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Original Research

Second-line treatment after docetaxel, cisplatin and 5-fluorouracil in metastatic squamous cell carcinomas of the anus. Pooled analysis of prospective Epitopes-HPV01 and Epitopes-HPV02 studies

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Abstract ***Background:*** Squamous cell carcinoma of the anus (SCCA) is a rare disease often diagnosed at a localised stage. For locally advanced recurrence or metastatic disease, DCF (docetaxel, cisplatin, 5-fluorouracil) demonstrated high efficacy and became one of the standard regimens. However, there is no standard of care in the second line.
Patients and methods: In the Epitopes-HPV01 and Epitopes-HPV02 prospective trials, 115 patients with advanced SCCA were treated with a DCF regimen in the first line. In these studies, second-line data were registered per protocol.
Results: After a median follow-up of >40 months, at progression, 73 patients received a second-line (L2) treatment. In this L2 population, median overall survival (mOS) was 13.5 months (95%CI 9.4–19.8), and median progression-free survival (mPFS) was 5.7 months (3.4–7.3) in L2. Fourteen patients presented an oligometastatic progression and were treated with an ablative treatment (surgery or radiotherapy); mOS was 48.3 months (NE–NE), and mPFS was 31.3 months (23.2–NE). Fifty-nine patients received a systemic treatment (chemotherapy or immunotherapy); mOS was 11 months (8.4–15.4) and mPFS was 4.9 months (3.3–7). The most frequent chemotherapy regimens were the reintroduction of DCF, paclitaxel, FOLFIRI and mitomycin plus fluoropyrimidine. No significant difference was observed between regimens ($p = 0.26$). Six patients received anti-PD1/L1-based immunotherapy.
Conclusion: Second-line treatments are effective in patients with SCCA. Ablative treatment is feasible and is probably the best option for patients with oligometastatic progression. If this is not possible, systemic therapy by an anti-PD1/L1 immunotherapy or chemotherapy can be recommended. Reintroduction of DCF, paclitaxel, FOLFIRI or mitomycin-C plus fluoropyrimidine are possible options.

1. Introduction

Squamous cell carcinoma of the anus (SCCA) is a rare malignancy associated with HPV infection, but its incidence rate is rising [1–5] In advanced disease, the combination of docetaxel, cisplatin and 5-fluorouracil (DCF) is one of the recommended regimens in first-line since the publication of the results of Epitopes-HPV02 phase II confirmatory study of the previous results of Epitopes-HPV01 trial [6,7]. Recently, results of the pooled analysis of 115 patients from updated data of Epitopes-HPV01 and 02 studies in first-line in SCCA were published and confirmed the modified DCF (mDCF) as one of the standards of care in first-line [8]. In this study, the objective response rate (ORR) was 87.7% with 40.3% of complete response, and the median progression-free survival (mPFS) was 12.0 months. Importantly, 24.5% of patients were still alive and free of recurrence at 5 years. The 5-year overall survival (OS) rate was 44.4% in the final analysis [8].

In second-line, there is no standard chemotherapy. Few retrospective studies with a limited number of patients described the experience of some reference centres [9–11]. Most frequently used regimens were platinum salts, paclitaxel or the association of mitomycin-C (MMC) and 5-fluorouracil (5FU). In these studies, the mPFS was about 3 months and the median OS (mOS) ranged between 7.0 and 15.0 months. Besides, anti-PD1 immunotherapies have demonstrated efficacy in chemorefractory metastatic SCCA in prospective single-arm studies. ORR between 10 and 24% were reported in these studies. Patients included in these early clinical trials achieved mPFS ranging from 2.0 to 4.1 months and mOS of 9.3–12.0 months [12–16].

In Epitopes-HPV01 and Epitopes-HPV02 studies, second-line treatments and their outcomes were prospectively registered. Here, we questioned the clinical impact of the second-line medical strategies applied for patients with SCCA previously treated by DCF chemotherapy.

2. Material and methods

2.1. Study design and participants

Epitopes-HPV01 is a cohort study supported by the Besancon University Hospital in France and performed by the regional cancer network of Franche-Comté. Epitopes-HPV02 is a phase II confirmatory study supported by the GERCOR and FFCD collaborative oncological groups, performed in 25 academic hospitals, cancer research centres and community hospitals in France. In both studies, we included patients aged 18 years or older with histologically confirmed SCCA, with metastatic disease or with unresectable local recurrence after chemoradiotherapy. Patients received 6 cycles of classic DCF (75 mg/m^2 docetaxel and 75 mg/m^2 cisplatin on day 1 and 750 mg/m^2 per day of fluorouracil for 5 days, every 3 weeks) or 8 cycles of mDCF (40 mg/m^2 docetaxel and 40 mg/m^2 cisplatin on day 1 and 1200 mg/m^2 per day of fluorouracil for 2 days, every 2 weeks) in first-line. Details of the protocols were published elsewhere [6–8,17]. At second-line, the treatment was at the discretion of the multidisciplinary board at each centre. The type of treatment and its outcomes were registered per protocol.

Epitopes-HPV01 and Epitopes-HPV02 studies were reviewed and approved by the independent Est-II French Committee for Protection of Persons on 9th July 2012 and 6th June 2014, respectively, and by the French Health Products Safety Agency on 6th July 2012 and 15th July 2014, respectively. Both studies were performed in accordance with the Declaration of Helsinki, and all patients provided written informed consent before study enrolment. These trials were registered as NCT01845779 and NCT02402842.

2.2. End-points

The primary end-point results of the Epitopes-HPV01 and Epitopes-HPV02 study were already published [6,8]. The main end-point of the Epitopes-HPV01 study was to evaluate the immune biomarkers before and after chemotherapy exposure [7,8], and for Epitopes-HPV02, the PFS rate at 1 year from the first DCF chemotherapy cycle [6,17].

The objective of this second-line post-hoc study was to evaluate the type and efficacy of second-line strategies after progression disease during or after DCF. The follow-up interval during the second-line was at the discretion of the investigator, and the central monitoring was performed per protocol.

The primary end-points of the study were investigator-assessed PFS and OS.

The end-points and statistical analysis details are described in the supplementary data.

3. Results

In Epitopes-HPV01, 51 patients were enrolled between 25th September 2012 and 18th January 2019 and 49 patients were included for first-line analysis. The database for Epitopes-HPV01 was locked for final analysis on 30th March 2021 with a median follow-up of 43.3 months (95%CI 35.2–62.6). Twenty-eight patients have progressed and were included in the second-line analysis. Among the twenty-one patients excluded for second-line analysis, 14 patients were in complete response, 5 patients died before second-line, 1 patient was lost of follow-up and 1 patients withdraw his consent (Fig. 1).

In Epitopes-HPV02, 69 patients were enrolled between 17th September 2014 and 7th December 2016, and 66 patients were included for first-line analysis. The database for Epitopes-HPV02 was locked for final analysis on 20th July 2020 with a median follow-up of 40.1 months (95%CI 39.4–40.7). Forty-five patients have progressed and were included for the second-line analysis. Twenty-one were excluded for this second-line analysis, 5 patients died, 15 patients presented no progression at the time of analysis (12 complete responders, 1 partial responder and 2 were still on first-line treatment) and 1 patient withdraw his consent (Fig. 1). Table 1 shows the baseline characteristics of patients treated in the second-line setting. Fifty-three (72.6%) patients received chemotherapy, 6 (8.2%) patients received an anti-PD1/L1 immunotherapy and 14 (19.2%) patients received an ablative treatment (surgery [4 patients] or radiotherapy [10 patients]) as the only second-line therapy at progression after first-line DCF.

In the overall population (n = 73), the mOS was 13.5 months (95%CI 9.4–19.8), and the 12-month OS rate was 51.2% (95%CI 40.1–65.3) (Fig. 2). The mPFS was 5.7 months (95%CI 3.4–7.3), and the 12-months PFS rate was 17.7% (95%CI 10.0–31.3) (Fig. 3).

Among 14 patients with ablative treatment, the mOS was 48.3 months (95%CI NE–NE), and mPFS was 31.3 months (95%CI 23.2–NE) (Fig. 4). Table 2.

Among 59 patients exposed to second-line medical therapies, mOS was 11.0 months (95%CI 8.4–15.4) and mPFS was 4.9 months (95%CI 3.3–7.0). An mPFS of 4.7 months (95%CI 3.0–6.6) was observed for patients exposed to chemotherapy compared with 6.2 months (95%CI 3.8–11.7) when immunotherapy was prescribed. In addition, the 12-month OS rate was 45.9% (95%CI 34.3–61.4), and the 12-month PFS rate was 7.0% (95% CI 2.4–20.3) (Fig. 4). The ORR was 25.5% (95%CI 14.3–39.6) for patients treated with chemotherapy, including 2 complete responses. An ORR of 50.0% (95% CI 6.8–93.2) was reported in patients exposed to immunotherapy, including one complete response.

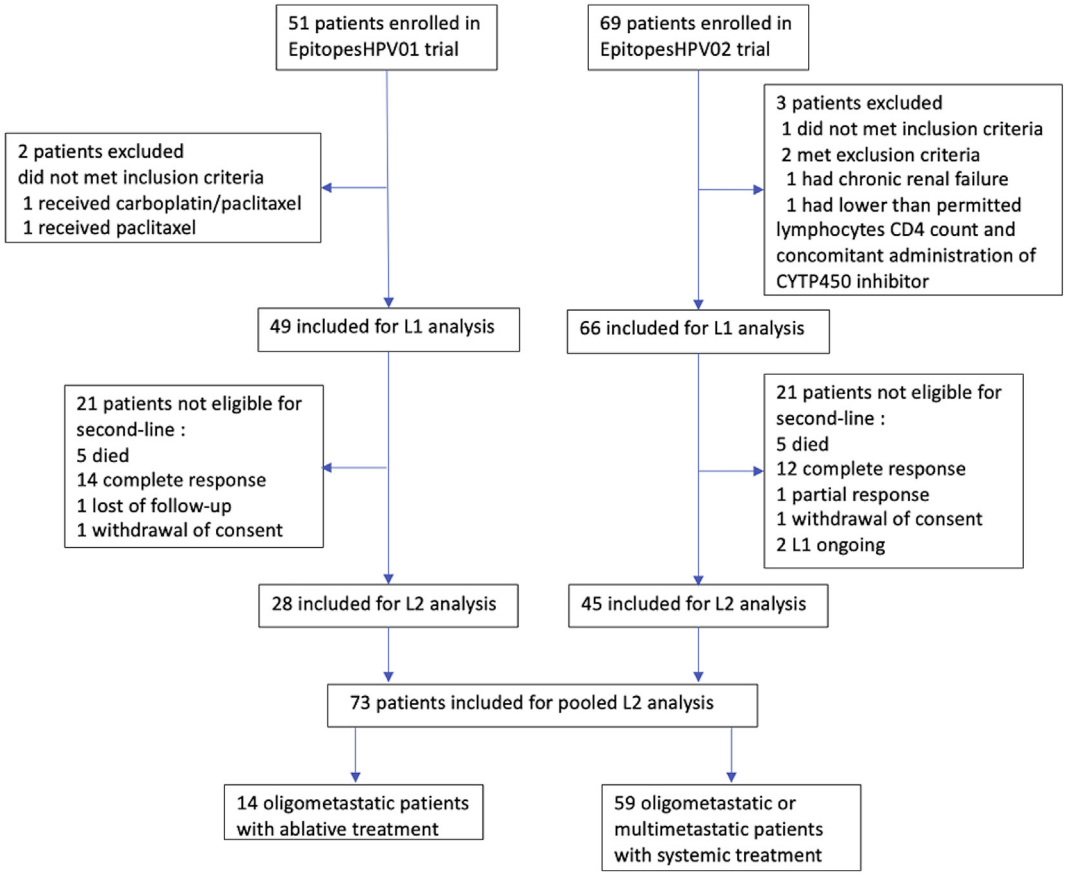

Fig. 1. Flowchart of the pooled population of Epitopes-HPV01 and Epitopes-HPV02 trials.

Among 53 patients treated with chemotherapy, 23 (43.4%) received a taxane-based chemotherapy (group 1), 12 (22.6%) were treated by MMC + fluoropyrimidine (group 2), 9 (17.0%) patients were exposed to FOLFIRI (group 3), and 9 (17.0%) to other regimens (cyclophosphamide plus etoposide, FOLFOX, temozolomide plus capecitabine, or methotrexate; group 4). An anti-EGFR was also prescribed in four patients (one in group 1, two in group 3, and one in group 4) in combination with chemotherapy (Table 1). The mPFS was 6.0 months (95%CI 3.3–13.6) for group 1, 4.7 months (95%CI 2.3–15.5) for group 2, 8.5 months (95%CI 2.5–15.7) for group 3, and 3.0 months (95%CI 2.1–11.8) for group 4. No statistical difference was observed between groups ($p = 0.2597$) (Fig. 5). In group 1, DCF was reintroduced in 9 patients at progression (mPFS 6.7 months, 95%CI 3.4–NE), and 14 patients received a paclitaxel ± carboplatin regimen (mPFS 5.0 months, 95%CI 2.7–13.6). The ORR was 36.4% (95%CI 17.2–59.3) in group 1, 75.0% (95%CI 34.9–96.8) in case of reintroduction of DCF, and 14.3% (1.8–42.8) for paclitaxel ± carboplatin. The median treatment-free interval (defined as the time between the end of the first-line treatment and the beginning of second-line) was 8.4 months for the whole population and 11.3 months for the DCF reintroduction population. Thirty-three patients received a third-line treatment during follow-up.

Ten patients achieved a complete response after the second-line treatment in the whole population. The characteristics of these patients are detailed in the supplementary data and Supplementary Table 1.

In the multivariate analysis for PFS, a good performance status ($p = 0.0047$) and an ablative treatment ($p = 0.0024$) were significantly associated with better PFS in the whole population ($n = 73$) (Table 3); while only ECOG-PS ($p = 0.0074$) was significantly associated with PFS in the systemic treatment population ($n = 59$) (Supplementary Table 2). In the multivariate analysis for OS, less than 3 involved sites ($p = 0.0203$), the good performance status ($p = 0.0115$) and the ablative treatment (0.0491) were significantly associated with better OS in the whole population (Supplementary Table 3).

4. Discussion

To the best of our knowledge, this is the largest study of second-line chemotherapy in advanced patients with SCCA and the first multicentric and prospectively analysed. Concerning those patients who received chemotherapy, the ORR was 25.5% (95%CI 14.3–39.6), with

Table 1
Baseline patient characteristics in second-line.

	Overall population (n = 73)
Gender	
Female	55 (75.3%)
Male	18 (24.7%)
Age	
Median (range)	58.5 (38.6–78.4)
ECOG-PS	
0	30 (48.4%)
1	25 (40.9%)
2	6 (9.7%)
3	1 (1.6%)
Missing	11
HIV-positive	
No	72 (98.6%)
Yes	1 (1.4%)
Number of sites involved	
1	34 (53.1%)
2	23 (35.9%)
3	4 (6.3%)
4 and more	3 (4.7%)
Missing	9
Best response in L1	
CR	27 (37.0%)
PR	39 (53.4%)
SD	5 (6.9%)
PD	2 (2.7%)
PFS in L1 < 12 months	
No	27 (37.0%)
Yes	46 (63.0%)
Treatment-free interval before L2	
Median (IQR)	8.4 (3.3–13.9)
Type of treatment in L2	
Ablative treatment	**14**
Surgery	4
CRT	2
SBRT	8
Immunotherapy	**6**
Anti-PD1/L1	5
Anti-PDL1 + hTERT vaccine	1
Chemotherapy	**53**
Taxane-based	23
mDCF reintroduction	9
Paclitaxel	12
Carboplatin + paclitaxel	1
Carboplatin + paclitaxel + cetuximab	1
MMC + fluoropyrimidine	12
FOLFIRI	7
FOLFIRI + anti-EGFR	2
FOLFOX	3
Cyclophosphamide + etoposide	4
Temozolomide + capecitabine + cetuximab	1
Methotrexate	1

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; HIV, human immunodeficiency virus; PFS, progression-free survival; L1, first-line; L2, second-line; CRT, chemoradiotherapy; SBRT, stereotaxic radiotherapy; hTERT, human telomerase; MMC, mitomycin-C.

an mPFS of 4.7 months (95%CI 3.0–6.6) and mOS of 11.0 months (95%CI 7.4–15.4). The most frequently used regimens were taxane-based, including the reintroduction of DCF in 9 patients, paclitaxel in 12 patients and carboplatin/paclitaxel in 2 patients. Other frequently used regimens were MMC/fluoropyrimidine and FOLFIRI. No statistical differences were observed between regimens. These results are comparable to published data. Sclafani *et al.* analysed 21 patients in second-line. Most patients received a platinum agent plus or minus a fluoropyrimidine (n = 9) or a paclitaxel-based regimen (n = 8). Overall, an objective response was observed in 6 of 18 assessable patients (33.3%); the mPFS was 3.2 months (IQR 2.5–7.1 months), including 2 patients with subsequent ablative treatment. The mOS was 14.9 months (IQR 9.4–37.4 months) [9]. Saint et al. [11] recently published their retrospective analysis on 19 patients who received the MMC plus 5FU regimen as the second-line treatment after failure to platinum-based regimens in the first-line. An objective response was observed in five patients (26.4%; 95%CI 6.6–46.2), including one complete response. mPFS was 3 months (95%CI 1–5) and mOS was 7 months (95%CI 2.2–11.8) [11]. Interestingly, 7 (33.3%) patients in the Sclafani's cohort and 7 (36.8%) in the Saint's cohort were previously exposed to the same molecules received at the first-line or localised stage. No difference in efficacy was reported between those patients who received the reintroduction of the same molecules and those who did not [11]. In line with these data, in our population, 23 (40.0%) patients with systemic treatment received a taxane-based regimen after progression with DCF. The ORR was 36.4% (95% CI 17.2–59.3) with 1 complete response and the mPFS was 6.0 (95% CI 3.3–13,6) months. In patients with the reintroduction of mDCF, mPFS was 6.7 (95% CI 3.4–NE) months, and the ORR was 75.0% (95% CI 34.9–96.8). These data confirm that the reintroduction of the same chemotherapy molecules is possible in patients who are considered as responders to the previous regimen.

Six patients were treated with immunotherapy in our cohort. All patients received an antiPD1/L1 antibody, and 1 patient received the human telomerase (hTERT) UCPVax vaccine. The ORR was 50.0% (95% CI 6.8–93.2), including 1 complete response with an anti-PD1 in monotherapy. The mPFS was 6.2 months (95% CI 3.8–11.7), with an mOS of 18.8 months (7.7–18.8). To date, 3 anti-PD1 antibodies, pembrolizumab, nivolumab, retifanlimab, demonstrated some efficacy in second- or third-line settings. Altogether, 268 patients received an anti-PD1 mAb in these studies. ORR was documented in 11.6–24% of patients. Eight patients (3%) presented a complete response. The mPFS was

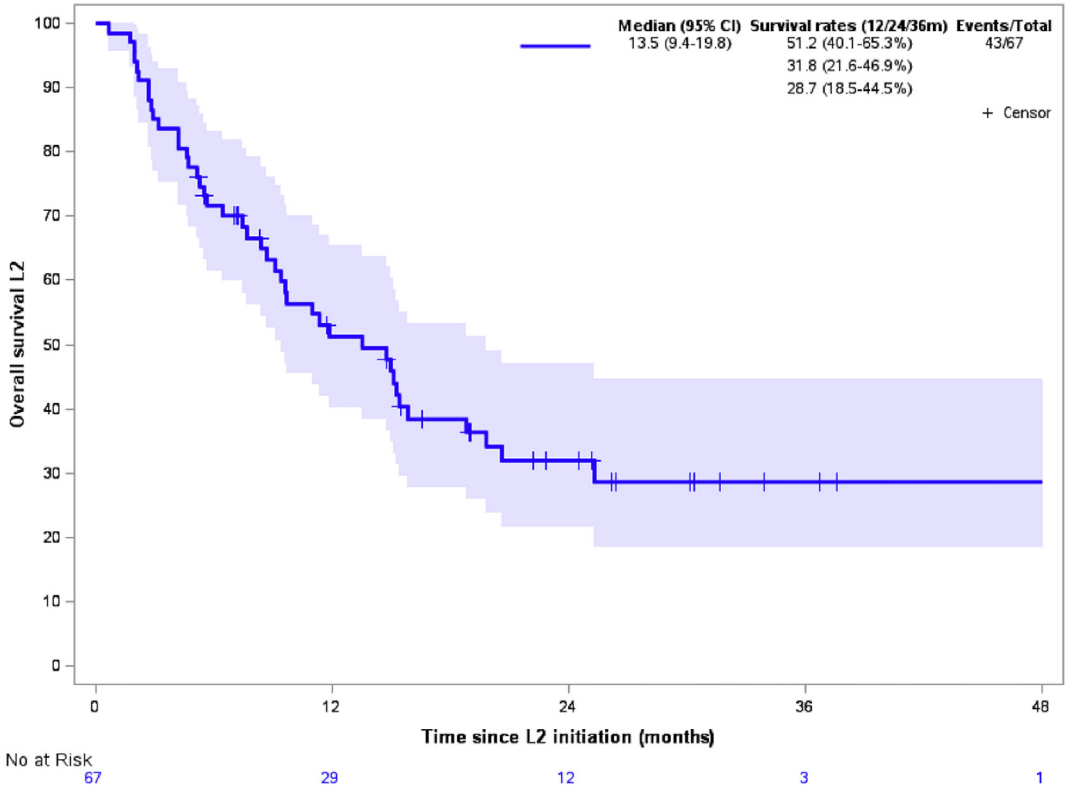

Fig. 2. Overall survival.

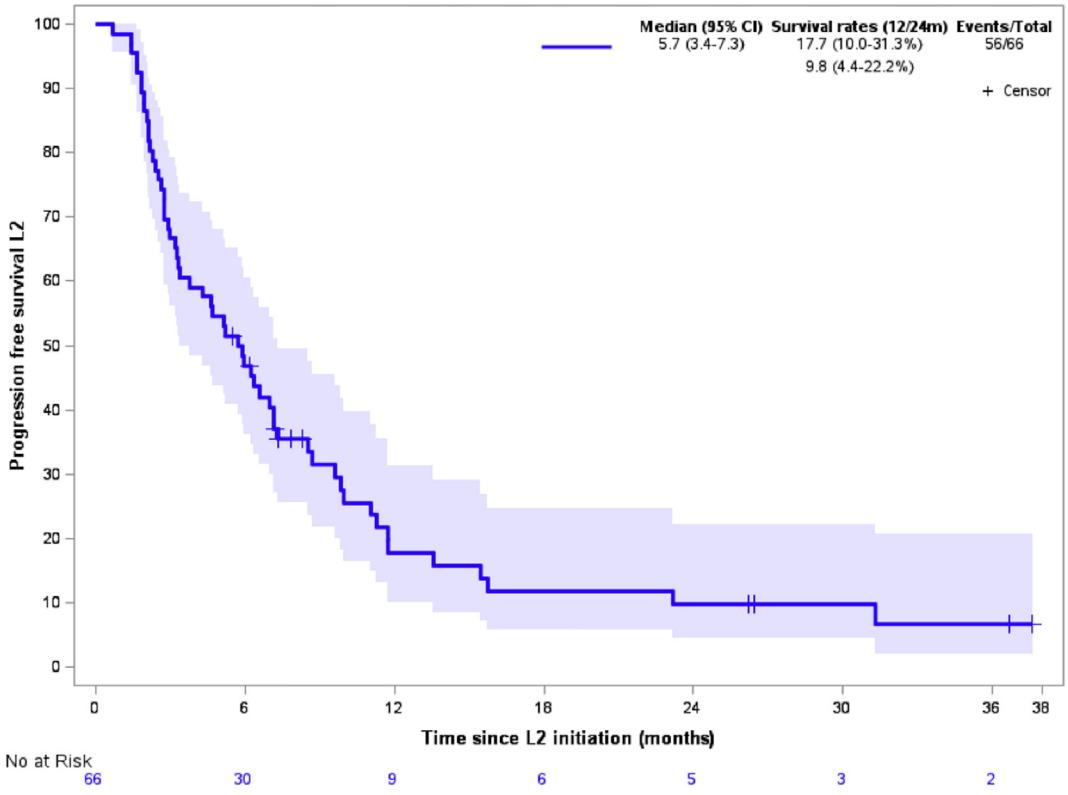

Fig. 3. Progression-free survival.

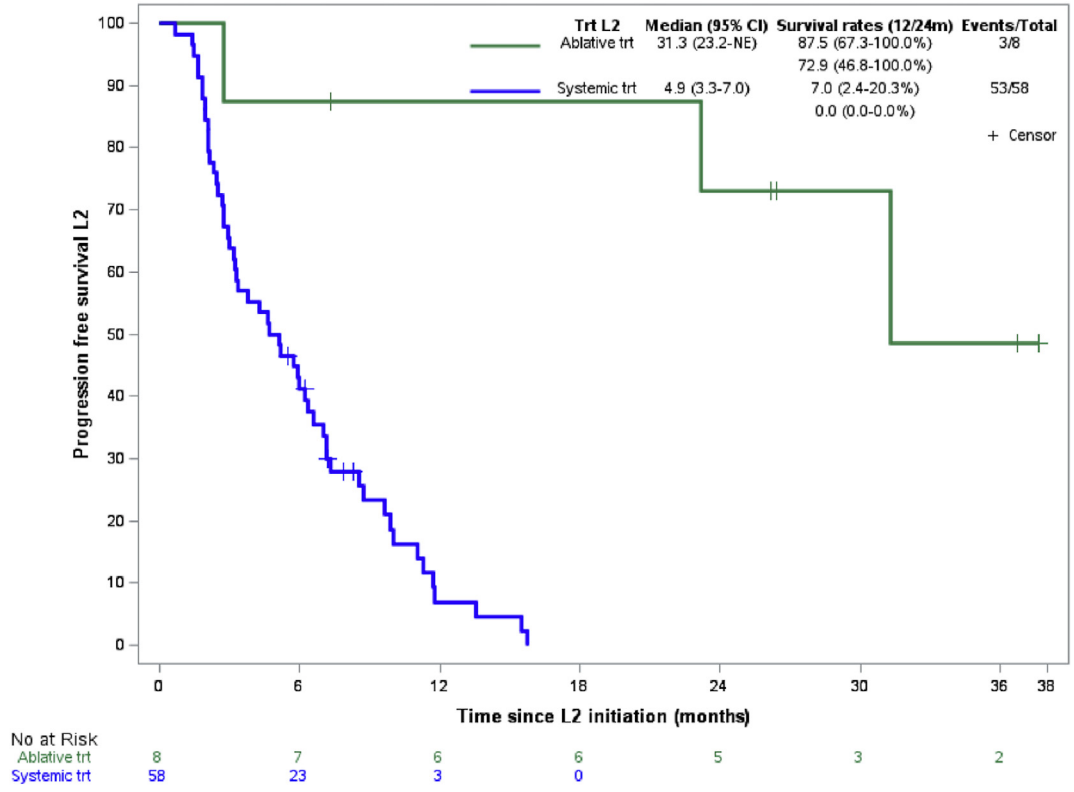

Fig. 4. Progression-free Survival according to the type of treatment.

2.0–4.1 months, and mOS was 9.3–12.0 months [12–16]. Despite the low number of patients in our cohort, the immunotherapy was effective in line with large phase II trials.

Fourteen patients underwent an ablative treatment at progression after the first-line DCF. In these patients, mPFS was 31.3 months and mOS was 48.3 months. Interestingly, 2 patients had multiple sites

Table 2
Characteristics of the patients treated with a local ablative therapy.

	Age (years)	Sex	Localisation in L1	PFS in L1 (months)	Recurrence sites	Type of treatment	PFS in L2 (months)	Relapse
1	58.5	F	Locally advanced	13	Pelvis	Surgery	31	Yes
2	54.4	F	Lung, pleural and bones	25	Lung	SBRT	36	No
3	66.1	F	Liver	17	Lung	SBRT	26	No
4	68.6	F	Locally advanced	10	Liver	SBRT	8	No
5	58.5	M	Lymph nodes, liver and bones	12	Brain	SBRT	3	Yes
6	47.4	F	Liver, lymph nodes, vulva and lung	12	Lung	SBRT	26	No
7	57.4	F	Liver, lung and lymph nodes	23	Lung	SBRT	17	No
8	72.4	F	Locally advanced	6	Pelvis	Surgery	33	No
9	58.5	F	Pleura	15	Lung	CRT	23	Yes
10	52.2	F	Liver	8	Distant lymph nodes	CRT	38	No
11	66.8	F	Locally advanced	8	Pelvis	SBRT	8	Yes
12	55.1	F	Lung	11	Lung	Surgery	28	No
13	64.4	F	Liver and lymph nodes	10	Liver	SBRT	30	No
14	56.0	F	Lung	34	Lung	Surgery	4	No

Abbreviation: PFS, Progression Free Survival; SBRT, Stereotactic Body Radiation Therapy; CRT, Chemoradiotherapy.

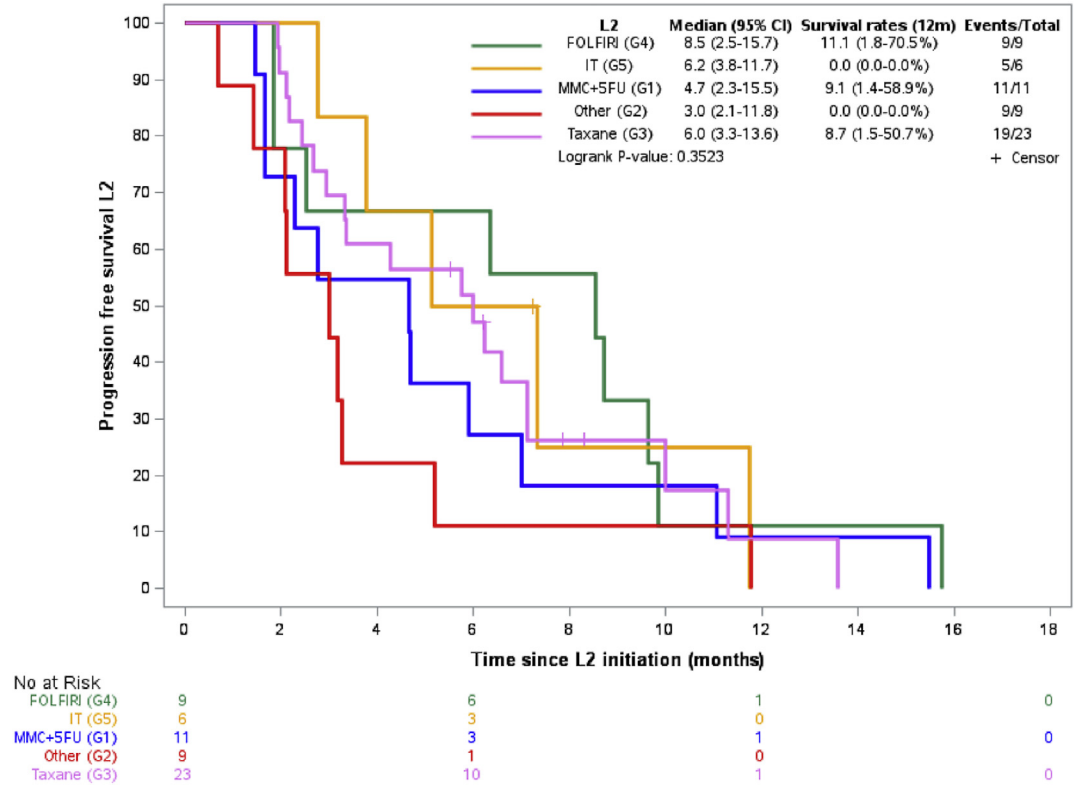

Fig. 5. Progression-free survival according to the systemic treatment regimens. Abbreviations: IT, immunotherapy; MMC, mitomycin-C; 5FU, 5-fluoropyrimidine.

Table 3
Univariate and multivariate analysis for PFS of the whole population (n = 73).

Factor	Univariate analysis					Multivariate analysis		
	No	No Event	HR	95%CI	P	HR	95%CI	p
Sex								
Male	18	18	1					
Female	55	40	0.597	0.333–1.071	0.0835			
Age								
<65	54	45	1					
≥65	19	13	0.756	0.390–1.467	0.4082			
Best response in L1								
CR	27	20	1					
PR	39	31	1.419	0.793–2.538				
SD	5	5	1.886	0.696–5.108				
PD	2	2	2.835	0.644–12.480	0.3507			
PFS in L1								
≥12 months	27	17	1					
<12 months	46	41	2.526	1.398–4.564	**0.0021**	1.735	0.834–3.608	0.1405
Number of involved sites								
<3	57	47	1					
≥3	7	7	2.480	1.079–5.699	**0.0324**	1.963	0.801–4.806	0.1400
ECOG L2								
0	30	23	1					
1	25	23	2.280	1.248–4.166		1.507	0.737–3.083	
2 + 3	7	7	6.737	2.655–17.094	**0.0001**	5.188	1.933–13.922	**0.0047**
Treatment L2								
Systemic treatment	59	54	1					
Ablative treatment	14	4	0.038	0.005–0.292	**0.0016**	0.041	0.005–0.323	**0.0024**

involved before DCF at first-line and presented a progression as an isolated metastasis in the lung with persistent complete response in other involved sites. An ablative treatment was then possible, highlighting the interest of DCF in the first-line. The long PFS and OS in this population, as well as a statistically significant prognostic factor in multivariate analysis, are clearly in favour of a curative-intent ablative treatment in selective patients with oligometastatic progression.

However, there is clearly an unmet need in those patients with no indication of ablative treatment in second-line because the complete response rate is limited to 5% with systemic treatment, and only 7% of patients were free of progression at 12 months. Then, several combination protocols are being evaluated in second-line to improve the outcome in this population. Recently, the first results of the CARACAS randomised phase 2 trial have been presented. This study compared avelumab (anti-PD-L1) alone or in combination with cetuximab in second or later lines in advanced patients with SCCA. Thirty patients were randomised in each arm. The ORR was higher (17% versus 10%), and the mPFS was longer (3.88 [95%CI 2.07–6.14] months versus 2.05 [95%CI 1.84–5.52] months) in the combination arm. However, long-term outcomes were similar between arms, suggesting an additive effect more than a synergic one of an anti-EGFR to immunotherapy [18]. Another anti-PDL1 mAb, atezolizumab, was also evaluated in chemorefractory advanced patients with SCCA in phase II 'basket' trial, in association with bevacizumab. Among 19 evaluable patients, 2 patients (11%) presented an objective response, with an mPFS of 4.1 months (95%CI 2.6-NA) and mOS of 11.6 months. Hence, the addition of an anti-VEGF/VEGFR antibody seems to have a limited effect on SCCA [19]. One hypothesis could be the potential antiangiogenic effect of the protein p16 [20], expressed in almost all SCCA [21]. The best combination data come from the association of a tumour therapeutic vaccine and an anti-PD1/L1 immunotherapy. In fact, ISA101, an HPV-16 E6 and E7 peptides targeting vaccine was evaluated in combination with nivolumab. ORR was 33% (8 of 24 evaluable patients, 90%CI 19%–50%), and the duration of response was 10.3 months (95%CI 10.3 - NR) [22]. Besides, UCPVax [23], in combination with atezolizumab, is being evaluated in a phase II VolATIL trial in HPV + squamous cell carcinomas (NCT03946358). In fact, in patients with advanced SCCA, the anti-tumour TH1 immunity against hTERT was better correlated with a good prognosis than that against HPV E6/E7 [6,24]. Hence, the anti-hTERT immunity enhancement may be an interesting goal in this disease to improve the efficacy of immunotherapy. Another target could be the MDSC because of its depletion was also significantly correlated with prognosis [24]. ANG2/TIE2 signalling is present in MDSC, and its inhibition could enhance anti-PD1/L1 activity [25]. BI836880, an anti-VEGF/ANG2 bispecific mAb, in combination with an anti-PD1, is being evaluated in different solid tumours, including SCCA (NCT03697304).

In conclusion, second-line treatment is effective in patients with advanced SCCA. Ablative treatment such as surgery or SBRT is feasible in selected patients and is probably the best treatment option in patients with oligometastatic progression of the disease and should be considered whenever is possible. Among systemic treatments, anti-PD1 immunotherapy is the best evidence-based regimen. However, its benefit is limited to 10–20% of patients. New promising immunotherapy combination trials are ongoing. Meanwhile, chemotherapy is a valid option. Even though there is no standard regimen in second-line, reintroduction of DCF, paclitaxel, FOLFIRI or MMC-fluoropyrimidine can be recommended.

Author contributions

Conceptualization, MS, CB, SK; methodology, AM, DW; validation, AV, DW, CB, SK; investigation and resources, AS, BB, TA, ES, MJ, FE H, N B-H, SP, M-CK, OB, JD, MZ, DS, FG, AP, CdlF, HA, AV, JT, TN, CB, SK; data curation, MS, AM, SK; writing-original draft preparation, MS, AM, SK; writing-review and editing, DW, CB, SK; supervision project administration, MJ, CB, SK.

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Conflict of interest statement

The authors declare no conflict of interest associated with this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.11.019.

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