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Research Article

Adverse Events in Patients Treated for Colorectal Cancer in Published Phase III Clinical Trials: A Systematic Review and Meta-Analysis

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Abstract

Background: Colorectal cancer (CRC) is one of the most common cancers diagnosed in the United States. The primary objectives of this systematic literature review and meta-analysis were to evaluate the frequency of the five most frequently reported adverse events (AEs) of any grade and five most frequently reported severe (grade ≥ 3) AEs in phase III clinical trials of patients with colorectal cancer overall and by drug class. **Methods:** Literature searches were performed to review articles published between January 1, 2012, and February 1, 2022 using ClinicalTrials.gov, PubMed, Citeline's TrialTrove, EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Clinical Answers, BIOSIS Previews, Northern Light Life Sciences Conference Abstracts, Embase, and Ovid MEDLINE. The study evaluated literature that reported on adult patients in Phase III clinical trials who were diagnosed with colon cancer, rectal cancer, or CRC. The risk of bias of all included trials was evaluated using the Cochrane risk-of-bias tool. All methodology was documented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. **Results:** Twenty-two articles were included in the review. The most frequent grade AEs overall were neuropathy peripheral (55.8%), hemoglobin abnormal (51.4%), neutrophil count abnormal (43.5%), rash (35.8%), and neutropenia (35.0%). The most frequent grade ≥3 AEs overall were neutropenia (27.3%), neutrophil count abnormal (21.1%), hyperbilirubinemia (16.5%), neurotoxicity (11.0%), and hypertension (9.9%). **Discussion:** The common adverse events reported in this review are in line with known side effects of treatments used for CRC, such as nausea, vomiting, diarrhea, and effects on blood-forming cells of the bone marrow. **Conclusion:** The most reported AEs in phase III clinical trials of patients with CRC varied based on treatment regimen and drug classes. This review provides a general interpretation of the most common AEs in treatments for patients with CRC, which may help tailor AE prevention and management.

Keywords: *colorectal, cancer, oncology, adverse events, systematic review*

Introduction

There are 106,180 new cases of colon cancer and 44,850 new cases of rectal cancer expected in the United States in the year 2022 [1]. The lifetime risk of developing colorectal cancer (CRC) is approximately 4.3% for men and 4.0% for women [1]. Excluding skin cancers, colorectal cancer (which includes colon and rectal cancer) is the third most common cancer diagnosed in the United States [1].

CRC occurs when tumors form in the large intestine, specifically in the colon or rectum. It can be referred to as colon cancer or rectal cancer, depending on its origin [2]. Colon and rectal cancers are frequently grouped together because the organs are made of the same tissues and are often referred to simply as colorectal cancer. Treatment may include surgery, chemotherapy, radiation, and/or drug therapy. The choice of treatment depends upon the location and

stage of CRC. Treatment options may include single drug chemotherapy regimens (e.g., fluorouracil), combination regimens (e.g., fluorouracil with leucovorin and irinotecan also known as FOLFIRI), targeted therapies (e.g., FOLFIRI + ziv-aflibercept), and immunotherapy (pembrolizumab). In patients with CRC, drug-related adverse events such as hand-foot syndrome (also referred to as palmar-plantar erythrodysesthesia) and diarrhea can be severe and significantly impact a patient's quality of life and adherence to treatment [3]. The severity of the AE and impact on quality of life can cause some patients to discontinue therapy, which could lead to a return or progression of the CRC [4]. Adverse events can guide clinicians in modifying dosages to maximize treatment efficacy and minimize toxicity [5].

It is important to continuously evaluate the AEs associated with medications to ensure that the benefits associated with a particular medication outweigh the potential risks. For a drug to be approved in the United States, there must be an acceptable benefit-risk ratio which considers the AEs being experienced by patients. As stated by the United States Food and Drug Administration (FDA), the benefit-risk assessment of a drug is used as a tool to support the FDA's internal decision making and improve transparency in the regulatory decision-making process [6]. AEs help identify a medication's risks and the assessment of the potential for harm is essential both before and after marketing [7]. By combining the data from multiple clinical trials with similar interventions, we can contextualize the frequency of AEs in patients with a particular disease.

The primary objectives of this systematic literature review and meta-analysis were to evaluate the frequency of the five most frequently reported AEs of any grade in phase III clinical trials of patients with CRC overall and by drug class and the five most frequently reported severe AEs (defined as Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) from phase III clinical trials of patients with CRC overall and by drug class. Secondary objectives included estimating the frequency of the most frequently reported AEs in the same population by stage of disease and by specific drugs of interest.

Methods

This analysis focused on the systematic identification of published phase III clinical trials that report the frequencies of AEs experienced by patients with CRC who are enrolled in clinical trials. We aggregated the AE data from available clinical trials and performed a meta-analysis to estimate frequencies of AEs across clinical trials. All methodology was documented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8].

The study population included adult patients who were at least 18 years old and were diagnosed with colon cancer, rectal cancer, or CRC. The interventions, comparators, and outcomes are listed in Table 1.

Literature searches were performed to review articles published between January 1, 2012, and February 1, 2022 to allow for the analysis of recent data. The following databases were used to identify relevant clinical trials: ClinicalTrials.gov, PubMed, Citeline's TrialTrove, EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Clinical Answers, BIOSIS Previews, Northern Light Life Sciences Conference Abstracts, Embase, and Ovid MEDLINE. The detailed search strategies and Medical Subject Headings (MeSH) terms included can be found in the Supplemental Information.

Article Selection

Articles found in any literature search previously described or manually found through ClinicalTrials.gov were evaluated for inclusion. Article selection was performed in two levels including review of the title and abstract followed by review of the full text. Two researchers performed each level of article selection independently and any discrepancies were resolved by discussion and consensus. If an article met all inclusion and exclusion criteria, it was included in the literature review for evaluation, data extraction, and meta-analysis. The article selection and data management were

performed using Rayyan, which is a web-based tool designed to help researchers track article selection when working on systematic reviews [9]. Articles that met the inclusion and exclusion criteria shown in Table 1 and Table 2 were used in the review.

Table 1. Inclusion Criteria

Patients	• Adult patients ≥ 18 years old • Patients diagnosed with colon cancer, rectal cancer, or CRC

Interventions	• Treatment with placebo OR no treatment OR treatment with supportive care OR treatment following surgery OR any drug regimen that includes:
	  • Currently marketed drugs that are included in the NCCN guidelines for colon cancer or rectal cancer
	  • Currently marketed drugs that are indicated for the treatment of CRC
	• These include, but are not limited to, any of the following:
	  • Single drug chemotherapy regimens
	  ○ Capecitabine (Xeloda)
	  ○ Fluorouracil (5-FU)
	  ○ Irinotecan (Camptosar)
	  ○ Oxaliplatin (Eloxatin)
	  ○ Trifluridine/tipiracil (Lonsurf)
	  • Chemotherapy combination regimens
	  ○ 5-FU with leucovorin (folinic acid)
	  ○ FOLFOX (5-FU with leucovorin and oxaliplatin)
	  ○ FOLFIRI (5-FU with leucovorin and irinotecan)
	  ○ XELIRI/CAPIRI (capecitabine with irinotecan)
	  ○ XELOX/CAPEOX (capecitabine with oxaliplatin)
	  • Targeted therapies
	  ○ Any combination regimen + cetuximab (Erbitux), bevacizumab (Avastin), or panitumumab (Vectibix)
	  ○ FOLFIRI + ziv-aflibercept (Zaltrap) or ramucirumab (Cyramza)
	  • Immunotherapy
	  ○ Pembrolizumab (Keytruda)
	  ○ Nivolumab (Opdivo)
	  ○ Nivolumab and ipililmumab (Yervoy) combination
	• Interventions will be required to be currently (as of date of review) commercially available

Comparators	• Any of the interventions listed above
Outcomes	• AE and Serious Adverse Event (SAE) numbers (n) or percentage (%) must be numerically reported in the results of the trial
Timeframe	• Trial results published between January 1, 2012, and February 1, 2022
Setting	• Clinical trial (phase III) • Geographic location is not restricted • Articles published in English language

Table 2. Exclusion Criteria

Patients	• Pediatric patients < 18 years old • Patients with no diagnosis of CRC
Interventions	• Treatment of CRC with only surgery (laparoscopy, colostomy, radiofrequency ablation, cryoablation) or radiation therapy (no drug therapy)
Comparators	• Treatment with only surgery (laparoscopy, colostomy, radiofrequency ablation, cryoablation) or radiation therapy (no drug therapy)
Outcomes	• No AE data reported as numbers (n) or percentages (%) • AE type/name reported too generally to map to a specific AE using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) • Safety data are not reported for CRC alone
Timeframe	• Articles published outside the pre-specified timeframe (i.e., before 2012)
Setting	• Pre-clinical, phase I-II studies • Non-interventional studies • Grey literature • Articles published in languages other than English
CRC: colorectal cancer	

Data Extraction

Data extraction from included clinical trials was performed in Microsoft Office Excel using a predefined list of variables for extraction. These variables are shown in Table 3. Data extraction was performed by one researcher and quality control of the extracted data was carried out by a second researcher. A pivotal trial was defined as a phase III clinical trial that was performed and completed by the manufacturer to support the initial drug approval application in the United States [10]. To identify pivotal trials for drugs approved for CRC in the past 10 years, we examined two locations: the FDA's Drug Trials Snapshots and the FDA approved prescribing information.

Table 3. Data Extraction Fields

Clinical Trial Information	Study identifier
	Title
	Authors
	Trial name/number
	Year of publication
	Geographic location of trial
	Pivotal vs. non-pivotal trial
	Comprehensive risk of bias assessment
	Inclusion/exclusion criteria
	Total sample size
Patient information	Age range
	Gender
	Race/Ethnicity
	Type of CRC (colorectal adenocarcinoma, gastrointestinal stromal tumor, etc.)
	Stage of disease
	Comorbidities present at baseline
Treatment information	Treatment regimen with specific drugs (using generic names)
	Drug classes included in treatment regimen
	Line of therapy
AE information	AE name
	MedDRA mapped term for AE
	Primary System Organ Class (SOC)
	AE grade
	Treatment-emergent adverse event (TEAE)
	Number and/or percentage of patients with AE
	AE Recording Details (e.g., only AEs of grade 3 or higher, only reported AEs that occurred in ≥ 10% of patients)
Other information	Efficacy and outcome data

Outcome

Any AE reported in an included clinical trial was considered the outcome of interest. For standardization purposes, a reference document which included a list of synonym terms and a mapping of AE names with MedDRA preferred terms (PTs) using MedDRA dictionary version 24.0 was used. MedDRA is a standardized medical terminology published by the International Council for Harmonisation. Severe AEs were defined as AEs of CTCAE grade ≥ 3 (i.e., severe or medically significant AEs, life-threatening AEs that require urgent intervention, or AEs that result in death) [11].

For meta-analysis purposes, mapped MedDRA PTs were used to identify and evaluate AEs. If clinical trials only reported events of certain grades or only reported AEs that exceed certain frequency thresholds or percentages, this information was recorded. If an AE did not map to a single MedDRA PT, it was not included in the meta-analysis. If an article reported the frequencies of multiple AEs grouped together (e.g., "nausea and vomiting," "nausea/vomiting," "mucositis and stomatitis," "mucositis/stomatitis," etc.), it was not included because it mapped to multiple distinct PTs.

AEs were recorded by specific CTCAE grade when reported in the literature. However, AEs reported in other terms (e.g., any grade AEs, SAEs, treatment-related, treatment-emergent as reported by the source) were recorded when specific grades were not.

Of note, one study reported both TEAE and drug-related TEAE, so only drug-related TEAE were included in this analysis. Additionally, some studies reported AE frequencies as "<1%" or "<0.1%." In these cases, a conservative approach was taken, and the frequencies were interpreted as 1% and 0.1%, respectively. If studies reported a decimal number of patients with an AE, then a conservative approach was taken here also, and the figure was rounded up.

Some studies reported AEs in a format where the increase or decrease of the laboratory value was not specified. For example, if a study listed an AE of "alanine aminotransferase," then this was evaluated as "alanine aminotransferase abnormal" for the purpose of this analysis. Studies that listed "alanine aminotransferase increased" or "alanine aminotransferase decreased" were converted to "alanine aminotransferase abnormal" for adequate comparison purposes. The same conversion was applied to aspartate aminotransferase, blood bilirubin, blood creatinine, haemoglobin, neutrophil count/neutrophils, platelet count, and lipase. The AEs of neutrophil count abnormal and neutropenia were not combined for this analysis since each could carry a different meaning.

Quality Assurance and Quality Control

An independent second researcher conducted quality control of the data reported in the review to ensure accuracy and completeness of the data that was extracted from the articles and included in this review.

Statistical Methods

Descriptive statistics were reported to summarize characteristics of the included clinical trials, including total sample sizes and AEs evaluated. Data was imported from Microsoft Office Excel to perform meta-analysis. Meta-analysis was conducted using random effects models in Comprehensive Meta-Analysis (CMA) v3 software. Many included trials were considered to be high risk using the Cochrane Collaboration Tool [11]. These trials were therefore all included in the main analysis, but a sensitivity analysis based on blinding status was subsequently performed. Funnel plots generated in CMA were used to qualitatively evaluate the risk of publication bias in the main analysis and heterogeneity between studies was evaluated and reported using Q and I^2 statistics with *p*-values. Data fields in CMA included a study identifier, treatment, event grade, event name, number of patients who experienced the AE, and total sample size.

Weighted estimates of the frequencies of specific, any grade, and grade ≥ 3 AEs in patients with CRC were calculated. Overall estimates of pooled event frequencies and 95% confidence intervals (CIs) for the most commonly occurring AEs in each subgroup were reported. *P*-values of less than 0.05 were considered statistically significant. The pooled estimates for the five most commonly occurring any grade and ≥ 3 AEs were reported to address the primary objective.

Results

Article Screening Results

There were 209 articles collected for review from the literature searches after removing duplicated articles (Figure 1). Of these articles, 93 articles were included after level 1 (title/abstract) screening. The most common reason for exclusion during level 1 screening was that articles were not Phase III clinical trials that focused on the cancer type of interest. These inclusions and publications from relevant clinical trials manually found from ClinicalTrials.gov were evaluated in level 2 (full text) screening. Several of the inclusions from level 1 screening were not retrieved for full text screening because no publications were found for the trial, only an abstract or protocol was found, only a subgroup analysis was found, or the article had trial results that were a duplicate of an already included article. Of the 41 articles

that were reviewed in level 2 screening, 22 were included in the final review (Figure 1). A total of 19 articles were excluded in level 2 screening for the following reasons: no specific safety results reported (n=12), not phase III clinical trial (n=2), duplicate trial results (n=2), publication date prior to 2021 (n=2), and irrelevant outcome (n=1).

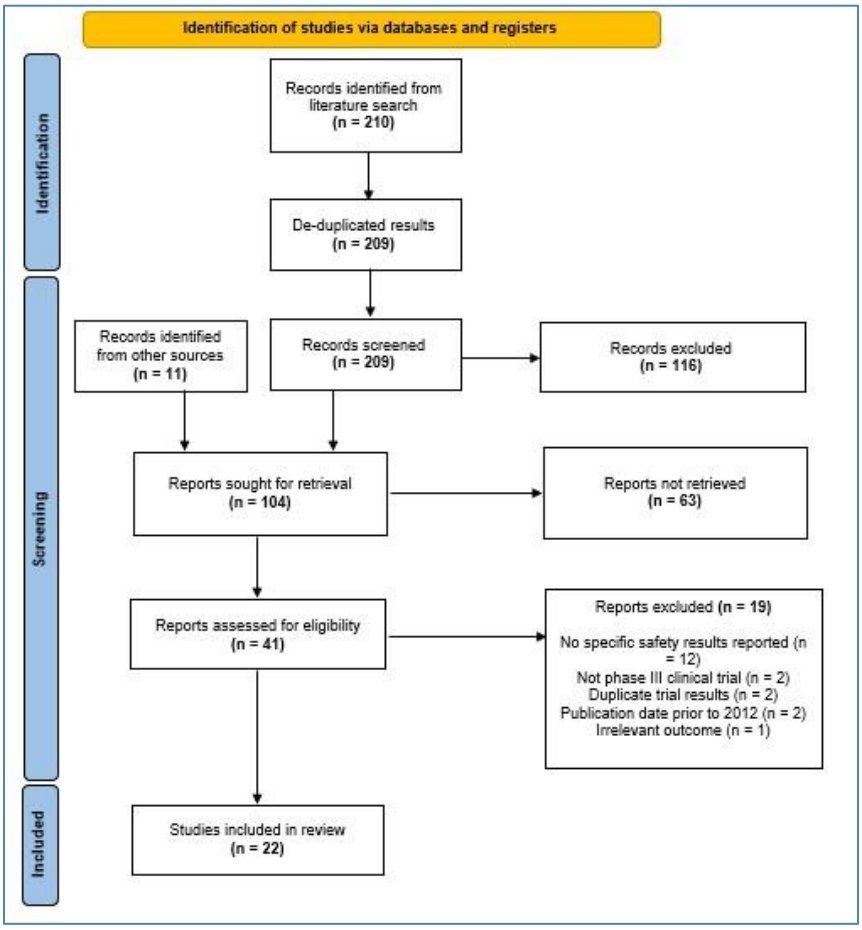

Figure 1. PRISMA Flow Diagram (8)

A summary of the included clinical trials is reported in Table 4. All trials were phase III and were limited to patients with CRC. The majority of patients in the included trials were White/Caucasian, male, and of older age, which is consistent with previous literature on patients who are at risk for CRC [12].

Table 4. Description of Included Articles

Trial Name	NCT Number	Location[1]	Type of CRC	Gender	Age: median (range) years unless otherwise specified	Race/ Ethnicity	Agents in Treatment Regimen	Sample Size	Ref
PETACC-8	NCT00265811	France	Adenocarcinoma, Stage III	44% F	60 (21-75)	NR	FOLFOX4 (fluorouracil, leucovorin, and oxaliplatin)	780	[13]
				40% F	60 (19-75)	NR	FOLFOX4 (fluorouracil, leucovorin, and oxaliplatin) + cetuximab	765	

RAVELLO	-	Intl.	RAS wild-type, metastatic	NR	NR	100% Caucasian	Regorafenib	11	[14]
TRIBE2	NCT02339116	Italy	Adenocarcinoma, unresectable, previously untreated, metastatic	39% F	61 (52-67)	NR	mFOLFOX-6 plus bevacizumab. At the time of disease progression, patients received FOLFIRI plus bevacizumab.	201	[15]
				47% F	60 (53-67)	NR	FOLFOXIRI + bevacizumab. Upon progression: FOLFOXIRI plus bevacizumab. Absence of progression: 5-FU/leucovorin plus bevacizumab.	132	
REGARD	NCT01853319	Turkey	Metastatic	58% M	56.5 (31-78)	NR	Regorafenib	100	[16]
PRIME	-	Intl.	Adenocarcinoma, metastatic	66.3% M	(27-85)	90.1% White	Panitumumab + FOLFOX4 (fluorouracil, leucovorin, and oxaliplatin)	539	[17]
				60.4% M	(24-82)	91.5% White	FOLFOX4 (fluorouracil, leucovorin, and oxaliplatin)	545	
Nordic ACT2	NCT01229813	Intl.	Metastatic	64% M	65 (38–74)	NR	Bevacizumab + erlotinib	36	[18]
				66% M	61 (32-76)	NR	Bevacizumab	35	
				53% M	65 (44-75)	NR	Bevacizumab	34	
				70% M	63 (45-79)	NR	Capecitabine	33	
XELAVIRI	NCT01249638	Germany	Adenocarcinoma, metastatic	64.6% M	Males:70, Females: 72	NR	Fluoropyrimidine + bevacizumab (plus irinotecan at progression)	212	[19]
				69.0% M		NR	Fluoropyrimidine + bevacizumab + irinotecan	210	
N0147	-	Intl.	Adenocarcinoma, Stage III	52.8% M	57.0 (25.0–82.0)	89.6% White, 5.7% Black or African American, 3.8% Asian, 0.9% American Indian or Alaska Native	FOLFIRI (fluorouracil, leucovorin, and irinotecan)	106	[20]
				55% M	59.0 (30.0–82.0)	85% White,7.5% Black or African American, 7.5% Asian	FOLFIRI (fluorouracil, leucovorin, and irinotecan) + cetuximab	140	

-	NCT01412957	Intl.	Adenocarcinoma	55.5% M	(30-82)	56.9% White	Panitumumab + best supportive care[2]	189	[21]
-	NCT02928224	Intl.	Metastatic	46.9% M, 53.1% F	(26-91)	82.5% White, 13.0% Asian, 4.1% Unknown/NR, 0.4% Black/African American	Encorafenib + binimetinib + cetuximab	222	[22]
							Encorafenib + cetuximab	216	
							Cetuximab + either irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan)	193	
SALTO	NCT01918852	Netherlands	Metastatic; primary site of colon, rectum, or rectosigmoid	69% M, 31% F	73 (66-78)	NR	Capecitabine +/- bevacizumab	80	[23]
				56% M, 44% F	74 (68-79)	NR	S-1 (Teysuno: tegafur/gimeracil/oteracil) +/- bevacizumab	80	
FRESCO	NCT02314819	China	Metastatic	56.8% M	55 (23-75)	NR	Fruquitinib + best supportive care	278	[24]
RECOURSE	NCT01607957	Intl.	Adenocarcinoma, metastatic	61.0% M	63.0 (27-82)	57.3% Caucasian, 34.5% Asian, 8.2% other/not collected	TAS-102 (trifluridine + tipiracil) + best supportive care	533	[25]
-	NCT01150045	Intl.	Adenocarcinoma, Stage III	54.6% M, 45.4% F	61.7 (21.8-88.7)	78.2% White, 12.7% Black/African American, 5.1% Asian, 4.0% other/not reported	Celecoxib + FOLFOX (folinic acid + fluorouracil + oxaliplatin) (3 or 6 months) (During FOLFOX)	1220	[26]
							Celecoxib + FOLFOX (folinic acid + fluorouracil + oxaliplatin) (3 or 6 months) (After FOLFOX)	1034	
				55.5% M, 44.5% F	61.0 (19.3-86.5)	80.0% White, 12.5% Black/African American, 3.4% Asian, 4.0% other/not reported	Placebo + FOLFOX (folinic acid + fluorouracil + oxaliplatin) (6 or 12 months) (during FOLFOX)	1214	
							Placebo + FOLFOX (folinic acid + fluorouracil + oxaliplatin) (3 or 6 months) (After FOLFOX)	1029	
ANZCTR 12610000509066	-	NR	Stage II-III	43.6% F, 56.4% M	62.4 (23.7-74.7)	NR	Oxaliplatin + leucovorin + 5-fluorouracil	197	[27]
				44.5% F, 55.5% M	63.7 (36.6-75.0)	NR	Oxaliplatin + capecitabine	211	

-	NCT01001377	Intl.	Adenocarcinoma, metastatic	63.1% M	61.0 (19-86)	53.3% White, 44.5% Asian, 1.2% Hispanic/Latino, 0.4% Black/African American, 0.2% Japanese, 0.4% other	Panitumumab	496	[28]
				63.6% M	60.5 (20-89)	51.6% White, 45.6% Asian, 1.4% Hispanic/Latino, 0.8% Black/African American, 0.6% other	Cetuximab	503	
-	NCT03288987	Iran	Metastatic	37.8% M, 62.2% F	Mean 56.26	NR	FOLFIRI-3 (with repeated irinotecan) [irinotecan, leucovorin, 5-FU] + bevacizumab biosimilar BE1040V	80	[29]
				34.1% M, 65.9% F	Mean 56.27	NR	FOLFIRI-3 (with repeated irinotecan) [irinotecan, leucovorin, 5-FU] + reference bevacizumab	44	
-	NCT00640471	Canada	Metastatic	66% M, 34% F	64.1 (27-88)	NR	Cetuximab + brivanib	372	[30]
				63% M, 37% F	63.4 (27-88)	NR	Cetuximab + placebo	373	
CONSIGN	NCT01538680	Intl.	Adenocarcinoma, metastatic	59% M, 41% F	62 (19-89)	83% White 2% Black 1% Asian 15% Other/not reported	Regorafenib	2864	[31]
-	NCT00561470	Intl.	Adenocarcinoma, metastatic	57.5% M, 42.5% F	61 (19-86)	NR	FOLFIRI + aflibercept	611	[32]
				59.6% M, 40.4% F	61 (21-82)	NR	FOLFIRI + placebo	605	
TRICOLORE / UMIN000007834	-	Japan	Adenocarcinoma, metastatic	58.8% M, 41.2% F	65 (29-85)	NR	mFOLFOX6 (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) + bevacizumab	242	[33]
				62.7% M, 37.3% F	64 (22-87)	NR	S-1 + irinotecan + bevacizumab	239	
-	-	China	Stage II-III	62.0% M, 38.0% F	NR	NR	Capecitabine +/- oxaliplatin	71	[34]
				58.8% M, 41.2% F	NR	NR	Capecitabine + celecoxib +/- oxaliplatin	68	

5-FU: Fluorouracil; CRC: Colorectal Cancer; NCT: National Clinical Trial; NR: Not Reported; M: Male; F: Female; Intl.: International; Ref: Reference

[1]International was defined as two or more countries included in the study

[2]Best supportive care consisted of antibiotics, analgesics, radiation for pain control (bone metastases only), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery or any other symptomatic therapy as clinically indicated

Heterogeneity between Studies

The heterogeneity between studies was evaluated in CMA v3 using I^2, *Q* statistics, and *p*-values. Heterogeneity was calculated separately for each outcome reported in this analysis. There was high heterogeneity for most outcomes, with a few exceptions. There were two outcomes in the metastatic subgroup associated with non-significant heterogeneity between studies. These were for grade ≥ 3 hyperbilirubinemia and grade ≥ 3 hypophosphatemia in patients treated with any treatment regimen (Table 5).

Table 5. Most frequently reported AEs of any grade in phase III clinical trials that included only patients with metastatic (stage IV) CRC, regardless of treatment regimen

CTCAE Grade	AE	Trials included in estimate	N	n	Estimate	95% CI		I^2	*Q*-value	*p*-value
						Lower	Upper			
Any	Fatigue	10	6802	2939	**44.2%**	33.3%	55.8%	98.296	880.296	<0.001
	Diarrhea	12	8440	2992	**36.8%**	28.5%	46.1%	98.189	1049.246	<0.001
	Rash	4	2386	1120	**35.3%**	21.6%	51.9%	98.026	354.632	<0.001
	Neutropenia	4	2279	1046	**35.0%**	23.4%	48.7%	94.220	121.115	<0.001
	Proteinuria	5	2259	1006	**34.3%**	25.9%	43.8%	94.424	143.482	<0.001
≥ 3	Neutropenia	6	3802	1235	**28.7%**	23.3%	34.7%	92.034	125.528	<0.001
	Hyperbilirubinemia	2	111	17	**16.5%**	9.0%	28.2%	22.250	1.286	0.2568
	Neurotoxicity	2	1417	185	**11.0%**	6.6%	17.8%	85.357	20.488	<0.001
	Hypertension	8	5855	779	**10.8%**	7.9%	14.6%	91.413	128.100	<0.001
	Hypophosphatemia	3	2975	187	**8.7%**	3.7%	18.9%	83.738	12.299	0.0021

AE: Adverse Event; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events

Most Frequent AEs Overall

The most frequently reported AEs of any grade and grade ≥ 3 overall in any patients with CRC, regardless of treatment regimen, are reported in Table 6. The most frequent any grade AEs overall were neuropathy peripheral (55.8%), hemoglobin abnormal (51.4%), neutrophil count abnormal (43.5%), rash (35.8%), and neutropenia (35.0%). The most frequent grade ≥ 3 AEs overall were neutropenia (27.3%), neutrophil count abnormal (21.1%), hyperbilirubinemia (16.5%), neurotoxicity (11.0%), and hypertension (9.9%).

Table 6. Most frequently reported AEs overall in phase III clinical trials of patients with CRC, regardless of treatment regimen

CTCAE Grade	AE	Trials included in estimate	N	n	Estimate	95% CI		I^2	Q-value	*p*-value
						Lower	Upper			
Any	Neuropathy peripheral	2	419	235	**55.8%**	45.1%	65.9%	66.136	5.906	0.0522
	Hemoglobin abnormal	2	1039	534	**51.4%**	39.9%	62.8%	92.756	55.214	<0.001
	Neutrophil count abnormal	2	547	292	**43.5%**	24.8%	64.2%	94.862	58.390	<0.001
	Rash	5	2575	1193	**35.8%**	23.2%	50.8%	97.798	363.290	<0.001
	Neutropenia	4	2279	1046	**35.0%**	23.4%	48.7%	94.220	121.115	<0.001
≥ 3	Neutropenia	8	5593	1815	**27.3%**	22.9%	32.1%	92.008	175.183	<0.001
	Neutrophil count abnormal	3	2976	839	**21.1%**	15.1%	28.8%	91.696	60.211	<0.001
	Hyperbilirubinemia	2	111	17	**16.5%**	9.0%	28.2%	22.250	1.286	0.2568
	Neurotoxicity	2	1417	185	**11.0%**	6.6%	17.8%	85.357	20.488	<0.001
	Hypertension	9	5993	782	**9.9%**	7.3%	13.2%	89.187	138.727	<0.001

AE: Adverse Event; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events

Most Frequent AEs by Drug Class

The analysis of the most frequently reported AEs by drug class is shown in Table 7 and Table 8. In patients with CRC who received chemotherapy, the most frequent AEs of any grade were anemia (70.0%), hemoglobin abnormal (56.4%), neutrophil count abnormal (43.5%), decreased appetite (38.5%), and alanine aminotransferase abnormal (36.0%) (Table 7). In these patients, the most frequent AEs grade ≥ 3 were neutropenia (27.3%), neutrophil count abnormal (21.1%), neurotoxicity (11.0%), hypertension (10.2%), and diarrhea (7.6%) (Table 8). Chemotherapy regimens consisted of fluorouracil, capecitabine, oxaliplatin, irinotecan, tegafur/gimeracil/oteracil, or trifluridine/tipiracil.

In patients with CRC who received targeted inhibitors, the most frequent AEs of any grade were fatigue (42.5%), rash (35.8%), proteinuria (34.6%), diarrhea (34.4%), and blood creatinine abnormal (33.4%) (Table 7). In these patients, the most frequent AEs of grade ≥ 3 were neutropenia (22.6%), hyperbilirubinemia (16.5%), hypertension (12.2%), hypophosphatemia (8.7%), and diarrhea (6.4%) (Table 8). Targeted inhibitor regimens consisted of cetuximab, regorafenib, panitumumab, erlotinib, bevacizumab, fruquintinib, brivanib alaninate, or aflibercept.

In patients with CRC who received folic acid analogs, the most frequent AEs of any grade were anemia (75.5%), neutropenia (60.8%), diarrhea (48.3%), thrombocytopenia (47.6%), and nausea (44.6%) (Table 7). In these patients, the most frequent AEs of grade ≥ 3 were neutrophil count abnormal (31.3%), neutropenia (27.9%), neurotoxicity (11.0%), hypertension (7.6%), and diarrhea (7.0%) (Table 8). Folic acid analog regimens consisted of leucovorin. Of note, one study included a treatment regimen of FOLFOXIRI + bevacizumab with varying treatment regimens subsequent to this depending on if disease progression was present or not. If there was disease progression, then patients received FOLFOXIRI + bevacizumab again. If there was no disease progression, then patients received maintenance 5-FU/leucovorin + bevacizumab. For this reason, the exact treatment regimen of each patient could not be identified so the treatment regimen for patients with no disease progression was not included in the folic acid analog regimen analysis.

Table 7. Most frequently reported AEs of any grade in phase III clinical trials of patients with CRC, by drug class

Drug Class	AE	Trials included in estimate	N	n	Estimate	95% CI		I^2	*Q*-value	*p*-value
						Lower	Upper			
Chemotherapy	Anemia	2	1697	1267	**70.0%**	40.8%	88.8%	98.971	291.429	<0.001
	Hemoglobin abnormal	2	601	339	**56.4%**	44.2%	67.8%	88.788	17.838	<0.001
	Neutrophil count abnormal	2	547	292	**43.5%**	24.8%	64.2%	94.862	58.390	<0.001
	Decreased appetite	5	2583	947	**38.5%**	29.1%	49.0%	95.882	169.993	<0.001
	Alanine aminotransferase abnormal	3	1890	729	**36.0%**	29.5%	43.0%	88.925	36.119	<0.001
Targeted Inhibitors	Fatigue	10	6458	2779	**42.5%**	30.9%	55.0%	98.367	918.450	<0.001
	Rash	5	2575	1193	**35.8%**	23.2%	50.8%	97.798	363.290	<0.001
	Proteinuria	5	1574	742	**34.6%**	24.2%	46.8%	94.874	117.058	<0.001
	Diarrhea	12	7491	2505	**34.4%**	25.7%	44.3%	98.152	973.889	<0.001
	Blood creatinine abnormal	2	1112	400	**33.4%**	14.5%	59.8%	98.267	230.844	<0.001
Folic acid analogs	Anemia	2	1458	1146	**75.5%**	39.6%	93.5%	99.146	234.207	<0.001
	Neutropenia	2	1458	894	**60.8%**	52.6%	68.3%	89.111	18.368	<0.001
	Diarrhea	3	1655	920	**48.3%**	32.0%	65.1%	97.619	126.007	<0.001
	Thrombocytopenia	2	1458	646	**47.6%**	33.4%	62.3%	96.630	59.351	<0.001
	Nausea	3	1655	818	**44.6%**	33.8%	56.1%	94.870	58.484	<0.001

AE: Adverse Event; CI: Confidence Interval

Table 8. Most frequently reported AEs of grade ≥ 3 in phase III clinical trials of patients with CRC, by drug class

Drug Class	AE	Trials included in estimate	N	n	Estimate	95% CI		I^2	*Q*-value	*p*-value
						Lower	Upper			
Chemotherapy	Neutropenia	8	5593	1815	**27.3%**	22.9%	32.1%	92.008	175.183	<0.001
	Neutrophil count abnormal	3	2976	839	**21.1%**	15.1%	28.8%	91.696	60.211	<0.001
	Neurotoxicity	2	1417	185	**11.0%**	6.6%	17.8%	85.357	20.488	<0.001
	Hypertension	4	1890	209	**10.2%**	5.5%	17.9%	92.444	79.404	<0.001
	Diarrhea	12	10286	835	**7.6%**	5.9%	9.8%	91.530	271.547	<0.001
Targeted inhibitors	Neutropenia	7	3029	893	**22.6%**	16.8%	29.5%	92.625	122.042	<0.001
	Hyperbilirubinemia	2	111	17	**16.5%**	9.0%	28.2%	22.250	1.286	0.2568
	Hypertension	9	5355	775	**12.2%**	9.5%	15.5%	83.848	80.486	<0.001
	Hypophosphatemia	3	2975	187	**8.7%**	3.7%	18.9%	83.738	12.299	0.0021
	Diarrhea	16	8951	700	**6.4%**	4.6%	8.8%	93.001	342.902	<0.001
Folic acid analogs	Neutrophil count abnormal	2	2626	822	**31.3%**	29.5%	33.2%	3.636	2.075	0.3543
	Neutropenia	6	4666	1557	**27.9%**	23.1%	33.3%	92.954	141.915	<0.001
	Neurotoxicity	2	1417	185	**11.0%**	6.6%	17.8%	85.357	20.488	<0.001
	Hypertension	2	1458	156	**7.6%**	2.3%	22.2%	96.882	64.144	<0.001
	Diarrhea	8	9311	744	**7.0%**	5.1%	9.6%	94.127	255.417	<0.001

AE: Adverse Event; CI: Confidence Interval

Most Frequent AEs for Specific Agents of Interest

In patients who received bevacizumab, the most frequent AEs of any grade were proteinuria (41.1%), hypertension (31.2%), diarrhea (29.6%), leukopenia (23.1%), and palmar-plantar erythrodysesthesia syndrome (19.8%) (Table 9). The most frequent AEs grade ≥ 3 in these patients were neutropenia (21.6%), hypertension (9.2%), diarrhea (8.1%), nausea (3.9%), and decreased appetite (3.8%) (Table 10). If a study listed its treatment as being ± a drug (e.g., ± bevacizumab), then it was not included in the bevacizumab subgroup analysis since it is unclear which patients took bevacizumab versus which patients did not.

In patients who received capecitabine, the most frequent AEs of any grade were palmar-plantar erythrodysesthesia syndrome (39.6%), nausea (38.6%), neutrophil count abnormal (35.2%), diarrhea (23.3%), and fatigue (17.9%) (Table 9). The most frequent AEs grade ≥ 3 in these patients were hypertension (7.7%), diarrhea (6.4%), neuropathy peripheral (4.0%), vomiting (3.1%), and fatigue (2.8%) (Table 10).

In patients who received FOLFOX (fluorouracil, leucovorin, and oxaliplatin), it was not possible to analyze the most frequent AEs of any grade due to an insufficient number of trials (<2 trials) that reported on this. However, the most frequent AEs grade ≥ 3 in these patients were neutropenia (36.7%), neurotoxicity (15.0%), diarrhea (5.9%), fatigue (4.7%), and mucosal inflammation (3.6%) (Table 10).

In patients who received FOLFIRI (fluorouracil, leucovorin, and irinotecan), the most frequent AEs of any grade were proteinuria (38.3%), hypertension (17.3%), hemorrhage (14.1%), and gastrointestinal perforation (0.6%) (Table 9). There was an insufficient number of trials to report a fifth most common AE. The most frequent AEs grade ≥ 3 in these patients were neutropenia (21.1%), diarrhea (10.4%), nausea (3.6%), vomiting (3.6%), and febrile neutropenia (2.1%) (Table 10).

Table 9. Most frequently reported AEs of any grade in phase III clinical trials of patients with CRC, for specific agents of interest

Agent[1]	AE	Trials included in estimate	N	n	Estimate	95% CI		I^2	*Q*-value	*p*-value
						Lower	Upper			
Bevacizumab	Proteinuria	2	525	222	**41.1%**	34.4%	48.2%	53.952	4.343	0.1140
	Hypertension	3	947	300	**31.2%**	26.7%	36.1%	55.356	8.960	0.0621
	Diarrhea	2	903	313	**29.6%**	11.9%	56.8%	98.065	155.077	<0.001
	Leukopenia	2	903	312	**23.1%**	8.7%	4.8%	94.713	56.740	<0.001
	Palmar-plantar erythrodysesthesia syndrome	2	903	228	**19.8%**	7.8%	4.2%	97.419	116.221	<0.001
Capecitabine	Palmar-plantar erythrodysesthesia syndrome	2	350	106	**39.6%**	7.1%	84.9%	98.062	103.214	<0.001
	Nausea	3	430	149	**38.6%**	26.0%	52.9%	86.731	22.610	<0.001
	Neutrophil count abnormal	2	350	160	**35.2%**	14.6%	63.4%	94.971	39.771	<0.001
	Diarrhea	3	430	123	**23.3%**	11.6%	41.3%	90.974	33.239	<0.001
	Fatigue	3	430	108	**17.9%**	3.8%	54.3%	96.610	88.493	<0.001
FOLFIRI (fluorouracil, leucovorin, and irinotecan)[2]	Proteinuria	2	1340	656	**38.3%**	23.5%	55.6%	96.507	85.897	<0.001
	Hypertension	2	1340	334	**17.3%**	6.0%	40.4%	97.937	145.449	<0.001
	Hemorrhage	2	1340	350	**14.1%**	6.3%	28.5%	96.011	75.212	<0.001
	Gastrointestinal perforation	2	1340	7	**0.6%**	0.3%	1.2%	0.000	0.961	0.8107

AE: Adverse Event; CI: Confidence Interval

[1]FOLFOX (fluorouracil, leucovorin, and oxaliplatin) analysis was not possible because only one study reported any grade AEs with this regimen.

[2]There is no fifth AE listed for FOLFIRI (fluorouracil, leucovorin, and irinotecan) since there were no more AEs that pooled any grade AEs from at least two trials with this regimen.

Table 10. Most frequently reported AEs of grade ≥ 3 in phase III clinical trials of patients with CRC, for specific agents of interest

Agent	AE	Trials included in estimate	N	n	Estimate	95% CI		I^2	*Q*-value	*p*-value
						Lower	Upper			
Bevacizumab	Neutropenia	2	814	174	**21.6%**	16.4%	28.0%	75.099	12.048	0.0072
	Hypertension	2	586	54	**9.2%**	6.5%	13.0%	24.250	5.280	0.2597
	Diarrhea	3	919	76	**8.1%**	5.5%	11.8%	54.591	13.213	0.0398
	Nausea	2	814	31	**3.9%**	2.8%	5.5%	0.000	2.275	0.5173
	Decreased appetite	2	814	36	**3.8%**	1.8%	7.8%	72.279	10.822	0.0128
Capecitabine	Hypertension	2	113	15	**7.7%**	0.6%	52.8%	71.836	3.551	0.0595
	Diarrhea	4	463	27	**6.4%**	3.1%	12.6%	54.253	8.744	0.0678
	Neuropathy peripheral	2	244	9	**4.0%**	2.1%	7.4%	0.000	0.557	0.4553
	Vomiting	2	291	9	**3.1%**	1.6%	5.9%	0.000	0.158	0.6910
	Fatigue	3	430	11	**2.8%**	1.0%	7.9%	56.717	6.931	0.0741
FOLFOX (fluorouracil, leucovorin, and oxaliplatin)	Neutropenia	3	2830	1069	**36.7%**	32.1%	41.6%	85.172	26.975	<0.001
	Neurotoxicity	2	1285	179	**15.0%**	10.0%	21.8%	79.013	9.530	0.0085
	Diarrhea	4	7278	521	**5.9%**	3.8%	9.2%	95.641	183.549	<0.001
	Fatigue	3	3714	171	**4.7%**	3.1%	7.0%	82.364	22.681	<0.001
	Mucosal inflammation	2	2629	122	**3.6%**	1.7%	7.8%	93.720	47.773	<0.001
FOLFIRI (fluorouracil, leucovorin, and irinotecan)	Neutropenia	3	1594	455	**21.1%**	14.1%	30.3%	92.172	51.099	<0.001
	Diarrhea	3	1594	199	**10.4%**	6.0%	17.3%	90.974	44.318	<0.001
	Nausea	3	1594	47	**3.6%**	1.8%	7.3%	80.629	20.649	<0.001
	Vomiting	3	1594	50	**3.6%**	2.2%	5.6%	53.311	8.567	0.0729
	Febrile neutropenia	2	378	7	**2.1%**	1.0%	4.4%	0.000	1.754	0.4161

AE: Adverse Event; CI: Confidence Interval

Most Frequent AEs in Patients with Metastatic Disease

A total of fifteen trials were limited to only patients with stage IV/metastatic CRC. The locations of metastases varied between trials and were often not reported. Regardless of treatment regimen, the most frequent AEs of any grade in patients with metastatic CRC were fatigue (44.2%), diarrhea (36.8%), rash (35.3%), neutropenia (35.0%), and proteinuria (34.3%) (Table 5). Rash and neutropenia were the only AEs that this analysis shared with the analysis of the most frequently reported any grade AEs overall in phase III clinical trials of patients with CRC regardless of treatment regimen (Table 6). The most frequent AEs of grade ≥ 3 in these patients were neutropenia (28.7%), hyperbilirubinemia (16.5%), neurotoxicity (11.0%), hypertension (10.8%), and hypophosphatemia (8.7%) (Table 5). All these AEs except hypophosphatemia were shared with the analysis of the most frequently reported grade ≥ 3 AEs overall in phase III clinical trials of patients with CRC regardless of treatment regimen (Table 6).

Risk of Bias

Since such a high percentage of trials did not include blinding, the protocol was amended to include these trials in the main analysis and conduct a subsequent sensitivity analysis (Table 11). Based on the results of the sensitivity analysis, there were differences in the most frequent AEs reported overall, regardless of treatment regimen, based on blinding status. The risk of bias of all included trials was evaluated using the Cochrane risk-of-bias tool (Table 12) (11). Eleven (50%) of the included trial publications were considered to be high risk and 9 (41%) were considered to have unclear risk using the Cochrane risk-of-bias tool. The risk of publication bias was also evaluated in the main analysis which included patients who received any treatment regimen using funnel plots generated in CMA v3. Overall, for the most frequently reported any grade or grade ≥ 3 AEs, there was asymmetry in most of the funnel plots (Supplemental Figure 1). A funnel plot was not included for grade ≥ 3 hyperbilirubinemia since there were only two rows of data.

Table 11. Most frequently reported AEs of any grade in phase III clinical trials of patients with CRC, regardless of treatment regimen, by blinding status

AE	Blinded (N=8)		Open-Label (N=7)	
	Estimate	**95% CI**	**Estimate**	**95% CI**
Rash	**66.6%**	55.8% - 75.9%	28.2%	16.8% - 43.2%
Fatigue	**51.9%**	32.6% - 70.7%	**37.0%**	24.5% - 51.6%
Alanine aminotransferase abnormal	**45.5%**	29.5% - 62.6%	24.1%	18.0% - 31.5%
Diarrhea	**40.5%**	26.8% - 55.8%	**32.4%**	22.2% - 44.7%
Aspartate aminotransferase abnormal	**40.4%**	8.3% - 83.5%	24.8%	15.9% - 36.7%
Hypertension	19.0%	13.0% - 26.8%	**32.5%**	28.7% - 36.6%
Blood creatinine abnormal[1]	-	-	**33.4%**	14.5% - 59.8%
Dermatitis acneiform[1]	-	-	**33.0%**	26.7% - 39.9%

AE, adverse event; CI, confidence interval
[1]Blood creatinine abnormal and dermatitis acneiform were not reported in any blinded trial
Bolded text indicates the top five most frequently reported AEs in blinded and open-label trials
The total number of trials does not sum to 22 because not all trials reported any grade AEs and some trials had an unclear blinding status

Table 12. Risk of bias assessment

Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall	Reference
+	+	+	−	+	+	?	[13]
+	?	+	+	−	+	?	[14]
+	+	−	−	+	+	−	[15]
−	−	−	−	+	+	−	[16]
+	−	+	+	−	+	−	[17]
+	−	−	−	+	+	−	[18]
+	−	−	−	+	+	−	[19]
+	+	?	?	+	+	?	[20]
+	−	−	−	+	+	−	[21]
+	?	−	−	−	+	−	[22]
+	+	−	−	+	+	−	[23]
+	+	+	+	?	+	?	[24]
+	?	+	?	+	+	?	[25]
+	+	+	?	−	+	?	[26]
+	+	?	?	−	+	?	[27]
+	−	−	−	+	+	−	[28]
+	+	+	+	+	+	+	[29]
+	?	+	+	+	+	?	[30]
−	−	+	+	−	+	−	[31]
+	+	+	+	+	+	+	[32]
+	−	−	−	−	+	−	[33]
+	?	?	?	−	+	?	[34]

+ low risk of bias based on the criteria

? unclear risk of bias based on the criteria

− high risk of bias based on the criteria

Discussion

The purpose of this systematic literature review and meta-analysis was to identify the most commonly reported AEs of any grade or grade ≥ 3 in phase III clinical trials that included patients with CRC. The most frequently reported AEs of any grade in this patient population overall, regardless of treatment regimen, were neuropathy peripheral, hemoglobin abnormal, neutrophil count abnormal, rash, and neutropenia. The most frequently reported AEs of grade ≥ 3 in this patient population overall, regardless of treatment regimen, were neutropenia, neutrophil count abnormal, hyperbilirubinemia, neurotoxicity, and hypertension. If neutropenia and neutrophil count abnormal were combined, then an additional AE would have been included in the list. The most frequent AEs of any grade in patients with metastatic CRC, regardless of treatment regimen, were fatigue, diarrhea, rash, neutropenia, and proteinuria. The most frequent AEs of grade ≥ 3 in these patients, regardless of treatment regimen, were neutropenia, hyperbilirubinemia, neurotoxicity, hypertension, and hypophosphatemia. These results are in line with known side effects of treatments used for CRC, such as nausea, vomiting, diarrhea, and effects on blood-forming cells of the bone marrow [35].

It is interesting to note that the subgroup analysis of metastatic patients showed AEs of any grade that differed slightly from the main group analysis. For example, for AEs of any grade, only rash and neutropenia were seen in both groups. For AEs of grade ≥ 3, the most common AEs were more similar with neutropenia, hyperbilirubuninemia, neurotoxicity, and hypertension all being common to both groups.

In the analysis of patients with CRC who received chemotherapy, the most frequent AEs of any grade were anemia, hemoglobin abnormal, neutrophil count abnormal, decreased appetite, and alanine aminotransferase abnormal. In the analysis of patients with CRC who received targeted inhibitors, the most frequent AEs of any grade were fatigue, rash, proteinuria, diarrhea, and blood creatinine abnormal. In the analysis of patients with CRC who received folic acid analogs, the most frequent AEs of any grade were anemia, neutropenia, diarrhea, thrombocytopenia, and nausea. These findings are mostly consistent with known side effects of each class of drugs.

In the analyses that evaluated specific agents of interests, the most frequent AEs of any grade for patients treated with bevacizumab were proteinuria, hypertension, diarrhea, leukopenia, and palmar-plantar erythrodysesthesia syndrome. These findings differ slightly from estimates of common AEs from previous literature which note common adverse reactions of bevacizumab to be epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, and exfoliative dermatitis [36]. The most frequent AEs of any grade for patients treated with capecitabine were palmar-plantar erythrodysesthesia syndrome, nausea, neutrophil count abnormal, diarrhea, and fatigue. These findings are consistent with estimates of common AEs from previous literature which note common adverse reactions of capecitabine to be diarrhea, hand-foot syndrome, nausea, vomiting, abdominal pain, fatigue/weakness, and hyperbilirubinemia [37].

As expected, there was large heterogeneity and large I^2 values for most outcomes reported in this meta-analysis when we evaluated AEs overall in patients treated with any regimen. This was likely due to the number of different treatment regimens used in combination across trials. This variety in combinations was likely due to treatment decisions made on the basis of the specific molecular subtype of disease, line of therapy, previous medical history, and stage of disease. It could also be due to differences in patient populations and inclusion/exclusion criteria.

Since many treatment regimens often included multiple agents from multiple drug classes with different safety profiles, it was not possible for us to definitively attribute any AE to a single agent in the treatment regimen. This makes interpretations of the safety profile of a specific drug in a treatment regimen not possible with this analysis.

It was not anticipated that most trials included in this meta-analysis would have a high risk of bias. The protocol was amended to include all trials in the main analysis and conduct a sensitivity analysis based on blinding status. It is possible that the results of the common AEs could be biased in open-label trials since patients knew what they were receiving.

This meta-analysis has several strengths and a few limitations. The strengths of this project include the quantitative evaluation of AEs in CRC using relevant and recent literature. We included the systematic literature review process using two levels of review with two independent researchers and incorporated data from multiple trials to allow for a robust meta-analysis. Since this analysis involved making inferences based on different populations of patients with CRC, it is important to have validity in the comparison which was addressed by using the meta-analysis methodology to calculate a comprehensive overall effect from the independent studies. Also, heterogeneity was addressed by using random effects models. The limitations include the potential of excluding relevant information by only including clinical trials conducted in the past 10 years, the possibility of including individual biases within the clinical trials, heterogeneity of the studies and study designs, heterogeneity of the study populations, potential selection bias, and subjective groupings of some adverse events to account for differences in reporting in the literature as well as updates to MedDRA. CMA software was used to evaluate the extent of heterogeneity. This software was also used to qualitatively assess the

effects of publication bias for any trials that may have been more likely to be published if they found significant effects. The Cochrane Criteria was utilized to identify trials with a high risk of bias. Lastly, there was the risk of search, information, and selection bias which was minimized by using a set of key terms and using two researchers to independently review each article. Since there were some instances where only one trial reported a specific AE, the AE in these instances was not included in the meta-analysis. This could have impacted the evaluation of results since the AE has the potential to be commonly occurring. There were also some instances where the AE was not mentioned at all in a publication if no patients in any trial experienced an AE or the AEs included were based on specific criteria (e.g., AEs were reported if they occurred in ≥ 10% of patients). These instances could have also resulted in a biased interpretation of results. While there have been more recent publications on this topic since the literature search cutoff, such as the C-cubed study and studies in left-sided metastatic colorectal cancer, the adverse event information from these studies does not deviate much from the results of this meta-analysis [38,39].

Conclusion

The most commonly reported AEs in phase III clinical trials of patients with CRC were largely dependent upon treatment regimen and drug classes. The results of this meta-analysis show the common AEs in this patient population by pooling patient data from several recent clinical trials. Opportunities for future research include evaluating the common AEs associated with specific agents, considering that many treatment regimens in this review combined multiple agents. Ultimately, this review will be useful for a general interpretation of the most common AEs in treatments for patients with CRC so that AE prevention and management can be better tailored to patients when possible.

Author Contributions

PY, MH, EW, and MS contributed to conception and design of the study. PY, MH, and EW conducted article screening, article selection, data extraction, and quality control of data extraction. PY performed the data analysis and drafted the manuscript. MH performed the quality control of the manuscript. PY, MH, EW, and MS contributed to manuscript review, revision, and approved the submitted version.

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Conflicts of Interest

PY, MH, EW, and MS are or were employees of Daiichi Sankyo, Inc. and receive or received salaries from Daiichi Sankyo, Inc. at the time of the study. MS owns stock in Daiichi Sankyo, Inc.

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