Targeting the Oncogenic Pathway as Opposed to the Primary Tumor Site: HER2 as an Example

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Disclosures for Dennis J Slamon, MD, PhD

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Speakers Bureau	Genentech BioOncology, Roche, GSK, sanofi-aventis

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- Similar molecular targets may be found in multiple tumor types
- Does the presence of the target predict response to the targeted agent?
- Trastuzumab in HER2-positive gastric cancer: The ToGA trial
- Lessons learned from translational research in tumors overexpressing HER2
- Are we moving toward a molecular taxonomy?

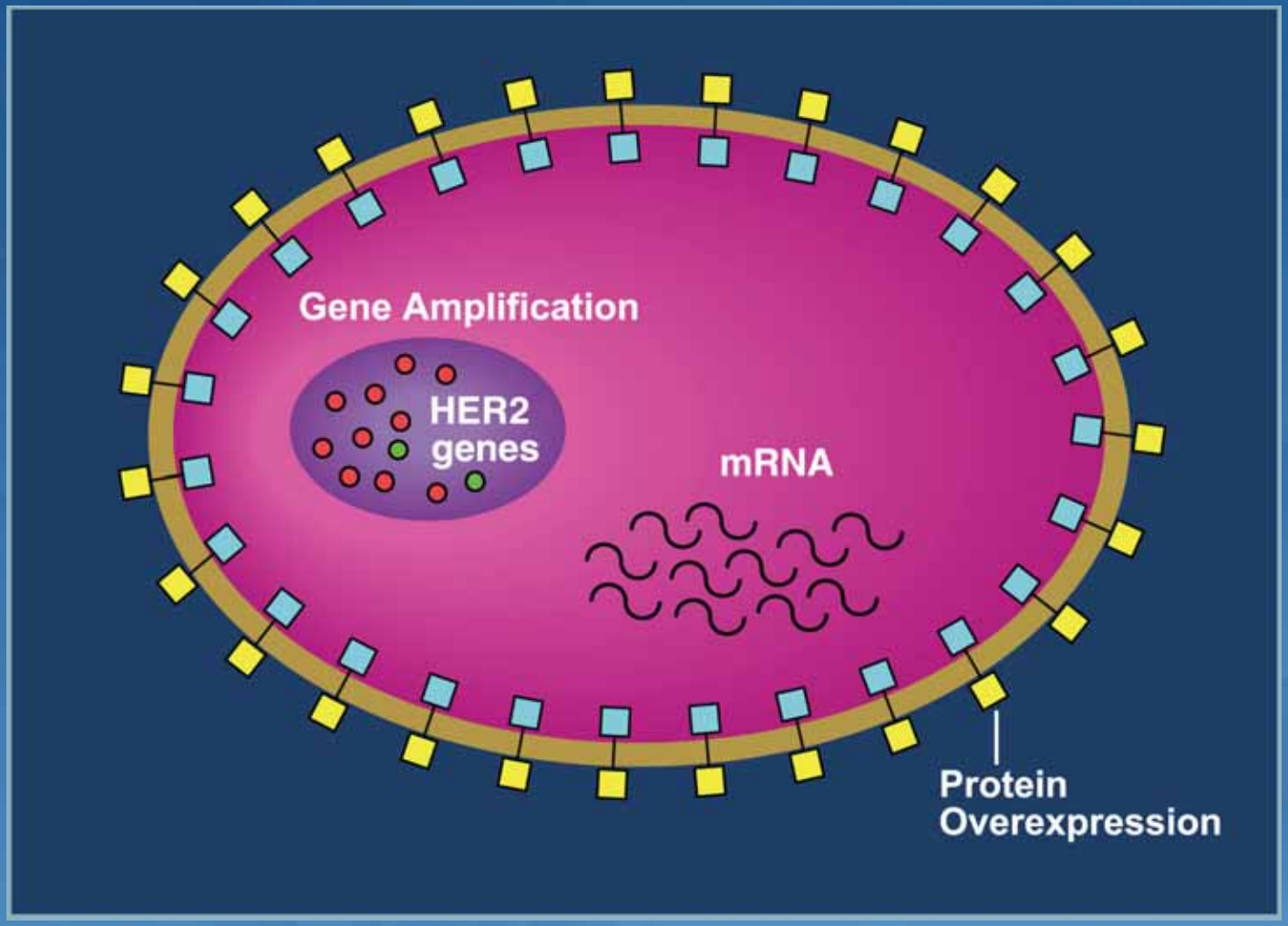
HER2 Overexpression in Diverse Tumors

	N	Rate of HER2 positivity	Definition of HER2 positivity
Invasive breast cancer (*JNCCN* 2006;4:S1)		**15-20%**	**IHC3+, FISH positive or ≥6 HER2 gene copies/cell**
NSCLC (*JCO* 2005:5007)	101	22.8%	FISH positive
Prostate (*J Urol* 2005:2174)	279	13.3%	Serum HER2/neu > 14 ng/mL
Recurrent/refractory ovarian or primary peritoneal carcinoma (*JCO* 2003:283)	837	11.4%	IHC2+ or 3+ overexpression
Uterine papillary serous cancers (ASCO 2003;Abstract 1870)	19	26%	IHC3+

HER2 Overexpression in Diverse Tumors

	N	Rate of HER2 positivity	Definition of HER2 positivity
Pancreatic cancer (GI Cancers Symposium 2010;Abstract 200)	207	26%	IHC Grade ≥2 and/or FISH positive
Ewing's sarcoma (*Eur J Cancer* 2005;41:1349)	113	16%	IHC ≥2+
Osteosarcoma (*Eur J Cancer* 2005;41:1349)	84	32%	IHC ≥2+
Bladder cancer (*Endocr Relat Cancer* 2001;8:11, *Cancer Res* 1993;53:2199)	**141**	**36%**	**FISH positive**
Advanced gastric cancer (ASCO 2009;Abstract 4556)	**3,807**	**22.1%**	**IHC3+ and/or FISH positive**

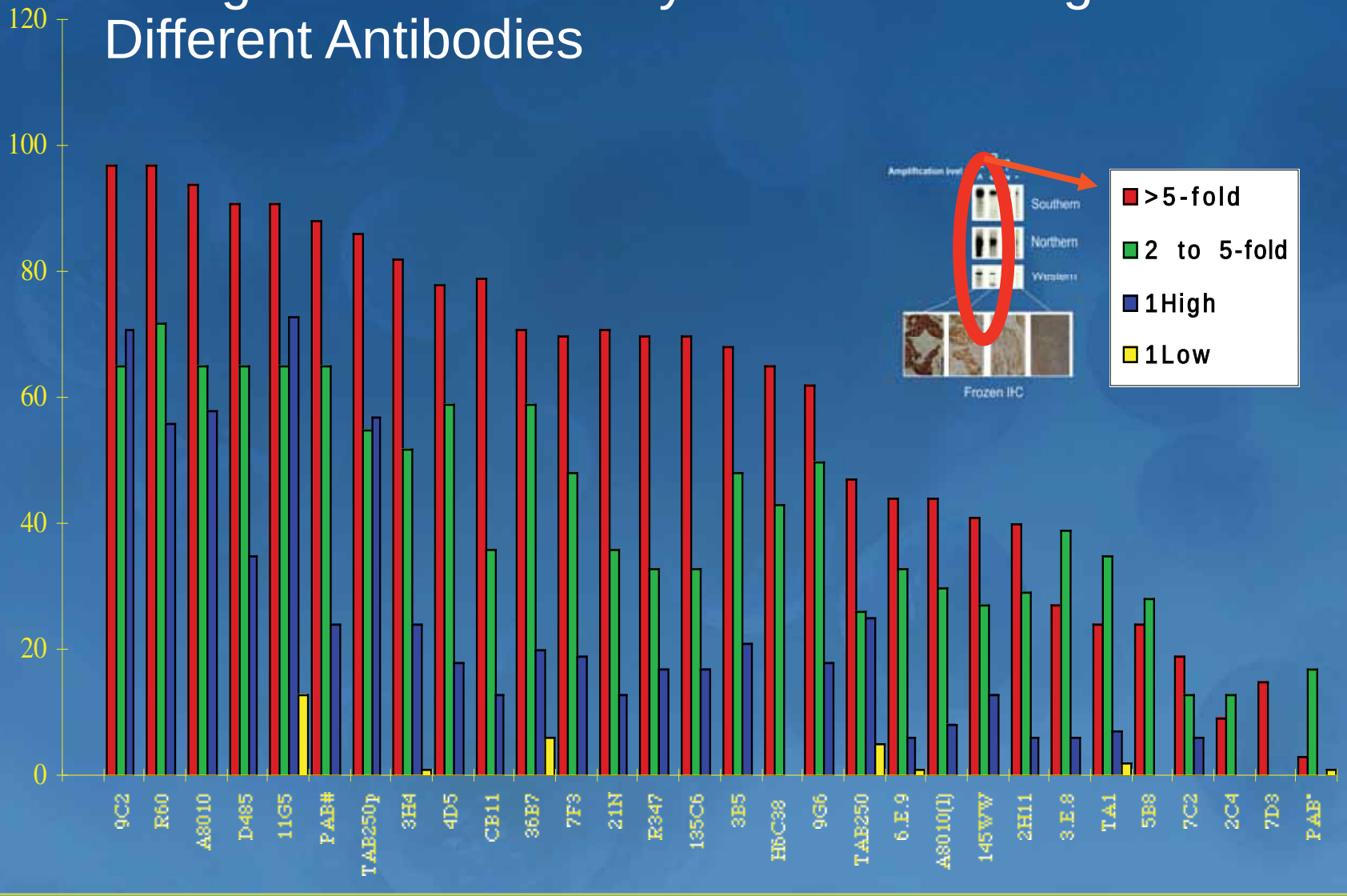
HER2 Gene Amplification Is Responsible for "Pathologic/Pathogenic" Overexpression



Testing Issues

- Integrity of the macromolecule being analyzed – degradation of DNA, RNA, or protein
- Accuracy of the reagent – variability of the antibodies
- Stability of the target, eg, fixation artifacts in proteins – altering antigenic sites and recognition that the pre-analytic phase cannot be controlled
- Accuracy of the testing method
- Heterogeneity of the sample being tested

Percent of Breast Cancers in Various Expression Categories Identified by Immunostaining with 28 Different Antibodies



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Does the Presence of the Target Predict Response to the Targeted Agent?

Sometimes…

- The tumor must rely on the oncogenic pathway as a primary means of growth
  - ER in hormone receptor-sensitive breast cancer
- Overexpression does not necessarily indicate "over-activity"
  - EGFR IHC-positive versus EGFR mutation-positive NSCLC
- Mechanism of target inhibition may impact tumor response
  - HER2-positive breast cancer may be resistant to trastuzumab but sensitive to lapatanib (or vice versa)

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Molecular Biology

- p53: 77%
- EGFR
- HER2/neu: Bang ASCO 2009 22%
- E-cadherin
- FHIT
- p16/p27
- COX-2

HER2 by IHC, CISH and FISH in Patients with Gastric Cancer (n = 182)

- HER2 expression = 15.9% (IHC); 3.8% (CISH/FISH)
- Rate of HER2 amplification for intestinal-type cancer is greater than for diffuse-type cancers, $p < 0.05$
- Tumors with HER2 amplification were associated with poor mean survival rates (922 vs 3,243 days) and 5-year survival rates (21.4% vs 63%, $p < 0.05$)

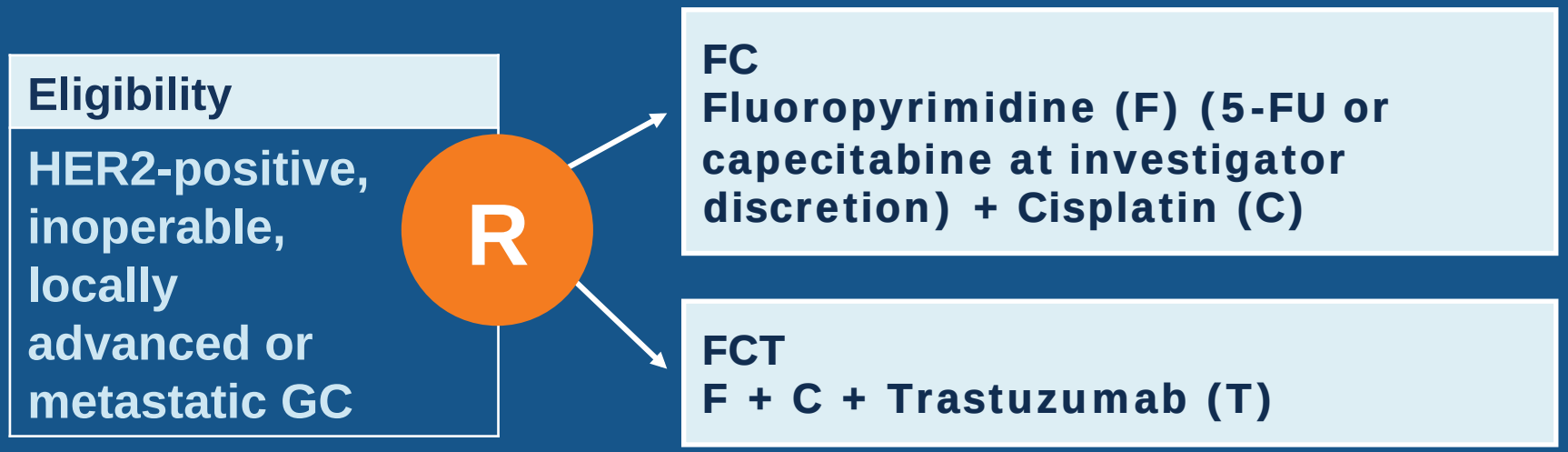
Park DI et al. *Dig Dis Sci* 2006;51(8):1371-9.

Efficacy Results from the ToGA Trial: A Phase III Study of Trastuzumab Added to Standard Chemotherapy (CT) in First-Line Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Advanced Gastric Cancer (GC)

Van Cutsem E et al.

Proc ASCO 2009;Abstract LBA4509.

ToGA Trial Design (N = 584)

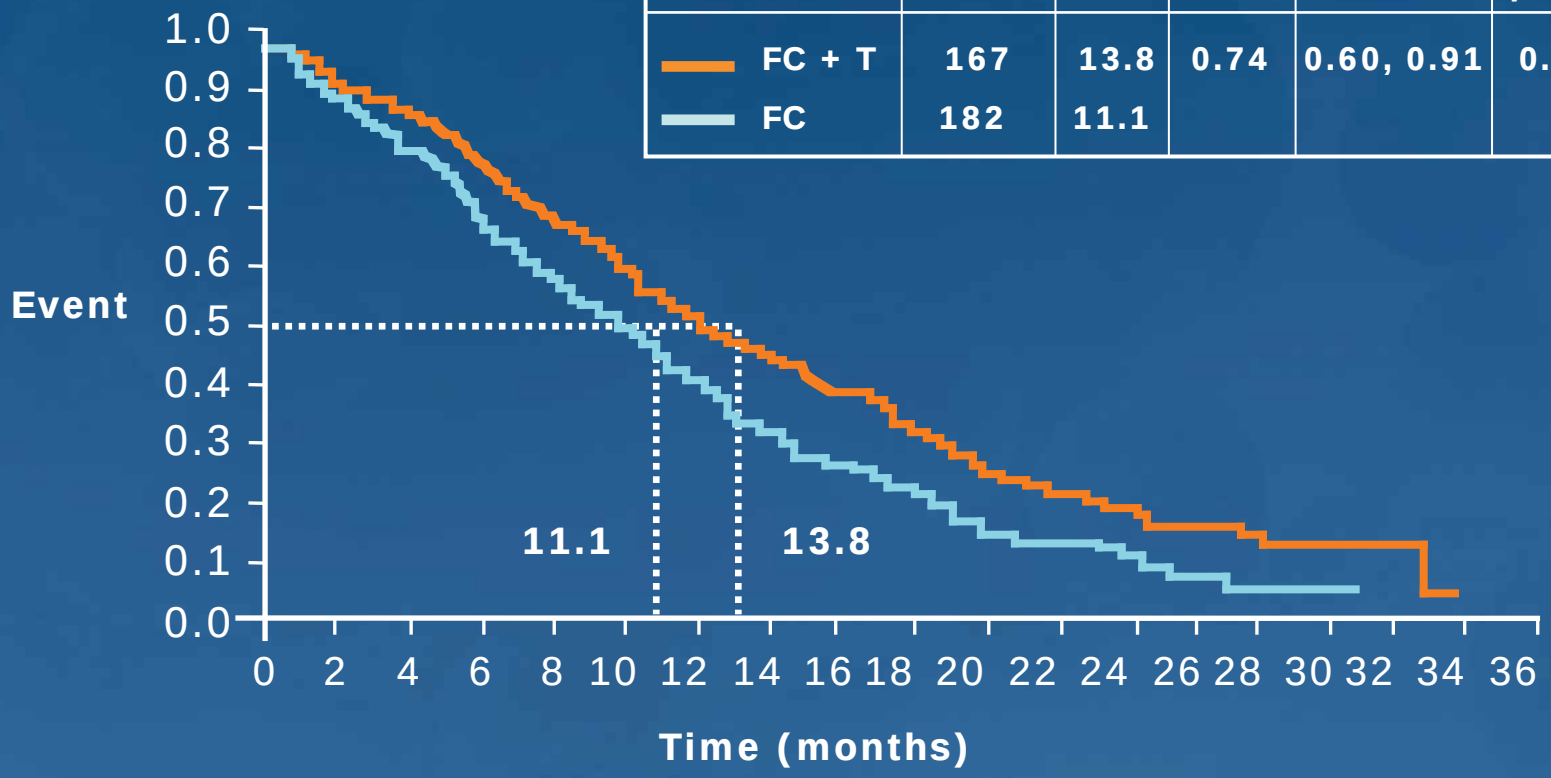


- **5-FU** = 800 mg/m^2/day continuous infusion d1-5 q3w x 6
- **Capecitabine** = 1,000 mg/m^2 bid d1-14 q3w x 6
- **Cisplatin** = 80 mg/m^2 q3w x 6
- **Trastuzumab** = 8 mg/kg loading dose ➔ 6 mg/kg q3w until PD

Van Cutsem E et al. ASCO 2009; Abstract LBA4509.

Primary Endpoint: Overall Survival – decreased relative risk of death by 26%

	Median				
	Events	OS	HR	95% CI	*p*-value
FC + T	167	13.8	0.74	0.60, 0.91	0.0046
FC	182	11.1			



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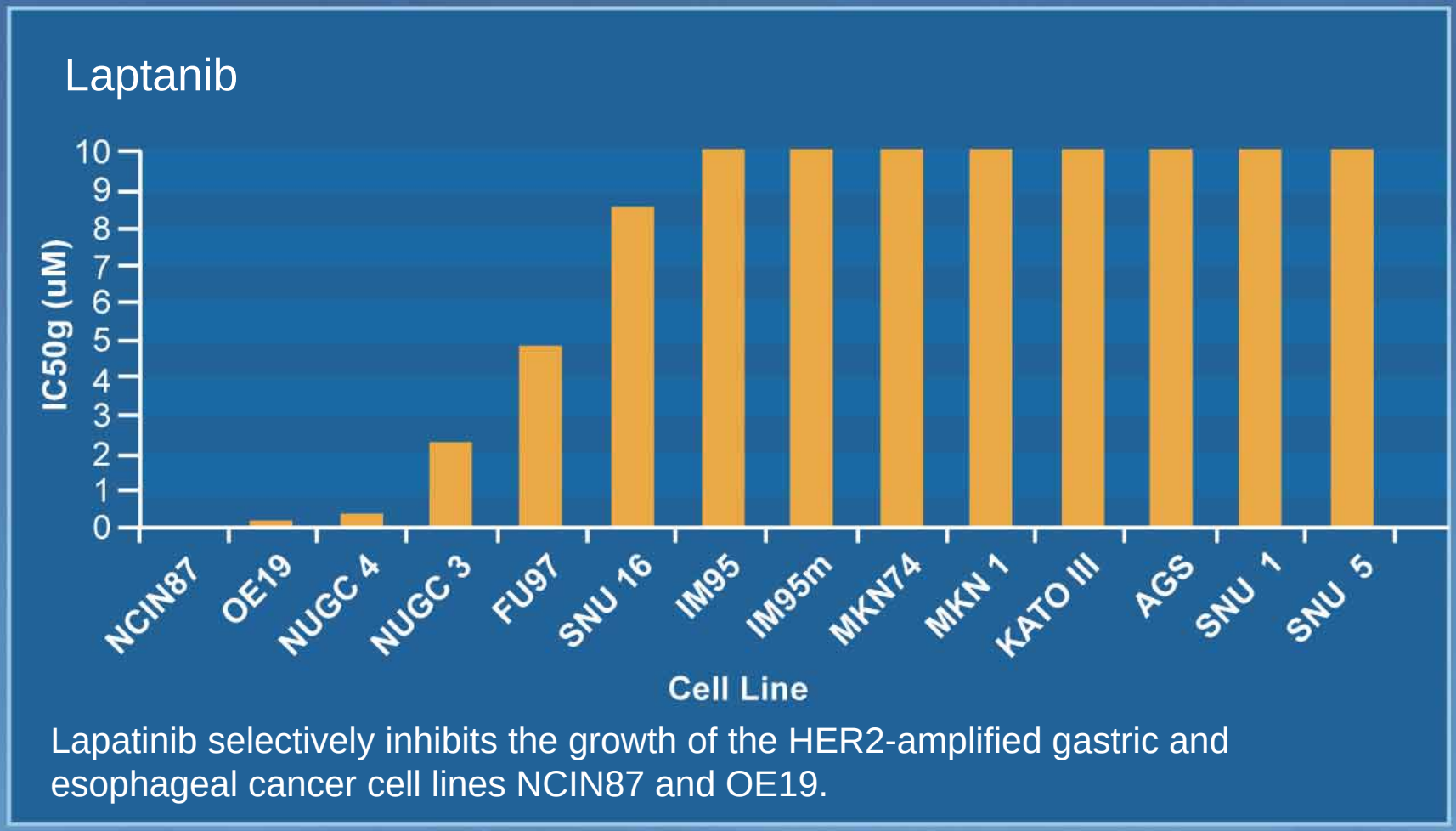
Lapatinib, a Dual EGFR and HER2 Kinase Inhibitor, Selectively Inhibits HER2-Amplified Human Gastric Cancer Cells and Is Synergistic with Trastuzumab In Vitro and In Vivo

Wainberg ZA et al.

Clin Cancer Res 2010;16(5):1509-19.

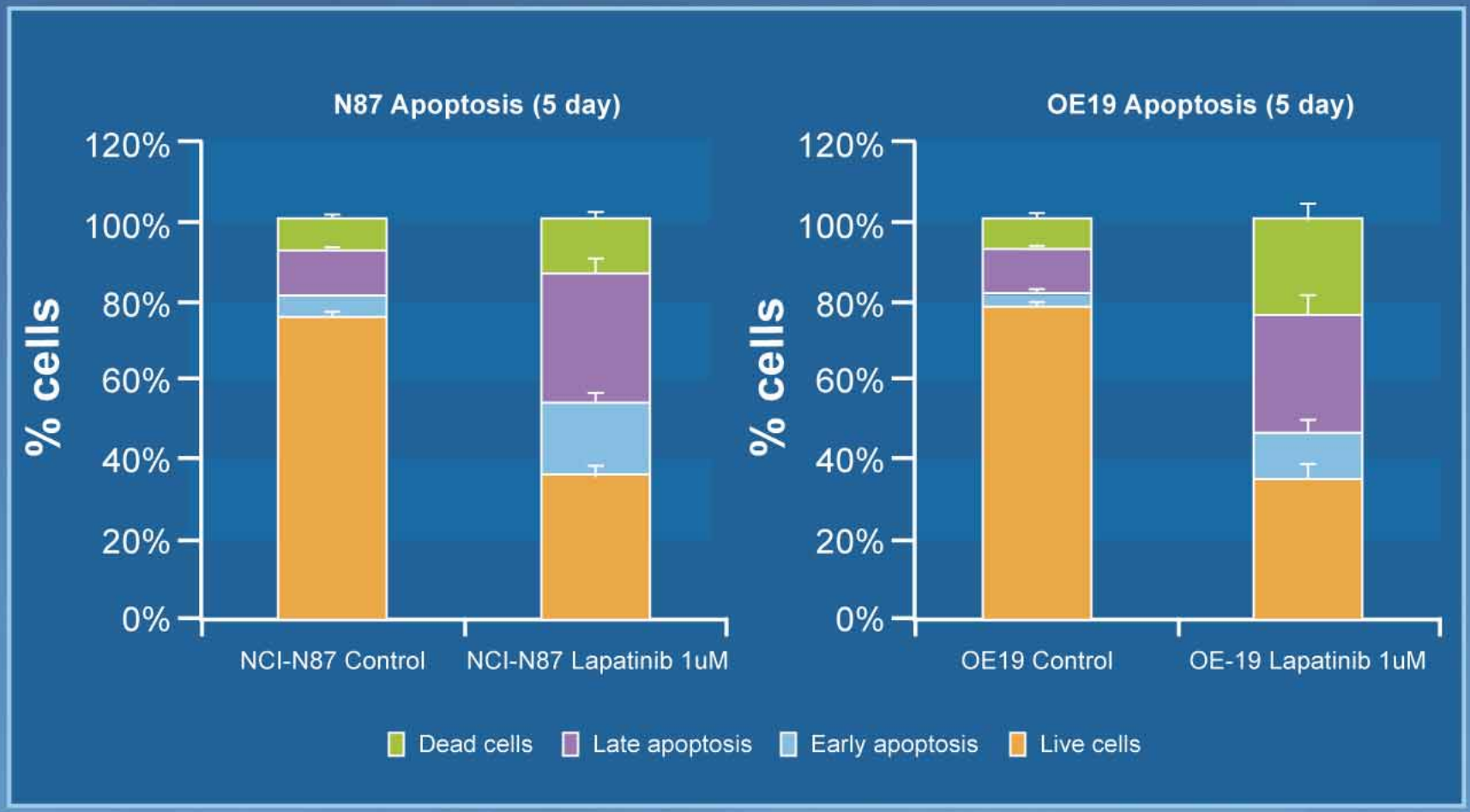
Cell Growth Inhibition by Lapatinib In Vitro



Lapatinib selectively inhibits the growth of the HER2-amplified gastric and esophageal cancer cell lines NCIN87 and OE19.

Reprinted with permission: Wainberg ZA E et al.
***Clin Cancer Res* 2010;16(5):1509-19, figure 1.**

Lapatinib Induces Apoptosis in HER2-Amplified Gastric Cell Lines



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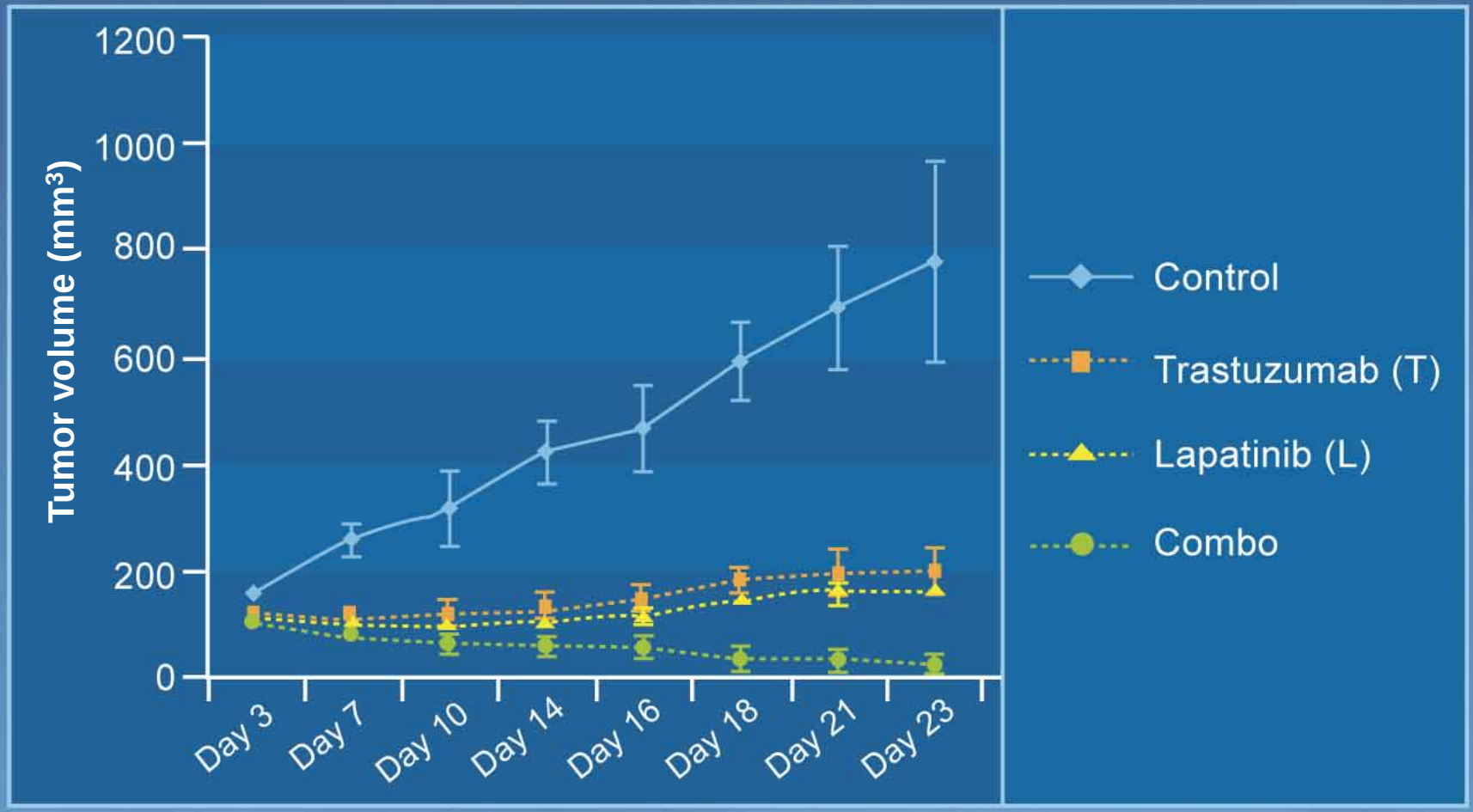
***Clin Cancer Res* 2010;16(5):1509-19, figure 3.**

Synergistic Antitumor Activity of Lapatinib and Trastuzumab in Combination (N87 Xenograft)



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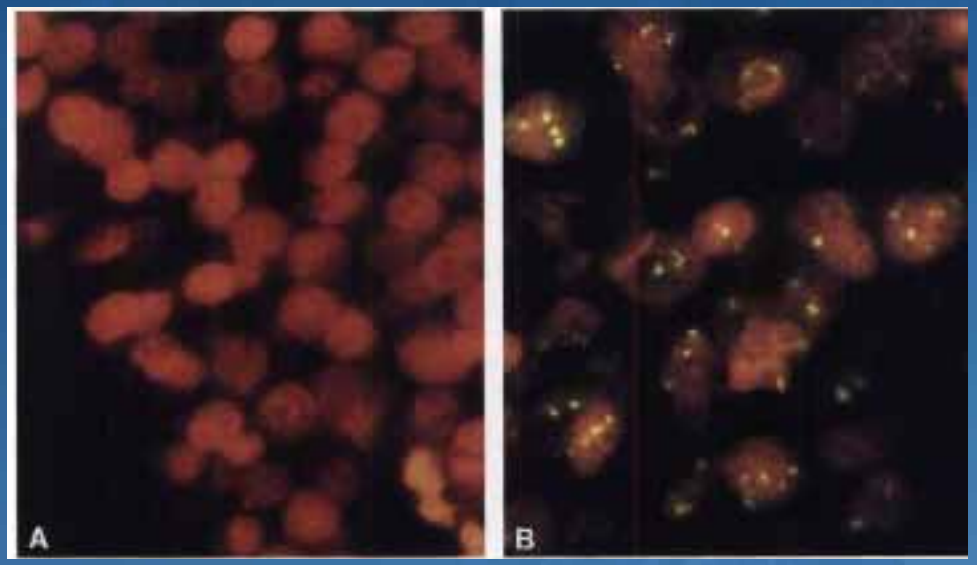
***Clin Cancer Res* 2010;16(5):1509-19, figure 6.**

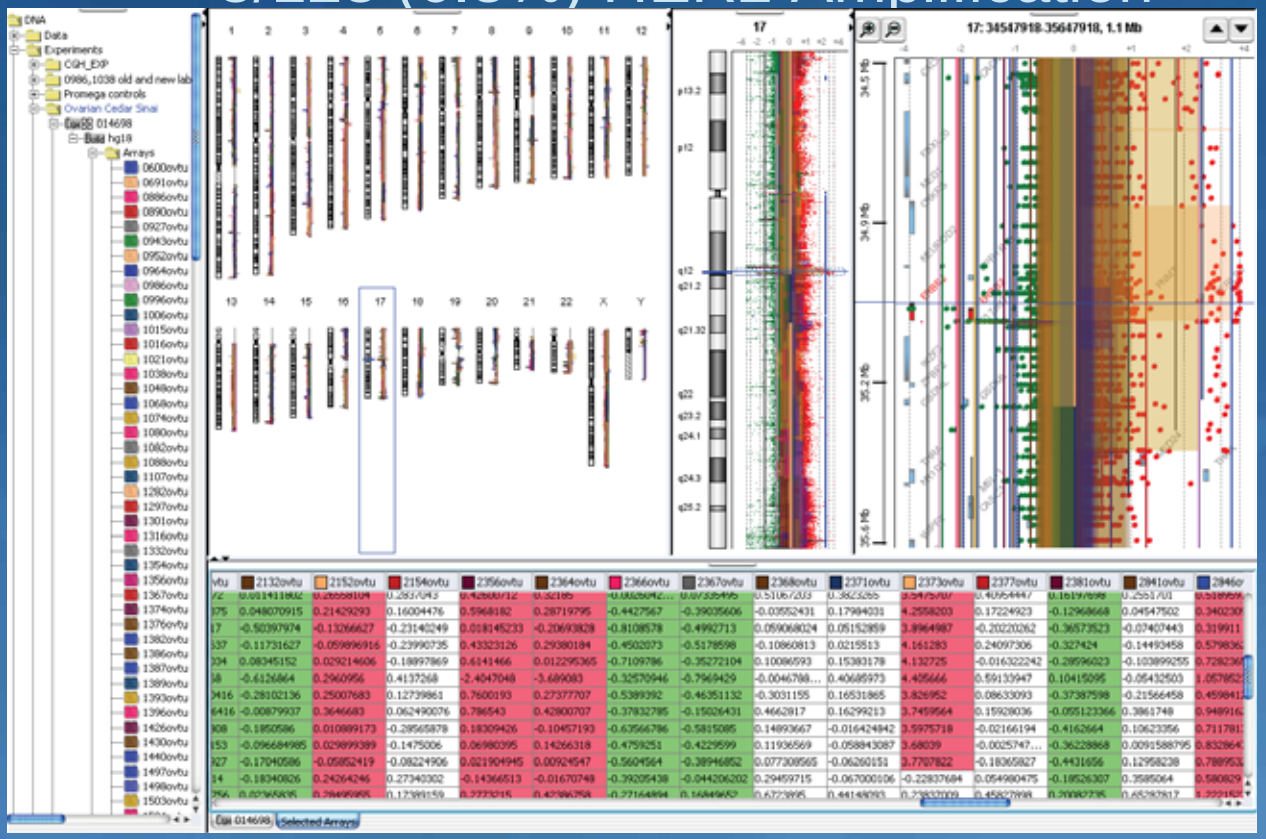
HER2 Gene Amplification in Salivary Gland Mucoepidermoid Carcinomas



HER2 Not Amplified **HER2 Amplification**

Agilent Array-CGH in Ovarian Cancer

- 8/128 (6.3%) HER2 Amplification



Lee Anderson, Slamon Lab (unpublished data)

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Maybe. . .