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The joint ECCO 15–34th ESMO Multidisciplinary Congress took place in Berlin, 20–24 September, 2009.
Helen Saul and *Robert Day-Webb* report

New drug shows promise for metastatic melanoma

An experimental drug, PLX4032, appears to dramatically and rapidly shrink tumours in patients with advanced melanoma, Dr. Paul Chapman (Memorial Sloan-Kettering Cancer Centre, New York, USA) told a Presidential session of the meeting (*Best Abstract #6*).

A phase I extension study showed tumour shrinkage in 25 out of 27 patients, 5 of whom had shrinkage of more than 30%. By RECIST (Response Evaluation Criteria in Solid Tumours) criteria, this represents a partial response. Additionally, two patients had complete responses. This equates to an overall response rate of 70% compared to conventional chemotherapy treatment which has a 13–15% response rate.

'We are very excited about these results,' said Dr. Chapman, who is lead author of the study. 'This is impressive as all the patients had metastatic disease and most of them had failed several prior therapies. A lot of these patients were pretty sick but many of them had a significant and rapid improvement in the way they function. We've had patients come off oxygen and we've got several patients who have been able to come off narcotic pain medication soon after starting treatment.'

'ALL THE PATIENTS HAD METASTATIC DISEASE AND MOST OF THEM HAD FAILED SEVERAL PRIOR THERAPIES'

PLX4032 is a novel, oral and highly selective drug that blocks the activity of the cancer-causing mutation of the BRAF gene, which is implicated in 50–60% of melanomas.

The initial dose escalation phase of this study (results presented at ASCO 2009) determined the maximum tolerated dose, 960 mg twice daily. This extension study took 31 metastatic melanoma patients with the BRAF mutation, all of whom had a very poor prognosis and who had also failed one, two or even three previous treatments. These patients were then treated at the maximum tolerated dose, with anti-tumour effects measured by RECIST every 8 weeks.

The drug was well tolerated with 97% of toxicities being either grade 1 or 2 and these were mainly rash and fatigue. Nearly a quarter of the patients also developed a non-melanoma skin cancer called squamous cell skin cancer. However, this was low grade and easily removed: 'We are very vigilant about this and although they are very easy to cut out, it's something we are keeping a close eye on,' said Dr. Chapman.

Dr. Chapman and his team are planning to start a phase II trial of 90 patients imminently and, in addition, a large phase III randomised controlled trial involving several hundred patients is planned to start either at the end of 2009 or early 2010 involving centres in North America, Europe and Australia.

Dr. Chapman said it was too early to be talking about a cure for advanced melanoma, but that this drug had potential: 'Most of us think that a drug like this would ultimately be part of the regimen, but that we might need additional drugs with it to complete the cure. Right now we are seeing dramatic responses but it's too early to say whether we've actually cured people because most patients still have evidence of some level of tumour on their skin. I think this is a huge step forward; whether or not it will be sufficient by itself really remains to be seen.'

'IT'S TOO EARLY TO SAY WHETHER WE'VE ACTUALLY CURED PEOPLE'

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R.D.-W

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ECCO 15–34th ESMO Multidisciplinary Congress

PARP inhibitor 'effective in metastatic breast cancer'

A novel PARP1 inhibitor has shown significant activity in metastatic triple-negative breast cancer, according to Dr. Cynthia Osborne (Baylor Sammons, Texas Oncology, US Oncology, Dallas, Texas, USA), one of the study investigators, Speaking at the ECCO-ASCO Presidential session, she said that a phase III trial had been set up on the basis of promising early results.

She said that first results from a randomised phase II trial showed that the poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, BSI-201, in combination with gemcitabine and carboplatin, significantly improved clinical benefit rate, progression-free and overall survival in patients with metastatic triple-negative breast cancer, compared to gemcitabine and carboplatin alone. (*ASCO Abstract # G2*).

Triple-negative breast cancer is an aggressive breast cancer subtype (tumours lack expression of oestrogen and progesterone receptors and there is no HER2 overexpression) and shares molecular and pathologic features with BRCA1-related breast cancers. BRCA-deficient cells are sensitive to inhibition of PARP1, a critical enzyme of cell proliferation and DNA repair, and thus represent a rational target of PARP inhibitor-based cancer therapy.

In the phase II study, 120 patients were randomly assigned to receive standard treatment (gemcitabine and carboplatin) with or without BSI-201. Analyses to date have shown that the addition of BSI-201 significantly improves clinical benefit rate (62% vs 21% without), overall response rate (48% vs 16% without), progression-free survival (6.9 vs 3.3 months without), and overall survival , (9.2 vs 5.7 months without). The drug was well tolerated with no additional toxicity.

'A final data analysis will be performed later this year,' Dr Osborne told the meeting.

'The promising safety and efficacy data from this phase II study has justified further investigation and a phase III trial began in June 2009. This is an open label, randomised safety and efficacy trial of gemcitabine and carboplatin with and without BSI-201 in metastatic triple-negative breast cancer in which the primary endpoints are overall and progression-free survival,' Dr. Osborne said.

Photo:franknuerenberger.de

Dr Cynthia Osbourne

(EJC Supplements 2009 7. 3: 7 #G2)

R.D.-W.

ECCO/EJC Young Investigators Award

The ECCO/EJC Young Investigators Award for 2009 was presented to Dr. Miranda Kusters (Surgical Resident, Catharina Hospital, Eindhoven, the Netherlands) in recognition of her work on local recurrence in rectal cancer (*#213*).

The study included 290 patients with locally advanced rectal carcinoma who underwent multimodality treatment at the Catharina Hospital between 1994 and 2006. Patterns of local recurrence were analysed according to location: presacral, postero-lateral, lateral, anterior, anastomotic or perineal. Patient, treatment and tumour characteristics were then related to the subsite to establish the mechanism of local relapse. 'By doing this the effect of the treatment on local control can be quantified' said Dr. Kusters.

The study found that preoperative radiotherapy caused a significant reduction in lateral local recurrence rate. Anastomotic recurrences were sterilised by preoperative radiotherapy, except when distal margins were less than 5mm; preoperative radiotherapy combined with total mesorectal excision surgery resulted in similar local recurrence rates to surgery with lateral lymph node dissection only.

In locally advanced rectal cancer the bilateral lymph node dissection prevented more local recurrences than the unilateral lymph node dissection, mainly in the presacral subsite. The lateral lymph nodes appeared to play a role in presacral local recurrence genesis.

Intra-operative radiotherapy to the area considered most at risk led to fewer outfield local recurrences than presacral intra-operative radiotherapy only; and postoperative chemotherapy prevented local recurrence rather than distant metastases. The location of the recurrence predicted the radicality of the resection and consequent survival.

'The worst complication after the treatment of rectal cancer is local recurrence,' said Dr. Kusters, adding, 'I was very surprised to be awarded the Young Investigators Award; I feel very honoured and want to thank ECCO and EJC for this amazing privilege!'

Photo:franknuerenberger.de

Dr Miranda Kusters receives her award from EJC Editor-in-chief Professor John Smyth.

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R.D.-W.

ECCO 15–34th ESMO Multidisciplinary Congress

The launch of the European Partnership

European politicians and Commissioners used their presentations at the ECCO 15–34th ESMO Congress to highlight the launch of the European Partnership for Action against Cancer. The Partnership, which aims to reduce the incidence of cancer in the EU by 15% by 2020, was officially launched in Brussels the week after the Congress (on 29 September, 2009).

'The overall aim of the Partnership, which is initially planned to run from 2009 to 2013, is to support member states in their effort to tackle cancer,' Health Commissioner Androulla Vassiliou told a Presidential session of the Congress.

'To better achieve this aim, the Partnership seeks to engage a wide range of stakeholders – including non-governmental organisations, patient groups, researchers, industry and organisations of health professionals – that all share the common commitment to fighting cancer.'

The Partnership will be built around the four 'pillars' of prevention, healthcare, cancer research priorities and the collection and analysis of comparable data for benchmarking, said Nick Fahy, head of health information at the Commission (DG for Health and Consumer Affairs), speaking in a later session.

Prevention will cover screening programmes for breast, cervical and colorectal cancer. There is an existing common commitment from all 27 Member States to run screening for these diseases 'but we have less than half the coverage of those screening programmes that we should have,' said Fahy, adding that, 'We also think we can do more in involving citizens themselves to become more aware of what they can do – what we call all do – in our everyday lives to much reduce our risk of cancer.'

'OUR FUTURE SUCCESS WILL DEPEND ON JOINT EFFORTS'

Healthcare provision is squarely the responsibility of Member States, but there is potential for each to learn from best practice elsewhere, he said. 'We want to see an improvement through a reduction in the inequalities between different strands of healthcare provision.' Accreditation and establishing standards will play a role: 'We can provide a tool to Member States and to health authorities to be able to accredit different centres to show they have reached the standards. And to be very clear about those that have not.'

In research, the aim will be to bring together the focus of research at European level, also involving the member states, but going beyond public sector funding to include stakeholders in the private and non-governmental sectors.

Benchmarking via the collection of comparable data and indicators at European level 'has proved to be a key took in driving progress,' Fahy said. Once scientific innovation has developed ways of doing better, political and social commitment is necessary to implement it. 'One of the most powerful ways of getting that political commitment is to be able to show citizens that the survival or outcome rates elsewhere are much better than where those people themselves live,' he said.

Slovenian MEP Alojz Peterle backed this point. Politicians 'are not specialised in the biology of cells, of cancer or genetics, but we are attentive to inequalities. We are attentive to the fact that there is a so-called iron curtain between east and west as far as your chances of surviving once you are diagnosed with cancer are concerned.

'Inequalities in a politician's view are a consequence of the lack of community of knowledge. If in a member state in the eastern side of the EU, a cancer patient has 60% less chance of surviving than a patient 5km away, in another member state, this means there is no partnership, no exchange of knowledge. We can do a lot, but we know enough to do more.'

The Partnership is intended to benefit citizens in all states, whatever the economic circumstances. Swedish MP Barbro Westerholm said, 'It's a small country, Sweden, with 9.1 million inhabitants, and we can't, on our own, create the critical mass needed to deliver research in all cancer areas. That's the same problem we have in rare diseases.

Photo:frankruerenberger.de

Health Commissioner Androulla Vassiliou

'Therefore we have to act as a part of an international network which includes all disciplines necessary to innovate and deliver in all areas of cancer research,' she said.

Fahy said that while inequality in outcomes across Europe is a challenge, 'it also represents an enormous possibility and hope.' If current knowledge and current techniques could be generalised across the EU, 'we could make an enormous difference, an enormous improvement to tackling cancer for many people across the EU.'

The reduction of 15% in comparison to current projected numbers of new cancer cases represents 500,000 lives that would otherwise be touched with cancer. That is a staggering number of people, Fahy said, 'but on the basis of the variations that we see now, it is an entirely achievable goal if we work together and if we bring the cooperation that we currently see the potential for, into reality.'

Europeans have spent nearly 60 years developing process for working together, taking 27 very different countries and cultures and finding ways of working together and achieving results that are better than any of us individually, or those countries individually could have achieved.

'We hope that this partnership will be an example of developing and building on those principles and taking that further for health in the future,' he said.

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The launch of the European Partnership

(continued from page 3)

Commissioner Vassiliou spoke on the same theme: 'A wide range of community actions through the Partnership will provide strong support for the efforts made by member states. The Partnership will show whether different stakeholders can work together and fight the problem in a spirit of solidarity with a common sense of purpose. It will be a test for us all. But it will also be an opportunity to turn our fine words into hard reality.

'Our future success will depend on joint efforts,' she concluded.

● With President of the European Commission, José Manuel Barroso, Commissioner Vassiliou launched the European Partnership for Action against Cancer in Brussels on 29th September, 2009.

She said the Partnership is an example of a new model of European governance: 'I hope that we will be able to combine the political authority of the EU institutions with the commitment and know-how of the full range of partners across Europe to bring about real change.'

President Barroso said that the Partnership would lead to better use of European resources, expertise and means. 'This represents another expression of the European Union's values, based on responsibility and solidarity, as well as efforts to place people firmly at the heart of our action.'

EU Member States, international organisations and experts were invited to participate in the first preparatory meeting for the Partnership, due to be held in Luxembourg in November, 2009. Other stakeholders can apply for participation.

The meeting is intended to agree the structure of the cooperation, on the role of different stakeholders and on the main actions, which are expected to start in 2010.

For further information, see *http://ec.europa.eu/health/ph_information/dissemination/diseases/cancer_partnership_en.htm*

Helen Saul

Prostate cancer hormone therapy 'raises heart disease risk'

Hormone therapy used to treat prostate cancer may raise the risk of heart disease with gonadotrophin releasing hormone (GnRH) agonists apparently posing the greatest threat, Ms Mieke Van Hemelrijck (King's College London, UK) said at a Presidential session (*Best Abstract #1BA*).

A Swedish study, the largest to date on the issue, compared risks among prostate cancer patients taking hormone therapy with those in the general population. Overall, the prostate cancer patients had 24% increased risk of a non-fatal heart attack, 19% increased risk of arrhythmia, 31% increased risk of ischaemic heart disease and 26% increased risk of heart failure. Their risk of death from a fatal heart attack was increased by 28%, and it rose by 5%, 21% and 26%, respectively, for the other conditions.

'If we have observed a causative effect, then for all hormone therapies put together, we estimate that compared with what's normal in the general population, about 10 extra ischaemic heart disease events a year will appear for every 1000 prostate cancer patients treated with such drugs,' said Ms Van Hemelrijck , the study's leader. 'However, not all types of therapy were associated with the risk of heart problems to the same degree. We found that drugs which block testosterone from binding to the prostate cells were associated with the least heart risk, while those that reduce the production of testosterone were associated with a higher risk. This may have implications for treatment choice.'

In a more detailed analysis by type of hormone therapy, GnRH agonists proved more risky than anti-androgen drugs: 'The finding that anti-androgens carry the least heart risk supports the view that circulating testosterone may protect the heart,' said Ms Van Hemelrijck.

The study involved more than 30,000 Swedish men with advanced prostate cancer who received hormone therapy as primary treatment for their disease between 1997 and 2006. The researchers compared their rates of heart problems to those in the general Swedish population. Most of the patients received one treatment, but 38% received both GnRH agonists and anti-androgens. The men were followed for an average of 3 years.

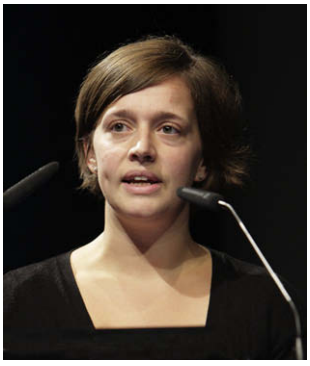

Photo:franknuerenberger.de

Ms Mieke Van Hemelrijck

'Because this was a large observational study, we cannot come up with a direct causal explanation, but these results indicate that doctors need to start taking heart disease into account before starting a prostate cancer patient on hormone therapy, especially as hormone therapy is not only used in metastatic disease but also in less advanced disease,' said Ms Van Hemelrijck.

The study showed a less pronounced increase in risk in men who already had a history of heart disease at the time of their diagnosis. 'This could be because these patients were already receiving treatment for their heart disease,' said Ms Van Hemelrijck.

'We now need studies verifying the association and exploring plausible biological mechanisms. Then we would know how to best use these treatments according to a patient's history of various types of heart disease and whether it would be a good idea to give patients heart medicines to counteract these side effects.'

(EJC Supplements 2009 7. 3:1 #1BA)

R.D.-W.

PODIUM

'We need a major shift in research priorities'

Professor Richard Sullivan (London, UK) chairs the European Cancer Research Managers (ECRM) Foundation. He spoke at the joint ECCO 15–34th ESMO Congress on the need for a shift in research priorities.

What are the key prioritisation issues in cancer research today?
The one overarching caveat is that prioritisation is a political process and needs to be holistic and inclusive. Different branches, divisions, disciplines and areas of cancer research need to be involved.

First, it's about looking at the evidence base for prioritisation – where are the strengths and the gaps – and in particular, highlighting whether the research gaps could be due to a lack of investment, a lack of faculty or infrastructure, or other issues which are related to the culture of the community. Prevention and surgical technology development are 2 areas in which levels of research investment activity are disappointingly and worryingly low.

Second, it's a question of research prioritisation with regards to developed and low-middle income countries. Does Europe have a moral responsibility to the rest of the world, to the global cancer patient? My standpoint is that, in terms of mutuality and solidarity, we do have a responsibility. Demographic trends show that most of the cancer burden is going to be in low-middle income countries over the next 50 years, but the amount of work being conducted and research being funded in this area is phenomenally low.

Third, we need to prioritise the kind of research policies that will promote creativity in cancer research. Bibliometric analyses in some areas show worrying trends that cancer research in certain areas is becoming less creative.

What might be the consequences of priority imbalance?
If it continues, we'll see an ageing population in developed countries struggling to cope with increasing costs and decreasing returns in outcomes with new technologies. The research being conducted won't deliver tangible improvements in outcomes because of this 'second translational gap'. There will also be a huge burden of cancer in developing countries and we will lack management strategies that actually work in these environments because the research and service development (health services management) support will not have been done.

Is this a question of prioritisation or simply a lack of funds?
It's easy to ask for more money, but the reality is that we've got to prioritise as well. One has to be careful about investment; the system can soak up a lot of money without necessarily improving quality or productivity.

A just-completed ECRM analysis shows that, on average, European public funders spend 74% of their money on fundamental biology and drug development research. Well over 70% of the cancer research initiatives at the European level are aimed at the same areas. In the US, the imbalance is even greater. There is no shortage of cancer drugs coming through the pipeline and the whole area of drug research is healthy, though we need to translate discoveries in fundamental cancer biology to the next generation of medicines more quickly and cost effectively.

What we need now is a reapportioning of budgets from the charitable sector and federal funders to carve out space for other areas of cancer research that are largely invisible to policymakers.

So how can these issues be resolved?
We need to separate the political process from the evidence base. We need cancer societies, membership bodies and patient groups to engage in well facilitated discussions. We can't leave it to federal and philanthropic funders. The initiative by ECCO to create a European Academy of Cancer Sciences and to have a dedicated oncopolicy track is exactly what is needed.

Second, it needs to be based on evidence. A whole range of methodologies are available: bibliometrics, demographics, epidemiology and the social sciences. The social sciences have a huge amount to offer in terms of good scientific studies producing excellent qualitative and semi-quantitative data to help understand the barriers or levers to activate the necessary changes. Advanced political analysis will ensure that all players understand how to drive change forward.

What should happen now?
Investment in fundamental cancer biology and drug development will continue and we now need to concentrate on some of the 'orphan' areas of cancer research such as paediatrics, prevention and surgical technologies. Radiotherapy and surgery will be the primary modalities in most low-middle income countries for the foreseeable future and so enhanced European research in this area would be a win-win situation, particularly if we can partner with global initiatives such as the IAEA's IMPACT programme.

I'd like to see a wide debate on low-middle income countries and what Europe should be doing to help. Chronic disease is a major, often unrecognised problem in developing countries and we can't afford to wait any longer. If we can galvanise support for HIV/AIDS and malaria, then we can do it for cancer. Now is the time to be thinking about a Global Fund for Cancer.

Robert Day-Webb