





**Setting the standards for treatment of cancer**  
*ASCO 2005*

*Karl Mahler, Head IR*  
*Orlando, May 16, 2005*





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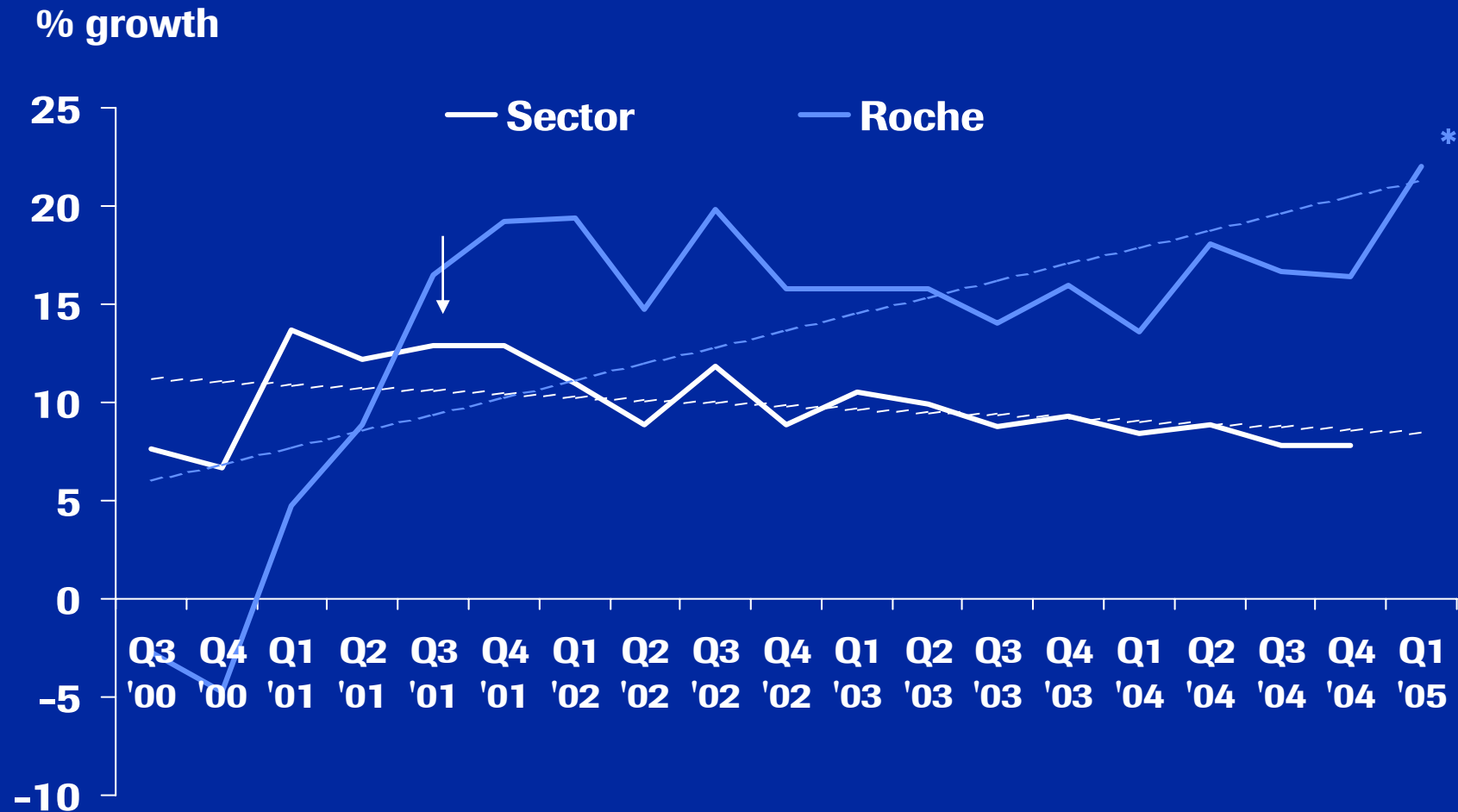
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**What we have on hand**

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**What we aim for**

# Roche: Leading growth rate in the specialty sector based on differentiated medicines



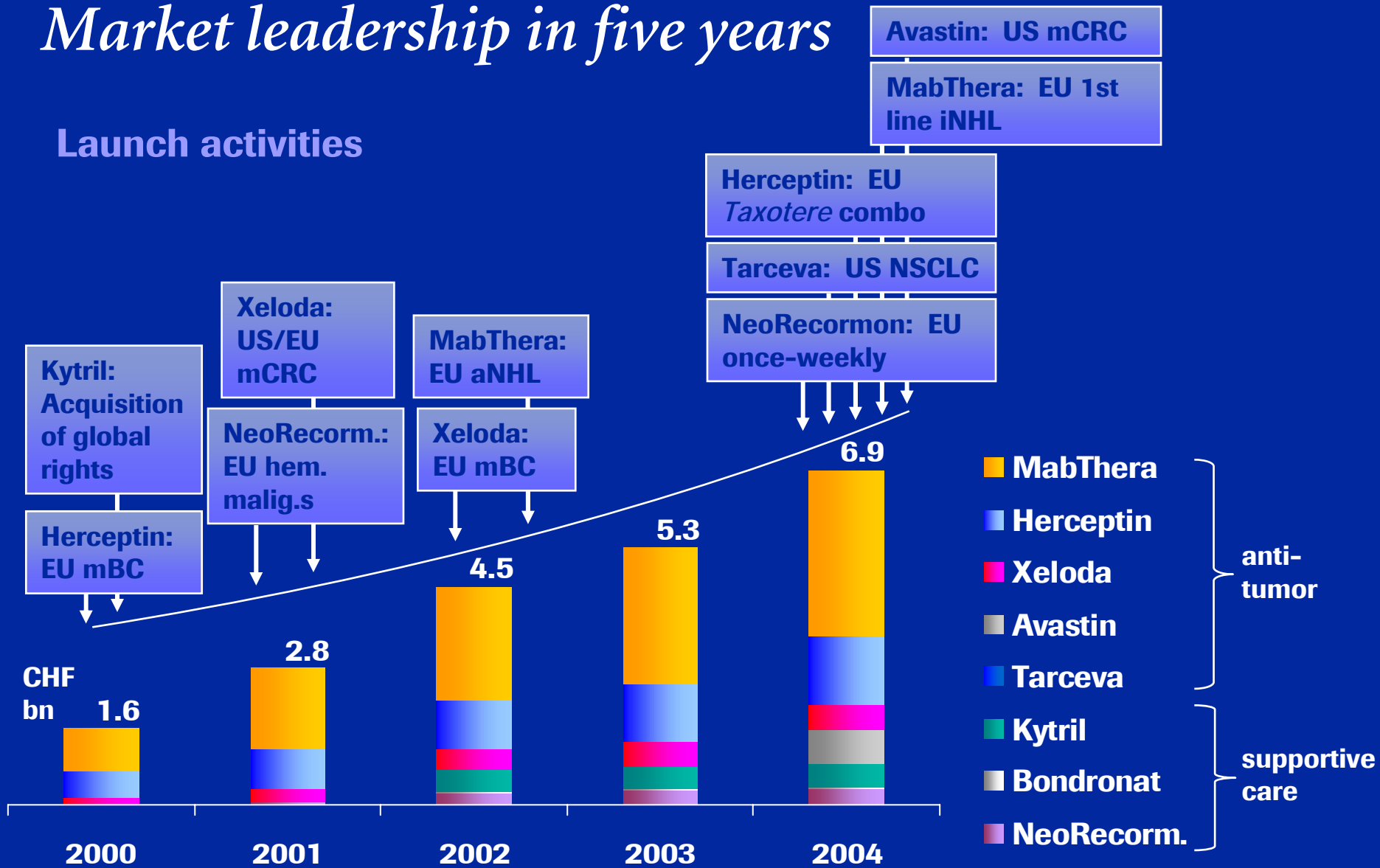
Source: IMS  
 \* Q1 '05 as reported

# Roche Oncology 2000-2004

## Market leadership in five years



### Launch activities



# How do the patients benefit?



*Ground-breaking news presented at ASCO 2005*

**Herceptin in adjuvant breast cancer**



**50% reduction in the risk of cancer recurrence**

**Avastin in metastatic breast cancer**



**49% improvement in OS**

**Avastin in NSCLC**



**30% improvement in OS**

**Tarceva in pancreatic cancer**



**24% improvement in OS**

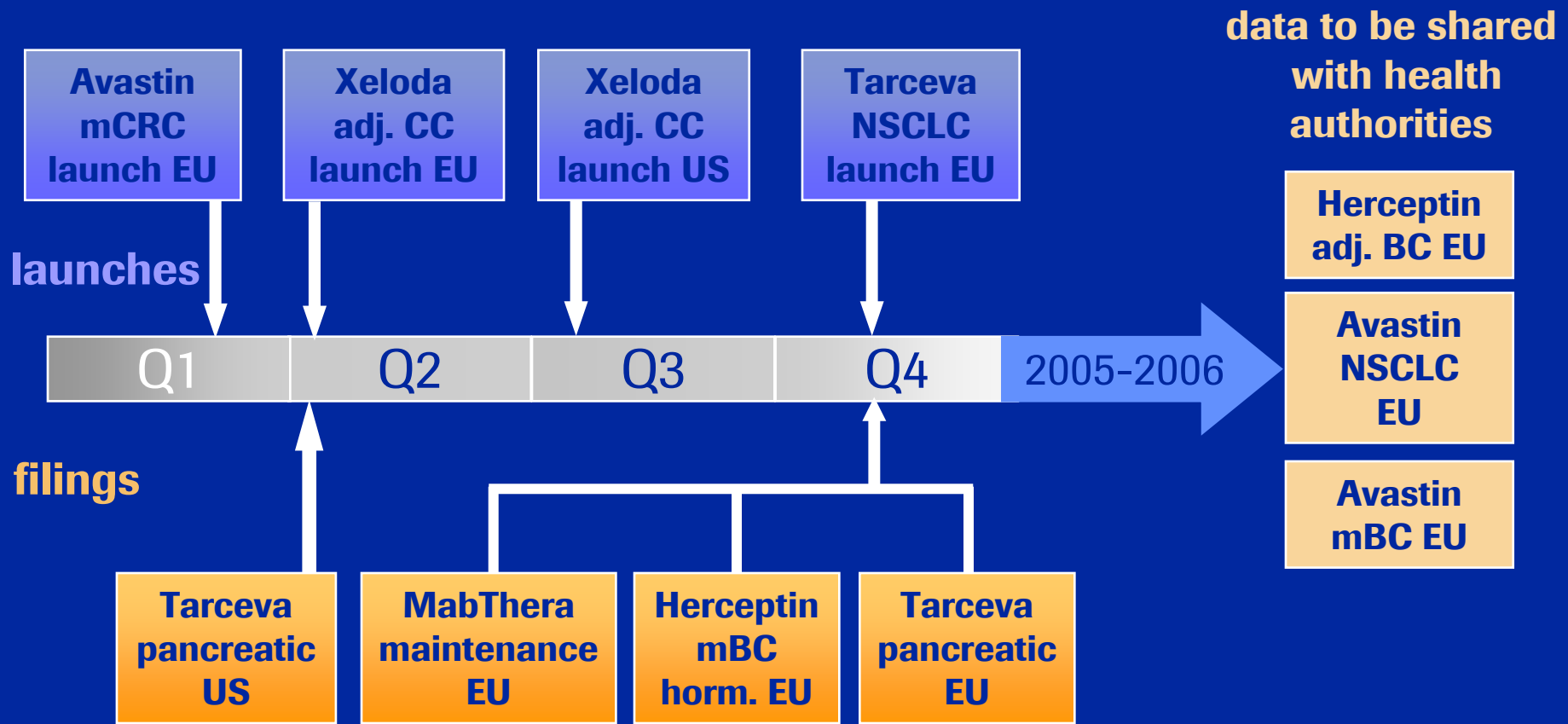
**MabThera in maintenance NHL**



**90% improvement in PFS**

# Heavy launch activities throughout 2005 ...

*... and more filings planned*



NB: Assuming normal approval process, barring unforeseen events

**What we have on hand**

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**What we aim for**

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## What we aim for

### *Expanding on a strong position*

- Maintain and expand leadership in oncology
- Set new standards for treatment of cancer
- Maximize the potential of the existing brands
- Develop new differentiated medicines

# Agenda



Introduction

- **Kapil Dhingra**

Avastin in NSCLC

- **Prof. A. Sandler**

Herceptin in adj. BC

- **Prof. J. Baselga**

Other ASCO key data

- **Kapil Dhingra**

Q&A

- **Key product team members**



**Setting the standards for treatment of cancer**  
*ASCO'05*

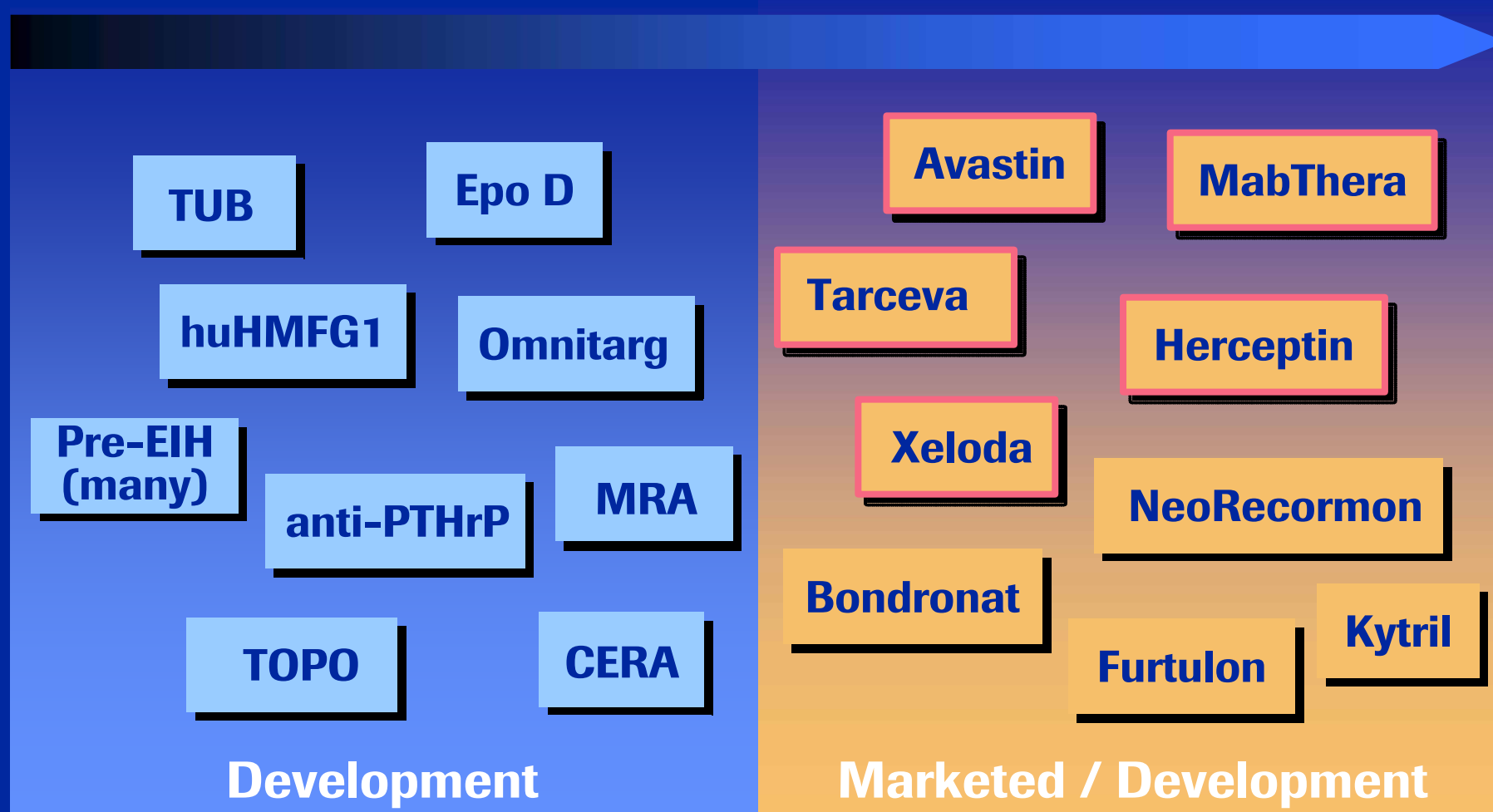
*Kapil Dhingra, Vice President, Oncology*  
*Orlando, May 16, 2005*



# Roche Oncology portfolio



*Five products with survival benefit*  
*Survival benefit in five tumor types*



# Roche at ASCO 2005



## *Unprecedented newsflow and wealth of data*

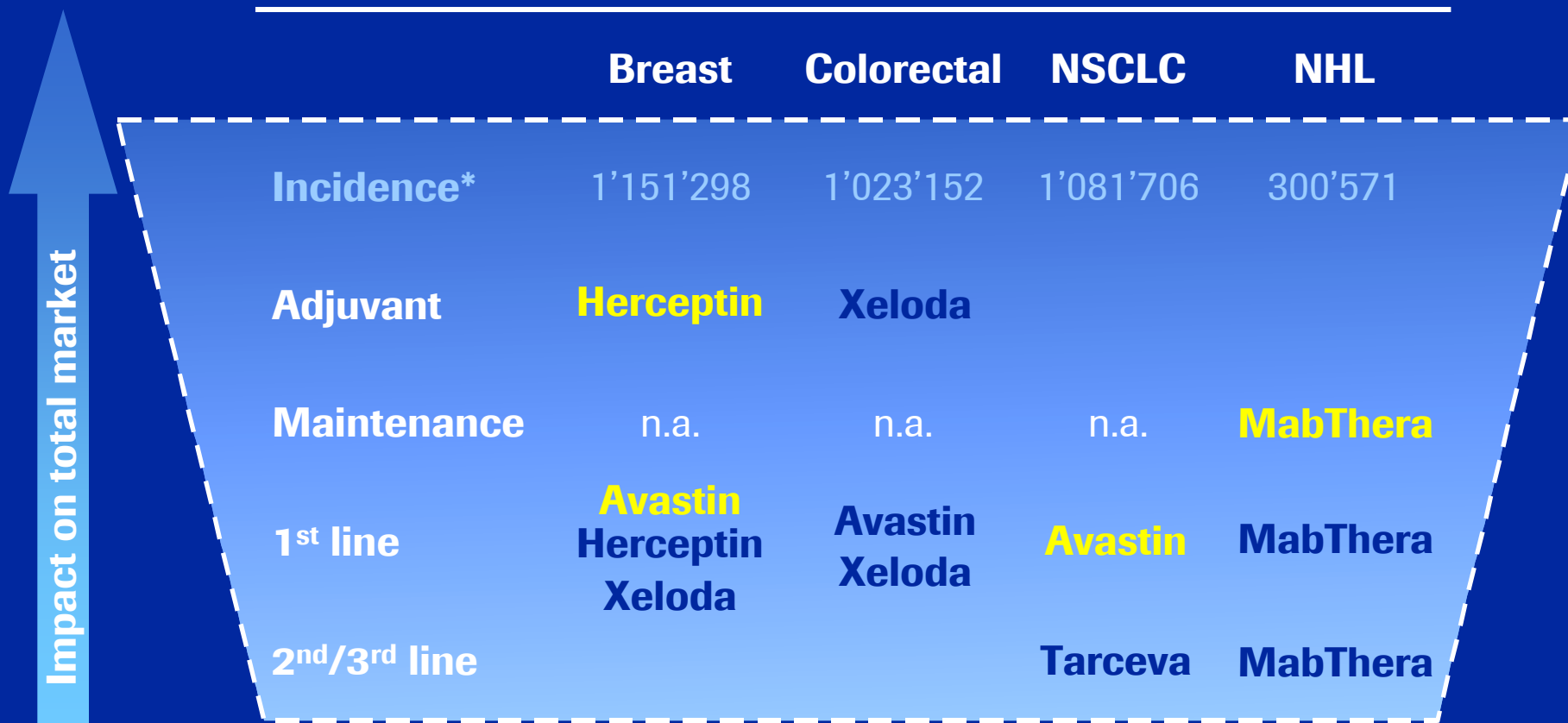
- 157 significant abstracts
- 8 major phase III trials presented
  - 3 Herceptin
  - 3 Avastin
  - 1 Tarceva
  - 1 MabThera
- 4 major indications with potential new standards of care

# Roche Oncology in 2005



*Science translated into patient benefit*

## Cancer types and Roche products with proven benefit



\* Worldwide, GLOBOCAN 2002

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**NSCLC**

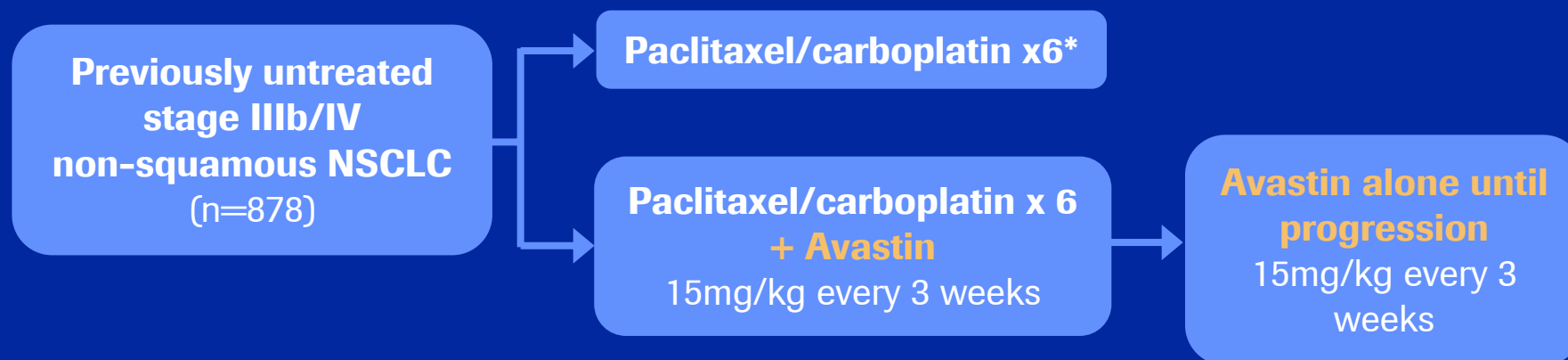
**- Avastin (Prof. A. Sandler)**

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# Avastin in 1st line NSCLC - E4599



## Study design



Primary endpoint overall survival

Secondary endpoint overall response rate, time to progression, toxicity

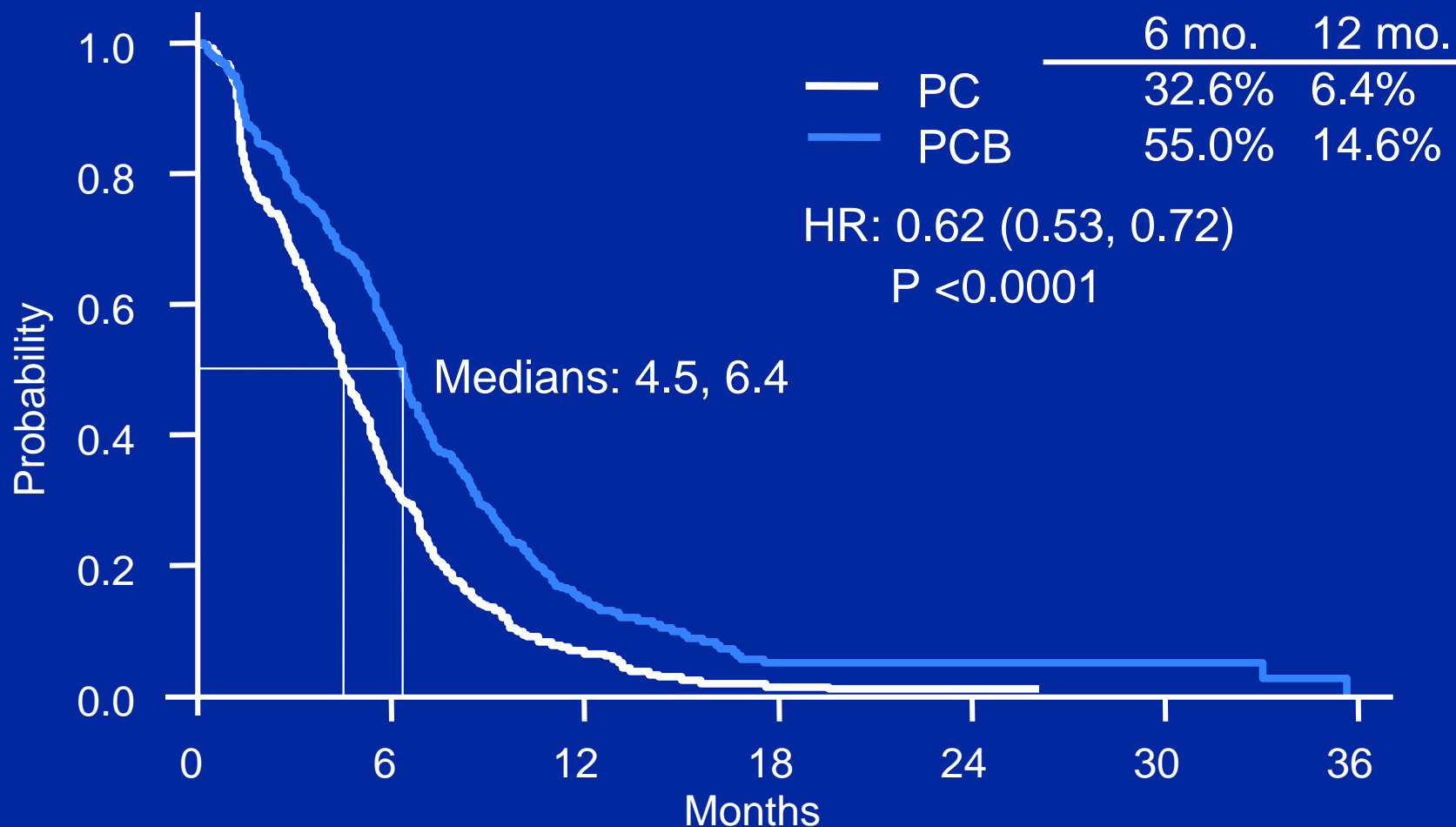
No crossover permitted

\*paclitaxel 200mg/m<sup>2</sup> i.v. every 3 weeks with carboplatin i.v. to AUC 6mg/mL every 3 weeks for a total of six cycles  
Sandler AL, et al. J Clin Oncol 2005;23 (June 1 Suppl): Abstract LBA4

# Avastin in 1st line NSCLC - E4599



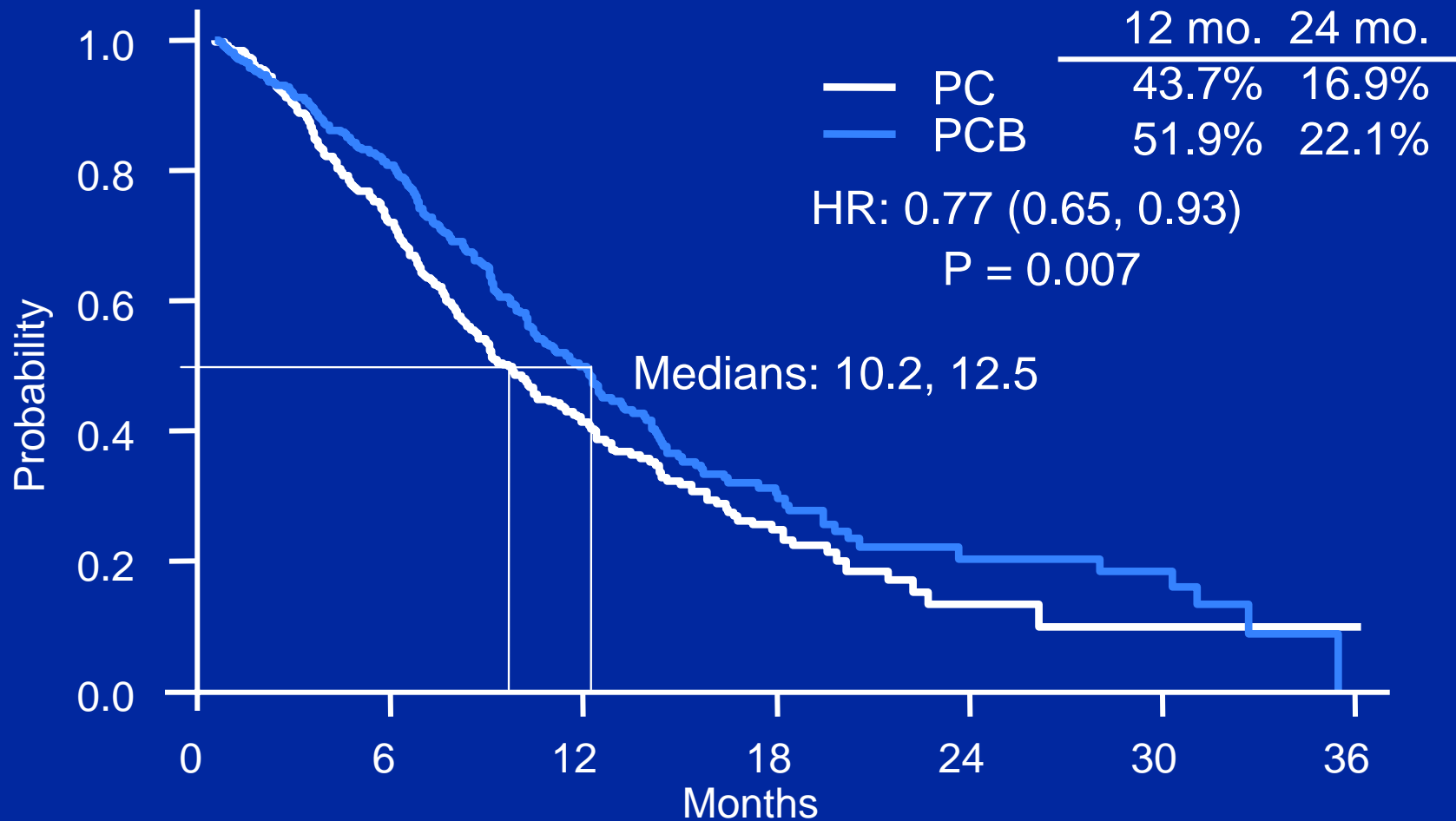
## *Progression-free survival by treatment*



# Avastin in 1st line NSCLC - E4599



## *Survival by treatment*



# Avastin in 1st line NSCLC - E4599



## *Hematologic toxicity*

	<b>PC (N = 427)</b>	<b>PCB (N = 420)</b>	
	<b>Grade 4</b>	<b>Grade 4</b>	<b>P value</b>
Neutropenia	16.4%	24%	0.006
Thrombocytopenia	0%	1.4%	0.01
Anemia	0.7%	0%	NS
Febrile neutropenia	1.9%*	3.3%*	NS

\*Includes one death on each arm due to neutropenic fever

# Avastin in 1st line NSCLC - E4599



## *Non-hematologic toxicity*

	<b>PC (% n)</b> <b>≥Grade 3</b>	<b>PCB (% n)</b> <b>≥Grade 3</b>	<b>p-value</b>
Hemorrhage	3 (0.7)	19 (4.5)	<.001
Hemoptysis	1 (0.2)	8 (1.9)	0.04
CNS	0	4 (1.0)	0.03
GI	2 (0.5)	5 (1.2)	NS
Other	1 (0.2)	4 (1.0)	NS
Hypertension	3 (0.7)	25 (6.0)	<.001
Venous thrombosis	13 (3.0)	16 (3.8)	NS
Arterial thrombosis	4 (1.0)	8 (1.9)	NS

# Avastin in 1st line NSCLC - E4599



## *Treatment effect in both genders*

	Male	Female
OS (HR)	0.69 p=0.003	0.96 P=0.80
PFS (HR)	0.53 P≤0.0001	0.68 P=0.002
RR (%)	12.2 vs 23.5 p=0.006	7.4 vs 31.7 P<0.0001

# Avastin in 1st line NSCLC - E4599



## *Possible Explanations for Survival Differences by Gender*

- Use of second and third-line treatment
  - EGFR tyrosine kinase inhibitors
  - Chemotherapy
- Imbalance in unmeasured baseline prognostic factors
  - Demographic
  - Molecular
- Statistical chance alone
- True difference

# Avastin in 1st line NSCLC



## *Conclusions*

- Avastin improves survival when added to PC chemotherapy in patients with non-squamous NSCLC
- Avastin also improves response rate and progression-free survival
- Avastin is associated with a small increase in serious bleeding, including hemoptysis

**First trial in many years to show survival benefit  
in first-line NSCLC**



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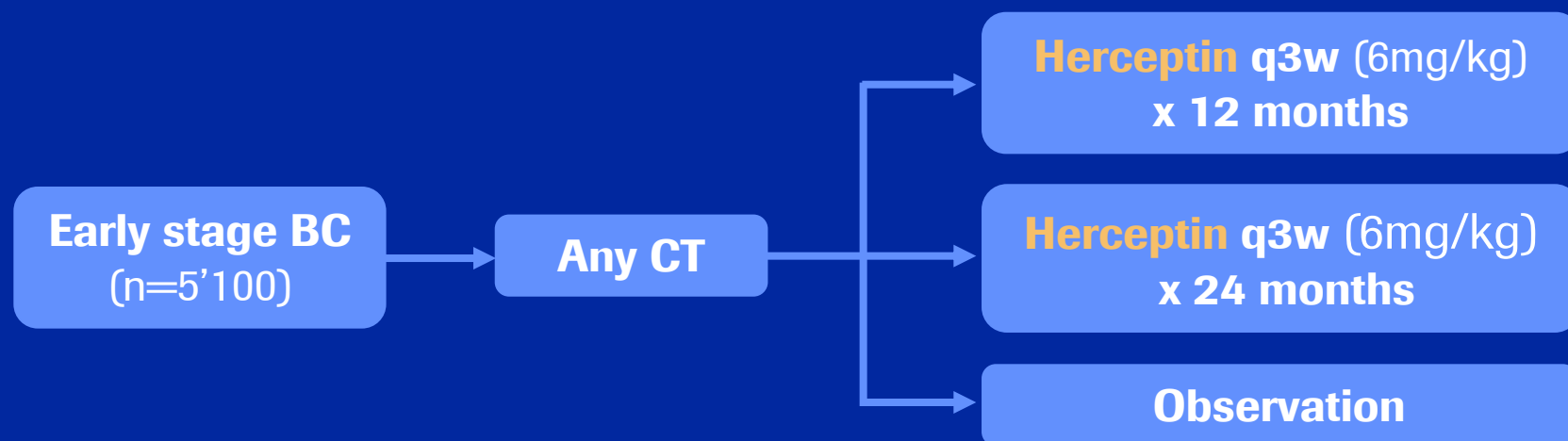
# **Adjuvant breast cancer - Herceptin (Prof. J. Baselga)**

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# Herceptin for adjuvant therapy of BC - HERA



## *Study design*



**Primary endpoint:** disease-free survival

**Secondary endpoint:** overall survival

**Patient population:**

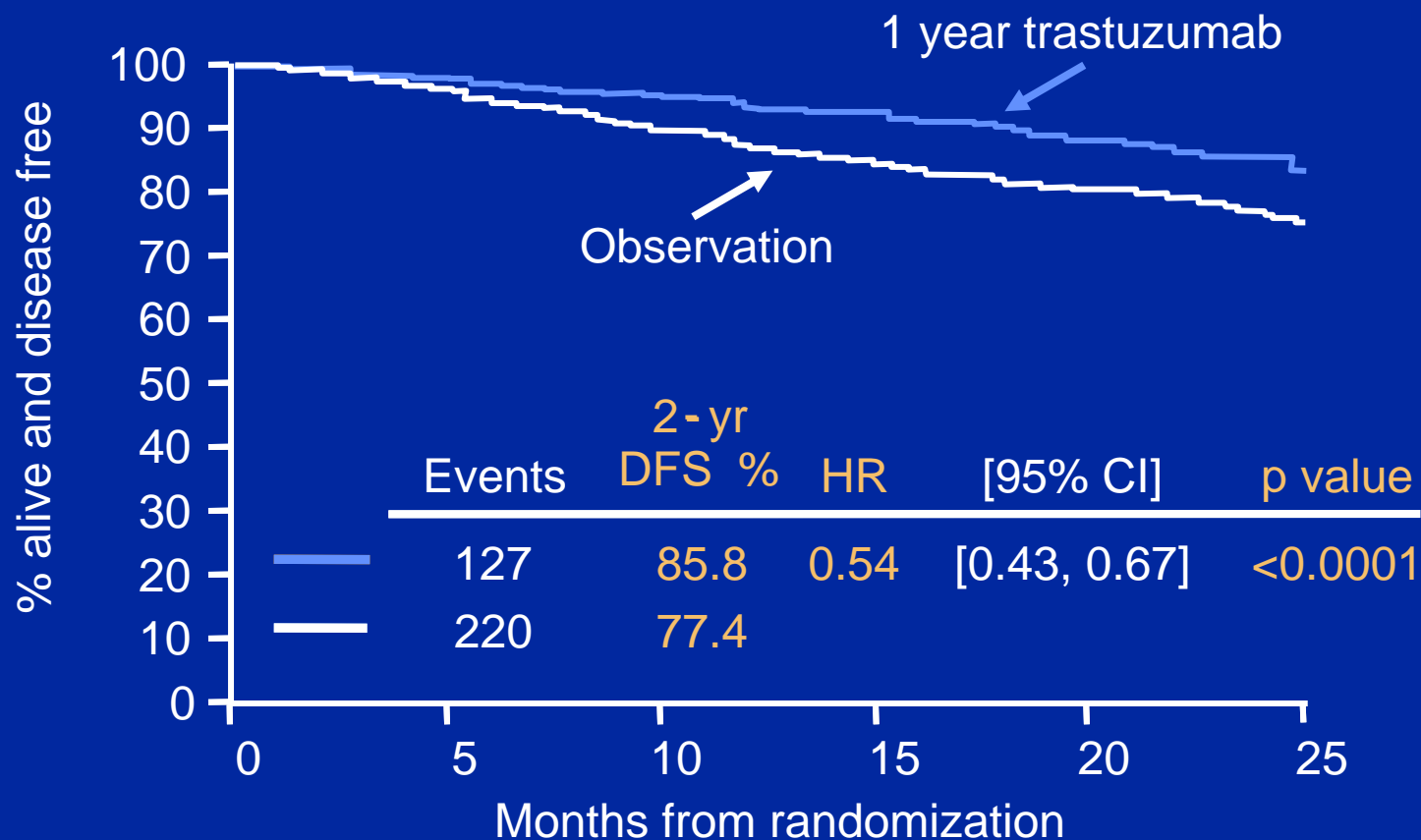
- wide range of chemotherapy regimens
- node -positive and -negative patients
- 5'100 patients, 39 countries, 480 sites
- Herceptin every 3 weeks, for 1 or 2 years

**Interim analysis:** pre-planned after 475 events

# Herceptin for adjuvant therapy of BC - HERA



## *Disease-free survival*



No. at risk	0	5	10	15	20	25
1 year trastuzumab (Blue line)	1694	1472	1067	629	303	102
Observation (Black line)	1693	1428	994	580	280	87

# Herceptin for adjuvant therapy of BC - HERA



## *Safety*

	<b>Observation N=1736</b>	<b>1 year trastuzumab N=1677</b>
<b>Decrease by <math>\geq 10</math> EF points and LVEF <math>&lt; 50\%</math></b>	2.2%	7.1%
<b>Same LVEF criteria <u>and</u> symptomatic CHF NYHA class III/IV, confirmed by cardiologist</b>	0% (95% CI: 0.00-0.21)	0.5% (95% CI: 0.25-1.02)
<b>Cardiac death</b>	0.1%	0%

# Herceptin for adjuvant therapy of BC - HERA



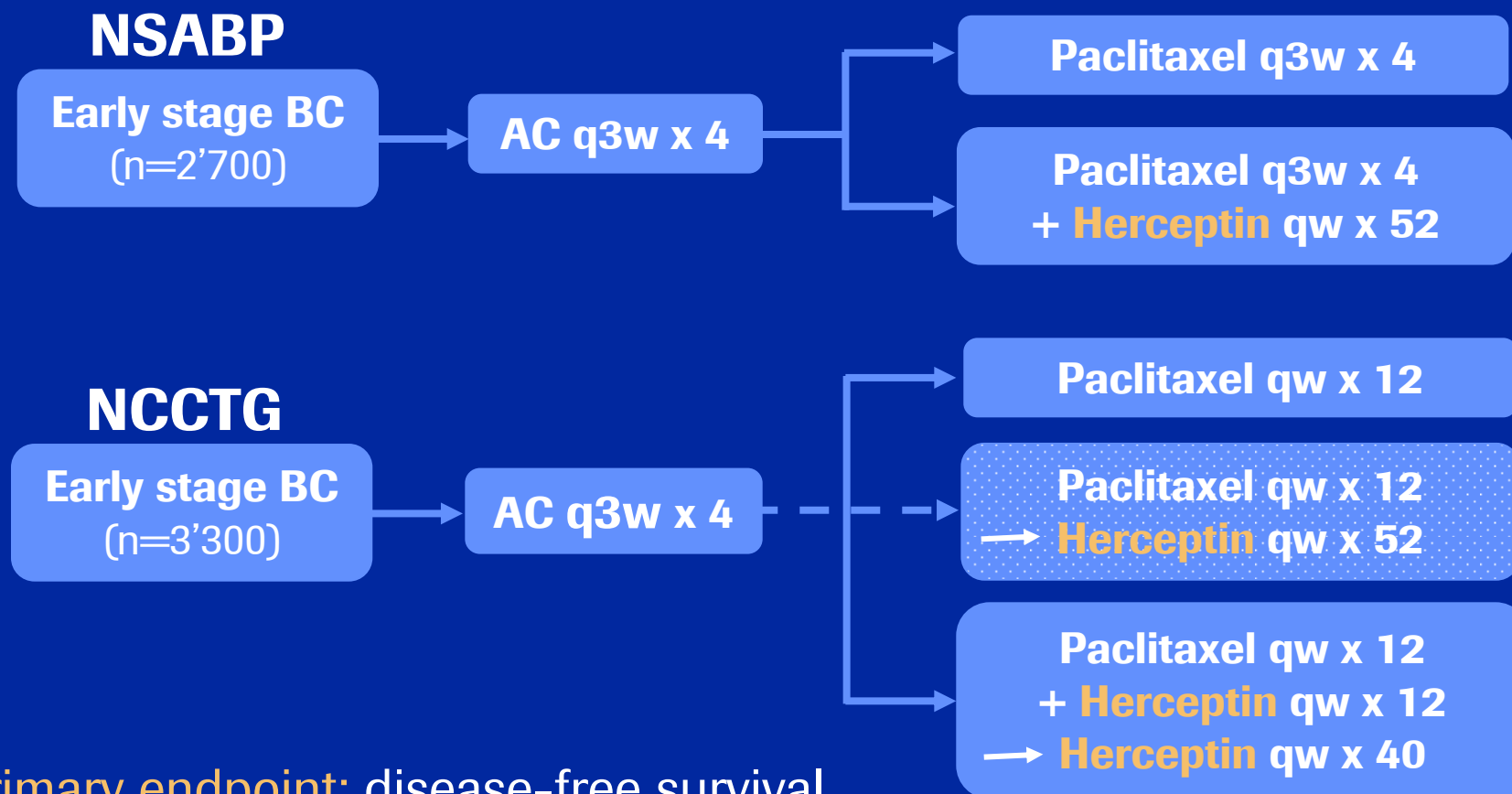
## *Conclusions*

- Highly significant improvement in DFS
  - 46% reduction in the risk of disease recurrence
- Both 12- and 24-months treatment arms showed significant DFS improvement compared to control arm
- The benefit was seen in all subgroups, independent of patients' baseline characteristics:
  - Nodal status
  - Hormone receptor status
  - Previous CT regimen
- Well tolerated, no unexpected safety issues
  - Very low incidence of congestive heart failures (0.5%)

# Herceptin in adjuvant BC - NSABP / NCCTG



## Study Design



Primary endpoint: disease-free survival

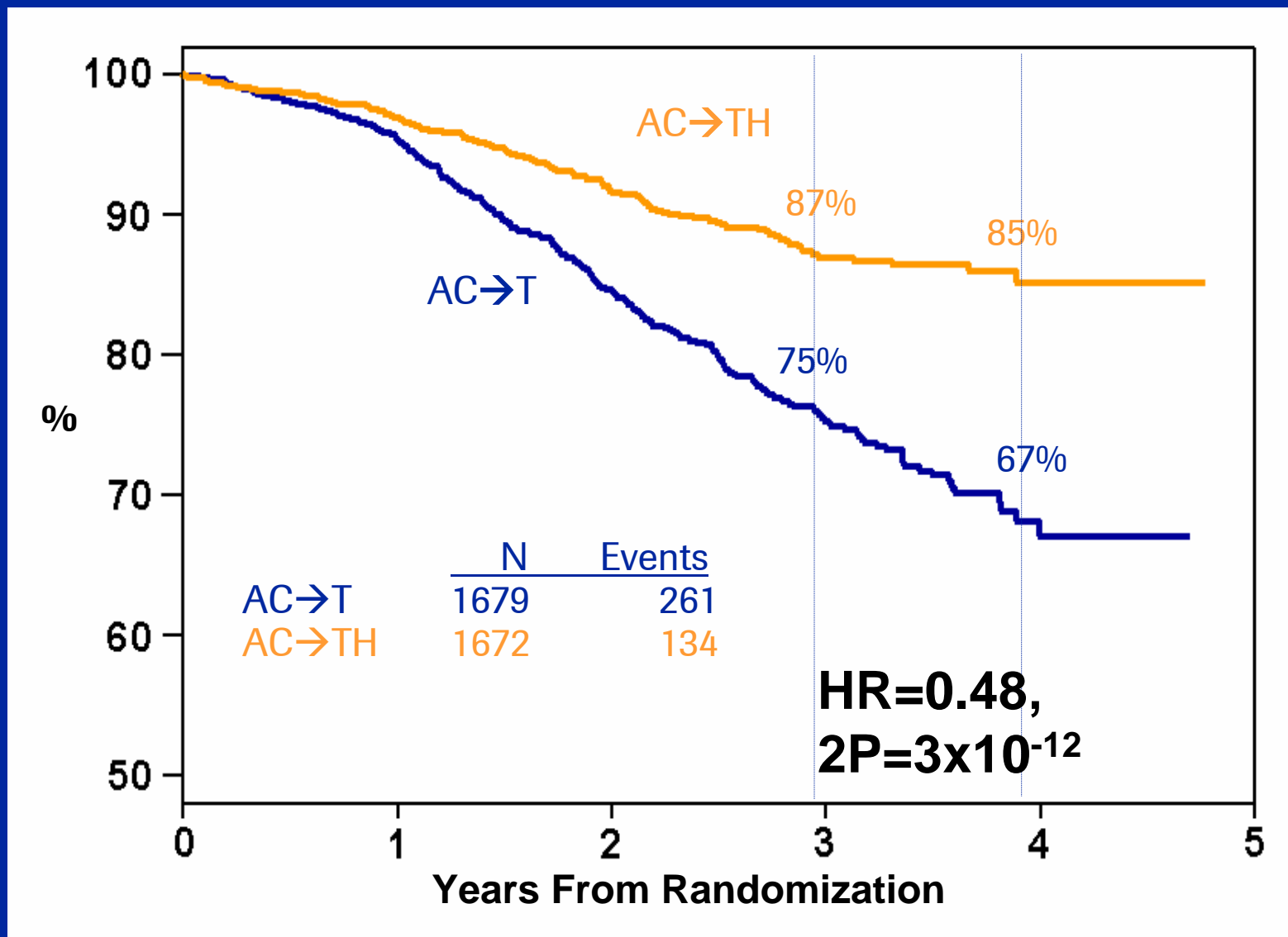
Secondary endpoint: overall survival

Sites in US / Canada

# Herceptin in adjuvant BC - NSABP / NCCTG



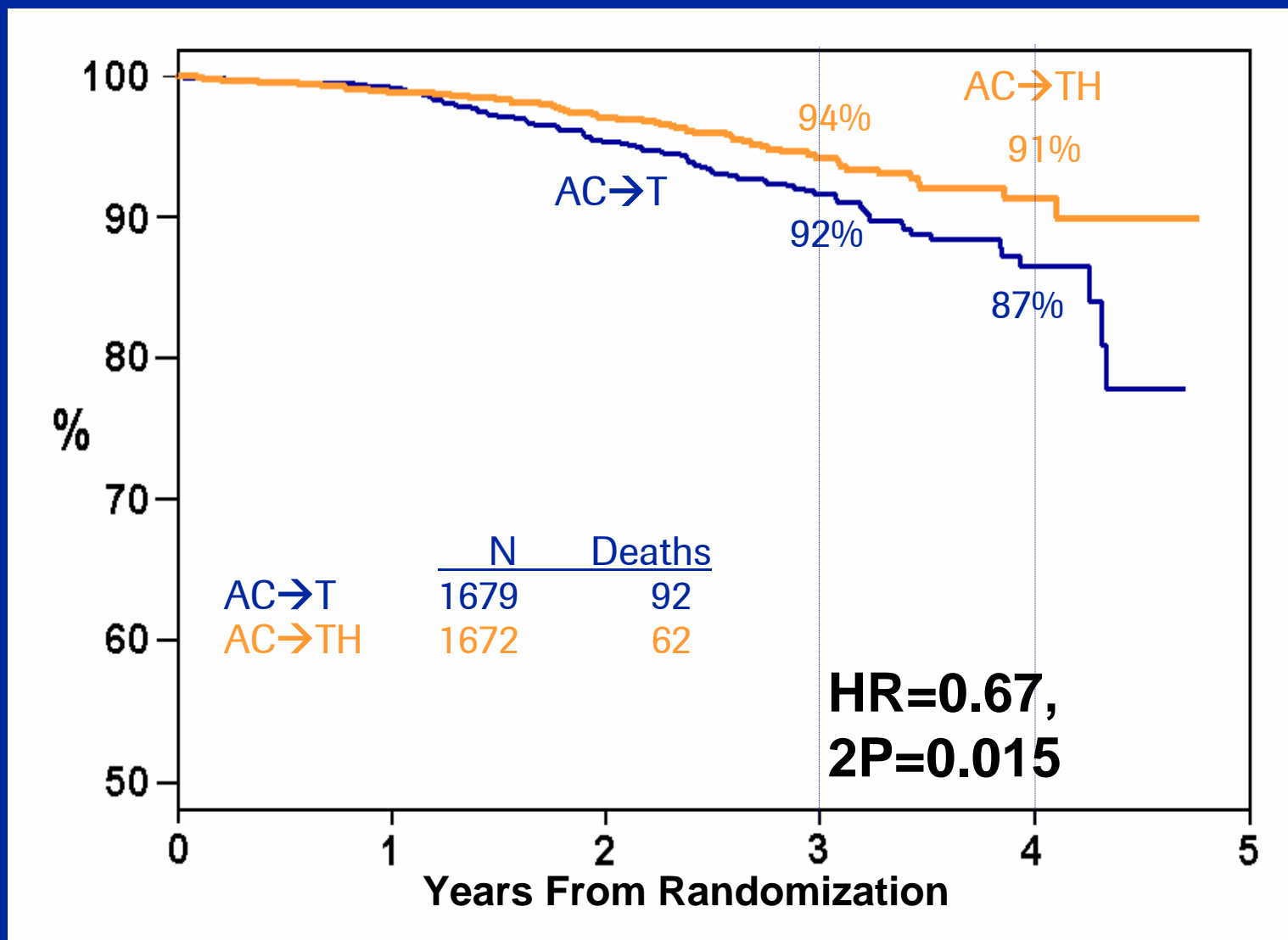
## *Disease-free survival*



# Herceptin in adjuvant BC - NSABP / NCCTG



## Overall survival

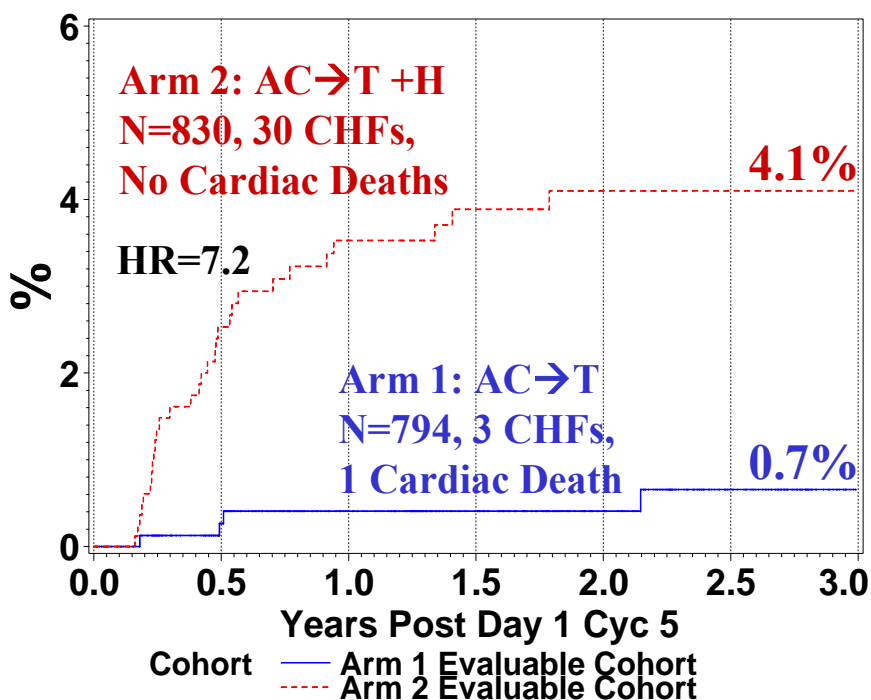


# Herceptin in adjuvant BC - NSABP / NCCTG



## Safety

**B-31: Cumulative Incidence of Cardiac Events in the Evaluable Cohort**



Yrs Post Day 1 Cyc 5	Cum Inc Arm 1 (%)	Cum Inc Arm 2 (%)	No. At Risk
0.5	0.3	2.5	1412
1.0	0.4	3.5	1168
1.5	0.4	3.9	924
2.0	0.4	4.1	719
2.5	0.7	4.1	532
3.0	0.7	4.1	357

# Herceptin in adjuvant BC – NSABP / NCCTG



## *Conclusions*

- Highly significant improvement in DFS
  - 52% reduction in the risk of the disease recurrence
- 49% improvement in overall survival
- Well tolerated, safety data consistent with previous Herceptin trials
  - Incidence of cardiac events 3-4% higher than in the comparative arm
- Both trials stopped recruitment (approx 2 yrs earlier than planned)

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**Adjuvant breast cancer**

**- Herceptin**

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**Metastatic breast cancer**

**- Avastin**

**Ovarian cancer**

**- Avastin**

**NHL maintenance**

**- MabThera**

**Pancreatic cancer**

**- Tarceva**

**NSCLC**

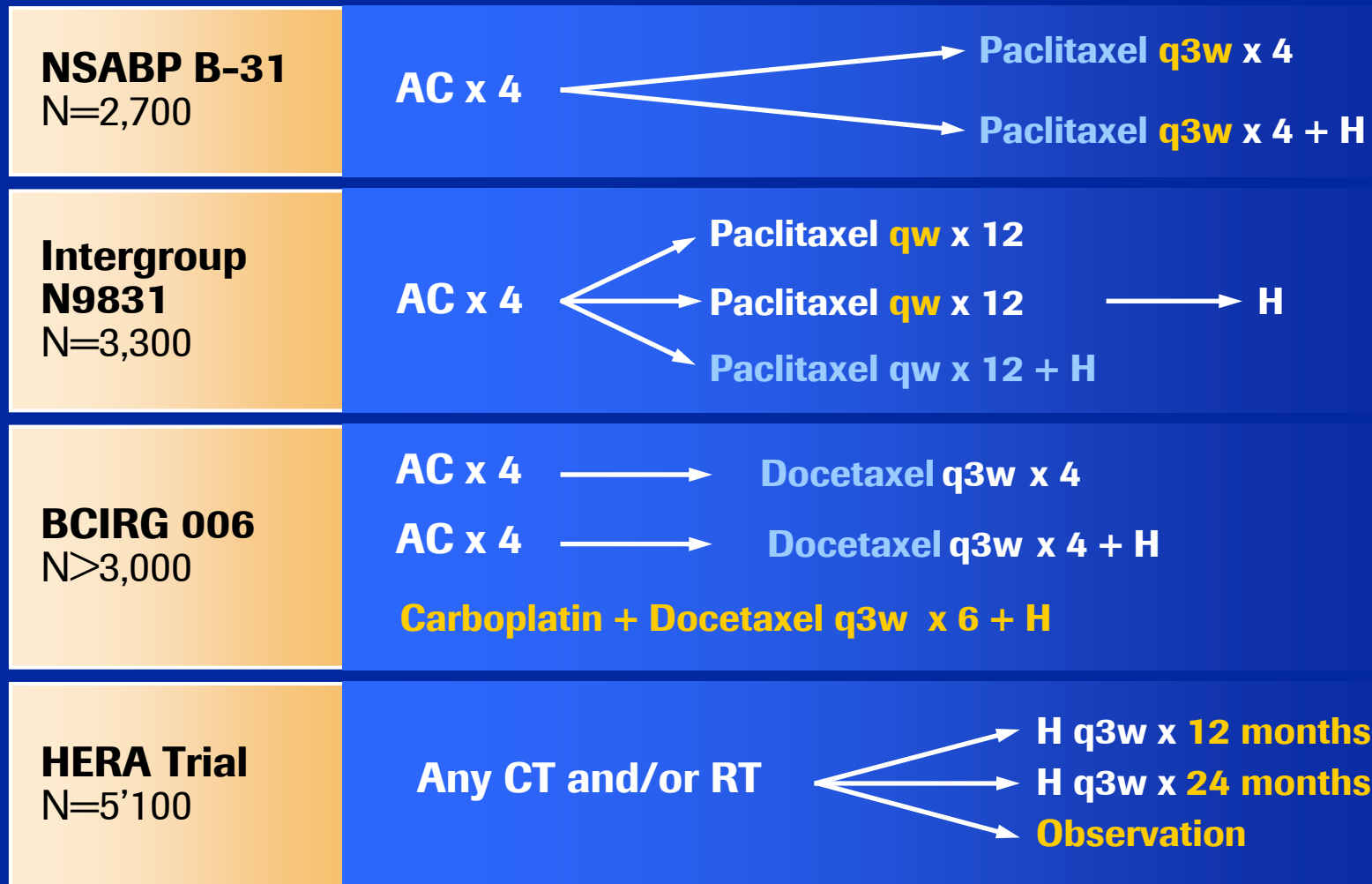
**- Tarceva, Avastin**

**Early development**

# Development program in adjuvant therapy



*A comprehensive program to realize the curative potential of Herceptin*



# Herceptin in adjuvant BC – summary



- Provides compelling benefit as adjuvant therapy of breast cancer
  - Benefit seen both with chemotherapy as well as following chemotherapy
- Favorable safety and tolerability
  - Lower incidence of symptomatic heart failure with sequential use of Herceptin as done in the HERA trial
- Filing: H1 2006

**Herceptin is set to become the standard of care for adjuvant therapy of HER2-positive breast cancer**



**Adjuvant breast cancer** - **Herceptin**

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**Metastatic breast cancer** - **Avastin**

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**Ovarian cancer** - **Avastin**

**NHL maintenance** - **MabThera**

**Pancreatic cancer** - **Tarceva**

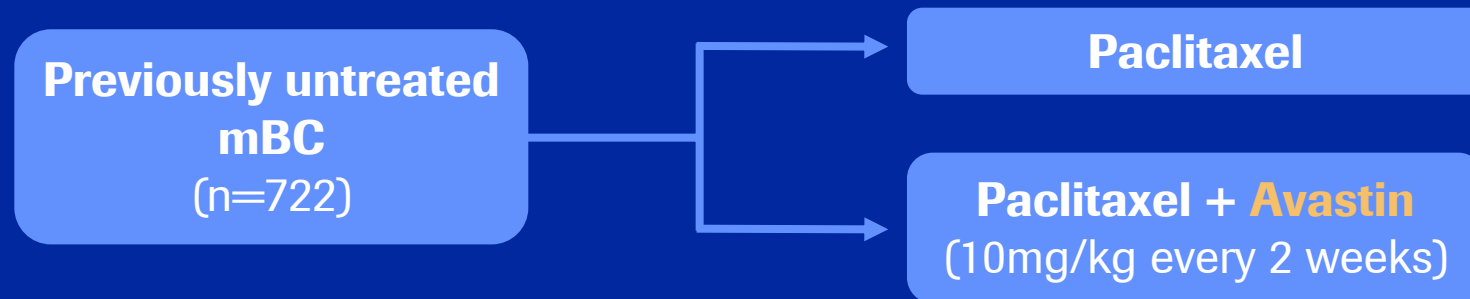
**NSCLC** - **Tarceva, Avastin**

**Early development**

# Avastin in first-line mBC - ECOG 2100



## *Study design*



**Primary endpoint:** progression-free survival

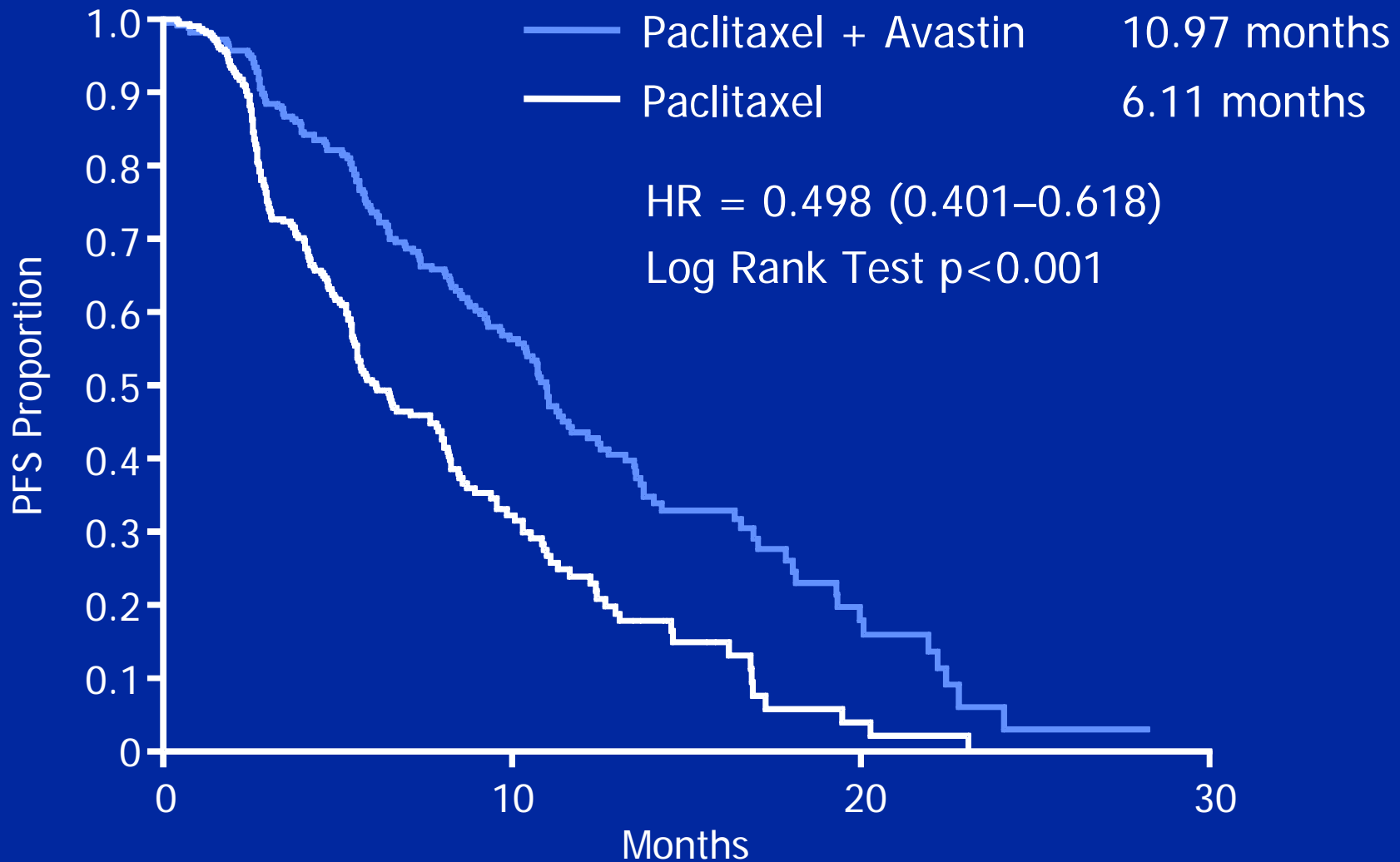
**Secondary endpoints:** time to treatment failure, response rate,  
duration of response, overall survival

Phase III, randomized, controlled, multicenter

# Avastin in first-line mBC - ECOG 2100



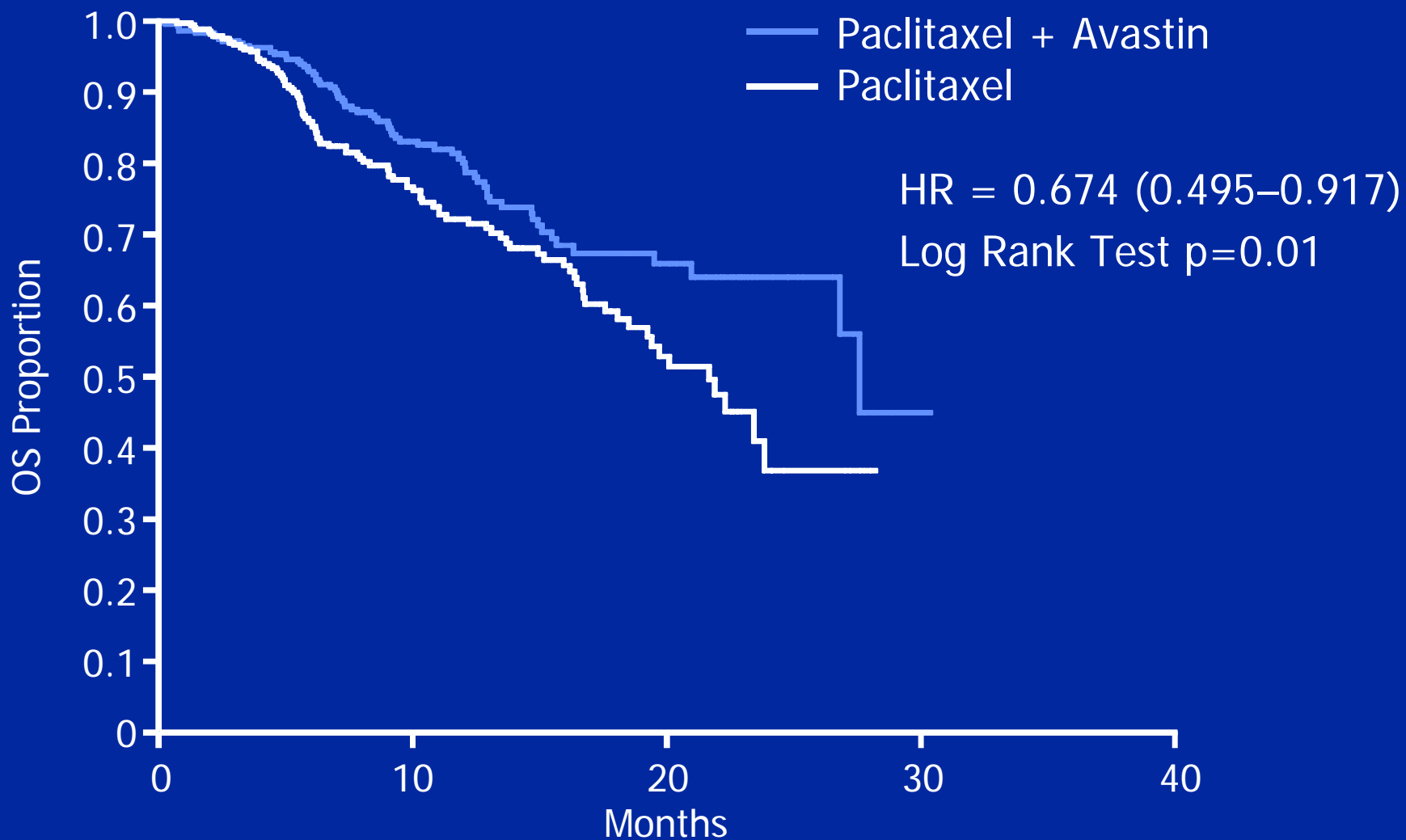
## *Progression-free survival*



# Avastin in first-line mBC - ECOG 2100



## *Overall survival*



# Avastin in first-line mBC - ECOG 2100



## Safety

	Paclitaxel (n=330)		Paclitaxel + Avastin (n=342)	
	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)
Hypertension*	0	0	13.0	0.3
Thromboembolic	0.3	0.9	1.2	0
Bleeding	0	0	0.6	0.3
Proteinuria**	0	0	0.9	1.5
Neuropathy***	13.6	0.6	19.9	0.6
Fatigue	2.7	0	4.7	0.3
Neutropenia	0	3.0	0.9	4.4
↓ LVEF	0	0	0.3	0

NCI-CTC v3.0, worst per patient

\*P=0.0001; \*\*P=0.0004; \*\*\*P=0.01

# Avastin in first-line mBC



## *Conclusions*

- 50% reduction in the risk of cancer progression (PFS)
- 33% reduction in the risk of death (OS)
- Adverse events similar to the previous trials with Avastin in mBC (serious bleeding and blood clots were rare)
- To initiate discussions with regulatory authorities (US; EU)

**Avastin-based treatment regimens will become standard of care for first-line treatment of metastatic breast cancer**



**Adjuvant breast cancer** - **Herceptin**

**Metastatic breast cancer** - **Avastin**

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**Ovarian cancer** - **Avastin**

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**NHL maintenance** - **MabThera**

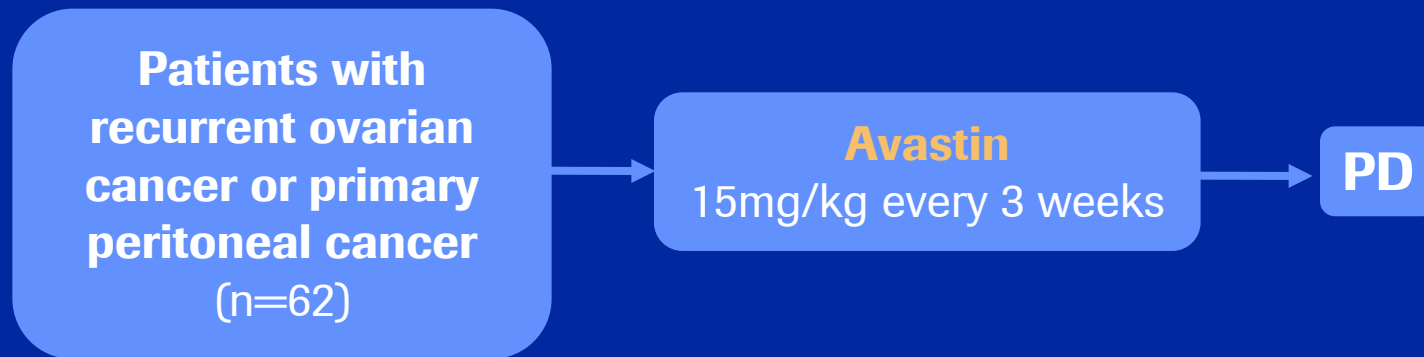
**Pancreatic cancer** - **Tarceva**

**NSCLC** - **Tarceva, Avastin**

**Early development**

# Avastin in ovarian cancer – Phase II trial

## *Study design*



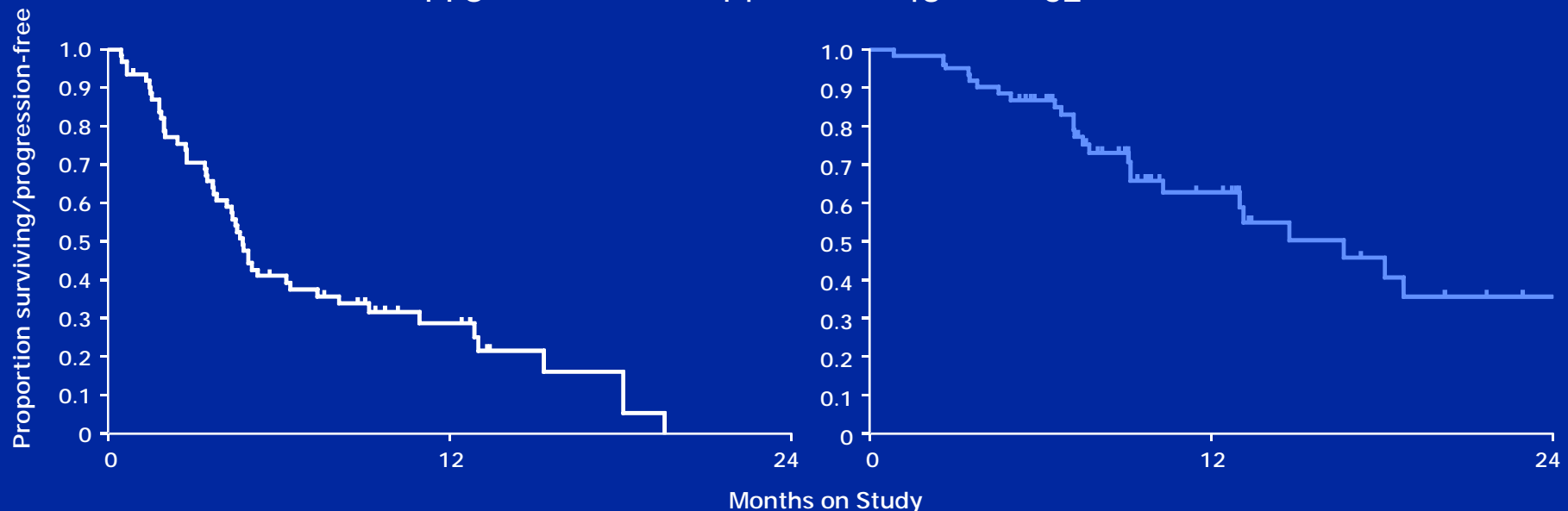
**Primary endpoint:** PFS at 6 months, ORR, safety

# Avastin in ovarian cancer - Phase II trial



## *Progression-free survival / Overall survival*

Surv/PFS	Censored	Failed	Total
— Survival	37	25	62
— PFS	14	48	62



- Promising single-agent activity in ovarian cancer
- Definitive evaluation planned in phase III trials



**Adjuvant breast cancer** - **Herceptin**

**Metastatic breast cancer** - **Avastin**

**Ovarian cancer** - **Avastin**

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**NHL maintenance** - **MabThera**

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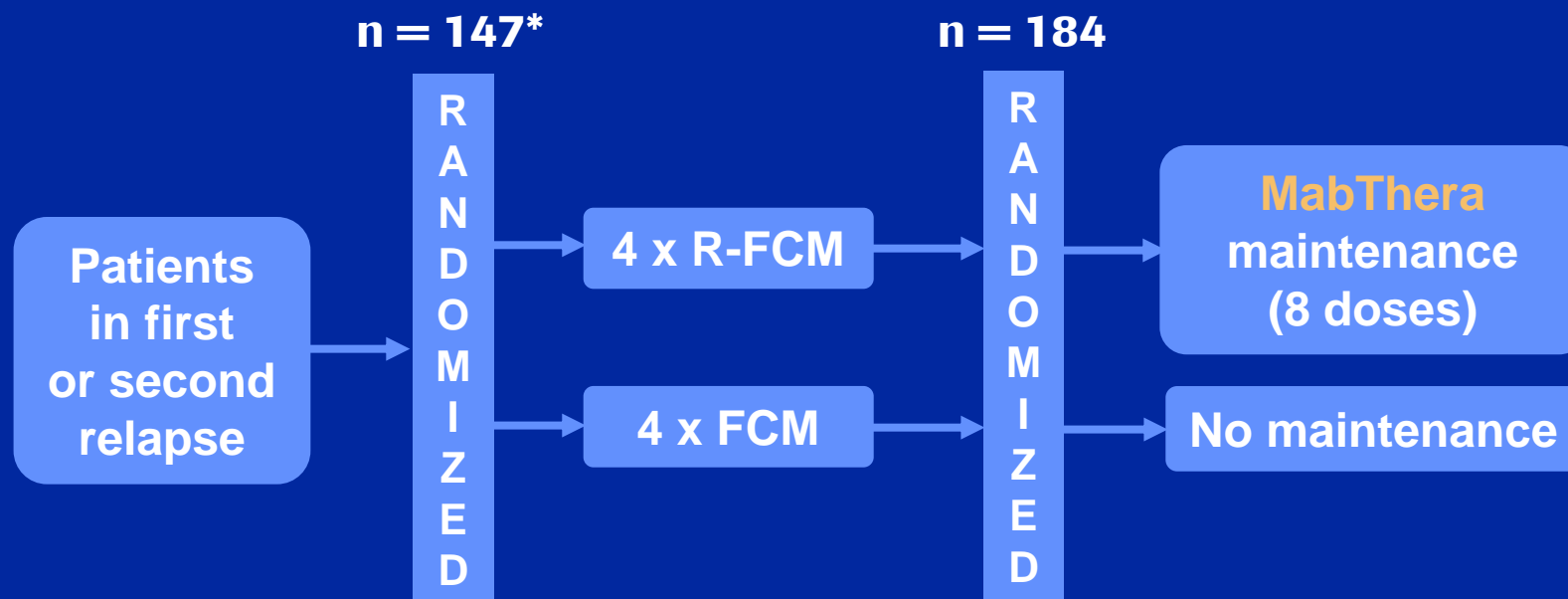
**Pancreatic cancer** - **Tarceva**

**NSCLC** - **Tarceva, Avastin**

**Early development**

# MabThera – GLSG (Hiddemann) trial

## *Maintenance in relapsed iNHL/MCL*



Primary endpoint: progression-free survival

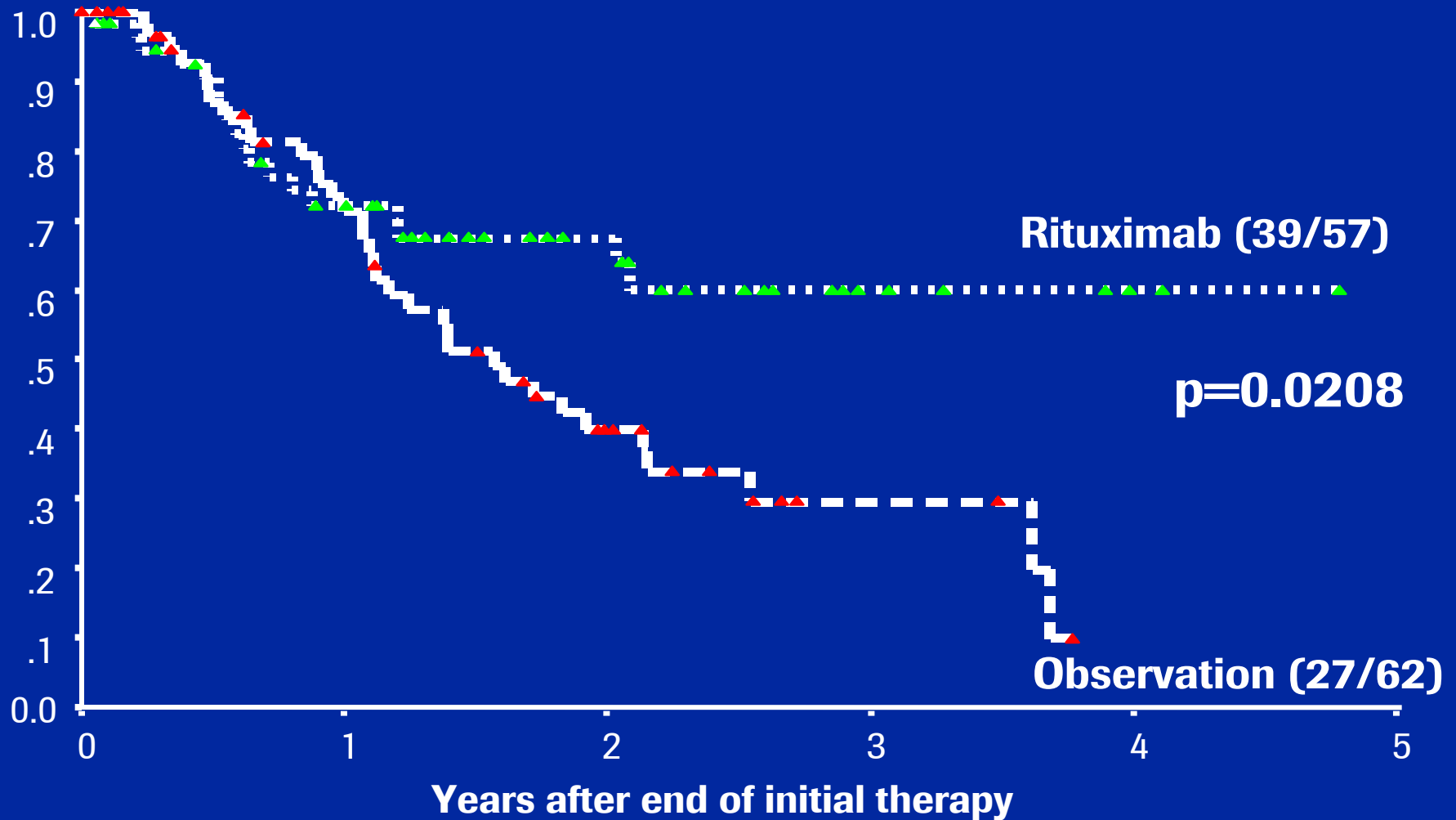
**Induction arm stopped early**

\* First randomization stopped after 147 pts., trial continued with all pts. receiving R-FCM induction

# MabThera – GLSG (Hiddemann) trial



*Maintenance significantly increases progression-free survival after R-FCM induction therapy*



# MabThera – GLSG (Hiddemann) trial



## *Conclusions*

- MabThera maintenance significantly improves outcome
  - Prolongation of remission time by more than 17 months (median PFS 19 months for observation vs 36+ months for MabThera)
- First randomized trial to show statistically significant benefit of MabThera maintenance after induction with MabThera + chemotherapy
- Fifth randomized study to show benefit of MabThera maintenance

**MabThera prolongs progression-free survival  
by >17 months versus no further treatment**



**Adjuvant breast cancer** - **Herceptin**

**Metastatic breast cancer** - **Avastin**

**Ovarian cancer** - **Avastin**

**NHL maintenance** - **MabThera**

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**Pancreatic cancer** - **Tarceva**

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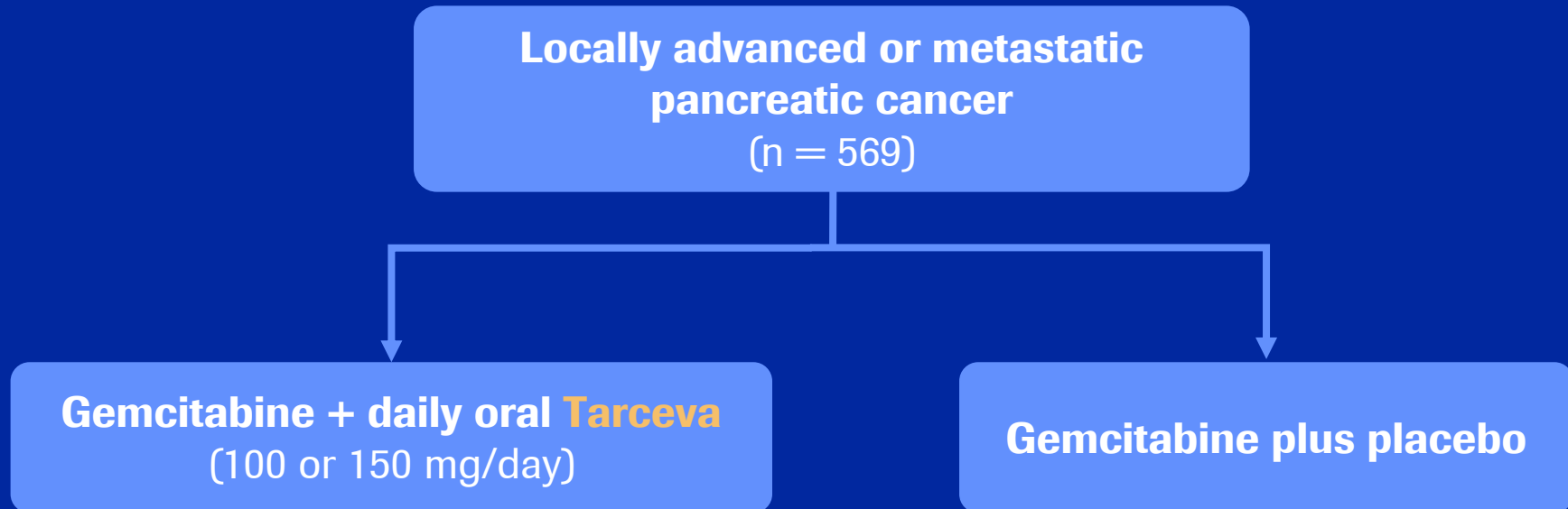
**NSCLC** - **Tarceva, Avastin**

**Early development**

# Tarceva in pancreatic cancer - PA3



## *Study design*

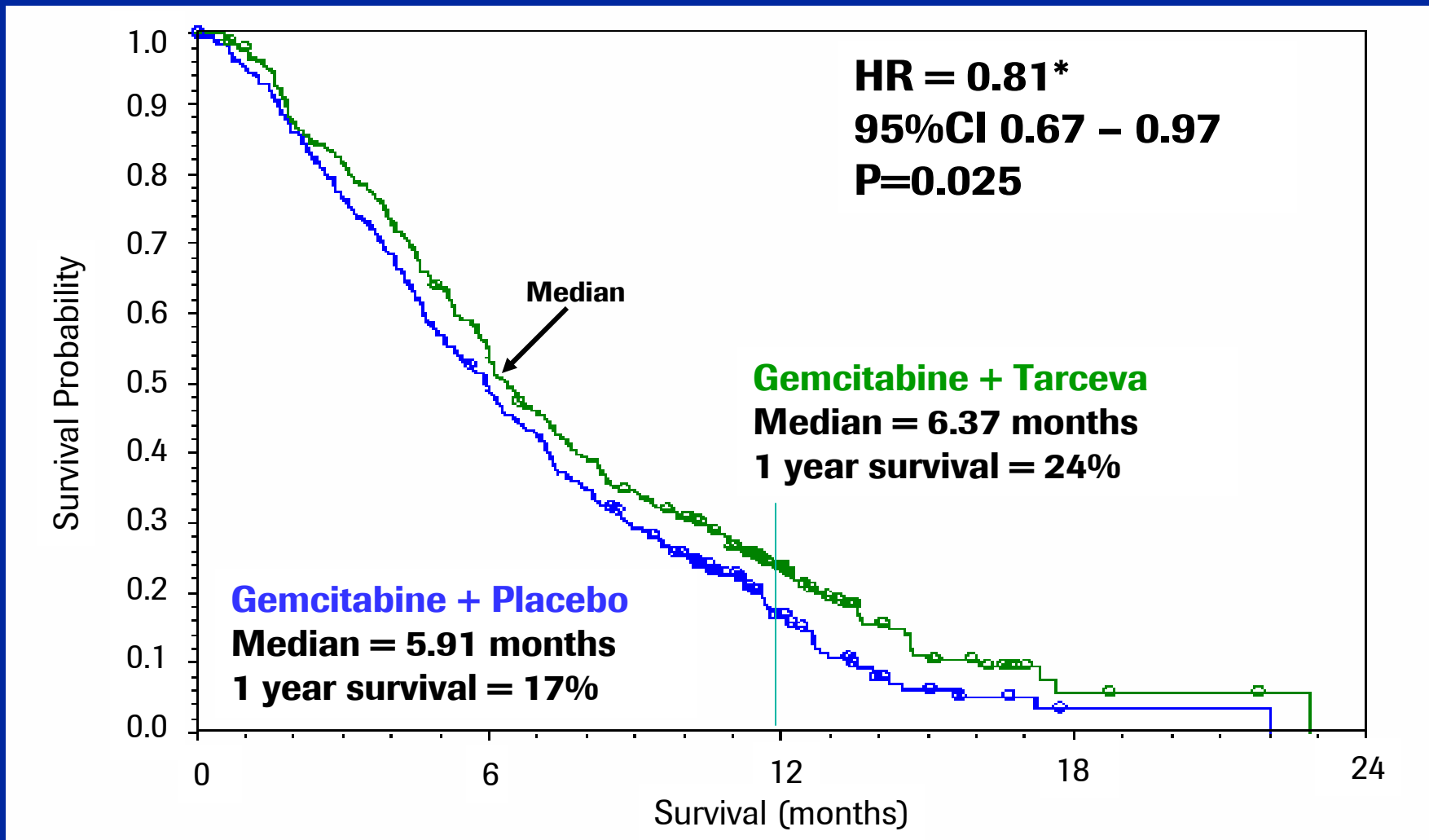


**Primary endpoint:** overall survival

**Secondary endpoints:** progression-free survival, response rate, quality of life, toxicity

# Tarceva in pancreatic cancer - PA3

## *Overall survival for all patients*



\* Adjusted for PS, pain and disease extent at randomization

# Tarceva in pancreatic cancer - PA3



## *Conclusions*

- First phase III trial to demonstrate survival benefit over gemcitabine monotherapy in pancreatic cancer (24% OS improvement)
- Benefit seen irrespective of EGFR positivity (HR: EGFR +ve 0.74; EGFR -ve 0.82)
- Tarceva plus gemcitabine is well tolerated
  - No increase in hematological toxicity
- Filed in US on May 2, 2005; EU filing planned in Q4 2005

**Adjuvant breast cancer** - **Herceptin**

**Metastatic breast cancer** - **Avastin**

**Ovarian cancer** - **Avastin**

**NHL maintenance** - **MabThera**

**Pancreatic cancer** - **Tarceva**

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**NSCLC** - **Tarceva, Avastin**

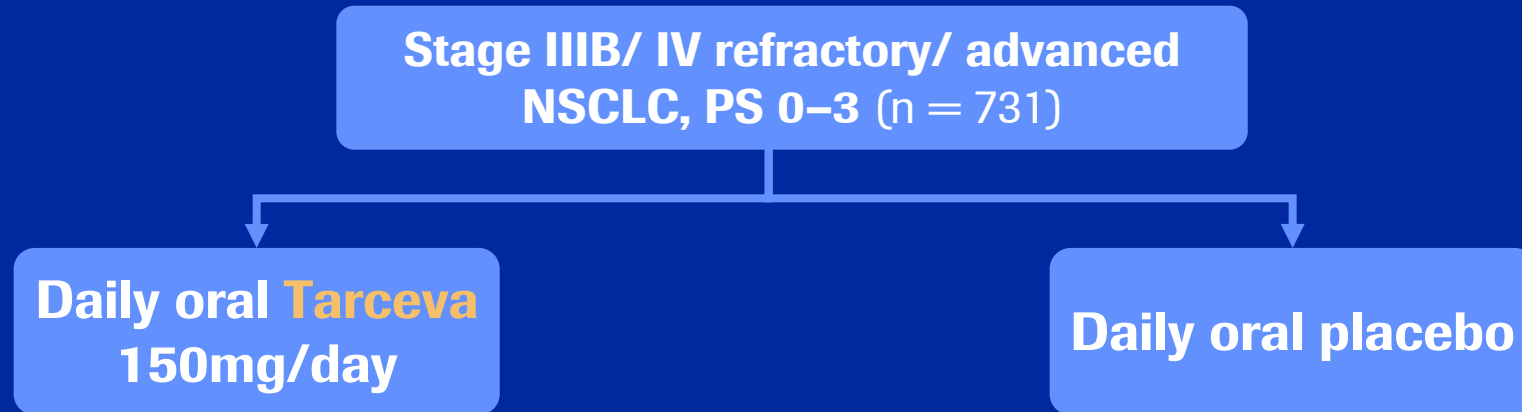
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**Early development**

# Tarceva - BR.21 trial (ASCO '04)



## *Phase III monotherapy in refractory NSCLC*



### **All predetermined endpoints met**

- **42.5 % improvement in median survival**
- 41 % improvement in one-year survival rate
- Improvement in time to symptom deterioration observed for key lung cancer symptoms
- Adverse events included mild or moderate cases of rash and diarrhea

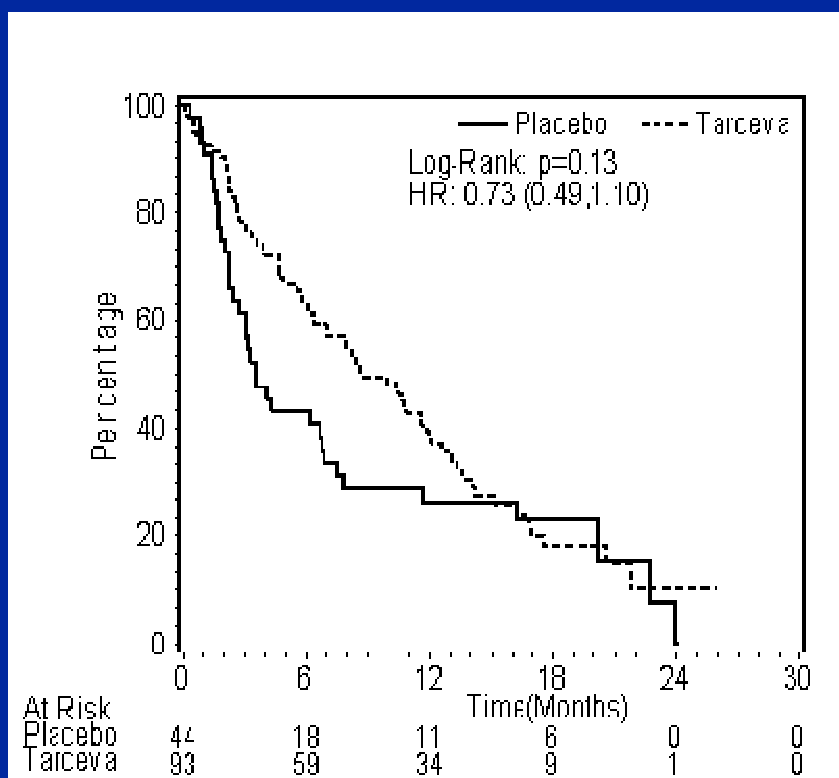
**The only placebo-controlled trial to demonstrate that an EGFR inhibitor prolongs survival**

# Tarceva in NSCLC - BR21

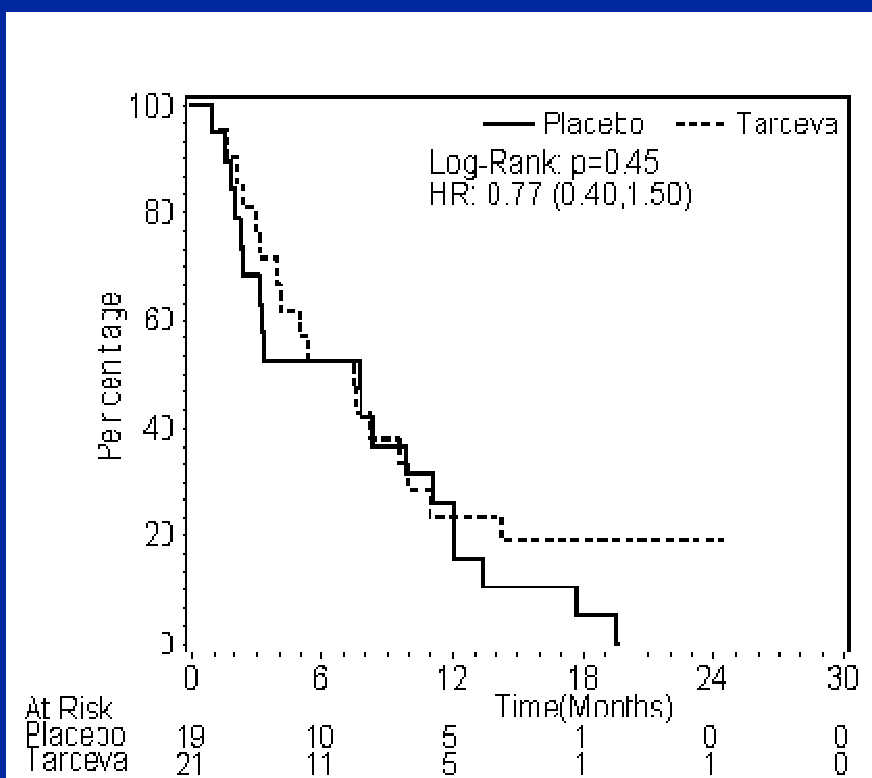


## *Survivals according to EGFR genotype*

### NO MUTATION



### + MUTATION



**P value for interaction= 0.97**

# Tarceva in NSCLC – BR21

## *Subpopulation analysis*



### **EGFR status<sup>1</sup>**

- Tarceva is an effective therapy for NSCLC irrespective of the presence of EGFR mutation

### **Smoking history vs EGFR expression as predictor of survival <sup>2</sup>**

- Tarceva demonstrates benefit in a broad range of subsets
- Smoking history predicts survival better than EGFR status
- Both smokers and non-smokers benefit from Tarceva

1-Tsao et al Abst 7007

2 Clark et al Abst 7033

# Tarceva + Avastin combination therapy



## NSCLC

- Encouraging antitumor activity observed: median overall survival 12.6 months; median PFS 7.0 months<sup>1</sup>
- Ongoing phase II trial comparing Avastin plus Tarceva to chemotherapy in second-line NSCLC
- Large randomized trial planned to investigate the benefit of adding Avastin to Tarceva in second-line NSCLC

## Potential in other cancer types

- Encouraging data in multiple other tumor types
  - RCC, metastatic BC, head and neck cancer

<sup>1</sup>Herbst R, et al. J Clin Oncol 2005;23:2544–55

**Adjuvant breast cancer**

**- Herceptin**

**Metastatic breast cancer**

**- Avastin**

**Ovarian cancer**

**- Avastin**

**NHL maintenance**

**- MabThera**

**Pancreatic cancer**

**- Tarceva**

**NSCLC**

**- Tarceva, Avastin**

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**Early development**

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# Omnitarg in ovarian cancer – Phase II trial



## *Promising single agent activity*

### **Patient population**

- Heavily pretreated ovarian cancer
- Median # of prior chemotherapy regimens: 5

### **Activity assessment\***

**n=60**

- |                             |                |
|-----------------------------|----------------|
| – Partial response (RECIST) | 2 (3.3%)       |
| – Partial response (CA125)  | 4 (7%)         |
| – <b>Σ responders</b>       | <b>6 (10%)</b> |
| – SD >6m                    | 3 (5%)         |

### **Well tolerated**

\*all rows are mutually exclusive, Abstract # 5051

# R1492 (KOS-862)



## *Preliminary evidence of antitumor activity*

### **Phase II activity in platinum-treated NSCLC**

- 55 pts enrolled/ 50 evaluable
- **PR 8%** (4/50 patients); **SD 26%** (13/50)
- Response duration 39.6 wk, PFS 7.7 wks; 26.6 wks (PR + SD)
- Safety: 7.4% Gr 3 sensory neuropathy; no myelosuppression

### **Phase II activity in mBC**

- All 12 pts with prior anthracycline + taxane therapy
- **PR in 2 of first 10** evaluable pts.
- Safety: Peripheral neuropathy, principal toxicity; 1 Gr 3
- Accrual ongoing in Stage 2 Simon Design

### **Phase IB combinations with carboplatin and with gemcitabine (ongoing)**

- Both combinations well tolerated so far; No PK interaction
- Antitumor activity observed with both combinations

# Roche R&D oncology pipeline today



*Total of 18 NMEs + 25 additional indications*

## phase 0 (5 NMEs + 1 AIs)

R769	oncology
R1507	oncology
R547	solid tumors
R1530	solid tumors
GEN	basal cell carcinoma
R1594	hematologic malignancies

## phase I (8 NMEs)

R1550	breast cancer
R1454	solid tumors
R1559	solid tumors
R1645	solid tumors
CHU	solid tumors
GEN	cancer therapy
ANT	solid tumors
ARQ	solid tumors

## phase II (4 NMEs + 5 AIs)

R1273	solid tumors
R1492	solid tumors
R1536	solid tumors
CHU	bone metastases
R744	CERA cancer related anaemia
R1415	Tarceva adjuvant NSCLC
R1415	Tarceva NSCLC (2nd line)
R1415	Tarceva glioblastoma
R435	Avastin ovarian cancer

## phase III/filed (1 NMEs + 19 AIs)

R1415	Tarceva	NSCLC
R105	MabThera	CLL (1st line)
R105	MabThera	CLL (relapsed)
R105	MabThera	mainten. iNHL
R1415	Tarceva	pancreatic cancer
R1415	Tarceva	NSCLC (1st line)
R340	Xeloda	adj. CC mono
R340	Xeloda	mCRC combo
R340	Xeloda	adj. CC combo
R340	Xeloda	adj. BC
R435	Avastin	adj. CC
R435	Avastin	pancreatic cancer
R435	Avastin	RCC
R435	Avastin	NSCLC
R435	Avastin	mBC
R597	Herceptin	adj. BC
R597	Herceptin	mBC combo
R597	Herceptin	gastric cancer
R925	Bondronat	MBP
CHU	Femara	BC

- Roche Managed Projects
- Participations
- Opt-in Opportunities
  - CHU Chugai
  - GEN Genentech
  - ANT Antisoma
  - BAS Basilea
  - IPS Ipsen
  - ISO Isotechnika
  - MED Medivir
  - ARQ ArQule
- Additional Indications

Status as of March 31, 2005

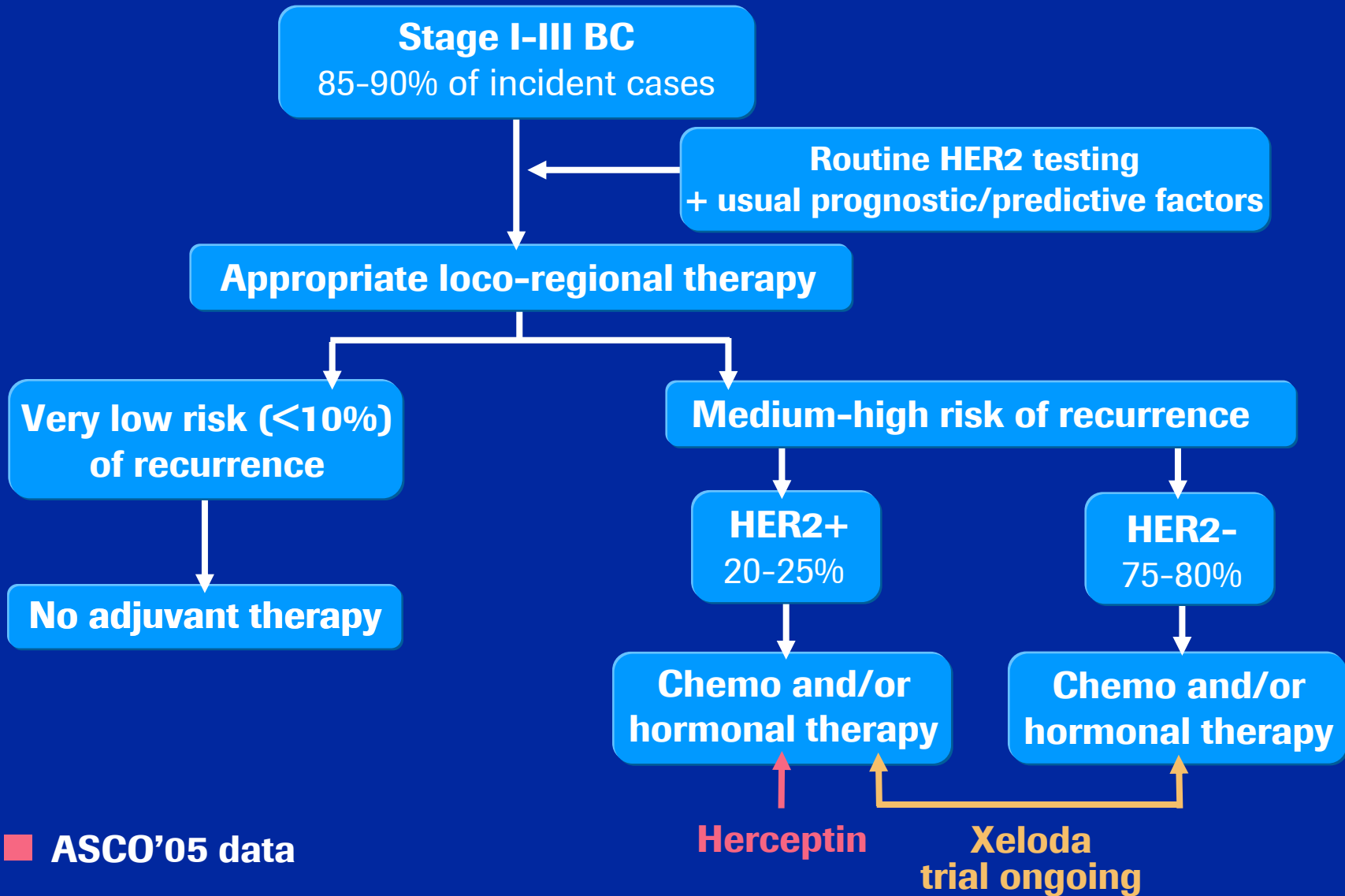


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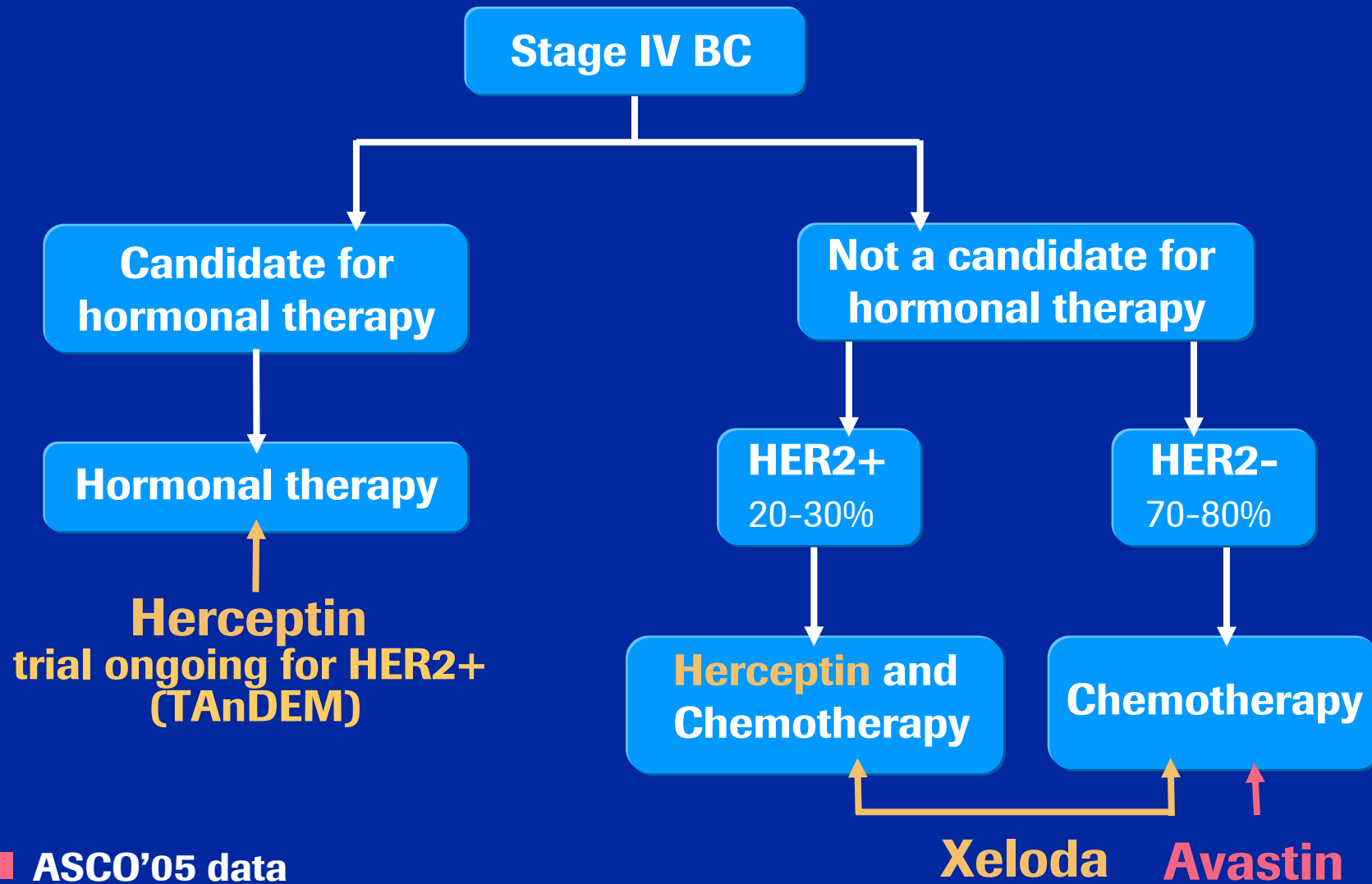
# Setting the standards for treatment of cancer

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# Setting the standard for adjuvant therapy in BC



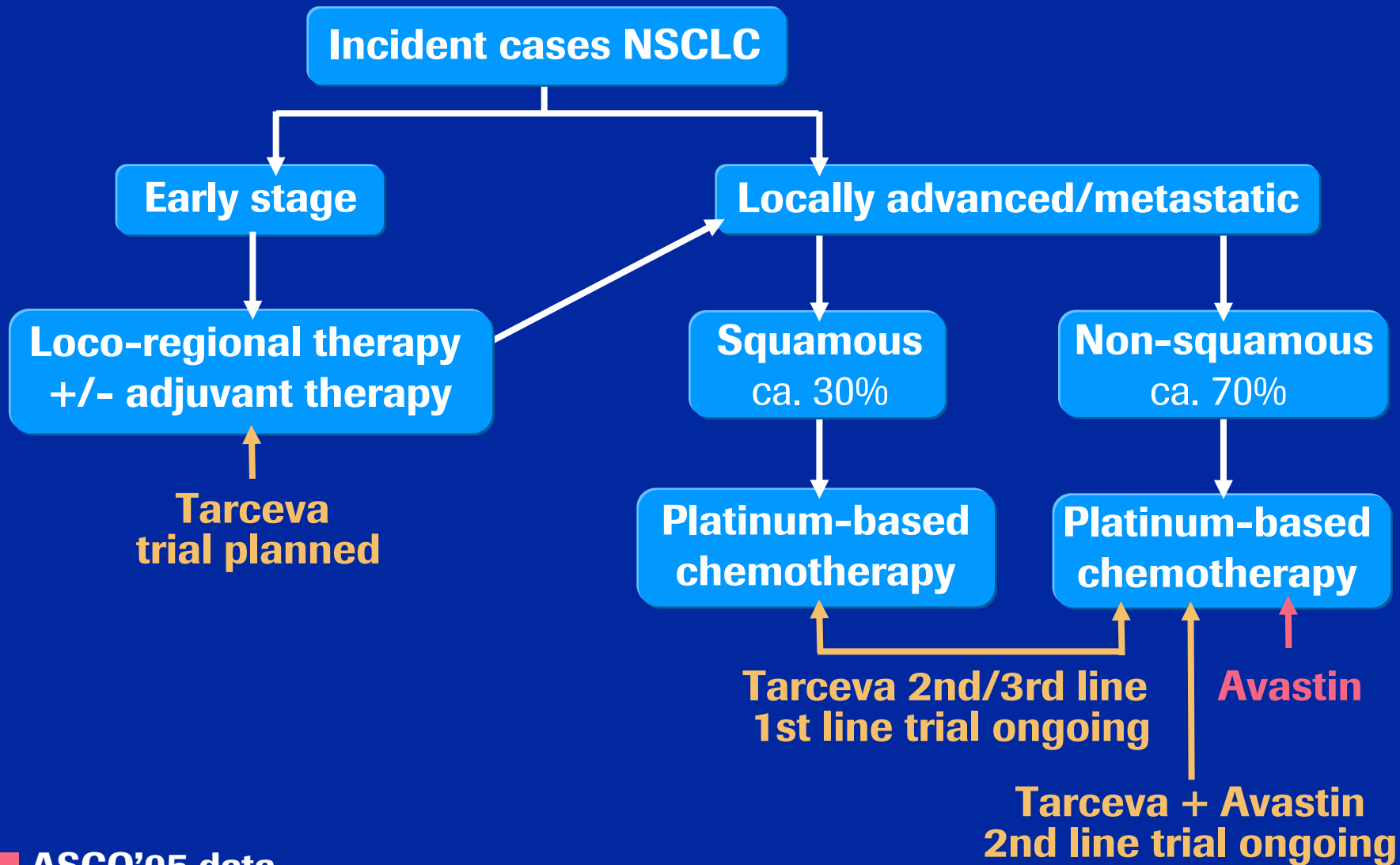
# Setting the standard for treatment of metastatic BC



■ ASCO'05 data

Xeloda Avastin

# Setting the standard for treatment of NSCLC



■ ASCO'05 data

# What we aim for

*Expanding on a strong position*



**Avastin**

**Herceptin**

**MabThera**

**Tarceva**

**Xeloda**

- 
- Establish as backbone therapy in solid tumors
  - Establish as the foundation of therapy for all HER2-positive breast cancer patients
  - Move into maintenance NHL and CLL
  - Move into 1st line and adjuvant NSCLC
  - Move into adjuvant colon and breast Ca

