con il Patrocinio di

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RAO

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Sacro Cuore Don Calabria
Cancer Care Center
Negrar - Verona

ESMO
Designated Centers of Integrated Oncology and Palliative Care

7ª edizione

Progetto CANOA

CARCINOMA MAMMARIO:

QUALI NOVITA' PER IL 2017?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

Coordinatori scientifici:
Stefania Gori
Giovanni L. Pappagallo

Ospedaletto di Pescantina (VR) 31 Marzo / 1 Aprile 2017
Villa Quaranta Park Hotel

PROGRAMMA

3- QUESITO CLINICO

Nelle pazienti con carcinoma mammario HR positivo/HER2 negativo in post-menopausa è opportuno considerare un trattamento ormonale con Fulvestrant rispetto ad AI?

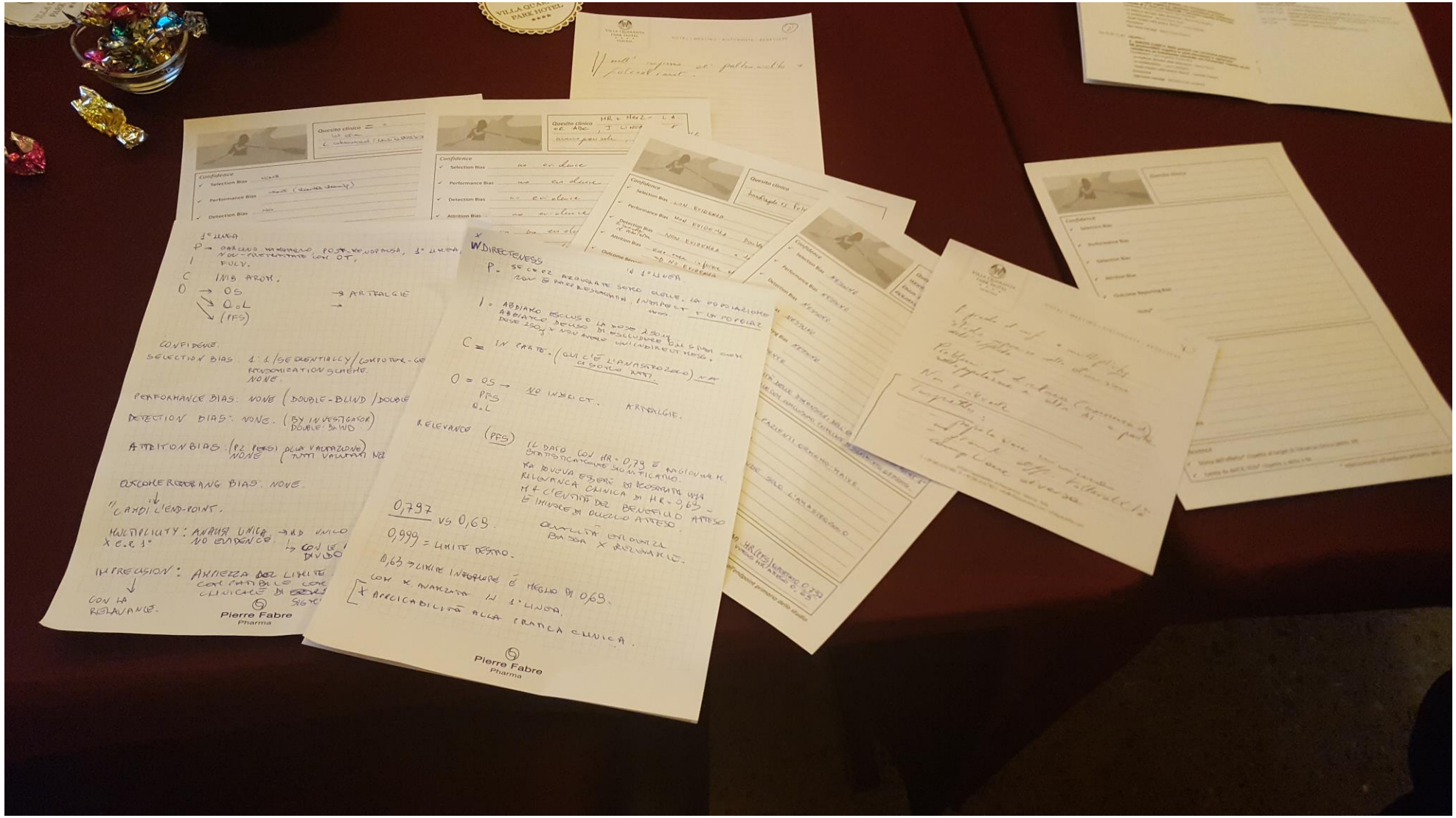
Coordinatori
Catia Angiolini, Giovanni L. Pappagallo alias "Gigi"

-Le evidenze derivanti dalla letteratura – Marta Pestrin

-Le problematiche – Luisa Carbognin

-Quale impatto nella pratica clinica? – Gabriele Zoppoli

Lavoro di gruppo….prima



Lavoro di gruppo….dopo!

Quesito clinico NELLE PAZIENTI CON CARCINOMA MAMMARIO HR POSITIVO/HER2 NEGATIVO IN POST-MENO PAUSA È OPPORTUNO CONSIDERARE UN TRATTAMENTO ORMONALE CON FULVESTRANT RISPETTO A D. A.I.?

Confidence

- ✓ Selection Bias: NESSUNO
- ✓ Performance Bias: NESSUNO
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- ✓ Outcome Reporting Bias: NESSUNO
- ✓ Multiplicity*: ASSENTE
- ✓ Imprecision*: VARIABILITÀ DELLE DIMENSIONI DELL'EFFETTO DELL'END-POINT 1° È COMPATIBILE CON CONCLUSIONI CLINICHE DI SIGNIFICATO OPPOSTO

Directness

- ✓ Population: INCLUSIONE DI PAZIENTI ORMONO-NAIVE.
- ✓ Intervention: NO INDIRECTNESS
- ✓ Comparator: IL COMPARATOR INCLUDE SOLO L'ANASTROZOLO
- ✓ Outcome: NO INDIRECTNESS

Relevance

- ✓ Stima dell'effetto* rispetto al target di rilevanza clinica (*delta, M*): HR (PFS) RIPORTATO 0,797 VERSUS HR ATTESO 0,69
- ✓ Limite dx dell'IC 95%* rispetto a *delta* o M: 0,999

** relativamente all'endpoint primario dello studio*

Grade e Pico

Nelle pazienti con carcinoma mammario HR positivo/HER2 negativo in post-menopausa è opportuno considerare un trattamento ormonale con Fulvestrant rispetto ad AI?

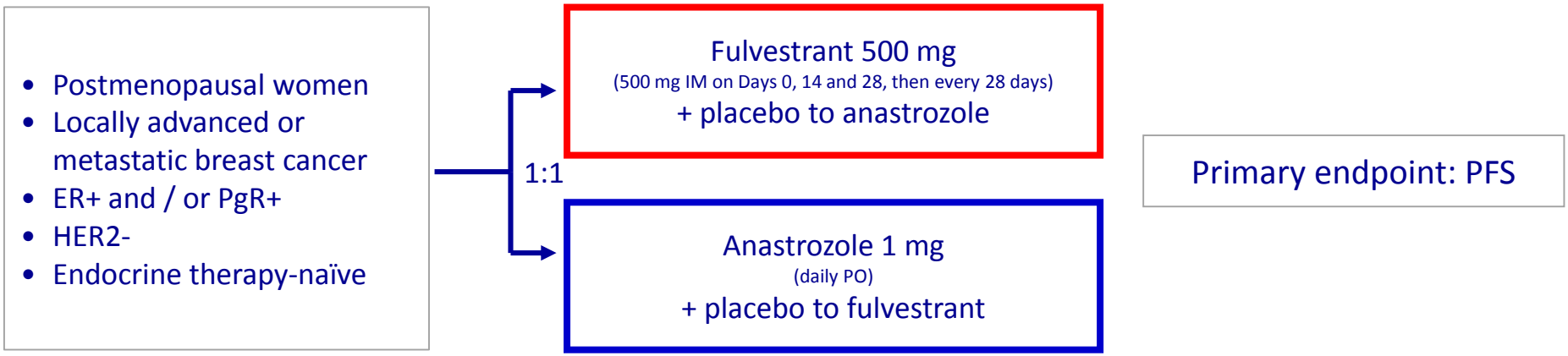
P.
Pz in post-menopausa affette da ca. mammario HR+/HER2 – *localmente avanzato o metastatico*
I.
Fulvestrant HD
C.
Inibitori delle aromatasi
O.
OS, PFS, QoL

Relevant studies addressing our question

Study	Phase	Setting	Comparator	Primary end-point
0025[#] JCO 2004	III	First line for post-m HR+ ABC pts	Tamoxifen	TTP 6.8 vs 8.3 m (HR: 1.18; 95% CI, 0.98 - 1.44; P 0 .088)
0020[#] JCO 2002	III	post-m HR+ mBC pts progressed after adjv. HT or after first-line HT	Anastrazole	TTP F was as effective as A (HR: 0.98; CI, 0.80 - 1.21; P 0 .84)
0021[#] JCO 2002	III	post-m HR+ mBC pts progressed after adjv. HT or after first-line HT	Anastrazole	TTP F was as effective as A (HR: 0.92; CI, 0.74-1.14; P 0 .43)
EFECT[#] JCO 2008	III	post-m HR+ mBC pts progressing or recurring after nonsteroidal AI	Exemestane	TTP Median TTP was 3.7 m for F and E (HR: 0.96;95% CI, 0.82 -1.13; P = .6)
FIRST[*] JCO 2009	II	First line for post-m HR+ ABC pts	Anastrazole	CBR 72.5% v 67.0% (odds ratio, 1.30; 95% CI, 0.72 to 2.38; P= .386)
FALCON[*] Lancet 2016	III	Hormonal treatment naïve post-m HR+ mBC pts	Anastrazole	PFS

[#]LD Fulvestrant: [*]HD Fulvestrant

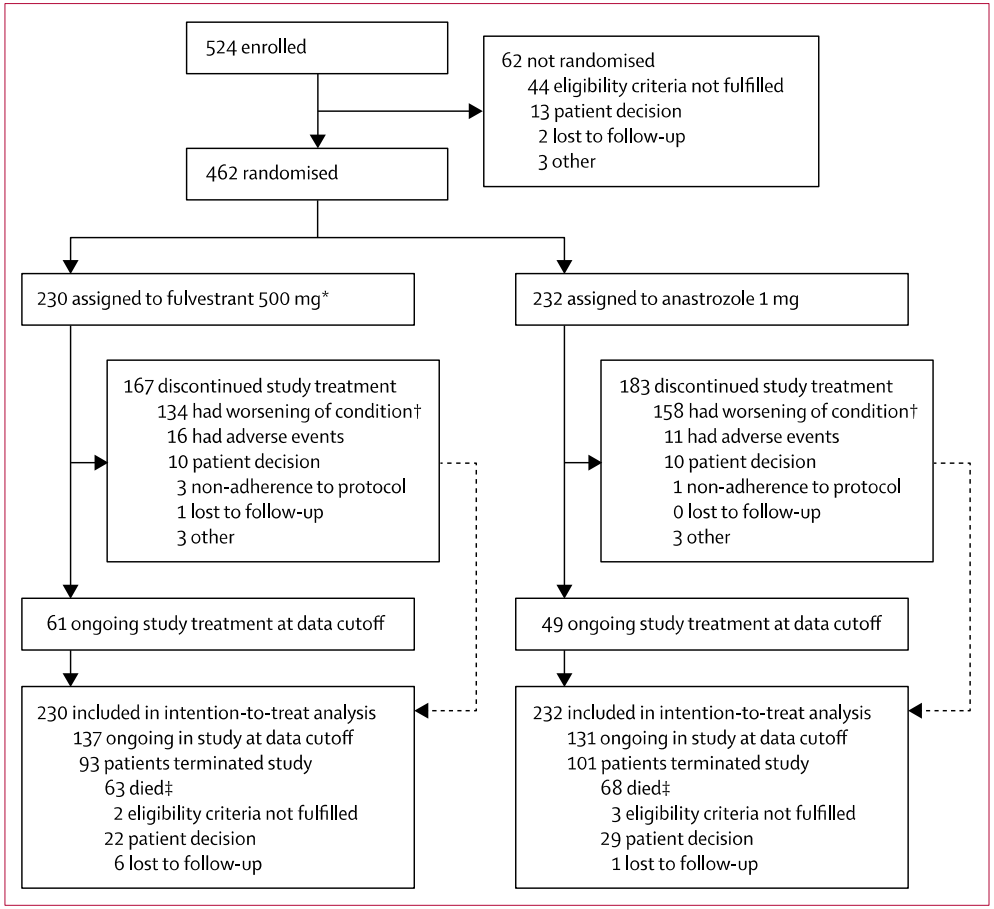
FALCON trial



- Randomised, double-blind, double-dummy, international, multicentre phase III study
- Follow-up for disease progression and survival
- Randomisation of 450 patients was planned to achieve 306 progression events; if the true PFS HR was 0.69 this would provide 90% power for statistical significance at the 5% two-sided level (log-rank test). A progression-free survival HR of 0·80 would deliver a statistically significant difference for the primary outcome.
- Stratification factors: prior chemotherapy for advanced disease (yes / no); measurable vs. non-measurable disease (at baseline); locally advanced vs. metastatic disease
- Subgroup analysis of PFS for pre-defined baseline covariates

Robertson, Lancet 2016

Consort Diagram and patient characteristics



	Fulvestrant 500 mg (n=230)	Anastrozole 1 mg (n=232)
Age (years)	64·0 (38–87)	62·0 (36–90)
Patients aged ≥65 years	108 (47%)	91 (39%)
Race		
White	175 (76%)	174 (75%)
Asian	36 (16%)	34 (15%)
Black or other	19 (8%)	24 (10%)
Time from diagnosis of breast cancer to randomisation		
≤2 months	102 (44%)	99 (43%)
>2 months to ≤1 year	58 (25%)	66 (28%)
>1 year	70 (30%)	67 (29%)
Receptor status		
Oestrogen receptor positive, progesterone receptor positive	175 (76%)	179 (77%)
Oestrogen receptor positive, progesterone receptor negative	44 (19%)	43 (19%)
Oestrogen receptor positive, progesterone receptor unknown	10 (4%)	7 (3%)
Oestrogen receptor negative, progesterone receptor positive	1 (<1%)	3 (1%)
Oestrogen receptor negative, progesterone receptor negative	0	0
Human epidermal growth factor receptor status		
Positive	0	1 (<1%)
Negative	230 (100%)	231 (100%)
WHO performance status*		
0	117 (51%)	115 (50%)
1	106 (46%)	105 (45%)
2	7 (3%)	12 (5%)

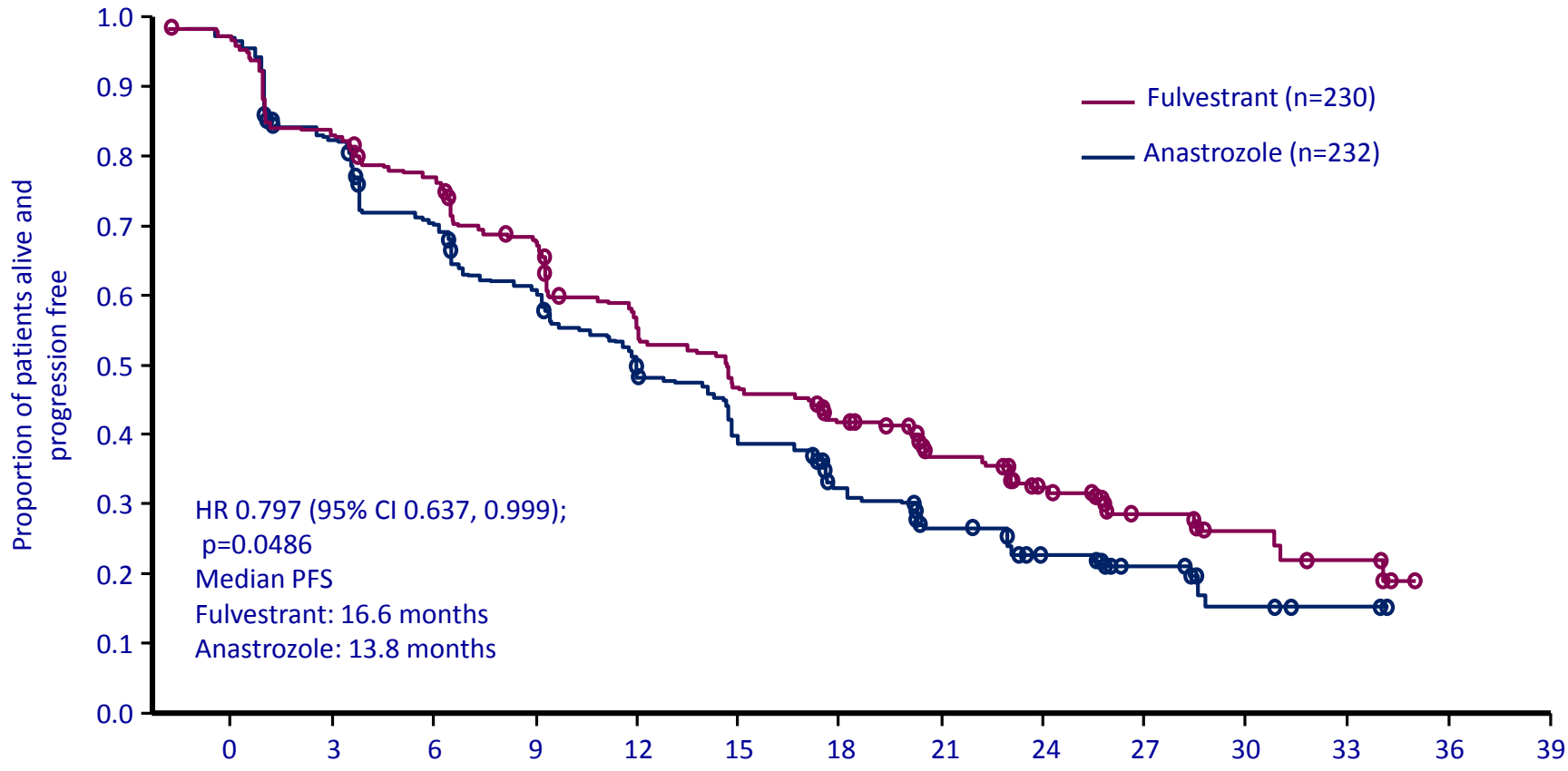
(Table 1 continues in next column)

	Fulvestrant 500 mg (n=230)	Anastrozole 1 mg (n=232)
(Table continued from previous column)		
Disease stage		
Locally advanced	28 (12%)	32 (14%)
Metastatic	202 (88%)	200 (86%)
Site of disease		
Visceral disease†	135 (59%)	119 (51%)
Bone or musculoskeletal only	24 (10%)	24 (10%)
Breast only	3 (1%)	2 (1%)
Skin or soft tissue only	8 (3%)	6 (3%)
Other non-visceral	60 (26%)	81 (35%)
Measurable disease	193 (84%)	196 (84%)
Previous treatment‡		
Chemotherapy		
Locally advanced or metastatic breast cancer§	36 (16%)	43 (19%)
Adjuvant	35 (15%)	27 (12%)
Neoadjuvant	11 (5%)	16 (7%)
Radiotherapy	53 (23%)	50 (22%)
Immunotherapy	0	0
Hormonal therapy	2 (1%)	1 (<1%)

Data are median (range) and n (%). *For WHO performance status, 0 represents normal activity, 1 represents restricted activity, and 2 represents being in bed 50% of the time or less. †Includes patients with site of baseline disease as any of the following: adrenal, bladder, CNS, oesophagus, liver, lung, peritoneum, pleura, renal, small bowel, stomach, pancreas, thyroid, colon, rectal, ovary, biliary tract, ascites, pericardial effusion, spleen, or pleural effusion. ‡Previous enrolment categories are not mutually exclusive. §Includes first-line, second-line, third-line, metastatic, and palliative chemotherapies (two patients were reported as deviations for having received second-line chemotherapy and one patient was reported in error to have received three previous lines of chemotherapy).

Table 1: **Patient baseline demographics and disease characteristics of the intention-to-treat population**

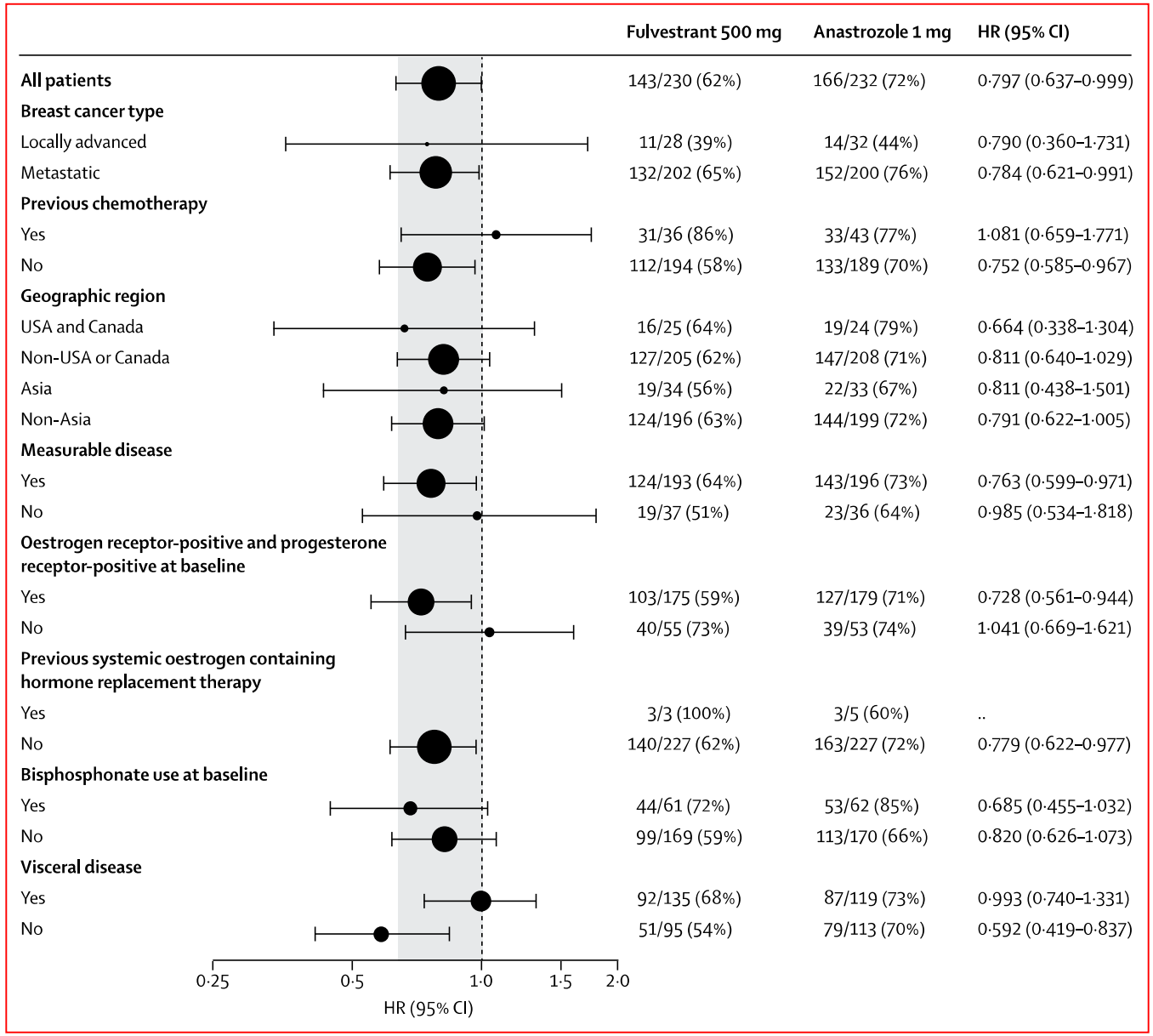
The Falcon trial: PFS results



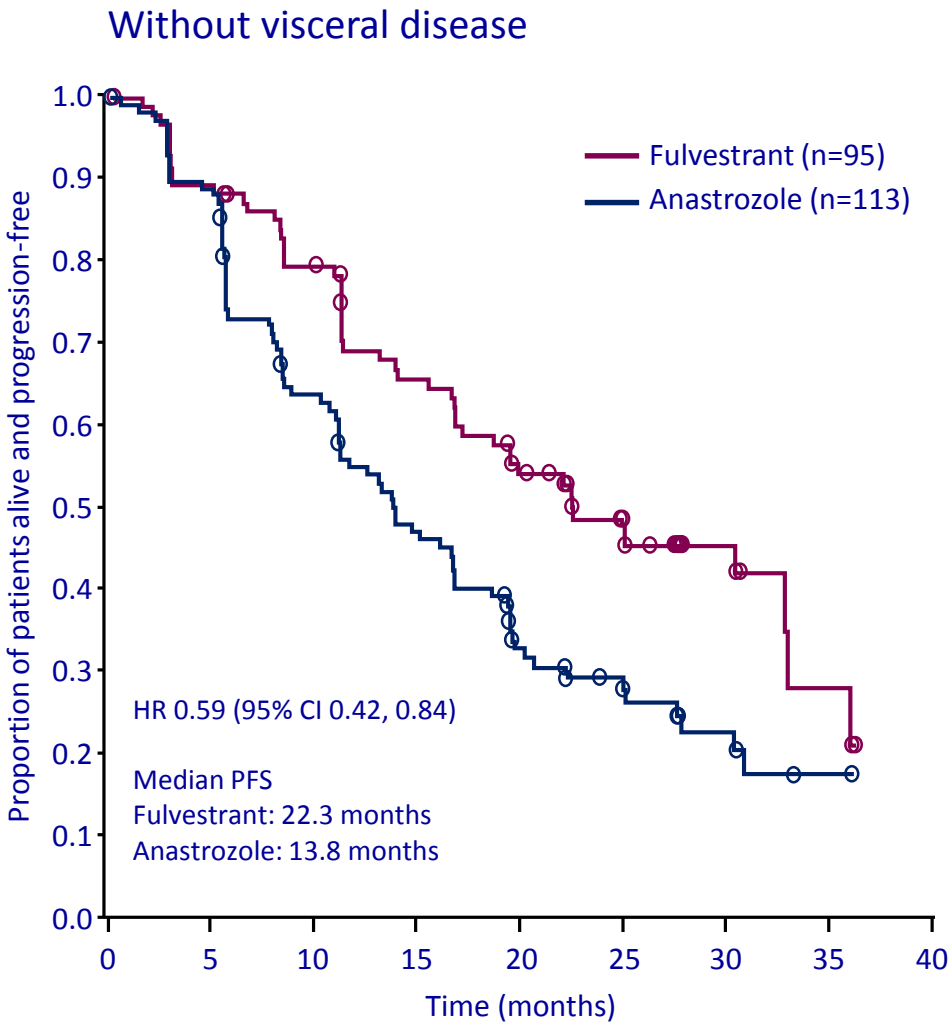
Number of patients at risk:														
Fulvestrant	230	187	171	150	124	110	96	81	63	44	24	11	2	0
Anastrozole	232	194	162	139	120	102	84	60	45	31	22	10	0	0

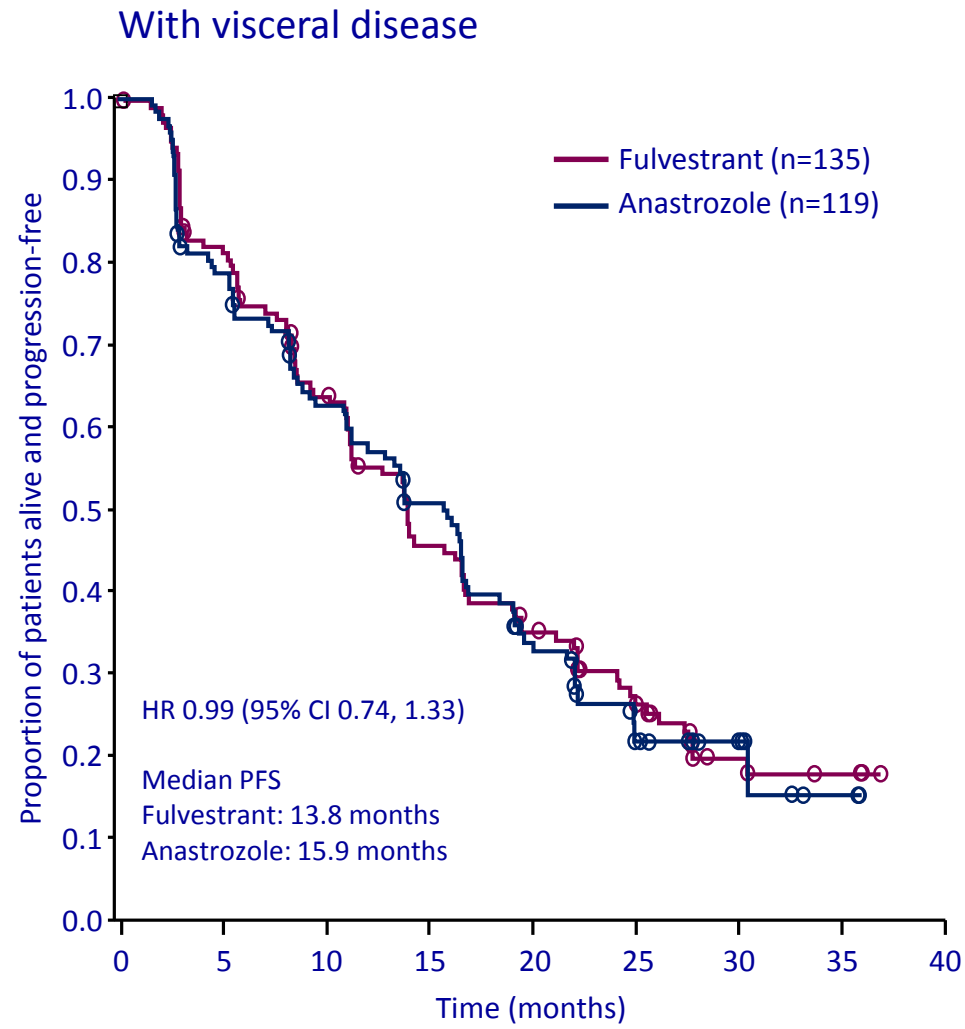
Robertson, Lancet 2016

Forest plot of PFS in patient subgroups



The Falcon trial: PFS results by visceral status





Robertson, Lancet 2016

The Falcon trial: adverse events and QoL

	Fulvestrant 500 mg (n=228)	Anastrozole 1 mg (n=232)
Patients with any adverse event	166 (73%)	173 (75%)
Arthralgia	38 (17%)	24 (10%)
Hot flush	26 (11%)	24 (10%)
Fatigue	26 (11%)	16 (7%)
Nausea	24 (11%)	24 (10%)
Back pain	21 (9%)	14 (6%)
Alanine aminotransferase increased	16 (7%)	7 (3%)
Myalgia	16 (7%)	8 (3%)
Hypertension	15 (7%)	21 (9%)
Insomnia	15 (7%)	13 (6%)
Diarrhoea	14 (6%)	13 (6%)
Constipation	13 (6%)	11 (5%)
Pain in extremity	13 (6%)	10 (4%)
Aspartate aminotransferase increased	12 (5%)	8 (3%)
Cough	12 (5%)	8 (3%)
Anaemia	9 (4%)	20 (9%)
Dyspnoea	9 (4%)	13 (6%)
Oedema peripheral	9 (4%)	13 (6%)

Data are n (%). Adverse events were graded according to Common Terminology Criteria for Adverse Events version 4.0.

Table 3: **Adverse events with a frequency of more than 5% in any treatment group irrespective of causality in the safety analysis population**

- Mean FACT-B and Trial Outcome Index scores were maintained and similar in both treatment groups
- Time to deterioration did not differ significantly between treatment groups for both TOI score and FACT-B total score

Robertson, Lancet 2016

Quality of trial

Confidence

- ✓ Selection Bias NESSUNO
- ✓ Performance Bias NESSUNO
- ✓ Detection Bias NESSUNO
- ✓ Attrition Bias NESSUNO
- ✓ Outcome Reporting Bias NESSUNO
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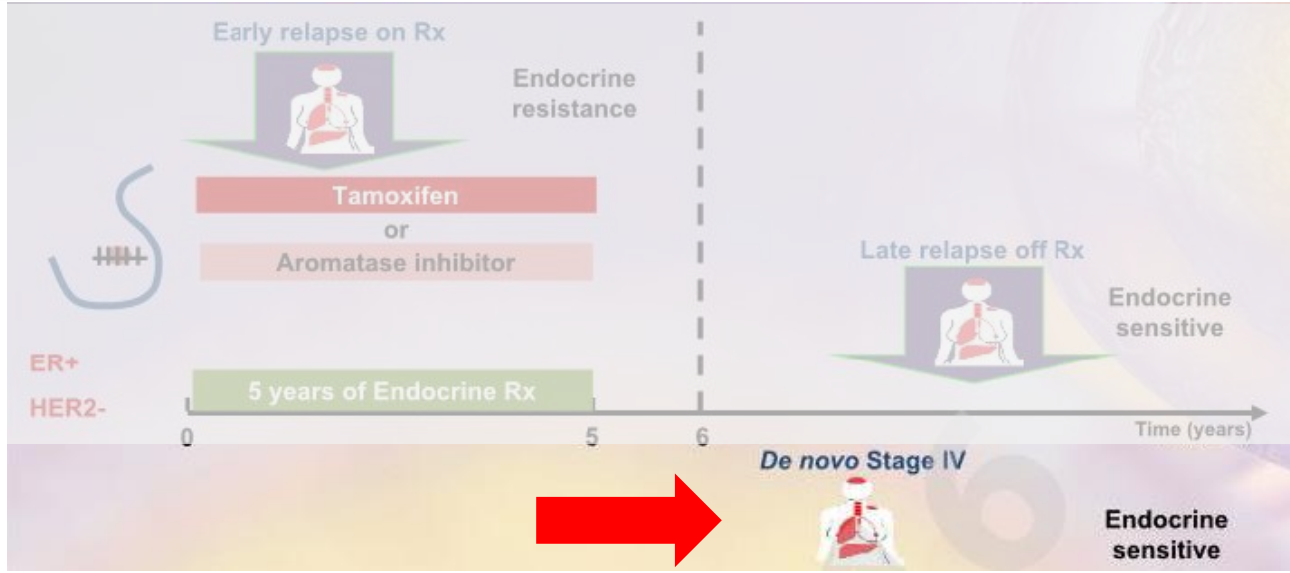
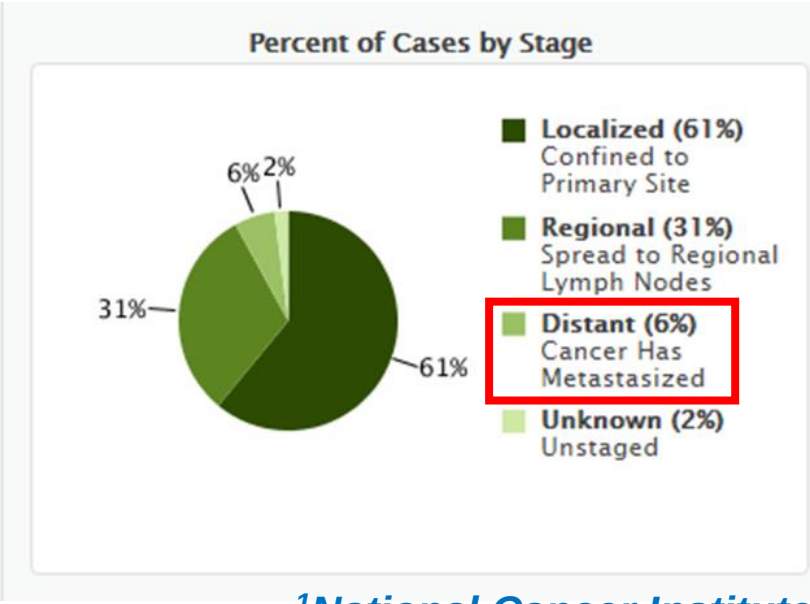
De Novo Stage IV in real life





SEER 2006-2012[1]:

~6% *De Novo* Stage IV

AIOM-AIRTUM 2016[2]:

~ 20,000 new *De Novo* Stage IV cases in 2016

[1]*National Cancer Institute. SEER stat fact sheet. Accessed March 26, 2017*

[2]**AIOM-AIRTUM: i numeri del cancro in Italia 2016**

De Novo Stage IV in recent 1st-Line Phase III Trials

	MONALEESA-2 (n=668)	PALOMA-2 (n=666)	SWOG-0226 (n=707)	FALCON (n=462)
Disease Free Interval				
De Novo MBC	34 %	34 %	39%	LABC 18 %
< 12 mo	2 %	22 %	nil	MBC 87 %
> 12 mo	64 %	42 %	(> 10 yr) 28%	
Prior Treatment				
Adjuvant Endocrine Rx	52 %	56 %	40 %	nil
Adjuvant Chemotherapy	37 %	NR	33 %	19 %
Chemotherapy for MBC	nil	nil	nil	17 %
Site of Disease				
Visceral	59 %	49 %	54 %	55 %
Bone only	22 %	22 %	22 %	NR
Median PFS for AI (control arm) (95 % CI)	14.7 mo (13.0 – 16.5)	14.5 mo (12.9 - 17.1)	13.5 mo (12.1 – 15.1)	13.8 mo (NR)

Johnston S, ESMO 2016

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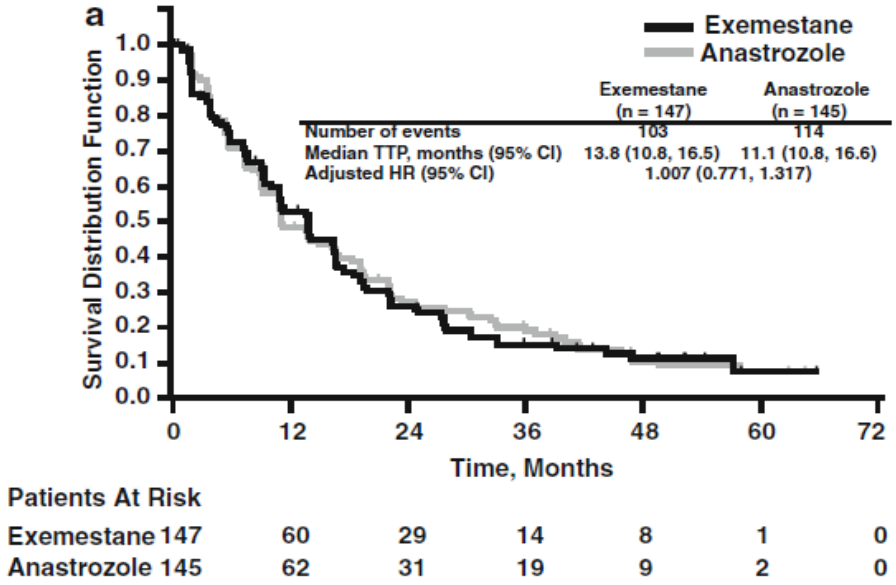
Anastrozole *vs.* other A.I.

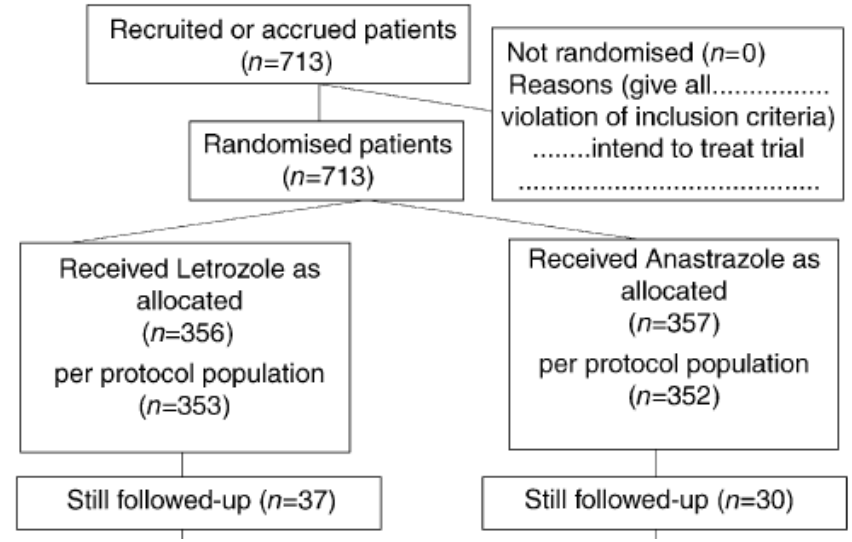
Anastrozole *vs.* Exemestane [1st Line]



	Patients, *n* (%)	
	Exemestane (*n* = 132)	Anastrozole (*n* = 128)
Complete response	2 (1.5)	3 (2.3)
Partial response	56 (42.4)	47 (36.7)
Stable disease	55 (41.7)	70 (54.7)
Stable disease ≥24 weeks	41 (31.1)	49 (38.3)
Stable disease <24 weeks	14 (10.6)	21 (16.4)
Progressive disease	16 (12.1)	8 (6.3)

Iwata H et al, BCRT 2013

Anastrozole *vs.* Letrozole [1st&2nd Line]



Efficacy parameter	Letrozole (*n* = 356)	Anastrozole (*n* = 357)	Adjusted *P* value
Median TTP, months (90% CI)	5.7 (5.1–6.0)	5.7 (4.6–6.1)	0.92
ORR, no. (%)	68 (19.1)[a]	44 (12.3)[b]	0.013
CR	24 (6.7)	13 (3.6)	
PR	44 (12.4)	31 (8.7)	
NC ⩾ 6 months	28 (7.9)	38 (10.6)	
PD	203 (57.0)	222 (62.2)	
NE	57 (16.0)	53 (14.8)	
Median DOR, months	22	25	0.645

Rose C et al, EJC 2003

A.I. as comparator in recent 1st-Line Phase III Trials

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Bone only	22 %	22 %	22 %	NR
Median PFS for AI (control arm)	14.7 mo	14.5 mo	13.5 mo	13.8 mo
(95 % CI)	(13.0 – 16.5)	(12.9 - 17.1)	(12.1 – 15.1)	(NR)

Johnston S, ESMO 2016

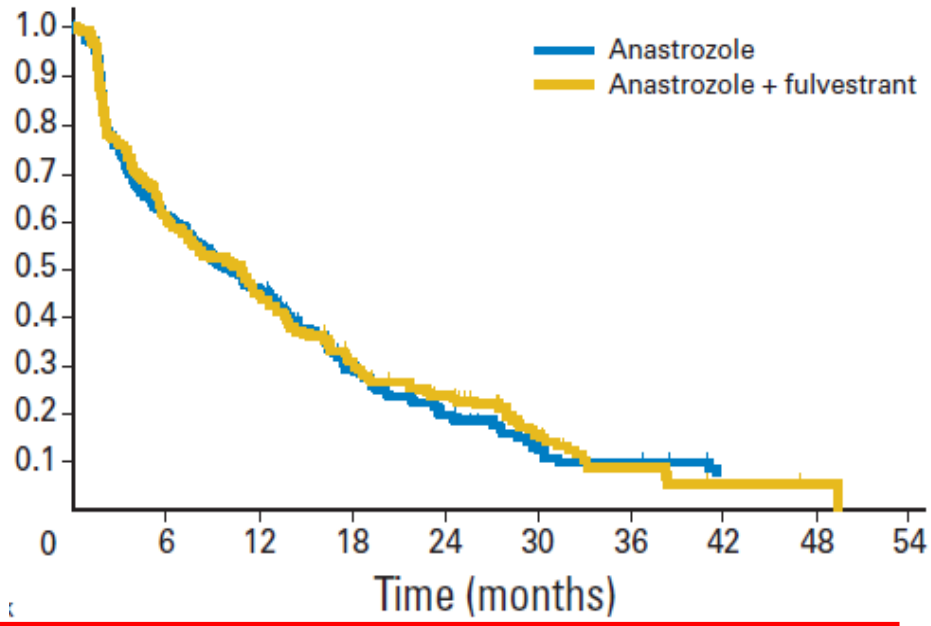
A.I. as comparator

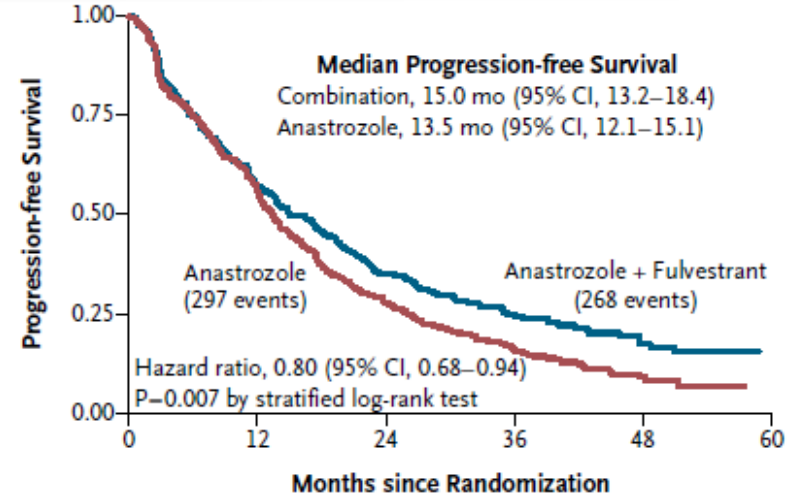
PFS / TTP of AIs as 1st-line endocrine therapy trials in HR+ MBC

Trial	Date	AI (months)	Tamoxifen (months)	AI + fulvestrant 250mg (months)	Hazard Ratio
Nabholtz et al *Anastrozole vs tamoxifen*	2000	11.1	5.6	-	0.81
Bonneterre et al *Anastrozole vs tamoxifen*	2001	8.2	8.3	-	0.99
Mouridsen et al *Letrozole vs tamoxifen*	2001	9.4	6.0	-	0.72
Chernozemsky et al *Exemestane vs tamoxifen*	2007	12.0	8.3	-	-
Paridaens et al *Exemestane vs tamoxifen*	2008	9.9	5.8	-	0.84
Mehta et al *Anastrozole vs anastrozole + fulvestrant 250mg*	2012	13.5	-	15.0	0.80
Bergh et al *Anastrozole vs anastrozole + fulvestrant 250mg*	2012	10.2	-	10.8	0.99
Range		8–13	6–8	10–15	

Johnston S, SABCS 2016

Fulvestrant [250 mg]+ Anastrozole
[Poly-endocrine Therapy]





No. at Risk						
Anastrozole + fulvestrant	349	199	114	53	21	8
Anastrozole	345	193	92	39	11	3

Previous treatment*				
AET	180	69.8	168	65.6
Endocrine therapy type*				
Antiestrogens	178	69.0	165	64.5
Enzyme inhibitors	5	1.9	3	1.2
GnRH agonists	8	3.1	7	2.7
Other hormone antagonists and related	0		1	0.4
Progestogens	1	0.4	0	
Recurrence‡				
During AET	69	26.7	59	23.0
0-12 months after stopping AET	14	5.4	18	7.0
> 12 months after stopping AET	85	32.9	78	30.5
Other	12	4.7	11	4.3

Characteristic	Anastrozole Alone (N=345)	Anastrozole and Fulvestrant (N=349)	Total (N=694)
Age — yr			
Median	65	65	65
Range	36–91	27–92	27–92
Prior adjuvant tamoxifen — no. (%)			
Yes	139 (40.3)	141 (40.4)	280 (40.3)
No	206 (59.7)	208 (59.6)	414 (59.7)
Prior adjuvant chemotherapy — no. (%)			
Yes	103 (29.9)	129 (37.0)	232 (33.4)
No	242 (70.1)	220 (63.0)	462 (66.6)

Bergh J et al, JCO 2012

Mehta RS et al, NEJM 2012

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Quale impatto nella pratica clinica?

Studio su una sottopopolazione relativamente piccola

Risultati significativi (ma clinicamente?)

Considerazioni sulla compliance delle pazienti

Ingresso sul mercato di un verosimile “nuovo standard” nel setting

Sottopopolazione con lesioni non viscerali (HR .59, 95%CI .42-.84, PFS 22.3 m)