Phase II Study of Irinotecan in Combination with Capecitabine on a 3-Weekly Schedule as First-Line Chemotherapy for Patients with Metastatic or Locally Advanced Colorectal Cancer

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Abstract: *Background*: Capecitabine has demonstrated non inferiority efficacy and improved safety compared with 5-fluorouracil (5-FU)/leucovorin (LV) in metastatic colorectal cancer (mCRC) without the inconvenience of an infusional therapy. The aim of the present study was to evaluate the efficacy and safety of capecitabine plus irinotecan (CPT-11) given every 3 weeks (XELIRI regimen) as first-line treatment in locally advanced (LA) or mCRC, in order to improve patient tolerability and quality of life. *Patients and methods*: Patients with LA or mCRC received CPT-11 225 mg/m^2 (180 mg/m^2 if > 65 years old) on day 1 and capecitabine 1000 mg/m^2 (750 mg/m^2 if > 65 years old) twice daily on days 2-15 every 3 week. Primary endpoints were objective response rate (ORR) and toxicity of the chemotherapeutic regimen. Secondary endpoints of overall survival (OS), progression-free survival (PFS), response duration and quality of life were also evaluated.

Results: Ninety-one patients were included. In an intention-to-treat analysis, complete response was achieved in 3 patients and partial response in 27, for an ORR of 33%. The disease control rate (ORR + stable disease) was 72.5%. Median time to progression and OS were 9.3 and 17.1 months respectively. Grade 3/4 neutropenia and diarrhea were the most commonly reported adverse vents.

Conclusion: The XELIRI regimen given every 3 weeks, as first-line therapy of LA or mCRC was effective and well tolerated, including elderly patients. Severe gastrointestinal toxicities and hematological events were manageable.

Keywords: CPT-11, Capecitabine, Irinotecan, XELIRI regimen, Colorectal cancer.

INTRODUCTION

Colorectal cancer (CRC) remains one of the most common types of cancer in Western countries [1], and at diagnosis, approximately 30% of patients with CRC already have metastatic disease and 50% of early-stage patients eventually develop metastases [2]. Until several years ago, 5-fluorouracil (5-FU) was the elective first-line therapy for mCRC. In an attempt to improve its efficacy, coadministration with leucovorin (LV) was instituted [3]. It was subsequently found that 5-FU infusion regimens provided a superior tumor response and achieved a slight increase in overall survival (OS) and safety benefits over bolus 5-FU [4], but this effect was associated with complications and the inconvenience of central venous access [5].

Capecitabine is an inactive oral prodrug that is preferentially converted to 5-FU in tumor tissue [6] representing an attractive oral alternative to intravenous 5-FU. Capecitabine as monotherapy was found to be at least as effective and well tolerated as 5-FU/LV as a first-line treatment of mCRC in three phase III trials [7]. Additionally, oral administration makes it more convenient, increasing acceptability and enabling chronic dosing, which results in continuous exposure to 5-FU without requiring central venous access.

Irinotecan (CPT-11) has been successfully used as monotherapy in the treatment of mCRC [8], as well as a second-line therapy after 5-FU failure [9]. Several studies have described CPT-11 in combination with 5-FU/LV as a feasible regimen in the first-line treatment of mCRC, with improved response rate, time to disease progression (TTP) and OS, and an acceptable safety profile compared with 5-FU/LV alone [10].

Several investigators tested the combination of irinotecan with capecitabine in an attempt to improve the results of available 5-FU/LV-based regimens. Encouraging efficacy results from phase II studies with combination regimens of capecitabine and irinotecan were reported as first line treatment on mCRC, not only on a weekly schedule (CAPIRI) but also on a 3-weekly dosing regimen (XELIRI) [11-15]. However, dose reductions of both drugs were necessary in most

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studies to improve safety profile of this regimen. Although some phase III trials have associated this combination with an elevated rate of hematological and gastrointestinal events [16,17], the CAIRO study showed that XELIRI was effective and had an acceptable toxicity with dose reduction [18]. This open-label phase II trial was designed to evaluate the efficacy and safety of the XELIRI regimen as first-line therapy in patients with LA or mCRC in an attempt to identify the optimal doses for the capecitabine-irinotecan combination.

MATERIAL AND METHODS

This study was a multicenter, open-label phase II clinical trial. The study was approved by the Ethics Committee of all centers involved and was conducted according to the Declaration of Helsinki, Good Clinical Practices and local regulatory requirements. Signed informed consent was obtained from all patients prior to study enrolment.

Patient Eligibility

Patients with histologically confirmed LA or mCRC between 18 and 75 years-old were eligible for entry into the study. Those with only one metastasis or local recurrence were confirmed by biopsy. Other selection criteria were the absence of previous chemotherapeutic treatment, except any adjuvant treatment completed at least 6 months before inclusion in the study, as well as no possibility for initial complete surgical resection. Patients had to present acceptable hematological counts (neutrophils ≥ 1,500/μL; platelets ≥ 100,000/μL; hemoglobin ≥ 10 g/dL), satisfactory renal function (creatinine ≤ 135 μmol/L or ≤ 1.5 mg/dL) and hepatic function (in the absence of hepatic metastases: bilirubin ≤ 1.25-fold the normal value; GPT/GOT ≤ 2.5-fold the normal value; alkaline phosphatase [ALP] ≤ 2.5-fold the normal value; in the presence of hepatic metastases: bilirubin ≤ 1.5-fold the normal value; GPT/GOT ≤ 5-fold the normal value; ALP ≤ 5-fold the normal value). Only patients with a performance status Eastern Cooperative Oncology Group (ECOG) ≤ 2 and those with a life expectancy of at least 3 months were eligible.

Treatment Schedule

XELIRI chemotherapy consisted of 225 mg/m^2 CPT-11 (180 mg/m^2 if > 65 years old) on day 1 and capecitabine 1000 mg/m^2 (750 mg/m^2 if > 65 years old) twice daily on days 2-15 every 3 week. Treatment was maintained until disease progression, drug intolerance, treatment patient refusal, investigator decision or death. Patients received standard hydration and antiemetics.

Study Assessments

Baseline evaluation included medical history, physical examination, a complete blood count and chemistry, serum levels of carcinoembryonic antigen (CEA) and baseline tumor measurements of by CT scan. Patients were assessed for response every 3 cycles (9 weeks) and for toxicity on days 1 and 9 of each application of the cytotoxic drugs. After 30 days of discontinuation of study treatment and then every 2 months, a follow-up examination, including clinical examination, blood samples and toxicity evaluation was performed until the progression of the disease or death.

Tumor response evaluation of mesurable lesions was based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1 [19]. Confirmed, partial or complete responses or stable disease required to be confirmed by a further scan taken at one month.

The objective response rate (ORR) was defined as the sum of complete and partial responses. In order to use a reference to characterize objective tumor response, evaluations at a baseline identified, measured and registered a maximum of 5 tumor lesions per organ and 10 lesions in total. From these lesions, those with the largest diameter and suitability for exact repeated measurements were selected and the sum of their largest diameters was used as the reference. OS was defined as the time between inclusion in the study and death and TTP until progression of disease. Response duration was defined as the time between an observation of objective response (partial or complete) and disease progression, whereas time to treatment failure covered the period from the beginning of the study until disease progression.

Toxicity was defined as the frequency of hematological and nonhematological, chemotherapy-associated adverse events and laboratory changes. Toxicity data were graded according to National Cancer Institute Common Terminology criteria for Adverse Events (NCI-CTC) version 2.0.

Quality of Life Measurement

The quality of life was evaluated with the EuroQoL at baseline, and every odd cycle and 30 days after

stopping study treatment. Evaluable patients included those who had at least three evaluations performed. In addition, the general health status was self-evaluated using the EQ Visual Analog Scale.

Statistical Analysis

Our hypothesis was that the proposed chemotherapeutic treatment would result in a 30% response rate. According to Simon's two-stage design, 81 patients were required for this objective, with a calculated α-error of 5% and a statistical power of 80%. Considering a maximum of 10% loss to follow-up, the total number of patients to be recruited was 90. In the first stage, 27 patients were to be assessed; we expected that more than 9 objective responses would be observed.

The primary endpoint of the study was to determine the ORR and tumor response according to the RECIST as parameters of efficacy. Additionally, the safety profile of the chemotherapeutic regimen was evaluated. Secondary endpoints included OS, disease-free survival, TTP and the quality of life of the patients.

For quantitative variables, the mean, standard deviation and median were calculated, whereas the qualitative variables were described using the absolute and relative frequencies. Antitumor efficacy was studied in two populations: intent-to-treat (ITT), and per protocol (PP). The ITT population was defined as all patients included in the study, whereas PP included only evaluable patients who met inclusion criteria. The response rates and their corresponding 95% confidence intervals (95%CIs) were calculated. Overall and progression-free survivals were estimated according to Kaplan-Meier methodology. All patients administered at least one cycle of chemotherapy were evaluated for toxicity.

RESULTS

Patient Characteristics

From February to December 2002, 91 patients with CRC were recruited and included in the ITT population. Of these 83 met the inclusion criteria (PP population). Forty one patients (45.1%) withdrew from the study because of disease progression. The study population was followed for up to a median of 18.0 months. Baseline characteristics of the patients are summarized in Table **1**. More than half of the patients evaluated were male (61.5%). The majority had an ECOG performance status of 0−1 (92.4%). Most of the patients showed metastasis in the liver (71.4%) and lung (41.8%). The median number of metastatic sites was 2 and the median lesion number was 4. Specific tumor characteristics are shown in Table **2**. At baseline, stage IV was found in 38 of 54 patients (70.4%) with colon cancer and 21 of 33 patients (63.6%) with rectal cancer. Approximately 75% of the patients had previously undergone surgery.

Table 1: Baseline General Characteristics (Intent-to-Treat Population)

	N = 91
Sex	
Male	56 (61.5)
Female	35 (38.5)
Age (years)[¥]	67.0 (29.6 -75)
ECOG performance status	
0	43 (47.3)
1	41 (45.1)
2	7 (7.7)
Time to diagnosis (months)[#]	14.1 ± 26.1
Primary tumor site	
Colon	54 (59.3)
Rectal	36 (36.3)
Colorectal	1 (4.4)
Site of metastases*	
Liver	65 (71.4)
Lung	38 (41.8)
Local recurrences	14 (15.1)
Bone	1 (1.1)
Lymph nodes	19 (20.9)
Others	14 (15.4)
Number of metastatic sites	
0	4 (4.4)
1	38 (41.8)
2	34 (37.4)
>2	15 (16.5)
Number of lesions	
1	6 (6.7)
2	11 (12.1)
3	15 (15.6)
> 3	59 (65.6)

*Patients can present more than one location.
Data are number of patients (%).
Exceptions:
[¥]: median (IQR: Q1–Q3).
[#]: mean (±SD).

Table 2: Baseline Tumor Characteristics (Intent-to-Treat Population) N=91

	Colon n =54	Rectal n = 33	Colorectal n =4
Grade			
GX	12 (23.1)	11 (33.3)	
G1	13 (25.0)	5 (15.2)	
G2	22 (42.3)	14 (42.4)	3 (75)
G3	5 (9.6)	2 (6.1)	1 (25)
G4		1 (3.0)	
Stage			
I	1 (1.9)	2 (6.1)	
II	5 (9.3)	4 (12.1)	
III	10 (18.5)	6 (18.2)	
IV	38 (70.4)	21 (63.6)	4 (100)
Pretreatment			
Surgery	41 (75.9)	24 (72.7)	3 (75)
Adjuvant chemotherapy	12 (22.2)	9 (27.3)	1 (25)
Radiotherapy		9 (27.3)	

Data are number of patients (%).

Treatment

A total of 633 cycles of CPT-11 and capecitabine were administered by the end of the study, with a median of 6.0 (range 1-18) cycles per patient. The administration of 100 cycles (16.1%) was delayed. Capecitabine dose was reduced in 26 cycles (4.1%), whereas CPT-11 dose was reduced in 22 cycles (3.5%).

Response

Tumor responses rates are shown in Table **3**. In the ITT population (n = 91), 39.6% (95% CI; 32.4-43.4%) of the patients showed stable disease (SD) according to RECIST criteria, and 29.7% (95% CI: 20.9-37.9%) had a partial response (PR). Three patients (3.3%; 95% CI: 2.4-4.8%) exhibited a complete response (CR) to therapy. The ORR (CR+PR) was 33.0% (95% CI: 23.3–42.7%). The disease control rate (ORR+ SD) was 72.5% (95% CI: 63.3-75.2%).

Table 3: Tumour Responses to the Therapy

	ITT population n = 91	PP population n =83
Complete response (CR)	3 (3.3) (95% CI 2.4-4.8%)	3 (3.6) (95% CI 2.3-4.6%)
Partial response (PR)	27 (29.7) (95% CI 20.9-37.9%)	24 (28.9) (95% CI 22.4-33.6%)
Stable disease (SD)	36 (39.6) (95% CI 32.4-43.4%)	33 (39.8) (95% CI 31.3-42.1%)
Progressive disease	17 (16.7) (95% CI 12.2-19.1%)	15 (18.1) (95% CI 12.4-22.3%)
Not assessable	8 (8.8) (95% CI 5.6-9.8%)	8 (9.6) (95% CI 5.3-11.8%)
Objective response rate (CR+PR)	30 (33.0) (95% CI 23.3-42.7%)	27 (32.5) (95% CI 22.4-42.6%)
Disease control rate (CR+PR+SD)	66 (72.5) (95% CI 63.3-75.2%)	60 (72.3) (95% CI 62.7-81.9%)

Data are number of patients (%).
Abbreviations: ITT, intention-to-treat; PP, per protocol.

The median OS was 17.1 months (95% CI: 13.3–20.9 months), the median TTP was 9.3 months (95% CI: 8.2–10.3 months), the median response duration was 9.3 months (95% CI: 5.4–13.3) and the median time to treatment failure was 8.8 months (95% CI: 6.9−10.6 months).

Safety

Adverse events are summarized in Table **4**. The most commonly reported grade 1 and 2 adverse events were anemia (78.6%) and alopecia (57.1%), followed by asthenia (52.3%) and diarrhea (45.2%), in patients under 65 years of age. Anemia was reported in 77.6% of the population over 65 years, and leukopenia and neutropenia each occurred in 45%. Most frequent grade 3 and 4 adverse events were neutropenia, diarrhea and asthenia in patients under 65 years of age (21.4%, 19.0% and 14.3%, respectively) and in the elderly population (24.5%, 30.6% and 22.4%, respectively). Grade 4 neutropenia was reported in 3 patients, and grade 4 diarrhea in one patient. No other

Table 4: Treatment –Related Adverse Events

Grade 1 and 2 Adverse Events Reported N=91		
	< 65years n = 42	**> 65years n = 49**
Anemia	33 (78.6)	38 (77.6)
Leukopenia	16 (38.1)	24 (49.0)
Neutropenia Neutropenia febril	17 (40.5) -	24 (49.0) -
Vomiting	15 (35.7)	12 (24.5)
Constipation	11 (26.2)	19 (38.8)
Diarrhea	19 (45.2)	8 (19.0)
Nausea	12 (28.6)	1 (2.4)
Anorexia	10 (23.8)	2 (4.8)
Mucositis	10 (23.8)	-
Alopecia	24 (57.1)	21 (42.9)
Hand-foot syndrome	11 (26.2)	-
Asthenia	22 (52.3)	20 (40.8)
Pain	14 (33.3)	19 (38.8)
Hepatic disorders	-	11 (22.4)

Data are number of patients (%).

Grade 3 and 4 adverse events reported N=91		
	< 65years n = 42	**> 65years n = 49**
Anemia	-	3 (6.1)
Leukopenia	5 (11.9)	7 (14.3)
Neutropenia Neutropenia febril	9 (21.4) 1	12 (24.5) 1
Vomiting	-	6 (12.2)
Diarrhea	8 (19.0)	15 (30.6)
Anorexia	-	5 (10.2)
Hand-foot syndrome	3 (7.1)	-
Asthenia	6 (14.3)	11 (22.4)
Pain	3 (7.1)	-
Hepatic disorders	3 (7.1)	-

Data are number of patients (%).

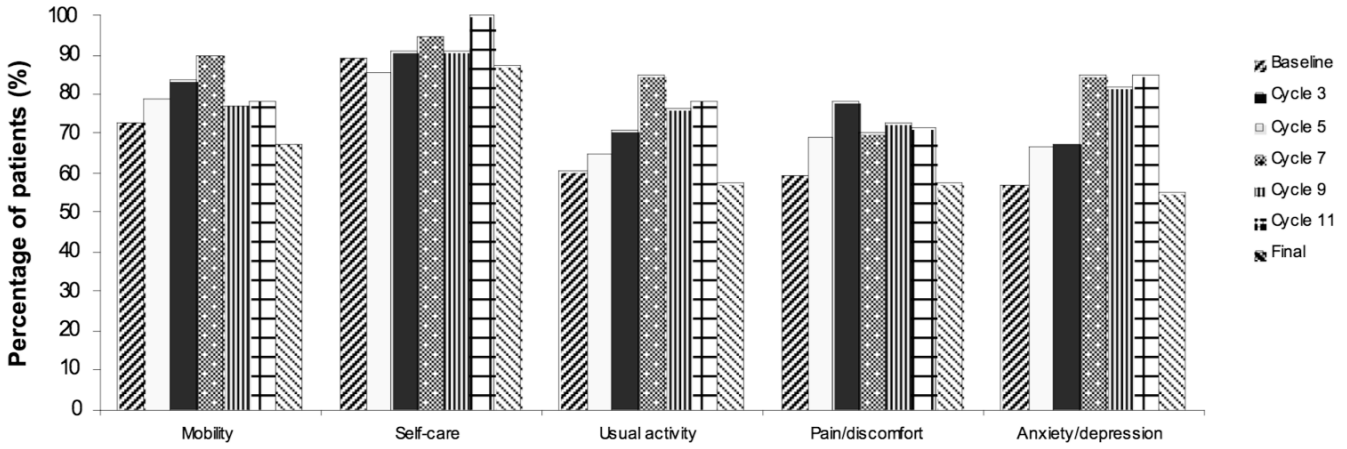

Figure 1: Evolution of patient self-reported health status over the study period.

It is represented the percentage of patients who self-responded good in the different dimensions of health status of the EuroQoL questionnaire (mobility, self-care, usual activity, pain/discomfort and anxiety/depression) at baseline, after every chemotherapeutic cycle and final visit.

grade 4 toxicities were recorded. Hand–foot syndrome, which is commonly associated with capecitabine administration, was reported as grade 3−4 in 3 patients (7.1%) under 65 years of age, and none of the elderly patients.

Overall, 80 patients (87.9%) died during the study period, 71 (88.8%) due to tumor progression and 3 (3.8%) due to toxicity. Five patients (6.3%) discontinued the study for toxicity.

Quality of Life

Evolution of the self-reported health status over the study period is represented in Figure **1**. In all dimensions of the EuroQoL test (mobility, self-care, usual activities, pain/discomfort and anxiety/ depression), a progressive improvement in patient's health status was observed after each cycle with the XELIRI regimen (odd cycles from the third to the eleventh). In the EuroQoL VAS test, patients reported their health state with increasing positive values (scores ≥ 50) over the study period. At baseline, the mean score was 74.7±17.5 (n = 83) which increased up to 82.0±13.9 (n = 19) after cycle 7. Overall improvement in both the qualitative and quantitative analysis of the EuroQoL questionnaire was slightly decreased at the end of the study.

DISCUSSION

Although 5-FU has been used for decades as a first-line therapy in mCRC, several studies have confirmed capecitabine as an alternative to 5-FU, either as a monotherapy or in combination regimens [7]. Treatment with 5-FU/LV has been assessed in combination with irinotecan (FOLFIRI), showing improved survival and an acceptable safety profile [10,20,21]. The aim of our study was to evaluate

Table 5: Comparison of our Results with Previous Studies

Study	Nº of patients	ORR (%)	TTP (moths)	OS (months)
Bajetta *et al.* [11]	134	46	8.3	ND
Borner *et al.* [12]	75	35	9.2	24.7
Cartwright T *et al.* [13)]	42	45	6.2	13.4
Patt YZ *et al.* [14)]	52	50	7.8	16.8
Fuchs *et al.* [16)]	145	38.6	5.8	18.9
Koopman M *et al.* [18]	402	41	7.8	17.4
Choi CK *et al.* [22]	43	51.3	10	15
Skof E *et al.* [23)]	87	49	10.3	30.7
Current study	91	33	9.3	17.1

capecitabine combined with irinotecan on a 3-weekly schedule (XELIRI), as oral administration of capecitabine provides additional benefits over infusion schedules by avoiding central venous catheter discomfort and reducing overload in hospitals. Our regimen showed benefits in terms of efficacy, with an ORR of 72.5% and a median TTP of 9.3 months, which is similar and consistent with findings for this regimen in other studies (Table **5**) [14,22,23].

In terms of safety, the risks and benefits of regimens with capecitabine and CPT-11 have long been debated. Some studies, such as BICC-C, EORTC or CAIRO, described greater toxicity for regimens with capecitabine compared to FOLFIRI or a sequential regimen with oxaliplatin [16-18]. In contrast, our results indicate that the toxicity commonly associated with these chemotherapeutics (hematological or gastrointestinal events) is manageable when a controlled dose-reduction schedule is applied in patients who are considered at risk. We reported a death rate due to toxicity of 3.8%, whereas the BICC-C and EORTC trials reported 3.5% and 11.3%, respectively for the CAPIRI regimen and 3.6% and 4.9%, respectively, for the FOLFIRI regimen. With respect to grade 3 and 4 toxicities, neutropenia was reported in 21.4% (24.5% in elderly population) and diarrhea in 19% (30.6% in elderly) of patients in our study, which were lower than other trials except for neutropenia in EORTC trial (BICC: 31.9% neutropenia and 47.5% diarrhea; EORTC: 1,9% and 37,2%, respectively).

In our study, the irinotecan dose was reduced according to the protocol in 22 cycles (3.5%) and the capecitabine dose was reduced in 26 cycles (4.1%) due to hematological and nonhematological toxicities. Moreover, the implementation of dose reductions in older patients contributed to a better tolerability profile in this population, which was thereafter done by other groups investigating the XELIRI regimen in patients with known risk factors (renal impairment, previous pelvic irradiation or older age) [14,24,25].

The combination of the oral fluoropyrimidine with oxaliplatin on a 2-weekly (CAPOX regimen) or 3-weekly schedule (XELOX regimen) has demonstrated noninferior efficacy and safety compared with combinations of oxaliplatin and 5-FU/FV in mCRC [26,27]. In a phase II trial conducted in Germany, both XELOX and XELIRI regimens were found to have similar efficacy and tolerability as first-line therapies of mCRC [28].

Other investigations of this type of cancer include targeting novel cellular entities, such as bevacizumab [29,30], cetuximab [31] or panitumumab [32]. Several investigations have demonstrated that bevacizumab with XELIRI is an effective regimen for mCRC first-line treatment with a good tolerability [30,33,34]. This 3-weekly schedule regimen may represent and advantageous alternative for the combination with bevacizumab or panitumumab.

Results from this non-comparative phase II clinical trial support the conclusions obtained in the literature available assessing this chemotherapeutic regimen as a feasible treatment for mCRC patients. Additionally, the XELIRI regimen, whose toxicity has been called into question in several studies, proved to be manageable on a 3-weekly dose schedule when a protocol for dose reduction was applied and clinical events were closely monitored, particularly in elderly patients. The quality of life of the patients was also enhanced with oral administration. The present study has some limitations that should be considered. One limitation of the study is that the planned capecitabine dose was lower in patients older than 65 years instead of adjusting the dose according to creatinine clearance which is a more accurate method. Reduction of irinotecan and capecitabine doses in order to improve tolerability could lead to a reduction in efficacy compared to the standard therapy with FOLFIRI that has higher dose intensity. Additionally, a clinical trial comparing the 3-weekly schedule with standard higher dosage regimens would have allowed us to obtain more robust conclusions. However, some of the reviewed studies also used a reduced dosage as in our study. Although the study was done in 2002, is interesting to report its results due the possibility to combine this scheme with new targeted therapies.

CONCLUSION

The results of our study indicate that a 3-weekly XELIRI regimen is effective as first-line chemotherapy in LA and mCRC. The implementation of a dose reduction schedule when necessary (e.g., risk population, toxicity), appears to result in a safer regimen than other schedules previously used. Replacing infused 5-FU/LV with oral capecitabine in combination with irinotecan also offers benefits to the patient by reducing discomfort and avoiding central venous access.

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