



La Ricerca Menarini 1979-2008

Dagli esordi alla commercializzazione

Dr. Carlo Alberto Maggi

Firenze, Convitto Della Calza 6 giugno 2008



Developing a new drug from discovery to the market

KEY FACTORS OF THE ENTERPRISE:

**INTELLECTUAL
PROPERTY**

Patentability - Absent in Italy until 1979

SCIENTIFIC

Know-how

ETHIC

**Medical and Social Need, Risk benefit ratio,
Orphan disease**

REGULATORY

Quality, Efficacy, Safety

INDUSTRIAL

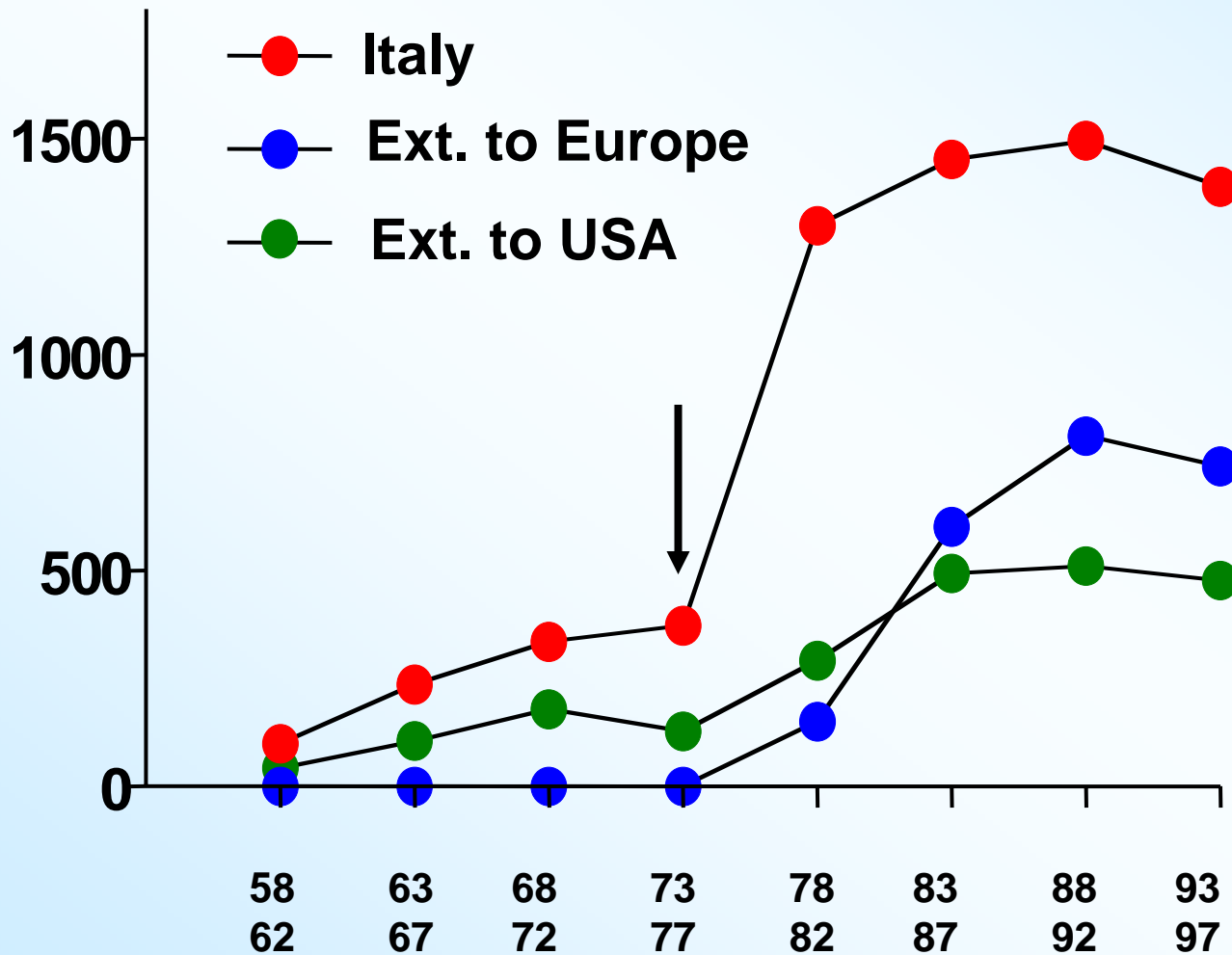
Technology, Feasibility of scale-up

ECONOMICS

Profit & loss, benefit to Health System



Pharmaceutical patents filed in Italy and extended to US/Europe





Menarini Ricerche S.p.A.



Menarini Ricerche S.p.A



1978: riconoscimento legislativo della proprietà brevettuale per i farmaci

R&D - 1978 : 11 impiegati; **2000** >700 impiegati

Investimento in R&D: 116 milioni di euro / anno

Aree di interesse

- Malattie cardiovascolari
- Oncologia
- Asma/dolore/infiammazione

Menarini Ricerche: scorporata dalla holding nel 1996

Organizzazione:

Firenze - Pomezia : discovery

Pisa - Lomagna: sviluppo chimico

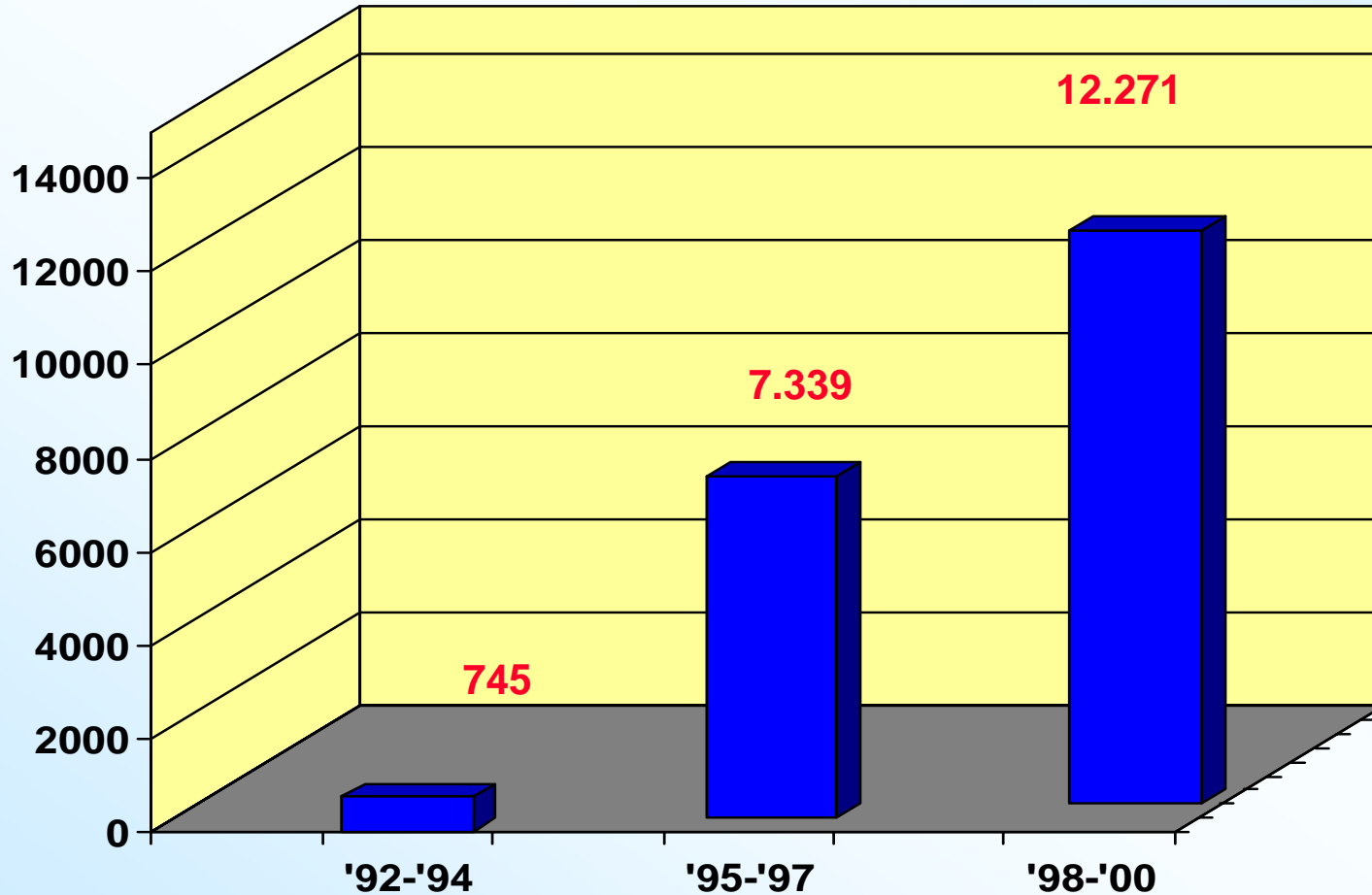
Berlino: sviluppo farmaceutico

Pomezia: farmacocinetica e tossicologia

Firenze - Barcellona : sviluppo clinico e procedure regolatorie



> 20.000 Patients Enrolled in Clinical Trials since 1992





European Registrations '97-'08

Product

Reference Member State

Dexketoprofen/oral and injective

Spain

(pain)

Currently marketed in 44 countries

Zofenopril - Zofenopril HCTZ

United Kingdom

(hypertension/AMI)

Currently marketed in 25 countries

Brivudin

Germany

(Herpes Zoster, PHN)

Currently marketed in 21 countries

Nebivolol

The Netherlands

(hypertension & heart failure)

Currently marketed in 56 countries

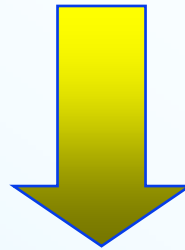


Dexketoprofen

Indication

Treatment of acute pain of moderate to severe intensity (oral and injective)

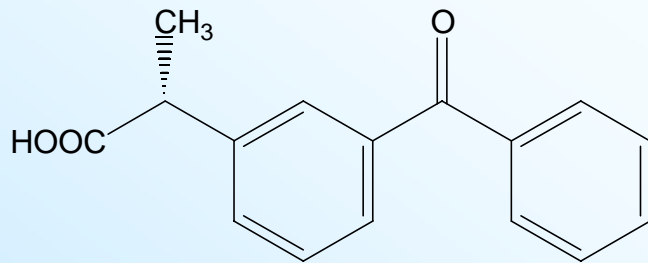
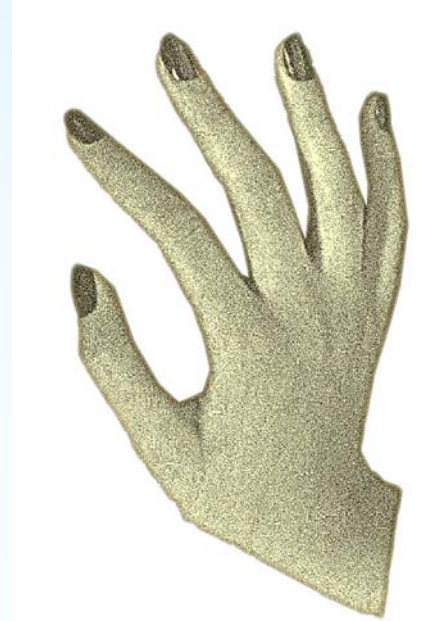
First registration — *Y 1996 (oral), Y 2002 (injective)*



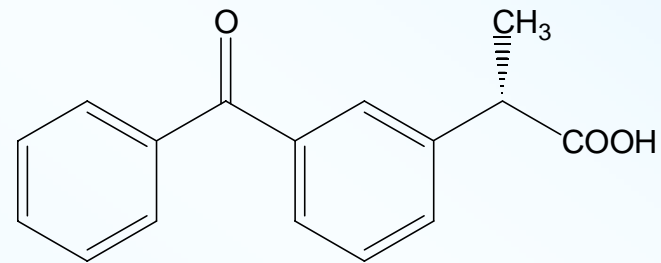
Y 2008

oral form marketed in 36 countries EU+non EU
injective form marketed in 8 countries EU+non EU

SOLO Dexketoprofen è la parte attiva del farmaco



(R)-(-)-ketoprofen



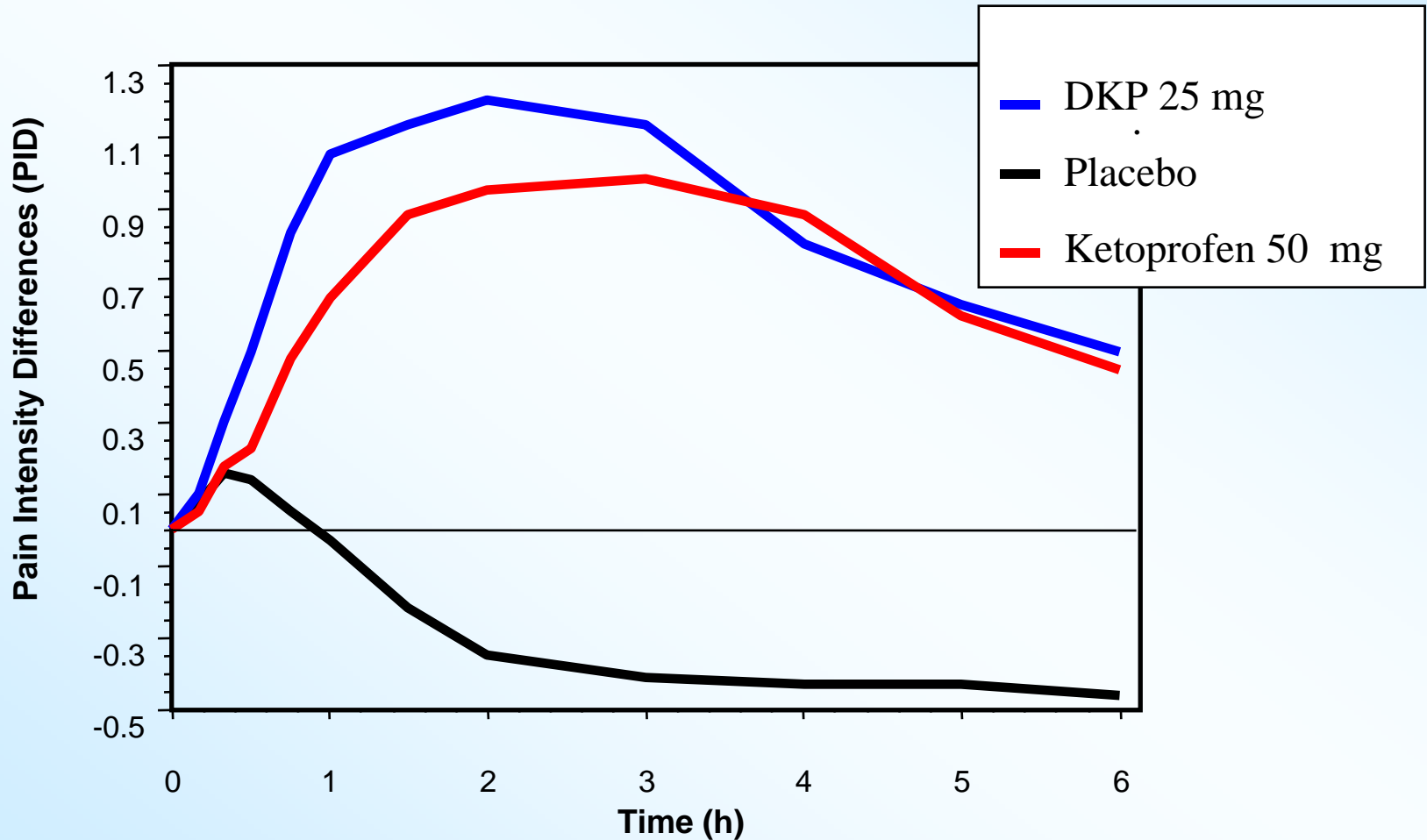
(S)-(+)-ketoprofen

dexketoprofen



Analgesic efficacy in dental pain (7-Ket Study)

DKP (25 mg) vs Ketoprofen (50 mg) and Placebo



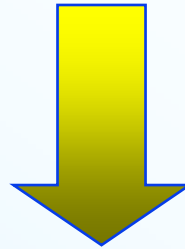
Brivudin



Indication

Treatment of acute Herpes Zoster and prevention of post herpetic neuralgia

First registration Y 2000



Y 2008

marketed in 21 countries EU+non EU



Brivudin: The most effective virustatic

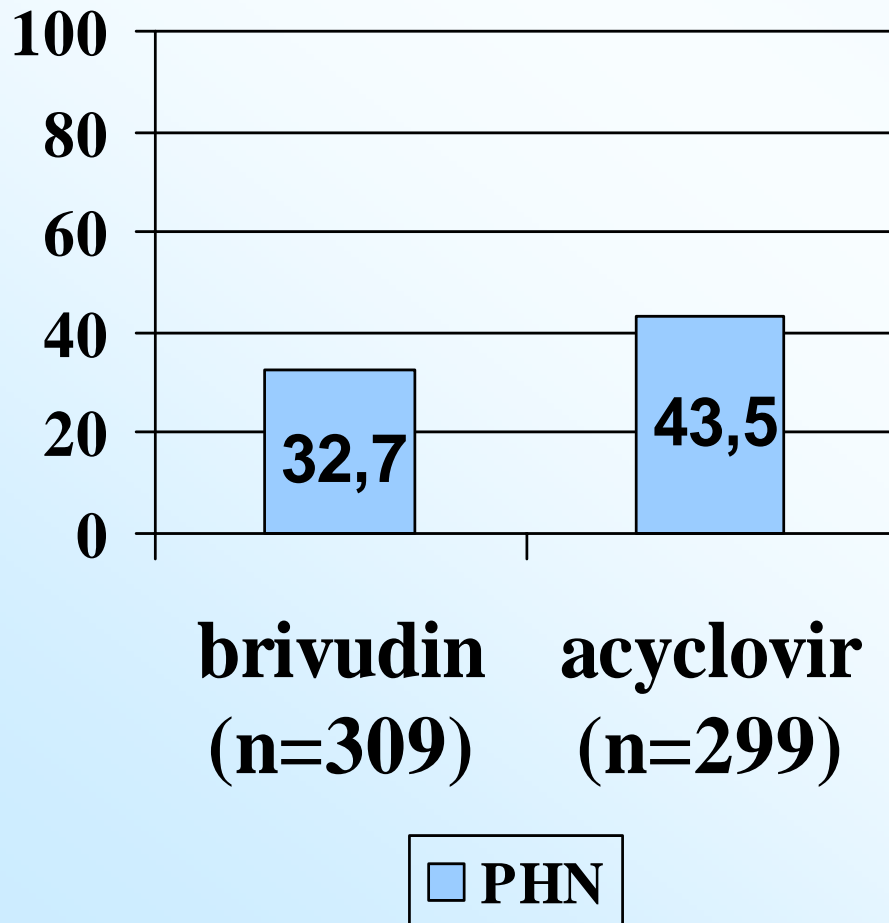
- **Once daily dosage**
- **Lowest substance load**
- **Highest antiviral action**
- **Marked reduction in risk of post-herpetic pain**



Surveillance study

Incidence of PHN

Brivudin 125mg o.d. for 7 days vs
Acyclovir 800mg x 5 for 7 days



The relative risk of contracting PHN after 7-day Brivudin 125mg therapy was **25 % lower** than after ACV therapy

(p= 0.0056)



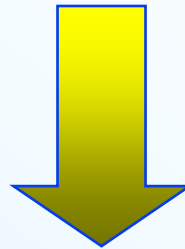
Zofenopril

Indication

Treatment of mild to moderate essential hypertension and acute myocardial infarction _____

First registration

*Y 1998 (hypertension),
Y 2000 (myocardial infarction)*

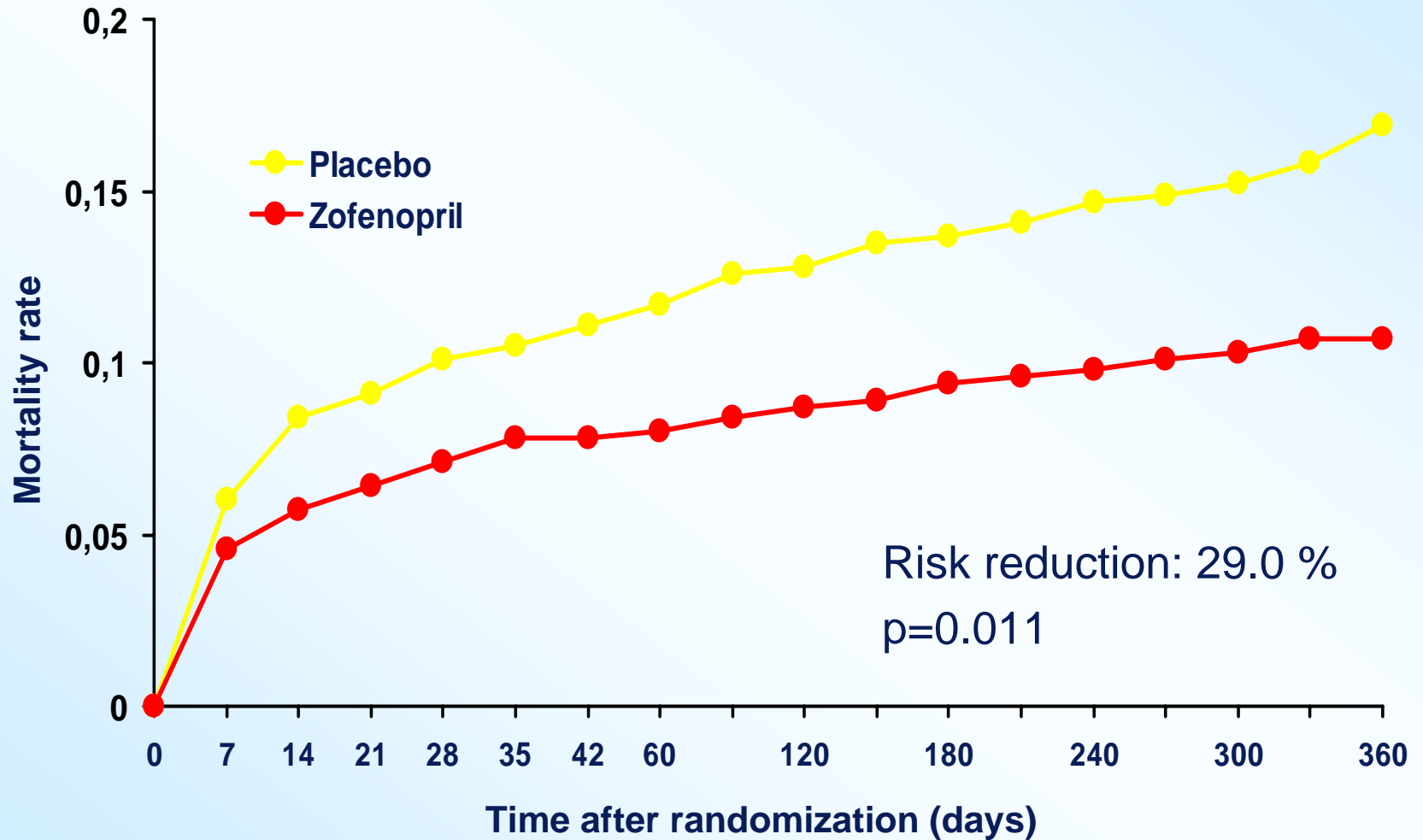


Y 2008

marketed in 25 countries EU+non EU



1-year mortality rate in the SMILE Study



Nebivolol

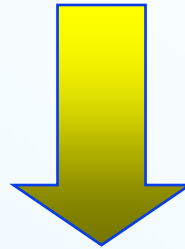


Indication

*Treatment of essential hypertension
and hearth failure*

First registration

*Y 1995 (hypertension),
Y 2005 (hearth failure)*



Y 2008

marketed in 56 countries EU+non EU



SENIORS

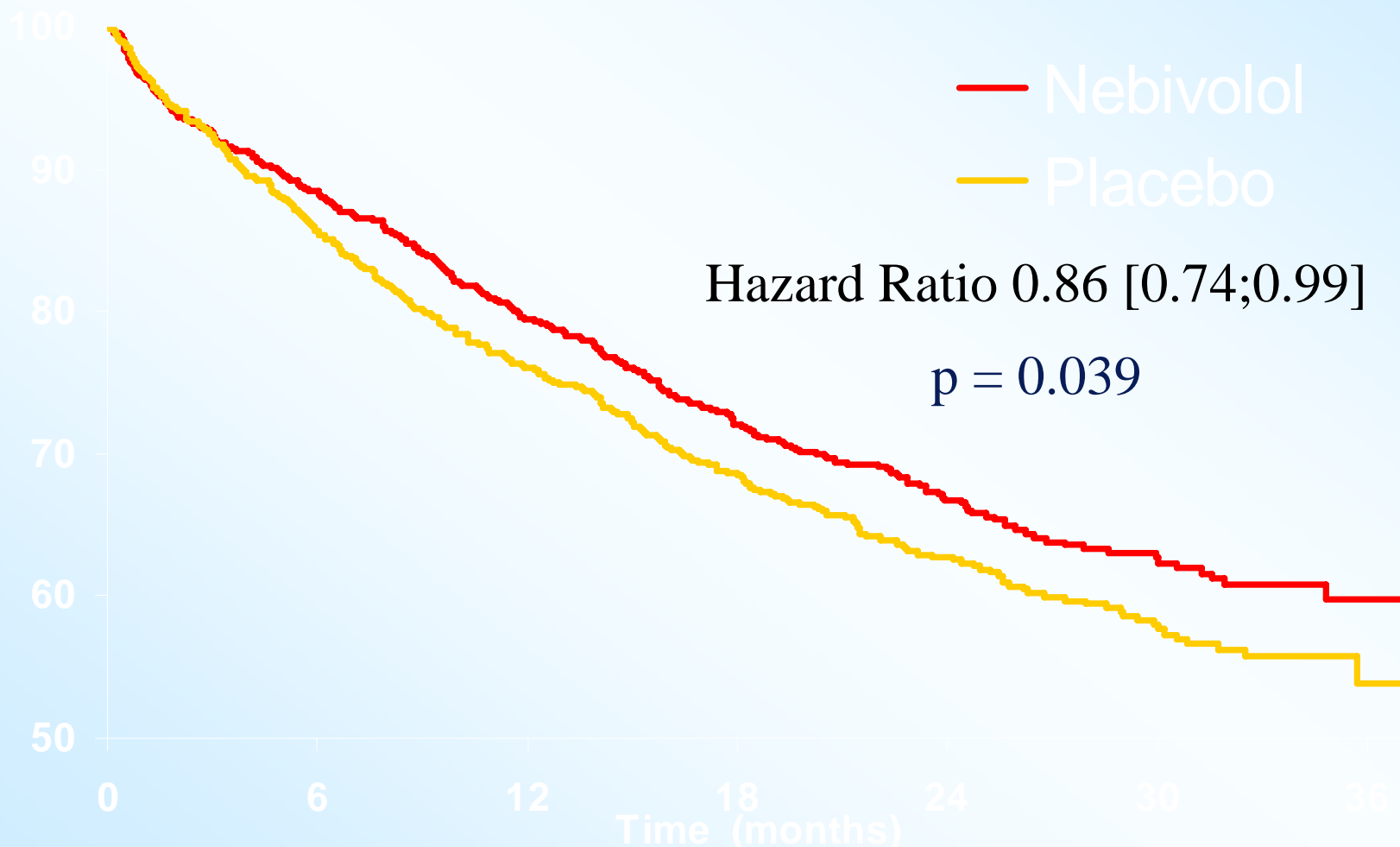
Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure

A randomised, double-blind, placebo-controlled phase III study



All cause mortality or CV hospital admission (primary outcome)

Event free
Survival %



No. of events: Nebivolol 332 (31.1%); Placebo 375 (35.3%)



Dexketoprofene

Brivudin

***FATTURATO TOTALE
ANNO 2007****

Nebivololo

522 Milioni di euro

Zofenopril

***Dati IMS**



ONCOLOGY

**A challenge and strategic opportunity
for Menarini Group
in the New Millennium**

Oncology in Menarini Group

Historical background



- 1987-1988:** Hiring of qualified and experienced researchers from Farmitalia, upgrade of Chemistry and Pharmacology Department to implement oncological research technologies.
- 1990:** Start of discovery for new anthracycline derivatives.
- 1994:** Start of biotech project for antitumor vaccines.
- 1997:** Start of clinical development of Sabarubicin.
- 1997:** Establishment of MR Chemical Development for cytotoxic drugs.
- 1999:** Start of discovery for new camptothecin derivatives.
- 2000:** Start of phase II clinical trial with Sabarubicin.
- 2002:** Agreement with Tanabe for co-development of camptothecin conjugate MEN4901 for treatment of colon carcinoma.
- 2003:** Start of clinical development of MEN4901.
- 2006:** Start of Phase II-III for Abagovomab, antitumor vaccine against ovarian carcinoma.



ONCOLOGY - PIPELINE

	Indication	Status	Patent/DP
<i>Abagovomab</i> (MEN 2234) Antitumor Vaccine	Ovarian cancer	Phase II-III	2020
<i>Sabarubicin</i> Anthracycline	Lung cancer	Phase III	2019
<i>Delimotecan</i> (MEN 4901) Topo I Inhibitor	Melanoma	Phase I	2021
<i>Histone</i> <i>Deacetylase</i>	Solid tumors	Discovery	2028

Ovarian cancer: incidence and mortality

Country/Region	Incidence		Mortality	
	Cases	Crude Rate *	Deaths	Crude Rate *
World	204499	6.6	124860	4.1
More developed regions	96769	15.8	62248	10.2
Less developed regions	107541	4.4	62512	2.5
Southern Europe	11649	15.7	6431	8.7
Italy	4797	16.3	2871	9.7

* annual rate per 100,000 persons at risk

Source: GLOBOCAN 2002

Ovarian Cancer Therapy: current status

**First Line
Induction therapy**

Surgery



**Tumor
relapse**



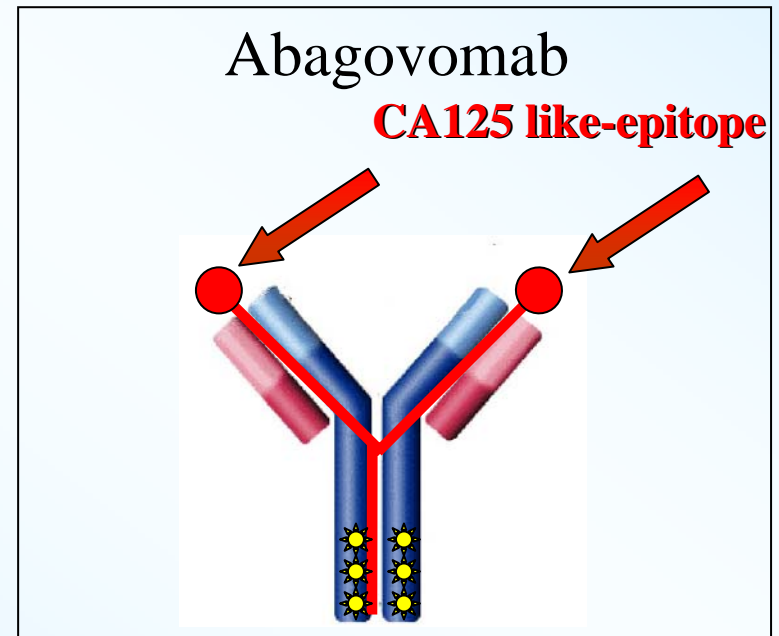
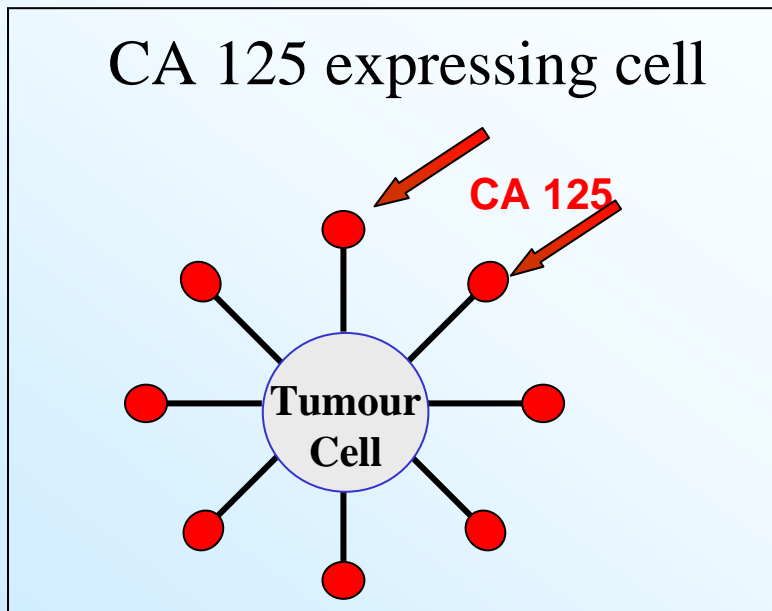
**Second Line
Salvage therapy**



**Carboplatin
Paclitaxel**

ABAGOVOMAB - Concept and Mechanism of Action

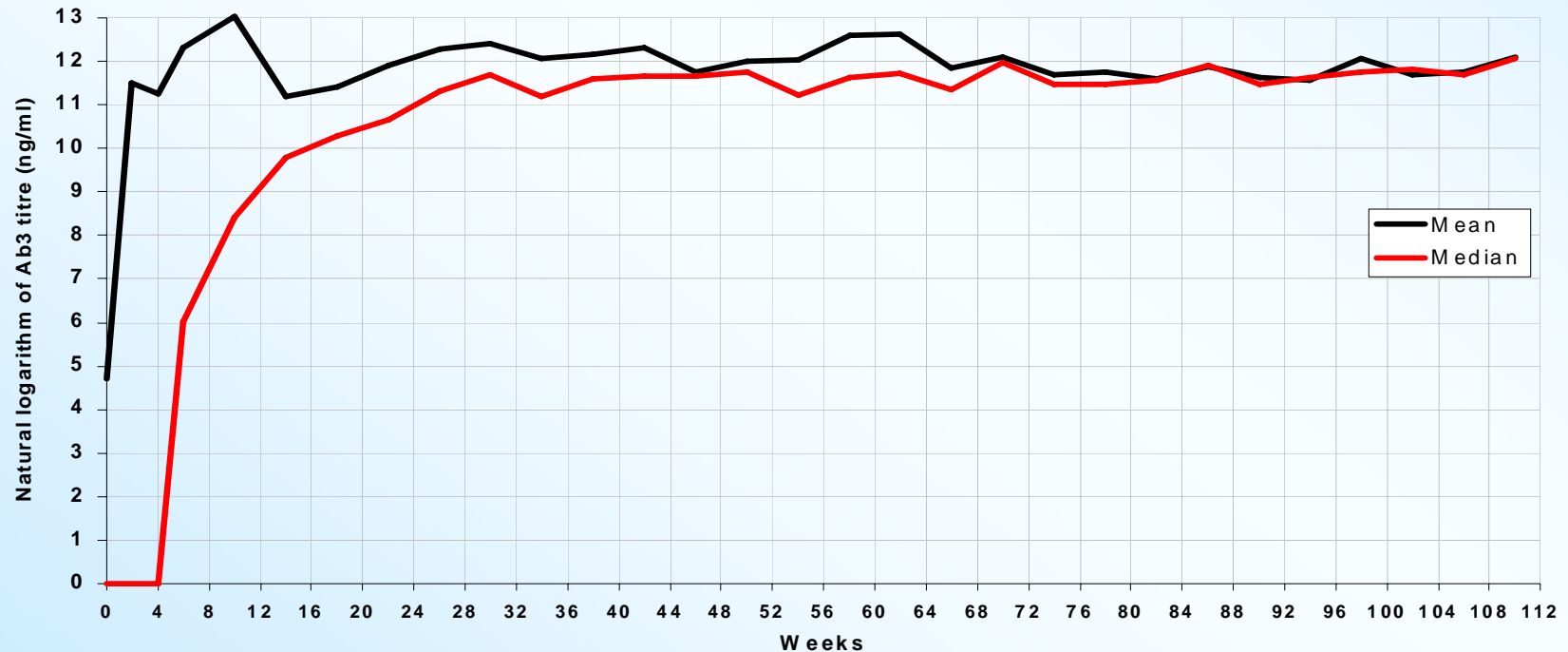
- ◆ a **MURINE** monoclonal antibody
- ◆ it mimics the structure of the tumor associated antigen CA125
- ◆ it is a **SURROGATE ANTIGEN,** thus acting as a **THERAPEUTIC VACCINE**





ABAGOVOMAB - *Proof of concept* in clinical experience

Serum Ab3 concentration in responding patients who received repeated monthly doses of Abagovomab



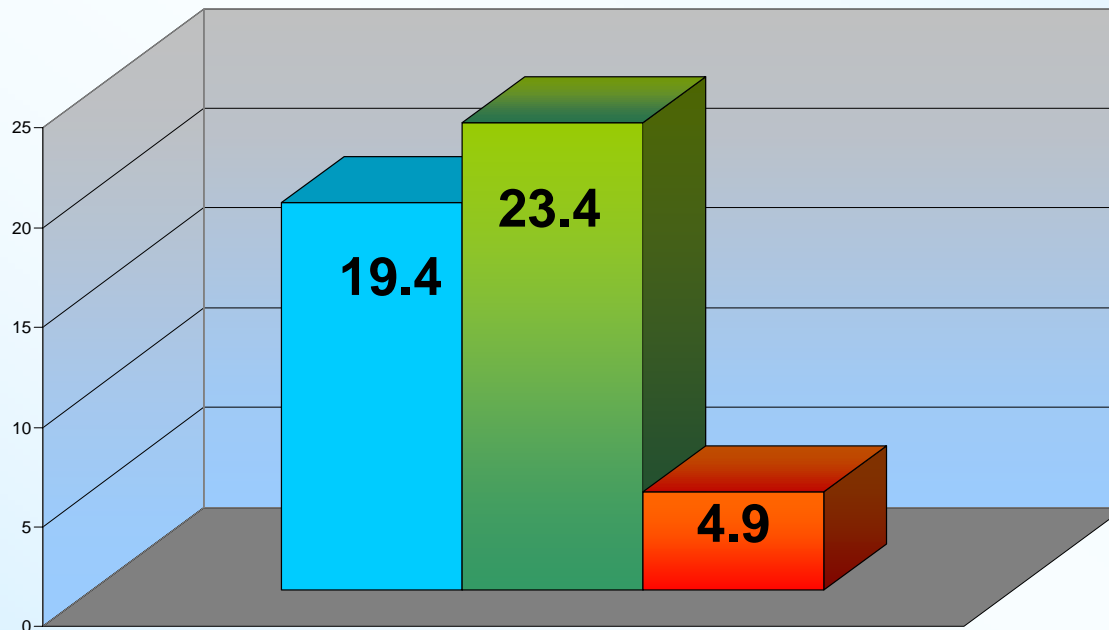





ABAGOVOMAB - *Proof of concept* in clinical

experience

Immune Response **and Outcome**

Median Survival (months)



-  Overall Population (n=119)
-  Immunological Responders Ab3+ (n=81)
-  Immunological Non-Responders Ab3- (n=38)

The MIMOSA Study

Rationale and Design

Monoclonal antibody

Immunotherapy for

Malignancies of

Ovary by

Subcutaneous

Abagovomab

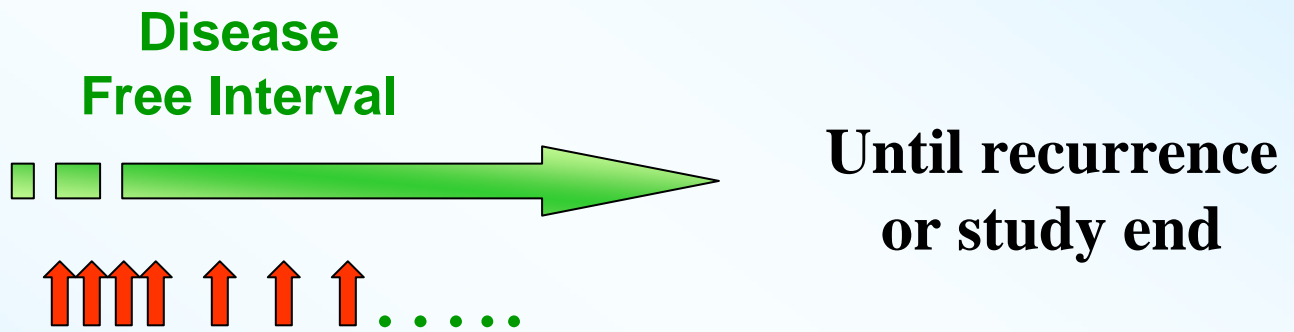
The MIMOSA Study - Abagovomab treatment

First Line
Induction therapy

Surgery



**Carboplatin
Paclitaxel**



Abagovomab given to prolong disease free interval

The MIMOSA Study design

advanced Stage III-IV epithelial ovarian cancer



Surgery

+



Chemotherapy

Complete Response

PR - SD - PD

Randomization

Not Eligible

2:1

Abagovomab

Placebo

Treatment will continue until progression

4 years CT scan follow up for recurrence
9 years survival follow up