GRUPPO B
QUESITO CLINICO:

Nelle pazienti in post-menopausa con carcinoma mammario HR positivo/HER2 negativo è opportuno considerare un trattamento ormonale di 1° linea con Ribociclib + letrozolo rispetto al letrozolo?

Le evidenze derivanti dalla letteratura.

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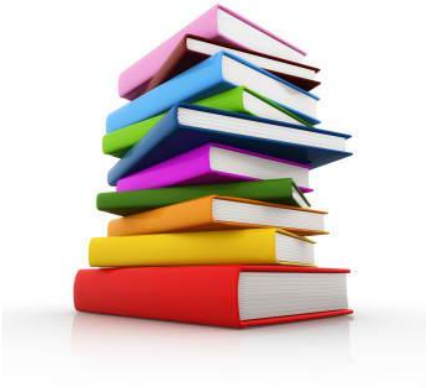
QUESITO STRUTTURATO
il metodo PICO

P opulation	Pazienti in post-menopausa con carcinoma mammario HR positivo/HER2 negativo recidivate o metastatiche in prima linea
I ntervention	Aggiunta di ribociclib a letrozolo
C omparison	Placebo + letrozolo
O utcomes	- PFS, OS, ORR* and CBR° (beneficio) - Safety e QoL (danno)

* ORR: overall response rate (complete or partial response)
° CBR: clinical benefit rate (overall response plus stable disease lasting 24 weeks or more)

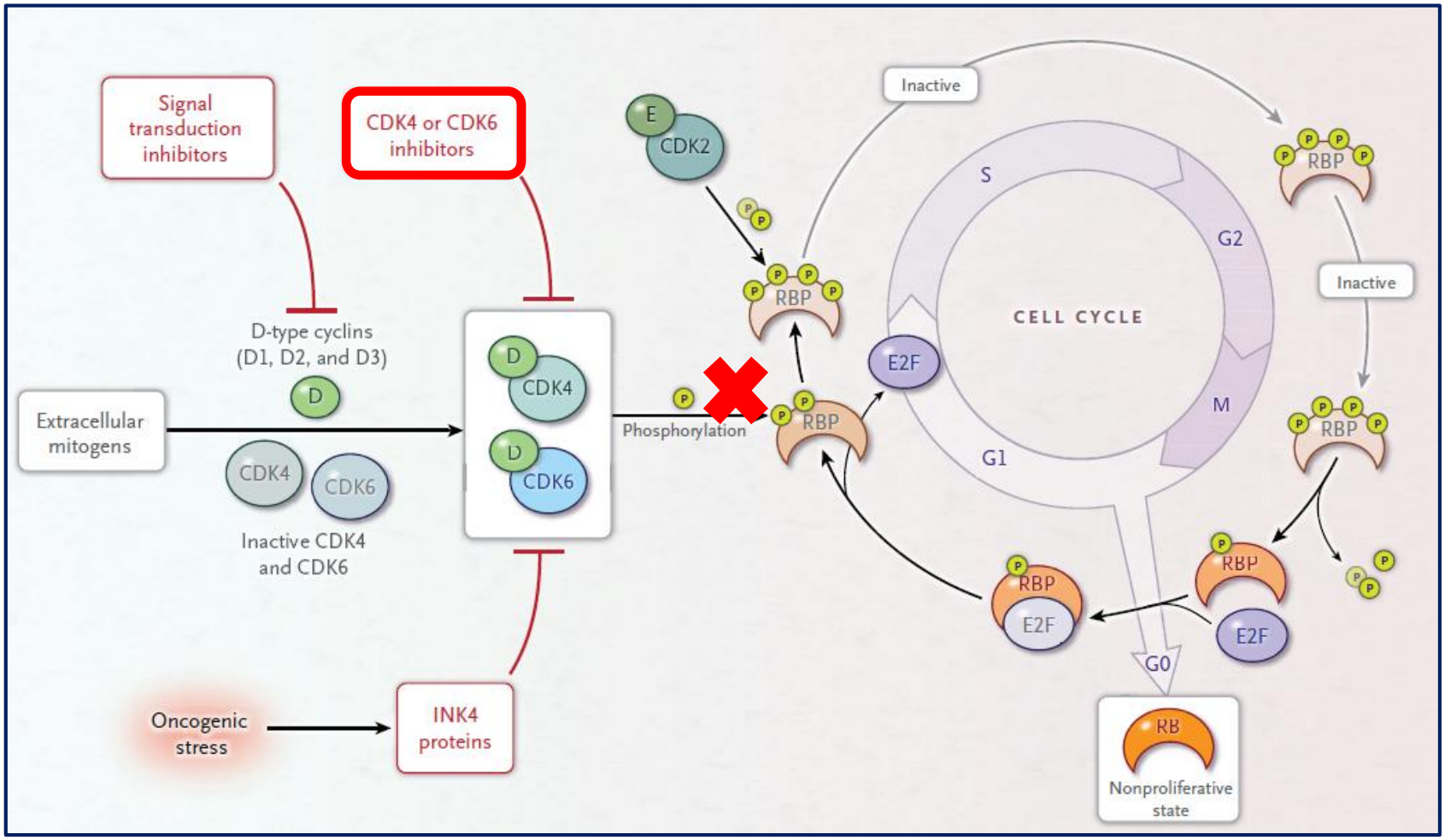
LE EVIDENZE DERIVANTI DALLA LETTERATURA



THE ROLE OF CDK 4/6 IN HR+ BREAST CANCER

- Up to 75% of breast cancer express the estrogen or progesterone receptor (HR+) [Anderson WE et al., Breast Cancer Res Treat 2002; Setiawan VW et al., Am J Eoidemiol 2009].
- Endocrine therapy is the standard of care for HR+/HER2- metastatic breast cancer (mBC) patients without rapidly progressive, symptomatic or significant visceral disease [Cardoso F et al., Breast 2014].
- However, resistance occurs in the majority of patients, requiring the administration of sequential therapy and the identification of effective treatment options that prolong or restore sensitivity to endocrine therapies [Osborne CK et al., Annu Rev Med 2011; Higgins MJ et al., J Clin Invest 2011].
- Cyclin-dependent kinase 4 and 6 (CDK4/6) overexpression and cyclin D1 amplification are frequently encountered in HR+ breast cancer, representing key mediators of endocrine resistance [Cancer Genome Atlas Network, Nature 2012; Zardavas D et al., Nat Rev Clin Oncol 2013].

CDK4/6-cyclin D inhibition is a potential target in HR+ mBC.



CDK4/6 inhibitors arrest the cell cycle at G1 by selective inhibition of CDK4/6.

Ami NS et al., Curr Treat Option in Oncol 2017.

CDK INHIBITORS IN PHASE III TRIALS IN ADVANCED HR+ BREAST CANCER

- **Palbociclib - «PALOMA» trials**
- **Ribociclib - «MONALEESA» trials**
- **Abemaciclib – «MONARCH» trials**

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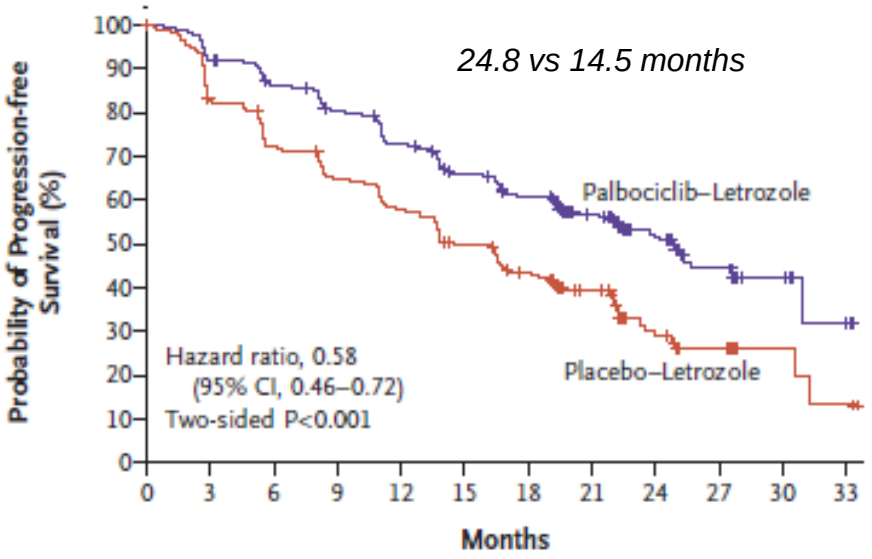
Palbociclib and Letrozole in Advanced Breast Cancer

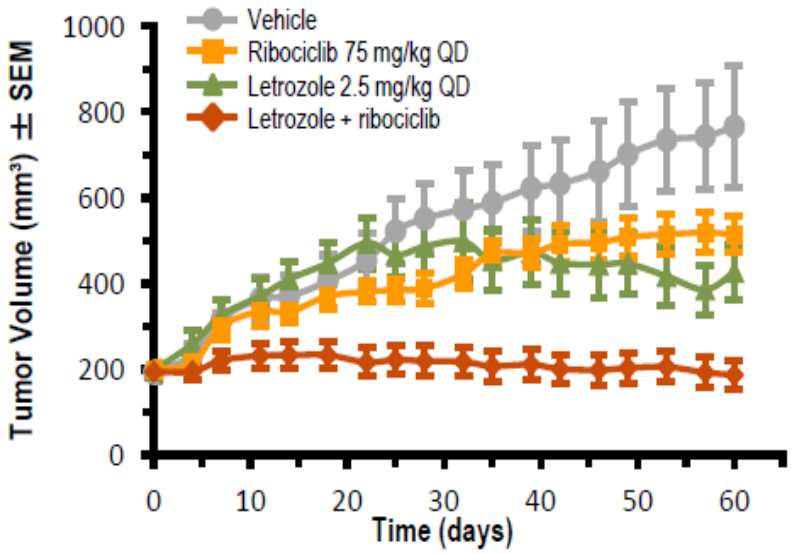
Richard S. Finn, M.D., Miguel Martin, M.D., Hope S. Rugo, M.D., Stephen Jones, M.D., Seock-Ah Im, M.D., Ph.D., Karen Gelmon, M.D., Nadia Harbeck, M.D., Ph.D., Oleg N. Lipatov, M.D., Janice M. Walshe, M.D., Stacy Moulder, M.D., Eric Gauthier, Pharm.D., Ph.D., Dongrui R. Lu, M.Sc., Sophia Randolph, M.D., Ph.D., Véronique Diéras, M.D., and Dennis J. Slamon, M.D., Ph.D.

PALOMA-2

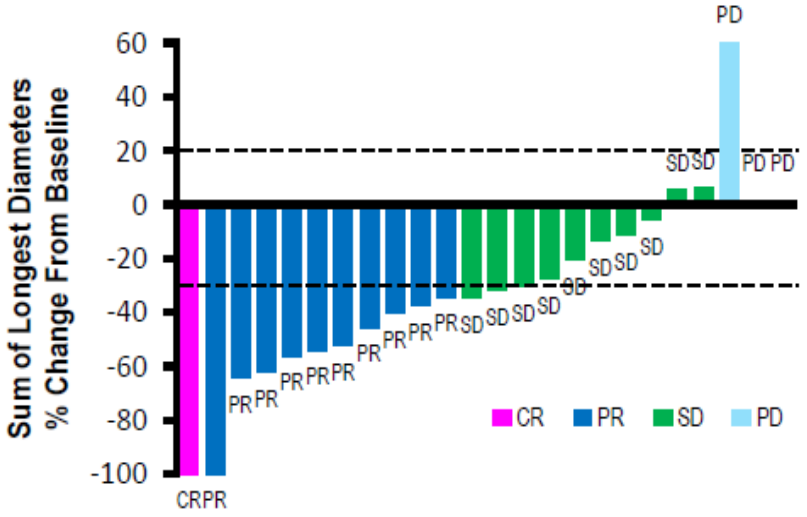


ACTIVITY OF RIBOCICLIB + LETROZOLE IN EARLY STUDIES

Inhibition of tumor growth in ER+ breast cancer xenograft model HBX34[1]



Patients with ER+/HER2– advanced breast cancer; first-line ribociclib + letrozole group[2] (n=24)

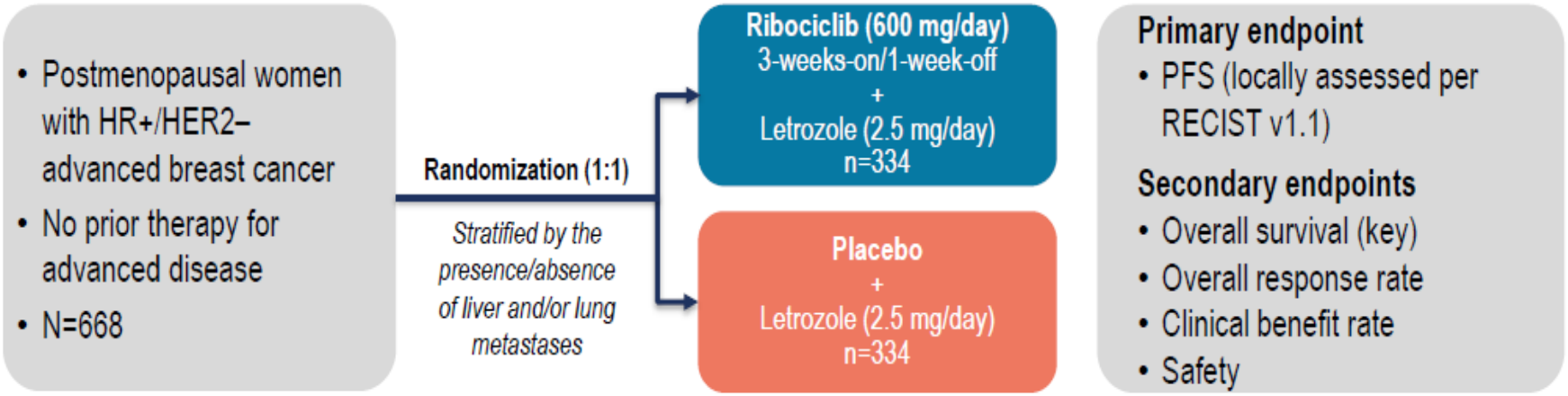


O'Brien NA et al., AACR 2014 (abstr 4756).
Juric D et al., ASCO 2016 (abstr 568).

Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer

G.N. Hortobagyi, S.M. Stemmer, H.A. Burris, Y.-S. Yap, G.S. Sonke, S. Paluch-Shimon, M. Campone, K.L. Blackwell, F. André, E.P. Winer, W. Janni, S. Verma, P. Conte, C.L. Arteaga, D.A. Cameron, K. Petrakova, L.L. Hart, C. Villanueva, A. Chan, E. Jakobsen, A. Nusch, O. Burdaeva, E.-M. Grischke, E. Alba, E. Wist, N. Marschner, A.M. Favret, D. Yardley, T. Bachelot, L.-M. Tseng, S. Blau, F. Xuan, F. Souami, M. Miller, C. Germa, S. Hirawat, and J. O'Shaughnessy

MONALEESA-2



- A prespecified interim analysis was planned after 70% disease progression or death events.
- No treatment crossover was allowed.

Hortobagyi GN et al., NEJM 2016.

KEY ENROLLMENT CRITERIA

Key Inclusion Criteria

- Post-menopausal women with locally advanced or metastatic BC.
- Histologically/cytologically confirmed ER+ and/or PgR+ disease.
- HER2- disease confirmed by in situ hybridization or IHC.
- ≥ 1 measurable lesion (RECIST 1.1) or ≥ 1 predominantly lytic bone lesion.
- ECOG performance status ≤ 1.

Key Exclusion Criteria

- Any prior systemic therapy for advanced/metastatic BC.
- Previous (neo)adjuvant therapy with a nonsteroidal IA, unless a disease-free interval >12 months.
- Inflammatory breast cancer.
- Central nervous system metastases.
- Active cardiac disease or history of cardiac dysfunction (including a QTcF > 450 msec).

Hortobagyi GN et al., NEJM 2016.

PATIENT BASELINE CHARACTERISTICS (1)

Characteristic	Ribociclib Group (N=334)	Placebo Group (N=334)
Median age (range) — yr	62 (23–91)	63 (29–88)
Race — no. (%)†		
White	269 (80.5)	280 (83.8)
Asian	28 (8.4)	23 (6.9)
Black	10 (3.0)	7 (2.1)
Other or unknown	27 (8.1)	24 (7.2)
ECOG performance status — no. (%)		
0	205 (61.4)	202 (60.5)
1	129 (38.6)	132 (39.5)
Disease stage — no. (%)		
III	1 (0.3)	3 (0.9)
IV	333 (99.7)	331 (99.1)
Hormone-receptor status — no. (%)		
Estrogen-receptor positive	332 (99.4)	333 (99.7)
Progesterone-receptor positive	271 (81.1)	278 (83.2)
Disease-free interval — no. (%)		
Newly diagnosed disease	114 (34.1)	113 (33.8)
Existing disease	220 (65.9)	221 (66.2)
≤12 mo	4 (1.2)	10 (3.0)
>12 to ≤24 mo	14 (4.2)	15 (4.5)
>24 mo	202 (60.5)	195 (58.4)
Unknown	0	1 (0.3)

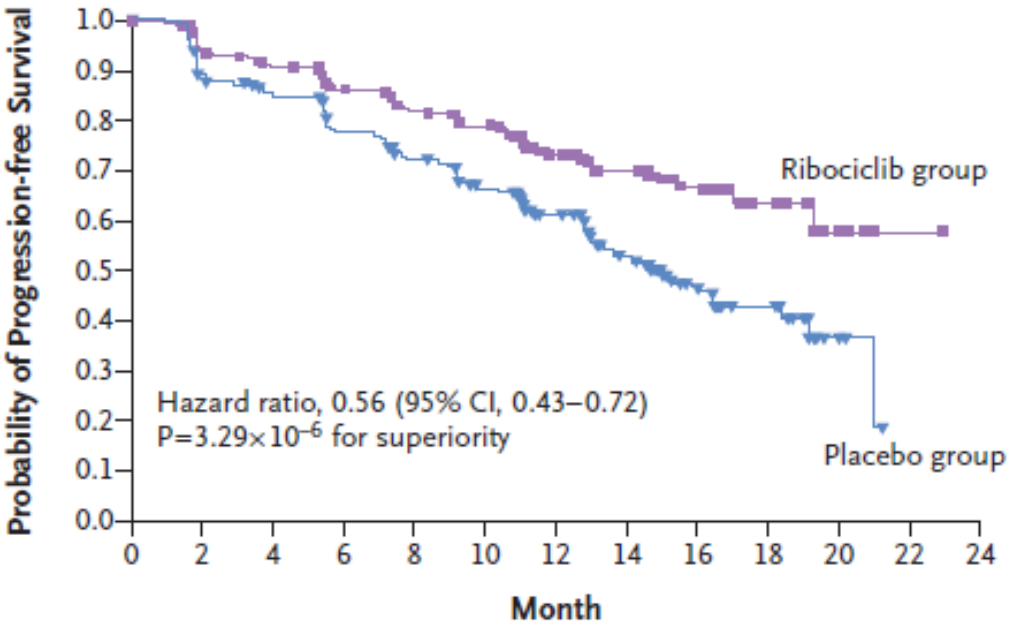
Hortobagyi GN et al., NEJM 2016.

PATIENT BASELINE CHARACTERISTICS (2)

Characteristic	Ribociclib Group (N=334)	Placebo Group (N=334)
Previous treatment — no. (%)‡		
Neoadjuvant or adjuvant chemotherapy	146 (43.7)	145 (43.4)
Neoadjuvant or adjuvant endocrine therapy	175 (52.4)	171 (51.2)
Anastrozole	47 (14.1)	42 (12.6)
Exemestane	19 (5.7)	25 (7.5)
Goserelin	6 (1.8)	3 (0.9)
Letrozole	34 (10.2)	25 (7.5)
Tamoxifen	140 (41.9)	145 (43.4)
Other	2 (0.6)	4 (1.2)
Metastatic sites — no. (%)		
0	2 (0.6)	1 (0.3)
1	100 (29.9)	117 (35.0)
2	118 (35.3)	103 (30.8)
≥3	114 (34.1)	113 (33.8)
Site of metastases — no. (%)		
Breast	8 (2.4)	11 (3.3)
Bone		
Any	246 (73.7)	244 (73.1)
Only	69 (20.7)	78 (23.4)
Visceral§	197 (59.0)	196 (58.7)
Lymph nodes	133 (39.8)	123 (36.8)
Other	35 (10.5)	22 (6.6)

Hortobagyi GN et al., NEJM 2016.

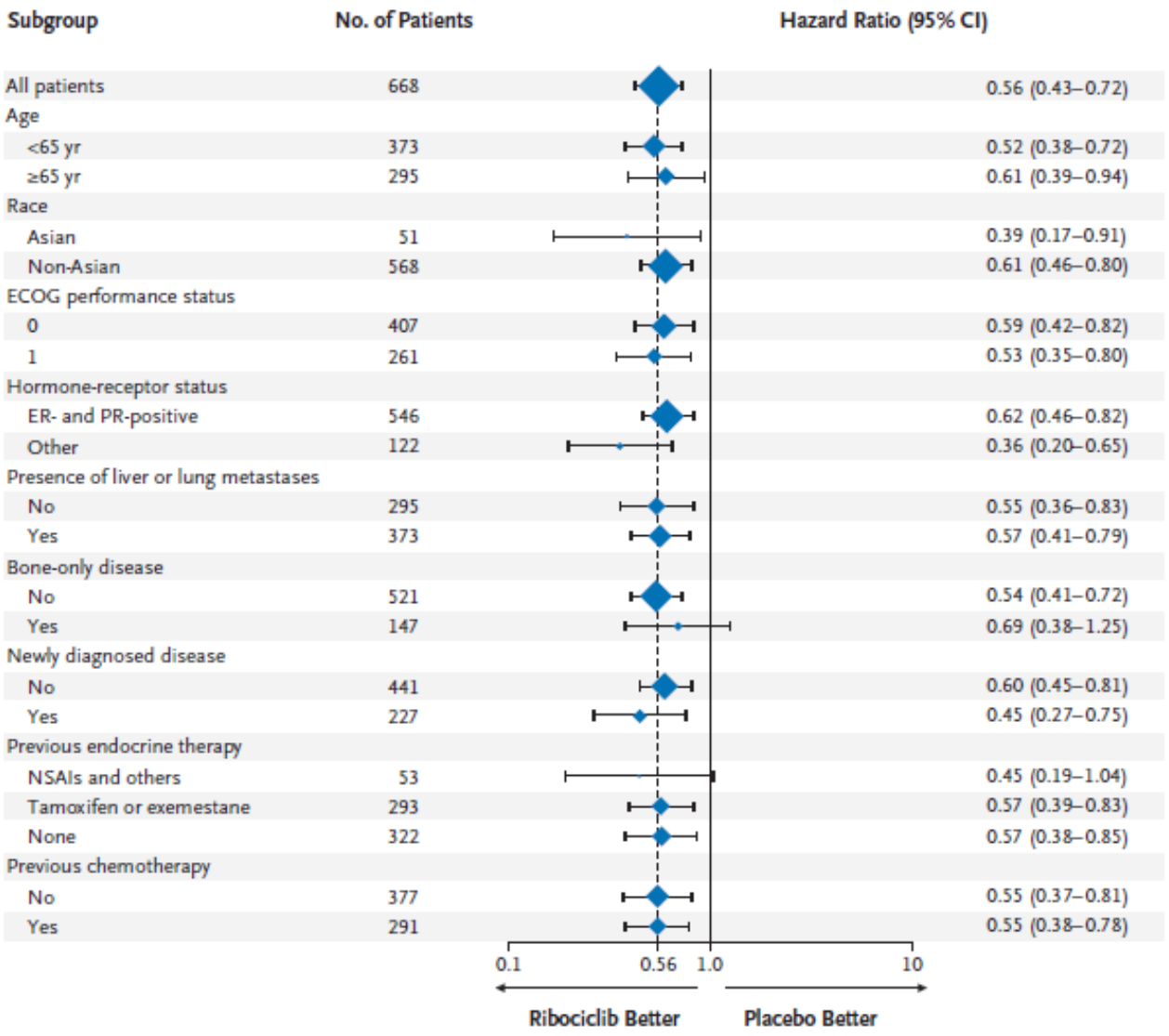
EFFICACY OF RIBOCICLIB + LETROZOLE: PFS



- The median duration of PFS was **NR** in the ribociclib group *vs* **14.7** months in the placebo group [HR 0.56].
- After 18 months, the PFS rate was **63%** (95% CI, 54.6-70.3) in the ribociclib group and **42.2%** (95% CI, 34.8-49.5) in the placebo group.
- OS data were immature at the cut-off data for interim analysis.

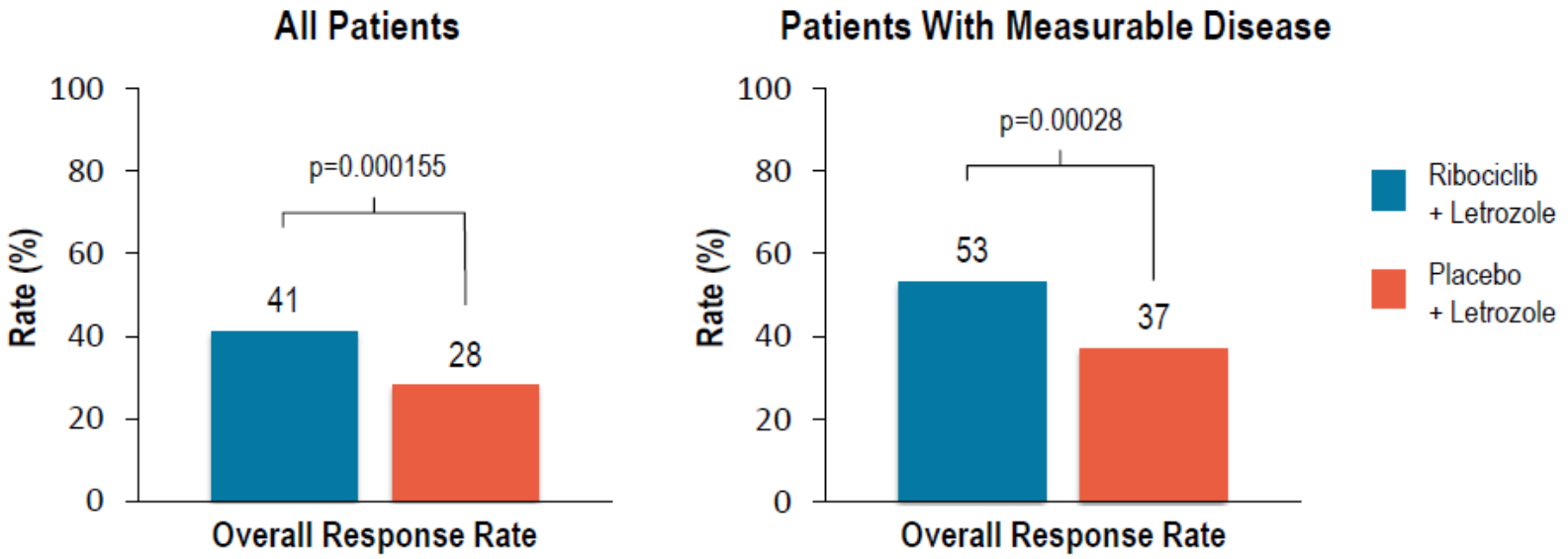
Hortobagyi GN et al., NEJM 2016.

SUBGROUP ANALYSIS OF PFS



Hortobagyi GN et al., NEJM 2016.

ORR



- ORR was **40.7%** in the ribociclib group and **27.5%** in the palcebo group in the ITT population and 55.7% and 37.1%, respectively, among patients with measurable disease at baseline (p<0.001 for both comparisons).

Hortobagyi GN et al., NEJM 2016.

CBR

Response	Ribociclib Group	Placebo Group
All patients — no.	334	334
Confirmed best overall response — no. (%)		
Complete response	9 (2.7)	7 (2.1)
Partial response	127 (38.0)	85 (25.4)
Stable disease	95 (28.4)	111 (33.2)
Neither complete response nor progressive disease*	66 (19.8)	75 (22.5)
Progressive disease	19 (5.7)	40 (12.0)
Unknown	18 (5.4)	16 (4.8)
Overall response†		
No. of patients	136	92
Percentage of patients (95% CI)	40.7 (35.4–46.0)	27.5 (22.8–32.3)
Clinical benefit‡		
No. of patients	266	243
Percentage of patients (95% CI)	79.6 (75.3–84.0)	72.8 (68.0–77.5)
Patients with measurable disease at baseline — no.	256	245
Confirmed best overall response — no. (%)		
Complete response	8 (3.1)	6 (2.4)
Partial response	127 (49.6)	85 (34.7)
Stable disease	95 (37.1)	111 (45.3)
Progressive disease	13 (5.1)	31 (12.7)
Unknown	13 (5.1)	11 (4.5)
Overall response†		
No. of patients	135	91
Percentage of patients (95% CI)	52.7 (46.6–58.9)	37.1 (31.1–43.2)
Clinical benefit§		
No. of patients	205	176
Percentage of patients (95% CI)	80.1 (75.2–85.0)	71.8 (66.2–77.5)

Hortobagyi GN et al., NEJM 2016.

ADVERSE EVENTS

Adverse Event	Ribociclib Group (N=334)			Placebo Group (N=330)†		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	329 (98.5)	221 (66.2)	50 (15.0)	320 (97.0)	105 (31.8)	3 (0.9)
Neutropenia‡	248 (74.3)	166 (49.7)	32 (9.6)	17 (5.2)	3 (0.9)	0
Nausea	172 (51.5)	8 (2.4)	0	94 (28.5)	2 (0.6)	0
Infections	168 (50.3)	12 (3.6)	2 (0.6)	140 (42.4)	7 (2.1)	1 (0.3)
Fatigue	122 (36.5)	7 (2.1)	1 (0.3)	99 (30.0)	3 (0.9)	0
Diarrhea	117 (35.0)	4 (1.2)	0	73 (22.1)	3 (0.9)	0
Alopecia	111 (33.2)	NA	NA	51 (15.5)	NA	NA
Leukopenia	110 (32.9)	66 (19.8)	4 (1.2)	13 (3.9)	2 (0.6)	0
Vomiting	98 (29.3)	12 (3.6)	0	51 (15.5)	3 (0.9)	0
Arthralgia	91 (27.2)	2 (0.6)	1 (0.3)	95 (28.8)	3 (0.9)	0
Constipation	83 (24.9)	4 (1.2)	0	63 (19.1)	0	0
Headache	74 (22.2)	1 (0.3)	0	63 (19.1)	1 (0.3)	0
Hot flush	70 (21.0)	1 (0.3)	0	78 (23.6)	0	0
Back pain	66 (19.8)	7 (2.1)	0	58 (17.6)	1 (0.3)	0
Cough	65 (19.5)	0	NA	59 (17.9)	0	NA
Anemia§	62 (18.6)	3 (0.9)	1 (0.3)	15 (4.5)	4 (1.2)	0
Decreased appetite	62 (18.6)	5 (1.5)	0	50 (15.2)	1 (0.3)	0
Rash	57 (17.1)	2 (0.6)	0	26 (7.9)	0	0
Increased alanine amino-transferase	52 (15.6)	25 (7.5)	6 (1.8)	13 (3.9)	4 (1.2)	0
Increased aspartate amino-transferase	50 (15.0)	16 (4.8)	3 (0.9)	12 (3.6)	4 (1.2)	0

Hortobagyi GN et al., NEJM 2016.

Adverse Event	Ribociclib Group (N=334)			Placebo Group (N=330)†		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	329 (98.5)	221 (66.2)	50 (15.0)	320 (97.0)	105 (31.8)	3 (0.9)
Neutropenia‡	248 (74.3)	166 (49.7)	32 (9.6)	17 (5.2)	3 (0.9)	0
Nausea	172 (51.5)	8 (2.4)	0	94 (28.5)	2 (0.6)	0
Infections	168 (50.3)	12 (3.6)	2 (0.6)	140 (42.4)	7 (2.1)	1 (0.3)
Fatigue	122 (36.5)	7 (2.1)	1 (0.3)	99 (30.0)	3 (0.9)	0
Diarrhea	117 (35.0)	4 (1.2)	0	73 (22.1)	3 (0.9)	0
Alopecia	111 (33.2)	NA	NA	51 (15.5)	NA	NA
Leukopenia	110 (32.9)	66 (19.8)	4 (1.2)	13 (3.9)	2 (0.6)	0
Vomiting	98 (29.3)	12 (3.6)	0	51 (15.5)	3 (0.9)	0
Arthralgia	91 (27.2)	2 (0.6)	1 (0.3)	95 (28.8)	3 (0.9)	0
Constipation	83 (24.9)	4 (1.2)	0	63 (19.1)	0	0
Headache	74 (22.2)	1 (0.3)	0	63 (19.1)	1 (0.3)	0
Hot flush	70 (21.0)	1 (0.3)	0	78 (23.6)	0	0
Back pain	66 (19.8)	7 (2.1)	0	58 (17.6)	1 (0.3)	0
Cough	65 (19.5)	0	NA	59 (17.9)	0	NA
Anemia§	62 (18.6)	3 (0.9)	1 (0.3)	15 (4.5)	4 (1.2)	0
Decreased appetite	62 (18.6)	5 (1.5)	0	50 (15.2)	1 (0.3)	0
Rash	57 (17.1)	2 (0.6)	0	26 (7.9)	0	0
Increased alanine amino-transferase	52 (15.6)	25 (7.5)	6 (1.8)	13 (3.9)	4 (1.2)	0
Increased aspartate amino-transferase	50 (15.0)	16 (4.8)	3 (0.9)	12 (3.6)	4 (1.2)	0

FN occurred in 5 (1.5%) patients in the ribociclib arm *vs* none in the placebo group

Hortobagyi GN et al., NEJM 2016.

TREATMENT EXPOSURE AND DOSE ADJIUSTMENTS

	Ribociclib + Letrozole n=334		Placebo + Letrozole n=330	
	Ribociclib	Letrozole	Placebo	Letrozole
Treatment exposure				
Median duration of exposure, months	12	13	12	12
Median relative dose intensity, %	88	100	100	100
Dose adjustments				
Dose interruptions, n (%)	257 (77)	132 (40)	134 (41)	107 (32)
Dose reductions due to AEs, n (%)	169 (51)	–	14 (4.2)	–

PATIENT DISPOSITION

	Ribociclib + Letrozole n=334	Placebo + Letrozole n=334
Treatment ongoing, n (%)	195 (58)	154 (46)
Treatment discontinued, n (%)	139 (42)	180 (54)
Primary reason for treatment discontinuation, n (%)		
Disease progression	87 (26)	146 (44)
Adverse events	25 (7.5)	7 (2.1)
Patient decision	12 (3.6)	13 (3.9)
Physician decision	10 (3.0)	13 (3.9)
Protocol deviation	3 (0.9)	1 (0.3)
Death	2* (0.6)	0

Hortobagyi GN et al., NEJM 2016.

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Grazie a tutti per l'attenzione

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OUTCOMES

• ***Importanti ed essenziali*** - PFS - (OS) - ORR - CBR	***(9-7)***
• ***Importanti ma non essenziali*** - Neutropenia G3/4 - Neutropenia febbrile - Ipertransaminasemia	***(6-4)***
• ***Non importanti*** - Nausea - Diarrea	***(3-1)***