Comisión Nacional del Mercado de Valores
A/A: Director del Área de Mercados
Paseo de la Castellana nº 19
28046 Madrid

Madrid, a 13 de diciembre de 2007

De conformidad con lo previsto en el artículo 82 de la Ley del Mercado de Valores en materia de **HECHOS RELEVANTES,** por la presente se informa que hoy 13 de Diciembre de 2007, a las 10:00 horas tendrá lugar una presentación a analistas en las instalaciones de Pharma Mar, S.A. sitas en Colmenar Viejo (Madrid).

Se acompaña un ejemplar de la información objeto de la presentación.

Atentamente,

Sebastián Cuenca
Secretario General de Zeltia, S.A.

Zeltia

Analyst Day
13 de Diciembre de 2007

Disclaimer

Este documento contiene proyecciones a futuro basadas en estimaciones efectuadas por el equipo directivo a fecha de hoy. Entre los distintos factores que podrían hacer cambiar dichas estimaciones se incluyen, sin ánimo limitativo, las siguientes: el éxito de las actividades de desarrollo de la Compañía; la utilidad de los descubrimientos derivados de dichas actividades; las dificultades propias del desarrollo de medicamentos, incluidas las incertidumbres relativas al plazo y resultados de las investigaciones preclínicas; dependencia de colaboradores; incertidumbre acerca de la entrada en ensayos clínicos de los productos de la compañía en fase de desarrollo e incertidumbre acerca de los resultados de dichos ensayos clínicos; incertidumbre acerca del adecuado reembolso de dicho productos por parte de la administración pública, aseguradores privados del sector salud y pagos provinentes de terceras partes; y la incertidumbre relativa a las futuras regulaciones que afecten al sector farmacéutico.

This information includes forward-looking statements based on Management's current expectations. Factors that could cause future results to differ materially from such expectations include, but are not limited to: the success of the Company's research strategy; the applicability of discoveries made therein; the difficulties inherent in the development of pharmaceuticals, including uncertainties as to the timing and results of preclinical studies; delayed achievements of milestones; reliance on collaborators; uncertainty as to whether the Company's potential products will succeed in entering human clinical trials and uncertainty as to the results of such trials; uncertainty as to whether adequate reimbursement for these products will exist from the government, private healthcare insurers and third-party payers; and the uncertainties as to the extent of future government regulation of the pharmaceutical business.

Agenda

Grupo Zeltia			
10:00	José María Fernández	Presidente	Introducción a la jornada
10:10	María Luisa de Francia	Directora Financiera	Financiación
PharmaMar			
10:40	Pedro Santabárbara	VP, Director Médico	Desarrollo clínico
	José Jimeno	VP, Director de Desarrollo Científico	Marcadores genéticos
11:40	Alfonso Casal	Director de Marketing y Ventas	Organización comercial
	Luis Mora	Subdirector General y Director Financiero	Mercados
12:15	Preguntas		
12:30	Café		
Neuropharma			
12:45	Belén Sopesén	Directora General	Presentación de la compañía
	Ana Martínez	Directora Científica	Estrategia de Investigación
	Teodoro del Ser	Director de Desarrollo Clínico	Desarrollo clínico
13:30	Preguntas		

Principales hitos del Grupo en 2007

- **Lanzamiento de Yondelis® en sarcoma de tejidos blandos en la UE**
- **Completado el reclutamiento en Fase III de Yondelis® en cáncer de ovario (mayo)**
- **Comienzo del ensayo estratificado de Fase II de Yondelis® en cáncer de mama**
- **Resultados de Fase II de Aplidin® en mieloma múltiple**
- **Entrada en clínica de NP-61**
- **Licencia modelo ratón transgénico GSK3 a JSW Research**
- **Préstamo BEI/ICO por €50m**
- **€43m captados mediante la Línea de Capital con Santander Global Banking & Markets (~3% del capital)**

Objetivos para 2008

- **Solicitud de comercialización de Yondelis® en cáncer de ovario**
- **Comercialización de Yondelis® para STB en todos los países de la UE; consolidación de la red de ventas**
- **Avance de los demás proyectos en el *pipeline***
- **Entrada de un nuevo compuesto en clínica**
- **Entrada en Fase II de NP-12**
- **Preparación de la IPO**

Una empresa única

- **Liderazgo mundial destacado en el desarrollo de fármacos de origen marino**
- **Una de las primeras biotecnológicas europeas por capitalización bursátil**
- **Una de las primeras empresas españolas por inversión en I+D+i**
- **Líneas de investigación totalmente innovadoras**

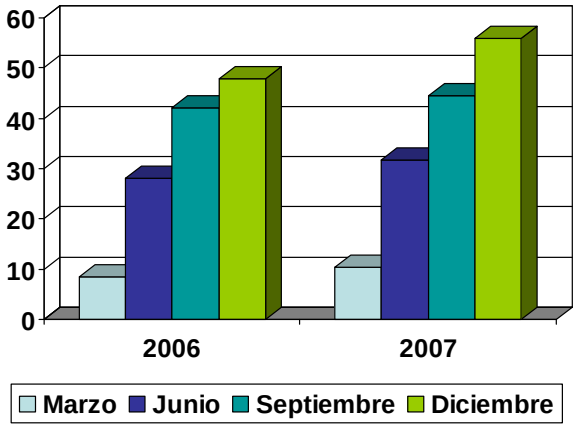
Financiación del Grupo

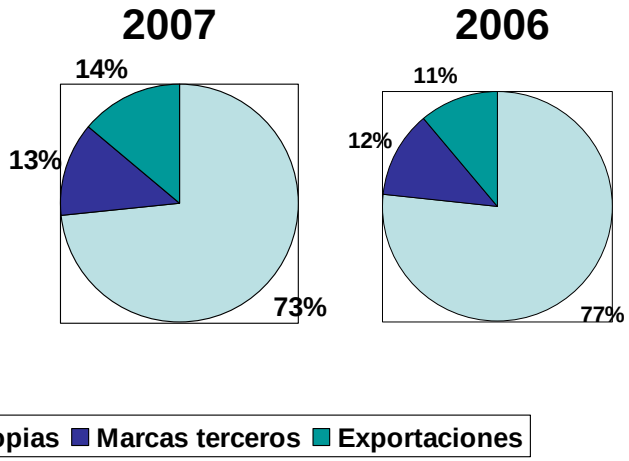
María Luisa de Francia
Directora Financiera

ZELNOVA

VENTAS POR TRIMESTRE

+16%





Bº BRUTO / VENTAS 50%

NUEVAS ACTUACIONES

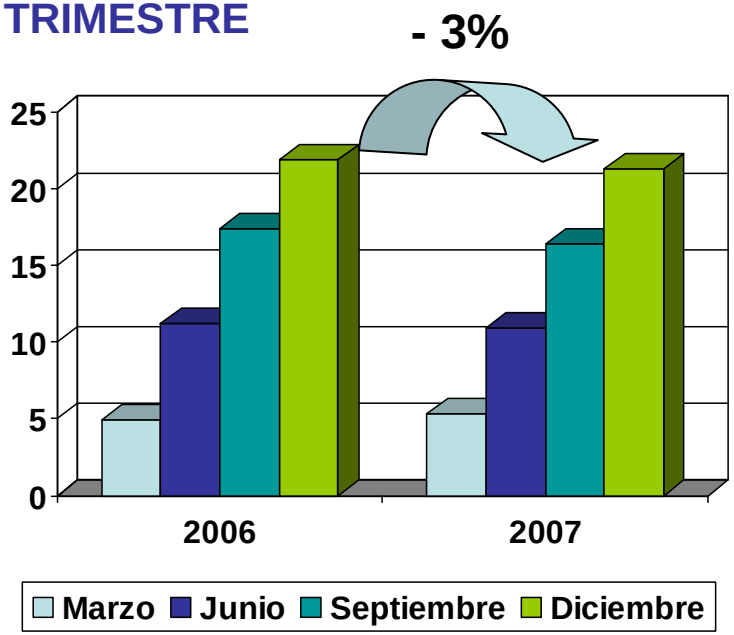
- Lanzamiento de una **nueva línea de productos** de jardinería en Italia
- En **mercado exterior**: Lanzamiento de un nuevo producto de agricultura ecológica

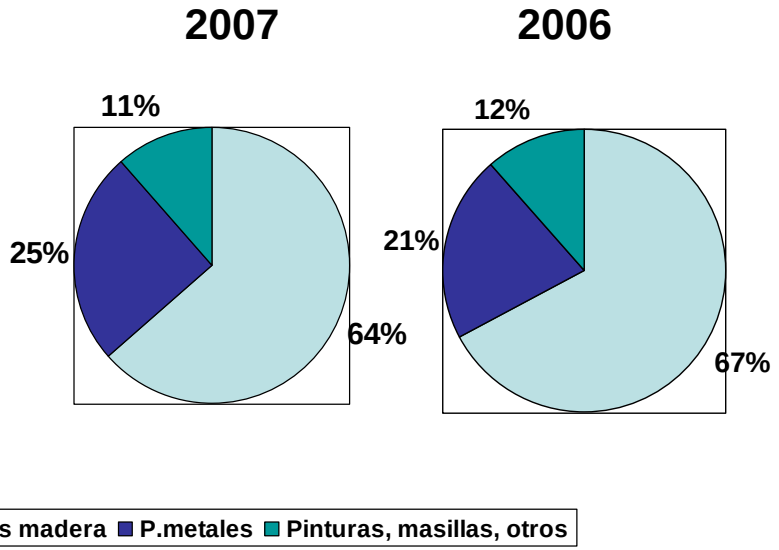
  Producción de aerosoles para Grecia

  Ampliación de la gama de productos para exportación

XYLAZEL

VENTAS POR TRIMESTRE



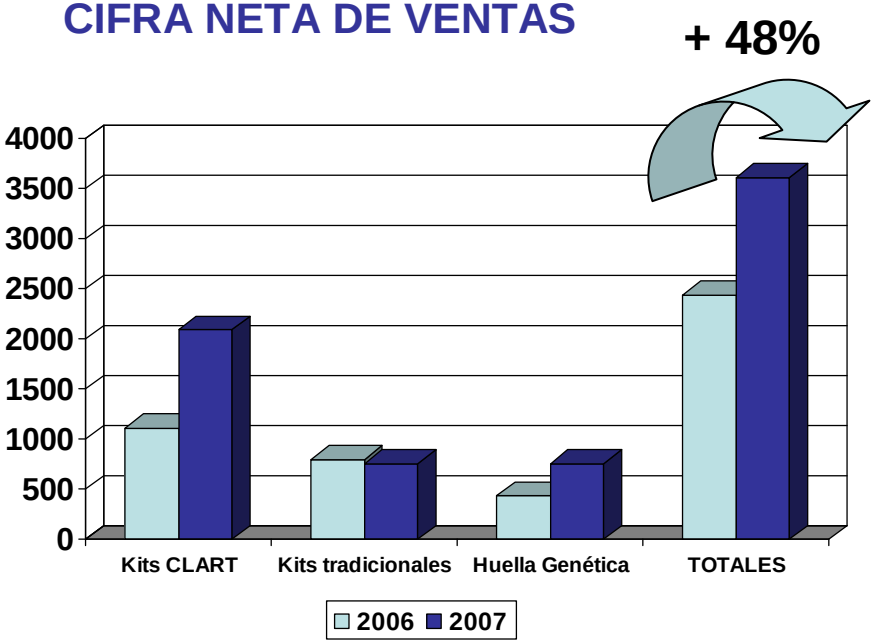


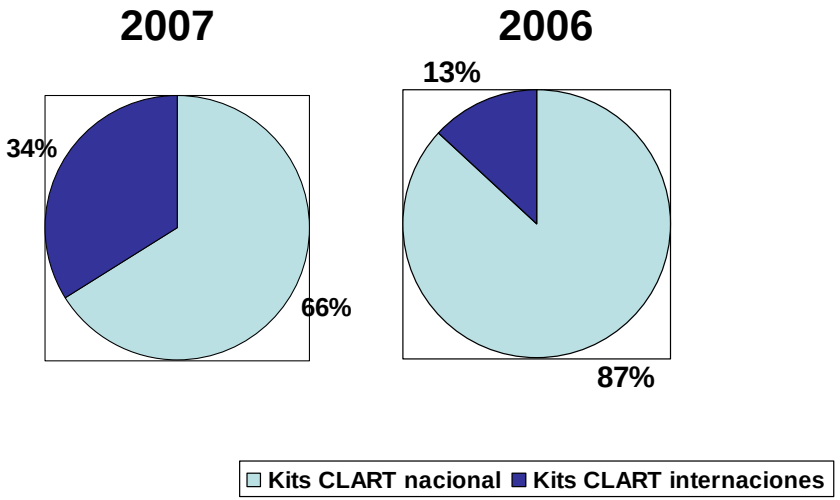
Bº BRUTO / VENTAS 64,5%

EN MARCHA LAS ACTUACIONES PARA ENTRAR EN NUEVOS NICHOS DE MERCADO: PINTURAS DE ALTA GAMA

GENOMICA

CIFRA NETA DE VENTAS





PRÓXIMAS ACTUACIONES:

- AUTOMATIZACION SISTEMA CLART (Clinical Array Technology)
- CONTINUACIÓN LANZAMIENTO INTERNACIONAL
- NUEVOS LANZAMIENTOS DE KITS DE DIAGNÓTICO TECNOLOGÍA CLART, EN PANEL RESPIRATORIO VÍRICO

POSICIÓN NETA DE TESORERÍA

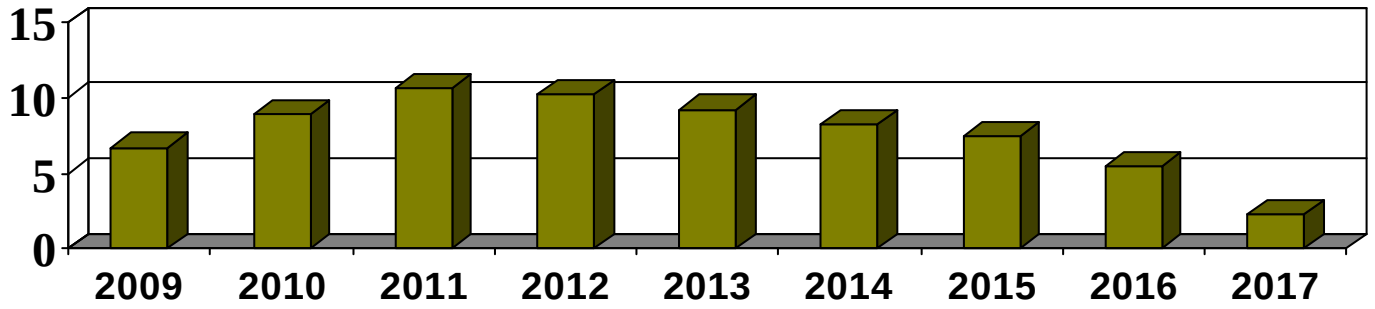
En Millones de euros	Sept 2007	E. Dic. 2007
Efectivo y equivalentes	86,2	96,0
Deuda a corto	(29,8)	(24,5)
Posición neta de tesorería	56,4	71,5

Deuda Largo plazo

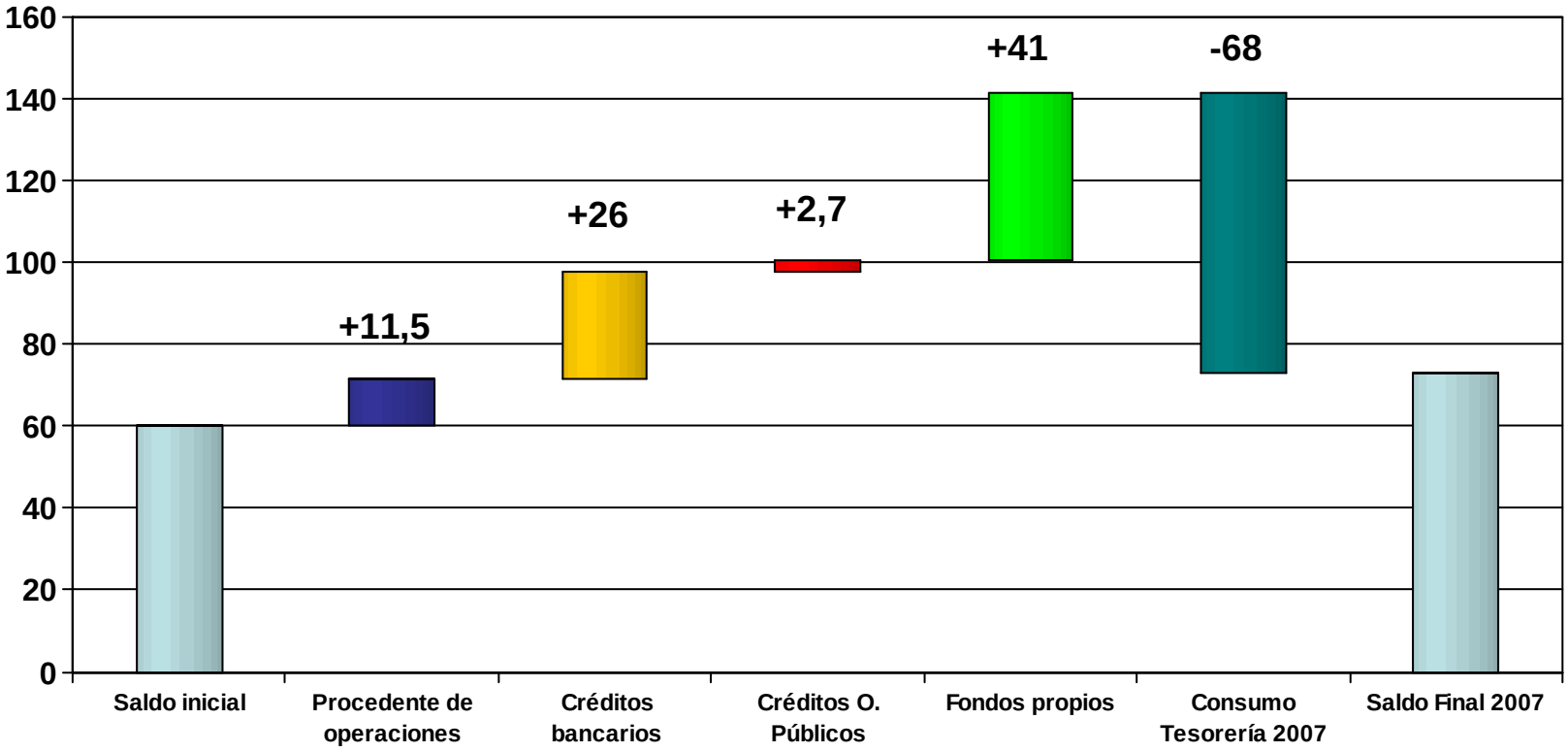
En Millones de euros	2006	E. 2007	E.2008
Préstamos	16,4	43,3	56,2
Anticipos reembolsables	26,5	26,2*	29,6
TOTAL	42,9	69,5	85,8

* Pendiente recibir 3MM de programas 2007

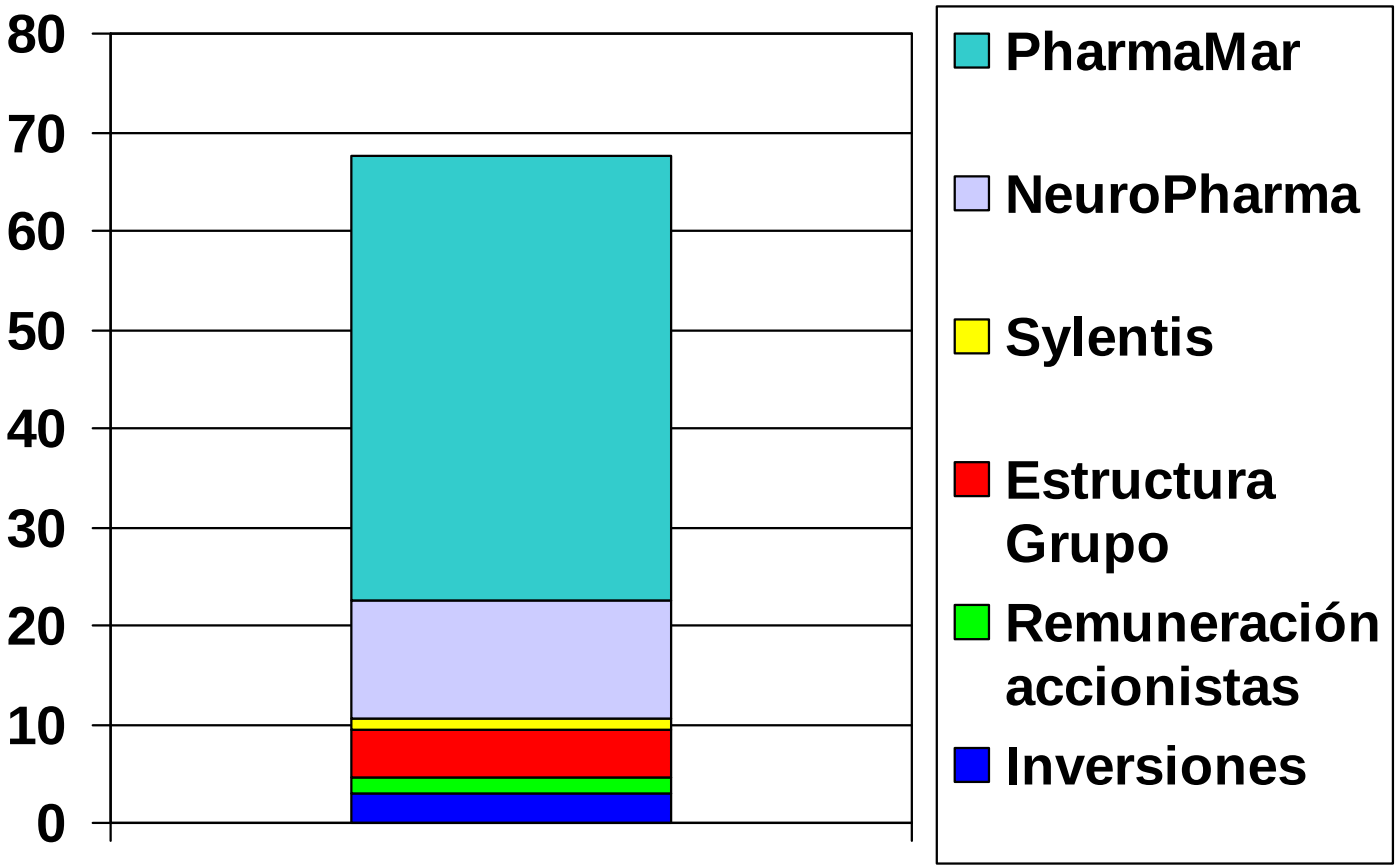
Vencimientos deuda a largo plazo



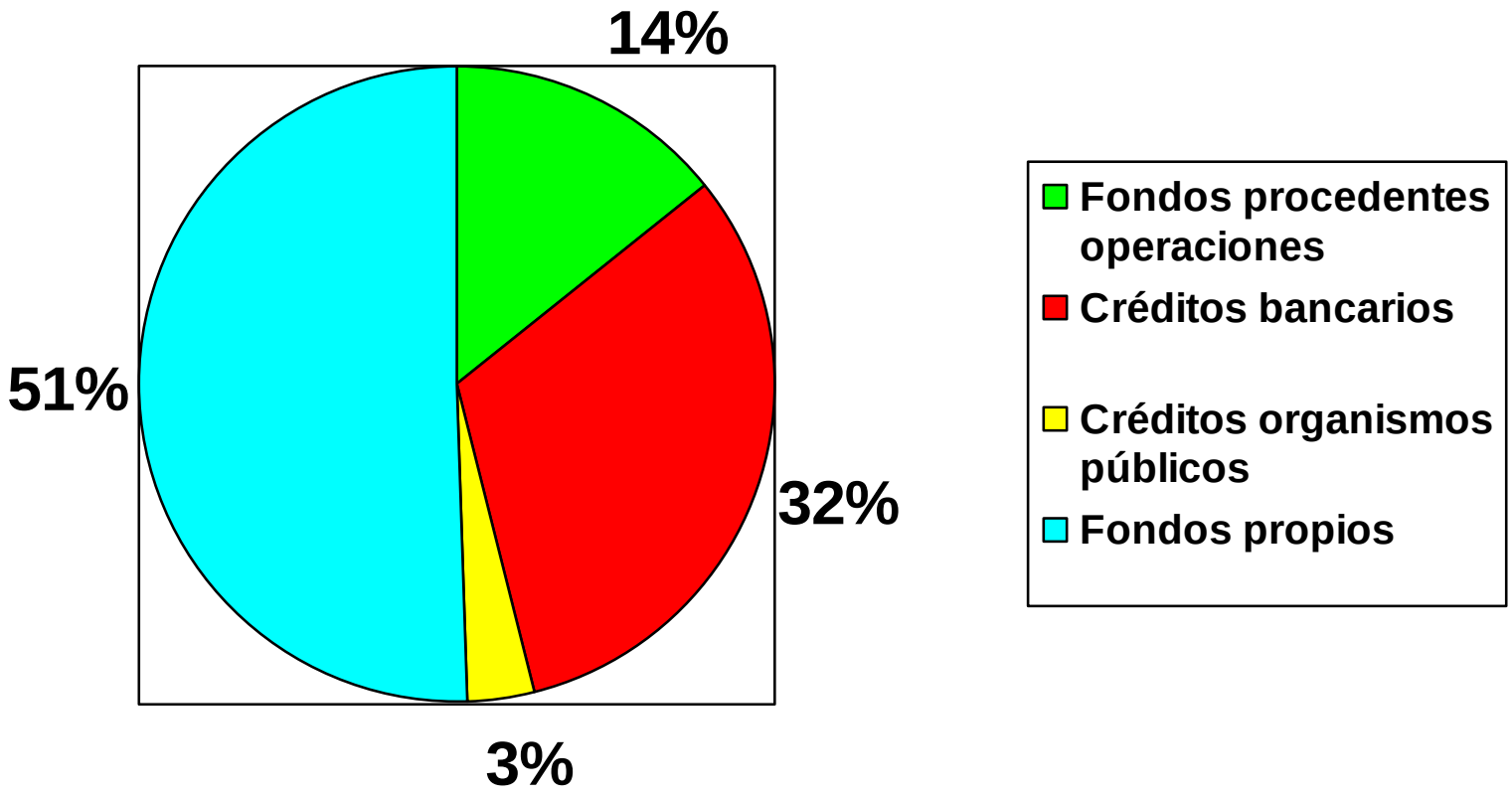
TESORERÍA GRUPO 2007



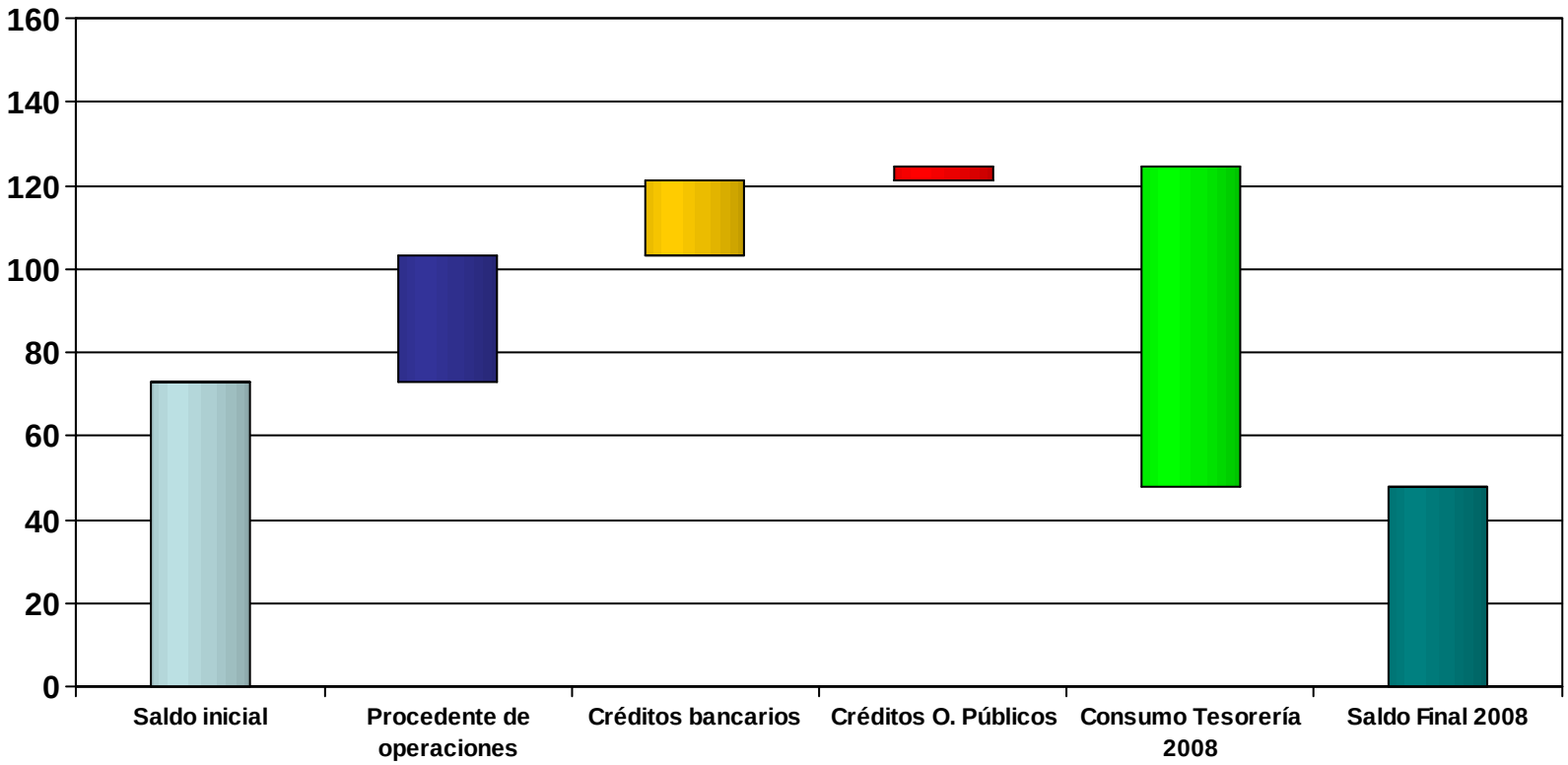
DISTRIBUCIÓN CASH BURN GRUPO 2007



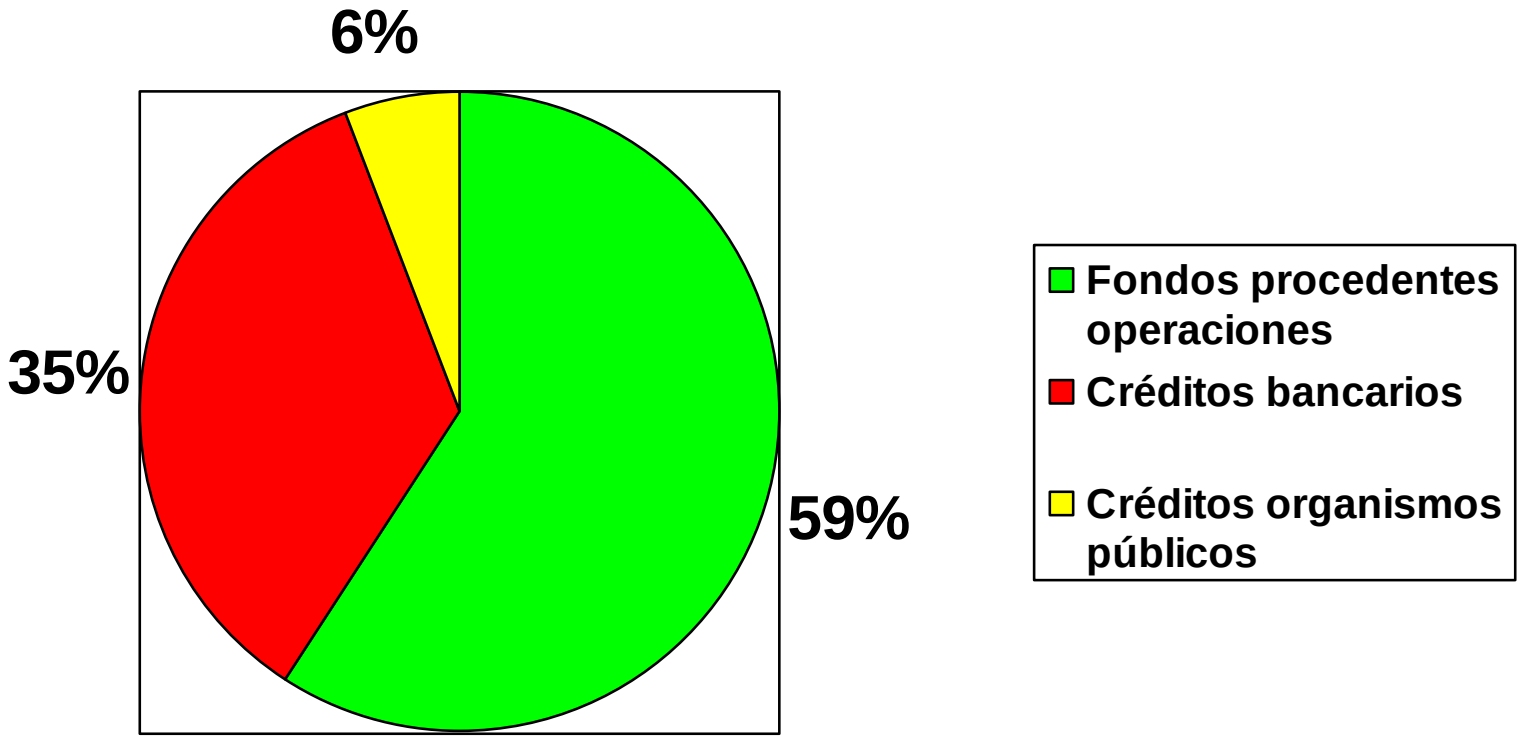
FUENTES DE FINANCIACIÓN 2007



TESORERÍA GRUPO 2008



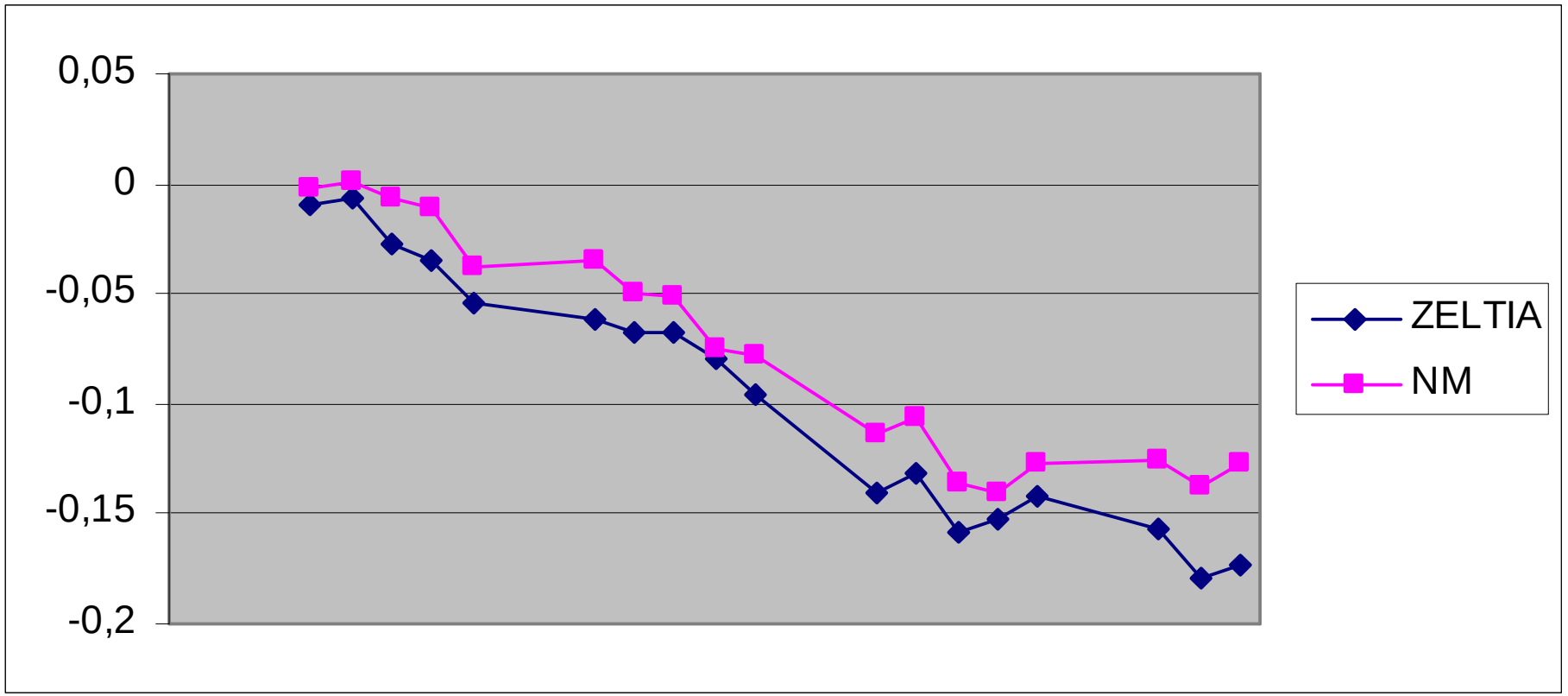
FUENTES DE FINANCIACIÓN 2008



EVOLUCIÓN VALOR ZELTIA – NUEVO MERCADO

2 A 28 DE NOVIEMBRE

- **Ampliación de capital: €15,6m por el 1%**



Clinical Development

Pedro Santabárbara
VP, Strategic Development & Medical Affairs

Yondelis®

Yondelis® Development Plan

SOFT TISSUE SARCOMA Data presented at - ASCO 06 & 07 - ESMO 06 - AACR 07	- STS-201: pivotal trial completed (n=270), led to - EC approval in September 2007 - 90% tumor control in myxoid liposarcomas - 1st line trial under discussion with EMEA in translocation-related sarcomas
OVARY Data presented at - ASCO 06 - ESMO 06	- Phase III trial comparing Yondelis® + Doxil *vs* Doxil in second line - Recruitment completed May 07 (n=672) - Filing expected in 2008
BREAST Data presented at - ASCO 00	- 2 Phase II trials completed - Activity in heavily pre-treated, unselected patients - Trial ongoing with pharmacogenomic selection
PROSTATE Data presented at - ASCO 05	- Phase II trial ongoing - Pharmacogenomic approaches being explored - Potential development in combination
LUNG	- Phase II trial planned, pharmacogenomic selection

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Yondelis® in Soft Tissue Sarcoma

- Sept 07 – European Commission approval based mainly on STS-201 trial results
- Yondelis dose/schedule: 1.5 mg/m^2 q3wk 24-h
- 1st line pivotal trial in translocation related sarcomas under discussion with EMEA

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STB: indicación aprobada

EMEA: "Yondelis® (q3wk 24-h) is indicated for the treatment of patients with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide or who are unsuited to received these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients"

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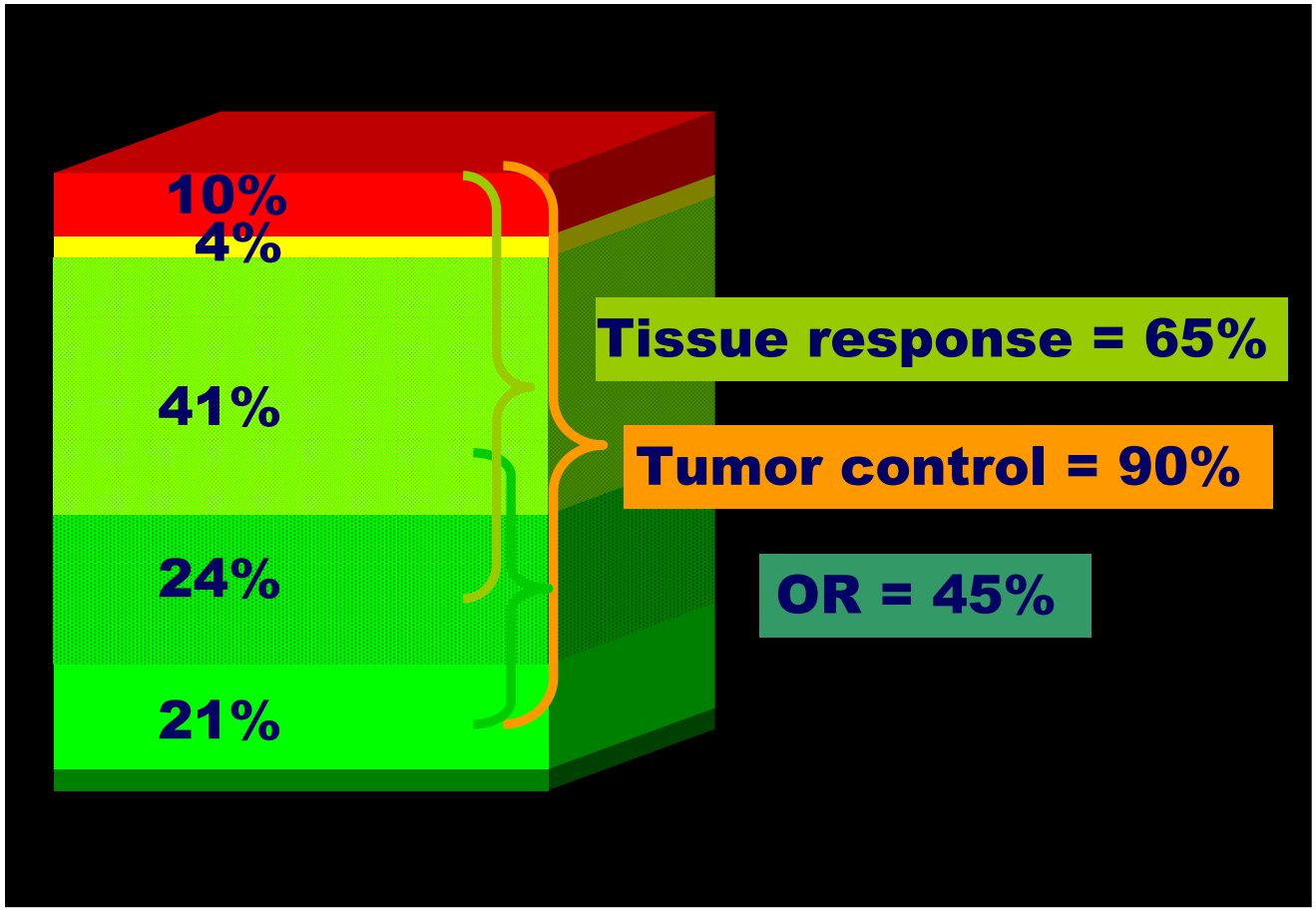
Yondelis® in Advanced Myxoid Liposarcomas
Patterns of Tumor Response

- PD
- SD
- SD/MR + tissue resp
- Delayed resp
- PR
- CR



F.Grosso_et al ASCO 07

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Yondelis Neoadjuvant Trial in Myxoid Liposarcomas - Key Design Features

- First Yondelis® trial in the neoadjuvant (pre-surgery) setting
- Treatment schedule: 1.5 mg/m^2 q3wk 24-h
- Primary objective: determine the pathological complete response rate in patients with localized myxoid liposarcomas
- Secondary objective: correlate molecular parameters in patient samples with clinical outcomes
- 22 patients to be treated in ~20 months

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Translocation Related Sarcoma Pivotal Trial
Key Design Features

- 1st line randomized phase III trial in TRS
- Treatment schedules (randomized)
  - **Trabectedin:** 1.5 mg/m^2 q3wk 24-h
  - **Doxorubicin-based chemotherapy**: as single agent or in combination with ifosfamide
- Primary endpoint: PFS centrally assessed in all randomized patients with centrally confirmed pathologic diagnosis of TRS
- Secondary endpoints: RR, OS, safety
- Expected 55% reduction in the relative risk of PD with Yondelis® (hazard ratio=0.45)
- Approximately 80 patients with confirmed TRS to be enrolled (~ 2 years)

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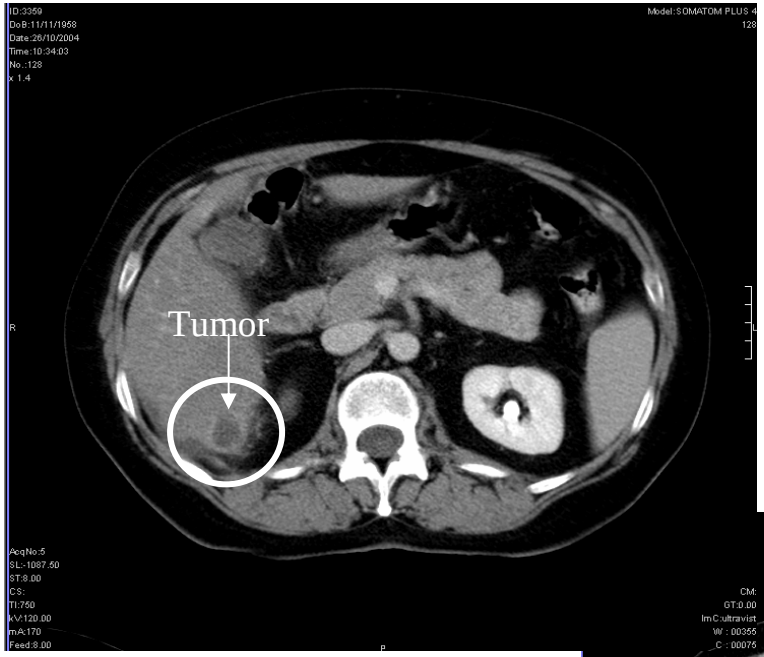
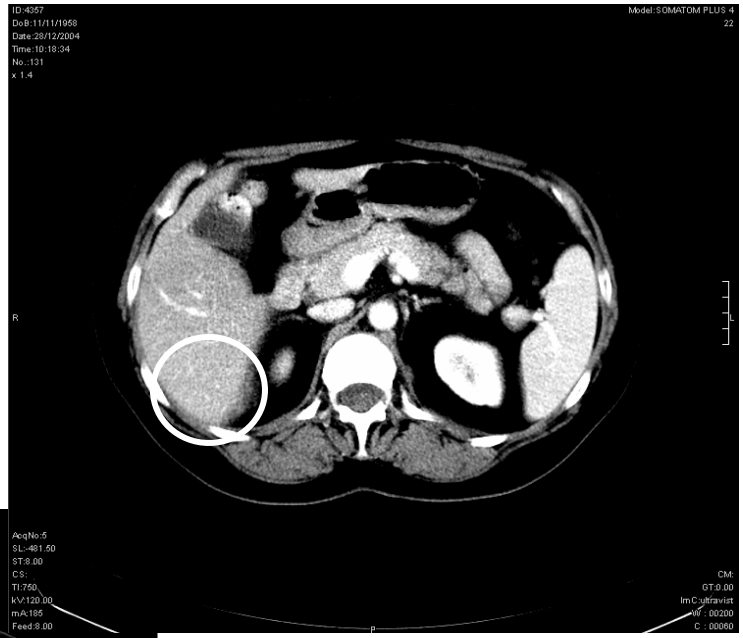
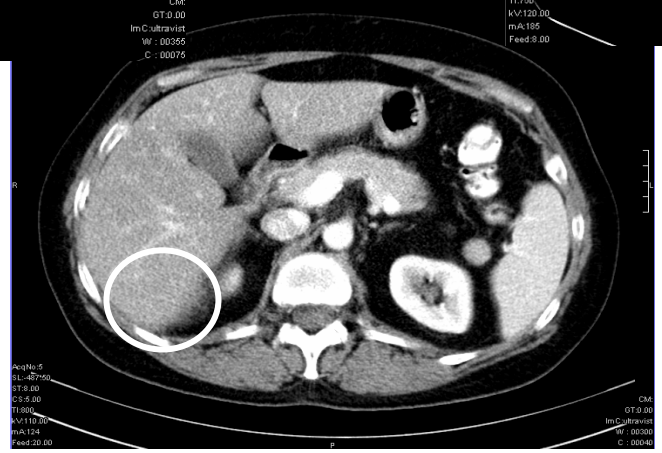
Yondelis® in Ovarian Cancer
Phase II Tumor Response



Baseline



Complete response
after 2nd cycle



Confirmed complete response after
4th cycle

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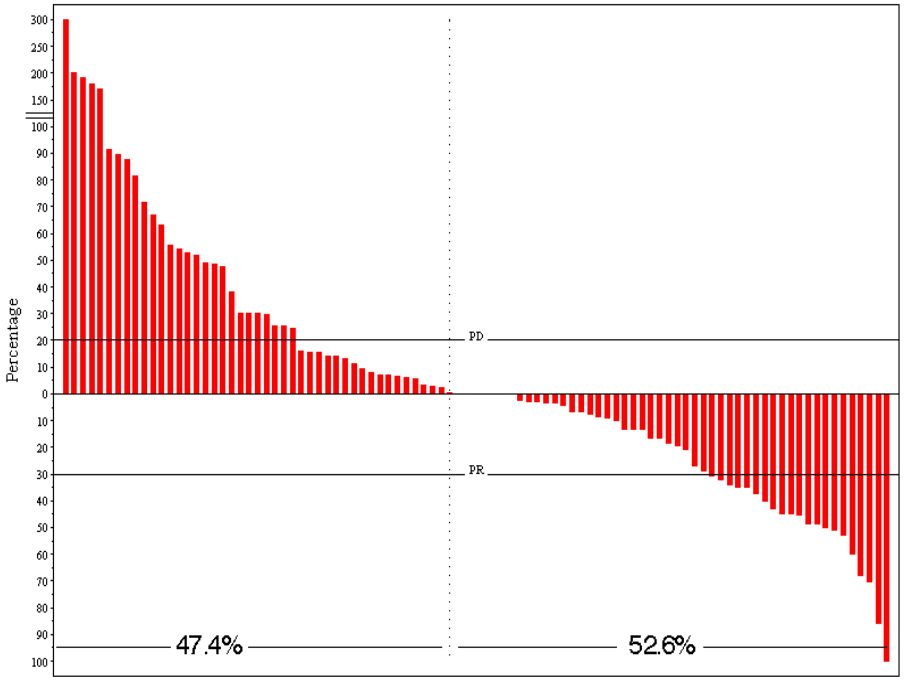
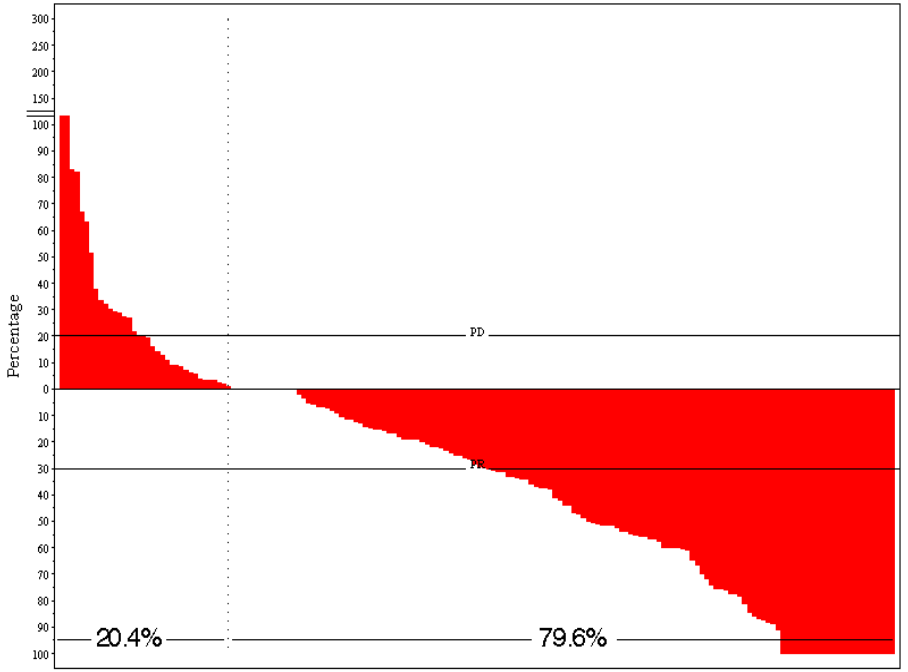
Yondelis® Single Agent in Advanced Relapsed Ovarian Cancer Impact on Tumor Growth

Platinum resistant population (n=95)



Platinum sensitive population (n=176)



Ref. S. McMeekin, J. M. del Campo et al ASCO'07

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Yondelis® in Ovarian Cancer
Pooled Analysis of Phase II data

	Platinum resistant (n=107)	Platinum sensitive (n=187)
CR	0 (0%)	20 (10.7%)
PR	8 (7.5%)	48 (25.7%)
CR+PR	8 (7.5%) 95% CI (3.3-14.2%)	68 (36.4%) 95% CI (29.5-43.7%)
SD	46 (43%)	73 (39%)
PD	50 (46.7%)	38 (20.3%)
NE	3 (2.8%)	8 (4.3%)

Ref. S. McMeekin, J. M. del Campo et al ASCO'07

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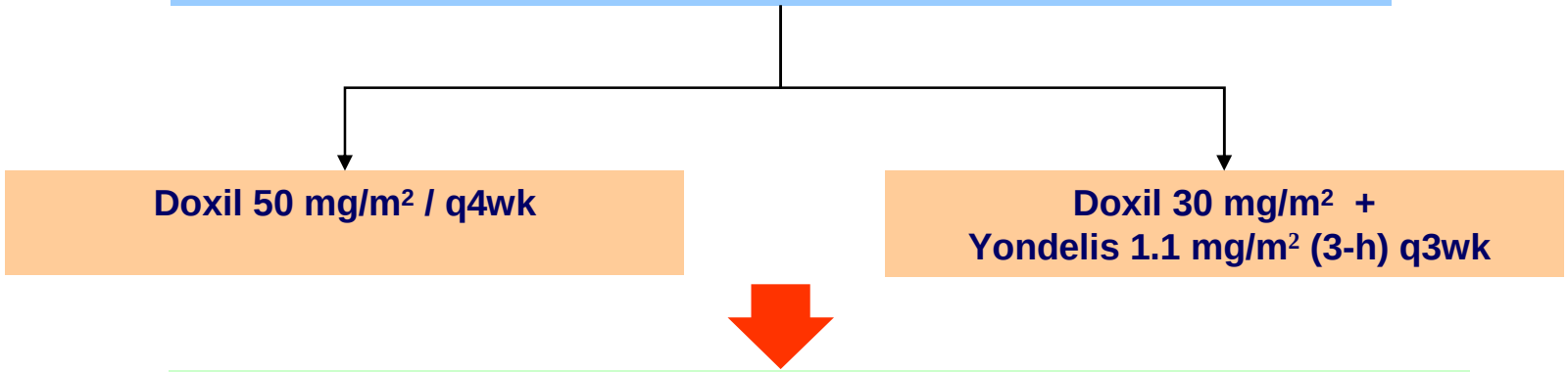
Yondelis® in Ovarian Cancer
Phase III Randomized Trial (OVA-301)

Began April 2005, recruitment completed. Filing expected 2008

Metastatic / Advanced Ovarian Cancer

Relapsed after first line with platinum based chemotherapy



Primary end point

PFS (16 wk to 22 wk), 415 events per independent review needed

Secondary end points

Overall Survival (62 wk to 83 wk), 520 events needed,

ORR, Safety

Positive Futility Analysis by IDMC

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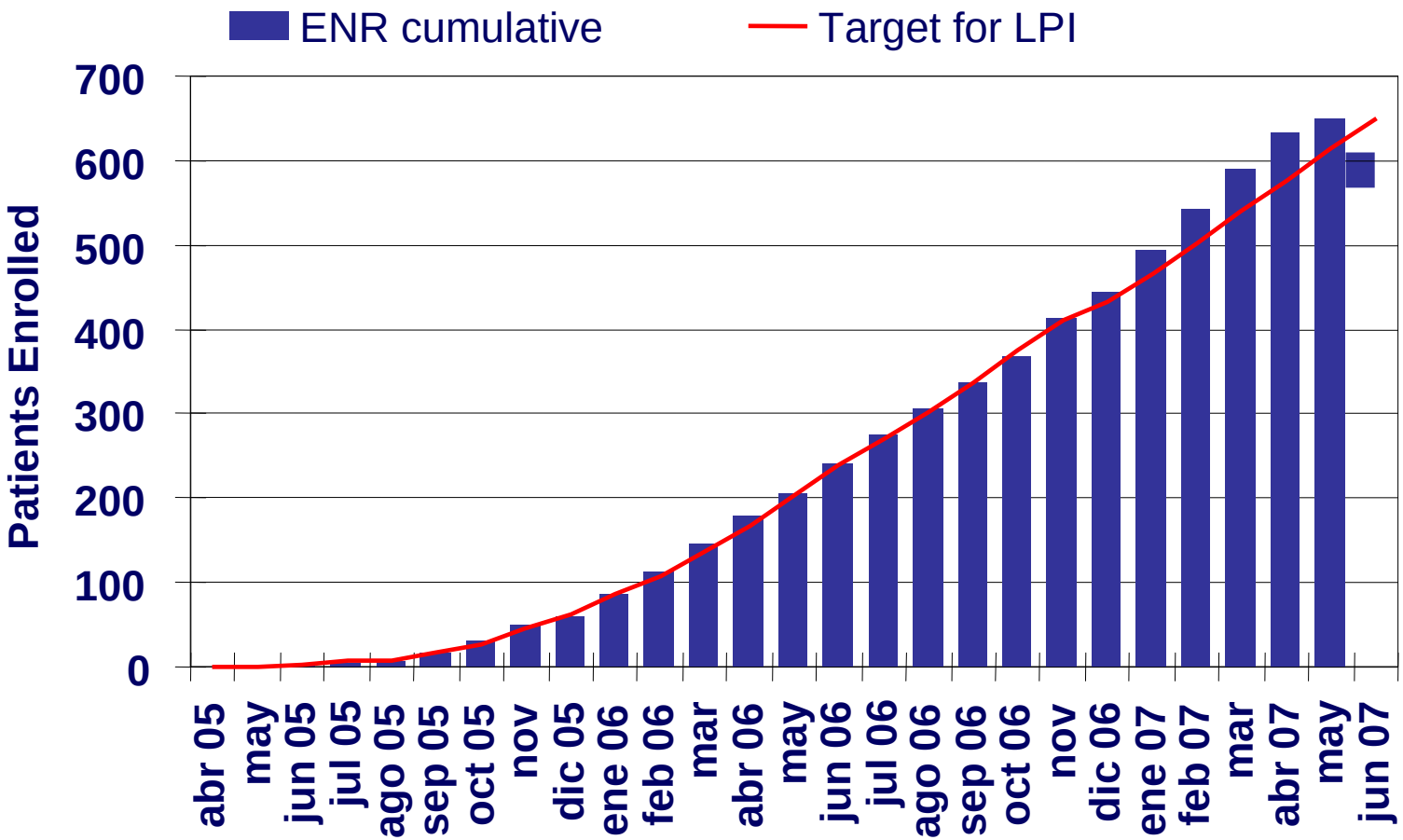
ET743-OVA-301
Enrollment by month

Total N = 672



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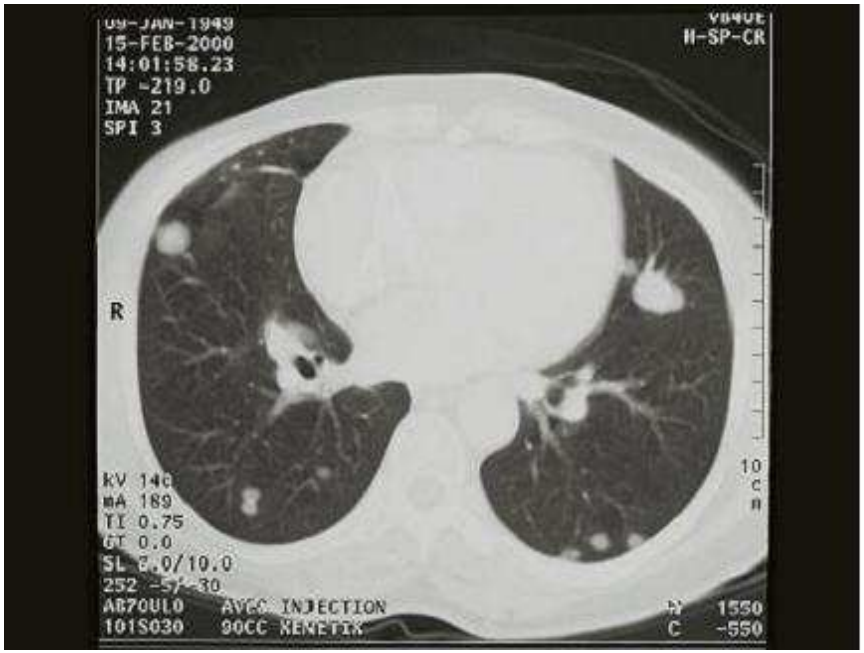
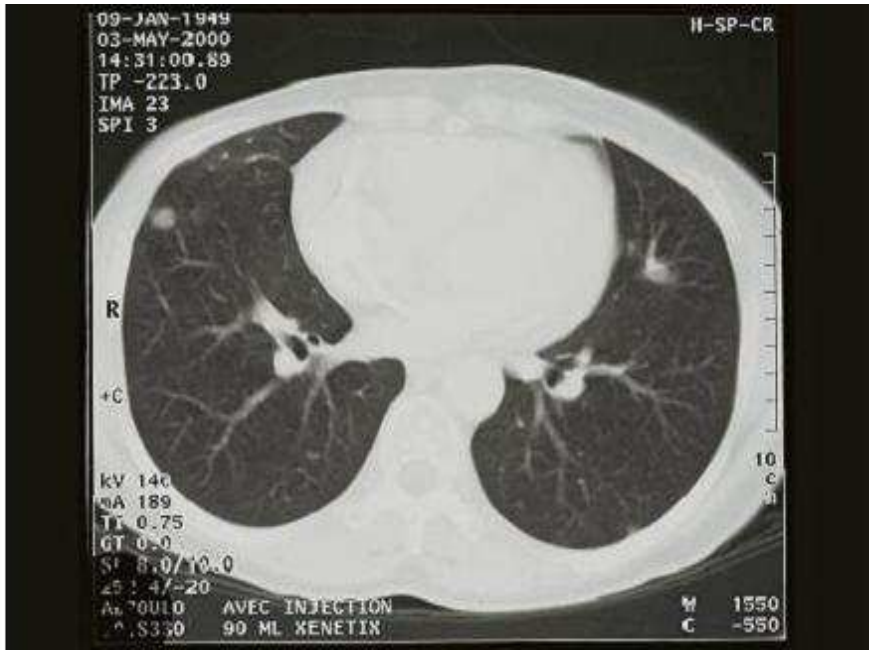
Yondelis® in Advanced Pretreated Breast Cancer





Baseline **PR after 2 cycles**

L. Zelek et al. BJC 2006

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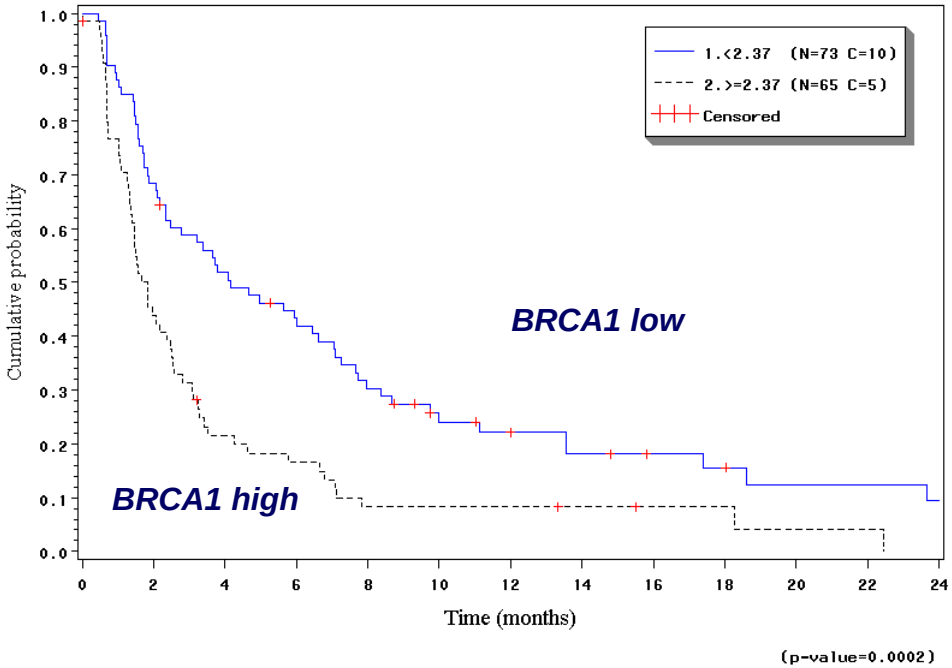
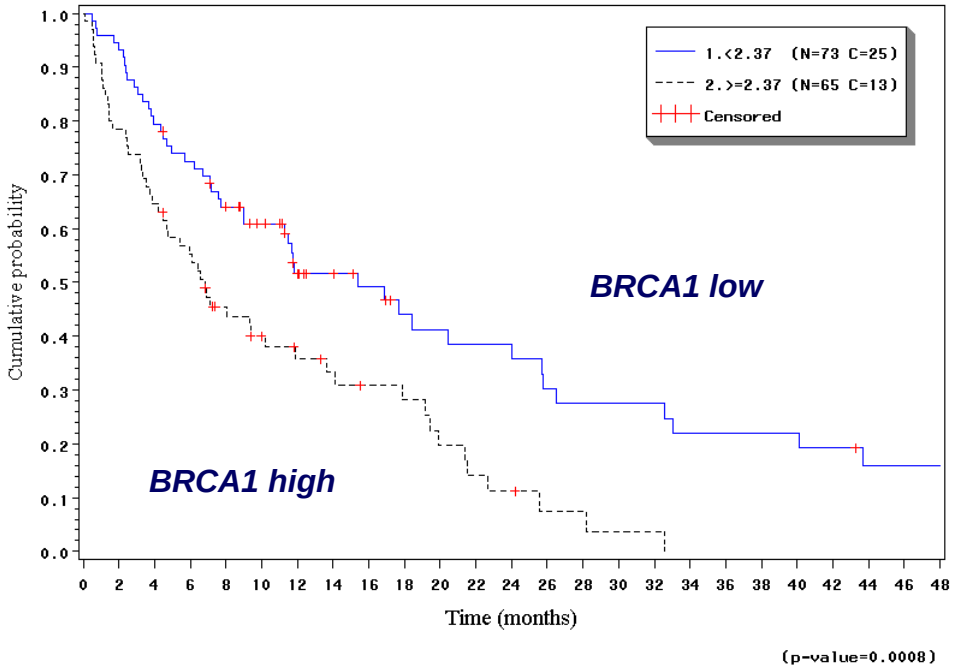
Molecular Signature of Sensitivity to Yondelis®

Impact of homologous recombinant repair functionality in the outcome of sarcoma patients treated with Yondelis®

PFS



Survival



P. Schöffski et al. AACR'07

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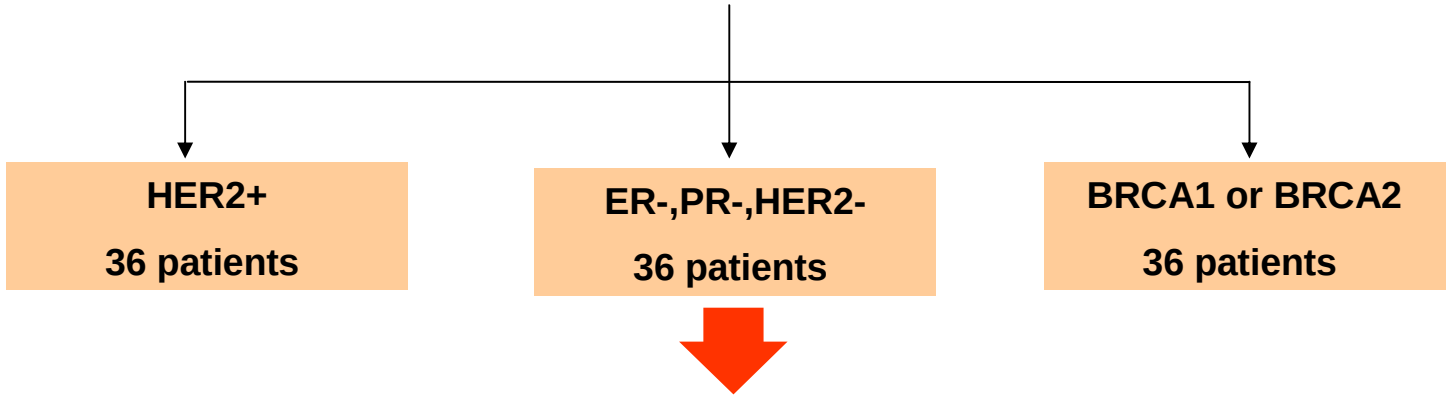
Yondelis® in Breast Cancer
Stratified Phase II Trial

108 MBC patients previously treated with anthracyclines + taxanes

3 cohorts



Sites in Italy, France, Israel, Poland & USA

Primary end point: objective response (externally reviewed)

Secondary end points: duration of response, PFS, safety profile

- **Futility analysis planned in each cohort with 36 evaluable patients**
- **If ≥6 /36 responses study will continue up to 107 patients per cohort**
- **Recruitment started in July 07; 35 patients enrolled in 5 months**
- **Final results expected Q209**

rma
Zeltia Group

Yondelis® in Prostate Cancer
Key Design Features

- Phase II trial with 2 Cohorts of patients treated
  - Cohort A (until May 2006)
    - 0.58 mg/m^2 3-h qwk
    - men with 0-1 prior chemotherapy regimens
    - 33 patients enrolled and treated
  - Cohort B (ongoing)
    - 1.2 mg/m^2 24-h q3wk
    - men previously treated with docetaxel
    - 9 patients enrolled and treated
- Primary endpoint: PSA response (PSA Working Group criteria)
- Secondary endpoints: Safety, RD, TTP

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Yondelis® in Prostate Cancer Results – Cohort A

- 32/33 men evaluable for response
- PSA response:
  - Overall: 4/32 (12.5%)
  - Taxane-refractory patients: 3/19 (16%)
  - Chemo-naïve patients: 1/8 (12.5%)
  - PSA declines of 95%, 77%, 72% and 54%
  - Duration of response: 13.8, 5.5, 4.9 and 4.6 months (median 5.2 mo.)
- The four PSA responders experienced significant symptomatic improvement (decreased pain)
- Three additional men with initial PSA decline >25% (did not meet 50% threshold)

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APLIDIN®

Aplidin® Development Plan

MULTIPLE MYELOMA Data presented at - AACR 07 - Inter. Symposium in MM 07	- Phase II trial after failure of standard treatment - Orphan Drug designation by FDA and EU - Development in combination (bortezomib / lenalidomide)
RENAL Data presented at - ESMO 06	- Activity as single agent in pre-treated patients - Combination-based development under implementation (sorafenib, bevacizumab, temsirolimus)
MELANOMA Data presented at - ESMO 05	- Activity as single agent - Phase I / II in combination with DTIC ongoing
NEUROBLASTOMA Data presented at - ASCO 06	- Phase I pediatric trial: Activity as single agent in Neuroblastoma - Scientific advice for phase II pivotal trial (EMEA)

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Aplidin® in Refractory/Relapsing Multiple Myeloma

- Treatment schedule
  - Aplidin® 5 mg/m^2, 3-h iv infusion, q2wk until progression
  - Given as single agent for 3 cycles
  - Dexamethasone (40 mg/day) day 1-4
    - Added after 3 cycles if progressive disease
    - Added after 4 cycles if stable disease
- 21 evaluable patients needed in II stage APL/DXA arm

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Aplidin® in Refractory/Relapsing Multiple Myeloma
Efficacy in evaluable patients

		Before amendment APL monotherapy	After amendment APL & DXA
Treated patients		23	15*
Too Early for evaluation		-	4
Total Evaluable for Efficacy		21	11
Efficacy	PR	1 (4.8%)	3 (27.3%)
	MR	1 (4.8%)	2 (18.2%)
	SD	7 (33.3%)	3 (27.3%)
	PD	11 (52.4%)	3 (27.3%)
	N/E	1 (4.8%)	0 (0.0%)

* 3 pts not received Dexa: #231, #232 & #238

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Zeltia Group

Aplidin® in Multiple Myeloma Clinical Development Plan

In 2nd line advanced Myeloma (I)

- Phase I-II: APLIDIN® + dexamethasone + 3rd agent (lenalidomide or bortezomib)
- Dose escalation phase:
  - APLIDIN® (1.8 mg/m^2 → 2.5 mg/m^2 → 3 mg/m^2) administered d1,8,15 q4wk or d1,15 q4wk regimen; 3-6 pts per dose level
  - Lenalidomide : One level below the RD → RD (25 mg/day, days 1 to 21 in 28-day cycles)
  - Dexamethasone: 20 mg/day, days 1-4 q4wk
  - Up to 20 pts in 4 centers (USA/EU)

Pharma Mar
Zeltia Group

Aplidin® in Multiple Myeloma
Clinical Development Plan

In 2nd line advanced Myeloma (II)

- Phase II: Further expansion up to 40 patients at the RD
- Phase III: APLIDIN® + lenalidomide + DEX

  vs.

  lenalidomide + DEX

  - 50% increase in TTP: 9 vs. 6 months
  - 150 patients / arm
  - Accrual phase ~ 30 months (assumes 10 pts/mo.)
  - Statistical analysis performed 39 months after study onset
  - 256 progression events

Pharma Mar
Zeltia Group

Aplidin® in Multiple Myeloma
Clinical Development Plan

In 3rd line advanced Myeloma

- Patients who progress on the control arm (lenalidomide + DEX) cross-over to APLD + DEX (up to 50 patients) if > 20% RR (to be confirmed) of response: potential for accelerated approval

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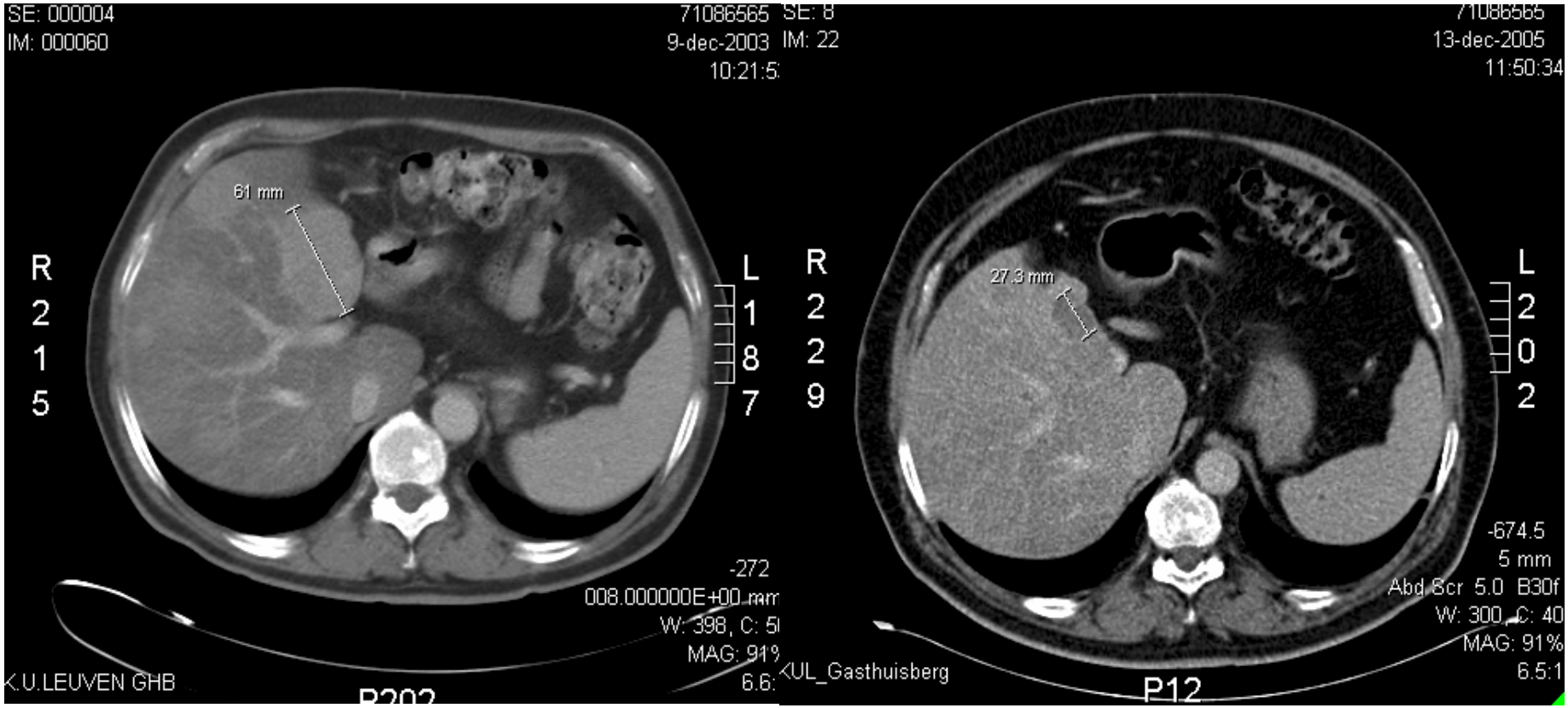
Zeltia Group

Aplidin® : Phase II – Renal Cell Carcinoma

Long-lasting Response



(courtesy of Prof Schoffsky)

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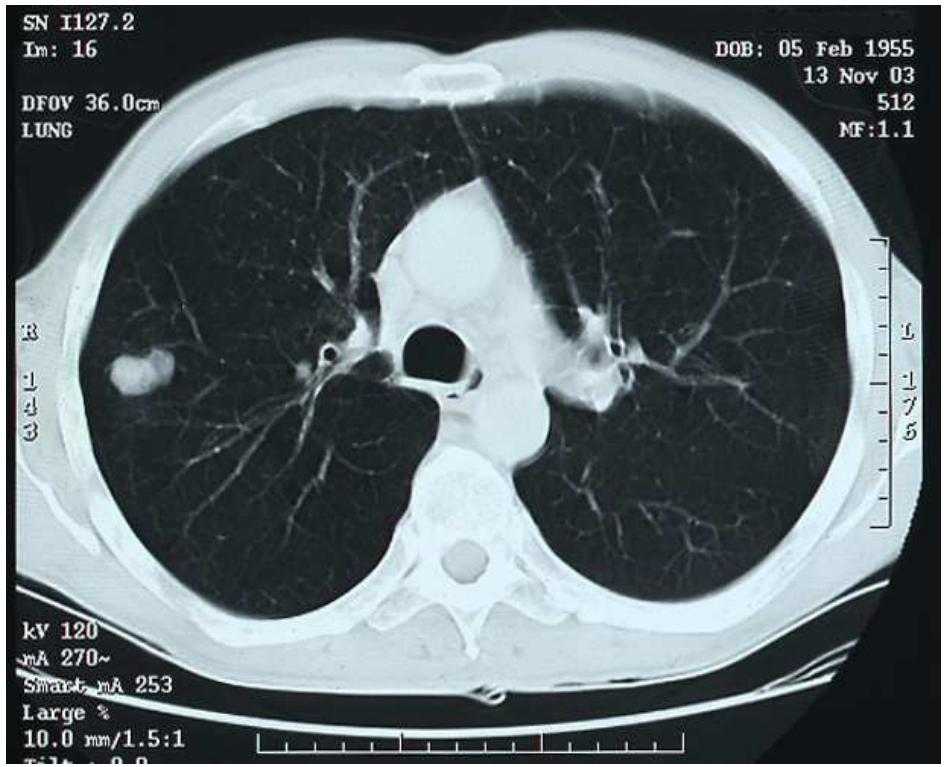
Aplidin® phase II Study in Patients with Advanced Pretreated and Progressive Renal Cancer

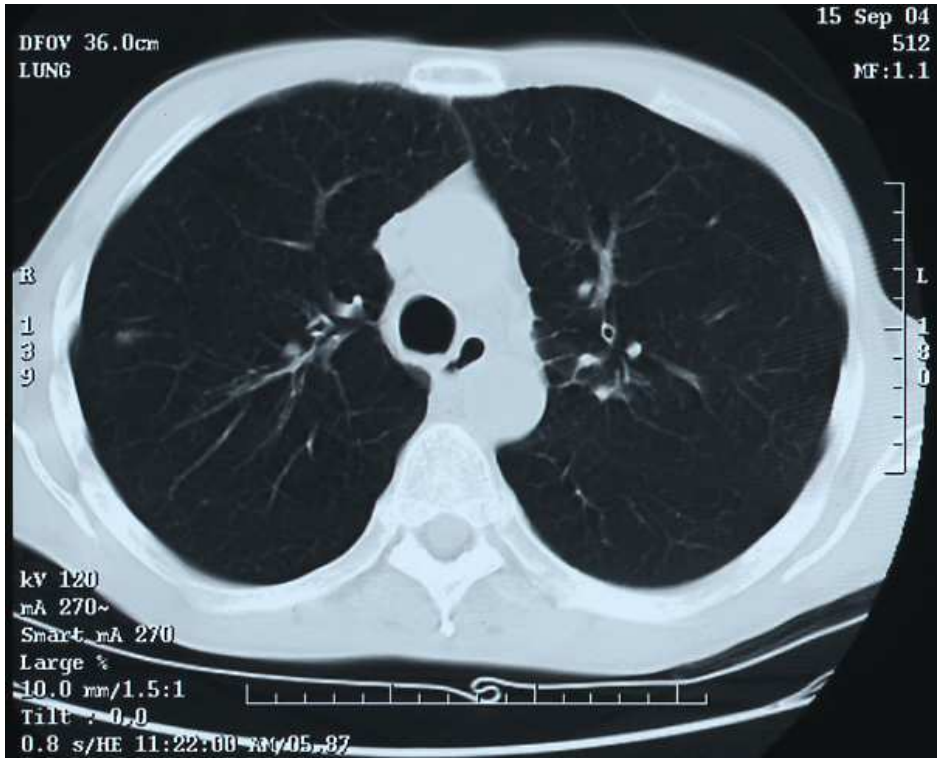
No. Patients	PR		SD > 3m		Rate Tumor Control
38	2	23.3+ m. 13.8+ m.	7	(3.3 – 12) (median 8 m)	9/ 38 (24%)

MA Climent et al. ESMO'06

Pharma Mar
Zeltia Group

Aplidin® Phase II Study in Advanced Pretreated Melanoma Long Lasting Response





Baseline **+21 cycles**

Courtesy of Dr T Eisen

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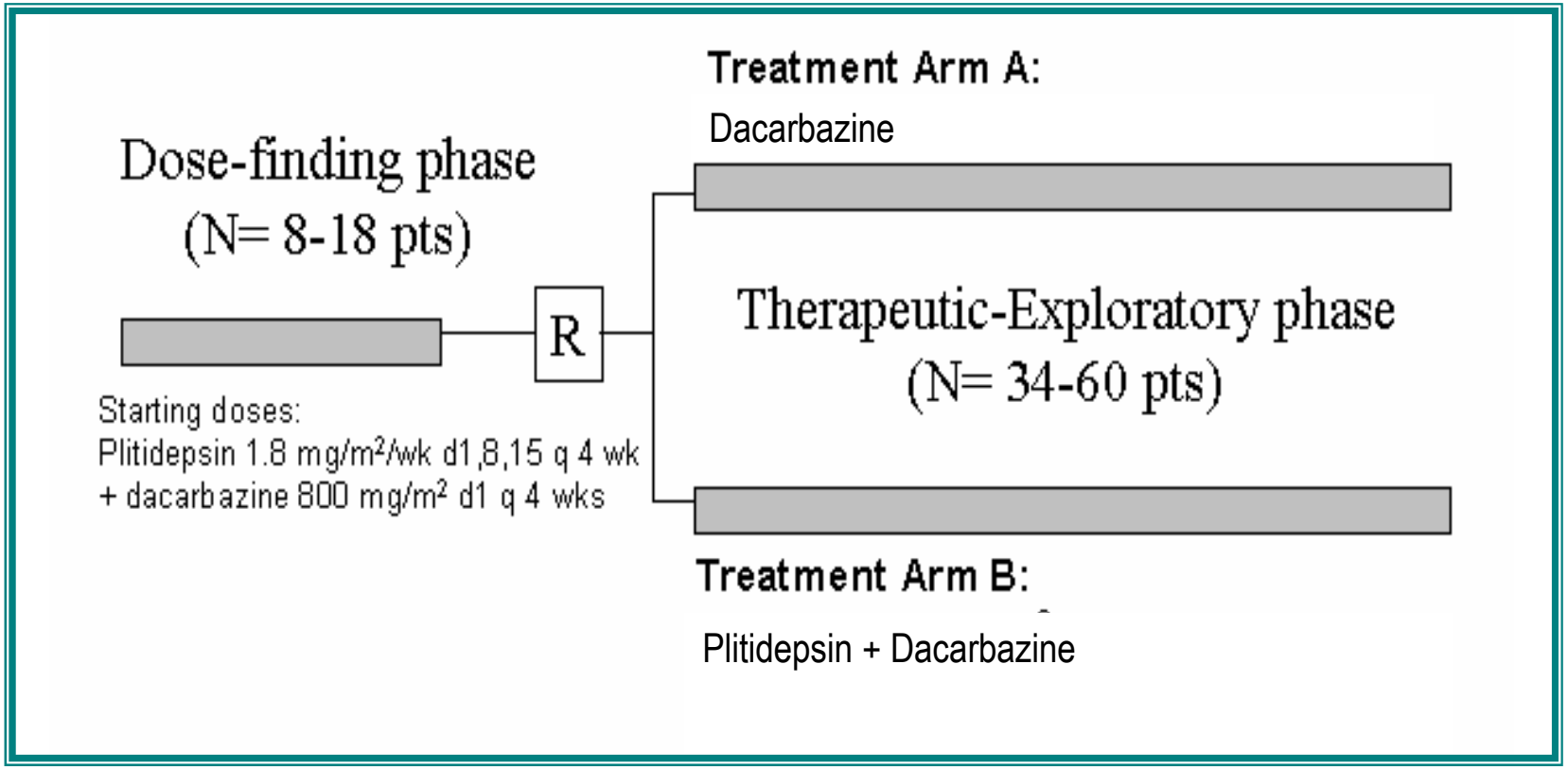
Zeltia Group

Aplidin® Malignant Melanoma Combination study



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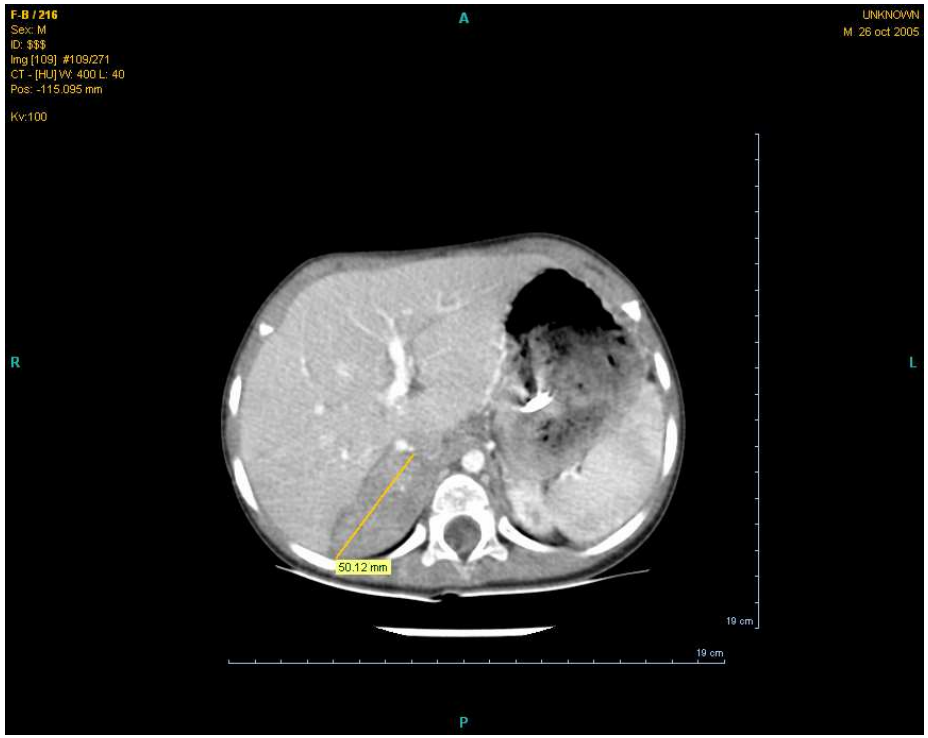
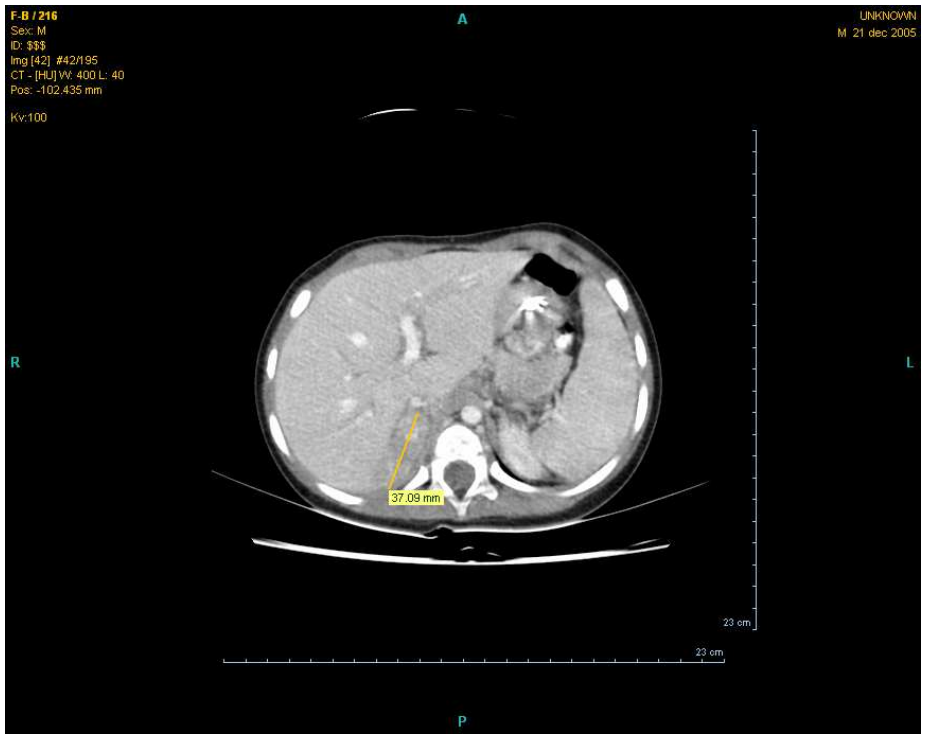
Aplidin® in Neuroblastoma
PR in Phase I

Poorly differentiated Neuroblastoma, 11 previous Chemotherapy lines



October 2005
Baseline



December 2005
After 3 infusions

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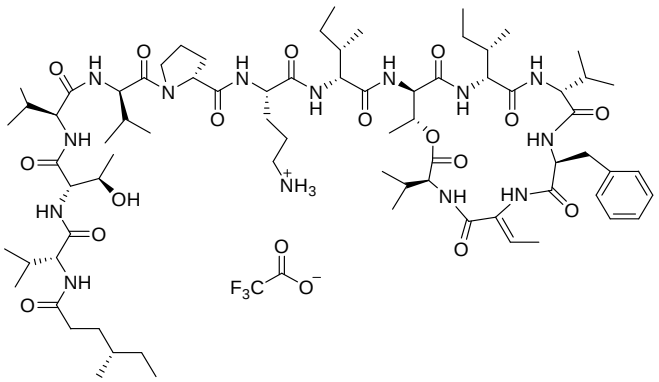
Compounds in Early Development

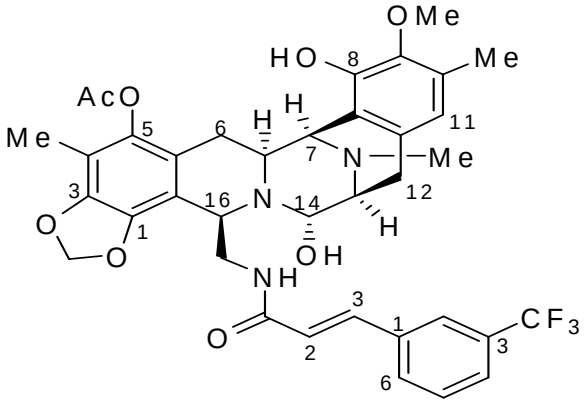
PM02734



Solid tumors

PM02734 + Erlotinib

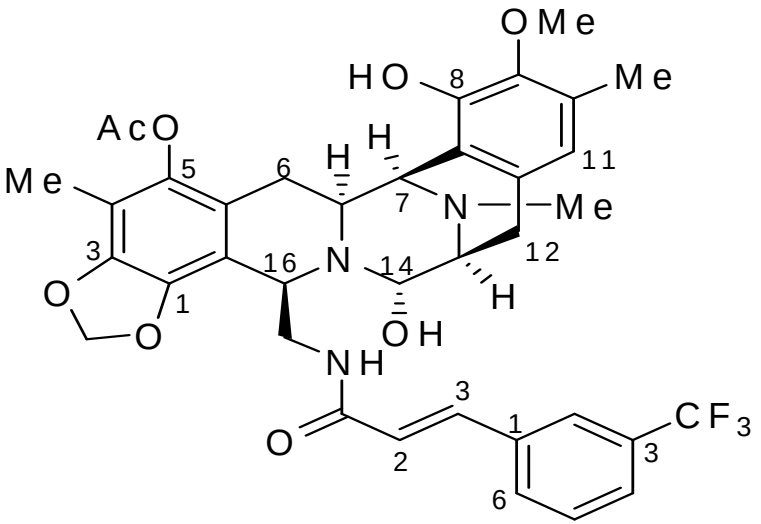
Zalypsis®



Solid tumors

2007 2008 2009

Zalypsis



Zalypsis (I)

- 4 clinical trials with different schedules of administration
- All trials ongoing:
  - **PM104-A-001-04: 1h-3h d1 q3wk.**
    - **1h:** MTD: 3600 µg/m^2 , RD: 3000 µg/m^2
    - **3h:** 2250 µg/m^2
  - **PM104-A-002-05: 1h d1-5 q3wk.** 475 µg/m^2
  - **PM104-A-003-05: 24h d1 q3wk.** 3200 µg/m^2
  - **PM104-A-004-05: 1h d1,8,15 q4wk.** 2500 µg/m^2

89 pts treated

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Zalypsis (II)

- Different solid **tumour** types included

- **Well tolerated:**
  - Frequent but generally mild toxicities: nausea, vomiting, anorexia, asthenia, injection site reactions, constipation, diarrhea
  - Dose limiting toxicities: hematological toxicity, emesis, transaminase elevations and asthenia

- **Signs of antitumor activity**: NSCLC, H&N carcinoma, Pleural Mesothelioma, Cervix carcinoma, Bladder carcinoma

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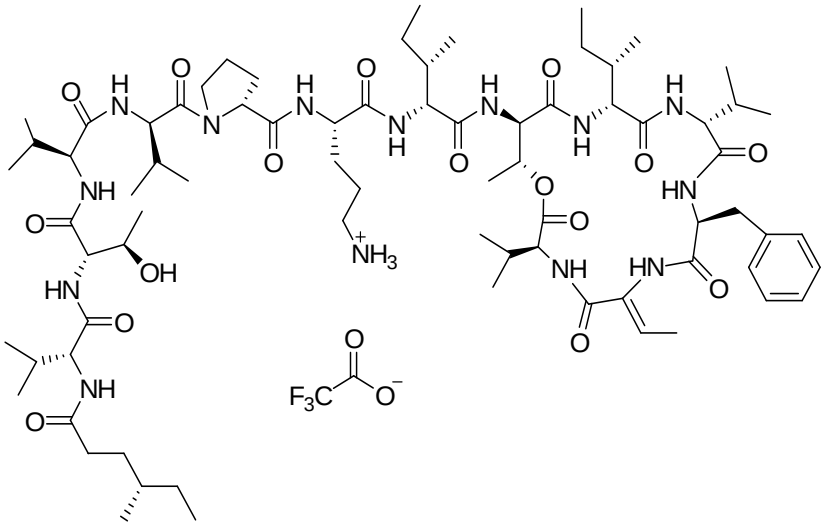
PM02734



PM02734 (I)

- 2 clinical trials with different schedules of administration
- All trials ongoing:
  - **PM02734-A-001-05: 30min d1q 3wk.** 1350 µg/m^2
  - **PM02734-A-002-05: 24h d1 q3wk.** 5467 µg/m^2

49 pts treated

Pharma Mar
Zeltia Group

PM02734 (II)

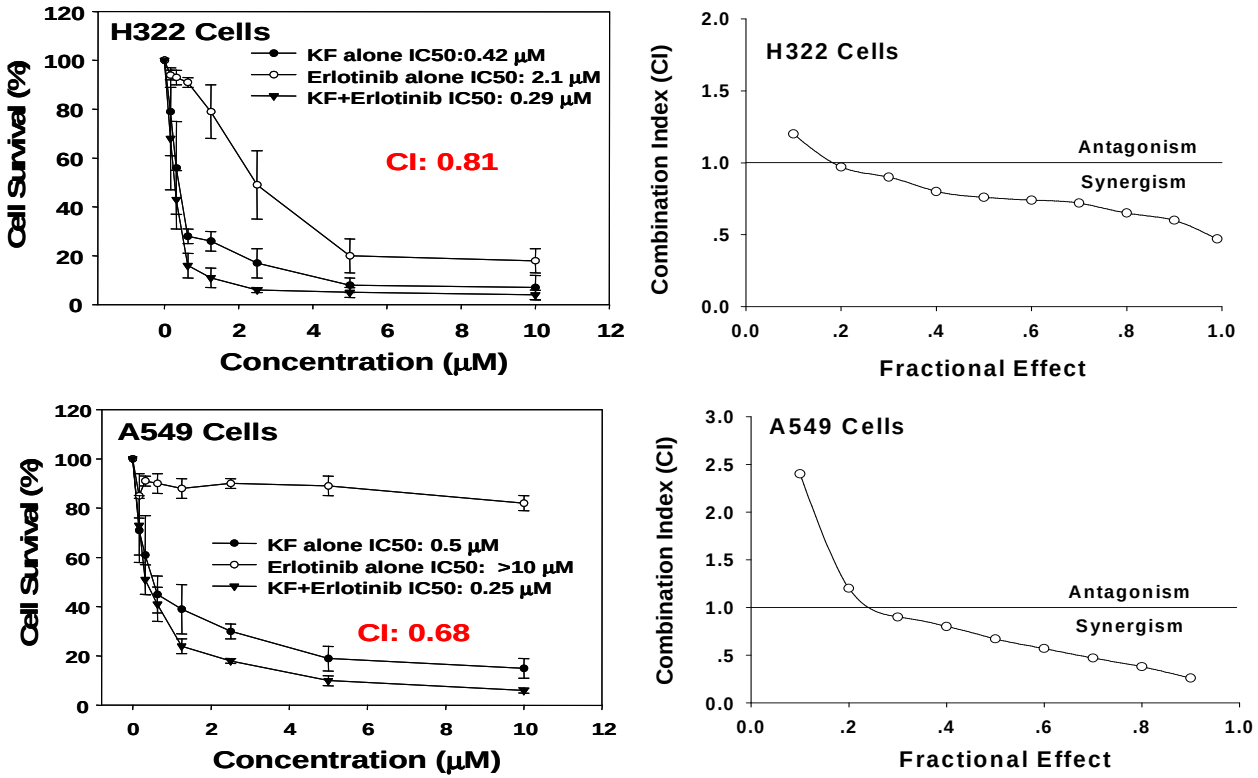
- Different solid **tumour** types included

- **Well tolerated:**
  - Frequent but generally mild toxicities: nausea, asthenia, constipation and pruritus
  - Dose limiting toxicity: transaminase elevations

- **Efficacy**: 1 CR. Large cell ca. esophagus with lymph node metastases at 2430 $\mu g/m^2$, 24-h schedule

Pharma Mar
Zeltia Group

PM02734 + Erlotinib



- In vitro data demonstrate a synergism between PM02734 and erlotinib
- Phase I trial to be implemented in Europe & USA

Pharma Mar
Zeltia Group

Pharmacogenomics of Yondelis

A model for customized – personalized development

José Jimeno MD, PhD

Vice President Scientific Development

“Conceptually, in 2007 therapeutic anticancer intervention in patients with solid tumors still implies the necessity to treat (empirically) a high number of patients to obtain benefit in a (limited) proportion of cases”.

- “The activity of a given drug in patients with advanced cancer is the result of a pharmacodynamic event against a pathway".

- “Such Putative Pathway(s) must be prevalent in cancer cells and relevant to the process of uncontrolled proliferation".

Marginal impact of new therapeutic schemes in survival for hormone-resistant prostate cancer patients

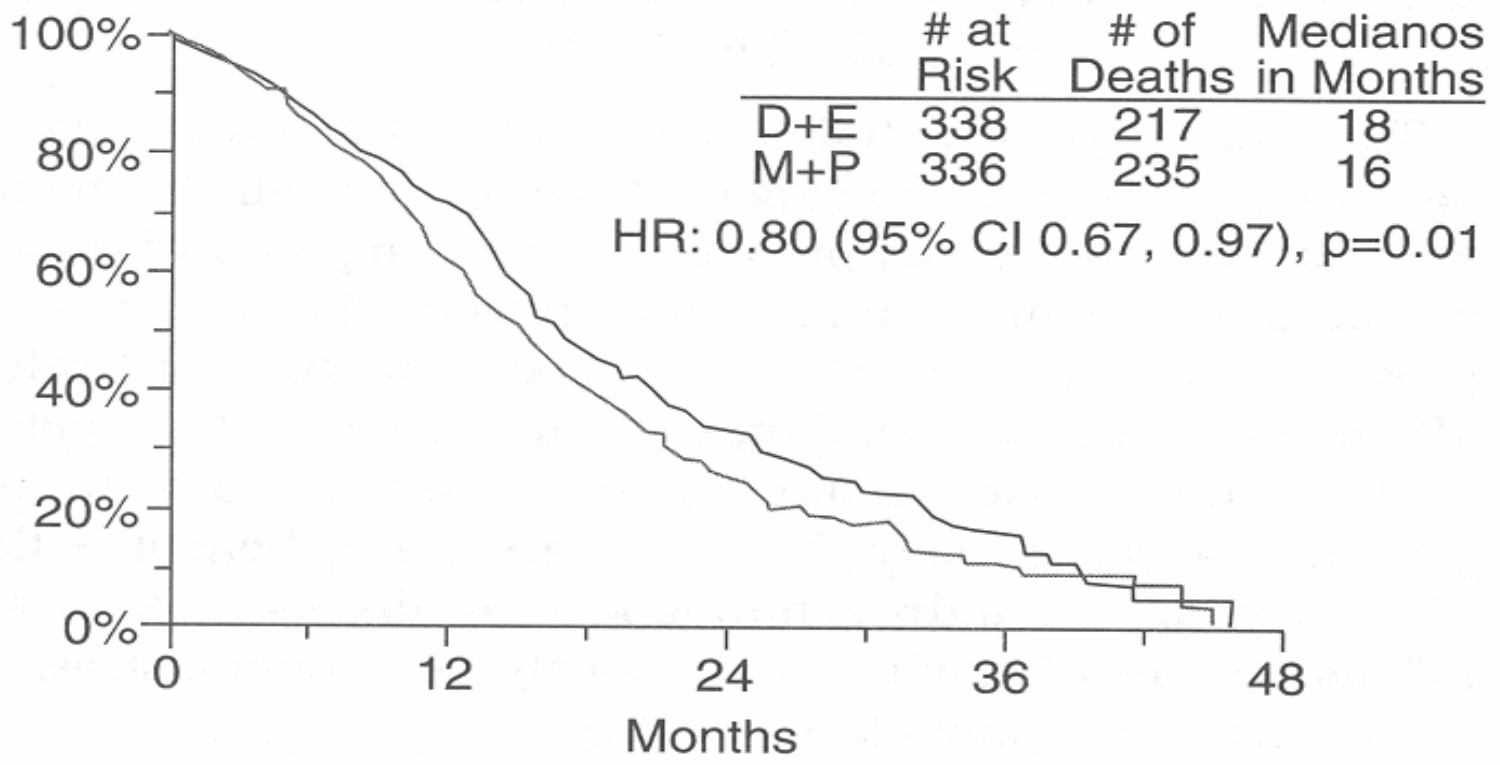
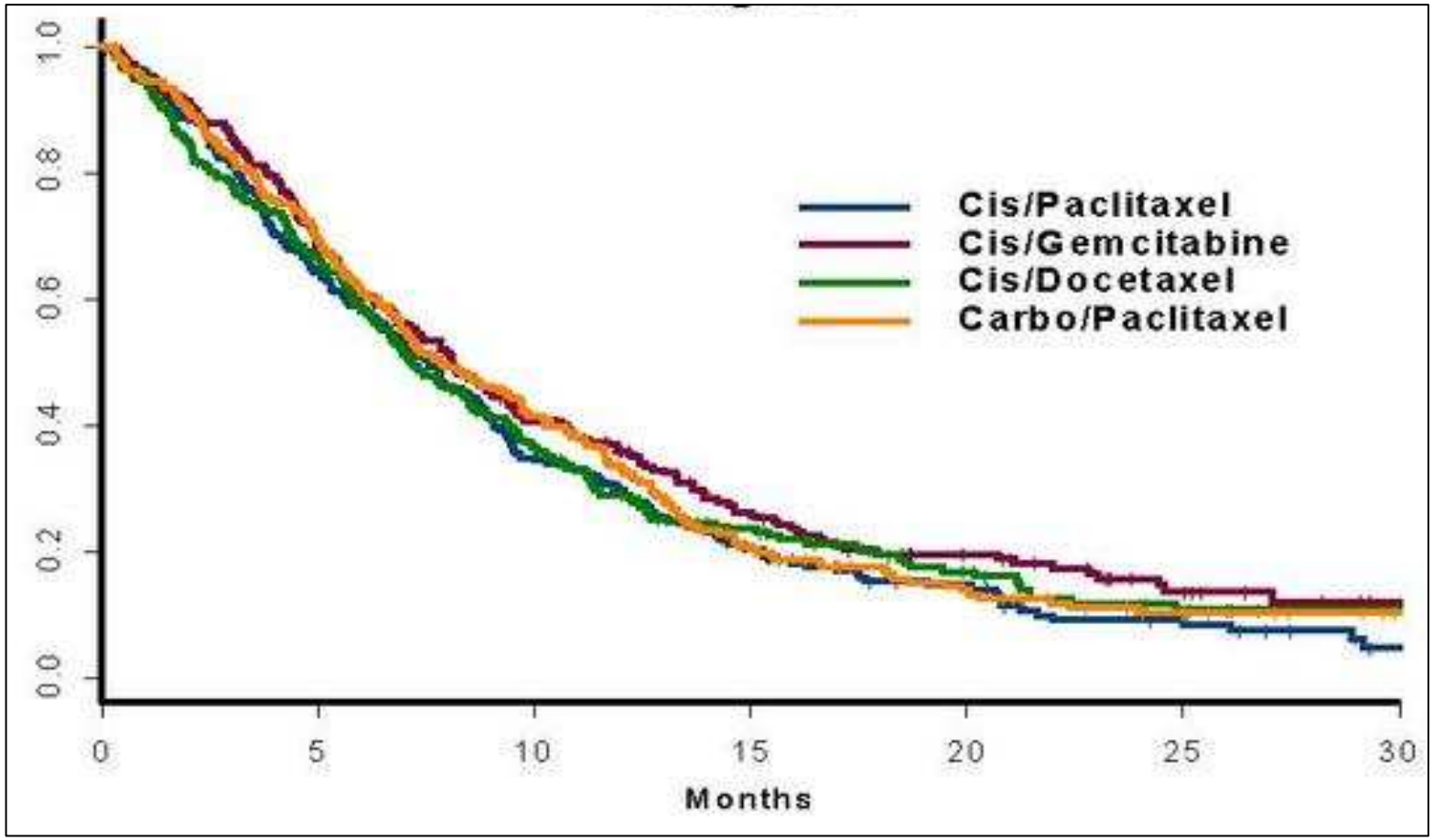


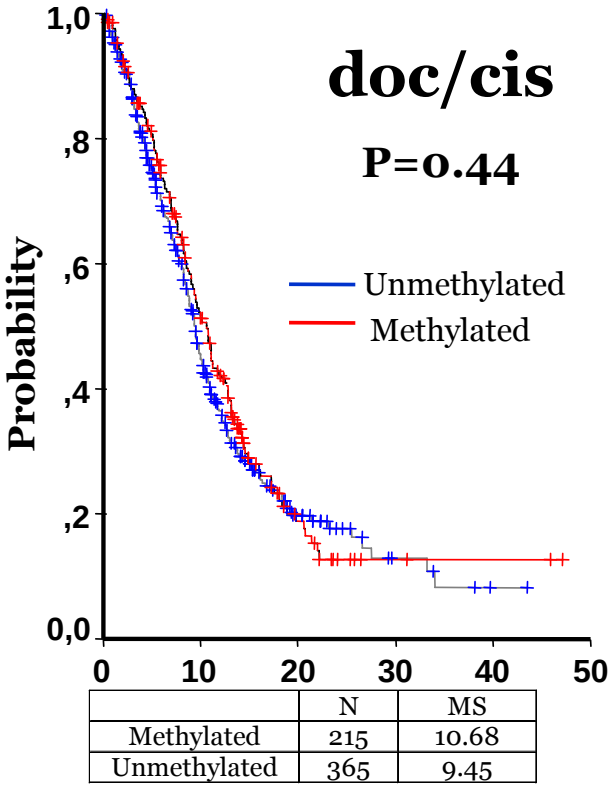
Fig. 3. Comparison of overall survival (OS) for docetaxel plus estramustine (D + E) and mitoxantrone plus prednisone (M + P) (abstract #3). HR = hazard ratio, CI = confidence interval.

NSCLC Stage IV Survival by Treatment Group (ECOG 1504)

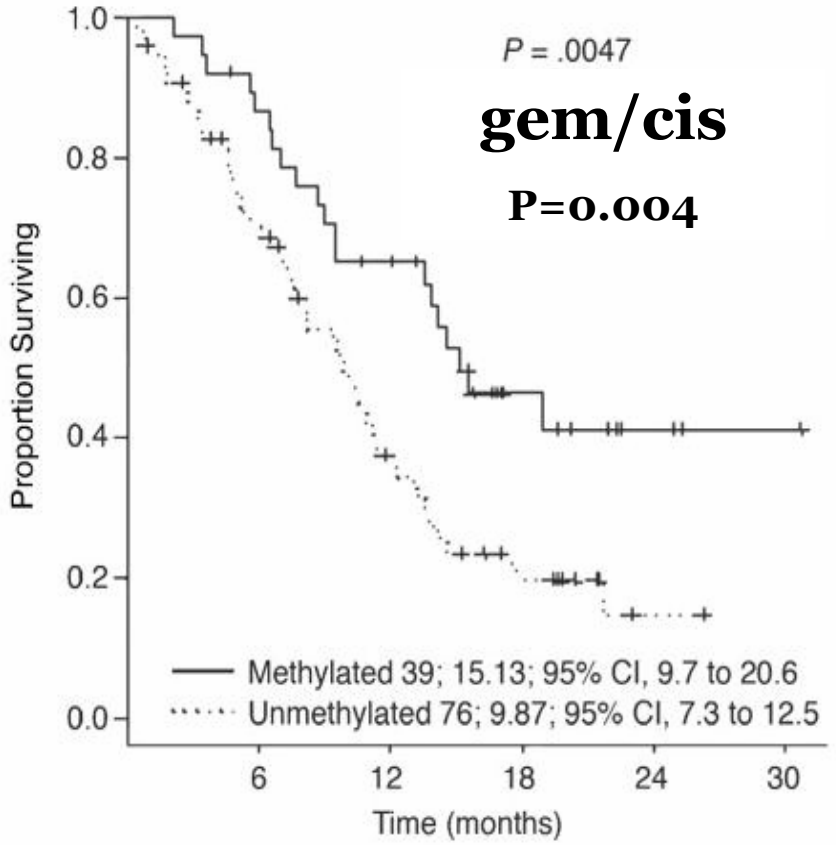


Schiller et al (NEJM, 2002)

14-3-3s methylation: a differential determinant of survival

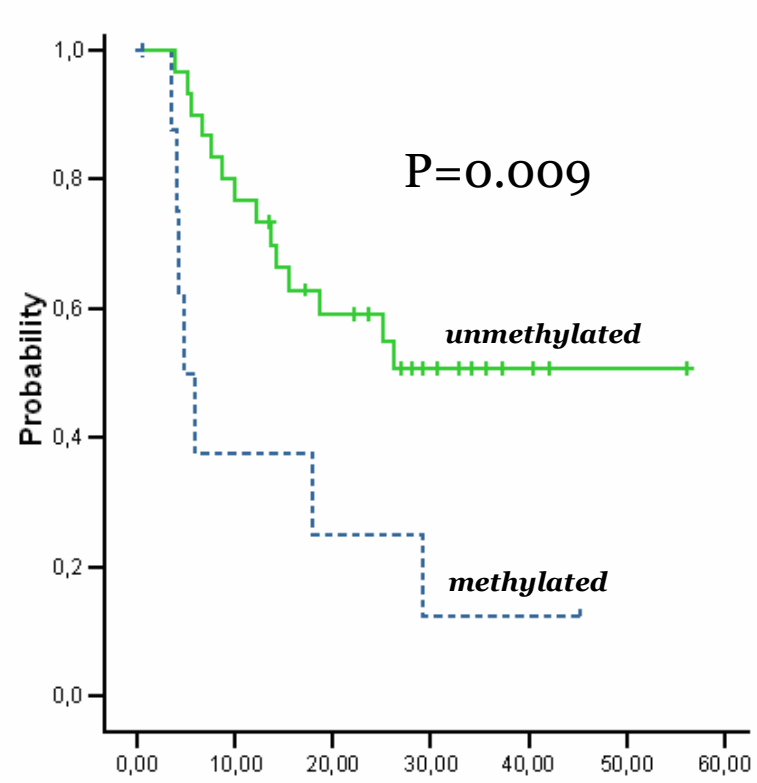


	N	MS
Methylated	215	10.68
Unmethylated	365	9.45



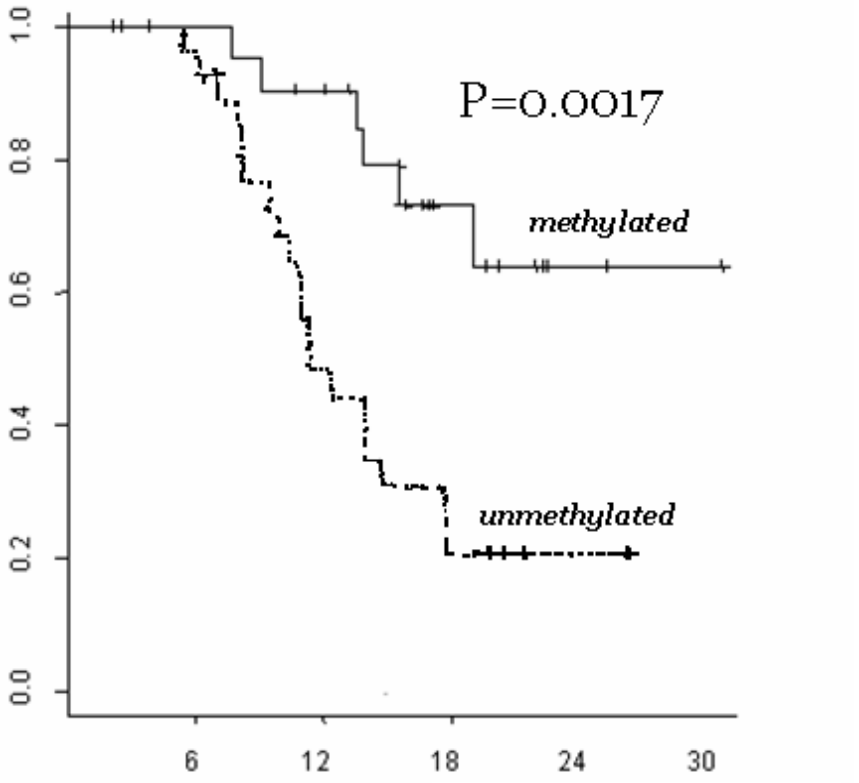
14-3-3s methylation in serum: a prognostic & predictive marker in NSCLC

Resected



Spanish Lung Cancer Group 2006

Stage IV responders to gem/cis



Ramirez et al, JCO 2005

Loss of BRCA1 → lower 14-3-3σ

(Aprelikova et al. J Biol Chem 2001)

An Economic Framework for Targeting Subsets of Cancer Patients Based on Molecular Signatures

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Thomas G. Roberts, MD, MSocSci
Division of Hematology/Oncology
Massachusetts General Hospital

Noonday Asset Management, L.P.
Program on the Pharmaceutical Industry
Massachusetts Institute of Technology

AACR
3 April 2006

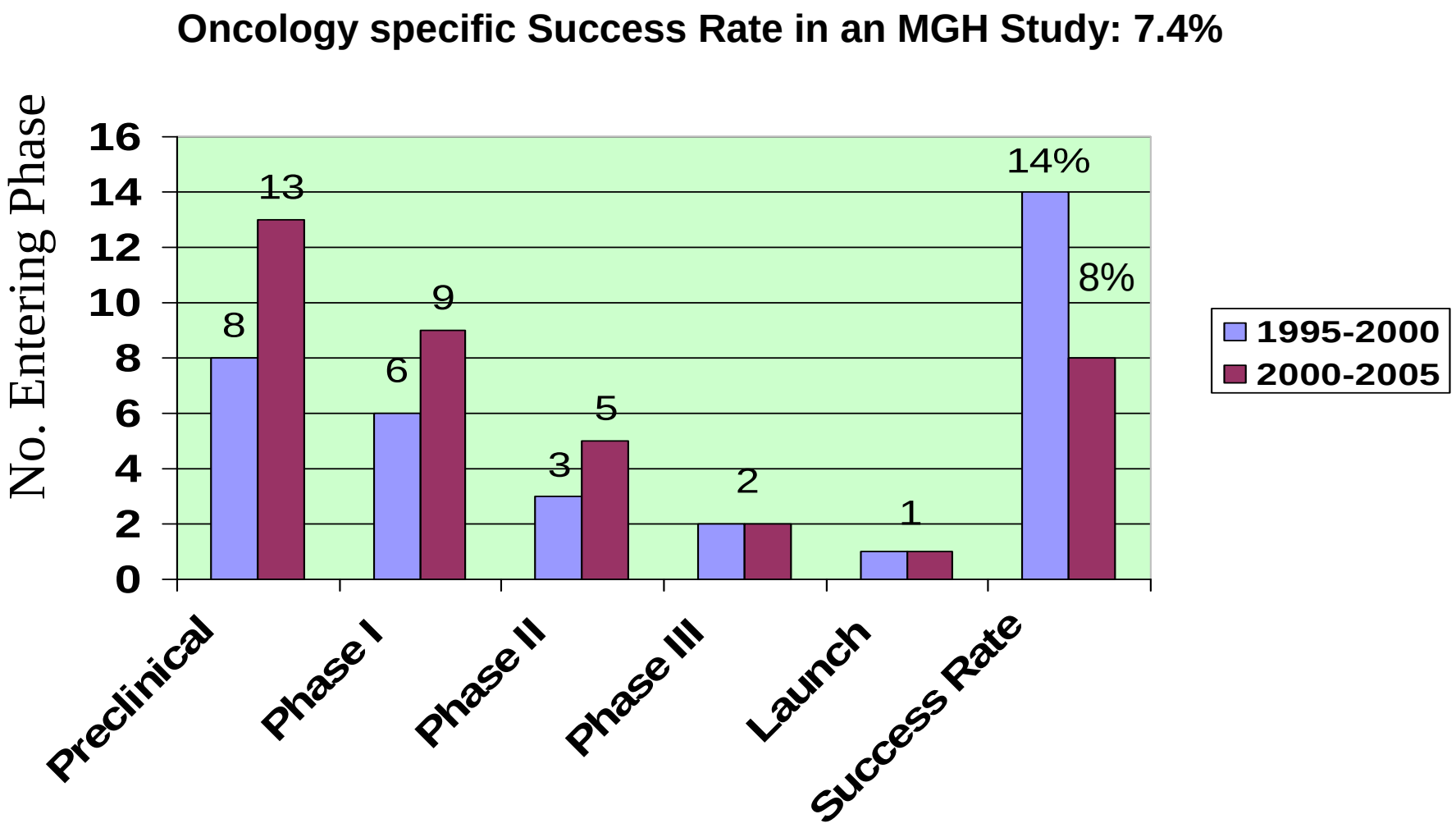
Three Challenges in Cancer Drug Development

1. Continued low success rates of cancer drugs entering clinical trials

2. Societal “Sticker Shock” from the cost of new drugs

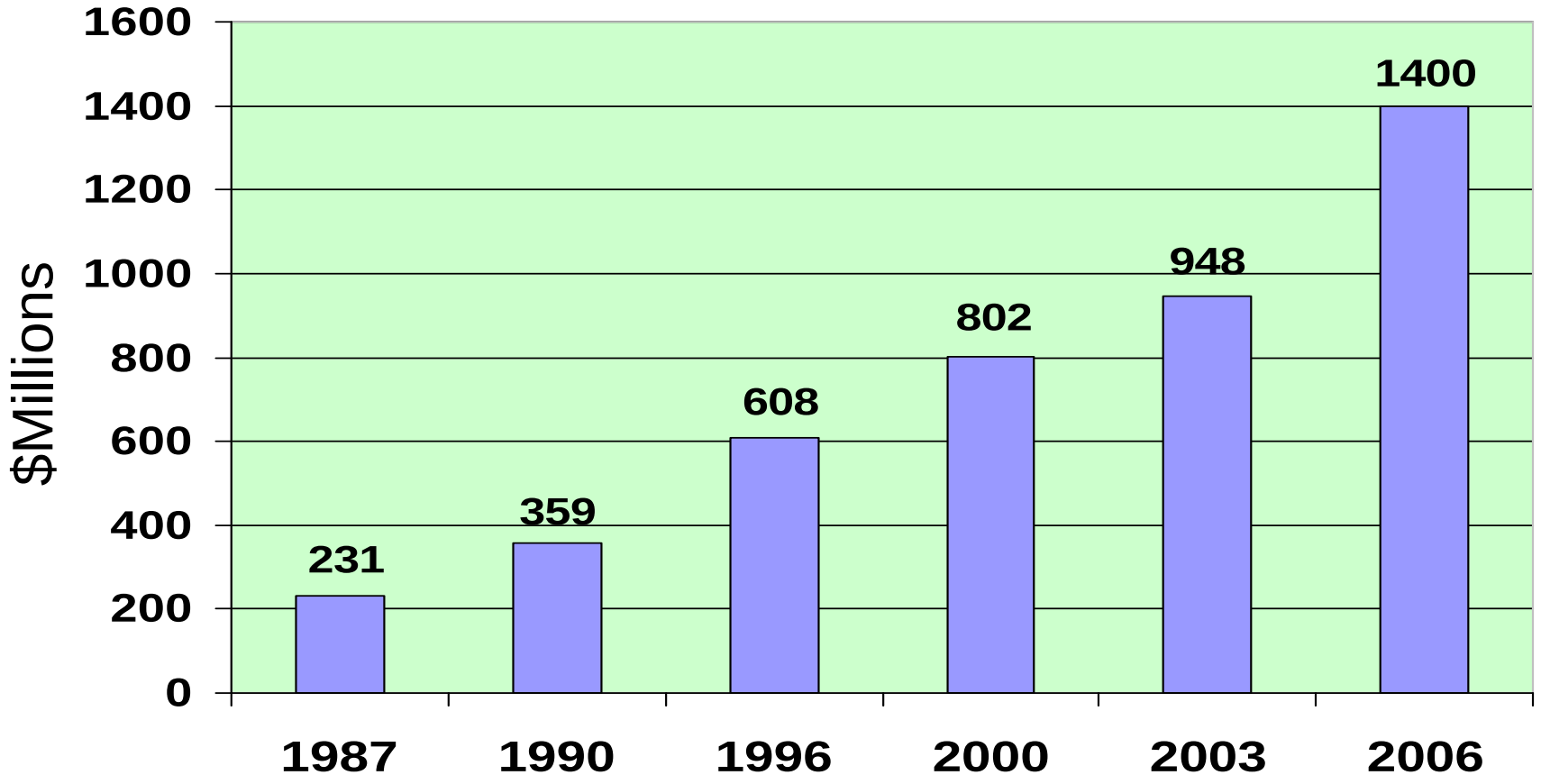
3. Modest benefit for most cancer drugs (new and old)

Success Rates at Each Stage of Development



Source: FDA; Roberts & Chabner et al. *JAMA*. 2004. *Bain Drug Economics Model*.

Recent Estimates of the Cost of Developing New Drugs



Source: *Tufts Center for the Study of Drug Development, Bain and Co., Wyeth*

Monthly Cost of Newer Targeted Agents

Agent	Manufacturer	Cancer	Cost/month
Erbitux	Imclone	Colon	$9,600
Avastin	Genentech	Lung	$8,800
		Breast	$7,700
		Colon	$4,400
Gleevec	Novartis	GIST	$3,816
Herceptin	Genentech	Breast	$3,195
Tarceva	OSI Pharma	Lung	$2,679
	Genentech		

Source: Public company disclosures, Rodman & Renshaw

Subset Approach to Drug Development

Model	Current Model	Future
Target ID to launch	10-12 yrs	5-7 yrs
Development cost	$800 Million	<$500 Million
Success rate	5-10%	25-50%
Patients per NDA	5,175	<2,500

Source: Pharma 2010: The Threshold of Innovation.

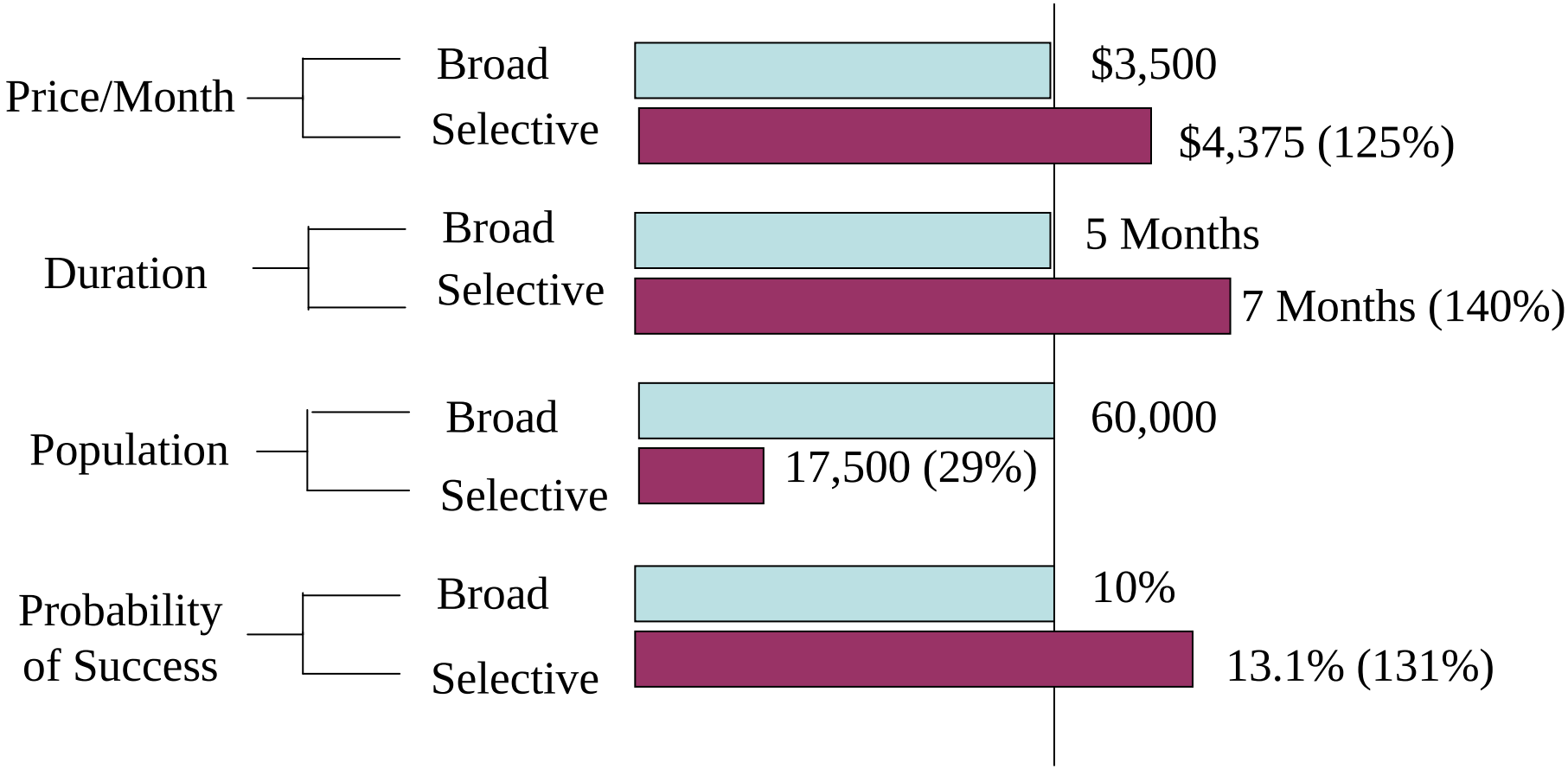
Forces that Could Increase Efforts of Biopharmaceutical Firms to Identify Responsive Subsets

- Stricter FDA approval criteria
- Competitive dynamics with other drugs
- Value-based reimbursement
- Post-approval FDA commitments (Selective Approval)
- Scientific advances!!!

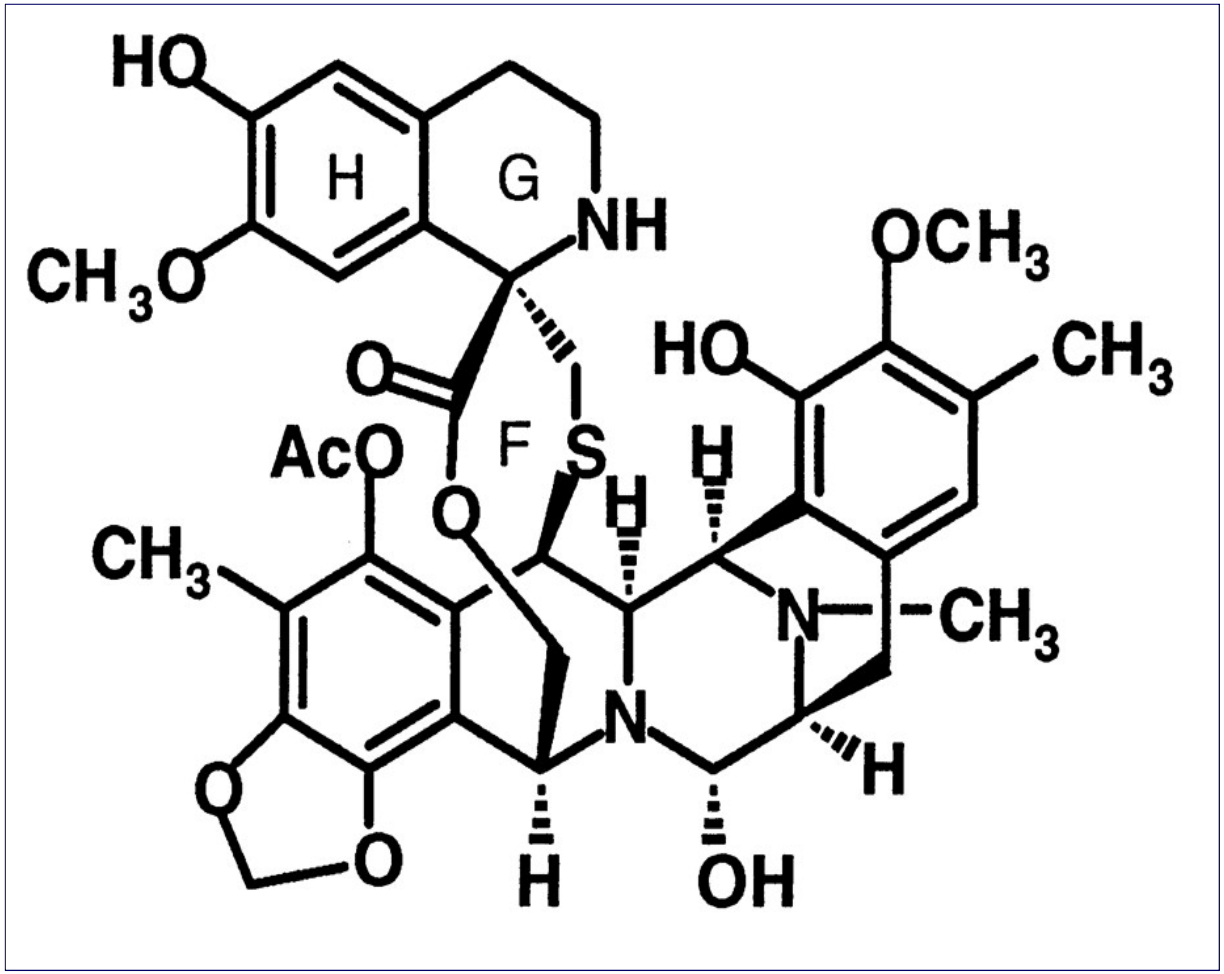
Source: Roberts & Chabner. NEJM 2004;351:501-505

Economic Framework (Sensitivity Analysis)

Net Present Value = $77 Million for Each Approach



Yondelis® ***(Trabectedin)***



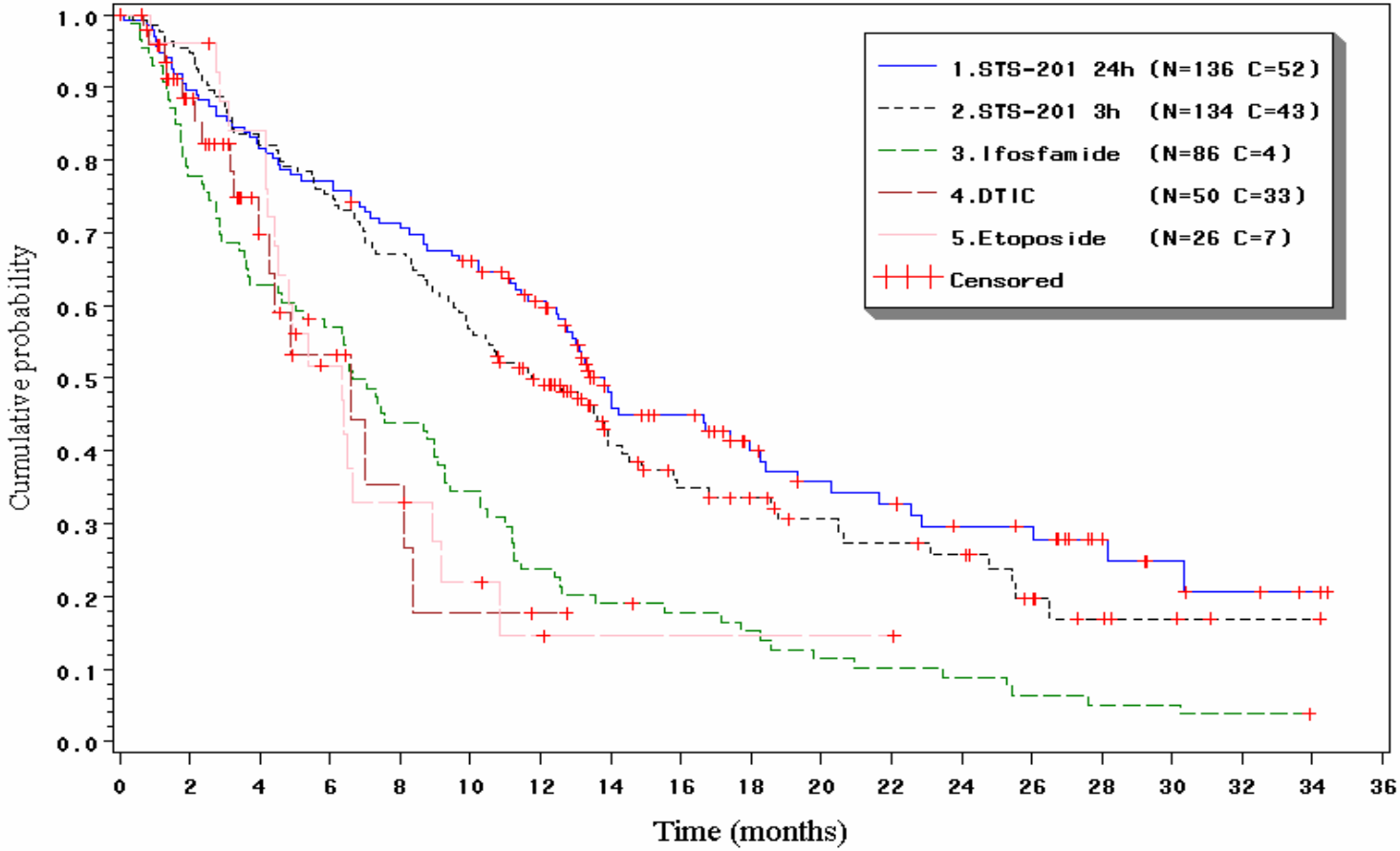
EMEA CHMP Positive Opinion

"Yondelis is indicated for the treatment of patients with advanced soft tissue sarcoma after failure to anthracyclines and ifosfamide, or who are unsuited to receive these agents"

Doc. Ref EMEA/CHMP/316962/London July 19th / 2007

+ than 50 tumor types included

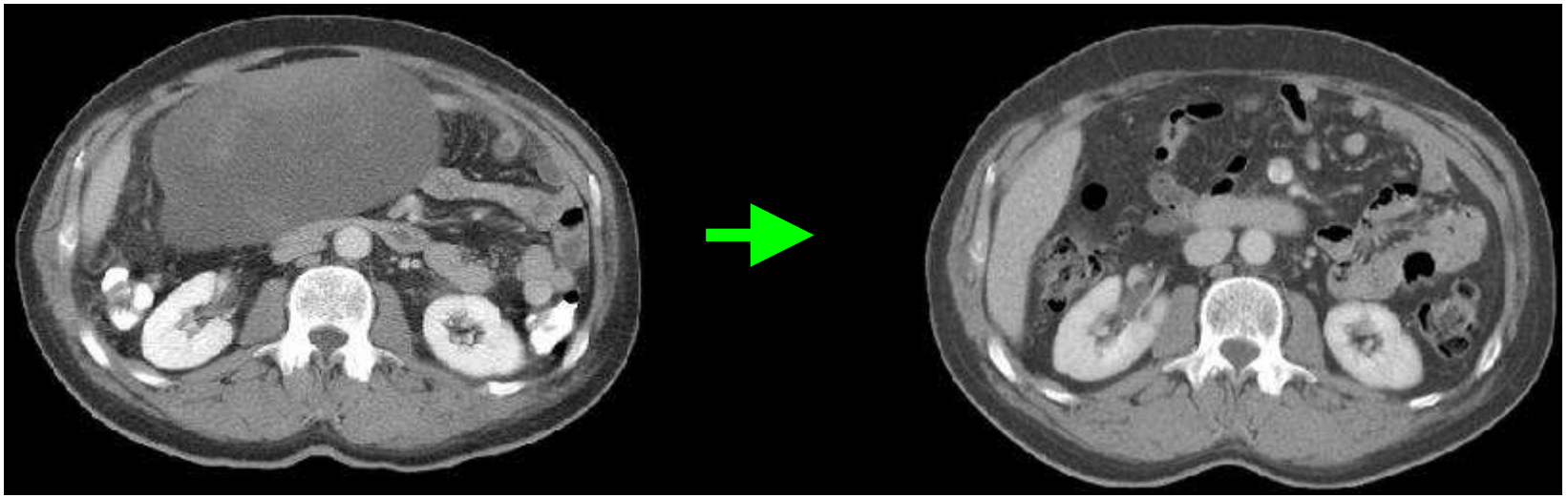
STS-201 and Historical Comparators
Active vs. Inactive Agents – STS pretreated patients
Overall Survival



Acknowledging the limitations of historical comparisons, both trabectedin schedules show substantially longer OS than "active" drugs in similar setting

Trabectedin in Advanced Myxoid Liposarcomas

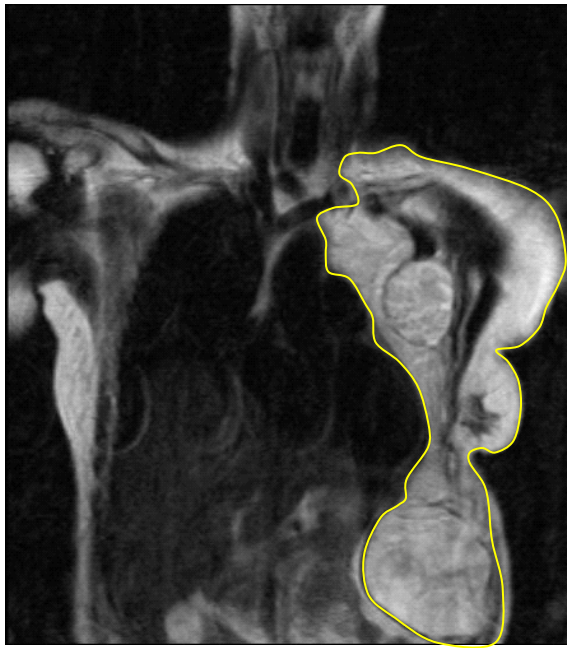
RECIST Acute Partial Response

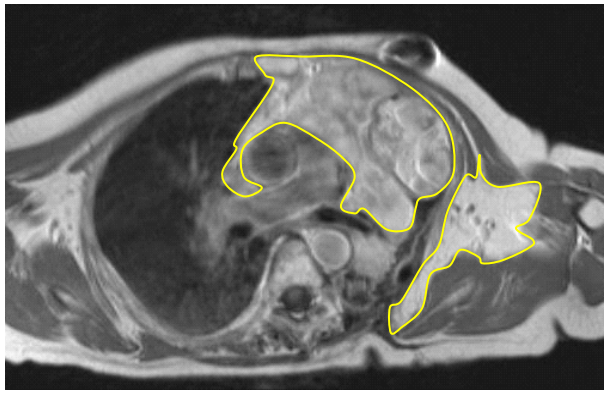


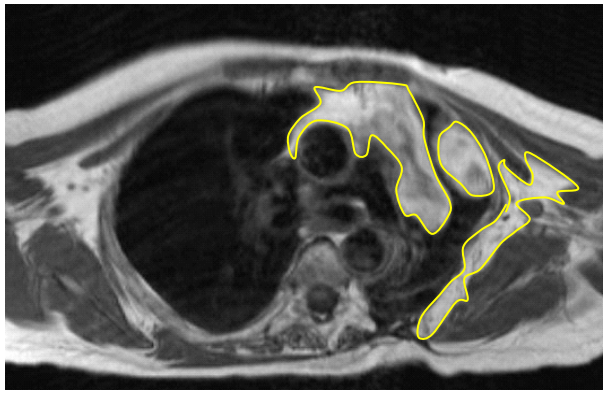
0 **+3 c**

F. Grosso_et al CTOS 06

Sarcoma Sinovial, YONDELIS® como tratamiento de 3ª línea

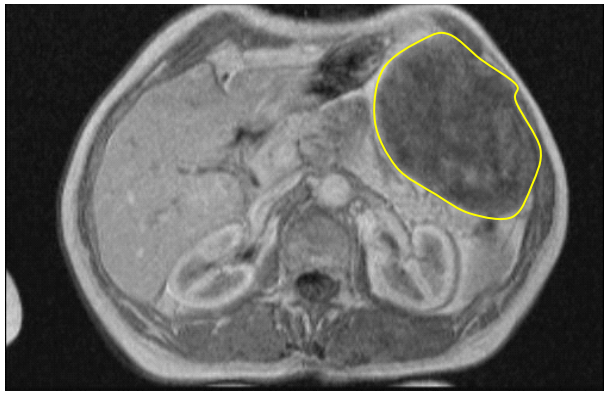


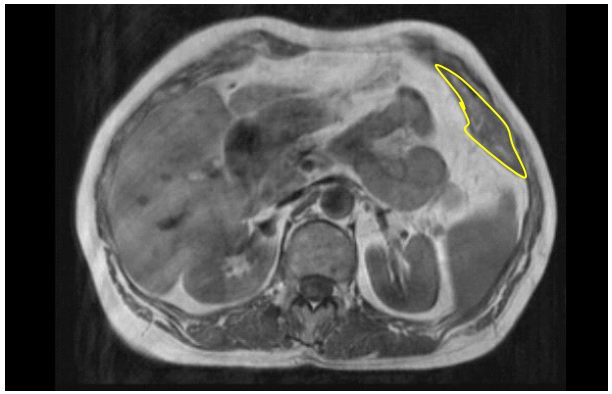




Basal

+15 ciclos



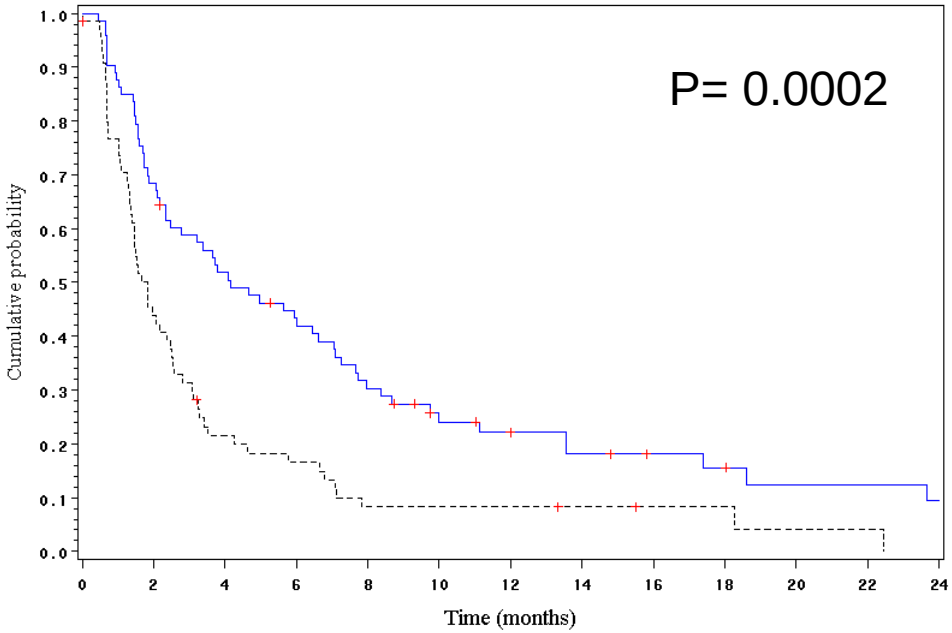


Clinical basis to anticipate a specific molecular signature correlated to sensitivity/resistance to Yondelis in sarcoma

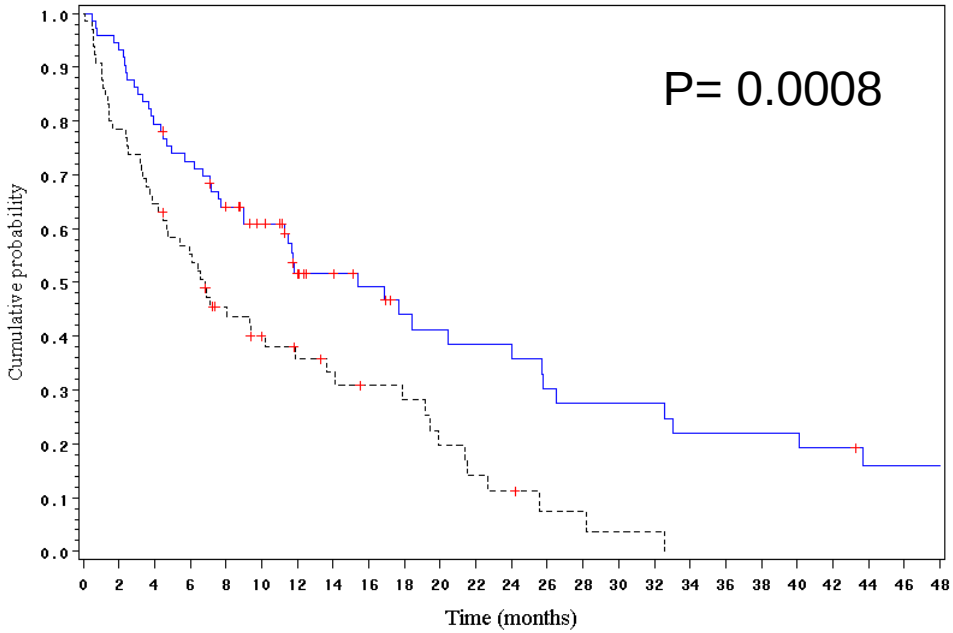
- Activity noted in a clinically relevant proportion of patients that are fully resistant to conventional CT.
- Yondelis induced responses and tumor control are generally long lasting.
- Emergence of acquired resistance in responsive patients is normally a late event.
- Experimental studies are ruling-out the classical resistance pathways (i.e. MDR, MRP, LRP) as the main drivers of treatment failure.

Impact of BRCA1 expression in the outcome of sarcoma patients treated with Yondelis

PFS



Survival

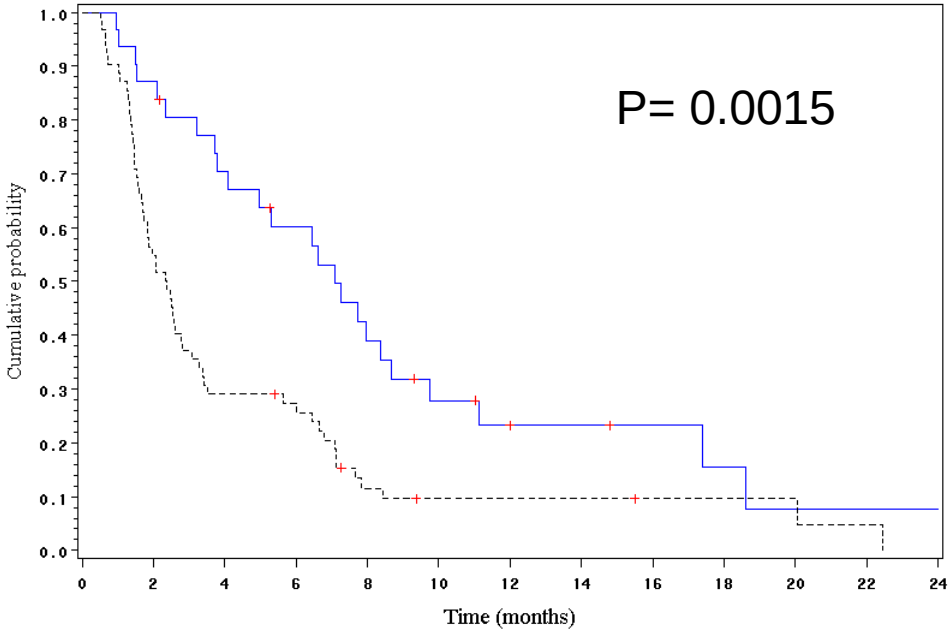


Low BRCA1 mRNA expression levels

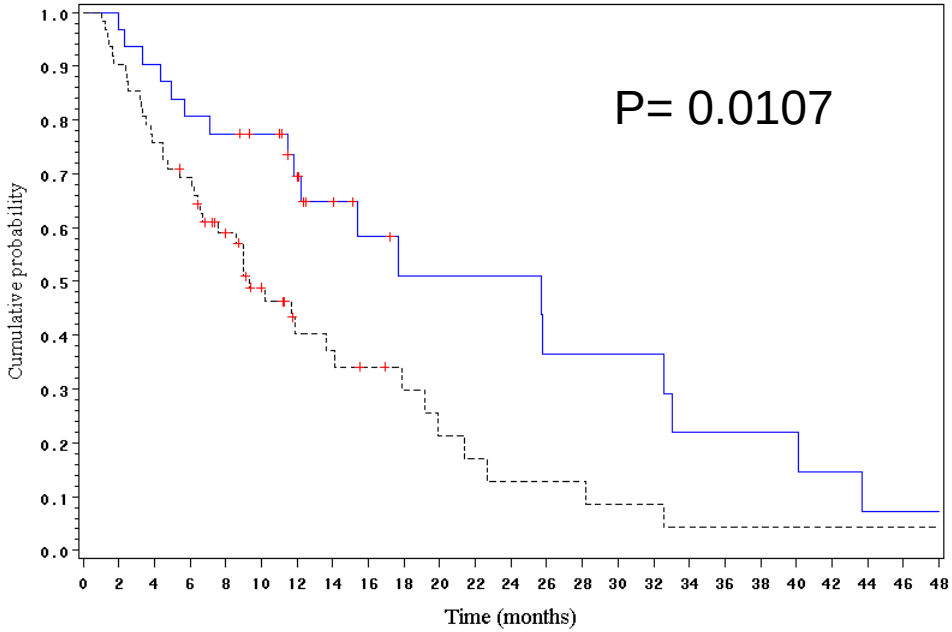
High BRCA1 mRNA expression levels

Impact of combined Low BRCA1 + High (ERCC1 or XPG) expression in the outcome of sarcoma patients treated with Yondelis

PFS



Survival



Subpob Favorable BRCA1 bajo + (XPG o ERCC1) alto

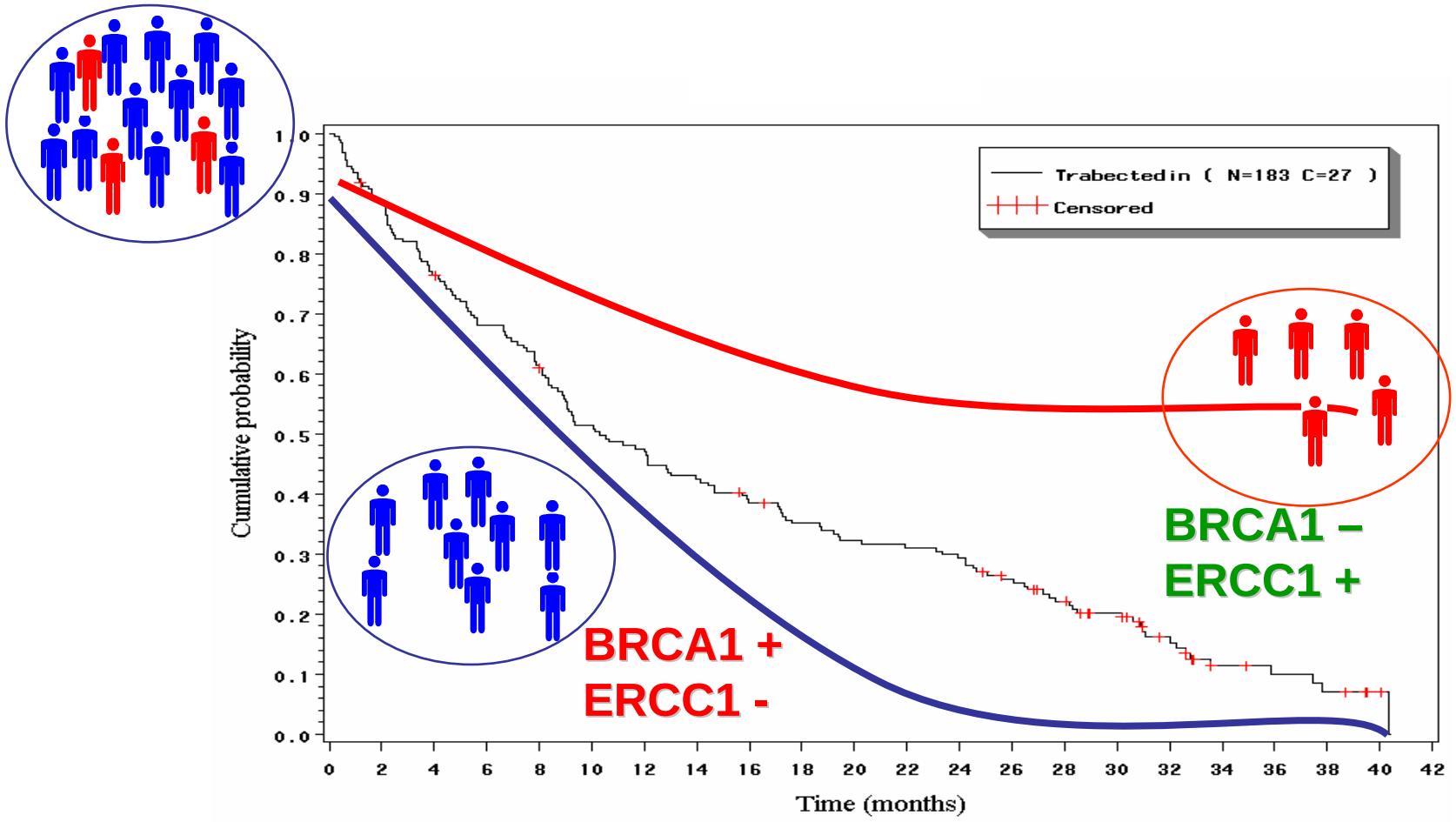
Resto pacientes STS

Low BRCA1+ High (ERCC1 or XPG)

Parameter	BRCA1<3.26 + (ERCC1>4.99 or XPG<1.55)	Other	P-value
CR + PR	21%	12%	*0.3361*
CR+PR+MR+SD≥6	69%	30%	0.0006
PFS≥6 Months rate	55%	26%	0.0107
Median PFS (KM)	7.1 m	2.4 mo	0.0015
PFS6 (KM)	60.2%	25.6%	0.0001
Median Survival (KM)	25.7m	9.3 mo	0.0107

Personalized Medicine

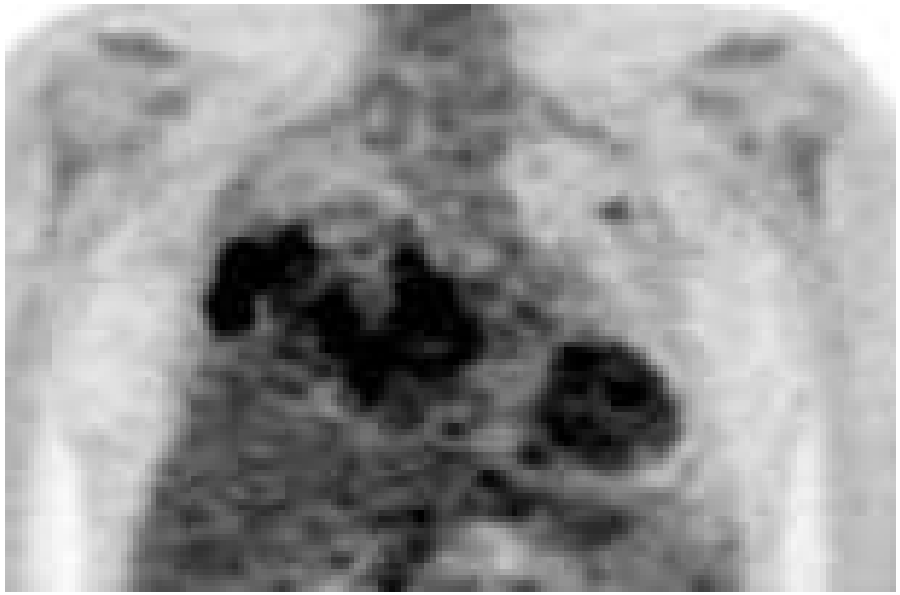
- **Providing the right drug to the right person/tumor**



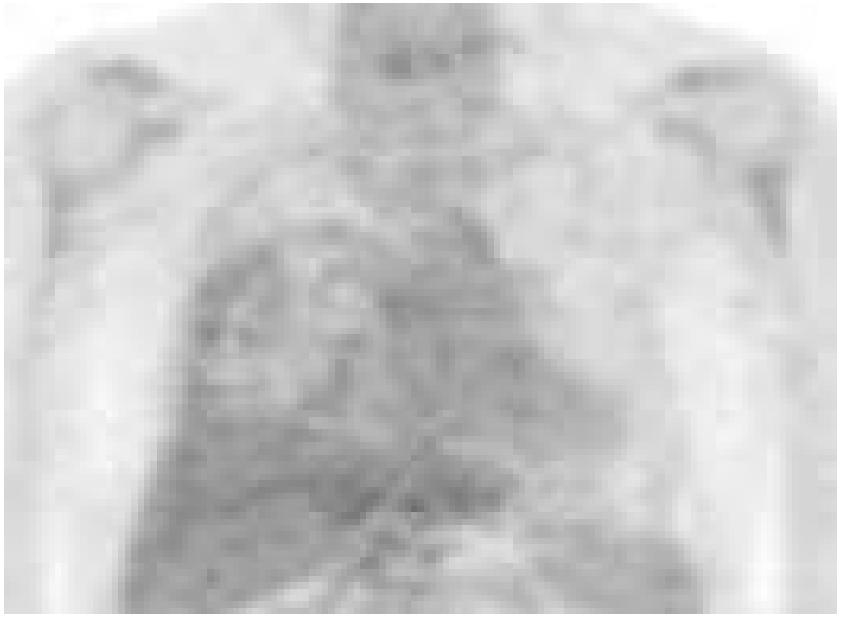
Kaplan-Meier survival plot of Yondelis in advance STS

JA Lopez et al. Proc ASCO, 2003

Acute Metabolic Response(FDG-PET) in a Mixoid Liposarcoma Patient relapsed to Doxorubicin+Ifosfamide



Base line

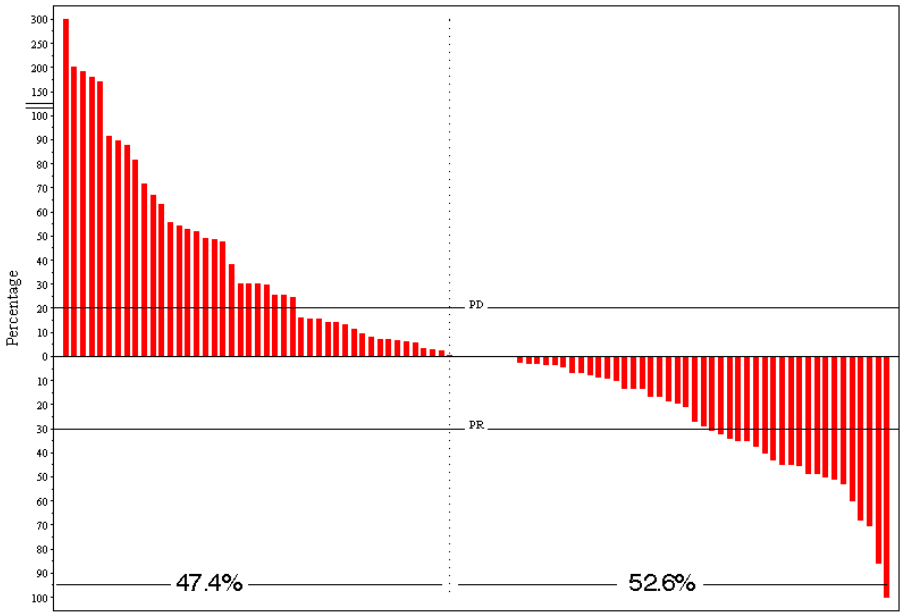


After 1 cycle

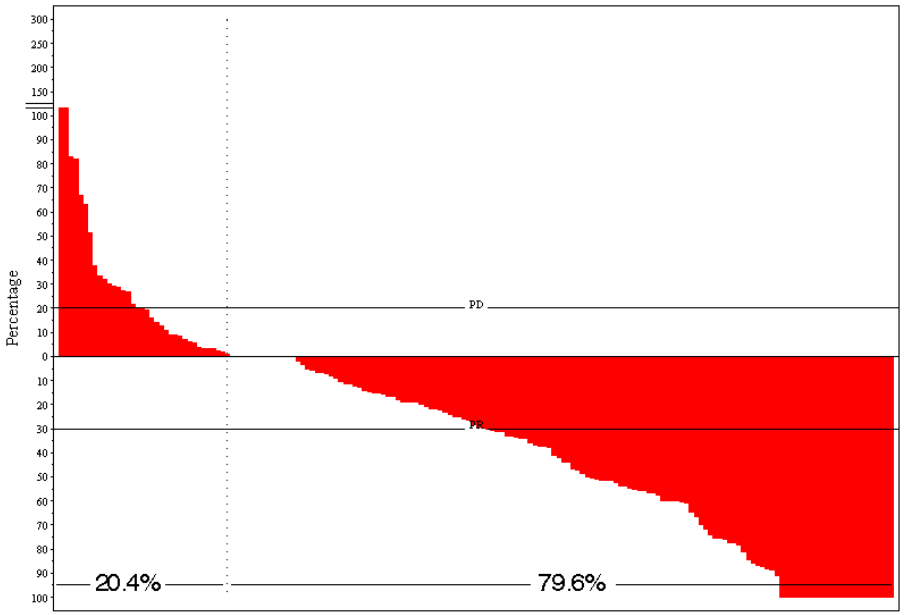
Courtesy of B.Benjamin, MDACC July 2007

Impact of Trabectedin in Advanced Relapsed Ovarian Cancer

Platinum Resistant (n=95)



Relapsed Platinum Sensitive (n=176)



S. McMeekin, et al ASCO'07

Weekly Yondelis in Advanced Taxotere Pretreated Prostate Cancer

Impact on Tumor Related Sympthoms

Oxycontin Dose (mg)

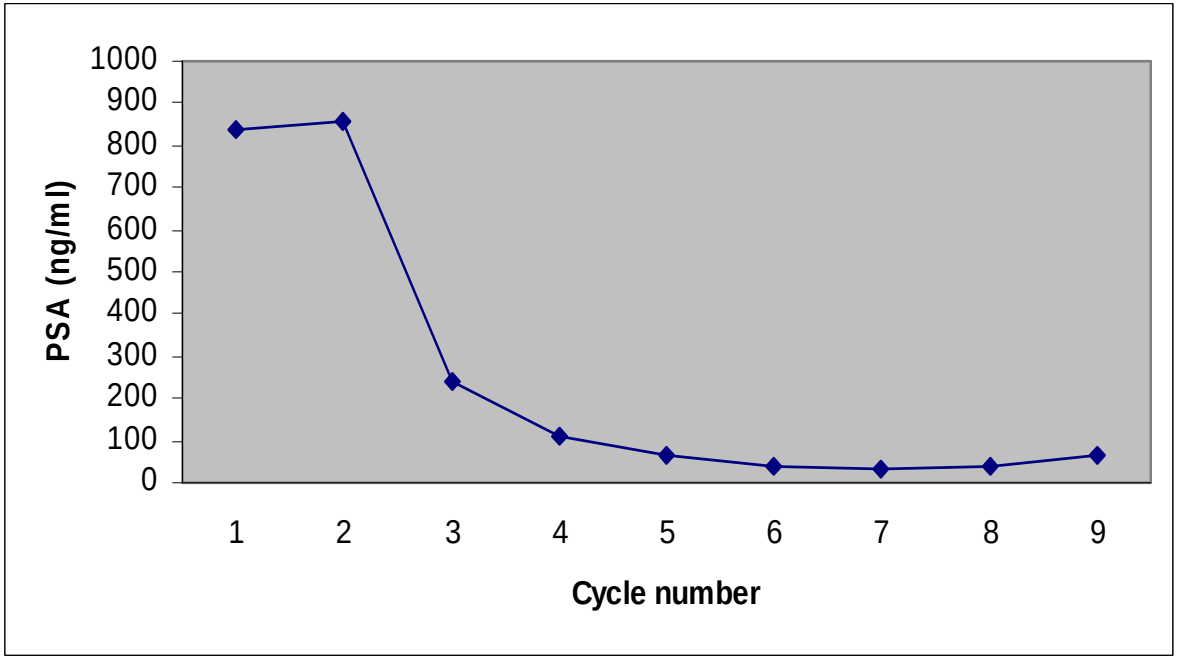
Cycle 1 – 20 TID (+ prn)

Cycle 2 – 20 BID

Cycle 3 – 10 BID

Cycle 4 – 10 QHS

Cycle 5 – OFF



* PSA response in taxotere resistant pts = 14%

D. Michaelson et al. Proc ASCO, 2005

Yondelis: Characteristics of Breast Cancer Patients with Objective Response

Age	PS	Prior CT Lines*	Prior CT Agents	Anthra. Clinical Resistance	Taxane Clinical Resistance	Site of Disease	OR	Number of Cycles	TTP
51	0	1+1	5	E	E	Lung, mediastinal nodes	PR	4	3.0
53	0	2+2	5	E	NA	Skin, mediastinal nodes	PR	12	11.3
57	1	1+1	4	E	E	Lung, liver	PR	10	7.3
46	0	1+2	5	E	R	Breast, axillary & peritoneal nodes	UPR	4	3.5
55	1	1+1	5	E	E	Liver	MR	5	5.0
53	0	0+3	7	E	E	Lung, pre-external soft tissue	MR	4	3

* Adjuvant + Advanced

(21 measurable pts; response rate 14%)

Pharmacogenomic Framework
a case for Yondelis

Tumor Type	# Exposed to CT(#)	% Target Population to Yondelis	# Cases/Y
• Breast	156.000	30%	50.000
• Prostate	46.000(*)	20%	10.000
• Lung	584.000(+)	20%	116.000

			176.000

Globocan 2002

patients with advanced disease

*note that due to the marginal impact of therapy just 40% and 20% of the population is exposed to 1st and 2nd CT lines!!

+ Numbers applicable to US+EU+Asia

Yondelis Strategic and Business Model Targeted Development is a model of major added value (1)

- Focusing on sensitive patients results in long lasting treatment time-frames
- The median N of cycles in highly sensitive sub-populations is 9 (up to 55)
- Yondelis lacks cumulative toxicities
- The economical model to be built on the basis of {# cases<>n of cycles}
- The cellular target (and the mechanism of resistance) for a given drug is independent of the tumor type.
- The proposed molecular signature should (must) harbour a trans-tumoral impact
- Thus applicable to other Yondelis sensitive malignancies.

Yondelis Strategic and Business Model Targeted Development is a model of major added value (2)

- Impact on success rates + developmental costs
- Premium Price
- Reinforcing the IP frame
- Credibility with the regulators
- Positive impact on patients
- Positive impact on the NPV

Patient endpoints in ASTS
Normal life with disease

Iron (trabectedin) n a
Between 6th n 7th c rse of T
July 07

Primum non nocere

Marketing & Sales

Europe

Alfonso Casal
Marketing & Sales Director

Estrategia comercial en Europa

Prioridades corto plazo:

- Red de ventas implantada en la “Europa Occidental”
- Establecer la actividad comercial de **PharmaMar** de acuerdo con la secuencia de acceso al mercado
- Adoptar la **estructura que optimice** la relación de:
  -crecimiento de ventas/inversión
  -oportunidades/riesgos

EUROPA:
Segmentación del mercado farmacéutico

W-E
88.4%

Nordic
5.6%

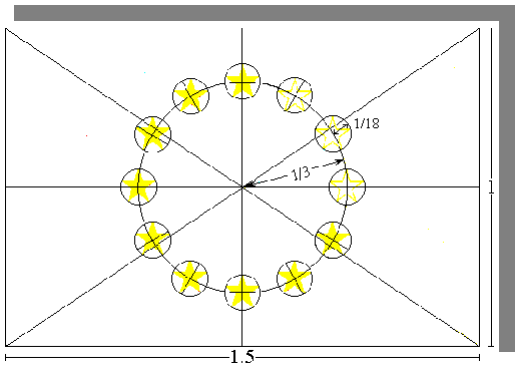
CEE
6%

Pharma Mar

2007:
La €uropa de Yondelis

- 27+3 países con diferentes:
  - -Sistemas Sanitarios
  - -Sistemas de Evaluación
  - -Precio y Reembolso
  - -Niveles económicos
  - -Modelos de adopción

- >22 idiomas
- > 450 Millones habitantes



Nuevos avances terapéuticos:
La armonización está aún lejos de ser completada

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Marketing y Ventas UE

MARKETING:

Concepto Pan-europeo, desarrollado desde Central con adaptación mínima a las necesidades locales

VENTAS:

- **Europa *Occidental***

-Actividad de promoción por PharmaMar, con presencia en los territorios principales cubriendo el 88% del mercado

-de acuerdo a calendario de acceso

-establecimiento de red de ventas en colaboración con Innovex

-Distribución, logística y servicios subcontratados a un distribuidor paneuropeo (IDIS International), bajo supervisión de PharmaMar

- **Países Nórdicos y Europa Central-Este**

-Distribuidor especializado en la región (Swedish Orphan International)

- **Grecia y Chipre**

-Distribuidor especializado en la región (Genesis Pharma)

Establecimiento de la Red de Ventas de PharmaMar
Colaboración con Innovex

-Europa *"Occidental"*

INNOVEX

PharmaMar

Establecimiento de la Red de Ventas

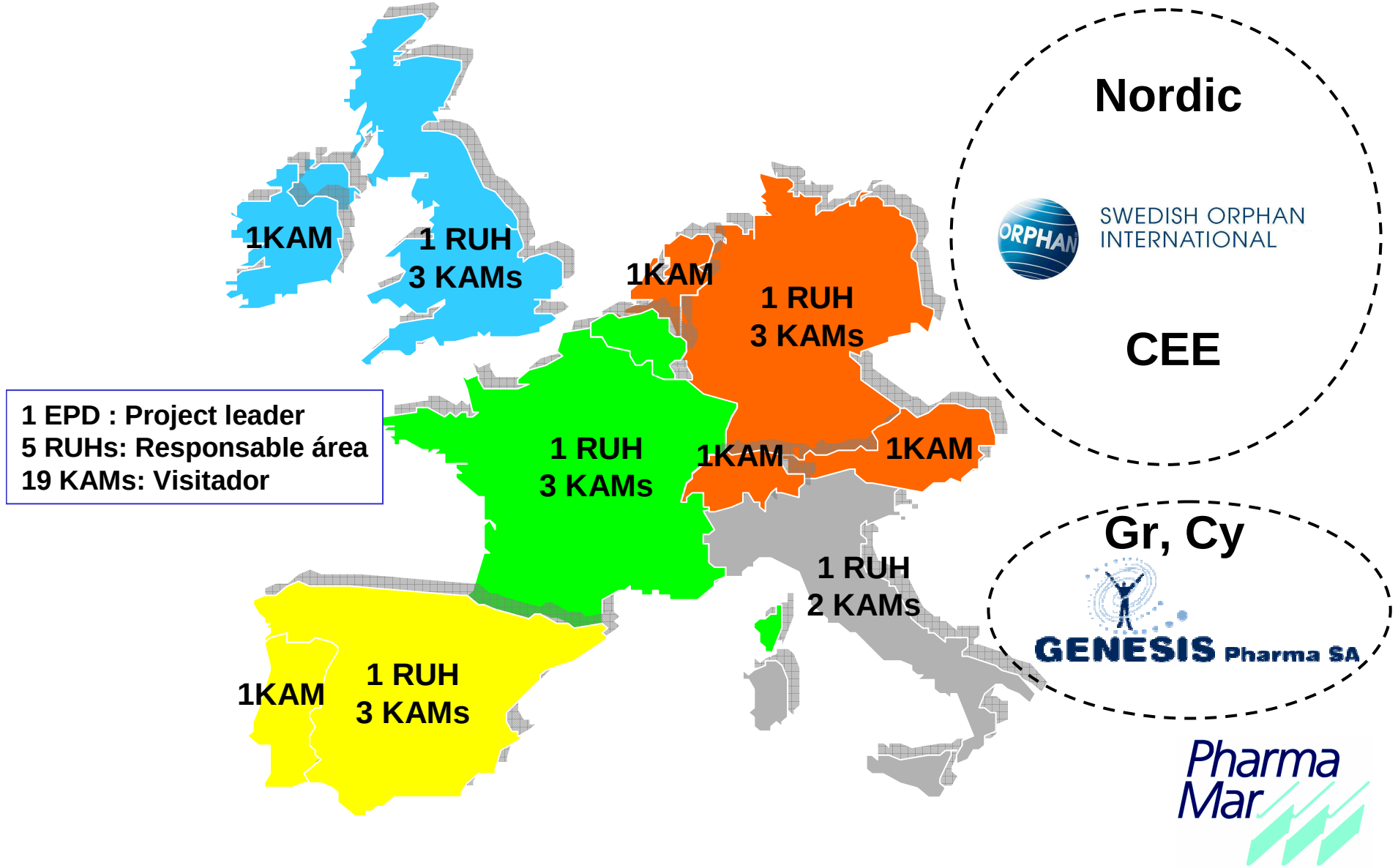
- Europa en regiones
  - Iberia (E+P)
  - F + B + Lux
  - Germania (D + CH + A + NL)
  - UK + Irl
  - Italia
- Concentración del target
- Potencial de mercado
- Acceso al mercado

Red de Ventas- 2007

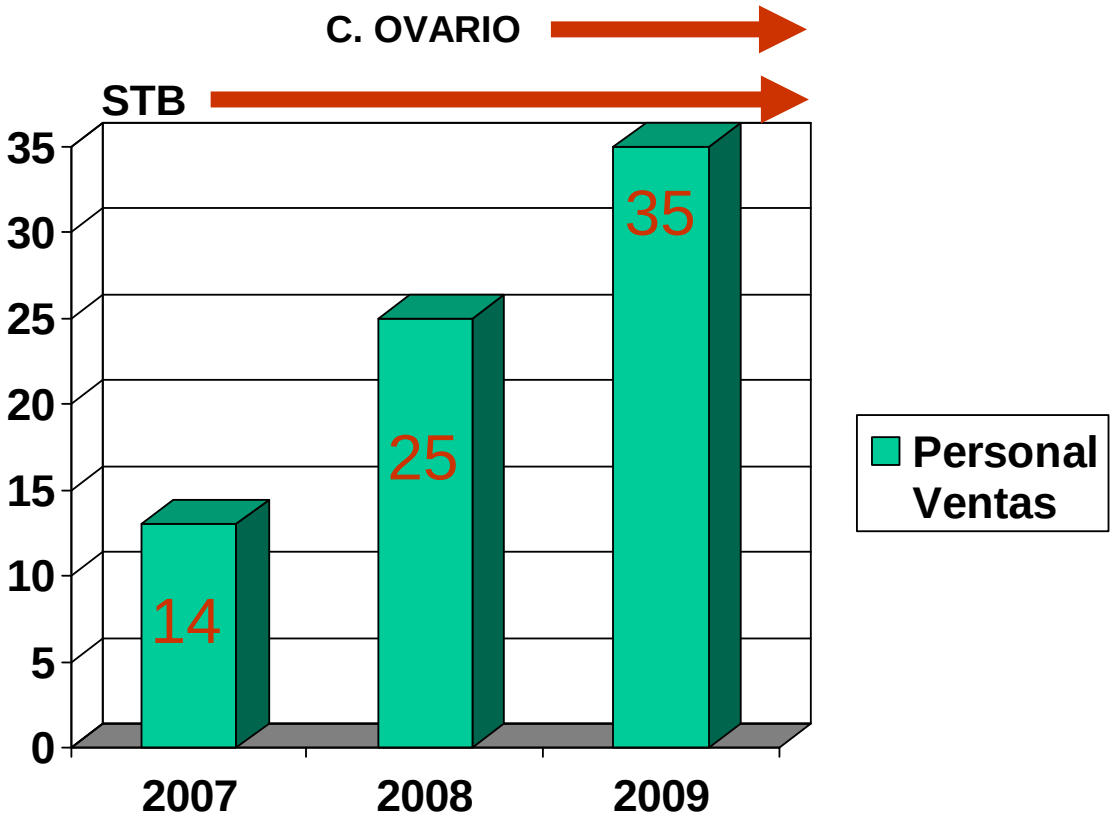
Red de ventas: personal de Innovex (grupo Quintiles)

	RESPONSABLE ÁREA (RUH)	VISITADOR (KAM)	TOTAL
UK	1	2	3
GERMANY	1	2	3
FRANCE	1	2	3
SPAIN	1	2	3
ITALY	1	-	1
TOTAL	5	8	13
PROJECT LEADER (EPD)			1
TOTAL EQUIPO			**14**

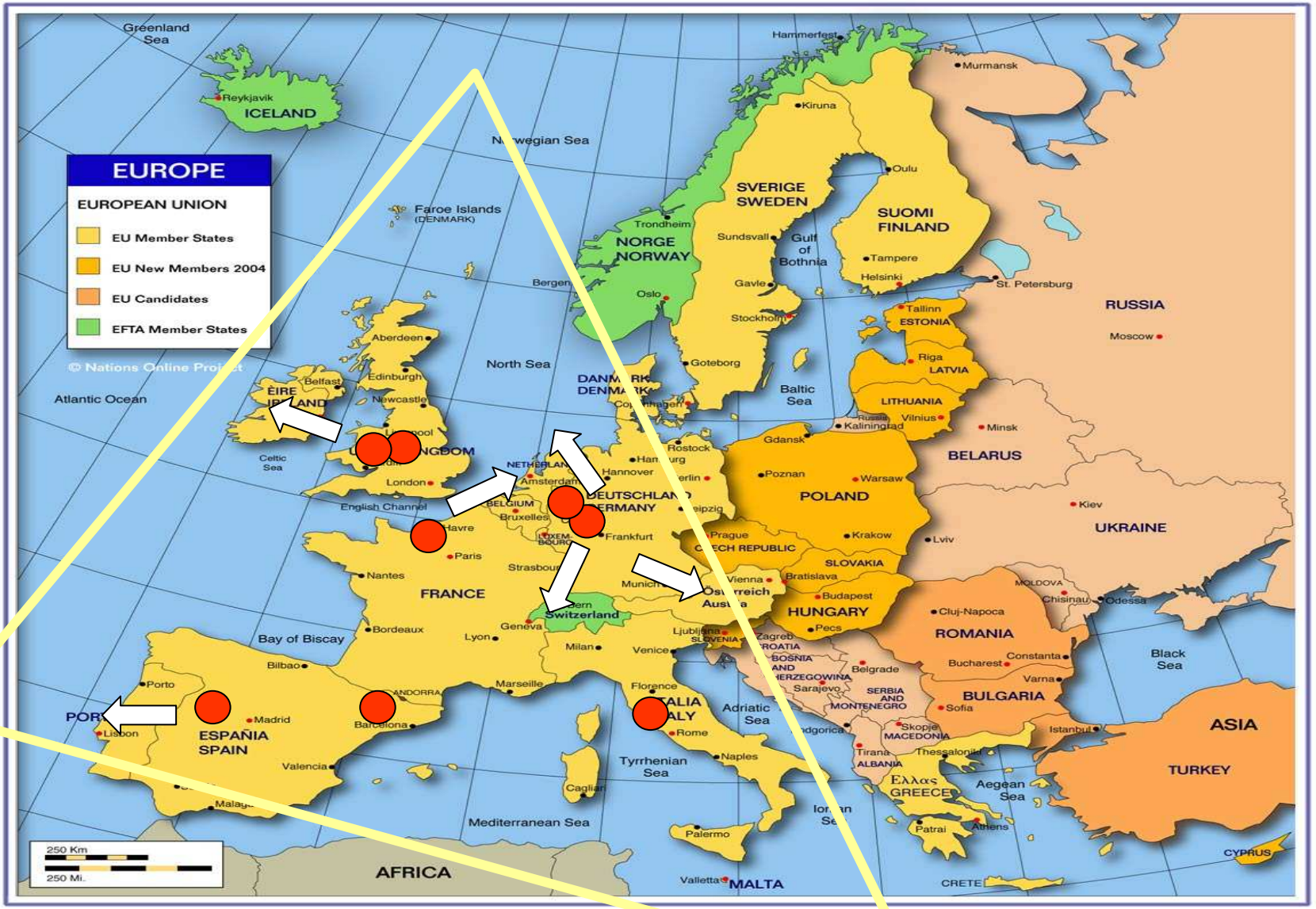
PharmaMar Salesforce End 2008



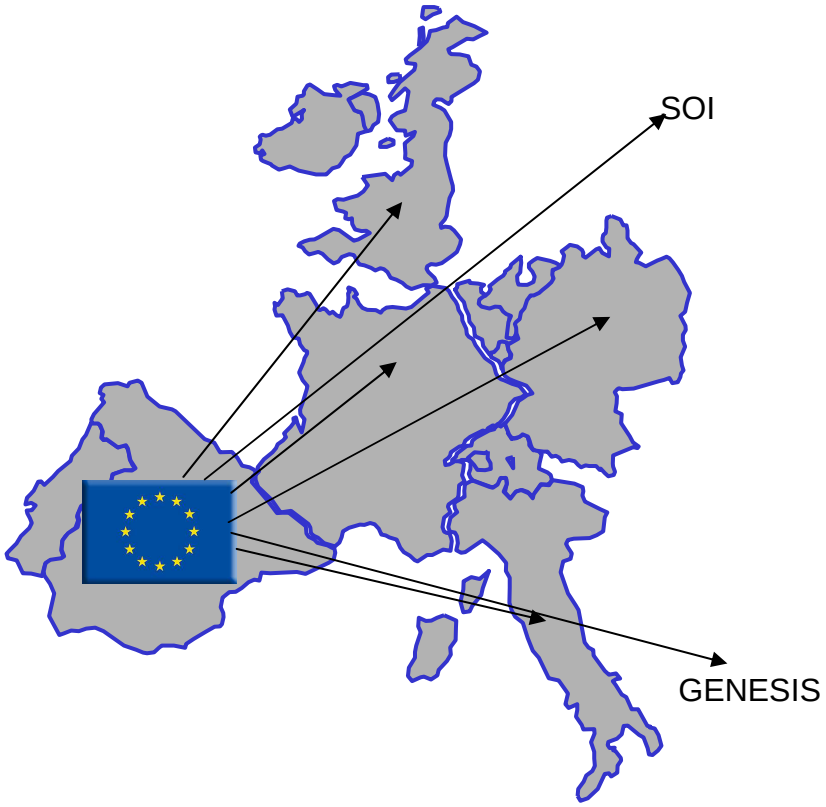
Evolución del Personal de Ventas PharmaMar (Innovex)



Infraestructura de oficinas de Innovex a disposición de la Red de Ventas de PharmaMar



HQ-Marketing Team End 2008



Product Management
P&R+Market Research
Training & Medical Information
Congresses & Events
M&S Support
Admin. Assistants

PharmaMar

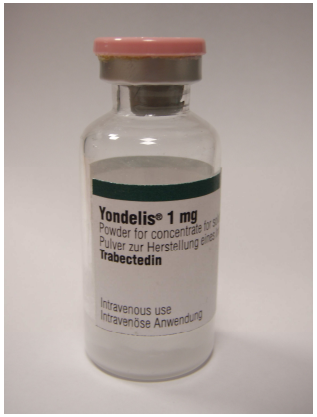
Distribución y Logística paneuropeas: IDIS International

-Europa *"occidental"*

IDIS
MANAGING WORLD MEDICINES

Pharma Mar

Modelo de Distribución y Logística paneuropeas (+): IDIS International



Acuerdos Comerciales y de Distribución: Swedish Orphan International y Genesis Pharma

-Países Nórdicos (Escandinavia + Bálticos)
-Europa Central-Este

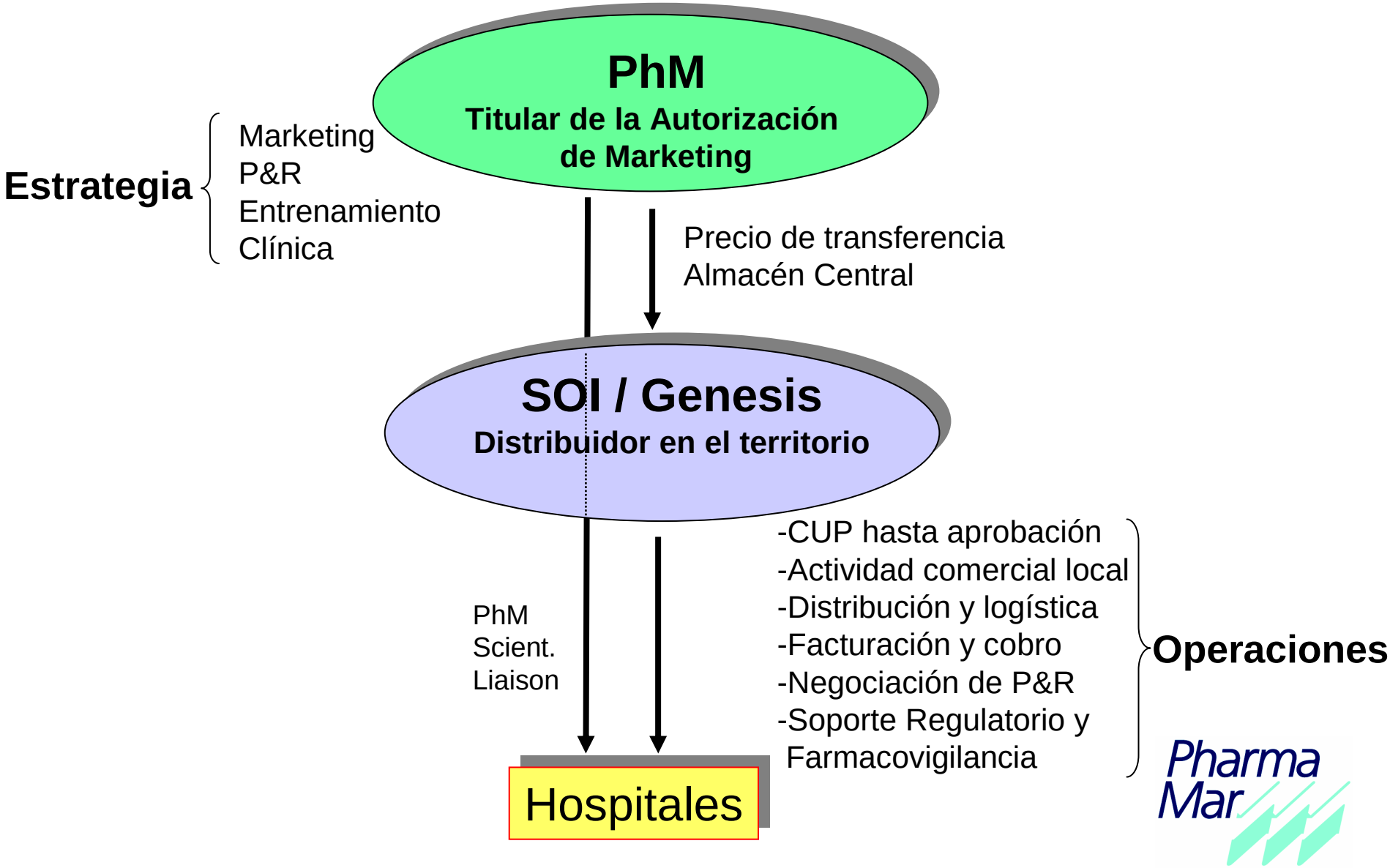
SWEDISH ORPHAN INTERNATIONAL

-Grecia y Chipre

GENESIS Pharma SA

Pharma Mar

Modelo Comercial y de Distribución (SOI + Genesis)



Operaciones comerciales-UE

Pharma Mar	Western Europe(-Gr/Cp)	Greece/Cyprus	Nordic Countries & CEE
Promotion & Detailing	PharmaMar (Quintiles) INNOVEX	Genesis Pharma GENESIS Pharma SA	Swedish Orphan International SWEDISH ORPHAN INTERNATIONAL
Distribution & Logistics	IDIS International IDIS MANAGING WORLD MEDICINES	Genesis Pharma GENESIS Pharma SA	Swedish Orphan International SWEDISH ORPHAN INTERNATIONAL

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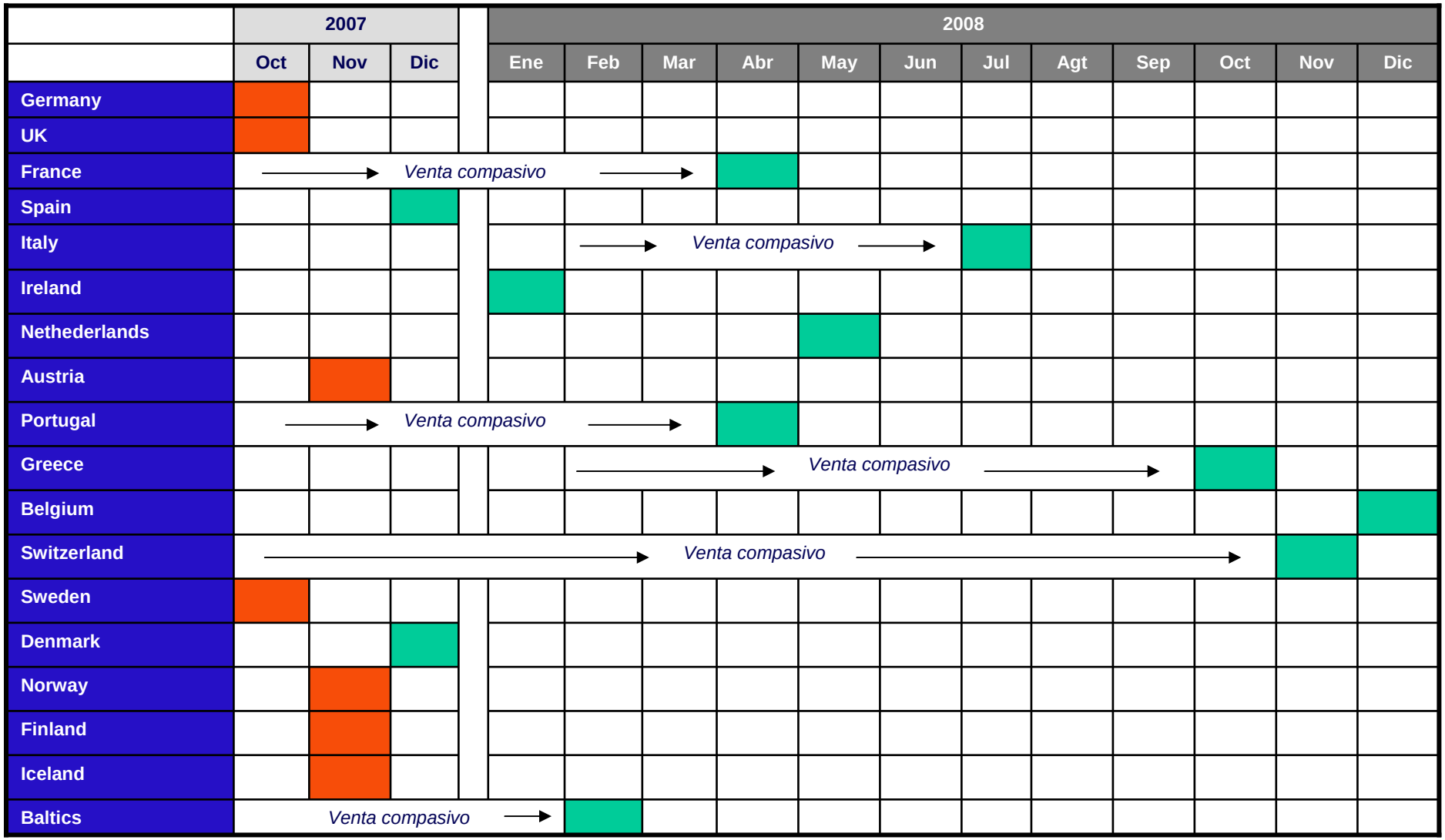
Calendario Previsto Lanzamientos



Precios oficiales Yondelis®

	VIAL 1 mg	Vial 0,25 mg
Germany	1.994 €	530 €
Austria	1.994 €	530 €
Finland	1.994 €	530 €
UK	1.366 £	363 £
Sweden	18.439 SKr	5.001 SKr
Iceland	188.081 IKr	49.991 IKr
Norway	15.800 NKr	4.220 NKr
Spain	**1.994 €**	**530 €**
Denmark	**1.994 €**	**530 €**

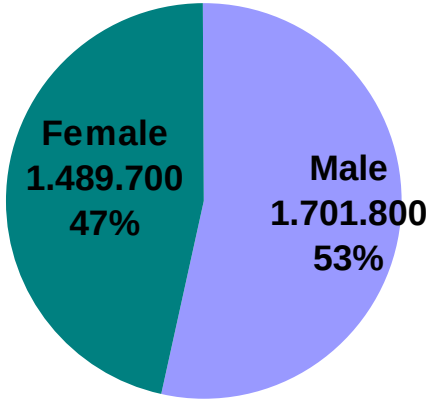
Mismo precio en todos los países

- Corredor de precios mínimo (Objetivo = 0)
- Precios solicitados : Vial 1 mg 1,994€, vial 0,25 mg 530€
- Precio por ciclo estándar de 5.048 €
- Precio por tratamiento medio 25.240 € (5 ciclos)

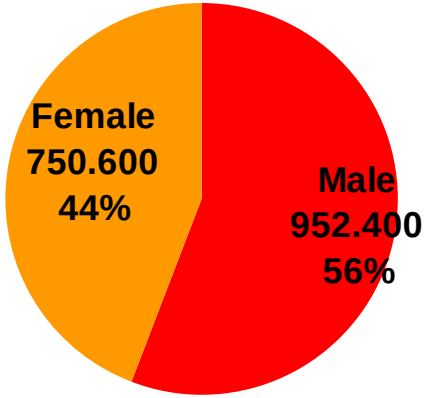
Luis Mora
Subdirector General
& Director Financiero

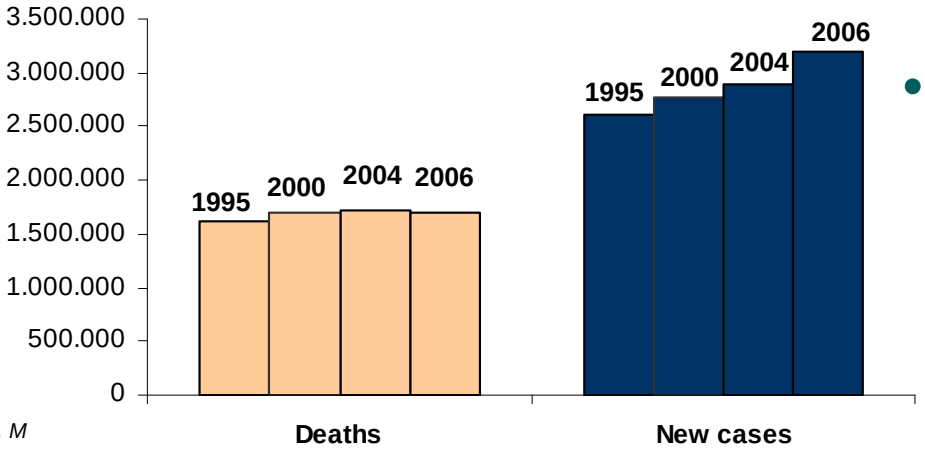
Cancer Figures Europe 2006

Number of new cancer cases
3,191,600



Number of cancer deaths
1,703,000





- For the period 1995-2006 cancer incidence has increased steadily while the number of deaths has reached a plateau

Source: J Ferlay, P Autier, M Boniol, H Heanue, M Colombet y P Boyle (Ann Oncol 2007)

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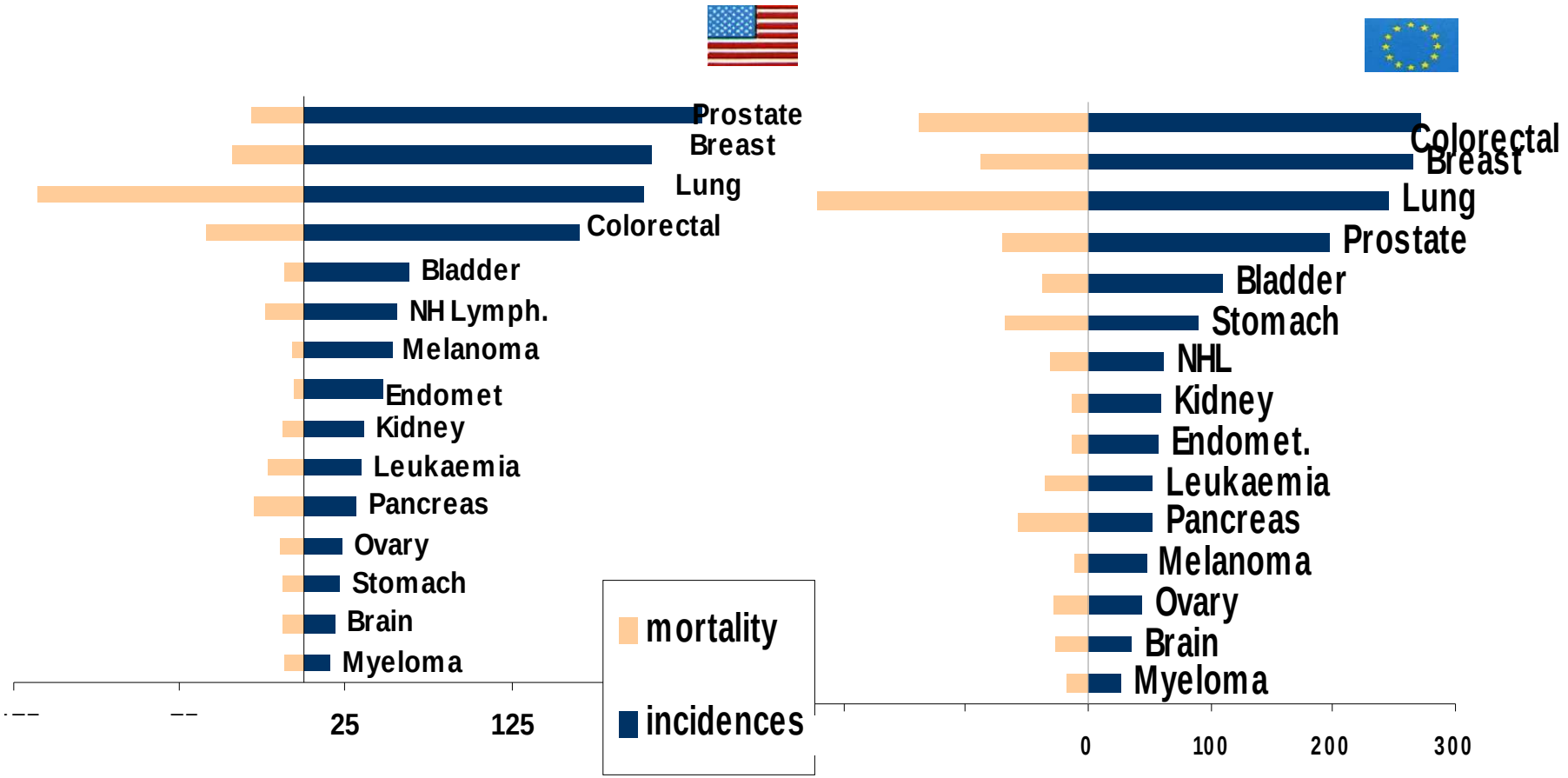
Incidences and Mortalities Main Cancer Types



Source: Globocan 2002

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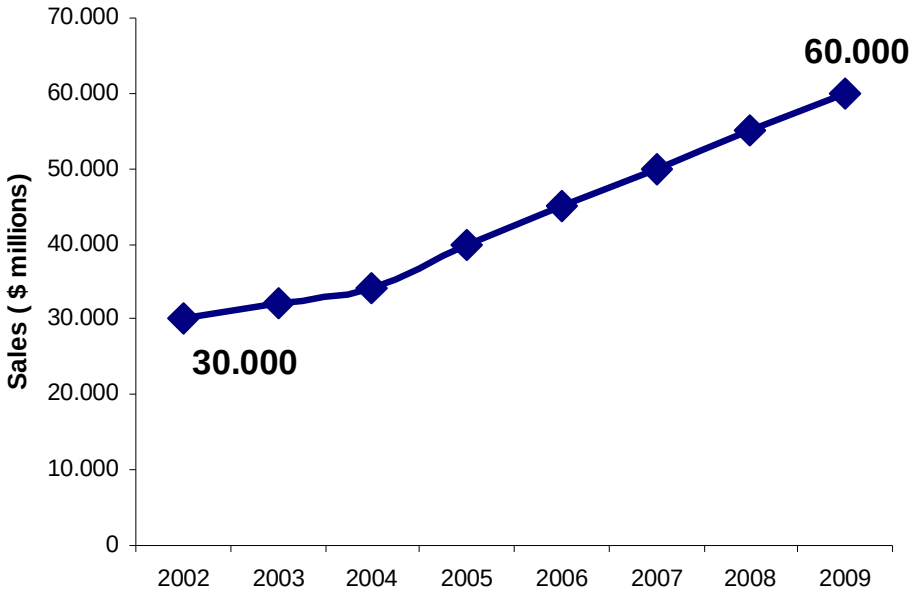
Cancer Market Overview

- **Cancer incidence will increase globally from 10 million new cases in 2000 to 15 million in 2020 (source UN population division, 1994)**
- **The rise in incidence will be driven by aging populations, trends in smoking prevalence and the growing adoption of unhealthy lifestyles***



- **Cancer market worth an estimated $35 billion in 2003, projected to grow to $60 billion by 2010, (CAGR of 8% over this period)****
- **The oncology market is the third largest pharmaceutical market, behind the cardiovascular and CNS therapy areas. Ongoing growth is being driven by an increased diagnosis of cancer and the rising costs of treatment**

**World Population Prospects, The 1998 Revision, Volume II: Sex and Age. The Population Division, Department of Economic and Social Affairs, United Nations Secretariat*
***Datamonitor, PharmaVitae, 2004*

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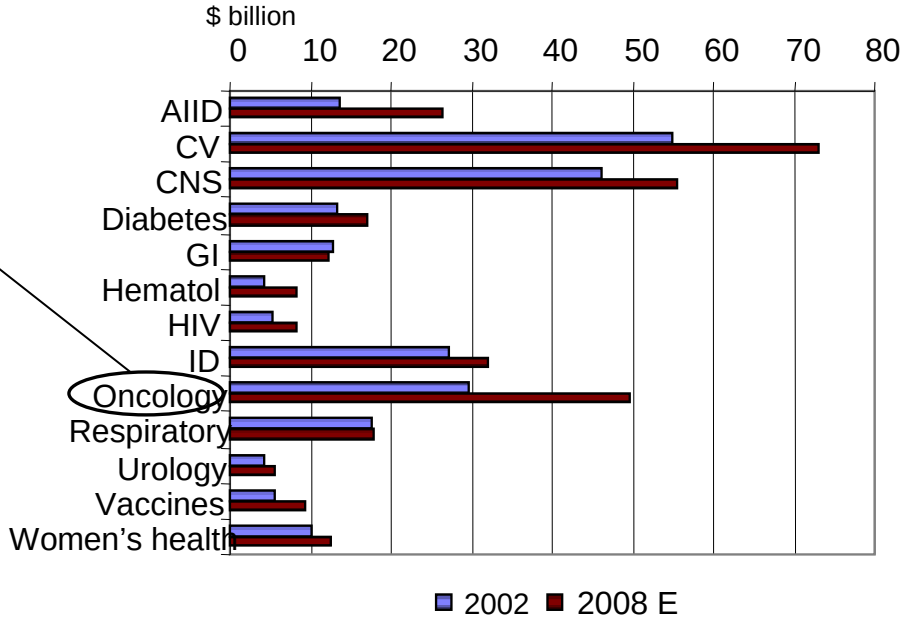
Cancer market overview

- The oncology market is the third largest pharmaceutical market, behind the cardiovascular and CNS therapy areas. Ongoing growth is being driven by an increased diagnosis of cancer and the rising costs of treatment *



*Datamonitor, PharmaVitae, 2004
** IMS September 2005

Ranking by therapeutic class ($ billion**)

2003

1	Hipocolesterolemiantes
2	Antiulcerosos
3	Antidepresivos
4	Antirreumáticos
5	Antipsicóticos
6	Antagonistas del calcio
7	Eritropoietinas
8	Antiepilépticos
9	Antidiabéticos orales
10	Antibióticos

2004

Hipocolesterolemiantes	27 $B
Oncología	**24**
Antiulcerosos	22
Antidepresivos	21
Antipsicóticos	14
Antihipertensivos	12
Anemia	12
Antiepilépticos	11
Antidiabéticos orales	10
Osteoporosis	9

2009

Oncología	**55 $B**
Hipocolesterolemiantes	38
Antidepresivos	26
Antiulcerosos	26
Antihipertensivos	24
Antipsicóticos	20
Inhibidores plaquetarios	18
Anemia	18
Osteoporosis	16
Antiepilépticos	15

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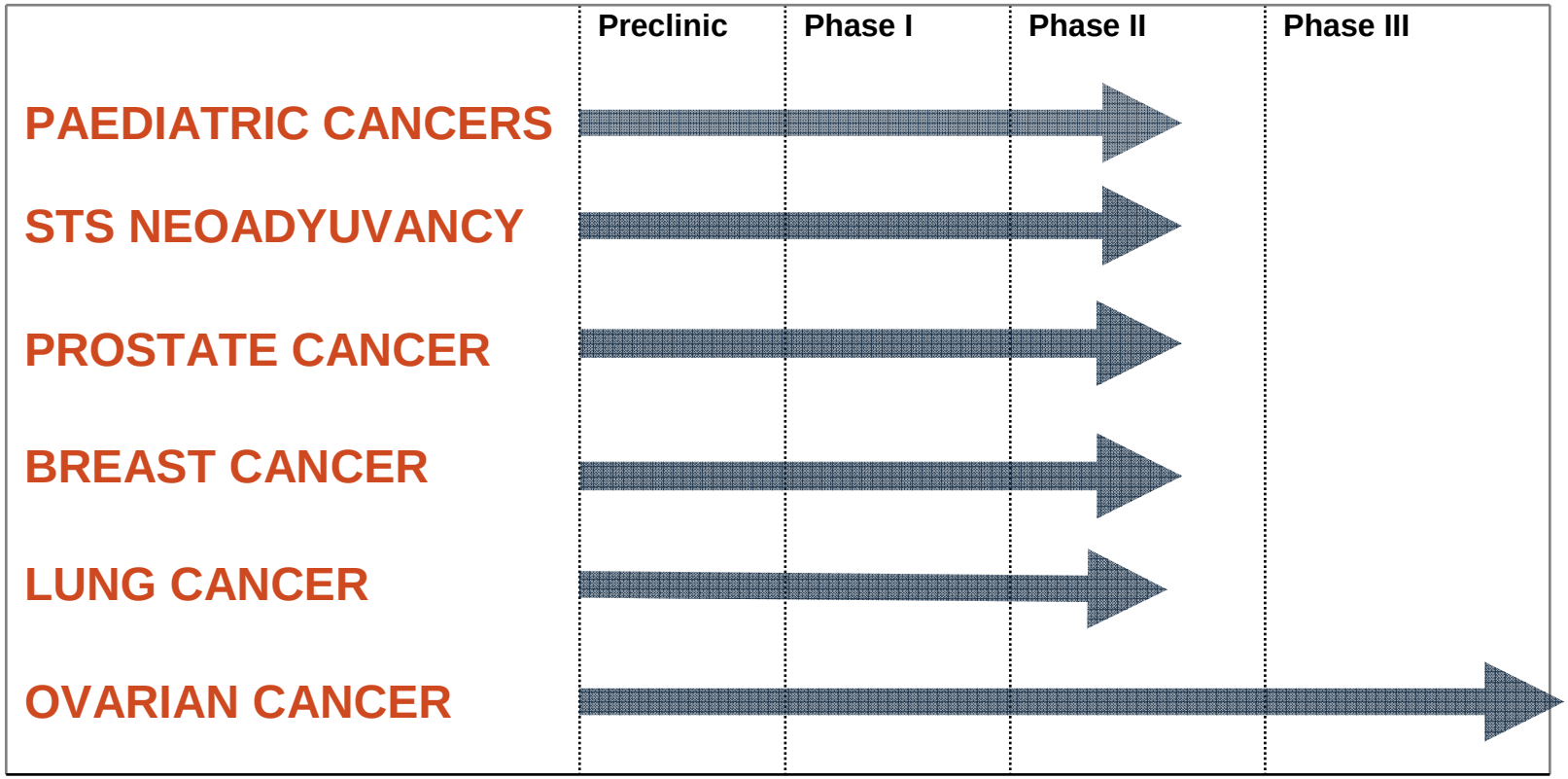
Yondelis®

Yondelis Life Cycle Program



Sound clinical data supports Yondelis broad portfolio development

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Yondelis®

- **Yondelis is indicated for the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents**
- **First drug approved for the treatment of STS in more than 20 years**
- **Strong efficacy data. Yondelis significantly increases time to disease progression (TTP)**
- **Pivotal trial shows prolongation of survival (OS secondary endpoint of ramdomised trial)**
- **Proven safety record after more than 4 years treating patients in compassionate programs**
- **Yondelis manageable and tolerable safety profile grants prolonged administration**

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Yondelis® in soft tissue sarcoma

- **STS are rare solid tumours with an incidence of about 3/100,000**
- **Sarcoma affects about 13,200 people each year in the European Union (EU-25)**
- **Soft tissue sarcomas are often associated with a considerable burden of illness: at diagnosis, many patients have advanced disease which cannot be cured**
- **Median survival from development of metastatic disease is 8-12 months**
- **Most STS subtypes are relatively insensitive to available chemotherapies**
- **Current standards of care are doxorubicin and ifosfamide but high unmet need after disease relapse**
- **Doxorubicin and ifosfamide are the current standard first-line therapies. Before approval of Yondelis there was no standard treatment for patients with advanced STS with relapse after failure of standard therapies**

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Update on STS competitors in development

Not a direct competitor (maintenance therapy)

	Pivotal trial	Approval
Pazopanib GSK	Phase II ongoing	
Deforolimus Ariad/Merk	Q307	2012 (E)
Sorafenib Bayer	Phase II ongoing	
Brostallicin Cell Therapeutics	Pivotal trial not yet announced	
E7389 Eisai	Phase II ongoing	

Existing pipeline has not proved improvement of efficacy over current therapies

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Yondelis Market Opportunity in STS

- **Market potential**
  Target EU population of about 4,000 patients
- **Specialised oncology sales force**
  Team of experienced oncology sales professionals to target European STS prescribers
- **Engage local companies in certain regions**
  SOI/Genesis
- **Strong revenues expected**
  Pricing >€25,000 per patient
- **Continuous clinical development of Yondelis in STS**
  Potential for moving to first line therapy

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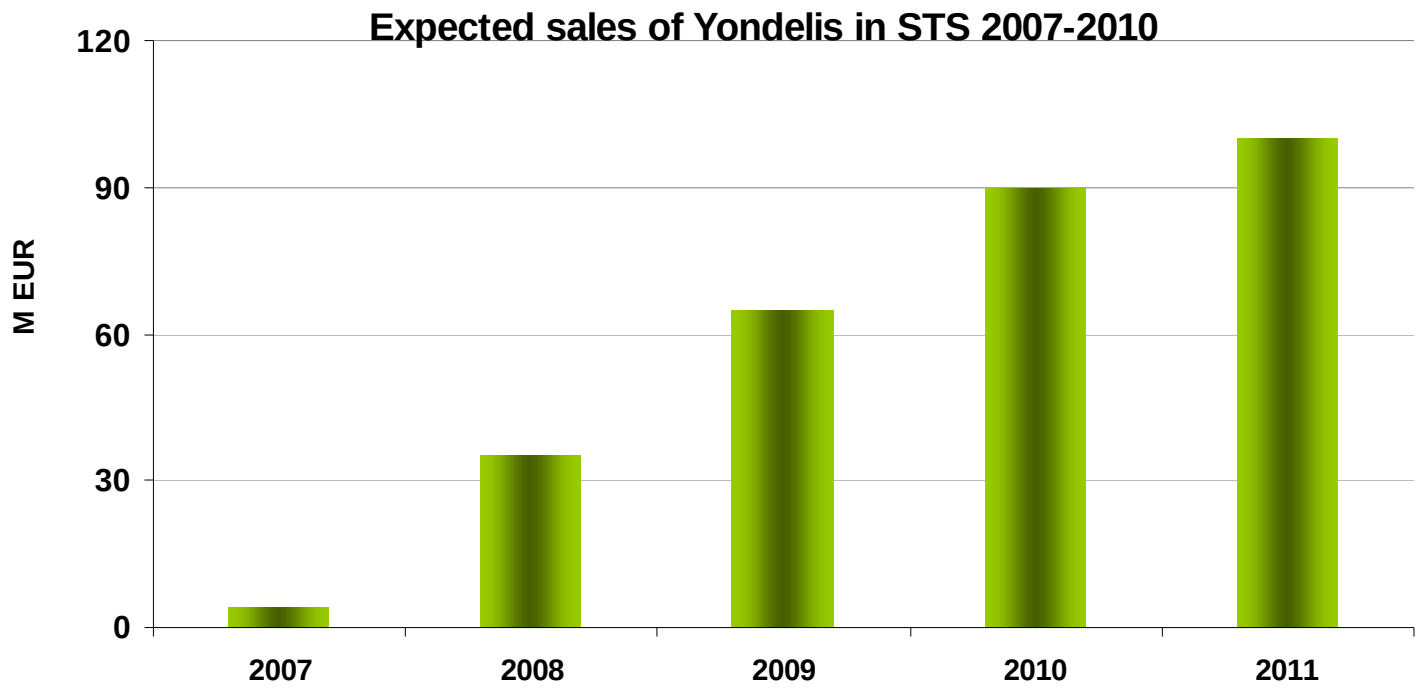
Yondelis Market Potential in STS



Peak sales: 100€ million

Ovarian cancer epidemiology

- **Ovarian cancer is the fifth most frequent cause of cancer deaths in women**
- **Each year approximately 45,000 new cases diagnosed in the EU (EU-25) and about 28,000 deaths each year**
- **Majority of patients diagnosed when disease is advanced and prognosis poor**
- **Standard first line chemotherapies paclitaxel + carboplatin. Vast majority of patients with advanced stage ovarian cancer will relapse**
- **Approximately 75% of patients will require further treatments**
- **Recurrent disease is an important problem: new therapies are needed to improve patient outcomes**

Source: Ferlay, P Autier, M Boniol, H Heanue, M Colombet y P Boyle (Ann Oncol 2007)

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Market for Yondelis in Ovarian Cancer

- **Patients requiring second line agents estimated around 30,000 per year in the EU**
- **Current therapies for relapsed ovarian caner include Hycamtin (topotecan), Caelyx (liposomal doxorubicin), taxanes and the combinations Gemzar+ carboplatin**
  - Hycamtin sales (2006)* : 225$m
  - Caelyx market leader with sales (2006)*: 206$m
- **Yondelis Phase III trial results may outperform safety and efficacy profile of competitors**
- **Yondelis expected to gain market from Caelyx and Topotecan to reach 35% share of the market**
- **Launch expected 2009, PEAK-SALES two years from launch (2011), 11.300 patients**
- **Launch in second indication has significant potential to maximize value of Yondelis**

•Assumed about 80% sales attributed to OC

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Breast Cancer

- **Lead cancer diagnosis in women**
- **Breast cancer affects approximately 270,000 women each year in Europe (EU-25)**
- **Over 50,000 die each year in the EU**
- **1 in 9 women develop breast cancer**
- **Increasing incidence of breast cancer in the world**
- **Survival has significantly improved but dead rate shows need for new therapies**

  Despite recent drug approvals in the adjuvant and metastatic setting, the overall survival remains below five years

Source: Globocan 2002 (2005) P Boyle y J Ferlay (Ann Oncol 2005)

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Market for Yondelis in Breast Cancer

- **Breast cancer market is anticipated to grow from its current size of $ 5.9 billion to $ 11.5 billion by 2011, with a CAGR of 9.8 per cent**
- **Fast growing market**
- **Metastatic patients represent about 50% of market. Triple resistant breast cancer women are estimated to be around 30%**
- **Large market potential for Yondelis of about 50,000 patients**
- **Yondelis could gain an important share of this market given its product profile**
- **Yondelis strategy in breast cancer represents a more personalized way to treat the disease**

Espicom 2006
Company estimates

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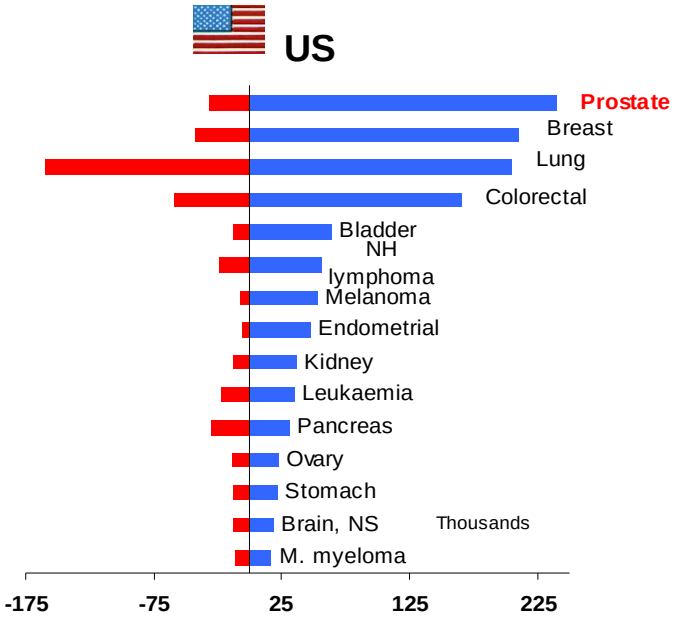
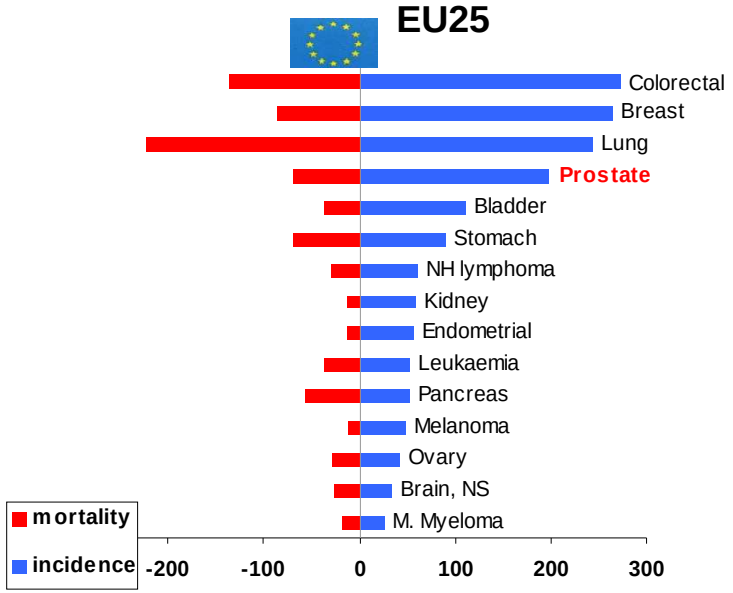
Prostate Cancer Overview

- Prostate cancer is the first leading cause of cancer in men in the US and the third most common cancer worldwide
- Approximately 200,000 new cases are diagnosed each year in the European Union and 234,460 are diagnosed in the US in 2006 with an estimated 27,350 deaths
  - More new cases per year than breast cancer or lung cancer
- The patient population suffering from prostate cancer increases at 4.8% per year
- Most patients develop hormone resistant disease (HRPC) with time





Market for Yondelis in Prostate Cancer

- **Value of the prostate cancer therapy worldwide market over $3 billion (2006), with a growth rate of over 5%**
- **One of the larger segments of the oncology market, alongside breast, non-small cell lung and colorectal cancers**
- **HRPC still an uncrowded market: Docetaxel (Sanofi Aventis) only product to show improvement in survival**
- **Large market potential for new therapies after Docetaxel relapse**
- **Very high unmet need in this market for new therapies**
- **Target Yondelis in UE ~ 10,000 patients/ year**

Source: Espicom

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NSCLC Overview

- **More than 1.2 million incident cases of lung and bronchial cancer diagnosed each year worldwide, causing approximately 1.1 million deaths annually**

  175,000 new patients diagnosed and 168,000 deaths in the US in 2007
  In UE, 208,000 new patients and 190.000 deaths

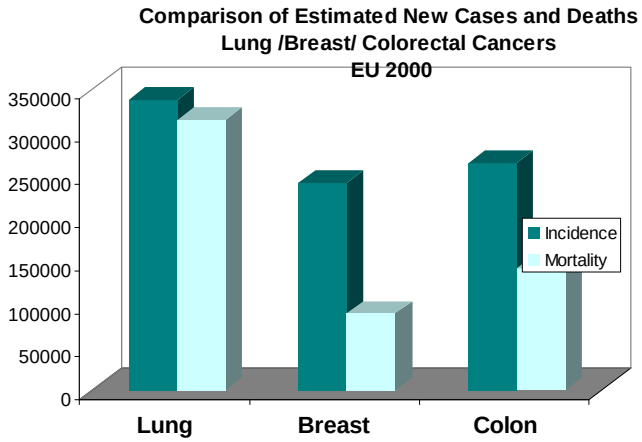
- **Lung cancer is the leading cause of cancer related death in the seven major pharmaceutical markets (US, France, Germany, Italy, Spain, UK and Japan**

  Deaths due to lung cancer exceed those of breast and colorectal cancers

- **Most commonly diagnosed in people in the age range of 55-65 years old**

- **Platinum-based chemotherapy is the cornerstone of NSCLC treatment**

  But response rate to these regimens remains very low



Source: Globocan 2000
American Cancer Society

NSCLC Overview

- **NSCLC drug market forecast to exceed $4.1 billion in 2012***
- **Market characterised by high incidence and poor survival**
  - Very high clinical unmet need
- **R&D very active in this sector**
  - Approximately 13 drugs in Phase III trials
  - But improvement in survival achieved by new drugs has been only marginal
- **40% of patients present with advanced-stage disease**
  - Only approximately one-third of these patients will respond to current standard chemotherapy
- **One of the most important challenges in NSCLC treatment is to tailor therapy specifically to each patient**
  - Yondelis may target around 30% of NSCLC population, in UE around 60,000 patients
- **Market largely dominated by cytotoxics, although targeted therapies are beginning to make an impact**
  - Chemotherapies will continue to be the backbone of disease treatment

Source: Decission Resources,2004

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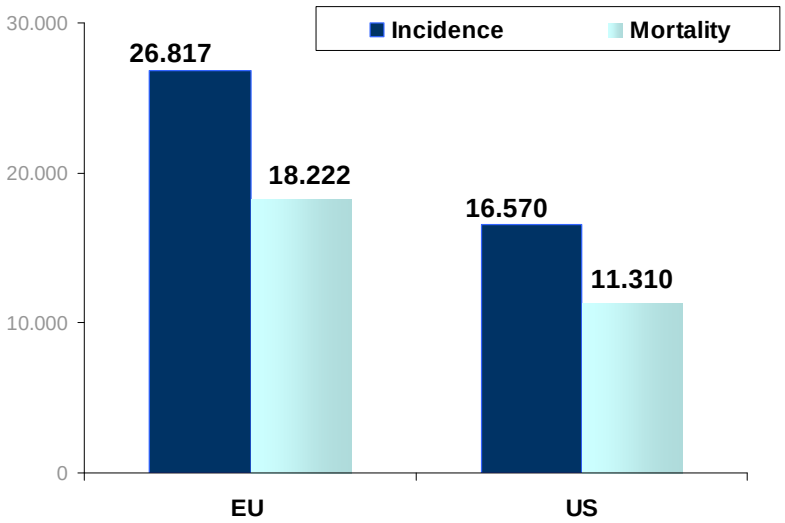
Aplidin

Multiple Myeloma Overview



- **Multiple Myeloma is the second most prevalent blood cancer after non-Hodgkin's lymphoma**
- **2% of all cancers and responsible for 1% of all cancer deaths**
- **Multiple myeloma is predominantly a cancer of the elderly, the average age at diagnosis is 70 years of age. Only 1-2 % of pats are younger than 40**
- **Little change in disease growth expected in the next five years, mainly due to the aging of the population**
- **Large prevalent population myeloma patients can survive for many years with therapeutic interventions**

Incidence and mortality data for US: American Cancer Society 2006
Incidence and mortality estimations for Europe: Globocan 2002

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Market Potential for Aplidin in Myeloma

- **Multiple myeloma is a disseminated disease: chemotherapy treatment only available option (radiotherapy and surgery ineffective)**
- **High sales of new agents expected because of the high volume usage**
  - Myeloma patients survive for many years undergoing a number of lines of therapy
- **New agents bortezomib, lenalidomide and thalidomide main market drivers**
- **Use of combinations of established and new agents expected to grow**
  - Aplidin positioned in second line APL + lenalidomide + DEX
- **High unmet clinical need**
  - for new therapies with reduced toxicity and new mode of action
  - for curative agents, there is still high mortality, as most patients will die

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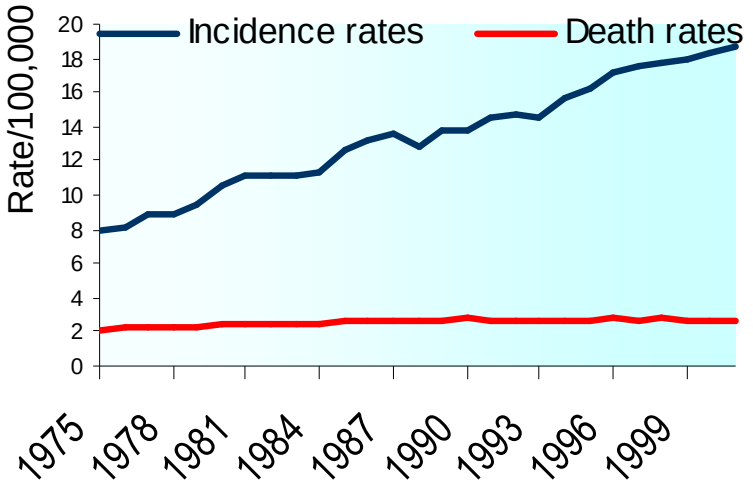
Melanoma Overview

- **Over 100,000 cases of melanoma diagnosed in the world's seven major pharmaceutical markets in 2006**
- **Melanoma is one of the fastest growing cancers: annual increase 3-7 % (Caucasians)**
- **EU incidence is about 45,000 new case per year and about 11,000 deaths. Early detection results in very large prevalence of about 180,000 cases (5 year prevalence)**
- **Most common cancer in young adults aged 20-30**
- **Disease is mainly diagnosed in early stages**
  Disseminated disease is about 4% at diagnosis
- **5-year survival remains high for localised disease (around 80%) but drops dramatically for regional (10%) or distant disease (4%)***



Incidence and Death Rates of Melanoma 1976-2001 in US SEER data

GLOBOCAN 2002, Cancer Incidence, Mortality and Prevalence Worldwide, International Agency for Research on Cancer
*5- Year Relative Survival Melanoma SEER all races, all ages by Diagnosis Year 1992-1999

Pharma Mar

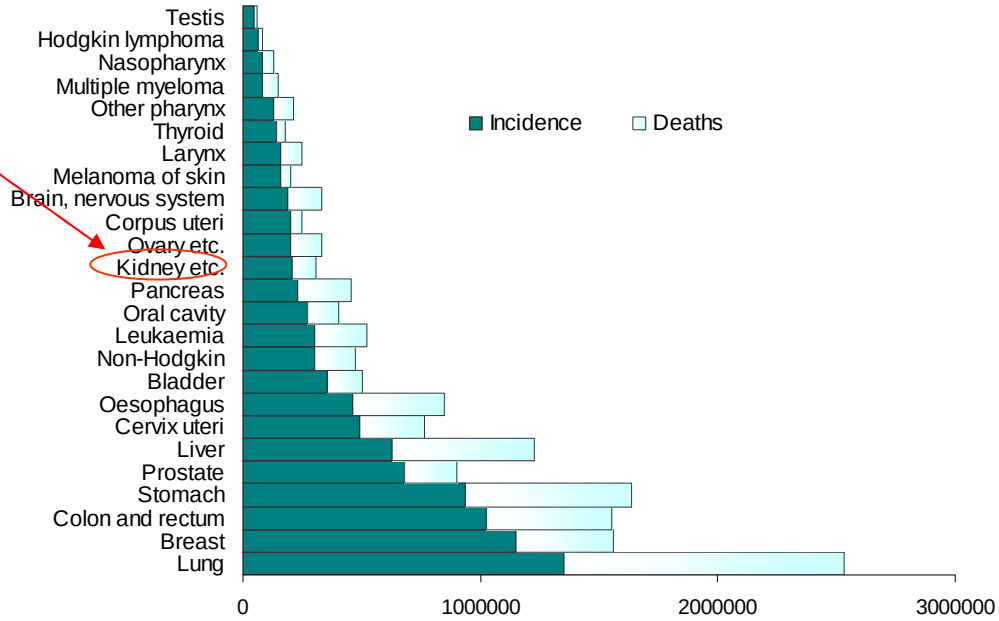
Market Potential for Aplidin in Melanoma

- **Market value estimated to be $391 million in 2003 projected to grow to $775 m in 2010**
- **Market for advanced disease around 15,000 new patients in EU**
- **But very high unmet need due to lack of clinical options for these patients**
  - Advanced melanoma associated with an extremely poor median survival (2 to 8 months) and a 5-year survival rate < 10%
  - No available treatment improves survival for patients with metastatic melanoma
- **Despite extensive R&D no significant advance in the last 30 years: only a few drugs approved for metastatic disease**
  - Dacarbazine DTIC (1975)
  - Aldesleukin IL-2 (1998)
- **Two main new agents in phase III trials are late stage pipeline:**
  - Pfizer's ticilimumab and Medarex/Bristol-Myers Squibb's ipilimumab
  - New entrants from 2009

Pharma Mar

Renal Cell Carcinoma

- **Renal cell carcinoma (RCC) represents 2–3% of adult cancers**
- **About 45,000 new cases detected each year in the EU and about 25,000 deaths. About 39,000 incidence cases and 13,000 deaths in the US in 2006**
- **During the past 2 decades, the incidence has increased by approximately 2% per year**
- **Surgical resection to remove the entire kidney or part of it only accepted curative treatment for early disease**
- **Very poor prognosis of patients with metastatic disease**
  - –Without treatment, these patients have a median survival rate of only 6-12 months



Market Potential for Aplidin in RCC

- **Market estimated to be worth around US$1 billion in 2006, with growth rate of 36%. Sales of RCC treatments to increase to US$3 billion by 2009 and over US$6 billion by 2012**

- **Management of metastatic disease has experienced a shift**
  - Until recently metastatic disease treated with cytokine therapy Schering-Plough's Intron A (interferon [IFN] alpha-2b) /Novartis' Proleukin (aldesleukin);

- **Better understand of tumour cell biology has lead to the launch of new targeted therapies**
  - Sorafenib (Nexavar; Bayer/Onyx)
  - Sunitinib (Sutent; Pfizer)
  - Bevacizumab (Avastin; Roche Pharmaceuticals)
  - Temsirolimus (Torisel, CCI-779; Wyeth)

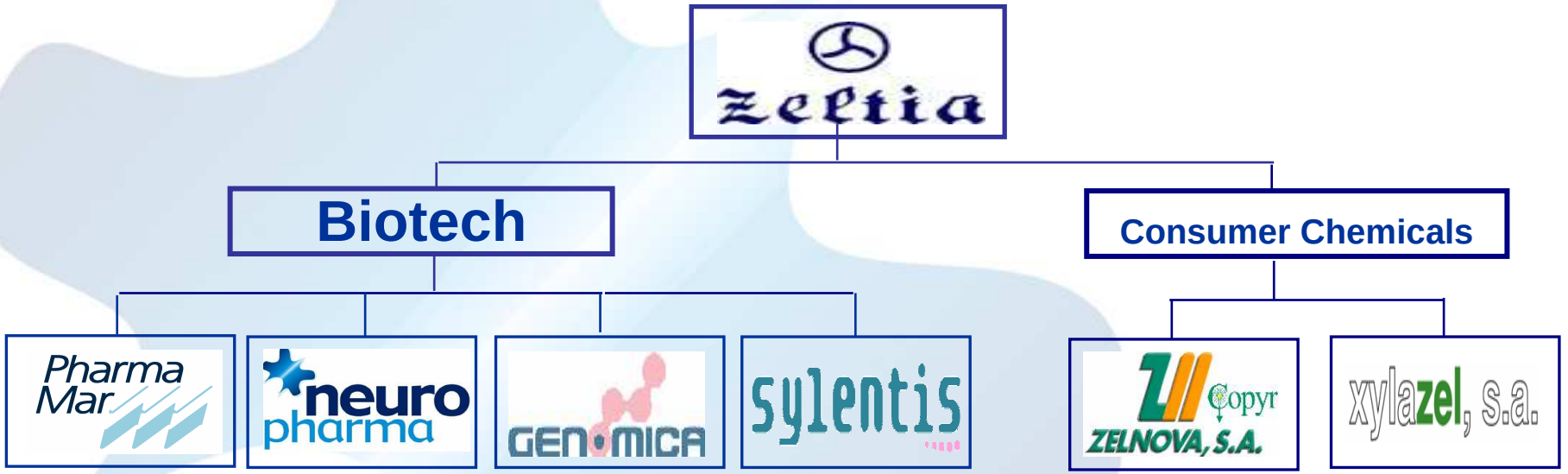
- **Opportunity for Aplidin**
  - As new agents move to earlier stages and adjuvant setting
  - Greater use of combination therapies instead of monotherapies
  - Around 50% of early-stage patients are not cured by surgery and 80% of patients with advanced disease fail to respond to approved therapies
  - Large market potential for Aplidin in UE > 25,000 patients per year.

Pharma Mar

Diciembre 2007

neuro pharma

Estructura del Grupo



100%
Marine derived anti-cancer drugs

59%
Marine and synthetic derived drugs for Alzheimer's treatment

100%
DNA analysis technology, diagnostic kits and microarrays

100%
RNA Interference New Therapy Approach

100%
Insecticides and air fresheners

100%
Wood and metal protection

Nuestra Misión

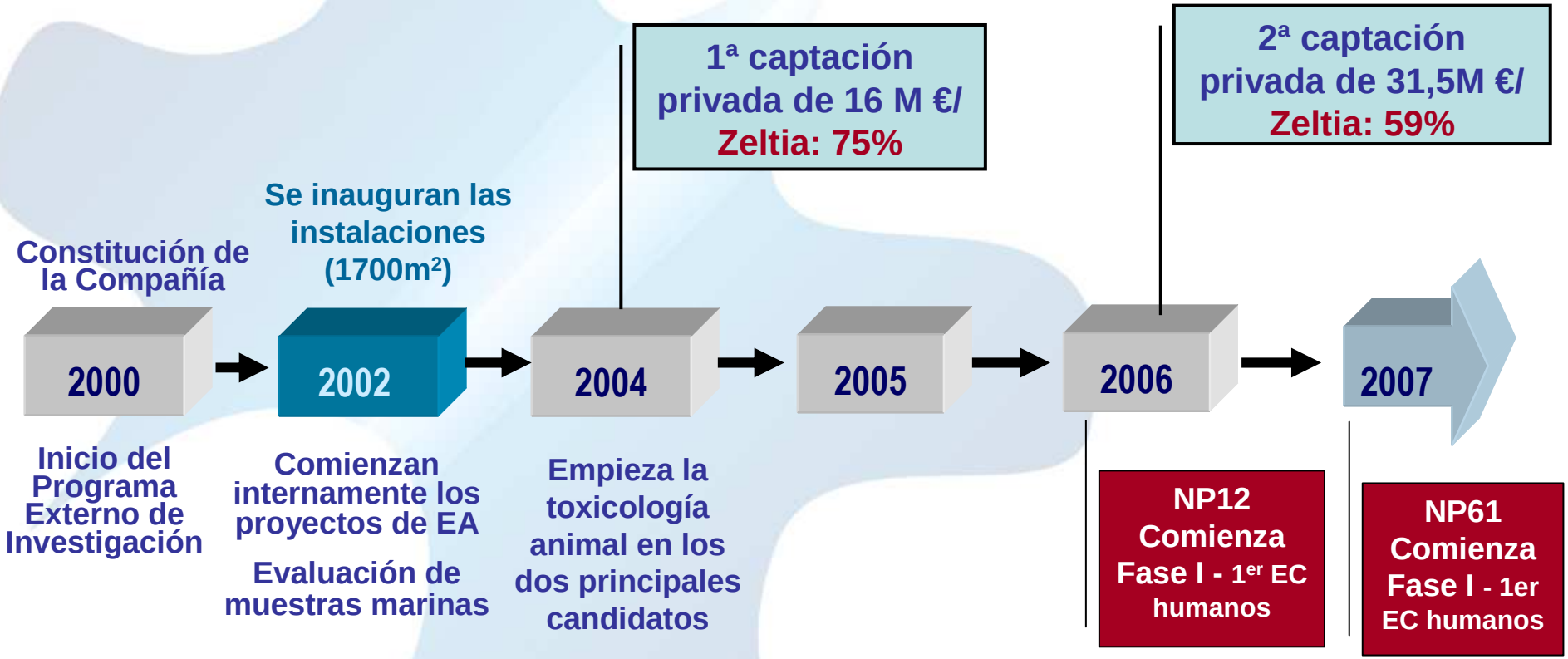
Investigar, desarrollar y comercializar compuestos innovadores, seguros y eficaces para tratar enfermedades del Sistema Nervioso.

Atención especial> Enfermedades Neurodegenerativas

↓

Enfermedad de Alzheimer

Breve Historia de la Compañía



Hitos

- **2006: Comienza la fase clínica del 1er compuesto para la Enfermedad de Alzheimer (Inhibidor de GSK3).**
- **2007: Comienza la fase clínica del 2º compuesto para la Enfermedad de Alzheimer (Modulador de ß Amiloide).**
- **2007: Licencia de un modelo de ratón transgénico a JSW (CRO)**
- **CDTI:**
  - **2006: Nanofarma – Subvención: 1 Mill.€/ 4 años**
  - **2007: Melius – Subvención: 5 Mill.€/ 4 años**
- **2007: Premio internacional Frost & Sullivan a la "Excelencia en Tecnología".**

Plan 2008-2009

- **2008: Un nuevo compuesto de origen marino será elegido para desarrollo.**
- **2008-2009: Compuesto (s) en Fase II**
- **2008-2009: Salida a Bolsa**
- **2009: Introducción de Terapia Celular en ensayos clínicos para lesiones medulares.**

Principales Activos

- **Personal: 60 empleados, 80% de los cuales son científicos altamente cualificados.**
- **Comité Científico Asesor: Expertos de prestigio nacional e internacional en el campo de la Neurociencia.**
- **Comité Clínico Asesor: Expertos clínicos de prestigio nacional e internacional en la Enfermedad de Alzheimer y Sistema Nervioso Central.**
- **Acuerdos de Colaboración: con instituciones académicas para investigación y desarrollo.**

Principales Activos

- **Nuestro propio sistema de screening para muestras de origen marino para explorar nuevas dianas eficaces en la Enfermedad de Alzheimer.**

- **Derechos para usar la librería marina de Pharmamar: más de 50.000 muestras marinas como nueva fuente de biodiversidad para encontrar moléculas de enfermedades del sistema nervioso.**

- **Derechos mundiales de licencia de dos ratones transgénicos que reproducen las principales características de la enfermedad de Alzheimer y de otras enfermedades neurodegenerativas.**

Principales Activos

- La cartera de patentes se compone de 162 expedientes reunidos en 23 familias de patentes, cada una de las cuales protege una invención determinada:
  - 44 son patentes concedidas
  - 118 son solicitudes de patente en tramitación

Neuropharma

- Financiación privada

2004 y 2006:
1ª y 2ª Colocación Privada

- **Banco Asesor: BANIF**
  - **Evaluación independiente:**
    - **Financiera**
    - **Científica**
- **Dirigida a: inversores locales privados**

2004: 1ª Colocación Privada

- ***Pre-money valuation:* 46 M €**

- **Principales Activos:**
  - **2 candidatos en fase de toxicología regulatoria con MoA innovador para EA.**
  - **Plataforma tecnológica para screening de muestras marinas.**
  - **Comité Científico Asesor: 7**
  - **Personal: 33 empleados**
  - **Solicitante y licenciatario exclusivo de 10 Familias de Patentes: 34 solicitudes de patente y 3 patentes concedidas.**

+ 16 M €

Zeltia vende: 25%
Zeltia conserva: 75%

- ***Post-money valuation:* 62 M €**

Operación financiera:

- **Objetivo: conseguir suficientes fondos para iniciar la fase I con los dos candidatos.**
- **Tasa media de éxito: 12,7%**
- **Zeltia adquirió el 7%**

2006: 2ª colocación privada

+ 31.5 M €

- ***Pre-money valuation:* 89 M €**

- **Principales Activos:**
  - **1 candidato en Fase I EECC**
  - **1 candidato preparando Fase I EECC**
  - **Nuevo proyecto: terapia cel.**
  - **Pipeline: compuestos de origen marino.**
  - **Personal: 60 empleados**
  - **Plataforma tecnológica para muestras marinas.**
  - **Comité Científico Asesor: 7**
  - **Comité Clínico Asesor: 5**
  - **23 Familias de Patente : 108 solicitudes de Patente y 42 Patentes Concedidas**

Zeltia conserva: 59%

Operación Financiera:

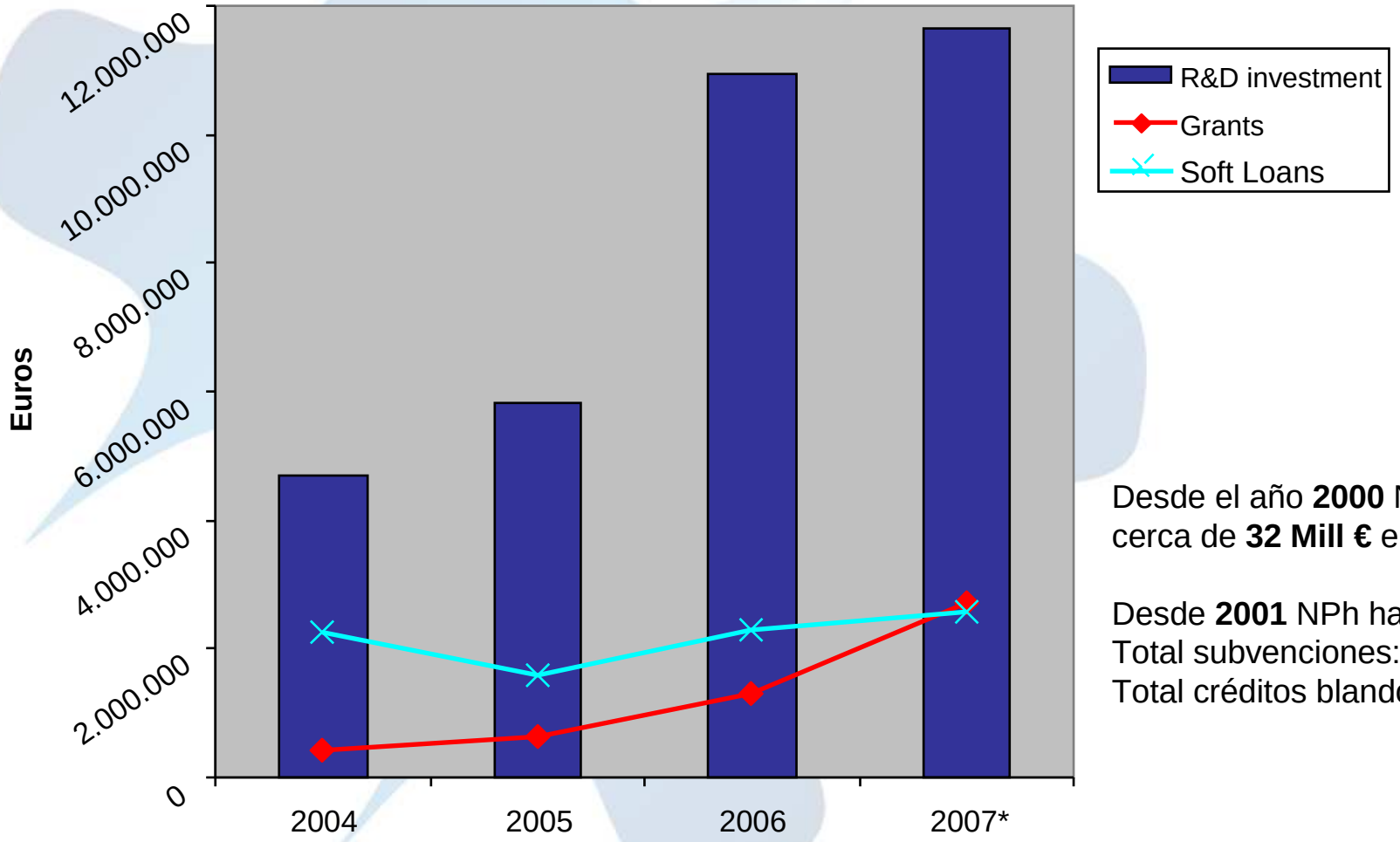
- **Objetivo: conseguir suficientes fondos para iniciar la fase II con ambos candidatos.**
- **Tasa media de éxito : 19%**
- **Zeltia adquirió: 13%**

- ***Post-money valuation:* 120,5 M €**

Neuropharma

- Financiación pública

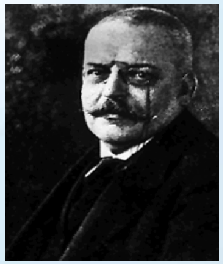
Financiación pública frente a inversión en I+D

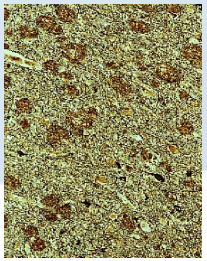


Desde el año **2000** NPh ha invertido cerca de **32 Mill €** en I+D.

Desde **2001** NPh ha recibido:
Total subvenciones: **6 Mill €**
Total créditos blandos: **11 Mill €**

Enfermedad de Alzheimer





"The first noticeable symptoms of the illness of this 51-year old woman was suspiciousness of her husband. Soon, a rapidly increasing memory impairment became evident. She could no longer orient herself in her own dwelling, dragged objects here and there and hid them, and, at times believing that people were out to murder her, started to scream loudly."

Alois Alzheimer (1907)

La enfermedad

- **Enfermedad neurodegenerativa clínicamente caracterizada por la pérdida progresiva de funciones cognitivas. El paciente sufre un deterioro progresivo que se caracteriza por:**
  - Pérdida de memoria
  - Alteración de la comprensión
  - Alteración de la expresión del lenguaje
  - Pérdida de reconocimiento
  - Pérdida de manejo de objetos o de maniobras

- **Enfermedad de origen desconocido que genera dos lesiones características en el cerebro:**
  - **Placas seniles** formadas por la agregación del péptido beta amiloide
  - **Ovillos neurofibrilares** formados por la proteína Tau hiperfosforilada

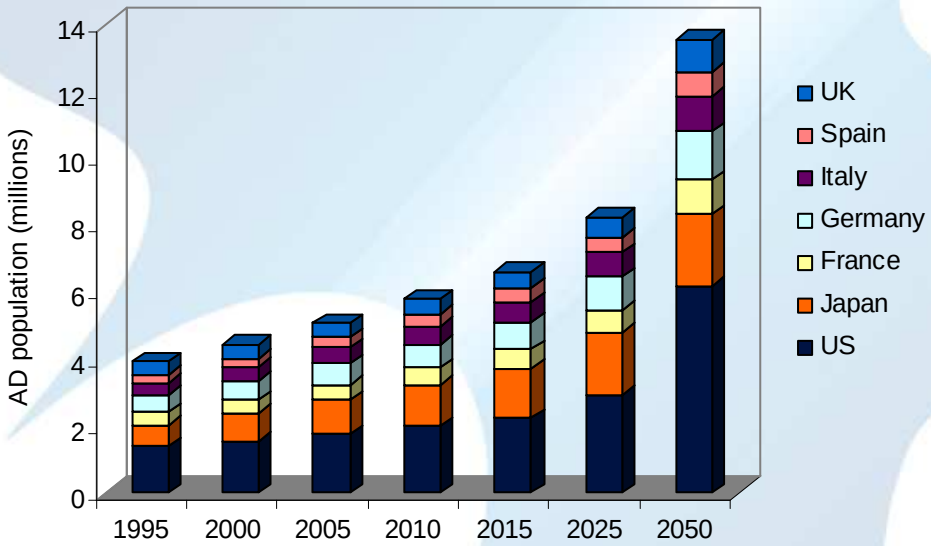
Coste (personal, económico y social)

- Produce un alto coste personal, lo que lleva frecuentemente a la depresión del enfermo al inicio, y a la incapacidad después.
  - **Estadio precoz** pérdida de memoria → **intermedio** (precisa ayuda) → **grave** (incapaz): el paciente ya incapacitado, ha de ser atendido por otras personas para llevar a cabo las mas elementales actividades de la vida diaria.

- Produce un alto coste social, superando los **100.000 Mill USD** a nivel mundial. Estos gastos, en los países desarrollados, rondan los 18.000 €/ año por paciente. Las principales partidas son:
  - Recursos sociosanitarios (cuidadores que dejan su empleo, transporte especial, Farmacia, etc.)
  - Recursos sanitarios (consultas, tratamientos, etc.)

Prevalencia de Alzheimer

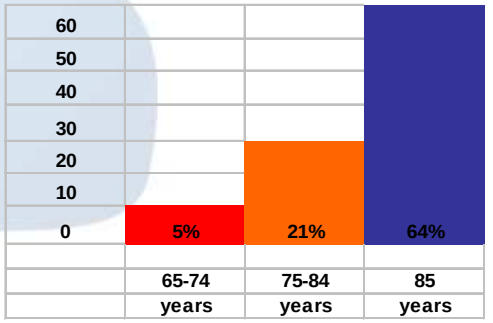
Se estima que alrededor de 27 millones de personas están afectadas de Alzheimer.



El número de enfermos de EA se triplicará para el año 2050, como resultado del envejecimiento de la población.

El aumento progresivo de la esperanza de vida aumentará la prevalencia, junto con la mejora de la asistencia sanitaria y de las técnicas de diagnóstico.

•La prevalencia de la enfermedad crece con la edad exponencialmente.



•Tasa media de diagnóstico en los 7 principales mercados del 55%

• Sólo el 64% de los casos diagnosticados recibe tratamiento específico.

Datamonitor Pipeline & Commercial Insight: Alzheimer's disease

Tratamiento

Alzheimer's disease remains, 100 years after its first description, a challenge both in diagnosis and treatment.

The introduction of various Alzheimer's drug, including the acetylcholnesterase inhibitors and the NMDA receptor antagonist Namenda, have substantially affected the disease course of Alzheimer's patient, but these drugs only offer symptom abatement during mild and moderate stages of the disease and are loosely related to disease progression arrrest.

Ambiguous data regarding the treatment of Alzheimer's has promoted a lack of uniformity in prescription selection and timing by neurologist and poor adherence to professional guidelines.

Alzheimer's Drug Development Summit – Washington November 2007

Discover the latest Disease Modifying Therapies and Pre-symptomatic approaches for AD Drug Development

Tratamiento actual

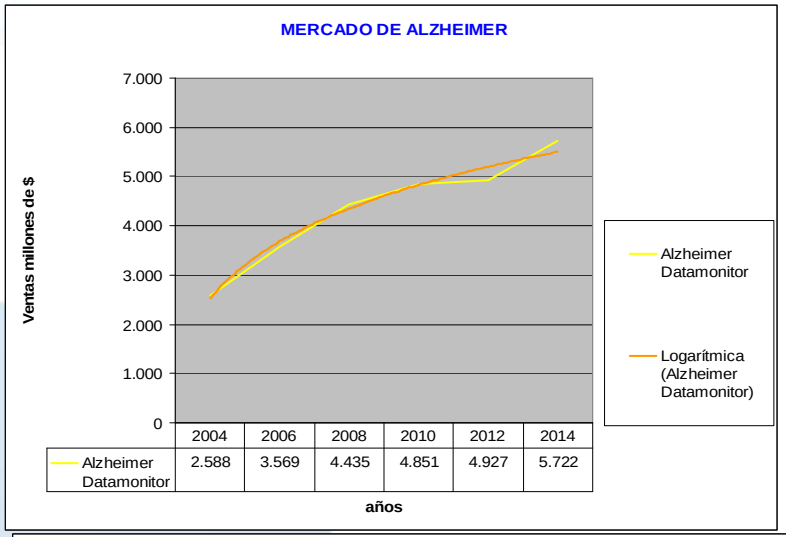
- En la actualidad, no existen tratamientos que puedan retrasar o modificar el curso neurodegenerativo de la enfermedad.
- Los tratamientos de hoy, producen sólo mejorías ligeras en los síntomas durante un breve período de tiempo. Al cabo de semanas o meses reaparece el empeoramiento previo, por la persistencia del proceso neurodegenerativo existente.
- Existen dos tipos de medicamentos en el mercado clasificados según su mecanismo de acción:
  - **Inhibidores de acetilcolinesterasa:** Producen un pequeño beneficio transitorio en las funciones cognitivas.
  - **Antagonistas del receptor de NMDA:** Produce ligeras mejorías transitorias en la autonomía en la fase severa.

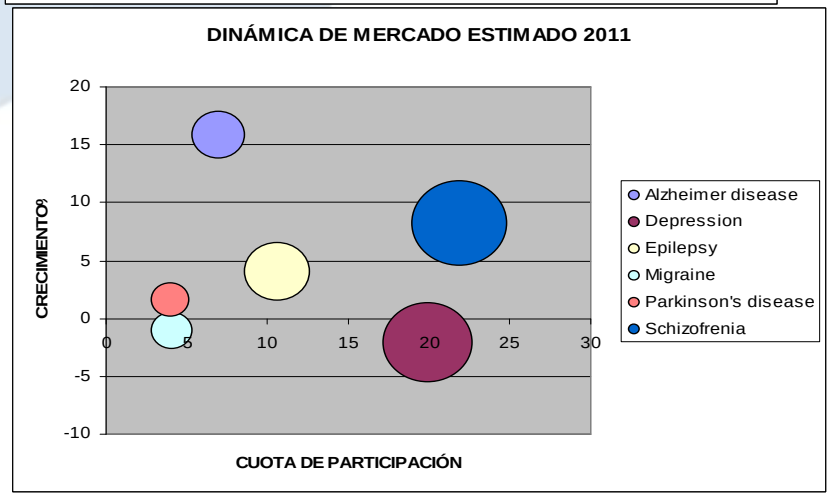
Mercado de Alzheimer

ALTO POTENCIAL DE MERCADO

3,9 b $ en 2005; crecimiento 20% frente a año anterior.

- Tratamiento actual: paliativo
- Mercado joven
- Mercado altamente insatisfecho
- Prevalencia creciente en los mercados desarrollados.
- Rápida introducción de nuevos tratamientos.
- El mercado de Alzheimer (+20%) se ha consolidado como el de mayor crecimiento dentro de SNC (media +12%)





Mercado de fármacos para EA

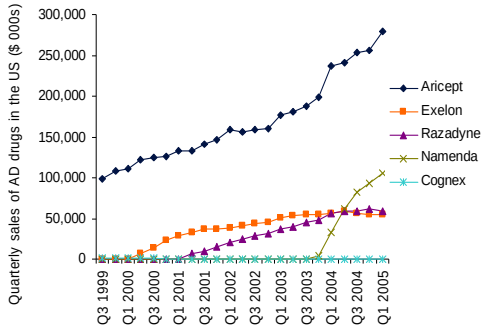
- Asciende en **3.900 Mill USD**. Este volumen se concentra en **cuatro** grandes productos que representan el 98% del mercado total.

Mercado de Alzheimer principales productos, 2004-05

Brand	Generic	Class	Marketing company	Sales ($m) 2004	Sales ($m) 2005	Growth 04-05 (%)	2005 Mkt. share (%)
Aricept	donepezil	CI	Pfizer	1,880	2,148	14.3%	54.7%
Exelon	rivastigmine	CI	Novartis	450	482	7.0%	12.3%
Reminyl/ Razadyne	galantamine	CI	J&J	427	478	12.0%	12.2%
Namenda	memantine	NMDAA	Forest	270	477	76.6%	12.1%
Ebixa	memantine	NMDAA	Lundbeck	113	175	54.6%	4.5%
Akatinol	memantine	NMDAA	Lundbeck	50	62	23.8%	1.6%
Prometax	rivastigmine	CI	Novartis	24	25	4.2%	0.6%
Axura	memantine	NMDAA	Merz	16	22	39.0%	0.6%
Others				45	60	33.3%	1.5%
Total				**3,275**	**3,929**	**20.0%**	**100.0%**

CI = cholinesterase inhibitor; NMDAA = NMDA receptor antagonist

SOURCE: IMS



- Ha sido el de mayor crecimiento dentro de sistema nervioso central, con **crecimientos anuales acumulados del 35% desde 2001** (la media de crecimiento del total mercado farmacéutico fue del 8,2% en ese período).

Mercado futuro: Pipeline

FASE III: Sólo tres productos se postulan como posibles candidatos a registro en 2010.

Nombre Comercial	Molécula	Mecanismo de acción	Compañía	Fase III
Flurizan	Tarenflurbil (R)-flurbiprofen	modulador Aß; Anti-inflamatorio	Myriad Genetics	US
Alzhemed	Tramiprosate	modulador Aß;	Neurochem	US
N/A	neramexane	Antagonista NMDA	Merz/Forest Labs	US

Datamonitor Pipeline & Commercial Insight: Alzheimer's disease

Mercado futuro: Pipeline

Key drugs in development: Neurochem's Alzhemed and Myriad's Flurizan

Greg Ventresca, Director, Healthcare Consulting. Datamonitor

Alzheimer's Drug Development Summit – Washington November 2007

Discover the latest Disease Modifying Therapies and Pre-symptomatic approaches for AD Drug Development

Mercado futuro: Pipeline

Sólo en dos casos podrían llegar a posicionarse como modificadores de la enfermedad

- ***Flurizan*:** agente selectivo para disminuir Abeta 42: Sólo da respuesta al tratamiento en estadios leves.
  - Fase III en **EA leve**: 2 estudios de larga duración en marcha. Datos: fin 08
- ***Alzhemed*:**
  - Fase III USA: resultados negativos (Agosto 2007)
  - Fase III UE: suspendido – finalización prematura
- ***Neramexane*:** El estudio en fase III comparativo de Neramexane en combinación con Inh. AChE frente al tratamiento establecido no muestra diferencia significativa en *primary endpoints.*

->**Xaliproden/** SANOFI (NGF ag; 5HT1A ag): 50% éxito según analistas (Lehman Mkt analysis)

Datamonitor Pipeline & Commercial Insight: Alzheimer's disease

Mercado futuro

PREVISIÓN DE VENTAS

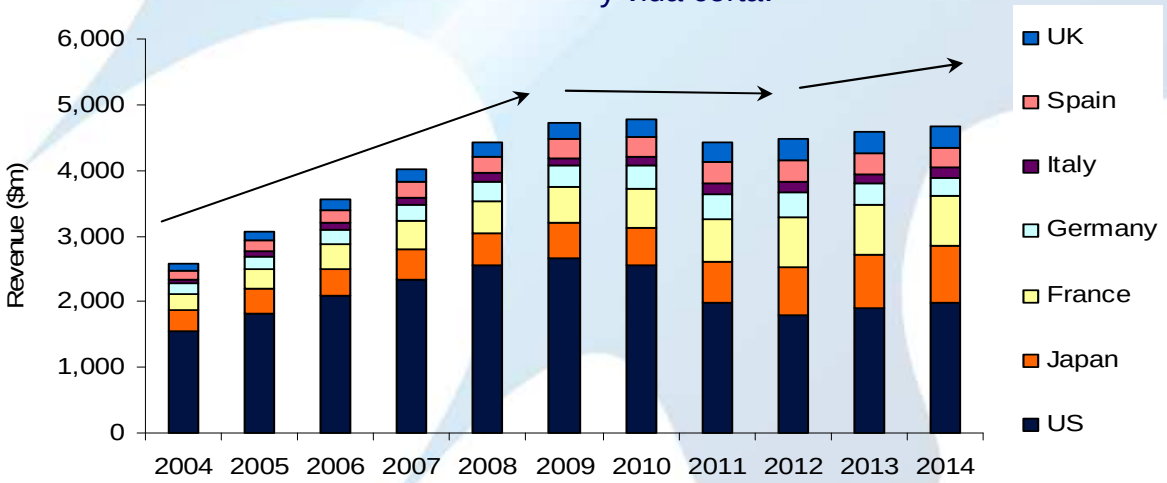
El mercado global de AD crecerá de 3,9 billones de $ USA en 2005 a 5,7 billones en 2015, con CMA de 8,4%, conducido por un crecimiento sostenido de los tratamientos actuales, nuevos lanzamientos y un envejecimiento paulatino de la población.

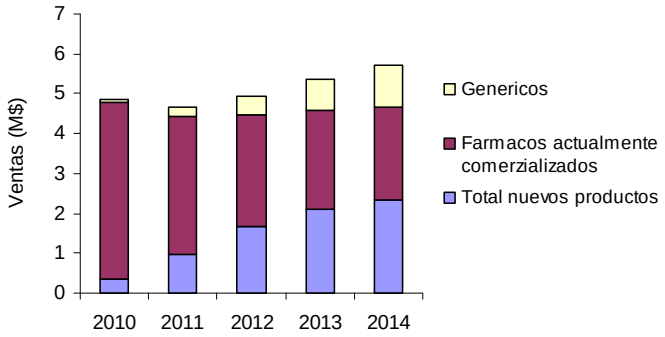
1º) Crecimiento sostenido de los tratamientos actuales de **2005** a 2009 (11.4% CMA).

2º) Entrada de genéricos en **2009**, reduciendo precios.

Posible entrada de **Neramexane/Flurizan/Alzhemed** a partir de 2010, con introducción lenta y vida corta.

3º) Posible entrada de fármacos modificadores de la enfermedad a partir del **2013-14**, que neutralizarán tendencia genéricos y restaurarán tasas de crecimiento del mercado.



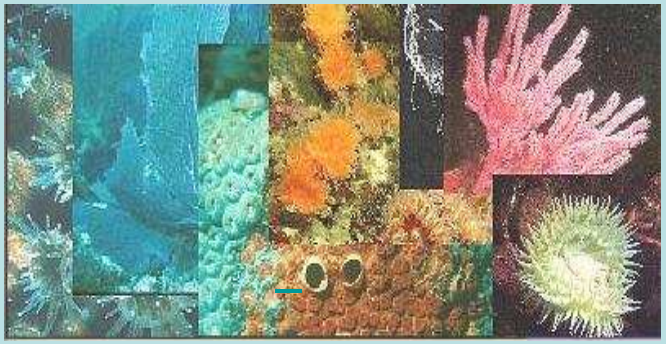


Datamonitor Pipeline & Commercial Insight: Alzheimer's disease

Investigación y Desarrollo

Estrategia

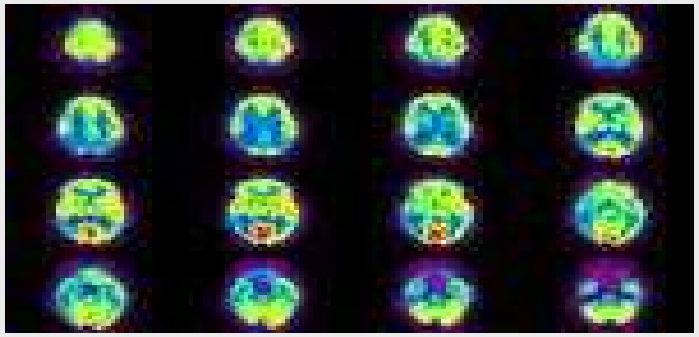
Diversidad estructural



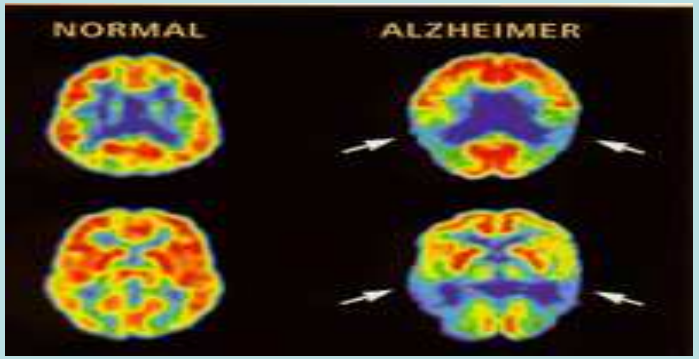
Productos naturales marinos

Química médica y diseño racional

Foco terapéutico

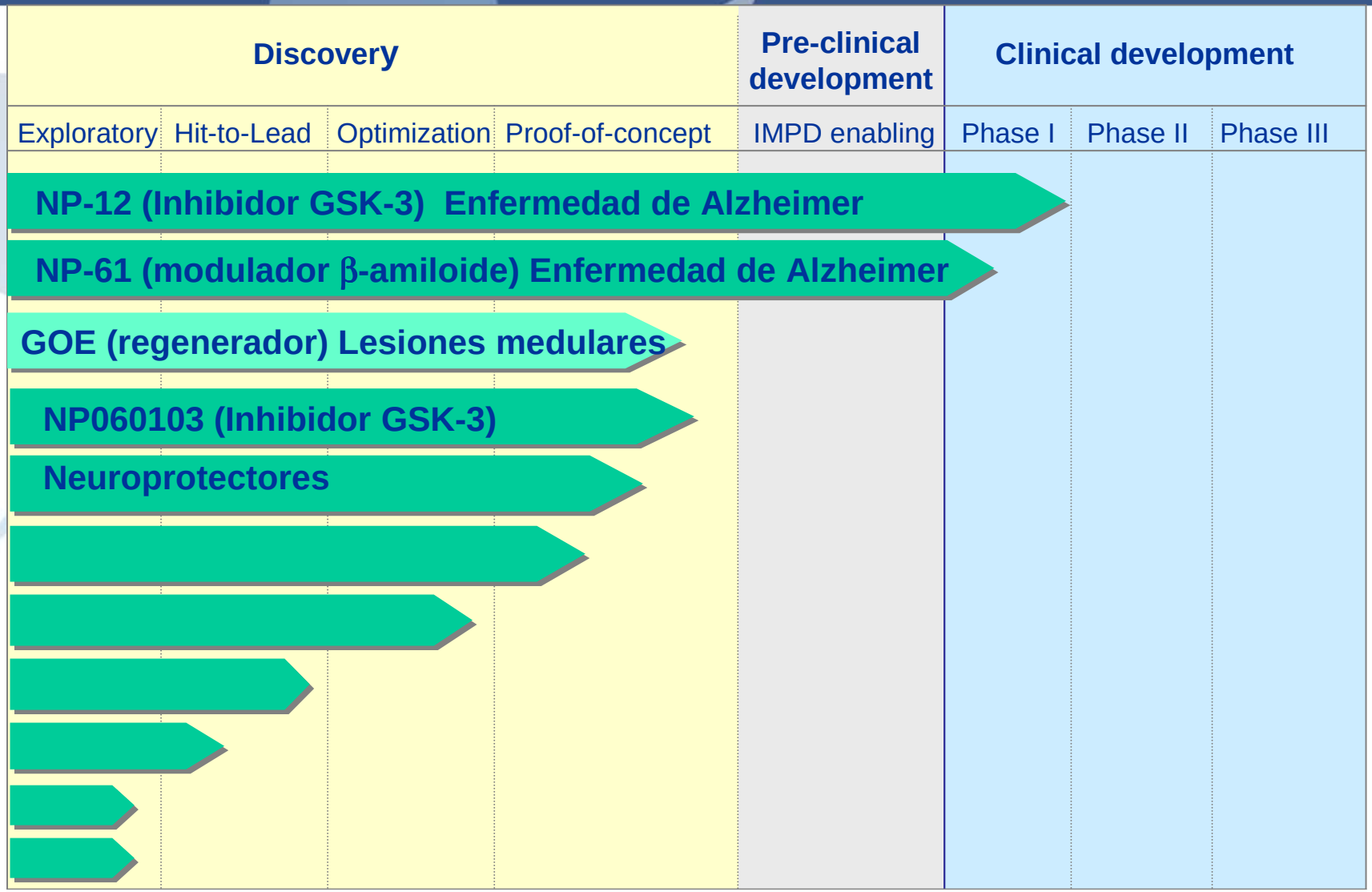


Enfermedades neurodegenerativas

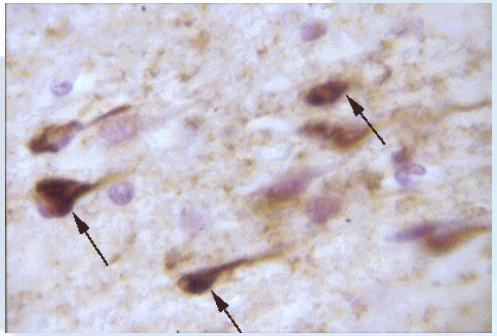


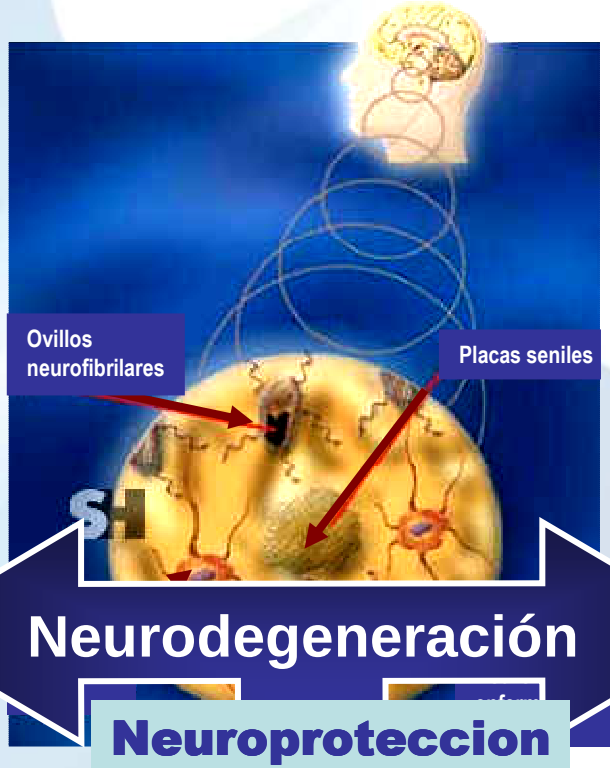
Enfermedad de Alzheimer

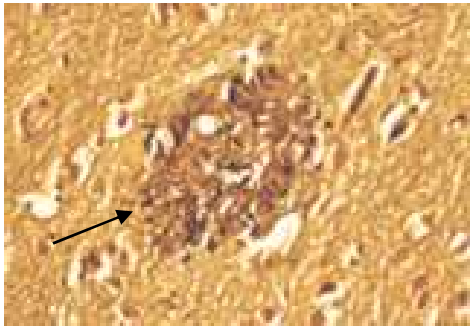
Pipeline 2007



Enfermedad de Alzheimer







Tau hiperfosforilada

β-amiloide

Neurodegeneración

Neuroproteccion

Inhibidores de GSK-3

Alteración neurotransmisores

Moduladores de β-amiloide

Inhibidores de GSK-3

Muestra de algunas compañías farmacéuticas que investigan en esta diana:

Schering-Plough

novo nordisk

Pfizer

Johnson & Johnson

sanofi aventis

L'essentiel c'est la santé.

Roche

VERTEX

AstraZeneca

UNITED KINGDOM

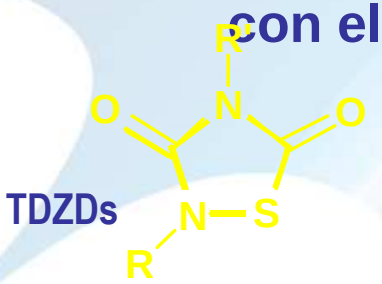
CHIRON

gsk GlaxoSmithKline

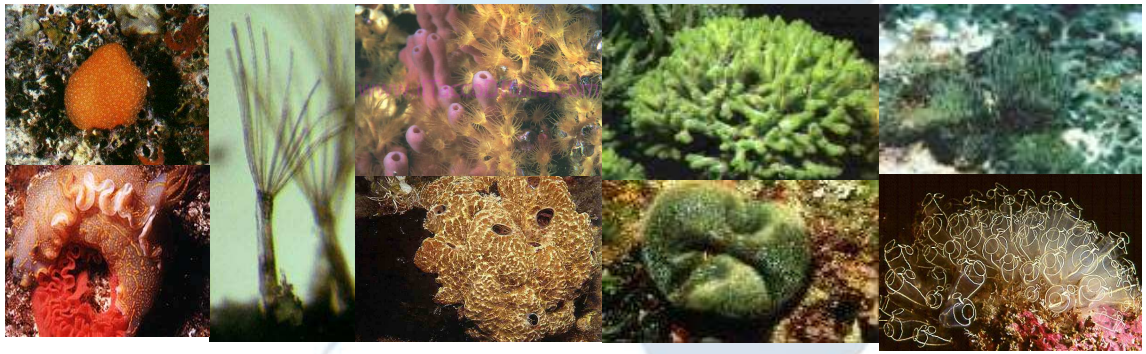
Inhibidores de GSK-3

Ventajas competitivas frente al mercado

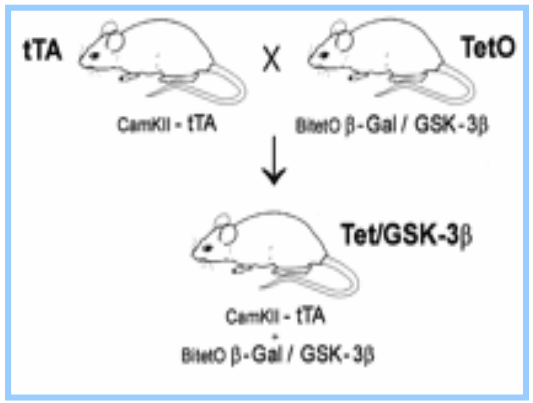
Desarrollo de inhibidores selectivos que no compiten con el ATP



Búsqueda de compuestos naturales marinos como nuevos y potentes inhibidores de GSK-3



Validación en un modelo transgénico único: (tet/GSK-3β)

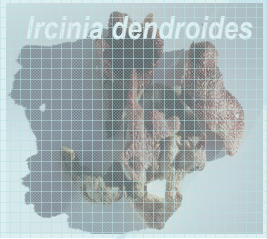


Inhibidores de GSK-3. Compuestos marinos

Manzaminas

Fistularina

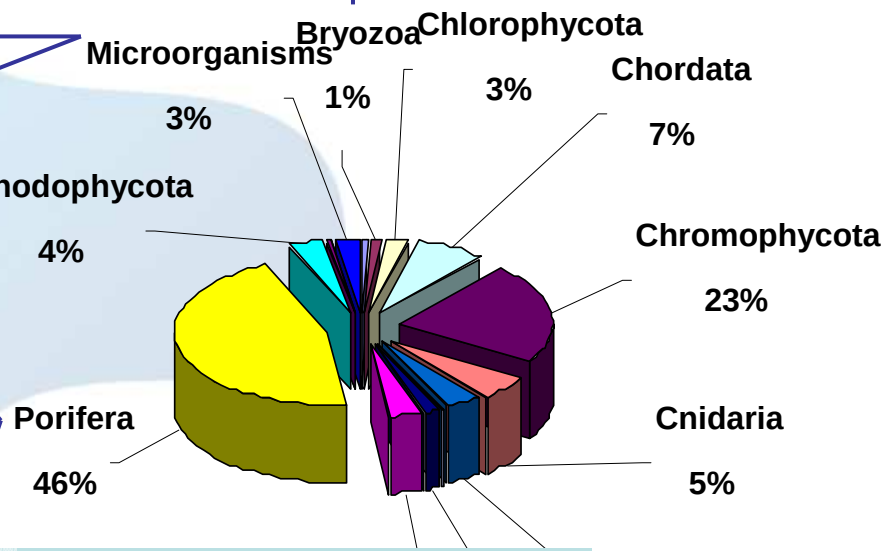
Oroidina



Palinurina

Prenilquinonas

EXTRACTOS POSITIVOS EN EL ENSAYO DE GSK3ß PER PHYLUM RESPECTO AL TOTAL DEL NUMERO DE EXTRACTOS PER PHYLUM



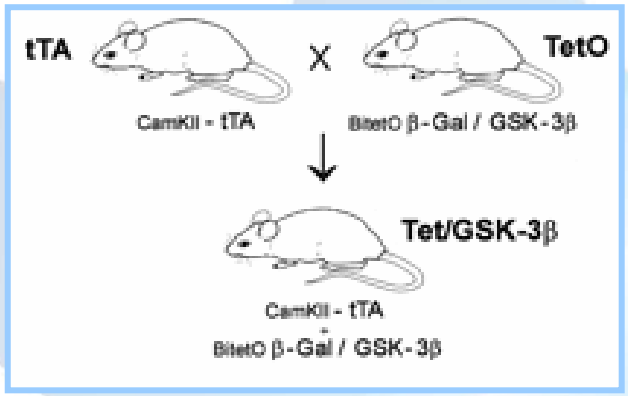
NP060103

PM<400, IP propia

Biodisponible por via oral

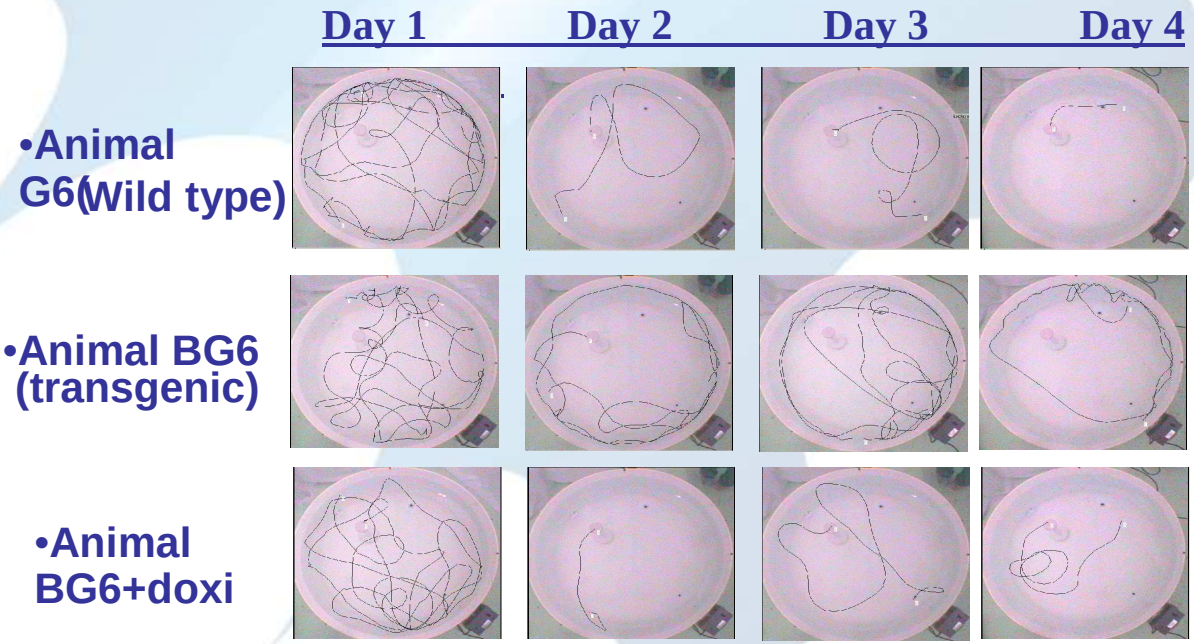
Penetración cerebral

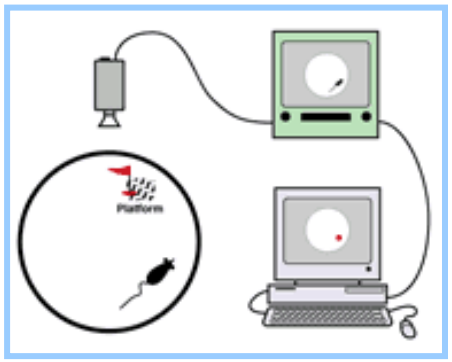
Inhibidores de GSK-3. Modelo animal



Diseño: 3 grupos; 15 animales/grupo

Grupos: G6, BG6, BG6+doxi





Generación de valor

-Ventaja competitiva

-Licencias: JSW y otras..

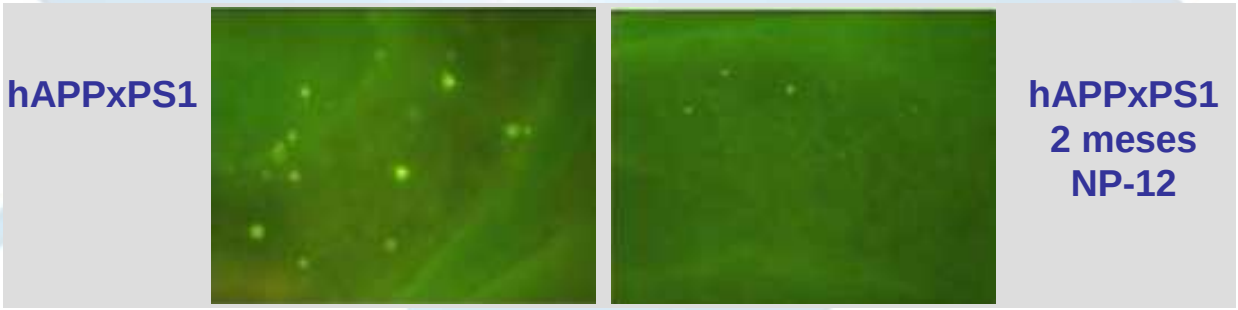
Inhibidores de GSK-3
NP-12

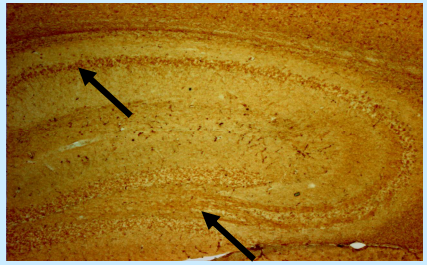
- Molécula sintética perteneciente a la familia de TDZDs
- Inhibidor de GSK-3 ATP-no competitivo
- Administración oral
- Perfil de seguridad bueno
- Eficaz en diferentes modelos animales
- Desarrollo clínico (fase I) en curso

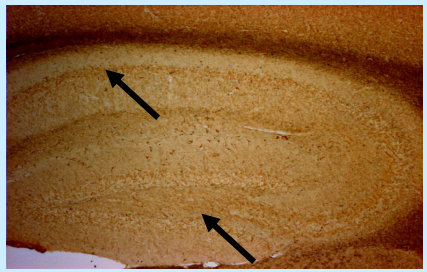
Indicaciones: Alzheimer y tauopatías en general

Inhibidores de GSK-3
NP-12

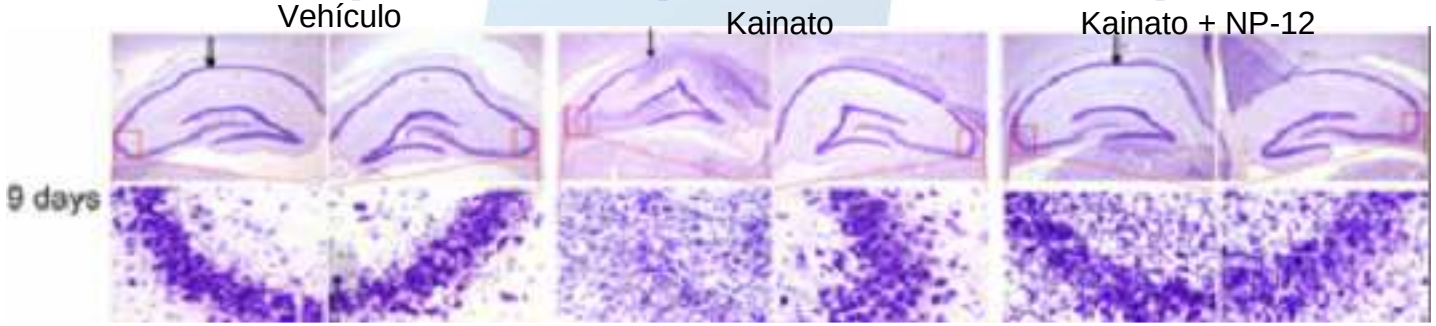
- Reduce la fosforilación de la proteina tau en cultivo celular e *in vivo* (tet/GSK-3)
- Reduce la placa amiloide y mejora la memoria (APPxPS1)

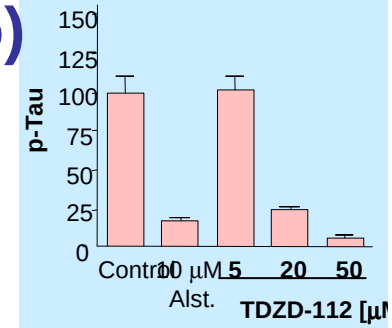



Tet/GSK-3+vehiculo


Tet/GSK-3+NP-12

- Es neuroprotector (excitotoxicidad por kainato)



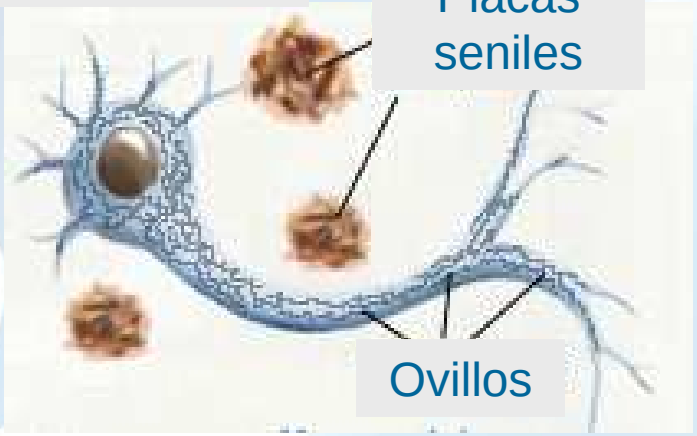


Inhibidores de GSK-3
NP-12

- **Modelo completo de Alzheimer (APPxtau) (en curso)**
  - Mejora de la capacidad de aprendizaje (MWM)
  - Reduce la fosforilación de la proteína tau
  - Reduce la carga de placa amiloide
  - Es neuroprotector. Reduce la pérdida neuronal

Estrategias terapéuticas en Alzheimer

Neurona enferma



Neurona sana

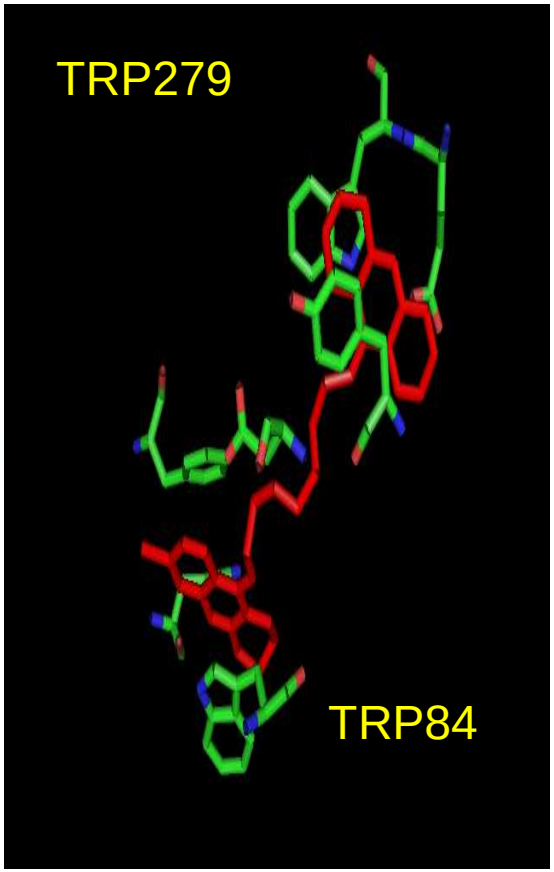
Péptido β-amiloide agregado

Moduladores de β-amiloide

Inhibidores de BACE

Moduladores del β-amiloide
NP-61

- Inhibidor sintético procedente de un programa de diseño racional de fármacos.
- Potente modulador de la biopatologia del β-amiloide (inhibidor de la agregación y de la producción).
- Inhibidor de la AChE (modulador del sistema colinérgico)
- Administración oral
- Perfil de seguridad adecuado
- Desarrollo clínico (fase I) en curso

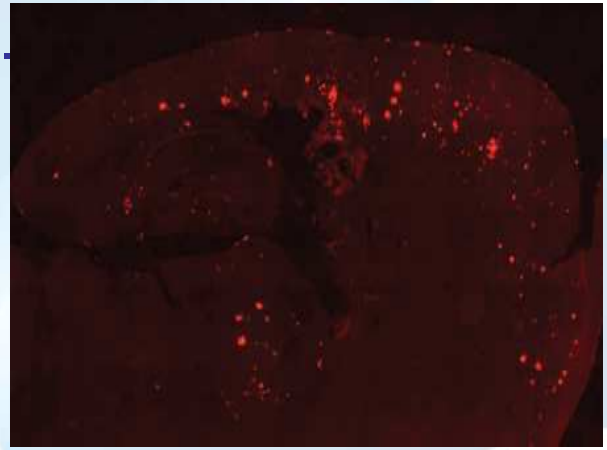


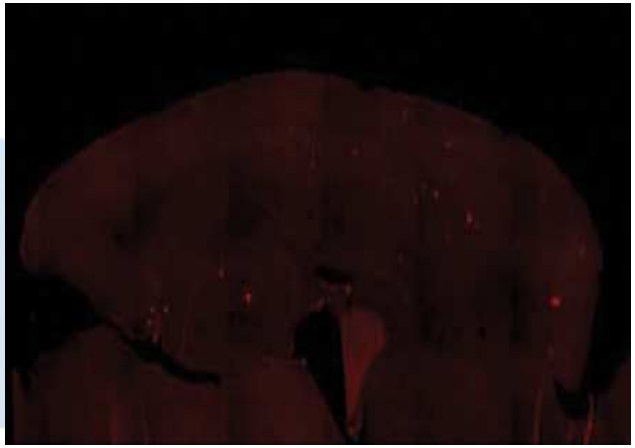
Indicaciones: Alzheimer (fases tempranas y tardías)

Moduladores del β-amiloide
NP-61

- Eficacia en modelos animales:
  - Reduce la placa amiloide *in vivo* en corteza e hipocampo (tratamiento oral, 3 meses).

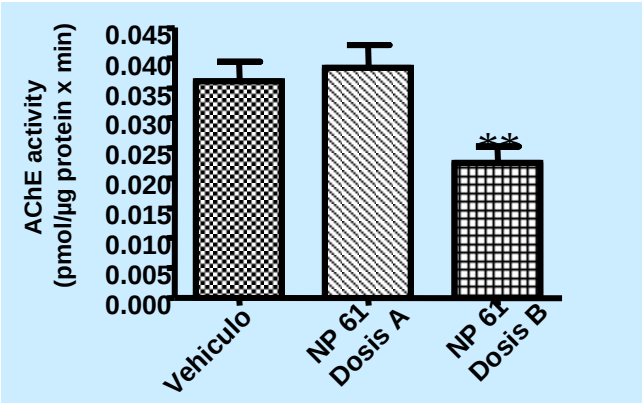
APPswd





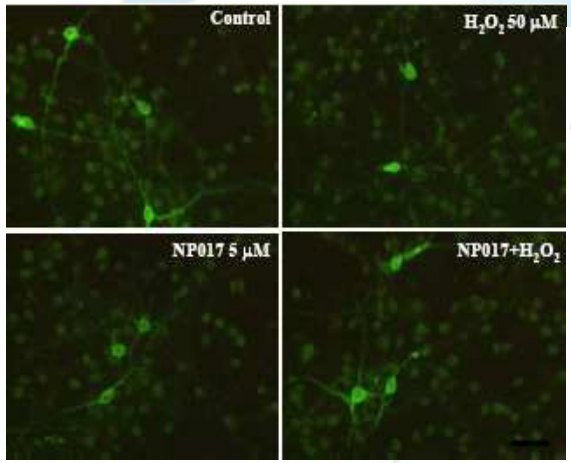
APPswd + NP-61

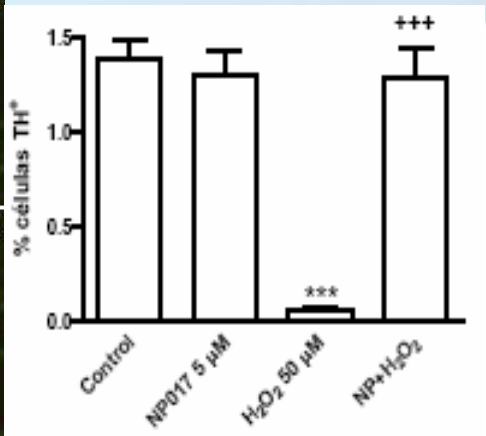
  - Disminuye la actividad de la AChE cerebral *in vivo* (tratamiento i.p., dosis única)

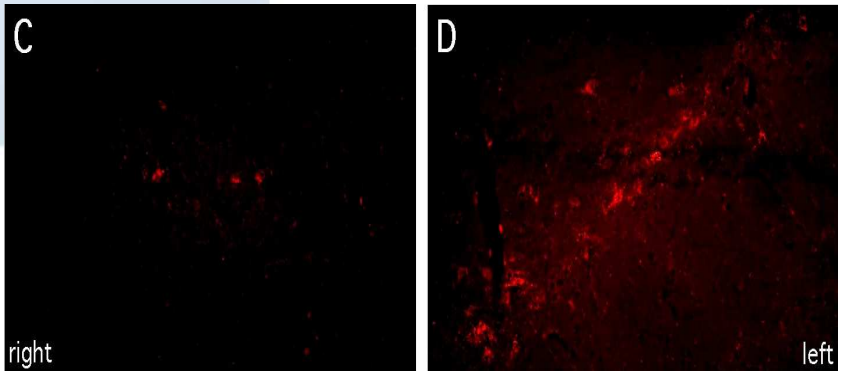


Proyectos en curso: Neuroprotección

- Moléculas sintéticas derivadas de metabolitos marinos aislados de un microorganismo. (Pm=300-350)
- Potentes neuroprotectores (nM) en diferentes modelos basados en cultivos celulares
- Protección de neuronas dopaminérginas en cultivo primario e *in vivo*

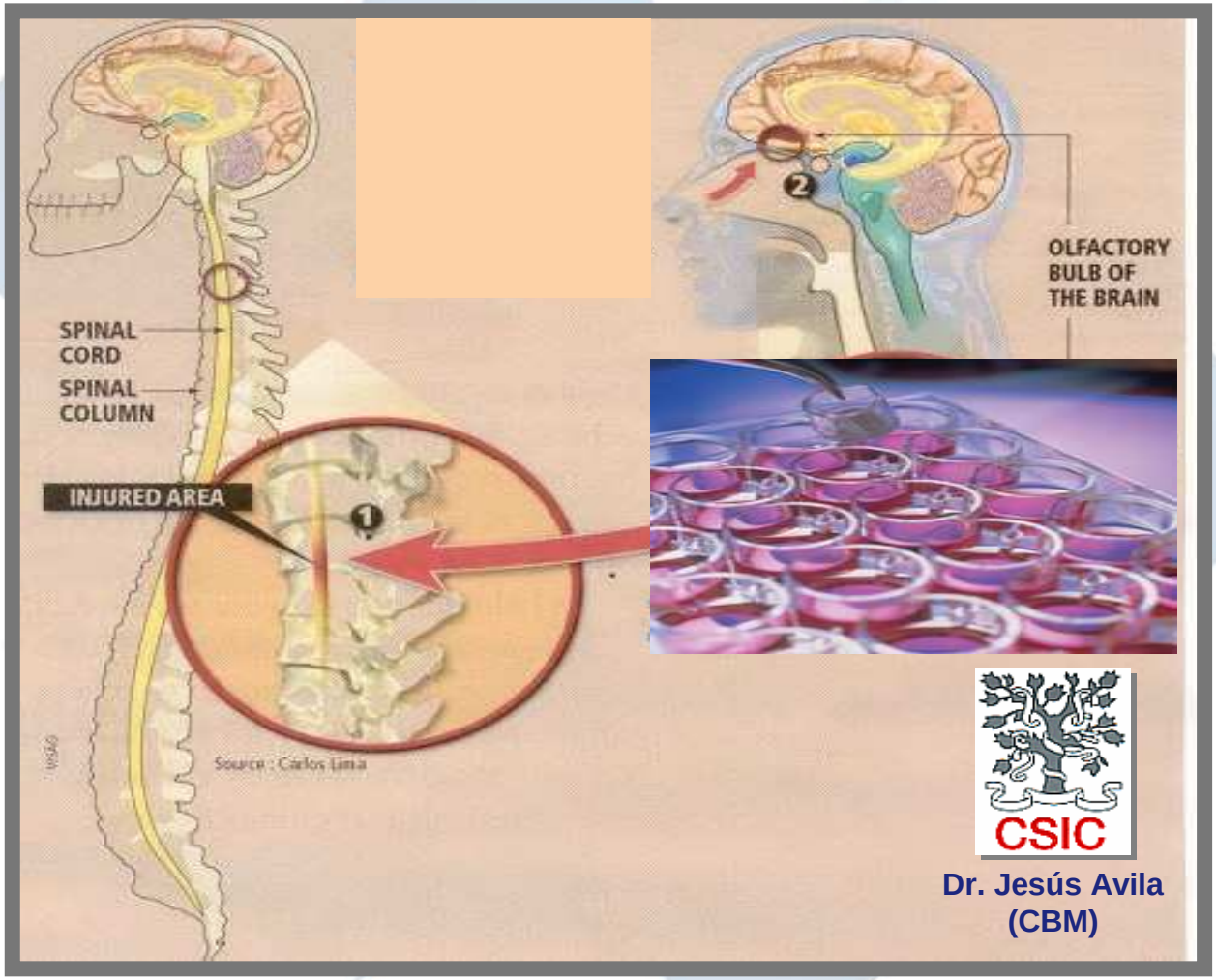






Posibilidad de abordar otras indicaciones

Proyectos en curso: Neuroregeneración (GEO)



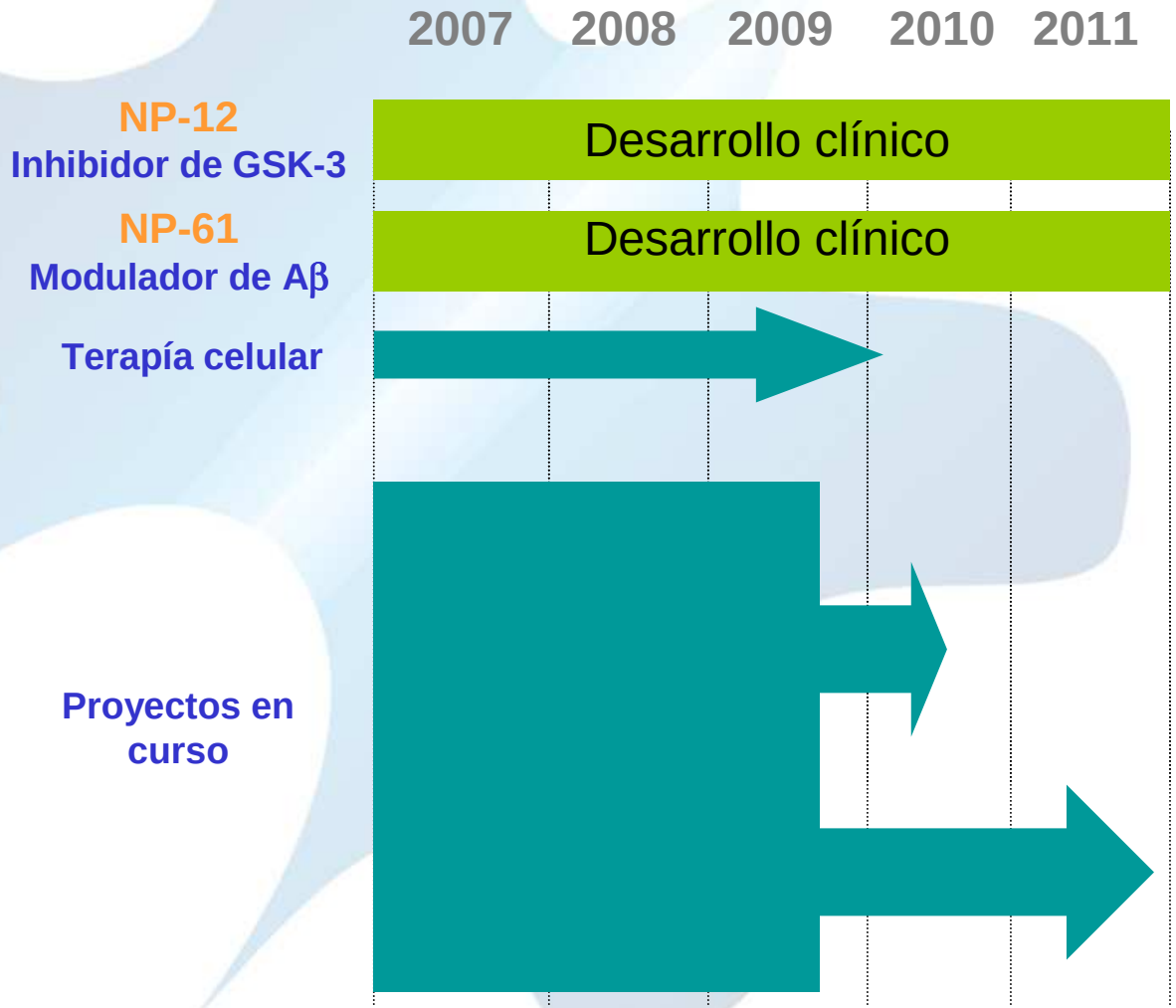
Dr. Jesús Avila (CBM)

Fuente ilimitada de células de glia para trasplantes en pacientes

Generación de líneas celulares inmortalizadas

Prueba de concepto realizada en ratas (CBM, CSIC)

Nuestro futuro



DESARROLLO CLÍNICO

NP-12

NP-61

Premisas generales

Rasgos comunes de ambos compuestos	NP-12	NP-61
Activo sobre diana fisiopatológica de EA	tau / β-A	β-A
Activo sobre otras dianas de la EA	inflamación	AChE
Efecto *modificador* a largo plazo	**+**	**+**
Efecto *sintomático* a corto plazo	**?**	**+**

Premisas generales

El desarrollo clínico de este tipo de compuestos:

- carece de precedentes estandarizados: colaboración con las agencias reguladoras.
- requiere discernir efecto a corto y largo plazo mediante:
  - estudios prolongados
  - marcadores subrogados
  - diseños y análisis especiales

Objetivos generales: Fase I

- Demostrar la seguridad en voluntarios sanos
  - adultos
  - ancianos específicamente
- Definir la farmacocinética
- Estudiar algunas condiciones especiales:
  - efecto del alimento
  - efecto del régimen de administración
- Explorar marcadores de actividad

Objetivos generales: Fase II

IIa) Estudiar la seguridad y tolerancia en pacientes

- tratados durante meses

IIb) Comprobar un efecto sobre la EA (prueba de concepto)

- discernir el efecto a corto, medio y/o largo plazo
- explorar cambios fisiopatológicos

IIb) Registrar el patrón de modificación de la enfermedad.

IIb) Definir las dosis potencialmente eficaces

Objetivos generales: Fase III

- Demostrar la eficacia:
  - efecto modificador de la enfermedad
  - efecto sintomático
- Definir el patrón de efectos adversos
- Comprobar un cambio fisiopatológico
- Comprobar otros eventuales efectos positivos
- Controlar la heterogeneidad de la EA

Desarrollo Clínico

	Fase I	Fase II	Fase III
Objetivo	Seguridad y farmacología. Actividad Interacciones ADME	Eficacia básica y pruebas de determinación de la dosis (rango) adecuada en pacientes afectados. Seguridad Eval. de eficacia Deter. nivel de dosis óptimo, pauta y ruta de administraciónn.	Estudios multicéntricos, comparativos con pacientes afectados para proporcionar información suficiente para el análisis estadístico de seguridad y eficacia válido/ definitivo.
Tamaño	~ 100 personas	100-300 pacientes	>1000 pacientes
Tiempo necesario	1 – 3 años	2 – 4 años	4 – 6 años
Objeto	Estudios de FD & FK	Estudios exploratorios, de ajuste de dosis.	Estudios confirmatorios

NP-12: Fase I
a) Plan

Ia) Dosis única ascendente

Ib) Dosis repetida ascendente (5 días)

Ic) Dosis repetida ascendente (14 días)

NP-12: Fase I
b) Estudios

estudio	voluntarios		Administración de NP-12			
	edad	Nº	Diseño	Formulación	Dosis	
Ia	**adultos**	**34** **34**	• **Doble ciego** • **Doble ciego**	• **Labrasol/agua** • **F05-052**	**Única** **Única**	**5 niveles** **5 niveles**
Ib	**ancianos**	**44**	• **Doble ciego**	• **F05-052**	**Múltiple** **5 días**	**4 niveles**
Ic	***ancianos***	***36***	• ***Doble ciego***	• ***F06-037F***	***Múltiple*** ***14 días***	***3 niveles***

NP-12: Fase I
c) Resultados

- Datos positivos de seguridad y tolerancia
- Definición progresiva de la farmacocinética
    - en adultos
    - en ancianos
- Estudio del efecto de la asociación con alimentos
- Estudio de marcadores

NP-12: Asesoramiento de las Agencias

Al finalizar la Fase I

- Solicitud de I.N.D. ante la F.D.A.
  - necesaria para desarrollo clínico en EEUU
- Solicitud de asesoramiento ante la E.M.E.A.
  - útil para el desarrollo clínico en Europa

NP-61: Fase I
a) Plan

Ia) dosis única ascendente

Ib) dosis repetida ascendente (14 días)

NP-61: Fase I
b) Estudios

estudio	voluntarios		Administración de NP-61			
	edad	Nº	Diseño	Formulación	Dosis	
Ia	**adultos** **ancianos**	**40** **30**	• **Doble ciego** • **Doble ciego**	• **F05-128F** • **F05-128F**	**Única** **Única**	**6 niveles** **4 niveles**
Ib	***ancianos***	***36***	• ***Doble ciego***	• ***F05-128F***	***Múltiple*** ***14 días***	***4 niveles***

NP-61: Fase I
c) Resultados

- datos positivos de seguridad y tolerancia
- definición progresiva de la farmacocinética
    - en adultos
    - en ancianos
- estudio del efecto de la asociación con alimentos
- estudio de marcadores

This information includes forward-looking statements based on Management´s current expectations. Factors that could cause future results to differ materially from such expectations include, but are not limited to: the success of the Company´s research strategy; the applicability of discoveries made therein; the difficulties inherent in the development of pharmaceuticals, including uncertainties as to the timing and results of preclinical studies; delayed achievements of milestones; reliance on collaborators; uncertainty as to whether the Company´s potential products will succeed in entering human clinical trials and uncertainty as to the results of such trials; uncertainty as to whether adequate reimbursement for these products will exist from the government, private healthcare insurers and third-party payors; and the uncertainties as to the extent of future government regulation of the pharmaceutical business.

neuro pharma

“Investigamos hoy para recordar mañana”