Using RWD to fill evidence gaps in the post-approval space

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Using RWD to Fill Evidence Gaps in the Post Approval Space:
New Dosing Regimen for Cetuximab

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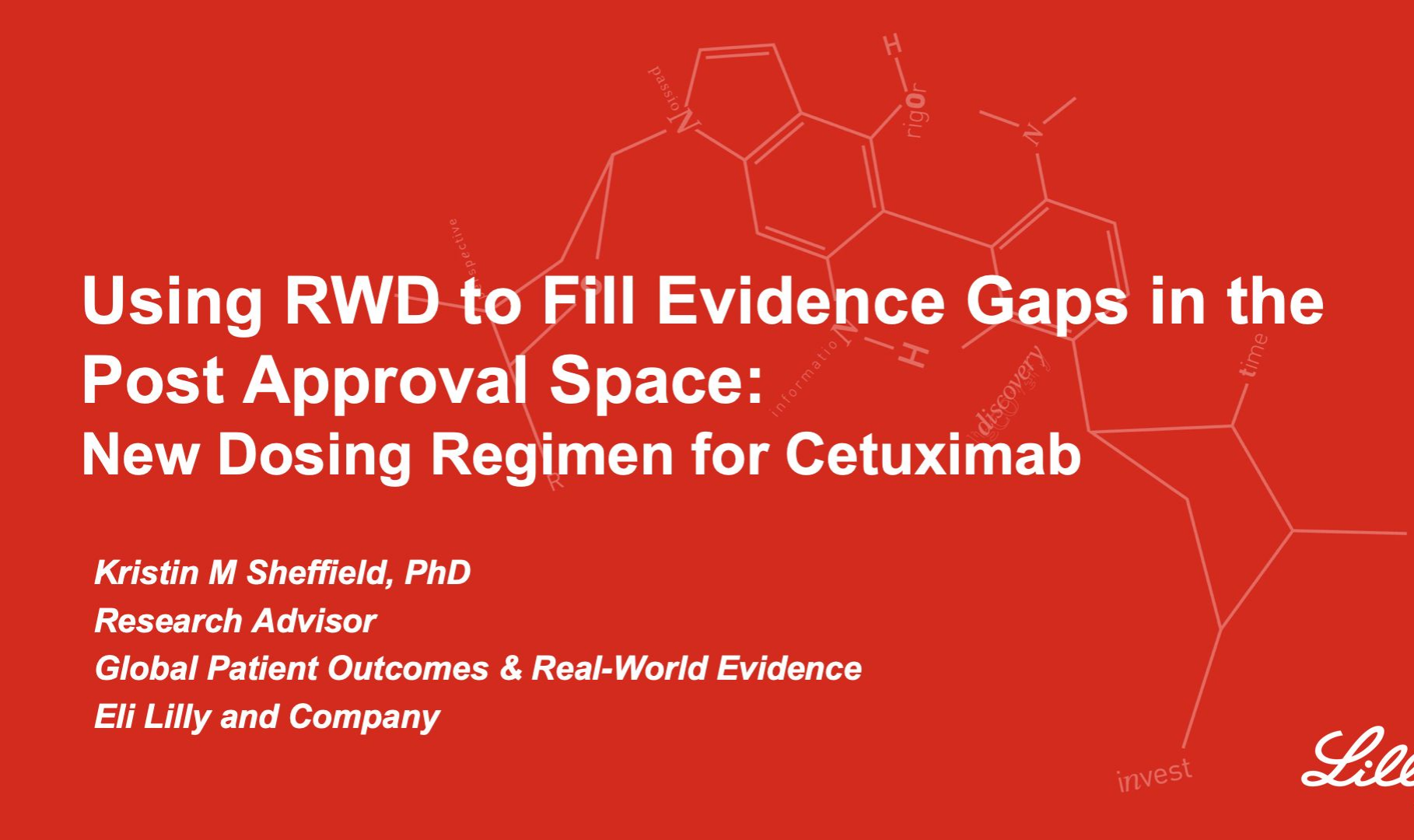

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Rationale for Biweekly Dosing Regimen

- Erbitux indication at 250mg/m^2 weekly dose (Q1W) was initially approved in 2004 for metastatic CRC (mCRC)
- Biweekly (Q2W) dosing at 500 mg/m^2 closely mirrors Q1W dosing based on PK exposure data[a], and is reflected in clinical guidelines[b] and widespread clinical practice[c]
- Q2W dosing would allow infusions to be scheduled with other biweekly treatments, potentially reducing frequency of visits
- Q2W dosing may lead to reduction in drug wastage and costs

[a]Tabernero et al 2010; [b]NCCN Guidelines 2020; [c]Pescott et al, 2020

FDA's Model-Informed Drug Development (MIDD) Pilot Program

MIDD Pilot Program

- Allows drug developers to discuss with FDA application of model-based approaches (exposure-based, biological, statistical) to the development and regulatory evaluation of medical products
- MIDD approaches can optimize drug dosing in the absence of dedicated trials
- Accepted in the Program and granted two meetings with FDA

Examples

Ramucirumab: Infusion time reduced from 60min to 30min for all indications

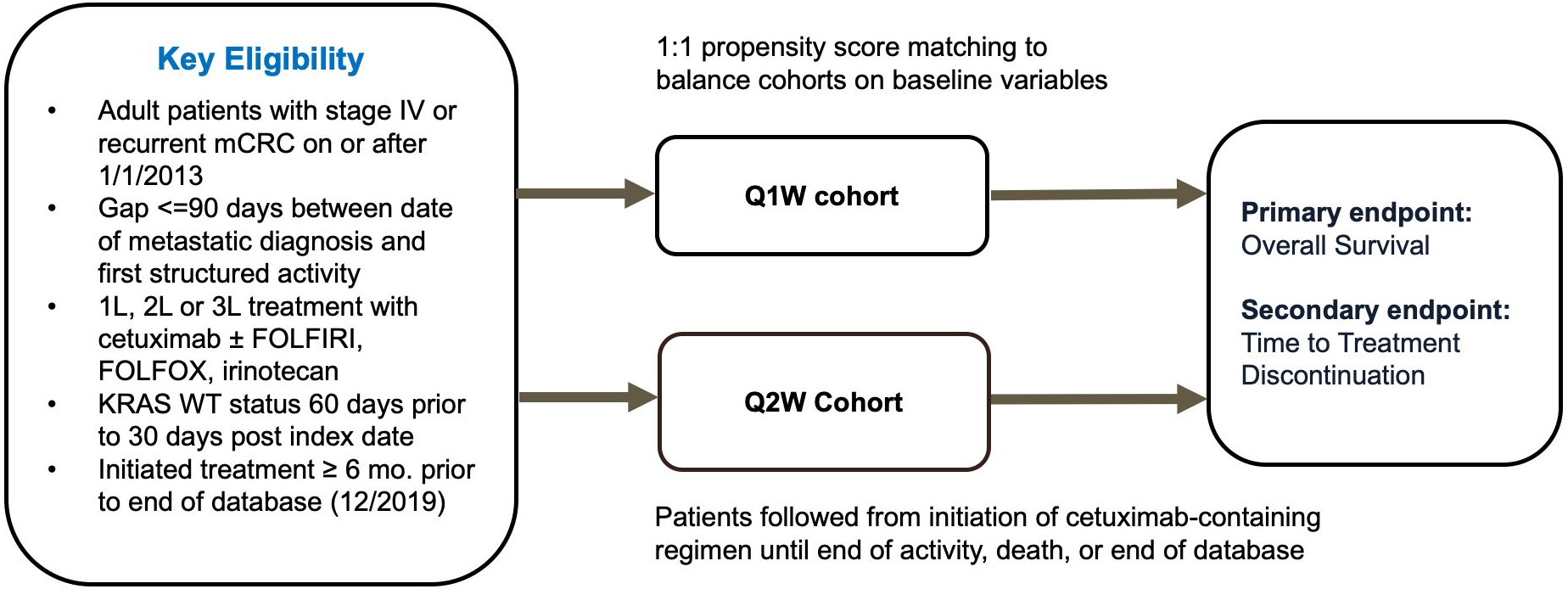
Nivolumab: Change in dosing regimen for monotherapy to 240mg Q2W vs 3mg/kg Q2W

Pembrolizumab: Change in dosing regimen to 400mg Q6W vs 200mg Q3W

Data Submitted to FDA to Support Label Change Under MIDD Pilot

- **Primary evidence**: Population pharmacokinetic modeling analyses
  - Compared predicted exposures of cetuximab 500 mg Q2W to observed cetuximab exposures in patients who received cetuximab 250 mg Q1W
  - Limitation: lacked treatment exposure-response data from Erbitux trials
- **Supportive evidence**: Meta-analysis of efficacy and safety
  - Pooled analyses of response rates, progression-free survival, overall survival, and AEs from published literature in pts with mCRC & SCCHN
- **Supportive evidence**: Real-world observational cohort study
  - Analyses of overall survival associated with Q2W vs. Q1W dosing schedules in patients with mCRC treated with cetuximab

Retrospective Observational Study* Using Flatiron Health EHR Data for mCRC



Patients were assigned to Q1W or Q2W cohort in a line of therapy if they had 70% or more cetuximab infusions with a gap of 4–10 or 11-18 days, respectively, from the previous infusion in that line. Patients who did not fall into either cohort were excluded from the analysis.

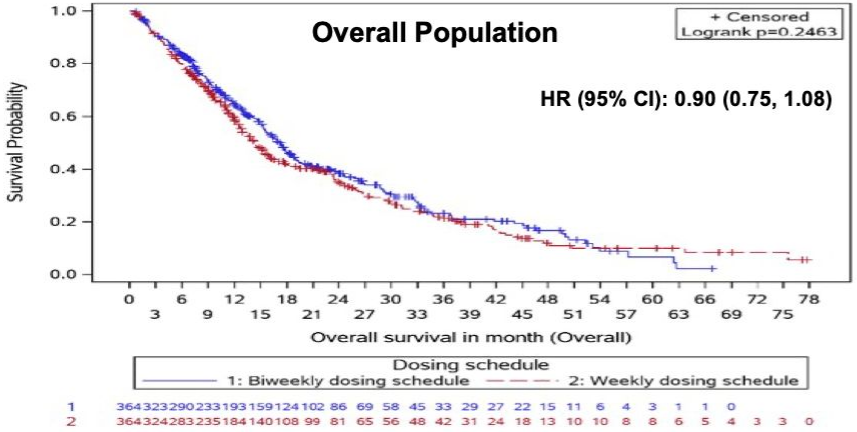
*Aggarwal, Han, Cui. Journal of Clinical Oncology 39, no. 3_suppl (Jan 20, 2021) 33-33

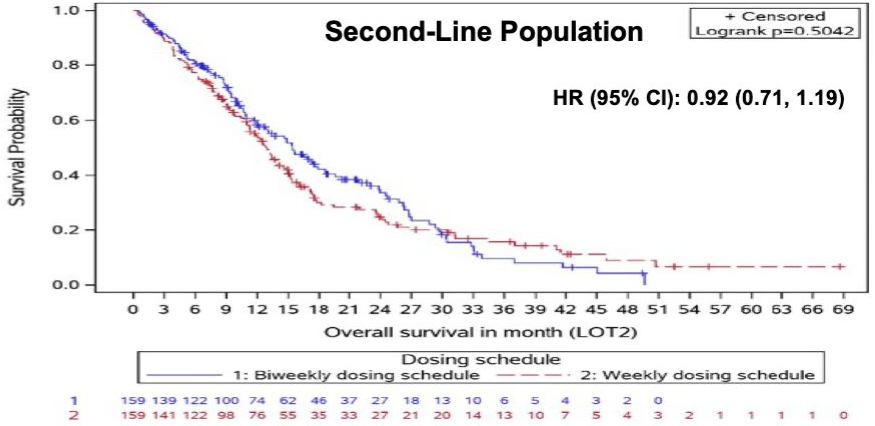
Results: Patient Dosing Schedule and Cetuximab Dosage by Line of Therapy

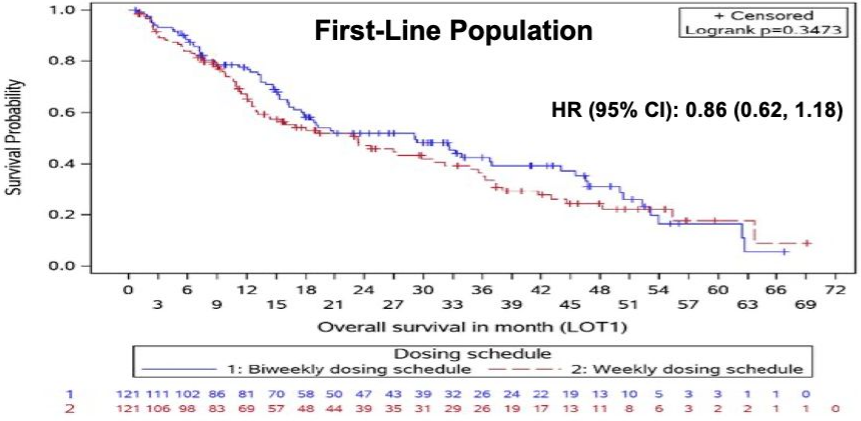
Dosing schedule	Overall N=1075	First-line therapy N=373	Second-line therapy N=477	Third-line therapy N=225
Q1W, n (%)	653 (60.7)	226 (60.6)	292 (61.2)	135 (60.0)
CET dosage[a] (mg/m^2), median (min, max)	246.1 (112.9, 336.1)	245.7 (141.5, 319.4)	246.6 (112.9, 336.1)	245.9 (148.4, 279.3)
Q2W, n (%)	422 (39.3)	147 (39.4)	185 (38.8)	90 (40.0)
CET dosage[a] (mg/m^2), median (min, max)	484.9 (185.0, 532.7)	486.0 (185.0, 522.0)	486.6 (201.3, 532.7)	481.0 (223.5, 530.2)

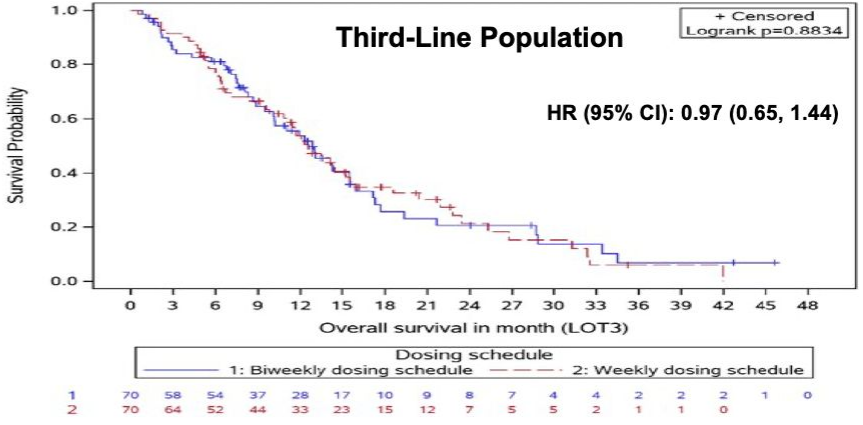
Abbreviations: CET = cetuximab; Q1W = weekly; Q2W = bi-weekly;
[a]Cetuximab dosage was calculated after excluding the first dose.

Overall Survival Propensity Score-Matched Q2W vs Q1W Dosing Cohorts by Line of Therapy









Sensitivity Analyses for OS - Overall Cohort

Definition	Dosing schedule	N	Censoring rate (%)	Median OS (95% CI), month	HR (95% CI)	Log-rank p-value
100% of cetuximab infusions with a gap of 4–10 or 11–18 days from previous infusion for Q1W or Q2W cohort	Q1W (ref)	130	23.1	9.3 (5.6, 11.9)	1.01 (0.77, 1.34)	0.092
	Q2W	130	26.2	8.1 (6.5, 10.9)		
Gap between adjacent cetuximab infusions of < 35 days for Q1W and < 70 days for Q2W cohort	Q1W (ref)	313	29.7	12.9 (12.0, 14.5)	0.91 (0.75, 1.10)	0.331
	Q2W	313	32.0	15.3 (12.3, 16.8)		
Non-missing ECOG PS data	Q1W (ref)	240	30.0	14.5 (13.0, 16.5)	0.88 (0.71, 1.10)	0.271
	Q2W	240	35.4	16.3 (14.6, 18.5)		
1 patient from Q2W cohort was matched to 2 patients in Q1W cohort	Q1W (ref)	506	29.8	14.3 (12.9, 16.0)	0.90 (0.77, 1.06)	0.223
	Q2W	364	35.4	17.2 (15.3, 18.8)		
Entropy-balancing to balance Q2W vs Q1W cohorts	Q1W (ref)	652	27.6	14.4 (12.5, 16.0)	0.83 (0.72, 0.96)	0.037*
	Q2W	421	37.5	17.2 (15.4, 18.7)		

*p<0.05

Study Limitations

- Propensity score methods only address measured confounding – potential for residual unmeasured differences between patients
- Data availability limited to what was documented in the database, (e.g. ECOG performance status missing for many patients)
- Analyses did not account for time-varying confounders, such as changes in treatment patterns over time
- Patients permitted to enter dosing cohorts up to 60 days after index date; time from index date to start of cetuximab is ‘immortal time’.

Discussion

- No significant differences observed in OS associated with Q2W and Q1W dosing schedules in main analyses for overall population and by line of therapy
  - Findings were robust to a number of sensitivity analyses
- FDA emphasized that PK modeling analyses were primary, and RWE results and meta-analyses were supportive in the overall assessment of dosing schedules
- FDA reviewers demonstrated strong understanding of the RWD and provided insightful comments on the analyses