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Original Article

Efficacy and Safety of Cetuximab Dosing (biweekly vs weekly) in Patients with *KRAS* Wild-type Metastatic Colorectal Cancer: A Meta-analysis

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Abstract

Background: Cetuximab 500 mg/m^2 biweekly (Q2W) plus chemotherapy is commonly used and recommended by NCCN guidelines. This meta-analysis compares efficacy and safety between Q2W versus weekly (Q1W) cetuximab dosing.

Methods: A systematic literature review was performed on Pubmed and RightFind (2007-2017) for patients with *KRAS* wild-type mCRC who received Q2W or Q1W cetuximab and other treatments. Observational studies and case reports were excluded. Randomized trials comparing Q2W and Q1W dosing, and single-arm trials with only Q2W schedule were included. CRYSTAL, a phase 3 randomized study with Q1W cetuximab dosing was paired with each single-arm study with a Q2W schedule and reweighted to achieve similar demographic/baseline characteristics. Overall survival (OS) and progression-free survival (PFS) with hazard ratios (HR), overall response rate (ORR) with odds ratios, and risk difference of adverse events of special interest (AESI) between Q2W versus Q1W cetuximab were analyzed.

Results: Five phase 2 studies with cetuximab Q2W/Q1W dosing schedules were identified: CECOG (phase 2; Q2W, *n* = 77; Q1W, *n* = 75), NORDIC 7.5 (phase 2; Q2W, *n* = 152) and NORDIC 7 (arm C of phase 3; Q1W, *n* = 109), CELINE (*n* = 60), OPTIMIX (*n* = 99), and APEC (*n* = 289) all phase 2, Q2W, single-arm studies paired with CRYSTAL Q1W dosing (*n* = 303). Efficacy was similar between Q2W versus Q1W administration; OS HR = 0.96, 95% confidence interval (CI) [0.89, 1.04]; PFS HR = 0.96, 95% CI [0.87, 1.05]; ORR odds ratio 1.16, 95% CI [0.96, 1.41]. Mean differences (Q2W-Q1W) across AESI rates were not clinically meaningful with no obvious directionality.

Conclusion: This meta-analysis demonstrated no significant differences in efficacy and safety between Q2W versus Q1W cetuximab administration in mCRC patients.

Keywords: cetuximab; colorectal cancer; biweekly; KRAS wild-type; meta-analysis.

Implications for Practice

This meta-analysis demonstrated similarity in clinical outcomes between Q2W and Q1W cetuximab dosing combined with chemotherapy in patients with KRAS wild-type mCRC. A Q2W dosing schedule of cetuximab may provide more flexibility to physicians when administering it in combination with chemotherapy and more recently approved targeted agents for mCRC. We anticipate particular interest from the medical community given the reduced burden a biweekly dosing schedule provides to both the patient and health care system, an outcome especially important during the current pandemic.

Introduction

Targeted therapies have changed the treatment landscape for cancer patients in recent years, acting with greater precision than traditional cytotoxic chemotherapies by selectively targeting malignant cells and reducing the side effects associated with nonspecific targeting of rapidly dividing healthy cells.[1] Targeted therapy drugs include monoclonal antibodies (mAbs) and oral small-molecule agents.[2] Cetuximab is an immunoglobulin G1 (IgG1) mAb targeting and binding the epidermal growth factor receptor (EGFR) expressed in cancer cells, competitively inhibiting ligand binding, downstream signaling, and stimulating degradation.[3] Improvements in progression-free survival (PFS) observed among a cohort of patients enrolled in the BOND trial contributed to the FDA approval of cetuximab in 2004.[4,5] Since then, multiple clinical trials have proven cetuximab is efficacious and safe as monotherapy or in combination with chemotherapy for patients with metastatic colorectal cancer (mCRC).[6-13] On-label

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use of cetuximab calls for Q1W dosing. This is out of step with typical chemotherapy, which is administered on a Q2W dosing schedule.[14] That being said, efficacy and safety of Q2W cetuximab have been investigated in multiple clinical studies,[14-16] and off-label cetuximab 500 mg/m^2 plus chemotherapy Q2W is commonly used and recommended by current international guidelines.[16,17]

On April 6, 2021, the FDA approved 500 mg/m2 every 2 weeks (Q2W) for cetuximab for patients with K-Ras wild-type, EGFR-expressing colorectal cancer (mCRC) or squamous cell carcinoma of the head and neck (SCCHN).[18] The feasibility of a Q2W cetuximab administration schedule was previously demonstrated in a 2-part, phase I, a dose-escalation study that included multiple Q2W doses.[3] Its prolonged half-life prompted for the closer evaluation of a routine Q2W dose. In terms of exposure, a 500 mg/m^2 Q2W dosing schedule aligned similarly with that of the 250 mg/m^2 currently approved weekly schedule (AUC0-t 35,794 vs 35,574 µg/mL*h). The pharmacokinetic data ultimately demonstrated the feasibility of a Q2W dosing schedule.[15] In addition, the safety profile of Q2W 500 mg/m^2 cetuximab administration was comparable to weekly 250 mg/m^2 cetuximab, given no new dose-limiting toxicities or treatment-related grade 3/4 adverse events (AEs).[3]

In practice, cetuximab Q2W may reduce the burden for both patients and medical staff. As mentioned previously, since typical chemotherapy regimens for mCRC are given Q2W, having a synchronized schedule with cetuximab would not only simplify the treatment course but also decrease the number of patient visits to the hospital. The efficiency gained as a consequence of the Q2W dosing schedule will ultimately reduce the cost of treatment for health care providers[3] and remove the need for an initial loading dose.[17]

Although the toxicity and efficacy profile of Q2W and Q1W cetuximab are comparable, real-world data suggest a Q2W dosing regimen is not yet widely adapted (Q2W, 32.3%; Q1W, 60.4%).[16,19] The US-based claims study indicated similar overall survival (OS) data when comparing cetuximab Q2W versus Q1W.[19] After weighing the data and adjusting for confounding variables, similar survival estimates were reported for time-to-treatment-discontinuation and time-to-next-treatment in patients receiving Q2W versus Q1W administration. The findings were consistent with published literature in which the activity and safety of FOLFOX4 plus cetuximab administered Q2W or Q1W were similar.[15] A more recent pooled analysis confirmed the noninferiority of cetuximab Q2W versus Q1W, suggesting improved OS with the Q2W schedule.[20]

While cetuximab is still only approved with an initial dose of 400 mg/m^2 followed by 250 mg/m^2 Q1W, the objective of this meta-analysis is to provide an in-depth assessment of the literature available, and to adequately assess the efficacy and safety profiles of cetuximab when given Q2W. Specifically, the incidence of OS, PFS, overall response rate (ORR), and any-grade AEs were assessed.

Methods

Literature Search

This meta-analysis was performed in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A systematic review of the literature concerning patients with KRAS exon 2, mutation-positive, wild-type mCRC who received cetuximab, published from 2007 to 2017 was performed using Pubmed and Rightfind.

Inclusion and Exclusion Criteria

Trials meeting the following criteria from the systematic literature review were included in the meta-analysis: (1) adult patients who received cetuximab Q2W at 500 mg/m^2 in combination with chemotherapy, (2) prospective studies, randomized/nonrandomized or single-armed clinical trials, and (3) reporting outcome of efficacy and safety, including OS, PFS, ORR, and AEs. Observational studies, case reports, and literature of meta-analysis were excluded. Literature lacking baseline characteristic information and/or key efficacy/safety results were also excluded. The purpose of our systematic literature review was to find clinical data with cetuximab Q2W dosing to compare with cetuximab Q1W dosing from the data from the pivotal trial, CRYSTAL.[10] Thus, patients with cetuximab Q1W dosing were not included in the systematic literature review.

Data Extraction and Analyses

The fixed-effect and random-effects methods, based on hazard ratios (HRs), as described by Borenstein et al.[21] were used to perform the meta-analysis. Higgin's I2 and tau2 were used to evaluate heterogeneity across the trials included in the meta-analysis.[22] For endpoints where the heterogeneity across the trial was significant, a random-effects model was used. Information extracted from each study included author names, publication year, patient baseline disease and demographic data, treatment administered, trial design, OS, PFS, and ORR.

The first-line mCRC indication for cetuximab was based on the pivotal study CRYSTAL, with cetuximab given Q1W.[10] NORDIC 7.5 phase 2 study was paired with NORDIC VII phase 3 study arm C, based on similarity of baseline characteristics. Other single-arm trials where patient-level data were available on a Q2W basis were paired with data from the CRYSTAL study (intervention arm: CET+FOLFIRI, mCRC indication) before inclusion in the meta-analysis. Previous references have suggested that there are no clinical differences in relative efficacy among the chemotherapy backbone of FOLFIRI, FOLFOX, FOLFOX4, or FOLFOX6 used as combination regimens.[14,23,24] Therefore, a meta-analysis incorporating the ideas found in NICE DSU document 18 was conducted, in an effort to assess the efficacy and safety of cetuximab when given on a bi-weekly basis.

Study Pairing and Entropy Balance Matching

As given in Fig. 1, a 2-step data synthesis approach was adopted to improve the comparability of criteria included in the studies under evaluation in this meta-analysis. The first step involved entropy balance matching, the process of reweighing Q1W patient-level data from CRYSTAL to improve balance with respect to a common set of baseline disease and demographic information reported from the single-arm trials (CELINE, OPTIMIX-ACROSS, and APEC[10]). The reweighted data were used to compute the HRs for OS, PFS, ORR from the fixed-effect model, and mean risk differences for safety findings. Information considered for demographic and baseline disease characteristics included age, gender, ECOG status, primary tumor site in the colon, prior therapy of adjuvant chemotherapy or surgery, metastasis status of

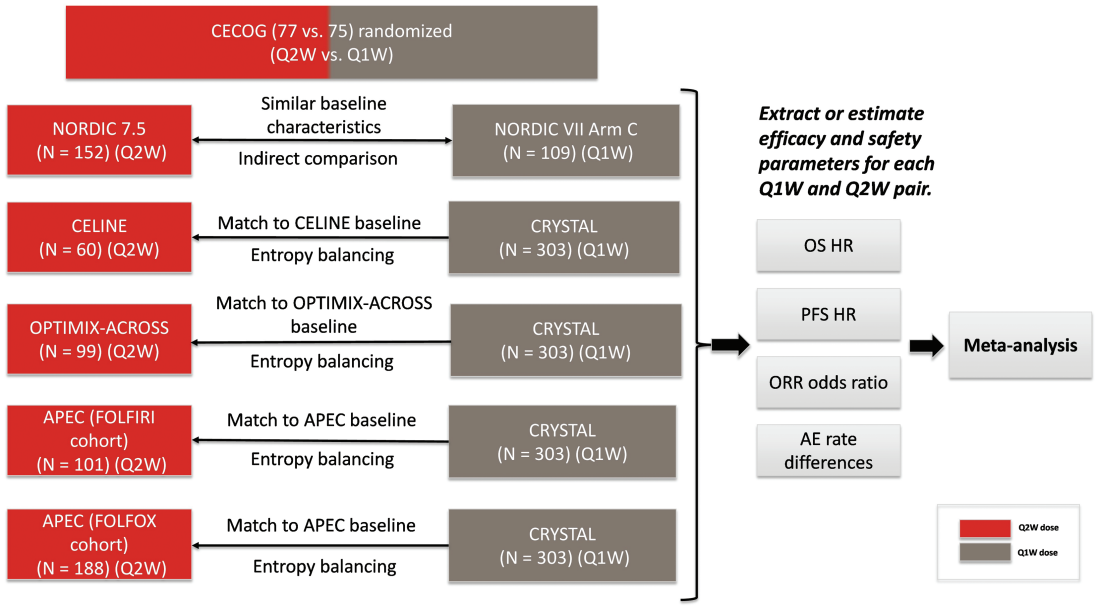

Figure 1. Study pairing and data synthesis. A 2-step data synthesis approach is outlined. The first step involved entropy balancing of Q1W patient-level data from CRYSTAL with the single-arm trials CELINE, OPTIMIX-ACROSS, and APEC. Re-weighted data were used to compute HRs for OS, PFS, and ORR from the fixed-effect model. The second step involved a pairwise meta-analysis comparing each of the aforementioned single-arm trials with reweighted CRYSTAL data and data from CECOG and NORDIC 7.5 (paired with NORDIC VII arm C). HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

M1 at diagnosis, and a number of organs with metastasis. A summary of baseline disease characteristics and demographic results before and post-reweighing is presented in Table 1.

The second step involved a pairwise meta-analysis to determine the efficacy and safety of Q2W versus Q1W cetuximab. This was done by comparing each of the single-arm trials with reweighted CRYSTAL data, as well as evaluating data from the CECOG[15] and NORDIC 7.5[25] studies. The CECOG study was a randomized trial, with an adequate sample size to provide quality evidence to compare Q2W versus Q1W cetuximab. The NORDIC 7.5 study was paired with NORDIC VII arm C because they both had similar baseline and disease characteristics in the Q2W cohort.

Outcome Measures and Quality Assessment

For studies that reported OS and PFS HR for weekly and biweekly dosages, the HRs were extracted directly for this meta-analysis. For studies that did not report HR but have published Kaplan-Meir (KM) curves, the KM curves were digitalized using XY scan to stimulate patient-level data as described by Guyot et al.[26] The HRs and 95% confidence intervals (CIs) were estimated and included for this meta-analysis. For single-arm studies with only KM curves of OS and PFS, the pairing method mentioned above was used.[27] ORRs were also extracted from publications, and outcomes were analyzed as binomial distributions.

The safety endpoints considered were grade 3 and 4 AEs, and included paronychia, neutropenia, diarrhea, acne-like rash, rash, dermatitis acneiform, palmar-plantar erythrodysesthesia syndrome, cardiopulmonary arrest, infusion-related reaction, hypomagnesemia, nail toxicity, and sepsis. The selected AEs are consistent with commonly seen AEs reported in the US product insert (USPI) for cetuximab. Outcomes were analyzed as binomial distributions.

Finally, summary data from the literature were extracted, and any discrepancies in eligibility or data extraction were reconciled by the data abstracter(s) and statistician. Trial data for endpoints were included in the analysis results, tables, and reports.

Testing for Heterogeneity and Risk of Bias

The heterogeneity between included studies was important in planning and executing the meta-analysis as well as interpreting the results. The following approaches were used to assess heterogeneity: comparison of inclusion/exclusion criteria, comparison of study design of the studies, evaluation of similarity in endpoints, examination of heterogeneity within the network of evidence, application of Higgin's I^2 and tau[2,22] and application of Cochran's Q to test the significance of overall heterogeneity.

It is noted that indirect comparisons, like any comparison of nonrandomized treatment groups, can be biased by both observed and unobserved cross-trial differences.[28] Although the use of patient-level data and matched indirect comparison can remove or reduce observed cross-trial differences, unobserved differences may result in residual confounders. R was used as the software to conduct this meta-analysis[29] using the "meta" package.[30]

Results

Study Characteristics

As given in Table 2, 7 publications were identified for the meta-analysis (CECOG, OPTIMIX-ACROSS, APEC, CELINE, NORDIC 7.5, FLEET 2, and Tabernero et al.). Of these, 5 phase 2 studies with Q2W +/- Q1W dosing were included: 1 phase 2 randomized study (CECOG) with Q2W and Q1W schedules (n = 152), 3 phase 2 single-arm studies (OPTIMIX-ACROSS, APEC, CELINE) with Q2W schedules (n = 448)

Table 1. Reweighting of patient-level baseline disease and demographic data from CRYSTAL.

Study: CELINE				**Study: OPTIMIX-ACROSS**			
Baseline characteristics	CELINE	CRYSTAL prior weighted	CRYSTAL post weighted	Baseline characteristics	OPTIMIX-ACROSS	CRYSTAL prior weighted	**CRYSTAL post weighted**
	Q2W (*N* = 60)	**Q1W (*N* = 303)**	**Q1W (*N* = 303)**		**Q2W (*N* = 99)**	**Q1W (*N* = 303)**	**Q1W (*N* = 303)**
Age, Median	64	60	64	Age, Median	64	60	64
Sex, Male	0.78	0.62	0.78	Sex, Male	0.67	0.62	0.67
ECOG status	0.85	0.60	0.85	ECOG status	0.52	0.60	0.52
Primary tumor site in colon	0.50	0.61	0.50	Primary therapy tumor site in colon	0.60	0.61	0.60
Prior therapy of adjuvant chemotherapy	0.07	0.25	0.07	Prior therapy of adjuvant chemotherapy	0.16	0.25	0.16
Number of organs with metastasis: 1 organ	0.57	0.44	0.57	Prior therapy of surgery	0.49	0.86	0.49
Number of organs with metastasis: 2 organs	0.23	0.44	0.23	Metastasis status of M1 at diagnosis	0.77	0.77	0.77
Study: APEC_FOLFIRI				**Study: APEC_FOLFOX**			
Baseline characteristics	**APEC_ FOLFIRI**	**CRYSTAL prior weighted**	**CRYSTAL post weighted**	**Baseline characteristics**	**APEC_ FOLFOX**	**CRYSTAL prior weighted**	**CRYSTAL post weighted**
	Q2W (*N* = 101)	**Q1W (*N* = 303)**	**Q1W (*N* = 303)**		**Q2W (*N* = 188)**	**Q1W (*N* = 303)**	**Q1W (*N* = 303)**
Age, <65 years	0.69	0.63	0.69	Age, <65 years	0.77	0.63	0.77
Sex, Male	0.65	0.62	0.65	Sex, Male	0.63	0.62	0.63
Primary tumor site in colon	0.55	0.61	0.55	Primary tumor site in colon	0.62	0.61	0.62
Prior therapy of adjuvant chemotherapy	0.47	0.25	0.47	Prior therapy of adjuvant chemotherapy	0.21	0.25	0.21

Abbreviations: ECOG status = Eastern Cooperative Oncology Group performance status; *N* = number of patients; Q1W = weekly; Q2W = biweekly.

which were paired with CRYSTAL (*n* = 303), and NORDIC 7.5 phase 2 prospective study (Q2W, *n* = 152) which was paired with arm C of NORDIC VII phase 3 study (Q1W, *n* = 109). Study treatment combinations included cetuximab with 5-FU, FOLFOX, FOLFOX4, FOLFOX6, FOLFIRI, or FLOX. Studies that were not included were FLEET 2[31] and Tabernero et al.[3] because they did not meet the selection criteria defined above. Tabernero et al.'s study was a phase 1 dose-escalating study that included cetuximab Q2W at 400 mg/m^2 (*n* = 13), 500 mg/m^2 (*n* = 14), 600 mg/m^2 (*n* = 12), and 700 mg/m^2 (*n* = 10) for CET Q2W. The cetuximab 500 mg/m^2 cohort had limited data available. In FLEET2, the Q2W and Q1W cohort had different demographics and baseline disease characteristics, which would have interfered with a meaningful comparison within the study. In addition, the small sample size of Q2W (*n* = 26) made it difficult to apply entropy balancing to cross-compare with other studies and further include in the meta-analysis.

Efficacy Analysis

Other than the CECOG study, the efficacy outcomes (OS HR, PFS HR, and ORR) comparing Q2W and Q1W schedules in Table 3 were calculated based on the cross-trial comparison techniques discussed in the statistical method section. These efficacy outcomes were subsequently incorporated in the meta-analysis with weight proportional to the variance of each efficacy endpoint.

Overall, the variation of study outcomes across studies that were included for the meta-analysis of OS was low. The pooled OS estimated from the fixed-effect model was HR = 0.96 (95% CI: 0.89-1.04) (Fig. 2A). Similarly, the variation of study outcomes across studies that were included for the meta-analysis of PFS was low. The pooled PFS estimated from the fixed-effect model was HR = 0.96 (95% CI: 0.87-1.05) (Fig. 2B). Finally, the variation of study outcomes across studies that were included for the meta-analysis of ORR was low. The pooled odds ratio estimated from the fixed effect model was 1.16 (95% CI: 0.96-1.41) (Fig. 2C).

Safety Analysis

The AE rates for this study presented in Table 4 were adjusted to match with the baseline disease characteristics of study CELINE, OPTIMIX-ACROSS, APEC-FOLFIRI arm, and APEC-FOLFOX arm, respectively. Mean differences (cetuximab Q2W – cetuximab Q1W) across the rates of AEs of special interest were not clinically meaningful with no obvious directionality: paronychia +6.2%, neutropenia +4.0%, diarrhea –4.6%, acne-like rash –1.0%, rash –3.1%, dermatitis acneiform –1.0%, palmar-plantar erythrodysesthesia syndrome –0.8%, cardiopulmonary arrest –4.1%,

Table 2. Selected clinical studies from targeted literature review.

Trial alias	Author (year)	Treatment	Trial design	*N*	Included or not included in meta-analysis
CECOG	Brodowicz et al. (2013)	CET (Q1W) + FOLFOX vs CET (Q2W) + FOLFOX	Ph2, randomized	Q1W = 75 Q2W = 77	Included; randomized trial with sufficient sample size to provide the highest quality evidence to support Q2W vs Q1W CET
OPTIMIX-ACROSS	Fernandez-Plana et al. (2014)	CET + FOLFOX4	Ph2, single-arm	Q2W = 99	Included[a]
APEC	Cheng et al. (2016)	CET + FOLFIRI or CET + FOLFOX	Ph2, single-arm	Q2W = 101 (CET + FOLFIRI) Q2W=188 (CET + FOLFOX)	Included[a]
CELINE	Kotake et al. (2017)	CET + 5-FU + FOLFOX6	Ph2, single-arm	Q2W = 60	Included[a]
NORDIC 7.5	Pfeiffer et al. (2015)	FLOX + CET for 16 weeks then Maintenance CET (Q1W vs Q2W)	Ph2, single-arm	Q1W = 109 Q2W = 152	Included; Inclusion criteria allowed for comparison of NORDIC 7.5 to NORDIC VII
	Tabernero et al. (2010)	CET monotherapy or CET + FOLFIRI		62	**Not Included;** Phase 1 trial, limited patient data at 500 mg/m2 dosing
FLEET2	Hazama et al. (2016)	CET + XELOX	Ph2, single-arm	Q1W = 14 Q2W = 26	**Not included;** small sample size, patient characteristics are significantly different between Q1W and Q2W cohorts

Abbreviations: CET = cetuximab; Ph = phase; Q1W = weekly; Q2W = biweekly.

Table 3. Clinical trial efficacy outcomes included in meta-analysis.

Study	*N* (Q2W vs Q1W)	OS HR of Q2W vs Q1W (95% CI)[a]	PFS HR of Q2W vs Q1W (95% CI)[a]	ORR (Q2W vs Q1W)[b]
CECOG	77 vs 75	1.16 (0.76, 1.79)	1.09 (0.74, 1.59)	62% vs 53%
NORDIC 7.5 vs NORDIC VII	152 vs 109	0.88 (0.64, 1.22)	0.85 (0.66, 1.09)	62% vs 51%
CELINE vs CRYSTAL	60 vs 303	1.05 (0.86, 1.28)	0.90 (0.64, 1.27)	70% vs 69%
OPTIMIX vs CRYSTAL	99 vs 303	1.12 (0.91, 1.39)	1.01 (0.77, 1.33)	61% vs 52%
APEC(FOLFIRI) vs CRYSTAL	101 vs 303	0.95 (0.82, 1.11)	0.96 (0.80,1.15)	54% vs 59%
APEC(FOLFOX) vs CRYSTAL	188 vs 303	0.85 (0.74, 0.99)	0.98 (0.84, 1.15)	61% vs 60%

[a]PFS and OS: HR <1 is in favor of Q2W schedule.
[b]The ORR in the Crystal study were adjusted by entropy balancing method (Fig. 1).
Abbreviations: CI, confidence interval; HR, hazard ratio; *N*, number of patients; Q1W, weekly; Q2W, biweekly; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

infusion-related reaction +0.7%, hypomagnesemia +0.7%, nail toxicity –1.2%, and sepsis +1.9%.

Discussion

On April 6, 2021, the FDA approved 500 mg/m^2 every 2 weeks (Q2W) for cetuximab for patients with K-Ras wild-type, EGFR-expressing colorectal cancer (mCRC) or squamous cell carcinoma of the head and neck (SCCHN).[18] The PFS and OS of Q1W were comparable to that of a Q2W schedule based on a meta-analysis.

The Q1W regimen may not be convenient or appropriate in all circumstances. Altering the cetuximab treatment schedule to Q2W administration can provide greater flexibility and convenience to patients who receive combinational therapy. When cetuximab is given in synchrony with chemotherapy, this may improve the patient's compliance to treatment and quality of life by the reducing frequency of clinic visits.[14] The results from the meta-analysis are also consistent with previously reported large retrospective data,[19] which concluded similarity of OS between the cetuximab Q1W and Q2W dosing schedules.

As Q2W dosing becomes a more common practice, it is also applied increasingly in recent clinical trials with cetuximab combinations. In the BREAKWATER phase 3 randomized study (NCT04607421), patients with metastatic BRAF V600E-mutant colorectal cancer receive cetuximab 500 mg/m^2 with Q2W dosing schedule when it is combined with encorafenib with or without chemotherapy.

From the cost-effectiveness perspective, the feasibility of the Q2W dosing option was also proved in a retrospective cohort study. It indicated the all-category health care costs with exposure to cetuximab Q2W versus Q1W in combination with chemotherapy for the treatment of mCRC were similar, after

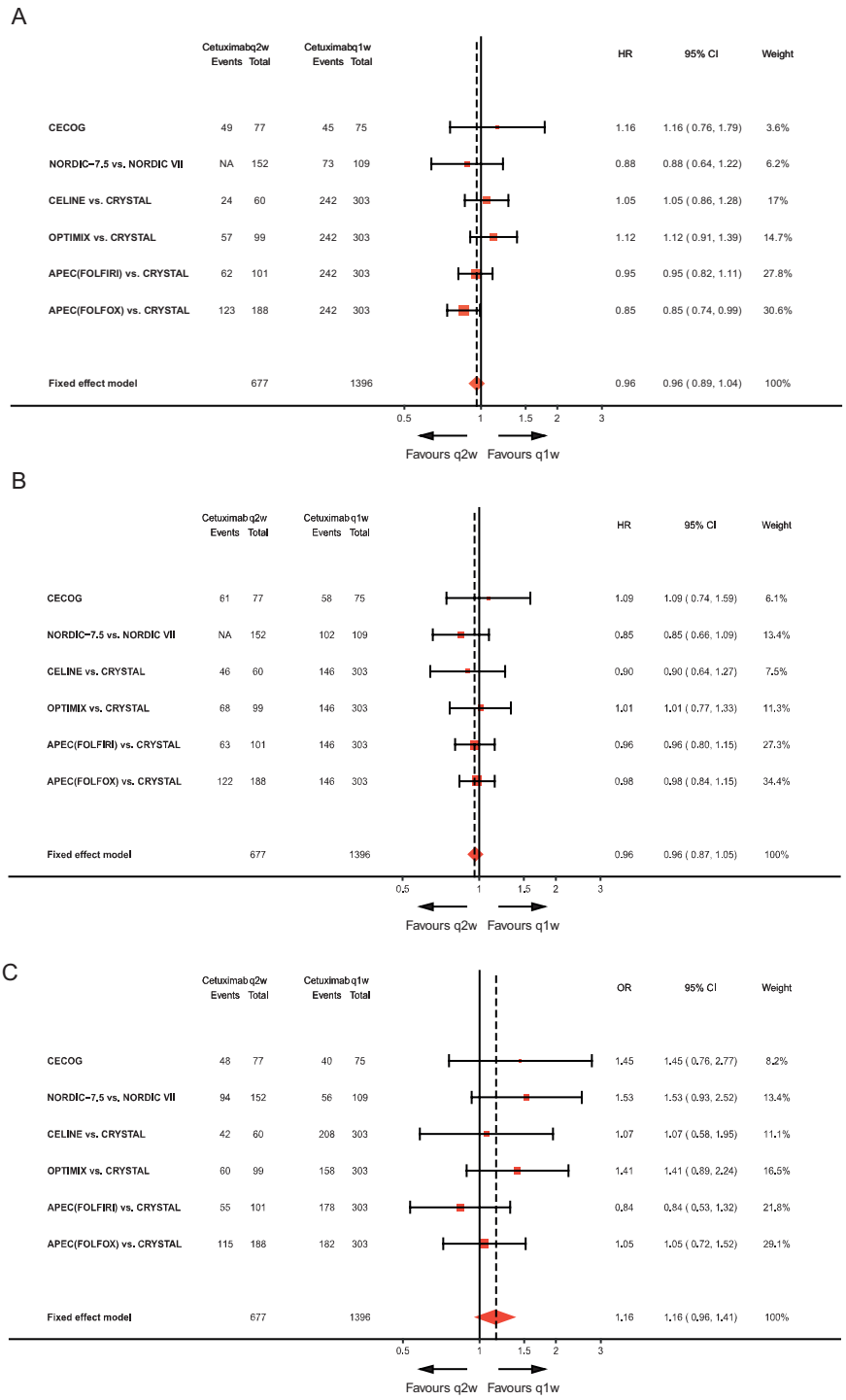

Figure 2. Forest-plot meta-analysis of (**A**) overall survival (OS), (**B**) progression-free survival (PFS), and (**C**) overall response rate (ORR). CI, confidence interval; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HR, hazard ratio; Q1W, weekly; Q2W, biweekly. Note: OS and PFS HR, and ORR odds ratio of CRYSTAL-CELINE, CRYSTAL-OPTIMiX-ACROSS, and CRYSTAL-APEC (FOLFIRI/FOLFOX) were calculated based on matching baseline disease characteristic of CRYSTAL study (where patient level data were available) to each of CELINE, OPTIMIX-ACROSS, APEC using an entropy balancing method. For OS, the weights were proportionalized to the OS events of each study. For PFS, the weights were proportionalized to the PFS events of each study. For ORR, the weights were proportional to the sample size of each study.

considering differences in baseline characteristics. The finding was based on CRC- and skin toxicity-related claims and is in line with published noninferiority trials involving OS with the Q2W regimen. A Q2W dosing schedule with cetuximab may lessen the burden of treatment without compromising efficacy or safety. It is thus an important dosing option when clinically indicated.

It is important to acknowledge the limitations of this study, which include the following: (1) limited clinical trial data to provide comparisons between Q2W and Q1W, (2) a limited amount of baseline characteristic variables based on data availability, and (3) analysis being limited to previously published populations with *KRAS* exon 2 wild-type tumors only,

Table 4. Incidence rate of grade 3/4 adverse events of special interest in each study and meta-analysis of risk difference.

Adverse events	Bi-weekly schedule						Weekly schedule						Pooled Risk Difference (%)[a]
	CECOGN = 77	NORDICN = 152	CELINEN = 60	OPTIMIXN = 99	APEC (FOLFIRI)N = 101	APECN (FOFOLX) N = 188	CECOGN = 75	NORDICN = 109	CRYSTAL[b] (CELINE)N = 303	CRYSTAL[b] (OPTIMIX) N = 303	CRYSTAL[b] (APEC)N = 303	CRYSTAL[b] (APEC)N = 303	Bi-weekly -Weekly Mean (95% CI)
Paronychia	NR	NR	18.3	NR	9.9	7.4	NR	NR	4.6	4.3	4.7	4	6.2 [2.6, 9.7]
Neutropenia	36	40	NR	32	35.6	38.8	31	49	29.1	29.4	29.5	29.4	4.0 [−0.9, 8.9]
Diarrhea	10	9	0	13.1	11.9	8.5	8	16	12.5	14.6	14.7	14.2	−4.6 [−7.6, −1.7]
Rash[a]	17	9	8.3	NR	4	15.4	15	29	7.4	10.7	9.7	9.5	−3.1 [−11.1, 4.9]
Dermatitis acneiform	8	NR	NR	NR	5	1.6	4	NR	NR	NR	4.6	4.8	−1.0 [−3.5, 1.6]
Palmar-plantar Erythrodysesthesia Syndrome	NR	NR	NR	NR	2	4.3	NR	NR	NR	NR	4	4.2	−0.8 [−3.4, 1.8]
Cardiopulmonary arrest	NR	NR	NR	NR	3	1.6	NR	NR	NR	NR	7.2	5.5	−4.1 [−6.7, −1.5]
Hypomagnesemia	1	NR	NR	1	NR	NR	1	NR	NR	NR	NR	NR	0.7 [−1.4, 2.7]
Nail toxicity	6	2	NR	6.1	NR	NR	8	6	NR	4.3	4.7	4	−1.2 [−4.6, 2.2]
Sepsis	NR	NR	NR	NR	4	2.1	NR	NR	NR	NR	1.4	0.8	1.9 [−0.2, 4.0]
Acne-like rash	25	NR	NR	15.2	10.9	18.6	19	NR	NR	18.6	17.4	16.7	−1.0 [−5.2, 3.1]
Infusion related reaction	3	NR	1.7	0	0	4.8	3	NR	0.8	0.8	1.4	1.5	0.7 [−0.7, 2.2]

[a]The estimated pooled risk difference is a weighted average effect size by sample size of each study through the selected studies.
[b]The adverse events rates for CRYSTAL study presented on this table were adjusted to match with the baseline disease characteristics of study CELINE, OPTIMAX, APEC-FOLFIRI arm and APEC FOLFOX arm respectively.
Abbreviations: *N*, number of patients; NR, not reported.

when current guidelines restrict use to *KRAS* and *NRAS* wild-type tumors (exons 2, 3, and 4).[19]

Conclusion

This meta-analysis demonstrated similarity in clinical outcomes, both in efficacy and safety, between Q2W and Q1W dosing schedules of cetuximab in combination with chemotherapy in *KRAS* wild-type mCRC. A Q2W dosing schedule may provide more flexibility to physicians when administering it in combination with chemotherapy and more recently approved targeted agents in the mCRC setting.

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Conflict of Interest

The authors of this study meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and have provided their approval for this manuscript to be published. **Aparna Parikh:** C2i Genomics, Roche, Eli Lilly and Company, Pfizer, Checkmate (H), Puretech, Plexxicon, Bristol-Myers Squibb, Novartis, PMV Pharma, Takeda (Other: fees outside the submitted work); **Elena Gonzalez-Gugel:** Eli Lilly and Company (E, OI); **Natalia Smolyakova:** Eli Lilly and Company (E, OI); **Min-Hua Jen:** Eli Lilly and Company (E, OI); **Nikki Toms:** Eli Lilly and Company (E, OI); **Yong Lin:** Eli Lilly and Company (E, OI); **Jong Seok Kim:** Eli Lilly and Company (E, OI); **Scott Kopetz:** Roche, Genentech, Merck, Karyopharm Therapeutics, Amal Therapeutics, Navire Pharma, Symphogen, Holy Stone, Biocartis, Amgen, Novartis, Eli Lilly and Company, Boehringer Ingelheim, Boston Biomedical, AstraZeneca/MedImmune, Bayer Health, Pierre Fabre, EMD SeronoÐedx Pharma, Jacobio, Natera, Repare Therapeutics, Daiichi Sankyo, Lutris, Pfizer, Ipsen, HalioDx (H).

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Author Contributions

Conception/design: E.G.-G., N.S., M.-H.J., N.T., Y.L., J.S.K., S.K. Collection and/or assembly of data: E.G.-G., M.-H.J. Data analysis and interpretation: N.S., M.-H.J., N.T., S.K. Manuscript writing: All authors. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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