

# Neoadjuvant anti-programmed cell death 1 therapy for locally advanced basal cell carcinoma in treatment-naive patients: A case series



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## BACKGROUND

Basal cell carcinoma (BCC) is the most common malignancy in the United States, with an estimated 4.3 million new cases diagnosed each year.<sup>1</sup> The majority of BCCs are treated with surgical excision. However, occasionally lesions are deemed unresectable or would result in considerable disfigurement if resected, thus requiring systemic therapy. Greater than 90% of BCCs exhibit mutations in the hedgehog signaling pathway, most commonly loss-of-function mutations in the tumor-suppressor gene *Patched* or activating mutations in the G-protein-coupled receptor *smoothened*,<sup>2,3</sup> leading to pathway overactivation and uncontrolled cellular proliferation.<sup>4</sup> Hedgehog pathway inhibitors, including vismodegib and sonidegib, are Food and Drug Administration–approved standard-of-care therapies for unresectable BCC. In clinical trials of hedgehog pathway inhibitors for locally advanced BCCs, objective response rates are estimated at 45%, with a median duration of response of 9.5 months.<sup>5–7</sup> Development of resistance is common, cures are rare, and adverse effects can be bothersome, leading to dosing interruptions or drug discontinuation.<sup>2,3</sup> There are no approved systemic therapies for patients who progress with or are intolerant to hedgehog pathway inhibitors.

### Abbreviations used:

BCC: basal cell carcinoma  
 PD-1: anti-programmed cell death 1  
 PD-L1: programmed cell death ligand 1

BCC has one of the highest rates of somatic mutations among all cancer types because of effects of ultraviolet radiation.<sup>8</sup> The abundance of ultraviolet-induced neoantigens in BCC suggests that these tumors could be sensitive to anti-programmed cell death 1 (PD-1) inhibition like other highly ultraviolet-mutated tumors are, including cutaneous squamous cell carcinoma and melanoma. There are few clinical data documenting efficacy of anti-PD-1 for locally advanced BCC in treatment-naive patients. Small series have reported clinical activity of PD-1 inhibitors in both locally advanced and metastatic BCC; however, all of these patients were previously treated with a hedgehog pathway inhibitor or chemotherapy.<sup>9–12</sup> A small nonrandomized trial also showed efficacy of second-line pembrolizumab with or without vismodegib in patients with BCC who previously progressed with or were intolerant of hedgehog pathway inhibitors.<sup>9,13</sup> To our knowledge, the use

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of PD-1 inhibitors as first-line or neoadjuvant therapy in locally advanced BCC or metastatic BCC has not been previously reported.

Here we present 2 patients with unresectable, locally advanced BCCs that responded to frontline treatment with PD-1.

## METHODS

### Histologic evaluation and immunohistochemical testing

Diagnostic pretreatment biopsies were obtained for both patients to confirm BCC. For patient 1, posttreatment biopsies were also collected 7 months after completion of PD-1. The pretreatment specimens were evaluated with routine histologic evaluation (hematoxylin-eosin–stained slides) and with immunohistochemical stains for CD3 (Agilent Dako GA503, Santa Clara, CA), CD4 (4B12 clone), and CD8 (C8/144B clone). Programmed cell death ligand 1 (PD-L1) staining was performed with the E1L3N clone in the CLIA certified Yale Surgical Pathology laboratory. The posttreatment specimens were stained for cytokeratin (MNF116 clone) to evaluate for residual carcinoma.

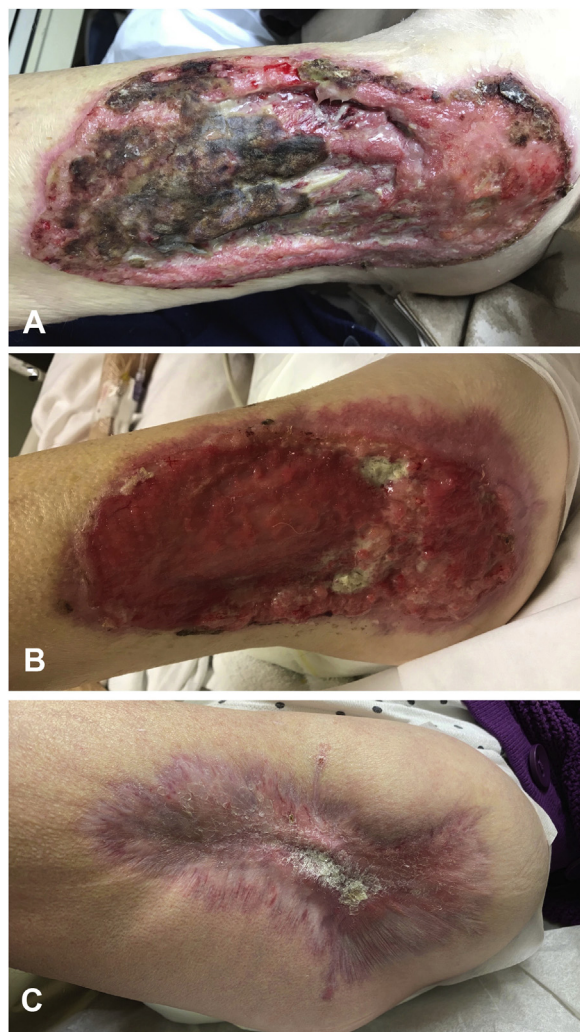
### Informed consent

Both cases were presented to and reviewed by the interdisciplinary team at the Yale Melanoma Tumor Board. The patients were deemed to have unresectable disease because of a combination of large tumor size, local invasion, and anatomic location for which surgery would have caused considerable disfigurement and morbidity. Both patients were offered therapy with hedgehog pathway inhibitor but declined. Subsequently, the expert consensus recommended PD-1, and both patients provided informed consent for it. Patient 1 consented for participation in the Yale Biospecimen and Data Repository protocol, which is approved by the Yale University institutional review board. Both patients consented for use of deidentified images.

## CASE PRESENTATIONS AND RESULTS

### Case 1

A 70-year-old woman received a diagnosis of a BCC of the left thigh, but she declined treatment and the lesion grew slowly during 15 years. At presentation, she was found to have a 20.5 × 12 × 3-cm ulcerated lesion on her left thigh, extending to bone (Fig 1, A). Associated symptoms included immobility, local pain, fatigue, and a 13-kg unintentional weight loss. On examination, she was cachectic and anemic (hemoglobin level of 4 g/dL) in the setting of chronic, slow drainage of serosanguinous fluid from her lesion, requiring a transfusion of 3 units of



**Fig 1.** Unresectable basal cell carcinoma of the left thigh of a 70-year-old female patient both before and after frontline treatment with nivolumab. **A**, Tumor at initial presentation. **B**, Before fifth cycle of nivolumab. **C**, Seven months after completion of nivolumab therapy.

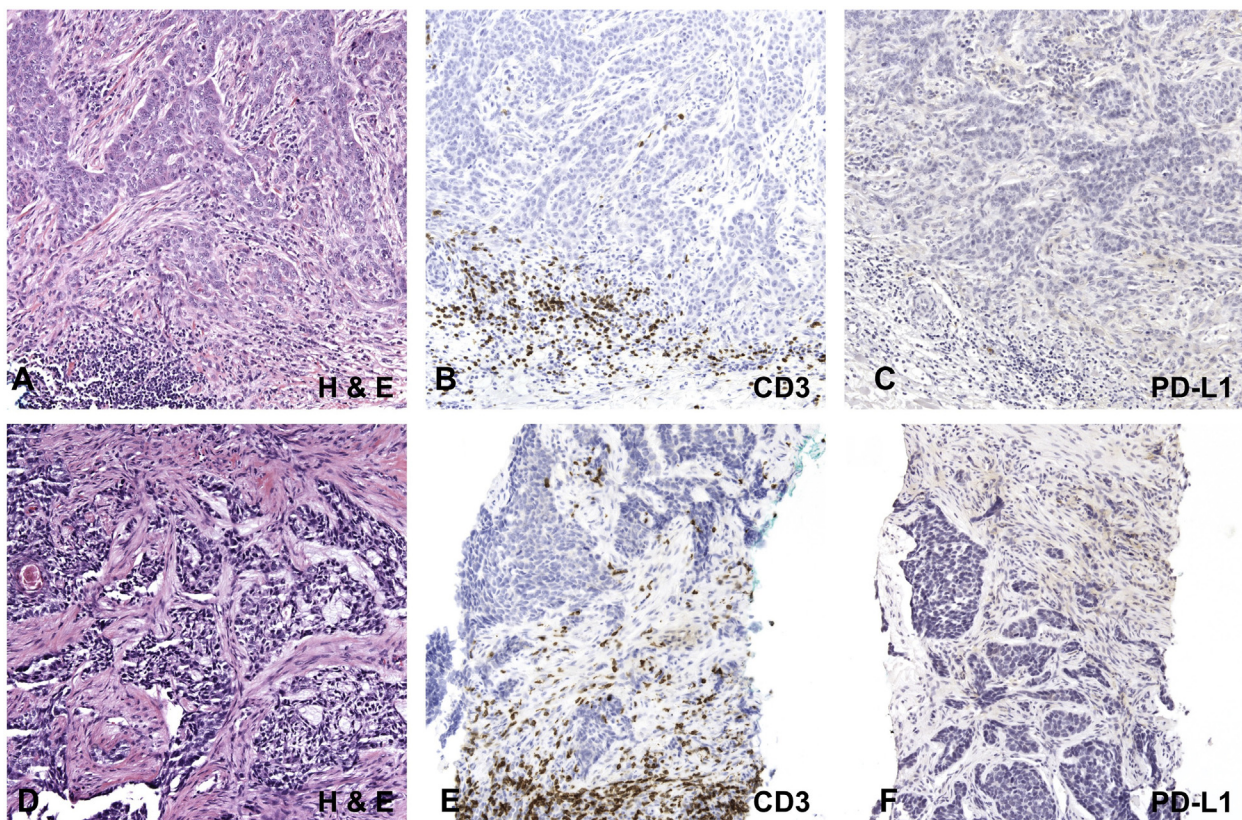
packed red blood cells. Biopsy confirmed BCC with focal keratinization and areas of ulceration (Fig 3, A). CD3, CD4, and CD8 immunohistochemical testing showed moderate lymphocytic inflammation at the base of the tumor, with both CD4<sup>+</sup> and CD8<sup>+</sup> T cells (Fig 3, B). PD-L1 staining was present in 0% of tumor cells; however, there was weak focal staining in some stromal cells (Fig 3, C). Extension of the tumor into the underlying vastus lateralis muscle was noted on computed tomographic imaging; however, there was no evidence of metastatic disease. The lesion was deemed unresectable and she began receiving systemic therapy with neoadjuvant intravenous nivolumab 480 mg every 4 weeks.

Tumor shrinkage was modest after cycle 1 and 2, and after cycle 3, the tumor was noticeably smaller,





**Fig 2.** Locally advanced, unresectable basal cell carcinoma on the back of a 77-year-old female patient before and after first-line treatment with pembrolizumab. **A**, Tumor at initial presentation. **B**, Before fifth cycle of pembrolizumab. **C**, Before seventh cycle of pembrolizumab.



**Fig 3.** Biopsy specimens from the thigh lesion of patient 1 (**A** to **C**) and largest back lesion from patient 2 (**D** to **F**). **A** and **D**, Photomicrograph of sections showing infiltrative basal cell carcinoma. **B** and **E**, Immunohistochemistry for CD3 showing the presence of T cells at the base of both tumors. **C** and **F**, Immunohistochemistry for programmed cell death ligand 1 showing the absence of staining on tumor cells; faint stromal staining was focally present. (**A** and **D**, Hematoxylin-eosin stain.) *H&E*, Hematoxylin-eosin; *PD-L1*, programmed cell death ligand 1.



with increased granulation tissue at its base. As treatment progressed, she noted improvement in energy, mobility, and appetite, with subsequent weight gain, and the tumor continued to shrink in width and depth (Fig 1, B). She tolerated treatment well. Her only adverse event was development of hypothyroidism, which was managed with levothyroxine. PD-1 was discontinued after 7 cycles because of the significant clinical response. Seven months after completion of therapy, she had a 12 × 7-cm healed scar on her left thigh, without clinical or radiologic evidence of active BCC (Fig 1, C). Scouting biopsies confirmed histologic clearance of the tumor, with negative results for keratin staining. She had a complete response and avoided the need for surgery.

### Case 2

A 77-year-old woman received a diagnosis of locally advanced BCCs of the back and chest (Fig 2, A), which had been present for greater than 25 years. The mass on the left anterior aspect of her chest measured 7 × 8 cm, and 2 masses on her back measured 15 × 20.5 cm and 3 × 6 cm. The largest fungating and ulcerated back mass had eroded down to paraspinal musculature with areas of bone focally exposed. The lesions were causing her significant pain, forcing her to sleep on her side, and had recently become malodorous. She reported abundant serosanguinous discharge, which was regularly soaking through pads and clothing, resulting in anemia (hemoglobin level of 9.1 g/dL) at her initial evaluation. Biopsies of these tumors showed infiltrative BCC (Fig 3, D). The biopsy from the larger back lesion was moderately inflamed, with both CD4<sup>+</sup> and CD8<sup>+</sup> T cells (Fig 3, E). PD-L1 staining was present in 0% of tumor cells; however, as in case 1 there was weak focal staining in some stromal cells (Fig 3, F). Magnetic resonance imaging and computed tomography of her chest revealed a 6 × 2.4-cm soft tissue mass in the left aspect of the anterior chest wall and an at least 20-cm ulceration of the posterior thoracic soft tissues, involving the thoracic spinous processes. There were also numerous smaller masses, including 1 on the left upper posterior aspect of the chest wall, all thought to be due to direct extension of the tumor. There was no evidence of metastatic disease on imaging. She was not a surgical candidate because of the size and depth of the lesions and began receiving 200 mg of intravenous pembrolizumab every 3 weeks.

Tumor shrinkage was noted after her first cycle, and the lesions continued to decrease at all subsequent visits. Before cycle 5, repeated computed tomographic imaging showed a 90% reduction in

size of the mass on the left anterior aspect of the chest wall, complete radiologic clearance of the lesion on the left upper posterior aspect of the chest wall, and reduction of the large back lesion, with improvement in pain and resolution of the malodorous discharge (Fig 2, B). Before her seventh cycle, the tumor on the anterior aspect of her chest measured 3 × 1 cm (94% reduction) and the lesion on her back was 7 × 14 cm (67% reduction), with significant thinning of the superior fungating portion (Fig 2, C). Her hemoglobin level improved to 11.7 g/dL without transfusion. She completed 7 cycles of pembrolizumab with a partial response and converted to resectability, but she declined further systemic treatment or surgery, both of which were offered. She tolerated pembrolizumab well, developing only a rash and mild facial swelling after her first cycle, which resolved with steroids and diphenhydramine. She was successfully retreated without additional adverse events.

### CONCLUSIONS

Here we report what is to our knowledge the first 2 cases of patients with locally advanced BCC successfully treated with anti-PD-1 as first-line, neoadjuvant therapy. Both patients achieved an impressive clinical response with reduction in tumor burden, 1 with a complete response that obviated the need for surgical intervention. Although there is scientific rationale to study anti-PD-1 and anti-PD-L1 agents in locally advanced and metastatic BCC, this is a rare disease state and there is limited clinical evidence of activity beyond case reports of patients treated with anti-PD-1 after progression on a hedgehog pathway inhibitor. Potential advantages to using anti-PD-1 over hedgehog pathway inhibitors include improved medication compliance given the intravenous route of administration and the potential for long-term durable responses, and potentially complete responses, as documented in patients with advanced melanoma treated with anti-PD-1 and as we document here for patient 1. Toxicity is a concern for both anti-PD-1 and hedgehog pathway inhibitors, although the majority of patients treated with anti-PD-1 tolerate it well.<sup>2,14,15</sup> Nonetheless, during the informed consent process, patients should be counseled in detail about the potential for serious immune-related adverse events. Additionally, resistance can occur with either hedgehog pathway inhibitors or anti-PD-1, and currently there are no validated biomarkers of response to guide treatment selection. Finally, treatment of BCC with hedgehog pathway inhibitors is known to affect the differentiation of the tumor, especially once resistance develops.<sup>16-19</sup> It is possible then, that pretreatment with hedgehog pathway inhibitors affects responses

observed with subsequent treatment with anti-PD-1 therapy. However, further studies are required because responses to anti-PD-1 therapy after hedgehog pathway inhibitor treatment for locally advanced or metastatic BCC in the literature are variable.

It is unclear whether PD-L1 status affects treatment response in locally advanced BCC.<sup>20</sup> There are a number of case reports and series of locally advanced, metastatic, or recurrent BCC successfully treated with anti-PD-1 therapy after treatment failure with a hedgehog pathway inhibitor, with various PD-L1 expression levels.<sup>10-12,21-23</sup> Others have also observed that lack of PD-L1 expression does not preclude responses, as was the case in our 2 patients.<sup>10-12,21-23</sup> There are reports of anti-PD-1 resistance in BCCs; however, this appears to occur most commonly in “cold” tumors (PD-L1 negative, minimal T-cell infiltrate),<sup>24</sup> but it is difficult to draw conclusions from this small number of cases.

Further research is needed to establish whether frontline anti-PD-1 therapy is warranted for unresectable locally advanced BCC and what the duration of treatment should be if patients respond. Goals of treatment include potentially sparing these patients from a large, morbid surgery or shrinking the tumor enough so that surgery is easier or even unnecessary. Although there are a number of clinical trials currently recruiting patients to evaluate efficacy of PD-1 inhibitors in advanced BCC (eg, NCT03132636, NCT03521830, NCT02834013), inclusion criteria require that patients have progressed with previous therapies, including a hedgehog pathway inhibitor.<sup>9</sup> Furthermore, there are no defined biomarkers of response in locally advanced or metastatic BCCs, and this should be prospectively studied if possible. Efforts should be made to enroll patients receiving tissue protocols to study pre- and posttreatment biopsies from patients with BCC treated with immune checkpoint inhibitors because these cases are rare.

We conclude that anti-PD-1 therapy may be a feasible frontline therapeutic option in patients with locally advanced BCC. Patient cases should be discussed at multidisciplinary tumor boards and patients must be counseled on the limited data in existence for this approach, in addition to the potential toxicities, lack of predictive biomarkers, and existing alternative approaches, including hedgehog pathway inhibitors.

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