Review

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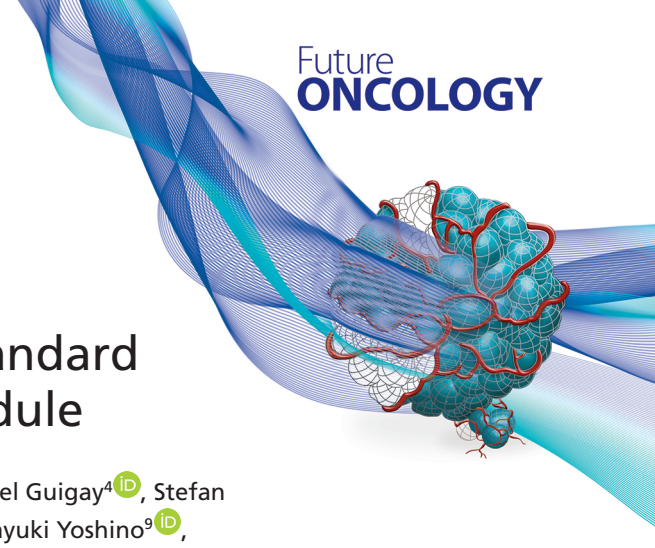

Cetuximab every 2 weeks versus standard weekly dosing administration schedule

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Cetuximab every 2 weeks (Q2W) dosing schedule is approved by the US FDA and by the Japanese Pharmaceuticals and Medical Devices Agency in patients with metastatic colorectal cancer and squamous cell carcinoma of the head and neck. Phase II trials have found comparable efficacy and safety for the weekly (Q1W) and Q2W schedules, and real-world studies have shown noninferiority of the Q2W compared with the Q1W schedule. Several guidelines recommend cetuximab Q2W administration as an alternative to the Q1W dosing schedule. Cetuximab Q2W can be administered with a Q2W dose of chemotherapy, making it a more convenient option to the Q1W schedule, potentially resulting in reduced costs for administration, increased flexibility for clinical staff and improved patient adherence.

Plain language summary – Every 2 weeks dosing schedule of cetuximab is a convenient alternative to the weekly schedule: Cetuximab is a drug for patients with colorectal cancer or cancer of the head and neck. It is usually administered once a week. However, studies have shown that cetuximab given once every 2 weeks instead has similar clinical benefits and side effects. Based on this evidence, the every 2 weeks dosing schedule has been approved for use in USA and Japan. The every 2 weeks dosing schedule is a convenient alternative to the weekly schedule. It may result in fewer hospital visits, improved patient quality of life, reduced healthcare costs and more flexibility for medical staff. This review summarizes the current evidence and benefits for the every 2 weeks dosing schedule.

Tweetable abstract: A review highlights comparable pharmacokinetics, efficacy and safety data reported for #cetuximab #every2weeks and weekly dosing schedules.

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Cetuximab is an EGFR antagonist indicated for the treatment of EGFR-expressing metastatic colorectal cancer (mCRC) and squamous cell carcinoma of the head and neck (SCCHN) [1,2]. Cetuximab is approved by the

European Commission (EC) [2] for the treatment of *RAS* wild-type (wt) mCRC in combination with irinotecan-based chemotherapy (CT) in any line; as first line in combination with folinic acid/fluorouracil/oxaliplatin (FOLFOX); and as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. In the USA, cetuximab is approved by the US FDA [1] for *KRAS* wt mCRC, with a limitation of use in *RAS* wt mCRC. For SCCHN, cetuximab is approved by the EC in combination with radiation therapy for locally advanced disease, as well as in combination with platinum-based CT for recurrent and/or metastatic disease [2]. The FDA approval is for use in locally or regionally advanced SCCHN in combination with radiation therapy; recurrent locoregional disease or metastatic SCCHN in combination with platinum-based therapy with fluorouracil; and recurrent or metastatic (R/M) SCCHN progressing after platinum-based therapy [1].

Weekly (Q1W) and every 2 weeks (Q2W) intravenous infusion schedules of cetuximab have been approved by the FDA [1] and by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) [3], while only the Q1W dosing schedule is currently approved by the EC [2]. For the Q1W schedule, a loading dose of 400 mg/m^2 is given over approximately 2 h, followed by subsequent weekly 250 mg/m^2 doses, infused over approximately 1 h [1,2]. Recent FDA approval [4] of the Q2W schedule (500 mg/m^2 intravenous infusion administered over 2 h) for patients with *KRAS* wt, EGFR-expressing mCRC or SCCHN was based on population pharmacokinetic (PK) modeling analyses (comparing the predicted exposures of 500 mg/m^2 Q2W with observed exposures of cetuximab 250 mg/m^2), and supported by pooled analyses of objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) from published studies in mCRC and SCCHN, as well as real-world OS data in patients with mCRC [5].

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for the treatment of colon cancer [6] and rectal cancer [7], and the Australian eviQ protocols [8] recommend cetuximab Q2W administration as an alternative to the Q1W dosing schedule. Although the Q2W dosing schedule is not recommended by the standard European Society of Medical Oncology (ESMO) guidelines, current ESMO recommendations for the management and treatment of CRC during the COVID-19 pandemic include considering the Q2W dosing schedule [9]. The less frequent dosing is an important safety aspect during pandemics. In clinical practice, a schedule of cetuximab 500 mg/m^2 Q2W is frequently used [10–12] as a convenient alternative to Q1W dosing, since FOLFOX and folinic acid/fluorouracil/irinotecan (FOLFIRI) are also administered Q2W [10,11,13]. Administering cetuximab Q2W rather than Q1W may improve patient adherence, improve their quality of life, and reduce healthcare costs [14–17]. Evidence from studies with other monoclonal antibodies (mAbs) in oncology, including panitumumab, supports the use of extended dosing intervals [18–21].

This review provides a comprehensive summary of evidence for the use of the cetuximab Q2W dosing schedule, highlighting the comparable PK, efficacy and safety data that have been observed between the Q1W and Q2W dosing schedules.

Pharmacokinetics & pharmacodynamics of cetuximab Q2W & Q1W dosing schedules

Early studies of the Q2W dosing schedule provided preliminary evidence for its comparable PK and pharmacodynamic (PD) profile to the Q1W schedule [22]. Subsequently, further PK and PD studies were conducted, including the EMR 62202-045 [23] trial and its secondary analysis [24].

The EMR 62202-045 trial was a phase I, open-label, multicenter, PK, PD and pharmacogenomic dose-escalation study of cetuximab Q2W or Q1W in the first-line treatment of *RAS*-unselected mCRC [23]. A total of 62 patients were included and assigned sequentially to either the standard Q1W (control) group or the dose-escalation group. During the first 6-week dose-escalation phase, patients received cetuximab monotherapy; in the second phase, they received the same dose of cetuximab in combination with FOLFIRI. The control group received an initial 400 mg/m^2 cetuximab dose, followed by 250 mg/m^2 Q1W, while the first cohort of nine patients in the dose-escalation group received an initial dose of 400 mg/m^2, followed by infusions of 400 mg/m^2 Q2W. If no or one patient in the dose-escalation group treated with the current dose experienced dose-limiting toxicity (defined as any grade 3/4 hematological or non-hematological toxicity), then subsequent cohorts were entered at the next dose level (doses were increased in steps of 100 mg/m^2, up to 700 mg/m^2). Patients in the dose-escalation cohort received the same initial and subsequent doses of cetuximab through the infusion cycles of each dose level. The primary objective was to determine the maximum tolerated Q2W dose [23]. Secondary objectives included safety, response, PFS, PK, PD and biomarkers associated with response to cetuximab [23].

At week 5, 500 mg/m^2 Q2W provided a similar mean exposure (area under the concentration time curve) to the reference Q1W schedule. Comparable minimum concentrations were maintained throughout the dosing interval

Table 1. Mean (SD) pharmacokinetics parameters at week 5 in the EMR 62202-045 study.

Dose, mg/m^2 (n)	Dosing schedule	C_{min}, μg/ml†	AUC_{0-t}, μg/ml/h†	$t_{1/2}$, h	CL, l/h
400/250 (n = 13)	Q1W	49.6 (26.1)	17,787 (6739)	100.6 (32.3)	0.027 (0.009)
400 (n = 8)	Q2W	25.6 (11.8)	28,202 (6711)	134.7 (38.6)	0.027 (0.007)
500 (n = 9)	Q2W	34.7 (16.0)	35,794 (8180)	137.0 (44.5)	0.026 (0.008)
600 (n = 10)	Q2W	47.3 (30.8)	44,392 (22,349)	133.2 (20.4)	0.028 (0.011)
700 (n = 6)	Q2W	69.9 (25.4)	60,927 (9340)	156.1 (48.5)	0.19 (0.004)

†C_{min} and AUC for Q2W schedules reached steady state on week 5, except for 700 mg/m^2 group when steady state reached around week 11.
AUC: Area under the concentration time curve; CL: Clearance; C_{min}: Minimum concentration; PK: Pharmacokinetics; Q1W: Weekly; Q2W: Every 2 weeks; SD: Standard deviation; $t_{1/2}$: Elimination half-life.

with the 500 mg/m^2 Q2W and 400/250 mg/m^2 Q1W dosing schedules (Table 1) [23]. These data demonstrated that cetuximab can be safely administered at doses of 400–700 mg/m^2 Q2W as monotherapy or in combination with FOLFIRI in the first-line treatment of *RAS*-unselected mCRC, but that the 500 mg/m^2 Q2W dose most closely aligned with the current standard weekly administration schedule and so should be the dose utilized in future studies. This study had several limitations. First, as a phase I trial, the study had a limited sample size, with only 14 patients treated with the proposed Q2W schedule. Although the cohorts were small, the efficacy outcomes: ORR, disease control rate (DCR), and PFS, appeared comparable between the two schedules. Second, no statistical comparison between the Q1W and Q2W schedules was conducted. This study was also not designed to demonstrate equivalence of the two schedules – this would require a larger trial powered for noninferiority analyses of key PK parameters. Thirdly, *KRAS* analyses were not presented by dose cohort, as the restriction to *KRAS* wt subjects further reduced sample size. Last, *RAS* analyses were not performed [23].

A secondary analysis of the EMR 62202-045 study, which assessed pretreatment and PD biomarkers for cetuximab efficacy using tissue samples, found evidence to support the functional equivalence of the Q1W and Q2W dosing schedules [24]. Furthermore, this study confirmed the higher efficacy of cetuximab treatment in *KRAS* wt compared with *KRAS* mutant (mt) mCRC, with responses reported in 55 versus 32% of patients (p = 0.144), and median PFS of 9.4 versus 5.6 months (p = 0.048), respectively [24]. In this study, immunohistochemical and microarray expression analyses of tumor and skin biopsies, as well as proteomic analyses of plasma samples were performed at baseline and at week 4. No marked difference was found between the two schedules with respect to their effect on PD biomarkers. This evidence provides a biological rationale supporting the functional equivalence of Q1W and Q2W dosing schedules. Based on the analyses of skin biopsies, Q1W and Q2W cetuximab schedules both resulted in significant inhibition or reduction of the levels of p-EGFR, p-MAPK and Ki-67, and significant upregulation of $p27^{Kip1}$ and p-STAT3 (all $p < 0.001$). The tumor biopsies showed a significant reduction in proliferation (p = 0.049), downregulation of p-EGFR ($p < 0.005$) and p-MAPK (p = 0.033), but no significant changes in $p27^{Kip1}$, p-STAT3 or p-Akt. Compared with baseline, a decrease in plasma levels of IL-8, macrophage inflammatory protein-1α, carcinoembryonic antigen, CA125 and CA19-9 observed during the cetuximab monotherapy phase was significantly associated with the response at week 6 ($p < 0.01$). However, an increase in TGF-α and EGF levels, and a decrease in soluble EGFR were also found. In *KRAS* wt mCRC patients, baseline levels of two EGFR ligands, epiregulin and amphiregulin, were higher in cetuximab-responsive tumors [24].

Comparable efficacy of Q2W & Q1W dosing schedules in mCRC based on phase II studies

Several studies have specifically compared cetuximab Q1W and Q2W schedules in combination with FOLFOX [13,25], FOLFIRI [13] or irinotecan [26] and found comparable efficacy and safety between the two dosing schedules [13,25,26]. Additional evidence for the use of the Q2W schedule comes from other studies of cetuximab in combination with CT in patients with *KRAS* wt [14,26–45] and *KRAS*-unselected [46–52] mCRC.

Comparable efficacy with first-line cetuximab plus FOLFOX or FOLFIRI

The CECOG/CORE 1.2.002 (CECOG-CORE2) [25] study was a randomized, phase II trial that evaluated cetuximab Q2W plus FOLFOX versus cetuximab Q1W plus FOLFOX in patients with *KRAS* wt mCRC [25]. The ORR (primary end point) was comparable between the two schedules, although it was higher but not significant for the Q2W arm (62 vs 53%), and it was similar to the ORR observed in the pivotal OPUS study [53] with cetuximab Q1W plus FOLFOX (57%). The secondary end points (PFS, OS, DCR and safety) were also comparable between the two arms [25].

Table 2. Comparable efficacy of first-line cetuximab every 2 weeks dosing schedule plus FOLFOX versus cetuximb weekly plus folinic acid/fluorouracil/oxaliplatin.

Study	Design	n	ORR, %	mPFS, months	mOS, months	Ref.
Studies evaluating Q2W schedule						
CECOG-CORE2	Randomized phase II	77	62.0	9.2	23.0	[25]
APEC	Nonrandomized phase II	188	61.2	11.1	27.0	[13]
OPTIMIX-ACROSS	Open-label Single-arm Nonrandomized phase II	99	60.6	10.1	20.8	[29]
FLEET†	Open-label Single-arm Nonrandomized phase II	37	64.9	13.1	38.1	[14]
CEBIFOX	Single-arm Nonrandomized phase II	57	64.9	10.1	28.7	[28]
CELINE†	Open-label Nonrandomized phase II	60	70.0	13.7	31.0	[27]
Ji *et al.*	Nonrandomized phase II	73	72.6	9.8	NR	[30]
Studies evaluating Q1W reference schedule						
CECOG-CORE2	Randomized phase II	75	53.0	9.5	25.8	[26]
OPUS	Randomized phase II	82	57.0	8.3	22.8	[53]

†*KRAS*/*BRAF* wt.
Outcomes with cetuximab Q2W or Q1W in combination with FOLFOX were consistent with previous data from the cetuximab plus FOLFOX arm of the OPUS study (*KRAS* wt).
FOLFOX: Folinic acid/fluorouracil/oxaliplatin; mOS: Median overall survival; mPFS: Median progression-free survival; NR: Not reported; ORR: Objective response rate; Q1W: Weekly; Q2W: Every 2 weeks; wt: Wild-type.

Efficacy outcomes from several nonrandomized, phase II studies [13,14,25,27–30] with cetuximab Q2W or Q1W in combination with FOLFOX were consistent with previous data from the cetuximab plus FOLFOX arm of the OPUS study (Table 2) [53]. FLEET [14] was an open-label, phase II trial in patients with *KRAS* wt mCRC, where administration of Q2W cetuximab with FOLFOX resulted in the ORR (primary end point) of 64.9%, compared with 57% in the OPUS study [50]. Median PFS and OS were also longer in the FLEET study than those reported in OPUS (PFS: 13.1 vs 8.3 months, and OS: 38.1 vs 22.8 months, respectively) [14,53]. In the CELINE [27] open-label, phase II trial that also evaluated patients with *KRAS* wt mCRC, the ORR with Q2W cetuximab in combination with FOLFOX was higher than that reported in the OPUS study (70 vs 57%). Furthermore, median PFS (13.7 vs 8.3 months) and OS (31.0 vs 22.8 months) were longer for the CELINE trial compared with OPUS [27].

The CEBIFOX [28] open-label, single-arm, phase II study investigating the cetuximab Q2W schedule in combination with FOLFOX6 in patients with *KRAS* exon 2 wt mCRC also reported higher ORR (primary end point; 64.9 vs 57%), longer median PFS (10.1 vs 8.3 months), and OS (28.7 vs 22.8 months), compared with the cetuximab Q1W dosing schedule in the OPUS study [14,28]. Similar findings for ORR (primary end point), PFS, and OS were reported (60.6%, 10.1 months and 20.8 months, respectively) in OPTIMIX-ACROSS [29], an open-label, phase II trial of cetuximab Q2W in combination with FOLFOX4 in *KRAS* wt mCRC, and are also comparable with the data for the Q1W schedule in OPUS [53]. Compared with the CEBIFOX trial, median PFS and OS were longer in the FLEET and CELINE studies, but these trials excluded patients with *BRAF* mt mCRC [14,27,28].

The open-label, phase II trial by Ji *et al.* [30] investigated the overall resection rate (primary end point) in patients with mCRC and unresectable liver metastases, who had received neoadjuvant FOLFOX6 plus cetuximab Q2W. In this study, ORR was 72.6%, with 71.2% of patients showing at least partial response, while the median time-to-progression was 9.8 months [30].

The hase II APEC study [13] assessed the efficacy and safety of 500 mg/m^2 cetuximab Q2W plus FOLFOX (Table 2) or FOLFIRI (Table 3) in *KRAS*/*RAS* wt mCRC. The best confirmed ORR (BORR; primary end point) in the *KRAS* wt population was 58.8% (61.2% in the cetuximab plus FOLFOX and 54.5% in the cetuximab plus FOLFIRI groups), while 64.7% of the *RAS* wt subgroup achieved BORR (62.7 and 68.4% for the two schedules, respectively). Of the secondary end points, median PFS was 11.1 months in the *KRAS* wt population and 13.0 months in the *RAS* wt population (13.3 months in the cetuximab plus FOLFOX and 12.8 months in the cetuximab plus FOLFIRI groups), while median OS was 26.8 months in the *KRAS* wt population and 28.4 months in the *RAS* wt population (27.8 and 28.7 months for the two schedules, respectively) [14]. The outcomes were comparable with those from prior pivotal studies, OPUS [53] and CRYSTAL [54].

Table 3. Comparable efficacy of first-line cetuximab Q2W dosing schedule plus FOLFIRI versus cetuximab Q1W plus FOLFIRI.

Study	Design	Biomarker selection	n	ORR, %	mPFS, months	mOS, months	Ref.
Studies evaluating Q2W schedule							
APEC	Nonrandomized phase II	*KRAS* wt	101	54.5	11.1	26.6	[13]
		RAS wt	57	68.4	12.8	28.7	
Personeni	Non-randomized phase II	*KRAS* wt	168	48.9	8.2	23.3	[31]
Studies evaluating Q1W reference schedule							
CRYSTAL	Randomized phase III	*KRAS* wt	316	57.3	9.9	23.5	[54]
		RAS wt	178	66.3	11.4	28.4	

Outcomes with cetuximab Q2W in combination with FOLFIRI were consistent with previous data from the pivotal CRYSTAL study of cetuximab Q1W plus FOLFIRI in *RAS* wt mCRC.
FOLFIRI: Folinic acid/fluorouracil/irinotecan; mCRC: Metastatic colorectal cancer; mOS: Median overall survival; mPFS: Median progression-free survival; ORR: Overall response rate; Q1W: Weekly; Q2W: Every 2 weeks; wt: Wild-type.

Table 4. Comparable outcomes of ≥third-line cetuximab Q2W plus irinotecan with those from prior studies of cetuximab Q1W plus irinotecan in KRAS-unselected or wild-type chemorefractory mCRC.

Study	Design	Biomarker selection	n	ORR, %	mPFS, months	mOS, months	Ref.
Studies evaluating Q2W schedule							
Jensen *et al.*	Non-randomized phase II	*(K)RAS*-unselected	174	16.7 (PR)	4.3	10.6	[36]
		KRAS exon 2 wt	104	25.0 (PR)	5.5	12.1	
Studies evaluating Q1W reference schedule							
BOND	Randomized Open-label phase III	*(K)RAS*-unselected	218	22.9 (PR)	4.1	8.6	[55]
Di Fiore *et al.*	Meta-analysis	*KRAS* exon 2 wt	182	42.3 (CR ± PR)†	5.5	13.2	[56]

†CR: 1.6%; PR: 40.7%.
CR: Complete response; mCRC: Metastatic colorectal cancer; mOS: Median overall survival; mPFS: Median progression-free survival; ORR: Overall response rate; PR: Partial response; Q1W: Weekly; Q2W: Every 2 weeks; wt: Wild-type.

Personeni *et al.* [31] also investigated the combination of cetuximab Q2W with FOLFIRI in a phase II study evaluating the efficacy of this schedule according to phosphatase and tensin homolog (PTEN) expression in patients with *KRAS* wt mCRC. Patients treated with cetuximab Q2W plus FOLFIRI had a longer median OS compared with those who received FOLFIRI alone (23.3 vs 17.7 months). The median PFS was also longer with the cetuximab Q2W plus FOLFIRI combination compared with FOLFIRI alone (8.2 vs 6.2 months) [31]. These efficacy findings are consistent with the outcomes from the CRYSTAL study (Table 3) [54].

Comparable efficacy with ≥third-line cetuximab plus irinotecan

In a phase II study that evaluated the addition of 500 mg/m^2 cetuximab to Q2W irinotecan in irinotecan-refractory patients with *RAS*-unselected mCRC, Q2W cetuximab was effective and safe when compared with a historical control for the 400/250 mg/m^2 Q1W schedule in the third-line treatment of mCRC [26]. The outcomes (ORR, PFS and OS) were comparable with those from prior studies [55–59] of the Q1W reference schedule plus irinotecan in *KRAS*-unselected or wt chemorefractory mCRC (Table 4).

Additional efficacy data from studies evaluating cetuximab Q2W plus CT are presented in the online Supplementary Information (Supplementary Tables 1–4).

Comparable safety with first-line cetuximab Q1W & Q2W dosing schedules in mCRC based on phase II studies

Safety with first-line Q2W cetuximab plus FOLFOX or FOLFIRI

The safety of the cetuximab Q2W schedule in combination with FOLFOX [13,25] or FOLFIRI [13] was assessed in the APEC [13], CECOG-CORE2 [25] and CEBIFOX [28] studies. Rates of individual grade 3/4 adverse events (AE) reported for the Q2W cetuximab plus FOLFOX schedule in APEC [13] and CECOG-CORE2 [25], and of grade 3–5 AEs reported in the CEBIFOX study [28] were generally comparable with those observed with the cetuximab Q1W plus FOLFOX schedule in the OPUS study [53] (Supplementary Table 5). Of the commonly reported cetuximab-related skin reactions, differences ≥5% in incidence were observed only for dermatitis acneiform (2 vs 2 vs 8%) and

rash (11 vs 15 vs 17%), for OPUS (Q1W), APEC (Q2W) and CECOG-CORE2 (Q2W), respectively [13,25,53]. Of the grade 3/4 AEs in special categories (as defined by the Medical Dictionary for Regulatory Activities preferred terms version 13.1), the incidences of acne-like rash and skin reactions were similar with cetuximab Q2W plus FOLFOX in APEC and CECOG-CORE2 versus cetuximab Q1W plus FOLFOX dosing in the OPUS study [13,25,53]. In the CEBIFOX study, 63% of patients reported ≥1 grade 3–5 treatment-related AEs (TRAE), including dermatitis acneiform (18%) and rash (4%) [28].

In the CECOG-CORE2 study, the rates of grade 3/4 AEs were similar in the Q2W and Q1W treatment arms (71 vs 72%) [25]. The Q2W arm had similar rates of dermatitis acneiform and rash compared with the Q1W arm (8 vs 4% and 17 vs 15%, respectively). Of the Grade 3/4 AEs in special categories, the rates of Grade 3/4 acne-like rash and skin reactions were similar between the cetuximab Q2W and the Q1W treatment arms (25 vs 19%, and 27 vs 24%, respectively), while the rate of infusion-related reactions was the same in both treatment arms (3%) [25] (Supplementary Table 6).

Of the common hematological AEs related to the combination of cetuximab with platinum-based CT in the CECOG-CORE2 study, neutropenia was reported in 48% of patients in the Q2W treatment arm compared with 41% in the Q1W arm. Overall, the rates of grade 3/4 neutropenic events occurring in ≥5% of patients were comparable between the Q2W and Q1W treatment arms (36 vs 31%), including Grade 4 neutropenic events (16 vs 18%) [25]. Hematological AEs were also the most frequently reported TRAEs with the cetuximab Q2W schedule in combination with FOLFOX in the CEBIFOX study, with grade 3–5 neutropenia occurring in 21% of patients [29], as well as in the APEC study, with 38.8% of patients reporting grade 3/4 neutropenia [13].

Rates of individual grade 3/4 AEs reported for cetuximab Q2W plus FOLFIRI in the APEC study [13] were also generally comparable with those in the CRYSTAL study [60] with cetuximab Q1W plus FOLFIRI (Supplementary Tables 5 & 6); ≥5% differences in incidence were observed only for neutropenia (36 vs 31%), stomatitis (9 vs 2.5%) and rash (4 vs 9%) [13,60]. Overall, the rates of grade 3/4 AEs reported for Q2W cetuximab plus FOLFOX or FOLFIRI were comparable to grade 3/4 AEs reported in the trials with the Q1W dosing schedule.

Comparable safety with ≥ third-line cetuximab plus irinotecan

Grade 3/4 AEs were not reported in the BOND study [55] or the study by Jensen *et al.* [26], except for acne-like rash, the rates of which were similar in the two studies (9 vs 10%; Supplementary Table 6).

A recently published meta-analysis of studies published between 2007 and 2017 compared the efficacy and safety outcomes of the cetuximab Q2W and Q1W dosing schedules in patients with *KRAS* wt mCRC [61]. It included randomized trials comparing the two dosing schedules and single-arm trials with the Q2W schedule (CECOG-CORE2, NORDIC 7.5, NORDIC 7, CELINE, OPTIMIX-ACROSS, and APEC paired with Q1W cetuximab dosing in the CRYSTAL study). The Q2W schedule showed similar efficacy compared with the Q1W dosing schedule in terms of OS (hazard ratio [HR] 0.96, 95% CI: 0.89–1.04), PFS (HR 0.96, 95% CI: 0.87–1.05), and ORR (odds ratio [OR] 1.16, 95% CI: 0.96–1.41). Furthermore, the analysis of selected grade 3/4 AEs found no significant differences between the two cetuximab dosing schedules [61].

Noninferiority studies of cetuximab Q2W dosing schedule in mCRC

PADIS study [10]

The PADIS pooled analysis of individual patient data from postauthorization studies in 1317 patients with *RAS* wt mCRC (irrespective of the number of metastatic sites), receiving first-line treatment with cetuximab Q1W or Q2W in combination with CT, included two noninterventional cohort studies, EREBUS [62] and ERBITAG [63], and three clinical trials, CEBIFOX [28], CECOG-CORE2 [25] and APEC [13]. This analysis assessed the noninferiority of cetuximab 500 mg/m^2 Q2W plus CT (as a first-line treatment) to the standard dosing schedule of 400 mg/m^2 followed by 250 mg/m^2 Q1W plus CT in *RAS* wt mCRC patients. The noninferiority was tested with an HR margin of 1.25 using a Cox proportional hazards regression model powered for a confirmatory comparison of the cetuximab dosing schedules. Differences in baseline characteristics were accounted for using inverse probability of treatment weighting (IPTW) based on propensity scores. The primary outcome measure was OS, and secondary outcomes included PFS, ORR, DCR, resection rate of lung/liver metastases and rates of prespecified serious AEs (SAE) [10].

The results showed noninferiority of the Q2W schedule versus Q1W for OS (Figure 1A). Median OS after IPTW was 24.7 months (95% CI: 23.1–26.8) for Q1W versus 27.9 months (95% CI: 26.1–31.2) for Q2W. Secondary efficacy outcomes and sensitivity analyses supported this conclusion. No statistical difference in PFS

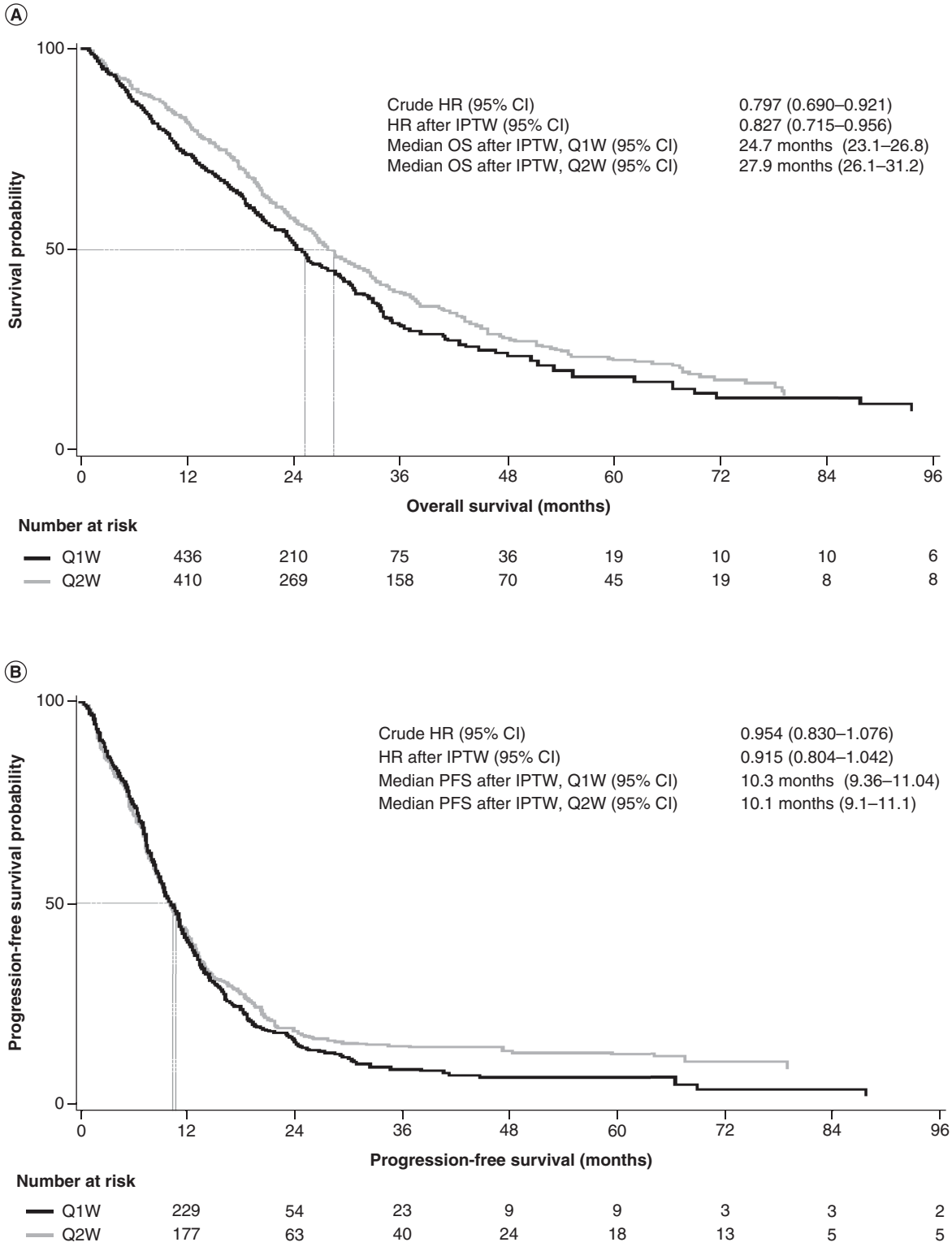

Figure 1. PADIS study results. (A) Q2W was noninferior to Q1W for median OS (months) after IPTW (27.9 vs 24.7). **(B)** Q2W was noninferior to Q1W for median PFS (months) after IPTW (10.1 vs 10.3).
HR: Hazard ratio; IPTW: Inverse probability of treatment weighting; OS: Overall survival; PFS: Progression-free survival; Q1W: Weekly; Q2W: Every 2 weeks.
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was observed between the Q2W and Q1W cohorts, although the Kaplan–Meier curves showed some advantage for the Q2W schedule (Figure 1B). Adjusted OR [95% CI] for ORR was 1.292 [1.031–1.617]) and for DCR 1.278 (0.987–1.655), and the rate of patients with lung/liver metastases resection was 1.419 (1.043–1.932), all favoring the Q2W schedule. The rate of any SAE after IPTW was 28.8% in the Q1W cohort and 30.7% in the Q2W cohort. The two schedules were well tolerated; the incidence rate for each individual SAE in both treatment cohorts was <5%. Compared with the Q1W schedule, the cetuximab Q2W arm had higher rates of leukopenia (1.6 vs 4.2%), skin reactions/skin infections (0.4 vs 2.0%) and mucositis (0.3 vs 1.1%) [10].

In this pooled analysis, most of the patients initiated their cetuximab treatment prior to 2013, when tumor location was not considered a prognostic factor and a predictor of survival and, therefore, did not influence the choice of the dosing schedule. In line with previous studies [60] in mCRC patients with *RAS* wt mCRC, PADIS found a similar proportion of patients with right-sided tumors in groups treated with the Q1W versus Q2W dosing schedules (21.0 vs 21.7%) [11].

The subsequent PADIS *post hoc* subgroup analyses [64,65] supported the noninferiority of the Q2W versus Q1W schedule observed for OS (HR [95% CI]) for both the left-sided tumor subgroup (0.754 [0.622–0.913]) and the right-sided tumor subgroup (0.754 [0.545–1.041]) [64,65], as well as for other response measures (OR [95% CI]), including ORR (1.387 [1.036–1.857] vs 0.928 [0.545–1.581]), DCR (1.408 [1.003–1.976] vs 0.998 [0.579–1.720]), and resection rates of lung/liver metastases (1.280 [0.899–1.824] vs 1.047 [0.416–2.634]) [65,66]. Overall, the rate of any SAE after IPTW was 29.0% in the Q1W cohort and 30.8% in the Q2W cohort [65,66]. No significant differences (OR [95% CI]) were found in frequency of any SAEs between the Q1W and Q2W dosing schedules for the left-sided tumor subgroup (1.186 [0.876–1.607]) and the right-sided tumor subgroup (1.061 [0.606–1.857]) [65,66].

QUICK study

The QUICK study tested the hypothesis of noninferiority of cetuximab Q2W versus Q1W plus CT for the treatment of mCRC in a line-agnostic setting, allowing inclusion of patients at all lines of treatment [11]. This study included 2943 real-world patients with mCRC from a US claims database treated with cetuximab in combination with CT. As the information on dosing was unavailable for most of the included patients, an algorithm was used to derive these data, based on the assumption that the cetuximab doses administered were 250 mg/m^2 in the Q1W group and 500 mg/m^2 in the Q2W group. The primary outcome measure was OS, while secondary outcomes included safety, time to treatment discontinuation or death and time to next treatment or death. Due to the lack of mortality data in the claims database, a previously published algorithm was used to define a proxy for death [12].

The OS results confirmed noninferiority (HR [95% CI]) of the Q2W dosing schedule versus Q1W (0.94 [0.85–1.03]; Figure 2). No difference was found for secondary outcomes, which were used as proxies for PFS. In the first-line subgroup analysis, no difference was found between the Q2W and Q1W schedules (p = 0.625) [11,67]. HR for OS was 1.10 (95% CI: 0.92–1.31) when unadjusted, and 1.05 (95% CI: 0.86–1.29) after IPTW [11]. In addition, a secondary analysis of the same database, analysing healthcare resource utilization and healthcare cost, demonstrated numerically lower overall healthcare resource utilization with Q2W versus Q1W dosing schedules (weighted mean, 8.1 vs 9.5 encounters per patient per month), and similar overall healthcare cost (weighted average, US$17,653 vs $16,469 per patient per month) [67].

Comparable efficacy & safety of Q2W & Q1W dosing schedules in SCCHN

In patients with first-line R/M SCCHN, studies of Q2W cetuximab with platinum-based CT, including cetuximab maintenance treatment, have found similar efficacy and safety outcomes to those reported in trials of the cetuximab Q1W dosing schedule [15,16,68–71] (Supplementary Table 7). Recent evidence for Q2W cetuximab dosing as maintenance therapy comes from the DIRECT [70] and TPExtreme [72] studies in patients with first-line R/M SCCHN.

DIRECT was a phase IV, observational, longitudinal trial that assessed the relative dose intensity of cetuximab administered in combination with platinum-based CT (EXTREME regimen) for up to six cycles as first-line therapy [70]. As part of the EXTREME regimen, cetuximab was given at an initial dose of 400 mg/m^2 followed by 250 mg/m^2 Q1W in combination with cisplatin (or carboplatin) plus 5-fluorouracil, and continued as maintenance treatment Q1W (250 mg/m^2) or Q2W (500 mg/m^2) until disease progression or intolerance. Median PFS was 4.5 months (95% CI: 4.1–5.1) and median OS was 9.4 months (95% CI: 7.2–13.3). No significant differences were observed in 12-month PFS and OS rates between patients who received cetuximab Q1W as maintenance

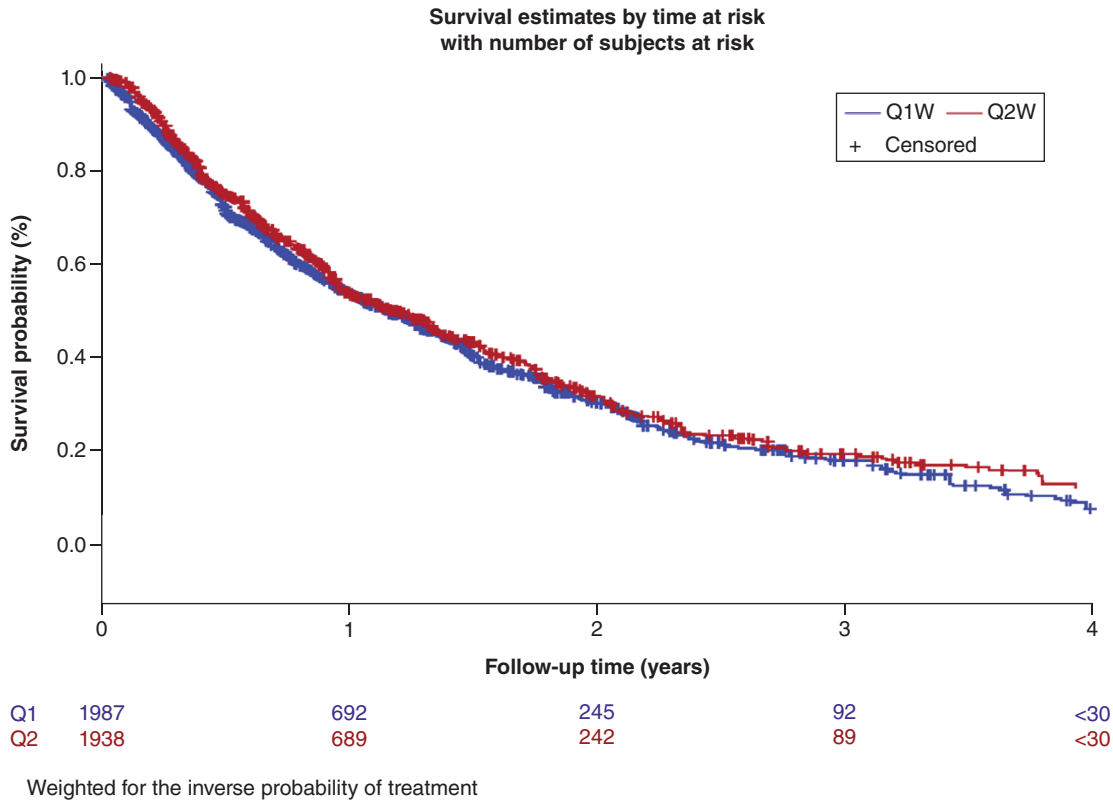

Figure 2. QUICK study results: Q2W was noninferior* to Q1W for overall survival in a line-agnostic setting.
*HR (95% CI), 0.94 (0.85–1.03).
HR: Hazard ratio; Q1W: Weekly; Q2W: Every 2 weeks.

therapy compared with those who received the Q2W cetuximab schedule, although a trend toward better survival was observed with the Q2W dosing schedule (12-month PFS rate: 18.2% for Q1W vs 27.5% for Q2W; p = 0.22, and 12-month OS rate: 62.6% for Q1W vs 77.0% for Q2W; p = 0.20) [70].

TPExtreme, a phase II, multicenter, open-label, randomized trial, compared the efficacy and safety of the TPEx regimen (docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2 plus Q1W cetuximab, followed by Q2W cetuximab as maintenance therapy until progression or unacceptable toxicity), with the standard EXTREME regimen (5-fluorouracil 4000 mg/m^2 plus cisplatin 100 mg/m^2 plus Q1W cetuximab, followed by Q1W cetuximab as maintenance therapy) [72]. Median OS (primary end point) did not differ significantly between the TPEx (14.5 months, 95% CI: 12.5–15.7) and the EXTREME (13.4 months, 95% CI: 12.2–15.4) regimens (HR 0.89, 95% CI:0.74–1.08; p = 0.23). However, the rate of ≥grade 3 AEs was significantly lower in the TPEx group compared with the EXTREME group (81 vs 93%; p < 0.0001), demonstrating a favorable safety profile of the TPEx regimen [72].

Conclusion

Our review highlights the comparable PK data, including similar cetuximab exposure and serum trough levels, and similar efficacy and safety outcomes that have been observed between the cetuximab Q1W and Q2W dosing schedules. Overall, the cetuximab Q2W schedule has been shown to be noninferior to the Q1W schedule for OS in the first- and later-line treatment of mCRC in clinical trials and real-world studies. Studies in patients with R/M SCCHN also support this alternative dosing schedule as maintenance therapy after platinum-based combination therapy.

Currently, the dosage and administration approved by the FDA includes cetuximab administration of initial and subsequent doses of 500 mg/m^2 as 120 minutes intravenous infusion every 2 weeks [1]. The FDA approval of cetuximab Q2W for patients with *KRAS* wt, EGFR-expressing mCRC, or R/M SCCHN [4], was based on

model-predicted PK data and supported by supplemental clinical data from literature and real-world evidence from a retrospective, observational, comparative effectiveness study in *KRAS* wt mCRC [5]. The study found no difference in OS between the two dosing schedules, although median OS for cetuximab Q2W was 2.9 months longer than with the Q1W schedule, and 5.8 months longer in patients receiving cetuximab as first-line treatment [5].

Several international guidelines for the management of CRC recommend cetuximab Q2W administration as an alternative to the Q1W dosing schedule [6–9]. Previous studies investigating extended dosing intervals with other mAbs in oncology, such as pembrolizumab [18] and atezolizumab [19], have found comparable efficacy and safety with standard, more frequent dosing schedules, offering more flexibility to patients and staff.

Based on the supportive evidence for comparable efficacy and safety, the administration of cetuximab Q2W is a convenient alternative to the Q1W schedule, and can help synchronize the administration of concomitant CT, which may lessen the burden of treatment without compromising efficacy or safety. In addition, the cetuximab Q2W schedule could also help to decrease healthcare costs by reducing the number of hospital visits, the need for specialized healthcare staff and lost days of work [15].

Future perspective

In recent years, extended dosing schedules for several oncology mAbs have been approved by regulatory bodies, including the FDA- and PMDA-approved cetuximab Q2W dosing schedule. Reducing the frequency of drug administration by enabling patients to be treated with extended dosing schedules that coincide with their CT is an important patient-centric aspect, lowering the already heavy burden, improving patient adherence and contributing to a better quality of life. Minimising the risk of hospital-acquired infections and reducing the number of hospital visits is also an important factor to consider, especially in the context of the current and any future pandemics. In the coming years, to address the unmet needs of patients and healthcare systems globally, exploring extended dosing schedules will become an increasingly important consideration in the design of future clinical trials of mAbs and other oncology treatments. Furthermore, in the ever-expanding oncology treatment landscape, lower frequency of administration will play an even greater role in treatment selection and the shared treatment decision-making process. In this context, extended dosing schedules, such as the alternative cetuximab Q2W dosing schedule, may bring benefits for patients, clinicians and healthcare systems. Finally, the FDA currently recommends the Q1W dosing schedule for cetuximab when combined with radiation therapy [1]; further evidence is required to support the concomitant Q2W administration of cetuximab with radiation therapy.

Executive summary

Pharmacokinetic/pharmacodynamic (PD) of cetuximab every 2 weeks (Q2W) & weekly (Q1W) dosing schedules

- A phase I, pharmacokinetic, PD and pharmacogenomic dose-escalation study of cetuximab Q2W or Q1W in the first-line treatment of *RAS*-unselected metastatic colorectal cancer (mCRC) observed similar pharmacokinetic parameters for both dosing schedules.
- Secondary analyses of the same study assessing pretreatment and PD biomarkers found evidence to support the functional equivalence of Q1W and Q2W dosing schedules, and no difference in their effects on PD biomarkers.

Comparable efficacy of Q2W & Q1W dosing schedules in mCRC based on phase II studies

- Several phase II studies showed comparable efficacy (overall survival, objective response rate, progression-free survival) between cetuximab Q1W and Q2W schedules in combination with FOLFOX/FOLFIRI (first-line) or irinotecan (≥third-line).

Comparable safety with first-line cetuximab Q1W & Q2W dosing schedules in mCRC based on phase II studies

- Safety with first-line cetuximab Q2W plus FOLFOX or FOLFIRI was comparable with the Q1W schedule in terms of grade 3/4 adverse events.
- A recently published meta-analysis found no significant differences between these two cetuximab dosing schedules.

Noninferiority studies of cetuximab Q2W dosing schedule in mCRC

- Pooled analyses of real-world studies and clinical trials showed noninferiority of the Q2W schedule compared with the Q1W schedule for overall survival in mCRC.

Comparable efficacy & safety of Q2W & Q1W dosing schedules in squamous cell carcinoma of the head and neck

- Cetuximab Q2W dosing with platinum-based CT, including cetuximab maintenance treatment, showed similar efficacy and safety outcomes to those reported in trials of Q1W dosing schedule in patients with first-line recurrent or metastatic squamous cell carcinoma of the head and neck.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2023-0282

Author contributions

All authors contributed equally to the writing of the manuscript, and reviewed and approved the final draft. J Tabernero and S Kasper contributed to data provision and analysis. C Bokemeyer contributed to the conceptual design of the manuscript and manuscript improvement. P Pfeiffer contributed to the conception, analysis and interpretation of data.

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References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. U.S. Food and Drug Administration. Erbitux Full Prescribing Information (2021). www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s277s280lbl.pdf (Accessed 12 November 2022).
2. European Medicines Agency. Summary of product characteristics, Erbitux (2022). www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf (Accessed 12 November 2022).
3. Japanese Pharmaceuticals and Medical Devices Agency. Package insert, Erbitux (2022).
4. U.S. Food and Drug Administration. FDA approves new dosing regimen for cetuximab (2021). www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-new-dosing-regimen-cetuximab (Accessed 20 November 2022).
5. Center for Drug Evaluation and Research. Approval package for Erbitux (2021). www.accessdata.fda.gov/drugsatfda_docs/nda/2021/125084Orig1s277,s280.pdf (Accessed: 20 November 2022).
6. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V2.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed (28 August 2023). To view the most recent and complete version of the guideline go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
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8. New South Wales Cancer Institute. Colorectal metastatic cetuximab (two weekly) (2015). www.eviq.org.au/medical-oncology/colorectal/metastatic/1681-colorectal-metastatic-cetuximab-two-weekly (Accessed 12 November 2022).
9. Vecchione L, Stintzing S, Pentheroudakis G, Douillard JY, Lordick F. ESMO management and treatment adapted recommendations in the COVID-19 era: colorectal cancer. *ESMO Open* 5(Suppl. 3), e000826 (2020).

•• **The guidelines by European Society of Medical Oncology recommend cetuximab every 2 weeks (Q2W) administration as an alternative to the weekly (Q1W) dosing schedule in colorectal cancer during the COVID-19 period.**

10. Kasper S, Foch C, Messinger D *et al.* Noninferiority of cetuximab every-2-weeks versus standard once-weekly administration schedule for the first-line treatment of RAS wild-type metastatic colorectal cancer. *Eur. J. Cancer* 144, 291–301 (2021).

• **A pooled analysis establishing the noninferiority of cetuximab Q2W to the Q1W dosing in the first-line setting for metastatic colorectal cancer.**

11. Lamy FX, Batech M, Boutmy E *et al.* Comparative effectiveness of weekly versus every-2-weeks cetuximab in metastatic colorectal cancer in a US-insured population. *J. Comp. Eff. Res.* 9(16), 1117–1129 (2020).

•• **A cohort study confirming the noninferiority of overall survival outcomes of cetuximab Q2W compared with Q1W dosing in patients with metastatic colorectal cancer.**

12. Loft M, Shapiro J, Lee M *et al.* Compliance with Therapeutic Goods Association prescribing information: weekly or second weekly cetuximab for the treatment of metastatic colorectal cancer. *Intern. Med. J.* doi:10.1111/imj.15835 (2022).
13. Cheng AL, Cornelio G, Shen L *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 II APEC Study. *Clin. Colorectal Cancer* 16(2), e73–e88 (2017).

• **A phase II study evaluating efficacy and safety of cetuximab Q2W plus FOLFOX/FOLFIRI in patients with KRAS or all RAS wild-type metastatic colorectal cancer in first-line settings.**

14. Soda H, Maeda H, Hasegawa J *et al.* Multicenter Phase II study of FOLFOX or biweekly XELOX and Erbitux (cetuximab) as first-line therapy in patients with wild-type KRAS/BRAF metastatic colorectal cancer: The FLEET study. *BMC Cancer* 15, 695 (2015).
15. Bossi P, Kornek G, Lanzetta G *et al.* Safety and feasibility of every-other-week maintenance cetuximab after first-line chemotherapy in patients with recurrent or metastatic head and neck squamous cell cancer. *Head Neck* 35(10), 1471–1474 (2013).

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16. Posch D, Fuchs H, Kornek G *et al.* Docetaxel plus cetuximab biweekly is an active regimen for the first-line treatment of patients with recurrent/metastatic head and neck cancer. *Sci. Rep.* 6, 32946 (2016).

17. Hubbard JM, Alberts SR. Alternate dosing of cetuximab for patients with metastatic colorectal cancer. *Gastrointest. Cancer Res.* 6(2), 47–55 (2013).

18. Lala M, Li TR, De Alwis DP *et al.* A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. *Eur. J. Cancer* 131, 68–75 (2020).

19. Morrissey KM, Marchand M, Patel H *et al.* Alternative dosing regimens for atezolizumab: an example of model-informed drug development in the postmarketing setting. *Cancer Chemother. Pharmacol.* 84(6), 1257–1267 (2019).

20. Weiner LM, Belldegrun AS, Crawford J *et al.* Dose and schedule study of panitumumab monotherapy in patients with advanced solid malignancies. *Clin. Cancer Res.* 14(2), 502–508 (2008).

21. Yang BB, Lum P, Chen A *et al.* Pharmacokinetic and pharmacodynamic perspectives on the clinical drug development of panitumumab. *Clin. Pharmacokinet.* 49(11), 729–740 (2010).

22. 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* 13(2), 113–119 (2008).

23. Tabernero J, Ciardiello F, Rivera F *et al.* Cetuximab administered once every second week to patients with metastatic colorectal cancer: a two-part pharmacokinetic/pharmacodynamic phase I dose-escalation study. *Ann. Oncol.* 21(7), 1537–1545 (2010).

•• **A two-part pharmacokinetic/pharmacodynamic phase I dose-escalation study analysis, which led to the US FDA approval of the cetuximab Q2W schedule.**

24. Tabernero J, Cervantes A, Rivera F *et al.* Pharmacogenomic and pharmacoproteomic studies of cetuximab in metastatic colorectal cancer: biomarker analysis of a phase I dose-escalation study. *J. Clin. Oncol.* 28(7), 1181–1189 (2010).

25. Brodowicz T, Ciuleanu TE, Radosavljevic D *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.* 24(7), 1769–1777 (2013).

• **A phase II study compared the efficacy and safety of cetuximab Q2W versus cetuximab Q1W in the first-line setting of KRAS wild-type metastatic colorectal cancer.**

26. Jensen BV, Schou JV, Johannesen HH *et al.* Cetuximab every second week with irinotecan in patients with metastatic colorectal cancer refractory to 5-FU, oxaliplatin, and irinotecan: KRAS mutation status and efficacy. *J. Clin. Oncol.* 28(Suppl. 15), 3573–3573 (2010).

27. Kotake M, Aoyama T, Munemoto Y *et al.* Multicenter phase II study of infusional 5-fluorouracil (5-FU), leucovorin, and oxaliplatin, plus biweekly cetuximab as first-line treatment in patients with metastatic colorectal cancer (CELINE trial). *Oncol. Lett.* 13(2), 747–753 (2017).

28. Kasper S, Meiler J, Knipp H *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* 19 (4), 236–247; e236 (2020).

29. Fernandez-Plana J, Pericay C, Quintero G *et al.* Biweekly cetuximab in combination with FOLFOX-4 in the first-line treatment of wild-type KRAS metastatic colorectal cancer: final results of a phase II, open-label, clinical trial (OPTIMIX-ACROSS Study). *BMC Cancer* 14, 865 (2014).

30. Ji JH, Park SH, Lee J *et al.* Prospective phase II study of neoadjuvant FOLFOX6 plus cetuximab in patients with colorectal cancer and unresectable liver-only metastasis. *Cancer Chemother. Pharmacol.* 72(1), 223–230 (2013).

31. Personeni N, Rimassa L, Verusio C *et al.* FOLFIRI and Cetuximab Every Second Week for First-Line Treatment of KRAS Wild-Type Metastatic Colorectal Cancer According to Phosphatase and Tensin Homolog Expression: A Phase II Study. *Clin. Colorectal Cancer* 14(3), 162–169 (2015).

32. Chayahara NEA. Phase II trial of bi-weekly cetuximab for recurrent or metastatic colorectal cancer (BIC-K trial). *Ann. Oncol.* 27, vii77–vii78 (2016).

33. Osumi H, Shinozaki E, Mashima T *et al.* Phase II trial of biweekly cetuximab and irinotecan as third-line therapy for pretreated KRAS exon 2 wild-type colorectal cancer. *Cancer Sci.* 109(8), 2567–2575 (2018).

34. Kang MJ, Hong YS, Kim KP *et al.* Biweekly cetuximab plus irinotecan as second-line chemotherapy for patients with irinotecan-refractory and KRAS wild-type metastatic colorectal cancer according to epidermal growth factor receptor expression status. *Invest. New Drugs* 30(4), 1607–1613 (2012).

35. Shitara K, Yokota T, Takahari D *et al.* Phase II study of combination chemotherapy with biweekly cetuximab and irinotecan for pre-treated metastatic colorectal cancer harboring wild-type KRAS. *Jpn J. Clin. Oncol.* 40(7), 699–701 (2010).

36. Jensen BV, Schou JV, Yilmaz M *et al.* Cetuximab plus irinotecan administered biweekly with reduced infusion time to heavily pretreated patients with metastatic colorectal cancer and related RAS and BRAF mutation status. *Int. J. Cancer* doi:10.1002/ijc.33448 (2020). (Online ahead of print).

37. Chen Y, Cao D, Bi F, Li Q, Qiu M. Biweekly cetuximab plus FOLFIRI/irinotecan as first/second-line chemotherapy for patients with KRAS wild-type metastatic colorectal cancer: a retrospective analysis in Southwest Chinese population. *Med. Oncol.* 31(5), 935 (2014).

38. Abdelwahab S, Azmy A, Abdel-Aziz H, Salim H, Mahmoud A. Anti-EGFR (cetuximab) combined with irinotecan for treatment of elderly patients with metastatic colorectal cancer (mCRC). *J. Cancer Res. Clin. Oncol.* 138(9), 1487–1492 (2012).
39. Folprecht G, Hamann S, Schütte K *et al.* Dose escalating study of cetuximab and 5-FU/folinic acid (FA)/oxaliplatin/irinotecan (FOLFOXIRI) in first line therapy of patients with metastatic colorectal cancer. *BMC Cancer* 14, 521 (2014).
40. Cremolini C, Antoniotti C, Lonardi S *et al.* Activity and Safety of Cetuximab Plus Modified FOLFOXIRI Followed by Maintenance With Cetuximab or Bevacizumab for RAS and BRAF Wild-type Metastatic Colorectal Cancer: A Randomized Phase II Clinical Trial. *JAMA Oncol.* 4(4), 529–536 (2018).
41. Tveit KM, Guren T, Glimelius B *et al.* Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. *J. Clin. Oncol.* 30(15), 1755–1762 (2012).
42. Pfeiffer P, Sorbye H, Qvortrup C *et al.* Maintenance Therapy With Cetuximab Every Second Week in the First-Line Treatment of Metastatic Colorectal Cancer: The NORDIC-7.5 Study by the Nordic Colorectal Cancer Biomodulation Group. *Clin. Colorectal Cancer* 14(3), 170–176 (2015).
43. Shitara K, Yuki S, Yoshida M *et al.* Phase II study of combination chemotherapy with biweekly cetuximab and irinotecan for wild-type KRAS metastatic colorectal cancer refractory to irinotecan, oxaliplatin, and fluoropyrimidines. *Invest. New Drugs* 30(2), 787–793 (2012).
44. Ychou M, Rivoire M, Thezenas S *et al.* Chemotherapy (doublet or triplet) plus targeted therapy by RAS status as conversion therapy in colorectal cancer patients with initially unresectable liver-only metastases. The UNICANCER PRODIGE-14 randomised clinical trial. *Br. J. Cancer* 126(9), 1264–1270 (2022).
45. Guren TK, Thomsen M, Kure EH *et al.* Cetuximab in treatment of metastatic colorectal cancer: final survival analyses and extended RAS data from the NORDIC-VII study. *Br. J. Cancer* 116(10), 1271–1278 (2017).
46. Sobrero AF, Maurel J, Fehrenbacher L *et al.* EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J. Clin. Oncol.* 26(14), 2311–2319 (2008).
47. Carneiro BA, Ramanathan RK, Fakih MG *et al.* Phase II study of irinotecan and cetuximab given every 2 weeks as second-line therapy for advanced colorectal cancer. *Clin. Colorectal Cancer* 11(1), 53–59 (2012).
48. Pfeiffer P, Nielsen D, Bjerregaard J *et al.* Biweekly cetuximab and irinotecan as third-line therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin and 5-fluorouracil. *Ann. Oncol.* 19(6), 1141–1145 (2008).
49. Martín-Martorell P, Roselló S, Rodríguez-Braun E *et al.* Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. *Br. J. Cancer* 99(3), 455–458 (2008).
50. Mrabti H, De La Fouchardiere C, Desseigne F *et al.* Irinotecan associated with cetuximab given every 2 weeks versus cetuximab weekly in metastatic colorectal cancer. *J. Cancer Res. Ther.* 5(4), 272–276 (2009).
51. Bouchahda M, Macarulla T, Liedo G *et al.* Feasibility of cetuximab given with a simplified schedule every 2 weeks in advanced colorectal cancer: a multicenter, retrospective analysis. *Med. Oncol.* 28(Suppl. 1), S253–S258 (2011).
52. Roca JM, Alonso V, Pericay C *et al.* Cetuximab given every 2 weeks plus irinotecan is an active and safe option for previously treated patients with metastatic colorectal cancer. *Chemotherapy* 56(2), 142–146 (2010).
53. Bokemeyer C, Bondarenko I, Hartmann JT *et al.* Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. *Ann. Oncol.* 22(7), 1535–1546 (2011).
54. Van Cutsem E, Lenz HJ, Köhne CH *et al.* Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. *J. Clin. Oncol.* 33(7), 692–700 (2015).
55. Cunningham D, Humblet Y, Siena S *et al.* Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N. Engl. J. Med.* 351(4), 337–345 (2004).
56. Fiore FD, Cutsem EV, Laurent-Puig P *et al.* Role of KRAS mutation in predicting response, progression-free survival, and overall survival in irinotecan-refractory patients treated with cetuximab plus irinotecan for a metastatic colorectal cancer: analysis of 281 individual data from published series. *J. Clin. Oncol.* 26(Suppl. 15), 4035 (2008).
57. Wilke H, Glynne-Jones R, Thaler J *et al.* Cetuximab Plus Irinotecan in Heavily Pretreated Metastatic Colorectal Cancer Progressing on Irinotecan: MABEL Study. *J. Clin. Oncol.* 26(33), 5335–5343 (2008).
58. Lim R, Sun Y, Im SA *et al.* Cetuximab plus irinotecan in pretreated metastatic colorectal cancer patients: the ELSIE study. *World J. Gastroenterol.* 17(14), 1879–1888 (2011).
59. Buzaid AC, Mathias Cde C, Perazzo F *et al.* Cetuximab Plus irinotecan in pretreated metastatic colorectal cancer progressing on irinotecan: the LABEL study. *Clin. Colorectal Cancer* 9(5), 282–289 (2010).
60. Van Cutsem E, Köhne CH, Láng I *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.* 29(15), 2011–2019 (2011).
61. Parikh AR, Gonzalez-Gugel E, Smolyakova N *et al.* Efficacy and Safety of Cetuximab Dosing (biweekly vs weekly) in Patients with KRAS Wild-type Metastatic Colorectal Cancer: A Meta-analysis. *The Oncologist* 27(5), 371–379 (2022).

62. Rouyer M, François E, Cunha AS *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 Cancer* 17(2), 129–139 (2018).

63. Sahm S, Goehler T, Hering-Schubert C *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.* 34(Suppl. 4), 651 (2016).

64. Kasper S, Cheng AL, Rouyer M *et al.* Overall survival with cetuximab every 2 weeks vs standard once-weekly administration schedule for first-line treatment of RAS wild-type metastatic colorectal cancer in patients with left and right-sided primary tumor location. Presented at: *ESMO World Congress on Gastrointestinal Cancer.* 30 June–3 July 2021.

65. Kasper S, Foch C, Esser R *et al.* Overall survival with cetuximab every-2-weeks versus standard once-weekly administration schedule for first-line treatment of RAS wild-type metastatic colorectal cancer in patients with left- and right-sided primary tumour location. *Eur. J. Cancer* 180, 85–88 (2023).

66. Kasper S, Cheng AL, Rouyer M *et al.* Comparison of cetuximab every-2-weeks versus standard once-weekly administration for the first-line treatment of RAS wild-type metastatic colorectal cancer among patients with left- and right-sided primary tumor location. Presented at: *ESMO.* 16–21 September 2021.

67. Pescott CP, Boutmy E, Batech M, Ronga P, Lamy FX. Real-world healthcare resource utilization and costs of weekly versus every-2-week cetuximab in metastatic colorectal cancer. *J. Comp. Eff. Res.* 10(5), 353–364 (2021).

68. Guigay J, Fayette J, Dillies AF *et al.* Cetuximab, docetaxel, and cisplatin as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma: a multicenter, phase II GORTEC study. *Ann. Oncol.* 26(9), 1941–1947 (2015).

69. Fury MG, Sherman E, Lisa D *et al.* A randomized Phase II study of cetuximab every 2 weeks at either 500 or 750 mg/m^2 for patients with recurrent or metastatic head and neck squamous cell cancer. *J. Natl Compr. Cancer Netw.* 10(11), 1391–1398 (2012).

70. Guigay J, Chamorey E, Lefebvre G *et al.* Observational, prospective, Phase IV study in patients with first-line recurrent and/or metastatic squamous cell carcinoma of the head and neck treated with cetuximab and platinum-based therapy: DIRECT. *Cancer Rep. (Hoboken)* 5(2), e1467 (2021).

- **A phase IV study compared the dose intensity of cetuximab Q2W versus Q1W in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck.**

71. Klinghammer K, Gauler T, Dietz A *et al.* Cetuximab, fluorouracil and cisplatin with or without docetaxel for patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (CeFCiD): an open-label phase II randomised trial (AIO/IAG-KHT trial 1108). *Eur. J. Cancer* 122, 53–60 (2019).

72. Guigay J, Aupérin A, Fayette J *et al.* Cetuximab, docetaxel, and cisplatin versus platinum, fluorouracil, and cetuximab as first-line treatment in patients with recurrent or metastatic head and neck squamous-cell carcinoma (GORTEC 2014-01 TPExtreme): a multicentre, open-label, randomised, Phase II trial. *Lancet Oncol.* 22(4), 463–475 (2021).