CP-1

Femara® Clinical Program

Margaret Dugan, MD

Group Leader, Oncology
Clinical Development and Research

Novartis Pharmaceuticals Corporation

NOVARTIS

CP-2

Femara® Phase III Studies

Two prospective, double-blind, randomized, well-controlled, multinational studies in postmenopausal women with breast cancer comparing Femara 2.5 mg versus tamoxifen 20 mg

Pivotal Study 025

First-line therapy in advanced breast cancer

Supportive Study 024

Preoperative treatment if ineligible for breast-conserving surgery

NOVARTIS

CP-3

Study 025

NOVARTIS

Study 025

CP-4

Study Design

	Core phase	Extension phase	Follow-up
RANDOMIZE	Femara® 2.5 mg PO QD	Crossover treatment if appropriate	All patients followed for survival every 6 months
	Tamoxifen 20 mg PO QD		

All treatments:
- Double-blind
- Given until progression

NOVARTIS

Study 025 CP-5

Inclusion Criteria

- Postmenopausal women
- Stage IIIB locally advanced or locoregional recurrence or metastatic breast cancer
- ER and/or PgR positive or both unknown
- Karnofsky Performance Status ≥ 50
- Measurable or evaluable disease

ER = Estrogen receptor.
PgR = Progesterone receptor.

NOVARTIS

Study 025 CP-6

Exclusion Criteria

- Recurrence on adjuvant tamoxifen therapy or within 12 months of completing tamoxifen therapy
- Prior endocrine treatment for metastatic disease
- > 1 systemic chemotherapy for recurrent or advanced disease

NOVARTIS

Study 025 CP-7

Study Endpoints

Primary endpoint

- Time to progression

Secondary endpoints

- Time to treatment failure
- Overall objective response* (CR + PR)
- Clinical benefit (CR + PR + SD ≥ 24 weeks)
- Duration of objective response
- Duration of clinical benefit
- Survival

*UICC criteria.

NOVARTIS

Study 025 CP-8

Patient Evaluations

- Baseline and every 3 months
  - Tumor measurements
  - Performance status
  - Laboratory
- Continuous
  - Adverse events
  - Survival

NOVARTIS

Study 025 CP-9

Primary Endpoint Statistical Considerations

- Assumptions
  - 20% reduction in risk of progression (hazard ratio = 0.80) to demonstrate superiority, 80% power
- Statistical test
  - Unadjusted Cox regression
  - 2 sided, 5% level
- Sample size
  - 450 patients per arm

NOVARTIS

Study 025 CP-10

Further Analyses

- Unadjusted analyses of rates of overall objective response and clinical benefit by logistic regression
- Adjusted multivariate analyses of TTP (Cox regression) and ORR (logistic regression) adjusting for all predefined baseline covariates
  - Prior adjuvant tamoxifen
  - Hormone receptor status
  - Dominant site of disease
- Stratified analyses of TTP (log-rank) and ORR (Mantel-Haenszel) adjusting for each baseline covariate one at a time

ORR = Objective response rate.

NOVARTIS

Study 025 CP-11

Study Enrollment

Total randomized:	**916 (458 Femara®, 458 tamoxifen)**
Number of centers:	**201**
Number of countries:	**29 (Europe, ROW, North America)**
Enrollment period:	**November 1996 - January 1999**
Cutoff date:	**March 8, 2000**

ROW = Rest of world.

NOVARTIS

Study 025 CP-12

Patient Populations

	n (%)		
Randomized	**Femara® N = 458**	**Tamoxifen N = 458**	**Total N = 916**
Initial treatment			
On treatment	**118 (26)**	**72 (16)**	**190 (21)**
Discontinued	**340 (74)**	**386 (84)**	**726 (79)**
Crossover treatment	**200 (44)**	**197 (43)**	**397 (43)**
Intent-to-treat	**453 (99)**	**454 (99)**	**907 (99)**

NOVARTIS

Study 025 CP-13

Demographics

		n (%)		
		Femara® N = 453	Tamoxifen N = 454	Total N = 907
Median age, years		65	64	65
Range		31 - 96	31 - 93	31 - 96
Karnofsky performance status				
100		113 (25)	119 (26)	232 (26)
90		140 (31)	145 (32)	285 (31)
80		117 (26)	111 (26)	228 (25)
70		53 (12)	39 (9)	92 (10)
50, 60		30 (7)	39 (9)	69 (8)
Race	Caucasian	385 (85)	393 (87)	778 (86)
	Black	12 (3)	13 (3)	25 (3)
	Oriental	28 (6)	25 (6)	53 (6)
	Other	28 (6)	23 (5)	51 (6)

NOVARTIS

Study 025 CP-14

Receptor Status

	n (%)		
Receptor status*	Femara® N = 453	Tamoxifen N = 454	Total N = 907
ER+ and PgR+	174 (38)	186 (41)	360 (40)
ER+ or PgR+	120 (26)	119 (26)	239 (26)
Both unknown	156 (34)	149 (33)	305 (34)

*Femara: ER and PgR negative (n = 2), ER negative and PgR unknown (n = 1).

NOVARTIS

CP-15

Disease Classification

	n (%)		
	Femara® N = 453	Tamoxifen N = 454	Total N = 907
Measurable ± EV ± NE	324 (72)	314 (69)	638 (70)
Evaluable ± NE	110 (24)	132 (29)	242 (27)
Nonevaluable only	19 (4)	8 (2)	27 (3)

EV = Evaluable; NE = Nonevaluable.

NOVARTIS

Study 025

CP-16

Sites of Disease

	n (%)		
	Femara® N = 453	Tamoxifen N = 454	Total N = 907
Dominant site of disease			
Soft tissue only	113 (25)	116 (25)	229 (25)
Bone ± soft tissue	146 (32)	130 (29)	276 (30)
Visceral ± bone ± soft tissue	194 (43)	208 (46)	402 (44)
Number of organ sites			
1	159 (35)	170 (37)	329 (36)
2	156 (34)	158 (35)	314 (35)
≥ 3	138 (30)	126 (28)	264 (29)

NOVARTIS

Study 025 CP-17

Disease Stage at Study Entry

	n (%)		
	Femara® N = 453	Tamoxifen N = 454	Total N = 907
Stage IIA/B	2 (< 1)	2 (< 1)	4 (< 1)
Stage IIIA	4 (1)	1 (< 1)	5 (< 1)
Stage IIIB	25 (6)	32 (7)	57 (6)
Stage IV at presentation	114 (25)	111 (24)	225 (25)
Stage IV recurrent	308 (68)	308 (68)	616 (68)
Median disease-free interval*			
Years	2.8	2.8	2.8
Range	0 - 35.4	0 - 35.6	0 - 35.6

*Includes all patients.

NOVARTIS

Study 025 CP-18

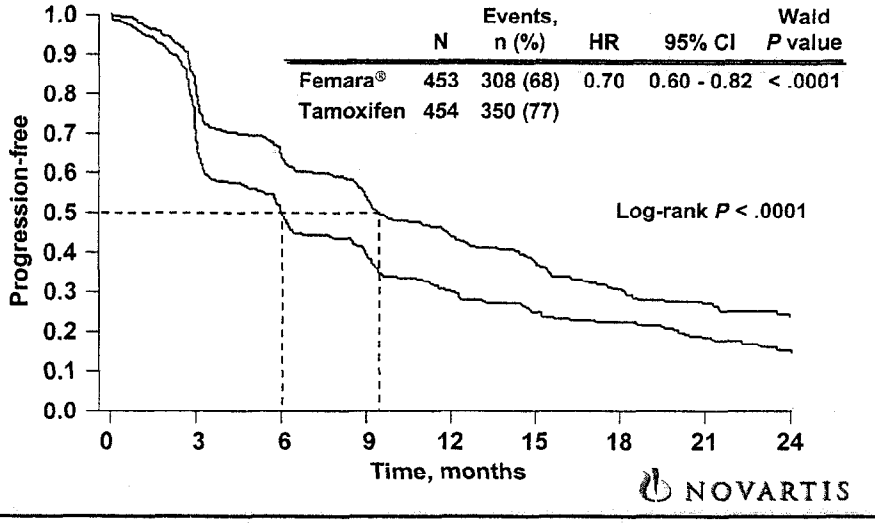
Prior Therapies

	n (%)		
	Femara® N = 453	Tamoxifen N = 454	Total N = 907
Prior systemic adjuvant therapy	160 (35)	176 (39)	336 (37)
Chemotherapy only	76 (17)	93 (20)	169 (19)
Tamoxifen only	58 (13)	53 (12)	111 (12)
Chemotherapy + tamoxifen	26 (6)	30 (7)	56 (6)
Median duration of adjuvant tamoxifen, years (range)	2.8	2.3	
Prior chemotherapy for recurrent or advanced disease	40 (9)	48 (11)	88 (10)

NOVARTIS

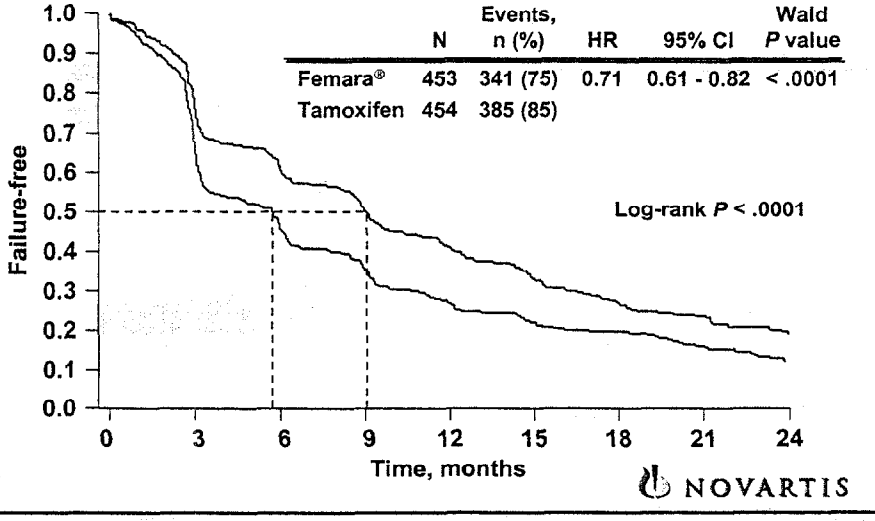
Study 025 CP-19

Time to Progression



Study 025 CP-20

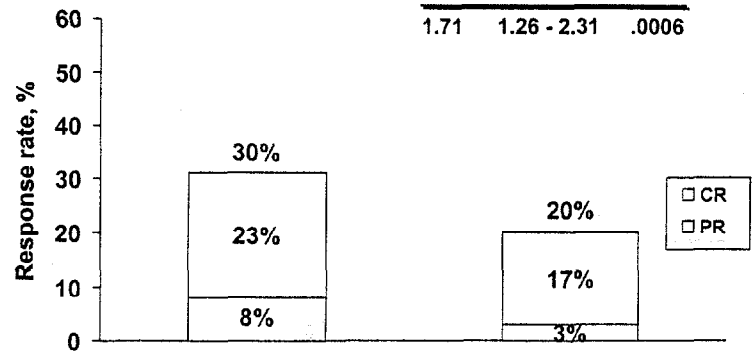
Time to Treatment Failure



Study 025 CP-21

Objective Response Rate

Odds ratio	95% CI	*P* value
1.71	1.26 - 2.31	.0006

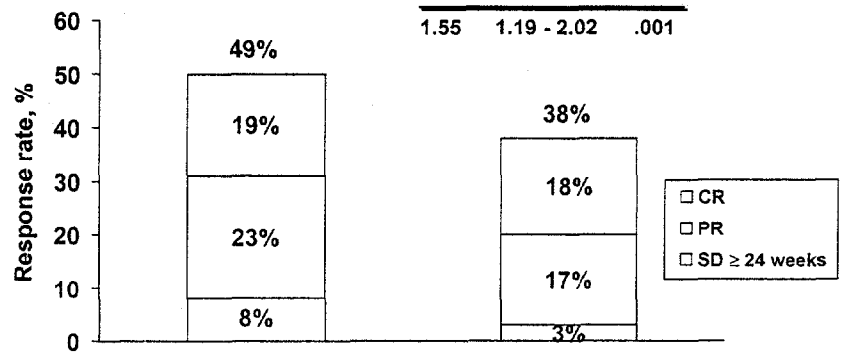


NOVARTIS

Study 025 CP-22

Clinical Benefit Rate

Odds ratio	95% CI	*P* value
1.55	1.19 - 2.02	.001



NOVARTIS

Study P25 CP-23

Median Duration of Response and Clinical Benefit*

	Femara® N = 453	Tamoxifen N = 454	Hazard ratio (95% CI)
Objective response (CR + PR), n (%)	137 (30)	92 (20)	
Median duration, months	23	23	0.84 (0.56 - 1.26)
Clinical benefit (CR + PR + SD ≥ 24 weeks), n (%)	221 (49)	173 (38)	
Median duration, months	19	19	0.81 (0.62 - 1.07)

*UICC criteria.

NOVARTIS

CP-24

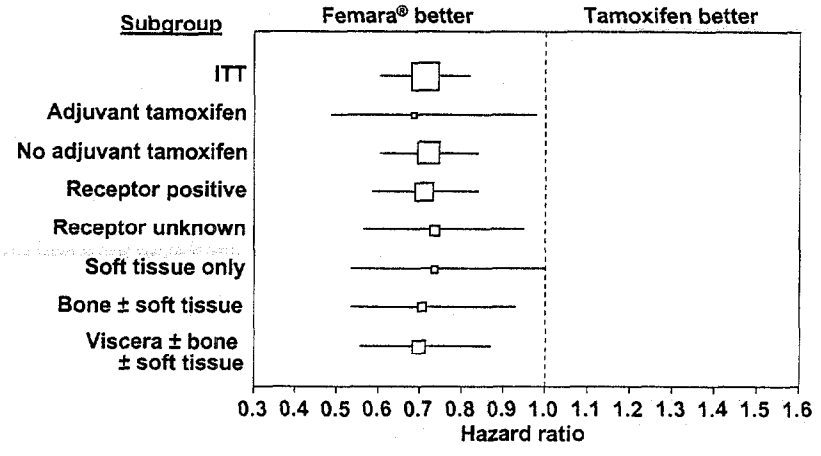
Stratified Analysis of Time to Progression

	Femara®		Tamoxifen		
	n/N	Median TTP, months	n/N	Median TTP, months	Log-rank *P* value
Prior adjuvant treatment					< .0001
None	250/369	9.7	284/371	6.0	
Adjuvant treatment	58/84	8.8	66/83	5.9	
Receptor status					.0001
ER+ and/or PgR+	199/294	9.7	235/305	6.0	
Unknown	109/159	9.2	115/149	6.0	
Dominant site					< .0001
Soft tissue only	68/113	12.9	84/116	6.4	
Bone ± soft tissue	100/146	9.7	97/130	6.2	
Viscera ± bone ± soft tissue	140/194	8.3	169/208	4.7	

NOVARTIS

Study 025 CP-25

Time to Progression Hazard Ratio and 95% CI



Cox regression analysis.

NOVARTIS

CP-26

Stratified Analysis of Overall Objective Response

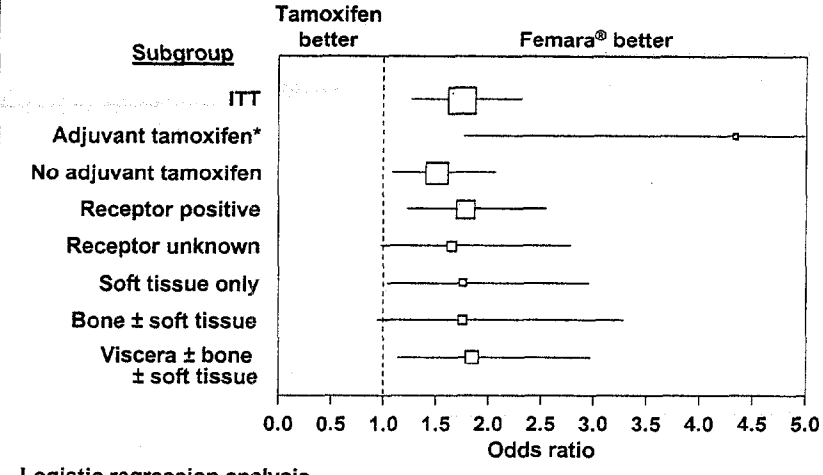
	n/N (%)		
	Femara®	Tamoxifen	*P* value*
Prior adjuvant treatment			< .001
None	113/369 (31)	85/371 (23)	
Adjuvant treatment	24/84 (29)	7/83 (8)	
Receptor status			< .001
ER+ and/or PgR+	92/294 (31)	63/305 (21)	
Unknown	45/159 (28)	29/149 (20)	
Dominant site			< .001
Soft tissue only	54/113 (48)	40/116 (35)	
Bone ± soft tissue	32/146 (22)	18/130 (14)	
Viscera ± bone ± soft tissue	51/194 (20)	34/208 (16)	

*Cochran Mantel-Haenszel.

NOVARTIS

Study 025 CP-27

Overall Objective Response Odds Ratio and 95% CI



Logistic regression analysis.
*Upper limit of 95% CI = 10.8

NOVARTIS

Study 025 CP-28

Efficacy Summary

Study 025 in first-line therapy demonstrated that Femara® is consistently superior to tamoxifen in

- **Time to tumor progression**
- **Time to treatment failure**
- **Response rate**
- **Clinical benefit rate**
- **All subgroup analyses of time to progression**

NOVARTIS

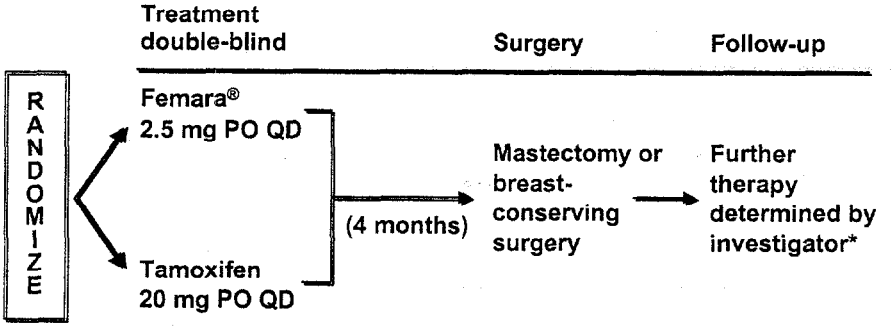
CP-29

Study 024

NOVARTIS

Study 024 CP-30

Study Design



*Yearly follow-up for 5 years for relapse and survival.

NOVARTIS

Study 024 CP-31

Entry Criteria

- Postmenopausal women with breast cancer
- Not eligible for breast-conserving surgery
- ER and/or PgR positive
- Clinical stage T2, T3, T4a,b,c, N0-2, M0
- Measurable disease

NOVARTIS

12 *Study 024* CP-32

Study Endpoints

Primary

- Response rate (CR + PR) by clinical palpation

Secondary

- Response rate by
  - Ultrasound
  - Mammography
- Breast-conserving surgery

Correlative science protocol

NOVARTIS

Study 024 CP-33

Primary Endpoint Statistical Considerations

- Assumptions
  - 65% response rate on tamoxifen
  - 15% difference in clinical response rate, 80% power
- Statistical test
  - Stratified* Mantel-Haenszel
  - 2 sided, 5% level
- Sample size
  - 151 patients per arm

*On tumor size (T2/>T2) and nodal involvement (Yes/no).

NOVARTIS

Study 024 CP-34

Study Enrollment

Enrollment period:	March 1998 - August 1999
Number of centers:	55
Number of countries:	16
Total randomized:	337 (162 Femara®, 175 tamoxifen)
Intent-to-treat:	324 (154 Femara, 170 tamoxifen)

NOVARTIS

Study 024 CP-35

Baseline Characteristics

	n (%)		
	Femara® N = 154	Tamoxifen N = 170	Total N = 324
Median age, years	68	67	67
Range	(44 - 91)	(48 - 89)	(44 - 91)
Receptor status*			
ER + and PgR +	90 (58)	91 (54)	181 (56)
ER + or PgR +	64 (42)	76 (45)	140 (43)
Tumor stage			
T2	77 (50)	91 (54)	168 (52)
T3	42 (27)	31 (18)	73 (23)
T4	35 (23)	48 (29)	83 (25)

*Tamoxifen: ER and PgR negative (n = 2), ER negative and PgR unknown (n = 1).

NOVARTIS

1 *Study 024* CP-36

TNM Stage

	Femara® N = 154	Tamoxifen N = 170	Total N = 324
Stage IIA (T2N0)	44 (29)	57 (34)	101 (31)
Stage IIB (T2N1,T3N0)	43 (28)	35 (21)	78 (24)
Stage IIIA (T2N2, T3N1, T3N2)	32 (21)	30 (18)	62 (19)
Stage IIIB* (T4a to T4c, any N)	35 (23)	48 (28)	83 (26)

*N_3 disease excluded.

NOVARTIS

Study 024 CP-37

Efficacy Results

	n (%)		
	Femara® N = 154	Tamoxifen N = 170	*P* value*
Response rate			
Clinical	85 (55)	61 (36)	< .001
Ultrasound	54 (35)	43 (25)	.042
Mammography	53 (34)	28 (17)	< .001
Breast-conserving surgery	69 (45)	59 (35)	.022

*Stratified Mantel-Haenszel chi-square test.

NOVARTIS

Study 024 CP-38

Efficacy Summary

Study 024 demonstrated in therapy-naive patients that Femara® is superior to tamoxifen in rate of response and breast-conserving surgery

NOVARTIS

CP-39

Safety

NOVARTIS

CP-40

All Adverse Events ≥ 10%*

	Percent of patients			
	Study 025		Study 024	
Adverse events	Femara® N = 455	Tamoxifen N = 455	Femara® N = 157	Tamoxifen N = 170
Bone pain	20	18	< 1	< 1
Hot flashes (NOS)	18	15	20	25
Back pain	17	17	3	2
Nausea	15	16	6	8
Dyspnea (NOS)	14	14	< 1	2
Arthralgia	14	13	3	3
Fatigue	11	11	5	5
Cough	11	10	2	2

*Adverse events ≥ 10% in either study, irrespective of drug relationship.

NOVARTIS

CP-41

Study 025
Selected Adverse Events

Adverse event	n (%) Femara® N = 455	Tamoxifen N = 455
Thromboembolic events	6 (1)	11 (2)
Pulmonary embolism*	1 (< 1)	1 (< 1)
Angina/MI	15 (3)	13 (3)
Cerebrovascular events	12 (3)	9 (2)
Fractures	25 (6)	27 (6)

*1 additional patient in study 024 had a PE (Femara group).

NOVARTIS

CP-42

Femara® Safety Summary

- Well tolerated
- Low incidence of adverse events

NOVARTIS

CP-43

Conclusions

NOVARTIS

CP-44

Clinical Conclusions

- Study 025 is the largest single, double-blind, randomized study in first-line therapy
  - Femara® is consistently superior to tamoxifen in multiple efficacy endpoints
    - TTP, TTF, ORR, clinical benefit
  - Femara is consistently superior to tamoxifen across prospectively defined study subsets
- Study 024 supports superior efficacy of Femara compared with tamoxifen
- Femara is safe and well tolerated

NOVARTIS

CP-45

Proposed New Indication

Femara® is indicated as first-line hormonal therapy in postmenopausal women with advanced breast cancer

NOVARTIS

CP-46

Summary

- Breast cancer remains an important health issue worldwide
- Newer endocrine therapies are needed in advanced breast cancer
- Aromatase inhibitors are established second line therapy
- Femara® is more potent and effective than either anastrozole or tamoxifen (preclinical)

NOVARTIS

CP-47

Summary

- Femara is superior to tamoxifen in the largest single, randomized clinical trial in first-line therapy
- Femara sets a new Standard of Care in the treatment of postmenopausal women with advanced breast cancer

NOVARTIS

CP-48

Questions and Answers

NOVARTIS