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REVIEW

Beyond second-line therapy in patients with metastatic colorectal cancer: a systematic review

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Background: The optimal chemotherapeutic regimen for use beyond the second line for patients with metastatic colorectal cancer (mCRC) remains unclear.

Materials and methods: We systematically searched the Cochrane Database of Systematic Reviews, EMBASE and Medline for records published between January 2002 and May 2017, and cancer congress databases for records published between January 2014 and June 2017. Eligible studies evaluated the efficacy, safety and patient-reported outcomes of monotherapies or combination therapies at any dose and number of treatment cycles for use beyond the second line in patients with mCRC. Studies were assessed for design and quality, and a qualitative data synthesis was conducted to understand the impact of treatment on overall survival and other relevant cancer-related outcomes.

Results: The search yielded 938 references of which 68 were included for qualitative synthesis. There was limited evidence to support rechallenge with chemotherapy, targeted therapy or both. Compared with placebo, an overall survival benefit for trifluridine/tipiracil (also known as TAS-102) or regorafenib has been shown for patients previously treated with conventional chemotherapy and targeted therapy. There was no evidence to suggest a difference in efficacy between these treatments. Patient choice and quality of life at this stage of treatment should also be considered when choosing an appropriate therapy.

Conclusions: These findings support the introduction of an approved agent such as trifluridine/tipiracil or regorafenib beyond the second line before any rechallenge in patients with mCRC who have failed second-line treatment.

Key words: metastatic colorectal cancer, rechallenge, regorafenib, treatment beyond the second line, trifluridine/tipiracil

Introduction

Colorectal cancer is one of the largest contributors to cancer-related mortality [1, 2]; however, the optimal chemotherapeutic regimen for use beyond the second line for patients with metastatic colorectal cancer (mCRC) remains unclear [1–4]. Although rechallenge with chemotherapy may be considered, this is not an option if residual toxicity is present [1, 3] and may lack efficacy in patients who have progressed on a similar regimen [5]. A systematic review of therapy in patients with mCRC previously treated with 5-fluorouracil (5-FU), oxaliplatin and irinotecan with or without targeted therapy concluded that conventional chemotherapeutic agents such as capecitabine, mitomycin C and gemcitabine have limited utility [6]. Subsequently, new evidence has emerged supporting the use of the oral nucleoside analogue trifluridine/tipiracil, and the multi-targeted tyrosine kinase inhibitor, regorafenib, beyond second line. Both treatments are recommended for third-line use in patients who have progressed through all available regimens (level of evidence I) [1, 7]. In addition to these, the number of prospective trials evaluating rechallenge and investigational compounds has continued to expand.

The increase in potential treatment options and the use of some agents in more than one line or as adjuvant therapy over time make the treatment landscape extremely complex, and appropriate treatments in the later lines difficult to define. We therefore conducted a systematic review to evaluate the efficacy, safety and patient-reported outcomes (PROs) associated with

investigational treatments, rechallenge, or therapies approved for mCRC beyond second line with the aim of identifying an optimal approach.

Methods

Search strategy

A literature search was conducted for English language studies published between January 2002 and May 2017 in the Cochrane Database of Systematic Reviews, EMBASE and Medline. The Cochrane Central Register of Controlled Trials and ClinicalTrials.gov were searched for ongoing studies. Conference abstracts from the American Association for Cancer Research, the American Society of Clinical Oncology (ASCO), the ASCO Gastrointestinal Cancers Symposium (ASCO-GI), the European Society for Medical Oncology (ESMO) and the ESMO World Congress on Gastrointestinal Cancer presented between January 2014 and June 2017 were searched. A search strategy was developed in Medline consisting of MeSH headings and text words for mCRC, refractory disease and third- or fourth-line therapy (supplementary material, available at *Annals of Oncology* online). This strategy was adapted for the other databases.

Eligibility criteria

Studies had to meet the following criteria:

Interventions. Eligible studies evaluated monotherapies or combination therapies for use beyond the second-line setting in patients with mCRC, and included efficacy, safety or PROs associated with: (i) investigational third- or fourth-line therapy, (ii) rechallenge with a first- or second-line therapy in a later-line setting or (iii) therapies licensed beyond the second line.

Study designs. Phase II or III randomised or non-randomised trials with ≥30 patients were included. We also included single-arm prospective, observational studies and retrospective 'real-world' studies; additional studies felt to be of interest by the authors but which did not conform to these inclusion criteria are included in the supplementary material for further reading (supplementary Table S1, available at *Annals of Oncology* online). Phase I trials, preclinical studies, narrative reviews, editorials, opinions, letters, non-English language publications and congress abstracts for which insufficient methodological details were reported to allow critical appraisal of study quality and/or the end points of interest were excluded.

Participants. Studies in patients with metastatic or advanced CRC who had failed to respond, or who had progressed or experienced recurrence following first- and second-line chemotherapy were included.

Comparators/controls. Patients assigned to a comparator or other control group could receive placebo, best supportive care (BSC) or another agent offered as a third- or fourth-line treatment.

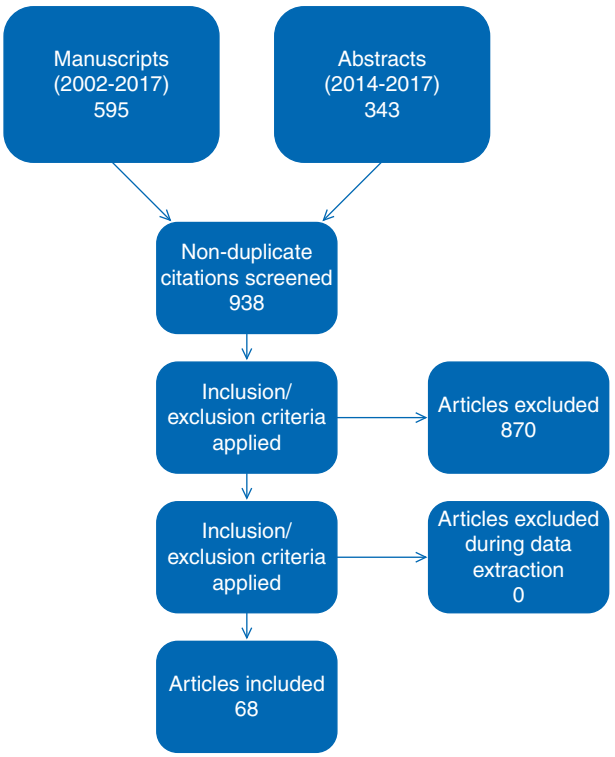

Figure 1. Study selection process.

Outcome measures. Outcomes of interest included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), health-related quality of life (QoL) or functional status, and grade 3–4 treatment-related adverse events (AEs).

Data extraction

A single trained reviewer screened all search results for eligibility before compiling selected studies into a customised extraction form in Excel (supplementary material, available at *Annals of Oncology* online). A senior reviewer assessed a subset of the results for accuracy and consistency of data extraction.

Risk of bias assessment

A single reviewer assessed the risk of bias for each study. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [8] and the Jadad et al. [9] criteria for randomised controlled trials (RCTs) were used to rate quality of evidence, with explicit questions to inform the process based on the 13-question modified RTI Item Bank for assessing the risk of bias and confounding used for observational studies of interventions or exposures [10].

Data synthesis

The results were summarised in the tables according to the three questions relevant to the treatment of patients with mCRC beyond the second line: what are the efficacy, safety and PRO data to support: (i) investigational drugs, (ii) rechallenge of patients who have progressed or experienced recurrence following first- and second-line chemotherapy and (iii) licensed drugs. The data were summarised narratively using a qualitative data synthesis approach.

Results

Search results

The search yielded a total of 938 citations; following two rounds of screening, 68 publications were included in the qualitative synthesis. Most excluded trials included patients on second-line treatment, or investigated <30 patients (Figure 1).

Details of included studies

One systematic review [11], 17 phase II/III explanatory RCTs [12–28] and 9 subanalyses [29–37] relating to 2 RCTs [21, 26] were included. In addition, 16 non-randomised, single-arm phase II studies, 5 prospective, observational studies, and 15 retrospective, real-world studies were included. Three studies were included as being studies beyond second line despite a lack of clarity around the study population [19, 26, 38].

Efficacy and safety of drugs approved for use beyond second line

Currently, there are two agents with an indication for use beyond second line in mCRC: trifluridine/tipiracil and regorafenib [1, 7]. Cetuximab and panitumumab are also indicated for *RAS* wild-type tumours not previously treated with endothelial growth factor receptor (EGFR) monoclonal antibodies [1, 39].

A summary of 22 publications of trifluridine/tipiracil and regorafenib beyond the second line in the mCRC setting is shown in Table 1. One systematic review comparing trifluridine/tipiracil and regorafenib using indirect methods reported similar efficacy for each in this setting [11]. The systematic review included one phase III RCT of trifluridine/tipiracil versus placebo in 800 patients (RECOURSE) [21] and two phase III RCTs of regorafenib versus placebo (CORRECT [17] and CONCUR [20]) in 964 patients. In RECOURSE, 82% of trifluridine/tipiracil-treated patients had received ≥3 prior lines of treatment [21]. In CORRECT and CONCUR, 74% and 62% of regorafenib-treated patients, respectively, had received ≥3 prior treatments [17, 20]. The hazard ratio (HR) for OS compared with placebo was similar for trifluridine/tipiracil and regorafenib, and indirect comparison confirmed their similar efficacy (Table 1) [11]. The indirect comparison confirmed an increased risk of grade ≥3 AEs for regorafenib versus trifluridine/tipiracil (Table 1) [11].

RECOURSE did not evaluate QoL outcomes; however, it did demonstrate that trifluridine/tipiracil was associated with a significant delay in worsening of European Cooperative Oncology Group (ECOG) performance status from a baseline of 0–1 to ≥2 versus placebo [21]. The median time to an ECOG performance status of ≥2 was 5.7 versus 4.0 months in the trifluridine/tipiracil and placebo groups, respectively (Table 1) [21]. In the two RCTs of regorafenib, QoL was prospectively analysed, with no differences between the regorafenib and placebo groups in deterioration of QoL and health status [17, 20]. ECOG performance status was not investigated for regorafenib [17, 20].

In RECOURSE, grade ≥3 AEs occurred in 69% and 52% of patients treated with trifluridine/tipiracil and placebo, respectively, with haematological toxicities the most common events; febrile neutropaenia occurred in 4% and 0% of patients (Table 1) [21]. For regorafenib, grade ≥3 AEs occurred in 54% of patients (14% and 0% in the two placebo arms), with hand–foot skin reaction (HFSR), hypertension, fatigue, gastrointestinal symptoms, increased liver enzymes and hypophosphataemia the most common events occurring at a higher frequency than with placebo (Table 1) [17, 20].

An updated survival analysis of the RECOURSE trial confirmed that the OS benefit of trifluridine/tipiracil relative to placebo was maintained over time compared with the original analysis (Table 1) [31]. Improvement in 1-year survival surpassed 10% in these heavily pretreated patients (trifluridine/tipiracil, 27.1%; placebo, 16.6%). Subanalyses of RECOURSE have shown a survival benefit for trifluridine/tipiracil over placebo in different patient subgroups (Table 1) [29, 30, 32]. Two further RCTs of trifluridine/tipiracil including the phase III TERRA trial and a phase II, randomised, double-blind trial similarly showed a survival benefit for trifluridine/tipiracil compared with placebo in Asian patients (Table 1) [16, 24].

Additional evidence for either trifluridine/tipiracil or regorafenib beyond the second line in mCRC is of low quality and consists of one non-comparative study of regorafenib together with related subanalyses [40–43], a retrospective study of trifluridine/tipiracil [44], and retrospective studies of regorafenib [45] or regorafenib compared with trifluridine/tipiracil (Table 1) [46–48]. A phase IIIB, single-arm study of 2872 patients treated for a median duration of 2.5 months with regorafenib reported median PFS and a safety profile that was consistent with those seen in phase III trials [40–43]. Three retrospective observational studies that compared regorafenib with trifluridine/tipiracil in 700 patients reported similar OS, PFS, disease control rate, and ORR for the two treatments beyond the second line [46–48]. One of these studies ($n = 37$) reported safety findings consistent with earlier trials; the most frequent grade ≥3 AEs were hepatotoxicity (17.4%) and hand–foot syndrome (13.0%) in the regorafenib group, and neutropaenia (14.3%) in the trifluridine/tipiracil group [47].

Efficacy and safety of investigational drugs beyond the second line

Twenty-eight studies of investigational compounds for the beyond second-line mCRC setting were analysed, including 11 explanatory RCTs [1, 12–15, 18, 19, 22, 23, 27, 28] and 3 subgroup analyses relating to 1 RCT [26, 35, 36]. The remaining studies were either phase II, single-arm [38, 49–57] or observational studies [58–61] (Table 2).

Treatments currently approved for first or second line. Five trials were of anti-EGFR therapies that were approved for first- or second-line treatment at the time of the study or later: four RCTs [12–15] and a single-arm study [51].

The pivotal trial of cetuximab evaluated its ability to reverse resistance to irinotecan as a strategy for patients transitioning to further lines of therapy [12]. Cetuximab plus irinotecan was compared with cetuximab alone in 329 patients previously treated with irinotecan receiving second-line (21%), third-line (36%) and further-line (43%) treatment, and was found to improve median time to progression, but not OS (Table 2). A randomised, open-label study of 572 patients who had failed prior treatment that included fluoropyrimidines, irinotecan and oxaliplatin [13]

Table 1. Efficacy and safety of drugs licensed for use beyond the second line

Author	Trial design/setting and line of treatment	*N*	Treatment and comparator	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Systematic review								
Abrahao et al. 2016 [11]	Systematic review of 3 RCTs	1764	REG versus FTD/TPI versus PBO	NR	OS HR: REG versus PBO: 0.71; 95% CI 0.60–0.83 FTD/TPI versus PBO: 0.69; 95% CI 0.57–0.83 REG versus FTD/TPI (indirect): 1.02; 95% CI 0.80–1.32	NR	NR	Any AE HR: REG versus PBO: 7.22; 95% CI 5.08–10.26 FTD/TPI versus PBO: 2.12; 95% CI 1.57–2.87 REG versus FTD/TPI (indirect): 3.40; 95% CI 2.14–5.42
Explanatory trials: FTD/TPI versus PBO								
Yoshino et al. 2012 [16]	Phase II, R, DB, PC/third line or later	169	FTD/TPI versus PBO	≥2 prior regimens, including FP, IR and OX	Median OS: 9.0 versus 6.6 mos; HR 0.56 95% CI 0.39–0.81; *P*=0.0011	Median PFS: 2.0 versus 1.0 mos; HR 0.41; 95% CI 0.28–0.59; *P*<0.0001	ORR: 1% versus 0% DCR: 43% versus 11%; *P*<0.0001 Median TTF: 1.9 versus 1.0 mos; HR 0.40; 95% CI 0.28–0.56; *P*<0.0001	Fatigue: 6% versus 4% Diarrhoea: 6% versus 0% Nausea: 4% versus 0% Anorexia: 4% versus 4% Febrile neutropaenia: 4% versus 0% Vomiting: 4% versus 0% Neutropaenia: 50% versus 0% Leukopaenia: 28% versus 0% Anaemia: 17% versus 5% Lymphopaenia: 10% versus 4% Thrombocytopaenia: 4% versus 0%
Mayer et al. 2015 [21]	Phase III, R, SB, PC/third line or later	800	FTD/TPI versus PBO	≥2 prior regimens, including FP, OX, IR, BE, and CET or PAN	Median OS: 7.1 versus 5.3 mos; HR 0.68; 95% CI 0.58–0.81; *P*<0.001	Median PFS: 2.0 versus 1.7 mos; HR 0.48; 95% CI 0.41–0.57; *P*<0.001	ORR: 1.6% (all PR) versus 0.4% (CR); *P*=0.29 DCR: 44% versus 16%; *P*<0.001	Any: 69% versus 52% Febrile neutropaenia: 4% versus 0% Neutropaenia: 38% versus 0% Leukopaenia: 21% versus 0% Anaemia: 18% versus 3%
Ohtsu et al. 2015 [30]	Phase III, R, SB, PC/third line or later (subanalysis of geographic subgroups)	800	FTD/TPI versus PBO	≥2 prior regimens, including FP, OX, IR, BE, and CET or PAN	OS HR by location: USA: 0.56; 95% CI 0.34–0.94; *P*=0.0277 Europe: 0.62; 95% CI 0.48–0.80; *P*=0.0002 Japan: 0.75; 95% CI 0.57–1.00; *P*=0.047	PFS HR by location: USA: 0.43; 95% CI 0.26–0.69; *P*=0.0004 Europe: 0.41; 95% CI 0.33–0.52; *P*<0.0001 Japan: 0.58; 95% CI 0.44–0.75; *P*<0.0001	NR	Any: USA: 73.4% versus 45.7% Europe: 70.7% versus 55.0% Japan: 66.3% versus 50.0%

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Table 1. *Continued*

Author	Trial design/setting and line of treatment	*N*	Treatment and comparator	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Van Cutsem et al. 2015 [31]	Phase III, R, SB, PC/ third line or later (age-based subanalysis)	800	FTD/TPI versus PBO	≥2 prior regimens, including FP, OX, IR, BE, and CET or PAN	Median OS (pts aged ≥65 yrs): 7.0 versus 4.6 mos; HR 0.62; 95% CI 0.48–0.80; *P*=0.0002	Median PFS (pts aged ≥65 yrs): HR 0.41; 95% CI 0.32–0.52; *P*<0.0001	DCR (pts aged ≥65 yrs): 48.7% versus 15.5%	Any: Age <65 yrs: 65.2% Age ≥65 yrs: 74.8% Age ≥75 yrs: 75.0%
Mayer et al. 2016 [33]	Phase III, R, SB, PC/ third line or later (subanalysis of pts with impaired renal and/or hepatic function)	800	FTD/TPI versus PBO	≥2 prior regimens, including FP, OX, IR, BE, and CET or PAN	OS HR by hepatic function: Normal: 0.63; 95% CI 0.50–0.80 Grade 1 impairment: 0.71; 95% CI 0.53–0.95 Grade 2 impairment: 0.44; 95% CI 0.21–0.92	OS HR by renal function: Normal: 0.64; 95% CI 0.51–0.81 Mild impairment: 0.71; 95% CI 0.53–0.96 Moderate impairment: 0.85; 95% CI 0.47–1.56	NR	NR
Mayer et al. 2016 [32]	Phase III, R, SB, PC/ third line or later (final survival results)	800	FTD/TPI versus PBO	≥2 prior regimens, including FP, OX, IR, BE, and CET or PAN	Median OS: 7.2 versus 5.2 mos; HR 0.69; 95% CI 0.59–0.81; *P*<0.0001	NR	NR	NR
Ohtsu et al. 2016 [34]	Phase III, R, SB, PC/ third line or later (subanalysis of neutropaenia onset as indicator of response)	800	FTD/TPI versus PBO	≥2 prior regimens, including FP, OX, IR, BE, and CET or PAN	Median OS by earliest Grade 3–4 neutropaenia onset: Cycle 1: 9.7 versus 5.3 mos; HR 0.45; 95% CI 0.32–0.64 Cycle 2: 8.7 versus 6.3 mos; HR 0.56; 95% CI 0.41–0.78 Cycle ≥3: 13.8 versus 10.2 mos; HR 0.36; 95% CI 0.17–0.75 No events: 5.5 versus 5.3 mos; HR 0.97; 95% CI 0.18–1.16	NR	NR	NR

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Table 1. *Continued*

Author	Trial design/setting and line of treatment	*N*	Treatment and comparator	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Tabernero et al. 2016 [35]	Phase III, R, SB, PC/ third line or later (subanalysis of impact of AE on QoL and treatment duration)	800	FTD/TPI versus PBO	≥2 prior regimens, including FP, OX, IR, BE, and CET or PAN	NR	NR	NR	Nausea: 1.9% versus 1.1% Vomiting: 2.1% versus 0.4% Diarrhoea: 3.0% versus 0.4% Fatigue: 3.9% versus 5.7% Asthaenia: 3.4% versus 3.0% Median exposure/duration times for all pts: 7 versus 6 weeks; for pts with 1 AE: 12 versus 10 weeks
Tabernero et al. 2017 [38]	Phase III, R, SB, PC/ third line or later (QTWIST subanalysis)	798	FTD/TPI versus PBO	≥2 prior regimens, including FP, OX, IR, BE, and CET or PAN	Mean time with Grade 3–4 TRAEs expected to impact QoL before PD (nausea, vomiting, diarrhoea, fatigue, asthenia, anorexia, FN): 0.92 versus 0.70 mos	TWIST: 2.56 versus 1.28 mos	TTP until death: 4.92 versus 4.70 mos QTWIST: 5.48 versus 3.98 mos; 95% CI 1.49–1.52	NR
Kim et al. 2016 [24]	Phase III, R, DB, PC/ third line or later	406	FTD/TPI versus PBO	≥2 prior regimens, including FP, OX + IR	Median OS: 7.8 versus 7.1 mos; HR 0.79; 95% CI 0.62–0.99; *P*=0.035	Median PFS: 2.0 versus 1.8 mos; HR 0.43; 95% CI 0.34–0.54; *P*<0.001	DCR: 44.1% versus 14.6%	Neutropaenia: 20.3% versus 0% Anaemia: 15.9% versus 5.9% Leukopaenia: 4.8% versus 0%
Real-world studies: FTD/TPI								
Kotani et al. [45]	RET, OBS	55	FTD/TPI	Prior therapy included 58.2% REG	Median PFS: 2.0 mos (range 1.7–2.3)	Median OS: 5.3 mos (range 3.5–7.2)	ORR: 3.7% DCR: 38.9%	Fatigue 3.6% Neutropaenia: 41.8% Leukopaenia: 27.2% Anaemia: 23.6% Febrile neutropaenia: 5.5%
Explanatory trials: REG versus PBO								
Grothey et al. 2013 [17]	Phase III, R, DB, PC/ second line or later	760	REG versus PBO	Previous FP, OX, IR and BE, and CET or PAN	Median OS: 6.4 versus 5.0 mos: HR 0.77; 95% CI 0.64–0.94; *P*=0.0052	Median PFS: 1.9 versus 1.7 mos; HR 0.49; 95% CI 0.42–0.58; *P*<0.0001	ORR (all PR): 1.0% versus 0.4% DCR: 41% versus 15%; *P*<0.0001	Any: 54% versus 14% Fatigue: 10% versus 6% Diarrhoea: 8% versus 1% Rash or desquamation: 6% versus 0% Hypophosphataemia: 4% versus <1% Anaemia: 3% versus 0%

Continued

Table 1. *Continued*

Author	Trial design/setting and line of treatment	*N*	Treatment and comparator	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Li et al. 2015 [20]	Phase III, R, DB, PC/ second line or later	204	REG versus PBO	≥2 prior regimens, including FP + OX or IR	Median OS: 8.8 versus 6.3 mos; HR 0.55; 95% CI 0.40–0.77; *P*=0.00016	Median PFS: 3.2 versus 1.7 mos; HR 0.31; 95% CI 0.22–0.44; *P*<0.0001	ORR (all PR): 4% versus 0%; *P*=0.045 DCR: 51% versus 7%; *P*<0.0001	Any: 54% versus 14% HFSR: 16% versus 0% Hypertension: 11% versus 3% Increased ALT: 7% versus 0% Increased AST: 6% versus 0% Hypophosphataemia: 7% versus 0%
Non-randomised studies: REG								
Van Cutsem et al. ECCO 2015 [41]	Phase IIIb, OL, SA/ third line or later in 96% of pts	2872	REG	Previous FP, OX, IR, BE, and CET or PAN	Median PFS: 2.7 mos; 95% CI 2.6–2.7	NR	NR	Fatigue: 18% Hypertension: 17% Diarrhoea: 6% HFSR: 14% Hypophosphataemia: 7% Increased ALT: 6% Increased AST: 7% Increased bilirubin: 13%
Van Cutsem et al. 2015 [42]	Phase IIIb, OL, SA/ third line or later in 96% of pts (no results reported)	2872	REG	Previous FP, OX, IR, BE, and CET or PAN	NR	NR	NR	NR
Van Cutsem et al. ASCO 2016 [44]	Phase IIIb, OL, SA/ third line or later in 96% of pts (age group subanalysis, ≥65 yrs)	2872	REG	Previous FP, OX, IR, BE, and CET or PAN	Median PFS by age: Aged <65 yrs: 2.7 mos Age ≥65 yrs: 2.6 mos	NR	NR	Grade ≥3 AEs, age ≥65 yrs versus <65 yrs Any: 60% versus 55% Hypertension: 18% versus 14% HFSR: 11% versus 16% Fatigue: 17% versus 11% Diarrhoea: 5% versus 5% Hypophosphataemia: 5% versus 5%
Van Cutsem et al. WCGI 2016 [43]	Phase IIIb, OL, SA/ third line or later in 96% of pts (age group subanalysis, ≥75 yrs)	268	REG	Previous FP, OX, IR, BE, and CET or PAN	Safety analysis—see safety column	PFS, age ≥75 yrs versus <75 yrs: 2.5 versus 2.7 mos	NR	Grade ≥3 AEs, age ≥75 yrs versus <75 yrs Any: 64% versus 56% Hypertension: 21% versus 15% HFSR: 9% versus 14% Fatigue: 22% versus 12% Diarrhoea: 6% versus 5% Hypophosphataemia: 5% versus 5%

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Table 1. *Continued*

Author	Trial design/setting and line of treatment	*N*	Treatment and comparator	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Real-world studies: REG; REG versus FTD/TPI								
Adenis et al. 2016 [46]	RET, OBS/third line or later	654	REG	≥2 previous regimens	Median OS: 5.6 mos; IQR 2.4–11.4 12-mo OS: 22%	Median OS (pts with high treatment benefit): 9.2 mos Median OS (pts with moderate treatment benefit): 5.2 mos	Median PFS: 2.7 mos; IQR 1.6–4.6 12-mo PFS: 7%	Any: 43.7% Fatigue: 14.5% HFSR: 9% Diarrhoea: 4.3% Hypertension: 4.6% Anorexia: 2.9%
Kotaka et al. WCGI 2016 [47]	RET, OBS	74	REG versus FTD/TPI	Previous FP, OX, IR, BE, and CET or PAN	Median PFS: 2.0 versus 2.1 mos; *P*=0.145	Median OS: 7.7 versus 7.9 mos; *P*=0.549	ORR: 3% versus 0%; *P*=0.330DCR: 95% versus 94%; *P*=0.956	NR
Sueda et al. 2016 [48]	RET, OBS/third line or later	37	REG versus FTD/TPI	≥2 previous standard regimens	CR: 0% versus 0% PR: 0% versus 0% SD: 30.4% versus 28.6%	Median PFS: 3.0 versus 2.1 mos	Median OS: 5.8 versus 6.3 mos	Any: 43.5% versus 14.3% HFSR: 13.0% versus 0% Hepatotoxicity: 17.4% versus 0% Neutropaenia: 0% versus 14.3% Hyperammonaemia: 8.7% versus 0%
Fukuoka et al. ASCO 2017 [49]	RET, OBS	589	REG versus FTD/TPI	Previous standard regimens	OS HR: 0.96; 95% CI 0.78–1.18	PFS HR 0.94	TTF HR 0.81; *P*=0.025	NR

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BE, bevacizumab; CET, cetuximab; CI, confidence interval; CR, complete response; DB, double-blind; DCR, disease control rate; FP, fluoropyrimidine; FTD/TPI, trifluridine/tipiracil; HFSR, hand–foot skin reaction; HR, hazard ratio; IQR, interquartile range; IR, irinotecan; mos, months; NR, not reported; OBS, observational; OL, open-label; ORR, objective response rate; OS, overall survival; OX, oxaliplatin; PAN, panitumumab; PBO, placebo; PC, placebo-controlled; PD, progressive disease; PFS, progression-free survival; PR, partial response; pts, patients; QoL, quality of life; QTWIST, quality-adjusted time without symptoms of disease or toxicity; R, randomised; RCT, randomised-controlled trial; REG, regorafenib; RET, retrospective; SA, single-arm; SB, single-blind; SD, stable disease; TRAEs, treatment-related adverse events; TTF, time to treatment failure; TTP, time to progression; TWIST, time without symptoms of disease or toxicity; yrs, years.

evaluated cetuximab plus BSC versus BSC alone and found that cetuximab plus BSC offered a survival benefit over BSC alone (Table 2). A phase II, randomised, open-label study of cetuximab, irinotecan and bevacizumab versus cetuximab and bevacizumab in 83 patients who had failed ≥1 previous irinotecan-based regimens reported an increase in OS with triple versus dual therapy (Table 2) [14]. However, this study struggled to accrue the requisite patients for meaningful comparison between the study arms and included a significant proportion of patients with only one or two prior treatments.

Panitumumab plus BSC versus BSC alone was evaluated in a phase III, randomised, open-label study of 463 patients who had failed 2 or 3 prior regimens that included fluoropyrimidines, irinotecan and oxaliplatin [15]. Versus BSC alone, panitumumab plus BSC did not affect median OS, but did prolong median PFS (Table 2). In a phase III, randomised, open-label study of 999 patients with wild-type *KRAS* who had previously failed irinotecan- and oxaliplatin-based chemotherapy [22], panitumumab was non-inferior to cetuximab with regard to OS (HR, 0.97; 95% CI 0.84–1.11). In a phase II, single-arm trial, panitumumab plus irinotecan yielded a median PFS of 5.5 months, with median OS of 9.7 months [51].

The use of cetuximab or panitumumab is now considered standard care in patients with a *KRAS/NRAS* wild-type genotype, including in the third-line setting in patients who have not previously received anti-EGFR treatment [1, 7]. However, it is not uncommon for patients with *RAS* wild-type expression to receive EGFR inhibitors as first-line therapy. Current guidelines recommend the use of either cetuximab or panitumumab in such patients as initial therapy [1, 7]. There is evidence that EGFR inhibition may not have a benefit in right-sided tumours [39, 62, 63], and the most recent NCCN guidelines note the lack of response to cetixumab and panitumumab in patients with right-sided tumours [7].

Agents not approved for treatment of mCRC. In a phase III, randomised, double-blind, placebo-controlled trial of 416 Chinese patients previously treated with ≥2 previous lines of chemotherapy [28], therapy with the vascular EGFR (VEGFR) inhibitor fruquintinib resulted in prolonged median OS versus placebo (Table 2). The most frequent fruquintinib-related grade ≥3 AEs were hypertension and HFSR.

The VEGFR inhibitor brivanib improved PFS but not OS in a phase III, randomised, double-blind, placebo-controlled trial [18] (Table 2). In this study, 745 patients, including 92% who had previously received ≥4 lines of chemotherapy, were assigned to either cetuximab plus brivanib or cetuximab plus placebo. Median OS was similar for cetuximab plus brivanib compared with cetuximab alone, but brivanib was associated with longer median PFS (Table 2). Compared with placebo, the addition of brivanib to cetuximab was associated with an excess of grade ≥3 AEs overall, as well as an excess of grade ≥3 fatigue, hypertension, rash and abdominal pain (Table 2).

A phase II/III randomised, double-blind, placebo-controlled study of 344 patients previously treated with irinotecan- and/or oxaliplatin-based chemotherapy, assigned patients to either weekly or fortnightly dalotuzumab, both in combination with cetuximab and irinotecan [23]. The trial was prematurely discontinued due to neither dalotuzumab dosing regimen meeting predefined continuation criteria. The impressive median OS (14.0 months) and PFS (5.6 months) achieved with cetuximab and irinotecan in the placebo arm likely reflect the inclusion of second-line patients since more than 40% of patients had just one or two prior lines of treatment.

Treatments targeting molecular subgroups. A phase II, randomised, open-label trial evaluated the *BRAF* kinase inhibitor vemurafenib in combination with irinotecan and cetuximab (VIC) compared with irinotecan plus cetuximab (IC) in 106 patients with *BRAF* V600E-mutated mCRC previously treated with one or two standard chemotherapy regimens [27]. OS was not reported, but VIC resulted in longer median PFS versus IC (Table 2). An excess of grade 3–4 nausea, neutropaenia and anaemia was reported for VIC compared with IC. Other trials dedicated to poor prognostic *BRAF*-mutated mCRC are ongoing and combine *BRAF* inhibitors with other targeted agents.

A phase II, single-arm trial evaluated pembrolizumab, an anti-programmed death 1 (PD-1) immune checkpoint inhibitor with activity against microsatellite instability-high (MSI-H) tumours, in 32 patients with mCRC with or without mismatch-repair deficiency [54], where 78% of patients had received ≥3 previous therapies. Mismatch-repair status predicted clinical benefit, with median PFS and OS not reached in the mismatch-repair deficiency cohort compared with 2.2 and 5.0 months, respectively, in patients with mismatch-repair proficient mCRC (HR for death, 0.22; $P = 0.05$).

Dual-targeted therapy was evaluated in a phase II, single-arm trial of trastuzumab plus pertuzumab in 57 patients with HER2+ mCRC [38]. In this study, the ORR was 37.5%.

Other investigational compounds. The interleukin-1α inhibitor xilonix (MABp1) was evaluated in a phase III, randomised, open-label, placebo-controlled study in 309 patients also receiving BSC and previously treated with oxaliplatin- or irinotecan-based chemotherapy [19]. Treatment response was significantly better for xilonix versus placebo (Table 2).

A phase III, randomised, double-blind, placebo-controlled trial evaluated the tyrosine kinase inhibitor nintedanib together with BSC versus placebo plus BSC in 768 patients previously treated with fluoropyrimidines, oxaliplatin, irinotecan and bevacizumab, and previous EGFR inhibitors in those with wild-type expression of *KRAS/NRAS* [26]. Median OS was similar for nintedanib and placebo, but median PFS was longer in the nintedanib group (Table 2).

A number of phase II, single-arm trials evaluated different investigational compounds in unselected patients receiving treatment beyond the second line, but did not indicate any clear survival benefit [49, 50, 52, 53, 56, 57].

Efficacy and safety of rechallenge in patients with progression or recurrence beyond the second line

In patients previously treated with irinotecan- and oxaliplatin-based chemotherapy, fluoropyrimidines, bevacizumab, and either cetuximab or panitumumab for those with *RAS* wild-type tumours, an option in clinical practice is to rechallenge after progression or recurrence [1, 64]. Unlike reintroduction of a treatment which may occur in situations where there is no progression on therapy, rechallenge involves administering a

Table 2. Efficacy and safety of investigational drugs beyond the second line

Author	Trial design/setting and line of treatment	*N*	Comparators	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Explanatory trials								
Cunningham et al. 2004 [12]	R, OL, AC/second and mostly third line and later	329	CET + IR versus CET	All patients were refractory to IR-based treatment	ORR (all PR): 22.9% versus 10.8%; *P*=0.007 SD: 32.6% versus 21.6%	Median DOR: 5.7 versus 4.2 mos	Median TTP: 4.1 versus 1.5 mos; HR 0.54; 95% CI 0.42–0.71; *P*<0.001 Median OS: 8.6 versus 6.9 mos; HR 0.91; 95% CI 0.68–1.21; *P*=0.48	Any: 65.1% versus 43.5%; *P*<0.001 Diarrhoea: 21.2% versus 1.7%; *P*<0.001 Asthenia: 13.7% versus 10.4% Acne-like rash: 9.4% versus 5.2% Nausea and vomiting: 7.1% versus 4.3% Abdominal pain: 3.3% versus 5.2% Stomatitis: 2.4% versus 0.9% Dyspnoea: 1.4% versus 13.0%; *P*<0.001 Fever: 2.4% versus 0% Hypersensitivity reaction: 0 versus 3.5%
Jonker et al. 2007 [13]	R, OL/second, third and fourth line and later	572	CET + BSC versus BSC	Previous FP, IR and OX	Median OS: 6.1 versus 4.6 mos; HR 0.77; 95% CI 0.64–0.92; *P*=0.005	PFS: HR 0.68; 95% CI 0.57–0.80; *P*<0.001	ORR (all PR): 8.0% versus 0; *P*<0.001 SD: 31.4% versus 10.9%; *P*<0.001	Any: 78.5% versus 59.1%; *P*<0.001 Fatigue: 33.0% versus 25.9% Dyspnoea: 16.3% versus 12.4% Abdominal pain: 13.2% versus 15.7% Other pain: 14.9% versus 7.3%; *P*=0.005 Non-neutropenic infection: 12.8% versus 5.5%; *P*=0.003 Rash 11.8% versus 0.4%; *P*<0.001 Anorexia: 8.3% versus 5.8% Hypomagnesaemia: 5.8% versus 0%; *P*<0.001
Saltz et al. 2007 [14]	Phase II, R, OL, AC/median 3 prior treatments (range 1–8)	83	CET + BE + IR versus CET + BE	Failed ≥1 IR-containing regimen	Median TTP: 7.3 versus 4.9 mos	ORR: 37% versus 20%	Median OS: 14.5 versus 11.4 months	Any: 23% versus 0 Diarrhoea: 28% versus 0 Fatigue: 9% versus 0 Nausea: 2% versus 0
Van Cutsem et al. 2007 [15]	Phase III, R, OL/third and fourth line	463	PAN + BSC versus BSC	2–3 prior including FP, IR and OX	Median PFS: 8 versus 7.3 wks; HR 0.54; 95% CI 0.44–0.66; *P*<0.0001	OS: HR 1.00; 95% CI 0.82–1.22	ORR (all PR): 10% versus 0%; *P*<0.0001 SD: 27% versus 10% Median (range) DOR: 17.0 (7.9–76.7) wks Median (range) TTR: 7.9 (6.7–15.6) wks	Any: 35% versus 20% Erythema: 5% versus 0 Dermatitis acneiform: 7% versus 0% Abdominal pain: 7% versus 4% General physical health deterioration: 7% versus 2% Fatigue: 4% versus 3% Dyspnoea: 5% versus 3% Anorexia: 3% versus 2% Constipation: 3% versus 1% Asthenia: 3% versus 2% HMG: 3% versus NR

Continued

Table 2. *Continued*

Author	Trial design/setting and line of treatment	*N*	Comparators	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Siu et al. 2013 [18]	Phase III, R, DB/92% of patients receiving fourth line and later	745	CET + BRI versus CET + PBO	Previous FP, IR and OX	Median OS: 8.8 versus 8.1 mos; HR 0.88; 95% CI 0.74–1.03; *P*=0.12	Median PFS: 5.0 versus 3.4 mos; HR 0.72; 95% CI 0.62–0.84; *P*<0.001	ORR: 13.6% versus 7.2%; *P*=0.004 Median DOR: 5.8 versus 5.4 mos; *P*=0.044	Any: AE 78% versus 53%; *P*<0.001 Fatigue: 25% versus 11%; *P*<0.001 Hypertension: 11% versus 1%; *P*<0.001 Rash: 10% versus 5%; *P*=0.01 Abdominal pain: 10% versus 5%; *P*=0.02 Dyspnoea: 8% versus 5% Diarrhoea: 7% versus 3%; *P*=0.008 Dehydration: 7% versus 2%; *P*<0.001 Anorexia: 5% versus 1%; *P*<0.001
Price et al. 2014 [22]	Phase III, R, OL, AC/ third line and later	999	PAN versus CET	Previous IR- and OX-based, and 5-FU, CAP, or RAL	Median OS: 10.4 versus 10.0 mos; HR 0.97; 95% CI 0.84–1.11	Median PFS: 4.4 versus 4.1 mos; HR 1.00; 95% CI 0.88–1.14	ORR: 22.0% versus 19.8% SD: 47% versus 49% Median TTR: 1.5 versus 2.6 wks Median DOR: 3.8 versus 5.4 mos	Skin toxicity: 13% versus 10% Infusion reactions: <0.5% versus 2% HMG: 7% versus 3%
Sclafani et al. 2015 [23]	Phase II/III, R, DB, PC/ second, third and fourth+ line	344	CET + IR + DAL q1w versus CET + IR + DAL q2w versus CET + IR	Previous IR and OX	Median PFS: 3.9 versus 5.4 versus 5.6 mos; HR 1.33; 95% CI 0.98–1.83; *P*=0.07 and HR 1.13; 95% CI 0.83–1.55; *P*=0.44	Median OS: 10.8 versus 11.6 versus 14.0 mos; HR 1.41; 95% CI 0.99–2.00; *P*=0.06 and HR 1.26; 95% CI 0.89–1.79; *P*=0.18	ORR (all PR): 21.6% versus 23.9% versus 26.1% SD: 20.7% versus 28.2% versus 39.6%	Any: 68.1% versus 76.5% versus 67.8% Drug-related SAE: 22.7% versus 19.3% versus 13.0% Diarrhoea: 18.5% versus 18.5% versus 20.0% Hyperglycaemia: 21.0% versus 17.6% versus 5.2% Dermatitis acneiform: 6.7% versus 10.9% versus 8.7% Rash: 6.7% versus 9.2% versus 4.3% Fatigue: 8.4% versus 4.2% versus 5.2% Asthenia: 5.0% versus 9.2% versus 1.5% Neutropaenia: 22.7% versus 34.5% versus 29.6% Leukopaenia: 3.4% versus 6.7% versus 5.2%

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Table 2. *Continued*

Author	Trial design/setting and line of treatment	*N*	Comparators	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Hickish et al. 2016 [19]	Phase III, R, OL, PC	40	XIL + BSC versus PBO + BSC	Previous OX or IR	ORR: 33% versus 19%; *P*=0.0045	NR	NR	SAEs 22% relative risk reduction versus PBO; *P*=0.062
Van Cutsem et al. 2016 [26]	Phase III, R, DB, PC	768	NIN + BSC versus PBO + BSC	Previous OX, IR, FP, (and anti-VEGF anti-EGFR in RAS wt)	Median PFS: 1.5 versus 1.4 mos; HR 0.58; 95% CI 0.49–0.69; *P*<0.0001 Median OS: 6.4 versus 6.1 mos; HR 1.01; 95% CI 0.86–1.19; *P*=0.8659	DCR: 26%; versus 11%; OR 2.96; 95% CI 2.00–4.4; *P*<0.0001	NR	SAEs: 39% versus 35% Fatigue 9% versus 6% Liver-related investigations: 16% versus 8%
Kopetz et al. 2017 [27]	Phase II, R, OL	106	IR + CET + VEM versus IR + CET	1–2 previous regimens	Median PFS: 4.4 versus 2.0 mos; HR 0.42; 95% CI 0.26–0.66; *P*<0.001	ORR: 16% versus 4%; *P*=0.08	DCR: 67% versus 22%	Nausea: 15% versus 0% Neutropaenia: 28% versus 7% Anaemia: 13% versus 0%
Lenz et al. 2017 [36]	Phase III, R, DB, PC/ third line (subanalysis of pts by prior REG treatment)	768	NIN + BSC versus PBO + BSC	Previous OX, IR, FP, (and anti-VEGF or anti-EGFR in RAS wt)	Median PFS in REG-exposed pts: 1.5 versus 1.4 mos; HR 0.61; 95% CI 0.47–0.79 Median PFS in REG-naive pts: 1.5 versus 1.4 mos; HR 0.62; 95% CI 0.51–0.76	Median OS in REG-exposed pts: 6.5 versus 4.6 mos; HR 0.90; 95% CI 0.69–1.17 Median OS in REG-naive pts: 6.3 versus 6.6 mos; HR 1.09; 95% CI 0.89–1.33	NR	NR
Lenz et al. 2017 [37]	Phase III, R, DB, PC/ third line (subanalysis of QoL results)	768	NIN + BSC versus PBO + BSC	Previous OX, IR, FP, BE (and anti-VEGF or anti-EGFR in RAS wt)	Physical functioning treatment difference: 2.66; 95% CI 0.87–4.34; *P*=0.002 QoL treatment difference: 1.61; 95% CI −0.04–3.27; *P*=0.0555	Time to deterioration of physical function: HR 0.84; 95% CI 0.69–1.03; *P*=0.0904 Time to deterioration of QoL: HR 0.90; 95% CI 0.75–1.08; *P*=0.2674	Pts with improved physical functioning: 17.2% versus 11.8%; *P*=0.0462 Pts with improved QoL: 30.3% versus 21.6%; *P*=0.0102	NR
Li et al. 2017 [28]	Phase III, R, DB, PC/ third line	416	FRU versus PBO	≥2 prior lines	Median OS: 9.30 versus 6.57 mos; HR 0.65; 95% CI 0.51–0.83; *P*<0.001	NR	NR	Hypertension: 21.6% versus NR Hand–foot syndrome: 10.8% versus NR Diarrhoea: 3.2% versus NR Proteinuria: 3.2% versus NR

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Table 2. *Continued*

Author	Trial design/setting and line of treatment	*N*	Comparators	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Non-randomised trials								
Chong et al. 2005 [50]	Phase II, SA/all third line	36	CAP + MMC	Previous first line of 5-FU, UFT, OX or IR, and second line of IR or CET	ORR (all PR): 15.2% SD: 48.5%	Median OS: 9.3 mos; 95% CI 6.9–11.7	Median FFS: 5.4 mos; 95% CI 4.6–6.2	Palmar-plantar erythema: 16.7% Nausea/vomiting: 8.3% Lethargy: 5.6% Diarrhoea: 2.8% Peripheral neuropathy: 2.8% Fever: 2.8% Anaemia: 8.3% Neutropaenia: 2.8% Thrombocytopaenia: 2.8%
Scartozzi et al. 2006 [51]	Phase II, SA/all third line	61	CAP + MMC	Previous 5-FU + OX/IR or OX alone	Median TTP: 3 mos (range 2–10)	Median OS: 6 mos (range 1–13)	PR: 8% SD: 40%	Stomatitis: 9.8% Diarrhoea: 8.2% HFSR: 3.3% Liver toxicity: 1.6% Neutropaenia: 3.3% Anaemia: 8.2% Thrombocytopaenia: 8.2%
André et al. 2013 [52]	Phase II, SA/12% of pts second line, rest third line	65	PAN + IR	Previous IR, OX and FP ± BE	ORR: 29.2%; 95% CI 18.2–40.3 CR: 4.6% PR: 24.6% SD: 33.8%	Median PFS: 5.5 mos; 95% CI 3.7–7.6	Median OS: 9.7 mos; 95% CI 6.6–15.8	Any: 55.3% Skin toxicity: 32.3% Diarrhoea: 15.4% Mucositis: 1.5% Neutropaenia: 12.3%
Lee et al. 2014 [53]	Phase II, SA/third line and later	41	GEM + UFT	Previous FP, OX and IR; no prior CET or BE	8-week PFS: 42.3%	Median PFS: 1.7 mos; 95% CI 1.6–1.8	Median OS: 9.2 mos; 95% CI 5.8–12.6 DCR: 36.6% ORR: 2.4% CR: 0 PR: 2.4% SD: 34.1%	Asthenia: 2.4% Dizziness: 2.4% Anorexia: 2.4% Neutropaenia: 19.5% Anaemia: 7.3% Thrombocytopaenia: 4.9%
Pietrantonio et al. 2014 [54]	Phase II, SA/third line and later	32	TEM	Previous treatment with FP, OX, IR, BE, CET or PAN	DCR: 31% ORR: 12% CR: 0% PR: 12% SD: 19%	Median PFS: 1.8 mos; 95% CI 1.7–3.9	Median OS: 8.4 mos; 95% CI 5.0–14.1	Thrombocytopaenia: 3.1% Anaemia: 0% Neutropaenia: 0%
Le et al. 2015 [55]	Phase II, SA/third line and later Cohort 1: pts with mismatch repair-deficient disease Cohort 2: pts with mismatch repair-proficient disease	32	PEMB	≥2 prior regimens	Immune-related ORR: 40%; 95% CI 12–74 and 0%; 95% CI 0–20	Immune-related PFS at 20 weeks: 78%; 95% CI 40–97 and 11%; 95% CI 1–35	ORR (all PR): 40% and 0 SD: 50% and 11% DCR: 90% and 11% Median DOR: not reached and NR Median TTR: 28 wks (range 13–35) and NR	Any: 41% Diarrhoea: 5% Bowel obstruction: 7% Anaemia: 17% Lymphopaenia: 20% Elevated ALT: 5% Hypoalbuminaemia: 10% Hyponatraemia: 7%

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Table 2. *Continued*

Author	Trial design/setting and line of treatment	*N*	Comparators	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Takahashi et al. 2016 [56]	Phase II, SA/second line in 11% of pts, third line or later in rest	37	CET + S-1	Previous IR, OX and FP, with PD on 5-FU	Median PFS: 5.5 mos; 90% CI 4.4–5.7	ORR: 29.7%; 95% CI 15.9–47.0	DCR: 73.0%; CR *n*=1; PR: *n*=10; SD: *n*=16 Median OS: 13.5 mos; 95% CI 8.5–16.5 Median TTF: 4.6 mos; 95% CI 3.2–5.6	Rash: 27.0% Dry skin: 13.5% Anorexia: 10.8% Paronychia: 10.8% Fatigue: 10.8% Diarrhoea: 10.8% Mucositis: 10.8% Neutropaenia: 10.8% Leukopaenia: 2.7% Thrombocytopaenia: 2.7% Anaemia: 5.4% Elevated bilirubin: 8.1%
Yoshida et al. 2016 [57]	Phase II, SA/third line and later	31	BE + S-1	>2 previous regimens, including OX and IR	DCR: 67.9%; 95% CI 47.6–84.1 CR: 0% PR: 0% SD: 67.9%	Median TTF: 3.0 mos; 95% CI 1.8–4.3	Median PFS: 3.7 mos; 95% CI 2.1–5.6 Median OS: 8.6 mos; 95% CI 7.0–11.2	Anorexia: 20% Diarrhoea: 10% Nausea: 7% Fatigue: 7% Mucositis/stomatitis: 3% Rash/desquamation: 3% Decreased Hb: 17% Decreased bilirubin: 7% Neutropaenia: 3% Elevated ALT: 3% Elevated AST: 3%
Calegari et al. 2017 [58]	Phase II, SA/third line and later	41	TEM	2 previous, including FP, IR, OX, BE (and anti-EGFR for wt KRAS)	ORR: 10% CR: 0% PR: 10% SD: 22% DCR: 32%	Median PFS: 1.9 mos (range 1.6–2.35)	Median OS: 5.1 mos (range 3.9–6.2)	Constipation: 9.7% Nausea: 2.4% Vomiting: 2.4% Anaemia: 4.9% Increased bilirubin: 2.4% Increased GGT: 4.8% Neutropaenia: 4.9% Thrombocytopaenia: 12.2%
Hurwitz et al. 2017 [39]	Phase IIa, SA	34	PERT + TRA	NR	ORR (all PR): 37.5%; 95% CI 21.1–56.2	CBR: 46.9%; 95% CI 29.1–65.3	Median DOR: 11.1 mos; 95% CI 2.8–not reached	NR
Real-world studies								
Vrdoljak et al. 2008 [59]	RET, OBS/second line in 58% of pts, third line and later in rest	36	CAP + MMC	Previous 5-FU, IR, OX, high-dose MET, or CAP	ORR: 13.9% CR: 5.6% PR: 8.3% SD: 38.9%	Median OS: 13 mos (range 3–21)	Median TTP: 4.5 mos (range 2–8)	Gastrointestinal toxicity: 1.1% HFSR: 4 cycles

Continued

Table 2. *Continued*

Author	Trial design/setting and line of treatment	*N*	Comparators	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Ferrarotto et al. 2012 [62]	RET, OBS/second line (12 pts), third line or later (97 pts)	109	MIT-C-based regimen	Previous 5-FU, IR and/or OX	Median TTF: 1.7 mos; 95% CI 1.5–2.1	Median OS: 4.5 mos; 95% CI 3.5–5.6	NR	Any: 5%
Larsen et al. 2012 [60]	P, OBS	34	CAP + BE	Previous 5-FU, OX and IR	Median PFS: 5.4 mos	Median OS: 12.2 mos	CR: 0 PR: 9% SD: 62%	Hypertension: 24% Thromboembolism: 3% Bleeding: 3% Palmar-plantar erythrodysesthesia: 3% Fatigue: 3% Neutropaenia: 3%
Jimenez-Fonseca et al. 2015 [61]	RET, OBS/third line and later	119	GEM + CAP	Previous FP, OX, IR, BE, CET, PAN	ORR: 6.72% CR: 0.84% PR: 5.88% SD: 37.81%	Median PFS: 2.87 mos; 95% CI 2.53–3.17	Median OS: 6.53 mos; 95% CI 5.33–8.77	HFSR: 0.87% Nausea/vomiting: 0.87% Diarrhoea: 2.61%

AC, active controlled; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BE, bevacizumab; BRI, brivanib; BSC, best supportive care; CAP, capecitabine; CBR, clinical benefit rate; CET, cetuximab; CI, confidence interval; CIS, cisplatin; CR, complete response; DAL, dalotuzumab; DB, double-blind; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; FFS, failure-free survival; FOLFOX4, OX + 5-FU + LEU; FP, fluoropyrimidine; FRU, fruquintinib; FU, fluorouracil; GEM, gemcitabine; GGT, gammaglutamyltransaminase; Hb, haemoglobin; HFSR, hand–foot skin reaction; HMG, hypomagnesaemia; HR, hazard ratio; IPI, ipilimumab; IR, irinotecan; LAP, lapatinib; LEU, leucovorin; MA, megestrol acetate; MET, methotrexate; MMC, mitomycin C; mos, months; NIN, nintedanib; NIV, nivolumab; NR, not reported; OBS, observational; OL, open-label; OR, odds ratio; ORR, objective response rate; OS, overall survival; OX, oxaliplatin; P, prospective; PAN, panitumumab; PBO, placebo; PD, progressive disease; PEM, pemetrexed; PEMB, pembrolizumab; PERT, pertuzumab; PFS, progression-free survival; PR, partial response; pts, patients; QoL, quality of life; qXw, every X weeks; R, randomised; RAL, raltitrexed; REG, regorafenib; RET, retrospective; SA, single arm; SAE, serious AE; SD, stable disease; TCR, tumour control rate; TEM, temozolomide; TRA, trastuzumab; TTF, time to treatment failure; TTP, time to progression; TTR, time to response; UFT, uracil-tegafur; VEGF, vascular endothelial growth factor; VEM, vemurafenib; wks, weeks; wt, wild-type; XELOX, OX + CAP; XIL, xilonix.

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therapy to which the tumour has already developed resistance [65]. Although mechanisms supporting rechallenge are not completely understood [66], rechallenge may have merits in symptomatic patients where the aim of therapy is short-term induction of an antitumour response. However, evidence for this strategy is limited. Overall, 15 published studies evaluating rechallenge beyond the second line met the inclusion criteria (Table 3), including 1 RCT [25], 2 phase II, single-arm trials [67, 68] and 10 prospective or retrospective observational studies [69–78].

Oxaliplatin rechallenge. A phase II, randomised, open-label study that evaluated capecitabine plus oxaliplatin (XELOX) in 46 patients previously treated with FOLFOX (84%), XELOX (7%) and irinotecan (9%) reported median OS of ≥9.2 months (Table 3) [25]. However, the eligibility criteria allowed for reintroduction of oxaliplatin and thus many patients may not have experienced progression on their earlier oxaliplatin-based regimen. A further phase II, single-arm study evaluating rechallenge with a modified FOLFOX regimen in 33 second- and third-line patients reported a median OS of 300 days [68].

Irinotecan rechallenge. Two real-world studies evaluated rechallenge with irinotecan and cetuximab as third-line or later treatment in patients previously exposed to fluoropyrimidine, oxaliplatin and irinotecan [70, 77]. These studies reported median OS of 6 and 7.3 months. Another real-world study reported a median OS of 18.4 months in 31 patients who had progressed following fluoropyrimidine plus irinotecan and/or oxaliplatin and received third-line or later treatment with bevacizumab plus FOLFIRI or FOLFOX [72]. This survival needs to be interpreted with caution, considering the small sample size and retrospective nature of the study; of note, one patient received treatment as second line.

Cetuximab rechallenge. In a phase II, single-arm trial of 39 patients with irinotecan- and cetuximab-refractory mCRC with a median of four prior treatment lines, cetuximab plus irinotecan yielded an ORR of 54% [67]. Median PFS was 6.6 months.

Bevacizumab rechallenge. A real-world study that evaluated FOLFOXIRI plus bevacizumab in 49 patients who had progressed after fluoropyrimidine, irinotecan, oxaliplatin and bevacizumab reported a median PFS of 5.8 months and a median OS of 11.9 months (Table 3) [76].

Discussion and conclusions

The results of this systematic review show that there is limited high-quality evidence on which to base recommendations for treatment of mCRC beyond the second line. In order to assess the available evidence, we identified three questions that are relevant to clinical practice. Given that novel treatments are continuously being evaluated in clinical trial programmes and existing treatments are obtaining expanded indications, the first question was aimed at future prospects for treatment in mCRC beyond the second line. The second and third questions were intended to establish whether there was sufficient evidence to favour either rechallenge with any approved compound or combination used in an earlier treatment line, or the use of an approved third- or fourth-line treatment approach.

There is currently a lack of high-quality, well-conducted RCTs through which to advance the evidence base. Discounting the use of BSC as a comparator and the reliance on open-label study designs with their inherent potential for bias, our search retrieved robust data to support the use of cetuximab and panitumumab at least in heavily pretreated patients with wild-type *KRAS/NRAS* expression [13]. However, both EGFR monoclonal antibodies are routinely used as first- and second-line treatments [1, 7]. Although one RCT showed favourable survival with the combination of cetuximab, irinotecan and bevacizumab [79], other studies have reported increased toxicity and reduced PFS in patients receiving bevacizumab plus EFGR inhibitors [80–82]. Of five compounds currently being investigated for use beyond the second line in mCRC that we identified based on high-quality phase II and III trials, only fruquintinib has demonstrated an OS benefit compared with placebo, but in a study that only included Chinese patients [28]. There is thus a clear unmet need for effective new therapies beyond the second line in mCRC. Recent results from the nivolumab plus ipilimumab cohort of the CheckMate-142 study have been published and show a high response and encouraging 12-month PFS (71%) and OS (85%) rates [83]. The combination had a manageable safety profile and clinically meaningful improvements in PROs from week 19 onwards [83]. Results of the Reverce study, which investigated the efficacy and safety of treatment sequence when using cetuximab and regorafenib in patients with mCRC naïve for anti-EGFR antibodies, have recently been presented at ASCO-GI [84].

There is little high-quality evidence to support rechallenge in patients who have failed second-line treatment with conventional chemotherapy. Although one randomised phase II trial reported impressive median OS with oxaliplatin rechallenge, the design of this study also permitted oxaliplatin reintroduction in patients who had not progressed on their earlier regimen [25]. Some real-world studies reported similarly impressive survival [72, 76], but these results must be interpreted with caution due to the small sample sizes and absence of control groups. A systematic review of therapy beyond the second line concluded that rechallenge with oxaliplatin might be an option in selected patients while also recognising the possible value of EGFR- and VEGF-directed therapy [6].

With regard to approved third- and fourth-line treatments, both trifluridine/tipiracil and regorafenib were evaluated in large, well-conducted phase II and III trials [16, 17, 20, 21, 24]. On the basis of the efficacy findings, treatment with either trifluridine/tipiracil or regorafenib is an appropriate first choice beyond the second line; thus, performance status and the safety profiles of each are likely to be determinant in the choice of treatment. Trifluridine/tipiracil is predominantly associated with haematological toxicities [16, 21, 24], whereas regorafenib is associated with HFSR, hypertension and liver toxicity [17, 20]. Maintenance of QoL is an important goal beyond the second line, and QoL was found to not deteriorate in patients treated with regorafenib versus placebo. Although QoL was not measured directly for trifluridine/tipiracil, ECOG performance status was maintained compared with placebo [21].

There are limitations to this systematic review, including those inherent in searching publication databases, such as adaptation

Table 3. Efficacy and safety of rechallenge in patients with progression or recurrence beyond the second line

Author	Trial design/setting and line of treatment	*N*	Treatment and comparator	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Explanatory trials								
Matsuda et al. 2016 [25]	Phase II, R, OL, AC/third line or later	46	CAP + OX ± BE in 14-d cycles versus CAP + OX ± BE in 21-d cycles	Previous OX and IR	Median TTF: 3.4 versus 3.4 mos; HR 1.053; 95% CI 0.54–2.05	DCR: 65.2% versus 63.6%; difference 1.6%; 95% CI 0.9–12.7	Median OS: 12.1 versus 9.2 mos; HR 0.672; 95% CI 0.316–1.428 Median PFS: 3.3 versus 4.3 mos; HR 1.15; 95% CI 0.62–2.12	Fatigue: 21.7% versus 27.3% Diarrhoea: 0% versus 9.1% Peripheral neuropathy: 0% versus 9.1% Allergic reaction: 4.4% versus 9.1% Hand–foot syndrome: 4.4% versus 4.6% Nausea: 4.4% versus 4.6% Thrombopaenia: 8.7% versus 0% Anaemia: 4.4% versus 0% Neutropaenia 0% versus 0%
Non-randomised trials								
Santini et al. 2012 [68]	Phase II, SA/Median 4 prior treatments (range 3–7)	39	CET + IR	Previous CET + IR following IR alone or FOLFIRI	ORR: 53.8%; 95% CI 39.1–63.7 CR: 5.1% PR: 48.7% SD: 35.9%; 95% CI 24.7–51.6	Median PFS: 6.6 mos; 95% CI 4.1–9.1	NR	Skin rash: 38.5% Diarrhoea: 7.7% Neutropaenia: 18%
Suenaga et al. 2015 [69]	Phase II, SA, OL/second and third line	33	mFOLFOX6 Q2W	Previous OX and IR	DCR after 12 wks: 39.4%; 95% CI 21.8–57.0 Overall DCR: 66.7%; 95% CI 49.7–83.6 CR: 0% PR: 6.1% SD: 33.3%	Median PFS: 98.0 d; 95% CI 55.7–140.3	Median OS: 300.0 d; 95% CI 229.3–370.7	Diarrhoea: 6.3% Anorexia: 3.1% Nausea: 3.1% Allergic reaction: 3.1% Neutropaenia: 28.1% Leukopaenia: 6.3%
Hartmann et al. 2004 [70]	Phase II, SA, OL/third line or later	50	IR	≥2 previous regimens, including first-line 5-FU + LEU	ORR: 13.3%; 95% CI 6.3–28.9 (all PR) SD: 51.1%; 95% CI 35.8–71.1	Median duration of response/SD: 4.2 mos; 95% CI 3.2–6.0	Median TTP: 3.0 mos; 95% CI 2.0–4.1 Median OS: 7.9 mos; 95% CI 6.1–11.1	Diarrhoea: 24% Pain: 14% Vomiting: 8% Cholinergic syndrome: 8% Infection: 6% Constipation: 4% Nausea: 4% Asthenia: 2% Cardiac dysrhythmia: 2% Cough: 2% Mucositis: 2%

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Table 3. *Continued*

Author	Trial design/setting and line of treatment	*N*	Treatment and comparator	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Real-world studies								
Gebbia et al. 2006 [71]	RET, OBS/second line (39 pts), third line or later (21 pts)	60	CET + IR	≥2 previous regimens, including IR + OX	ORR: 20% (all PR) SD: 30%	Median TTP: 3.1 mos (range 1.2–9.0)	Median OS: 6.0 mos (range 2–13)	Nausea: 33% Stomatitis: 8% Diarrhoea: 27% Fever: 15% Asthenia/malaise: 13% Hypersensitivity reaction: 2% Acne-like reaction: 13% Leukopaenia: 18% Anaemia: 3% Thrombocytopaenia: 3%
Bitossi et al. 2008 [72]	P, OBS/third line or later	37	GEM + 5-FU	≥2 previous regimens, including IR + OX	DCR: 62.2% CR: 0% PR: 10.8% SD: 51.4%	Median OS: 8.9 mos (IQR 6.3–12.1)	Median TTP: 4.2 mos (IQR 2.9–6.3)	Mucositis: 5.4% Neutropaenia: 8.1% Thrombocytopaenia: 8.1% Leukopaenia: 0%
Lievre et al. 2009 [73]	RET, OBS/second line (1 pt), third line or later (30 pts)	31	FOLFOX4 + BE, or FOLFIRI + BE	Previous FP + IR and/or OX	ORR: 32.2% CR: 3.2% PR: 29% SD: 38.8% DCR: 71%	Median PFS: 9.7 mos; 95% CI 6.6–13.6	Median OS: 18.4 mos; 95% CI 13.6–not reached	Diarrhoea: 3.2% Nausea/vomiting: 6.4% Mucositis: 6.4% Neurotoxicity: 12.9% Asthenia: 9.7% Neutropaenia: 3.2% Anaemia: 3.2%
Park et al. 2012 [74]	RET, OBS/second line (17 pts), third line or later (23 pts)	40	BE + FOLFOX, BE + FOLFIRI, BE + 5-FU + FOL or BE alone	Previous OX-, IR-, CAP or 5-FU-based regimens	ORR: 7.5% (all PR)	Median OS: 14.0 mos (range 7.8–20.2)	Median PFS: 6.1 mos (range 3.9–8.3)	NR
Ruzzo et al. 2012 [75]	RET, OBS/third line	59	CET + IR	Previous IR-based regimen	Median OS: 21 wks; 95% CI 17–26 HR (high versus low Let-7a levels): 0.82; 95% CI 0.73–0.91; *P*=0.01	Median PFS: 12 wks; 95% CI 9–14 HR (high versus low Let-7a levels): 0.88; 95% CI 0.79–0.98; *P*=0.03	NR	NR
Yanai et al. 2012 [76]	RET, OBS/second line or later	99	OX	Previous OX with hypersensitivity reaction	Worsening of hypersensitivity reaction: 6 pts	Treatment discontinuation reason: PD: 56% Hypersensitivity reaction: 21% Neurotoxicity: 13% Other: 10%	NR	Hypersensitivity reaction: 6%

Continued

Table 3. *Continued*

Author	Trial design/setting and line of treatment	*N*	Treatment and comparator	Prior treatment	Primary outcome	Main secondary outcome	Other secondary outcomes	Safety (grade ≥3 AEs)
Chaix et al. 2014 [77]	P, OBS/third line or later	49	BE + FOLFIRINOX	≥2 previous regimens, including FP, IR, OX + BE	ORR: 18%; 95% CI 8–35 SD: 45%; 95% CI 28–68 DCR: 73%; 95% CI 43–90	Median PFS: 5.8 mos; 95% CI 3.4–6.8	Median OS: 11.9 mos; 95% CI 8–18	Nausea/vomiting: 2% Diarrhoea: 10% Mucositis: 2% Asthenia: 10% Peripheral neuropathy: 10% Anaemia: 12% Neutropaenia: 18% Thrombocytopaenia: 12% Febrile neutropaenia: 6%
Spindler et al. 2014 [78]	P, OBS/third line	108	CET + IR	Previous FP, OX + IR	ORR: 20%	Median PFS: 3.9 mos; 95% CI 2.6–4.7	Median OS: 7.3 mos; 95% CI 5.8–9.9	NR
Kidd et al. 2015 [79]	RET, OBS	173	REG	Previous treatment with all approved therapies	Response or SD: 61% PD: 33%	After discontinuation of REG: Median OS: 6.5 mos; 95% CI 4.9–9.4	Survival probability: At 6 mos: 52% At 12 mos: 27%	NR

5-FU, 5-fluorouracil; AC, active-controlled; AEs, adverse events; BE, bevacizumab; CAP, capecitabine; CET, cetuximab; CI, confidence interval; CR, complete response; d, day(s); DCR, disease control rate; FOLFIRI, irinotecan, leucovorin and 5-fluorouracil; FOLFIRINOX, oxaliplatin, irinotecan, leucovorin and 5-fluorouracil; FOLFOX, oxaliplatin, leucovorin and 5-fluorouracil; FP, fluoropyrimidine; GEM, gemcitabine; HR, hazard ratio; IQR, interquartile range; IR, irinotecan; LEU, leucovorin; MIT-C, mitomycin-C; mos, months; mFOLFOX, modified FOLFOX; NR, not reported; OBS, observational; OL, open-label; ORR, objective response rate; OS, overall survival; OX, oxaliplatin; P, prospective; PD, progressive disease; PFS, progression-free survival; PR, partial response; pts, patients; Q2W, every 2 weeks; R, randomised; RET, retrospective; SA, single-arm; SD, stable disease; TTF, time to treatment failure; TTP, time to progression; wks, weeks.

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of a single search strategy across different databases, the possibility that the specific keywords chosen and/or adapted may allow some studies to be missed, and the necessity of relying on the authors' self-reported research designs. Other limitations for this analysis were that due to the inclusion of a variety of study designs, populations and outcomes, it was necessary to assess the data using a qualitative synthesis rather than a meta-analysis; and that the complexity and potential disparity in the patients included in the trials may obscure treatment differences and make defining an ideal therapy for later-line treatment extremely difficult. Patients with HER2+ or MSI-H tumours increase the complexity of mCRC, and for these patients pooling results to reach an overall conclusion may not be applicable. To that end, a scale to estimate the magnitude of clinical benefit, such as the ESMO scale [85], may be useful to further delineate treatment effects in patients with mCRC. The US Food and Drug Administration has recently approved pembrolizumab for the treatment of patients with MSI-H tumours, and recommendations for the use of nivolumab or pembrolizumab in these patients have been included in the latest NCCN guidelines [7, 86].

In conclusion, although there are several targeted agents (HER2, PD-1) that show promising results in small populations, our findings support the preferred use of trifluridine/tipiracil or regorafenib as the current approach most likely to yield improvements in OS in most patients receiving treatment of mCRC beyond the second line. There was no evidence to suggest better efficacy for either treatment, but tolerability and QoL of the patient should be considered when selecting a treatment beyond the second line. In contrast, the evidence supporting rechallenge with a previously used chemotherapeutic agent remains limited and should be withheld for later use in patients with good performance status who are willing to receive a further line of treatment. There is an unmet need for novel therapies to complement the use of currently available management strategies.

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