VARIABLES FOR THE LEFT SUBGROUP

The propensity score for ORR was derived from the following variables: age, type of first concomitant chemotherapy, ECOG PS score, tumor stage at diagnosis, liver metastases, peritoneum metastases, number of metastatic sites, liver comorbidity, musculoskeletal system disease, respiratory system diseases, mental disorders, prior radiotherapy, prior adjuvant chemotherapy, prior surgery, number of distinct comorbidities, primary tumor site (colon/rectum/colon-rectum), and duration between diagnosis of mCRC and cetuximab initiation. All the covariates included in the propensity score showed a good balance (SDiff ≤ 0.1) after inverse probability of treatment weighting (IPTW).

VARIABLES FOR THE RIGHT SUBGROUP

The propensity score for ORR was derived from the following variables: age, type of first concomitant chemotherapy, ECOG PS score, tumor stage at diagnosis, liver metastases, peritoneum metastases, other metastases, number of metastatic sites, kidney comorbidity, liver comorbidity, cerebrovascular diseases, endocrine and metabolic diseases, prior radiotherapy, prior adjuvant chemotherapy, prior surgery, number of distinct comorbidities and duration between diagnosis of mCRC and cetuximab initiation. All covariates included in the propensity score showed a good balance (SDiff ≤ 0.1) after “inverse probability of treatment weighting (IPTW); with the exception of type of first concomitant therapy, the tumor stage at diagnosis, and prior radiotherapy that presented only a sufficient balance (SDiff > 0.1 and < 0.25). The “sufficient” balance of these two variables was likely due to the low number of patients in some of their categories.

- **ORR, DCR** were assessed via **Logistic regression** after inverse probability treatment weighting
  - For the main analysis, if the best overall response (BOR) was unknown, patients were considered non-responders
  - In the sensitivity analyses patients with an unknown BOR were considered as responders if they had received cetuximab for ≥12 weeks

	Rate % (95% CI)		OR after IPTW (95% CI)
	Q1W	Q2W	Q2W vs Q1W
ORR			
Sensitivity analysis			
Overall*	63.9 (60.4, 67.3)	68.4 (64.5, 72.3)	1.226 (0.971, 1.548)
Left subgroup	67.6 (63.2, 71.9)	73.1 (68.5, 77.7)	1.304 (0.962, 1.767)
Right subgroup	47.8 (39.0, 56.5)	49.0 (38.9, 59.0)	1.048 (0.619, 1.771)
DCR			
Sensitivity analysis			
Overall*	80.9 (78.2, 83.7)	82.5 (79.3, 85.7)	1.108 (0.834, 1.473)
Left subgroup	81.6 (78.0, 85.2)	85.1 (81.5, 88.8)	1.292 (0.889, 1.878)
Right subgroup	66.3 (58.1, 74.5)	71.8 (62.7, 80.8)	1.291 (0.727, 2.294)

CI, confidence interval; DCR, disease control rate; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OR, odds ratio; ORR, overall response rate; Q1W, once weekly; Q2W, every-2-weeks.

*Includes patients with right-sided, left-sided, and unknown primary tumor locations

MAIN ANALYSIS ARTICLE

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Original Research

Noninferiority of cetuximab every-2-weeks versus standard once-weekly administration schedule for the first-line treatment of *RAS* wild-type metastatic colorectal cancer

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Abstract ***Aim:*** This study assessed whether cetuximab 500 mg/m^2 administered every 2 weeks (Q2W), when combined with chemotherapy as a first-line (1L) treatment, was noninferior to the approved dose (400 mg/m^2 followed by 250 mg/m^2 once weekly [Q1W]) for overall survival (OS) in adults with *RAS* wild-type metastatic colorectal cancer (mCRC).
Methods: This pooled analysis included patients receiving 1L treatment with cetuximab Q1W or Q2W in combination with chemotherapy from post-authorisation studies with patient-level data available to the sponsor. Baseline characteristics were adjusted with a propensity score using inverse probability of treatment weighting (IPTW). Noninferiority in terms of OS was tested with a noninferiority margin for the hazard ratio (HR) of 1.25 using a Cox proportional hazards regression model. Secondary outcomes were progression-free survival (PFS), overall response rate (ORR) and rates of lung/liver metastases resection and serious adverse events.

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Results: OS time was noninferior in the Q2W cohort (n = 554) compared to the Q1W cohort (n = 763), with a HR after IPTW (95% confidence interval) of 0.827 (0.715–0.956) and median OS times of 24.7 (Q1W) and 27.9 (Q2W) months. There were no major differences in PFS (HR: 0.915 [0.804–1.042]). The odds ratios (ORs) after IPTW for ORR (1.292 [1.031–1.617]) and the rates of lung/liver metastases resection (1.419 [1.043–1.932]) favoured the Q2W regimen. No differences were noted in the occurrence rate of any SAE between groups; the OR after IPTW was 1.089 (0.858–1.382).

Conclusions: The cetuximab Q2W regimen was noninferior to the Q1W regimen for OS in the 1L treatment of mCRC.

1. Introduction

Colorectal cancer (CRC) is a major cause of morbidity and mortality, with metastases reported in 25% of patients with newly diagnosed disease [1]. Approximately half of all patients with CRC die of metastatic disease; the overall five-year survival of these patients is <10% [1]. Current first-line (1L) standard of care for patients with unresectable metastatic CRC (mCRC) is chemotherapy in combination with monoclonal antibodies (mAbs), including anti–epidermal growth factor receptor (EGFR) mAbs such as cetuximab or panitumumab or the anti–vascular endothelial growth factor mAb bevacizumab [2–5].

Cetuximab is approved by the European Commission and in many other countries for the treatment of patients with EGFR-expressing, *RAS* wild-type (wt) mCRC (1) in combination with irinotecan-based chemotherapy, (2) in 1L in combination with 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX), and (3) as a monotherapy for patients who have failed oxaliplatin- and irinotecan-based therapy or who are intolerant to irinotecan [6]. The approved schedule of cetuximab is an initial dose of 400 mg/m^2 of body surface area, followed by subsequent doses of 250 mg/m^2 once-weekly (Q1W). The efficacy and safety of weekly cetuximab in patients with *RAS* wt mCRC are well documented [7–11]. However, in clinical practice, a schedule of cetuximab 500 mg/m^2 every 2 weeks (Q2W) is frequently used [12–15]. In terms of pharmacokinetics, the cetuximab 500-mg/m^2 Q2W regimen has shown a similar profile to the 250-mg/m^2 Q1W regimen and may be a convenient alternative to the Q1W schedule, as the administration schedules of FOLFOX and FOLFIRI (LV calcium [folinic acid], fluorouracil, and irinotecan hydrochloride) are also biweekly [16]. In addition, a recent comparison of healthcare costs between the Q1W and Q2W regimens in a US claims database study showed no cost differences between them [17]. The cetuximab Q2W regimen is recommended in treatment guidelines in the United Kingdom and France, as well as in National Comprehensive Cancer Network guidelines [2,3,18,19].

This analysis investigated whether 1L treatment with the cetuximab Q2W regimen is noninferior to the Q1W regimen in terms of overall survival (OS) when used in combination with chemotherapy in patients with *RAS* wt mCRC.

2. Methods

2.1. Study design

This study is a pooled analysis of post-authorisation studies (non-interventional studies [NIS] and clinical trials [CT]), conducted in European Union and Asia-Pacific countries using patient-level data available to the marketing authorisation holder at the time of study initiation, in patients with confirmed *RAS* wt mCRC receiving 1L treatment with cetuximab Q1W or Q2W in combination with chemotherapy from 2007 to 2018 [13,15,20–23]. Patients were categorised into two mutually exclusive cohorts, Q2W or Q1W, based on the administration schedule planned and reported by the treating physician at treatment initiation. Patients were followed up from the date of cetuximab initiation (defined as the index date) until all-cause death, loss to follow-up or study withdrawal, or the end of the individual study observation period. As no contact with patients was required and no additional data were collected, no additional informed consent was required for this study.

2.2. Selection of studies and patients

The studies selected for pooled analysis were required to have been conducted after approval of cetuximab; to have been sponsored by Merck KGaA, Darmstadt or external investigators; to have patient-level data available to Merck KGaA at the time of study initiation; to have their enrolment period completed at the time of initiation of this pooled analysis; to have evaluated the

efficacy of cetuximab as a 1L treatment for the main study outcome; and to have included patients with confirmed *RAS* wt mCRC irrespective of the number/localization of metastatic sites. Based on these criteria, five NIS/CT were selected: two NIS (EREBUS, ERBITAG [intermediate data cutoff, December 7, 2018]) and three CT (CEBIFOX, CECOG/CORE 1.2.002, APEC) (Table 1) [13,15,20–23]. Additional inclusion criteria applied to individual patients are presented in Supplementary Appendix 1. Most of the patients included in the underlying studies of this pooled analysis initiated a 1L treatment with cetuximab at a time when tumor sidedness was not considered a prognostic and predictive factor [24–26]. Consequently, information on tumor sidedness was not only not collected, but it was also not expected to impact the choice of the administration schedule by the physician for patients included in this pooled analysis. However, since then, it has been collected in all studies except CORE-2. As a consequence, even if the information on distribution of sidedness is now available at individual study level, it was not extracted for this pooled analysis and is not part of the analytic data set. Thus, it could not be adjusted for in the inverse probability of treatment weighting (IPTW).

2.3. Study outcomes

The primary outcome of OS was defined as the time elapsed between the index date and all-cause death. For patients who did not die during the OS observation period, OS was censored at the last date the patient was known to be alive. Secondary outcomes included progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), resection rate of lung/liver metastases, and rates of pre-specified serious adverse events (SAEs). PFS, ORR, and DCR were defined based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 for the EREBUS study and the APEC, CECOG/CORE 1.2.002, and CEBIFOX trials; the RECIST version was not specified for the ERBITAG study. All outcomes except OS were censored at switch to second-line mCRC treatment. SAEs were censored within 30 days after the end of cetuximab treatment and within 12 months after the index date. All censoring criteria applied to each outcome are shown in Supplementary Appendix 2. ORR and DCR definitions are provided in Supplementary Appendix 3. For the main analysis, if the best overall response (BOR) was unknown, patients were considered non-responders. Sensitivity analyses of ORR and DCR were added (Supplementary Appendix 4); these considered patients with an unknown BOR as responders if they had received cetuximab for ≥12 weeks.

Several analyses of patients who underwent surgical resection of lung/liver metastases were conducted, including in patients with ≥1 R0 or R0/R1 resection of lung or liver metastases and patients for whom all resections achieved an outcome of R0 or R0/R1. The safety outcome included the proportion of patients with ≥1 SAE regardless of causality to cetuximab during the first year of 1L treatment. In addition, rates of pre-specified SAEs were assessed (Supplementary Appendix 5).

2.4. Statistical analyses

Sample size calculation to compare OS between the two cetuximab administration schedules was based on a noninferiority design [27–30]. The null hypothesis (H_0) was that the Q2W schedule was inferior to the Q1W schedule in terms of the hazard ratio (HR) for OS, with a noninferiority margin for a HR of $\Delta_0 = 1.25$. The margin Δ_0 was defined based on the known activity of the Q1W schedule as a 1L treatment for *RAS* wt mCRC. A meta-analysis in a similar setting reported a HR for cetuximab Q1W in combination with chemotherapy versus chemotherapy alone of 0.77 [31], which corresponded to a margin of consideration of 1.3. A margin of 1.25 was considered more conservative than a margin of 1.3 and seemed adequate to assess noninferiority in this study. Based on this noninferiority margin and a power of 80% to reject H_0 with a one-sided type I error rate of 2.5%, 631 deaths were required for confirmatory analysis; with an estimated event rate of 60%, the required overall sample size was 1054 patients (527 per cohort).

A propensity score–based methodology was used to account for potential confounding bias and to achieve acceptable balance among the measured baseline covariates. Propensity scores for each outcome variable were estimated from multivariable logistic regression models, with cetuximab administration schedule (Q2W versus Q1W) as the dependent variable and relevant baseline covariates as explanatory variables. Selected baseline covariates were included based on their association with the outcome, $p < 0.20$ in a univariate model, and if they had <20% of data missing. In addition, some mandatory variables of clinical relevance, such as Eastern Cooperative Oncology Group performance status, were forced into the model (Supplementary Appendix 6). The propensity score was then used in the outcome model, using IPTW, and weights were stabilised and truncated [32]. Weight truncating was performed to reduce the impact of patients with extreme values. Here, all patients with a weight less than the first percentile were set to have a weight identical to that percentile; similarly, all patients with a weight greater than the 99th percentile of the observed weights were set to have that weight. OS and PFS were analysed using Cox proportional hazards methods, while logistic regression analyses were used for ORR, DCR, resection and SAE rates. For OS, noninferiority was concluded if the upper boundary of the two-sided 95% confidence interval (CI) of the HR for Q2W versus Q1W was below the noninferiority

margin of 1.25. Various sensitivity analyses were conducted to assess the robustness of the results (Supplementary Appendix 4).

3. Results

3.1. Studies included and patient baseline characteristics

In total, 1317 patients with *RAS* wt mCRC were included; the majority were from the NIS (974), with 694 (91.0%) in the Q1W cohort and 280 (50.5%) in the Q2W cohort. In the Q1W cohort, 84.3% of patients originated from the ERBITAG study (Table 1). Although several baseline differences were noted between the 2 cohorts (see Tables 2 and 3), the IPTW achieved adequate balance between them, with all variables included in the propensity score having a standardised difference of <0.1 (Fig. 1). The distribution of propensity scores for the OS analyses by cetuximab administration schedule showed good overlap between Q1W and Q2W, indicating most patients had a similar probability to be treated by either administration schedule (Supplementary Fig. 1). Similar proportions of patients with primary right-sided tumors were present in the Q1W and Q2W cohorts—21.0% and 21.7%, respectively (Supplementary Table 2).

3.2. Overall survival

The median OS after IPTW was 24.7 (95% CI: 23.1–26.8) and 27.9 (95% CI: 26.1–31.2) months in the Q1W and Q2W cohorts, respectively (Fig. 2). In total, 755 events were observed, which exceeded the number required (631) for sufficient power for confirmatory analysis. Noninferiority of the Q2W regimen versus the standard Q1W regimen was demonstrated by an HR of 0.827 after IPTW, with the upper boundary of the 95% CI (0.715–0.956) falling below 1 and well below the noninferiority margin of 1.25. Sensitivity analyses restricted to NIS, as per the actual schedule of administration received and restricted to patients with *BRAF* wt status revealed that all HRs had an upper 95% CI limit below the noninferiority margin of 1.25, supporting the robustness of the primary analysis (Fig. 3).

3.3. Secondary efficacy outcomes

No relevant differences in PFS were observed between the Q2W and Q1W cohorts (Fig. 4). Median PFS after IPTW (95% CI) was 10.3 (9.4–11.0) and 10.1 (9.1–11.1) months in the Q1W and Q2W cohorts, respectively (HR [95% CI], 0.915 [0.804–1.042]). IPTW-weighted PFS rates suggested that at 36, 48 and 72 months after the first cetuximab administration, there was a higher PFS probability for the Q2W versus Q1W regimen (Fig. 4). Adjusted odds ratios (ORs [95% CI]) for the ORR (1.292 [1.031–1.617]), DCR (1.278 [0.987–1.655]), and rate of any lung/liver resection (1.419 [1.043–1.932]) all favoured the Q2W regimen (Fig. 5).

3.4. Safety

The OR after IPTW (1.089 [0.858–1.382]) indicated no statistically significant difference in the risk of SAE

Table 1
Studies included in the pooled analysis of patients with *RAS* wt mCRC.

Study	Type	Description	Q1W (N = 763) n (%)	Q2W (N = 554) n (%)
EREBUS [13]	Non-interventional	Conducted in France between 2009 and 2016 identifying patients between 2009 and 2010 through registries of dispensations in hospital pharmacies and clinical data and cetuximab use in routine clinical practice collected based on available medical files. Patients were followed for 24 months from initiation of cetuximab and for 60 months for vital status	51 (6.7)	176 (31.8)
ERBITAG [15]	Non-interventional	Conducted in Germany between 2010 and 2018 in >750 patients with *RAS* wt mCRC who received first-line treatment with cetuximab in combination with chemotherapy	643 (84.3)	104 (18.8)
CEBIFOX [21]	Clinical trial	Conducted in Germany between 2009 and 2016; 57 patients with *KRAS* wt mCRC received cetuximab Q2W in combination with FOLFOX6 as first-line therapy	0	37 (6.7)
CECOG/CORE 1.2.002 [20,22]	Clinical trial	Conducted in 12 European countries from 2007 to 2012; 152 patients with *KRAS* wt mCRC were randomised 1:1 to first-line treatment with FOLFOX4 plus cetuximab Q1W or FOLFOX4 plus cetuximab Q2W	69 (9.0)	71 (12.8)
APEC [23]	Clinical trial	Conducted in 12 Asia-Pacific countries between 2009 and 2014; 289 patients with *KRAS* exon 2 wt mCRC were randomised to receive cetuximab Q2W in combination with FOLFOX or FOLFIRI as first-line therapy at 22 sites between September 2007 and September 2009	0	166 (30.0)

FOLFIRI: leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride; FOLFOX: leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin; FOLFOX4: 5-fluorouracil, leucovorin, and oxaliplatin, all Q1W; FOLFOX6: 5-fluorouracil, leucovorin, and oxaliplatin, all Q2W; mCRC: metastatic colorectal cancer; Q1W: once weekly; Q2W: once every 2 weeks; wt: wild-type.

Table 2
Patient baseline characteristics.

Characteristic	Q1W (N = 763)	Q2W (N = 554)
Age (years), median (interquartile range)	66 (57–73)	60 (53–69)
Male, n (%)	520 (68.2)	364 (65.7)
Tumor stage at diagnosis, n (%)		
Stage I–II	60 (7.9)	27 (4.9)
Stage III	154 (20.2)	59 (10.6)
Metastatic	441 (57.8)	331 (59.7)
Unknown	108 (14.2)	137 (24.7)
Primary tumor site, n (%)		
Colon	446 (58.5)	361 (65.2)
Rectum	295 (38.7)	175 (31.6)
Colon and rectum	22 (2.9)	18 (3.2)
BRAF status, n (%)		
Wild-type	257 (33.7)	414 (74.7)
Mutant	35 (4.6)	55 (9.9)
Unknown[a]	471 (61.7)	85 (15.3)
Site of metastasis,[b] n (%)		
Liver only	325 (42.6)	210 (37.9)
Liver and other	240 (31.5)	229 (41.3)
Lung	188 (24.6)	160 (28.9)
Other	402 (52.7)	318 (57.4)
Number of metastases sites, n (%)		
1 distant site	466 (61.1)	287 (51.8)
2 distant sites	215 (28.2)	187 (33.8)
≥3 distant sites	82 (10.7)	80 (14.4)
ECOG performance status, n (%)		
0	247 (32.4)	280 (50.5)
1	377 (49.4)	222 (40.1)
2	57 (7.5)	32 (5.8)
≥3	5 (0.7)	3 (0.6)
Unknown	77 (10.1)	17 (3.1)
Prior adjuvant chemotherapy, n (%)		
Yes	234 (30.7)	106 (19.1)
No	529 (69.3)	448 (80.9)

ECOG: Eastern Cooperative Oncology Group; Q1W: once weekly; Q2W: once every 2 weeks.
Compared with those in the Q2W cohort, patients in the Q1W cohort were older (median age, 66 versus 60 years) and were more likely to be diagnosed at stage III (20.2% versus 10.6%). The proportion of patients with primary rectal cancer (38.7% versus 31.6%), or with liver-limited metastasis (42.6% versus 37.9%), or who had received prior adjuvant chemotherapy (30.7% versus 19.1%) was higher in the Q1W cohort than in the Q2W cohort. In the Q1W and Q2W cohorts, 81.8% and 90.6% of respective patients had an ECOG PS of 0 or 1. IPTW was used to adjust for differences in baseline characteristics between the treatment groups.
[a] Overall, 99% of patients with missing *BRAF* status were from the ERBITAG study, where *BRAF* testing was not required and no post hoc testing of tumor samples was performed, as was the case in the other included studies.
[b] Patients may have metastasis at >1 site.

Table 3
Cetuximab treatment and concomitant chemotherapy.

Treatment	Q1W (N = 763)	Q2W (N = 554)
Cetuximab exposure		
Duration, median (interquartile range), weeks	23.1 (12.0–41.0)	29.9 (15.0–53.4)
First dose, median (interquartile range), mg/m^2	400 (400–400)	500 (500–500)
Total dose, median (interquartile range), mg/m^2	4650 (2650–7885)	5935 (3003–10,000)
Concomitant chemotherapy, n (%)		
FOLFIRI	377 (49.4)	202 (36.5)
FOLFOX	306 (40.1)	328 (59.2)
FOLFOXIRI	9 (1.2)	5 (0.9)
Fluoropyrimidine only	36 (4.7)	9 (1.6)
Other oxaliplatin-based chemotherapy	11 (1.4)	1 (0.2)
Other irinotecan-based chemotherapy	24 (3.1)	9 (1.6)

FOLFIRI: leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride; FOLFOX: leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin; FOLFOXIRI: folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan; Q1W: once weekly; Q2W: once every 2 weeks.
The duration of cetuximab treatment was shorter in the Q1W cohort than that in the Q2W cohort (median duration, 23.1 and 29.9 weeks, respectively); consequently, the total dose of cetuximab received by patients was lower in the Q1W cohort. FOLFIRI was the most frequently used chemotherapy regimen in the Q1W cohort, while FOLFOX was the most frequently used chemotherapy regimen in the Q2W cohort.

occurrence between the Q1W and Q2W cohorts. The rate of any SAE after IPTW (95% CI) was 29.00% (25.76–32.24%) in the Q1W cohort and 30.78% (26.94–34.62%) in the Q2W cohort. Leukopenia, skin reaction/skin infection, infusion-related reactions, diarrhoea, and mucositis occurred more frequently in the Q2W cohort; nausea/vomiting, anorexia, and colitis/enteritis occurred more frequently in the Q1W cohort. In both groups, incidence rates for all individual SAEs were <5%, indicating good tolerability of both regimens (Table 4; Supplementary Appendix 5).

4. Discussion

To the best of our knowledge, this is the first study to directly compare cetuximab Q2W and Q1W administration schedules when combined with chemotherapy as a 1L treatment for patients with *RAS* wt mCRC with sufficient power to allow for confirmatory testing of noninferiority of the Q2W regimen in terms of OS. The Q2W schedule was found to be noninferior to the Q1W schedule for OS (primary outcome). In addition, no clinically relevant difference was observed in the occurrence of any SAE between cohorts.

The use of pooled individual data from several studies made it possible to obtain the required sample size and adjust for differences in baseline characteristics of patients receiving cetuximab Q2W versus Q1W using propensity scores. This analysis also provided long-term follow-up data on OS after treatment with each regimen. The Q2W regimen may be a more convenient option for patients, potentially improving

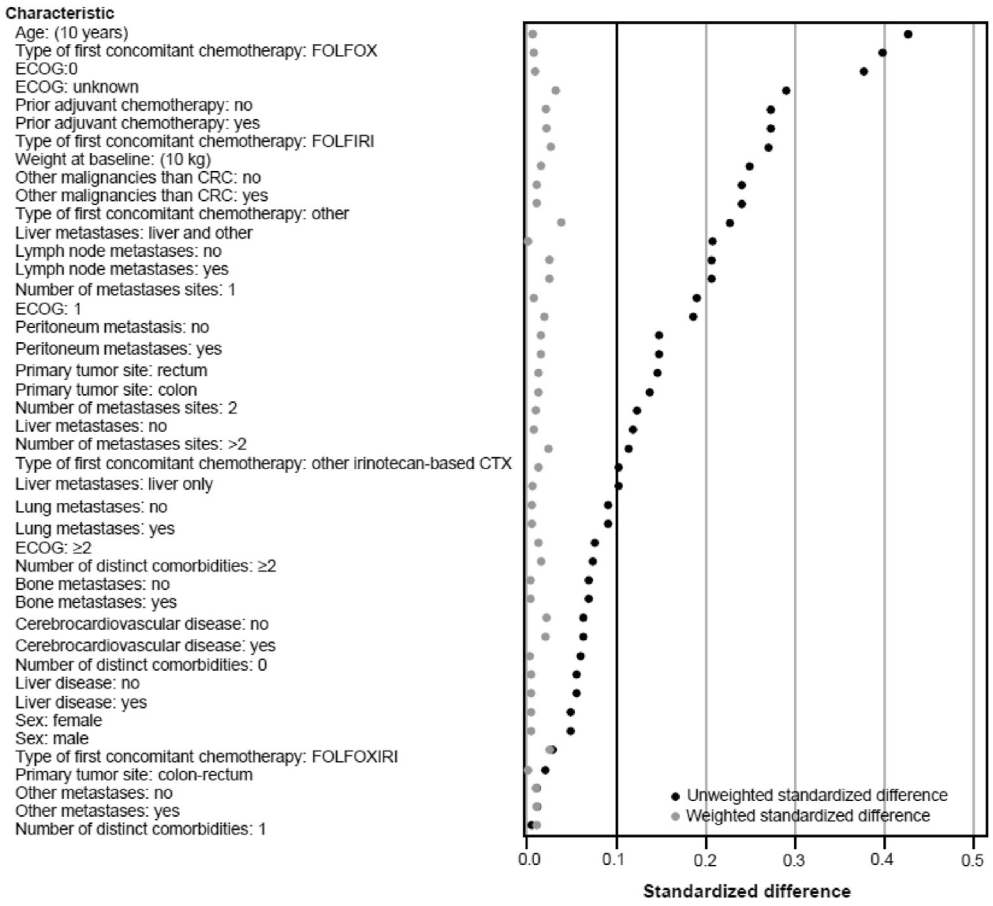


Fig. 1. Standardised differences between the cetuximab Q1W and Q2W cohorts before and after weighting for selected variables in the propensity score model for overall survival, by administration schedule. CRC: colorectal cancer; CTX: chemotherapy; ECOG: Eastern Cooperative Oncology Group; FOLFIRI: leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride; FOLFOX: leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin; FOLFOXIRI: folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan; Q1W: once weekly; Q2W: once every 2 weeks.

patient quality of life owing to less frequent administrations, reduced frequency of hospital visits, potentially fewer dose adjustments, and fewer dose omissions. However, no prior clinical trials have compared quality of life using these two regimens in mCRC; thus, there is a paucity of published data to support this conclusion. Still, our results showing the noninferiority of cetuximab Q2W versus Q1W in terms of OS align with prior studies comparing these regimens in different settings and using different methodologies [12,14,20,33–37].

While the distribution of patients with right-sided tumor was similar in the administration schedule cohorts, the performance status (PS) did not adjust for it because the data were not available at time of analysis (Supplementary Table 2). Patients with right-sided tumors are known to have worse prognosis (HR for OS, 2.03) [26]. Thus, this characteristic may have been a confounder between the association of the administration schedule and the outcomes. However, most of the patients included in this pooled analysis initiated their 1L treatment with cetuximab before 2013, at a time when tumor sidedness was not yet considered a prognostic and predictive factor and would not have been associated with choice of schedule [24,25]. As expected, the distribution of right-sided tumors is similar between both cohorts based on data available for four of five studies. Furthermore, the observed proportion of right-sided tumors (Q1W and Q2W cohorts: 21.0% and 21.7%, respectively) is in line with the proportions observed in other mCRC studies in patients with *RAS* wt disease—23%, 22%, and 31%, respectively, in the CRYSTAL, FIRE-3, and CALGB/SWOG 80405 studies (Supplementary Table 2) [26].

The E-value is a measure of the impact of unmeasured confounding (ie, sidedness) on an outcome (i.e. OS) [38]. Based on the E-value, only a strong association between tumor sidedness and OS (HR $>$ 4) could overturn the conclusion on noninferiority by moving the upper limit of the CI for the HR for OS (0.956 in this analysis) beyond the noninferiority margin of 1.25 (see calculation of the E-value in Supplementary Appendix 7). Conversely, a small association between tumor sidedness and OS (HR $>$ 1.2) or ORR (OR $<$0.8) could

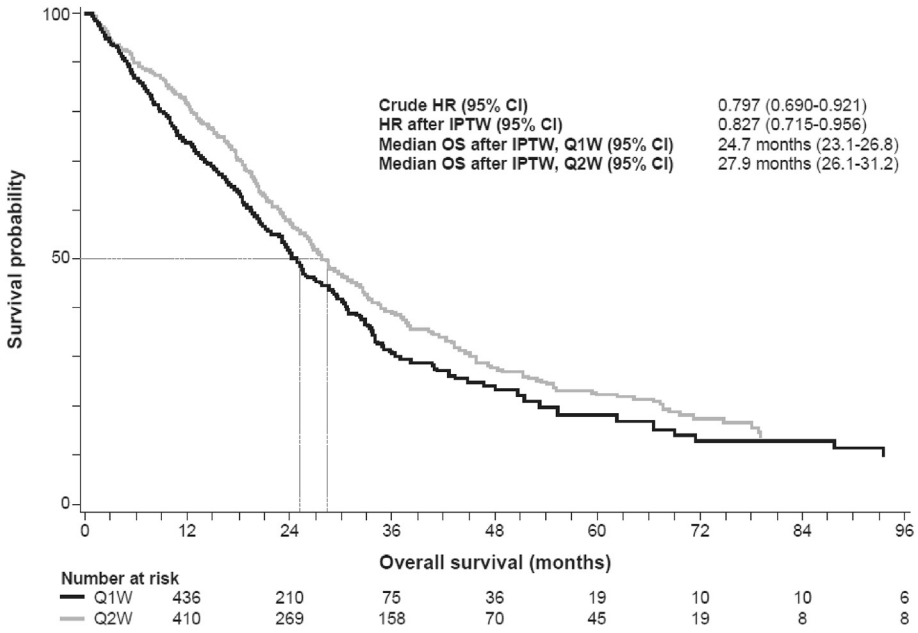


Fig. 2. OS for the cetuximab Q1W and Q2W cohorts (Cox regression after IPTW). CI: confidence interval; IPTW: inverse probability of treatment weighting; HR: hazard ratio; OS, overall survival; Q1W: once weekly; Q2W: once every 2 weeks.

overturn any claims of superiority of the Q2W schedule as the current upper border of the CI is close to 1.

Using a combination of NIS/CT for analysis is associated with variations in patient selection criteria, patient care, and outcomes data collected across studies, which increases overall heterogeneity. To reduce this heterogeneity, baseline differences were balanced using IPTW. Furthermore, restricting the study population to patients originating from NIS gave very similar results to the main analysis. Moreover, another analysis using a Cox proportional hazards model for OS after IPTW and further adjustment by study type (NIS versus CT) as a covariate also met the noninferiority criterion. While the presence of heterogeneity cannot be ignored, our results suggest that it did not impact the general conclusions reached for the primary or secondary objectives of this study. The methodologies used to collect data varied considerably for several study outcomes. For example, tumor assessments were performed at regular intervals (i.e. every 8 weeks) in the included CT, which provided an objective methodology not considered 'symptom driven'. Conversely, in routine clinical practice (and thus in the included NIS), tumor assessments may only be performed when the clinician

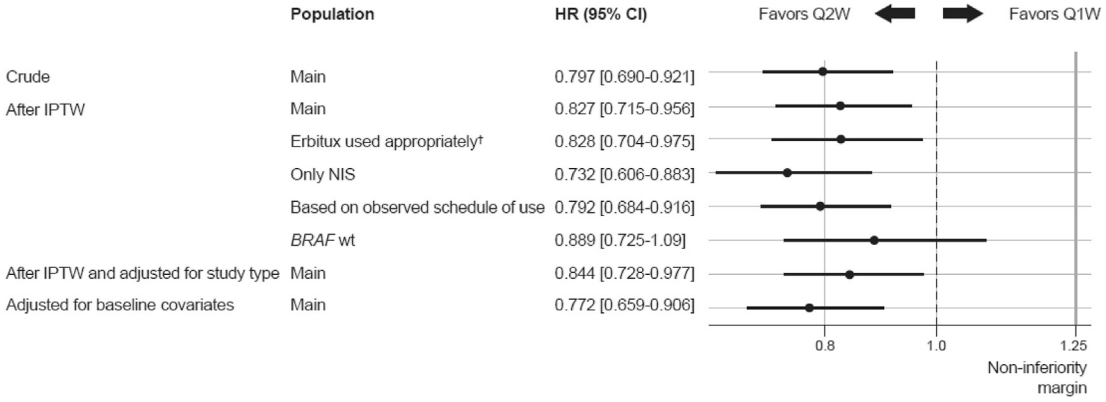


Fig. 3. Hazard ratios and corresponding CIs for OS (main and sensitivity analyses)*. 1L: first-line; CI, confidence interval; HR: hazard ratio; IPTW: inverse probability of treatment weighting; NIS: non-interventional studies; OS, overall survival; Q1W: once weekly; Q2W: once every 2 weeks; wt: wild-type. *Description of sensitivity analysis is provided in Supplementary Appendix 1. †If treated in accordance with the label or clinical practice guidelines for use of cetuximab in 1L treatment of mCRC: (1) For Q1W patients, an initial dose of 400 mg/m^2 cetuximab (ie, 360–440 mg/m^2) and subsequent weekly doses of 250 mg/m^2 (ie, 225–275 mg/m^2) in combination with FOLFOX, FOLFIRI, FOLFOXIRI, or another irinotecan-based chemotherapy; (2) For Q2W patients, an initial dose of 500 mg/m^2 cetuximab (ie, 450–550 mg/m^2) and subsequent doses of 500 mg/m^2 (ie, 450–550 mg/m^2) every two weeks in combination with FOLFOX, FOLFIRI, FOLFOXIRI, or another irinotecan-based chemotherapy.

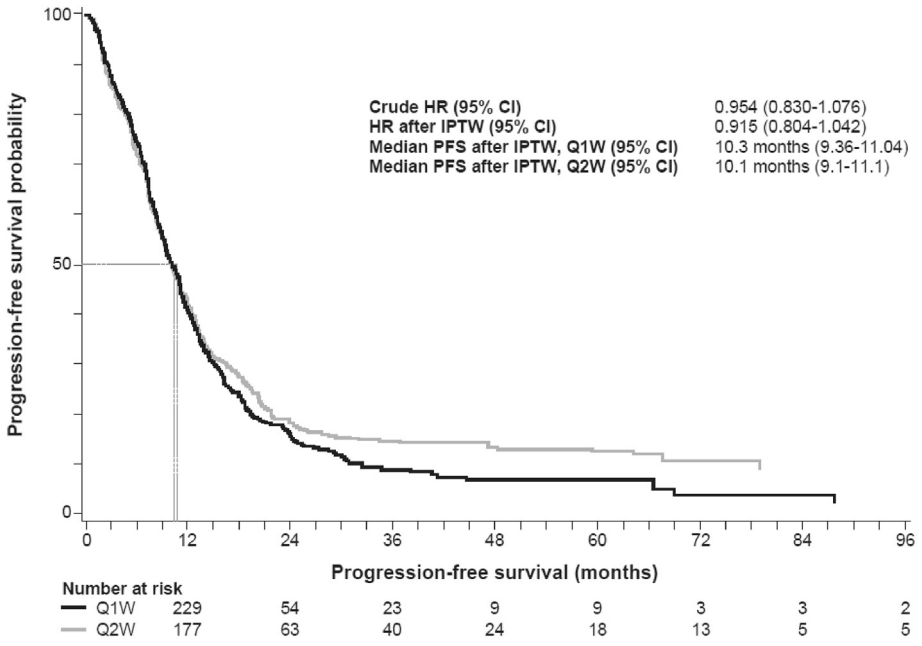
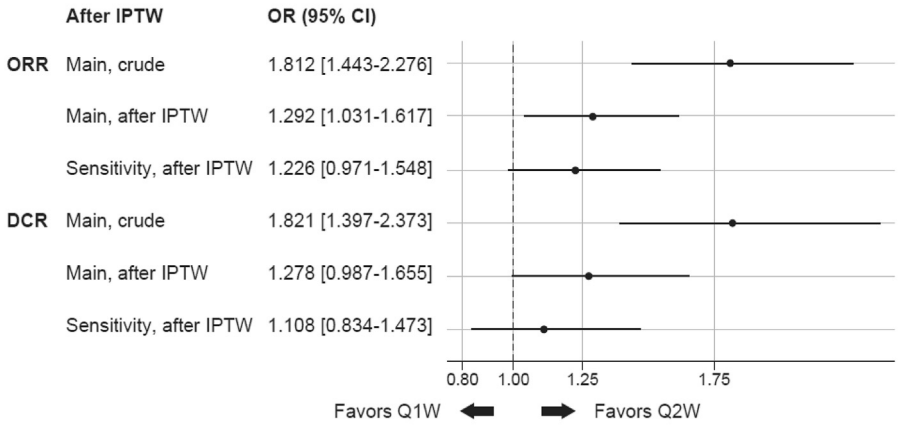


Fig. 4. PFS in the cetuximab Q1W and Q2W cohorts (Cox regression with adjustment using IPTW). HR: hazard ratio; IPTW: inverse probability of treatment weight; PFS, progression-free survival; Q1W: once weekly; Q2W: once every 2 weeks.

A.



B.

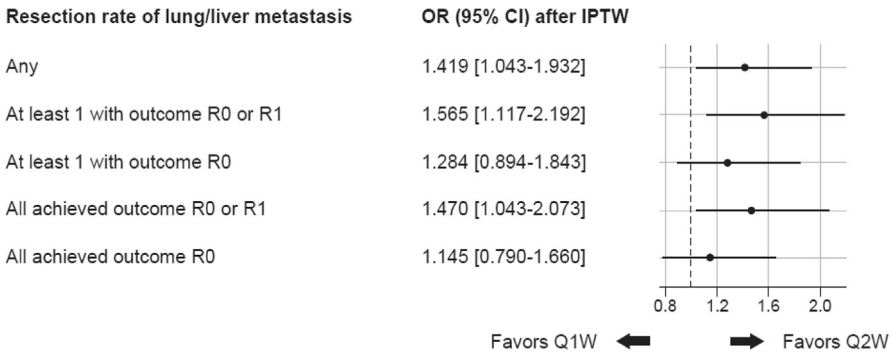


Fig. 5. ORs and corresponding CIs for (A) ORR, DCR, and (B) resection rates of lung/liver metastasis. CI, confidence interval; DCR: disease control rate; IPTW: inverse probability of treatment weighting; OR: odds ratio; ORR: overall response rate; Q1W: once weekly; Q2W: once every 2 weeks; R0: no cancer cells seen microscopically at the primary tumor site; R1: cancer cells present microscopically at the primary tumor site.

Table 4
Serious adverse events, weighted on the propensity score.[a]

Event (n, %)	Q1W (N = 763)	Q2W (N = 554)	Q2W versus Q1W OR after IPTW (95% CI)
Any SAE	220 (28.8)	170 (30.7)	1.089 (0.858–1.382)
≥1 of classified SAEs	66 (8.7)	73 (13.2)	1.687 (1.196–2.380)
Diarrhoea	29 (3.8)	27 (4.9)	1.388 (0.803–2.399)
Leukopenia	12 (1.6)	23 (4.2)	2.204 (1.158–4.198)
Nausea/vomiting	19 (2.5)	12 (2.2)	0.893 (0.449–1.778)
Skin reaction/skin infection	3 (0.4)	11 (2.0)	5.717 (1.648–19.838)
Infusion-related reaction	7 (0.9)	6 (1.1)	1.298 (0.463–3.642)
Mucositis	2 (0.3)	6 (1.1)	3.083 (0.675–14.073)
Anorexia	5 (0.7)	2 (0.4)	0.427 (0.072–2.555)
Colitis/enteritis	5 (0.7)	2 (0.4)	0.492 (0.073–3.296)

CI, confidence interval; IPTW: inverse probability of treatment weighting; OR: odds ratio; Q1W: once weekly; Q2W: once every 2 weeks; SAE: serious adverse event.
[a] Baseline confounders were balanced after weighting.

suspects a significant change such as progression. The absence of regular and predefined tumor assessment schedules in the included NIS may have reduced the probability of capturing tumor response and led to delays in capturing progression [39,40]. However, an analysis of progression or death as a binary endpoint (yes versus no), not considering the time to the event (i.e. logistic regression sensitivity analysis), did not show any relevant difference between the treatment groups (OR after IPTW: 1.078 [0.843–1.379]). This finding was similar to that for the main PFS model (HR after IPTW: 0.915 [0.804–1.042]). Furthermore, because of the consistent use of RECIST for tumor assessment in all studies, misclassification of response and progression outcomes was not considered a major issue. In addition, information on primary tumor sidedness was not available in all studies at the time of the setup of the pooled database; therefore, it was not possible to adjust for right- versus left-sided tumors in the ITPW. In the EREBUS study, SAEs were reported only during the first year of treatment; consequently, for our safety analysis, the time considered was limited in all studies to 12 months after cetuximab initiation.

5. Conclusion

In summary, this pooled analysis confirmed the non-inferiority of cetuximab Q2W versus Q1W as a 1L treatment in combination with chemotherapy in terms of OS for patients with *RAS* wt mCRC, and secondary efficacy outcomes and sensitivity analyses supported this conclusion. No clinically relevant differences were observed in the overall rates of reported SAEs between the Q2W and Q1W regimens. In addition, the Q2W regimen may potentially provide an improvement in patient QOL.

Conflict of interest statement

SK discloses honoraria (self) from Merck, Amgen, Roche, Sanofi, Aventis, Servier, and Lilly; honoraria (institution) from Merck, Amgen, Roche, and Lilly; advisory/consultancy roles with Merck, Amgen, Roche, Sanofi, Aventis, Servier, and Lilly; research grants/funding (self) from Merck and Lilly; research grants/funding (institution) from Merck and Lilly; travel/accommodation expenses from Merck, Amgen, Roche, Sanofi, Aventis, Servier, and Lilly. FXL and CF are full-time employees of Merck KGaA, Darmstadt, Germany. RE is a full-time employee of Merck KGaA, Darmstadt, Germany, and holds shares of Merck KGaA. WC is a full-time employee of Merck Serono, Shanghai, China, an affiliate of Merck KGaA, Darmstadt, Germany. TB discloses personal fees from Roche (lecture fee), personal fees from Amgen (lecture fee, advisory board), personal fees from Bayer (lecture fee, advisory board), personal fees from Novartis (lecture fee, advisory board), personal fees from PharmaMar (lecture fee, advisory board), personal fees from Eisai (lecture fee, advisory board), and personal fees from Lilly (lecture fee, advisory board), outside the submitted work. CZ discloses consultancy and speaker's honoraria from Roche, Novartis, BMS, MSD, Imugene, ARIAD, Pfizer, Merrimack, Merck KGaA, FibroGen, AstraZeneca, Tesaro, Gilead, Servier, Shire, Lilly, and Athenex. DM and VR were employees of Prometris GmbH at the time the work was performed, which provided statistical services for Merck KGaA. All remaining authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.11.013.

Author contribution

SK, CF, DM, RE, FXL, VR and WC were involved in the study concepts, study design and quality control of data and algorithms. SK, ALC, MR, TB, and CZ were involved with data acquisition. DM, VR, and WC were involved in statistical analysis. All authors were involved in data analysis and interpretation, manuscript preparation, manuscript editing and manuscript review.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, and data interpretation. The authors had access to all data in the study and had final responsibility for the decision to submit for publication.

References

[1] Rodriguez-Bigas MA, Lin EH, Crane CH. In: Kufe D, Pollock R, Weichselbaum R, editors. Holland-frei cancer medicine. 6th ed. Hamilton (ON): BC Decker; 2003.
[2] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer Version 3. 2020 [March 2020]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
[3] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer, Version 4.. 2020 [March 2020]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf.
[4] Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27(8):1386–422.
[5] Yoshino T, Arnold D, Taniguchi H, Pentheroudakis G, Yamazaki K, Xu R-H, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol 2018;29(1):44–70.
[6] ERBITUX (cetuximab). Summary of Product Characteristics. 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf.
[7] Van Cutsem E, Köhne C-H, Láng I, Folprecht G, Nowacki MP, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011;29(15):2011–9.
[8] Stintzing S, Modest DP, Rossius L, Lerch MM, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. Lancet Oncol 2016;17(10):1426–34.
[9] Loree JM, Dowers A, Tu D, O'Callaghan CJ, Edelstein D, Quinn H, et al. Expanded RAS and BRAF V600 testing as predictive biomarkers for single agent cetuximab in the randomized phase III CO.17 trial. J Clin Oncol 2019;37:537.
[10] Qin S, Li J, Wang L, Xu J, Cheng Y, Bai Y, et al. Efficacy and tolerability of first-line cetuximab plus leucovorin, fluorouracil, and oxaliplatin (FOLFOX-4) versus FOLFOX-4 in patients with RAS wild-type metastatic colorectal cancer: the open-label, randomized, phase III TAILOR trial. J Clin Oncol 2018;36(30):3031–9.
[11] Bokemeyer C, Van Cutsem E, Rougier P, Ciardiello F, Heeger S, Schlichting M, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: pooled analysis of the CRYSTAL and OPUS randomised clinical trials. Eur J Canc 2012;48(10):1466–75.
[12] Pfeiffer P, Nielsen D, Bjerregaard J, Qvortrup C, Yilmaz M, Jensen B. Biweekly cetuximab and irinotecan as third-line therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin and 5-fluorouracil. Ann Oncol 2008;19(6):1141–5.
[13] Rouyer M, François E, Sa Cunha A, Monnereau A, Noize P, Robinson P, et al. Effectiveness of cetuximab as first-line therapy for patients with wild-type KRAS and unresectable metastatic colorectal cancer in real-life practice: results of the EREBUS cohort. Clin Colorectal Canc 2018;17(2):129–39.
[14] Lamy F-L, Batech M, Salim S, Boutmy E, Pescott C, Ronga P. Real-world study of cetuximab used every other week versus weekly in US patients with metastatic colorectal cancer (mCRC). J Clin Oncol 2019;37:e15087.
[15] Sahm S, Goehler R, Hering-Schubert C, Janssen J, Neumann UP, Schwittay M, et al. Outcome of patients with KRAS exon 2 wildtype (KRAS-wt) metastatic colorectal carcinoma (mCRC) with cetuximab-based first-line treatment in the noninterventional study ERBITAG and impact of comorbidity and age. J Clin Oncol 2017;34:651.
[16] Tabernero J, Pfeiffer P, Cervantes A. Administration of cetuximab every 2 weeks in the treatment of metastatic colorectal cancer: an effective, more convenient alternative to weekly administration? Oncologist 2008;13(2):113–9.
[17] Pescott C, Batech M, Boutmy E, Ronga P, Lamy F-X. Real-world costs of cetuximab + chemotherapy administered every two weeks versus weekly for treatment of metastatic colorectal cancer. J Clin Oncol 2020;38:22.
[18] National Institute for Health and Care Excellence. Cetuximab and panitumumab for previously untreated metastatic colorectal cancer. 2017 [January 2020]; Available from: https://www.nice.org.uk/Guidance/ta439.
[19] Phelip JM, Tougeron D, Léonard D, Benhaim L, Desolneux G, Dupré A, et al. Metastatic colorectal cancer (mCRC): French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR). Dig Liver Dis 2019;51(10):1357–63.
[20] Brodowicz T, Ciuleanu TE, Radosavljevic D, Shacham-Shmueli E, Vrbanec D, Plate S, et al. FOLFOX4 plus cetuximab administered weekly or every second week in the first-line treatment of patients with KRAS wild-type metastatic colorectal cancer: a randomized phase II CECOG study. Ann Oncol 2013;24(7):1769–77.
[21] Kasper S, Meiler J, Knipp H, Höhler T, Reimer P, Steinmetz T, et al. Biweekly cetuximab plus FOLFOX6 as first-line therapy in patients with RAS wild-type metastatic colorectal cancer: the CEBIFOX trial. Clin Colorectal Cancer 2020;19(4):236–47. published online March 19, 2020.
[22] Kaczirek K, Ciuleanu TE, Vrbanec D, Marton E, Messinger D, Liegl-Atzwanger B, et al. FOLFOX4 plus cetuximab for patients with previously untreated metastatic colorectal cancer according to tumor RAS and BRAF mutation status: updated analysis of the CECOG/CORE 1.2.002 study. Clin Colorectal Canc 2015;14(2):91–8.
[23] Cheng AL, Cornelio G, Shen L, Price T, Yang T-S, Chung IJ, et al. Efficacy, tolerability, and biomarker analyses of once-every-2-weeks cetuximab plus first-line FOLFOX or FOLFIRI in patients with KRAS or all RAS wild-type metastatic colorectal cancer: the phase 2 APEC study. Clin Colorectal Canc 2017;16(2):e73–88.
[24] Modest DP, Schulz C, von Weikersthal LF, Quietzsch D, von Einem JC, Schalhorn A, et al. Outcome of patients with metastatic

colorectal cancer depends on the primary tumor site (midgut vs. hindgut): analysis of the FIRE1-trial (FuFIRI or mIROX as first-line treatment). Anti Canc Drugs 2014;25(2):212–8.
[25] Seligmann JF, Elliott F, Richman SD, Southward K, Barrett J, Quirkeet P, et al. Primary tumor location (Ptl) as a prognostic and predictive factor in advanced colorectal cancer (Acrc): data from 2075 patients (Pts) in randomised trials. Ann Oncol 2014; 25:iv172.
[26] Arnold D, Lueza B, Douillard J-Y, Peeters M, J Lenz H-, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol 2017;28(8):1713–29.
[27] Lakatos E, Lan KK. A comparison of sample size methods for the logrank statistic. Stat Med 1992;11(2):179–91.
[28] Com-Nougue C, Rodary C, Patte C. How to establish equivalence when data are censored: a randomized trial of treatments for B non-Hodgkin lymphoma. Stat Med 1993;30(12):1353–64.
[29] Collett D. Sample size determination in survival analysis. In: Balakrishnan N, et al., editors. Wiley StatsRef: statistics reference online. John Wiley & Sons; 2014.
[30] Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. Biometrics 1983;39(2):499–503.
[31] van Helden EJ, Menke-van der Houven van Oordt CW, Heymans MW, Ket JCF, van den Oord R, Verheul HMW. Optimal use of anti-EGFR monoclonal antibodies for patients with advanced colorectal cancer: a meta-analysis. Canc Metastasis Rev 2017;36(2):395–406.
[32] Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health 2010;13(2):273–7.
[33] Mrabti H, De la Fouchardiere C, Desseigne F, Dussart S, Negrier S, Errihani H. Irinotecan associated with cetuximab given every 2 weeks versus cetuximab weekly in metastatic colorectal cancer. J Canc Res Therapeut 2009;5(4):272–6.
[34] Li J, Li J. Therapeutic effect of biweekly cetuximab combined with first-line chemotherapy on KRAS/RAS wild-type advanced colorectal cancer. Int J Clin Exp Med 2019;12(10):12348–55.
[35] Yu Y, Zhang W, Sun Y, Yang L, Cui C, Zeng Y, et al. [FOLFOX/XELOX plus cetuximab administered weekly versus biweekly as a first- line treatment for patients with KRAS/RAS wild-type metastatic colorectal cancer: a retrospective study]. Chin J Clin Oncol 2018;45(23).
[36] Matsuda A, Yamada T, Jamjittrong S, Shinji S, Ohta R, Sonoda H, et al. Comparison between biweekly and weekly cetuximab in patients with metastatic colorectal cancer: a meta-analysis. Anticancer Res 2020;40(6):3469–76.
[37] Parikh A, Gugel EG, Smolyakova N, Jen MH, Toms N, Lin Y, et al. A meta-analysis of efficacy and safety of cetuximab with biweekly vs. weekly dosing. Ann Oncol 2020;31:S435.
[38] VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167(4): 268–74.
[39] US Department of Health and Human Services; US Food and Drug Administration; Office of the Commissioner. Guidance for industry: computerized systems used in clinical investigations. 2007 [March 2020]; Available from: https://www.fda.gov/files/drugs/published/Guidance-for-Industry–Computerized-Systems-Used-in-Clinical-Investigations.pdf.
[40] Dancey JE, Dodd LE, Ford R, Kaplan R, Mooney M, Rubinstein L, et al. Recommendations for the assessment of progression in randomised cancer treatment trials. Eur J Canc 2009;45(2):281–9.