Current Options for Third-line and Beyond Treatment of Metastatic Colorectal Cancer. Spanish TTD Group Expert Opinion

Ana Fernández-Montes,[1] Cristina Grávalos,[2] Carles Pericay,[3] Mª José Safont,[4] Manuel Benavides,[5] Elena Élez,[6] Pilar García-Alfonso,[7] Beatriz García-Paredes,[8] Alfredo Carrato,[9] Enrique Aranda[10]

Abstract

Colorectal cancer (CRC) is a public health problem: it is the third most common cancer in men (746,000 new cases/year) and the second in women (614,000 new cases/year), representing the second leading cause of death by cancer worldwide. The survival of patients with metastatic CRC (mCRC) has increased prominently in recent years, reaching a median of 25 to 30 months. A growing number of patients with mCRC are candidates to receive a treatment in third line or beyond, although the optimal drug regimen and sequence are still unknown. In this situation of refractoriness, there are several alternatives: (1) To administer sequentially the 2 oral drugs approved in this indication: trifluridine/tipiracil and regorafenib, which have shown a statistically significant benefit in progression-free survival and overall survival with a different toxicity profile. (2) To administer cetuximab or panitumumab in treatment-naive patients with RAS wild type, which is increasingly rare because these drugs are usually indicated in first- or second-line. (3) To reuse drugs already administered that were discontinued owing to toxicity or progression (oxaliplatin, irinotecan, fluoropyrimidine, antiangiogenics, anti-epidermal growth factor receptor [if RAS wild-type]). High-quality evidence is limited, but this strategy is often used in routine clinical practice in the absence of alternative therapies especially in patients with good performance status. (4) To use specific treatments for very selected populations, such as trastuzumab/lapatinib in mCRC human epidermal growth factor receptor 2-positive, immunotherapy in microsatellite instability, intrahepatic therapies in limited disease or primarily located in the liver, although the main recommendation is to include patients in clinical trials.

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Introduction

Colorectal cancer (CRC) is a public health problem, and it is the third most common cancer in men (746,000 new cases every year) and the second in women (614,000 new cases every year), and represents the second leading cause of death by cancer worldwide.[1] In Spain, 41,441 cases were expected in 2015, representing the second most common tumor in both genders.[2] It is believed that in 2035, the standardized mortality rate for colon cancer will be reduced by 12.4%, but for rectal cancer, there will be an increase of 10%, which is consistent with other European countries.[3] The

[1]Medical Oncology, Complejo Hospitalario Universitario de Ourense, Orense, Spain
[2]Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain
[3]Medical Oncology, Hospital de Sabadell, Corporación Sanitaria Parc Tauli, Sabadell, Barcelona, Spain
[4]Medical Oncology, Hospital General Universitario de Valencia, València, Spain
[5]Medical Oncology, Hospital Universitario Regional y Virgen de la Victoria, Málaga, Spain
[6]Medical Oncology, Hospital Universitari Vall d'Hebron, Passeig de la Vall d'Hebron, 119-129, 08035 Barcelona, Spain
[7]Medical Oncology, Hospital Universitario Gregorio Marañón, Madrid, Spain
[8]Medical Oncology, Hospital Clínico San Carlos, Instituto de Investigación Hospital Clínico San Carlos (IdISSC). CIBERONC, Madrid, Spain
[9]Medical Oncology, Hospital Universitario Ramón y Cajal, Universidad de Alcalá de Henares, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), CIBERONC, Madrid, Spain
[10]Medical Oncology, Hospital Reina Sofía, University of Córdoba, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), CIBERONC, Córdoba, Spain

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Address for correspondence: Ana Fernández-Montes, MD, Complejo Hospitalario Universitario de Ourense, Calle Ramón Puga Noguerol, 54, 32005 Ourense, Spain
E-mail contact: afm1003@hotmail.com

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prognosis for metastatic CRC (mCRC) is poor, with survival rates of 15% at 5 years and a median survival of 24 to 36 months.[4-6]

Standard first- and second-line treatments are based on combinations of fluoropirimidines plus oxaliplatin or irinotecan, associated to an antiagiogenic monoclonal antibody or anti-epidermal growth factor receptor (EGFR), which is chosen based on the RAS mutational status, although the optimal sequence is still unknown.[5,7]

We are facing a molecularly heterogeneous disease, with various biomarkers both prognostic and predictive of response. Only the presence of RAS activating mutations (KRAS/NRAS), present in 30% to 45% of mCRC, has proven to be a negative predictive biomarker of response to anti-EGFR.[8]

Although there are no validated predictive biomarkers of response other than RAS, there are other biomarkers of special interest. These include BRAF mutation, human epidermal growth factor receptor 2 (HER2) amplification, microsatellite instability (MSI-H), and ALK/ROS/NTRK fusion/rearrangements.

The BRAF mutation, present in 8% to 10% of mCRC, is located in the EGFR signaling pathway, and it is a factor of poor prognosis and has specific clinical features (predominance in women, right colon, and extrahepatic involvement). Despite being a controversial issue, the evidence suggesting that it is a marker of resistance to anti-EGFR drugs is increasing.[9]

On the other hand, HER2, a receptor of the EGFR family, whose amplification is associated with resistance to anti-EGFR drugs, is a biomarker whose blockade at different levels is under investigation.[10]

MSI, by somatic or germline pathway, results in hypermutability and lymphocyte infiltration with sensitivity to anti-programmed cell death protein 1 (PD-1) and anti-CTLA4 therapies.[11,12]

Finally, ALK, ROS, and NKTR fusions and rearrangements occur in 0.2% to 2.4% of mCRC and lead to a constitutive activation of tyrosine kinase receptors and, like BRAF mutations, they are associated with right colon tumors, elderly patients, lymph node involvement, absence of mutations in RAS, and also resistance to anti-EGFR agents.[13]

There is a growing number of patients with mCRC who are candidates to receive a treatment in the third line or beyond, although the optimal drug regimen and sequence are still unknown. The aim of this article is to review the scientific evidence of the available therapeutic options in the third line and beyond and to establish the therapeutic recommendations agreed upon by the Group for Digestive Tumour Therapy (TTD Group).

Approved Drugs for Refractory mCRC

Trifluridine/Tipiracil

Trifluridine/tipiracil is an oral drug consisting of trifluridine, a thymidine analogue, which incorporates to the tumoral DNA inducing DNA dysfunction, and tipiracil hydrochloride, a thymidine phosphorylase inhibitor, responsible for trifluridine degradation, whose dosage consists of 35 mg/m^2/twice daily on days 1 to 5 and 8 to 12 every 28 days. In the phase III double-blind placebo-controlled study, RECOURSE, trifluridine/tipiracil achieved a significant benefit in overall survival (OS)[14] (Table 1). The tolerance profile to trifluridine/tipiracil was favorable, with grade (G) 3 to 4 neutropenia (38%) as the most relevant toxicity (only 4% were febrile neutropenia). Other G3 to 4 toxicities were rare (< 5%): nausea/vomiting, hyporexia, asthenia, and diarrhea. Despite not having a specific quality of life (QoL) assessment, the median time for the deterioration of the performance status (PS) of 0 to 1 versus ≥ 2 was significantly longer in the trifluridine/tipiracil arm (5.7 vs. 4.0 months), and 84% of the patients had a PS 0 to 1 at the end of treatment.[15] Subsequently, the phase III study, TERRA, confirmed the benefits of trifluridine/tipiracil in Asian patients regardless of whether they had received biological agents or not[16] (Table 1).

There is also evidence of efficacy in the real-life population. The United States expanded access program in 549 patients confirmed a

Table 1 Phase III Studies in mCRC With Regorafenib or Trifluridine/Tipiracil: Efficacy and Safety Data

Phase III Studies	Regorafenib				Trifluridine/Tipiracil			
	CORRECT[17]		CONCUR[18]		RECOURSE[14,15]		TERRA[16]	
Prior Biological Therapies	100% BEV 100% Anti-EGFR		60%		100% BEV 100% Anti-EGFR		BEV or EGFR or Both 55% vs. 49%	
	REGO	BSC	REGO	BSC	Trifluridine/Tipiracil	BSC	Trifluridine/Tipiracil	BSC
N	505	255	136	68	534	266	271	135
mOS, mos	6.4	5.0	8.8	6.3	7.1	5.3	7.8	7.1
	HR 0.77 $P = .0052$		HR 0.55 $P = .0002$		HR 0.68 $P < .001$		HR 0.79 $P = .035$	
mPFS, mos	1.9	1.7	3.2	1.7	2.0	1.7	2.0	1.8
	HR 0.49 $P < .0001$		HR 0.31 $P < .0001$		HR 0.48 $P < .001$		HR 0.43 $P < .001$	
ORR, %	1.0	0.4	4.4	0	1.6	0.4	1.1	0
					$P = .29$		$P = .55$	
DCR					44	16	44.1	14.6
					$P < .001$		$P < .001$	

Abbreviations: BEV = bevacizumab; BSC = best supportive care; DCR = disease control rate; EGFR = epidermal growth factor receptor; HR = hazard ratio; mCRC = metastatic colorectal cancer; mOS = mean overall survival; mPFS = median progression-free survival; ORR = objective response rate; REGO = regorafenib.

Table 2 Real-life Studies With Trifluridine/Tipiracil and Regorafenib in Refractory mCRC

Trifluridine/Tipiracil

Study	N	Starting Dose	PS	PFS, mos	OS, mos	Toxicity G3-4, %	Most Relevant Toxicity
USA[19]	549	35 mg/m^2/12h	0-1	2.7	NR	43	Neutropenia
Italian RWD[20]	341	35 mg/m^2/12h	0: 59% 1: 39% 2: 2%	2.4	6.2	47	Neutropenia
Spain[21]	636	35 mg/m^2/12h	0: 33% 1: 67%	NR	NR	57	Neutropenia (42%) Febrile neutropenia (1.3%) Anemia (15%)
UK[22]	78	35 mg/m^2/12h	1	NR	6.6	39	Neutropenia

Regorafenib

Study	N	Starting Dose < 160 mg/d	PS	PFS, mos	OS, mos	Toxicity G3-4, %	Most Relevant Toxicity
REBECCA[24]	654	20%	0-1: 90% > 1: 10%	2.7	5.6	56	Fatigue 14.5%, PPE 9%, HBP 5%, diarrhea 4%, anorexia 3%
CONSIGN[25]	2.872	0%	0: 47% 1: 53%	2.7	NA	57	HBP 15%, PPE 14%, fatigue 13%, diarrhoea 5%,
CORRELATE[26]	1.037	30%	0-1: 87% > 1: 13%	2.8	7.6	36	Fatigue 10%, HBP 8%, PPE 7%
RECORA[27]	461	46%	0-1: 81% > 1: 19%	3.1	5.8	57	Mucositis 13%, diarrhea 23%, HBP 7%, hand-foot syndrome 19%, asthenia 15 %

Abbreviations: G = grade; HBP = high blood pressure; mCRC = metastatic colorectal cancer; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; PS = performance status; PPE = palmar-plantar erythrodysesthesia.

safety profile similar to that of the RECOURSE study.[19] A post-hoc analysis showed no difference in treatment duration or toxicity in patients aged over 65 years. Another Italian study, including 341 patients in the Italian compassionate use program, showed an estimated progression-free survival (PFS) at 6 months of 19% and a median OS (mOS) of 6.2 months. One hundred twenty-one patients received both regorafenib and trifluridine/tipiracil, and no differences were observed in the first or second PFS and OS between the 2 sequences.[20] Other experiences of expanded use in countries such as Spain or Great Britain also obtained comparable results to those of the RECOURSE study.[21,22] In terms of predictive factors of response, no differences were observed regarding age or RAS status in the RECOURSE study.[15] A post hoc analysis revealed a potential relationship between the development of G3 to 4 neutropenia and OS.[23] The Italian real world data (RWD) study showed a PS 0, a normal lactate dehydrogenase, and time from diagnosis > 18 months, which were independently associated with a greater likelihood of being progression-free at 6 months[20] (Table 2).

A recent analysis of the RECOURSE[28] compared patients with good prognostic characteristics (GPCs), defined as low tumor burden (< 3 metastatic sites), indolent disease (≥ 18 months since diagnosis of first metastasis), Eastern Cooperative Oncology Group PS 0 to 1, and no liver metastasis and patients with poor prognostic characteristics (PPCs), defined as high tumor burden and/or aggressive disease. When treated in late-line mCRC, patients with GPCs showed a median OS of 9.3 months versus 5.3 months in patients with PPCs (hazard ratio [HR], 0.46; 95% confidence interval [CI], 0.37-0.57; $P < .0001$); regardless of age (≥ 65 vs. < 65 years), Eastern Cooperative Oncology Group PS (0-1), KRAS status (mutant vs. wild-type [wt]), and liver metastasis (yes/no). No liver metastasis was the best prognostic factor: mOS in such patients treated with trifluridine/tipiracil was 16.4 months and 7.6 months in the GPC (n = 97) and PPC (n = 35) groups, respectively (HR, 0.42; 95% CI, 0.24-0.74; $P < .0019$).

Regorafenib

Regorafenib is an oral tyrosine kinase inhibitor that blocks several protein kinases involved in tumor angiogenesis (VEGFR1-3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF) and tumoral microenvironment (PDGFR and FGFR); the dosage consists of 160 mg/day for 21 days in 28-day cycles.

Table 3 Clinical Trials With Anti-EGFR

Study	Phase	N	Drug Regimen	DCR	ORR	PFS, mos	OS, mos	Grade 3/4 Toxicity
NCT00079066 Jonker et al 2007[35]	III	287 285	Cetuximab Placebo	39.4 10.9 $P < .0001$	8% 0% $P < .001$	HR, 0.68 (95% CI, 0.57-0.80) $P < .001$	6,1 4.6 $P = .86$	Rash (11.8) Asthenia (33) Dyspnoea (16.3) Abdominal pain (13.2)
Cunningham et al, NEJM 2004[36]	II	218 111	Cetuximab/ irinotecan Irinotecan	55.5% 32.4% $P < .0010$	22.9 10.8 $P = .007$	4.1 1.5 $P < .001$	8.6 6.9 $P = .48$	Neutropenia (9.4 vs. 0) Asthenia (13.7 vs. 10.4) Acne (9.4 vs. 5.2)
Saltz et al, JCO 2004[37]	II	57	Cetuximab	45.8%	9%	NR	6.4	Allergy (3.5) Acne (18) Asthenia (9)
Van Cutsem et al, JCO 2007[39]	III	231 232	Panitumumab BSC	NR	10% 0%	2 1.8 $P < .001$	HR, 1 (95% CI, 0.82-1.22) $P = .8$	Acne (7) Cutaneous (2) Erythema (5) Asthenia (4)
Kim et al, BJC 2016[40]	III	189 188	Panitumumab BSC	68.8% 21.8% $P =$ NR	27% 1.6% $P < .001$	3.6 1.7 $P < .001$	10 7.4 $P = .0135$	Hypomagnesemia (6) Rash (6) Acne (6)
NCT01001377 Price et al, Lancet Oncol 2014[41]	III	499 500	Panitumumab Cetuximab	67.5 69 $P =$ NS	13% 10% $P =$ NS	4.4 4.1 $P =$ NS	10.4 10.0 $P =$ NS	Cutaneous (13% P, 10% C) Infusion-related (0.5 P, 2 C) Hypomagnesemia (7 P, 3 C)

Abbreviations: BSC = best supportive care; C = cetuximab; CI = confidence interval; DCR = drug control rate; EGFR = epidermal growth factor receptor; HR = hazard ratio; NR = not reported; NS = non-significant; ORR = objective response rate; OS = overall survival; P = panitumumab; PFS = progression-free survival.

The randomised, double-blind phase III study, CORRECT, comparing regorafenib with placebo, showed a significant increase in OS[17] (Table 1). However, 67% of patients treated with regorafenib required dose reduction, and 54% had G3 to 4 toxicity, mainly within the first 2 cycles: hand-foot syndrome (17%), asthenia (10%), diarrhea (37%), hypertension (37%), and rash (30%). Despite toxicity, no significant differences were seen in the QoL. The CONCUR study confirmed the efficacy and safety of regorafenib in an Asian population[18] (Table 1). This study, unlike the CORRECT study,[17] allowed the inclusion of patients without prior biological treatment; therefore, its main benefit regarding PFS and OS could be related with the difference in the prior exposure to non-targeted agents.

Given the toxicity seen, alternative dosages have been investigated. The ReDOS study analyzed a weekly dose escalation from 80 to 160 mg/day in the first cycle versus standard dose.[29] The percentage of patients who started the third cycle with 160 mg/d was significantly higher in the experimental arm and, in addition, they had longer OS, better QoL, and less G3 to 4 toxicities (high blood pressure, 7% vs. 15% and asthenia, 13% vs. 18%). In the REARRANGE study,[30] flexible dosing showed numerical improvement on several parameters that improved tolerance, such as fatigue, hypertension, or hand-foot syndrome, although the study did not meet its primary endpoint of improving regorafenib global tolerability in the reduced- and intermittent-dose groups. The average treatment duration was 3.2 months in the standard group; 3.7 months in the reduced-dose group; and 3.8 months in that with alternating weeks. The median PFS was not different across groups (approximately 2 months). With the future results from the REGOCC study,[31] we expect to open the door to a dose modification of regorafenib without impact on efficacy.

We also have observational and real-life studies, such as the REBECCA study[24] that analyzed 654 patients within the French compassionate use program (Table 2) and had results consistent with those of the CORRECT study.[17] A PS > 1, time from diagnosis < 18 months, a regorafenib dose < 160 mg/d, > 3 metastatic sites, and liver metastases were identified as poor prognosis factors for survival. The CONSIGN study[25] in 2872 patients had a toxicity profile similar to that of the CORRECT study. The subgroup analysis did not show any differences in PFS for patients > 75 years old, but had a slight increase in G3 to 4 toxicity (high blood pressure and fatigue). An exploratory analysis suggested that patients with PS 0 without hepatic involvement and diagnosis > 18 months had better PFS. The CORRELATE study in 1037 patients confirmed a safety profile consistent with the data published. The starting dose for almost one-half of patients was less than 160 mg/day, and PFS and OS were within the range observed in phase III trials.[26] Real-life studies reinforce the importance of PS and the selection of patients for the treatment with regorafenib.[27]

In the CORRECT study, a retrospective analysis of circulating tumoral DNA and various genes such as KRAS, PIK3CA, and BRAF was performed without identifying any predictive biomarker of response or survival.[32] A study analyzing the role of CCL5/CCR5 polymorphisms in the efficacy of regorafenib has been recently

published, noting a potential role of these polymorphisms as predictive and prognostic markers of toxicity.[33]

Comparing Trifluridine/Tipiracil and Regorafenib

A meta-analysis of the main randomized studies with trifluridine/tipiracil and regorafenib was performed in 2018. No differences in efficacy were seen, although regorafenib presented greater toxicity.[34] Currently, we do not have biomarkers or studies that tell us what the optimal sequence of treatment in refractory mCRC is; thus, the choice of treatment will depend on the characteristics and preferences of each patient and the safety profile of the drugs.

Anti-EGFR Treatment

De Novo Anti-EGFR Treatment

Cetuximab was the first anti-EGFR monoclonal antibody to be incorporated into routine clinical practice, showing its efficacy in all treatment lines. Like panitumumab, its development has gone from refractoriness to first line. Several studies support the use of anti-EGFR monoclonal antibodies in monotherapy and in combination with irinotecan for refractory mCRC[35-38] (Table 3). It is worth mentioning the results of the retrospective analysis of patients in the BOND study,[35] in whom the mutational state of the exon 2 of KRAS was determined.[38] In cases with a mutation in KRAS exon 2 wt treated with cetuximab + best supportive care (BSC) compared with BSC alone, PFS was 3.7 versus 1.9 months (HR, 0.40; 95% CI, 0.30-0.54; $P < .001$), and OS was 9.5 versus 4.8 months (HR, 0.55; 95% CI, 0.41-0.74; $P < .001$), respectively.

The activity of panitumumab has been studied in monotherapy in mCRC refractory to oxaliplatin/irinotecan in 3 phase III studies: 2 compared panitumumab + BSC versus BSC alone,[39,40] and the third compared panitumumab versus cetuximab (ASPECCT study).[41] In the first study, patients with mCRC and KRAS exon 2 wt presented better PFS and objective response rate (ORR) than those with the mutations (12.3 vs. 7.3 weeks and 17% vs. 0%, respectively).[42] The second phase III study, more recent and limited to patients with KRAS exon 2 wt mCRC, also showed benefit in OS, the main study objective.[40] To date, differences in terms of efficacy and safety to use one or another antibody have not been documented. The phase III study ASPECCT, with a non-inferiority design, found no significant differences between panitumab and cetuximab in OS (10.2 vs. 9.9 months) or PFS (4.2 vs. 4.4 months). The toxicity profile was consistent with previous studies.[43]

Therefore, there is robust evidence to recommend that those patients with RAS wt mCRC, showing progression to a standard treatment that does not include anti-EGFR therapy, receive a cetuximab- or panitumumab-based treatment either in monotherapy or in combination with irinotecan.

Rechallenge With Anti-EGFR

Rechallenge is at present a strategy with great clinical interest. It consists in the re-administration of a drug or treatment to which the tumor has developed resistance. Rechallenge must be differentiated from reintroduction, defined as the administration of a therapy with which the patient has experienced some benefit and that had been discontinued without progression.[44,45]

Different studies try to provide evidence about the potential use of re-administering anti-EGFR agents and thus, various strategies and combinations with chemotherapeutic agents, have been tested.[46-50] In a phase II randomized trial, Cremolini et al[51] evaluated the role of the treatment with cetuximab and irinotecan in a total of 29 patients with RAS and BRAF wt mCRC who had progressed to a first-line irinotecan- and cetuximab-based therapy. The study found a response rate of 21% (95% CI, 10%-40%) and a disease control rate (DCR) of 54% (95% CI, 6%-70%), showing that this rechallenge strategy with may be active in patients with acquired resistance to this therapy. Also, these results indicate the possible role of the liquid biopsy in the selection of candidates for rechallenge. In this sense, dynamic molecular typing of the tumor, as recently published by Parseghian et al,[52] may provide crucial information about clonal selection phenomena that will help to define a significant cutoff point for the mutated allelic fraction of plasma emerging mutations. This would allow identifying better those patients susceptible of maintaining a blockade with anti-EGFR to the progression of a prior treatment with these antibodies or reintroduce it after a biological pressure-free period. However, there are no clinical trials nowadays standardizing the determination of the mutational status of RAS/BRAF in plasma or any criteria for rechallenging with anti-EGFR.[53]

Rechallenge With Chemotherapy ± Antiangiogenics

Therapeutic options for patients treated with irinotecan, oxaliplatin, fluoropyrimidines, anti-angiogenics, and anti-EGFR (RAS wt tumors) are limited, and one possible therapeutic strategy is "rechallenge." As mentioned above, we define this strategy as the reuse of a treatment in patients who have progressed with this regimen, and not those who discontinued treatment without progression, which is considered reintroduction.[44,45]

From a theoretical viewpoint, it is difficult to explain that once the tumor has acquired resistance to a treatment, it will respond again to the same regimen, although there are data indicating a clinical benefit with symptomatic improvement, generally of short duration. The evidence that supports the "rechallenge" is scarce and tends to be based on phase II and retrospective studies.[44] Some of the studies that will be presented in this section consider both rechallenge and reintroduction options.

Rechallenge With Oxaliplatin

At present, first-line oxaliplatin-based therapy is the standard treatment of mCRC. However, cumulative sensory neuropathy is a dose-limiting toxicity and often requires therapy to be stopped in patients who are still responding. A pooled analysis of the OPTIMization of OXaliplatin studies (OPTIMOX) shows that the reintroduction of oxaliplatin in sensitive patients after an oxaliplatin-free interval of at least 6 months is a reasonable strategy. Thus, oxaliplatin reintroduction is an important option to be considered in third line.[54,55]

Nonetheless, some studies have evaluated the rechallenge strategy. The ORION study assessed the rechallenge with XELOX (capecitabine and oxaliplatin) in patients previously treated with oxaliplatin, reporting a mOS $\geq$ 9.2 months. Of the 46 patients included, 45.5% had progressed with the first oxaliplatin treatment, whereas the rest had discontinued treatment owing to toxicity or scheduled vacations. The study compared the rechallenge with

XELOX biweekly with every 3 weeks without finding differences in efficacy.[56] In another phase II study, 33 patients rechallenged with modified FOLFOX6 (folinic acid, 5-fluorouracil, and oxaliplatin) in the third line reached an ORR of 6%, a PFS of 3.2 months, and an OS of 10 months.[57]

A recent retrospective study in 95 patients rechallenged with oxaliplatin reported a median time to treatment failure (TTF) of 3.7 months and an OS of 12.2 months. In the control arm, in which 29 patients were treated with anti-EGFR and irinotecan, the TTF and OS were 4.8 months and 11.4 months, respectively. The DCR for the rechallenge with oxaliplatin was 47.4% (ORR, 6%).[58]

The retrospective study REOX analyzed 83 patients receiving rechallenge with oxaliplatin in $\geq$ the third line. Bevacizumab and cetuximab were added in 42% and 6%, respectively. DCR was 56%, the median TTF was 6.0 months, and OS was 10.0 months. The response to the first exposure to oxaliplatin was predictive of long-term survival.[59]

Rechallenge With Irinotecan and/or Triple Therapy

Two real-life studies have evaluated a rechallenge with irinotecan and cetuximab as a third-line treatment or beyond in patients exposed to all available treatments, reporting an OS of 6.0 and 7.3 months, respectively.[60,61]

Triple therapies (FOLFOXIRI [folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan] or FOLFORINOX [folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin]) have been retrospectively studied in 21 patients with an ORR of 38%, DCR of 62%, PFS of 4 months, and OS of 8.6 months. Most cycles required dose adjustment and treatment delays.[62]

Rechallenge With Chemotherapy and Bevacizumab

A real-life study assessing FOLFOXIRI + bevacizumab in 49 patients who had progressed with fluoropyrimidine, irinotecan, oxaliplatin, and bevacizumab, has reported a PFS of 5.8 months and an OS of 11.9 months.[63]

A retrospective study of bevacizumab + FOLFOX/FOLFIRI in 46 patients who had received all the available treatments, reported a 22% ORR, a PFS of 8.9 months, and an OS of 13.8 months in third-line therapy.[64] In a series with 31 polytreated patients, the OS was 18.4 months.[65] Another retrospective study in 35 patients treated with chemotherapy + bevacizumab in the third- or fourth-line reported 20% ORR, PFS of 5.98 months, and OS of 14.7 months.[66]

In a third-line treatment with bevacizumab + capecitabine, a series of 34 heavily pre-treated patients reported a PFS of 5.4 months and an OS of 12.2 months with good tolerance. However, only 4 patients had previously received bevacizumab.[67]

In summary, the rechallenge with previously used drugs may be an alternative for some patients, although no prospective clinical trials support its use.

Immunotherapy

Biomarkers

MSI-H mCRC represents ~5% of patients with mCRC[68] and is considered a highly immunogenic tumor with very high tumor mutation burden (TMB) as compared with microsatellite stability (MSS) mCRC. Although the complexity of TMB is high and its accessibility limited, it is one of the best-known characteristics of the CRC subtypes.[69] It can be measured and has been largely explored as a biomarker for immunotherapy. Programmed death-ligand 1 (PD-L1) expression in tumor microenvironment has also been largely investigated as a biomarker. These and other biomarkers are under intensive research with too many controversies around (heterogeneous expression of PD-L1, assay interpretation, lack of standardization platforms, etc) but have demonstrated some success in identifying patients most likely to benefit from immune checkpoint inhibitors. It is likely we will see hereafter and according to published results in the MSI-H population with mCRC treated in these non-randomized phase II studies, PD-L1 expression does not seem to be a good biomarker as a companion diagnostic as it is in the case of other tumors.[70]

Pretreated MSI-H mCRC

Checkmate 142 is a multiple cohort phase II study in heavily pretreated patients with MSI-H mCRC. In one cohort, nivolumab monotherapy at 3 mg/kg every 2 weeks was administered to 74 patients.[71,72] In another cohort, 119 patients were treated with the combination of nivolumab, at the same dose, plus ipilimumab at 1 mg/kg every 3 weeks × 4 doses and then nivolumab monotherapy at the same doses.[73]

Both cohorts were heavily pretreated with at least 2 previous lines (30% and 36%, respectively) or even 3 or more (54% and 40%, respectively). This heavily pre-treated population with MSI-H mCRC is very similar to the patients with mCRC treated in the phase III trials with trifluridine/tipiracil[14,16] and regorafenib.[17,18] Another relevant aspect is the distribution of patients based on their PD-L1 expression, where only 28% and 23% of the patients included in each cohort had a PD-L1 expression $\geq$ 1%.

The primary endpoint in both studies was the investigator-assessed ORR by Response Evaluation Criteria in Solid Tumors (RECIST), v1.1, which was higher in the combination cohort (58%). More relevant, ORR was independent of PD-L1 expression, which is not what we see in other tumors treated with these agents. The median PFS (mPFS) and OS were not reached in the combination study: PFS and OS at 24 months were 60% and 74%, respectively, which seems very high and with G3 to 4 treatment-related adverse events in 31% of patients. To highlight these results, and although they are indirect comparisons, they look much better than those obtained in a similar heavily pretreated population that received trifluridine/tipiracil or regorafenib.

Pembrolizumab (anti PD-1) has also been studied in MSI-H pretreated patients with mCRC. A phase II trial evaluated 41 patients with progressive metastatic carcinoma, including colorectal, with and without mismatch-repair deficiency (cohorts A and B, respectively), and non-colorectal mismatch-deficient (cohort C). Focusing on patients with mCRC, the objectives of mPFS and OS were not reached in cohort A, whereas in cohort B, both endpoints were 2.2 and 5.0 months respectively. TMB revealed a mean of 1782 somatic mutations per tumor in MSI-H tumors, as compared with 73 in MSS tumors, and was associated with prolonged PFS ($P < .02$).[74] The phase II open-label study (KEYNOTE-164) has evaluated pembrolizumab in 61 previously treated patients mCRC with MSI-H/deficient mismatch repair. At a median follow-up of 31.3 months (range, 0.2-35.6 months), pembrolizumab provided

an ORR of 33%, a median OS of 31.4 months, and a median PFS of 2.3 months, which seems to be very similar to the results obtained with other immune checkpoint inhibitors in this population.[12,74,75]

Pretreated MSS mCRC

Contrary to what happens in MSI-H mCRC, patients with MSS mCRC do not seem to respond to checkpoint inhibitors. The phase III study IMblaze370[76] compared atezolizumab (anti PD-L1) versus atezolizumab plus cobimetinib (MEK1/2 inhibitor) versus regorafenib in 365 heavily pretreated patients with mCRC, 92% of them MSS. Atezolizumab in monotherapy or combined with cobimetinib was not superior to regorafenib. The mOS was 7.1, 8.9, and 8.5 months, respectively, and 12-month OS was 27%, 38%, and 36.6%, respectively; figures clearly lower than those seen in the MSI-H cohorts but similar to those seen in the population treated with trifluridine/tipiracil or regorafenib (Table 2). A recent randomized (2:1) phase II trial compared durvalumab (anti PD-L1) combined with tremelimumab (anti CTLA-4) versus BSC in 180 refractory patients with MSS mCRC.[77] The primary endpoint mOS was 6.6 versus 4.1 months (HR, 0.72; $P = .07$), and mPFS was 1.8 versus 1.9 months. Sixty-four percent of patients experienced G $\geq$ 3 treatment-related adverse events.

In conclusion, today and despite the absence of positive phase III trials, nivolumab or pembrolizumab in monotherapy or a combination of nivolumab plus ipilimumab is probably the best alternative in pretreated patients with MSI-H mCRC. The results of an open-label, phase Ib trial (REGONIVO, EPOC1603) has been recently communicated. This study enrolled 50 patients with advanced gastric (n = 25) or colorectal (n = 25) cancer and a median of 3 prior treatment lines. They were treated with regorafenib plus nivolumab in a dose-finding phase, and an objective tumor response was observed in 7 patients with MSS CRC and 1 patient with MSI-H CRC.[78] Other ongoing trials in both populations (MSI-H and MSS) in earlier lines and combined with many other agents will better define the best strategy, particularly in the MSS population.

Promising Molecular Anti-targeted Therapies

Anti-BRAF Agents

Mutations in the BRAF gene are present in nearly 10% of patients with CRC. It is associated with poor prognosis, with a median mOS of 12 months. BRAF V600E represents approximately the 96% of all BRAF mutations.[79]

Anti-BRAF agents are potent and selective oral inhibitors of serine-threonine kinase BRAF containing the activating mutation V600E ($BRAF^{V600E}$). In mCRC, several clinical trials have been conducted using first-generation inhibitors (vemurafenib 960 mg/12h and dabrafenib 150 mg/12h) and one using a second-generation inhibitor (encorafenib 450 mg/day).

Unlike the good results obtained in melanoma, the efficacy of BRAF inhibitors (BRAFi) in monotherapy for mCRC is disappointing, with a 0% to 5% ORR.[80,81] Preclinical studies have described the development of mechanisms of resistance to BRAF blockade, with a quick reactivation of the EGFR-mediated MAPK pathway. Therefore, drug combination strategies have been designed to simultaneously block several effectors of this pathway. The results of these trials are dissimilar, obtaining a modest benefit from the 2-drug combinations[82-86] but a more promising benefit from 3-drug combinations.[84,85,87-90]

Thirty percent of patients with BRAF mutation have MSI.[91] In the KEYNOTE-164 study, 15% (n = 9) of the population was BRAF-mutated V600 E obtaining an ORR of 55%. On the other hand, in the Checkmate 142 study, 24% (n = 29) of the population presented this mutation with an ORR of 55%. The analyses of these studies indicate that immunotherapy benefits this population subgroup regardless of the BRAF stage.

The BEACON study is a randomized phase III trial comparing the standard treatment (FOLFIRI/irinotecan ± cetuximab) versus a dual-therapy (encorafenib + cetuximab) versus triple therapy (encorafenib + binimetinib + cetuximab) (NCT02928224) in second-line therapy. The results in the 29 patients enrolled in the safety lead-in phase using the triple therapy were promising, with an ORR of 48% (10% complete responses), DCR of 93%, PFS of 8.0 months, and OS of 15.3 months.[92] The final results of this study, with 655 patients included, show that the triple combination (encorafenib + binimetinib + cetuximab) increased OS compared with control (9 months vs. 5.4 months; HR, 052; 95% CI, 0.39-0.70; $P < .001$), as well as TR 26% versus 2% for triplet and control, respectively. On the other hand, the dual combination showed an increase in OS compared with the control arm (8.4 months; HR, 0.60; 95% CI, 0.45-0.79; $P = .001$). Although this is a 2-line study, 35% of patients were treated in third or subsequent lines, which means that the treatment represent a possibility in this subgroup.[93]

Anti-HER2 Drugs

Several HER2 inhibitors have been tested in mCRC: 2 recombinant humanized monoclonal antibodies directed against various extracellular epitopes of the HER2 receptor: trastuzumab (ligand-independent inhibition) and pertuzumab (ligand-dependent inhibition), both administered intravenously, and an oral inhibitor of the intracellular domains of tyrosine kinase (ErbB1) EGFR and HER2 (ErbB2) receptors, lapatinib.

As it happens with BRAFi, in preclinical studies, HER2 inhibitors have not shown efficacy in monotherapy but in combination. These findings served as the basis for the design of HERACLES, a phase II study with 3 cohorts. In cohort A (trastuzumab intravenously [IV] loading dose 4 mg/kg followed by 2 mg/kg/weekly + lapatinib 1000 mg/day orally continuous, in 21-day cycles), in 27 patients with mCRC KRAS exon 2 wt and HER2 amplification (immunohistochemistry: 3+ or 2+ plus fluorescence in situ hybridization +) resistant to standard therapies (including anti-EGFR). The results were: ORR of 30% (95% CI, 14%-50%), DCR of 74%, and a median duration of response of 38 weeks, with a good toxicity profile (22% of G3 toxicity).[10]

A subsequent phase IIa study including various refractory solid tumors with different molecular alterations ("Mypathway basket trial") reproduced these good results. In the cohort of 37 patients with mCRC with HER2 amplification, treatment with trastuzumab (loading dose 8 mg/kg followed by 6 mg/kg every 3 weeks) + pertuzumab (loading dose 840 mg followed by 420 mg every 3 weeks) obtained an ORR of 38% (95% CI, 23%-55%), with a median duration of response of 11 months.[94]

Anti-ALK Drugs, Fusions

The incidence of genetic fusions (ALK, ROS1, and NTRK1/2/3) in mCRC is between 0.2% and 2.4%. Currently, few data on the role of these molecular alterations in mCRC are available. Apart from the publication of some clinical cases treated successfully with these kinase inhibitors (ceritinib, ALK or entrectinib, ALK, ROS1, and TrkA-B-C-), the combined results from 2 phase I clinical trials (ALKA-372-001 and STARTRK-1) with entrectinib (600 mg/day) have been reported[95] as well as 3 phase I/II clinical trials with larotrectinib (TrkA-B-C inhibitor, 100 mg/12 hours)[96] in solid tumors (including patients with refractory CRC: 15% with gastrointestinal tumors and 7% with mCRC), with promising results (long-term responses) that need to be confirmed.

Fruquintinib

It represents a new generation of tyrosine kinase inhibitors (TKIs) that blocks VEGFR 1-3 with higher power and high selectivity. After the promising results of a phase Ib/II trial[97] with fruquintinib at a dose of 5 mg/day for 21 days in a 28-day cycle, the results of FRESCO, a randomised (2:1) double-blind phase III placebo-controlled study including 416 Chinese patients with refractory mCRC ($\geq$ 2 previous treatment lines, although only 30% and 14% of patients in both arms had received prior treatment with anti-VEGF and anti-EGFR, respectively) were published.[98]

The study has been positive regarding all efficacy parameters: OS (main objective): 9.3 versus 6.6 months (HR, 0.65; 95% CI, 0.51-0.83; $P < .001$); PFS: 3.7 versus 1.8 months (HR, 0.26; 95% CI, 0.21-0.34; $P < .001$); ORR (4.7% vs. 0%; $P = .01$); and DCR (62.2% vs. 12.3%; $P < .001$). G3 to 4 adverse events were more frequent in the fruquintinib arm (61.2% vs.19.7%). Its efficacy in Western patients treated with all available drugs is still to be determined.

Drugs With Poor Results or Insufficient Evidence

Some drugs, with some preclinical anti-tumor activity or in phase I to II studies, have not managed to increase survival in phase III clinical trials in refractory mCRC. Here below are the most relevant.

Nindetanib is a triple angiokinase inhibitor of VEGFR 1-3, PDGF-alpha/beta, and FGFR 1-3, administered orally. In the phase III study, LUME-Colon1, comparing nindetanib versus placebo, PFS and OS were not clinically significant, and no improvement in the QoL was seen.[99]

Napabucasin is a STAT3 inhibitor and a gene transcription factor, overexpressed in CRC and necessary to keep its stem cells. A phase III study compared napabucasin versus placebo without showing any benefits in DCR, PFS, or OS.[100]

Dalotuzumab is a monoclonal antibody against insulin-like growth factor receptor. The phase III study compared dalotuzumab (10 mg/kg weekly), dalotuzumab (7.5 mg/kg twice weekly), or placebo combined with cetuximab and irinotecan. The study was prematurely terminated with PFS and OS not significant, but elevated, suggesting that patients did not have strictly refractory mCRC.[101]

Brivanib is a VEGFR 2-3 and FGFR-1-3 TKI. The phase III study, CO.20, compared cetuximab associated with brivanib or placebo. Although the brivanib arm obtained better results in terms of PFS ($P < .001$) and ORR, there were no differences in the OS, the main objective of the study.[102]

Xilonix (MABp1) is an antibody that inhibits interleukin-1-alpha, which has been investigated in 2 phase III studies comparing MABp1 versus placebo. In the first study, weight gain and clinical improvement was significant with MABp1 (33% vs. 19%; $P = .0045$), and the OS was 11.5 months and 4.2 months depending on whether or not patients met the aim of weight gain ($P < .0001$).[103] A second phase III study of Xilonix versus placebo (NCTO1767857), which started in 2013 and was completed in 2017, has not yet reported its results.[104]

Mitomycin-C (MMC) is an alkylating agent widely used in gastrointestinal tumors before the arrival of biological agents. A pooled analysis of several phase II studies and case series (n = 681) of MMC combined with fluoropyrimidine reported an ORR of 7%, DCR of 39%, PFS of 2.8 months, and OS of 7.5 months. Although the authors conclude that MMC combined with fluoropyrimidine is a valid option when standard treatments fail, the efficacy of this combination has not been tested in any phase III study, and currently, there is not enough evidence to recommend its use on a routine basis.

Interventional Techniques: Chemoembolization and Radioembolization

Hepatic artery infusion (HAI), transarterial chemoembolisation (TACE), and radioembolization (selective internal radiation therapy [SIRT]) are among the local treatments for predominantly hepatic metastases not susceptible of surgery or radio-frequency treatments.

HAI of chemotherapy could be useful patients in advanced line, especially with oxaliplatin. A randomized phase II study (HEARTO) included patients with unresectable mCRC refractory or intolerant to fluoropyrimidine, irinotecan, oxaliplatin, anti-VEGF therapy, and anti-EGFR therapy for wt KRAS tumors. Patients were randomized to HAI raltitrexed (3 mg/m^2 over 1 hours) followed by oxaliplatin (130 mg/m^2 over 2 hours) every 3 weeks versus standard of care in a 2:1 ratio. The study was prematurely terminated, owing to insufficient accrual, with 27 patients; mPFS was significantly longer in the HAI group versus standard of care (6.7 and 2.2 months, respectively), although no differences were seen in mOS. In spite of the low recruitment, the study provides evidence for the benefit and safety of HAI with raltitrexed and oxaliplatin in liver-only chemoresistant mCRC.[105]

A phase I/II trial has evaluated HAI of oxaliplatin combined with intravenous 5-fluorouracil (5-FU) and l-leucovorin in patients with CRC with unresectable liver metastases and systemic chemotherapy failure. In phase I, none of the 6 enrolled patients exhibited dose-limiting toxicity, and the recommended dose for oxaliplatin by HAI was estimated as 100 mg/m^2. In phase II, 7 additional patients were included. The 6-month survival rate was 53.3%, less than the expected 80%, and the OS was 6.9 months. This combination therapy was feasible and safe, but the expected efficacy was not achieved.[106]

There are several studies with TACE in refractory patients. A first multicenter study in 55 patients, some with extrahepatic disease,

Table 4 Clinical Trials in Refractory mCRC: Recruiting, Active but Not Recruiting, or Not Recruiting Yet

Study	Phase	N	Drugs	Molecular Profile	Objectives	Status	Geographical Area
NCT02390947	III	543	Famitinib vs. placebo	–	OS	Unknown	China
NCT02332499	III	450	Anlotinib vs. placebo	–	OS	Completed	China
NCT03829462 NEXT-REGIRI	III	78	Regorafenib + irinotecan vs. regorafenib	–	OS	Recruiting	France
NCT03522649	III	668	Napabucasin + FOLFIRI vs. napabucasin	–	OS	Recruiting	China
NCT02870582	III	510	Donafenib vs. placebo	–	OS	Active	China
NCT04322539 FRESCO-2	III	522	Fruquitinib or placebo	–	OS	Active, not yet recruiting	US
NCT03520946 RAMTAS	II rand	144	Ramucirumab + FTD/TPI FTD/TPI	–	OS	Recruiting	Germany
NCT03647839 MODULATE	II rand	90	Nivolumab + BNC105 Nivolumab + BBI-608	MSS	ORR (iRECIST)	Recruiting	Australia
NCT03475004	II rand	40	Pembrolizumab + binimetinib + bevacizumab vs. binimetinib + bevacizumab	–	ORR	Recruiting	US
NCT02316340	II rand	78	Vorinostat + hidroxicloroquina vs. regorafenib	–	PFS	Active, not recruiting	US
NCT02870920	II rand	179	Durvalumab + tremelimumab + BSC vs BSC		OS	Active, not recruiting	Canada
NCT03800602	II	28	Nivolumab + metformina	MSS	ORR (RECIST)	Recruiting	US
NCT03542877	II	44	Cabozantinib	–	PFS	Active, not recruiting	US
NCT03087071	II	84	Panitumumab + trametinib in cetuximab-refractory mCRC	EGFR mt KRAS mt or NRAS mt or BRAF mt in DNAcl	ORR	Recruiting	US
NCT03843749	II	30	Pirotinib + trastuzumab	HER2+	ORR	Recruiting	China
NCT03190616	II	54	Apatinib	–	PFS	Completed	China
NCT01930864	II	41	Irinotecan + metformin	–	No PD 12w	Recruiting	Brazil
NCT02723578	II	50	Pemetrexed + erlotinib	–	ORR and PFS	Completed	Korea
NCT03405272	II	110	AcMo anti-EGFR recombinante (SCT200)	RAS y BRAF wt	ORR	Unknown	China
NCT03843853	II	50	Pemetrexed + S-1 + bevacizumab	–	PFS	Not recruiting yet	China
NCT03711058	I-II	54	Nivolumab + copanlisib (TKI PI3Kinasa)	Cohort MSS	MTD ORR	Recruiting	US
NCT03436563	I-II	59	M7824	CMS4 o MSI+	ORR	Recruiting	US
NCT03332498	I-II	42	Pembrolizumab + ibrutinib	–	MTD DCR	Active, not recruiting	US
NCT03206073	I-II	35	Durvalumab + pexal-vac oncolytic vírus Durvalumab + tremelimumab Durvalumab + tremelimumab + pexa-vac	–	Tolerance	Recruiting	US
NCT03531632	I-II	52	MGD007 + MGA012	–	MTD	Active, not recruiting	US
NCT02393755	I-II	39	Nintedanib + capecitabina	–	MTD PFS 18 w	Active, not recruiting	US
NCT03258398	I-II	56	eFT508 + avelumab	MSS	MTD	Completed	US
NCT03576963	I-II	45	Nivolumab + guadecitabine	MSS	MTD ORR	Recruiting	US
NCT03144804	II	32	Lamivudine	TP53 mutant/deleted	ORR	Recruiting	US
NCT03668431	II	25	Dabrafenib + trametinib + PDR001	BRAF V600E mutant	ORR	Recruiting	US
NCT04166435	II	30	Temozolomide + olaparib	MGMT promoter hipermetilated	ORR	Recruiting	US
NCT03981146	II	36	Nivolumab	Strong class II expression MSS	DCB	Recruiting	UK
NCT03086538	II	29	Pemetrexed + erlotinib	EGFR overexpressed	ORR	Recruiting	Korea

Table 4 Continued

Study	Phase	N	Drugs	Molecular Profile	Objectives	Status	Geographical Area
NCT03832621	II	100	Nivolumab + ipilimumab + temozolomide	MGMT silenced	8-month PFS rate	Recruiting	Italy
NCT03457896	II	35	Neratinib + cetuximab or trastuzumab	HER2 amplified	PFS	Recruiting	US
NCT03909724	II	60	Sunitinib malate or TAS102	—	PFS	Recruiting	Netherlands
NCT03946917	I/II	38	JS001 and regorafenib	MSS	MTD, DLT, ORR	Recruiting	China
NCT04166383	II	27	VB-111 and nivolumab	—	Safety and BOR	Active, not yet recruiting	US
NCT03657641	I/II	75	Pembrolizumab and regorafenib	—	DLT, PFS, OS	Recruiting	US
NCT04067986	II	62	Camrelizumab and apatinib	—	ORR	Recruiting	China
NCT03403634	II	12	Celecoxib, interferon alfa-2b, rintatolimod	—	Change in TILs	Recruiting	US
NCT04322539 FRESCO-2	III	522	Fruquitinib or placebo	—	OS	Active, not yet recruiting	US
NCT03983993 NIPAVect	II	26	Niraparib and panitumumab	RAS wt	CBR	Recruiting	US
NCT04119830	IIa	25	Pembrolizumab and rintatolimod	MSS	ORR	Active, not yet recruiting	US
NCT04096417	II	24	Pemigatinib	FGFR alterations	ORR	Active, not yet recruiting	US
NCT03981614	II	112	Binimetinib and palbociclib or TAS 102	KRAS/NRAS mt	PFS	Recruiting	US
NCT03087071	II	84	Panitumumab with or without trametinib	KRAS/NRAS/BRAF V600E mt EGFR ectodomain mutation	ORR	Recruiting	US
NCT03992456	II	120	Panitumumab or TAS 102 or regorafenib	KRAS/NRAS/BRAF V600E wt	OS	Active, not yet recruiting	US
NCT03043313 MOUNTAINEER	II	110	Tucatinib plus trastuzumab	HER2 overexpression or amplification	ORR	Recruiting	US
NCT03791398 BrUOG379	Ib/II	34	ONC201 + nivolumab	—	MTD, PFS	Recruiting	US
NCT03592641	II	15	Savonitinib	MET amplified	ORR	Recruiting	US
NCT03446157	II	57	Palbociclib and cetuximab	KRAS/NRAS/BRAF V600E wt	DCR	Recruiting	US
NCT04044430	I/II	38	Encorafenib, binimetinib, and nivolumab	BRAF V600Emt	ORR	Recruiting	US
NCT03524820	II	60	Cetuximab or cetuximab/ chemotherapy rechallenge	KRAS/NRAS/BRAF V600E wt	ORR	Recruiting	Israel
NCT03712943	I	28	Regorafenib + nivolumab	MSS	MTD	Recruiting	US
NCT03274804	I	20	Pembrolizumab + maraviroc[a]	MSS	Tolerability	Completed	Germany
NCT03626922	Ib	33	Pembrolizumab + pemetrexed ± oxaliplatin	MSS	MTD	Not recruiting yet	US

Clinicaltrials.gov consulted 06-04-2020.
Abbreviations: BOR = best overall response; BSC = best supportive care; CBR = clinical benefit rate; cfDNA = circulating free DNA; DCG = durable clinical benefit; DCR = drug control rate; DLT = dose-limiting toxicity; EGFR = epidermal growth factor receptor; FGFR = fibroblast growth factor receptor; FTD/TPI = Trifluridine/tipiracil; FOLFIRI = folinic acid, 5-fluorouracil, and irinotecan; HER2 = human epidermal growth factor receptor 2; mCRC = metastatic colorectal cancer; MSI+ = microsatellite instability; MSS = microsatellite stability; mt = mutated; MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; rand = randomized; RECIST = Response Evaluation Criteria in Solid Tumors; TILs = tumor-infiltrating lymphocytes; TKI = tyrosine kinase inhibitor; US = United States; W = weeks; wt = wild type.
[a]Maraviroc CCR 5 (chemokine receptor 5) inhibitor.

assessed the embolization with irinotecan according to the "drug-elluting beds" system (DEBIRI), achieving ORR of 66% and 75% at 6 and 12 months, respectively, with PFS of 11 months and OS of 19 months.[107] After that, a phase III randomised clinical trial in 74 patients poly-treated in ≥ third-line without extrahepatic involvement showed greater OS with DEBIRI versus FOLFIRI (22 vs. 15 months; $P = .03$).[108]

SIRT in hepatic artery with yttrium-90 showed, in a phase III study in 46 patients with chemotherapy-refractory mCRC and exclusively liver disease, a better PFS with the combination of 5-FU + SIRT versus 5-FU alone (4.5 vs. 2.1 months: HR, 0.51; 95% CI, 0.28-0.94; $P = .03$).[109] At the same time, its benefits have been confirmed in retrospective case reviews.[110] Likewise, promising results with other radiopharmaceuticals such as radioactive holmium (166Ho-microspheres) have also been reported.[111]

National Comprehensive Cancer Network guidelines recommend the use of locoregional therapy for hepatic metastases in non-resectable mCRC refractory to chemotherapy with the objective of increasing local control and survival. They conclude that HAI, TACE, and SIRT show similar efficacy,[112] based on the results of the meta-analysis.[113]

Recommendations and Conclusions

The survival of patients with mCRC has increased prominently in recent years, reaching a median of 25 to 30 months. This increase in survival is owing to the sum of several strategies: the continuum of care, multidisciplinary care, resection of metastatic disease, local ablative therapies in oligometastatic disease, the selection of drugs based on biomarker expression, oral drugs approved for refractory mCRC, rechallenge with drugs previously used, the administration of drugs targeted against new molecular targets (compassionate use), and the inclusion in clinical trials.

Currently, many patients who have progressed with previous lines of regimens containing oxaliplatin, irinotecan, fluoropyrimidines, anti-angiogenic, and anti-EGFR (RAS wt) maintain a good performance status and are candidates for $\geq$ third-line treatments.

In this situation of refractoriness, there are several alternatives. One is to sequentially administer the 2 oral drugs approved in this indication: trifluridine/tipiracil and regorafenib, which have shown a statistically significant benefit in PFS and OS with a different toxicity profile. Derived from the fact that the evidence of these drugs comes from randomized studies, we are faced with a level of evidence "I" and in turn an "A" degree of recommendation (I, A), although there is not enough evidence to establish the optimal sequence of these 2 drugs.

Another option is to administer cetuximab or panitumumab in patients with RAS wt if they have not previously received it (I, A), which is increasingly rare because they are usually indicated in first- or second-line therapy.

A third alternative is to reuse drugs already administered and discontinued owing to toxicity or progression (oxaliplatin, irinotecan, fluoropyrimidine, antiangiogenics, anti-EGFR [if RAS wt]), such as oxaliplatin reintroduction, which is an important option to be considered in third line, mainly after an oxaliplatin-free interval of 6 months.

High-quality evidence is limited, but this strategy is often used in routine clinical practice especially in patients with good PS in the absence of alternative therapies.

Further from the BEACON results in the 35% of patients treated in third or subsequent lines, the use of double or triple chemotherapy seems advisable in this subgroup of patients.

Another option is to use specific treatments for very selected populations such as trastuzumab + lapatinib in mCRC HER2+, immunotherapy in MSI+, or intrahepatic therapies in limited disease or primarily located in the liver, and if the results of the phase III study BEACON are positive, a therapy based on BRAF inhibitors + anti-EGFR in BRAF-mutated tumors.

The main recommendation is to include patients in clinical trials. Studies evaluating the synergy of inhibition between BRAF and EGFR in BRAF-mutated tumors, and studies assessing the resistance to EGFR inhibitors are ongoing. In general, ongoing phase III studies in refractory mCRC are scarce, because most studies are phase II or I to II with drugs with new mechanisms of action such as vasculature disruptor agents, autophagy modulators, STAT3 inhibitors, immune check point inhibitors, CCR5 inhibitors, etc. (Table 4).[114] It is noteworthy that many of these studies are already selecting patients by the molecular profile of the CRC and many are MSS. From the ongoing studies, those offering the possibility of a quick move to daily practice, such as the combination of irinotecan + regorafenib (phase III study NEXT-REGIRI) or trifluridine/tipiracil + ramucirumab (randomised phase II study RAMTAS), are of special interest if the results are positive.

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