

Case #2: Management of Locally Advanced, Endocrine-Responsive Breast Cancer Parts I and II

Vladimir Semiglazov, MD
NN Petrov Research Institute of Oncology
St Petersburg, Russia



Comparison Between Neoadjuvant and Adjuvant Therapies: Risks and Benefits

- Disease-free survival (DFS) and overall survival (OS) are equivalent in patients treated with the same adjuvant or neoadjuvant chemotherapy regimen¹
- Neoadjuvant therapy has the following clinical advantages²:
 - Improves surgical options
 - Response to neoadjuvant therapy is a predictor of long-term outcome
 - Pathologic CR correlates with improved DFS and OS
 - Neoadjuvant therapy can be offered to candidates for adjuvant therapy, regardless of tumor size
- Neoadjuvant therapy is also associated with significantly increased risk of locoregional disease recurrence, especially when radiotherapy without surgery was used¹

1. Mauri D, et al. *J Natl Cancer Inst.* 2005;97(3):188-194.

2. Kaufmann M, et al. *J Clin Oncol.* 2006;24(12):1940-1949.

Appropriately Selected Neoadjuvant Therapies Can Improve Surgical Outcomes

- For postmenopausal women with hormone receptor–positive disease, neoadjuvant therapy with anastrozole, letrozole, or exemestane provided objective response and superior rates of breast-conserving surgery than treatment with tamoxifen¹⁻⁴
- For women with operable breast cancer, preoperative anthracycline-based neoadjuvant chemotherapy allowed significantly higher rates of breast-conserving surgery, compared with postoperative chemotherapy (68% vs 60%, $P = .002$)⁵
- Women with HER2-positive tumors who added trastuzumab to neoadjuvant chemotherapy had an significant increase in pCR rate.^{6,7}

1. Smith IE, et al. *J Clin Oncol.* 2005;23(22):5108-5116.

2. Ellis MJ, et al. *J Clin Oncol.* 2001;19(18):3808-3816.

3. Semiglazov V, et al. *Eur J Cancer.* 2006;4:117

4. Semiglazov V, et al. *J Clin.Oncol.* 2005;23(Suppl I);Abstract 530.

5. Fisher B, et al. *J Clin Oncol.* 1998;16(8):2672-2685.

6. Buzdar AU, et al. *J Clin Oncol.* 2005;23(16):3676-3685.

7. Gianni L et al. *Lancet.* 2010;375(9712):377-384.

Phase III Randomized Clinical Trials AI vs TAM

	Drug	N	Clinical Response	US Response	Increase in BCS
P024 ¹	Letrozole	154	55%	35%	45%
4 months	Tamoxifen	170	36%	25%	35%
IMPACT ²	Anastrozole	113	37%	24%	46%
3 months	Tamoxifen	108	36%	20%	22%
	Both	109	39%	28%	26%
PROACT ³	Anastrozole	228	50%	40%	38%
3 months	Tamoxifen	223	46%	35%	30%

1. Ellis M, et al. *Breast Cancer Res Treat.* 2007;105(Suppl 1):33-43. 2. Smith IE, et al. *J Clin Oncol.* 2005;23(22):5108-5116. 3. Cataliotti L, et al. *Cancer.* 2006;106(10):2095-2103.

ER-Negative Tumors: Higher pCR to Chemotherapy

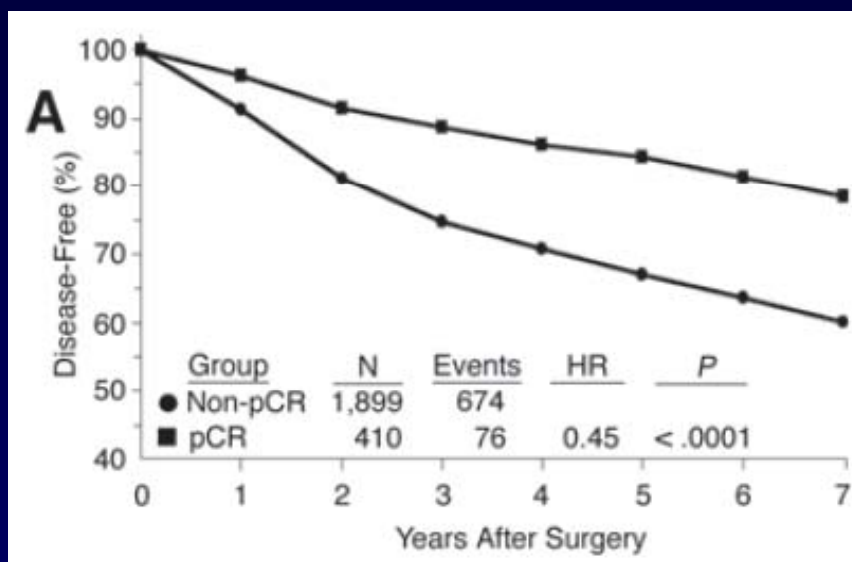
Table 8. Hormone receptor content and pCR

Author	No. of Patients	Regimen	% HR Negative	% pCR in HR Negative	% pCR in HR Positive
Houston (pooled data)	1,018	Pooled data	NA	20.6	5.6
von Minckwitz et al ⁴ (Geparduo)	913	dd AD/AC- docetaxel	26.3	22.8	6.2
Gianni et al ⁵⁰ (ECTO)	438	AP-CMF	38.2	42.2	11.6
Bear et al ²¹ (NSABP-B27)	2411	AC v AC-docetaxel	32	16.7	8.3
von Minckwitz et al ⁶ (Gepartrio)	286	DAC/DAC-NX	31.9	36.6	10.1
von Minckwitz et al ³⁰ (Gepardo)	250	dd AD+/Tam	43.9	15.4	1.1

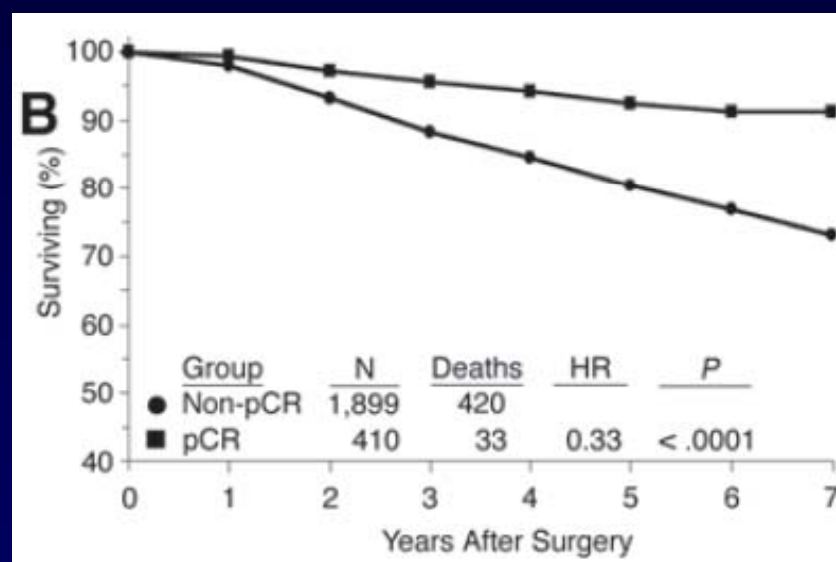
Abbreviations: dd, dose dense; pCR, pathologic complete remission; HR, hormone receptor; NA, not available; AD, doxorubicin and docetaxel; AC, doxorubicin and cyclophosphamide; ECTO, European Cooperative Trial in Operable Breast Cancer; AP, doxorubicin and paclitaxel; CMF, cyclophosphamide, methotrexate, and fluorouracil; DAC, docetaxel, doxorubicin and cyclophosphamide; NX, vinorelbine and capecitabine; Tam, tamoxifen.

Pathologic Complete Response to Neoadjuvant Chemotherapy Is Correlated with Improved Disease-Free and Overall Survival (NSABP B-27)

Disease-free survival

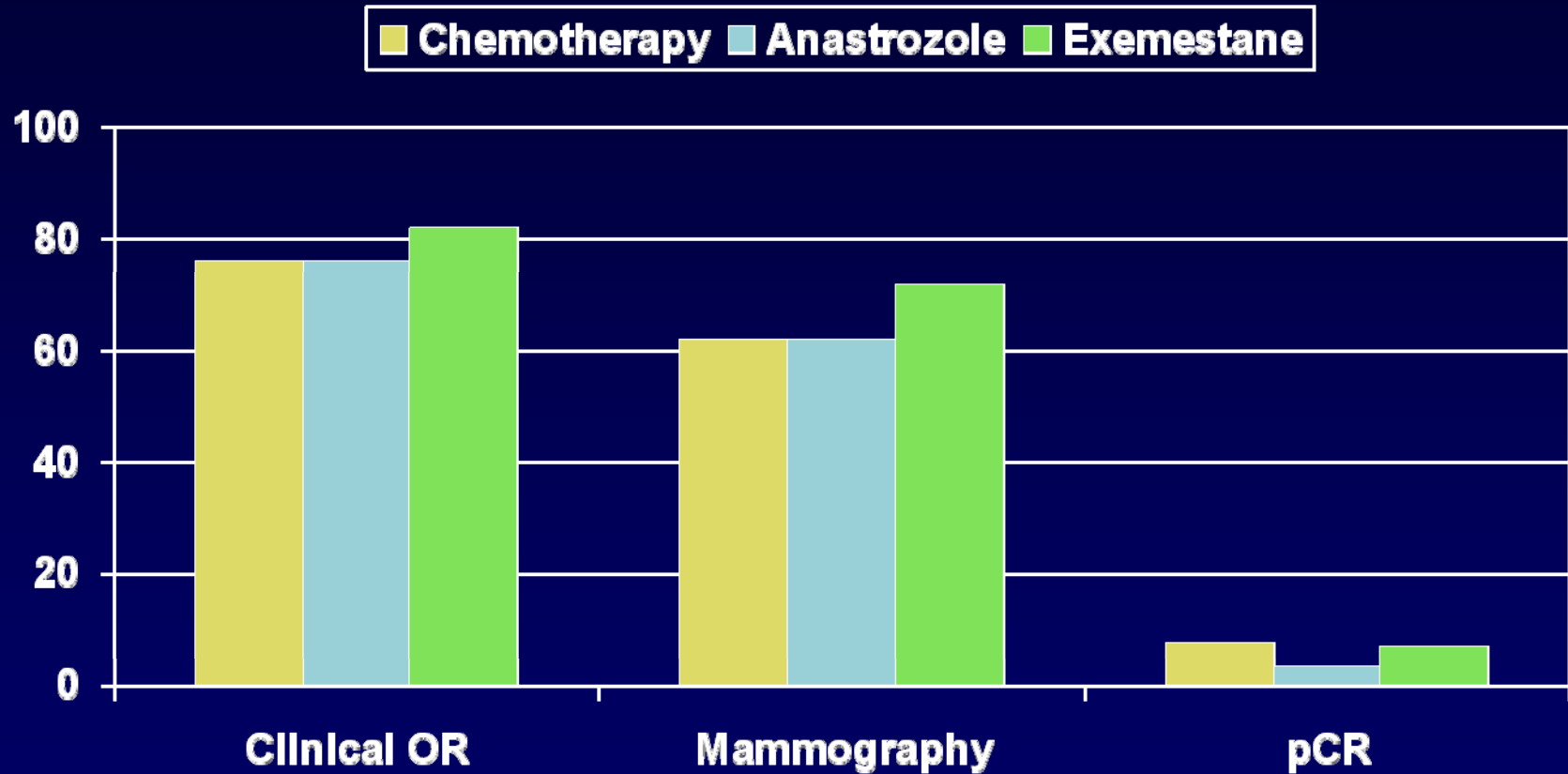


Overall survival



- There was no significant difference in overall survival (OS) between the treatment arms (data not shown).
- Pathologic CR (pCR) was a significant predictor of OS, regardless of treatment.

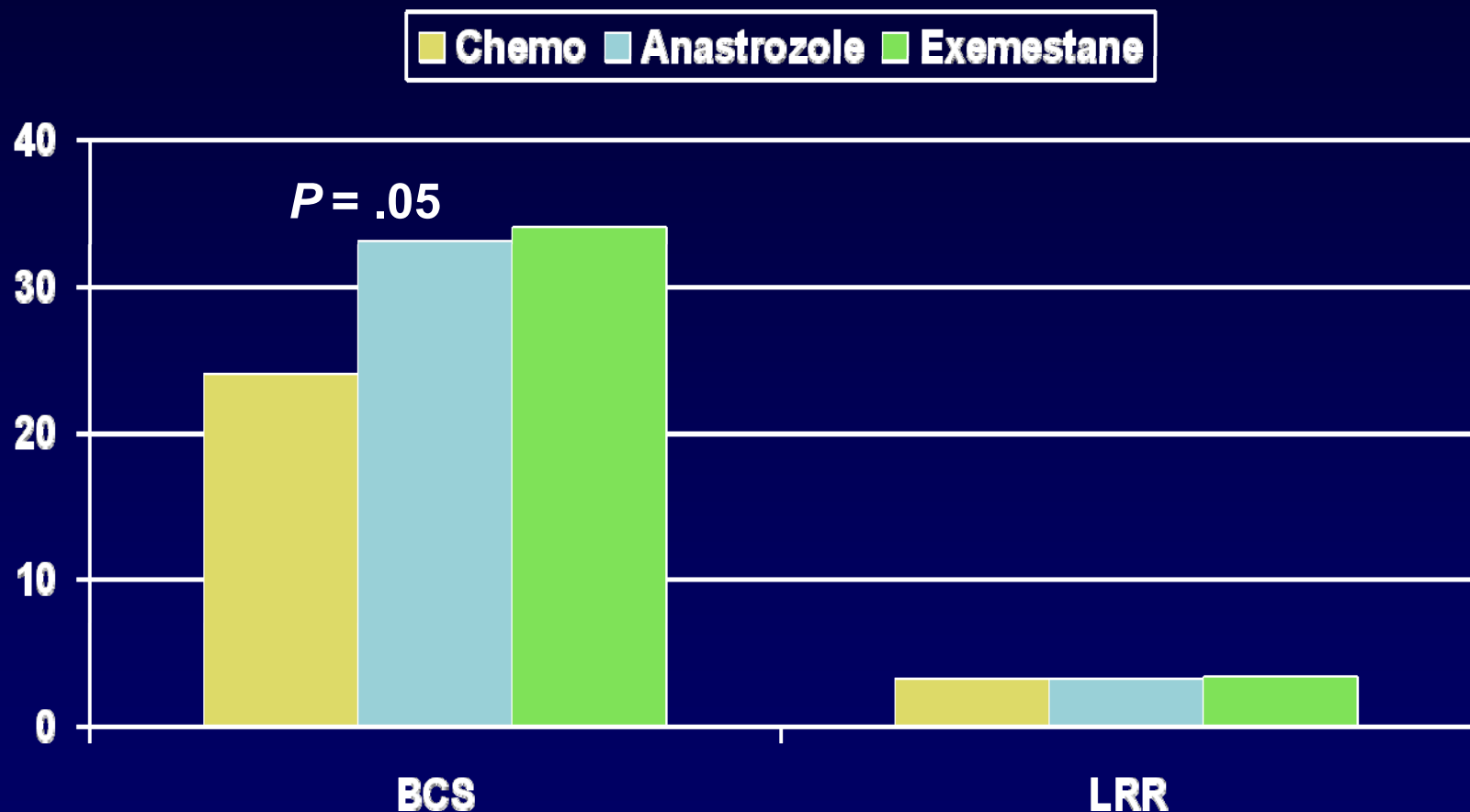
Neoadjuvant Chemotherapy vs Hormonal Therapy: Response



Semiglazov V, et al. *Eur J Cancer*. 2006;4:117.

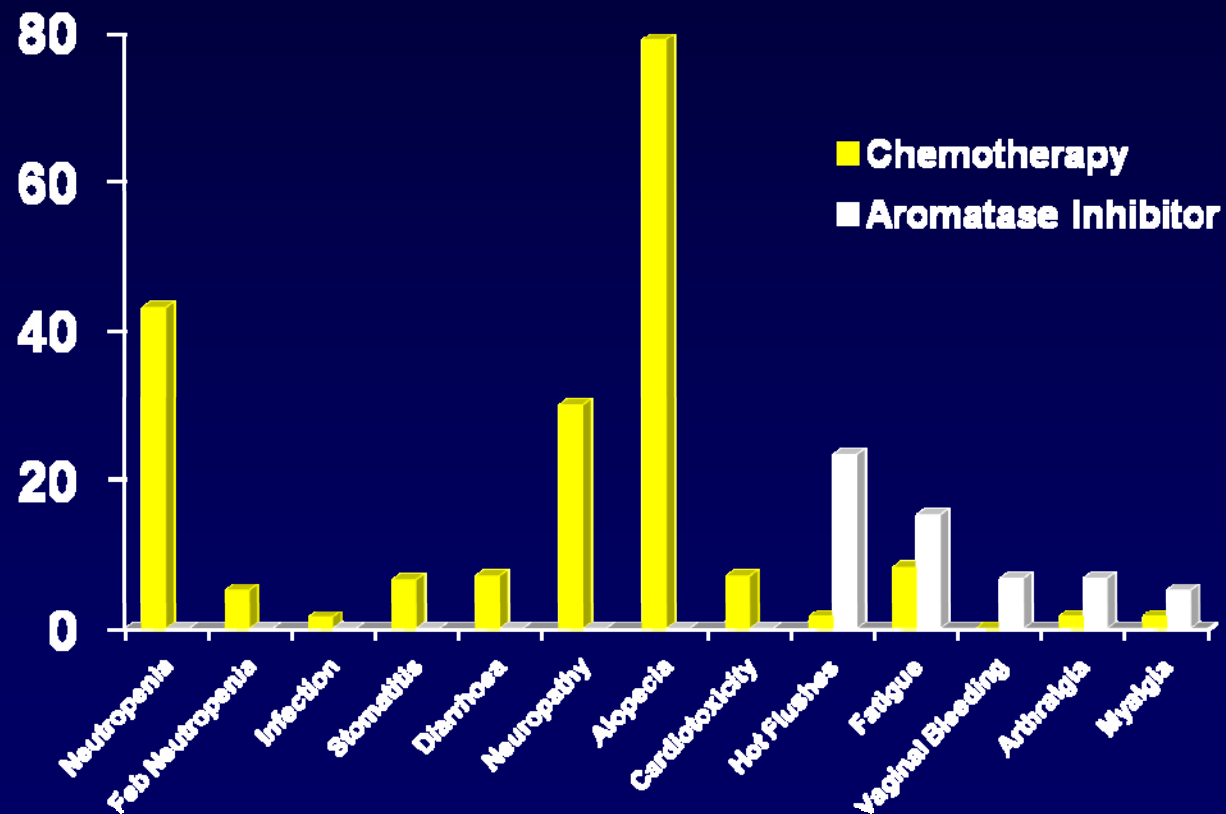
Semiglazov V, et al. *Cancer*. 2007;110(2):244-254.

Neoadjuvant Chemotherapy vs Hormonal Therapy: Breast Conserving Surgery



Semiglazov V, et al. *Eur J Cancer*. 2006;4:117.
Semiglazov V, et al. *Cancer*. 2007;110(2):244-254.

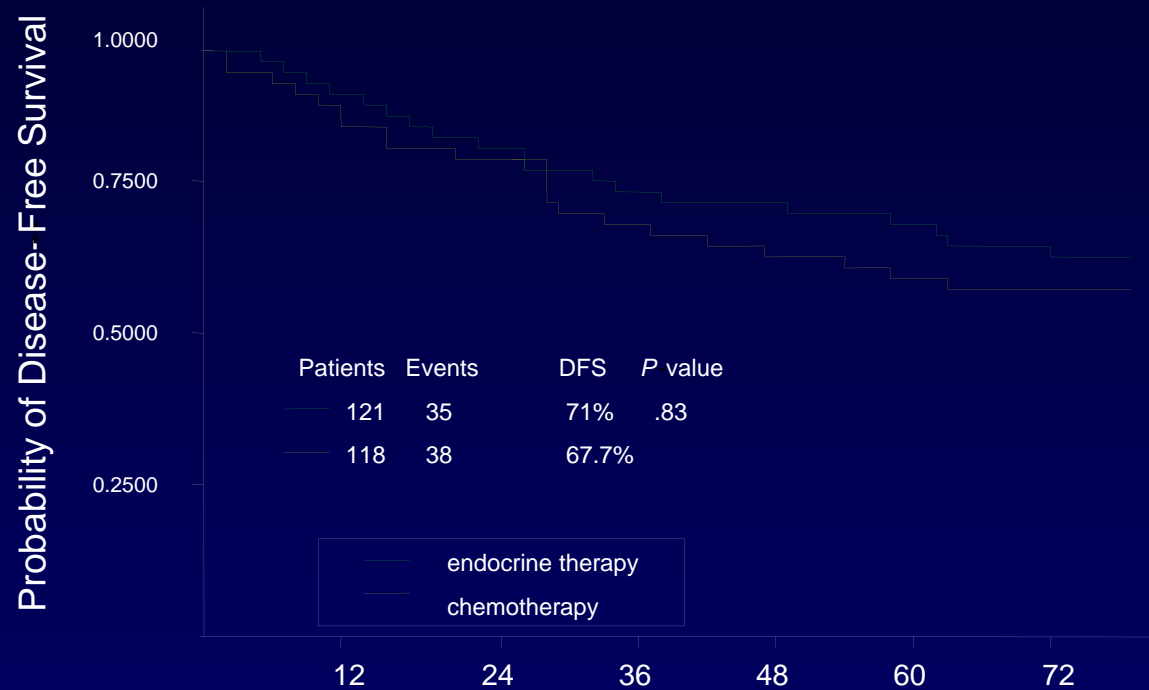
Neoadjuvant Chemotherapy vs Hormonal Therapy: Side Effects



Semiglazov V, et al. *Eur J Cancer*. 2006;4:117.

Semiglazov V, et al. *Cancer*. 2007;110(2):244-254.

Neoadjuvant Chemotherapy vs Hormonal Therapy: DFS (ITT)



Five-years DFS (intent to treat) in 121 patients who received neoadjuvant endocrine therapy and 118 women who received chemotherapy

Akashi Neoadjuvant Study

National Cancer Center Hospital (Tokyo, Japan)

- **N = 87 postmenopausal women with operable ER and PR positive breast tumors >3 cm who received neoadjuvant endocrine therapy (anastrozole or tamoxifen x 4 months)**
 - **21-gene recurrence score (Oncotype DX[®]) determined from pretreatment core biopsy specimens (ten 3- μ m sections and 2 hematoxylin and eosin sections from each core needle biopsy)**
- **Primary tumors were clinically assessed by measuring their size in 2 dimensions with calipers (WHO response criteria)**
- **Relapse-free survival was defined as time from the initiation of treatment to local, regional, or distant treatment failure**

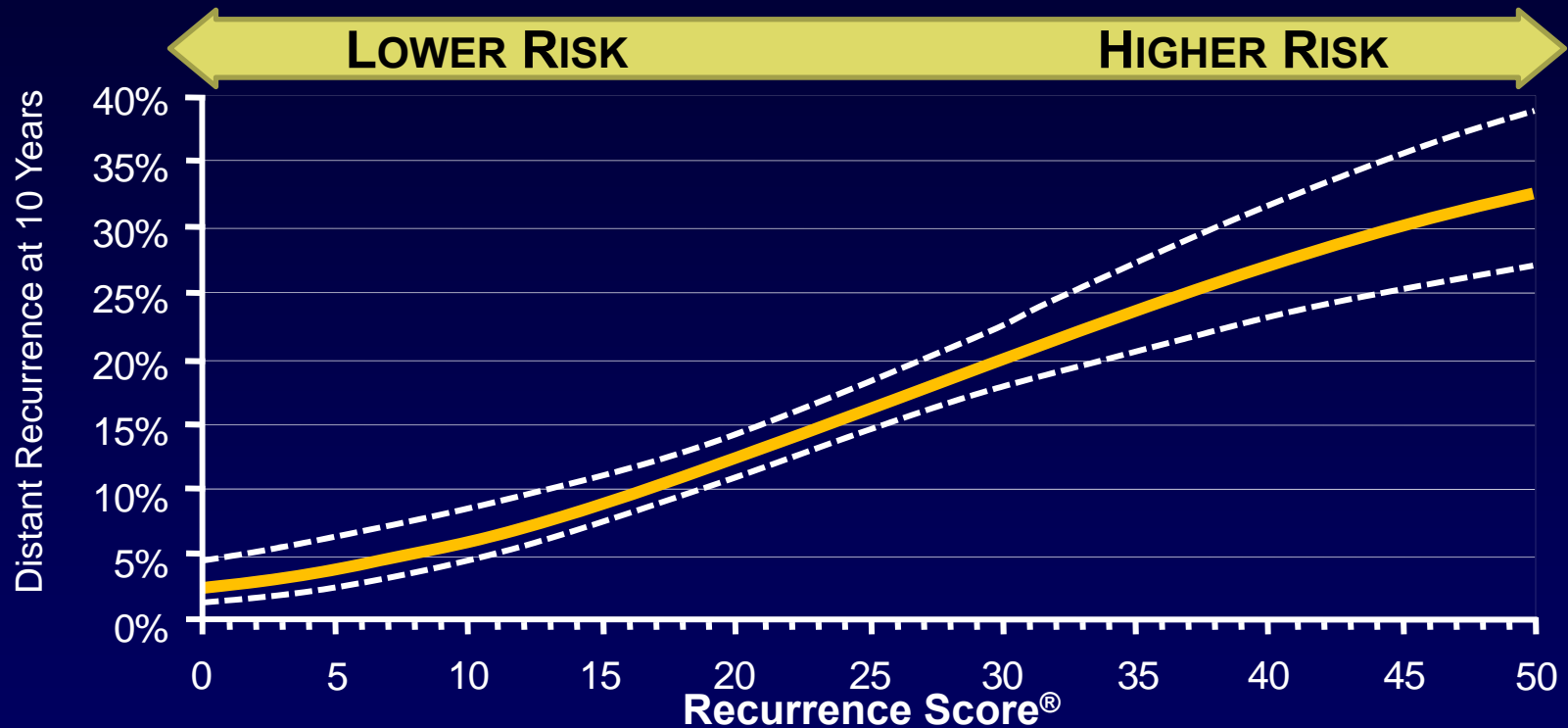
The Recurrence Score Predicts Response to Neoadjuvant Endocrine Treatment

Clinical Response Rate by Recurrence Score (RS)

Neoadjuvant treatment	RS <18	RS 18-30	RS ≥31	N	P value trend
Tamoxifen	2 (67%)	2 (33%)	2 (40%)	14	0.53
Anastrozole	5 (63%)	3 (30%)	3 (27%)	29	0.13
All	7 (64%)	5 (31%)	5 (31%)	43	0.11

- Low RS tended to have better clinical response than intermediate and high RS
- RS tended to predict response both in tamoxifen and anastrozole groups
- Low RS tended to have better relapse-free survival than intermediate and high RS (5-year RFS: 100% vs 84% and 73% respectively)

Exploratory Neoadjuvant Studies Are Consistent with Adjuvant Studies



In both the adjuvant AND neoadjuvant settings:

The lower the Recurrence Score:

- The lower the benefit of chemotherapy
- The greater the benefit of endocrine therapy

The higher the Recurrence Score:

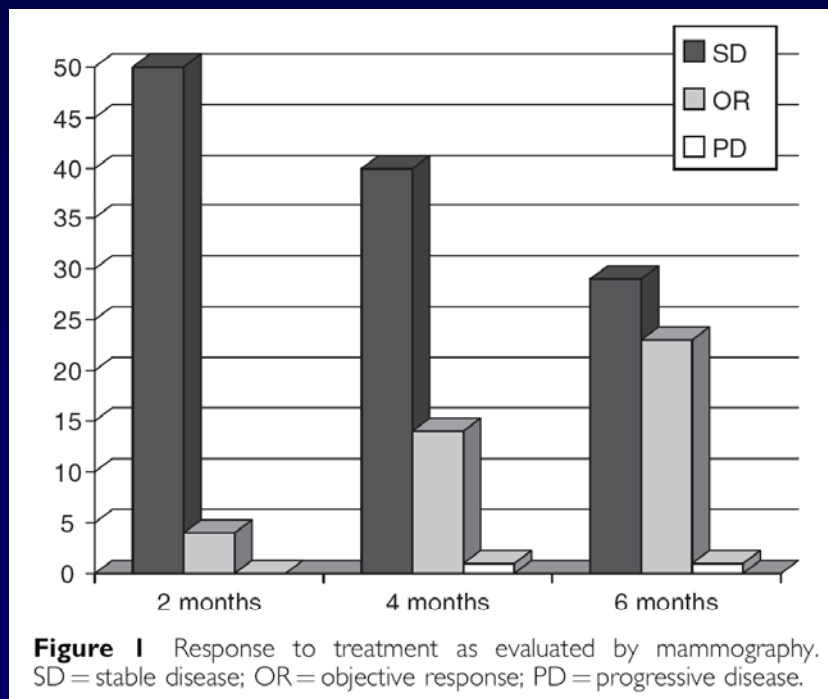
- The greater the benefit of chemotherapy
- The lower the benefit of endocrine therapy

Response to Aromatase Inhibitors

Letrozole¹

	% CR
3 months	9.5
6 months	28.6

Exemestane²



1. Dixon JM. *Breast Cancer Res Treat.* 2004;88(Supp; 1):Abstract 405. 2. Barnadas A, et al. *Br J Cancer.* 2009;100(3):442-449.

My Opinion

Part I. Option 1. Neoadjuvant Endocrine Therapy.

Part II. Option 2. Continue with same endocrine agent since 12 weeks is a too short period for response evaluation in endocrine-responsive disease.