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Early Approval for Sutent

Sunitinib malate (Sutent) has received early European approval, based only on phase II data. The European Commission granted conditional marketing authorization for advanced and/or metastatic renal cell carcinoma (mRCC), after failure of interferon alpha and interleukin-2 therapies.

The approval is conditional until the Committee for Human Medicinal Products (CHMP) reviews phase III data, which was due to be submitted in August, 2006. The phase II data showed an objective response rate.

The drug was also given conditional approval for unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance. This was based on phase III data, which showed a significant increase in time to tumour progression.

Dr Sylvie Négrier (Centre Léon Bérard, Lyons, France), said, "For many years, the options available for people with metastatic kidney cancer have been very limited. To have approximately 35 percent of patients in the pivotal study respond to this treatment is truly remarkable."

The most common treatment-related side effects (experienced by at least 20% of patients) included fatigue, gastrointestinal disorders such as diarrhoea and nausea, skin discolouration; loss of taste and anorexia. Serious side effects included pulmonary embolism (1.1%), thrombocytopenia (1.1%), tumour haemorrhage (0.9%), febrile neutropenia (0.4%), and hypertension (0.4%). The manufacturer, Pfizer, says that patients should be screened and treated for hypertension; temporary suspension of sunitinib is recommended in patients with sever hypertension not controlled with medical management.

Sunitinib has Orphan Drug designation in the EU for mRCC and GIST, rare cancers which affect less than 0.5% of the European population. It was approved by the US' Food and Drug Administration for the treatment of these diseases in January 2006 – the first time the FDA had approved a new cancer medicine for 2 indications simultaneously.

New Guidelines on Infections in Leukaemia

New guidelines for preventing and treating infections in patients with leukaemia were presented at the 14th International Symposium on Infections in the Immunocompromised Host (Crans-Montana, Switzerland, July 2–5, 2006).

The European Guidelines on Antimicrobial Therapy in Patients with Acute Leukaemia are the result of consensus reached by an expert panel of 58 infectious diseases specialists, microbiologists, clinical researchers and haematologists from Europe, Israel and Australia.

Four organisations collaborated on the new guidelines: the European Organisation for Research and Treatment in Cancer (EORTC); The European Group for Blood and Marrow Transplantation (EBMT); The Supportive Care Group of the European Leukemia Net (ELN) and the Immunocompromised Host Society (ICHS).

The long road to consensus started at the 1st European Conference on Infections in Leukemia (ECIL; Juan-les-Pins, France, 30 Sept–1 Oct 2005). Six working groups were set up to review data from the literature to answer specific 'closed' questions on the prevention and treatment of bacterial and invasive fungal infections mortality in neutropenic patients. Most data came from large prospective trials and meta-analyses.

Special attention was paid to developing evidence-based recommendations, identifying risk populations, infection-related mortality and risk-benefit ratio. Each proposal is scored according to the Centers for Disease Control and Prevention (CDC) grading for the level of evidence (I, II, III) and level of recommendation (A = strongly recommended; through to E = never recommended).

The guidelines cover 6 areas:

- Fluoroquinolone prophylaxis in neutropenic patients
- Aminoglycosides for antibacterial prophylaxis
- Glycopeptides for antibacterial prophylaxis
- Empirical antifungal therapy
- Antifungal prophylaxis, including stem cell transplant recipients
- The management of invasive candidiasis and aspergillosis

Professor Catherine Cordonnier (Hôpital Henri Mondor, Creteil, France), the driving force behind the development of the new guidelines, said, "We thought it was time to formulate up-to-date guidelines that will help clinicians choose the best treatment for their leukaemic patients and thereby reduce morbidity and mortality."

The ECIL guidelines are due to be published in full by the end of 2006.

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NICE gives green light to Herceptin...

Herceptin is to be funded by the National Health Service (NHS) in England and Wales following a final appraisal by the National Institute for Health and Clinical Excellence (NICE). The decision follows an unsuccessful appeal by a local primary care trust (PCT) on the grounds of patient selection, the length of treatment and cost-effectiveness.

The drug is therefore recommended for women with early stage HER2-positive breast cancer, except where there are concerns about the woman's cardiac function. It is to be given at 3-week intervals for a year or until disease recurrence (whichever is the shorter period) following surgery, chemotherapy and radiotherapy if applicable.

Cardiac function should be assessed prior to the commencement of therapy and treatment should not be offered where left ventricular ejection fraction is 55% or less; or where there are other specific concerns such as poorly controlled hypertension.

The appeal, by Newbury and Community PCT – which is responsible for funding the treatment in its area – was submitted on the grounds that the guidance "is perverse in light of the evidence submitted". It alleged that NICE had failed to specify which groups of patients should receive trastuzumab; had not provided guidance on how long after primary treatment the drug is recommended; that the one-year duration of treatment is open to question; that use in a research setting should have been included as part of the guidance; and that there is no evidence that the Appraisal Committee had considered the impact of providing trastuzumab on other patient groups whose care might be displaced.

The Appeal Committee dismissed all points. PCTs and NHS Trusts, which manage the implementation of NICE-approved therapies, have 3 months in which to fully implement use of the treatment.

Dr Alison Jones (Royal Free Hospital, London, UK), said, "It is now vital that all women are routinely tested for their HER2 status upon diagnosis, along with all other appropriate tests, to ensure that these new guidelines are followed and Herceptin treatment is made available to all patients likely to benefit."

.....but not Avastin or Erbitux

Neither bevacizumab (Avastin, Roche Products) nor cetuximab (Erbitux, Merck Pharmaceuticals) was recommended for the treatment of metastatic colorectal cancer in new guidelines from NICE. The decision – which for bevacizumab hung on its price – echoed that of the Scottish Medicines Consortium several weeks earlier.

The angiogenesis inhibitor bevacizumab is a recombinant humanised monoclonal IgG1 antibody that targets the human vascular endothelial growth factor. It is licensed in the UK in combination with intravenous 5-fluorouracil plus folinic acid with or without irinotecan for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

The NICE Committee noted that all bevacizumab studies demonstrated statistically significant gains in progression-free survival and some also found statistically significant gains in overall survival and tumour response rate. It was "persuaded" that the results could be considered generalisable to NHS practice in England and Wales.

However, estimates of cost-effectiveness were less convincing. Models by the manufacturer and by an assessment group were considered by the Committee but "neither source resulted in a cost-effectiveness estimate that was compatible with the best use of NHS resources".

In June, 2006, the Scottish Medicines Consortium similarly found that the drug improved overall and disease-free survival compared to standard regimes. "However, the economic case has not been demonstrated", it said.

Cetuximab is a recombinant monoclonal antibody that blocks the human epidermal growth factor receptor (EGFR). It is licensed in combination with irinotecan for the treatment of patients with EGFR-expressing metastatic colorectal cancer after failure of cytotoxic therapy that included irinotecan.

For cetuximab, the Committee agreed that there was some evidence of effectiveness but said the relative effectiveness compared with current standard care remains uncertain. It concluded that cetuximab, whether as a second- or subsequent-line treatment for metastatic colorectal cancer "would not be a cost-effective use of NHS resources."

Life-long monitoring after anthracyclines

All patients treated with anthracyclines should have life-long cardiac monitoring, say researchers from the Netherlands. While it is well-known that chemotherapy may damage the heart, a new study found that the damage may get progressively worse over the years.

The original study included 31 long-term survivors of osteogenic sarcomas or malignant fibrous histiocytomas. They were treated between 1977 and 1999 with moderate or high doses of doxorubicin. Most were children and adolescents but the age range was 10 to 38 years.

All had cardiac assessment 9 years after treatment; 29 were re-assessed 14 years after treatment; and 22 patients were included in the most recent assessment after a median time of 22 years (15 to 27.5 years).

This time, 45% had diastolic dysfunction compared with 18% in 1997; and 27% had systolic dysfunction compared with 9% in 1997. The 6 patients with impaired systolic function also had abnormalities in the motion of the heart wall with suggestions of ischaemic heart disease in 2 of them (*Annals of Oncology doi:10.1093/annonc/mdl156*).

Lead author Dr Inge Brouwer (University of Groningen, the Netherlands) said, "The natural course of subclinical abnormalities was largely unknown and it was unclear whether we could expect progressive cardiac deterioration.

"Our results suggest that after treatment with anthracyclines there is an ongoing deterioration of cardiac function and it is possible that this deterioration will continue, although we don't know if and when there will be further progression. For this reason regular echocardiography seems important to monitor heart function."

EUROFILE

EU Re-Opens Debate on Animal Experimentation

The long-awaited proposals for the revision of Directive 86/609, which governs animal experimentation in the EU, look likely to be published in the next six months. DG Environment, the European Commission directorate-general which has responsibility for laboratory animals has launched a public consultation. An expert report and preliminary impact assessment have already been produced.

The Commission has adopted a careful approach to the consultation. Perhaps its experience with the consultation on the chemicals policy, REACH, where thousands of identical responses were received from animal rights groups, has led it to offer two quite different versions. One is for the public and the other for experts in "animal welfare, animal testing, animal science, natural sciences (especially biology, medicine, pharmacology and toxicology), legal and economic affairs related to these areas."

Dr. Mark Matfield is scientific advisor to the Association for International Cancer Research (AICR), and director of the European Biomedical Research Association (EBRA) which seeks to explain to the public the reasons for using animals in scientific research and supports academic scientists who do so. He said that it was very important for academic researchers to respond to the consultation. "The expert version of the consultation is designed to solicit comments on the preliminary findings of the impact assessment that is being conducted on the proposals for the revision. This means that the questionnaire gives a detailed explanation of the new provisions that are being considered for inclusion in the new Directive. This is the first time the proposals have been set out in such detail", he said.

Reading between the lines of the consultation document, it appears that the overall effect of the proposals will be to create a new Directive similar to the United Kingdom's national legislation, considered by many to be the most rigorous of any EU Member State. This looks likely to result in a significant increase in administrative burden both for researchers and the national authorities in those member states with more relaxed legislation.

DG Environment has already commissioned an expert report from the Animal Health and Welfare Panel of the European Food Safety Authority (EFSA) which is expected to inform proposals for the Directive's revision. But researchers have expressed their disquiet about the scientific basis for some of the findings. In a letter to the official responsible for laboratory animals in DG Environment, the Royal Society (the UK national academy of science), noted that the report cited 'internet searches' and 'circumstantial anecdotes' as the basis for some of its recommendations.

''ACADEMIC RESEARCHERS MUST RESPOND TO THE CONSULTATION''

Professor Ole Petersen, Vice President of the Royal Society, who sits on the Society's Animals in Research Committee, said: "In highlighting our concerns to the European Commission we are acting on our responsibility as the national academy of science to ensure that the process of setting scientific opinion, policy and legislation is transparent and based upon strong scientific evidence."

The EFSA committee was asked to examine a number of questions, including experiments carried out on foetal and embryonic forms of animals. "The report does not provide a clear answer; no recommendations based on scientific data are proposed. The summary says that 'the weight of evidence suggests that consciousness does not occur in the foetus until it is delivered and starts to breath air', which suggests that there is no clear reason to include embryonic and foetal forms as protected forms, but this is not stated explicitly", says the letter from Professor Eric Keverne, chairman of the Society's Animals in Research Committee. "Furthermore, we are concerned about the forms of evidence cited and the lack of referencing of the evidence cited in the report. For example, there are several unscientific and unreferenced statements that potentially have important implications for the revision of the Directive."

A requirement for ethical review as well as authorisation of projects may also cause cancer researchers some misgivings. This is commendable in itself, but likely to lead to duplication and delays if the requirements are not dovetailed in some way. Furthermore, a ban on euthanasia using carbon dioxide (CO_2) is being considered, as are the inclusion of some invertebrate species, and the provision of information from ethical review and project authorisation to the public.

It is of overriding importance that proposals are based on sound scientific principles, said Professor Sir Walter Bodmer, former director general of the UK's largest cancer charity, and now Head of the CRUK Cancer and Immunogenetics laboratory at the Weatherall Institute of Molecular Medicine, University of Oxford, UK "This applies, for example, to the issue of CO_2 euthanasia and the inappropriate grouping of invertebrate species for regulation. It is also important to avoid unnecessary prescriptive duplication of administrative effort, as in the apparent suggestion of separate systems for ethical review and project authorisation.

''PROPOSALS MUST BE BASED ON SOUND SCIENTIFIC PRINCIPLES''

"A key recommendation that needs changing is the proposal that all non-confidential information from ethical review and project authorisation be made public. This is entirely inappropriate and unnecessary. Any real need for such completeness of information is covered by freedom of information acts. The UK approach of publishing anonymous non-technical summaries of all project authorisations, written by the applicants and checked as part of the authorisation procedure, should be followed," he said.

Mary Rice
Brussels

CE Mark for IGRT Platform

A 3D ultrasound image-guided radiation therapy (IGRT) platform – called Restitu – has received CE Mark approval. The equipment will become available throughout Europe.

According to Canadian manufacturer, Resonant Medical Inc, Restitu will enable fundamental improvements in radiotherapy planning and delivery. The system allows radiation oncologists to accurately visualise cancerous lesions and organs at risk at time of treatment planning, and then correct for daily changes in position, shape and volume over the course of a patient's treatment, the company says.

The CE Mark implies that a product complies with essential requirements of relevant European health, safety and environmental protection legislation.

Savene approved in Europe

The detoxifying agent, Savene, has been granted marketing approval by the European Commission (EC). The drug protects against accidental exposure to anthracyclines during chemotherapy.

Savene is a catalytic inhibitor of the topoisomerase II enzyme. It is given when intravenous chemotherapeutics accidentally leak into the surrounding tissue. This extravasation is thought to occur in 0.1% to 1.0% of all treatments, can cause painful scarring and may lead to postponement of further chemotherapy. Current treatment often involves surgical removal of damaged tissue followed by plastic surgery and rehabilitation.

The drug is known as Totect in the US, where the Food and Drug Administration (FDA) has found it approvable. This means that Danish manufacturer, TopoTarget, has been asked to clarify specific manufacturing issues ahead of the expected final approval.

The company is expecting to launch Savene in Europe by the end of 2006. As TopoTarget's first product, it will have been brought to market in 7 years. It has Orphan Drug status both in Europe and the US; and therefore now has marketing exclusivity for 10 years in Europe and, following final approval by the FDA, for 7 years in the US.

Data Protection: "Problems Are Surmountable"

Problems associated with the secondary use of medical data could be overcome, according to a senior doctor. Emeritus Professor, Robert Souhami (University College London, UK), says that overly strict interpretation of the law, rather than the law itself, is causing unnecessary delays and restrictions.

In the UK, the law permits secondary use of data without consent or full anonymisation "provided that the likely benefit to the public is demonstrably proportionate to the risk of identification and the consequent distress caused," he says (*BMJ* 2006; 333:315–6).

However, the situation on the ground is piecemeal and researchers encounter various interpretations of the rules and highly restrictive demands from different regulatory bodies. Such difficulties are damaging population-based research – "an own goal at a time when a national system of health records would give us unequalled opportunities for research to improve health".

Professor Souhami calls for a new, simplified and consistent process in which the reasons for decisions are clearly argued and stated. "Researchers, regulators, and funders need a single framework of guidance concerning requirements for consent, anonymisation of data, and access to data for different research types, populations and diseases. There must be assured standards of data security and confidentiality in handling data."

"NATIONAL HEALTH RECORDS GIVE UNEQUALLED OPPORTUNITIES FOR RESEARCH"

The public should be informed participants in this form of research, and the national health service (NHS) should make its research mission explicit when people use the service.

"These changes are all achievable," Professor Souhami writes. "The public, researchers, funders, and regulators should all take part in developing effective mechanisms of research governance using personal data. They all have, after all, a shared aim in supporting research for public benefit."

ATM mutation "doubles breast cancer risk"

Women with a damaged version of the ATM gene have double the risk of developing breast cancer, according to UK researchers. They found that the faults in the gene which cause the rare childhood disease, ataxia-telangiectasia, also confer breast cancer susceptibility.

Ataxia-telangiectasia develops in those who have inherited 2 faulty copies of the gene. It is the carriers of the disease, who have one faulty copy and are otherwise healthy, who have the higher breast cancer risk.

The study (*Nature Genetics 2006 38: 873–5*) included 433 breast cancer patients with a family history of the disease but with no faults in breast cancer genes BRCA1 or BRCA2. They found 12 ATM gene mutations in the patient group, compared with 2 among controls. Detailed statistical analysis estimated that the faulty ATM gene was associated with a relative risk of breast cancer of 2.37.

Links between breast cancer and the ATM gene have been reported for 20 years but so far there has been no agreement about which mutations increase the risk, and by how much. Author Professor Nazneen Rahman (Institute of Cancer Research, Sutton, UK) said, "Our study provides strong evidence for the first time that damaged ATM genes definitely have a moderate effect on breast cancer risk in a small number of women. Women who carry these genetic faults could benefit from targeted screening and new treatments in the future, but we need to learn much more about ATM before this information will feed into clinical practice."

ATM, like BRCA1 and BRCA2, is a DNA repair gene. Between half to one percent of the UK population carry the single mutation. Less than one percent of the 41,000 breast cancer cases are estimated to be carriers.

PODIUM

A Salute to Patient Participation!

Dr. Paola Mosconi

Dr. Paola Mosconi is Head of Medical Research and Consumer Involvement at the Oncology Department, Mario Negri Institute, Milan, Italy. She researches patient involvement in aspects of care and outcome, and is a co-founder, in Italy, of the European Breast Cancer Coalition, Europa Donna. Her current project, PartecipaSalute, involves lay people, patients' associations and scientific-medical representatives in the health debate.

How involved are Italian patients in the healthcare debate?
We have no official forum in our national health service for a debate involving doctors and patients. Various projects are on-going but the lack of official dialogue makes Italy different from other parts of Europe and the States.

We have many patient and citizen associations, but most aim to remedy problems in our national health service rather than becoming involved more generally in the health debate.

What are the barriers to patient involvement?
It's a mixture. The research community and physicians have traditionally taken a paternalistic approach and some think it a waste of time to involve lay people who may not understand the technicalities of clinical research, how EMEA makes its decisions, and so on. Even where lay people are involved, such as on ethical committees, they tend to be limited to issues of informed consent, rather than being involved more widely in debating the research priorities of the national health system.

At the same time, members of patient groups often defer to physicians and have limited awareness of their potential as active partners in the debate.

What is PartecipaSalute?
It's a project run jointly by the Mario Negri Institute, the Italian Cochrane Group and the scientific journalism agency, Zadig; and is funded by the bank foundation, Compagnia di San Paolo. It started 2 years ago and aims to involve lay people, patients' associations and scientific-medical representatives in the health debate.

How will it achieve this aim?
The first step is to collate information on experiences of collaboration. There is more activity than we thought: of 74 scientific associations responding to our survey, half had some kind of collaboration with patient groups. But there was no information about this on their websites.

We want to empower patients and lay members of ethics committee through an educational website and a training course. We'll also be organising joint initiatives between patients and the medical community.

How successful has the training component been?
Our website (*www.partecipasalute.it*) carries good quality information, presented in an active way. It doesn't give passive accounts of clinical trials, epidemiology, and so on, but helps readers understand the news, judge it and decide for themselves how "real" an advance is. This is completely new in Italy.

On the training course, we've found statistics the most difficult area to teach. We are not trying to create mini doctors or statisticians but we think it important for those on ethics committees to have a better understanding of results and of the literature. It will help them participate more actively in discussions.

What problems have you faced?
The Cochrane Group now translates the summary of the Cochrane review for lay people. This is helpful information and promotes evidence-based medicine. However, many Cochrane reviews conclude that there is not enough evidence to answer the posed question. This is a difficult message to get across and a real problem for us. Patients interpret it as saying: nothing is true, nothing is complete. At the training course, some people stopped participating after 2 days because they felt it was impossible to know anything, that nothing is evidence-based. Now we select carefully which reviews we publish because we do not want people to think there is no good information.

Is there any danger that projects like PartecipaSalute will alienate the medical profession?
We have to take the medical profession with us. We work closely with a group of GPs, who are interested in the programme and our website. They find it a useful tool to suggest to patients – younger people especially, who have access to the internet – to support the decision they are making with the patient.

There will be objections from some in the medical community – especially about the involvement of patient groups in deciding research priorities and questions – but the project is new and we haven't come across this yet.

What initiatives are in the pipeline?
We want to continue collecting information from patient associations about their experiences and, more generally, to help them work with medical societies to write future protocols for study. We want to facilitate this collaboration, and will carry out a joint initiative to help patient associations and medical societies work more closely. We believe it is possible for patient groups to be brought in at the beginning, to have a say in what kind of research is carried out; what the research questions are. This is the way ahead.