European Journal of Cancer 166 (2022) 73–86

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Systematic review and non-inferiority meta-analysis of randomised phase II/III trials on S-1-based therapy versus 5-fluorouracil- or capecitabine-based therapy in the treatment of patients with metastatic colorectal cancer

Jeroen W.G. Derksen*, Karel C. Smit, Anne M. May, Cornelis J.A. Punt

Julius Center for Health Sciences and Primary Care, Department of Epidemiology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

Received 23 November 2021; received in revised form 21 January 2022; accepted 5 February 2022
Available online 10 March 2022

KEYWORDS
Metastatic colorectal cancer;
S-1;
Fluoropyrimidines;
Treatment;
Non-inferiority;
Meta-analysis

Abstract ***Background:*** S-1 is an oral fluoropyrimidine that is increasingly used in Western countries for the treatment of metastatic colorectal cancer (mCRC). We conducted a non-inferiority meta-analysis on the efficacy of S-1-based therapy versus 5-fluorouracil (5-FU)- or capecitabine-based therapy in the treatment of patients with mCRC.
Methods: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and Opengrey were searched for randomised clinical trials until May 2021. Data were extracted for progression-free survival (PFS), overall survival (OS), objective response rate (ORR) and adverse events. Pooled effect estimates, stratified by treatment line, with corresponding 99% confidence intervals (CI) were presented. For PFS, a pre-defined non-inferiority margin (ΔNI) of 1.25 was selected.
Results: Ten studies (n = 2117) were included, of which six studies reported PFS and OS data and 10 studies reported ORR data. S-1-based therapy was shown to be non-inferior to 5-FU/capecitabine-based therapy in terms of PFS (HR_{total} 0.95, 99% CI 0.83–1.08) with its CI upper limit well below ΔNI, and at least as efficacious in terms of OS (HR_{total} 0.93, 99% CI 0.81–1.07), and ORR (RR_{total} 1.06, 99% CI 0.90–1.24).
Conclusions: S-1-based therapy is non-inferior to 5-FU/capecitabine-based therapy in the treatment of mCRC regarding PFS and at least as efficacious as 5-FU/capecitabine-based

* *Corresponding author*: Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, PO Box 85500, 3508 GA, Utrecht, the Netherlands.
E-mail address: h.w.g.derksen-2@umcutrecht.nl (J.W.G. Derksen).

https://doi.org/10.1016/j.ejca.2022.02.004

therapy in terms of ORR and OS. These data support the use of S-1 in mCRC patients who are intolerant to 5-FU/capecitabine-based treatment.

1. Introduction

In metastatic colorectal cancer (mCRC), the standard first-line chemotherapy backbone comprises a fluoropyrimidine, i.e. intravenous 5-fluorouracil (5-FU) or oral capecitabine, often in combination with irinotecan and/or oxaliplatin, with or without a targeted agent [1,2]. The oral fluoropyrimidine S-1 is a 5-FU prodrug given as a fixed-dose combination of tegafur, gimeracil and oteracil and is considered as part of the standard of care for patients with unresectable mCRC in Asian countries [3].

Previous meta-analyses suggested that S-1-based regimens might be associated with comparable efficacy and, except for diarrhoea, less toxicity compared to capecitabine-based regimens [4–6] and 5-FU-based regimens [6–8]. However, these reviews were limited by either not incorporating recently updated trial data, including trials in Western patients, or potential bias caused by the inclusion of multiple publications of the same trial [9].

The results of the phase III SALTO trial, comparing S-1 to capecitabine in Western mCRC patients, demonstrated that first-line treatment with S-1 was associated with a significantly lower incidence of hand–foot syndrome (HFS) compared with capecitabine, without compromising on efficacy, although the study was not powered to show non-inferiority [10,11]. Retrospective series in Western mCRC patients have shown the tolerability of S-1 in Western mCRC patients who discontinued treatment with capecitabine for reasons of HFS or cardiac toxicity [12,13]. Together, these data indicated that S-1 may be considered as a suitable alternative to capecitabine in Western mCRC patients, specifically in those with intolerance due to HFS or cardiac toxicity.

As per December 2021, the use of S-1 has been approved by the European Medicines Agency (EMA) as monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab, for the treatment of patients with mCRC for whom it is not possible to continue treatment with another fluoropyrimidine due to HFS or cardiovascular toxicity that developed in either the adjuvant or metastatic setting [14].

Subsequently, we aim to provide up-to-date and conclusive evidence on the non-inferiority of S-1-based regimens compared to 5-FU- or capecitabine-based therapy in the treatment of patients with mCRC by means of a systematic review of randomised clinical phase II and III trials and a non-inferiority meta-analysis.

2. Methods

2.1. Literature search

For the searching of the electronic scientific databases, i.e. MEDLINE (PubMed), Embase and Cochrane Central Register of Controlled Trials (CENTRAL), a sensitive search strategy without date restriction was applied using medical subject headings pertaining to the study design, population and intervention relevant to this review. In addition, grey literature was searched for using OpenGrey, an online database containing bibliographical references of grey literature in Europe. Reference lists of review papers included in our search results were screened for potentially relevant publications. When publications could not be retrieved online, but contact information was provided, authors were contacted. The full search strategies for all utilised databases are provided in Appendix A1. Two reviewers (JWGD and KCS) reviewed the literature independently, and discrepancies were resolved by discussion until consensus was reached. This systematic review was registered at the International prospective register of systematic reviews (PROSPERO) with identification number CRD42021264921 and performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

2.2. Inclusion criteria

Studies were not restricted based on treatment line and had to meet the following eligibility criteria: (1) patients with age >18 years; (2) histologically proved colorectal cancer with distant metastases (mCRC); (3) palliative S-1-based (mono or combination) therapy, compared with 5-FU- or capecitabine-based (mono or combination) therapy (5-FU/Cap); and (4) prospective phase II or phase III randomised clinical trials.

2.3. Data extraction

The reviewer involved in data extraction (JWGD) collected the following study characteristics and parameters: authors, publication year, study phase (II/III), treatment line, design, non-inferiority margin, primary

end point, region, multi/mono-centre, enrolment period, treatment regimen per arm, number of patients, sex, median age (range), ECOG performance status (PS), treatment beyond second line, median number of cycles, median progression-free survival (PFS, months) with corresponding p-values and median overall survival (OS, months) with corresponding p-values.

2.4. Study quality assessment

Two reviewers (JWGD and KCS) independently examined the quality of all included studies, based on the revised Cochrane risk-of-bias tool for randomised trials (RoB 2). Non-inferiority trials included in the current meta-analysis were additionally evaluated based on the unique risk of bias issues for equivalence or non-inferiority trials, i.e. sources of bias that may artificially reduce the differences between study arms, including selection, performance, detection and attrition, as proposed by the EPC Workgroup of the Agency for Healthcare Research and Quality [15]. Disagreements were resolved by discussion until an agreement was reached. Studies with a high overall risk of bias were not included in the analysis. Due to the low number of included trials ($n < 10$), funnel plot asymmetry tests were omitted and asymmetry was visually evaluated to check for the existence of publication bias.

2.5. Statistical analysis

The primary outcome was PFS, and the secondary outcomes were OS, objective response rate (ORR) and adverse events. For the time-to-event outcomes, PFS and OS, hazard ratios (HRs) with their 95% confidence intervals (CIs) were extracted from the individual studies. In order to support our meta-analysis, median survival and time to progression with corresponding p-values were extracted. Analyses were based on the intention-to-treat population of the included studies with PFS and OS data. Pooled HRs are provided for the total population of mCRC patients, and per subgroup of treatment line, including 99% CIs. When treatment arms of individual studies compared 5-FU or capecitabine with S-1, using the same combination therapy, a direct evaluation of 5-FU/capecitabine-based therapy versus S-1-based therapy in this meta-analysis is justified. Sensitivity analyses were performed by comparing the observed overall effect estimate to the estimate when studies with a divergent design were omitted. The aim of this meta-analysis is to show that the effect of S-1-based therapy is not inferior to the effect of 5-FU/capecitabine-based therapy by a specified amount, called the non-inferiority margin (ΔNI). Here, a pre-defined ΔNI of 1.25 for PFS was selected based on the trial with the most conservative ΔNI in this review, i.e. Yamada, 2018 [16]. Thus, non-inferiority of S-1-based therapy relative to 5-FU/capecitabine-based therapy is established when the upper limit of the 99% CI of the pooled HR_{total} remains <1.25.

Data for our meta-analysis on the ORR and treatment-related toxicities were extracted from the primary publications of studies included in this review. For ORR, we extracted the number of patients with a complete or partial response and divided this by the total number of patients with evaluable lesions for response analysis. Then, risk ratios (RRs) and 99% CIs were calculated. For toxicity data, adverse events were analysed by treatment regimen where we separated oxaliplatin- and irinotecan-containing S-1 combination therapies. The selection of toxicities for meta-analysis was based on two criteria: incidence $\geq$5% and reported by the majority of the publications, i.e. by $\geq$3/5 oxaliplatin-containing and by $\geq$2/3 irinotecan-containing therapy trials. Pooled effect sizes were calculated as RRs including their 95% CI.

Meta-analyses of all outcomes mentioned above were conducted in Review Manager 5.4 using random-effect models with generic inverse-variance weighing to minimise the imprecision of the pooled effect estimate. All tests were two-sided, and heterogeneity was assessed by the Cochran Q-test and quantified by the I^2 index.

3. Results

3.1. Literature search and study quality

The PRISMA flowchart with a complete overview of the systematic search is presented in Fig. 1. A total of 457 unique references were identified through our sensitive systematic search in MEDLINE, Embase, CENTRAL and OpenGrey until May 21, 2021, of which 174 review, registry registration, or duplicate references were removed, leaving 283 references for title and abstract screening (Fig. 1). Eligibility screening based on title and abstract led to the exclusion of 267 references. Two additional potentially relevant publications were found in one of the retrieved review articles. In total, 18 publications were sought for retrieval, of which four publications—even after contacting two authors—could not be obtained (Appendix A2). The remaining 14 publications were assessed for eligibility. Ten publications with (updated) PFS, OS or ORR outcomes were included [11,16–24], and for the analysis on ORR, four corresponding primary publications of the same trials were included [10,25–27].

There were no major differences in study and patient characteristics among the studies included (Table 1). Two studies with a noticeable difference in study design include the publication by Yamada *et al.* [16] and Kato *et al.* [22]. In the study by Yamada *et al.*, the chemotherapy regimen accompanying the fluoropyrimidine differed between the two arms, i.e. S-1 plus irinotecan and bevacizumab in the intervention arm versus 5-FU

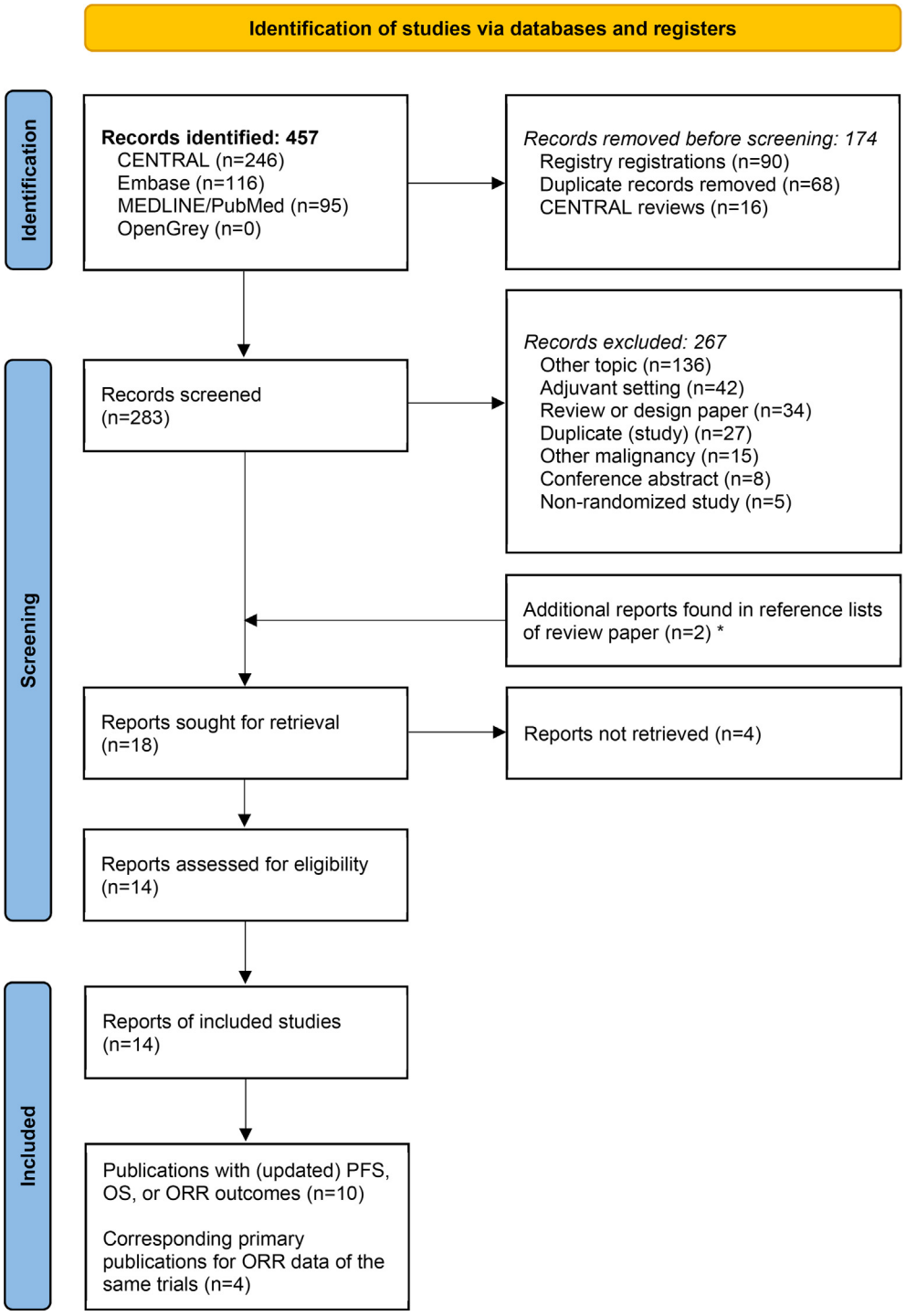

Fig. 1. PRISMA flow diagram for the systematic review and meta-analysis of randomised (non-inferiority) studies on treatment with S-1 in patients with metastatic colorectal cancer. *Ning *et al.*, 2017, and Tian *et al.*, 2011. Flowchart adjusted from M.J. Page *et al.* [37].

plus oxaliplatin and bevacizumab, or capecitabine plus oxaliplatin and bevacizumab in the control arm. In the study by Kato *et al.*, treatment concerned both first line and second line. Since the majority of patients in this study were treated in first-line setting (78%), and no significant bias between the two groups was observed according to the authors, this reference was considered a first-line study in the current meta-analysis.

For the primary outcome, five studies were rated as low risk of bias [10,16,19,20,26], whereas five other studies were rated as some concerns for risk of bias because of concerns arising from the randomisation process [22,24], missing outcome data [21], measurement of the outcome [25,27] and/or selection of the reported results [21,22] (Appendix A3). Visual inspection of the funnel plots indicated no apparent asymmetry, and

Table 1
Study and patient baseline characteristics of included studies.

Study	Phase	Line	Design	ΔNI	Primary endpoint	Region	Centre	Enrolment period	Arm	N (ITT)	Men	Median age (range)	ECOG PS ≥ 2	≥2nd line	Median no. of cycles
Kim *et al.* 2014 [17] (primary publication: Hong *et al.* 2012 [26])	III	First	NI	1.43	PFS	Korea	Multi-centre	May 2008 Sept 2009	Cap + Ox	172	102 (59%)	126 (73%) ≤65 years	4 (2%)	NR	Cap: 6 (5–9) Ox: 6 (5–9)
									S-1 + Ox	168	109 (65%)	121 (72%) ≤65 years	4 (2%)	NR	S-1: 9 (5–10.5) Ox: 8 (4.5–9)
Baba *et al.* 2017 [18] (primary publication: Yamada *et al.* 2013 [25])	III	First	NI	1.33	PFS	Japan	Multi-centre	Feb 2009 Mar 2011	mFOLFOX6 + Beva	255	159 (62%)	63 (39–79)	0	203 (80.2%)	12 (range 1–97+)
									S-1 + Ox + Beva	256	170 (66%)	63 (33–79)	0	209 (81.6%)	8 (range 1–58)
Yamada *et al.* 2018 [16]	III	First	NI	1.25	PFS	Japan	Multi-centre	June 2012 Sept 2014	mFOLFOX6 + Beva or Cap + Ox + Beva	243	143 (58.8%)	65 (29–85)	0	206 (87.7%)	NR
									S-1 + IRI + Beva	241	151 (62.7%)	64 (22–87)	0	198 (87.6%)	NR
Kwakman *et al.* 2019 [11] (primary publication: Kwakman *et al.* 2017 [10])	III	First	SU	NR	HFS incidence	Netherlands	Multi-centre	Jan 2014 July 2015	Cap (+/− Beva)	81	56 (69%)	73 (66–78)	8 (10%)[a]	40 (49%)	8 (IQR 4–12)
									S-1 (+/− Beva)	80	45 (56%)	74 (68–79)	8 (10%)[a]	41 (51%)	9 (IQR 3–13)
Kim *et al.* 2015 [19]	II	First	Efficacy and safety	NR	Response Rate	South Korea	Multi-centre	Apr 2008 Aug 2011	Cap + Ox	44	27 (61.4%)	66 (29–76)	1 (2.3%)	30 (68.2%)	5 (range 1–19)
									S-1 + Ox	42	28 (66.7%)	67 (46–83)	2 (4.8%)	28 (66.7%)	6 (range 1–39)
Yamazaki *et al.* 2015 [20]	II	First	Efficacy and safety	NR	PFS	Japan	Multi-centre	July 2008 July 2009	mFOLFOX6	49	23 (46.9%)	61.0 (27–76)	0	45 (91.8%)	11 (range 1–69)
									S-1 + Ox + LV	56	33 (58.9%)	60.5 (27–77)	0	56 (100%)	12 (range 1–63)
Sadahiro *et al.* 2020 [21]	II	First	Efficacy and safety	NR	1-y PFS	Japan	Mono-centre	Dec 2013 Jan 2018	FOLFIRI + Beva	59	28 (59.6%)	64 (38–83)	0	NR	15 (range 2–44)
									S-1 + IRI + Beva	61	33 (64.7%)	65 (23–79)	0	NR	17 (range 4–58)
Kato *et al.* 2012 [22]	II	First[b]	Efficacy and safety	NR	Safety (AE)	Japan	Multi-centre	Nov 2007 Feb 2010	mFOLFIRI + Beva	30	18 (60%)	62.5 (46–77)	0	NA	NR
									S-1 + IRI + Beva	30	17 (57%)	62 (31–73)	0	NA	NR
Yasui *et al.* 2015 [23] (primary	III	Second	NI	1.333	PFS	Japan	Multi-centre	Jan 2006 Jan 2008	FOLFIRI	213	123 (57.7%)	63 (32–75)	0	168 (78.9%)	4 (range 1–27)
									S-1 + IRI	213	120 (56.3%)	61 (29–75)	0	153 (71.8%)	4 (range 1–23)

(*continued on next page*)

Table 1 (*continued*)

Study	Phase	Line	Design	ΔNI	Primary endpoint	Region	Centre	Enrolment period	Arm	N (ITT)	Men	Median age (range)	ECOG PS ≥ 2	≥2nd line	Median no. of cycles
publication: Muro *et al.* 2010 [27])															
Liu *et al.* 2015 [24]	II	Second	Efficacy and safety	NR	Response Rate	China	Mono-centre	Oct 2009 Oct 2011	Cap + Ox S-1 + Ox	35 35	20 (57.1%) 19 (54.3%)	60 (37–70) 60 (35–72)	0 0	NR NR	NR, at least 2 NR, at least 2

ITT, intention-to-treat; PS, performance status; ΔNI, non-inferiority margin; SU, superiority; PFS, progression-free survival; HFS, hand–foot syndrome; AE, adverse event; LV, leucovorin; Beva, bevacizumab; NR, not reported; NA, not applicable; IQR, interquartile range.

[a] WHO PS 2.

[b] incl. n = 13 (22%) patients treated as second-line.

therefore, we assume a low risk of publication bias (Appendix A4).

3.2. Efficacy of S-1-based therapy versus 5-FU/capecitabine-based therapy

Ten studies (n = 2117) were included in the meta-analysis: 1062 patients received S-1-based therapy and 1055 patients received 5-FU/capecitabine-based therapy. Nine studies were conducted in Asia, and one study was conducted in Europe. We were able to extract HRs for PFS and OS from six studies [11,16–18,20,23], whereas ORR data were available from 10 studies [10,16,19–22,24–27].

3.2.1. Progression-free survival

As the upper limit of the 99% CI of the HR_{total} for PFS did not reach the pre-defined ΔNI of 1.25, S-1-based therapy was shown to be non-inferior to 5-FU/capecitabine-based therapy (HR_{total} 0.95, 99% CI 0.83–1.08) (Fig. 2). When stratified by treatment line, a pooled $HR_{subgroup}$ of 0.92 (99% CI 0.80–1.06) was observed for first-line treatment and a $HR_{subgroup}$ of 1.06 (99% CI 0.82–1.37) for second-line treatment. No significant heterogeneity was detected for PFS (I^2 = 12%, P = 0.34).

Sensitivity analysis showed that the direction of the estimator of the HRs for PFS and non-inferiority was not influenced by the omission of the study by Yamada *et al.* [16] in which the combination therapy differed between the intervention and control arm.

In addition, median PFS (months) per arm was reported by four other studies: three first-line studies [19,21,22] and one second-line study [24]. An overview of studies and median PFS data are presented in Appendix A5. Except for the study by Kim *et al.* [19], which reported a median time to progression of 7.4 months for the control arm versus 6.1 months for the S-1-based arm, the other three studies reported a comparable time to progression with differences ranging from 0.2 to 0.7 months [21,22,24]. All four studies reported no statistically significant difference in PFS between 5-FU/capecitabine-based versus S-1-based therapy (P > 0.05).

3.2.2. Overall survival

Although the end point OS was a secondary outcome in all of the included studies, our results indicate that S-1-based therapy is at least as effective as 5-FU/capecitabine-based therapy in terms of OS (HR_{total} 0.93, 99% CI 0.81–1.07) (Fig. 3). When stratified by treatment line, a pooled $HR_{subgroup}$ of 0.94 (99% CI 0.80–1.10) was observed for first-line treatment and a $HR_{subgroup}$ of 0.90 (99% CI 0.68–1.19) for second-line treatment. No significant heterogeneity was detected for OS (I^2 = 0%, P = 0.82).

Sensitivity analysis showed that the direction of the estimator of the HRs for OS and its significance were

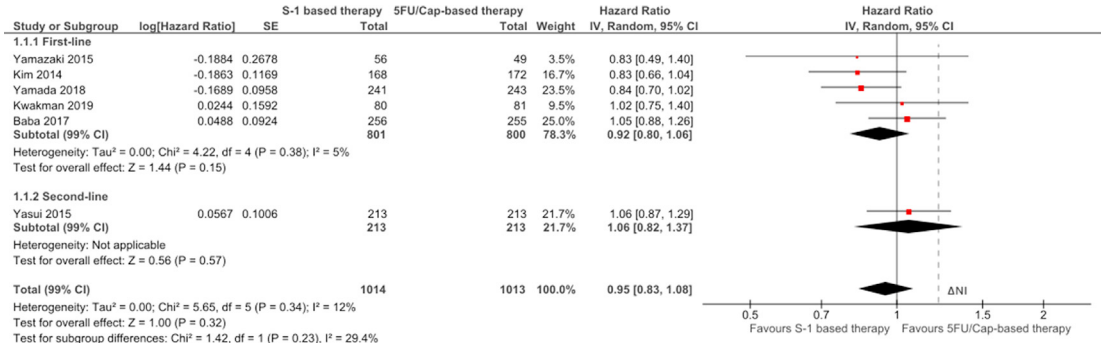

Fig. 2. Forest plot for the comparison S-1-based therapy versus 5-FU/capecitabine-based therapy, outcome PFS. S-1, oral anticancer drug composed of tegafur (FT), 5-chloro-2, 4-dihydroxypyridine (gimestat [CDHP]) and oteracil potassium (Oxo); 5-FU, 5-fluorouracil; Cap, capecitabine; SE, standard error; IV, inverse variance; CI, confidence interval; ΔNI, non-inferiority margin; PFS, progression-free survival.

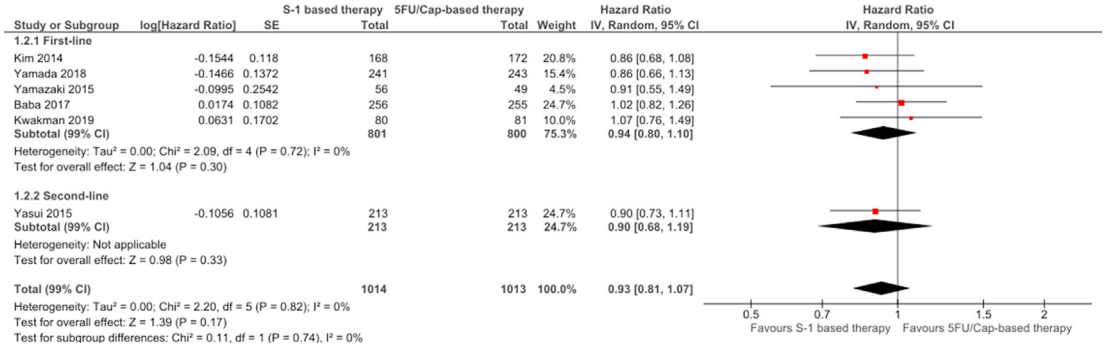

Fig. 3. Forest plot for the comparison S-1-based therapy versus 5-FU/capecitabine-based therapy, outcome OS. S-1, oral anticancer drug composed of tegafur (FT), 5-chloro-2, 4-dihydroxypyridine (gimestat [CDHP]) and oteracil potassium (Oxo); 5-FU, 5-fluorouracil; Cap, capecitabine; SE, standard error; IV, inverse variance; CI, confidence interval; OS, overall survival.

both not influenced by the omission of the study by Yamada *et al.* [16] in which the combination therapy differed between the intervention and control arm.

In addition, median OS (months) per arm was reported by three other studies: two first-line studies [19,21] and one second-line study [24]. An overview of these studies and median OS data are presented in Appendix A5. All three studies reported no statistically significant difference in OS between 5-FU/capecitabine-based therapy versus S-1-based therapy ($P > 0.05$).

3.2.3. Objective response rate

Based on the pooled risk ratio for response, i.e. a complete or partial response to treatment, it was shown that S-1-based therapy is at least as effective as 5-FU/capecitabine-based therapy in terms of ORR (RR_{total} 1.06, 99% CI 0.90–1.24) (Fig. 4). When stratified by treatment line, a pooled $RR_{subgroup}$ of 1.04 (99% CI 0.87–1.25) was observed for first-line treatment and a pooled $RR_{subgroup}$ of 1.19 (99% CI 0.77–1.84) for and second-line treatment. Moderate heterogeneity was detected for ORR ($I^2 = 48\%$, $P = 0.04$).

Sensitivity analyses showed that the direction of the estimator of the RRs for response and its significance were both not influenced by the omission of the studies by Yamada *et al.* [16] and Kato *et al.* [22] that used a different combination therapy in the intervention and control arm and a heterogeneous patient population including both first and second-line treatment, respectively.

3.3. Adverse events of S-1-based therapy versus 5-FU/capecitabine-based therapy

We were able to extract treatment-related toxicity data from five studies that investigated oxaliplatin-containing S-1 combination therapy [19,20,24–26] and three studies that investigated irinotecan-containing S-1 combination therapy [21,22,27].

3.3.1. Oxaliplatin-containing S-1 combination therapy

In total, 12 treatment-related toxicities from oxaliplatin-containing S-1 combination therapies were selected for meta-analysis (Table 2). Significant differences in any grade toxicity between S-1 based therapy and 5-FU/capecitabine-based therapy include leukopenia (RR 0.85, 95% CI 0.76, 0.94), HFS (RR 0.50, 95% CI 0.27, 0.91) and diarrhoea (RR 1.35, 95% CI 1.17, 1.55).

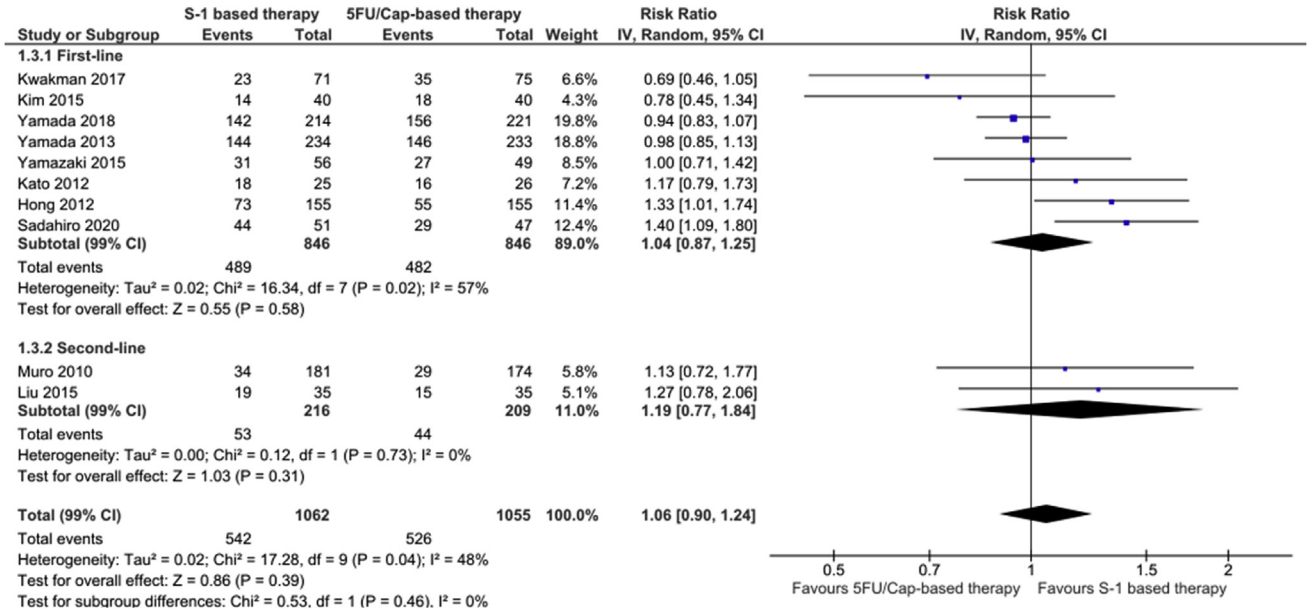

Fig. 4. Forest plot for the comparison S-1-based therapy versus 5-FU/capecitabine-based therapy, outcome ORR. S-1, oral anticancer drug composed of tegafur (FT), 5-chloro-2, 4-dihydroxypyridine (gimestat [CDHP]) and oteracil potassium (Oxo); 5-FU, 5-fluorouracil; Cap, capecitabine; IV, inverse variance; CI, confidence interval; ORR, objective response rate.

Table 2
Any grade and ≥grade 3 treatment-related toxicities of S-1 based versus 5-FU/capecitabine-based therapy, stratified by treatment regimen.

	Any grade toxicities						≥ Grade 3 toxicities					
	S-1 based therapy		5-FU/ capecitabine-based therapy		Effect size [b]	95% CI	S-1 based therapy		5-FU/ capecitabine-based therapy		Effect size [b]	95% CI
	Events	Total	Events	Total	RR		Events	Total	Events	Total	RR	
Oxaliplatin-containing S-1 combination therapy												
Leukopenia	223	552	265	543	0.85	0.76, 0.94	14	552	27	543	0.63	0.28, 1.43
Neutropenia	287	517	318	508	0.87	0.71, 1.06	83	517	136	508	0.50	0.15, 1.66
Thrombocytopenia	333	552	260	543	1.17	0.91, 1.50	55	552	27	543	1.65	0.56, 4.85
Anaemia	190	517	169	508	1.09	0.96, 1.25	27	517	15	508	1.71	0.91, 3.22
Anorexia	354	517	315	508	1.12	0.99, 1.28	33	517	12	508	2.55	1.33, 4.89
Fatigue	266	475	238	466	1.10	0.99, 1.23	23	475	12	466	1.84	0.93, 3.65
Diarrhoea	271	552	199	543	1.35	1.17, 1.55	50	552	20	543	2.41	1.45, 4.02
Nausea	307	552	308	543	0.99	0.89, 1.09	18	552	12	543	1.36	0.65, 2.82
Vomiting	155	496	151	492	1.02	0.87, 1.21	9	496	12	492	0.73	0.30, 1.79
Hand–foot syndrome	66	496	112	492	0.50	0.27, 0.91	2	496	5	492	0.49	0.10, 2.35
Sensory neuropathy	447	552	429	543	1.03	0.98, 1.08	50	552	48	543	1.22	0.44, 3.36
Stomatitis or mucositis	216	552	195	543	1.22	0.85, 1.77	10	552	0	543	5.30	1.16, 24.17
Irinotecan-containing S-1 combination therapy												
Leukopenia	200	290	218	286	0.91	0.82, 1.00	51	290	43	286	1.17	0.81, 1.70
Neutropenia [a]	184	290	228	286	0.80	0.68, 0.94	102	290	125	286	0.80	0.65, 0.98
Thrombocytopenia	84	290	69	286	1.21	0.93, 1.58	1	290	2	286	0.73	0.05, 10.03
Anaemia	193	261	146	258	1.26	1.03, 1.54	23	261	15	258	1.53	0.82, 2.86
Anorexia	194	290	181	286	1.05	0.94, 1.19	29	290	17	286	1.37	0.31, 6,19
Fatigue	196	290	188	286	1.04	0.93, 1.16	19	290	10	286	1.36	0.34, 5.42
Diarrhoea	212	290	167	286	1.17	0.92, 1.49	51	290	17	286	1.86	0.55, 6.35
Nausea	150	290	161	286	0.93	0.77, 1.13	9	290	12	286	0.78	0.14, 4.20
Vomiting	5	80	11	75	0.43	0.04, 4.14	2	80	1	75	1.51	0.19, 11.92
Stomatitis or mucositis	130	290	116	286	1.08	0.70, 1.65	6	290	1	286	6.03	0.73, 49.64
Hypertension	7	80	9	75	0.73	0.28, 1.91	1	80	1	75	0.94	0.10, 8.82

CI, confidence interval; RR, risk ratio. RRs below 1 favour S-1 based therapy, while RRs above 1 favour 5-FU/capecitabine-based therapy. Hand–foot syndrome was not scored in the irinotecan-containing S-1 combination therapy trials

[a] Excluding grade 1 neutropenia for one of the included studies since Kato *et al.* presented G0 and G1 combined.

[b] Pooled effect size as RR from inverse variance random-effects model.

Significant differences in toxicities ≥grade 3 include anorexia (RR 2.55, 95% CI 1.33, 4.89), diarrhoea (RR 2.41, 95% CI 1.45, 4.02) and stomatitis/mucositis (RR 5.30, 95% CI 1.16, 24.17).

3.3.2. Irinotecan-containing S-1 combination therapy

In total, 11 treatment-related toxicities were selected for meta-analysis (Table 2). Significant differences in any grade toxicity between S-1 based therapy and 5-FU/capecitabine-based therapy include neutropenia (RR 0.80, 95% CI 0.68, 0.94) and anaemia (RR 1.26, 95% CI 1.03, 1.54). Toxicities ≥grade 3 were only significant for neutropenia (RR 0.80, 95% CI 0.65, 0.98). Of note, HFS was not evaluated in any of these studies.

Only one study compared mono-chemotherapy of capecitabine with S-1 [10], which showed significantly less any grade and ≥grade 3 HFS but more ≥grade 3 anorexia and any grade diarrhoea in S-1 treated patients.

4. Discussion

We demonstrate non-inferiority for S-1-based systemic regimens compared to 5-FU/capecitabine-based regimens in the treatment of mCRC in terms of PFS. Previous meta-analyses have shown that, besides tolerable toxicity profiles, S-1 is associated with a comparable efficacy as 5-FU/capecitabine-based regimens [4–8]. However, these meta-analyses were limited by either not incorporating the latest evidence or potential bias caused by the inclusion of multiple publications of the same trial. Our updated meta-analysis results confirm previously drawn conclusions and is the first to show that S-1-based therapy is non-inferior to 5-FU/capecitabine-based therapy in the treatment of mCRC regarding PFS. Moreover, we additionally indicated that S-1-based therapy is at least as effective as 5-FU/capecitabine-based therapy in terms of OS and ORR.

Toxicity profiles of fluoropyrimidines and S-1 have already been well-documented. In short, it has been reported that Asian patients treated with S-1 experience less complaints of HFS compared to patients treated with capecitabine [28], which contributes to maintaining daily quality of life, especially since capecitabine can be given as long-term (maintenance) therapy. On the other hand, it was reported that Asian patients treated with S-1 may be at increased risk of any grade diarrhoea compared to capecitabine [5]. Results of the randomised phase III SALTO trial showed that Western mCRC patients treated with S-1 may experience more anorexia, but a lower incidence and severity of HFS compared to capecitabine [10]. Together with the observation that significantly lower rates of dose reductions and higher relative dose intensities occur in Western patients treated with S-1, these findings suggest that S-1 may be better tolerated than capecitabine without compromising on efficacy [11]. Of note, the maximal tolerated dose and the toxicity profile of S-1 differ between Asian and Western patients. Although this ethnic variability is not completely understood, the different dosing schedules result in comparable fluoropyrimidine exposure in blood plasma over time in both ethnic groups [29].

Regarding our analyses on treatment-related adverse events, the data show that S-1-based schedules are associated with less HFS and haematological toxicities, but more anorexia and diarrhoea. In schedules with S-1 in combination with oxaliplatin, a higher incidence of stomatitis/mucositis was observed. These data may allow the selection of the fluoropyrimidine based on physician and patient preference.

Our study has some limitations. First, the majority of included studies were performed in Asian populations. However, given the currently available data on S-1 in metastatic colorectal cancer and the fact that EMA has recently approved the use of S-1 in patients who are intolerant to other fluoropyrimidines, it is not expected that a prospective non-inferiority phase 3 trial in a Western patient population will be of interest to the oncological community and/or will receive appropriate funding. Hence, we do not expect that more evidence from randomised studies in Western patients will become available. Further, in the analysis of ORR, moderate heterogeneity was detected due to variation in the treatment effect potentially caused by features of the population, intervention, or comparator factors. Although results for response rate should be interpreted with caution, we would argue that statistical tests for heterogeneity have limited power—especially in case of $n < 10$ studies—and allow for a more liberal p-value cut-off, e.g. $P < 0.1$, for a decision on clinical heterogeneity [30]. Moreover, nearly all CIs of the included studies contain 1, which supports the main conclusion of non-inferiority of S-1-based therapy versus 5-fluorouracil- or capecitabine-based therapy. A second limitation is that it was not possible to study the influence of individual dosing regimens on the results of our meta-analysis. Although this may further improve precision, most fluoropyrimidine dosing and S-1 dosing regimens were fairly similar among the included studies. Lastly, none of the presented studies included an anti-EGFR antibody therapy. Although the safety and efficacy of S-1 in combination with anti-EGFR antibody therapy has been shown in Asian patients with mCRC [31,32], we suggest that the safety of this combination in Western patients should be further explored given the safety concerns that have been raised by combining

capecitabine with anti-EGFR antibody therapy in Western mCRC patients [33].

It should be noted that we selected a slightly less stringent non-inferiority margin as compared to the previously used margin of 1.23 for the approval of capecitabine [34]. However, to increase preciseness of our meta-analysis results, the pooled HRs are presented with corresponding 99% CIs, and the HR_{total} for PFS – with an upper limit of 1.08 – also remains below the previously used margin of 1.23.

Strengths of this meta-analysis include our methodological approach as we adhered to the AHRQ Methods Research Report on Assessing Equivalence and Non-inferiority, in which it was recommended that meta-analyses including and addressing questions evaluated by non-inferiority trials should additionally assess risk of bias unique to these trials, and in the interpretation of results, these meta-analyses should pre-define and apply a ΔNI [15,35]. In addition, as it is methodologically inappropriate to draw non-inferiority conclusions solely based on statistical significance [36], we considered the study designs of the included studies, evaluated their unique risk of bias issues and interpreted the obtained pooled estimates of our primary outcome using a justified and pre-defined ΔNI.

To conclude, in this meta-analysis of randomised phase II and III clinical trials, it was shown that S-1-based therapy is non-inferior to 5-FU/capecitabine-based therapy in the treatment of mCRC regarding PFS. In addition, S-1-based therapy was shown to be at least as effective as 5-FU/capecitabine-based therapy in terms of ORR and OS. Our results support a switch to S-1 in patients who experience 5-FU/capecitabine-induced severe symptoms of HFS or cardiac toxicity, which indication was recently approved by the EMA.

Ethics approval

Ethics approval is not applicable for the current work.

CRediT author contributions statement

Jeroen W.G. Derksen: Conceptualisation, Methodology, Data curation, Formal analysis, Visualisation, Writing—original draft; Karel C. Smit: Conceptualisation, Methodology, Data curation, Writing—review & editing; Anne M. May: Conceptualisation, Methodology, Supervision, Writing—review & editing; Cornelis J.A. Punt: Conceptualisation, Methodology, Supervision, Writing—review & editing.

Funding

The current work was supported by an unrestricted scientific grant from Nordic Pharma.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jeroen W.G. Derksen and Anne M. May declare institutional financial interests with Nordic Pharma; Cornelis J.A. Punt declares an advisory role for Nordic Pharma; Karel C. Smit reports no competing interests.

Acknowledgements

Not applicable.

Appendix A1. Full search strategies

The following sensitive search strategies were applied to the individual databases.

MEDLINE (PubMed)

((S-1) OR (Teysuno) OR (Tegafur-gimeracil-oteracil)) AND (randomized) AND ((colorectal cancer) OR (colon) OR (rectal))

Embase

'gimeracil plus oteracil potassium plus tegafur' AND randomized AND 'colorectal cancer'

CENTRAL

#1 (S-1) OR (Teysuno) OR (Tegafur-gimeracil-oteracil)
#2 (randomized)
#3 (colorectal cancer) OR (colon) OR (rectal)
#4 #1 AND #2 AND #3

OpenGrey

Using keywords pertaining to population and intervention:

#1 Colorectal cancer S-1
#2 Colon cancer S-1
#3 Rectal cancer S-1
#4 Colorectal cancer Teysuno
#5 Colon cancer Teysuno
#6 Rectal cancer Teysuno

Appendix A2. Publications not obtained

Authors	Title	Year	Journal	Authors contacted
J. Ning *et al.*	Efficacy and safety of s-1 and oxaliplatin (sox) as first-line chemotherapy for metastatic colorectal cancer	2017	Anhui Med Pharm J	Yes
S. Tian *et al.*	Clinical assessment of efficacy and safety of irinotecan combined with s-1 as second-line treatment in patients with metastatic colorectal cancer	2011	J Qiqihar Univ Med	Yes
D. Zhou *et al.*	Clinical Study on S-1 plus Irinotecan in the Treatment of FOLFOX-resistant Advanced Colorectal Cancer	2014	Anti-tumour pharmacy	No, contact information not available
M. Zong *et al.*	Comparison of clinical effectiveness of oxaliplatin plus capecitabine versus oxaliplatin plus S-1 in treatment of advanced colorectal cancer	2018	Tumour	No, contact information not available

Appendix A3. Risk of bias assessment

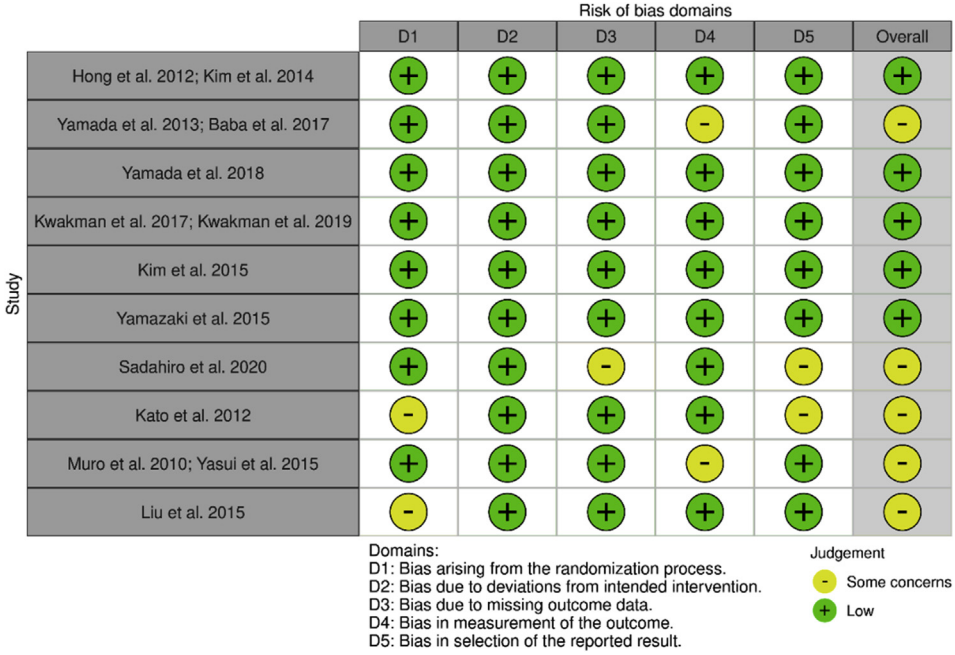

Fig. A4a. Traffic light plot for the RoB2 domains.

Study	E1	E2	E3	E4	E5	E6	E7	E8	Overall
Hong et al. 2012; Kim et al. 2014	Low	Low	Low	Low	Low	Low	Low	Low	Low
Yamada et al. 2013; Baba et al. 2017	Low	Low	Low	Low	Low	Low	Some concerns	Low	Some concerns
Yamada et al. 2018	Low	Low	Low	Low	Low	Low	Some concerns	Low	Some concerns
Kwakman et al. 2017; Kwakman et al. 2019	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kim et al. 2015	NA	NA	NA	NA	NA	NA	NA	NA	NA
Yamazaki et al. 2015	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sadahiro et al. 2020	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kato et al. 2012	NA	NA	NA	NA	NA	NA	NA	NA	NA
Muro et al. 2010; Yasui et al. 2015	Low	Low	Low	Low	Low	Low	Some concerns	Low	Some concerns
Liu et al. 2015	NA	NA	NA	NA	NA	NA	NA	NA	NA

Domains:
E1: Inconsistent application of inclusion/exclusion criteria
E2: Patients selected for anticipated nonresponse or good response in one arm
E3: Poor adherence
E4: Use of concomitant treatments
E5: Protocol violations
E6: Inadequate outcome measurement techniques
E7: Lack of blinding outcomes assessor
E8: Drop out, loss to follow-up

Fig. A4b. Unique non-inferiority design-related risk of bias (AHRQ).

Appendix A4. Funnels plots for assessment of publication bias

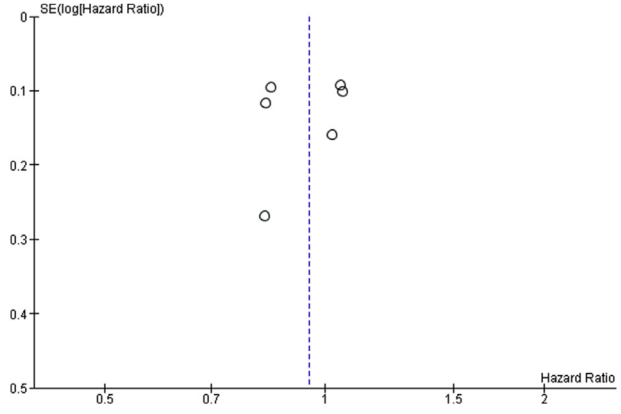

Fig. A4a. Funnel plot of comparison of S-1-based therapy versus regular CTx, outcome PFS.

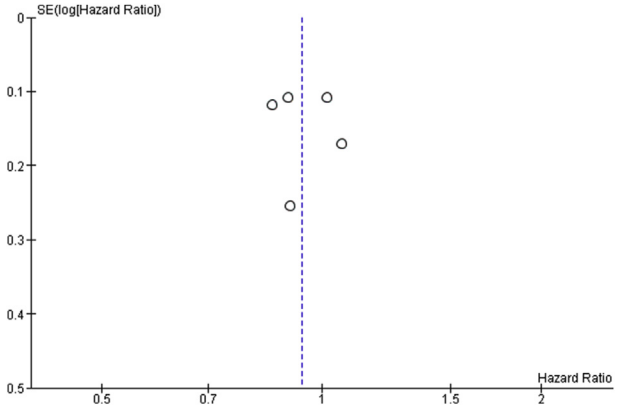

Fig. A4b. Funnel plot of comparison of S-1-based therapy versus regular CTx, outcome OS.

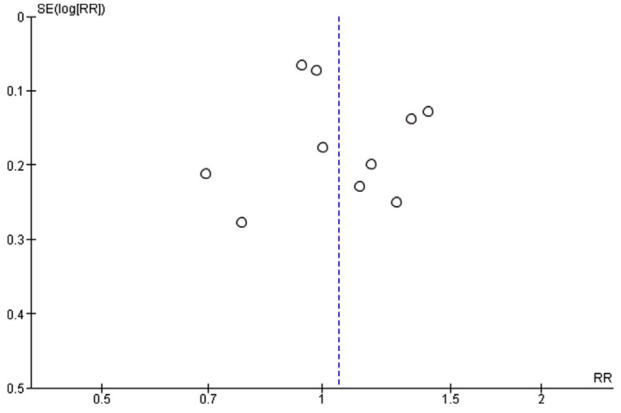

Fig. A4c. Funnel plot of comparison of S-1-based therapy versus regular CTx, outcome ORR.

Appendix A5. Results of included studies only reporting median PFS and/or median OS

Study	Arm	Median PFS (months)	P-value PFS	Median OS (months)	P-value OS
Kim *et al.* 2015 [19]	Cap + Ox	7.4	P = 0. 599	20.1	P = 0.340
	S-1 + Ox	6.1		18.7	
Sadahiro *et al.* 2020 [21]	FOLFIRI + Beva	10.0	P = 0.375	28.8	P = 0.823
	S-1 + IRI + Beva	10.2		29.7	
Kato *et al.* 2012 [22]†	Cap + Ox	10.6	P = 0.71	NR	NR
	S-1 + Ox	11.3		NR	
Liu *et al.* 2015 [24]	mFOLFIRI + Beva	8.2	P > 0.05	19.2	P > 0.05
	S-1 + IRI + Beva	8.5		18.8	

PFS, progression-free survival; OS, overall survival; NR, not reported; † incl. n = 13 (22%) patients treated as second-line.

References

[1] Van Cutsem E, Cervantes A, Adam R, Sobrero A, Krieken van JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27(8):1386–422.

[2] Chiorean EG, Nandakumar G, Fadelu T, Temin S, Alarcon-Rozas AE, Bejarano S, et al. Treatment of patients with late-stage colorectal cancer: ASCO resource-stratified guideline. JCO Glob Oncol 2020;6:414–38.

[3] Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, Hamaguchi T, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol 2020;25(1):1–42.

[4] Ye JX, Liu AQ, Ge LY, Zhou SZ, Liang ZG. Effectiveness and safety profile of S-1-based chemotherapy compared with capecitabine-based chemotherapy for advanced gastric and colorectal cancer: a meta-analysis. Exp Ther Med 2014;7(5):1271–8.

[5] Chen J, Wang J, Xu T. Comparison of efficacy and safety of S-1 and capecitabine in patients with metastatic colorectal carcinoma: a systematic review and meta-analysis. Medicine (Baltimore) 2019;98(30):e16667.

[6] Wang Z, Wang MM, Zhou WL, Ye CY, Dai WP, Liu XL, et al. A meta-analysis of efficacy and safety of S-1 monotherapy or combination therapy as first-line treatment in metastatic colorectal cancer. Int J Colorectal Dis 2020;35(8):1567–74.

[7] Ye JX, Chen JW, Ge LY, Liu AQ, Zhou SZ. Effectiveness and safety of S-1-Based therapy compared with 5-fluorouracil-based therapy for advanced colorectal cancer: a meta-analysis. Gastroenterol Res Pract 2014;2014.

[8] Chen J, Wang J. Efficacy and safety assessment of S-1-based regimens comparing to intravenous fluorouracil-based ones in Asian patients with metastatic colorectal carcinoma: a system review and meta-analysis. Medicine (Baltimore) 2019;98(23):e15999.

[9] Senn SJ. Overstating the evidence: double counting in meta-analysis and related problems. BMC Med Res Methodol 2009;9:10.

[10] Kwakman JJM, Simkens LHJ, Rooijen van JM, Wouw van de AJ, Ten Tije AJ, Creemers GJM, et al. Randomized phase III trial of S-1 versus capecitabine in the first-line treatment of metastatic colorectal cancer: SALTO study by the Dutch Colorectal Cancer Group. Ann Oncol 2017;28(6):1288–93.

[11] Kwakman JJM, Werkhoven van E, Simkens LHJ, Rooijen van JM, Wouw van de YAJ, Ten Tije AJ, et al. Updated survival analysis of the randomized phase III trial of S-1 versus capecitabine in the first-line treatment of metastatic colorectal cancer by the Dutch colorectal cancer group. Clin Colorectal Cancer 2019;18(2):e229–30.

[12] Kwakman JJM, Baars A, Boot H, Pruijt JFM, Winther SB, Pfeiffer P, et al. Tolerability of the oral fluoropyrimidine S-1 after hand-foot syndrome-related discontinuation of capecitabine in western cancer patients. Acta Oncol 2017;56(7):1023–6.

[13] Kwakman JJM, Baars A, Zweeden van AA, Mol de P, Koopman M, Kok WEM, et al. Case series of patients treated with the oral fluoropyrimidine S-1 after capecitabine-induced coronary artery vasospasm. Eur J Cancer 2017;81:130–4.

[14] European Medicines Agency. CHMP post-authorisation summary of positive opinion for Teysuno (II-45). Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/teysuno; 2021.

[15] Treadwell J, Uhl S, Tipton K, Singh S, Santaguida L, Sun X, et al. Assessing equivalence and noninferiority. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Methods Research Report. (Prepared by the EPC Workgroup under Contract No. 290-2007-10063.) AHRQ Publication No. 12-EHC045-EF.

[16] Yamada Y, Denda T, Gamoh M, Iwanaga I, Yuki S, Shimodaira H, et al. S-1 and irinotecan plus bevacizumab versus mFOLFOX6 or CapeOX plus bevacizumab as first-line treatment in patients with metastatic colorectal cancer (TRICOLORE): a randomized, open-label, phase III, noninferiority trial. Ann Oncol 2018;29(3):624–31.

[17] Kim ST, Hong YS, Lim HY, Lee J, Kim TW, Kim KP, et al. S-1 plus oxaliplatin versus capecitabine plus oxaliplatin for the first-line treatment of patients with metastatic colorectal cancer: updated results from a phase 3 trial. BMC Cancer 2014;14.

[18] Baba H, Yamada Y, Takahari D, Matsumoto H, Yoshida K, Nakamura M, et al. S-1 and oxaliplatin (SOX) plus bevacizumab versus mFOLFOX6 plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer: updated overall survival analyses of the open-label, noninferiority, randomised phase III: SOFT study. ESMO Open 2017;2(1).
[19] Kim JH, Zang DY, Chung IJ, Cho SH, Park KU, Oh HS, et al. A muti-center, randomized phase II study of oxaliplatin and S-1 versus capecitabine and oxaliplatin in patients with metastatic colorectal cancer. J Cancer 2015;6(10):1041–8.
[20] Yamazaki K, Kuwano H, Ojima H, Otsuji T, Kato T, Shimada K, et al. A randomized phase II study of combination therapy with S-1, oral leucovorin, and oxaliplatin (SOL) and mFOLFOX6 in patients with previously untreated metastatic colorectal cancer. Cancer Chemother Pharmacol 2015;75(3):569–77.
[21] Sadahiro S, Suzuki T, Okada K, Saito G, Miyakita H, Ogimi T, et al. Oral S-1 with 24-h infusion of irinotecan plus bevacizumab versus FOLFIRI plus bevacizumab as first-line chemotherapy for metastatic colorectal cancer: an open-label randomized phase II trial. Oncology 2020;98(9):637–42.
[22] Kato S, Andoh H, Gamoh M, Yamaguchi T, Murakawa Y, Shimodaira H, et al. Safety verification trials of mFOLFIRI and sequential IRIS plus bevacizumab as first- or second-line therapies for metastatic colorectal cancer in Japanese patients. Oncology 2012;83(2):101–7.
[23] Yasui H, Muro K, Shimada Y, Tsuji A, Sameshima S, Baba H, et al. A phase 3 non-inferiority study of 5-FU/l-leucovorin/irinotecan (FOLFIRI) versus irinotecan/S-1 (IRIS) as second-line chemotherapy for metastatic colorectal cancer: updated results of the FIRIS study. J Cancer Res Clin Oncol 2015;141(1):153–60.
[24] Liu HQ, Wang YG, Li GZ, Song WG, Wang RL. Clinical study of tegafur-gimeracil-oteracil potassium capsule (s-1) and oxaliplatin combination chemotherapy in advanced colorectal cancer. J Cancer Res Therapeut 2015;11(2):331–5.
[25] Yamada Y, Takahari D, Matsumoto H, Baba H, Nakamura M, Yoshida K, et al. Leucovorin, fluorouracil, and oxaliplatin plus bevacizumab versus S-1 and oxaliplatin plus bevacizumab in patients with metastatic colorectal cancer (SOFT): an open-label, non-inferiority, randomised phase 3 trial. Lancet Oncol 2013;14(13):1278–86.
[26] Hong YS, Park YS, Lim HY, Lee J, Kim TW, Kim KP, et al. S-1 plus oxaliplatin versus capecitabine plus oxaliplatin for first-line treatment of patients with metastatic colorectal cancer: a randomised, non-inferiority phase 3 trial. Lancet Oncol 2012;13(11):1125–32.
[27] Muro K, Boku N, Shimada Y, Tsuji A, Sameshima S, Baba H, et al. Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study). Lancet Oncol 2010;11(9):853–60.
[28] Zhang X, Cao C, Zhang Q, Chen Y, Gu D, Shen Y, et al. Comparison of the efficacy and safety of S-1-based and capecitabine-based regimens in gastrointestinal cancer: a meta-analysis. PLoS One 2014;9(1):e84230.
[29] Kwakman JJM, Punt CJA. Oral drugs in the treatment of metastatic colorectal cancer. Expet Opin Pharmacother 2016;17(10):1351–61.
[30] Fletcher J. What is heterogeneity and is it important? Br Med J 2007;334(7590):402.
[31] Samura H, Oki E, Okumura H, Yoshida T, Kai S, Kobayashi K, et al. A phase I/II study of S-1 and irinotecan (IRIS) combined with cetuximab in patients with RAS wild-type metastatic colorectal cancer (KSCC1401). Cancer Chemother Pharmacol 2020;86(2):285–94.
[32] Takahashi T, Emi Y, Oki E, Kobayashi K, Tsuji A, Shimokawa M, et al. Multicenter phase II study of combination therapy with cetuximab and S-1 in patients with KRAS exon 2 wild-type unresectable colorectal cancer previously treated with irinotecan, oxaliplatin, and fluoropyrimidines (KSCC 0901 study). Cancer Chemother Pharmacol 2016;78(3):585–93.
[33] Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet 2011;377(9783):2103–14.
[34] Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 2008;26(12):2006–12.
[35] Treadwell JR, Uhl S, Tipton K, Shamliyan T, Viswanathan M, Berkman ND, et al. Assessing equivalence and noninferiority. J Clin Epidemiol 2012;65(11):1144–9.
[36] Acuna SA, Dossa F, Baxter N. Meta-analysis of noninferiority and equivalence trials: ignoring trial design leads to differing and possibly misleading conclusions. J Clin Epidemiol 2020;127:134–41.
[37] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.