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Phase II Study of Preoperative Treatment with External Radiotherapy Plus Panitumumab in Low-Risk, Locally Advanced Rectal Cancer (RaP Study/STAR-03)

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Panitumumab • Radiotherapy • *KRAS* • Rectal cancer

ABSTRACT

Background. Treatment with fluoropyrimidines and concomitant long-course external radiotherapy (RTE) is the standard of care in locally advanced rectal cancer (LARC) preoperative chemoradiation. A randomized phase II study (RaP/STAR-03) was conducted that aimed to evaluate the activity and safety of the monoclonal antibody anti-epidermal growth factor receptor panitumumab as a single agent in combination with radiotherapy in low-risk LARC preoperative treatment.

Materials and Methods. Patients had adenocarcinoma of the mid-low rectum, cT3N− or cT2–T3N+, *KRAS* wild-type status, and negative circumferential radial margin. Panitumumab was administered concomitant to RTE. Rectal surgery was performed 6–8 weeks after the end of preoperative treatment. The adjuvant chemotherapy regimen was FOLFOX. The primary endpoint was the pathologic complete response (pCR) rate. The sample size was calculated using Simon's two-stage design. A pCR of 16% was considered to qualify the experimental treatment for further testing.

Results. Ninety-eight patients were enrolled in 13 Italian centers from October 2012 to October 2015. Three panitumumab infusions were administered in 92 (93.4%) patients. The RTE compliance was median dose 50.4 Gy; ≥28 fractions in 82 (83.7%) patients. Surgical treatment was performed in 92 (93.9%) patients, and no severe intraoperative complications were observed. A pCR was observed in 10 (10.9%) patients (95% confidence interval, 4.72%–17.07%). Pathological downstaging occurred in 45 (45.9%) patients. Grade 3 toxicities were observed in 22 (22.3%) patients, and the common adverse events were skin rash in 16 (16.3%) patients. No grade 4 toxicities were reported.

Conclusion. The pCR rate (our primary endpoint), at only 10.9%, did not reach the specified level considered suitable for further testing. However, the analysis showed a good toxicity profile and compliance to concomitant administration of panitumumab and RTE in preoperative treatment of LARC. The pCR evaluation in all wild-type *RAS* is ongoing. *The Oncologist* 2018;23:912–918

Implications for Practice: The aim of the RaP/STAR-03 study was to evaluate the activity and safety of monoclonal antibody anti-epidermal growth factor receptor (EGFR) panitumumab as a single agent without chemotherapy in low-risk, locally advanced rectal cancer (LARC) preoperative treatment. Nevertheless, the use of panitumumab in combination with radiotherapy in preoperative treatment in patients with *KRAS* wild type and low-risk LARC did not reach the pathologic complete response primary endpoint. This study showed a good toxicity profile and compliance to combination treatment. Further analysis of *NRAS* and *BRAF* on tissue and circulating levels of the EGFR ligands and vascular factors (soluble vascular endothelial growth factor, E-selectin) may provide insight on the potential molecular pathways involved in the anti-EGFR response.

BACKGROUND

Rectal cancer occurs in the bowel region below the peritoneal reflection, including approximately 15 cm of intestine above the anal verge, and it accounts for about 35% of the total colorectal cancer incidence in Europe [1]. Surgery is the cornerstone of rectal cancer treatment, but it still results in a high incidence of local recurrences (25%–40%) and distant metastases. Local recurrence from rectal cancer has substantially decreased over the last 30 years. The introduction of standardized surgery and total mesorectal excision have decreased the local recurrence rate to less than 10% and have increased survival [2].

Despite these substantial improvements, local control is far from optimal. First, the reduction in the local recurrence rates achieved with the introduction of total mesorectal excision (TME) technique has been particularly impressive in uncontrolled, small, single-institutional series (mainly testing the impact of TME in comparison with historical data with more conventional surgical techniques).

The pathologic complete response (pCR) rate has been considered a prognostic factor for patients with locally advanced rectal cancer (LARC) undergoing preoperative treatment, and pCR has been associated with favorable disease-free survival (DFS) and overall survival (OS) [3, 4].

More than 30 years ago, Moertel et al. [5] demonstrated that radiotherapy (RT) combined with fluorouracil significantly increased the OS of patients with LARC. Subsequently, several studies conducted by the European Organization for Research and Treatment of Cancer Radiotherapy Group [6] and the Fédération Francophone de Cancérologie Digestive [7] have confirmed the benefit of this combination in terms of complete pathologic tumor response (pT0) in the RT and RT combined with chemotherapy (CRT) groups (5.3% vs. 13.7%; $p < .0001$ and 3.6% vs. 11.4%; $p < .0001$), respectively.

Currently, preoperative fluoropyrimidine-based CRT followed by TME is the standard treatment in LARC tumors to enable surgery to be more effective and provide locoregional control and increase the pCR, but an improvement in OS [7–9] has not been shown.

Several randomized phase III trials (STAR-01, ACCORD 12/0405-Prodige2, NSABP R-04) evaluated the addition of oxaliplatin to preoperative fluoropyrimidine-based CRT, and of these, the preliminary results have not shown a significant effect on early pathological response [10–13], with the exception of the German CAO/ARO/AIO-04 study [14].

Furthermore, there was a great interest in the integration into RT and CRT protocols of biological agents such as anti-vascular endothelial growth factor (VEGF) monoclonal antibodies, considering that the inhibition of the VEGF signaling axis can act as a radiosensitizer for tumor-associated endothelial cells, thus inhibiting tumor neoangiogenesis and reducing vascular density [15]. Moreover, anti-VEGF agents can also lead to vascular normalization, decreasing tumor hypoxia and improving radiosensitivity. Nevertheless, the results of several phase I and II trials are not conclusive and do not definitively demonstrate a clear benefit from the addition of bevacizumab in terms of pCR or improved patient outcomes [16].

Another important membrane growth factor in several neoplasms among which rectal cancer is represented is epidermal growth factor receptor (EGFR), a transmembrane glycoprotein, which is a member of the tyrosine kinase growth factor receptor superfamily. EGFR represents an important therapeutic target in cancer and regulates cellular growth, survival, proliferation, and differentiation. In rectal cancer, EGFR is overexpressed in 50%–70% of primary tumors [17]. In patients with rectal cancer after preoperative chemoradiotherapy, EGFR overexpression is related to a decrease in the pathological response, disease-free survival and overall survival [18, 19].

Preliminary data suggest that an EGFR-targeted agent in combination with RT may be synergistic, as RT increases EGFR expression within tumor cells, while EGFR blockade sensitizes the cells to the effects of RT [20, 21]. In the setting of locally advanced head and neck cancer, the addition of cetuximab to RT has enhanced locoregional control and survival [22, 23]. Various mechanisms for this cetuximab synergistic activity have been proposed, including the inhibition of repopulation during the latter phase of radiotherapy [24, 25].

In our previous StarPan/STAR-02 study [26] the addition of panitumumab to chemoradiotherapy was evaluated, showing a higher pCR rate in patients with high-risk LARC, in comparison with the results of previous preoperative rectal cancer trials with anti-EGFR monoclonal antibodies. However, the combination treatment was associated with a very high incidence of grade 3–4 gastrointestinal toxicity. Because the integration of anti-EGFR monoclonal antibodies into preoperative treatments for rectal cancer is promising in terms of response rate, although there are high rates of toxicity, we conducted a randomized, phase II study to evaluate the efficacy and safety of panitumumab alone in combination with external beam radiotherapy as the preoperative regimen in low-risk LARC.

MATERIALS AND METHODS

Study Design and Patients

We conducted a multicenter phase II study approved by the local ethical committee, registered with the health authorities (EudraCT 2011-000649-20). The primary endpoint was pCR rate. Secondary endpoints were to assess safety, pathological downstaging, R0 (circumferential resection margin [CRM] >1 mm) resection rate, sphincter-saving surgery, time of DFS, OS, and correlation between biological and metabolic markers and pathological response.

The eligibility criteria included histologically proven rectal adenocarcinoma of the mid-low rectum (within 12 cm from the anal verge), wild-type *KRAS* gene status, Karnofsky performance status ≥70%, stage cT3N−M0 and cT2–3N+M0 (N+ stage is defined as ≥3 lymph nodes of diameter ≥0.5 cm measured by endorectal ultrasound or ≥1 lymph node of diameter ≥1 cm measured by magnetic resonance imaging [MRI]), no previous treatment with chemotherapy or radiation therapy, neutrophil count ≥1,500/µL, platelet count ≥100.000/µL, hemoglobin ≥9.0 g/dL, serum creatinine <1.5 × upper limit of normal (ULN), alanine aminotransferase and aspartate aminotransferase ≤2.5 × ULN, total bilirubin <1.5 × ULN, and signed written informed consent. Patients with distant metastases were excluded from the study.

The baseline evaluation included history, physical examination (including digital rectal examination), recording of concomitant medication, laboratory tests (hematology and clinical

chemistry, carcinoembryonic antigen, and cancer antigen 19.9), full colonoscopy, rigid rectoscopy, biopsy, endorectal ultrasound and/or pelvis magnetic resonance, and thorax and abdomen-pelvis computed tomography.

Eligible patients were enrolled and treated with the preoperative treatment with panitumumab, in combination with external pelvic radiotherapy, followed by surgery with TME and adjuvant chemotherapy with FOLFOX4. Panitumumab was administered by intravenous (IV) infusion at a dose of 6 mg/kg once every 2 weeks for three cycles in combination with radiotherapy. RT was delivered up to a dose of 5,040 cGy in daily fractions of 1.8 Gy on 5 consecutive days per week (day 1–day 38). 5–6 weeks after the end of preoperative treatment, the patients were restaged with rectal palpation and pelvic MRI. Rectal surgery with TME was performed 6–8 weeks after the end of preoperative treatment. A radical resection (R0) was defined as the removal of all macroscopic tumor tissue, no evidence of distant metastases, the absence of microscopic residual tumor, free resection margins, and lymphoadenectomy extending beyond the involved nodes at postoperative pathologic examination. A resection was judged as nonradical if a microscopic (R1) or macroscopic (R2) residual tumor (distance between the tumor and CRM $\leq$1 mm) was found. Furthermore, each specimen was classified using a tumor regression grade proposed by Dworak et al. [27]. Tumor downstaging was determined by comparing the pathologic stage with the baseline clinical TNM stage; pCR was defined as the absence of viable tumor cells in the primary tumor and lymph nodes (ypT0N0).

Patients who proceeded to rectal surgery received adjuvant chemotherapy with FOLFOX performed between a minimum of 4 weeks and a maximum of 6 weeks after rectal surgery for 12 cycles. The patients were treated in the adjuvant setting until completion of the chemotherapy regimen or until withdrawal of consent or unacceptable toxicities.

Statistical Analysis

The primary endpoint was the pCR rate after preoperative treatment. A pCR of 16% was considered to qualify the experimental treatment for further testing. The sample size was calculated using Simon's two-stage design. A pCR rate of $\leq$7% was ruled out as futile. The first stage required at least 3 patients out of 29 to have a confirmed pCR before proceeding to the second stage. In the second stage, 63 assessable patients could be added, and if a total of 11 or more patients achieved a confirmed pCR, then the primary endpoint would have been met. A maximum of 100 patients could be enrolled to ensure 92 treated patients. A time-to-event distribution of secondary endpoints was estimated with the Kaplan-Meier method.

Collateral Studies

The pathological response and overall survival was measured in correlation with the biopathological characterization of rectal biopsy: immunohistochemistry (p53, BCL2, Ki67, TS, EGFR, ERK, PTEN, GLUT1) at baseline and after 2 weeks of treatment; cDNA microarrays of biopsy at baseline and after 2 weeks of treatment; mutational status evaluation of genes for intracellular effectors (*NRAS*, *BRAF*, *PIK3CA*) of rectal biopsy at baseline and the evaluation of serum biomarkers (EGF, TGF-α, soluble EGFR, VEGF, E-selectin) on days 1, 14, 28, and 38.

Fluorodeoxyglucose (FDG) positron emission tomography (PET) scan evaluation was performed for early prediction of

Table 1. Patient demographics and disease characteristics ($n = 98$)

Characteristics	n (%)
Age, years, median (range)	66 (42–88)
Sex	
Male	73 (74.5)
Female	25 (25.5)
Karnofsky performance status, median (range)	100 (70–100)
Histological grading	
G1	6 (6.1)
G2	49 (50.0)
G3	16 (16.3)
Unknown	27 (27.6)
Histological type	
Adenocarcinoma	98 (100)
Other	0 (0)
Distance from the anal margins, cm, median (range)	6.0 (1.5–15.0)
Clinical stage at diagnosis	
cT2 N−	2 (2.1)
cT2 N+	2 (2.1)
cT3 N−	33 (33.6)
cT3 N+	56 (57.2)

response (baseline and after 2 weeks of treatment). Changes in quality of life assessment were evaluated using the EQ-5D Health Questionnaire (EuroQol Group, Rotterdam, The Netherlands) six times: before the start of preoperative treatment, during treatment (week 4), after the end of treatment, before and after surgery, and after the end of adjuvant treatment. Questionnaire compliance rates were ascertained at each measurement time.

RESULTS

Patients and Treatment

From October 2012 to October 2015, 98 patients were enrolled in 13 Italian centers. All 98 patients were evaluated for safety, and 92 were assessable for response.

Patient characteristics are listed in Table 1. The majority of patients were male (74.5%); their median age was 66 years (range 42–88 years), and their median Karnofsky performance status was 100 (range 70–100). The median distance from the anal margin was 6 cm (range 1.5–15 cm). The clinical stage was cT2 in 4/98 (4.1%) and cT3 in 89/98 (90.8%) of patients. The majority of patients, 59/98 (60.2%), had lymph node involvement (cN+).

The dose intensity of panitumumab and radiotherapy is reported in Table 2. The panitumumab dose intensity >90% was delivered in 92/98 (93.9%) of patients. The full dose of planned radiotherapy was administered in 82/98 (83.7%), and >90% was administered in 83/98 (84.7%) of patients.

Surgical Procedures and Pathological Responses

The data on the surgical procedures and the pathological responses are listed in Table 3. Six patients did not undergo

Table 2. Dose intensity of neoadjuvant treatment

Dose intensity (n = 92)	>90 (%)	60–90 (%)	<60 (%)
Panitumumab	93.9	5.1	1.0
Radiotherapy	83.7	13.3	0

Table 3. Surgical parameters and pathological response (n = 92)

Surgical parameters and pathological response	n (%)
Type of surgical treatment	
Anterior resection	78 (79.6)
Hartmann resection	2 (2.0)
Abdominal perineal resection	5 (5.1)
Sphincter preserving	
Yes	11 (11.2)
No	67 (68.4)
Macroscopic residual tumor	
Yes	3 (3.1)
No	89 (90.8)
Response in evaluable patients (n = 92)	
ypT0N0	10 (10.9)
Pathological downstaging	45 (45.9)

surgery: two patients because disease progression during the neoadjuvant treatment, one patient because of refusal, two patients lost to follow-up, and one for unknown reasons. Ninety-two (93.9%) patients underwent surgery and were evaluable for pathological response. TME surgery was performed in all patients. Seventy-eight (79.6%) were treated with a low anterior resection, two (2.0%) with a Hartmann's procedure, and five (5.1%) with an abdominoperineal resection. No postoperative deaths occurred; only in three (3.1%) patients intraoperative complication occurred, such as bleeding, organ damage, or packaging of ileostomy. Resection R0 at the primary tumor site was achieved in 89/92 (90.8%) of patients. Anal sphincter loss was performed in 67/92 (68.4%). Pathological complete response (ypT0N0) was 10.9% (95% confidence interval, 4.72%–17.07%), observed in 10/92 patients. Compared with the clinical stage before preoperative treatment, pathological downstaging (T and/or N) occurred in 45 (45.9%) patients.

Safety Analysis

All 98 patients were evaluated for toxicity. Adverse events observed during neoadjuvant treatment are listed in Table 4. Skin rash was the most observed toxicity, with 16 (16.3%) patients developing grade 3 skin rash. Grade 3 diarrhea occurred in two (2.1%) patients. No grade 4 toxicities were observed. All grades of skin rash occurred in 89 (89.9%) patients, diarrhea in 32 (32.6%), and anemia in 14 (14.3%).

Postoperative Treatment

Postoperative treatment was planned between a minimum of 4 weeks and a maximum of 6 weeks after surgery; 46 (46.9%) patients received chemotherapy according to the FOLFOX regimen for 12 cycles. Of the 65 patients known to be evaluated for safety, 16 (16.3%) developed toxicity of grade ≥3, particularly neutropenia, in 11 (11.2%) patients, and leucopenia in 5 (5.1%).

Discussion

In this phase II trial, the addition of panitumumab to radiotherapy in low-risk LARC was not shown to reach the primary endpoint pCR (10.9%). This was the first preoperative trial in LARC that did not use chemotherapy in addition to monoclonal antibody and radiotherapy. In the literature there have been several phase II studies conducted using cetuximab or panitumumab in combination with fluoropyrimidine ± oxaliplatin, some of which are summarized in Table 5.

In the Belgian study [28], 40 patients were treated with cetuximab in combination with capecitabine 650 and 825 mg/m^2 twice daily (recommended dosage) continuously for the duration of radiotherapy (45 Gy in 25 fractions) with pCR in 2 (5%) patients. No pCR was obtained in 28 patients treated with cetuximab in combination with capecitabine 825 mg/m^2 twice daily on radiotherapy days (45 Gy in 25 fractions) [29]. Velenik

et al. [30] treated 37 patients with cetuximab added to capecitabine 825 mg/m^2 twice daily continuously for the duration of radiotherapy (45 Gy in 25 fractions), obtaining pCR in 3 (8%) patients. In another study, cetuximab and 5-fluorouracil 225 mg/m^2 per day continuous infusion concomitantly with radiotherapy (45–50.4 Gy in 25–28 fractions) were administered to 40 patients, with pCR in 3 (7.5%) patients [31]. The association of cetuximab with capecitabine 825 mg/m^2 twice daily (days 1–14 and 22–35), oxaliplatin 50 mg/m^2 (days 1, 8, 22, and 29), and radiotherapy (50.4 Gy in 28 fractions) was evaluated in 48 patients and a pCR was reached in 4 (8%) patients [32].

Two other phase II trials evaluated the addition of cetuximab to capecitabine plus irinotecan and radiotherapy. Cetuximab was added to capecitabine 825 mg/m^2 twice daily (5 days a week), irinotecan 40 mg/m^2 (days 1, 8, 15, 22, and 29), and radiotherapy (50.4 Gy in 28 fractions) in 10 patients, with pCR in 2 (20%) patients [33]. In the MARGIT study [34], 50 patients received cetuximab in combination with capecitabine 500 mg/m^2 twice daily continuously, irinotecan 40 mg/m^2 (days 1, 8, 15, 22, and 29), and radiotherapy (50.4 Gy in 28 fractions), obtaining pCR in 4 (8%) patients. The biological mechanisms for the disappointing results of cetuximab in combination with fluoropyrimidine-based chemoradiotherapy in these phase II studies [28–32, 34] may arise because of changes in tumor cell proliferation and cell cycle distribution after cetuximab administration with cell arrest in G1 or G2-M and failure to pass through the S phase.

These activities are lacking when 5-fluorouracile with capecitabine is administered in monotherapy [28–31] or in combination with oxaliplatin with intermittent schedules [32]. Capecitabine with 5-fluorouracil and oxaliplatin both produced their optimal cytotoxic and radiosensitizing effect when cells proliferate into the S, G2, and M phases. The activity of fluoropyrimidines in combination with irinotecan seems to be preserved only with a full capecitabine dose [33, 34].

The use of panitumumab was evaluated in two studies. In the first, the StarPan/STAR-02 study [26], 5-fluorouracil 225 mg/m^2 was administered continuously (without intervals), and IV oxaliplatin 60 mg/m^2 was administered weekly, over a 6

Table 4. Preoperative treatment toxicities

Preoperative treatment toxicities	Grade 1–2, n (%)	Grade 3–4, n (%)	All grades, n (%)
Hematological			
Anemia	13 (13.2)	1 (1.0)	14 (14.3)
Leucopenia	6 (6.1)	0 (0)	6 (6.1)
Neutropenia	2 (2.0)	0 (0)	2 (2.0)
Thrombocytopenia	5 (5.1)	0 (0)	5 (5.1)
Gastrointestinal			
Diarrhea	30 (30.6)	2 (2.0)	32 (32.6)
Stomatitis	8 (8.2)	1 (1.0)	9 (9.2)
Abdominal pain	7 (7.1)	1 (1.0)	8 (8.1)
Nausea	2 (2.0)	0 (0)	2 (2.0)
Anorexia	0 (0)	0 (0)	0 (0)
Vomiting	0 (0)	0 (0)	0 (0)
Cutaneous			
Rush	72 (73.5)	16 (16.3)	89 (89.8)
Nails	5 (5.1)	0 (0)	5 (5.1)
Asthenia	11 (11.2)	0 (0)	11 (11.2)
Radiodermatitis	11 (11.2)	0 (0)	11 (11.2)
Proctitis	4 (4.1)	0 (0)	4 (4.1)
Cystitis	4 (4.1)	0 (0)	4 (4.1)
Allergic reaction	2 (2.0)	1 (1.0)	3 (3.0)

Table 5. Phase II studies of preoperative chemoradiation using anti-epidermal growth factor receptor monoclonal antibodies

Study	Phase	No. pts	mAb	5FU	Cape	Oxa	Iri	RT dose, Gy	pCR, %
Machiels, 2007 [28]	I/II	40	Cet		+			45	5
Eisterer, 2009 [29]	II	28	Cet		+			45	0
Velenik, 2010 [30]	II	37	Cet		+			45–50.4	8.1
Bertolini, 2009 [31]	II	40	Cet	+				50.4	7.5
Rödel, 2008 [32]	I/II	48	Cet		+	+		50.4	8
Hong, 2007 [33]	II	10	Cet		+		+	50.4	20
Horisberger, 2009 [34]	II	50	Cet		+		+	50.4	8
Pinto, 2011 [26]	II	60	Pan	+		+		50.4	21.1
Helbling, 2013 [35]	II	40	Pan		+			45	10
Present study	II	98	Pan					50.4	10.9

Abbreviations: +, in combination; 5FU, 5-fluorouracil; Cape, capecitabine; Cet, cetuximab; Iri, irinotecan; mAb, monoclonal antibody; Oxa, oxaliplatin; Pan, panitumumab; pCR, pathologic complete response; pts., patients; RT, radiotherapy.

week period; radiotherapy (50.4 Gy in 28 fractions) and panitumumab at an IV dose of 6 mg/kg over 1 hour was administered 2 weeks before the start of chemoradiotherapy (day −14) and then in combination with chemoradiotherapy every 2 weeks, for a total of 3 times, obtaining a higher rate of pCR in 12/60 (20%) patients, reporting a high-grade (3–4) toxicity rate. In this study, the high pCR was probably due to the different chemotherapy schedules applied that could overcome the antagonistic effect of anti-EGFR monoclonal antibodies.

In the second study, the SAKK 41/07 phase II trial [35], 40 patients with wild-type *KRAS* LARC were randomized to receive IV panitumumab 6 mg/kg every 2 weeks for 8 weeks plus capecitabine 825 mg/m^2 twice daily throughout RT (total dose of 45 Gy in 25 fractions of 1.8 Gy over 5 weeks), starting 7 days after the first panitumumab administration. The primary endpoint was pathological near-complete (pNC) or complete tumor response (CR) rate (pNC/CR), defined as grade 3 (pNCR) or grade 4 (pCR) histological regression by Dworak classification (DC). The results obtained were translated into a high pNC/CR rate, mostly grade 3 DC. The most common toxicities were grade ≥3, such as diarrhea (10%), hand-foot syndrome (2%), fatigue (2%), acneiform skin rash (2%), and anastomotic leakage (15%), which led to treatment discontinuation in five patients; furthermore, there were two deaths during the safety monitoring period resulting from anastomotic leakage.

In our study, no grade 4 toxicities were reported, only the specific side effects associated with panitumumab such as skin rash (16.3% grade 3 and 89.9% all grades).

The role of *KRAS* mutation in determining the response to EGFR-targeted monoclonal antibodies in the preoperative setting is not very clear. In previous phase II studies in LARC that did not select patients by *KRAS* status, *KRAS* and/or *BRAF* mutation did not correlate with pCR after preoperative treatment containing cetuximab or panitumumab, probably because of the low numbers of patients in these studies [26, 36–40]. In our study, we excluded patients with tumors harboring *KRAS* mutation. Further mutational status evaluation of genes for intracellular effectors such as *NRAS* and *BRAF* is ongoing.

On the basis of previous results of the StarPan RaP-02 study that showed how ^{18}F-FDG uptake was decreased only by panitumumab administration and markedly by combination therapy compared with the basal value, correlated with a reduction in tumor cell proliferation after panitumumab alone and later the addition of chemoradiotherapy to panitumumab increasing cytotoxic activity, in our study, earlier PET evaluation was used as a marker of cellular proliferation downregulation.

Conclusion

The use of anti-EGFR monoclonal antibodies in combination with radiotherapy alone in preoperative treatment in patients with *KRAS* wild-type, low-risk LARC did not reach the primary endpoint, resulting in a pCR rate of 10.9%.

The analysis showed a good toxicity profile and compliance to concomitant administration of panitumumab and external radiotherapy in the preoperative treatment of LARC. The main toxicity was cutaneous without affecting treatment adherence. Further analysis of tissue *NRAS* and *BRAF* and circulating levels of the EGFR ligands (TGF-α, EGF) and vascular factors (soluble VEGF, E-selectin) will provide insight into the potential molecular pathways involved in the anti-EGFR response and could serve as a predictor of tumor downstaging.

Compared with what is described in the treatment of locoregionally advanced head and neck cancer with concomitant high-dose radiotherapy plus cetuximab that improves locoregional control and reduces mortality without increasing the common toxic effects associated with radiotherapy, in LARC there are no positive data that support the use of only anti-EGFR with radiotherapy. Nevertheless, it is estimated that 30%–40% of rectal cancer occurs in patients aged 75 years or more. Data on adherence to preoperative CRT and its safety remain poor because of the under-representation of older patients in randomized clinical trials and the discordance of the results from retrospective studies. A higher prevalence of comorbidities and a degradation of performance status limits the use of standard therapies in older patients. Perhaps in frail elderly patients, the use of single agent anti-EGFR antibody in combination with radiotherapy might be a prospective strategy.

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