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Gefitinib 'has missed the mark'. . .

Phase III trials including gefitinib (ZD1839, Iressa) — an epidermal growth factor receptor (EGFR) inhibitor — may have been under-powered, say US researchers (*Lancet* 2003 **362**: 62–64). "The risk is that EGFR inhibitors might be declared ineffective and abandoned prematurely", they said.

Despite positive results in the phase II setting, gefitinib was subsequently found to provide no benefit in either survival, tumour response or time to progression. In one phase III trial, it was used in combination with paclitaxel and carboplatin; in another, with gemcitabine and cisplatin. The trials included 2000 previously untreated non-small cell lung cancer (NSCLC) patients.

"PHASE III TRIALS MAY HAVE BEEN UNDER-POWERED"

The negative results in the large phase III trials may be explained by a dilution effect due to the inclusion of patients with 'insensitive' tumours. The required sample size is determined by both the prevalence of target expression and the magnitude of effect among patients with tumours 'sensitive' to the agent, they said. The authors calculated that the phase III trials were under-powered if 50% or fewer of the patients had 'sensitive' tumours.

Gefinitib may have "missed its mark", the authors say, because of inadequate dosing and delivery of the drug, or because it targeted the same population of tumour cells as the cytotoxic drug. Antagonism between the EGFR inhibitor and chemotherapy agents could also have occurred.

Several EGFR inhibitors are in clinical development. They include monoclonal antibodies targeting the extracellular ligand-binding domain of the receptor and small molecules that inhibit the activation of the receptor tyrosine kinase. "Ongoing and future research with EGFR inhibitors should include pre-clinical studies to determine predictive factors that might identify the most appropriate patients. . . and clinical studies to validate these markers", the researchers conclude.

Emma Cannell
EJC Scientific Editor

. . . what mark?

An alternative suggestion is that gefitinib does not act through the epidermal growth factor receptor (EGFR). This was discussed at the American Association of Cancer Research (AACR, 2003, Washington DC, USA, 11–14 July 2003). Rumours have abounded since the IDEAL trials showed that even patients with very low EGFR expression responded to the drug-a finding that was not predicted by the study's designers (*from 'Does hope match the hype for targeted drugs' by Hannah Brown).*

Research presented at AACR 2003 was based on tumour samples taken from 157 patients enrolled in the IDEAL 1 and 2 trials. They were categorised as negative, weak, moderate, or strong for membrane EGFR staining. There was no consistent association between the extent of expression and objective tumour response or symptomatic improvement — 15% of patients with minimum expression achieved an objective tumour response with gefitinib.

This means that gefitinib has unidentified modes of action, in addition to its affinity for EGFR, and highlights the fact that we still have much to learn about the biological implications of small-molecule drugs.

The success of imatinib mesylate (Glivec) in chronic myeloid leukaemia and some gastrointestinal tumours has set expectations high, but the unique features of both drug and disease (driven by a single molecular abnormality) suggest that similar success may be hard to come by in other tumours. "Solid tumours may well have multiple molecular lesions driving their proliferation," says Hilary Calvert (University of Newcastle, UK). "We would have to hit several pathways to have a significant effect on the tumour."

Therein lies the problem. For patients to reap the full benefits of the targeted approach and to be spared any 'safety-net' treatment with conventional chemotherapeutic agents, hundreds of drugs with specific activity against the most prevalent mutations will have to be developed.

This has cost implications, says Dr Paul Workman (Cancer Research UK Centre for Cancer Therapeutics, London). Pharmaceutical companies will have to focus their efforts on much more narrow indications and, therefore, smaller potential markets. The costs of their products will be high because of the high technology involved in drug development. And health-care providers will be forced to switch from a one-size-fits-all policy to buying treatments to counteract numerous different types of mutations.

Workman believes, though, that some costs will be offset because fewer patients will be given ineffective treatments.

The unabridged version of this story was originally published in The Lancet Oncology (*Lancet Oncol* 2003; **4:** 452).

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EORTC boost translational research

The EORTC is underlining its commitment to translational research with a new Fund and a new Advisory Committee. It is aiming to capitalise on its strength in clinical trials, and has already allocated 2 million Euros to translational research.

Dr Francoise Meunier, Director General of EORTC, said, "The EORTC is recognised as a centre of excellence in clinical research and we have a very strong track record. But the EORTC also has a laboratory division that includes various groups: the Functional Imaging Group (former PET group), the Pharmacology and Molecular Mechanisms Group, the Receptor and Biomarker Group and the Pathology Group. The Board and the Executive have decided to integrate these further and improve cooperation between preclinical work in the laboratory and clinical trials."

Applications for EORTC grants are assessed by the newly formed Translational Research Advisory Committee (TRAC). The aim is ensure that opportunities for translational research are properly exploited within EORTC clinical trials.

Groups applying for clinical research grants will be able to apply for extra funding from the Translation Research Fund if further validation or laboratory research is appropriate to their trial. The EORTC is aiming to reinforce intergroup cooperation.

Professor Ian Stratford (University of Manchester, UK), TRAC chairman, says the EORTC is well placed to conduct translational research because many clinicians involved in EORTC trials are more receptive than some others to the importance of interaction with laboratories. "The EORTC feels there is a need for greater understanding of what is going on at the molecular level during clinical trials. We need to know what parameters are affecting survival or the outcome of treatment. For example, in the age of molecular targets, if a drug is designed to hit particular target and therefore inhibit the growth of a cancer cell, it is important that we know that the individual patient's tumour expresses that target. Otherwise, the treatment is inappropriate," he said.

Dr Meunier said that it is a particularly appropriate time to instigate more translational research, because there are many novel agents available for screening at present. The EORTC backed four translational research projects in 2001, seven in 2002 and five in 2003. Funding has already been secured to cover the next 5 years.

The projects selected for funding in 2003 are:

- *EORTC PAMM group and EORTC NDDG.* "Genotyping of drug-metabolising enzymes and drug-transporters involved in the pharmacokinetics of (new) anticancer agents to predict dose–response and dose–toxicity relationships"
- *EORTC Soft Tissue and Bone Sarcoma group.* "The generation of tissue arrays for tumour material of patients treated in EORTC-STBG trials. Translational archive with Glivec-based trials as starting point"
- *EORTC Breast Cancer Group.* "TGIF 2: Scientific proposal. Second microarray analysis from breast cancer samples (Validation set) of patients included in EORTC 10994/BIG 00-01 trial"
- *EORTC Melanoma Group.* "*In situ* characterisation of the dendritic cells and chemokine receptors CXCR4, CCR7 and CCR10 in melanoma progression"
- *EORTC Genito-Urinary Tract Group.* "Gene expression profiling in renal cell carcinoma"

The cigarette of the future

The ingredients of cigarettes vary 3–10-fold within and between brands, according to Dr Nigel Gray (European Institute of Oncology). Cigarettes are unnecessarily poisonous and need proper regulation, he said.

"CIGARETTES ARE UNNECESSARILY POISONOUS AND NEED PROPER REGULATION"

There are around 4800 compounds in cigarettes, of which 64 have been identified as carcinogens and at least 13 as major toxins. Dr Gray proposed that priority compounds should be identified and regulated. Upper limits should be set at the current median level, and this process repeated in future. Two priority compounds that should prompt immediate action are benzo(a)pyrene (a squamous carcinogen that correlates with tar) and nitrosamines (derived from soil and also linked with adenocarcinoma). He proposed that nitrosamines — produced during the curing of tobacco — could be easily removed.

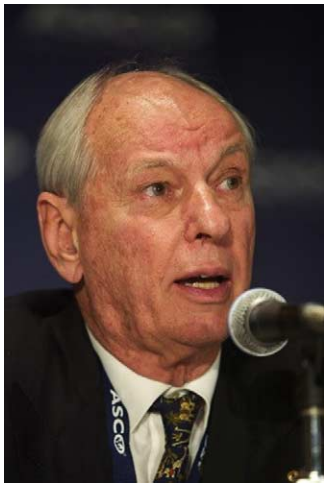


Photo courtesy © ASCO/Todd Buchanan 2003

Dr Nigel Gray

Additives should also be regulated, he said. Many (up to 600) are added to provide so-called flavour, so attempts to limit these would lead to fewer brands and provoke opposition from industry. However, the European Union is about to require proof of their safety when burnt.

Finally, he proposed regulation of nicotine, which is seriously addictive. The holes in the filters allow smokers to self-titrate, making it difficult to calculate the levels of nicotine they inhale. Dr Gray's "cigarette of the future" would deliver a nominated dose of nicotine in the cigarette rod and abolish filter ventilation and self-titration.

Substituting the cigarette with "clean nicotine" could be a long-term solution along with better nicotine replacement products, said Dr Gray: "We need over-the-counter, addictive, clean, recreational nicotine".

Emma Cannell
EJC Scientific Editor

'Full information required' in breast screening

Women need to be fully informed of the potential harms as well as benefits of breast cancer screening, UK researchers say (*BMJ* 2003; **327**: 101–3). They say the question of whether the benefits outweigh the harms "is essentially a value judgement", and conclude, "The information inviting women to screening must be improved."

The authors state that the percentage reduction in mortality "remains unknown and incalculable" while unnecessary treatments arising from overdiagnosis encompass segmental excisions, mastectomies and even radiotherapy. Ductal carcinoma *in situ* (DCIS), which has "an uncertain natural course" accounts for 20% of cancers detected by screening, they say.

"Most women who are screened have neither suffered nor been educated about the reality of the uncertainties, harms and limitations of screening or the consequences of finding pathology of borderline importance," they write.

Screening programmes should aim not to improve uptake, but rather to develop flexible decision aids "to meet women's desires for balanced information", they say. While admitting that some women do not want to take responsibility for their citizens, they say, "it is part of grown up decision-making."

In reply, Julietta Patnick, Director of the UK's National Health Service Cancer Screening Programmes, said that the information leaflet that accompanies an invitation to screening had been extensively researched. Focus groups drawn from a diverse range of women were involved. She said the women did not find information on DCIS helpful. It appeared in original drafts, and was removed. Further, she said, "women did not want too much numerical data, particularly about risk."

The leaflet is under constant review, but she concluded, "We are confident breast screening is saving lives, and so we very strongly encourage women to accept their invitation for a mammogram, but in the end it is not our choice, it's up to the individual woman."

Dr John Nottingham (Northampton General Hospital, UK) co-authored a paper on informed consent for cervical cytology screening in 1999 (*Cytopathology*, 1999; **10(4)**:221–228). He acknowledged the "great efforts" made since to improve women's understanding of the principles of screening, but said, "Unfortunately, there is clearly someway to go."

He said it is "disappointing" that the NHS screening leaflet omits to mention the potential consequences of being screened. "While these eventualities may only affect a minority. . ., they are surely worthy of mention in a pamphlet purporting to tell it how it is, especially since most of these women are healthy before undertaking the screening test", he said. "Surely it is time truly informed consent was given to participants in screening programmes so they know exactly what it is they are signing up to?"

Radiotherapy for DCIS

Radiotherapy can be recommended for patients with ductal carcinoma *in situ* (DCIS) treated by complete local excision, say researchers from the UK, Australia and New Zealand. However, there is "little evidence" for the use of tamoxifen (*Lancet* 2003; **362**: 95–102).

The study included 1701 patients recruited from screening programmes between 1990 and 1998. They all had complete surgical excision and then received adjuvant radiotherapy or tamoxifen, both or neither.

Tamoxifen reduced ipsilateral invasive disease, but not overall DCIS. Radiotherapy reduced both, but had no effect on contralateral disease. There was no evidence of an interaction between radiotherapy and tamoxifen.

The results confirm previous reports of the benefits of radiotherapy, but "unresolved issues remain", the researchers say. Radiotherapy may not be necessary for patients at low risk of recurrence. Further trials of tamoxifen or of the newer endocrine agents (with randomisation stratified by hormone receptor status) are needed to assess the role of these agents in prevention of ipsilateral recurrence and contralateral disease, they say.

Orphan drug status for APL. . .

The marine-derived compound, APL (Aplidin), has been granted orphan drug status by the European Commission for the treatment of acute lymphoblastic leukaemia (ALL). This follows assent by the Committee for Orphan Medicinal Products (COMP) of the European Medicines Evaluation Agency (EMEA) and allows producer Pharma-Mar 10 years' marketing exclusivity, subject to regulatory approval.

APL is in phase II clinical trials for solid tumours including renal, colorectal, head and neck, pancreatic and non-small cell lung cancers. It has shown "very promising preclinical results" in ALL, the company says, and orphan drug status will support efforts to develop it as an effective treatment for the condition.

APL induces apoptosis, combined with blocking cell division in the G1/G2 phase of the cell cycle. It inhibits the secretion of vascular endothelial growth factor (VEGF), and inhibits the protein palmytoil thiosterase.

. . .but no marketing authorisation for ET-743

However, the Committee for Proprietary Medicinal Products (CPMP) has refused to grant initial marketing authorisation for Ecteinascidin 743 (ET-743 or Yondelis) for the treatment of advanced soft tissue sarcoma (STS) in the European Union. The drug, also produced by Pharmamar, was granted orphan drug status by CPMP in May 2001.

ET-743 is a novel marine-derived agent, which is thought to bind to the minor groove of the DNA, inhibiting cell proliferation, and leading to p53-independent apoptosis of cancer cells.

The company's registration dossier included results from 183 adult patients with previously treated STS. In 63 of these patients, both doxorubicin and ifosfamide had failed. Treatment with ET-743 gave a long lasting response rate of 9.5% in these patients and 26% were alive for at least 2 years, compared with the median life expectancy of STS patients of less than one year.

FECS' New Board of Directors

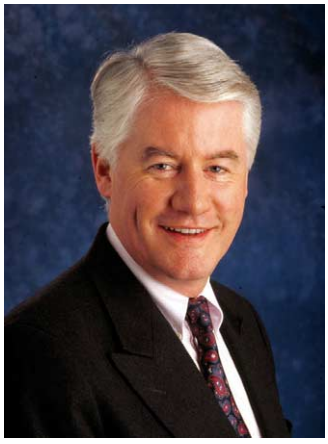
At its meeting in Brussels on 10th June 2003, the Council of the Federation of European Cancer Societies (FECS) elected its new Board of Directors for the period 2003–2005.

The new Board took office immediately after the ECCO-12 conference, on 25 September 2003, and will serve until the end of the ECCO 13 conference, on 3 November 2005.

Professor Harry Bartelink took over the Presidency of FECS. Professor Bartelink is chairman of the Radiotherapy Division at The Netherlands Cancer Institute in Amsterdam and Professor in Clinical Experimental Radiotherapy of the University of Amsterdam. He is responsible for patient care and scientific research with a particular interest in breast cancer and translational research. Professor Bartelink is the outgoing President of the European Society of Therapeutic Radiology and Oncology (ESTRO).

Professor John Smyth was voted into the office of President-elect. Professor Smyth is Professor of Medical Oncology and Director of the Cancer Research Centre at the University of Edinburgh. John Smyth was President of the European Society of Medical Oncology (ESMO) from 1992 to 1994. He is the current Editor-in-Chief of *EJC*.

Professor William J. Gullick, outgoing President and Chairman of the Board of Directors, will be Past-President. Professor Gullick is Professor of Cancer Biology at the University of Kent (UK) and is a member of the Cancer Research Group. William J. Gullick is President-Elect of European Association for Cancer Research (EACR).



Professor John Smyth

Professor Heinz Ludwig was elected Secretary General. Professor Ludwig is Professor of Internal Medicine and Head of the Department of Internal Medicine and Medical Oncology at the Wilhelminen Hospital in Vienna. Heinz Ludwig is President of the European Society of Medical Oncology (ESMO) until December 2003, when he will become Past-President.

Professor Michael Stevens was elected Treasurer. Professor Stevens is Professor of Paediatric Oncology and Head of the Division of Child Health (Department of Clinical Medicine) at the University of Bristol (UK). He is also Honorary Consultant Paediatric Oncologist at the Bristol Royal Hospital for Children. Michael Stevens is the outgoing President of the European Branch of the International Society of Paediatric Oncology (SIOP Europe).

The Board of Directors 2003–2005 also comprises a representative of the European Society of Surgical Oncology (ESSO) and a representative of the European Oncology Nursing Society (EONS): **Professor Luigi Cataliotti** is President-Elect of the European Society of Surgical Oncology (ESSO) and President of the European Society of Mastology (EUSOMA). He is Professor of General Surgery at the University of Florence.

Mr Jan Foubert is Lecturer in Nursing and Midwifery at the Erasmus Hogeschool, Brussels, and Education Manager at the Institut Jules Bordet, Brussels. He is the new President of the European Oncology Nursing Society.

Carine Lecoq
Administrative Coordinator,

Combination chemo 'beneficial' in bladder cancer

Patients with invasive bladder cancer had a "clear survival benefit" from neoadjuvant, platinum-based combination chemotherapy, according to the Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. The international group found that the treatment "showed a significant benefit to overall survival."

The ABC Collaboration conducted a systematic review and meta-analysis (*Lancet* 2003; **361**: 1927–1934). They included updated data for 2688 individual patients from 10 available randomised studies. Overall survival increased from 45% to 50% at five years. The improvement was seen regardless of the type of local treatment and did not vary between subgroups of patients. However, there was no evidence to support the use of single-agent platinum.

The authors say that neoadjuvant chemotherapy, given before local treatment may reduce primary tumour volume and could be effective in control of metastatic disease when the volume of micrometastases is likely to be small. Further, patients may be able to tolerate chemotherapy better before they have received potentially debilitating local treatment with surgery or radiotherapy. However, the randomised trials which have been undertaken over almost 20 years have "mostly been of modest size and shown inconclusive results."

The meta-analysis used individual patient data which allowed time-to-event analyses, important in diseases like bladder cancer where prolongation of survival, rather than cure, is anticipated for most patients.

The meta-analysis found improvements in disease-free survival, loco regional disease-free survival and metastases-free survival, which lent support to the primary finding of improved overall survival. However, few of the trials in the meta-analysis measured toxicity of quality of life in ways that allowed the data to be combined in a meta-analysis.

"Promising new drug regimens or treatment approaches should be compared in randomised trials against neoadjuvant platinum-based combination chemotherapy," the researchers say.

An accompanying editorial (*Lancet* 2003; **361**: 1922–1923) says their conclusion "should be considered valid" but points out that the relative benefit of potentially toxic chemotherapy is "extremely modest." The meta-analysis defines a new 'standard of care', but is only the beginning. Further work "will need to not only identify far more active regimens in this disease, but also more clearly identify patients who are most likely to benefit from available therapies," it states.

PODIUM

Parent power!

Antonya Cooper is Chairman of the Neuroblastoma Society which has its 20th Anniversary this year. She and her husband Alastair were founder members of the Society after the death of their son Hamish in 1981. She spoke regularly to groups of health professionals and at conferences, co-edited a book on how parents experience the medical world, and encouraged open discussion of the death of a child at a time when this was rare.

Antonya Cooper

What does the Neuroblastoma Society do?

The Society was set up by a group of parents whose children suffered from neuroblastoma. Neville and Janet Oldridge, whose son Matthew had died a little while before Hamish, started the ball rolling. We were keen to focus the sums of money which were flooding in from friends and relatives into something more useful than TVs for children's wards. We wanted to set up a fund which would support medical research into the treatment and cure for neuroblastoma. We're now a society with 300 members — many of whom are not involved in fundraising because they are deeply involved with the treatment of their child — even so; the latest accounts show that we made grants to researchers approaching £250,000 in 2002.

We also act as a support system for parents. Neuroblastoma is relatively rare and only 80 to 90 cases are diagnosed each year. One of our trustees is responsible for befriending families, and aims to put those who contact us in touch with a member who can provide some support.

We produce a booklet that should be handed to the parents of any newly diagnosed child by their paediatric oncologist. It answers questions about the condition and treatments, and has just been updated; this is the 3rd edition. But all too often the booklet is shoved in a cupboard and parents don't get to see it, because, even today, some medics find the deaths of children so distressing that they fail to engage with the parents. It is immensely frustrating.

Most medics are very caring, but the moment there is talk of the final weeks, days, or hours, some cannot cope and withdraw in order to protect themselves. Much more of a team approach is needed because families can be left desperately isolated. The situation has improved massively in the 22 years since Hamish died, but there is still a long way to go.

Are you involved in lobbying?

Only in a small fashion, and we tend to target scientists we know rather than politicians. We approached the MP Stephen Dorrell when he was Junior Minister for Health, though. We wanted a meagre £1000 for the Medical Research Council to look into the possibility of using a non-invasive urine test in nationwide screening for neuroblastoma in newborns. Even that was refused. The test, despite its variable results, could help parents who go for weeks before diagnosis. All too often we hear of parents who know their child is ill, but are not able to get their family doctor and primary healthcare team to recognise it.

Does the Society have a position on Tissue Banking?

Not officially, but we discussed it at our AGM. Many parents are desperate for parts of their children's bodies to be used in research so that something may come of their deaths. The current political climate in the UK has been coloured by the use of children's organs without parents' consent, but I think most parents feel the opposite and would like to contribute to research. Weeks before my son Hamish died, we offered his body for research, but it was not needed at the time. When parents' offers are accepted, they want to know what if anything happened to their child's body, but unfortunately, too often the line goes dead on them and they get no satisfactory response.

How do professionals respond to the Society?

We are taken very seriously by the 23 different centres in the UK that deal with neuroblastoma, and especially by those in the research field. It is so important for healthcare professionals to listen to and involve parents as part of the team. We had a good experience with our consultant, but many don't. I met a consultant at one of the big UK neuroblastoma centres who clearly was ill at ease discussing pain control in terminally-ill children, even though I'm not the parent of a current patient. Others disagree, but I believe you cannot allow a terminally-ill child to be in pain. Children being cared for at home in their last weeks need a central line with morphine to control pain. Dying children should not suffer.

What is the Society's goal?

Ultimately, not to exist at all when there are good treatments and a cure for neuroblastoma. There have been small steps forward in the past 20 years, but it's a very aggressive tumour, and difficult to diagnose because of its rarity and non-specific symptoms. It's going to be a long haul.