WE WILL BE STARTING AT 1PM ET

EP 05

Life sciences case studies: Using RWE to support decision making

Leveraging RWD to address evidence gaps across the drug development lifecycle

Incorporate Integrated Evidence (RCTs, EHR, Genomics, Claims, Scans, etc)

1 Discovery / Translational	2 Clinical Development	3 Regulatory Approval	4 Market Access	5 Post-Approval
MOA / Resistance ID	Trial design	Natural history	Natural history	Commercial planning
Biomarker / Target prioritization	Patient recruitment	Unmet need	Long-term survival extrapolation	Post marketing studies
Unmet need	Treatment patterns / SOC	RWD historical comparator	Indirect treatment comparison	Label expansion
		Hybrid trials	Reassessment of marketed drug, HTA	

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(Non-exhaustive)

Agenda

Comparative effectiveness analysis of Tafinlar® (dabrafenib) + Mekinist® (trametinib) NSCLC for PCODR submission in Canada

Fen Ye, MS
Director, RWE & Data Science
Novartis

Using RWE to support EXKIVITY (mobocertinib) program in NSCLC Patients with EGFR Exon 20 insertion mutations

Mark Lin, PhD
Senior Director, Global Evidence & Outcome Research in Oncology
Takeda

Use case of natural history study using Flatiron-FMI NSCLC CGDB to support Lumakras™ regulatory filing

Hil Hsu, PhD, MPH
Senior Manager, Center for Observational Research
Amgen

Victoria Chia, PhD, MPH
Director, Center for Observational Research
Amgen

Where **would you like** to use RWE the most across the drug development lifecycle?

A. Discovery/Translational Research
B. Clinical Development
C. Regulatory Approval
D. Market Access
E. Post Approval

Comparative effectiveness analysis of Tafinlar® (dabrafenib) + Mekinist® (trametinib) NSCLC for PCODR submission in Canada

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04.27.2022

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Novartis Oncology

Comparative effectiveness analysis of Tafinlar® (dabrafenib) + Mekinist® (trametinib) NSCLC for PCODR submission in Canada

Fen Ye
Director, Real-world Evidence and Data Science, Novartis
April 27, 2022

NOVARTIS | Reimagining Medicine

ResearchX: Using RWE to support decision-making

Disclaimer

- Fen Ye is an employee of Novartis Pharmaceuticals Corporation
- This real-world study is sponsored by Novartis Pharmaceuticals Corporation
- The opinions expressed in this presentation and on the following slides are solely those of the presenter and not necessarily those of Novartis Pharmaceuticals Corporation. (“NPC”). NPC does not guarantee the accuracy or reliability of the information provided herein

Contents

HTA, health technology assessment

Background & Opportunity

BRAF V600E mutations is rare

- Occurring in approximately 1%-2% of patients with advanced non-small cell lung cancer (aNSCLC).
- Estimated incidence in Canada: ~160 newly diagnosed patients with BRAF V600 NSCLC per year

Available evidence and opportunity

- BRF11392 is a phase II, multicenter, 3-cohort, nonrandomized, noncomparative, open-label trial assessed the efficacy and safety of TAFINLAR® (dabrafenib) capsules, alone or in combination with MEKINIST® (trametinib) tablets, in patients with BRAF V600E mutation-positive NSCLC.
  - FDA approved the combination in June 2017
  - In Canada, negative HTA opinion due to lack of comparator
- Innovative HTA strategy for Canada: real-world data to generate comparative effectiveness

HTA submission strategy through RWE & stakeholder engagement

Evaluation of Taf + Mek in a traditional, multi-national, randomized, prospectively conducted clinical trial was not feasible, because of the:

1) **Large sample size required**
2) **Rarity of the mutation**
3) **Extended duration of time study would require**

Single arm trial (SAT): rare population with few options → **Registration** 👍 / **Reimbursement** 👎

The Canadian Story of Taf + Mek in BRAF^{V600E} NSCLC (Ph2 SAT)

2017

Negative HTA recommendation in 2L
- Evidence uncertainty and limitations; 'nice' vs 'must'-have

2019

Clinicians & patient organizations requested access
- High need for a targeted therapy option

2020

Start 1L NSCLC submission
- including RWE comparative effectiveness and RWE use data

2021

Positive HTA recommendation in 1L

1L, first-line; 2L, second-line; BRAF, v-raf murine sarcoma viral oncogene homolog B1; HTA, health technology assessment; Mek, Mekinist; NSCLC, non-small cell lung cancer; SAT, single arm trial; Taf, Tafinlar.

Innovative approach to address lack of comparative data (published)

RW comparison to confirm findings of external cohort analysis

	External cohort analysis *(Trial vs. RWD)*	Real-world comparison*(RWD vs. RWD)*
Congress abstract	**ISPOR EU 2020** External Control Analysis of Overall Survival in BRAFV600 Mutated Metastatic NSCLC: Comparing Single-Arm Dabrafenib+Trametinib Clinical Trial Outcomes with Real-World Standards of Care	**ESMO 2021** Clinical outcomes of patients with BRAFv^{600}-mutated metastatic NSCLC (mNSCLC) receiving first-line (1L) dabrafenib-trametinib vs other standard of care in real-world practice
Population	Metastatic NSCLC (stage IV) with *BRAF* mutation	Metastatic NSCLC (stage IV) with ***BRAF* V600** mutation
Data source	Taf + Mek: Cohort C of BRF113928 phase II trial Comparators: Flatiron	Taf + Mek: Flatiron Comparator: Flatiron
Comparisons	Taf + Mek vs. chemo Taf + Mek vs. pembro + chemo	Taf + Mek vs. chemo Taf + Mek vs. pembro + chemo Taf + Mek vs. pembro /irrespective of PD-L1 status Taf + Mek vs. pembro /PD-L1 high only
Variables considered for weighting	Age, gender, race, smoking status, and ECOG status	Age, gender, race, stage at initial diagnosis, smoking status, and ECOG status and histology
Endpoints	Overall survival Progression-free survival Time to treatment discontinuation (exploratory)	Overall survival Real-world progression-free survival

1L, first-line; ECOG, Eastern Cooperative Oncology Group; ESMO, European Society For Medical Oncology; ISPOR, The Professional Society for Health Economics and Outcomes Research; Mek, Mekinist; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death- ligand 1; pembro, pembrolizumab; PFS, progression-free survival; Taf, Tafinlar.

RWE study methods: patient matching

Propensity score (PS) model, based on individual patient-level data, was applied to minimize potential bias related to the comparators for both studies (trial vs RWD and RWD vs RWD)

PS weighting was chosen over other methods (e.g. PS matching and multivariable analysis) due to limited sample size. PS weighting utilizes the entire study population and simultaneously adjusts for confounders

PS was estimated using logistic regression modelling treatment assignment as a function of baseline characteristics

Stabilized IPTW was based on the PS used to estimate the ATT (trials vs RWD) or ATE (RWD vs RWD)

To assess covariate balance, the distributions of baseline covariates, along with SMD pre- and post-weighting were summarized. An SMD of < 0.25 was considered as balanced.

ATE, average treatment effect; IPTW, inverse probability of treatment weighting; PS, propensity score; SMD, standardized mean difference.

External cohort analysis (Trial vs. RWD) results

Table 1: Baseline Characteristics of the different cohorts before and after weighting

Parameter	1L Dabrafenib + trametinib trial cohort	1L chemotherapy RW cohort		1L PD(L)1 + chemotherapy RW cohort		2L+ Dabrafenib + trametinib trial cohort	2L PD(L)1 RW cohort	
		Pre-weighting	Post-weighting	Pre-weighting	Post-weighting		Pre-weighting	Post-weighting
Sample size	N=36	N=64	N=37	N=34	N=27.8	N=57	N=42	N=54
Sex (%)								
Female	61.1	54.7	57.5	41.2	45.1	49.1	54.8	54.9
Male	38.9	45.3	42.5	58.8	54.9	50.9	45.2	45.1
Age at index								
Mean (SD)	67.8 (11.0)	66.5 (9.1)	68.0 (7.0)	69.4 (8.1)	68.0 (8.0)	65.1 (10.1)	67.8 (8.2)	64.5 (10.2)
Age group at index (%)								
Under 54	8.3	6.3	8.8	2.9	6.6	14.0	4.8	15.6
55 to 64	30.6	42.2	25.9	23.5	21.8	36.8	31.0	38.7
>=65	61.1	51.6	65.3	73.6	71.6	49.2	64.3	45.7
Race (%)								
White	83.3	76.6	85.5	79.4	84.5	86.0	78.6	84.7
Other	16.7	23.5	14.5	20.6	15.5	14.0	21.4	15.3
ECOG at Baseline (%)								
0	36.1	25.0	37.1	29.4	38.4	29.8	11.9	27.2
1	61.1	64.1	59.9	47.1	58.3	61.4	73.8	64.0
2	2.8	10.9	2.9	23.5	3.2	8.8	14.3	8.8
Stage at initial diagnosis (%)								
I	NA	7.8	7.8	8.8	11.5	NA	7.1	9.5
II	NA	7.8	8.3	2.9	0.5	NA	4.8	4.1
III	NA	26.6	19.8	2.9	2.5	NA	23.8	21.6
IV	NA	56.3	63.5	82.4	79.7	NA	64.3	64.9
Missing	100	1.6	0.7	2.9	5.7	100	0	0

ECOG-PS: Eastern Cooperative Oncology Group-Performance Status; NA: Not Available; RW: Real-world; SD: Standard Deviation

More results of the external control analysis are available: "Control Analysis of Overall Survival in BRAFV600 Mutated Metastatic NSCLC: Comparing Single-Arm Dabrafenib+ Trametinib Clinical Trial Outcomes with Real-World Standards of Care."
Value in Health 23 (2020): S423.
https://www.valueinhealthjournal.com/article/S1098-3015(20)32409-8/fulltext

1L, first-line; 2L, second-line; PD-L1, programmed death- ligand 1.

Real-world comparison (RWD vs. RWD) results

Table 1. Baseline Characteristics After Weighting*

	Dab-tram	ICI + PDC	Dab-tram	ICI	Dab-tram	PDC
N	47.2[a]	27.7[a]	44.4[a]	30.3[a]	48.3[a]	30.3[a]
Mean (SD) age at 1L therapy initiation, years	70.89 (9.16)	71.6 (9.81)	71.42 (8.68)	73.07 (8.72)	72.35 (8.81)	71.25 (8.53)
Male gender, n (%)	23.3 (49)	14 (50)	20.1 (45)	12.2 (40)	21 (43)	10.2 (34)
Race, n (%)						
White	33.5 (71)	20.6 (74)	33 (74)	24.1 (80)	32.5 (67)	22.0 (73)
Black/African American	4.0 (8)	2.3 (8)	5.4 (12)	3.6 (12)	2.3 (5)	1.1 (4)
Other	9.7 (20)	4.8 (17)	6.0 (13)	2.6 (9)	13.5 (28)	7.2 (24)
Stage at initial diagnosis, n (%)						
Stage I and II	4 (8)	2.6 (9)	3.6 (8)	2.6 (9)	4.5 (9)	2.5 (9)
Stage III and IV	43.2 (92)	25.2 (91)	40.8 (92)	27.7 (91)	43.8 (91)	27.8 (92)[b]
Smoking status, n (%)						
History of smoking	29.9 (63)	19.4 (70)	30.4 (68)	20.6 (68)	30.4 (63)	16.5 (54)
No history of smoking	17.3 (37)	8.3 (30)	14 (32)	9.7 (32)	17.9 (37)	13.8 (46)
ECOG PS, n (%)						
0	10.2 (22)	6.8 (25)	9 (20)	7.8 (26)	12.1 (25)	6.9 (23)
1	10.2 (22)	9.8 (35)	9.4 (21)	6.5 (22)	14.3 (30)	7.6 (25)
2	8.1 (17)	0 (0)	6.4 (14)	5 (17)	6.8 (14)	5.5 (18)
Missing	18.6 (39)	11.1 (40)	19.7 (44)	11 (36)	15.1 (31)	10.3 (34)

*Pre-weighted data can be viewed by scanning the QR code

[a]For each comparison, patients in the dab-tram and SoC cohorts were assigned a weight (estimated by propensity score) corresponding to the inverse probability of the patient being assigned to the dab-tram or SoC cohort, respectively, based on baseline covariates. The sample sizes of the weighted cohorts correspond to the sum of all weighted patients per cohort.

[b]Total percentage is greater than 100% due to rounding.

Dab-tram, dabrafenib plus trametinib; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune-checkpoint inhibitor; PDC, platinum-doublet chemotherapy; pre-w pre-weighting; post-w, post-weighting; SD, standard deviation.

More results of the real-world vs real-world comparative analysis are available: “Clinical outcomes of patients with BRAFv^{600}-mutated metastatic NSCLC (mNSCLC) receiving first-line (1L) dabrafenib-trametinib vs other standard of care in real-world practice." Annals of Oncology 32 (2021): S988.
Value in Health 23 (2020): S423.
https://www.annalsofoncology.org/article/S0923-7534(21)04093-X/fulltext

RWE use in Canada's HTA submission addressed the lack of comparative data

APPROACH

(A) External cohort analysis: BRF113928 (single arm phase 2) vs. Flatiron RW cohorts

- **Provided comparative data vs. pembro + chemo and vs. chemo**
- **Was the main clinical data source to develop the CEA and BIA**
- **Enabled continuous discussions/collaboration with medical community and patient organizations**

(B) Comparative effectiveness study: Taf + Mek RWD vs. comparators RWD

- **Confirmed the results of the external cohort study (A)**
- **Addressed HTA queries (e.g. additional comparison vs. pembro–mono)**
- **Provided additional data supporting the use of Taf + Mek in 1L**

RESULTS

2021 – Positive HTA recommendation in 1L NSCLC

- Integration of RWE as core evidence for HTA submission positively impacts outcomes
- RWE **reduced the uncertainty** and limitations of a single arm trial leading to **better informed decisions**

Learnings

- Use of real-world data could overcome geographic limitation
- External control analysis for rare population could be enriched by RW vs RW comparison
- RWD vendor could increase data sophistication and enhance the relevance of RWE

1L, first-line; BIA, business impact assessment; CEA, cost-effectiveness analysis; HTA, health technology assessment; KOL, key opinion leaders; Mek, Mekinist; pembro, pembrolizumab; Taf, Tafinlar.

For Study BRF113928(clinical study), the authors would like to thank the patients, their families and caregivers, and the participating clinical sites and teams

Thanks to Novartis Global and Canadian teams for the collaboration on this real-world study

Use case of natural history study using Flatiron-FMI NSCLC CGDB to support Lumakras™ regulatory filing

Hil Hsu, PhD, MPH

Senior Manager, Center for Observational Research

Amgen

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USE CASE OF NATURAL HISTORY STUDY USING FLATIRON-FMI NSCLC CGDB TO SUPPORT LUMAKRAS™ REGULATORY FILING

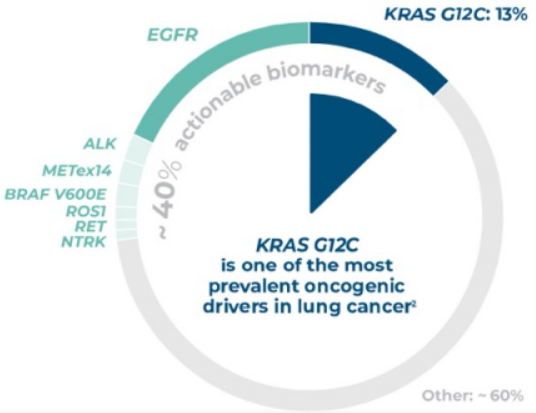
Hil Hsu, PhD, MPH
Senior Manager
Center for Observational Research

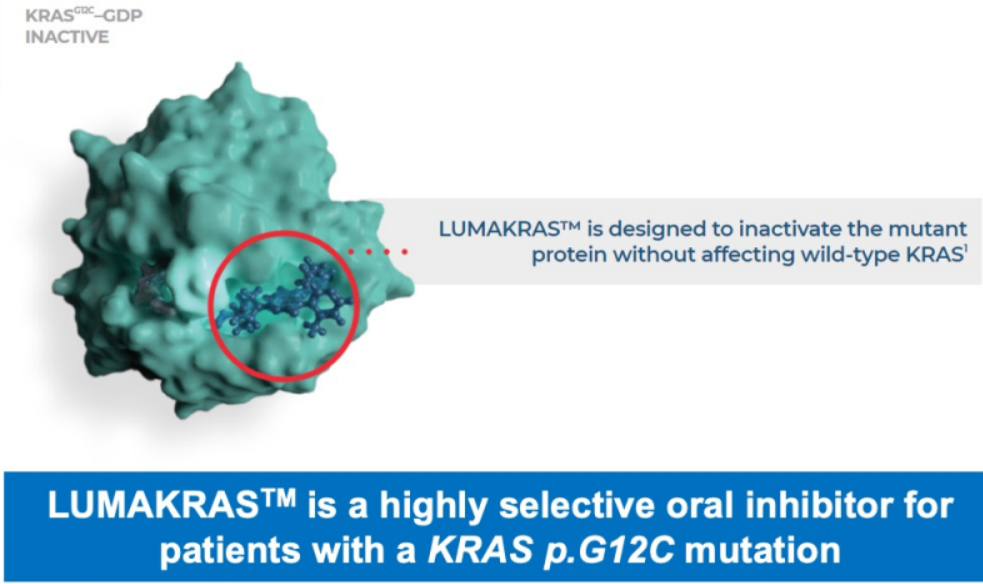
AMGEN®

KRAS p.G12C IS AN ONCOGENIC DRIVER MUTATION WHICH IS BLOCKED BY LUMAKRAS™

13% of patients with non-squamous NSCLC have an actionable *KRAS p.G12C* mutation

Prevalence of oncogenic drivers in non-squamous NSCLC





LUMAKRAS™ is a highly selective oral inhibitor for patients with a *KRAS p.G12C* mutation

Source: https://www.lumakrashcp.com/understanding-kras-mutation-lung-cancer

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REAL-WORLD EVIDENCE (RWE) NEEDED TO CONTEXTUALIZE SINGLE-ARM CLINICAL TRIAL DATA FOR LUMAKRAS

GOAL

Achieve accelerated approval for FDA based on single-arm clinical trial in a rare disease with high unmet need

NEED

RWE to better understand disease and contextualize trial results in the absence of randomized comparator

SOLUTION

New RWE collaboration with high quality fit-for-purpose data

AMGEN

NATURAL HISTORY STUDY

- Characterized advanced non-small cell lung cancer (advNSCLC) patients (n=7,069) in the Flatiron-FMI NSCLC CGDB and the subset (n=743) with *KRAS p.G12C* mutation
  - Study period: 01/01/2011 to 09/30/2019

- Described patient demographics, clinical characteristics, co-mutations, treatment patterns, and outcomes (real-world overall survival and progression-free survival)

- Employed robust analytic methods to account for timing of biomarker testing and avoid overestimation of survival due to immortal time bias

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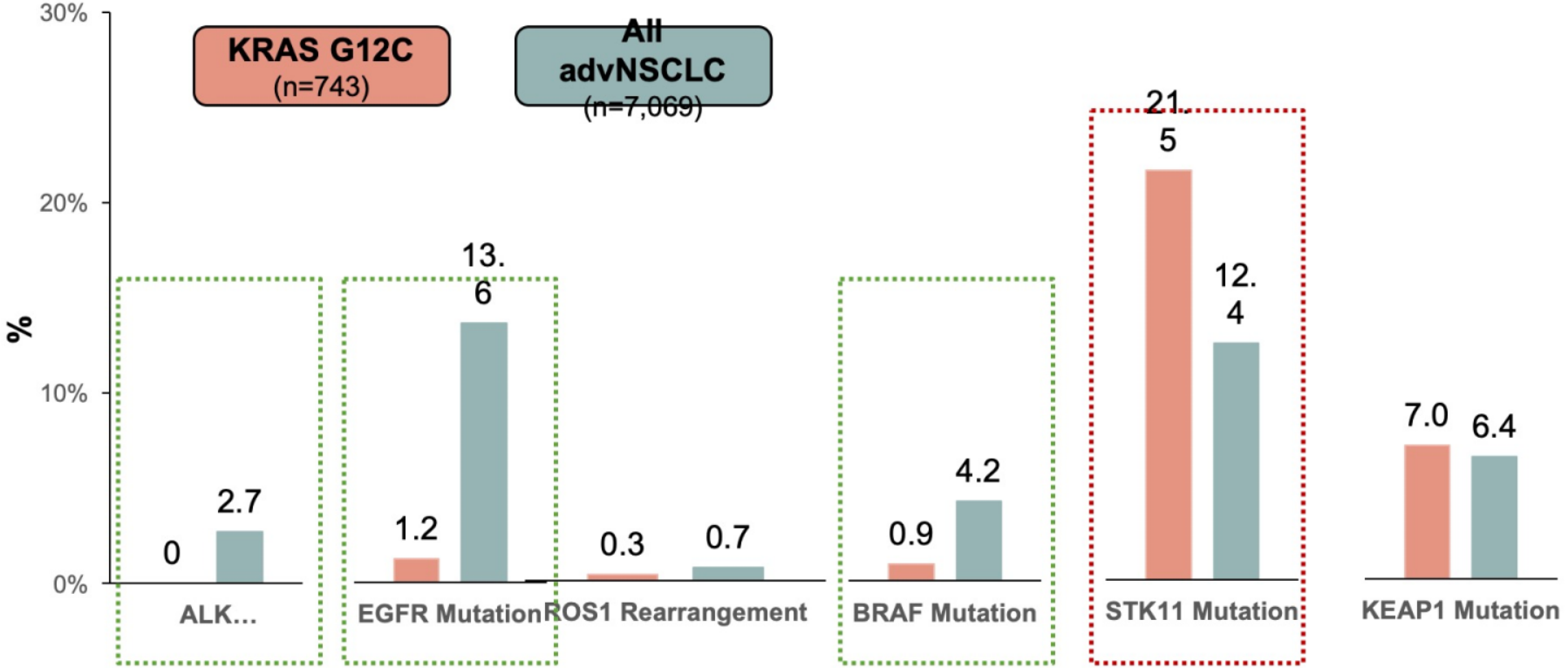
PATIENT CHARACTERISTICS

	KRAS G12C (n=743)	All advNSCLC (n=7,069)
Median Age at Advanced Diagnosis (Range)	68 (29-85)	68 (24-85)
Female	**61.1%**	50.0%
Ever Smokers	**96.8%**	81.9%
Non-Squamous	**90.8%**	76.1%
Diagnosed in 2015 or Later	82.2%	82.2%

Study period: 01/01/2011 to 09/30/2019

AMGEN

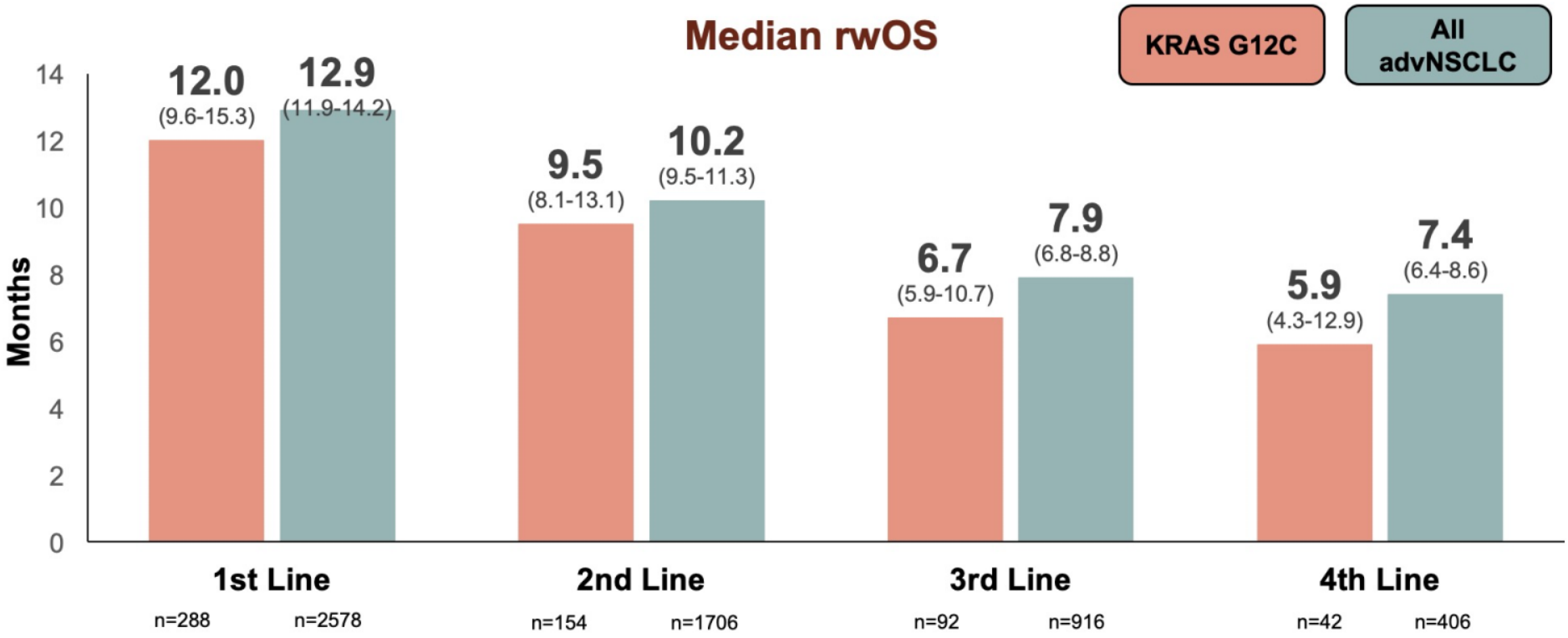
MUTUAL EXCLUSIVITY WITH OTHER ACTIONABLE DRIVER MUTATIONS AND MORE STK11 CO-MUTATION IN *KRAS p.G12C* AND ALL advNSCLC PATIENTS



Study period: 01/01/2011 to 09/30/2019

AMGEN

SIMILARLY POOR OUTCOMES WITH EXISTING THERAPIES IN *KRAS p.G12C* AND ALL advNSCLC PATIENTS



Study period: 01/01/2011 to 09/30/2019

AMGEN

KEY TAKEAWAYS

Large data source linking rich clinical and genomic data in mostly community oncology patients nationwide

Publications were developed on the natural history to benchmark outcomes in a rare biomarker-defined patient population[1,2]

Study reports were completed and included in the NDA to provide context on the current standard of care

FDA included Amgen's RWE study results in the Multidisciplinary Review, agreeing with Amgen's description of current standard of care

1. Aggarwal et al. Annals of Onc 2020 (ESMO 2020) 2. Spira et al. Lung Cancer 2021

AMGEN

Using RWE to support EXKIVITY (mobocertinib) program in NSCLC patients with EGFR exon 20 insertion mutations

Mark Lin, PhD

Senior Director, Global Evidence & Outcome Research in Oncology

Takeda

04.27.2022

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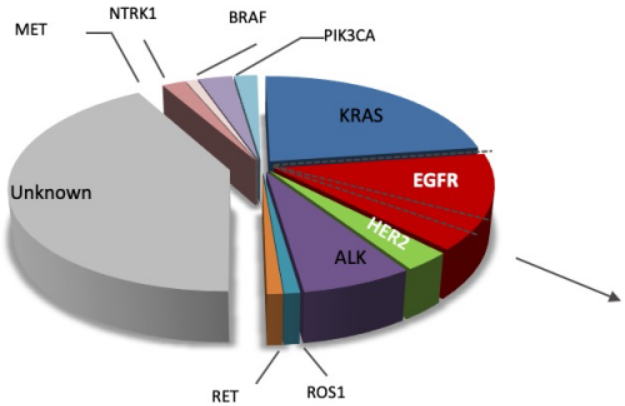
Using Real World Evidence (RWE) to support EXKIVITY (Mobocertinib) program in NSCLC Patients with EGFR Exon 20 Insertion Mutations

Mark Lin, PhD
Global Evidence & Outcome Oncology
Takeda Pharmaceutical Co.

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

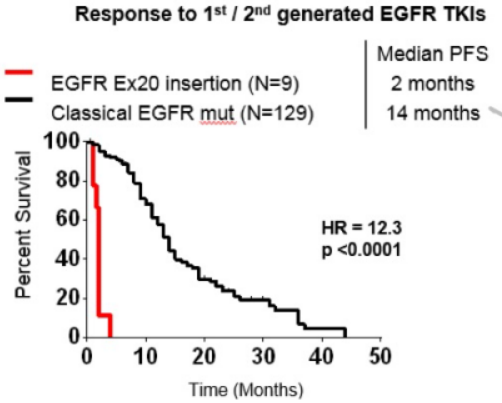
NSCLC patients with EGFR Exon 20 insertion mutations are underserved with the historically available therapies

- Non-small cell lung cancer (NSCLC) represents up to 85% of all lung cancers
- NSCLC is highly heterogeneous with different driver mutations



***EGFR* exon 20 2.1%**

- No approved *EGFR* target therapies exist for NSCLC with *EGFR* Exon 20 mutations



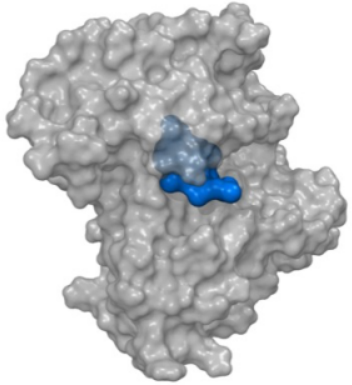
PFS of ex20 ins pts is significantly worse than PFS of pts with other uncommon mutations

- *EGFR* TKIs, currently available (or commonly used for treatment), are not effective for Exon 20 mutation

Source: 1. Leduc C et al., Ann Oncol 2017;28:2715–2724. 2. Jorge S et al. Braz J Med Biol Res 2014;47:929–39. 3. Kobayashi Y & Mitsudomi T. Cancer Sci 2016;107:1179–86. 4. Arcila M et al. Mol Cancer Ther 2013;12:220–29. 5. Oxnard G et al. J Thorac Oncol 2013;8:179–84.3. Robichaux et al WCLC 2016 and Yasuda H, et al. Sci Transl Med. 2013;5:216ra177

Mobocertinib (TAK-788) is an EGFR/HER2 Tyrosine Kinase Inhibitor (TKI) with a Focus of EGFR Exon 20 insertion

- A TKI designed to potentially inhibit oncogenic variants containing activating mutations in Exon 20 or other uncommon mutations, with selectivity over WT EGFR.
- Based on preclinical assays, TAK-788 potently inhibited:
  - EGFR exon 20 insertions
  - HER2 exon 20 insertions/point mutations
  - EGFR common mutations ± T790M
  - EGFR uncommon mutations
- Similar to afatinib, TAK-788 was designed to bind EGFR irreversibly (via Cys797)
  - Increased potency
  - Greater overall selectivity



Crystal structure of EGFR in complex with TAK-788

Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor (*EGFR*) exon 20 insertion mutations.

Mobocertinib Antitumor Activity in Platinum-Pretreated Patients (PPP) cohort of *EGFR*ex20ins^{+} mNSCLC

Mobocertinib Efficacy in the single arm trial PPP Cohort (N=114; data cutoff: 1 November 2020)

Efficacy	Per IRC	Per Investigator
Confirmed ORR, n (%) [95% CI]	32 (28) [20–37]	40 (35) [26–45]
Median DoR (95% CI), months	17.5 (7.4–20.3)	11.2 (5.6–NR)
Median PFS (95% CI), months	7.3 (5.5–9.2)	7.3 (5.6–8.8)
Median OS (95% CI), months	24.0 (14.6–28.8)	

[a]DoR per Kaplan-Meier estimates; [b]DCR defined as confirmed CR or PR, or best response of stable disease for at least 6 weeks after initiation of study drug
CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; *EGFR*ex20ins, *EGFR* exon 20 insertion; IRC, independent review committee; mNSCLC, metastatic NSCLC; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PPP, platinum-pretreated patients; PR, partial response

Use of RWD as External Control to Support Regulatory Approval and Market Access of Mobocertinib

Clinical Development…

- Demonstrates mobocertinib is first-in-class oral TKI that selectively targets exon 20 insertion mutations
- Efficacious clinical data

POTENTIAL CHALLENGES

1. Single arm trial design
2. Lack of standard of care and historic control of rare *EGFR* exon 20 NSCLC patients

RWD

- Raise awareness and underdiagnosis of the rare population
- Establish natural history and real- world treatment patterns
- Assess the benefit of current treatment in the target population
- Provide comparative evidence for single-arm trials
- Accelerate regulatory and market access submission

Support Mobocertinib Single-Arm Trial with External Controls using multiple data source

- In the absence of direct comparison evidence from a head-to-head randomized controlled trial, indirect comparison with external controls can be used to bridge the gap of comparative evidence.
- Data sources for external controls
  - Real-world data, e.g., electronic health records (EHR), claims, medical chart review study, registries.
  - Other clinical trials

Multiple real-world data sources used to support mobocertinib

Germany Medical Chart Review

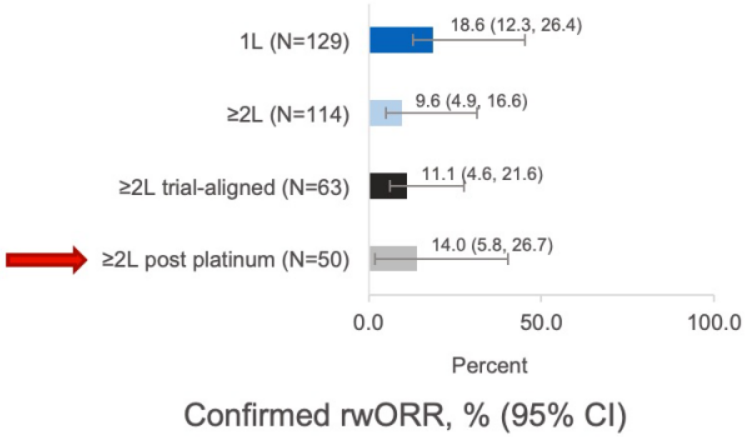
- Stage IV NSCLC patients with *EGFR* exon 20 insertions treated in 12 German academic centers.
  - ✓ High quality data curated by investigator
  - ✓ Provide data source outside of US
  - ✓ Detailed clinical endpoint (ORR, PFS, OS etc)
  - ✓ Sample size: *EGFR* Exon 20 NSCLC patients in the database are N=104 (1st line)

Flatiron EHR-derived database

- The Flatiron Health database is a longitudinal, demographically and geographically diverse database derived from de-identified electronic health record data.
  - ✓ Agency is familiar with this database from prior submissions
  - ✓ Detailed clinical endpoint (ORR, PFS, OS etc)
  - ✓ Sample size: estimated *EGFR* Exon 20 NSCLC patients in the database are N=237 (1st line)

Benchmark analysis: Confirmed rwORR from RWD (Flatiron EHR)

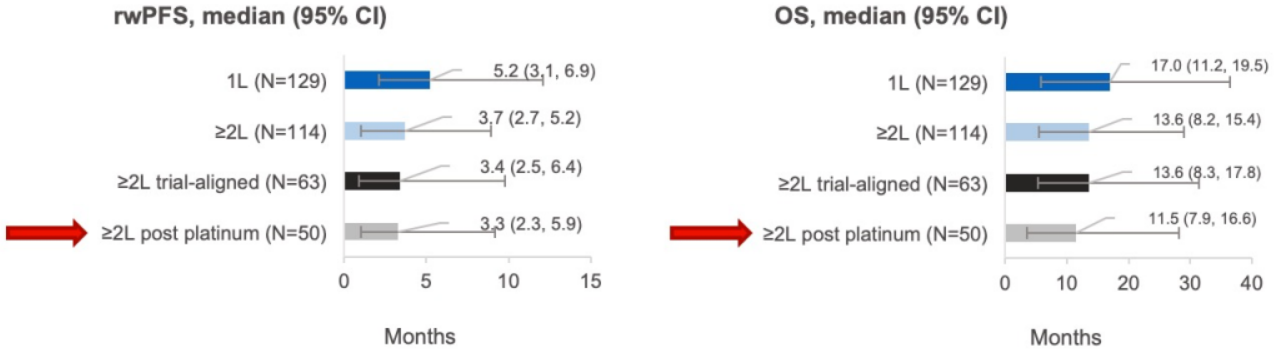
Confirmed rwORR was poor in all cohorts, particularly in the PPP cohorts (14%)



1L, first line; ≥2L, second or later line; CI, confidence interval; rwORR, real-world overall response rate.

Benchmark analysis: Median OS and rwPFS from RWD

- In the 1L cohort, median rwPFS and median OS (mOS) were 5.2 months and 17.0 months, respectively
- In the ≥2L cohorts, median rwPFS ranged from 3.3 to 3.7 months and mOS ranged from 11.5 to 13.6 months



1L, first line; ≥2L, second or later line; CI, confidence interval; OS, overall survival, rwPFS, real-world progression-free survival.

Weighing method to Match Baseline Characteristics

Study Population

- **Mobocertinib:** platinum-pretreated patients with EGFR exon20ins+ NSCLC treated with mobocertinib in NCT02716116 (cutoff: 1 Nov 2020)
- **RWD:** platinum-pretreated patients with EGFR exon20ins+ NSCLC whose baseline characteristics were aligned with key eligibility criteria of mobocertinib pivotal trial (data cutoff: 29FEB2020)

After weighting, baseline characteristics were balanced between the mobo trial and Flatiron RWD patients.

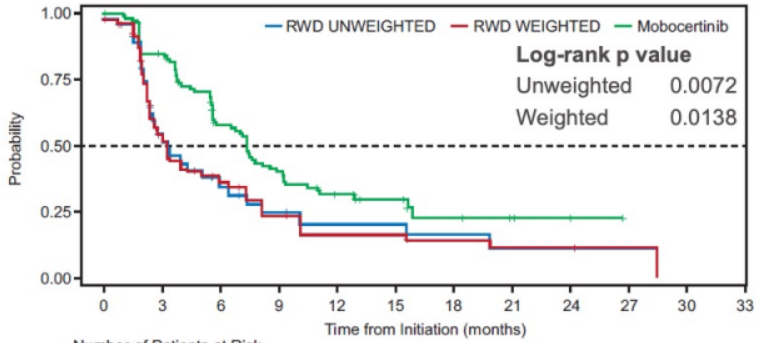
Variables	Mobo population	Unweighted Flatiron RWD	Weighted	
			Flatiron RWD	P value
Sample size	114	50	109	
Age (years): mean (SD)	59.6 (11.5)	64.3 (10.3)	60.8 (16.2)	0.506
Sex: female (%)	75 (66)	34 (68)	72 (66)	0.998
History of smoking: Yes (%)	33 (29)	21 (42)	30 (27)	0.774
Brain mets: Yes (%)	40 (35)	17 (34)	42 (38)	0.634
Months since initial diagnosis: mean (SD)	23.8 (27.9)	17.2 (20.3)	20.9 (34.7)	0.471

Mobocertinib Was Associated with Improved Outcomes vs. RWD

Odds ratio >1 or hazard ratio <1 favors mobocertinib

Outcome (95% CI)	Mobocertinib (N = 114)	RWD		Relative treatment effect of mobo vs RWD	
		Unweighted (N = 50)	Weighted (N = 109)	Unweighted	Weighted
cORR (INV), %	35.1 (26.4, 44.6) (per investigator)	14.0 (5.8, 26.7)	11.9 (5.8, 18.0)	Odds ratio 3.32 (1.68, 6.58)	Odds ratio 3.75 (2.05, 6.89)
cORR (IRC), %	28.1 (20.1, 37.3) (per IRC)	14.0 (5.8, 26.7)	11.9 (5.8, 18.0)	Odds ratio 2.40 (0.98, 5.88)	Odds ratio 2.88 (1.42, 5.85)
Median PFS, months	7.3 (5.6, 8.8) (per investigator)	3.3 (2.3, 5.9)	3.3 (2.2, 7.3)	Hazard ratio 0.57 (0.36, 0.89)	Hazard ratio 0.57 (0.36, 0.90)
Median OS, months	24.0 (14.6, 28.8)	11.5 (7.9, 16.6)	12.4 (7.1, 16.6)	Hazard ratio 0.54 (0.34, 0.84)	Hazard ratio 0.53 (0.33, 0.83)

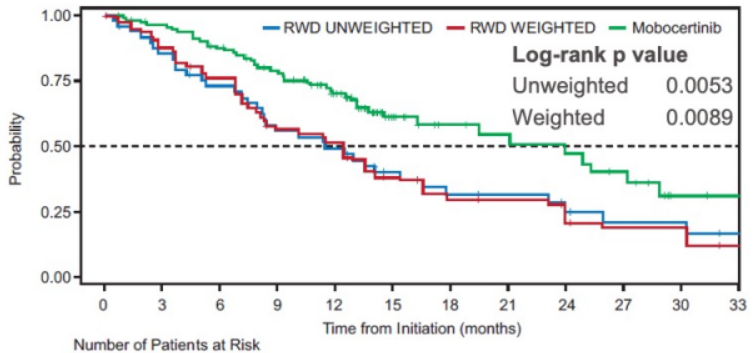
Progression-free survival



Number of Patients at Risk

RWD UNWEIGHTED	50	20	11	7	5	5	3	2	2	1	0
RWD WEIGHTED	109	38	23	14	9	9	6	4	4	2	0
Mobocertinib	114	84	53	35	22	10	6	4	2	0	

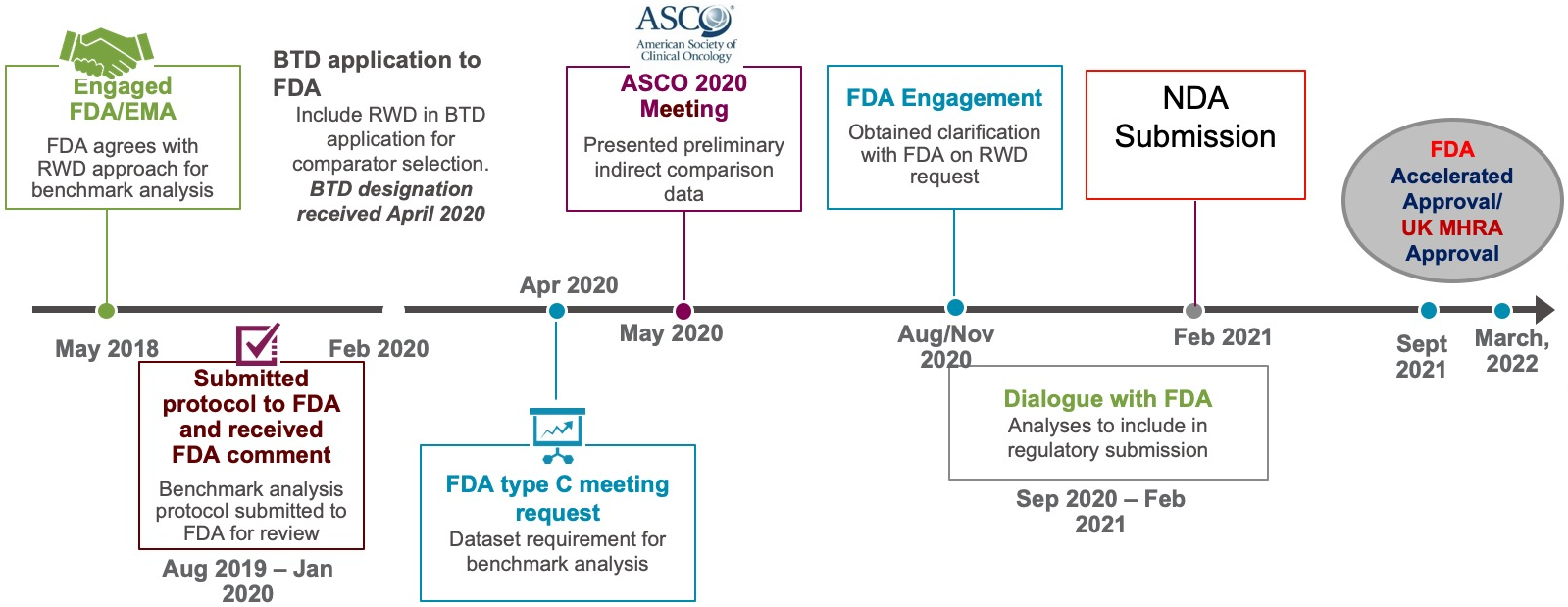
Overall survival



Number of Patients at Risk

RWD UNWEIGHTED	50	41	34	25	22	15	11	10	7	5	5	3
RWD WEIGHTED	109	90	77	56	51	30	21	21	12	9	9	4
Mobocertinib	114	106	95	82	51	25	17	15	13	10	3	2

Path to Approval Includes Multiple Touchpoints with Regulatory Agencies



Key learnings

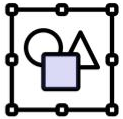
- Align with internal Team, leverage resources and react fast
- Proactively engage with key stakeholders, early discussion with Agency
- Representative database align with trial population and sufficient sample size
- Different agency may have different requirement, plan for different stages of analysis

Tying it all together

RWD can help generate new insights and evidence, improve oncology care, and bring the **right treatment** to the **right patient** at the **right time**...

Learn from more patients with broader representation to inform decision-making on a global scale

Accelerate Health Authority and Health Technology Assessment decisions, and access for patients



Integrate different data modalities to enhance the value of RWD

Q&A

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

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Centering the patient’s voice: A discussion

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