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Abiraterone shows promise in metastatic prostate cancer

The androgen blocking agent abiraterone acetate significantly improved overall survival in men with metastatic prostate cancer resistant to hormone therapy, according to data presented at the 35th Annual ESMO Meeting (Milan, Italy, 8–12 October 2010).

"These results are likely to alter the standard of care for men with advanced prostate cancer who have progressed despite receiving docetaxel-based chemotherapy, a critically important area of unmet need," said study author Johann de Bono (Institute of Cancer Research, London, UK).

The phase III COU-AA-301 study into abiraterone acetate (a selective androgen biosynthesis inhibitor that blocks the enzyme CYP17, thereby inhibiting persistent androgen synthesis) was double blind. It included 1195 patients with metastatic advanced prostate cancer, who had failed up to two chemotherapy regimens (one of which contained docetaxel). They were randomised to receive abiraterone acetate (1000 mg once daily) plus prednisone/prednisolone (5 mg twice daily, n = 797) or placebo plus prednisone/prednisolone (n = 398).

Treatment with abiraterone acetate resulted in a 35% reduction in the risk of death (HR = 0.65; $p < 0.0001$) compared with placebo. Median survival was 14.8 months versus 10.9 months, and time to disease progression 10.2 months versus 6.6 months ($p < 0.0001$), respectively.

Patients who received abiraterone acetate showed significant improvements in secondary endpoints including time to Prostate Specific Androgen (PSA) progression, and an increase in radiographic progression free survival. Adverse effects included fluid retention and hypokalemia.

"A key question now is how to work out which patients will benefit from the drug," said De Bono

● Results from a combined phase I and II study, presented at ESMO by Chris Parker (Institute of Cancer Research, London, UK) showed treatment of castration-resistant prostate cancer with radium 223 chloride resulted in a low incidence of adverse effects. Radium 223 chloride is a first in class agent: bone targeted radium 223 emits alpha particles with an ultra short range of 2–10 cell diameters resulting in highly localised cytotoxic effects. The latest analysis found severe Grade 4 haematologic toxicity in 1% patients, Grade 3 anaemia in 4%, and Grade 3 toxicity for platelets or white blood cells in 3%. The results add to the phase II trial in 292 patients, presented at ASCO 2010, which showed that median overall survival was 65 weeks in the radium 223 group versus 46 weeks in the placebo group (p = 0.017).

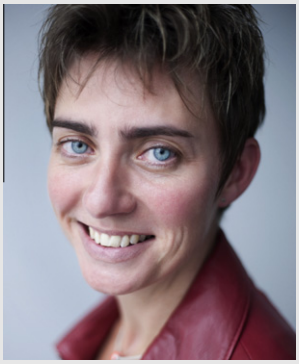
More coverage of ESMO 2010 on page 2

Breast screening 'should be considered' in younger women

Biennial mammographic screening may halve the risk of dying from breast cancer among women aged 40–49, according to a study in the Netherlands. Researchers say in a forthcoming issue of *EJC (doi:10.1016/j.ejca.2010.09.041)* that their work 'adds convincing evidence of the effectiveness of biennial mammographic screening in women aged 40–49.'

The study included 272 breast cancer deaths; 1360 referents aged 40–69 were sampled from the population invited for screening. The odds ratio (OR) for dying of breast cancer was calculated in screened versus unscreened women.

In women aged 40–49, the effect of screening was OR = 0.50, similar to that among those aged 50–59 (OR = 0.54) or 60–69 (OR = 0.65). Dr. Mireille Broeders (National Expert and Training Centre for



Breast Cancer Screening, Nijmegen, the Netherlands), one of the authors of the study, said that the effect of screening in case control

Continued on page 4

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35th Annual ESMO Meeting; Milan, Italy; 8–12 October 2010

Peri-menopausal women 'require regular monitoring'

Perimenopausal breast cancer patients with oestrogen receptor positive disease need to have their menopausal status regularly screened to check if they have become eligible for an aromatase inhibitor (AI), delegates at a satellite symposium heard.

"While tamoxifen is the gold standard of treatment for pre-menopausal women, AIs have become the dominant approach for menopausal women, either as an upfront treatment or planned switch," said Dr. Alison Jones (Royal Free and University College London Hospitals, UK). A meta-analysis has demonstrated a 30 % reduction in the risk of recurrence by starting with tamoxifen and switching to an AI, she said. Menopause status should be confirmed by measuring levels of LH, FSH and oestradiol, with tests every 3–6 months, and at the time when a switch is being considered.

In the same symposium Matti Aapro, (Clinique de Genolier, Switzerland) highlighted the under-use of adjuvant therapy among older women with breast cancer. Around half of women over 80, he said, do not receive adjuvant treatment for breast cancer in accordance with guidelines.

"One of the reasons elderly women do not receive appropriate treatment is because of misconceptions about life expectancy. In reality, fit women of 80 with no co-morbidities have a life expectancy of 10 years," said Aapro. "It's important to realise that age should not dictate the decision making process and that it is reasonable to use AIs in this group. The SWITCH trial showed clear evidence of the benefit of switching to AIs in this age group."

AIs preserve cognitive function more effectively than tamoxifen, have less effect on cholesterol and less risk of venous thromboembolism, he said. Side effects such as osteoporosis can be dealt with by exercise, calcium supplementation, Vitamin D and bisphosphonate drugs.

Progression free survival benefits in triple negative breast cancer

The addition of cetuximab to chemotherapy produced a significant reduction in risk of progression for women with metastatic triple negative breast cancer, the BALI-1 study concluded. However, the phase II study, presented in the Presidential Symposium, did not meet its primary endpoint of a greater than 20% objective response to therapy.

Around 15–18% of breast cancers are triple negative and do not express receptors for oestrogen, progesterone or HER2. They are associated with a particularly poor prognosis because of their rapid spread and lack of response to hormone or anti-HER2 therapies. The monoclonal antibody cetuximab specifically targets epidermal growth factor receptor (EGFR), expressed by around half of all breast cancer tumours.

In the BALI-1 study, 173 patients with triple negative, metastatic breast cancer were randomised to receive either cetuximab plus up to six 3-weekly cycles of cisplatin (n = 115); or cisplatin alone (n = 58). An overall response rate was seen in 20.0% patients receiving the cetuximab/cisplatin combination compared to 10.3% among those receiving cisplatin alone (p = 0.11). Adding cetuximab to cisplatin doubled the median length of progression-free survival, from 1.5 to 3.7 months (HR = 0.675, p = 0.032).

"I'm convinced that cetuximab has a role in treating breast cancer, but I think that we need to design a more appropriate trial," said José Baselga, the principal investigator of the study, from the Massachusetts General Cancer Center, Boston, MA, USA. "In this advanced-disease population, this type of improvement is rarely seen."

● Eric Van Cutsem (University Hospital Gasthuisberg, Leuven, Belgium) presented data on cetuximab in patients with KRAS wild-type metastatic colorectal cancer (mCRC). Further analysis of the randomised CRYSTAL trial found that those who experienced early tumour shrinkage (reduction of at least 20% within 8 weeks) during first line cetuximab-based treatment lived for a median of 28.3 months. No such correlation between early tumour shrinkage and long term survival was observed in the control arm (chemotherapy alone); median survival in this group was 21 months. The phase III CRYSTAL trial had previously demonstrated that mCRC patients with KRAS wild-type tumours achieved a median survival of 23.5 months. "These new data indicate that early tumour shrinkage with personalized cetuximab therapy correlates with significantly improved survival," he said.

Positive study for bevacizumab in ovarian cancer

Bevacizumab added to standard first-line chemotherapy in advanced epithelial ovarian cancer improved progression free survival compared with chemotherapy alone, concluded the phase III ICON-7 study. However, the benefit diminished with time.

After surgery, 1528 women were randomly assigned either to 6 cycles of carboplatin/paclitaxel (n = 392) or the same chemotherapy plus bevacizumab given concurrently and then alone as maintenance for up to an additional 12 cycles (n = 367).

At 12 months, women taking bevacizumab (a monoclonal antibody that binds vascular endothelial growth factor) on top of chemotherapy had 15% reduced risk of their disease progressing compared to those taking chemotherapy alone ($p < 0.0010$). The effect dwindled with time; the median time to progression was 19 months for the bevacizumab arm versus 17.3 months for the control arm (p = 0.0041).

The ICON-7 results are consistent with the Gynecologic Oncology Group (GOG 0 218) study, presented at ASCO. The overall survival data from ICON 7 will not be mature for a further two years.

Janet Fricker was sponsored to attend the meeting by Bayer Health Care

EUROFILE

The First Oncopolicy Forum

Members of the cancer community gathered at the first ECCO Oncopolicy Forum were told that the European Commission is keen to fund more investigator-driven clinical research which will lead to better cancer therapies and surgical procedures. The Commission has also invited the Forum to engage in a new healthcare initiative aimed at the ageing population in Europe.

With a focus on partnerships, the first Forum (Brussels, 26 October, 2010) served as an arena for policymakers and representatives from the European Council of Ministers, European Parliament, the European Commission's directorates for research and health, WHO, cancer centres and societies, industry, nursing and patient organisations to bring each other up to speed on new and existing initiatives.

Unable to attend in person, EU research commissioner Máire Geoghegan-Quinn outlined the Commission's strategy for 2020 in a video message to delegates, asking the forum to participate in a pilot partnership involving health research. Expected to be launched in 2011, it aims to enable Europeans to live independently for longer and increase healthy lifespan by an average of 2 years.

The pilot partnership would be "a framework for pooling resources and tackling bottlenecks," Geoghegan-Quinn told delegates. "We need a co-ordinated approach, working together rather than in isolation. EU funding is small compared to industry and national funding. It's easier to achieve goals if we act together," she added.

The pilot scheme is an attempt to streamline the existing EU model for public-private partnerships. It would bring together EU and national stakeholders across policy areas and industrial sectors in order to identify research agendas, coordinate investments in the demonstration phases of projects and fast-track standards and authorisations. It would also offer EU seedcorn funding to attract investment in the R&D packages developed by stakeholders.

Jan-Willem van de Loo, head of cancer research and co-ordination of policy orientated activities at DG Research, told delegates, "DG Research has an important role to play in primary and secondary [health]care. We focus more on trying to structure translational research by partnering, and we are dipping more into elderly and child research and off-label [orphan] drugs."

Clinical research on cancer could fit within the remit of the pilot partnership on healthy ageing: "We are very interested in funding more clinical research, especially investigator driven research as 70% of phase-1 trials are initiated by industry, not academia," he said. "We need better chemo[therapies] and better surgeries. These are considered blunt therapies but they do save lives."

Imaging and diagnostics have recently appeared as funding lines in the current EU research programme, Framework 7, which offers up to 50% of the funding for consortia led joint research actions, he said.

However, multi-stakeholder partnerships pose distinct problems which can hinder rather than aid progress in cancer, warned Richard Sullivan, director of the Centre for Global Oncopolicy at the European Institute of Oncology. "Partnerships need partners of equal bargaining power else you get free-riders and side effects," he told delegates. "We need to understand each other's agendas. Where there is both competition and collaboration, it's very difficult. There are constraints on partners and trade offs with own agendas. Forced co-operation does not add value, this has been shown time and time again," he said.

One delegate told *EJC News*, "Richard Sullivan has voiced what many here feel they cannot or dare not voice publicly."

Belgium succeeded in putting cancer on the political agenda during its EU presidency (July – December 2010). Olivier Belle, advisor to the acting Belgian deputy prime minister and minister for public health, Laurette Onkelinx, told delegates that European health ministers favoured voluntary multi-stakeholder partnerships as a tool for collaboration, especially the EU cancer partnership launched in September 2009. This is because healthcare is legally a national matter and "member states want to keep control," he told the Forum.

The EU Cancer partnership seeks to have integrated national cancer plans in place in all 27 EU countries by 2013. Widespread disparities exist across the EU with some member states lacking plans altogether and others encompassing cancer in wider national plans on chronic diseases. "Through identifying weaknesses and gaps in their plans [together], we hope this [target] will happen naturally. But we won't impose anything from above," he stressed.

Yet EU ministers meeting in July 2010 concluded that every member state should have a national cancer plan. Despite lacking the legal status to enforce this, Belle was certain this conclusion carried weight. "Although it has no legal power, the text has a semi-legal power to promote political conclusions," he said. "Ministers have identified the need to work together and develop the tools to speak a common language. Those conclusions are not legally binding but politically very important to forward the fight against cancer. By 2013, this will be done."

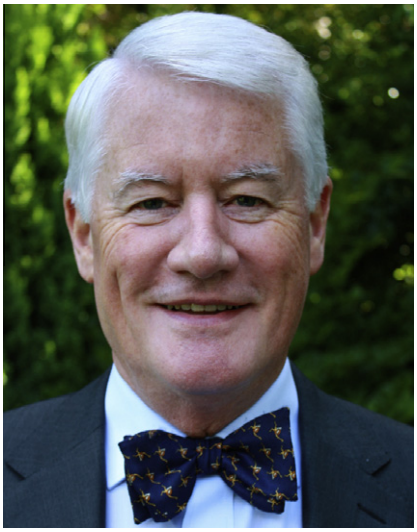
Chronic diseases were discussed again at an informal EU ministers meeting a week before the Forum. Belle told delegates, "The main conclusion we drew was the need to develop an integrated approach to deal with them, and specifically cancer. This needs to go beyond the [national] health systems. We absolutely need to reshape the health system model in order to improve the lack of appropriate co-ordination," he said.

Saffina Rana
Brussels

For further information on the EU cancer partnership, see EJC News EUROFILE EJC 2009;14:2441

PODIUM

A decade of change at EJC



Professor John Smyth served as Chair of Medical Oncology at the University of Edinburgh for 30 years; now, as Emeritus Professor, he is Assistant Principal for Cancer Research Development. He chairs the Expert Advisory Group for Oncology and Haematology for the UK's Commission on Human Medicine and is a former President both of ESMO and of FECS. Professor Smyth has been Editor-in-Chief of EJC for 10 years and will step down at the end of 2010.

How different was EJC when you took over in 2000?

10 years ago, *EJC* had a relatively small readership confined to Europe; it's now much more widely read, its visibility has improved greatly, partly because of online usage which is one of the great revolutions in all journalism. In 2009, *EJC* got 900,000 downloads and this year we will probably hit 1 million. Our online usage has doubled in 5 years, and in 2009, only 40% was from Western Europe. North America accounted for 26% and Asia 21%. Our manuscripts reflect the same change: we receive a lot from Asia and Australasia, and increasingly from North America. *EJC* is still a European journal but the biggest difference over the last 10 years is its visibility and therefore, one hopes, its relevance.

How far would you have predicted this change?

My ambition was confined to Europe. I'd been President of ESMO and later on, of FECS, and I wanted to make the *EJC* representative of the whole European cancer scene. I wouldn't have predicted

Breast screening in younger women *Continued from page one*

studies – which compare screened with unscreened women – tends to be larger than that seen in randomised controlled trials (RCTs).

"RCTs usually evaluate women invited versus women not invited. With case control studies you're looking at women who have actually had the screening examination, which is different from women who are invited and who may or may not take up the invitation. In RCTs you also get contamination of the groups: not all of the women who are invited actually come for screening and further, some of the women in the control group go and get a mammogram even though they are not invited through the programme. This cross-over dilutes the effect."

She said the approximate halving of breast cancer mortality risk has been reported before, and was backed by new data from Sweden (*Cancer 2010, doi:10.1002/cncr.25650*). It found a relative risk of dying from breast cancer of 0.71 among women aged 40–49 who attended screening. However, at almost the same time, another study was published, albeit among women aged 50–69 years, which found a much smaller effect with screening (*N Engl J Med 2010;363:1203-10*). This study, in Norway, looked at women living in counties with screening programmes and compared them to historical controls. It found that screening was associated with only a 10% reduction in breast cancer mortality.

The *EJC* data covers women screened between 1975 and 1990 with analogue mammography and Dr. Broeders said the effect of screening might be larger with newer technology. "Trials have found that digital mammography tends to perform better in younger women. This, combined with the fact that breast cancer incidence in the Netherlands has increased immensely between the ages 45 and 49, means we should carefully consider a reduction in the age that we start screening.

'WE SHOULD CAREFULLY CONSIDER A REDUCTION IN THE AGE THAT WE START SCREENING'

"But there are aspects to consider. We don't really know what digital mammography does in terms of the mortality reduction, and we know even less about its effect in younger women because there are few digital programmes running that screen younger women. We also need to look at the cost effectiveness of lowering the age limit. We don't know enough about it yet, but I think there's certainly reason enough to look at this group and reconsider.

"The UK is moving the age limit for screening down from 50 to 47 but in the Netherlands we would probably first do a pilot on the impact of digital mammography in women under 50. For us, it may be too soon to go for a national change because of the limited evidence on digital screening in younger women in Europe. There is some US data but it's difficult to compare the results because screening in the US is different – they use a different dose in mammography, and so on – and it is difficult to generalise from their results to our situation. We need data on screening younger women with digital mammography in our own health environment. And obviously, we would look at potential harms as well as benefits."

PODIUM

such interest from Asia. This change isn't confined to *EJC*; it reflects the interest in cancer research in China in particular but also in Korea and Japan, and the more open way they are sharing information with the rest of the world.

What other changes in the landscape have you had to respond to?

The explosion of scientific knowledge in 10 years has been extraordinary; every journal is challenged by the worldwide generation of factual information. Editors have to sort out what is relevant and appropriate to their readership – which can be particularly difficult with a multidisciplinary journal – but all editors have to sort the good from the less good, the truth from what is doubtful and get the balance of papers right for their journal. This year, we will review more than 2000 manuscripts. With web access near-universal, public expectation – and that includes politicians – that this scientific knowledge will be truly useful in the healthcare sense is limitless. Journals have to balance what is speculative information and what will change healthcare or practice. I want to give our editors credit for the excellent job they have done. We are a small group, we have worked as a team together, most of us for 10 years, including our publishers, Elsevier, yourself as news editor, and Amanda Wren and the ECCO web page. Together we've put across scientific knowledge but also aimed to help the oncology community in its broadest sense, to understand the issues that are being debated and inform decision-making.

Would you pick out any particular high points?

The editorial team was aware of the risk of information overload and responded with reviews, summaries and developing special issues. They appear 3 times a year and focus on a particular issue in cancer research. They have been well-received and made an important contribution to our overall educational goal.

The other high point was when we broke through the emotional barrier of an impact factor of 4. Our goal is basically education and knowledge sharing, and our increased readership is testament to our success. We are a multidisciplinary journal with no society base, so raising impact factor is always going to be difficult, but you can't ignore it and I feel that getting into the 4s was an achievement.

We now have a rejection rate of 80%, which ironically is also an achievement. It puts a huge burden of responsibility on editors who are unquestionably turning down some good papers but if it's hard to get a paper published in a journal it shows that the journal has a reputation that's worthwhile.

The other thing that pleases me is that our top 10 downloads consistently show a balance between the disciplines: clinical research, basic research, epidemiology and so on.

Have there been low points?

It's not a low point exactly, but one disappointment would be that we have struggled to persuade colleagues in Europe to publish practice-changing trial results in *EJC*. We fully understand the pressure on cooperative groups and writing committees, but it would be a huge boost to European oncology if important pivotal trials could be published in Europe before they appear in *JCO* or *NEJM*. It's difficult to compete as editor in chief of *EJC* with *NEJM*, but if some of these trials were published in Europe first, it would quickly act as a catalyst for other groups to do the same thing.

More personally, the death of Jon Pritchard, our paediatric oncology editor, was a great sadness for myself and the editorial team. He was an extremely loyal servant of the journal and we miss him.

What challenges have there been for the journal in the past decade?

The greatest challenge has been to find a balance between the different sectors of the oncology community we service: clinical trials, epidemiology, translational research, and so on. And how to handle increasing numbers of papers. I believe in peer review, especially when you have to turn down the lion's share of what is sent in, but in a world that's extremely busy, it's a challenge to persuade colleagues to review literature. There is an argument that material can just be put out on the web and readers can make up their own mind. I passionately disagree with this trend, because one of the roles of editors is to use their experience, wisdom and judgement to sort out what is important. It is extremely unwise to encourage people to read something and then make up their own minds whether it is true or false.

How do you feel about leaving EJC?

I will miss the discussion and debate with editors; it has been the most fabulous continuing professional development. Sometimes it's a real struggle to keep up with the literature but to have this opportunity – and be forced! – to read so much has been an education. I shall miss that. All of the editors have been genuinely engaged; it has been intellectually satisfying for us all. It's been an exceptional privilege in fact and I wish the incoming team the best of luck!

Helen Saul