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Quality of life in patients with advanced breast cancer (aBC) treated with ribociclib (RIB) in the real-world RIBANNA trial

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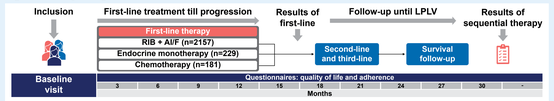
INTRODUCTION

- In addition to disease control, maintaining a high health-related quality of life (QoL) is a major treatment goal for patients (pts) with advanced breast cancer (aBC).
- In the pivotal MONALEESA (ML) trials, the CDK4/6 inhibitor ribociclib (RIB) in combination with an aromatase inhibitor (AI) or fulvestrant (F) demonstrated significant improvement of survival in pre- and postmenopausal pts with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2−) aBC while maintaining QoL.[1-5]
- Following approval of RIB in 2017, the non-interventional study (NIS) RIBANNA was initiated to collect real-world data on the safety and effectiveness of RIB plus endocrine therapy for first-line (1L) treatment of aBC.[6]
- We have used the 7th interim analysis data to characterize the QoL of aBC pts treated with RIB in 1L.

METHODS

- RIBANNA is a prospective, multicenter NIS investigating RIB for aBC in Germany.
- Pts could be allocated to one of three treatment cohorts: RIB + AI/F, endocrine monotherapy (ET), or chemotherapy (CT). **Figure 1** provides an overview of the study design.

Figure 1. Study Design



AI, aromatase inhibitor; F, fulvestrant; LPLV, last patient last visit, RIB: ribociclib.
N = number of patients enrolled in the study at the time of the 7th interim analysis.

- The Safety Analysis Set (SAF) comprised all enrolled pts who had received at least one dose of the respective treatment, without any documented protocol deviation leading to exclusion from the analysis if present (as determined by medical review).
- The Full Analysis Set (FAS) included all pts from the SAF, for whom at least one post-baseline effectiveness evaluation was recorded.
- Here, we present patient-reported outcomes (PROs) utilizing the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire QLQ-C30 as an established PRO instrument.
  - The paper-based questionnaires were distributed to all pts, regardless of the treatment regimen, in both 1L and subsequent lines of therapy, provided they had consented to participate in the questionnaire sub study.
- Data are shown as mean difference from baseline and mean first time to (definitive) deterioration by at least 10%.
  - Time to deterioration is defined as the time from baseline to the first worsening by 10% of the baseline value.
  - Time to definitive deterioration is defined as the time from baseline to the first worsening by 10% of the baseline value without subsequent improvement above this threshold.
- Time-to-event data were assessed using the Kaplan-Meier (K-M) method. Percentiles (25%, 50%, 75%) of the event's time distribution are presented along with their two-sided 95% confidence interval (CI).
- All PROs constituted exploratory endpoints, and all analyses were descriptive and intended for hypothesis generation only.

RESULTS

Patient Enrollment and Follow-Up Duration

- This analysis includes data from the enrollment of the first patient on October 9th 2017 until the data cutoff on September 30th 2024.
- The median duration of follow-up was 2.8 years and ranged from 0.0 to 6.9 years.
- A total of 2,567 pts were enrolled: 2,157 in the RIB + AI/F cohort, 229 in the ET cohort and 181 in the CT cohort. Of these, 1,999 pts (RIB + AI/F), 201 (ET), and 161 (CT) were included in the SAF, and 1,852 (RIB + AI/F), 183 (ET), and 139 (CT) were included in the FAS.
- Due to the overwhelming data from ML trials, there were only small numbers of pts in the real-world setting treated with only ET or CT. Thus, we decided to analyze only the datasets from RIB + AI/F cohort.
  - In the RIB + AI/F cohort, pts' mean age was 65.5 ± 11.6 years (range: 27.9–92.9), 7.7% were pre-menopausal and 2.8% peri-menopausal, 7.2% had ECOG-PS >1, 25.7% had grade 3 (G3) histology, 96.8% showed metastases, and 73.7% presented with locally advanced disease.

Results for Functional and Symptom Scales of EORTC QLQ-C30

- The EORTC QLQ-C30 questionnaire has a score range of 0 to 100 for all its scales and single items. A higher score on a functioning scale (like physical or emotional functioning) indicates better functioning and a higher QoL. Conversely, a higher score on a symptom scale (like fatigue or pain) indicates a greater burden of symptoms or problems.
- The completion rates for the EORTC QLQ-C30 were 83.5% at baseline, 74.2% at 12 months and 42.6% at 72 months (**Table 1**).

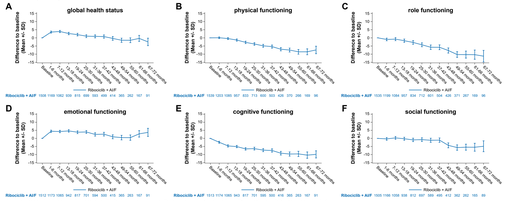
Table 1. EORTC QLQ-C30 Completion Rates

Time point (months)	Number of pts in the study	Number of pts with questionnaire	Completion Rate
0	1852	1546	83.5%
3	1504	1152	76.6%
6	1425	1144	80.3%
9	1371	1024	74.7%
12	1314	975	74.2%
15	1255	897	71.5%
18	1204	831	69.0%
21	1151	770	66.9%
24	1083	716	66.1%
27	1025	645	62.9%
30	963	580	60.2%
33	911	487	53.5%
36	859	371	43.2%
39	822	289	35.2%
42	779	451	57.9%
45	736	420	57.1%
48	699	393	56.2%
51	610	339	55.6%
54	531	292	55.0%
57	456	257	56.4%
60	375	200	53.3%
63	303	152	50.2%
66	251	118	47.0%
69	187	87	46.5%
72	136	58	42.6%

Pts, patients.
EORTC QLQ-C30 questionnaire completion rate over time.

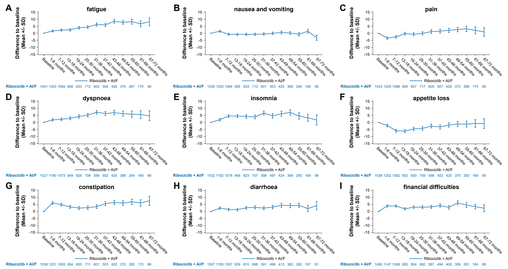
- Across domains, pts generally sustained a stable QoL as determined by EORTC QLQ-C30 functional (**Figure 2**) and symptom scale scores (**Figure 3**) after initiating treatment with RIB + AI/F.
  - Some functional scores (e.g. **Figure 2B**, **C**, **E**) showed a trend towards decline, though most did not exceed -10 points in difference to baseline (a threshold often considered to denote clinical relevance) even at the latest timepoint (72 months).[7] Global Health Status (GHS) (**Figure 2A**) and emotional functioning (**Figure 2D**) showed an initial trend towards improvement with positive difference-to-baseline values over time.
  - While some symptom scores such as pain (**Figure 3C**) and appetite loss (**Figure 3F**) initially showed a trend towards reduction of symptoms, most remained stable or increased slightly over time. The mean change from baseline did not exceed 10 points for any of the symptom scores at any time point, suggesting the changes were not clinically relevant.

Figure 2. Change from Baseline in Functional Scale Scores of EORTC QLQ-C30 for Pts Enrolled in 1L RIB + AI/F (FAS)



AI, aromatase inhibitor; F, fulvestrant; FAS, full analysis set; RIB, ribociclib; 1L, first-line; Pts, patients; SD, standard deviation.
A higher score indicates better functioning and a higher quality of life; therefore, positive changes from baseline indicate improvement. Mean baseline values were: (A) 54.2 points for global health status, (B) 65.1 points for physical functioning, (C) 56.3 points for role functioning, (D) 56.1 points for emotional functioning, (E) 77.6 points for cognitive functioning, (F) 63.1 points for social functioning.

Figure 3. Change from Baseline in Symptom Scale Scores of EORTC QLQ-C30 for Pts Enrolled in 1L RIB + AI/F (FAS)

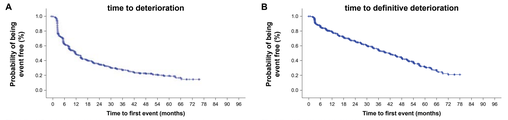


AI, aromatase inhibitor; F, fulvestrant; FAS, full analysis set; RIB, ribociclib; 1L, first-line; Pts, patients; SD, standard deviation.
A higher score indicates a greater burden of symptoms or problems; therefore, a negative change from baseline indicates a reduction. Mean baseline values were: (A) 48.1 points for fatigue, (B) 12.1 points for nausea and vomiting, (C) 40.1 points for pain, (D) 34.4 points for dyspnoea, (E) 41.9 points for insomnia, (F) 28.5 points for appetite loss, (G) 18.9 points for constipation, (H) 11.4 points for diarrhoea, (I) 17.7 points for financial difficulties.

Selected EORTC QLQ-C30 Subscales Over Time: GHS

- EORTC GHS is a commonly evaluated PRO in aBC, and corresponding results have been published for the ML trials.[3,4,5,8]
- In the RIB + AI/F cohort, GHS did not change significantly throughout the study, although an initial trend toward improvement (mean change from baseline at 7-12 months: + 3.9 points) was observed, followed by a gradual decrease over time (−2.5 points at 67-72 months) (**Figure 2A**). However, these observed changes were fairly small and therefore not considered clinically relevant.[7]
- In many pts of the RIB + AI/F cohort, GHS deteriorated initially (**Figure 4A**), but did recover in many cases, resulting in a much longer time to definitive deterioration (**Figure 4B**).
  - Median time to deterioration of GHS by ≥ 10% was 12.2 months (**Table 2**).
  - Median time to definitive deterioration of GHS by ≥ 10% was 41.3 months (**Table 2**).

Figure 4. Time to (Definitive) Deterioration of GHS by ≥ 10% for Pts Enrolled in 1L RIB +AI/F (FAS)



AI, aromatase inhibitor; F, fulvestrant; FAS, full analysis set; 1L, first-line; Pts, patients; RIB, ribociclib.
+ denotes censored events. (A) Time to deterioration is defined as the time from baseline to the first worsening by 10% of the baseline value. (B) Time to definitive deterioration is defined as the time from baseline to the first worsening by 10% of the baseline value without subsequent improvement above this threshold.

Table 2. Time to (Definitive) Deterioration of GHS for Pts Enrolled in 1L RIB +AI/F (FAS)

	≥ 10% time to deterioration	≥ 10% time to definitive deterioration
	RIB + AI/F N=1543	RIB + AI/F N=1505
Number of censored observations	689	896
Number of events	854	609
K-M estimator for time to event (months)		
75%-Quantile [95% CI]	3.7 (3.3, 4.6)	14.9 (12.6, 17.7)
50%-Quantile [95% CI]	12.2 (11.8, 14.5)	41.3 (36.3, 44.9)
25%-Quantile [95% CI]	41.5 (35.9, 51.3)	66.5 (63.3, .)

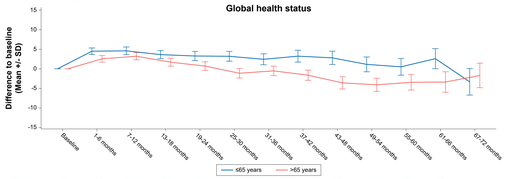
AI, aromatase inhibitor; CI, confidence interval; F, fulvestrant; FAS, full analysis set; K-M, Kaplan-Meier; 1L, first-line; Pts, patients; RIB, ribociclib
Time to deterioration is defined as the time from baseline to the first worsening by 10% of the baseline value.
Time to definitive deterioration is defined as the time from baseline to the first worsening by 10% of the baseline value without subsequent improvement above this threshold.

- Median time to definitive deterioration of GHS by ≥ 10% was comparable to or even longer than that observed for the RIB arms in the ML trials:
  - ML-2: 30.3 months for pts with no progression-free survival (PFS) event and 24.0 months for pt with a PFS event[3]
  - ML-3: 35.9 months[4]
  - ML-7: 35.8 months[5]
- However, comparisons between RIBANNA and ML outcomes should be interpreted with caution due to differences in the investigated pt populations. For example, more pts with de novo disease and disease-free interval (DFI) <12 months (treatment-free interval in RIBANNA) and less pts with visceral disease were included in RIBANNA compared to the ML trials. Moreover, RIBANNA pts were on average older than pts in the ML trials.

EORTC QLQ-C30 GHS According to Age

- PROs including GHS have been previously published for three age groups (<65 years, 65–74 years, and ≥75 years) in a pooled analysis of the ML-2, ML-3, and ML-7 trials.[8]
- In the RIBANNA RIB + AI/F cohort, the mean difference to baseline in GHS score showed positive values denoting improvement until 66 months in pts ≤65 years, whereas pts >65 years generally had lower values (**Figure 5**).
- Time to definitive deterioration of GHS by ≥ 10% (**Figure 6**, **Table 3**) differed only slightly between age subgroups, and only after approximately 35 months (**Figure 6**). This time point coincides with the median PFS for pts on 1L treatment with RIB + AI/F in RIBANNA, which is also 35 months.[9]

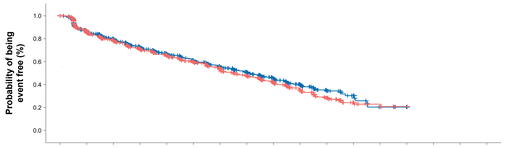
Figure 5. Change from Baseline in GHS According to Age Subgroup for Pts Enrolled in 1L RIB +AI/F (FAS)



≤65 years	738	595	522	468	404	349	287	249	210	183	130	85	44
>65 years	770	574	540	471	411	360	306	250	204	182	132	82	47

AI, aromatase inhibitor; F, fulvestrant; FAS, full analysis set; RIB, ribociclib; 1L, first-line; Pts, patients; SD, standard deviation.
A higher score indicates better functioning and a higher quality of life; therefore, positive changes from baseline indicate improvement. Mean baseline values were: 55.8 points for pts ≤65 years and 52.7 points for pts >65 years.

Figure 6. Time to Definitive Deterioration of GHS by ≥ 10% According to Age Subgroup for Pts Enrolled in 1L RIB +AI/F (FAS)



≤65 years	737	517	436	355	298	254	207	166	117	74	36	18	6	1	0
>65 years	708	509	420	350	295	247	199	159	114	74	43	20	11	1	0

AI, aromatase inhibitor; F, fulvestrant; FAS, full analysis set; RIB, ribociclib; 1L, first-line; Pts, patients; SD, standard deviation.
+ denotes censored events. Time to definitive deterioration is defined as the time from baseline to the first worsening by 10% of the baseline value without subsequent improvement above this threshold.

Table 3. Time to Definitive Deterioration of GHS According to Age Subgroup for Pts Enrolled in 1L RIB +AI/F (FAS)

	Treatment group		Log rank test
	≤65 years N=737	>65 years N=768	p-value
Number of censored observations	443	453	
Number of events	294	315	
K-M estimator for time to event (months)			0.2926
75%-Quantile [95% CI]	15.2 (12.4, 18.1)	14.9 (12.0, 17.7)	
50%-Quantile [95% CI]	42.3 (36.5, 48.1)	39.1 (35.9, 44.8)	
25%-Quantile [95% CI]	69.0 (64.2, .)	63.3 (57.2, .)	

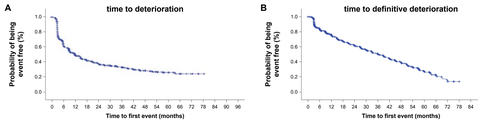
AI, aromatase inhibitor; CI, confidence interval; F, fulvestrant; FAS, full analysis set; K-M, Kaplan-Meier; 1L, first-line; Pts, patients; RIB, ribociclib
Time to definitive deterioration is defined as the time from baseline to the first worsening by 10% of the baseline value without subsequent improvement above this threshold.

- The median time to definitive deterioration was shorter than that observed for the RIB arm in the pooled analysis of ML trials:
  - RIBANNA
    - ≤65 years: 42.3 months vs. >65 years: 39.1 months
  - Pooled analysis of ML-2, ML-3 & ML-7
    - <65 years: 57.7 months vs. 65–74 years: non-estimable vs. ≥75 years: 55.3 months[8]

Selected EORTC QLQ-C30 Subscales Over Time: Role Functioning

- Among EORTC subscales, role functioning (RF) has not been studied well in aBC so far.
- RF showed a continuous decrease over time in the overall RIB + AI/F cohort (**Figure 2C**).
  - However, only from 43-48 months onward, a deterioration of 7.8 points from baseline was observed, which is considered just a small change and may therefore not be clinically relevant.[7]
- Similar to GHS, RF initially declined in many pts by ≥ 10%, but later increased again, resulting in a longer time to definitive deterioration (**Figure 7**).
  - Median time to deterioration of RF by ≥ 10% was 12.0 months (**Table 4**).
  - Median time to definitive deterioration of RF by ≥ 10% was 27.4 months (**Table 4**).

Figure 7. Time to (Definitive) Deterioration of RF by ≥ 10% for Pts Enrolled in 1L RIB +AI/F (FAS)



AI, aromatase inhibitor; F, fulvestrant; FAS, full analysis set; 1L, first-line; RIB, ribociclib.
+ denotes censored events. (A) Time to deterioration is defined as the time from baseline to the first worsening by 10% of the baseline value. (B) Time to definitive deterioration is defined as the time from baseline to the first worsening by 10% of the baseline value without subsequent improvement above this threshold.

Table 4. Time to (Definitive) Deterioration of RF for Pts Enrolled in 1L RIB +AI/F (FAS)

	≥ 10% time to deterioration	≥ 10% time to definitive deterioration
	RIB + AI/F N=1543	RIB + AI/F N=1532
Number of censored observations	745	753
Number of events	798	779
K-M estimator for time to event (months)		
75%-Quantile [95% CI]	3.4 (3.2, 3.6)	5.9 (4.4, 6.4)
50%-Quantile [95% CI]	12.0 (9.5, 14.7)	27.4 (24.5, 30.3)
25%-Quantile [95% CI]	63.0 (45.3, .)	57.1 (51.9, 60.1)

AI, aromatase inhibitor; CI, confidence interval; F, fulvestrant; FAS, full analysis set; K-M, Kaplan-Meier; 1L, first-line; RIB, ribociclib
Time to deterioration is defined as the time from baseline to the first worsening by 10% of the baseline value.
Time to definitive deterioration is defined as the time from baseline to the first worsening by 10% of the baseline value without subsequent improvement above this threshold.

Limitations

- As this study is non-interventional, it cannot be ruled out that the observed associations are subject to bias and may be influenced by confounders.
- In particular, this analysis is subject to survival bias due to mortality.
- Additionally, the questionnaire completion rates (**Table 1**) declining over time suggest that survival bias might pertain not only to pts who died, but potentially also to pts who were alive but not able to complete the questionnaire, as suggested by the observed progressive cognitive decline even in pts who completed the questionnaires (**Figure 2E**).

CONCLUSIONS

- RIBANNA provides, for the first time, real-world QoL data on RIB in a large cohort of pts with HR +/HER2- aBC, confirming findings from the pivotal clinical ML trials.
- Across all EORTC QLQ-C30 subscales, no major changes were observed.
- In the RIB + AI/F cohort, EORTC GHS changes over time were comparable to the randomized clinical trials ML-2, ML-3 and ML-7, where GHS was maintained throughout the study.[3-5]
- The time to definitive deterioration of GHS by ≥10% was similar between age groups (≤65 years: 42.3 months; >65 years: 39.1 months) but was on average 15 months shorter than in the pooled analysis of ML-2, ML-3, and ML-7 – suspectedly due to differences in pts population.[8]
- Stable values across all subscales of the analyzed QoL instruments during treatment with RIB + AI/F suggest that there is no relevant deterioration in QoL under therapy, which is a reassuring outcome in the real-world setting.

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