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

Basic research

Medical practice

Clinical research

Teaching
EORTC GROUPS

**TREATMENT DIVISION**
- Brain
- Breast
- Infectious Disease
- Elderly
- GI
- GU
- GYN
- Head & Neck
- Haematooconology
  - Leukemia
  - Lymphoma
  - Children Leukemia
- Lung

**RESEARCH DIVISION**
- Melanoma
- Sarcoma
- Quality of Life
- 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
RESTRICTURING 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)
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).
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.
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

Accrual of Study 26981

Accrual in EORTC trial 62005
(946 patients) - GIST

Accrual of study 62005

- Theoretical
- Study

05/06/2001 05/12/2001 05/06/2002 05/12/2002
Glivec Study in GIST
Overall survival

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

RANDOMIZE

FEC_{100} or Canadian CEF

Docetaxel (D) x 3

ED x 3

Local therapy ± TAM

Disease-free survival

N=1300

Tru-cut biopsies

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

Accrual of study 10994

- Theoretical
- Study

Expected today: 1272
Observed today: 1207

Expected 1y: 281
Observed 1y: 115
Expected 2y: 641
Observed 2y: 440

Date range from 1/07/01 to 1/07/05
p53 status assessed in 514 tumours

- N = 600 tumours (deliveries 1, 2, 3 & 4)
- N = 514 (86%) >20% tumour cells (at least one sample)
  - p53 functional test
    - failed: 6
    - succeeded: 508
- N = 86 (14%) < 20% tumour cells
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
Identification of molecular apocrine breast tumours by microarray analysis

P Farmer¹,², H Bonnefoi³,⁴,⁵, V Becette⁶, M Tubiana-Hulin⁶, P Fumoleau⁷, D Larsimont⁸, G MacGrogan⁹, J Bergh¹⁰, D Cameron¹¹, D Goldstein¹,², S Duss², A-L Nicoulaz², M Fiche¹², C Brissken², M Delorenzi¹,² and R Iggo*²

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

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

TGIF 2

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

TGIF 3

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

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

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

Host-tumour interaction in Inflammatory breast cancer tumours included in EORTC 10994 study
**CLINICAL APPLICATION OF GENOMICS 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

Gene-expression profile

Interesting hypothesis that deserves further testing!

Amsterdam Gene profile

Competitive Gene Profiles
COMPARATIVE STUDIES

Rotterdam Gene profile

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)
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 RNALater® (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
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. Winnepenninckx1*; V. Lazar2*; S. Michiels2,3*; Ph. Dessen 2; M. Stas4; M-F. Avril5 ; T. Robert2; O. Balacescu2; A.M.M. Eggermont6; G. Lenoir7; A. Sarasin8; T. Tursz9; J. van den Oord1 ; A. Spatz10

JNCI 2006;98:472-82

EORTC MELANOMA GROUP
DMFS

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

P=0.002

OS

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

P=0.041
Adjuvant Intermediate Doses of IFN-α2b vs Observation in Stage IIB-III Melanoma
1388 pts
EORTC 18991

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

IN STAGE III

Eggermont
Overall Logrank test: p<0.0001

Number of patients at risk:

<table>
<thead>
<tr>
<th>Stage of disease at random</th>
<th>O</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 (micro)</td>
<td>81</td>
<td>543</td>
</tr>
<tr>
<td>N2 (palpable)</td>
<td>237</td>
<td>713</td>
</tr>
</tbody>
</table>

Overall survival probability (Stage III, N1 vs N2)
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

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 Autoantibodies 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

1. Local Pathologist
   - Paraffin blocks/glass slides and pathology forms and reports

2. Tumor Bank Administrator (TBA)
   - Remote access to digital images and relevant clinical data

3. VTB (Virtual Tumor Bank, EORTC Data Center)
   - Paraffin blocks/glass slides and pathology forms and reports

4. Review Pathologist(s)
   - Digital images of representative tumor(s) and relevant clinical data
Support for Translational Research within EORTC protocols

Tumor Bank Administrator (TBA)

1. Search VTB website for possible available material

2. Request for material for project made to the TBA

3. TBA communicates with hospital/laboratory to send locally-stored material to the researcher(s)

4. Locally stored material is sent from the hospital/laboratory to the researcher(s)

Hospital/Laboratory where possible research material is located

VTB (Virtual Tumor Bank, EORTC Data Center)
Patient information Sheet/Informed consent (PIS/IC)

STANDARD EORTC RECOMMENDATIONS

- 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 Study ID and Seq ID

Locally and centrally stored tissue sample information

Tissue information entered by local data manager remotely

Web Interface to VTB for Histology Review

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

VISTA DATABASE

VTB DATABASE

VTB System

CRF data managed by trial data manager

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

Enter username and password and click login.

Username: Janine
Password:  

Login VTB
Login Search Engine

If you don't have a login ID and password you can ask for registration [here].

Help Section

This site requires a modern browser like Firefox or Internet Explorer 6. Some elements of this site will not function correctly in older versions.

URL: [http://vtb.eortc.be](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 Department
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)**

<table>
<thead>
<tr>
<th>Country</th>
<th>City</th>
</tr>
</thead>
<tbody>
<tr>
<td>BE</td>
<td>Leuven</td>
</tr>
<tr>
<td>NL</td>
<td>Rotterdam</td>
</tr>
<tr>
<td>NL</td>
<td>Nijmegen/Arnhem</td>
</tr>
<tr>
<td>NL</td>
<td>NKI/AMC</td>
</tr>
<tr>
<td>FR</td>
<td>IGR</td>
</tr>
<tr>
<td>BE</td>
<td>Bordet/Erasme</td>
</tr>
<tr>
<td>NL</td>
<td>Leiden</td>
</tr>
<tr>
<td>FR</td>
<td>Lyon</td>
</tr>
<tr>
<td>DE</td>
<td>Berlin</td>
</tr>
<tr>
<td>UK</td>
<td>Leeds</td>
</tr>
<tr>
<td>CH</td>
<td>Lausanne</td>
</tr>
<tr>
<td>UK</td>
<td>Royal Marsden</td>
</tr>
<tr>
<td>PL</td>
<td>Warsaw</td>
</tr>
<tr>
<td>FR</td>
<td>Dijon</td>
</tr>
<tr>
<td>DK</td>
<td>Aarhus</td>
</tr>
<tr>
<td>NO</td>
<td>Oslo</td>
</tr>
<tr>
<td>ES</td>
<td>Madrid</td>
</tr>
<tr>
<td>SL</td>
<td>Ljubljana</td>
</tr>
</tbody>
</table>
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 ONCOLOGISTS/SCIENTISTS**
  - ESTABLISH PROGRAM

- **SUPPORT EORTC TO INSTITUTES**
  - TRANSLATION RESEARCH UNIT
  - STATS
  - REGULATORY AFFAIRS UNIT
  - TISSUE BANK

- **GRANT OPPORTUNITIES**
  - NETWORK PRESTIGE - DATA CENTER TRIALS LINK
  - EU-GRANT APPLICATIONS
  - ATTRACK CANCER LEAGUES / FUND RAISING
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
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 ORGANIZATION

PROUD TO BE EUROPEAN