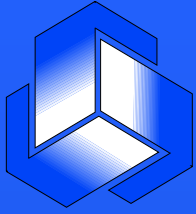


Clinical trial insurance
European issues and perspectives: the point
of view of EORTC, an international
academic network

Denis Lacombe

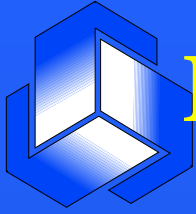
Assistant Director Medical Affairs
EORTC Data Center, Brussels, Belgium

Berlin Nov. 11, 2005

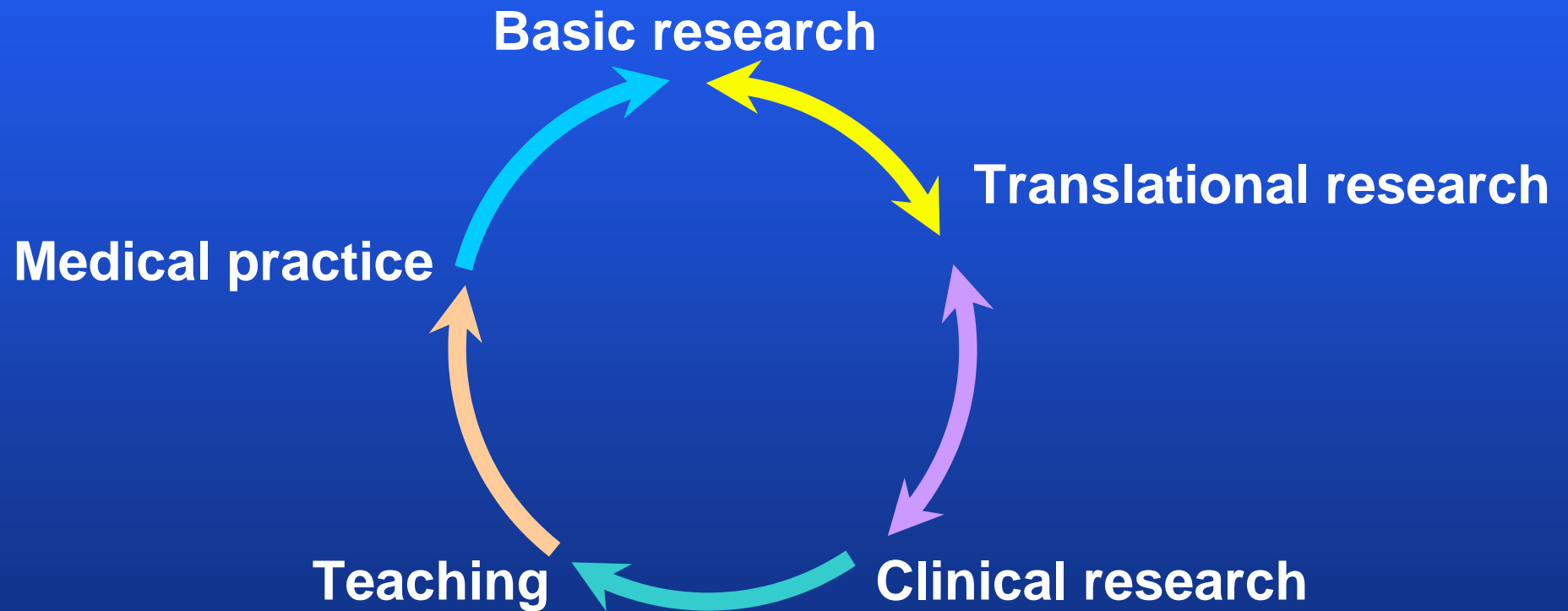


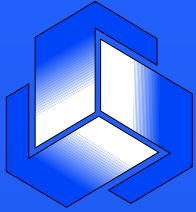
Contents

- **What is the EORTC**
- **Why Europe needs independent research addressing public health issues**
- **European framework for CT Insurance**
- **Example of Germany and Switzerland**



Medical practice and medical research depend on each other

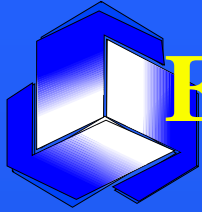




European Organization for Research and Treatment of Cancer (EORTC) (I)

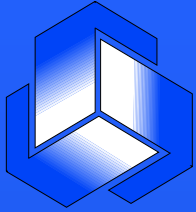
Private and not for profit organization

- Main mission: promote and conduct research to improve cancer care
 - Core activity: conduct clinical trials
 - ◆ International
 - ◆ Multidisciplinary
 - ◆ Develop new treatments
 - ◆ Define new standards of care
 - ◆ Large academic trials



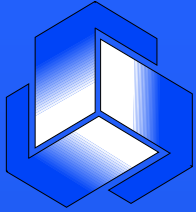
European Organization for Research and Treatment of Cancer (EORTC) (II)

- To conduct, develop, coordinate research in Europe on treatment of cancer and related problems
- Multidisciplinary and multinational efforts (investigator network, more than 200 institutions)
- To decrease the time needed to evaluate new therapeutic or prevention modalities
- To disseminate state-of-the-art knowledge with the final goal of improving the standard of cancer care



EORTC missions (I)

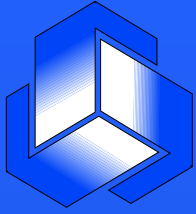
1. To provide a European platform to discuss, develop and conduct clinically oriented cancer research following the highest standards of quality
 - to optimize cancer treatment strategies (public health questions)
 - to develop and/or improve existing local (surgery, radiotherapy) and systemic treatment modalities
 - to test new concepts or develop new treatment approaches (laboratory and translational research)



EORTC missions (II)

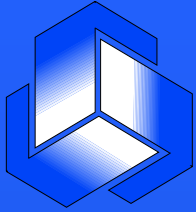
- 2. To facilitate collaboration across research groups and across countries**
 - When trials are very large
 - When tumor are very “rare”
 - When the European approach > to national approach

- 3. To promote clinically oriented cancer research in general**
 - Organizing/participating in conferences
 - Organizing courses to disseminate know-how
 - Interacting with health policy makers to promote clinical research in general and academia in particular



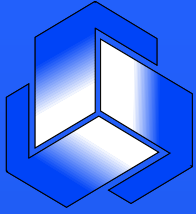
Challenges of academic clinical research

- Need to update and harmonize rules for clinical trials
- 2 types of clinical trials
 - drug development
 - therapeutic strategies
 - ◆ multidisciplinary approach



The importance of academic clinical trials

- **Need to continuously improve standard treatment**
 - by exploring new multimodality treatments
 - by exploring new (registered) drug combinations
 - by exploring new surgical/radiotherapy techniques

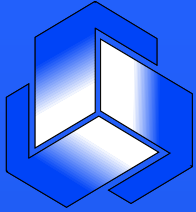


EORTC Boost Trial (Beast Cancer)

5,569 patients (1989-1996)

Belgium	817
Germany	374
France	1185
Spain	21
Switzerland	306
The Netherlands	2603
U.K.	146
Israel	102
Australia	15



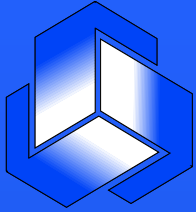


Debulking surgery after chemo in ovarian cancer (55865): 319 patients

- **Debulking surgery significantly lengthened both progression free and overall survival ($P < 0.01$) and reduced the risk of death by 33% (after adjustment for prognostic factors)**
- **Surgery was not associated with death or severe morbidity**

CONCLUSIONS

- **The six months increase in median survival outweighs the morbidity associated with surgery**



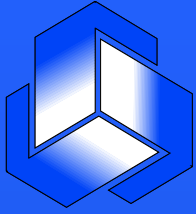
Chemotherapy in operable osteosarcoma (80861) 407 patients - 2 drugs vs. multidrug regimen

- **No difference in disease free survival**
- **No difference in overall survival**
- **Higher cost of the multidrug regimen (44 weeks)**
- **Better feasibility of the 2-drug regimen (6 cycles)**

CONCLUSIONS

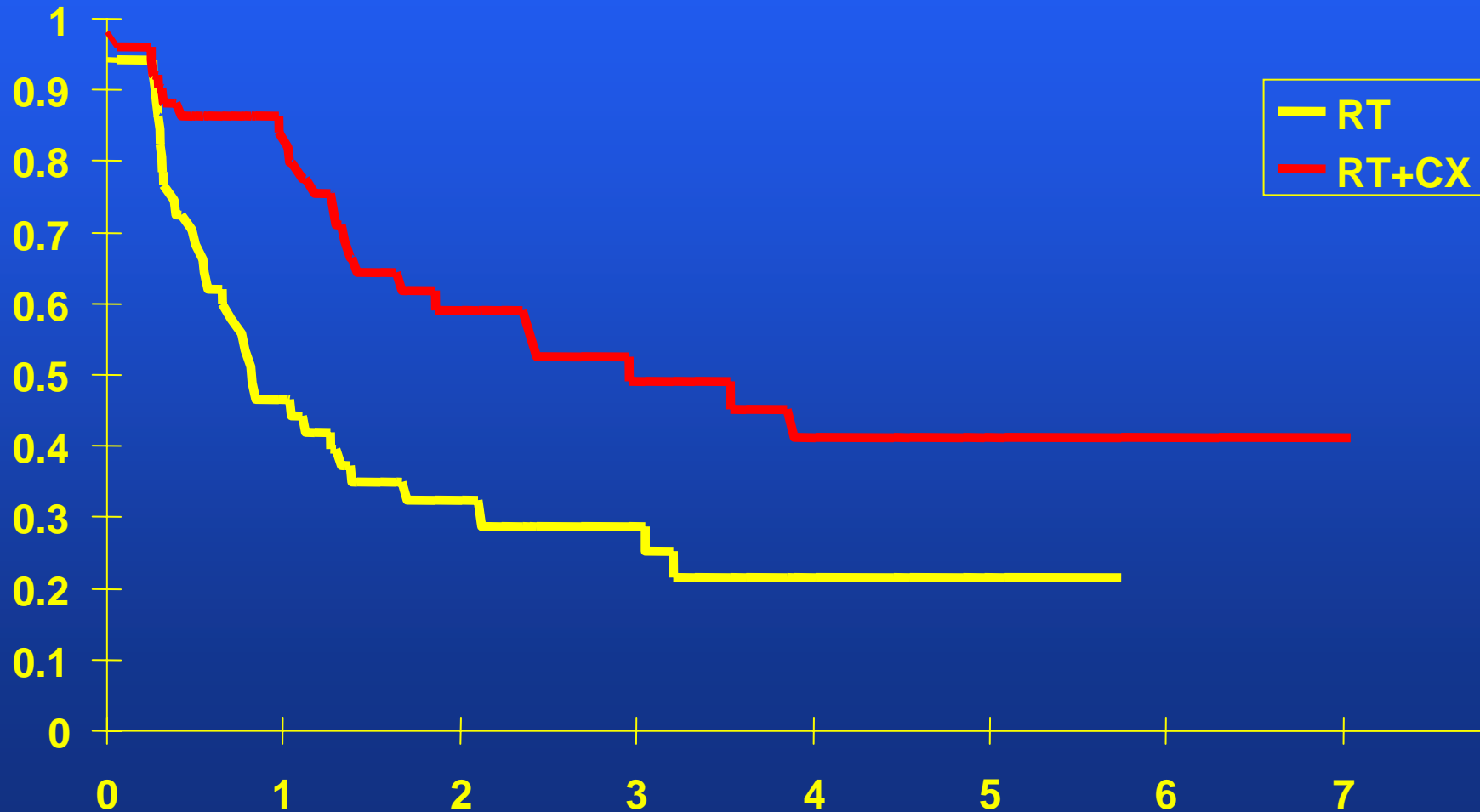
- **No substantial advantage of the multidrug regimen**
- **The shorter 2-drug regimen is preferable**

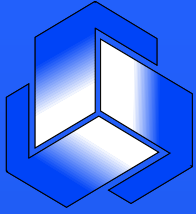
Lancet, Vol 350, September 1997 12



Radio-chemotherapy in locally advanced anal cancer (22851)

results: colostomy free survival ($p = 0.002$)





EORTC RTX and GU Groups trial 22863

(M. Bolla et al., N Engl J Med, 337 (5), 1997: 295-300)

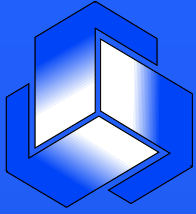
**T1-T2 G3 or
T3-T4 any G
Prostate Cancer**



**Pelvic RTX alone
(50 Gy/ 5 weeks
+20 Gy boost / 2 weeks)**

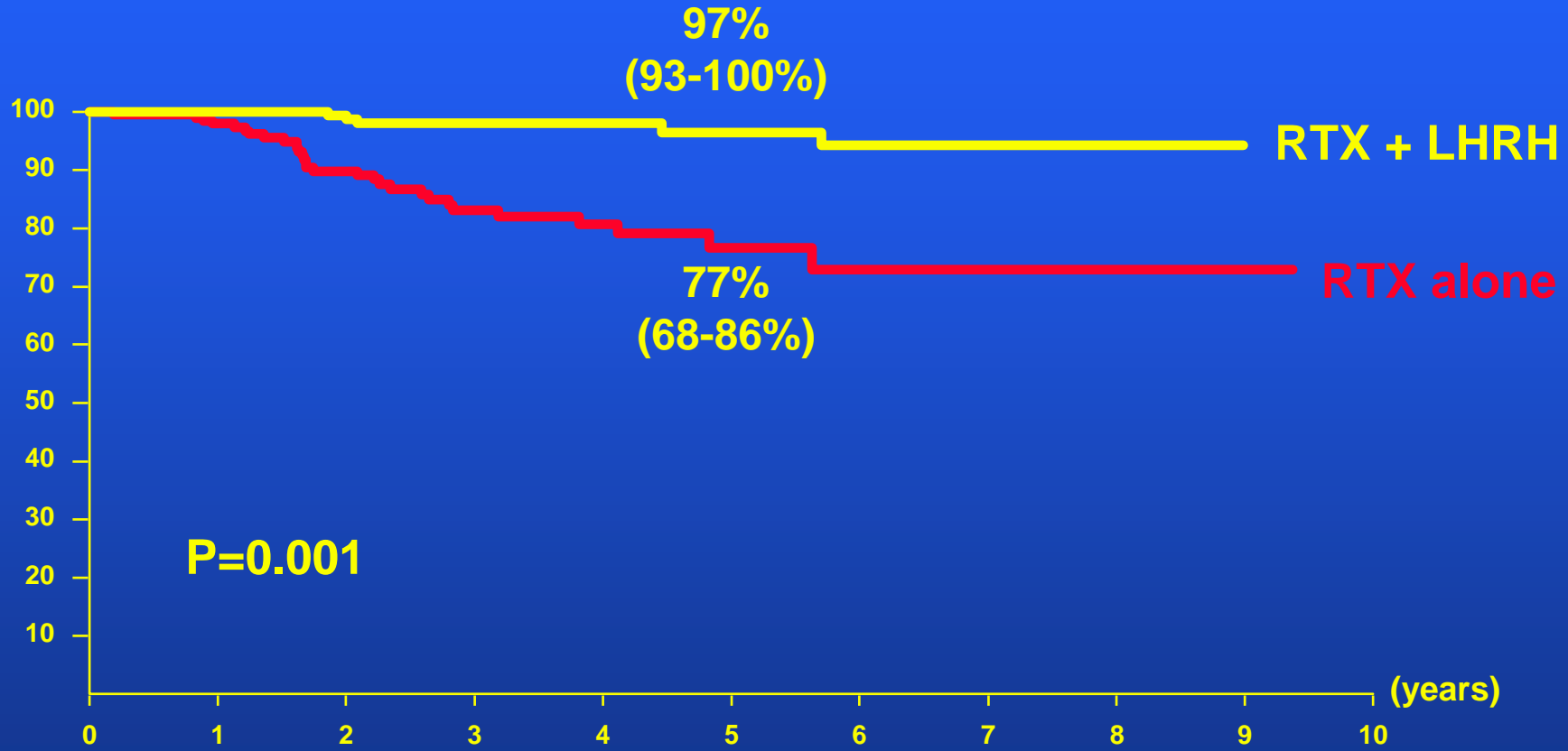
**Pelvic RTX
+3 years adjuvant LHRH
(Zoladex 3.6 mg monthly
subcutaneous injection, strating
dl of RTX)**

- 415 patients entered between 1987 and 1995
- Median duration of follow-up 45 months
- Adjuvant hormonal treatment improves survival (P=0.001) as compared to radiotherapy alone.

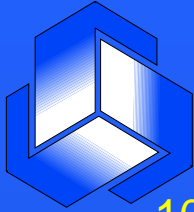


EORTC RTX&GU Groups 22863

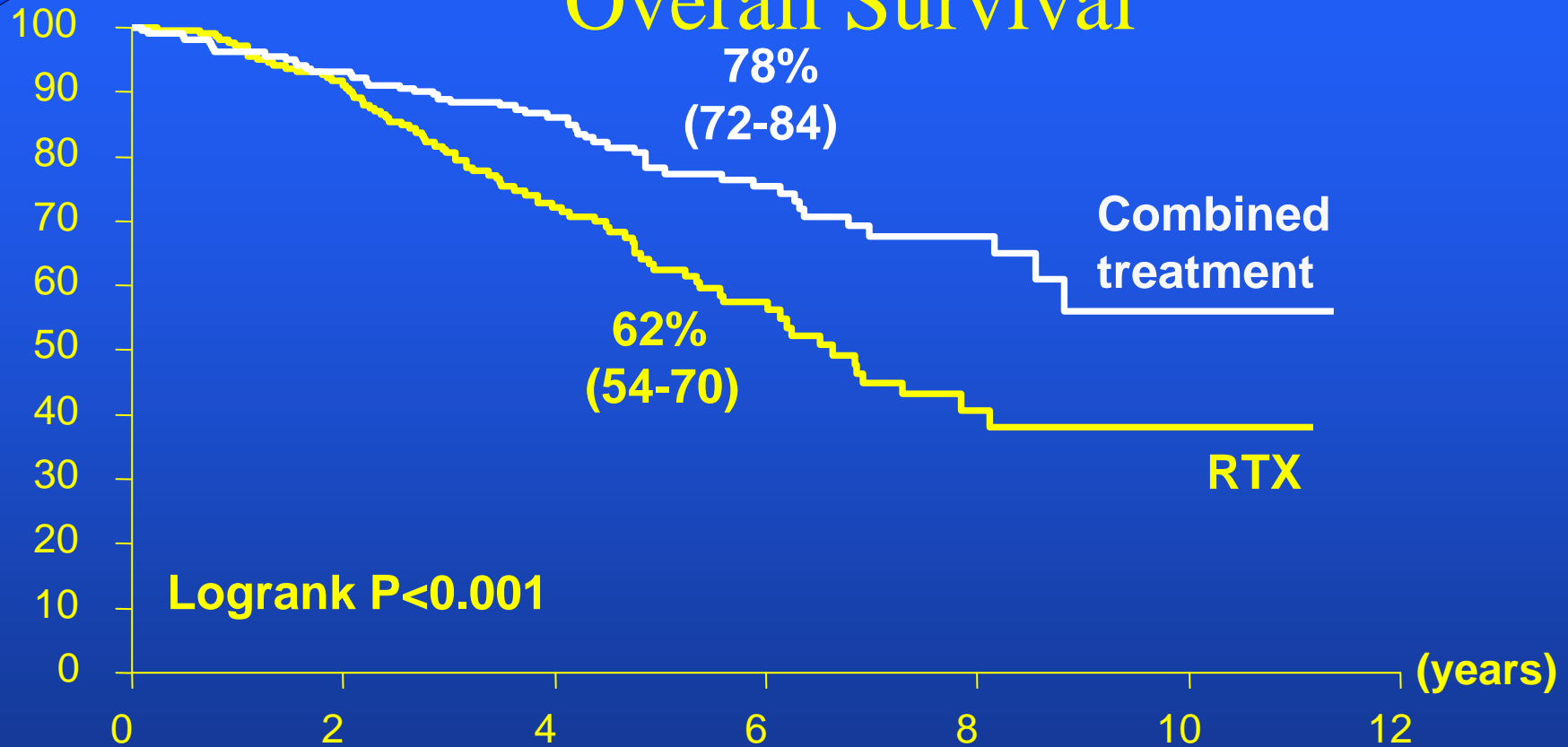
Local control



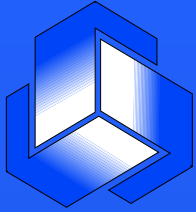
O	N	Number of patients at risk :										Treatment	
30	208	180	127	82	55	31	19	10	6	1	—	RTX	
5	207	190	142	111	82	54	38	18	7	0	—	RTX+LHRH	



Advanced Prostate Cancer Overall Survival



O	N	Number of patients at risk :						
		0	2	4	6	8	10	
81	208	177	106	46	16	3	—	RTX
50	207	183	142	71	24	5	—	RTX+LHRH



Recent examples of major EORTC trials leading to change practice

- **Head & Neck cancer**

Concomitant cisplatin and radiotherapy post surgery

New England Journal of Medicine, May 2004

TPF regimen in inoperable patients (ASCO 2005)

- **Glioblastoma**

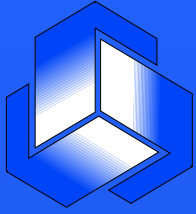
Temozolomide with radiotherapy as adjuvant treatment

New England Journal of Medicine, March 2005-educational grant readily used for extension of registrations

- **GIST**

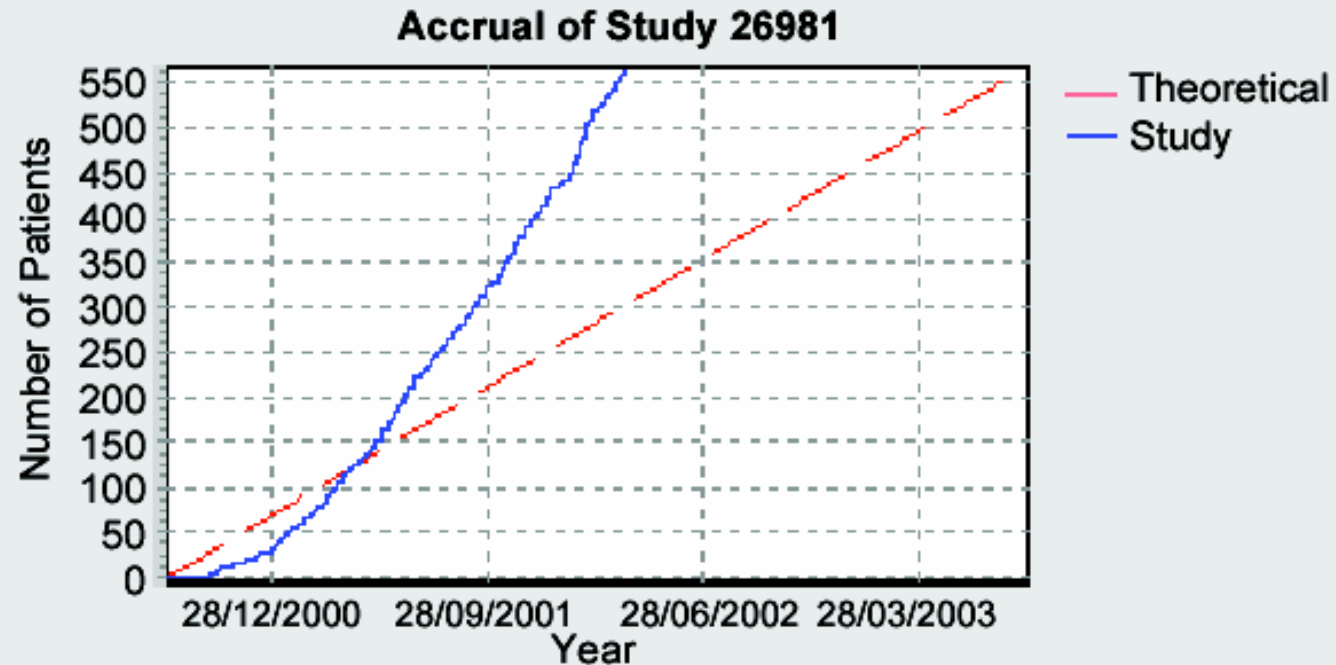
Role of Glivec, educational grant used for extension of registration.

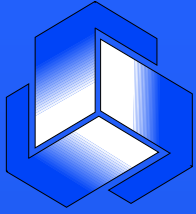
The Lancet, September 2004



Radiotherapy / Temozolomide adjuvant study in Glioblastoma

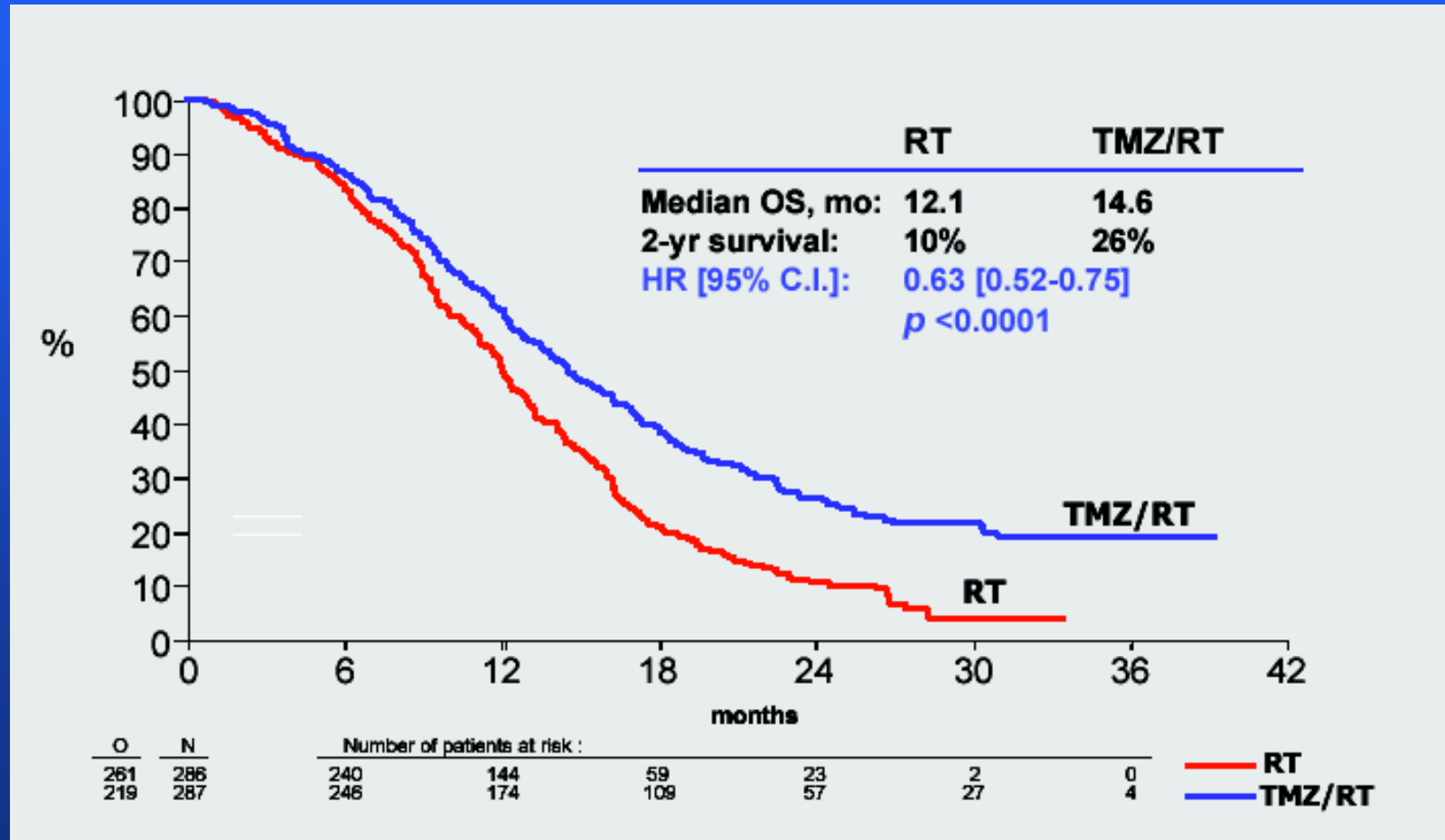
- 85 institutions, 14 countries, 573 patients

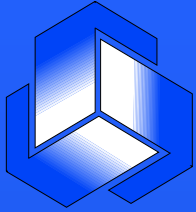




Radiotherapy / Temozolomide adjuvant study in Glioblastoma

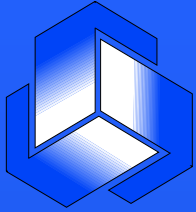
Overall Survival





Phase II (62001) trial of Imatinib Study design

- EORTC Phase I study of imatinib 400-1000 mg daily identified 800 mg o.d. as feasible phase II dose (van Oosterom et al, Lancet 2001;358:1421)
- 27 evaluable patients with GI stromal tumor (GIST) and 24 non GIST patients required.
- GISTs were KIT positive by DAKO antibody immunohistochemistry
- Good organ function, PS \leq 2, measurable disease
- Disease assessed using RECIST criteria, toxicity by NCI CTC 2.0

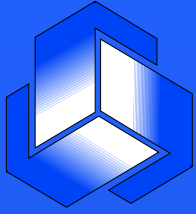


EORTC Phase II - 62001

GISTs (n= 27)

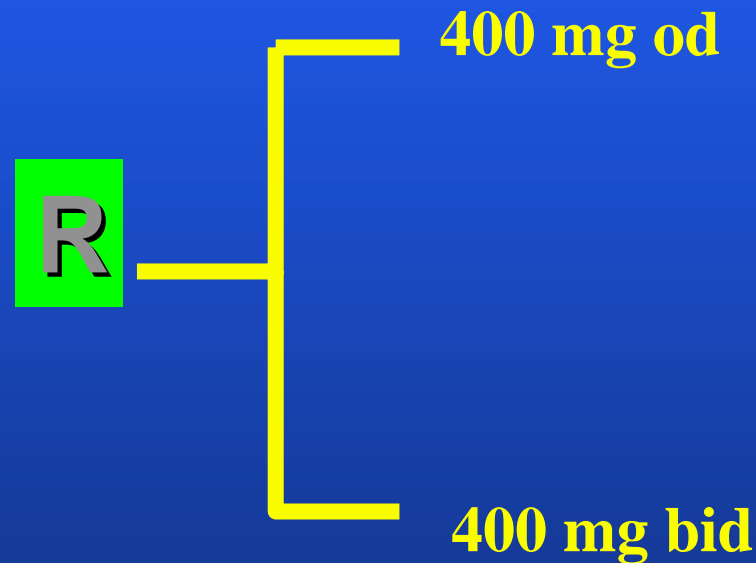
- Objective response rate 71 %
- Progression free at 12 months 74 %

I. Judson, ASCO 2002

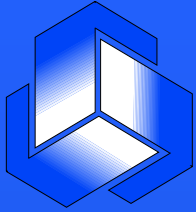


Glivec®/Gleevec®: Randomized phase III study in GIST (EORTC 62005)

(Parallel by US intergroup and EORTC/SSG/ISG/AGITG)

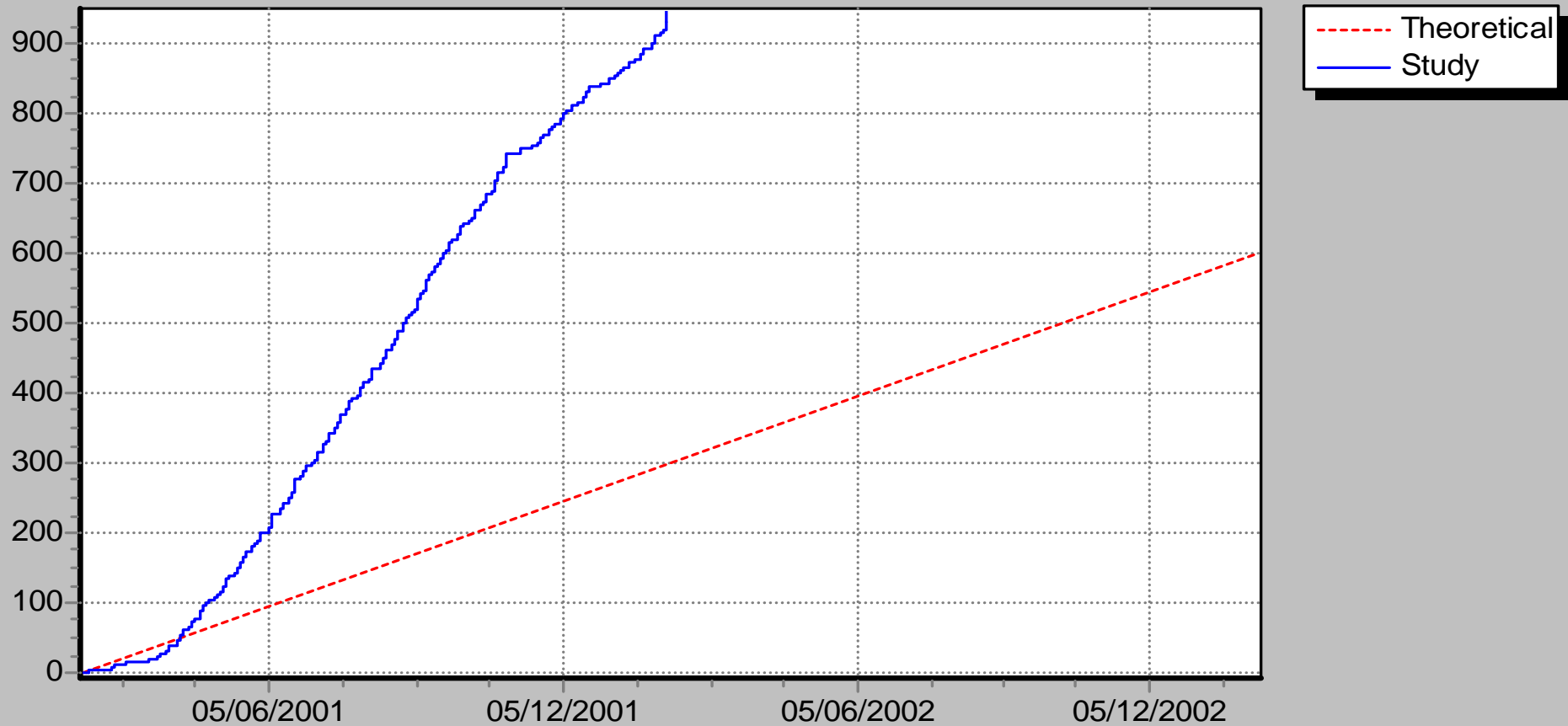


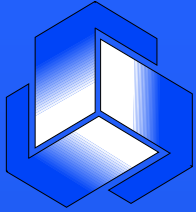
P.G. Casali et al, abstract 1650, p. 413a, Asco Proc. 2002
G.D. Demetri et al, abstract 1651, p. 413a, Asco Proc. 2002



Accrual in EORTC trial 62005 (946 patients)

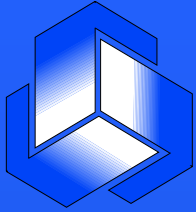
Accrual of study 62005





GIST

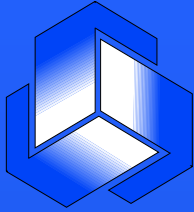
- **Gastro Intestinal Stroma Tumors**
- **Rare disease (incidence 16/1.000.000)**
 - 5000 cases/year in total of Europe
 - No market potential for pharmaceutical industry
- **Metastasize to liver + peritoneal, rarely extra-abdominal**
- **Until august 2000 no treatment available for metastatic disease**
- **Estimated survival once recurred/metastatic**
 - 50% 2 yr survival



Glivec® - Imatinib- STI 571

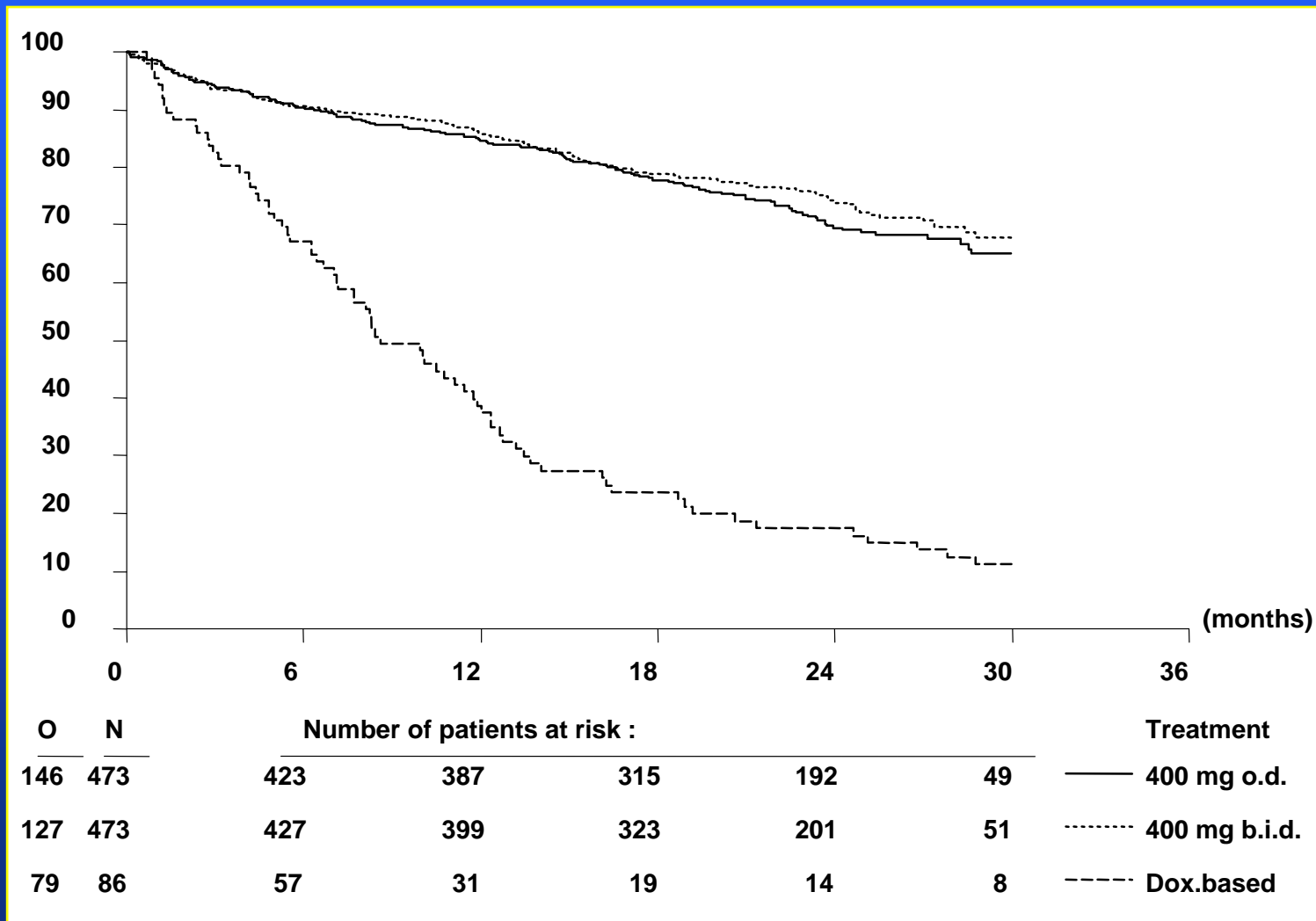
July 2000: start company sponsored GIST phase I-II studies	Feb 2001: start cooperative group GIST phase III studies	May 2002: GIST registration (400/mg/day)
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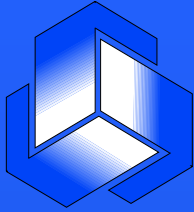




Glivec Study in GIST

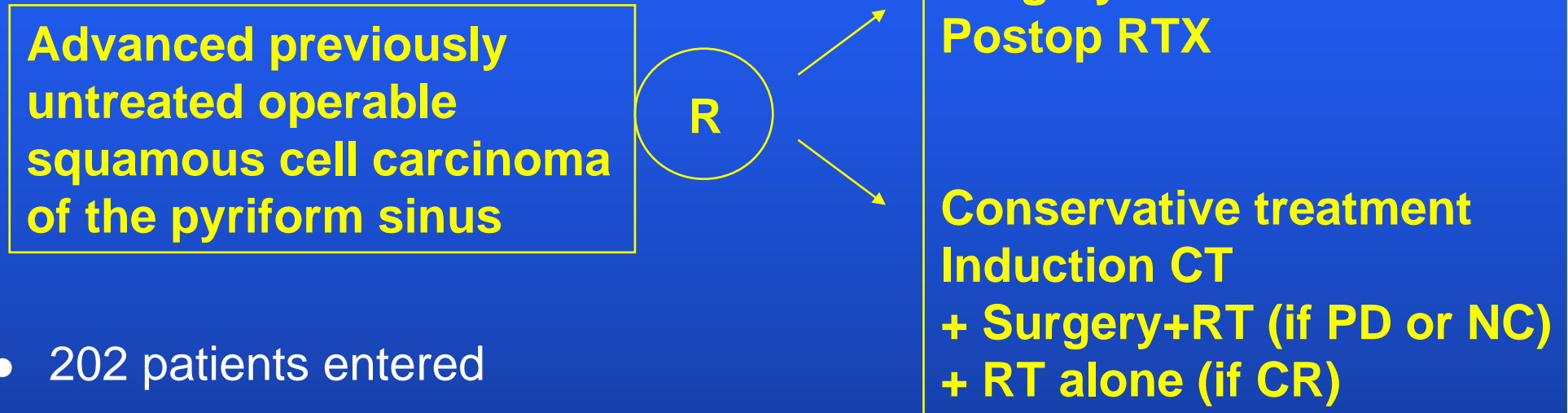
Overall survival



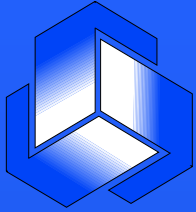


EORTC Head & Neck Group (24891)

(JL Lefèbvre *et al*, J Natl Cancer Inst vol. 88, 1996: pp. 890-899)

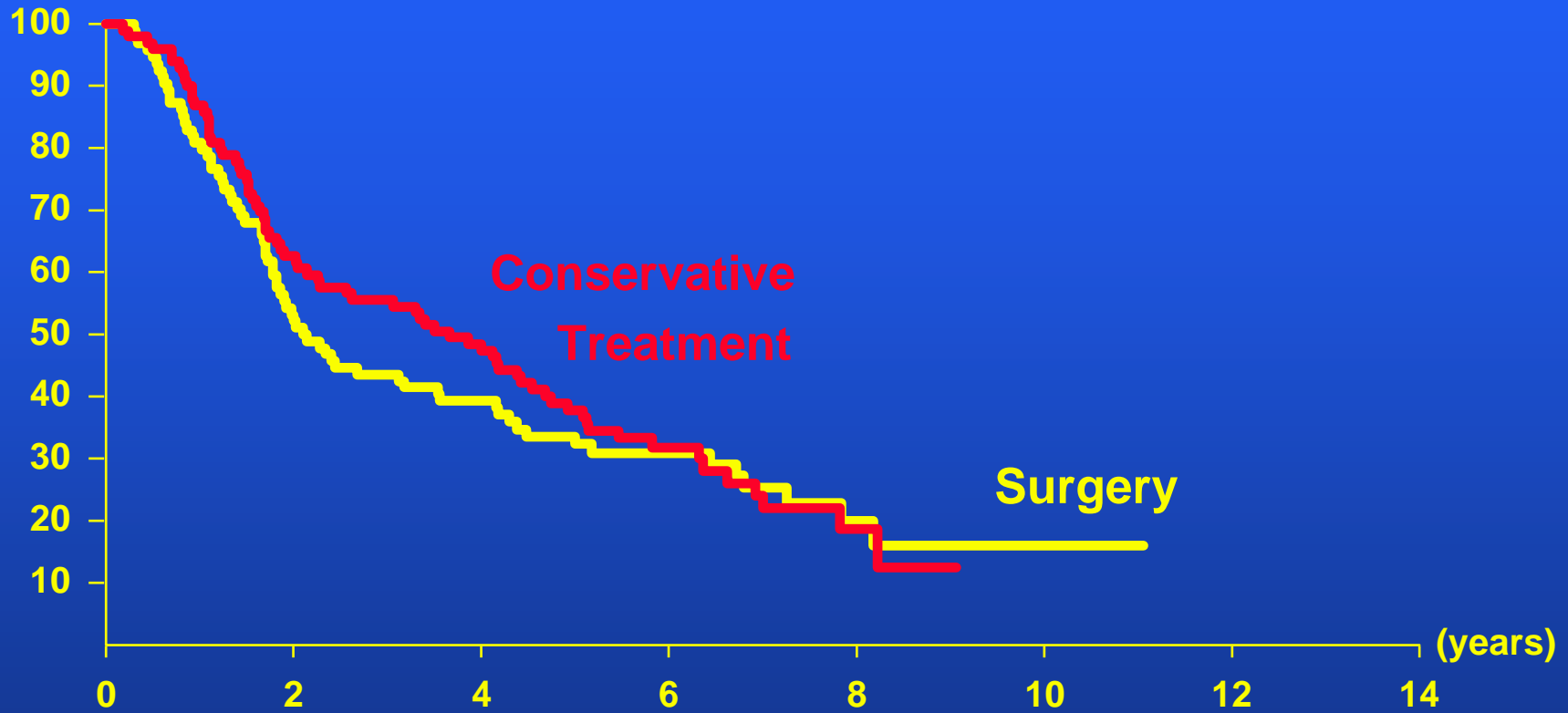


- 202 patients entered
- Trial stopped at interim analysis for early evidence of equivalence of survival on the 2 arms
- Larynx preservation without jeopardizing survival appears feasible in 42% of the patients. The conservative management becomes the EORTC standard treatment for operable hypopharyngeal cancer

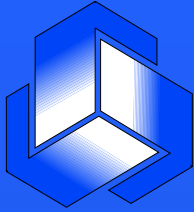


EORTC Head & Neck Group (24891)

Overall survival

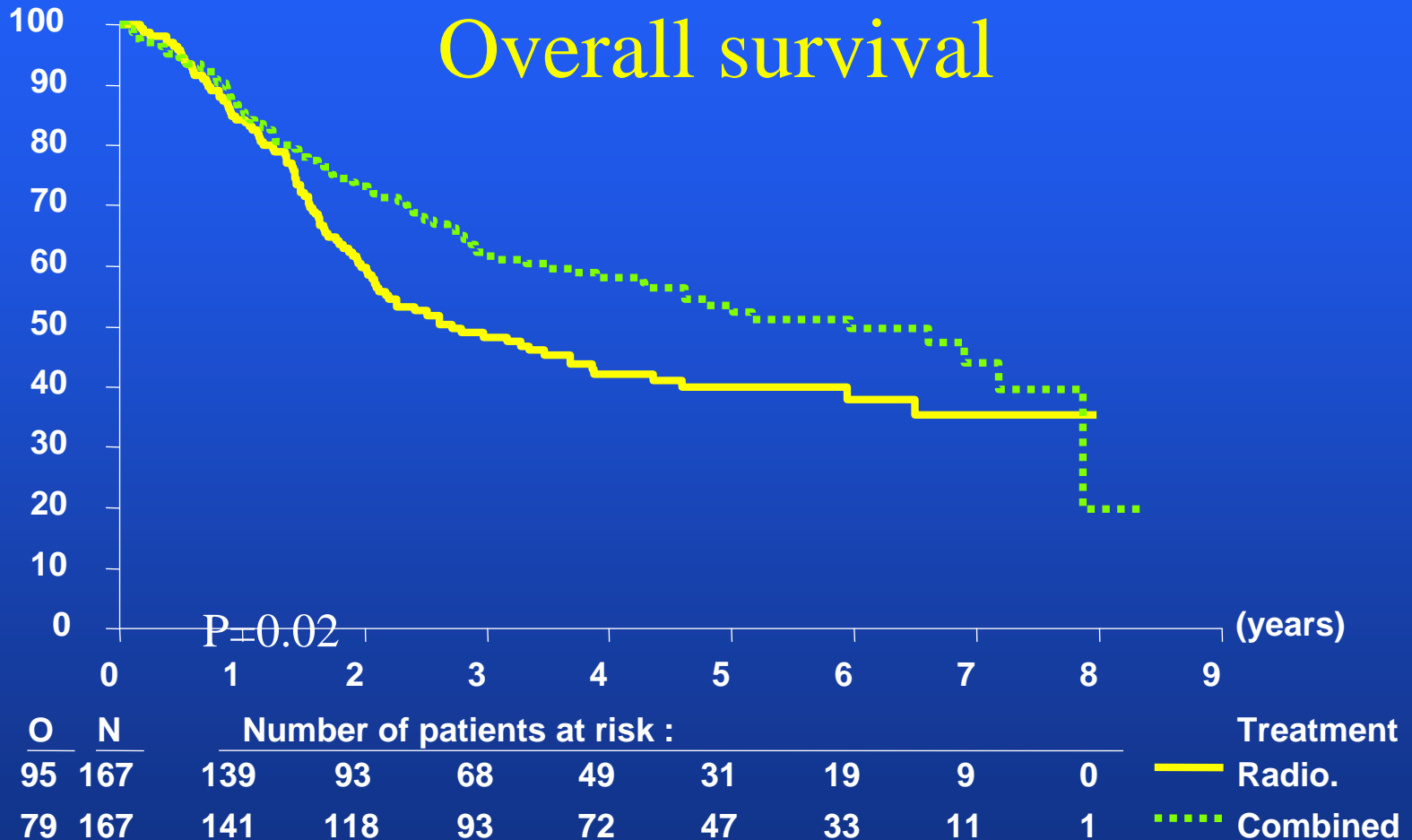


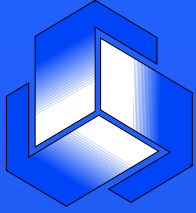
O	N	Number of patients at risk :							
70	94	49	35	17	7	2	0	—	
73	100	62	47	18	3	0	0	—	



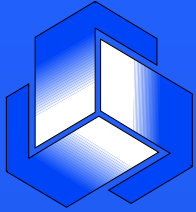
Postoperative Chemoradiotherapy in Head & Neck Cancer

Overall survival



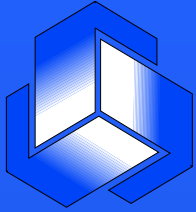


Current issues with clinical trial insurance in Europe



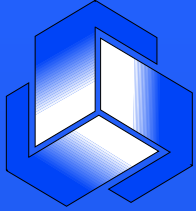
Clinical trial insurance and the European Directive 2001/20/EC

- Clinical trial insurance is not defined by the CTD
- CTD mentions the requirement for CT insurance
- CTD has been an opportunity for MS to revisit pharmaceutical national regulations
- Increased responsibility of ECs has prompted them to review insurance with scrutiny but lack of education
- Fragmentation of the territories



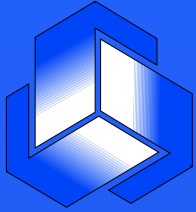
Clinical trial insurance (I)

- A field particularly unknown by
 - insurance companies
 - clinical trialists
 - ECs
 - CAs
- In 2005, a major source of discussions with all participants
- Claim increase in Europe

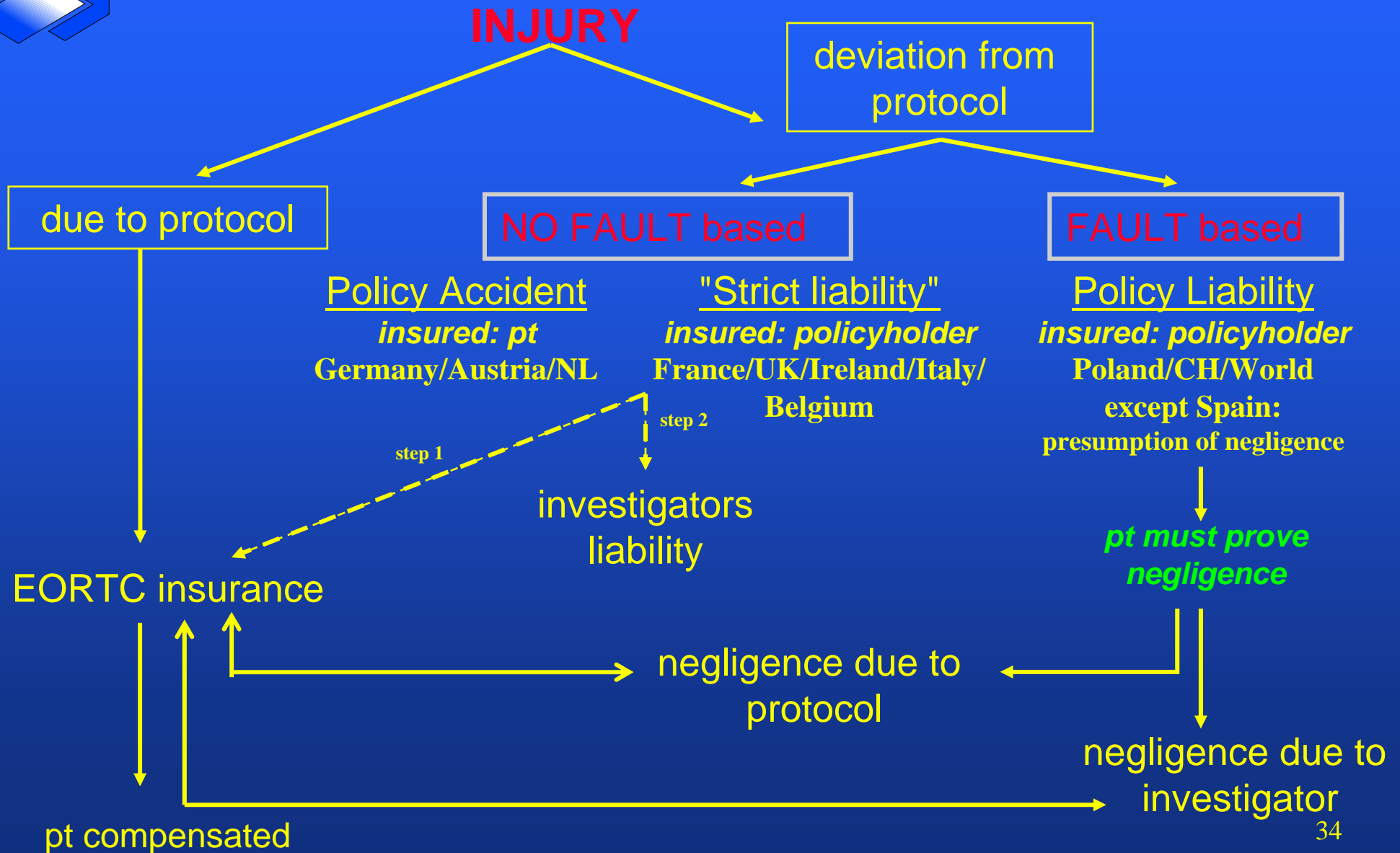


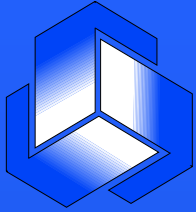
Clinical trial insurance (II)

- **Remains a national issue**
- **MS have different systems and may involve different ministries not liaising appropriately to each other**
 - **trial agencies**
 - **ministry of health**
 - **ministry of economy**
- **European level: unclear to which European DG it should be referred to**



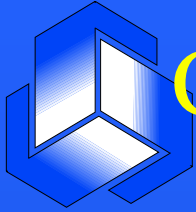
Current European situation





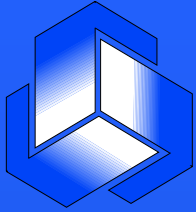
Clinical trial insurance (III)

- **Huge variability per country in term of**
 - **compensation**
 - **juridical background: policy accident, strict liability, policy liability**
 - **duration of compensation**
 - **exclusion**
 - **costs**
 - **annual versus protocol specific insurance**
- **Major misunderstanding by ECs leading to delays**
- **Urgent need to initiate a European forum to address this critical issue**

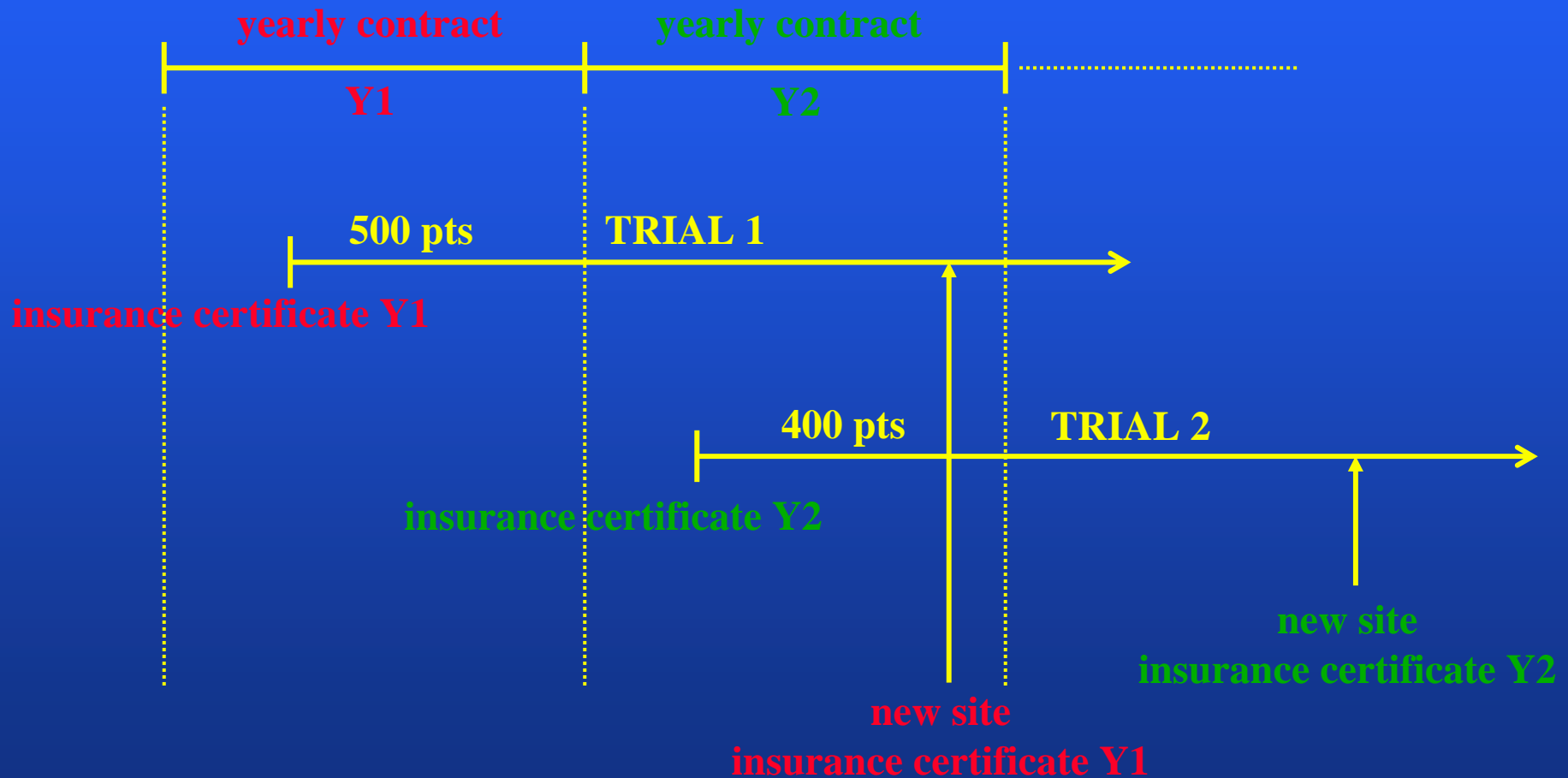


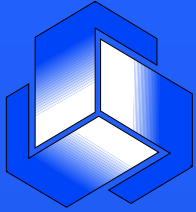
Current issues with clinical trial insurance and the new European framework

- **Is clinical trial linked to "sponsorship"?**
 - if so, are there some academic situations where CT insurance can be waived?
 - how far this is applicable to all academic sponsors
 - some countries have such systems (Italy, decree Dec. 2004)
- **ECs → single opinion process: a failure?**
 - appraisal of insurance varies within a country between EC?



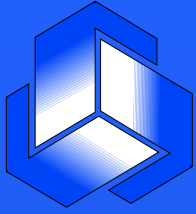
Contracting insurance / insurance certificates / annual policies





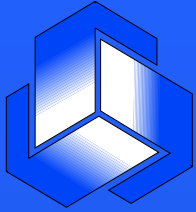
Examples of EC requirements

- **Yearly renewal of certificates when an annual policy is in place**
- **Requirement for change of study title on insurance certificate when protocol and insurance conditions by central EC**
- **Requirement for additional certificate to be signed by EORTC representatives despite a certificate and a policy in good standing are provided**
- **Insurance coverage rejected by local committees despite being approved by central EC**



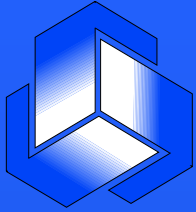
Insurance costs EORTC clinical trials 1996-2005





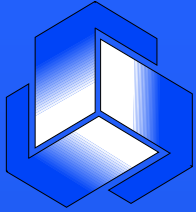
Legal requirements for insurance compensation for clinical trials (I)

Territories	Type of policy	Limits imposed by law (in €)	Common practice (in €)	Period of the coverage after the study closure
Austria	"Accident" no-fault based	No limits imposed	370.000/pt 2 mio 550/trial 5 mio 100/year	plus 3 years
Belgium	"Strict liability" no-fault based	No limits imposed	500.000/pt 2 mio/trial 5 mio/year	plus 5 years
France	"Strict liability" no-fault based	762.245/pt 4 mio 573/trial 7 mio 600/year		Statutory period according to the French Code civil
Germany	"Accident" no-fault based	500.000/pt	<u>Imposed by the Pool</u> 50 mio/ year	plus 5 years
Italy	"Strict liability" no-fault based	No limits imposed	<u>Usually claimed by ECs</u> 1 mio/pt 10 mio/trial 15 mio/year	plus 2 years



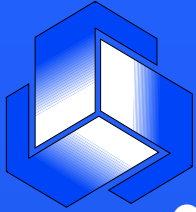
Legal requirements for insurance compensation for clinical trials (II)

Territories	Type of policy	Limits imposed by law (in €)	Common practice (in €)	Period of the coverage after the study closure
Poland	"Liability" fault based	500.000/center and limit for all pts included in this center		plus 3 years
Spain	"Liability" fault based	250.000/pt 2 mio 500/trial 2 mio 500/year		plus 1 year
Switzerland	"Liability" fault based	No limits imposed	10 mio CHF/trial <u>Bodily injury</u> 1 mio/pt <u>Property damages</u> 50.000/pt <u>Invasion personal privacy</u> 100.000/pt	plus 5 years
The Netherlands	"Accident" no-fault based	450.000/pt 3 mio 500/trial 5 mio/year		plus 4 years



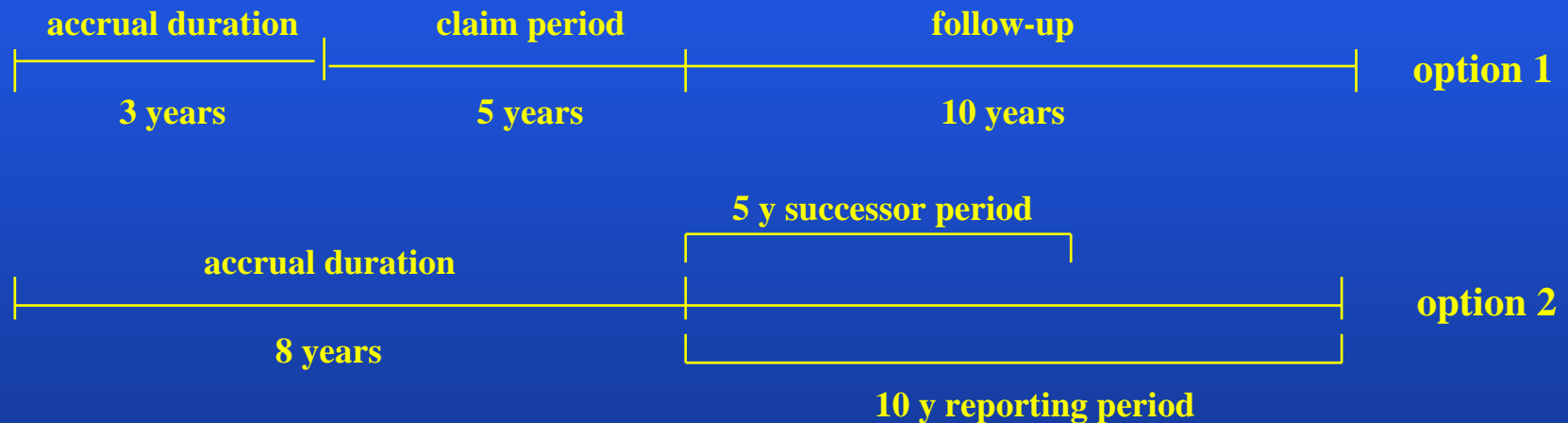
Specific German issues (I)

- **In 1997**
 - **high prohibitive costs for insurance in Germany as compared to Europe**
 - **negotiation EORTC - Gerling - Münchner Rück (Pool)**
 - **interruption of EORTC activities for 6 months in Germany**
 - **amicable solution annual policy renewed on acceptable quotation**

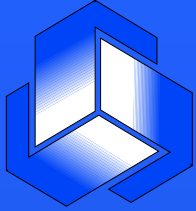


Specific German issues (II)

- In 2004-2005
 - annual policy being challenged
 - new exclusion clause on trial duration and Interferon

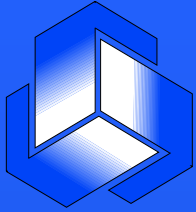


- ◆ Interferon trial excluded → to increase risk of suicide (?)
- solution agreed in option 2 → annual policy continued
- interruption of trials in Germany for 2 months



Current uncertainties in Germany

- Varying number of copies to be submitted to ECs
- Communication with ECs
 - with central
 - with local through central
 - with local directly



Increased Costs in Germany

EORTC Study 22033- 26033

Ethics Committee and MSCA Costs

- Germany

MSCA- 1600 Euro

Local EC- 160 Euro

Total for Germany - 1760 Euro

- Other EU Member States

Total EC and MSCA Costs

Austria- No Costs

Belgium- No Costs

Denmark- 918 Euro

France- No Costs

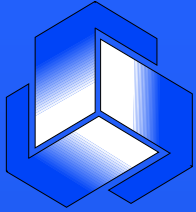
Italy- No Costs

Portugal- 1000 Euro

Spain- 100,70 Euro

The Netherlands- No Costs

United Kingdom- 212,69 Euro



Increased Costs in Germany

EORTC Study 65041

Ethics Committee and MSCA Costs

- Germany

MSCA- 2800 Euro

Central EC- 3000 Euro

Local EC- 1370 Euro

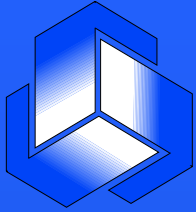
Local EC- 600 Euro

- Other EU Member States

- Belgium- No Costs

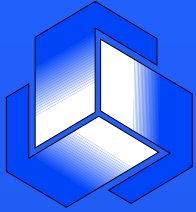
- United Kingdom- 200 Euro

Total for Germany - 7770 Euro



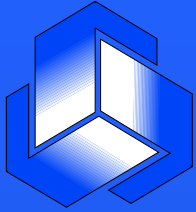
Most frequent insurance incertitudes

- **Definition of end of trial**
 - end of accrual, end of treatment, end of follow-up
- **Definition of follow-up**
- **In case of change of law / conditions during the course of the study**
 - prior any EC obtained but dossiers being sent out
 - after at least one EC obtained but no patient in
 - during accrual: how about for new patient?
 - when addressing a new site during the course of the study



Insurance issues in Switzerland

- **Programme interrupted 2 years ago**
 - requirement for legal representative on Swiss territory
 - respective responsibilities of the EORTC and its Swiss representative
 - 6 month discussion
- **2005: new insurance requirements issued in April**
 - higher compensation
 - moral damage
 - material damage (vacations)
 - loss of annual policy



Current European framework

- Insurance for academic trials is more expensive than in USA
- European framework drives patients into "suers"
- Risk to impair academic research performance
- Halt of therapeutic improvement