European Journal of Cancer 228 (2025) 115750

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Original research

Outcome of systemic therapy in patients with advanced rare skin cancers: A retrospective multicenter DeCOG study of 209 patients

Selma Ugurel [a,*], Nessr Abu Rached [b], Thilo Gambichler [b], Miriam Mengoni [c], Thomas Tüting [c], Jessica C. Hassel [d], Robin Reschke [d], Georg C. Lodde [e], Jan-Malte Placke [e], Dirk Schadendorf [e], Lydia Reinhardt [f], Alexander Kreuter [g], Martin Gschnell [h], Jochen Utikal [i], Michael Erdmann [j], Pia Dücker [k], Doris Helbig [l], Cindy Franklin [l], Christoffer Gebhardt [m], Gabriela Poch [n], Katharina C. Kähler [o], Michael Weichenthal [o], Ralf Gutzmer [p], Lucie Heinzerling [q], Carsten Weishaupt [r], Peter Mohr [s], Kai-Martin Thoms [t], Berenice Lang [u], Bastian Schilling [v], Sebastian Haferkamp [w], Michael Sachse [x], Julia Welzel [y], Franziska Jochims [z], Ulrike Raap [aa], Gaston Schley [ab], Patrick Terheyden [ac], Edgar Dippel [ad], Christoph Pöttgen [ae], Jürgen C. Becker [e,af], Alpaslan Tasdogan [e], Teresa Amaral [ag], Lena Nanz [ag], Ulrike Leiter [ag]

[a] *Department of Dermatology, Bielefeld University, Medical School and University Medical Center OWL, Klinikum Bielefeld Rosenhöhe, Bielefeld, Germany*
[b] *Department of Dermatology, Ruhr-University Bochum, Bochum, Germany*
[c] *Department of Dermatology, University of Magdeburg, Magdeburg, Germany*
[d] *Department of Dermatology and National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany, German Cancer Research Center, Heidelberg, Germany*
[e] *Department of Dermatology, University Hospital Essen, University of Duisburg-Essen, and German Cancer Consortium (DKTK), partner site Essen/Düsseldorf, Essen, Germany*
[f] *Skin Cancer Center at the National Center for Tumor Diseases Dresden, Department of Dermatology, University Hospital Carl Gustav Carus, Dresden, Germany*
[g] *Department of Dermatology, Helios Kliniken Oberhausen and Duisburg, Oberhausen, Germany*
[h] *Department of Dermatology, University of Marburg, Marburg, Germany*
[i] *Department of Dermatology, University Medical Center Mannheim, Ruprecht-Karl University of Heidelberg, Mannheim, and Skin Cancer Unit, German Cancer Research Center (DKFZ), Heidelberg, Germany*
[j] *Department of Dermatology, University Hospital Erlangen, Erlangen, Germany*
[k] *Department of Dermatology, Klinikum Dortmund, Dortmund, Germany*
[l] *Department of Dermatology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany*
[m] *Department of Dermatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*
[n] *Department of Dermatology, Charité – Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany*
[o] *Department of Dermatology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany*

* Correspondence to: Department of Dermatology, Bielefeld University, Medical School and University Medical Center OWL, Klinikum Bielefeld Rosenhöhe, An der Rosenhöhe 27, Bielefeld 33647, Germany.

E-mail addresses: selma.ugurel@klinikumbielefeld.de (S. Ugurel), Nessr.AbuRached@ruhr-uni-bochum.de (N. Abu Rached), Thilo.Gambichler@ruhr-uni-bochum.de (T. Gambichler), miriam.mengoni@med.ovgu.de (M. Mengoni), thomas.tueting@med.ovgu.de (T. Tüting), Jessica.Hassel@med.uni-heidelberg.de (J.C. Hassel), robinniklas.reschke@med.uni-heidelberg.de (R. Reschke), georg.lodde@uk-essen.de (G.C. Lodde), jan-malte.placke@uk-essen.de (J.-M. Placke), dirk.schadendorf@uk-essen.de (D. Schadendorf), Lydia.Reinhardt@ukdd.de (L. Reinhardt), alexander.kreuter@helios-gesundheit.de (A. Kreuter), gschnell@med.uni-marburg.de (M. Gschnell), Jochen.Utikal@umm.de (J. Utikal), Michael.Erdmann@uk-erlangen.de (M. Erdmann), Pia.Duecker@klinikumdo.de (P. Dücker), doris.helbig@uk-koeln.de (D. Helbig), cindy.franklin@uk-koeln.de (C. Franklin), ch.gebhardt@uke.de (C. Gebhardt), gabriela.poch@charite.de (G. Poch), kkaehler@dermatology.uni-kiel.de (K.C. Kähler), mweichenthal@dermatology.uni-kiel.de (M. Weichenthal), Ralf.Gutzmer@muehlenkreiskliniken.de (R. Gutzmer), Lucie.Heinzerling@med.uni-muenchen.de (L. Heinzerling), carsten.weishaupt@ukmuenster.de (C. Weishaupt), Peter.Mohr@elbekliniken.de (P. Mohr), kai.thoms@med.uni-goettingen.de (K.-M. Thoms), berenice.lang@unimedizin-mainz.de (B. Lang), b.schilling@med.uni-frankfurt.de (B. Schilling), sebastian.haferkamp@klinik.uni-regensburg.de (S. Haferkamp), michael.sachse@klinikum-bremerhaven.de (M. Sachse), Julia.Welzel@uk-augsburg.de (J. Welzel), Franziska.Jochims@medizin.uni-leipzig.de (F. Jochims), Raap.Ulrike@klinikum-oldenburg.de (U. Raap), gaston.schley@helios-gesundheit.de (G. Schley), patrick.terheyden@uksh.de (P. Terheyden), dippele@klilu.de (E. Dippel), christoph.poettgen@uk-essen.de (C. Pöttgen), j.becker@dkfz.de (J.C. Becker), alpaslan.tasdogan@uk-essen.de (A. Tasdogan), Teresa.Amaral@med.uni-tuebingen.de (T. Amaral), Lena.Nanz@med.uni-tuebingen.de (L. Nanz), Ulrike.Leiter@med.uni-tuebingen.de (U. Leiter).

https://doi.org/10.1016/j.ejca.2025.115750
Received 3 August 2025; Accepted 23 August 2025
Available online 30 August 2025

[p] Department of Dermatology, Johannes Wesling Medical Center, Ruhr University Bochum, Minden, Germany
[q] Department of Dermatology, Ludwigs Maximilians University München, München, Germany
[r] Department of Dermatology, University Hospital Münster, Münster, Germany
[s] Department of Dermatology, Elbe-Klinikum Buxtehude, Buxtehude, Germany
[t] Department of Dermatology, University Medical Center Göttingen, Göttingen, Germany
[u] Department of Dermatology, University Hospital Mainz, Mainz, Germany
[v] Department of Dermatology, University Hospital Würzburg, Würzburg, and Department of Dermatology, University Hospital, Goethe-University, Frankfurt, Germany
[w] Department of Dermatology, University Hospital Regensburg, Regensburg, Germany
[x] Department of Dermatology, Klinikum Bremerhaven, Bremerhaven, Germany
[y] Department of Dermatology, University Hospital Augsburg, Augsburg, Germany
[z] Department of Dermatology, University Hospital Leipzig, Leipzig, Germany
[aa] Department of Dermatology, University Hospital Oldenburg, Oldenburg, Germany
[ab] Department of Dermatology, Klinikum Schwerin, Schwerin, Germany
[ac] Department of Dermatology, University Hospital Lübeck, Lübeck, Germany
[ad] Department of Dermatology, Klinikum Ludwigshafen, Ludwigshafen Germany
[ae] Department of Radiotherapy, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
[af] Translational Skin Cancer Research (TSCR), Department of Dermatology and West German Cancer Center, University of Medicine Duisburg-Essen, Essen, Germany
[ag] Department of Dermatology, University Hospital Tübingen, Tübingen, Germany

ARTICLE INFO

Keywords:
Angiosarcoma
Kaposi sarcoma
Cutaneous adnexal carcinoma
Pleomorphic dermal sarcoma
Immune checkpoint inhibition
Chemotherapy
Targeted therapy

ABSTRACT

Introduction: For rare skin cancers, few data exist on the outcome of systemic therapies, particularly immune checkpoint inhibition (ICI). The present study analysed the real-world use of different systemic therapies including ICI, and its outcome in patients with advanced rare skin cancers.
Methods: This retrospective multicenter study included patients who received systemic therapy for advanced, non-resectable cutaneous angiosarcoma (AS), Kaposi sarcoma (KS), pleomorphic dermal sarcoma (PDS), or cutaneous adnexal carcinoma (CAC). Study endpoints were best overall response (BOR), progression-free survival (PFS) and overall survival (OS).
Results: 209 patients (77 AS; 81 KS; 14 PDS; and 37 CAC) from 30 centers were included. As first-line treatment AS and KS patients predominantly received chemotherapy (77.9 %; 63.0 %), while PDS and CAC patients mostly received ICI (64.4 %; 43.2 %). BOR in first-line across all therapy types was 65.5 % in KS, 50.0 % in PDS, 41.6 % in AS, and 10.8 % in CAC. BOR for ICI was 66.6 % for PDS, 58.3 % for AS, 33.3 % for KS, and 4.3 % for CAC, irrespective of treatment line. 1-year PFS rate upon any first-line therapy was 70.7 % for PDS, 45.7 % for KS, 25.6 % for AS, and 18.5 % for CAC ($p < 0.001$). 1-year tumor-specific OS rate was 97.3 % in KS, 84.2 % in AS, 67.7 % in PDS, and 65.4 % in CAC ($p < 0.001$).
Conclusions: Type and outcome of systemic therapy differed between cancer entities. Efficacy of ICI was high in PDS and AS, moderate in KS, and low in CAC. Patients with advanced CAC revealed an extremely poor prognosis regardless of the type of therapy used.

1. Introduction

The most common types of skin cancer such as melanoma and squamous cell carcinoma are known for their strong immunogenicity, leading to the high treatment efficacy of immune checkpoint inhibitors (ICI) reported in clinical trials. For rare skin cancer entities, only few data exist on the frequency of use of systemic therapies, especially ICI, and its treatment outcome.

These rare skin cancers comprise the heterogenous groups of cutaneous sarcomas and cutaneous adnexal carcinomas. Cutaneous sarcomas are tumors of mesenchymal origin including angiosarcoma (AS), Kaposi sarcoma (KS), and pleomorphic dermal sarcoma (PDS) [1]. Cutaneous adnexal carcinomas (CAC) contain per se a large and diverse number of tumor entities, deriving from sebaceous, apocrine or eccrine glands or hair follicle structures [2]. Although these tumors all originate in the skin, they exhibit distinct etiologies, cellular origins, and carcinogenic drivers, including chronic UV radiation, viral infections, or unknown factors. There is no exact data on incidences, but compared to other non-melanoma skin cancers (NMSC) these tumors are rare to extremely rare. Due to their intermediate to often even high malignancy, depending on the cancer entity, a significant proportion of patients develop non-resectable disease such as locally advanced primary tumors, as well as regional or distant metastases. Besides locoregional methods such as radiotherapy or cryosurgery, these patients are in the need of systemic treatment. Due to the rarity of the respective cancer entities, data from prospective clinical trials are rare or absent.

The present study aimed at investigating the frequency of use of different types of systemic therapy, with a special focus on ICI immunotherapy, and its outcome in patients with advanced rare skin cancers. We focused on the most common of these rare skin cancer entities, and used a German-wide retrospective multicenter approach collecting real-world data from specialized, board-certified skin cancer centers.

2. Patients and methods

2.1. Patient registry

Patients with rare skin cancers presenting at board-certified skin cancer centers of the German Dermatologic Cooperative Oncology Group (DeCOG) were retrospectively identified via the respective digital clinic information systems according to the following inclusion criteria: histologically confirmed angiosarcoma (AS), Kaposi sarcoma (KS), pleomorphic dermal sarcoma (PDS), or cutaneous adnexal carcinoma (CAC), and systemic treatment for non-resectable locally advanced or metastatic disease between April 1, 2001 and September 30th, 2023. Systemic therapies were grouped and analyzed as immune checkpoint inhibitors, ICI (nivolumab, pembrolizumab, ipilimumab, as single agents or combination), chemotherapy (paclitaxel, doxorubicin, cisplatin, carboplatin, as single agents or combinations), targeted therapy (cetuximab, trametinib, pazopanib, alpelisib), interferon(IFN)-alpha, and others. Data were extracted from local patient files and captured within a central electronic data registry. The study was approved by the ethics committee of the University Duisburg-Essen (22–10810-BO). Study endpoints were best overall response (BOR), progression-free survival (PFS) and overall survival (OS).

Patient, tumor, and treatment characteristics were recorded. Concerning treatment characteristics, disease stage, ECOG overall performance status, and serum LDH level at treatment start were recorded. The type of therapy, drugs used, and treatment response was documented for the respective lines of therapy. Treatment response was determined as BOR recorded from treatment start until disease progression or start of the next treatment line, and was evaluated according to clinical evaluation in the interdisciplinary skin cancer board at each respective center according to RECIST [14]. During therapy, patients underwent regular staging procedures consisting of imaging techniques such as CT, MRI or PET-CT at least every three months. If there was suspicion of disease progression, staging was anticipated. PFS and OS were defined as time from therapy start until disease progression or death, respectively; if no such event occurred, the date of the last patient contact was used as endpoint of survival assessment (censored observation).

2.2. Statistical analysis

To test comparability between disease groups, clinical and demographic patient characteristics were evaluated. Numerical variables were described by median and inter-quartile range (IQR); patient cohorts were compared using Wilcoxon rank-sum test or two-sided chi-square tests, as appropriate. Survival probabilities with 95 % confidence intervals (CI) were calculated using Kaplan-Meier analysis. The two-sided log rank test was used for comparison of survival between groups. P-values < 0.05 were considered statistically significant. Statistical analyses were performed with the statistical software SPSSv21 (SPSS Inc., Chicago, IL, USA) and STATA/ICv15.1 (StataCorp LLC, College Station, TX, USA). Data analyses were conducted from December 15, 2023 to March1st, 2024.

3. Results

3.1. Patient characteristics

A total of 209 patients who had received systemic therapy for advanced rare skin cancer were identified at 30 skin cancer centers according to the above described criteria. Of those, 81 patients had KS, 77 had AS, 37 had CAC, and 14 had PDS (Table 1, Fig. 1A). The CAC cohort included patients with the following tumors: Porocarcinoma (n = 13), apocrine adenocarcinoma (n = 4), eccrine sweat gland carcinoma (n = 4), apocrine sweat gland carcinoma (n = 3), hidradenocarcinoma (n = 3), sebaceous carcinoma (n = 2), malign cylindroma (n = 2), adenoid cystic carcinoma (n = 1), cutaneous apocrine carcinoma (n = 1), malign nodular hidradenoma (n = 1), syringocystic carcinoma (n = 1), and CAC not otherwise specified (n = 2). Within the skin cancer entities, significant differences in gender, age, concomitant immunosuppression, and primary tumor localization were observed as expected (all $p < 0.001$; Table 1). AS and PDS were predominantly localized on the head and neck (72.5 % and 78.5 %, respectively), KS on the lower extremities (71.6 %), and CAC on the trunk (43.2 %). Additionally, significant differences between entities were found for stage at primary

Table 1
Patient characteristics (total cohort, n = 209).

	AS	KS	PDS	CAC	P value
	N = 77 (%)	N = 81 (%)	N = 14 (%)	N = 37 (%)	
Sex					**< 0.001**
male	48 (62.6)	75 (92.6)	13 (92.9)	21 (56.8)	
female	29 (37.7)	6 (7.4)	1 (7.1)	16 (43.2)	
Age					
Median yrs (IQR)	77 (69;84)	62 (51;75)	78 (63;79)	64 (56;75)	
Immunosuppression					**< 0.001**
no	64 (83.1)	51 (63.0)	8 (57.1)	35 (94.6)	
yes	13 (16.9)	30 (37.0)	6 (42.9)	2 (5.4)	
Hematologic disease	2 (2.6)	4 (4.9)	3 (21.4)	2 (5.4)	
Iatrogenic/OTR	1 (1.3)	5 (6.3)	2 (14.2)	0	
Other cancer	10 (13.0)	0	1 (7.1)	0	
HIV	0	21 (25.9)	0	0	
Localisation of primary tumor					**< 0.001**
Face	25 (32.5)	3 (3.7)	3 (21.4)	7 (18.9)	
Scalp/Neck	31 (40.3)	1 (1.2)	8 (57.1)	7 (18.9)	
Trunk	11 (14.3)	2 (2.5)	1 (7.1)	16 (43.2)	
Lower extremity	9 (11.7)	58 (71.6)	2 (14.3)	6 (16.2)	
Upper extremity	1 (1.3)	5 (6.2)	0	0	
Genital/anal	0	4 (4.9)	0	1 (2.7)	
Others/multiple	0	8 (9.9)	0	0	
Stage at primary diagnosis					**0.009**
Primary tumor	62 (80.5)	64 (79.0)	13 (92.9)	23 (62.2)	
Local recurrence	2 (2.6)	0	0	0	
In-transit metastases	0	8 (9.9)	0	5 (13.5)	
Lymph node metastases	6 (7.8)	4 (4.9)	0	8 (21.6)	
Distant metastases	6 (7.8)	5 (6.2)	1 (7.1)	1 (2.7)	
PD-L1 expression (tumor)					**< 0.001**
Unknown/ not done	61 (73.2)	77 (95.1)	9 (64.3)	27 (73.0)	
positive	13 (18.2)	0	5 (35.7)	5 (13.5)	
negative	2 (2.6)	4 (4.1)	0	5 (13.5)	
Pre-treatment (non-systemic)					**0.028**
None	44 (57.1)	50 (61.7)	4 (28.6)	11 (29.7)	
Surgery R0/R1	8 (10.4)	6 (7.4)	1 (7.1)	4 (10.8)	
Surgery + Radiotherapy	4 (5.2)	3 (3.7)	2 (14.2)	5 (13.5)	
Radiotherapy	20 (26.0)	15 (18.5)	6 (42.9)	17 (45.9)	
Electrochemotherapy	1 (1.3)	2 (2.5)	0	0	
Cryotherapy	0	3 (3.7)	0	0	
Others	0	2 (2.4)	0	0	

Percentages are given per column. AS, angiosarcoma; KS, Kaposi sarcoma; PDS, pleomorphic dermal sarcoma; CAC, cutaneous adnexal carcinoma. IQR, inter-quartile range; OTR, organ transplant recipient.

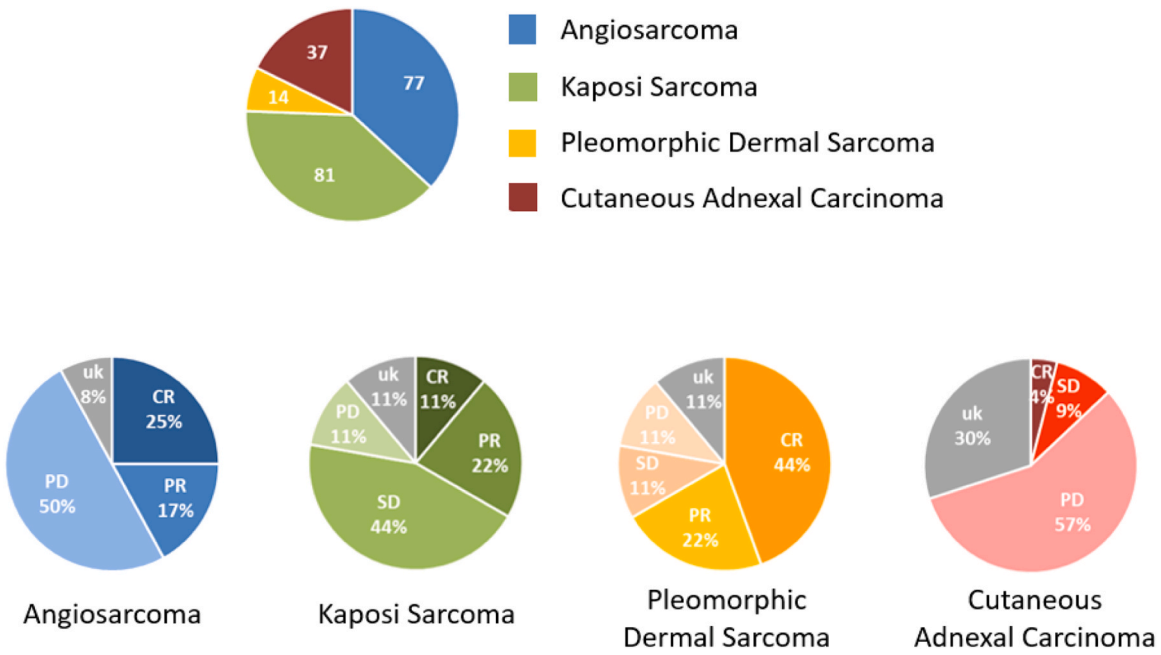

Fig. 1. Schematic presentation of (A) the patient numbers in the total cohort (n = 209), and (B) the percentage of best overall response to immune checkpoint inhibition therapy of all lines by cancer entity (n = 53). AS, angiosarcoma; KS, Kaposi sarcoma; PDS, pleomorphic dermal sarcoma; CAC, cutaneous adnexal carcinoma.

diagnosis (p = 0.009), prior non-systemic treatment (p = 0.028), and PD-L1 expression (p < 0.001). Most of AS (57.1 %) and KS (61.7 %) were not pre-treated, whereas 64.2 % of the PDS patients previously had received surgery, radiotherapy or both. In CAC, 45.9 % of patients were pre-treated with radiotherapy, 10.8 % with surgery, and 13.5 % with a combination of both (Table 1).

3.2. Systemic treatment

At baseline of systemic therapy, the skin cancer entities showed differences in terms of tumor spread and stage of disease (p < 0.001; Table 2). 79.3 % of AS patients and 75.3 % of KS patients were treated for their primary tumor or locally advanced disease, while this was the case in only 28.6 % of PDS and 16.2 % of CAC patients, respectively (p < 0.001; Table 2). Regarding metastatic sites, only 9.1 % of AS patients and 16.0 % of KS patients had visceral metastasis at therapy start, whereas these were present in 64.3 % of PDS and 48.6 % of CAC patients (p < 0.001; Table 2). Further differences between skin cancer entities were found regarding serum LDH activity (p < 0.001), and ECOG status (p = 0.028). ECOG of 2 or more was found in 21.4 % of PDS and 18.2 % of AS patients, but only in 10.8 % of CAC and in 8.6 % of KS patients. Regarding the type of first-line treatment, 77.9 % of AS and 63.0 % of KS patients received chemotherapy. In AS, 65 % were treated with paclitaxel and 28.3 % with doxorubicin. KS patients received doxorubicin in 94 %. In contrast, PDS patients were predominantly treated with ICI as first-line therapy (64.4 %, all patients received PD-1 inhibitor monotherapy), followed by chemotherapy with doxorubicine in 21.4 %. CAC patients received most frequently ICI as first-line therapy (43.2 %; all anti-PD-1 monotherapy), followed by chemotherapy in 29.7 % and targeted therapy in 21.6 % (p < 0.001; Table 2). Details on second-line therapy are presented in Suppl Table 1.

3.3. Treatment response

Response rates (BOR) to first- and second-line therapy are shown in Table 2, BOR to the respective treatment types are listed in Table 3. In first-line, an objective response (CR+PR, ORR) was achieved in 41.6 % of AS patients; for chemotherapy the ORR was 36.7 %, and for ICI therapy it was 66.7 %. In KS, 65.5 % ORR was observed, 74.3 % in patients treated with chemotherapy, and 29.6 % under IFNalpha. Only one KS patient was treated with ICI showing a stable disease, see Table 3. In PDS an ORR of 50 % was reported. 3 patients were treated with chemotherapy, for these the ORR was 33.3 %, the disease control rate (DCR, CR+PR+SD) was 100 %. Of 9 patients treated with ICI, 66.6 % showed CR or PR, the DCR was 77.7 %, Table 3. CAC patients showed the lowest ORR (10.8 %) to first-line systemic therapy, the DCR in this skin cancer entity was 26.2 %, Table 2. 54.1 % (n = 20) of the CAC patients had a primary progression (BOR=PD) under systemic treatment. Of 11 CAC patients treated with chemotherapy, 62.5 % showed a primary progression, 12.5 % a partial response and 25.0 % a stable disease. No complete response was observed, Table 3.

A progression upon or after first-line systemic treatment was recorded in 70.3 % of CAC, 51.9 % of AS, 42 % of KS, and 7.1 % of PDS patients. After disease progression, 77 patients of the total cohort underwent further treatment lines (Table 2). Of those, 23 were AS patients of whom 11 received another type of chemotherapy, 4 received ICI, and 5 received a combination of chemotherapy and targeted therapy. 34 KS patients were treated in second-line, 20 with chemotherapy, 10 with IFNalpha, and 3 with ICI. For PDS, no patient was treated in second-line. 19 CAC patients received subsequent treatment, whereof 7 received chemotherapy, 3 ICI, 2 IFNalpha, and 6 were treated with targeted therapy.

Analyzing specifically the subgroup of patients treated with ICI immunotherapy regardless of treatment line, PDS and AS showed high OR rates of 66.6 % (6/9 patients) and 58.3 % (7/12 patients), respectively (Fig. 1B). KS patients showed a moderate ORR of 33.3 % (3/9 patients), and CAC patients revealed a very low ORR of only 4.3 % (1/23 patients), Table 4, Fig. 1B. Agents used for ICI immunotherapy are presented in Suppl Table 2.

3.4. Survival outcomes

The median follow-up time of the total patient cohort (n = 209) accounted for 18 months (IQR:5;44). It was longest for KS (38 months, 95 %-CI=17.5;73), followed by AS (11 month, 95 %-CI=2.5;25) and PDS (10 months, 95 %-CI=2.0;20). CAC patients had the shortest follow-

Table 2
Systemic first-line therapy (total cohort, n = 209).

	AS	KS	PDS	CAC	P value
	N = 77 (%)	N = 81 (%)	N = 14 (%)	N = 37 (%)	
Overall performance status (ECOG) at start of first-line therapy					**0.029**
0	34 (44.2)	53 (65.5)	7 (50.0)	20 (54.1)	
1	19 (24.7)	10 (12.3)	3 (21.4)	7 (18.9)	
2	13 (16.9)	6 (7.4)	1 (7.1)	4 (10.8)	
3	1 (1.3)	1 (1.2)	2 (14.3)	0	
Tumor stage at start of first-line therapy					**< 0.001**
Primary tumor	40 (52.0)	52 (64.2)	2 (14.3)	3 (8.1)	
Locally advanced	21 (27.3)	9 (11.1)	2 (14.3)	3 (8.1)	
In-transit metastases	0	2 (2.5)	0	1 (2.7)	
Lymph node metastases	9 (11.7)	5 (6.2)	1 (7.1)	12 (32.4)	
Distant metastases	7 (9.1)	13 (16.0)	9 (64.3)	18 (48.6)	
Type of treatment					**< 0.001**
Chemotherapy	60 (77.9)	51 (63.0)	3 (21.4)	11 (29.7)	
Targeted therapy	2 (2.6)	1 (1.2)	2 (14.3)	8 (21.6)	
ICI immunotherapy	6 (7.8)	1 (1.2)	9 (64.4)	16 (43.2)	
Interferon-alpha	1 (1.3)	27 (33.3)	0	0	
Others	2 (2.6)	1 (1.2)	0	2 (5.4)	
Chemotherapy plus targeted therapy	6 (7.8)	0	0	0	
Best overall response					**< 0.001**
CR	14 (18.2)	16 (19.8)	2 (14.3)	1 (2.7)	
PR	18 (23.4)	37 (45.7)	5 (35.7)	3 (8.1)	
SD	15 (19.5)	14 (17.3)	3 (21.4)	6 (16.2)	
PD	17 (22.1)	9 (11.1)	1 (7.1)	20 (54.1)	
Mixed response	1 (1.3)	0	0	0	
unknown	12 (15.6)	5 (6.1)	3 (21.4)	7 (18.9)	
ORR	32 (41.6)	53 (65.5)	7 (50.0)	4 (10.8)	
DCR	47 (61.1)	67 (82.8)	10 (71.4)	10 (26.2)	
Reason for end of treatment					**< 0.001**
Progression	21 (27.3)	12 (14.8)	0	22 (59.5)	
Toxicity	13 (16.9)	10 (12.3)	3 (21.4)	2 (5.4)	
Patient's wish	5 (6.5)	11 (13.6)	1 (7.1)	2 (5.4)	
Regular end of treatment (CR/PR)	16 (20.8)	29 (35.8)	2 (14.3)	1 (2.7)	
Death	6 (7.8)	0	1 (7.1)	1 (2.7)	
others	2 (2.6)	3 (3.7)	2 (14.3)	1 (2.7)	
unknown	0	0	4 (28.6)	4 (10.8)	
Progression under/after treatment					**< 0.001**
yes	40 (51.9)	34 (42.0)	1 (7.1)	26 (70.3)	
no	22 (28.6)	42 (51.9)	7 (50.0)	4 (10.8)	
unknown	15 (19.5)	5 (6.2)	6 (42.8)	7 (18.9)	
Death					**< 0.001**
yes	29 (37.7)	11 (13.6)	5 (35.7)	19 (51.4)	
no	30 (39.0)	66 (81.5)	9 (64.3)	9 (24.3)	
unknown	18 (23.4)	4 (4.9)	0	9 (24.3)	
Cause of death					**0.028**
Skin cancer	13 (44.8)	3 (30.0)	3 (60.0)	17 (89.5)	
Other cancer	1 (3.4)	0	1 (20.0)	1 (5.3)	
Other causes	12 (41.4)	6 (60.0)	1 (20.0)	1 (5.3)	
unknown	3 (10.3)	1 (10.0)	0	0	

Patient and tumor characteristics at start of systemic first-line therapy, and therapy outcome parameters. ORR, objective response rate; DCR, disease control rate; AS, angiosarcoma; KS, Kaposi sarcoma; PDS, pleomorphic dermal sarcoma; CAC, cutaneous adnexal carcinoma.

up with a median of 6 months (95 %-CI: 2.0;18.5). For the total patient cohort the median PFS after start of first-line systemic therapy was 6 months (95 %-CI=3.7;8.29); its 1-year PFS rate was 29.8 % (95 %-CI=20.9;38.6). Differentiating between the four skin cancer entities, the median PFS was not reached for PDS, 66 months (95 %-CI=30.9;101.1) for KS, 15 months (95 %-CI=7.3;22.6) for AS, and only 3 months (95 %-CI=1.6;4.3) for CAC (Table 5; Fig. 2A). Similarly, the 1-year PFS rate was 70.7 % for PDS, 45.7 % for KS, 25.6 % for AS, and only 18.5 % for CAC ($p < 0.001$).

A total of 64 patients (30.6 %) had died during follow-up; 19 patients (51.4 %) in the CAC group, 29 (37.7 %) in the AS group, 5 (35.7 %) in the PDS group, and 11 (13.6 %) in the KS group ($p < 0.001$; Table 2). Cause of death was the respective skin cancer disease in the majority of cases (36/64, 56.3 %). 4.6 % (3/64) died from other cancers, and 37.5 % (24/64) died from other causes, with significant differences between the skin cancer entities ($p = 0.028$; Table 2). In CAC patients the skin cancer-related death rate was highest with 46 % (17/37), followed by PDS with 21.5 % (3/14), and AS with 16.8 % (13/77). KS showed the lowest skin cancer-related deaths (3.7 %, 3/81).

Regarding tumor-specific survival (TSS), the median TSS was not reached for AS, KS, and PDS, and accounted for 23 months (95 %-CI=11.8;34.1) in the CAC group. The 1-year TSS rate was highest in KS (97.3 %), followed by AS (84.2 %), PDS (67.7 %), and CAC (65.4 %); $p < 0.001$ (Table 5 and Fig. 2b).

The median OS of the total patient cohort was not reached. This was also true for the subgroups AS, KS, and PDS. The median OS for CAC was 13 months (95 %-CI=2.4;23). The 1-year OS rate of the total patients was 85.8 % (95 %-CI=80.5;91.1). Specified for the respective entities, the 1-year OS rates were 97.3 % (KS), 71.8 % (AS), 60.9 % (CAC), and 54.0 % (PDS) (Table 5; Fig. 2c).

4. Discussion

Patients with non-resectable advanced rare skin cancer have a high medical need of an efficient systemic therapy, but currently, treatment options are limited. The optimal therapy approach probably differs between cancer entities due to their strong heterogeneity. Conventional therapies include chemotherapy and anti-angiogenic targeted agents, but rarely result in durable responses. This multicenter retrospective study analysed treatment outcomes to different types of systemic therapy, with a focus on ICI immunotherapy, in the advanced rare skin cancer entities AS, KS, PDS and CAC. The use of ICI differed between cancer entities and showed high response rates in PDS and AS (66.6 % and 58.3 %), moderate in KS (33.3 %), and low in CAC (4.3 %).

Cutaneous angiosarcomas (AS) have been reported to have a poor prognosis with a 5-year OS of 33 % [3]. AS can be classified into primary (spontaneous) and secondary forms. Primary AS has been associated with BRCA1 and BRCA2 mutations, exposure to certain chemicals, or to

Table 3
Best overall response to first-line therapy by skin cancer entity (total cohort, n = 209).

	Chemotherapy	ICI immuno-therapy	Targeted therapy	IFNalpha	others
Angiosarcoma	**N = 60**	**N = 6**	**N = 2**	**N = 1**	**N = 2**
CR	7 11.7 %	3 50 %	1 50.0 %	1 100.0 %	0
PR	15 25.0 %	1 16.7 %	0	0	0
SD	15 25.0 %	0	1 50.0 %	0	0
PD	13 21.7 %	2 33.3 %	0	0	1 100.%
Unknown	10 16.7 %	0	0	0	0
ORR (CR+PR)	**22 36.7 %**	**4 66.7 %**	**1 50 %**	**1 100 %**	**0**
DCR (CR+PR+SD)	37 61.7 %	4 66.7 %	2 100.0 %	1 100.5 %	0
Kaposi sarcoma	**N = 51**	**N = 1**	**N = 1**	**N = 27**	**N = 1**
CR	13 25.5 %	0	0	4 14.8 %	0
PR	30 58.8 %	0	0	4 14.8 %	1 100 %
SD	5 9.8 %	1 100 %	0	8 29.6 %	0
PD	3 5.9 %	0	1 100 %	6 22.2 %	0
Others (NED)	0	0	0	1 3.7 %	0
ORR (CR+PR)	**43 74.3 %**	**0**	**0**	**8 29.6 %**	**1 100 %**
DCR (CR+PR+SD)	48 84.1 %	0	0	16 59.2 %	1 100 %
Pleomorphic dermal sarcoma	**N = 3**	**N = 9**	**N = 2**	**N = 0**	**N = 0**
CR	0	4 44.4 %	0	0	0
PR	1 33.3 %	2 22.2 %	0	0	0
SD	2 66.7 %	1 11.1 %	0	0	0
PD	0	1 11.1 %	2 100.0 %	0	0
Unknown	0	1 11.1 %	0	0	0
ORR (CR+PR)	**1 33.3 %**	**6 66.6 %**	**0**	**0**	**0**
DCR (CR+PR+SD)	3 100.0 %	7 77.7 %	0	0	0
Cutaneous adnexal carcinoma	**N = 11**	**N = 16**	**N = 8**	**N = 0**	**N = 0**
CR	0	1 6.3 %	0	0	0
PR	2 18.2 %	0	1 12.5 %	0	0
SD	2 18.2 %	2 12.5 %	2 25.0 %	0	0
PD	7 63.3 %	8 50.0 %	5 62.5 %	0	0
Unknown	0	5 31.3 %	5 31.3 %	0	0
ORR (CR+PR)	**2 18.2 %**	**1 6.3 %**	**1 12.5 %**	**0**	**0**
DCR (CR+PR+SD)	4 36.4	3 18.8 %	3 37.5 %	0	0

Table 4
Best overall response to immune checkpoint inhibition, all therapy lines (n = 53).

	AS N = 12	KSN= 9	PDSN= 9	CACN= 23	P
CR	3 25 %	1 11.1 %	4 44.4 %	1 4.3 %	**0.004**
PR	2 16.6 %	2 22.2 %	2 22.2 %	0 0 %	
SD	0 0 %	4 44.4 %	1 11.1 %	2 8.6 %	
PD	6 50 %	1 11.1 %	1 11.1 %	13 56.5 %	
Unknown	1 8.3 %	1 11.1 %	1 11.1 %	7 30.4 %	
ORR (CR+PR)	**7 58.3 %**	**3 33.3 %**	**6 66.6 %**	**1 4.3 %**	
DCR (CR+PR+SD)	7 **58.3 %**	7 77.7 %	7 77.7 %	3 12.9 %	

AS, angiosarcoma; KS, Kaposi sarcoma; PDS, pleomorphic dermal sarcoma; CAC, cutaneous adnexal carcinoma.

Table 5
Survival outcome according to skin cancer entity (total cohort, n = 209).

Probability of	AS	KS	PDS	CAC
Progression-free survival (PFS)				
1-year rate(95 % CI)	25.6 % (11.9;39.3)	45.7 % (29.3;62.1)	70.7 % (41.9;99.5)	18.5 % (3.8;33.2)
2-year rate (95 % CI)	10.3 % (7;19.9)	31.4 % (16.1;46.7)	70.7 % (41.9;99.5)	7.4 % (0;17,2)
5-year rate (95 % CI)	not reached	8.6 % (0;17.8)	70.7 % (41.9;99.5)	not reached
Tumor-specific survival (TSS)				
1-year rate(95 % CI)	84.2 % (83.2;93.8)	97.3 % (93.6;100)	67.7 % (41.2;94.0)	65.4 % (47.6;83.2)
2-year rate (95 % CI)	78.8 % (67.2;90.4)	95.8 % 91.1;100)	67.7 % (41.2;94.0)	29.4 % (7.5;51.3)
5-year rate (95 % CI)	66.5 % (47.9;85.1)	92.7 % (85.2;100)	67.7 % (41.2;94.0)	14.7 % (0:37.8)
Overall survival (OS)				
1-year rate(95 % CI)	71.8 % (60.2;83.4)	97.3 % (93.6;100)	54.0 % (22.2;85.7)	60.9 % (43.3;78.5)
2-year rate (95 % CI)	59.4 % (45.5;73.3)	94.1 % (88.4;99.8)	54.0 % (22.2;85.7)	27.3 % (6.7;47.8)
5-year rate (95 % CI)	43.4 % (26.6;60.2)	84.9 % (74.7;95.1)	54.0 % (22.2;85.7)	13.7 % (0;35.2)

AS, angiosarcoma; KS, Kaposi sarcoma; PDS, pleomorphic dermal sarcoma; CAC, cutaneous adnexal carcinoma.

chronic UV-radiation. Notably primary AS, particularly in the head and neck region, exhibits a high tumor mutation burden (TMB). Secondary AS often follows radiation therapy or develops in areas of chronic lymphedema. Advanced AS are often responsive to chemotherapy, with response rates to taxanes ranging from 18 % to 89 % [4]. However, these responses are not durable, and the median PFS ranges from 4.0 to 9.5 months only [5]. The 5-year survival for patients with AS was shown to be only 30 %–40 %[4]. As a subset of AS are characterized by high TMB, ICI immunotherapy appears meaningful [5–7]. Some case series reported encouraging initial clinical responses to ICI. A multicenter phase II study (SWOGS169-cohort51) of ipilimumab plus nivolumab in AS showed an OR rate of 25 % in 16 patients [8]. In our AS patient cohort, the ORR to ICI in any treatment line was indeed high with 58.3 % in n = 12 patients treated. The ORR to chemotherapy in first-line was comparatively low with 36.7 % in n = 60 patients. Thus, it can be concluded that ICI immunotherapy could be considered as first-line therapy in AS.

Pleomorphic dermal sarcoma (PDS) is today the most common tumor within the rare group of cutaneous sarcomas, showing a local relapse rate of 5–28 %; metastases occur in 8–20 % [9]. The TMB in PDS was reported to be extremely high due to the common UV-induced pathogenesis of these tumors [10]. For systemic treatment in advanced PDS case reports and small case series are available. Chemotherapy regimens such as doxorubicin, adriamycin, and ifosfamid are used, but offer only short-lived disease control [10,11]. ICI were investigated in a

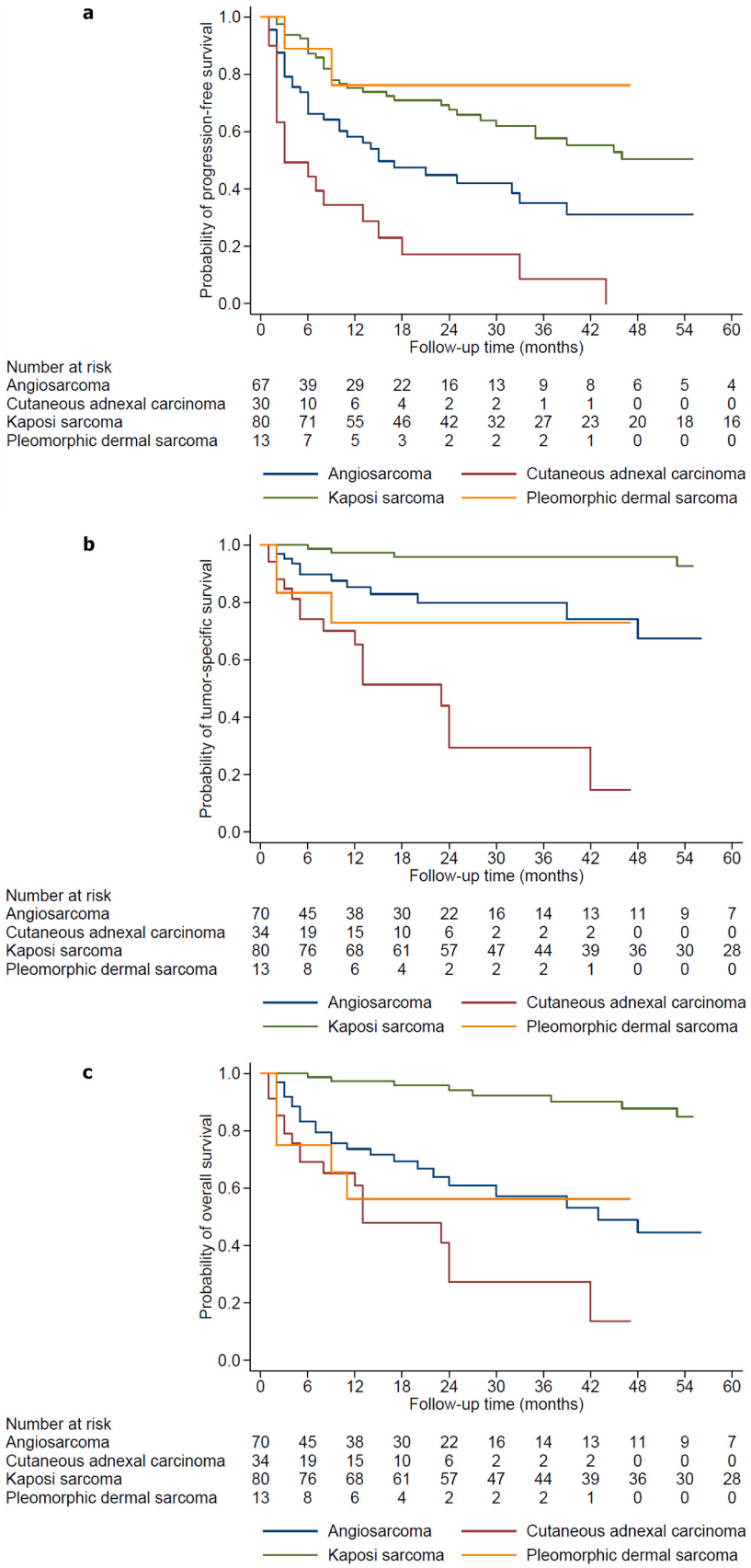

Fig. 2. Survival according to skin cancer entity. (a) Probability of progression-free survival (PFS), $p < 0.001$; (b) probability of tumor-specific survival (TSS), $p < 0.001$; (c) probability of overall survival (OS), $p < 0.001$. P-values were calculated using the log rank test.

multicenter phase II study treating soft tissue sarcomas of various type with pembrolizumab resulting in an ORR of 40 % for patients with undifferentiated pleomorphic sarcomas [11]. Burgess and coworkers reported in 2020 an ORR of 16 % in (9/40) patients with soft tissue sarcomas of different types [12]. In the PDS patient cohort investigated in our present study, we found a high ORR of 66.6 % in n = 9 patients treated with ICI immunotherapy in any treatment line. In comparison, the ORR to chemotherapy was 33.3 % only in n = 3 first-line treated PDS patients. These results lead to the conclusion, that in advanced PDS immunotherapy with ICI currently is the most effective systemic treatment and should be considered as first-line therapy.

In patients with classic and endemic forms of Kaposi sarcoma (KS), those with visceral disease or extensive cutaneous lesions often require systemic treatments alone or additional to local treatment strategies. So far, predominantly doxorubicine was recommended for systemic therapy of KS. However, long-time durable responses of KS under chemotherapy are rare [13]. KS is often observed in immunosuppressed patients, suggesting that it might be a good target for immune activation by ICI therapy. In a series of 9 HIV-positive KS patients receiving ICI, an OR rate of 66 % was shown [14]. Nivolumab was effective in HIV-negative KS, showing an ORR of 71 % [13]. In the KS patient cohort investigated by us, we confirmed the frequent use of chemotherapy in first-line (63.0 % of n = 81 patients). Also as expected, the OR rate to chemotherapy was high with 84.3 %. Upon ICI immunotherapy in any line, the OR rate was lower with 33.3 % of n = 9 patients. Still, the durability of response might be better under ICI. Thus, in KS a comparative prospective trial testing first-line chemotherapy versus ICI immunotherapy is needed to direct future treatment decisions.

Cutaneous adnexal carcinomas (CAC) are a highly heterogenous group of malignant neoplasms, and currently have limited effective treatment options for advanced disease[15]. CACs can arise from various adnexal structures including follicular, sebaceous, apocrine, or eccrine differentiation. Thus, CACs demonstrate molecular heterogeneity, which contributes to their diverse clinical and histological presentation as well as response to therapy. While some CACs, particularly those in sun-exposed areas, may have a high TMB, which is generally associated with better response to immunotherapy, however, the mutational landscape varies significantly between tumors and even within different areas of the same tumor. High expression levels of PD-L1 were reported in sebaceous carcinomas[16,17]. In two case reports, the use of pembrolizumab with or without chemotherapy demonstrated clinical efficacy against metastatic sebaceous carcinoma [18,19]. One patient remained on pembrolizumab despite requiring systemic corticosteroids due to secondary adrenal insufficiency[18]. In our present study, from 23 CAC patients treated with ICI immunotherapy in any line, only 1 patient showed an objective response (OR rate 4.3 %). This extremely poor response outcome in a real-world patient cohort leads us to the conclusion, that ICI immunotherapy currently is not a recommendable first-line treatment option in non-resectable CAC. Since the OR rate of CAC to any other first-line systemic treatment investigated by us was also low (10.8 % of n = 37 patients), we conclude that there is a high and urgent need of new treatment strategies for this prognostically poor cancer entity.

Our study has some limitations. First, its retrospective nature leads to a selection bias of the patients provided for analysis by each center. Additionally, it has to be mentioned that the number of patients in some of the cancer entities, particularly in PDS, are rather small. However, its real-world setting provides results which are not restricted to skin cancer patients who are otherwise healthy, but include all kinds of patients presenting at the respective study centers.

Taken together, our study provides encouraging results demonstrating ICI immunotherapy as a highly efficient treatment option in the advanced rare skin cancer entities PDS and AS, as well as in advanced KS, here of moderate efficacy. In CAC, ICI immunotherapy did not show efficacy and should therefore not be used as first-line treatment outside of clinical trials. Our results are based on retrospective data, and should be confirmed in prospective clinical studies, if possible.

CRediT authorship contribution statement

Alexander Kreuter: Resources, Validation, Writing – review & editing. **Franziska Jochims:** Resources, Validation, Writing – review & editing. **Lydia Reinhardt:** Resources, Validation, Writing – review & editing. **Martin Gschnell:** Resources, Validation, Writing – review & editing. **Gaston Schley:** Resources, Validation, Writing – review & editing. **Ulrike Raap:** Resources, Validation, Writing – review & editing. **Edgar Dippel:** Resources, Validation, Writing – review & editing. **Michael Erdmann:** Resources, Validation, Writing – review & editing. **Patrick Terheyden:** Resources, Validation, Writing – review & editing. **Jochen Utikal:** Resources, Validation, Writing – review & editing. **Jürgen C. Becker:** Resources, Validation, Writing – original draft, Writing – review & editing. **Doris Helbig:** Resources, Validation, Writing – review & editing. **Christoph Pöttgen:** Resources, Validation, Writing – review & editing. **Pia Dücker:** Resources, Validation, Writing – review & editing. **Teresa Amaral:** Resources, Validation, Writing – review & editing. **Christoffer Gebhardt:** Resources, Validation, Writing – review & editing. **Alpaslan Tasdogan:** Resources, Validation, Writing – review & editing. **Cindy Franklin:** Resources, Validation, Writing – review & editing. **Ulrike Leiter:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Kähler Katharina C:** Resources, Validation, Writing – review & editing. **Lena Nanz:** Data curation, Formal analysis, Resources, Software, Validation, Visualization, Writing – review & editing. **Gabriela Poch:** Resources, Validation, Writing – review & editing. **Ralf Gutzmer:** Resources, Validation, Writing – review & editing. **Michael Weichenthal:** Resources, Validation, Writing – review & editing. **Thilo Gambichler:** Resources, Validation, Writing – review & editing. **Nessr Abu Rached:** Resources, Validation, Writing – review & editing. **Lucie Heinzerling:** Resources, Validation, Writing – review & editing. **Selma Ugurel:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Peter Mohr:** Resources, Validation, Writing – review & editing. **Miriam Mengoni:** Resources, Validation, Writing – review & editing. **Carsten Weishaupt:** Resources, Validation, Writing – review & editing. **Berenice Lang:** Resources, Validation, Writing – review & editing. **Hassel Jessica Cecile:** Resources, Validation, Writing – review & editing. **Kai-Martin Thoms:** Resources, Validation, Writing – review & editing. **Thomas Tüting:** Resources, Validation, Writing – review & editing. **Lodde Georg:** Resources, Validation, Writing – review & editing. **Sebastian Haferkamp:** Resources, Validation, Writing – review & editing. **Schilling bastian:** Resources, Validation, Writing – review & editing. **Robin Reschke:** Resources, Validation, Writing – review & editing. **Dirk Schadendorf:** Resources, Validation, Writing – review & editing. **Julia Welzel:** Resources, Validation, Writing – review & editing. **Michael Sachse:** Resources, Validation, Writing – review & editing. **Jan-Malte Placke:** Resources, Validation, Writing – review & editing.

Funding

This study was designed by the members of Committee for Rare Skin Cancers, and performed within the network of study centers of the German Dermatologic Cooperative Oncology Group (DeCOG). No financial funding was employed.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Selma Ugurel: relevant financial activities (research support from Bristol Myers Squibb and Merck Serono; speakers and advisory board

honoraria from Bristol Myers Squibb, Merck Sharp and Dohme, Merck Serono, Novartis and Roche, and travel support from Bristol Myers Squibb, and Merck Sharp and Dohme).

Nessr Abu Rached: received funding, travel support, and/or personal honoraria for lectures from Novartis Pharma, Janssen-Cilag GmbH and Johnson & Johnson that were independent of the work submitted.

Thilo Gambichler: relevant financial activities (speakers and/or advisory board honoraria from BMS, Sanofi/Regeneron, MSD, Novartis Pharma, Roche, Abbvie, Almirall, UCB, Sun Pharmaceutical, Janssen, Lilly, Pfizer, Pierre Fabre, Merck-Serono).

Miriam Mengoni: relevant financial activities (speakers or advisory board honoraria from Merck Sharp and Dohme, Novartis, Bristol-Myers Squibb, Sun Pharma, Pierre Fabre and Kyowa Kirin and travel support from Sun Pharma, Delcath and Pierre Fabre).

Jessica C. Hassel: relevant financial activities (research support from Bristol Myers Squibb; speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp and Dohme, Novartis, Roche, Pierre Fabre and Sanofi Aventis, and travel support from Bristol Myers Squibb and Pierre Fabre).

Robin Reschke: travel support from SunPharma.

Georg C. Lodde received travel support from Sun Pharma, Pierre Fabre, research funding from Novartis.

Jan-Malte Placke served as consultant and/or has received honoraria from Bristol-Myers Squibb, Novartis, Sanofi, MedKomAkademie and received travel support from Bristol-Myers Squibb, Novartis, Pierre Fabre and Therakos.

Dirk Schadendorf: relevant financial activities (Roche, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Sanofi, Regeneron, Array, Pierre Fabre, 4SC, Helsinn, Philogen, InFlarX, Merck-Serono, Sun-Pharma, Ultimovacs, Sandoz).

Jochen Utikal is on the advisory board or has received honoraria and travel support from Amgen, Bristol Myers Squibb, GSK, Immunocore, LeoPharma, Merck Sharp and Dohme, Novartis, Pierre Fabre, Rheacell, Roche and Sanofi outside the submitted work

Doris Helbig: relevant financial activities (Pierre Fabre and Sanofi-Aventis).

Cindy Franklin: relevant financial activities (advisory board or has received honoraria from Bristol Myers Squibb, Immunocore and Novartis and received travel grants from Bristol Myers Squibb, Novartis and Pierre Fabre).

Christoffer Gebhardt: relevant financial activities (advisory board or honoraria from Almirall, Amgen, Beiersdorf, BioNTech, Bristol-Myers Squibb, Immunocore, Janssen, MSD Sharp & Dohme, Novartis, Pierre-Fabre Pharma, Regeneron, Roche, Sanofi Genzyme, SUN Pharma and Sysmex, research funding from Bristol-Myers Squibb, Novartis, Regeneron and Sanofi, outside the submitted work, co-founder of Dermagnostix and Dermagnostix R&D).

Gabriela Poch: relevant financial activities (speakers honoraria or travel support from MSD, BMS, Novartis, Sun Pharma, Pierre Fabre and Amgen).

Katharina C. Kähler: relevant financial activities (Honoraria: BMS, MSD, Novartis, Sanofi-Aventis, Immunocore, Philogen; Consulting or Advisory Role: BMS, MSD, Pierre Fabre, Philogen, Sun Pharma;

Research Funding: Novartis; Travel, Accommodations, Expenses: BMS, MSD, Novartis, Roche, Pierre Fabre, Sun Pharma).

Michael Weichenthal: relevant financial activities (speakers and advisory board honoraria from Merck, Bristol-Myers Squibb, Roche, Novartis, Sanofi, Pierre Fabre, Beiersdorf, Sun Pharma, and Takeda).

Ralf Gutzmer: grants (to institution) from Almirall Hermal, Amgen, Kyowa Kirin, Merck Serono, Recordati, Regeneron Pharmaceuticals, Sanofi, and Sun Pharmaceutical Industries; consulting fees from 4SC, Almirall Hermal, Bristol Myers Squibb, Delcath, Immunocore, Kyowa Kirin, Merck Serono, MSD, Novartis Pharmaceuticals, Pierre Fabre, Sanofi, and Sun Pharmaceutical Industries; honoraria from Almirall Hermal, Bristol Myers Squibb, Merck Serono, MSD, Novartis Pharmaceuticals, Pierre Fabre, Regeneron Pharmaceuticals, Sanofi, and Sun Pharmaceutical Industries; support for attending meetings and/or travel from Pierre Fabre and Sun Pharmaceutical Industries.

Lucie Heinzerling: relevant financial activities (speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp and Dohme, Merck Serono, Novartis, Amgen, Curevac, Pierre Fabre, Sanofi and Roche).

Peter Mohr: relevant financial activities (payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: MSD, Novartis, BMS, Pierre Fabre, Sanofi Genzyme, Immunocore, Regeneron, Delcath, Sun Pharma; participation on a Data Safety Monitoring Board or Advisory Board: MSD, Novartis, BMS, Pierre Fabre, Sanofi Genzyme, Immunocore, Regeneron, Delcath, Sun Pharma, Biotech; support for attending meetings and/or travel: MSD, BMS, Sun Pharma, Novartis).

Kai-Martin Thoms: relevant financial activities (speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp & DOhme, Pierre Fabre, Novartis, Roche, Immunocore, Sanofi, Sun Pharma, Amgen, LEO, Galderma, Almirall, Candela, and Lilly).

Berenice Lang: relevant financial activities (Pierre Fabre, Galderma, Sanofi, SUN Pharma, Novartis, Pfizer, Biofrontera, Almirall, Loreal).

Bastian Schilling: relevant financial activities (speakers and advisory board honoraria from Sanofi, Pierre Fabre Pharmaceuticals, Regeneron, Immunocore and SUN Pharma).

Sebastian Haferkamp: relevant financial activities (research support from Bristol Myers Squibb; speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp and Dohme, Novartis, Sanofi and Roche).

Julia Welzel: speakers and advisory board honoraria and travel support from Abbvie, Almirall, BMS, Boehringer Ingelheim, Janssen, Infectopharm, Leo, Lilly, Mibe, MSD, Novartis, Pfizer, Sanofi.

Franziska Jochims: relevant financial activities (congress participation from Pierre-Fabre, UCB)

Gaston Schley: relevant financial activities (BMS and Kiowa Kirin).

Patrick Terheyden served as consultant and/or received honoraria form Almirall, Bristol Myers Squibb, Biofrontera, Kyowa Kirin, L'Oréal, Merck Sharp & Dohme, Novartis, Pierre-Fabre, Sanofi, 4SC, and travel support from Bristol Myers Squibb outside the submitted work.

Jürgen C. Becker: is receiving speaker's bureau honoraria from Amgen, MerckSerono, Pfizer, Sanofi and Sun Pharma and is a paid consultant/advisory board member/DSMB member for Almirall, Boehringer Ingelheim, ICON, Pfizer, Regeneron and Sanofi. His group receives research grants from Alcedis, Merck Serono/IQVIA, and Regeneron.

Teresa Amaral: reports personal fees for advisory board membership from Delcath and Philogen; personal fees as an invited speaker from BMS, Neracare, Novartis and Pierre Fabre; personal fees for a writing engagement from CeCaVa and Medtrix; institutional fees as local principal investigator (PI) from Agenus Inc., AstraZeneca, BioNTech, BMS, HUYA Bioscience, Immunocore, IO Biotech, MSD, Pfizer, Philogen, Regeneron, Roche and University Hospital Essen; institutional fees as coordinating PI from Unicancer; institutional research grants from iFIT and Novartis; institutional funding from MNI - Naturwissenschaftliches und Medizinisches Institut, Neracare, Novartis, Pascoe, Sanofi and Skyline-Dx; non-remunerated membership of the American Society of Clinical Oncology (ASCO) and the Portuguese Society for Medical Oncology; and a role as clinical expert in the area of medical oncology for Infarmed.

Ulrike Leiter: relevant financial activities (research support from Merck Sharp and Dohme; speakers and advisory board honoraria from Merck Sharp and Dohme, Novartis and Roche, Sanofi Aventis and travel support from Sun Pharma).

All other authors declared to have no conflicts of interest.

Acknowledgements

We thank the patients who participated in this study, their families,

and the staff members at the study sites who cared for them.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115750.

References

[1] Kohlmeyer J, Steimle-Grauer SA, Hein R. Cutaneous sarcomas. J Dtsch Dermatol Ges 2017;15(6):630–48.
[2] Garcia A, Nelson K, Patel V. Emerging therapies for rare cutaneous cancers: a systematic review. Cancer Treat Rev 2021;100:102266.
[3] Guan L, Palmeri M, Groisberg R. Cutaneous angiosarcoma: a review of current evidence for treatment with checkpoint inhibitors. Front Med 2023;10:1090168.
[4] Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcoma. Lancet Oncol 2010;11(10):983–91.
[5] Barrios DM, Do MH, Phillips GS, Postow MA, Akaike T, Nghiem P, et al. Immune checkpoint inhibitors to treat cutaneous malignancies. J Am Acad Dermatol 2020;83(5):1239–53.
[6] Ramakrishnan N, Mokhtari R, Charville GW, Bui N, Ganjoo K. Cutaneous angiosarcoma of the head and Neck-A retrospective analysis of 47 patients. Cancers 2022;14(15).
[7] Lobrano R, Paliogiannis P, Zinellu A, Palmieri G, Persico I, Mangoni AA, et al. PD-L1 expression in cutaneous angiosarcomas: a systematic review with Meta-Analysis. Curr Oncol 2023;30(5):5135–44.
[8] Wagner MJ, Othus M, Patel SP, Ryan C, Sangal A, Powers B, et al. Multicenter phase II trial (SWOG S1609, cohort 51) of ipilimumab and nivolumab in metastatic or unresectable angiosarcoma: a substudy of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART). J Immunother Cancer 2021;9(8).
[9] Bregeon B, Jullie ML, Begueret H, Khammari A, Dreno B. Could anti-PD-1 be a therapeutic alternative for metastatic pleomorphic dermal sarcoma? Eur J Dermatol 2019;29(6):650–1.
[10] Klein S, Mauch C, Wagener-Ryczek S, Schoemmel M, Buettner R, Quaas A, et al. Immune-phenotyping of pleomorphic dermal sarcomas suggests this entity as a potential candidate for immunotherapy. Cancer Immunol Immunother 2019;68(6):973–82.
[11] Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol 2017;18(11):1493–501.
[12] Petitprez F, de Reyniès A, Keung EZ, Chen TW, Sun CM, Calderaro J, et al. B cells are associated with survival and immunotherapy response in sarcoma. Nature 2020;577(7791):556–60.
[13] Delyon J, Biard L, Renaud M, Resche-Rigon M, Le Goff J, Dalle S, et al. PD-1 blockade with pembrolizumab in classic or endemic kaposi's sarcoma: a multicentre, single-arm, phase 2 study. Lancet Oncol 2022;23(4):491–500.
[14] Galanina N, Goodman AM, Cohen PR, Frampton GM, Kurzrock R. Successful treatment of HIV-Associated kaposi sarcoma with immune checkpoint blockade. Cancer Immunol Res 2018;6(10):1129–35.
[15] Lee RH, Wai KC, Chan JW, Ha PK, Kang H. Approaches to the management of metastatic adenoid cystic carcinoma. Cancers 2022;14(22).
[16] Seok J, Lee DY, Kim WS, Jeong WJ, Chung EJ, Jung YH, et al. Lung metastasis in adenoid cystic carcinoma of the head and neck. Head Neck 2019;41(11):3976–83.
[17] Mahmood U, Bang A, Chen YH, Mak RH, Lorch JH, Hanna GJ, et al. A randomized phase 2 study of pembrolizumab with or without radiation in patients with recurrent or metastatic adenoid cystic carcinoma. Int J Radiat Oncol Biol Phys 2021;109(1):134–44.
[18] Sung MW, Kim KH, Kim JW, Min YG, Seong WJ, Roh JL, et al. Clinicopathologic predictors and impact of distant metastasis from adenoid cystic carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 2003;129(11):1193–7.
[19] Umeda M, Nishimatsu N, Masago H, Ishida Y, Yokoo S, Fujioka M, et al. Tumor-doubling time and onset of pulmonary metastasis from adenoid cystic carcinoma of the salivary gland. Oral Surg Oral Med Oral Pathol Oral Radio Endod 1999;88(4):473–8.