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Pooled analysis of post-progression treatments after first-line ribociclib + endocrine therapy in patients with HR+/HER2− advanced breast cancer in the MONALEESA-2, -3, and -7 studies

Background: The MONALEESA (ML) studies showed significant PFS & OS benefits for 1L ribociclib (RIB) + endocrine therapy (ET) in patients (pts) with pre/peri & postmenopausal advanced breast cancer. The benefit of RIB beyond study treatment (tx) was also observed, with improvements in PFS2 & delays in time to 1st subsequent chemotherapy (CT). While there is currently no preferred tx for the next line post-progression on a CDK4/6 inhibitor (CDK4/6i), except alpelisib in pts with a *PIK3CA* mutation, guidelines encourage multiple lines of ET or ET-based therapies before switching to CT (except for visceral crisis). This pooled exploratory analysis of the ML studies examined outcomes of various tx strategies post progression on RIB + ET.

Methods: Data from pts receiving 1L therapy in ML-2, -3, & -7 (NSAI cohort only & excluding pts with early relapse [≤ 12 mo after end of (neo)adjuvant ET] whose prognosis is closer to that of 2L pts) were pooled & pts receiving 1st subsequent therapies after progression were analyzed. Three groups of subsequent therapies were assessed: ET only, CT, & targeted therapy. Subsequent CT comprises CT +/- any other therapy; targeted therapy includes CDK4/6i, mTORi, PI3Ki, AKTi, etc, +/- ET. Subsequent CT & targeted therapy groups are mutually exclusive. Median duration of study tx, 1st subsequent therapy, & OS (from randomization to death) were analyzed by KM methods. Weighted Cox regressions were performed using inversed propensity scoring matching method (inverse probability tx weighting [IPTW]) to ensure compatible pt characteristics between tx arms. These are not randomized comparisons; only baseline characteristics were used for the estimation of propensity scores in the IPTW, imbalance of prognostic factors at progression may exist.

Results: Median follow-up time was 74 mo. 461 pts treated with RIB (81%) & 440 (86%) with PBO discontinued study tx & received a subsequent therapy. In the RIB arms, the most common 1st subsequent therapies were ET only (40%), CT (29%), combination with targeted therapy (28%), & other (4%); for the PBO arms, 34% received CT as a 1st subsequent therapy & 31% each received ET only or combination with targeted therapy (5% received other). In 14% & 20% of pts in the RIB & PBO arms, the 1st subsequent therapy was a CDK4/6i, of these 31% & 12% were RIB. In general, regardless of type of 1st subsequent therapy, the duration of both the study tx & the 1st subsequent therapy was longer for pts treated with RIB vs PBO (Table). In both RIB & PBO arms, pts who received subsequent CT had the shortest duration on study tx, whereas those who received subsequent targeted therapy combination had the longest. Among pts on 1L RIB + ET, after matching pre-randomization baseline characteristics, subsequent CDK4/6i use was associated with the longest mOS (84 [84-NE] mo), followed by ET only (60 [51-68] mo), then a non-CDK4/6i targeted therapy (52 [43-72] mo); post-progression CT was associated with the shortest mOS (37 [32-48] mo).

Conclusions: This large, pooled analysis of the ML studies shows that, in general, duration of any subsequent therapy was numerically longer post-1L RIB + ET vs PBO + ET, & subsequent CT was used less frequently for pts on RIB vs PBO. Both findings confirm that upfront tx with RIB does not worsen pt outcomes. This trend in enhancement of outcomes of subsequent therapies seen with 1L RIB suggests a post-tx effect that merits further exploration.

Table.

Median Duration, mo	All	CT	ET Only	Any Targeted Therapy	Any CDK4/6i	RIB
RIB + ET, n	461	132	184	128	65	20
1L RIB + ET	**19.3**	**13.5**	**17.4**	**24.8**	**29.4**	**47.4**
First subsequent therapy	**10.5**	**7.6**	**8.3**	**15.0**	**22.8**	**34.2**
PBO + ET, n	440	150	136	134	86	10
1L PBO + ET	**14.7**	**9.2**	**14.9**	**22.5**	**28.0**	**29.9**
First subsequent therapy	**8.9**	**9.0**	**7.4**	**9.4**	**14.7**	**21.1**