available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

NEWS. . .NEWS. . .NEWS

EU Directive postponed to protect MRI

The European Commission is to postpone for 4 years its legislation on workers' exposure to electromagnetic fields. The move is in response to fears that the Directive (2004/40/EC) could halt the use of Magnetic Resonance Imaging (MRI).

Member states were due to implement the Directive by April 2008. Postponement until 30 April 2012 'will allow enough time to prepare a substantive amendment to the Directive in order to take account of recent research findings on the possible impact of the exposure limits on MRI,' a statement from the Commission stated.

The Directive was a health and safety initiative, intended to limit European workers' exposure to electromagnetic fields. It was adopted by Parliament and Council in April 2004 and was based on information from the International Commission on Non-Ionising Radiation Protection (ICNIRP).

Concerns about possible problems caused by the Directive were first raised in 2006; the Commission then launched a study in Germany, France, Belgium and the UK, to look at the implications of the exposure limits on the practice of MRI. The results should be finalised by the end of January, 2008.

Vladimir Špidia, EU Commissioner for Employment, Social Affairs and Equal Opportunities, said, 'The Commission remains committed to the protection of the health and safety of workers. However, it was never the intention of this Directive to impede the practice of MRI. Obviously, the Commission recognises MRI as a technology offering clear benefits to patients, and continues to support MRI research financially.'

Postponement 'will allow time to review the current Directive and amend those provisions which have been shown to be problematic by recent scientific studies. While this review is ongoing, the Commission recommends that Member States put the transposition of the current Directive on hold.'

The future amendment will aim to ensure that limits will not have an adverse effect on the practice of MRI, while ensuring appropriate protection of personnel.

The postponement was widely welcomed by interested parties. The Alliance for MRI, a coalition of European Parliamentarians, patient groups, leading European scientists and the medical community, has campaigned against the Directive, on the grounds that it would have prevented healthcare staff from assisting patients during imaging. Some young, elderly, frail or confused patients cannot be imaged without this care and would either be denied imaging or have to undergo alternative procedures such as X-rays, it claims.

'THE COMMISSION REMAINS COMMITTED TO THE PROTECTION OF WORKERS'

'We look forward to working with the European Commission prior to the proposal to amend the directive,' said Alliance spokesperson Professor Gabriel Krestin (University Medical Center, Rotterdam, The Netherlands). 'It is essential that the EC assesses closely the full impact the Directive will have, taking into consideration the social, economic and environmental impact of the legislation.

'Any new legislation must be evidence based and founded on sound science. There has been no proven harmful effect of MRI to either patients or workers over the past 25 years, during which time over 500 million examinations have been undertaken,' he said.

'MRI SHOULD BE EXEMPTED FROM THE DIRECTIVE

'The increase in cancer survival seen over the past decades is, to a large extent, due to more precise diagnostic tools – MRI included,' said Professor Dag Rune Olsen, Chair of ESTRO's Physics Committee. 'The EC must learn from their experience with this Directive and consult widely before implementing Directives that impact negatively on research and patient care.'

The Alliance believes that MRI should be exempted from the Directive to ensure the future unimpeded use of MRI, particularly for cutting edge research and interventional MRI. A statement from the organisation stated that concerns about electromagnetic exposure could be addressed through responsible guidance to medical and service personnel.

Helen Saul

EJC News is edited by
Helen Saul
Tel.: +44 1865 843340,
E-mail address: h.saul@elsevier.com

doi: 10.1016/j.ejca.2007.11.018

Need for a paradigm shift in clinical trial design

Clinical trials in the 21st century should have a translational component bound in from the beginning, Professor Martine Piccart (Institut Jules Bordet, Brussels, Belgium) told the Opening Session at ECCO-14 (Barcelona, 23–27 September, 2007). 'It is our responsibility as investigators to address this paradigm shift in clinical trial design,' she said.

Genetic signatures thought to be related to prognosis need to be validated at the clinical level. 'We still have a lot of work to do. We have discovered a number of signatures but very few have been independently validated,' she said.

Validated signatures 'will boost our understanding of metastatic disease progression and its susceptibility to treatment,' she said, but clinicians are looking for key pieces of information: how to identify patients who can be spared expensive and toxic drugs, how to identify for an individual patient which therapy will work best, and, where possible, how to identify which active therapy will be least toxic.

Some genetic signatures seem to predict outcome in a powerful way and outperform clinical pathology. But many have been identified in small retrospective studies, which raises questions about their relevance. There is a need for 'a revolution' in the design

'VERY FEW GENETIC SIGNATURES HAVE BEEN INDEPENDENTLY VALIDATED'

and conduct of clinical trials in cancer, she said, towards 'clinical-omic' trials in which every effort is made to gather patient and tumour material. High throughput genomic and proteomic platforms should allow the creation of a more comprehensive picture of the tumour biology and the particularities of the host.

Trials should no longer be designed for the whole breast cancer population, but should be tailored to relevant molecular subtypes. 'Much more intense cross talk with basic scientists needs to occur – early on – with molecular hypotheses (for example of reduced or enhanced treatment benefit) being incorporated upfront and served by adequate statistical power,' she said.

Breast cancer leads the field in terms of being considered in terms of its molecular subtypes, but other cancers are making ground. A presidential session at ECCO-14 heard that a novel therapy for colorectal cancer may be effective only in patients whose tumours lack KRAS mutations.

Dr Rafael Amado (Amgen Inc) presented data on panitumumab (Pmab), a fully human antibody against the epidermal growth factor receptor (EGFR). It is approved for treating metastatic colorectal cancer (mCRC) in the US (Late Breaking Abstract #7).

Mutations in KRAS (a small G protein that acts downstream of EGFR) have been correlated with lack of response to anti-EGFR antibodies in colorectal cancer, but the importance of these mutations in identifying patients who could benefit from therapy has not been previously assessed.

A phase III randomised controlled trial was conducted in collaboration with academic researchers in the US, Belgium and Italy. Patients with chemo-refractory mCRC received best supportive care with or without Pmab. KRAS status was determined in 427 of 462 randomised patients.

In the treatment group, progression-free survival (PFS) was 12.3 weeks for those with wild-type KRAS, and 7.4 weeks for those with mutant KRAS. In the control group, median PFS was 7.3 weeks in both KRAS groups.

'Efficacy of Pmab monotherapy in CRC is confined to patients with tumours lacking KRAS mutations,' Dr Amado concluded. 'KRAS status should be considered as a selection marker in CRC patients who are candidates for Pmab therapy.'

In a similar vein, Professor Rob Tollenaar (Leiden University Medical Center, The Netherlands) described how full-genome molecular expression profiling in patients with stage II colon cancer had identified 2 groups with distinct clinical outcomes.

In the first group of 75% patients, 90% were likely to survive for at least 5 years with no distant metastases. Among the remaining patients, only 65% had 5-year survival without distant metastases. Patients in the second group were likely to benefit from adjuvant chemotherapy, he said (#3007).

While discoveries like this are obviously good news for both patients and budget holders, the shift towards considering cancers in terms of their molecular subtypes presents a challenge to industry.

'INDUSTRY NEEDS TO ACCEPT THE REALITY OF MARKET SEGMENTATION'

At the opening session, Dr Kapil Dhingra, (Hoffman La Roche) said that, as target populations become smaller, it may no longer be possible to conduct randomised trials in large populations. A cancer described according to its molecular subtype might affect only 150 people in the US. Traditional trials take years to conclude and are not a realistic way to look for return on investment in rare diseases.

'Regulators need to think about how to approach the new world as cancer continues to segment,' he said. New endpoints – biomarkers based on primary endpoints including novel imaging methods – will have to be used. He said there was a need for continuous interaction and dialogue between sponsors and regulators in order 'to develop drugs in an intelligent fashion.'

High quality assays for measurements of novel endpoints would be needed to help balance the costs of development, along with novel trial designs and early testing in early stage patients. Post-marketing surveillance was likely to have an increasing role in the new environment, he predicted; drugs would receive limited approval and most understanding of the drug and its targets would happen in Phase IV trials.

He called for regulators to 'accept new thinking' on drug development and said that industry 'needs to accept the reality of market segmentation.' Overall, he concluded, 'We need to focus our resources on drugs which have the potential for transforming the disease, rather than having incremental benefits.'

Helen Saul

EUROFILE

Slovenian Presidency makes cancer a priority

For the first time since public health became an EU competence, oncologists will see their subject being made a top priority for a national Presidency. The Slovenians, who take up this role on January 1 2008, have said that they intend to take an 'action-oriented, integrated and multi-sectoral policy response' to the public health challenge caused by cancer.

Speaking at the 2007 European Health Forum, Gastein, Dr Marija Seljak, Director-General of the Public Health Directorate in the Slovenia Ministry of Health, said that the EU Presidency was always a big challenge but even more so for a small, relatively new Member State. Notwithstanding, she went on to outline an ambitious programme to tackle what she described as the demographic problem of cancer. 'The decision to focus on cancer during the Slovenian Presidency of the European Union in 2008 offers an important opportunity to reassess how Europe is responding to the public health challenge of cancer.

'The population of the EU will become significantly older over the next 20 years', she said. 'Projections suggest that in 2010, 3 million Europeans will develop cancer and nearly 2 million are expected to die due to cancer. Projections for 2020 suggest that 3.4 million Europeans will develop cancer and over 2.1 million will die as a result of the disease.'

Projections for other chronic, non-communicable diseases, often linked to the same risk factors as cancer, were also alarming, she said. 'With an ageing population and a growing disease burden, this presents welfare and health systems with a double burden of rising costs and a deteriorating dependency ratio between the working and non-working population. Attending to the long term environmental and lifestyle risk factors that underpin the chronic disease burden, including cancer, is therefore an economic as well as a social and health policy priority. While research into cancer aetiology is constantly bringing about new and more advanced treatments, addressing the long term disease burden requires a focus on risk factors and prevention throughout life.'

The challenges were four-fold, said Dr. Seljak. In the area of primary prevention and care, they would seek to promote healthy lifestyles and reduce exposure to risk factors in order to prevent as many cancers as possible.

Screening and early detection would also be a priority. 'We will encourage Member States to detect as early as possible those cancers which could not be prevented. Screening is one of the most efficient activities in cancer management and insufficient adherence to secondary prevention significantly increases the burden of cancer in Europe. Differences in implementation of recommendations and in the development of efficient policies and programmes for cancer screening need to be discussed and assessed. Successfully managed screening programmes for certain types of cancers can contribute significantly to better survival rates across the Europe', she said.

'IN 2010, 3 MILLION EUROPEANS ARE EXPECTED TO DEVELOP CANCER'

On the subject of treatment and care, the Presidency would aim to improve health outcomes as well as quality of life for those with cancer and their families, and to give the best possible treatment and care to cancer patients, exchanging best practices regarding diagnosis, treatment, rehabilitation and palliative care. 'The issues related to treatment and integrated care of cancer patient are one of those, which, together with the successful screening policies, significantly contribute to patient survival and their quality of life. Socio-economic differences both within and between countries are often the consequence of differences in approaches to treatment and supportive activities and continued care in Europe', said Dr. Seljak.

Fourthly, the Presidency would encourage research that aims to identify causes and develop strategies for prevention, diagnosis, treatments and cure.

The main event of the Presidency will be a conference, held in Slovenia on 7–8 February 2008, which will provide an opportunity to reassess how Europe is responding to the public health challenges of cancer as a chronic disease and look for opportunities to reduce the burden of cancer in the EU, particularly in the priority areas outlined above. 'We hope that cancer will once again be high on the European agenda as a result of this meeting', said Dr. Seljak. The conference will provide a lot of the groundwork for the informal Council of Health Ministers to be held on 17/18 April, 2008, and the Slovenians hope that this meeting will adopt formal conclusions on cancer.

Oncologists are enthusiastic about the prospect of their subject taking a seat at the top table. 'ECCO is delighted that the Slovenian government has given cancer such a high priority. Although oncologists know the scale of the problem, which will increase significantly over the next decades, it is not always evident to others, and we are most encouraged that it has been recognised at such a high political level. We look forward to working with the Slovenian presidency to help all those who suffer from cancer, as well as those who treat and care for them, and those who carry out the research which is so essential to progress cancer care, education, awareness and prevention in the future', said Professor Alex Eggermont, President of the European CanCer Organisation.

'ATTENDING TO LONG TERM RISK FACTORS IS AN ECONOMIC POLICY PRIORITY'

Mary Rice
Brussels

Fetal microchimerism might ward off breast cancer

Fetal microchimerism is significantly more common in women who have not developed breast cancer than in women with the disease say researchers (Cancer Research 2007;**67**:9035–38). So, can fetal immune cells that cross into a mother's blood stream reduce her risk of developing breast cancer?

'Fetal cells routinely enter the maternal blood stream where they can survive for years', explains first author V K Gadi (Fred Hutchinson Cancer Research Center, Seattle, WA, USA). 'Since breast cancer is less common in women who have had a child, we hypothesised that fetal allogeneic immune cells might be affording them protection.'

As an initial test of their hypothesis, the team analysed the blood of 82 women: 35 with breast cancer and 47 healthy controls. 74% and 72% of these women, respectively, had been pregnant at least once. 63% and 62%, respectively, had given birth to at least one son. Using real-time PCR the team tested the blood of these women for a male-specific gene, DYS14, that could not be of maternal origin and was presumed to indicate foetal microchimerism.

'Fetal cells were found in 43% of the healthy women but in just 14% of those with breast cancer', explains Gadi. 'That translates into an odds ratio of 4·4 (95%CI 1·34–16·99), and of 5·9 (1·26–6·69) when restricting the analysis to women who actually gave birth to a son.'

Protection might lie in the priming of fetal immune cells against maternal cancer antigens, thus providing a back-up allogeneic immune surveillance system. However, the cells could be a double-edged sword. 'Fetal microchimerism may be associated with certain autoimmune diseases, which are more common in women', explains David Abraham (University College London, London, UK). 'How-ever, the development of these diseases and possible breast cancer protection may be different things; more studies are needed to understand the underlying mechanisms.'

Adrian Burton

*This story originally appeared in Lancet Oncol 2007;***8**:964

'Contaminated' survival results in kidney cancer

Progression-free survival (PFS) will become the end point for trials in advanced kidney cancer, predicted Professor Ronald Bukowski (Cleveland Clinical Foundation Taussig Cancer Center. Ohio, USA) in his state-of-the art lecture at the 1st European Multidisciplinary Meeting on Urological Cancers (Barcelona, November 2–4, 2007).

'As patients have access to agents, they will contaminate survival results and what we'll be left with is progression free survival. This will be our standard as we evaluate results,' Professor Bukowski told the meeting.

Prof Bukowski said the Treatment Approaches in Renal Cancer Global Evaluation (TARGET) Trial in which he was an investigator, had experienced such problems and was 'contaminated' because of patients' access to other agents.

In the clinic, while the treatment paradigm in renal cell carcinoma (RCC) was evolving, sunitinib was the standard of care, he said. The combination of bevacizumab and INFα would be licensed shortly, giving clinicians the choice of 2 up front therapies, said Prof Bukowski 'although there would not be a good way of choosing between them'.

Professor Cora Sternberg (La Sapienza University, Rome, Italy) concurred with Professor Bukowski, saying targeted therapies had clearly changed the way clinicians thought about the disease. But while targeted therapies were a major advance, they did not cause a response as defined by RECIST (Response Evaluation Criteria in Solid Tumors).

'They stabilise the disease but we have not cured any patients. Can we commute a death sentence into a chronic disease that patients can live with, like diabetes or hypertension?' asked Professor Sternberg.

Professor Peter Mulders (Radboud University, Nijmegen, The Netherlands) said: 'Targeted therapies' effect on metastases or primary tumours can be spectacular. We see things we never saw with immunotherapy but it's a chronic therapy although there is a substantial delay in disease progression.'

Duration of treatment is a major question and clinicians are unsure when to terminate therapy. Other questions remain. For example, it has yet to be established whether there is a dose response to tyrosine kinase inhibitors (TKIs); suitable pre clinical markers need to be identified; researchers need to establish how to measure response. Professor Bukowski said giving TKIs sequentially was attractive because of ease of administration and evidence of response when switching from one agent to another, but clinicians needed better definitions of failure.

Similarly, combining targeted therapies was an option: sunitinib and bevacizumab could be given at full doses for a few months, he said: 'This is an important possibility in treatment-naïve patients and trials will be important to indicate if this is possible.'

Maya Anaokar (who was sponsored to attend the meeting by Munro and Forster, on behalf of Pfizer)

Positive opinion for bevacizumab

The European Committee for Medicinal Products for Human Use (CHMP) has issued a positive recommendation for bevacizumab (Avastin) for the first-line treatment of patients with advanced RCC.

The decision was based on data from the phase III Avoren trial, which found that progression free survival among patients receiving bevacizumab plus interferon (a current standard of care) was 10.2 months, compared to 5.4 months for those on interferon alone.

Data on overall survival are pending.

PODIUM

Relief as BRCA1 patent remains curtailed

Photo courtesy of A. Lescure/Institut Curie

Molecular geneticist Professor Gert Matthijs (Catholic University of Leuven, Gasthuisberg, Belgium) has been challenging patents on the BRCA1 gene since the first was granted to Myriad Genetics in 2001. He successfully fought off an appeal by the company in September 2007, meaning that the patent is now limited in scope and will not affect diagnostics in Europe.

Why you?

I can't explain. I believe in public healthcare and the principle of mutuality: no-one decides which disease he or she will get, let alone with which mutation he or she is born, so everybody should have the same access to healthcare. The principle is under pressure. Also, the way in which a patent interferes with a genetic service is complex, and thus geneticists had a duty to defend the case on behalf of patients.

How did your involvement start?

When I heard, back in 2001, that the BRCA1 gene was covered by a wide, all-encompassing patent, I felt that we had to do something. I became the reluctant volunteer who took on the case. Dr. Dominique Stoppa-Lyonnet (Institut Curie, Paris) had initiated French opposition to the patents, and I expanded this into European action. We were supported by various genetic organisations; we hired keen patent lawyers and kept each other going.

How significant is the recent judgement?

The judgement – by the Appeal Board at the European Patent Office (EPO), Munich – relates to the most fundamental of 3 patents on BRCA1. Myriad Genetics' original patent covered the entire gene, sequence and protein, and all possible applications. In January 2005, this patent was reduced to a claim on a probe to detect the gene, and the Appeal Board has now confirmed that decision. The difference between the final and the original patent is enormous.

What if the decision had gone the other way?

It would have prevented us from offering diagnostics. The gene sequence would have belonged to the patent owners and we would not have been able to test for predisposition to familial breast or ovarian cancer without a licence. And we would not have been able to get a licence on reasonable terms. Different labs were previously offered licences with huge conditions attached: an up-front fee of $50,000 with a further fee for each mutation searched for. So, in practice, Myriad Genetics would have had a monopoly on the service.

On what grounds did you win?

The EPO confirmed that DNA or amino acid sequences in patent applications are an essential technical feature and have to be correct. Sequencing errors are not acceptable. The ruling acts against those that rush to the patent office with sloppy sequences, and should improve the quality of patents in general. The decision is definitive; further appeals are not possible.

What do the other 2 patents on BRCA1 cover?

The 3 patents overlap. The first deals more specifically with the diagnostic test for predisposition to familial breast and ovarian cancer; this was revoked entirely in May 2004. The last originally contained claims on a series of individual mutations; this was reduced to a claim on a probe to detect a frequent Ashkenazi mutation in January 2005. Appeals on both are outstanding.

Will the EPO's decision have any impact in the States?

Not directly. European law does not affect US patents. The same arguments could be used – and many of our American colleagues dispute the monopolisation of the BRCA genes –but the patenting system is different. To change anything there, one would have to go to court, and a small regional lab could never make enough profit to pay off a risky court case. In the US, the patent will stand for 20 years.

Does the judgement reflect a change in the legal climate?

Not really. We may have won the battle but lost the war. The patent claim was quashed on the basis of typing errors. As a result, patents without errors may be more solid than before. On the other hand, because diagnostics is moving towards the use of micro-arrays that include many mutations and genes, the manufacturers of these micro-arrays have to obtain a myriad of licences. I believe that the system will become unworkable, and crash itself.

Patents which promote progress have to be distinguished from those which block it. As long as innovation remains possible, it's fine. If someone can improve on PCR, that's wonderful. We need challenge and competition; if we patent a gene, innovation becomes impossible. I'm hopeful that the patent office is considering this.

What is the next step?

I chair the Patenting and Licensing Committee of the European Society of Human Genetics that was created to go beyond this individual patent fight. Early in 2008 we will be issuing recommendations on why it is better for genes not to be patented.

Helen Saul