available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

NEWS. . .NEWS. . .NEWS

New Communications Manager at ECCO

Dr. Amanda Wren

Amanda Wren has joined ECCO – the European CanCer Organisation (formerly FECS) as Communications Manager. She will be developing communication and marketing strategies to promote congresses and events for ECCO and its member societies.

Ms Wren founded *Nature*'s Spanish bureau in 1998, and remained as bureau chief; she was later director of international communications at the Spanish National Cancer Research Centre (CNIO), also in Madrid. She worked for a time for a public relations company, and said that her move to ECCO was "to return 'home' to the field of oncology".

"From a communications point of view it's also very exciting to have a brand new canvas at the launch of ECCO. My goal will be to promote all ECCO initiatives in multidisciplinary education and advocacy as well as further ECCO's mission – that every cancer patient deserves the best."

doi:10.1016/j.ejca.2007.12.004

Chemotherapy for Hodgkin's lymphoma

Chemotherapy should be routinely added to radiotherapy in certain types of Hodgkin's lymphoma, according to the results of a major EORTC trial. It concluded that a chemo-radiotherapy combination – rather than radiotherapy alone – should be the new standard treatment for localised Hodgkin's lymphoma in which the tumour is above the diaphragm.

The pan-European study (*NEJM* 2007;**357**:1916–27) included 1538 patients with untreated clinical stage I or II supradiaphragmatic disease, who were categorised as having a favourable or unfavourable prognosis.

Among those with a favourable prognosis, the estimated 5-year event-free survival rate was significantly higher after three cycles of MOPP-ABV (mechlorethamine, vincristine, procarbazine, prednisolone with doxorubicin, bleomycin and vinblastine) plus involved-field radiotherapy than after subtotal nodal radiotherapy alone (98% versus 74%).

Among those with an unfavourable prognosis, 4 courses of a doxorubicin-containing regimen were as effective as 6 cycles. Involved-field radiotherapy yielded a disease control rate similar to that with subtotal nodal radiotherapy.

Lead author Dr Christophe Fermé (Institut de Cancérologie Gustave Roussy, Villejuif, France) said: the results show that duration of chemotherapy can be tailored according to risk factors. "Moreover, our findings point to a new role for adjuvant radiotherapy with smaller radiation fields, allowing for the reduction of toxic effects associated with large fields. A remaining question now under investigation is whether patients with early-stage Hodgkin's disease can be cured with chemotherapy alone".

Thalidomide in myeloma

Thalidomide combined with melphalan and prednisolone (MP) should be the new standard of care for previously untreated elderly patients with myeloma, say French researchers (*Lancet* 2007;**370**:1209–18).

Newly diagnosed patients were randomly assigned to receive either MP, MP plus thalidomide (MPT), or reduced-intensity stem cell transplantation using melphalan. The study included 447 patients and, at a follow-up of 51.5 months, median overall survival was 51 months for MPT, compared to 33 for MP or 38 for the stem cell transplantation group. Some of the MPT group were still alive at the end of the study.

An editorial (*Lancet* 2007;**370**:1191-2) said the results are concordant with 2 other studies. "We now have extensive evidence to support the introduction of MPT as the standard of care for elderly patients with multiple myeloma," it concluded.

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

Molecular Targets and Cancer Therapeutics

19th Annual AACR-NCI-EORTC Conference

October 22–26, 2007, San Francisco, California, USA

First in Class and Novel Agents

● OSI-906 is the first selective IGF-R1 kinase inhibitor to enter phase I trials. Insulin-like growth factor receptor is a cell surface enzyme expressed by many human cancer cells known to drive tumor growth. In laboratory experiments, OSI-906 reduced growth of 15 cell lines including colorectal, lung, breast, pancreatic and pediatric tumors. When tested in mice with human colorectal cancer tumors in combination with erlotinib, thus ensuring the blockade of both IGF-R1 and EGFR tumor receptors, tumor growth was completed arrested and tumor size reduced by 22%. Phase I studies are ongoing. (*Proffered paper #1; Poster #C192*).

● Two leukemia stem cell (LSC) specific targeting agents were discussed for the treatment of AML (*Plenary session 1 #3*). Cancer stem cell research is the most advanced in leukemia where a well-defined cell population has been identified. Parthenolide (PLT), a sesquiterpene lactone, occurring naturally in the plant feverfew, is used for the relief of migraine, to help prevent blood clots, as an anti-inflammatory for arthritis and has been shown to induce death of human LSC *in vivo*. The clinical use of PLT is limited by its poor pharmacological properties and therefore, dimethylamino-parthenolide (DMAPT), a PTL analog was developed which has shown very selective LSC toxicity and potent inhibition of NF-KB. In preclinical studies it demonstrated 70% oral bioavailability and was well-tolerated. A second compound, TDZD-8 is a non-parthenolide, LSC-specific compound that selectively induces apoptosis, eradicating both primary AML stem and progenitor cells within 2 hours or less when compared to PLT without significant normal haematopoietic stem and progenitor cell toxicity. TDZD-8 may employ a unique, previously unknown mechanism to rapidly target leukemia cells. Drug manufacturing is underway and phase I studies are scheduled to begin.

Anti-angiogenesis and Functional Imaging

● Researchers and clinicians are using functional imaging to study the effects of anti-angiogenesis agents and to identify biomarkers predictive of response that may help to select patients for treatment. Dynamic contrast-enhanced MRI and US (DCE-MRI, DCE-US), and functional CT and PET, can be used to measure tumour blood flow, vessel permeability and blood volume distribution as well as to analyse potential tumor biomarkers.

Functional imaging aided drug development in the first clinical study combining combrestatin A4 phosphate (CA4P), a vascular disruptive agent (VDA), and bevacizumab (*Poster #B2*). Preliminary results suggest that single agent CA4P causes significant tumor necrosis as a result of vascular shutdown. However, tumour re-growth can occur due to blood vessels that survive in the tumour rim. Preclinical models show that this re-growth can be prevented by an anti-VEGF antibody agent which acts to inhibit the neo-vasculature of the surviving tumor rim. This synergistic anti-tumor activity was confirmed in patients with advanced solid tumors administered CA4P (45, 54 or 63 mg/m^2) and bevacizumab (10 mg/ kg) every 14 days. Functional DCE-MRI demonstrated that CA4P induced statistically significant reductions in tumour perfusion and vascular permeability that were sustained by the co-administration of bevacizumab. Stable disease lasting more than 2-4 months and improved tumor marker levels were observed in 3/6 patients and no grade 3 / 4 toxicities were recorded. Additional studies of this novel drug combination are required.

Molecular Markers and Patient Selection

● A phase III EORTC/NCIC study demonstrated that the presence of a methylated MGMT gene promoter in tumour tissue was an independent positive predictive factor of patient response to TMZ (*Plenary Session 2 #3*). It established temozolomide (TMZ) and radiotherapy (RT) as the new standard of care for newly diagnosed glioblastoma (GBM).

The use of MGMT as a predictive biomarker was confirmed in a phase I/IIa EORTC study of GBM patients prospectively stratified for MGMT status prior to treatment with dose-intense adjuvant TMZ/RT in combination with cilengitide, a highly selective integrin inhibitor targeting the tumour and its vasculature. The study reached the predefined primary endpoint with 69% of patients alive and progression free at six months and a median PF survival of 8.1 months. In a defined patient subgroup with methylated MGMT gene promoter in the tumour tissue, 91% of patients had a PFS of six months and the median has not yet been reached. A phase III study is currently underway.

Rational Drug Combination

● The rationale behind EGFR combination therapy is to augment the antitumour effects and to mitigate the observed skin toxicity. In NSCL cancer, however, combination studies have been largely negative.

The sequence in which these agents are administered may be important when treating tumors that rely on the EGFR pathway for proliferation. This reliance can be overcome by administering drugs in sequence or by giving the anti-EGFR agent in a pulse-like manner followed by the cytotoxic agent. Increasing knowledge of the mechanisms of resistance to EGFR inhibitors has led to clinical studies evaluating the combination of EGFR inhibitors with a second anti-EGFR drug or with inhibitors of HSP90, protein glycosylation (i.e. tunicamycin), mTOR, IGFR, AKT1 or MAPK. The dose-limiting skin rash seen with EGFR-inhibitors can be antagonised, without mitigating the antitumour effect, with topical anti-inflammatory agents, immunosup pressants, moisturising agents and phosphatase inhibitors such as Vitamin K (*Invited Abstract CN07#1*).

Colette D. Lukan, MD, FRCPC,
EORTC Communications Manager

For the full report, see www.eortc.be

EUROFILE

Private-public drive to cut delays in drug development

The EU's new Joint Technology Initiatives (JTIs) are intended to bring together EU and private funds to implement a research programme whose priorities are set by industry. Among the first to be launched will be the Innovative Medicines Initiative JTI (IMI), with a budget of €2 billion up to 2017. IMI will address bottlenecks in the drug development process, including, from 2009, cancer treatments.

Half of the funding will come from EU funds, half from the pharmaceutical industry, represented by European Federation of Pharmaceutical Industries and Association (EFPIA). If all goes to plan – the legislation is currently being scrutinised by EU ministers and European Parliament – the programme should start at the beginning of 2008.

An organisation set up in Brussels will manage funds and issue calls for proposals, a role normally reserved for the European Commission. Although the Commission will be represented on the IMI board and have a strong role in overseeing its work, this devolution of power is a radical departure for EU research programmes.

The IMI is also intended to be a change from the traditional pattern of collaboration in the pharmaceutical industry, in which companies work on a one-to-one basis with partners such as universities to develop new drugs. The EU wants to see more research and development on tools and methodologies that can be used by all companies active in the drug development process. So, rather than look for new drug targets or candidate compounds, IMI will address research bottlenecks in the drug development process. This should reduce development times, enable faster access to more targeted medicines and an earlier return on research investment.

Tools and methods will be developed to better predict the suitability, safety and efficacy of drugs early in the development process, before costly clinical trials begin. 'Intelligent infrastructures will be established for data integration and knowledge management between industry, academia and clinical centres. This is intended to stop the duplication of research efforts in both the public and the private sector. Finally, education and training gaps will be addressed.

The EU money will be used to support academics participating in projects, clinical centres, patient organisations, public authorities and small and medium-sized enterprises. EFPIA member companies will cover the costs of their part of the research collaboration.

Projects will be selected on a yearly basis from a strategic research agenda developed by EFPIA, in consultation with researchers and other stakeholders. The content of the first call for proposals was expected in draft form in December, 2007. Cancer research is expected to feature in the second call, in 2009, with topics aimed at improving predictivity of efficacy evaluation of cancer treatments (see *http://www.imi-europe.org/*).

Reaction to the IMI from the cancer research community has been generally positive. Françoise Meunier, director general of the European Organisation for Research and Treatment of Cancer (EORTC), thinks the IMI has potential. 'IMI should be able to contribute to accelerating access to new drugs, and as a collaborative tool between industry and academia it can benefit both parts and bring cohesion to the European landscape,' she said.

'IT'S A VERY DARING AND NOVEL THING TO DO'

'It's a very daring and novel thing to do,' commented Gordon McVie, co-ordinator of clinical research at the European Institute of Oncology in Milan. He is impressed by the matching of EU and industry funds, the promised reduction in bureaucracy and the transparency of the project selection processes. 'All the things that you would want in a science research programme appear to be in there.'

The fact that industry is setting the agenda does not pose a problem, he said: 'Fostering the business of cancer research in Europe is unthinkable without the industry, so I think it's an enlightened approach'.

The European Cancer Research Managers' Forum, however, has reservations about tying such a large amount of public funding to industry priorities. 'We don't consider it a bad thing, but we don't necessarily consider it a good thing. You need to be very cautious with something like this,' explained Seth Eckhouse, director of the ECRM secretariat and co-author of its recent report on cancer research funding in Europe.

'IT MAY FAVOUR LOW-RISK PROJECTS OVER FUNDAMENTAL RESEARCH'

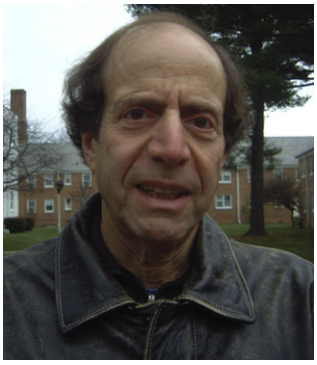
The danger is that such public-private partnerships draw funds away from more fundamental research, instead favouring projects that industry identifies as having low-risk, predictable outcomes, he said. Meanwhile the competition for remaining funds goes up, with the risk that researcher productivity falls.

Finally, public-private partnerships tend to direct funds to centres that are already strong. 'When you are using public funds to help finance private research these funds tend go to where there are significant labs already set up, where they have a really good base of highly trained researchers already in place, where pharma companies exist already,' Eckhouse explained, highlighting France, the UK and Germany as the countries most likely to benefit. 'You are not addressing the widening R&D gap, the haves and have-nots, East and West, that we see in Europe.'

Ian Mundell
Brussels

PODIUM

Novel trial designs for novel agents



Dr. Richard Simon is chief statistician for the Division of Cancer Treatment and Diagnosis at the US' National Cancer Institute. He, with Larry Norton, developed the Norton-Simon hypothesis, which used a mathematical model of tumour growth to develop the suggestion that tumours given less time to re-grow between treatments are more likely to be destroyed. Dr Simon has developed novel clinical trial designs for the emerging generation of cancer treatments.

How do molecular targeted drugs challenge traditional assumptions?

They are forcing us to recognise that some cancer types that we have previously treated uniformly in clinical trials are diverse diseases, and that only some patients have tumours that are likely to be responsive to particular drugs. When a drug specifically targets a deregulated EGFR pathway, say, we need to know which tumours have this deregulated pathway. EGFR-inhibitors originally appeared to have a low response rate. Then a couple of studies showed that the patients who responded in Phase II were those who, for the most part, had tumours with mutations in the EGFR gene. The situation was more complex than it originally looked.

What are the implications for clinical trial design?

Clinical trials are traditionally designed with broad eligibility criteria, followed by post hoc subset analysis, looking for the groups who benefited most from the drug. The design of most phase III clinical trials assumes that there are no large differences in the population treated – who responds and who doesn't. With molecularly targeted drugs, it seems in many cases that this is an untenable premise.

There's a lot at stake?

Yes. With improved design, the size of trials can be reduced in some cases. The number of patients you need in a clinical trial is critically influenced by the size of treatment effect you expect. Where there is a large benefit, you don't need a large trial; if there's a small benefit, you need a very large trial. In the past, trials have been large because they were designed to detect small treatment benefit.

Why have benefits been small?

In some cases because only a small proportion of patients who were treated actually benefited. The overall average benefit was diluted by the majority of patients who don't benefit at all. For example, chemotherapy after surgery for breast cancer has a small net effect. But 85% of patients are cured by surgery alone, and of those not cured by surgery, only a proportion will benefit from the drug. You don't know ahead of time which patients can benefit from the drug so you wind up with a huge clinical trial.

Nowadays with molecular targeted agents, and microarrays to predict prognosis beforehand, you can enrich the eligible patients by selecting only those unlikely to be cured by surgery, and those whose tumours contain the targets of the drug being tested. Consequently the treatment effect you see in some cases is larger than that seen in all comers with the same stage and primary site. You can't always predict perfectly who will benefit but if you can enrich the patients eligible for the trial you can have a much smaller trial.

How widely used is selection?

Herceptin was probably the first drug to use the approach in metastatic breast cancer. There was a relatively poor assay for patients whose tumours overexpress *Her2*; without selecting patients, the drug would not have had the same effectiveness and it would have taken years longer to get approval. Subsequently, Herceptin was evaluated in early stage breast cancer (stage II, with lymph node involvement but no apparent involvement elsewhere) among women selected using an improved assay. The effectiveness of the drug was almost of a magnitude never seen before for a solid tumour. It reduced the hazard of recurrence by 50%.

Selection enables clinical trials to be smaller and, when benefits are large, results are more reproducible. It leads to early recognition of the effectiveness of a drug, and early approval. There are tremendous economic benefits; we don't have to pay for the administration of drugs that won't benefit. When big trials for all-comers show a statistically significant benefit, you end up approving drugs that don't benefit most people taking them. They all get the toxic effects and we pay for drugs that don't help most people taking them.

How does this change affect industry?

It makes life hard for companies. In order to use this approach in a phase III trial, you need to decide in advance which patients are likely to benefit most. That's a big burden for companies. Even when a drug is known to target the EGFR gene, it might not be clear which is the best assay to use.

Lots of companies are in a hurry to get to pivotal trials, and that's a problem

PODIUM

if they have to decide how they should predefine patients; it can increase the complexity of the development process. Some regulatory agencies want to know the assay is essential so they like to see the results of drug treatment among patients who were negative as well as positive for the assay. So companies also have to treat the negatives, and may have to treat more patients because the negatives not likely to benefit, or, if they do, the effect will be smaller.

There is also the potential for restricting the market for a drug and, traditionally, companies wouldn't want to use this approach at all. But many I have talked to understand that, scientifically, this is the right way, and are interested in trying to utilise it, even if it causes complications.

Are the principles understood?

There is a lot of confusion. Predictive biomarkers are often confused with surrogate endpoint biomarkers; they are totally different. Surrogate endpoint markers are not used before treatment but claim to be an alternative to measuring clinical outcome. They are very difficult to validate.

Regulatory agencies do not like subset analyses, and they are cautious even in regard to preplanned analyses. But this is the way forward.

Is the science sufficiently sound to identify subgroups before trials?

For some drugs, it is not. We are in an interim period. We don't really understand the biology of any tumour and this is the limitation in selecting patients. There is still a certain empiricism: phase I and II is the time to gain enough understanding about drugs to determine how to select patients. Phase II trials used to determine whether there was enough evidence to go on to phase III. Now they must go beyond that, and try to identify which patients are good candidates for the drug. Phase II is an important development period, the time to intensively figure out which patients are the best candidates and which tests to use.

Has the tradition of broad eligibility been overturned?

We have not gone far in changing the design of clinical trials. But there are statistical strategies that don't rely on post hoc subset analyses. Pre-planned strategies allow you to do a clinical trial without restricting eligibility. These analyses are not dredging data for every possible factor, but are designed to look at a limited number of biological features related to the target of the drug.

What is an adaptive randomised clinical trial?

An adaptive randomised clinical trial (RCT) reduces the burden of looking for predictive biomarkers at phase II. Sometimes companies starting phase III trials have no compelling data on the patients most likely to benefit, or the right assay. A traditional phase III trial with broad eligibility followed by post-hoc subset analyses, means that a further RCT is needed to test the hypothesis that came out of the phase III.

My colleague and I wanted to roll these questions into the phase III trial, even if we didn't know ahead of time how to identify patients who would benefit. We came up with a way of identifying a predictive biomarker, and doing prospective subset analysis in the group identified, all within the same phase III trial.

So – where there is no predictive biomarker at the start of a trial, a broad group of patients is randomised. When the study ends, the new treatment is compared to standard care for all patients, using a 0.04 threshold of significance, not the usual 0.05. A statistically significant result means that the treatment has an overall benefit for all eligible patients. However, if this is not significant, a further preplanned analysis can be done. All patients will have to have given tumour specimens. From these specimens on a portion of the patients and the outcome, you try to figure out which patients had a better outcome on the new treatment. If a predictive biomarker is identified, a single subset analysis can be done on the remaining patients – those who were not used to develop the predictive biomarker. Treatment versus control is tested in these patients, using a 0.01 threshold of significance. The overall analysis could give a false positive, as could the single subset analysis, but the chance of a false positive is 0.05, as it would be in a traditional trial.

This is adaptive in that the subset is not identified at the start of the trial. It is not a perfect design but it is valid. It will only work for the subset if the treatment effect is large within this group (there probably wouldn't be enough patients in the subset to find a small effect).

We are trying to introduce the idea that you can do a prospective analysis at the end of the trial. It is not retrospective because it was preplanned. A common objection is that people say the trial didn't stratify by the predictive marker. Prospective actually means prospective analysis not prospective stratification, but some innovative ideas get held up by convention.

Are there other uses for the adaptive concept?

There could be a predictive biomarker for selecting patients but the optimal cut off point may be unknown. In a similar way, the trial would proceed without exclusions for the biomarker. At the end, the optimal threshold for the treatment evaluation is determined in a statistically rigorous way that takes account of the threshold optimization.

In adaptive designs the analyses should be rigorously preplanned. Either the sample size or the analysis plan may not be as strictly determined at start of trial as is traditional. But we have to be careful if adaptive means everything goes. We have to be adaptive in a way that enables valid analysis.

Is it difficult for collaborators to accept new statistical concepts?

We have a whole generation of clinical investigators trained in statistical principles but some of that training is coming back to haunt us! Some principles – like *never trust a subset analysis unless the study reaches overall significance* – are not appropriate for studies of molecularly targeted drugs in which a focused subset analysis is pre-planned to protect the overall 5% type 1 error rate. These principles were useful in protecting us against data dredging in previous trials, but are not the right principles now and there will have to be period of readjustment.

Helen Saul