety and toxicity of radiation immunotherapy combinations, retrospective reviews of over 200 patients treated with ipilimumab combined with radiation to multiple sites with diverse dose and fractionation schemes did not report any significant increase in toxicity with the combination [28, 29]. Although there have been some reports of potential additive toxicity with immunotherapy radiation combination in the CNS, a large phase III randomized trial combining a palliative radiation dose (8Gy $\times$ 1) with ipilimumab in approximately 400 patients also did not report any significant added toxicity with this combination [30]. Thus, while the combination appears to be relatively safe and well tolerated, additional prospective data are required to confirm this across the multiple different immunotherapy drugs, as well as with hypofractionated SBRT dosing or definitive radiation doses.

Regarding radiation dose and fractionation effects, there is a body of literature addressing issues of single fraction versus multifraction radiation and whether a dose threshold exists for enhancing immune responses. In the authors’ opinion, this is still an open question as both preclinical and clinical reports have demonstrated improved outcomes using single fraction versus multifraction radiation doses, as well as hypofractionated SBRT dosing versus conventional daily dosing. The dose used here in this patient (500cGy  $\times$  4 fractions) is a modified palliative dose regimen that was used in this case given immediate proximity to the bowel, which is a highly radiosensitive tissue.

Our current phase II randomized SBRT immunotherapy trial uses 950cGy  $\times$  3 fractions, and there are additional trials ongoing that will compare the efficacy of different radiation dose/fractionation schemes. This also raises the intriguing question of combining ablative or definitive SBRT dosing with immunotherapy in the oligometastatic state, which is another area of ongoing investigation.

Interestingly, our patient had *JAK1* mutations (*JAK1* K860fs\*16 and *JAK1* P430fs\*2) that would appear to be inactivating, as they delete the kinase domain. Recently, resistance to anti-PD-1 agents was associated with the emergence of a *JAK1*-inactivating mutation, which was postulated to be responsible for the progression of disease that occurred in a melanoma patient after initial response [31]. At least in our patient, *JAK1*-inactivating mutations did not appear to interfere with the patient's response. It is plausible that homozygous inactivation of *JAK1* is needed for resistance.

## CONCLUSION

Our patient highlights several seminal points. First, ultra-rare tumors generally do not have dedicated trials; hence, individual cases can be critical to stimulating further study and to informing practice. Second, the patient's tumor had MSI-H and high mutational burden, suggesting that these genomic characteristics are important in diseases beyond colorectal cancer for selecting patients for anti-PD-1 immunotherapy. Whether or not the addition of SBRT to immunotherapy amplifies the effects of immunotherapy outside the radiation field (abscopal effect), as has been shown in preclinical studies, and can be partially responsible for this patient's striking and rapid response also merits further investigation [25]. A randomized clinical trial of immunotherapy with and without SBRT is ongoing (ClinicalTrials.gov Identifier: NCT02843165). Additionally, an National Cancer Institute study of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors was recently opened (ClinicalTrials.gov Identifier: NCT02834013). Importantly, in this regard, the patient had a remarkable response despite *JAK1*-inactivating alterations that have recently been implicated in resistance to anti-PD-1 agents [31]. Of interest, in this case, before therapy, the patient was deteriorating quickly, and liquid (blood) "biopsy" to assess ctDNA provided an early readout ( $n = 19$  alterations) that led to suspicion of high tumor mutational burden and suggested

immunotherapy as an option. Tissue genomics confirmed the high tumor mutational burden and demonstrated an MMR defect. Taken together, this patient further illustrates the bridge between genomics and the immune system, and its importance in selecting patients for treatment [32–34].

## GLOSSARY OF GENOMIC TERMS AND NOMENCLATURE

**CT:** Computerized Tomographic  
**ctDNA:** Circulating tumor DNA  
**CTLA-4:** Cytotoxic T-lymphocyte Antigen 4  
**FAS-L:** Fas ligand  
**MHC:** Major Histocompatibility Complex  
**MMR:** Mismatch Repair Gene  
**MSI-H:** high microsatellite instability  
**PD-1:** Programmed cell Death protein 1  
**SBRT:** Stereotactic Body Radiation Therapy  
**TCR:** T-cell Receptor

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## AUTHOR CONTRIBUTIONS

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## DISCLOSURES

**Andrew Sharabi:** StemImmune (C/A); Varian, AstraZeneca (H); **Sandip Pravin Patel:** MedImmune, Genentech, Pfizer, Amgen, Xcovery, Lilly, Bristol-Myers Squibb (RF); Boehringer Ingelheim, Merck (H); **Razelle Kurzrock:** XBiotech, Actuate Therapeutics (C/A); Genentech, Pfizer, Sequenom, Guardant, Foundation Medicine, Merck Serono (RF); CureMatch Inc. (OI). The other authors indicated no financial relationships. (C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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