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ORIGINAL RESEARCH

A phase II study of retifanlimab (INCMGA00012) in patients with squamous carcinoma of the anal canal who have progressed following platinum-based chemotherapy (POD1UM-202)☆

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Background: Locally advanced or metastatic squamous carcinoma of the anal canal (SCAC) has poor prognosis following platinum-based chemotherapy. Retifanlimab (INCMGA00012), a humanized monoclonal antibody targeting programmed death protein-1 (PD-1), demonstrated clinical activity across a range of solid tumors in clinical trials. We present results from POD1UM-202 (NCT03597295), an open-label, single-arm, multicenter, phase II study evaluating retifanlimab in patients with previously treated advanced or metastatic SCAC.

Patients and methods: Patients ≥18 years of age had measurable disease and had progressed following, or were ineligible for, platinum-based therapy. Retifanlimab 500 mg was administered intravenously every 4 weeks. The primary endpoint was overall response rate (ORR) by independent central review. Secondary endpoints were duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety.

Results: Overall, 94 patients were enrolled. At a median follow-up of 7.1 months (range, 0.9-19.4 months), ORR was 13.8% [95% confidence interval (CI) 7.6% to 22.5%], with one complete response (1.1%) and 12 partial responses (12.8%). Responses were observed regardless of human immunodeficiency virus or human papillomavirus status, programmed death ligand 1 (PD-L1) expression, or liver metastases. Stable disease was observed in 33 patients (35.1%) for a DCR of 48.9% (95% CI 38.5% to 59.5%). Median DOR was 9.5 months (range, 5.6 months-not estimable). Median (95% CI) PFS and OS were 2.3 (1.9-3.6) and 10.1 (7.9-not estimable) months, respectively. Retifanlimab safety in this population was consistent with previous experience for the PD-(L)1 inhibitor class.

Conclusions: Retifanlimab demonstrated clinically meaningful and durable antitumor activity, and an acceptable safety profile in patients with previously treated locally advanced or metastatic SCAC who have progressed on or are intolerant to platinum-based chemotherapy.

Key words: anal cancer, clinical trial, INCMGA00012, PD-(L)1 inhibitor, phase II, retifanlimab

INTRODUCTION

Although rare, the incidence of anal cancers has been increasing worldwide,[1] especially in women.[1,2] Most recent estimates from 2020 indicated that there were ∼50 000 new cases worldwide.[3] Almost all primary cancers of the anal canal (85%-95%) are of squamous cell histology.[4,5] As with cervical cancer and most oropharyngeal cancers, a causal relationship with oncogenic strains of human papillomavirus (HPV) has been established.[6,7]

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Most patients with squamous carcinoma of the anal canal (SCAC) have localized disease at initial diagnosis; however, 10%-30% of patients develop systemic metastases.[8] For localized SCAC, chemoradiation is the standard of care with reported 5-year disease-free survival of 57.8% and 67.8% with cisplatin/fluorouracil plus radiotherapy and mitomycin/fluorouracil plus radiotherapy, respectively.[9,10] For relapsed and/or metastatic disease, platinum-based chemotherapy is the standard of care with an absolute 5-year survival rate of 30%.[11-13] Recently, the phase II InterAACT study demonstrated carboplatin with paclitaxel as a preferred regimen for locally advanced or metastatic disease.[11,14] However, both median overall survival (OS) and median progression-free survival (PFS) remain low with this regimen, at ~20 and 8.1 months, respectively.[14] A single-arm phase II confirmatory study of docetaxel, cisplatin, and fluorouracil has also demonstrated promising efficacy for advanced anal cancer.[15,16] There is no approved systemic therapy or consensus on standard of care for patients whose disease has progressed after platinum-based treatment.[11,13] Currently, there are only anecdotal reports of short duration of response (DOR) with nonplatinum salvage chemotherapy.[17]

Patients with human immunodeficiency virus (HIV) infection are at a higher risk (25- to 35-fold) of developing SCAC owing to ineffective clearance of the HPV infection.[18] Additional risk factors among other patients include history of high lifetime number of sexual partners, HPV-driven gynecologic cancers, and immunosuppressive conditions including organ transplantation, hematologic malignancies, and cigarette smoking.[19-22]

HPV oncoproteins promote malignant transformation of anal squamous epithelium via destruction of cell cycle regulation and cell maturation.[23] In addition, HPV oncoproteins dysregulate various cellular and molecular pathways within the tumor microenvironment to evade tumor host immune response.[24] Binding of programmed death ligand 1 (PD-L1) expressed on tumor cells to their receptor, programmed death protein-1 (PD-1), on the surface of T cells results in functional inactivation of T cells and consequent evasion of immune surveillance.[25] Immune checkpoint blockade for SCAC is a promising approach based on the biologic and clinical similarities to HPV-driven cancers, such as cervical cancer and some squamous cell cancers of the head and neck, where PD-(L)1 inhibitor therapy has proven to be effective.[26-29] As such, restoring immune function via treatment with PD-1 inhibitors such as nivolumab[30] and pembrolizumab[31,32] has shown promising activity in advanced SCACs.

Retifanlimab (INCMGA00012) is a humanized, hinge-stabilized, immunoglobulin G4κ monoclonal antibody that binds to PD-1, preventing the interaction between PD-1 and its ligands, which is essential to sustain/restore T-cell antitumor function and is characteristic to the immune checkpoint blockade class.[33-35] Retifanlimab has demonstrated clinical activity and acceptable tolerability across a range of advanced solid tumors in phase I studies. For example, in cervical cancer, which is HPV driven, durable responses to retifanlimab were seen in heavily pretreated patients.[36] The POD1UM-202 study was designed to assess safety and clinical activity of retifanlimab in patients with locally advanced or metastatic SCACs who have progressed on or were intolerant to platinum-based therapy.

METHODS

Study design

The POD1UM-202 study is an open-label, single-arm, multicenter, phase II study of retifanlimab in patients with locally advanced or metastatic SCACs who have progressed after treatment with platinum-based chemotherapy (clinicaltrials.gov NCT03597295; EudraCT: 2018-002070-51). This study was conducted across 40 study centers in France, the UK, Italy, Spain, Denmark, the USA, Norway, Belgium, and Germany. Patients received a 500-mg dose of retifanlimab every 4 weeks as an intravenous infusion (day 1 of each 28-day cycle) for up to 26 cycles.

The study protocol and all amendments were approved by the institutional review boards or ethics committees of all participating sites, and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local regulations. All patients provided written informed consent before study entry.

Patient eligibility

Eligible patients were ≥18 years of age with confirmed diagnosis of locally advanced or metastatic SCAC, had disease progression on or after platinum-based therapy, were ineligible for or intolerant to platinum-based chemotherapy, had measurable disease per RECIST version 1.1, and had an Eastern Cooperative Oncology Group performance status 0 or 1. Patients who had received platinum-based therapy had received no more than two lines of prior systemic therapy for metastatic disease and patients who were ineligible for platinum-based therapy received at least one prior line of systemic therapy. Patients with well-controlled HIV were also eligible if they met the following criteria: $CD4^+$ count ≥300/μl, undetectable viral load, and were receiving highly active antiretroviral therapy.

Key exclusion criteria were previous treatment with any anti-PD-(L)1 therapy, radiotherapy within 14 days of first dose of study treatment [28 days for pelvic radiotherapy, 6 months for high dose (>30 Gy in 2-Gy fractions) thoracic region radiotherapy], active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance doses of corticosteroids (defined as >10 mg of prednisone or equivalent), known active central nervous system metastases and/or carcinomatous meningitis, clinically significant cardiovascular or pulmonary conditions, and active infections requiring systemic therapy.

Outcomes and assessments

The primary endpoint was overall response rate (ORR), defined as the percentage of patients having a complete response (CR) or partial response (PR), according to RECIST

version 1.1 as determined by independent central radiographic review (ICR). Secondary endpoints were DOR, disease control rate (DCR), PFS, OS, and safety of retifanlimab. Exploratory study endpoints evaluated efficacy parameters according to modified RECIST version 1.1 for immune-based therapeutics (iRECIST) as assessed by the investigator, immunogenicity of retifanlimab, the impact of retifanlimab on HIV control, biomarkers predictive of clinical outcomes, and health-related quality of life (HRQoL) [European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire (EORTC QLQ-C30), EuroQol five dimensions questionnaire (EQ-5D), and EORTC QLQ-Anal Cancer (ANL27)[37]; Supplementary Methods, available at https://doi.org/10.1016/j.esmoop.2022.100529].

The primary endpoint of radiographic response by ICR was assessed by computed tomography or magnetic resonance imaging every 8 weeks during treatment, and at least every 12 weeks for long-term follow-up. Adverse events (AEs; Common Terminology Criteria for Adverse Events version 5.0) were monitored throughout the study and for 28 ($\pm$7) days after the last dose of study treatment, and immune-related AEs (irAEs) were monitored for 90 days after the last dose of study treatment. HIV management testing (in patients known to be HIV positive), including HIV viral load and $CD4^+$ cell count, was carried out at screening and every 8 weeks during the first year of treatment; every 3 months during the second year of treatment; and every 6 months during the follow-up period of the study. Tumor tissues were collected during screening for evaluation of HPV, mismatch repair (MMR) protein expression, PD-L1 expression [scored for both tumor proportion score (TPS) and immune cells], and mRNA profiling (Supplementary Methods, available at https://doi.org/10.1016/j.esmoop.2022.100529). Plasma samples from screening were used to measure plasma tumor mutation burden (pTMB) by circulating free DNA analysis, and serum samples were collected to analyze the presence of antidrug antibodies (Supplementary Methods, available at https://doi.org/10.1016/j.esmoop.2022.100529). HRQoL assessments were self-administered and scheduled to be carried out at screening and every cycle until cycle 5, and in alignment with tumor response assessments, as applicable. After cycle 5, HRQoL assessments were carried out before imaging assessments (every 8 weeks during treatment, every 12 weeks during follow-up) and at the end-of-treatment visit.

Statistical methods

The planned sample size of 81 was based on the assumption that the expected ORR was 24%.[30] This would provide 80% power to exclude a lower confidence limit of 13% with alpha equal to 0.025 (one-sided). No formal hypothesis testing was planned.

Summary of patient demographics, baseline characteristics, and disposition, as well as efficacy and safety analyses were conducted on the full analysis set, which included all enrolled patients who received at least one dose of retifanlimab. ORR was estimated with 95% confidence intervals (CIs) calculated based on the exact method for binomial distributions. Median OS and PFS were estimated using Kaplan–Meier method with 95% CIs calculated based on the method of Brookmeyer and Crowley.

Table 1. Patient demographics and baseline characteristics (N = 94)

Characteristic	Values
Age, median (range), years	64 (37-94)
≥65, *n* (%)	46 (48.9)
≥75, *n* (%)	10 (10.6)
Female, *n* (%)	61 (64.9)
Race, *n* (%)	
White	72 (76.6)
Black	1 (1.1)
Other[a]	15 (16.0)
Missing[b]	6 (6.4)
ECOG PS, *n* (%)	
0	39 (41.5)
1	55 (58.5)
M1 staging, *n* (%)	76 (80.9)
Most common sites of metastases, *n* (%)	
Lymph nodes	61 (64.9)
Liver	39 (41.5)
Lung	31 (33.0)
Known HIV-positive status, *n* (%)	9 (9.6)
HPV status, *n* (%)	
Positive	54 (57.4)
Negative	4 (4.3)
Unknown	36 (38.3)
Hypercalcemia at baseline, *n* (%)	11 (11.7)
Prior therapy, *n* (%)	
Radiotherapy (no sensitizing chemotherapy)[c]	16 (17.0)
Chemoradiation therapy	69 (73.4)
Platinum-based therapy[d]	91 (96.8)

ECOG PS, Eastern Cooperative Oncology Group performance status; HIV, human immunodeficiency virus; HPV, human papillomavirus.
[a]Includes 'not available', 'not reported', and 'not collected' from sites in France and Norway.
[b]Not reported.
[c]Followed by chemotherapy.
[d]Three patients had protocol-defined exclusions (hearing loss, myelodysplastic syndrome, and platinum intolerance).

RESULTS

Patients

Between 8 October 2018 (enrollment of first patient) and 8 June 2020 (data cut-off date), 94 patients were enrolled and treated with retifanlimab. At data cut-off, 76 patients (80.9%) had discontinued treatment owing to clinical [n = 37 (39.4%)] or radiographic [n = 21 (22.3%)] progression, AEs [n = 6 (6.4%)], death [n = 6 (6.4%)], physician decision [n = 2 (2.1%)], and lost to follow-up and withdrawal by patient [each n = 1 (1.1%)]. Eighteen patients (19.1%) were continuing the study treatment.

Baseline demographics and disease characteristics are shown in Table 1. There was a female preponderance, consistent with the epidemiology of the disease. Approximately 10% of the study population were known to be HIV positive. Most patients (80.9%) had distant metastases (M1) at study entry, with 70% having more than one site of metastatic disease. Baseline hypercalcemia was present in 11 patients (11.7%), consistent with the advanced nature of the disease. All patients had received platinum-based

Table 2. Objective response by ICR ($N = 94$)

Variable	Value
Objective response rate (95% CI), %	13.8 (7.6-22.5)
Best overall response, *n* (%)	
Complete response	1 (1.1)
Partial response	12 (12.8)
Stable disease	33 (35.1)
Progressive disease	43 (45.7)
Not evaluable	5 (5.3)
Disease control rate (95% CI), %	48.9 (38.5-59.5)

CI, confidence interval; ICR, independent central radiographic review.

therapy, except three who had protocol-defined exclusions (hearing loss, myelodysplastic syndrome, and platinum intolerance). Most patients (87.2%) had also received prior radiotherapy, as either chemoradiotherapy (73.4%) or radiotherapy alone (17.0%). Forty-three patients (45.7%) had prior surgery or procedure, which included an exenteration procedure in 21 patients. Among patients with tumor biopsies available for review at baseline, 44 of 67 (66%) evaluable samples were TPS $\geq$1% (23 had TPS $<$1%) and 66 of 67 (99%) samples were immune cells $\geq$1%; MMR deficiency was rare (2 of 69 evaluable samples). Consistent with the disease biology of HPV-driven anogenital cancers, 93% (54 of 58 evaluable samples) were positive for HPV (majority were HPV 16).

Efficacy

The median duration of follow-up was 7.1 months (range, 0.9-19.4 months). The ORR was 13.8% (95% CI 7.6% to 22.5%) based on confirmed tumor responses by ICR according to RECIST version 1.1 (Table 2). One patient (1.1%) had a CR and 12 patients (12.8%) had PR; 11 of these 13 responders had an initial response by the week 8 scan. An additional 33 patients (35.1%) had stable disease (SD), for an overall DCR of 48.9% (95% CI 38.5% to 59.5%). Characteristics of the responding patients are described in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100529. All responders had received prior platinum-based chemotherapy and radiotherapy or chemoradiation. A subgroup analysis of ORR demonstrated that responses were observed in patients regardless of age, sex, race, ethnicity, Eastern Cooperative Oncology Group performance status, HIV status, liver metastases, HPV status, or PD-L1 expression level. No responders had MMR-deficient tumors per central testing. Sensitivity analyses of ORR based on investigator-assessed tumor response according to iRECIST version 1.1 and conventional RECIST showed a similar ORR [14.9% (95% CI 8.4% to 23.7%)].

Measurable tumor shrinkage was demonstrated in 40 of 87 patients (46.0%) based on ICR (sum of diameters; Figure 1A). Four patients with best response of SD per ICR had $\geq$30% reduction in the target lesions and eight patients, also with SD by ICR, had $\geq$20% reduction. Measurable shrinkage of target liver disease was recorded in eight of these patients (24%), which included major responses in two patients with bulky liver metastases at baseline.

With a median follow-up of 5.6 months (range, 1.6-14.8 months), the estimated median DOR in responders was 9.5 months (95% CI 5.6 months-not estimable) (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100529). Estimated event-free probabilities of confirmed responders surviving without disease progression for at least 6 and 12 months were 64.9% (95% CI 24.9% to 87.4%) and 43.3% (95% CI 7.5% to 76.3%), respectively. The median duration of SD was 5.1 months (95% CI 3.7-7.5 months); for patients with any degree of disease control (CR + PR + SD; $n = 46$), the median DOR was 7.4 months (95% CI 5.1-11.0 months; Figure 1B).

The duration of treatment and responses based on ICR in all assessable patients are shown in Figure 2. Of the 13 confirmed responders, 1 patient (with CR) discontinued treatment following a single infusion because of an intractable skin rash and 1 patient started a new anticancer therapy while still responding to retifanlimab. The estimated median PFS was 2.3 months (95% CI 1.9-3.6 months; Figure 3A). Median PFS for both confirmed responders (11.0 months) and for patients with SD (5.1 months) was longer than that for nonresponders (1.7 months). For patients with any degree of disease control (CR + PR + SD; $n = 46$), the median PFS was 7.4 months (95% CI 5.1-11.0 months). The estimated median OS was 10.1 months (95% CI 7.9 months-not estimable) (Figure 3B). The estimated probability of surviving for at least 12 months was 45.7% (95% CI 31.6% to 58.6%). The median OS for confirmed responders and patients with SD was not reached after median follow-up times of 9.7 months (range, 4.7-19.4 months) and 7.4 months (range, 1.8-11.4 months), respectively. The median OS for nondisease control patients (patients with progressive disease or missing response) was 7.7 months (95% CI 5.1-9.1 months).

Safety

The median duration of retifanlimab treatment was 2.8 months (range, 0.03-19.4 months) and the median number of infusions administered was 4 (range, 1-18). As would be expected, treatment-emergent adverse events (TEAEs) were common in this population with advanced cancer. Ninety patients (95.7%) experienced at least one TEAE and 55 (58.5%) had grade $\geq$3 TEAEs (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100529). Fifty-five patients (58.5%) had treatment-related AEs; the most common ($>$5% incidence) AEs were pruritus (11.7%), fatigue (9.6%), diarrhea (8.5%), asthenia (7.4%), nausea (6.4%), increased aspartate aminotransferase, and hypothyroidism (each 5.3%). Eleven patients (11.7%) had grade $\geq$3 treatment-related TEAEs; the most common was fatigue, which occurred in two patients (2.1%). TEAEs led to treatment discontinuation in seven patients (7.4%); dose interruption in one patient (1.1%), and dose delay in 25 patients (26.6%), though the majority of these were for reasons unrelated to treatment.

Fifty-one patients (54.3%) experienced serious AEs, with the most commonly reported being abdominal pain (5.3%),

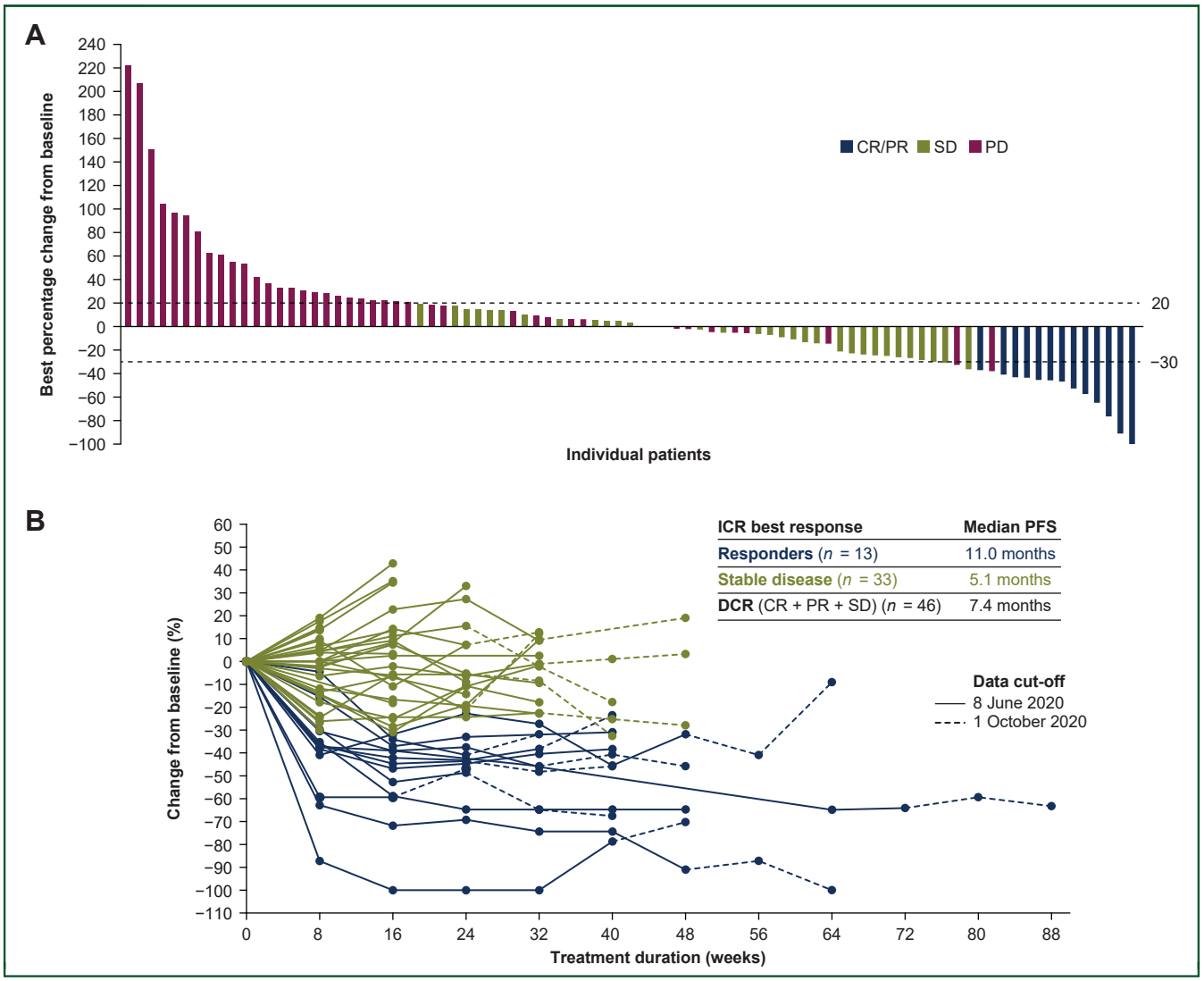

Figure 1. (A) Best percentage change from baseline in target lesion size (sum of diameters) for individual patients,[a] and (B) percentage change from baseline over time in sum of longest diameter of target lesions in responders and patients with SD.

Confirmed best objective response is shown for each patient in the figure. Upper limit of dotted line indicates criteria for PD (≥20% increase in sum of target lesion diameters), and lower limit indicates criteria for PR (≥30% decrease in sum of target lesion diameters).

CR, complete response; DCR, disease control rate; ICR, independent central radiographic review; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a]Out of 94 patients enrolled in the study, 7 patients are not shown as they had missing baseline or postbaseline target lesion assessments.

and anemia and urinary tract infection (each 4.3%). Six patients had serious AEs that were considered related to retifanlimab by the investigator (adrenal insufficiency, abdominal pain, immune-mediated enterocolitis, herpes zoster, lymphangiosis carcinomatosa attributed by the investigator to treatment as a case of suspected hyperprogression, and hepatitis, each $n = 1$). With the exception of lymphangiosis carcinomatosa (which was fatal), these resolved with standard measures.[38]

Twenty-four patients (25.5%) experienced immune-related adverse events (irAEs), which are a class effect of the inhibitors (Table 3). Most irAEs were grade ≤2 in severity, and only two patients (2.1%) experienced irAEs leading to retifanlimab discontinuation (one because of pneumonitis and the other because of palmar-plantar erythrodysesthesia syndrome). As expected, nearly half of the irAEs were endocrine related, with thyroid irAEs being the most frequently reported, followed by skin reactions, pneumonitis, and colitis. In general, these were mild and manageable with immunosuppression or endocrine replacement as per established treatment guidelines.[38] No new immune-related toxicity was reported. Four patients (4.3%) were reported to have had an infusion reaction (infusion-related reaction, dyspnea, pruritus, and pyrexia, each $n = 1$); all were grade ≤2 in severity and did not necessitate discontinuation of therapy. Eighty-four of 94 patients with SCAC were tested for antidrug antibodies; none were positive for treatment-emergent anti-retifanlimab antibodies.

A subgroup safety analysis based on baseline characteristics showed no clinically meaningful difference in TEAEs. In the nine patients who were known to be HIV positive, none

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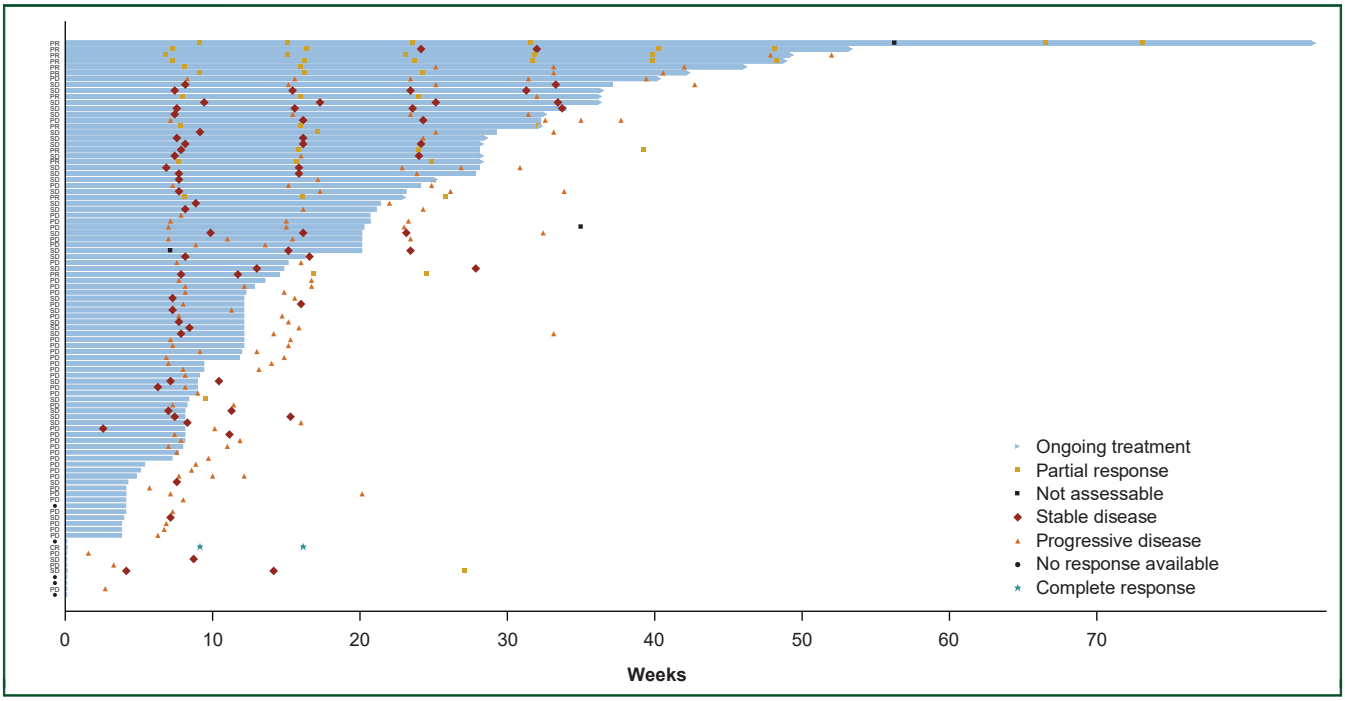

Figure 2. Duration of treatment and best objective responses[a] by ICR according to RECIST version 1.1 (full analysis set). Confirmed best objective response is shown for each patient in the figure.
ICR, independent central radiographic review.
[a]Out of 94 patients enrolled in the study, 5 patients are not shown, as they had missing postbaseline target lesion assessments.

had opportunistic infections, fatal AEs, AEs leading to infusion interruption or delay, irAEs, or an infusion reaction. Viral control was maintained throughout the study in all patients who are HIV positive, as assessed by serial $CD4^+$ counts and viral load measurements.

No significant trends were noted in laboratory assessments. In particular, clinically significant myelosuppression was not observed despite the near-universal exposure to prior pelvic radiotherapy and chemotherapy in the study population.

Translational analyses

No association was observed between pTMB status and OS ($P = 0.18$) (Supplementary Figure S2A, available at https://doi.org/10.1016/j.esmoop.2022.100529). In contrast, tumor mRNA expression profiling demonstrated a significant association between Tumor Inflammation Signature and OS ($P = 0.019$) and PD-L1 mRNA and OS ($P = 0.0088$) (Supplementary Figure S2B and C, available at https://doi.org/10.1016/j.esmoop.2022.100529). Correlation of responses with PD-L1 expression score on tumor cells and immune cells is shown in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100529.

Patient-reported outcomes

EQ-5D-5L and EORTC QLQ-C30 data were available at baseline for 80 of 94 (85%) and 79 of 94 (84%) patients, respectively. Summary scores were correlated with RECIST version 1.1 outcomes. On both scales, there was a trend to improvement in HRQoL over the first four cycles (average duration of treatment) in patients with a response of SD or better (Supplementary Figure S3A and B, available at https://doi.org/10.1016/j.esmoop.2022.100529).

A nonvalidated instrument (QLQ-ANL27) was introduced late in the study and data collection was limited to ~30% of patients; therefore, QLQ-ANL27 data were not analyzed in this exploratory analysis.

DISCUSSION

POD1UM-202 studied patients who had progressed on platinum chemotherapy and have no standard treatment options. Thirteen patients (13.8%) with advanced SCAC treated with retifanlimab 500 mg every 4 weeks achieved an objective response, and another 33 patients (35.1%) had SD leading to a DCR of 48.9%, which is clinically meaningful given the lack of therapeutic options for this population with poor prognosis.[13] Responses were durable (median, 9.5 months), which exceeds historical expectations for this population with salvage chemotherapy.[17] In addition, responses were observed across all subgroups of interest, including patients with PD-L1 negative (defined as TPS <1%) tumors, patients who were HIV positive, and patients with liver metastases, thus allowing broad applicability of the results to clinical practice. Response and SD were both associated with prolongation of PFS and OS. The high proportion of liver metastases (27%) that responded to retifanlimab is also notable, as this organ in some reports is less responsive to immunotherapy (e.g. in melanoma and non-small cell lung cancer).[39]

The efficacy of retifanlimab in the current study is consistent with that observed in previously treated recurrent or advanced

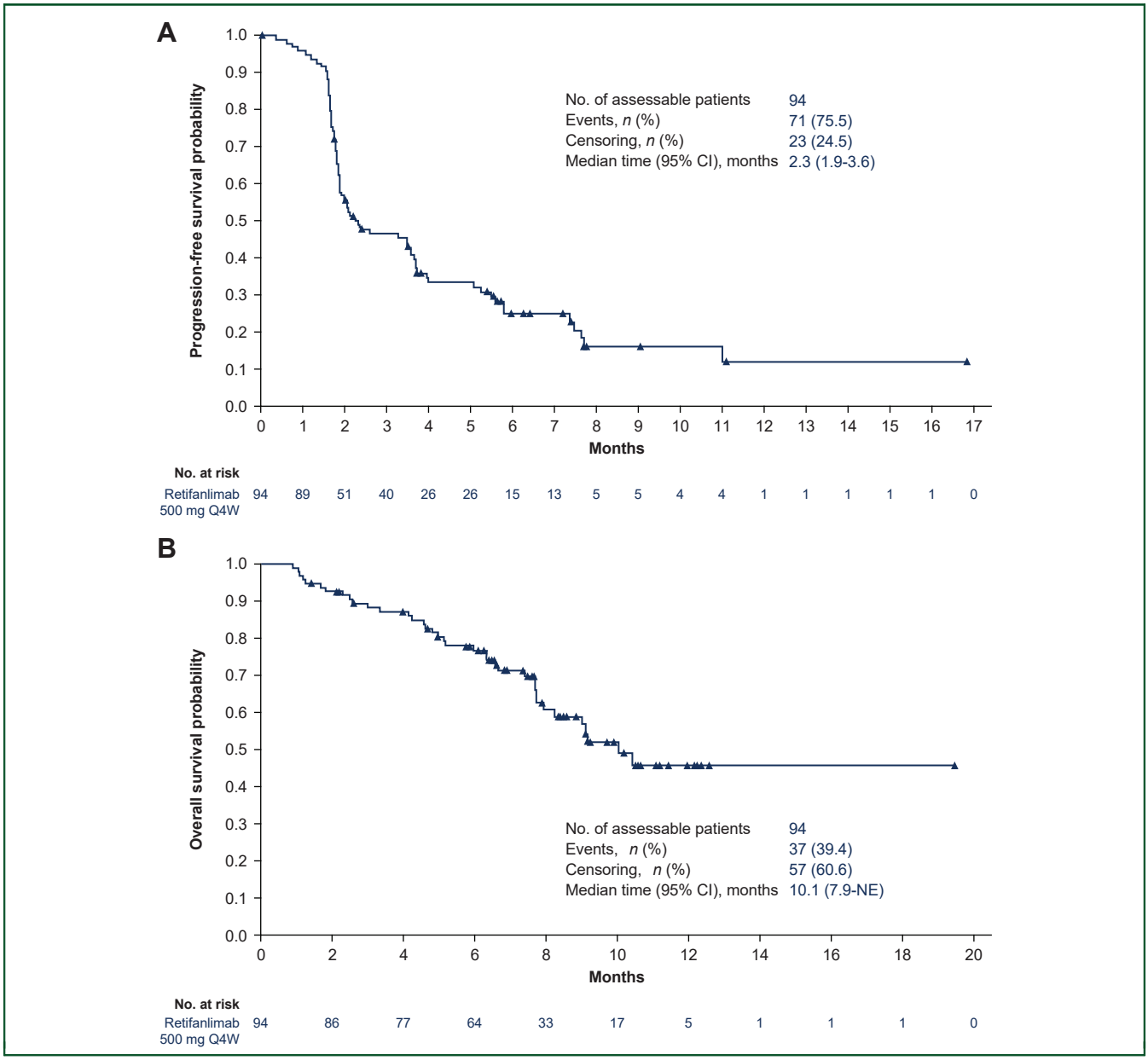

Figure 3. Kaplan–Meier estimate of (A) progression-free survival and (B) overall survival.
CI, confidence interval; NE, not estimable; Q4W, every 4 weeks.

Table 3. Summary of immune-related adverse events (regardless of attribution to treatment) (*N* = 94)

Immune-related adverse events, *n* (%)	Any grade	Grade ≥3
Any	24 (25.5)	6 (6.4)
Hypothyroidism	8 (8.5)	0
Hyperthyroidism	4 (4.3)	0
Pruritus	4 (4.3)	0
Pneumonitis	3 (3.2)	1 (1.1)
Rash maculopapular	2 (2.1)	1 (1.1)
Acute kidney injury	1 (1.1)	1 (1.1)
Adrenal insufficiency	1 (1.1)	1 (1.1)
Colitis	1 (1.1)	0
Dermatitis	1 (1.1)	0
Interstitial lung disease	1 (1.1)	1 (1.1)
Myositis	1 (1.1)	0
Palmar-plantar erythrodysesthesia syndrome	1 (1.1)	0
Rash	1 (1.1)	1 (1.1)
Rash erythematous	1 (1.1)	0

cervical cancer (confirmed responses achieved in 19.4% of patients; DCR 58.1%).[40] The ORR (13.8%) in our study is within the range of 10%-18% reported in pivotal trials of other PD-(L)1 inhibitors in previously treated HPV-driven malignancies; similarly, the DCR, median DOR, and median OS are all comparable with other PD-(L)1 inhibitors (DCR, 37%-41%; median DOR, 9.7-18.4 months; median OS, 8.0-9.4 months).[26,27,41-44] It is noteworthy that despite the relatively modest ORRs observed in these trials, a survival benefit for PD-1 inhibition versus standard of care has been demonstrated in advanced cervical and head and neck cancer. This likely reflects the unique biology of HPV-driven cancer, which is well-suited to therapeutic strategies directed at checkpoint blockade.[45,46] Consequently, PD-(L)1 inhibitors have already received US Food and Drug Administration approval in these cancers.[47-49] The efficacy of retifanlimab in POD1UM-202, which has been

rigorously assessed by independent reviewers, also compares well with previous PD-(L)1 inhibitor experience in previously treated SCAC: nivolumab (ORR, 24.0%; median OS, 11.5 months; median PFS, 4.1 months),[30] pembrolizumab (ORR, 11.6%-17.0%; median OS, 9.3-12.0 months; median PFS, 2.0-3.0 months),[31,50] and avelumab (ORR, 10.0%; median OS, not mature; median PFS, 2.1 months)[51] in previously treated SCAC.[30,31,50-52]

Retifanlimab demonstrated a safety and tolerability profile consistent with that reported for the PD-(L)1 inhibitor class. Most severe and serious AEs were not attributed to treatment with retifanlimab. The incidence, severity, and need for treatment discontinuation because of immune-related toxicities were all consistent with prior PD-(L)1 experience. Immune toxicity with retifanlimab treatment can be managed through standard guidelines,[38,53] which is critically important to practicing clinicians. Retifanlimab was well tolerated in all subgroups of interest, including patients known to be HIV positive with no opportunistic infections and no loss of HIV control. Despite prior exposure to myelosuppressive chemotherapy and pelvic radiotherapy, no patient experienced clinically significant myelosuppression, making retifanlimab an attractive alternative to standard-of-care myelosuppressive salvage chemotherapy.

A retrospective analysis of HIV-positive patients on antiretroviral therapy with metastatic SCAC receiving different lines of therapy had outcomes similar to those of patients who are HIV negative.[54] The inclusion of patients who are HIV positive in POD1UM-202 was important, as this provides valuable information for clinical decision making in this group of patients who are at particularly high-risk for SCAC yet have historically been understudied in and/or excluded from clinical trials.[55]

In this study, we aimed to determine meaningful biomarkers to allow identification of patients most likely to respond to retifanlimab. No correlation between pTMB and OS was found in our study, similar to previous results in SCAC.[56] However, we did observe a positive correlation between the tumor inflammation mRNA signature and OS, similar to that reported for other cancer types.[57] Further, there was a strong positive correlation between PD-L1 mRNA expression and OS perhaps, in part, reflecting the inflamed status of these tumors. Further evaluation of this correlation in subsequent studies is warranted.

In POD1UM-202, retifanlimab demonstrated clinically meaningful and durable antitumor activity and an acceptable safety profile in patients with locally advanced or metastatic SCAC who have progressed on or who are intolerant to platinum-based chemotherapy. These encouraging results support further investigation of retifanlimab in SCAC. A phase III trial, POD1UM-303/InterAACT 2 (NCT04472429), has been initiated evaluating retifanlimab in combination with carboplatin and paclitaxel in first-line therapy in patients with inoperable locally recurrent or metastatic SCAC.

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DATA SHARING

Incyte Corporation (Wilmington, DE, USA) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized datasets owned by Incyte

Corporation for the purpose of conducting legitimate scientific research. Researchers may request anonymized datasets from any interventional study (except phase I studies) for which the product and indication have been approved on or after 1 January 2020 in at least one major market (e.g. US, EU, JPN). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte Corporation's clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at: https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960

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