EUROPEAN JOURNAL OF CANCER 44 (2008) 2333–2337

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End of the road for yet another melanoma vaccine

Time to pause and rethink

A large phase III trial into a melanoma vaccine has been halted early after an interim analysis found potential evidence of harm. The analysis revealed a significant trend in reduced overall survival among patients receiving the vaccine.

The finding sheds new light – and doubt – on other vaccines in trials and suggests that new approaches examining vaccine development in advanced metastatic disease are necessary, before further adjuvant vaccine trials in melanoma patients can take place.

Lead author, Professor Alexander Eggermont (Erasmus University Medical Center, Rotterdam, Netherlands), President of European CanCer Organisation (ECCO), told *EJC*: 'After a negative, potentially harmful outcome in the four largest and most recent adjuvant vaccine trials in melanoma (ECOG 1694 in stage IIB-III, Canvaxin in stage III, Canvaxin in resected stage IV and EORTC 18961 in stage II), we have a serious problem that we need to address. We can't simply continue with what we have been doing.'

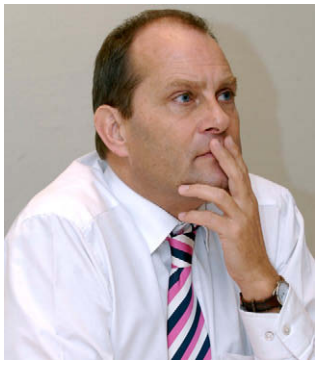

Photo by Alain Dereymaeker

Professor Alexander Eggermont

doi:10.1016/j.ejca.2008.09.021

The EORTC trial (18961) included 1314 patients with stage II, resected primary melanoma. They were randomised to receive vaccination treatment, or observation, and the aim was to detect a difference in disease-free survival at 5 years.

The vaccine used was intended to induce an antibody response to the GM2 ganglioside, which is overexpressed on 95% of melanomas and rarely found on normal cells. GM2 is a prognostic factor in melanoma; patients with anti-ganglioside antibodies do better than those without. In the conjugate vaccine used in the EORTC trial, the ganglioside-KLH is coupled with a carrier protein and the immunostimulant QS-21.

The rationale for the study came from a small trial in the early 1990s looking at the IgG and IgM titres produced by a BCG/GM2 vaccine combination (*Livingstone et al, JCO, 1992*). A subgroup analysis among 115 patients (all seronegative patients before vaccination) found that those treated with the combination were significantly more likely to be disease free at 4 years, than those given BCG alone ($p = 0.02$). The study helped build the hypothesis, and suggested that a definitive trial for the vaccine was worthwhile.

In the EORTC trial, about half the patients had confirmed sentinel node negative tumours; the rest had unknown node status. Those with sentinel node involvement and therefore early stage III tumours were excluded from the trial. The trial was well balanced for patient characteristics such as age, sex, and Breslow thickness.

The second interim analysis, at 232 events, found that the vaccine had almost no toxicity, with only 2% patients in the vaccine group suffering more severe fatigue than those being observed. But there was evidence of active harm and the trial was stopped.

'WE HAVE A SERIOUS PROBLEM THAT WE NEED TO ADDRESS. WE CAN'T SIMPLY CONTINUE.'

In the intention-to-treat population, patients who received the vaccine had a 33% increase in risk of distant metastasis by the end of the study. It was not statistically significant ($p = 0.08$) but the curves were diverging, suggesting that the vaccine was detrimental. There was little difference in outcome in patients with confirmed node-negative status. But in those who were not staged, the vaccine group had a 47% increased risk of developing distant metastases ($p = 0.08$ again), compared with observation.

The figures for overall survival among the intention to treat population were even bleaker, with 35 deaths

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in the observation group, compared with 56 in the vaccine group (hazard ratio 1.66, $p = 0.02$).

For the primary endpoint, relapse free survival, the trial met the criteria for futility. 'It is so disappointing,' said Professor Eggermont. 'There are hundreds of reported studies in stage IV metastatic melanoma showing an overall response of less than 4%.' The discussions always say that vaccines should be used earlier in the disease, before patients become immunosuppressed. That's what we did, but when we look at our whole patient population, the vaccine had absolutely no effect: the number of events in the observation group was exactly the same as in the vaccine group.

'The futility analysis gave us statistical proof that this trial will never become positive, no matter how long the follow up. We had to stop this trial on the basis of that analysis. But on the basis of the detrimental findings on distant metastasis free and overall survival, we must not only stop this trial, we must stop further patients being vaccinated. The idea that repeated vaccination might be detrimental is dramatic, but right now there is a definite trend in that direction.'

The results should prompt a relook at other studies. ECOG 1694, for example, compared high dose interferon (HDI) with the GM2 vaccine in 880 patients in a higher risk group. Many were stage III, node-positive. An interim analysis found that the HDI was better; the vaccine was seen as doing nothing. 'That conclusion is no longer valid. The vaccine curve is actually some way below the observation curve. This trial is now being looked at completely differently because of our results,' said Professor Eggermont.

'WE MUST NOT ONLY STOP THIS TRIAL, WE MUST STOP FURTHER PATIENTS BEING VACCINATED.'

Trials using other vaccines – melacine and oncolysate – failed to show a significant benefit, but there was no difference in outcome compared to placebo. However, two trials using Canvaxin, which induces a specific T cell reaction (a different mode of action to the GM2 vaccine) both showed a trend towards a worse outcome in patients given the vaccine plus BCG; compared with those given BCG alone. One trial was in stage III patients, the other in stage IV. The trends were not significant, but both trials were closed on interim analysis, when it was established that the vaccine arm could never become better than BCG, and that survival in the vaccine arm in both trials was appreciably inferior to the control arm.

'We have a problem here,' said Professor Eggermont. 'In the 3–4 largest adjuvant vaccine trials ever done, using different types of vaccine, in different stages of melanoma (II, III, IV) we have seen that the vaccine was worse than the comparison group. It is time to make an issue of this. Do we really understand what we are doing with repeated vaccination?'

Hypothetically there could be induction of tolerance. Any stimulation of the immune system is followed by an inhibiting effect, which dampens the response. Normally, this is necessary to prevent an allergic reaction to any antigen. But it could be that repeated vaccinations induce a dangerous level of dampening, increasing T suppressor cells more than active tumour killing T cells, and favouring growth of the tumour.

The issue for the future of melanoma vaccines will be to improve immunomonitoring so that positive or negative responses to the vaccine can be detected, Professor Eggermont said: 'In any future adjuvant trial, we will need monitoring techniques that are good enough to detect any harmful effects. This is quite a shift from our prior belief that vaccines would not be harmful.'

Currently available monitoring tools have yet to be standardised, he said. 'There are hundreds of small trials using monitoring tools to examine the cytotoxic response to vaccines, but they're not giving the same outcome between labs. We have a poor system to show what works. We may be able to give vaccines every week, or every 3 weeks, but we need to be able to demonstrate along the way that what happens in the patient is the desired activation of the immune system without the induction of immunosuppressive immune responses that we must avoid. If we can not convincingly demonstrate this during vaccination schedules we may be viewing this approach too optimistically and naïvely.

'THE COMPLEXITY OF WHAT WE'RE DEALING WITH IS OFTEN UNDERESTIMATED'

'It makes the development of vaccines extremely complex. The problems of developing vaccines in immunosuppressed patients with advanced disease are not overcome by using the vaccines at earlier stages of disease. The negative outcomes of these trials mean that this really is a problem. We need a lot of research and further understanding for the field to move forward.'

It could be that coupling a vaccine with a CTL-4, a PD-1 or similar immune-response-modulating antibody, which prevents the development of immunosuppression, may be a way forward, he said: 'Perhaps these antibodies will prove to be important to help vaccine development and avoid the suppressor mechanisms, and help us towards better understanding. But there are a lot of questions here; we only partially understand what is happening in patients.'

'Our report will have an effect on participation in trials. Vaccine trials are generally very popular; patients understand and like the concept of harnessing their immune system to fight their cancer. In the end, it appeals to everybody, it's the Holy Grail: a relatively non-toxic therapy. But the complexity of what we're dealing with is often underestimated. Right now, vaccine development needs some new answers and new molecules in order to move forward.'

Helen Saul

WHO tackles behaviour change

The World Health Organization (WHO)'s Regional Committee for Europe is attempting to promote healthy behaviour, and to improve the governance of health systems. At a meeting in Georgia (15–18th September, 2008) 250 representatives of the countries in the WHO European Region passed resolutions on these complex and persistent issues in public health.

Efforts to change behaviour, and to improve the governance and performance of health systems, both have a long history and patchy success. WHO Director-General Dr. Margaret Chan said: 'I applaud your courage in tackling these problems. Though difficult, they represent the most important barriers to health development facing every country in the world.'

A paper presented at the meeting acknowledged the difficulties inherent in promoting healthy lifestyles. Health promotion activities – and mass public health campaigns in particular – have often failed to have the desired effect in terms of reducing disease incidence and burden, simply because compliance with the message, in the form of the intended behaviour change, is harder to achieve than its precursors of raising awareness, providing knowledge and altering attitudes.'

The paper stresses that interventions must be based on sound theory backed up by solid evidence, coupled with a well-documented implementation strategy. The critical factors for success need to be outlined and their feasibility, robustness and replicability assessed in different settings across the region.

Addressing the meeting, His Excellency Mikheil Saakashvili, President of Georgia, said that a health system should not be seen as a burden to government, but as a real producer of economic gain: 'The success of any country should be judged on its ability to ensure that all citizens have equal access to quality health care services.'

• As if to underline some of the difficulties inherent in promoting health lifestyles, a recent UK-based study found that true levels of children's physical activity are likely to be 6 times lower than national data suggest (*Arch Dis Child 2008; doi 10.1136/adc.2007.135905*).

Annual health surveys indicate that UK children have been increasingly physically active over the past few years, but data relies on information supplied by parents.

The research team monitored levels of physical activity in 130 children aged between 6 and 7 years over one week.

Parents said their children were physically active for an average of 146 minutes a day. The accelerometer readings showed that this figure was actually 24 minutes a day. Only 3% boys and 2% girls were complying with recommended daily amounts of activity (60 minutes per day).

The authors conclude: Marked improvements in surveillance of physical activity will be necessary in order to meet the major public health challenges of the 21st century, particularly where physical acitivity has been implicated in the aetiology of diseases.'

Scottish turnaround on pemetrexed

Following a second re-submission of evidence, the Scottish Medicines Consortium has accepted pemetrexed as monotherapy for second-line treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC). Use is restricted to patients with good performance status who would otherwise be eligible for treatment with docetaxel.

The guidance supports a tailored approach to lung cancer treatment based on histology. It was based on a retrospective subgroup analysis of a study (*JCO 2004*;**22**(9):1589–97), which showed an increase in survival with pemetrexed compared to docetaxel (9.3 vs 8 months, respectively) in patients with non-squamous histology. A prospective, randomised, phase III study (*J Clin Oncol 2008*;**26**(21):3543–51) also showed a survival benefit according to histotype.

Elsewhere in the UK, the National Institute for Health and Clinical Excellence (NICE) does not differentiate between NSCLC histotypes and guidelines do not recommend pemetrexed for the treatment of locally advanced or metastatic NSCLC. An appraisal for use of the drug in first-line treatment is being conducted.

Pemetrexed is a multi-targeted agent. It inhibits the enzyme thymidylate synthase, decreasing the thymidine necessary for pyrimidine synthesis. It is also an anti-folate that works by disrupting folate-dependent metabolic processes involved in cancer cell replication and survival.

Bortezomib in multiple myeloma

Bortezomib, in combination with melphalan and prednisolone, has been approved by the European Medicines Agency (EMEA) for the treatment of patients with previously untreated multiple myeloma (MM), who are not eligible for high-dose chemotherapy with bone marrow transplant.

The drug, a proteasome inhibitor, was approved in Europe in 2005 for MM after first relapse. Professor Jesús San Miguel (University of Salamanca, Spain) was principal investigator for the phase III VISTA trial, on which the approval was based. Bortezomib 'has already made an important contribution,' he said. 'The marketing authorisation from the EMEA is encouraging as it suggests that more patients may benefit from earlier treatment.'

The VISTA trial (*NEJM* 2008;**359**(9): 906–17) found that bortezomib-melphalan-prednisolone increased time to disease progression to 24 months, compared with 16.6 months in the control group, who received melphalan-prednisolone alone (Hazard ratio for bortezomib group, 0.48, $p = 0.001$). The hazard ratio for overall survival was 0.61 for the bortezomib group ($p = 0.008$); complete response rates were 30% and 4% for the bortezomib and control groups respectively.

33rd European Society for Medical Oncology Congress Stockholm, Sweden; 12–16th September 2008

Gefitinib in NSCLC

Gefitinib could become first-line treatment for non-smoking, chemotherapy-naïve Asian patients with advanced non small cell lung cancer (NSCLC), researchers claim.

The phase III IPASS (Iressa versus carboplatin/paclitaxel in Asia) study included 1,217 patients with stage IIIB/IV NSCLC who had not received chemotherapy and who were non-smokers or former light smokers. The study was conducted in 7 Asian countries.

After 22 months of follow-up, 453 (74.4%) patients in the gefitinib group experienced disease progression, compared to 497 (81.7%) patients in the combination arm (hazard ratio 0.74; $p < 0.0001$).

A sub-analysis found that progression-free survival (PFS) in patients with EGFR mutations was significantly better in the gefitinib group compared to those receiving chemotherapy (hazard ratio 0.48; $p < 0.0001$). For those without the mutation, the chemotherapy arm did better.

Presenting the results at the Presidential Symposium (*Late Breaking Abstract #2*), Dr. Tony Mok (Chinese University of Hong Kong, China), said that 60% of Asian NSCLC patients carry EGFR mutations, compared to only 15% of Western NSCLC patients: 'Since so many Asian patients with NSCLC have the mutation, we'll be able to use clinical criteria to select those who will be suitable for gefitinib. But for western patients, where mutations are rarer, mutation analysis will be needed'.

Intravenous iron

Intravenous iron added to darbepoetin alfa (DA) in patients with chemotherapy-induced anaemia was well-tolerated and improved haematological response, Dr. Michael Auerbach (Baltimore, Maryland, USA) told the meeting (*Late Breaking Abstract #9*). He said it is a safe procedure which would allow oncologists to save money through more effective use of erythropoiesis-stimulating drugs and blood transfusions.

Trabectedin in ovarian cancer

The combination of trabectedin and pegylated liposomal doxorubicin significantly increased progression-free survival (PFS) in women with relapsed ovarian cancer, compared to doxorubicin alone, researchers said.

The randomised phase III OVA-301 trial included 672 patients in 124 hospitals in 21 countries. Median PFS – the primary endpoint of the study – was 7.3 months in the combination group, compared to 5.8 months for those treated only with doxorubicin (hazard ratio 0.79; $p = 0.02$). The drug appeared to be more active in patients whose disease was slower to relapse: in women whose relapse occurred more than 6 months after initial chemotherapy, median PFS was 9.2 months for the combination, versus 7.5 months in the doxorubicin group.

Data on overall survival are immature but, a positive trend was seen in the combination group, with a 15% reduction in the risk of death. (*Late Breaking Abstract #8*)

Head and neck cancer

The addition of cetuximab (Erbitux) to platinum-based chemotherapy increased overall survival in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). Researchers said that, compared to chemotherapy alone, patients receiving both therapies also had improved progression-free survival and increased response rate, while quality of life was maintained (*Abstract #693*).

The randomised phase III EXTREME study included 442 patients. Median overall survival was increased by nearly 3 months (10.1 vs 7.4 months; $p = 0.04$) in the group receiving cetuximab.

Lead investigator Professor Jan Vermorken (Antwerp University Hospital, Belgium) said that the new drug was associated with improvements in pain and swallowing, and was not accompanied by additional, detrimental effects on quality of life: 'Indeed, the life quality benefits that our patients experience due to the tumour shrinkage induced by Erbitux therapy can make a real difference.'

Cost analysis of kidney cancer drugs

Sunitinib (Sutent) is a cost effective alternative to sorafenib, temsirolimus and bevacizumab plus interferon alpha as first line therapy for metastatic renal cell carcinoma (RCC), researchers say.

Cost-effectiveness analyses in Sweden, Spain and the US, each found that sunitinib was likely to be the most cost effective of the options in terms of quality adjusted life years (QALY) gained (*Abstracts 479, 931, 1146*).

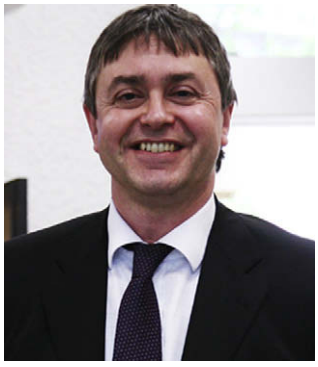
The findings will provide cold comfort in the UK, where the National Institute of Health and Clinical Excellence (NICE) recently issued a preliminary decision not to recommend any of the new agents as treatment options for advanced or metastatic RCC. The decision was seen to be based on the price of the drugs rather than their clinical effectiveness (see *EJC News 2008;**44**:15*); final guidance is expected in January 2009.

Dr. Ulrika Harmenberg (Karolinska Institute, Stockholm, Sweden), one of the authors of the Swedish analysis, said that sunitinib is widely used for good and intermediate-risk RCC patients in Sweden. Each patient is considered individually, and not all receive it, but she said that most centres routinely prescribe it.

Patients are followed up carefully to check for disease progression, she said, and she stressed the need to identify predictive markers. 'We need biomarkers to give us a better way of selecting the patients who will benefit. It is important to find a better way of following up patients – such as the new imaging methods – which wil be able to tell us early on who is benefiting from the treatment, and who isn't.'

PODIUM

A new director at IARC



Professor Christopher Wild, Professor of Molecular Epidemiology and Director of the Leeds Institute of Genetics, Health and Therapeutics (UK) takes up the post of Director of the International Agency for Research on Cancer (IARC, Lyon, France) in January, 2009.

What is IARC's role as we approach the second decade of the 21st century?
There are a number of roles for the Agency, but our primary activity is research. One major role is to identify the environmental and genetic causes of human cancer; another is to evaluate prevention strategies to reduce the worldwide cancer burden. I believe the best approach in both these areas is through the integration of laboratory science and epidemiology – something I feel strongly should be promoted. Such an approach could be followed, for example, to investigate the link between cancer and nutrition, obesity and physical activity.

What needs to be done in low- and medium-resource countries?
The Agency has a special role to play in countries with less national capacity to conduct the necessary research independently. Part of this process is to support the work on cancer registration, to better define the scale of the problem and provide clues to the major causes of cancer. There are now more people with cancer in such countries than in high-resource countries, and that gap is projected to widen. It is therefore a natural area for an international cancer agency to focus upon. My own experience in West Africa taught me that in order to succeed it is vital to establish good working relationships with local scientists to make the most of our combined research efforts.

What is IARC's role in collaborative research?
To establish the causes of cancer you increasingly need large, multi-centre, prospective studies. There are many opportunities for the Agency to bring researchers together, for example to study the impact of early life exposures on cancer risk in later life through a coordination of some of the mother-child cohorts now being established around the world. The Agency's scientists however should also have an intellectual contribution to collaborative research, not only a co-ordinating role.

Should IARC be involved in training?
The Agency should use its experience, knowledge and international contacts in the training of cancer researchers by organising training courses and fellowship programmes with an emphasis on stimulating training in low-resource and middle-resource countries. This should involve Agency staff travelling to those countries, and adapting the content of courses to local contexts. Not only would this help Agency staff understand the challenges being faced, but it also demonstrates a commitment that can be an encouragement to national researchers who see their work receiving international interest.

Some have been concerned by IARC's move towards epidemiology and away from laboratory investigations in recent years.
We need both. My own background is in molecular epidemiology, conducting top quality laboratory research linked to epidemiology. If you understand the underlying mechanisms of cancer you can translate that knowledge into the development of, say, biomarkers, and these can be used in population studies investigating causes or prevention. So I would want to strengthen our laboratory capacity, but with the perspective of its application in epidemiological and intervention studies. There are new areas of laboratory research such as proteomics or metabolomics, which permit novel approaches that would be of value to the Agency's work.

Will IARC become directly involved in policy making?
The strength of the Agency is in research, not policy making. We should therefore contribute to the body of evidence for other national agencies or the World Health Organization (WHO) to establish and advocate cancer policies. However, I do think the Agency needs to have the perspective of the eventual translation of its findings into public-health policy. There is also a case for the Agency evaluating the implementation of, say, prevention strategies in health-care settings – particularly in low-resource and middle-resource countries.

Is there a need for greater transparency in the Monograph programme?
Transparency is vital for confidence. We need to be absolutely clear to the outside world regarding the standards and processes that the Agency applies in its high-profile work, particularly in the Monographs programme. Having said that, the Agency is remarkably open in its workings and very much open to scrutiny, but I am always willing to listen to suggestions for improvements.

Is there a need to raise IARC's profile?
There is definitely a need for the Agency's work and achievements to be disseminated not just to the scientific community, but more widely. The Agency has a huge opportunity to harness the skills and good will of all the people who have worked here over the years and perhaps create a kind of IARC alumni association. Through these people there may be a way to make the work of IARC more widely known. It's my hope we can achieve this.

The full interview, by Adrian Burton, appears in Lancet Oncol 2008;9:706–7