



Anti-PD-1 for the treatment of advanced cutaneous squamous cell carcinoma in elderly patients: a French multicenter retrospective survey

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Abstract

Background Anti-PD1 agents are currently recommended as first-line treatment in advanced cutaneous squamous cell carcinoma (acSCC) by updated European guidelines. Although acSCC frequently affects elderly patients with multiple comorbidities, this subset of patients is often excluded of registration clinical trials.

Purpose To assess anti-PD-1 efficacy and safety in elderly acSCC patients in real-life conditions and describe this specific population with oncogeriatric evaluation tools.

Methods A multicenter retrospective study including acSCC patients at least 70 years old treated with PD-1 inhibitors was conducted in French referral centers. The primary endpoint was the overall response rate (ORR). Secondary endpoints included safety data, time to response (TTR), duration of response (DOR), overall survival (OS), and progression-free survival (PFS).

Results 63 patients were included. ORR was 57.1% (95% CI 44.0–69.5), median TTR and DOR were 3 and 5.5 months respectively. Median OS was not reached (95% CI 12.5 months-not reached) at data cut-off after a median follow-up of 8 months while median PFS was 8 months. (95% CI 5 months-not reached). Grade 3–5 adverse effects occurred in 47.6% of patients. 41.3% of patients experienced degradation of ECOG performance status during anti-PD-1 treatment. Nutritional state worsened in 27% of patients and 57.1% lost weight during treatment.

Conclusion In this particular subset of acSCC patients PD-1 inhibitors obtain results similar to those obtained in younger populations included in pivotal clinical trials, with acceptable safety. A specific oncogeriatric evaluation at treatment initiation and during follow-up appears important in this setting most notably to help manage toxicity.

Keywords Skin neoplasms (MeSH) · Immunotherapy (MeSH) · Aged (MeSH) · Cutaneous squamous cell carcinoma · Anti-PD-1

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most frequent skin cancer in caucasians, with a steadily rising incidence over time (Que et al. 2018; Burton et al. 2016; Fitzmaurice et al. 1990). Despite its overall favorable clinical outcome when an adequate surgery is performed, it may progress to advanced stages (acSCC) in up to 5–20% of patients

(Amaral et al. 2019), with locally advanced tumor (40%) no longer amenable to surgery or to radiation therapy, or with locoregional or distant secondary lesions (60%) (Soura et al. 2019; Hillen et al. 2018).

For several decades, surgery associated with adjuvant radiotherapy, platinum salts-based chemotherapies and epidermal growth factor (EGFR)-inhibiting agents have been the mainstays of therapeutic strategies in acSCC patients with limited clinical results, few sustained responses, significant toxicity especially for metastatic disease and finally a questionable benefit/risk ratio in the specific setting of elderly patients (Hillen et al. 2018; Maubec 2020; Leus et al. 2020; Cowey et al. 2020).

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Updated 2020 European guidelines now recommend the use of anti-PD-1 agents as a first-line treatment in acSCC patients who are not candidates for curative surgery or curative radiation (Stratigos et al. 2020b) based on several pivotal clinical trials evaluating their efficacy and safety (Migden et al. 2018, 2020; Rischin et al. 2020; Grob et al. 2020; Maubec et al. 2020). However, although this specific population is particularly affected with acSCC, elderly and frail patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 2 or more were often not included in these studies partly as a result of investigators' decision related to the anticipation of serious side effects in these fragile patients.

To gain more accurate insights regarding the interest of PD-1 inhibitors in this specific population in real-life conditions, a multicenter retrospective assay was conducted in French referral centers with the aim to assess the benefit/risk ratio of these agents in acSCC elderly patients through specific oncogeriatric scores.

Materials and methods

Patients and collected data

Patients treated with a PD-1 inhibitor (cemiplimab, nivolumab, or pembrolizumab) for a histologically confirmed acSCC between January 1st, 2018 and May 15th, 2020 in seven French oncodermatological referral centers were retrospectively identified. Inclusions criteria were: age of 70 or more at treatment implementation; first perfusion carried out before January 16th, 2020; at least one follow-up evaluation after treatment introduction. Patients participating in industrial trials or concurrent academic study were not included. Data were retrospectively retrieved from computerized patients' medical charts and submitted to anonymized analysis. The study was approved by the Institutional Review Board of the Montpellier University Hospital (notification number: IRB-MTP_2020_04_202000386).

Collected baseline data included: demographic parameters (age, gender, past profession), primary tumor data (date of diagnosis, location, diameter, histopathological features including maximal thickness and presence of perineural invasion), and treatments used before and after anti-PD-1 introduction. Three main acSCC subsets were defined: locally advanced cSCC (laSCC), cSCC with regional progression only (rcSCC), and cSCC with distant metastasis (mcSCC).

Anti-PD-1 efficacy and safety endpoints

For each patient, tumor response to the anti-PD-1 agent was evaluated using clinical assessment [by the physician

in charge] and/or imaging when applicable (according to Response Evaluation Criteria In Solid Tumors (RECIST1.0) criteria when possible). The Best Observed Response (BOR) was rated as complete (CR) or partial response (PR), stable disease (SD) or progressive disease (PD) as usually defined (Eisenhauer et al. 2009).

The primary endpoint was the Overall Response Rate (ORR; rate of CR or PR). Secondary endpoints included: Disease Control Rate (DCR; rate of CR, PR or SD), time to first observed response (TTR), duration of response (DOR) calculated from the first observed response to progression, death or data cutoff whatever event came first, progression-free survival (PFS) and overall survival (OS), calculated from treatment implementation until first progression, death from any cause or data cut-off whatever event came first, and safety data using the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 5.0) 2021 with a special attention to grade 3–5 Adverse Events (AE). DOR after anti-PD-1 discontinuation owing to protracted CR, high-quality PR or limiting toxicity until first progression, death, or data cutoff whatever event came first was also calculated.

Oncogeriatric parameters

To better evaluate the status of these elderly patients a number of validated oncogeriatric scores and indexes were used and applied to the population under scope:

- G8 score identifying elderly cancer patients (> 75 years old) requiring a specific geriatric assessment (Soubeyran et al. 2014) when a score of 14 or less is obtained.
- Lee's prognostic index stratifying 50-year-old or older patients into a high-, intermediate-, and low-risk group for 4-year mortality (Lee et al. 2006), scores of 13 and 14 or more being associated with a 4-year risk of mortality of 59% and 64% respectively.
- Charlson comorbidity index rating associated disorders (Charlson et al. 1987), with a score of 7 or more being associated with an estimated 10 year survival of 0%.

Other oncogeriatric variables of interest in this population included: education level, nutritional state throughout the course of the treatment, associated morbid conditions (diabetes, immunodeficiency), functional disabilities like walking difficulties, number of drugs received at baseline, place of living, distance between the place of living and hospital, along with Activities of Daily Living (ADL)/Instrumental Activities of Daily Living (IADL) scores and Mini-Mental State Examination (MMSE).

Statistical analysis

Efficacy and safety analyses included all patients included in this study. For ORR and DCR, point estimates and 95%

CI were assessed using the Clopper and Pearson exact binomial method. PFS and OS were calculated using the Kaplan–Meier method.

Exploratory univariable analysis investigating a possible relationship between ORR and several selected, possibly relevant parameters (age, gender, ECOG PS, disease status, unfavorable prognosis factors status (Stratigos et al. 2020a) (poorly or undifferentiated tumor, presence of perineural invasion, thickness > 6 mm, initial tumor size > 2 cm), PD-1 inhibitor, concurrent radiotherapy, immunodeficiency) was performed using a logistic regression model to estimate crude odds ratios (ORs). Multivariable analysis was planned for parameters reaching the level of statistical significance ($p \leq 0.05$) in univariable analysis.

Results

Patients characteristics (data summarized in Tables 1, 2)

A total of 63 patients were included, 51 male (81%), with a median age of 83 years (range: 70–102): 44.4% ($n = 28$) lacSCC, 36.5% ($n = 23$) rcSCC and 19.0% ($n = 12$) mcSCC. Primary tumor location was mostly head and neck (77.8%, $n = 49$) followed by limbs (17.5%, $n = 11$) and trunk (4.8%, $n = 3$).

Anti-PD-1 regimen and subsequent treatments (data summarized in Table 2)

Cemiplimab was the most used (82.5%, $n = 52$), followed by nivolumab (12.7%, $n = 8$), and pembrolizumab (4.8%, $n = 3$); all three molecules were used with either a fixed or a weight-adjusted dose. Only one patient received two different anti-PD-1 during the course of the disease (nivolumab followed by cemiplimab) and another one received the three molecules; in both cases, efficacy and tolerance of each anti-PD1 were separately assessed. Anti-PD-1 agents were used as first-line, second-line or third-line or beyond systemic treatment in 61.9% ($n = 39$), 22.2% ($n = 14$) and 15.9% ($n = 10$) of the patients respectively. Median anti-PD-1 treatment duration was 4.2 months (SD 4.1; range 0–17.3) at data cutoff. Median follow-up duration after first anti-PD-1 administration was 8.0 months (SD 5.4; range 1–28) at data cutoff.

Concurrent radiotherapy was used in 10 patients (15.9%) with a mean time of 8.0 days between PD-1 inhibitor implementation and first radiotherapy session. Only one of these 10 patients was treated with

radiotherapy on two different occasions during the course of immunotherapy.

Treatment efficacy (data summarized in Table 3)

Regarding the primary endpoint, an objective response was observed in 36/63 patients with an ORR of 57.1% (95%CI 44.0–69.5). BOR was CR and PR in 12 (19.0%) and 24 (38.1%) patients respectively (Fig. 1). SD was observed in 7 additional patients (11.1%) with a DCR of 68.3% (95% CI 55.3–79.4). The response could not be properly evaluated in 3 patients (4.8%) owing to significant and fast degradation of general status (2 patients) or early treatment discontinuation related to severe AE occurrence after two infusions (1 patient).

Median TTR in responding patients was 3.0 months (SD 1.6; range 1–10) and median DOR at data cutoff was 5.5 months (SD 4.0; range 1–19). The DOR exceeded 6 months in 14 of 36 responding patients (38.9%). When PD-1 inhibitor was discontinued after protracted CR ($n = 9$) or high-quality PR ($n = 6$), median DOR after discontinuation was 5.0 months (SD 3.7; range 0.1–13.2) vs 6.7 months when treatment was permanently interrupted for limiting AEs after response achievement (SD 3.4; range 1.2–10.8).

Median PFS was 8 months (95% CI 5–not reached) with 6- and 12 month PFS rates of 56.6% (95% CI 45.0–71.2) and 44.3% (95% CI 31.3–62.7) respectively (Fig. 2A). Two patients were excluded of PFS analysis because of initial progression observed after two initial months of treatment but antiPD1 was maintained in both cases with secondary stable disease or sustained PR after a few months.

Median OS was not reached at data cut-off (95% CI 12.5–not reached) with 6- and 12 month OS rates of 75.2% (95% CI 64.9–87.0) and 65.8% (95% CI 54.0–80.2) respectively (Fig. 2B). 42 patients (66.7%) were alive at data cutoff of whom 22 (34.9%) were still receiving an PD-1 inhibitor. Patients flow charts are available as Appendices (Fig A1 and A2).

Regarding univariable analysis of predefined parameters possibly related to ORR, none of these characteristics reached the threshold of statistical significance (see Table A1 in Appendices) and subsequent multivariable analysis was thus not performed as a consequence.

Safety

55/63 patients (87.3%) experienced one or several AEs of any grade rated as possibly or probably related to immunotherapy (summarized in Table 4) including grade 3–5 AEs in 30 patients (47.6%), and 5 (7.9%) deaths. Specific safety data for each anti-PD-1 are reported in Appendices (Table A.2).

Table 1 Patients and tumor characteristics at baseline of patients with advanced cutaneous squamous cell carcinoma treated with anti-PD-1

Characteristics	lacSCC (n=28)	rcSCC (n=23)	mcSCC (n=12)	Total (n=63)
Age				
Mean \pm SD	83.5 \pm 7.6	82.8 \pm 6.9	80.8 \pm 7.9	82.7 \pm 7.5
Median (range)	82.5 (70–102)	83 (72–95)	81.5 (70–97)	83 (70–102)
Sex, N (%)				
Male	23 (82.1)	19 (82.6)	9 (75)	51 (81)
Female	5 (17.9)	4 (17.4)	3 (25)	12 (19)
ECOG PS score, N (%)				
0	5 (17.9)	1 (4.3)	2 (16.7)	8 (12.7)
1	12 (42.9)	12 (52.2)	6 (50)	30 (47.6)
2	5 (17.9)	6 (26.1)	4 (33.3)	15 (23.8)
3	5 (17.9)	3 (13)	0	8 (12.7)
4	1 (3.6)	1 (4.3)	0	2 (3.2)
Immunosuppression, N (%)				
No	23 (82.1)	19 (82.6)	11 (91.7)	53 (84.1)
Yes	5 (17.9)	4 (17.4)	1 (8.3)	10 (15.9)
Oncological/hematological diseases	2 (7.1)	4 (17.4)	0	6 (9.5)
Transplanted patients	0	0	1 (8.3)	1 (1.6)
Immunosuppressive therapies	3 (10.7)	0	0	3 (4.8)
Location, N (%)				
Head/neck	27 (96.4)	16 (69.6)	6 (50)	49 (77.8)
Temple/ear/lip area	10 (35.7)	9 (39.1)	3 (25)	22 (34.9)
Other	17 (60.7)	7 (30.4)	3 (25)	27 (42.9)
Trunk	1 (3.6)	1 (4.3)	1 (8.3)	3 (4.8)
Arm/leg	0	6 (26.1)	5 (41.7)	11 (17.5)
Maximum diameter, N (%)				
< 2 cm	6 (21.4)	6 (26.1)	3 (25)	15 (23.8)
\geq 2 cm	18 (64.3)	13 (56.5)	6 (50)	37 (58.7)
NE	4 (14.3)	4 (17.4)	3 (25)	11 (17.5)
Clark index, N (%)				
< V	3 (10.7)	2 (8.7)	3 (25)	8 (12.7)
V	18 (64.3)	19 (82.6)	5 (41.7)	42 (66.7)
NE	7 (25)	2 (8.7)	4 (33.3)	13 (20.6)
Tumor thickness, N (%)				
< 6 mm	2 (7.1)	7 (30.4)	4 (33.3)	13 (20.6)
\geq 6 mm	11 (39.3)	5 (21.7)	4 (33.3)	20 (31.7)
NE	15 (53.6)	11 (47.8)	4 (33.3)	30 (47.6)
Tumor histologic differentiation, N (%)				
Well or moderately differentiated	24 (85.7)	13 (56.5)	7 (58.3)	44 (69.8)
Poorly or undifferentiated	2 (7.1)	6 (26.1)	3 (25)	11 (17.5)
NE	2 (7.1)	4 (17.4)	2 (16.7)	8 (12.7)
Desmoplasia, N (%)				
0	0	0	0	0
Perineural invasion, N (%)				
5 (17.9)	6 (26.1)	3 (25)	14 (22.2)	
PD-L1 expression				
< 50%	3 (10.7)	1 (4.3)	1 (8.3)	5 (7.9)
\geq 50%	0	0	2 (16.7)	2 (3.2)
NE	25 (89.3)	22 (95.7)	9 (75)	56 (88.9)

ECOG PS eastern Cooperative Oncology Group performance status, lacSCC locally advanced cutaneous squamous cell carcinoma, mcSCC advanced cutaneous squamous cell carcinoma with distant metastasis, NE not evaluated, rcSCC advanced cutaneous squamous cell carcinoma with regional progression only, SD standard deviation

Table 2 Previous treatments, anti-PD-1 regimen and following treatments

Characteristics	lacSCC (<i>n</i> = 28)	rcSCC (<i>n</i> = 23)	mcSCC (<i>n</i> = 12)	Total (<i>n</i> = 63)
Number of treatments before the assessed anti-PD-1 initiation				
Mean ± SD	1.4 ± 1.5	1.8 ± 1	2.4 ± 1.4	1.8 ± 1.4
Median (range)	1 (0–5)	2 (1–5)	2 (1–6)	2 (0–6)
Treatments used before the assessed anti-PD-1, <i>N</i> (%)				
Surgery	15 (53.6)	20 (87)	12 (100)	47 (74.6)
Radiotherapy	10 (35.7)	4 (17.4)	7 (58.3)	21 (33.3)
Radiochemotherapy	1 (3.6)	1 (4.3)	1 (8.3)	3 (4.8)
Cetuximab	4 (14.3)	7 (30.4)	3 (25)	14 (22.2)
Carboplatin and cetuximab	3 (10.7)	3 (13)	2 (16.7)	8 (12.7)
5-FU, carboplatin, and cetuximab	1 (3.6)	1 (4.3)	1 (8.3)	3 (4.8)
Paclitaxel and cetuximab	2 (7.1)	1 (4.3)	0	3 (4.8)
Methotrexate	2 (7.1)	0	0	2 (3.2)
Another PD-1 inhibitor (one or more)	1 (3.6)	2 (8.7)	1 (8.3)	4 (6.3)
Gamma-knife	0	0	1 (8.3)	1 (1.6)
Acitretin and nicotinamide	1 (3.6)	1 (4.3)	0	2 (3.2)
Local treatment (topical 5-FU, DPT...)	0	1 (4.3)	0	1 (1.6)
Number of systemic treatments before the assessed anti-PD-1 initiation				
Mean ± SD	1.5 ± 0.9	1.7 ± 0.9	1.8 ± 1.3	1.6 ± 1.0
Median (range)	1 (1–4)	1 (1–4)	1 (1–5)	1 (1–5)
Time between first diagnosis and anti-PD-1 initiation, in years				
Mean ± SD	1.8 ± 1.9	1.8 ± 1.4	2.7 ± 2.3	2.0 ± 1.9
Median (range)	1.1 (0.1–7.4)	1.1 (0.3–6.2)	2.1 (0.4–8.6)	1.1 (0.1–8.6)
Anti-PD-1 regimen				
Cemiplimab	21 (75)	20 (87)	11 (91.7)	52 (82.5)
3 mg/kg every 2 weeks	6 (21.4)	7 (30.4)	4 (33.3)	17 (27)
350 mg every 3 weeks	14 (50)	11 (47.8)	6 (50)	31 (49.2)
3 mg/kg every 2 weeks and then 350 mg every 3 weeks	1 (3.6)	2 (8.7)	1 (8.3)	4 (6.3)
Nivolumab	5 (17.9)	2 (8.7)	1 (8.3)	8 (12.7)
3 mg/kg every 2 weeks	2 (7.1)	1 (4.3)	0	3 (4.8)
240 mg every 2 weeks	2 (7.1)	0	1 (8.3)	3 (4.8)
480 mg every 4 weeks	1 (3.6)	1 (4.3)	0	2 (3.2)
Pembrolizumab	2 (7.1)	1 (4.3)	0	3 (4.8)
2 mg/kg every 3 weeks	2 (7.1)	0	0	2 (3.2)
200 mg every 3 weeks	0	1 (4.3)	0	1 (1.6)
Concurrent radiotherapy				
No	26 (92.9)	16 (69.6)	11 (91.7)	53 (84.1)
Yes	2 (7.1)	7 (30.4)	1 (8.3)	10 (15.9)
Number of treatments after the assessed anti-PD-1				
Mean ± SD	0.2 ± 0.7	0.3 ± 0.5	0.5 ± 1.2	0.3 ± 0.8
Median (range)	0 (0–3)	0 (0–2)	0 (0–4)	0 (0–4)
Treatments used after immunotherapy, <i>N</i> (%)				
Radiotherapy	2 (7.1)	1 (4.3)	1 (8.3)	4 (6.3)
Cetuximab	2 (7.1)	1 (4.3)	1 (8.3)	4 (6.3)
Carboplatin and cetuximab	0	1 (4.3)	1 (8.3)	2 (3.2)
Paclitaxel and cetuximab	1 (3.6)	0	1 (8.3)	2 (3.2)
Paclitaxel and carboplatin	0	0	1 (8.3)	1 (1.6)
Gemcitabine	0	0	1 (8.3)	1 (1.6)
Another anti-PD1 (one or more)	1 (3.6)	2 (8.7)	0	3 (4.8)

lacSCC locally advanced cutaneous squamous cell carcinoma, mcSCC advanced cutaneous squamous cell carcinoma with distant metastasis, rcSCC advanced cutaneous squamous cell carcinoma with regional progression only, SD standard deviation

Table 3 Tumor response to PD-1 inhibitor (cemiplimab, nivolumab or pembrolizumab)

Outcome	Total (n=63)	lacSCC (n=28)	rcSCC (n=23)	mcSCC (n=12)
Best overall response, N (%)				
Complete response	12 (19)	5 (17.9)	3 (13.0)	4 (33.3)
Partial response	24 (38.1)	10 (35.7)	9 (39.1)	5 (41.7)
Stable disease	7 (11.1)	4 (14.3)	2 (8.7)	1 (8.3)
Progressive disease	17 (27.0)	8 (28.6)	7 (30.4)	2 (16.7)
Not evaluable	3 (4.8)	1 (3.6)	2 (8.7)	0
Overall response rate, % (95% CI)	57.1 (44.0–69.5)	53.6 (33.9–72.5)	52.2 (30.6–73.2)	75.0 (42.8–94.5)
Disease control rate, % (95% CI)	68.3 (55.3–79.4)	67.9 (47.6–84.1)	60.9 (38.5–80.3)	83.3 (51.6–97.9)

CI confidence interval, lacSCC locally advanced cutaneous squamous cell carcinoma, mcSCC advanced cutaneous squamous cell carcinoma with distant metastasis, rcSCC advanced cutaneous squamous cell carcinoma with regional progression only

The most frequently observed AEs were fatigue (34.9%, $n=22$), anemia (23.8%, $n=15$), weight loss (20.6%, $n=13$), decreased lymphocyte count (17.5%, $n=11$), and hypothyroidism (11.1%, $n=7$). Deaths were caused by tumor bleeding (2), rectal bleeding (1), infectious pneumonitis (1) and multi-visceral sepsis (1).

AEs led to PD-1 inhibitor discontinuation in 18 patients (28.6%), but disease progression was an associated reason for interrupting treatment in 9 of these cases (14.3%).

Oncogeriatric evaluation (data summarized in Tables 5, 6)

G8 score was only scarcely evaluated at baseline (29.6%) and was ≤ 14 in most cases (77.8%). 38.1% of patients were submitted to a standard geriatric evaluation immediately before anti-PD-1 implementation. Lee prognostic score was thereby calculated at some time in most patients (68.3%) with a score of 13 or more in 60.5% while Charlson comorbidity index score was available for all patients with a score of 7 or more in a large majority (85.7%).

Interestingly, 41.3% of patients experienced degradation of ECOG PS score between the first and last PD-1 inhibitor infusion with a mean variation of 1 point while the nutritional state worsened in 27% of patients and 57.1% lost weight during treatment.

Discussion

Owing to encouraging results obtained with PD-1 inhibitors in advanced melanoma (Weber et al. 2015; Ribas et al. 2015) and the high tumor mutational burden (a putative biomarker of response to PD-1 inhibitors) identified in cSCC in general and likely related to dominant UV-driven oncogenesis, a beneficial effect of these molecules in acSCC was expected (Hall et al.

2020; Wu et al. 2020; Boussiotis 2016). Off-label use of nivolumab (Sellah et al. 2019; Blum et al. 2018) along with specific clinical trials investigating cemiplimab (Migden et al. 2018, 2020; Rischin et al. 2020) and pembrolizumab (Grob et al. 2020; Maubec et al. 2020) indeed reported the efficacy of these molecules in this setting compared to conventional chemotherapy and EGFR-inhibitors (Keeping et al. 2021). However, specific real-life data regarding efficacy and tolerance of anti-PD-1 in acSCC are currently scarce (Hanna et al. 2020; Salzmann et al. 2020; Shalhout et al. 2021; In et al. 2021; Valentin et al. 2021; Guillaume et al. 2021; Baggi et al. 2021), especially in elderly, fragile patients with poor ECOG performance status and often excluded of clinical trials as a consequence. Furthermore, it has been demonstrated that an older age was associated with worse OS (Xu et al. 2018).

Nonetheless, our survey clearly confirms that the results obtained with PD-1 inhibitors in this particular subset of acSCC patients are similar to those obtained in younger populations included in pivotal clinical trials, with acceptable safety. A synoptic comparison between this study and prior reports of anti-PD1 in acSCC (Migden et al. 2018, 2020; Rischin et al. 2020; Grob et al. 2020; Maubec et al. 2020; Hanna et al. 2020; Salzmann et al. 2020; Shalhout et al. 2021; In et al. 2021; Valentin et al. 2021; Guillaume et al. 2021; Baggi et al. 2021) is presented in Appendices (Table A.3).

As anticipated, the patients included in the present survey were older than in most previously published studies with a median age of 83 years, a majority of patients between 80 and 89 year-old at inclusion and about 20% of 90-year old and older patients. Of note, the median age of patients included in clinical trials (Migden et al. 2018, 2020; Rischin et al. 2020; Grob et al. 2020; Maubec et al. 2020) was between 71 to



Fig. 1 Results of cemiplimab associated with concurrent radiotherapy in a 73 year-old man with metastatic cutaneous squamous cell carcinoma of the scalp previously treated with first-line carboplatin, 5-FU, and cetuximab and second-line carboplatin and cetuximab (left) after 14 radiotherapy sessions for a total of 30 Gy and 1 (middle) and 3 (right) month(s) of concurrent cemiplimab

83 years old (patients' age ranged from 29 to 102 years old). Additionally, baseline ECOG PS score was at least 2 in 39.7% of this population and 15.9% suffered from immunosuppression, mainly related to onco/hematological diseases, while such patients were excluded in previously published prospective studies.

In our study, ORR was 57.1% with a CR rate of 19%, results slightly better than those obtained in prior trials. This difference might partly be explained by the concurrent use of radiotherapy in almost 16% of patients in the present study (a treatment not allowed in clinical trials) even though univariable analysis did not confirm a statistically significant association between the response and this treatment possibly owing to a lack of robustness. Of interest a study evaluating the efficacy of durvalumab, an anti-PD-L1, associated with chemoradiation is to be soon implemented (Lin et al. 2021). Conversely, the DOR and PFS were shorter than previously reported, which might be related to the absence of a priori selection of patients regarding general status with an immune response possibly declining over time as a consequence and/or to a higher frequency of limiting AEs in these fragile patients leading to more frequent premature treatment interruptions. This latter hypothesis is supported by the rate of grade 3 to 5 AEs observed in our study (47.6%), quite comparable to previous data obtained with cemiplimab (between 39.3 and 50.8%) but significantly higher than with pembrolizumab (between 6.7 and 7%, but only for treatment related AEs). These differences might also be explained by the increased risk of drug interactions owing to associated medications (Gambichler et al. 2022) and the possible overestimation of the liability of the anti-PD-1 agent in AE occurrence, which was not assessed by an independent committee in our study. Immunotherapy's role in some of the AE reported in this study might hence be questionable, they might be linked to the natural evolution of the disease (e.g. tumor hemorrhage), or to the patients' comorbidities (e.g. esophageal varices hemorrhage).

Fatigue, diarrhea, nausea, pruritus, and hypothyroidism were the most frequently reported AEs in acSCC treated with PD-1 inhibitors in previous studies and these events were similarly observed in our survey. Interestingly, weight loss and lymphocytes count decrease were not particularly notified as frequent AEs in prior reports and they might be more specifically observed in elderly patients. Of note, in this study as in the previously mentioned ones (Migden et al. 2018, 2020; Rischin et al. 2020; Grob et al. 2020; Maubec et al. 2020; Hanna et al. 2020; Salzmann et al. 2020; Shalhout et al. 2021; In et al. 2021; Valentin et al. 2021;

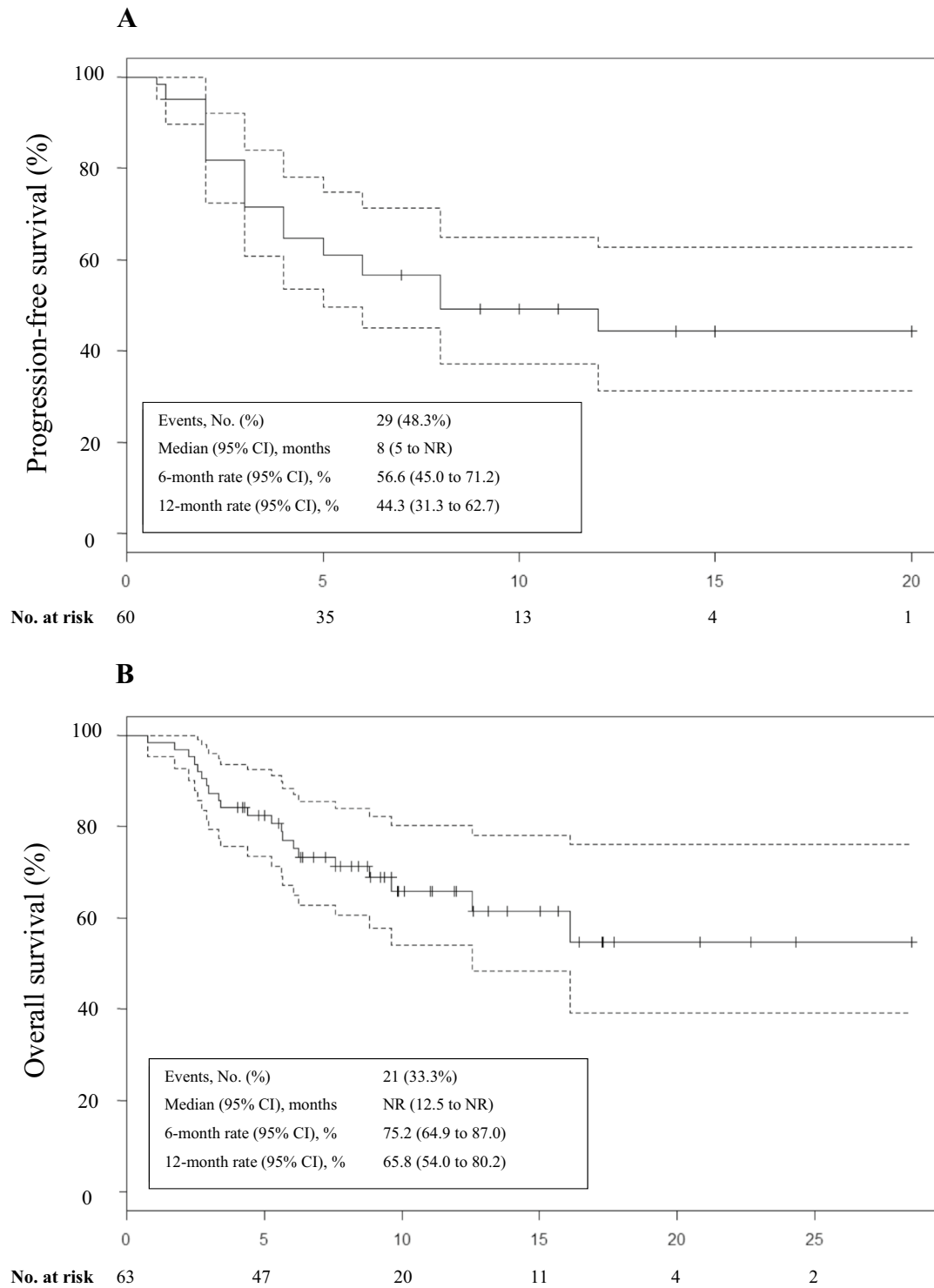


Fig. 2 Kaplan–Meier estimates of **A** progression-free survival and **B** overall survival (*CI* confidence interval, *NR* not reached)

Table 4 Reported adverse effects according to National Cancer Institute's Common Terminology Criteria Toxicity Grade that occurred in $\geq 5\%$ of the 63 patients included during the course of the assessed anti-PD-1 treatment

Adverse effect	Grade 1–2, <i>N</i> (%)	Grade 3, <i>N</i> (%)	Grade 4, <i>N</i> (%)	Grade 5, <i>N</i> (%)
Fatigue	16 (25.4)	6 (9.5)	0	0
Anemia	11 (17.5)	4 (6.3)	0	0
Weight loss	13 (20.6)	0	0	0
Lymphocyte count decreased	6 (9.5)	5 (7.9)	0	0
Hypothyroidism	7 (11.1)	0	0	0
Lung infection	3 (4.8)	1 (1.6)	0	1 (1.6)
GGT and/or alkaline phosphatase increased	4 (6.3)	1 (1.6)	0	0
Pruritus	5 (7.9)	0	0	0
Eosinophilia	5 (7.9)	0	0	0
Creatinine increased	5 (7.9)	0	0	0
Tumor hemorrhage	2 (3.2)	0	0	2 (3.2)
Dry skin	3 (4.8)	1 (1.6)	0	0
Eczema	4 (6.3)	0	0	0
None or not confirmed	8 (12.7)			

NB: 1 patient who was treated with CEMPLIMAB contracted a CoVID-19 infection. The grade of this infection was not evaluated

GGT gamma-glutamyl transferase

Guillaume et al. 2021; Baggi et al. 2021), the most frequently AEs reported were usually different from the well-known immune-related-AEs (irAEs) expected with anti-PD-1 agents (Gambichler et al. 2022). Pathophysiology of these non-irAEs might be related to several intricately associated triggering factors in this elderly population. In the present study, most patients required at least partial assistance for daily-life activities, were heavily medicated but chronic cognitive impairment was only scarcely identified. Their overall geriatric prognosis was unfavorable according to Lee prognostic index score and Charlson comorbidity index score. Dynamics of general status during antineoplastic treatments is a crucial data in these fragile patients, with chemotherapy likely to alter patients' overall condition and quality of life while EGFR inhibitors, generally better tolerated, can sometimes generate significant AE as well. In the present study, about 40% of patients experienced a degradation of their ECOG PS score between the first and last anti-PD-1 infusions, with a mean variation of 1 point, and 25% a worsening of their nutritional status while more than 50% of the patients lost weight, often drastically. Additionally, at the date of anti-PD-1 introduction, more than one third of patients already suffered from malnutrition, rated as severe in one third of these patients. Overall, these results call attention to

the mandatory use of a specific geriatric initial staging and follow-up in elderly acSCC patients receiving an antineoplastic treatment, including anti-PD-1, to reassess the benefit/risk ratio on a regular basis.

Several specific strengths are to be emphasized in this survey: the significant number of patients included, comparable with most prior reports in real-life conditions (63 versus 18 to 76, with a mean number of patients of 36); a multicenter data collection in seven French cities with a likely relevant representativeness of acSCC patients; an accurate outcome assessment in all but three patients; the real-life conditions regarding patients' characteristics, treatments, outcome, and side effects with the inclusion of elderly, fragile patients with heavy comorbidities usually excluded from most industrial trials while such patients are among the most likely ones to develop acSCC and to experience limiting side effects and perhaps less likely to respond to immunotherapy owing to possible immunosenescence (Daste et al. 2017)); the use of specific geriatric tools, an assessment procedure not previously and specifically reported in immunotherapy-treated acSCC although highly relevant in these elderly patients who are likely to represent the majority of individuals treated with anti-PD-1 in a real-life setting.

Table 5 Patients treated with anti-PD-1 for advanced cutaneous squamous cell carcinoma: oncogeriatric data

Characteristics, <i>N</i> (%)	lacSCC (<i>n</i> =28)	rcSCC (<i>n</i> =23)	mcSCC (<i>n</i> =12)	Total (<i>n</i> =63)
Age				
<80	8 (28.6)	7 (30.4)	5 (41.7)	20 (31.7)
80–89	14 (50)	11 (47.8)	5 (41.7)	30 (47.6)
90–99	5 (17.9)	5 (21.7)	2 (16.7)	12 (19)
≥100	1 (3.6)	0	0	1 (1.6)
G8 screening tool score				
>14	3 (10.7)	1 (4.3)	0	4 (6.3)
≤14	6 (21.4)	5 (21.7)	3 (25)	14 (22.2)
NE	19 (67.9)	17 (73.9)	9 (75)	45 (71.4)
Standard geriatric evaluation before anti-PD-1 initiation				
No	15 (53.6)	16 (69.6)	8 (66.7)	39 (61.9)
Yes	13 (46.4)	7 (30.4)	4 (33.3)	24 (38.1)
ADL score				
<3/6	3 (10.7)	1 (4.3)	0	4 (6.3)
≥3/6	15 (53.6)	11 (47.8)	5 (41.7)	31 (49.2)
NE	10 (35.7)	11 (47.8)	7 (58.3)	28 (44.4)
IADL score				
<4/8	11 (39.3)	4 (17.4)	1 (8.3)	16 (25.4)
≥4/8	5 (17.9)	8 (34.8)	4 (33.3)	17 (27)
NE	12 (42.9)	11 (47.8)	7 (58.3)	30 (47.6)
MMSE score				
<20/30	5 (17.9)	3 (13)	1 (8.3)	9 (14.3)
≥20/30	9 (32.1)	6 (26.1)	3 (25)	18 (28.6)
NE	14 (50)	14 (60.9)	8 (66.7)	36 (57.1)
Education level				
≤9 years of education	8 (28.6)	8 (34.8)	5 (41.7)	21 (33.3)
10–12 years of education	1 (3.6)	1 (4.3)	0	2 (3.2)
University level	2 (7.1)	2 (8.7)	1 (8.3)	5 (7.9)
Other level of education	2 (7.1)	2 (8.7)	1 (8.3)	5 (7.9)
NE	15 (53.6)	10 (43.5)	5 (41.7)	30 (47.6)
Lee prognostic index score				
<13	9 (32.1)	4 (17.4)	4 (33.3)	17 (27)
≥13	11 (39.3)	11 (47.8)	4 (33.3)	26 (41.3)
NE	8 (28.6)	8 (34.8)	4 (33.3)	20 (31.7)
Charlson comorbidity index score				
<7	8 (28.6)	1 (4.3)	0	9 (14.3)
≥7	20 (71.4)	22 (95.7)	12 (100)	54 (85.7)
Diabetes				
No	21 (75)	19 (82.6)	10 (83.3)	50 (79.4)
Yes	7 (25)	4 (17.4)	2 (16.7)	13 (20.6)
Yes, controlled without medication	1 (3.6)	1 (4.3)	0	2 (3.2)
Yes, controlled with oral antidiabetic drugs only	3 (10.7)	1 (4.3)	0	4 (6.3)
Yes, requiring insulin therapy	3 (10.7)	2 (8.7)	2 (16.7)	7 (11.1)
Without end-organ damage	1 (3.6)	1 (4.3)	1 (8.3)	3 (4.8)
With end-organ damage	2 (7.1)	1 (4.3)	1 (8.3)	4 (6.3)
Malnutrition at anti-PD-1 initiation^a				
No	20 (71.4)	13 (56.5)	8 (66.7)	41 (65.1)
Moderate malnutrition	6 (21.4)	6 (26.1)	2 (16.7)	14 (22.2)
Severe malnutrition	2 (7.1)	4 (17.4)	2 (16.7)	8 (12.7)

Table 5 (continued)

Characteristics, <i>N</i> (%)	lacSCC (<i>n</i> =28)	rcSCC (<i>n</i> =23)	mcSCC (<i>n</i> =12)	Total (<i>n</i> =63)
Depression and/or anxiety				
No	7 (25)	7 (30.4)	4 (33.3)	18 (28.6)
Yes	13 (46.4)	12 (52.2)	3 (25)	28 (44.4)
NE	8 (28.6)	4 (17.4)	5 (41.7)	17 (27)
Walking difficulties^b				
No	6 (21.4)	6 (26.1)	1 (8.3)	13 (20.6)
Yes	11 (39.3)	7 (30.4)	3 (25)	21 (33.3)
NE	11 (39.3)	10 (43.5)	8 (66.7)	29 (46)
Number of treatments at anti-PD-1 initiation				
< 5	8 (28.6)	8 (34.8)	4 (33.3)	20 (31.7)
5–9	12 (42.9)	8 (34.8)	4 (33.3)	24 (38.1)
≥ 10	8 (28.6)	7 (30.4)	4 (33.3)	19 (30.2)
Place of living				
Own house/apartment without help	14 (50)	14 (60.9)	5 (41.7)	33 (52.4)
Own house/apartment with help	8 (28.6)	5 (21.7)	5 (41.7)	18 (28.6)
Nursing home	6 (21.4)	4 (17.4)	2 (16.7)	12 (19)
Distance between the place of living and the hospital				
< 50 km	19 (67.9)	12 (52.2)	10 (83.3)	41 (65.1)
50–99 km	5 (17.9)	4 (17.4)	1 (8.3)	10 (15.9)
≥ 100 km	4 (14.3)	7 (30.4)	1 (8.3)	12 (19)

ADL: activities of daily living; *IADL* instrumental activities of daily living, *lacSCC* locally advanced cutaneous squamous cell carcinoma, *mcSCC* advanced cutaneous squamous cell carcinoma with distant metastasis, *MMSE* Mini-Mental State Examination, *NE* not evaluated, *rcSCC* advanced cutaneous squamous cell carcinoma with regional progression only

^aMalnutrition was defined based on BMI (body mass index) and/or serum albumin levels according to French guidelines (Haute Autorité de Santé, 2007). https://www.has-sante.fr/upload/docs/application/pdf/denutrition_personne_agee_2007_-_recommandations.pdf

^bWalking difficulties: walking speed < 1 m/sec, altered get-up and go test, known walk alterations, or need to use a cane or a rollator

Conversely, some limitations are to be acknowledged: the retrospective design limiting data comprehensiveness and homogeneity, especially regarding response evaluation often not based on standardized criteria like RECIST with possible reduced statistical robustness as a consequence; the lack of systematic evaluation of oncogeriatric parameters in all patients; the small number of patients receiving pembrolizumab and nivolumab, precluding a significant comparison of the different molecules; the use of heterogeneous, both body weight-adjusted and flat doses of anti-PD-1, even though pharmacokinetic data support an equivalent exposure to the molecule (Ogungbenro et al. 2018).

Conclusion

This study clearly confirms the efficacy of anti-PD-1 agents to treat elderly acSCC patients in a real-life setting with no significant loss of efficiency compared to younger patients. Age should not be a limiting factor when prescribing immunotherapy anymore. However, AEs, including weight loss may have major consequences in these frail patients and must be closely monitored, especially by specific geriatric evaluation tools used at baseline and regularly throughout the course of treatment to ensure that it remains beneficial. The use of concurrent radiotherapy should be closer examined in larger studies.

Table 6 Deleterious effects of anti-PD-1 on elderly patients' general health

Characteristics, <i>N</i> (%)	Cemiplimab (<i>n</i> =52)	Nivolumab (<i>n</i> =8)	Pembrolizumab (<i>n</i> =3)	Total (<i>n</i> =63)
Aggravation of ECOG PS score between first and last known anti-PD-1 administration				
No	32 (61.5)	3 (37.5)	2 (66.7)	37 (58.7)
Yes	20 (38.5)	5 (62.5)	1 (33.3)	26 (41.3)
Malnutrition^a at the last known anti-PD-1 administration				
No	25 (48.1)	5 (62.5)	3 (100)	33 (52.4)
Moderate malnutrition	13 (25.0)	2 (25)	0	15 (23.8)
Severe malnutrition	13 (25.0)	1 (12.5)	0	14 (22.2)
NE	1 (1.9)	0	0	1 (1.6)
Worsening of nutritional state between first and last known anti-PD-1 administration				
No	35 (67.3)	7 (87.5)	3 (100)	45 (71.4)
Yes	16 (30.8)	1 (12.5)	0	17 (27)
NE	1 (1.9)	0	0	1 (1.6)
Weight loss between first and last known anti-PD-1 administration				
No	19 (36.5)	4 (50)	2 (66.7)	25 (39.7)
Yes	31 (59.6)	4 (50)	1 (33.3)	36 (57.1)
< 10%	24 (46.2)	2 (25)	1 (33.3)	27 (42.9)
10–15%	4 (7.7)	1 (12.5)	0	5 (7.9)
> 15%	3 (5.8)	1 (12.5)	0	4 (6.3)
NE	2 (3.8)	0	0	2 (3.2)

ECOG PS eastern cooperative oncology group performance status, NE not evaluated)

^aMalnutrition was defined based on BMI and/or serum albumin levels according to French guidelines (Haute Autorité de Santé, 2007). https://www.has-sante.fr/upload/docs/application/pdf/denutrition_perso_nne_agee_2007_-_recommandations.pdf

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Declarations

Conflict of interest The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: David AZRIA: co-founder of NovaGray (outside the field of the present article); Olivier DEREURE: investigator and/or consultant and/or member of advisory boards and/or speaker for: BMS, MSD, Sanofi Merck GmbH; Brigitte DRENO: investigator and/or consultant and/or advisory boards and/or speaker for: BMS, Regeneron, Merck; Caroline GAUDY MARQUESTE: speaker for BMS; Eve MAUBEC: consultant and/or advisory board; Sanofi, Novartis; research funding for AP-HP: MSD; Travel accommodations: Pierre Fabre, Sanofi, MSD; Nicolas MEYER: investigator and/or consultant and/or advisory boards and/or speaker for: BMS, MSD, Sanofi Merck GmbH; Nicolas MOLINARI: grants from GSK and Astra Zeneca, outside the submitted work. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent for publication The patient pictured on Fig. 1 has given his written consent for publication of his photographs and associated data. No other patient is recognizable from the data presented in this article.

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