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Cetuximab versus bevacizumab maintenance following prior 8-cycle modified FOLFOXIRI plus cetuximab in Asian postmenopausal women with treatment-naive KRAS and BRAF wild-type metastatic colorectal cancer

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Abstract

Objective: To assess the efficacy and safety of cetuximab (CE) versus bevacizumab (BE) maintenance treatment after prior 8-cycle modified 5-fluorouracil, folinate, oxaliplatin, and irinotecan (FOLFOXIRI) plus CE induction therapy in treatment-naive KRAS and BRAF wild-type (wt) metastatic colorectal cancer (mCRC).

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Methods: From 2012 to 2017, prospectively maintained databases were reviewed to assess Asian postmenopausal women with treatment-naive KRAS and BRAF wt mCRC who underwent modified FOLFOXIRI plus CE induction therapy, followed by CE or BE maintenance until disease progression or death. Co-primary clinical endpoints were progression-free survival (PFS) and overall survival (OS).
Results: A total of 222 women were included (CE n = 110 and BE n = 112). At a median follow-up of 27.0 months (interquartile range, 6.5–38.6 months), median PFS was 21.9 months (95% confidence interval [CI] 16.4–24.4) and 17.7 months (95% CI 11.3–19.0) for CE and BE groups, respectively (hazard ratio [HR] 0.31, 95% CI 0.15–0.46); median OS was 26.0 months (95% CI 23.4–28.7) and 22.7 months (95% CI 21.2–24.3) for CE and BE groups, respectively (HR 0.22, 95% CI 0.11–0.37).
Conclusions: CE maintenance treatment is more poorly tolerated but has a slightly more modest survival benefit compared with BE maintenance treatment in mCRC.

Keywords
Cetuximab, bevacizumab, colorectal cancer, progression-free survival, overall survival, postmenopausal women

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Introduction

Evidence-based statistics demonstrated that 43% of metastatic colorectal cancers (mCRC) are KRAS and BRAF wild-type (wt),[1,2] and the treatment of such patients remains a challenge.[2,3] Their median survival time is highly variable, ranging from 6 to 18 months, with a large range within each study subgroup.[4–6] Furthermore, optimal treatment strategies are highly controversial, aiming to balance a favorable effect on progression-free survival (PFS) and overall survival (OS) versus adverse events (AEs) in these patients.[6]

Combination treatment schedules with a modified 5-fluorouracil, folinate, oxaliplatin, and irinotecan (FOLFOXIRI) regimen plus a molecularly targeted drug (cetuximab [CE] or bevacizumab [BE]) in the first-line setting have been acknowledged as the standard processing scheme on the basis of published clinical efficacy and safety profiles.[6–8] Previous investigators have carried out prospective Phase 1 and 2 trials to establish the safety and efficacy of modified FOLFOXIRI plus CE in the setting of KRAS and BRAF wt mCRC.[6,9–11] The most recent randomized phase 2 clinical trial demonstrated that excluding patients with other RAS-mutated tumors from the KRAS and BRAF wt population may improve the benefit associated with adding CE to modified FOLFOXIRI, which is considered the best approach due to its potential to maximize the survival benefit as initial management in patients with KRAS and BRAF wt mCRC.[6,12] Nevertheless, no data regarding postmenopausal women or a comparison of CE and BE are available. Furthermore, no optimal schedule has yet been confirmed for postmenopausal women whose tumors harbor KRAS and BRAF wt mutations and whose disease progresses following a first-line combination of modified FOLFOXIRI. Additionally, PFS and OS with this schedule have never been assessed in Asian postmenopausal women.

We therefore conducted a retrospective review of Asian postmenopausal women

with treatment-naive KRAS and BRAF wt mCRC. To our knowledge, this is the first analysis that directly compares the efficacy and safety of CE against BE as maintenance treatment following prior 8-cycle modified FOLFOXIRI plus CE induction therapy.

Materials and methods

Study design and patient eligibility

This study was approved by the Medical Ethics Committee from The First Affiliated Hospital, Sun Yat-sen University, and an exemption from informed consent was obtained from our responsible Investigational Ethics Review Board. The clinical and molecular characteristics and outcome data for Asian postmenopausal women with treatment-naive KRAS and BRAF wt mCRC retrieved from a registry database were identified at four medical centers from August 2012 to August 2017. Patient data regarding drug delivery, general condition, and survival status were obtained from medical records.

The cohort consisted of 334 Asian postmenopausal women who had undergone first-line 8-cycle modified FOLFOXIRI plus CE induction therapy followed by CE or BE maintenance. The main inclusion criteria were: age 60 to 76 years; histologically confirmed adenocarcinoma of the colon or rectum; harboring KRAS and BRAF wt mutations, regardless of NRAS; a life expectancy $\geq$2 years excluding the mCRC diagnosis; at least one measurable lesion assessed in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1;[13] treatment-naive mCRC according to RECIST version 1.1; adequate hematologic, liver, bone marrow and renal function, as previously described;[12,14] and an Eastern Collaborative Oncology Group score of 0 to 1. The main exclusion criteria were: KRAS- and BRAF-mutated mCRC with progression following induction therapy with modified FOLFOXIRI plus CE; a history of chemotherapy for mCRC; without rigid proctoscopy; gastrointestinal perforation; intestinal obstruction; severe circulatory diseases (e.g. clinically significant cardiovascular events within 6 months or cardiovascular events requiring medication); severe organ failure; uncontrolled metabolic dysfunction; discontinuation or interruption of CE or BE regimen; tumor invading major blood vessels; a high risk of bleeding; focal or mental deficits; a New York Heart Association classification of 3; delirium or other cognitive impairment;[15] and no or poor pretreatment image data or inadequate medical records. Data were collected by four investigators (one per institution) and were reviewed by a fifth investigator. The co-primary clinical endpoints were PFS and OS; the secondary clinical endpoint was AEs.

Definitions of the descriptive variables

The definition of treatment-naive KRAS and BRAF wt mCRC in the present study is in line with a previous report.[16] The first occurrence of metastatic disease, which was confirmed by adequate radiological imaging, was considered unresectable. Disease progression or tumor response was assessed using RECIST version v1.1. PFS was defined as the time from the onset of maintenance to the evidence of progression or death from any cause, whichever occurred first; OS was defined as the time from the onset of maintenance to death from any cause. For PFS evaluation, cases were censored at the final follow-up if progression or death did not occur. For OS evaluation, cases were censored at the final follow-up if death did not occur.

Tissue handling was consistent with ESMO consensus guidelines.[17] At least 50% tumor content was provided on primary or metastatic samples. The DNeasy kit (Qiagen Inc., Valencia, CA, USA) was used to extract DNA from formalin-fixed, paraffin-

embedded tumor tissue. The time from tissue sampling to fixation was limited to less than 10 minutes to reduce the degradation of proteins and nucleic acids. The fixation time was between 6 and 12 hours. Biomarker analyses (KRAS and BRAF mutations) were performed within 1 month using PCR as previously described.[11]

Symptoms were assessed every 3 months throughout the follow-up period. Disease assessment by contrast-enhanced computed tomography was performed every 4 weeks until disease progression, withdrawal, unacceptable AEs, or death. Safety assessments (physical examination, AEs, and routine laboratory tests) were performed at least every 2 weeks for the initial 12 weeks of treatment and at least every 4 weeks thereafter. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Study design and treatment

A retrospective multi-center study was carried out in which eligible patients received 8-cycle modified FOLFOXIRI plus CE induction therapy every 2 weeks for up to eight cycles, as described by Cremolini et al.,[8] followed by CE (intravenous 500 mg/m^2 over 60 minutes, q2w) or BE (intravenous dose of 5 mg/kg over 30 minutes, q2w) maintenance. Maintenance treatment was continued until disease progression, withdrawal, unacceptable AEs, or death for patients who were stable or better after the completion of initial induction therapy.

Statistical analysis

The statistical methods used in this study have previously been described.[14] Briefly, categorical data and continuous data were compared using the chi-square test or Mann–Whitney U-test and Student's t test, respectively. The reverse Kaplan–Meier method was used to assess the median period of follow-up. Co-primary endpoints (survival curves) were estimated using Kaplan–Meier methods. In the multivariate analyses, hazard ratios (HRs) and appropriate 95% confidence intervals (CIs) were assessed using the logistic regression model and Cox proportional hazard model, respectively. Statistical analyses were performed using SPSS software, version 24.0 (IBM, Inc., Armonk, NY, USA). All P values were two-sided. P values of 0.05 or less were considered statistically significant.

Results

Comparison of baseline data

Between August 2012 and August 2017, 334 postmenopausal women were enrolled in the study. One hundred and twelve patients were deemed ineligible on the basis of exclusion criteria, leaving 222 patients. Of these, 110 received CE (mean age, 68.5 years [SD 7.62]) and 112 received BE (mean age, 68.4 years [SD 6.88]) (Figure 1). Patient characteristics are summarized in Table 1, and similar baseline characteristics were observed between groups regardless of other gene mutations. The median duration of follow-up was 27.0 months (interquartile range, 6.5–38.6 months). There were no significant between-group differences in patient demographics or baseline characteristics. However, disease progression occurred significantly more frequently in the BE group than in the CE group (38.4% vs 25.5%, respectively; P = 0.039) (Table 2). During maintenance treatment, a 25% dropout rate was detected.

Comparison of efficacy

At the final follow-up, the median PFS was 21.9 months (95% CI 16.4–24.4 months) in the CE group and 17.7 months (95% CI 11.3–19.0) in the BE group. The median

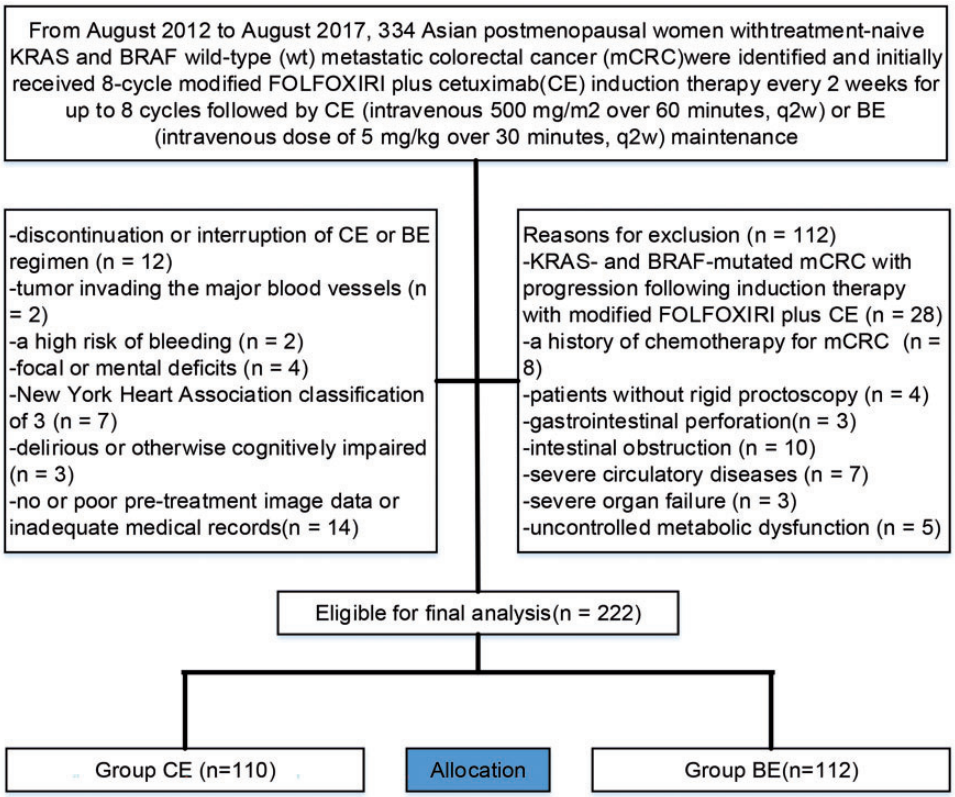

Figure 1. Flow diagram demonstrating methods for the identification of studies to retrospectively assess the efficacy and safety of CE versus BE in maintenance treatment following prior 8-cycle modified FOLFOXIRI plus CE induction therapy in Asian postmenopausal women with treatment-naive KRAS and BRAF wild-type (wt) metastatic colorectal cancer (mCRC).
CE: cetuximab; BE: bevacizumab; FOLFOXIRI, 5-fluorouracil, folinate, oxaliplatin, and irinotecan.

OS was 26.0 months (95% CI 23.4–28.7) in the CE group and 22.7 months (95% CI 21.2–24.3) in the BE group. Significant between-group differences were detected in the median PFS (HR 0.31, 95% CI 0.15–0.46; $P<0.005$) (Figure 2) and median OS (HR 0.22, 95% CI 0.11–0.37; $P=0.026$) (Figure 3).

Adverse events

Regarding the safety profile, the incidence of main treatment-related AEs is summarized in Table 3. BE appeared to be safer than CE regarding skin toxicity, according to the observed toxicity profile. The frequency and severity of treatment-related AEs were in accordance with the known safety profile. Skin toxicity occurred in 27 patients (12.2%) in both groups, including two (0.9%) with hand–foot syndrome, which occurred during the first 3 months of the CE maintenance phase in 19 patients and during the first 7 months of the BE maintenance phase in eight patients. Hypertension was significantly more frequent in the CE group than in the BE group (21.8% vs 10.7%, respectively; $P=0.025$). Dose modifications for AEs were required in some patients, occurring

Table 1. Patient demographics between groups.

Variable	CE (n = 110)	BE (n = 112)	*P*-value
Age at onset (years)	68.5 ± 7.62	68.4 ± 6.88	0.217[a]
Primary tumor site			0.650[b]
Right-sided (cecum to transverse colon)	47	46	
Left-sided (splenic flexure to rectum)	45	44	
Multiple sites	18	22	
Site of specimen			0.673[b]
Primary tumor	91	95	
Metastatic tumor	19	17	
Duration of treatment (months)	26.5 ± 13.24	26.6 ± 15.27	0.143[a]
Performance status (ECOG)			0.764[b]
0	43	46	
1	67	66	
Number of metastatic sites			0.623[b]
1	23	21	
>1	74	76	
Unknown	13	15	
Response to prior induction treatment			0.829[b]
Stable disease	58	56	
Partial response	21	24	
Complete response	19	22	
No change	12	10	
Time from induction treatment to start of maintenance treatment			0.465[b]
≤2 weeks	97	95	
>2 weeks	13	17	

[a]Analyzed using an independent samples t-test; [b]Analyzed using the Mann–Whitney test. CE: cetuximab; BE: bevacizumab; ECOG: Eastern Collaborative Oncology Group.

in 22 cases who had a dose reduction (16 [14.5%] for CE and six [5.4%] for BE; P = 0.022) due to grade 3 to 4 neutropenia. Other grade 3/4 AEs included diarrhea (n = 32 [14.4%]), asthenia (n = 25 [11.3%]), and stomatitis (n = 13 cases [5.9%]).

Discussion

Our study followed Asian postmenopausal women with treatment-naive KRAS and BRAF wt mCRC for a median duration of more than 2 years. Our results confirm the feasibility of CE or BE maintenance following prior 8-cycle modified FOLFOXIRI plus CE induction treatment. The superiority of CE over BE in the setting demonstrates a tendency to be positive.

Our study results, in line with other similar studies,[6,15,16] provide evidence that CE tends to improve the survival benefit of patients with treatment-naive KRAS and BRAF wt mCRC. In a previous prospective, multi-center randomized Phase 2 trial,[6] 143 enrolled patients with RAS and BRAF wt mCRC were randomized to undergo a first-line induction treatment of modified FOLFOXIRI plus CE followed by CE or BE. In the maintenance population of this study, the median PFS was 13.3 months (95% CI 11.2–17.3 months) for CE and 10.8 months (95% CI 9.3–13.9 months) for BE (HR, 0.73; 95% CI 0.46–1.17), while

Table 2. Comparison of treatments of Asian postmenopausal women with KRAS and BRAF wt mCRC at the final follow-up.

Variable	CE (n = 110)	BE (n = 112)	*P*-value
Disease progression	28 (25.5%)	43 (38.4%)	0.039*,[a]
Metastatic brain/leptomeningeal tumors	22 (20%)	25 (22.3%)	0.672[a]
>3 metastases[#]	26 (23.6%)	31 (27.7%)	0.491[a]

*Statistically significant values. [a]Analyzed using the chi-square test. [#]involving the brain, bone, lung, and liver. CE: cetuximab; BE: bevacizumab; wt: wild-type; mCRC: metastatic colorectal cancer.

the median OS was 37.5 months (95% CI 32.0 to not estimable) for CE and 37.0 months (95% CI 30.0 to not estimable) for BE (HR, 0.98; 95% CI 0.52–1.87). It is unclear why these similar treatment regimens failed to translate into parallel gains in survival benefit. A potential explanation for the worse-than-expected median PFS or median OS performance of the maintenance phase between the trial and our study may be the choice of the research object or that we do not fully understand how the menopausal hormone affects KRAS and BRAF wt mCRC.[17–19] In our study, the choice of CE as monotherapy instead of its combination with BE might have affected the survival benefit. Of additional interest is the large effect of CE on mCRC treatment in the first year and its minimal effect thereafter. As expected, not all cases completed the maintenance period and a 25% dropout rate was observed, but this was significantly lower than the previous report of 33%.[6] Nevertheless, the importance of converting BE into CE as maintenance was not predetermined at the time of implementing this treatment schedule, mainly because of objective factors (i.e., BE deficiency).

RAS-mutated mCRC, defined by mutations in KRAS and NRAS exons 2 to 4, is associated with a poor PFS and/or OS, reflecting an interaction between RAS-mutated subtypes.[6,20,21] Frequent debate has occurred regarding the influence of RAS-mutated subtypes of patients, particularly those with mCRC harboring mutations in KRAS and BRAF.[22,23] There is also a paucity of survival data in the published studies about Asian postmenopausal women with treatment-naive KRAS and BRAF wt mCRC. However, survival data reported with CE maintenance tend to be favorable even when compared with other forms of maintenance in cases with fewer previous therapies.[6,9,15] Although our study recognizes a distinct separation of PFS or OS curves favoring the continuation of CE maintenance rather than the switch to BE maintenance, our subjects were limited to Asian postmenopausal women. A strong adherence to protocol regimen in treatment following prior 8-cycle modified FOLFOXIRI plus CE was reintroduced in 71.6% of patients with treatment-naive KRAS and BRAF wt mCRC.[6] Although the reintroduction of CE or BE used during the maintenance phase is supported by previous trials,[6,10,15] the continuation of CE beyond progression failed to provide encouraging outcomes in the CAPRI-GOIM trial.[24,25] In contrast to prior reports,[6,24] however, we detected a non-significant interaction between drug and mutation status; in relation to PFS and OS, there appeared to be trends towards a greater CE benefit compared with BE although this was limited by the population size.

Our study has a number of limitations. First, its retrospective nature reduces the power to draw reliable conclusions, and

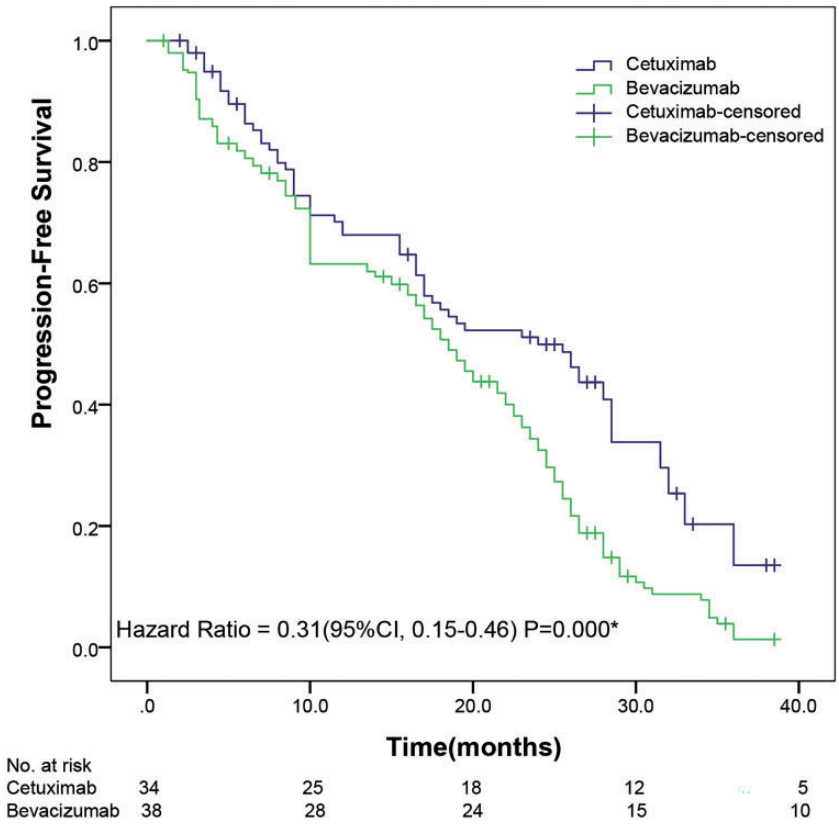

Figure 2. Kaplan–Meier curves for progression-free survival.
The median progression-free survival (PFS) time was 21.9 months (95% confidence interval [CI] 16.4–24.4) and 17.7 months (95% CI 11.3–19.0) for the CE and BE groups, respectively. A significant difference was observed in PFS between groups. *The hazard ratio was calculated using a Cox proportional-hazards model, with the type of age, site of primary tumor, number of metastatic sites, and performance status as covariates and CE/BE therapy as the time-dependent factor. Regarding PFS, the log-rank test gave a $P < 0.005$.
CE: cetuximab; BE: bevacizumab.

all potential confounding variables (i.e., underlying diseases) may not have been addressed in the study. Second, the small number of patients may have introduced bias, preventing us from drawing preferred conclusions about the maintenance approach. Third, our analysis lacks generalizability because the study population only included Asian postmenopausal women with treatment-naive KRAS and BRAF wt mCRC. Finally, the power tended to be underestimated, mainly because of repeated observations of each subject.

In conclusion, the results reported here stimulate a growing body of evidence that CE maintenance following prior 8-cycle modified FOLFOXIRI plus CE induction therapy in Asian postmenopausal women with treatment-naive KRAS and BRAF wt mCRC tends to be more poorly tolerated but has a slightly more modest, if any, survival benefit compared with BE maintenance. In light of our findings, we are not

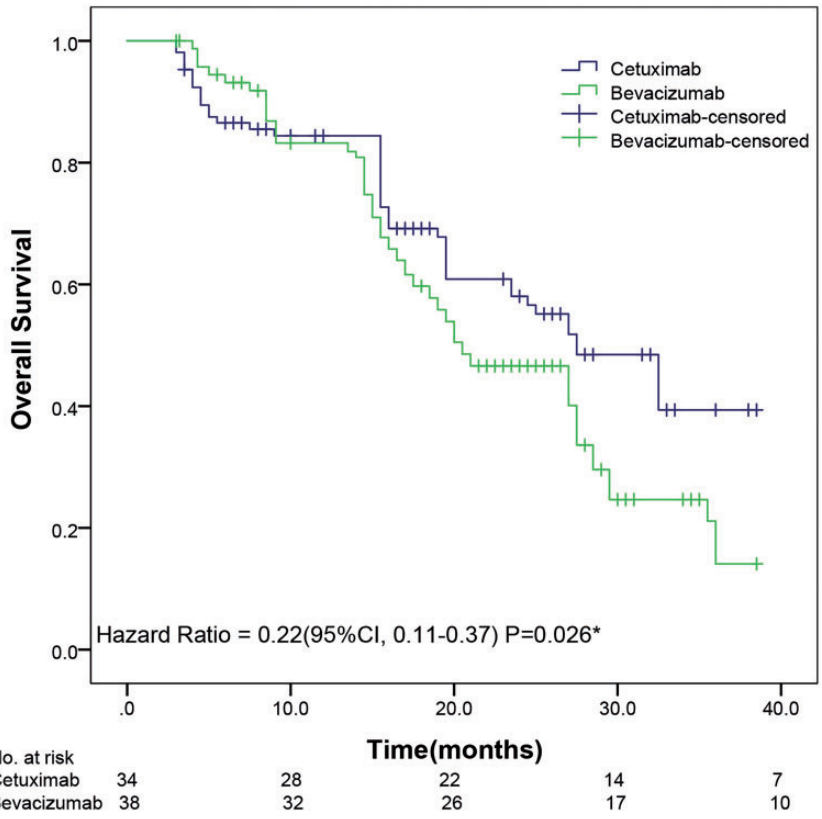

Figure 3. Kaplan–Meier curves for overall survival.
The median overall survival (OS) time was 26.0 months (95% CI 23.4–28.7) and 22.7 months (95% CI 21.2–24.3) for the CE and BE groups, respectively. A significant difference was detected in OS between groups. *The hazard ratio was calculated using a Cox proportional-hazards model, with the type of age, site of primary tumor, number of metastatic sites, and performance status as covariates and CE/BE therapy as the time-dependent factor. Regarding OS, the log-rank test gave a P = 0.026.
CE: cetuximab; BE: bevacizumab.

Table 3. Comparison of the incidence of major treatment-related grade 3 or 4 AEs between groups at the final follow-up.

AEs	CE (n = 110)	BE (n = 112)	*P*-value
Skin toxicity	19 (17.3%)	8 (7.1%)	0.021*,[a]
Hypertension	24 (21.8%)	12 (10.7%)	0.025*,[a]
Neutropenia	16 (14.5%)	6 (5.4%)	0.022*,[a]
Diarrhea	17 (15.5%)	15 (13.4%)	0.662[a]
Asthenia	11 (10.0%)	14 (12.5%)	0.556[a]
Stomatitis	5 (4.5%)	8 (7.1%)	0.410[a]

*Statistically significant values. [a]Analyzed using the Chi-square test. AEs: adverse events; CE: cetuximab; BE: bevacizumab.

currently advocating the use of BE maintenance as a clinical decision in Asian postmenopausal women with treatment-naive KRAS and BRAF wt mCRC. Further evidence-based prospective assessment of the long-term efficacy and safety of CE or BE in a similar setting should be performed to confirm our findings.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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