CO110

Systematic literature review (SLR) and meta-analysis of clinical outcomes for second-line and higher (≥2L) targeted therapies for advanced colorectal cancer (aCRC)

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Background

- Colorectal cancer (CRC) is the third most common type of cancer and the second leading cause of mortality worldwide[1]
- Outcomes in advanced CRC (aCRC) patients remain poor, with an estimated 5-year survival of 15% in the US[2]
- However, an unmet need remains to identify novel treatment options still in these subpopulations but even more in the broader pretreated aCRC patient population with unknown biomarkers[3-7]
- Conventional first-line treatment of aCRC includes fluorouracil plus leucovorin and irinotecan (FOLFIRI), fluorouracil plus leucovorin and oxaliplatin (FOLFOX), and capecitabine plus oxaliplatin (XELOX), while newer treatment strategies incorporate targeted therapies (VEGF or EGFR inhibitors) in combination with chemotherapy
- However, continuation of care with treatment options following disease progression or failure of response to initial therapies remain limited. Currently, regorafenib and trifluridine plus tipiracil (TAS-102) are recommended for use beyond the second line and may help to prolong survival by a few months
- Study objective was to conduct a systematic literature review (SLR) and perform a meta-analysis of clinical studies to quantify clinical response and survival outcome benchmarks of clinically relevant treatment options in a previously treated aCRC population

Methods

Systematic literature review

- The SLR was conducted from January 2000 through July 2021 in accordance with PRISMA guidelines (PICOTS criteria in **Table 1**)
- Embase, MEDLINE, and the CENTRAL electronic databases were searched via Ovid, with further manual screenings of ASCO 2019-2021 and ESMO 2019-2020 oncology congress proceedings, as well as the US Clinical Trial Registry
- To evaluate a benchmark of clinical outcomes from standard-of-care treatments for the population of interest, eligible studies for meta-analysis were further restricted to interventions (**Table 1**) relevant for HTAs and clinical guideline recommendations of continuum of care systemic therapy for aCRC

Table 1. PICOTS criteria to identify trials for the systematic literature review

Category	Inclusion criteria	Exclusion criteria
Population	**Adult patients with:** • Histologically proven locally advanced, unresectable, or metastatic (unresectable stage III or stage IV) colorectal cancer • Previously treated for advanced disease with standard therapies • Recurrent disease when disease stage not specified • ECOG 0 or 1	**Studies exclusively in patients with:** • ECOG 2 or higher • Stage I or II disease • CNS metastasis • Prior treatment with anti-PD-1 or anti-PD-L1
Interventions	**Relevant for inclusion in study selection:** • Any pharmacologic treatment licensed by the FDA or EMA for any indication (including off-label treatments) **Relevant for meta-analysis:** ***Population 1: patients with at least 1 prior line of treatment***: • FOLFOX + (bevacizumab or aflibercept or ramucirumab or cetuximab or panitumumab) • FOLFIRI + (bevacizumab or aflibercept or ramucirumab or cetuximab or panitumumab) • CAPEOX + bevacizumab ***Population 2: Patients with at least 2 prior lines of treatment:*** • Regorafenib or TAS-102 (trifluridine/tipiracil)	• Radiation without chemotherapy • Surgical intervention without systemic treatment • Other nonpharmacologic treatments (eg, hyperthermia) • Treatments targeting liver metastases
Comparators	• Unrestricted	—
Outcomes	**At least 1 of the following outcomes:** • Overall survival; Progression-free survival; Time to progression; Duration of response; Objective response rate (including CR, PR, SD, PD); Drug-related adverse events; Grades 3-5 adverse events (all, drug-related); Discontinuation due to adverse events; Serious events; Patient-reported outcomes (eg, EQ-5D, EORTC QLQ-C30)	—
Study design	• Randomized controlled trial • Nonrandomized clinical trials, including single-arm interventional studies	• Observational studies, noninterventional studies, case reports/series
Time	• Published year 2000 or later	• Published year 1999 or earlier
Language	• English	• Non-English

CNS, central nervous system; CR, complete response; ECOG, eastern cooperative oncology group; PD, progressive disease; PD-1: programmed cell death protein 1; PD-L1: programmed death ligand 1; PR, partial response; SD, stable disease.

Meta-analyses

Objective response rate (ORR)

- Reported number of responders (partial or complete), number of evaluable participants, and/or ORR was preferred; however, when not reported in articles, ORR was derived by adding complete and partial response events and dividing by the total number of participants
- Clopper-Pearson 95% confidence interval (CI) was computed for each treatment group of a study, and the Freeman-Tukey double arcsine transformation was used to normalize and stabilize proportion estimates
- Results presented as forest plot of treatment effects, fixed and random effects pooled estimate of ORR with 95% CI, I^2 and τ^2 statistics, and *P* value for the Cochran's Q test for heterogeneity

Progression-free survival (PFS) and overall survival (OS)

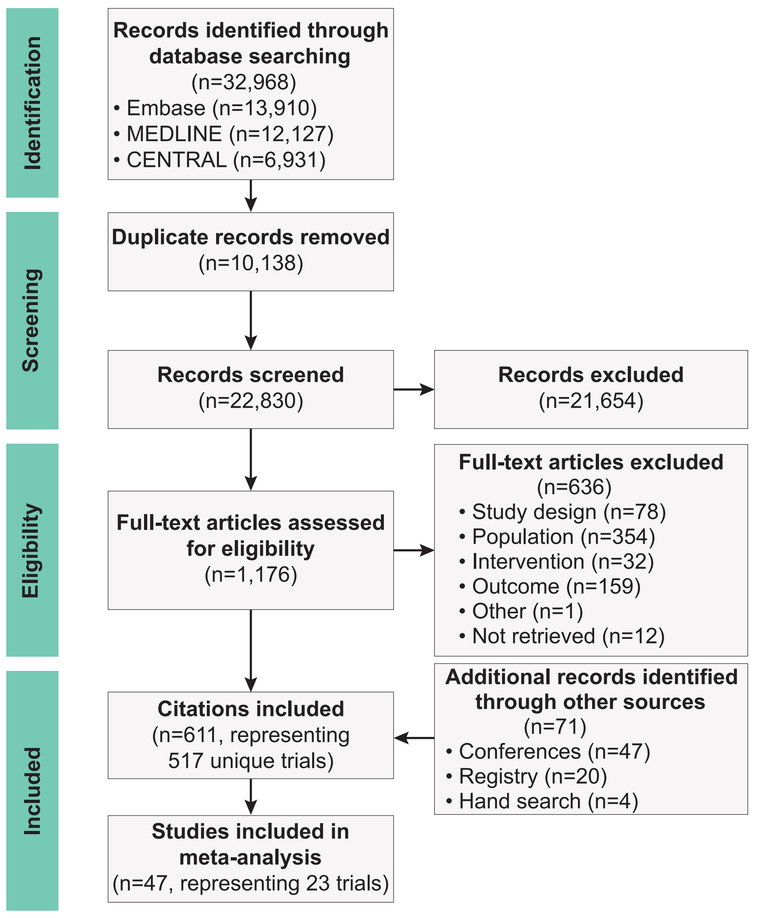
- Analyses were conducted by pooling survival Kaplan-Meier (KM) curves via methods described by Combescure et al[8]
- Summary survival probabilities were obtained from the product of the pooled conditional survival probabilities
- Survival curves were manually digitized, and pseudo individual patient data of trial sources were estimated by applying Guyot's algorithm[9]
- Meta-analyses were performed to combine results from multiple studies to obtain a precise estimate of overall treatment effect or resolve uncertainty around the efficacy of therapies[10]
- Pooling of survival curves was estimated using the MetaSurv package with R version 4.0.1

Results

Systematic literature review

- The database search identified 32,968 relevant records for screening, and a total of 611 citations met the screening inclusion criteria (**Figure 1**)
- The final screening stage resulted in the inclusion of 23 randomized controlled trials (RCTs) into the evidence base that were eligible for meta-analysis (**Table 1**). Of these, 18 studies investigated relevant chemotherapy plus targeted therapy regimens in the second-line setting, and 5 studies investigated regorafenib or TAS-102 in the third-line or later setting
- Among included studies in this review, reported ORR ranged from 0.9% to 47.7%, median OS ranged from 7.1 to 53.6 months, and median PFS ranged from 2.0 to 21.4 months

Figure 1. PRISMA flow diagram

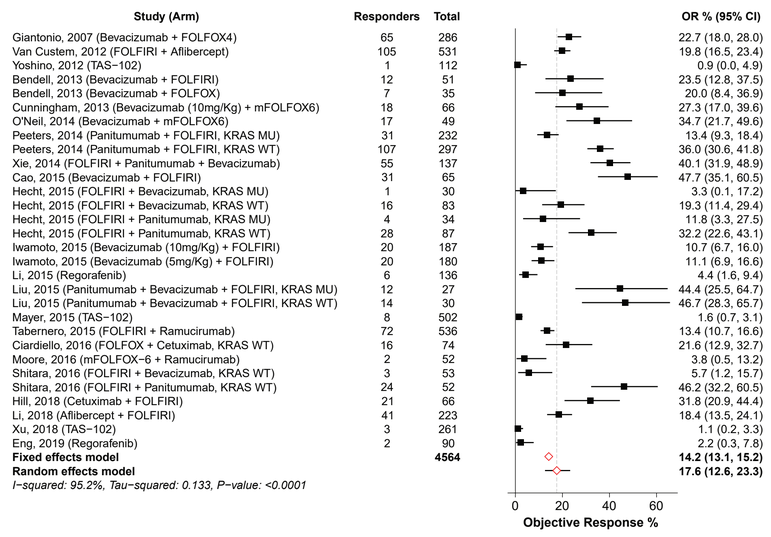


Note: n refers to number of unique records or citations.

Meta-analyses

- ORR
  - There were 30 treatment arms (22 studies) included in the meta-analysis of ≥2L chemotherapy and targeted therapies among RCTs. The random effect ORR pooled estimate was 17.6% (95% CI 12.6-23.3). The corresponding statistics for heterogeneity were I^2=95.2%, τ^2=0.133, and P<0.0001 (**Figure 2**)
  - 2L-only treatments – Based on 25 treatment groups (17 studies), the random effects ORR pooled estimate was 22.5% (95% CI: 18.1, 27.2; I^2: 89.2%) among 3463 participants (figure not shown)
  - 3L and higher treatments – Based on 5 treatment groups (5 studies), the random effects ORR pooled estimate was 1.7% (95% CI: 0.8, 2.7) among 1101 participants (figure not shown)

Figure 2. Forest plot and pooled results for objective response rates in treatments from clinical trials in advanced CRC patients



Total participants refer to number of evaluable patients.
Responders denotes the number of participants who observed an objective response (complete response + partial response).
CI, confidence interval; OR, objective response.

PFS and OS

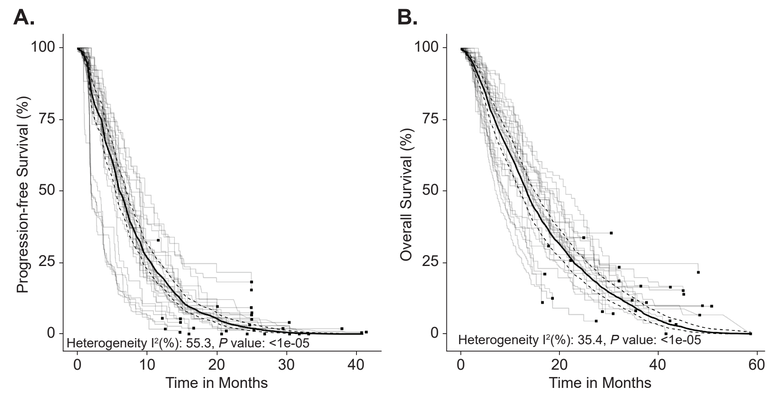
- There were 29 KM PFS survival curves (22 studies) included in the meta-analysis of ≥2L chemotherapy and targeted therapies among RCTs. The median PFS was 6.1 months (95% CI 5.5-7.0). The PFS rates at 6, 12, and 24 months were 50.4%, 20.3%, and 2.4%, respectively (**Table 2** and **Figure 3A**)
- There were 27 KM OS survival curves (21 studies) included in the meta-analysis of ≥2L chemotherapy and targeted therapies among RCTs. The median OS was 13.3 months (95% CI 11.8-14.7). The OS rates at 6, 12, and 24 months were 78.4%, 55.3%, and 23.3%, respectively (**Table 3** and **Figure 3B**)
- PFS and OS outcomes were worse in patients who received third or later lines of treatment (**Table 2, Table 3**)

Table 2. Pooled results of progression-free survival in ≥2L, 2L-only, and 3L and higher treatment of advanced CRC

	2L or higher setting (N = 4725)	2L setting (N = 3582)	3L and higher setting (N = 1143)
Number of studies	22	17	5
Number of arms	29	24	5
Number (%) of events	3913 (82.8)	2932 (81.9)	981 (85.8)
Person-months[a]	29,180.7	25,390.0	3790.7
Event rate per 100 person-months	13.4	11.5	25.9
Median PFS, months (95% CI)[b]	6.1 (5.5, 7.0)	7.0 (6.4, 7.4)	2.3 (2.0, 2.8)
Rate at 6 months in %[b] (95% CI)	50.4 (44.3, 57.4)	56.7 (52.5, 61.3)	21.7 (14.7, 32.0)
Rate at 12 months in %[b] (95% CI)	20.3 (16.8, 24.6)	23.8 (20.4, 27.8)	6.1 (3.4, 10.9)
Rate at 18 months in %[b] (95% CI)	7.2 (5.4, 9.6)	8.9 (6.9, 11.5)	--
Rate at 24 months in %[b] (95% CI)	2.4 (1.5, 4.1)	3.2 (1.9, 5.3)	--

Progression-free survival is defined as time from date of first dose to disease progression or death by any cause, whichever occurs first.
[a]Calculated as the total time-at-risk (in months) for all individuals across all studies.
[b]Estimates derived from the random effects pooled survival curve using the methodology from Combescure et al (2014).

Figure 3. Kaplan-Meier plots and pooled survival curve of (A) progression-free survival and (B) overall survival in ≥2L treatment of advanced CRC



KM estimates of PFS among 29 study arms and for OS among 27 study arms.The grey lines represent the KM estimates for survival events in each study. The black square represents the end of follow-up for each corresponding study.
The thick black line represents the random effects pooled survival curve estimate for PFS or OS outcomes with 95% confidence bands (dashed lines).
P value refers to Cochran's Q test for heterogeneity.

Table 3. Pooled results of overall survival in ≥2L, 2L-only, and 3L and higher treatment of advanced CRC

	2L or higher setting (N = 4357)	2L setting (N = 3214)	3L and higher setting (N = 1143)
Number of studies	21	16	5
Number of arms	27	22	5
Number (%) of events	3241 (74.4)	2448 (76.2)	793 (69.4)
Person-months[a]	57,018.0	48,129.5	8888.5
Event rate per 100 person-months	5.7	5.1	8.9
Median OS, months (95% CI)[b]	13.3 (11.7, 14.6)	14.9 (13.6, 16.1)	8.2 (7.1, 9.1)
Rate at 6 months in %[b] (95% CI)	78.4 (74.2, 82.8)	81.5 (78.5, 84.7)	64.4 (58.7, 70.6)
Rate at 12 months in %[b] (95% CI)	55.3 (49.7, 61.4)	61.1 (57.2, 65.3)	33.3 (27.8, 39.8)
Rate at 18 months in %[b] (95% CI)	35.4 (30.4, 41.3)	40.9 (36.6, 45.8)	15.4 (11.0, 21.7)
Rate at 24 months in %[b] (95% CI)	23.3 (19.5, 27.8)	27.4 (24.0, 31.3)	3.7 (1.1, 13.0)

Overall survival is defined as time from date of first dose to death by any cause.
[a]Calculated as the total time-at-risk (in months) for all individuals across all studies.
[b]Estimates derived from the random effects pooled survival curve using the methodology from Combescure et al (2014).

Conclusions

- This study has provided clinical outcome benchmarks for standard treatments used in the advanced CRC patient population
- Results indicate limited efficacy with these treatments in the second-line or later setting with worsening outcomes in later lines
- Given the burden of CRC in terms of its incidence and mortality, further research into novel and emerging therapeutic options following treatment failure is warranted

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