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Frequent PD-L1 expression in primary and metastatic penile squamous cell carcinoma: potential opportunities for immunotherapeutic approaches

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Background: Despite aggressive multimodal therapy, locally advanced and/or metastatic penile squamous cell carcinoma (SqCC) is associated with significant morbidity and mortality, indicating a need for new therapeutic options. Given the emerging clinical utility of immunotherapeutics, we sought to assess the incidence and potential clinical significance of PD-L1 expression in penile SqCC.

Patients and methods: Using an anti-PD-L1 primary antibody (clone 5H1), immunohistochemistry was carried out on whole tumor sections from 37 patients with penile SqCC treated at our institution between 2005 and 2013. PD-L1-positive tumors were defined as those with membranous staining in ≥5% of tumor cells. Association between PD-L1 expression and clinicopathologic parameters was examined using Fisher's exact test. Correlation between PD-L1 expression in primary tumors and matched metastases was assessed using the Spearman rank correlation coefficient (ρ). The difference in cancer-specific mortality between PD-L1-positive and -negative groups was examined using the log-rank test.

Results: Twenty-three (62.2%) of 37 primary tumors were positive for PD-L1 expression, and there was strong positive correlation of PD-L1 expression in primary and metastatic samples ($\rho = 0.72$; $0.032 < P < 0.036$). Primary tumor PD-L1 expression was significantly associated with usual type histology ($P = 0.040$) and regional lymph node metastasis ($P = 0.024$), as well as decreased cancer-specific survival ($P = 0.011$).

Conclusions: The majority of primary penile SqCC tumors express PD-L1, which is associated with high-risk clinicopathologic features and poor clinical outcome. These data provide a rational basis for further investigation of anti-PD-1 and anti-PD-L1 immunotherapeutics in patients with advanced penile SqCC.

Key words: penile cancer, squamous cell carcinoma, PD-L1, immunohistochemistry, immunotherapy

introduction

Squamous cell carcinoma (SqCC) is the most common primary neoplasm of the penis [1]. The vast majority of penile SqCC present as clinically localized disease, for which organ-preserving surgical excision and/or radiation are usually sufficient for primary treatment and management of subsequent local recurrences, and overall, low-stage tumors have a good prognosis with high possibility of cure [2]. In contrast, locally advanced penile SqCC, particularly those with spread to regional lymph nodes, may require a multimodal approach, including primary lymphadenectomy, adjuvant radiation, and/or chemotherapy; despite these aggressive treatment strategies, however, high-stage tumors have a poor prognosis with significant morbidity and mortality [2]. Thus, there is a clear need for additional therapeutic options for patients with locally advanced and/or metastatic penile SqCC.

Recent advances in immunotherapy offer promising new treatments for some solid tumors [3]. The PD-1/PD-L1 immune checkpoint pathway, for example, is one of the major

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targets of a new generation of immunotherapeutics. PD-1, a co-inhibitory receptor present on a subset of CD8-positive cytotoxic T cells, interacts with its ligand PD-L1 on tumor cell membranes, resulting in suppression of T-cell activation and proliferation, and thereby, dampening of the host anti-tumor immune response [4]; inhibiting the PD-1/PD-L1 interaction, therefore, should augment tumor cell killing by cytotoxic T cells. Indeed, immunotherapeutic approaches targeting PD-1 or PD-L1 have been shown to enhance anti-tumor activity in preclinical models [5, 6], and anti-PD-1 and anti-PD-L1 immunotherapeutics have yielded promising results in early and late phase clinical trials [7–13], with recent Food and Drug Administration (FDA) approval for use in melanoma and lung SqCC.

Membranous PD-L1 expression has been described in a diverse assortment of human malignancies, including breast cancer and melanoma [14, 15]. In addition, PD-L1 expression is frequently reported in primary SqCC of a variety of other organs, including lung, head and neck, and cervix [16–18]. Despite intensive study of PD-1/PD-L1 pathway molecules and possible anti-PD1 and anti-PD-L1 immunotherapies in other urologic malignancies, including bladder cancer, kidney cancer, and prostate cancer [19, 20], to our knowledge, PD-L1 expression has not been previously examined in penile SqCC. Thus, in this study, we sought to assess the prevalence and clinicopathologic significance of membranous PD-L1 expression by immunohistochemistry in primary and metastatic penile SqCC.

materials and methods

patient selection

This cohort of penile SqCC patients has been described previously [21]. Briefly, penile SqCC cases diagnosed between 2005 and 2013 were retrospectively identified from the surgical pathology records database at the University of Michigan Health System. Tissue from 37 patients, including 37 primary tumors and 9 matched metastases, was available for the purposes of this study. HPV DNA genotyping, p16 immunohistochemistry (IHC), and targeted next-generation sequencing was carried out previously (see supplementary Materials, available at *Annals of Oncology* online for details) [21].

PD-L1 IHC

For all primary and metastatic tumors, PD-L1 IHC was carried out on representative whole tissue sections using an anti-PD-L1 primary antibody (clone 5H1; 1:500 dilution), as described previously [20], and the percentage of tumor cells with membranous staining was assessed together by two study pathologists (MJM and RM) blinded to patient clinicopathologic parameters. Primary tumors were considered positive for PD-L1 expression if ≥5% of tumor cells showed membranous staining. The relative intensity (moderate or severe) of host inflammatory response was recorded, as well as the presence or absence of PD-L1 IHC staining in tumor-infiltrating mononuclear cells (using a ≥5% cut-off).

statistical analysis

Association between PD-L1 IHC staining and clinicopathologic parameters or common molecular alterations was examined using Fisher's exact test. Correlation between PD-L1 expression in primary tumors and matched metastases was assessed using the Spearman rank correlation coefficient (ρ). The difference in cancer-specific mortality between PD-L1-positive and -negative groups was examined using the log-rank test. Cancer-specific mortality was measured from the time of diagnosis to death or date of last follow-up (at which point the patient was censored). All statistical analyses were carried out using SAS, version 9.4 (Cary, NC), and statistical significance was defined as $P < 0.05$.

results

Of the 37 primary penile SqCC tumors examined, 23 (62.2%) were positive for PD-L1 expression (see Materials and methods); essentially, all positive samples showed moderate to strong membranous staining (Figure 1), and the percentage of tumor cells staining ranged from 5% to 70% (median = 20%). The other 14 primary penile SqCC tumors were negative for PD-L1 expression (Figure 2), although very focal weak to moderate membranous staining (<5% of tumor cells) was seen in four cases. Clinicopathologic characteristics of PD-L1-positive and PD-L1-negative primary penile SqCC tumors are presented in Table 1.

Twenty-four primary penile SqCC tumors were of usual type histology; the remainder of tumors were of varied histologic subtypes, including warty (five), papillary (four), verrucous (two), warty/basaloid (one), and basaloid (one). Primary tumors with usual type histology were significantly more likely to express PD-L1 ($P = 0.040$), with an odds ratio of 4.8 relative to other histologic subtypes (95% confidence interval = 1.13–20.46). In contrast, among primary tumors with warty or verrucous type histology, none were PD-L1 positive (compared with 76.7% of primary tumors with other histologic subtypes; $P < 0.001$).

Ten primary penile SqCC tumors were well differentiated, 17 were moderately differentiated, and 10 were poorly differentiated. Overall, there was a non-statistically significant trend toward association between higher histologic grade (i.e. more poorly differentiated) and PD-L1 expression ($P = 0.197$), with 80.0% of poorly differentiated tumors being PD-L1-positive (compared with 40.0% of well-differentiated tumors). Similarly, PD-L1 expression by primary tumors showed a non-statistically significant trend toward association with higher pathologic stage (T2–4 versus T1, $P = 0.130$), with 70.8% of T2–4 tumors being PD-L1-positive (compared with 40.0% of T1 tumors).

In contrast to histologic grade and pathologic stage, there was a clear association between lymph node status and PD-L1 expression in primary penile SqCC tumors. Primary tumors in patients with lymph node metastases were significantly more likely to express PD-L1 ($P = 0.024$), with an odds ratio of 10.91 relative to primary tumors in patients without lymph node metastases (95% confidence interval = 1.19–100). Furthermore, in the nine patients with matched primary and metastatic penile SqCC tumors, there was strong positive correlation of PD-L1 membranous staining in primary and metastatic samples ($\rho = 0.72$; $0.032 < P < 0.036$; Figure 3). All nine matched primary tumors were PD-L1-positive; seven (77.8%) matched metastatic tumors were PD-L1-positive, and two (22.2%) matched metastatic tumors were PD-L1-negative.

Overall, there was a non-statistically significant trend toward association between higher clinical stage and primary penile SqCC tumor PD-L1 expression (clinical stage I versus II–IV, $P = 0.073$), with 70.8% of stage II–IV tumors being PD-L1-positive (compared with 36.4% of stage I tumors). No other significant associations were identified between primary tumor

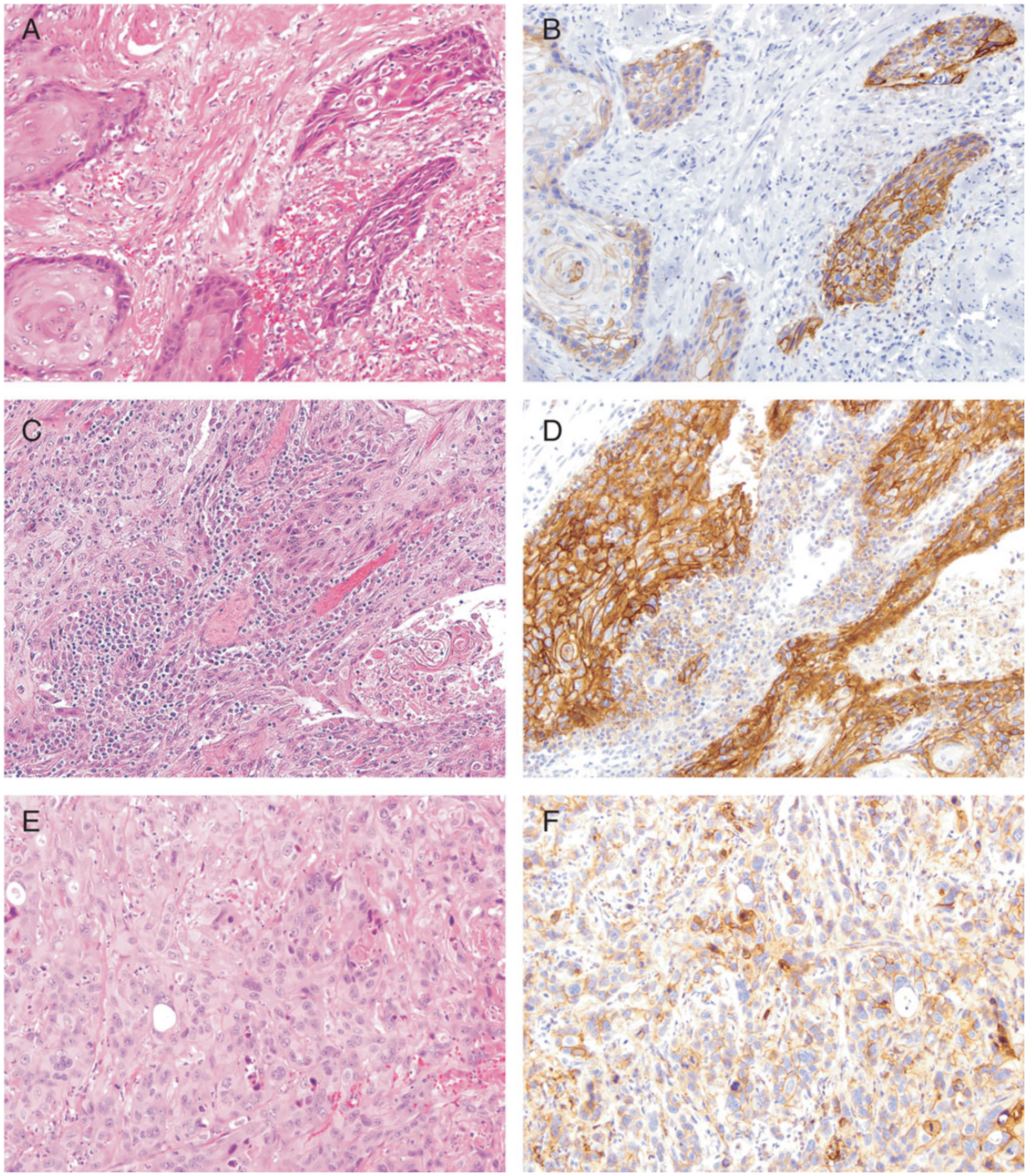

Figure 1. Positive PD-L1 expression in primary penile squamous cell carcinoma tumors. (B, D, and F) PD-L1 IHC demonstrates frequent moderate to strong membranous staining in primary penile squamous cell carcinoma, including well differentiated (A and B), moderately differentiated (C and D), and poorly differentiated (E and F) tumors. Magnification, ×20.

PD-L1 expression and other examined clinicopathologic parameters, including age, circumcision status, HPV status, and p16 expression.

Thirty-six of the primary penile SqCC tumors examined in this study were previously interrogated by our group for recurrent molecular alterations (somatic mutations and copy number alterations) using a targeted next-generating sequencing approach [21]. In that prior study, the five most common prioritized somatic mutations involved *TP53*, *CDK2NA*, *PIK3CA*, *HRAS*, and *NFE2L2*, and the five most frequent prioritized copy number alterations involved *CDK2NA*, *MYC*, *CCND1*, *SOX2*, and *EGFR*. In the current study, we sought to integrate our primary penile SqCC tumor PD-L1 expression results with these prior molecular data. As shown in supplementary Table S1, available at *Annals of Oncology* online, there were no significant associations between primary tumor PD-L1 expression and specific molecular alterations, although by logistic regression, there was a non-statistically significant trend toward association between increased total number of molecular alterations and PD-L1 expression ($P = 0.16$), with an odds ratio of 1.36 compared with a sample with one fewer alteration (95% confidence interval = 0.88–2.11).

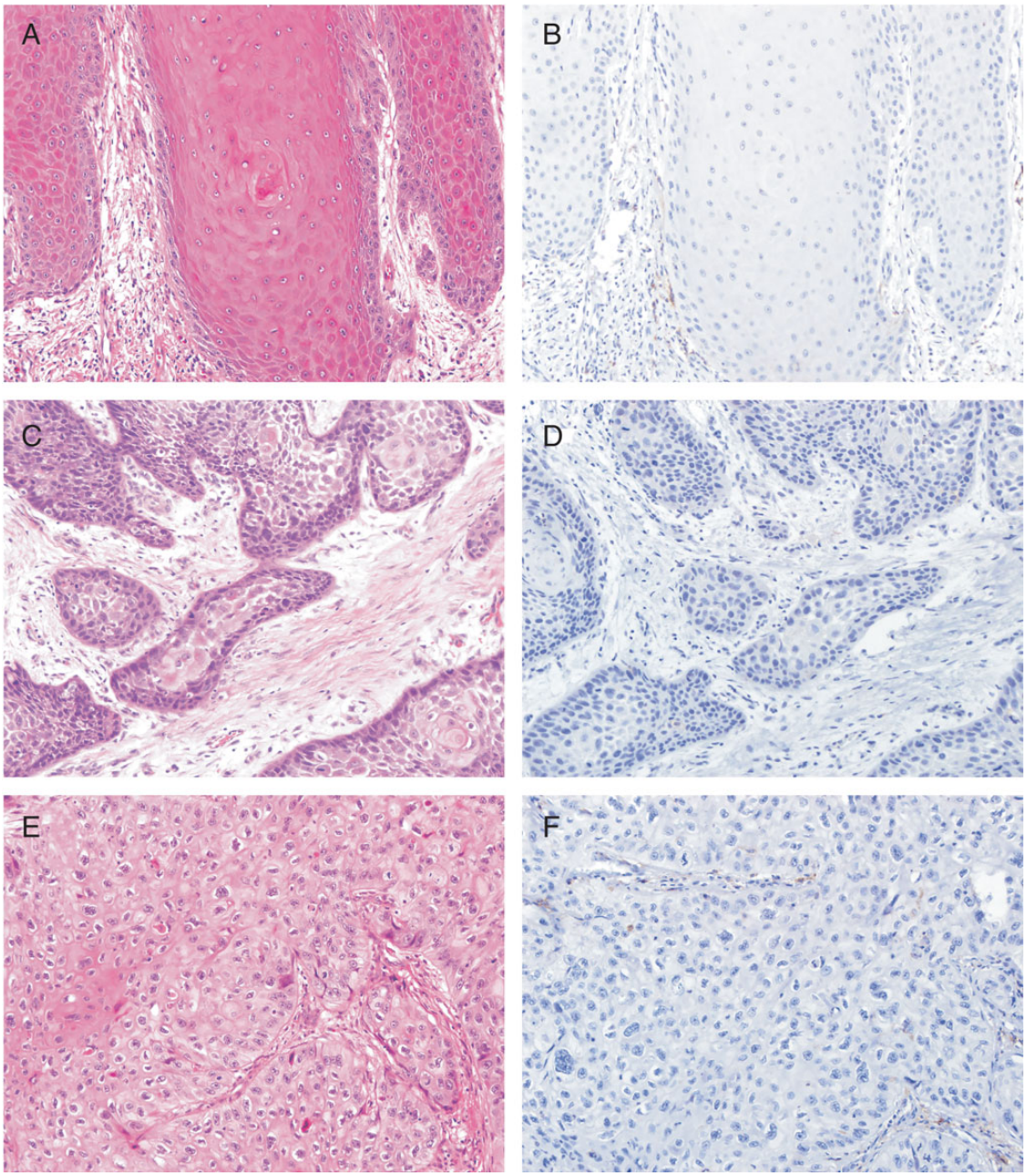

Figure 2. Negative PD-L1 expression in primary penile squamous cell carcinoma tumors. (B, D, and F) PD-L1 IHC is negative in a subset of primary penile squamous cell carcinoma, including well differentiated (A and B), moderately differentiated (C and D), and poorly differentiated (E and F) tumors. Magnification, ×20.

Of the patients with primary penile SqCC tumors examined in this study, two experienced local recurrence, five had distant progression, and seven died of disease. Importantly, although primary tumor PD-L1 expression was not significantly associated with local recurrence (10.0% versus 0.0% of PD-L1-positive and -negative tumors, respectively, $P = 0.501$), patients with PD-L1-positive primary tumors were more likely to have distant progression (25.0% versus 0.0% of PD-L1-positive and -negative tumors, respectively, $P = 0.063$) and die of disease (31.8% versus 0.0% of PD-L1-positive and -negative tumors, respectively, $P = 0.029$). In addition to pathologic stage (T2–4 versus T1), histologic subtype (usual versus other), and lymph node status (N1–3 versus N0/NX), primary tumor PD-L1 expression (positive versus negative) was significantly associated with decreased cancer-specific survival [log-rank test statistic = 6.54, $P = 0.011$; supplementary Table S2, available at *Annals of Oncology* online]. (Hazard ratios from proportional hazards models were not estimable because there were no observed lethal events for patients with T1 pathologic stage, non-usual histologic subtype, or negative PD-L1 expression.)

Finally, no significant associations were detected between the intensity of host inflammatory response or presence of PD-L1 staining on tumor-infiltrating mononuclear cells and primary penile or metastatic SqCC tumor PD-L1 expression,

Table 1. Association of primary tumor PD-L1 expression with clinicopathologic parameters

Parameter	PD-L1-positive ($n = 23$)	PD-L1-negative ($n = 14$)	*P* value
Age			
≤65 years	11 (47.8%)	9 (64.3%)	0.498
>65 years	12 (52.2%)	5 (35.7%)	
Circumcision status			
Yes	4 (22.2%)	2 (18.2%)	1.000
No	14 (77.8%)	9 (81.8%)	
Histologic subtype			
Usual	18 (78.3%)	6 (42.9%)	**0.040**
Other[a]	5 (21.7%)	8 (57.1%)	
Histologic grade			
Well	4 (17.4%)	6 (42.9%)	0.197
Moderate	11 (47.8%)	6 (42.9%)	
Poor	8 (34.8%)	2 (14.2%)	
HPV status			
Positive	2 (10.5%)	3 (21.4%)	0.629
Negative	17 (89.5%)	11 (78.6%)	
p16 expression			
Positive	5 (22.7%)	5 (38.5%)	0.444
Negative	17 (77.3%)	8 (61.5%)	
Pathologic stage			
pT1	4 (19.0%)	6 (46.2%)	0.130
pT2–4	17 (81.0%)	7 (53.8%)	
Lymph node status			
pN0/NX	11 (52.4%)	12 (92.3%)	**0.024**
pN1–3	10 (47.6%)	1 (7.7%)	
Clinical stage			
I	4 (19.0%)	7 (50.0%)	0.073
II-IV	17 (81.0%)	7 (50.0%)	
Local recurrence			
Yes	2 (10.0%)	0 (0.0%)	0.501
No	18 (90.0%)	14 (100.0%)	
Distant progression			
Yes	5 (25.0%)	0 (0.0%)	0.063
No	15 (75.5%)	14 (100.0%)	
Cancer-specific mortality			
Yes	7 (31.8%)	0 (0.0%)	**0.029**
No	15 (68.2%)	14 (100.0%)	

HPV, human papillomavirus.
[a]Other includes warty, papillary, verrucous, warty/basaloid, and basaloid subtypes.
Statistically significant associations are in bold.

examined clinicopathologic factors, or clinical outcome (data not shown).

discussion

To our knowledge, this is the first study to examine PD-L1 expression in penile SqCC, and we found that nearly two-thirds of primary tumors are PD-L1-positive, with strong positive correlation of membranous PD-L1 staining in primary and metastatic tumors. PD-L1 expression is more frequent in primary tumors with usual type histology and regional lymph node metastasis (both relatively poor prognostic factors), and furthermore, PD-L1-positive primary tumors are significantly associated with decreased cancer-specific survival. These results suggest that PD-L1-positive tumors may define a subset of clinically aggressive penile SqCC and provide a rational basis for subsequent investigation of anti-PD-1 and anti-PD-L1 immunotherapeutics in the treatment of patients with locally advanced and/or metastatic penile SqCC. Indeed, based on the results of monotherapy clinical trials in other malignancies [7–11], which suggest that patients with PD-L1 expression by tumor cells have a greater response to PD-1 and/or PD-L1 inhibition, our findings suggest that a subset of penile SqCC tumors may be susceptible to enhanced immune-mediated killing with anti-PD-1 and/or anti-PD-L1 immunotherapeutics.

In our study, PD-L1-positive primary penile SqCC tumors are associated with several high-risk clinicopathologic features, including usual type histology and regional lymph node metastasis, as well as decreased cancer-specific survival. The relatively small sample size and lack of observed lethal events in certain strata, however, limit further analysis with proportional hazards models; we cannot entirely exclude, therefore, that the detected association between primary penile SqCC tumor PD-L1 expression and decreased cancer-specific survival is due to the effect of covariates (i.e. lymph node status, etc.). In this regard, it is interesting to note the strong association between lack of primary tumor PD-L1 expression and warty or verrucous type histology, as these subtypes typically belie better clinical outcomes [2]. Importantly, the incidence of HPV infection was relatively low in our cohort (15.2%), as was the frequency of HPV-related histologic subtypes (i.e. warty and basaloid). Therefore, additional independent studies are needed to clarify the relationship between HPV status and PD-L1 expression in penile SqCC.

Recently published work from our group utilized targeted next-generation sequencing to identify recurrent molecular alterations (somatic mutations and copy number alterations) in a large cohort of penile SqCC [21], including the majority of tumors evaluated for PD-L1 expression in the current study. Although no significant association was detected between primary tumor PD-L1 expression and specific molecular alterations, there was a non-statistically significant trend toward increased total number of molecular alterations in PD-L1-positive tumors. These results conform to the emerging paradigm of increased PD-L1 expression and/or response to PD-1/PD-L1 pathway inhibition in tumors with high mutational load [22–25]. In addition, in our previous study, we demonstrated that penile SqCC shares a similar spectrum of molecular alterations with lung SqCC [21], which provides additional circumstantial support for the potential efficacy of PD-1/PD-L1 inhibition in penile SqCC.

Before implementation of clinical trials for anti-PD1 or anti-PD-L1 therapeutics in penile SqCC, however, several additional considerations are necessary. For anti-PD-L1 immunotherapy, for example, there are several compounds currently in clinical trials [26, 27], and each compound is linked to a specific companion diagnostic PD-L1 IHC assay. These assays utilize different primary antibodies and have unique, predefined cut-offs for determining positive PD-L1 expression [28]. In our study, we utilized the anti-PD-L1 clone 5H1, which has been validated in early phase clinical trials (e.g. the initial phase I trials with

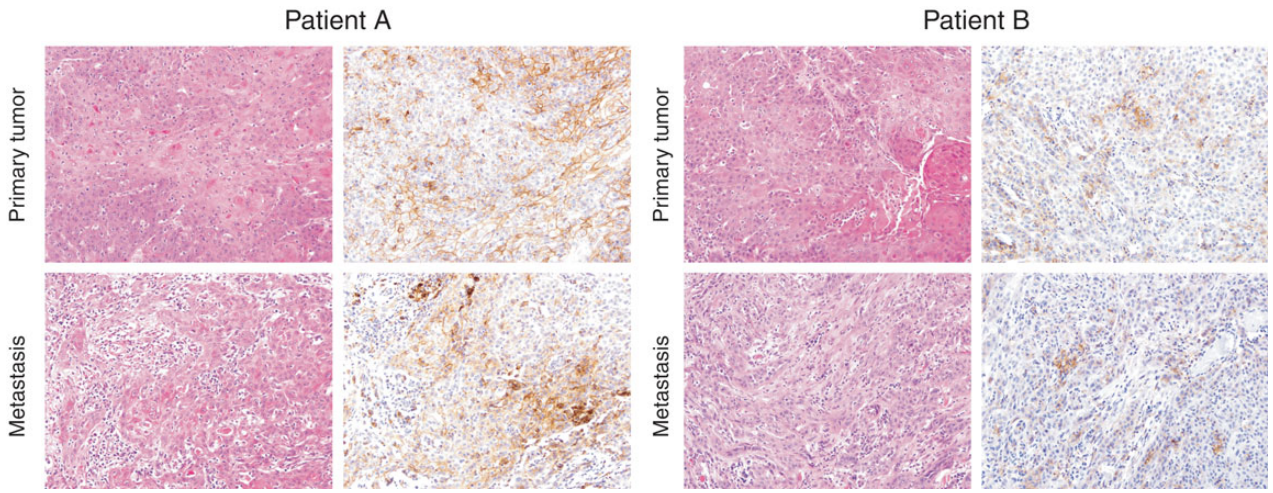

Figure 3. Concordant PD-L1 expression in matched primary and metastatic penile squamous cell carcinoma tumors. PD-L1 IHC (right panels) in matched primary and metastatic penile squamous cell carcinoma from two patients. For patient A, both the primary and metastatic tumor show high positive PD-L1 expression, while for patient B, both the primary and metastatic tumor show low positive PD-L1 expression. The percentage of cells with membranous staining shows strong positive correlation ($\rho = 0.72$; $0.032 < P < 0.036$) between matched primary and metastatic penile squamous cell carcinoma tumors. Magnification, ×20.

the anti-PD-1 immunotherapeutic BMS-936558). Overall, from a clinical workflow perspective, however, PD-L1 IHC was relatively straightforward to evaluate in penile SqCC, as the majority of tumors were either completely negative or showed moderate to strong membranous staining in a significant proportion (≥20%) of tumor cells (Figures 1 and 2). In borderline cases (i.e. those samples with weak to moderate membranous staining in 1%–10% of tumor cells), digital quantitation and/or internal consultation are recommended to reach a consensus. Finally, several recently published clinical trials, including two evaluating the efficacy of the anti-PD-1 immunotherapeutic nivolumab for treatment of advanced tumors [8, 9], have demonstrated clinical response that is independent of tumor PD-L1 expression. These results suggest that PD-L1 expression may not be a reliable predictive biomarker for therapeutic response, and this possibility should be considered when designing clinical trials for compounds that target the PD-1/PD-L1 immune checkpoint pathway.

The major strengths of this study include: its novelty, the use of whole tissue sections, the use of a previously published/validated anti-PD-L1 antibody, and the integration of PD-L1 expression with pre-existing detailed molecular data. In particular, utilizing whole tissue sections has significant advantages over tissue microarray (TMA) approaches (which are commonly used in biomarker investigation studies), as whole tissue sections allow for a more comprehensive assessment of tumor protein expression. This is especially important for PD-L1 IHC, which can show patchy, non-uniform distribution of membranous staining. The major weakness of this study is the relatively low rate of observed lethal events, which limits the conclusions that can be drawn from survival analysis and may indicate a need for subsequent large, multi-institutional validation.

In conclusion, the majority of penile SqCC show membranous PD-L1 expression, and there is strong positive correlation of PD-L1 expression in primary and metastatic tumors. PD-L1 expression is more common in primary tumors with usual type morphology and regional lymph node metastasis, and PD-L1-positive primary tumors are significantly associated with decreased cancer-specific survival. These data provide a rational basis for further exploration of targeted anti-PD-1 and anti-PD-L1 immunotherapeutics as new treatment options for advanced penile SqCC.

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disclosure

The authors have declared no conflicts of interest.

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A phase II study (ARCHER 1042) to evaluate prophylactic treatment of dacomitinib-induced dermatologic and gastrointestinal adverse events in advanced non-small-cell lung cancer

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Background: ARCHER 1042, a randomized phase II trial, explored the impact of prophylactic treatment on select dermatologic adverse events of interest (SDAEI), diarrhea, and mucositis associated with dacomitinib, an oral irreversible pan-human epidermal growth factor receptor (HER) inhibitor, in development for advanced non-small-cell lung cancer (NSCLC).

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