Use of cytokine-induced killer cell therapy in patients with colorectal cancer: a systematic review and metaanalysis

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ABSTRACT

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Dr Kevin Aaron Fenix; kevin.fenix@adelaide.edu.au **Background** The number of clinical studies evaluating the benefit of cytokine-induced killer cell (CIK) therapy, an adoptive immunotherapy, for colorectal cancer (CRC) is increasing. In many of these trials, CIK therapy was coadministered with conventional cancer therapy. The aim of this review is to systematically assess the available literature, in which the majority were only in Chinese, on CIK therapy for the management of CRC using metaanalysis and to identify parameters associated with successful CIK therapy implementation.

Methods Prospective and retrospective clinical studies which compared CIK therapy to non-CIK therapy in patients with CRC were searched for electronically on MEDLINE, Embase, China National Knowledge Infrastructure, and Wanfang Data databases. The clinical endpoints of overall survival (OS), progression-free survival (PFS), OS and PFS rates, overall response rate (ORR), and toxicity were metaanalyzed using HR and relative ratio (RR), and subgroup analyses were performed using chi-square (χ^2) test and I-squared (l^2) statistics for study design, disease stage, cotherapy type, and timing of administration.

Results In total, 70 studies involving 6743 patients were analyzed. CIK therapy was favored over non-CIK therapy for OS (HR=0.59, 95% CI: 0.53 to 0.65), PFS (HR=0.55, 95% CI: 0.47 to 0.63), and ORR (RR=0.65, 95% CI: 0.57 to 0.74) without increasing toxicity (HR=0.59, 95% CI: 0.16 to 2.25). Subgroup analyses on OS and PFS by study design (randomized vs non-randomized study design), disease stage (Stage I-III vs Stage IV), cotreatment with dendritic cells (DCs) (CIK vs DC-CIK therapy), or timing of therapy administration (concurrent vs sequential with coadministered anticancer therapy) also showed that the clinical benefit of CIK therapy was robust in any subgroup analysis. Furthermore, cotreatment with DCs did not improve clinical outcomes over CIK therapy alone. **Conclusion** Compared with standard therapy, patients who received additional CIK cell therapy had favorable outcomes without increased toxicity, warranting further investigation into CIK therapy for the treatment of CRC.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related death worldwide.¹

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cytokine-induced killer cell (CIK) therapy is an adoptive immunotherapy used to treat both solid and hematological cancers for over 20 years. It is predominantly used in China, with multiple studies reporting benefits in patients with colorectal cancer (CRC). Despite this, CIK therapy treatment regimens are not widely used, possibly due in part to the majority of the literature about CIK therapy in CRC being reported in Chinese. Further, CIK therapy is commonly combined with other therapies but it is currently not known if there is a specific combination or treatment regimen that is optimal for CRC.

WHAT THIS STUDY ADDS

⇒ We report the most comprehensive systematic review to date of CIK therapy for patients with CRC, combining both Chinese and English language reports. Patients with CRC who received additional CIK therapy had better survival outcomes than with standard therapy alone. We also showed that the addition of dendritic cells to CIK therapy, common for CRC treatment, did not provide any clinical benefit over CIK therapy alone and that CIK therapy is effective whether given concurrently or sequentially to standard treatment regimens.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our systematic review of Chinese and English publications shows that patients with CRC benefit from the addition of CIK therapy to standard treatment protocols and warrants further international studies.

Patients with locally advanced CRC, including regional lymph node metastases, have a 5-year survival of 75%, which reduces to 15% if there are distant metastases.² Survival outcomes for locally advanced and metastatic CRC have steadily improved due to advancements in surgical techniques, perioperative care, and

therapeutic options. However, tumor recurrence and therapy resistance remain a challenge, creating the need for new treatment options.³

During the last decade, immunotherapy has revolutionized cancer treatment, with clinical efficacy established for multiple solid and hematological cancers.⁴ Immune checkpoint inhibitors have provided significant clinical benefit, particularly in solid cancers with a high tumor mutation burden.⁵ In advanced CRC cases, they have become the standard of care for high microsatellite instability/deficient mismatch repair tumors.⁶⁷ Adoptive immunotherapy involves the administration of immune cells expanded and modified in ex vivo culture. Most treatments have focused on chimeric antigen receptor T (CAR-T) cell therapy. However, other technologies including dendritic cell (DC) therapy, natural killer (NK) cell therapy, and cytokine-induced killer cell (CIK) therapy are being studied. Unlike immune checkpoint inhibitors, none of the adaptive immunotherapy products are Food and Drug Administration approved for CRC treatment.⁸

CIK therapy is an autologous, adoptive immunotherapy generated by expanding a heterogeneous population of immune effector cells from peripheral blood mononuclear cells (PBMCs).⁹ The cell therapy product contains conventional T cells (CD3+CD56-), natural killer (NK)like T cells (CD3+CD56+), and NK cells (CD3-CD56+).¹⁰ NK-like T cells are considered the main effector cells in CIK therapy, being able to recognize tumor cells in a major histocompatibility complex class I unrestricted manner.^{11 12} Hence, guidelines for CIK therapy patient transfusion require that the cell therapy product contain at least 40% of NK-like T cells.¹³ While CIK therapy is normally combined with conventional chemotherapy, multiple trials which combine CIK therapy with other immunotherapies are being investigated. One of the more popular combinations is combining CIK therapy with autologous DC therapy (DC-CIK therapy) with reports suggesting an improvement in antitumor activity.¹⁴ China has been a leader in CIK therapy trials for multiple solid tumors, and CIK therapy is commonly provided for CRC treatment in some Chinese hospi $tals.^{15\,16}$

To date, there is a plethora of publications of varying study quality examining the clinical benefit of CIK therapy for CRC. The latest systematic review investigating the clinical efficacy of CIK therapy with chemotherapy in patients with CRC was published in 2017.¹⁶ Since then more studies have been published that support its clinical benefit,^{17–20} warranting an updated systematic review to consolidate the evidence for CIK therapy in CRC management. Many of the reports originate in China and are written in Chinese. The objective of this work, therefore, is to systematically assess by meta-analysis the available literature on CIK therapy for the management of CRC, written in either English or Chinese. It includes both prospective and retrospective studies and also analyzed the benefit of parameters commonly modified in trials,

such as the addition of DCs (DC-CIK therapy) or chemotherapy regimens.

METHODS

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.²¹

Study selection and search

Studies which compared efficacy of CIK therapy, with or without another anticancer treatment, with no treatment or non-CIK anticancer treatment in adult patients with CRC diagnosis were identified on MEDLINE, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang Data databases. CNKI and Wanfang Data were included as there were multiple studies published in Chinese alone, which were not registered with Embase or MEDLINE. The search strategy for Embase and MEDLINE is described in online supplemental tables S1 and S2, respectively. For CNKI and Wanfang Data, the following search keywords were used: "cytokine-induced killer cells," "CIK," "rectal cancer," "colorectal cancer," "colon cancer," and "clinical trials." No limits were placed on the language in which studies were published and the final search was performed in July 2022. Both prospective and retrospective studies with a parallel-arm design were considered, and the CIK therapy arm included patients who received CIK or DC-CIK (CIK/DC-CIK) therapy. Studies that did not report efficacy endpoints were excluded from this systematic review.

Data extraction and quality assessment

Data collection was performed independently by two authors, and discrepancies were resolved by discussion. For studies reported in Chinese, authors who are native to the Chinese language performed the data extraction and translated them into English for collation. The following information was extracted: (1) study characteristics: study design, study site, and recruitment period; (2) patient and disease characteristics: number of patients, age, gender, primary tumor location, and tumor stage; (3) study intervention: type of CIK therapy and non-CIK anticancer therapy received; (4) clinical efficacy endpoints: overall survival (OS); progression-free survival (PFS); 1-year, 3-year, and 5-year OS rates; 1-year, 3-year, and 5-year PFS rates; and overall response rate (ORR); and (5) toxicity.

For studies where patients received curative-intent treatment, disease-free survival (DFS) and DFS rates were extracted as PFS and PFS rates. Risk of bias was assessed for the following domains and graded as high, low, or unclear: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) imbalance in baseline characteristics, (6) incomplete outcome data, and (7) uniformity of non-CIK/DC-CIK

anticancer treatment administered between intervention and control arms.

Data synthesis and analysis

Review Manager 5.4.1²² was used for pooling data at the study level and statistical analysis. For the multiintervention-arm study, the control arm was split equally into each intervention arm, so that each pairwise comparison can be entered separately. Pooled estimates of effect were expressed as a HR calculated using an inverse variance model for OS and PFS, and risk ratios (RRs) were calculated using the Mantel-Haenszel model for survival rates and ORRs. When individual studies did not describe OS and/or PFS HRs and associated 95% CIs, they were estimated from the published Kaplan-Meier curves using a previously described method.^{23 24} The HR and 95% CI were estimated under the assumption of Gaussian distribution for the study that reported median PFS with a p-value.²⁵

As heterogeneity due to clinical diversity was expected to be high, a random-effects model was used for all the quantitative analyses performed in this review. Heterogeneity across studies was further assessed by visual inspection and statistical using chi-square (χ^2) test and I-squared (I^2) statistics for each analysis. A p-value threshold of 0.10 was employed to determine statistical significance for χ^2 test, and I^2 of 30% or less was considered to be a low degree of heterogeneity, 30% to 60% to be a moderate degree, and 60% or more to be a high degree.

Subgroup analyses were carried out on OS and PFS endpoints to investigate possible sources of heterogeneity. The following subgroup analyses were performed in this review: (1) quality of study design: randomized studies versus non-randomized studies, (2) cancer staging: Stage I–III after resection of primary versus Stage IV (unresectable, metastatic, or recurrent) CRC, (3) CIK therapy type: CIK therapy versus DC-CIK therapy, and (4) CIK therapy administration timing in relation to other anticancer therapy: concurrent versus sequential. The subgroup interactions were tested by using the formal statistical test, χ^2 test, with significance set at 10%.

RESULTS Search results

Through our electronic search, 333 records were identified: 129 from Embase, 38 from MEDLINE, 60 from CNKI, and 106 from Wanfang Data. After removing duplicate publications and studies in which titles and/ or abstracts indicated were ineligible, 106 records were assessed in detail. An additional 36 records were excluded for only a single study arm, lack of information on clinical efficacy endpoints of interest, overlapping patient cohorts with another publication, being unable to extract data specific to patients with CRC, inability to locate original abstracts or full-text articles, patients in all study arms receiving CIK therapy, and patients in the control arm being healthy subjects. Thus, 70 studies containing 16 English^{17–20} ^{26–37} and 44 Chinese²⁶ ^{38–90} language articles were selected for study synthesis (figure 1).

Study and patient characteristics

Standardized study cohorts are summarized in table 1. Two studies^{18 90} were abstracts with the rest being full-text articles. All studies were single-center studies performed in mainland China. Fifty-four studies^{25–27 30 32 34 35 38–40 42–51 53 55–61 63–73 75 76 78–81 83–89 91} were prospective and 15 studies^{17–20 29 33 36 37 41 52 54 62 74 77 82} were retrospective in nature. Of the prospective studies, $38^{18 19}$ 27 28 31 35 36 38 39 43–46 48 49 51 52 56 58 60–62 64–68 71–74 79–82 84 86 88 90

were randomized controlled studies.

Overall, 6743 patients with CRC, 3203 in CIK therapy (intervention) arm, and 3540 in non-CIK therapy (control) arm were available for analysis. The median age ranged from 43.2 to 80.0 years old with the youngest being 18 and the oldest being 92 years old. For studies which provided the patient's gender, 3592 out of 6017 patients (59.7%) were males. Primary tumor location was reported in 30 studies, with 1657 colon and 1744 rectum cancer patients. Patients with CRC diagnosed with all cancer stages were considered for analysis. Three studies evaluated purely patients with Stage III CRC,^{50 52 63} while 29 studies evaluated patients with Stage IV CRC.^{20 26 28 30 35 37 40 44 46 48 51 57 58 60 66-68 73-76 78 82 83 ^{85 87-89} The remaining studies considered patients with multiple stages. Among patients with known cancer stages, 3109 (66.6%) of them had Stage IV disease.}

stages, 3109 (66.6%) of them had Stage IV disease, comprising the largest group followed by 1148 patients (24.5%) with Stage III disease, 375 patients with Stage II disease, and 46 patients with Stage I disease. Cancer staging for the remaining 1672 patients was either unknown or reported in ranges.

Interventions

In 25 studies,¹⁷ ¹⁸ ²⁰ ²⁶ ²⁸ ²⁹ ^{32–36} ³⁸ ³⁹ ⁴⁴ ⁴⁵ ^{47–49} ⁵⁴ ⁵⁶ ⁶³ ⁶⁹ ⁷³ ⁷⁵ ⁸⁵

patients in the intervention arm received CIK therapy, while in 45 studies^{19 25 27 30 31 37 40–43 46 50–53 55 57–62 64–68 70–72 74 76–84}

^{86-89 91} DC-CIK therapy was administered. Chemotherapy was the most common cotreatment with CIK or DC-CIK therapy, being used in 66 studies.^{17-20 25-27 29-53 55-78 80-88 91} The most commonly used chemotherapy regimens were FOLFOX and XELOX, being administered in 43¹⁷ ¹⁸ 26 30-32 34-38 40 42 44 47 49 50 54 56-65 68-70 72-75 77 78 81-84 87 90 and 24¹⁷ 27 28 31 32 34 35 37 39-41 46 57 66 69 71 85 86 88 studies, respectively. Other less commonly used regimens included 5-fluorouracil monotherapy in six studies,^{30 33 36 39 53 77} capecitabine monotherapy in seven studies,^{17 33 36 53 56 75 82} FOLFIRI in eight studies,^{19 20 41 46 74 76 81 86} and FOLFOXIRI in two studies.^{74 86} In total, 2847 patients in the intervention arm and 3033 patients in the control arm were confirmed to have received chemotherapy as a part of the study intervention. In 10 studies, local therapy was administered together with CIK/DC-CIK therapy: radiofrequency ablation in three studies,^{28 74 86} radiotherapy in six studies,^{19 47 50 54 56 77} transarterial chemoembolization in

Identification

Screening

Eligibility Assessment

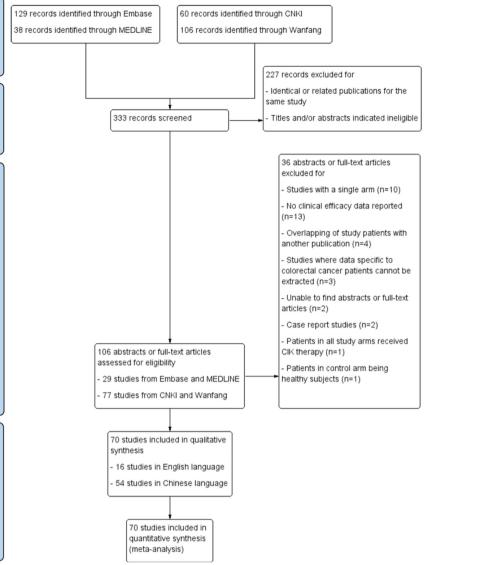


Figure 1 Flow chart of study selection.

nclusion

one study,⁸⁸ and microwave hyperthermia in one study.⁵⁴ In two studies, some or all patients in the intervention arm received CIK/DC-CIK therapy alone.^{41 79}

Risk of bias assessment

Risk of bias assessment is shown in online supplemental figure 1. Among the 38 studies reported to be prospective randomized controlled studies, only nine studies^{27 32 35 43 59 66 70 78 89} described the method of randomization and no study discussed allocation concealment. None of the included studies provided clarity on the blinding of patients, study personnel, or investigators. However, it was considered unlikely that a lack of blinding would affect the clinical efficacy endpoints evaluated in the review, namely OS, PFS, OS rate and PFS rate, and ORR. All the studies were thus assessed to be at low risk of performance and detection bias secondary to insufficient blinding. Demographic and clinical characteristics of patients were generally well-balanced across the studies. Four studies^{18 27 49 58} were at unclear risk of selection bias due to a lack of patient characteristics information across treatment arms. Imbalance in age, cancer stage, and history of primary cancer resection were noted for three studies,^{17 36 37} and they were similarly assessed to be at unclear risk of selection bias. An unclear risk of performance bias due to uncertainty around uniformity of non-CIK/DC-CIK treatment across the intervention and control arms was identified in 21 studies^{18 20 27 30 33 37 41 42 46 50 51 53 56 60 74 77-79 81 82 86} with all the studies except one failing to adequately describe study interventions or the proportion of patients receiving various interventions. In the remaining one study,⁷⁶ patients in the intervention arm received DC-CIK therapy alone, while those in the control arm received the best supportive care. The risk of attrition bias was rated unclear for 18 studies^{17-20 26 28 30 32 34-38 40 66 77 81 83 88} which did not reveal the number of patients lost in follow-up and for one study³⁶ in which 18.8% of patients withdrew from the study prematurely.

	Study	Study	Patient	Age, vears		Colon				
Study ID	type	RCT	(u)	(range)	Male (%)	primary (%)	Stage	Intervention arm(s) (n)	Control arm (n)	Outcomes
Bian e <i>t al⁹¹</i>	٩	Yes	84	39–78	54.8	73.8	Ⅲ .	DC-CIK+ChT (42)	ChT (42)	OS, PFS, ORR, SE
Cai e <i>t al</i> ³⁸	۵.	Yes	80	I	62.5	I	-	CIK+ChT (40)	ChT (40)	OS, PFS, SE
Cai and Li ³⁹	٩	No	72	I	69.4	0.0	≡-	CIK+ChT (40)	ChT (32)	OS, SE
Cai ⁴⁰	٩	No	06	30-70	70.0	1	≥	DC-CIK+ChT (45)	ChT (45)	OS, PFS, SE
Chao <i>et al⁴¹</i>	с	No	66	I	68.2	I	NI-III	DC-CIK±ChT (33)	No treatment or ChT (33)	OS, SE
Chen <i>et al</i> ⁴²	٩	Yes	60	30-65		100.0	∧I-III	DC-CIK+ChT (30)	ChT (30)	OS, PFS, SE
Chen ⁴³	٩	Yes	06	32–76	65.0	I	≡-	DC-CIK+ChT (45)	ChT (45)	OS, PFS
Chu <i>et al⁴⁴</i>	д.	Yes	89	I	51.7	I	≥	CIK (30) and CIK+ChT (29)	ChT (30)	OS, PFS, SE
Deng <i>et al</i> ⁴⁵	۵.	Yes	60	I		1	NI-III	CIK+ChT (30)	ChT (30)	OS, PFS, SE
Dong ⁴⁶	٩	No	40	18-75	52.5	37.5	≥	DC-CIK+ChT (20)	ChT (20)	OS, PFS, SE
Du <i>et al²⁶</i>	٩	Yes	60	I	53.3	68.3	≥	CIK+ChT (30)	ChT (30)	OS, PFS, SE
Fan e <i>t al⁴⁷</i>	д.	Yes	81	32–83		0.0	≡	CIK+ChT+RT (41)	ChT+RT (40)	OS, PFS, ORR, SE
Fang ⁴⁸	٩	Yes	52		59.6	1	≥	CIK+ChT (26)	ChT (26)	ORR, SE
Feng <i>et al</i> ⁴⁹	٩	No	40	51-55	70.0	I	≡-	CIK+ChT (20)	ChT (20)	OS, PFS
Feng and Wang ⁵⁰	д.	Yes	50	41–79	66.0	Ι	≡	DC-CIK+ChRT (25)	ChRT (25)	PFS, ORR, SE
Gao <i>et al²⁷</i>	٩	No	26	I		1	> >	DC-CIK+ChT (13)	No treatment (13)	OS, PFS, SE
Guo and Ma ⁵¹	٩	Yes	68	41–83	57.4	27.9	≥	DC-CIK+ChT (34)	ChT (34)	ORR
He and Zhang ⁵²	щ	I	100	40-80	60.0	1	≡	DC-CIK+ChT (50)	ChT (50)	OS, ORR
Jiang ⁵³	Ъ	No	98	22–78	64.3	I	VI-III	DC-CIK+ChT (50)	ChT (48)	ORR
Leng <i>et al</i> ⁵⁴	£	I	06	29–66	57.8	0.0	N-III	CIK+IMRT+microwave hyperthermia (45)	IMRT+microwave hyperthermia (45)	ORR, SE
Li et a/ ⁵⁵	Ъ	Yes	40	I	70.0	I	-	DC-CIK+ChT (20)	ChT (20)	OS, ORR
Li et a/ ⁵⁶	д.	No	130	I	56.2	43.0	-	CIK+ChT+RT (65)	ChT+RT (65)	ORR, SE
Li et a/ ²⁸		I	60	I	63.3	63.3	≥	CIK+RFA (30)	RFA (30)	ORR, SE
Li et a/ ²⁹	н	I	137	I	60.6	I	NI-II	CIK+ChT (66)	ChT (71)	ORR, SE
Lin et a/ ³⁰	Ъ	Yes	255	I	54.9	56.1	≥	DC-CIK+ChT (134)	ChT (121)	SO
Liu ⁵⁷	٩	Yes	56	32–72	55.4	I	≥	DC-CIK+ChT (28)	ChT (28)	ORR, SE
l iu et al ⁵⁸	۵.	No	18	28-73	55.6	1	≥	DC-CIK+ChT (9)	ChT (9)	ORR, SE

Table 1 Continued	nued									
Study ID	Study type	RCT	Patient (n)	Age, years (range)	Male (%)	Colon primary (%)	Stage	Intervention arm(s) (n)	Control arm (n)	Outcomes
Liu <i>et al</i> ⁶⁰	Ъ	Yes	58	35-80	63.8	I	≥	DC-CIK+ChT (29)	ChT (29)	ORR
Liu <i>et al</i> ⁶¹	д.	Yes	80	22-82	61.3	I	N-I	DC-CIK+ChT (40)	ChT (40)	ORR
Liu et a/ ⁶²	щ	I	06	I	64.4	0.0	N-I	DC-CIK+ChT (45)	ChT (45)	ORR
Lin et a/ ³¹	д.	Yes	70	I	68.6	40.0	N-II	DC-CIK+ChT (35)	ChT (35)	OS, ORR, SE
Liu ⁵⁹	٩	Yes	68	30-79	59.7	69.1	N-III	DC-CIK+ChT (34)	ChT (34)	OS
Lv et al ⁶³	с.	Yes	85	I	51.8	I	≡	CIK+ChT (43)	ChT (42)	ORR, SE
Ma ⁶⁴	Ъ.	Yes	50	49–77	60.0	I		DC-CIK+ChT (25)	ChT (25)	ORR, SE
Niu ⁶⁵	Ъ.	Yes	50	34–62	64.0	1	NI-III	DC-CIK+ChT (25)	ChT (25)	ORR
Pan <i>et al</i> ²⁰	щ	I	252	I	61.5	63.5	≥	CIK+ChT (126)	ChT (126)	OS, PFS
Pan <i>et al</i> ¹⁷	œ	I	122	I	63.9	64.8	N-II	CIK+ChT (60)	ChT (62)	ORR
Peng <i>et al</i> ³²	പ	Yes	46	I	63.0	I	-	CIK+ChT (23)	ChT (23)	ORR
Pu <i>et al</i> ⁶⁶	Ъ.	Yes	98	1	38.8	1	≥	DC-CIK+ChT (49)	ChT (49)	SE
Rui <i>et al⁶⁷</i>	Ъ.	Yes	06	18-60	57.8	53.3	≥	DC-CIK+ChT (45)	ChT (45)	OS, ORR
Sun ⁶⁸	д.	No	60	41–68	51.7	I	≥	DC-CIK+ChT (30)	ChT (30)	OS, ORR, SE
Wang <i>et al</i> ⁶⁹	Ъ.	No	110	I	60.0	63.6		CIK+ChT (55)	ChT (55)	OS, ORR
Wang <i>et al⁷⁰</i>	Ъ.	Yes	104	32-69	58.7	I	NI-III	DC-CIK+ChT (52)	ChT (52)	ORR
Wang <i>et al⁷¹</i>	٩	Yes	68	I	64.1	I	NI-III	DC-CIK+ChT (34)	ChT (34)	OS, ORR, SE
Wang <i>et al</i> ¹⁸	щ	I	377	1		I	1	CIK+ChT (97)	ChT (280)	ORR
Weng <i>et al</i> ⁷²	Ъ.	Yes	235	I	55.3	56.6	NI-III	DC-CIK+ChT (124)	ChT (111)	ORR
Weng <i>et al</i> ⁷³	с.	Yes	96	25-76	59.6	I	≥	CIK+ChT (48)	ChT (48)	ORR
Wu ⁷⁴	щ	I	132	I	66.7	51.5	≥	DC-CIK+ChT+RFA (62)	ChT+RFA (70)	OS
Xie <i>et al</i> ¹⁹	щ	I	142	I	55.6	I	NI-III	DC-CIK+ChT±RT (71)	ChT±RT (71)	OS, ORR
Xu <i>et al</i> ³³	щ	I	116	I	46.6	54.3	NI-II	CIK+ChT (32)*	ChT (82)*	OS, ORR
Yan <i>et al⁷⁵</i>	٩	No	114	I	56.1	I	≥	CIK+ChT (72)	ChT (42)	OS, PFS, ORR
Yin ⁷⁶	٩	No	80	I	61.3	60.0	≥	DC-CIK+ChT (40)	ChT (40)	OS, PFS, ORR
Ying <i>et al⁷⁷</i>	щ	I	102	20-86	54.9	I		DC-CIK+ChT+RT (51)	ChT+RT (51)	PFS, ORR
Yuan <i>et al⁷⁸</i>	д.	Yes	42	45-78	73.8	I	≥	DC-CIK+ChT (21)	ChT (21)	OS
Yue ⁷⁹	с.	Yes	110	1	47.3	53.6	NI-III	DC-CIK (55)	BSC (55)	OS, PFS, ORR
Zang <i>et al</i> ⁸⁰	Ъ.	Yes	06	I	66.7	I	NI-III	DC-CIK+ChT (45)	ChT (45)	OS
Zhang <i>et al⁸¹</i>	٩	Yes	63	24-82	61.9	I	N-III	DC-CIK+ChT (32)	ChT (31)	SO
Zhang <i>et al</i> ³⁴	д.	Yes	60	I	63.3	56.7	> -	CIK+ChT (30)	ChT (30)	OS, SE
										Continued

Table 1 Continued	nued									
	Study		Patient	Patient Age, years			i			
Study ID	type	RCT	(u)	(range)	Male (%)	primary (%)	Stage	Intervention arm(s) (n) Control arm (n)	Control arm (n)	Outcomes
Zhang et al ⁸²	с	I	84	1	54.8	I	≥	DC-CIK+ChT (42)	ChT (42)	OS, PFS, ORR, SE
Zhang <i>et al</i> ²⁵	٩	No	112	I	52.2	52.0	N-III	DC-CIK+ChT (65)	ChT (47)	ORR
Zhang ⁸³	٩	Yes	118	46–78	49.2	I	\geq	DC-CIK+ChT (59)	ChT (59)	OS, PFS
Zhang ⁸⁴	٩	No	06	43–73	67.8	51.1	VI-III	DC-CIK+ChT (45)	ChT (45)	SE
Zhao ⁸⁷	٩	Yes	30	32–67	70.0	I	≥	DC-CIK+ChT (15)	ChT (15)	ORR
Zhao ³⁵	٩	Yes	122	I	67.2	58.7	≥	CIK+ChT (61)	ChT (61)	ORR, SE
Zhao ⁸⁵	٩	Yes	90	40–59	63.3	I	≥	CIK+ChT (45)	ChT (45)	ORR, SE
Zhao <i>et al</i> ⁸⁶	٩	No	148	I	62.8	I	=	DC-CIK+ChT+RFA (73)	ChT+RFA (75)	SO
Zhou ⁸⁹	٩	Yes	60	45-80	68.3	78.3	≥	DC-CIK+ChT (30)	ChT (30)	OS, ORR
Zhou <i>et al⁸⁸</i>	٩	No	06	I		I	≥	DC-CIK+TACE (45)	TACE (45)	ORR, SE
Zhu et al ³⁶	с	I	96	1	57.3	62.1	2-1-1	CIK+ChT (21)	ChT (75)	OS, PFS, ORR, SE
Zhu <i>et al³⁷</i>	œ	I	351	19–92	65.2	30.8	≥	DC-CIK+standard care (100)	Standard care (251)	ORR, SE
*Sixteen and 18 patients in intervention arm and 47 and 35 patients in control arm were treated in ad BSC, best supportive care; ChRT, concurrent chemoradiotherapy; ChT, chemotherapy; ClK, cytokine intensity-modified radiotherapy; n, number; ORR, overall response rate; OS, overall survival; PFS, prc RFA, radiofrequency ablation; RT, radiotherapy; TACE, transarterial chemoembolization; U, unknown.	patients in in irtive care; C d radiothera; ncy ablation	ttervention ar hRT, concur oy; n, numbé ; RT, radiothé	rm and 47 and rent chemora ∍r; ORR, overa ∍rapy; TACE, i	d 35 patients in c diotherapy; ChT, all response rate, transarterial chei	control arm w chemotherar : OS, overall s moembolizati	ere treated in adju y; CIK, cytokine- urvival; PFS, proç on; U, unknown.	uvant and palli induced killer gression-free (*Sixteen and 18 patients in intervention arm and 47 and 35 patients in control arm were treated in adjuvant and palliative setting, respectively. BSC, best supportive care; ChRT, concurrent chemoradiotherapy; ChT, chemotherapy; CIK, cytokine-induced killer cell; DC-CIK, CIK therapy with autologous dendritic cell therapy; IMRT, intensity-modified radiotherapy; n, number; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; P, prospective; R, retrospective; RCT, randomized controlled trial; RFA, radiofrequency ablation; RT, radiotherapy; TACE, transarterial chemoembolization; U, unknown.	n autologous dendritic cell ospective; RCT, randomiz	therapy; IMRT, ed controlled trial;

Α

Study or Subgroup	log[Hazard Ratio]	SE	CIK +/- DC Total	Control Total	Woight	Hazard Ratio IV, Random, 95% Cl	Hazard Ratio IV, Random, 95% Cl
Chao 2016	-0.8675		33	33	2.4%	0.42 [0.23, 0.77]	
3ao 2014	-1.6607		13	13	0.8%	0.19 [0.07, 0.55]	
_i 2015	-0.3857		65	65	5.3%	0.68 [0.46, 1.01]	
_i 2016		0.6892	30	30	0.5%	1.66 [0.43, 6.41]	
_i 2022	-0.5621		66	71	4.0%	0.57 [0.36, 0.90]	_ _
_in 2016	-0.6162		134	121	13.0%	0.54 [0.44, 0.67]	+
iu 2014b	-1,7148		9	9	0.6%	0.18 [0.05, 0.65]	
iu 2016c	-0.1165		45	45	3.9%	0.89 [0.56, 1.41]	<u> </u>
v 2014	-0.2107		43	42	1.3%	0.81 [0.35, 1.87]	
Pan 2020a	-0.7765		126	126	7.0%	0.46 [0.33, 0.64]	
Pan 2020b	-0.9943		60	62	1.7%	0.37 [0.18, 0.77]	
Peng 2017	-1.1087		23	23	0.9%	0.33 [0.12, 0.92]	
Pu 2021	-0.7765		49	49	2.1%	0.46 [0.24, 0.88]	
Rui 2012	-0.5798		45	45	3.9%	0.56 [0.35, 0.90]	
Vang 2019	-0.6675		97	280	4.6%	0.51 [0.34, 0.78]	
Vena 2013	-0.3711		124	111	8.1%	0.69 [0.51, 0.93]	
Vu 2018		0.1949	62	70	5.5%	0.63 [0.43, 0.92]	
(ie 2017		0.1669	71	71	7.1%	0.62 [0.45, 0.86]	
(u 2021	-0.0202		18	35	2.3%	0.98 [0.52, 1.83]	
(in 2013	-0.4005		40	40	4.3%	0.67 [0.43, 1.04]	
ring 2010		0.2919	51	51	2.7%	0.62 [0.35, 1.10]	
Thang 2014	-0.9163		30	30	1.4%	0.40 [0.18, 0.89]	
Zhang 2015	-0.4943		42	42	4.2%	0.61 [0.39, 0.95]	
Zhang 2022	-0.3011		45	45	4.5%	0.74 [0.48, 1.14]	
Zhao 2016		0.1987	61	61	5.3%	0.62 [0.42, 0.92]	
Zhu 2014	-0.6349		100	251	2.4%	0.53 [0.29, 0.97]	
Fest for overall effect	= 0.01; Chi ^z = 28.16, i : Z = 10.68 (P < 0.000		⁹ = 0.30); I ² =	11%			0.01 0.1 10 100 Favours CIK/DC-CIK Favours non-CIK/DC-CIK
			CIK +/- DC	Control		Hazard Ratio	Hazard Ratio
tudy or Subgroup	log[Hazard Ratio]	SE	Total			IV, Random, 95% Cl	IV, Random, 95% Cl
)u 2013	-0.4308	0.199	30	30	5.8%	0.65 [0.44, 0.96]	
∋ao 2014	-1.6094		13	13	1.7%	0.20 [0.07, 0.55]	
.i 2015	-0.2485		65	65	7.1%	0.78 [0.58, 1.05]	
i 2016	-0.5447		30	30	4.5%	0.58 [0.35, 0.96]	
i 2022	-0.5108	0.233	66	71	5.0%	0.60 [0.38, 0.95]	
in 2016	-0.6931		134	121	7.7%	0.50 [0.39, 0.64]	-
iu 2016c	-1.1087		45	45	3.6%	0.33 [0.18, 0.61]	
°an 2020a	-0.5798		126	126	7.2%	0.56 [0.42, 0.75]	
Vang 2019	-0.4813		97	280	6.1%	0.62 [0.43, 0.89]	
Veng 2013	-1.3093		124	111	6.3%	0.27 [0.19, 0.38]	
Vu 2018	-0.5621		62	70	5.9%	0.57 [0.39, 0.83]	
(ie 2017	-0.4943		71	71	5.8%	0.61 [0.41, 0.90]	
(u 2021	-0.5798		16	47	4.0%	0.56 [0.32, 0.98]	
'in 2013			40	40	5.0%	0.68 [0.43, 1.08]	
	-0.3857						
ring 2010	-0.3711	0.2413	51	51	4.8%	0.69 [0.43, 1.11]	
'ing 2010		0.2413			4.8% 1.8%	0.69 [0.43, 1.11] 0.21 [0.08, 0.55]	
/ing 2010 Zhang 2014 Zhang 2015	-0.3711 -1.5606 -0.6539	0.2413 0.4924 0.2477	51 30 42	51 30 42	1.8% 4.7%		
/ing 2010 Zhang 2014 Zhang 2015 Zhang 2022	-0.3711 -1.5606 -0.6539 -0.5276	0.2413 0.4924 0.2477 0.1983	51 30 42 45	51 30	1.8% 4.7% 5.8%	0.21 [0.08, 0.55]	
/ing 2010 Zhang 2014 Zhang 2015 Zhang 2022 Zhao 2016	-0.3711 -1.5606 -0.6539 -0.5276 -0.1863	0.2413 0.4924 0.2477 0.1983 0.1829	51 30 42 45 61	51 30 42 45 61	1.8% 4.7% 5.8% 6.2%	0.21 [0.08, 0.55] 0.52 [0.32, 0.85] 0.59 [0.40, 0.87] 0.83 [0.58, 1.19]	
'ing 2010 Thang 2014 Thang 2015 Thang 2022 Thao 2016	-0.3711 -1.5606 -0.6539 -0.5276 -0.1863	0.2413 0.4924 0.2477 0.1983	51 30 42 45	51 30 42 45	1.8% 4.7% 5.8%	0.21 [0.08, 0.55] 0.52 [0.32, 0.85] 0.59 [0.40, 0.87]	
ring 2010 Chang 2014 Chang 2015 Chang 2022 Chao 2016 Chu 2013 To tal (95% CI)	-0.3711 -1.5606 -0.6539 -0.5276 -0.1863	0.2413 0.4924 0.2477 0.1983 0.1829 0.6014	51 30 42 45 61 21 1169	51 30 42 45 61 75 1424	1.8% 4.7% 5.8% 6.2%	0.21 [0.08, 0.55] 0.52 [0.32, 0.85] 0.59 [0.40, 0.87] 0.83 [0.58, 1.19]	

Figure 2 Comparison of CIK/DC-CIK therapy versus non-CIK/DC-CIK therapy for (A) overall survival (OS) and (B) progression-free survival (PFS). Twenty-six studies involving 3,303 patients and twenty studies involving 2,593 patients contributed data to OS and PFS analysis respectively. CIK, cytokine-induced killer cell; DC, dendritic cell.

Overall survival and progression-free survival

There were 26 studies^{17 19 20 27 29 32 33 36 38 39 41 43 47 48 53 55–57 60 63 67 75 77 79 81 86}

⁶⁰ ⁶³ ⁶⁷ ⁷⁵ ⁷⁷ ⁷⁹ ⁸¹ ⁸⁶ involving 3303 patients which contributed data to the meta-analysis on OS (figure 2A). The pooled HR was 0.59 (95% CI: 0.53 to 0.65) indicating the OS benefit of CIK/DC-CIK therapy over the control arm. Heterogeneity among the studies was low (I^2 =11%, p=0.30). For PFS, 20 studies^{18–20} ^{26–30} ^{33–36} ⁵⁶ ⁶² ⁷² ⁷⁴ ⁷⁶ ⁷⁷ ⁸² ⁸⁴ involving 2593 patients contributed the data to the meta-analysis (figure 2B). The pooled HR was 0.55 (95% CI: 0.47 to 0.63), again favoring CIK/DC-CIK therapy. Heterogeneity among the studies was moderate (I^2 =54%, p=0.002).

Overall survival rates

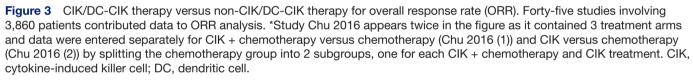
In total, 27 (2459 patients), ¹⁷ ¹⁹ ²⁰ ²⁷ ²⁹ ³² ³³ ³⁶ ³⁸ ³⁹ ⁴¹ ⁴³ ⁴⁷⁻⁴⁹ ⁵³ ⁵⁵⁻⁵⁷ ⁶⁰ ⁶³ ⁶⁷ ⁷⁵ ⁷⁷ ⁷⁹ ⁸¹ ⁸⁶ ¹⁹ (2167 patients), ¹⁷⁻²⁰ ²⁷⁻²⁹ ³³ ³⁵ ³⁶ ³⁸ ³⁹ ⁴¹ ⁴⁸ ⁴⁹ ⁵⁶ ⁶⁷ ⁷⁷ ⁸⁶ and 10 (1401 patients) ¹⁷⁻²⁰ ²⁷ ²⁹ ³³ ³⁶ ⁴¹ ⁵⁶ studies contributed data for 1-year, 3-year, and 5-year OS rate meta-analyses, respectively (online supplemental figure 2). The pooled RR for all the analyses favored CIK/DC-CIK therapy. The 1-year OS rate was 91.7% in the intervention arm and 79.4% in

the control arm with a pooled RR of 0.47 (95% CI: 0.32 to 0.67). Heterogeneity among the studies was moderate (\vec{I} =51%, p=0.002). The 3-year OS rate was 67.7% in the intervention arm and 51.8% in the control arm with a pooled RR of 0.67 (95% CI: 0.59 to 0.77). There was a moderate level of heterogeneity among the studies (\vec{I} =32%, p=0.09). The 5-year OS rate was 61.2% in the intervention arm and 45.5% in the control arm with an RR of 0.69 (95% CI: 0.54 to 0.88). Heterogeneity among the studies was high (\vec{I} =73%, p=0.0001).

Progression-free survival rates

We identified 10 (1166 patients), ^{17 19 20 27 29 33 36 37 56 77} 10 (1156 patients), ^{17 19 20 27 29 33 35 56 77} and 7 (872 patients) studies^{17 19 20 27 29 33 56} that contributed data for metaanalysis on 1-year, 3-year, and 5-year PFS rates, respectively (online supplemental figure 3). All the analyses indicated the superiority of CIK/DC-CIK therapy over non-CIK/DC-CIK therapy. The observed 1-year PFS rate was 86.5% in the intervention arm and 68.1% in the control with the pooled RR of 0.43 (95% CI: 0.33 to 0.55). Heterogeneity among the studies was low (I^2 =0%, p=0.48). The 3-year PFS rate was 47.8% in the

~	CIK +/-		Contr			Risk Ratio (Non-event)	Risk Ratio (Non-event)
Study or Subgroup			Events		-	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bian 2013	29	42	21	42	2.2%	0.62 [0.36, 1.07]	
Cai 2017	28	45	15	45	2.6%	0.57 [0.37, 0.87]	
Chen 2014a	16	30	13	30	2.4%	0.82 [0.50, 1.35]	
Chen 2014b	35	50	21	50	2.4%	0.52 [0.32, 0.84]	
Chu 2016 (1)	25	29	8	15	1.1%	0.30 [0.10, 0.85]	
Chu 2016 (2)	16	30	7	15	2.0%	0.88 [0.48, 1.61]	
Deng 2018	27	30	18	30	1.0%	0.25 [0.08, 0.80]	
Dong 2018	6	20	5	20	2.7%	0.93 [0.64, 1.37]	
Du 2013	12	30	11	30	2.7%	0.95 [0.64, 1.41]	
Fan 2013	38	41	30	40	0.9%	0.29 [0.09, 0.99]	
Feng 2017	22	25	16	25	0.9%	0.33 [0.10, 1.09]	
Guo 2019	27	34	20	34	1.6%	0.50 [0.23, 1.08]	
He 2018	43	50	31	50	1.6%	0.37 [0.17, 0.80]	
Jiang 2016	34	50	19	48	2.5%	0.53 [0.33, 0.84]	
Leng 2016	43	45	37	45	0.7%	0.25 [0.06, 1.11]	
Liu 2016a	24	29	15	29	1.4%	0.36 [0.15, 0.86]	
Liu 2016b	24	40	23	40	2.3%	0.94 [0.56, 1.59]	
Liu 2016c	14	45	10	45	3.1%	0.89 [0.69, 1.14]	-
Liu 2019	21	35	11	35	2.5%	0.58 [0.37, 0.93]	
Liu 2020	29	34	20	34	1.4%	0.36 [0.14, 0.88]	
Lv 2014	29	43	26	42	2.1%	0.85 [0.48, 1.52]	
Ma 2019	21	25	12	25	1.2%	0.31 [0.12, 0.81]	
Niu 2016	17	25	9	25	1.9%	0.50 [0.26, 0.95]	
Pu 2021	33	49	18	49	2.5%	0.52 [0.33, 0.81]	
Sun 2020	26	30	20	30	1.1%	0.40 [0.14, 1.14]	
Wang 2014	36	55	28	55	2.5%	0.70 [0.45, 1.11]	
Wang 2016	28	52	22	52	2.7%	0.80 [0.55, 1.16]	
Wang 2017	20	34	10	34	2.5%	0.58 [0.37, 0.92]	
Weng 2013	40	124	25	111	3.3%	0.87 [0.75, 1.02]	*
Weng 2014	9	48	5	48	3.3%	0.91 [0.77, 1.07]	-
Wu 2018	38	62	19	70	2.8%	0.53 [0.38, 0.75]	
Yan 2014	32	74	10	42	3.1%	0.74 [0.57, 0.97]	
Yin 2013	15	40	9	40	3.0%	0.81 [0.60, 1.08]	
Yuan 2016	9	20	7	20	2.3%	0.85 [0.51, 1.41]	
Yue 2016	1	55	0	55	3.4%	0.98 [0.93, 1.03]	1 I I I I I I I I I I I I I I I I I I I
Zang 2019	40	45	31	45	1.3%	0.36 [0.14, 0.91]	
Zhang 2011	21	32	13	31	2.2%	0.59 [0.34, 1.04]	
Zhang 2015	19	42	12	42	2.8%	0.77 [0.55, 1.07]	
Zhang 2016	30	65	21	47	2.8%	0.97 [0.69, 1.37]	
Zhang 2017	32	59	20	59	2.9%	0.69 [0.50, 0.97]	
Zhao 2015	15	15	15	15		Not estimable	
Zhao 2016	10	54	4	51	3.3%	0.88 [0.76, 1.03]	-
Zhao 2018	43	45	35	45	0.7%	0.20 [0.05, 0.86]	
Zhao 2019	47	73	10	75	2.9%	0.41 [0.30, 0.57]	
Zhou 2015	14	30	9	30	2.6%	0.76 [0.51, 1.15]	
Zhou 2016	21	45	10	45	2.9%	0.69 [0.50, 0.94]	
Total (95% CI)		1975		1885	100.0%	0.65 [0.57, 0.74]	♦
Total events	1159		751				
Heterogeneity: Tau² =				44 (P =	0.00001)	; I² = 85%	
Test for overall effect:	Z = 6.28 ((P < 0.0	00001)				Favours CIK/DC-CIK Favours non-CIK/DC-CIK



intervention arm and 30.5% in the control arm. The pooled RR was 0.76 (95% CI: 0.66 to 0.87) and heterogeneity among the studies was moderate ($I^2=53\%$, p=0.02). At 5 years, the PFS rate was 46.0% in the intervention arm and 25.9% in the control arm. The pooled RR was 0.71 (95% CI: 0.59 to 0.87) and heterogeneity among the studies was high ($I^2=68\%$, p=0.005).

Overall response rate

The ORR was 58.7% in the intervention (CIK/DC-CIK) and 39.8% in the control (non-CIK/DC-CIK) arm for 3860 patients from 45 studies²⁵²⁶³¹³⁵⁴⁰⁴²⁻⁴⁷⁵⁰⁻⁵⁴⁵⁹⁻⁶⁶⁶⁸⁻⁷⁶⁷⁸⁻⁸³⁸⁵⁻⁸⁹⁹¹ (figure 3). The pooled RR was 0.65 (95% CI: 0.57 to 0.74), and heterogeneity among the studies was high (I^2 =85%, p<0.00001).

Toxicity

Toxicity during the study intervention was reported by 31 studies with the majority of the data being provided in a descriptive manner. Two studies^{18 85} compared the rate of any adverse events between the treatment arms, and 11 studies^{30 35 39 40 42 54 59 60 68 70 87 91} reported adverse events of interest for each arm. Many of the described side effects

were thought to be related to chemotherapy administered together with CIK/DC-CIK therapy, including bone marrow suppression, nausea, vomiting, neuropathy, diarrhea, and liver dysfunction. Meta-analysis undertaken indicated equivalent adverse event rate from CIK/DC-CIK and non-CIK/DC-CIK therapy (HR=0.59, 95% CI: 016 to 2.25) with the pooled adverse event rate of 53.5% and 68.3%, respectively (online supplemental figure 4). Heterogeneity was high between the studies (I²=80%, p=0.02). Fever was the most frequently reported adverse event associated with CIK/DC-CIK infusion, affecting 6.7% to 29.9% of patients receiving CIK/DC-CIK therapy. Fever, in general, spontaneously resolved or only required symptomatic management.

Subgroup analyses

Potential sources of heterogeneity were explored by performing subgroup analysis on OS and PFS by study design (randomized vs non-randomized study design), disease stage (Stage I–III vs Stage IV), CIK therapy type (CIK vs DC-CIK therapy), or timing of CIK/DC-CIK therapy administration (concurrent vs sequential with coadministered anticancer therapy).

Randomized studies versus non-randomized studies

Of the 25 studies which provided OS HRs, 8 studies 30 32 34 35 63 66 67 72 involving 991 patients were prospective randomized studies and 17 studies $^{17-20}$ 27 29 33 37 41 56 58 62 74 76 77 82 84 involving 2252

patients were either prospective non-randomized or retrospective studies. An OS benefit of CIK/DC-CIK therapy was demonstrated for both randomized studies (HR=0.57; 95% CI: 0.50 to 0.66) and non-randomized studies (HR=0.59, 95% CI: 0.51 to 0.67) (figure 4A). A test for

			CIK +/- DC	Control		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2.2.1 Randomised							
Lin 2016	-0.6162	0.1101	134	121	14.3%	0.54 [0.44, 0.67]	-
Lv 2014	-0.2107	0.4281	43	42	1.2%	0.81 [0.35, 1.87]	
Peng 2017	-1.1087	0.5231	23	23	0.8%	0.33 [0.12, 0.92]	
Pu 2021	-0.7765	0.3319	49	49	2.0%	0.46 [0.24, 0.88]	
Rui 2012	-0.5798	0.2398	45	45	3.8%	0.56 [0.35, 0.90]	
Weng 2013	-0.3711	0.1542	124	111	8.3%	0.69 [0.51, 0.93]	
Zhang 2014	-0.9163	0.4074	30	30	1.4%	0.40 [0.18, 0.89]	
Zhao 2016	-0.478	0.1987	61	61	5.3%	0.62 [0.42, 0.92]	
Subtotal (95% CI)			509	482	37.2%	0.57 [0.50, 0.66]	•
Heterogeneity: Tau ² =	= 0.00; Chi ² = 4.89, df	= 7 (P =	0.67); l² = 09	%			
Test for overall effect	Z = 7.69 (P < 0.0000)1)					
2.2.2 Non-randomise	ed						
Chao 2016	-0.8675	0.3072	33	33	2.4%	0.42 [0.23, 0.77]	
Gao 2014	-1.6607		13	13	0.8%	0.19 [0.07, 0.55]	
Li 2015	-0.3857		65	65	5.3%	0.68 [0.46, 1.01]	
Li 2022	-0.5621		66	71	3.9%	0.57 [0.36, 0.90]	
Liu 2014b	-1,7148		9	9	0.5%	0.18 [0.05, 0.65]	
Liu 2016c	-0.1165		45	45	3.9%	0.89 [0.56, 1.41]	
Pan 2020a	-0.7765		126	126	7.1%	0.46 [0.33, 0.64]	
Pan 2020b	-0.9943		60	62	1.6%	0.37 [0.18, 0.77]	
Wang 2019	-0.6675		97	280	4.6%	0.51 [0.34, 0.78]	_ _
Wu 2018		0.1949	62	70	5.5%	0.63 [0.43, 0.92]	
Xie 2017		0.1669	71	71	7.3%	0.62 [0.45, 0.86]	
Xu 2021	-0.0202		18	35	2.2%	0.98 [0.52, 1.83]	
Yin 2013	-0.4005		40	40	4.2%	0.67 [0.43, 1.04]	
Yina 2010		0.2919	51	51	2.6%	0.62 [0.35, 1.10]	
Zhang 2015	-0.4943		42	42	4.1%	0.61 [0.39, 0.95]	
Zhang 2022	-0.3011		45	45	4.4%	0.74 [0.48, 1.14]	_ _
Zhu 2014	-0.6349		100	251	2.4%	0.53 [0.29, 0.97]	
Subtotal (95% CI)	0.0040	5.0011	943	1309	62.8%	0.59 [0.51, 0.67]	◆
Heterogeneity: Tau ² = Test for overall effect			= 0.18); I ² =	23%			
Total (95% CI)			1452	1791	100.0%	0.58 [0.53, 0.64]	•
Heterogeneity: Tau ² =	- 0.00 [,] Chiế - 26.97	4f - 24 /0			.00.070	5.55 [0.55, 0.04]	· · · · · · · · · · · · · · · · · · ·
			= 0.30), I*=	/ 70			0.01 0.1 1 10
Test for overall effect Test for subgroup dif							Favours CIK/DC-CIK Favours non-CIK/DC-CIK

В

_			CIK +/- DC	Control		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2.4.1 Randomised							
Du 2013	-0.4308	0.199	30	30	6.0%	0.65 [0.44, 0.96]	
Lin 2016	-0.6931	0.1268	134	121	8.0%	0.50 [0.39, 0.64]	-
Weng 2013	-1.3093	0.1793	124	111	6.5%	0.27 [0.19, 0.38]	- - -
Zhang 2014	-1.5606	0.4924	30	30	1.9%	0.21 [0.08, 0.55]	
Zhao 2016	-0.1863	0.1829	61	61	6.4%	0.83 [0.58, 1.19]	
Subtotal (95% CI)			379	353	29.0 %	0.47 [0.31, 0.72]	◆
Heterogeneity: Tau ² =	= 0.18; Chi ² = 24.32, (df=4 (P <	0.0001); P	= 84%			
Test for overall effect:	Z = 3.48 (P = 0.0005	5)					
2.4.2 Non-randomise	ed						
Gao 2014	-1.6094	0.5161	13	13	1.8%	0.20 [0.07, 0.55]	
Li 2015	-0.2485	0.1512	65	65	7.3%	0.78 [0.58, 1.05]	
Li 2022	-0.5108	0.233	66	71	5.2%	0.60 [0.38, 0.95]	_
Liu 2016c	-1.1087	0.3093	45	45	3.8%	0.33 [0.18, 0.61]	
Pan 2020a	-0.5798	0.1468	126	126	7.4%	0.56 [0.42, 0.75]	
Wang 2019	-0.4813	0.1874	97	280	6.3%	0.62 [0.43, 0.89]	
Wu 2018	-0.5621	0.1936	62	70	6.2%	0.57 [0.39, 0.83]	
Xie 2017	-0.4943	0.1984	71	71	6.1%	0.61 [0.41, 0.90]	
Xu 2021	-0.5798	0.2855	16	47	4.2%	0.56 [0.32, 0.98]	
Yin 2013	-0.3857	0.2338	40	40	5.2%	0.68 [0.43, 1.08]	
Ying 2010	-0.3711	0.2413	51	51	5.1%	0.69 [0.43, 1.11]	
Zhang 2015	-0.6539	0.2477	42	42	4.9%	0.52 [0.32, 0.85]	_
Zhang 2022	-0.5276	0.1983	45	45	6.1%	0.59 [0.40, 0.87]	
Zhu 2013	-1.273	0.6014	21	75	1.4%		
Subtotal (95% CI)			760	1041	71.0%	0.59 [0.52, 0.67]	•
Heterogeneity: Tau ² =	= 0.00; Chi ² = 14.19, (df = 13 (P	= 0.36); I ^z =	8%			
Test for overall effect	Z = 8.55 (P < 0.0000	01)					
Total (95% CI)			1139	1394	100.0%	0.54 [0.47, 0.63]	•
Heterogeneity: Tau ² =	= 0.06; Chi ² = 41.69, (df = 18 (P	= 0.001); l ²	= 57%			
Test for overall effect:							0.01 0.1 1 10 100 Favours CIK/DC-CIK Favours non-CIK/DC-CIK
Test for subaroup dif			= 0.31), ² =	= 4.5%			Favours CINDC-CIK Favours non-CINDC-CIK

Figure 4 Subgroup analysis by study design for (A) overall survival (OS) and (B) progression-free survival (PFS). Twenty-five studies involving 3,243 patients and nineteen studies involving 2,533 patients contributed data to OS and PFS analysis respectively.

subgroup difference did not reach statistical significance (I^{2} =0%, p=0.80). For PFS subgroup analysis, 732 patients from five randomized studies^{26 30 34 35 72} and 1801 patients from 14 non-randomized studies^{18–20 27 29 33 36 56 62 74 76 77 82 84} were analyzed. A benefit from CIK/DC-CIK therapy was again shown for both prospective randomized (HR=0.47, 95% CI: 0.31 to 0.72) and non-randomized studies (HR=0.59, 95% CI: 0.47 to 0.63) (figure 4B). A test for subgroup differences was not statistically significant (I^{2} =4.5%, p=0.31).

Stage I-III versus Stage IV

Four studies^{32 56 63 77} involving 363 patients with Stage I– III CRC and 12 studies^{20 28 30 33 35 37 58 66 67 74 76 82} involving 1595 Stage IV patients contributed data to the subgroup analysis on OS by the disease stage. HR for Stage I-III patients was 0.64 (95% CI: 0.48 to 0.85), while that for Stage IV patients was 0.57 (95% CI: 0.50 to 0.65) and the benefit of CIK/DC-CIK therapy was observed across all stages of CRC (online supplemental figure 5A). Test for subgroup differences failed to reach statistical significance ($I^2=0\%$, p=0.48), although the observed 95% CI was much narrower for Stage IV patients. For the subgroup analysis on PFS, four studies^{27 33 56 77} involving 321 patients with Stage I-III disease and eight studies^{20 26 28 30 35 74 76 82} involving 1045 Stage IV patients were analyzed. A benefit from CIK/DC-CIK therapy was demonstrated for both Stage I-III (HR=0.60, 95% CI: 0.40 to 0.88) and Stage IV disease (HR=0.59, 95% CI: 0.52 to 0.67) (online supplemental figure 5B). A test for subgroup difference was not statistically significant $(I^2 = 0\%, p = 0.94).$

CIK therapy versus DC-CIK therapy

Ten studies 17 18 20 28 29 29 32 34 35 56 63 (1391 patients) and 16 studies^{19 27 30 33 37 41 58 62 66 67 72 74 76 77 82 84} (1912 patients) which evaluated CIK and DC-CIK therapy, respectively, were assessed in the subgroup analysis on OS by the type of CIK therapy. HR for studies examining CIK therapy was 0.57 (95% CI: 0.47 to 0.69), while that for studies examining DC-CIK therapy was 0.61 (95% CI: 0.54 to 0.69) (figure 5A). Both types of CIK therapy were found to benefit OS. A test for subgroup differences did not reach statistical significance ($\vec{I}=0\%$, p=0.58). Subgroup analysis on PFS by CIK therapy type contained nine studies 18 20 26 28 29 $^{34-36}$ 56 involving 1294 patients, where the intervention arm contained CIK therapy, and 11 studies^{19 27 30 33 62 72 74 76 77 82 84} involving 1299 patients, where the intervention arm contained DC-CIK therapy. PFS benefit was demonstrated for both CIK-examining (HR=0.63, 95% CI: 0.53 to 0.74) and DC-CIK-examining studies (HR=0.50, 95% CI: 0.41 to 0.61) (figure 5B). A test for subgroup differences met statistical significance $(I^2=66.5\%, p=0.08)$ with improved HR seen for DC-CIK, although HRs for the two subgroups overlapped each other, suggesting that the advantage of DC-CIK over CIK therapy alone may not be clinically meaningful.

Concurrent CIK/DC-CIK therapy versus sequential CIK/DC-CIK therapy

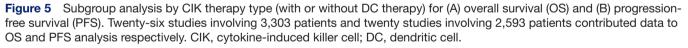
Subgroup analysis was performed comparing studies where CIK/DC-CIK therapy was administered either concurrently or sequentially with the non-CIK/DC-CIK therapy. For OS analysis, 16 studies^{19 20 28 33 35 37 41 56 58 62 63 67 72 74 82 84} involving 2000 patients with concurrent administration and 8 studies^{17 27 29 30 32 34 66 77} involving 846 patients with sequential administration were considered (figure 6A). CIK/DC-CIK therapy administered in either manner improved OS; the HR was 0.63 (95% CI: 0.56 to 071) for concurrent administration and 0.59 (95% CI: 0.53 to 0.65) for sequential administration. A test for subgroup differences reached statistical significance ($I^2=76.3\%$, p=0.04) with lower HR being observed for sequential administration, although 95% CIs of the two subgroups overlapped each other. Subgroup analysis on PFS was similarly in favor of CIK/DC-CIK therapy for both concurrent (HR=0.56, 95% CI: 0.46 to 0.67) and sequential administration (HR=0.54, 95% CI: 0.46 to 0.63) (figure 6B). Twelve studies^{19 20 26 28 33 35 56 62 72 74 82 84} involving 1460 patients who had concurrent administration and five studies^{27 29 30 34 77} involving 580 patients who had sequential administration were evaluated, and a test for subgroup differences did not meet statistical significance ($\Gamma = 0\%$, p=0.43).

DISCUSSION

Chemotherapy with/without biological therapy remains the standard treatment for patients with CRC with the high-risk resected disease, and the majority of those with advanced disease. This therapeutic approach is associated with limited survival benefit, unlike immunotherapy, which has demonstrated long-term survival outcome in some solid tumors owing to its mechanism of action.^{92 93} New therapeutic approaches which involve modulation of the immune system may provide new treatment options for a broader range of patients with CRC and improve their survival outcome. Autologous adoptive immunotherapy such as CIK therapy represents a highly personalized cancer treatment. While it remains a non-standard treatment option for solid cancers, there are a growing number of clinical trials examining such immunotherapy.⁹⁴

Our study demonstrated that providing CIK or DC-CIK therapy to patients with CRC improved OS, PFS, and ORR compared to standard treatment. The upper 95% CI of pooled HRs for 5-year OS rate and 3-year and 5-year PFS rates exceeded 0.85, a commonly applied cut-off to delineate no effect from an important effect, raising the possibility that the observed benefit for these endpoints may not be precise. However, for all the other endpoints, the observed HRs favoring CIK/DC-CIK therapy appeared robust. The OS and PFS benefit of CIK/ DC-CIK therapy persisted when prospective randomized studies alone were examined in the subgroup analysis, with no subgroup differences being identified compared with non-randomized studies. While the number of Δ

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Study or Subgroup	log[Hazard Ratio]	SE	CIK +/- DC (Total		Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% Cl
4.1.1 CIK	iog[nazaru Kato]	3L	Total	Total	weight	IV, Nanuolii, 55% Ci	IV, Randoll, 55% CI
Li 2015	-0.2485	0 1512	65	65	7.7%	0.78 [0.58, 1.05]	
Li 2016		0.6892	30	30	0.6%	1.66 [0.43, 6.41]	
Li 2022	-0.5621		66	71	4.0%	0.57 [0.36, 0.90]	
Lv 2014	-0.2107		43	42	1.4%		
Pan 2020a	-0.2107	0.4281	43	42	6.7%	0.81 [0.35, 1.87] 0.46 [0.33, 0.64]	
Pan 2020a Pan 2020b	-0.7785	0.3739	60	62	1.8%	0.37 [0.18, 0.77]	
Pan 20200 Peng 2017	-0.9943	0.3739	23	23	1.8%	0.33 [0.18, 0.77]	
			23 97	23	1.0%		
Nang 2019	-0.6675					0.51 [0.34, 0.79]	
Zhang 2014	-0.9163		30	30	1.5%	0.40 [0.18, 0.89]	
Zhao 2016 Subtatal (OEV, CD	-0.478	0.1987	61 601	61 790	5.2% 34.4%	0.62 [0.42, 0.92]	
Subtotal (95% CI) Heterogeneity Tau ² =	= 0.03; Chi² = 12.54, d	- ∀f= 0 /Ρ -			34.4%	0.57 [0.47, 0.69]	•
Test for overall effect:			- 0.10),1 - 2	0.10			
.1.2 DC+CIK	0.0075						
Chao 2016	-0.8675		33	33	2.6%	0.42 [0.23, 0.77]	
3ao 2014	-1.6607		13	13	0.9%	0.19 [0.07, 0.55]	
_in 2016	-0.6162		134	121	11.0%	0.54 [0.44, 0.67]	• •
_iu 2014b	-1.7148		9	9	0.6%	0.18 [0.05, 0.65]	
Liu 2016c	-0.1165		45	45	4.0%	0.89 [0.56, 1.41]	
Pu 2021	-0.7765	0.3319	49	49	2.2%	0.46 [0.24, 0.88]	
Rui 2012	-0.5798		45	45	3.9%	0.56 [0.35, 0.90]	
Veng 2013	-0.3711		124	111	7.5%	0.69 [0.51, 0.93]	-
Vu 2018		0.1949	62	70	5.4%	0.63 [0.43, 0.92]	
(ie 2017		0.1669	71	71	6.7%	0.62 [0.45, 0.86]	-
(u 2021	-0.0202		18	35	2.4%	0.98 [0.52, 1.83]	
'in 2013	-0.4005	0.2263	40	40	4.3%	0.67 [0.43, 1.04]	
ing 2010		0.2917	51	51	2.8%	0.62 [0.35, 1.10]	
hang 2015	-0.4943		42	42	4.2%	0.61 [0.39, 0.95]	
hang 2022	-0.3011		45	45	4.4%	0.74 [0.48, 1.14]	-+-
hu 2014	-0.6349	0.3077	100	251	2.5%	0.53 [0.29, 0.97]	
ubtotal (95% CI)			881	1031	65.6%	0.61 [0.54, 0.69]	•
Heterogeneity: Tau ² = Test for overall effect:	= 0.01; Chi ² = 18.24, d Z = 7.87 (P < 0.0000	df = 15 (F)1)	° = 0.25); I ² =	18%			
Heterogeneity: Tau² = Test for overall effect:							0.001 0.1 1 10 1000
Fest for subgroup dif	rz = 9.91 (P < 0.0000 ferences: Chi² = 0.31)1) , df=1 (i	° = 0.58), I² =	0%			Favours CIK/DC-CIK Favours non-CIK/DC-CIK
Fest for subgroup dif	2 = 9.91 (P < 0.000 ferences: Chi ² = 0.31	, df = 1 (i	° = 0.58), I² = CIK +/- DC (Hazard Ratio	
Fest for subaroup dif	ferences: Chi² = 0.31	, df = 1 (i		Control	Weight	Hazard Ratio IV, Random, 95% CI	Favours CIK/DC-CIK Favours non-CIK/DC-CIK
Fest for subaroup dif Study or Subgroup 1.2.1 CIK	ferences: Chi² = 0.31 log[Hazard Ratio]	, df = 1 (i <u>SE</u>	CIK +/- DC (Total	Control Total		IV, Random, 95% CI	Favours CIMDC-CIK Favours non-CIMDC-CIK
"est for subgroup dif Study or Subgroup J.2.1 CIK	ferences: Chi¤ = 0.31 log[Hazard Ratio] -0.4308	, df= 1 (l <u>SE</u> 0.199	CIK +/- DC (Control	Weight 5.8%	IV, Random, 95% CI 0.65 [0.44, 0.96]	Favours CIMDC-CIK Favours non-CIMDC-CIK
Test for subgroup diff Study or Subgroup J.2.1 CIK Du 2013 J. 2015	ferences: Chi² = 0.31 log[Hazard Ratio] -0.4308 -0.2485	, df= 1 (1 SE 0.199 0.1512	CIK +/- DC (Total 30 65	Control Total 30 65	5.8% 7.1%	V, Random, 95% Cl 0.65 [0.44, 0.96] 0.78 [0.58, 1.05]	Favours CIMDC-CIK Favours non-CIMDC-CIK
Test for subgroup diff Study or Subgroup J.2.1 CIK Du 2013 J. 2015	ferences: Chi¤ = 0.31 log[Hazard Ratio] -0.4308	, df= 1 (l <u>SE</u> 0.199	CIK +/- DC (Total	Control Total 30	5.8%	IV, Random, 95% CI 0.65 [0.44, 0.96]	Favours CIMDC-CIK Favours non-CIMDC-CIK
Test for subgroup diff Study or Subgroup .2.1 CIK Du 2013 .2015 .2016 .2022	ferences: Chi ² = 0.31 log[Hazard Ratio] -0.4308 -0.2485 -0.5447 -0.5108	, df = 1 (l SE 0.199 0.1512 0.2577 0.233	CIK +/- DC (Total 30 65 30 66	Control Total 30 65 30 71	5.8% 7.1% 4.5% 5.0%	V, Random, 95% Cl 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.60 [0.38, 0.95]	Favours CIMDC-CIK Favours non-CIMDC-CIK
Test for subgroup diff Study or Subgroup .2.1 CIK Du 2013 .2015 .2016 .2022	ferences: Chi ^a = 0.31 log[Hazard Ratio] -0.4308 -0.2485 -0.5447 -0.5108 -0.587	, df = 1 (l SE 0.199 0.1512 0.2577	CIK +/- DC (Total 30 65 30 66 126	Control Total 30 65 30	5.8% 7.1% 4.5% 5.0% 7.1%	N, Random, 95% Cl 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.60 [0.38, 0.95] 0.56 [0.42, 0.74]	Favours CII//DC-CIK Favours non-CII//DC-CIK
est for subgroup dif 	ferences: Chi ² = 0.31 log[Hazard Ratio] -0.4308 -0.2485 -0.5447 -0.5108	, df = 1 (l SE 0.199 0.1512 0.2577 0.233	CIK +/- DC (Total 30 65 30 66	Control Total 30 65 30 71	5.8% 7.1% 4.5% 5.0%	IV, Random, 95% CI 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.60 [0.38, 0.95] 0.56 [0.42, 0.74] 0.62 [0.43, 0.89]	Favours CII//DC-CIK Favours non-CII//DC-CIK
est for subgroup diff :udy or Subgroup :2.1 CIK bu 2013 i 2015 i 2016 i 2022 'an 2020a Vang 2019	ferences: Chi ^a = 0.31 log[Hazard Ratio] -0.4308 -0.2485 -0.5447 -0.5108 -0.587	, df = 1 (l SE 0.199 0.1512 0.2577 0.233 0.148 0.1874	CIK +/- DC (Total 30 65 30 66 126	Control Total 30 65 30 71 126	5.8% 7.1% 4.5% 5.0% 7.1%	IV, Random, 95% CI 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.60 [0.38, 0.95] 0.56 [0.42, 0.74] 0.62 [0.43, 0.89]	Favours CII//DC-CIK Favours non-CII//DC-CIK
est for subgroup dif .2.1 CIK .0.2013 .1 2015 .1 2015 .1 2016 .1 2022 'an 2020a Vang 2019 .5 ang 2014	ferences: Chi ² = 0.31 -0.4308 -0.2485 -0.5447 -0.5108 -0.587 -0.4813	, df = 1 (1 SE 0.199 0.1512 0.2577 0.233 0.148 0.1874 0.4924	CIK +/- DC (Total 30 65 30 66 126 97	Control Total 30 65 30 71 126 280	5.8% 7.1% 4.5% 5.0% 7.1% 6.1%	N, Random, 95% Cl 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.60 [0.38, 0.95] 0.56 [0.42, 0.74]	Favours CII//DC-CIK Favours non-CII//DC-CIK
est for subgroup diff tudy or Subgroup .2.1 CIK u 2013 12015 12015 12022 an 2020a Vang 2019 hang 2014 hao 2016 hao 2016 hao 2016	ferences: Chi ² = 0.31 -0 4308 -0 4308 -0 2485 -0.5447 -0.5108 -0.587 -0.4813 -1.5606 -0.1863	, df = 1 (1 SE 0.199 0.1512 0.2577 0.233 0.148 0.1874 0.4924	CIK +/- DC (Total 30 65 30 66 126 97 30 61 21	Control Total 30 65 30 71 126 280 30 30 61 75	5.8% 7.1% 4.5% 5.0% 7.1% 6.1% 1.8% 6.2% 1.3%	N, Random, 95% CI 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.66 [0.42, 0.74] 0.62 [0.43, 0.89] 0.21 [0.08, 0.55] 0.83 [0.58, 1.19] 0.28 [0.09, 0.91]	Favours CII//DC-CIK Favours non-CII//DC-CIK
est for subgroup diff tudy or Subgroup .2.1 CIK u 2013 12015 12015 12022 an 2020a Vang 2019 hang 2014 hao 2016 hao 2016 hao 2016	ferences: Chi ² = 0.31 -0 4308 -0 4308 -0 2485 -0.5447 -0.5108 -0.587 -0.4813 -1.5606 -0.1863	, df = 1 (1 SE 0.199 0.1512 0.2577 0.233 0.148 0.1874 0.4924 0.1829	CIK +/- DC (Total 30 65 30 66 126 97 30 61	Control Total 30 65 30 71 126 280 30 61	5.8% 7.1% 4.5% 5.0% 7.1% 6.1% 1.8% 6.2%	N, Random, 95% CI 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.60 [0.38, 0.95] 0.56 [0.42, 0.74] 0.62 [0.43, 0.89] 0.21 [0.08, 0.55] 0.83 [0.58, 1.19]	Favours CII//DC-CIK Favours non-CII//DC-CIK
est for subgroup dif 	ferences: Chi ² = 0.31 -0 4308 -0 4308 -0 2485 -0.5447 -0.5108 -0.587 -0.4813 -1.5606 -0.1863	. df = 1 (1 SE 0.199 0.1512 0.2577 0.233 0.148 0.1874 0.4924 0.4924 0.4924 0.6017 df = 8 (P =	CIK +/- DC (Total 30 65 30 66 126 97 30 61 21 526	Control Total 30 65 30 71 126 280 30 30 61 75 768	5.8% 7.1% 4.5% 5.0% 7.1% 6.1% 1.8% 6.2% 1.3%	N, Random, 95% CI 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.66 [0.42, 0.74] 0.62 [0.43, 0.89] 0.21 [0.08, 0.55] 0.83 [0.58, 1.19] 0.28 [0.09, 0.91]	Favours CII//DC-CIK Favours non-CII//DC-CIK
rest for subgroup diff Study or Subgroup L2.1 CIK U2 2013 1 2015 1 2016 1 2016 1 2020 Vang 2019 Thang 2014 Chao 2016 hu 2013 Subtotal QPS (CI) reterogeneity: Tau ² = est for overall effect	ferences: Ch [#] = 0.31 log[Hazard Ratio] -0.4308 -0.2495 -0.5447 -0.5108 -0.587 -0.4813 -1.5606 -0.1863 -1.273 =0.02; Ch [#] = 11.91,	. df = 1 (1 SE 0.199 0.1512 0.2577 0.233 0.148 0.1874 0.4924 0.4924 0.4924 0.6017 df = 8 (P =	CIK +/- DC (Total 30 65 30 66 126 97 30 61 21 526	Control Total 30 65 30 71 126 280 30 30 61 75 768	5.8% 7.1% 4.5% 5.0% 7.1% 6.1% 1.8% 6.2% 1.3%	N, Random, 95% CI 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.66 [0.42, 0.74] 0.62 [0.43, 0.89] 0.21 [0.08, 0.55] 0.83 [0.58, 1.19] 0.28 [0.09, 0.91]	Favours CII//DC-CIK Favours non-CII//DC-CIK
est for subgroup diff study or Subgroup .2.1 CIK Ju 2013 J 2015 J 2016 J 2016 J 2020 Vang 2019 Vang 2019 Vang 2014 Chao 2016 Mu 2013 Subtotal (95% CI) Heterogeneity: Tau ^a = est for overall effect: .2.2 DC-CIK	ferences: ChP = 0.31 log[Hazard Ratio] -0.4308 -0.2495 -0.5447 -0.5108 -0.587 -0.4813 -1.500 -0.1883 -1.273 :0.002; ChP = 11.91, Z = 5.30 (P < 0.0000)	, df = 1 (1 SE 0.199 0.1512 0.2577 0.233 0.148 0.1874 0.4924 0.4924 0.6017 df = 8 (P = 01)	CIK +/, DC (Total 30 65 30 66 126 97 30 61 21 526 526 526 526	Control Total 30 65 30 71 126 280 30 61 75 768 3%	5.8% 7.1% 4.5% 5.0% 7.1% 6.1% 1.8% 6.2% 1.3% 44.8%	V, Random, 95% C1 0.65 (0.44, 0.96) 0.78 (0.58, 105) 0.58 (0.35, 0.96) 0.60 (0.38, 0.95) 0.56 (0.42, 0.74) 0.62 (0.43, 0.89) 0.21 (0.08, 0.55) 0.83 (0.58, 1.19) 0.28 (0.09, 0.91) 0.63 (0.53, 0.74)	Favours CII//DC-CIK Favours non-CII//DC-CIK
rest for subgroup diff study of Subgroup .2.1 CIK Ju 2013 12016 12016 12012 12016 12020 Nang 2014 chao 2016 Chao 2016 Chao 2016 Chao 2016 Chao 2016 Chao 2016 Chao 2016 Chao 2017 Carlor Company	ferences: Chi [#] = 0.31 log[Hazard Ratio] -0.4308 -0.2485 -0.5447 -0.5108 -0.5447 -0.4813 -1.6306 -0.1883 -1.273 0.02; Chi [#] = 11.91, Z = 5.30 (P < 0.0000 -1.6094	. df = 1 (1 SE 0.199 0.1512 0.2577 0.233 0.148 0.1874 0.4924 0.4924 0.1829 0.6017 df = 8 (P = 11) 0.5163	CIK +/, DC (Total 30 65 30 66 126 97 30 61 21 526 = 0.16); P = 3 13	Control Total 30 65 30 71 126 280 30 6 30 30 30 30 30 30 30 30 30 75 768 3%	5.8% 7.1% 4.5% 5.0% 7.1% 6.1% 1.8% 6.2% 1.3% 44.8%	N, Random, 95% Cl 0.65 (0.44, 0.96) 0.78 (0.58, 1.05) 0.58 (0.35, 0.96) 0.60 (0.38, 0.96) 0.61 (0.38, 0.96) 0.62 (0.42, 0.74) 0.62 (0.43, 0.89) 0.21 (0.08, 0.55) 0.83 (0.58, 1.19) 0.28 (0.09, 0.91) 0.63 (0.53, 0.74) 0.20 (0.07, 0.55)	Favours CII//DC-CIK Favours non-CII//DC-CIK
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Test for subgroup diff study or Subgroup L.2.1 CIK Du 2013 1.2015 1.2016 1.2022 Vang 2019 Vang 2019 Vang 2019 Chao 2018 Chao 2018 Chao 2018 Chao 2014 L.2.2 DC-CIK J.2.2	Iog[Hazard Ratio] -0.4308 -0.4308 -0.2485 -0.5447 -0.5108 -0.587 -0.4813 -1.5630 -0.1863 -1.273 =0.02; Chi ^p = 11.91, Z = 5.30 (P < 0.0002 -1.6094 -0.6931 -1.1087 -1.3093 -0.5621 -0.4943 -0.5788 -0.3761 -0.5781 -0.3751 -0.5781 -0.3751 -0.5781 -0.3751 -0.5781 -0.5872 -0.5872 -0.5872 -0.5872 -0.5872 -0.5872 -0.5872 -0.5872 -0.5872 -0.5872 -0.5872 -0.5872 -0.5872 -0.5782 -0.5772 -0.5782 -0.	. df = 1 (1 SE 0.199 0.1512 0.2577 0.233 0.482 0.4924 0.4924 0.4924 0.4924 0.4924 0.4924 0.4924 0.4924 0.4924 0.4924 0.4924 0.4924 0.2556 0.2335 0.492 0.4924 0.2577 0.2477 0	CIK +/. DC (Total 30 66 30 66 126 126 97 30 61 126 97 30 61 126 97 30 61 126 97 30 61 126 97 30 61 126 97 30 61 126 126 126 126 126 126 126	Control Total 30 65 30 71 1266 280 30 30 61 75 768 3% 13 121 45 171 70 71 71 70 71 40 51 42	5.8% 7.1% 4.5% 5.0% 7.1% 6.1% 6.2% 1.3% 44.8% 44.8% 7.7% 5.8% 6.3% 5.9% 5.8% 4.0% 5.0% 4.0%	V. Random, 95% CI 0.65 (D.44, 0.96) 0.78 (D.58, 1.05) 0.58 (D.35, 0.96) 0.61 (D.38, 0.96) 0.62 (D.42, 0.74) 0.62 (D.42, 0.74) 0.62 (D.43, 0.89) 0.21 (D.00, 0.55) 0.63 (D.58, 1.19) 0.20 (D.07, 0.55) 0.57 (D.39, 0.64) 0.32 (D.13, 0.64) 0.57 (D.39, 0.83) 0.61 (D.41, 0.90) 0.66 (D.42, 0.24) 0.66 (D.43, 1.06) 0.66 (D.43, 1.02)	Favours CII//DC-CIK Favours non-CII//DC-CIK
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est for subgroup diff Study or Subgroup L2.1 CIK U2.013 1.2015 1.2016 1.2020 an 2020a vang 2019 chang 2014 chao 2016 chu 2013 vang 2019 chao 2016 chu 2013 vang 2019 chao 2016 chu 2013 vang 2019 chao 2016 vang 2017 vang 2017 vang 2018 de 2017 vang 2018 de 2017 vang 2013 vang 2018 de 2017 vang 2013 vang 2018 de 2017 vang 2013 vang 2018 de 2017 vang 2013 vang 2018 de 2017 vang 2018 de 2017 de 2017 de 2018 de 2017 de 2017 de 2018 de 2017 de 2017 de 2018 de 2017 de 2017 de 2017 de 2018 de 2017 de 2017 de 2018 de 2017 de 2017 de 2018 de 2017 de 2017 de 2018 de 2018 de 2017 de 2018 de 2017 de 2018 de 2018 de 2017 de 2018 de 2018 de 2017 de 2018 de 2018 de 2018 de 2017 de 2018 de 2018 d	Iog[Hazard Ratio] -0.4308 -0.2495 -0.547 -0.547 -0.547 -0.547 -0.547 -0.547 -0.547 -0.547 -0.547 -0.547 -0.547 -0.547 -0.547 -0.547 -0.547 -0.547 -0.543 -1.73 -0.527 -0.6831 -1.1087 -1.5934 -0.5276 -0.3987 -0.3971 -0.5276 -0.05276	. df = 1 (1 SE 0.199 0.1512 0.2577 0.233 0.1542 0.233 0.1482 0.4824 0.4824 0.4824 0.4824 0.4824 0.4824 0.4824 0.4824 0.4824 0.4824 0.4824 0.4924 0.2938 0.2938 0.2938 0.2938 0.2938 0.2938 0.2497 0.1986 0.2477 0.1983 3f = 0.(47) 0.2477 0.1983 3f = 10 (f 1) 1) 1) 1) 1) 1) 1) 1) 1) 1)	CIK +/. DC (Total 30 65 30 66 97 30 61 21 526 97 30 61 21 526 97 30 61 21 526 97 30 61 21 526 526 63 97 30 64 21 526 527 526 64 527 526 65 527 526 65 527 526 527 526 527 526 527 527 527 527 527 527 527 527	Control Total 30 65 30 67 11 126 280 61 75 768 3% 13 121 45 51 111 70 71 42 45 656 556%	5.8% 5.0% 5.0% 6.1% 6.2% 1.3% 44.8% 1.7% 5.2% 5.2% 5.8% 5.0% 5.8% 5.0% 5.2%	N, Random, 95% CI 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.60 [0.38, 0.96] 0.61 [0.42, 0.74] 0.62 [0.42, 0.74] 0.62 [0.42, 0.74] 0.63 [0.58, 1.19] 0.20 [0.07, 0.55] 0.53 [0.58, 1.19] 0.20 [0.07, 0.55] 0.53 [0.53, 0.74] 0.20 [0.07, 0.55] 0.57 [0.39, 0.83] 0.57 [0.39, 0.83] 0.57 [0.39, 0.83] 0.57 [0.32, 0.86] 0.58 [0.43, 1.08] 0.68 [0.43, 1.08] 0.68 [0.43, 1.08] 0.68 [0.43, 1.08] 0.59 [0.40, 0.87] 0.59 [0.41, 0.61]	Favours CII//DC-CIK Favours non-CII//DC-CIK

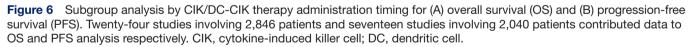


randomized studies assessed was small, HRs and associated 95% CIs reported by each study, especially for the OS endpoint, were all comparable, indicating consistency in the results and so strengthening the overall finding.

Subgroup analysis by CRC disease stage indicated a lack of differences for both OS and PFS. However, the observed 95% CIs associated with the pooled HRs were persistently narrower for Stage IV patients compared with Stage I–III patients, with the upper limits of 95% CIs for Stage I– III patients exceeding 0.85 for both endpoints. Together with the uncertainties around the best way to incorporate CIK/DC-CIK therapy into the established 3–6 months of monoadjuvant or doublet-adjuvant chemotherapy, depending on the disease stage and accompanying other prognostic factors, our study highlights that patients with Stage IV disease may be a more suitable target to evaluate CIK/DC-CIK therapy application, at least initially. The immunosuppressive effect of cancer surgery, including T cell and NK cell dysfunction and expansion of myeloidderived suppressor cells and regulatory T cells in the postoperative period has been described previously,⁹⁵ although how this affects the antitumor activity of CIK/ DC-CIK therapy is not known.

Subgroup analysis based on combining DC therapy with CIK therapy revealed statistically significant subgroup differences in favor of DC-CIK over CIK therapy for PFS,

Α							
			CIK +/- DC			Hazard Ratio	Hazard Ratio
Study or Subgroup 5.2.1 Concurrent	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Chao 2016	-0.8675	0 2072	33	33	2.8%	0.42 [0.23, 0.77]	
Li 2015	-0.3857		65	65	5.9%	0.68 [0.46, 1.01]	
Li 2016		0.6892	30	30	0.6%	1.66 [0.43, 6.41]	
Liu 2014b	-1.7148		9	9	0.7%	0.18 [0.05, 0.65]	
Liu 2016c	-0.1165		45	45	4.5%	0.89 [0.56, 1.41]	
Lv 2014	-0.2107		43	42	1.5%	0.81 [0.35, 1.87]	
Pan 2020a Rui 2012	-0.7765 -0.5798		126 45	126 45	7.6% 4.3%	0.46 [0.33, 0.64] 0.56 [0.35, 0.90]	
Weng 2013	-0.3711		124	111	4.5%	0.69 [0.51, 0.93]	
Wu 2018		0.1949	62	70	6.1%	0.63 [0.43, 0.92]	
Xie 2017	-0.478	0.1669	71	71	7.7%	0.62 [0.45, 0.86]	
Xu 2021	-0.0202		18	35	2.6%	0.98 [0.52, 1.83]	
Zhang 2015	-0.4943		42	42	4.7%	0.61 [0.39, 0.95]	
Zhang 2022 Zhao 2016	-0.3011	0.2209	45 61	45 61	5.0% 5.9%	0.74 [0.48, 1.14] 0.62 [0.42, 0.92]	
Zhao 2016 Zhu 2014	-0.478		100	251	2.8%	0.53 [0.29, 0.97]	
Subtotal (95% CI)	-0.0343	0.5077	919	1081	71.3%	0.63 [0.56, 0.71]	•
Heterogeneity: Tau ² = Test for overall effect:			= 0.33); I ^z = 1	11%			
5.2.2 Sequential							
Gao 2014	-1.6607		13	13	1.0%	0.19 [0.07, 0.55]	
Li 2022	-0.5621		66	71	4.5%	0.57 [0.36, 0.90]	
Lin 2016 Pan 2020b	-0.6162 -0.9943		134 60	121 62	13.0% 2.0%	0.54 [0.44, 0.67] 0.37 [0.18, 0.77]	
Peng 2017	-1.1087		23	23	1.0%	0.33 [0.12, 0.92]	
Pu 2021	-0.7765		49	49	2.5%	0.46 [0.24, 0.88]	
Ying 2010	-0.478	0.2919	51	51	3.1%	0.62 [0.35, 1.10]	
Zhang 2014	-0.9163	0.4074	30	30	1.7%	0.40 [0.18, 0.89]	
Subtotal (95% CI) Heterogeneity: Tau ² =			426 0.52); I² = 0%	420	28.7%	0.51 [0.43, 0.60]	•
Test for overall effect:	Z = 8.07 (P < 0.0000)1)					
Total (95% CI)			1345		100.0 %	0.59 [0.53, 0.65]	•
Heterogeneity: Tau ² =	0.04 · ONE - 37.43 /						
			= 0.24); I*=	16%			0.01 0.1 1 10 100
Test for overall effect: Test for subgroup dif	Z = 9.76 (P < 0.0000)1)					0.01 0.1 1 10 100 Favours CIK/DC-CIK Favours non-CIK/DC-CIK
Test for overall effect Test for subgroup dif	Z = 9.76 (P < 0.0000)1)					
Test for overall effect: Test for subgroup dif B	Z = 9.76 (P < 0.0000 ferences: Chi ² = 4.23)1) I, df=1 (F	P = 0.04), I ² =	76.3% Control		Hazard Ratio	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect: Test for subgroup dif B <u>Study or Subgroup</u>	Z = 9.76 (P < 0.0000)1) 1, df = 1 (F	^o = 0.04), I ² =	76.3% Control	Weight	Hazard Ratio IV, Random, 95% Cl	Favours CIK/DC-CIK Favours non-CIK/DC-CIK
Test for overall effect: Test for subgroup dif B <u>Study or Subgroup</u> 5.4.1 Concurrent	Z = 9.76 (P < 0.0000 ferences: Chi ² = 4.23 log[Hazard Ratio])1) , df = 1 (F SE	P = 0.04), ² = CIK +/- DC (Total	76.3% Control Total		IV, Random, 95% CI	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect: Test for subgroup dif B Study or Subgroup 5.4.1 Concurrent Du 2013	Z = 9.76 (P < 0.0000 ferences: Chi ² = 4.23 log[Hazard Ratio] -0.4308	01) , df = 1 (F <u>SE</u> 0.199	P = 0.04), I ² = CIK +/- DC (<u>Total</u> 30	76.3% Control Total 30	6.6%	IV, Random, 95% CI 0.65 [0.44, 0.96]	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect: Test for subgroup dif B Study or Subgroup 5.4.1 Concurrent Du 2013 Li 2015	Z = 9.76 (P < 0.0000 ferences: Chi ² = 4.23 log[Hazard Ratio] -0.4308 -0.2485	01) 6, df = 1 (F SE 0.199 0.1512	P = 0.04), P = CIK +/- DC (Total 30 65	76.3% Control Total 30 65	6.6% 7.9%	V, Random, 95% Cl 0.65 [0.44, 0.96] 0.78 [0.58, 1.05]	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect: Test for subgroup dif B Study or Subgroup 5.4.1 Concurrent Du 2013	Z = 9.76 (P < 0.0000 ferences: Chi ² = 4.23 log[Hazard Ratio] -0.4308	01) 6, df = 1 (F 5, df = 1 (F 5, df = 1 (F 5, df = 1 (F 5, df = 1 (F) 5,	P = 0.04), I ² = CIK +/- DC (<u>Total</u> 30	76.3% Control Total 30	6.6%	V, Random, 95% Cl 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96]	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect Test for subgroup diff B 5.4.1 Concurrent Du 2013 Li 2015 Li 2016 Liu 2016c Pan 2020a	Z = 9.76 (P < 0.0000 ferences: Ch ^µ = 4.23 log[Hazard Ratio] -0.4308 -0.2485 -0.5447 -1.1087 -0.5798	01) 5, df = 1 (F 0.199 0.1512 0.2577 0.3093 0.1468	2 = 0.04), ² = CIK +/- DC (C Total 30 65 30 45 126	76.3% Control Total 30 65 30	6.6% 7.9% 5.2% 4.2% 8.0%	V, Random, 95% Cl 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.33 [0.18, 0.61] 0.56 [0.42, 0.75]	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect Test for subgroup diff Study or Subgroup 5.4.1 Concurrent Du 2013 Li 2016 Li 2016 Li 2016 Li 2016 Vieng 2013	Z = 9,76 (P < 0.000 [erences: Chi ² = 4.23 log[Hazard Ratio] -0.4308 -0.2485 -0.5447 -1.1087 -0.5798 -1.3093	0.199 0.199 0.1512 0.2577 0.3093 0.1468 0.1793	2 = 0.04), I ² = CIK +/- DC (Total 30 65 30 45 126 124	76.3% Control Total 30 65 30 45 126 111	6.6% 7.9% 5.2% 4.2% 8.0% 7.1%	V, Random, 95% Cl 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.33 [0.18, 0.61] 0.56 [0.42, 0.75] 0.27 [0.19, 0.38]	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect Test for subgroup diff B 5.4.1 Concurrent Du 2013 Li 2016 Li 2016 Pan 2020a Weng 2013 Wu 2018	Z = 9.76 (P < 0.000 (erences: Chi ² = 4.23 -0.4308 -0.2485 -0.5447 -1.1097 -0.5798 -1.3093 -0.5621	01) s, df = 1 (F 0.199 0.1512 0.2577 0.3093 0.1468 0.1793 0.1936	2 = 0.04), I ² = CIK +/- DC (Total 30 65 30 45 126 124 62	76.3% Control Total 30 65 30 45 126 111 70	6.6% 7.9% 5.2% 4.2% 8.0% 7.1% 6.7%	V, Random, 95% Cl 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.33 [0.18, 0.61] 0.56 [0.42, 0.75] 0.27 [0.19, 0.38] 0.57 [0.39, 0.83]	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect Test for subgroup diff B 54.1 Concurrent Du 2013 Li 2016 Li 2016 Eui 2016c Pan 2020a Weng 2013 Wu 2018 Xie 2017	Z = 9.76 (P < 0.0000 [erences: Chi ⁼ = 4.23 -0.4308 -0.4308 -0.5447 -1.1087 -0.5798 -1.3093 -0.5621 -0.4943	11) 5, df= 1 (F 0.199 0.1512 0.2577 0.3093 0.1468 0.1793 0.1984	P = 0.04), P = CIK +/- DC (Total 30 65 30 45 126 124 62 71	76.3% Control Total 30 65 30 45 126 111 70 71	6.6% 7.9% 5.2% 4.2% 8.0% 7.1% 6.7% 6.6%	V, Random, 95% Cl 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.33 [0.18, 0.61] 0.56 [0.42, 0.75] 0.27 [0.19, 0.38] 0.57 [0.39, 0.83] 0.61 [0.41, 0.90]	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect. Test for subgroup diff B <u>Study or Subgroup</u> <u>5.4.1 Concurrent</u> Du 2013 Li 2016 Li 2016 Liu 2016c Pan 2020a Weng 2013 Wu 2018 Xie 2017 Xiu 2021	Z = 9.76 (P < 0.0000 ferences: Chi ² = 4.23 -0.4308 -0.2485 -0.5447 -1.1087 -0.5798 -1.3093 -0.5621 -0.4943 -0.5798	01) 5, df = 1 (F 0.199 0.1512 0.2577 0.3093 0.1468 0.1793 0.1936 0.1984 0.2855	P = 0.04), P = CIK +/- DC (Total 30 65 30 45 126 124 62 71 16	76.3% Control Total 30 65 30 45 126 111 70 71 47	6.6% 7.9% 5.2% 4.2% 8.0% 7.1% 6.7% 6.6% 4.6%	IV, Random, 95% CI 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.33 [0.18, 0.61] 0.56 [0.42, 0.75] 0.27 [0.19, 0.38] 0.57 [0.39, 0.83] 0.61 [0.41, 0.90] 0.56 [0.32, 0.98]	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect Test for subgroup diff B 54.1 Concurrent Du 2013 Li 2015 Li 2016 Liu 2016 Pan 2020a Weng 2013 Wu 2018 Xie 2017 Xiu 2021 Zhang 2015	Z = 9.76 (P < 0.0000 (erences: Chi ² = 4.23 -0.4308 -0.4308 -0.2485 -0.5447 -1.1087 -0.5798 -1.3093 -0.5621 -0.4943 -0.5798 -0.6539 -0.6539	11) 5, df = 1 (F 0.199 0.1512 0.2577 0.3093 0.1468 0.1793 0.1984 0.1985 0.2875 0.2477	P = 0.04), ² = CIK +/- DC C Total 30 65 30 45 124 62 71 16 42	76.3% Control Total 30 65 30 45 126 111 70 71 47 42	6.6% 7.9% 5.2% 4.2% 8.0% 7.1% 6.7% 6.6% 4.6% 5.4%	IV, Random, 95% CI 0.65 (0.44, 0.96) 0.78 (0.58, 1.05) 0.33 (0.18, 0.61) 0.56 (0.42, 0.75) 0.27 (0.19, 0.38) 0.57 (0.39, 0.83) 0.61 (0.41, 0.90) 0.56 (0.32, 0.98) 0.52 (0.32, 0.85)	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect Test for subgroup diff B 5.4.1 Concurrent Du 2013 Li 2016 Liu 2016 Liu 2016 Liu 2016 Veng 2013 Weng 2013 Wu 2018 Xie 2017 Xiu 2021 Zhang 2015 Zhang 2022	Z = 9.76 (P < 0.0000 [erences: Chi ² = 4.23 -0.4308 -0.4308 -0.2485 -0.5447 -1.1087 -0.5798 -1.3093 -0.65271 -0.4943 -0.6578 -0.65798 -0.65276	01) 5, df= 1 (F 0.199 0.1512 0.2577 0.3093 0.1468 0.1793 0.1984 0.2855 0.2477 0.2477 0.2983	P = 0.04), P = CIK +/- DC C Total 30 65 30 45 126 124 62 71 16 42 45	76.3% Control Total 30 65 300 45 126 111 70 71 42 45	6.6% 7.9% 5.2% 4.2% 8.0% 7.1% 6.7% 6.6% 4.6% 5.4% 6.6%	IV, Random, 95% CI 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.33 [0.18, 0.61] 0.56 [0.42, 0.75] 0.27 [0.19, 0.38] 0.57 [0.39, 0.83] 0.61 [0.41, 0.90] 0.56 [0.32, 0.98] 0.52 [0.32, 0.85]	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect Test for subgroup diff B 54.1 Concurrent Du 2013 Li 2016 Liu 2016 Evan 2020a Weng 2013 Wu 2018 Xie 2017 Xiu 2021 Zhang 2015 Zhang 2015 Zhang 2015 Zhang 2015 Subtotal (95% CI)	Z = 9.76 (P < 0.0000 [erences: Chi ² = 4.23 -0.4308 -0.4308 -0.2485 -0.5447 -1.1087 -0.5798 -1.3093 -0.5621 -0.4943 -0.5798 -0.6539 -0.5276 -0.1863	11) , df= 1 (F 0.199 0.1512 0.3093 0.1468 0.1793 0.1984 0.1984 0.2855 0.2477 0.1983 0.1829	P = 0.04), P = CIK +/ DC 0 Total 30 65 126 124 62 71 16 42 45 61 717	76.3% Control Total 30 65 30 45 126 111 70 71 47 42 45 61 743	6.6% 7.9% 5.2% 4.2% 8.0% 7.1% 6.7% 6.6% 4.6% 5.4%	IV, Random, 95% CI 0.65 (0.44, 0.96) 0.78 (0.58, 1.05) 0.33 (0.18, 0.61) 0.56 (0.42, 0.75) 0.27 (0.19, 0.38) 0.57 (0.39, 0.83) 0.61 (0.41, 0.90) 0.56 (0.32, 0.98) 0.52 (0.32, 0.85)	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect Test for subgroup diff B <u>54.1 Concurrent</u> Du 2013 Li 2016 Li 2016 Pan 2020a Weng 2013 Wu 2018 Xie 2017 Xu 2021 Zhang 2015 Zhang 2015 Zhang 2016	Z = 9.76 (P < 0.0000 [erences: Chi ² = 4.23 -0.4308 -0.4308 -0.2485 -0.5447 -1.1087 -0.5798 -1.3093 -0.5621 -0.4943 -0.5798 -0.6339 -0.5276 -0.1863 ±0.07; Chi ² = 29.76, d	11) , df = 1 (F 0.199 0.1512 0.2577 0.3093 0.1468 0.1936 0.1938 0.1938 0.1984 0.2855 0.2477 0.1983 0.1829 df = 11 (P	P = 0.04), P = CIK +/ DC 0 Total 30 65 126 124 62 71 16 42 45 61 717	76.3% Control Total 30 65 30 45 126 111 70 71 47 42 45 61 743	6.6% 7.9% 5.2% 4.2% 8.0% 7.1% 6.6% 5.4% 6.6% 5.4%	N, Random, 95% CI 0.65 (0.44, 0.96) 0.78 (0.58, 1.05) 0.58 (0.35, 0.96) 0.33 (0.18, 0.61) 0.57 (0.14, 0.61) 0.57 (0.39, 0.83) 0.67 (0.39, 0.83) 0.61 (0.41, 0.90) 0.56 (0.32, 0.98) 0.52 (0.32, 0.98) 0.52 (0.32, 0.85) 0.59 (0.40, 0.87) 0.83 (0.56, 1.19)	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect Test for subgroup diff B 5.4.1 Concurrent Du 2013 Li 2016 Li 2016 Li 2016 Li 2016 Li 2016 Vien 2013 Wieg 2013 Wu 2018 Xie 2017 Xiu 2021 Zhang 2015 Zhang 2015 Zhang 2015 Subtotal (95% CI) Heterogeneity, Tau ^a =	Z = 9.76 (P < 0.0000 [erences: Chi ² = 4.23 -0.4308 -0.4308 -0.2485 -0.5447 -1.1087 -0.5798 -1.3093 -0.5621 -0.4943 -0.5798 -0.6339 -0.5276 -0.1863 ±0.07; Chi ² = 29.76, d	11) , df = 1 (F 0.199 0.1512 0.2577 0.3093 0.1468 0.1936 0.1938 0.1938 0.1984 0.2855 0.2477 0.1983 0.1829 df = 11 (P	P = 0.04), P = CIK +/ DC 0 Total 30 65 126 124 62 71 16 42 45 61 717	76.3% Control Total 30 65 30 45 126 111 70 71 47 42 45 61 743	6.6% 7.9% 5.2% 4.2% 8.0% 7.1% 6.6% 5.4% 6.6% 5.4%	N, Random, 95% CI 0.65 (0.44, 0.96) 0.78 (0.58, 1.05) 0.58 (0.35, 0.96) 0.33 (0.18, 0.61) 0.57 (0.14, 0.61) 0.57 (0.39, 0.83) 0.67 (0.39, 0.83) 0.61 (0.41, 0.90) 0.56 (0.32, 0.98) 0.52 (0.32, 0.98) 0.52 (0.32, 0.85) 0.59 (0.40, 0.87) 0.83 (0.56, 1.19)	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect Test for subgroup diff B 54.1 Concurrent Du 2013 Li 2015 Li 2016 Liu 2016 Pan 2020a Weng 2013 Wu 2018 Xie 2017 Xu 2021 Zhang 2015 Zhang 2015 Zhang 2015 Zhang 2015 Zhang 2015 Zhang 2015 Subtotal (95% CI) Heterogenety, Tay ² = Test for overall effect 5.4.2 Sequentia Gao 2014	Z = 9.76 (P < 0.0000 [erences: Chi ² = 4.23 -0.4308 -0.4308 -0.2485 -0.5447 -1.1087 -0.5798 -1.3093 -0.5621 -0.4943 -0.5776 -0.4943 -0.5776 -0.1863 0.5276 -0.1863 :0.07; Chi ² = 29.76, (Z = 6.07 (P < 0.0000 -1.6094	11) , df = 1 (F 0.199 0.1512 0.2577 0.3093 0.1468 0.1793 0.1468 0.1793 0.1984 0.2855 0.2477 0.1983 0.1829 df = 11 (P 11) 0.5161	P = 0.04), P = CIK +/- DC (Total 30 30 45 126 124 62 71 16 42 71 16 42 61 71 71 16 45 61 71 71 71 16 45 61 71 71 71 71 71 71 71 71 71 7	76.3% Control Total 30 45 126 1111 70 711 47 42 45 61 114 743 63% 13	6.6% 7.9% 4.2% 8.0% 7.1% 6.6% 5.4% 6.6% 7.0% 75.9%	N, Random, 95% CI 0.65 [0.44, 0.96] 0.78 [0.58, 1.05] 0.58 [0.35, 0.96] 0.33 [0.18, 0.81] 0.56 [0.42, 0.75] 0.27 [0.19, 0.38] 0.57 [0.39, 0.83] 0.61 [0.41, 0.90] 0.56 [0.32, 0.98] 0.52 [0.32, 0.85] 0.59 [0.40, 0.87] 0.56 [0.46, 0.67] 0.56 [0.46, 0.67] 0.20 [0.07, 0.55]	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
Test for overall effect Test for subgroup diff B 5.4.1 Concurrent Du 2013 Li 2016 Li 2016 Li 2016 Li 2016 Li 2016 Var 2018 Weng 2013 Wu 2018 Xie 2017 Xiu 2021 Zhang 2015 Zhang 2015 Zhang 2015 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect 5.4.2 Sequential Gao 2014 Li 2022	Z = 9.76 (P < 0.0000 [erences: Chi2 = 4.23 -0.4308 -0.4308 -0.2485 -0.5447 -1.1087 -0.5798 -1.3093 -0.5621 -0.4943 -0.5798 -0.5276 -0.1863 :0.07; Chi2 = 29.76, o Z = 6.07 (P < 0.0000 -1.6094 -0.5108	11) , df = 1 (F 0.199 0.1512 0.2577 0.3093 0.1468 0.1936 0.1936 0.1984 0.2855 0.2477 0.1983 0.2477 0.1983 0.2477 0.1983 0.2471 0.2471 0.2473	P = 0.04), P = CIK +/- DC (Total 30 65 300 45 126 124 62 71 16 42 45 61 717 717 = 0.002); P =	76.3% Control Total 30 65 30 65 30 45 126 111 70 71 74 2 45 65 65 63% 13 71	6.6% 7.9% 5.2% 4.2% 8.0% 7.1% 6.6% 5.4% 6.6% 7.0% 75.9% 2.0% 5.7%	N, Random, 95% CI 0.65 [0.44, 0.96] 0.78 [0.56, 1.05] 0.58 [0.35, 0.96] 0.35 [0.14, 0.61] 0.65 [0.42, 0.75] 0.27 [0.19, 0.38] 0.57 [0.33, 0.83] 0.57 [0.33, 0.83] 0.57 [0.32, 0.98] 0.52 [0.32, 0.98] 0.52 [0.32, 0.83] 0.58 [0.40, 0.87] 0.83 [0.56, 1.19] 0.56 [0.46, 0.67] 0.20 [0.07, 0.56] 0.60 [0.38, 0.95]	Favours CIK/DC-CIK Favours non-CIK/DC-CIK Hazard Ratio
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but not for OS. DCs are major antigen-presenting cells and the essential link between the innate and adaptive immune systems.⁹⁶ Coculturing of CIK cells with DCs results in increased CIK cytolytic function, including cytotoxic activity against a tumor cell line resistant to CIK cells cultured in the absence of DCs.¹⁴ This review observed more patients who received DC-CIK therapy than CIK therapy; however, the results suggest that the addition of DC therapy to CIK therapy does not have a strong clinical benefit, as only statistical significance was observed for PFS and not for OS. This result points to the need for future clinical trials investigating the benefit of including DC therapy in CIK therapy, and whether other

combinations such as immune checkpoint inhibitors or CAR-T incorporation with CIK therapy may be of better value for patients with CRC.

Subgroup differences were similarly detected for OS for concurrent versus sequential administration of CIK/DC-CIK. Subgroup analyses for both PFS by CIK therapy type and OS by CIK therapy administration timing had similar HRs with highly overlapping 95% CIs, making it unclear whether the differences are clinically meaningful. The timing of CIK/DC-CIK delivery for patients with CRC may not be critical and could be selected based on logistical issues.

There have been two previous publications that systematically reviewed the literature for CIK/DC-CIK therapy in CRC.^{16 97} In 2010, Zhang and Schmidt-Wolf, in cooperation with Stanford University, established the International Registry on CIK Cells (IRCC) to evaluate clinical trials of CIK therapy.^{97 98} The registry identifies both prospective and retrospective clinical trials involving CIK therapy for cancer treatment from PubMed, Web of Science Core Collection, WHO International Clinical Trials Registry Platform, ClinicalTrials.gov as well as proceedings of the American Society of Clinical Oncology and European Cancer Conference Annual Scientific Meetings. In addition, the IRCC incorporates clinical trials submitted by individual researchers for inclusion.⁹⁹ In 2020, the registry recorded 106 clinical trials, of which only 6 examined CIK therapy in patients with CRC.⁹⁷ This contrasts with the 29 trials including 2610 patients with CRC reported in the published systematic review and meta-analysis in 2017 by Zhang et al, which purely compared the clinical benefit of CIK therapy plus chemotherapy to CIK therapy in patients with CRC with advanced disease.¹⁶ They also used two Chinese databases, CNKI and Wanfang Data, in addition to the English databases Cochrane Library, Embase, and PubMed. The majority of the studies were published in Chinese similar to our findings.

To date, China has taken the lead in research of adoptive immunotherapy including CIK therapy.^{15 100} Therefore, the inclusion of articles published in Chinese was necessary to comprehensively review the currently available literature examining the clinical efficacy of CIK therapy in CRC. Additionally, the current work included clinical trials which compared CIK therapy with non-CIK treatment not limited to chemotherapy, to increase the number of trials assessed. Consequently, the review considered 70 studies involving 6743 patients and is the largest systemic review on CIK/DC-CIK therapy in CRC. It meta-analyzed OS and PFS, the two most important clinical endpoints in assessing the efficacy of any cancer therapy. Endpoints covered by Zhang¹⁶ were limited to OS and DFS rates as well as ORR. The CRC population covered by this review is also broader having included patients at all stages.

This study has a number of limitations. The heterogeneity observed in the clinical study design requires caution when interpreting results. There are general guidelines for the production of CIK therapy. The CIK therapy product is generated from PBMCs cultured for 21-28 days in the presence of anti-CD3 stimulation and the cytokines interferon-gamma and interleukin-2. Prior to transfusion, the therapy product is expected to have minimum percentage of NK-like T cells.¹⁰¹ While having basic production guidelines makes reproducing this therapy achievable, we observed heterogeneity in the culture systems used to generate these cells, including the media, concentration of stimuli and cytokines used, and intervals of cytokine addition in culture. Characterization of the cell therapy product prior to transfusion to meet the guidelines was normally not provided.

Clinical parameters such as anticancer treatment history, demographics, and number of treatment cycles were also observed to be heterogeneous among the studies analyzed. These variables could contribute to the heterogeneity observed in our analysis that was not rectified by our subgroup analyses. As the studies identified were all undertaken in China, clinical trials in non-Chinese ethnicity are needed to confirm its efficacy outside of Chinese patients. Finally, the possibility of publication bias was raised as only a handful of studies reported negative outcomes of CIK/DC-CIK therapy for the efficacy endpoints assessed.

Despite these limitations, our data strongly support that complementing conventional treatment regimens with CIK/DC-CIK therapy in patients with CRC provides clinical benefits. By highlighting the parameters that contribute to the heterogeneity in the study designs, we suggest that standardization of these will lead to greater adoption of CIK therapy worldwide.

CONCLUSION

CIK therapy in combination with standard treatments, in particular chemotherapy, provides clinical benefits for patients with CRC. The benefit existed whether the included studies were prospective and randomized or not, strengthening the finding. CIK therapy was well tolerated, with fever being the most common adverse event. While DC therapy is commonly combined with CIK therapy for patients with CRC, our study suggests that this may not provide extra benefit. The findings support further evaluation of the clinical utility of CIK therapy in CRC.

Contributors Conception and design: CMYL, YT, and KAF. Collection and/or assembly of data: CMYL, YT, RL, and JL. Data analysis and interpretation: CMYL, YT, BD, ES, and KAF. Manuscript writing: CMYL, YT, ES, PD, and KAF. Final approval of manuscript: CMYL, YT, BD, RL, JL, PD, ES, TP, GJM, and KAF. Guarantor: KAF

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Competing interests None declared.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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