Nadia Harbeck | nadia.harbeck@med.uni-muenchen.de

Descriptive analysis of hepatic safety in patients with HR+/HER2− breast cancer treated with ribociclib + endocrine therapy

Nadia Harbeck,[1] William Jacot,[2] Meritxell Bellet Ezquerra,[3] Sara M. Tolaney,[4] Hope S. Rugo,[5] Fatima Cardoso,[6] Sara A. Hurvitz,[7] Joohyuk Sohn,[8] Binghe Xu,[9] Melissa Gao,[10] Natalia Bolotova,[11] Juan Pablo Zarate,[12] Eleanor Sum,[12] Michelino De Laurentiis[13]

[1]Breast Center, Department of Obstetrics and Gynecology, LMU University Hospital Munich, Germany; [2]Institut Regional du Cancer de Montpellier, Montpellier, France; [3]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, USA; [6]Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; [7]University of Washington, Fred Hutchinson Cancer Center, Seattle, WA, USA; [8]Yonsei Cancer Center, Seoul, Korea; [9]Department of Medical Oncology Cancer Hospital, Chinese Academy of Medical Sciences (CAMS),and Peking Union Medical College (PUMC), Beijing, China; [10]Novartis Pharma AG, Basel, Switzerland; [11]Novartis Pharma, Nürnberg, Germany; [12]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [13]Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale," Naples, Italy.

KEY FINDINGS & CONCLUSIONS

- Across the ML, C-1, and NATALEE trials, cases of transaminase elevation were generally low grade, occurred in a small subset of patients, and were manageable with recommended dose modification guidance
- Transaminase elevations occurred early in treatment and median duration of ≥G3 events ranged from 0.7 to 1.6 months
- Severe cases (Hy's law) were rare and took longer to resolve but were reversible after discontinuation of RIB
- The similar incidence of transaminase elevations across the trials at both the RIB 600-mg and RIB 400-mg doses in patients with HR+/HER2− breast cancer suggests that dose does not play a key causative role in these AEs
- These findings validate the current monitoring and management guidelines in the RIB label allowing timely identification and management of transaminase elevations

Scan to obtain:
- Poster

Copies of this poster obtained through Quick Response (QR) code are for personal use only and may not be reproduced without permission of the authors.

Reused with permission from the European Society for Medical Oncology (ESMO). This abstract was accepted and previously presented by Harbeck N et al. at ESMO, Breast Cancer Congress, May 15-17; Berlin, Germany. 277P, ESMO Open, Volume 9,Issue S4, 2024. All rights reserved.

Poster presented at: 2024 NCODA International Fall Summit; October 23-25; Orlando, Florida.
This study is sponsored by Novartis Pharma AG.

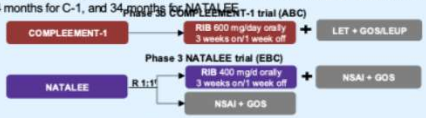
INTRODUCTION

- Ribociclib (RIB) in combination with endocrine therapy (ET) has shown significant progression-free survival and overall survival benefits in patients with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2−) advanced breast cancer (ABC) in the phase 3 MONALEESA (ML)-2, ML-3, and ML-7 trials[1-6]
- Efficacy and safety data from the expanded phase 3b COMPLEEMENT-1 (C-1) trial with a patient population representative of real-world clinical practice also support the use of RIB + ET for treating patients with HR+/HER2− ABC[7]
- In addition, RIB has demonstrated significant invasive disease-free survival benefit in patients with HR+/HER2− early breast cancer (EBC) in the phase 3 NATALEE trial[8]
- Transaminase elevations are a known adverse event (AE) with RIB + ET treatment, based on clinical safety data from the ML, C-1, and NATALEE trials[1-8]
- The incidence, duration, and management of these AEs should be continually assessed to determine risk and maximize the treatment benefit with RIB + ET[9-11]
- We present a descriptive analysis of transaminase elevations with RIB + ET across multiple phase 3 trials

METHODS

- Data from 4 phase 3 registrational and one phase 3b (expanded population) trials in the EBC and ABC settings were evaluated (**Figure 1**)

Figure 1. Trial Study Designs



AJCC, American Joint Committee on Cancer; CT, chemotherapy; FUL, fulvestrant; GOS, goserelin; LET, letrozole; LEUP, leuprolide; NSAI, nonsteroidal aromatase inhibitor; PBO, placebo; R, randomized; TAM, tamoxifen. [a]Stratified by presence/absence of liver/lung metastases. [b]Stratified by presence/absence of liver/lung metastases and prior ET. [c]FUL administered intramuscularly on cycle 1 day 1, cycle 1 day 15, and day 1 of every 28-day cycle thereafter. [d]Stratified by presence/absence of liver/lung metastases, prior CT for advanced disease and ET partner (TAM vs NSAI). [e]TAM: 20 mg/day, NSAI: anastrozole 1 mg/day or letrozole 2.5 mg/day; GOS: 3.6 mg every 28 days. [f]Stratified by menopausal status (premenopausal/women and men vs postmenopausal women). AJCC 8th edition Anatomic Stage Group (group II vs group III); prior neoadjuvant/adjuvant CT (yes/no); geographical region (North America/Western Europe/Oceania vs rest of the world).

- Across the ML, C-1, and NATALEE trials, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were monitored via serial liver function tests
  - All trials recommended permanent RIB discontinuation for AEs lasting >28 days; this is not mandated per label
- The incidence, time to onset, and duration of transaminase elevations were evaluated for each trial
- The median follow-up was 15.3 months for ML-2, 20.4 months for ML-3, 19.2 months for ML-7, 25.4 months for C-1, and 34 months for NATALEE

RESULTS

Baseline Characteristics and Disease History

- For each study, baseline demographics and clinical characteristics were generally similar between patients with or without transaminase elevations (**Table 1**)

Table 1. Baseline Clinical Characteristics of Patients With or Without Transaminase Elevation in RIB + ET Arms[a,b]

Parameter	ML-2 N=334		ML-3 N=483		ML-7 N=248[c]		C-1 N=3246		NATALEE N=2525	
	ALT/AST elevation		ALT/AST elevation		ALT/AST elevation		ALT/AST elevation		ALT/AST elevation	
	Yes n=78	No n=256	Yes n=83	No n=400	Yes n=52	No n=196	Yes n=581	No n=2665	Yes n=535	No n=1990
Age, median (range), years	62.5 (31-82)	62.0 (23-91)	61.0 (37-84)	64.0 (31-89)	45.0 (29-55)	42.0 (25-58)	58.0 (20-89)	58.0 (23-92)	55.0 (25-82)	52.0 (24-90)
Race, n (%)										
Asian	7 (9)	21 (8)	9 (11)	36 (9)	20 (39)	62 (32)	36 (6)	191 (7)	74 (14)	266 (13)
Black	2 (3)	8 (3)	0	3 (<1)	3 (6)	1 (<1)	3 (<1)	26 (1)	6 (1)	35 (2)
White	62 (80)	207 (81)	71 (86)	335 (84)	28 (54)	111 (57)	475 (82)	2078 (78)	423 (79)	1435 (72)
Other[d]	3 (4)	11 (4)	2 (2)	12 (3)	0	9 (5)	34 (6)	119 (4)	19 (4)	132 (7)
Unknown	4 (5)	9 (4)	1 (1)	14 (4)	1 (2)	13 (7)	33 (6)	251 (9)	13 (2)	122 (6)
Baseline hepatic status, n (%)[e]										
Normal function	70 (90)	208 (81)	61 (74)	329 (82)	45 (87)	175 (89)	NR	NR	456 (85)	1836 (92)
Mild impairment	8 (10)	45 (18)	22 (27)	68 (17)	7 (14)	21 (11)			76 (14)	144 (7)
Moderate impairment	0	0	0	0	0	0			1 (<1)	2 (<1)
Missing	0	3 (1)	0	3 (<1)	0	0			2 (<1)	8 (<1)
BMI, median (range), kg/m²	25.8 (18-47)	26.9 (17-53)	26.6 (18-44)	26.3 (16-49)	24.8 (18-40)	23.7 (15-48)	26.7 (15-53)	25.8 (13-53)	27.9 (17-53)	25.9 (16-56)
Menopausal status, n (%)										
Premenopausal	0	0	0	0	52 (100)	196 (100)	150 (26)	689 (26)	212 (40)	895 (45)
Postmenopausal	78 (100)	256 (100)	83 (100)	400 (100)	0	0	425 (73)	1943 (73)	322 (60)	1087 (55)
Missing	0	0	0	0	0	0	6 (1)	33 (1)	0	0
Prior CT, n (%)[f]										
Yes	0	0	3 (4)	1 (<1)	5 (10)	28 (14)	288 (50)	1508 (57)	445 (83)	1785 (90)
No	78 (100)	256 (100)	80 (96)	399 (100)	47 (90)	168 (86)	293 (50)	1157 (43)	90 (17)	205 (10)
ET partner, n (%)										
Letrozole	78 (100)	256 (100)	0	0	40 (77)	172 (88)	581 (100)	2665 (100)	389 (73)	1419 (71)
Anastrozole	0	0	0	0	13 (25)	24 (12)	0	0	160 (30)	644 (31)
Fulvestrant	0	0	83 (100)	400 (100)	0	0	0	0	0	0
Goserelin	0	0	0	0	52 (100)	196 (100)	0	0	211 (39)	891 (45)

BMI, body mass index; NR, not reported. [a]Based on AEs by preferred term. [b]Descriptive results only; no statistical comparisons were made between groups. [c]Only patients in the RIB + NSAI cohort are included here; patients treated with RIB + tamoxifen in ML-7 were excluded. [d]Includes Native American and Pacific Islander. [e]Hepatic impairment groups are based on National Cancer Institute Organ Dysfunction Working Group criteria. [f]Prior CT in the ABC setting reported for ML-2, -3, -7 and C-1 trials; prior (neo/adjuvant) CT in the EBC setting reported for NATALEE.

Transaminase Elevation Adverse Events

- The rates of all-grade (G) ALT and AST elevations (by preferred term) with RIB + ET ranged between 12% and 19% across all trials (**Table 2**)
  - Rates of ≥G3 events were low, occurring in <8% of patients across trials
- No G5 events were reported across the trials
- Bilirubin elevation was rare (≤2% across trials)

Table 2. Rates of Transaminase Elevations in RIB + ET Arms[a]

AE, n (%)	ML-2 N=334	ML-3 N=483	ML-7 N=335	C-1 N=3246	NATALEE N=2525
ALT elevation					
All G	52 (16)	70 (14)	43 (13)	526 (16)	492 (19)
G1/2	21 (6)	29 (6)	25 (7)	277 (9)	300 (12)
G3	25 (7)	32 (7)	18 (5)	209 (6)	159 (6)
G4	6 (2)	9 (2)	0 (0)	40 (1)	33 (1)
AST elevation					
All G	50 (15)	64 (13)	40 (12)	459 (14)	426 (17)
G1/2	31 (9)	35 (7)	28 (8)	275 (8)	308 (12)
G3	16 (5)	23 (5)	12 (4)	159 (5)	100 (4)
G4	3 (<1)	6 (1)	0 (0)	25 (<1)	18 (<1)

[a]AEs by preferred term.

Cases of Hy's Law

- Cases of Hy's law occurred in ≤1% of patients and were effectively managed by discontinuing RIB (**Table 3**)
  - Resolution of cases occurred within 2.1 to 17.5 months across all trials
  - None of the reported cases in the trials were fatal

Table 3. Outcomes and Management of Hy's Law Cases in RIB + ET Arms[a]

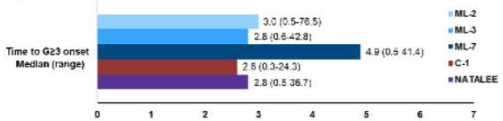
	ML-2[b] N=334	ML-3[b] N=483	ML-7[b] N=335	C-1[c] N=3246	NATALEE[c] N=2525
n (%)	4 (1)	2 (<1)	0	7 (<1)	8 (<1)
Time to resolution, months	Within 3.2-5.1[d]	Within 4.0 and 17.5[d]	N/A	2 patients[d]: within 2.1-3.4 4 patients: recovering at the time of the last available report	6 patients[d]: within 2.1-10.0 2 patients: recovering at the time of the last available report
Outcomes	All cases resolved	All cases resolved	N/A	6 cases resolved or resolving; 1 ongoing at time of last available report	All cases resolved or resolving

N/A, not applicable; ULN, upper limit of normal.
[a]Based on laboratory assessment. [b]Concurrent elevations of ALT or AST >3 × ULN and of total bilirubin >2 × ULN, with normal alkaline phosphatase levels and in the absence of cholestasis. [c]Concurrent elevations of ALT or AST >3 × ULN and of total bilirubin >2 × ULN, with normal alkaline phosphatase levels.
[d]ALT or AST levels recovered to normal ranges.

Time to Onset, Duration, and Resolution

- Among those with ≥G3 ALT/AST elevation, median time to onset was early and ranged from 2.6 to 4.9 months across all trials (**Figure 2**)
  - Median duration was 0.7 to 1.6 months and resolved with dose modifications (**Table 4**)
- Median time to onset for ≥G2 ALT/AST elevation across all trials was similar to ≥G3 events and ranged from 2.2 to 6.3 months

Figure 2. Time to Onset of ≥G3 ALT or AST Elevations in RIB + ET Arms[a,b]



[a]Based on laboratory assessment. [b]Time to onset based on Kaplan-Meier methods was not estimable; therefore, all time to onset data were based on simple summary statistics for patients who experienced events.

Table 4. Timing and Duration of ≥G3 Transaminase Elevations in RIB + ET Arms[a]

ALT or AST elevation	ML-2 N=334	ML-3 N=483	ML-7 N=248[b]	C-1 N=3246	NATALEE N=2525
≥G3 elevations occurring within the first 6 months of treatment, n/N (%)	30/44 (68)	46/58 (79)	14/25 (56)	280/338 (83)	165/214 (77)
Duration of ≥G3 events, median (95% CI), months[c]	0.8 (0.6-1.2)	0.8 (0.5-0.9)	0.9 (0.7-1.2)	1.6 (1.3-2.0)	0.7 (0.7-0.9)

[a]Based on laboratory assessment. [b]Only patients in the RIB + NSAI cohort are included here; patients treated with RIB + tamoxifen in ML-7 were excluded. [c]Estimated using Kaplan-Meier methods.

Management of Transaminase Elevation Adverse Events

- Permanent discontinuations of RIB due to ALT or AST elevations occurred in ≤7% of patients across all trials (**Table 5**)
- Discontinuations due to elevated bilirubin were rare (<1% in C-1; none in ML and NATALEE trials)
- Across all trials, ≤10% of patients had dose interruptions and ≤3% had dose adjustments
- While the use of corticosteroids to manage liver-related AEs associated with RIB treatment has been discussed in the literature,[12-15] systemic corticosteroid use was limited by all the trial protocols; thus, the available data from studies with RIB do not allow firm conclusions

Table 5. RIB Dose Modifications Due to ALT and AST Elevations in RIB + ET Arms[a]

All grades, n (%)	ML-2 N=334	ML-3 N=483	ML-7 N=335	C-1 N=3246	NATALEE N=2525
Permanent discontinuation					
ALT elevation	15 (4)	22 (5)	8 (2)	197 (6)	180 (7)
AST elevation	9 (3)	13 (3)	5 (1)	129 (4)	71 (3)
Dose interruption					
ALT elevation	17 (5)	38 (8)	16 (5)	245 (8)	255 (10)
AST elevation	12 (4)	37 (8)	11 (3)	209 (6)	171 (7)
Dose adjustment[b]					
ALT elevation	10 (3)	5 (1)	5 (1)	50 (2)	49 (2)
AST elevation	5 (1)	6 (1)	4 (1)	29 (<1)	16 (<1)

[a]AEs by preferred term. [b]Data reported as "dose reduced" in C-1 trial.

References

1. Tripathy D *et al. Lancet Oncol*. 2018;19(7):904-915. **2.** Slamon DJ et al. *J Clin Oncol*. 2018;36(24):2465-2472. **3.** Hortobagyi GN et al. *N Engl J Med*. 2016;375(18):1738-1748. **4.** Im SA et al. *N Engl J Med*. 2019;381(4):307-316. **5.** Slamon DJ et al. *N Engl J Med*. 2020;382(6):514-524. **6.** Hortobagyi GN et al. *N Engl J Med*. 2022;386(10):942-950. **7.** De Laurentiis M et al. *Breast Cancer Res Treat*. 2021;189(3):689-699. **8.** Slamon DJ et al. *N Engl J Med*. 2024;390(12):1080-1091. **9.** Jahan N et al. *J Clin Oncol*. 2021;39(15_suppl): e13037. **10.** Ettl J. *Breast Care (Basel)*. 2019;14(2):86-92. **11.** Kisqali. Prescribing information. Novartis Pharmaceuticals Corp. **12.** Finnsdottir S et al. *Acta Oncologica*. 2021;60(2):195-198. **13.** Schaeffer S et al. *Front Oncol*. 2023;13:1256783. **14.** Topcu A et al. *J Oncol Pharm Pract*. 2022;28(1):242-246. **15.** Meunier L et al. *JHEP Reports*. 2024; doi: 10.1016/j.jhepr.2024.101098.

Disclosures

NH reports personal fees for consulting and lectures from AstraZeneca, Daiichi Sankyo, MSD, Pierre Fabre, Roche, Sandoz/Hexal, Amgen, Exact Sciences, Gilead, Seagen; **WJ** reports institutional research grant, advisory board, travel from AstraZeneca; advisory board, travel from Eisai, Novartis, Roche, Pfizer, Eli Lilly, Chugai, Gilead; advisory board from MSD, BMS, Seagen; institutional research grant, advisory board from Daichi Sankyo; **MBE** reports advisory board, speakers bureau and travel expenses from Pfizer, Novartis, Lilly; advisory board from Stemline-Menarini; **BT** reports institution grants from Eli Lilly, Novartis, AstraZeneca, Merck, Roche, Pfizer, Genentech/Roche, Exelixis, Bristol Myers Squibb, Eisai, Nanostring, Cyclacel, Sanofi, Odonate, Gilead; personal fees from Eli Lily, Novartis, AstraZeneca, Merck, Roche, Pfizer, Genentech/Roche, Exelixis, Bristol Myers Squibb, Eisai, NanoString, Puma Biotechnology, Sanofi, Odonate Therapeutics, Seagen, G1 Therapeutics, Athenex, OncoPep, Kyowa Kirin, Daiichi Sankyo, Cytomx, Samsung Bioepis, Celcuity, Menarini Therapeutics, Gilead, OncoSec, Chugai Pharmaceuticals, Ellipses Pharma, 4D Pharma, BeyondSpring Pharma, OncXerna, Infinity Pharmaceuticals, Zentalis, Zymeworks; **HR** reports grants from Prevalion, Macrogenics, OBI Pharma, Eisai, Pfizer, Novartis, Eli Lilly, GlaxoSmithKline, Genentech, Celcion, Merck; fees for travel, accommodations, expenses from Novartis, Roche/Genentech, OBI Pharma, Bayer, and Pfizer; speakers bureau for Genomic Health; **FC** reports statistical analysis, medical writer for the work under consideration for Novartis; personal fees outside the submitted work from Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daichi Sankyo, Eisai, GE Oncology, Genentech, GSK, MacroGenics, Medscape, Merck Sharp & Dohme, Merck, Mylan, Mundipharma, Novartis, Pfizer, Pierre Fabre, Prime Oncology, Roche, Sanofi, Samsung Bioepis, Teva, Seagen, Orikahyam, Gilead, IQVIA, touch IME; **SH** reports grants from Ambrx, Amgen, AstraZeneca, Arvinas, Bayer, Cytomx, Daichi Sankyo, Dignitana, Genentech/Roche, Gilead, GlaxoSmithKline, Immunomedics, Lily, Macrogenics, Novartis, OBI Pharma, Pfizer, Pieris, Puma, Radius, Sanofi, Seattle Genetics, Zymeworks, Phoenix Molecular Designs; other from Lilly; **JS** reports research grant/funding to institution from MSD, Roche, Novartis, AstraZeneca, Lilly, Pfizer, Bayer, GSK, Celltrion, Daichi Sankyo; **BX** reports advisory fees from Novartis, payment or honoraria for lectures from AstraZeneca, Pfizer, Roche, Eisai; **MG, NB, JPZ, ES** report employment and stock ownership from Novartis; **MD** reports speakers honoraria, advisory board honoraria from Pfizer, Novartis, Roche, Celgene, AstraZeneca, Eisai, Eli Lilly, MSD, Pierre Fabre, Exact Science, Daichi Sankyo, Gilead, Seagen, Stemline-Menarini, Veracyte, Takeda, Ipsen.

Acknowledgments

The authors would like to thank the patients enrolled in these studies and their families as well as the study investigators. The authors would also like to thank Jiwen Wu for providing statistical support.

Medical editorial assistance was provided by Nucleus Global and Novartis Healthcare Pvt. Ltd, Hyderabad, India, and was funded by Novartis Pharmaceuticals Corporation. Authors had final responsibility for the poster.