Comparative effectiveness of ribociclib plus fulvestrant versus palbociclib plus letrozole as first-line treatment of HR+/HER2− advanced breast cancer assessed by matching-adjusted indirect comparison

330P

Peter A. Fasching,[1] Thomas E. Delea,[2] Yen-Shen Lu,[3] Richard DeBoer,[4] Sara Hurvitz,[5] Aaron Moynahan,[2] David Chandiwana,[6] Brad Lanoue,[6] Huilin Hu,[6] Astrid Thuerigen,[7] Joyce O'Shaughnessy[8]

[1]University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Department of Gynecology and Obstetrics, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [2]Policy Analysis Inc (PAI), Brookline, MA, USA; [3]National Taiwan University Hospital, Taipei, Taiwan; [4]Peter MacCallum Cancer Centre, Victoria, Australia; [5]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [7]Oncology, Novartis Pharma AG, Basel, Switzerland; [8]Department of Medical Oncology, Baylor University Medical Center, Texas Oncology and US Oncology, Dallas, TX, USA

Introduction

- CDK4/6 inhibitors are standards of care in the 1L treatment of patients with HR+/HER2− advanced breast cancer (ABC); but, to date, no head-to-head comparisons of CDK4/6 inhibitors have been performed in this population
- Both Phase III MONALEESA (ML)-3 (postmenopausal) and ML-7 (pre- or perimenopausal) trials have reported a statistically significant improvement in OS with ribociclib (RIB) treatment in 1L (**Table 1**)[1,2]; 1L populations: ≈ 50% and 100% in ML-3 and ML-7, respectively. Other pivotal 1L CDK4/6 inhibitor studies include PALOMA (P)-2, MONARCH-3, and ML-2, for which OS data are still not mature
- The Phase II P-1 trial of palbociclib (PAL) reported OS in 1L postmenopausal patients[3]
- Despite the differences in endocrine therapy (ET) partners, a comparison between ML-3 and P-1 would aid in understanding potential differences in survival outcomes in these 1L postmenopausal populations
- The PARSIFAL study demonstrated no differences in fulvestrant (FUL) and letrozole (LET) when combined with PAL;[4] an unpublished analysis of ML-2 and ML-3 similarly demonstrated no differences between the ET backbones with the addition of RIB[5]
- This analysis used matching-adjusted indirect comparison (MAIC),[6] a method employed to estimate the comparative effectiveness of treatments after adjusting for differences in the patient population of the study with available individual patient data
- MAIC has been used in other analyses,[7] and health technology assessment agencies have acknowledged MAIC as a valid method of comparing treatments that can account for imbalances in trial populations

Table 1. Survival Outcomes Previously Reported for ML-3 and P-1

Active vs Ctrl Arm	mPFS, mo	HR (95% CI)	mOS, mo	HR (95% CI)
ML-3 (ITT; N = 726)[1,a]	20.6 vs 12.8	0.59 (0.49-0.71)	NR vs 40.0	0.72 (0.57-0.92)
1L (n = 365)[a]	33.6 vs 19.2	0.55 (0.42-0.72)	NR vs 45.1	0.70 (0.48-1.02)
P-1 (ITT; N = 165)[3]	20.2 vs 10.2	0.49 (0.32-0.75)	37.5 vs 33.3	0.81 (0.49-1.35)

[a] PFS values from descriptive update at final OS analysis. Median PFS for ITT at primary analysis was 20.5 vs 12.8 mo (HR, 0.59 [95% CI, 0.48-0.73]). Median was not reported for the 1L population at that time (HR, 0.577 [95% CI, 0.415-0.802]).[8]

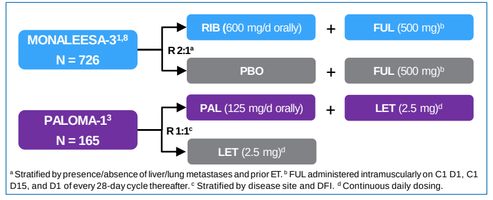
Objective

To analyze survival outcomes in patients treated in the 1L setting in the ML-3 and P-1 trials using MAIC

Methods

Study Details

Figure 1. Study Designs



[a] Stratified by presence/absence of liver/lung metastases and prior ET. [b] FUL administered intramuscularly on C1 D1, C1 D15, and D1 of every 28-day cycle thereafter. [c] Stratified by disease site and DFI. [d] Continuous daily dosing.

1L, first line; C, cycle; CNS, central nervous system; Ctrl, control; D, day; DFI, disease-free interval; ECOG, Eastern Cooperative Oncology Group; ITT, intent to treat; m, median; NR, not reached; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PBO, placebo; PFS, progression-free survival; R, randomized; SMD, standardized mean difference.

Table 2. Key Eligibility Criteria for ML-3 and P-1

Study	Patients	Prior CT for ABC	Prior ET for ABC	CNS Metastases
ML-3[1,a]	Postmenopausal HR+/HER2- ABC, ECOG PS 0-1	None	≤ 1 line	Allowed if stable[a]
P-1[3]			None	None

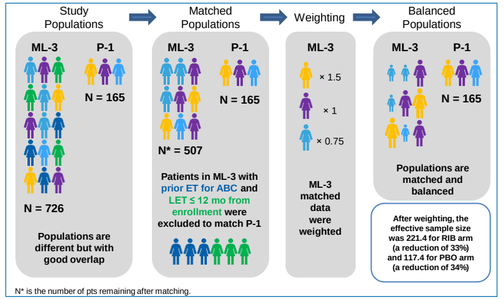
[a] 5 and 2 patients with stable CNS mets received treatment with RIB + FUL and PBO + FUL in ML-3.

- Patients with early relapse (≤ 12 months of completion of [neo]adjuvant treatment) were allowed in both studies; P-1 did not allow (neo)adjuvant letrozole use ≤ 12 mo of enrollment

MAIC Methodology

- An anchored comparison was not feasible due to different ET partners in the two trials. A network meta-analysis was not conducted, as it would require a significant number of connections to construct the evidence network and too many assumptions of differences in trial design not modifying the effects of treatment; therefore, an unanchored comparison was performed
- This unanchored MAIC was conducted using individual patient data (IPD) from ML-3 and published aggregated data from P-1[3]
- To match patients in P-1, those in ML-3 were limited to (**Figure 2**):
  - No prior ET for advanced disease and no (neo)adjuvant LET ≤ 12 mo prior to enrollment
- Patients in each arm of ML-3 were then weighted to match average baseline characteristics of patients of those published for P-1[3]; weights were calculated using method of moments
  - The distribution of weights was examined to diagnose population overlap
- Reconstructed IPD for PFS and OS for P-1[3] were derived from the digitized Kaplan-Meier (KM) curves using an adaptation of a published algorithm[9]
- PFS and OS for ML-3 were re-estimated for each arm and then compared with data from P-1 using weighted KM methods and weighted Cox regression analyses
- Effective sample size is indicative of the stability of the estimate

Figure 2. MAIC Overview and Attrition



Results

- After weighting, patients were well balanced on all characteristics (SMD = 0%)
- The distribution of weights for each arm is shown in **Figure 3**
- Baseline characteristics before and after weighting are shown in **Table 3**
- In this analysis, RIB + FUL was associated with a numerically longer PFS vs PAL + LET
  - Unweighted mPFS, 27.1 vs 20.0 mo (HR, 0.839 [95% CI, 0.595-1.184]; P = .319); weighted mPFS, 27.8 vs 20.0 mo (HR, 0.784 [95% CI, 0.551-1.117]; P = .178)
- For PBO + FUL vs LET:
  - Unweighted mPFS, 14.7 vs 10.1 mo (HR, 0.652 [95% CI, 0.477-0.891]); weighted mPFS, 16.5 vs 10.1 mo (HR, 0.579 [95% CI, 0.412-0.812])

Figure 3. Distribution of Weights

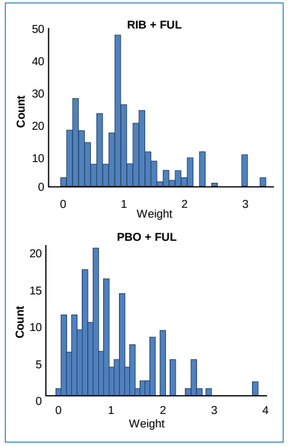


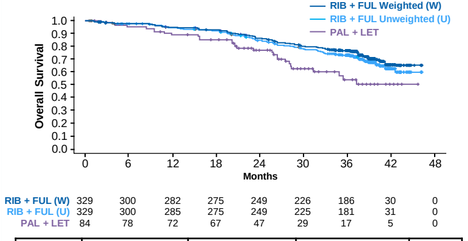
Table 3. Baseline Patient Characteristics

	Unweighted						Weighted			
	P-1	ML-3		SMD		ML-3		SMD	
	PAL + LET	LET	RIB + FUL	PBO + FUL	Active	Ctrl	RIB + FUL	PBO + FUL	Active	Ctrl
Patients, n	84	81	329	178	--	--	329	178	--	--
Age, %										
< 65 years	56.0	51.9	56.8	52.2	1.3	0.6	56.0	51.9	0	0
≥ 65 years	44.0	48.1	43.2	47.8	−1.3	−0.6	44.0	48.1	0	0
ECOG PS, %										
0	54.8	55.6	61.7	69.1	10.0	20.0	54.8	55.6	0	0
1	45.2	44.4	38.0	30.9	−10.4	−20.0	45.2	44.4	0	0
Stage, %										
II/III	2.4	1.2	1.2	1.1	−6.2	-0.7	2.4	1.2	0	0
IV	97.6	98.8	98.8	98.9	6.2	0.7	97.6	98.8	0	0
Site of metastasis, %										
Visceral	44.0	53.1	57.4	60.7	19.1	10.9	44.0	53.1	0	0
Bone only	20.2	14.8	23.1	20.8	4.9	11.1	20.2	14.8	0	0
Prior chemotherapy, %[a]	40.5	45.7	54.7	54.5	20.4	12.5	40.5	45.7	0	0
Prior ET, %[a]										
Tamoxifen	28.6	29.6	38.9	43.3	15.5	20.2	28.6	29.6	0	0
Anastrozole	9.5	13.6	20.1	23.0	21.2	17.4	9.5	13.6	0	0
Letrozole	2.4	1.2	15.2	9.6	32.9	26.5	2.4	1.2	0	0
Exemestane	4.8	2.5	5.8	7.3	3.2	16.0	4.8	2.5	0	0
Time to disease recurrence, %										
> 12 months	29.8	37.0	39.5	45.5	14.6	12.2	29.8	37.0	0	0
≤ 12 months	17.9	17.3	27.7	27.5	16.6	17.5	17.9	17.3	0	0
De novo	52.4	45.7	32.8	27.0	−28.5	−28.0	52.4	45.7	0	0

[a](Neo)adjuvant setting.

- mOS was significantly longer for RIB + FUL vs PAL + LET in the unweighted (HR, 0.587 [95% CI, 0.388-0.888]; P = .0116) and weighted (HR, 0.513 [95% CI, 0.328-0.801]; P = .0033) analyses (**Figure 4**)
- For PBO + FUL vs LET, the unweighted mOS was 40.0 vs 33.1 mo (HR, 0.816, [95% CI, 0.533-1.250]); weighted mOS was 40.4 vs 33.1 mo (HR, 0.735 [95% CI, 0.460-1.174])
- **Figure 5** shows the results of the Cox regression analysis
  - RIB + FUL treatment was associated with a trend toward improved PFS compared with PAL + LET and a significant benefit observed for OS
  - PBO + FUL was associated with significant benefit in PFS with a trend toward improved OS results vs LET

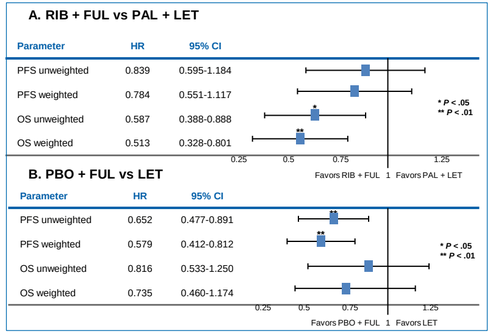
Figure 4. Overall Survival for RIB + FUL vs PAL + LET



Weighted	RIB + FUL, Median Mo	PAL + LET, Median Mo[a]	HR (95% CI)	P
No	Not reached	37.5	0.587 (0.388-0.888)	.0116
Yes	Not reached	(28.4, not reached)	0.513 (0.328-0.801)	.0033

[a]Median value from published data. The KM curve here was based on digitized data, which only reaches 50.9%; as such, the median was not reached in this analysis, and the OS for this arm may be slightly overestimated, meaning this analysis may be conservative.

Figure 5. Cox Regression Analysis of PFS and OS



Conclusions

- This MAIC adjusting for differences in patient populations in the ML-3 and P-1 trials demonstrated a significant OS benefit and a trend toward improved PFS for RIB + FUL vs PAL+ LET as 1L therapy for postmenopausal women with HR+/HER2− ABC
- Comparison of the endocrine monotherapy arms of these two trials showed that the trend favored FUL over LET, similar to previously published results comparing ET monotherapies (including FALCON and FIRST).[10-13] However, additional studies have indicated that this trend is lost with the addition of a CDK4/6 inhibitor[4,5]
- These results provide additional support for the use of 1L RIB + FUL in this patient population

Limitations

- These results are based on unanchored indirect comparison. Only characteristics reported for the P-1 trial[3] were controlled for using MAIC; results may therefore be confounded by other unreported factors
- The finding that PFS was more favorable for the control arm of ML-3 vs P-1 and that there was a trend of improved OS with PBO + FUL vs LET is consistent with published randomized controlled trials (FALCON/FIRST) of FUL vs NSAIs,[12,13] suggesting that unobserved confounding may be limited
- PFS and OS for P-1 were based on reconstructed IPD. Although the KM curves based on the KM data were similar to the reported curves, it was not feasible to exactly match the reported curves from P-1

References

1. Slamon DJ, et al. *N Engl J Med* 2020;382(6):514-524. 2. Im S-A, et al. *N Engl J Med* 2019;381:307-316. 3 Finn RS, et al. *Lancet Oncol*2015;16:25-35. 4. Llombart-Cussac, et al. *J Clin Oncol*. 2020;38:15, suppl. 1007. 5. Data on file. Novartis Pharmaceuticals Corp; 2020. 6. Phillippo DM, et al. *Med Decis Making*. 2018;38:200-211. 7. Signorovitch J, et al. *Curr Med Res Opin*. 2014;31:3115-322. 8. Slamon DJ, et al. *J Clin Oncol* 2018;36:2465-2472. 9. Guyot P, et al. *BMC Med Res Methodol*. 2012;12:9. 10. Zhang J, et al. *Medicine*. 2017;96:e7846. 11. Telford C, et al. *J Clin Oncol*. 2017;35(15 suppl) abstract E12545. 12. Robertson JFR, et al. *Lancet*. 2016;388:2997-3005. 13. Ellis MJ, et al. *J Clin Oncol*. 2015;33:3781-3787.

Acknowledgements

The authors would like to thank the patients enrolled in these studies and their families as well as the study investigators. Medical editorial assistance was provided by MediTech Media, Ltd and was funded by Novartis Pharmaceuticals Corporation. Authors had final responsibility for the poster.

Disclosures

PF: personal fees: Novartis, Roche, Pfizer, Celgene, Daiichi-Sankyo, TEVA, Merck Sharp and Dohme, Myelo Therapeutics, Macrogenics, Eisai, Puma, Cepheid, Lilly, AstraZeneca; research grant: BioNTech, Novartis; **TD:** nothing to disclose; **Y-SL:** personal fees: Novartis, Pfizer, Boehringer Ingelheim, Eisai, research grant: Novartis, Roche, Merck Sharp and Dohme, Pfizer; other: Novartis; **RDB:** personal fees: Novartis, Eli Lilly, Roche, Genomic Health; **SH:** research grant: Ambryx, Amgen, Bayer, OBI Pharma, Bimarin, Cascadian, Daiichi Sankyo, Dignitana, Genentech, GSK, Lilly, Macrogenics, Medivation, Merrimack, Novartis, OBI Pharma, Pfizer, Pieris, Puma, Roche, Seattle Genetics; other: Lilly, Novartis, OBI Pharma; **AM:** nothing to disclose; **DC, BL, HH, AT:** employment, stock ownership: Novartis; **JOS:** personal fees: AstraZeneca, Novartis, Pfizer, Lilly, Merck, Seattle Genetics.

Presented at the European Society for Medical Oncology Virtual Congress 2020; 19-21 September 2020

This analysis was sponsored by Novartis Pharmaceuticals Corporation.

Scan the QR code for additional materials

Text: Qe830d

To: 8NOVA (86682) US only
+18324604729 North, Central, and South Americas; the Caribbean; China
+447860024038 UK, Europe, and Russia
+46737494608 Sweden and Europe

Visit the web at:
http://novartis.medicalcongressposters.com/Default.aspx?doc=e830d

Presenter email address: Peter.Fasching@uk-erlangen.de

Standard data or message rates may apply.