National Cancer Institute

Preoperative Therapy in Invasive Breast Cancer

Reviewing the State of the Science and Exploring New Research Directions

"Window of opportunity" studies: Biologic opportunities and ethical issues

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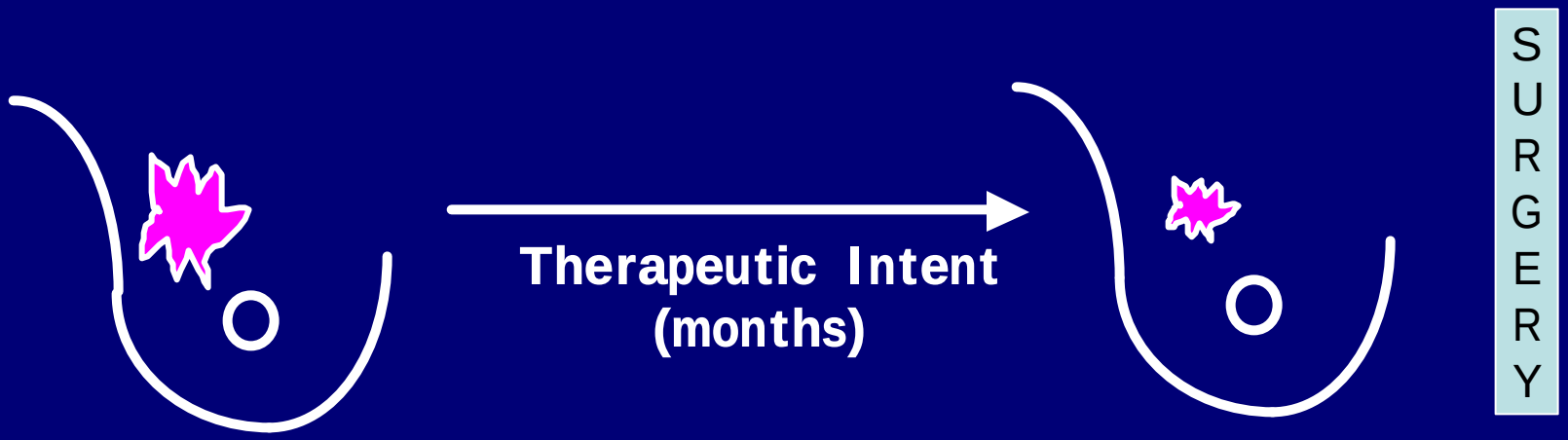
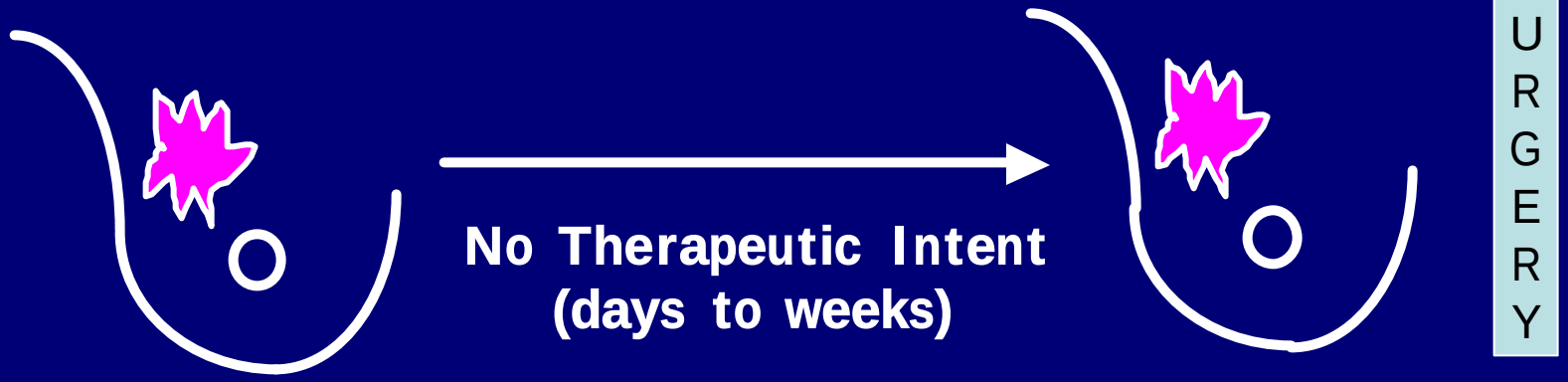
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Different Window Designs





Why conduct “window studies”?

- Demonstrate that potential chemoprevention agents have relevant biological effects against tumor cells
- Identify tumor resistance or sensitivity profiles to targeted agents
- Demonstrate a biological agent has expected mechanism of action
- Establishing “biologically effective dose”

Practical constraints for “no therapeutic intent” window studies

- Ethical and practical difficulties of conducting studies when there is no expected patient benefit
- Restricted to “non-toxic” agents with a very well established toxicity profile
- Logistics of sample collection and consent
- Relies on robust “surrogate endpoints” for clinical events or relevant biological effects
- Surgical setting may present special difficulties with certain agents

Examples of agents assessed in window studies

- Endocrine agents with low short term toxicity
- Dietary components
- Commonly used drugs with “incidental anticancer activity” (COX2 inhibitors and statins)
- Signal transduction inhibitors with a very well established toxicity profile

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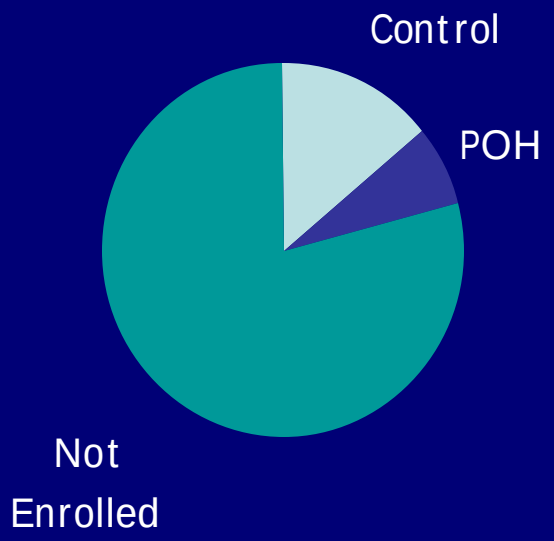
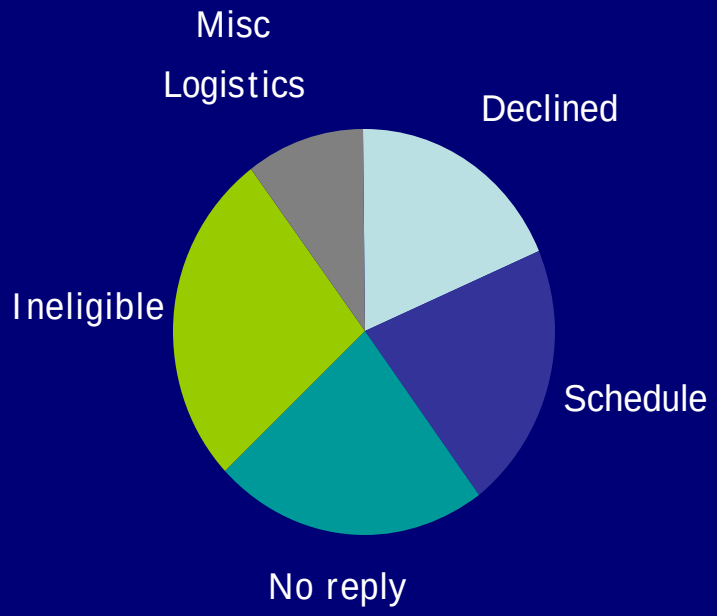
Perillyl Alcohol Window study

All patients screened
N = 267



Reasons for non-participation
N = 230



Stearns et al, Clinical Cancer Research, 10: 7583-7591, 2004

Ethical Issues

- Potential for patient harm in the early disease setting
- Discussion of research with patients who are experiencing a high level of distress due to a recent diagnosis of breast cancer
- May interfere with subsequent clinical trial accrual

Paired Samples (no dedicated tissue accrual)

Type of lesion on biopsy	Number of patients	% times lesion the same
IDC	26	15 (58%)
ILC	4	1
IDC/ILC	1	1
DCIS	4	3
Atypical Medullary	1	0
ALL	36	20 (56%)

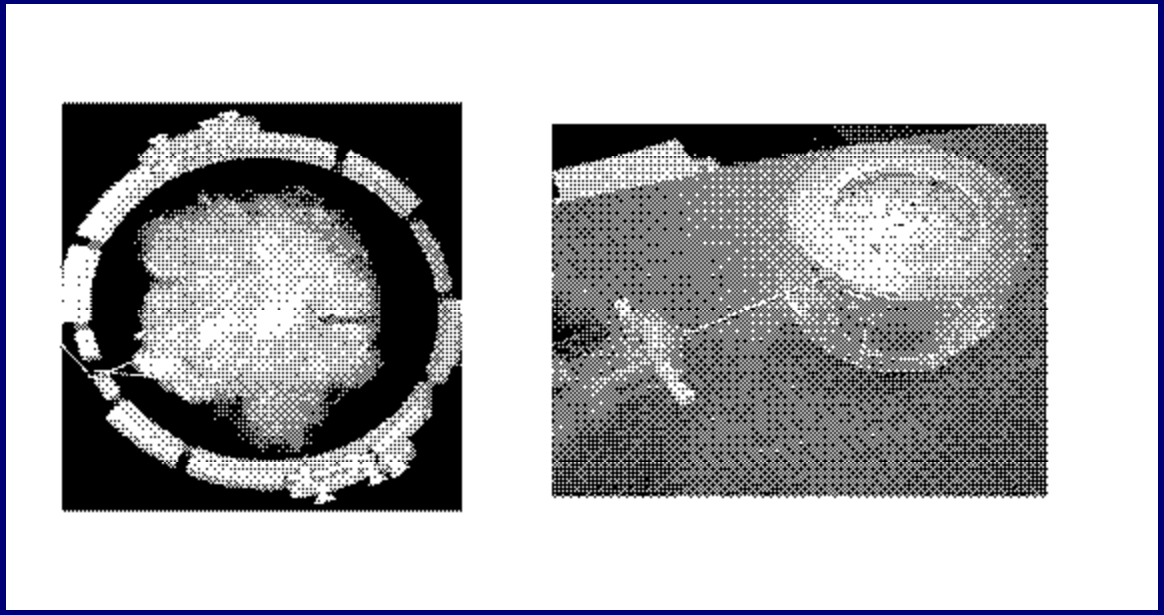
Stearns et al, Clinical Cancer Research, 10: 7583-7591, 2004

Dedicated frozen tissue acquisition

T Stage	N	# Cores/pat	Ave # Cores > 60% cancer	# patients with a 60% cancer core	# patients with any cancer in core
T0 (DCIS)	11	3.5	0.0	1	5
T1	85	3.8	1.2	49	70
T2	40	5.1	2.0	31	40
T3	8	5.0	2.3	6	7
T4	6	3.0	1.0	4	5

Clinically Applicable Frozen Tumor Tissue Collection and Gene Expression-Based Predictions of Breast Cancer Phenotypes Tebbit et al, submitted

Options to improve Tissue Acquisition at surgery



Obtain extra samples during diagnostic radiology

Dedicated device to obtain samples at lumpectomy

Clinically Applicable Frozen Tumor Tissue Collection and Gene Expression-Based Predictions of Breast Cancer Phenotypes Tebbit et al, submitted

Dedicated frozen tissue acquisition

Biopsy Device	N	# Cores/pat	# Cores > 60% cancer	# patients with a 60% cancer core	# patients with any cancer in core
YES	**18**	**6.2**	**2.3**	**15** P=0.001	**17** P=0.37
NO	**75**	**4.9**	**1.7**	**19**	**53**

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Ki67 is a PD biomarker

	Mammography Response Cases(%)	Clinical Response Cases (%)	Ki67 Response Cases (%)
Letrozole	32/79 (40.5)	56/79 (70.9)	54/78 (69.2)
Tamoxifen	21/90 (23.3)	45/90 (50.0)	35/88 (39.8)
P value *	0.0167	0.0059	0.0002

*Mantel-Haenszel for L versus T

Tao, Y et al J Steroid Biochem Mol Biol 95:91-5, 2005

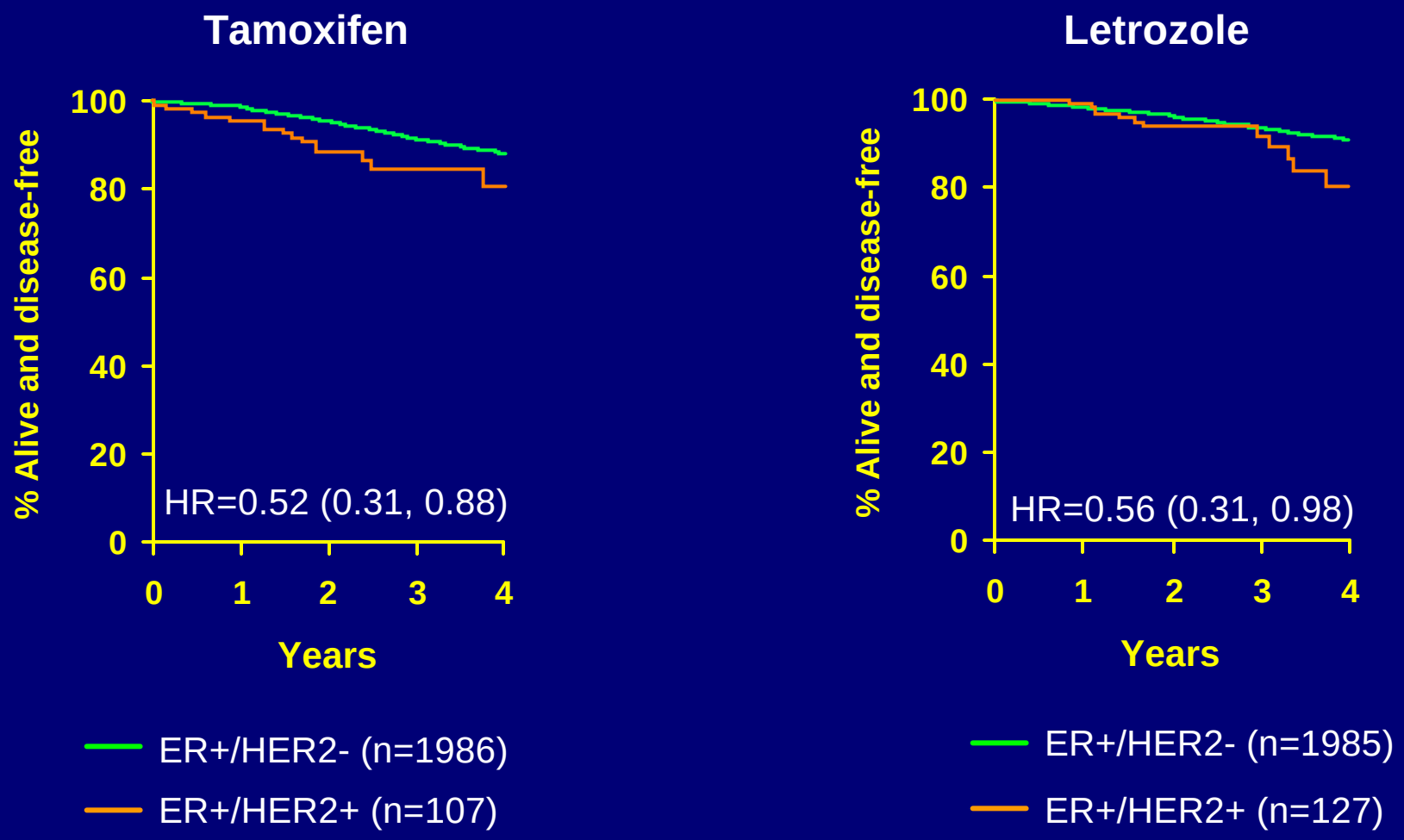
Effect of Letrozole on Proliferation by HER2 Status

	HER2 FISH+	HER2 FISH-	Total	Fisher
Cell cycle CR - Yes	2	111	113	
Cell cycle CR - No	15	73	88	
Total	17	184	201	0.0001

P024 letrozole arm combined with Edinburgh letrozole audit series.

Ellis et al. *J Clin Oncol*. 2006;24:3019.

DFS: ER+/HER2 by Treatment



Viale et al. SABCS, 2005. Abstract 44.

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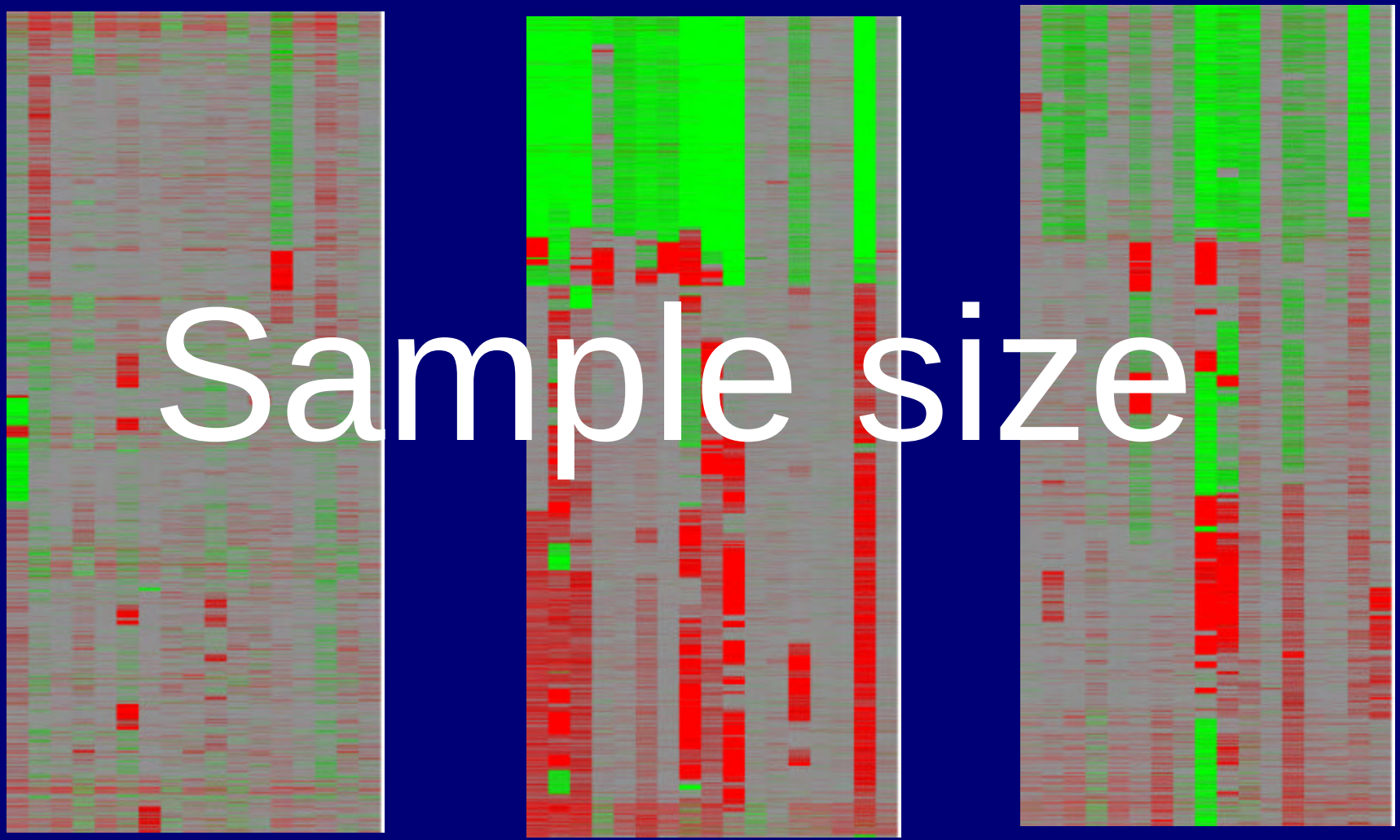
Correlative Science Approach

Ki67 analysis
Agilent whole genome 44K chip
Agilent 244K array CGH
Gene Resequencing
IHC with phosphoprotein-specific antibodies

Ki67 analysis
IHC with phosphoprotein-specific antibodies
Tumor response

Array Comparative Genomic Hybridization

7 8 17



ACOSOG Z1031

Accrual 78/375

PI M.J. Ellis.
Status Active: http://www.ctsu.org/.

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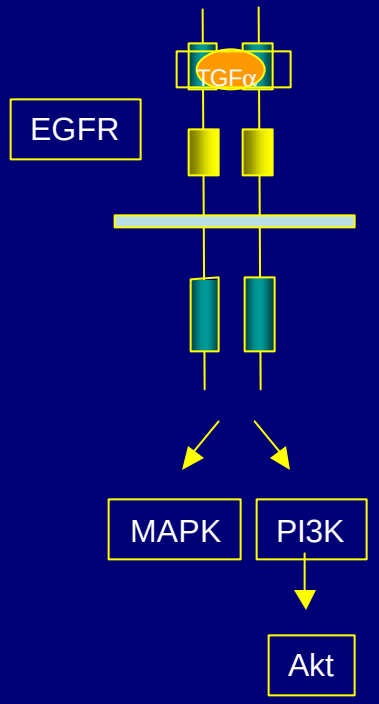
VICC BRE0222: EGFR inhibitor erlotinib in untreated operable breast cancer

Breast Cancer T1-2/N0-1 (core biopsy) → **Erlotinib (7-10 days)** → **Surgery**

Ki-67 TUNEL → **Ki-67 TUNEL**

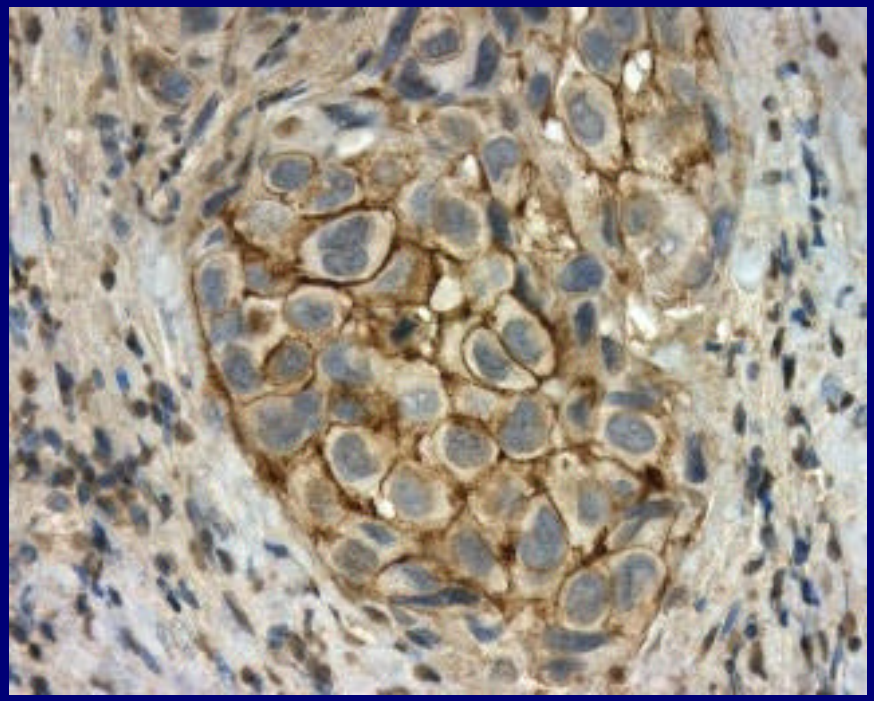
EGFR
P-EGFR
HER2
ER/PR



Is there a biomarker that can identify breast cancers in which the EGFR inhibitor reduces proliferation and that can, thus, be used for patient selection into trials with these drugs?

Arteaga, C Preliminary data

Erlotinib inhibits EGFR phosphorylation in treatment-naive breast cancers



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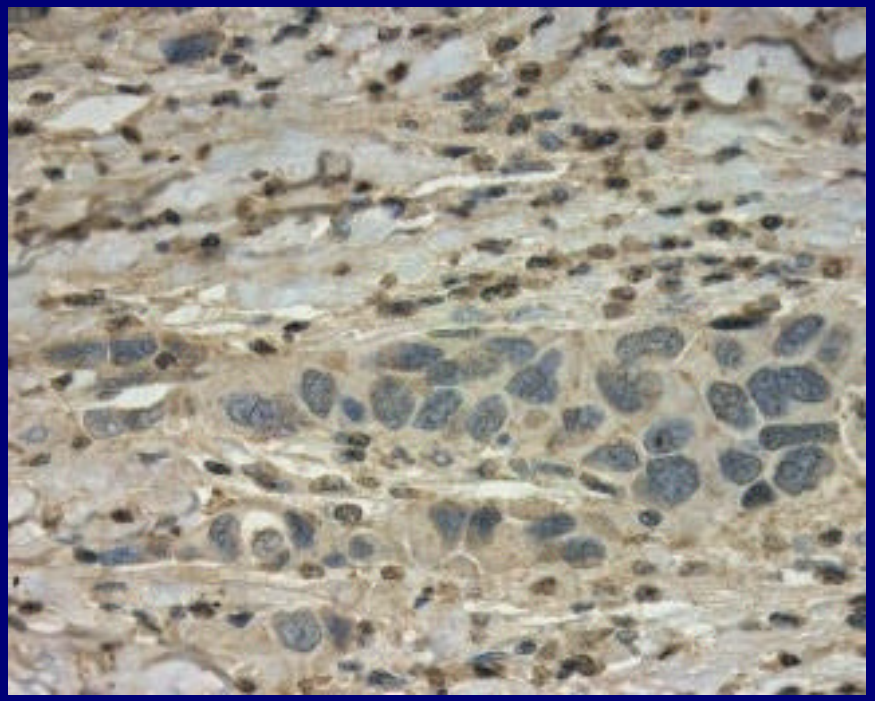
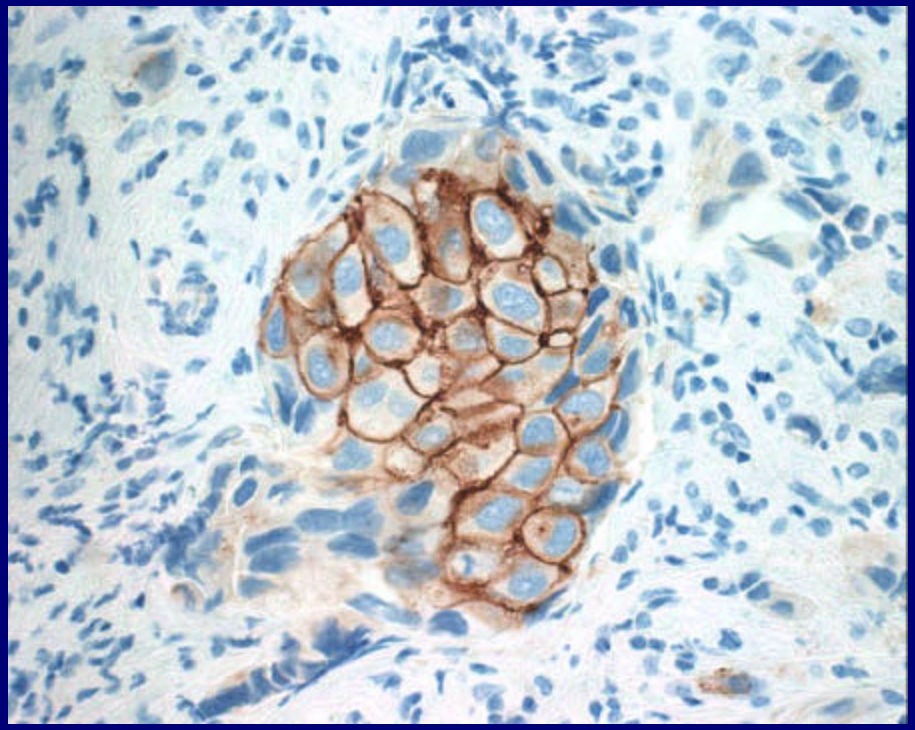


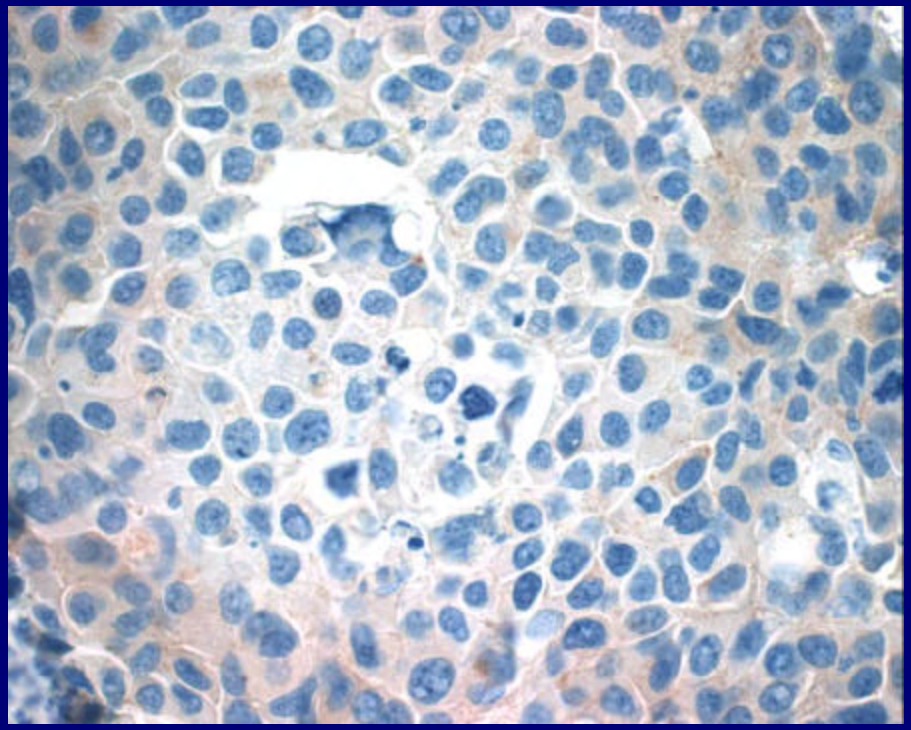
Post

Arteaga, C Preliminary data

Erlotinib inhibits HER2 phosphorylation in treatment-naive breast cancers



Pre

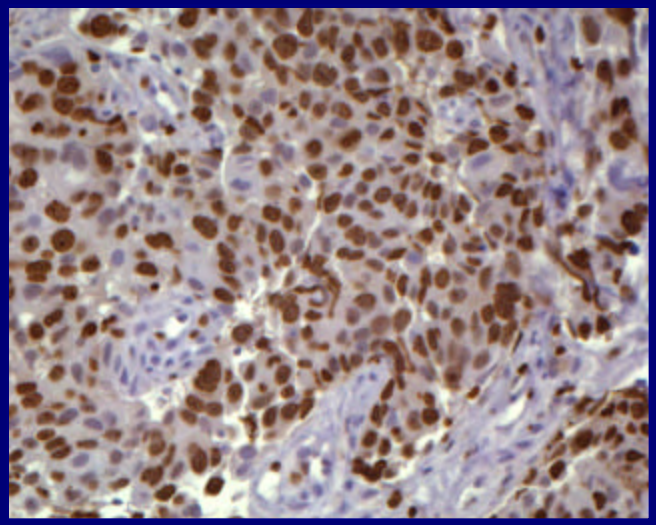


Post

Arteaga, C Preliminary data

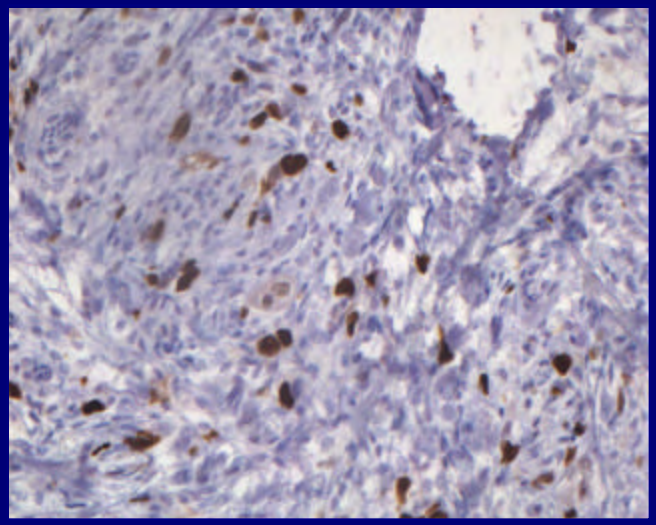
Erlotinib inhibits proliferation of breast cancer cells in primary tumors

70%*



Pre-treatment

10%



Post-treatment

* % Ki67+ cells

Arteaga, C Preliminary data

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“Phase 0” clinical trials

OPINION

Compressing drug development timelines in oncology using phase ‘0’ trials

Shivaani Kummar, Robert Kinders, Larry Rubinstein, Ralph E. Parchment, Anthony J. Murgo, Jerry Collins, Oxana Pickeral, Jennifer Low, Seth M. Steinberg, Martin Gutierrez, Sherry Yang, Lee Helman, Robert Wiltrout, Joseph E. Tomaszewski and James H. Doroshow

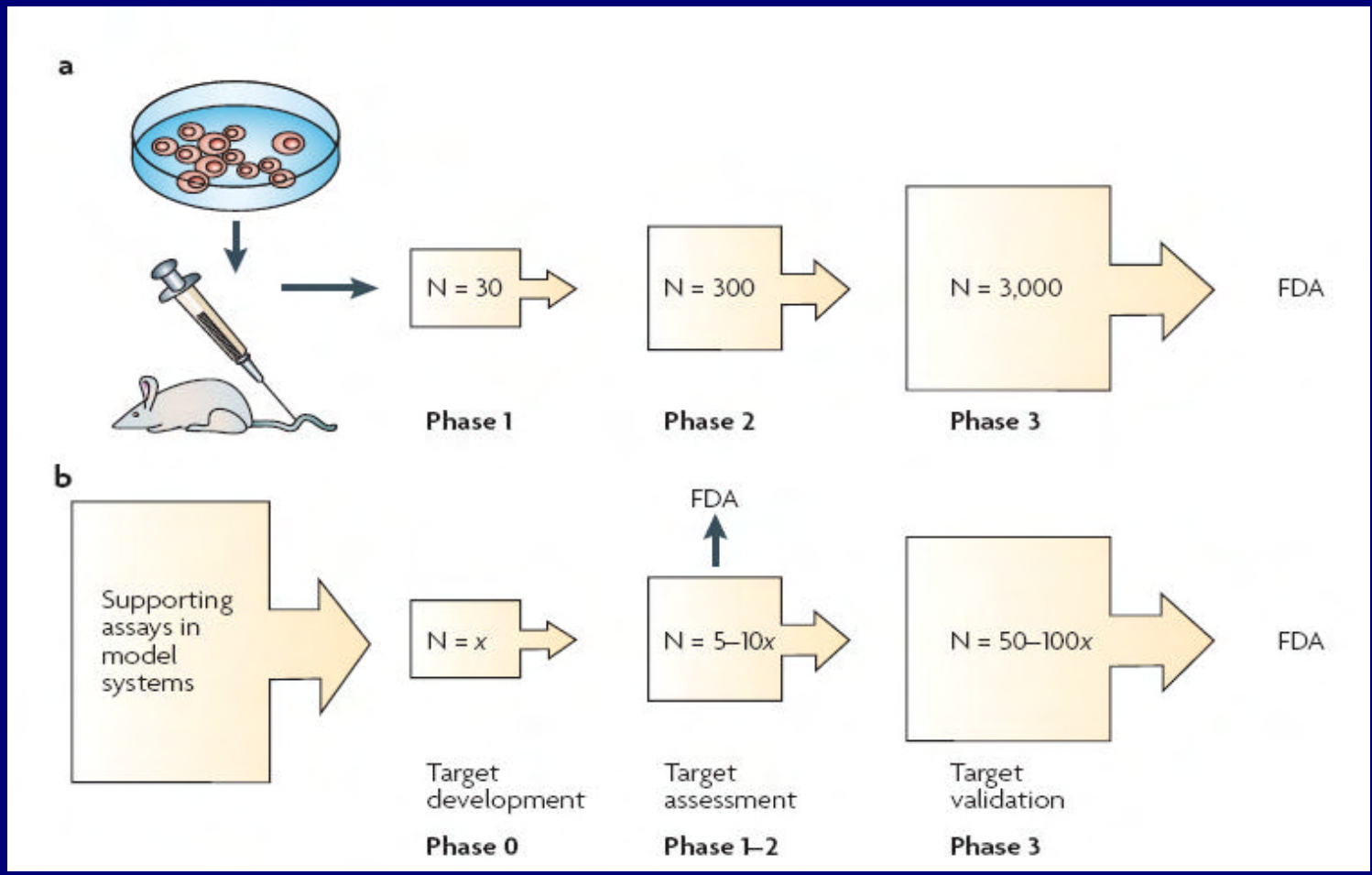
Nature Reviews Cancer, 7: 131-139 2007

Desirable Biomarker Characteristics

- Accuracy
- Dynamic range
- Precision
- Reproducibility
- Robustness
- Sensitivity

Nature Reviews Cancer, 7: 131-139 2007

Phase 0 clinical trial (advanced disease)



Nature Reviews Cancer, 7: 131-139 2007

Conclusions

- Window of opportunity studies are feasible but remain challenging
- Clinical barriers are determined by the intent of the study, the nature of the agent and the sample size
- Scientific barriers are determined by the quality of the biomarker analysis and the mechanism of action of the agent