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Efficacy of pembrolizumab in patients with pituitary carcinoma: report of four cases from a phase II study

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ABSTRACT

Pituitary carcinoma is an aggressive tumor characterized by metastatic spread beyond the sellar region. Symptoms can be debilitating due to hormonal excess and survival is poor. Pituitary carcinomas recur despite conventional multimodality treatments. Given the recent advances in the use of immune checkpoint inhibitors (CPIs) to treat various solid cancers, there has been interest in exploring the role of immunotherapy for treating aggressive, refractory pituitary tumors. We treated 4 patients with pituitary carcinoma with pembrolizumab as part of a phase II clinical trial. Two patients (patients 1 and 2) with functioning corticotroph pituitary carcinomas (refractory to surgery, radiotherapy and chemotherapy) had partial radiographic (60% and 32% per Immune-Related Response Evaluation Criteria In Solid Tumors, respectively) and hormonal responses. Patient 1's response continues 42 months after initiation of pembrolizumab and his tumor tissue obtained after treatment with temozolomide demonstrated a hypermutator phenotype with *MSH2* and *MSH6* gene mutations. Patient 2's tumor after exposure to temozolomide was not sampled, but prior somatic mutational testing was negative. One patient with a non-functioning corticotroph tumor (patient 3) had a best response of stable disease for 4 months. One patient with a prolactin-secreting carcinoma (patient 4) had progressive disease. The latter 2 patients' tumors did not demonstrate a hypermutator phenotype after treatment with temozolomide. Programmed death-ligand 1 staining was negative in all tumors. We report 2 cases of corticotroph pituitary carcinoma responsive to pembrolizumab after prior exposure to alkylating agents. The role of CPIs in treating patients with pituitary carcinoma, the relationship between tumor subtype and response to immunotherapy and mechanisms of hypermutation in this orphan disease require further study.Trial registration number: NCT02721732.

INTRODUCTION

Pituitary carcinoma (PC) is defined as a pituitary adenoma that has metastasized outside the sellar region.[1] Unlike pituitary adenomas that are common and usually benign,[2] PCs are aggressive, rare tumors that account for an estimated 200–300 cases annually in the USA.[3]

Similar to pituitary adenomas, PCs originate from the various cell types within the anterior pituitary gland and can be functioning (hormone secreting) or non-functioning. PCs more often are lactotroph or corticotroph tumors, producing prolactin (PRL) or adrenocorticotropic hormone (ACTH), respectively. These tumors can be clinically apparent, causing signs and symptoms of hormone excess, or they can be clinically silent, demonstrating expression of PRL or ACTH via immunohistochemistry but not causing Cushing syndrome or clinical features of hyperprolactinemia.

Given the rarity of PC, no well-defined standard therapy exists. Most patients undergo resection if feasible, focal radiotherapy, and medical therapy (for functioning tumors). Temozolomide has emerged as a first-line chemotherapy for PC.[4] The combination of temozolomide with capecitabine (CAPTEM) has also been shown to result in high response rates and prolonged survival in PC.[5] However, prolonged use of temozolomide can be associated with bone marrow suppression, and recurrences are common in clinical practice. With the advent of immunotherapy as a fourth pillar for the treatment of various solid malignancies, there has been interest in exploring the role of checkpoint inhibitors (CPIs) for treatment of pituitary tumors.

CPIs, including antibodies against programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), significantly prolong survival in 30%–40% of patients with various solid cancers.[6] Mutation status, PD-L1 expression and the presence of tumor-infiltrating lymphocytes (TILs) are potential biomarkers of response to CPIs.[6] Different thresholds have been used to define a 'hypermutator' phenotype.[7 8] Tumors with a large number of somatic mutations

(commonly >10 mutations per Mb) and/or mutations in mismatch repair (MMR) or DNA polymerase genes are referred to as hypermutated tumors.[7 8] A hypermutator phenotype is seen across different tumor types with varying frequencies and can either happen de novo or as a result of exposure to alkylating agents.[9] Marked response to CPIs have been reported in two patients with corticotroph PC, including one tumor with a hypermutator phenotype.[10 11]

Here, we report four cases of refractory PC treated with pembrolizumab. Two out of four patients had a radiographic and hormonal response to CPI therapy.

METHODS

In this open-label, phase II trial, patients with advanced rare cancers whose tumors had progressed within the previous 6 months received pembrolizumab 200 mg intravenously every 21 days.[12] Immune-Related Response Evaluation Criteria In Solid Tumors (irRECIST)[13] was applied to report responses. The adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.03. PD-L1 staining was performed by Qualtek using Merck 22C3 antibody for PD-L1. Based on the percentage and intensity of membrane staining, an H-score from 0 to 300 was assigned to tumor samples.[14] To measure TILs, we performed a morphological assessment of H&E-stained sections to determine the overall average abundance value of TILs within tumor nests for the whole sample, using a scale of 0 (absent) to 3. High TIL score was defined as a TIL density score ≥2. PD-L1 and TIL scores were completed by a board-certified pathologist.

The data cut-off for report of these data was May 4, 2020. It was planned to enroll 15 patients in this cohort; however, due to rarity of PC and resultant slow accrual, we decided to report on the current four patients.

RESULTS

We treated four patients with PC with pembrolizumab (table 1). All patients tolerated the treatment well with mild adverse events (table 2).

Patient 1

A white male in his mid-30s presented with visual field deficits and Cushingoid features. Imaging revealed a pituitary macroadenoma and he underwent tumor resection. Histological examination demonstrated a corticotroph adenoma. The patient received radiotherapy for residual disease. In the following 3 years, he underwent another resection and two additional courses of focal radiotherapy for progressive disease. Fifty-four months after the initial diagnosis, he reported abdominal fullness and discomfort and was found to have liver lesions on imaging. Biopsy of a liver lesion demonstrated neuroendocrine carcinoma immunoreactive for ACTH and synaptophysin, consistent with metastatic corticotroph PC. He was treated with standard doses of temozolomide for 16 cycles and CAPTEM for 2 cycles before undergoing right orbital exenteration and additional focal radiotherapy for symptomatic progressive right orbital disease. The resected tissue was analyzed by next-generation sequencing (NGS) using a 400-gene panel and demonstrated a hypermutator phenotype with 76 individual gene mutations, including *MSH2* and *MSH6* mutations. He subsequently received local treatment to the liver lesions (percutaneous microwave frequency ablation) and portacaval lymphadenopathy (radiotherapy), bilateral adrenalectomy for uncontrolled Cushing disease and an additional eight cycles of standard dose temozolomide and four cycles of CAPTEM without response. Given a somatic *FGFR4* mutation, he was enrolled into a phase I trial of an FGFR-targeted treatment and completed two cycles. His intracranial and extracranial disease continued to progress, requiring radiotherapy to the liver, resection of disease adjacent to the left optic nerve and further intracranial radiotherapy to a suspected right temporal tumor, eventually complicated by radiation necrosis.

Ultimately, after six lines of systemic chemotherapy, the patient was enrolled in the phase II trial of pembrolizumab. Staging after two cycles of pembrolizumab demonstrated resolution of the lesions in the middle cranial fossa and prepontine cisterns and significant improvement of disease in the bilateral sphenoid and posterior ethmoid sinuses (figure 1A&B). In addition, there was an interval decrease in the retroperitoneal adenopathy; the size of the liver metastases remained stable. His overall best radiographic response was partial response (60% per irRECIST criteria), which persists 42 and 22 months after the first and last dose of pembrolizumab, respectively. Plasma ACTH levels were 48 and 85 pg/mL (range 0–46) prior to initiation of pembrolizumab and became undetectable after treatment, where it remains to date (figure 1C). He completed 29 cycles of pembrolizumab and tolerated it very well. His subsequent treatments have been geared toward the management of radiation necrosis. He has remained cancer free 42 months after his first dose of pembrolizumab, and he is alive 118 months after the diagnosis of PC. Analysis of liver tumor tissue obtained prior to trial enrollment demonstrated negative PD-L1 staining and a TIL score of 2. He is currently in his early 50s, and his Eastern Cooperative Oncology Group (ECOG) status is 2, mainly due to functional blindness secondary to progressive radiation-induced optic neuropathy in the left eye.

Patient 2

A Hispanic woman in her early 20s presented with Cushingoid features and was found to have a pituitary macroadenoma. Resection of the mass revealed a necrotic tumor consistent with infarcted/necrotic pituitary adenoma and strong ACTH staining. Eight months later, the patient required additional resection of the corticotroph adenoma. She received stereotactic radiosurgery for residual disease; a year later, she required

Table 1 Demographic, clinical characteristics and outcome of four patients with pituitary carcinoma treated with pembrolizumab

ID	Race/Sex	Tumor subtypes	Time from PA to PC Dx (mo)	Extent of disease beyond sellar region	Prior surgeries	Radiation courses	Medical treatments	Molecular data					Best response (irRECIST)	Best response (tumor marker)	PFS after first dose of pembrolizumab (mo)	Survival time after PC Dx (mo)
								NGS	PD-L1 IHC	TIL	MSS	TMB				
1	White male	Corticotroph tumor—functioning	54	Intracranial: suprasellar, sphenoid sinus, bilateral optic nerves Extracranial: orbital, intraabdominal LNs, liver	3 CNS/orbit surgeries Liver biopsy Microwave ablation of liver lesion×2 Bilateral adrenalectomy	1. Cavernous sinus 2. Sellar region 3. Sellar region 4. Right orbit 5. Portocaval lymph nodes 6. Liver metastasis 7. Left optic nerve 8. Liver metastasis	1. TMZ×16 cycles (PD) 2. CAPTEM×2 cycles (PD) 3. TMZ×8 cycles (PD) 4. CAPTEM×4 cycles (PD) 5. FGFR inhibitor×2 cycles (PD) 6. CCNU and BEV×1 cycle (SD, stopped due to cellulitis) 7. Pembrolizumab ×29 cycles (PR)	400-gene panel: 76 mutations including: *MSH2* G862E, *MSH6* G1157D—after 18 cycles of TMZ	neg	2	NA	NA	PR	CR	42 mo	118 alive
2	Hispanic female	Corticotroph tumor—functioning	45	Intracranial: cavernous sinus, left frontal dural deposit Extracranial: bone, liver and pleura	2 CNS surgeries Bilateral adrenalectomy	1. Pituitary fossa	1. TMZ×7 cycles (PD) 2. CAPTEM×7 cycles (SD, stopped due to poor tolerance) 3. Pembrolizumab ×12 cycles—ongoing (PR)	146 gene panel: no mutations—obtained prior to exposure to TMZ	neg	NA	Stable	NA	PR	PR	12	30 alive
3	Black male	Corticotroph tumor—non-functioning	131	Intracranial: cavernous sinus, sphenoid sinus, supraclinoid region, dural based Extracranial: bone	3 CNS surgeries Vertebroplasty and vertebral body biopsy	1. Sellar region 2. Spine 3. Skull base 4. Right frontal dural-based lesion	1. TMZ×12 cycles (PD) 2. TMZ×7 cycles (SD) 3. TMZ×2 cycles (PD) 4. IDO1 pathway inhibitors×11 cycles (PD) 5. Pembrolizumab×6 cycles 6. CAPTEM×6 cycles (SD) 7. CDK pathway inhibitor 3 cycles (SD)	Foundation One: *CREBBP* splice site 2086_2113+49del77—after 21 cycles of TMZ	neg	neg	Stable	Low	SD	NA	4	113 alive
4	White female	Prolactin tumor—functioning	81	Intracranial: suprasellar, cavernous sinus, anterior clinoid, superior orbital fissure Extracranial: bone, liver	1 CNS surgery Sacral mass biopsy	1. Sellar region 2. Spine	1. Cisplatin and etoposide×1 cycle (PD) 2. TMZ×12 cycles (PD) 3. TMZ×2 cycles (PD) 4. CAPTEM×2 cycles (PD) 5. Pembrolizumab x 6 cycles (PD) 6. PD-1/PD-L1 pathway inhibitors x 2 cycles (PD) 7. Bevacizumab, temsirolimus, valproic acid×2 cycles (PD) 8. Peptide receptor Radionuclide therapy with lutetium-177×1 treatment (PD)	Sacral metastasis: no mutations on a 50-gene panel—prior to TMZ liver metastasis: Foundation One: no mutations— —after 14 cycles of TMZ	neg	2	Stable	Intermediate	PD	PD	4	47 deceased

Continued

Table 1 Continued

ID	Race/Sex	Tumor subtypes	Time from PA to PC Dx (mo)	Extent of disease beyond sellar region	Prior surgeries	Radiation courses	Medical treatments	Molecular data: NGS	Molecular data: PD-L1 IHC	Molecular data: TIL	Molecular data: MSS	Molecular data: TMB	Best response (irRECIST)	Best response (tumor marker)	PFS after first dose of pembrolizumab (mo)	Survival time after PC Dx (mo)

BEV, bevacizumab; CAPTEM, capecitabine and temozolomide; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosurea; CDK, cyclin-dependent kinase; CNS, central nervous system; CR, complete response; *CREBBP*, CREB binding protein; Dx, diagnosis; FGFR, fibroblast growth factor receptor; *IDO1*, indoleamine 2,3-dioxygenase 1; IHC, immunohistochemistry; irRECIST, Immune-Related Response Evaluation Criteria in Solid Tumors; LN, lymph nodes; mo, months; *MSH*, mutS homolog; MSS, microsatellite status; NA, not available; neg, negative; NGS, next-generation sequencing; PA, pituitary adenoma; PC, pituitary carcinoma; PD-1, programmed death-1; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; TIL, tumor-infiltrating lymphocytes; TMB, tumor mutational burden; TMZ, temozolomide.

Table 2 Adverse events

ID	Event	Grade	Attribution
1	Fever	2	Unlikely
1	Fatigue	1	Definite
1	Maculopapular rash	1	Possible
1	Anorexia	1	Possible
1	Myalgia	1	Possible
1	Nausea	1	Possible
2	Fatigue	2	Possible
3–4	Fatigue	1	Possible

bilateral adrenalectomy for refractory Cushing disease. She continued to have rising ACTH levels, as high as 20 000 pg/mL, associated with severe skin hyperpigmentation. Treatment with the somatostatin analog pasireotide resulted in only a transient clinical response. Due to persistently rising ACTH levels, reaching a peak of nearly 85 000 pg/mL, restaging was performed 45 months after initial diagnosis. MRI of the brain showed stable disease, but MRI of the spine showed numerous lesions throughout the axial skeleton, compatible with metastatic disease. She was started on temozolomide and her ACTH decreased to the 1000 pg/mL range. She received 14 cycles of temozolomide-containing regimens but had to stop due to grade 2 fatigue and nausea. Ultimately, after two lines of systemic therapy, she was enrolled in the pembrolizumab trial and achieved a partial unconfirmed radiographic response (32% reduction in sum of liver lesions per irRECIST) after 15 cycles without significant adverse events as of the reporting of this manuscript. After an initial rise in ACTH levels after commencing pembrolizumab (from 2000 to 27 460 pg/mL over a 3-month period), her ACTH levels started to decline 3 weeks after the peak and was associated with improved skin coloration (figure 2). Her tumor tissue prior to exposure to temozolomide (studied with a 146-gene NGS panel) showed no mutations and stable microsatellite status (MSS); PD-L1 staining was negative. No additional tumor samples were obtained after exposure to temozolomide. She is currently in her late 20s, and her ECOG status is 1.

Patient 3

A black man in his late teens presented with visual field deficits on a routine eye examination, which led to the diagnosis of pituitary macroadenoma. Resection was performed, and histology was consistent with a corticotroph adenoma, which was clinically non-functioning (a silent corticotroph adenoma). He received radiotherapy to the sellar region followed by tumor debulking. Approximately 10 years after the initial diagnosis, he presented with severe back pain. Imaging revealed complete replacement of T8 by a lesion and additional small lesions in multiple other thoracic and lumbar vertebrae. Vertebroplasty was performed and T8 biopsy revealed PC. He

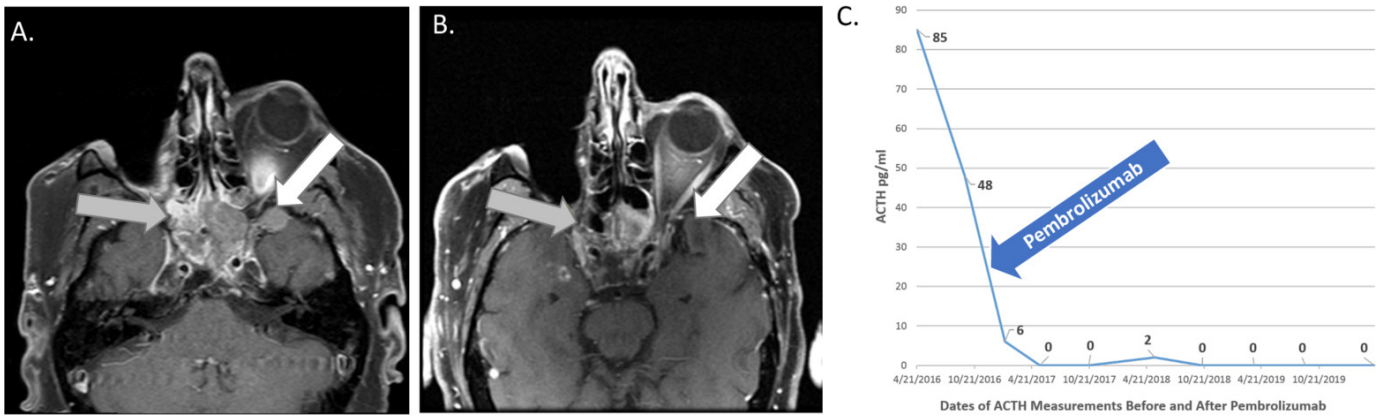

Figure 1 Response to pembrolizumab in patient 1. (A) T1 postcontrast MRI obtained prior to pembrolizumab treatment demonstrates a lobulated enhancing mass within the sphenoid sinus and posterior ethmoid air cells (gray arrow) with extension to the anterior and inferior aspects of the left temporal lobe (white arrow). (B) MRI of the brain after two cycles of pembrolizumab demonstrates significant improvement of the enhancing mass in the cavernous sinus and resolution of the nodule extending to the left temporal lobe. (C) The adrenocorticotropic hormone (ACTH) level became undetectable after treatment with pembrolizumab. (Reference ranges for ACTH are 0–46 pg/mL (before 4/19/18) and 7–63 pg/mL (after 04/19/18); ACTH levels are listed as '0' if the reported value was less than the lower limit of detection for the assay.)

underwent radiotherapy to the skull base and spine and transsphenoidal debulking, followed by two courses of temozolomide (nine cycles). Due to progressive disease, he had a fourth tumor resection. Foundation One molecular testing showed *KRAS* amplification, a *CREBBP* splice site mutation, multiple DNA variants of uncertain significance, low tumor mutational burden, stable MSS and negative PD-L1 immunohistochemical staining. One

Figure 2. Patient 2's hormonal response to pembrolizumab

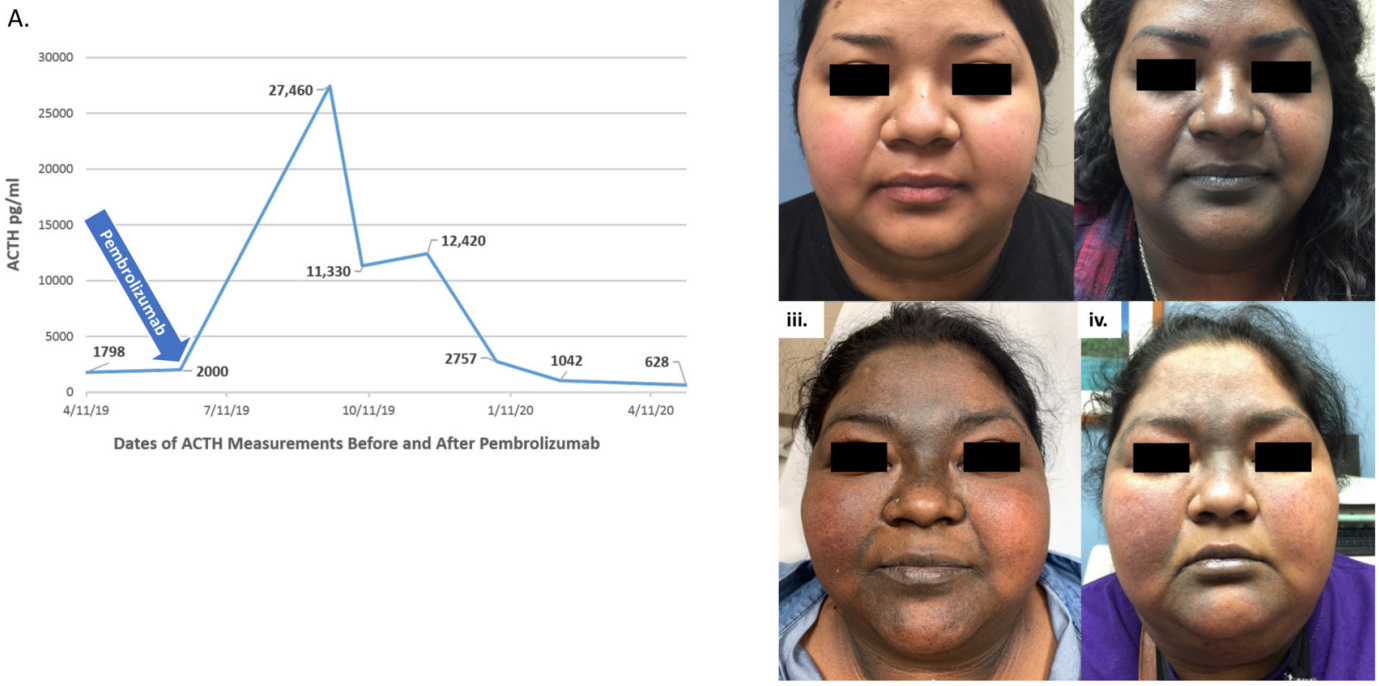

Figure 2 Clinical response in patient 2. (A) Adrenocorticotropic hormone (ACTH) levels became significantly elevated after starting pembrolizumab and then gradually declined but have not yet nadired as of the last evaluation. (B) Overview of the patient's skin pigmentation changes. (i) Two and a half years before the diagnosis of pituitary carcinoma, the patient had normal skin coloration and an ACTH level of 160 pg/mL. (ii) At diagnosis of pituitary carcinoma, when the ACTH was 84 851 pg/mL, the patient had become remarkably hyperpigmented. Ten months after treatment with pembrolizumab commenced and when the ACTH was 628 pg/mL (iv), her skin pigmentation was noticeably lighter compared with pictures obtained 6 months earlier (iii), after 4 months of therapy, when her ACTH was >11 000 pg/mL. (Reference ranges for ACTH are 0–46 pg/mL (before 4/19/18) and 7–63 pg/mL (after 04/19/18).).

year later, he had progression of dural-based lesions, and he enrolled in a phase I trial of treatment targeting the indoleamine 2,3 dioxygenase 1 pathway, with a continued slow increase in central skull base lesions. Ultimately, he enrolled in the pembrolizumab trial and completed six cycles, with a best radiographic response of stable disease for 4 months. Due to progressive partial palsy of the right oculomotor nerve and gradual progression of the skull base disease infiltrating the right cavernous sinus (without progressive disease per irRECIST), he came off study. He is currently in his late 30s, and his ECOG status is 1.

Patient 4

A white Middle Eastern woman in her early 50s was diagnosed with a macroprolactinoma that did not respond to conventional dopamine agonist therapy. She was found to have osseous metastasis to the spine 81 months after diagnosis of the lactotroph adenoma. NGS with a 134-gene panel on a sacral metastasis showed no mutations. She received one cycle of cisplatin and etoposide followed by palliative radiotherapy to the thoracic and lumbosacral spine. She then received 12 cycles of standard dose temozolomide. She had an increase in PRL levels and new tumors in the liver. She was re-challenged with two additional cycles of temozolomide and then switched to CAPTEM for two cycles, but she experienced enlarging lesions in bone and liver and an ongoing rise in PRL levels. She then enrolled in the pembrolizumab trial. Her overall response was progressive disease per irRECIST. During pembrolizumab therapy, her PRL rose from 2139 to 5879 ng/mL (range 4.8–23.3). Tissue analysis prior to trial enrollment showed negative PD-L1 staining and a TIL score of 2. A subsequent liver biopsy showed stable MSS and intermediate tumor mutational burden. She died of progressive disease 46 months after the diagnosis of PC.

DISCUSSION

CPIs have changed the outcomes of many patients with cancer, and their approvals by the US Food and Drug Administration (FDA) are on the rise, including the first tumor-agnostic approval for pembrolizumab for microsatellite instability-high or mismatch repair deficient solid tumors.[15] Despite small numbers of patients, our current report of four cases, which supplements four previously published cases,[10 11] provides the basis for further defining the role of CPIs in the treatment of PC.

In this study, we describe the positive radiographic and hormonal responses to pembrolizumab in two patients, both of whom had ACTH-secreting PC refractory to prior lines of systemic therapy. Patient 1's response has been durable for 42 months. Genomic analysis of tumor tissue obtained from this patient after 16 cycles of temozolomide demonstrated mutations in 76 genes of a 400-gene panel, including *MSH2* G862E and *MSH6* G1157D, indicative of a hypermutator phenotype. *MSH2* and *MSH6* are essential mismatch repair (MMR) system components that detect base-base mismatches or insertion/deletion loops and perform error removal and DNA resynthesis.[16] MMR-deficient tumors have a large proportion of mutant neoantigens that result in in vivo expansion of neoantigen-specific T-cell clones that are reactive to the mutant neopeptides within the tumor and therefore increase responsiveness to CPI.[17] Patient 2's tumor after exposure to temozolomide was not sampled so its mutation status postchemotherapy is unknown. Interestingly, the two tumors that did not demonstrate a response (patients 3 and 4) did not demonstrate a hypermutator phenotype after exposure to temozolomide.

In patient 1, hypermutation might have been due to exposure to temozolomide; however, the patient's temozolomide-naïve tissue is not available for NGS testing for comparison. Lin *et al* reported a case of marked response to nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) in a corticotroph PC.[11] The authors performed genomic analysis of the tumor before and after exposure to temozolomide and demonstrated the emergence of a hypermutator phenotype after temozolomide exposure. Conversely, Caccese *et al* reported rapid disease progression of a corticotroph PC with MMR deficiency treated with pembrolizumab.[18] This case, however, in contradistinction to the first published case and our two responders, was complicated by ongoing hypercortisolism, which may have attenuated the beneficial effects of CPI therapy. A correlation between MMR deficiency and high mutational burden has been reported in gliomas,[19] but this correlation in PC remains to be identified.

Elevated PD-L1 expression is a predictor of response to anti-PD-1/PD-L1 therapies in some tumors, and companion PD-L1 diagnostic expression assays have been approved by the FDA. One study evaluated PD-L1 RNA and protein expression in 48 pituitary tumors and demonstrated increased expression of PD-L1 RNA and protein in functioning (somatotroph and lactotroph) pituitary adenomas compared with clinically non-functioning (null cell and gonadotroph) adenomas.[20] Elevated PD-L1 expression was positively correlated with increased TILs and was enriched in primary tumors compared with recurrent tumors. In our case series, all patients had negative PD-L1 staining, including our patient with a durable response, indicating that PD-L1 staining may not be an indicator of response to CPIs in PC. However, this needs to be confirmed in larger studies. Two of four patients with available pretrial TIL data had TIL scores of 2 (patient 1 (responder) and patient 4 (non-responder)). It is not yet clear if PD-L1 expression and/or the presence of TILs are predictors of response to CPIs in pituitary tumors.

The composition of various types of immune cells within the tumor microenvironment and their interaction with tumor cells play an important role in the ability of CPIs to mount immune responses against pituitary tumor cells. One study that analyzed CD11b-expressing cells (expressed on monocytes, neutrophils, natural killer cells, granulocytes and macrophages) in 16 non-functioning pituitary tumors demonstrated that a higher proportion of $CD11^{+}$

cells (>10%) was associated with a more expansile and mitotically active tumor.[21] This study also demonstrated that tumors invading the cavernous sinus had a greater presence of immunosuppressive macrophages (M2) than did non-invasive tumors (M2/M1 ratio >1 vs M2/M1 ratio <1). The correlation between increased number of immunosuppressive M2 macrophages and invasive behavior has been described in many cancer types.[22] Another study evaluated different immune cell populations in 35 human pituitary tumors and demonstrated increased number of $CD68^+$ macrophages in sparsely granulated GH and null cell tumors compared with densely granulated GH and corticotroph tumors.[23] In addition, the number of $CD68^+$ macrophages has been shown to positively correlate with tumor size and local invasion.[24] Evaluating the immune cell composition of tumors is needed for successful clinical development of CPI therapy in pituitary tumors. Our study did not include an analysis of the tumor immune cell composition.

Drugs that target CTLA-4 are more likely than other CPIs to cause hypophysitis and pituitary dysfunction, and their combination with medications that target PD-1 further heightens that risk.[25] Isolated ACTH deficiency can also occur after use of single-agent PD-1 inhibitors.[26] Importantly, although recovery of anterior pituitary hormone secretion can be seen, central adrenal insufficiency is usually permanent.[27] This raises the question as to whether there may be an increased intrinsic susceptibility of corticotroph tumors to immune checkpoint inhibition, as observed in our study (patients 1 and 2) as well as the two other previously published cases.[10 11]

It has also been hypothesized that pituitary tumors may particularly be sensitive to anti-CTLA-4 antibodies due to the ectopic expression of CTLA-4 on pituitary tumors, which may be in part responsible for higher rates of hypophysitis after anti-CTLA-4 versus anti-PD-1 therapy. Our case of a responder treated with pembrolizumab monotherapy demonstrates that PD-1 blockade alone may be sufficient to induce a remarkable response in a hypermutated PC. It would be interesting to know if patients without a hypermutator phenotype who did not respond to PD-1 blockade alone would have a response to dual anti-CTLA-4 and anti-PD-1 therapy. The ongoing phase II trials of nivolumab and ipilimumab in patients with aggressive pituitary tumors (NCT04042753 and NCT02834013) have the potential to address this question.

CONCLUSION

Determining the efficacy of CPIs is difficult in rare tumors such as PC due to the challenges involved with conducting large clinical trials for an orphan disease. Here, we report four patients with PC treated with pembrolizumab—in whom two partial responses were seen in patients with ACTH-secreting PC. Further studies are needed to determine if the response to CPIs in patients with PC is unique to corticotroph tumors and to further clarify how the response correlates to the mutational status of the tumor and the tumor microenvironment.

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Competing interests No, there are no competing interests.

Patient consent for publication Obtained.

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Data availability statement Data are available on reasonable request. All relevant data and material are available at MD Anderson Cancer Center on request.

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