EORTC

CLINICAL CANCER RESEARCH
THE IMPORTANCE OF
TRANSLATIONAL RESEARCH

MD/PhDs in the DRIVING SEAT

Alexander Eggermont, MD, PhD
President EORTC

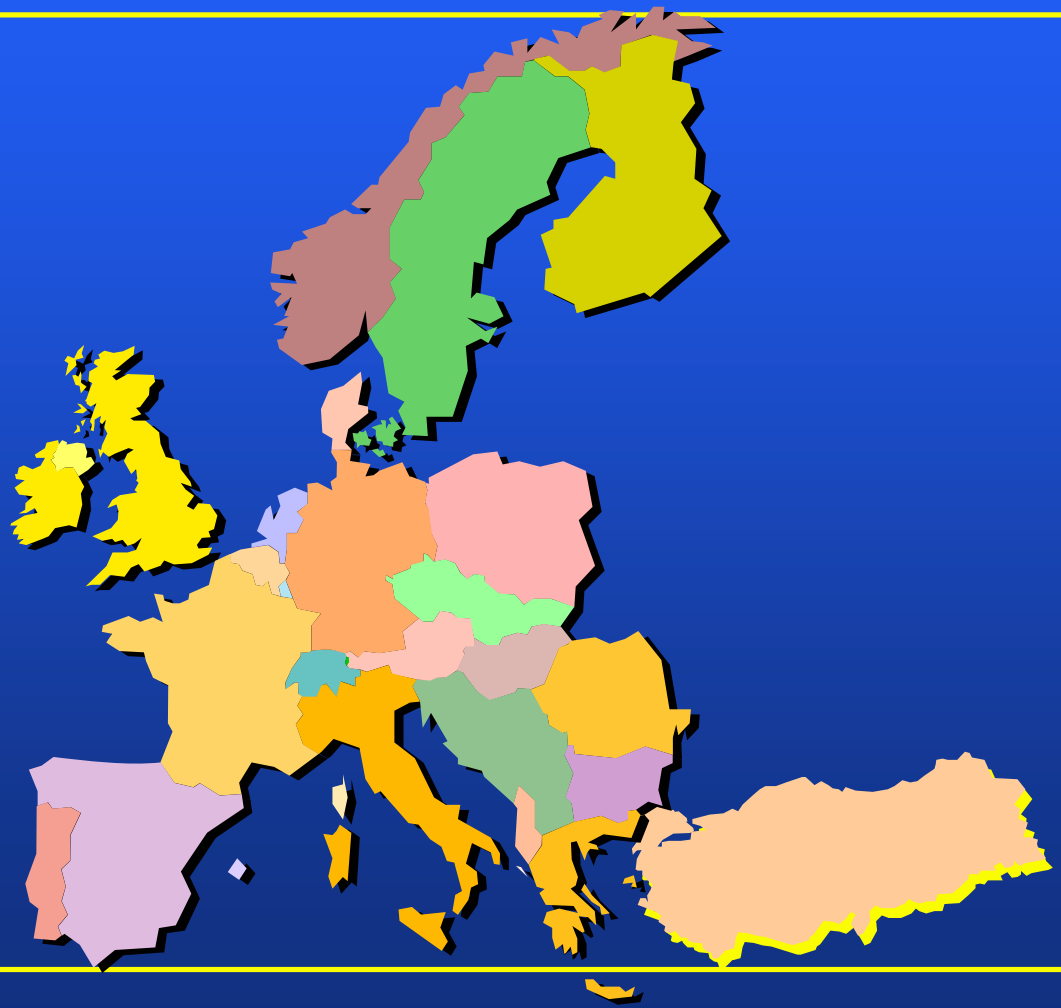
EORTC

- **Private and Not for Profit Organization**
- **Main mission: promote and conduct research to improve cancer care**

EORTC

- **Core activity: conduct clinical trials**
  - **International, Multidisciplinary, Multicenter**
  - **Answer treatment outcome questions**
  - **Answer biologic/mechanistic questions**
  - **Develop new treatments**
  - **Define new standards of care**
  - **Large Academic trials**

European Organization for Research and Treatment of Cancer



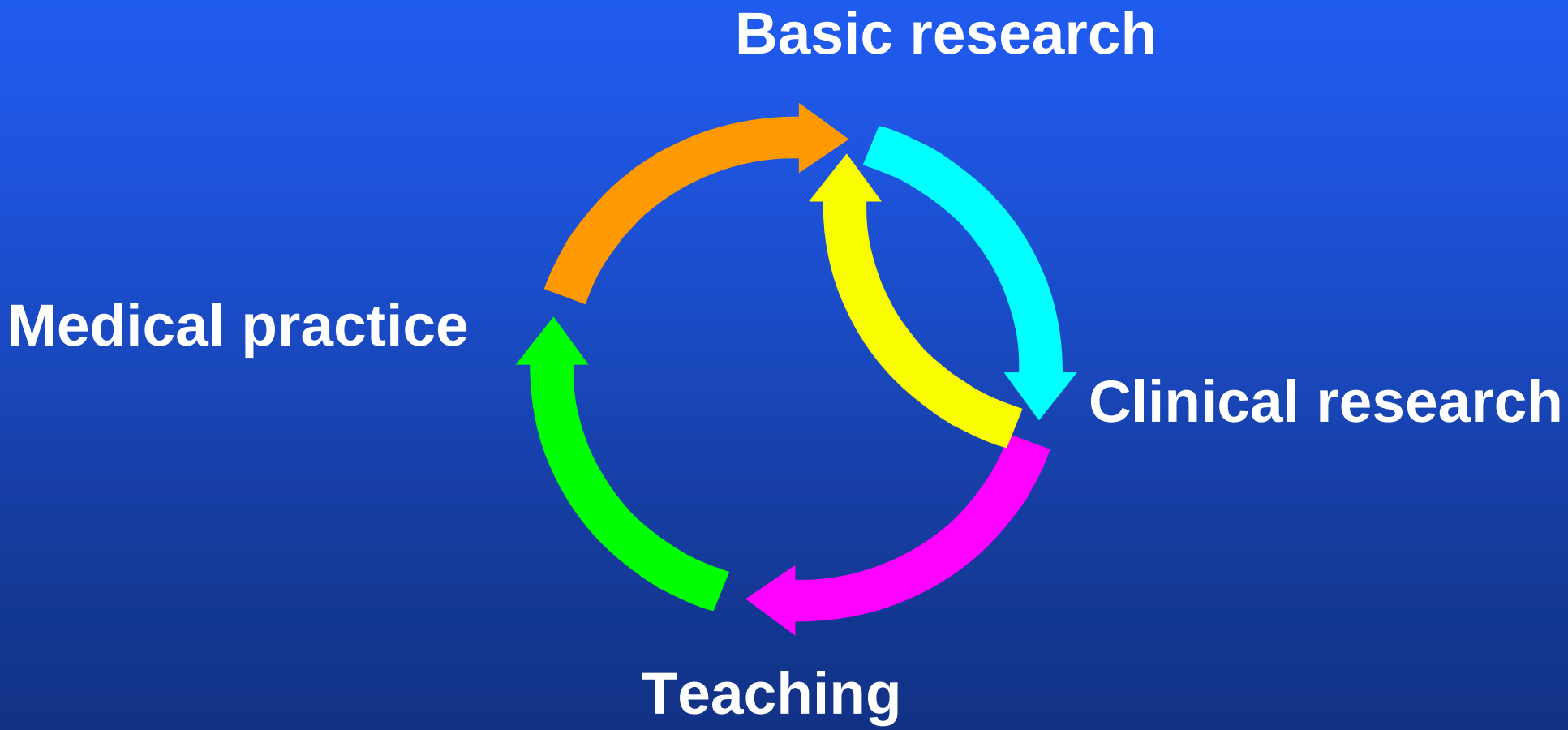
± 6000 new patients recruited in 2005

± 100 clinical trials

in 40.000 patients

150.000 pts in F.U.

TRANSLATIONAL RESEARCH CRUCIAL COMPONENT OF CLINICAL TRIALS



EORTC GROUPS

- **TREATMENT DIVISION**
  - Brain
  - Breast
  - Infectious Disease
  - Elderly
  - GI
  - GU
  - GYN
  - Head & Neck
  - Haematooncology
    - Leukemia
    - Lymphoma
    - Children Leukemia
  - Lung
  - Melanoma
  - Sarcoma
  - Quality of Life
- **RESEARCH DIVISION**
  - Pathobiology (pathology and biomarkers)
  - PAMM (pharmacology and molecular mechanisms)
    - Screening
    - Functional imaging

RESTRUCTURING OF THE EORTC
THE IMPORTANCE OF TRANSLATIONAL RESEARCH

- TRANSLATIONAL RESEARCH FUND
- TRAC (Transl Res Advisory Committee for protocol development)
- TR – UNIT at headquarters
- INTEGRATION SCIENTISTS into Steering Cie Tumour Groups
- INTEGRATION OF LABORATORY RESEARCH GROUPS
  - Mergers inside the Lab Res Division: Biopathology ; PAMM/FIG
  - TRAC recommendations to protocols
- NETWORK OF CORE INSTITUTES
  - accruing power + academic lab infrastructure

RESTRUCTURING OF THE EORTC
THE IMPORTANCE OF TRANSLATIONAL RESEARCH

- **TRANSLATIONAL RESEARCH FUND**
- **2 million EURO allocated**
  - **Seeding money for 22 projects**
  - **Reports at EGAM:**
    - **Brain (Temozolomide trial)**
    - **Breast (p53 trial)**
    - **Gist (mutations)**

EORTC

EORTC
European Organisation for Research and Treatment of Cancer

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Newly Diagnosed Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert-Charles Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

ABSTRACT

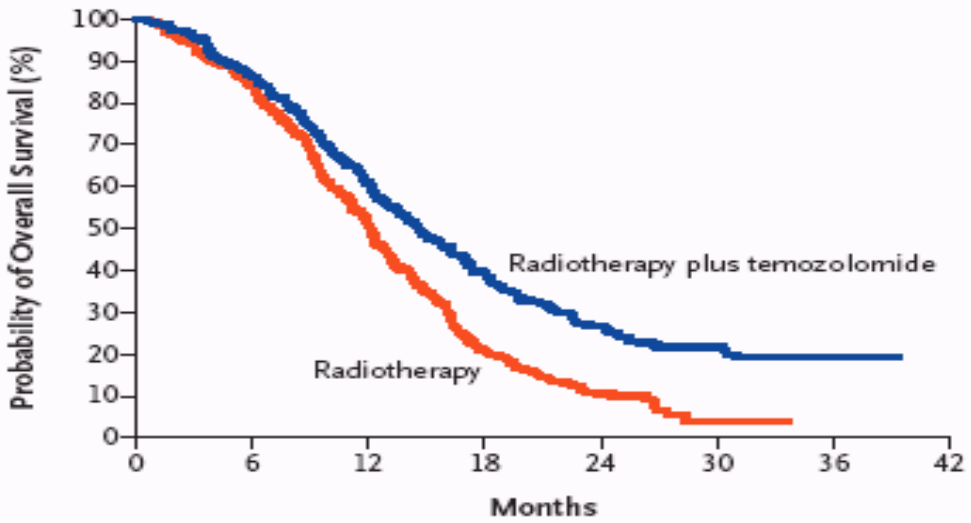


Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

EORTC

EORTC
European Organisation for Research and Treatment of Cancer

ORIGINAL ARTICLE

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

Monika E. Hegi, Ph.D., Annie-Claire Diserens, M.Sc., Thierry Gorlia, M.Sc., Marie-France Hamou, Nicolas de Tribolet, M.D., Michael Weller, M.D., Johan M. Kros, M.D., Johannes A. Hainfellner, M.D., Warren Mason, M.D., Luigi Mariani, M.D., Jacoline E.C. Bromberg, M.D., Peter Hau, M.D., René O. Mirimanoff, M.D., J. Gregory Cairncross, M.D., Robert C. Janzer, M.D., and Roger Stupp, M.D.

ABSTRACT

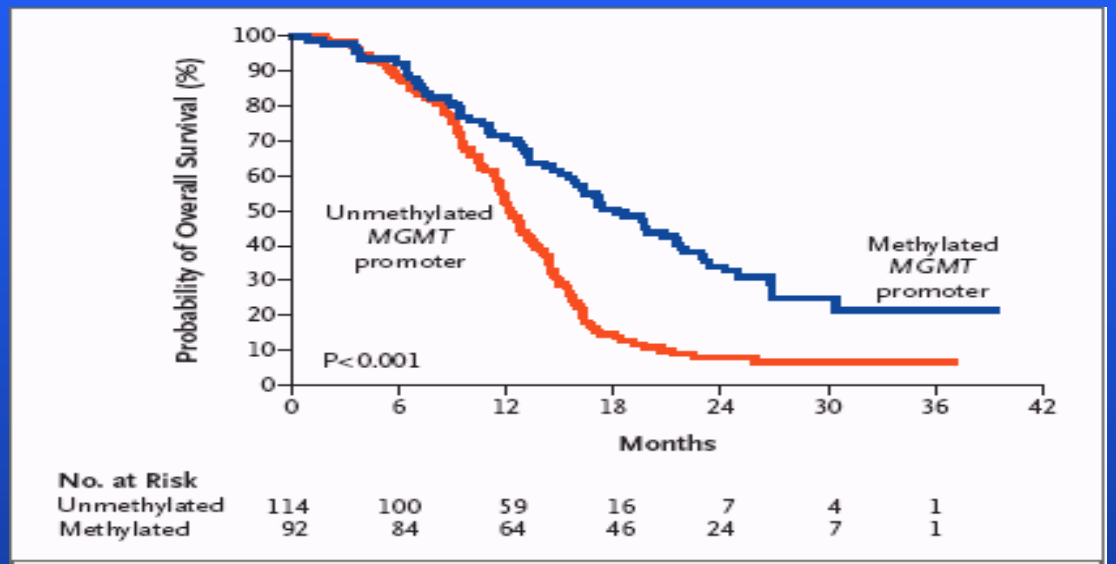
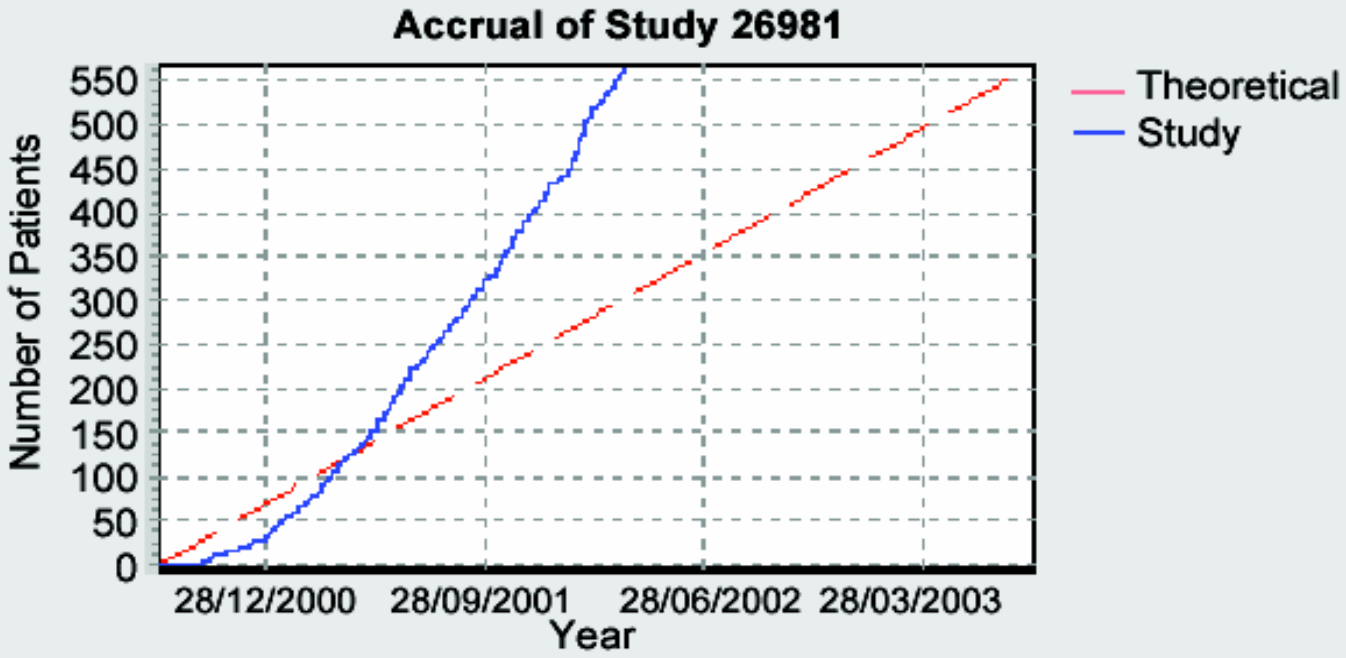


Figure 2. Kaplan–Meier Estimates of Overall Survival, According to *MGMT* Promoter Methylation Status.

The difference in survival between patients with a methylated *MGMT* promoter (92 patients, 65 of whom died) and those with an unmethylated *MGMT* promoter (114 patients, 105 of whom died) was highly significant ($P<0.001$ by the log-rank test), indicating that the *MGMT* methylation status has prognostic value. In the group of patients with a methylated *MGMT* promoter, there was a risk reduction of 55 percent (hazard ratio for death, 0.45; 95 percent confidence interval, 0.32 to 0.61), as compared with the group with an unmethylated *MGMT* promoter.

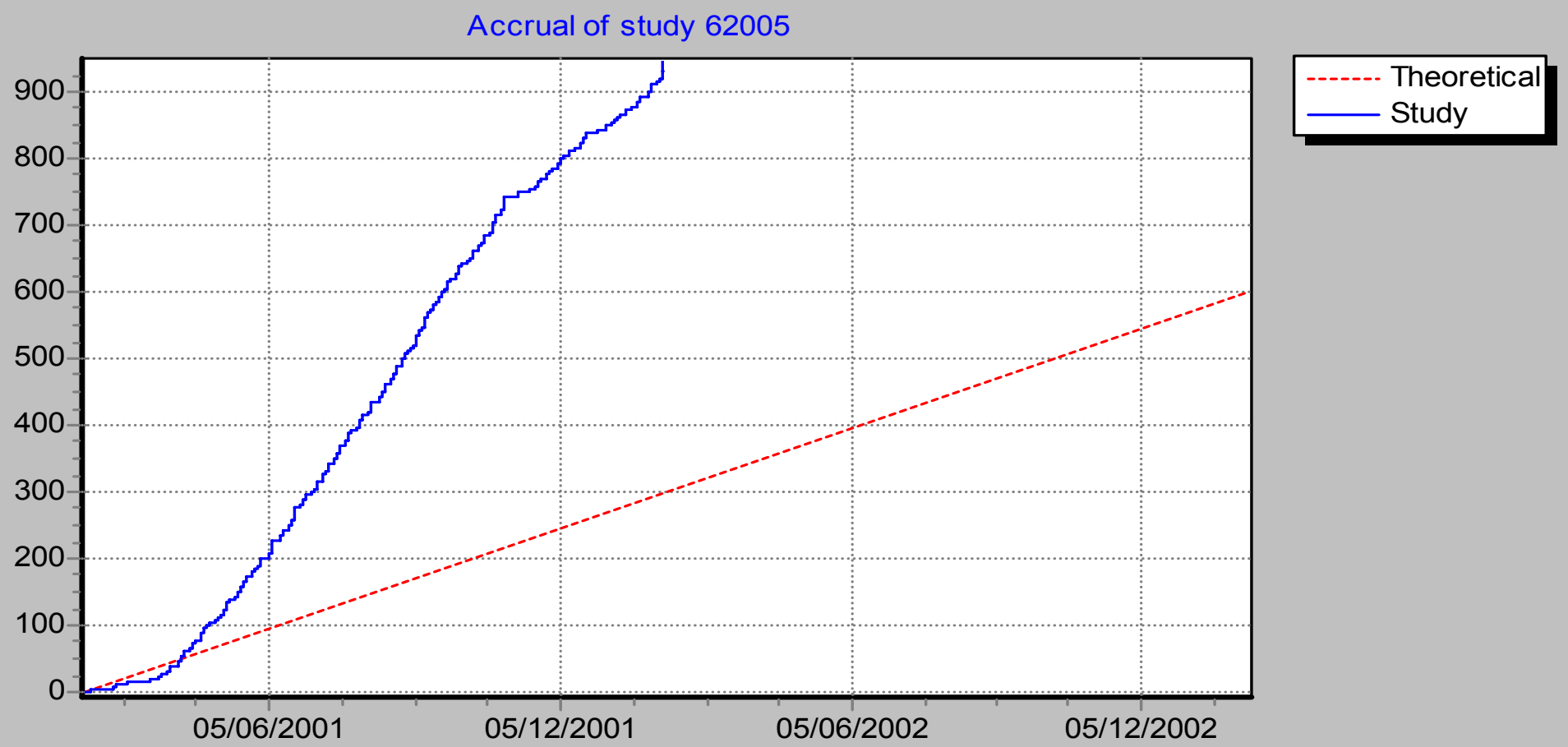
Radiotherapy / Temozolomide adjuvant study in Glioblastoma

- 85 institutions, 14 countries, 573 patients

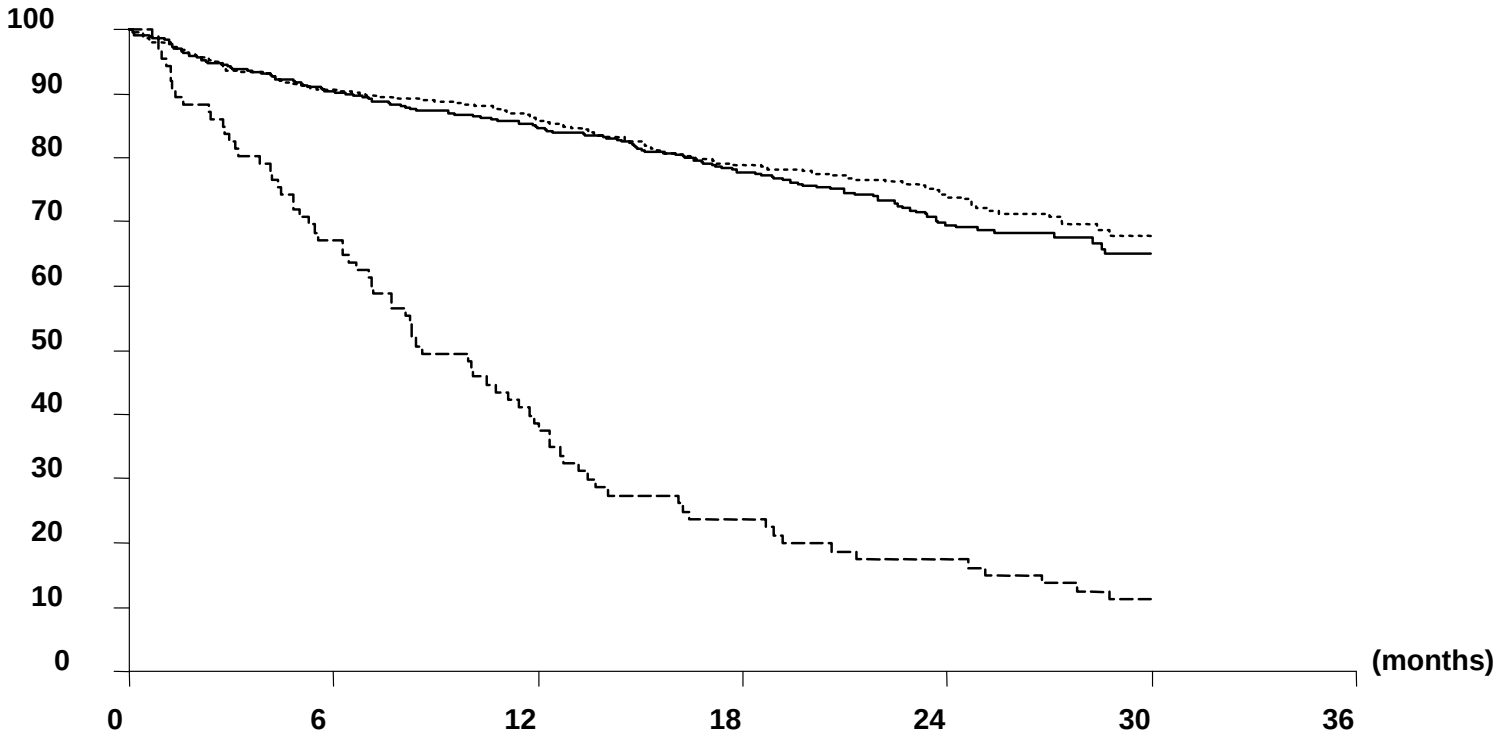


New Engl. J Med, March 2005

Accrual in EORTC trial 62005 (946 patients) - GIST



Glivec Study in GIST
Overall survival



O	N	Number of patients at risk :					Treatment
146	473	423	387	315	192	49	400 mg o.d.
127	473	427	399	323	201	51	400 mg b.i.d.
79	86	57	31	19	14	8	Dox.based

The Lancet Sept. 2004

TRANSLATIONAL RESEARCH
GIST TUMOR TRIAL

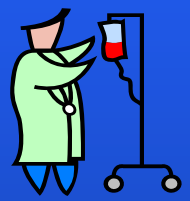
- **TRANSLATIONAL RESEARCH FUND**
- **Mutation analysis**
  - **Response to Gleevec**
  - **Dose response**
  - **6 mutations discovered**

THE EORTC 10994/ BIG 01-00 TRIAL:
Taxane benefit in p-53 mutated tumors?

Large tumors

N=1300

Tru-cut biopsies



RANDOMIZE

FEC_{100} or Canadian CEF

Docetaxel (D) x 3

ED x 3

Local therapy ±TAM

Disease-free survival

Snap frozen sample

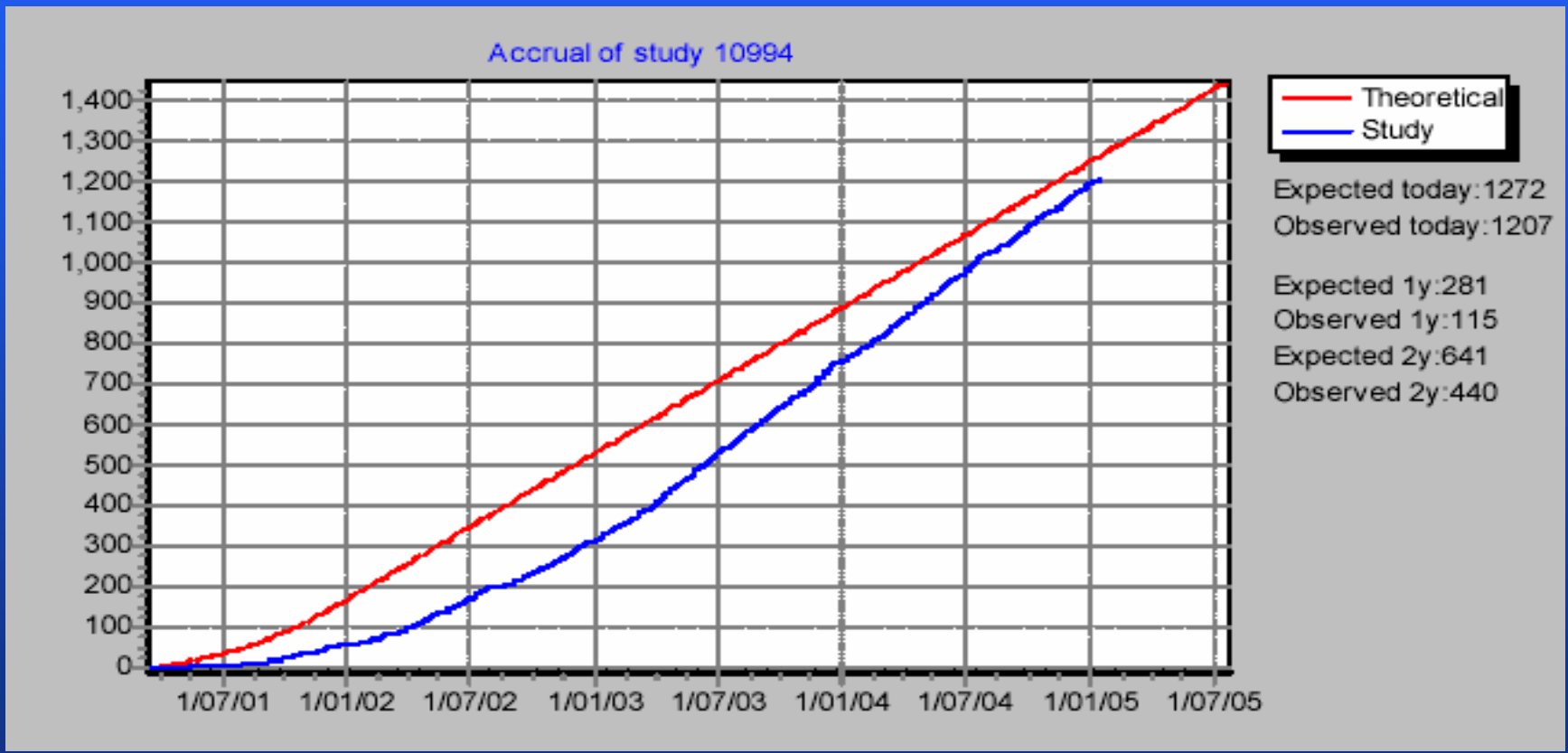
p53 analysis (functional assay)

Microarray gene profiling

Molecular signature of taxane's benefit ?

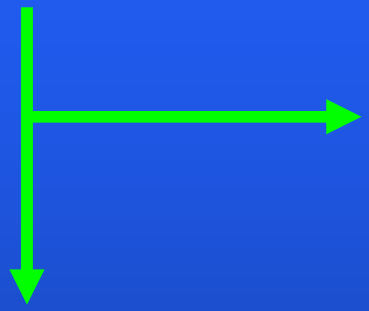
Hypothesis: ↑ DFS at 3y by 5% in p53– and 20% in p53+

EORTC 10994 – BIG 01-00
Accrual in a Complex Trial



p53 status assessed in 514 tumours

N = 600 tumours
(deliveries 1, 2, 3 & 4)



N = 86 (14%)
< 20% tumour cells

N = 514 (86%)
>20% tumour cells
(at least one sample)

p53 functional test

- failed : 6
- succeeded : 508

TGIF studies in EORTC 10994: collaboration between EORTC, ISREC (NCCR) and MEDIC

TGIF 1 → 49 pts

Identification of a 3rd group of breast cancer (Molecular apocrine in add. to luminal and basal groups) Oncogene (in press)

TGIF 2 → 200 pts

Is there a gene profile which predicts for complete pathological response after neoadjuvant chemotherapy (Study ongoing)

TGIF 3 → 100 pts

Host-tumour interaction in Inflammatory breast cancer tumours included in EORTC 10994 study

Richard Iggo and Herve Bonnefoi

TGIF studies in EORTC 10994

Identification of a 3rd group of breast cancer

Oncogene (2005) 00, 1–12

www.nature.com/onc

ORIGINAL PAPER

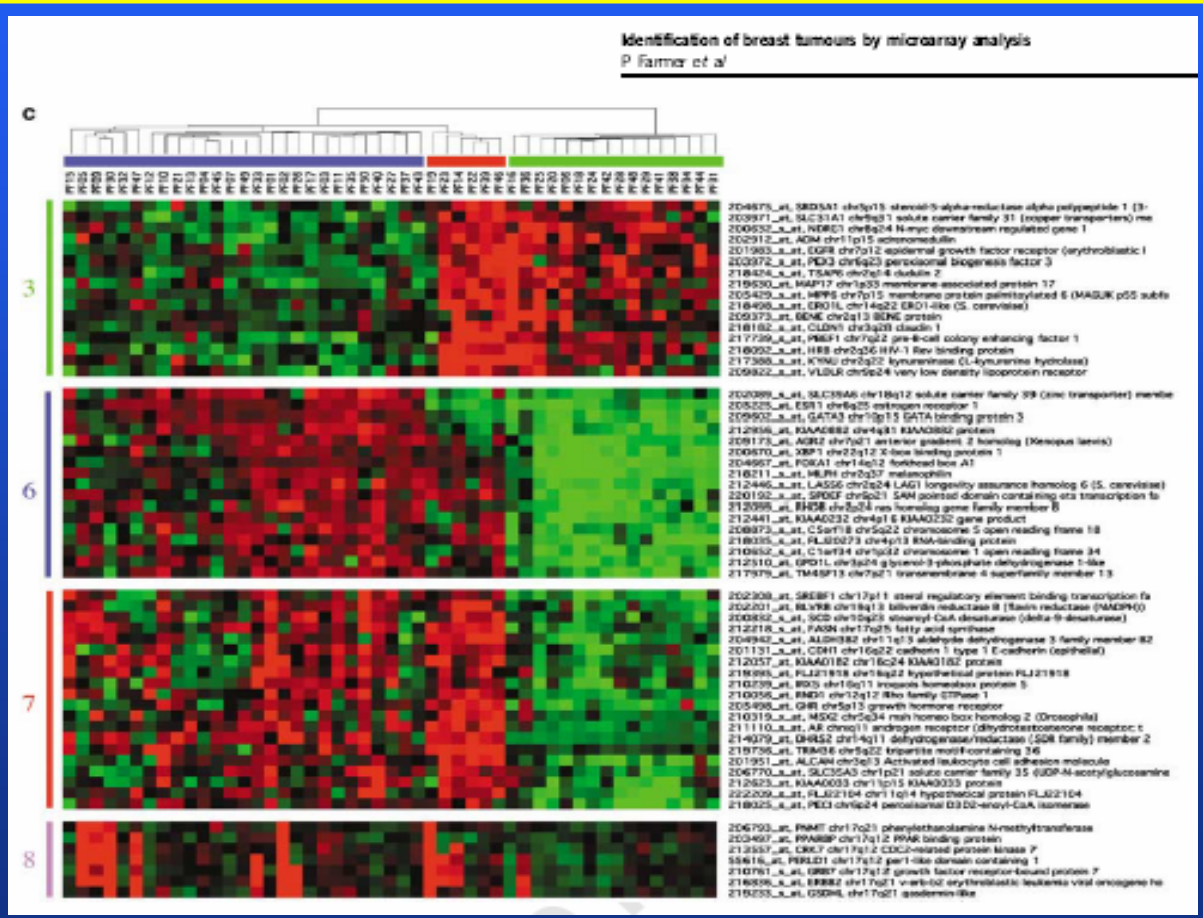
Identification of molecular apocrine breast tumours by microarray analysis

P Farmer[1,2], H Bonnefoi[3,4,5], V Becette[6], M Tubiana-Hulin[6], P Fumoleau[7], D Larsimont[8], G MacGrogan[9], J Bergh[10], D Cameron[11], D Goldstein[1,2], S Duss[2], A-L Nicoulaz[2], M Fiche[12], C Brisken[2], M Delorenzi[1,2] and R Iggo*[,2]

[1]Swiss Institute of Bioinformatics (SIB), Lausanne, Switzerland; [2]National Centre of Competence in Research (NCCR) Molecular Oncology, Swiss Institute for Experimental Cancer Research (ISREC), Epalinges, Switzerland; [3]Hôpitaux Universitaires de Genève, Geneva, Switzerland; [4]for the Swiss Group for Clinical Cancer Research (SAKK); [5]European Organization on Research and Treatment of Cancer (EORTC), Brussels, Belgium; [6]Centre René Huguenin, St-Cloud, France; [7]Centre René Gauducheau, Nantes, France; [8]Institut Jules Bordet, Brussels, Belgium; [9]Institut Bergonié, Bordeaux, France; [10]for the Swedish Breast Cancer Group (SweBCG); [11]for the Anglo-Celtic Cooperative Oncology Group (ACCOG); [12]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

TGIF studies in EORTC 10994

Identification of a 3rd group of breast cancer



GIF studies in EORTC 10994: collaboration between EORTC, ISREC (NCCR) and MEDIC

TGIF 1 → **49 pts**

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Is there a gene profile which predicts for complete pathological response after neoadjuvant chemotherapy (Study ongoing)

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Host-tumour interaction in Inflammatory breast cancer tumours included in EORTC 10994 study

Richard Iggo and Herve Bonnefoi

TGIF studies in EORTC 10994: collaboration between EORTC, ISREC (NCCR) and MEDIC

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TGIF 3 → **100 pts**

Host-tumour interaction in Inflammatory breast cancer tumours included in EORTC 10994 study

H. Bonnefoi

MINDACT: first main project

Microarray for **N**ode Negative **D**isease may **A**void **C**hemo **T**herapy

CLINICAL APPLICATION OF GEN

OMICS FOR IMPROVED TREATMENT TAILORING

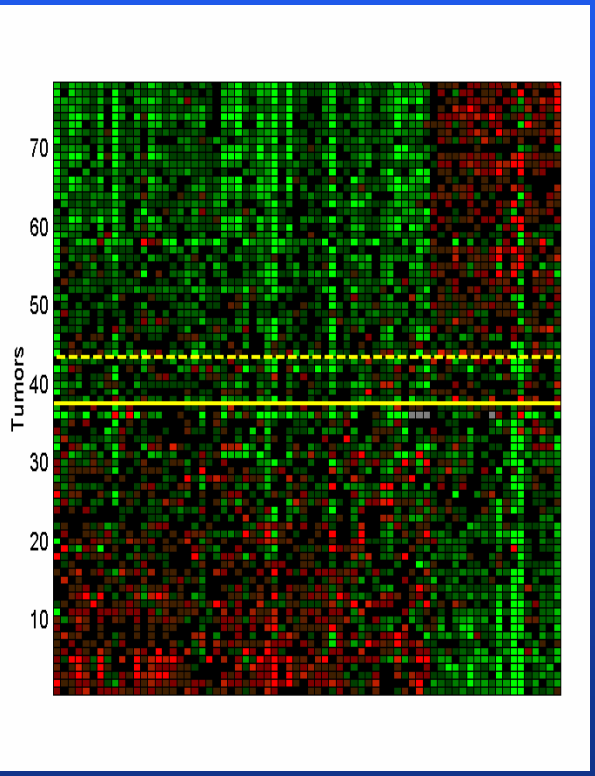
BENEFITS:

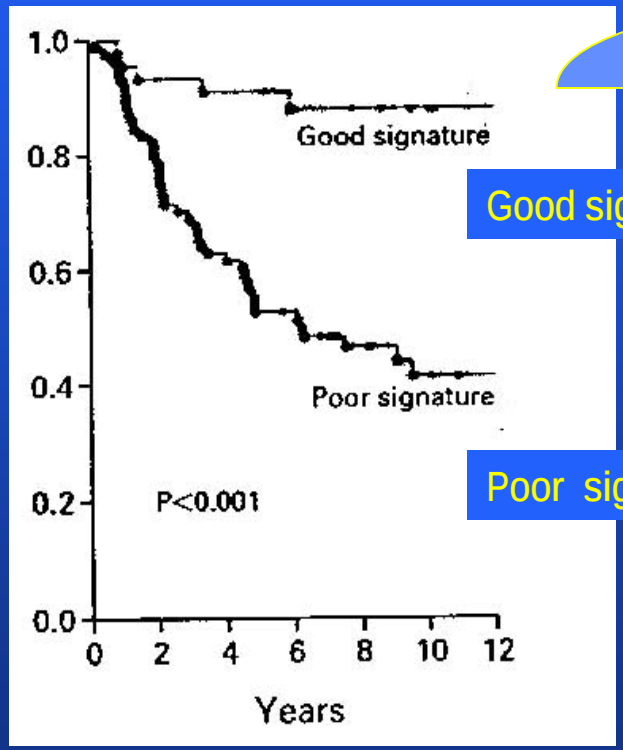
- Reduce toxicity & side effects
- Reduce cancer care costs
- Reduce burden on health care systems

IMPROVED RISK ASSESSMENT OF EARLY BREAST CANCER THROUGH GENE EXPRESSION PROFILING

microarray

Gene-expression profile





Good signature

Poor signature

Interesting hypothesis that deserves further testing!

Amsterdam Gene profile

N Engl J Med, Vol 347 (25), Dec. 2002

Competitive Gene Profiles
COMPARATIVE STUDIES

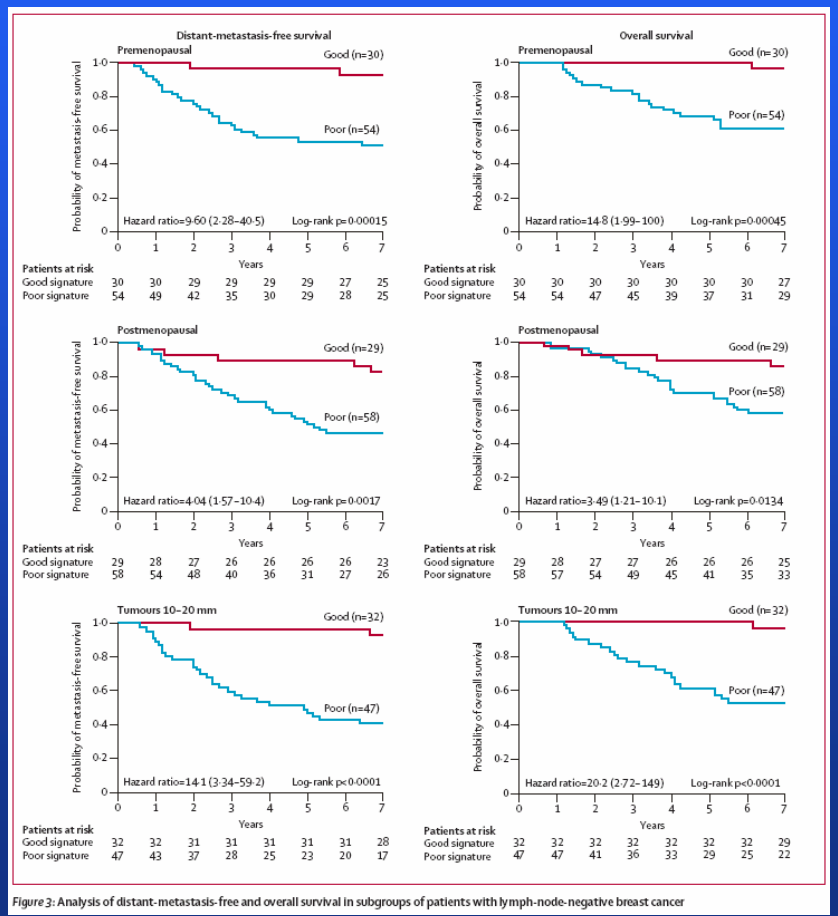


Figure 3: Analysis of distant-metastasis-free and overall survival in subgroups of patients with lymph-node-negative breast cancer

Rotterdam Gene profile

*Lancet 2005; **365:671-9** , JCO 2006; **24(11):1665-71***

MINDACT:

20 Trial # 10041:
A prospective, randomized study comparing the 70-gene classifier with the common clinic pathologic criteria in selecting patients for adjuvant chemotherapy in node negative breast cancer patients (MINDACT)

MINDACT:

Main eligibility criteria:

- Women < 60 years old, with cytologically or histologically proven operable breast cancer and negative sentinel node or negative axillary clearance
- Unifocal, unilateral BC. DCIS or LCIS is allowed provided invasive cancer is present
- Breast conserving surgery or mastectomy, sentinel node procedure or full axillary clearance
- Fixation of the breast tumor in RNA*later*® (not in formalin) or liquid nitrogen is mandatory. Tumor samples sent to NKI / Antoni van Leeuwenhoek Hospital and checked for their "quality" and accessibility for micro array analyses. Materials obtained using 2 trucut biopsies (14 G needle) or by surgery are acceptable
- Radiotherapy in case of breast conserving surgery and according to local institutional policy after mastectomy
- No previous chemotherapy

MINDACT:

Treatment Scheme:

Register all patients for assessing clinical/pathological risk (criteria) and genomic risk (70-gene signature)

If clinical/pathological risk is different from the genomic risk then proceed with the 1st randomization:

- (R1) between clinical/pathological or genomic assessment for determination of high or low risk

If clinical/pathological and genomic assess both a high risk or if the risks were discordant and patient was assigned by R1 to chemotherapy then proceed with the 2nd randomization:

- (R2) between anthracycline-based chemotherapy (A) or docetaxel-capecitabine (B)

If the patient is deemed eligible (all hormono-sensitive patients are eligible for R3) for the below endocrine question then proceed with the 3rd randomization:

- (R3) between endocrine therapy of 2 year Tamoxifen + 5 years letrozole or 7 years letrozole

Stratification for: all steps: institutions, R3: risk of recurrence on tamoxifen

Main endpoint: Distant metastases free survival at 5 years

Secondary endpoint(s): Efficacy (DFS, OS) of chemotherapy in women with discordant clinical/pathological risk from the genomic risk, Safety, Translational questions (both prognostic and predictive) for chemotherapy and endocrine therapy

DMFS and SURVIVAL of primary cutaneous melanoma are predicted by genome-wide expression profiling

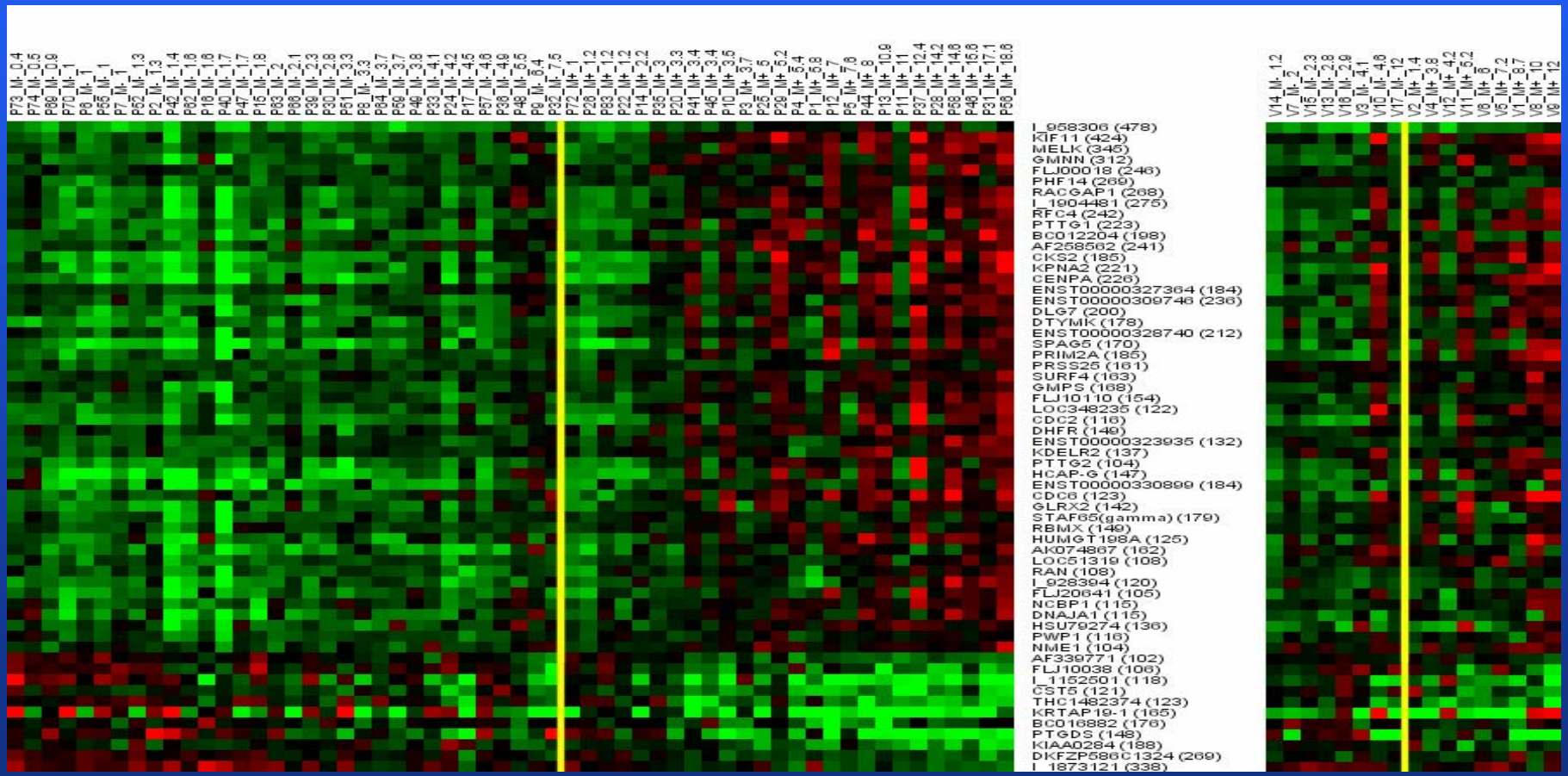
V. Winnepenninckx[1*]; V. Lazar[2*]; S. Michiels[2,3*]; Ph. Dessen [2]; M. Stas[4]; M-F. Avril[5] ; T. Robert[2]; O. Balacescu[2]; A.M.M. Eggermont[-6] ;G. Lenoir[7] ; A. Sarasin[8] ; T. Tursz[9] ; J. van den Oord[1] ; A. Spatz[10]

JNCI 2006;98:472-82

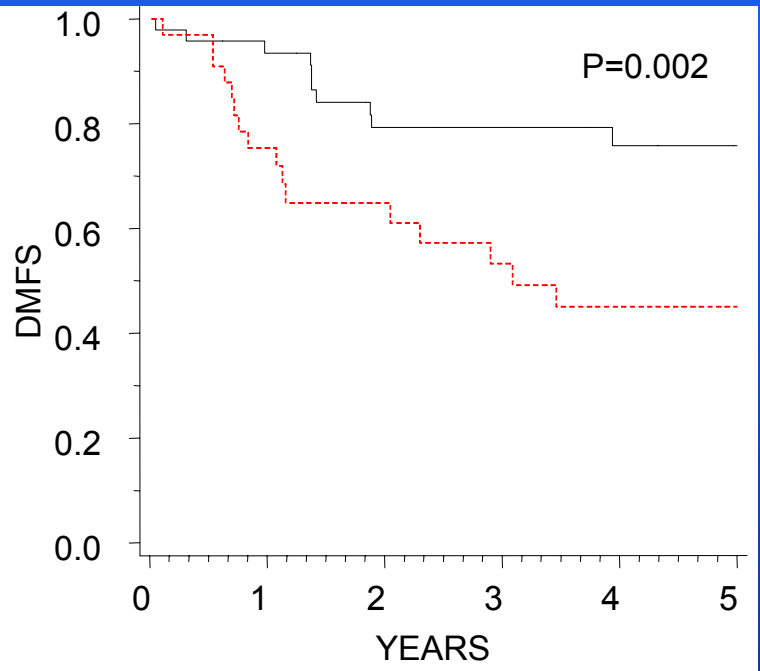
EORTC MELANOMA GROUP

EORTC

EORTC
European Organisation for Research and Treatment of Cancer



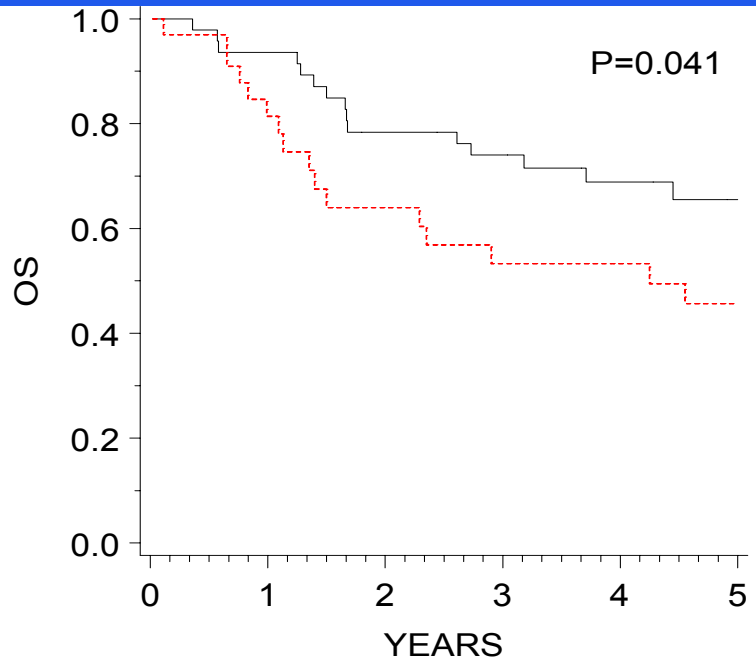
DMFS



Patients at risk

Left cluster	47	41	33	32	21	16
Right Cluster	33	23	17	13	11	10

SURVIVAL



Patients at risk

Left cluster	47	43	36	33	22	16
Right Cluster	33	25	18	15	15	12

EORTC MG 18952

Adjuvant Intermediate Doses of

IFN-α2b vs Observation

in Stage IIB-III Melanoma

1388 pts

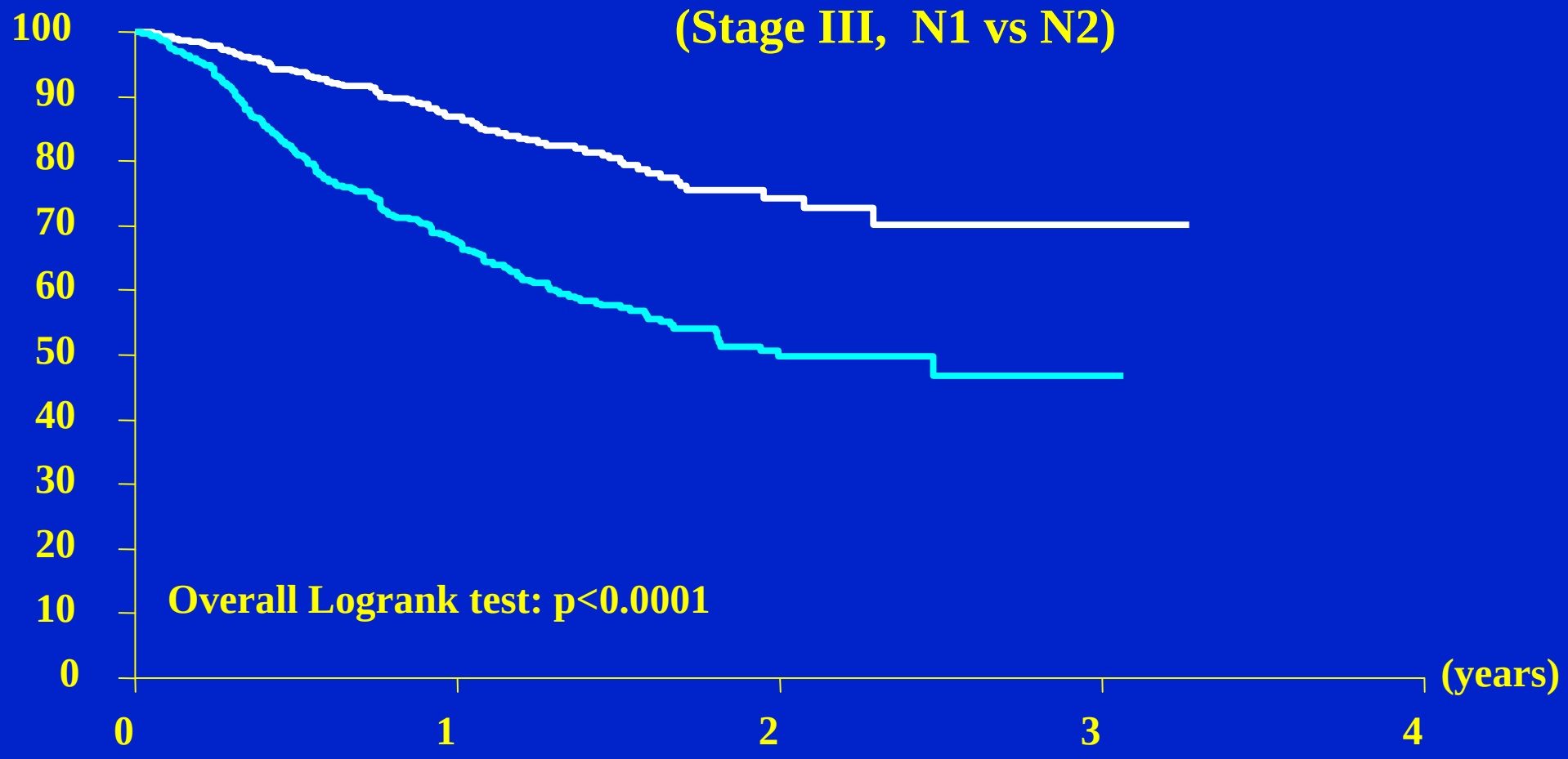
EORTC MELANOMA GROUP

EORTC 18991

LONGTERM (5yrs) PEG-INTRON vs Observation 1256 pts

IN STAGE III

EORTC 18991 DMFS



EORTC 18991

PEG-INTRON IN STAGE III

5YRS PEG-INTRON vs OBSERVATION
1256 PTS

STAGE III ONLY

± 50% SN

ENDPOINTS

DMFS, OS

QoL, Costs

EORTC 18952, 18961, 18991
4000 randomized patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prognostic Significance of Autoimmunity during Treatment of Melanoma with Interferon

Helen Gogas, M.D., John Ioannovich, M.D., Urania Dafni, Sc.D., Catherine Stavropoulou-Giokas, M.D., Konstantina Frangia, M.D., Dimosthenis Tsoutsos, M.D., Petros Panagiotou, M.D., Aristidis Polyzos, M.D., Othonas Papadopoulos, M.D., Alexandros Stratigos, M.D., Christos Markopoulos, M.D., Dimitrios Bafaloukos, M.D., Dimitrios Pectasides, M.D., George Fountzilas, M.D., and John M. Kirkwood, M.D.

EORTC 18952, 18961, 18991
4000 randomized patients

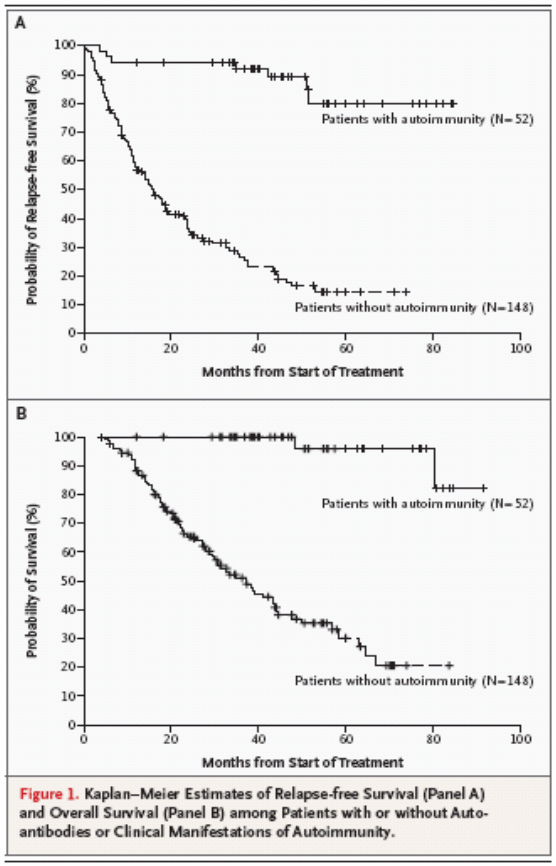


Figure 1. Kaplan–Meier Estimates of Relapse-free Survival (Panel A) and Overall Survival (Panel B) among Patients with or without Auto-antibodies or Clinical Manifestations of Autoimmunity.

EORTC BIOBANK

Clinical TRIAL-RELATED biorepository

with high quality of specimens AND data:

TISSUE COLLECTION at the EORTC

- TMAs for large trials
- Paraffin blocks and unstained slides

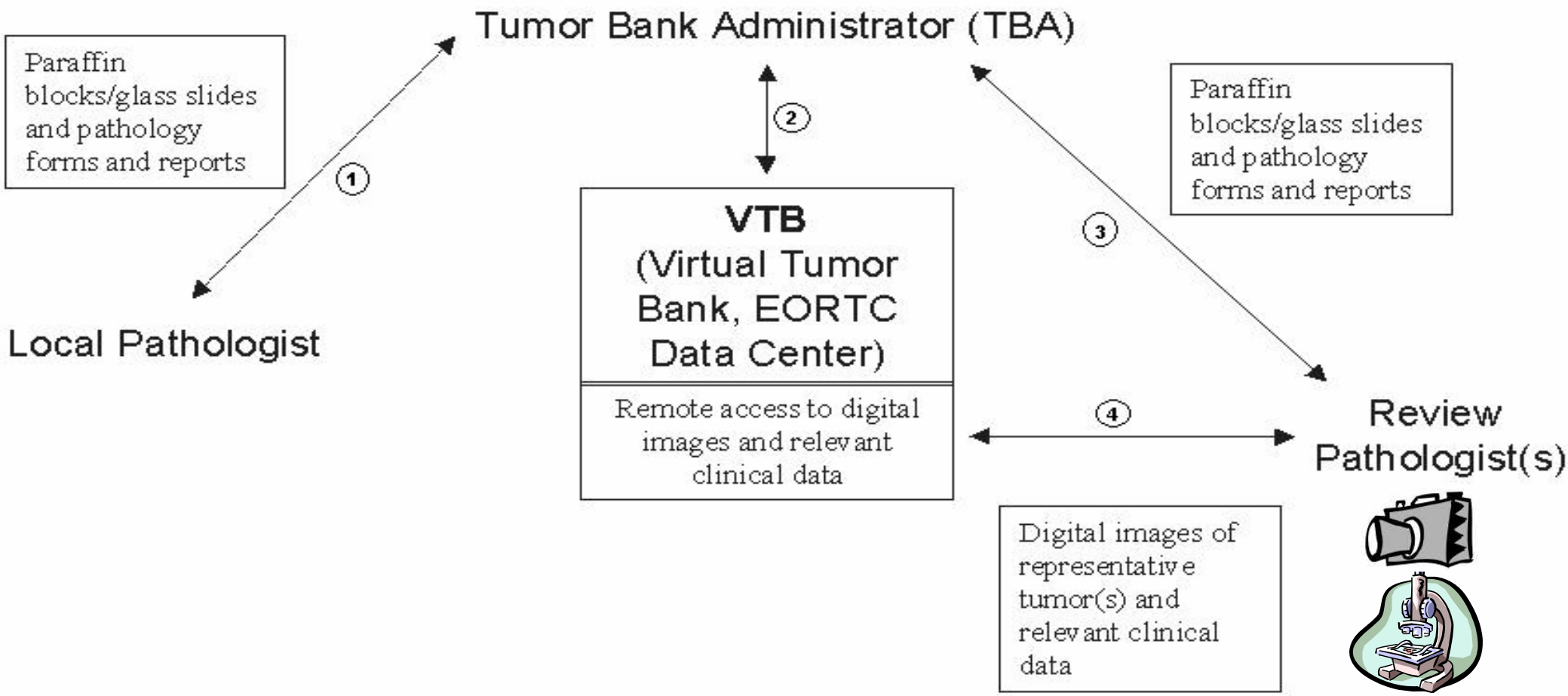
VIRTUAL TISSUE BANK

- Frozen tissue and cells, liquids, nucleic acids

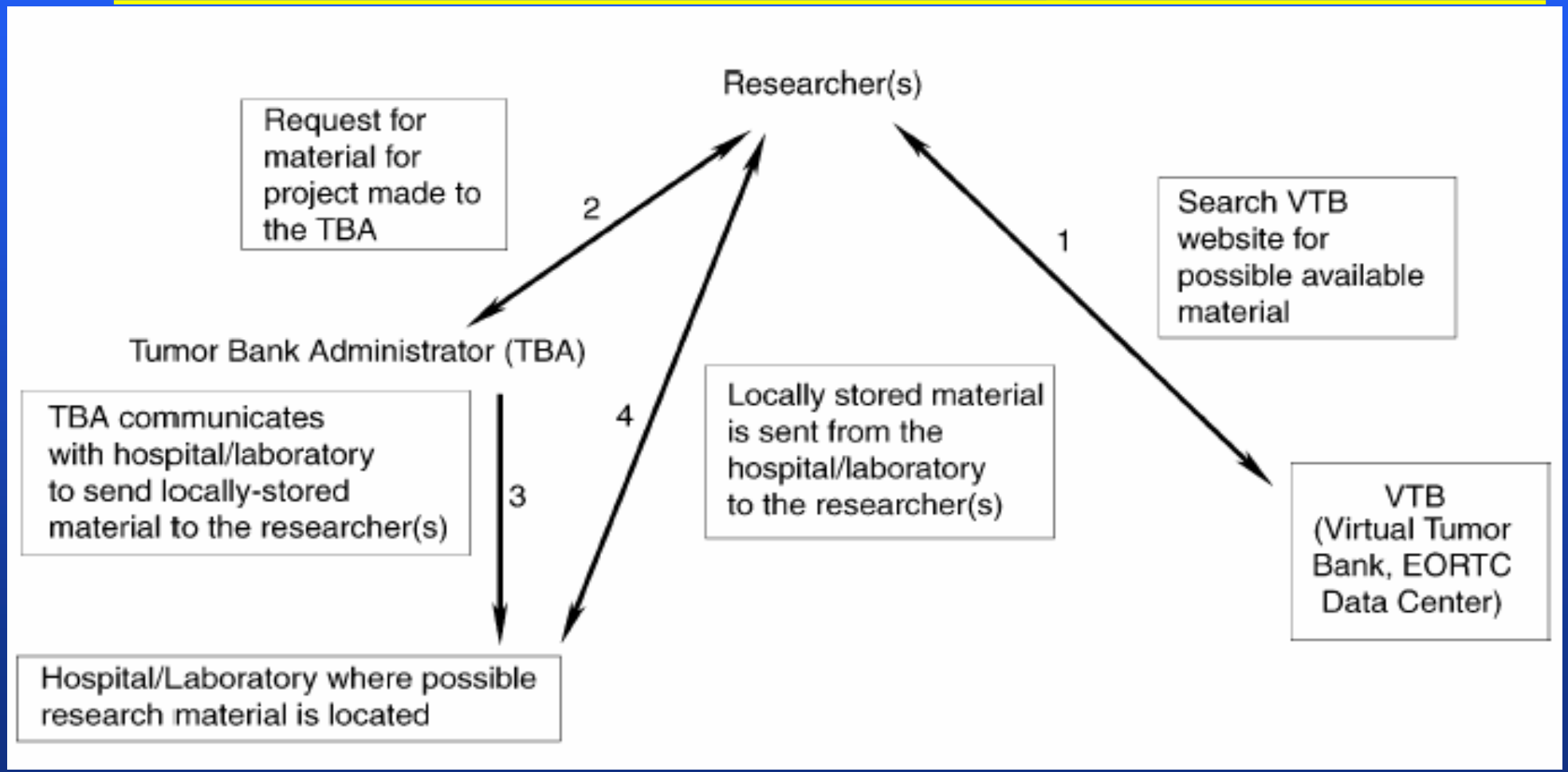
EORTC Tumor Bank - Aims

- To standardize / support histology review across EORTC trials
- Create tumor bank
  - Real tumor bank
    - (centralized storage of paraffin embedded tissue blocks and glass slides [stained/unstained] at the EORTC Data Center)
  - Virtual tumor bank
    - (information and histological images on centralized and decentralized stored material)
  - Legal issues
  - Access and use
- Facilitate translational research

Material and Data Flowchart during histology review



Support for Translational Research within EORTC protocols



Patient information Sheet/Informed consent (PIS/IC)

STANDARD EORTC RECOMMENDATIONS

Eur J Cancer. 2003 Nov;39(16):2256-63

- **in case of optional research on biological material separate documents for clinical PIS/IC and the one related to translational research**
- **in case of mandatory research on biological material within a clinical trial, only one PIS/IC covering both aspects**
- **explanation about research on biological material must be clear and transparent and should include:**
  - **information about possibility to reveal any kind of hereditary nature of disease**
  - **protection of patient rights and identity**
  - **benefits for research**
  - **voluntary aspects**
    - **in case of optional research**
    - **in using material for future cancer research**
    - **on sending the material to a third party**
  - **agreement for an additional tissue sampling**
  - **explanation about intellectual property rights**

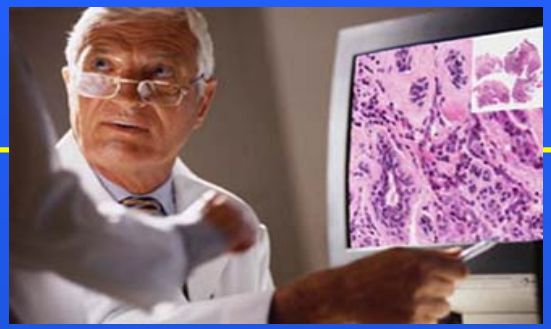
Real Tumor Bank (EORTC Data Center)

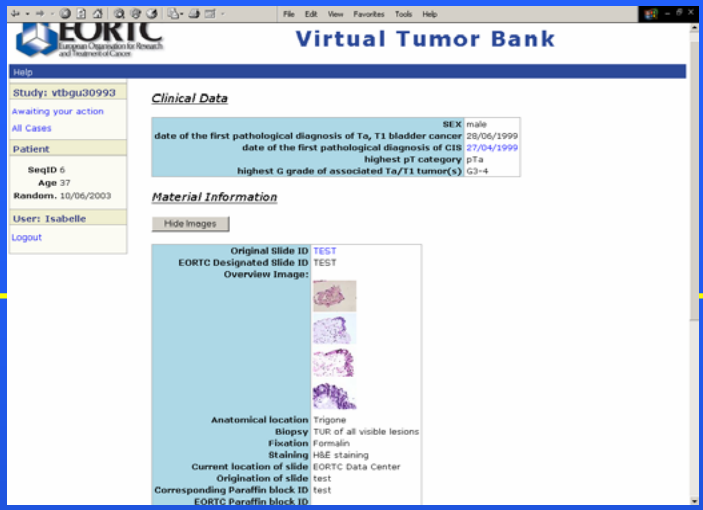
Paraffin Embedded Tissue Blocks (3000)

Glass Slides (13,000)

Virtual Tumor Bank (VTB) - Software and Goals

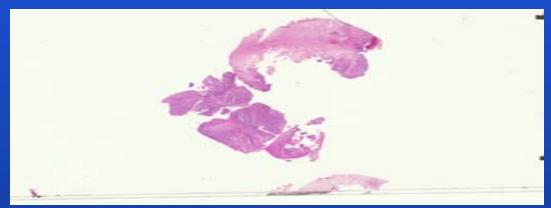
- Design and construction of a pathology database for pathology and material data and a link to the EORTC clinical database
- Construction of a website (Virtual Tumor Bank) to allow users to access patient's pathology, clinical and material (including images) data online and allow online pathology review to take place.
- Construction of an online search engine to allow researchers to search for tissue material, view tissue information (including images) and check on tissue availability for their research projects.





Virtual slides can be produced from the glass slides collected and stored with the tissue records within the VTB.

This will support histology review and provide further assistance to researchers.



Virtual Tumor Bank

VISTA and VTB databases linked together by StudyID and SeqID

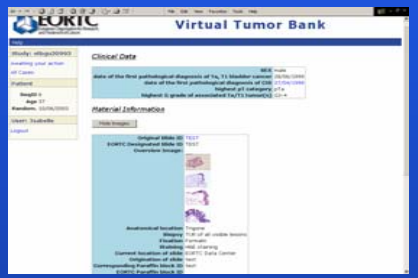
Locally and centrally stored tissue sample information

Tissue information entered by local data manager remotely

VISTA DATABASE

VTB DATABASE

VTB System



Web Interface to VTB for Histology Review

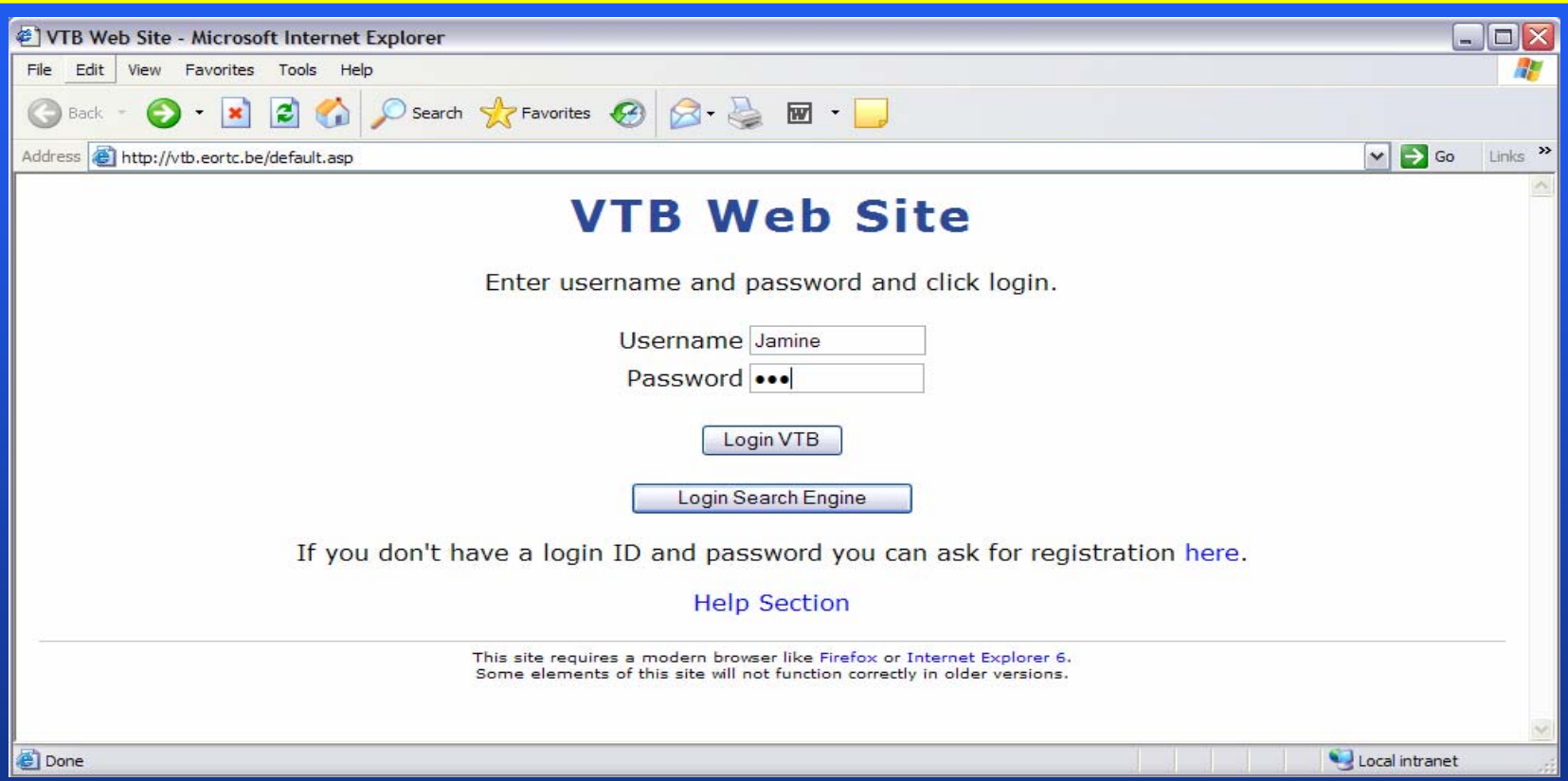
CRF data managed by trial data manager

Online tissue search engine to allow scientists locate material for their research projects

CRF data (pathology, patient information, translational research data, PIS-IC)

Tumor Bank Facilities

VTB Web Site



URL: http://vtb.eortc.be

Tumor Bank Status (March 2006)

Study/disease-oriented frozen tissue banks are immediately accessible in the NOCI.

- **Physical tumor bank at the EORTC Data Center**
  - **1,063 pts**
  - **6 trials (4 adjuvant)**
- **Virtual Tumor Bank**
  - **805 pts**

Strategy for development

- **11,000 specimens are being included in the VTB from 4 large trials (2-5yrs)**
- **Collection of material in the EORTC Tissue repository is key (mandatory) for inclusion in eligible trials**
- **Sequential collection of FNAs material pre-/post-treatment**
- **Integration of the facility in the EORTC NOCI institutions and TR units: interaction EORTC NOCI-PI**

Comprehensive Pathology Departement WITHOUT WALLS

- **Core expertise:**

  Morphology expertise, IHC, molecular pathology
- **Reference technical platforms** & centralized facilities
- Common **SOPs** in interaction with CRD groups
- Common **QC**: targets identification
- **Education**: fellowship, young investigators network
- **Lab Networks**: Exchange programs

RESTRUCTURING OF THE EORTC
THE IMPORTANCE OF TRANSLATIONAL RESEARCH

- SECURE AND FACILITATE CORE FOR TR

- NETWORK OF CORE INSTITUTES
  - accruing power + academic lab infrastructure

EORTC NOCI

- **AFFILIATE INSTITUTES**
  - Large peripheral hospitals
  - Some academic centers, cancer institutes
  - Regional link with NOCI center

- **NETWORK OF CORE INSTITUTES**
  - Large academic centres
  - Big Cancer Institutes
  - **CRUCIAL basic/translational science infrastructure**

Core Institutions
FIRST CORE (18)

- Leuven (BE)
- Rotterdam (NL)
- Nijmegen/Arnhem (NL)
- NKI/AMC (NL)
- IGR (FR)
- Bordet/Erasme (BE)
- Leiden (NL)
- Lyon (FR)
- Berlin (DE)
- Leeds (UK)
- Lausanne (CH)
- Royal Marsden (UK)
- Warsaw (PL)
- Dijon (FR)
- Aarhus (DK)
- Oslo (NO)
- Madrid (ES)
- Ljubljana (SL)

GEOGRAPHICAL DISTRIBUTION OF NOCI INSTITUTIONS
starting CORE

Core Institutions
EXPANSION 2ND of CORE (18)

- Karolinska (Swe)
- Gent (Be)
- Heidelberg//Mannheim (Ge)
- Milano 1-2 (It)
- Barcelona (Sp)
- Bordeaux (Fr)
- Paris Curie (Fr)
- Utrecht (NL)
- Vienna (Aust)
- Munich (Ge)
- Glasgow (UK)
- Porto (Port)
- Manchester (UK)
- Gdansk (Pol)
- Istanbul (Tur)
- Budapest (Hun)
- Prague (Tch)
- Roma (It)

GEOGRAPHICAL DISTRIBUTION OF NOCI INSTITUTIONS
1ST + 2ND CORE (35 CENTERS)

EORTC NOCI

- **INNER CORE**
  - 30 CENTERS ?
  - ACCRUAL + TRANSLATIONAL RESEARCH
  - DYNAMIC 30
- **OUTER SHELL**
  - 100 - 150 CENTERS ?
  - ACCRUAL + quality to provide TR

EORTC NOCI
PRIORITY LIST

- TRIAL TUMOUR BANK
  - INDEPENDENCE (VARIOUS MODELS)
- NOCI TRIALS
  - BASKET TRIAL
  - DVT / CANCER TRIAL
- TR GRANTS FOR NOCI
- NOCI YOUNG OONCOLOGISTS/SCIENTISTS
  - ESTABLISH PROGRAM
- SUPPORT EORTC TO INSTITUTES
    - TRANSLAT RESEARCH UNIT
    - STATS
    - REGULATORY AFFAIRS UNIT
    - TISSUE BANK
- GRANT OPPORTUNITIES
    - NETWORK PRESTIGE - DATA CENTER TRIALS LINK
    - EU-GRANT APPLICATIONS
    - ATTRACK CANCER LEAGUES / FUND RAISING

EORTC
Outcomes of Success last 24 months

- **TOP PUBLICATIONS (IF > 10)**
  - **4 X NEW ENGLAND JOURNAL OF MEDICINE**
  - **5 X LANCET**
  - **3 X JNCI**
  - **14 X J CLIN ONCOL**
  - **3 x BLOOD**

EORTC RESTRUCTURING

- **THE USA-PERSPECTIVE**

- *“ TO ACHIEVE ALL THIS WITH THE BUDGET THAT THE EORTC RUNS ON IS NOTHING SHORT OF A MIRACLE”*

  - **(OVERHEARD AT NCI-AUDIT)**

EORTC
A EUROPEAN ORGANIZATON

PROUD TO BE EUROPEAN