乳腺癌分子靶向药物治疗进展

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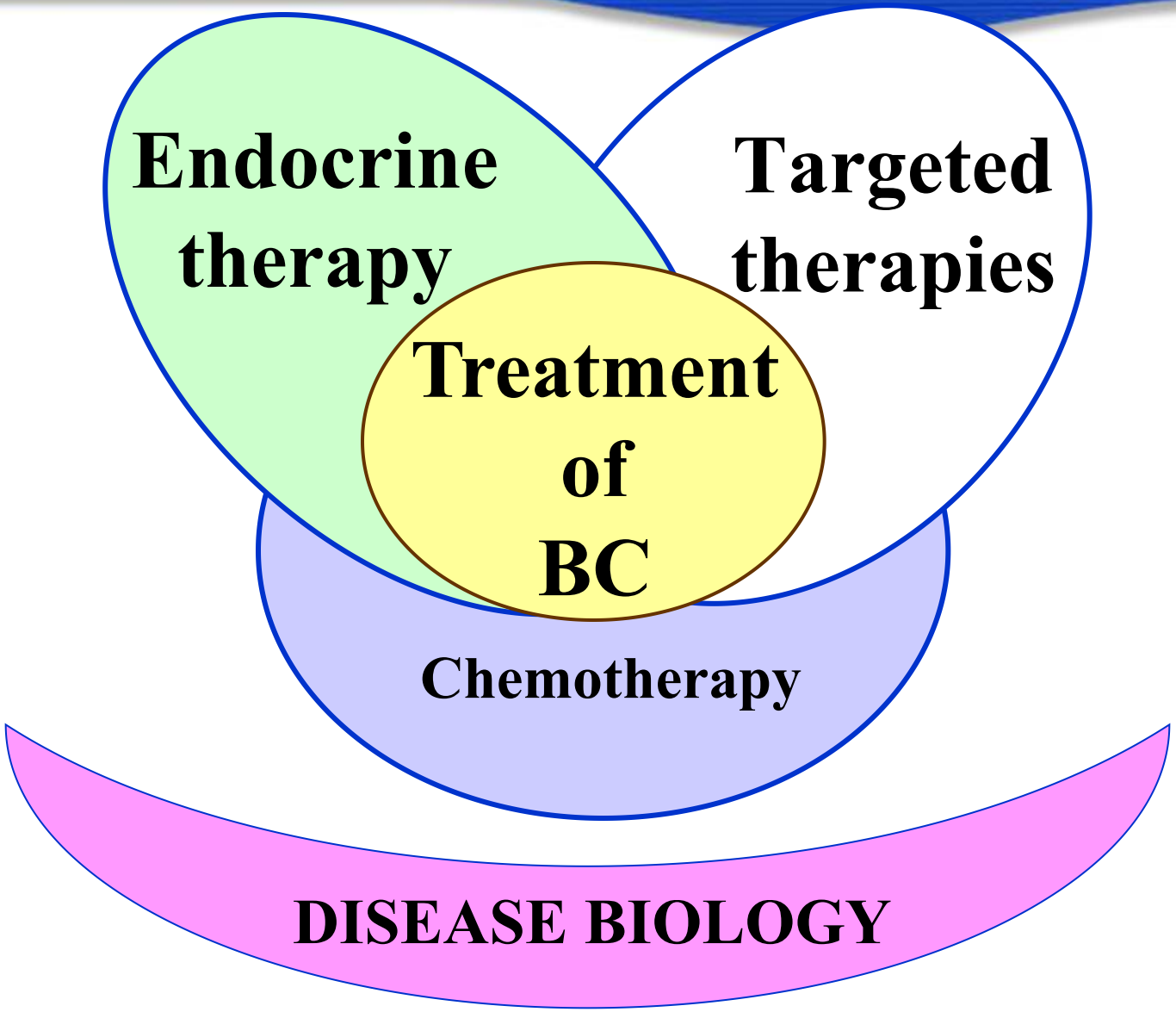
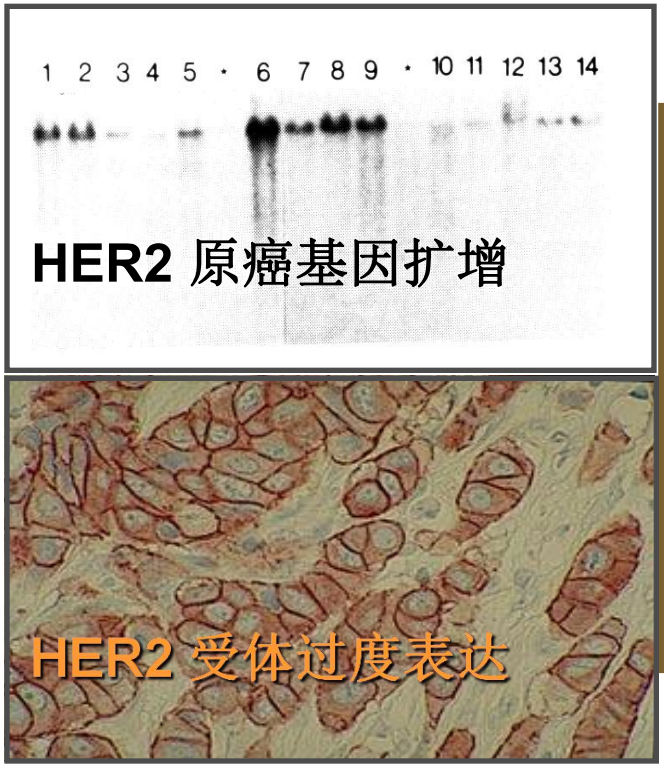
HIGHLIGHTS IN BREAST CANCER



乳腺癌分子靶向药物治疗

- 针对HER2受体的靶向药物
- 针对表皮生长因子受体(EGFR)的靶向治疗
- 针对肿瘤血管生成的分子靶向药物
- 其他信号通路抑制剂——mTOR，Ras， MEK等

HER2在约20%～30%的乳腺癌组织中过度表达



中位生存期的缩短

HER2 扩增/过度表达	3 年
HER2 正常表达	6 - 7 年

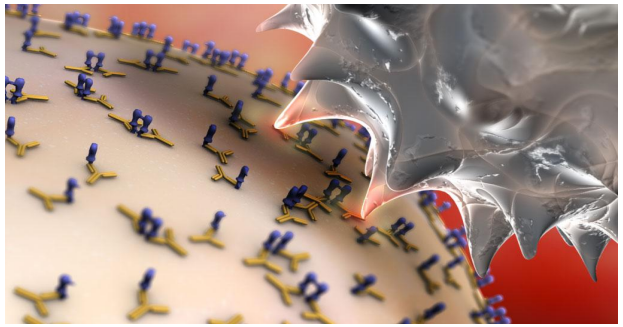
- HER2阳性与内分泌治疗及部分化疗耐药密切相关，是重要的预后指标
- HER2成为乳腺癌治疗的理想靶点，是预测赫赛汀疗效的重要指标

赫赛汀(曲妥珠单抗):
人源化抗HER2单克隆抗体

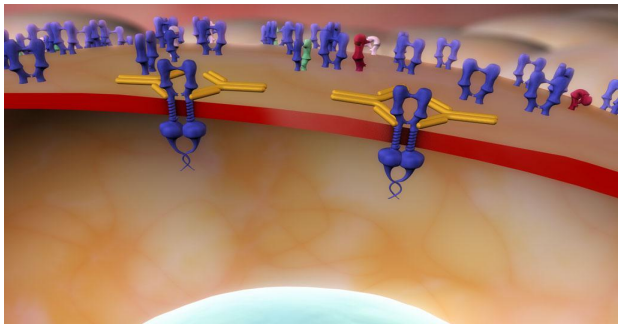
- 高度亲和性 (K_d=0.1nM) 和特异性
- 95% 人源化, 5% 鼠抗, 显著降低免疫原性 (HAMA)

- 全球第一种治疗实体瘤的单克隆抗体

赫赛汀的作用机制



Activation of ADCC



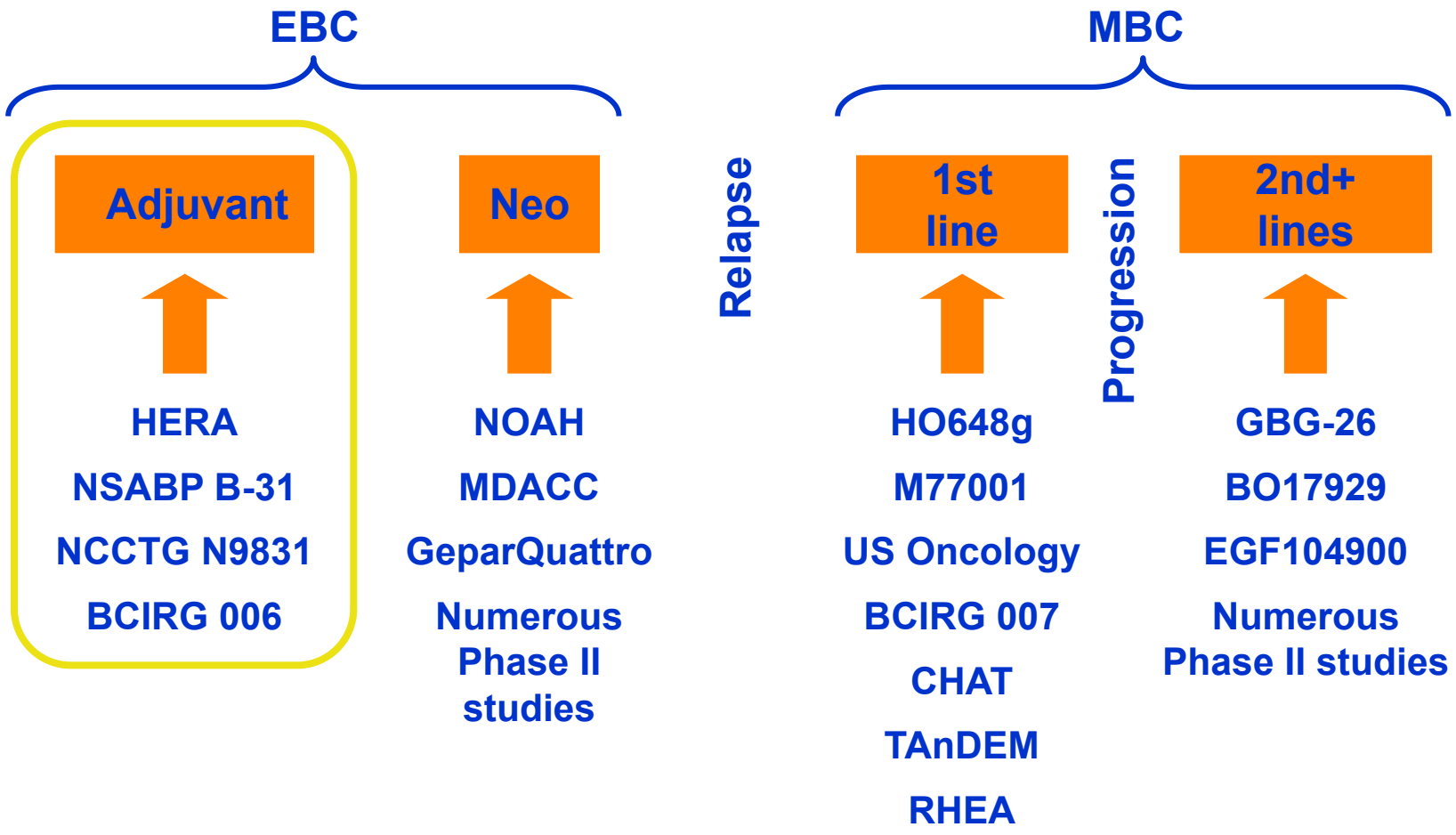
Inhibition of HER2-mediated signalling

Additional mechanisms

- Prevents formation of truncated HER2 (p95)
- Inhibition of HER2-regulated angiogenesis

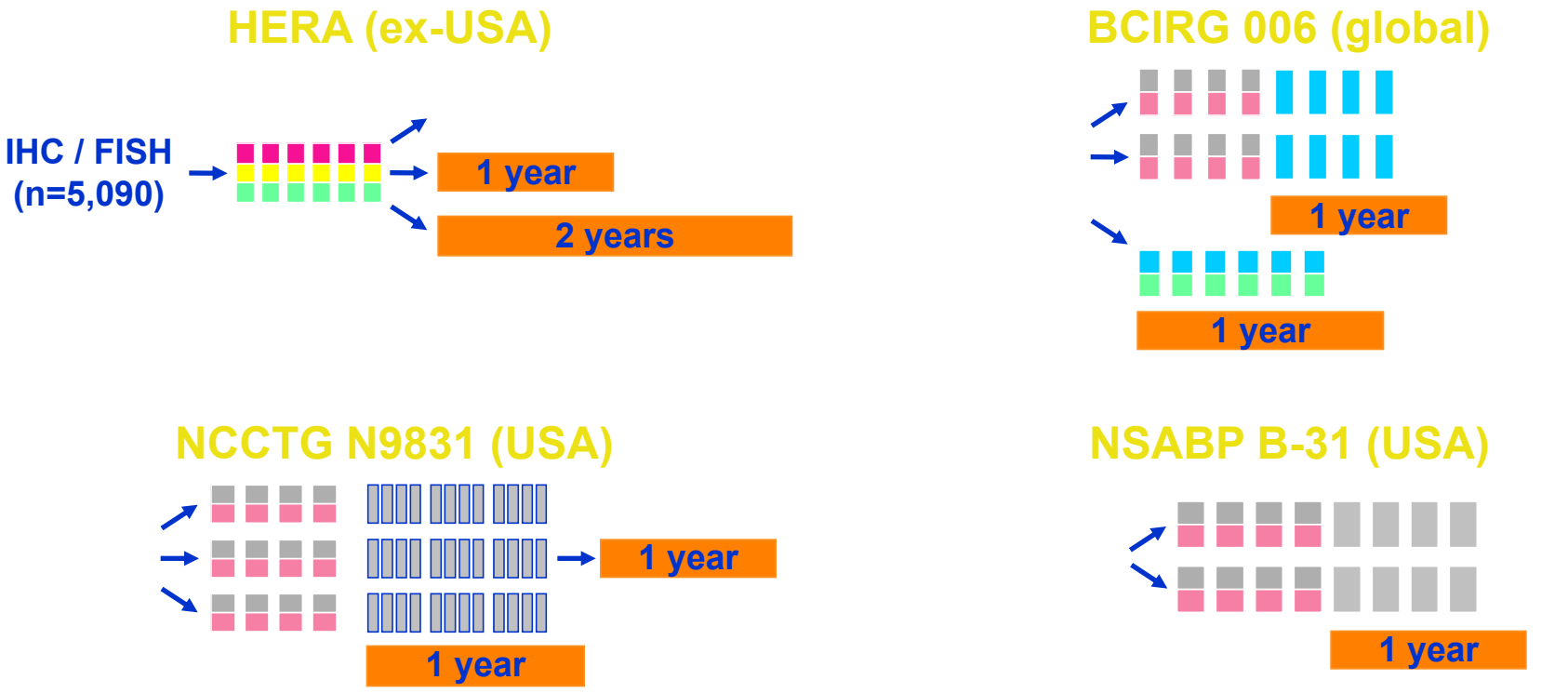
ADCC, antibody-dependent cellular cytotoxicity

赫赛汀已成为HER2阳性乳腺癌的基础治疗



HER2, human epidermal growth factor receptor 2
EBC, early breast cancer; MBC, metastatic breast cancer

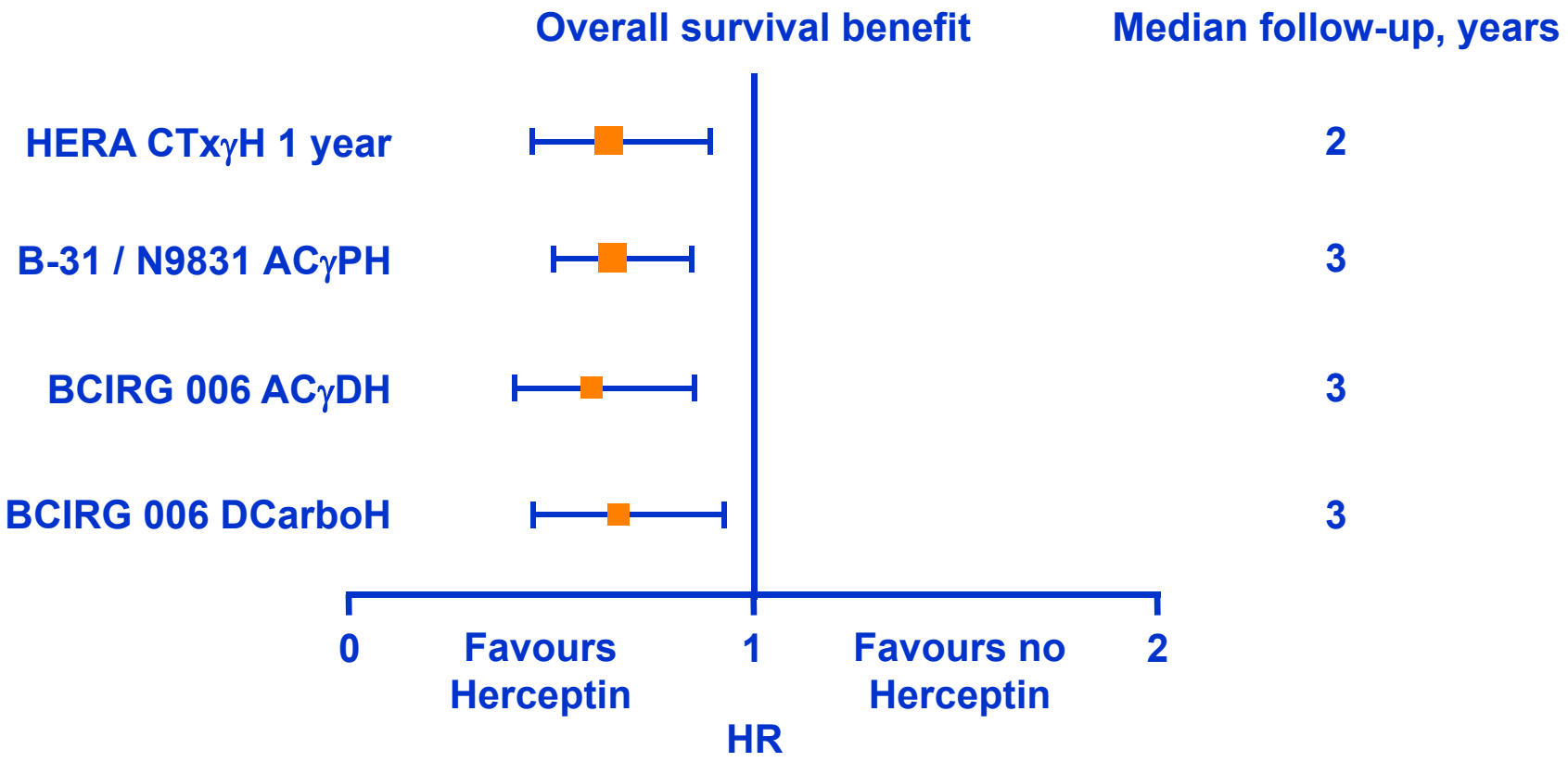
>13,000 患者入组的赫赛汀四大辅助临床研究



IHC, immunohistochemistry
FISH, fluorescence *in situ* hybridisation
CTx, chemotherapy

Piccart-Gebhart et al 2005
Romond et al 2005; Slamon et al 2006

赫赛汀可减少三分之一的死亡风险

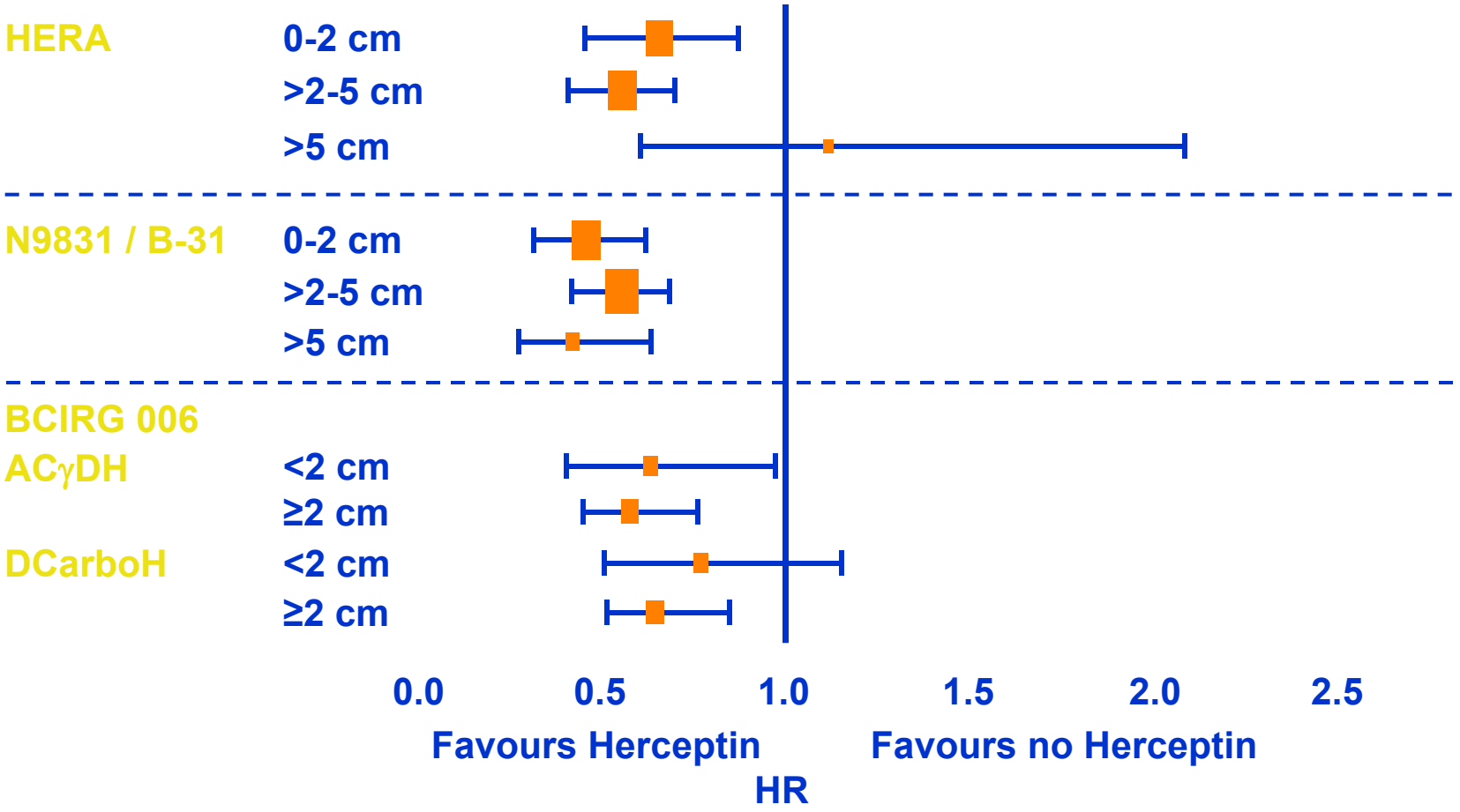


■ Size of square represents sample size; horizontal bars indicate 95% confidence intervals

H, Herceptin; AC, doxorubicin, cyclophosphamide
P, paclitaxel; D, docetaxel; Carbo, carboplatin
HR, hazard ratio

Slamon et al 2006
Perez et al 2007; Smith et al 2007

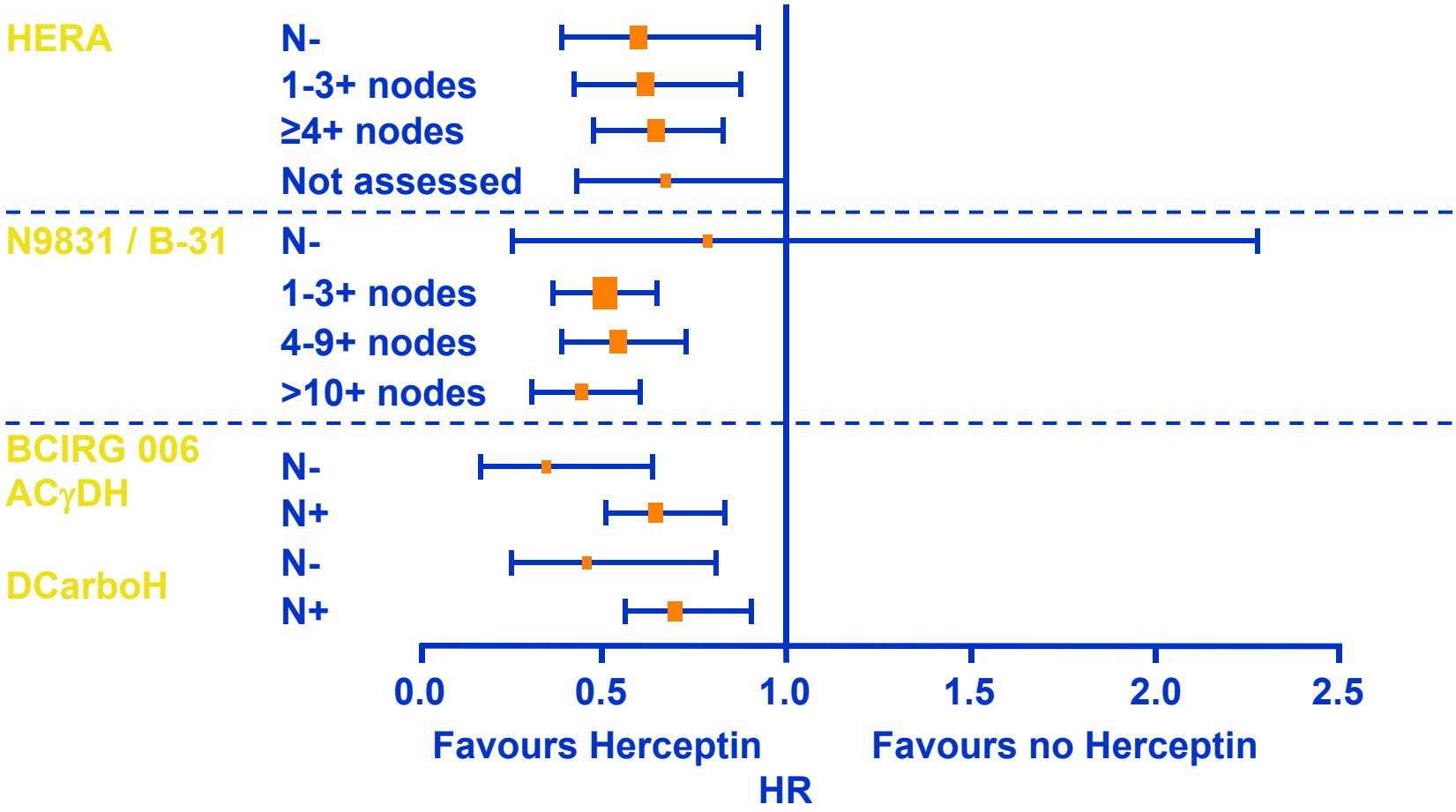
无论肿瘤大小，赫赛汀均显示DFS获益



Slamon et al 2006
Perez et al 2007; Smith et al 2007

DFS, disease-free survival

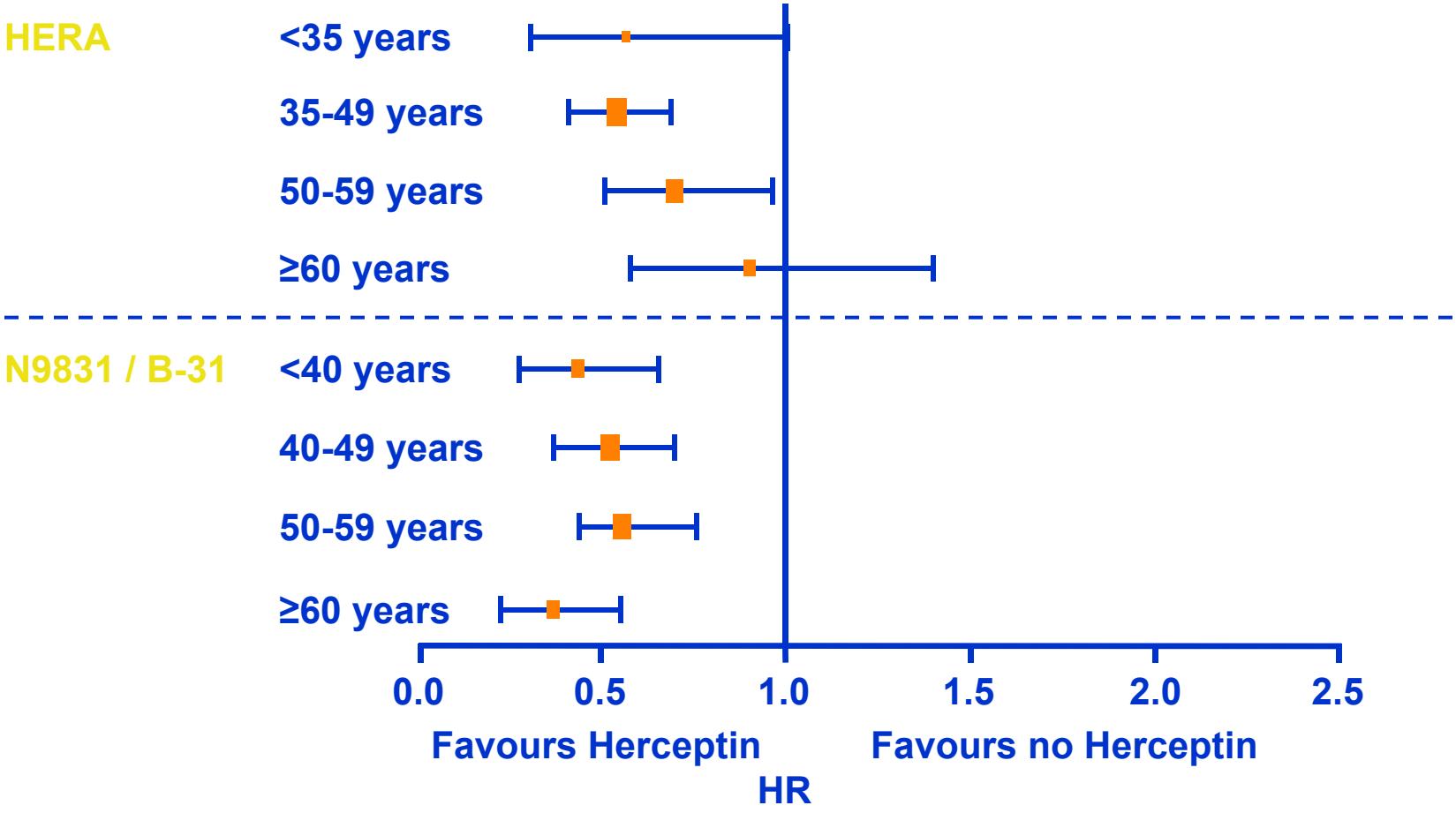
无论淋巴结情况，赫赛汀均显示DFS获益



N, node

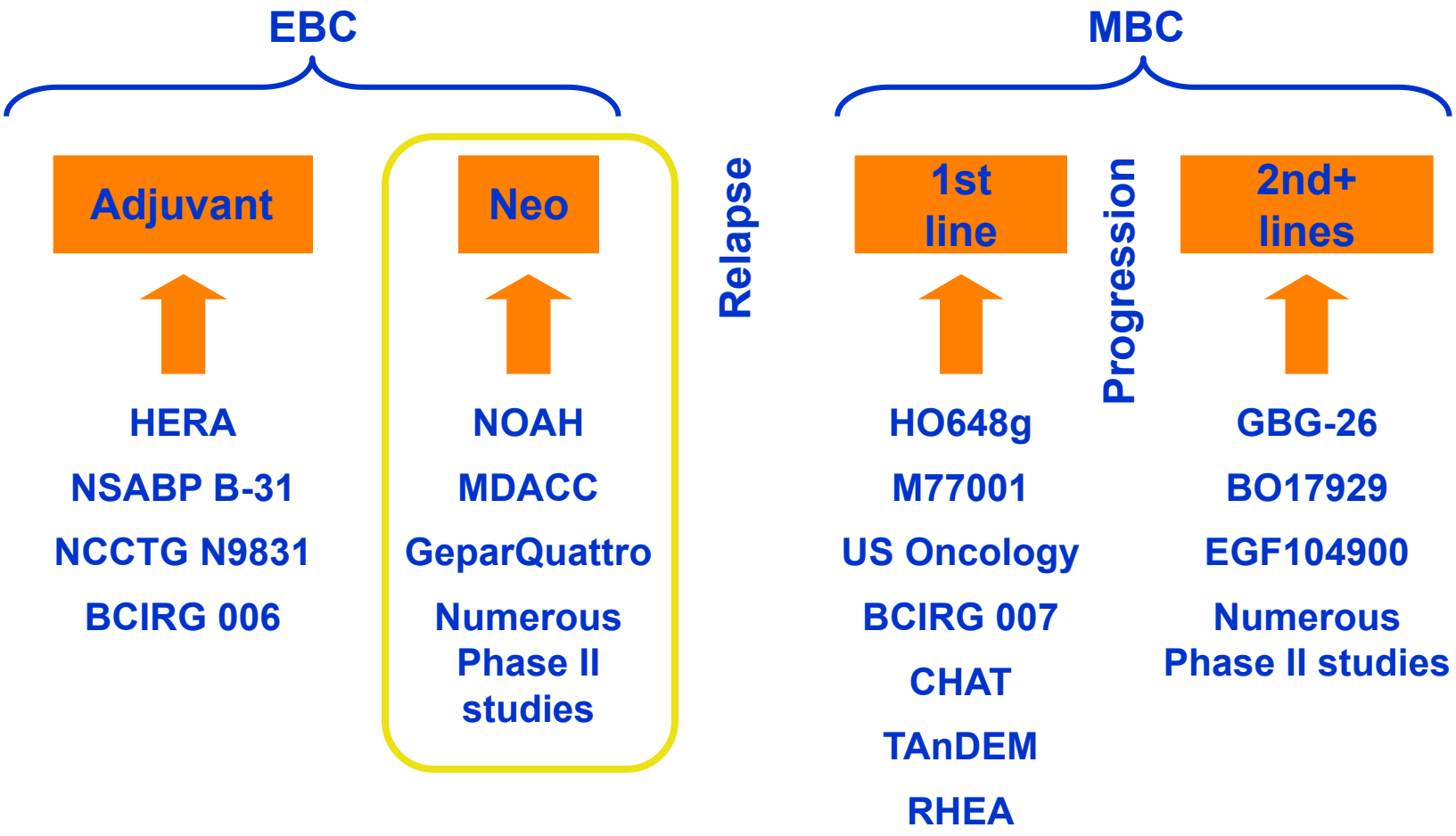
Slamon et al 2006
Perez et al 2007; Smith et al 2007

无论年龄大小，赫赛汀均显示DFS获益

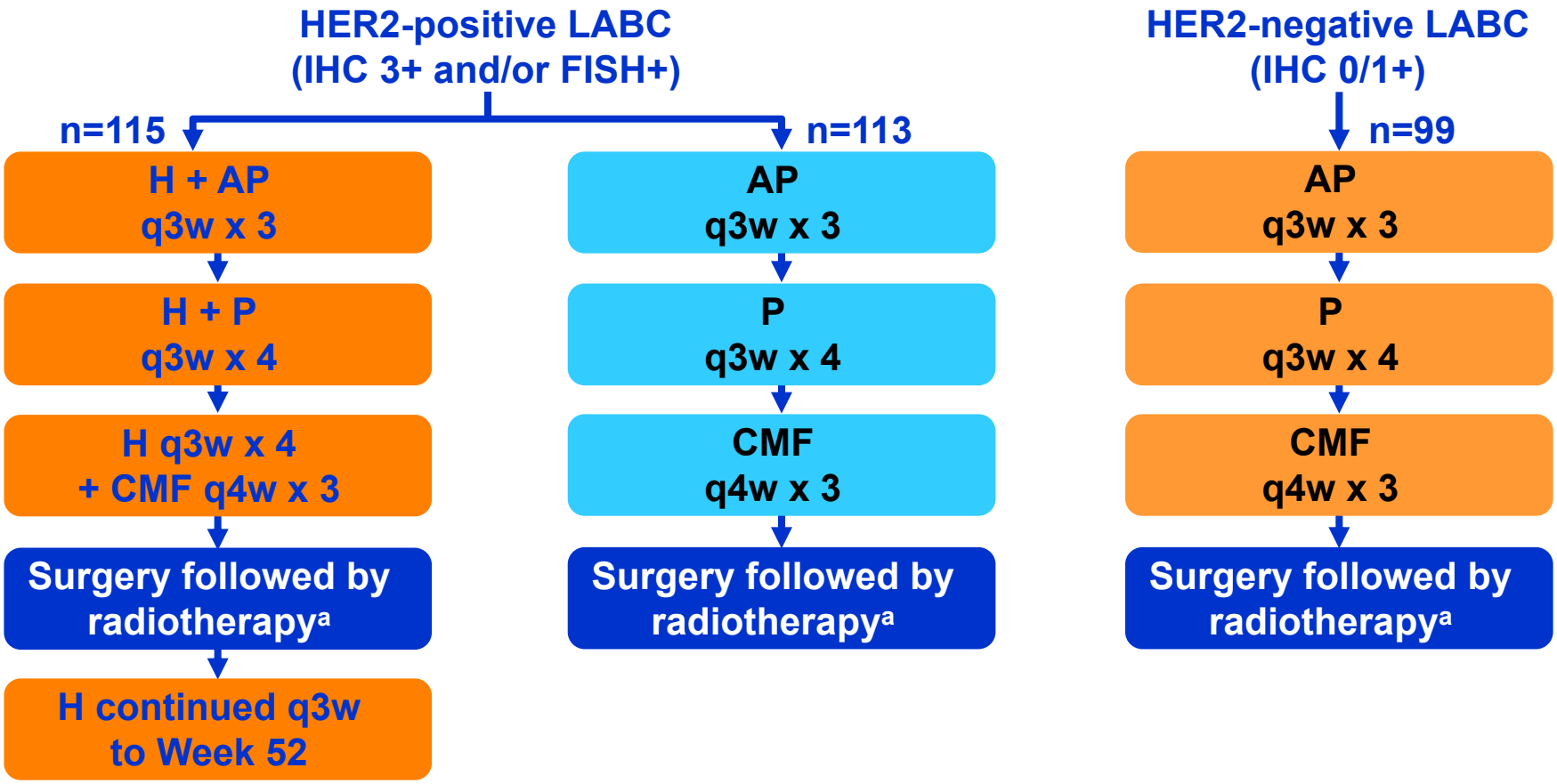


Perez et al 2007; Smith et al 2007

赫赛汀的新辅助治疗研究进展



NOAH study: neoadjuvant Herceptin for LABC



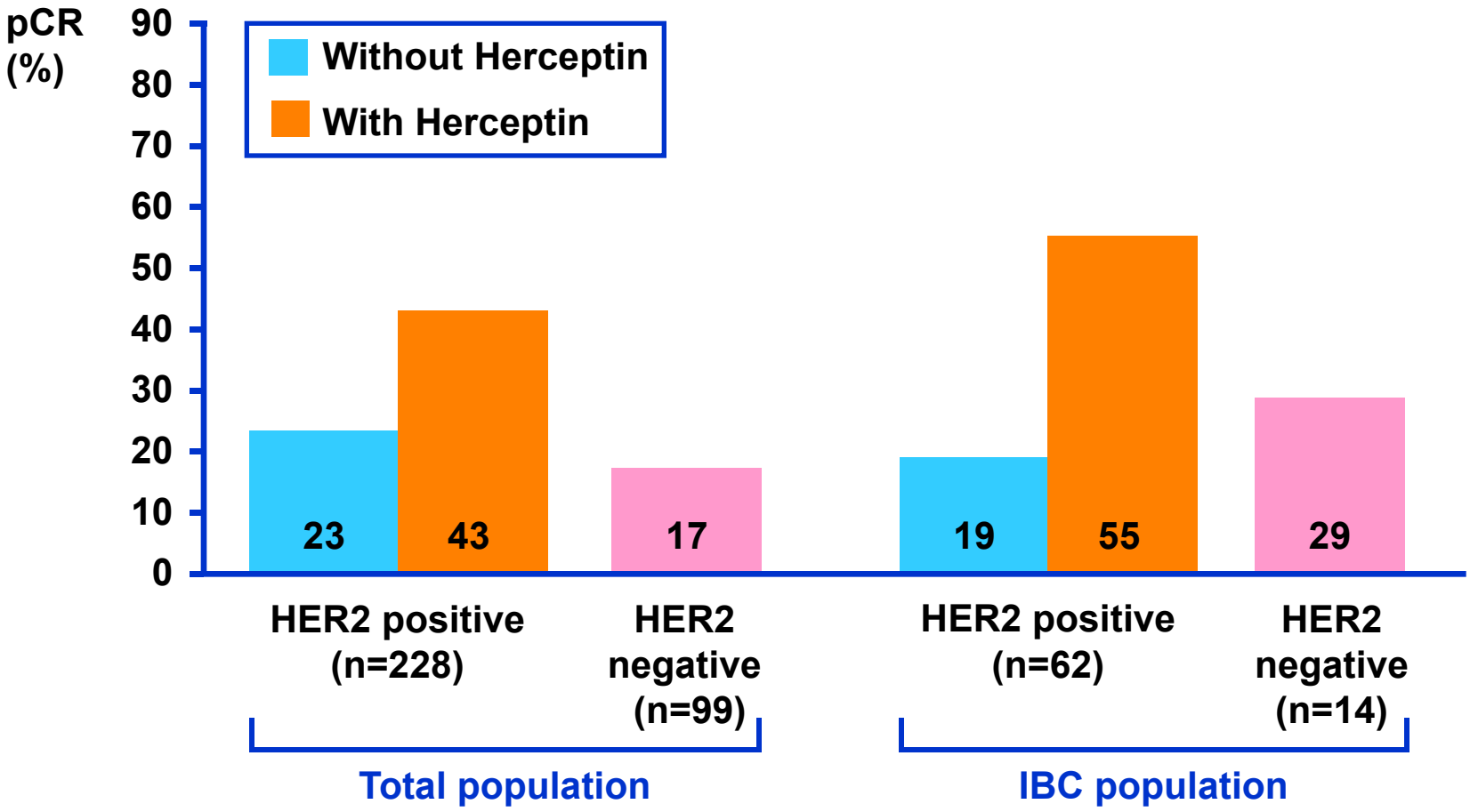
[a]Hormone receptor-positive patients receive adjuvant tamoxifen

AP, doxorubicin 60 mg/m^2, paclitaxel 150 mg/m^2; H, Herceptin 8 mg/kg loading then 6 mg/kg

P, paclitaxel 175 mg/m^2; CMF, cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2

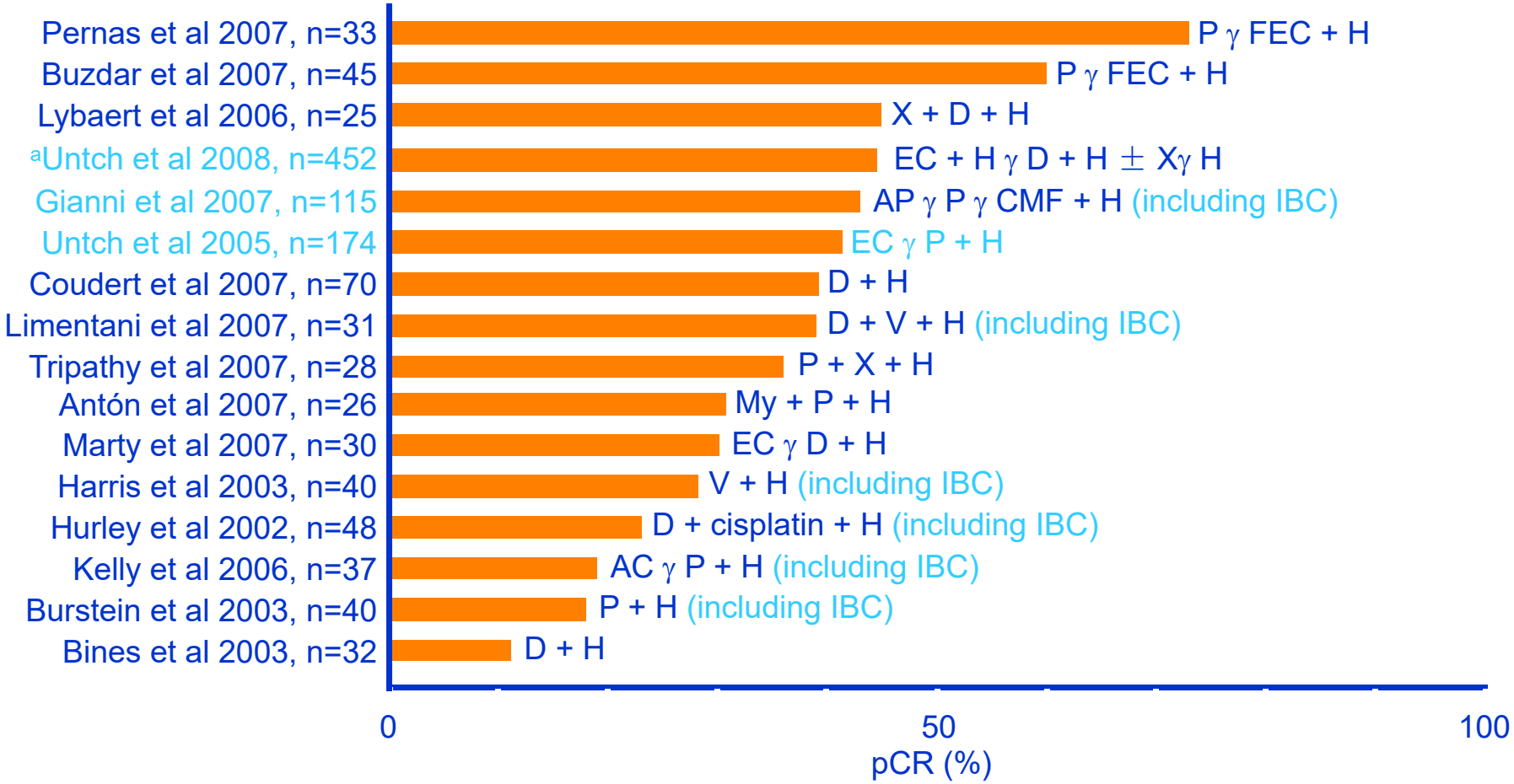
LABC, locally advanced breast cancer; q3w, every 3 weeks; q4w, every 4 weeks

NOAH研究中赫赛汀新辅助显著提高了pCR率



pCR, pathological complete response in the breast
IBC, inflammatory breast cancer

新辅助化疗中加入赫赛汀®明显提高疗效(16个相关研究，1,226例患者入组)

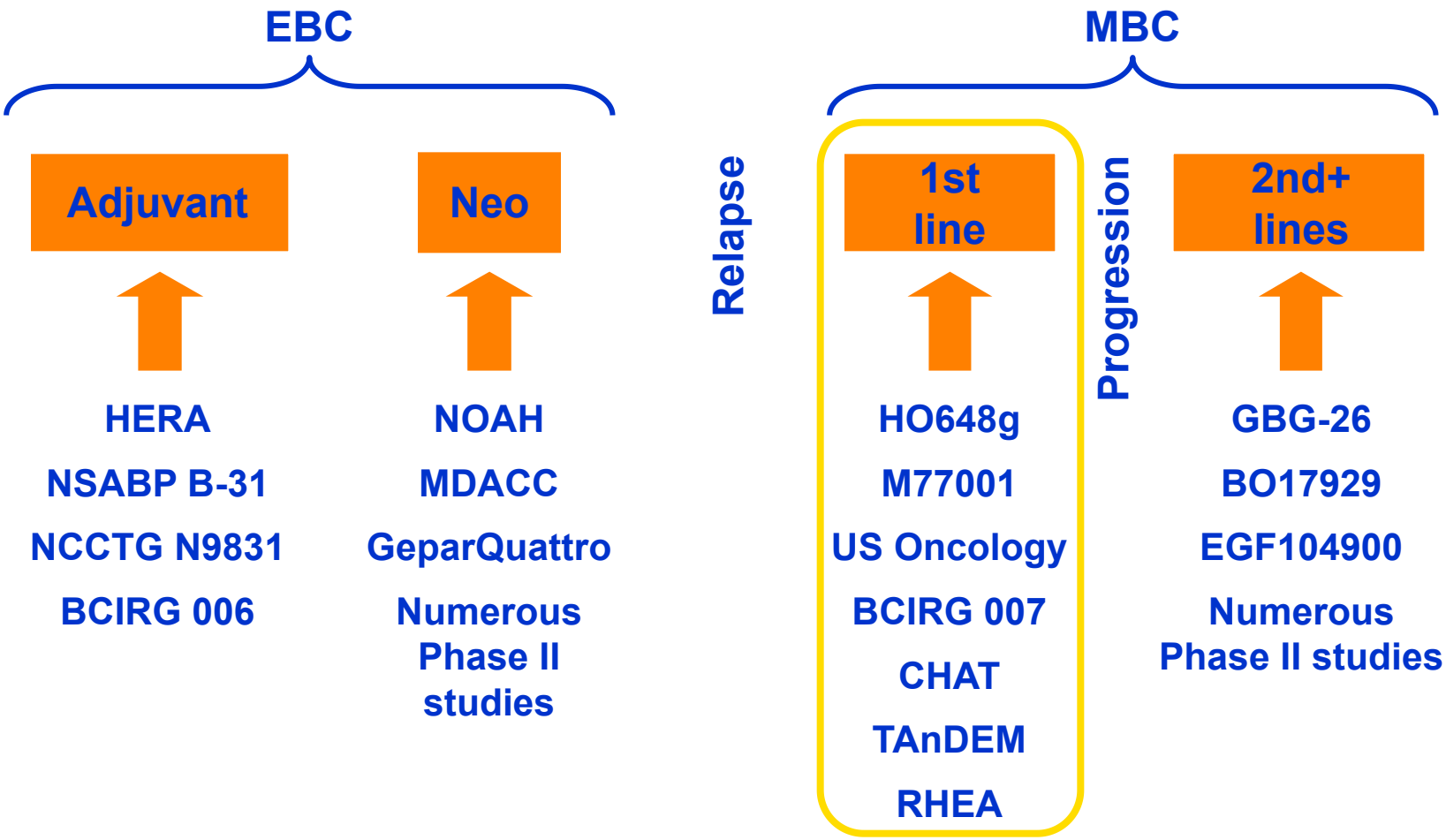


[a]X was given either concurrently or sequentially with D + H

EC, epirubicin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide

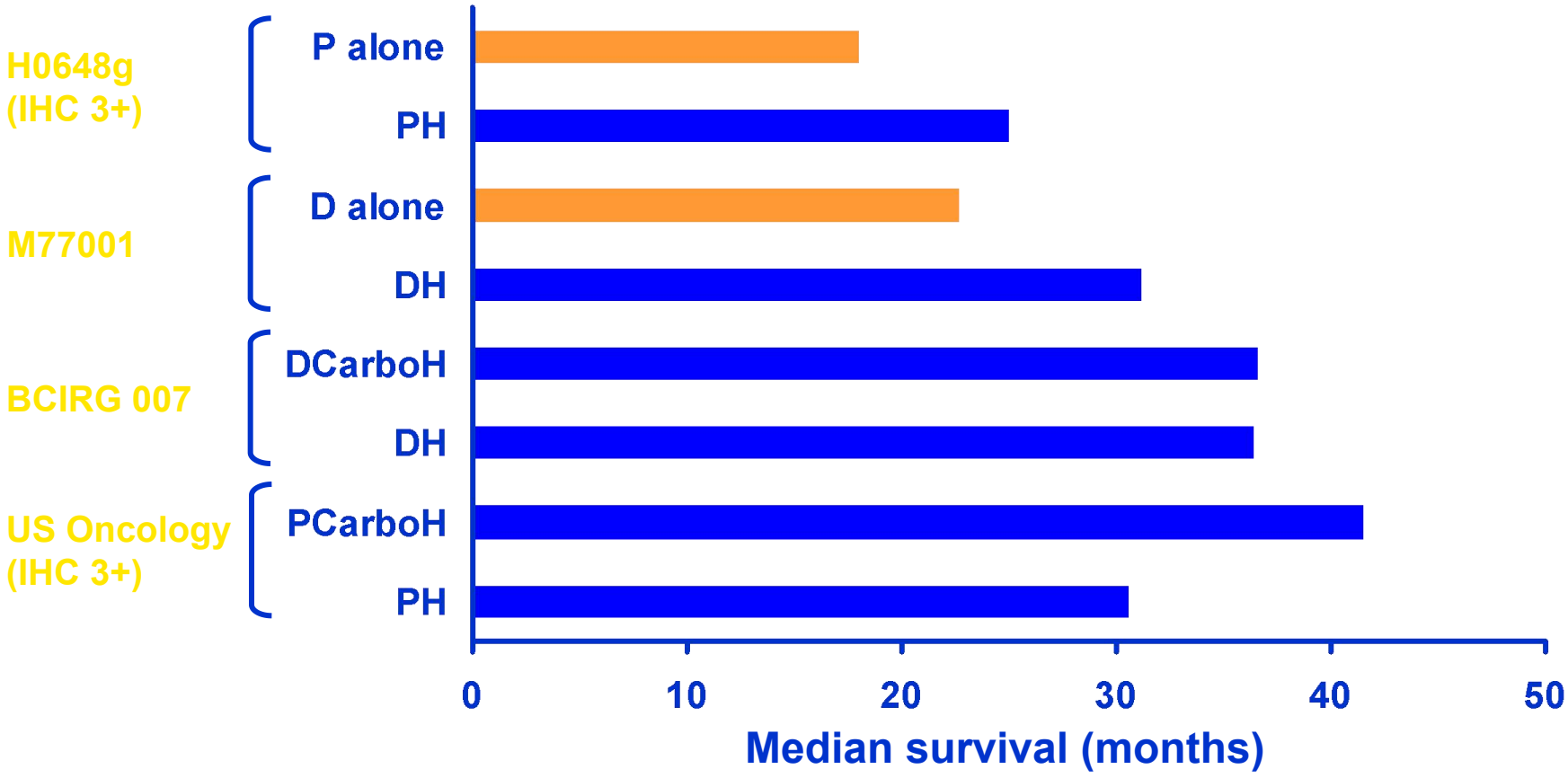
My, Myocet; X, Xeloda

赫赛汀已成为HER2阳性乳腺癌的基础治疗



HER2, human epidermal growth factor receptor 2
EBC, early breast cancer; MBC, metastatic breast cancer

一线赫赛汀治疗显著延长患者的生存时间



IHC, immunohistochemistry; P, paclitaxel
H, Herceptin; D, docetaxel; Carbo, carboplatin

Smith et al 2001; Marty et al 2005
Robert et al 2006; Pegram et al 2007

TAnDEM--赫赛汀联合阿那曲唑治疗HER-2（+）激素敏感性转移性乳腺癌

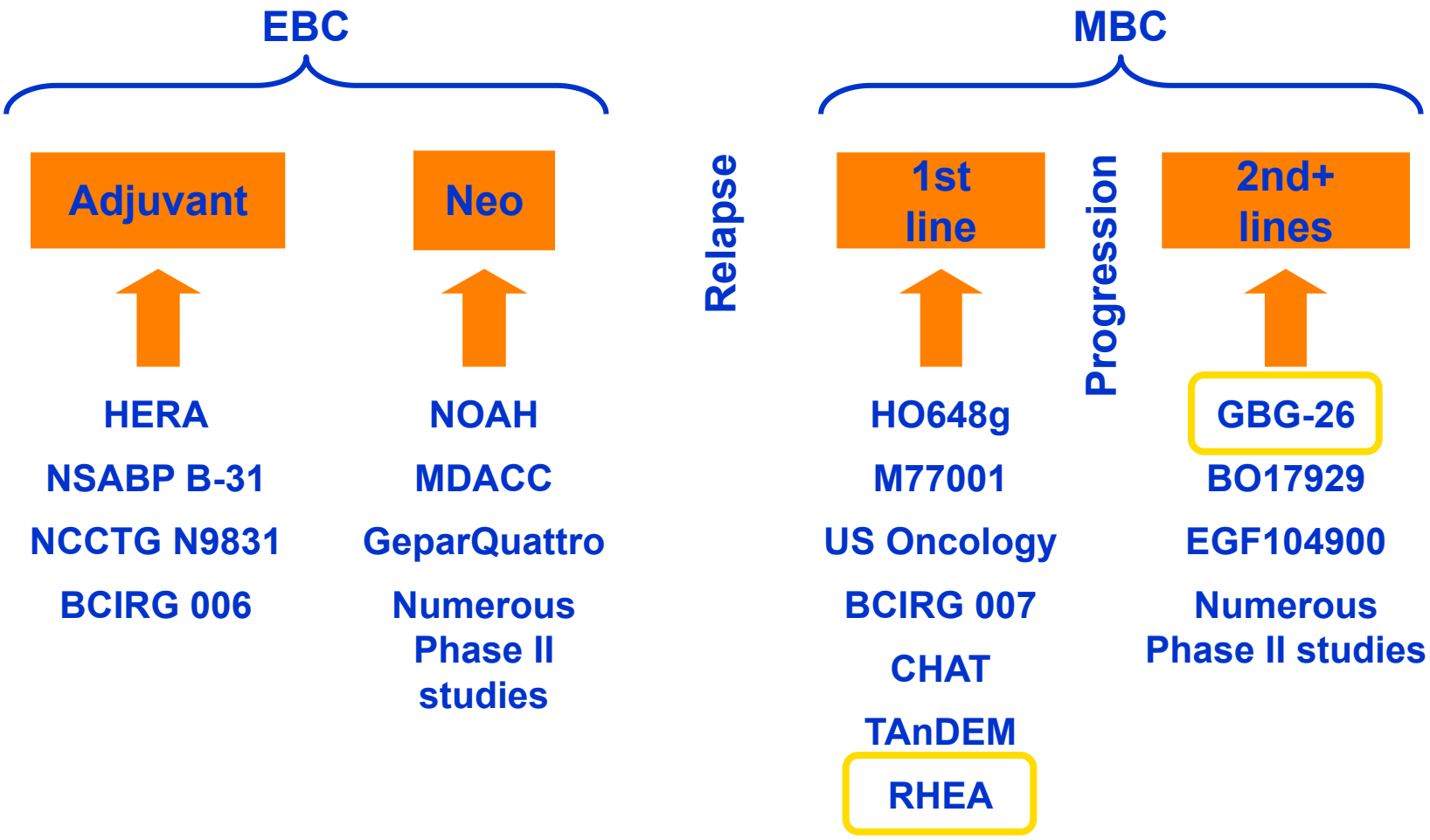
◆临床研究结果（2006年圣安东尼奥）

	H+AI	AI
ORR	20.3%	6.8%
CBR	42.7%	27.9%
PFS	4.8 月	2.4月
TTP	4.8 月	2.4月
OS	28.5月	23.9月

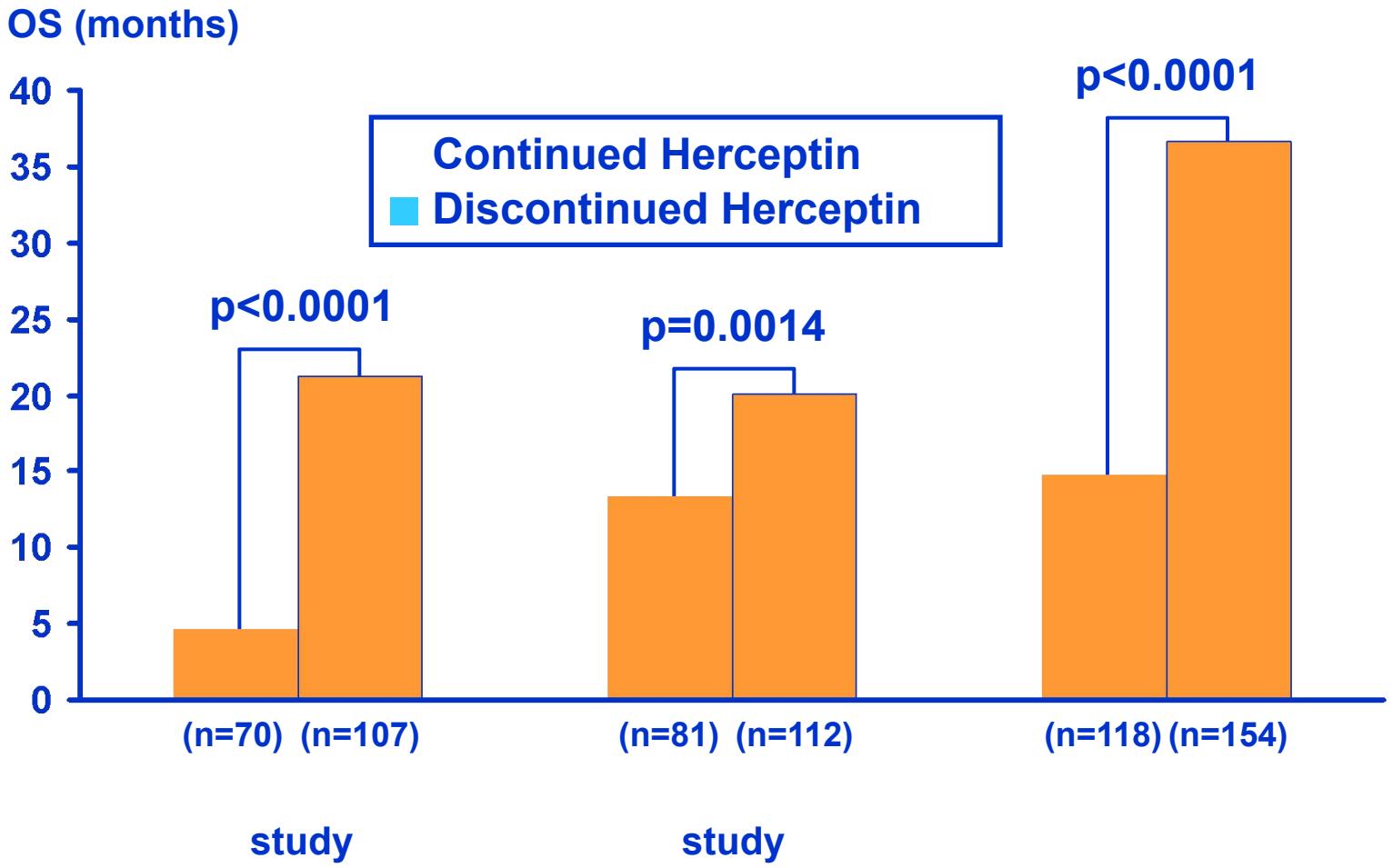
2007年3月欧洲推荐

赫赛汀联合芳香化酶抑制剂治疗HER2与激素受体阳性转移性乳癌

疾病进展后如何合理选择赫赛汀个体化治疗方案



Herceptin improves OS if continued beyond progression



OS, overall survival

Extra et al 2006
Jackisch et al 2007; Menard et al 2008

赫赛汀在多线治疗中的作用

- 赫赛汀治疗的最大获益是持续治疗
- 临床证据提示含赫赛汀方案治疗中进展并不等于赫赛汀耐药，调整化疗药并继续赫赛汀治疗仍可获益.
- 赫赛汀通过持续抑制HER2 ，在多线治疗中病人仍可获益

赫赛汀辅助治疗的心脏安全性

	Arm	n	Asymptomatic LVEF decline, %[a]	Severe CHF, %	Cardiac death, n
HERA	H 1 year	1,678	3.0	0.6	0
NSABP B-31	ACγPH	947	NR	3.8[cum (5 yr)]	0
NCCTG N9831	ACγPH	570	NR	3.3[cum (3 yr)]	0
BCIRG 006	ACγDH	1,068	18.0	1.9	0
	DCarboH	1,056	8.6	0.4	0

[a]Data not comparable due to different assessment criteria
CHF, congestive heart failure; [cum], cumulative incidence
LVEF, left ventricular ejection fraction; NR, not reported

Slamon et al 2006
Rastogi et al 2007
Suter et al 2007
Perez et al 2008

Potential Risk Factors for Congestive Heart Failure

Risk Factors		No. of Pts	No. with CHF (%)	P value	Relative risk (95% CI)
Age	< 50	486	11 (2.3%)	0.03	Ref. group
	50-59	313	16 (5.1%)		2.3 (1.1-4.9)
	60+	148	8 (5.4%)		2.4 (1.0-6.0)
History of smoking	No	562	18 (3.2%)	0.26	1.5 (0.8-2.8)
	Yes	371	17 (4.6%)		
Left-sided tumor & radiation	No	587	23 (3.9%)	0.71	0.9 (0.4-1.8)
	Yes	351	12 (3.4%)		
Family history of cardiac disease	No	864	32 (3.7%)	0.72	1.2 (0.4-4.1)
	Yes	67	3 (4.5%)		

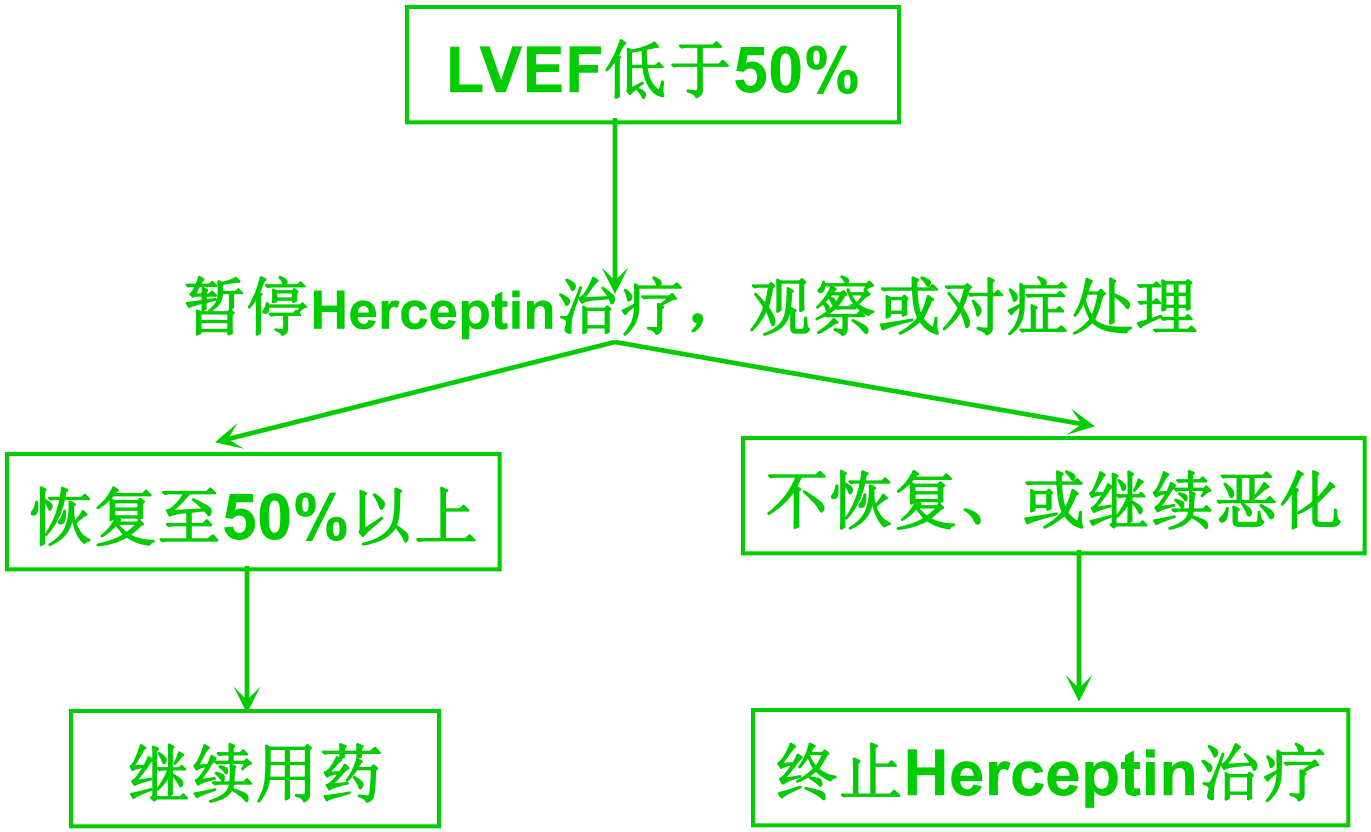
Risk Factors		No. of Pts	No. with CHF (%)	P value	Relative Risk (95% CI)
Hypertensive medications	No	732	22 (3.0%)	0.02	2.3 (1.2 - 4.6)
	Yes	192	13 (6.8%)		
Diabetes medications	No	897	35 (3.9%)	--	--
	Yes	37	0 (0.0%)		
Lipid medications	No	857	34 (4.0%)	0.32	0.4 (0.1 - 2.7)
	Yes	68	1 (1.5%)		
Baseline LVEF	<54	70	9 (12.9%)	0.0003	Ref. group
	55-64	452	17 (3.8%)		0.3 (0.1 – 0.6)
	65+	425	9 (2.1%)		0.2 (0.1 – 0.4)
Post-AC LVEF	<54	111	14 (12.6%)	<0.0001	Ref. group
	55-64	468	17 (3.6%)		0.3 (0.1 – 0.6)
	65+	351	4 (1.1%)		0.1 (.03 – 0.3)

- Age >50 (5.1%-5.4%)
- Use of hypertensive medications (6.8%)
- Baseline LVEF 50-54 (12.9%)

Rastogi et al. Abstract LBA513 ASCO 2007

- 考虑到心脏不良反应事件，临床上不建议Trastuzumab与蒽环类药物联合。
- Trastuzumab可以在AC方案后与紫杉醇联合使用或者在化疗完成后序贯使用。
- 目前Trastuzumab治疗疗程为1年，建议每三个月一次进行心功检查。

心功能监测


LVEF低于50%
暂停Herceptin治疗，观察或对症处理
恢复至50%以上
不恢复、或继续恶化
继续用药
终止Herceptin治疗

赫赛汀临床应用

2008年NCCN复发或IV期乳腺癌指南

HR阴性，HER2阳性具有内脏危象复发或IV期乳腺癌

- 曲妥珠单抗±化疗

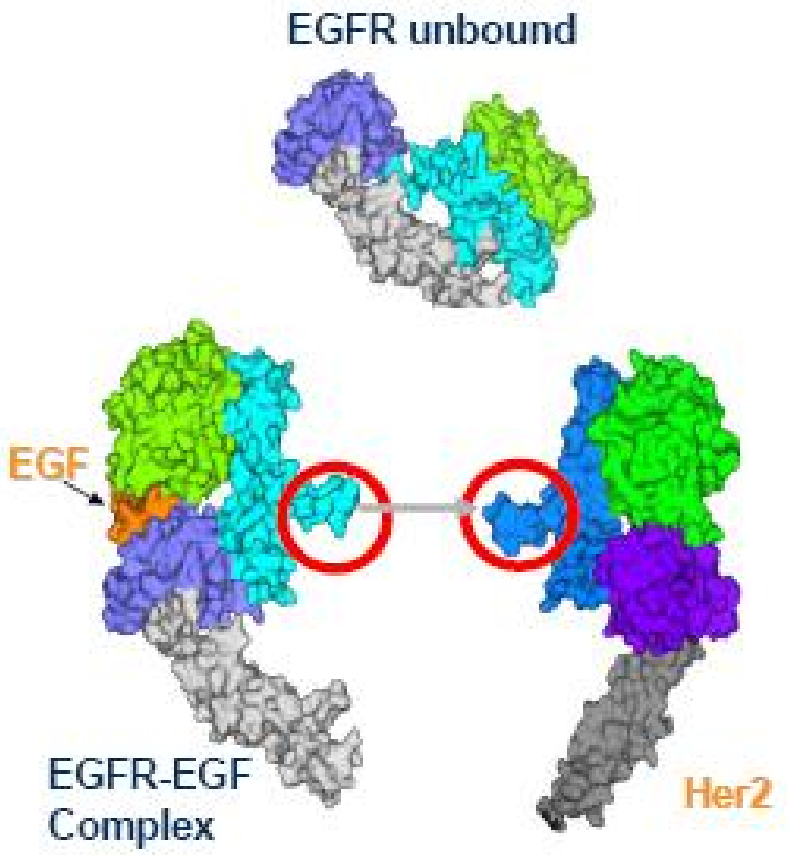
赫赛汀联合辅助化疗方案

- AC →TH
- AC →DH
- TCH
- 化疗→H
- DH →FEC

用法：每周方案　首剂4mg/kg，维持2mg/kg
三周方案　首剂8mg/kg，维持6mg/kg

帕妥珠单抗Pertuzumab(2C4)：anti HER2 agent

- 以HER-2为靶位的人源化单克隆抗体
- 与HER-2 受体胞外结构域II区结合，抑制二聚体的形成
- 抑制HER2 与 EGFR 和HER3形成二聚体。

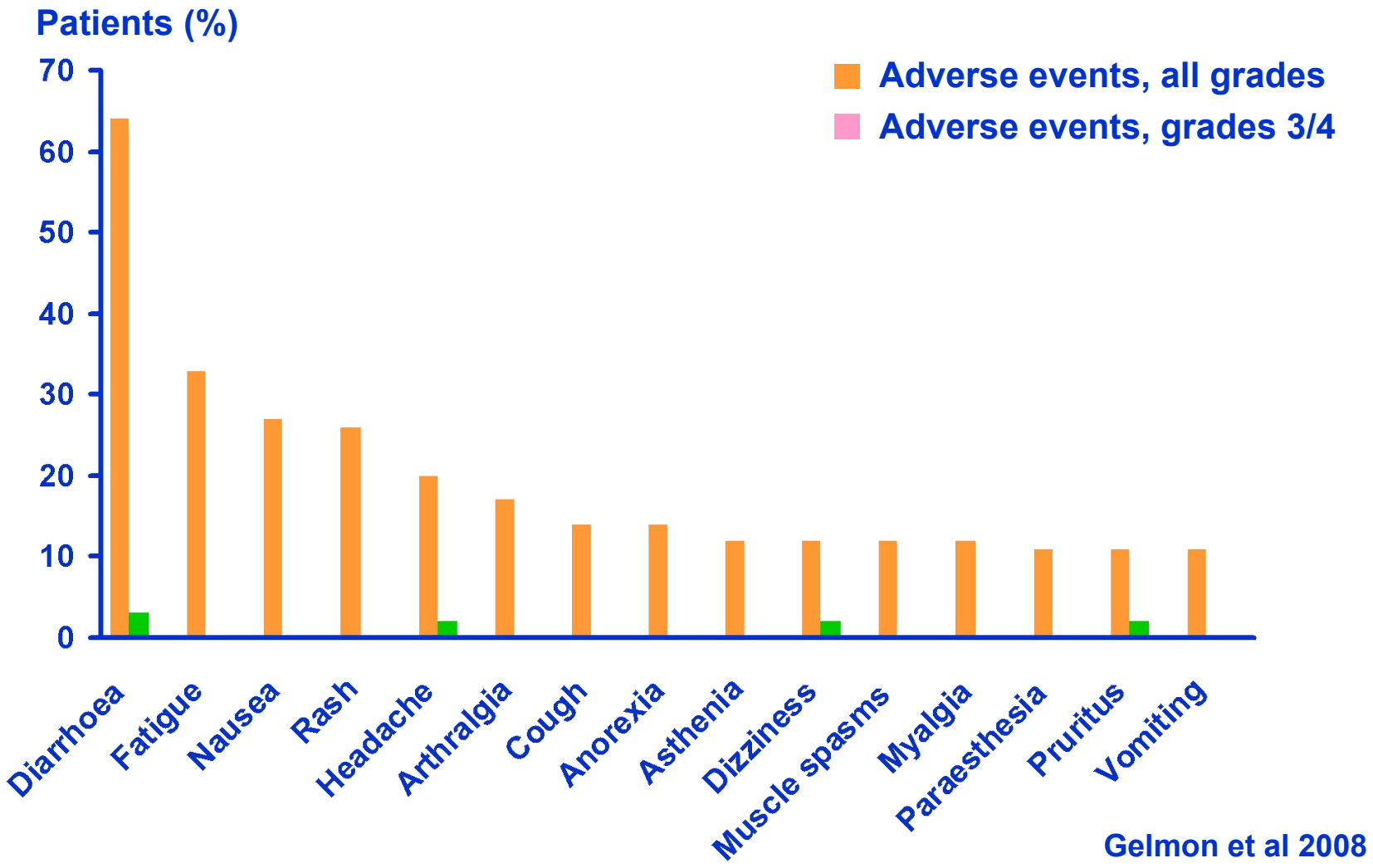


Herceptin + pertuzumab provides clinical benefit to patients progressing on Herceptin

Response	n (%) n=66
CR	5 (7.6)
PR	11 (16.7)
ORR	16 (24.2)
SD for 6 months (≥ Cycle 8)	17 (25.8)
CBR	33 (50.0)
PD	33 (50.0)
Median PFS	24 weeks

Gelmon et al 2008

Herceptin + pertuzumab is a well-tolerated combination

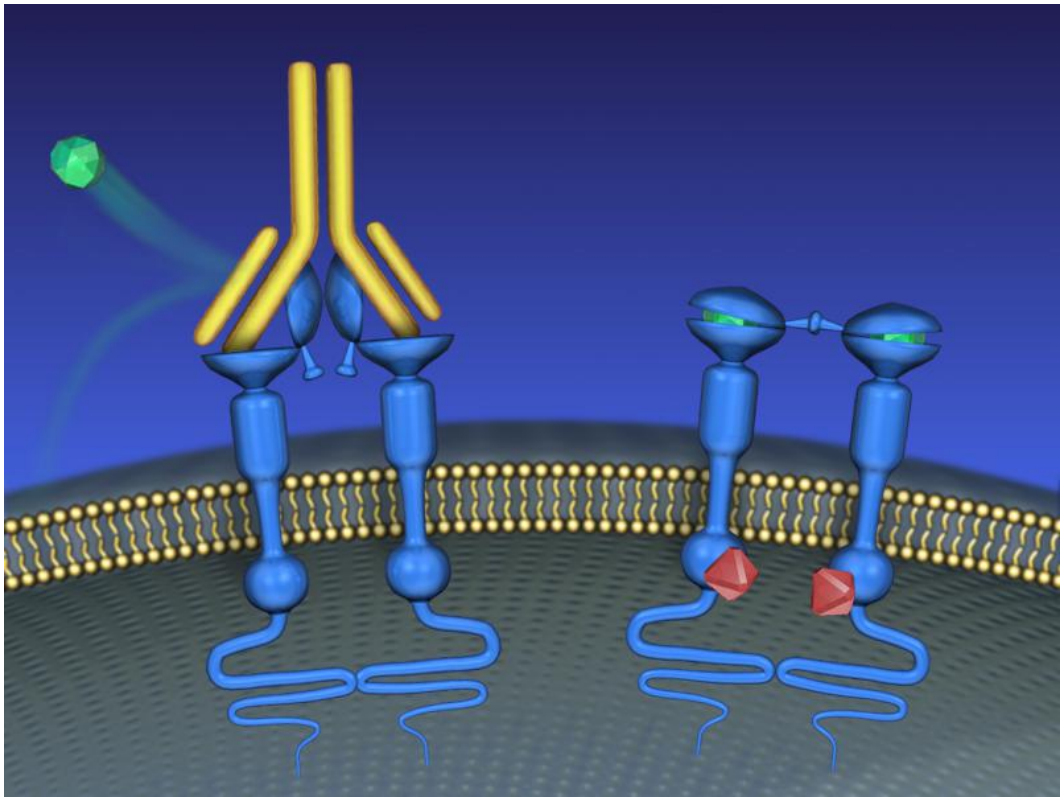


Gelmon et al 2008

- 针对HER2受体的靶向药物
- 针对表皮生长因子受体(EGFR)的靶向治疗
- 针对肿瘤血管生成的分子靶向药物
- 其他信号通路抑制剂——mTOR，Ras， MEK等

针对EGFR的靶向治疗

- 小分子酪氨酸激酶抑制剂(SMTKIs)
- EGFR单克隆抗体(MAbs)
- 多靶点抗肿瘤抑制剂

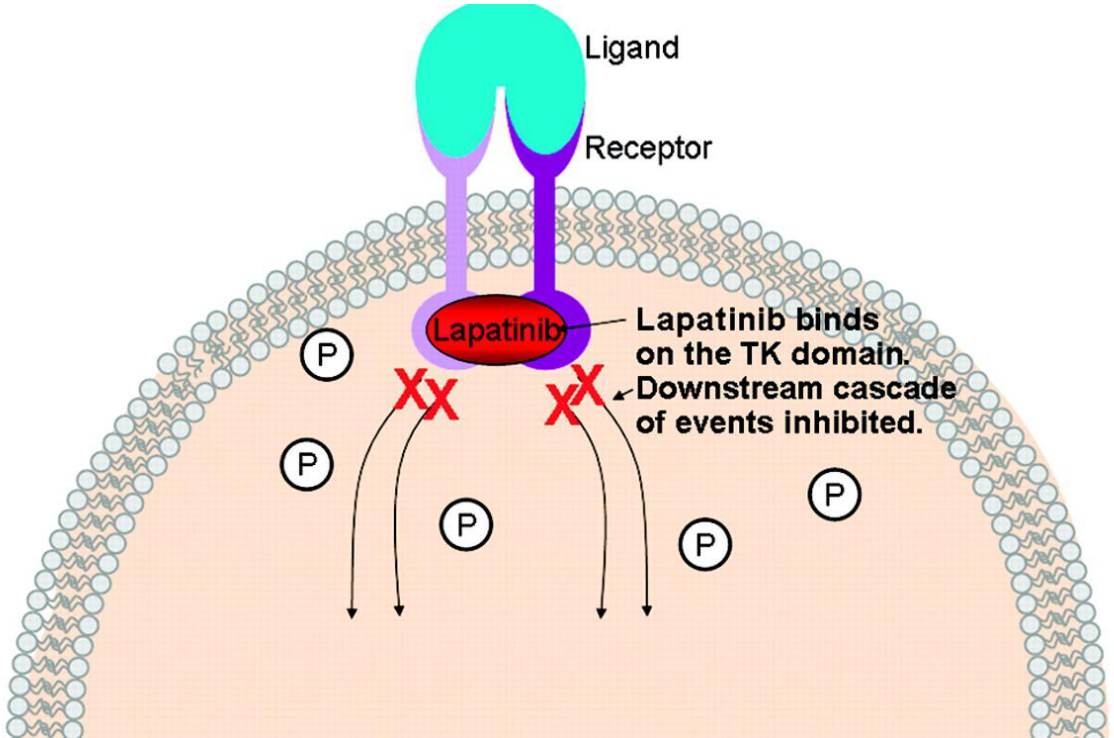


酪氨酸激酶抑制剂

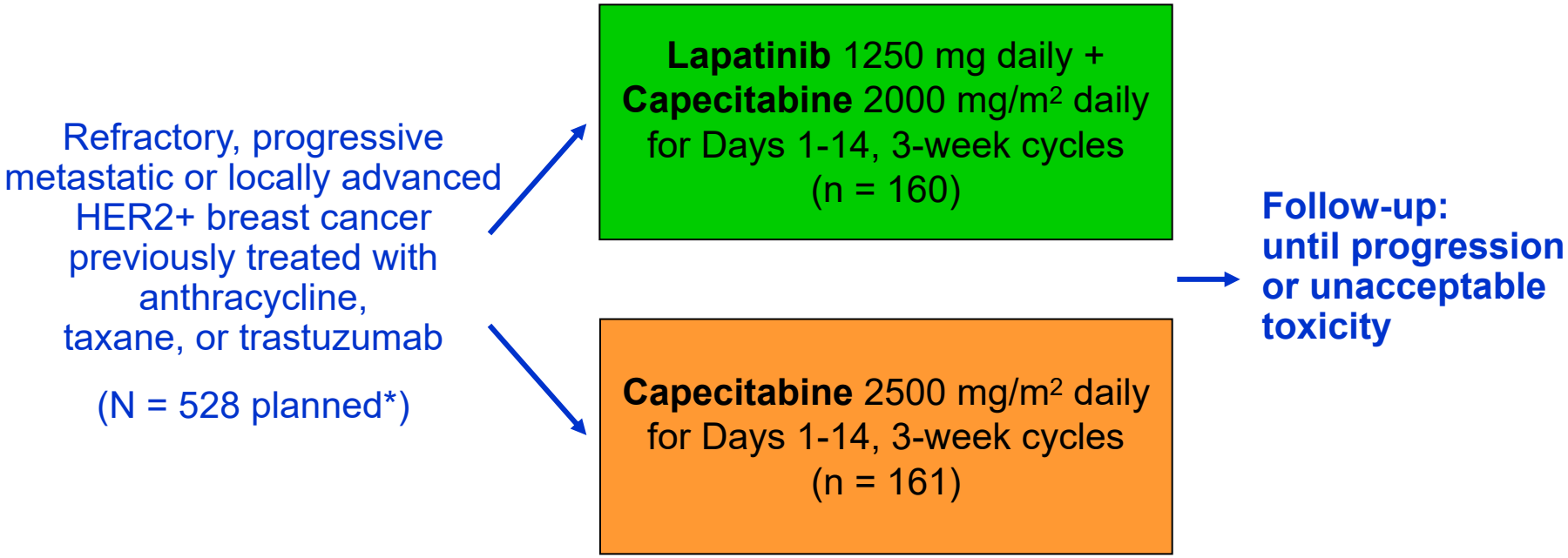
- 拉帕替尼（Lapatinib，Tykerb）
- 吉非替尼（ZD1839，Iressa，Gefitinib，易瑞沙）
- 埃罗替尼（Tarceva，erlotinib）

Lapatinib (Tykerb)

- 口服的TKI
- 双重抑制剂:EGFR 和HER-2



EGF100151: Lapatinib + Capecitabine in Advanced Breast Cancer

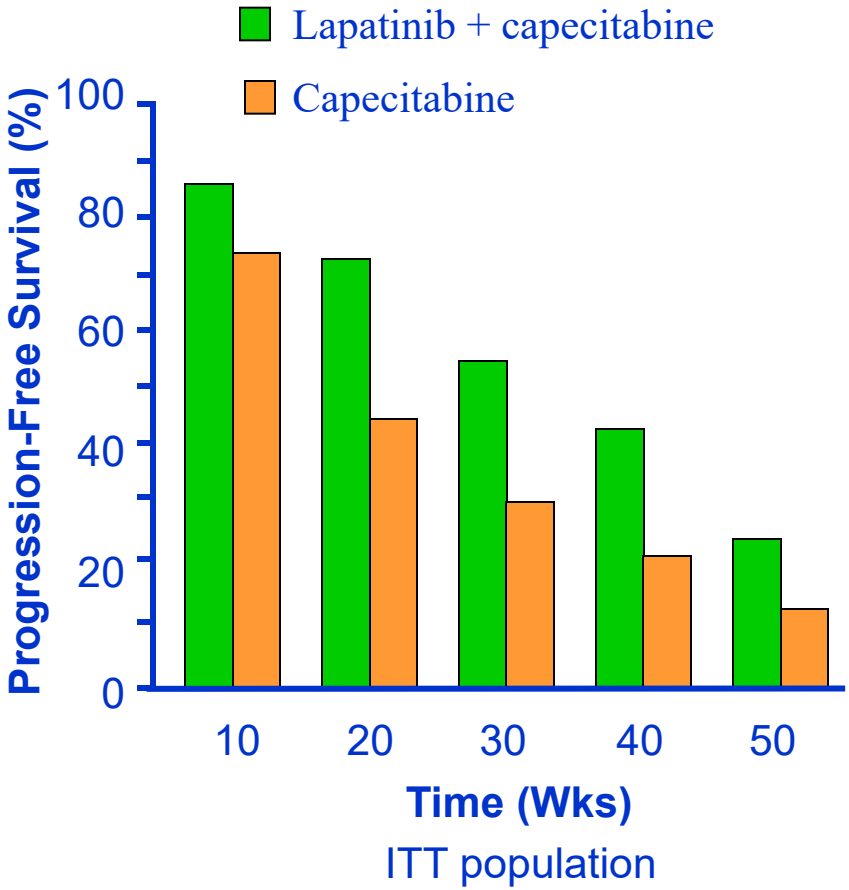


*Study enrollment terminated early by IDMC due to superiority of combination arm in primary endpoint.

Geyer CE, et al. ASCO 2006. Clinical Science Symposium.

EGF100151: Lapatinib + Capecitabine in Advanced Breast Cancer (cont'd)

- Longer time to progression
  - 36.9 vs 19.7 wks (P = .00016)
- Longer progression-free survival
  - 36.9 vs 17.9 wks (P = .000045)
- Fewer progressions or deaths
  - 38% vs 48%
- Response (independent review)
  - Overall: 22.5% vs 14.3% (P = .113)



ITT population

Geyer CE, et al. ASCO 2006. Clinical Science Symposium.

2007.3 FDA批准

拉帕替尼联合卡培他滨治疗HER2过度表达且经蒽环类、紫杉类药物和曲妥珠单抗治疗后复发的晚期或者转移性乳腺癌

Lapatinib for Brain Metastases in Her2+ Cancer

Lin et al. ASCO 2006; NCI-CTEP 6969 trial

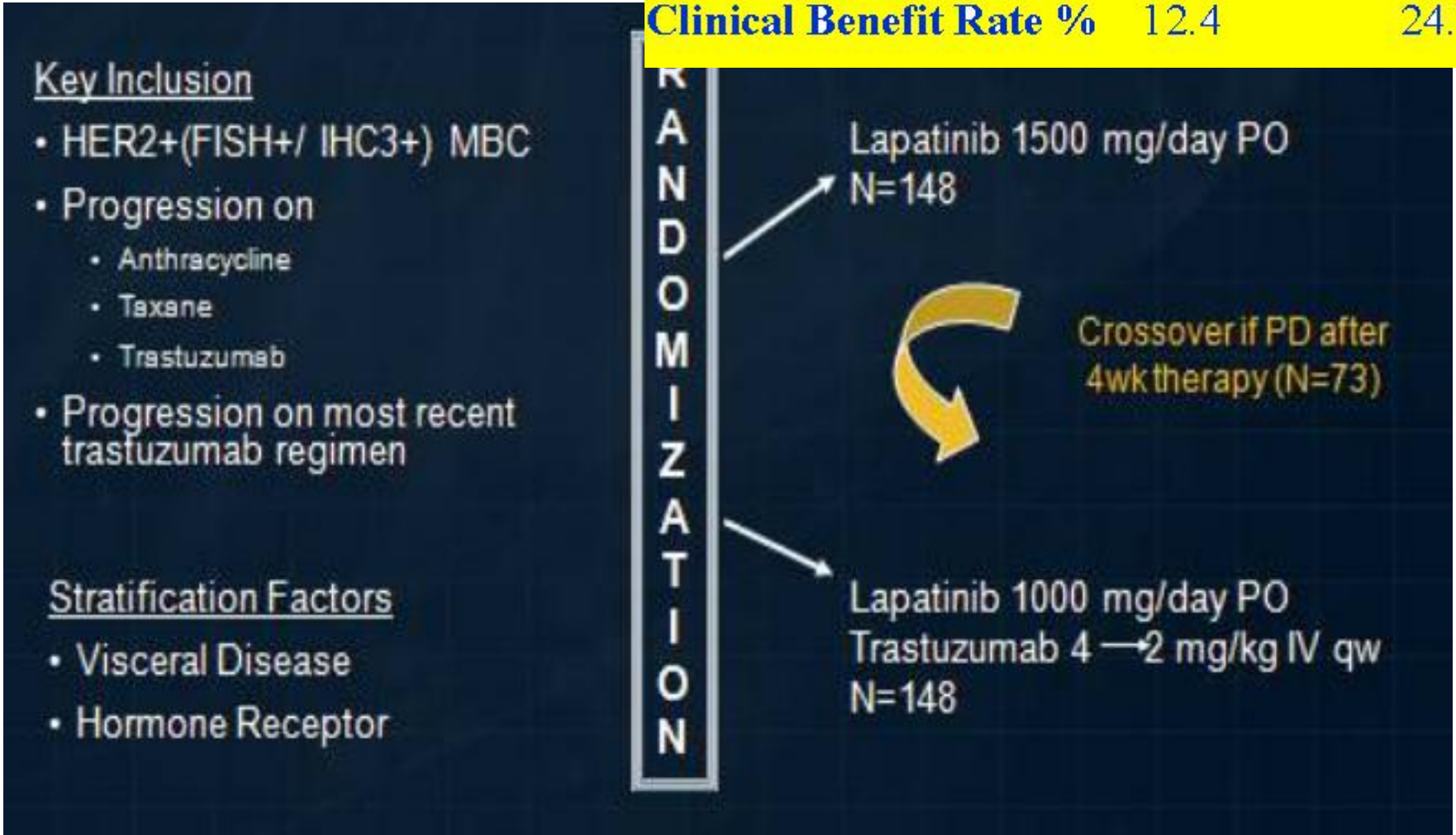
- 39 patients (38 patients progression after radiothrapy)
  New/progressive measurable (≥ 1 cm) brain metastases
- Treatment: Lapatinib 750 mg po BID
- Result

1. 2 patients PR 158d and 347d
2. 5 patients SD ≥ 16 weeks Median TTP 3.2 months MST 6.57 months
3. 1 patient had response, but did not meet RECIST

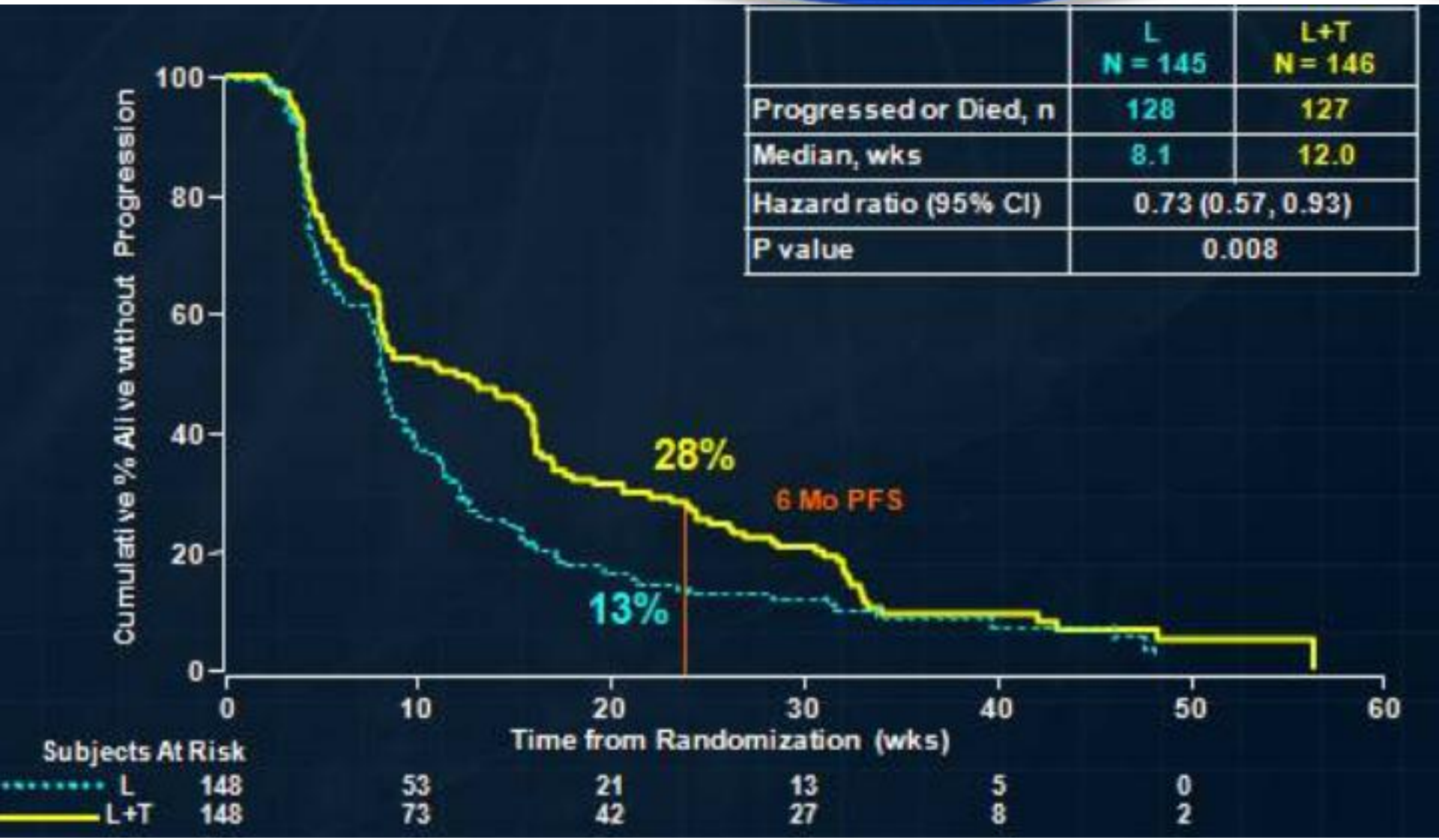
Lapatinib成为Trastuzumab耐药或脑转移患者新选择

Lapatinib+Trastuzumab for Trastuzumab progressing on Her2+ Cancer ASCO 2008

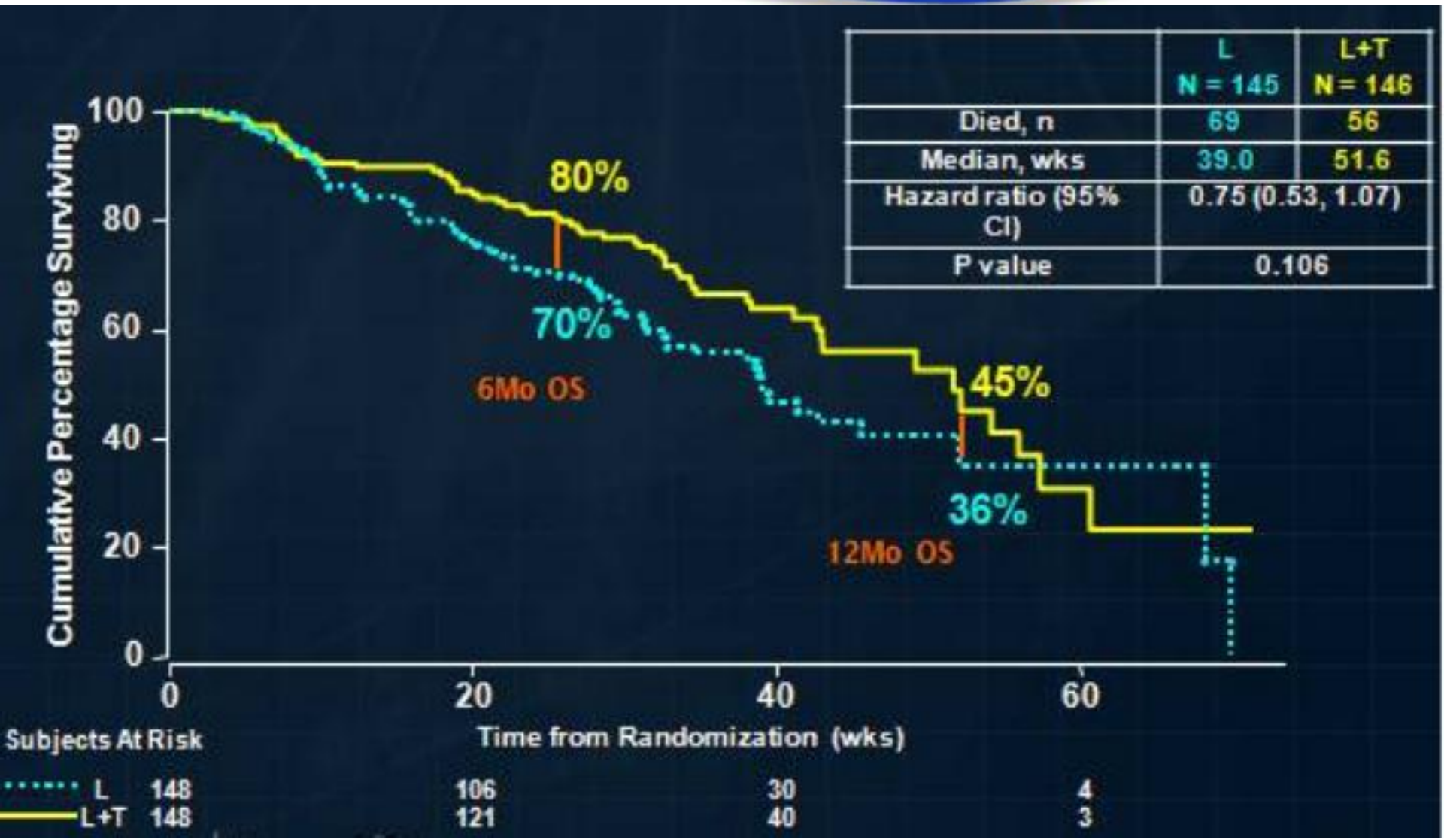
	L	L+T
Response Rate, %	6.9	10.3
Clinical Benefit Rate %	12.4	24.7



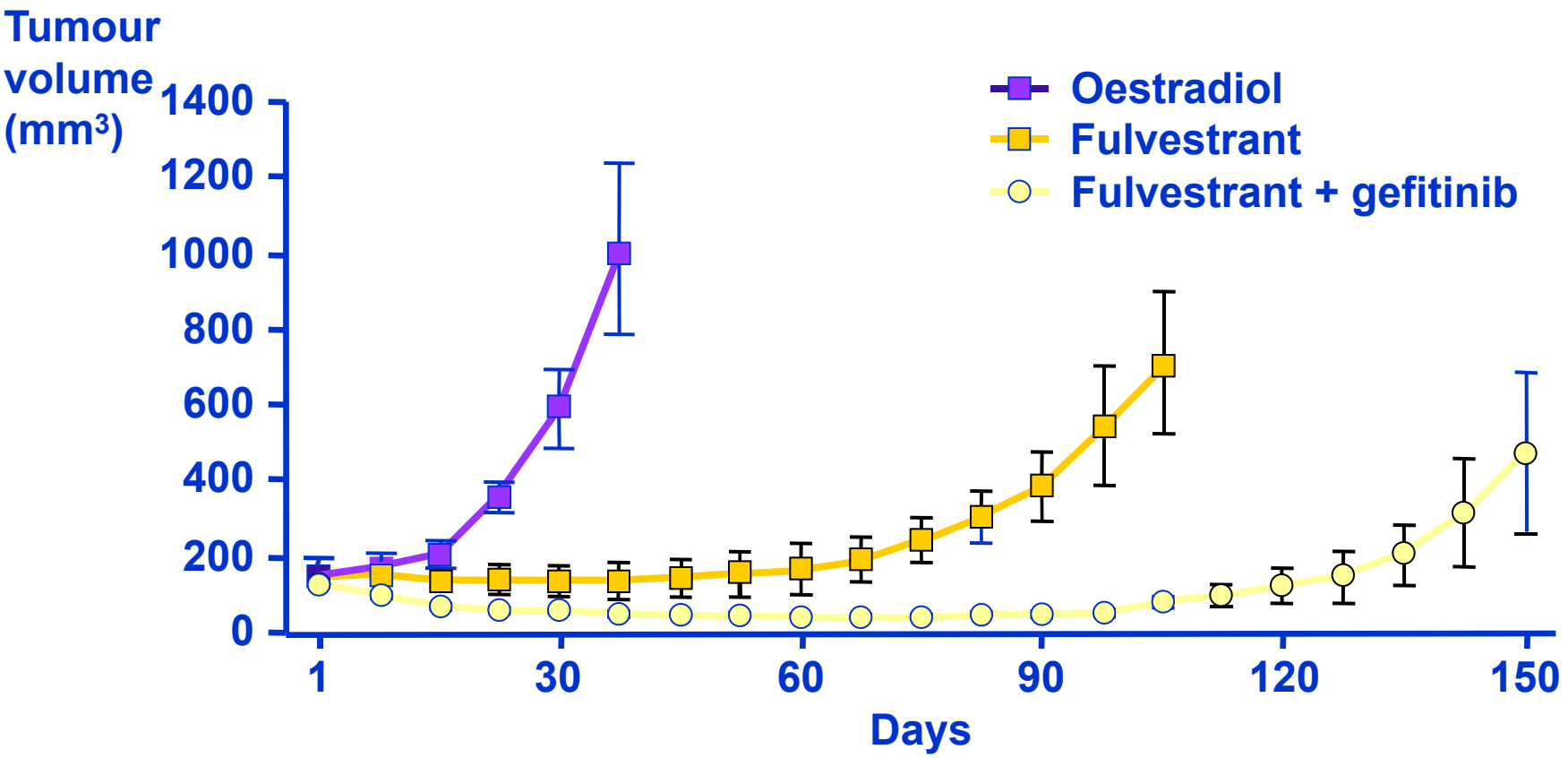
Progression-Free Survival



Overall Survival in ITT Population



Gefitinib--表皮生长因子受体酪氨酸激酶抑制剂



Fulvestrant plus gefitinib delays resistance in MCF-7 / HER2 tumours in vivo

Massarweh et al. Breast Cancer Res Treat 2002

Phase II Trial of Gefitinib in Advanced Breast Cancer

- Acquired resistance to TAM (n=27) or ER-negative tumours (n=27) Gefitinib LD 1000 mg (D1) Daily dose 500 mg/day until disease progression or unacceptable toxicity

	ER-positive (n=9)	ER-negative (n=18)
Partial response	1	1
Stable disease	5	1
Clinical benefit	6 (66%)	2 (11%)
Progressive disease	3	16

Robertson et al. ASCO Proc. 2003

Erlotinib--小分子EGFR 酪氨酸激酶抑制剂

N0234： Erlotinib + Gemcitabine

Erlotinib （150 mg orally daily ）
+
gemcitabine （ 1000 mg/m2 ,
Days 1、8, 3-week cycles ）

previous therapy with either
an anthracycline or a taxane for MBC

A partial response (PR) rate of 17% has been reported (ASCO 2005)

N0234： Erlotinib + Gemcitabine

◆Result

	TN	NON-TN	P
PR	25%	14%	0.30
CBR	25%	22%	0.75
PFS	72d	98d	0.13
OS	227d	738d	0.0002

TN*=ER (-) /PR(-) /HER-2 (-)三阴

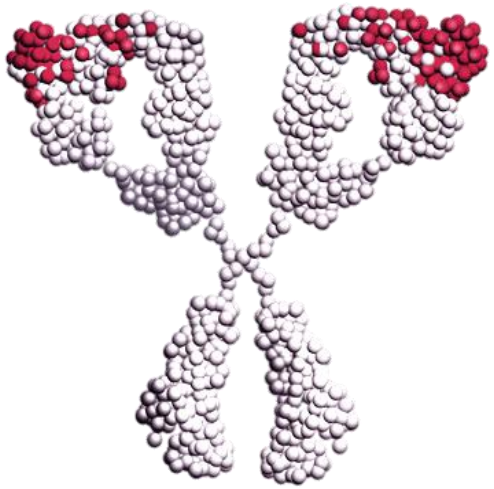
ASCO 2007

西妥昔单抗(Cetuximab， erbitux， C225，爱必妥)

- Cetuximab是针对HER-1的特异性单克隆抗体
- 动物试验显示，Cetuximab可有效抑制乳腺癌细胞增殖和生长，现有不少研究机构开始应用Cetuximab单药或与化疗药物联合治疗EGFR 阳性乳腺癌。

泰欣生（尼妥珠单抗, Nimotuzumab）

- **泰欣生®是一个针对EGFR的单抗药物，通过与EGFR胞外区3A表位结合，竞争性抑制配体与EGFR的结合，使受体失去活性：**



- **IgG_1型单克隆抗体，分子量为150KD**
- **95%人源化**
- **激发ADCC和CDC效应抑制肿瘤细胞**
- **比内源性配体亲合力更高（$K_d=10^{-9}$）**

古巴：泰欣生®联合新辅助化疗治疗乳腺癌

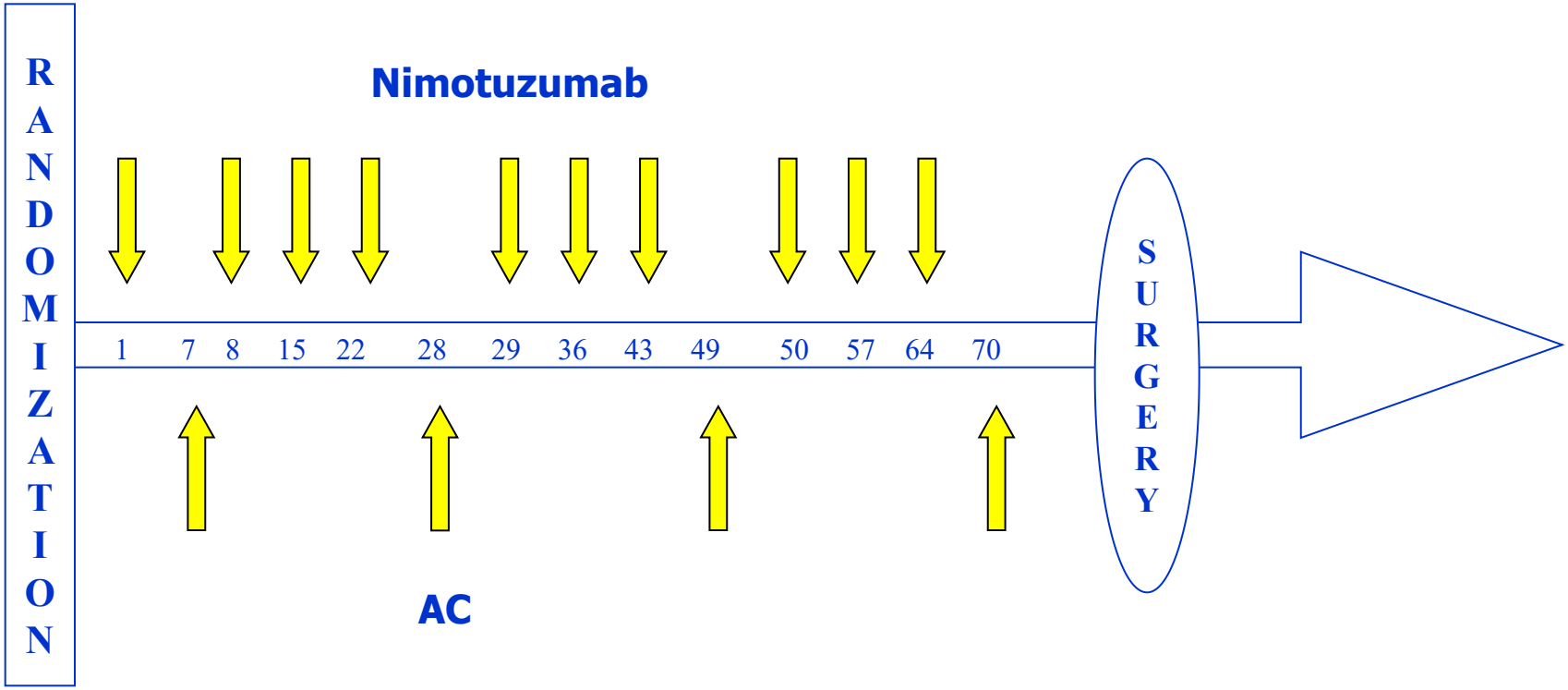
III期初治乳腺癌患者 → 泰欣生（50/100/200/400mg，qw）
＋
阿霉素（60mg/m^2，q3w）
＋
环磷酰胺（600mg/m^2，q3w）

研究终点

- 评估尼妥珠单抗联合化疗药物治疗局部晚期乳腺癌患者新辅助化疗的安全性、药代动力学及疗效。

J. Soriano, N. Batista, et al. European Journal of Cancer Supplements, Vol 5 No 4, Page 116

用药方案



J. Soriano, N. Batista, et al. European Journal of Cancer Supplements, Vol 5 No 4, Page 116

疾病控制情况

➢ 疾病控制情况

共有13例患者入组，12例患者可评估：9例PR，3例SD。

Patients	Dose	Age	Race	TNM	Stage	Diagnose	NG	ER	HER-2
01	50	45	W	T4bN0M0	IIIB	IDC	3	Neg	Neg
02	50	40	W	T3N1M0	IIIA	ILC	3	Neg	3 +
03	50	44	W	T3N1M0	IIIA	IDC	3	Pos	2 +
05	100	59	B	T4bN1M0	IIIB	IDC	3	Neg	Neg
06	100	63	B	T4bN1M0	IIIB	IDC	2	Neg	Neg
13	100	46	B	T3N1M0	IIIA	IDC	1	Pos	Neg
07	200	64	W	T4bN1M0	IIIB	IDC	3	Neg	Neg
08	200	42	W	T3N1M0	IIIA	IDC	3	Pos	Neg
09	200	42	W	T4aN1M0	IIIB	IDC	3	Neg	3 +
10	400	58	W	T4bN0M0	IIIB	IDC	2	Pos	Neg
11	400	59	B	T4bN1M0	IIIB	IDC	3	Neg	3 +
12	400	34	W	T3N1M0	IIIA	IDC	1	Pos	Neg

J. Soriano, N. Batista, et al. European Journal of Cancer Supplements, Vol 5 No 4, Page 116

结　论

- 安全性：
  - 在50、100、200和400mg中，未见剂量限制性毒性
  - 临床未见心脏毒性；联合治疗安全性高，患者耐受性良好
  - 常见不良反应为：皮疹、皮肤反应、恶心、呕吐；红斑,丘疹及色素沉着较常见，通常发生在面部及上肢上部，能自行缓解
- 初步结论：

泰欣生治疗乳腺癌有效，联合治疗在50，100，200和400mg 剂量下是安全的，有很好的耐受性

J. Soriano, N. Batista, et al.　European Journal of Cancer Supplements, Vol 5 No 4, Page 116

苏尼替尼（Sunitinib）--小分子多靶点酪氨酸激酶抑制剂

2006年1 月美国FDA 批准上市，用于治疗晚期肾细胞癌和胃肠道间质瘤。

- Selective inhibitor of:
  - PDGFR
  - VEGFR2 (KDR)
  - KIT
  - FLT3

Sunitinib in Breast Cancer Patients

multicentric phase II study with 64 patients

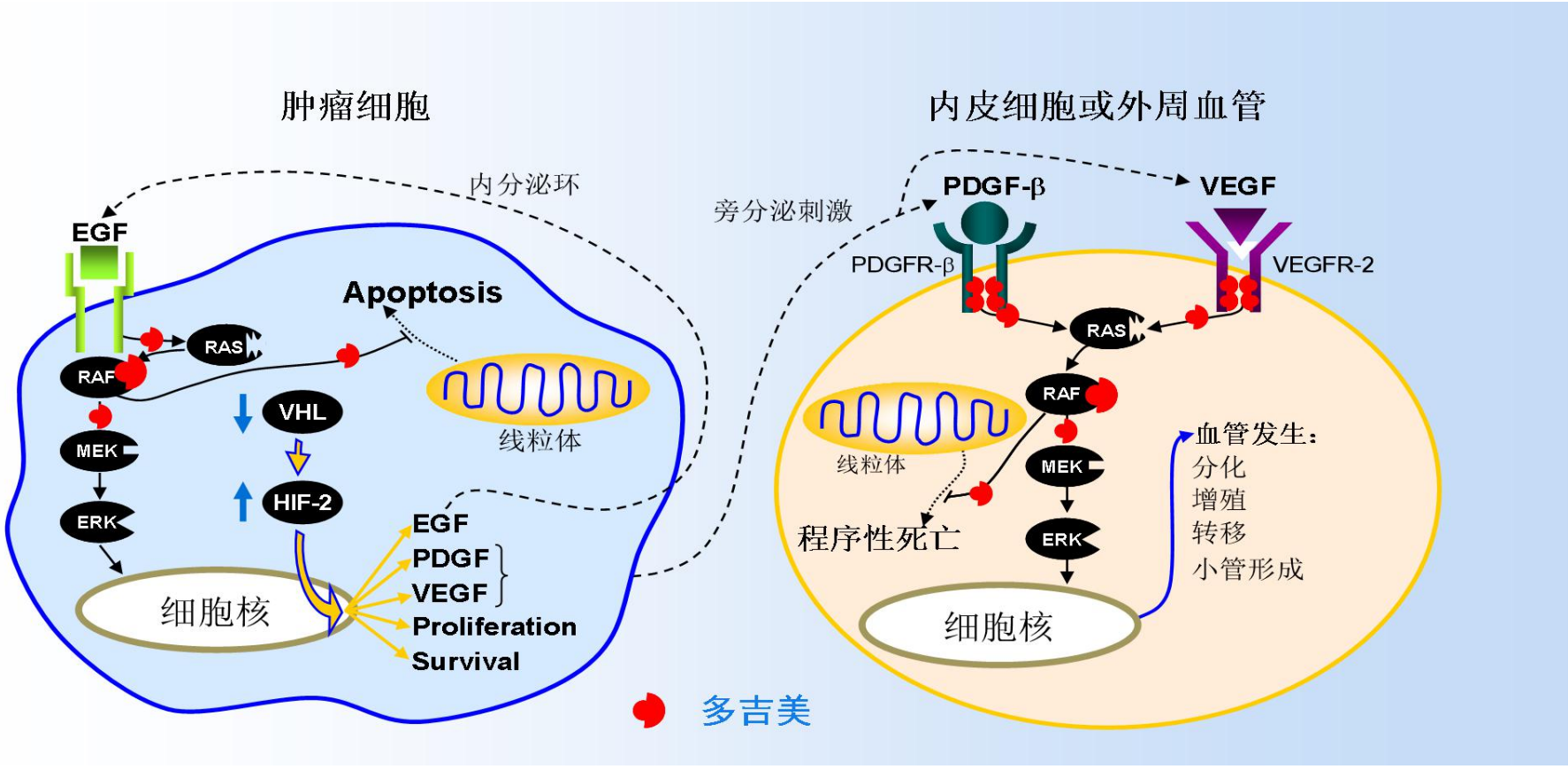
sunitinib 50 mg/d

	N=64
Partial Response*	7 (11%)
Stable Disease ≥ 6 months	3 (5%)
Overall Clinical Benefit	10 (16%)

*One PR not yet confirmed.

patients had received 3.5 different chemotherapies
(anthracycline or taxane)
85% of patients had received adjuvant chemothera

索拉非尼(sorafenib)： 口服信号转导抑制剂,在Raf激酶水平和受体酪氨酸激酶VEGFR-2和PDGFR-β阻断Raf/MEK/ERK途径,抗肿瘤血管生成及肿瘤细胞增殖



- 多激酶抑制剂：丝氨酸/苏氨酸：C-Raf (Raf-1)和B-Raf1

  酪氨酸激酶受体：VEGFR-2、 VEGFR-3、 PDGFR-b、 FLT-3和 c-KIT

Wilhelm S et al. *Clin Cancer Res.* 2004;64:7099-7109.

Sofitinib phase II in MBC

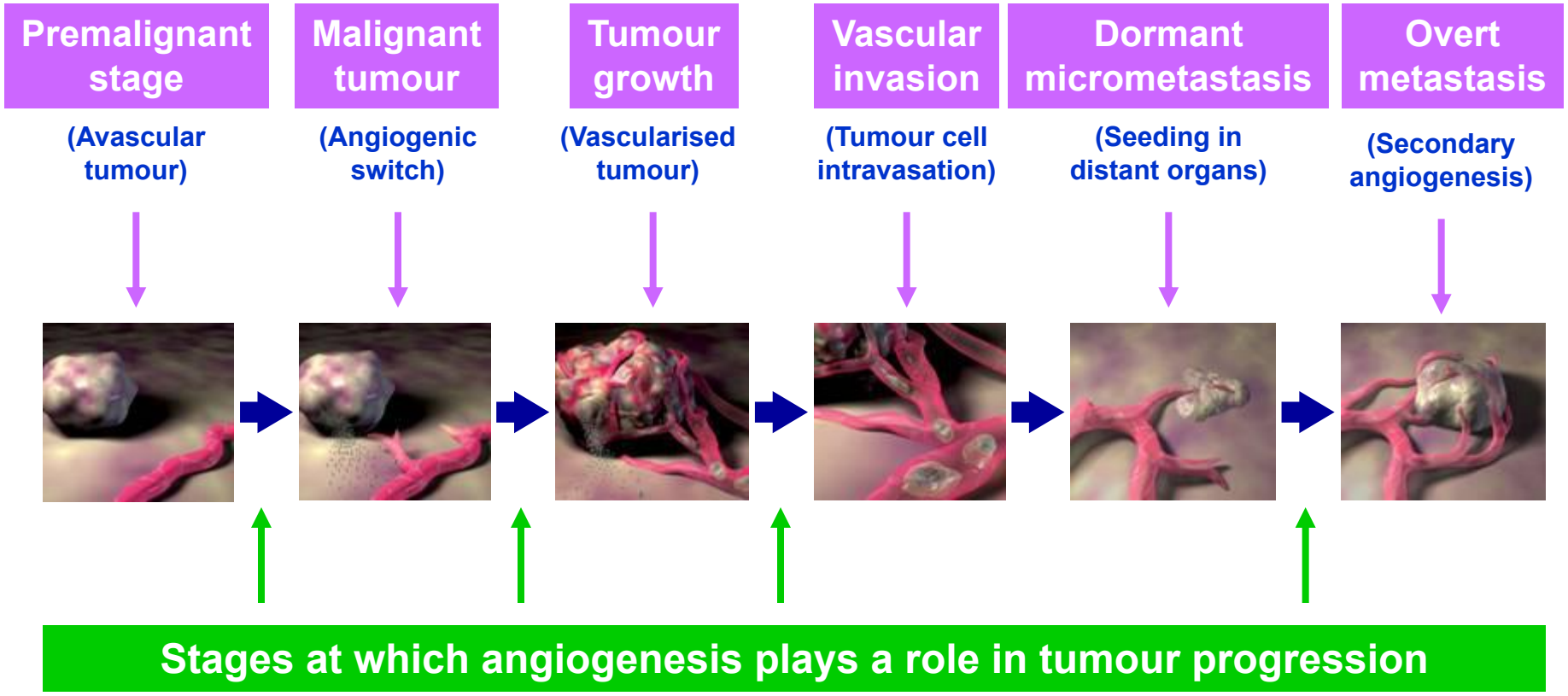
N = 54; 69% ≥ 4 prior chemotherapy regimens for MBC	n (%)
Partial response (unconfirmed)	1 (2)
Stable disease	20 (37)
≥16 weeks	12 (22)
Progressive disease	31 (57)
Not evaluable	2 (4)

Median progression-free survival was 55.5 days (range 0-329 days)

Bianchi et al, *ECCO* 2005

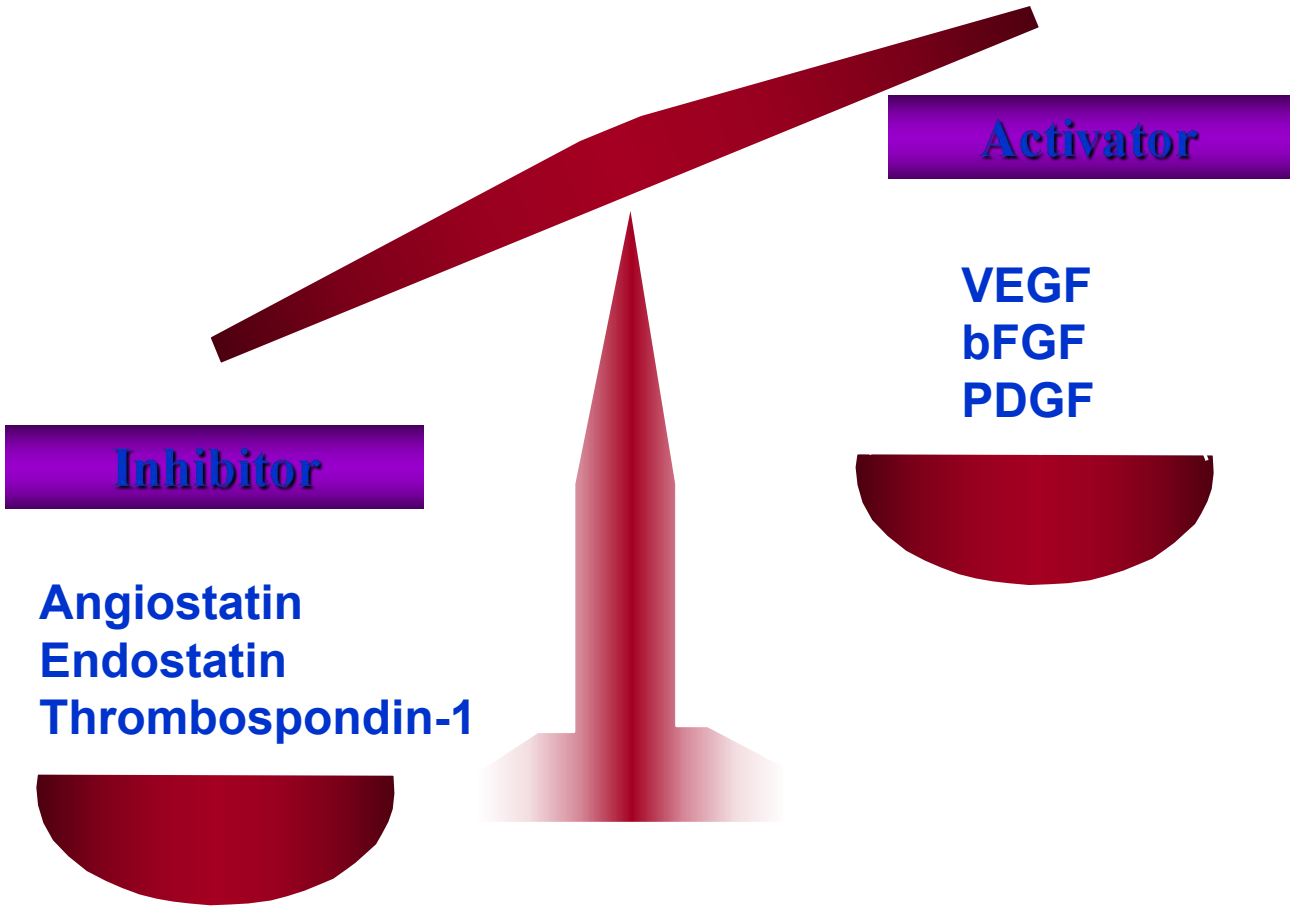
- 针对HER2受体的靶向药物
- 针对表皮生长因子受体(EGFR)的靶向治疗
- 针对肿瘤血管生成的分子靶向药物
- 其他信号通路抑制剂——mTOR，Ras， MEK等

Angiogenesis is involved throughout tumour formation, growth and metastasis



Adapted from Poon RT, et al. J Clin Oncol 2001;19:1207–25

血管生成的双向调节机制



Bevacizumab (Monoclonal Antibody to VEGF)

Humanized to avoid immunogenicity (93% human, 7% murine)

Recognizes all isoforms of vascular endothelial growth factor, $K_d = 8 \times 10^{-10}$M

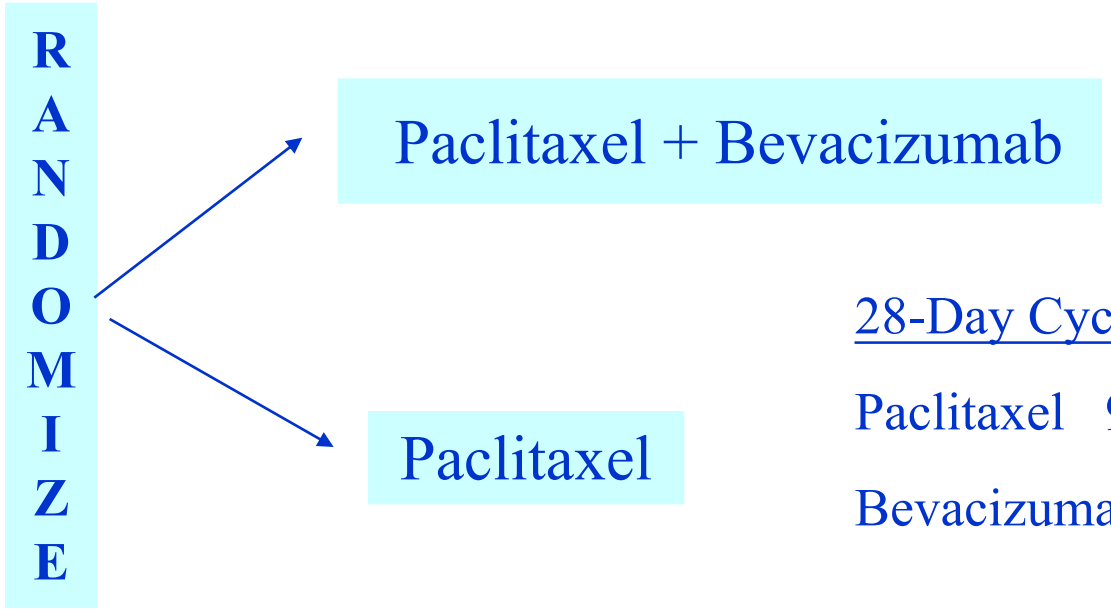
Terminal half life 17-21 days

E2100: Study Design

-线治疗晚期乳腺癌的III期临床研究

715 cases Stratify:

- DFI ≤ 24 mos. vs. > 24 os.
- < 3 vs. ≥ 3 metastatic sites
- Adjuvant chemotherapy yes vs. no
- ER+ vs. ER- vs. ER unknown
- age

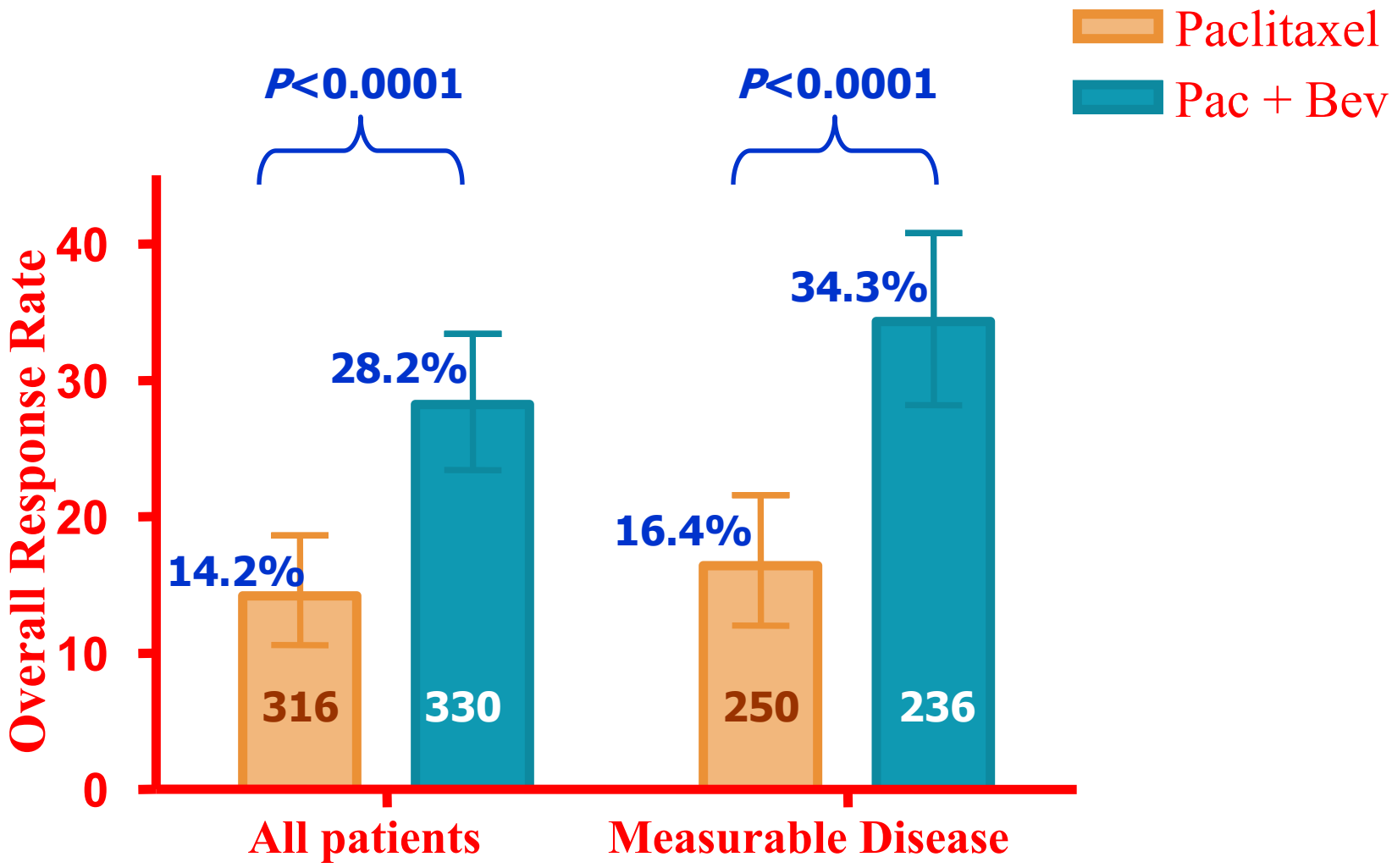


28-Day Cycle:

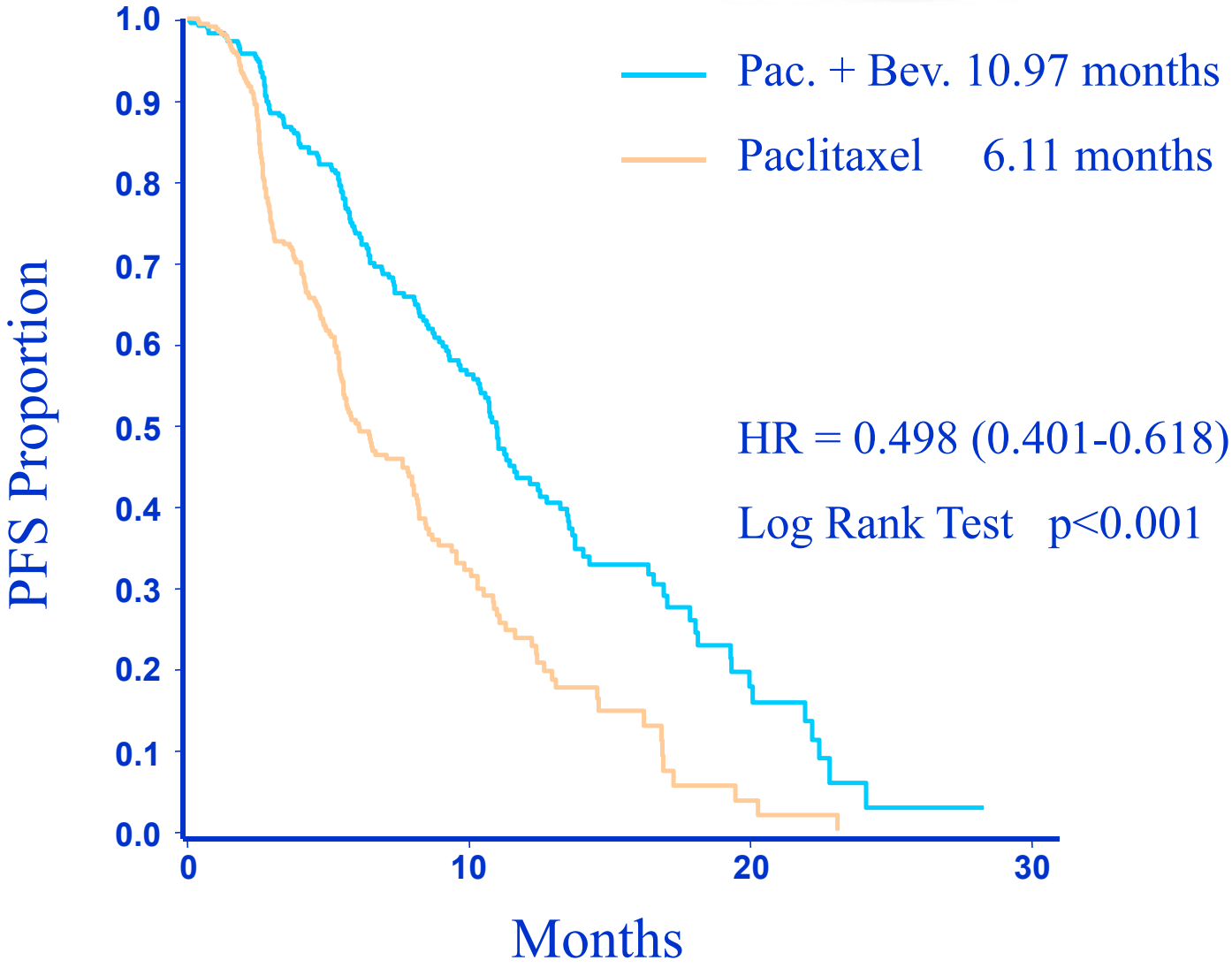
Paclitaxel 90 mg/m^2 D1, 8 and 15

Bevacizumab 10 mg/kg D1 and 15

E2100: Response



E2100: Progression Free Survival



Bevacizumab Toxicity
NCI-CTC Grades 3 and 4

	Paclitaxel		Pac. + Bev.	
	Grade 3	Grade 4	Grade 3	Grade 4
HTN*	0%	0%	13%	0.3%
Thromboembolic	0.3%	0.9%	1.2%	0%
Bleeding	0%	0%	0.6%	0.3%
Proteinuria**	0%	0%	0.9%	1.5%

NCI-CTC v3.0, worst per patient

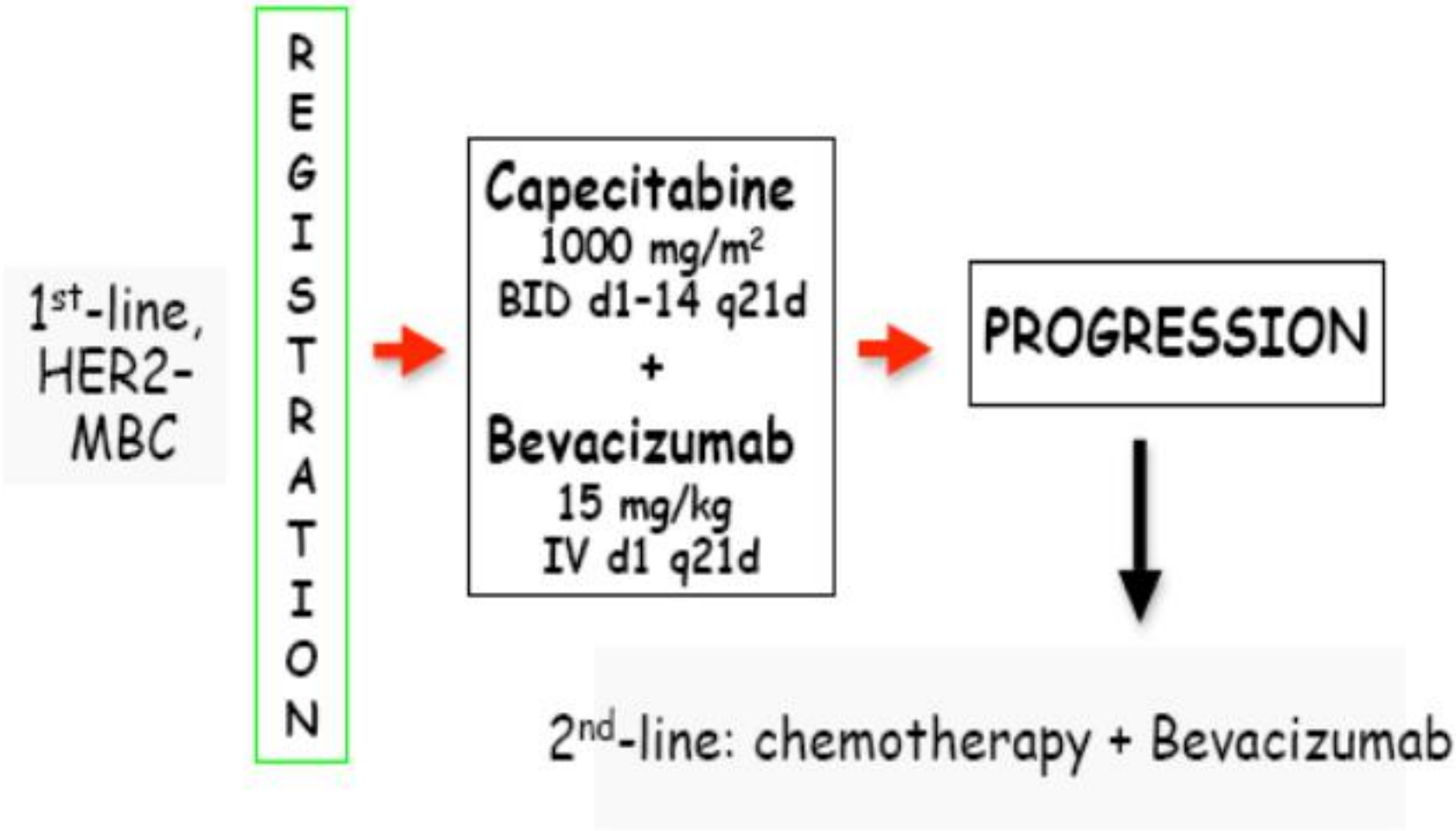
*$P<0.0001$; **$P=0.0004$

NCCN

- 2006年美国NCCN指南已推荐Bevacizumab联合紫杉醇用于晚期乳腺癌的治疗。

Phase II trial of Capecitabine + Bevacizumab

2007 ASCO

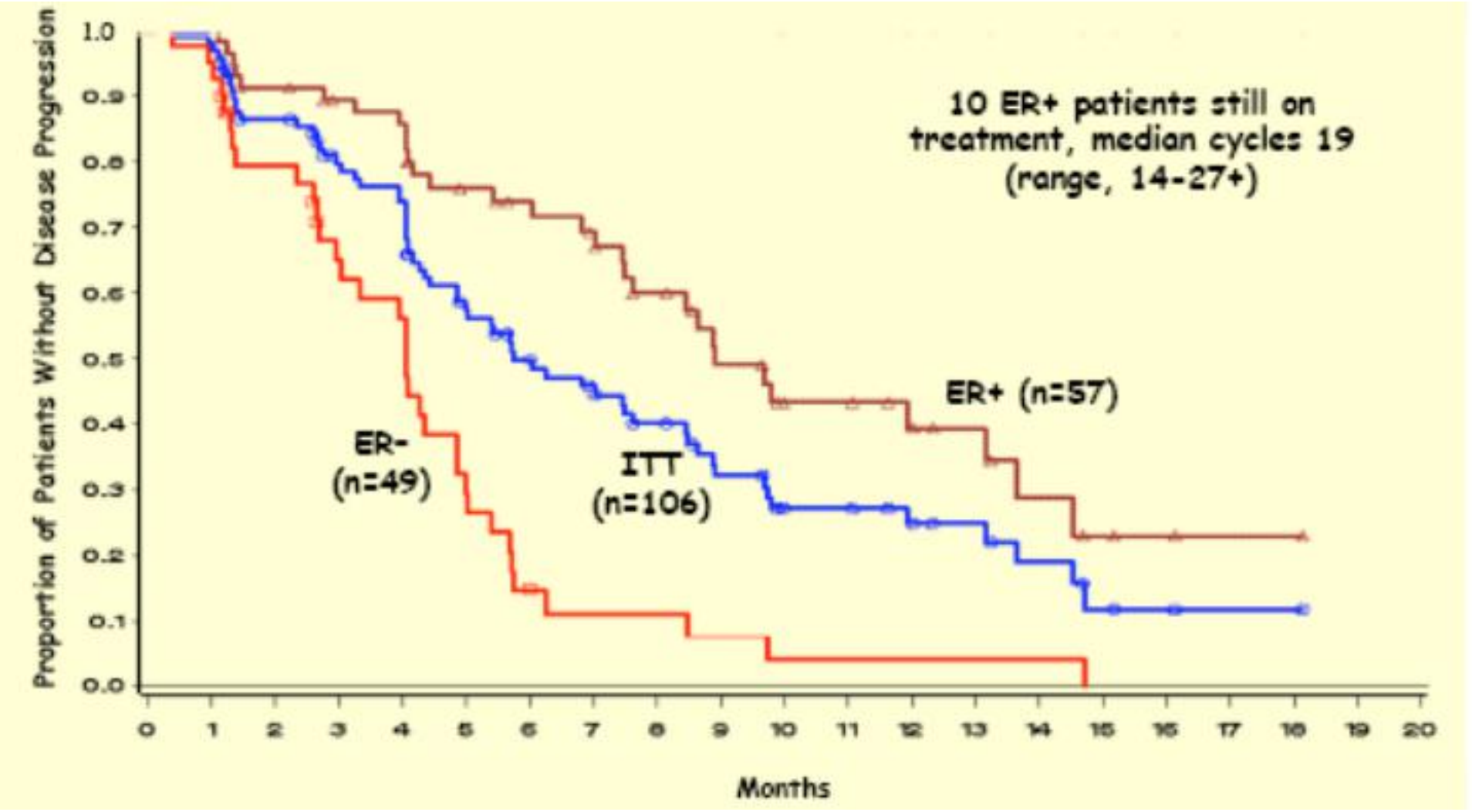


Result

	ITT† n=106	ER- n=49	ER+ n=57
Median TTP, months (95% CI)	5.7 (4.9-8.4)	4.0 (3.0-4.9)	8.9 (7.5-13.6)
Median OS, months (95% CI)	16.0+ (12.9-*)	7.5 (5.6-16)	16.6+ (15.1-*)
ORR (CR+PR)	38%	27%	47%

†HER2*neu* negative pts
*Not reached
ER+ vs. ER- p<0.0001
Median follow-up: 12.9 months (range 0.5 - 20.7)

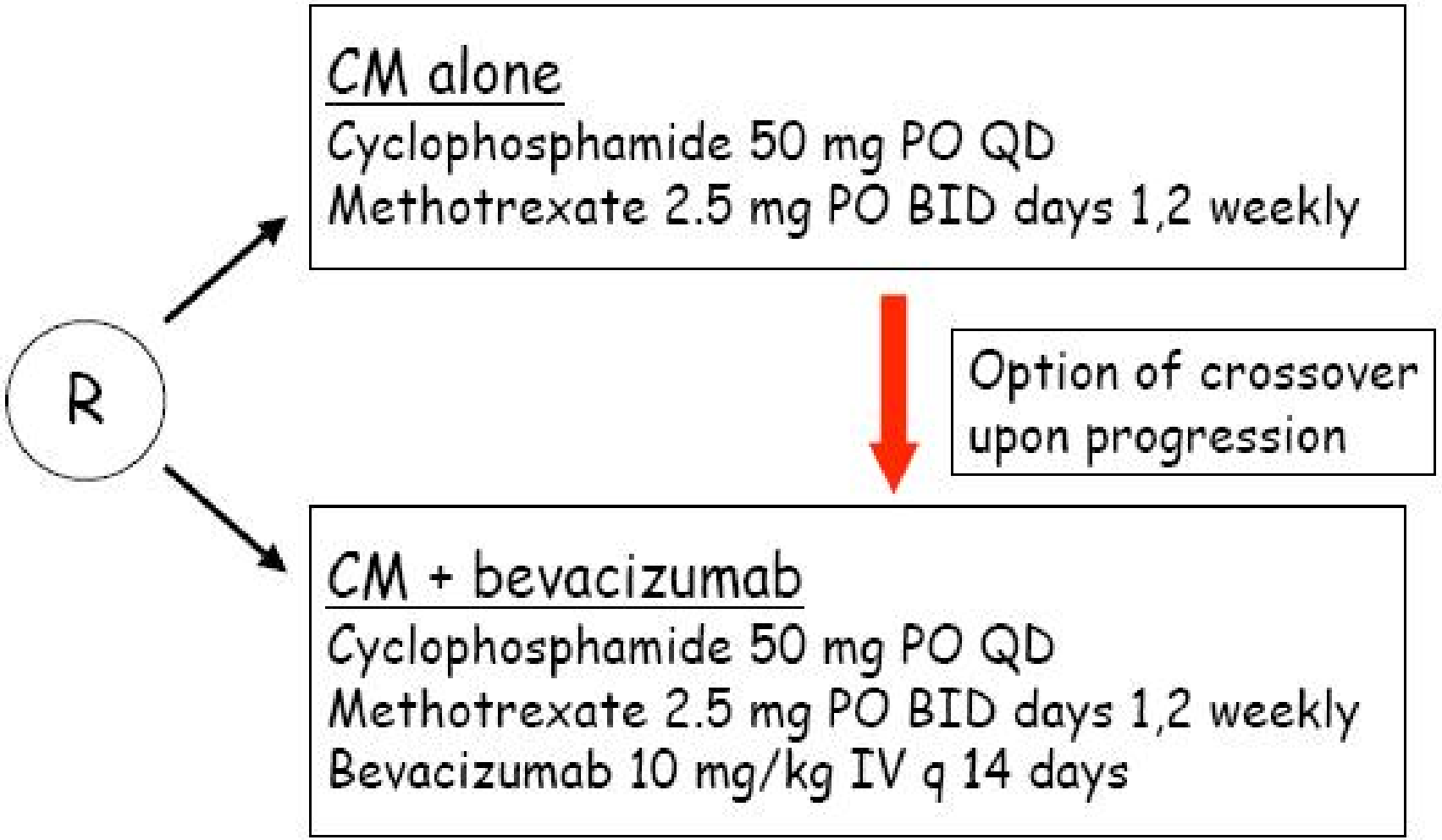
Sledge et al Proc*ASCO* 2007


Proportion of Patients Without Disease Progression
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Months
10 ER+ patients still on treatment, median cycles 19 (range, 14-27+)
ER+ (n=57)
ITT (n=106)
ER- (n=49)

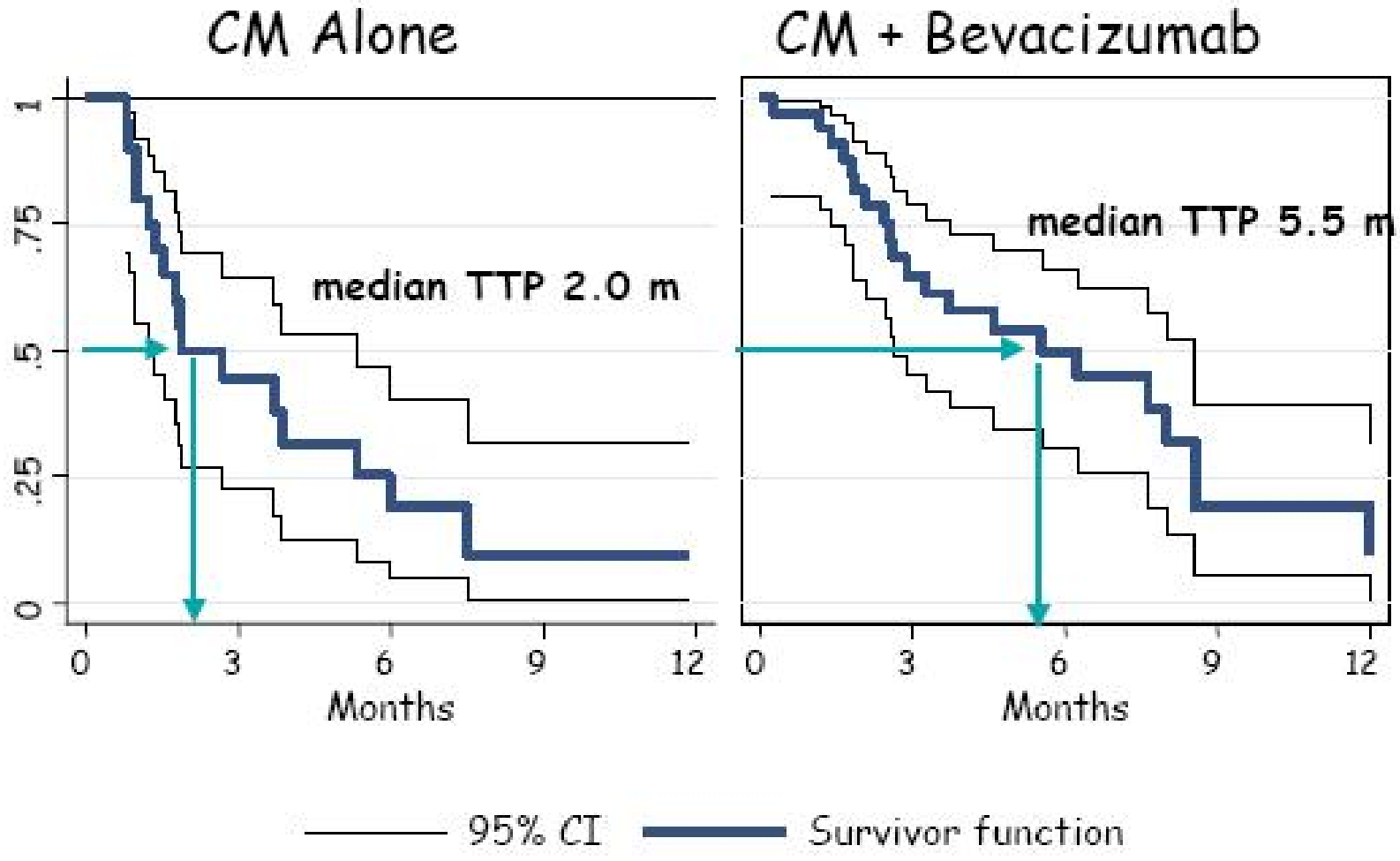
抗血管生成给药方式

- 许多化疗药低剂量时具有抗血管生成作用
- 连续规律的低剂量化疗（metronomic chemotherapy）称为抗血管生成化疗(antiangiogenic chemotherapy)
- 低剂量化疗的优势

Metronomic chemotherapy+bevacizumab



Metronomic chemotherapy+bevacizumab



Burstein et al SABCS 2005

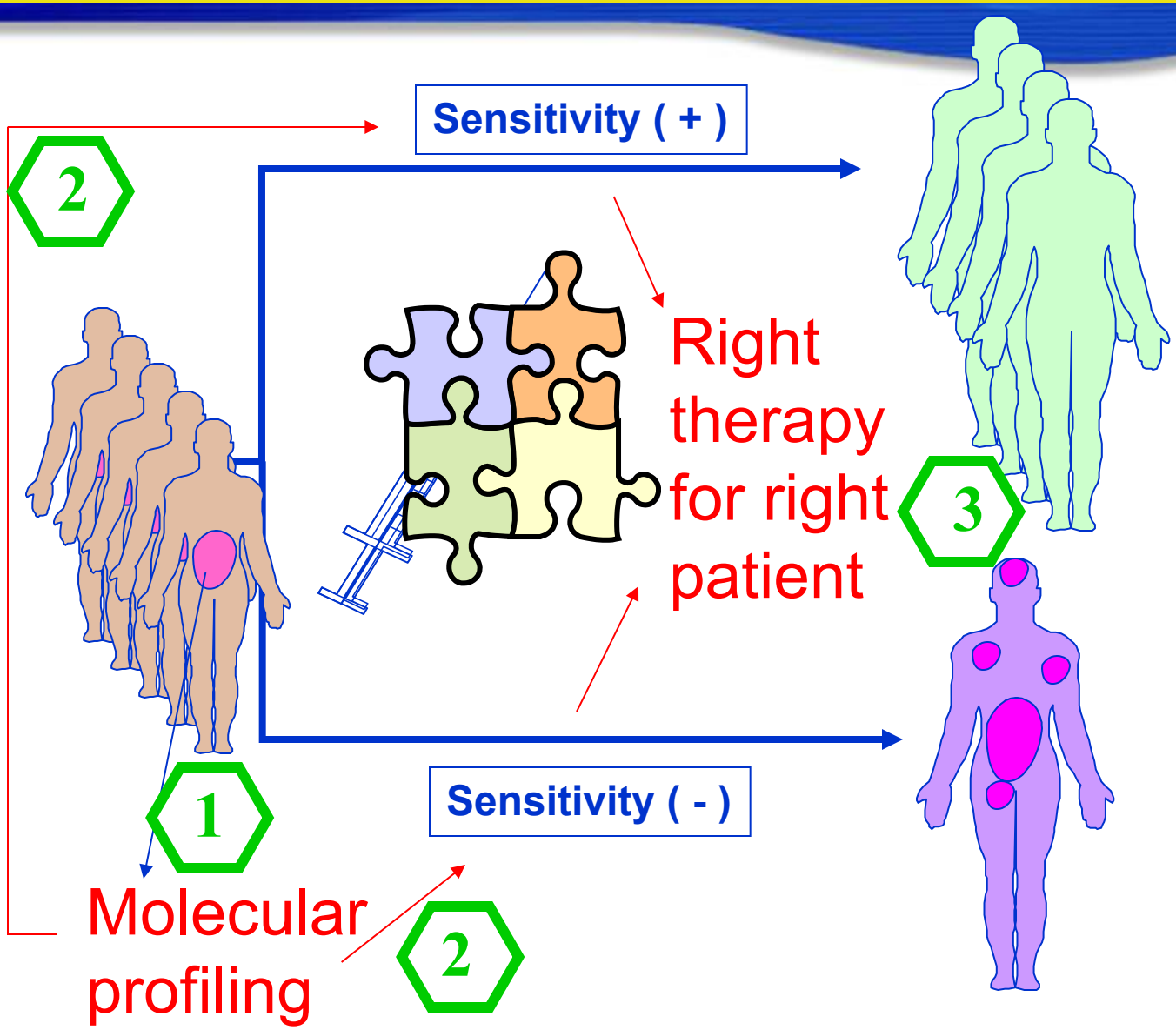
Conclusions

- 肿瘤血管的形成是抗肿瘤治疗中一个非常重要的靶
- 抗新生血管治疗与其他治疗方法可能有协同效应
  - 降低毒性，不增加副反应
  - 可与放疗、化疗、生物靶向治疗联用

其他

- 细胞周期抑制剂—779 （ temsirolimus、CCI-779）
- 法尼基转移酶抑制剂(farnesyl transferase inhibitors，FTIs)
- Bcl-2反义核酸G3139

The Future - Tailored Therapy



谢 谢！