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Rui-Zhi Liu
West China Hospital, Sichuan University
Jia-Yao Wang
West China Hospital, Sichuan University
Li-Li Yang
West China Hospital, Sichuan University
Ming-Yi Zhang
West China Hospital, Sichuan University
Jia-Qi Liu
West China Hospital, Sichuan University
Shuang Zhang
West China Hospital, Sichuan University
Hong-Shuai Li
West China Hospital, Sichuan University
Ji-Yan Liu
liujiyan1972@163.com

West China Hospital, Sichuan University

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Case Report: Two Cases Of Partial Response to Anti-EGFR Antibody-drug Conjugate Plus PD-1 Blockade in Advanced Penile Squamous Cell Carcinoma

Rui-Zhi Liu[1, 2, †], Jia-Yao Wang[1, †], Li-Li Yang[3, †], Ming-Yi Zhang[1], Jia-Qi Liu[1], Shuang Zhang[1], Hong-Shuai Li[1, *], Ji-Yan Liu[1, *]

[1]Department of Biotherapy, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China

[2]School of Medical and Life Sciences, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China

[3]Department of Medical Oncology, Chengdu Shangjinnanfu Hospital, West China Hospital of Sichuan University, Chengdu, Sichuan, China

[†]These authors have contributed equally to this work

[*]Correspondence: Hong-Shuai Li, MD, PhD, Department of Biotherapy, Cancer Center, West China Hospital, Sichuan University, No. 37 Guoxue Lane, Wuhou District, Chengdu 610041, Sichuan, China (e-mail: lihongshuai456@163.com).

[*]Correspondence: Ji-Yan Liu, MD, PhD, Department of Biotherapy, Cancer Center, West China Hospital, Sichuan University, No. 37 Guoxue Lane, Wuhou District, Chengdu 610041, Sichuan, China (e-mail: liujiyan1972@163.com).

Abstract

Background: Advanced penile squamous cell carcinoma (PSCC) is a rare malignancy with limited effective systemic treatment options. The development of new treatment strategies is therefore particularly important in this setting.

Case presentation: We report two cases diagnosed with advanced PSCC and bilateral inguinal lymph node metastases. The tumor was EGFR-positive, HPV-negative, and had a PD-L1 tumor proportion score of 1%, a TP53 p.Q317* mutation, low tumor mutational burden, and microsatellite-stable status. After thorough and extensive communication, the patients and their families agreed to assume the risks and requested first-line therapy with an anti-EGFR ADC (Becotatug Vedotin) plus a PD-1 inhibitor (Pucotenlimab). After treatment, the patients achieved a partial response according to RECIST v1.1, accompanied by marked clinical regression of the inguinal lesion. Treatment-related adverse events were limited to manageable grade 1 decreased appetite, rash, fatigue, and hepatic dysfunction.

Conclusions: These cases suggest that anti-EGFR ADC plus PD-1 inhibition may represent a feasible and biologically rational first-line treatment option for advanced PSCC. Further prospective evaluation of this strategy is warranted.

Keywords: penile squamous cell carcinoma, antibody-drug conjugate, EGFR, PD-1 blockade, immunotherapy

Introduction

Penile squamous cell carcinoma (PSCC) is a rare malignancy, accounting for approximately 0.4%–0.6% of all male cancers in the United States and Europe, with a higher incidence in developing regions of Asia, Africa, and South America[1]. A subset of PSCC is associated with human papillomavirus (HPV) infection, whereas other cases arise through HPV-independent pathways. Tumor stage is critically important in this disease, and prognosis is strongly influenced by nodal status. The overall 5-year survival rate is approximately 50%, exceeding 85% in patients without lymph node metastasis, declining to 29%–40% in those with nodal involvement, and approaching 0% in patients with pelvic lymph node metastases[2,3]. Current guidelines primarily recommend chemotherapy-based approaches for advanced disease. However, the efficacy of conventional cytotoxic agents in PSCC is limited, with commonly used single agents generally producing response rates below 20%[4]. Although combination regimens have shown relatively higher activity, with TIP regarded as the preferred option and PF also used in selected patients, reported response rates remain modest and treatment-related toxicities are often substantial[5]. These limitations underscore the need for new treatment approaches that are both biologically informed and clinically feasible in this rare genitourinary tumor.

Over the past decade, EGFR-directed therapies and immune checkpoint inhibition have emerged as two potentially relevant therapeutic directions in PSCC. EGFR signaling appears biologically important in penile squamous carcinogenesis and we previously reported universal EGFR expression across tumor specimens from nearly 200 patients

with PSCC treated at our institution, with overexpression observed in 92% of cases[6,7]. In parallel, anti-EGFR monoclonal antibody-based approaches have shown preliminary clinical activity[8-12]. Similarly, immune checkpoint blockade has demonstrated promise in selected patients with advanced penile cancer[13-15]. However, currently available EGFR-directed and PD-1-based approaches have generally relied on conventional chemotherapy, either as separate combination strategies or together in triplet regimens[16,17]. Although these approaches may enhance antitumor efficacy, they may also increase treatment complexity and toxicity.

Anti-EGFR antibody-drug conjugates (ADCs) represent an appealing alternative by coupling EGFR-directed targeting with intracellular delivery of a cytotoxic payload[18]. This design may exploit EGFR expression in PSCC through selective binding, internalization, and intracellular release of the payload, thereby enabling more tumor-selective drug delivery[19]. Beyond targeted delivery, ADCs may also potentiate immune checkpoint blockade[20]. Conceptually, this provides a strong rationale for combining anti-EGFR ADCs with PD-1 inhibition in PSCC, with the potential to improve efficacy while limiting off-target toxicity. Despite this rationale, clinical evidence supporting anti-EGFR ADC plus PD-1 inhibition in advanced PSCC remains lacking. Here, we describe a patient with advanced PSCC who was treated with this combination as first-line therapy and achieved an early partial response.

Case presentation A

The first patient is a 38-year-old man with no significant past medical history first noted enlargement of the left inguinal lymph node in June 2025. In December 2025, progressive enlargement of the right inguinal lymph nodes was also observed. In January 2026, he underwent excisional biopsy of a left inguinal lymph node at a local hospital, which demonstrated metastatic moderately differentiated keratinizing squamous cell carcinoma. At presentation to our center, physical examination revealed a small ulcerative penile lesion with scant purulent discharge. Histopathologic assessment of the left inguinal lymph node confirmed invasive keratinizing squamous cell carcinoma. Hematoxylin and eosin staining showed the characteristic morphologic features of keratinizing squamous cell carcinoma, and EGFR immunohistochemistry using a Roche assay (clone 5B7) demonstrated positive tumor cell expression (**Figure 1.1A-B**). PD-L1 expression was also evaluated by immunohistochemistry using a Roche assay (clone SP263) and showed a tumor proportion score (TPS) of 1% (**Figure 1.1C**). Molecular testing using next-generation sequencing revealed a TP53 p.Q317 mutation, low tumor mutational burden (1.65 muts/Mb), and microsatellite-stable status. CT performed at our institution showed bilateral inguinal lymphadenopathy with heterogeneous enhancement, small bilateral hydroceles, and subcutaneous soft tissue swelling involving the perineum and proximal left thigh. Taken together, these clinical, radiologic, and pathologic findings supported a diagnosis of PSCC with bilateral inguinal lymph node metastases, corresponding to cT1N2M0, stage IIIB. Surgical evaluation determined that the inguinal disease was unresectable because of vascular invasion; therefore, systemic therapy was

administered with palliative rather than neoadjuvant intent. He had an Eastern Cooperative Oncology Group performance status of 1 and was considered suitable for first-line chemotherapy, but declined conventional chemotherapy because of concerns about substantial treatment-related toxicity.

Given the limited effective systemic treatment options for advanced PSCC and the patient's refusal of chemotherapy, the available treatment options were discussed in detail with the patient, who ultimately chose first-line therapy with an anti-EGFR ADC (Becotatug Vedotin, 2.0 mg/kg intravenously every 3 weeks) plus a PD-1 inhibitor (Pucotenlimab, 200 mg intravenously every 3 weeks). The first cycle was administered on February 14, 2026, followed by cycle 2 on March 5, 2026, cycle 3 on March 26, 2026, cycle 4 on April 16, 2026, and cycle 5 on May 7, 2026.

An early clinical response was observed during treatment. After the first cycle, shrinkage of the inguinal tumor margin became apparent. Following the second cycle, the inguinal lesion had nearly regressed clinically, with extrusion of necrotic tumor material and progressive restoration of the surrounding tissue architecture (**Figure 2.1 A**). Computed tomography performed after 2 cycles demonstrated a partial response according to RECIST v1.1, which was sustained on follow-up CT after cycle 4 (**Figure 2.1 B**). Treatment-related adverse events were limited to grade 1 decreased appetite, fatigue, and hepatic dysfunction, with hepatic toxicity limited to mild ALT elevation (peak 49 U/L); all events were manageable, and no acneiform rash or peripheral neuropathy was observed. A timeline of the patient's clinical course is provided in **Figure 3**.

Case presentation B

The second patient presented with painless penile swelling, ulceration, and purulent discharge in November 2025 with no apparent precipitating factors. He initially sought treatment at a local health clinic; the specific treatment details are unknown. Due to poor efficacy, the area of penile ulceration enlarged, and began to develop white secretions. On April 8, 2026, an excisional biopsy of the penile neoplasm was performed at an outside hospital, and the pathological diagnosis confirmed a well-differentiated squamous cell carcinoma.

The patient was subsequently referred to our hospital for further management. Physical examination revealed a massive penile mass encasing the penis, characterized by penile swelling, ulceration, white secretions, and inguinal lymphadenopathy. Pathological examination of the penile mass biopsy showed squamous epithelial dysplasia and formation of squamous cell carcinoma (SCC). Immunohistochemistry (IHC) was positive for EGFR (**Figure 1.2A-B**), and the PD-L1 Combined Positive Score (CPS) was 15 (**Figure 1.2C**). Genetic testing revealed a TP53 p.E271K mutation, microsatellite stable (MSS) status, and a low tumor mutational burden (TMB: 2.43 mut/Mb). A CT scan at our institution revealed a penile space-occupying lesion with multiple enlarged lymph nodes in the bilateral inguinal, obturator, and external iliac vascular regions, highly suggestive of malignancy with lymph node metastasis. Based on the clinical presentation, imaging findings, and pathological results, a diagnosis of penile squamous cell carcinoma with bilateral inguinal lymph node metastasis was established, corresponding to cT4N3M0,

stage IV. Given the extensive regional lymph node metastases, the patient was classified as having locally advanced penile cancer. Due to the large volume of the local lesion and invasion into surrounding tissues, radical surgical resection was not feasible and direct surgical excision was technically difficult.

After thorough discussion with the patient regarding currently available systemic treatment options, the patient refused standard chemotherapy and requested off-label therapy, independently opting for a combination of an ADC and a PD-1 inhibitor. The specific regimen consisted of Vebecotamab 135 mg IV plus Pucotenlimab 200 mg IV, administered once every 3 weeks (q3w). The first cycle was administered on May 8, 2026. Following this first cycle, the penile tumor showed a marked visible reduction, with significant improvement in ulceration and purulent discharge (**Figure 2.2 A**). The second cycle was completed on May 29, 2026. Following two cycles of systemic therapy, follow-up CT scans demonstrated shrinkage of both the primary lesion and the metastatic lymph nodes. The radiological response was evaluated as Partial Response (PR) (**Figure 2.2 B**). The only treatment-related adverse event was a Grade 1 rash. The patient's clinical course is illustrated in **Figure 3**.

Discussion

These two cases highlight the potential clinical efficacy of an anti-EGFR ADC plus PD-1 inhibitor as first-line therapy for advanced PSCC. The treatment achieved an early partial response alongside marked local improvement and manageable toxicity. In advanced PSCC, rapidly progressing nodal disease frequently results in ulceration, infection, pain,

and bleeding, leading to a substantial decline in quality of life; thus, early local control is particularly meaningful. Notably, the response in these patients extended beyond radiographic shrinkage to include the visible regression of inguinal lesions, demonstrating the potential of this combination to provide robust local disease control.

Current data in advanced penile cancer indicate that EGFR-directed therapies are biologically relevant. EGFR overexpression and activation of the EGFR-RAS signaling pathway have been implicated in PSCC, and this biologic rationale was also reflected in our patient, whose tumor was EGFR-positive. In these cases, EGFR positivity was identified by immunohistochemistry rather than by next-generation sequencing. This difference between protein-level and gene-level assessment is not unexpected, as EGFR overexpression may occur in the absence of a detectable genomic alteration and may reflect transcriptional or post-transcriptional regulation rather than a DNA-level change. Recently anti-EGFR monoclonal antibody-based regimens have shown encouraging activity in advanced or locally advanced PSCC, including an early retrospective series of 17 patients with locally advanced or metastatic penile squamous cell carcinoma, in which cetuximab-based therapy demonstrated antitumor activity and produced partial responses in 4 patients, as well as several previously published observations, including our own studies, demonstrating marked responses to anti-EGFR monoclonal antibody-based treatment. However, these strategies have generally incorporated chemotherapy as an essential backbone. Although such regimens may improve antitumor efficacy, they may

also increase treatment complexity and treatment-related toxicity, particularly in patients with poor local control, prior treatment exposure, or compromised general condition.

Against this background, anti-EGFR ADCs are of particular interest because they offer a mechanistically distinct way to exploit EGFR expression in PSCC. Becotatug Vedotin is a novel EGFR-targeted antibody-drug conjugate composed of a humanized anti-EGFR monoclonal antibody linked to MMAE via a valine-citrulline linker, and has shown promising efficacy with manageable toxicity in previously treated recurrent/metastatic nasopharyngeal carcinoma[21-23]. By enabling tumor-selective targeting and intracellular delivery of a cytotoxic payload, anti-EGFR ADCs may represent a more precise EGFR-directed strategy than currently available monoclonal antibody-based approaches that generally require combination with chemotherapy. This design may improve drug delivery while potentially limiting off-target toxicity. In addition, although targeted payload delivery is likely the principal mechanism, some anti-EGFR ADC constructs may also retain limited EGFR-directed biologic activity through their antibody component[24].

The rationale for combining anti-EGFR ADCs with PD-1 blockade is complementary rather than merely parallel. Accumulating evidence suggests that ADCs can augment antitumor immunity by inducing immunogenic cell death and subsequent tumor antigen release, thereby promoting dendritic cell activation, antigen presentation, and T-cell priming[25,26]. In this framework, ADCs may do more than selectively deliver cytotoxic therapy; they may also render tumors more immunologically visible and thus more

susceptible to PD-1 inhibition. This combinatorial rationale is further supported by progress in other genitourinary malignancies, particularly urothelial carcinoma. In previously untreated advanced urothelial carcinoma, enfortumab vedotin plus pembrolizumab demonstrated clear superiority over platinum-based chemotherapy, with improved progression-free and overall survival, higher objective response rates, and increased complete response rates, thereby establishing ADC plus PD-1/PD-L1 blockade as a clinically meaningful therapeutic strategy[27]. Similarly, in the phase Ib/II RC48-C014 study, disitamab vedotin plus toripalimab showed promising activity in locally advanced or metastatic urothelial carcinoma, with a high objective response rate, durable disease control, encouraging long-term survival outcomes, and a manageable safety profile, further supporting the clinical feasibility of ADC-immunotherapy combinations in genitourinary tumors[28]. This concept may be particularly relevant in the present case, in which the tumor had a PD-L1 tumor proportion score of only 1%, low tumor mutational burden, and microsatellite-stable status, all of which are generally associated with a lower likelihood of benefit from immune checkpoint blockade alone[29]. Although this mechanism remains inferential, it provides a biologically plausible explanation for the early activity observed with anti-EGFR ADC plus PD-1 inhibition in this patient.

Taken together, these mechanistic considerations and the early clinical response observed in our patient suggest that anti-EGFR ADC plus PD-1 inhibition may represent a potentially relevant therapeutic strategy in advanced PSCC. This possibility is

particularly important in penile cancer, where therapeutic development remains difficult. Compared with more common genitourinary malignancies, prospective trials in penile cancer remain scarce, and therapeutic advances often arise from small series, institutional experience, and translational insights rather than from large randomized studies. In this setting, clinically informative cases may be especially valuable when they highlight new treatment options or emerging clinical issues that warrant timely dissemination. We believe the present cases fit that role by illustrating the potential clinical activity of anti-EGFR ADC plus PD-1 inhibition as a first-line strategy in advanced PSCC. Notably, patients with HPV-negative, TP53-mutated and TMB-low PSCC have historically demonstrated dismal outcomes[30-32]. In stark contrast, this cases report reveals a partial response to the combination of an EGFR-directed ADC and PD-1 blockade, which suggests that our regimen offers a viable therapeutic avenue for patients typically refractory to immunotherapy. Furthermore, as a chemotherapy-free strategy, it provides a markedly improved safety profile, representing a significant clinical advantage.

This report is limited by its single-patient nature and relatively short follow-up, and therefore no firm conclusions can be drawn regarding the magnitude or durability of benefit associated with this regimen. In addition, because Becotatug Vedotin and anti-PD-1 therapy were initiated simultaneously, the individual contribution of each agent cannot be determined from this case. Given the known activity of PD-1 monotherapy in advanced PSCC, the observed response cannot be attributed with certainty to either agent alone or to the combination. Nevertheless, our group is also exploring this strategy in the

second-line and neoadjuvant settings and has applied for a related clinical trial, which may help further clarify its activity, safety, and potential clinical utility in PSCC. Clinical trial number: not applicable.

Conclusion

In summary, anti-EGFR ADC plus PD-1 inhibition produced an early partial response in patients with advanced PSCC treated in the first-line setting, with only manageable grade 1 toxicities. This observation highlights a novel treatment option in advanced PSCC and supports further prospective evaluation of this biologically rational therapeutic strategy.

Data Availability

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

This study was conducted in strict accordance with the Declaration of Helsinki. Both patients described above were enrolled in the same clinical trial evaluating systemic therapy for PSCC, which was approved by the Ethics Committee on Clinical Trial, West China Hospital of Sichuan University (Approval No. 2025(1385)). The trial is registered at ClinicalTrials.gov (NCT07054307). Written informed consent for participation in this study was obtained from both patients.

Consent to publish

Written informed consent for publication of this case report was obtained from both patients. This includes consent for the publication of clinical details, pathological findings, and any accompanying images.

Author contributions

RZ L: Writing – review & editing, Writing – original draft, Visualization. HS L: Writing – review & editing, Writing – original draft, Conceptualization. JY W: Writing – review & editing, Writing – original draft. MY Z: Writing – review & editing, Writing – original draft. JQ L: Writing – review & editing. S Z: Writing – review & editing. JY L: Writing – review & editing, Writing – original draft, Conceptualization.

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Conflict of interest

The authors declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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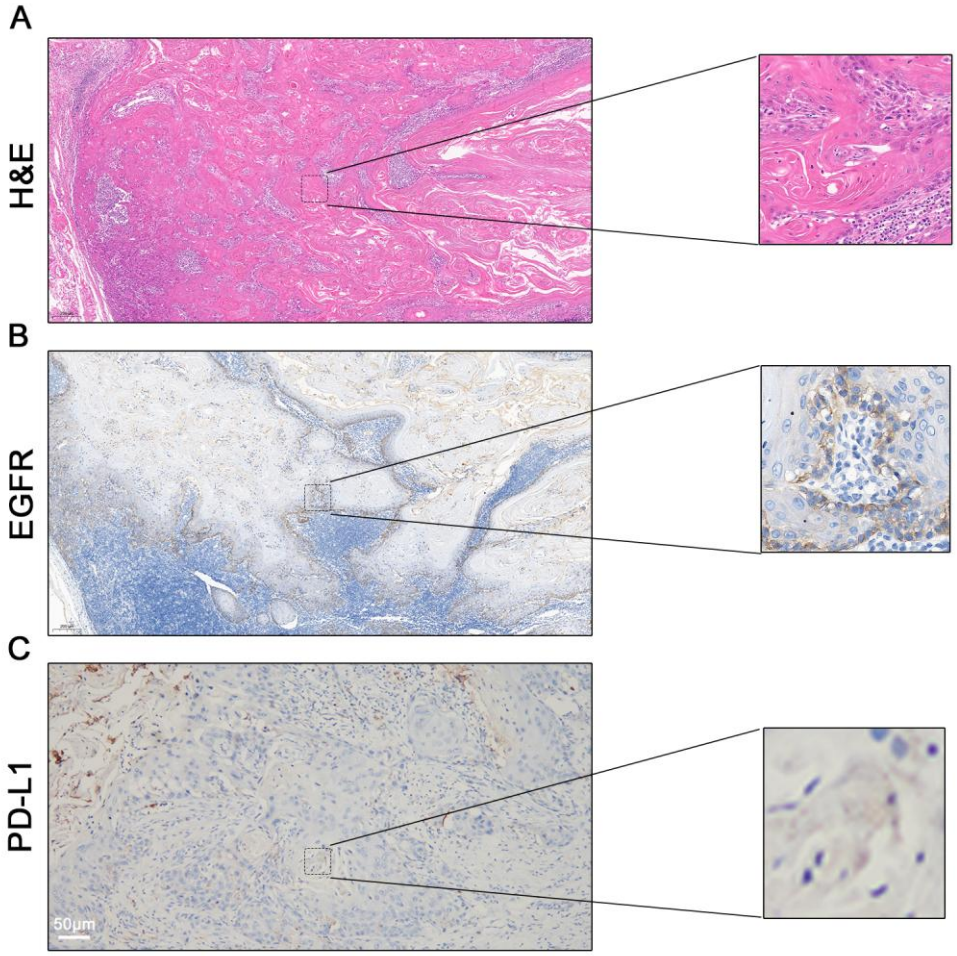


Figure 1.1 Representative histopathologic and immunohistochemical findings. (A) Hematoxylin and eosin staining showing invasive keratinizing squamous cell carcinoma. (B) EGFR immunohistochemistry demonstrating positive expression in tumor cells. (C) PD-L1 immunohistochemistry showing low expression.

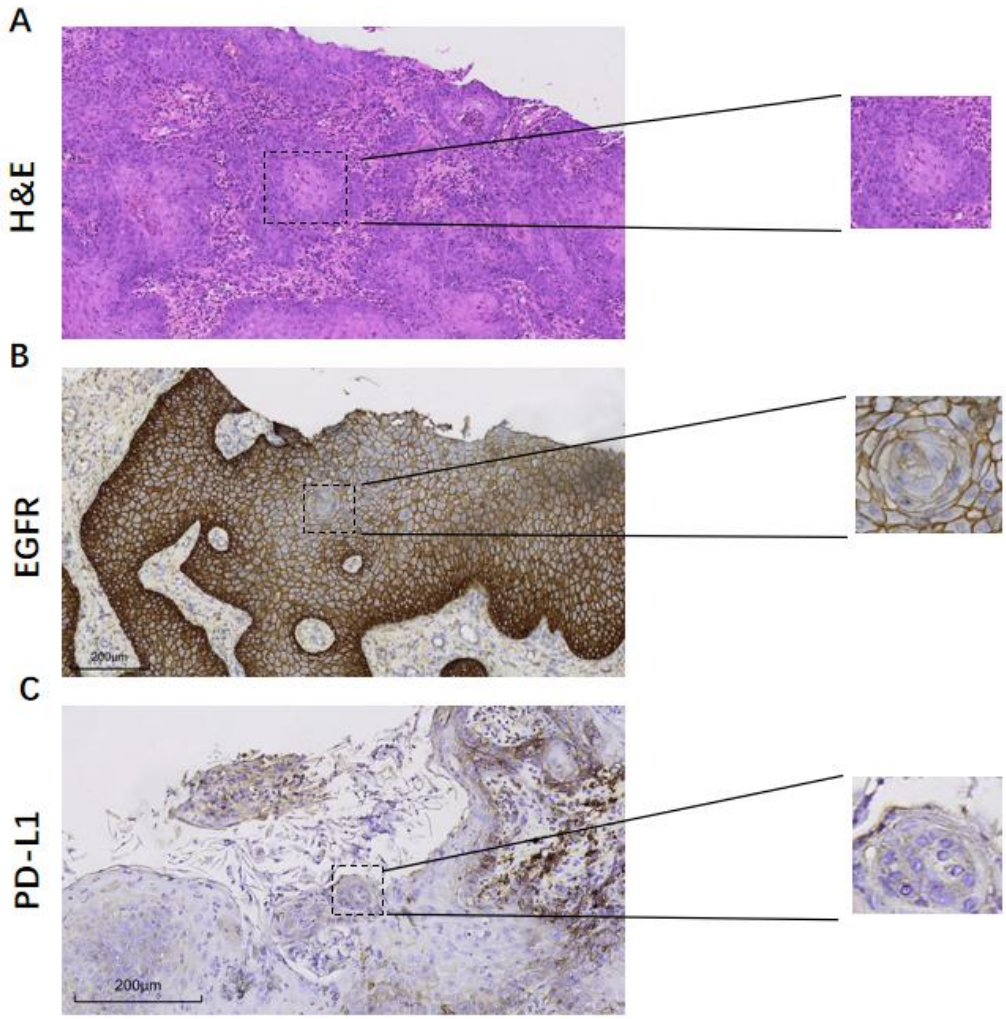


Figure 1.2 Representative histopathologic and immunohistochemical findings. (A) Hematoxylin and eosin staining showing invasive keratinizing squamous cell carcinoma. (B) EGFR immunohistochemistry demonstrating positive expression in tumor cells. (C) PD-L1 immunohistochemistry showing high expression.

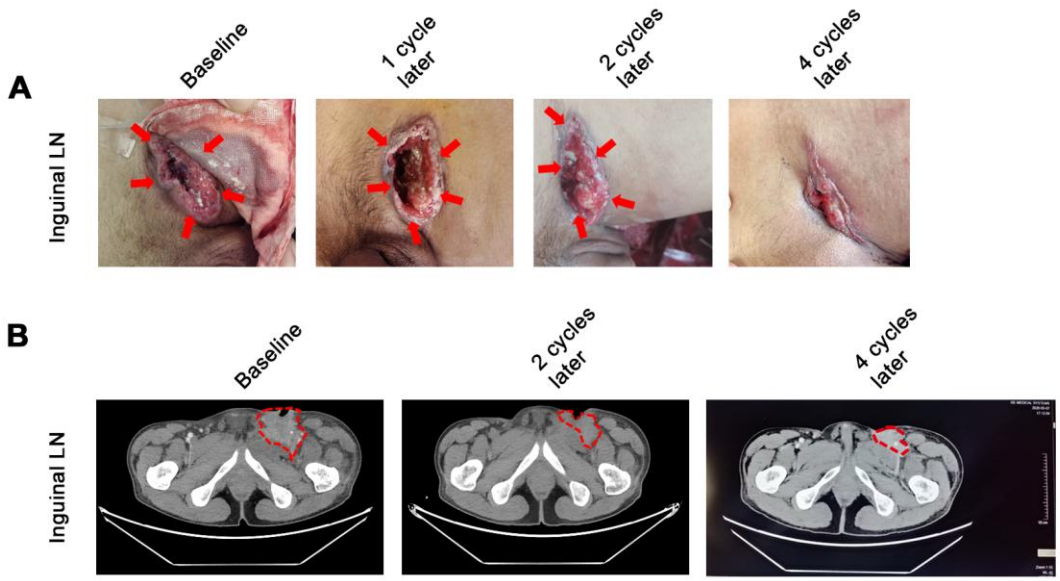


Figure 2.1 Before-and-after clinical and radiographic changes following anti-EGFR ADC plus PD-1 inhibition in a patient with advanced PSCC. (A) Clinical appearance before and after treatment. (B) Computed tomography before and after treatment.

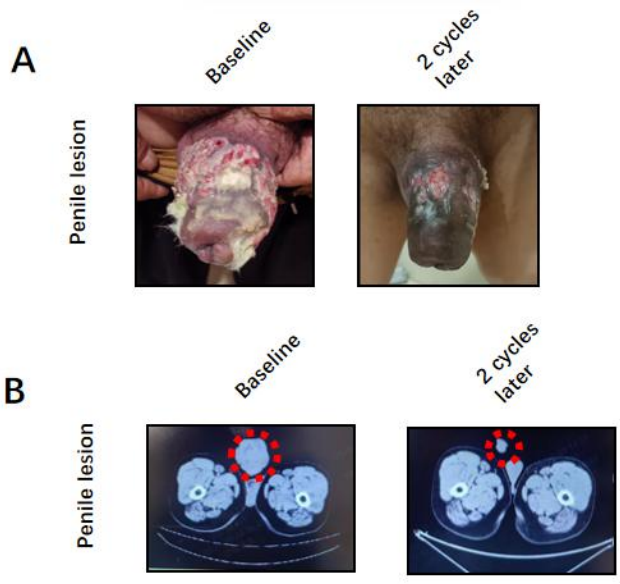
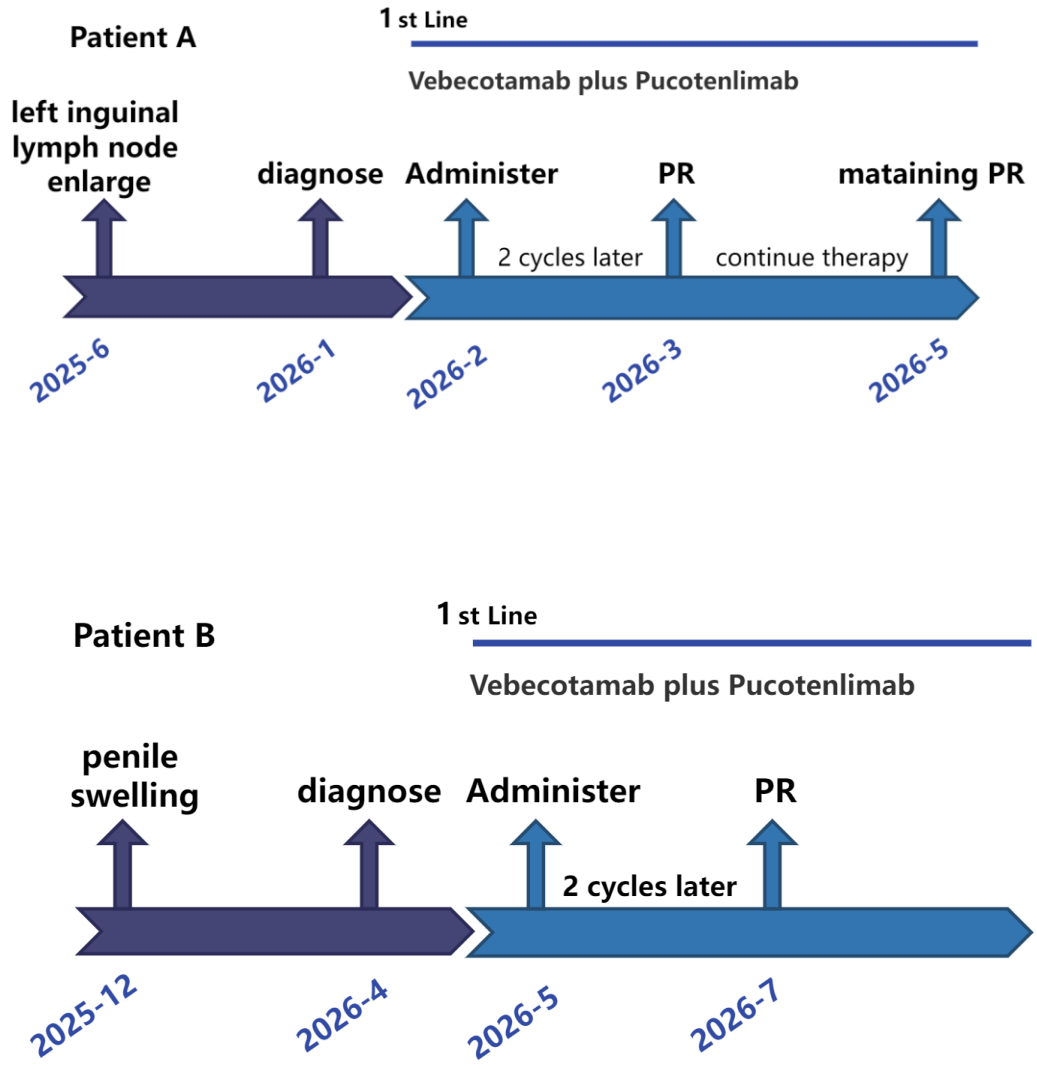


Figure 2.2 Before-and-after clinical and radiographic changes following anti-EGFR ADC plus PD-1 inhibition in a patient with advanced PSCC. (A) Clinical appearance before and after treatment. (B) Computed tomography before and after treatment.

Figure 3. Timeline of the patients' clinical course



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