ESMO BREAST CANCER

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Updated Overall Survival Results From the First-Line Population in the Phase III MONALEESA-3 Trial of Postmenopausal Patients With HR+/HER2− Advanced Breast Cancer Treated With Ribociclib + Fulvestrant

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Declaration of Interests

- I am an academic and I am 100% employed by UZ and KU-Leuven
- Member of “oncology drugs”- working group CTG RIZIV/INAMI
- Honorarium paid to institution
- Lectures, ad board, steering committee, DMSB, travel (payment UZ-Leuven)
- Ad Board payments to institution: Amgen, Astra Zeneca, Eli Lilly, Gilead, Novartis, Pfizer, Roche
- No other COI for this topic

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Background HR+/HER2- ABC

- CDK4/6 (-) avoid hyperphosphorylation of Rb (Retinoblastoma protein)→Induce G1 cell cycle arrest
  - Combined with ET, CDK4/6 (-) improve PFS (greatest therapeutic achievement past 20 yrs)

- The MONALEESA-2, -3, and -7 trials showed a statistically significant OS benefit with ribociclib + ET vs placebo + ET in pre-, peri-, and postmenopausal pts[1-3]
- The MONALEESA-3 evaluated ribociclib + fulvestrant in 1L (treatment naive) and 2L (≤ 1 line of ET) postmenopausal pts[2]
  - Final protocol-specified OS analysis (39.4 mo mFU), ribociclib was associated with a statistically significant OS benefit over placebo (HR, 0.72 [95% CI, 0.57-0.92]; *P*=.00455)[2]
  - An exploratory OS analysis (56.3 mo mFU) confirmed the consistent OS benefit of ribociclib and demonstrated a median OS of 53.7 mo with ribociclib vs 41.5 mo with placebo (HR, 0.73 [95% CI, 0.59-0.90]) in the ITT population[4]
    - However, the median OS was not reached in the ribociclib arm for the 1L population

- Here we report an exploratory analysis of OS in the 1L subgroup of MONALEESA-3, with median follow-up of 70.8 mo

ABC, advanced breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ITT, intent to treat; NR, not reached; OS, overall survival.

References: 1. Hortobagyi GN, et al. *N Engl J Med*. 2022;386:942-950. 2. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524. 3. Im S-A, et al. *N Engl J Med*. 2019;381:307-316. 4. Slamon DJ, et al. *Ann Oncol*. 2021;32:1015-1024.

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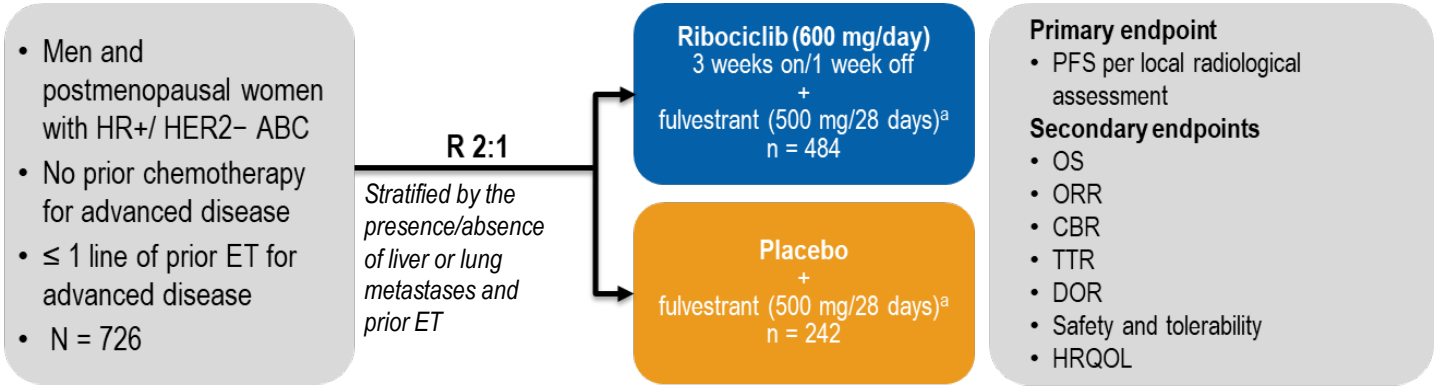
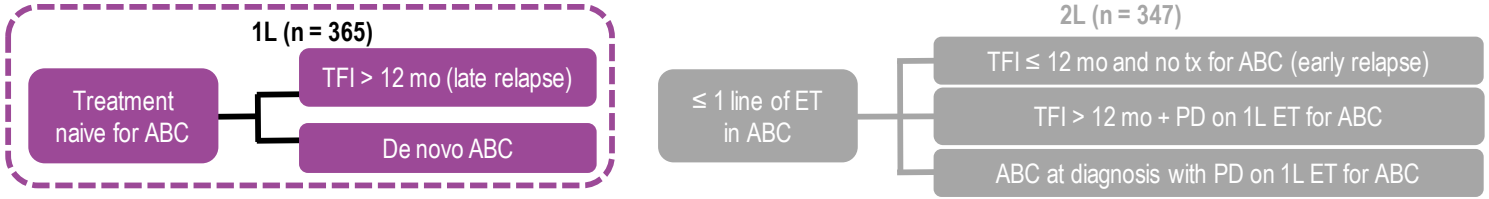
MONALEESA-3 Study Design and Patients

Study Design



Patient Population Definitions



1L, first line; 2L, second line; ABC, advanced breast cancer; CBR, clinical benefit rate; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRQOL, health-related quality of life; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TFI, treatment-free interval; TTR, time to response; tx, treatment.

[a] One additional dose on cycle 1 day 15.

Reference: Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-2472.

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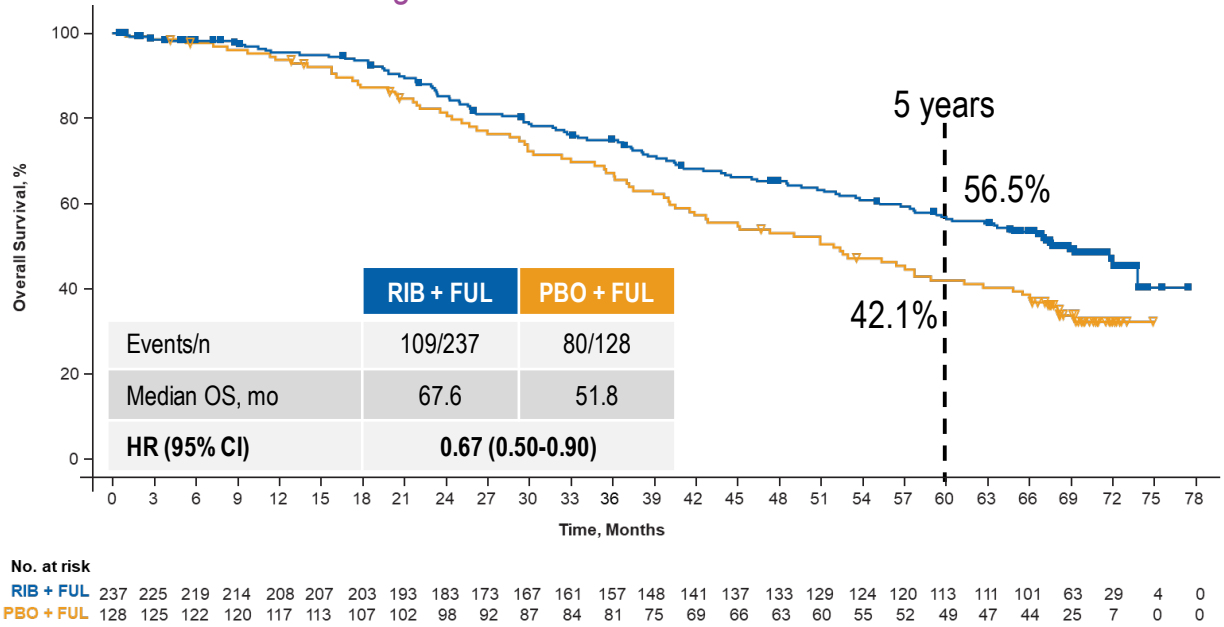
Median OS With First-Line Ribociclib Was 67.6 Months*

Ribociclib demonstrated a 15.8-month longer median OS and a relative reduction in the risk of death of 33% vs placebo



- Median duration of follow-up from randomization to data cutoff was 70.8 months (minimum, 67.3 months)
- At 5 years, the survival rate of patients receiving ribociclib was 56.5%

FUL, fulvestrant; OS, overall survival; PBO, placebo; RIB, ribociclib.
Data cutoff, January 12, 2022.
* Patients continuing study treatment at the time of data cutoff (January 12, 2022): 16.5% with ribociclib + fulvestrant vs 8.6% with placebo + fulvestrant.

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Subsequent Therapy After Discontinuation

Post-discontinuation CDK4/6i use was higher in the placebo arm vs the ribociclib arm

Parameter, n (%)	Ribociclib + Fulvestrant N = 237	Placebo + Fulvestrant N = 128
Patients who discontinued study treatment	**198 (83.5)**	**117 (91.4)**
Patients who received first subsequent antineoplastic therapy	**162 (81.8)**	**105 (89.7)**
Chemotherapy alone	25 (12.6)	19 (16.2)
Chemotherapy + hormonal or other therapy[a]	16 (8.1)	15 (12.8)
Hormonal therapy alone	71 (35.9)	30 (25.6)
Hormonal therapy + targeted or other therapy[b]	45 (22.7)	40 (34.2)
Targeted therapy alone or other therapy	5 (2.5)	1 (0.9)
Patients who received a CDK4/6i in any subsequent line of therapy	**33 (16.7)**	**41 (35.0)**
Palbociclib	17 (8.6)	32 (27.4)
Ribociclib	13 (6.6)	7 (6.0)
Abemaciclib	6 (3.0)	3 (2.6)

CDK4/6i, cyclin-dependent kinases 4 and 6 inhibitor.
Data cutoff, January 12, 2022.
[a] Includes patients who received chemotherapy in combination with any non-chemotherapy.
[b] Includes patients who received hormonal therapy + other therapy without chemotherapy.

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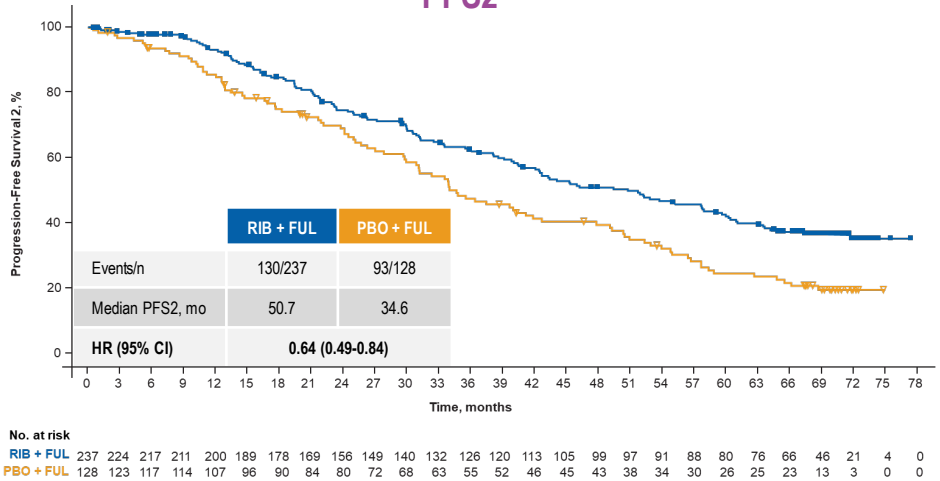
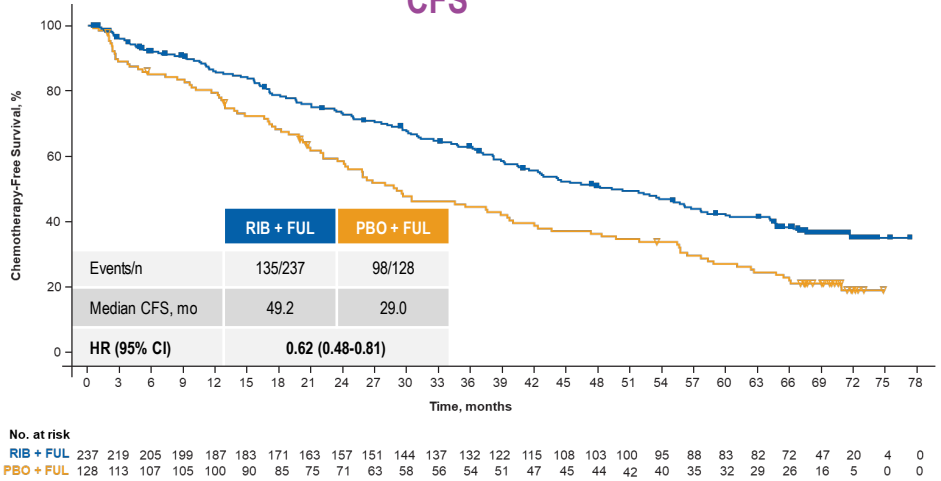
First-Line Ribociclib Delayed PFS2 and Improved CFS

PFS2



CFS



- Ribociclib also delayed TTC (HR, 0.57 [95% CI, 0.42-0.79])

Outcome	Definition
PFS2	Time from randomization to first documented disease progression after discontinuation from study treatment while receiving next-line therapy (reported by investigator) or death from any cause, whichever occurred first
CFS	Time from randomization to the beginning of the first chemotherapy or death
TTC	Time from randomization to the beginning of the first subsequent chemotherapy

CFS, chemotherapy-free survival; FUL, fulvestrant; PBO, placebo; PFS2, progression-free survival 2; RIB, ribociclib; TTC, time to chemotherapy.
Data cutoff, January 12, 2022.

No New Safety Signals Were Observed With First-Line Ribociclib

After a median follow-up of 70.8 months (~6 years), no new safety signals were identified

- Frequency of adverse events remained generally consistent with prior analyses of MONALEESA-3
- The rates of adverse events of special interest (all grades) remained stable in the ribociclib and placebo arms, respectively:
  - Neutropenia, 73.8% and 4.7%
  - Leukopenia, 32.5% and 1.6%
  - Hepatobiliary toxicity, 26.6% and 17.2%
  - Prolonged QT interval, 10.5% and 0.8%
  - Interstitial lung disease/pneumonitis, 3.4% and 0.8%

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Conclusions

- In this exploratory analysis of MONALEESA-3, with a median follow-up of 70.8 months (~6 years), ribociclib + fulvestrant demonstrated the longest median OS (67.6 months) observed for a 1L population in a Phase III trial setting in ABC to date
  - Median OS was prolonged by 15.8 months with ribociclib vs placebo in the 1L population
  - Consistent with prior analyses, ribociclib continued to demonstrate an OS benefit in the 2L population
- Ribociclib prolonged PFS2, CFS, and TTC compared with placebo, demonstrating the benefits of ribociclib beyond study treatment
- These impressive results in the 1L setting showed that the OS benefit of ribociclib was maintained through extended follow-up and further support the use of ribociclib in HR+/HER2− ABC

1L, first line; 2L, second line; ABC, advanced breast cancer; CFS, chemotherapy-free survival; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival; PFS2, progression-free survival 2; TTC, time to chemotherapy.

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Acknowledgments

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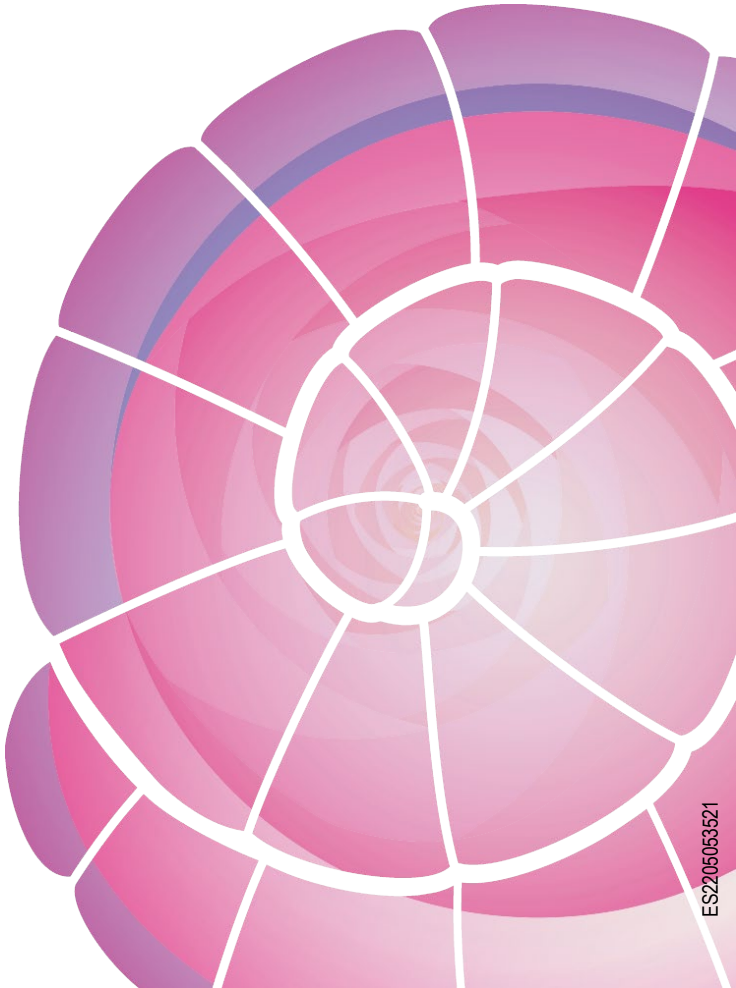

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