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Wider Brief for Sunitinib

Sunitinib malate (Sutent) has received full marketing authorisation in Europe for the first-line treatment of advanced and/or metastatic renal cell carcinoma (RCC). This broadens the indications conditionally authorised by the European Commission in July 2006. Manufacturer Pfizer said the drug is the first multiple receptor tyrosine kinase inhibitor to be approved in the EU for first-line use in metastatic RCC.

The original marketing approval was subject to the condition that Pfizer would provide further data on the drug's impact on clinical endpoints such as progression-free survival (PFS).

Phase III data from a randomised, international, multi-centre trial was submitted. It included 750 patients with previously untreated, metastatic clear-cell RCC. They received sunitinib malate or interferon-alfa, the current standard of care (*N Engl J Med* 2007;**356**:115–24).

The median progression-free survival was significantly longer in the sunitinib group (11 months) than in the interferon alfa group (5 months). Researchers said the improvement was

''THE BENEFIT EXTENDED ACROSS ALL SUBGROUPS''

greater than expected when the number of patients needed was calculated, so that the trial's primary end point was met in the interim analysis.

Sunitinib was also associated with a higher objective response rate than was interferon alfa (31% versus 6%).

On adverse effects: grade 3 or 4 treatment-related fatigue was significantly higher in the interferon-alfa group, whereas diarrhoea was more frequent in the sunitinib group. Those receiving sunitinib reported a significantly better quality of life.

The researchers state that the patients in the study were "relatively unselected" and say that those with coexisting conditions such as hypertension and diabetes were allowed to enter as long as such conditions were controlled medically. When outcome was analysed according to known prognostic factors and risk groups, "the benefit of sunitinib extended across all clinical prognostic subgroups studied, although the number of patients in the poor-risk group was small."

Clear-cell RCC over expresses many cellular receptors related to angiogenesis and the maintenance of the tumour's microvascular environment.

''NO OVERALL SURVIVAL BENEFIT HAS BEEN REPORTED''

Sunitinib and other agents such as sorafenib and bevacizumab target angiogenic growth factors and clinical trials "indicate that inhibition of angiogenesis is a promising strategy for the treatment of clear-cell RCC," the researchers conclude.

Sorafenib Results

In the same issue, the TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial) study group reported a phase II randomised, double-blind, placebo-controlled trial of sorafenib, another multikinase inhibitor of tumour-cell proliferation and angiogenesis.

The TARGET study included 903 patients and also found a significant increase in progression-free survival with sorafenib (5.5 months, versus 2.8 months in the placebo group). Common adverse events included dermatologic symptoms and diarrhoea, and serious adverse events, including cardiovascular adverse events were more common. However, the overall rate was considered acceptable "in the context of an apparent clinical benefit in patients with a fatal disease" (*N Engl J Med* 2007;**356**:125–34).

An accompanying editorial (*N Engl J Med* 2007;**356**:185–7) points out that no overall survival benefit has been reported with either sunitinib or sorafenib: "For this reason, further follow-up or additional trials are needed to establish the role of sunitinib and sorafenib in the treatment of this disease."

Clinical trials of these drugs and of temsirolimus in patients with advanced RCC "show how promising treatments can emerge from an understanding of the molecular genetics and biology of tumours," the editorial states. While these drugs down-regulate angiogenesis, they also affect other processes and can inhibit cell proliferation in vitro, where angiogenesis is not required. "Hence these agents probably act through more than one mechanism."

"Elucidating how these drugs inhibit tumour growth is paramount for the development of the next generation of drugs and for their rational combination," it concludes.

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Gonorrhoea and Bladder Cancer

Men with a history of gonorrhoea have double the normal risk of bladder cancer, say US researchers. Their report is the first prospective study to confirm the link.

The research came out of the Health Professionals Follow-Up Study which has monitored the health of 51,529 men in the USA since 1986 through detailed questionnaires and medical records. The researchers identified 286 cases of bladder cancer for which complete information on gonorrhoea history was available.

Lead author Dr. Dominique Michaud (Harvard School of Public Health, USA) said: "Gonorrhoea is an infection that often recurs, causing local inflammation and symptoms such as incomplete emptying of the bladder. The inflammation itself or the associated symptoms could be contributing to the development of bladder cancer. The severity and frequency of these symptoms may dictate the extent of the increased risk."

A history of gonorrhoea increased the risk of invasive bladder cancer to a greater degree than superficial cancer (*Brit J Cancer* 2007;**96**:1).

Call for Better Use of Prostate Cancer Biopsies

Routine collection of additional information from prostate cancer biopsies could allow better decisions about the best choice of treatment, say UK researchers.

A systematic review of the published evidence revealed a link between perineural invasion (PNI) and a poorer outlook for prostate cancer patients. To date, the clinical significance of PNI has been unclear and current guidelines for pathologists make no mention of PNI. Individual doctors therefore decide whether to check for it or not.

The review (*Cancer* 2007;**109**:13–24) found a significant association between PNI and the risk of disease recurrence. However, few studies have been conducted so far. The researchers recommend that PNI should be assessed in every case of prostate cancer to determine more precisely the level of associated risk and thus aid decisions about treatment.

Lead author Dr. Patricia Harnden (St. James University Hospital, Leeds, UK) said that if PNI is found in a prostate biopsy "it could mean the difference between choosing watchful waiting and immediately treating the cancer, or perhaps giving a longer course of therapy. Pathology is not being used to its full potential in prostate cancer if PNI is not looked for."

She called for the UK's Royal College of Pathology to make it mandatory for doctors to record PNI.

Professor John Toy, medical director of Cancer Research UK said the identification of a prognostic marker would be of great value. "PNI in a prostate biopsy may be such a marker. We must ensure that no opportunity to gather potentially important information about prostate cancer is wasted."

Professor Adrian Newland, president of the UK's Royal College of Pathologists said the College "endorses the view expressed in the paper that well-designed studies using pre-defined stringent protocols are now required to provide robust objective estimates of risk, following identification of PNI in prostatic core biopsies, as an aid in the planning of treatment for men diagnosed with prostate cancer."

Louis-Jeantet Prize for Medicine

Professor Stephen West (Cancer Research UK's London Research Institute) has been awarded the 2007 Louis-Jeantet Prize for Medicine. He was chosen for pioneering work into the DNA repair process, which has yielded insights into the development of cancer.

Professor West demonstrated for the first time why faults in the BRCA2 gene can lead to breast and ovarian cancer. He also identified a key protein in DNA repair, work that may provide future targets for destroying the ability of cancer cells to repair themselves.

He received the Euro 475,000 award along with Dr. Venki Ramakrishnan (UK Medical Research Council's Laboratory of Molecular Biology in Cambridge). Dr. Ramakrishnan and colleagues determined the atomic structure of a subunit of the ribosome, with implications for the design of new antibiotics.

Professor West studied biochemistry at Newcastle University, UK, and then worked at Yale University, USA. He set up a research group at the Clare Hall Laboratories in 1985, and has been there ever since. He has received numerous other awards throughout his career.

He said: "This award is testament to the hard work and dedication of the many students and researchers who have worked in my laboratory over the years. They have contributed to the development of new ideas and directions."

Professor Stephen West

The Louis-Jeantet Prize is awarded annually to between one and three scientists engaged in biomedical research across Europe. Each prize winner received Euro 400,000 to pursue their research and Euro 75,000 for personal use.

New Name for Novel Agent

AstraZeneca has announced that AZD2171, its oral vascular endothelial growth factor (VEGF) signalling inhibitor, is to be known as Recentin. The drug is currently in phase II/III development for advanced non-small cell lung cancer (NSCLC) and advanced colorectal cancer (CRC).

New Gene Signature in Breast Cancer

An "invasiveness" gene signature (IGS) is strongly associated with clinical outcome in women with breast cancer, say US researchers. They used the IGS to stratify patients with early breast cancer into groups with substantially different relapse rates. It also identified more than 90% of patients in whom metastatic breast cancer developed.

The signature was derived from the small subclass of cancer cells which are believed to be tumorigenic (the mass of the tumour is increasingly believed to be non-tumorigenic). The tumorigenic cells in breast cancer are, they say, characterised by CD44 expression but low levels of CD24. They identified 186 genes differentially expressed in the tumorigenic cells compared with normal breast epithelium.

The 186 gene signature was associated with risk of death and metastasis not only in breast cancer but also in lung cancer, prostate cancer and medulloblastoma. "This finding suggests that the IGS represents general biologic features shared by several different types of tumour", they write (*N Eng J Med* 2007;**356**:217–26).

An accompanying editorial ((*N Eng J Med* 2007;**356**:294–6) notes that there is now a "small flood" of prognostic signatures for breast cancer. Early attempts to combine signatures to provide a robust and accurate tool that would be useful in clinical practice have been disappointing. A recent comparison of 4 signatures found significant agreement in the outcome predicted for the same patients, but a combination of signatures was no better than each individually. "They may be regarded as different pictures of the same beast," the author wrote.

It remains to be seen whether limiting the use of unnecessary adjuvant therapy would provide sufficient incentive for the widespread use of prognostic signatures, the editorial concluded: "Further incentives may be on the horizon: as pharmacologic inhibitors for specific pathways become available, the signatures that define tumours according to their vital pathways may provide crucial guidance for designing drug combinations of choice."

Tamoxifen: "High Discontinuation Rates"

Discontinuation rates for women on tamoxifen may be higher than previously thought, say researchers in Ireland. They say that almost a quarter of women receiving tamoxifen stop treatment within a year.

"Persistence with tamoxifen cannot be assumed," they write (*Cancer 2007 doi:10.1002/cncr.22486*). Their study "raises concerns about persistence with other oral hormonal therapies for breast cancer and oral anti-neoplastics in general. This is of particular importance as longer durations of adjuvant therapy may be recommended for breast cancer in the future and as cancer survivorship becomes a priority area in clinical practice and research."

Thomas Barron (Trinity College Dublin, Ireland) and colleagues reviewed pharmaceutical data from a national database of 2816 women aged 35 years and older who started tamoxifen for breast cancer. At 12 months, 22 percent had ceased using the drug; at 24 months, it was 28 percent; at 3.5 years, 35 percent.

Women aged between 35 and 44 or over 75 were most likely to discontinue tamoxifen, as were those who reported using an antidepressant within a year of starting to use it.

Lung Cancer Vaccine in Phase III Trial

A therapeutic vaccine for non-small cell lung cancer (NSCLC) is to be tested in an international phase III trial. The trial, START (Stimulating Targeted Antigenic Responses in NSCLC) will be run by Merck KGaA and is due to include more than 1300 lung cancer patients in 30 countries.

The vaccine, Stimuvax, is designed to stimulate the immune system to recognise and react to a molecule called MUC1, which is more abundant on tumour cells than healthy cells.

Reassurance on Imatinib

Imatinib "does not induce cardiac left ventricular failure in GIST (gastrointestinal stromal tumour) patients", say researchers in a forthcoming *EJC* paper (doi:10.1016/j.ejca.2007.01.018). Analysis of the largest study ever performed in GIST did not confirm reports of cardiac toxicity.

Two recent papers have reported on possible cardiac toxicity and caused great concern among physicians, investigators and patients. One (*Nat Med* 2006;**12**:908–16) did not report the number of patients with chronic myeloid leukaemia (CML) exposed to the drug, but provided elegant experimental model evidence documenting the possible role of ABL in cardiac cells. The other (*Cancer Letters,* 2006;**243**:16–22) described 2 patients (one with GIST, one with CML) who developed cardiac failure, and suggested that brain natriuretic peptide may be an early marker of cardiac toxicity.

The current analysis, led by Professor Jaap Verweij (Erasmus Medical Center, Rotterdam, the Netherlands), included 946 patients with advanced or metastatic GIST. They were included in a large study run jointly by the EORTC, the Italian Sarcoma Group and the Australasian Gastrointestinal Trials Group.

In the original trial, patients were randomised to receive one of two doses of imatinib. A total of 24,574 exposure-months were analysed in the current report, and researchers found no excess of cardiac events.

During the study period (median follow up was 47 months), there were 10 cases of cardiac failure or cardiac events. Detailed examination of these cases led the researchers to conclude that for only 2 of the patients, the possibility of a cardiomyopathic effect could not be ruled out.

"The rate of cardiac deaths in this study is not higher than to be expected in an otherwise 'healthy' population of this age range", the researchers say. Regular cardiac assessment in patients with metastatic GIST treated with imatinib "does not seem indicated, but cardiac monitoring can be considered in imatinib adjuvant studies".

UICC My Child Matters Awards: 2006 Winners

The International Union Against Cancer (UICC) announced the 2006 recipients of its *My Child Matters* awards on Dec 15, 2006. 12 projects from Romania, Bolivia, Indonesia, Kenya, Mali, and Peru received up to €50,000 each, which will help to increase the dissemination of paediatric-cancer information to health-care professionals and the general public, and also improve early diagnosis and access to care.

"Cancer, and childhood cancer in particular, remains one of the great untackled health problems of low and middle-income nations", says Franco Cavalli, President of the UICC who led the *My Child Matters* advisory steering committee. "In rich nations nearly 80% of children with cancer are cured, but in poor countries nearly 80% may die. However, relatively little money can help bring about important advances in cancer awareness, care, and support in these countries. Fortunately, these nations have [many] dedicated people with the right ideas to bring about change. These are the people to whom our awards go."

One such person is Adela Ratiu (Institute of Oncology 'Prof Dr. Alex Trestioreanu', Bucharest, Romania) who hopes to use her funding to develop childhood cancer registries in Romania. "Our problems are the unknown burden of childhood cancer as well as the low survival rate. There is a methodology of data collection but it is not compliant with the International Agency for Research on Cancer rules and there are no cancer registries. We hope to improve the current situation with this award", she says. Ratiu's team will develop registries in Bucharest and Cluj-Napoca in order to study the timelines of childhood cancer diagnosis, the efficiency of the referral system, and the availability of best standard treatments.

Bolivia has other problems, explains Yolanda Ernst (Oncology Institute of Eastern Bolivia, Santa Cruz de la Sierra), another recipient of the 2006 UICC funding. "Children usually arrive at our institute with very advanced cancer. One of the reasons is that primary and secondary-care doctors have insufficient training in oncology for them to suspect cancer in children." To help remedy the situation, Ernst's team will run ongoing educational programmes in oncology for urban and rural physicians, training them to recognise cases of cancer in time for treatment to be more effective.

Nicholas Anthony Othieno Abinya (University of Nairobi, Kenya) wants to use his funding to reduce the mortality associated with Burkitt's lymphoma in Kenya, by educating communities in affected areas about how to detect the disease and seek treatment early. "Data from the Kenya Medical Research Institute, Nairobi, show that Burkitt's lymphoma is the most common single malignant entity found in childhood", he explains. "We intend to educate people in the high-risk populations to recognise symptoms early, and to institute appropriate health-seeking measures. [We also want] to see if a preventable factor is identifiable." The Kenya team hopes to trace patients from various hospitals. Their families will then be interviewed and environmental surveys done to pinpoint any such factors.

Across the Indian Ocean in Indonesia, Melissa Luwia (Vice President of the Social Services of the Indonesian Cancer Foundation, Jakarta) aims to increase community knowledge about leukaemia and retinoblastoma. Data from the Ciptomangunkusumo Hospital in Jakarta show a high mortality rate (50–60%) as a result of delays in diagnosis and treatment. "Parents are still not well informed about the importance of early detection and prompt treatment", explains Luwia. "We plan to inform parents via focus group discussions, community events such as popular music performances, and radio talk shows. We also hope to increase the knowledge of health-care providers by organising training, printing educational materials, and arranging meetings for medical professionals."

Other selected projects seek to offer everything from psychological and legal support for families of children with cancer, to purchase of computers and hiring teachers so that these children can learn more about their disease and communicate with others in the same situation.

"Some 80% of all children with cancer live in resource-constrained countries, and positive impacts on cancer awareness and cancer care could translate into thousands of children saved", remarked Isabel Mortara, Executive Director of the UICC (Geneva, Switzerland). "The results coming in from our 2005 award winners show that this is a reality. It is with enormous satisfaction that we present these awards and with enormous hope that they will continue to make a difference."

Adrian Burton

For details about the awards, contact Jose Julio Divino (divino@uicc.org)

http://www.mychildmatters.org/pages/my-child-matters/my-child-matters.htm

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Projects to receive funding

Indonesia

Integrated community-based leukaemia—Melissa Luwia

Early detection and prompt treatment of retinoblastoma—Rita Sitorus

Romania

Assessment of childhood cancer burden in Romania and ways of improvement—Adela Ratiu

Building a future for Romanian children—Rodica Cridland

Improvement of diagnostic services—Doina Mihaila

Kenya

Establishment of awareness of the occurrence of Burkitt's lymphoma—Nicholas Anthony Othieno Abinya

Peru

Update in paediatric oncology in Peru—Gustavo Sarria Bardales

Development of attention capacities and the improvement of support services of "Albergue para Enfermos de cancer Señor de la Divina Misericordia"—Nelly Isabel Therese Huamani

Bolivia

Project to fight childhood cancer and improve paediatric oncological early diagnosis—Yolanda Ernst

Free leukaemia diagnosis for children—Ricardo Amaru Lucana

Learning to grow under special conditions—Lucia Parejas

Mali

Oncopaedia—Boubakar Togo

PODIUM

Protocol and Treatment Deviations

Dr. Elena Muşat

Dr. Elena Muşat completed her medical training in Romania, where she specialised in radiation oncology. She undertook further training in radiotherapy and oncology in France, before moving to the EORTC Data Center, Brussels, in 2004. She is the lead author of a paper in this issue of EJC on quality assurance in a phase III breast cancer trial.

What is the breast cancer trial aiming to discover?

The trial objective is to assess the role of internal mammary node and supraclavicular irradiation in women with stage I–III breast cancer. This is a large, international, multi-centre trial including 4004 patients.

What level of deviation from protocol did you find?

Major deviations from protocol were found in 8% of the patients in the experimental arm, compared with 2% in the control arm. This 6% difference between the two arms is particularly important (in this trial) since there is evidence that suboptimal radiotherapy may negate the survival benefit.

What impact do deviations from protocol have on study results?

I would expect to see deviations in all large clinical trials (acceptable and unacceptable) but how they affect trial outcome cannot be predicted. This trial was designed to detect a difference of 4% in survival at 10 years: we were expecting to see survival improve from 75% to 79% with irradiation. That is a small benefit and any kind of deviation may affect the outcome for the patient and the trial.

The trial was originally designed for intermediate to high risk patients. When the statistics were reviewed, we found that the majority of patients were lower risk than was initially anticipated. The sample size was then increased to correct this difference. Also it is especially important to ensure and report on the quality of radiotherapy given to these patients.

What will the discrepancy between trial arms mean for the whole trial?

We don't know yet. It should be reassuring for participants to know that the vast majority received optimal treatment. Clearly it would be unethical to design a trial to find out how much delayed or non-optimal treatment would affect outcome, but we can use data from large trials to try to retrospectively answer such questions. I could only find two publications which showed that good treatment technique improved survival, compared to non-optimal radiotherapy. Another report was a retrospective epidemiological study among older patients in the UK and the answer was not definitive because of high levels of co-morbidity among patients. Even the EBCTCG (Early Breast Cancer Trialists' Collaborative Group) meta-analysis, which showed a survival benefit with radiotherapy in early breast cancer, did not have sufficient power to definitively identify an optimal radiotherapy treatment.

What sort of errors occur in treatment?

Random errors can occur in a similar manner in both arms, and will often balance each other out. Such errors are dealt with in the statistical testing, but can still have an impact on the results of the trial. Systematic errors may be additive and may make a difference to patient outcomes. In this trial we found a systematic error, a selection bias introduced by investigators. Participants were at lower risk than expected because investigators believed that high risk patients should have radiotherapy and preferred to treat them outside of the protocol. (This will affect the representativeness of the trial, and possibly the potential to generalise the results.) Sometimes patients switched arms, so that high-risk patients in the non-treatment arm received treatment. There were also anatomical or technical reasons which prevented radiotherapists giving the correct treatment to the supraclavicular nodes.

Is sufficient attention paid to quality assurance in the interpretation of studies?

It is important for the primary analysis to be performed on an intent-to-treat basis. But afterwards more refined analyses need to be performed to exclude ineligible patients or those with treatment deviations. Ideally each of these subsequent analyses should be planned prospectively and regarded as sensitivity analyses. If their results deviate from the primary analysis, further investigation of the reasons is needed. Prospective planning of such analyses is not yet current practice.

Why not?

If patients with treatment deviations are excluded, patient numbers in the treatment arm will be reduced, leading to an imbalance in type of deviation and type of patient in each arm. As it is impossible to remove the same type of patients from the control arm, bias is introduced which makes statisticians reluctant to perform these refined analysis.

What is gained from these refined analyses?

We suggest that refined analyses will verify the robustness of the primary analysis. We hope it will turn out this way, but it remains to be seen. Although the trial is closed, we are waiting for the final results over the next 5 years. As yet we have no information on the number of relapses.