Pathological response and safety of two neoadjuvant strategies with bevacizumab in MRI-defined locally advanced T3 resectable rectal cancer: a randomized, noncomparative phase II study


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Background: In T3 rectal cancer (RC), preoperative chemoradiotherapy [5-fluorouracil (5-FU–RT)] reduces local recurrences, but does not affect overall survival. New therapeutic options are still necessary to improve clinical outcomes.

Patients and methods: This randomized, noncomparative, open-label, multicenter, two arms, phase II study was conducted in MRI-defined locally advanced T3 resectable RC. In arm A, patients received 12-week bevacizumab plus 5-FU, leucovorin and oxaliplatin (Folfox-4) followed with bevacizumab–5-FU–RT before total mesorectal excision (TME). In arm B, patients received only bevacizumab–5-FU–RT before TME. Primary end point was pathological complete response (pCR) rate.

Results: Forty-six patients were randomized in arm A and 45 patients in arm B. In arm A, the rate of pCR was 23.8% [95% confidence interval (CI) 12.1% to 39.5%] statistically superior to the defined standard rate of 10%, P = 0.015. In arm B, the rate of pCR of 11.4% (95% CI 3.8% to 24.6%) was not different from 10%, P = 0.906. No death occurred during the study period, from the start until 8 weeks following surgery. Postoperative fistulas were reported for 16 patients (7 in arm A and 9 in arm B).

Conclusion: Even if the addition of bevacizumab induced manageable toxicities including an increased risk of postoperative fistula and no treatment-related death, arm B did not achieve the expected pCR rate in the population of patients included. Induction bevacizumab–Folfox-4 followed by bevacizumab–5-FU–RT is promising. It is however necessary to continue investigations in the management of locally advanced RC.

Clinical Trials.gov Identifier: NCT 00865189.

Key words: neoadjuvant, chemoradiotherapy, bevacizumab, oxaliplatin, 5-FU, rectal cancer

Distant metastases occurred in >30% of patients [2–4]. A role for adjuvant chemotherapy in RC has been recently suggested [5]; nevertheless, 20%–50% of patients exposed to preoperative CT-RT discontinued adjuvant chemotherapy [2, 6].

Then, new regimens were assessed in T3/T4 RC patients. One option was to add oxaliplatin to fluoropyrimidine, since oxaliplatin-based chemotherapies had superior efficacy in stage III colon cancer versus fluoropyrimidine alone [7, 8].

Another option might be the addition of bevacizumab, a VEGF, which improved the outcome of metastatic CRC when added to CT [9, 10]. Willett et al. were the first to evaluate neoadjuvant bevacizumab with 5-fluorouracil (5-FU–RT in

We conducted a study to evaluate two multimodal neoadjuvant treatments in MRI-defined T3 resectable RC patients.

**patients and methods**

INOVA (INduction Optimisation aVec Avastin*) is a randomized, noncomparative, open-label, multicenter, phase II study in patients with MRI-defined locally advanced T3 RC. The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki and ICH GCP. All patients provided informed consent before any study procedure was carried out. This study is registered on ClinicalTrials.gov (NCT 00865189).

**study population**

Main eligibility criteria included age between 18 and 75 years; histologically confirmed rectal adenocarcinoma; MRI-defined locally advanced T3 RC within 10 cm from the anal margin: T3N0–1 in the lower rectum, with a distal tumor edge <5 cm from the anal margin, or T3N0 in the mid-rectum with a tumor spread ≥5 mm into the perirectal fat or T3N1–N2; ECOG performance status 0–1. No prior CT or pelvic RT was allowed.

Eligible patients were allocated to treatment by adaptive (minimization method), balanced, centralized randomization, stratified by center, tumor site (lower, mid-rectum) and lymph node involvement (N+, N−).

**treatment plan**

In arm A, treatment started with a 12-week induction therapy (bevacizumab-CT) followed by 3–4 weeks of rest (sequence 1). Then, 7-week preoperative bevacizumab–CT-RT were followed by 6–8 weeks of rest (sequence 2) completed by surgery. In arm B, patients were only treated with sequence 2 and surgery (supplementary Material S1, available at Annals of Oncology online). After surgery, treatment was left to the investigator’s discretion.

Induction therapy included six cycles of bevacizumab + 5-FU/leucovorin (LV)/oxaliplatin (Folfox-4). On day 1, patients received bevacizumab 5 mg/kg followed by oxaliplatin 85 mg/m² combined with LV 200 mg/m² followed by 5-FU bolus 400 mg/m², then 5-FU infusion 600 mg/m². On day 2, patients received LV infusion 200 mg/m² followed by 5-FU bolus 400 mg/m² then 5-FU 600 mg/m² as a 22-h infusion.

Preoperative bevacizumab–CT-RT started with bevacizumab 5 mg/kg, 2 weeks before CT-RT. Then, a 24 h infusion of 5-FU at the dose of 225 mg/m²/day was administered for 5 days/week, along with RT during 5 weeks. Bevacizumab was given at cycles 1, 3 and 5. The total dose of RT was 45 Gy delivered in 25 fractions of 1.8 Gy, 5 days/week. The clinical target volume (CTV) included the rectum, the internal iliac, mesorectal and presacral nodes. The anal canal was excluded in case of planned conservative surgery. Otherwise, the CTV included the ischio-rectal fossae. CRT had to be temporary stopped in case of acute diarrhea grade 3.

Total mesorectal excision (TME) was planned 7 weeks (±1) after the completion of bevacizumab–CT-RT. Surgical procedure is detailed in supplementary Material S2, available at Annals of Oncology online.

**evaluation**

Pathological response was assessed locally and reviewed centrally. Complete response (CR) was defined as the absence of residual tumor cells in the resected specimen including lymph nodes (ypT0N0).

No record or collection of surgical status and pathological assessment were planned for patients who prematurely discontinued study treatment.

Those patients had to be followed for safety, disease progression and survival up to 5 years.

An independent data safety monitoring board (DSMB) reviewed all adverse events (AEs).

**statistical considerations**

The primary end point was the proportion of patients achieving pCR (ypT0N0). Secondary efficacy end points were compliance, pathologic tumor downstaging (ypT0–pT2), recurrence rate, 5-year DFS and OS. Other end points included the incidence of AEs and serious AE.

AEs were graded according to Common Terminology Criteria for Adverse Events version 3.0.

Forty-one patients had to be included in each arm to show a difference between 10% (estimated as the minimum acceptable by the scientific committee) and the expected proportion of 25% with α = 0.05 and a power of 80% using a binomial test.

The primary analysis was based on the intent-to-treat (ITT) population, which included all randomized and treated patients. For analysis of primary end point, pCR rate (with its 95% Clopper Pearson confidence interval) was calculated and compared with 10% using a binomial test in each arm. The primary analysis was carried out using data from the local review with no replacement of missing data.

No comparison between the arms was planned.

**results**

**patients and disease characteristics**

Between October 2007 and July 2010, 46 patients were included in arm A and 45 in arm B within 15 sites. All patients received at least one dose of treatment (supplementary Material S3, available at Annals of Oncology online).

Table 1 shows the main baseline characteristics. RC was moderately differentiated for 13 (28%) in arm A and 18 patients (40%) arm B. The tumor was localized in the lower rectum for ~40% of patients. Thirty-four patients (73.9%) in arm A and 37 (82.2%) in arm B had lymph node involvement.

**treatment compliance**

In arm A, 43 patients (93.5%) completed six cycles of bevacizumab–Folfox-4. Median relative dose intensities were 97%, 98% and 98% for oxaliplatin, 5-FU and bevacizumab, respectively. Of the 42 patients (91.3%) in arm A and the 45 patients (100%) in arm B who entered sequence 2, 41 (98%) and 45 patients (100%) completed it. Overall, 38 (90%) and 40 patients (89%) received the planned dose of 5-FU; 36 (86%) and 40 (89%) received the planned dose of bevacizumab; 41 (98%) and 45 (100%) received the planned dose of RT in arm A and arm B, respectively. TME was carried out after completion of the neoadjuvant treatment of 42 patients (91.3%) in arm A and 44 (97.8%) in arm B. One patient in arm B had an ileal colostomy because of peritoneal carcinosis (supplementary Material S4, available at Annals of Oncology online). The median interval between the start of RT and the surgery was 12 [8, 12] weeks in arm A and 12 [10, 12] weeks in arm B.

Per protocol, no information regarding surgical status of patients who discontinued treatment was available. However, all these patients underwent a surgery out of the INOVA study (as indicated by investigators to the authors). The reasons for treatment discontinuation are detailed in the safety section.
efficacy

Main efficacy results are shown in Table 2. The resection was macroscopically complete for 41 patients (97.6%) in arm A and 43 (97.7%) in arm B.

In arm A, among the 42 patients who underwent TME within the study, pCR was observed in 10 patients [23.8% (95% confidence interval (CI) 12.1% to 39.5%)] by the local review. According to the centralized review, 9 of 39 patients showed pCR [23.1% (95% CI 11.1% to 39.3%)]. The latter were also assessed as having pCR in the local review. The pCR rate was statistically superior to 10% according to local and centralized reviews, \( P = 0.015 \) and \( P = 0.026 \), respectively. Pathological tumor downstaging was observed in 21 patients [51.2% (95% CI 35.9% to 66.5%)].

In arm B, 5 of 44 patients achieved pCR [11.4% (95% CI 3.8% to 24.6%)]. This rate was not different from 10%, \( P = 0.906 \).

In a sensitivity analysis (ITT), 10 of 46 patients [21.7% (95% CI 10.9% to 36.4%), \( P = 0.028 \)] and 5 of 45 patients [11.1% (95% CI 3.7% to 24.1%), \( P = 0.946 \)] achieved pCR, respectively, in arms A and B.

Of note, no disease progression was observed during treatment sequence 1 or 2.

discussion

The compliance was good for both regimens and the rate of macroscopically complete resection was substantial (98%). Sterilization was observed in 23.8% (95% CI 12.1% to 39.5%) of patients in arm A and 11.4% (95% CI 3.8% to 24.6%) of patients in arm B. In arm A, the pCR rate was statistically higher than 10%. Except for one intestinal perforation in arm A, the addition of bevacizumab induced manageable grade 3/4 toxicities. The patient who experienced intestinal perforation recovered completely. Postoperative fistula was reported for 17.6% of patients. The majority was anastomatic (94%) and resolved (75%).

The incidence of anastomotic leakage and fistula is poorly described in the literature. Sauer et al. reported fistula in 11% of patients treated with preoperative CT-RT. Gerard et al. reported an incidence of 7.4%. Of note, these results were confirmed in a recent study using close monitoring, where fistula was reported for 8.5% of patients treated with capecitabine–RT (45 Gy). A review showed that the rate of anastomotic leak ranged from 2.4% to 19% [13].

In INOVA study, the incidence of postoperative fistula was similar in arm A and B, suggesting that neoadjuvant chemotherapy did not influence the incidence of this AE. Then, with a rate of 17.6% of fistula in INOVA, it is important to consider a possible role of bevacizumab in this complication. Studies assessing bevacizumab plus chemoradiation to treat LARC (locally advanced RC) reported a rate of fistula and anastomotic leakage ranging from 1.5% to 8% and from 2.5% to 16%, respectively [11, 12, 14–21] (supplementary Material S5, available at Annals of Oncology online). It is plausible that impaired healing during surgery recovery can cause fistula and anastomatic leakage.

The addition of oxaliplatin during 5-FU–RT led to a pCR rate of 16%–19.2% [22–25].

safety

In arm A, 501 AEs were reported for 46 patients (100%) (Table 3). Twenty-three patients (50%) experienced at least one of the 43 grade 3–4 AEs.

Postoperative fistulas were reported for seven patients (15.2%). One fistula occurred on healthy tissue and six were anastomotic. All patients but one recovered.

Three patients prematurely discontinued induction CT because of AEs: phlebitis \((n = 1)\), rectal fistula \((n = 1)\) and thrombophlebitis of the jugular vein \((n = 1)\). The last two patients and two others with gastrointestinal perforation \((n = 1)\) and occlusive syndrome related to hernia \((n = 1)\) did not start CT-RT. An additional patient prematurely discontinued CT-RT for ileitis.

In arm B, 191 AEs were reported in 44 patients (97.8%). Nine patients (20%) experienced at least one of the 13 grade 3–4 AEs including 6 related to bevacizumab in five patients (11.1%).

Postoperative anastomotic fistulas were reported and in nine patients (20%). In all, six patients recovered completely whereas one patient recovered with sequelae. Two patients did not recover at the time of analysis.

No patient in arm B discontinued treatment prematurely.

No death occurred in both arms from the study start until 8-week postsurgery.

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Table 1. Patients and disease characteristics—ITT \((N = 91)\)

<table>
<thead>
<tr>
<th></th>
<th>Arm A ((N = 46))</th>
<th>Arm B ((N = 45))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>60.6 (40.2–73.7)</td>
<td>60.1 (24.3–76.0)</td>
</tr>
<tr>
<td>Male (^a)</td>
<td>51 (67.4%)</td>
<td>30 (66.7%)</td>
</tr>
<tr>
<td>ECOG performance status at selection (^a)</td>
<td>0 (87.0%)</td>
<td>38 (84.4%)</td>
</tr>
<tr>
<td></td>
<td>1 (13.0%)</td>
<td>7 (15.6%)</td>
</tr>
<tr>
<td>Histological type (^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lieberkühniën adenocarcinoma</td>
<td>46 (100.0%)</td>
<td>44 (97.8%)</td>
</tr>
<tr>
<td>Well differentiated</td>
<td>29 (63.0%)</td>
<td>23 (51.1%)</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>13 (28.3%)</td>
<td>18 (40.0%)</td>
</tr>
<tr>
<td>Missing</td>
<td>4 (8.7%)</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>Colloid carcinoma</td>
<td>0 (0.0%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Tumor localization (^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle rectum (5–10 cm)</td>
<td>28 (60.9%)</td>
<td>27 (60.0%)</td>
</tr>
<tr>
<td>Low rectum (&lt;5 cm)</td>
<td>18 (39.1%)</td>
<td>18 (40.0%)</td>
</tr>
<tr>
<td>Radiological TNM stage (^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3N0M0</td>
<td>10 (21.7%)</td>
<td>8 (17.8%)</td>
</tr>
<tr>
<td>T3N1M0</td>
<td>31 (67.4%)</td>
<td>28 (62.2%)</td>
</tr>
<tr>
<td>T3N2M0</td>
<td>5 (10.9%)</td>
<td>9 (20.0%)</td>
</tr>
<tr>
<td>Node involvement—MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node-positive</td>
<td>34 (73.9%)</td>
<td>37 (82.2%)</td>
</tr>
<tr>
<td>1–3</td>
<td>27 (58.7%)</td>
<td>30 (66.7%)</td>
</tr>
<tr>
<td>≥4</td>
<td>7 (15.2%)</td>
<td>7 (15.6%)</td>
</tr>
<tr>
<td>Vascular invasion (embolus)—MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of surgery planned (^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection/anastomosis</td>
<td>30 (65.2%)</td>
<td>31 (68.9%)</td>
</tr>
<tr>
<td>Abdominoperineal resection</td>
<td>9 (19.6%)</td>
<td>6 (13.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (10.9%)</td>
<td>6 (13.3%)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (4.3%)</td>
<td>2 (4.4%)</td>
</tr>
</tbody>
</table>

\(^a\) n (%).

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Several trials assessed neoadjuvant CT followed by CT-RT [17, 22–25] (supplementary Material S6, available at *Annals of Oncology* online). The pCR rate of arm A was in the same range to that found in the phase II trial reported by Chau et al. [26], 77 MRI poor-risk LARC patients were treated with 12-week neoadjuvant capecitabine/oxaliplatin 130 mg/m² followed by 6-week capecitabine–RT with encouraging results. Indeed, the pCR rate was 21% (95% CI 12% to 32%). Later, Chua et al. [27] published the results on 105 patients reporting a pCR rate of 21% (95% CI 12% to 32%). Later, Chua et al. [27] published the results on 105 patients reporting a pCR rate of 21% (95% CI 12% to 32%).

In a randomized phase II study conducted by Fernandez-Martos et al., strategy with 12-week induction chemotherapy with capecitabine–oxaliplatin 130 mg/m² followed by capecitabine–oxaliplatin–RT then surgery was compared with capecitabine–oxaliplatin–RT followed by surgery then adjuvant chemotherapy with capecitabine–oxaliplatin (130 mg/m²) (3-weekly) [28]. Rates of pCR were similar between groups, 14% (95% CI 6.4% to 26.2%) versus 13% (95% CI 5.6% to 25.8%), respectively.

Nogué et al. evaluated four cycles induction bevacizumab–capcitabine–oxaliplatin (130 mg/m²) followed by bevacizumab–capcitabine–oxaliplatin–RT then TME in 47 patients with MRI-defined poor-prognosis LARC. Pathological CR was reported for 16 patients [36% (95% CI 22.3% to 51.3%)] on the 45 patients who had surgery [17].

Marechal et al. compared induction chemotherapy including two cycles of modified Folfox-6 (oxaliplatin 100 mg/m²) followed by conventional CT-RT before TME, with conventional CT-RT followed by TME in 57 patients with LARC. However, T2 tumors were included (7%), MRI circumferential margin assessment was lacking for eight patients (14%) and no stratification on disease characteristics was carried out at randomization. The pCR was a secondary end point and was similar in both arms [28% (95% CI 11.3% to 43.9%) versus 25% (95% CI 9.0% to −41.0%)] [29].

In arm B of INOVA, a pCR rate of 11.4% (95% CI 3.8% to 24.6%) seems low when compared numerically with arm A. Two other trials used the same schedule for bevacizumab, combined with a different fluoropyrimidine and their results were close to those achieved here [20, 21]. In a phase II trial, Velenik et al. assessed preoperative bevacizumab–capecitabine–fractionated RT in 61 patients. They reported a pCR of 13.3% [20]. Gasparini et al. reported a pCR rate of 14% in patients treated with the same CT-RT as that used by Velenik in the study cited above [18]. These results were close to those achieved in our trial.

Dellas et al. evaluated bevacizumab–capecitabine–oxaliplatin–RT in 70 patients. The rate of pCR was 17.4% (95% CI 10.4% to 26.6%) [21]. Landry et al. assessed a different bevacizumab–capecitabine–oxaliplatin–RT since one dose of oxaliplatin was added on day 15 and the total dose of RT was reduced (45 Gy instead of 50.4 Gy). The pCR rate was 17% (90% CI 9% to 27%) [20].

The strengths of INOVA include a treatment-controlled design and a centralized MRI review for patients’ selection. Safety evaluation was carried out during treatment and during the perioperative period, and reviewed by an independent DSMB.

Thus, INOVA showed encouraging ypCR rate in arm A with no unexpected AE or toxic death observed during the treatment or the perioperative period. The incidence of fistula

### Table 2. Efficacy—IT (N = 91)

<table>
<thead>
<tr>
<th>Sterilization rate</th>
<th>Sterilization of the tumor, n (%)</th>
<th>95% Clopper Pearson CI</th>
<th>Standard proportion (%)</th>
<th>P Binomial test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arm A (n = 46)</strong></td>
<td><strong>Local review (n = 42)</strong></td>
<td>10 (23.8)</td>
<td>(12.1% to 39.5%)</td>
<td>10.0%</td>
</tr>
<tr>
<td>Missing data (n = 4)</td>
<td>Centralized review (n = 39)</td>
<td>9 (23.1)</td>
<td>(11.1% to 39.3%)</td>
<td>10.0%</td>
</tr>
<tr>
<td><strong>Arm B (n = 45)</strong></td>
<td><strong>Local review (n = 44)</strong></td>
<td>5 (11.4)</td>
<td>(3.8% to 24.6%)</td>
<td>10.0%</td>
</tr>
<tr>
<td>Missing data (n = 1)</td>
<td>Centralized review (n = 43)</td>
<td>5 (11.6)</td>
<td>(3.9% to 25.1%)</td>
<td>10.0%</td>
</tr>
<tr>
<td><strong>Tumor downstaging</strong></td>
<td><strong>Surgical specimen (T and N) downstaging</strong></td>
<td><strong>n (%)</strong></td>
<td><strong>Downstaging based on the T stage only</strong></td>
<td><strong>n (%)</strong></td>
</tr>
<tr>
<td><strong>Arm A (n = 46)</strong></td>
<td>Local review (n = 41)</td>
<td>27 (65.9%)</td>
<td>(51.3% to 80.4%)</td>
<td>21 (51.2%)</td>
</tr>
<tr>
<td>Missing data (n = 7)</td>
<td>Centralized review (n = 39)</td>
<td>25 (64.1%)</td>
<td>(49.0% to 79.2%)</td>
<td>19 (48.7%)</td>
</tr>
<tr>
<td><strong>Arm B (n = 45)</strong></td>
<td>Local review (n = 44)</td>
<td>24 (54.5%)</td>
<td>(39.8% to 69.3%)</td>
<td>19 (43.2%)</td>
</tr>
<tr>
<td>Missing data (n = 2)</td>
<td>Centralized review (n = 43)</td>
<td>24 (55.8%)</td>
<td>(41.0% to 70.7%)</td>
<td>17 (39.5%)</td>
</tr>
</tbody>
</table>
was high (17.6%), comparable in arms A and B, and in the range of previously reported trials of bevacizumab in LARC [11, 12, 14–21]. Pathological CR rates achieved with neoadjuvant CT followed by CT-RT in several phase II studies (supplementary Material S5, available at Annals of Oncology online) support further randomized clinical trials to compare standard CT-RT with and without neoadjuvant sequence and investigate a potential impact on survival.

In conclusion, the strategy based on induction bevacizumab–Folfox-4 followed by bevacizumab–5-FU–RT is feasible and showed promising results but was associated with an increased risk of postoperative fistula. Neoadjuvant bevacizumab did not improve pCR rate in the population of patients included. It is necessary to continue investigations in the management of LARC.

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### Disclosure

AA: advisory board for Roche; CB: honoraria for advisory board from Roche; FM: honoraria from Roche for participation in conferences as speaker and in advisory board meetings; TA: consultant or advisor for Roche and honoraria from Roche; MP and ZM are employees from Roche; DA, GM, FB, JFB and PM have declared no conflicts of interest.

### References


