Title

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Journal

Journal of the National Cancer Institute, 115(12)

Authors

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Publication Date

2023-12-06

DOI

10.1093/jnci/djad155

Peer reviewed

OXFORD

JNCI: Journal of the National Cancer Institute, 2023, **115(12),** 1605–1615

https://doi.org/10.1093/jnci/djad155
Advance Access Publication Date: August 11, 2023
Article

Safety and efficacy of immune checkpoint inhibitors in advanced penile cancer: report from the Global Society of Rare Genitourinary Tumors

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Received: June 20, 2023. **Revised:** July 26, 2023. **Accepted:** August 02, 2023

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Abstract

Background: Treatment options for penile squamous cell carcinoma are limited. We sought to investigate clinical outcomes and safety profiles of patients with penile squamous cell carcinoma receiving immune checkpoint inhibitors.

Methods: This retrospective study included patients with locally advanced or metastatic penile squamous cell carcinoma receiving immune checkpoint inhibitors between 2015 and 2022 across 24 centers in the United States, Europe, and Asia. Overall survival and progression-free survival were estimated using the Kaplan-Meier method. Objective response rates were determined per Response Evaluation Criteria in Solid Tumours 1.1 criteria. Treatment-related adverse events were graded per the Common Terminology Criteria for Adverse Events, version 5.0. Two-sided statistical tests were used for comparisons.

Results: Among 92 patients, 8 (8.7%) were Asian, 6 (6.5%) were Black, and 24 (29%) were Hispanic and/or Latinx. Median (interquartile range) age was 62 (53-70) years. In all, 83 (90%) had metastatic penile squamous cell carcinoma, and 74 (80%) had received at least second-line treatment. Most patients received pembrolizumab monotherapy (n = 26 [28%]), combination nivolumab-ipilimumab with or without multitargeted tyrosine kinase inhibitors (n = 23 [25%]), or nivolumab (n = 16 [17%]) or cemiplimab (n = 15 [16%]) monotherapies. Median overall and progression-free survival were 9.8 months (95% confidence interval = 7.7 to 12.8 months) and 3.2 months (95% confidence interval = 2.5 to 4.2 months), respectively. The objective response rate was 13% (n = 11/85) in the overall cohort and 35% (n = 7/20) in patients with lymph node–only metastases. Visceral metastases, Eastern Cooperative Oncology Group (ECOG) performance status of 1 or higher, and a higher neutrophil/lymphocyte ratio were associated with worse overall survival. Treatment-related adverse events occurred in 27 (29%) patients, and 9.8% (n = 9) of the events were grade 3 or higher.

Conclusions: Immune checkpoint inhibitors are active in a subset of patients with penile squamous cell carcinoma. Future translational studies are warranted to identify patients more likely to derive clinical benefit from immune checkpoint inhibitors.

Penile squamous cell carcinoma is a rare cancer, particularly in developed countries, with 2070 estimated new cases and 470 estimated deaths in the United States during 2022 (1). In comparison, it represents up to 10% of cancers in male individuals in developing countries (2). A common management strategy for locally advanced penile squamous cell carcinoma is neoadjuvant chemotherapy using paclitaxel, ifosfamide, and cisplatin, followed by lymph node dissection (3-5). In this context, the overall response rate is around 50%, and the median overall survival ranges from 17 to 27 months (5-7). Alternatively, adjuvant chemotherapy with paclitaxel, ifosfamide, and cisplatin or 5-fluorouracil is a suitable treatment option, with a median overall survival of approximately 22 months for patients with locally advanced penile squamous cell carcinoma who did not receive neoadjuvant chemotherapy (8). Platinum-based chemotherapy regimens are also part of the first-line therapy for unresectable locally advanced or metastatic penile squamous cell carcinoma based on data from small, nonrandomized trials, given the challenges of conducting phase 3 trials in rare malignancies.

Once patients with locally advanced or metastatic penile squamous cell carcinoma progress following first-line platinum-based chemotherapy, the treatment algorithm becomes less clear. Unfortunately, the low prevalence of penile squamous cell carcinoma, the hurdles faced in clinical trial accrual in high-income countries (ie, ClinicalTrials.gov ID NCT02837042), and the scarce funding of trials in developing countries limit the availability of clinical data (9,10). The median overall survival for those with metastatic penile squamous cell carcinoma after progression on first-line chemotherapy is less than 6 months (11). Furthermore, taxane-based chemotherapy regimens for recurrent penile squamous cell carcinoma yield variable response rates (0%-20%) (12,13). Immune checkpoint inhibitors offer a promising treatment option for patients with penile squamous cell carcinoma based on accumulating biological and clinical evidence from case reports (14-19), case series (20), and umbrella trials (21-24). In addition, prior studies have shown that penile squamous cell carcinoma tumor samples exhibit a high programmed cell death 1 ligand 1 (PD-L1) positivity rate in tumor cells (32%-67%) and tumor-infiltrating immune cells (64%-80%), rendering them reasonable targets for anti–programmed cell death 1 protein (PD-1)/PD-L1 immune checkpoint inhibitor regimens (25-32). Favorable outcomes with immune checkpoint inhibitors in human papillomavirus (HPV)–driven head and neck squamous cell carcinoma (33) and cervical cancer (34) further support their use in HPV-associated penile squamous cell carcinoma (30%-50% of penile squamous cell carcinoma patients) (35). For instance, nivolumab vs targeted therapy or chemotherapy for head and neck squamous cell carcinoma demonstrated a prolonged median overall survival (7.5 vs 5.1 months) and a higher overall response rate (13.3% vs 5.8%), despite a similar progression-free survival (PFS) (2.0 vs 2.3 months) (33). In addition, in cervical cancer, pembrolizumab vs placebo yielded an increase in median PFS (10.4 vs 8.2 months) and median overall survival (24.4 vs 16.4 months), with a higher objective response rate (65.9% vs 50.8%) (34).

Clinical trials evaluating new therapies for penile squamous cell carcinoma face accrual challenges and have frequently closed early (ie, ClinicalTrials.gov IDs NCT02837042 and NCT02541903). Currently, several clinical trials assessing immune checkpoint inhibitors for penile squamous cell carcinoma with or without chemotherapy are underway (36-41). To overcome the hurdles of delayed clinical trial accrual, we used the international consortium of the Global Society of Rare Genitourinary Tumors (GSRGT) that aims to improve the clinical outcomes of poorly studied rare genitourinary tumors (10,42). We assembled a retrospective, multi-institutional, international cohort of patients with advanced penile squamous cell carcinoma treated with immune checkpoint inhibitors and report on their efficacy and safety profiles.

Methods

Patient population

This retrospective study was covered by the institutional review board review at Dana-Farber Cancer Institute (protocol No. 21-329) and local institutional review boards at participating sites according to the Declaration of Helsinki, and individual patient consent was waived. A subset of patients was derived from Italian centers, all of which were also enrolled in the Meet-URO23 (I-RARE study), a multicenter observational (both retrospective and prospective) registry study for rare genitourinary cancers. The study was approved by the ethics committee of Istituto Oncologico Veneto, Padua, Italy (No. 2021/19/PU) and by local institutional review boards at each participating site.

Deidentified data from 24 participating institutions in the GSRGT consortium from the United States, Europe, and Asia (Supplementary Table 1, available online) were obtained and are currently housed at Dana-Farber Cancer Institute. The patients included in this study 1) had a biopsy-proven advanced penile squamous cell carcinoma; 2) received any line of immune checkpoint inhibitor therapy (at least 1 dose), defined as anti–PD-1/PD-L1 alone or in combination with anti–cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), chemotherapy, or tyrosine kinase inhibitors between 2015 and 2022; and 3) did not receive immune checkpoint inhibitors as adjuvant or neoadjuvant therapies. Demographic data on sex, race, and ethnicity were self-reported. Patients who did not identify as Asian, American Indian, Alaska Native, Black or African American, Pacific Islander, Native Hawaiian, or White were grouped as "Others" when defining racial groups. Clinical and laboratory variables were assessed at baseline and included Eastern Cooperative Oncology Group (ECOG) performance status, neutrophil/lymphocyte ratio, visceral metastases, and the number of prior lines of systemic therapy. HPV status was determined by either P16 immunohistochemistry or HPV DNA testing, depending on availability at each center. Similarly, tumor proportion score from PD-L1 immunohistochemistry was used to document PD-L1 status.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics. The median follow-up of the overall cohort was calculated using the inverse Kaplan-Meier method. Overall survival was calculated from the time of initiation of immune checkpoint inhibitor treatment to death from any cause or censored on the date of the last follow-up. PFS was calculated from the time of immune checkpoint inhibitor initiation to radiologic or clinical progressive disease or death from any cause or censored on the date of the last follow-up. Overall survival and PFS were estimated using the Kaplan-Meier method, and log-rank tests were performed to compare them between categorical subgroups. Duration of response was defined as the duration between the date of the first response and the date of radiologic progressive disease, clinical progressive disease, or death, whichever occurred first. Objective response rate was determined by the clinical investigator per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria whenever feasible. Disease-control rate was defined as the proportion of patients with partial response, complete response, and stable disease as the best response. Treatment-related adverse events were reported and graded using the Common Terminology Criteria for Adverse Events, version 5.0. Clinical variables previously associated with response to immune checkpoint inhibitors in other genitourinary cancers were investigated (43-45). Multivariable Cox proportional hazards regression models for overall survival and PFS were fitted, adjusting for the following variables selected a priori: ECOG performance status (≥1 vs 0), neutrophil/lymphocyte ratio (continuous), visceral metastases (presence vs absence), and the number of prior therapy lines (≥1 vs 0). *P* values less than .05 was considered statistically significant. Statistical analyses were performed using SAS, version 9.4, statistical software (SAS Institute Inc, Cary, NC), and all statistical tests used for comparisons were 2-sided.

Results

GSRGT penile squamous cell carcinoma cohort

Among 92 patients with advanced penile squamous cell carcinoma treated with immune checkpoint inhibitors, the median (interquartile range [IQR]) age was 62 (53-70) years, and 34 (37%) were known current or former smokers. In this international cohort, 61 (66%) patients were from the United States, whereas 29 (32%) and 2 (2.2%) patients were from European and Asian institutions, respectively (Table 1; Supplementary Table 2, available online). In the overall cohort, 61 (74%) were White, 8 (9.6%) were Black or African American, and 8 (9.6%) were Asian. The median follow-up time was 21.9 months. Immune checkpoint inhibitor treatment was administered in the metastatic setting for 90% (n = 83) of patients, while the remainder received immune checkpoint inhibitors for locally advanced, unresectable disease. Metastatic involvement of visceral organs was present in 54 (59%) patients, with 44 (48%) having metastasis to the lungs, 10 (11%) to the liver, and 19 (21%) to other visceral organs (Table 1; Supplementary Table 2, available online).

Immune checkpoint inhibitors were administered in the second-line setting or beyond for 74 (80%) patients. The most common immune checkpoint inhibitor regimens were single-agent pembrolizumab (n = 26 [28%]), nivolumab (n = 16 [17%]), and cemiplimab (n = 15 [16%]). In addition, 23 (25%) patients received combination regimens with nivolumab and ipilimumab with or without a multitargeted vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor. Among 49 patients with available HPV data, 17 (35%) had evidence of HPV infection either by immunohistochemistry or HPV testing, whereas among 26 patients with available PD-L1 data, 20 (77%) had a tumor proportion score of 1% or higher. Three patients were living with HIV. Of 32 patients with available data on microsatellite instability, all tumors were microsatellite stable. The median (IQR) tumor mutation burden among 18 patients with available genomic data was 9.7 (4-12). Baseline demographics and clinical characteristics of the overall cohort are shown in Table 1.

Clinical outcomes

Among 92 patients treated with immune checkpoint inhibitors for advanced penile squamous cell carcinoma, the median overall survival was 9.8 months (95% confidence interval [CI] = 7.7 to 12.9 months), and the 12-month overall survival rate was 33%, whereas the median PFS was 3.2 months (95% CI = 2.5 to 4.2 months) and the 6-month PFS rate was 25% (Figure 1). Of 85 patients evaluable for response, an objective response rate occurred in 11 (13%) patients: 2 patients with a complete response and 9 with a partial response, with a median (IQR) duration of response of 8.1 (4.7-23.6) months and a maximum duration of response of 40.9 months. In addition, 24 (28%) patients had stable disease, for an overall disease-control rate of 41%. Of 77 patients who discontinued treatment, the main reasons were progression or death in 65 of 77 (84%) patients, toxicity in 11 (14%) patients, and patient preference in 2 (2.6%) patients.

Table 1. Baseline characteristics of patients with penile squamous cell carcinoma receiving immune checkpoint inhibitor therapy

Characteristic	Total (N = 92)
Age at immune checkpoint inhibitor initiation, median (IQR), y	62 (53-70)
Self-reported race, No. (%)	
Asian	8 (9.6)
Black or African American	8 (9.6)
White	61 (73)
Other[a]	6 (7.2)
Unknown[b]	9
Self-reported ethnicity, No. (%)	
Hispanic/Latinx	24 (29)
Non-Hispanic/Non-Latinx	58 (71)
Unknown[b]	10
Region, No. (%)	
North America	
South	24 (26)
Northeast	17 (18)
West	11 (12)
Midwest	9 (9.8)
Europe	29 (32)
Asia	2 (2.2)
Smoking status, No. (%)	
Never	50 (60)
Current/former	34 (40)
Unknown[b]	8
Disease extension, No. (%)	
Metastatic	83 (90)
Locally advanced	9 (10)
Site of metastases (n = 83),[c] No. (%)	
Bone	24 (29)
Liver	10 (12)
Lung	44 (53)
Lymph nodes only	22 (27)
Other visceral	19 (23)
Systemic therapy lines before immune checkpoint inhibitor initiation, No. (%)	
0	18 (20)
1	45 (49)
2	23 (25)
3	4 (4.3)
4	2 (2.2)
Immune checkpoint inhibitor regimen used, No. (%)	
Pembrolizumab monotherapy	26 (28)
Nivolumab monotherapy	16 (17)
Cemiplimab monotherapy	15 (16)
Nivolumab + ipilimumab + multitarget VEGF receptor tyrosine kinase inhibitor	12 (13)
Nivolumab + ipilimumab	11 (12)
Other[d]	12 (13)
ECOG performance status at immune checkpoint inhibitor initiation, No. (%)	
0	31 (36)
1	44 (51)
≥2	11 (13)
Unknown[b]	6
HPV status, No. (%)	
Positive	17 (35)
Negative	32 (65)
Unknown[b]	43
PD-L1 tumor proportion score, No. (%)	
≥1%	20 (77)
<1%	6 (23)
Unknown[b]	66
Concurrent HIV infection, No. (%)	
No	89 (97)
Yes	3 (3.3)
Neutrophil/lymphocyte ratio, No. (%)	
≥5	42 (47)
<5	47 (53)
Unknown[b]	3

[a] The "Other" race group included patients who did not self-identify as Alaska Native, American Indian, Asian, Black or African American, Native Hawaiian, Pacific Islander, or White. ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; HPV = human papillomavirus; PD-L1 = programmed cell death 1 ligand 1; VEGF = vascular endothelial growth factor.
[b] Missing values were not included in the denominator for calculation of percentage in subgroups.
[c] Sum of sites of metastases is more than 83 because 27 patients had more than 1 site of metastasis.
[d] Includes 6 patients on retifanlimab monotherapy, 2 patients on durvalumab + HPV vaccine, 1 patient each on durvalumab and tremelimumab, lorigerlimab, pembrolizumab + carboplatin + paclitaxel, and pembrolizumab + cisplatin + docetaxel.

Furthermore, of the 74 patients treated in second-line or later settings, the median overall survival was 8.3 months (95% CI = 7.5 to 12.8 months), and the median PFS was 3.3 months (95% CI = 2.2 to 4.7 months). Sixty-eight patients treated in second-line or later settings were evaluable for response, and the objective response rate was 13% (n = 9), while the disease-control rate was 40% (n = 27). Clinical outcomes were similar among the 18 patients who received immune checkpoint inhibitors in the first-line setting and among the 74 patients treated with immune checkpoint inhibitors in subsequent lines (Table 2; Supplementary Table 2, available online). The median (IQR) overall survival of patients treated with immune checkpoint inhibitor monotherapy (n = 65) was 9.5 (7.7-13.0) months, and the median (IQR) PFS was 2.8 (2.1-3.4) months (Supplementary Figure 1, available online). The objective response rate was 8.5% (95% CI = 2.8% to 18.7%), while the median (IQR) duration of response was 8.1 (4.7-19.0) months, with a maximum duration of response of 23.6 months. Two patients received the combination of pembrolizumab and platinum-based chemotherapy in the first-line setting, and 1 patient achieved a partial response. Clinical outcomes by treatment regimen are shown in Supplementary Table 3 (available online). In patients with metastatic penile squamous cell carcinoma, those with lymph node–only disease vs visceral and/or bone metastatic disease had a median overall survival of 11.4 months (95% CI = 7.9 months to not reported) vs 7.7 months (95% CI = 6.4 to 12.5 months) (log-rank test; $P = .023$), a median PFS of 2.8 months (95% CI = 1.9 months to not reported) vs 3.3 months (95% CI = 2.3 to 4.2 months) (log-rank test; $P = .056$), and the objective response rate was 35% (7/20) vs 7% (4/58) (odds ratio = 6.77, 95% CI = 1.47 to 36.6, $P = .056$), respectively (Supplementary Table 4, and Supplementary Figure 2, available online). There was no statistically significant difference in overall survival, PFS, or objective responses rate among patients with vs without bone metastases (n = 21 vs n = 55 patients, respectively) (Supplementary Figure 3, Supplementary Table 4, available online).

Safety profiles

Treatment-related adverse events of any grade occurred in 27 (29%) patients (Table 3). Grade 3 to 4 treatment-related adverse events were reported in 9 (10%) patients, whereas no grade 5 treatment-related adverse events were reported. The most common treatment-related adverse events were hepatitis, occurring in 9 (10%) patients, followed by diarrhea and/or colitis in 8 (8.7%) and skin and thyroid adverse events in 7 (7.6%) patients each. Of

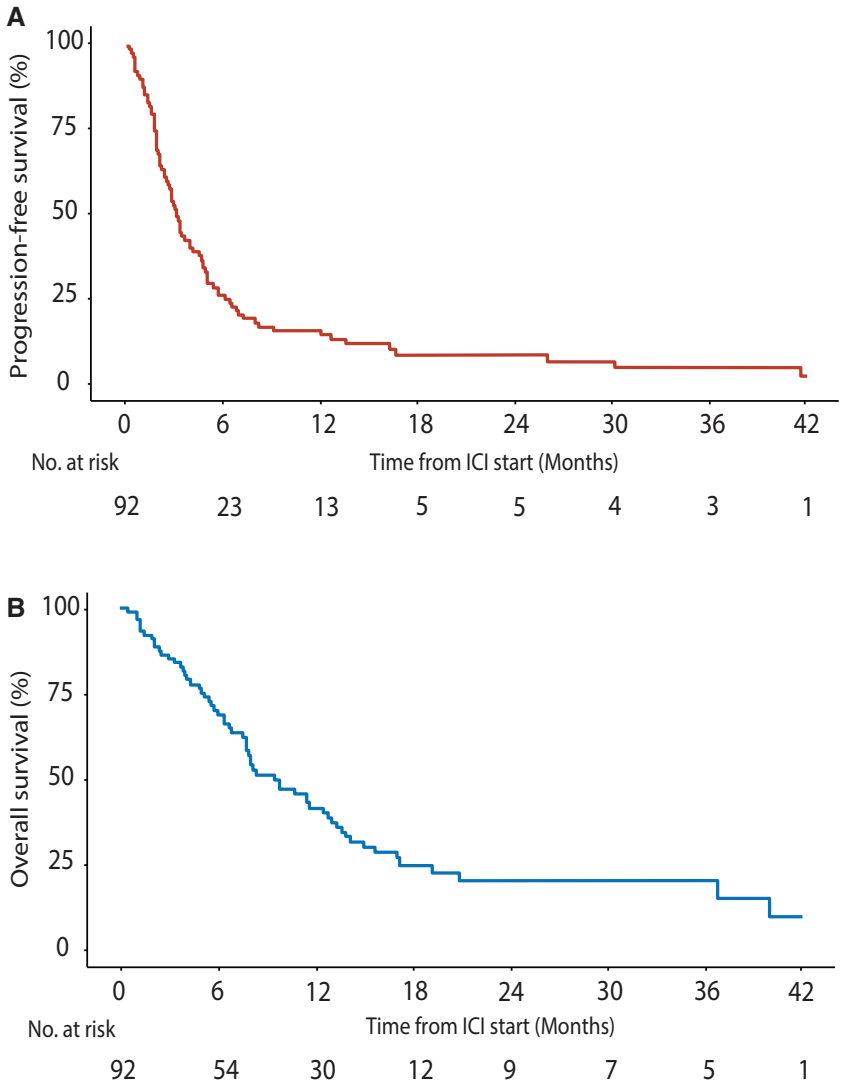

Figure 1. Progression-free survival (**A**) and overall survival (**B**) of 92 patients with penile squamous cell carcinoma treated with immune checkpoint inhibitor (ICI)–based regimens.

Table 2. Clinical outcomes by number of prior lines of systemic therapy[a]

	Overall cohort (N = 92)	Immune checkpoint inhibitor in second or later lines (n = 74)	Immune checkpoint inhibitor in the first line (n = 18)
Overall survival, median (95% CI), mo	9.8 (7.7 to 12.8)	8.3 (7.5 to 12.8)	11.6 (5.6 to not reported)
PFS, median (95% CI), mo	3.2 (2.5 to 4.2)	3.3 (2.2 to 4.7)	2.9 (2.1 to 4.9)
Objective response rate, No. (%)	11 (13)	9 (13)	2 (12)
Disease-control rate, No. (%)	35 (41)	27 (40)	8 (47)
Complete response	2 (2.4)	2 (2.9)	0 (0)
Partial response	9 (11)	7 (10)	2 (12)
Stable disease	24 (28)	18 (26)	6 (35)
Progressive disease	50 (59)	41 (60)	9 (53)
Not evaluable	7	6	1

[a] CI = confidence interval; PFS = progression-free survival.

the 27 patients with treatment-related adverse events, 7 (26%) required hospitalization, and 7 (26%) required systemic steroids, of whom 4 received high-dose glucocorticoids (>1 mg/kg). Incidence of any-grade treatment-related adverse events increased from 21% (n = 14/67) among patients receiving anti–PD-1/PD-L1 monotherapy (including 2 patients who received chemoimmunotherapy) to 31% (n = 4/13) in those receiving combination immune checkpoint inhibitor therapy (anti–PD-1 and anti-CTLA4), and 75% (n = 9/12) among patients receiving the triplet regimen of nivolumab, ipilimumab, and multitargeted VEGF receptor tyrosine kinase inhibitor. Notably,

Table 3. Safety profiles of patients with penile squamous cell carcinoma, by regimen type

	Overall cohort (N = 92)		Anti–PD-1/PD-L1[a] (n = 67)		Anti–PD-1 + anti-CTLA4 (n = 13)		Anti–PD-1 + anti-CTLA4 + tyrosine kinase inhibitor (n = 12)	
	Any grade	Grade 3 to 4	Any grade	Grade 3 to 4	Any grade	Grade 3 to 4	Any grade	Grade 3 to 4
Treatment-related adverse events, No. (%)								
Any event	27 (29)	9 (9.8)	14 (21)	4 (6.0)	4 (31)	2 (15)	9 (75)	3 (25)
Skin	7 (7.6)	–	3 (4.5)	–	2 (15)	–	2 (17)	–
Diarrhea/colitis	8 (8.7)	1 (1.1)	2 (3.0)	–	–	–	6 (50)	1 (8.3)
Thyroid	7 (7.6)	1 (1.1)	1 (1.5)	–	2 (15)	1 (7.7)	4 (33)	–
Pneumonitis	1 (1.1)	–	1 (1.5)	–	–	–	–	–
Hepatitis	9 (9.8)	4 (4.3)	–	–	2 (15)	2 (15)	7 (58)	2 (17)
Fatigue	3 (3.3)	1 (1.1)	2 (3.0)	–	1 (7.7)	1 (7.7)	–	–
Other	12 (13)	5 (5.4)	9 (13)	4 (6.0)	2 (15)	1 (7.7)	1 (8.3)	–
Systemic steroids, No. (%)	7 (7.6)		4 (6.0)		2 (15)		1 (8.3)	
Discontinued because of toxicity, No. (%)	11 (12)		7 (10)		2 (15)		2 (17)	

[a] Two patients received concurrent chemotherapy. CTLA4 = 4, cytotoxic T-lymphocyte–associated antigen; PD-1 = programmed cell death 1 protein; PD-L1 = programmed cell death 1 ligand 1.

7 of 9 (78%) patients with hepatitis and 6 of 8 (75%) patients with colitis and/or diarrhea received triplet therapy (Table 3).

Prognostic markers of survival outcomes and response to immune checkpoint inhibitors

On multivariable analysis, ECOG performance status of 1 or higher (hazard ratio [HR] = 2.86, 95% CI = 1.54 to 5.31, adjusted $P = .0009$), neutrophil/lymphocyte ratio (HR = 1.04 95% CI = 1.01 to 1.06, adjusted $P = .011$), and the presence of visceral metastases (HR = 2.09, 95% CI = 1.16 to 3.75, adjusted $P = .014$) (Supplementary Figure 4, available online) were associated with worse overall survival, whereas higher age was associated with better overall survival (HR = 0.97, 95% CI = 0.95 to 0.99, adjusted $P = .013$) (Supplementary Table 5, available online). For clinical utility, a neutrophil/lymphocyte ratio cutoff of 5 was determined based on the median value of that ratio in the cohort and prior data in other cancer types (43,46,47). Patients with a neutrophil/lymphocyte ratio below 5 and without visceral metastases had a statistically significantly longer overall survival of 36.8 months (95% CI = 9.8 months to not reported) than the 5.7 months (95% CI = 3.7 to 13 months) for patients with a ratio of 5 or higher and concurrent visceral metastases or an overall survival of 9.8 months (95% CI = 7.7 to 15 months) for patients with either of the factors ($P < .01$) (Figure 2). On multivariable analysis, age (HR = 0.97, 95% CI = 0.95 to 0.99, adjusted $P = .01$), neutrophil/lymphocyte ratio (HR = 1.04, 95% CI = 1.00 to 1.08, adjusted $P = .03$), ECOG performance status of 1 or higher (HR = 2.76, 95% CI = 1.59 to 4.79, adjusted $P = .0003$), and visceral metastases (HR = 1.63, 95% CI = 0.96 to 2.76, adjusted $P = .07$) were associated with PFS (Supplementary Figure 5, available online).

We next examined the subset of patients with available HPV data (17 with HPV-positive penile squamous cell carcinoma vs 32 with HPV-negative penile squamous cell carcinoma). There were no significant differences in survival outcomes. The median overall survival of patients with HPV-positive vs HPV-negative penile squamous cell carcinoma was 12.5 months (95% CI = 7.5 months to not reported) vs 13.8 months (95% CI = 9.8 to not reported) ($P = .72$), while the median PFS of HPV-positive vs HPV-negative penile squamous cell carcinoma was 2.6 months (95% CI = 2.1 months to not reported) vs 3.9 months (95% CI = 3.2 to 6.9 months) ($P = .95$) (Supplementary Figure 6, available online).

In an exploratory analysis, we examined clinical and laboratory variables to identify prognostic markers of response to immune checkpoint inhibitor treatment. Other than the association between lymph node–only disease and improved clinical outcomes in patients with response-evaluable metastatic penile squamous cell carcinoma (n = 76), we found that patients with lung metastases had a lower objective response rate (2/41 [4.9%]) than those who did not (objective response rate = 9/35 [26%]; odds ratio = 0.15, 95% CI = 0.01 to 0.82, $P = .019$). There were no significant differences in objective response rates by other sites of metastases, HPV status, PD-L1 positivity, or other clinical characteristics (Supplementary Table 6, available online).

Discussion

In this international retrospective study, we show that immune checkpoint inhibitor–based therapies exhibit activity in a subset of patients with penile squamous cell carcinoma without new safety signals. Moreover, few patients derive durable clinical benefit from immune checkpoint inhibitors as frontline or subsequent therapies.

Penile Cancer Radio- and Immunotherapy Clinical Exploration Study (PERICLES) is a recent phase 2, single-center trial that included 32 patients with penile squamous cell carcinoma treated with atezolizumab with or without radiation; it did not meet its primary endpoint, with a 1-year PFS of 12% (48). In this trial, the objective response rate was 16.6%, and HPV status was not predictive of clinical outcomes. Furthermore, in an ongoing basket phase 2 clinical trial by the French AcSé prospective program, 43 patients with relapsing or refractory penile squamous cell carcinoma who received nivolumab in the second-line or later setting were included. In this study, the objective response rate was 14%, with 2 patients with a complete response and 4 patients with a partial response. In addition, the 12-month overall survival rate was 34.5%, and median overall survival was 8.5 months (49). In a basket phase 2 clinical trial of nivolumab and ipilimumab in rare genitourinary tumors, among 5 evaluable patients with penile squamous cell carcinoma, 2 (40%) had stable disease (23). In a phase 1 study of cabozantinib, nivolumab, and ipilimumab, among 3 evaluable patients, 1 had a partial response and 2 had stable disease (22). Overall, our findings from a larger

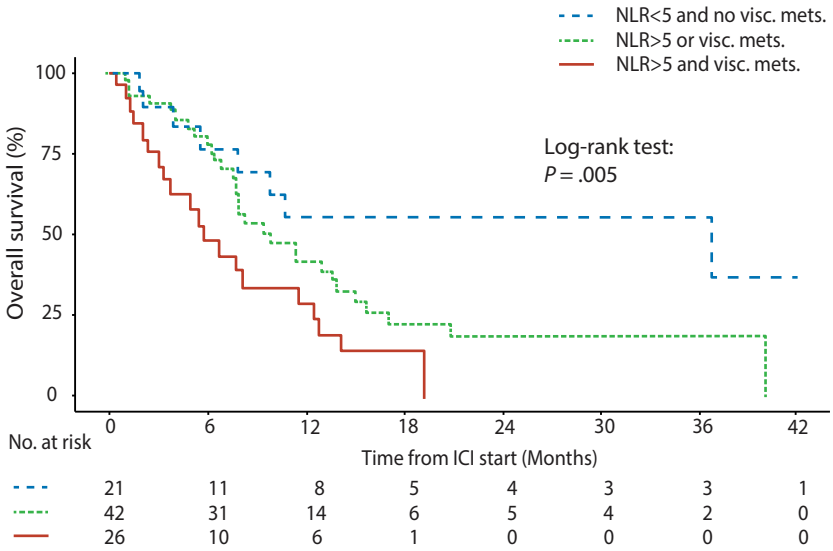

Figure 2. Overall survival by neutrophil/lymphocyte ratio (NLR) and status of visceral metastases. ICI = immune checkpoint inhibitor.

retrospective dataset are consistent with prior preliminary findings from ongoing clinical trials.

Notably, pembrolizumab is approved by the US Food and Drug Administration for all solid tumors with microsatellite instability (50,51) or high tumor mutation burden (≥10 mutations per megabase pair) (52-54). Unfortunately, microsatellite instability is exceedingly rare in penile squamous cell carcinoma (55), and the incidence of a tumor mutation burden of 10 mutations per megabase pair or higher has been reported to be 10% to 15% (56,57). The modest prevalence of both tumor-agnostic biomarkers in patients with penile squamous cell carcinoma may contribute to the limited activity of immune checkpoint inhibitors observed.

In a retrospective study, 17 patients with stage IV penile squamous cell carcinoma received platinum-based chemotherapy plus anti–epidermal growth factor receptor and anti–PD-1 immune checkpoint inhibitor therapy and had 2-year PFS and overall survival rates of 68.4% and 62.9%, respectively (20). In addition, 47% (n = 8) of the patients experienced grade 3 or higher treatment-related adverse events. The authors concluded that treatment combinations, including targeted agents, may exhibit more activity than chemoimmunotherapy combinations. These efforts have been advanced for the prospective evaluation of the combination of paclitaxel, ifosfamide, and cisplatin with nimotuzumab (anti–epidermal growth factor receptor) and triprilimab (an anti–PD-1 agent) as neoadjuvant therapy for locally advanced penile squamous cell carcinoma (ClinicalTrials.gov ID NCT04475016). It is crucial to recognize, however, that such combination regimens are associated with toxicities, and the contribution of individual components to efficacy is unclear in the absence of randomization. Nevertheless, the rarity of this orphan disease likely makes it infeasible to conduct large phase 2 or 3 randomized clinical trials. Although in our cohort combination therapy did not appear to improve clinical outcomes, the modest sample size limits this observation. Notably, combination therapy regimens demonstrated higher rates of treatment-related adverse events than immune checkpoint inhibitor monotherapy regimens.

In our cohort, only 1 in 4 patients with lymph node–only disease had responses and demonstrated improved clinical outcomes compared with visceral or bone involvement. As such, this cohort of patients may derive the most benefit. Patients receiving immune checkpoint inhibitors in the first-line or second-line or later settings had similar clinical outcomes, in part because of a potential inherent selection bias. It is possible that patients in our cohort who were treated with immune checkpoint inhibitors in the first-line setting were ineligible for platinum-based chemotherapy. We eagerly await the evaluation of immune checkpoint inhibitor treatment in the first-line setting for advanced penile squamous cell carcinoma and look forward to the subgroup analysis by metastatic sites. The ongoing HERCULES (ClinicalTrials.gov ID NCT04224740) (58) and EPIC (59) trials will investigate immune checkpoint inhibitors in the first-line setting and assess the impact of the addition of chemotherapy to pembrolizumab or cemiplimab for the management of penile squamous cell carcinoma, respectively. This investigation is of particular interest because only 2 patients in our study received chemoimmunotherapy, and only 1 responded to treatment.

Patients with HPV-positive head and neck squamous cell carcinoma (33) and cervical cancer (34) tend to have improved clinical outcomes when receiving immune checkpoint inhibitors. Furthermore, several reports have suggested that patients with HPV-positive penile squamous cell carcinoma have a more immunogenic microenvironment, which may translate to better clinical outcomes than their HPV-negative counterparts, making immunotherapy a potential focus for penile squamous cell carcinoma therapy (60,61). Acknowledging the modest sample sizes and the missing data, we did not observe markedly different clinical outcomes between patients with HPV-positive and HPV-negative penile squamous cell carcinoma. Other clinical and laboratory biomarkers were prognostic markers among patients with penile squamous cell carcinoma, however, in line with findings in other cancer types (43,44,46). For instance, neutrophil/lymphocyte ratio and visceral metastases were associated with differential clinical outcomes and may be useful tools for clinicians as biomarkers for patients likely to derive clinical benefit from immune checkpoint inhibitors.

Our study was limited by its retrospective nature and potential selection bias as patients were mostly treated at academic centers and in countries where immune checkpoint inhibitors are available. Moreover, most patients treated in our study received immune checkpoint inhibitor therapy for metastatic penile squamous cell carcinoma in second-line or later settings. Thus, our study should be carefully interrogated in this context. In addition, objective response rates were a mixture of objective response

assessments per RECIST criteria and investigator-based evaluations. Furthermore, the incidence of treatment-related adverse events may be affected by the treatment of certain patients outside of clinical trials, treatment discontinuation because of early progression, or suboptimal capture of events. Furthermore, the biomarker findings in this study are exploratory and require further validation in prospective cohorts. Finally, we did not have sufficient data to perform robust subanalyses of the association of clinical outcomes and tumor genomic or transcriptomic studies, PD-L1 immunohistochemistry status, or microsatellite instability status.

The findings of this international GSRGT cohort study of patients with advanced penile squamous cell carcinoma suggest that immune checkpoint inhibitor–based therapy is safe and associated with clinical benefit in a small subset of patients (objective response rate = 13% overall and 8.5% with monotherapy). Future biomarker-based translational studies are needed to elucidate our findings further and to benefit patients with penile squamous cell carcinoma receiving immune checkpoint inhibitor therapy. Given that penile squamous cell carcinoma is an orphan disease with suboptimal systemic therapy options and formidable challenges in trial accrual, a paradigm of high-quality, real-world studies to investigate the activity of new agents should be considered to make therapeutic advances.

Data availability

Patient-level data are publicly available and attached to the supplement of this manuscript.

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Funding

No funding was obtained for this study.

Conflicts of interest

Talal El Zarif reports honoraria from Art tempi. Amin H. Nassar acknowledges support from the Prime Center (SW-011); Consultant: The Oncology Research Information Exchange Network (ORIEN); Writing/Editor fees: editor of Elsevier Practice Update Bladder Cancer Center of Excellence. Bassel Nazha has served as an advisory board member for Exelixis, paid consultant for Cardinal Health, paid case discussant for AmerisourceBergen, and a speaker (education) from Medical Logix. Andrew W. Hahn is on the advisory board of Janssen and Intellisphere; travel support: Dava Oncology. Noha Abdel-Wahab received a K01 Mentored Research Scientist Development Award from the National Institute of Allergy and Infectious Diseases (K01AI163412) and received the University of Texas MD Anderson Cancer Center Institutional Research Grant, Division of Internal Medicine Development Award, and Survivorship Seed Money Award; received speaker fees and consulting fees from ChemoCentryx. Marco Maruzzo is on the advisory board of MSD,

BMS, Merck Serono, Astellas, Janssen-Cilag, Pfizer, Eli Lilly, EISAI, Bayer, and IPSEN. Yuanquan Yang is on the advisory board of Exelixis; Consulting and Honoraria: The Whiteoak Group, AstraZeneca; Research support to institution: Incyte, Amgen, Novartis. Lorenzo Antonuzzo reports research funding (to institution) from Novartis, Merck Serono, Bristol-Myers Squibb, and AstraZeneca; personal honoraria as invited speaker from Roche, Bristol-Myers Squibb, Servier, AstraZeneca, Amgen, and MSD; participation in advisory board for Amgen, Merk Serono, Ely Lilly, AstraZeneca, Incite, Bristol-Myers Squibb, Servier, and MSD. Rana R. McKay is a consultant/advisory board Aveo, AstraZeneca, Bayer, BMS, Calithera, Caris, Dendreon, Exelixis, Janssen, Lilly, Merck, Myovant, Novartis, Pfizer, Sorrento Therapeutics, SeaGen, Sanofi, Telix, and Tempus; research funding from Bayer, AstraZeneca, Oncternal, and Tempus. Alessio Cortellini acknowledges consultant/Scientific Advisory Board roles at MSD, AstraZeneca, and IQVIA; speaker fees from AstraZeneca, Pierre-Fabre, and EISAI; and writing/editor fees from BMS. Ravindran Kanesvaran is a speaker, on the advisory board, and received honoraria from AstraZeneca, BMS, MSD, Merck, Pfizer, Novartis, Astellas, Eisai, Ipsen, Bayer, and Johnson &Johnson. Alberto Farolfi has received personal honoraria for lectures from AstraZeneca, GSK-Tesaro, and Clovis and institutional research grants from Astellas, MSD, and Bayer; was on the advisory board of Janssen, AstraZeneca, and GSK-Tesaro. Matthew I. Milowsky stock and other ownership interests in Pfizer, Merck, Gilead Sciences; consulting or advisory role with Loxo/Lilly; research funding (institution) from Merck, Roche/Genentech, Bristol-Myers Squibb, Seagen, G1 Therapeutics, Mirati Therapeutics, Incyte, Alliance Foundation Trials, Alliance for Clinical Trials in Oncology, Clovis Oncology, Arvinas, ALX Oncology, Loxo, and Hoosier Cancer Research Network; and other relationships with Elsevier (co-editor, Clinical Genitourinary Cancer) and Medscape. Toni K. Choueiri reports institutional or personal paid or unpaid support for research, advisory boards, consultancy, and honoraria from Alkermes, AstraZeneca, Aravive, Aveo, Bayer, Bristol-Myers Squibb, Calithera, Circle Pharma, Eisai, EMD Serono, Exelixis, GlaxoSmithKline, Gilead, IQVA, Infinity, Ipsen, Janssen, Kanaph, Lilly, Merck, Nikang, Nuscan, Novartis, Pfizer, Roche, Sanofi, Scholar Rock, Surface Oncology, Takeda, Tempest, Up-To-Date, CME events (Peerview, OncLive, MJH, and others), outside the submitted work; institutional patents filed on molecular alterations and immunotherapy response/toxicity, and ctDNA; equity in Tempest, Pionyr, Osel, Precede Bio, CureResponse; committees include NCCN, GU Steering Committee, ASCO/ESMO, ACCRU, and KidneyCan; medical writing and editorial assistance support may have been funded by Communications companies in part; no speaker's bureau; mentored several non-US citizens on research projects with potential funding (in part) from non-US sources/foreign components. The institution (Dana-Farber Cancer Institute) may have received additional independent funding of drug companies or royalties potentially involved in research around the subject matter. T. K. Choueiri is supported in part by the Dana-Farber/Harvard Cancer Center Kidney SPORE (2P50CA101942-16) and Program 5P30CA006516-56, the Kohlberg Chair at Harvard Medical School and the Trust Family, Michael Brigham, Pan Mass Challenge, Hinda and Arthur Marcus Fund and Loker Pinard Funds for Kidney Cancer Research at DFCI. Guru P. Sonpavde is on the advisory board of EMD Serono, BMS, Merck, Seattle Genetics/Astellas, Janssen, Bicycle Therapeutics, Pfizer, Gilead, Scholar Rock, G1 Therapeutics, Eli Lilly/Loxo Oncology, Lucence Health, IMV, and Vial; a consultant/scientific advisory board of Suba Therapeutics, Syapse; research support to institution from Sanofi, AstraZeneca, Gilead, Helsinn, Lucence, EMD Serono, Jazz Therapeutics, Genecentric; is a speaker for BIO—INFORMAÇÃO BRASILEIRA DE ONCOLOGIA Ltd, Seagen, Gilead, Natera, Exelixis; data safety monitoring committee (honorarium) from Mereo; Employment: Spouse employed by Myriad; Writing/Editor fees: Uptodate, editor of Elsevier Practice Update Bladder Cancer Center of Excellence

The remaining authors report that there are no potential competing interests pertaining to this work.

Acknowledgement

The authors thank the patients and families whose contributions have made this study possible. We also thank the investigators of the Global Society of Rare Genitourinary Tumors and staff members at the participating centers who have contributed to our work. This work has been presented as a rapid oral presentation at the American Society of Clinical Oncology Genitourinary Cancers Symposium 2023.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7-33.
2. Clark PE, Spiess PE, Agarwal N, et al.; National Comprehensive Cancer Network. Penile cancer: clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2013;11(5):594-615.
3. National Comprehensive Care Network. *NCCN Guidelines: Penile Cancer*. https://www.nccn.org/guidelines/. Accessed March 1, 2023.
4. Joshi VB, Chadha J, Chahoud J. Penile cancer: updates in systemic therapy. *Asian J Urol*. 2022;9(4):374-388.
5. Pagliaro LC, Williams DL, Daliani D, et al. Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: a phase II study. *J Clin Oncol*. 2010;28(24):3851-3857.
6. Pettaway CA, Pagliaro L, Theodore C, Haas G. Treatment of visceral, unresectable, or bulky/unresectable regional metastases of penile cancer. *Urology*. 2010;76(2 suppl 1):S58-S65.
7. Dickstein RJ, Munsell MF, Pagliaro LC, Pettaway CA. Prognostic factors influencing survival from regionally advanced squamous cell carcinoma of the penis after preoperative chemotherapy. *BJU Int*. 2016;117(1):118-125.
8. Sharma P, Djajadiningrat R, Zargar-Shoshtari K, et al. Adjuvant chemotherapy is associated with improved overall survival in pelvic node-positive penile cancer after lymph node dissection: a multi-institutional study. *Urol Oncol*. 2015;33(11):496.e17-496.e23.
9. Pond GR, Di Lorenzo G, Necchi A, et al. Prognostic risk stratification derived from individual patient level data for men with advanced penile squamous cell carcinoma receiving first-line systemic therapy. *Urol Oncol*. 2014;32(4):501-508.
10. Bandini M, Ahmed M, Basile G, et al. Author correction: a global approach to improving penile cancer care. *Nat Rev Urol*. 2022;19(4):253.
11. Wang J, Pettaway CA, Pagliaro LC. Treatment for metastatic penile cancer after first-line chemotherapy failure: analysis of response and survival outcomes. *Urology*. 2015;85(5):1104-1110.
12. Di Lorenzo G, Federico P, Buonerba C, et al. Paclitaxel in pretreated metastatic penile cancer: final results of a phase 2 study. *Eur Urol* 2011;60(6):1280-1284.
13. Challapalli A, Pearson S, Mitra AV, et al. A phase II trial of cabazitaxel as second line chemotherapy in relapsed locally

advanced and/or metastatic carcinoma of the penis. *J Int Med Res*. 2019;47(10):4664-4672.
14. Trafalis DT, Alifieris CE, Kalantzis A, Verigos KE, Vergadis C, Sauvage S. Evidence for efficacy of treatment with the anti-PD-1 mab nivolumab in radiation and multichemorefractory advanced penile squamous cell carcinoma. *J Immunother*. 2018;41(6):300-305.
15. Chahoud J, Skelton WP 4th, Spiess PE, et al. Case report: two cases of chemotherapy refractory metastatic penile squamous cell carcinoma with extreme durable response to pembrolizumab. *Front Oncol*. 2020;10:615298.
16. Denis C, Sakalihasan S, Frères P, Withofs N, Sautois B. Cemiplimab for cisplatin resistant metastatic penile cancer. *Case Rep Oncol*. 2021;14(2):972-976.
17. Baweja A, Mar N. Metastatic penile squamous cell carcinoma with dramatic response to combined checkpoint blockade with ipilimumab and nivolumab. *J Oncol Pharm Pract*. 2021;27(1):212-215.
18. Proietti I, Skroza N, Filippi L, et al. Metastatic penile squamous cell carcinoma successfully treated with cemiplimab in an HIV patient. *Dermatol Ther*. 2021;34(2):e14744.
19. Du Y, Zhang X, Zhang Y, et al. PD-1 inhibitor treatment in a penile cancer patient with MMR/MSI status heterogeneity: a case report. *Hum Vaccin Immunother*. 2022;18(6):2121122.
20. Yan R, Ma H, Jiang L, et al. First-line programmed death receptor-1 (PD-1) inhibitor and epidermal growth factor receptor (EGFR) blockade, combined with platinum-based chemotherapy, for stage IV penile cancer. *BJU Int*. 2023;131(2):198-207.
21. Hahn AW, Chahoud J, Campbell MT, et al. Pembrolizumab for advanced penile cancer: a case series from a phase II basket trial. *Invest New Drugs*. 2021;39(5):1405-1410.
22. Apolo AB, Nadal R, Girardi DM, et al. Phase I study of cabozantinib and nivolumab alone or with ipilimumab for advanced or metastatic urothelial carcinoma and other genitourinary tumors. *J Clin Oncol*. 2020;38(31):3672-3684.
23. McGregor BA, Campbell MT, Xie W, et al. Results of a multicenter, phase 2 study of nivolumab and ipilimumab for patients with advanced rare genitourinary malignancies. *Cancer*. 2021;127(6):840-849.
24. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med*. 2018;379(4):341-351.
25. Udager AM, Liu TY, Skala SL, et al. Frequent PD-L1 expression in primary and metastatic penile squamous cell carcinoma: potential opportunities for immunotherapeutic approaches. *Ann Oncol*. 2016;27(9):1706-1712.
26. Chu C, Yao K, Lu J, et al. Immunophenotypes based on the tumor immune microenvironment allow for unsupervised penile cancer patient stratification. *Cancers (Basel)*. 2020;12(7):1796.
27. Cocks M, Taheri D, Ball MW, et al. Immune-checkpoint status in penile squamous cell carcinoma: a North American cohort. *Hum Pathol*. 2017;59:55-61.
28. De Bacco MW, Carvalhal GF, MacGregor B, et al. PD-L1 and p16 expression in penile squamous cell carcinoma from an endemic region. *Clin Genitourin Cancer*. 2020;18(3):e254-e259.
29. Ottenhof SR, Djajadiningrat RS, Thygesen HH, et al. The prognostic value of immune factors in the tumor microenvironment of penile squamous cell carcinoma. *Front Immunol*. 2018;9:1253.
30. Deng C, Li Z, Guo S, et al. Tumor PD-L1 expression is correlated with increased TILs and poor prognosis in penile squamous cell carcinoma. *Oncoimmunology*. 2017;6(2):e1269047.
31. Davidsson S, Carlsson J, Giunchi F, et al. PD-L1 expression in men with penile cancer and its association with clinical outcomes. *Eur Urol Oncol*. 2019;2(2):214-221.
32. Montella M, Sabetta R, Ronchi A, et al. Immunotherapy in penile squamous cell carcinoma: present or future? Multi-target analysis of programmed cell death ligand 1 expression and microsatellite instability. *Front Med (Lausanne)*. 2022;9:874213.
33. Ferris RL, Blumenschein G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375(19):1856-1867.
34. Colombo N, Dubot C, Lorusso D, et al.; KEYNOTE-826 Investigators. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med*. 2021;385(20):1856-1867.
35. Schlenker B, Schneede P. The role of human papilloma virus in penile cancer prevention and new therapeutic agents. *Eur Urol Focus*. 2019;5(1):42-45.
36. ClinicalTrials.gov. *A Study of Avelumab in Penile Cancer Who Are Unfit for or Have Progressed After Platinum-Based Chemotherapy*. https://clinicaltrials.gov/ct2/show/NCT03391479. Updated June 18, 2023. Accessed January 1, 2023.
37. ClinicalTrials.gov. *PEnile Cancer Radio- and Immunotherapy CLinical Exploration Study (PERICLES)*. https://clinicaltrials.gov/ct2/show/NCT03686332. Updated May 10, 2023. Accessed January 1, 2023.
38. ClinicalTrials.gov. *Maintenance Avelumab Immunotherapy in Patients With Locally Advanced or Metastatic Squamous Cell Penile Carcinoma (PULSE)*. https://clinicaltrials.gov/ct2/show/NCT03774901. Updated April 21, 2023. Accessed January 1, 2023.
39. ClinicalTrials.gov. *Pembrolizumab Combined With Cisplatin-based Chemotherapy as First-line Systemic Therapy in Advanced Penile Cancer (HERCULES)*. https://clinicaltrials.gov/ct2/show/NCT04224740. Updated June 18, 2023. Accessed January 1, 2023.
40. ClinicalTrials.gov. *Efficacy of INCMGA00012 in Penile Squamous Cell Carcinoma (ORPHEUS) (ORPHEUS)*. https://clinicaltrials.gov/ct2/show/NCT04231981. Updated January 19, 2023. Accessed January 1, 2023.
41. ClinicalTrials.gov. *A Phase II Study of Ipilimumab, Cabozantinib, and Nivolumab in Rare Genitourinary Cancers (ICONIC)*. https://clinicaltrials.gov/ct2/show/NCT03866382. Accessed January 1, 2023.
42. Padua TC, Marandino L, Raggi D, et al. A systematic review of published clinical trials in the systemic treatment of adrenocortical carcinoma: an initiative led on behalf of the global society of rare genitourinary tumors. *Clin Genitourin Cancer*. 2023;21(1):1-7.
43. Nassar AH, Mouw KW, Jegede O, et al. A model combining clinical and genomic factors to predict response to PD-1/PD-L1 blockade in advanced urothelial carcinoma. *Br J Cancer*. 2020;122(4):555-563.
44. Lalani AA, Xie W, Martini DJ, et al. Change in Neutrophil-to-lymphocyte ratio (NLR) in response to immune checkpoint blockade for metastatic renal cell carcinoma. *J Immunother Cancer*. 2018;6(1):5.
45. Khaki AR, Li A, Diamantopoulos LN, et al. A new prognostic model in patients with advanced urothelial carcinoma treated with first-line immune checkpoint inhibitors. *Eur Urol Oncol*. 2021;4(3):464-472.
46. Valero C, Lee M, Hoen D, et al. Pretreatment neutrophil-to-lymphocyte ratio and mutational burden as biomarkers of tumor response to immune checkpoint inhibitors. *Nat Commun*. 2021;12(1):729.
47. Murthy NY, Rauthan A, Patil P, et al. Neutrophil-lymphocyte ratio as a prognostic marker in a resource constraint setting for metastatic malignancies treated with immune checkpoint inhibitors. *Ann Oncol*. 2019;30(suppl 11):XI5.

48. de Vries HM, De Feijter J, Bekers E, et al. Clinical results of PERICLES: a phase II trial investigating atezolizumab +/− radiotherapy for advanced squamous cell carcinoma of the penis. *J Clin Oncol*. 2022;40(6_suppl):3–3.
49. Pouessel D, Beylot-Barry M, Esma SB, et al. 715P Nivolumab in pretreated metastatic penile squamous cell carcinoma: results of the penile cohort from the French AcSé prospective program. *Ann Oncol*. 2021;32(suppl 5):S720.
50. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26):2509-2520.
51. Lemery S, Keegan P, Pazdur R. First FDA approval agnostic of cancer site—when a biomarker defines the indication. *N Engl J Med*. 2017;377(15):1409-1412.
52. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol*. 2020;21(10):1353-1365.
53. Andre T, Shiu KK, Kim TW, et al.; KEYNOTE-177 Investigators. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383(23):2207-2218.
54. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2020;38(1):1-10.
55. Stoehr R, Wendler O, Giedl J, et al. No evidence of microsatellite instability and loss of mismatch-repair-protein expression in squamous cell carcinoma of the penis. *Pathobiology*. 2019;86(2-3):145-151.
56. Spiess PE, Li R, Grivas P, et al. Penile squamous cell carcinoma (PSCC) with elevated tumor mutational burden (TMB): a genomic landscape study. *J Clin Oncol*. 2023;41(6_suppl):4–4.
57. Nazha B, Wu S, Brown JT, et al. Comprehensive genomic profiling of penile squamous cell carcinoma and impact of HPV status on immune-checkpoint inhibition-related biomarkers. *J Clin Oncol*. 2022;40(6_suppl):4–4.
58. Maluf FC, Trindade K, Preto DDA, et al. A phase II trial of pembrolizumab combined with platinum-based chemotherapy as first-line systemic therapy in advanced penile cancer: HERCULES (LACOG 0218) trial. *J Clin Oncol*. 2023;41(6_suppl):TPS14-TPS14.
59. Renninson E, Challapalli A, Foulstone E, et al.; EPIC Trial Collaborators A phase II trial of cemiplimab alone or in combination with standard of care chemotherapy in locally advanced or metastatic penile carcinoma (EPIC Trial). *J Clin Oncol*. 2022;40(16_suppl):TPS5094-TPS5094.
60. Djajadiningrat RS, Jordanova ES, Kroon BK, et al. Human papillomavirus prevalence in invasive penile cancer and association with clinical outcome. *J Urol*. 2015;193(2):526-531.
61. Chahoud J, Netto F, Lazcano Segura R, et al. Tumor immune microenvironment alterations in penile squamous cell carcinoma using multiplex immunofluorescence and image analysis approaches. *J Clin Oncol*. 2020;38(6_suppl):4–4.