

Chemotherapy With or Without Anti-EGFR Agents in Left- and Right-Sided Metastatic Colorectal Cancer: An Updated Meta-Analysis

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ABSTRACT

Background: Previous meta-analyses have suggested primary tumor location as a predictive factor for efficacy of anti-epidermal growth factor receptor (EGFR) therapies in patients with metastatic colorectal cancer (mCRC). However, the recent phase III TAILOR trial addressing this issue was not included in those analyses. This meta-analysis incorporated data from the TAILOR trial to evaluate the efficacy of chemotherapy plus anti-EGFR agents (cetuximab [Cet] or panitumumab [Pani]) versus chemotherapy alone for *RAS* wild-type (wt) right- and left-sided mCRC. **Patients and Methods:** A PubMed-based literature search was conducted to identify randomized controlled trials (RCTs) studying the additional efficacy of Cet/Pani in combination with chemotherapy versus chemotherapy alone in *RAS* wt left- and right-sided mCRC. Study-level pooled analyses of hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS) and odds ratios (ORs) for objective response rate (ORR) were performed. **Results:** Three first-line RCTs (CRYSTAL, PRIME, and TAILOR) and one second-line RCT (20050181) were included. Significant OS benefits from Cet/Pani were observed in the left-sided (HR, 0.76; 95% CI, 0.66–0.86) but not right-sided subgroups (HR, 0.99; 95% CI, 0.78–1.27). However, the addition of Cet/Pani to chemotherapy significantly improved PFS and ORR in both the left-sided (HR, 0.70; 95% CI, 0.57–0.86, and OR, 3.28; 95% CI, 1.95–5.51, respectively) and right-sided subgroups (HR, 0.76; 95% CI, 0.59–0.99, and OR, 1.78; 95% CI, 1.08–2.93, respectively). **Conclusions:** The addition of Cet/Pani to chemotherapy significantly benefits PFS and ORR in patients with *RAS* wt right-sided mCRC, indicating that anti-EGFR therapies may remain an option for selected patients.

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Background

Colorectal cancer (CRC) is the third most common malignant disease affecting both men and women in the Asia-Pacific region.¹ Several studies have reported heterogeneity in developmental, microbial, gut floral, molecular, genetic, and clinical outcomes of left- and right-sided CRC tumors.^{2–7} These differing characteristics are associated with differential prognosis, and patients with right-sided CRC are reported to have a worse prognosis.^{8,9}

A recent meta-analysis including 14 prospective studies in metastatic CRC (mCRC) reported a 56% increase in mortality in right-sided compared with left-sided tumors,¹⁰ indicating the prognostic relevance of primary tumor location (PTL). In addition, several post hoc analyses of randomized controlled trials (RCTs) and retrospective studies have suggested PTL to be a predictive factor for treatment benefits, especially in patients treated with targeted therapies.^{11–16} A recent pooled analysis of 6 first- or second-line RCTs evaluating the efficacy of chemotherapy + cetuximab (Cet) or panitumumab (Pani) versus chemotherapy ± bevacizumab (Bev) reported significant improvement in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) with chemotherapy + Cet/Pani in patients with *RAS* wild-type (wt) left-sided tumors, but no significant survival benefits in those with *RAS* wt right-sided tumors.¹⁷ In addition, subgroup analysis with Bev in the control arm showed significantly worse PFS and numerically worse OS with chemotherapy + Cet/Pani in patients with *RAS* wt right-sided mCRC.¹⁷ Because of these findings, Bev is increasingly being considered the preferred targeted agent in patients with right-sided tumors.¹⁸

The choice between chemotherapy + Cet/Pani and chemotherapy alone nonetheless remains clinically relevant to patients with *RAS* wt right-sided mCRC when they are not candidates for Bev therapy. Prior meta-analyses of trials investigating chemotherapy + Cet/Pani

versus chemotherapy alone failed to show significant improvements in OS, PFS, or ORR with the addition of Cet/Pani in these tumors,^{10,17} but these studies may have had inadequate sample size and statistical power. The recent Chinese phase III TAILOR trial, which investigated the efficacy of chemotherapy + Cet versus chemotherapy alone in the *RAS* wt population, was not included in the previous analyses.¹⁹ By including all the relevant RCTs, our meta-analysis aimed to reevaluate the efficacy of chemotherapy plus anti-epidermal growth factor receptor (EGFR) agents (Cet/Pani) compared with chemotherapy alone in relation to PTL in patients with *RAS* wt mCRC.

Patients and Methods

This meta-analysis was reported in accordance with PRISMA guidelines.²⁰

Study Selection and Data Extraction

A PubMed-based literature search through the end of December 2017 was performed using the following search or MeSH terms: metastatic colorectal cancer, primary tumor location, sidedness, left-sided tumor, and right-sided tumor. In addition, we conducted searches of the major oncology congress websites, including ASCO and ESMO. After screening titles and abstracts, potentially relevant studies were retrieved and assessed for eligibility criteria. Reference lists of the included publications were manually checked to identify additional potential studies.

Studies that met the following criteria were eligible for the quantitative analysis: (1) RCTs that reported *RAS* wt (*KRAS/NRAS* exon 2–4 wt) mCRC; (2) studies that enrolled patients treated with either chemotherapy + anti-EGFR agents (Cet/Pani) or chemotherapy alone; and (3) studies that reported treatment outcomes (OS, PFS, and ORR) as HRs and odds ratios (ORs), with stratification for PTL (left vs right). The most recent and complete publications were included when duplicate data or subgroup analysis of the same study was found.

Relevant data were extracted by 2 independent investigators (Z.X. Wang, H.X. Wu) and verified by a third investigator (M.M. He). Any discrepancies among investigators were resolved through consensus.

Statistical Analyses

HRs and ORs with 95% CIs in the literature were synthesized to obtain overall treatment effects based on PTL (left vs right). Potential heterogeneity among the studies was determined using Cochran's *Q* statistic and *I*² statistic. In the presence of significant heterogeneity ($P < .10$ or $I^2 > 50\%$), random-effects meta-analytic models were used to calculate the pooled HRs and ORs. Otherwise, the analysis was performed using the fixed-effects models.

Multivariate random-effects meta-regression models were used to evaluate the interaction effect between PTL and treatment with Cet/Pani after adjustment for the anti-EGFR agent, chemotherapy backbone, and treatment line. All *P* values were 2-sided. Statistical analyses were performed using R 3.4.1 (The R Foundation) with the package "metaphor."

Results

Study Characteristics

The search yielded a total of 1,252 potentially relevant studies, of which 4 RCTs ultimately fulfilled the study criteria (CRYSTAL,^{8,21} PRIME,^{11,22} TAILOR,¹⁹ and 20050181^{23,24}; ClinicalTrials.gov identifiers: NCT00154102, NCT00364013, NCT01228734, and NCT00339183, respectively) (Figure 1). Baseline characteristics of the included trials are summarized in Table 1. A total of 1,539 patients were included, of which 325 were diagnosed with right-sided *RAS* wt mCRC and 1,214 with left-sided mCRC (Table 1). In all 4 trials, primary tumors originating in the cecum, appendix, ascending colon, hepatic flexure, and transverse colon were classified as right-sided tumors.

Effect of PTL on OS Benefits With Anti-EGFR Agents

A significant improvement in OS was observed in patients with left-sided *RAS* wt tumors treated with chemotherapy + Cet/Pani compared with chemotherapy alone (HR, 0.76; 95% CI, 0.66–0.86; $P < .0001$; Figure 2A), without significant evidence for between-study heterogeneity ($P = .150$; $I^2 = 43.7\%$). However, addition of Cet/Pani to chemotherapy provided no OS benefits in patients with *RAS* wt right-sided tumors (HR, 0.99; 95% CI, 0.78–1.27; $P = .945$; $P_{\text{heterogeneity}} = .860$; $I^2 = 0\%$; Figure 2A). After adjustment for anti-EGFR agent, chemotherapy backbone, and treatment line, the treatment effect of Cet/Pani on OS differed significantly according to PTL ($P_{\text{interaction}} = .044$; Table 2).

Effect of PTL on PFS Benefits With Anti-EGFR Agents

Because there was significant heterogeneity between the studies ($P_{\text{heterogeneity}} = .094$; $I^2 = 53.4\%$) in the left-sided subgroup, a random-effects model was used for the PFS analysis. The pooled HRs of 0.70 (95% CI, 0.57–0.86; $P = .001$) showed that patients with left-sided *RAS* wt mCRC treated with chemotherapy + Cet/Pani had a significantly higher PFS compared with those treated with chemotherapy alone (Figure 2B). Unlike OS, a significant improvement in PFS with Cet/Pani was detected in patients with *RAS* wt right-sided tumors (HR, 0.76; 95% CI, 0.59–0.99; $P = .040$; Figure 2B), absent between-study heterogeneity ($P_{\text{heterogeneity}} = .926$; $I^2 = 0\%$). Multivariate meta-regression analysis revealed no significant

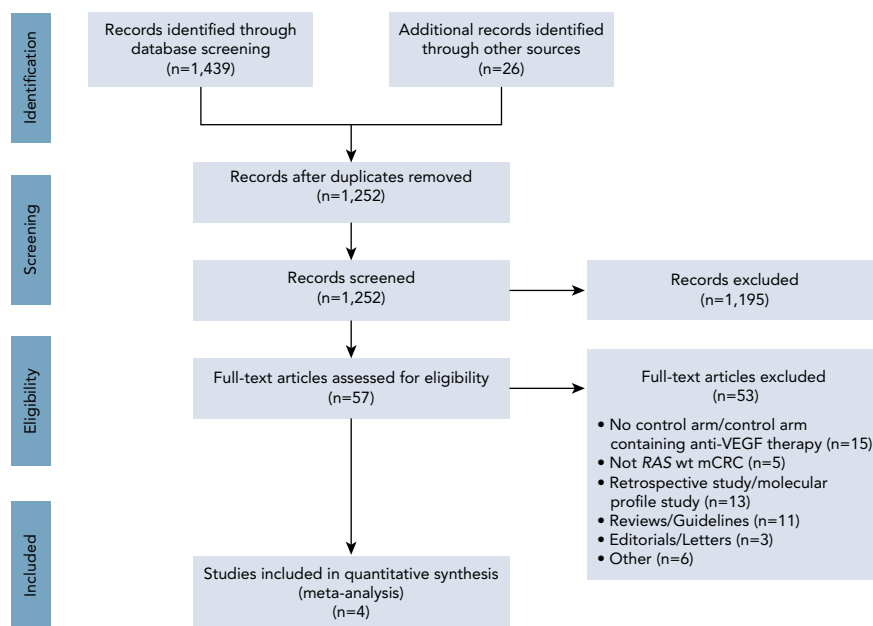


Figure 1. Search results summarized according to PRISMA guidelines.

Abbreviations: mCRC, metastatic colorectal cancer; VEGF, vascular endothelial growth factor; wt, wild-type.

interaction between PTL and the efficacy of Cet/Pani on PFS ($P_{\text{interaction}} = .591$; Table 2).

Effect of PTL on ORR Benefits With Anti-EGFR Agents

The addition of Cet/Pani to chemotherapy significantly improved ORR in both patients with *RAS* wt left-sided tumors (OR, 3.28; 95% CI, 1.95–5.51; $P < .0001$; $P_{\text{heterogeneity}} = .002$; $I^2 = 80.1\%$) and those with *RAS* wt right-sided tumors (OR, 1.78; 95% CI, 1.08–2.93; $P = .024$; $P_{\text{heterogeneity}} = .527$; $I^2 = 0\%$; Figure 2C). Multivariate meta-regression analysis indicated no significant interaction between PTL and the treatment effect of Cet/Pani on ORR ($P_{\text{interaction}} = .134$; Table 2).

Because treatment line was a significant predictor of the treatment effect of Cet/Pani on ORR ($P_{\text{interaction}} = .024$; Table 2), we performed a pooled analysis of ORR based on the 3 first-line RCTs. ORRs in patients with *RAS* wt left-sided tumors were 68.9% (314 of 456) in those treated with

chemotherapy + Cet/Pani and 45.6% (208 of 456) in those treated with chemotherapy alone ($P < .0001$). In patients with *RAS* wt right-sided tumors, 50 of 116 (43.1%) treated with chemotherapy + Cet/Pani achieved an objective response compared with 42 of 135 (31.1%) treated with chemotherapy alone ($P = .001$).

Discussion

Previous studies have reported differences in the efficacy of anti-EGFR agents in *RAS* wt mCRC according to PTL.^{4,8} Notably, 2 meta-analyses including the CALGB 80405, FIRE-3, and PEAK studies showed significantly better OS, PFS, and ORR with first-line chemotherapy plus anti-EGFR antibodies than with chemotherapy + Bev in patients with *RAS* wt left-sided mCRC.^{10,17} In contrast, patients with *RAS* wt right-sided tumors appeared to gain more benefits from chemotherapy + Bev.^{10,17} These data led the NCCN Clinical Practice Guidelines in Oncology

Table 1. Baseline Characteristics of Included Trials

Trial	Phase	Study Population	Included Patients, ^a n (%)	Patients With Right-Sided Tumors, ^b n (%)	Chemotherapy Backbone	Anti-EGFR Agent	Treatment Line
CRYSTAL ^{8,21}	III	All <i>RAS</i> wt and tumor side confirmed	364 (29.9)	84 (23.1)	FOLFIRI	Cetuximab	First
PRIME ^{11,22}	III	All <i>RAS</i> wt and tumor side confirmed	416 (35.2)	88 (21.2)	FOLFOX	Panitumumab	First
TAILOR ¹⁹	III	All <i>RAS</i> wt and tumor side confirmed	391 (77.6)	83 (21.2)	FOLFOX	Cetuximab	First
20050181 ^{23,24}	III	All <i>RAS</i> wt and tumor side confirmed	368 (31.0)	70 (19.0)	FOLFIRI	Panitumumab	Second

Abbreviations: EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil/leucovorin/irinotecan; FOLFOX, fluorouracil/leucovorin/oxaliplatin; wt, wild-type.
^aPatients in the study population and its percentage in the all-randomized population.

^bIncluded patients with right-sided tumors and its percentage in the study population. In all 4 included trials, primary tumors originating in the cecum, appendix, ascending colon, hepatic flexure, and transverse colon were classified as right-sided.

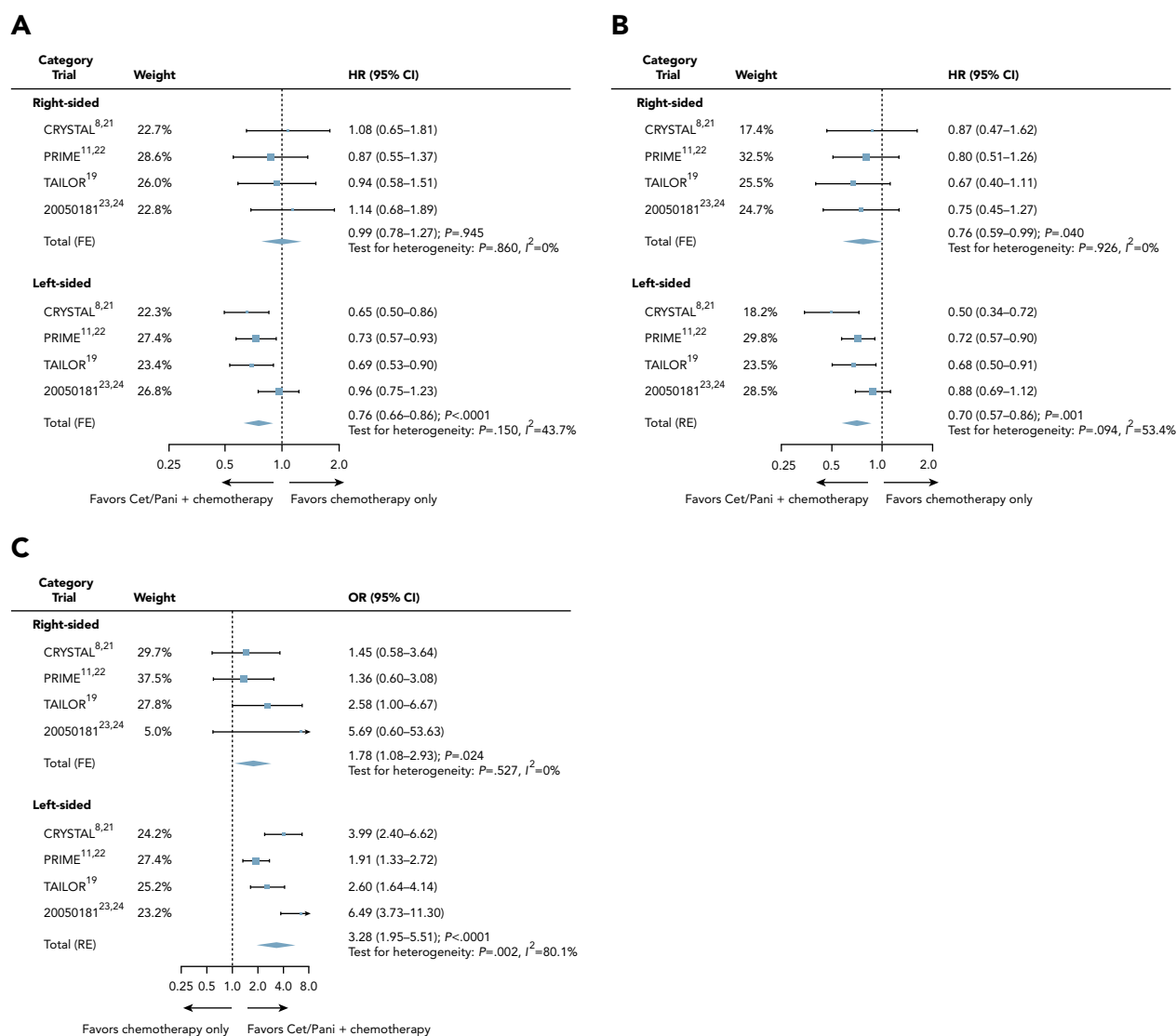


Figure 2. Forest plots showing the HRs for (A) overall survival and (B) progression-free survival and the odds ratio for (C) objective response rate comparing chemotherapy + Cet or Pani with chemotherapy only, with stratification for tumor location. Interaction test between tumor side and treatment effect were (A) *P*=.044, (B) *P*=.591, and (C) *P*=.134.

Abbreviations: Cet, cetuximab; FE, fixed-effects model; HR, hazard ratio; Pani, panitumumab; RE, random-effects model.

(NCCN Guidelines) for Colon Cancer to recently recommend against use of anti-EGFR agents in the frontline treatment of *RAS* wt right-sided mCRC.¹⁸

Our updated meta-analysis confirmed that adding Cet/Pani to chemotherapy clearly benefited patients with *RAS* wt left-sided tumors in terms of OS, PFS, and ORR. In contrast, the treatment effect of Cet/Pani on OS was significantly attenuated in the *RAS* wt right-sided subgroup, which corroborates previous observations that have convincingly shown fewer benefits from anti-EGFR therapy in patients with right-sided tumors.^{4,8,25} To the best of our knowledge, our study is the first to show that the addition of Cet/Pani to

chemotherapy could still significantly improve PFS and ORR in patients with right-sided *RAS* wt mCRC. In previous meta-analyses, we noticed a numerical trend toward better PFS and ORR favoring chemotherapy + Cet/Pani over chemotherapy alone, but results were not statistically significant.^{10,17} A possible reason for our different findings might be the additional inclusion of the TAILOR trial, which provided a greater statistical power from the increased sample size of patients with *RAS* wt right-sided tumors, absent between-study heterogeneity.

The improved ORR (from 31% to 43% in the first line) with chemotherapy + Cet/Pani versus chemotherapy alone suggests that anti-EGFR agents are

Table 2. Multivariate Random-Effects Meta-Regression Analyses for Treatment Effect of Anti-EGFR Therapy

Variable	Overall Survival		Progression-Free Survival		Objective Response Rate	
	HR _{interaction} (95% CI)	P _{interaction} ^a	HR _{interaction} (95% CI)	P _{interaction}	OR _{interaction} (95% CI)	P _{interaction} ^a
Tumor side						
Left vs right	0.75 (0.57–0.99)	.044	0.92 (0.69–1.24)	.591	1.53 (0.88–2.66)	.134
Anti-EGFR agent						
Pani vs Cet	1.03 (0.75–1.41)	.871	1.09 (0.78–1.52)	.606	0.69 (0.40–1.17)	.166
Chemotherapy backbone						
FOLFOX vs FOLFIRI	1.02 (0.73–1.42)	.922	1.17 (0.77–1.76)	.458	0.81 (0.44–1.49)	.490
Treatment line						
First- vs second-line	1.34 (0.85–2.11)	.206	1.36 (0.82–2.27)	.235	2.76 (1.15–6.65)	.024

Abbreviations: Cet, cetuximab; EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil/leucovorin/irinotecan; FOLFOX, fluorouracil/leucovorin/oxaliplatin; HR, hazard ratio; Pani, panitumumab.

^aBolded *P* values indicate statistical significance.

worthy of consideration for patients with *RAS* wt right-sided tumors when cytoreduction is set as the therapeutic goal. A previous study showed a strong correlation between ORR and the R0 resection rate among patients with initially unresectable liver metastases.²⁶ Notwithstanding that right-sided tumors have a more dismal prognosis than left-sided tumors, several studies have reported favorable survival outcomes after curative-intent hepatectomy even in patients with right-sided tumors (median OS >3 years),^{27,28} suggesting that these patients may also substantially benefit from improvements in the rate of conversion to resectability. Recent subgroup analysis data from the TRIBE study revealed significantly improved ORR and PFS, and OS favoring the triplet chemotherapy (fluorouracil/oxaliplatin/irinotecan [FOLFOXIRI]) + Bev versus FOLFIRI + Bev in patients with right-sided mCRC.²⁹ The ORR was as high as 63.9% in right-sided tumors and reached 81.3% among *RAS*/*BRAF* wt right-sided tumors.²⁹ Therefore, in patients with right-sided tumors for whom cytoreduction is the goal, FOLFOXIRI + Bev would be the preferred therapeutic regimen when they fulfill the clinical criteria for use of FOLFOXIRI (ie, age 18–75 years and performance status 0–2 if age ≤70 years, or 0 if age 71–75 years).³⁰ In prior meta-analyses of the CALGB 80405, FIRE-3, and PEAK studies, chemotherapy doublets plus anti-EGFR agents exhibited a numerically superior ORR to chemotherapy doublets plus Bev,^{10,17} whereas no trials have compared chemotherapy doublets plus anti-EGFR agents with FOLFOXIRI alone head-to-head. In view of the increased toxicity of FOLFOXIRI compared with chemotherapy doublets³¹ and the different toxicity profiles between Bev and anti-EGFR agents,^{32–34} a chemotherapy doublet plus anti-EGFR antibody would still be a reasonable option for patients with *RAS* wt right-sided tumors when they need significant tumor response but are not candidates for either FOLFOXIRI or Bev therapy.

Currently, the role of anti-EGFR therapy in patients with right-sided mCRC seems limited when the treatment goal is prolongation of disease control. Prior meta-analyses of the 3 first-line trials comparing chemotherapy plus anti-EGFR agents versus chemotherapy + Bev revealed significantly better PFS and numerically better OS favoring chemotherapy + Bev in patients with *RAS* wt right-sided mCRC.^{10,17} This finding led to increasing preference for using Bev as the targeted agent in initial therapy for right-sided tumors.¹⁷ Nonetheless, the choice between chemotherapy plus anti-EGFR agents and chemotherapy alone is still clinically relevant to patients with *RAS* wt right-sided mCRC when they have contraindications to Bev therapy. Notably, our study found that the addition of Cet/Pani to chemotherapy significantly improved PFS in patients with *RAS* wt right-sided mCRC, which suggests the non-negligible activity of anti-EGFR agents in disease stabilization for these patients. In view of the rather dismal prognosis of patients with right-sided mCRC,^{3,25} prolongation of disease stabilization could potentially delay fitness deterioration and offer them a better chance to be included in future clinical trials, even though improvement in OS was not shown. Thus, a chemotherapy doublet in combination with anti-EGFR antibody could be considered for patients with *RAS* wt right-sided tumors when disease stabilization is the goal and Bev therapy is not feasible.

We acknowledge certain limitations in our analysis. First, this meta-analysis was performed at the study level rather than the individual patient level. Thus, some of the unreported information at the individual patient level, such as *BRAF* status, might affect our findings. The prevalence of *BRAF* mutation with stratification for PTL was reported in the PRIME, 20050181, and TAILOR studies and was generally balanced between treatment arms across these studies.^{17,19} The efficacy data of anti-EGFR therapy with stratification for both *BRAF* status and

PTL was only available in the TAILOR study, which showed that OS and PFS were even worse with anti-EGFR therapy for *RAS* wt/*BRAF*-mutant right-sided tumors, but seemed to favor anti-EGFR therapy for *RAS*/*BRAF* wt right-sided tumors.¹⁹ This finding, which corroborates previous observations,^{35,36} suggests that anti-EGFR agents are highly unlikely to yield benefits in *RAS* wt/*BRAF*-mutant right-sided tumors. Therefore, for patients with right-sided tumors, it could be justified to confine anti-EGFR therapy to those with *RAS*/*BRAF* wt tumors.

Second, our meta-analysis was based on post hoc subset analysis data regarding either historically examined *RAS* status or retrospectively collected PTL information. Consequently, a substantial proportion of patients who had a *KRAS*/*NRAS* mutation, non-evaluable *RAS* status, or missing data regarding PTL were excluded from the all-randomized population. Misclassification of tumor sidedness might also have occurred during retrospective data collection. Therefore, our findings may experience potential biases and should be interpreted with caution. However, given that no available trial prospectively examines the impact of PTL on efficacy of anti-EGFR therapy in *RAS* wt mCRC, our meta-analysis still presents reasonably compelling evidence regarding this issue.

Third, the 4 included trials were different in study design; however, there was no heterogeneity among the studies within the right-sided subgroup for all 3 end points, suggesting the robustness of the pooled analysis data for right-sided tumors.

Conclusions

Given the ORR and PFS benefits of chemotherapy + Cet/Pani versus chemotherapy alone, anti-EGFR therapies should not be excluded from treatment of *RAS* wt right-sided mCRC. A chemotherapy doublet plus anti-EGFR antibody remains an option for patients with *RAS* wt right-sided tumors when Bev therapy is not feasible, independent of treatment goal; for those in need of cytoreduction but ineligible for FOLFOXIRI, chemotherapy doublets with anti-EGFR agents could also be considered.

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