Beyond synthetic controls: Near-term opportunities for regulatory RWE

Pranav Abraham, PhD
Director, Global Health Economics, Rare Hematology
Bristol Myers Squibb

Lynn Howie, MD
Medical Director
Flatiron Health

Kristin Sheffield, PhD
Research Advisor
Eli Lilly and Company

Christopher Gayer, PhD (Moderator)
Director of Product Management
Flatiron Health

flatiron | Research x

Agenda

1. **LYNN HOWIE** — Near-term opportunities to leverage RWE for regulatory use
2. **PRANAV ABRAHAM** — Using RWD to provide natural history information
3. **KRISTIN SHEFFIELD** — Using RWD to fill evidence gaps in the post-approval space: New dosing regimen for cetuximab
4. **ALL SPEAKERS** — Panel discussion and audience Q&A

POLL

Which of these applications of RWE has your organization historically considered or incorporated in regulatory submissions?

Near-term opportunities to leverage RWE for regulatory use

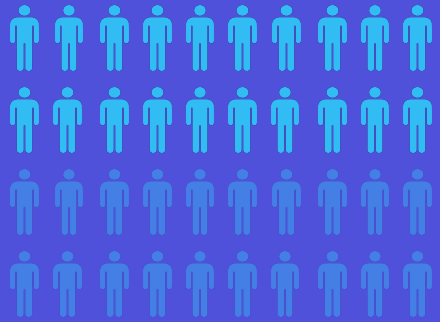
Lynn Howie, MD
Medical Director, Flatiron Health

October 27, 2021

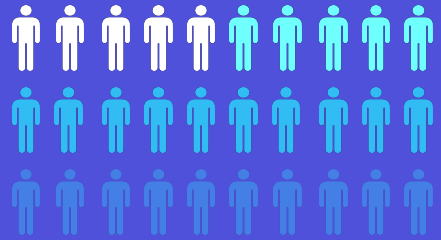
flatiron | Research x

Our need to understand cancer is only growing…

Pre 1990's
Cancer was a histological and anatomical diagnosis with systemic therapy (chemotherapy) as our main option



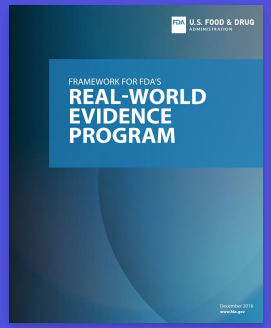
1990s
Targeted therapies such as monoclonal antibodies and tyrosine kinase inhibitors increased biological understanding of cancers



Today
Cell therapy, immunotherapy, pan-tumor therapy and more, treats patients of different genomic make up in a personalized manner

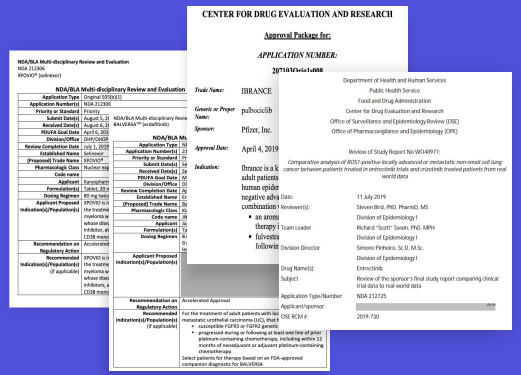
flatiron

Our understanding of the role of RWE use has come a long way in a short amount of time



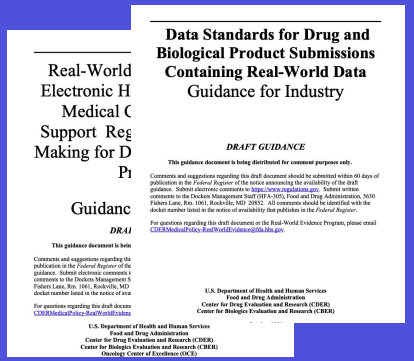
FDA RWE Framework

December 2018



Actionable Regulator Feedback

In Process



RWD/RWE Guidances

In Process

flatiron

Flatiron's experience shapes our perspective on regulatory RWE

Supported **12** briefing packages & **7** information requests

Participated in **7** health authority meetings[†]

Flatiron RWE used in **14** submissions*

Since 2019, we've received regulator input/feedback on 22 unique RWE project opportunities with more than a dozen life science partners

flatiron

[†]Includes formal and informal meetings and written response only

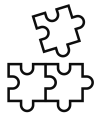
*Inclusive of submissions where Flatiron has provided direct regulatory support.

FDA has signaled specific circumstances in which RWD can complement traditional evidence

Significant unmet need, limited available therapies

Rare cohorts of interest, making randomized trials infeasible

Expected **large effect size** from preliminary data (e.g., from clinical trials)



Existing body of evidence around safety / efficacy of a drug in related population(s)

"In limited instances, FDA has accepted RWE to support drug product approvals… often when using a parallel assignment control arm is **unethical or not feasible and usually when the effect size is expected to be large**, based on preliminary data."

—

FDA's framework for RWE program

flatiron

- Duke Margolis Whitepaper: Determining Real-World Data's Fitness for Use and the Role of Reliability
- Framework for FDA's Real-world evidence program

Regulatory feedback has highlighted common limitations of RWE that are critical to consider for a given use case

Key Examples

Endpoint definition and measurement	Lack of a) standardized definition of real-world efficacy outcome endpoints and/or b) characterizing concordance between real world and clinical trial measures of efficacy
RWD missingness	RWD are subject to different types of missingness (e.g., ECOG available at index), which may impact outcomes and conclusions
Cohort comparability	• Clinical trial eligibility criteria may not be available in RWD for real-world cohort selection resulting in non-equivalent populations impacting outcome comparisons and conclusions • Unmeasured confounders currently blocks time-to-event real-world endpoints

Near term opportunities for regulatory RWE

Using RWD to provide natural history information

Pranav Abraham, PhD
Director, Worldwide Health Economics & Outcomes Research, Bristol Myers Squibb

October 27, 2021

flatiron | Research x

WWHEOR/Oncology

Using RWD to provide natural history information

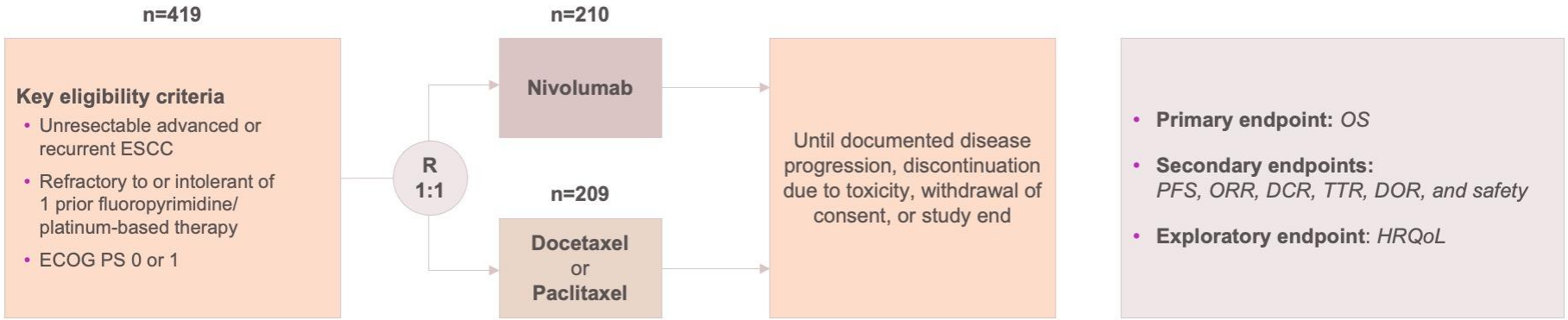
October 27, 2021

Pranav Abraham
Director, Worldwide Health Economics & Outcomes Research

Bristol Myers Squibb™

The need for RWD in Esophageal Squamous Cell Carcinoma

ATTRACTION-3 (ATT-3) was a global, multicenter, phase 3, randomized, open-label trial of nivolumab vs docetaxel or paclitaxel in patients with confirmed esophageal squamous cell carcinoma, refractory or intolerant to 1 prior fluoropyrimidine and platinum-based combination therapy



- **Second-line (2L) nivolumab therapy appeared to confer survival advantage compared with taxanes (10.9 vs 8.4 months) in ATT-3**
- **Patient enrollment occurred predominantly in Asia and hence regulatory concerns around applicability of ATT-3 to the US population (Western patients,18/419)**

Abbreviations: ATT *RWD: Real World Data; OS: Overall Survival; PFS: Progression Free Survival; ORR: Overall Response Rate; DCR: Disease Control Rate; TTR: Time to Response; DOR: Duration of Response; HRQoL: Health Related Quality of Life*

The need for RWD in Esophageal Squamous Cell Carcinoma

Evidence gaps

The prognosis of patients with unresectable, locally advanced or metastatic esophageal squamous cell carcinoma (adv/met ESCC) was poor in the USA

Outcomes of patients receiving 2L therapy for adv/met ESCC remained uninvestigated

Real world outcomes of second-line (2L) therapies as per NCCN treatment guidelines for adv/met ESCC was unexplored

Key research questions

What are the demographics, clinical characteristics and treatment patterns for patients with adv/met ESCC in the US?

What is the overall survival for adv/met ESCC patients who received at least two lines of therapy?

How different is survival among patients who received taxane 2L therapy and those who received non-taxane 2L therapy?

Leveraging RWD to support ATTRACTION-3 results

- BMS identified a cohort of real-world US patients receiving routine clinical management for adv/met ESCC using Flatiron database
- **86 adv/met ESCC patients** in the US receiving 2L treatment were identified during the period from 01/2011 – 01/2019
- In all patients who received 2L therapy median (95% CI) **OS from start of 2L was 6.7** (5.1–8.3) months. Median (95% CI) OS was **7.3 (5.9–11.5) months in patients who received 2L taxane-based therapy (n = 37)**
- Median OS observed in patients receiving taxane therapy in ATTRACTION-3 (8.4 months) was comparable to those in Flatiron database (7.3 months)

Outcomes	*ATTRACTION-3*[1]		*Flatiron Data*[2]	
Treatment arms	Nivolumab	Docetaxel or paclitaxel	All 2L patients	Taxane Therapies
Patients, *n*	210	209	86	37
Age (range), *years*	64 (57-69)	67 (57-72)	64 (36-83)	63 (36-81)
Male, *n (%)*	179 (85%)	185 (89%)	61 (70.9%)	29 (78.4)
Race, *n (%)*				
Asian	201 (96%)	200 (96%)	6 (7%)	2 (5.4%)
White	9 (4%)	9 (4%)	52 (60.5%)	22 (59.5%)
Median OS (95% CI), months	10.9 (9.2–13.13)	8.4 (7.2–9.9)	6.7 (5.1-8.3)	7.3 (5.9-11.5)
12-month survival (95% CI), %	47 (40–54)	34 (28–41)	28.4 (23-34)	29.3 (21-38)

Inclusion Criteria

Diagnosis of adv/met EC (index date), aged 18 years or older at index date, ≥ 1 month of medical data following and including index date, confirmed squamous or adenosquamous EC, received platinum and fluoropyrimidine based treatment as 1L for adv/met EC on or after the index date, received paclitaxel or docetaxel as 2L, ECOG score 0 or 1 any time after the index date

Exclusion criteria

Other primary cancers any time during the study period, with CT study medications on or after the index date, with autoimmune disease, interstitial lung disease or pulmonary fibrosis, diverticulitis or gastrointestinal ulcerative disease, brain metastases, pregnant, received paclitaxel or docetaxel before index date or nivolumab, pembrolizumab, durvalumab, atezolizumab, avelumab, ipilimumab, tremelimumab or immunotherapy any time during the study period

1. Kato K, et al. *Lancet Oncol* 2019;11:1506–17.
2. Abraham P, et al. *Adv Ther.* 2020;37:3392–403.

Impact of Real-World Evidence for BMS in Esophageal Squamous Cell Carcinoma

Key insights

Only **23-33% of patients treated in 1L received 2L therapy**. Survival among all patients receiving 2L therapy for adv/met ESCC was generally poor

Small proportion of patients receiving 2L therapy and poor survival highlighted the **unmet need for more effective therapies**

Clinical characteristics and outcomes **were comparable across regions in advanced stages of disease applicable to the US population and medical practice**

Impact

Inclusion of the Flatiron data along with other real-world analyses strengthened the BMS FDA filing to receive approval of this indication in June 2020.

Nivolumab was the first and only IO therapy approved for 2L ESCC regardless of PD-L1 expression in the US

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

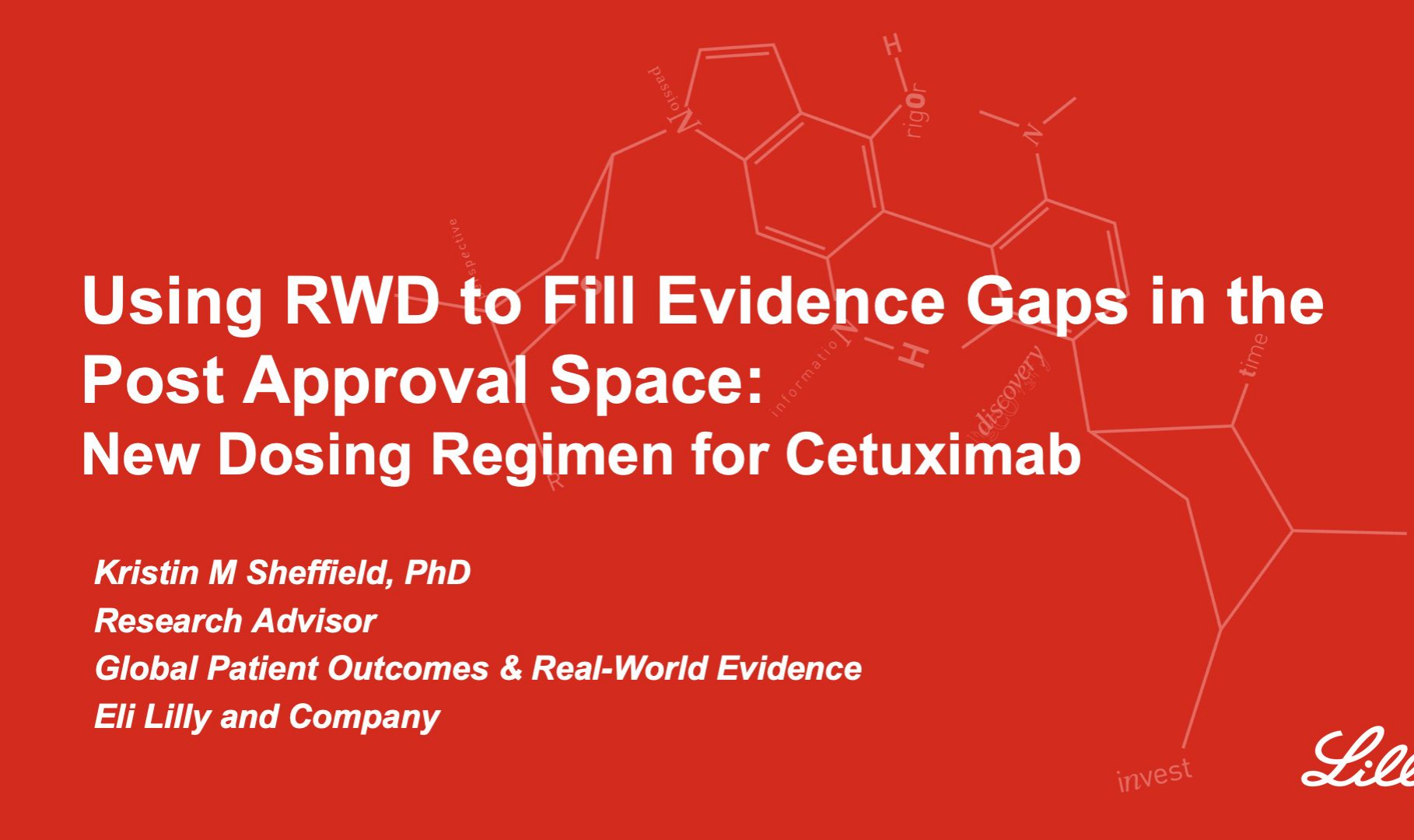
Kristin M. Sheffield, PhD
Research Advisor, Global Research Outcomes
& Real-World Evidence, Eli Lilly and Company

October 27, 2021

flatiron | Research x

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

Kristin M Sheffield, PhD
Research Advisor
Global Patient Outcomes & Real-World Evidence
Eli Lilly and Company



Disclaimer

- The views and opinions expressed in the following are those of the individual presenters and should not be attributed to their company, directors, officers, employees, volunteers, affiliates, or any organization with which the presenters are employed or affiliated.

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

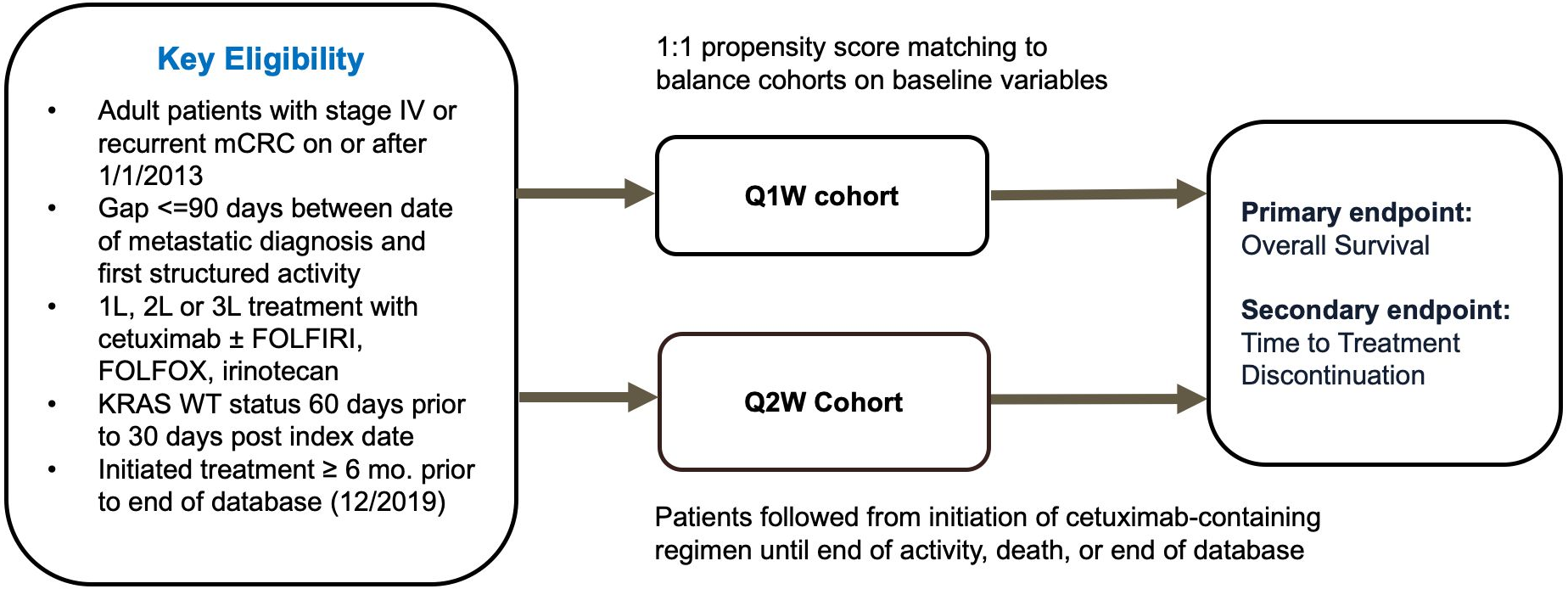
Nivolumab: Change in dosing regimen for monotherapy to 240mg Q2W vs 3mg/kg Q2W

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.

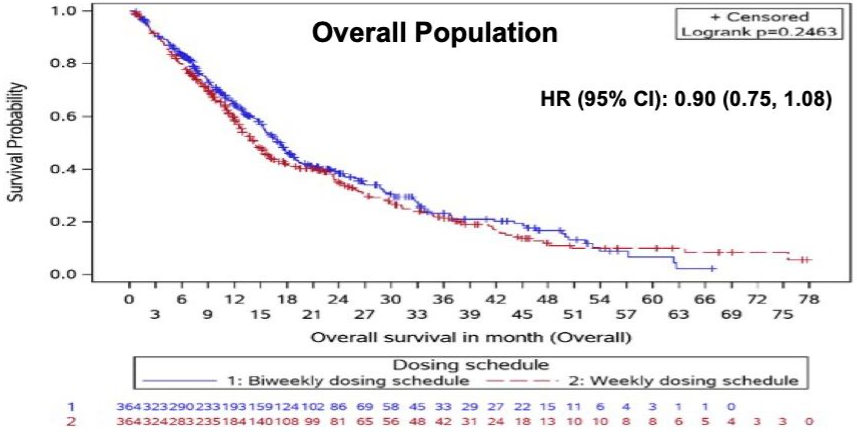
*Aggarwal, Han, Cui. Journal of Clinical Oncology 39, no. 3_suppl (Jan 20, 2021) 33-33

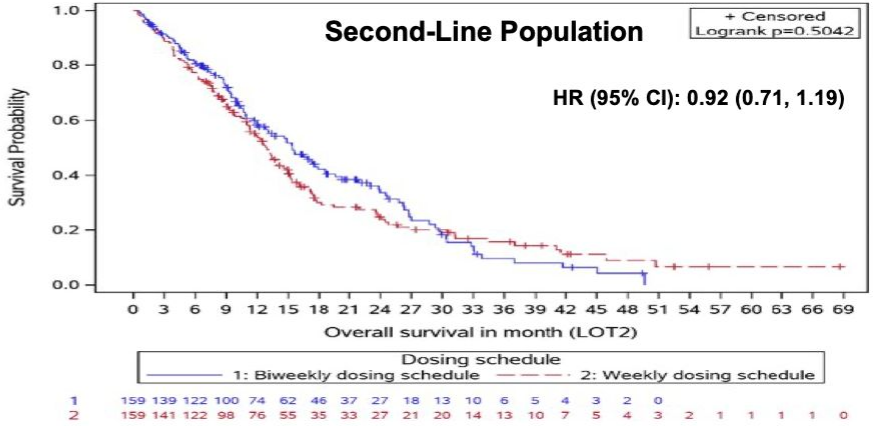
Results: Patient Dosing Schedule and Cetuximab Dosage by Line of Therapy

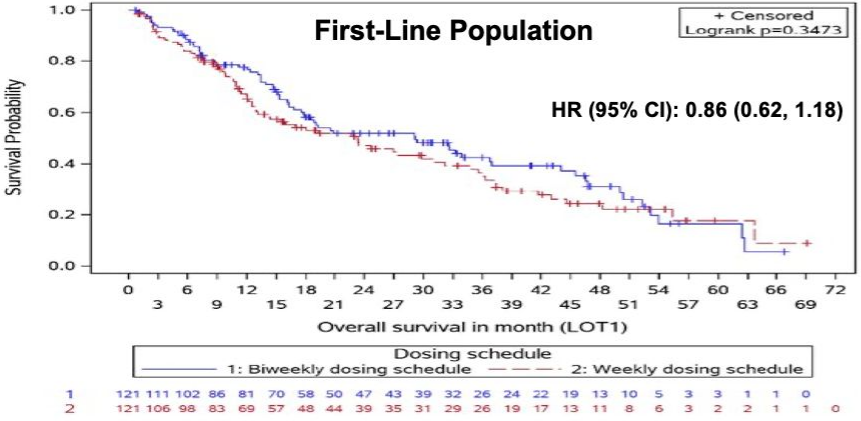
Dosing schedule	Overall N=1075	First-line therapy N=373	Second-line therapy N=477	Third-line therapy N=225
Q1W, n (%)	653 (60.7)	226 (60.6)	292 (61.2)	135 (60.0)
CET dosage[a] (mg/m^2), median (min, max)	246.1 (112.9, 336.1)	245.7 (141.5, 319.4)	246.6 (112.9, 336.1)	245.9 (148.4, 279.3)
Q2W, n (%)	422 (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)

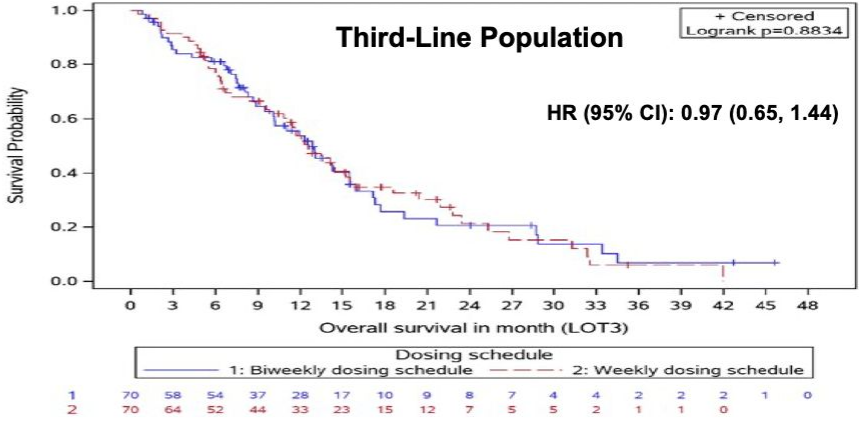
Abbreviations: CET = cetuximab; Q1W = weekly; Q2W = bi-weekly;
[a]Cetuximab dosage was calculated after excluding the first dose.

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

POLL

Over the next 1-2 years, which regulatory applications of RWE do you think your organization should pursue?

Q&A

Please submit questions through the Q&A feature at the bottom of your screen

Pranav Abraham, PhD
Director, Global Health Economics, Rare Hematology
Bristol Myers Squibb

Lynn Howie, MD,
Medical Director
Flatiron Health

Kristin Sheffield, PhD
Research Advisor
Eli Lilly and Company

Christopher Gayer, PhD (Moderator)
Director of Product Management
Flatiron Health

flatiron | Research x

New season coming March 2022

Thank you

For more content, including past ResearchX sessions, visit **rwe.flatiron.com**

Thank you

Email additional questions to rwe@flatiron.com

flatiron | Research x