- **QUESITO 2**

Nelle pazienti postmenopausa con carcinoma mammario HR èositivo/HER2 negativo è opportuno considerare un trattamento ormonale di 1° linea con Ribociclib + letrozolo rispetto al letrozolo?

LE PROBLEMATICHE

Maria Vittoria Dieci

The NEW ENGLAND JOURNAL of MEDICINE 2016

ORIGINAL ARTICLE

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

- **CONFIDENCE**
- **DIRECTNESS**
- **RELEVANCE**

CONFIDENCE - Selection Bias

- method used for randomization and allocation concealment not specified (link to protocol/full text at NEJM.org)

without food.[20] Randomization was stratified according to the presence or absence of liver or lung metastases. Patients received treatment until

STUDY OVERSIGHT

The trial protocol and statistical analysis plan are available with the full text of this article at NEJM.org. Any modifications were approved by an

CONFIDENCE - Selection Bias

- Baseline characteristics were well balanced between the two groups

	Ribo+Let (n=334)	Plac+Let (n=334)
Age, median (range)	62 (23-91)	63 (29-88)
White **Asian** **Black** **Other/UK**	269 (80.5%) 28 (8.4%) 10 (3%) 27 (8.1%)	280 (83.8%) 23 (6.9%) 7 (2.1%) 24 (7.2%)
ECOG 0 **ECOG 1**	205 (61.4%) 129 (38.6%)	202 (60.5%) 132 (39.5%)
Stage III **Stage IV**	1 (0.3%) 333 (99.7%)	3 (0.9%) 278 (83.25)
ER+ **PgR+**	332 (99.4%) 271 (81.1%)	333 (99.7%) 278 (83.25)

	Ribo+Let (n=334)	Plac+Let (n=334)
Disease-free interval		
Newly metastatic disease	114 (34.1%)	113 (33.8%)
Existing disease	220 (65.9%)	221 (66.2%)
≤12 m	4 (1.2%)	10 (3%)
12-24m	14 (4.2%)	15 (4.5%)
>12 m	202 (60.5%)	195 (58.4%)
Prior neo-/adj CT	146 (43.7%)	145 (43.4%)
Prior neo-/adj HT	175 (52.4%)	171 (51.2%)
AI	100 (30%)	92 (27%)
Tam	140 (42%)	145 (43%)
Metastatic sites		
0	2 (0.6%)	1 (0.3%)
1	100 (29.9%)	117 (35%)
2	118 (35.3%)	103 (30.8%)
≥3	114 (34.1%)	113 (33.8%)
Site of metastasis		
Breast	8 (2.4%)	11 (3.3%)
Bone, any	246 (73.7%)	244 (73.1%)
Bone, only	69 (20.7%)	78 (23.4%)
Visceral	197 (59%)	196 (58.7%)
Lymph nodes	133 (39.8%)	123 (36.8%)
Other	35 (10.5%)	22 (6.6%)

CONFIDENCE - Performance Bias

- Placebo-controlled
- Double-blind

STUDY DESIGN

In this randomized, double-blind, placebo-controlled, phase 3 trial conducted in 29 countries, patients at 223 trial centers were randomly assigned to receive either oral ribociclib (600 mg per day on a 3-weeks-on, 1-week-off schedule in 28-day treatment cycles) plus letrozole (2.5 mg per day on a continuous schedule) or placebo plus letrozole. We selected the ribociclib dose of

Detection Bias

- Primary endpoint was locally assessed PFS as per RECIST 1.1. Shedule of assessment was the same for both groups.

ASSESSMENTS

Tumor assessments (computed tomography or magnetic resonance imaging) were performed at screening, every 8 weeks during the first 18 months, every 12 weeks thereafter until disease progression (including in patients who discontinued treatment for reasons other than progressive disease), and at the end of treatment. An

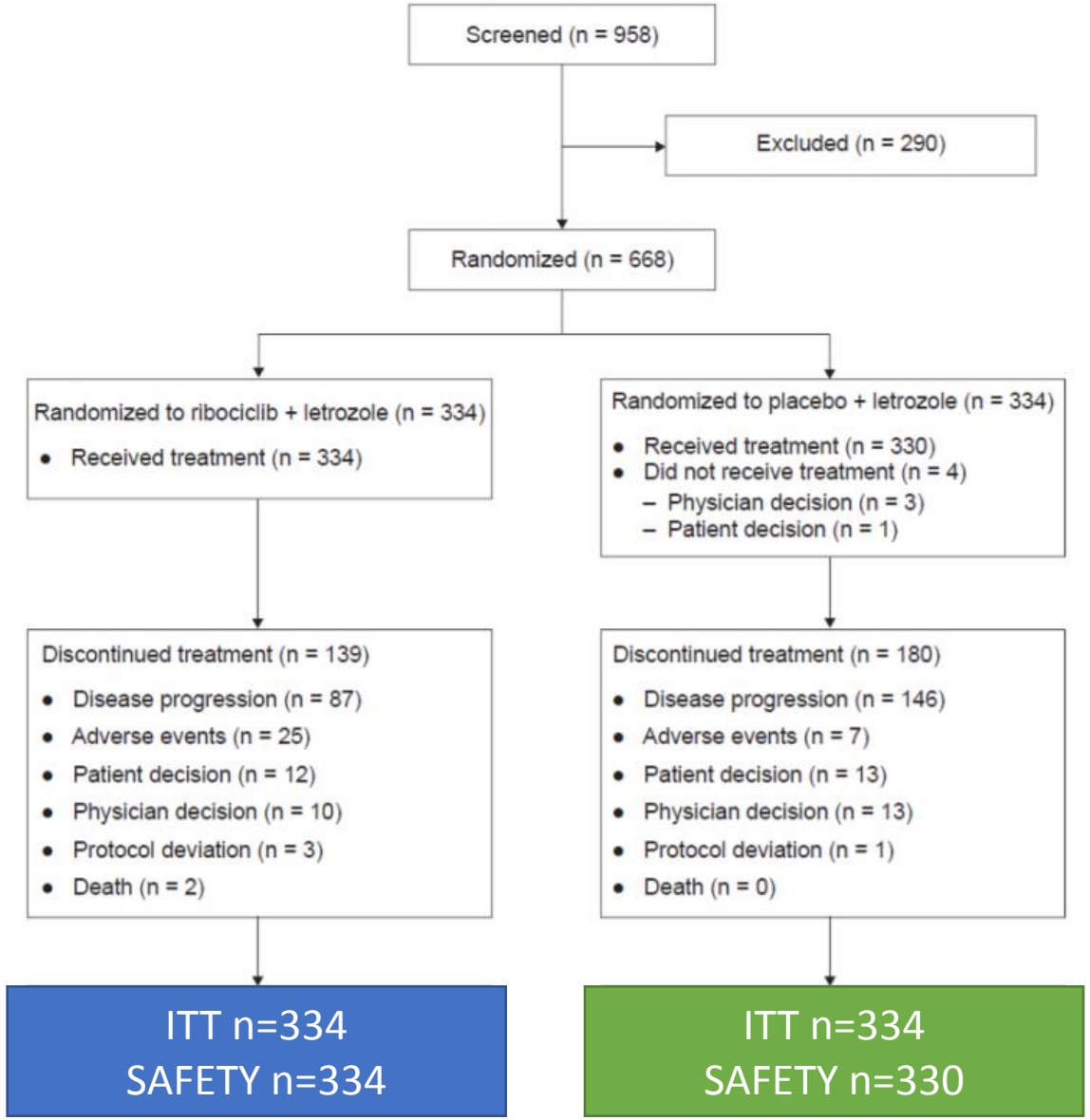
CONFIDENCE - Detection Bias

- Investigators were kept blind to participants' exposure to intervention. However, specific AEs related to the intervention (i.e. neutropenia) might have altered the blinding.

- An independent review committee whose members were unaware of treatment assignments prospectively reviewed all imaging data.

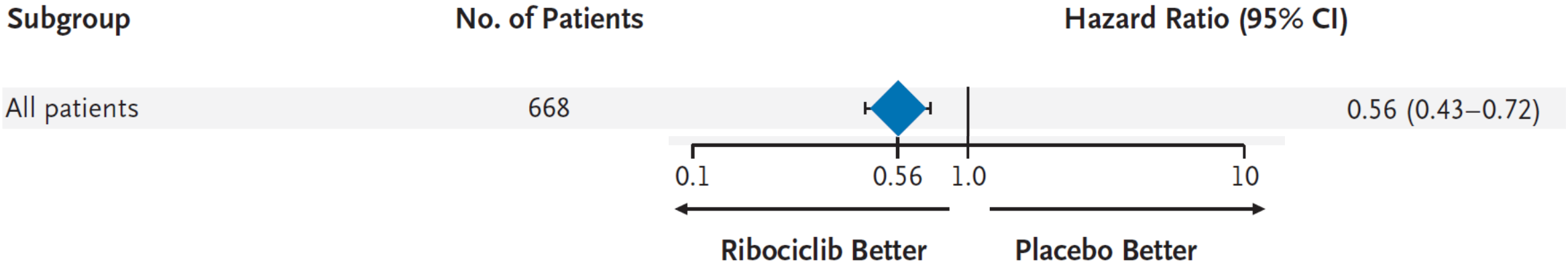
CONFIDENCE - Attrition bias

- No Attrition bias



CONFIDENCE - Precision

- Pre-specified interim analysis planned after PD or death observed in 211 patients (70% of total events)→ superiority of ribociclib+letrozole HR 0.56 or less with $p<1.29x10^{-5}$.
- Interim analysis triggered at 211 events but at the time of data cut-off 243 pts had events.



DIRECTNESS

- **POPULATION**
- INTERVENTION
- **COMPARATOR**
- **OUTCOME**

DIRECTNESS - Population

- Selected according to cardiac performance (multiple cardiac testing before study)

Supplementary Methods

Patient exclusion criteria – cardiac disease or cardiac dysfunction

Patients with active cardiac disease or a history of cardiac dysfunction were excluded from the study:

- History of angina pectoris, symptomatic pericarditis, or myocardial infarction within 12 months prior to study entry
- History of documented congestive heart failure (New York Heart Association functional classification III–IV)
- Documented cardiomyopathy
- Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated Acquisition (MUGA) scan or echocardiogram (ECHO)
- History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality in the previous 12 months
- On screening, any of the following cardiac parameters: bradycardia (heart rate < 50 at rest), tachycardia (heart rate >90 at rest), PR interval >220 msec, QRS interval >109 msec, or QTcF >450 msec
- Systolic blood pressure >160 or <90 mmHg

DIRECTNESS - Population

- Endocrine sensitive population (most of the patients were ET naive or relapsed >24 months after the end of adjuvant ET)

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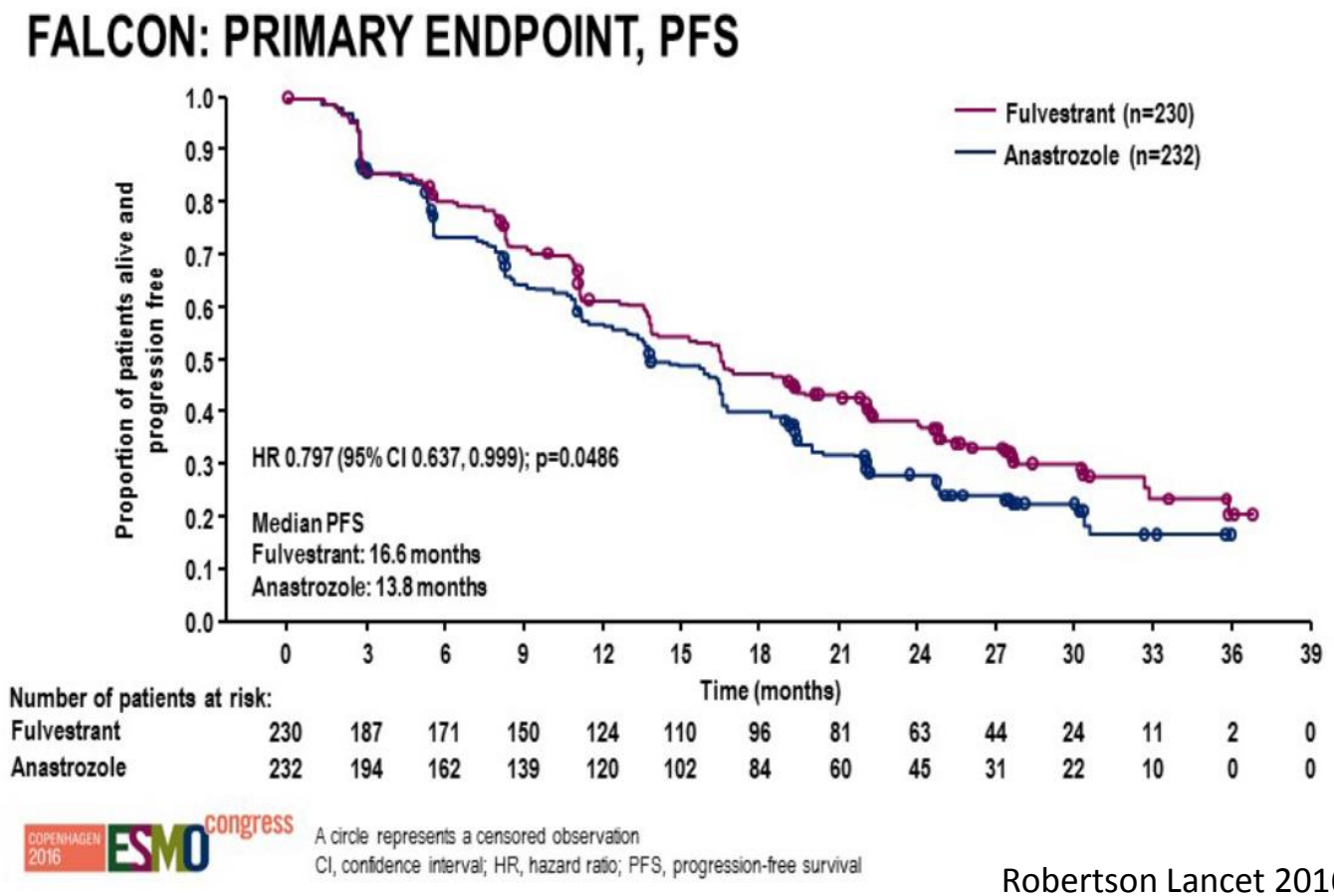
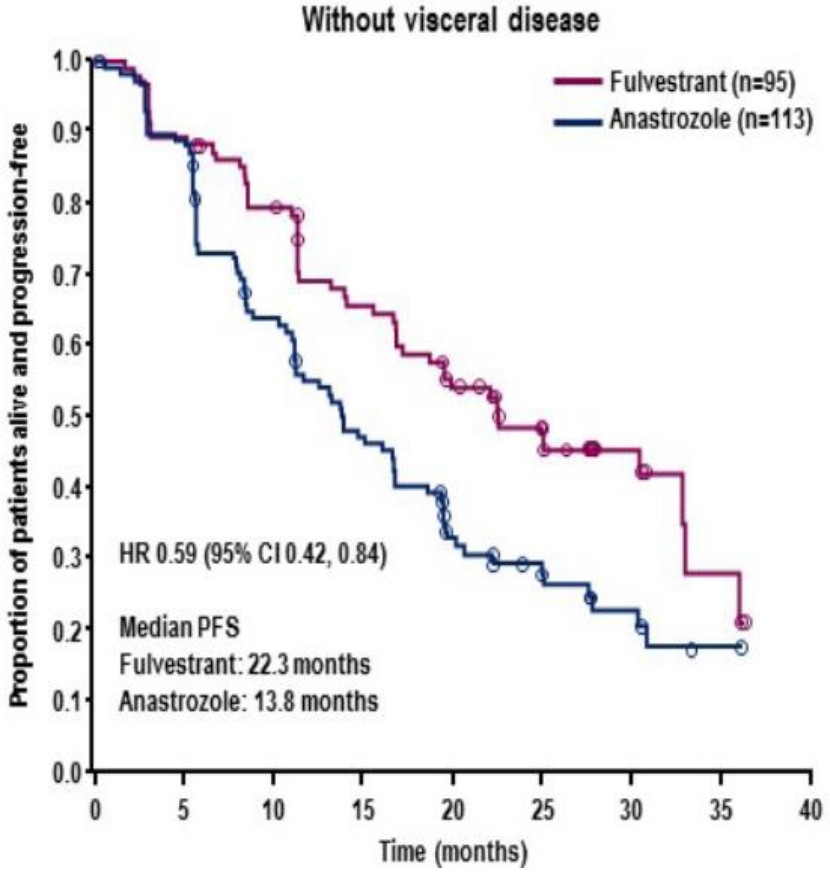
- No stratification based on previous ET.

DIRECTNESS - Comparator

- In light of actual evidence, probably fulvestrant is a better comparator than AI, mainly for ET-naive patients (52% of the MONALEESA-2 population) without visceral disease.





Robertson Lancet 2016

DIRECTNESS - Outcome

- Some secondary outcomes were not reported, limiting a full benefit/risk assessment.

- **Primary outcome**
  - **PFS**
- **Secondary outcomes**
  - **OS**
  - **ORR, CBR**
  - **Safety**
  - **QoL**

	MONALEESA-2			
	Ribo+Let		Plac+Let	
	Any G %	G≥3 %	Any G %	G≥3 %
Any AE	99	81	97	33
Neutropenia	74	59	5	1
Febrile neutropenia	2	--	0	--
Anemia	19	1	5	1
Thrombocytopenia	9	1	1	0
Fatigue	37	3	30	1
Nausea	52	2	29	1
Vomiting	29	4	16	1
Diarrhea	35	1	22	1
Arthralgia	27	1	29	1
Alopecia	33	NA	16	NA
Rash	17	1	8	0
ALT increase	16	9	4	1

RELEVANCE

- Effect size: HR 0.56 (95%CI 0.43-0.72)

- Median PFS 14.7 months in the control arm vs >24 months (median not reached) in the experimental arm: Delta PFS → 10 months