A window of opportunity phase II study of enzastaurin in chemonaive patients with asymptomatic metastatic colorectal cancer


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Background: Preclinically, protein kinase C and AKT activation can be inhibited by enzastaurin and reduce tumor growth of colorectal cancer cells. In asymptomatic patients with metastatic colorectal cancer (mCRC), enzastaurin activity was evaluated by measuring the 6-month progression-free survival (PFS) rate in a window study design.

Patients and methods: Chemonaive patients with asymptomatic mCRC who did not require immediate chemotherapy-induced tumor reduction received a 400-mg thrice daily loading dose of enzastaurin on day 1 of cycle 1, followed by 500 mg once daily for the remaining 28-day cycles. Progression was assessed on the basis of radiographic imaging, rise in carcinoembryonic antigen or lactate dehydrogenase (LDH) levels or by appearance of clinical symptoms.

Results: Twenty-eight patients received daily enzastaurin. The 6-month PFS rate was 28% [95% confidence interval (CI) 13%–45%] and median PFS was 1.9 months (95% CI 1.8–4.5 months). Twelve (43%) patients had stable disease with a median duration of 6.1 months. The survival rate at 20 months was 77% (95% CI 47%–92%). No grade 4 toxicity was reported and grade 3 toxic effects were observed in three patients with one patient showing probable drug-related elevation of liver transaminases.

Conclusion: The window design in asymptomatic patients with mCRC can be safely applied to assess the activity and safety of novel cytostatic agents like enzastaurin.

Key words: asymptomatic, chemonaive, enzastaurin, metastatic colorectal cancer, window study

introduction

Colorectal carcinoma (CRC) is one of the most common cancers worldwide, accounting for 9% of all cancer incidences [1]. Despite current surgical and systemic chemotherapeutic treatment options, 50% of all patients with CRC will develop metastatic disease. Regimens of 5-fluorouracil in conjunction with leucovorin (5-FU–LV), administered in combination with oxaliplatin or irinotecan and, more recently, bevacizumab and cetuximab, have become the mainstay of standard therapy in the treatment of metastatic colorectal cancer (mCRC) [2].

The process of metastasis and progression of CRC partly depend on increased angiogenesis, making this process a valid target for therapy [3]. Antiangiogenic compounds have demonstrated efficacy in mCRC, including improved overall survival (OS) with the vascular endothelial growth factor inhibitor, bevacizumab [4]. Protein kinase C (PKC) and AKT pathways are also associated with neoangiogenic tumor growth in CRC and targeting these pathways has shown benefits in nonclinical models [5, 6]. Consequently, determining antitumor activity of enzastaurin, an oral serine–threonine kinase inhibitor that targets PKC and AKT pathways, in patients with mCRC might provide a new approach to inhibit angiogenesis [6].

Novel agents typically are first tested in later stages of tumor disease [7]. Therefore, in cancer types with many established treatment options, such as mCRC, a patient may be treated with a new drug only after failing several standard treatment regimens. While ethically this approach is justified, patients with multiple prior lines of therapy may suffer from several comorbidities and from treatment-resistant tumor. Such a setting may obscure the potential efficacy or toxicity profile of a novel agent, especially if it has cytostatic activity. An alternative approach consists of investigating novel agents in patients who do not require immediate standard antitumor treatment. Such trials are known as ‘window of opportunity
studies’ or in short ‘window studies’. This type of design has been used in oncology [8–11]. Prerequisites for a window trial are the ability to safely delay approved standard treatment, to closely monitor patients for possible tumor progression and a favorable toxicity profile of the novel agent. In mCRC patients who are initially asymptomatic, start of standard treatment can often be safely postponed without compromising OS, provided patients are observed closely, disease burden is low and, a requirement added recently, they are not eligible for metastatic tumor resection in the case of chemotherapy-induced tumor reduction [12–14].

On the basis of these important selection criteria, we conducted a multicenter, open-label, phase II window study of enzastaurin in asymptomatic patients with mCRC and good performance status (PS) who could safely delay chemotherapy for metastatic disease. The primary objective was to assess the 6-month progression-free survival (PFS) rate. In contrast to the standard definition of PFS, progression was defined not only on radiographic imaging [including 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (FDG–PET)] but also by a rise in serum carcinoembryonic antigen (CEA) or lactate dehydrogenase (LDH) or clinical worsening. Secondary objectives included the evaluation of objective response rate, time-to-event efficacy measures and safety, including OS and electrocardiogram (ECG) assessments for QTc prolongation.

**patients and methods**

**eligibility criteria**

Specific selection criteria were followed to include only chemonaive patients (including those who had completed adjuvant chemotherapy 26 months before study entry) with Eastern Cooperative Oncology Group (ECOG) PS of zero or one and who could safely delay standard first-line therapy with curative intent. Patients should have low disease burden as determined by LDH <1.5× the upper limit of normal (ULN) [15, 16]. Patients also had to be asymptomatic for tumor-associated symptoms: persistent pain requiring regular narcotic analgesics, weight loss >5% (unless related to surgery or other illness), persistent nausea requiring medication, obstructive bowel symptoms, and persistent fever with or without night sweats [13]. Additionally, only patients with morphologically documented stage IV adenocarcinoma of the colon or rectum with at least one measurable lesion as defined by the RECIST were included [17]. A partial response is defined as a decrease in the largest diameter by more than 30%, stable disease (SD) as less than a 30% decrease and less than a 20% increase and progressive disease as more than a 20% increase or the appearance of new lesions. Prior adjuvant therapy was permitted if it was completed 6 months before enrollment. All patients had to be at least 18 years of age and have adequate bone marrow reserve and organ function. Patients were excluded if there was evidence of central nervous system metastases, presence of a serious concomitant disorder incompatible with the study, a second primary malignancy not adequately treated within the past 2 years, ECG abnormalities indicative of recent myocardial injury (e.g. myocardial infarction) or medically significant electrophysiological disease (e.g. arrhythmias that were not controlled by medication). All patients had to be off phenytoin, phenobarbital, or carbamazepine.

Patients provided written informed consent before participation in the study, and participation was limited to a maximum of 2 years after enzastaurin treatment was stopped. The study was approved by the ethical committees for each country/region or medical institution and was conducted in accordance with the ethical principles in the Declaration of Helsinki, good clinical practice, and applicable laws and regulations.

**treatment plan**

On the first day, enzastaurin was orally administered as a loading dose of three 400-mg doses given 5–6 h apart (total 1200 mg) and within 30 min after completing meals. After the first day and the loading dose, enzastaurin was administered as a 500-mg dose once daily for the remainder of cycle 1 and continuously administered for all subsequent cycles (one cycle = 28 days). The planned duration of treatment, in the absence of disease progression or other cause for discontinuation, was six cycles.

**baseline and treatment assessments**

At baseline, the following assessments were done: medical history and physical examination, ECOG PS, tumor measurement of palpable or visible lesions, radiological tests [mandatory chest and abdominal/pelvic computerized tomography (CT) scans and recommended FDG–PET scan], CEA, serum chemistry (including LDH and alkaline phosphatase), hematology and slit-lamp ocular examination.

Before each cycle, patients were evaluated for the following: ECOG PS, serum CEA, hematology, serum chemistry with LDH, medical history and physical examination, and assessment of adverse events using the National Cancer Institute—Common Terminology Criteria for Adverse Events grades. For the first 2 months on treatment, monthly radiological assessments of the target lesions were done and if no progression was observed, radiological assessments were conducted every 2 months. At the end of at least 24 weeks after the first dose of enzastaurin (or six cycles), radiological imaging studies were assessed for disease progression at 6 months. Patients who had a response or stable disease (SD) but who discontinued enzastaurin and had not progressed were followed every 2 months until disease progression or the end of the study. After disease progression, patients were followed approximately every 3 months until death or the end of the study.

PFS was defined as the time from the date of the first enzastaurin dose to the first date of documented progressive disease (PD) or death due to any cause, whichever occurred first. PD was defined as an increase in tumor size on the basis of radiographic imaging (including FDG–PET), rise in LDH or CEA, or clinical worsening. OS was measured from the date of the first dose to the date of death due to any cause. The duration of SD for patients with SD was measured from the date of the first dose until the first date of documented PD or death due to any cause, whichever occurred first.

Twelve-lead ECGs (centrally collected and reviewed by two independent cardiology readers) were done at screening and during cycle 1 on day 1 and day 2: before the loading dose, after the third 400-mg dose of the loading dose, and before the once-daily 500-mg dose on day 2. In addition, a 12-lead ECG was carried out on day 1 of cycle 2, at least 2–4 h after receiving the daily enzastaurin dose or at the expected steady-state level for the daily dosing.

**pharmacokinetic evaluations**

Plasma samples for pharmacokinetic evaluation were collected from patients and assayed for enzastaurin using a validated liquid chromatography with tandem mass spectrometry method (LC/MS/MS; Advion BioSciences, Inc., Ithaca, NY) [18]. Blood samples for pharmacokinetic evaluation were collected during cycles 1, 2, and 3 for each patient. Plasma concentration–time data from cycles 2 and 3 (steady state) were overlaid with data from other single-agent enzastaurin studies to evaluate whether enzastaurin disposition in patients with mCRC was similar to patients with other tumor types.

**statistical considerations**

We planned to enroll 40 patients, expecting that 35 patients would be assessable after completing the first cycle of therapy. If at least 5 of the 35
assessable patients were progression free at 6 months, the conclusion would be that the regimen was worthy of further study. If the true 6-month progression-free rate was 5%, there was a 3% probability of falsely concluding that the regimen was worthy of further study. If the true 6-month progression-free rate was 20%, there was an 86% probability of correctly concluding that the regimen was worthy of further study. Clinical judgment on the basis of previous studies conducted in asymptomatic mCRC patients [13, 19] and the anticipated antitumor activity of enzastaurin as observed in early single-agent studies [20, 21] provided the rationale to measure a PFS rate of 20% in this study. The 6-month progression-free rate was estimated from the Kaplan–Meier estimate for PFS, along with a 95% confidence interval (CI), using data from all treated patients.

ECG assessments were conducted to monitor for clinically significant toxic effects and to document alterations in change from baseline for QTcB (Bazett’s correction) intervals and heart rate. QT intervals were adjusted using Bazett’s (QTcB) and Fredericia’s (QTcF) correction [22]. The pretreatment ECG on day 1 of cycle 1 was used as baseline. Given that pharmacokinetic samples were collected at the same time as the ECG recordings on day 1 (1–4 h after the third enzastaurin dose) and on day 2 of cycle 1, an analysis of the relationship between QTc change from baseline and enzastaurin concentration was carried out. A linear mixed-effect model was used to run this analysis with enzastaurin concentration as a fixed effect, RR change from baseline as a covariate, and patient as a random effect [23, 24].

results

Patients were enrolled from September 2005 to March 2008, when the study was closed due to slow enrollment and the intended sample size of 40 patients was not likely to be enrolled within a reasonable time period.

patient characteristics

Thirty patients entered the study. Of the 30 patients, 28 patients were enrolled for treatment (Table 1). Two patients received no study drug for the following reasons: the first had disease progression and the second failed to meet protocol entry criteria. Most patients had prior surgery (86%) and 10 (36%) patients received adjuvant chemotherapy (Table 1). Except for one patient, all patients had LDH levels <1.5× ULN at a mean of 187 U/l, which was considered in normal range for all the study centers (Table 1). One patient with elevated LDH levels was allowed to enter the study because of a lack of tumor-associated symptoms and a historically stable CEA level. CEA levels varied at baseline with a mean of 7.7 μg/l (Table 1). Seven (25%) patients received six or more cycles of therapy, six received six cycles and one received seven cycles.

efficacy

The 6-month PFS of the 28 treated patients was 28% (95% CI 13%–45%) with 5 patients censored from the PFS analysis. The median PFS was 1.9 months (95% CI 1.8–4.5 months). At 3 months, 43% of the patients had been discontinued from enzastaurin treatment (Figure 1). None of the patients had a complete or partial response and 12 patients (43%) had SD. Some minor responses were observed as illustrated by the waterfall plot (Figure 2). The remaining 15 patients (54%) had PD and response could not be determined in one patient. The median duration of SD for the 12 patients was 6.1 months (95% CI 3.6 to not estimable).

All patients were closely monitored for tumor size by RECIST [17], serum LDH and CEA levels [15, 16], and clinical symptoms. In 5 of 28 patients (18%), either elevated CEA or LDH levels led to discontinuation. Three of five patients had concomitant increases of CEA and LDH, while in the other two there was no overlap. In one patient, doubling or near-doubling of CEA levels led to discontinuation after 1 month and in three patients after 2 months. LDH levels increasing by >50 U/l from baseline or >1.5× ULN (350 U/l) led to discontinuation of one patient after 1 month and three patients after 2 months. In the three patients (11%) who had both CEA and LDH elevations, radiological assessment also detected progression in two. Because radiological assessment led to discontinuation for 11 of 28 patients (39%), CT scans were the most sensitive surveillance tool.

safety

No grade 4 toxicity was observed (Table 2). One patient had an isolated grade 3 transaminase elevation that resolved after stopping enzastaurin and was hence deemed to be enzastaurin related. Two patients each had one nonlaboratory grade 3 toxicity including dyspnea, limb edema, and nodal arrhythmia atrial fibrillation. One patient discontinued therapy due to myocardial infarction and a subsequent cerebral hemorrhage leading to death. These events were not considered to be related to enzastaurin on the basis of the preexisting conditions. A third patient suffered from cardiac failure and this incident was
reported as a serious adverse event possibly related to enzastaurin. However, a definitive assessment was not possible due to the patient’s past cardiac disease. Slit-lamp ocular examinations were unremarkable in all patients.

QTc prolongation risks were assessed after the start of the enzastaurin loading dose, at days 1 and 2 of cycle 1 and after longer term exposure at day 1 of cycle 2 (Table 3). The loading dose was not associated with a QTc prolongation at C\text{max} or at trough as determined by QTcB and QTcF (Table 3). Eleven patients (eight males and three females) had a QTcB >450 ms (39%) and seven patients (six males and one female) had a QTcF >450 ms (25%) (Table 4). However, four of the seven...
Table 2. Summary of maximum drug-related CTCAE toxic effects (N = 28)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Number (% of patients)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT, SGPT</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AST, SGOT</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2 (7)</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>γGT</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonlaboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metabolic</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Edema; limb</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GI</td>
<td>4 (14)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rigors/chills</td>
<td>2 (7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CTCAE, Common Terminology Criteria for Adverse Events; N, total number of patients; ALT, alanine transaminase; AST, aspartate transaminase; SGPT, serum glutamic pyruvic transaminase; SGOT, serum glutamic oxaloacetic transaminase; γGT, γ-glutamyl transeptidase; GI, gastrointestinal.

Table 3. Comparison of QTcB and QTcF assessments in patients with asymptomatic mCRC after receiving loading dose of enzastaurin

<table>
<thead>
<tr>
<th>Loading dose (day 1 and day 2 of cycle 1)</th>
<th>QTcB (mean)</th>
<th>QTcB (range)</th>
<th>QTcF (mean)</th>
<th>QTcF (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, N = 29</td>
<td>416.5</td>
<td>367–490</td>
<td>417</td>
<td>366–490</td>
</tr>
<tr>
<td>Pre-dose (day 1 cycle 1), N = 29</td>
<td>426.4</td>
<td>399–535</td>
<td>426</td>
<td>390–535</td>
</tr>
<tr>
<td>Cmax (day 1 cycle 1), N = 28</td>
<td>429.4</td>
<td>390–520</td>
<td>429</td>
<td>390–520</td>
</tr>
<tr>
<td>‘Trough’ (day 1 cycle 1), N = 27</td>
<td>435.8</td>
<td>400–507</td>
<td>433</td>
<td>400–507</td>
</tr>
<tr>
<td>‘Steady state’ (day 1 cycle 2, 2–4 h after enzastaurin), N = 22</td>
<td>436.2</td>
<td>374–549</td>
<td>436</td>
<td>374–549</td>
</tr>
</tbody>
</table>

mCRC, metastatic colorectal cancer; N, total number of patients.

Table 4. Comparison of QTcB and QTcF assessments in patients with asymptomatic mCRC after 28 days of treatment with oral enzastaurin

<table>
<thead>
<tr>
<th>One cycle exposure</th>
<th>Change from baseline to day 1 cycle 2 (ms)</th>
<th>QTcB, n (%) patients (N = 22)</th>
<th>QTcF, n (%) patients (N = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0</td>
<td>6 (27.2)</td>
<td>1 (4.5)</td>
<td></td>
</tr>
<tr>
<td>0–10</td>
<td>5 (22.7)</td>
<td>7 (31.8)</td>
<td></td>
</tr>
<tr>
<td>10–20</td>
<td>6 (27.2)</td>
<td>7 (31.8)</td>
<td></td>
</tr>
<tr>
<td>20–30</td>
<td>4 (18.2)</td>
<td>3 (13.6)</td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>1 (4.5)</td>
<td>4 (18.2)</td>
<td></td>
</tr>
</tbody>
</table>

mCRC, metastatic colorectal cancer; N, total number of patients.

associated increased QTcF interval. QTc prolongation was not associated with the time-matched exposure levels of enzastaurin or its metabolites.

pharmacokinetics

Plasma concentration data at steady state were available from 25 patients during cycle 2 and 16 patients during cycle 3. The concentration–time profile of enzastaurin was comparable to that seen in a previous phase I study [25]. The exposures in cycle 2 and cycle 3 were comparable, showing that exposures of enzastaurin are not altered following continuous administration (data not shown).

discussion

Although slow enrollment prevented this study from achieving its planned sample size of 35 assessable patients, the protocol-defined primary objective was reached with a PFS rate at 6 months of 28% compared with the projected 20%. Several factors need to be considered when interpreting the study results other than the statistical factors associated with not achieving the required sample size.

First, no objective responses, as defined by RECIST, were observed [17]. This is not unexpected for an antiangiogenic compound and is reminiscent of the early single-agent studies with bevacizumab [26]. Because of its presumed mechanism of action as a cytostatic drug, enzastaurin activity may be best assessed by analyzing changes of tumor size from baseline (Figure 2). As illustrated by a ‘waterfall plot,’ a reduction of tumor size from baseline was associated with some patients who had SD. Hence, a response as typically seen for conventional cytotoxic agents was not seen here.

Secondly, the antitumor activity of enzastaurin may be on the basis of the presence of its target in mCRC. There are few studies evaluating the expression of PKC-β in patients with CRC [27]. On the basis of a recent immunohistochemistry study, only 18% of the examined samples showed a detectable level of PKC-β and a trend between high PKC-β expression and poor survival was observed [28]. Hence, the PFS rate at 6 months of 28% may reflect activity of enzastaurin in a patient population in which PKC-β expression is either present or active in a proportion of the tumors.

Thirdly, the selection of asymptomatic patients with mCRC for this study is unique. To our knowledge, only two other
studies have been conducted in asymptomatic patients with mCRC cancer: the Nordic Gastrointestinal Tumor Adjuvant Therapy Group (Nordic Trial) [20] and the combined Australasian Gastrointestinal Trials Group (AGITG) and National Cancer Institute of Canada [13]. Compared with these trials, we also had >80% of the patients with PS status of zero [13]. Because OS rate was not the primary objective of this study, only censored survival information was available at study closure. The censored survival rate at 20 months was 77% (95% CI 47% to 92%). Considering the patient selection and the censor rate, it is difficult to compare this information with OS from other studies in patients with mCRC. Since the enzastaurin treatment was interrupted as soon as PD was present, and appropriate chemotherapy could be given, OS is not primarily an efficacy measure of enzastaurin but rather a safety measure of the window design. A detailed long-term follow-up of the OS is presented elsewhere (Glimelius et al., [29]).

It is also difficult to compare disease progression end points of our study with those from previous studies in mCRC patients [13, 20]. In previous studies in asymptomatic patients with mCRC, time-to-symptoms (TtS) was selected as an end point. TtS was ~5 months in the AGITG study [13] and ~5.9 months in the Nordic Trial [20]. In contrast to the previous studies, we used tumor surveillance tools with higher sensitivity: (i) None of the previous studies used LDH and/or CEA levels to discontinue patients. Exceeding the recommended guidelines for CEA assessments, in which two values above baseline measured every 2–3 months are an indication of PD [30], investigators were allowed to declare progression if LDH or CEA values were already rising after 1 month. (ii) LDH levels were used to exclude patients with high tumor burden and we monitored LDH levels monthly to detect rapidly growing tumors [15, 16]. (iii) We monitored patients closely at the beginning of the study using monthly CT scans for the first 2 months of treatment and then every 2 months thereafter. The earlier studies employed monthly clinical assessments with radiological assessment of tumor growth every 3 months [13] or every 2 months in the Nordic trial [20]. Thus, it is likely that we were detecting patients earlier in their progression compared with the previous studies, explaining the shorter PFS compared with the other studies. Unfortunately, the FDG–PET imaging in this study was not consistently carried out but may further improve the surveillance for tumor progression in future window trials [31]. However, in a prospective study in patients with mCRC treated with an irinotecan–5-fluorouracil combination, FDG–PET imaging after 4 weeks of treatment (two cycles) could not reliably predict responses [32].

Because patients were selected on the basis of high PS, low disease burden, and minimal tumor-associated symptoms, they represent a better-than-average phase I or II population to conduct QTc risk-assessment studies. Median age was, however, 7 years higher than is average in mCRC chemotherapy trials (69 versus 62 years) [15]. Such studies are being increasingly requested by regulatory authorities for novel oncology drugs [33, 34]. In our study, QTc prolongations of >30 m compared with baseline were observed, but they did not reproduce at subsequent administration. Given the similarities to the findings in healthy volunteers [19], the baseline variability of QTc results in cancer patients, the lack of consistent QTc prolongation in patients treated for ≥28 days, and the missing correlation of QTc prolongation with exposure data, it remains doubtful whether enzastaurin has a risk for causing medically significant QTc prolongation in cancer patients. Finally, enzastaurin was well tolerated with the exception of one patient who had grade 3-transaminase elevation without clinical symptoms of hepatitis and whose case was similar to previously reported isolated liver enzyme elevations [35].

In summary, although the study was stopped early because of poor enrollment, enzastaurin may have weak single-agent activity in some patients with mCRC. However, as with bevacizumab, its activity may be detected when it is combined with cytotoxic agents. Recent studies in animals show that enzastaurin is not cytotoxic, but a potent inhibitor of tumor angiogenesis and lymphangiogenesis [36], and support this analogous concept to bevacizumab. Lastly, we consider that a window trial in asymptomatic mCRC patients is justified and safe and can be used to evaluate new drugs like enzastaurin provided that stringent selection criteria and close monitoring are applied.

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references

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