



HAL
open science

Panitumumab in combination with chemoradiotherapy for the treatment of locally-advanced anal canal carcinoma: Results of the FFCD 0904 phase II trial

Véronique Vendrely, Philippe Ronchin, Mathieu Minsat, Karine Le Malicot, Claire Lemanski, Xavier Mirabel, Pierre-Luc Etienne, Astrid Lièvre, Ariane Darut-Jouve, Christelle de la Fouchardière, et al.

► To cite this version:

Véronique Vendrely, Philippe Ronchin, Mathieu Minsat, Karine Le Malicot, Claire Lemanski, et al.. Panitumumab in combination with chemoradiotherapy for the treatment of locally-advanced anal canal carcinoma: Results of the FFCD 0904 phase II trial. *Radiotherapy & Oncology*, 2023, 186, pp.109742. 10.1016/j.radonc.2023.109742 . hal-04163679

HAL Id: hal-04163679

<https://univ-rennes.hal.science/hal-04163679>

Submitted on 13 Sep 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Journal Pre-proofs

Original Article

Panitumumab in combination with chemoradiotherapy for the treatment of locally-advanced anal canal carcinoma: results of the FFCD 0904 phase II trial

Véronique Vendrely, Philippe Ronchin, Mathieu Minsat, Karine Le Malicot, Claire Lemanski, Xavier Mirabel, Pierre-Luc Etienne, Astrid Lièvre, Ariane Darut-Jouve, Christelle de la Fouchardière, Nicolas Giraud, Gilles Breysacher, Delphine Argo-Leignel, Elsa Thimonnier, Nicolas Magné, Meher Ben Abdelghani, Côme Lepage, Thomas Aparicio, for FFCD investigators/ Collaborators,

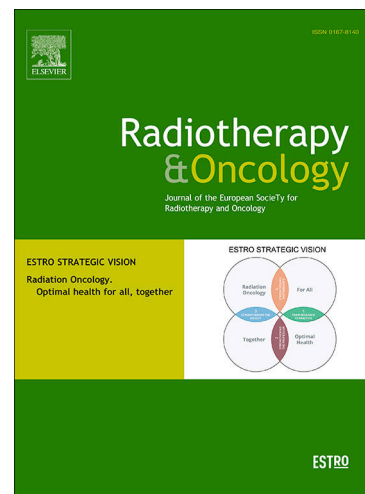
PII: S0167-8140(23)00280-3
DOI: <https://doi.org/10.1016/j.radonc.2023.109742>
Reference: RADION 109742

To appear in: *Radiotherapy and Oncology*

Received Date: 26 January 2023
Revised Date: 29 May 2023
Accepted Date: 5 June 2023

Please cite this article as: Vendrely, V., Ronchin, P., Minsat, M., Le Malicot, K., Lemanski, C., Mirabel, X., Etienne, P-L., Lièvre, A., Darut-Jouve, A., de la Fouchardière, C., Giraud, N., Breysacher, G., Argo-Leignel, D., Thimonnier, E., Magné, N., Ben Abdelghani, M., Lepage, C., Aparicio, T., for FFCD investigators/Collaborators, Panitumumab in combination with chemoradiotherapy for the treatment of locally-advanced anal canal carcinoma: results of the FFCD 0904 phase II trial, *Radiotherapy and Oncology* (2023), doi: <https://doi.org/10.1016/j.radonc.2023.109742>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Panitumumab in combination with chemoradiotherapy for the treatment of locally-advanced anal canal carcinoma: results of the FFCD 0904 phase II trial
Panitumumab in combination with chemoradiotherapy for the treatment of locally-advanced anal canal carcinoma: results of the FFCD 0904 phase II trial

Véronique Vendrely^{1,2*}, Philippe Ronchin³, Mathieu Minsat⁴, Karine Le Malicot⁵, Claire Lemanski⁶, Xavier Mirabel⁷, Pierre-Luc Etienne⁸, Astrid Lièvre⁹, Ariane Darut-Jouve¹⁰, Christelle de la Fouchardière¹¹, Nicolas Giraud¹, Gilles Breysacher¹², Delphine Argo-Leignel¹³, Elsa Thimonnier¹⁴, Nicolas Magné¹⁵, Meher Ben Abdelghani¹⁶, Côme Lepage¹⁷, Thomas Aparicio¹⁸ for FFCD investigators/Collaborators

¹ Radiation Oncology Department, CHU Bordeaux, Bordeaux, France; ² BRIC (BoRdeaux Institute of onCology), UMR1312, INSERM, University of Bordeaux, F-33000, Bordeaux, France ; ³ Radiotherapy department, Azuréen Cancer Center, Mougins, France ; ⁴ Radiation Oncology, Institut Curie, Paris, France; ⁵ Fédération Francophone de Cancérologie Digestive, university of Burgundy, Biostatistics, Dijon, France ; EPICAD INSERM LNC-UMR 1231, University of Burgundy, Dijon, France; ⁶ Department of Radiation Oncology, , Montpellier Cancer Institute (ICM), Montpellier, France ; ⁷ Radiotherapy Department, Centre Oscar Lambret, Lille, France ; ⁸ Oncology Department, Centre CARIO-HPCA, Plerin, France; ⁹ Gastroenterology Department, Rennes University Hospital, Rennes 1 University, Inserm U1242 COSS (Chemistry Oncogenesis Stress Signaling), Rennes, France ; ¹⁰ Institut de cancérologie de Bourgogne GRReCC, DIJON, France ; ¹¹ Oncology Department, Centre Léon Bérard, Lyon, France; ¹² Oncology Department, Hôpitaux civils de Colmar, Colmar, France ; ¹³ Radiotherapy and Oncology Department, CHBS-Hôpital du Scorff, Lorient, France; ¹⁴ Radiotherapy Department, Annecy Genevois, Pringy, France; ¹⁵ Radiotherapy and Oncology Department, Institut de Cancérologie Lucien Neuwirth, Saint Priest en Jarez, France; ¹⁶ Oncology Department, Centre Paul Strauss, Strasbourg, France; ¹⁷ Department of hepato-

gastroenterology· University hospital of Dijon, Dijon, France ; ¹⁸ Gastroenterology and Digestive Oncology Department, Saint Louis Hospital, AP-HP, Paris, France

*Corresponding author:

Pr Véronique Vendrely, Radiation Oncology Department, Hôpital Haut-Lévêque, Avenue de Magellan, 33604 Pessac, France

Tel: +33 5 57 62 33 00; Fax: +33 5 57 62 33 05

Email : veronique.vendrely@chu-bordeaux.fr

Short title: Chemoradiotherapy with panitumumab for locally advanced anal cancer

Electronic word count (Introduction + Material and methods + Results + Discussion) : 2939

Number of figures and tables: 4

Financial support statement: AMGEN provided Panitumumab treatment

Abbreviations: CT: chemotherapy, CRT: chemoradiotherapy, CTV: clinical tumor volume, DL: dose level; DLT: dose-limiting toxicities; EGFR: epidermal growth factor receptor 5FU: 5 fluorouracil, GTV: gross tumor volume, ICT: induction chemotherapy; IMRT: intensity-modulated radiation therapy, ISMC: Independent Safety Monitoring Committee, MMC: Mitomycin C, MTD: maximum tolerated dose, Pmab: Panitumumab, PTV: planning tumor volume, RT: radiotherapy

Credit author statement :

V.Vendrely : Study design, data collection, data analysis and interpretation, writing, supervising ; P.Ronchin : data collection and revision ; M.Minsat : data collection and revision ; K.Le Malicot : study design, data analysis and interpretation, revision ; C.Lemanski : data collection, data analysis and interpretation ; X.Mirabel : data collection and revision ; PL.Etienne : data collection and revision ; A.Lièvre : Data collection, data analysis and interpretation, revision ; A.Darut-Jouve : data collection and revision ; C.De la Fouchardière : data collection and revision ; N.Giraud : data analysis and writing ; G.Breysacher : data collection and revision ; D. Argo-Leignel : data collection and revision ; E. Thimonnier : data collection and revision ; N.Magné : data collection and revision ; M. Ben Abdelghani : data collection and revision ; C.Lepage : supervising and revision; T.Aparicio : study design, data collection, data analysis and interpretation, revision

Highlights

- This phase II trial studied the tolerance and complete response rate at 8 weeks of panitumumab combined with MMC-5FU-based chemoradiotherapy for locally advanced anal cancers.
- Panitumumab in combination with chemoradiotherapy failed to meet the expected complete response rate (80%).
- Disease-free survival at 3 years was 62.2% [IC95%: 46.5- 74.6], similar to usual DFS with standard CRT for locally advanced anal cancers.
- The association exhibited a poor tolerance despite reduced doses of 5FU and panitumumab defined in a previous phase 1 study

Abstract

Background and purpose: Standard treatment of squamous cell carcinoma of the anus (SCCA) is 5-fluorouracil (5FU) and mitomycin C (MMC) based chemoradiotherapy (CRT). This phase II study (EudraCT: 2011-005436-26) assessed the tolerance and complete response (CR) rate at 8 weeks of panitumumab (Pmab) combined with MMC-5FU-based CRT.

Methods: Patients with locally advanced tumors without metastases (T2 >3 cm, T3-T4, or N+ whatever T stage) were treated with IMRT up to 65 Gy and concomitant CT according to the doses defined by a previous phase I study (MMC: 10 mg/m²; 5FU: 400 mg/m²; Pmab: 3mg/kg). The expected CR rate was 80%.

Results: Forty-five patients (male: 9, female: 36; median age: 60.1 [41.5-81]) were enrolled in 15 French centers. The most common related grade 3-4 toxicities observed were digestive (51.1%), hematologic (lymphopenia: 73.4%; neutropenia: 11.1%), radiation dermatitis (13.3%), and asthenia (11.1%) with RT interruption in 14 patients. One patient died because of mesenteric ischemia during the CRT, possibly related to treatment. In ITT analysis, the CR rate at 8 weeks after CRT was 66.7% [90%CI: 53.4-78.2]. Median follow-up was 43.6 months [IC 95%: 38.61-47.01]. Overall survival, recurrence-free and colostomy-free survival at 3 years were 80% [95%CI: 65.1-89], 62.2% [IC95%: 46.5-74.6] and 68.8 % [IC95%: 53.1-80.2] respectively.

Conclusion: Panitumumab in combination with CRT for locally advanced SCCA failed to meet the expected CR rate and exhibited a poor tolerance. Furthermore, late RFS, CFS, and OS did not suggest any outcome improvement to justify further clinical trials.

Highlights

- This phase II trial studied the tolerance and complete response rate at 8 weeks of panitumumab combined with MMC-5FU-based chemoradiotherapy for locally advanced anal cancers.
- Panitumumab in combination with chemoradiotherapy failed to meet the expected complete response rate (80%).
- Disease-free survival at 3 years was 62.2% [IC95%: 46.5- 74.6], similar to usual DFS with standard CRT for locally advanced anal cancers.
- The association exhibited a poor tolerance despite reduced doses of 5FU and panitumumab defined in a previous phase 1 study

Keywords: Anal cancer; Squamous cell carcinoma; Epidermal growth factor receptor; Panitumumab; Chemoradiotherapy; Immunotherapy.

ClinicalTrials.gov identifier: NCT01581840

1. Introduction

Squamous cell carcinoma of the anus (SCCA) is a relatively rare yet increasing disease, reaching around 48,000 new cases worldwide in 2018 (1). With an indolent natural history and a low rate of distant metastases, SCCA is usually amenable to chemo-radiotherapy (CRT), the standard for non-metastatic tumors. To achieve good loco-regional control while preserving the anal function to avoid colostomy, a combination of radiotherapy (RT) up to 54-65 Gy total doses to the tumor, associated with chemotherapy (CT) is recommended according to guidelines (2,3). In this setting, 5-Fluorouracil (5FU) infusions and Mitomycin C (MMC) boluses

associated with RT have demonstrated improved local outcomes, progression-free (PFS) and overall survivals (OS) compared to RT alone in various randomized trials (4–8). Nevertheless, while showcasing excellent results for small localized tumors motivating de-escalation projects, response rates remain disappointing for locally-advanced diseases, paving the way for intensification trials. Several strategies have been tested throughout the years, for instance, RT dose boosting up to 66 Gy (9), induction chemotherapy, or adjuvant chemotherapy with cisplatin and 5FU (7–9), but all failed to showcase relevant benefits.

Anti-epidermal growth factor receptor (EGFR) agents have shown improved disease control and event-free survival associated with CT in several neoplasms, e.g. colo-rectal or HNSCC cancers, with acceptable toxicity profiles. EGFR is overexpressed in the squamous cell carcinomas of the anal canal (10) and is co-expressed with c-Met and VEGFR1 in anal cancers, especially in HIV-positive individuals (11). EGFR overexpression was also identified in the human HPV-16-immortalized anal epithelial cell line (12). Based on these observations, combinations of standard CRT and anti-EGFR agents, like Panitumumab (Pmab) or Cetuximab, have been theorized to be clinically helpful in locally advanced SCCA. Treatment protocols incorporating these drugs have been tried in a few trials, like in ACCORD 16 or E3205 (both with Cetuximab), but were associated with unexpected toxicity both in immune-competent and deficient patients, as well as disappointing efficacy results (13–16). As similar toxicity profiles may be expected with Pmab but Cetuximab was used directly in phase 2 trial in combination with radiotherapy, we hypothesized that a dose adaptation could be needed (17). In our previous phase I study, we assessed the optimal CT doses of 5FU, MMC, and Pmab in association with RT based on the determination of their maximum tolerated doses (MTD) (18), decreasing the continuous intravenous infusion of 5FU to 400 mg/m² per day over 4 days on weeks 1 and 5 and panitumumab to 3 mg/kg every two weeks while keeping the MMC dose at 10mg/m² on

week 1 and 5. In this phase 2 trial, our objective was to assess the efficacy as well as the overall protocol tolerance.

2. Materials and methods

a. Patient eligibility and study design

In this French open prospective single-arm phase II study, eligible patients had histologically proven anal squamous cell carcinoma and locally advanced non-metastatic tumors (stage T2 >3cm or T3-4 irrespective of the N stage, or N+ irrespective of the T stage). Other requirements included an age of 18 years or older; a WHO performance status of 0 or 1; a life expectancy exceeding 3 months. HIV patients could be included in the case of blood CD4+ > 400 cells/mm³.

Exclusion criteria were notably the presence of previous anti-EGFR therapy or pelvic radiation therapy, as well as significant coronaropathy or recent myocardial infection. All patients underwent digital rectal examination, tumor biopsy, ultrasound-endoscopy, magnetic resonance imaging (MRI) of the pelvis, CT-scan of the whole body, and 18fluorodeoxyglucose positron emission tomography with computed tomography (FDG PET/CT).

b. Radiotherapy

A total radiation dose of 65 Gy recommended in intensity-modulated RT (IMRT) was delivered in two consequent sequences, without any planned break. In the first sequence, a dose of 45 Gy (5 fractions of 1.8 Gy per week over 5 weeks) was delivered to the pelvis. In the second sequence, a dose boost of 20 Gy (10 fractions of 2 Gy per week over 2 weeks) was delivered to the tumor and involved nodes. Delineation of the pelvic clinical target volume (CTV) included external and internal iliac, mesorectal, presacral, and inguinal nodes as well as ischio-rectal fossae. The gross tumor volume (GTV) included the anal tumor and involved nodes that were to receive the total dose of 65 Gy. Anisotropic margins of 10 mm were added to the pelvic CTV and GTV to obtain the pelvic and tumoral planning tumor volumes (PTV) respectively.

Contouring of target volumes was performed by the radiation oncologist on a CT scan with and without contrast infusion, taking into account initial clinical examination, imaging, and endoscopy findings. Doses were prescribed according to the International Commission on Radiological Units 83 guidelines (19). For each patient, treatment position was verified using orthogonal X-rays or cone beam CT on RT days 1 and 2, and then at least once weekly.

c. Standard CT plus Panitumumab

All patients received a combination of 5FU, MMC, and Pmab according to the phase I MTD assessment [18]. During the radiation therapy, patients received a continuous intravenous infusion of 5FU (400 mg/m²) over 4 days on weeks 1 and 5, MMC (10 mg/m²) as a bolus on weeks 1 and 5, plus Pmab (3 mg/kg) by infusion on weeks 1, 3, 5 and 7. Dose modifications of 5FU, MMC, and Pmab were recommended in case of toxicities > grade 2. Any toxicity, disease progression, RT interruption > 7 days due to toxicity, patient refusal to continue the treatment and patients lost to follow-up led to premature discontinuation of the treatment. The CRT protocol is detailed in Figure 1.

d. Study objectives

The primary objective was the complete response (CR) rate at 8 weeks post-CRT. CR was defined as the clearing of all disease targets on clinical and MRI examinations. Secondary objectives investigated recurrence-free survival (RFS) defined as any progression observed on clinical or radiological (MRI, PET-CT, echo-endoscopy) evaluations. Tumor response was assessed 6 weeks after the beginning of treatment, 8 weeks and 4 months after the end of treatment, every 4 months for 2 years then every 6 months for 3 years. This outcome included response rates at 6 weeks after the beginning of the CRT (classically assessed before the RT boost) and 16 weeks post-CRT. Colostomy-free and overall survivals were also collected.

Colostomy-free survival was defined as the time between the date of inclusion and the date of colostomy or death (from any cause) in the absence of colostomy. Alive patients without a

colostomy were censored at date of last news. Toxicity was graded according to the National Cancer Institute Common Adverse Events Criteria v4.0.

e. Patient follow-up and data assessment

Patient health, weight assessments, CRT tolerability, laboratory assessments, and clinical examinations were collected at each CT session, 6 weeks after the first CT and 8 weeks after the last Pmab administration. Toxicity, patient health, weight, and toxicities were evaluated once a week during the RT period. Hematology, platelet counts, and electrolytes were evaluated before each Pmab infusion. Tumor response evaluations by pelvic MRI and/or rectal echo-endoscopy were performed 6 weeks after the beginning of treatment, then at 8 weeks and 16 weeks after the end of treatment, then every 4 months for 2 years and every 6 months for 3 years. Positron emission tomography-computed tomography (PET-CT) was mandatory at initial staging, at 6 months after the end of treatment, and in case of recurrence suspicion. Patients' data were reviewed by an independent safety monitoring committee (ISMC) after treatment of 12 first patients and for all patients.

f. Statistical methods

According to a Simon 2-stage design with a one-sided type I alpha error of 5% and power of 90%, 45 patients had to be included to test the following hypotheses: under the null hypothesis (H₀), a complete response rate at 8 weeks of 60% was not considered interesting for further investigation, whereas, under the alternative hypothesis (H₁), a complete response rate of 80% was considered interesting. The first interim analysis was conducted in July 2017, after the accrual of 26 patients. Seventeen patients met the efficacy criterion, and therefore, the trial was continued. The final analysis was done on the 45 patients included as expected within 2 years. All analyses were performed on an intention-to-treat basis (ITT) meaning all the patients included whatever their eligibility criteria. Baseline characteristics were described using

descriptive statistics as percentages for categorical and ordinal variables, mean (with standard deviation), and median (with inter-quartile and min-max intervals) for continuous variables.

For survival analyses, censored data were estimated and plotted using the Kaplan-Meier method. The median times and rates at different temporalities were described as well as their 95% confidence intervals.

Treatment modalities (chemotherapy, surgery, and radiotherapy) were also described. Toxicity was described according to the relation to treatment (linked or not) and according to the maximal grade for each System Organ Class (SOC) and Preferred Term (PT). A statistical analysis plan was written and signed before the lock of the database. Statistical analyses were done using SAS version 9.4.

g. Informed consent and Ethics approval

All participating patients signed informed consent. The study protocol was approved by the National Ethics Committee, PC/AP 11-2012. The study was conducted according to the principles of the Declaration of Helsinki, the International Conference on Harmonization Guideline on Good Clinical Practice, the French laws and regulations.

3. Results

Between January 2016 and November 2017, 45 patients were enrolled in 15 centers. The characteristics of the study population are outlined in Table 1. The median age was 60 years (range, 41.5-81.0). Most patients had T2 >3 cm (42%) or T3 (40%) tumors and tended to bear higher nodal burdens (57.8% of N positive). The median pre-therapeutic tumor diameter was 45 mm (range, 13-97 mm). Three patients were HIV-positive out of 43 patients tested.

For the whole population (45 patients), the median duration of CRT was 52 days (range, 30-76). The median radiation dose was 65 Gy (range, 36-65 Gy), delivered in 3D-RT (4.4%), IMRT (22.2%), or tomotherapy (71.1%). Reproducibility was ensured by cone beam CT for 38 (84.4%) patients. Seven (15.6%) patients could not finish the planned CRT sequence but 5

achieved a total dose between 59,4 and 63,2 Gy. One (2.2%) patient died during the treatment due to an intercurrent disease (mesenteric ischemia) possibly favored by CRT. This 77 year old female presented with comorbidities such as arteritis (femoral stenting) and high blood pressure. She was hospitalized in the ER one week after the second mitomycin infusion with severe dehydration, vomiting and acute kidney injury. The CT scan showed a grelic occlusion and mesenteric calcifications that could sign mesenteric ischemia. Dose constraints to the bowel were respected Fourteen (31.1%) patients had RT interruptions due to toxicity with a median interruption duration of 6 days (2-15 days). Among them, 8 had RT interruptions superior to one week, which occurred before reaching 60 Gy.

All patients received 2 cycles of 5FU and all but one received 2 cures of MMC. For Pmab, 8 (17.8%) patients received 3 out of 4 injections, and 2 (4.4%) only 2 injections. 5FU doses had to be adapted for 10 (22.2%) and postponed for 12 (26.7%) patients, mostly due to toxicity. MMC doses were modified for 8 (17.8%) patients and postponed for 12 (26.7%) patients. Pmab had to be postponed at least once for 22 (48.9%) patients.

During CRT, grade 3 and 4 side effects linked to the treatment were respectively reported in 88.9% and 37.8% of patients. Most common grade 3-4 toxicities were digestive (at least one grade 3 and 4 adverse event in 44.4% and 6.7% patients) mainly due to diarrhea (24.4% grade 3 and 2.2% grade 4), hematologic with lymphopenia (35.6% grade 3 and 37.8% grade 4) and neutropenia (11.1% grade 3), radiation dermatitis (13.3% grade 3) and asthenia (11.1% grade 3). Observed toxicities are detailed in Table 2.

At 8 weeks post-CRT, most side effects had regressed. Only 3 (6.7%) patients reported grade 3 adverse events, all post-radiation local symptoms (proctitis or pelvic pain).

In ITT analysis, at 8 weeks after the end of CRT, CR was observed in 30 (66.7% [90%CI: 53.4-78.2]) patients. PR was observed in 10 (22.2%) patients, and four (8.9%) presented tumor progression.

The early evaluation performed during CRT (before the RT boost, 6 weeks after treatment start) already showed 11 (25.0%) complete and 24 (54.5%) partial responses.

At 16 weeks post-CRT, 40 (93.0%) patients had at least one objective response on either clinical or radiological assessments. From the composite of clinical and radiological evaluations, excluding the patient that died before the end of CRT, 36 patients (81.9%) were deemed responsive according to the clinician. Among them, 27 (61.4%) showed complete response, and 9 (20.5%) partial response. One (2.3%) had a stable disease, and 7 (15.9%) presented with progressive disease.

Median follow-up was 43.6 months [95%CI: 38.61-47.01]. Recurrence-free and colostomy-free survival at one year were 75.6% [95%CI: 60.2-85.6] and 82.2% [95%CI: 67.6-90.7] (Figure 2A and 2B). Recurrence-free and colostomy-free survival at 3 years were 62.2% [95%CI: 46.5- 74.6] and 68.8% [95%CI: 53.1-80.2] respectively (Figure 2A and 2B). Overall survival was 95.6% (95%CI: 83.5-99.7) at one year and 80% (95%CI: 65.1-89.0) at 3 years (Figure 2C). Median OS was not reached. Ten patients died during follow-up: 6 because of cancer progression, 1 because of intercurrent disease (mesenteric infraction and grelic occlusion occurring during the CRT course), and 3 of other causes (septic shock following prostatectomy, pancreatic cancer, and unknown cause). Eight patients (17.7%) patients had a colostomy with abdominoperineal amputation due to a tumor recurrence for 6 patients, recto-vaginal fistula for one, and intense rectal pain for one.

4. Discussion

In this phase II study, we aimed to assess the efficacy and tolerance of adding Pmab to standard exclusive CRT in 45 patients treated for locally advanced SCCA. The main objective was the rate of complete response at 8 weeks post-CRT, seeking to reach more than 60% (80% expected) of complete responses at this time point. The tolerance and efficacy of an anti-EGFR agent (cetuximab) associated with standard 5FU/MMC-based CRT were first reported in 2015

in a phase I study including 13 patients with locally advanced SCCA, showcasing a high toxicity profile (dose-limiting toxicities were myelotoxicity and diarrhea) (20). This toxicity was also highlighted in the long-term results of the ACCORD 16 trial with 88% grade 3-4 toxicity, mostly digestive (56%), dermatologic (31%), infectious (25%), or hematologic (19%) (13). In this trial, clinical endpoints at 5 years were also disappointing compared to the historic phase III CRT trials (14). Similarly, in 2017, high rates of toxicity were shown with CDDP-5FU and cetuximab in a phase 2 study with 19 (32%) patients experiencing grade 4 toxicities and 3 deaths related to treatment among 61 patients included. In this trial, however, IMRT was not mandatory and 28 patients in arm A had induction chemotherapy, which could have worsened the toxicity (16). Considering cetuximab in combination with radiotherapy had never been assessed in a phase 1 trial, we first conducted a phase I study to assess the optimal CT doses of 5FU, MMC, and Pmab in association with RT based on the determination of their maximum tolerated doses (MTD) (18).

Our CRT protocol included a radiation therapy course up to 65 Gy to the tumor. Even if the ACCORD 03 trial couldn't find a clear benefit of induction CT (ICT) and/or high dose RT, a trend was observed with the CFS at 5 years in the arm receiving ICT plus standard CRT plus high dose boost delivered after a 3-week interruption (9,21). This RT course was delivered without any pre-scheduled pause, as recommended by the ISMC after the end of phase I based on several signals in the literature vowing to reduce as much as possible the overall treatment length due to a possible impact on treatment efficacy and post-therapeutic endpoints (22–24). Interestingly, current trials investigate moderate dose with simultaneous integrated boost to decrease toxicity and shorten overall treatment time (25). Moreover, IMRT was recommended and a safety analysis was planned after 12 patients had been treated. Despite these safety measures, 15.6% of patients could not reach the end of the protocol, including one death due to mesenteric ischemia possibly favored by CRT. Almost 90% of patients experienced grade 3

and 37% grade 4 toxicities, resulting in treatment interruption for one-third of patients, that could have been detrimental to the efficacy. Hematological toxicity, especially regarding lymphopenia, was rather high even in HIV negative patients. Chemotherapy dose adaptations or delays were also required for up to half of patients regarding Pmab administration. This profile of tolerance seems to be lower than expected compared to the results of observational UK or German cohorts of patients treated with standard CRT (26,27). This toxicity could be related to the high total dose (65 Gy) rather than to the addition of panitumumab. However all the interruptions of more than one week were related to toxicity, and occurred before reaching 60 Gy. Therefore we assume that the higher radiotherapy dose was not responsible but rather panitumumab treatment. A high rate of toxicity with Pmab has been also demonstrated in the VITAL phase 2 trial, which included 58 patients treated by CRT with standard doses of Pmab (6mg/kg), MMC (10 mg/m², days 1 and 29) and 5FU (1000 mg/m²/d, days 1-4 and 29-32) and up to 60 Gy RT dose (28). Unexpectedly, our patients experienced similar rates of toxicity even with lower doses of Pmab and 5FU defined according to a phase I trial. In terms of efficacy, the expected CR rate at 8 weeks of more than 60% was almost reached with 66.7% but a 90%CI between 53.4 and 78.2. These results were similar to those reported in the phase 2 trials with cetuximab between 55 and 65% (14–16). However, our primary objective choice could be criticized since anal cancer response can be slow and assessment at 8 weeks after the end of chemoradiotherapy could be too short for the best response assessment (29). Therefore, we decided to also look at the 16-week response assessment and RFS, CFS, and OS at 1 and 3 years. Unfortunately, the complete response rate at 16 weeks was not improved compared to 8 weeks. Moreover, even if one-year RFS and CFS remained satisfactory, 3-year RFS and CFS were disappointing with 62% and 68% respectively, similar to those described in the VITAL phase 2 trial (28). Of note, our study only included patients with locally advanced disease (T2>3 cm, T3-4 or N+) whose 3-year DFS usually remains below 70% as stated in the recent German

cohort (27) or in the ACT II trial where the 3-year DFS was between 80% and 84% for T1-T2, but only 62%, 65%, 62% or 67% for T3-T4 tumors according to each treatment arm, and 68% for N positive tumors (30). Even if our trial results are consistent and not lower for such patients, Pmab failed to improve efficacy at the cost of increased toxicity. Our study present different limitations: the 3cm size cut-off could be questionable to define locally advanced tumors, however we chose this cut-off according to the ACCORD-16 study, which tested cetuximab in addition to radiotherapy and concurrent chemotherapy with CDDP and 5FU (13). Moreover, in the FFCD-ANABASE cohort, a 3 cm-size was identified as a prognostic/predictive factor (31). HPV status was not available in tumor samples which is also a limitation, however since more than 90% of patients present with HPV positive anal tumors (31), to evaluate HPV positivity impact on the outcome would have required a much more important number of patients. Finally, with 45 patients included in 15 centers, the number of patients per center is low and can create challenges from the perspective of quality assurance. However, this was a prospective study with well-defined patient management and quality control to which all centers complied.

5. Conclusion

Panitumumab in combination with CRT for locally advanced anal cancer failed to meet the expected CR rate and exhibited poor tolerance. Furthermore, late DFS, CFS, and OS did not suggest any outcome improvement to justify further clinical trials.

References:

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018 Nov;68(6):394–424.
2. Glynne-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A, et al. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Eur J Surg Oncol.* 2014;40(10):1165–76.
3. Moureau-Zabotto L, Vendrely V, Abramowitz L, Borg C, Francois E, Goere D, et al. Anal cancer: French Intergroup Clinical Practice Guidelines for diagnosis, treatment and follow-

- up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SNFCP). *Dig Liver Dis.* 2017 Aug;49(8):831–40.
4. Nigro ND, Vaitkevicius VK, Considine BJ. Combined therapy for cancer of the anal canal: a preliminary report. 1974. *Dis Colon Rectum.* 1993;36(7):709–11.
 5. Flam M, John M, Pajak TF, Petrelli N, Myerson R, Doggett S, 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.* 1996 Sep;14(9):2527–39.
 6. Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol Off J Am Soc Clin Oncol.* 1997;15(5):2040–9.
 7. Northover J, Glynne-Jones R, Sebag-Montefiore D, James R, Meadows H, Wan S, 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.* 2010 Mar;102(7):1123–8.
 8. Ajani JA. Fluorouracil, Mitomycin, and Radiotherapy vs Fluorouracil, Cisplatin, and Radiotherapy for Carcinoma of the Anal Canal: A Randomized Controlled Trial. *JAMA.* 2008 Apr 23;299(16):1914.
 9. Peiffert D, Tournier-Rangeard L, Gérard JP, Lemanski C, François E, Giovannini M, et al. Induction Chemotherapy and Dose Intensification of the Radiation Boost in Locally Advanced Anal Canal Carcinoma: Final Analysis of the Randomized UNICANCER ACCORD 03 Trial. *J Clin Oncol.* 2012 Jun 1;30(16):1941–8.
 10. Alvarez G, Perry A, Tan BR, Wang HL. Expression of epidermal growth factor receptor in squamous cell carcinomas of the anal canal is independent of gene amplification. *Mod Pathol Off J U S Can Acad Pathol Inc.* 2006 Jul;19(7):942–9.
 11. Walker F, Abramowitz L, Benabderrahmane D, Duval X, Descatoire V, Hénin D, et al. Growth factor receptor expression in anal squamous lesions: modifications associated with oncogenic human papillomavirus and human immunodeficiency virus. *Hum Pathol.* 2009 Nov;40(11):1517–27.
 12. Wechsler EI, Tugizov S, Herrera R, Da Costa M, Palefsky JM. E5 can be expressed in anal cancer and leads to epidermal growth factor receptor-induced invasion in a human papillomavirus 16-transformed anal epithelial cell line. *J Gen Virol.* 2018 May;99(5):631–44.
 13. Deutsch E, Lemanski C, Pignon JP, Levy A, Delarochefordiere A, Martel-Lafay I, et al. Unexpected toxicity of cetuximab combined with conventional chemoradiotherapy in patients with locally advanced anal cancer: results of the UNICANCER ACCORD 16 phase II trial. *Ann Oncol.* 2013 Nov;24(11):2834–8.
 14. Levy A, Azria D, Pignon JP, Delarochefordiere A, Martel-Lafay I, Rio E, et al. Low response rate after cetuximab combined with conventional chemoradiotherapy in patients

- with locally advanced anal cancer: Long-term results of the UNICANCER ACCORD 16 phase II trial. *Radiother Oncol*. 2015 Mar;114(3):415–6.
15. Sparano JA, Lee JY, Palefsky J, Henry DH, Wachsman W, Rajdev L, et al. Cetuximab Plus Chemoradiotherapy for HIV-Associated Anal Carcinoma: A Phase II AIDS Malignancy Consortium Trial. *J Clin Oncol Off J Am Soc Clin Oncol*. 2017 Mar;35(7):727–33.
 16. Garg MK, Zhao F, Sparano JA, Palefsky J, Whittington R, Mitchell EP, et al. Cetuximab Plus Chemoradiotherapy in Immunocompetent Patients With Anal Carcinoma: A Phase II Eastern Cooperative Oncology Group–American College of Radiology Imaging Network Cancer Research Group Trial (E3205). *J Clin Oncol*. 2017 Mar;35(7):718–26.
 17. Casadei Gardini A, Passardi A, Fornaro L, Rosetti P, Valgiusti M, Ruscelli S, et al. Treatment of squamous cell carcinoma of the anal canal: A new strategies with anti-EGFR therapy and immunotherapy. *Crit Rev Oncol Hematol*. 2018 Mar;123:52–6.
 18. Vendrely V, Lemanski C, Gnep K, Barbier E, Hajbi FE, Lledo G, et al. Anti-epidermal growth factor receptor therapy in combination with chemoradiotherapy for the treatment of locally advanced anal canal carcinoma: Results of a phase I dose-escalation study with panitumumab (FFCD 0904). *Radiother Oncol*. 2019 Nov;140:84–9.
 19. ICRU. International Commission on Radiation Units and Measurements. Prescribing, recording, and reporting photon-beam intensity-modulated radiation therapy (IMRT). ICRU Report 83. *J ICRU*. 2010;1–106.
 20. Leon O, Guren MG, Radu C, Gunnlaugsson A, Johnsson A. Phase I study of cetuximab in combination with 5-fluorouracil, mitomycin C and radiotherapy in patients with locally advanced anal cancer. *Eur J Cancer*. 2015 Dec;51(18):2740–6.
 21. Faivre JC, Peiffert D, Vendrely V, Lemanski C, Hannoun-Levi JM, Mirabel X, et al. Prognostic factors of colostomy free survival in patients presenting with locally advanced anal canal carcinoma: A pooled analysis of two prospective trials (KANAL 2 and ACCORD 03). *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2018 Dec;129(3):463–70.
 22. Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappan J, et al. RTOG 0529: A Phase 2 Evaluation of Dose-Painted Intensity Modulated Radiation Therapy in Combination With 5-Fluorouracil and Mitomycin-C for the Reduction of Acute Morbidity in Carcinoma of the Anal Canal. *Int J Radiat Oncol*. 2013 May;86(1):27–33.
 23. Rivin Del Campo E, Matzinger O, Haustermans K, Peiffert D, Glynne-Jones R, Winter KA, et al. Pooled Analysis of external-beam RADiotherapy parameters in phase II and phase III trials in radiochemotherapy in Anal Cancer (PARADAC). *Eur J Cancer Oxf Engl 1990*. 2019 Nov;121:130–43.
 24. Glynne-Jones R, Sebag-Montefiore D, Adams R, McDonald A, Gollins S, James R, et al. “Mind the gap”--the impact of variations in the duration of the treatment gap and overall treatment time in the first UK Anal Cancer Trial (ACT I). *Int J Radiat Oncol Biol Phys*. 2011;81(5):1488–94.
 25. Sebag-Montefiore D, Adams R, Bell S, Berkman L, Gilbert DC, Glynne-Jones R, et al. The Development of an Umbrella Trial (PLATO) to Address Radiation Therapy Dose

- Questions in the Locoregional Management of Squamous Cell Carcinoma of the Anus. *Int J Radiat Oncol*. 2016 Oct;96(2):E164–5.
26. Muirhead R, Drinkwater K, O’Cathail SM, Adams R, Glynne-Jones R, Harrison M, et al. Initial Results from the Royal College of Radiologists’ UK National Audit of Anal Cancer Radiotherapy 2015. *Clin Oncol*. 2017 Mar;29(3):188–97.
 27. Martin D, Schreckenbach T, Ziegler P, Filmann N, Kalinauskaite G, Tinhofer I, et al. Evaluation of prognostic factors after primary chemoradiotherapy of anal cancer: A multicenter study of the German Cancer Consortium-Radiation Oncology Group (DKTK-ROG). *Radiother Oncol*. 2022 Feb;167:233–8.
 28. Feliu J, Garcia-Carbonero R, Capdevila J, Guasch I, Alonso-Orduna V, Lopez C, et al. VITAL phase 2 study: Upfront 5-fluorouracil, mitomycin-C, panitumumab and radiotherapy treatment in nonmetastatic squamous cell carcinomas of the anal canal (GEMCAD 09-02). *Cancer Med*. 2020 Feb;9(3):1008–16.
 29. Glynne-Jones R, Glynne-Jones R, James R, Meadows H, Begum R, Cunningham D, et al. Optimum time to assess complete clinical response (CR) following chemoradiation (CRT) using mitomycin (MMC) or cisplatin (CisP), with or without maintenance CisP/5FU in squamous cell carcinoma of the anus: Results of ACT II. [Internet]. *J Clin Oncol* 30, 2012 (suppl; abstr 4004). 2012. Available from: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=114&abstractID=98280
 30. James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, 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*. 2013 May;14(6):516–24.
 31. Vendrely V, Lemanski C, Pommier P, LE Malicot K, Saint A, Rivin Del Campo E, et al. Treatment, outcome, and prognostic factors in non-metastatic anal cancer: The French nationwide cohort study FFCD-ANABASE. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2023 Feb 21;183:109542.

Figure legends

Figure 1: Treatment protocol.

Treatment consisted in 2 radiotherapy (RT) periods (45Gy in 5 weeks and a RT boost of 20Gy in 2 weeks with concomitant chemotherapy (CT) sessions of 5FU/MMC at RT weeks 1 and 5 :

MMC: 10 mg/m² at J1 and J29

5FU: 400 mg/m² from J1 to J4 and from J29 to J32

Panitumumab: 3 mg/kg on RT weeks 1, 3, 5 and 7

Doses were assessed from previous phase 1 trial

Figure 1

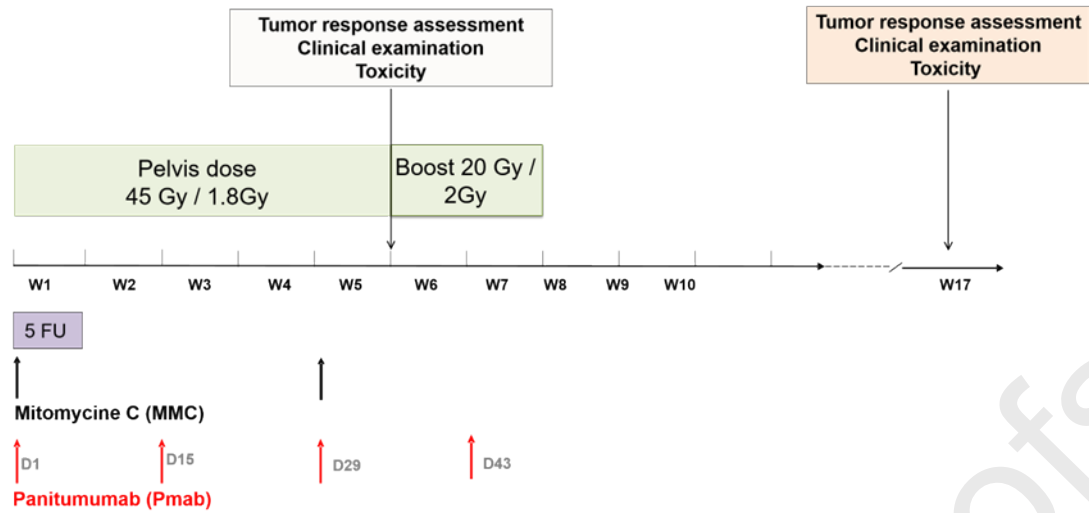
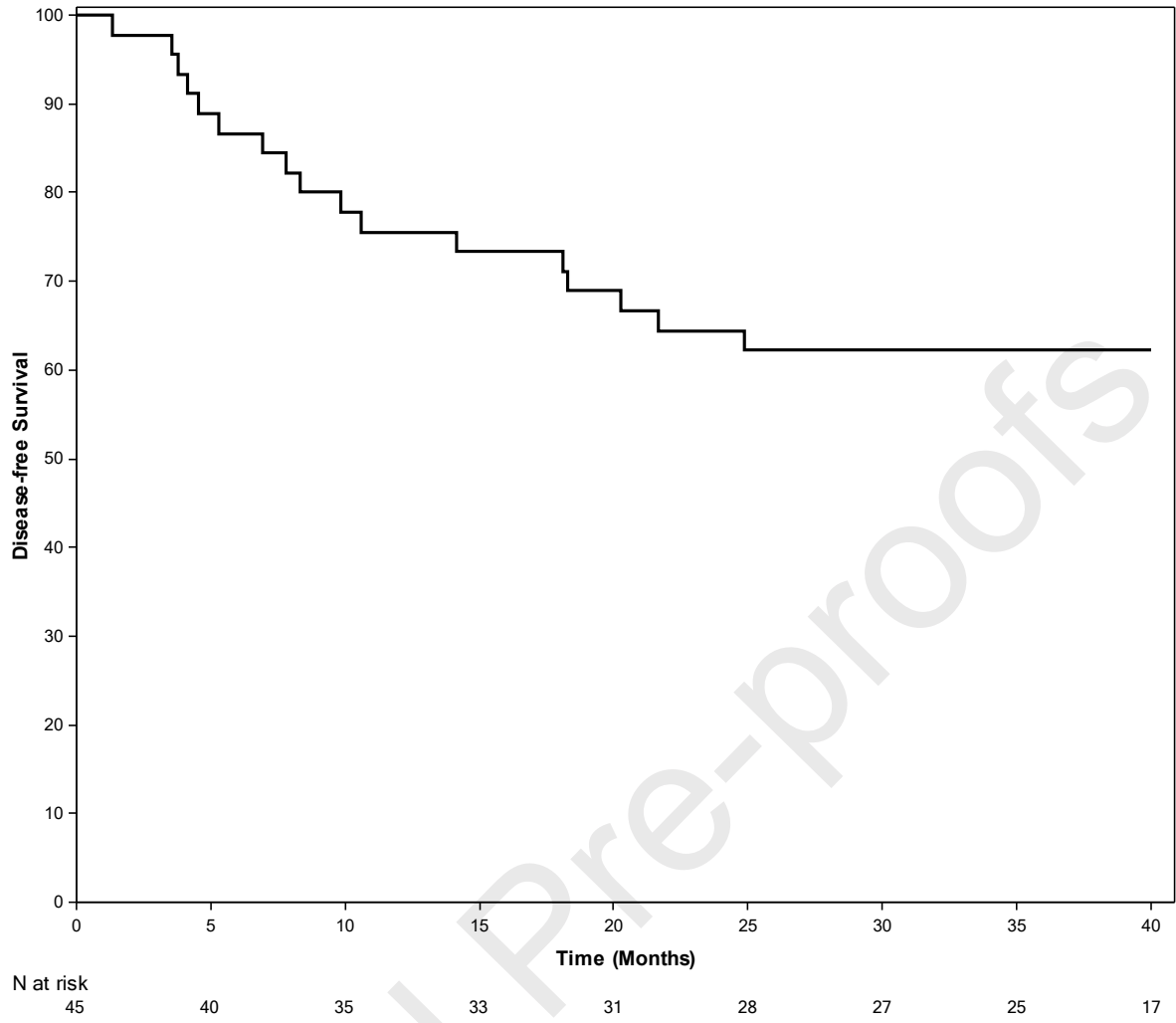
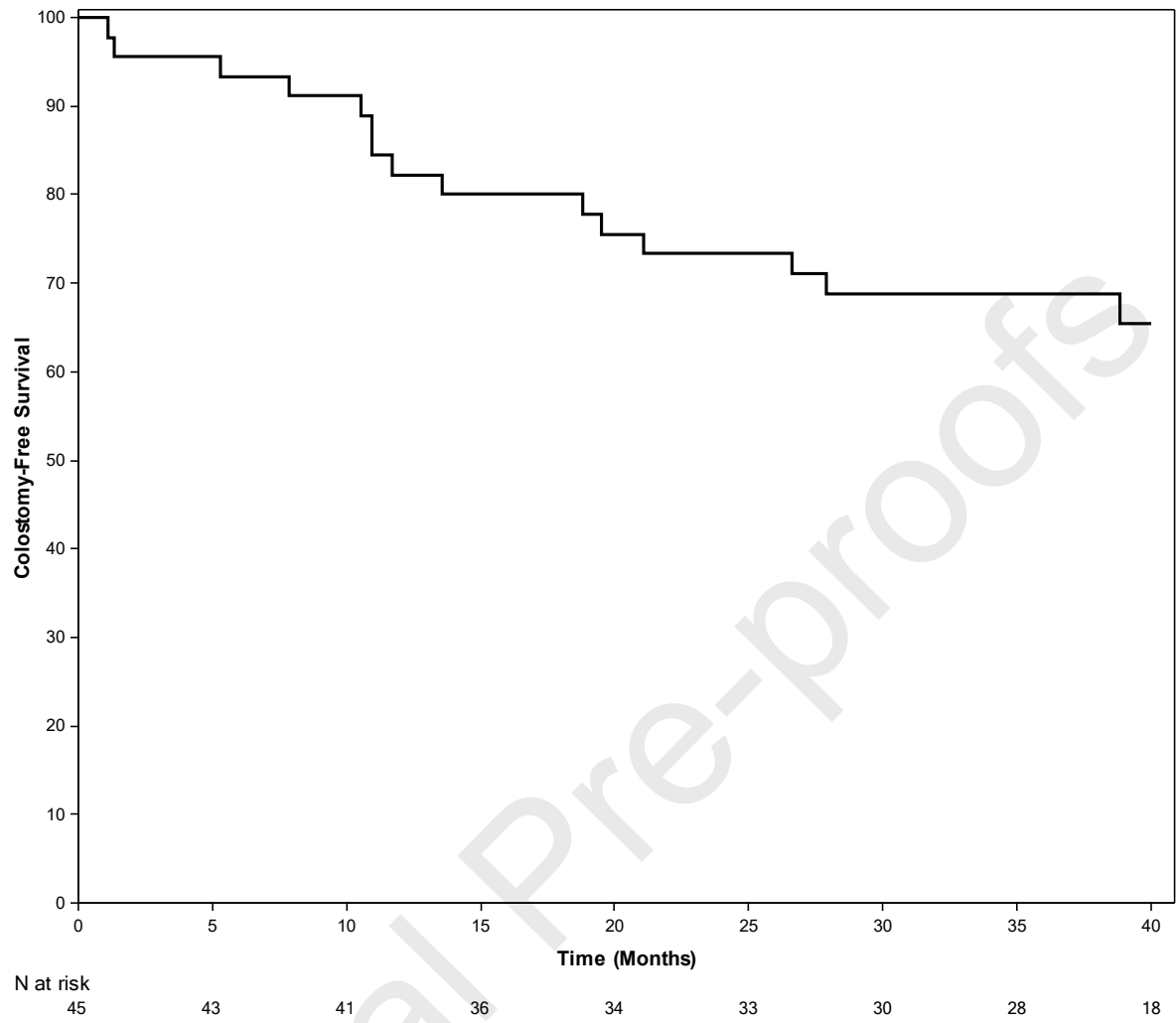


Figure 2: Kaplan-Meier estimates of disease-free survival (A), colostomy-free survival (B) and overall survival (C)

Figure 2
A



B



C

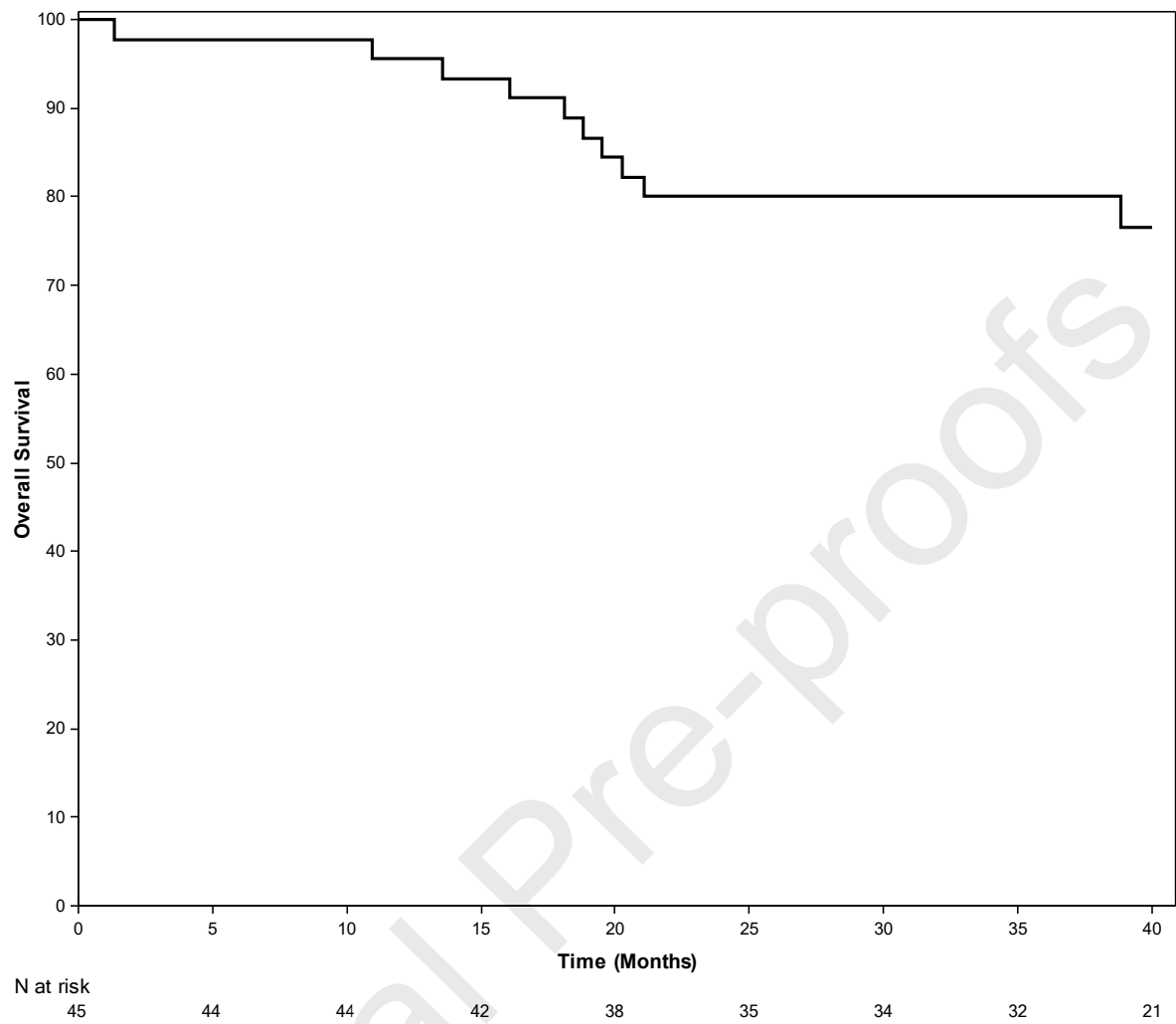


Table 1: Patient characteristics

		Median (range) Or N (%)
Gender	Male	9 (20)
	Female	36 (80)
Median age, years (range)		60 (41.5-81.0)
HIV status (N=43)	Positive	3 (6.7)
	Negative	40 (88.9)
	Unknown	2 (4.4)
ECOG PS status	0	31 (68.9)
	1	14 (31.1)

Median tumor size, cm (range)		4.5 (1.3 ; 9.7)
T-stage	T1	1 (2.2)
	T2	19 (42.2)
	T3	18 (40.0)
	T4	7 (15.6)
N-stage	N0	13 (28.9)
	N1/N2/N3	32 (71.1)

Table 2: Tolerance

	Related to treatment		
	Gr 3	Gr 4	Gr 5
Maximal Toxicities	N(%)	N(%)	N(%)
At least one toxicity	40 (88.9)	17 (37.8)	1 (2.2)
Acute coronary syndrom	1 (2.2)		
Vertigo	1 (2.2)		
Dermatitis	12 (26.6)		
Vaginal and perineal mucitis	8 (17.8)		
Diarrhea and rectitis	13 (28.9)	1 (2.2)	
Lymphopenia	16 (35.6)	17 (37.8)	
Neutropenia	5 (11.1)		
Mesenteric ischemia			1 (2.2)
Sepsis		2 (4.4)	
Anorexia	2 (4.4)		
Asthenia	5 (11.1)		

Conflict of interest

Pr Véronique Vendrely declare consulting fees and lectures honorarias from BMS, Servier and AMGEN. Pr Astrid Lièvre declare consulting fees and honorarias from AAA, Astellas, BMS, Incyte, Pierre Fabre, Servier, Amgen, Bayer, Leo-Pharma, Novartis, Mylan, Sandoz, Sanofi and Viartis. Pr Thomas Aparicion declare consulting fees and lectures honoraria from Pierre Fabre, Amgen, Servier, MSD and BMS. Pr Côme Lepage declare consulting fees from Amgen, AAA, Pierre Fabre and Ipsen.

The others authors declare no competing interests.