



**“Progressione dopo inibitori dell'aromatasi:
linee ormonali disponibili”**

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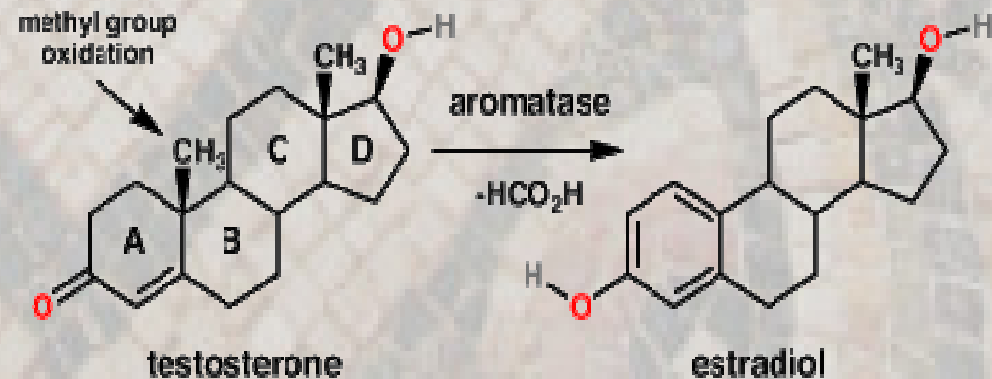
Rimini 26 Marzo 2011

Linee ormonali disponibili:

- AI di classe diversa (NSAI, SAI)
- SERDs (Fulvestrant)
- SERMs (Tamoxifene, Toremifene)
- Estrogeni
- Progestinici (MA, MPA)

Inibitori dell' aromatasi

- 1998 Superiori ai Progestinici come terapia di II linea nel MBC.
- 2000 uguali o superiori a Tam. come terapia di I linea nel MBC.
- 2002 vantaggio vs Tam. in terapia adiuvante (up front, switch, extended).



Strategia sequenziale tra Inibitori dell' Aromatasi

A Qualitative Systematic Review of the Evidence Base for Non-cross-resistance between Steroidal and Non-steroidal Aromatase Inhibitors in Metastatic Breast Cancer

- Fonti bibliografiche: Medline, Embase e Cochrane. 11 studi valutati.
 - 9 NSAI → SAI, 1 SAI → NSAI, 1 NSAI → NSAI.
 - 1 randomizzato doppio-cieco (EFFECT).
 - 10 non randomizzati od osservazionali.
- Pazienti in recidiva o progressione dopo terapia adiuvante, prima o seconda linea di endocrinoterapia con AI.
- Outcome valutati: CB (CR, PR, SD), PD and ORR.

A Qualitative Systematic Review of the Evidence Base for Non-cross-resistance between Steroidal and Non-steroidal Aromatase Inhibitors in Metastatic Breast Cancer

Risultati:

➤ NSAII → Exemestane :

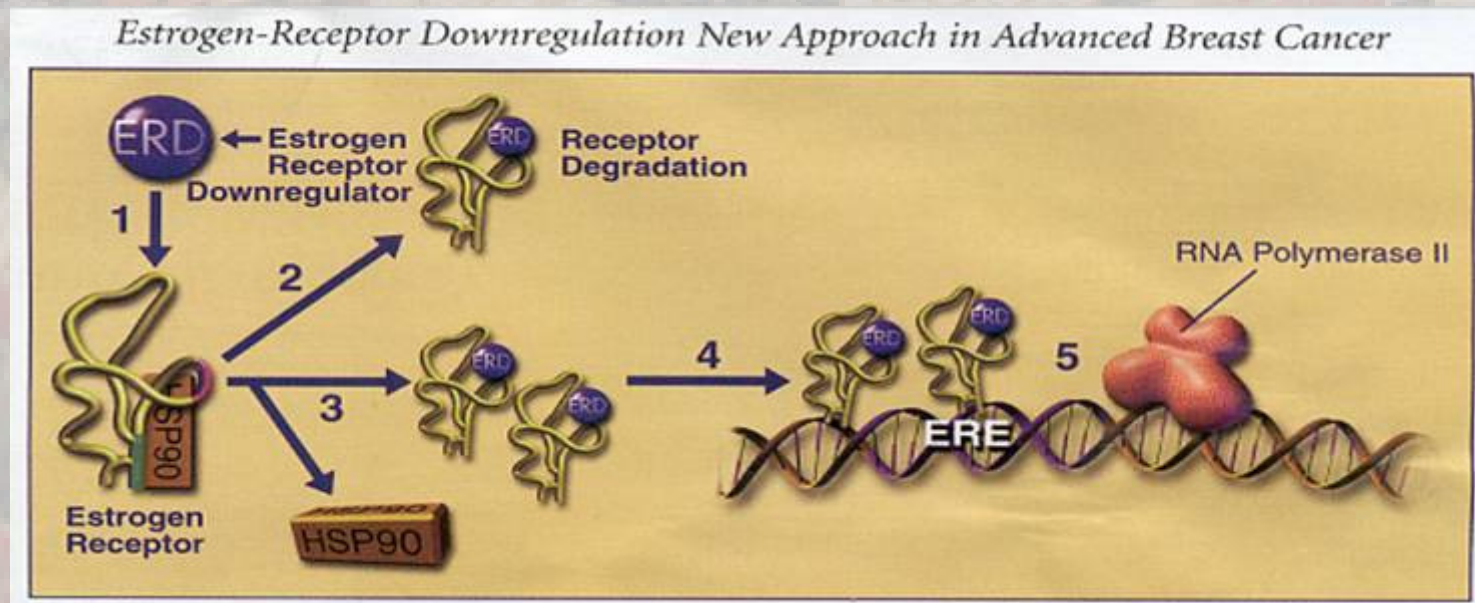
➤ Exemestane → NSAII:

Pz.	CB	TTP
1021	12 - 55 %	3,7 - 5,2 mesi
18	55,6 %	9,3 mesi

■ **Conclusioni:** L'assenza di cross-resistenza, per entrambe le sequenze, giustifica lo switch tra AI, specialmente nelle pazienti con buona e duratura risposta ad una precedente linea ormonale e malattia non-viscerale.

Evidenze a favore di Fulvestrant dopo AI:

- Ingle et al., JCO 2006.
- Perey et al., Breast Cancer Treat. 2004.
- Mello et al., Med Oncol., 2010



NCCTG (North Central Cancer Treatment Group Trial N0032)

- Studio Fase II, Fulvestrant 250 mg. dopo trattamento con AI e Tam → AI

**CB 52,4% nelle pz in
progressione ad AI e 28,6%
nelle pazienti in progressione a
TAM + AI**

Best Response Achieved

Response	Prior Hormonal Therapy					
	Total (N = 77)		AI Only (n = 21)		AI and Tam† (n = 56)	
	No.	%	No.	%	No.	%
PR	11	14.3	6	28.6	5	8.9
Stable*	16	20.8	5	23.8	11	19.6
Clinical benefit, PR + stable	27	35.1	11	52.4	16	28.6

Abbreviations: AI, aromatase inhibitor; Tam, tamoxifen; PR, partial response.

*For at least 6 months.

†Sequentially (not in combination).

Clinical benefit of fulvestrant in postmenopausal women with advanced breast cancer and primary or acquired resistance to aromatase inhibitors: final results of phase II Swiss Group for Clinical Cancer Research Trial (SAKK 21/00)

- Studio Fase II, 90 pz., pretrattati con AI di cui 84% anche con Tam. o Tor.
 - Gruppo A: 70 pz. AI sensibili
 - Gruppo B: 20 pz. AI resistenti

	Group A	Group B
SD \geq 24 weeks, <i>n</i> (%)	18 (27)	6 (32)
PR, <i>n</i> (%)	1 (1) CB 28%	0 (0) CB 37%
CR, <i>n</i> (%)	0 (0)	1 (5)
Disease progression ^a , <i>n</i> (%)	44 (66)	12 (63)
Not assessable, <i>n</i> (%)	4 ^b (6)	0 (0)
CB, <i>n</i> [% (90% CI)]	19 [28 (19–39)]	7 [37 (19–58)]
Median duration of CB, months (range) ^c	10.8 (5.6–50.1)	9.0 (5.5–17.0)
Median TTP months (95% CI)	3.6 (3.0–4.8)	3.4 (2.5–6.7)
Median TTF, months (95% CI)	3.6 (3.0–4.6)	3.4 (2.5–6.7)
Median duration of treatment, months (range)	3.8 (0.9–52)	3.8 (1.8–17.9+)

- La precedente risposta agli AI non sembra essere predittiva di risposta al Fulvestrant.

Prolonged time to progression with fulvestrant for metastatic breast cancer

- 73 pz., studio di coorte. 19,2% Fulvestrant in prima linea; 58,9% in seconda, 21,9% in terza.
- TTP rispettivamente di 13, 6, 12 mesi.

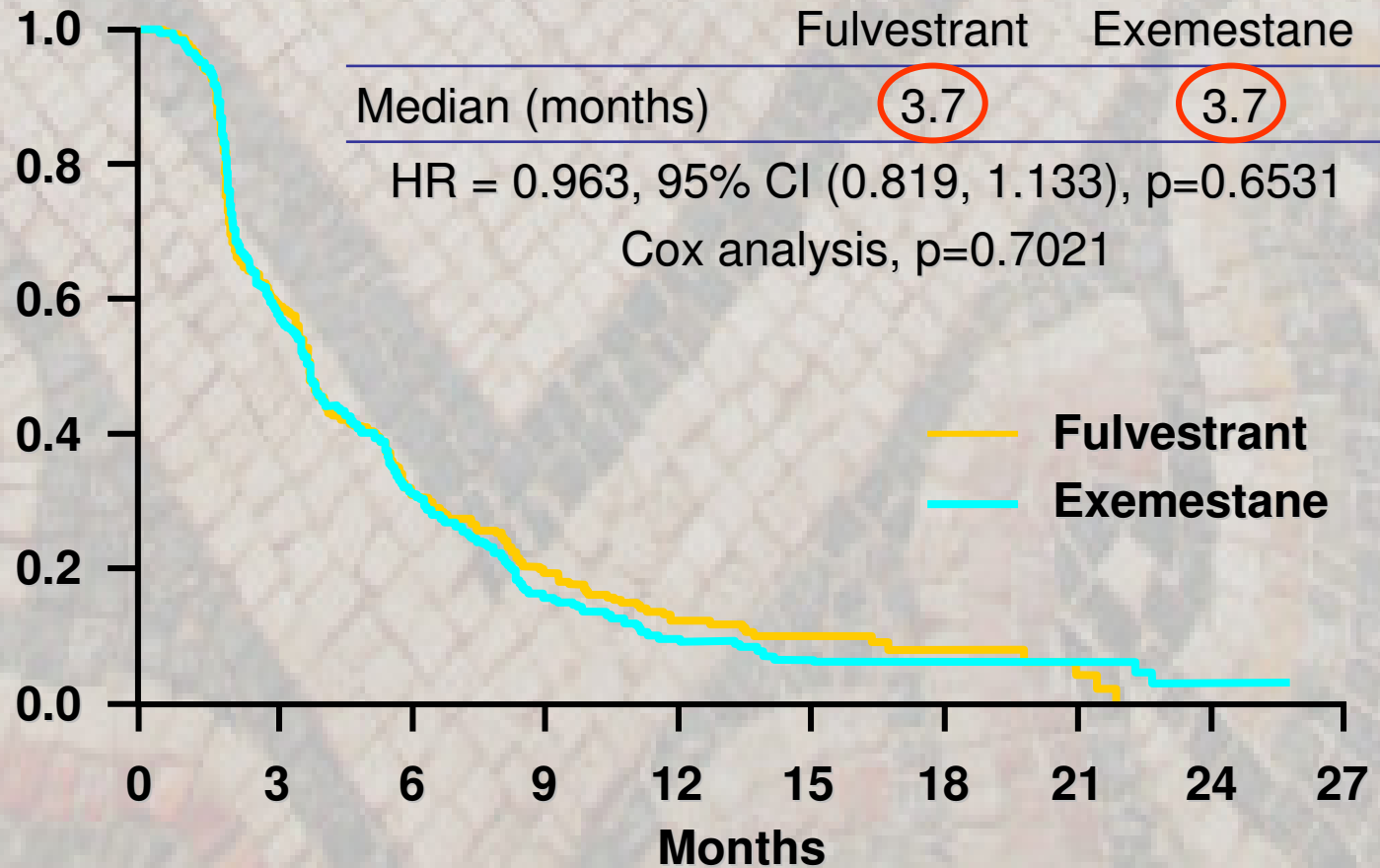
Status	TTP (months)	<i>P</i>
ER/PgR+	13 (1.94–51.67)	0.009
ER/PgR–	6 (0.1–36.34)	
ER+	11 (0.1–51.67)	0.9
ER–	10 (3.02–29.04)	
PgR+	13 (3–8)	0.008
PgR–	6 (0.1–36.34)	

Double-Blind, Randomized Placebo Controlled Trial of Fulvestrant Compared With Exemestane After Prior Nonsteroidal Aromatase Inhibitor Therapy in Postmenopausal Women With Hormone Receptor–Positive, Advanced Breast Cancer: Results From EFACT

- 693 pz, in progressione o recidiva dopo NSAI.
- Fulvestrant 250 mg. (**con loading dose**) vs Exemestane 25 mg.
- End point primario: TTP.
- End points secondari: OS, OR, CB, DOR, QoL.

EFFECT : Time to progression

Proportion of patients progression-free



At risk:

Fulvestrant

Exemestane

351	195	96	50	25	12	4	2	0	0
342	190	98	41	21	12	8	6	1	0

Double-Blind, Randomized Placebo Controlled Trial of Fulvestrant Compared With Exemestane After Prior Nonsteroidal Aromatase Inhibitor Therapy in Postmenopausal Women With Hormone Receptor–Positive, Advanced Breast Cancer: Results From EFACT

Risultati:

- Median TTP : 3,7 mesi in entrambi i gruppi (p= 0.653)
- OR: Fulvestrant 7,4% vs Exemestane 6,7% (p= 0.736)
- CB: Fulvestrant 32,2% vs Exemestane 31,5% (p= 0.853)
- DOR: Fulvestrant 13,5 mesi vs Exemestane 9,8 mesi.

Double-Blind, Randomized Placebo Controlled Trial of Fulvestrant Compared With Exemestane After Prior Nonsteroidal Aromatase Inhibitor Therapy in Postmenopausal Women With Hormone Receptor–Positive, Advanced Breast Cancer: Results From EFACT

Conclusioni:

- Efficacia sovrapponibile di Exemestane e Fulvestrant.
- Assenza di cross-resistenza tra AI steroidei e NSAI.
- Entrambi i farmaci sono risultati ben tollerati.

Fulvestrant

A Review of its Use in the Management of Hormone Receptor-Positive Metastatic Breast Cancer in Postmenopausal Women

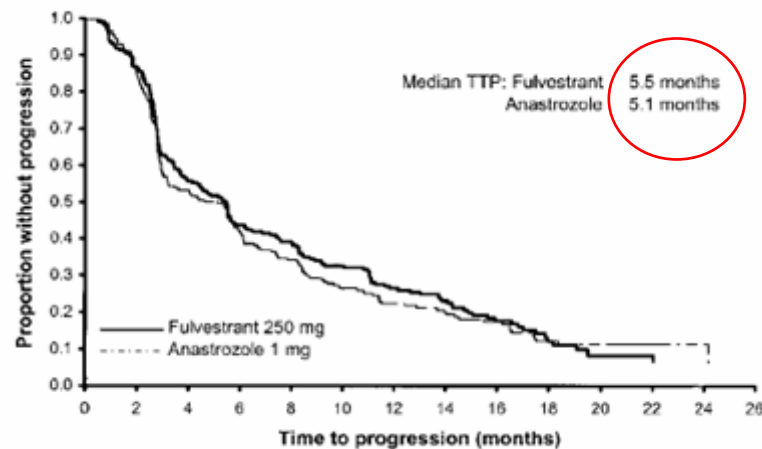
Trial	Definition/description
As second-line therapy following progression after prior endocrine therapy	
Chinese trial ^[26]	Evaluation of the efficacy and tolerability of fulvestrant and anastrozole in Chinese patients
CONFIRM ^[27]	COMparisoN of Faslodex In Recurrent or Metastatic breast cancer
EFECT ^[28]	Evaluation of Faslodex versus Exemestane Clinical Trial
FACT ^[29]	Fulvestrant and Anastrozole Clinical Trial
FINDER1 ^[30]	Faslodex INvestigation of Dose evaluation in Estrogen-Receptor-positive advanced breast cancer in Japan
FINDER2 ^[31]	Faslodex INvestigation of Dose evaluation in Estrogen-Receptor-positive advanced breast cancer in Western women
IPEP ^[32]	In-Practice Evaluation Program
SOFEA ^[33]	Study Of Faslodex with or without concomitant arimidex versus Exemestane following progression on nonsteroidal Aromatase inhibitors
0020 ^[34]	Evaluation of the efficacy and tolerability of fulvestrant and anastrozole
0021 ^[35]	Evaluation of the efficacy and tolerability of fulvestrant and anastrozole
As first-line therapy without prior endocrine therapy for advanced disease	
FIRST ^[36]	Fulvestrant fIRst-line Study comparing endocrine Treatments
NEWEST ^[25]	Neoadjuvant Endocrine therapy for Women with Endocrine Sensitive Tumours
0025 ^[37]	Evaluation of the efficacy and tolerability of fulvestrant and tamoxifen

Fulvestrant 250 mg terapia di II linea

STUDIO 0020: INTERNAZIONALE

Fulvestrant, Formerly ICI 182,780, Is as Effective as Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing After Prior Endocrine Treatment

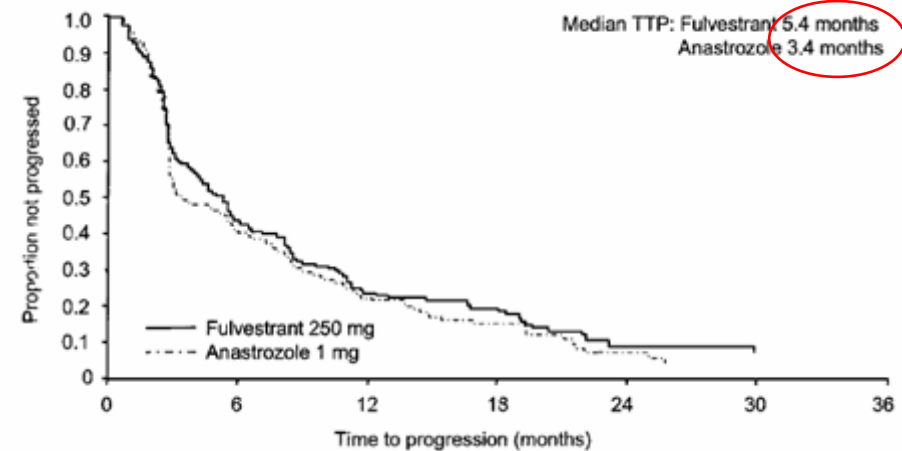
By A. Howell, J.F.R. Robertson, J. Quaresma Albano, A. Aschermannova, L. Mauriac, U.R. Kleeberg, I. Vergote, B. Erikstein, A. Webster, and C. Morris



STUDIO 0021: NORDAMERICANO

Double-Blind, Randomized Trial Comparing the Efficacy and Tolerability of Fulvestrant Versus Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing on Prior Endocrine Therapy: Results of a North American Trial

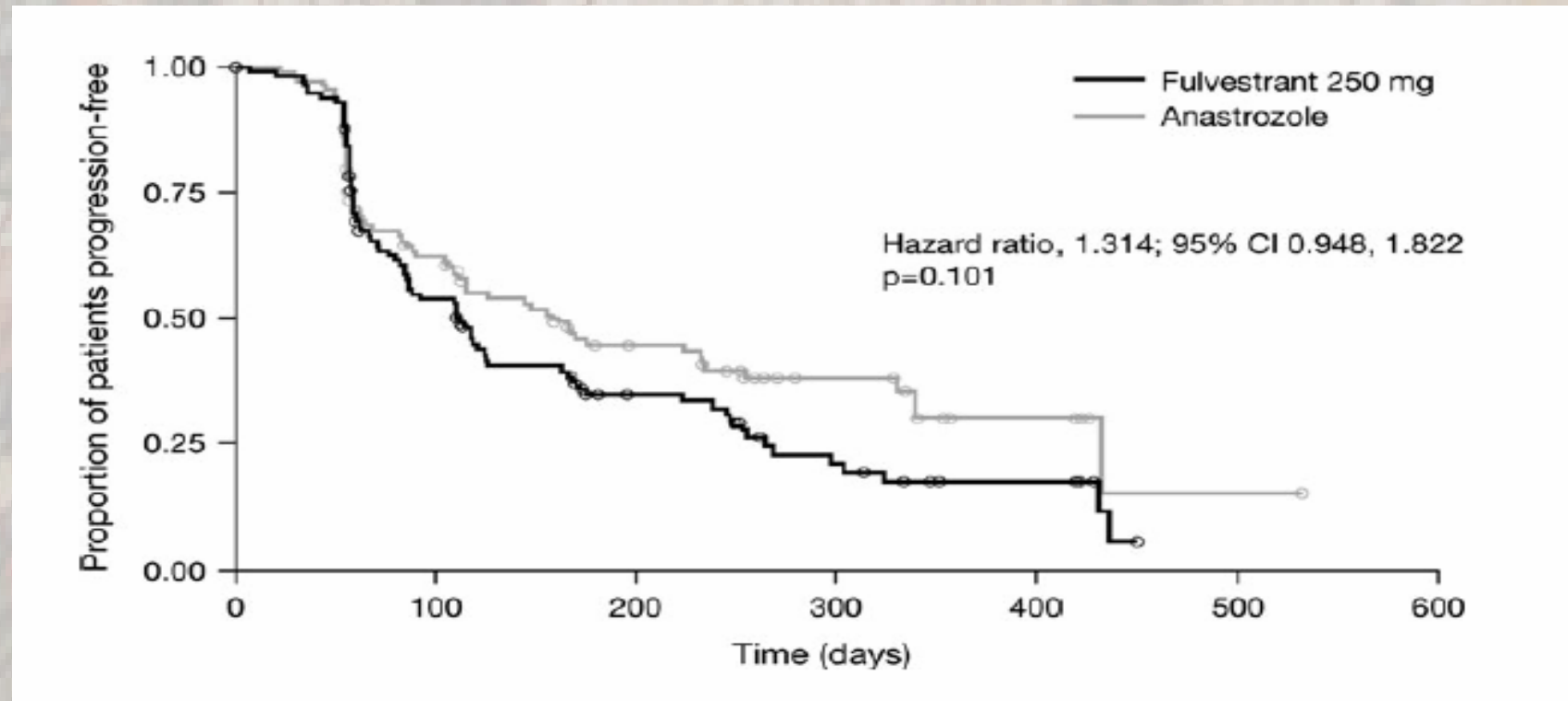
By C.K. Osborne, J. Pippen, S.E. Jones, L.M. Parker, M. Ellis, S. Come, S.Z. Gerler, J.T. May, G. Burton, I. Dimery, A. Webster, C. Morris, R. Elledge, and A. Buzdar



- Fulvestrant ed Anastrozolo hanno dimostrato la stessa efficacia in TTP.

Fulvestrant 250 mg terapia di II linea

Fulvestrant 250 mg versus anastrozole for Chinese patients with advanced breast cancer: results of a multicentre, double-blind, randomised phase III trial

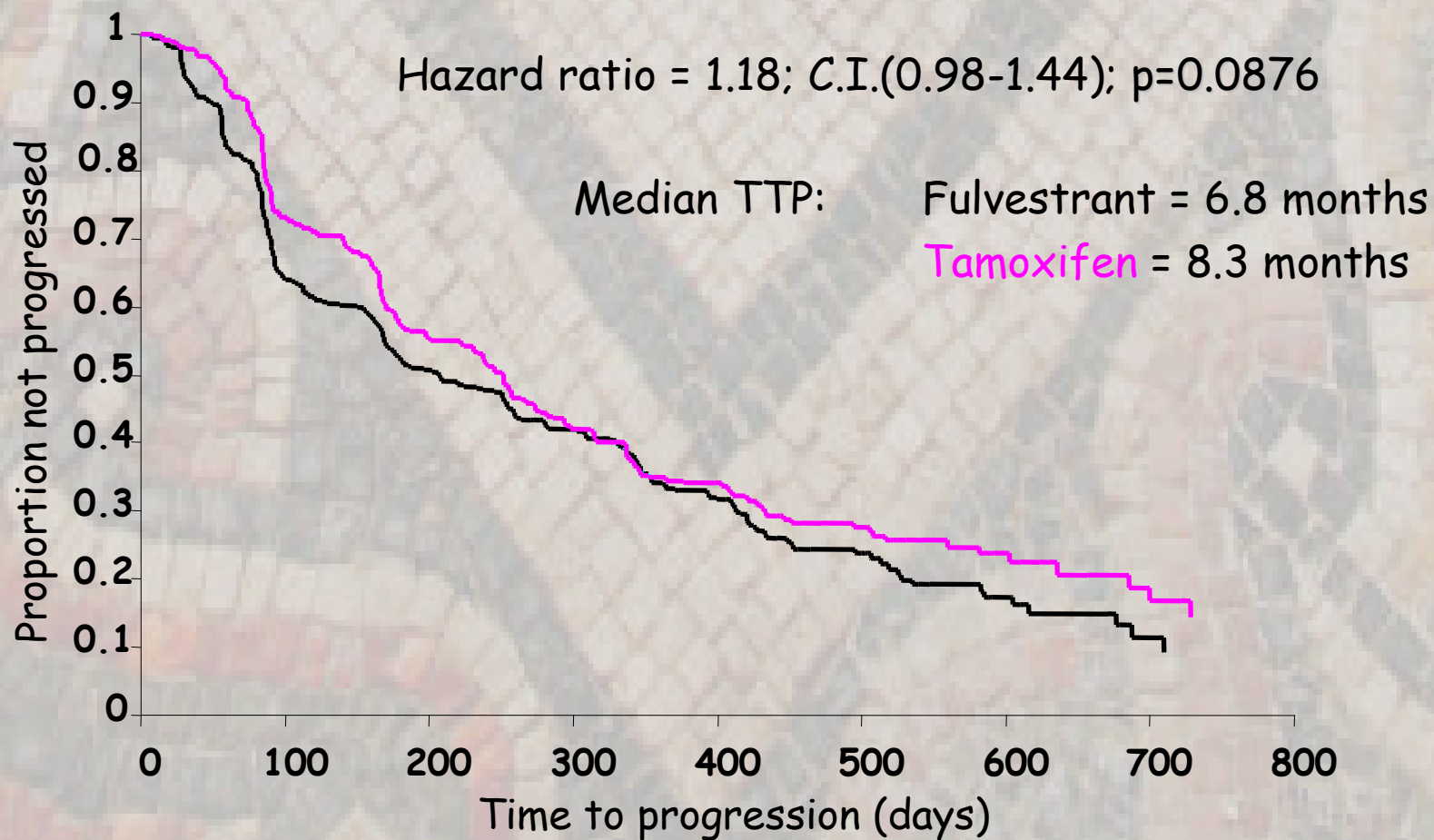


- 234 pz. End point primario TTP (110 gg Fulvestrant vs 159 gg AI)
Conferma i risultati degli Studi 0020 e 0021.

Fulvestrant 250 mg terapia di I linea

Trial 0025: Fulvestrant vs Tamoxifen

■ Studio fase III, 587 pz.



■ Efficacia sovrapponibile ad un follow up di 14,5 mesi

Howell A., et al., JCO 2004

Fulvestrant in the treatment of advanced breast cancer: A systematic review and meta-analysis of randomized controlled trials

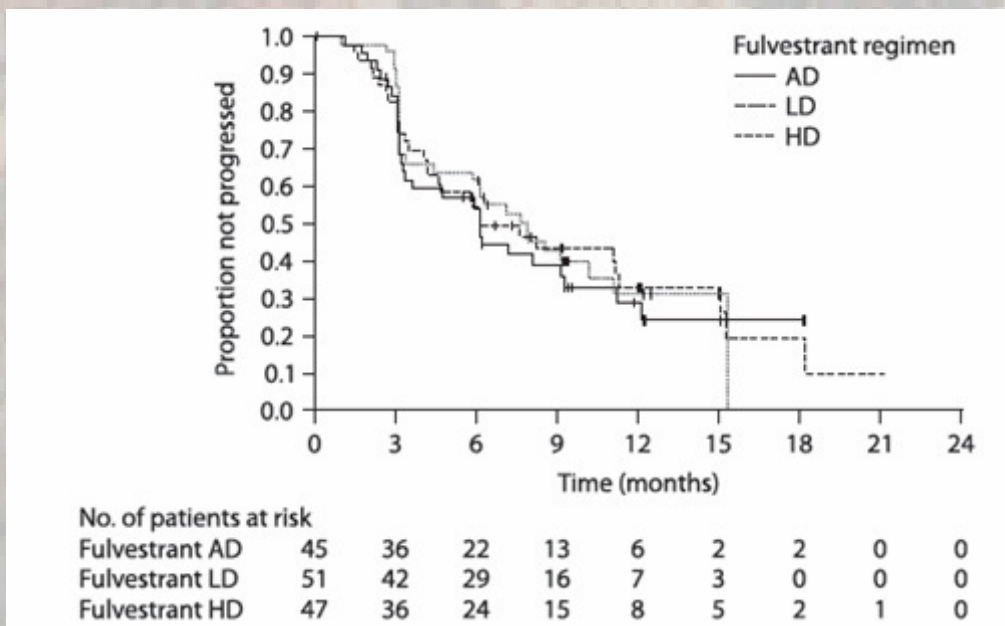
Author [Ref.]	Year	Regimen	Line	No. of pts.
Howell et al. [15]	2002	Fulvestrant 250 mg (IM) once monthly	Second	222
		Anastrozole 1 mg/day orally		229
Osborne et al. [16]	2002	Fulvestrant 250 mg (IM) once monthly	Second	206
		Anastrozole 1 mg/day orally		194
Chia et al. [17]	2008	Fulvestrant 250 mg (IM) once monthly	Second or greater	351
		Exemestane 25 mg/day orally		342
Howell et al. [18]	2004	Fulvestrant 250 mg (IM) once monthly	First	313
		Tamoxifen 20 mg/day orally		274

- Differenze statisticamente non significative tra Fulvestrant 250 mg. ed altri agenti ormonali in TTP, CB, ORR, OS.

Fulvestrant 500 mg terapia di II linea

Three dose regimens of fulvestrant in postmenopausal Japanese women with advanced breast cancer: results from a double-blind, phase II comparative study (FINDER1)

- Studio Fase II, 143 pz. giapponesi in progressione o recidiva dopo trattamento endocrino. Confronto tra AD, LD, HD.
- End point primario: **ORR**. AD (11,1%), LD (17,6%), HD (10,6%).



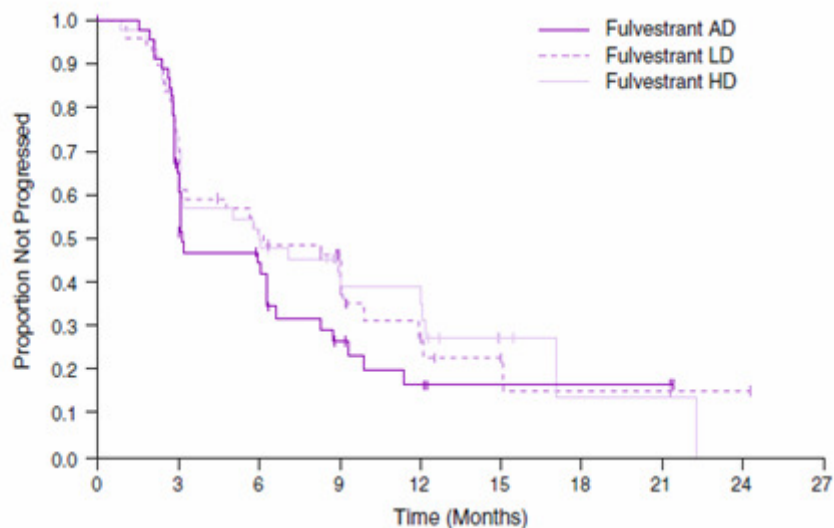
- End point secondario TTP.
AD (6,0), LD (7,5), HD (6,0).

Conclusioni: efficacia e profili di tollerabilità sovrapponibili.

Fulvestrant 500 mg terapia di II linea

Results of a phase II study comparing three dosing regimens of fulvestrant in postmenopausal women with advanced breast cancer (FINDER2)

- Studio Fase II, 144 pz. occidentali in progressione o recidiva dopo trattamento endocrino. Confronto tra AD, LD, HD.
- End point primario: ORR. AD (8,5%), LD (5,9%), HD (15,2%).



Tick marks indicate censored observations
AD, approved dose; HD, high dose; LD, loading dose

- End point secondario TTP. AD (3,1), LD (6,1), HD (6,0).
- **Conclusioni: efficacia e profili di tollerabilità sovrapponibili.**

Pritchard K. Et al., Breast Canc. Res.Treat. 2010

Fulvestrant 500 mg terapia di II linea

Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250 mg With Fulvestrant 500 mg in Postmenopausal Women With Estrogen Receptor–Positive Advanced Breast Cancer

Studio Fase III, doppio cieco, multicentrico, 736 pz.

Fulvestrant 500 mg.

Fulvestrant 250 mg.

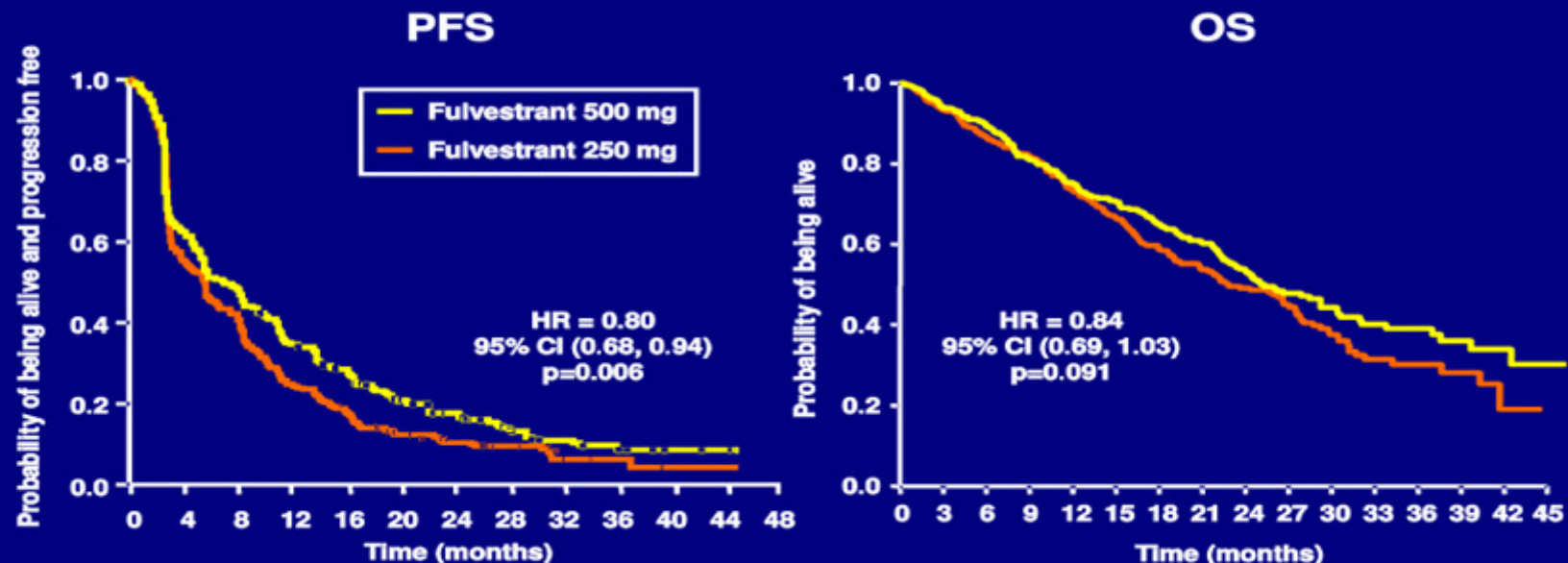
- **End Point Primario:** PFS. Fulvestrant HD 6,5 mesi vs Fulvestrant AD 5,5 mesi.
- **End points Secondari:** ORR (9,1% vs 10,2%), CBR (45,6% vs 39,6%)
DoCB (16,6 vs 13,9 mesi), OS (25,1 vs 22,8 mesi).

Fulvestrant 500 mg terapia di II linea

San Antonio Breast Cancer Symposium - Cancer Therapy and Research Center at UT Health Science Center – December 8-12, 2010

CONFIRM: fulvestrant 500 mg vs 250 mg

Second-line ET (n=736)



CONFIRM, Comparison of Faslodex in Recurrent Metastatic Breast Cancer;
PFS, progression-free survival; OS, overall survival

Di Leo et al. J Clin Oncol 2010

Conclusioni:

Fulvestrant 500 mg. è associato ad un aumento statisticamente significativo in PFS. Dati non ancora maturi per OS (seconda analisi pianificata nel 2011)

Di Leo A. et al., JCO 2010

Fulvestrant 500 mg terapia di I linea

Activity of Fulvestrant 500 mg Versus Anastrozole 1 mg As First-Line Treatment for Advanced Breast Cancer: Results From the FIRST Study

Studio Fase II,
randomizzato, aperto,
multicentrico, 205 pz.

Fulvestrant 500 mg.

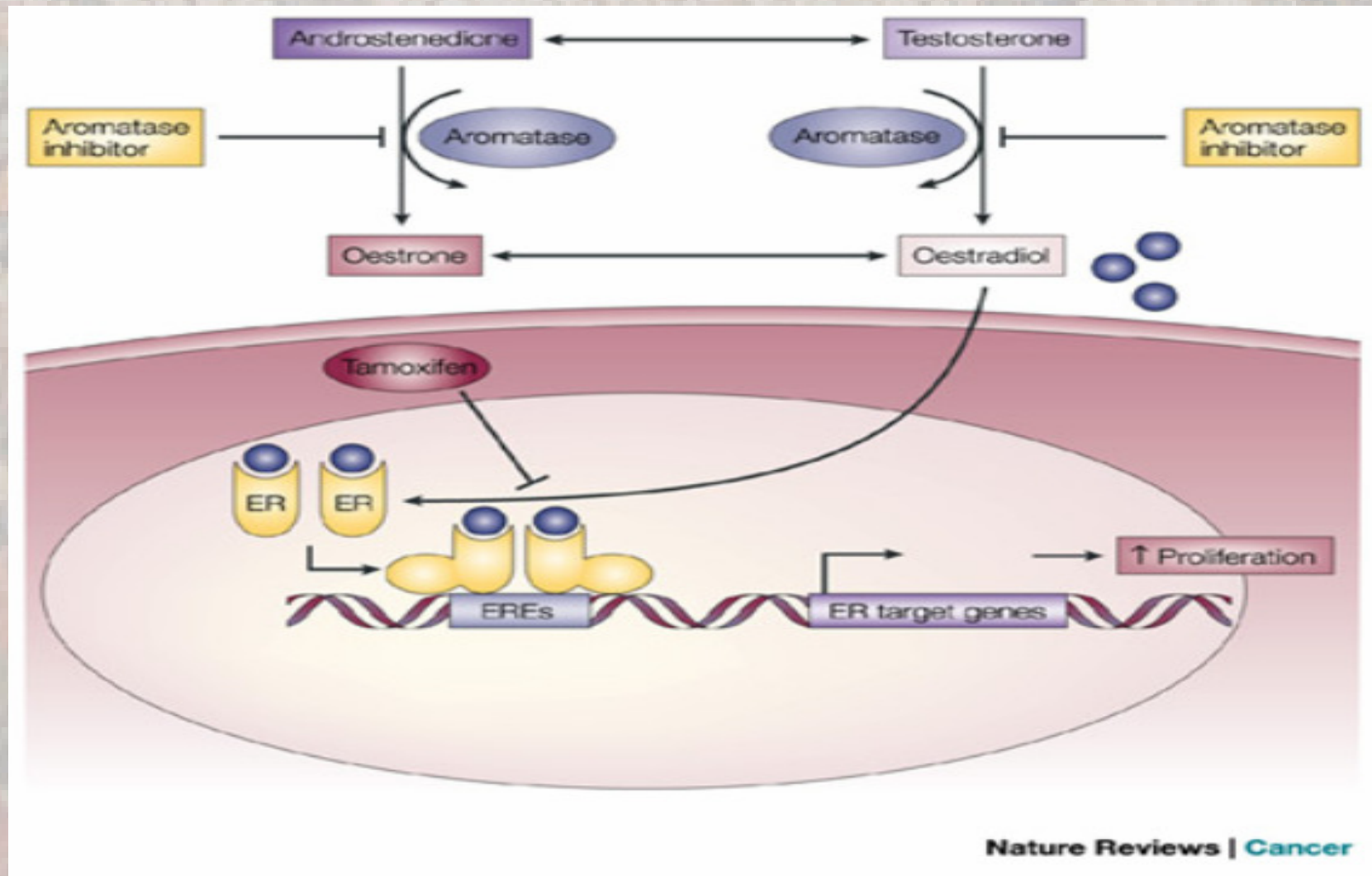
Anastrozolo 1 mg.

- End point primario: CBR . Fulvestrant 72,5% vs Anastrozolo 67% (p 0.386).
- End points secondari: ORR. Fulvestrant 36% vs Anastrozolo 35,5%.(p 0.947)
TTP. Fulvestrant NR vs Anastrozolo 12,5 mesi (p 0.0496)

Studi di associazione : Fulvestrant + AI

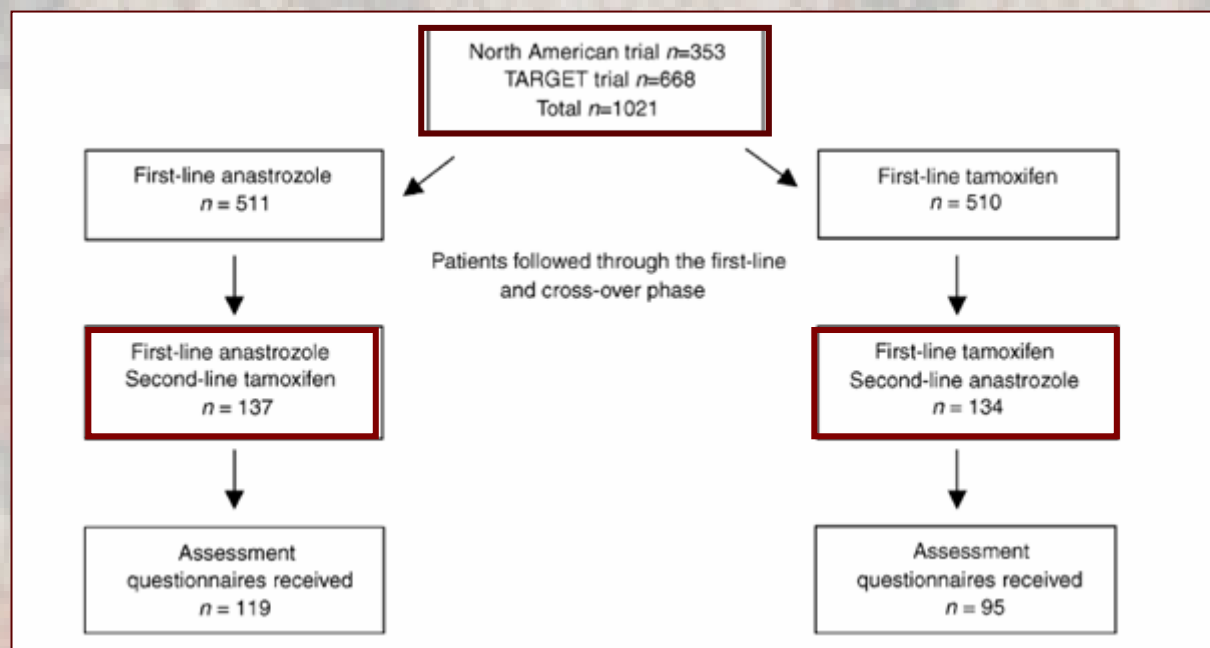
- **SOFEA Trial:** II linea (dopo NSAI), Fase III, LD , 750 pz.
 - Fulvestrant + Anastrozolo
 - Fulvestrant + placebo
 - Exemestane
- **FACT Trial:** I linea, Fase III, LD, 514 pz.
 - Fulvestrant LD + Anastrozolo vs Anastrozolo
- **SWOG Trial:** I linea, Fase III, AD, 690 pz.
 - Fulvestrant AD + Anastrozolo
 - Anastrozolo

AI e Tam.: strategie a confronto



Efficacy of tamoxifen following anastrozole ('Arimidex') compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women

■ Disegno dello studio:

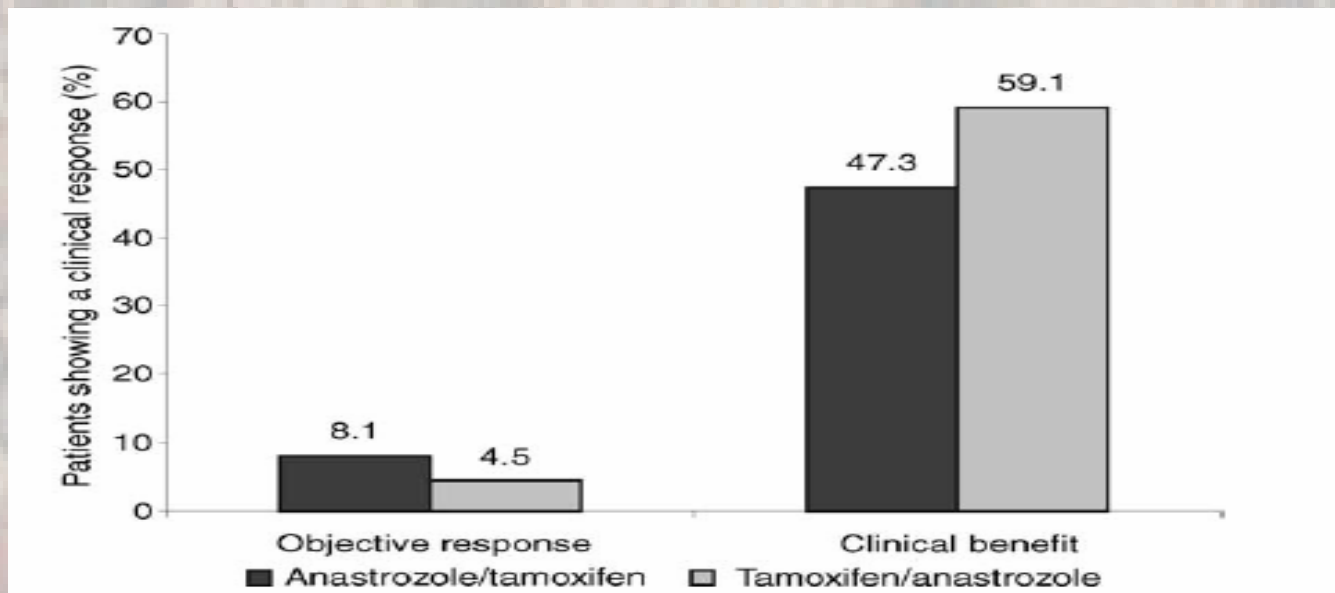


119 pz valutate:
OR 10,1%
CB 48,7%

95 pz. valutate:
OR 7,4%
CB 56,8%

Efficacy of tamoxifen following anastrozole ('Arimidex') compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women

■ OR e CB nel sottogruppo di pz. con ER/Pgr+

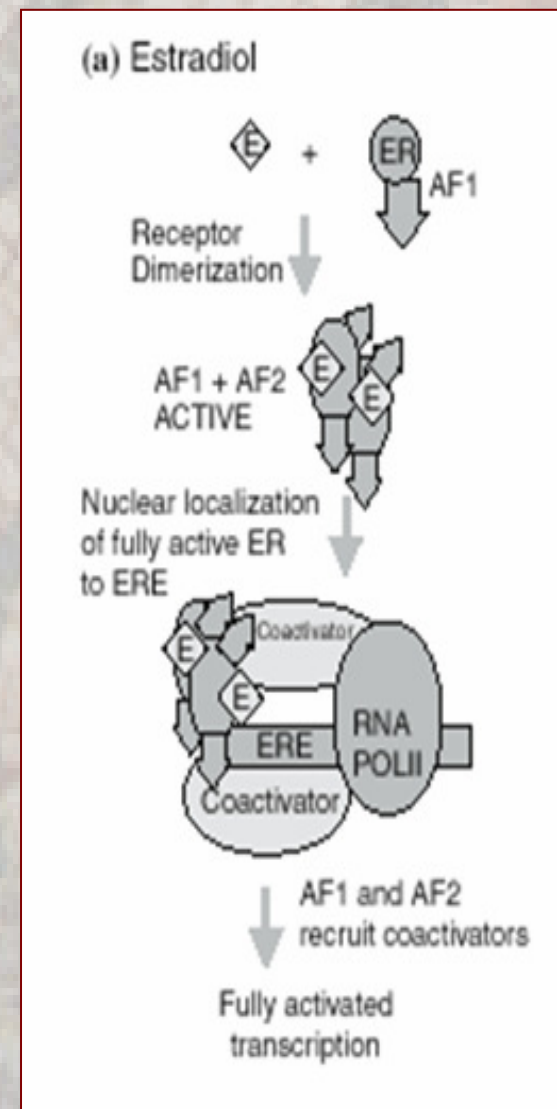


■ Tam. può essere efficace come seconda linea nelle pz. in progressione ad Anastrozolo.

ESTROGENI

Razionale

- Alte dosi di estrogeni o dietilstilbestrolo sono state utilizzate per molti anni con beneficio per il trattamento del carcinoma della mammella.
- Studi in vitro dimostrano che le cellule di carcinoma mammario che hanno sviluppato una ipersensibilità agli estrogeni:
 - Raggiungono la massima stimolazione alla crescita con basse concentrazioni di estradiolo
 - Sono inibite nella crescita a concentrazioni maggiori di estradiolo (meccanismo pro-apoptotico).



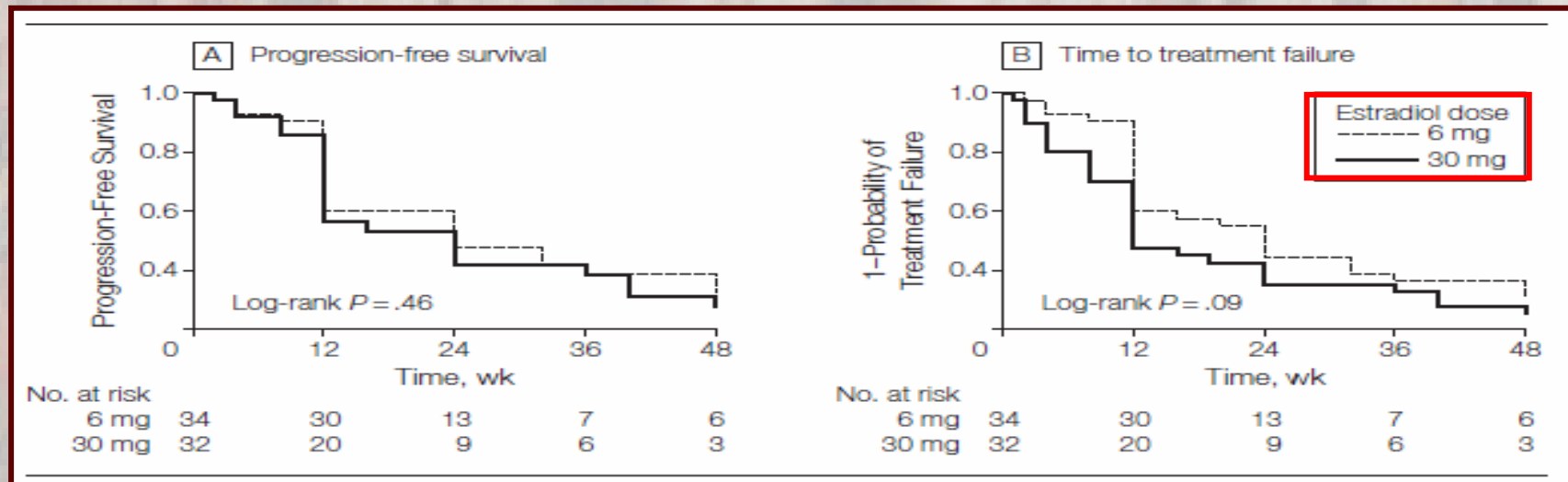
Lower-Dose vs High-Dose Oral Estradiol Therapy of Hormone Receptor–Positive, Aromatase Inhibitor–Resistant Advanced Breast Cancer

- Studio Fase II, 66 pz., MBC a progressione da AI in I linea
PFS ≥ 24wk o in Adj ≥ 2 y.
- Confronto: Estradiolo 6mg. vs 30 mg.
- End point primario: CBR

	Response	
	6 mg (n = 34)	30 mg (n = 32)
Complete remission	0	0
Partial response	3 (9)	1 (3)
Stable disease	7 (20)	8 (25)
Progression disease	21 (62)	16 (50)
Not assessable	3 (9)	7 (22)

Lower-Dose vs High-Dose Oral Estradiol Therapy of Hormone Receptor–Positive, Aromatase Inhibitor–Resistant Advanced Breast Cancer

- End points secondari: PFS e TTF



- **Conclusioni:** risultati simili tra i due dosaggi in CB, con minori eventi avversi di grado ≥ 3 alla dose di 6 mg.

Matthew Ellis et al., JAMA 2009

High-Dose Estrogen as Salvage Hormonal Therapy for Highly Refractory Metastatic Breast Cancer: A Retrospective Chart Review

- 26 pz.
 - 2 pz. Dietilstilbestrolo (DES) 15 mg/die
 - 22 pz. Estradiolo 30 mg/die
 - 2 pz. Estradiolo 6 mg/die
- Metastasi: viscerali 65%, ossee 31%, tessuti molli 4%.
- Mediana di 4 terapie ormonali e 3 chemioterapie precedenti.

High-Dose Estrogen as Salvage Hormonal Therapy for Highly Refractory Metastatic Breast Cancer: A Retrospective Chart Review

■ CB e RR

Response	Value
Measurable disease (n = 20)	
CR	1 (5)
PR	4 (20)
SD	4 (20)
PD	11 (55)
Objective response rate (CR + PR)	5 (25)
Bone-only disease (n = 6)	
Disease control \geq 6 mo	3 (50)
Disease control \leq 6 mo	0
PD	3 (50)
Total clinical benefit (CR + PR + SD)	12 (46)
Median TTP, mo (n = 26)	5
Median time of response or clinical benefit, mo (n = 12)	27

Conclusioni: gli estrogeni ad alte dosi sono un'opzione terapeutica per le pazienti con MBC pluritrattate.

High-Dose Estrogen as Salvage Hormonal Therapy for Highly Refractory Metastatic Breast Cancer: A Retrospective Chart Review

- Eventi avversi correlati alle alte dosi di estrogeni.

AE	Grade 1*	Grade 2*		Grade 3*
Fluid retention	7 (27)	1 (4) [†]	31%	-
Vaginal bleeding	5 (19)	2 (8) ^{†‡}	27%	-
Fatigue	3 (12)	-		-
Nausea	3 (12)	2 (8) [§]	15%	-
Pruritus	2 (8)	-		-
Venous thromboembolism	-	-		1 (4) [¶]

Quale spazio per i progestinici ?

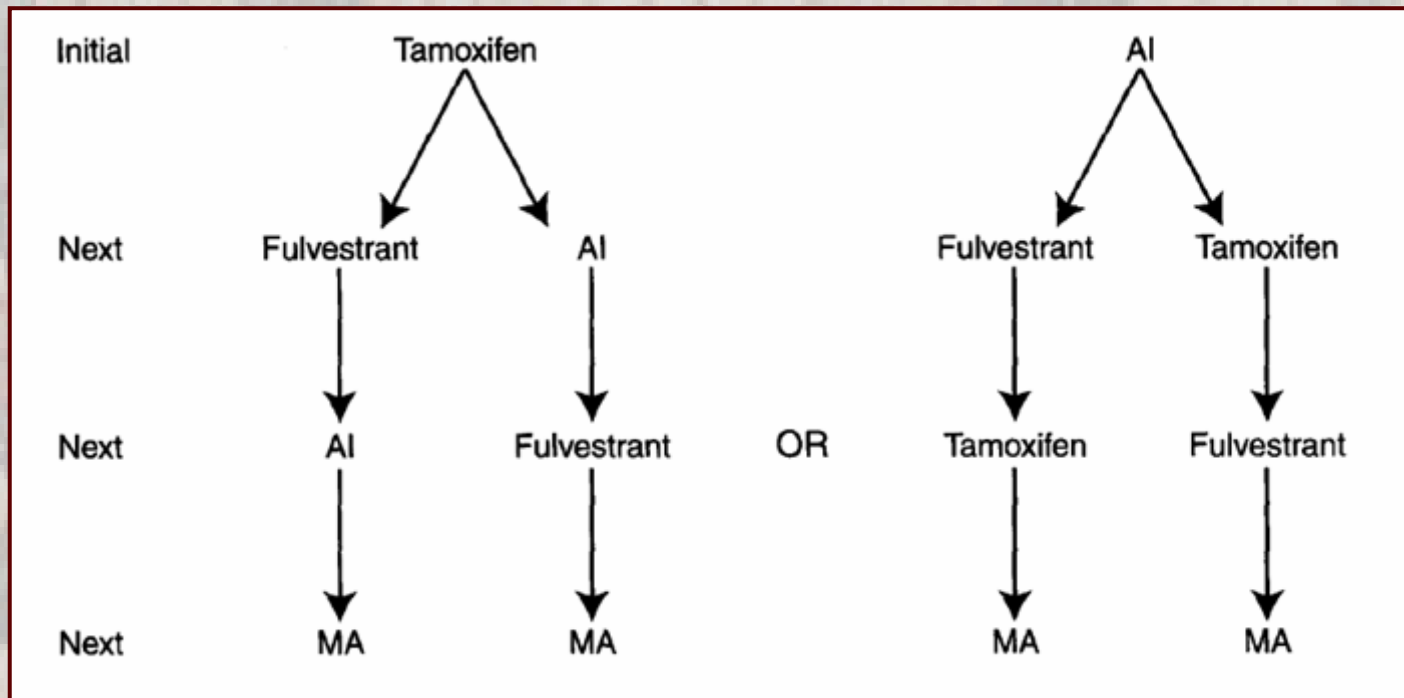
■ Studi di fase III con AI vs con MA in II linea

Autore	Farmaco	Pazienti	RR (CB) (%)	PFS mediana (mesi)	OS mediana (mesi)	FU mediano (mesi)
Buzdar AU, 1998	Anastrozolo 1 mg	263	12,6	4,8	26,7	31
	MA 160 mg	253	12,2	4,6	22,5	
Dombernowsky P, 1998	Letrozolo 2,5 mg	174	23,6*	5,6	25,7*	33
	MA 160 mg	189	16,4	5,5	21,8	
Buzdar AU, 2001	Letrozolo 2,5 mg	199	16	3,2	29	18
	MA 160 mg	201	15	3,4	26	
Kaufmann M, 2000	Exemestane 25 mg	366	15 (37,4)	5,1*	Non raggiunta	12,5
	MA 160 mg	403	12,4 (34,6)	4,2	123,4 settimane	

*Statisticamente significativo; RR risposte obiettive.

Superiorità AI vs progestinici

Sequencing of Hormonal Therapy in Postmenopausal Women with Metastatic Breast Cancer



■ **Conclusioni:** indipendentemente dalle sequenze ormonali impiegate precedentemente i progestinici sono un'opzione terapeutica in terza o quarta linea.

Optimal sequence of hormonotherapy in advanced breast cancer

Gianfilippo Bertelli^a and Robert Paridaens^b

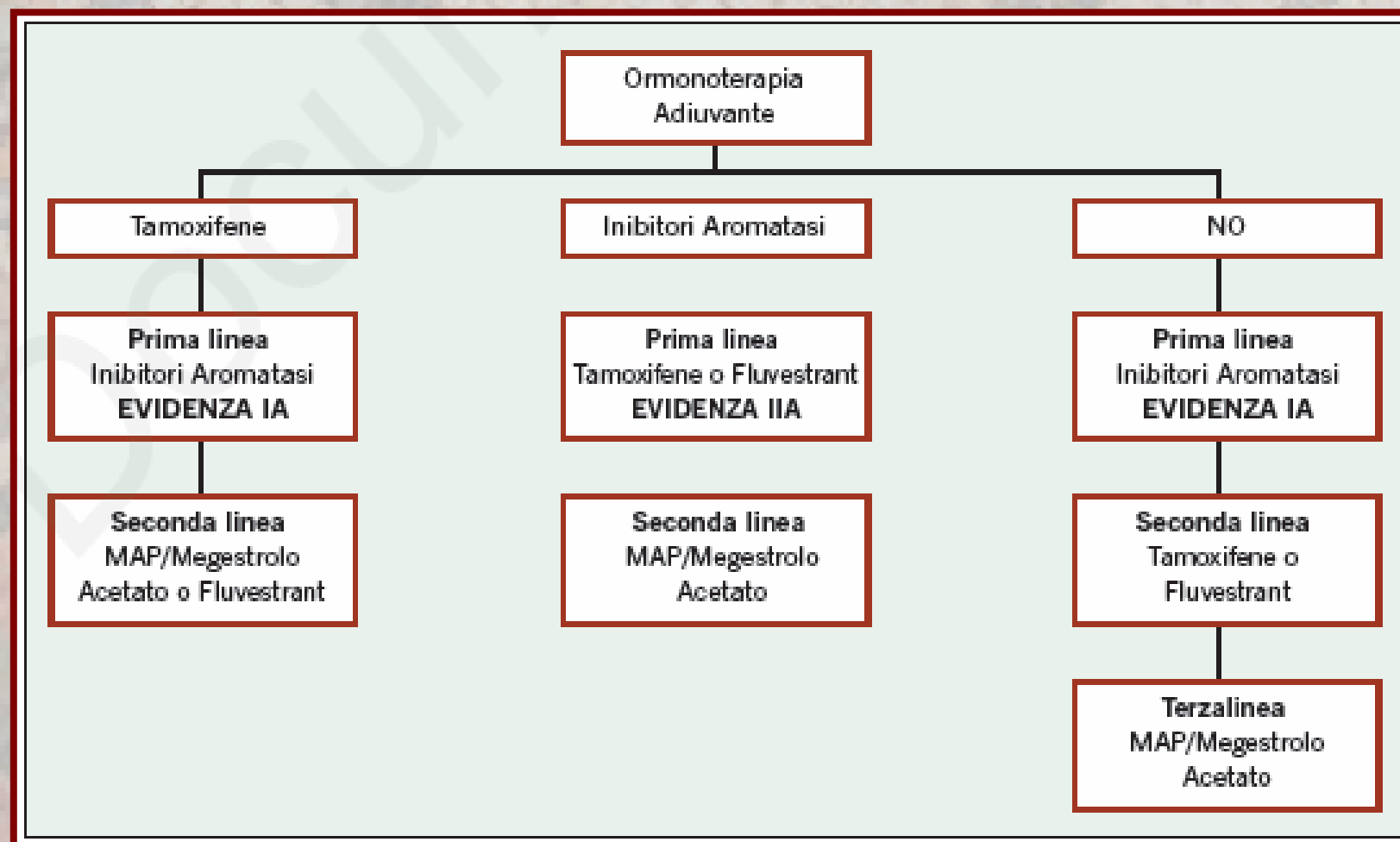
■ **Prima linea:**

- Pazienti "naive" : AI
- Tam in adj: AI o Fulvestrant
- AI in adj: Tamoxifen o Fulvestrant

■ **Seconda e terza linea:**

- Tamoxifen, Fulvestrant, MA, MPA.

Linee Guida AIOM 2010



“Progressione dopo inibitori dell'aromatasi: linee ormonali disponibili.....”

Conclusioni:

- Nelle pazienti ormonoresponsive è necessario considerare l'impiego di successive linee ormonali, specialmente nelle pazienti con un prolungato intervallo libero da malattia, senza interessamento viscerale e responsive a precedenti linee ormonali.
- Necessità di approfondire e validare strategie terapeutiche sovrapponibili e sequenziali.

“...sequenze culturali Romana e Medioevale...
...nella Domus del Chirurgo”



Rimini