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Original Research

Phase I dose-escalation of trifluridine/tipiracil in combination with oxaliplatin in patients with metastatic colorectal cancer

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Abstract ***Background and objectives:*** Pre-clinical data have shown that combining trifluridine/tipiracil with oxaliplatin enhances anti-tumour activity compared with either monotherapy. A phase I dose-escalation study was conducted to determine the maximum tolerated dose (MTD), recommended dose (RD) for phase II and pharmacokinetic profile of this combination in patients with metastatic colorectal cancer (mCRC) who had progressed after at least 1 prior line of treatment.

Methods: Using a 3 + 3 design, patients received escalating trifluridine/tipiracil doses from 25, then 30 and to 35 mg/m^2 twice daily, days 1–5, q14 days, together with a fixed dose of 85 mg/m^2 of oxaliplatin day 1, q14 days. An intermediate cohort with a lower oxaliplatin dose (65 mg/m^2) was also investigated. After MTD determination, additional patients were treated to define the RD.

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Results: Twenty-four patients were enrolled. One dose-limiting toxicity of grade 3 febrile neutropenia was observed at the highest dose level, which was established as the MTD and subsequently the RD. The most common drug-related adverse events (AEs) were asthenia, nausea, diarrhoea, peripheral neuropathy, neutropenia, decreased appetite, thrombocytopenia, vomiting, anaemia and peripheral sensory neuropathy. Most drug-related AEs (93.0%) were of grade 1–2. Pharmacokinetic parameters of trifluridine/tipiracil were not influenced by oxaliplatin co-administration. Best overall responses at the RD (n = 14) included 1 patient with partial response (7.1%) and 7 patients with stable disease (50.0%).
Conclusion: The combination of trifluridine/tipiracil and oxaliplatin in patients with mCRC has a manageable safety profile with some efficacy. The RD is 35 mg/m^2 of trifluridine/tipiracil twice daily, days 1–5, q14 days and 85 mg/m^2 of oxaliplatin day 1, q14
Clinicaltrials.gov number: NCT02848443.

1. Introduction

Trifluridine/tipiracil (also known as TAS-102) is an oral chemotherapeutic agent approved for the treatment of chemorefractory metastatic colorectal cancer (mCRC). In the pivotal phase III, randomised, double-blind trial (RECOURSE) on 800 patients with mCRC refractory or intolerant to standard treatments, including fluoropyrimidines, trifluridine/tipiracil plus best supportive care (BSC) showed a 1.8-month improvement in median overall survival (primary end-point) over placebo plus BSC (7.1 months versus 5.3 months; hazard ratio for death, 0.68; $p < 0.0001$) [1]. Trifluridine/tipiracil was also found to have a favourable safety profile with toxicity generally manageable by dose delay/reduction or supportive care [1].

Oxaliplatin is a platinum derivative, with modest anti-tumour activity when used alone, and it is therefore usually administered in combination with other agents, such as fluoropyrimidines [2].

Results of pre-clinical studies have suggested improved efficacy of trifluridine/tipiracil when combined with oxaliplatin compared with either monotherapy, supporting the rationale for clinical use. The combination trifluridine/tipiracil and oxaliplatin showed synergistic activity, for both fixed and variable agent ratios, in terms of DNA damage and apoptosis in CRC cell lines *in vitro* [3]. The combination also enhanced inhibition of tumour growth compared to either monotherapy in a CRC and gastric cancer xenograft–bearing nude mouse model, with activity in 5-fluorouracil–resistant gastric tumours [4], and increased markers of immunogenic cell death versus either monotherapy in murine microsatellite-stable CRC cells *in vitro* [5].

We conducted a phase I dose-escalation study with the primary objective of determining the maximum tolerated dose (MTD) and recommended dose (RD) and assessing the safety profile of trifluridine/tipiracil in combination with oxaliplatin in patients with mCRC who had progressed after at least one prior line of treatment. Secondary objectives included characterisation of the regimen's pharmacokinetic (PK) profile and analysis of its anti-tumour activity.

2. Methods

2.1. Study design and treatments

This was an open-label, dose-escalation study using a conventional 3 + 3 design conducted in 6 centres (3 in France and 3 in Spain) to determine the MTD, RD and safety profile of trifluridine/tipiracil with oxaliplatin, as well as the evaluation of pharmacokinetics (ClinicalTrials.gov number: NCT02848443).

An institutional review board or ethics committee approved the study at each participating centre and country. All patients provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

2.1.1. Dose escalation

To reduce the additive toxicity of the chemotherapy combination, such as neutropenia, trifluridine/tipiracil regimen was adapted to a 14-day treatment cycle instead of the standard 28-day cycle. The study design considered 3 dose levels of trifluridine/tipiracil starting at 25 then 30 and 35 mg/m^2 orally twice daily on days 1–5, followed by a 9-day recovery period from days 6–14, together with oxaliplatin as a 2-h fixed dose infusion of 85 mg/m^2 on day 1 of each treatment cycle. At each dose level, and in case of dose-limiting toxicity (DLT), a de-escalation to 65 mg/m^2 of oxaliplatin was permitted. As chemotherapy-induced nausea and vomiting (CINV) remains a significant concern for patients receiving chemotherapy, prophylactic anti-emetic agents (e.g. dexamethasone with ondansetron or granisetron) were recommended for acute and delayed emesis after administration of moderate emetogenic agents such as oxaliplatin.

Patients could remain on combination therapy or trifluridine/tipiracil monotherapy until disease progression, development of unacceptable toxicity, investigator decision or withdrawal of consent.

At each dose level and before escalation to the next level, a safety study board comprising representatives from the study sponsor and investigators reviewed individual patient safety, DLTs and PK. DLTs were defined as toxicities related to the combination (Table 1) and those occurring within the first 28 days of therapy (2 treatment cycles).

The MTD was defined as the highest dose level at which less than 33% of evaluable patients treated experienced a DLT during cycle 1 or 2 of treatment. Once the MTD was established, additional patients at that dose level were enrolled to generate further safety data. At the completion of dose escalation, the study board evaluated safety to define the RD.

2.1.2. Patient selection

Eligible patients were aged ≥18 years with histologically confirmed mCRC pre-treated with at least one line of standard chemotherapy for metastatic disease. In addition, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, a life expectancy of >3 months, adequate bone marrow, liver and kidney function and at least 1 evaluable or measurable metastatic lesion per revised Response Evaluation Criteria In Solid Tumours (RECIST), version 1.1 [6]. Key exclusion criteria included grade ≥2 peripheral neuropathy and prior treatment with trifluridine/tipiracil. There was no upper limit to the number of prior anti-neoplastic regimens received, and prior exposure to oxaliplatin was permitted, provided the treatment was not discontinued for toxicity due to oxaliplatin and the patient had not experienced grade ≥3 hypersensitivity (or grade 1–2 not controlled with pre-medication) due to oxaliplatin.

2.2. Safety and efficacy assessments

Safety assessments comprised physical examination including vital signs, weight, performance status assessment, documentation of adverse events (AEs) and concomitant medication, with regular monitoring of haematology and biochemistry (on days 1 and 8 of treatment cycles 1 and 2 and on day 1 of subsequent cycles) and urinalysis (day 1 of each cycle). Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, and Levi grading [7] (for peripheral sensory neuropathy). At this stage, patients were not required to have measurable disease. Anti-tumour activity was assessed by radiological assessments according to revised RECIST, version 1.1, at baseline (within 28 days prior to day 1 of cycle 1), then every 4 cycles of treatment and at the end of treatment.

2.3. Pharmacokinetics

Samples for PK analysis were collected for all patients treated in dose escalation, except additional patients enrolled to determine the RD. The predicted exposure to trifluridine/tipiracil at each dose level was not to exceed the exposures previously observed at the monotherapy MTD of 35 mg/m^2 twice daily. Whole blood samples (5 mL) were obtained at pre-defined time points on days 1, 2 and 5 of cycle 1 and days 1 and 5 of cycle 2. Blood concentrations of trifluridine (FTD), 5-trifluoromethyluracil (FTY; inactive FTD metabolite) and tipiracil (TPI) were determined by a validated method using solid-phase extraction followed by liquid chromatography with tandem mass spectrometric detection; oxaliplatin was determined by a validated method using inductively coupled plasma with tandem mass spectrometric detection.

For each patient in the PK analysis, a non-compartmental analysis (NCA) was performed on individual concentration–time data. Measured concentration versus time profiles were compared with the predicted concentrations at steady state using a population PK model previously developed [8]. Briefly, the covariates of each patient were used in the model to simulate the patient concentrations by generating an external Visual Predictive Check (VPC). The patient data set was simulated 500 times.

Table 1
Criteria used to define dose-limiting toxicities.

Toxicity[a]	Criteria
Haematological	Grade 4 neutropenia lasting >7 days
	Grade ≥3 febrile neutropenia
	Grade 3 (if associated with bleeding) or 4 thrombocytopenia
Non-haematological	Grade ≥3 nausea, vomiting or diarrhoea lasting >48 h uncontrolled by optimal anti-emetic/anti-diarrhoeal support
	Grade ≥3 peripheral sensory neuropathy
	Any other grade ≥3 toxicity (excluding alopecia, nausea, vomiting, diarrhoea and hypersensitivity to to oxaliplatin)
	Any drug-related toxicity leading to a >2-week delay in starting cycle 3 or preventing administration of ≥80% of the planned cumulative dose of the combination during cycles 1 and 2

[a] Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, and Levi grading (for peripheral sensory neuropathy).

2.4. Statistical analyses

No formal statistical hypothesis testing was performed. The safety population included all patients who received at least 1 dose of the combination therapy. Patients who could not complete 80% of planned doses for cycles 1 and 2 of the combination or dropped out for reasons other than DLT were not evaluable for DLT and had to be replaced.

3. Results

3.1. Patients

Between 09 May 2016 and 30 November 2017, 24 patients with mCRC were included and treated: 17 patients in dose escalation to determine the MTD and 7 additional patients to determine the RD. Baseline characteristics of the population are summarised in Table 2. The median age of patients was 61 years (range, 32–78), 71% were aged ≤65 years, 62.5% were male and all patients had an ECOG performance status of 0 or 1. Patients were heavily pre-treated: 75% had received ≥2 prior anti-neoplastic regimens, 62.5% had received prior oxaliplatin for metastatic disease and 37.5% had received oxaliplatin in the adjuvant or neo-adjuvant setting.

3.2. Dose escalation

Seventeen patients were enrolled into 4 cohorts according to dose level (Table 3). Two patients were considered not evaluable and were replaced as anticipated per protocol. One patient was prematurely withdrawn due to discovery of brain metastasis that was asymptomatic before treatment. The second patient did not receive corticosteroids to prevent CINV as recommended by the protocol and current guidelines and experienced a long-lasting episode of grade 3 vomiting and was dropped out of the study. After discussion, the study board considered that the anti-emetic treatment taken by the patient was not optimal, and this patient therefore did not reach the DLT criteria and had to be replaced.

No DLTs were observed in patients treated at dose levels 1 and 2 or at the lower oxaliplatin dose level of

Table 2
Baseline characteristics of the patient population.

Characteristic	All patients (N = 24)	Recommended dose[a] (N = 14)[b]
Age, years		
Median	61.0	62.5
Range	32.0; 78.0	32.0; 78.0
Gender, n (%)		
Female	9 (37.5)	3 (21.4)
Male	15 (62.5)	11 (78.6)
ECOG performance status, n (%)		
0	13 (54.2)	7 (50.0)
1	11 (45.8)	7 (50.0)
Primary diagnosis, n (%)		
Colon	17 (70.8)	10 (71.4)
Rectum	7 (29.2)	4 (28.6)
Primary tumour site, n (%)		
Left colon	5 (26.3)	5 (38.5)
Right colon	5 (26.3)	2 (15.4)
Transverse colon	1 (5.3)	1 (7.7)
Other[c]	3 (15.8)	1 (7.7)
Rectum	5 (26.3)	4 (30.8)
Disease duration, years		
Median	2.5	2.5
Range	0.6; 11.4	0.6; 11.4
Time from diagnosis to first metastasis, months		
Median	24.3	28.0
Range	6.4; 79.5	6.4; 79.5
Number of prior regimens for metastatic disease, n (%)		
1	6 (25.0)	4 (28.6)
2	10 (41.7)	6 (42.9)
≥3	8 (33.3)	4 (28.6)
Patients with prior oxaliplatin for metastatic disease, n (%)	15 (62.5)	10 (71.4)
Patients with prior oxaliplatin in adjuvant or neo-adjuvant setting, n (%)	9 (37.5)	4 (28.6)

ECOG, Eastern Cooperative Oncology Group; MTD, maximum tolerated dose; n, number of patients; RD, recommended dose.
[a] 35 mg/m^2 of trifluridine/tipiracil twice daily days 1–5 q14 days; 85 mg/m^2 of oxaliplatin on day 1.
[b] 7 patients in dose escalation and an additional 7 patients for confirmation of the MTD and determination of RD.
[c] Missing data for primary tumour site.

Table 3
Dose-escalation cohorts.

Dose level	Trifluridine/tipiracil (mg/m^2) twice daily, days 1–5	Oxaliplatin (mg/m^2), day 1	No. of patients	Outcome
1	25	85	4[a]	No DLTs
2	30	85	3	No DLTs
3	35	85	7[a]	1 DLT of grade 3 febrile neutropenia
Intermediate	35	65	3	No DLTs

DLT, dose-limiting toxicity; No., number.
[a] Includes one patient who was not evaluable for DLT.

65 mg/m^2 (intermediate dose level; Table 3). One DLT of grade 3 febrile neutropenia was observed at dose level 3 (cycle 2). After full recovery, the patient continued with a reduced dose of trifluridine/tipiracil (30 mg/m^2) and oxaliplatin (65 mg/m^2). After this DLT, a further 3 patients were treated at dose level 3 and no further DLTs were reported. The MTD was thus set as the maximal planned dose of 35 mg/m^2 of trifluridine/tipiracil twice daily with 85 mg/m^2 of oxaliplatin.

3.3. Recommended dose

An additional 7 patients were then enrolled at this dose to further assess safety, and none of these patients reported toxicities that would meet the DLT criteria. The RD was therefore defined as 35 mg/m^2 of trifluridine/tipiracil twice daily with 85 mg/m^2 of oxaliplatin by the study board.

3.4. Treatment exposure

As of 30 November 2017, the median number of treatment cycles given at the RD was 4 (range, 2–20). Median treatment duration was 9.2 weeks (range, 4–39.0) for trifluridine/tipiracil and 9.4 weeks (range, 4–37.7) for oxaliplatin. Four of 14 patients treated at the RD were ongoing at the time of data cut-off.

3.5. Safety

All patients except 1 experienced at least 1 drug-related AE. The most common drug-related AEs were predominantly myelosuppressive and gastrointestinal in nature (Table 4). AEs associated with oxaliplatin-related neurotoxicity included peripheral neuropathy (8/24 patients, 33.3%), peripheral sensory neuropathy (5/24, 20.8%), neurotoxicity (3/24, 12.5%) and paraesthesia (2/24, 8.3%). Most drug-related AEs (93.0% of events) were of grade 1 or 2, and there were no deaths due to drug-related AEs. The most common grade 3–4 drug-related AE was neutropenia (4/26 patients, 16.7%).

Nineteen serious AEs were reported in 7 patients. Six of these events were drug related, including 2 events of vomiting (grades 2 and 3), 2 of anaemia (grades 3 and 4) and 1 each of thrombocytopenia and febrile neutropenia (both grade 3). The grade 3 vomiting led to study drug discontinuation during cycle 2, as described previously. For the other events, a treatment interruption was required to allow patients to recover from the toxicity within a maximum delay of 2 weeks. Overall, 9 patients (37.5%) had AEs requiring a dose delay to recover from toxicity and 3 patients (12.5%) a trifluridine/tipiracil dose reduction, mainly for haematological toxicity. There was 1 death during the treatment period due to disease progression. Oxaliplatin-related neurotoxicity grade $\geq$2 was observed in 4 patients and led to oxaliplatin discontinuation in all cases.

3.6. Pharmacokinetics

The effect of oxaliplatin on PK parameters of FTD, TPI and FTY was assessed in 17 patients at the 4 dose levels. Plasma concentrations of FTD and FTY were consistent with previous data obtained in monotherapy. In contrast, plasma concentrations of TPI were approximately 1.5-fold to twofold lower than expected. These results were confirmed by predicting the patient concentrations with the population PK model, which enabled comparison of the measured concentrations with previous PK data for FTD and TPI. The obtained external VPC in Fig. 1 shows that the median FTD concentrations measured in this study were comparable with the predicted median concentration. The limited number of patients led to a relatively large confidence interval (CI) for simulated P5, median and P95. Median concentrations for TPI were below the predicted median concentration and fell partly outside the predicted CI for the median concentration.

3.7. Efficacy

In the 24 patients included in the study, the disease control rate (DCR) was 58.4%, with 1 patient having partial response (4.2%), 13 patients (54.2%) with stable disease, 9 patients (37.5%) with progressive disease and 1 non-evaluable patient (4.2%) (Fig. 2). At the RD (n = 14), the DCR was 57.1%, with 1 patient having partial response (7.1%) and 7 patients (50.0%) with stable disease.

Table 4
Summary of adverse events.

Number of patients with at least one event, on treatment	All patients (N = 24)		Recommended dose[a] (N = 14)[b]	
	All grades	Grade ≥3	All grades	Grade ≥3
All AEs, n (%)				
Any AEs	24 (100)	11 (45.8)	14 (100)	7 (50.0)
Serious AEs	7 (29.2)	7 (29.2)	4 (28.6)	4 (28.6)
AEs leading to trifluridine/tipiracil dose reduction	3 (12.5)	1 (4.2)	2 (14.3)	1 (7.1)
AEs leading to study drug withdrawal	4 (16.7)	4 (16.7)	1 (7.1)	1 (7.1)
AEs leading to death	1 (4.2)	1 (4.2)[c]	0	0
Drug-related AEs	23 (95.8)	7 (29.2)	14 (100)	5 (35.7)
Most frequent drug-related AEs (in ≥5 patients), n (%)				
Asthenia	14 (58.3)	1 (4.2)	9 (64.3)	1 (7.1)
Nausea	11 (45.8)	0	5 (35.7)	0
Diarrhoea	9 (37.5)	0	6 (42.9)	0
Peripheral neuropathy	8 (33.3)	1 (4.2)	7 (50.0)	1 (7.1)
Neutropenia	7 (29.2)	4 (16.7)	3 (21.4)	2 (14.3)
Decreased appetite	6 (25.0)	0	3 (21.4)	0
Thrombocytopenia	6 (25.0)	1 (4.2)	3 (21.4)	1 (7.1)
Vomiting	6 (25.0)	1 (4.2)	4 (28.6)	1 (7.1)
Anaemia	5 (20.8)	2 (8.3)	2 (14.3)	1 (7.1)
Peripheral sensory neuropathy	5 (20.8)	0	3 (21.4)	0

AE, adverse event; n, number of patients.
[a] 35 mg/m^2 of trifluridine/tipiracil twice daily days 1–5 q14 days; 85 mg/m^2 of oxaliplatin on day 1.
[b] 7 patients in dose escalation and an additional 7 patients for confirmation of the maximum tolerated dose and determination of RD.
[c] Malignant neoplasm progression.

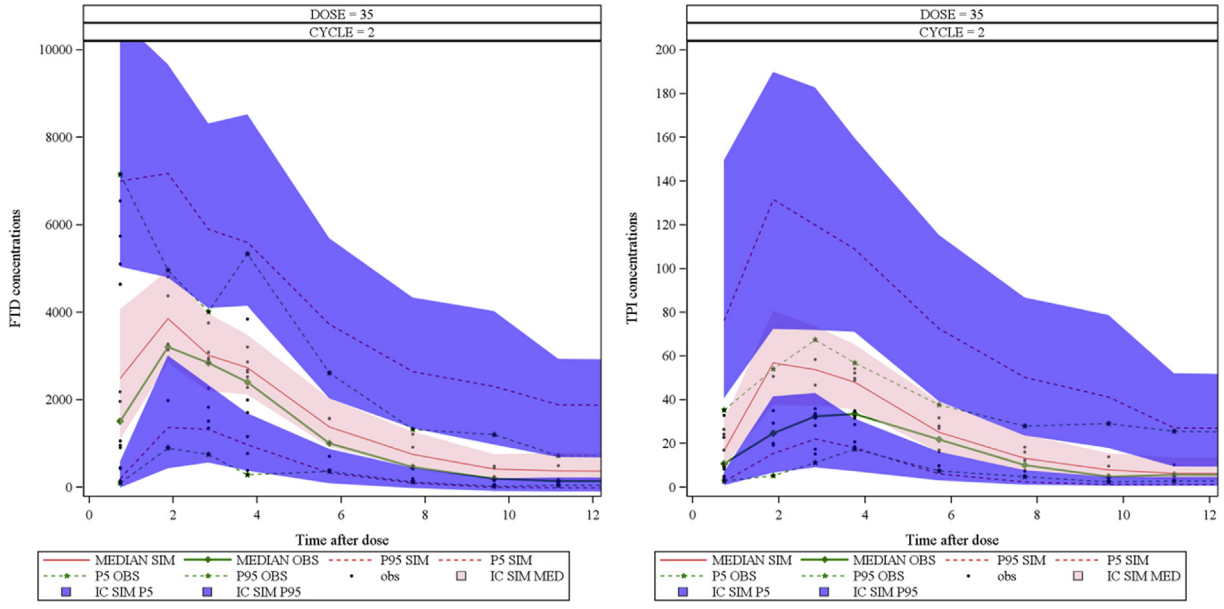

Fig. 1. **Visual Predictive Check (VPC) for FTD (left panel) and TPI (right panel).** Data represented are for the dose of 35 mg/m^2 of trifluridine/tipiracil during cycle 2 at steady state (n = 17). FTD concentration is shown in ng/ml and time after dose in hours. FTD, trifluridine; IC, interval of confidence; n, number of patients; TPI, tipiracil; SIM, simulated; OBS, observed.

4. Discussion

This phase I dose-escalation study met its primary objective of establishing the MTD and RD of trifluridine/tipiracil with oxaliplatin (the maximal planned dose of both components administered on a 14-day cycle) for future trials.

The tolerability profile of the combination was good, with only 1 DLT reported (grade 3 febrile neutropenia at the maximal planned dose) and no unexpected drug-related AEs. Most drug-related AEs were of grade 1 or 2; grade ≥3 events were primarily haematological and manageable with basic supportive care and treatment delays, reductions or interruptions.

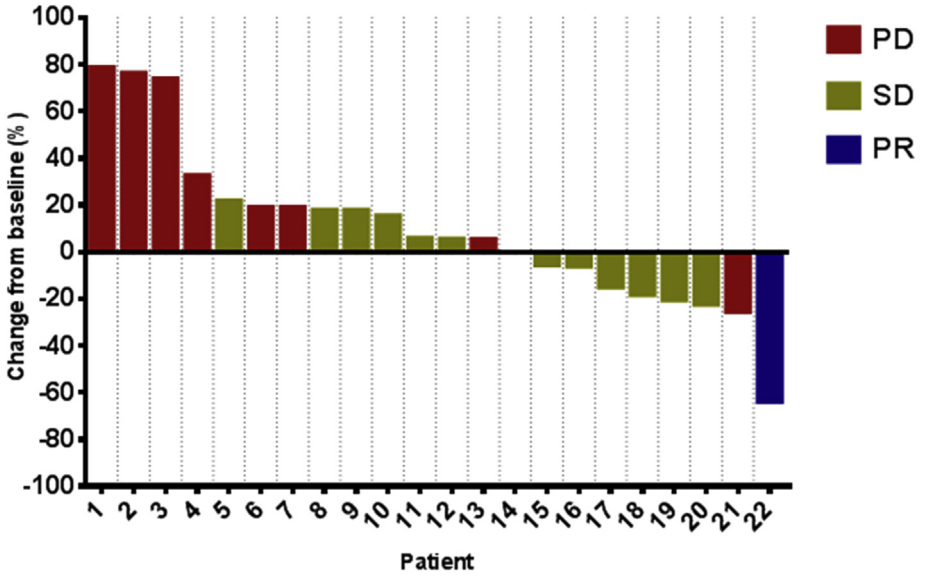

Fig. 2. **Change in tumour size from baseline in all patients with measurable disease.** Bar chart shows the best relative change of the sum of the lesions diameters from baseline (%) during the treatment period (n = 22). n, number of patients; PD, progressive disease; PR, partial response; SD, stable disease.

Trifluridine/tipiracil monotherapy is associated with haematological and gastrointestinal toxicities [9]. Oxaliplatin, as monotherapy, has a good safety profile but is associated with peripheral neuropathy [10]. In patients treated with trifluridine/tipiracil in RECOURSE, grade ≥3 neutropenia was reported in 38% of patients and grade ≥3 febrile neutropenia in 4% [1]. The addition of oxaliplatin to 5-fluorouracil/leucovorin in the phase III trial of oxaliplatin for first-line therapy in mCRC was associated with increased incidence of grade 3–4 neutropenia, from 5.3% to 41.7% [11]. In the present study, the incidence of grade 3–4 neutropenia was 16.7%, showing that addition of oxaliplatin did not result in a substantial additive effect in the incidence of haematological toxicity. Similarly, the combination showed no evidence of increased oxaliplatin-related toxicity, including neurotoxicity and hepatotoxicity. Indeed, the frequency of neurotoxicity was notably low in this study (grade ≥2 neurotoxicity in 4/24 patients), especially considering that the population included patients pretreated with oxaliplatin; grade 2–3 neurotoxicity was previously observed in 44% of patients treated with FOLFOX4 (5-fluorouracil/leucovorin/oxaliplatin) [12].

The PK results, obtained using a population PK model and an NCA approach, did not show an impact of co-administration of oxaliplatin on the PK of FTD. Plasma concentrations of TPI were lower than expected, but this finding does not impact efficacy as the effects of trifluridine/tipiracil are driven by FTD concentrations (which were similar to monotherapy concentrations).

In the 14 patients treated at the RD, the overall response rate was 7.1% with 1 confirmed partial response, which was promising given that this patient had received 4 prior treatment lines, including oxaliplatin for metastatic disease. These data should be interpreted with caution as the population was heterogeneous with patients having received different numbers of prior treatment lines, with or without oxaliplatin (10 patients treated at the RD had prior oxaliplatin for metastatic disease), and due to the small study sample size. Indeed, one limitation of this study was that it was not powered to detect efficacy. In addition, the pharmacodynamics of the combination were not evaluated and should be explored in future trials. Another limitation is that median duration for oxaliplatin was 9.4 weeks, so it is difficult to evaluate the impact of cumulative exposure on rates of neurotoxicity at this stage of study. There are currently no data on monotherapy with FTD/TPI using the 14-day cycle of administration, although our results support further exploration of this dosing schedule, in particular for combination regimens with other agents.

In conclusion, trifluridine/tipiracil with oxaliplatin was well tolerated, with no unexpected drug-related AEs, and the anti-tumour activity of the combination appears promising for patients with mCRC who have received at least 1 prior line of standard chemotherapy (including regimens other than oxaliplatin and fluoropyrimidines). The expansion phase of this study evaluating the safety and efficacy of trifluridine/tipiracil with oxaliplatin at the RD, combined with either bevacizumab or nivolumab, is now underway.

Conflict of interest statement

Catherine Leger, Nadia Amellal and Ronan Fougeray are or were employees of Servier at the time of the study. Guillem Argilés is was part of advisory boards of Bayer, Servier, Roche, Amgen, Merck Serono, Sanofi Symphogen and BMS has received travel expenses from Servier, Merck Serono, Amgen, Sanofi and Roche.

Thierry André has received consulting, advisory fees and/or travel expenses from Roche/Genentech, Amgen, Bristol-Myers Squibb, MSD Oncology and Servier and honoraria from Roche/Genentech, Sanofi, XBiotech and Novartis. Antoine Hollebecque has received consulting or advisory fees from Lilly and Amgen and travel expenses from Servier and Amgen. Laetitia Dahan was part of advisory boards of Sanofi, Lilly, Celgene and Baxalta. Andrés Cervantes has received honoraria for attending advisory boards from Merck Serono, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda and Astelas. He has received speaker fees from Merck Serono, Roche, Angem, Bayer, Servier and Foundation Medicine and research funding from Genentech, Merck Serono, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astelas, Fibrogen, Amcure, Sierra Oncology, Astra Zeneca, Medimmune, ABBVIE, BMS and MSD. Josep Tabernero was part of advisory boards of Bayer, Boehringer Ingelheim, Genentech/Roche, Lilly, MSD, Merck Serono, Merrimack, Novartis, Peptomyc, Roche, Sanofi, Symphogen and Taiho. Aitana Calvo has no disclosure to declare. There are no other potential conflicts of interest to declare.

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