

ASSESSMENT OF THE THERAPEUTIC RESPONSE IN BREAST CANCER (ASTHER)
Expression of Interest (call OI.FP6.2002) for an Integrated Project prepared by Hagay Sobol

1. BACKGROUND

There is an urgent need to set up a European based effort to fight against breast cancer. This is the most common cancer among women in the western-world. The lifetime risk is about 10 %, and more than 250 000 new cases are diagnosed every year in Europe. Although strong efforts have been consented by each country in fighting this flail, the overall 5 year-survival rate is no more than 60 %. This situation is mainly explained by the fact that breast cancer is a heterogeneous disease encompassing different morphological types (12 subtypes) or clinical forms (ex: medullary or inflammatory breast cancers, male breast cancer, early or late onset) and presentations (hereditary versus sporadic cases). Currently all these specificities are ignored for selection of a therapeutic strategy. To make a decision with respect to systemic therapy, common prognostic factors such as tumour size, lymph node involvement, grade, hormonal receptor status are used in combination with few other parameters. However, they only imperfectly predict therapeutic outcome, explaining in part the existence of 40 % of therapeutic failure. In addition, the incidence of some breast cancer forms varies within Europe from north to south, probably due to different environmental exposures and/or genetic background. To improve the situation for breast cancer patients it will be crucial to study the different phenotypes, each of which represents an informative model of breast carcinogenesis. This will lay out the ground for the development of new diagnostic and prognostic tools as well as screening strategies and new therapeutic targets. Finally, to make progress in the field of breast cancer treatment, a Europe-wide collaborative and interdisciplinary effort is required. The present lack of coordinated action and lack of understanding of phenotypic diversity cause a number of serious impediments:

- There are large discrepancies between diagnoses in different centers and limited expertise outside of main Reference Centres resulting in a number of breast cancer forms being misclassified.
- There is a lack of proper phenotypic, molecular and functional characterization of breast tumours (less than 60% of breast cancer have hormone receptor determination). This knowledge will result in defining a novel diagnostic and/or therapeutic grid.
- Current efforts of individual research groups or countries cannot provide sufficient impetus to establish the very large and comprehensive series of incident and retrospective breast cancers and analytical procedures needed to adequately address the heterogeneity of the disease.
- There are only few preclinical models with limited relevance to screen active agents and combinations.
- There is limited clinical development in relation to the different forms of breast cancer and to the limited technological developments in Europe while scientific expertise is present (ex: trastuzumab, mainly developed in the USA).
- There are no useful definitions of target populations for appropriate treatment (ex: sporadic versus hereditary cases) and validated therapeutic strategies are scarce.

2. LIST OF ACHIEVEMENTS AND ACTIONS TO REACH THEM

A concerted action of European reference cancer centres, academic and private research laboratories will enhance multidisciplinary efforts to overcome the limitations of knowledge and the shortcomings of breast cancer treatment. Accordingly, clinical and pathological, molecular-epidemiological, functional and pharmaco-genomics as well as proteomic research approaches, integrating European Therapy or Diagnostic Oriented SMEs or Companies and relying on modern information technologies, will be brought together to pursue the following goals:

- **To establish a “European Consortium of Clinical, Biological Resources and Exploitation” for the improvement of breast cancer treatment by establishing:**
 - large cohorts of non-selected retrospective and incident breast cancer cases, as well as cohorts of homogeneous breast cancer patients (particular clinical situations selected on their potential predictive value),
 - population-based control groups,
 - repositories of biological materials (*i.e.* blood, serum, normal and tumour breast tissues),
 - a comprehensive data warehouse stocked with clinical (diagnostic, survival follow-up after systemic treatment), pathological (diagnostic and prognostic markers) epidemiological (information obtained by standardised interview and molecular (genetics and expression) data,
 - high-throughput technology platforms and bioinformatic centres
- **To use these tools towards:**
 - Identification of factors useful for the prediction of response, non-response, and toxicity under loco-regional and/or systemic breast cancer treatment.
 - Identification of host factors (predisposing and modifier genes) increasing breast cancer risk and/or affecting its natural history.
 - Identification of new therapeutic targets by means of comparative analyses of defined groups of breast cancer (*i.e.* inflammatory breast cancer of very poor prognosis versus medullary breast cancer of particular good outlook, or sporadic versus hereditary breast cancers).
 - Identification of target patient groups for the application of specific treatments, (*i.e.* conventional versus new drugs; breast preservation versus mastectomy)
 - Improvement of diagnostic, prognostic and epidemiological expertise (bioclinical profiles) in order to improve care management and screening,
- **To validate the data obtained from basic science approaches through clinical trials** in unselected cohorts as well as selected homogeneous cohorts of patients and thus to produce 20 to 30 new parameters, and to selected therapeutic innovations (5-10 new agents, 2-5 multimodality strategies).
- **To disseminate this knowledge** to researchers, students, medical doctors, patients, patient associations and charities, health authorities and regulatory bodies,
- **To stimulate investments of pharmaceutical companies.**

- **To improve public health systems and care management of breast cancer patients throughout the European community.**
- **To raise attention to ethical aspects** (particularly in gene patenting and monopoly situation) **and legal issue, impacts on patients and acceptance of new strategies.**
- **To improve women's health and health perspectives throughout Europe.**

2.1 Contribution to Genomics and Biotechnology for Health.

The scientific activities of the ASTHER consortium will allow to design breast cancer prevention programs and improve diagnosis as well as provide useful markers to predict response, non-response and toxicity of systemic drugs, and providing new pharmacological targets. This will be crucial for the development of new diagnostic tools and therapeutic approaches to strengthen the European expertise in this field and to allow European citizens to benefit from improvements in medical care. Thus the network idea of major reference centres will receive impetus and further stimulate and improve European clinical research and the willingness of SMEs involved in diagnosis and services as well as pharmaceutical companies to develop anti-cancer drugs.

2.2 Constitution in the European Research Area of a multidisciplinary consortium to elaborate and disseminate new diagnostic and therapeutic strategies for fighting breast cancer in Europe.

The ASTHER Integrated Project will combine the currently individual efforts to generate a powerful European multidisciplinary anti breast cancer consortium. This will be achieved by combining complementary capacities of different working groups experienced in molecular-epidemiology, genomics, genetics, proteomics, clinical trial, public health, ethics as well as attracting health-economics research interests in order to procreate interactive productive breast cancer research. Expected benefits and contributions will be:

- A powerful clinical network for the establishment of large incident and retrospective patient cohorts (ex: the French Cancer Centre Network accesses about 40% of the new French breast cancers cases, or the German GENICA study collects incident cases of a defined geographic area).
- Concerted actions of numerous laboratories to provide various technology platforms for high-throughput analysis.
- Comprehensive data mining opportunities through powerful biostatistics and bioinformatics units.
- The development of new pharmacological agents, products and services.
- The establishment of public health centres to conduct clinical trials and to address ethical, legal, social and economic issues related to breast cancer.
- A link of interests of patients, professionals and academic organisations to share and disseminate knowledge on diagnostic and therapeutic strategies.
- The improvement of European and national as well as charity funding,
- The enhancement of European expertise in medical progress especially with respect to drug development therapeutic strategies in breast cancer.

3. FORESEEN ACTIVITIES OF THE PROJECT

3.1 Definition of breast cancer phenotypes for the assessment of new diagnostic parameters.

The development of new breast cancer drugs and the potential prediction of response, non-response and toxicity of systemic drugs will highly depend on the knowledge of molecular characteristics of various phenotypic expressions of breast cancer. For this reason activities must focus on selected forms of breast cancer in order to understand the underlying mechanisms of tumorigenesis. From this, conclusions will be drawn for other breast cancer entities. Based on known potential therapeutic failures or inappropriate treatment the following breast cancer phenotypes will be focused on:

- **Extreme forms of breast cancer**, i.e. associated with poor prognosis, very good prognosis, early and late onset.
- **Breast cancers suggesting the involvement of host factors**, i.e. familial breast cancer, male breast cancer, free margin local recurrence, breast cancer with multiple primary tumours, breast cancer with second primary cancers following medical intervention.
- **Breast cancers with limited access to the biological materials**, i.e. infraclinical breast cancers (incidence of which is increasing) and rare forms of breast cancer.
- **A Steering Committee assisted by the Scientific Committee will set criteria for the definition of these breast cancer forms and develop standardised study protocols.** This is to guaranty uniform approaches independent from the experience of present/future (call for proposals launched by the consortium) collaborators, but also to address the diversity of breast cancer within European and medical needs. They will also guide the consortium on the therapeutic innovations to be proposed and studied.

3.2 Research program and tentative agenda.

The research program includes:

- **Molecular identity - Determination of phenotype associated molecular profiles** : The combined approach of biology tools, morphology and imaging as well as epidemiology will allow to better define the various forms of breast cancer, a prerequisite for a better diagnosis and to appropriate care management.
- **Predictogram 1 - Identification of factors useful for the prediction of response, non-response and toxicity of known and new breast cancer treatments** : Based on combined approaches and comparative analyses (different forms of breast cancers), isolated or clusters of biological factors associated with a particular tumour behaviour will be identified and used

as predictive factors of particular outlook and subsequently to select appropriate treatments. Such factors can also be used as therapeutic targets, *i.e.* by designing a specific antibody or a synthetic molecule against a cell-surface receptor.

- ***Predictogram 2 - Identification of host factors related to genetic susceptibility to or affecting the natural history of breast cancer*** : A germ-line mutation is a considerable risk factor of developing a particular tumour (BRCA1 and breast cancer), but also effects the natural history by increasing the risk of multifocal and/or bilateral disease, as well as of multiple primary cancers. Conversely, it is expected that some therapeutic failures are related to a particular genetic background (free margin local recurrence, radiosensitivity, occurrence of particular malignancies following a specific treatment).
- ***Pharmacogrid and molecular identity - Development of pharmacological models for the correlation of systemic treatment effects and molecular profile***: There are only few biological systems to valid a therapeutic agent with reference to a given genetic profile. Thus, genetically defined cell lines, xenografts and animal models will be generated and validated within the consortium. Characterization of their sensitivity/resistance to known and experimental agents will be conducted.
- ***Predictogram and therapeutic strategies - Determination of appropriate therapeutic strategies based on predictive factors (tumours and/or host related), and impacts on patients' and health system organisation*** : New factors will allow to identify among tumours with similar profile based on current prognostic parameters, cases predicted to be associated with a particular outlook or those sharing a particular pharmacological target to chose the appropriate treatment. However efficacy of a medical intervention depends not only on efficacy but also on patients' acceptability and health system organisation as well as on cultural factors.

The tentative agenda includes:

1.year: Organisation and assignment of responsibilities, preparation of paper works (legal and ethical prerequisites) and establishment of logistics. This will include the formal constitution of the Steering Committee, Scientific Committee as well as local sub-committees and functional units, the selection of breast cancer subentities to be studied; the establishment of patient materials repositories, the preparation of standardized study protocols for patient recruitment and recruitment of controls as well as analytical procedures, and the establishment of databases. Assessment of retrospective cohorts and first analyses of selected types of breast cancers.

2. - 4.year: Recruitment of incident cases and controls (epidemiological and clinical data, biological samples).
Molecular analyses by multimodality approaches (micro-array, proteomics, tissue-array, germline and somatic mutation analyses).

2. - 5. year: Statistical analyses. Establishment of biological models to test the efficacy of therapeutic agents with reference to the genetic background and assessment of selected parameters or therapeutic strategies through early clinical trials. Finally, production of 20 to 30 new parameters, selection of therapeutic innovations (5-10 new agents, 2-5 multimodality strategies).

1-5. year: Ethical, legal, social and economical issues will be considered throughout the project.

3.3 Technological Developments.

- **Data bases & exchange procedures**
 - Establishment and use of clinical databases (diagnostic and follow-up data of patients), epidemiological (interview data of patients and controls), molecular, clinical trials, and image databases, biological sample repositories. Establishment and use of common medical guidelines for care management.
 - Standardized study protocols and data mining programs,
 - Training and dissemination of technology and methodology within the consortium.
- **Methodological taskforce.**
 - Quality control of clinical, epidemiological, and molecular data assessment.
 - Definition, validation of surrogate endpoints for different forms of breast cancer.
 - Design and analysis of specific demonstration clinical trials.

3.4 Dissemination and demonstration activities.

• **Intellectual property, patent protection and exploitation.**
Initial members of the Consortium will have agreed on an IP and dissemination chart. A specific taskforce will thereafter define optimal management of ASTHER-IP, patents and rights in keeping with EU laws and recommendations.

• **Clinical trials incorporating new parameters and definition of care management strategies.**
Phenotype based selection of the drugs/agents and associations to be studied. Setting up of early clinical trials to evaluate their efficacy in the prediction or in the care management. Definition of new medical guidelines for care management.

• **Evaluation of societal impacts**
The impacts on care management with reference to the type of tumour, the identification of new predictive parameters as well as host factors (such as the genetic predisposition) and the acceptability of medical interventions will be analysed. The ethical, legal and economic impact on public health organisation will be considered.

- **Dissemination and integration activities.**
 - Training programs for medical students, researchers, engineers and technicians, methodologists, and society.
 - Particularly, building of a bioinformatic expertise to use, adapt and implement integrative, analytic and simulation tools. The focus will be put on the formation of biologists and clinicians to relevant computational approaches.
 - Exchange programs for medical specialists in training, pre and postdoctoral researchers (ex: PhD students of the Marie Curie training program "breast cancer" will benefit).
 - For all these purposes, interactions with universities and professional teaching programs will be considered.
 - A website dedicated to the consortium members to implement databases, and with restricted access for other professionals and public.

4. EUROPEAN EXPERTISE NEEDED FOR A SUCCESSFUL ASTHER- IP

4.1 Critical mass.

• The consortium integrates several types of partners: Networks, Institutions with several groups, independent groups, patients' associations and SMEs or Companies. Cooperations between partners are already existing. They have joined the ASTHER project on the basis of a common interest in oncology and particularly in breast cancer as a model of carcinogenesis. Such an organisation may be used for other type of cancers. The objectives require multidisciplinary, multicentric diagnostic, therapeutic expertises in the field of oncology strongly articulated on genomics and proteomics, clinical trial taskforce, pharmacologic platforms and biostatistics and bioinformatics taskforce. Presently, about **10 000 tumours** have already been collected ready for analyses, and certain prospective cohorts are in progress (**population based series & controls**) and other will be easily constituted. Furthermore, because our main goals are predicted to influence care management, and more generally to have important societal impacts, partners involved in ethics, social science and health economics participate to the consortium.

• **Major Networks and Patients' Associations** : 1) GENICA supported by the German Federal Ministry of Education and Sciences (interdisciplinary group of experts from clinic to molecular cancer genetics belonging the German Human Genome Project; H. Brauch); 2) Italian National Network supported by the Italian Research Ministry (exploring at the genomic, post-genomic level the responses of normal and neoplastic breast cells to estrogens; M. de Bortoli); 3) The French Cancer Centres Network in association with the National Institute of Health supported by the French Research Ministry (Federation of Comprehensive Cancer Centers with genomic and post-genomic plate-forms, family cancer clinics, and clinical research; H. Sobol); 4) French Atomic Energy Commission (genomic, post-genomic technology, and Training; X. Gidrol); 5) FAM CANCER REG EAST EUR / FWP5-QLRI-CT-1999-00063 (a network of Eastern countries mainly devoted to host factors in oncology; J. Lubinski); 6) The Breast Med Consortium / PL ICA3-2001-20001 (Profile of breast cancer in mediterranean area; Y-J. Bignon); 6) CRISCOM-1 FWP5-QLG7-CT-2001-3036 (devoted to the risk communication: lay people's expectations and providers practices; C. Julian-Reynier); 7) A European Network devoted to Ethics, Social Sciences and Health Economics (F. Eisinger); 8) Cancer League and EuropaDonna (patients associations and charity).

• **SMEs and companies**: SMEs are involved either in providing services in information systems, biotechnology, bioinformatics or diagnosis. Cooperations are already existing with major pharmaceutical companies.

• Our initiative **could be coordinated with proposed NOE or other IP**: 1) NE: Clinical Practice Guideline in Oncology (T. Philip); 2) NE: ProTec2Combat (Proteomics Technologies to Combat Major Diseases; J. E. Celis); 3) NE: ENSIFAB (European Network for Studies in Familial Breast Cancer, D. Eccles; and 4) IP: Polygenic susceptibility to breast cancer (P. Devilee).

4.2 Management, organisation and budget.

• Management.

The **Governing Council** will comprise 5 persons : the chairperson for the Network (H. Sobol for FNCLCC / INSERM), and 4 of the leads of main networks (H. Brauch for GENICA, M. de Bortoli for the INN, A-L. Børresen-Dale for NOWAC, and C-J. Cornelisse). This group will meet four times a year to report on targets set and achieved to co-inside with annual conferences, the workshops for core task group and training sessions. The **Steering Committee** will be composed of **core members** (C) participating in at least 3 specific activities : Clinic & Collection (Cl), Research (R), Development (Dt), Integration & dissemination (I & D), and **selected associated members** (A) involved in one or two activities based on their particular expertise (bioinformatics, ethics), while the other associate partners will support the core group and participate to Workpackages and/or Resources & Expertise Committees. The Steering Committee will review current data and identify specific research tasks and needs for clinical and biological material to feed back to the Network with identification of methods for addressing deficits in research material or analysis allowing core group associates to target local country specific resources and deficiencies with the help of experts from across the network (2 formal meetings a year, video conferences and/or telephone conferences when needed). A **Scientific Committee** will be set up to help the Steering Committee in selecting projects and in evaluating the programs. It will be composed of experts from the consortium and calls for proposals will be launched for external advisors. A **Management Committee** with fully staffed secretariat and officers with adequate administrative support will be set up to coordinate all the activities of the network and particularly to manage financial aspects. For this purpose, an active and substantial support will be given by **FNCLCC & INSERM**. Partners will be funded according to the level of support required to achieve the objectives of the network. Calls for proposals will be launched by the consortium to invite new members in to undertake specific tasks (such as Companies for pharmacological development or groups with a specific scientific expertise).

• Organisation.

The ASTHER project will allow the national networks or organisations and laboratories to work together (18 European or associated countries and at least 400 active partners). For this purpose two types of committees will be defined within the Consortium : 1) **Ressource or Expertise Committees** (Biotechnology comt, Pharmacological comt); and 2) **Workpackages** dedicated to a specific group of projects and using one or more resources from the previous committees in order to reach the foreseen objectives (Molecular profile, Predictogram, Pharmacological grid, Societal impacts). Each Workpackage or Ressource Committee will group several **projects or taskforces**, respectively and will be managed by a **dedicated committee** and composed of **leaders of each project**. Workshops will be organised regularly. **Scientific officers** will be the joints between the different operational or resource committees and the Management organisation (Governing Ccl, and management Comt).

• Budget.

Depending on the final number of partners involved, the total budget needed to carry out the research action of ASTHER-IP is estimated to be **80-100 Millions Euro**.

4.3 The ASTHER consortium (Coord: coordinator; C: core member; A: associated member; C: clinic & collection; R: research; Dt: development; I & D: integration & dissemination)

Country & Network & Institution	Contact (C, A)	Cl, R, Dt, I & D	Selected Fields	Country & Network & Institution	Contact	C, R, Dt, I & D	Selected Fields
France & FNCLCC / INSERM, CEA				Istituto Regina Elena, Roma	P. G. Natali (C)	Cl, R, Dt	Therapy
Institut Paoli Calmettes, Marseille	H. Sobol , Coord	Cl, R, Dt, I & D	Genom-Health Eco	Università degli studi di Firenze	S. Bianchi (A)	R, Dt	Pathology
Institut Gustave Roussy , Villejuif	M. Marty (C)	Cl, R, Dt, I & D	Genom-PostG	Cter Stud & Prevention of Cancer, Firenze	D. Gordon (A)	R, I & D	Ethics-Social
Centre Val d 'Aurelle, Montpellier	C. Theillet (C)	Cl, R, Dt, I & D	Genom-PostG	Eastern & Central Country Consortium			
Centre René Huguenin, Saint-Cloud	R. Lidereau (C)	Cl, R, Dt, I & D	Genom-Pharmaco	Pomeranian Med Univ, Szczecin, Poland	J. Lubinski (C)	Cl, R, Dt, I & D	Genet-Pathology
Centre Oscar Lambret, Lilles	J-P. Peyrat (C)	Cl, R, Dt, I & D	PostG-Ethics	Masaryk Mem. Cancer Instit, Brno, Czech Rep	L. Foretova (C)	Cl, R, Dt, I & D	Genet-Epidemio
Centre Léon Berard, Lyon	A. Puisieux (C)	Cl, R, Dt, I & D	Genom-Therapy	Medical Academy of Latvia, Riga, Latvia	A. Irmejs(C)	Cl, R, Dt, I & D	Genet-Pub Health
Institut Curie, Paris	H. Magdelenat (C)	Cl, R, Dt, I & D	Genom-PostG	Univ Hosp, Vilnius, Lituania	P. Elsakov (A)	Cl, R	Genetics
Centre J. Perrin, Clermont-Ferrand	Y-J. Bignon (C)	Cl, R, Dt, I & D	Genom-BiolInfo	National Instit of Oncology, Budapest, Hungary	E. Olah (C)	Cl, R, Dt	Genom-Epidemio
CNRS / Hôpital Saint Louis, Paris	H. deThé (C)	Cl, R, I & D	Mol Cell Biology	The Netherlands			
CNRS & ESIL / Univ de la Mediterranee	D. Thieffry (A)	R, I & D	BiolInfo-BioMath	Leiden University Medical Centre	C. Cornelisse (C)	Cl, R, Dt, I & D	Genom-Anim Model
CEA, / Lab Functional Genomicx, Evry	X. Gidrol (C)	R, Dt, I & D	Genom-PostG	Norway & NOWAK			
CEA / INSTN, Saclay	C. Jimonet (A)	I & D	Training	The Norwegian Radium, Oslo	A.-L. Børresen (C)	Cl, R, Dt, I & D	Genom-PostG
Austria				Spain			
Institute of Anatomy, Histology, Innsbruck	L. A. Huber (A)	R, I & D	PostG-Imaging	Hospital & Univ of Navarra, Pamplona	JM. Martinez-P (A)	Cl, R	Mol Cytogenet
University of Vienna, Medical School	R. Zeillinger (C)	R, Dt, I & D	Cell Detection	Sweden			
Belgium				Karolinska Inst. Stockholm	C. Tishelman (A)	I & D	Health Eco
Ghent University Hospital	L. Messiaen (A)	R, Dt	Mol Genetics	Lund University Hospital	A. Borg (A)	Cl, R	Genom-PostG
Denmark & Danish Cancer Society				Turkey			
Institute of Cancer Biology, Copenhagen	A. Lykkesfeldt (C)	Cl, R, Dt, I & D	Genom-Pharmaco	Bilkent University, Ankara	M. Ozturk (C)	Cl, R, Dt, I & D	Genom-PostG
Germany & GENICA				Hacettepe University, Ankara, Turkey	S. Ruacan (C)	Cl, R, Dt, I & D	Genet-Therapy
Institute of Clinical Pharmacology, Stuttgart	H. Brauch (C)	R, Dt, I & D	Mol Genetics	UK			
Arbeitsmedizin, Bochum	T. Brüning (C)	R, Dt, I & D	Occup Med-Epidemio	University of Aberdeen Medical School	A. Schofield (C)	Cl, R, Dt, I & D	Genom-Drug Resist
Deutsch. Krebsforschungszentr, Heidelberg	U. Hamann (A)	R, I & D	Mol Genetics	Dept of Oncology, University of Cambridge	P. Pharoah (C)	Cl, R, I & D	Genet-Epidemio
Med Univ- und Poliklinik Univ Bonn	Y. Ko (C)	Cl, R, I & D	Oncology	Imperial College, Amersmith Hospital, London	R.C. Coombes (A)	Cl, R	Therapy
Finland				Lancaster Institute	R. Chadwick (A)	I & D	Ethics-Legal
Oulu University Hospital	R. Winqvist (A)	Cl, R,	Mol Genetics	GKT School of Medicine, Guy's Hospital, London	E. Solomon (C)	Cl, R, Dt, I & D	Genom-Genet
Italy & INN				Princess Anne Hospital, Southampton	D. Eccles (C)	Cl, R, Dt, I & D	Genet-Screening
Institute for Cancer Res & Treat , Torino	M. de Bortoli (C)	Cl, R, Dt, I & D	Genom-BiolInfo	Great Ormond Street Hospital	J. Mackay (C)	Cl, R, Dt, I & D	Genet-Clin Trial
University of Ferrara,	M. Negrini (C)	Cl, R, I & D	Genom-Training	SMEs & Companies			
Consorzio Mario Negri Sud, S.M. Imbaro	S. Alberti (C)	Cl, R, Dt, I & D	Genom-Drug discov	Ipsogen, Marseille, France	V. Fert (A)	R, Dt	PreclinPharm-Genom
IDI-IRCCS, Roma	G. Russo (A)	R, I & D	Genom-Anim Model	Exonhit, Paris, France	L . Bracco (A)	R, I & D	DrugDiscov-BiolInfo
Dipartimento di Patologia Generale, Napoli	A. Weisz (C)	R, Dt, I & D	Genom-BiolInfo	Isoft, Paris, France	H. Perdrix (C)	R, Dt, I & D	Genom-BiolInfo
National Cancer Research Institute, Genoa	S. Parodi (C)	R, Dt, I & D	DrugDisco-Pharmaco	Diagnogene, Aurillac, France	C. Pradeyrol (C)	R, Dt, I & D	Genom-Diagnosis
Istituto de Pathologia, Pisa,	G. Bevilacqua (A)	R, Dt	Pathology	Patients Associations & Charities			
				Cancer League & Europadonna			
						I & D	