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ORIGINAL REPORT

Cetuximab Plus Chemoradiotherapy for HIV-Associated Anal Carcinoma: A Phase II AIDS Malignancy Consortium Trial

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ABSTRACT

Purpose

Squamous cell carcinoma of the anal canal (SCCAC) is characterized by high locoregional failure (LRF) rates after definitive chemoradiation (CRT), associated with anogenital human papilloma virus, and often appears in HIV infection. Because cetuximab enhances the effect of radiation therapy in human papilloma virus–associated oropharyngeal SCC, we hypothesized that adding cetuximab to CRT would reduce LRF in SCCAC.

Methods

Forty-five patients with stage I to III SCCAC and HIV infection received CRT: 45 to 54 Gy radiation therapy to the primary tumor and regional lymph nodes plus eight once-weekly doses of concurrent cetuximab and two cycles of cisplatin and fluorouracil. The study was designed to detect at least a 50% reduction in 3-year LRF rate (one-sided α, 0.10; power, 90%), assuming a 35% LRF rate from historical data.

Results

The 3-year LRF rate was 42% (95% CI, 28% to 56%; one-sided $P = .9$) by binomial proportional estimate using the prespecified end point (LRF or alive without LRF and followed < 3 years), and 20% (95% CI, 10% to 37%) by Kaplan-Meier estimate in post hoc analysis using definitions and methods consistent with historical data. Three-year rates by Kaplan-Meier estimate were 72% (95% CI, 56% to 84%) for progression-free survival and 79% (95% CI, 63% to 89%) for overall survival. Grade 4 toxicity occurred in 26%, and 4% had treatment-associated deaths.

Conclusion

HIV-associated SCCAC is potentially curable with definitive CRT. Although addition of cetuximab may result in less LRF, the 20% recurrence and 26% grade 4 toxicity rates indicate the continued need for more-effective and less-toxic therapies.

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INTRODUCTION

There is an approximately 60-fold increase in the risk of squamous cell carcinoma of the anal canal (SCCAC) in individuals with HIV infection compared with the general population.[1] Sphincter-sparing definitive chemoradiation (CRT), including concurrent radiation plus fluorouracil (FU) and mitomycin-C or cisplatin, is potentially curative but is associated with high rates of dermatitis, GI toxicity, myelosuppression, and other toxicities.[2-6] Locoregional failure (LRF) may occur in approximately 30% and is associated with significant morbidity, distant recurrence, and mortality.[5] New approaches are needed to develop more effective therapies that result in improved local and systemic disease control.

SCCAC is commonly associated with human papillomavirus (HPV) infection.[7-9] The HPV-associated E5 protein amplifies the mitogenic signals mediated by the epidermal growth factor receptor (EGFR),[10] which is broadly expressed in epithelial cancers, including squamous cell carcinoma of the anogenital tract and oropharynx.[11,12] Because the anti-EGFR antibody cetuximab prolongs survival when used in combination with radiation therapy (RT) in patients with locally advanced SCC of the oropharynx,[13,14] another cancer that is typically associated with HPV infection,[15-17] we hypothesized that the addition of cetuximab to CRT

ASSOCIATED CONTENT

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would improve locoregional control in patients with SCCAC. We therefore designed two trials that were concurrently conducted to determine the effectiveness of cetuximab plus CRT in patients with HIV infection (AMC045) and without HIV infection (E3205). We herein report the results of the AMC045, which is the first prospectively conducted clinical trial to our knowledge in patients with SCCAC and HIV infection, and also report the results of E3205 is a separate accompanying report.[18] Both trials were single-arm phase II trials evaluating cetuximab plus the same CRT regimen of cisplatin, FU, and external beam RT.

METHODS

Eligibility Criteria

Patients were required to have histologically confirmed anal canal or perianal (anal margin) squamous cell carcinoma (or tumors of nonkeratinizing histology, such as basaloid, transitional cell, or cloacogenic histology) and stage I (excluding well-differentiated stage I anal margin cancer), II (T2N0, T3N0), IIIA, or IIIB disease. Other requirements include age 18 years or older; Eastern Cooperative Oncology Group performance status 0 to 2; no prior potentially curative surgery, RT, or chemotherapy for this malignancy; no prior pelvic radiotherapy; no other concurrent malignancies except for nonmelanomatous skin cancer; and adequate organ function. Further details are described elsewhere in the E3205 report.[18]

Study Objectives

The primary objective was to estimate the LRF rate at 3 years. Secondary objectives included response rate (complete and partial), progression-free survival (PFS), colostomy-free survival (CFS), overall survival (OS), quality of life (QOL), and overall toxicity. Correlative science objectives included characterizing the effect of CRT on HIV viral load, CD4 lymphocyte count, and opportunistic infection; incidence of anogenital HPV infection; and association between LRF and EGFR, phosphatidylinositol 3-kinase, and Akt gene expression (to be reported separately).

Study End Point Definitions

LRF was defined as progression/relapse of disease in the anal canal and/or regional organs and/or regional lymph nodes. PFS was defined as time from registration to progression, relapse, or death from any cause. CFS was defined as date of registration until date that colostomy was required or death from any cause. OS was defined as time from registration until death from any cause. Response was classified according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.0) and required radiologic confirmation at least 4 weeks after initial objective response.[19] Tumor assessments were made by physical examination and computerized tomography of the abdomen and pelvis at baseline, within 4 weeks of the completion of protocol treatment, every 6 months if patient was 1 to 4 years from registration, and annually thereafter. National Cancer Institute Common Adverse Events Criteria, version 3.0, was used to grade toxicity. QOL was also evaluated using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and CR38 Colorectal Cancer Module at baseline; at weeks 5 (after cycle 1), 12 (after completion of therapy), and 26 (ie, month 6); and again at months 12, 24, and 36 after beginning therapy. Formalin-fixed paraffin-embedded tumor biopsy specimens were assessed for HPV DNA using previously described methods.[20]

Statistical Considerations

The study was designed to detect at least a 50% reduction in 3-year LRF rate (one-sided α, 0.10; power, 90%), the primary study end point, and assumed a 3-year LRF rate of approximately 35% on the basis of historical data, as described in an accompanying report.[18] For the primary study end point definition and analysis plan, patients were classified into two groups as a binary variable, including failure (defined as LRF, or follow-up $<$ 3 years without LRF) or no failure (alive without an LRF event and followed for at least 3 years), and evaluated by binomial proportion. PFS, CFS, and OS were estimated using the Kaplan-Meier method, with 95% CIs calculated using Greenwood's formula. Event rates at 3 years were evaluated, because prior studies indicated that most events related to SCCAC or its treatment occurred within 3 years.[2-4 5,6,21] The cutoff date for the data analysis was September 10, 2015.

Informed Consent and Regulatory Approval

The study was reviewed and approved by the Cancer Evaluation Therapy Program of the National Cancer Institute (AIDS Malignancy Consortium trial 045) and by the institutional review board at each participating institution (ClinicalTrials.gov identifier NCT00324415). All patients provided written informed consent.

Cetuximab, Chemotherapy, and RT

The treatment schema is shown in Figure 1. Criteria for treatment modifications are summarized. RT compliance was monitored by the Quality Assurance Review Center (Lincoln, RI). Concurrent RT consisted of 1.8 Gy once per day 5 days per week for a minimum of 5 weeks and was based on prechemotherapy tumor volumes (minimum, 45.0 Gy; maximum, 54.0 Gy). Intensity-modulated RT was used at the discretion of the treating physician according to the guidelines outlined in this protocol. The total dose of irradiation to the primary tumor was 45 Gy for T1 or T2 lesions or between 50.4 Gy and 54.0 Gy for T3 or T4 lesions or T2 disease with clinical evidence of residual disease after 45 Gy. The total dose to the inguinal nodes was 30.6 Gy for N0 or N1 disease or 50.4 to 54.0 Gy for N2 or N3 disease, for clinical evidence of residual disease after 45 Gy, or for any lymph node $>$ 3 cm (see Data Supplement for additional specific details).

RESULTS

Patient Characteristics

A total of 45 patients were accrued between March 21, 2007 and April 4, 2011 at eight sites. The characteristics of the study population are outlined in Table 1.[22] All patients had squamous cell histology. Poor risk features included male sex in 91%, T3 lesion in

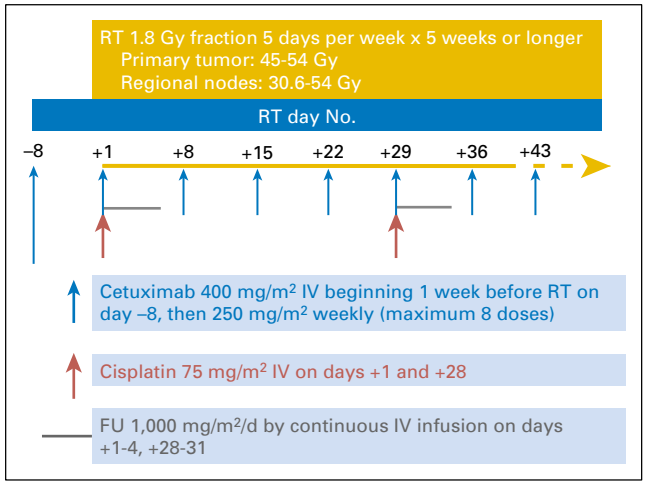

Fig 1. Treatment schema. FU, fluorouracil; IV, intravenous; RT, radiation therapy.

27%, and positive regional nodes in 35%. Twenty-five of 30 tumors evaluated (83%) were HPV positive.

Treatment Administration and Overall Safety

Two patients withdrew after enrollment and did not receive RT but are nevertheless including in the efficacy analysis. Information regarding chemotherapy dose intensity and RT administration is summarized in Table 2. Treatment was completed as per protocol in 37 patients (82%), whereas the remaining eight patients (18%) withdrew because of an adverse event in four patients (9%) and for other reasons in four patients (9%). Dose modifications were required for cisplatin in four patients (9%), FU in four patients (9%), and cetuximab in nine patients (20%); for cetuximab, this included dose delay in five patients, reduction in two patients, and discontinuation or unknown in one patient each. RT was delivered per protocol in 68%, with minor deviations in 16% and major deviations in 16%. For the major deviations, in six patients the mesorectum was not fully contoured; in three of these patients, lymph nodes were not fully contoured as well. The remaining deviations were assigned because of difficulty in meeting normal tissue volume constraints related to small bowel and femoral heads.

Grade 1 to 4 adverse events are summarized in Table 3. There were also two treatment-associated deaths (grade 5 events) due to GI bleeding in one patient and wound infection leading to sepsis in another patient, both occurring within 1 month of beginning therapy. The most common grade 3 to 4 adverse events occurring in 10% or more of patients included diarrhea in 31% (31% grade 3, 0% grade 4), neutropenia in 29% (20% grade 3, 9% grade 4), dehydration in 24% (22% grade 3, 2% grade 4), infection in 23% (16% grade 3, 7% grade 4), hypokalemia in 20% (13% grade 3, 7% grade 4), thrombocytopenia in 18% (9% grade 3, 9% grade 4), anemia in 11% (7% grade 3, 4% grade 4), and nausea in 11% (11% grade 3, 0% grade 4). Four patients (8%) had opportunistic infections, and five patients (11%) had delayed grade 1 or 2 toxicities related to radiation. Opportunistic infections included oral thrush in two patients, oral thrush and pneumonia in one patient, and cerebral toxoplasmosis in one patient. Eleven patients (24%) received granulocyte colony stimulating factor for treatment or prevention of neutropenia at the discretion of the treating physician.

Primary End Point: LRF at 3 Years

At 3 years, seven patients had an LRF event (16%), four patients (9%) died of causes other than anal cancer without an LRF event, and 34 surviving patients (75%) did not have an LRF event; of the 34 surviving patients without an LRF event, 22 patients

Table 1. Patient Characteristics

Characteristic	No.	%
No. of patients	45	
Median age (range), years	47 (33-65)	
HIV-associated factors		
Median (range) CD4 count at study entry	401/μL (91-2,883)	
Median (range) HIV load at study entry (n = 43)	68 copies/mL (20-70,560)	
CDC risk group*		
Homosexual/bisexual contact	38	80
Heterosexual contact	6	13
Intravenous drug use	2	4
Transfusion	2	4
ART at study entry	41	91
Demographics		
Sex		
Male	41	91
Female	4	9
Ethnicity (n = 44)		
Hispanic	7	16
Non-Hispanic	37	84
Race		
White	28	62
Black	13	29
Other	4	9
ECOG PS (n = 44)		
0	34	77
1	10	23
Disease characteristics		
Disease stage[22]		
I	11	24
II	19	42
IIIA	3	7
IIIB	12	27
Clinical T stage		
1	13	29
2	20	44
3	12	27
Clinical N stage (n = 43)		
0	28	65
1	3	7
2	8	19
3	4	9
HPV-positive (n = 30)	25	83
Tumor location		
Above dentate line	2	4
Anal canal	26	58
Perianal skin	3	7
Anal canal and perianal skin	14	31
Anal margin	0	0

Abbreviations: ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus.
*Some patients had more than one CDC risk factor for HIV infection.

Table 2. Treatment Administered

Treatment	Cetuximab Plus Concurrent Chemoradiotherapy (N = 43)
Cisplatin, % intended dose intensity	
Mean (SD)	106 (34)
Median (range)	100 (50-205)
FU, % intended dose intensity	
Mean (SD)	93 (40)
Median (range)	100 (13-206)
IMRT, No. (%)	28 (65)
Total radiation dose, Gy	
Mean (SD)	45.5 (5.2)
Median (range)	45.0 (39.6-60.5)
Time to completion of radiation, days	
Mean (SD)	40.6 (10.6)
Median (range)	37 (16-71)
Radiation dose modification, No. (%)	
Not completed due to toxicity	3 (7)
Treatment interruption	19 (44)
Treatment interruption > 7 days	6 (14)
Median No. days interruption (range)	5 (1-21)

Abbreviations: FU, fluorouracil; IMRT, intensity-modulated radiation therapy; SD, standard deviation.

Table 3. Grade 1 to 4 Adverse Events

Type of Adverse Event	Worst Grade (%)		
	1 or 2	3	4
Hematologic			
Neutropenia	24	20	9
Thrombocytopenia	33	9	9
Anemia	53	7	4
Febrile neutropenia	—	9	—
Nonhematologic			
Constitutional			
Anorexia	29	2	—
Dehydration	20	22	2
Fatigue	38	4	—
Weight loss	31	—	—
GI			
Nausea	38	11	—
Vomiting	18	4	—
Diarrhea (without prior colostomy)	78	31	—
Rectum, hemorrhage	4	—	—
Stomatitis (by examination, oral cavity)	53	7	—
Genitourinary	—	2	—
Elevated creatinine	—	2	—
Other genitourinary	11	—	—
Infection	16	16	7
Metabolic			
Acidosis	2	—	2
Hypoalbuminemia	11	—	—
Hypocalcemia	20	—	—
Hyperglycemia	2	—	—
Hypomagnesemia	11	—	—
Hypokalemia	27	13	7
Hyponatremia	20	4	—
Pulmonary (including infiltrates)	16	7	—
Skin			
Rash	22	2	—
Ulceration	11	—	—
Vascular (thrombosis)	—	2	—
Worst grade toxicity*	13	46	26

*Percentage of patients who had grade 2, 3, or 4 toxicity as worst grade reported.

(49%) were followed for ≥ 3 years, and 12 patients (27%) were followed for < 3 years. The 3-year LRF rate was 42% (95% CI, 28% to 56%; P under $H_0 = .9$) by binomial proportional estimate using the prespecified end point (LRF or alive without LRF and followed < 3 years). The 3-year LRF rate was 20% (95% CI, 10% to 37%) by Kaplan-Meier estimate in post hoc analysis using definitions and methods consistent with historical data. The LFR was substantially higher using the former definition, because patients followed for < 3 years were considered failures (12 of 19 LRF events). LRF rates were not significantly different in the 68% of patients who had no RT deviations and the 32% who did have deviations and was not associated with LRF in multivariate logistic regression analysis that also included HIV viral load at baseline, absolute CD4 lymphocyte count at baseline, current antiretroviral treatment (yes/no), stage (I *v* II *v* IIIA-B), sex, T > 5 cm (yes/no), positive nodes (yes/no).

Secondary End Points: Objective Response and Other Clinical Outcomes

The complete response rate was 62% (95% CI, 47% to 76%) and the overall response rate was 67% (95% CI, 51% to 80%). Complete and overall response rates were not significantly associated with HIV viral load at baseline, absolute CD4 count at baseline, or disease stage. Kaplan-Meier estimates for PFS, CFS, and OS, are shown in Figures 2A to 2C. At the time of the analysis, with a median follow-up time of 56 months (range, 0 to 68 months) in surviving patients, 10 patients died (including six from anal cancer, four from other causes), 13 patients had a PFS event (including nine with disease progression [seven locoregional, two distant] and four with death from other causes), and four patients had a colostomy. Three-year rates were 72% (95% CI, 56% to 84%) for PFS, 77% (95% CI, 60% to 87%) for CFS, and 79% (95% CI, 63% to 89%) for OS. For the four patients who died of causes other than anal cancer, two deaths occurred within 1 month of beginning therapy, as previously described, and two deaths occurred after completing therapy (acute myelogenous leukemia at 25 months and cardiac failure at 25 months).

QOL

Using the Quality of Life Questionnaire C30 (Fig 3; Appendix Table A1, online only), there were significant differences between baseline and subsequent time points in global health status (week 5), physical functioning (week 12), role functioning (week 12), and social functioning (week 12), reflecting an adverse but transient impact of treatment on the QOL. There were no significant changes noted in cognitive functioning. There was a significant difference in emotional functioning between baseline and month 24. With regard to symptom scales, there were significant differences between baseline and week 5 in fatigue, anorexia, and diarrhea (and also at months 6 and 24 for diarrhea). There were also differences in pain (months 6, 12, and 24), insomnia (months 12 and 24), constipation (month 12), and financial difficulties (months 6 and 12) compared with before therapy. There were no differences in nausea and vomiting or dyspnea. Using the QLQ-CR38 (Appendix Table A2, online only), there were also significant differences compared with baseline body image and sexual enjoyment (week 5), sexual functioning (month 12), and future perspective (week 2, month 12). With regard to symptom scales, there were significant differences compared with baseline with regard to micturition problems, chemotherapy adverse effects, GI symptoms (week 5), male sexual problems (week 5 and months 12, 24, and 36), and defecation problems (months 12 and 36),

Changes in CD4 Lymphocyte Count and HIV Viral Load

Absolute CD4 counts decreased significantly from baseline (401/μL, range, 91 to 1,283) to the end of treatment (median, 153/μL; range, 27 to 662; median change, −218/μL; $P < .001$), but recovered after completion of therapy (median, 278/μL; range, 46 to 941; median change, +102/μL; $P < .001$). There were no differences in HIV viral load before and after therapy, with more than one-half having undetectable viral load. Four patients (8%; 95% CI, 3% to 21%) developed an opportunistic infection.

DISCUSSION

It is estimated that there were approximately 37 million people worldwide living with HIV/AIDS at the end of 2014,[23] including approximately 1.2 million HIV-infected individuals in the United

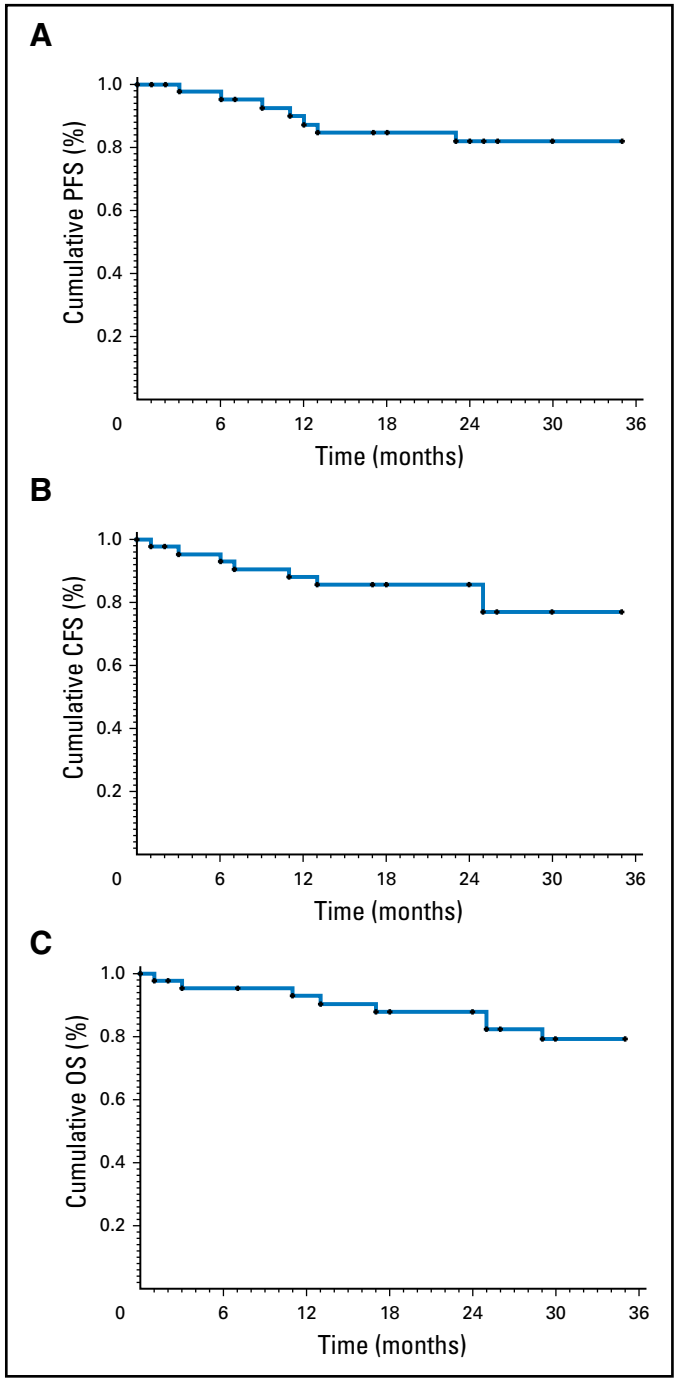

Fig 2. Kaplan-Meier estimates of (A) progression-free survival (PFS), (B) colostomy-free survival (CFS), and (C) overall survival (OS).

States.[24] Improved antiretroviral therapy beginning in the 1990s led to substantial declines in mortality from HIV infection in the United States,[25] which continues in the United States and globally.[26] HIV testing is now recommended as a component of routine medical care, not just for individuals with known risk factors,[27-29] including patients with cancer.[30] Although improved antiretroviral therapy has also resulted in substantially fewer HIV-associated cancers such as lymphoma and Kaposi's sarcoma, the incidence of other cancers has increased, including anal carcinoma.[1] Approximately 1% of women and 28% of men with anal cancer also have HIV infection.[31]

We herein report the results of the first prospectively conducted trial, to our knowledge, of CRT for the treatment of SCCAC associated with HIV infection. At the time this trial was initiated, a number of retrospective case reviews involving a limited number of patients indicated that clinical outcomes were inferior and toxicity rates with CRT excessive.[32-38] We chose to use cisplatin and FU as the chemotherapy regimen in combination with standard doses of RT, because substituting cisplatin for mitomycin-C was associated with less myelosuppression and comparable or improved disease control in prior trials including patients not know to have HIV infection.[39-41] In addition, we added concurrent treatment with the EGFR inhibitor cetuximab because of evidence that it enhanced the effects of RT and improved local disease control in oropharyngeal SCC,[13,14] which is also commonly associated with HPV infection.[7,8] We therefore performed two prospective trials evaluating cetuximab plus CRT in patients with HIV infection (AMC045) and without known HIV infection (E3205).[18] When the two trials are considered together, a noteworthy finding is that patients with HIV infection had similar clinical outcomes as those who did not have HIV infection, with approximately 70% being alive and recurrence free at 3 years. Treatment tolerance and the overall adverse effect profile were also similar in the two populations. These findings are consistent with population-based data indicating that although cancer-specific mortality is increased in HIV-infected individuals compared with the general population for some cancers (eg, colorectal, pancreas, larynx, lung, melanoma, and breast cancer), this is not true for anal cancer.[42] Although comparison of efficacy and toxicity observed in the two studies targeting populations differing by HIV status is limited by the modest sample size and more advanced disease for the HIV-negative cohort, our findings nevertheless provide additional data suggesting that SCCAC in HIV-infected individuals may be treated with curative intent similar to immunocompetent individuals. Although treatment was associated with a transient reduction in CD4 lymphocyte counts, opportunistic infections were uncommon, HIV viral load did not change, and CD4 counts recovered after completion of CRT. Although CRT was also associated with adverse patient-reported symptoms (eg, fatigue, anorexia) and impaired QOL, most symptoms resolved after completion of therapy.

The AMC045 and E3205 trials were primarily designed to determine whether adding cetuximab reduced the rate of LRF, which occurs in approximately 30% of patients treated with CRT alone. In comparison with patients enrolled on the E3205 trial, patients with HIV infection enrolled in AMC045 were more likely to be men (reflecting known demographics for HIV infection) and more likely to have T1 disease (reflecting differing eligibility criteria). In both trials, LRF rates were approximately 20% at 3 years, indicating that LRF rates were lower than historical data using similar definitions.[3,5] Although this study did not meet its prespecified primary end point, the majority of the LRF events were categorized as failures because of insufficient follow-up and not due to a truly higher LRF rate when similar definitions of LRF were used compared with historical data.

In conclusion, this is the first prospective trial, to our knowledge, of a CRT regimen in patients with HIV-associated

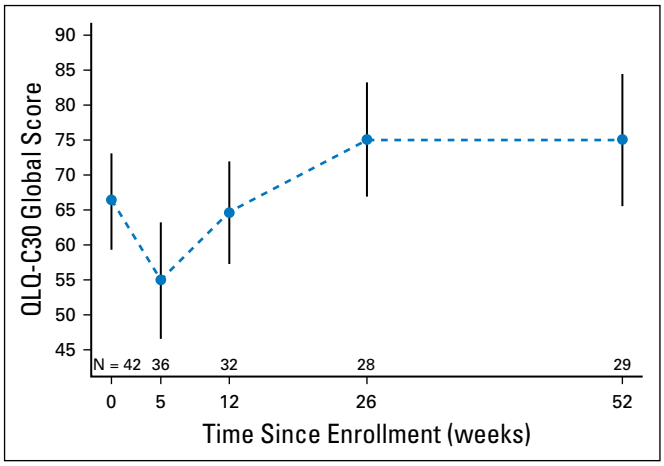

Fig 3. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (QLQ-C30) global score at baseline and at weeks 5 (after cycle 1), 12 (after completion of therapy), 28 (ie, month 6), and 52 after beginning therapy.

SCCAC that demonstrates comparable efficacy, tolerance, and toxicity when compared with the same CRT regimen plus cetuximab in a concurrently conducted trial in an HIV-negative population. These finding suggest that patients with HIV-associated SCCAC should be treated with potentially curative intent with CRT in a manner similar to patients without known HIV infection. However, the 20% LRF rate and 26% grade 4 toxicity rate indicate the continued need for more-effective and less-toxic therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Patel P, Hanson DL, Sullivan PS, et al: Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med 148: 728-736, 2008

2. Flam M, John M, Pajak TF, et al: Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: Results of a phase III randomized intergroup study. J Clin Oncol 14: 2527-2539, 1996

3. Ajani JA, Winter KA, Gunderson LL, et al: Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: A randomized controlled trial. JAMA 299: 1914-1921, 2008

4. Gunderson LL, Winter KA, Ajani JA, et al: Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: Survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol 30:4344-4351, 2012

5. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research: Epidermoid anal cancer: Results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. Lancet 348: 1049-1054, 1996

6. James RD, Glynne-Jones R, Meadows HM, et al: Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): A randomised, phase 3, open-label, 2 × 2 factorial trial. Lancet Oncol 14:516-524, 2013

7. Williams GR, Lu QL, Love SB, et al: Properties of HPV-positive and HPV-negative anal carcinomas. J Pathol 180:378-382, 1996

8. Varnai AD, Bollmann M, Griefingholt H, et al: HPV in anal squamous cell carcinoma and anal intraepithelial neoplasia (AIN). Impact of HPV analysis of anal lesions on diagnosis and prognosis. Int J Colorectal Dis 21:135-142, 2006

9. Palefsky JM, Barrasso R: HPV infection and disease in men. Obstet Gynecol Clin North Am 23: 895-916, 1996

10. Tsai TC, Chen SL: The biochemical and biological functions of human papillomavirus type 16 E5 protein. Arch Virol 148:1445-1453, 2003

11. Lê LH, Chetty R, Moore MJ: Epidermal growth factor receptor expression in anal canal carcinoma. Am J Clin Pathol 124:20-23, 2005

12. Paliga A, Onerheim R, Gologan A, et al: EGFR and K-ras gene mutation status in squamous cell anal carcinoma: A role for concurrent radiation and EGFR inhibitors? Br J Cancer 107:1864-1868, 2012

13. Bonner JA, Harari PM, Giralt J, et al: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354:567-578, 2006

14. Bonner JA, Harari PM, Giralt J, et al: Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 11:21-28, 2010

15. Mork J, Lie AK, Glattre E, et al: Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. N Engl J Med 344: 1125-1131, 2001

16. Herrero R, Castellsagué X, Pawlita M, et al: Human papillomavirus and oral cancer: The International Agency for Research on Cancer multicenter study. J Natl Cancer Inst 95:1772-1783, 2003

17. D'Souza G, Kreimer AR, Viscidi R, et al: Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 356:1944-1956, 2007

18. Garg M, Lee JY, Kachnic LA, et al: Phase II trials of cetuximab (CX) plus cisplatin (CDDP), 5fluorouracil (5FU) and radiation (RT) in immunocompetent (ECOG 3205) and HIVpositive (AMC045) patients with squamous cell carcinoma of the anal canal (SCAC): Safety and preliminary efficacy results. J Clin Oncol 30, 2012 (suppl; abstr 4030)

19. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-216, 2000

20. Palefsky JM, Holly EA, Ralston ML, et al: Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men. J Infect Dis 177:361-367, 1998

21. Northover J, Glynne-Jones R, Sebag-Montefiore D, et al: Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). Br J Cancer 102: 1123-1128, 2010

22. American Joint Committee on Cancer: AJCC Cancer Staging Manual (ed 5). Philadelphia, PA, Lippencott-Raven, 1997

23. UNAIDS: Fact Sheet 2015. http://www.unaids.org/sites/default/files/media_asset/20150901_FactSheet_2015_en.pdf

24. Centers for Disease Control and Prevention: HIIV in the United States: At a glance. http://www.cdc.gov/hiv/statistics/overview/ataglance.html

25. Palella FJ Jr, Delaney KM, Moorman AC, et al: Declining morbidity and mortality among patients with advanced human immunodeficiency virus

infection. HIV Outpatient Study Investigators. N Engl J Med 338:853-860, 1998

26. World Health Organization: Global Health Observatory (GHO) data: Number of deaths due to HIV/AIDS. http://www.who.int/gho/hiv/epidemic_status/deaths_text/en/

27. Branson BM, Handsfield HH, Lampe MA, et al: Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep 55:1-17, 2006; quiz CE1-4

28. Qaseem A, Snow V, Shekelle P, et al: Screening for HIV in health care settings: A guidance statement from the American College of Physicians and HIV Medicine Association. Ann Intern Med 150: 125-131, 2009

29. Bartlett JG, Branson BM, Fenton K, et al: Opt-out testing for human immunodeficiency virus in the United States: Progress and challenges. JAMA 300: 945-951, 2008

30. Chiao EY, Dezube BJ, Krown SE, et al: Time for oncologists to opt in for routine opt-out HIV testing? JAMA 304:334-339, 2010

31. Shiels MS, Pfeiffer RM, Chaturvedi AK, et al: Impact of the HIV epidemic on the incidence rates of anal cancer in the United States. J Natl Cancer Inst 104:1591-1598, 2012

32. Chadha M, Rosenblatt EA, Malamud S, et al: Squamous-cell carcinoma of the anus in HIV-positive patients. Dis Colon Rectum 37:861-865, 1994

33. Peddada AV, Smith DE, Rao AR, et al: Chemotherapy and low-dose radiotherapy in the treatment of HIV-infected patients with carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 37:1101-1105, 1997

34. Hoffman R, Welton ML, Klencke B, et al: The significance of pretreatment CD4 count on the outcome and treatment tolerance of HIV-positive patients with anal cancer. Int J Radiat Oncol Biol Phys 44:127-131, 1999

35. Holland JM, Swift PS: Tolerance of patients with human immunodeficiency virus and anal carcinoma to treatment with combined chemotherapy and radiation therapy. Radiology 193:251-254, 1994

36. Place RJ, Gregorcyk SG, Huber PJ, et al: Outcome analysis of HIV-positive patients with anal squamous cell carcinoma. Dis Colon Rectum 44: 506-512, 2001

37. Kim JH, Sarani B, Orkin BA, et al: HIV-positive patients with anal carcinoma have poorer treatment tolerance and outcome than HIV-negative patients. Dis Colon Rectum 44:1496-1502, 2001

38. Cleator S, Fife K, Nelson M, et al: Treatment of HIV-associated invasive anal cancer with combined chemoradiation. Eur J Cancer 36:754-758, 2000

39. Doci R, Zucali R, La Monica G, et al: Primary chemoradiation therapy with fluorouracil and cisplatin for cancer of the anus: Results in 35 consecutive patients. J Clin Oncol 14:3121-3125, 1996

40. Peiffert D, Seitz JF, Rougier P, et al: Preliminary results of a phase II study of high-dose radiation therapy and neoadjuvant plus concomitant 5-fluorouracil with CDDP chemotherapy for patients with anal canal cancer: A French cooperative study. Ann Oncol 8:575-581, 1997

41. Meropol N, Shank B, Colacchio T, et al: Combined-modality therapy of poor risk anal canal carcinoma: A phase II study of the CALGB. Proc Am Soc Clin Oncol 18:237a, 1999 (abstr 909)

42. Coghill AE, Shiels MS, Suneja G, et al: Elevated cancer-specific mortality among HIV-infected patients in the United States. J Clin Oncol 33: 2376-2383, 2015

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Appendix

Table A1. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 Data

Category	Visit	No.	Mean	SD	Median	Minimum	Maximum
Global score	Baseline	42	66.27	22.01	66.67	8.33	100.00
	Week 5/day 29	36	54.86	24.35	54.17	0.00	100.00
	Week 12	32	64.58	20.08	66.67	25.00	100.00
	Week 26	28	75.00	21.03	79.17	33.33	100.00
	Month 12	29	75.00	24.70	83.33	25.00	100.00
	Month 24	15	78.89	23.96	83.33	25.00	100.00
	Month 36	9	80.56	22.44	83.33	33.33	100.00
Physical functioning	Baseline	44	87.42	15.57	96.67	53.33	100.00
	Week 5/day 29	38	69.25	25.59	73.33	13.33	100.00
	Week 12	32	82.08	18.58	86.67	46.67	100.00
	Week 26	28	86.43	18.81	96.67	33.33	100.00
	Month 12	29	87.13	19.59	100.00	26.67	100.00
	Month 24	16	82.50	21.89	93.33	46.67	100.00
	Month 36	9	88.89	19.44	100.00	46.67	100.00
Role functioning	Baseline	44	75.76	32.04	100.00	0.00	100.00
	Week 5/day 29	38	53.95	37.05	66.67	0.00	100.00
	Week 12	32	75.00	31.11	100.00	0.00	100.00
	Week 26	28	80.36	28.35	100.00	0.00	100.00
	Month 12	29	79.31	32.63	100.00	0.00	100.00
	Month 24	16	83.33	23.57	100.00	33.33	100.00
	Month 36	9	87.04	33.10	100.00	0.00	100.00
Emotional functioning	Baseline	44	71.97	24.08	75.00	8.33	100.00
	Week 5/day 29	38	67.84	24.77	75.00	25.00	100.00
	Week 12	32	76.04	20.38	75.00	25.00	100.00
	Week 26	28	76.98	23.10	83.33	22.22	100.00
	Month 12	29	78.83	26.51	91.67	0.00	100.00
	Month 24	16	82.81	22.66	95.83	33.33	100.00
	Month 36	9	75.93	24.10	75.00	25.00	100.00
Cognitive functioning	Baseline	44	84.85	21.51	100.00	16.67	100.00
	Week 5/day 29	38	77.19	24.64	83.33	16.67	100.00
	Week 12	32	85.94	16.46	91.67	50.00	100.00
	Week 26	28	87.50	16.74	100.00	33.33	100.00
	Month 12	29	85.06	25.33	100.00	0.00	100.00
	Month 24	16	85.42	20.07	91.67	33.33	100.00
	Month 36	9	85.19	24.22	100.00	33.33	100.00
Social functioning	Baseline	44	79.17	24.94	83.33	0.00	100.00
	Week 5/day 29	38	62.72	31.34	66.67	0.00	100.00
	Week 12	32	75.00	23.57	66.67	16.67	100.00
	Week 26	28	80.36	27.98	91.67	0.00	100.00
	Month 12	29	78.74	30.83	100.00	0.00	100.00
	Month 24	16	81.25	20.97	83.33	33.33	100.00
	Month 36	9	83.33	33.33	100.00	0.00	100.00
Fatigue	Baseline	44	27.53	21.50	27.78	0.00	100.00
	Week 5/day 29	38	51.90	30.24	52.78	0.00	100.00
	Week 12	32	34.03	24.10	33.33	0.00	88.89
	Week 26	28	29.37	28.88	22.22	0.00	100.00
	Month 12	29	24.52	22.69	22.22	0.00	88.89
	Month 24	16	22.92	23.82	22.22	0.00	66.67
	Month 36	9	20.99	28.02	0.00	0.00	77.78

(continued on following page)

Table A1. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 Data (continued)

Category	Visit	No.	Mean	SD	Median	Minimum	Maximum
Nausea and vomiting	Baseline	44	7.20	13.64	0.00	0.00	66.67
	Week 5/day 29	38	21.05	21.81	16.67	0.00	66.67
	Week 12	32	10.94	21.42	0.00	0.00	83.33
	Week 26	28	7.14	13.93	0.00	0.00	50.00
	Month 12	29	7.47	10.53	0.00	0.00	33.33
	Month 24	16	8.33	16.10	0.00	0.00	50.00
	Month 36	9	9.26	14.70	0.00	0.00	33.33
Pain	Baseline	44	39.39	35.05	33.33	0.00	100.00
	Week 5/day 29	38	50.00	36.35	50.00	0.00	100.00
	Week 12	32	30.73	29.67	33.33	0.00	100.00
	Week 26	28	24.40	30.25	16.67	0.00	100.00
	Month 12	29	26.44	31.34	16.67	0.00	100.00
	Month 24	16	18.75	27.13	0.00	0.00	83.33
	Month 36	9	22.22	34.36	0.00	0.00	100.00
Dyspnea	Baseline	44	12.12	22.84	0.00	0.00	100.00
	Week 5/day 29	38	19.30	22.77	0.00	0.00	66.67
	Week 12	32	10.42	17.84	0.00	0.00	66.67
	Week 26	28	13.10	18.90	0.00	0.00	66.67
	Month 12	29	16.09	24.59	0.00	0.00	66.67
	Month 24	16	16.67	24.34	0.00	0.00	66.67
	Month 36	9	11.11	23.57	0.00	0.00	66.67
Insomnia	Baseline	44	34.09	36.29	33.33	0.00	100.00
	Week 5/day 29	38	38.60	35.96	33.33	0.00	100.00
	Week 12	32	26.04	31.38	16.67	0.00	100.00
	Week 26	28	25.00	30.93	16.67	0.00	100.00
	Month 12	29	19.54	24.43	0.00	0.00	100.00
	Month 24	16	18.75	20.97	16.67	0.00	66.67
	Month 36	9	18.52	24.22	0.00	0.00	66.67
Appetite loss	Baseline	43	13.95	22.10	0.00	0.00	100.00
	Week 5/day 29	38	39.47	33.65	33.33	0.00	100.00
	Week 12	32	17.71	22.38	0.00	0.00	66.67
	Week 26	28	14.29	26.34	0.00	0.00	100.00
	Month 12	28	16.67	32.08	0.00	0.00	100.00
	Month 24	16	10.42	20.07	0.00	0.00	66.67
	Month 36	9	14.81	24.22	0.00	0.00	66.67
Constipation	Baseline	44	18.18	28.26	0.00	0.00	100.00
	Week 5/day 29	36	21.30	25.39	0.00	0.00	66.67
	Week 12	32	17.71	26.75	0.00	0.00	100.00
	Week 26	28	15.48	26.42	0.00	0.00	100.00
	Month 12	29	8.05	19.22	0.00	0.00	66.67
	Month 24	16	8.33	14.91	0.00	0.00	33.33
	Month 36	9	18.52	17.57	33.33	0.00	33.33
Diarrhea	Baseline	44	25.00	30.61	16.67	0.00	100.00
	Week 5/day 29	38	40.35	31.15	33.33	0.00	100.00
	Week 12	32	20.83	26.44	0.00	0.00	100.00
	Week 26	28	14.29	19.09	0.00	0.00	66.67
	Month 12	29	13.79	20.93	0.00	0.00	66.67
	Month 24	16	10.42	15.96	0.00	0.00	33.33
	Month 36	9	14.81	24.22	0.00	0.00	66.67
Financial difficulties	Baseline	44	38.64	38.68	33.33	0.00	100.00
	Week 5/day 29	38	39.47	35.39	33.33	0.00	100.00
	Week 12	32	33.33	33.87	33.33	0.00	100.00
	Week 26	28	23.81	28.48	16.67	0.00	100.00
	Month 12	29	17.24	26.16	0.00	0.00	100.00
	Month 24	16	29.17	36.26	16.67	0.00	100.00
	Month 36	9	22.22	28.87	0.00	0.00	66.67

Abbreviation: SD, standard deviation.

Table A2. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire CR38 Data

Category	Visit	No.	Mean	SD	Median	Minimum	Maximum
Body image	Baseline	44	20.45	21.43	22.22	0.00	77.78
	Week 5/day 29	38	35.67	33.89	27.78	0.00	100.00
	Week 12	31	25.99	25.15	22.22	0.00	88.89
	Week 26	28	21.43	29.31	11.11	0.00	100.00
	Month 12	29	17.62	24.22	11.11	0.00	100.00
	Month 24	16	24.31	26.05	11.11	0.00	100.00
	Month 36	9	16.05	12.56	11.11	0.00	33.33
Sexual functioning	Baseline	43	25.97	28.48	16.67	0.00	100.00
	Week 5/day 29	37	17.57	22.89	16.67	0.00	100.00
	Week 12	31	18.28	20.35	16.67	0.00	66.67
	Week 26	26	30.77	25.25	33.33	0.00	83.33
	Month 12	26	35.26	23.25	33.33	0.00	83.33
	Month 24	16	26.04	25.07	25.00	0.00	66.67
	Month 36	9	31.48	22.74	33.33	0.00	66.67
Sexual enjoyment	Baseline	16	72.92	25.00	66.67	33.33	100.00
	Week 5/day 29	7	28.57	23.00	33.33	0.00	66.67
	Week 12	7	52.38	17.82	66.67	33.33	66.67
	Week 26	10	66.67	22.22	66.67	33.33	100.00
	Month 12	12	61.11	19.25	66.67	33.33	100.00
	Month 24	6	72.22	25.09	66.67	33.33	100.00
	Month 36	5	60.00	27.89	66.67	33.33	100.00
Future perspective	Baseline	43	48.06	35.11	33.33	0.00	100.00
	Week 5/day 29	36	56.48	36.36	66.67	0.00	100.00
	Week 12	31	38.71	36.61	33.33	0.00	100.00
	Week 26	28	35.71	33.86	33.33	0.00	100.00
	Month 12	28	34.52	30.74	33.33	0.00	100.00
	Month 24	16	37.50	38.25	33.33	0.00	100.00
	Month 36	9	33.33	37.27	33.33	0.00	100.00
Micturition problems	Baseline	44	23.23	20.73	22.22	0.00	88.89
	Week 5/day 29	38	41.81	22.14	33.33	11.11	77.78
	Week 12	31	29.03	21.79	33.33	0.00	66.67
	Week 26	28	22.22	22.22	22.22	0.00	77.78
	Month 12	29	21.46	16.25	22.22	0.00	44.44
	Month 24	16	18.06	24.97	11.11	0.00	88.89
	Month 36	9	13.58	22.07	0.00	0.00	66.67
Chemotherapy adverse effects	Baseline	44	12.63	14.30	11.11	0.00	44.44
	Week 5/day 29	38	37.28	25.54	33.33	0.00	100.00
	Week 12	31	27.60	18.84	22.22	0.00	66.67
	Week 26	28	15.08	17.16	11.11	0.00	55.56
	Month 12	29	14.56	17.09	11.11	0.00	55.56
	Month 24	16	15.97	13.44	11.11	0.00	44.44
	Month 36	9	13.58	24.71	11.11	0.00	77.78
GI symptoms	Baseline	44	25.00	19.10	22.50	0.00	80.00
	Week 5/day 29	38	38.29	20.24	40.00	6.67	80.00
	Week 12	31	20.86	14.41	20.00	0.00	46.67
	Week 26	28	20.06	16.28	20.00	0.00	60.00
	Month 12	29	21.09	19.26	20.00	0.00	80.00
	Month 24	16	17.71	14.84	13.33	0.00	50.00
	Month 36	9	14.07	17.78	6.67	0.00	53.33
Defecation problems	Baseline	36	25.55	20.67	23.81	0.00	76.19
	Week 5/day 29	34	30.53	20.34	28.57	0.00	100.00
	Week 12	27	22.99	15.52	19.05	0.00	61.90
	Week 26	22	21.43	14.30	19.05	0.00	57.14
	Month 12	24	17.06	15.57	14.29	0.00	66.67
	Month 24	16	17.98	15.58	14.29	0.00	52.38
	Month 36	8	17.86	19.84	9.52	9.52	66.67
Stoma-related problems	Baseline	1	57.14	—	57.14	57.14	57.14
	Week 5/day 29	1	52.38	—	52.38	52.38	52.38
	Week 12	1	61.90	—	61.90	61.90	61.90
	Week 26	1	80.95	—	80.95	80.95	80.95
	Month 12	1	42.86	—	42.86	42.86	42.86
	Month 24	0	—	—	—	—	—
	Month 36	0	—	—	—	—	—

(continued on following page)

Table A2. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire CR38 Data (continued)

Category	Visit	No.	Mean	SD	Median	Minimum	Maximum
Weight loss	Baseline	42	15.87	22.38	0.00	0.00	100.00
	Week 5/day 29	38	41.23	35.88	33.33	0.00	100.00
	Week 12	31	19.35	29.53	0.00	0.00	100.00
	Week 26	28	14.29	27.86	0.00	0.00	100.00
	Month 12	29	11.49	24.03	0.00	0.00	100.00
	Month 24	15	6.67	13.80	0.00	0.00	33.33
	Month 36	9	14.81	24.22	0.00	0.00	66.67
Male sexual problems	Baseline	38	19.30	26.15	8.33	0.00	100.00
	Week 5/day 29	31	44.09	39.80	33.33	0.00	100.00
	Week 12	21	33.33	34.16	33.33	0.00	100.00
	Week 26	26	34.62	34.94	25.00	0.00	100.00
	Month 12	23	38.41	37.41	33.33	0.00	100.00
	Month 24	13	41.03	35.10	33.33	0.00	100.00
	Month 36	7	57.14	33.13	50.00	16.67	100.00

Abbreviation: SD, standard deviation.