2022 ASCO® ANNUAL MEETING

A randomized phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER2 negative breast cancer: MAINTAIN Trial

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Disclosures

- Employment/Stock: Spouse - EQRX, Grail (Prior Employee)
- Advisory/Consulting: Eli-Lilly, Pfizer, Novartis, AstraZeneca, Daiichi Sankyo, Puma, 4D Pharma, Oncosec, Immunomedics, Puma, Merck, Seattle Genetics, Mersana, and Cyclocel
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Background

- CDK 4/6 inhibition with endocrine therapy (ET) is standard of care in HR+, HER2- metastatic breast cancer (MBC)
  - Ribociclib with ET improves progression-free and overall survival in phase III trials
- Anti-proliferative effect of CDK 4/6 inhibition can reverse upon discontinuation
- Observational data support potential benefit of treating with a CDK 4/6 inhibitor and switching ET after CDK 4/6 inhibitor progression
- No prospective randomized trials reported with this approach

Hortobagyi GN et al, NEJM 2022; Lu YS et al, Clinical Cancer Research 2022; Slamon DJ et al, Annals of Oncology 2021
Fry DW et al, Molecular Cancer Therapeutics 2004; Ma CX et al, Clinical Cancer Research 2017, Wander SA et al, JNCCN 2021

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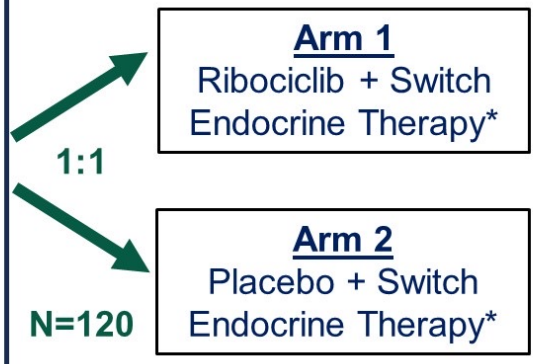
Schema

Key Entry Criteria

- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed



Primary Endpoint

- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints

- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

- Fulvestrant as endocrine therapy in pts with progression on a prior aromatase inhibitor for MBC and no prior fulvestrant; Protocol amended to allow exemestane as endocrine therapy if progression on prior fulvestrant (September 2018); Ribociclib 600 mg administered 3 weeks on/1 week off

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Statistical Considerations

- Investigator-initiated, multi-center trial open at 13 US sites
- **Primary Endpoint**
  - PFS: Time from randomization to progressive disease or death
    - Radiographic disease assessment every 12 weeks
- **Sample Size**
  - 120 evaluable and randomized pts to achieve 80% power to detect a difference in PFS of 3 months, with a one-sided log-rank at 2.5%
- **Data Cutoff**
  - January 4, 2022, with median follow up of 18.2 months

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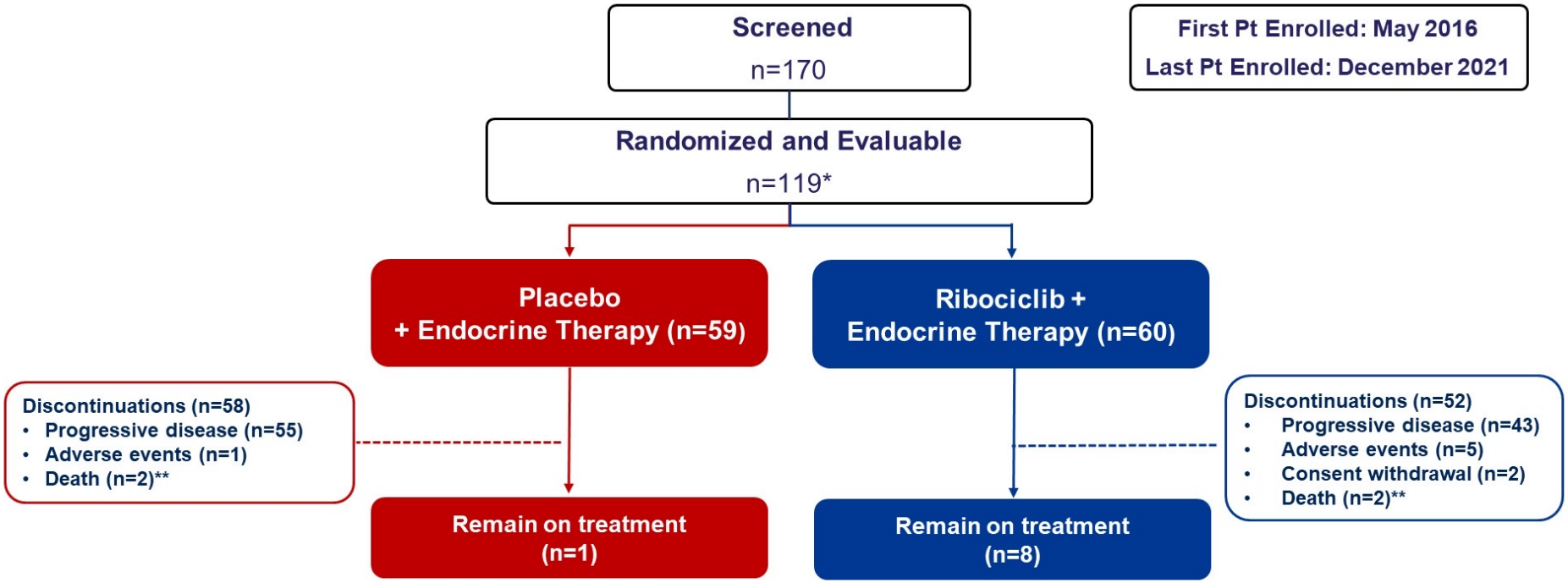
Consort Diagram



* 1 randomized pt excluded who took ribociclib/placebo alone without endocrine therapy

** Treatment-related deaths in ribociclib (n=2) and placebo (n=1) arms, and 1 death unrelated to treatment in placebo arm

Patient Characteristics and Prior Treatment

	Placebo (n=59)	Ribociclib (n=60)
Female - no. (%)	58 (99%)	60 (100%)
Median age – years (IQR)	59 (52-65)	55 (48-67)
Race or ethnic group – no. (%)		
White	42 (71%)	46 (77%)
Black	8 (14%)	5 (8%)
Asian	2 (3%)	5 (8%)
Other or not specified	7 (12%)	4 (7%)
ECOG PS – no. (%)		
0	38 (64%)	40 (67%)
1	21 (36%)	20 (33%)
De Novo Metastasis at Dx - no. (%)* **	32 (54%)	21 (35%)
Visceral Metastasis – no. (%)	35 (59%)	36 (60%)
Bone-Only Disease – no. (%)	9 (15%)	13 (22%)
≥ 2 prior ET for MBC – no. (%)	11 (19%)	11 (18%)
Chemotherapy for MBC – no. (%)	7 (12%)	4 (7%)

	Placebo (n=59)	Ribociclib (n=60)
Prior CDK 4/6 inhibitor – no. (%)		
Palbociclib*	51 (86%)	52 (87%)
Ribociclib**	8 (14%)	6 (10%)
Abemaciclib	0 (0%)	2 (3%)
Median duration of prior CDK 4/6 inhibitor - months (IQR)	17 (11-23.5)	15.5 (12-21)
Prior CDK 4/6 inhibitor duration– no. (%)**		
≤ 12 months	21 (36%)	18 (30%)
> 12 months	38 (64%)	42 (70%)
Prior CDK 4/6 inhibitor in metastatic setting - no. (%)	59 (100%)	60 (100%)
Intervening treatment after progression on prior CDK 4/6 inhibitor - no. (%)	6 (10%)	1 (2%)

* Includes 1 pt who did not tolerate prior abemaciclib and 2 pts with insurance issues with ribociclib; ** Includes 1 pt who did not tolerate prior palbociclib;
p=0.035; * 10 pts (17%) in placebo arm and 7 pts (12%) pts in ribociclib arm on prior CDK4/6 inhibitor ≤ 6 months; IQR = interquartile range

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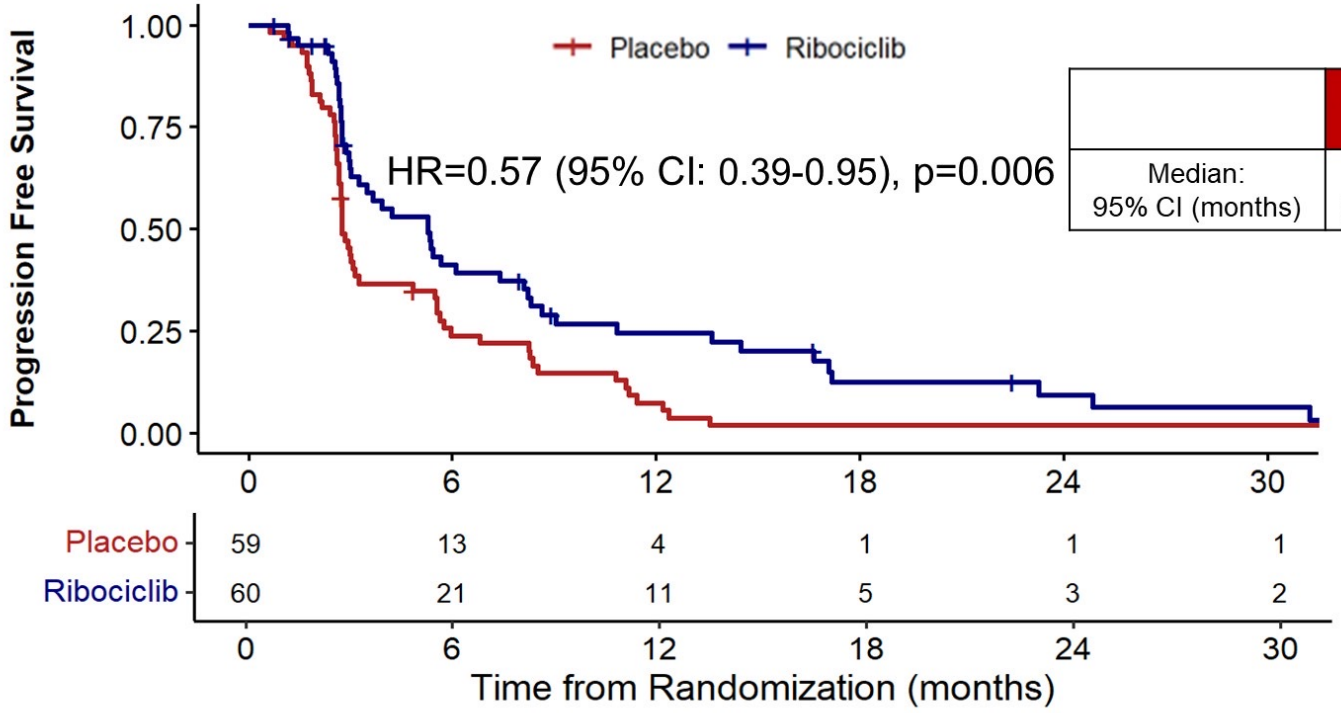
Primary Endpoint: Progression Free Survival (PFS)



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	**2.76** (2.66-3.25)	**5.29** (3.02-8.12)

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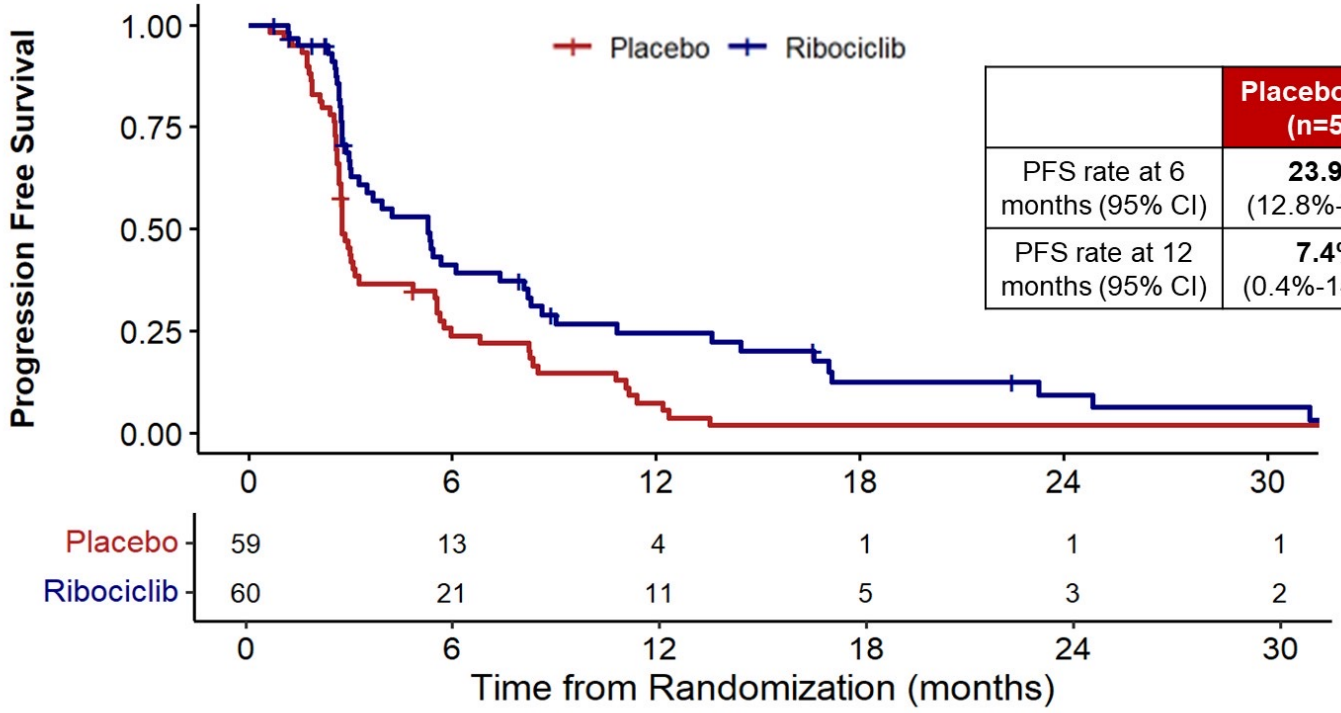
Progression Free Survival at 6 and 12 months



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
PFS rate at 6 months (95% CI)	**23.9%** (12.8%-35%)	**41.2%** (27.8%-54.6%)
PFS rate at 12 months (95% CI)	**7.4%** (0.4%-14.3%)	**24.6%** (12.5%-36.7%)

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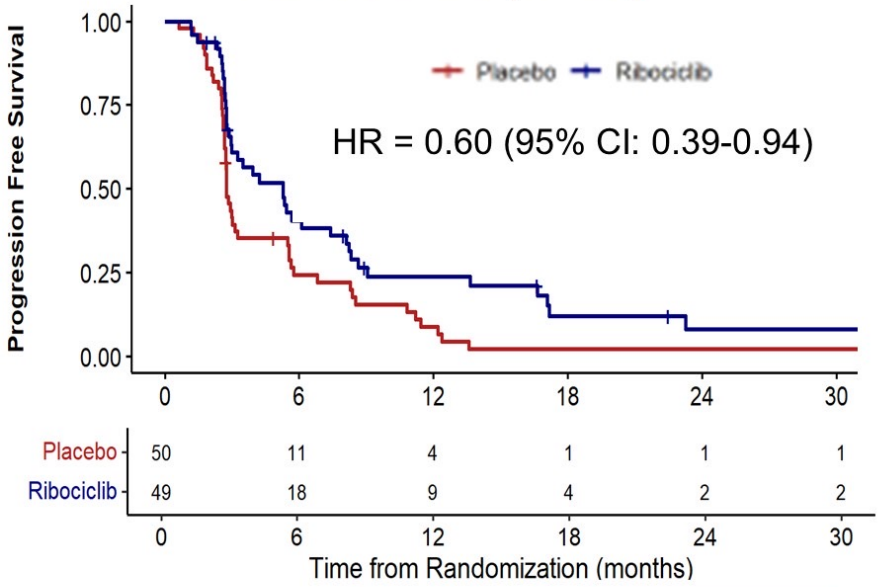
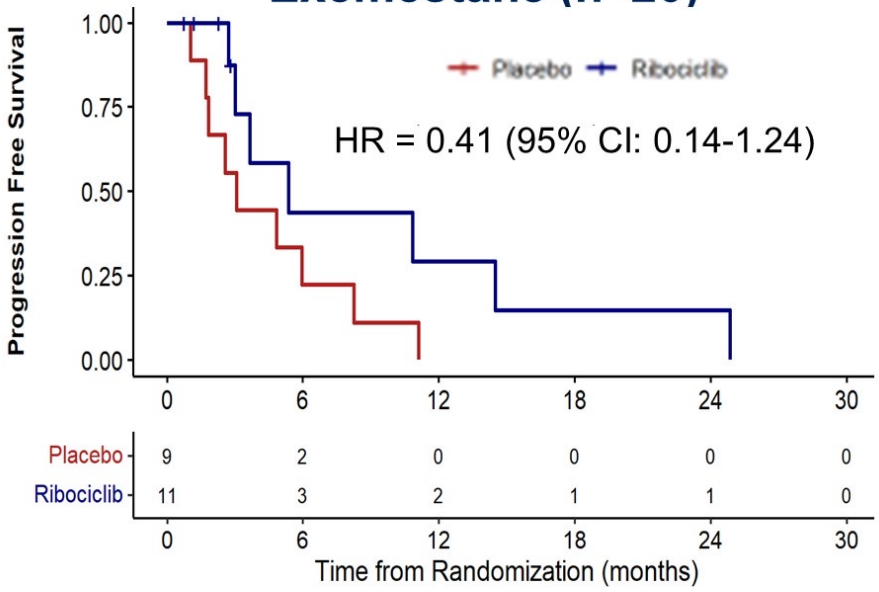
Exploratory Analysis
PFS in Fulvestrant or Exemestane Subgroups

Fulvestrant (n=99)



	Placebo (n=50)	Ribociclib (n=49)
Median (95% CI) (mos)	**2.76** (2.66-3.25)	**5.29** (2.96-8.12)

Exemestane (n=20)



	Placebo (n=9)	Ribociclib (n=11)
Median (95% CI) (mos)	**3.06** (1.84-5.95)	**5.36** (3.02-14.50)

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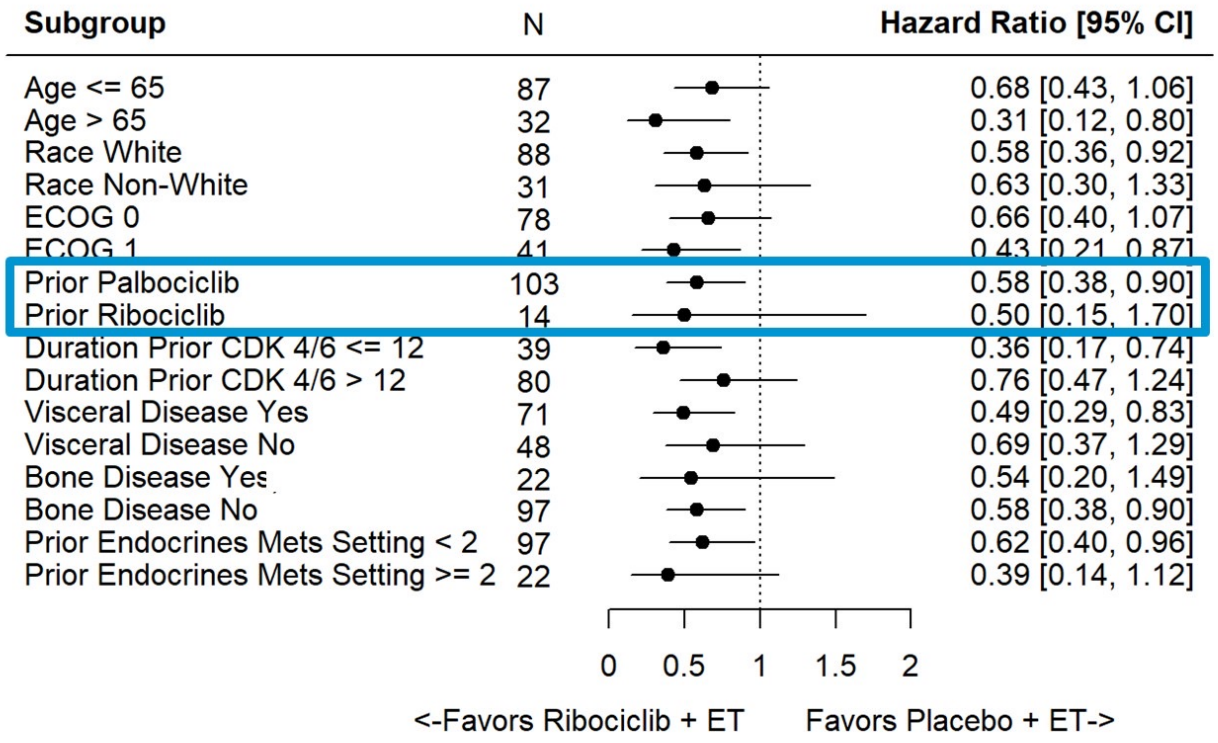
Progression Free Survival by Subgroup



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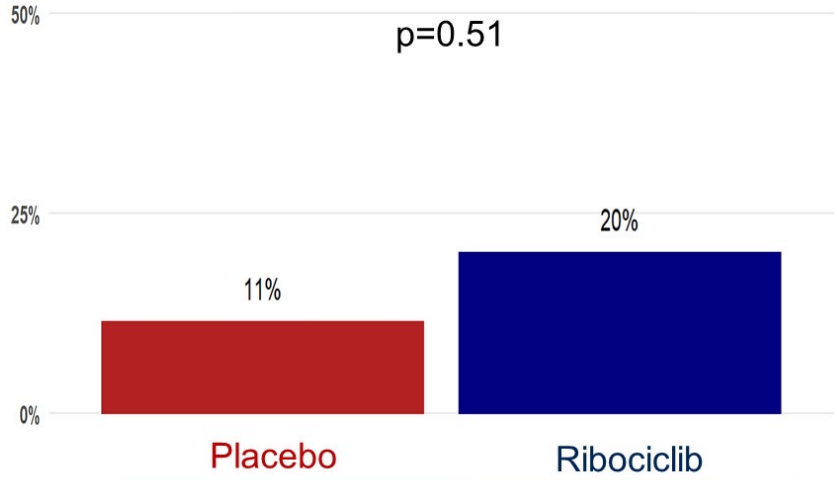
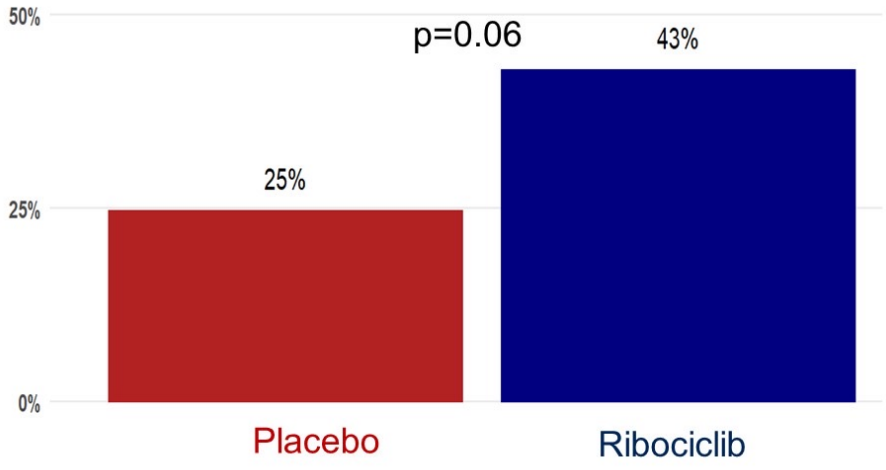
Overall Response and Clinical Benefit Rate

Overall Response Rate (n=70)



	Placebo + ET (n=35)	Ribociclib + ET (n=35)
CR	0 (0%)	2 (6%)
PR	4 (11%)	5 (14%)
Median DOR (IQR) (mos)	14.8 (6.7-21.3)	18.8 (11.4-50.2)

Clinical Benefit Rate (n=105)



	Placebo + ET (n=57)	Ribociclib + ET (n=49)
CR, PR, or SD ≥ 24 weeks	14 (25%)	21 (43%)

IQR = Interquartile Range, CR = Complete response, PR = Partial Response, DOR = Duration of Response, SD = Stable Disease

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Treatment Exposure and Dose Adjustment

	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Ribociclib/placebo dose adjustments, n (%)		
Dose interruptions	20 (34%)	36 (60%)
Dose interruptions due to AEs	12 (20%)	32 (53%)
Longest interruption due to AEs, median (range), days	10.5 (7.8-15.5)	7 (7-8)
Dose reductions	5 (8.5%)	15 (25%)
Dose reductions due to AEs	5 (8.5%)	14 (23%)
> 1 Dose reduction due to AEs	1 (2%)	2 (3%)

Treatment-related AE discontinuations: Ribociclib: pain (n=1), pneumonitis (n=2), nausea (n=1), neutropenia (n=1). Placebo: LFT abnormality (n=1)

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Treatment-Related Adverse Events

	Placebo + ET (n=59)			Ribociclib + ET (n=60)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hematologic						
Neutropenia*	9 (15%)	0 (0%)	1 (2%)	43 (72%)	23 (38%)	1 (2%)
Anemia	13 (22%)	1 (2%)	0 (0%)	14 (23%)	1 (2%)	0 (0%)
Thrombocytopenia	3 (5%)	0 (0%)	0 (0%)	15 (25%)	0 (0%)	0 (0%)
Non-Hematologic						
ALT increased	12 (20%)	1 (2%)	0 (0%)	10 (17%)	0 (0%)	0 (0%)
AST increased	17 (29%)	4 (7%)	0 (0%)	15 (25%)	1 (2%)	0 (0%)
Vomiting	3 (5%)	0 (0%)	0 (0%)	9 (15%)	0 (0%)	0 (0%)
Fatigue	19 (32%)	0 (0%)	0 (0%)	20 (33%)	1 (2%)	0 (0%)
Headache	6 (10%)	0 (0%)	0 (0%)	5 (8%)	0 (0%)	0 (0%)
Diarrhea	6 (10%)	0 (0%)	0 (0%)	9 (15%)	0 (0%)	0 (0%)
Pneumonitis	0 (0%)	0 (0%)	0 (0%)	2 (3%)	1 (2%)	0 (0%)
Infection	3 (5%)	0 (0%)	0 (0%)	6 (10%)	3 (5%)	0 (0%)

- Febrile Neutropenia: 2 pts (3%) in ribociclib arm and 0 pt (0%) in placebo arm
- Post-baseline QTcF >480 ms, based on ECG data: 1 pt (2%) in ribociclib arm and 1 pt (2%) in the placebo arm
- Treatment-related deaths (n=3): 1 pt with sepsis, neutropenia, and disease progression in ribociclib arm. 1 pt with pneumonia without fever or neutropenia in each arm

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Fulvestrant and Baseline *ESR1* Mutation Status and Co-Occurring Alterations (n=78 evaluable with ctDNA)

ESR1 Mutant at Study Entry (42%)

ESR1 Mutation (N=33)	N	Rate
D538G		
D538G	7	21.2%
D538G + non-Y537S	5	15.2%
Y537S		
Y537S	3	9.1%
Y537S + non-D538G	1	3%
D538G + Y537S	7	21.2%
E380Q	4	12.1%
Y537C	1	3%
Y537N	5	15.2%

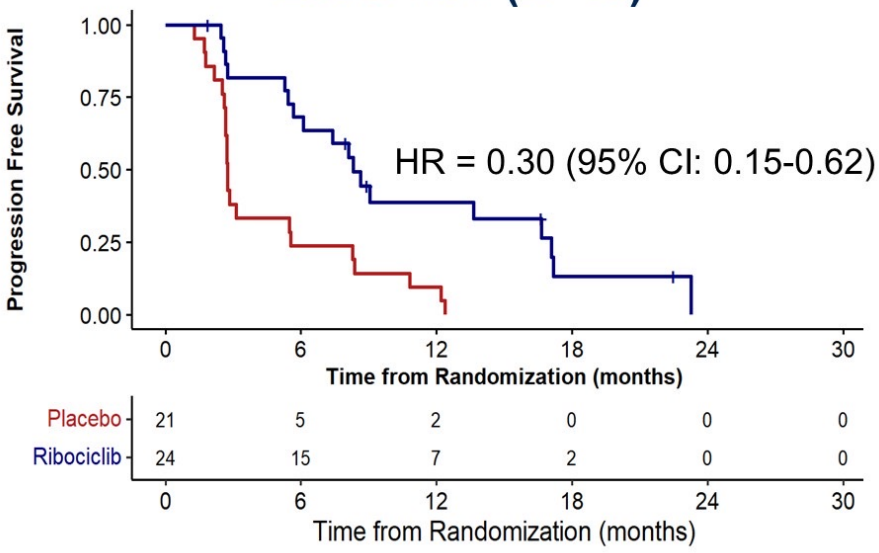
Co-Occurring Alterations

Co-Occurring Alteration	*ESR1* Mutant (n=33)	*ESR1* WT (n=45)
p53 mutation	10 (30%)	15 (33%)
PIK3CA mutation	7 (21%)	15 (33%)
CCND1 amplification	8 (24%)	1 (2%)
FGFR1 amplification	6 (9%)	3 (6%)

Biocept (San Diego, CA) using the Thermo Fisher assay, cutoff: 0.1% variant allele frequency; Excludes 2 pts with exemestane with *ESR1* mutation: Y537D and D538G

Exploratory Analysis
PFS: Fulvestrant and *ESR1* Mutation Status

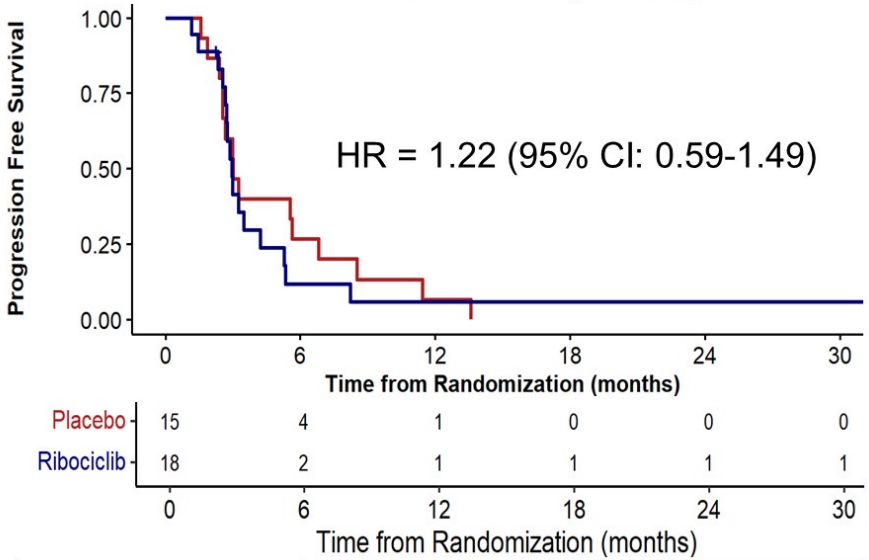
ESR1 WT (n=45)



	Placebo (n=21)	Ribociclib (n=24)
Median (95% CI) (mos)	**2.76** (2.66-5.49)	**8.32** (5.65-16.63)

0/24 pts (0%) had *CCND1* and/or *FGFR1* amplification on ribociclib arm

ESR1 Mutant (n=33)



	Placebo (n=15)	Ribociclib (n=18)
Median (95% CI) (mos)	**3.02** (2.53-5.62)	**2.96** (2.66-4.21)

9/18 (50%) pts with *CCND1* and/or *FGFR1* amplification on ribociclib arm

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Conclusion

- **First randomized trial to show the benefit of ribociclib and switching ET after CDK 4/6 inhibitor progression**
  - Ribociclib + ET led to a statistically significant improvement in PFS compared to placebo + ET in pts with tumor progression following prior CDK 4/6 inhibitor
  - Palbociclib was the prior CDK4/6 inhibitor in 87% of pts
  - 43% risk reduction of progression or death with ribociclib vs. placebo in ITT population
  - Higher PFS rate at 6 months and 12 months, as well as improved clinical benefit rate, with ribociclib vs. placebo
  - Ribociclib + ET demonstrated a manageable safety profile

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Summary of Subgroup Analyses

- In fulvestrant subgroup (83% pts), 40% risk reduction of progression or death with ribociclib vs. placebo
  - Fulvestrant alone had a limited median PFS of 2.76 months (95% CI: 2.66-3.25) after CDK 4/6 inhibitor progression, consistent with recent trials in the same space
- In an exploratory analysis, the benefit seems limited to *ESR1* WT in the fulvestrant subgroup
  - However, ESR1 mutant cohort was small, with a higher rate of CCND1 and/or FGFR1 amplifications, and these data are hypothesis-generating

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