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Tolerability of First-Line Treatment With Ribociclib for Metastatic Breast Cancer Using 2 Large US Data Sources

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KEY FINDINGS & CONCLUSIONS

- This analysis of 1L RW use of RIB in HR+/HER2− MBC from 2018 to 2022 from the EHR and the KRD reflects an increase in use starting in 2022 in the KRD
- In the RW setting, rates of AEs of special interest for RIB (neutropenia, QT prolongation, and liver enzyme elevation) are comparable with published RCT data,[1,5] among the overall cohorts as well as pts 65 y and older
  - New onset CVD-related medical conditions (causality unassessable) were infrequent and consistent with RW reports of the CDK4/6 inhibitor class[11]
- Dosing patterns observed in the RW followed RIB labeling; the majority (85%) of pts were started on 600 mg daily dosing and 34% were dose-reduced, consistent with what was observed in RCTs[9,10]
- The analysis reaffirms the safety of 1L RIB + ET in pts with HR+/HER2− MBC, as reported across all 3 MONALEESA RCTs, with no new RW tolerability-related medical conditions observed

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INTRODUCTION

- Ribociclib (RIB) + endocrine therapy (ET) is recommended by the National Comprehensive Cancer Network® (NCCN®) as NCCN category 1 preferred CDK4/6 inhibitor for first-line (1L) treatment of hormone receptor-positive/human epidermal growth factor receptor-2 negative (HR+/HER2−) metastatic breast cancer (MBC) with no visceral crisis in postmenopausal patients (pts) or premenopausal pts with ovarian ablation/suppression.* In addition to progression-free survival and overall survival benefits, 1L RIB + ET demonstrated a tolerable and manageable safety profile across all phase 3 MONALEESA (MONALEESA-2, -3, and -7) randomized controlled trials (RCTs)[1-6]
- In addition to results from the RCTs, real-world (RW) evidence can inform clinicians and pts alike of the safety and tolerability of 1L RIB + ET
- The objective of these retrospective database studies was to describe the RW tolerability of 1L RIB + ET in pts diagnosed with HR+/HER2− MBC in the United States, including pts aged ≥65 y; results are reported from 2 independent analyses conducted in 2 large national-footprint US databases (administrative healthcare claims and enriched electronic health records)

METHODS

- Two observational, retrospective national cohort studies were conducted using the nationwide, longitudinal, electronic health record (EHR)–derived Flatiron Health database, which comprises deidentified pt-level data originating from ≈ 280 US cancer clinics (≈ 800 sites of care; primarily community oncology settings) and is curated via technology-enabled abstraction,[7,8] and the deidentified Komodo Research Database (KRD), which comprises closed medical and pharmacy claims in the United States that pertain to 150+ payers, with members with commercial, managed-Medicare (excluding FFS), and Medicaid insurance. The KRD contains US census–level representation of all ages, incomes, races, and ethnicities to capture large, diverse pt cohorts. Selection criteria for pts, index date, baseline, and follow-up periods are available in **Table 1**
- The datasets complement each other in depth and breadth, pt types (e.g., health insurance-wise, such as Medicare fee-for-service, commercial insurance, etc.), pt age, and inclusion of community/academic settings. This highlights the importance of querying each separately. They are presented side by side for complementarity, without direct comparisons

Outcomes and variables

- New-onset medical conditions of interest, selected from adverse events (AEs) reported in 1L RIB + ET RCTs, were summarized. Cardiovascular disease (CVD)–related conditions were only available in the KRD and captured as reported in administrative claims data. Variables were based on clinician documentation in enriched EHR and diagnosis (*ICD-10-CM*) codes in the KRD. For all conditions, grades are not available in the data. The conditions captured reflect all-grade mentions
- RIB dosing patterns were summarized, as abstracted from the EHR and available in the database
- In the KRD, CVD-related medical conditions were described based on the presence of ≥2 medical claims (on different days) in any setting (inpatient, emergency department, or outpatient), with a diagnosis code for the condition of interest in any position (e.g., primary or secondary). A sensitivity analysis was conducted for CVD-related medical conditions based on the presence of ≥1 medical claim in any setting, with a diagnosis code at any position for the condition

Data analysis and statistical methods

- Descriptive analyses of pt characteristics as well as tolerability-related and/or CVD-related medical conditions were reported. Descriptive statistics were reported using counts and proportions for categorical variables and means, medians, SD, and IQR for continuous variables

Table 1. Study-Specific Selection Criteria, Index Date Definitions, and Study Periods

	EHR	KRD
Index date	Date of 1L initiation containing RIB (+ ET) between Mar 2017 and Aug 2022	Date of first paid pharmacy claim for RIB, initiating 1L RIB + ET between Feb 2018 and Dec 2022
Baseline/ preindex period	Period before index date; all records available	≥12-month period of continuous enrollment prior to index date
Potential follow-up period	From the index date up to the data cutoff (i.e., Nov 2022)	From the index date up to the data cutoff (i.e., June 2023)
Selection criteria	Inclusion criteria: • Included in Flatiron Health EHR-derived database • ≥2 documented clinical visits on different days on or after Nov 1, 2011 • Has pathology consistent with breast cancer • Has metastatic diagnosis date on or after Nov 1, 2015 • Treated with RIB + ET in 1L • HR+/HER2− confirmed status prior to or up to 30 days after index date • ≥3 months of potential follow-up time before data cutoff (Nov 30, 2022) Exclusion criteria: • Lacking relevant unstructured documents in the Flatiron database for review by the abstraction team • ≥90-day gap between metastatic date and first structured activity after metastatic date	Inclusion criteria: • ≥1 RIB paid pharmacy claim in the index period • Adult age ≥18 years as of the index date • ≥2 medical service claims with code for BC separated by ≥30 days and ≥1 claim with code for BC prior to the index date • ≥2 medical service claims with code for secondary neoplasm separated by ≥30 days, with the first code occurring no earlier than 30 days from first diagnosis for BC, and ≥1 claim with code for a secondary neoplasm prior to index date • Continuous health plan enrollment for ≥12 months prior to and ≥1 month of follow-up after index date Exclusion criteria: • Had a diagnosis for primary cancers other than BC before the first diagnosis for secondary neoplasm • Had surgical procedures for BC or prior treatments for BC (e.g., chemotherapy, targeted therapy, ET [except ≤60 days prior to index date], or immunotherapy) during the 12-month washout period • Evidence of participation in clinical trial prior to or at the index date

RESULTS

- A total of 373 (EHR) and 350 (KRD) pts who received 1L RIB + ET satisfied the selection criteria, of whom 5.9% and 9.4% self-identified as Black/African American, respectively (**Table 2**)
- Pts in the EHR had a mean age of 62.6 y (SD, 12.6), with 183 pts (49.1%) aged ≥65 y and 65 pts (17.4%) aged ≥75 y. Median (IQR) body mass index at index was 28.2 kg/m^2 (24.5-33.0 kg/m^2), with stages at initial diagnosis (including preindex) as follows: de novo metastatic (IV, 30.3%); stages I (11.8%), II (32.4%), or III (16.6%); or not documented (8.8%). ECOG performance status at index was 0 (38.9%), 1 (31.6%), 2 (4.6%), 3/4 (2.7%), or unknown (22.3%), and 92.5% received care in a community practice setting
- In the KRD, the mean age was 56.5 y (SD, 10.5); 57 pts (16.3%) were aged ≥65 y, and 16 pts (4.6%) were aged ≥75 y† (consistent with the dataset profile favoring working-age populations). The mean NCI Comorbidity Index score (± SD [median]) was 0.4 ± (0.6 [0.2]). Hypertension (47.7%), obesity (32.3%), and COPD (22.3%) were the most common preindex comorbidities in the KRD
- The majority of pts in both studies received an aromatase inhibitor as ET partner (EHR, 76.1%; KRD, 80.6%). Among these pts, 16.2% of pts in the EHR and 20.1% of pts in the KRD received luteinizing hormone–releasing hormone agonist (LHRH; e.g., leuprolide, goserelin) in the 1L setting
- An increase in the use of 1L RIB in RW clinical practice in 2022 was observed in the KRD, where more pts initiated 1L RIB + ET in 2022 (40.6%); the remainder started 1L RIB between 2018 and 2021 (**Figure 1**)

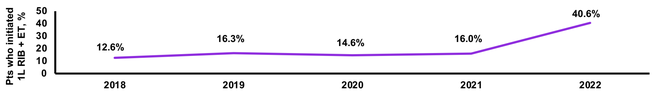
† Due to the small cell counts and sample size, point or other types of estimates are not available for this subset of pts.

Table 2. Demographic and Clinical Characteristics (EHR and KRD)[a]

	EHR N = 373	KRD N = 350
Age		
Mean, years (SD)	62.6 (12.6)	56.5 (10.5)
≥65 y, n (%)	183 (49.1)	57 (16.3)
≥75 y, n (%)	65 (17.4)	16 (4.6)
Female, n (%)	369 (98.9)	349 (99.7)
Race, n (%)		
White	237 (63.5)	141 (40.3)
Black or African American	22 (5.9)	33 (9.4)
Hispanic or Latino	–	45 (12.9)
Asian or Pacific Islander	17 (4.6)	23 (6.6)
Other	43 (11.5)	16 (4.6)
Unknown	54 (14.5)	92 (26.3)
Ethnicity, n (%)		
Hispanic or Latino	37 (9.9)	–
Not Hispanic or Latino	253 (67.8)	–
Unknown	83 (22.3)	–
Region, n (%)		
South	149 (39.9)	107 (30.6)
Midwest	55 (14.7)	81 (23.1)
Northeast	43 (11.5)	57 (16.3)
West	93 (24.9)	104 (29.7)
Other/missing	33 (8.8)	1 (0.3)
Endocrine therapy partner, n (%)		
Aromatase inhibitor	284 (76.1)	279 (80.6)[b]
Fulvestrant	89 (23.9)	67 (19.4)[b]
LHRH agonist use in 1L, n (%)[c]	46 (16.2)	56 (20.1)

[a] EHR and KRD study designs differ; therefore, comparisons cannot be made directly. [b] Four pts had evidence of aromatase inhibitor + fulvestrant use in the KRD; percentage based on 346 pts. [c] Percentage calculated based on pts treated with an aromatase inhibitor.

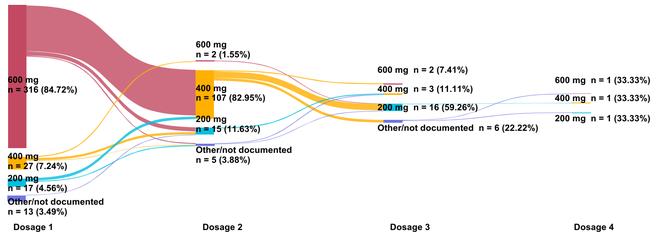
Figure 1. 1L RIB Treatment Initiation by Index Year (in the KRD)



RIB dosing (from EHR)

- The majority of pts (84.72%) were started on RIB 600 mg once daily (QD), whereas a small subset (7.24% and 4.56%) was started on 400 mg QD and 200 mg QD, respectively (**Figure 2**)
- Thirty-four percent of pts who started on 600 mg were dose reduced to 400 mg
- Of the pts who dose reduced, 27% had a mention of adverse effect of therapy (not specified) as a reason in the chart at the end of the last treatment episode
  - Previously published clinical evidence demonstrated that pts treated with 1L RIB for HR+/HER2− MBC, with dose reductions, retained their clinical benefits[9,10]

Figure 2. RIB Dose Received by Pts in EHR



RW safety and tolerability of 1L RIB + ET

- New-onset any-grade AEs‡ in pts treated with 1L RIB + ET were as follows: neutropenia in 53.4% (EHR) and 21.3% (KRD) of pts, elevated liver enzymes in 9.0% (EHR) and 4.6% (KRD) of pts, and QT prolongation in 4.0% (EHR) and 2.0% (KRD) of pts (**Table 3**)
- Incidence of AEs in pts aged ≥65 y and ≥75 y was consistent with that in the overall cohort (**Table 4**)

‡ Grade was not available for either dataset.

Table 3. New Onset of Tolerability-Related Medical Conditions in the Overall Cohorts[a]

Condition	EHR		KRD	
	Pts at risk, n	New onset, n (%)	Pts at risk, n[b]	New onset, n (%)
Neutropenia	367	196 (53.4)	333	71 (21.3)
Liver enzyme elevation/ elevated transaminases	366	33 (9.0)	349	16 (4.6)
QT interval prolongation	373	15 (4.0)	346	7 (2.0)

[a] EHR and KRD study designs differ; therefore, comparisons cannot be made directly. [b] The denominator is different for each condition, as per the at-risk pool for each condition.

Table 4. New Onset of Tolerability-Related Medical Conditions in Pts Aged ≥65 and ≥75 Years[a]

Condition	EHR				KRD	
	Aged ≥65 y		Aged ≥75 y		Aged ≥65 y	
	Pts at risk, n	New onset, n (%)	Pts at risk, n	New onset, n (%)	Pts at risk, n[b]	New onset, n (%)
Neutropenia	183	93 (50.8)	65	31 (47.7)	56	8 (14.3)
Liver enzyme elevation/elevated transaminases	183	20 (10.9)	65	9 (13.8)	57	2 (3.5)
QT interval prolongation	183	10 (5.5)	65	2 (3.1)	57	1 (1.8)

[a] EHR and KRD study designs differ; therefore, comparisons cannot be made directly. [b] The denominator is different for each condition, as per the at-risk pool for each condition.

CVD-related medical conditions of interest

- Evidence of newly diagnosed CVD-related medical conditions (e.g., cardiomyopathy, congestive heart failure, cardiac arrhythmias, hypertension, ischemic heart disease, and pericardial disease), regardless of causality, was relatively low. These conditions were available only in the KRD, as evidenced by the presence of ≥2 diagnosis codes indicative of the specific condition (**Table 5**)
- The new onset of such CVD-related medical conditions in pts aged ≥65 y was consistent with that in the overall cohort (**Table 6**)
- A sensitivity analysis based on the presence of ≥1 diagnosis code of a newly diagnosed or suspected CVD-related medical condition was consistent with the main analysis (available only in the KRD)

Table 5. New-Onset CVD-Related Medical Conditions in Pts Receiving 1L RIB + ET in the Overall Population in the KRD

CVD-related medical conditions	Pts at risk, n[a]	New-onset CVD-related medical conditions, n (%)
Cardiomyopathy	348	0
Congestive heart failure	336	5 (1.5)
Cardiac arrhythmias	324	10 (3.1)
Hypertension	183	15 (8.2)
Ischemic heart disease	327	3 (0.9)
Pericardial disease	341	0

[a] The denominator is different for each CVD-related medical condition, given that pts with observed diagnoses codes in the baseline period were removed from the at-risk pool for each event.

Table 6. New-Onset CVD-Related Medical Conditions in Pts Aged ≥65 Years Receiving 1L RIB + ET in the KRD

CVD-related medical conditions	Pts at risk, n[a]	New-onset CVD-related medical conditions, n (%)
Cardiomyopathy	56	0
Congestive heart failure	54	1 (1.9)
Cardiac arrhythmias	50	1 (2.0)
Hypertension	11	2 (18.2)
Ischemic heart disease	50	0
Pericardial disease	57	0

[a] The denominator is different for each CVD-related medical condition, given that pts with observed diagnoses codes in the baseline period were removed from the at-risk pool for each event.

Limitations

- The 2 studies have different designs and data sources, making comparisons across the 2 infeasible. However, enriched/EMR and administrative healthcare claims constitute main sources of national footprint data in the United States; therefore, they are presented for complementarity purposes. Further, some baseline variables are available in one but not the other analytic study dataset (e.g., body mass index, stage at initial diagnosis, ECOG performance status, NCI Comorbidity Index score)
- In the KRD administrative healthcare database, assessment of AE-related and CVD-related medical conditions was based on the identification of medical claims with primary or secondary diagnoses codes. Administrative healthcare claims are used for reimbursement purposes. As such, underreporting may be possible for mild AE-related conditions that did not result in a reimbursement request for healthcare services. Claims-based algorithms, especially for cardiovascular conditions, have been tested with varying degrees of complexity (requiring, for example, a minimum of 2 claims, or inpatient hospitalization, or primary diagnosis code indicative of the disease, etc.). Therefore, we used a minimum of 2 diagnosis codes for these purposes here, while also conducting a sensitivity analysis utilizing a minimum of 1 diagnosis code (with consistent results)
- Given the nature of the data in both datasets, no causality can be inferred between a 1L RIB regimen and the reported tolerability-related and CVD-related medical conditions

References

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