

Nivolumab for metastatic squamous cell carcinoma of the anal canal: a retrospective study with exploratory biomarker analyses of PD-L1 Combined Positive Score and Nectin-4 and c-MET expression

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Abstract

Background

Nivolumab monotherapy is a standard treatment for previously treated metastatic squamous cell carcinoma of the anal canal (SCCA) in Western countries. However, data from Japan are limited due to the rarity of this disease. In addition, predictive biomarkers and novel therapeutic targets for SCCA are not well established.

Methods

We retrospectively reviewed medical records of patients with metastatic SCCA who received nivolumab monotherapy at our institution between May 2020 and April 2025. Exploratory biomarker analyses included PD-L1 Combined Positive Score (CPS) and Nectin-4 and c-MET expression in available pretreatment tumor samples.

Results

Twelve patients with metastatic SCCA were treated with nivolumab monotherapy. The objective response rate was 33% (95% CI 14–61). Median progression-free survival was 3.3 months (95% CI 1.6–24.6), and median overall survival was not reached (95% CI 4.8-NA). No treatment discontinuations or deaths related to adverse events were observed. One patient with PD-L1 CPS 15 achieved a partial response. Nectin-4 expression was positive in all evaluable cases, whereas none of patients showed c-MET positivity.

Conclusions

Our Japanese real-world data showed the efficacy and acceptable safety profile of nivolumab for metastatic SCCA. Exploratory biomarker analyses suggested the potential utility of PD-L1 CPS as a biomarker and identified frequent Nectin-4 expression, warranting its further investigation as a potential therapeutic target in SCCA.

Introduction

Anal cancer, of which squamous cell carcinoma is the most common histological subtype, is a very rare cancer with age-standardized incidence rates mostly between 1 and 2 per 100,000 per year [1]. According to Japanese statistics, there were an estimated 1,098 new cases of anal cancer in 2016, accounting for 0.1% of all malignant tumors [2]. Although the number of cases is smaller in Japan than in Western countries, the incidence of squamous cell carcinoma of the anal canal (SCCA) has been increasing for several decades in many locations around the world, including in Japan in recent years [3]. Most patients with SCCA are diagnosed with localized disease, and the majority of those with localized SCCA are cured by definitive chemoradiotherapy. However, 25% of patients develop distant metastases. [4].

For patients with metastatic SCCA, systemic chemotherapy has long been the standard treatment. Because metastatic SCCA is rare, there have been few large-scale randomized controlled trials. Recently, the first phase III trial, the POD1UM-303/InterAACT-2 study, demonstrated a significant improvement in progression-free survival (PFS) with the addition of the anti-PD-1 antibody retifanlimab to carboplatin plus paclitaxel in patients with metastatic SCCA [5]. Based on this result, carboplatin plus paclitaxel combined with retifanlimab is now a recommended first-line treatment option for metastatic SCCA in the NCCN guidelines [6].

For second-line or subsequent treatment, immune checkpoint inhibitors (ICIs) have been recommended for patients who have not previously received immunotherapy. In the phase II NCI9673 trial, nivolumab monotherapy demonstrated an objective response rate (ORR) of 24%, a median PFS of 4.1 months, and a median overall survival (OS) of 11.5 months in previously treated patients with metastatic SCCA [7]. Similar clinical activity has also been reported with pembrolizumab or retifanlimab in this setting [8–10]. Based on these results, the NCCN guidelines list nivolumab, pembrolizumab, or retifanlimab as preferred regimens for second-line or subsequent treatment [6]. However, the efficacy and safety of ICI monotherapy in Japanese patients with metastatic SCCA have not been previously reported.

Predictive biomarkers for the efficacy of ICIs have not been well established in metastatic SCCA. Moreover, therapeutic options remain limited, highlighting the need for novel agents and treatment strategies. Although antibody–drug conjugates (ADCs) have recently demonstrated significant clinical benefits across multiple malignancies, their efficacy has not been established in metastatic SCCA. Therefore, identifying targetable membrane proteins may facilitate future drug development for this disease. Nectin-4 has emerged as a promising therapeutic target for ADCs, including enfortumab vedotin, which has demonstrated significant clinical benefits in urothelial carcinoma [11]. In addition, c-MET-targeting ADCs, such as telisotuzumab vedotin, have shown promising efficacy in c-MET–overexpressing non-small cell lung cancer [12]. However, the expression and therapeutic relevance of these targets in metastatic SCCA remain unclear.

Therefore, we evaluated the efficacy and safety of nivolumab monotherapy in Japanese patients with metastatic SCCA and conducted exploratory biomarker analyses of PD-L1, Nectin-4, and c-MET expression.

Patients and methods

Patient eligibility

We retrospectively reviewed the medical records of patients with metastatic SCCA who received nivolumab monotherapy as second- or later-line treatment at our institution between May 2020 and April 2025.

Because nivolumab was not approved in Japan, it was used off-label use after approval by the off-label use committee at our institution. The following patient characteristics were collected from the medical

records: age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), disease status, metastatic organs, microsatellite instability status (MSI), p16 status, prior treatments, ORR, duration of response (DOR), PFS, and OS. This retrospective study was approved by the Institutional Review Board of the National Cancer Center Hospital (approval number: 2023-017). Informed consent was obtained via an opt-out method.

Treatment and evaluation

Nivolumab 240 mg was administered on day 1 each 14-day cycle until disease progression or the occurrence of unacceptable toxicity. Clinical staging was done according to the 8th edition of the Union for International Cancer Control -TNM classification by multidisciplinary team discussion based on the findings of endoscopy, thin-slice computed tomography, and positron emission tomography if needed. In the safety analysis, we evaluated adverse events linked to nivolumab use according to the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 5.02. Objective tumor response was evaluated in patients who had target lesions according to RECIST version 1.1, with computed tomography assessment repeated every 6 to 8 weeks after nivolumab therapy.

Exploratory biomarker analyses

Patients for whom pretreatment tumor tissue samples were available were included in the exploratory biomarker analyses. To evaluate the efficacy of ICIs, PD-L1 Combined Positive Score (CPS) was assessed using the 28 – 8 antibody. Furthermore, from the perspective of novel therapeutic development, immunohistochemical (IHC) staining for Nectin-4 and c-MET was performed to evaluate their expression profiles. The expression of PD-L1, nectin-4, and c-MET was analyzed using formalin-fixed paraffin-embedded tissue specimens. IHC staining for Nectin-4 and c-MET was performed using an anti-Nectin-4 rabbit monoclonal antibody (EPR15613-68; Abcam, Cambridge, UK) and an anti-c-MET rabbit monoclonal antibody (SP44; Ventana Medical Systems, Tucson, AZ, USA), respectively. These IHC methods have been validated in several studies [13–16]. The staining intensities were evaluated as negative, weak, moderate, or strong, in accordance with previous reports. For Nectin-4 staining, a histochemical scoring system (H-score) was used to quantify staining heterogeneity within tumor tissue, based on the percentage of cells with different staining intensities: $H\text{-score} = 1 \times (\% \text{ of weakly stained cells}) + 2 \times (\% \text{ of moderately stained cells}) + 3 \times (\% \text{ of strongly stained cells})$. Nectin-4 positivity was defined as an H-score ≥ 100 . On the other hand, c-MET positivity was defined as strong membranous staining in $\geq 10\%$ of tumor cells, based on previously reported criteria.

Statistical analysis

PFS was defined as the period between the initiation of treatment and the occurrence of disease progression or death due to any cause, whichever came first. OS was defined as the period between the initiation of treatment and death due to any cause. Survival curves were estimated by the Kaplan–Meier

method. All statistical analyses were performed in EZR (Easy R), which is a modified version of R Commander designed to add statistical functions that are frequently used in biostatistics.

Results

Patient characteristics and treatment

Twelve patients with histologically confirmed SCCA were administered nivolumab at our hospital between May 2020 and April 2025. Their baseline characteristics are shown in Table 1. Median age was 63 (range, 43–85) years and 9 patients (75%) were female. The reasons for unresectable disease were distant metastases in 6 patients (50%) and recurrent disease in 6 patients (50%). The lung and liver were the most common metastatic sites. Of the patients evaluated for MSI status, 9 (75%) were microsatellite stable (MSS) and none had MSI-high status. All patients had received ≥ 1 prior systemic chemotherapy regimen for unresectable SCCA, and more than half had received ≥ 2 prior lines of treatment.

Table 1
Patients characteristics

Characteristic		N = 12 (%)
Age, years, median (range)		63 (43–85)
Sex	Male	3 (25)
	Female	9 (75)
ECOG PS	0	5 (42)
	1	6 (50)
	2	1 (8)
Reason of unresectable	Recurrence	6 (50)
	Distant metastasis	6 (50)
Site of distant metastasis	Lung	8 (67)
	Liver	8 (67)
	Lymph node	5 (42)
MSI status	MSS	9 (75)
	MSI-H	0 (0)
	Unknown	3 (25)
p16 status	Positive	4 (33)
	Negative	1 (8)
	Unknown	7 (58)
Prior chemotherapy	1	5 (42)
	2	6 (50)
	≥ 3	1 (8)
Data are shown as the number (percentage), unless otherwise indicated. Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MSI, microsatellite instability; MSS, microsatellite stable; MSI-H, microsatellite instability-high.		

Efficacy

The median follow-up time was 28.2 months (95% CI 28.2–47.6). According to the RECIST 1.1 criteria, the ORR and disease control rate were 33% (95% CI 14–61) and 58% (95% CI 32–81), including 1 patient (8%) had a complete response, 3 (25%) had a partial response, and 3 (25%) had stable disease (Table 2, Fig. 1). Among the 12 patients, 2 responders were continuing treatment without disease progression at the data cutoff, whereas the remaining 10 patients discontinued treatment due to progression (Fig. 1). Among the 4 patients who had an objective response, median DOR was not reached (range 8.7–41.5 months). The median PFS was 3.3 months (95% CI 1.6–24.6) (Fig. 2a), and the median OS was not reached (95% CI 4.8-NA). The 1-year OS rate was 80.0% (95% CI 50.8–92.9). (Fig. 2b). Subsequent treatments were paclitaxel monotherapy in 2 patients and an investigational treatment in 1 patient. Each patient's details are shown in Table 3.

Table 2
Best objective response in patients

Best response	N = 12 (%)
Complete response	1 (8)
Partial response	3 (25)
Stable disease	3 (25)
Progressive disease	5 (42)
Objective response rate	33% (95% CI 14–61)
Disease control rate	58% (95% CI 32–81)
Data are shown as the number (percentage) or percentage (95% CI).	

Table 3
Overview of patients

Age	Sex	PS	Metastatic sites	MSI	p16	Prior systemic therapy	Response	PFS (mo)	OS (mo)
82	M	2	Lung, LN	N/A	-	FP	PD	1.9	2.1
67	F	0	Liver	N/A	N/A	FP	PD	2.3	4.2
77	F	1	Lung, Liver, LN	N/A	N/A	FP + RT, CBDCA + PTX	PD	1.4	4.8
43	M	1	Lung, Liver	MSS	N/A	5-FU + MMC+RT, FP, PTX	PD	1.6	5.8
78	F	0	Lung	MSS	-	FP + RT, CBDCA + PTX	SD	3.5	7.5
61	F	0	Lung, Liver	MSS	-	FP	PD	2.4	7.7
85	M	1	Lung, Liver	MSS	N/A	Cape + RT, PTX	SD	3.6	8.9
53	F	0	Liver	MSS	N/A	FP	SD	3.2	21.3
61	F	0	Lung, Liver	MSS	N/A	FP	PR	10.0	22.4
64	F	1	Lung, LN	MSS	N/A	5-FU + MMC+RT, CBDCA + PTX	PR	28.2	28.2
57	F	1	Lung, Liver, LN	MSS	+	FP + RT, CBDCA + PTX	PR	24.6	31.2
57	F	1	LN	MSS	+	FP, PTX+CBDCA	CR	47.6	47.6

Abbreviations: PS, performance status; MSI, microsatellite instability; MSS, microsatellite stable; N/A, not available; LN, lymph node; FP, fluorouracil plus cisplatin; RT, radiotherapy; CBDCA, carboplatin; PTX, paclitaxel; Cape, capecitabine; MMC, mitomycin C; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival.

Toxicity

Table 4 summarizes the toxicity profile of nivolumab. Treatment-related adverse events occurred in 11 of 12 patients (92%). The most common adverse event of any grade was increased alanine aminotransferase, which occurred in 6 patients (50%); all events were grade 1. There were no discontinuations due to adverse events. Other common adverse events were fatigue and hypothyroidism, which occurred in 3 patients each (25%). No treatment-related deaths occurred.

Table 4
Adverse events during nivolumab treatment

Adverse event (N = 12)	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Hematological					
Leukopenia	2 (17)	1 (8)	0 (0)	0 (0)	3 (25)
Neutropenia	1 (8)	0 (0)	1 (8)	0 (0)	2 (17)
Anemia	5 (42)	2 (17)	0 (0)	0 (0)	7 (58)
Thrombocytopenia	1 (8)	0 (0)	0 (0)	0 (0)	1 (8)
Non-hematological					
Hypothyroidism	0 (0)	3 (25)	0 (0)	0 (0)	3 (25)
Fatigue	3 (25)	0 (0)	0 (0)	0 (0)	3 (25)
Alanine aminotransferase increased	6 (50)	0 (0)	0 (0)	0 (0)	6 (50)
Aspartate aminotransferase increased	4 (33)	0 (0)	0 (0)	0 (0)	4 (33)
Rash	1 (8)	0 (0)	0 (0)	0 (0)	1 (8)
Pruritus	1 (8)	0 (0)	0 (0)	0 (0)	1 (8)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hyperglycemia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pneumonitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

PD-L1, Nectin-4, and c-MET expression by IHC

The results of the exploratory analysis using tumor tissue specimens are summarized in Table 5. Pretreatment tumor tissue samples were available for IHC analysis from 6 patients. Regarding PD-L1 expression, 4 patients (67%) had a CPS ≥ 5 . Of these 4 patients, 1 patient (25%) with PD-L1 CPS 15 achieved a partial response. All 6 patients demonstrated positive Nectin-4 expression with H-scores of ≥ 100 . In contrast, none of the patients demonstrated c-MET positivity according to previously reported criteria.

Table 5
Exploratory analysis using tissue specimens

CPS score (28 – 8)	Nectin-4 expression, H-score*	c-MET expression**	Response	PFS (mo)	OS (mo)
15	positive (230)	negative	PD	1.9j	2.1
5	positive (160)	negative	PD	1.4	4.8
0	positive (270)	negative	PD	2.4	7.7
0	positive (300)	negative	SD	3.6	8.9
5	positive (290)	negative	SD	3.2	21.3
15	positive (300)	negative	PR	10.0	22.4
Abbreviations: CPS, Combined Positive Score; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival.					
*Nectin-4 expression positivity was defined as an H-score ≥ 100 , calculated as “H-score = 1 $\times$ (% of weakly stained cells) + 2 $\times$ (% of moderately stained cells) + 3 $\times$ (% of strongly stained cells).”					
**c-MET expression positivity was defined as strong membranous staining in $\geq 10\%$ of tumor cells.					

Discussion

To our knowledge, this is the first report from Japan evaluating nivolumab monotherapy for metastatic SCCA including exploratory biomarker analyses. In this retrospective study, nivolumab monotherapy demonstrated promising antitumor activity with an acceptable safety profile in previously treated Japanese patients with metastatic SCCA. The ORR was 33%, and the disease control rate was 58%. The median PFS was 3.3 (range, 1.6–24.6) months, while the median OS was not reached. Importantly, no unexpected or serious adverse events were observed.

The efficacy and safety of ICI monotherapy for metastatic SCCA have been reported in several previous studies [7–10]. In the present study, nivolumab monotherapy showed clinical activity that was comparable to that reported in previous studies of ICIs for metastatic SCCA. In the phase II NCI9673 trial, nivolumab monotherapy achieved an ORR of 24%, a median PFS of 4.1 months, and a median OS of 11.5 months. In our cohort, the ORR was 33% and the median PFS was 3.3 months. Although median OS was not reached in our study, this finding should be interpreted with caution because of the small sample size and limited number of events. Notably, durable responses were observed in several patients, and 2 responders remained on nivolumab monotherapy without disease progression at the time of the data cutoff. Similar efficacy has also been reported with pembrolizumab or retifanlimab in previously treated metastatic SCCA with ORRs ranging from 11% to 17%, a median PFS of approximately 2–3 months, and a median OS of approximately 10–12 months [8–10]. These findings suggest that nivolumab monotherapy may also provide meaningful clinical benefits in the Japanese population.

The therapeutic landscape of metastatic SCCA has recently evolved following the POD1UM-303/InterAACT-2 trial, in which the combination of carboplatin, paclitaxel, and retifanlimab demonstrated superior clinical outcomes in the first-line setting [5]. As a result, ICI monotherapy may no longer be routinely used after progression on first-line chemoimmunotherapy. However, several clinically important issues remain unresolved. Patients with early recurrence after definitive chemoradiotherapy were not included in the POD1UM-303/InterAACT-2 trial, and the efficacy of treatment with the combination of carboplatin, paclitaxel, and retifanlimab in that population remains unclear. In addition, ICIs may still play an important role in the second-line setting for patients who for some reason are unable to receive ICIs as part of first-line treatment. In our cohort, most patients had refractory disease following chemoradiotherapy, platinum-based chemotherapy, and/or taxane-based treatment, and more than half received nivolumab in the third-line or later setting. These findings suggest that ICIs may retain clinical activity even in heavily treated patients, provided that prior ICI therapy has not been administered.

Our exploratory biomarker analyses also yielded potentially relevant findings. First, PD-L1 CPS assessed using the 28 – 8 antibody assay showed a possible association with clinical benefits from nivolumab monotherapy. Among patients with CPS ≥ 5 , antitumor responses were observed, including 1 patient who achieved a durable response. Our findings are generally consistent with those of the KEYNOTE-158 SCCA cohort, in which responses were observed predominantly in patients with CPS ≥ 1 , with an ORR of approximately 15% [9], though direct comparisons should be made with caution because KEYNOTE-158 evaluated PD-L1 expression using the 22C3 assay. To our knowledge, few reports have evaluated CPS using the 28 – 8 assay in SCCA. Therefore, our results suggest a potential association between PD-L1 CPS assessed using 28 – 8 assay and nivolumab efficacy in metastatic SCCA.

Furthermore, favorable Nectin-4 expression was observed in all 6 evaluable cases. To our knowledge, this is the first report to evaluate Nectin-4 expression in SCCA, and these findings may provide a rationale for future therapeutic development targeting Nectin-4 in this disease. In urothelial carcinoma, the combination of pembrolizumab and enfortumab vedotin, a Nectin-4–targeting ADC, has demonstrated significant clinical benefits [17]. Based on those findings, a similar therapeutic strategy may warrant investigation in metastatic SCCA. Given that paclitaxel is currently used as part of first-line treatment, replacing paclitaxel with enfortumab vedotin may represent a promising approach for developing novel treatment strategies aimed at achieving greater therapeutic efficacy. In contrast to the consistent Nectin-4 expression observed in our cohort, no patients showed c-MET positivity according to previously reported criteria. A comprehensive biomarker analysis of 199 SCCA reported a low frequency of MET alterations, with no MET amplification identified by in situ hybridization [18]. Taken together, these findings suggest that c-MET may be a less promising therapeutic target in SCCA.

Our study has some limitations. First, our study had a single-center retrospective design and small sample size, and therefore further validation in larger cohorts is warranted. However, given the rarity of SCCA in Japan, large-scale studies remain challenging. Previous reports have suggested that genetic background factors, including the HPV16 genotype and PIK3CA mutations, are commonly observed regardless of ethnicity [4, 19, 20], highlighting the importance of international collaboration in future

SCCA research. Second, p16 status was evaluable in only 5 of the 12 patients. Because human papillomavirus-related status may influence the efficacy of ICIs, the limited availability of p16 data represents an important limitation. Although both p16-positive patients achieved a durable clinical response, the small number of evaluable cases precluded meaningful assessment of the association between p16 status and treatment outcomes.

In conclusion, this is the first report from Japan to evaluate nivolumab monotherapy for metastatic SCCA, including exploratory biomarker analyses. Our real-world data from Japanese patients support the efficacy and acceptable safety profile of nivolumab monotherapy in this patient population. The exploratory biomarker analyses suggest that the potential utility of PD-L1 CPS as a biomarker and identified frequent Nectin-4 expression, warranting its further investigation as a potential therapeutic target in SCCA. Further studies are needed to validate these findings.

Declarations

5. Acknowledgments

None

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Figures

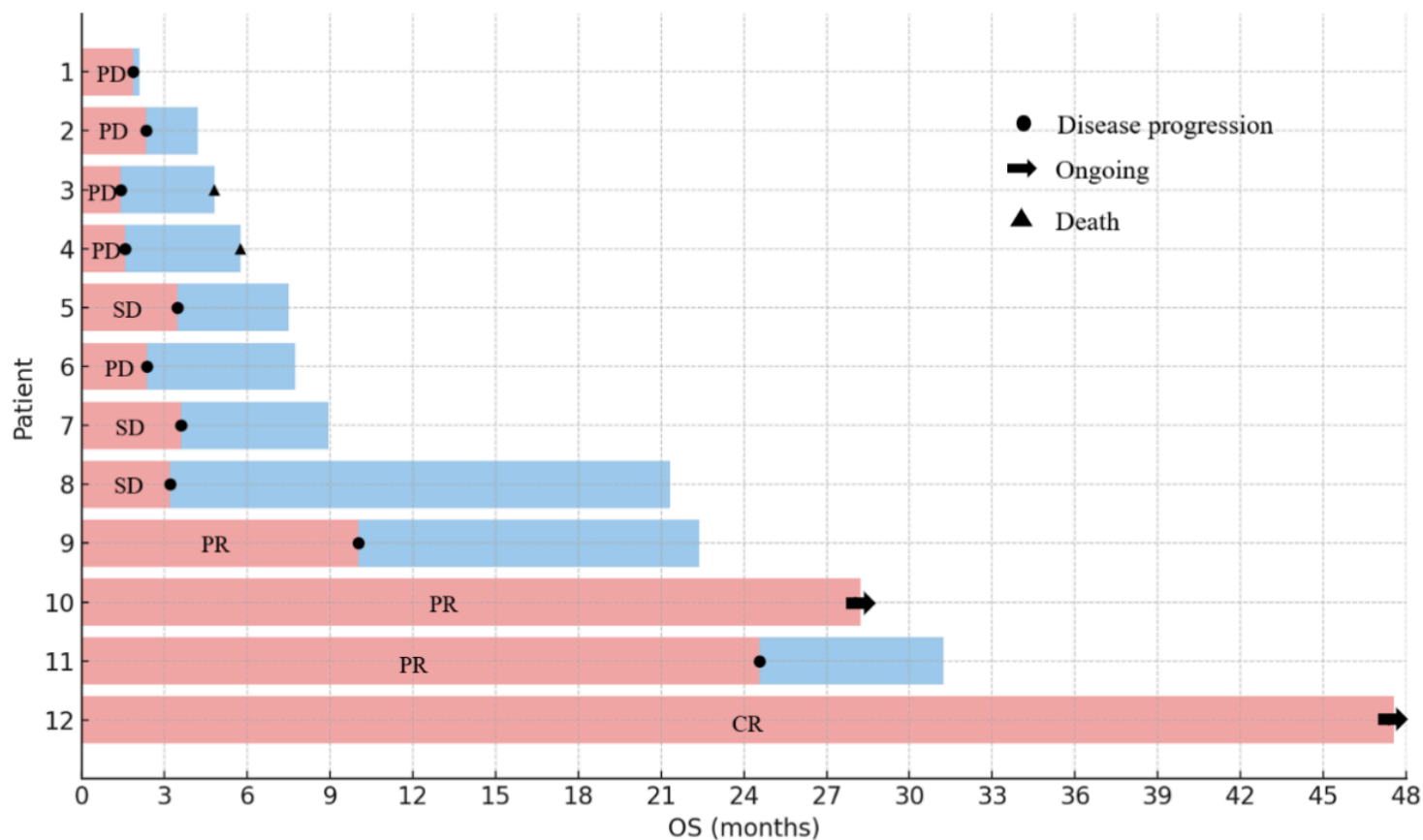
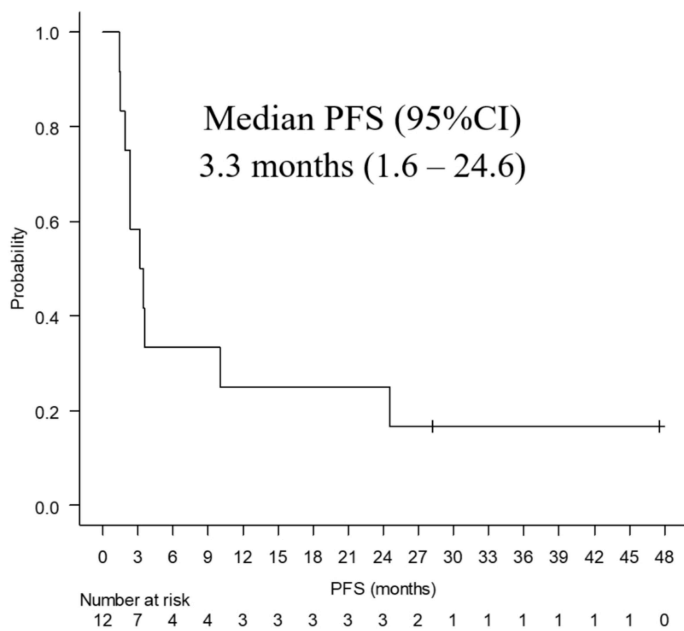


Figure 1

Swimmer plot showing treatment duration and clinical outcomes in patients treated with nivolumab. Each bar represents an individual patient. Circles indicate disease progression, triangles indicate death, and arrows indicate ongoing treatment at the data cutoff.

Treatment exposure and response durations

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival.



(a)

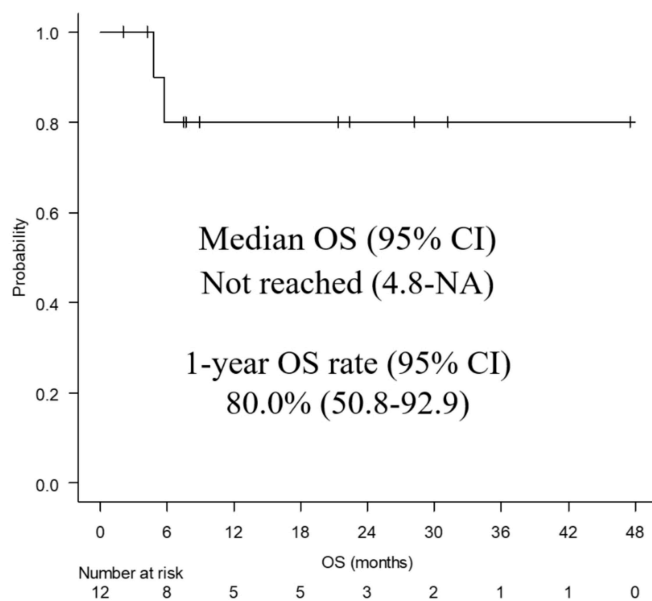


Figure 2

Kaplan–Meier estimates of (a) PFS and (b) OS.

A. Kaplan–Meier curve for progression-free survival (PFS) in patients with metastatic squamous cell carcinoma of the anal canal treated with nivolumab. Median PFS was 3.3 months (95% CI 1.6-24.6).

B. Kaplan–Meier curve for overall survival (OS) in patients with metastatic squamous cell carcinoma of the anal canal treated with nivolumab. Median OS was not reached (95% CI 4.8-NA), and the 1-year OS rate was 80.0% (95% CI 50.8-92.9).