Oral drugs in the treatment of metastatic colorectal cancer

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Pilar García-Alfonso, Andrés Jesús Muñoz Martín, Laura Ortega Morán, Javier Soto Alsar, Gabriela Torres Pérez-Solero, Montserrat Blanco Codesido, Pilar Aitana Calvo Ferrandiz and Silvina Grasso Cicala

***Abstract*:** Colorectal cancer (CRC) is one of the most common forms of cancer, with an estimated 1.36 million new cases and almost 700,000 deaths annually. Approximately 21% of patients with CRC have metastatic disease at diagnosis. The objective of this article is to review the literature on the efficacy and safety of oral drugs available for the treatment of metastatic colorectal cancer (mCRC). Several such drugs have been developed, and fluoropyrimidines are the backbone of chemotherapy in this indication. They exert their antitumour activity by disrupting the synthesis and function of DNA and RNA. Oral fluoropyrimidines include prodrugs capecitabine, tegafur, eniluracil/5-fluorouracil, tegafur/uracil, tegafur/gimeracil/oteracil and trifluridine/tipiracil (FTD/TPI). Oral drugs offer several advantages over injectable formulations, including convenience, flexibility, avoidance of injection-related adverse events (AEs) and, in some circumstances, lower costs. However, oral drugs may not be suitable for patients with gastrointestinal obstruction or malabsorption, they may result in reduced treatment adherence and should not be co-administered with drugs that interfere with absorption or hepatic metabolism. Oral fluoropyrimidines such as capecitabine, as monotherapy or in combination with oxaliplatin, irinotecan or bevacizumab, are as effective as intravenous 5-fluorouracil (5-FU) in first-line treatment of mCRC. Other oral fluoropyrimidines, such as FTD/TPI, are effective in patients with mCRC who are refractory, intolerant or ineligible for 5-FU. In addition, oral fluoropyrimidines are used in adjuvant treatment of mCRC. Regorafenib is an oral multikinase inhibitor used in patients in whom several previous lines of therapy have failed. Frequent AEs associated with oral drugs used in the treatment of CRC include hand-foot syndrome and gastrointestinal and haematological toxicities.

Keywords: adjuvant, capecitabine, colorectal cancer, first-line, metastatic, S-1, TAS-102, UFT

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Correspondence to:
Pilar García-Alfonso
Oncología Médica, Hospital General Universitario Gregorio Marañón, Calle Doctor Esquerdo 46, Madrid, 28009, Spain
pgarcaalfonso@gmail.com

Andrés Jesús Muñoz Martín
Laura Ortega Morán
Javier Soto Alsar
Gabriela Torres Pérez-Solero
Montserrat Blanco Codesido
Pilar Aitana Calvo Ferrandiz
Oncología Médica, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Silvina Grasso Cicala
Medical Affairs Servier, Madrid, Spain

Metastatic colorectal cancer

Colorectal cancer (CRC) is the third most common form of cancer worldwide after lung and breast cancers.[1] Approximately 1.9 million new cases of CRC and 935,000 deaths occurred worldwide in 2020.[1] At diagnosis, 21% of patients with CRC have metastatic disease.[2]

Risk factors for CRC can be divided into modifiable and non-modifiable.[3,4] Modifiable risk factors include smoking and alcohol consumption, sedentary lifestyle with high meat consumption, high-fat and low-fibre diet, very low salt intake and low calcium and selenium intake.[3–5] Non-modifiable risk factors include age, personal/family history and genetic predisposition.[3,4]

Treatment options for metastatic colorectal cancer (mCRC) include surgery, ablation, embolisation, radiotherapy and systemic therapy.[6] Systemic therapy options, in turn, include chemotherapy with fluoropyrimidines, alone or in combination with oxaliplatin or irinotecan, and biological therapy targeting vascular endothelial

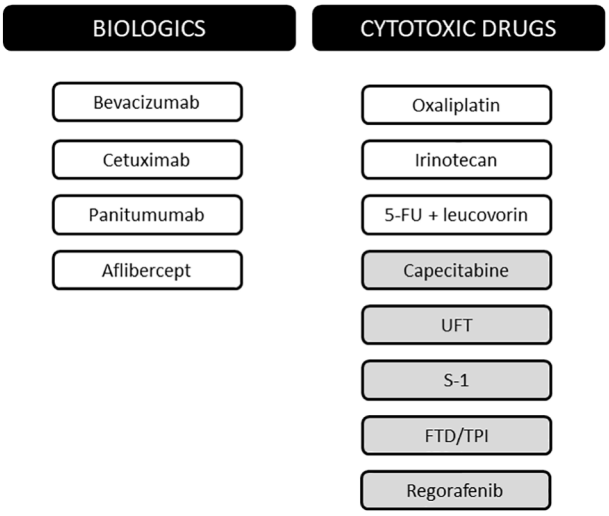

Figure 1. Therapies available for the treatment of metastatic colorectal cancer.
Unshaded: drugs administered by injection; shaded: oral drugs.
5-FU, 5-fluoruracil; FTD/TPI, trifluridine/tipiracil; S-1, tegafur/gimeracil/oteracil; UFT, tegafur/uracil.

growth factor (VEGF), epidermal growth factor receptor (EGFR) or multiple receptor tyrosine kinases, as in the case of regorafenib (Figure 1).[7]

Oral drugs offer a number of potential advantages over intravenous (IV) drugs, including improved convenience and lower costs.[8–12] These are particularly important in patients with mCRC, who are often prescribed complex therapeutic regimens. Several oral drugs are now available for systemic treatment of mCRC, including capecitabine, tegafur/gimeracil/oteracil (S-1), trifluridine/tipiracil (FTD/TPI, formerly TAS-102) and regorafenib.

Fluoropyrimidines are the mainstay of chemotherapy in mCRC.[13] The original member of this class, 5-fluorouracil (5-FU), was first synthesised in the 1950s.[14] Since then, several other fluoropyrimidines have been approved, resulting in a notable improvement in prognosis in patients with CRC.[13,15] More recently, the multiple kinase inhibitor regorafenib was approved for the treatment of mCRC: in 2012 in the USA and in 2013 in Europe.[16,17] Another recent addition to this group is FTD/TPI, which was approved in the USA in 2015 and in Europe in 2016.[18,19]

This article reviews the literature on the efficacy and safety of oral drugs available for the treatment of mCRC.

Oral fluoropyrimidines

Oral fluoropyrimidine-based medicines can be broadly divided into two groups: (a) 5-FU prodrugs; and (b) combinations of 5-FU (or a 5-FU prodrug) with a dihydropyrimidine dehydrogenase (DPD) inhibitor. Prodrugs of 5-FU, such as capecitabine and tegafur, are characterised by the addition of a pyrimidine ring with a fluorine atom at position 5. As a result, they have much higher oral bioavailability and more predictable pharmacokinetics than 5-FU.[20]

5-Fluorouracil (5-FU)

5-FU is a pyrimidine analogue that acts as an antimetabolite of uracil, causing cell death. After entering the cell, 5-FU is converted to one of several active metabolites. These metabolites, in turn, inhibit the enzymes thymidylate synthase and uracil-DNA-glycosylase, interfering with DNA synthesis and repair, respectively. In addition, one of the 5-FU metabolites is incorporated into RNA, thereby disrupting its processing and function.[21,22]

Bioavailability of unmodified 5-FU after oral administration varies widely (0–80%) between patients and in the same patient. This variation is due primarily to differences in the activity of DPD, the enzyme responsible for its degradation. As a result, the efficacy and toxicity of oral 5-FU have been described as unpredictable and erratic. Therefore, the oral route of administration is seldom used for 5-FU.[21,23,24]

Capecitabine

The development of oral capecitabine was prompted by the need for improved tolerability and convenience compared with intravenous 5-FU regimens.[8]

Capecitabine is a fluoropyrimidine carbamate with an oral bioavailability approaching 100%. It is a prodrug of 5-FU, which is its only active metabolite. Following absorption in the intestine, capecitabine is converted to 5-FU in three metabolic steps, the last of which is catalysed by thymidine phosphorylase.[25] This enzyme is found in higher concentrations in solid tumours than in surrounding tissues, which means that capecitabine produces fewer systemic adverse events than an IV formulation of 5-FU.[25–27]

Both in the USA and in Europe, capecitabine is approved for first-line monotherapy of mCRC

and for adjuvant treatment of stage III (Dukes' stage C) colon cancer.[27,28]

Capecitabine monotherapy. Capecitabine was compared with bolus IV 5-FU/leucovorin (LV) in first-line treatment of patients with mCRC in two identically designed open-label phase III studies (Table 1).[29,30] In a prospectively planned integrated analysis of these studies, capecitabine was associated with a significantly higher overall response rate than 5-FU/LV (26% *versus* 17%; $p < 0.0002$). Median time to response and duration of response were similar. In addition, there were no significant differences in time to disease progression (TTP) or overall survival (OS) with capecitabine and 5-FU/LV (TTP: 4.6 months *versus* 4.7 months, $p = 0.95$; OS: 12.9 months *versus* 12.8 months, $p = 0.48$).[31]

In patients with mCRC, first-line capecitabine monotherapy demonstrated a more favourable safety profile than bolus IV 5-FU/LV.[39] The incidence of diarrhoea, stomatitis, nausea, alopecia and grade 3 or 4 neutropenia was significantly lower with capecitabine than with 5-FU/LV ($p < 0.001$ for all). However, capecitabine was also associated with a significantly higher incidence of hand-foot syndrome than 5-FU/LV ($p < 0.001$). Compared with those who received 5-FU/LV, patients treated with capecitabine required significantly fewer dose reductions (33.9% *versus* 42.2%, $p = 0.0037$) and hospitalisations due to adverse events (11.6% *versus* 18.0%, $p < 0.005$).[39] The safety profile of capecitabine was similar in elderly patients with advanced CRC.[40]

Capecitabine monotherapy has been associated with cardiovascular adverse events, including cardiac arrhythmias, angina pectoris, myocardial infarction, heart failure and cardiomyopathy, in 3–9% of patients with CRC.[27,41] Most of these patients had a history of cardiovascular dysfunction and caution is recommended in this population.[27,28] The incidence of cardiovascular adverse events associated with capecitabine is similar to that observed with IV 5-FU.[42–44]

Capecitabine in combination with chemotherapy. In patients with mCRC, capecitabine has been used as part of combination regimens with several drugs, including oxaliplatin, irinotecan, bevacizumab and cetuximab.

In a meta-analysis of eight randomised controlled trials comparing capecitabine plus oxaliplatin (CAPOX or XELOX) and 5-FU plus LV plus oxaliplatin (FOLFOX) in the first-line treatment of patients with mCRC, there were no statistically significant differences between the two treatment regimens in terms of overall response rate, progression-free survival (PFS) or OS. However, the incidence of thrombocytopenia ($p = 0.0005$), hand-foot syndrome ($p < 0.00001$) and diarrhoea ($p < 0.00001$) was significantly higher with XELOX compared with FOLFOX, while FOLFOX was more commonly associated with neutropenia than XELOX ($p < 0.00001$).[45]

Capecitabine plus irinotecan (XELIRI) as first-line chemotherapy demonstrated promising efficacy and safety results in a phase II, single-arm study of patients with mCRC.[46]

In a meta-analysis of six randomised controlled trials that compared XELIRI with 5-FU/LV plus irinotecan (FOLFIRI) in first-line treatment of patients with mCRC, there were no significant differences in overall response rate, PFS or OS between the two regimens.[47]

Capecitabine in combination with biological drugs. Capecitabine has also been combined with biological drugs bevacizumab and cetuximab. Capecitabine plus bevacizumab combination was evaluated in first-line treatment of elderly patients with mCRC in two phase II[48,49] and one phase III trial.[50] In the phase II trials, capecitabine plus bevacizumab combination was associated with an overall response rate of 34–65%, a median PFS of 10.8–11.5 months and OS of 18.0–21.2 months.[48,49] Capecitabine plus bevacizumab combination was compared with capecitabine alone in the phase III, randomised, open-label study in patients aged ⩾70 years.[50] Median PFS was significantly longer with capecitabine plus bevacizumab than with capecitabine alone (9.1 months *versus* 5.1 months, $p < 0.0001$). Overall response rate was also significantly higher with capecitabine plus bevacizumab than with capecitabine alone (19% *versus* 10%, $p = 0.04$). No significant differences were detected in OS (20.7 months *versus* 16.8 months, $p = 0.18$).[50] Commonly reported grade 3 or 4 treatment-related adverse events in this population include hand-foot syndrome, diarrhoea and deep vein thrombosis.[48–50]

Table 1. Key clinical trials of oral fluoropyrimidines.

Author (reference)	Study design	Treatment (*n*)	ORR, %	PFS, months	TTP, months	OS, months	Safety
Capecitabine							
Hoff *et al.*[29]	MC, OL, R, phase III	CAPE 1250 mg/m² PO BID d1–14 q3w (302)	24.8 ($p = 0.005$ *versus* LEU + 5-FU)	NR	4.3	12.5	CAPE: ↓ diarrhoea, stomatitis, nausea, alopecia ($p < 0.0002$ *versus* LEU + 5-FU); ↓ G3/4 stomatitis, neutropenia ($p < 0.0001$); ↑ G3 hand-foot syndrome ($p < 0.00001$), G3/4 hyperbilirubinemia
		LEU 20 mg/m² IV then IV 5-FU 425 mg/m² OD d1–5 q4w (303)	15.5	NR	4.7	13.3	
Van Cutsem *et al.*[30]	MC, OL, R, phase III	CAPE 1250 mg/m² PO BID d1–14 q3w (301)	18.9	NR	5.2	13.2	CAPE: ↓ stomatitis, alopecia ($p < 0.00001$); ↑ hand-foot syndrome ($p < 0.00001$); ↓ G3/4 stomatitis, neutropenia ($p < 0.00001$); ↑G3 hand-foot syndrome ($p < 0.00001$), uncomplicated G3/4 hyperbilirubinaemia ($p < 0.0001$)
		LEU 20 mg/m² IV then IV 5-FU 425 mg/m² OD d1–5 q4w (301)	15.0	NR	4.7	2.1	
Eniluracil/5-FU							
Schilsky *et al.*[32]	MC, R, OL, phase III	Eniluracil 11.5 mg/m² PO BID d1–28 q5w+ 5-FU 1.15 mg/m² PO BID d1–28 q5w (485)	NR	20.0	NR	13.3	Eniluracil/5-FU: ↓ grade 3 or 4 granulocytopenia
		LEU 20 mg/m² IV then IV 5-FU 425 mg/m² OD d1–5 q4w (479)	NR	22.7 ($p = 0.01$ *versus* eniluracil/5-FU)	NR	14.5	
S-1							
Kwakman *et al.*[33]	MC, R, OL, phase III	CAPE 1250 mg/m² for patients <70 years old or 1000 mg/m² for patients ⩾70 years old PO BID d1–14 + BEV 7.5 mg/kg IV d1 q3w (80)	17 ($p = 0.09$ *versus* S-1)	8.2 ($p = 0.93$ *versus* S-1)	NR	NR	CAPE: ↑ any grade hand-foot syndrome ($p = 0.0005$), grade 3 hand-foot syndrome ($p = 0.003$) S-1: ↑ grade 3 anorexia ($p = 0.03$).
		S-1 30 mg/m² PO BID d1–14 + BEV 7.5 mg/kg IV d1 q3w (80)	32	8.4	NR	NR	
Hong *et al.*[34]	MC, R, OL, phase III	S-1 40 mg/m² PO BID d1–14 + OXA 130 mg/m² IV d1 q3w (SOX, 168)	47 ($p = 0.029$ *versus* CAPOX)	8.5 ($p = 0.93$ *versus* CAPOX)	NR	21.2 ($p = 0.18$ *versus* CAPOX)	SOX: ↑ grade 3–4 neutropenia, thrombocytopenia, diarrhoea CAPOX: ↑ any grade hand-foot syndrome
		CAPE 1000 mg/m²PO BID d1–14 +OXA 130 mg/m² IV d1 q3w (CAPOX, 172)	36	6.7	NR	20.5	
Yasui *et al.*[35]	MC, R, OL, phase III	IRI 125 mg/m² IV d1, 15 + S-1 40–60 mg/m² PO BID d1–14 q4w (IRIS; 213)	NR	5.8	NR	17.8	IRIS: ↑grade 3 diarrhoea
		LEU 20 mg/m² IV d1 + IRI 150 mg/m² IV d1 + 5-FU 400 mg/m² IV d1 then 5-FU 2400 mg/m² IV d1–2 q4w (FOLFIRI; 213)	NR	5.1	NR	17.4	FOLFIRI: ↑grade3 or 4 neutropenia

(Continued)

Table 1. (Continued)

Author (reference)	Study design	Treatment (*n*)	ORR, %	PFS, months	TTP, months	OS, months	Safety
Trifluridine/tipiracil							
Mayer *et al.*[36]	MC, R, DB, phase III	FTD/TPI 35 mg/m^2 BID d1–5, 8–14 q4w + BSC (534)	NR	2.0 ($p < 0.001$ *versus* PBO)	NR	7.1 ($p < 0.001$ *versus* PBO)	FTD/TPI: neutropenia 38%, leukopenia 21%
		PBO + BSC (266)	NR	1.7	NR	5.3	PBO: neutropenia <1%, leukopenia 5%
Regorafenib							
Grothey *et al.*[37]	MC, R, DB, phase III	REG 160 mg OD d1–21 q4w + BSC (505)	NR	1.9 ($p < 0.0001$ *versus* PBO)	NR	6.4 ($p = 0.0052$ *versus* PBO)	REG: ↑grade3 or 4 hand-foot syndrome, fatigue, diarrhoea, hypertension, rash or desquamation
		PBO + BSC (255)	NR	1.7	NR	5.0	
Li *et al.*[38]	MC, R, DB, phase III	REG 160 mg OD d1–21 q4w + BSC (136)	NR	3.2 ($p < 0.0001$ *versus* PBO)	NR	8.8 ($p = 0.00016$ *versus* PBO)	REG: ↑grade3 or 4 hand-foot syndrome, hypertension, hyperbilirubinaemia, hypophosphataemia, ALT increased, AST increased, lipase increased, maculopapular rash
		PBO + BSC (68)	NR	1.7	NR	6.3	

5-FU, 5-fluorouracil; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BEV, bevacizumab; BID, twice daily; BSC, best standard of care; CAPE, capecitabine; d, day; DB, double blind; FTD, trifluridine; G, grade; IRI, irinotecan; IV, intravenous; IRI, irinotecan; LEU, leucovorin; MC, multicentre; NR, not reported; OD, once daily; OL, open label; ORR, overall response rate; OS, overall survival; OXA, oxaliplatin; PBO, placebo; PFS, progression-free survival; PO, oral; qxw, every *x* weeks; R, randomised; REG, regorafenib; S-1, tegafur plus gimeracil plus oteracil; TPI, tipiracil; TTP, time to progression; UFT, uracil plus ftorafur (tegafur).

Several studies have examined the efficacy of capecitabine plus irinotecan (CAPIRI) plus bevacizumab as first-line treatment of patients with mCRC.[51–53] The addition of bevacizumab improved PFS, but not OS.[52] CAPIRI plus bevacizumab had an acceptable tolerability profile.[51–53]

First-line capecitabine plus cetuximab was evaluated in elderly patients (70 years or older) with advanced CRC in a phase II trial. In patients with wild-type *KRAS*, capecitabine plus cetuximab combination was associated with a response rate of 48.3% and a median PFS of 8.4 months. However, the high incidence of paronychia and grade 3 or 4 acne-like rash necessitated dose reductions in 27.3% of patients. This reduced the incidence of paronychia, but not of acne-like rash.[54]

The phase III COIN study investigated the efficacy of first-line CAPOX or FOLFOX *versus* CAPOX or FOLFOX plus cetuximab and found no difference in terms of OS or PFS.[55] A subanalysis of this study compared CAPOX plus cetuximab with FOLFOX plus cetuximab and showed a longer PFS for FOLFOX plus cetuximab and worse tolerance with CAPOX plus cetuximab, with significantly higher incidences of diarrhoea and hand-foot syndrome.[56] For these reasons, the use of anti-EGFR antibodies with capecitabine-based chemotherapy is not recommended.

Eniluracil/5-FU

Eniluracil (5-ethynyluracil) is a potent and irreversible inhibitor of DPD, the primary rate-limiting enzyme responsible for catabolism of 5-FU.[57–59] Eniluracil does not appear to have any inherent toxicity and most of the administered dose is excreted in urine unchanged.[58] In patients with mCRC, eniluracil has been shown to reduce DPD activity in the primary tumour, metastases and normal tissues to undetectable levels.[60] Co-administration with eniluracil results in complete oral bioavailability of 5-FU, increases its half-life from about 20 minutes to up to 6.5 hours and makes its pharmacokinetics linear and predictable.[57,61,62]

In a multicentre phase III study, oral eniluracil plus 5-FU showed decreased efficacy compared with standard 5-FU/LV regimen as first-line therapy in patients with mCRC (Table 1).[32] Median OS was 13.3 months with eniluracil plus 5-FU *versus* 14.5 months with 5-FU/LV, and PFS was 20 weeks *versus* 22.7 weeks, respectively. It was hypothesised that in this study, excess eniluracil could have been diminishing 5-FU efficacy by competing for enzymes that convert 5-FU to its active metabolites, and that by reducing the dose and schedule of eniluracil, higher efficacy could be achieved in future trials.[63] The outcome of this phase III trial was unexpected because preclinical and early clinical data were considered to be encouraging.[63] At present, eniluracil is not approved for the treatment of mCRC.

Tegafur and tegafur/uracil (UFT)

Tegafur (ftorafur) is a furanyl nucleoside analogue and a prodrug of 5-FU. Oral tegafur is absorbed in the gastrointestinal (GI) tract and metabolised to 5-FU primarily by cytochrome P450 enzymes in the liver and, to a lesser extent, by soluble enzymes in tumour tissue, which leads to a gradual, but sustained level of 5-FU in tumours.[64,65] Tegafur has a plasma half-life of 5–12 h.[24]

In phase I and II studies, tegafur demonstrated efficacy similar to that of IV 5-FU and was associated with fewer haematological adverse events than 5-FU.[66,67] However, tegafur was also characterised by severe GI and central nervous system (CNS) toxicity (depression, headache, lethargy, dizziness) which has limited its use.[68]

UFT is an oral, fixed-dose combination of tegafur and uracil (1:4), developed in an attempt to improve the efficacy of tegafur.[65] Uracil acts as a competitive substrate of DPD, thereby reducing the inactivation of 5-FU.[65] This allows for lower doses of tegafur to be administered, which, in turn, decreases neurotoxicity.[24]

Several studies evaluated UFT in combination with leucovorin in patients with mCRC. A multicentre phase III study compared oral UFT plus leucovorin (UFT 300 mg/m^2/day and leucovorin 75 or 90 mg/day, both for 28 consecutive days of 35-day cycles) with IV bolus 5-FU plus LV (5-FU 425 mg/m^2/day and LV 20 mg/m^2/day, both for five consecutive days of 28-day cycles) in previously untreated patients with mCRC.[69] This study showed equivalence in OS with UFT plus LV (12.4 months) *versus* 5-FU/LV (13.4 months, $p = 0.630$). There was also no difference in the overall response rate between the two treatments (11.7% *versus* 14.5%, $p = 0.232$). The incidence of several adverse events was lower in the UFT

plus LV group compared with the IV 5-FU/LV group, including diarrhoea, nausea, vomiting, stomatitis, mucositis, neutropenia and documented infections. The authors concluded that UFT plus LV was an equally effective, but safer and more convenient alternative to IV 5-FU/LV.[69] Another phase III study compared the efficacy of UFT plus LV *versus* IV 5-FU/LV in previously untreated patients with mCRC, but no statistically significant difference in time to progression was observed between treatments.[70] UFT was also effective in heavily pre-treated patients with mCRC.[71]

UFT has been studied in several other combinations, including UFT plus LV plus oxaliplatin (TEGAFOX), UFT plus LV plus irinotecan (TEGAFIRI) and TEGAFIRI plus cetuximab. In patients with mCRC, these combinations showed efficacy similar to equivalent IV 5-FU combinations.[72,73]

Depending on the administration schedule, myelosuppression or diarrhoea were the dose-limiting toxicities of UFT in phase I studies.[20] Compared with 5-FU, UFT has a more favourable safety profile.[73] Unlike other fluoropyrimidines, UFT rarely causes hand-foot syndrome. UFT has been shown to be a safe alternative to 5-FU in patients with partial DPD deficiency.[74]

UFT is approved for the treatment of mCRC in 60 countries, including Japan and the Philippines.[75,76] UFT is approved in combination with LV for first-line therapy of mCRC in 12 European countries, including France and the UK.[76]

Tegafur/gimeracil/oteracil (S-1). S-1 is a combination of tegafur and two 5-FU modulators, gimeracil (5-chloro-2,4-dihydroxypyridine; CDHP) and oteracil or oxonic acid, at the molar ratio of 1:0.4:1.[77,78] Gimeracil is a reversible inhibitor of DPD that is 200 times more potent than uracil.[77] Its addition increases the serum half-life of tegafur and its concentration in tumour tissues. GI toxicity commonly associated with fluoropyrimidines results from phosphorylation of 5-FU by orotate phosphoribosyl transferase. Oteracil inhibits this enzyme, decreasing 5-FU phosphorylation in the GI tract and thereby reducing the GI toxicity of tegafur.[77]

Most phase III studies of S-1 in mCRC have been conducted in Asian patients (Table 1). In a phase III study conducted by Hong *et al.*,[34] S-1 plus oxaliplatin (SOX) as first-line treatment for mCRC was non-inferior to CAPOX with regard to PFS. As a result, the authors concluded that SOX could be an alternative to CAPOX as first-line chemotherapy for patients with mCRC.[34] In another phase III study conducted in Asian patients with mCRC, first-line treatment with SOX plus bevacizumab was shown to be non-inferior to FOLFOX plus bevacizumab.[79] The results of this study lead to an update of the Asian guidelines for first-line treatment of mCRC, with SOX plus bevacizumab becoming the first choice.[80]

In second-line treatment of mCRC, S-1 plus irinotecan (IRIS) and FOLFIRI were associated with similar PFS and OS in Asian patients.[81] The median PFS in patients treated with IRIS was 5.8 months compared with 5.1 months in the FOLFIRI group.[81] In an updated report on this study, OS was higher in patients treated with IRIS than in patients treated with FOLFIRI.[35] These results show that IRIS may be an alternative option to FOLFIRI in Asian patients.

The randomised phase III TRICOLORE study conducted in Japan demonstrated that IRIS plus bevacizumab was non-inferior to FOLFOX or CAPOX plus bevacizumab with respect to PFS as first-line treatment of mCRC, and could be a new standard treatment in this indication.[82]

To our knowledge, the only phase III study conducted in western patients, the SALTO study, evaluated S-1 monotherapy *versus* capecitabine in the first-line treatment of mCRC.[33] Relative to capecitabine, S-1 produced similar efficacy outcomes including response rate, PFS and OS.[33]

S-1 was first approved in Japan in 1999 for the treatment of gastric cancer and was subsequently approved in Japan for six additional indications including CRC.[83] In Europe, S-1 was authorised in March 2011 for the treatment of advanced gastric cancer in combination with cisplatin.[84]

DPD deficiency

DPD is the first enzyme in the 5-FU catabolism pathway, and is responsible for the elimination of over 80% of systemic 5-FU.[85] Due to mutations in the *DPYD* gene, approximately 3–5% of the general population have partial DPD deficiency, and 0.2% have complete DPD deficiency.[74]

The use of 5-FU and 5-FU prodrugs is associated with severe and life-threatening adverse events in patients with DPD deficiency, including stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. As a result, the European Medicines Agency (EMA) recommends that patients should be tested for DPD activity before receiving 5-FU, capecitabine or tegafur.[86] Patients with complete DPD deficiency should not receive any of these drugs. In patients with partial DPD deficiency, administration of reduced doses is permissible but should be accompanied by vigilant adverse event monitoring.[86] In the USA, the prescribing information for capecitabine warns of an increased risk of severe or fatal adverse events in patients with DPD deficiency.[28] It advises that treatment be withheld or stopped in patients receiving capecitabine who present with acute early-onset or unusually severe adverse effects, but does not explicitly recommend testing for DPD activity before starting treatment. Instead, patients should be counselled to notify their healthcare provider if they have a known DPD deficiency.

Trifluridine/tipiracil (FTD/TPI)

FTD is a nucleoside analogue and the active cytotoxic component of the FTD/TPI combination. FTD is a thymidylate synthase inhibitor, but a less potent one than 5-FU. On the other hand, FTD metabolites are much more readily incorporated into DNA than 5-FU metabolites, and this is believed to be the primary mechanism of FTD cytotoxicity. Importantly, the antineoplastic effect of FTD was retained in xenograft models resistant to 5-FU. However, the oral bioavailability of FTD is low due to extensive metabolism in the GI tract and liver by thymidine phosphorylase. Co-administration of FTD with a thymidine phosphorylase inhibitor (TPI) increases exposure to FTD 38-fold and peak plasma concentration 22-fold. The optimal molar ratio of FTD to TPI is 1:0.5, which is available as a fixed-dose combination.[87–90] Preclinical studies suggest that FTD is not metabolised by DPD; therefore, it could be a useful alternative to 5-FU or its prodrugs in patients with DPD deficiency.[91] However, before FTD can be recommended in this setting, studies in humans would need to confirm this information.

FTD/TPI monotherapy

FTD/TPI has been studied in the treatment of patients with mCRC who had two or more lines of previous therapy and were refractory, intolerant to or ineligible for 5-FU. In a phase II study in Japanese patients, FTD/TPI plus best supportive care was associated with significantly longer median PFS and OS than placebo plus best supportive care.[92] In the randomised phase III TERRA study conducted in China, the Republic of Korea and Thailand, FTD/TPI was associated with significantly longer OS compared with placebo, while the incidence of serious adverse events was similar.[93] In a phase III (RECOURSE) international study, compared with placebo plus best standard of care, FTD/TPI plus best standard of care showed statistically significant improvements in median PFS (1.7 months *versus* 2.0 months; $p < 0.001$) and OS (5.3 months *versus* 7.1 months; $p < 0.001$) (Table 1).[36] In a post-hoc analysis of RECOURSE, low tumour burden and indolent disease were indicators of good prognosis in later-line treatment of patients with mCRC; patients with no liver metastases appeared to have the best prognosis, with a median OS of 16.4 months.[36]

Based on the phase III RECOURSE study, the US Food and Drug Administration (FDA) approved FTD/TPI for the treatment of patients with mCRC who have previously been treated with fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy, and anti-VEGF biological therapy, and, if *RAS* wild-type, an EGFR therapy.[18] The EMA approved FTD/TPI for the treatment of adult patients with mCRC who have previously been treated with, or are not considered candidates for, available therapies including fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapies, anti-VEGF agents and anti-EGFR agents.[19]

FTD/TPI in combination with biological drugs

FTD/TPI plus bevacizumab combination was evaluated in first-line treatment of patients with mCRC who are ineligible for intensive therapy in a phase II study (TASCO1).[94] In the primary analysis, FTD/TPI plus bevacizumab was associated with longer PFS (9.2 months) than capecitabine plus bevacizumab [7.8 months; hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.48, 1.06].[94] An ongoing randomised phase III study (SOLSTICE) will compare FTD/TPI plus bevacizumab *versus* capecitabine plus bevacizumab in this indication (EudraCT2017-004059-22).[95]

The combination of FTD/TPI with bevacizumab was also investigated in patients with refractory

mCRC. In the phase I/II C-TASK FORCE study, FTD/TPI plus bevacizumab was associated with a 16-week PFS rate of 42.9%, suggesting that this combination could become a potential treatment option for patients with refractory mCRC.[96] Another randomised, phase II study showed that the median OS was significantly longer in the FTD/TPI plus bevacizumab arm (10.3 months) than in the FTD/TPI alone arm (7.3 months; HR 0.42, 95% CI 0.18, 0.99, $p < 0.05$). Median PFS was also significantly longer with combination therapy (5.9 months) than with FTD/TPI monotherapy (2.6 months; HR 0.51, 95% CI 0.28, 0.92, $p < 0.03$).[97] In addition, a phase Ib/II BiTS study, which evaluated the efficacy and safety of FTD/TPI plus bevacizumab in patients with mCRC who were refractory or intolerant to standard therapies, showed that at 16 weeks the PFS rate was 40.9%, the response rate was 0.0% and the disease control rate was 59.1%. The median PFS, median time to treatment failure and median OS were 4.2 months, 4.2 months and 8.7 months, respectively.[98]

Safety. Adverse events (of any grade) commonly associated with FTD/TPI include neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhoea, vomiting, abdominal pain, pyrexia, leukopenia and anaemia.[18,19,36] In the TASCO1 study, GI and haematological adverse events were more common in patients who received FTD/TPI plus bevacizumab combination than in patients who received capecitabine plus bevacizumab. Conversely, hand-foot syndrome was more common in the capecitabine plus bevacizumab group than in the FTD/TPI plus bevacizumab group (52.6% *versus* 3.9%).[94] Strategies for the management of adverse events with FTD/TPI include dose reductions, withholding treatment and prophylactic administration of myeloid growth factors.[99]

Regorafenib

Regorafenib is a small-molecule multikinase inhibitor. Regorafenib is metabolised in the liver by cytochrome P450 3A4 and UDP-glucuronosyltransferase 1A9.[100] Regorafenib has two main active metabolites, M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl). Regorafenib, M-2 and M-5 inhibit a number of kinases involved in oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E) and angiogenesis [vascular endothelial growth factor receptor (VEGFR)1, VEGFR2, VEGFR3, TIE2], as well as kinases involved in other processes (PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2).[100,101]

In 2012, regorafenib was approved in the USA for the treatment of patients with mCRC who have previously been treated with fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy and anti-VEGF therapy, as well as anti-EGFR therapy for patients with wild-type *KRAS* gene.[16] In 2013, regorafenib was approved for the treatment of mCRC in Europe.[17]

The efficacy of regorafenib monotherapy in the management of previously treated patients with mCRC was evaluated in two randomised, placebo-controlled, phase III studies.[37,38] In the international CORRECT study, regorafenib was associated with significantly longer OS (6.4 months *versus* 5.0 months, $p = 0.0052$) and PFS (1.9 months *versus* 1.7 months, $p < 0.0001$) compared with placebo.[37] Similar results were observed in the CONCUR study that was conducted in Asian patients. Relative to placebo, OS (8.8 months *versus* 6.3 months, $p = 0.00016$) and PFS (3.2 months *versus* 1.7 months, $p < 0.0001$) were significantly longer with regorafenib.[38]

Treatment-related adverse events were reported in 93% and 97% of patients who received regorafenib in CORRECT and CONCUR, respectively.[37,38] The most common serious adverse event in both studies was hand-foot syndrome (17% and 16%, respectively).[37,38]

Oral *versus* IV drugs

Patients prefer oral to IV palliative chemotherapy, provided that oral therapy is equally effective.[8] This review shows that most oral drugs commonly used in the treatment of mCRC have similar efficacy compared to IV drugs. The only oral treatment that appears to be less effective is eniluracil plus oral 5-FU, as it was associated with inferior PFS and OS in patients with mCRC;[32] this is why eniluracil is no longer being developed. Regarding safety, oral and IV drugs have shown different patterns of side effects and future research may help to determine the basis for these differences.[102]

Oral formulations have a number of advantages compared with IV formulations, including higher patient preference, avoiding infusions and the use of central catheters, fewer injection-associated adverse events and lower costs.[8,10–12] A study

assessing patient preference for oral *versus* IV palliative chemotherapy has shown that patients with incurable cancer have a clear preference for oral chemotherapy, but are generally not willing to sacrifice efficacy for their preference. In this study, nine out of 10 patients with cancer preferred oral to IV chemotherapy. At the same time, two-thirds of patients were not prepared to accept reduced effectiveness.[8] In a randomised crossover study, in which patients with advanced CRC received IV 5-FU or oral UFT for one cycle and then switched to the other treatment for the second cycle, 84% of patients preferred the oral UFT regimen because of convenience and less toxicity.[10] Similarly, in another randomised crossover study, previously untreated patients with mCRC received oral UFT or bolus IV 5-FU for one cycle, switched to the other treatment for the second cycle and were then able to choose one of the regimens to continue their treatment until disease progression; 90% of patients chose UFT and only 10% chose 5-FU.[12] Collectively, these results confirm that patients with CRC prefer oral therapy. Commonly cited reasons included convenience, flexibility and less disruption to normal daily activities.[9,10,12] However, when the toxicity of an oral formulation is greater than the toxicity of an IV formulation, patients with CRC prefer the latter.[103] In addition, IV anticancer therapy is associated with thromboembolic adverse events due to the use of venous catheters.[104] Finally, orally administered fluoropyrimidines have been associated with lower costs of managing adverse events and less time lost due to treatment than IV 5-FU.[11]

At the same time, oral drugs have some disadvantages. For instance, they may not be suitable for patients with GI obstruction or malabsorption. In addition, treatment adherence may be reduced due to the fact that oral drugs are self-administered.[13] Finally, care must be taken to avoid co-administration with drugs that can interfere with absorption or hepatic metabolism. Antacids, salicylates, antibiotics and anticonvulsants should be taken with caution. For example, acute phenytoin intoxication was observed in patients receiving tegafur or capecitabine, presumably because these drugs interfere with phenytoin metabolism.[105,106]

The approval and introduction of capecitabine have made treatment of mCRC significantly more convenient compared with IV 5-FU.[13] At present, the usual first-line chemotherapy regimens consist of capecitabine or 5-FU in combination with irinotecan or oxaliplatin,[7] with many physicians choosing oral capecitabine in preference to IV 5-FU in fragile older patients. Current European guidelines recommend, among other therapies, CAPOX plus bevacizumab in first-line treatment of mCRC, and capecitabine alone or CAPOX in the adjuvant treatment of CRC.[7] However, capecitabine is associated with a number of adverse events, particularly hand-foot syndrome. While the severity of hand-foot syndrome with capecitabine is usually low, it may, nevertheless, become significant during prolonged use or in elderly patients.[13,94]

S-1 has shown efficacy similar to that of capecitabine and produced a lower incidence of hand-foot syndrome. However, S-1 has mostly been studied in Asian patients and its use outside of this population is limited. Further research into the efficacy and safety of S-1 in western patients is warranted.

Regorafenib and FTD/TPI are recommended by the European guidelines for use in a third line setting in mCRC.[7] Similar to capecitabine, regorafenib is commonly associated with hand-foot syndrome, while FTD/TPI often leads to haematological toxicities. While haematological toxicities are a concern, they tend to have less impact on the patient's quality of life than more symptomatic adverse events such as hand-foot syndrome. Thus, differences between the safety and tolerability profiles of the two agents, and in particular the propensity of regorafenib to cause hand-foot syndrome and liver dysfunction, may explain why FTD/TPI appears to be associated with better treatment adherence compared with regorafenib.[107] In a recent study, treatment adherence was approximately two to three times greater with FTD/TPI than with regorafenib; duration of treatment was also significantly longer with FTD/TPI than regorafenib.[107,108]

Conclusion

Therapies available for the treatment of mCRC include combinations of 5-FU or 5-FU prodrugs and DPD inhibitors (capecitabine, tegafur, eniluracil/5-FU, UFT, S-1), as well as a 5-FU analogue plus thymidine phosphorylase inhibitor combination (FTD/TPI) and a multikinase inhibitor (regorafenib). With the exception of eniluracil/5-FU, these oral therapies appear to be as effective as IV therapies, while also offering several advantages such as greater convenience and flexibility, avoidance of injection-related adverse

events and, in some circumstances, lower costs. However, oral therapies are not suitable for patients with malabsorption and cannot be co-administered with drugs that affect hepatic metabolism. Unlike 5-FU and its prodrugs, FTD/TPI and regorafenib may have utility in patients with DPD deficiency; however, well-designed clinical trials are needed to confirm this. FTD/TPI and regorafenib appear to have similar efficacy, but treatment adherence and persistence are higher with FTD/TPI than with regorafenib.[106] This may be because haematological adverse events that are commonly associated with FTD/TPI cause less disruption and distress to patients than the hand-foot syndrome commonly associated with regorafenib. Efficacy data from recent trials of oral and biological drug combinations, such as FTD/TPI with bevacizumab, have been encouraging.[94,96–98] and demonstrate how such innovative regimens could continue to improve outcomes in the future. Clinical trials of regorafenib in combination with checkpoint inhibitors, such as nivolumab and pembrolizumab,[109,110] are ongoing, and the results of these studies are eagerly awaited.

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Pilar García-Alfonso and Silvina Grasso Cicala contributed to the design of the manuscript and reviewed and approved all drafts.

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Conflict of interest statement

The authors declare relevant conflicts of interest relating to: consultancy services or participation in advisory boards (*); speaking engagements (†); receipt of research funding (‡); support for attendance at congresses or other events (including travel and accommodation) (§); employment of self or a close family member (#); and participation in speaker bureaux (¶); for the following named commercial entities.

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ORCID iD

Pilar García-Alfonso https://orcid.org/0000-0002-4373-9978

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