Pooled analysis of 115 patients from updated data of Epitopes-HPV01 and Epitopes-HPV02 studies in first-line advanced anal squamous cell carcinoma

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Abstract

Aims: The addition of docetaxel to cisplatin and 5-fluorouracil (DCF) has shown promising efficacy in advanced squamous cell carcinoma of the anus (SCCA). Preliminary results of Epitopes-HPV01 study showed a high rate of long-lasting complete response to DCF. The prospective, multicenter, Epitopes-HPV02 trial then confirmed the high efficacy of the modified DCF (mDCF) regimen in terms of complete response rate and long-term survival in metastatic or non-resectable locally advanced recurrent SCCA. Here, we present updated results of the Epitopes-HPV01 and Epitopes-HPV02 studies.

Patients & methods: Epitopes-HPV01 is a prospective study performed by the regional cancer network of Franche-Comté, France. Epitopes-HPV02 is a phase II study supported by two French collaborative oncological groups, performed in 25 centers. Both studies included patients with metastatic, or with unresectable local recurrent SCCA, treated with DCF regimen.

Results: In Epitopes-HPV01, 51 patients were enrolled between September 2012 and January 2019, and 49 patients were included for analysis; while 69 patients were included between September 2014 and December 2016 in Epitopes-HPV02, and 66 patients for analysis. Pooled analysis of 115 patients showed a median progression-free survival of 12.2 months [95% confidence interval (CI) 10.6–16.1] [11.0 months (9.3–16.0) in -HPV02, and 15.6 months (11.2–34.5) in -HPV01, ($p = 0.06$)]. The median overall survival was 39.2 months (26.0–109.1) [36.3 in -HPV02 (25.2–NR), and 61.1 months (21.4–120.0) in -HPV01 ($p = 0.62$)]. Objective response rate was 87.7% (90.9% in -HPV02 and 83.3% in -HPV01) with 40.3% of complete response (45.5% in -HPV02 and 33.3% in -HPV01). No differences were observed between standard DCF ($n = 54$) and mDCF ($n = 58$) in terms of OS ($p = 0.57$) and PFS ($p = 0.99$). 5-years PFS and OS rates were 24.5% and 44.4%, respectively, in the whole population. No treatment-related death was observed.

Conclusion: Updated results of Epitopes-HPV01 and 02 studies, as well as the pooled analysis, confirm mDCF as a standard treatment in patients with advanced SCCA.

Keywords: advanced, anal squamous cell carcinoma, chemotherapy, docetaxel, metastatic

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Introduction

Squamous cell carcinoma of the anus (SCCA) is still considered a rare malignancy, accounting for less than 3% of all gastrointestinal tumors.[1] Nevertheless, the incidence rate has been increasing in recent decades and it is estimated that it will continue to grow in the foreseeable future, due mostly to its association with human papillomavirus (HPV) infection, predominantly genotype HPV-16.[2]

About 15% of patients are diagnosed in metastatic stage,[3] and around 25–40% of patients will experience disease recurrence after curative intent chemoradiotherapy (CRT) for localized disease.[4] In patients with resectable locoregional progression, a salvage abdominoperineal resection is recommended. However, in patients with nonresectable local recurrences or with distant metastases, systemic chemotherapy is the standard approach.

Historically, the prognosis of patients with advanced disease was poor, with no prospectively validated chemotherapy regimen. Most of the referral centers used the combination of cisplatin and 5-fluorouracil (CF), or carboplatin and paclitaxel (CP) based on retrospective analysis.[5–8] The median progression-free survival (PFS) was 5.8–7.0 months, and the 5-years overall survival (OS) rate was less than 20%.[6,7,9]

Docetaxel – a microtubule-stabilizing agent – exerts cytotoxic functions by blocking dividing cells in G2/M phase, leading to apoptosis. Docetaxel-based chemotherapy has also been involved in the modulation of anti-tumor immune responses. Indeed, docetaxel was described to induce calreticulin, a damage-associated molecular patterns related to the immunogenic cell death.[10] Another possible effect might be the depletion of immunosuppressive cells, sustaining the potential restoration of effective tumor immunity.[11] We have previously shown a promising result with the addition of docetaxel to cisplatin and 5-fluorouracil (5FU) (DCF). Four out of eight consecutive patients presented a long-lasting remission in the Epitopes-HPV01 cohort study,[12] setting a clinical rational for a prospective, multicenter, phase II, Epitopes-HPV02 study.[13] Results of this Epitopes-HPV02 trial, including 66 evaluable patients, confirmed the efficacy of this combination, confirming the DCF regimen as a new option in first-line chemotherapy.[14] The primary end-point was surpassed with 47% of patients without progression at 1 year from the first DCF cycle. The objective response rate (ORR) was 89% with 45% complete response, and the OS rate was 83% at 1 year. Moreover, severe toxicities were halved with the modified DCF (mDCF) regimen compared with standard DCF (sDCF).[14] Here, we present updated results of Epitopes-HPV01 and 02 studies, and the pooled analysis of both studies.

Methods

Study design and participants

Epitopes-HPV01 is a cohort study supported by the Besançon University Hospital in France, and performed by the regional cancer network of Franche-Comté. We included patients with histologically confirmed SCCA, with metastatic disease, or with unresectable local recurrence after CRT, for whom a first-line chemotherapy by DCF was validated in the multidisciplinary committee. The primary end-point was to evaluate the immune biomarkers before and after chemotherapy exposure. Secondary end-points were OS (defined as the time between the treatment initiation date and the date of death from any cause), and PFS [defined as the time between the treatment initiation date and the date of first progression (local, regional, metastatic, or secondary cancer)]. This study was reviewed and approved by the independent Est-II French Committee for Protection of Persons on 9 July 2012, and by the French Health Products Safety Agency on 6 July 2012. The results of first eight patients were published previously.[12] Here, we present for the first time the final results of the Epitopes-HPV01 trial.

Epitopes-HPV02 is a phase II study supported by the GERCOR and FFCD collaborative oncological groups, performed in 25 academic hospitals, cancer research centres, and community hospitals in France. We included patients aged 18 years or older with histologically confirmed SCCA, with metastatic disease, or with unresectable local recurrence after CRT; ECOG performance status of 0 or 1; with at least one evaluable lesion according to the response evaluation criteria in solid tumors (RECIST) criteria version 1.1; and with adequate organ function. Human immunodeficiency virus (HIV)-positive patients were allowed unless their CD4 count was less than 400 cells per mm^3. The whole protocol was published elsewhere.[10,14] The primary end-point was the PFS rate at 1 year from the first DCF chemotherapy

cycle. Secondary end-points were PFS, OS, ORR by RECIST criteria v1.1, safety, health-related quality of life (HRQOL), and tissue and immune biomarkers. This study was approved by the independent Est-II French Committee for Protection of Persons on 6 June 2014, and by the French Health Products Safety Agency on 15 July 2014.

Epitopes-HPV01 and Epitopes-HPV02 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 [ClinicalTrials.gov identifier: NCT 01845779] and [ClinicalTrials.gov identifier: NCT02402842].

Statistical analysis

Median and interquartile range (IQR) were provided for the description of continuous variables and frequency, and percentages were provided for the description of categorical variables. Medians and proportions were compared using Wilcoxon Mann–Whitney test and chi-square test (or Fisher's exact test, if appropriate), respectively. The median PFS and OS, and the proportion of patients who met these endpoints at specific timepoints were estimated by the Kaplan–Meier method; 95% confidence intervals (CIs) were determined with the log–log transformation. Median follow up was calculated by the reverse Kaplan–Meier method. Cox proportional-hazard models were used to estimate hazard ratios (HRs) and their 95% CIs for factors associated with PFS. The association of baseline parameters with PFS was evaluated in a prespecified exploratory analysis using the univariate Cox model. As a prespecified exploratory analysis, the association of baseline parameters with PFS was first assessed using univariate Cox analyses, and then parameters with p values of less than 0.05 were entered into a final multivariable Cox regression model. All analyses were performed using SAS (version 9.4) (SAS, Cary, NC, USA).

Results

In Epitopes-HPV01, 51 patients were enrolled between 25 September 2012 and 18 January 2019 and 49 patients were included for analysis. Two patients in Epitopes-HPV01 study did not received DCF and were excluded for analysis; one patient had a recent history of stroke and received carboplatin/paclitaxel regimen without 5FU, and the second patient had been treated previously with cisplatin and 5FU in combination with radiotherapy for a non-resectable locally advanced recurrence, and received only paclitaxel after enrolment (Figure 1). Table 1 shows the patient characteristics at baseline. The database for Epitopes-HPV01 was locked for final analysis on 20 July 2020 with a median follow up of 37.8 months (95% CI 30.6–62.6). An objective response was reached by 40 (83.3%) of 48 evaluable patients, including 16 (33.3%) with a complete response. At data lock, 18 (36.7%) patients were alive and progression free. The median PFS was 15.6 months (11.2–34.5) with 43.3% (29.1–56.8) and 34.5% (22.7–52.4) of patients still alive and without progression at 24 months and 36 months, respectively (Figure 2A). The median OS was 61.1 months (21.4–120.0) with 64.4% (49.0–76.2) and 57.0% (41.5–69.9) still alive at 24 and 36 months, respectively (Figure 2B)

In Epitopes-HPV02, 69 patients were enrolled between 17 September 2014 and 7 December 2016 and 66 patients were included for analysis (Figure 1).[13] We locked the database for Epitopes-HPV02 for updated analysis on 20 July 2020 with a median follow up of 40.1 months (95% CI 39.4–40.7). At data lock, 13 (19.7%) patients were still alive and free of progression. The updated results of the Epitopes-HPV02 study confirm a high response rate (90.9% of ORR with 45.5% of complete response rate) and a median PFS of 11.0 months (95% CI 9.3–16.0) with 24.9% (15.2–35.8) and 20.1% (11.4–30.6) of patients still alive and without progression at 24 and 36 months, respectively (Figure 2A). No statistical differences for OS ($p = 0.57$) and PFS ($p = 0.99$) were observed between sDCF and mDCF. The median OS was 36.3 months (21.4–120.0) with 66.3% (53.5–76.4) and 51.3% (38.3–62.8) of patients still alive at 24 and 36 months from the first DCF cycle, respectively (Figure 2B).

No significant differences were observed between Epitopes-HPV01 and -HPV02 populations in terms of PFS ($p = 0.06$) and OS ($p = 0.62$) (Figure 2A and B).

The pooled analysis of 115 patients described in Table 1. The median PFS was 12.2 months (95% CI 10.6–16.1) (Figure 2C), and the median OS was 39.2 months (95% CI 26.0–109.1) (Figure 2D), and confirmed a similar benefit between sDCF and mDCF. The median PFS was 12.2 months with sDCF (95% CI 9.3–22.4) and

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Table 1. Baseline patient characteristics at inclusion.

	Overall population *n* = 115	HPV01 *n* = 49	HPV02 *n* = 66	*p* value
Gender				
Female	87 (75.7%)	33 (67.3%)	54 (81.8%)	0.0738
Male	28 (24.3%)	16 (32.7%)	12 (18.2%)	
Age				
Mean (SD)	60.2 (9.3)	61.0 (9.8)	59.5 (9.0)	0.9142
Median (min–max)	60.0 (38.6;84.0)	59.4 (38.7;84.0)	60.0 (38.6;78.4)	
Q1–Q3	53.6–66.7	54.4–68.7	53.6–65.8	
ECOG-PS				
0	72 (62.6%)	31 (63.3%)	41 (62.1%)	0.0072
1	37 (32.2%)	12 (24.5%)	25 (37.9%)	
2	6 (5.2%)	6 (12.2%)	0 (0.0%)	
HIV status				
Negative	109 (94.8%)	45 (91.8%)	64 (97.0%)	0.3991
Positive	6 (5.2%)	4 (8.2%)	2 (3.0%)	
Chemoradiotherapy				
Missing	5	5	0	0.5493
No	40 (34.0%)	19 (37.5%)	21 (31.8%)	
Yes	70 (66.0%)	25 (62.5%)	45 (68.2%)	
Concomitant chemotherapy	(*n* = 70)	(*n* = 25)	(*n* = 45)	
Missing	3	2	1	0.7706
CDDP + 5FU	7 (10.5%)	1 (4.3%)	6 (13.6%)	
Capecitabine	1 (1.5%)	0 (0.0%)	1 (2.3%)	
MMC	1 (1.5%)	0 (0.0%)	1 (2.3%)	
MMC + CDDP + 5FU	1 (1.5%)	0 (0.0%)	1 (2.3%)	
MMC + Cape/5FU	56 (83.6%)	22 (95.7%)	34 (77.3%)	
MMC + Cape + CDDP + 5FU	1 (1.5%)	0 (0.0%)	1 (2.3%)	
Surgery				
Missing	5	5	0	0.5887
No	89 (80.9%)	35 (79.5%)	54 (81.8%)	
Yes	21 (19.1%)	9 (20.5%)	12 (18.2%)	

(Continued)

Table 1. (Continued)

	Overall population *n* = 115	HPV01 *n* = 49	HPV02 *n* = 66	*p* value
Stage				
Locally advanced	25 (21.7%)	19 (38.8%)	6 (9.1%)	0.0002
Synchronous metastases	29 (25.2%)	13 (26.5%)	16 (24.2%)	
Metachronous metastases	61 (53.1%)	17 (34.7%)	44 (66.7%)	
Number of sites involved				
Mean (SD)	2.3 (1.3)	2.0 (1.3)	2.4 (1.3)	0.0600
Median (min–max)	2.0 (1.0;8.0)	2.0 (1.0;8.0)	2.0 (1.0;6.0)	
Q1–Q3	1.0–3.0	1.0–2.0	1.0–3.0	
Type of treatment				
sDCF	54 (47.0%)	18 (36.7%)	36 (54.6%)	0.0285
mDCF	58 (50.4%)	28 (57.2%)	30 (45.4%)	
DCarboF	3 (2.6%)	3 (6.1%)	0 (0.0%)	

5FU, 5-fluorouracil; Cape, capecitabine; CDDP, cisplatin; DCarboF, docetaxel 40 mg/m^2, carboplatin AUC 4, 5FU 2400 mg/m^2, every 2 weeks; ECOG-PS, Eastern Cooperative Oncology Group performance status; mDCF, modified DCF; MMC, mitomycin; SD, standard deviation; sDCF, standard DCF.

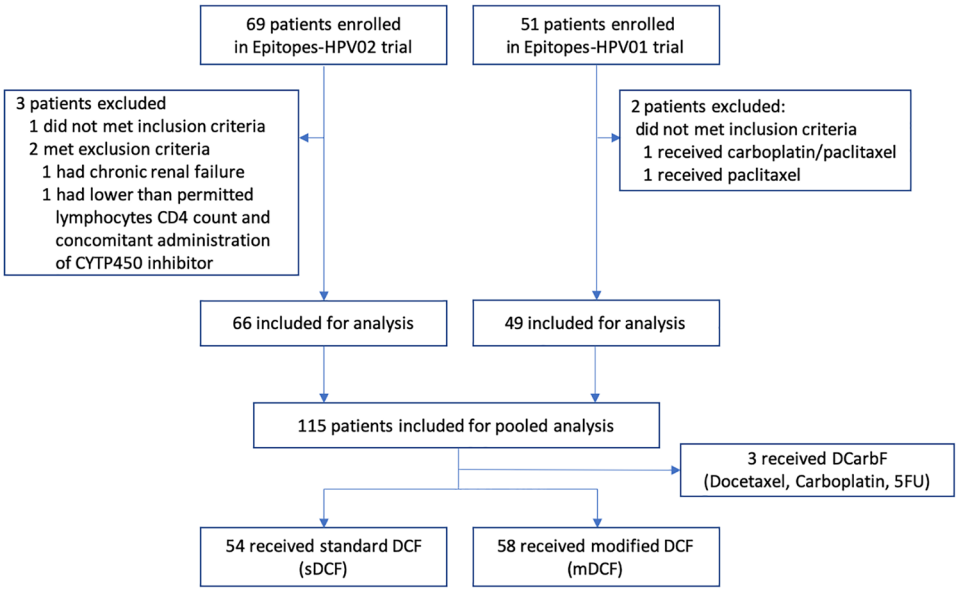

Figure 1. Flowchart of the pooled population of Epitopes-HPV01 and Epitopes-HPV02 trials.
DCF, docetaxel added to cisplatin and 5FU; 5FU, 5-fluorouracil; mDCF, modified DCF; sDCF, standard DCF.

14.5 months with mDCF (95% CI 10.1–18.9), $p = 0.99$ (Figure 2E). The PFS rate in the whole population was 50.7% at 1 year, 32.5% at 2 years, and 26.0% at 3 years, with no disease progression after 3 years at the time of analysis. The median OS was 36.3 months with sDCF (95% CI 24.8–120.0) and 50.2 months with mDCF (95% CI 26.0–50.2), $p = 0.57$. The OS rates at 24 and

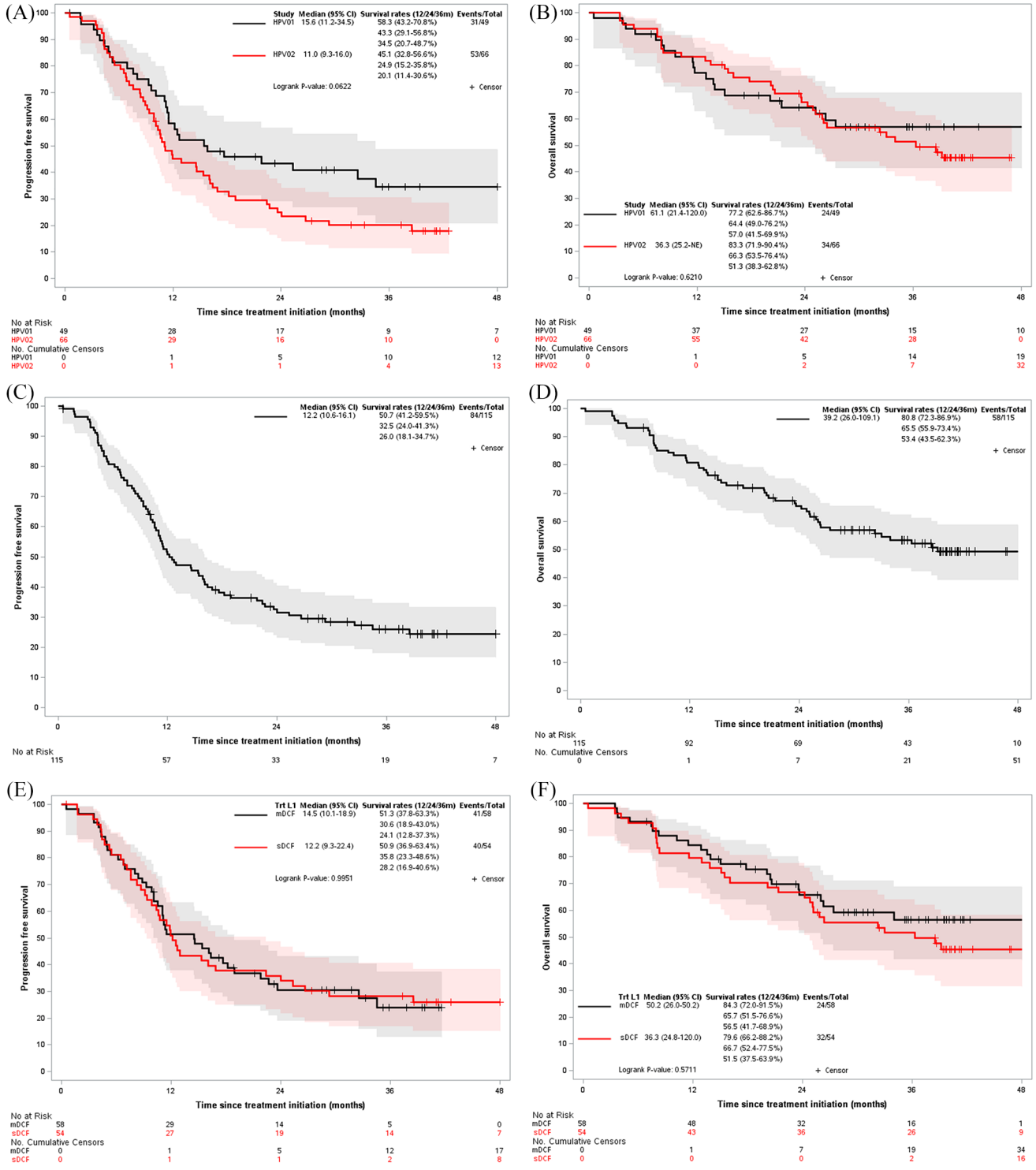

Figure 2. (A) PFS of Epitopes-HPV01 and Epitopes-HPV02 populations; (B) OS of Epitopes-HPV01 and Epitopes-HPV02 populations; (C) PFS of the pooled population; (D) OS of the pooled population; (E) PFS of sDCF and mDCF populations; (F) OS of sDCF and mDCF populations.

DCF, docetaxel added to cisplatin and 5FU; CI, confidence interval; 5FU, 5-fluorouracil; mDCF, modified DCF; OS, overall survival; PFS, progression-free survival; sDCF, standard DCF.

36 months were 66.7% (52.4–77.5) and 51.5% (37.5–63.9) with sDCF, and 65.7% (51.5–76.6) and 56.5% (41.7–68.9) with mDCF (Figure 2F). No treatment-related death was observed in the whole population. Estimated 5-year PFS and OS rates were 24.5% and 44.4%, respectively. Three variables were identified as worst prognostic factors significantly associated with the PFS in univariate and multivariate analysis: age (<65 years), number of involved sites (⩾3), and ECOG-PS of 2 (Table 2).

Regarding the *post hoc* efficacy analysis of DCF in subgroups of interest, seven patients with immunosuppressive condition were enrolled in the trial. A patient with history of heart graft with synchronous disease with right iliac and inguinal lymph node involvement and multiple lung metastases, presented a complete response after mDCF. A regional recurrence with left iliac and inguinal lymph nodes enlargement was diagnosed after 22.1 months of PFS, and a new radiological complete response was observed after the rechallenge with taxane. Six HIV positive patients were included; all six patients were male, two (33.3%) had an ECOG-PS of 2, and two (33.3%) had more than three sites involved. Two complete responses, two partial responses, and two stable diseases were observed as best responses. The median PFS was 7.7 months (3.5–NA). Two complete responders were still disease-free at the time of analysis with a PFS of 41 months and 27 months.

In the subgroup of chemotherapy-naive patients with synchronous metastases, none of the 29 (25.2%) patients presented a disease-progression at first evaluation during DCF administration. The ORR was reached in 26 (89.7%) patients, including 16 (55.2%) patients with a complete response. The median PFS was 16.4 (10.7–32.5) months, and the median OS was not reached.

Of the 115 patients, 58 (50.4%) (30 patients in Epitopes-HPV02 and 28 patients in Epitopes-HPV01) underwent complementary treatment after DCF: 29 patients (17 patients in Epitopes-HPV02 and 12 patients in Epitopes-HPV01) had surgery for their metastatic disease, 18 patients (6 patients in Epitopes-HPV02 and 12 patients in Epitopes-HPV01) received radiotherapy (with or without chemotherapy), and 9 patients (5 patients in Epitopes-HPV02 and 4 patients in Epitopes-HPV01) were treated with a combination of surgery and radiotherapy. Pathological complete response was reported in 19 (65.5%) of the 29 patients who underwent surgery for their metastatic disease. The mPFS was 24.0 months (15.4–38.5), and the mOS was 109.1 months (36.3–NR).

Meanwhile, among 57 (49.6%) of 115 patients who did not receive complementary treatment, The ORR was observed in 44 of 56 evaluable patients (78.6%, 65.6–88.4), including 16 (28.6%) complete responses. The median PFS was 8.3 months (5.4–10.7) with a median OS of 20.2 months (11.7–61.1).

Discussion

Early outstanding results from the Epitopes-HPV01 study confirmed the rational for the confirmatory prospective multicenter Epitopes-HPV02 phase II study, and validated the mDCF regimen as a new standard in advanced SCCA. The final results of Epitopes-HPV01, as well as the pooled analysis of both studies, confirm the interest of mDCF in this situation with long-lasting responses.

The OS Kaplan–Meier curves of Epitopes-HPV02 and Epitopes-HPV01 populations are comparable. The median OS was 39.2 months, with more than half of patients still alive at 36 months in both populations (51.3% and 57.0% in -HPV02 and -HPV01 populations, respectively) with no disease progression after this period and almost no disease-related deaths thereafter, resulting in an expected OS rate at 5 year of 44.4% (33.3–51.9). These results are highly encouraging compared with published data with less than 20% of patients alive at 5 years.[6,7,9] The median PFS was 12.2 months, and was non-significantly higher in the Epitopes-HPV01 population (11 and 15.6 months in -HPV02 and -HPV01 populations, respectively) despite more patients with poorer performance status and comorbidities than Epitopes-HPV02 population.

Then, these results compare favorably with the recently published InterAACT randomized phase II trial with a "pick the winner" trial design. The primary endpoint was ORR of carboplatin plus paclitaxel (CP) and cisplatin plus 5FU (CF). Secondary endpoints were grade 3/4 adverse events and HRQoL, assessed in a hierarchic

Table 2. PFS: univariate/multivariate analysis.

Factor	Univariate analysis					Multivariate analysis ($n = 115$)		
	No	No event	HR	95% CI	*p*	HR	95% CI	*p*
Years								
<65	78	65	1					
⩾65	37	19	0.482	0.289–0.806	**0.0054**	0.552	0.325–0.938	**0.0281**
Treatment								
sDCF	54	40	1					
mDCF	58	41	1.000	0.644–1.552	0.9984			
Advanced disease diagnosis								
Metachronous metastases	61	48	1					
Synchronous metastases	29	20	0.702	0.416–1.184				
Locally advanced disease	25	16	0.646	0.366–1.139	0.2026			
Number of involved sites								
<3	79	50	1					
⩾3	36	34	2.521	1.618–3.927	<**0.0001**	2.110	1.322–3.366	**0.0017**
Neutrophils to Lymphocytes ratio								
⩽3.8	30	24	1					
>3.8	32	25	1.047	0.597–1.835	0.8733			
Hemoglobin (g/dl)								
<10	7	5	1					
⩾10	55	44	0.897	0.355–2.269	0.8191			
Lymphocytes (/mm^3)								
<1000	26	22	1					
⩾1000	36	27	0.720	0.410–1.267	0.2549			
Platelets (/mm^3)								
<15000	5	4	1					
⩾15000	57	45	0.796	0.285–2.223	0.6628			
ECOG-PS								
0	72	53	1					
1	37	26	1.191	0.744–1.905		1.072	0.665–1.729	
2	6	5	6.481	2.471–16.999	**0.0007**	6.112	2.281–16.379	**0.0014**

CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mDCF; modified DCF; PFS, progression-free survival; sDCF, standard DCF.

model to compare these two chemotherapy regimens. Therefore, if ORR was not different, grade 3/4 adverse events would be assessed. A total of 91 patients were enrolled and 74 patients (39 in CP arm and 35 in CF arm) were evaluable for final efficacy analysis. Unfortunately, InterAACT trial failed to demonstrate its primary endpoint, with an ORR of 59% with CP, and 57% with CF. The complete response rate was slightly in favor of CF (17.1% *versus* 12.8%).[15] The median PFS was longer in the CP arm compared with the CF arm (8.1 *versus* 5.7 months) although not statistically significant ($p = 0.375$), and there was a trend for improved median OS after adjusting for stratification factors (HR 1.78, 95%CI 0.98–3.23; p 0.059). Grade 3/4 toxicity rates were also similar between the two arms (71% with CP and 76% with CF).

Hence, mDCF has better efficacy (complete response rate, 40.3% *versus* 12.8%) and tolerance (grade 3/4 toxicity rate, 53% *versus* 71%) profile than CP. However, this is not a head-to-head comparison and should be interpreted with caution. Interestingly, the conversion from positive to negative HPV ctDNA by liquid biopsy, which is highly predictive of better prognosis, was achieved in 17.9% (5/28) of patients with doublet chemotherapy in InterAACT trial compared with 61.1% (22/36) of patients with DCF in the Epitopes-HPV02 trial (Table 3).

Besides, DCF was also effective in the subgroup of immunosuppressive patients, with long-lasting complete response in 42.9% of them. Based on these data, we believe that mDCF should be a novel standard option in patients with advanced SCCA. Carboplatin plus paclitaxel may be reserved for those with a contraindication to 5FU or cisplatin (e.g., impaired renal function, active cardiovascular disease).

In this pooled analysis, age (<65 years), number of involved sites (≥3), and ECOG-PS of 2 were associated significantly with worse prognosis, confirming previous published Epitopes-HPV02 data.[14] Early onset of tumor at younger age may be related to tumor aggressiveness, but this should be confirmed in a larger cohort in advanced disease.

One-half of the patients received a multidisciplinary approach after DCF, which is comparable with retrospective data of Eng and colleagues, where 43% (33 of 77) of patients underwent complementary treatment after first-line chemotherapy. Median PFS and OS were longer compared with those patients who received palliative systemic chemotherapy in our trial (median PFS, 24.0 months *versus* 8.3 months; median OS, 109.1 months *versus* 20.2) in line with Eng and colleagues' data (median PFS, 16 months *versus* 5 months; median OS, 53 months *versus* 17 months). These results confirm the conclusion of the retrospective analysis delivered by Eng and colleagues suggesting that the treatment of metastatic SCCA should include a multimodal strategy whenever that is possible.[6]

Our study has several limitations. No randomization was done to compare DCF with other chemotherapy regimens, or to compare sDCF with mDCF. However, there was no prospectively validated regimen before DCF to be considered as a control arm, and our scientific committee had decided not to compare with other chemotherapy regimens with known modest activity.[13] Moreover, the results of Epitopes-HPV01 and Epitopes-HPV02 are similar, with no statistical differences between both regimens, and confirm the best results ever seen in this situation in the largest prospective cohort in first-line advanced SCCA.

Besides, the immunomonitoring analysis of Epitopes-HPV01 and Epitopes-HPV02 studies demonstrated that, (i) myeloid-derived suppressor cells (MDSC) has a major prognostic role in advanced SCCA patients as a first-line treatment, (ii) DCF was capable of depleting MDSC, iii) and of improving anti-tumor immune activity.[16] Hence, considering these abilities and the good tolerance profile of mDCF, this regimen has been established as a good candidate as a chemotherapy backbone for combination with immune checkpoint inhibitors.[14] In fact, checkpoint inhibitors such as programmed cell death protein-1 and programmed cell death-ligand 1 (PD1/PD-L1) antibodies are promising new treatments for advanced SCCA. Nivolumab and pembrolizumab have demonstrated their activity in chemotherapy refractory patients in a phase II and Ib/II trials, respectively. Objective responses were observed in 11–24% of patients, with estimated 12-month PFS and OS rates 15–18% and 47–48%, respectively.[17–19] To date, a

Table 3. Results from prospective InterAACT and Epitopes-HPV trials in SCCA.

Total patients enrolled	Rao *et al.*[15] *n* = 91		Kim *et al.*[12] *n* = 120	
Chemotherapy regimen (evaluable patients)	**CF (*n* = 35)**	**CP (*n* = 39)**	**sDCF (*n* = 54)**	**mDCF (*n* = 58)**
Objective response rate (%)	57.1	59	92.5	86.2
Complete response rate (%)	17.1	12.8	49.1	34.5
Median PFS (months)	5.7	8.1	12.2	14.5
PFS rate at 1 year (%)	~15	~15	50.9	51.3
PFS rate at 3 years (%)	~4	~11	28.2	24.1
Median OS (months)	12.3	20.0	36.3	50.2
OS rate at 3 years (%)	~25	~25	51.5	56.5
Grade III/IV toxicity rate (%)	76	71	83	53
HPV ctDNA clearance (%)	17.9		61.1	

CF, cisplatin plus 5FU; CP, carboplatin plus paclitaxel; DCF, docetaxel added to cisplatin and 5FU; 5FU, 5-fluorouracil; HPV, human papilloma virus; mDCF, modified DCF; OS, overall survival; PFS, progression-free survival; SCCA, squamous cell carcinoma of the anus; sDCF, standard DCF.

randomized phase II SCARCE trial is already ongoing to evaluate the interest of mDCF regimen in association with an anti-PD-L1 antibody.[20]

In summary, DCF is so far the best evidence-based chemotherapy regimen in advanced SCCA. Updated results of Epitopes-HPV01 and 02 study, as well as its pooled analysis, confirm mDCF as the regimen of choice in patients with advanced SCCA.

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Author's note

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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