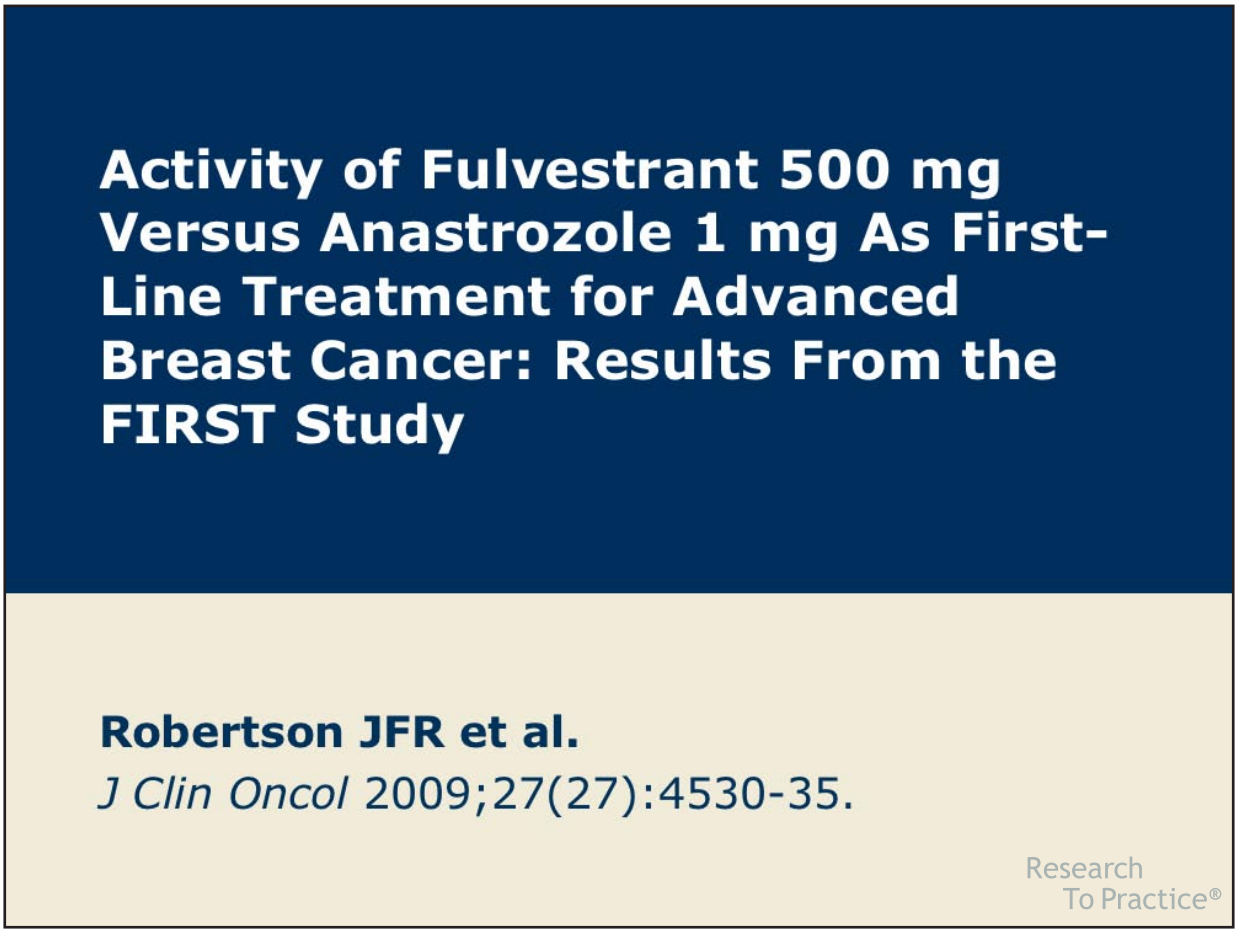
High-Dose Fulvestrant for the Treatment of Postmenopausal Patients with Hormone Receptor-Positive Advanced Breast Cancer

Presentations discussed in this issue:

Robertson JF et al. **Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: Results from the FIRST study.** *J Clin Oncol* 2009;27(27):4530-5. **Abstract**

Di Leo A et al. **CONFIRM: A Phase III, randomized, parallel-group trial comparing fulvestrant 250 mg vs fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer.** SABCS 2009;**Abstract 25**.

Slides from a journal article and from a presentation at SABCS 2009



Introduction

- Evidence suggests that doses of fulvestrant higher than the approved dose (AD;250 mg/month) have greater pharmacological activity (*Oncologist* 2007;12:774).
- Phase II trial NEWEST demonstrated that neoadjuvant fulvestrant high dose (HD; 500 mg/month) is more effective than AD at downregulating the ER pathway in patients with advanced breast cancer (SABCS 2007, Abstract 23).
- Phase III trials have demonstrated that fulvestrant AD is as effective as anastrozole as second-line therapy for advanced breast cancer (*Cancer* 2003;98:229).
- **Current study objective**:
  - Assess the efficacy of first-line fulvestrant HD versus anastrozole in postmenopausal patients with advanced breast cancer (BC).

Source: Robertson JFR et al. *J Clin Oncol* 2009;27(27):4530-35.

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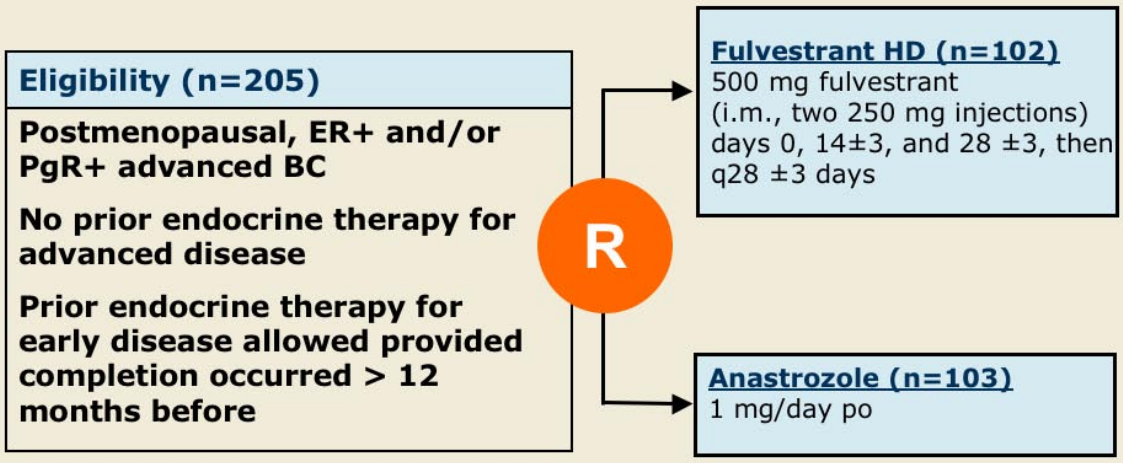
FIRST: A Phase II, Open-Label Multicenter Trial of Fulvestrant HD Versus Anastrozole



Source: Robertson JFR et al. *J Clin Oncol* 2009;27(27):4530-35.

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Efficacy Results

Clinical Response	Fulvestrant HD (n=102)	Anastrozole 1 mg (n=103)	P-value
Clinical benefit rate (CBR)	72.5%	67.0%	0.386
Complete response	0%	1.0%	—
Partial response	31.4%	31.1%	—
Stable disease ≥ 24 wks	41.2%	35%	—
Median duration of response	Not reached	14.2 mos	—
Median duration of clinical benefit	Not reached	Not reached	—
Objective response rate (ORR)*	36.0%	35.5%	0.947

*Fulvestrant HD, n=89; anastrozole, n=93.

Source: Robertson JFR et al. *J Clin Oncol* 2009;27(27):4530-35.

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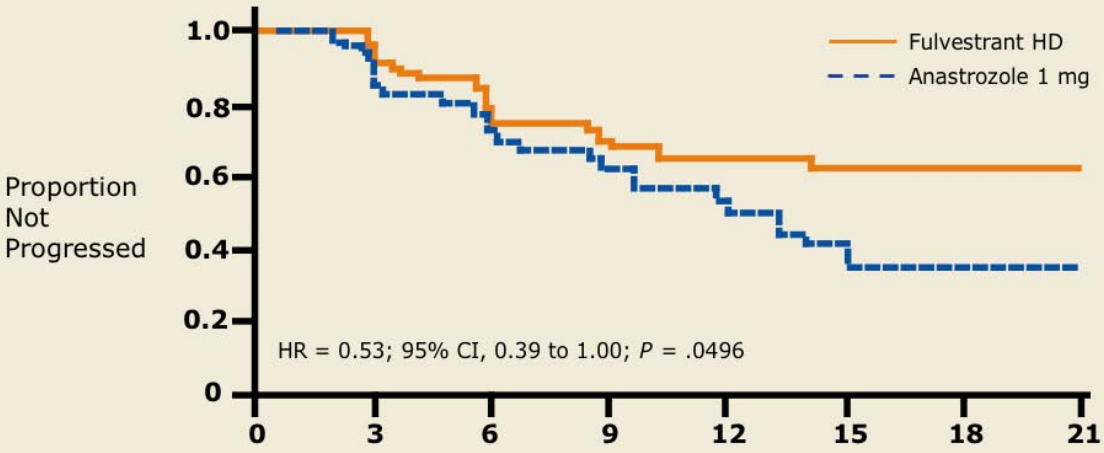
Time to Progression (TTP)



Anastrozole median TTP: 12.5 months
Fulvestrant HD median TTP: Not reached

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Prespecified Adverse Events (Safety Population)

Adverse Event*	Fulvestrant HD (n=101)	Anastrozole 1 mg (n=103)	P-value
GI disturbances	27.7%	22.3%	0.420
Hot flashes	12.9%	13.6%	1.000
Ischemic cardiovascular disorders	0%	1.0%	1.000
Joint disorders	13.9%	9.7%	0.391
Urinary tract infections	4.0%	1.0%	0.210
Weight gain	1.0%	0%	0.495

**Only adverse events with incidences > 1% are shown.*

Source: Robertson JFR et al. *J Clin Oncol* 2009;27(27):4530-35.

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Summary and Conclusions

- First-line fulvestrant HD was as effective as anastrozole for the treatment of postmenopausal patients with advanced BC in terms of CBR and ORR.
  - CBR: 72.5% vs 67.0% (*p*-value=0.386)
  - ORR: 36.0% vs 35.5% (*p*-value=0.947)
- Median TTP, duration of response and duration of clinical benefit favored fulvestrant HD over anastrozole in this trial setting.
  - The early separation of the Kaplan-Meier curves for TTP suggests that fulvestrant HD may benefit patients who progress early.
  - The longer duration of response and duration of clinical benefit (data not shown) indicate patients' responses are more durable with fulvestrant HD.
- Fulvestrant HD was well tolerated with an adverse event profile comparable to anastrozole.
- CONFIRM trial results (SABCS 2009;Abstract 25) provide additional information on the role of fulvestrant HD for the treatment of advanced BC.

Source: Robertson JFR et al. *J Clin Oncol* 2009;27(27):4530-35.

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CONFIRM: A Phase III, Randomized, Parallel-Group Trial Comparing Fulvestrant 250 mg vs Fulvestrant 500 mg in Postmenopausal Women with Estrogen Receptor-Positive Advanced Breast Cancer

Di Leo A et al.

SABCS 2009;Abstract 25.

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Introduction

- Fulvestrant is approved for the treatment of postmenopausal women with advanced breast cancer (BC) that have progressed or relapsed following endocrine therapy.
- The efficacy of fulvestrant is well established at the approved dose of 250 mg/month (F250).
- Phase II trials NEWEST[1] and FIRST[2] have demonstrated that a 500 mg dose of fulvestrant (F500) has improved biological and clinical activities ([1]SABCS 2007;Abstract 23, [2]*JCO* 2009;27:4530).
- **Current study objectives:**
  - Compare the biological activity of F250 versus F500 in postmenopausal patients with estrogen receptor (ER)-positive advanced BC.

Source: Di Leo A et al. SABCS 2009;Abstract 25.

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CONFIRM Study Design

Accrual: 736 (Closed)

Eligibility

Postmenopausal

ER-positive, advanced disease

R

F250
(1 injection i.m.) + Placebo (1 injection i.m.) days 1, 14 (2 placebo injections), 28 and every 28 days thereafter

F500
(2 injections 250 mg i.m.) days 1, 14, 28, and every 28 days thereafter

Source: Di Leo A et al. SABCS 2009;Abstract 25.

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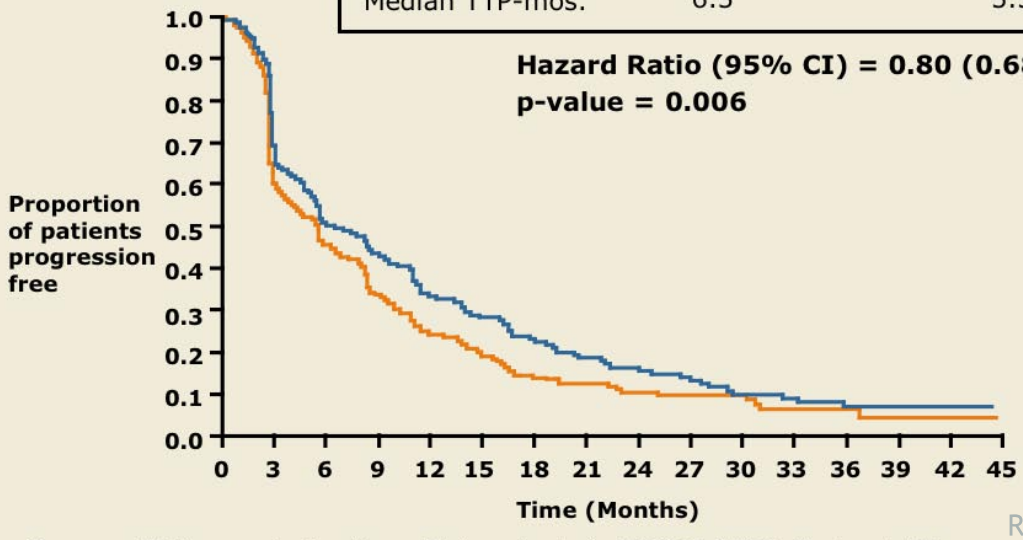
Time to Progression (ITT Analysis)

	Fulvestrant 500	Fulvestrant 250
% progressed	82	85.8
Median TTP-mos.	6.5	5.5

Hazard Ratio (95% CI) = 0.80 (0.68 - 0.94)
p-value = 0.006



Source: With permission from Di Leo A et al. SABCS 2009;Abstract 25.

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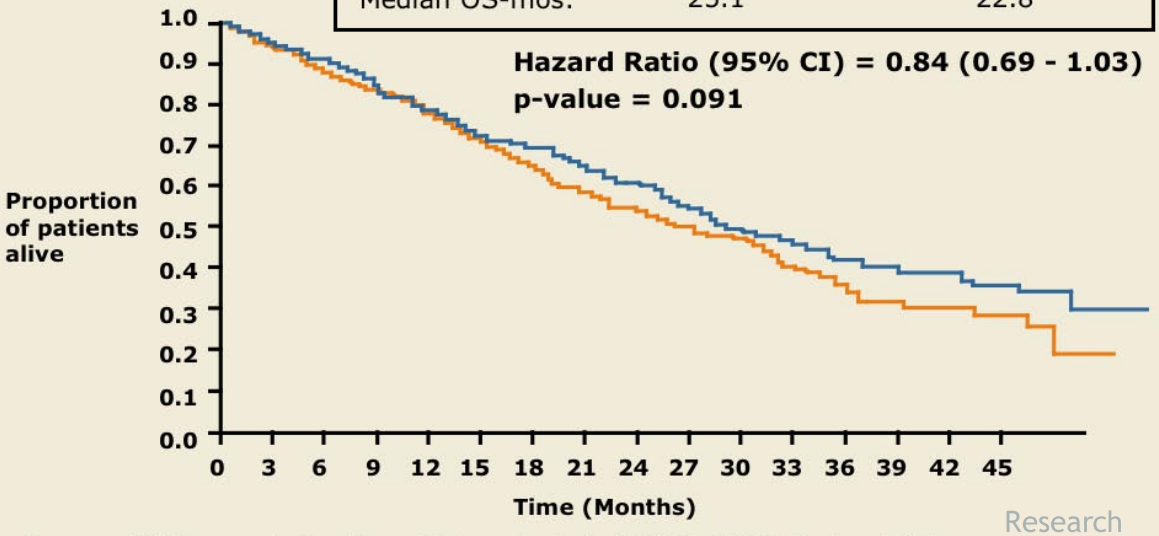
Overall Survival (50% events)

	Fulvestrant 500	Fulvestrant 250
% died	48.3	54.3
Median OS-mos.	25.1	22.8



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Objective Response and Clinical Benefit

	F500 (n=362)	F250 (n=374)	Odds ratio (95% CI)
Objective response rate (%) Complete response (%) Partial response (%)	9.1 1.1 8.0	10.2 0.3 9.9	0.94 (0.57 – 1.55) — —
Clinical benefit rate (%)	45.6	39.6	1.28 (0.95 – 1.71)
Progressive disease (%)	38.7	44.7	—
Median duration of clinical benefit (months)	16.6	13.9	—

Source: Di Leo A et al. SABCS 2009;Abstract 25.

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Pre-specified Adverse Events*

	F500 (n=361)		F250 (n=324)	
	All (%)	≥ Grade 3 (%)	All (%)	≥ Grade 3 (%)
Gastrointestinal disturbances	20.2	2.2	20.3	0.2
Joint disorders	18.8	2.2	18.7	2.1
Injection site reactions	13.6	0.2	13.4	0
Hot flashes	8.3	0	6.1	0
Urinary tract infections	2.2	0.2	2.1	0.2
Ischemic cardiovascular disorders	1.4	0	1.9	0.8
Thromboembolic events	0.8	0.5	1.6	1.0

** Shown are only those adverse events with an incidence of ≥1%.*

Source: Di Leo A et al. SABCS 2009;Abstract 25.

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Conclusions

- TTP was increased in a statistically significant manner with F500 compared to F250.
  - TTP improvement likely a consequence of an increase in the rate of and prolonged duration of disease stabilization.
- The 50% events overall survival analysis appeared to favor F500, although statistical significance has not yet been reached.
  - 75% events overall survival analysis is expected in 2011.
- F500 was well tolerated, with a safety profile consistent with that of F250 and no evidence of dose-dependence for any adverse event.
- Exploratory analyses are underway to identify biologically and clinically defined patient cohorts that might derive the largest benefit from F500 (data not shown).

Source: Di Leo A et al. SABCS 2009;Abstract 25.

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