



**HAL**  
open science

## First-line chemotherapy with raltitrexed in metastatic colorectal cancer: an Association des Gastro-entérologues Oncologues (AGEO) multicentre study

Claire Gallois, Emilie Hafliger, Edouard Auclin, Audrey Perret, Clélia Coutzac, Anthony Turpin, Anna Pellat, Violaine Randrian, Debora Basile, Roger Faroux, et al.

### ► To cite this version:

Claire Gallois, Emilie Hafliger, Edouard Auclin, Audrey Perret, Clélia Coutzac, et al.. First-line chemotherapy with raltitrexed in metastatic colorectal cancer: an Association des Gastro-entérologues Oncologues (AGEO) multicentre study. *Digestive and Liver Disease*, 2022, 54 (5), pp.684-691. 10.1016/j.dld.2021.08.009 . hal-04099081

HAL Id: hal-04099081

<https://cnrs.hal.science/hal-04099081v1>

Submitted on 22 Jul 2024

**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

## **First-line chemotherapy with raltitrexed in metastatic colorectal cancer: an Association des Gastro-entérologues Oncologues (AGEO) multicentre study**

Claire Gallois<sup>a</sup>, Emilie Hafliger<sup>b</sup>, Edouard Auclin<sup>c</sup>, Audrey Perret<sup>d</sup>, Clelia Coutzac<sup>e</sup>, Anthony Turpin<sup>f</sup>, Anna Pellat<sup>g</sup>, Violaine Randrian<sup>h</sup>, Debora Basile<sup>i</sup>, Roger Faroux<sup>j</sup>, Simon Pernet<sup>k</sup>, Christophe Locher<sup>l</sup>, Vincent Hautefeuille<sup>m</sup>, Olivier Dubreuil<sup>n</sup>, Lola-Jade Palmieri<sup>o</sup>, Marie Dior<sup>p</sup>, Pascal Artru<sup>b</sup> and Julien Taieb<sup>a\*</sup>

### **Authors' Affiliations**

a- Paris University; Assistance Publique-Hôpitaux de Paris, Department of Gastroenterology and Digestive Oncology, Hôpital Européen Georges Pompidou, Paris, France.

b - Department of Gastroenterology and Digestive Oncology, Hôpital privé Jean Mermoz, Lyon, France

c – Paris University; Assistance Publique-Hôpitaux de Paris, Department of Medical Oncology, Hôpital Européen Georges Pompidou, Paris, France.

d - Department of Cancer Medicine, Gustave Roussy Cancer Institute, Villejuif, France

e- Centre Léon Bérard, Cancer Research Center of Lyon (CRCL), Lyon, France.

f – Univ. Lille, CNRS UMR9020, Inserm UMR-S 1277 - Canther - Cancer Heterogeneity, Plasticity and Resistance to Therapies, CHU Lille, Department of Medical Oncology, Lille, France

g – Sorbonne University, Department of Digestive Oncology, Hôpital Saint-Antoine, Paris, France

h - Department of Hepato-gastroenterology, Centre Hospitalier Universitaire de Poitiers, Poitiers University, Poitiers, France

i- Department of Medicine (DAME), University of Udine, Udine, Italy

j - Department of Hepato-gastroenterology, Hôpital de La Roche-sur-Yon, La Roche-sur-Yon, France

k - Department of Medical Oncology, Institut Bergonié, Bordeaux, France

l - Department of Hepato-gastroenterology, Centre Hospitalier de Meaux, Meaux, France

m - Department of Hepato-gastroenterology and Digestive Oncology, Centre Hospitalier Universitaire d'Amiens, Amiens, France

n - Department of Digestive Oncology, Groupe hospitalier Diaconesses Croix Saint Simon, Paris, France

o – Paris University ; Department of Hepato-gastroenterology, Hôpital Cochin, Paris, France

p - Department of Hepato-gastroenterology, Hôpital Louis Mourier, Colombes, France

**Word count: 3436**

\* **Corresponding author:** Julien Taieb, Department of Gastroenterology and Digestive Oncology, Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75015 Paris, France.

Tel: +331.56.09.35.51; Fax: +331.56.09.50.69; E-mail: jtaieb75@gmail.com

**Funding information**

The authors received no specific funding for this work.

## **Abstract**

### **Background**

In case of contraindication or intolerance to fluoropyrimidines, raltitrexed is a validated alternative in metastatic colorectal cancer (mCRC), associated or not with oxaliplatin. Little is known about the outcomes of raltitrexed combined with irinotecan or targeted therapies.

### **Methods**

This retrospective multicentre study enrolled mCRC patients treated with first-line raltitrexed-based chemotherapy. Treatment-related toxicities were recorded. Progression-free survival (PFS) and overall survival (OS) were calculated from treatment start.

### **Results**

75 patients were treated with raltitrexed alone, TOMOX, or TOMIRI with or without bevacizumab. Grade 3-4 adverse events were seen in 31% of patients, without significant difference between the different treatment schedules. Among the 36 patients with a history of fluoropyrimidine-induced cardiac toxicity, none developed cardiovascular events on raltitrexed.

Median PFS and OS were 10.6 (95% CI 8.2 – 13.1) and 27.4 months (95% CI 24.1-38.1), respectively. Considering the chemotherapy regimen, TOMOX was significantly associated with better PFS and OS compared to TOMIRI and raltitrexed alone.

### **Conclusions**

In patients with mCRC not eligible for fluoropyrimidines, first-line raltitrexed-based chemotherapy had an acceptable safety profile. PFS and OS were consistent with usual survival data in mCRC, and significantly better in patients treated with TOMOX, independently of associated targeted therapies.

**Key words:** metastatic colorectal cancer; raltitrexed; chemotherapy toxicity; survival

## 1. Introduction

Fluoropyrimidines (intravenous 5-fluorouracil or oral capecitabine) are the cornerstone of first-line chemotherapy in metastatic colorectal cancer (mCRC), in combination with oxaliplatin and/or irinotecan and antiangiogenic or anti-EGFR targeted therapies. However, in rare cases, the use of fluoropyrimidine may be contraindicated or not recommended and raltitrexed is a potential alternative treatment. The primary contraindications are dihydropyrimidine dehydrogenase (DPD) deficiency (0.3% of the general population)[1] and severe cardiovascular co-morbidities, and secondary contraindications should be discussed after potential life-threatening toxicities on fluoropyrimidine therapy, such as cardiovascular events in 1.5 to 12% of cases[2,3] (angina-like symptoms, myocardial infarction, major arrhythmias and heart failure), induced or not by coronary vasospasm, or severe gastrointestinal toxicities (mucositis, diarrhoea). Cardiovascular contraindications should always be discussed with a cardiologist.

Raltitrexed is a direct and specific thymidylate synthase inhibitor, whereas 5-fluorouracil (5-FU) must be metabolized to fluorodeoxyuridine monophosphate before inhibition can occur[4]. It has been compared in mCRC to 5-FU in several randomized trials, as monotherapy [5,6] or associated with oxaliplatin in a regimen generally called TOMOX [7–11]. Another modality of raltitrexed administration was reported by Guo et al., showing in patients with refractory CRC liver metastasis that hepatic artery infusion (HAI) with TOMOX had an efficacy and safety profile similar to that of HAI with FOLFOX [12]. By contrast, in the current literature, data on raltitrexed in combination with irinotecan or targeted agents remain scarce. Two phase II trials [13,14] showed efficacy and safety profiles of raltitrexed in combination with irinotecan (TOMIRI) similar to those of TOMOX. For targeted therapy associated with raltitrexed-based chemotherapy, two phase II trials with TOMOX or TOMIRI associated with bevacizumab in a second-line setting were presented at ESMO congresses [15,16] and showed that the combinations were feasible and that toxicity was acceptable. Samalin et al. showed that TOMOX bevacizumab was not associated with better survival outcomes, compared to FOLFOX6 bevacizumab, probably partly due to low accrual rate in this trial [15], and the other trial by Zhu et al. is still in progress (interim results presented at the ESMO Asia Congress 2019)[16]. To our

knowledge, only one case has been reported for anti-EGFR associated with raltitrexed-based chemotherapy [17].

The aim of this study was to describe retrospectively in real life in mCRC patients with absolute or relative contraindications to fluoropyrimidines the efficacy and tolerability of raltitrexed-based chemotherapy combined or not with targeted therapy in the first-line setting.

## **2. Methods**

### *2.1 Patients*

This retrospective, multicentre study involved fourteen French centres from AGEO (Association des Gastro-entérologues Oncologues) and one Italian medical centre. All consecutive patients with mCRC, with initially resectable metastatic disease or not, and treated with first-line raltitrexed-based chemotherapy, with or without targeted therapy, since 2006, were included. Patients developing contraindications for fluoropyrimidine-based chemotherapy regimens during the first 3 cycles in their first-line setting and switching to raltitrexed-based chemotherapy (keeping the same drugs associated) were enrolled in our study. Switching to raltitrexed beyond 3 cycles of fluoropyrimidine-based chemotherapy was considered as an exclusion criterion. However, patients who had received more than 3 cycles of fluoropyrimidine during adjuvant chemotherapy were not excluded.

### *2.2 Data collection*

Data collected concerned a history of adjuvant treatments, baseline clinico-pathological characteristics, first-line raltitrexed-based chemotherapy (indication, protocol), tolerability according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0 [18], the best response, the date of surgery or ablation of metastases if any, the date of progression, subsequent raltitrexed-based lines, date of last news and date of death. Response rate (objective response rate and disease control rate) and progression rate were assessed according to RECIST 1.1 criteria.

Progression-free survival (PFS) and overall survival (OS) were evaluated from treatment start.

Data were obtained from electronic review according to strict privacy standards.

The study was conducted in accordance with the French regulatory requirements (Commission Nationale Informatique et Libertés) and the Declaration of Helsinki. All patients alive at the time of the study received appropriate verbal information or an information note and gave their consent for anonymous data collection. In accordance to French national laws and Clinical research Guidelines, this retrospective observational study did not require formal ethical committee approval.

### *2.3 Statistical analyses*

Median (interquartile range) values and proportions (percentage) were used for continuous and categorical variables, respectively. Median and proportions were compared using the Wilcoxon-Mann-Whitney test and the chi<sup>2</sup>-test (or Fisher's exact test, if appropriate), respectively.

PFS was defined as the time between the start of raltitrexed treatment and tumor progression or death, whichever occurred first. OS was defined as the time between raltitrexed start and death from any cause. Patients known to be alive were censored at the date of their last follow-up.

PFS and OS were estimated using the Kaplan-Meier method and described using median or rate at specific time points with their 95% confidence intervals (95% CI). Follow-up was calculated using the reverse Kaplan-Meier method.

The primary endpoint was PFS. Secondary endpoints were OS and response rate (defined as the sum of partial and complete responses to raltitrexed therapy).

All analyses were performed using SAS version 9.4 (SAS Institute, Cary NC) and R software version 2.15.2 (R Development Core Team, Vienna, Austria; <http://www.r-project.org>). P values of less than 0.05 were considered statistically significant, and all tests were two-sided.

## **3. Results**

### *3.1 Patient characteristics*

A total of 75 mCRC patients treated first-line with a raltitrexed-based chemotherapy were included. Their median age was 69 years (range 29-87), 68% were men and 35% had two or more metastatic sites (Table 1). The main reasons for prescribing raltitrexed were a history of fluoropyrimidine-related

cardiac toxicity in 48% of cases (acute coronary syndrome: 23%, angina: 20%, heart failure: 4% or arrhythmia: 3%), cardiovascular comorbidities in 25% of cases, other fluoropyrimidine-induced toxicities in 17% of cases, DPD deficiency in 7% of cases, and non-confirmed DPD deficiency in 3% of cases. Patients in whom the main reason for prescribing raltitrexed was cardiovascular comorbidities were older and in poorer general condition compared to those with a history of fluoropyrimidine-related cardiac toxicity (mean age: 74.2 years versus 65.4 years,  $p=0.001$  and WHO-PS 0-1 rate of 71% versus 94%, respectively,  $p=0.02$ ).

Twenty two patients (29%) had received fluoropyrimidine-based adjuvant chemotherapy, including 10 with more than 3 cycles of fluoropyrimidine before the introduction of raltitrexed. The median number of fluoropyrimidine treatment cycles prior to the introduction of raltitrexed for the first metastatic line was 2.5 (range: 0-3). Raltitrexed was given alone in 13% of cases ( $N=10$ ), combined with oxaliplatin in 69% of cases ( $N=52$ ) and with irinotecan in 17% of cases ( $N=13$ ). No targeted therapy was associated with chemotherapy in 58 patients (77%), and bevacizumab was associated in 17 patients (23%). The dosage of raltitrexed was 3 mg/m<sup>2</sup> every 3 weeks for 83% of patients.

Compared to patients treated with TOMOX or TOMIRI-based chemotherapy, patients treated with raltitrexed alone were older (mean age of 79.2 years compared to 65.8 years and 62 years, respectively), in poorer general condition (67% of WHO-PS 0-1 compared to 92% and 85%, respectively), had higher CEA levels (median baseline CEA level of 60.3 ng/mL compared to 9 ng/mL and 23 ng/mL, respectively) and had less frequent use of associated targeted therapy (10% compared to 23% and 31%, respectively). However, no major differences in baseline characteristics were observed between patients treated with TOMOX and those treated with TOMIRI (supplemental Table 1).

### *3.2 Treatment tolerability*

The proportion of patients with grade 3-4 toxicities (excluding neurotoxicity) was 31%: neutropenia (13%), asthenia (9%), anaemia (8%), aspartate aminotransferase/alanine aminotransferase increase (7%), diarrhoea (5%), nausea/vomiting (4%), renal failure (4%), thrombocytopenia (3%) and cardiac toxicity (1%) (Table 2). 7% of patients had febrile neutropenia. The rate of grade 3-4 adverse events was not significantly different depending on the chemotherapy protocol (31% for TOMOX, 23% for



TOMIRI and 40% for raltitrexed alone,  $p=0.6$ ) (Table 3), or on whether or not bevacizumab was added to the chemotherapy (29% versus 32%,  $p=0.8$ ). In patients treated with TOMOX-based chemotherapy, only one patient developed grade 3 neuropathy (2%).

Three patients died during treatment: the first following the second cycle of TOMIRI due to grade 5 diarrhoea complicated by acute renal failure and septic shock, the second after the third cycle of TOMOX with grade 3 diarrhoea and cardiac ischemia, and the third patient after the third cycle of TOMIRI due to decompensation of chronic heart failure by atrial fibrillation probably not related to anti-cancer treatments.

Among the 19 patients in whom the use of fluoropyrimidine was contraindicated due to cardiovascular comorbidities, 3 (16%) had a cardiovascular event: one patient with decompensation of heart failure and bacterial lung disease, and the other 2 patients died of probable myocardial infarction and decompensation of heart failure, respectively. By contrast, among the 36 patients with a history of fluoropyrimidine-induced cardiac toxicity, none developed cardiovascular events on raltitrexed.

### *3.3 Response rate*

Table 4 shows the best response rates according to chemotherapy regimen. TOMOX-based chemotherapy was significantly associated with a better objective response rate (ORR), compared to TOMIRI-based and raltitrexed chemotherapy (60%, 23% and 10%, respectively,  $p=0.003$ ). ORR was numerically better when bevacizumab was added to chemotherapy with an ORR of 59% versus 49% without bevacizumab ( $p = 0.5$ ), and the TOMOX bevacizumab regimen was associated with the best ORR: 75% (N=9 patients).

Seventeen patients (23%) underwent surgical resection and 4 other patients (5%) thermal ablation of liver/pulmonary metastases. Among these 21 patients with local treatment, 19 were treated with a TOMOX-based chemotherapy and 2 with a TOMIRI-based chemotherapy; 5 patients were still in remission after a median duration of follow-up of 25.5 months after the date of local treatment.

### *3.4 Survival*

In the overall population, after a median follow-up of 51.3 months (95% CI 41.9-not reached), 66 patients (88%) progressed and 53 patients (71%) died, with a median PFS of 10.6 months (95% CI 8.2 – 13.1) and a median OS of 27.4 months (95% CI 24.1-38.1). Patients treated with TOMOX-based chemotherapy had significantly longer median PFS compared to patients treated with TOMIRI-based chemotherapy and raltitrexed-only chemotherapy (11.6 [95% CI 9.9-18.8], 6.1 [95% CI 2.6-not reached] and 3.2 months [95% CI 1.5-not reached], respectively,  $p < 0.0001$ ). The same results were observed for median OS (34.9 [95% CI 26.1-48.4], 28.3 [95% CI 12.1-not reached] and 12.6 months [95% CI 3.8-not reached], respectively,  $p = 0.03$ ) (Figure 1).

When bevacizumab was added to chemotherapy, there was a trend towards better survival with a median PFS of 15.3 months (95% CI 9.9-34) versus 9.2 months (95% CI 6.7-12.4) ( $p = 0.3$ ) and median OS of 37.6 months (95% CI 21.6 – not reached) versus 26.8 months (95% CI 21.1 – 36.3) without bevacizumab ( $p = 0.6$ ) (Figure 1).

In the whole population, patients who underwent secondary resection or thermal ablation of their metastases had a median OS of 38.1 months (95% CI 31.8 – not reached) compared to 21.6 months (95% CI 16.9 – 36.3) for those who did not undergo local treatment ( $p = 0.05$ ).

For patients without secondary resection or thermal ablation, median OS was 25.1 months (95% CI 20.2 – 48.8) for those treated with TOMOX-based chemotherapy, 20.7 months (95% CI 12.1- not reached) for those treated with TOMIRI-based chemotherapy, 45.0 months (95% CI 14 – not reached) when bevacizumab was added to chemotherapy, and 20.7 months (95% CI 4.3 – 28.3) in those treated without bevacizumab.

According to the main reasons for prescribing raltitrexed, patients with a history of fluoropyrimidine-related cardiac toxicity had significantly longer median OS compared to patients with cardiovascular comorbidities (28.3 months [95% CI 22.7 – 48.8] versus 16.9 months [95% CI 7.03-49.21] respectively,  $p = 0.01$ ), and PFS was not significantly different between the two groups (medians PFS: 10.6 months [95% CI 7.9-18.8] and 6.7 months [95% CI 2.8 – 12.6] respectively,  $p = 0.4$ ).

### *3.5 Subsequent lines based on raltitrexed*

Among the 75 patients, 22 and 4 received respectively a second line and a third line of chemotherapy based on raltitrexed. For second-line treatments, the regimens were: TOMIRI (N=4), TOMIRI bevacizumab (N=7), TOMIRI aflibercept (N=1), TOMOX (N=4), TOMOX bevacizumab (N=3), and raltitrexed (N=1), and 2 patients were treated with hepatic intra-arterial oxaliplatin associated with TOMIRI bevacizumab and raltitrexed alone, respectively. For third-line treatment, the regimens reported were TOMIRI bevacizumab (N=2) and TOMIRI (N=2).

Fifty percent (N=4) of patients treated with TOMOX-based chemotherapy had grade 3-4 adverse events (2 patients with anaphylactic reaction to oxaliplatin, and 2 with haematological adverse events) compared to 25% (N=4) of patients treated with TOMIRI-based chemotherapy (1 patient with diarrhoea and 3 patients with haematological adverse events).

Similarly, the addition of bevacizumab to chemotherapy in subsequent lines was not associated with more toxicities (data not shown). The patient who received 8 cycles of TOMIRI aflibercept had grade 4 asthenia, grade 2 diarrhoea and no other toxicities.

#### **4. Discussion**

In patients with mCRC, first-line raltitrexed-based chemotherapy had an acceptable safety profile apart from a non-negligible death rate during treatment (4%), without increased toxicity depending on the other chemotherapy drug associated with raltitrexed or with the addition of bevacizumab. The PFS and OS data for our whole population are consistent with literature data for mCRC in first-line settings, with a median PFS of 10.6 months and a median OS of 28.3 months [19–22].

Although we cannot draw any conclusions about the difference in efficacy between the different regimens in this retrospective study, we observed that patients treated with a TOMOX-based protocol presented encouraging oncological outcomes with an ORR of 60%, a median PFS of 11.6 months and a median OS of 34.9 months. By contrast, patients treated with chemotherapy based on raltitrexed alone had the poorest outcomes, probably partly due to baseline poorer prognostic factors.

The vast majority of patients in our study (83%) received raltitrexed every 3 weeks at a dose of 3 mg/m<sup>2</sup>, which is more convenient for the patient than dosing every 2 weeks for 5-FU-based chemotherapy.

The grade 3-4 toxicity rate (31%) observed here is slightly greater than that described in therapeutic trials testing raltitrexed [5,7-11], probably because our study population included non-selected real-world patients with a contraindication to receiving a fluoropyrimidine and substantial comorbidities, unlike randomized trials comparing 5-FU with raltitrexed. The most common side effects (all grades) were asthenia, nausea/vomiting, diarrhoea, myelosuppression, and an increase in AST/ALT, which are classic and known toxicities of raltitrexed [5,7-11]. Notably, our population had a 7% increase in AST/ALT grade 3-4, which is consistent with data from trials with TOMOX or TOMIRI [7-11,13,14], and is a complication most often reversible and easily manageable. Among the 55 patients with cardiovascular co-morbidities contraindicating the use of a fluoropyrimidine or a history of fluoropyrimidine-induced cardiac toxicity, 3 (5%) had cardiovascular events during treatment, which is consistent with the literature [3,23], but 2 of them died from this complication. These two toxic deaths are probably linked more to severe cardiovascular comorbidities than to the treatment itself, but we must nonetheless remain vigilant in this frail population at risk of cardiovascular events. As described in four case reports [24-26], no patient in our study who had a cardiovascular event on fluoropyrimidine developed cardiac toxicity on raltitrexed, which therefore represents a particularly safe alternative in this situation.

Compared to fluoropyrimidine, there were no cases of hand-foot syndrome and only 10% of grade 1-2 mucositis, which are both classic and frequent side effects of fluoropyrimidine.

In addition, we observed 3 deaths (4%) during treatment after 2 and 3 cycles of raltitrexed-based chemotherapies, including one death with a strong causal link with TOMIRI (diarrhoea complicated by hypovolemic shock, renal failure and sepsis), the other two patients having died of decompensation of chronic heart failure. In the various therapeutic trials of raltitrexed-based chemotherapy in mCRC, a non-negligible percentage of raltitrexed-related deaths was observed, ranging from 2.6% to 5%, [5,6,13,14], most often due to a combination of gastrointestinal toxicity (diarrhoea), myelosuppression and sepsis, secondary to a poor adjustment of the doses and deviations from the protocols. By contrast, treatment-related death rates in trials with FOLFOX or FOLFIRI are < 3% [27-30]. The adjuvant therapeutic trial PETACC-1, comparing raltitrexed and 5-FU in stage III CRC, was prematurely closed after 17 (1.9%) raltitrexed-related deaths which were considered unacceptable in the adjuvant setting

[31]. In fact, it is necessary to follow good clinical practice recommendations when using raltitrexed, in particular regarding monitoring of renal function before each administration, in order to avoid unexpected serious toxicities due to the plasma accumulation of raltitrexed. Thus, unlike 5-FU, 40-50% of the administered dose of raltitrexed is excreted by the kidney (versus 5% for 5-FU), and therefore raltitrexed is contraindicated if creatinine clearance is < 25 mL/min and the dose should be reduced if creatinine clearance is between 25 mL/min and 65 mL/min [32,33].

The TOMOX-based protocol was associated with particularly prolonged OS (median 34.9 months) compared with therapeutic trials based on FOLFOX as first line with a median OS of 25-30 months [21,22,34], probably partly due to the subgroup of patients who underwent curative treatment of metastases (surgery or radiofrequency ablation), 24% of whom still had not relapsed after a median follow-up of 25.5 months. Unlike first-line therapeutic trials in mCRC, patients with initially resectable metastases were not excluded from our study. Thus, excluding patients who underwent secondary resection or thermal ablation of metastases, the median OS in our study patients treated with TOMOX-based chemotherapy was 25.1 months, very similar to what has been reported with first line FOLFOX. Conversely, patients treated with chemotherapy based on raltitrexed alone had poorer prognostic features at baseline (age, WHO-PS and CEA levels) and a poorer outcome, probably partly because the choice of this regimen by practitioners could be favored in patients with a worse general condition, more co-morbidities and / or non-resectable metastatic lesions, due to the retrospective nature of the study. Bevacizumab tended to be associated with better ORR, PFS and OS when added to raltitrexed-based chemotherapy, with a median PFS of 15.3 months and a median OS of 37.6 months, which is also consistent with the literature on survival data with FOLFOX or FOLFIRI associated with bevacizumab in the first line treatment setting [19–22].

The strengths of our study are that it was multicentre, involved patients treated only with first-line raltitrexed-based chemotherapy, and that it is the first study to include many patients treated with first-line raltitrexed-based chemotherapy in combination with bevacizumab. Indeed, the only two as yet unpublished studies, by Samalin et al. and Zhu et al. [15,16], with TOMOX or TOMIRI associated with bevacizumab, were in the second-line setting.

However, our work also has some limitations, in particular its retrospective nature and the low number of patients in the different treatment subgroups, which precludes relevant subgroup comparisons by limiting the statistical power of the results.

In conclusion, first-line raltitrexed-based chemotherapy with or without bevacizumab in patients with mCRC has an acceptable tolerability profile when good prescription rules are observed, especially after cardiac complications with fluoropyrimidine (mainly coronary complications) with efficacy results very similar to what is reported with fluoropyrimidine-based regimens, and seems thus a practical effective and safe alternative in patients with a contraindication to fluoropyrimidine. However, we must nevertheless remain vigilant regarding these often frail patients with cardiovascular co-morbidities who are more at risk of toxicity from chemotherapy and in whom there are rare cases of treatment-related death. Our encouraging results on bevacizumab associated with raltitrexed-based chemotherapy in the first metastatic line should be validated prospectively.

### **Declaration of Competing Interest**

CG has participated in consulting and/or advisory boards for Servier and Sanofi, and has received support for travel to meetings from Amgen. PA has participated in consulting and/or advisory boards for Lilly, Celgene, Shire, Servier, Merck KGaA, Sanofi, Roche Genentech, Pfizer, Pierre Fabre and Amgen. CC has received honoraria from Amgen and Servier, has participated in an advisory board for Servier, and has received support for travel to meetings from Amgen, Bayer, Roche, Mundipharma and Servier. AT reports personal fees from Mylan, personal fees from Merck Serono, personal fees from Amgen, non-financial support from Merck-Serono, non-financial support from Sanofi, and non-financial support from Pfizer outside the submitted work. AP has participated in consulting and/or advisory boards for Servier and Amgen, and has received support for travel meetings from Ipsen. SP has participated in consulting and/or advisory boards for Amgen, Sanofi, Pierre Fabre, Servier, Merck, Roche, has received support for travel to meetings from Amgen, Bayer, and Servier, and has received research grants from Roche, Planet Vegetal. VH has participated in consulting and/or advisory boards for Sanofi, Merck, Amgen, and has received support for travel to meetings from Amgen and Sanofi. JT

has participated in consulting and/or advisory boards for Lilly, Celgene, Shire, Servier, Merck KGaA, Sanofi, Roche Genentech, Pfizer, and Amgen. The other authors declare no conflict of interest.

### **Acknowledgements**

The study was sponsored by AGEO, which was responsible for study design, management, analyses and interpretation. We thank all participating patients and their families and the participating centres.

### **References**

- [1] Diasio RB, Beavers TL, Carpenter JT. Familial deficiency of dihydropyrimidine dehydrogenase. Biochemical basis for familial pyrimidinemia and severe 5-fluorouracil-induced toxicity. *J Clin Invest* 1988;81:47–51. <https://doi.org/10.1172/JCI113308>.
- [2] Deboever G, Hiltrop N, Cool M, Lambrecht G. Alternative treatment options in colorectal cancer patients with 5-fluorouracil- or capecitabine-induced cardiotoxicity. *Clin Colorectal Cancer* 2013;12:8–14. <https://doi.org/10.1016/j.clcc.2012.09.003>.
- [3] Kelly C, Bhuvana N, Harrison M, Buckley A, Saunders M. Use of raltitrexed as an alternative to 5-fluorouracil and capecitabine in cancer patients with cardiac history. *Eur J Cancer* 2013;49:2303–10. <https://doi.org/10.1016/j.ejca.2013.03.004>.
- [4] Zalberg JR, Cunningham D, Van Cutsem E, Francois E, Schornagel J, Adenis A, et al. ZD1694: A novel thymidylate synthase inhibitor with substantial activity in the treatment of patients with advanced colorectal cancer. Tomudex Colorectal Study Group. *J Clin Oncol* 1996;14:716–21. <https://doi.org/10.1200/JCO.1996.14.3.716>.
- [5] Cocconi G, Cunningham D, Van Cutsem E, Francois E, Gustavsson B, van Hazel G, et al. Open, randomized, multicenter trial of raltitrexed versus fluorouracil plus high-dose leucovorin in patients with advanced colorectal cancer. Tomudex Colorectal Cancer Study Group. *J Clin Oncol* 1998;16:2943–52. <https://doi.org/10.1200/JCO.1998.16.9.2943>.
- [6] Cunningham D, Zalberg JR, Rath U, Oliver I, van Cutsem E, Svensson C, et al. Final results of a randomised trial comparing “Tomudex” (raltitrexed) with 5-fluorouracil plus leucovorin in advanced colorectal cancer. ‘Tomudex’ Colorectal Cancer Study Group. *Ann Oncol* 1996;7:961–5.

<https://doi.org/10.1093/oxfordjournals.annonc.a010800>.

[7] Seitz J-F, Bennouna J, Paillot B, Gamelin E, François E, Conroy T, et al. Multicenter non-randomized phase II study of raltitrexed (Tomudex) and oxaliplatin in non-pretreated metastatic colorectal cancer patients. *Ann Oncol* 2002;13:1072–9. <https://doi.org/10.1093/annonc/mdf183>.

[8] Scheithauer W, Kornek GV, Schuell B, Ulrich-Pur H, Penz M, Raderer M, et al. Second-line treatment with oxaliplatin + raltitrexed in patients with advanced colorectal cancer failing fluoropyrimidine/leucovorin-based chemotherapy. *Ann Oncol* 2001;12:709–14.

<https://doi.org/10.1023/a:1011194712661>.

[9] Neri B, Doni L, Fulignati C, Perfetto F, Turrini M, Andreoli F, et al. Raltitrexed plus oxaliplatin as first-line chemotherapy in metastatic colorectal carcinoma: a multicentric phase II trial. *Anticancer Drugs* 2002;13:719–24.

[10] Cascinu S, Graziano F, Ferrà F, Catalano V, Massacesi C, Santini D, et al. Raltitrexed plus oxaliplatin (TOMOX) as first-line chemotherapy for metastatic colorectal cancer. A phase II study of the Italian Group for the Study of Gastrointestinal Tract Carcinomas (GISCAD). *Ann Oncol* 2002;13:716–20. <https://doi.org/10.1093/annonc/mdf091>.

[11] Gravalos C, Salud A, García-Girón C, García-Carbonero R, León AI, Sevilla I, et al. A randomized phase II study to compare oxaliplatin plus 5-fluorouracil and leucovorin (FOLFOX4) versus oxaliplatin plus raltitrexed (TOMOX) as first-line chemotherapy for advanced colorectal cancer. *Clin Transl Oncol* 2012;14:606–12. <https://doi.org/10.1007/s12094-012-0843-x>.

[12] Guo J-H, Zhang H-Y, Gao S, Zhang P-J, Li X-T, Chen H, et al. Hepatic artery infusion with raltitrexed or 5-fluorouracil for colorectal cancer liver metastasis. *World J Gastroenterol* 2017;23:1406–11. <https://doi.org/10.3748/wjg.v23.i8.1406>.

[13] Feliu J, Castañón C, Salud A, Mel JR, Escudero P, Pelegrín A, et al. Phase II randomised trial of raltitrexed-oxaliplatin vs raltitrexed-irinotecan as first-line treatment in advanced colorectal cancer. *Br J Cancer* 2005;93:1230–5. <https://doi.org/10.1038/sj.bjc.6602860>.

[14] Aparicio J, Vicent JM, Maestu I, Bosch C, Galán A, Busquier I, et al. First-line treatment with irinotecan and raltitrexed in metastatic colorectal cancer. Mature results of a multicenter phase II study. *Oncology* 2005;68:58–63. <https://doi.org/10.1159/000084821>.



- [15] Samalin E, Senellart H, Thezenas S, Jacquot S, Ellis S, Khemissa F, et al. Multicenter randomized phase II trial (BEVATOMOX) assessing the raltitrexed, oxaliplatin and bevacizumab combination versus FOLFOX6 bevacizumab as 2nd line treatment in metastatic colorectal cancer (mCRC). *Annals of Oncology* 2017;28:v179. <https://doi.org/10.1093/annonc/mdx393.055>.
- [16] Zhu JL, Li S, Zhu C. Efficacy and safety of the combination of bevacizumab with raltitrexed-based chemotherapy as second-line therapy in patients with metastatic colorectal cancer (mCRC): An interim analysis of a multicenter phase II trial. *Annals of Oncology* 2019;30:ix39. <https://doi.org/10.1093/annonc/mdz421.036>.
- [17] Geurs F, Vandewaeter S, Ponette S, Ponette J, Knape S, Demetter P. Successful and well-tolerated second line therapy with cetuximab, irinotecan, and raltitrexed in progressive liver disease due to metastatic colon cancer. *J Gastrointest Cancer* 2008;39:26–8. <https://doi.org/10.1007/s12029-009-9060-4>.
- [18] CTCAE\_4.03\_2010-06-14\_QuickReference\_5x7.pdf n.d.
- [19] Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2014;371:1609–18. <https://doi.org/10.1056/NEJMoa1403108>.
- [20] Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran S-E, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;15:1065–75. [https://doi.org/10.1016/S1470-2045\(14\)70330-4](https://doi.org/10.1016/S1470-2045(14)70330-4).
- [21] Rivera F, Karthaus M, Hecht JR, Sevilla I, Forget F, Fasola G, et al. Final analysis of the randomised PEAK trial: overall survival and tumour responses during first-line treatment with mFOLFOX6 plus either panitumumab or bevacizumab in patients with metastatic colorectal carcinoma. *Int J Colorectal Dis* 2017;32:1179–90. <https://doi.org/10.1007/s00384-017-2800-1>.
- [22] Venook AP, Niedzwiecki D, Lenz H-J, Innocenti F, Fruth B, Meyerhardt JA, et al. Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial. *JAMA* 2017;317:2392–401. <https://doi.org/10.1001/jama.2017.7105>.

- [23] Khan K, Rane JK, Cunningham D, Rao S, Watkins D, Starling N, et al. Efficacy and Cardiotoxic Safety Profile of Raltitrexed in Fluoropyrimidines-Pretreated or High-Risk Cardiac Patients With GI Malignancies: Large Single-Center Experience. *Clin Colorectal Cancer* 2019;18:64-71.e1. <https://doi.org/10.1016/j.clcc.2018.09.010>.
- [24] Paiva CE, Paiva BSR, Garita R, Michelin OC, Okoshi K. Acute coronary syndrome associated with continuous 5-Fluorouracil infusion in a patient with metastatic colorectal cancer-a case report with a discussion on this clinical dilemma. *J Gastrointest Cancer* 2009;40:133–7. <https://doi.org/10.1007/s12029-009-9101-z>.
- [25] Gundling F, Fuchs M, Nowak L, Antoni D, Hoffmann E, Schepp W. ["Iatrogenic acute coronary syndrome"--59 year old patient with adenocarcinoma of ascending colon and stenocardia while receiving adjuvant chemotherapy with 5-fluorouracil]. *Z Gastroenterol* 2006;44:975–9. <https://doi.org/10.1055/s-2006-927004>.
- [26] Köhne CH, Thuss-Patience P, Friedrich M, Daniel PT, Kretzschmar A, Benter T, et al. Raltitrexed (Tomudex): an alternative drug for patients with colorectal cancer and 5-fluorouracil associated cardiotoxicity. *Br J Cancer* 1998;77:973–7. <https://doi.org/10.1038/bjc.1998.160>.
- [27] Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000;355:1041–7. [https://doi.org/10.1016/s0140-6736\(00\)02034-1](https://doi.org/10.1016/s0140-6736(00)02034-1).
- [28] de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;18:2938–47. <https://doi.org/10.1200/JCO.2000.18.16.2938>.
- [29] Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;22:229–37. <https://doi.org/10.1200/JCO.2004.05.113>.
- [30] Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000;18:136–47.

<https://doi.org/10.1200/JCO.2000.18.1.136>.

[31] Popov I, Carrato A, Sobrero A, Vincent M, Kerr D, Labianca R, et al. Raltitrexed (Tomudex) versus standard leucovorin-modulated bolus 5-fluorouracil: Results from the randomised phase III Pan-European Trial in Adjuvant Colon Cancer 01 (PETACC-1). *Eur J Cancer* 2008;44:2204–11.

<https://doi.org/10.1016/j.ejca.2008.07.002>.

[32] Jansman FG, Sleijfer DT, Coenen JL, De Graaf JC, Brouwers JR. Risk factors determining chemotherapeutic toxicity in patients with advanced colorectal cancer. *Drug Saf* 2000;23:255–78.

<https://doi.org/10.2165/00002018-200023040-00001>.

[33] Van Cutsem E, Cunningham D, Maroun J, Cervantes A, Glimelius B. Raltitrexed: current clinical status and future directions. *Ann Oncol* 2002;13:513–22.

<https://doi.org/10.1093/annonc/mdf054>.

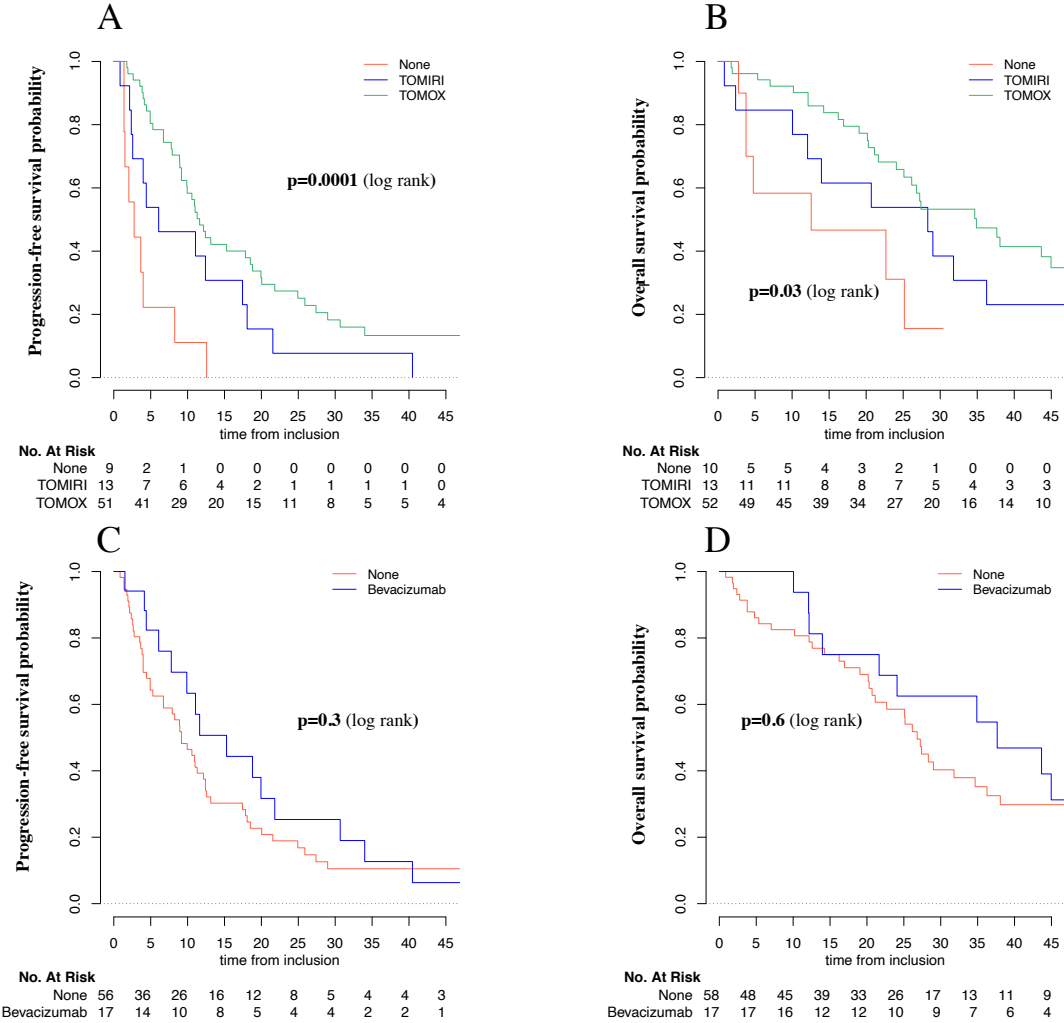
[34] Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. *Ann Oncol* 2014;25:1346–55. <https://doi.org/10.1093/annonc/mdu141>.

## **Figure Legends**

### **Figure 1. Survival according to chemotherapy or targeted therapy combined with raltitrexed**

A: Progression-free survival according to chemotherapy regimen; B: Overall survival according to chemotherapy regimen; C: Progression-free survival according to bevacizumab combined or not with chemotherapy; D: Overall survival according to bevacizumab combined or not with chemotherapy

**Figure 1. Survival according to chemotherapy or targeted therapy combined with raltitrexed**



A: Progression-free survival according to chemotherapy regimen; B: Overall survival according to chemotherapy regimen; C: Progression-free survival according to bevacizumab combined or not with chemotherapy; D: Overall survival according to bevacizumab combined or not with chemotherapy

**Table 1. Patient characteristics**

| <b>Characteristics</b>                |                    | <b>Whole population N=75 (%)</b> | <b>Missing data, n</b> |
|---------------------------------------|--------------------|----------------------------------|------------------------|
| <b>Gender</b>                         | male               | 51 (68%)                         | 0                      |
|                                       | female             | 23 (31%)                         |                        |
| <b>Age, years</b>                     | median (range)     | 69 (29-87)                       | 0                      |
|                                       | < 65               | 23 (31%)                         |                        |
|                                       | ≥ 65               | 52 (69%)                         |                        |
| <b>Adjuvant chemotherapy</b>          | no                 | 49 (65%)                         | 0                      |
|                                       | yes                | 26 (35%)                         |                        |
|                                       | protocol           | 5-FU (4%)                        |                        |
|                                       |                    | capecitabine (15%)               |                        |
|                                       |                    | FOLFOX (54%)                     |                        |
|                                       |                    | CAPOX (8%)                       |                        |
|                                       |                    | FOLFOX                           |                        |
|                                       |                    | bevacizumab (4%)                 |                        |
|                                       |                    | TOMOX (11%)                      |                        |
|                                       |                    | TOMUDEX (4%)                     |                        |
|                                       | duration           | < 3 months (46%)                 |                        |
|                                       |                    | 3 months (23%)                   |                        |
|                                       |                    | 6 months (31%)                   |                        |
| <b>Number of metastatic sites</b>     | < 2                | 49 (65%)                         | 0                      |
|                                       | ≥ 2                | 26 (35%)                         |                        |
| <b>Location of the primary tumour</b> | right colon        | 20 (27%)                         | 2                      |
|                                       | right + left colon | 3 (4%)                           |                        |
|                                       | transverse colon   | 2 (3%)                           |                        |
|                                       | left colon         | 48 (66%)                         |                        |
| <b>RAS</b>                            | wild-type          | 28 (47%)                         | 15                     |
|                                       | mutated            | 32 (53%)                         |                        |
| <b>BRAF</b>                           | wild-type          | 40 (91%)                         | 31                     |

|   |                                     |   |             |    |
|---|-------------------------------------|---|-------------|----|
|   | mutated                             |   | 4 (9%)      |    |
| <b>MMR status</b>   | pMMR                                |   | 41 (93%)    | 31 |
|   | dMMR                                |   | 3 (7%)      |    |
| <b>Main reason for prescribing raltitrexed</b>                    | fluoropyrimidine-induced            |   | 36 (48%)    | 0  |
|   | cardiac toxicity                    | angina (39%)<br>acute coronary<br>syndrome (45%)<br>heart failure (8%)<br>arrhythmia (5%) |             |    |
|   | cardiovascular<br>comorbidities     |   | 19 (25%)    |    |
|   | DPD deficiency                      |   | 5 (7%)      |    |
|   | other                               |   | 15 (20%)    |    |
| <b>Number of cycles before the introduction of raltitrexed</b>    | 5-FU                                | mean ( $\sigma$ )   | 2.8 (3.2)   | 0  |
|   | capecitabine                        | mean ( $\sigma$ )   | 3.9 (5.2)   |    |
| <b>Time to introduction of raltitrexed for metastatic disease</b> | from the start                      |   | 41 (54%)    |    |
|   | after 1-3 cycles                    |   | 41 (55%)    |    |
| <b>Chemotherapy protocol</b>                                      | Raltitrexed                         |   | 9 (12%)     | 0  |
|   | TOMOX                               |   | 40 (53%)    |    |
|   | TOMIRI                              |   | 9 (12%)     |    |
|   | Raltitrexed bevacizumab             |   | 1 (1%)      |    |
|   | TOMOX bevacizumab                   |   | 12 (16%)    |    |
|   | TOMIRI bevacizumab                  |   | 4 (5%)      |    |
| <b>Dosage of raltitrexed</b>                                      | 2.5 mg/m <sup>2</sup> every 2 weeks |   | 13 (17%)    | 0  |
|   | 3 mg/m <sup>2</sup> every 3 weeks   |   | 62 (83%)    |    |
| <b>Baseline PS</b>  | 0 -1                                |   | 62 (87%)    | 4  |
|   | 2                                   |   | 9 (13%)     |    |
| <b>Baseline CEA (ng/mL)</b>                                       | median (range)                      |   | 15 (0-2169) | 17 |
| <b>Number of cycles</b>   | mean ( $\sigma$ )                   |   | 7.9 (5.1)   | 0  |

5-FU: 5-fluorouracil; MMR: mismatch repair; pMMR: proficient mismatch repair; dMMR: deficient mismatch repair; DPD: dihydropyridine; PS: WHO performance status; CEA: carcinoembryonic antigen

**Table 2. Adverse events (excluding neuropathy)**

|                           | <b>Highest grade of adverse events</b> |                  |                |
|---------------------------|--|------------------|----------------|
|                           | <b>N=75 (%)</b>                        |                  |                |
|                           | <b>Grade 1-2</b>                       | <b>Grade 3-4</b> | <b>Grade 5</b> |
| <b>All</b>                | 40 (53%)                               | 23 (31%)         | 3 (4%)         |
| <b>Asthenia</b>           | 51 (68%)                               | 7 (9%)           | 0              |
| <b>Mucositis</b>          | 8 (10%)                                | 0                | 0              |
| <b>Hand-foot syndrome</b> | 0                                      | 0                | 0              |
| <b>Nausea/vomiting</b>    | 25 (33%)                               | 3 (4%)           | 0              |
| <b>Diarrhoea</b>          | 21 (28%)                               | 4 (5%)           | 1 (1%)         |
| <b>Alopecia</b>           | 0                                      | 0                | 0              |
| <b>Anaemia</b>            | 19 (25%)                               | 6 (8%)           | 0              |
| <b>Thrombocytopenia</b>   | 11 (15%)                               | 2 (3%)           | 0              |
| <b>Neutropenia</b>        | 8 (11%)                                | 10 (13%)         | 0              |
| <b>AST/ALT increased</b>  | 15 (20%)                               | 5 (7%)           | 0              |
| <b>Renal failure</b>      | 5 (7%)                                 | 0                | 0              |
| <b>Cardiac toxicity</b>   | 1 (1%)                                 | 1 (1%)           | 2 (3%)         |

AST: aspartate aminotransferase; ALT: alanine aminotransferase



**Table 3. Grade  $\geq 3$  adverse events according to chemotherapy regimen**

|                           | Grade $\geq 3$ adverse events N(%) |         |               |         |                          |         |
|---------------------------|------------------------------------|---------|---------------|---------|--------------------------|---------|
|                           | TOMOX (N=52)                       |         | TOMIRI (N=13) |         | raltitrexed alone (N=10) |         |
|                           | Grade 3-4                          | Grade 5 | Grade 3-4     | Grade 5 | Grade 3-4                | Grade 5 |
| <b>All</b>                | 16 (31%)                           | 1 (2%)  | 3 (23%)       | 2 (15%) | 4 (40%)                  | 0       |
| <b>Asthenia</b>           | 4 (8%)                             |         | 1 (8%)        |         | 2 (20%)                  |         |
| <b>Mucositis</b>          | 0                                  |         | 0             |         | 0                        |         |
| <b>Hand-foot syndrome</b> | 0                                  |         | 0             |         | 0                        |         |
| <b>Nausea/vomiting</b>    | 2 (4%)                             |         | 0             |         | 1 (10%)                  |         |
| <b>Diarrhoea</b>          | 3 (6%)                             |         | 0             | 1 (8%)  | 0                        |         |
| <b>Alopecia</b>           | 0                                  |         | 0             |         | 0                        |         |
| <b>Neurotoxicity</b>      | 1 (2%)                             |         | 0             |         | 0                        |         |
| <b>Anaemia</b>            | 5 (10%)                            |         | 1 (8%)        |         | 0                        |         |
| <b>Thrombocytopenia</b>   | 1 (2%)                             |         | 0             |         | 1 (10%)                  |         |
| <b>Neutropenia</b>        | 7 (13%)                            |         | 2 (15%)       |         | 1 (10%)                  |         |
| <b>AST/ALT increased</b>  | 5 (10%)                            |         | 0             |         | 0                        |         |
| <b>Renal failure</b>      | 0                                  |         | 0             |         | 0                        |         |
| <b>Cardiac toxicity</b>   | 0                                  | 1 (2%)  | 1 (8%)        | 1(8%)   | 0                        |         |

AST: aspartate aminotransferase; ALT: alanine aminotransferase

**Table 4. Best response according to chemotherapy regimen**

|  | <b>Progressive disease</b> | <b>Stable disease</b> | <b>Partial response</b> | <b>Complete response</b> | <b>Not evaluable</b> |
|--|----------------------------|-----------------------|-------------------------|--------------------------|----------------------|
| <b>Whole population (N=75)</b>               | 11 (14.7%)                 | 22 (29.3%)            | 30 (40.0%)              | 5 (6.7%)                 | 7 (9.3%)             |
| <b>TOMOX-based chemotherapy (N=52)</b>       | 3 (5.8%)                   | 15 (28.8%)            | 26 (50.0%)              | 5 (9.6%)                 | 3 (5.8%)             |
| <b>TOMIRI-based chemotherapy (N=13)</b>      | 3 (23.1%)                  | 5 (38.5%)             | 3 (23.1%)               | 0                        | 2 (15.4%)            |
| <b>raltitrexed-based chemotherapy (N=10)</b> | 5 (50%)                    | 2 (20%)               | 1 (10%)                 | 0                        | 2 (20%)              |
| <b>TOMOX (N=40)</b>                          | 2 (5%)                     | 13 (32%)              | 19 (47%)                | 3 (7%)                   | 3 (7%)               |
| <b>TOMOX bevacizumab (N=12)</b>              | 1 (8%)                     | 2 (17%)               | 7 (58%)                 | 2 (17%)                  | 0                    |
| <b>TOMIRI (N=9)</b>                          | 3 (33%)                    | 2 (22%)               | 2 (22%)                 | 0                        | 2 (22%)              |
| <b>TOMIRI bevacizumab (N=4)</b>              | 0                          | 3 (75%)               | 1 (25%)                 | 0                        | 0                    |