Received: 21 March 2024 | Revised: 7 June 2024 | Accepted: 21 June 2024

DOI: 10.1002/cncr.35483

ORIGINAL ARTICLE

Efficacy and safety of nivolumab monotherapy in patients with unresectable clear cell sarcoma and alveolar soft part sarcoma (OSCAR Trial/NCCH1510)

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Funding information
Japan Agency for Medical Research and Development, Grant/Award Number: JP16lk0201044; Ono Pharmaceutical

ABSTRACT

Background: Clear cell sarcoma (CCS) and alveolar soft part sarcoma (ASPS) are rare, and standard systemic therapy is not established except for sunitinib in ASPS. It is known that CCS and ASPS have a common biological feature of melanoma and Xp11.2/TFE3 translocation renal cell carcinoma, and immune-checkpoint inhibitors (ICIs) are effective in these tumors. The authors conducted a phase 2 trial to evaluate the efficacy and safety of nivolumab for CCS and ASPS.

Methods: The number of patients expected to be enrolled was 15–25 and was determined based on the Bayesian design. The primary end point was the confirmed objective response rate (ORR) according to the central review and the secondary

This study was presented at the Connective Tissue Oncology Society (CTOS) 2020 Annual Meeting (virtual); November 18–21, 2020.

This trial is registered in the UMIN Clinical Trials Registry (identifier: UMIN000023665) (umin.ac.jp/ctr/).

end points included ORR, progression-free survival (PFS), overall survival (OS), and safety.

Results: A total of 26 patients (CCS, 12; ASPS, 14) were enrolled. Efficacy and safety were analyzed on 25 and 26 patients, respectively. The minimum number of responses required for a positive conclusion regarding the efficacy was four. However, only one patient (4.0%) with ASPS had a partial response. Complete response, stable disease, progression disease, and not evaluable were 0%, 60%, 32%, and 4.0%, respectively. Adverse events of grade 3 or 4 occurred in 57.7% (15 of 26). The median PFS was 4.9 months (95% confidence interval [CI], 3.7–8.6 months) and the median OS was 15.8 months (95% CI, 8.2–not reached).

Conclusions: The primary end point of the ORR was not met for CCS and ASPS on the central review. Further studies are needed to evaluate ICIs in patients with ASPS.

KEYWORDS
alveolar soft part sarcoma, clear cell sarcoma, MITF-associated tumor, nivolumab, OSCAR Trial

INTRODUCTION

Clear cell sarcoma (CCS) is a rare sarcoma that accounts for approximately 1% of soft tissue sarcoma (STS) and often occurs in the tendons and aponeurosis of the foot of patients in adolescents or young adults.[1–3] CCS has much in common with melanoma, especially in pathological findings, immunohistochemical profiles, and clinical behaviors such as lymph node metastasis, therefore it was previously known as malignant melanoma of soft parts.[4,5] The most distinctive difference between the two is the presence of Ewing sarcoma breaking region 1-activating transcription factor 1 (*EWSR1-ATF1*) or Ewing sarcoma breaking region 1-cAMP response element-binding protein 1 (*EWSR1-CREB1*) fusion genes in CCS.[1,6] There is no standard chemotherapy for unresectable and advanced CCS because of its rarity, despite lymph node metastasis and lung metastasis being known to occur over a long period even after complete resection.

Alveolar soft part sarcoma (ASPS) is also a rare sarcoma that accounts for 0.5%–0.9% of STS and often occurs in deep soft tissues such as the extremities and the buttocks of young female patients.[2,3] The product of ASPS chromosome region, candidate 1-transcription factor binding to IGHM enhancer 3 (*ASPSCR1-TFE3*) fusion gene is caused by unbalanced chromosomal translocation of der-(17) t-(X;17) (p11; q25), it develops and causes phosphorylation of mesenchymal-epithelial transcription (MET) and activation of downstream signals.[1] There was no standard chemotherapy except for tyrosine kinase inhibitors (TKI) with anti-angiogenesis for unresectable and advanced ASPS because of its rarity, despite being generally considered to be highly malignant and often metastasize to the lungs, brain, and bones.[7–9]

Microphthalmia transcription factor (*MITF*) is a gene named after it was identified in mice exhibiting microphthalmia.[10] Although CCS and ASPS belong to sarcoma category in histopathological classification, they might also be viewed as MITF-associated tumors.[11] MITF, TFEB (transcription factor EB), TFEC (transcription factor EC), and TFE3 are collectively called the MITF family.[4,6,11–14] In addition to CCS and ASPS, MITF-associated tumors include malignant melanoma and Xp11.2 translocation clear cell renal carcinoma. MITF-associated tumors are generally strongly resistant to chemotherapy and radiotherapy.[11]

Nivolumab is a fully human immunoglobulin (Ig) G4 monoclonal antibody directed against the negative immunoregulatory human cell surface receptor programmed death-1 (PD-1) and is also well-known as the first immune-checkpoint inhibitor (ICI).[15–17] Nivolumab is also known to have favorable efficacy regarding MITF-associated tumors. Nivolumab 3 mg/kg every 2 weeks showed significant improvements in overall survival and progression-free survival (PFS) compared with dacarbazine among previously untreated patients with metastatic melanoma without a *BRAF* mutation.[18] Nivolumab 3 mg/kg every 2 weeks also showed significant improvements in overall survival (OS) compared with everolimus among patients with previously treated advanced renal-cell carcinoma.[19] In addition, various ICIs have recently been shown to be effective especially in patients with ASPS, either as monotherapy or in combination with TKIs.[20–22]

This multicenter phase 2 trial aimed to assess the efficacy and the safety of nivolumab in patients with unresectable CCS and ASPS that are considered to be MITF-associated tumors. Patients eligible for the study were not required to have prior chemotherapy, but prior antiangiogenic TKI was only required for patients with ASPS.

MATERIALS AND METHODS

Patients and treatment

NCCH1510/OSCAR (a clinical trial of nivolumab [Opdivo] in patients with unresectable clear cell sarcoma and alveolar soft part sarcoma), a phase 2, multicenter, single-arm, investigator-initiated trial, evaluated the efficacy and safety of nivolumab in patients with unresectable CCS

and ASPS (clinical trial registration identifier: UMIN000023665). The patients were registered with an institutional pathological diagnosis at each trial site, and the diagnoses were centrally reviewed by a subspecialized STS pathologist (A.Y.) based on the World Health Organization classification. The trial was conducted at four sites in Japan from November 2016 to January 2018. The main eligibility criteria were histologically confirmed CCS or ASPS, required no prior chemotherapy, prior antiangiogenic TKI was only required for patients with ASPS, age ≥18 years, Eastern Cooperative Oncology Group performance status of 0–1, and ≥1 measurable tumor according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Furthermore, patents with symptomatic brain metastases, carcinomatous meningitis, or spinal metastases requiring surgical intervention at the time of enrollment, and pericardial effusion, pleural effusion, or ascites requiring treatment were excluded from the tri. Patients with active other cancer than CCS and ASPS, a history of interstitial lung disease or pulmonary fibrosis, harboring an infection requiring systemic treatment, complicated with active autoimmune disease or history of chronic/recurrent autoimmune disease, and some others conflict with general criteria were excluded. Patients were administered nivolumab 240 mg intravenously once every 2 weeks until withdrawal of consent, unacceptable toxicity appeared, or disease progression. This trial was conducted according to the ethical principles of the Declaration of Helsinki and the study protocol was approved by the institutional review board at each trial institution. All patients provided written informed consent to participate in the trial.

End points

The primary end point was the overall response rate (ORR), and the responses were evaluated based on RECIST version 1.1 every 8 weeks for the first 24 weeks, and every 12 weeks thereafter by central review. Complete response (CR) and partial response (PR) are assessed according to RECIST version 1.1. The confirmation of response was required at least 4 weeks after the initial evaluation. The secondary end points were the ORR by investigator assessment, PFS, OS, and safety. Adverse events (AEs) were evaluated and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

Statistical analysis

The efficacy analysis included patients who received at least one dose of nivolumab, met the key eligibility criteria, and had at least one measurable lesion at baseline by central assessment. We planned to enroll 15–25 patients with CCS and ASPS, which was determined based on the Thall and Simon's Bayesian design.[23] As a prior distribution, we assumed a mean of 5% for the no-effect response rate and used the Beta distribution with shape parameters of 10 and 190 (Beta [10, 190]) based on investigator assessment. We also assumed a mean of 30% for the response rate of nivolumab based on other clinical trial results regarding nivolumab in other MITF-associated tumors and then used Beta (0.6, 1.4).[18,19] Based on these settings, three responders were required to achieve a posterior probability >95% that the response rate of nivolumab was at least >5% for 15–21 patients (or four responders for 22–25 patients). This design controlled the type I error rate at the target level of <0.10.[24] Safety analyses included all treated patients who received at least one nivolumab dose.

The ORR and exact 95% confidence interval (CI) based on the Clopper–Pearson method were estimated. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Patient baseline characteristics

Of 26 patients enrolled for the OSCAR trial between November 2016 and January 2018 at four institutions in Japan, one patient was excluded from the efficacy analysis because of pathological ineligibility by central pathological review (Figure 1). The efficacy analysis included 25 patients: 11 and 14 in CCS and ASPS, respectively. The median follow-up time was 14.0 (range, 3.6–26.2) months. Table 1 shows the baseline patient characteristics of the efficacy analysis (n = 25). Most patients were young adults with a median age of 34.0 (range, 28–42), eight male and 17 female patients were included, respectively.

Table 1 also shows the baseline tumor characteristics of the efficacy analysis (n = 25). Almost half of the patients with CCS and ASPS had primary tumors in the limbs, five (46%) in CCS and seven (50%) in ASPS, respectively.

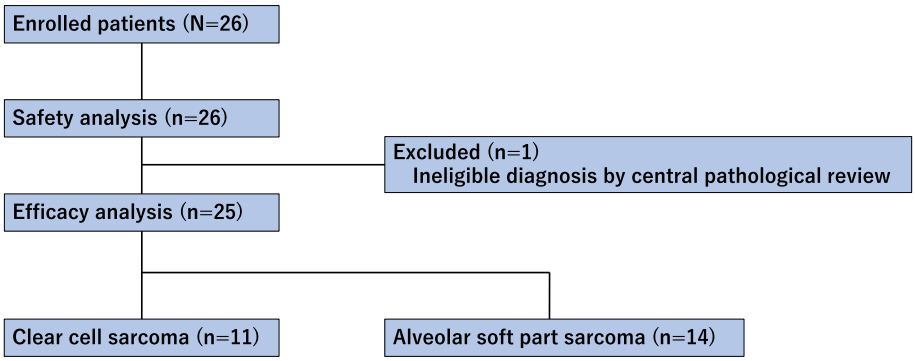

FIGURE 1 Flow diagram for the OSCAR trial. One patient was excluded from the efficacy analysis cohort due to the ineligible pathological diagnosis by central pathological review.

TABLE 1 Patient characteristics at baseline.

	Overall, $N = 25$, No. (%)	CCS, $n = 11$, No. (%)	ASPS, $n = 14$, No. (%)
Age, median (range)	34 (18–54)	45 (18–54)	31 (21–42)
Sex			
Male	8 (32.0)	6 (54.5)	2 (14.3)
Female	17 (68.0)	5 (45.5)	12 (85.7)
PS (ECOG)			
0	16 (64.0)	7 (63.6)	9 (64.3)
1	9 (36.0)	4 (36.4)	5 (35.7)
Primary site			
Limbs	12 (48.0)	5 (45.5)	7 (50.0)
Buttocks	4 (16.0)	2 (18.2)	2 (14.3)
Others	9 (36.0)	4 (36.4)	5 (35.7)
Metastatic site			
Lung	21 (84.0)	8 (72.7)	13 (92.9)
Bone	10 (40.0)	4 (36.3)	6 (42.9)
Liver	6 (24.0)	3 (27.3)	3 (21.4)
Lymph node	7 (28.0)	6 (54.5)	1 (7.1)
Brain	3 (12.0)	0 (0)	3 (21.4)
Fusion gene			
Positive	13 (52.0)	9 (81.8)	4 (28.6)
Negative	0 (0)	0 (0)	0 (0)
Unknown	12 (48.0)	2 (18.2)	10 (71.4)
Prior chemotherapy[a]			
0	3 (12.0)	3 (27.3)	0 (0)
1	8 (32.0)	1 (9.1)	7 (50.0)
2	4 (16.0)	3 (27.3)	1 (7.1)
≥3	10 (40.0)	4 (36.4)	6 (42.9)
Prior RT			
Yes	9 (36.0)	0 (0)	9 (64.3)
No	16 (64.0)	11 (100)	5 (35.7)
Prior TKI			
Yes	17 (68.0)	3 (27.3)	14 (100)
No	8 (32.0)	8 (72.7)	0 (0)

Abbreviations: ASPS, alveolar soft part sarcoma; CCS, clear cell sarcoma; ECOG, Eastern Clinical Oncology Group; PS, performance status; RT, radiation therapy; TKI, tyrosine kinase inhibitor.

[a]Prior chemotherapy includes cytotoxic agents, TKIs, and trial agents.

Efficacy

In the efficacy analysis ($n = 25$), the ORR by central review (primary end point) was 4.0% (95% CI, 0.1–20.4). The best overall responses of CR, PR, and stable disease (SD) were 0 (0%), 1 (4.0%), and 15 (60.0%), respectively (Table 2). The number of required responders in the efficacy analysis did not exceed the prespecified number. Figure 2 shows the antitumor activity regarding maximum tumor shrinkage in patients with CCS and ASPS as a waterfall and swimmer plot by central review. Almost all of the patients with CCS harbored tumor progression tendencies. The antitumor activity regarding maximum tumor shrinkage in patients with CCS and ASPS as a waterfall and

TABLE 2 Efficacy results.

	Overall, *N* = 25, No. (%)	CCS, *n* = 11, No. (%)	ASPS, *n* = 14, No. (%)
CR	0 (0)	0 (0)	0 (0)
PR	1 (4.0)	0 (0)	1 (7.1)
SD	15 (60.0)	6 (54.5)	9 (64.3)
PD	8 (32.0)	4 (36.4)	4 (28.6)
NE	1 (4.0)	1 (9.1)	0 (0)
ORR	1 (4.0)	0 (0)	1 (7.1)
DCR	16 (64.0)	6 (54.5)	10 (71.4)
Median PFS (months)	4.9	4.1	6.0
(95% CI)	(3.7–8.6)	(1.8–8.9)	(3.7–9.3)
Median OS (months)	15.8	13.2	NR
(95% CI)	(8.2–NR)	(5.9–21.9)	(6.1–NR)

Abbreviations: ASPS, alveolar soft part sarcoma; CCS, clear cell sarcoma; CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not evaluable; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progression disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

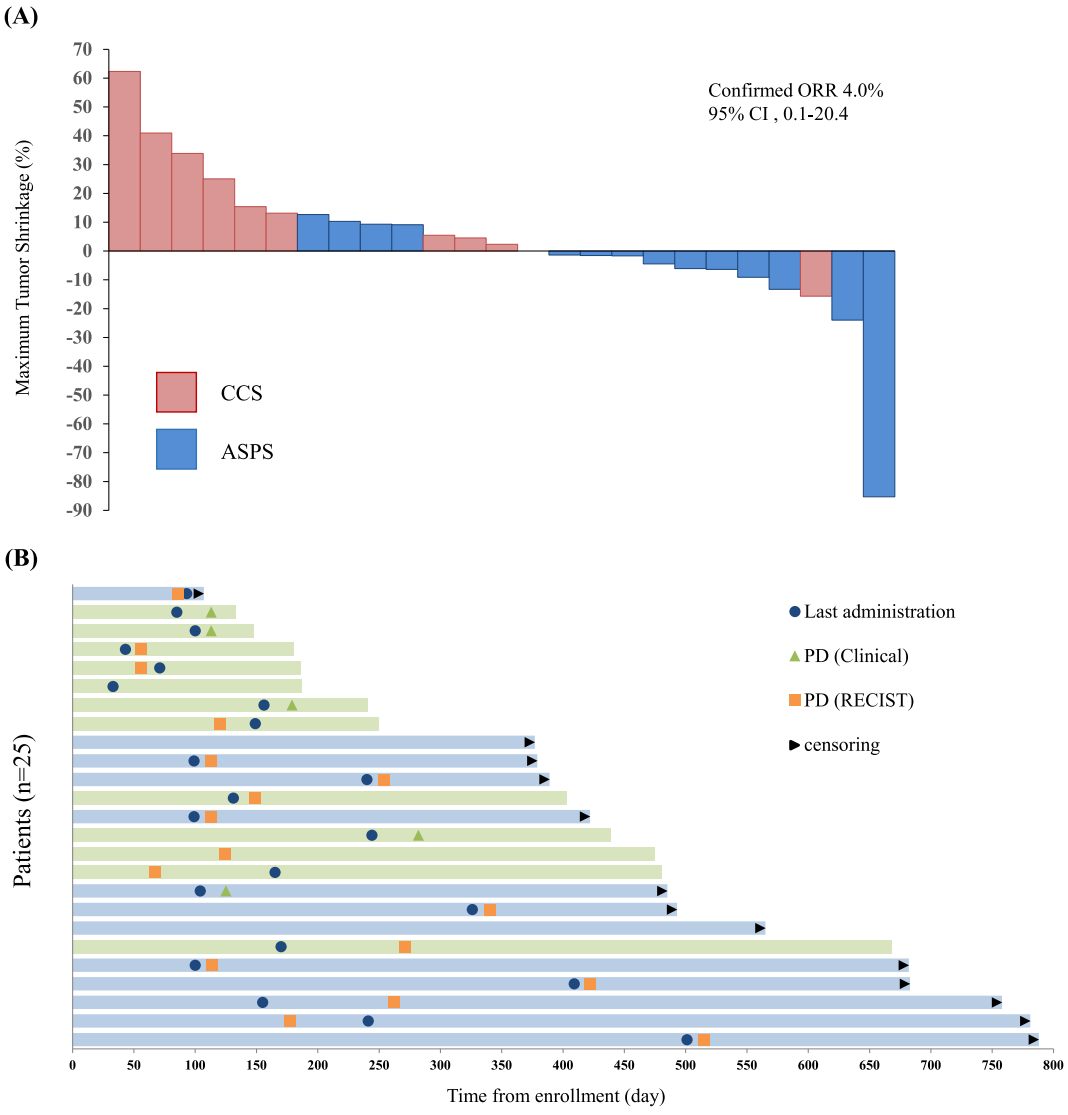

FIGURE 2 Individual antitumor activity (central review). (A) Waterfall plots in the overall population. (B) Swimmer plots in the overall population. ASPS indicates alveolar soft part sarcoma; CCS, clear cell sarcoma; ORR, overall response rate; PD, progression disease.

swimmer plots by investigator assessment are shown in Figure S1. Spider plot by central and investigator assessment are shown in Figure S2.

The ORR by central review was 0% (95% CI, 0.0–28.5) in CCS and 7.1% (95% CI, 0.2–33.9) in ASPS, respectively. The ORR by investigator assessment was 0% (95% CI, 0.00–28.5) in CCS and 14.3% (95% CI, 1.8–42.8) in ASPS, respectively. The median PFS was 4.9 (95% CI, 3.7–8.6) months in the efficacy analysis (n = 25), 4.1 (95% CI, 1.8–8.9) months in CCS, and 6.0 (95% CI, 3.7–9.3) months in ASPS, respectively. The median OS was 15.8 (95% CI, 8.2–not reached [NR]) months in the efficacy analysis, 13.2 (95% CI, 5.9–21.9) months in CCS, and NR (95% CI, 6.1–NR) months in ASPS, respectively (Figure 3). In the efficacy analysis (n = 25), the median 1-year PFS rate was 16% (95% CI, 5.0–32.5) and the median 1-year OS rate was 71% (95% CI, 48.4–84.9), respectively.

The pharmacokinetics of nivolumab regarding efficacy among patients with CCS and ASPS, conducted as translational research in the OSCAR trial, did not show any special result (Figure S3).

Safety

In the safety analysis, AEs greater than grade 1 occurred in all patients (100%), grade 2 in nine (34.6%), grade 3 in 13 (50%), and grade 4 in two (7.7%) respectively. The most common nonhematological AE was hypoalbuminemia in 15 patients (57.7%) and the second most common was nausea in seven (26.9%). The most common hematological AE was anemia in 14 (53.8%). Table 3 shows AEs ≥grade 3. No deaths related to AEs were reported. The AE that led to the discontinuation of study treatment occurred in one patient (3.8%)

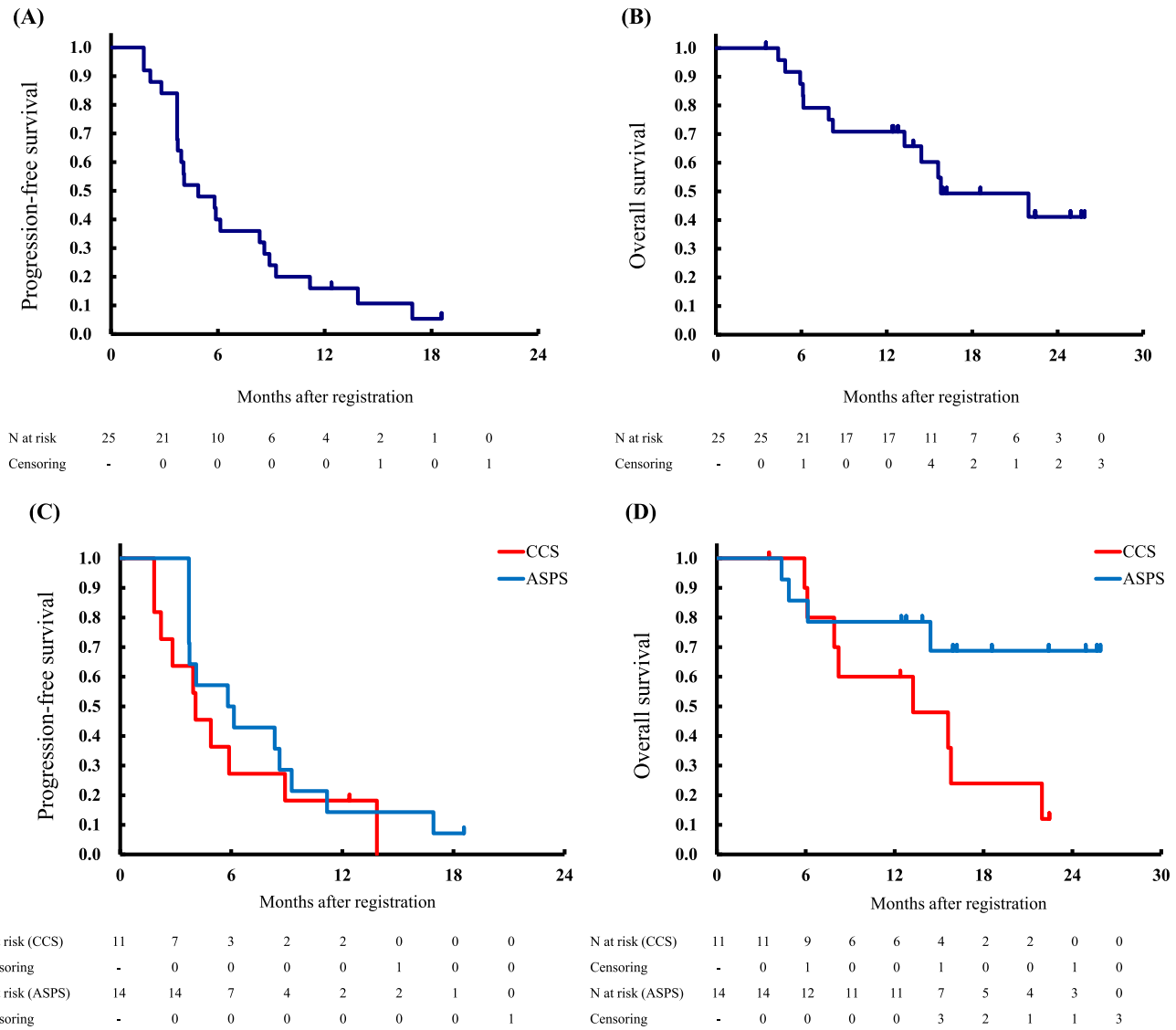

FIGURE 3 Kaplan–Meier plots (central review). (A) Progression-free survival in the overall population. (B) Overall survival in the overall population. (C) Progression-free survival in CCS and ASPS. (D) Overall survival in CCS and ASPS. ASPS indicates alveolar soft part sarcoma; CCS, clear cell sarcoma.

TABLE 3 Safety results (AEs ≥grade 3).

	Overall, *N* = 26, No. (%)	CCS, *n* = 12, No. (%)	ASPS, *n* = 14, No. (%)
Nonhematologic			
Hypoalbuminemia	4 (15.4)	3 (25.0)	1 (7.1)
Diarrhea	1 (3.8)	1 (8.3)	0 (0)
Hepatobiliary disorders	1 (3.8)	1 (8.3)	0 (0)
Arterial bleeding	1 (3.8)	1 (8.3)	0 (0)
AST increased	1 (3.8)	1 (8.3)	0 (0)
ALT increased	1 (3.8)	1 (8.3)	0 (0)
Mucositis oral	1 (3.8)	0 (0)	1 (7.1)
Colitis	1 (3.8)	0 (0)	1 (7.1)
Symptomatic epilepsy	1 (3.8)	0 (0)	1 (7.1)
Diabetic ketoacidosis	1 (3.8)	0 (0)	1 (7.1)
Hyperglycemia	1 (3.8)	0 (0)	1 (7.1)
Hematologic			
Anemia	5 (19.2)	3 (25.0)	2 (14.3)
White blood cell decreased	1 (3.8)	0 (0)	1 (7.1)
Neutrophil count decreased	1 (3.8)	0 (0)	1 (7.1)

Abbreviations: AEs, adverse events; ALT, alanine transaminase; ASPS, alveolar soft part sarcoma; AST, aspartate transaminase; CCS, clear cell sarcoma.

was persistent herpes zoster. Other ≥grade 3 AEs of arterial bleeding, oral mucositis, maculopapular rash, colitis, hepatobiliary disorders, symptomatic epilepsy, diarrhea, and diabetic ketoacidosis have been reported in single patients.

DISCUSSION

No new safety signals were observed in CCS and ASPS patients treated with nivolumab, however, the clinical efficacy was not observed in the OSCAR trial. Some ICIs demonstrated their efficacy in MITF-associated tumors,[18,19] and it may be necessary to consider that there are other influencing factors in CCS and ASPS like tertiary lymphoid structures among patients with other sarcoma.[25,26] In nonbiomarker-driven clinical trials regarding sarcoma, ICIs monotherapy did not demonstrate antitumor efficacy.[27,28] Sarcomas are generally thought of as nonimmunogenic/cold tumors for ICIs, therefore further consideration might be needed to improve immunogenic/hot tumors including amelioration of tumor microenvironment (TME).[29–31] On the other hand, the results of the OSCAR trial and the pembrolizumab trial in rare sarcomas including ASPS and CCS, which were different phase 2 trials, but there was no clear difference in PFS and OS.[32] Regarding the difference in effectiveness between atezolizumab and nivolumab for patients with ASPS,[22] it cannot be denied that they are anti–PD-L1 inhibitor and anti–PD-1 inhibitor, respectively, and that racial differences may be involved.

TKIs like cediranib or pazopanib have demonstrated modest efficacy for ASPS in recent clinical trials.[8,33] A feature of these TKIs is that the duration of response does not last for a long time, therefore, further development is desirable. A recent clinical trial using a combination of TKI and ICI was conducted to evaluate the efficacy in patients with sarcomas including ASPS and showed favorable results, especially in ASPS.[20,21] Unfortunately, however, this study did not address patients with CCS and included only a small number of Asian patients. Therefore, further clinical developments focused on TKIs and ICIs for patients with ASPS across different races are required, and completely novel approaches regarding therapeutic developments for patients with CCS are needed.

Fifteen patients (57.7%) experienced grade 3 or higher AEs of any relationship to nivolumab. The details of AEs ≥grade 3 were anemia of five (19.2%), hypoalbuminemia of four (15.4%), and other adverse events of one each (3.8%). Only one patient (3.8%) discontinued nivolumab due to persistent herpes zoster (Table 3). These safety profiles were considered to be consistent with previous reports regarding nivolumab monotherapy.[17,18]

The key limitations of the OSCAR trial were the open-label design, enrollment of only Japanese patients, and the mixture of results on patients with CCS and ASPS. We investigated a relatively small sample size and did not plan the statistical setting to separately assess the efficacy of nivolumab in patients with CCS and ASPS. The PFS of 4.9 months and OS of 15.8 months were difficult to evaluate due to the indolent characteristics of CCS and ASPS.

In conclusion, the primary end point of the ORR in this study was not met for CCS and ASPS. However, one patient with ASPS (7.1%) showed PR with nivolumab and nivolumab also showed a tolerable safety profile for patients with CCS and ASPS. Further studies were considered to be needed to evaluate the efficacy of ICIs especially for patients with ASPS.

AUTHOR CONTRIBUTIONS

Tadaaki Nishikawa: Conceptualization, methodology, investigation, validation, formal analysis, visualization, writing–original draft, writing–review and editing, supervision, resources, and project administration. **Shigeki Kakunaga**: Conceptualization, methodology, investigation, validation, formal analysis, resources, writing–original draft, and writing–review and editing. **Kenji Tamura**: Conceptualization, methodology, investigation, validation, formal analysis, writing–original draft, writing–review and editing, and resources. **Masashi Ando**: Conceptualization, methodology, investigation, validation, formal analysis, writing–original draft, writing–review and editing, and resources. **Toshifumi Ozaki**: Conceptualization, methodology, investigation, validation, formal analysis, resources, writing–original draft, and writing–review and editing. **Akira Kawai**: Conceptualization, methodology, investigation, validation, formal analysis, resources, writing–original draft, and writing–review and editing. **Takafumi Ueda**: Conceptualization, methodology, investigation, validation, formal analysis, resources, writing–original draft, and writing–review and editing. **Mamiko Kawasaki**: Conceptualization, methodology, software, data curation, funding acquisition, project administration, writing–original draft, writing–review and editing, validation, investigation, and formal analysis. **Sawako Tomatsuri**: Conceptualization, methodology, software, data curation, investigation, validation, formal analysis, funding acquisition, project administration, writing–original draft, and writing–review and editing. **Nobuko Okamura**: Conceptualization, methodology, software, data curation, investigation, validation, formal analysis, funding acquisition, project administration, writing–original draft, and writing–review and editing. **Masahisa Kamikura**: Conceptualization, methodology, software, data curation, investigation, validation, formal analysis, funding acquisition, writing–original draft, writing–review and editing, and project administration. **Akinobu Hamada**: Conceptualization, methodology, investigation, validation, formal analysis, writing–original draft, and writing–review and editing. **Akihiko Yoshida**: Conceptualization, methodology, investigation, validation, formal analysis, writing–original draft, and writing–review and editing. **Akihiro Hirakawa**: Conceptualization, methodology, software, data curation, investigation, validation, formal analysis, supervision, visualization, writing–review and editing, and writing–original draft. **Taro Shibata**: Conceptualization, methodology, software, data curation, investigation, validation, formal analysis, supervision, writing–original draft, writing–review and editing, and visualization. **Kenichi Nakamura**: Conceptualization, methodology, software, data curation, investigation, validation, formal analysis, supervision, writing–original draft, writing–review and editing, visualization, and project administration. **Kan Yonemori**: Conceptualization, methodology, investigation, validation, formal analysis, supervision, funding acquisition, project administration, resources, writing–original draft, and writing–review and editing.

ACKNOWLEDGMENTS

We thank all the patients, physicians, and clinical research coordinators, especially Mari Takahashi, who participated in this study. This study was supported by the Japan Agency for Medical Research and Development (AMED) (JP16lk0201044) and by ONO Pharmaceutical Co., Ltd. Nivolumab was provided by Ono. Ono had the opportunity to review the final manuscript but did not have the right to prevent publication.

CONFLICT OF INTEREST STATEMENT

Tadaaki Nishikawa reports fees for participating on a speakers' bureau from Chugai Pharma, Eisai, Genmab, MSD, Roche Diagnostics, Sanofi, and Takeda; and institutional research funding from AstraZeneca and Daiichi-Sankyo. Akira Kawai reports fees for participating on a speakers' bureau and/or acting in a consulting/advisory role and institutional research funding from Boehringer Ingelheim, Taiho Pharmaceutical, and Takara Bio. Akihiko Yoshida reports research funding from Daiichi-Sankyo and Chugai Pharma. Akihiro Hirakawa reports consulting fees from Ono Pharmaceutical, Astellas Pharma, Kissei Pharmaceutical, Nippon Shinyaku, Kyowa Kirin International, Chugai Pharma, AbbVie, Novartis, and Taiho Pharmaceutical; and fees for participating on a speakers' bureau from Chugai Pharma and Takeda. Kan Yonemori reports fees for participating on a speakers' bureau and/or acting in a consulting/advisory role from Pfizer, Eisai, AstraZeneca, Eli Lilly, Takeda, Chugai, MSD, FujiFilm Pharma, Bayer, Asteras, Boehringer Ingelheim, Daiichi-Sankyo, PDR Pharma, and Sanofi; and institutional research funding from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc, Daiichi-Sankyo, AstraZeneca, Taiho, Pfizer, Novartis, Takeda, Chugai, Ono, Seattle Genetics, Eisai, Eli Lilly, Genmab, Boehringer Ingelheim, Kyowa Hakko Kirin, Nihon Kayaku, Sanofi, and Haihe. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Nishikawa T, Kakunaga S, Tamura K, et al. Efficacy and safety of nivolumab monotherapy in patients with unresectable clear cell sarcoma and alveolar soft part sarcoma (OSCAR Trial/NCCH1510). *Cancer*. 2024;130(22):3836-3844. doi:10.1002/cncr.35483