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27th ESMO Congress, Nice, 18–22 October 2002

Iressa disappoints in NSCLC

The novel agent ZD1839 (Iressa) showed no added benefit when combined with gemcitabine/cisplatin in a phase III clinical trial of patients with advanced non-small cell lung cancer (NSCLC), researchers reported at ESMO. In a trial described as "robust" and "well-designed", researchers said the efficacy results were "definitive".

The results were presented at the Presidential Symposium. The study, led by Professor Guiseppe Giaccone (Vrije Universiteit, Amsterdam, The Netherlands) included 1093 patients from sites across Europe and the USA. Patients had stage III/IV disease and performance status of 0–2, and were chemo-naive. In a 3-armed trial, they were randomised to receive either chemotherapy plus placebo, or chemotherapy plus ZD1839 at one of two dose levels. The primary endpoint was overall survival, with the study powered to detect a 33% increase, equivalent to an absolute increase of 2.3 months. Other endpoints included progression-free survival, time to worsening of symptoms, objective tumour response, quality of life and safety.

"FURTHER STUDY IS WARRANTED IN OTHER SETTINGS"

"ZD1839 showed no added benefit in survival or any of the endpoints when combined with gemcitabine/cisplatin", the study concluded. However, the study confirmed its safety and tolerability: the toxicity profile of ZD1839 combined with the chemotherapy was comparable to the chemotherapy alone, with the exception of dose-dependent diarrhoea and skin rash.

ZD1839 is an orally administered epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). One possible reason for the lack of added benefit is that the chemotherapy might directly or indirectly affect EGFR function or expression and thereby reduce or abrogate the effects of ZD1839. Another is that the chemotherapy and ZD1839 might both target the same cell population so that the chemotherapy response masks that of ZD1839.

Despite the disappointing results, the researchers concluded that, because of the good toxicity profile, and more encouraging data on monotherapy ZD1839 in refractory NSCLC, further study of the agent "is warranted in other settings".

"DIFFERENT PARADIGMS HAVE TO BE FOLLOWED"

At a press conference on the findings, Dr Larry Norton (Memorial Sloan-Kettering, New York, USA) was quoted: "With Genentech's anti-VEGF announcement recently, SWOG's evidence of interference by tamoxifen in the efficacy of breast cancer adjuvant therapy, and the Iressa results, I think we're seeing a pattern emerge that is really (paradoxically) quite hopeful."

"We've said that these new therapies are dramatically unlike chemotherapy but we've tried to develop them as if they were. Now we know they're not, and Iressa has to be used following different paradigms."

Manufacturer AstraZeneca said it "remains committed to understanding how these agents can best be used to provide patient benefit."

MCR is "key to improving standards"

ESMO's Minimal Clinical Recommendations (MCRs) are "important in achieving high common standards of medical practice for cancer patients" said Dr Rolf Stahel (Switzerland), Chairman of the ESMO Guidelines Task Force. The MCRs now cover 23 diseases and topics, and are intended to describe "a basic standard of care that ESMO would consider necessary in all countries of Europe."

Dr Stahel said that the MCRs, which answer clinical questions, are patient-centred and evidence-based, represent "the beginning of a process'. They are updated annually and are being translated by several national organisations.

At a session on the guidelines at the Congress, a voting system allowed delegates to participate. A poll established that 30% had consulted the guidelines in the previous year.

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Everything old is new again

The resurrection of old drugs may be possible through the individualisation of therapy. This was the theory proposed by Dr George Sledge (Indiana University School of Medicine, Indianapolis, USA) at the Congress. "Low response drugs in the general population may become high activity drugs in selected populations", he said.

Systemic chemotherapy is routinely used in the treatment of metastatic breast cancer (MBC). However, MBC is characterised by an accumulation of mutations and as the disease progresses it becomes more resistant to standard chemotherapies. New agents are constantly being sought.

New technologies (proteomics, gene-chip methods) have increased our molecular knowledge and enabled many new targeted drugs to be developed. "New drugs currently in development target factors that make a cancer cell vulnerable, such as its unlimited growth, immortal and invasive properties", he said. These agents include selective oestrogen receptor modulators, aromatase inhibitors, farnesyl transferase inhibitors, cyclin-dependent kinase inhibitors.

As therapy becomes increasingly individualised, patients whose cancers have known characteristics will be able to receive targeted therapy. The remaining unselected patients, may therefore become a more homogenous population and it is conceivable that they may benefit more from existing treatments. "If we can predict response to individual agents then low response drugs in a general population may become high activity drugs in a selected population," he said. Quoting Eden Phillpotts, he added, "The universe is full of magical things patiently waiting for our wits to grow sharper".

Emma Cannell
Nice

Telling the family

"Patients may need help in discussing their condition with family and friends", said Dr Alexander Marmé (University of Heidelberg, Germany). "When a patient is breaking bad news, emotional expression and body contact, the absence of professional distance and specialist knowledge are all important factors", he said.

He devised a protocol, called GOALS, and said, "It is about identifying the right place and the right moment to talk about these things when emotions are high."

The one-day workshop proposed for patients consists of advice and discussion on:

- Getting together for an important conversation, which should not be disturbed by daily life;
- Opening: both sides should indicate a need or desire to talk;
- Acknowledging each other's emotions;
- Learning about the disease;
- Strategy to develop open conversation.

Dr Marmé said that patients' quality of life is dependent not only on medical care but also on the psychological and social support provided by the people around them. Anxiety is a problem, enhanced by a lack of knowledge. "The patient is afraid of talking about their illness with relatives. They don't know how to deal with it. The lack of communication causes additional stress in personal relationships."

First European Patient Seminar

ESMO's first European Patient Seminar, held at the 27th Congress, is part of a drive to disseminate knowledge to cancer patients and the public, in order to improve the quality of diagnosis, treatment and follow-up care of patients with malignant diseases. "Empowering patients through education allows them to become real partners with their oncologists, and thus better control their situation by making informed decisions," the society said.

ESMO has drawn up a list of questions that a patient should ask during his/her first appointment with a physician following diagnosis. They include: "What are the pros and cons of the treatments you mentioned?" "When do you think I will be able to resume my usual activities?" and "Can your team advise me on nutrition?"

The seminar included specialists talking about new treatments, patients sharing their experiences and a discussion of strategies intended to make patients' lives more fulfilling.

Doctors "too embarrassed to discuss sex"

"Concerns over body image, altered moods, pain and hormonal changes brought on by cancer and its treatment can dramatically affect sexual well-being", Professor Lesley Fallowfield (University of Sussex, UK) told the Congress. Yet doctors, nurses and patients are often too embarrassed to discuss it. "Doctors should look out for the quiet unheard distress of patients," she said.

Arimidex approved in Europe

Anastrozole (Arimidex) has gained approval in Europe for use as adjuvant treatment in postmenopausal women with early breast cancer. The UK Medicines Control Agency approved the application, and under the Mutual Recognition Process, the drug is now also approved for this use in Austria, Germany, Italy, Portugal and Spain.

The decision was based on the first results from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial. Anastrozole is already approved in the US, New Zealand, Belgium and Luxembourg.

The drug has been approved for "adjuvant treatment of postmenopausal women with oestrogen-receptor positive early invasive breast cancer who are unable to take tamoxifen therapy because of high risk of thromboembolism or endometrial abnormalities."

EUROFILE

Dietary problems in highly developed countries

Recognising that both cancer and cardiovascular disease are diet-related and cause about one third of the disease burden in the EU, the European Commission has formally recognised diet as a health determinant. A session on Nutrition and Food Policy at the European Health Forum, Gastein, Austria (25–28 September 2002) aimed to raise awareness of nutrition among health professionals, and to make recommendations that might help reduce health inequalities between the richest and poorest in Europe.

The Gastein Forum is a fascinating event, bringing together public health experts, politicians and policymakers, the pharmaceutical industry, patient groups, and other health professionals in an informal atmosphere to thrash out solutions to the many public health problems that beset Europe as a whole.

"ONCOLOGISTS CONTRIBUTED LITTLE TO THE DEBATE"

Karen Lock of the London School of Hygiene and Tropical Medicine (UK) is currently researching the global burden of nutrition-based diseases for the World Health Organization (WHO). Lock and her colleagues split the risk factor "wrong nutrition" into sub-categories. By looking at, for example, low fruit and vegetable consumption, obesity or underweight, the researchers acquired valuable data. They were surprised by the low levels of fruit and vegetable consumption in many countries, and by the significant impact ("more than we had expected") underconsumption has on health.

The Commission's interest in nutrition is based on article 152 of the Amsterdam Treaty, which came into effect in May 1999. This obligates it to look at health issues across all other policies and Directorates General. Strangely, the Commission was not represented at the session, despite many requests from the organisers. This led to much debate outside the meeting about the uphill struggle that David Byrne, Commissioner for Health and Consumer Protection (DG Sanco), has with his colleagues in other DGs, particularly Agriculture, in his attempt to implement Article 152.

Unfortunately, EU-wide measures are often limited by national legislations, said Camilla Sandvik, who left DG Sanco a couple of weeks before the meeting. "This is why the work of the European Commission is basically about health demands and the avoidance of disease." She presented a catalogue of measures, fully or partly financed by the European Commission, like Eurodiet (2000), the French Initiative (2000) or the White Paper on Food Safety (2000). "The action plan on food policy is not yet published, but a documents exists to build the foundation for work in the nutrition sector", she said, Web sites on nutrition went online in 2002 and projects on obesity and breastfeeding started. Sandvik raised cross-policy problems such as experts' recommendation to eat more fish. "How can we tell people to eat more fish, if there are not enough fish available?" she asked. First the fishing sector has to be reformed, only then do other measures make sense.

Unsaid but implied by Sandvik was that the Common Agricultural Policy (CAP) has a lot to answer for in terms of bad nutrition in Europe. Liselotte Schäfer Elinder, Research Manager, Swedish Institute of Public Health, called for the reform of CAP, the most cost-intensive sector of the EU. 90% of the budget for agriculture is spent on subsidies. "This causes a high price level of food in the EU, much higher than on the world market", said Schäfer Elinder. Ample proof that price and availability of food play an important role in nutrition comes from Mediterranean countries. Because fruits are cheap and milk products expensive, all segments of the population eat relatively healthily. In the rest of Europe it is primarily better-educated people who eat sufficient fruit and vegetables.

Given that diet is implicated in at least 30% of cancers, what did oncologists contribute to this debate? Surprisingly, very little. Only one representative of an oncology organisation was listed as a participant, compared with at least 20 with an interest in cardiovascular disease. So the emphasis in the discussions was almost solely on the latter.

"PRICE AND AVAILABILITY OF FOOD ARE IMPORTANT"

A pity, says Kathy Redmond, News Editor of CancerFutures and a health policy consultant, who attends the meeting regularly. "I think Gastein is a "must" for any person either involved or interested in European health policy. European legislation is impacting more and more on the provision of cancer services nationally and it is vital that cancer professionals start contributing to policy discussions at an early stage, when policy can be shaped, as opposed to complaining when legislation is in place and unlikely to change."

"The European Health Forum offers a unique opportunity to engage in informal policy discussions. It is not everyday you get the opportunity of meeting the Health Commissioner and his officials in such an informal setting," she says.

Maybe next year oncology will be better represented? It is a shame to let a valuable chance to influence policy with such an impact on the health of EU citizens slip away.

Mary Rice
Gastein
The European Health Forum Gastein website can be visited at www.ehfg.org

The Flims Alumni Club—a portrait

The Flims Workshop on Methods in Clinical Cancer Research was developed and has been run by a FECS, AACR and ASCO collaboration since 1999. Its aim, each year, is to select an outstanding group of young trainees in any subspecialty involving care for cancer patients and give them intensive training in the principles of good clinical trial design.

The course consists of lectures, interactive seminars and, most importantly, the development of each participant's own protocol. The concept and feasibility of these protocols form the basis for participants' selection. Thus many good quality research protocols are generated, which participants' institutions have vouched to help conduct. A recent evaluation of the Flims course found that approximately 50% of the protocols developed by Flims fellows are submitted and approved by ethical committees, and that most participants remain involved in clinical research, with many continuing to design protocols.

We found the week in Flims one of the most stimulating of our entire oncology training. It provided mentoring and an opportunity to interact with international and multidisciplinary colleagues. It fuelled our interest in enhancing the quality of trials, and promoted networking with like-minded specialists in other oncology disciplines and from other countries.

As former participants, we founded the Flims Alumni Club (FAC) as a non-profit making organization in 2001 during ECCO 11 in Lisbon. Its main aims are:

- To foster the active involvement of young cancer specialists in clinical as well as translational research.
- To promote the teaching, study and dissemination of methods in cancer research, and thus help to increase the quality of clinical trials and translational research.
- To promote the concept of a multidisciplinary approach as the cornerstone of modern oncology.
- To foster the mobility of young cancer clinicians among different European countries, promoting a network for educational exchanges.
- To provide a forum to disseminate accurate information, address issues relevant to young cancer specialists, and develop a sense of community by fostering interactions among members.

Active members must have participated in the Flims course and remain actively involved in oncology research, while associate members are due to participate in the workshop in the next 2 years. Institutions and individuals can also become sustaining members.

At ESMO 2002 in Nice, FAC organised a well-received joint meeting with ESMO Young Medical Oncologists. It focused on multidisciplinary interaction and research education in modern oncology curricula, as well as management of premalignant breast lesions.

For the future, a FAC session at ECCO 2003 in Copenhagen is planned. A list of members' research interests is being drawn up to encourage networking; and a grant email alert service is being set up to assist FAC members looking for research funding. A FAC website will be developed in 2003. FAC wants to provide a platform for discussion to further promote knowledge in good clinical trial design, via website and future symposia. The Flims Alumni network will help young European researchers to plan research periods at institutions where translational research is conducted. FAC aims to complement current oncology organisations, and its members are strongly encouraged to join and support their national and respective specialty's organisations.

We have received official endorsement, logistic support and generous financial assistance from FECS, AACR and ASCO.

Razvan Popescu, Fatima Cardoso, Fabrice André, Vanesa Gregorc, Engin Huseyin, Miroslav Kreacic, Jean-Philippe Spano, Georges Vlastos and Jean-Charles Soria on behalf of the Flims Alumni Club.

Map of UK Cancer Research

Shortfalls in spending on cancer prevention, and research into patient care and survival have been identified by the UK's National Cancer Research Institute (NCRI). The NCRI has produced a breakdown of spending on cancer research in the UK, according to geography, scientific area and cancer type.

The NCRI is a partnership between the major cancer research funding organisations in the UK, including charities and Government sectors. Member organisations spend more than Euro 570 million per year on cancer research.

Basic biological research accounts for 41% of research spending, the NCRI says, with 22% going on research into treatment and 16% on research into aetiology. However, patient care and survival research receives only 6% of the money, and research into prevention, just 2%.

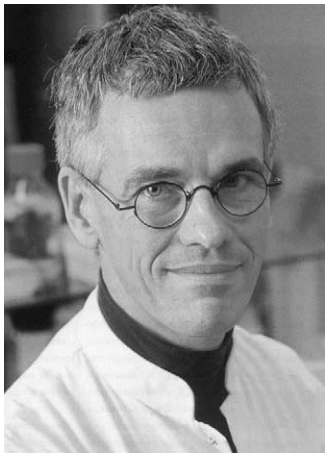
In general the relative proportion of funding spend on different disease types follows incidence and mortality figures. An exception is lung cancer, which receives 3% of the funding, but accounts for 15% of the incidence and 22% of the mortality.

As a result of the report, Strategic Planning Groups are to be established in palliative care, and prevention. Dr Mike Richards, the Government's National Cancer Director will head the former; Dr Trevor Hince, Cancer Research UK, the latter.

PODIUM

Ask the right question!

Jaap Verweij is Professor of Experimental Chemotherapy, Erasmus University Medical Center, Rotterdam, The Netherlands. He is Vice-President of EORTC, a former Chairman of its Early Clinical Studies Group, Soft Tissue and Bone Sarcoma Group and New Treatment Committee. He is co-ordinating a course on protocol writing and trial methodology at Flims, Switzerland June 21–27 2003.



Professor Jaap Verweij

What's the problem?
Clinical researchers find it extremely difficult to pinpoint their question and then design a protocol that will answer it.

What are the pitfalls in protocol design?
To take an example: People do not realise that a phase II trial is a screening study with limited potential. It never gives a definitive answer. So if you want to know what happens when two active drugs are given in combination, a phase II study will never give a meaningful answer, because it only screens for activity and you already know each of the agents is active in its own right. Of course, no one wants to start an expensive phase III study, which requires a lot of patients, without having the preliminary information. But if, in this example, you only want to know whether the combination is feasible, a single arm phase II trial is sufficient. The other question is: is one of the agents superior to the other? In this scenario, you have to run a randomised phase II study to get an early hint but even experienced investigators hardly ever do this.

Trials seem to be getting bigger all the time. Is this a design fault?
Not necessarily. The problem is that people are trying to answer too many questions in one trial, and this makes things very complex. It may still be feasible—you can do very complex trials even on one patient—but you must realise what the outcome of the trial means. Sometimes, especially in phase III trials and in most prevention trials, you can't avoid running large trials. But we can obtain a lot of information from phase I and II trials as long as we realise their limitations.

Does proper design reduce the size of trials?
In many circumstances we may be able to use fewer patients but some trials will need to be bigger. The point is that the outcome of properly designed trials is less ambiguous. Too many studies are inconclusive. We may not like the answer we get, but it's far worse not to find out anything at all.

Does every researcher need these skills?
Anyone considering an academic career in clinical cancer research, whether as a medical oncologist, surgeon or radiotherapist, needs to know how to perform a study that will give an unambiguous answer. You need to understand trial design even to read and interpret the literature. You can easily misread a conclusion if the trial is not appropriately designed.

Are there pockets of expertise across Europe?
No, the same mistakes are made everywhere. Good design requires expertise and experience. I was self-taught and it has taken 50 years! I hope the younger generation will benefit from our mistakes. In fact, younger researchers are easier to teach. Older researchers find it more difficult to accept that their trials may not be properly designed.

What do you expect researchers to get out of the Flims course?
A good protocol! They are selected for Flims on the basis of the feasibility of their idea for a study. We can't change an unfeasible study into a good one, but we can take a less-than-appropriate design, and improve it. We hope they will go and perform the study. So we're really trying to attract those aiming for a career in academia and patient-oriented research.

Presumably it takes more than a good protocol to get a study up and running?
That's true and we try to make students on the course aware of financial and ethical issues, implications for nursing staff and so on. Studies need approval from regulatory and ethics bodies, and students need to be practical and realistic. If you design a phase III study that requires 600 patients, no institution will be able to run this alone. You may have to join forces with other groups.

How attractive is a career in clinical research?
Clinical researchers earn less than clinicians so salaries are a concern, but fortunately science still has a wide appeal. It can be tremendously frustrating. Studies fall flat all the time. That's science and you have to be able to cope with it. But if you at least have a proper design, you have a better chance of getting the result you want.

Applications for Flims 2003 should be made by 15 February 2003, to Workshop on Methods in Clinical Cancer Research, FECS, Avenue E. Mounier 83, 1200 Brussels. www.fecs.be/education/films2003. The course was originally made possible by a generous grant from the US Department of Health and Human Services, National Cancer Institute.