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.

**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]...
| 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 | NR                      |                         | Any AE HR: REG versus PBO: 7.22; 95% CI 5.08–10.26 |
| **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 | ORR: 1% versus 0%; DCR: 43% versus 11%; P < 0.0001 | Median TTF: 1.9 versus 1.0 mos; HR 0.41, 95% CI 0.28–0.59; 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 | 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%; Any: USA: 73.4% versus 45.7%; Europe: 70.7% versus 55.0%; Japan: 66.3% versus 50.0%; |
| 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 | PFS HR by location: USA: 0.43; 95% CI 0.26–0.69; P = 0.0004 | NR                      |                       |
| 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;   | 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; 99% CI 0.50–0.80;   | OS HR by renal function: Normal: 0.64; 95% CI 0.51–0.81                            | 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;   | NR                                                                                   | NR                       |                                                                                       |
| Ohtsu et al. 2016 [34]         | Phase III, R, SB, PC/third line or later (subanalysis of neutropenia 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 neutropenia onset Cycle 1: 9.7 versus 5.3 mos; HR 0.45; 95% CI 0.32–0.64 | NR                                                                                   | NR                       |                                                                                       |

*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: 21.1% 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: 20.0 mos (range 1.7–23) | 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 |                                          |     | FTD/TPI                   | Prior therapy included 58.2% REG | Median PFS: 2.0 mos (range 1.7–23) | 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% |
| Kotani et al. [43]        | RET, OBS                                   | 55  | FTD/TPI                   | Prior therapy included 58.2% REG | Median PFS: 2.0 mos (range 1.7–23) | 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 |                                          |     | 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: 19 versus 17 mos; HR 0.49; 95% CI 0.42–0.58; P<0.0001 | ORR (all PR): 1.0% versus 0.4% DCR: 41.4% 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
| 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 = 0.0045 | 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 | |
| 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% |
| 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) |
|--------|------------------------------------------|---|--------------------------|----------------|----------------|-----------------------|-------------------------|---------------------|
| 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 | Median OS (pts with high treatment benefit): 9.2 mos | Median PFS: 2.7 mos; IQR 1.6–4.6 | Any: 43.7% | Fatigue: 14.5% |
| | | | | | 12-mo OS: 22% | 12-mo PFS: 7% | 12-mo PFS: 7% | Fatigue: 14.5% | |
| | | | | | | | | | |
| Kotaka et al. WCGI 2016 [47] | RET, OBS | 74 | REG versus FTD/TPI | Previous FP, OX, IR, BE, and CET or PAN | Median PFS: 20 versus 21 mos; P=0.145 | ORR: 3% versus 0%; P=0.330 | DCR: 95% versus 94%; P=0.956 | Any: 43.5% | HFSR: 13.0% |
| | | | | | | | | | |
| Sueda et al. 2016 [48] | RET, OBS/third line or later | 37 | REG versus FTD/TPI | ≥2 previous standard regimens | CR: 0% versus 0% | Median PFS: 3.0 versus 2.1 mos | Median OS: 5.8 versus 6.3 mos | Any: 14.3% | HFSR: 13.0% |
| | | | | | PR: 0% versus 0% | | | | |
| | | | | | SD: 30.4% versus 28.6% | | | | |
| | | | | | | | | | |
| 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 | Any: 14.3% | HFSR: 13.0% |
| | | | | | | | | | |

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; TIF, 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 cetuximab 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 BRAFV600E-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, neutropenia 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) |
|-------------------|--------------------------------------------|----|-------------|------------------------------------------------------|----------------|------------------------|--------------------------|------------------------|
| 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 |  | Any: 65.1% versus 43.5%; P<0.001 Diarrhoea: 21.2% versus 1.7%; P<0.001 Anemia: 13.7% versus 10.4% Acne-like rash: 9.4% versus 5.2% Nausea and vomiting: 7.1% versus 4.3% |
| 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; 99% 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: 78.9% 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 Any: 35% versus 20% Erythema: 5% versus 0 Dermatitis aciform: 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 |
| 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, 99% 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 |  |  |  |  |
| 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; 99% 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 |
| 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, CA, P, 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; 99% CI 0.88–1.14 | ORR: 22.0% versus 19.8% | SD: 47% versus 49% | Median TTR: 1.5 versus 26 wks |
| Sclafani et al. 2015 [23] | Phase II/III, R, DB, PC/second, third and fourth+ line | 344 | CET + 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=0.007 and HR 1.13; 95% CI 0.83–1.55; P=0.044 | Median OS: 10.8 versus 11.6 versus 14.0 mos; HR 1.41; 99% CI 0.99–2.00; P=0.06 and HR 1.26; 95% CI 0.89–1.79; P=0.18 | Any: AE 68.1% versus 76.5% versus 67.8% | Drug-related SAE 22.7% versus 19.3% versus 13.0% | 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% | Neutropenia: 22.7% versus 34.5% versus 29.6% | Leukopenia: 3.4% versus 6.7% versus 5.2% |
| 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.  | 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=0.002 |
| 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 | DCR: 26%; versus 11%; OR 2.96; 95% CI 2.00–4.44; P<0.0001 | NR                        | SAEs: 39%; relative risk reduction versus PBO, P=0.002 |
| 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% |
| Lenz et al. 2017 [36] | Phase III, R, DB, PC/third line            | 768 | NIN + BSC versus PBO + BSC                                                      | Previous OX, IR, FP, (and anti-VEGF 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 OS in REG-naive pts: 1.5 versus 1.4 mos; HR 0.62; 95% CI 0.51–0.76 | NR                        | Nausea: 28% versus 7% |
| Lenz et al. 2017 [37] | Phase III, R, DB, PC/third line            | 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 | Time to deterioration of physical functioning: HR 0.84; 95% CI 0.69–1.03; P=0.00904 | NR                        | Hypertension: 21.6% versus 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<0.0001 | NR                     | NR                        | Diarrhoea: 3.2% versus NR |
| 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%             | 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% |
|                        |                                            |    |             |                                                                                 | SD: 48.5%                       |                               |                          | Nausea/vomiting: 8.3%   |
|                        |                                            |    |             |                                                                                 | Median TTP: 3 mos (range 2–10)   | Median OS: 6 mos (range 1–13)  |                          | Lethargy: 5.6%          |
|                        |                                            |    |             |                                                                                 | PR: 8%                          | SD: 40%                        |                          | Diarrhoea: 2.8%         |
|                        |                                            |    |             |                                                                                 | Stomatitis: 9.8%                 |                                |                          | Peripheral neuropathy: 2.8% |
|                        |                                            |    |             |                                                                                 | Diarrhoea: 8.2%                  |                                |                          | Fever: 2.8%              |
|                        |                                            |    |             |                                                                                 | HFSR: 3.3%                      |                                |                          | Anaemia: 8.3%            |
|                        |                                            |    |             |                                                                                 | Liver toxicity: 1.6%             |                                |                          | Neutropaenia: 2.8%       |
|                        |                                            |    |             |                                                                                 | Anaemia: 8.2%                    |                                |                          | Thrombocytopaenia: 2.8%  |
|                        |                                            |    |             |                                                                                 | Thrombocytopaenia: 8.2%          |                                |                          | Any: 55.3%               |
|                        |                                            |    |             |                                                                                 | Skin toxicity: 32.3%             |                                |                          | Diarrhoea: 15.4%         |
|                        |                                            |    |             |                                                                                 | Mucositis: 1.5%                  |                                |                          | Neutropaenia: 12.3%      |
|                        |                                            |    |             |                                                                                 | Asthenia: 2.4%                   |                                |                          | Aneurysma: 2.9%          |
|                        |                                            |    |             |                                                                                 | Dizziness: 2.4%                  |                                |                          | Thrombocytopaenia: 4.9%  |
| 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                | Median OS: 6 mos (range 1–13) |                          | Any: 41%                |
|                        |                                            |    |             |                                                                                 | PR: 8%                          | SD: 40%                        |                          | Diarrhoea: 5%            |
|                        |                                            |    |             |                                                                                 | Stomatitis: 9.8%                 |                                |                          | Bowel obstruction: 7%    |
|                        |                                            |    |             |                                                                                 | Diarrhoea: 8.2%                  |                                |                          | Anaemia: 17%             |
|                        |                                            |    |             |                                                                                 | HFSR: 3.3%                      |                                |                          | Lymphopenia: 20%         |
|                        |                                            |    |             |                                                                                 | Liver toxicity: 1.6%             |                                |                          | Elevated ALT: 3%         |
|                        |                                            |    |             |                                                                                 | Anaemia: 10%                     |                                |                          | Hyponatraemia: 7%        |
| Author | Trial design/setting and line of treatment | \(N\) | Comparators | Prior treatment | Primary outcome | Main secondary outcome | Other secondary outcomes | Safety (grade \(\geq 3\) 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 | Rash: 27.0% Dry skin: 13.5% Anorexia: 10.8% Paronychia: 10.8% Fatigue: 10.8% Diarrhoea: 10.8% Mucositis: 10.8% Neutropenia: 10.8% Leukopenia: 2.7% Thrombocytopenia: 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 OR: 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 |
| 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) |
| Hurwitz et al. 2017 [39] | Phase IIa, SA | 34 | PERT + TRA | NR | ORR (all PR): 37.9%; 95% CI 21.1–56.2 | CBR: 46.9%; 95% CI 29.1–65.3 | Median DOR: 11.1 mos; 95% CI 28–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 |
| 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  | 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, metotrexate; MMC, mitomycin C; mos, months; NIN, nintedanib; NV, 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.
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 EGFR 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
| 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 | Fatigue: 21.7% versus 27.3% Diabetes: 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: 44% versus 4.6% Thrombopaenia: 8.7% versus 0% Anaemia: 4.4% versus 0% Neutropaenia 0% versus 0% |
| 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 FOLFI R       | 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 4.1–91 | NR                                                                                       | Skin rash: 38.5% Diabetes: 7.7% Neutropaenia: 18%                                      |
| Suenaga et al. 2015 [69]    | Phase II, SA/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: 36.4%; 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: 31.1%; 95% CI 35.8–71.1 | Median duration of response/SD: 4.2 mos; 95% CI 3.2–60 | 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% |

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% Thrombocytopenia: 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% ORR: 32.2% CR: 32% PR: 29% SD: 38.8% DCR: 71% | Median OS: 8.9 mos (IQR 6.3–12.1) | Median TTP: 4.2 mos (IQR 2.9–6.3) | Mucositis: 5.4% Neutropenia: 81% Thrombocytopenia: 8.1% Leukopenia: 0% Diarrhoea: 3.2% Nausea/vomiting: 6.4% Mucositis: 6.4% Neurotoxicity: 12.9% Asthenia: 9.7% Neutropenia: 3.2% Anaemia: 3.2% |
| 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 | | | | |
| Park et al. 2012 [74] | RET, OBS/second line (17 pts), third line or later (23 pts) | 40 | BE + FOLFOX, BE + FOLFI, 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 | | | |
| Yanai et al. 2012 [76] | RET, OBS/second line or later | 99 | OX | Previous OX with hypersensitivity reaction | Worsening of hypersensitivity reaction: 6 pts | | | |

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   | 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 3.4–68 | Median OS: 11.9 mos; 95% CI 8–18 | Nausea/vomiting: 2% Diarrhoea: 10% Mucositis: 2% Asthenia: 10% Peripheral neuropathy: 10% Anemia: 12% Neutropaenia: 18% Thrombocytopenia: 12% Febrile neutropaenia: 6% |
| Spindler et al. 2014| 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 | Survival probability: At 6 mos: 52% At 12 mos: 27% |
| Kidd et al. 2015    | RET, OBS                                  | 173| REG                      | Previous treatment with all approved therapies | Response or SD: 61% PD: 33% | Median OS: 6.5 mos; 95% CI 4.9–9.4 | NR | 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; FOLFIRINOX, irinotecan, oxaliplatin, leucovorin and 5-fluorouracil; FOLFIRI, irinotecan, leucovorin, 5-fluorouracil 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.
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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