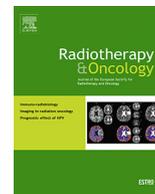




Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Original Article

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)



Véronique Vendrely^{a,*}, Claire Lemanski^b, Khemara Gnep^c, Emilie Barbier^d, Farid El Hajbi^e, Gerard Lledo^f, Laëtitia Dahan^g, Eric Terrebonne^a, Sylvain Manfredi^c, Xavier Mirabel^e, Vincent Mammari^f, Didier Cowen^g, Come Lepage^h, Thomas Aparicioⁱ, for FFCD investigators/Collaborators¹

^aCHU de Bordeaux, Pessac; ^bInstitut Regional du Cancer Montpellier; ^cCentre Eugene Marquis, Rennes; ^dBiostatistics, FFCD, EPICAD INSERM LNC-UMR 1231, University of Burgundy and Franche Comté, Dijon; ^eCentre Oscar Lambret, Lille; ^fHopital prive Jean Mermoz, Lyon; ^gCHU La Timone, Marseille; ^hEPICAD INSERM LNC-UMR 1231 University of Burgundy and Franche Comté, Dijon; and ⁱCHU APHP – Saint-Louis, Paris, France

ARTICLE INFO

Article history:

Received 20 December 2018
Received in revised form 14 May 2019
Accepted 15 May 2019
Available online 8 June 2019

Keywords:

Anal cancer
Squamous cell carcinoma
Epidermal growth factor receptor
Panitumumab
Chemoradiotherapy
Immunotherapy

ABSTRACT

Background and purpose: Standard treatment of epidermoid anal cancer is 5-fluorouracil (5FU) and mitomycin C (MMC) based chemoradiotherapy (CRT). This phase I study aims to evaluate the addition of panitumumab (Pmab) to CRT and to determine the maximum tolerated dose (MTD) of Pmab and 5-FU in combination with CRT.

Materials and methods: Immunocompetent patients with locally advanced tumour without metastases (Stage T2, T3 or T4, whatever N stage; Stage N1–N3 whatever T stage) followed two RT periods (45 Gy in 5 weeks and 20 Gy in 2 weeks, separated by a 2-week break) with concomitant CT sessions of 5FU/MMC at RT weeks 1, 5 and 8. Pmab was administered on RT weeks 1, 3, 5, 8 and 10 according to a pre-defined dose escalation schedule.

Results: Ten patients were enrolled. One was excluded due to unmet dose constraints respect. Three patients received dose level (DL) 0 (Pmab 3 mg/kg + 5FU 600 mg/m²/day) and six received DL-1 (Pmab 3 mg/kg + 5FU 400 mg/m²/day). Dose-limiting toxicities occurred in all patients at DL 0 and 2 at DL-1. Most common grade 3–4 toxicities observed at DL 0 were haematologic (100%), dermatitis (67%), and anaemia (67%). No death occurred. Four months after ending CRT, five and two patients had a local complete response and a partial response, respectively. One patient had a colostomy with abdomino-perineal amputation due to a tumour recurrence.

Conclusions: The MTD is 5FU at 400 mg/m²/day, MMC at 10 mg/m² and Pmab at 3 mg/kg. The effect of the MTD on tumour response is evaluated in the phase 2 study.

© 2019 Elsevier B.V. All rights reserved. Radiotherapy and Oncology 140 (2019) 84–89

Abbreviations: CT, chemotherapy; CRT, chemoradiotherapy; CTV, clinical tumour volume; DL, dose level; DLT, dose-limiting toxicities; EGFR, epidermal growth factor receptor; 5FU, 5 fluorouracil; GTV, gross tumour 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 tumour volume; RT, radiotherapy.

* Corresponding author at: Service de radiothérapie, Hôpital Haut-Lévêque, Avenue de Magellan, 33604 Pessac Cedex, France.

E-mail address: veronique.vendrely@chu-bordeaux.fr (V. Vendrely).

¹ Please see the [Supplementary Appendix](#) for a list of the FFCD 0904 Investigators/Collaborators.

<https://doi.org/10.1016/j.radonc.2019.05.018>

0167-8140/© 2019 Elsevier B.V. All rights reserved.

Epidermoid anal cancer, a rare disease, had increased annual incidence in the recent decades due to high prevalence of HPV and HIV infections [1,2]. Chemoradiotherapy (CRT) is the current standard of care achieving a good loco-regional control and preserving anal function to avoid a colostomy and to maintain good quality of life in patients with locally limited tumours. While there is no global consensus in the radiotherapy (RT) dose to be delivered, French Intergroup Clinical Practice guidelines recommend total doses of 59.4–65 Gy to the tumour [2,3]. 5-Fluorouracil (5-FU) infusion plus mitomycin C (MMC) intravenous bolus combined with RT significantly improved local control and survival outcomes in randomized controlled trials [4–8]. CRT led to a 32% higher

colostomy-free rate, and clinical and pathological complete response reached 80% and 83%, respectively [5–7]. The observed effects persisted within long-term follow-up [9–11]. However, recurrence-free and global survival results still remain disappointing for locally advanced tumours thus leading to conduct more treatment intensification trials.

The epidermal growth factor receptor (EGFR) is overexpressed in the squamous cell carcinomas of the anal canal [12] and is co-expressed with c-Met and VEGFR1 in anal cancers especially in HIV-positive individuals [13]. EGFR overexpression was recently identified in human HPV-16-immortalized anal epithelial cell line [14]. These observations suggest EGFR-based targeted therapies as a potential candidate for combined modality treatment of anal cancers [15]. The addition of an anti-EGFR targeted therapy, such as panitumumab (Pmab) or cetuximab to standard CT resulted in an acceptable toxicity profile and a clinically relevant improvement of survival outcomes in patients with locally advanced colorectal cancer [16,17] and in patients with resectable oesophageal carcinoma [18]. However, results of the UNICANCER ACCORD 16 trial with cetuximab associated with CRT showed unexpected acute toxic effects and failure to prove clinical benefit on survival outcomes [19,20]. Substantial toxicities of cetuximab combined with CRT were further observed in immune-competent patients and in HIV positive patients with anal carcinoma [21,22], thus confirming the toxicity of cetuximab-based CRT in patients with locally advanced anal cancer. As cetuximab and Pmab have different signalling pathways, different toxicity profiles may be expected [15]. Pmab could be appropriately used in combination to CRT for the treatment of epidermoid anal cancer. This phase 1 study aims to evaluate the tolerability and the maximum tolerated dose (MTD) of Pmab added to standard CRT for the treatment of locally advanced carcinoma of the anal canal.

Material and methods

Patient eligibility and study design

This open prospective multicenter single-arm phase I study included adult males or females, with histologically proven squamous cell carcinoma of the anal canal, with locally advanced tumour without metastases (AJCC TNM Stage T2 > 3 cm or T3 or T4, whatever N stage; Stage N1–N3 whatever T stage [23]), WHO

general health status 0 or 1, life expectancy above 3 months, and blood CD4+ ≥400 cells/mm³ in HIV positive individuals only. Patients with previous anti-EGFR treatment, or previous pelvic RT, or other previous malignancy within 5 past years, or known or suspected central nervous system metastasis were not included (full list of exclusion criteria in Table A.1). All eligible patients had to follow the two RT periods (5 and 2 weeks) and the CT sessions (Fig. 1).

All participating patients signed an informed consent. The study protocol was approved by the Ethics Committee at site. 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.

Radiotherapy

Conformational 3D RT or intensity-modulated radiation therapy (IMRT) was planned into two sequences separated by a 2-week 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 tumour and involved nodes. Delineation of pelvic clinical target volume (CTV) included external and internal iliac, mesorectal, presacral and inguinal nodes as well as ischio-rectal fossae. The gross tumour volume (GTV) included the anal tumour and the involved nodes that were to receive the total dose of 65 Gy (pelvic + boost doses). Anisotropic 10 mm margin was added to the CTV and to the GTV in order to define the planning target volume (PTV) for the first and second sequences respectively. Contouring of target volumes used initial examinations, imaging and endoscopy findings. Dose prescriptions followed the International Commission on Radiological Units 62 guidelines [24]. Dose constraints were organ dependent ([25,26], see Appendix Table A.2.). 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. In case of grade 3–4 toxicities, RT delivery was delayed until toxicity grade was ≤grade 2.

Standard CT plus Panitumumab

All patients received a combination of 5FU, MMC and Pmab. During the first RT sequence, patients received a continuous

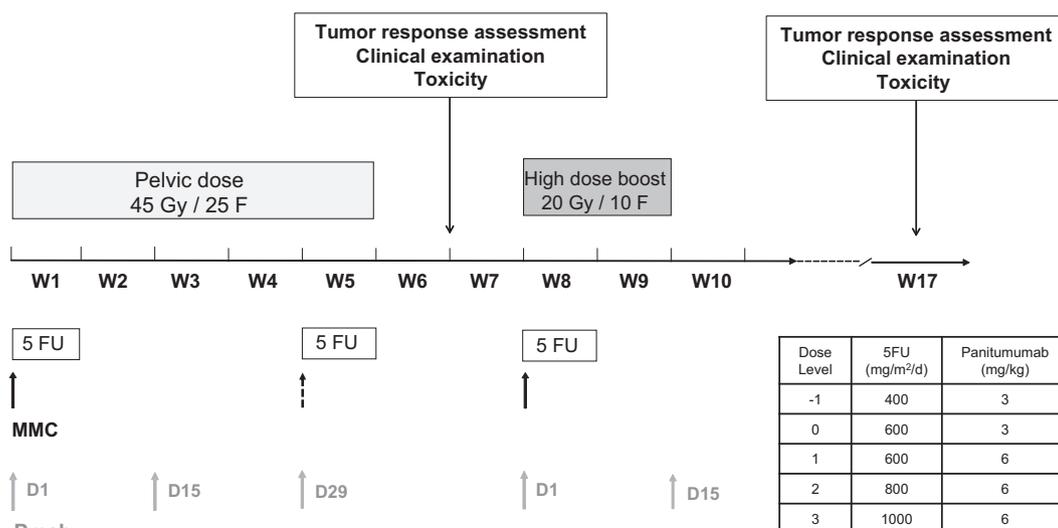


Fig. 1. Schedule of chemoradiotherapy. The CRT modality applied to each dose-escalation level. D: Day, F: Fraction, 5FU: 5 fluorouracil, IMRT: intensity-modulated radiation therapy, MMC: mitomycin, W: Week.

intravenous infusion of 5FU on Days 1–4 and Days 29–32 and MMC (10 mg/m²) as a bolus on Days 1 and 29, plus Pmab by infusion on Days 1, 15 and 29. During the additional RT boost sequence, patients received 5FU on Days 1–4, MMC on Day 1 and Pmab on Days 1 and 15. 5FU and Pmab doses were defined according to a dose escalation process with five DL. Two Pmab doses (3 mg/kg and 6 mg/kg) and four 5FU doses (400, 600, 800 and 1000 mg/m²/day) were to be tested (Fig. 1). The MTD corresponds to the preceding DL defining the dose-limiting toxicities (DLT). Patients' individual data were reviewed by an Independent Safety Monitoring Committee (ISMC) defining DLT and MTD, and made decision for escalating to the upper DL. Dose modifications of 5FU, MMC and Pmab were allowed for toxicities observed 48 hours before or during the injections (see Appendix Table A.3). The CT modality initially planned was modified due to the acute toxicity observed with DL 0. A decrease in 5FU dose from 600 to 400 mg/m²/day and suppression of MMC injection during RT boost sequence were used at DL-1. 5FU and MMC treatments weren't discontinued in case of skin toxicities related to Pmab. 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.

Dose-limiting toxicity and all toxicities assessment

DLT were defined as any specific toxicities occurring during CRT plus Pmab and within 30 days after the end of the RT, or after treatment withdrawal. Specific toxicities were febrile neutropenia, neutropenic infection, neutropenia (grade 4 lasting ≥ 7 days), thrombocytopenia (grade 3+ lasting ≥ 7 days, and grade 4), nausea (grade 3), vomiting and diarrhoea despite appropriate concomitant treatment, fatigue (grade 3 lasting ≥ 7 days and grade 4), skin toxicity (grade 3+), any other grade 3 toxicity (except alopecia), incomplete first CRT period (patient received $<75\%$ of planned doses), CT or RT delayed for ≥ 7 days due to toxicities. All toxicities were assessed using Clinical Trials Criteria for Adverse Events (CTCAE) version 4.0.

Patient follow-up and data assessment

Patient health, weight assessments, CRT tolerability, laboratory assessments and clinical examinations were collected 48 h before each CT session, 6 weeks after the first CT and 8 weeks after the last Pmab administration. Proctoscopy results were reviewed before the first CT session and 6 weeks after. Toxicity, patient health, weight and toxicities were evaluated once a week during the RT periods. Haematology, platelet counts and electrolytes were evaluated before each Pmab infusion. Tumour response evaluations by pelvic MRI and/or rectal echo-endoscopy, and thoracic-abdomino-pelvic CT were performed 6 weeks after the beginning of treatment, during the treatment break, 8 weeks and, 4 months after end of treatment, then every 4 months for 2 years and every 6 months for 3 years.

Statistical methods

The primary study endpoint was to evaluate DLT and MTD of Pmab and 5FU added to standard CRT. This was a dose escalation study using a 3 + 3 design. A minimum of 9 and a maximum of 24 patients were required, corresponding to a minimum of 3 patients per DL (and 6 at the recommended dose). The tumour response to treatment was evaluated as a secondary endpoint at 6, 8 and 16 weeks after last RT day. Qualitative and continuous variables were described using usual descriptive statistics (SAS, Version 9.4): numbers, percentages and medians with ranges (min–max).

Results

Ten patients were enrolled in 6 centres between June 2012 and March 2015. Three patients were treated at DL 0 and 6 patients at DL-1. One patient included in the DL-1 group was excluded before treatment due to unmet dose constraints. Median age was 57 years (Table 1). No colostomy was performed prior to first CRT. All patients were HIV and HBs negative. Tumour and nodal stages were T3 or N1, respectively, for most of patients. Median tumour diameter was 40 mm (range 15–80).

All patients had a total RT dose of 65 Gy delivered in 35 fractions by IMRT (7 patients) or 3D RT (2 patients, No. 2 DL 0 and No. 8 DL-1). Two patients (No. 1 DL 0 and No. 8 DL-1) had a daily RT cancelled due to toxicities. At DL 0, patient No. 1 had no CT session at week 5 due a non-haematologic toxicity leading to a decrease in 5FU and MMC doses at week 8 (Table 2). Febrile neutropenia was reported at week 4 and aggravated to grade 3 neutropenia at week 7. Patient No. 2 had reduced 5FU and MMC doses at week 8 and then discontinued CT due to toxicities related to both CT and RT. This patient had thrombocytopenia at week 5, episodes of severe diarrhoea at week 5 and 10, and dermatitis at week 5. Dermatitis was downgraded to 1 at weeks 8, 9 and 10. Patient No. 3 had a reduced 5FU dose at week 8 due to toxicities. Anal pain, cystitis, proctitis and dermatitis were all graded 3 at week 5. At week 8 and 10, anal pain was downgraded to 1, cystitis to grade 2, proctitis to grade 1 and dermatitis to grade 1.

All six patients treated at the DL-1 had Pmab injections as planned to the protocol (Table 3). Only 2 patients had further reduction in the 5FU dose due to toxicities. Patient No. 4 had 5FU infused at a dose 300 mg/m²/day at week 5 and at week 8, due to non-haematologic toxicity. Fatigue (grade 3) and anorexia (grade 3) were reported as DLT at week 4 and week 5, respectively. Patient No. 6 had the 5FU dose reduced due to a haematologic toxicity at week 3. Lymphopenia (grade 3) not leading to a dose modification were reported for patient No. 7 at weeks 1 and 2. Anal pain (grade 3) was reported at week 3.

All patients at each DL reported at least one toxicity event of grade 1–2 (mainly diarrhoea, nausea, platelet count decreased, white blood cell, anaemia, dermatitis and fatigue, Table A.4 in Appendix). At DL 0, all patients experienced at least one grade 3–4 toxicity: white blood cell decreased (all patients), neutrophil count decreased (all patients), anaemia (2 patients), dermatitis (2 patients). At DL-1, 3 patients experienced at least one grade 3–4 toxicity: lymphocyte count decreased (2 patients), anorexia (1 patient) and fatigue (1 patient).

At 6 weeks after the beginning of CRT, complete response (CR) and partial response (PR) were achieved for one patient, each, treated at DL 0 (Table 4). PR and stable disease (SD) were achieved for 4 and 2 patients, respectively at DL-1. At 16 weeks after the end of CRT, all patients treated at DL 0 had a CR. At DL-1, CR was achieved in one patient who had a PR evaluated 8 weeks after last CRT. Two

Table 1
Patient and tumour characteristics at baseline.

	Nb. Patients (N = 9)	%
Female/male	7/2	78/22
Median age, range (years)	57.4 (52.0–71.1)	
Median weight, range (Kg)	62.8 (48–87)	
WHO general health		
0/1	6/3	67/33
Tumour stage		
T2/T3/T4	1/6/2	11/67/22
Nodal stage		
N0/N1/N2/N3	2/4/2/1	22/45/22/11
Median tumour size, range (mm)	40, 15–80	

WHO: World Health Organisation.

Table 2

Treatment outcomes at dose level 0.

Patient No.	RT completed	CT Session Week No.	Pmab Dose (mg/kg)	5FU Dose (mg/m ² /day)	MMC Dose (mg/m ²)	Reason for dose modification	DLT
1	yes*	1	3	150	10	Wrong CT prescription	Febrile neutropenia, neutropenia (G3), incomplete 1st CT
		3	3	NA	NA		
		5	0	0	0		
		8	3	113	8		
2	yes	10	3	NA	NA	Non-haematologic and haematologic toxicities	Thrombocytopenia (G3), diarrhoea (G3), dermatitis (G3)
		1	3	600	10		
		3	3	NA	NA		
		5	3	600	10		
		8	3	400	8		
3	yes	10	0	NA	NA	Non-haematologic tox.	Anal pain (G3), dermatitis (G3), cystitis (G3), proctitis (G3)
		1	3	600	10		
		3	3	NA	NA		
		5	3	600	10		
3		8	3	450	10	Non-haematologic DLT	
		10	3	NA	NA		

* One daily RT was cancelled due to toxicity. CT: chemotherapy, DLT: dose-limiting toxicities, FU: fluorouracil, MMC: mitomycin C, NA: not applicable, Pmab: Panitumumab, RT: radiotherapy, tox: toxicity.

Table 3

Treatment outcomes at dose level-1.

Patient No.	RT completed	CT Session Week No.	Pmab dose (mg/kg)	5FU dose (mg/m ² /day)	MMC dose (mg/m ²)	Reason for dose modification	DLT
4	yes	1	3	400	10	Non-haematologic tox.	Fatigue (G3), anorexia (G3)
		3	3	NA	NA		
		5	3	300	NA		
		8	3	300	10		
		10	3	NA	NA		
6	yes*	1	3	400	10	Non-haematologic tox.	None
		3	3	NA	NA		
		5	3	400	NA		
		8	3	302	10		
		10	3	NA	NA		
7	yes	1	3	400	10	No dose modification	Lymphopenia episodes (G3), anal pain (G3)
		3	3	NA	NA		
		5	3	400	NA		
		8	3	400	10		
		10	3	NA	NA		
8	yes*	1	3	400	10	No dose modification	None
		3	3	NA	NA		
		5	3	400	NA		
		8	3	400	10		
		10	3	NA	NA		
9	yes	1	3	400	10	Haematologic tox.	None
		3	3	NA	NA		
		5	3	300	NA		
		8	3	300	10		
		10	3	NA	NA		
10	yes	1	3	400	10	No dose modification	None
		3	3	NA	NA		
		5	3	400	NA		
		8	3	400	10		
		10	3	NA	NA		

* Patients No. 6 and No. 8 received 45.7 Gy and 45.3 Gy respectively at PVT1. CT: chemotherapy, DLT: dose-limiting toxicities, FU: fluorouracil, MMC: mitomycin C, NA: not applicable, Pmab: Panitumumab, RT: radiotherapy, tox.: toxicity.

patients remained with a PR. Based on a last data update done in March 2017, patient No. 8 (DL-1) with PR at 16 weeks had an abdomino-perineal amputation 9 months after last CT session due to a tumour recurrence. No death was reported. Patient No. 2 (DL 0) with CR at 16 weeks had a partial internal lateral sphincteromyotomy 6 months after last CT session because of a persistent rectovaginal fistula.

Discussion

This phase 1 study evaluated the tolerability and safety of panitumumab added to 5FU/MMC plus RT in 9 patients with locally advanced carcinoma of the anal canal. The main objective determined the MTD of Pmab and 5FU, combined to standard MMC and RT modalities. The RT modality included a high dose boost

Table 4
Tumour response.

Patient No.	Dose level	Tumour response		
		6 weeks [*]	8 weeks ^{**}	16 weeks ^{**}
1	0	PR	CR	CR
2	0	CR	CR	CR
3	0	Not evaluable	PR	CR
4	-1	SD	PR	-
6	-1	PR	CR	CR
7	-1	SD	PR	PR
8	-1	PR	PR	PR
9	-1	PR	PR	CR
10	-1	PR	PR	Not evaluable [†]

^{*} After beginning of CRT.

^{**} after the end of CRT.

[†] Due to the presence of a recto-vaginal fistula. CR: complete response (all lesions disappeared in all examinations), PR: partial response (tumour size decreased by at least 30% in MRI evaluation or a significant decrease in clinical examination), SD: stable disease (no progression [i.e., at least a 20% increase in tumour size or a significant increase in MRI evaluation or a significant increase in clinical examination]), or no CR or no PR.

administered after a 2-week interruption of the CRT leading to a total dose of 65 Gy. Even if the dose intensification schedule of the ACCORD 03 trial didn't demonstrate 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 [27].

The low number of dose limiting toxicities observed at DL-1 established the MTD as 5FU continuous infusion 400 mg/m²/day on RT weeks 1, 5 and 8, MMC infusion 10 mg/m² on Day 1 of each RT period, and Pmab infusion on Days 1, 15 and 29 of standard RT period and Days 1 and 15 of the boost RT period. Non-haematologic toxicities (dermatitis, anal pain) were the frequently reported DLT. As all patients at DL 0 experienced one or more DLT, a decrease in 5FU dose from 600 to 400 mg/m²/day, 2 injections of MMC instead of 3 and Pmab at 3 mg/kg were recommended for use at DL-1. Such adaptation led to a relevant reduction in the DLT number, with only 2 out of 6 patients experiencing DLT (fatigue, anorexia, lymphopenia, anal pain) at DL-1. A lower general toxicity was also observed at this DL with only half of patients experiencing grade 3–4 toxicity (vs. all at DL 0).

The toxicity and efficacy of cetuximab added to 5FU/MMC and RT were firstly reported in a phase 1 study including 13 patients with locally advanced anal cancer [28]. Patients received a weekly cetuximab standard dose starting 1 week before CRT and for 6 weeks. 5FU/MMC were administered concomitantly on RT weeks 1 and 5, according to a predefined dose escalation, similarly to the CRT design of Olivatto et al. [29] The high toxicity profile of cetuximab and failure to show a relevant benefit on survival outcomes were also confirmed with the long term results of the Unicancer ACCORD 16 trial [20]. Three out of 11 patients had dose-limiting toxicity events (diarrhoea, febrile neutropenia and thrombocytopenia) at the dose level 1. Dermatitis (63%), haematologic toxicity (54%), and diarrhoea (36%) were the most common grade 3–4 toxicities. A less favourable toxicity profile was further evidenced in the phase 2 E3205 study evaluating cetuximab with cisplatin/5FU [19]. In this study, 32% of patients had grade 4 toxicities (mainly neutropenia and infection) and 5% (3 patients) died for treatment-related events. A similar rate of treatment-related deaths was observed in HIV positive patients receiving the same CRT regimen as in the study of Garg et al. [21].

In our study evaluating Pmab no patient had a treatment related death. Grade 3–4 toxicities were experienced by 67% of patients, with a high frequency at DL 0. The starting dose level considering 3 infusions of 5FU 600 mg/m² plus 3 injections of MMC and 5 injections of Pmab 3 mg/kg concomitant to RT periods as designed in the protocol was too ambitious and led to a high rate

of DLT and severe haematologic toxicities. After ISMC decision, DL-1 modality was adapted with the suppression of the interim MMC injection at CT on week 5, plus a reduction in the 5-FU dose by 33%. As a result, DLT and general toxicities were also reduced.

Our study has several limitations. First, the radiotherapy schedule included a break of 2 weeks between the standard and the RT dose boost, which may have reduced the clinical benefit as compared to a continuous RT schedule. Standard 3D RT conformal techniques have the disadvantage to prolong the treatment duration due to the frequent need for an interruption due to acute toxicity. Such treatment interruption could negatively impact CRT benefit [25]. Second, the planning technique varied between patients (3D RT vs IMRT) that would likely have some bearing on toxicity. At the initiation of this phase 1 study the French National Authority for Health guidelines recommending the use of IMRT in anal cancer treatment were not published and effective yet (published in 2015). In our phase 1 study, 2 patients only out of 9 had radiation dose delivered by 3D RT, which may limit the interpretation of the results with regard to the other patients treated with IMRT. All in all, the toxicity profile of these two patients was not different from the toxicity profile of the seven patients receiving IMRT, whatever the CT dose level. The ISMC then recommended the use of IMRT for all patients to be enrolled in the phase 2 study to limit the interruption between the two RT periods, to reduce the RT toxicity profile and to comply with the current French RT recommendations.

Based on the acceptable toxicity profile observed at the MTD, the ISMC favorably recommended the progression to the phase 2 study with substantial modifications of the CRT modality. The pelvic RT dose and dose boost were delivered consecutively using IMRT for all patients. Then, the CT modality was adapted with 5FU 400 mg/m² infusions on RT week 1 and 5, MMC 10 mg/m² injections on RT Days 1 and 29, and Pmab 3 mg/kg on RT Days 1, 15, 29 and 43. The safety surveillance was also reinforced with the inclusion of an interim analysis of the toxicity observed on 12 out of 45 patients. The phase 2 is currently ongoing for patients' follow-up. Tumour response rates, survival outcomes and safety results are expected in 2019.

At the selected MTD, Pmab administered concomitantly to 5FU/MMC showed a low toxicity profile. First efficacy results in terms of complete and partial tumour response rates observed 4 months after end of treatment are promising for the phase 2 study currently ongoing.

Financial support statement

AMGEN provided panitumumab treatment.

Declaration of Competing Interest

TA reported personal fees from Amgen outside the submitted work.

Acknowledgements

The authors acknowledge all sub-investigators and the clinical staff at each hospital for their active participation and contribution to the well-conduct of this study. We thank C. Foucher (Clin-sciences, Dijon, France) for writing and editing assistance of the manuscript. We thank K. Le Malicot, C. Montereymard, S. Etievant, S. Pierre, C. Choine, F. Guiliani, N. Lasmi, G. Arnould, N. Guiet, M. Maury-Negre, H. Fattouh, N. Le Provost, D. Gonzalez, and C. Girault for editing support. We thank la Ligue Contre le Cancer for their support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2019.05.018>.

References

- Jemal A, Simard EP, Dorell C, Noone AM, Markowitz LE, Kohler B, et al. Annual report to the nation on the status of cancer, 1975–2009, featuring the burden and trends in human papillomavirus (HPV)-associated cancers and HPV vaccination coverage levels. *J Natl Cancer Inst* 2013;105:175–201. <https://doi.org/10.1093/jnci/djs491>.
- Glynne-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A, Arnold D, European Society for Medical Oncology (ESMO), European Society of Surgical Oncology (ESSO), European Society of Radiotherapy and Oncology (ESTRO). Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Eur J Surg Oncol* 2014;40:1165–76. <https://doi.org/10.1016/j.ejso.2014.07.030>.
- 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, FFCO, GERCOR, UNICANCER, SFCD, SFED, SFRO, SNFCP). *Dig Liver Dis* 2017;49:831–40. <https://doi.org/10.1016/j.dld.2017.05.011>.
- Nigro ND, Seydel HG, Considine B, Vaitkevicius VK, Leichman L, Kinzie JJ. Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. *Cancer* 1983;51:1826–9.
- Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. *Lancet*. 1996;348:1049–54.
- Bartelink H, Roelofsens 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* 1997;15:2040–9.
- 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;14:2527–39.
- Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson 3rd AB, Thomas Jr CR, et al. Radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA* 2008;299:1914–21. <https://doi.org/10.1001/jama.299.16.1914>.
- 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;102:1123–8. <https://doi.org/10.1038/sj.bjc.6605605>.
- Gunderson LL, Winter KA, Ajani JA, Pedersen JE, Moughan J, Benson 3rd AB, 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* 2012;30:4344–51. <https://doi.org/10.1200/JCO.2012.43.8085>.
- 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;14:516–24. [https://doi.org/10.1016/S1470-2045\(13\)70086-X](https://doi.org/10.1016/S1470-2045(13)70086-X).
- 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* 2006;19:942–9.
- 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;40:1517–27. <https://doi.org/10.1016/j.humpath.2009.05.010>.
- 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;99:631–44. <https://doi.org/10.1099/jgv.0.001061>.
- 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;123:52–6. <https://doi.org/10.1016/j.critrevonc.2018.01.007>.
- Pinto C, Di Bisceglie M, Di Fabio F, Bochicchio A, Latiano T, Cordio S, et al. Phase II study of preoperative treatment with external radiotherapy plus panitumumab in low-risk, locally advanced rectal cancer (RaP Study/STAR-03). *Oncologist* 2018;23:912–8. <https://doi.org/10.1634/theoncologist.2017-0484>.
- Merx K, Martens UM, Kripp M, Hoehler T, Geissler M, Gaiser T, et al. Panitumumab in combination with preoperative radiation therapy in patients with locally advanced RAS wild-type rectal cancer: results of the multicenter explorative single-arm phase 2 study NEORIT. *Int J Radiat Oncol Biol Phys* 2017;99:867–75. <https://doi.org/10.1016/j.ijrobp.2017.06.2460>.
- Ruhstaller T, Thuss-Patience P, Hayoz S, Schacher S, Knorrnschild JR, Schneider A, et al. Neoadjuvant chemotherapy followed by chemoradiation and surgery with and without cetuximab in patients with resectable esophageal cancer: a randomized, open-label, phase III trial (SAKK 75/08). *Ann Oncol* 2018;29:1386–93. <https://doi.org/10.1093/annonc/mdy105>.
- 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;24:2834–8. <https://doi.org/10.1007/s00280-018-3556-1>.
- 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;114:415–6. <https://doi.org/10.1016/j.radonc.2015.02.008>.
- 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;35:718–26. <https://doi.org/10.1200/JCO.2016.69.1667>.
- Sparano JA, Lee JY, Palefsky J, Henry DH, Wachsman W, Rajdev L, et al. Plus chemoradiotherapy for HIV-associated anal carcinoma: a phase II AIDS malignancy consortium trial. *J Clin Oncol* 2017;35:727–33. <https://doi.org/10.1200/JCO.2016.69.1642>.
- Edge SB, Byrd DR, Compton CC, Fritz AG, Fl Greene, Trotti A, editors. *AJCC Cancer Staging Manual*. New York Dordrecht Heidelberg London: Springer; 2010. ISBN 978-0-387-88440-0.
- Myerson RJ, Garofalo MC, El Naqa I, Abrams RA, Apte A, Bosch WR, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. *Int J Radiat Oncol Biol Phys* 2009;74:824–30. <https://doi.org/10.1016/j.ijrobp.2008.08.070>.
- Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappen J, et al. 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 Biol Phys*. 2013;86:27–33. <https://doi.org/10.1016/j.ijrobp.2012.09.023>.
- Noël G, Antoni D, Barillot I, Chauvet B. Delineation of organs at risk and dose constraints. *Cancer Radiother* 2016;20:S36–60. <https://doi.org/10.1016/j.canrad.2016.07.032>.
- 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 carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. *J Clin Oncol* 2012;30:1941–8. <https://doi.org/10.1200/JCO.2011.35.4837>.
- 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;51:2740–6. <https://doi.org/10.1016/j.ejca.2015.08.029>.
- Olivatto LO, Vieira FM, Pereira BV, Victorino AP, Bezerra M, Araujo CM, et al. Phase 1 study of cetuximab in combination with 5-fluorouracil, cisplatin, and radiotherapy in patients with locally advanced anal canal carcinoma. *Cancer* 2013;119:2973–80. <https://doi.org/10.1002/cncr.28045>.